UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE FARMACIA
Departamento de Química Orgánica y Farmacéutica

TESIS DOCTORAL
Development and applications of the aza-vinylogous Povarov reaction of α-ketoimines

Desarrollo y aplicaciones de la reacción de Povarov aza-viníloga de α-cetoiminas

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Giulia Bianchini

Directores

José Carlos Menéndez Ramos
María Teresa Ramos García

Madrid, 2018

FACULTAD DE FARMACIA
DEPARTAMENTO DE QUÍMICA ORGÁNICA Y FARMACÉUTICA

DEVELOPMENT AND APPLICATIONS OF THE AZA-VINYLOGOUS POVAROV REACTION OF α-KETOIMINES

DESARROLLO Y APLICACIONES DE LA REACCIÓN DE POVAROV AZA-VINÍLOGA DE α-CETOIMINAS

TESIS DOCTORAL

GIULIA BIANCHINI

Directores: José Carlos Menéndez Ramos
María Teresa Ramos García

Madrid, Enero de 2017

Index

Summary 1
Resumen 7
1 – Introduction 15
    1.1 - The importance of the 1,2,3,4-tetrahydroquinoline scaffold 17
    1.2 - The Povarov reaction, a powerful method for the synthesis of tetrahydroquinolines 20
        1.2.1. – Introduction 20
        1.2.2 - Acyclic dienophiles 21
        1.2.3 - Cyclic dienophiles 23
        1.2.4 - Vinylogous dienophiles 25
    1.3 - Enantioselective Povarov reactions 28
        1.3.1. – Chiral Lewis acid catalysis 28
        1.3.2 - Chiral Brønsted acid catalysis 31
        1.3.3 - Chiral urea catalysis 36
    1.4 - Mechanistic debate 41
2 – Objectives 47
3 -Studies on the racemic aza-vinylogous Povarov reaction 53
    3.1 – Introduction 55
    3.2 - Aza-vinylogous Povarov reactions starting from arylimines 57
    3.3 - Aza-vinylogous Povarov reactions starting from α-ketoimines 60
4 - Development and optimization of an enantioselective organocatalytic aza-vinylogous Povarov reaction 69
    4.1 – Introduction 71
    4.2 – Development of an enantioselective vinylogous Povarov reaction involving α,β-unsaturated hydrazones as dienophiles 74
5 - Synthesis of 2-acyl and 2- arylquinolines based on the azavinylogous Povarov reaction 85

5.1 – Introduction 87
5.2 – Development of a protocol for the synthesis of 2-acylquinolines *via* oxidative elimination of the C-4 hydrazone substituent 92
5.3 – Extension of the elimination-based method to the synthesis of 2-arylquinolines 98
5.4 – Synthesis of quinolines via migration of the hydrazone group 100

6 – 2 Acylquinoline derivatives as multitarget- directed antitubercular agents 105
6.1 - Tuberculosis: a global plague 107
6.2 - Strategies for the development of new tuberculosis treatments 109
6.3 - Quinoline derivatives in tuberculosis therapy. Screening of 2-acylquinolines against *Mycobacterium tuberculosis* 110
6.4 - A multi-target ligand strategy based on 2-acylquinoline structures 113

7 – Synthesis of 2,6 methanobenzo[*e*][1,4] diazocine derivatives and their investigation as neuroprotective agents 121
7.1 – Introduction 123
7.2 – Synthesis of derivatives of the 2,6-methanobenzo[*e*][1,4] diazocine nucleus 126
7.3 – Derivatives of the 2,6-methanobenzo[*e*][1,4] diazocine nucleus as neuroprotective agents 134

8 – Molecular docking studies on luotonin analogues 145
8.1 – Introduction 147
8.2. – Cancer and the camptothecins 148
8.3. – A,B Ring-modified luotonin A analogues 151
8.4. – D Ring-modified luotonin A analogues 161

9 – Development of a general and scalable flow protocol for peptide synthesis 169
9.1 – Flow chemistry 171
9.2 – Peptide synthesis 174
9.3 – Precedents to our work 176
9.4 – Optimization of mixed anhydride activation under flow conditions 178
9.5 – Scope of the mixed anhydride activation method under flow conditions 182
9.6 – Studies on stereocenter integrity 185

9.7 – Towards the synthesis of segetalin A, a bioactive natural cyclic peptide 186

10 – Experimental section 191

10.1 – General experimental information 193

10.2 – Synthesis of racemic 1,2,3,4-tetrahydroquinolines *via* $InCl_3$-catalysed Povarov reactions 195

    10.2.1 – Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines 195

        10.2.1.1. Synthesis of arylimines **1a**-**g** 195

        10.2.1.2. Synthesis of α,β-unsaturated *N*,*N*-dimethylhydrazones **2a**-**e** 196

        10.2.1.3. Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines **3a**-**h** 199

    10.2.2 – Synthesis of 2-acyl-1,2,3,4-tetrahydroquinolines 201

        10.2.2.1. Synthesis of α-ketoimines **4a**-**q** 201

        10.2.2.2. Synthesis of 2-acyl-1,2,3,4-tetrahydroquinolines **5a**-**u** 210

    10.2.3 – Synthesis of spiro[indolin-3,2’-quinoline] compounds 228

        10.2.3.1. Synthesis of α-ketoimines **4r**-**s** 228

        10.2.3.2. Synthesis of spiro[indolin-3,2’-quinoline] derivatives **5v** and **5w** 230

10.3 – Synthesis of enantiopure 2-acyl-1,2,3,4-tetrahydroquinolines *via* chiral urea-catalyzed Povarov reaction 232

    10.3.1 – Synthesis of chiral urea catalyst **A** 232

    10.3.2 – Synthesis of enantiomerically pure 2-acyl-1,2,3,4-1tetrahydroquinoline compounds **6a**-**o** 236

10.4 – Synthesis of highly functionalized quinolines 246

    10.4.1 – Synthetic procedure to obtain 2-acylquinolines 246

        10.4.1.1. Synthesis of 2-acyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile derivatives **7a**-**c**,**e**-**n** 246

        10.4.1.2 – Synthesis of 2-acylquinoniles **8a**-**j** and **8m**-**o** 255

    10.4.2 – Synthesis of 2-acylquinoline-4-carbonitriles **9a**-**b** 265

    10.4.3 – Synthesis of 2-acyl-4-(dimethylhydrazonomethyl)-quinolines **9c**,**d** 267

10.4.4 – Synthesis of 2-arylquinolines 269
10.4.4.1. Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolin-4-carbonitrile derivatives **10a**-**h** 269
10.4.4.2. Synthesis of 2-arylquinolines **11a**-**h** 275
10.4.5 – Synthesis of quinolines via C4-C3 migration of the hydrazone substituent 281
10.5 – Mechanistic study 286
10.5.1 – Synthesis of intermediate **I** 286
10.5.2 – Synthesis of intermediate **II** 287
10.6 – Synthesis of antitubercular hybrid quinolines **13a**-**i** 288
10.7 – Synthesis of benzo-fused bicyclic systems 295
10.7.1 – Synthesis of aldehydes **14a**-**k** 295
10.7.2 – Synthesis of 1,2,3,6-tetrahydro-2,6-methano-benzo[*e*][1,4] diazocines derivatives **15a**-**k** 304
10.7.3 – Synthesis of 1,2,3,4,5,6-hexahydro-2,6-methano-benzo[*e*][1,4] diazocine products **16a**-**k** 310
10.7.4 – Synthesis of an enantiomerically pure 1,2,3,4,5,6-hexahydro-2,6-methano benzo[*e*][1,4] diazocine 319
10.8 – Peptide synthesis 320
10.8.1 – Flow synthesis of dipeptides at a 0.5 mmol scale 320
10.8.2 – Flow peptide synthesis at a 10 mmol scale 321
10.8.3 – Procedure for the synthesis of linear precursors to segetalin A 334

11 – Conclusions 338

Appendix: Selected spectra 345

Summary

Introduction

Nitrogen heterocycles are one of the most interesting classes of organic molecules and the development of methods for their synthesis has long since stimulated the interest of the scientific community. 1,2,3,4-Tetrahydroquinoline represents one of the most important heterocyclic moieties, being present in many natural compounds and in numerous classes of pharmacologically active agents. One of the most efficient methods for the synthesis of 1,2,3,4-tetrahydroquinolines is the reverse electron-demand [4+2] cycloaddition of *N*-arylimines and electron-rich dienophiles, usually known as the Povarov reaction. This thesis is devoted to the development of a new variation of this reaction, the aza-vinylogous Povarov reaction, including its organocatalytic enantioselective version, and the study of some of its applications.

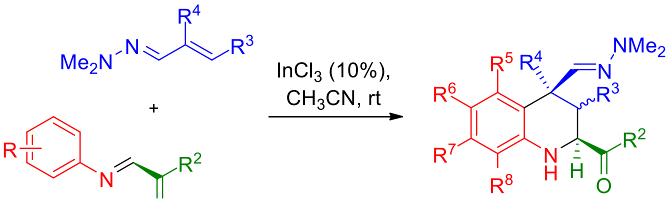
Objectives

The objectives of this thesis can be summarized as follows:

1. Investigation of the Lewis-acid catalyzed aza-vinylogous Povarov reaction between α,β-unsaturated *N*,*N*-dimethylhydrazones and a variety of α-ketoimines as a route to C4-functionalized 2-acyl-1,2,3,4-tetrahydroquinolines.
2. Development of an organocatalytic, asymmetric version of the reaction.
3. Development of new methods for the synthesis of 2-acylquinolines from the products of the aza-vinylogous Povarov reaction.
4. Synthetic access to 2-acylquinolines should allow their study as antitubercular compounds, which is of interest because quinoline is considered a privileged structure in this area. An additional family of compounds, namely 2-acylquinoline-N-acylhydrazones, was also designed based on the multitarget-oriented drug concept.
5. Synthesis of 2,6-methanobenzo[*e*][1,4]-diazocine derivatives, taking advantage of the presence of *cis*-carbonyl and hydrazone functions at the tetrahydroquinoline C-2 and C-4 positions. Owing to the analogy between these structures and that of cytisine, an $\alpha_4\beta_2$ acetylcholine nicotinic receptor partial agonist, we also planned the pharmacological study of our compounds as neuroprotective agents.
6. As a contribution to the work of our group in the development of new luotonin A-inspired topoisomerase I inhibitors as anticancer agents, one of the objectives of this thesis was the computational study of the interaction of three families of analogues with the topoisomerase I-DNA complex.
7. Finally, the objective of a three-month stay at the Department of Chemistry, Cambridge University, in partial fulfillment of the requirements for the European Ph. D. label, was the development of a new method for peptide synthesis under flow conditions.

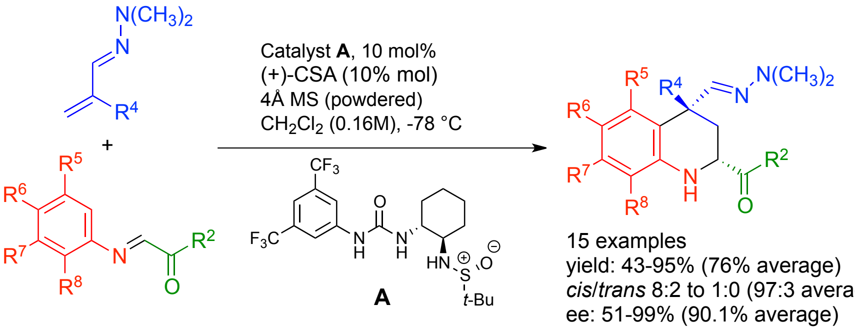
Results and discussion

1. The $InCl_3$-catalyzed aza-vinylogous Povarov reaction between α,β-unsaturated *N*,*N*-dimethylhydrazones and *α*-ketoimines affords 2-acyl-4-(dimethylhydrazonomethyl)-1,2,3,4-tetrahydroquinolines. The reaction highly favours a *cis* relationship between the C-2 and C-4 functional groups and generates a quaternary stereocenter at the C-4 position. The generality of the method was underscored by the preparation of compounds substituted at all carbons of the tetrahydroquinoline system. 2-Spiro tetrahydroquinolines were also accessible by using isatin-derived imines as the diene component.



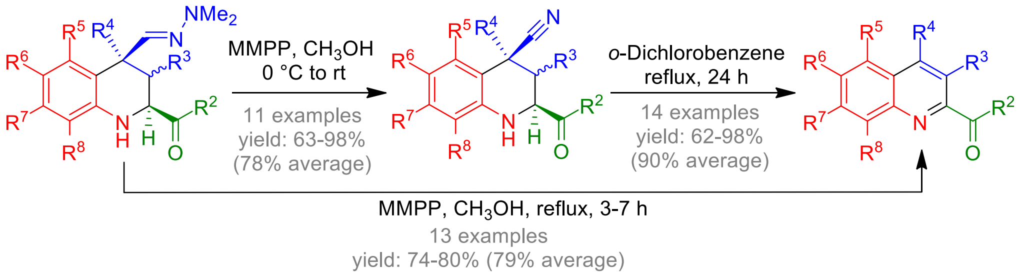
21 examples
yield: 30-95% (70% average)
cis/trans: 55:45 to 100:0 (86:14 average)

2. An asymmetric, organocatalytic version of the aza-vinylogous Povarov reaction was developed by treating *N*,*N*-dimethylhydrazones and *α*-ketoimines in the presence of a combination of Jacobsen's chiral urea catalyst and camphorsulfonic acid at – 78 °C in dichloromethane containing 4 Å molecular sieves. This is a challenging transformation in that the scarce precedent for asymmetric Povarov reactions does not include cases in which both the diene and the dienophile bear basic nitrogen atoms. Furthermore, the use of acyclic dienophiles is unprecedented in the presence of urea or thiourea-derived chiral catalysts. The reaction generates a quaternary stereocenter in high stereocontrol, a very important synthetic goal that has rarely been achieved in Povarov chemistry.

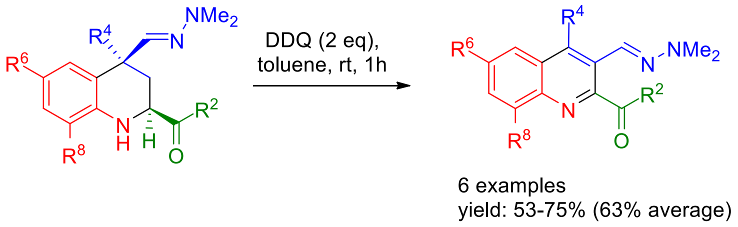


15 examples
yield: 43-95% (76% average)
cis/*trans* 8:2 to 1:0 (97:3 average)
ee: 51-99% (90.1% average)

3. The products of the aza-vinylogous Povarov reactions were identified as suitable precursors to 2-acylquinolines, which is a relevant finding due to the scarcity of literature procedures for their preparation and the great importance of quinoline derivatives. In our first approach, this goal was achieved by oxidation of the dimethylhydrazone group to a nitrile with magnesium monoperoxyphthalate, followed by elimination of hydrogen cyanide and dehydrogenation under thermal conditions. Alternatively, the whole transformation could be carried out in a single operation by treatment of the starting materials with magnesium monoperoxyphthalate in refluxing methanol.

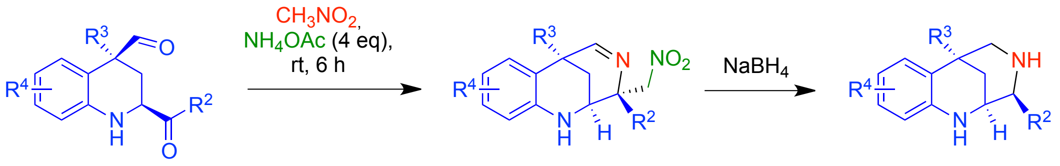


4. In an alternative approach, C3-functionalized 2-acylquinolines were also obtained by treatment of the aza-vinylogous Povarov reaction products with DDQ at room temperature. These condicions induced the migration of the dimethylhydrazonomethyl moiety to the quinoline C-3 position, with concomitant aromatization.

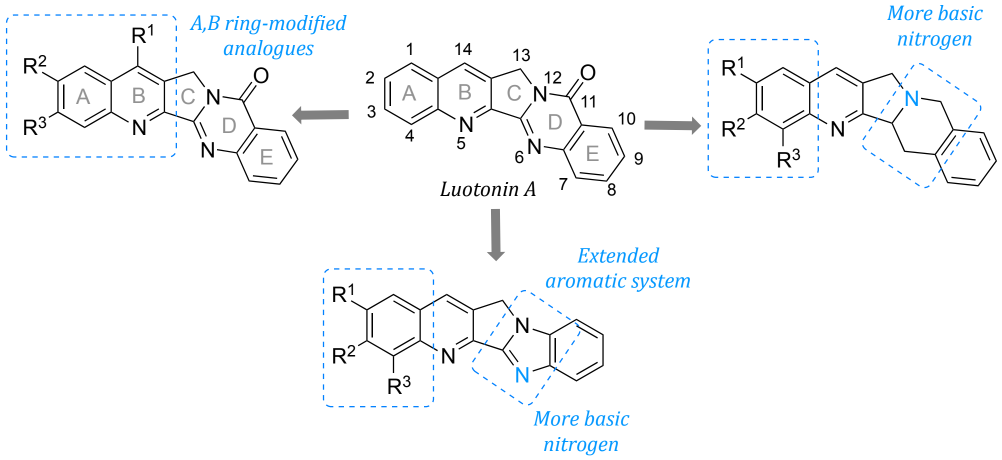


5. 2-Acylquinolines were screened for antitubercular activity, with promising results. N-acylhydrazones of these 2-acylquinolines, designed to liberate the same active species as the antitubercular drug isoniazide upon oxidative metabolism, showed improved antitubercular activities.
6. A three-component reaction between 1,5-dicarbonyl compounds derived from the hydrolysis of the hydrazones obtained in the Povarov reaction, nitromethane and ammonium acetate furnished derivatives of the 2,6-methanobenzo[*e*][1,4]diazocine framework, with the fully diastereoselective generation of a new quaternary stereocenter. The sodium borohydride reduction of these compounds *via* a

reduction/retro aza-Mannich/reduction sequence was again diastereoselective, and involved loss of the nitromethyl group. These compounds were assayed as neuroprotective agents, with promising results.



7. The interactions of three families of luotonin analogues with the topoisomerase I-DNA complex were investigated computationally. This study was used to assist the rationalization of the topoisomerase inhibition and cytotoxic activity of these molecules and to aid new compound design.



8. A new method for peptide synthesis under flow conditions, based on carboxyl activation by mixed anhydride generation, was developed. In order to underscore the flexibility of the method, its application to the synthesis of the bioactive natural cyclic hexapeptide segetalin A was also investigated.

Conclusions

The aza-vinylogous Povarov reaction provides an excellent method for the synthesis of highly functionalized tetrahydroquinolines bearing a quaternary carbon, and can be performed in an enantioselective fashion in the presence of the combination of chiral urea catalyst with a Brønsted acid. These tetrahydroquinolines are interesting starting materials and can be transformed into a number of bioactive frameworks, in particular 2-acylquinolines and 2,6-methano-benzo[*e*][1,4]diazocines.

Resumen

Introducción

Los heterociclos nitrogenados son una de las clases más interesantes de compuestos orgánicos, por lo que el desarrollo de métodos para su síntesis ha estimulado desde hace mucho tiempo el interés de la comunidad científica. La 1,2,3,4-tetrahidroquinolina es una de las estructuras heterocíclicas más importantes y está presente en un gran número de productos naturales y compuestos con actividad farmacológica. Uno de los métodos más eficaces para la síntesis de 1,2,3,4-tetrahidroquinolinas es la cicloadición [4+2] de demanda electrónica inversa entre *N*-ariliminas y dienófilos de elevada densidad, conocida habitualmente como la reacción de Povarov. La finalidad de esta tesis es el desarrollo de una nueva variante de este proceso, la reacción de Povarov aza-viníloga, así como una version organocatalítica enantioselectiva de la misma y el estudio de algunas de sus aplicaciones.

Objetivos

Los objetivos de esta tesis pueden resumirse como sigue:

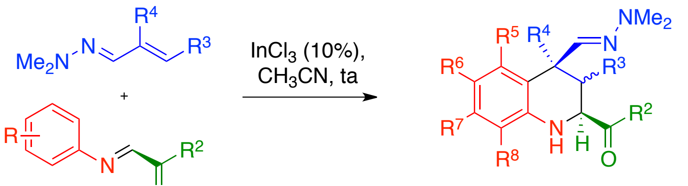
1. Investigación de la reacción de Povarov aza-viníloga entre *N*,*N*-dimetilhidrazonas α,β-insaturadas y α-cetoiminas para la síntesis de 2-acil-1,2,3,4-tetrahidroquinolinas funcionalizadas en C-4.
2. Desarrollo de una versión organocatalítica enantioselectiva de la reacción.
3. Desarrollo de nuevos métodos de síntesis de 2-acilquinolinas a partir de los productos de la reacción de Povarov aza-viníloga.
4. El acceso sintético a derivados de 2-acilquinolina debe permitir su estudio como agentes antituberculosis, que es de interés debido a que la quinolina se considera una estructura privilegiada en este campo. Se diseñó también una familia de 2-acilquinolina-N-acilhidrazonas, utilizando el concepto de fármacos multidiana.
5. Síntesis de derivados del esqueleto de 2,6-metanobenzo[*e*][1,4]-diazocina, aprovechando la presencia de grupos carbonilo e hidrazona en las posiciones C-2 y C-4 del sistema de tetrahidroquinolina, con disposición *cis*. Debido a la analogía de estas estructuras con la citisina, un alcaloide que actúa como agonista parcial de receptores nicotínicos $\alpha_4\beta_2$, también se planificó el estudio de estos compuestos como agentes neuroprotectores.
6. Como contribución al trabajo de nuestro grupo en el desarrollo de nuevos inhibidores de topoisomerasa I como agentes antitumorales, se planificó el estudio computacional de la

interacción de tres familias de análogos del alcaloide luotonina A con el complejo topoisomerasa I-ADN.

7. Finalmente, el objetivo de una estancia de tres meses en el Departamento de Química de la Universidad de Cambridge University, realizada como parte de los requisitos para la Mención Europea en el título de doctor, fue el desarrollo de un nuevo método de síntesis de péptidos en condiciones de flujo.

Resultados y discusión

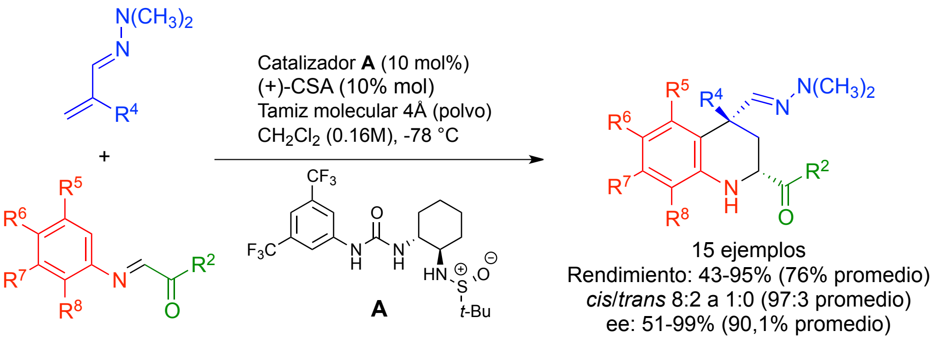
1. La reacción de Povarov aza-vinílogа entre *N*,*N*-dimetilhidrazonas α,β-insaturadas y α-cetoiminas catalizada por $InCl_3$ proporciona 2-acil-4-(dimetilhidrazonometil)-1,2,3,4-tetrahidroquinolinas. En esta reacción está altamente favorecida una relación *cis* entre los grupos funcionales en C-2 y C-4 y se genera un estereocentro cuaternario en C-4. Se demostró la generalidad del método mediante la preparación de derivados sustituidos en todos los carbonos del anillo de tetrahidroquinolina. Se accedió también a esqueletos de 2-espiro tetrahidroquinolina utilizando iminas derivadas de isatina como el componente diénico.



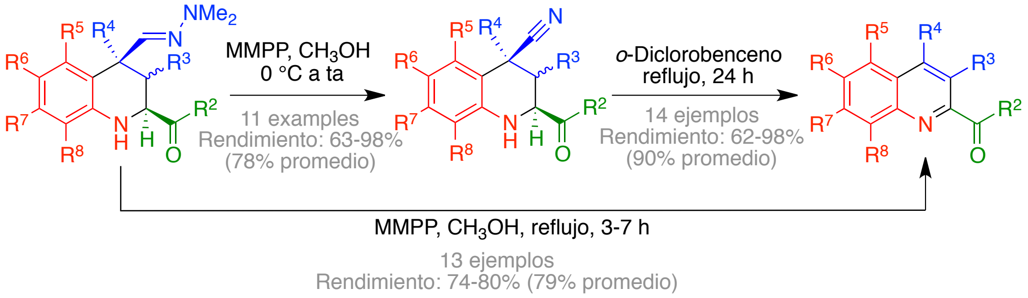
21 ejemplos
Rendimiento: 30-95% (70% promedio)
cis/trans: 55:45 a100:0 (86:14 promedio)

2. Se ha desarrollado una versión asimétrica, organocatalítica de la reacción de Povarov aza-vinílogа, por tratamiento de *N*,*N*-dimetilhidrazonas y *α*-cetoiminas en presencia de una combinación de la urea quiral de Jacobsen y ácido canfosulfónico a – 78 °C en diclorometano, en presencia de tamiz molecular de 4 Å. Esta transformación supone un desafío considerable porque los escasos precedentes de reacciones de Povarov asimétricas no incluyen ejemplos en los que tanto el dieno como el dienófilo contengan átomos básicos de nitrógeno. Además, nunca se ha descrito el empleo de dienófilos acíclicos en presencia de ureas o tioureas quirales. Esta reacción genera de forma

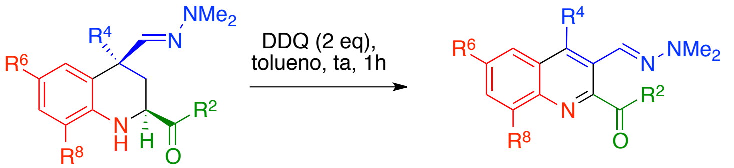
altamente controlada un estereocentro cuaternario, lo que constituye un objetivo sintético muy importante que raras veces se ha logrado mediante química de Povarov.



3. Los productos de las reacciones de Povarov aza-vinílogas fueron identificados como precursores adecuados para la síntesis de 2-acilquinolinas, un descubrimiento interesante debido a la escasez de precedentes bibliográficos de la preparación de estos compuestos y a la gran importancia de los derivados de quinolina. Este objetivo se logró mediante la oxidación del grupo de dimetilhidrazona a nitrilo con monoperoxiftalato de magnesio, seguida de eliminación de cianuro de hidrógeno y deshidrogenación en condiciones térmicas. Alternativamente, fue posible llevar a cabo la transformación en una sola operación por tratamiento de los compuestos de partida con monoperoxiftalato de magnesio en methanol a reflujo.



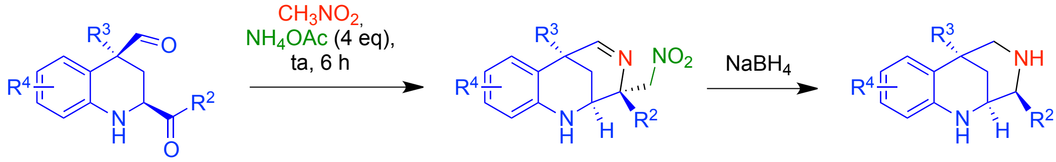
4. En una aproximación alternativa, se obtuvieron 2-acilquinolinas funcionalizadas en C-3 por tratamiento de los productos de las reacciones de Povarov aza-vinílogas con DDQ a temperatura ambiente. Estas condiciones indujeron la migración del grupo dimetilhidrazonometilo a la posición C-3 del sistema de quinolina, acompañada de aromatización.



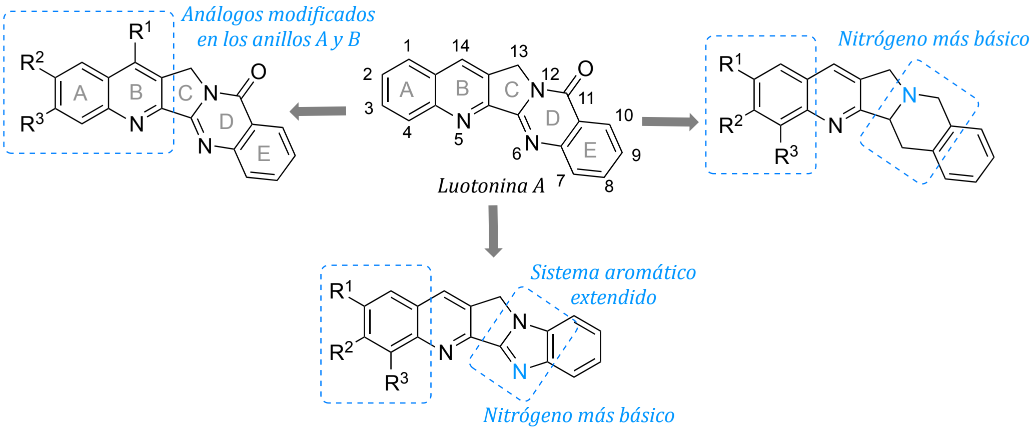
6 ejemplos
Rendimiento: 53-75% (63% promedio)

5. Los derivados de 2-acilquinolina se estudiaron como agentes antituberculosis, con resultados prometedores. Algunas N-acilhidrazonas de estos compuestos, diseñadas para liberar la misma especie activa que el fármaco antituberculoso isoniazida en su metabolismo oxidativo, mostraron una actividad mejorada.

6. Una reacción de tres componentes entre compuestos 1,5-dicarbonílicos, procedentes de la hidrólisis de la function hidrazona de los productos de la reacción de Povarov, nitrometano y acetate amónico proporcionó derivados del esqueleto de 2,6-metanobenzo[*e*][1,4]diazocina, generándose de forma completamente diastereoselectiva un nuevo estereocentro cuaternario. La reducción de estos compuestos con borohidruro sódico condujo a un proceso dominó diastereoselectivo de reducción/reacción retro aza-Mannich/reducción, en el que se perdió el grupo nitrometilo. Estos compuestos se ensayaron como agentes neuroprotectores, con resultados muy prometedores.



7. Se investigó computacionalmente la interacción de tres familias de análogos de luotonina con el complejo topoisomerasa I-ADN. Este estudio sirvió para racionalizar los resultados de inhibición enzimática y la acción citotóxica de estos compuestos, así como para el diseño de nuevos derivados.



8. Se desarrolló un nuevo método de síntesis de péptidos en condiciones de flujo, basado en la activación del grupo carboxilo de los aminoácidos por generación de un anhídrido mixto. Para poner de manifiesto la flexibilidad de este método, se estudió su aplicación a la síntesis del hexapéptido cíclico natural bioactivo segetalina A.

Conclusiones

La reacción de Povarov aza-viníloga constituye un método excelente para la sintesis de 2-acil-1,2,3,4-tetrahidroquinolinas altamente funcionalizadas, portadoras de un carbono cuaternario. Esta reacción se llevó a cabo también en forma enantioselectiva, utilizando un proceso de co-catálisis basado en el empleo de un catalizador quiral de urea combinado con un ácido de Brønsted. Estas tetrahidroquinolinas fueron excelentes materiales de partida para transformaciones sintéticas adicionales que condujeron a varios esqueletos bioactivos, incluyendo derivados de 2-acilquinolina y 2,6-metanobenzo[*e*][1,4]diazocina.

1 - Introduction

1.1 – The importance of the 1,2,3,4-tetrahydroquinoline scaffold

Heterocyclic compounds, and nitrogen heterocycles in particular, are one of the most interesting classes of organic molecules and the development of methods for their synthesis has long since stimulated the chemical community. In this context, 1,2,3,4-tetrahydroquinoline represents one of the most important heterocyclic moieties, being present in several natural compounds[1] and in numerous biologically active agents endowed with a wide range of properties such as antiviral, antibacterial, antifungal, antimalarial, antitumor and ion-channel blocking activities. In Figure 1.1, a few examples of natural tetrahydroquinolines are reported, such as the two alkaloids isolated from *Streptomyces sp*. called benzastatins C and D[2] (**Ia** and **Ib**, Figure 1) and pyrroloquinoline alkaloids, like martinellic acid **IIa** and martinelline **IIb**[3], isolated from the roots of the tropical plant *Martinella iquitosensis,* whose synthesis have represented a stimulating goal for several groups. Regarding pharmacologically active molecules, we show in Figure 1.2 the structures of the antifungal tetrahydroquinoline **IIIa**[4], the tubulin polymerization inhibitor **IV**[5] and the derivatives **Va**[6] and **Vb**[7], active on ion channels.

The relevance of tetrahydroquinoline scaffold is not limited to natural products and medicinal chemistry, considerable is also their application as coordination ligands in

---

[1] Michael J.P. *Nat. Prod. Rep.*, **2008**, *25*, 166.

[2] (a) Kim W.G., Kim J.P., Kim C.J., Lee K.H., Yoo I.D. *J. Antibiot.*, **1996**, *49*, 20. (b) Kim W.G., Kim J.P., Yoo I.D. *J. Antibiot.*, **1996**, *49*, 26.

[3] Witherup K.M., Ransom R.W., Graham A.C., Bernard A.M., Salvatore M. J., Lumma W.C., Anderson P.S., Pitzenberger S.M., Varga S.L. *J. Am. Chem. Soc.*, **1995**, *117*, 6682.

[4] Suvire F.D., Sortino M., Kouznetzov V.V., Vargas L.Y., Zacchino S.A., Cruz U.M., Enriz R.D. *Bioorg. Med. Chem.*, **2006**, *14*, 1851.

[5] Liou J.P., Wu Z.Y., Kuo C.C., Chang C.Y., Lu P.Y., Chen C.M., Hsieh H.P., Chang J.Y. *J. Med. Chem.*, **2008**, *51*, 4351.

[6] Maillard M.C., Perlman M.E., Amitay O., Baxter D., Berlove D., Connaughton S., Fischer J.B., Guo J.Q., Hu L.Y., McBurney R.N., Nagy P.I., Subbarao K., Yost E.A., Zhang L., Durant G.J. *J. Med. Chem.*, **1998**, *41*, 3048.

[7] Gore V.K., Ma V.V., Yin R., Ligutti J., Immke D., Doherty E.M., Norman M.H. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3573.

asymmetric synthesis[8] and as dyes[9], providing the basis for some industrial applications such as the construction of dye-sensitive solar cells.

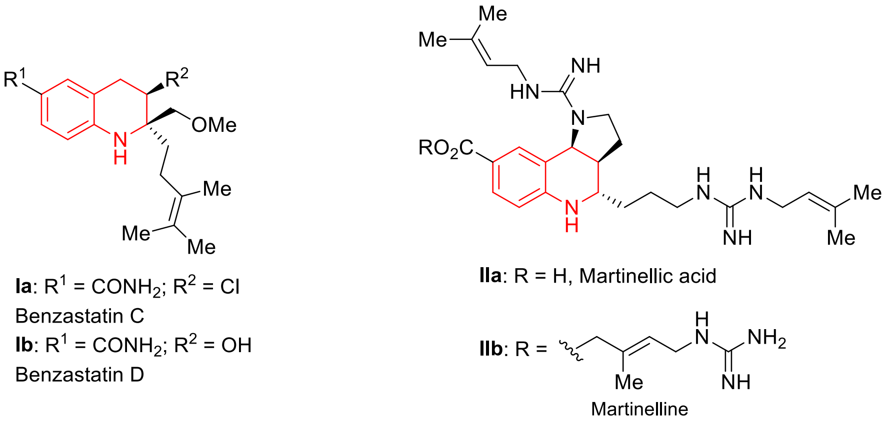


Figure 1.1 - Representative 1,2,3,4-tetrahydroquinoline-based alkaloids

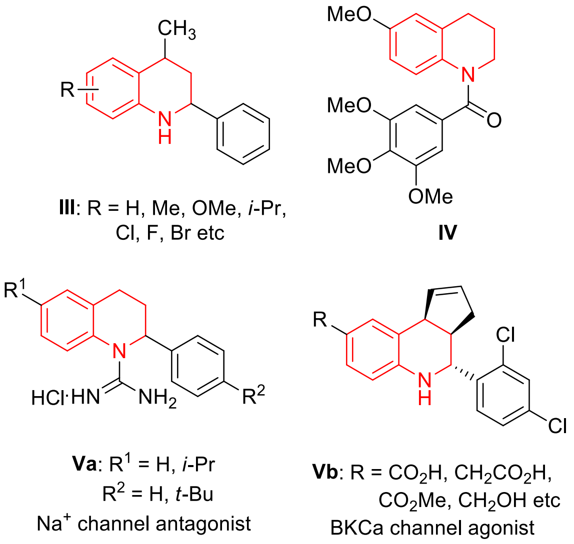


Figure 1.2 - Representative pharmacologically active tetrahydroquinolines

Because of the value of 1,2,3,4-tetrahydroquinoline family, the development of efficient and versatile synthetic methodologies giving access to these nitrogen heterocycles with high chemical diversity is still a big challenge that continues to be investigated. A large number of

---

[8] (a) Pullmann T., Engendahl B., Zhang Z., Holscher M., Zanotti-Gerosa A., Dyke A., Francio G., Leitner W. *Chem. Eur. J.*, **2010**, *16*, 7517. (b) Liu H., Wang M., Wang Y., Wang Y., Sun H., Sun L. *Catal. Commun.*, **2009**, *11*, 294.

[9] Chen R., Yang X., Tian H., Sun L. *J. Photochem. Photobiol. A*, **2007**, *189*, 295.

methods are available,[10] but we will concentrate on one specific procedure, the Povarov reaction, that is closely related to the work developed in this Thesis.

---

[10] For reviews of the synthesis of tetrahydroquinolines, see: (a) Katritzky A.R., Rachwal S., Rachwal B. *Tetrahedron,* **1996**, *52*, 15031. (b) Kouznetsov V., Palma A., Ewert C., Varlamov A. *J. Heterocycl. Chem*., **1998**, *35*, 761. (c) Sridharan V., Suryavanshi P., Menéndez J.C. *Chem. Rev*., **2011**, *111*, 7157. (d) Nammalwar B., Bunce R.A. *Molecules*, **2014**, *19*, 204.

1.2 – The Povarov reaction, a powerful method for the synthesis of tetrahydroquinolines

1.2.1. Introduction

Hetero Diels-Alder (HDA) reactions constitute one of the most effective methods for the construction of six-membered heterocycles. They can be classified into oxa-Diels-Alder reactions (from carbonyl compounds) and aza-Diels-Alder reaction (from imines). This last variant includes an effective method to synthetize 1,2,3,4-tetrahydroquinolines, namely the reverse electron-demand acid-catalysed [4+2] cycloaddition of *N*-arylimines and electron rich dienophiles, developed by the Russian chemist L. S. Povarov in the 1960s[11] and now usually known as the Povarov reaction[12] (Figure 1.3).

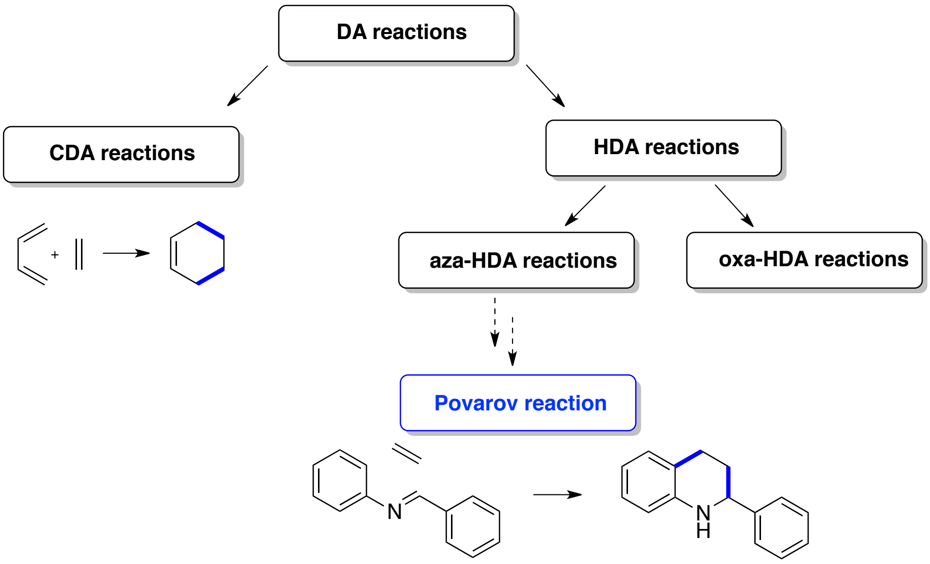


Figure 1.3 – Classification of Diels-Alder reactions.

The Povarov reaction, after its discovery, remained almost unexplored until the 1990s, with only a few exceptions that proceeded in very low or moderate yields.[13] In 1993, the first

---

[11] Povarov L.S. *Russ. Chem. Rev.*, **1967**, *36*, 656.

[12] For reviews, see (a) Povarov L.S. *Russ. Chem. Rev.*, **1967**, *36*, 656. (b) Kouznetsov V.V. *Tetrahedron*, **2009**, *65*, 2721. (c) Bello C., Ramón D., Lavilla R. *Curr. Org. Chem.* **2010**, *14*, 332. (d) Bello Forero J.S., Jones Jr J., da Silva F.M. *Curr. Org. Chem.*, **2016**, *13*, 157..

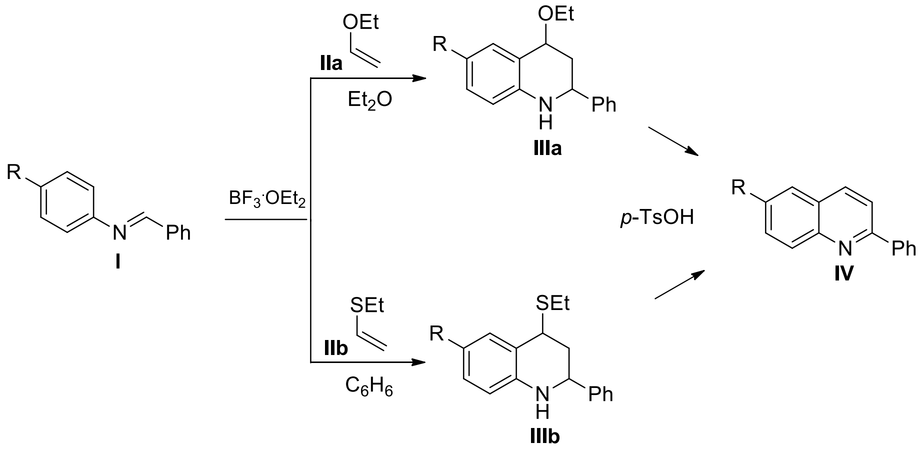
[13] Joh T., Hagihara H. *Tetrahedron Lett.*, **1967**, 4199.

multi-component Povarov reaction was published,[14] and two years later Lewis acids were identified as suitable catalysts for this transformation.[15] These two articles re-awakened the interest of the synthetic community on the Povarov reaction, which remains a very active research field with more than one hundred articles published on the topic in the 2015-2016 period.

We will next briefly discuss the Povarov reactions classifying them into three categories according to the acyclic, cyclic or vinylogous nature of the dienophile.

1.2.2 – Acyclic dienophiles

The first dienophiles employed in the Povarov reaction were acyclic vinyl compounds, which allow obtaining C-2 and C-4-disubstitued tetrahydroquinolines. Thus, the initial work from Povarov's laboratory[16] involves the reaction of *N*-arylimine **I** with ethyl vinyl ether **IIa** or ethyl vinyl sulphide **IIb**, catalysed by $BF_3{\cdot}Et_2O$ as a Lewis acid, affording 2,4 disubstitued tetrahydroquinolines **IIIa** and **IIIb** that were converted into quinolines **IV** under vacuum distillation in acidic conditions (Scheme 1.1).



Scheme 1.1.

As mentioned above, Kobayashi and co-workers published in 1995 a three-component imino Diels-Alder condensation catalysed by lanthanide triflates, disclosing them as new

---

[14] Narasaka K., Shibata T. *Heterocycles,* **1993**, *35*, 1039.

[15] Kobayashi S., Ishitani H., Nagayama S. *Synthesis*, **1995**, 1195.

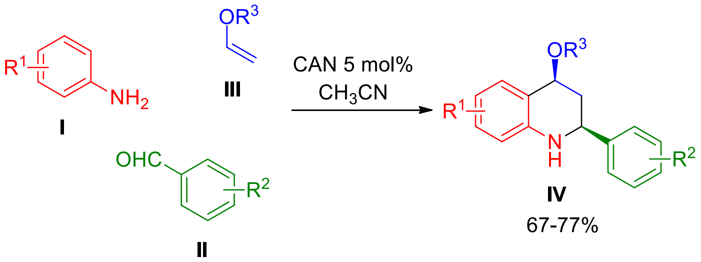
[16] (a) Povarov, L. S.; Mikhailov, B. M. Izv. *Akad. Nauk SSR, Ser. Khim.* **1963**, 953. (b) Povarov, L. S.; Grigos, V. I.; Mikhailov, B. M. Izv. *Akad. Nauk SSR, Ser. Khim.* **1963**, 2039.

Povarov catalysts, albeit with poor diastereoselectivities in many cases (Scheme 1.2).[15] Nowadays it is recognized that the Povarov reaction can be catalysed by a wide range of Lewis acids ($Yb(OTf)_3$, $Sc(OTf)_3$, $CuBr_2$, $ZnCl_2$, $InCl_3$, etc), Brønsted acids (TfOH, HCl, TsOH, etc) and metal salts.

	R^1	**III**: X = O; R = Et	**IV**: X = S; R = Ph
a	H	96%	75% (57:43)
b	OCH_3	77% (67:33 - *cis*:*trans*)	0
c	Cl	95%	quant

Scheme 1.2.

In this context, our group discovered that ceric ammonium nitrate (CAN), acting in this case as a Lewis acid rather than as an oxidant,[17] catalyses the three-component Povarov reaction between anilines **I**, aromatic aldehyde **II** and vinyl ethers **III** in acetonitrile, affording 2,4 disubstituted tetrahydroquinolines **IV** in good yields (67-77%) with excellent diastereoselectivities (dr = 92:8 to 97:3 – *cis*:*trans*), as shown in Scheme 1.3.[18]



R^1 = H, Me, OMe, Cl, F
R^2 = H, Me, Cl
R^3 = Et, Bu

Scheme 1.3.

---

[17] For a review of the use of CAN as a catalyst in organic synthesis: Sridharan V., Menéndez J.C. *Chem. Rev.*, **2010**, *110*, 3805.

[18] Sridharan V., Avendaño C., Menéndez J.C. *Synthesis,* **2008**, *7*, 1039.

1.2.3 – Cyclic dienophiles

Cyclic dienophiles are the most popular dienophiles employed in this reaction and have been thoroughly investigated for the synthesis of polycyclic, fused tetrahydroquinolines. A few examples are shown in Figure 1.4.

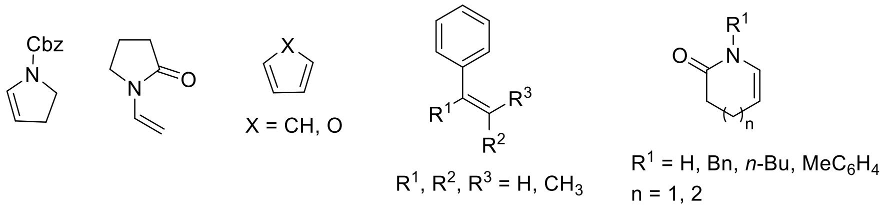


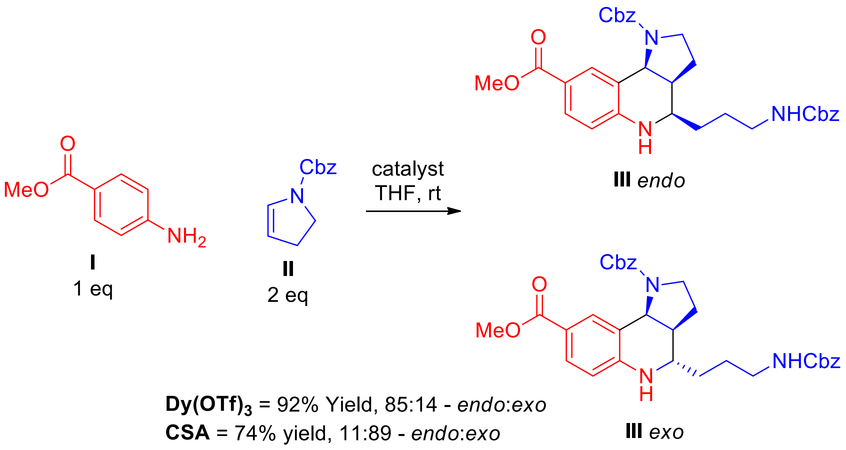
Figure 1.4 – Some examples of cyclic dienophiles.

The Povarov reaction involving this type of dienophile affords polysubstituted fused tetrahydroquinolines with the generation of three stereocenters in the positions C-2, C-3 and C-4. Generally, the *endo*/*exo* (*cis*:*trans*) selectivity is low, although with a preference for the *endo* (*cis*) product.

Inspired by the intriguing structures of martenillinic acid **IIa** and martinelline **IIb** (Fig. 1.1), Batey *et al.* took advantage of the ability of some nitrogen-containing heterocyclic alkenes to act as Povarov dienophiles to develop an efficient procedure to obtain the tricyclic core **III** of these alkaloids (Scheme 1.4).[19] They employed an ABB'-type multicomponent reaction, where the pirroline derivative **II** has a dual role, acting as an electron rich dienophile and an equivalent to the aldehyde fragment in the imine. Curiously, they found that a lanthanide catalyst affords the *endo* product preferentially, while camphorsulfonic acid (CSA), acting as a Brønsted acid, gives the *exo* isomer as the main product, with a good correlation between the diastereoselectivity and the pKa of the acid employed.

---

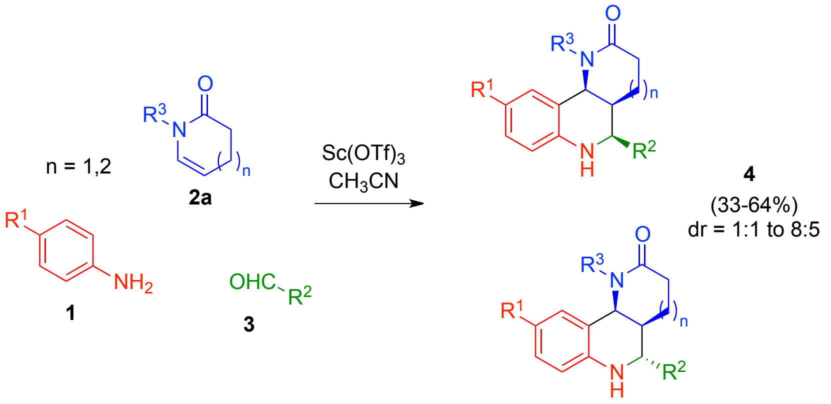
[19] Powell D.A., Batey R.A. *Org. Lett.*, **2002**, *4*, 2913.



Dy(OTf)$_3$ = 92% Yield, 85:14 - *endo*:*exo*
CSA = 74% yield, 11:89 - *endo*:*exo*

Scheme 1.4.

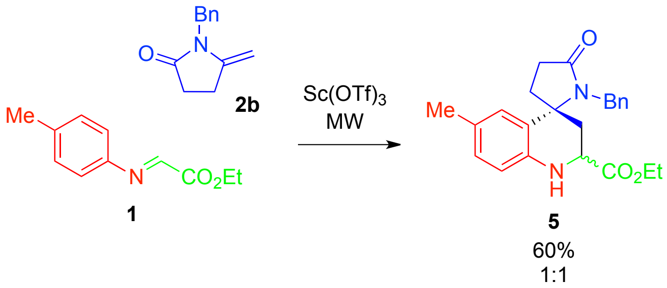
Lavilla and co-workers[20] demonstrated the possibility to employ unsaturated lactams with endo- and exocyclic double bonds as dienophiles. In the case of six- and seven-membered lactams with an endocyclic bond **IIa**, the Sc(OTf)$_3$-catalysed reaction with a wide variety of imines **I** affords the tricyclic products **IV** with moderate yields and diastereoselectivities (Scheme 1.5 - A). In the reaction involving the pyrrolidone **IIb** as dienophile, the spiro tetrahydroquinoline **V** was obtained, as a 1:1 diastereomeric mixture (Scheme 1.5 - B).



Scheme 1.5 – A

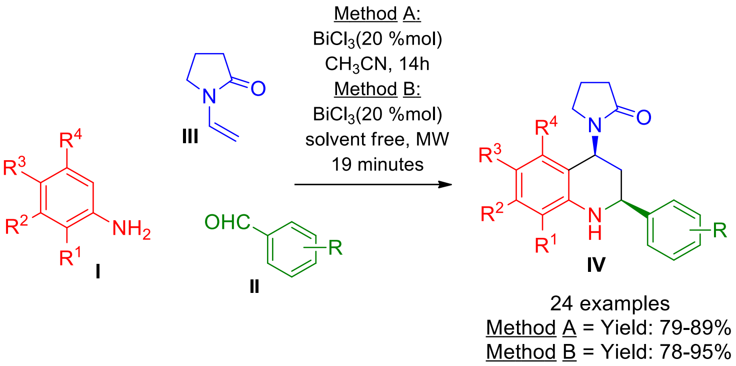
---

[20] Vicente-Garcia E., Catti F., Ramón R., Lavilla R. *Org. Lett.*, **2010**, *4*, 860.



Scheme 1.5 – B

Finally, we will mention a reaction reported by Kouznetsov starting from anilines **I**, aromatic aldehydes **II** and *N*-vinylpyrrolidone **III**, a liquid dienophile that allows a solvent-free procedure. The reaction afforded 2-aryl-4-(2-oxopyrrolidyn-1-yl)-1,2,3,4-tetrahydroquinolines **4** in good yields (78-95%) with high diastereoselection and a broad scope in the aniline (Scheme 1.6).[21]



Scheme 1.6.

1.2.4 – Vinylogous dienophiles

Recently a new type of Povarov reaction has emerged: the vinylogous version. The Povarov reaction is defined as vinylogous when an extended unsaturated function is present in the dienophile (Type I reactions) or in the imine (Type II reactions),[22] that allow to obtain tetrahydroquinolines with an alkene substituent at the C-4 or C-2 position, respectively (Fig. 1.5).

---

[21] Astudillo L.S., Gutiérrez M., Gaetea H., Kouznetsov V.V., Meléndez C.M., Palenzuela J.A., Vallejos G. *Lett. Org. Chem.*, **2009**, *6*, 208.

[22] This classification was proposed in: Sridharan V., Avendaño C., Menéndez J.C., *Synlett* **2007**, 1079.

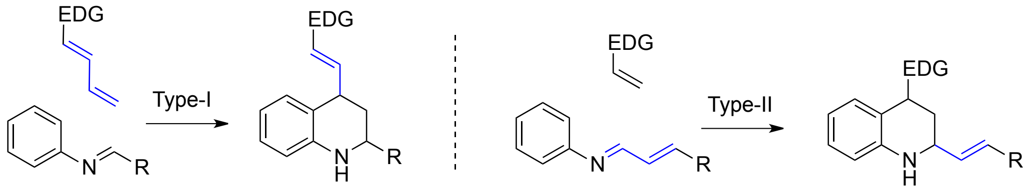
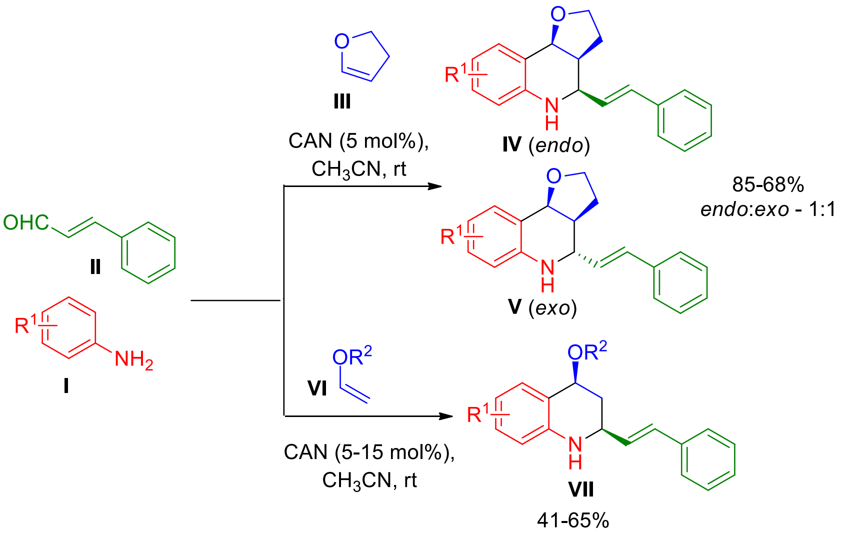


Figure 1.5 – Type I and type II vinylogous Povarov reaction.

The type II Povarov reaction has been employed for the synthesis of stirylquinolines, an interesting scaffold studied as inhibitor of HIV integrase. To this end, our group studied the reaction between anilines **I**, cinnamaldehydes **II**, 2,3-dihydrofuran **III** and catalytic amount of CAN (5%) that afford 2,3,3a,4,5,9b-hexahydro-4-styrylfuro[3,2c]quinolines **IV** *exo* and *endo* in equimolar proportion (Scheme 1.7). The vinylogous Povarov reaction between compounds **1** and **2** with the acyclic vinyl ether **5**, extensively employed in the Povarov reaction, has been studied as well employing CAN as catalyst. The reaction affords the 2-styryl-1,2,3,4-tetrahydroquinoline **6** with total diastereoselectivity with the *cis* isomer as the only product (Scheme 4).[23]



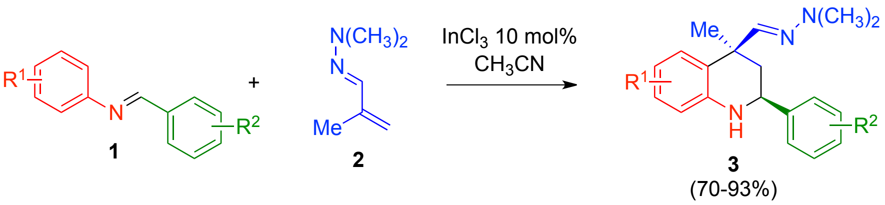
Scheme 1.7.

---

[23] Sridharan V., Avendano C., Menéndez J.C. *Tetrahedron*, **2009**, *65*, 2087.

The reaction also shows a total regioselectivity, since the ethyl vinyl ether attacks the imine carbon, activated by nitrogen coordination of the Lewis acid, without involving the γcarbon.

An example of a vinylogous dienophile involved in a type I Povarov reaction was developed by our group,[24] using as the dienophile an α,β-unsaturated *N*,*N*-dimethylhydrazone **2**. Thus, the reaction between methacrolein dimethylhydrazone **2** and *N*-arylimines **1** in the presence of 10% of $InCl_3$ as catalyst affords tetrahydroquinolines in good to excellent yields (70-93 %) with the formation of two C-C bonds and the fully diastereoselective generation of two stereocenters, one of which (C-4) is quaternary (Scheme 1.8). This was the first example of the use of an α,β-unsaturated hydrazine as the dienophile, rather than the diene, of a cycloaddition-type process. The reaction is totally diastereoselective, with the *cis* tetrahydroquinoline as the only product, as shown by NOE studies and later confirmed by single crystal X-Ray diffraction.



Scheme 1.8.

More recently, a few examples of enantioselective Povarov reactions involving a vinylogous dienophile have been investigated, as will be discussed below.[25]

It is relevant to note that Povarov reactions are usually limited to *N*-arylimines, derived from aromatic aldehydes. Aromatic α-ketoimines are almost unexplored and furthermore the introduction of a carbonyl function could represent a strategic synthetic function for the synthesis of more complex chemical structure. To our knowledge just a few examples of Povarov reaction involving α-ketoimines have been reported in the literature, in the most cases ethyl glyoxal, few examples of aromatic glyoxal derivatives and more rarely vinyl indole.[20,26]

---

[24] Sridharan V., Perumal P.T., Avendano C., Menéndez J.C. *Org. Biomol. Chem.*, **2007**, *5*, 1351.

[25] (a) Bergonzini G., Gramigna L., Mazzanti A., Fochi M., Bernardi L., Ricci A. *Chem. Commun.*, **2010**, *46*, 327. (b) Caruana L., Fochi M., Ranieri S., Mazzanti A., Bernardi L. *Chem. Commun.*, **2013**, *49*, 880.

[26] Bunescu A., Wang Q., Zhu J. *Org. Lett.* **2014**, *16*, 1756.

1.3 – Enantioselective Povarov reactions

The interest of the tetrahydroquinoline scaffold as the key component of bioactive compounds and natural products makes a synthetic protocol to obtain enantiomerically pure compounds an exciting goal for the synthetic community. Nevertheless, even though the Povarov reaction was discovered about fifty years ago, the development of its asymmetric versions has been quite recent and no really general methods are yet available.[27]

A brief summary about the history of the asymmetric Povarov reaction is summarized below, where is possible to identify three main stages: the first one consists of its discovery through the chiral Lewis acids catalytic strategy, the second one is its intensive study with the popular and effective chiral Brønsted acids catalysis and the third period is recent and it is based on the freshly discovered chiral urea and achiral Brønsted acid co-catalysis strategy, developed by Jacobsen's group.

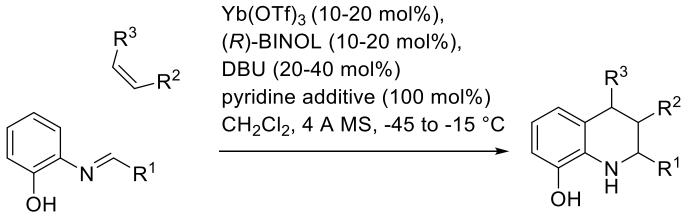
1.3.1 – Chiral Lewis acid catalysis

In the 90s, catalysis with chiral Lewis acid was very popular. Ishitani and Kobayashi took advantage from this new powerful synthetic tool to publish the first catalytic asymmetric Povarov reaction in 1996,[28] where a chiral complex formed by ytterbium triflate, (*R*)-BINOL and 1,8-diazabicyclo[5.4.0]undec-7-ene **A** (Figure 1.6) catalysed the reaction between *o*-hydroximines and different substituted dienophiles with modest yield (58-74%), good diastereoselectivity (94:6 to 99:1 – *cis*:*trans*) and modest to good enantioselectivity (68-91% ee) (Scheme 1.9).

---

[27] For reviews of asymmetric Povarov reaction see: (a) Masson G., Lalli C., Benohoud M., Dagousset G. *Chem., Soc. Rev.*, **2013**, *42*, 902. (b) Jiang X., Wang R. *Chem. Rev.*, **2013**, *113*, 5515. (c) Fochi M., Caruana L., Bernardi L. *Synthesis*, **2014**, *46*, 135.

[28] Kobayashi S., Ishitani H., Hachiya I., Araki M. *Tetrahedron*, **1994**, *50*, 11623.



R¹: Naphthalene ; **R²**:H; **R³**: OEt
Yield: 74%
dr: 99:1
ee: 91%

R¹: Naphthalene; **R²**,**R³**: -CH_2CH_2O-
Yield: 67%
dr: 93:7
ee: 86%

R¹: Ph; **R²**:H; **R³**: OEt
Yield: 58%
dr: 94:6
ee: 77%

R¹: C_6H_{11}; **R²**,**R³**: -CH_2CHCH-
Yield: 58%
dr: 99:1
ee: 73%

Scheme 1.9.

This catalytic system suffers some drawbacks; the main one is the fact that the reaction only works on *o*-aminophenol-derived imines, which are able to give a bidentate coordination with the catalyst complex, necessary for the enantio-induction. Furthermore, the addition of 2,6-disubstituted pyridines is required to allow an additional interaction with the substrate in such way that a complex supramolecular system is formed, which is able to shield one side of the imine substrate, as shown in Figure 1.6.

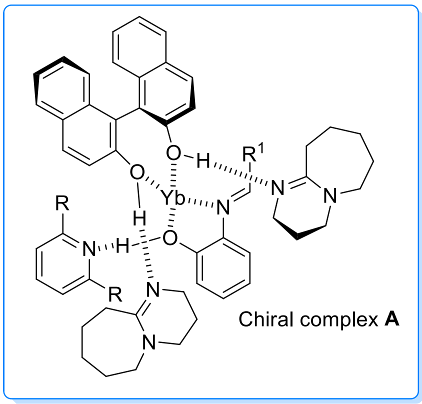
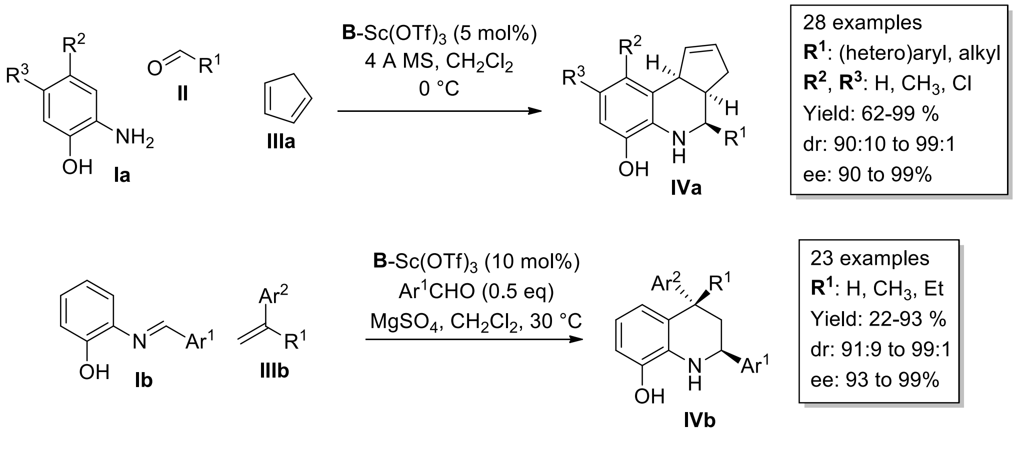


Figure 1.6.

Another interesting example of an asymmetric Povarov reaction catalysed by a chiral Lewis acid complex was reported in 2010 by Feng and coworkers.[29] They studied the preparation of compounds **IVa** in good yields and with good diastereo- and enantioselectivities *via* an inverse electron-demand aza-Diels-Alder reaction between *o*-hydroxyanilines **Ia**, aldehydes **II** and cyclopentadiene **III** as dienophile. The use of compound **III** makes this reaction one of the few examples where a carbon-only dienophile has been employed in an asymmetric Povarov reaction, probably because it is more difficult finding an effective chiral catalyst, in contrast to the heteroatom-containing dienophiles. Two years later, the same group published an extension of the method, where they employed *o*-aminophenol-derived imines **Ib**, α-alkylstyrenes **IIIb** and the chiral *N*,*N'*-dioxide - Sc(OTf)$_3$ complex **B** as catalyst (Figure 1.7). The reaction afforded tetrahydroquinolines **IVb** with modest to good yields, good enantio- and diasteroselectivities and with a broad scope, although with the limitations imposed by the obligatory presence of the C$_8$-OH substituent (Scheme 1.10).



Scheme 1.10.

---

[29] Xie M., Chen X., Zhu Y., Gao B., Lin L., Liu X., Feng X. *Angew. Chem. Int. Ed.*, **2010**, *49*, 3799. (b) Xie M., Chen X., Zhu Y., Zhao X., Xia Y., Lin L., Feng X. *Chem. Eur. J.*, **2011**, *17*, 13800. For a review, see: (c) Liu X., Lin L., Feng X. *Acc. Chem. Res.*, **2011**, *44*, 574.

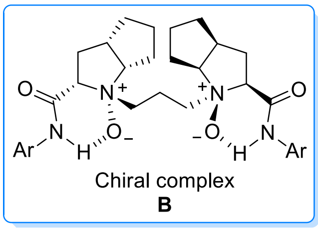
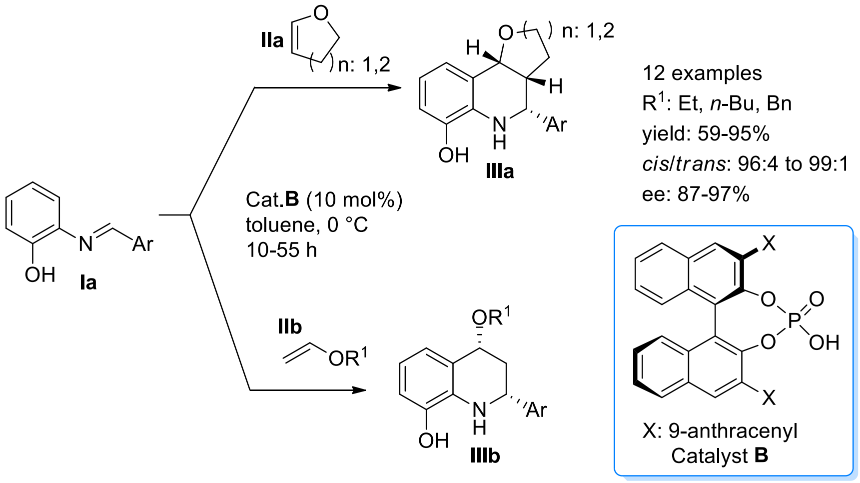


Figure 1.7.

1.3.2 – Chiral Brønsted acid catalysis

After the first catalytic enantioselective Povarov reaction from Ishitani and Kobayashi, just one more report[30] was published before 2006, when thanks to the discovery and the success of chiral Brønsted acids catalysis, in particular phosphoric acids, finally several enantioselective Povarov reactions were disclosed.

The first asymmetric Povarov reaction catalysed by a Brønsted acid still relied on the orientation associated to an *o*-hydroxy substituent and was published by Akiyama and co-workers.[31] The reaction involved *o*-hydroxy imines **Ia**, cyclic or acyclic vinyl ethers (**IIa** and **IIb**) and (*R*)-BINOL-derived chiral phosphoric acid **C** as catalyst (Scheme 1.11). The reaction allowed obtaining tetrahydroquinolines as products with good yields and good diastereo-



Scheme 1.11.

---

[30] Sundararajan G., Prabagaran N., Varghese B. *Org. Lett.*, **2001**, *3*, 1973.

[31] Akiyama T., Morita H., Fuchibe K. *J. Am. Chem. Soc.*, **2006**, *128*, 13070.

and enatioselectivities. Also in this case, a supermolecular transition state complex has to be formed to achieve a good enantioinduction, as shown in figure 1.8.

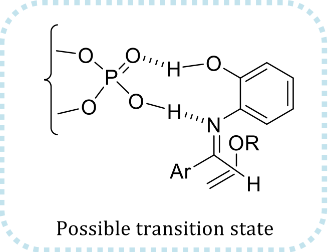
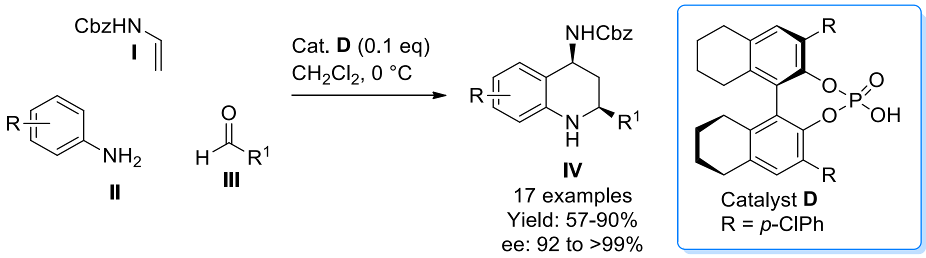


Figure 1.8.

Povarov reactions involving an enecarbamate as dienophile have been widely studied.[32] The first example of such a reaction was reported by Masson and Zhu.[33] Furthermore, this was also the first example of an asymmetric Povarov reaction involving aliphatic aldehydes and the first solution to the structural limitation of the use of *o*-hydroxyanilines of Akyiama's protocol. The reaction between benzyl *N*-vinyl carbamate **I**, anilines **II** and aldehydes **III** was catalysed by (*R*)-H_8-BINOL-derived phosphoric acid **D** (Scheme 1.12).



Scheme 1.12.

The reaction afforded tetrahydroquinolines in good to high yields, good diastereoselection (up to 99:1) and high enantioselectivity (up to 99% ee), with the resulting *cis* products showing a reversal of the enantiofacial selectivity with respect to Akyiama's catalyst, although in both cases chiral phosphoric acids derived from (*R*)-BINOL were employed. This difference in the absolute configuration can be explained with a different transition state complex (Figure 1.9). While in Akyiama's model the catalyst activated only

---

[32] (a) Xu F.X., Huang D., Han C., Shen W., Lin X., Wang YG. *J. Org. Chem.*, **2010**, *75*, 8677. (b) Huang D., Xu F., Chen T., Wang Y., Lin X. *RSC Adv.*, **2013**, *3*, 573. (c) Wang C., Han Z.Y., Luo H.W., Gong L.Z. *Org. Lett.*, **2010**, *12*, 2266.

[33] Liu H., Dagousset G., Masson G., Retailleau P., Zhu J. *J. Am. Chem. Soc.*, **2009**, *131*, 4598.

the imine affording the 2*R*,4*R* isomer, in Zhu's process the catalyst activated both diene and dienophile through two H-bonds with the imine nitrogen and the NH of carbamate respectively, affording the 2*S*,2*S* isomer. The crucial role of the carbamate NH was confirmed using the methyl derivative, which afforded the final product in low yield and low enantioselectivity. Two years later, the same group expanded this methodology to the synthesis of C-2, C-3 and C-4 polisubstituted tetrahydroquinolines employing *β*-substituted acyclic enecarbamates.[34]

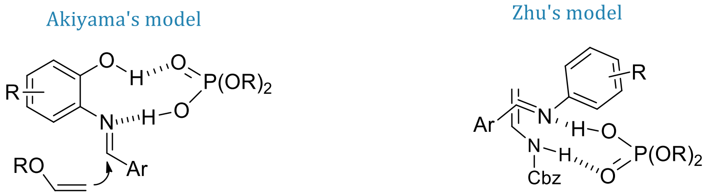
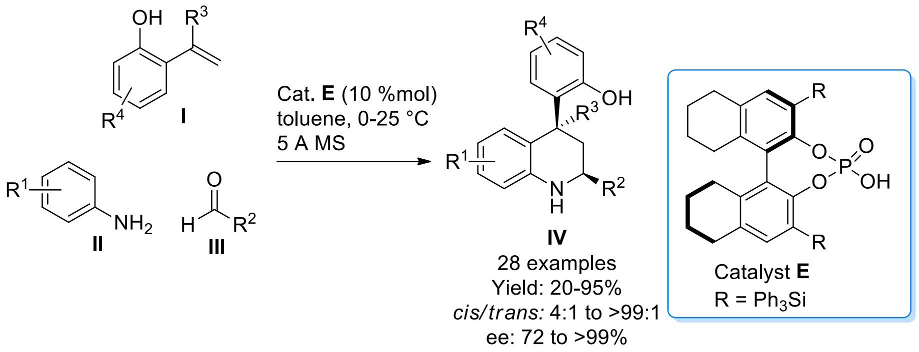


Figure 1.9.

Gong and co-workers[35] reported an enantioselective three-component Povarov reaction employing 2-hydroxystyrene **I** as dienophile and phosphoric acid **E** as the catalyst, affording *cis* tetrahydroquinolines **IV** in high stereoselectivities up to 99:1 (dr) and 97% (ee) (Scheme 1.13). This synthetic procedure allowed to generate two stereocenters, one of them quaternary (C-4), and could be applied to a wide range of aldehydes and anilines.



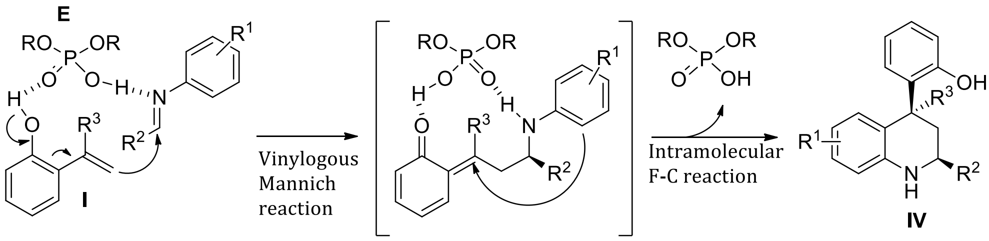
Scheme 1.13.

---

[34] Dagousset G., Zhu J., Masson G. *J. Am. Chem. Soc.*, **2011**, *133*, 14804.

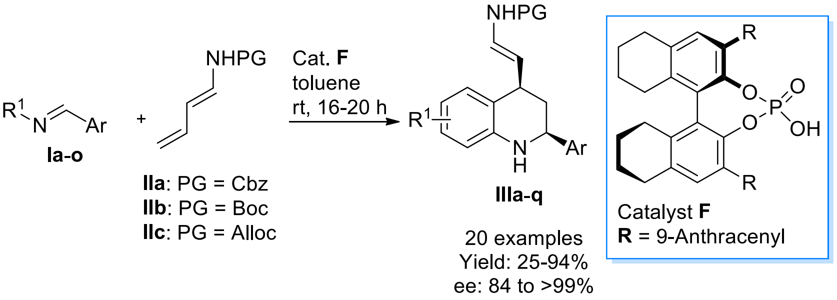
[35] Shi F., Xing G.J., Tao Z.L., Luo S.W., Tu S.J., Gong L.Z. *J. Org. Chem.*, **2012**, *77*, 6970.

A computational study has also been conducted, revealing this reaction to proceed in a stepwise fashion *via* a vinylogous Mannich reaction followed by a Friedel-Crafts intramolecular cyclization, where the catalyst acted as bidentate species activating both the diene and the dienophile (Scheme 1.14).



Scheme 1.14.

Finally, we will discuss chiral Brønsted acid-catalyzed enantioselective vinylogous Povarov reactions. Caruana and coworkers, in 2013,[36] reported the reaction between three different carbamates derived from 1-aminodienes **II**, *N*-aryl imines **I** and a catalytic amount of (*R*)-H8-BINOL- derived catalyst **F**. This reaction afforded tetrahydroquinolines **III** in moderate to excellent yields (25-94%), a complete *cis* diastereoselection and good to excellent enantioselectivities (84 to >99% ee) (Scheme 1.15).



Scheme 1.15.

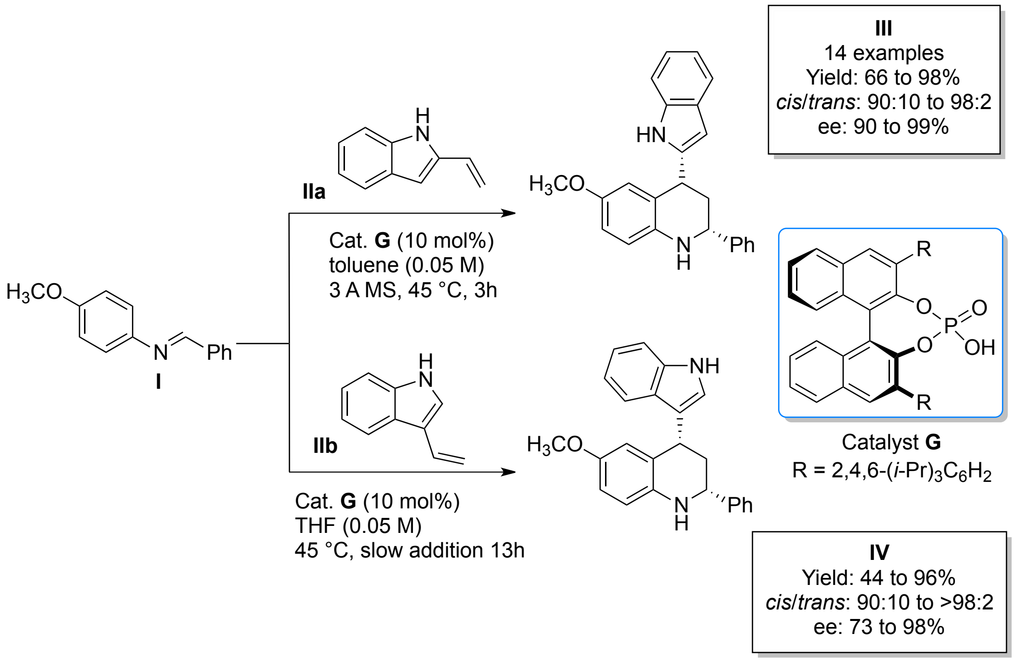
A further catalytic enantioselective vinylogous Type I Povarov reaction was developed by Ricci's group[37] that involved the use of 2- and 3-vinylindoles **IIa** and **IIb** as dienophiles and a chiral phosphoric acid ((*S*)-TRIP derivative) **G** as catalyst (Scheme 1.16). In the case of 2-

---

[36] Caruana L., Fochi M., Ranieri S., Mazzanti A., Bernardi L. *Chem. Commun.*, **2013**, *49*, 880.

[37] Bergonzini G., Gramigna L., Mazzanti A., Fochi M., Bernardi L., Ricci A. *Chem. Commun.*, **2010**, *46*, 327.

vinylindole **IIa**, toluene, molecular sieves and a temperature at 45 °C have been found as the best reaction conditions to obtain tetrahydroquinolines **III** in modest to good yields and with very good diastereo- and enantioselectivities. In the case of the more electron-rich and sensitive olefin **IIb**, milder reaction conditions were applied and tetrahydroquinolines **IV** were obtained in modest to good yields and with good diastereoselectivity and good enantiomeric purity. It is important to note that the peculiar reactivity of vinylindole allowed the preparation of enantioenriched indole compounds that can be easily converted into more complex chemical scaffolds.



Scheme 1.16.

To conclude, chiral phosphoric acids have shown a good capacity of enantioinduction in the Povarov reaction. A drawback of these catalysts is the requirement of an acidic H either in the imine component, as in the *o*-hydroxyaniline-derived imines, or in the dienophile, such as the acidic proton of the NH in the carbamate substrates. This feature is necessary for both reactivity and enantioselectivity. In fact, the catalyst protonates the imine species, activating

it toward nucleophilic attack, and is finally regenerated by recovering a proton from the substrates, and thus a group able to transfer a proton to the catalyst is a requirement.[38]
This mechanism for catalyst regeneration has been proved experimentally, as mentioned above. An additional such study has been reported by Zhu,[39] who showed that BINOL-phosphoric acid catalysts were able to catalyse the reaction between indoles and imines, but the reaction did not take place with *N*-alkyl indoles.

Regarding the origin of enantioselectivity, Simón and Goodman[38] hypothesized a transition-state complex to explain the enatioselectivity achieved in more than 40 reactions with imines and BINOL derived acids, where the enantio-induction of this kind of catalysts is tightly correlated to dual H-bond coordination. Furthermore, is commonly accepted that the chiral discrimination requires the presence of at least of three interactions.[40] Two of these interactions are the H-bonds between the catalyst and the imine and nucleophile. The third is the steric interaction between the hindered groups in the catalyst and the substrate, which allows one of the two possible enantiomeric transition states and hence one of the two enantiomers.

1.3.3 – Chiral urea catalysis

Jacobsen introduced in 2010 a new method to induce enantioselectivity that combines two organocatalytic strategies: Brønsted acids catalysis and the H-bond donor catalysis typical of urea and thiourea compounds.[41,42] It was recognized that chiral Brønsted acids are able to induce enantioselectivity and the complex responsible for the enantioinduction is formed by the achiral (H^+), which activates the neutral substrate, and by the chiral conjugated base. On the other hand, doubly H-bonding agents, especially urea and thiourea derivatives, have long been recognised as powerful tool in organocatalysis for the activation

---

[38] (a) Simón L., Goodman J.M. *J. Org. Chem.*, **2011**, *76*, 1775. For a review of the work of the Goodman group on the stereochemistry of bifunctional phosphoric acid catalyzed reactions of imines, see: (b) Reid J.P., Simón L., Goodman J.M. *Acc. Chem. Res.*, **2016**, *49*, 1029.

[39] Jia Y.X., Zhong J., Zhu S.F., Zhang C.M., Zhou Q.L. *Angew. Chem. Int. Ed.*, **2007**, *46*, 5565.

[40] (a) Easson L.H., Stedman E.J. *Biochem.*, **1933**, *27*, 1257. (b) Vadim A.D. *Chirality*, **1997**, *9*, 99.

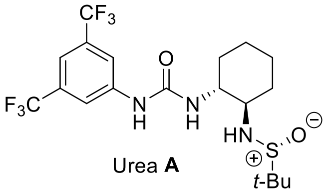
[41] Xu H., Zuend S.J., Woll M.G., Jacobsen E.N. *Science*, **2010**, *327*, 986.

[42] Xu H., Zhang H., Jacobsen E.N. *Nat. Protoc.*, **2014**, *9*, 1860.

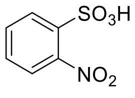
of carbonyl groups and derivatives through weak hydrogen bonds.[43] These bidentate H-bonding catalysts have been also employed with success in enantioselective reactions.[44]

The new catalytic system envisioned by Jacobsen was based on the idea that neutral chiral H-bonds donor species, such as urea or thiourea derivatives, can be associated to the negatively charged conjugated base of strong achiral Brønsted acids to form a complex molecular system by noncovalent interactions and to control nucleophilic addiction reactions by allowing then to take place only from one face of the complex.

With this catalytic system, Jacobsen and co-workers studied the Povarov reaction and after intensive optimization work they selected as co-catalysts the chiral sulfinamidourea **A** and the strong Brønsted acid NBSA (*o*-nitrobenzensulphonic acid).



Urea **A**



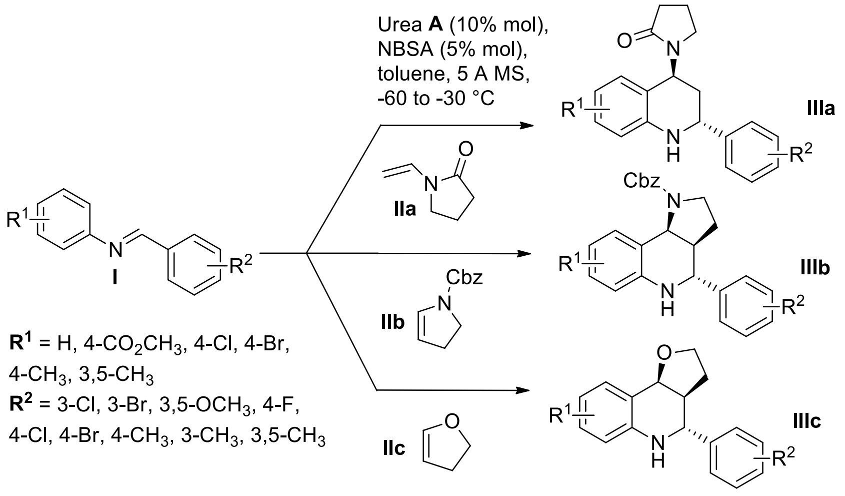
NBSA

This cooperative catalytic system was able to promote the reaction between a wide range of imines **I** and different dienophiles, including *N*-vinyloxazolidinone **IIa**, *N*-benzyloxycarbonyl-2,3-dihydropyrrole **IIb** and 2,3-dihydrofuran **IIc**, affording highly substituted tetrahydroquinolines **III** with good yields and enantioselectivities, as shown in Scheme 1.17. In contrast to the chiral Brønsted acids catalysis, this approach does not require any acidic proton in the reaction substrates.

---

[43] For double H-bonding agents, see the following reviews: (a) Schreiner P.R. *Chem. Soc. Rev.*, **2003**, *32*, 289. (b) Doyle A.G., Jacobsen E.N. *Chem. Rev.*, **2007**, *107*, 5713. For urea derivatives as catalysts, see: (c) WittKopp A., Schreiner P.R. *Chem. Eur. J.*, **2003**, *9*, 407. (d) Held F.E., Tsogoeva S.B. *Catal. Sci. Technol.*, **2016**, *6*, 645.

[44] (a) Okino T., Hoashi Y., Furukawa T., Xu X., Takemoto Y. *J. Am. Chem. Soc.*, **2005**, *127*, 119. (b) Berkessel A., Cleemann F., Mukherjee S., Müller T.N., Lex J. *Angew. Chem. Int. Ed.*, **2005**, *44*, 807. (c) Yoon T.P., Jacobsen E.N. *Angew. Chem. Int. Ed.*, **2005**, *44*, 466. (d) Raheem I.T., Thiara P.S., Peterson E.A., Jacobsen E.N. *J. Am. Chem. Soc.*, **2007**, *129*, 13404.



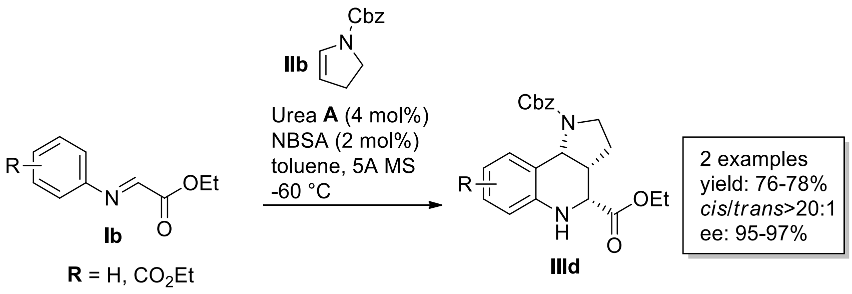
IIIa
15 examples
yield: 72-92% (average 84%)
trans/cis: >20:1
ee: 95-99% (average 97%)

IIIb
14 examples
yield: 45-73% (average 84%)
trans/cis: 1.4:1 to 4.2:1
ee: 90-98% (average 97%)

IIIc
1 example
yield: 92%
trans/cis: 4:1
ee: 91%

Scheme 1.17

On the other hand, the use of α-ketoimines was hardly explored since only two examples were studied, restricted to the case of an ester substituent and only with cyclic dienophiles (Scheme 1.18).

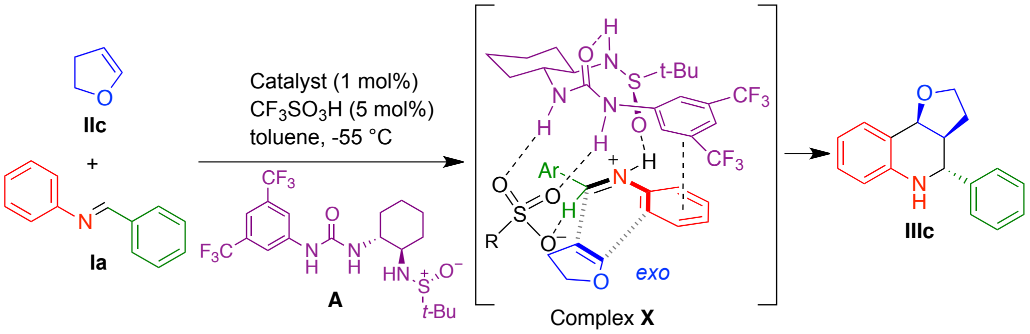


2 examples
yield: 76-78%
cis/trans>20:1
ee: 95-97%

Scheme 1.18.

The diastereoselection depends on the dienophile: with *N*-vinyloxazolidinone the reaction showed a very good *exo*-selectivity (*exo*/*endo* up to 99/1); the diastereoselectivity decreased with 2,3-dihydrofuran and *N*-benzyloxycarbonyl-2,3-dihydropyrrole (*exo*/*endo* - 4:1). Moreover, the 2,4-*trans* diastereoisomer (*exo* approach) is obtained instead of the more common *cis* product (*endo* approach) isolated with other catalysts for the case of acyclic dienophiles.

A detailed mechanistic study of the reaction between imine **Ia** and dienophile **IIc** has been undertaken. A computational analysis, combined with ^{1}H-NMR experiments, led to propose a concerted but non-synchronous mechanism (see Section 1.4 below) and identified complex **X** as the lowest-energy transition structure. In this complex, the sulfinamidourea and triflate groups act as dual H-bond acceptors and the iminium species as a dual H-bond donor, through the iminium nitrogen and the formyl proton (Scheme 1.19). Finally, the enantio-induction could be ascribed to stabilizing π-π interactions between the aromatic component of the catalyst and the aryl moiety derived from the aniline fragment of imine.



Scheme 1.19.

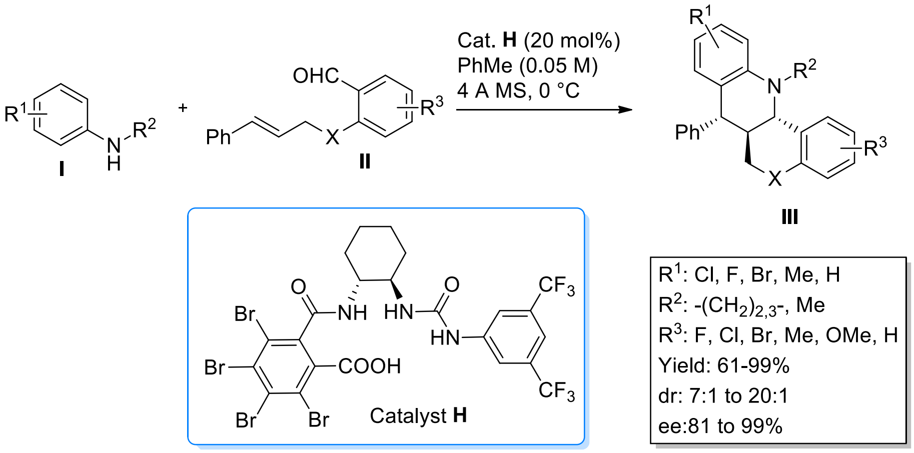
Finally, following the new catalytic style triggered by Jacobsen, in 2013[45] Seidel's group present a new catalytic system originated from a different fusion of the two main catalytic approach studied: the Brønsted acids catalysis and the (thio)urea catalysis. They introduced a new catalyst where a carboxylic acid is covalently bonded to an anion-recognition site, namely a thiourea moiety. Furthermore, they applied the new catalytic strategy to develop the first example of a catalytic enantioselective intramolecular aza Diels-Alder reaction. The catalyst **H** was identified as the more effective specie for the three component Povarov reaction between secondary-aniline type amines **I**, such as indoline, and aldehyde **II**.[46] It is important to note that the employment of secondary amines remains far less studied in these reactions especially for the need of N-H acidic protons, but in this case this is dictated to reduce the propensity for forming hydrogen bonds with catalytic anion, impeding maybe in

---

[45] Min C., Mittal N., Sun D.X., Seidel D. *Angew. Chem.* Int. Ed., **2013**, *52*, 14084.

[46] Min C., Lin C.-T., Seidel D. *Angew. Chem.*, **2015**, *127*, 6708.

this way the enantio-induction by the chiral complex. Even if the authors reported an X-Ray structure of the catalyst that elucidated the intramolecular interactions, an explanation of the enantioinduction for the substrate aggregation to the catalyst remains to be established.



R^1: Cl, F, Br, Me, H
R^2: $-(CH_2)_{2,3}-$, Me
R^3: F, Cl, Br, Me, OMe, H
Yield: 61-99%
dr: 7:1 to 20:1
ee:81 to 99%

Scheme 1.20.

To conclude, the field of asymmetric Povarov reactions has grown in recent years with the development of new catalytic systems. Nevertheless, existing methodology still has limitations and has not been explored in many situations, for example in systems where basic nitrogen atoms are present in the diene or in both the diene and the dienophile, as happens in the reactions discussed in this Thesis.

1.4 – Mechanistic debate

The mechanism of the Povarov reaction is a debated issue. Usually the classical Diels-Alder reactions have a one-step concerted mechanism, but the synchronicity decreases with the asymmetricity of the dienophile, as a consequence of an asymmetric distribution of the electron-density, making the one-step process asynchronous. The decrease in synchronicity follows a direct relationship with the polar character of the reaction, namely of the solvent, dienophile, activated imine complex that would stabilize more or less the zwitterionic transition state and favouring so the concerted, albeit asynchronous, or the stepwise process. Thus, the scientific community working on the Povarov reaction is divided into two groups, one of them supporting a stepwise mechanism via a domino Mannich/Friedel-Crafts process with the ionic intermediate (**I**) and the other one a concerted [4+2] cycloaddition mechanism with an asynchronous transition state (**II**) (Fig. 1.10).

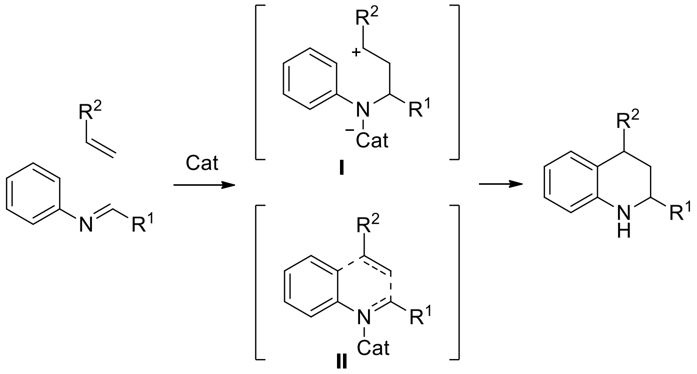


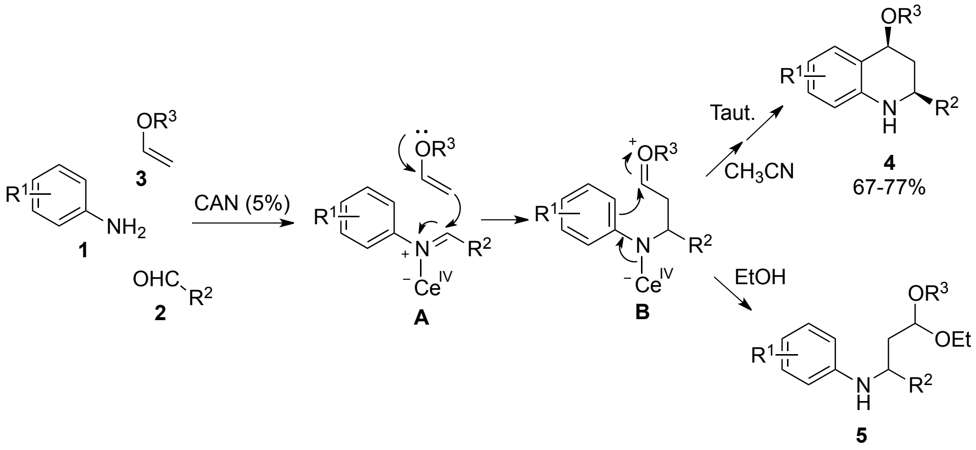
Figure 1.10.

In support of the stepwise mechanism, which is the most commonly accepted one, some experimental studies[47] have been carried out trapping the ionic intermediate with a nucleophile (EtOH for example). Thus, as shown previously in Scheme 1.3,**¡Error! Marcador no definido.**[b] the one-pot reaction between anilines **I**, aldehyde **II** and vinyl ether **III** proceed in acetonitrile in good yields and with excellent diastereoselectivity. Interestingly, when the reaction was carried out in ethanol, acetals **V** (as illustrated below in Scheme 1.21) were

---

[47] (a) Baudelle R., Melnyk P., Déprez B., Tartar A. *Tetrahedron,* **1998**, *54*, 4125. (b) Hermitage S., Howard J.A.K., Jay D., Pritchard R.G. *Org. Biomol. Chem*., **2004**, *2*, 2451. (c) Alves M.J., Azoia N.G., Fortes A.G. *Tetrahedron*, **2007**, *63*, 727.

isolated as the major product together with small amounts of the corresponding tetrahydroquinoline **IV**. With this proof it is possible propose that in these conditions the reaction proceeded *via* a stepwise mechanism in which the vinyl ethers added to the Lewis acid (CAN)-activated *N*-aryl imine complex **A** to generate the oxonium species **B**, which subsequently underwent an intramolecular electrophilic substitution reaction to afford tetrahydroquinolines **IV**. On the other hand, when the reaction was performed in ethanol, the oxonium species **B** was captured by the nucleophilic solvent affording acetals **V**, which confirmed the generation of the carbocation intermediate and hence the stepwise mechanism.[48]

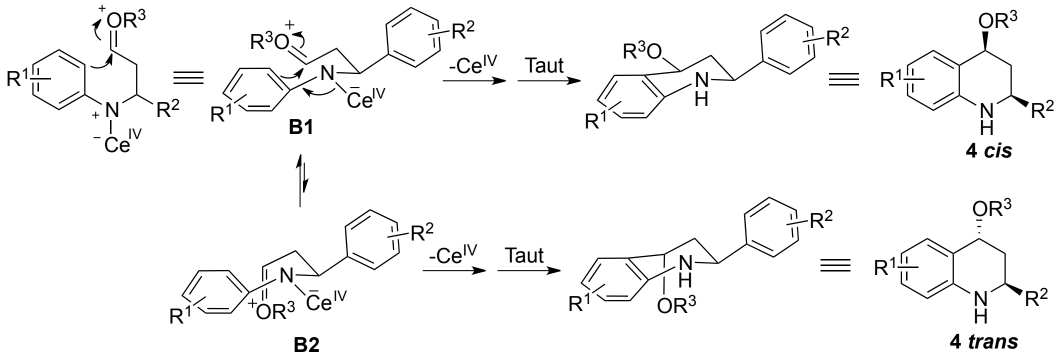


Scheme 1.21.

The diastereoselectivity can be attributed to a chair-like conformation of the transition state. The major *cis* product would be originated from the transition state **B1**, where the alkoxy and aryl groups are located in equatorial positions, by cyclization followed by tautomerization *via* a [1,3] hydrogen shift. The minor *trans* product would arise from the more hindered, less favoured transition state **B2** (Scheme 1.22).

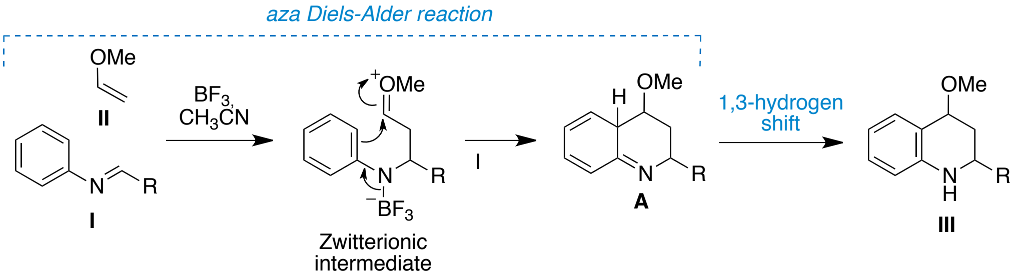
---

[48] For selected articles that support the stepwise mechanism: (a) Hermitage S., Howard J.A.K., Jay D., Pritchard R.G., Probert M.R., Whiting A. *Org. Biomol. Chem.*, **2004**, *2*, 2451. (b) Alves M.S., Azoia N.G., Fortes A.G. *Tetrahedron*, **2007**, *63*, 727. (c) Haghdadi M., Mousavi S.S., Ghasemnejad H. *J. Serb. Chem. Soc.*, **2016**, *81*, 67.



Scheme 1.22.

A recent theoretical study by Domingo et al.[49] analysed the mechanism of a Lewis acid-catalysed Povarov reaction in acetonitrile shown in Scheme 1.23. They concluded that the Lewis acid-catalysed Povarov reaction is a domino process with two sequential steps (i) the Lewis acid-promoted aza Diels-Alder reaction affording cycloadduct **I**; and (ii) a 1,3-proton shift that yields the final product **III**. Furthermore, the first step presents two stages: the first one is the attack of the electron-rich olefin **II** onto the Lewis acid-activated imine carbon activates the imine **I**; this is the rate-determining step of the reaction. The second step is the formation of the second C-C bond by attack of the aromatic ring onto the intermediate cationic species; this step restores the neutrality, making the overall process thermodynamically favoured. These authors state that the two stages of the Diels-Alder step are highly asynchronous and consequently can be viewed as a non-concerted process, due to the high stabilization of the zwitterionic intermediate.

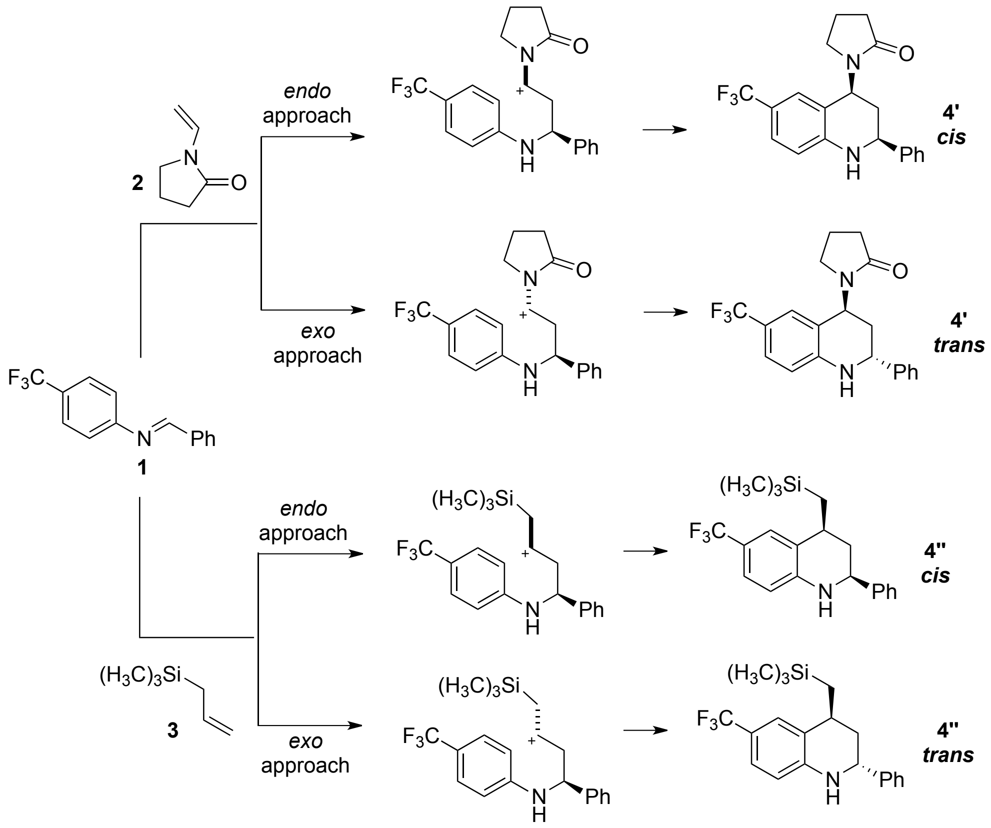


Scheme 1.23.

---

[49] Domingo L.R., Aurell M.J., Sáez J.A., Mekelleche S.M. *RSC Adv.*, **2014**, *4*, 25268.

A more recent DFT (density functional theory) study by the same group[50] investigates the *cis*/*trans* selectivity in the Brønsted acid-catalysed Povarov reaction of *N*-arylimine **I** and vinylpyrrolidinone **II** or allyltrimethylsilane **III** affording tetrahydroquinolines **IV** (Scheme 1.24). They found that the reaction proceeds through a stepwise mechanism: an initial attack of the dienophile to the carbon atom of the protonated imine, forming the cationic intermediate along the *endo*/*exo* stereoisomeric approaches, followed by a fast intramolecular Friedel-Crafts reaction to yield the final products. Moreover, in the reaction where the pyrrolidinone acts as the dienophile, the energetic study indicated that the *endo* approach is preferred over the *exo* mode, permitting the *cis* isomer as the kinetic product. On the other hand, employing allyltrimethylsilane as reactive, the main product was the *trans* tetrahydroquinoline from the *exo* approach. Analysis of the electron density of the transition states reveals that the van Der Waals interactions, participating in the transition states



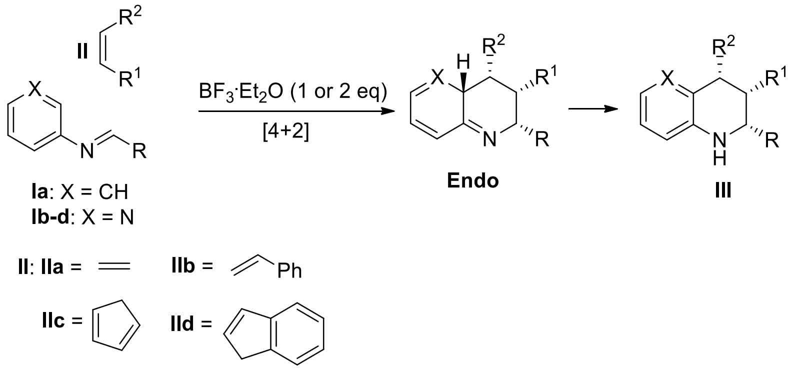
Scheme 1.24.

---

[50] Domingo L.R., Gutiérrez M.R., Emamian S. *RSC Adv.*, **2016**, *6*, 17064.

involving the reaction with pyrrolidinone, compensate the electronic repulsions present in the transition state, favouring an *endo* approach; the same repulsions, in the case of the allyltrimethylsilane reaction, force an *exo* approach. These theoretical energetic studies confirm their experimental data observed.

The second possibility is a concerted mechanism involving an asynchronous [4+2] cycloaddition, as postulated in a first moment by Povarov. Palacios, Cossío and coworkers[51] by combining a computational study with experimental work, concluded that the $BF_3{\cdot}Et_2O$-catalysed Povarov reaction between imine **I** and olefins **II** proceeds through an asynchronous concerted process to afford tetrahydroquinoline **III** with high regio- and diastereolectivity *via* an *endo* transition state (Scheme 1.25).

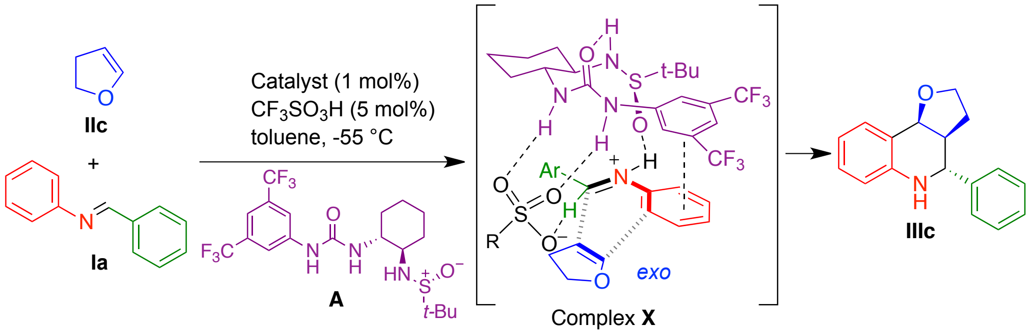


Scheme 1.25.

In the same year, as previously discussed, Jacobsen's group[41] published an asymmetric Povarov reaction catalysed by the cooperative catalysis of a chiral sulfinamidourea and a strong Brønsted acid. In the study they carried out an experimental and computational analysis of the mechanism of the addiction of dihydrofuran **II** to the imine **I** activated complex. Their analysis supported a concerted, although highly asynchronous, cycloaddition, followed by a rapid deprotonation/rearomatization step (Scheme 1.26).

---

[51] Palacios F., Alonso C., Arrieta A., Cossio F.P., Ezpeleta J.M., Fuertes M., Rubiales G. *Eur. J. Org. Chem.*, **2010**, 2021.

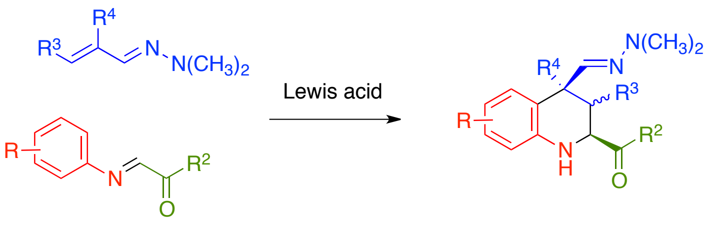

IIc
+
Ia
Catalyst (1 mol%)
CF_3SO_3H (5 mol%)
toluene, -55 °C
CF_3
F_3C
O
N
H
N
H
HN
+
S
O^-
t-Bu
A
H
O
N
S
t-Bu
CF_3
N
H
N
O
H
CF_3
+
N
H
Ar
O
O
S
H
R
O^-
O
exo
Complex X
O
N
H
IIIc

Scheme 1.26.

2 – Objectives

1. Studies on the aza-vinylogous Povarov reaction

We have investigated the Lewis-acid catalyzed reaction between α,β-unsaturated *N*,*N*-dimethylhydrazones and a variety of *α*-ketoimines, which can be viewed as a variation of the aza-vinylogous Povarov reaction. This work had been initiated in our group,[52] but the generality and scope of the process remained to be established.

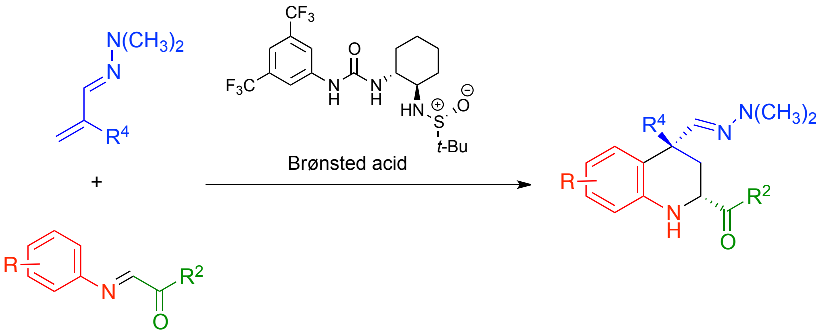


2. Asymmetric organocatalytic aza-vinylogous Povarov reactions

Our second objective was to demostrate the application of Jacobsen's technique of combining a Brønsted acid with a chiral urea catalyst to the aza-vinylogous Povarov reaction of α-ketoimines. This is a challenging reaction because it involves the use of a basic dienophile, which could interfere with the required protonation of the imine nitrogen, and indeed there is no precedent for asymmetric Povarov reactions in which both the diene and the dienophile bear basic nitrogen atoms. Furthermore, the planned reaction generates a quaternary stereocenter, which is an important synthetic goal and very unusual in Povarov chemistry. As another point of interest, the use of acyclic dienophiles is unprecedented in the presence of urea or thiourea-derived catalysts.

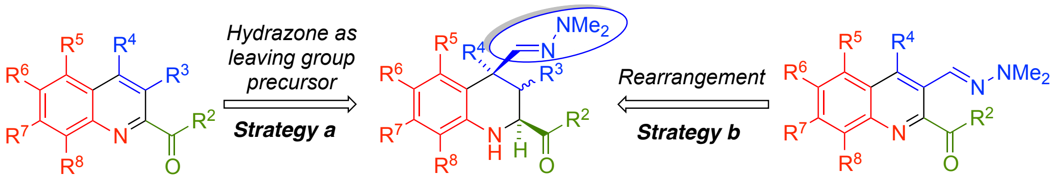
---

[52] Ribelles P. Tesis doctoral, Universidad Complutense, 2013.



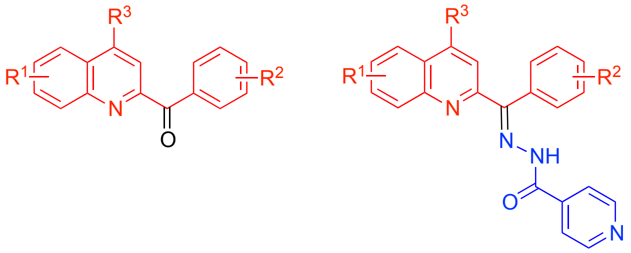
3. *Synthesis of 2-acylquinolines*

Due to the scarcity of literature procedures for the preparation of 2-acylquinolines and the importance of this heterocyclic framework, we set out to develop such methods from the products of the aza-vinylogous Povarov reactions. To this end, we examined two types of strategies, based on: (a) The transformation of the dimethylhydrazone fragment into a good leaving group under oxidative conditions. (b) The migration of the dimethylhydrazonomethyl moiety to the quinoline C-3 position.



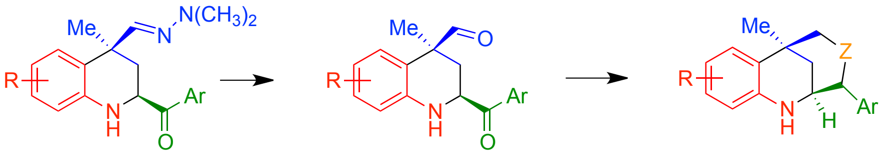
4. *2-Acylquinolines and their hydrazones as antitubercular agents*

Quinoline can be viewed as a privileged structure in the development of antitubercular compounds. Due to the absence of data on the activity of 2-acylquinolines, probably associated to the lack of suitable synthetic methods, we became interested in screening representative compounds from our recently synthesized library. Due to the promising results obtained, we obtained an additional family of compounds based on the concept of molecular hybridization. These compounds were N-acylhydrazones of the 2-acylquinolines and were designed to liberate the same active species as the antitubercular drug isoniazide upon oxidative metabolism.



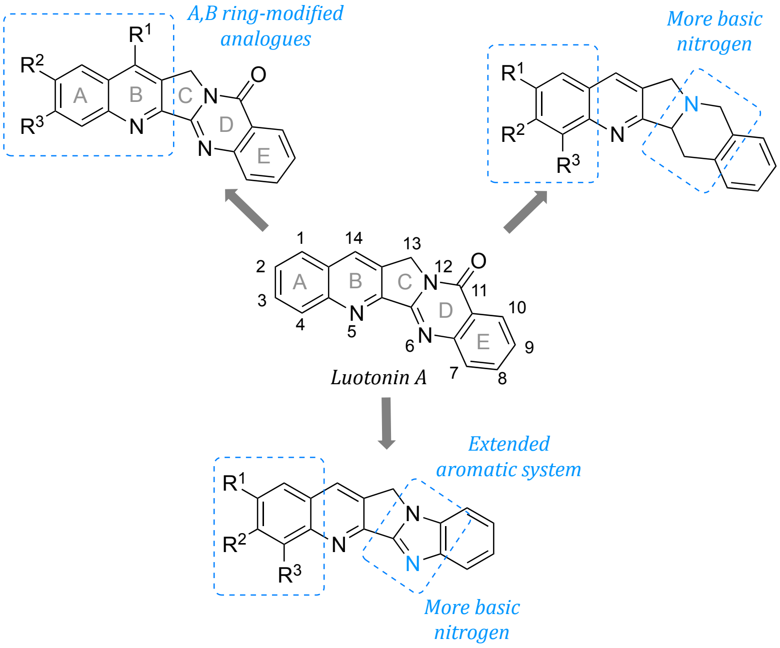
5. Synthesis and pharmacological study of 2,6-methanobenzo[e][1,4]-diazocine derivatives

One of the attractive aspects of the products from the aza-vinylogous Povarov products is the combined presence of carbonyl and hydrazone functions at the tetrahydroquinoline C-2 and C-4 positions, respectively, coupled with their *cis* arrangement. This provides strategic possibilities to generate structurally diverse natural-product like heterocyclic libraries from simple starting materials *via* the generation of additional rings. In an application of this idea, we planned the synthesis of bicyclic structures from 1,5-dicarbonyl compounds derived from the hydrolysis of the hydrazones obtained in the Povarov reaction. Owing to the analogy between these structures and that of cytisine, an $\alpha_4\beta_2$ acetylcholine nicotinic receptor partial agonist that has potential interest in neurodegenerative diseases, we also planned the pharmacological study of our compounds as neuroprotective agents.



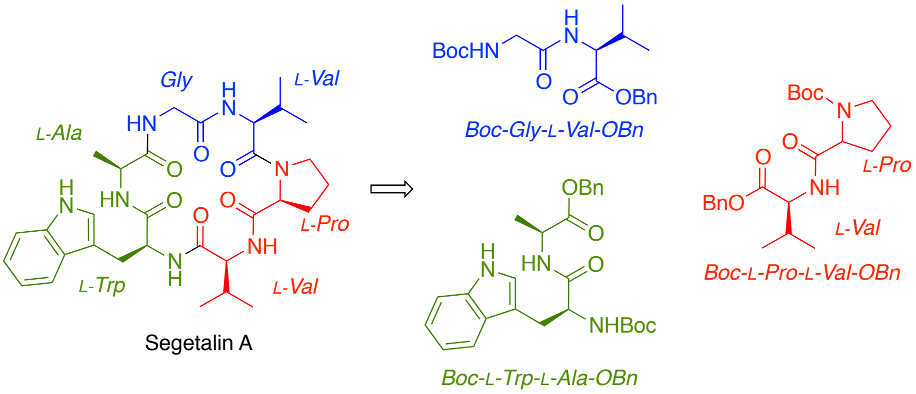
6. Molecular docking studies on luotonin analogues

As a contribution to the work of our group in the development of new luotonin A-inspired topoisomerase I inhibitors as anticancer agents, one of the objectives of this thesis was the computational study of the interaction of three families of analogues. The purpose of this study was to aid compound design and to assist the rationalization of the topoisomerase inhibition and cytotoxic activity of these molecules.



7. Development of a general and scalable flow protocol for peptide synthesis

This part of the Thesis was carried out during a three-month stay at the Department of Chemistry, Cambridge University, under the supervision of Professor Steven V. Ley, in partial fulfillment of the requirements for the European Ph. D. label. It involves the development of a new method for peptide synthesis under flow conditions, based on carboxyl activation by mixed anhydride generation. In order to underscore the flexibility of the method, it was applied the synthesis of the bioactive natural cyclic peptide segetalin A.



3 – Studies on the racemic aza-vinylogous Povarov reaction

3.1 - Introduction

1-Azadienes are versatile building blocks for the efficient construction of nitrogen heterocycles. They can represent a strategic starting point to create structural diversity and complexity in only a few reaction steps. For instance, α,β-unsaturated hydrazones are simple chemical entities endowed with various possible reactivities (Fig. 3.1). In the first place, when $R^3 = NMe_2$, the α,β-unsaturated hydrazones may act as a dienes in hetero Diels-Alder reactions with normal electron demand thanks to the electron-donating effect of the dimethylamino function. Moreover, the β carbon is a good Michael acceptor; the electron rich nitrogen atom of the azadiene may react as nucleophile and the double bond could be hydrolysed, oxidised or reduced allowing the installation of new functional groups. Finally, there is the possibility to introduce chiral moiety as substituent on the nitrogen allowing an asymmetric induction of the reactions previously mentioned.

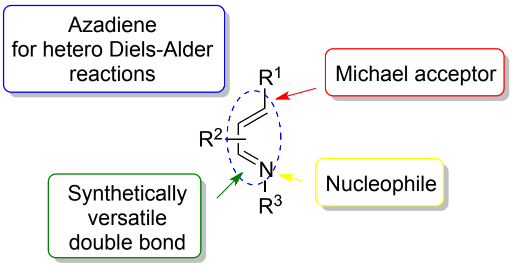


Figure 3.1.

Owing to the electron acceptor effect of the nitrogen, 1-azadienes present a low electronic density. In order to allow their use in normal electron demand Diels-Alder reactions, Ghosez[53] introduced an electron-donating dimethylamino group at the nitrogen atom, inverting the electronic distribution of the system.[54]

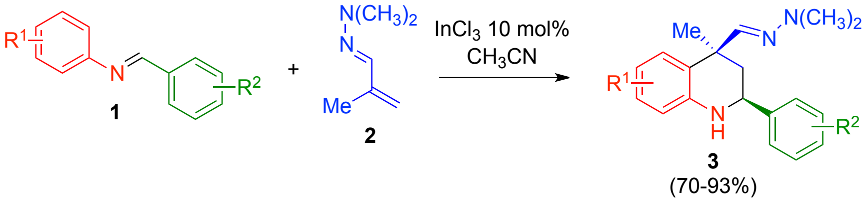
---

[53] Serckx-Poncin B., Hesbain-Frisque A.M., Ghosez L. *Tetrahedron Lett.*, **1982**, *23*, 3261.

[54] For selected examples of these hetero Diels-Alder reactions, see: (a) Villacampa M., Pérez J.M., Avendaño C., Menéndez J.C. *Tetrahedron*, **1994**, *50*, 10047. (b) Pérez J.M., López-Alvarado P., Avendaño C., Menéndez J.C. *Tetrahedron*, **2000**, *56*, 1561. (c) de la Fuente J.A., Manzanaro S., Vicent M.J., Martín M.J., Salvador-Tormo N., Pérez J.M., Blanco M.M., Avendaño C., Menéndez J.C. *Bioorg. Med. Chem.*, **2004**, *12*, 6505.

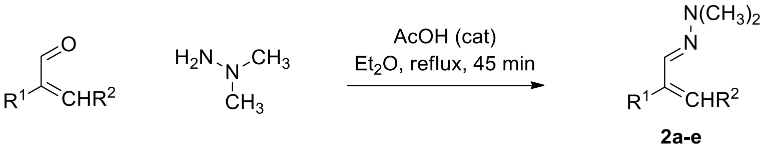
3.2 - Aza-vinylogous Povarov reactions starting from arylimines

As discussed in Section 1.2.4, our group has developed the first type I vinylogous Povarov reaction involving a *N*,*N*-dimethyl-*α*,*β*-unsaturated hydrazone as the dienophile (Scheme 3.1).



Scheme 3.1.

Because we needed some of these compounds as starting materials for subsequent synthetic work or as references for chiral HPLC studies, we had to re-synthesize them. The hydrazones **2**, required as starting materials, were obtained in excellent yields following a literature procedure,[55] through the condensation of *N*,*N*-dimethylhydrazine with acrolein derivatives in the presence of glacial acetic acid as catalyst (Scheme 3.2 and Table 3.1). The final products are stable for long periods if stored at at 5 °C; they have low boiling points, requiring that solvents are removed in the absence of vacuum during work-up.



Scheme 3.2.

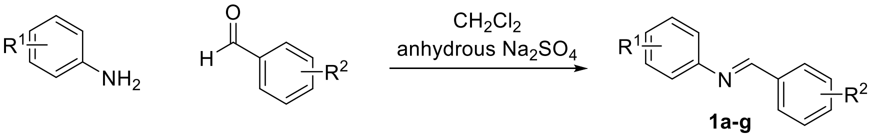
Table 3.1. Synthesis of α,β-unsaturated hydrazones as dienophiles

Hydrazone	R^1	R^2	Yield (%)
2a	CH_3	H	95
2b	CH_2CH_3	H	90
2c	H	H	95
2d	H	CH_2CH_3	95
2e	CH_3	CH_2CH_3	90

---

[55] Waldner A. *Helv. Chim. Acta,* **1988**, *71*, 486.

The arylimines **1** used as dienes were prepared mixing aldehydes and anilines in dichloromethane in the presence of anhydrous sodium sulphate to remove the water formed during the condensation and thus displace the reaction equilibrium towards the formation of the product (Scheme 3.3). The imines were obtained in quantitative yield and were employed in the Povarov reactions without purification.



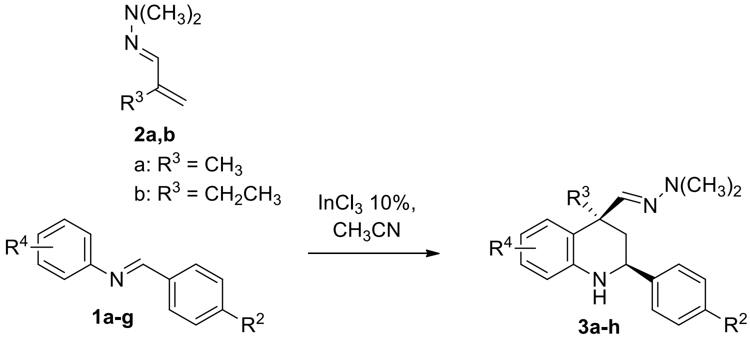
Imine	R1	R2
1a	4-OCH_3	H
1b	4-OCH_3	4-Cl
1c	4-OCH_3	4-OCH_3
1d	4-OCH_3	4-CH_3
1e	2,4-$(CH_3)_2$	H
1f	4-CH_3	4-OCH_3
1g	3,5-$(OCH_3)_2$	4-CH_3

Scheme 3.3.

With the starting materials in hand, we carried out the aza-vinylogous Povarov reactions in the previously determined conditions, *i.e.* in acetonitrile containing 10 % mol of indium trichloride, at room temperature, to obtain 2-aryl-1,2,3,4-tetrahydroquinolines **3a-h** (Scheme 3.4 and Table 3.2). With the exception of **3g**, these were previously known compounds.[56] The reaction leading to **3h**, where a substituent is present in the quinoline C-5 position, was the only one that lacked full diastereoselectivity (*cis*:*trans* – 80:20), presumably due to steric hindrance towards the ring-closing process.

---

[56] Sridharan V., Ribelles P., Estévez V., Villacampa M., Ramos M.T., Perumal P.T., Menéndez J.C. *Chem. Eur. J.*, **2012**, *18*, 5056.



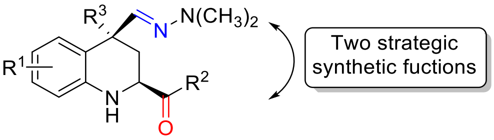
Scheme 3.4.

Table 3.2. Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines

Cmpd	**R²**	**R³**	**R⁴**	**Yield (%)**
3a	H	CH_3	6-OCH_3	90
3b	Cl	CH_3	6-OCH_3	87
3c	OCH_3	CH_3	6-OCH_3	80
3d	CH_3	CH_3	6-OCH_3	93
3e	H	CH_3	6,8-$(CH_3)_2$	80
3f	OCH_3	CH_3	6-CH_3	72
3g	H	CH_2CH_3	6,8-$(CH_3)_2$	61
3h	CH_3	CH_3	5,7-$(OCH_3)_2$	72

3.3 - Aza-vinylogous Povarov reactions starting from α-ketoimines

While the use of ethyl glyoxylate in Povarov chemistry is relatively well established,[57] to our knowledge glyoxal derivatives have only been previously employed by Zhu,[26] although with a very limited structural variation in the glyoxal fragment. On the other hand, the use of these substrates in our vinylogous reaction was almost unexplored.[24,56] Therefore, we decided to investigate the use of a variety of α-ketoimines in our aza-vinylogous Povarov reaction. We were attracted to this idea by the realization that the introduction of a carbonyl function in the C-2 position represents a strategic possibility to create a more wide chemical variety and more complex structures with additional synthetic steps. This work had been initiated in our group,[52] but the generality and scope of the process remained to be established.



For the synthesis of the required α-ketoimines **4a-q** (Scheme 3.5 and Table 3.3) the procedure chosen was the same one previously described for the arylimines. As in the previous case, yields were quantitative and the crude imines were directly used in the next step.

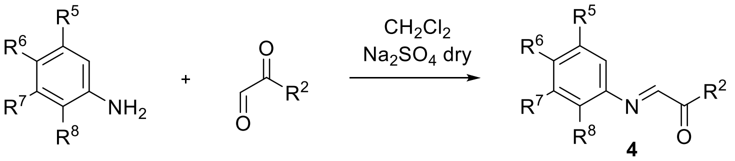
The anilines employed were all of commercial origin. Regarding the glyoxals, some of them (4-methoxyphenyl and 4-fluorophenyl) are commercially available as hydrates containing an unknown amount of water, and so the amount of aldehyde used was optimized by gradual addition until no aniline was detected by ^{1}H-NMR. Phenylglyoxal is commercially available as a monohydrate. Finally, ethyl glyoxylate,[58] 2-furyl- and 2-thienylglyoxal[59] were obtained according to literature methods. Glyoxal derivatives were stored at 5 °C to prevent their polymerization.

---

[57] For a representative recent example, see: Nan G.M., Liu W. *Chin. Chem. Lett.*, **2015**, *26*, 1289.

[58] Bailey P.D., Smith P.D., Pederson F., Clegg W., Rosair G.M., Teat S.J. *Tetrahedron Lett.*, **2002**, *43*, 1067.

[59] Saldabol N.O., Popelis J., Slavinska V. *Chem. Heterocycl. Compd.*, **2002**, *38*, 783.

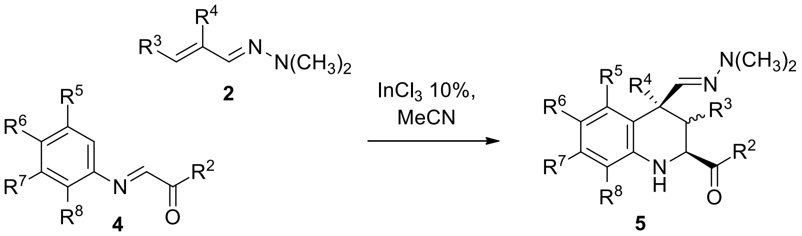


Scheme 3.5.

Table 3.3. Synthesis of *α*-ketoimines

Cmpd	**R^2**	**R^5**	**R^6**	**R^7**	**R^8**
4a	C_6H_5	H	4-OCH_3	H	H
4b	4-FC_6H_4	H	4-OCH_3	H	H
4c	4-$OCH_3C_6H_4$	H	4-OCH_3	H	H
4d	C_6H_5	H	CH_3	H	CH_3
4e	4-FC_6H_4	CH_3	H	CH_3	H
4f	4-FC_6H_4	H	CH_3	H	CH_3
4g	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3
4h	4-$OCH_3C_6H_4$	H	CH_3	H	H
4i	OEt	H	4-OCH_3	H	H
4j	OEt	H	CH_3	H	CH_3
4k	2-furyl	H	4-OCH_3	H	H
4l	2-thienyl	H	4-OCH_3	H	H
4m	OEt	H	CH_3	H	H
4n	C_6H_5	H	CH_3	H	H
4o	C_6H_5	CH_3	H	CH_3	H
4p	4-FC_6H_4	H	CH_3	H	H
4q	C_6H_5	H	H	H	H

We next studied the Povarov-type reaction between *α*-ketoimines **4** and substituted *α,β*-unsaturated hydrazones **2**, which furnished the target tetrahydroquinolines **5** (Scheme 3.6 and Table 3.4).



Scheme 3.6.

Table 3.4. Synthesis of 2-acyl-1,2,3,4-tetrahydroquinolines

Cmpd	**R^2**	**R^3**	**R^4**	**R^5**	**R^6**	**R^7**	**R^8**	**Yield (%)** [a]	***2,4-cis* : *trans*** [b]
5a	C_6H_5	H	CH_3	H	6-OCH_3	H	H	72	82 : 18
5b	4-FC_6H_4	H	CH_3	H	6-OCH_3	H	H	75	84 : 16
5c	4-$OCH_3C_6H_4$	H	CH_3	H	6-OCH_3	H	H	70	83 : 17
5d	C_6H_5	H	CH_2CH_3	H	6-OCH_3	H	H	63	91 : 09
5e	C_6H_5	H	CH_3	H	CH_3	H	CH_3	95	98 : 02
5f	4-FC_6H_4	H	CH_3	CH_3	H	CH_3	H	50	55 : 45 [c]
5g	4-FC_6H_4	H	CH_3	H	CH_3	H	CH_3	68	83 : 17
5h	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	CH_3	72	86 : 14
5i	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	H	30	88 : 22
5j	C_6H_5	H	CH_2CH_3	H	CH_3	H	CH_3	56	80 : 20
5k	4-$OCH_3C_6H_4$	H	CH_2CH_3	H	OCH_3	H	H	56	79 : 21
5l	4-FC_6H_4	H	CH_2CH_3	H	CH_3	H	CH_3	55	81 : 19
5m	OEt	H	CH_3	H	6-OCH_3	H	H	88	100 : 0
5n	OEt	H	CH_3	H	CH_3	H	CH_3	86	84 : 16
5o	OEt	H	CH_2CH_3	H	6-OCH_3	H	H	74	87 : 13
5p	2-furyl	H	CH_3	H	6-OCH_3	H	H	88	100 : 0
5q	2-thienyl	H	CH_3	H	6-OCH_3	H	H	72	90 : 10
5r	C_6H_5	H	CH_3	CH_3	H	CH_3	H	63	100 : 0[c]
5s	C_6H_5	CH_2CH_3	H	H	6-OCH_3	H	H	66[c]	100 : 0[c]
5t	C_6H_5	H	H	H	6-OCH_3	H	H	72	100 : 0
5u	C_6H_5	CH_2CH_3	CH_3	H	6-OCH_3	H	H	73 [c]	57 : 43[b]

a: Isolated yield of the 2,4-*cis* isomer, with the exception of **5f**, for which an overall yield is given. In the cases **5r** and **5s** this still represents a *ca*. 1:1 misture of diastereomers, owing to the presence of a substituent at C-3. **b:** The *cis*:*trans* diastereoselection in 2,4-disubstituted compounds was determined by ^{1}H-NMR of the crude reaction product. **c**: The C-2 and C-4 substituents are *cis*, and the group at C-3 can be *cis* or *trans* with regard to them with the following ratios: **5r**: 52:48; **5s**: 50:50.

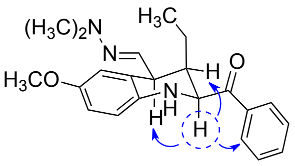
The generality of the method was underscored by the fact that compounds **5** were substituted at all positions of both rings of the tetrahydroquinoline system. The R^2 substituent was usually a phenyl group, either unsubstituted (derivatives **5a**, **d**, **e**, **j** and **5r**-**u**) or bearing electron-withdrawing (compounds **5b**, **f**, **g** and **l**) or electron-releasing (entry **5c**, **h**, **i** and **k**) groups. Furthermore, heteroaryl moieties were also tolerated, as shown by the presence of 2-furyl and 2-thienyl moieties in **5p** and **5q**. The installation of an ester group at

C-2 was also possible (**5m–o**). In the aniline fragment, hydrogen or an electron-releasing group could be accommodated, with the para methoxy group usually giving the best results.

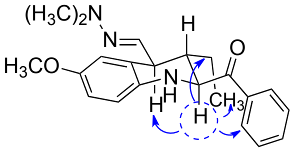
In a few cases (**5d**, **f** and **j-l**), the yield was lower; these examples are associated to the presence of a substituent at C-5 or with a bulkier group at C-4. Compounds **5s** and **5t** are noteworthy in that the aza-vinylogous Povarov reaction had previously failed when α-unsubstituted acrolein derivatives were employed as dienophiles, and hence the R^4 = H substitution had never been achieved.

The reaction shows a 8:2 to 1:0 diastereoselection in favour of the isomer with a *cis* arrangement between the 4-dimethylhydrazonomethyl and 2-acyl groups, with both substituents in equatorial positions, as assessed by NOE data (see below) and in agreement with X-Ray diffraction studies previously performed on a 2-aryl analogue of our compounds.[56] Derivative **5f** is the only exception, since it was obtained as a 1:1 - *cis*:*trans* mixture; this can be explained through steric interference between the C-5 and C-4 substituents when the 4-dimethylhydrazonomethyl group is equatorial. In the case of compound **5t**, where C-4 is not a quaternary center, we observed a good yield and a full *cis* diastereoselection.

In the cases of derivatives **5s** and **5u**, bearing a C-3 ethyl substituent, the reaction presented a slightly lower yield and also a modest diastereoselectivity: the C-2 and C-4 groups were *cis*, with complete selectivity, and the group at C-3 can be *cis* or *trans*, with no selectivity. Therefore, these compounds were obtained as ca. 1:1 mixtures of compounds **5s'/5s''** and **5u'/5u''**. These relative configurations were studied through NOE analysis of both diastereomers of derivative **5s**, which could be separated by flash chromatography.

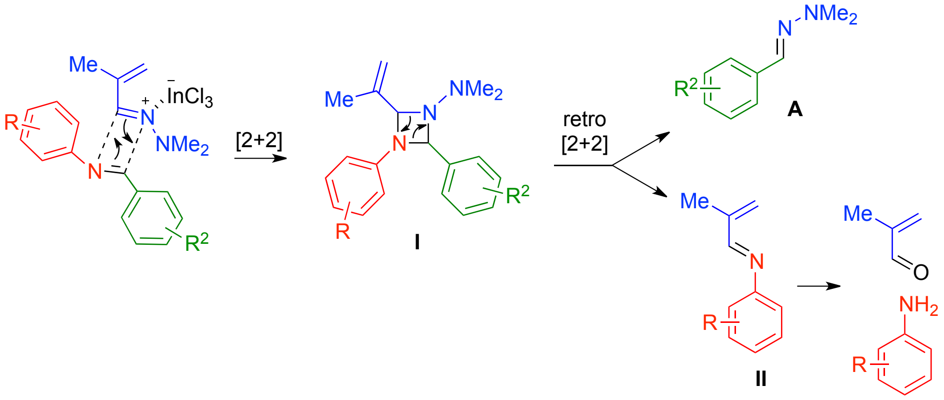


5s'



5s''

There are two main differences between the Povarov reaction involving the α-ketoimines and the previous reaction employing arylimines derived from aromatic aldehydes. The first one is the absence of secondary products often observed in the reactions starting from *N*-arylimines. The first of these side reactions is a transimination process that leads to the isolation of variable amounts of benzaldehyde *N*,*N*-dimethylhydrazone derivatives[60] **A** as side products. Based on previous mechanistic proposals for the few known transimination reactions of imines, which are based on [2+2] cyclization-retrocyclization processes,[61] the mechanism summarized in Scheme 3.7 may be proposed. An initial [2+2] cycloadition would afford the diazetidine cycloadduct **I**, and a subsequent retro [2+2] fragmentation would give the observed transimination product **A** and **II**. The unstable[62] *N*-aryl derivative of methacrolein **II** would be hydrolysed into the corresponding aniline and methacrolein dimethylhydrazone, which was not detected due to its volatility.



Scheme 3.7.

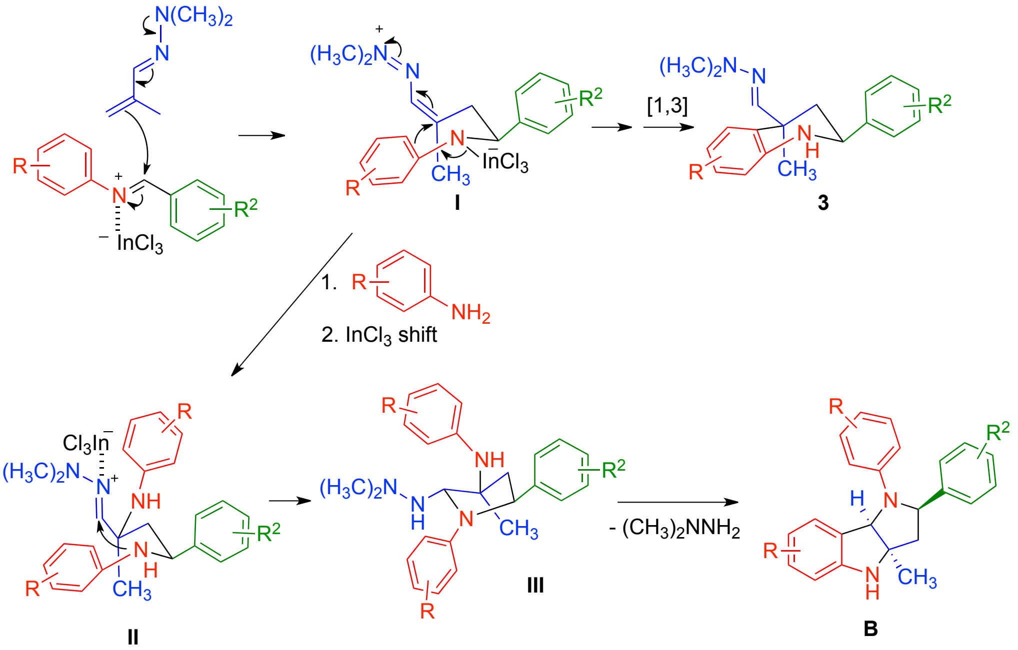
A second type of side products are the hexahydropyrrolo[3,2-*b*]indole derivatives **B**, which come from addition of a molecule of aniline (presumably arising from the previous mechanism), followed by shift of the indium catalyst to the hydrazone nitrogen and a second cyclization, with concomitant elimination of dimethylhydrazine (Scheme 3.8).

---

[60] Petroski R.J. *Synth. Commun.* **2006**, *36*, 1727.

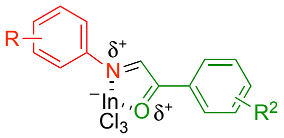
[61] (a) Babu G., Perumal P.T. *Tetrahedron*, **1999**, *55*, 4793. (b) Fernández R., Lassaleta J.M. *Synlett*, **2000**, 1228.

[62] Said S.B., Skarzewski J., MLochowski J. *Synthesis,* **1989**, 223.



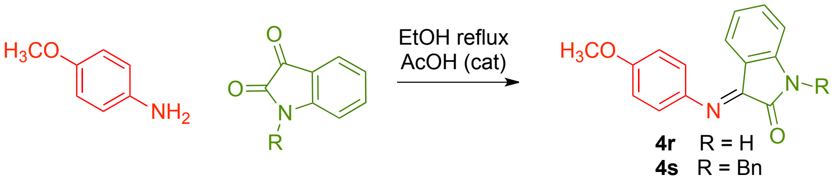
Scheme 3.8.

The different chemical behaviour in our case can be attributed to a higher affinity of the Lewis acid to the *α*-ketoimine moiety, due to chelation with nitrogen and oxygen. This would prevent the coordination with the hydrazine nitrogen required for the formation of cycloadduct **I** in Scheme 3.7 and the catalyst exchange between both nitrogens requiredto form intermediate **II** in Scheme 3.8.

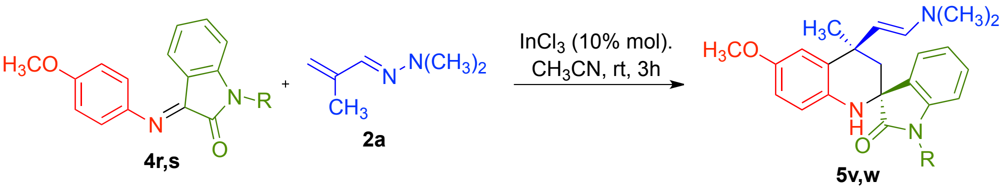


The second difference is the increased diastereoselectivity found for our reactions in comparison to the case of *α*-ketoimines. One possible explanation involves considering the *cis* isomer as the kinetic product and the *trans* isomer as the more stable thermodynamic product. This hypothesis is supported by the observation that at a higher temperature (40 °C) the *cis*:*trans* ratio of compound **5t** changed from 1:0 to 1:1. The higher stability of the *trans* isomer has been previously proposed in other Povarov reactions.[50] The expected higher electrophilicity of the imine end of the diene, associated to the presence of the electron-withdrawing acyl substituent, would favour the predominance of the kinetic reaction product.

In order to complete the study of the scope of the aza-vinylogous Povarov reaction with α-ketoimines, we also verified the possibility of reactions starting from isatin-derived imines **4r** and **4s.** The required starting imines were obtained in quantitative yields by refluxing the starting aniline and isatins in ethanol with a catalytic amount of acetic acid (Scheme 3.9), and the Povarov-type reaction under the usual conditions afforded spiro compounds **5v** and **5w**, as single diastereomers (Scheme 3.10 and Table 3.5).



Scheme 3.9.

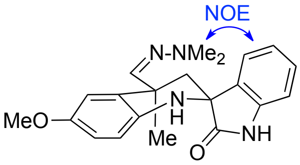


Scheme 3.10.

Table 3.5. Synthesis of spiro[indoline-3,2'- quinoline]derivatives

Cmpd	R	Yield (%)	dr
5v	H	51	1:0
5w	Bn	44	1:0

The relative configuration of compounds **5v** and **5w** was assigned based on the observation of a NOE effect between the dimethyl group of hydrazone and the 4' and 7' aromatic protons of isatin.



Although the structures are different, this result is in agreement with a literature precedent that unambiguously determined the configuration of a spiro Povarov product derived from isatin by X-ray diffraction analysis.[63]

---

[63] Shi F., Xing G.J., Zhu R.Y., Tan W., Tu S. *Org. Lett.*, **2013**, *15*, 128.

4 – Development and optimization of an enantioselective organocatalytic aza-vinylogous Povarov reaction

4.1 - Introduction

In this chapter we describe the development and optimization of an asymmetric version of our aza-vinylogous Povarov reaction involving α,β-unsaturated hydrazones as dienophiles and α-ketoimines as dienes to obtain highly substituted tetrahydroquinolines.

It is pertinent to note that, while α-dicarbonyl compounds are finding a role as substrates for asymmetric transformations,[64] α-ketoimines have received very little attention in asymmetric reactions, with ethyl glyoxylate being the only derivative used.[41,65] One example of the use of ketoimines as dienes has been reported by Tu and co-workers,[66] who investigated a Povarov reaction involving isatins as precursors to the imine substrate.

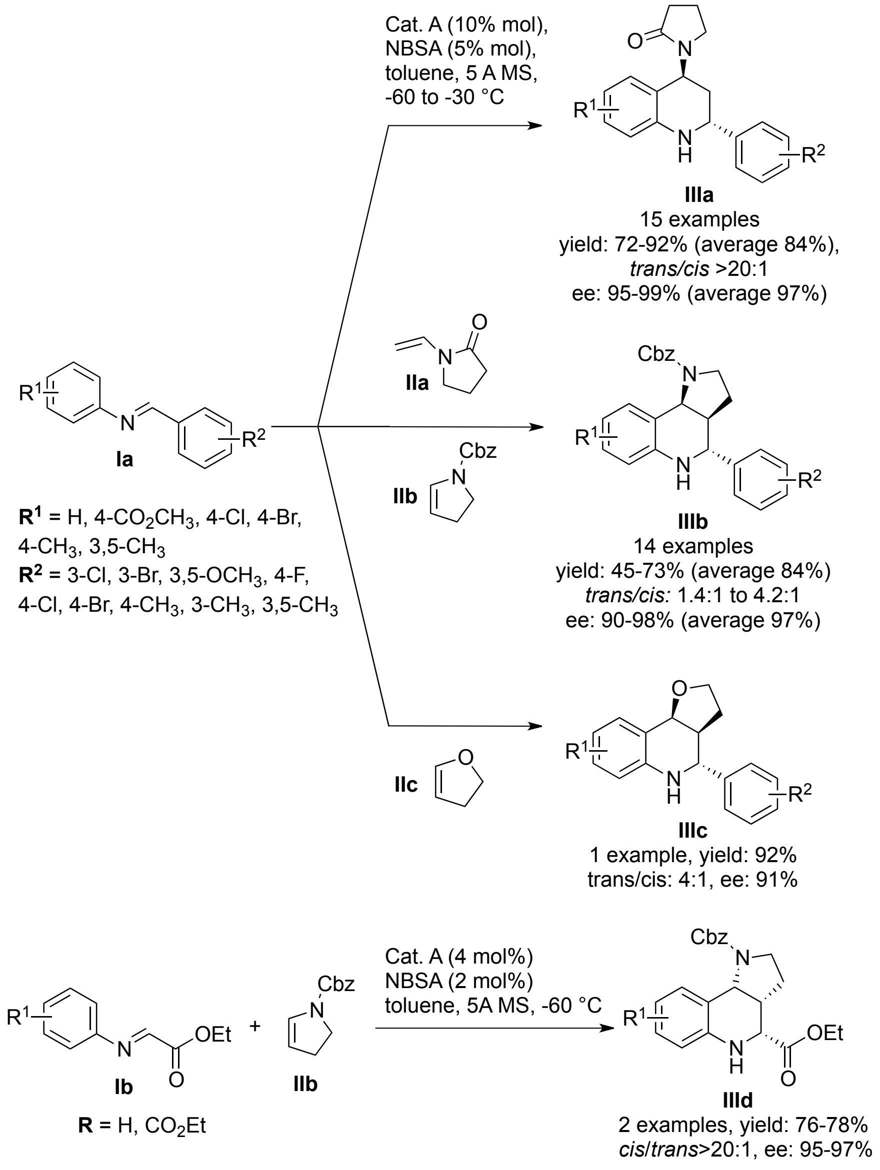
As discussed in Chapter 1, the cooperative catalytic system formed by a chiral urea and an achiral Brønsted acid developed by Jacobsen's group has the advantage over the better-studied chiral phosphoric acids of having less restrictions in terms of substrate structure. The scope of the Jacobsen´s work on tetrahydroquinoline and fused tetrahydroquinoline synthesis is summarized in Scheme 4.1. In this reaction, diastereoselection is quite variable and is highly dependant on the imine and the dienophile. The *exo* product is the main isomer observed with imines derived from aromatic aldehydes. The *endo* product was the main product obtained with imines derived from ethyl glyoxylate, although only two examples were examined.

---

[64] Raimondi W., Bonne D., Rodriguez J. *Chem. Commun.* **2102**, *48*, 6763.

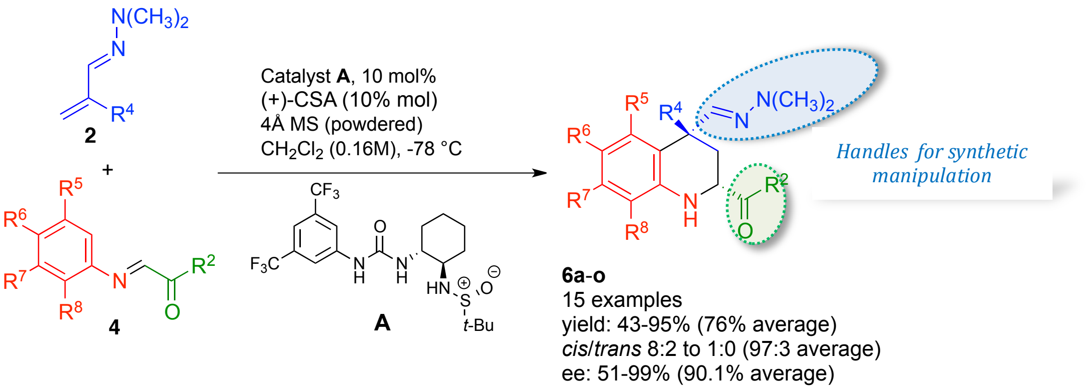
[65] Gerard B., O'Shea M.W., Donckele E., Kesavan S., Akella L.B., Xu H., Jacobsen E.N., Marcaurelle L.A. *ACS Comb. Sci.*, **2012**, *14*, 621.

[66] Shi F., Xing G.J., Zhu R.-Y.,Tan W., Tu S. *Org. Lett.*, **2013**, *15*, 128.



Scheme 4.1

In this Chapter, we describe our studies on the application of Jacobsen's catalyst to the aza-vinylogous Povarov reaction of α-ketoimines. This is a challenging reaction because it involves the use of a basic dienophile, which could interfere with the required protonation of the imine nitrogen, and indeed to our knowledge there is no precedent for asymmetric Povarov reactions in which both the diene and the dienophile bear basic nitrogen atoms. Furthermore, our method generates a quaternary stereocenter, which is an important synthetic goal and very unusual in Povarov chemistry.[29c,35] As another point of interest, the use of acyclic dienophiles is unprecedented in the presence of urea or thiourea-derived catalysts. Finally, our method has the advantage of using (+)-camphorsulfonic acid, (+)-CSA, an inexpensive and commercially available Brønsted acid, in contrast to the *o*-nitrobenzensulfonic acid (NBSA) used by Jacobsen and co-workers.

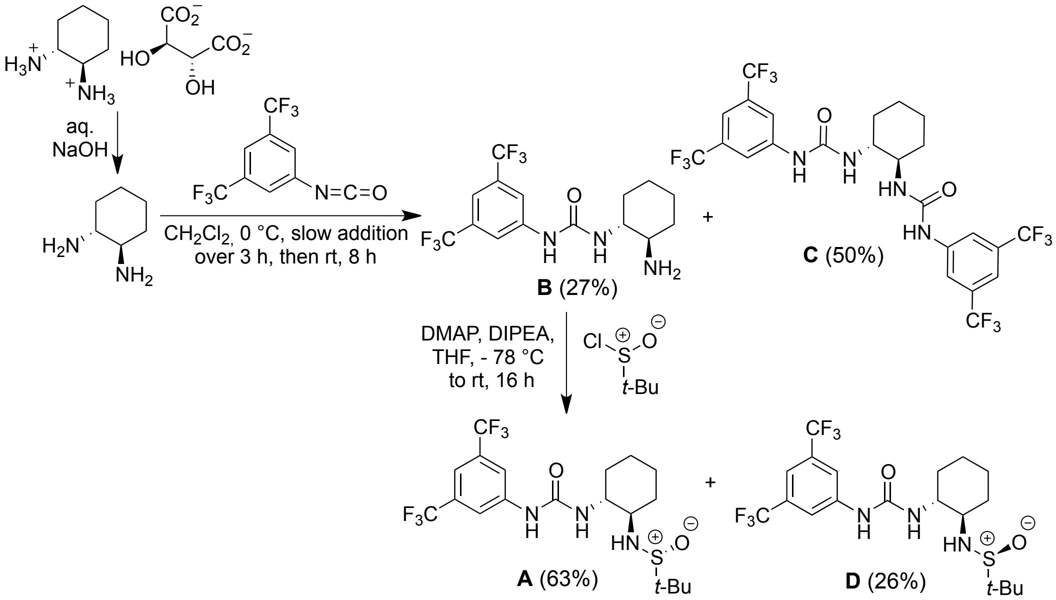


Scheme 4.1.

The joint use of α-ketoimines and α,β-unsaturated hydrazones leads to compounds with the possibility of further synthetic modification due to the presence of suitable functional groups at C-2 and C-4 with a *cis* relationship, potentially allowing an increase of the structural complexity *via* subsequent cyclization processes.

4.2 - Development of an enantioselective vinylogous Povarov reaction involving α,β-unsaturated hydrazones as dienophiles

The synthesis of Jacobsen's catalyst was performed according to a literature method,[67] as summarized in Scheme 4.2. Treatment of commercially available (*R*,*R*)-1,2-diammoniumcyclohexane (+)-tartrate with sodium hydroxide, to liberate the free base, followed by 3,5-bis(trifluoromethyl)phenyl isocyanate afforded urea derivative **B** (27%) together with the double addition product **C** (50%). Finally, treatment of **B** with (*R*)-*tert*-butylsulfinyl chloride furnished the target catalyst **A** in 63% yield, together with 26% of its diastereomer **D**.



Scheme 4.2.

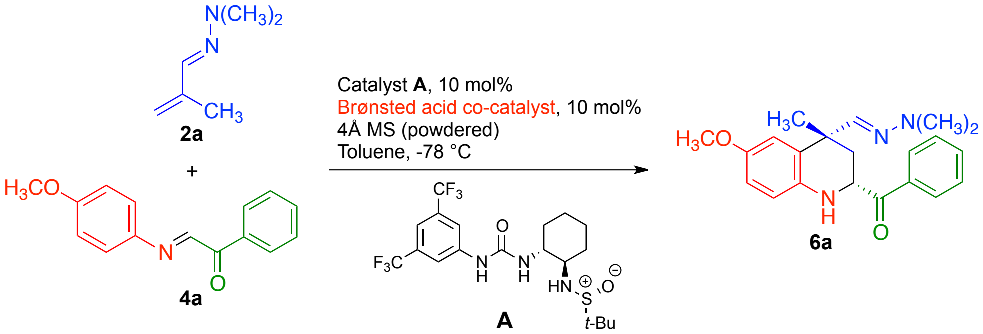
Using as a representative example the reaction leading to compound **6a** in the presence of Jacobsen's catalyst **A** and powdered 4Å molecular sieves to prevent imine hydrolysis by traces of water, we first analysed the performance of several Brønsted acids to choose the best co-catalyst for the reaction (Scheme 4.3 and Table 4.1). *o*-Nitrobenzensulfonic acid (NBSA), the co-catalyst considered optimal by Jacobsen, gave a poor result in our case (entry 1) and has the further disadvantage of not being commercially available.[68] Toluenesulfonic

---

[67] Xu H., Zhang H., Jacobsen, E.N. *Nat. Protoc.* **2014**, *9*, 1860.

[68] For the synthesis of NBSA, see the Experimental Section of this thesis.

and methanesulfonic acids gave similar results (entries 2 and 3). The first acid additive to give a good enantiomeric excess was triflic acid (entry 4), which was also associated to a much shorter reaction time, probably due to its higher acidity. The use of 10% of *S*(+)-camphorsulfonic (CSA) led to further improvements in yield, diastereo- and enantioselection, and was regarded as optimal in spite of the long reaction time (entry 5). Decreasing the load of (+)-CSA led to increased reaction times and a drop in diastereo- and enantioselectivity (entry 6), which was particularly noticeable when acid concentration was reduced to 2.5% (entry 7). Finally, the relevance of the configuration of the acid co-catalyst was investigated. As shown in entry 8, the similarity of the results obtained for *S*(+)- and *R*(-)-CSA (entries 5 and 8) allows concluding that it does not influence the catalytic system, potentially allowing the use of the catalyst in racemic form. The reaction was assumed to follow the same



Scheme 4.4.

Table 4.1. Brønsted acid optimization in the synthesis of ***6a***

Entry	Brønsted acid (mol%)	t (h)	Yield (%)	dr (*cis*:*trans*)	ee *cis* (%)
1	NBSA (10%)	72	59	75 : 25	33
2	TsOH (10%)	72	63	78 : 22	64
3	MsOH (10%)	72	80	78 : 22	49
4	TfOH (10%)	5	70	87 : 13	90
5	(+)-CSA (10%)	48	96	92 : 08	95
6	(+)-CSA (5%)	72	67	86 : 14	90
7	(+)-CSA (2.5%)	72	63	75 : 25	28
8	(-)-CSA (10%)	48	93	90 : 10	93

stereochemical course described by Jacobsen for the standard Povarov reaction (see below) and therefore the absolute configuration of **6a** to be (2*R*,4*R*).

We next examined briefly the possibility to vary the chiral urea catalyst, comparing the results obtained in the presence Jacobsen's sulfamidourea **A**, its precursor **B**, the side product **C**, diastereomer **D** obtained along **A**, and Takemoto's catalyst **E** (Figure 4.1). While compounds **B** and **E** did not promote the reaction, presumably because the presence of a basic amino group prevented imine protonation, the symmetric derivative **C** and diastereomer **D** afforded product **6a**, albeit with modest diastereoselection and without any significant enantioinduction. Therefore, catalyst **A** was maintained as the optimal choice.

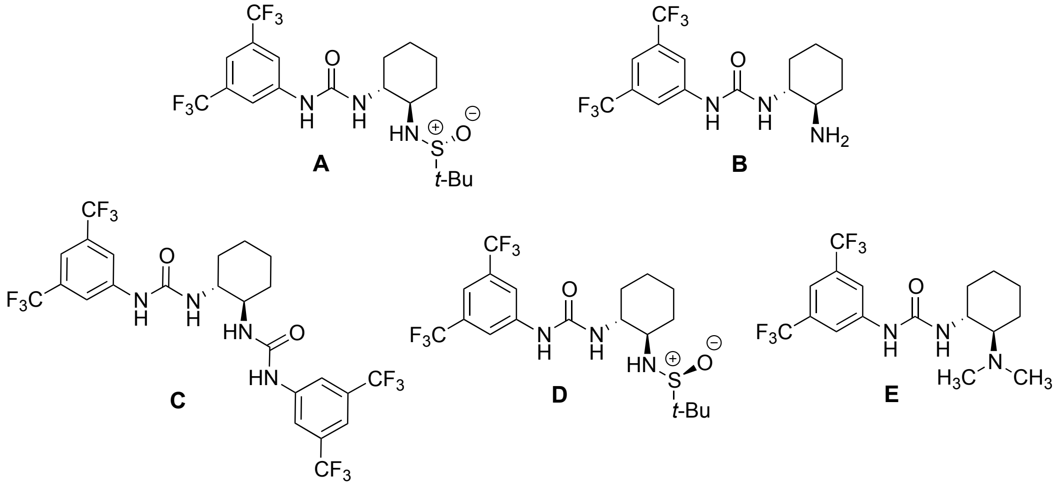
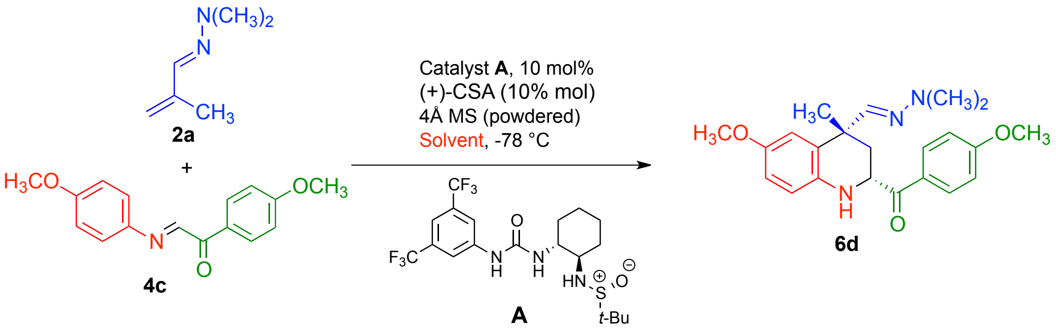


Figure 4.1.

Table 4.2. Urea catalyst optimization

Catalyst	t (h)	Yield of 6a (%)	dr (*cis*:*trans*)	ee *cis* (%)
A	4	96	92:08	95
B	3	0	NA	NA
C	3	83	72:28	0
D	48	57	82:18	7.5
E	4	0	NA	NA

For further optimization studies, we chose the reaction starting from imine **4c** (Scheme 4.4), which only gave a modest 63% enantiomeric excess under the conditions described above. As shown in Table 4.3, we first analysed the role of the reaction medium. A change from toluene, an apolar aprotic solvent (entry 1), to polar aprotic solvents such as acetonitrile and tetrahydrofuran (entries 2 and 3) led to a loss of enantioselectivity, presumably due to a reduced ability to generate the complex H-bond network necessary for good enantio-induction. In entry 4 we report the yield (71%), diastereo- (66:24 – *cis*:*trans*) and enantioselectivity (75% ee) of the Povarov reaction in chloroform as solvent; interestingly, when chloroform was replaced by dichloromethane (entry 5) the yield improved to 78% and a rise in diastereo- (85:15 - *cis*:*trans*) and enantioselectivity (85% ee) was also observed. In this case we also analysed the effect of lowering the amount of catalyst (entries 6 and 7), but



Scheme 4.4.

Table 4.3. Solvent and concentration optimization

entry	Brønsted acid (mol %)	solvent	M	t (h)	yield (%)	dr (*cis*:*trans*)	ee *cis* (%)
1	(+)-CSA (10%)	Toluene	0.08	72	81	84:16	63
2	(+)-CSA (10%)	MeCN	0.08	20	76	97:03	39
3	(+)-CSA (10%)	THF	0.08	20	66	80:20	45
4	(+)-CSA (10%)	$CHCl_3$	0.08	20	71	66:24	75
5	(+)-CSA (10%)	CH_2Cl_2	0.08	20	78	85:15	85
6	(+)-CSA (5%)	CH_2Cl_2	0.08	26	63	86:14	77
7	(+)-CSA (2.5%)	CH_2Cl_2	0.08	48	59	58:42	69
8	(+)-CSA (10%)	CH_2Cl_2	0.16	3	95	98:02	94
9	(+)-CSA (10%) (no chiral urea)	CH_2Cl_2	0.16	4	52	80:20	31[a]

[a] In the absence of the urea catalyst, the major product was the opposite (2*S*,4*S*) enantiomer, presumably formed by a mechanism different to the one proposed in Scheme 4.6.

the results obtained confirmed 10 mol% as the best option. Finally, while all the reactions described so far were performed with at 0.08 M concentration of substrates, a doubling in concentration to 0.16 M (entry 8) allow to reach a very good yield (95%), together with very good diastereo- (98:02 −*cis*:*trans*) and enantioselectivities (94%). Importantly from a practical point of view, the reaction time was drastically reduced, from 20 h to 3 h. It is pertinent to mention at this point that the absence of undesired products arising from transamination reactions has to be counted as a relevant advantage of the chiral urea-based method, since all previous attempts carried out in our group to achieve stereocontrol in aza-vinylogous Povarov reactions starting from SAMP/RAMP-derived chiral hydrazones as dienes or in the presence of chiral phosphonic acids as Brønsted acid catalysts had been plagued by this problem.[69]

Based on this optimization, we studied the scope of the reaction with a wide range of α-ketoimines **4** and α,β-unsaturated hydrazones **2a** and **b**, as shown in Scheme 4.4. The reaction afforded polysubstitued tetrahydroquinolines **6** in good to excellent yields (56-95%, 76% average), diastereo- (8:2 to 1:0 – *cis*:*trans*, average 97:3) and enantioselectivities (51-99%, 90.1% average). During the process, two new C-C bonds are formed and two new stereocenters are generated, one of which is quaternary (C-4). Compounds **6** thus obtained are endowed with an hydrazone moiety at C-4 and an acyl group at C-2, allowing further transformations.

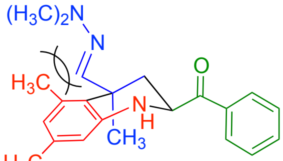
The R^2 substituent is usually a phenyl group, either unsubstituted (entries 1, 2, 5, 12, 13 and 15), or bearing electron-withdrawing (entries 3 and 14) or electron-releasing (entries 4 and 6) groups. Moreover, heteroaryl moieties are also tolerated, as shown by the presence of 2-furyl and 2-thienyl units in entries 8-10. The presence of an ester group at C-2 was also possible (entries 7 and 11). The R^4 substituent is usually a methyl group, but a more hindered ethyl group is also possible (entries 2, 8 and 9).

In the starting aniline, a substituent in every position of the ring is generally possible without loss in yield or stereoselectivity. The only exception was associated to the presence of a group at C-8 (entry 5), which did not affect the diastereoselection (100:0) but decreased the yield (57%) and enantioselectivity (51%), maybe due to a steric hindrance that hampers the formation of the chiral intermediate complex able to induce enantioselection. A group at C-5 led to diminished *cis*-*trans* diastereoselectivity (77:23, entry 13), which can be ascribed

---

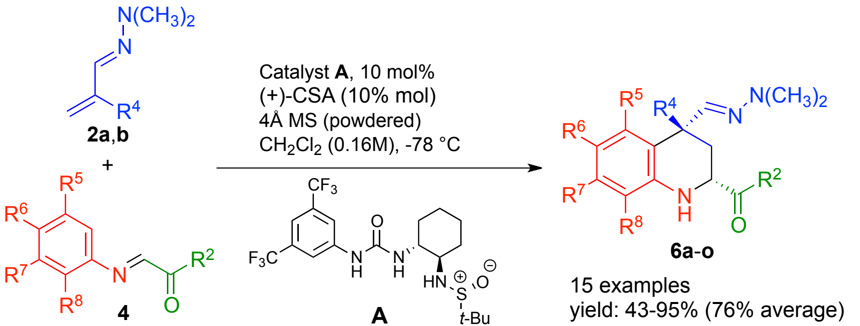
[69] Diana K. Becerra, unpublished work.

to repulsive interactions between the C-5 and C-4_{eq} dimethylhydrazonomethyl substituents in the *cis* structure.



6m

Is important to note that the conditions of the asymmetric version of the reaction represent an improvement in yields (56-95% with an average of 76%) over the racemic version (30-95% with an average of 69%) and especially an excellent diastereoselectivity, which was complete in many cases while the racemic version mostly shows a 8:2 – *cis*:*trans* selection.



15 examples
yield: 43-95% (76% average)
cis/*trans* 8:2 to 1:0 (97:3 average)
ee: 51-99% (90.1% average)

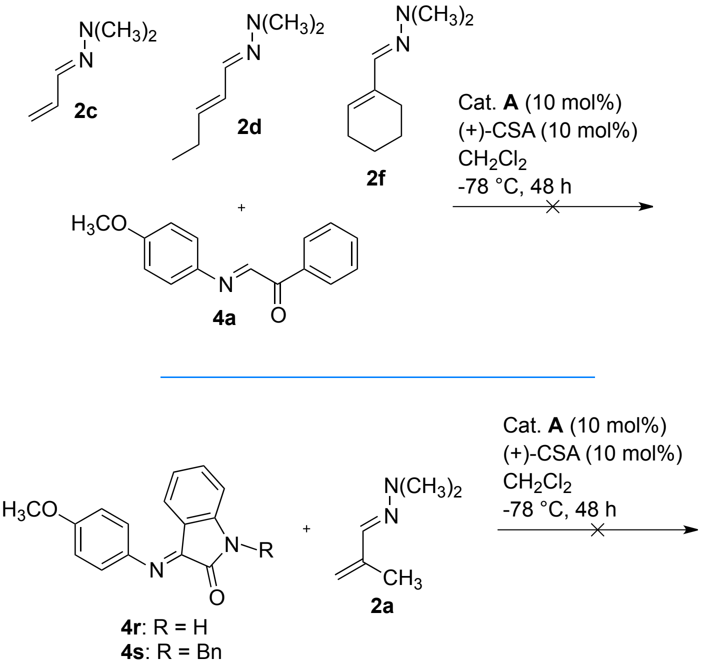
Scheme 4.4.

Table 4.4. Scope of the asymmetric aza-vinylogous Povarov reaction of α-ketoimines

Entry	Imine	Cmp	R^2	R^4	R^5	R^6	R^7	R^8	t (h)	yield (%)	dr (*cis*: *trans*) [a]	ee *cis* (%) [b]
1	**4a**	**6a**	C_6H_5	CH_3	H	OCH_3	H	H	5	75	98:02	95
2	**4a**	**6b**	C_6H_5	CH_2CH_3	H	OCH_3	H	H	3	82	100:0	97
3	**4b**	**6c**	4-FC_6H_4	CH_3	H	OCH_3	H	H	5	95	96:04	90
4	**4c**	**6d**	4-$OCH_3C_6H_4$	CH_3	H	OCH_3	H	H	5	95	100:0	95
5	**4d**	**6e**	C_6H_5	CH_3	H	CH_3	H	CH_3	5	57	100:0	51
6	**4h**	**6f**	4-$OCH_3C_6H_4$	CH_3	H	CH_3	H	H	4	68	96:04	94
7	**4i**	**6g**	OCH_2CH_3	CH_3	H	OCH_3	H	H	4	56	100:0	83
8	**4k**	**6h**	2-furyl	CH_2CH_3	H	OCH_3	H	H	3	93	97:03	94
9	**4l**	**6i**	2-thienyl	CH_2CH_3	H	OCH_3	H	H	3	91	96:04	97
10	**4l**	**6j**	2-thienyl	CH_3	H	OCH_3	H	H	3	93	100:0	94
11	**4m**	**6k**	OCH_2CH_3	CH_3	H	CH_3	H	H	3	52	100:0	91
12	**4n**	**6l**	C_6H_5	CH_3	H	CH_3	H	H	3	95	97:03	99
13	**4o**	**6m**	C_6H_5	CH_3	CH_3	H	CH_3	H	5	72	77:23	90
14	**4p**	**6n**	4-FC_6H_4	CH_3	H	CH_3	H	H	3	70	97:3	85
15	**4q**	**6o**	C_6H_5	CH_3	H	H	H	H	5	43	100:0	97

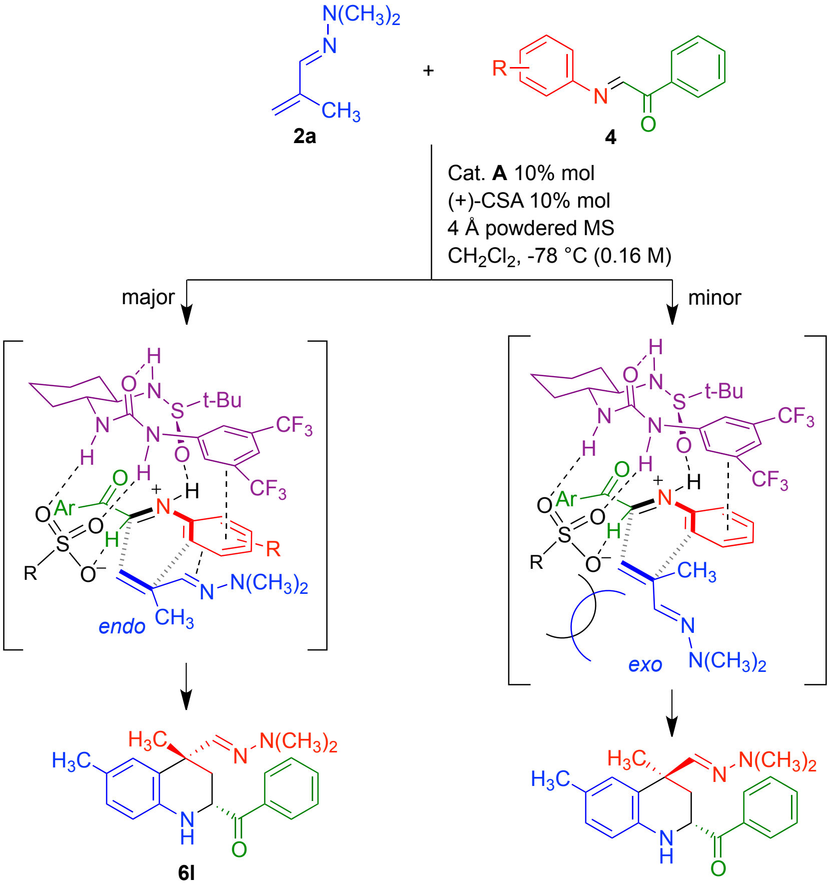
[a] Determined by ^{1}H-NMR in the crude reaction mixtures. [b] Determined by HPLC, using an analytical ULTRON ES-OVM chiral column. This column has ovomucoid, chemically bonded to a silica support, as its chiral-recognition element.

We next attempted to introduce further structural diversity at C-3 and C-4 by use of hydrazones **2c**, **2d** and **2f** but they failed to react with compound **4a** under our standard conditions. These results show, on one hand, the importance of the electron-releasing effect of the methyl substituent present in compound **2a** for the dienophile to have a sufficient electron density and, on the other, the hindrance caused by the presence of substituents at the nucleophilic end of the dienophile. Similarly, an attempt to prepare spiro tetrahydroquinoline derivatives by reaction between isatin-derived ketoimines **4r** and **4s** and hydrazone **2a** was unsuccessful (Scheme 4.5).



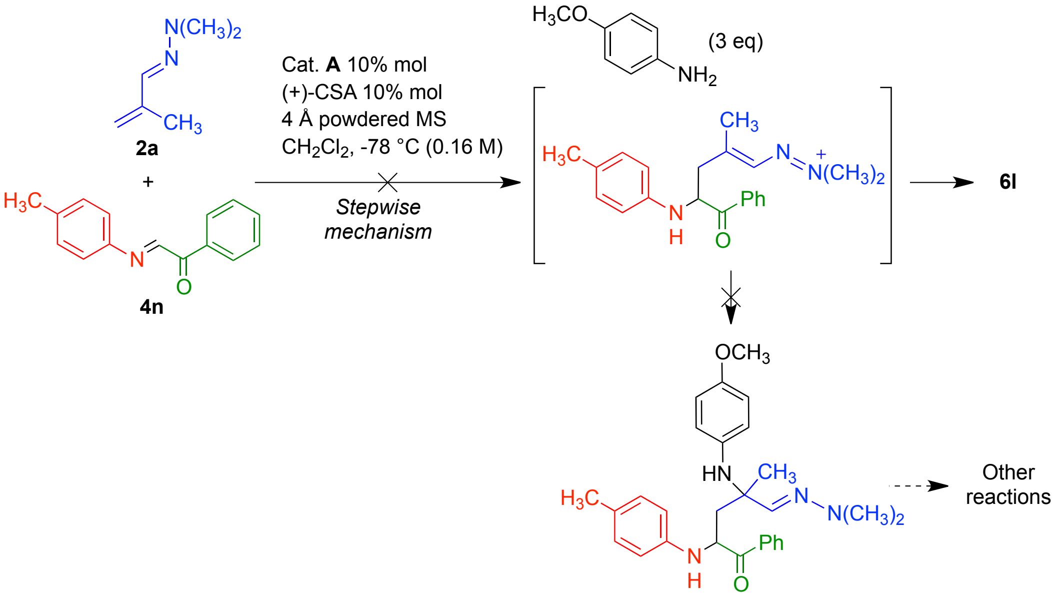
Scheme 4.5.

Assuming a concerted pathway and a behaviour for the catalytic system similar to the one described by Jacobsen, the mechanism shown in Scheme 4.6 can be proposed. The high selectivity in favour of the *cis* arrangement for the 2-acyl and 4-hydrazonomethyl substituents arises from an *endo* approach of the diene, which is presumably favoured by π-π interactions with the aromatic ring belonging to the aniline fragment (diene in the *s-trans* conformation) or dipole-dipole interactions between the hydrazone and acyl moieties (diene in the *s-cis* conformation). The higher diastereoselectivity of the reactions promoted by CSA can be explained by repulsive interactions between the bulky camphenyl substituent and the hydrazone substituent in the transition state leading to the *trans* product. The importance of the interaction between the sulfonic group of the Brønsted acid promoter and the imine proton is confirmed by the failure of the reaction starting from isatin derivarives **4r** and **4s**, which had worked well in the racemic case.



Scheme 4.6.

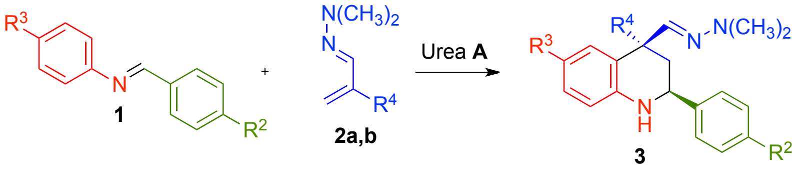
In order to verify the concerted nature of the mechanism, we performed one experiment in the presence of a nucleophile in an attempt to trap the putative zwitterionic intermediate of the stepwise mechanism. While we had previously employed ethanol for this purpose, in this case we selected *p*-anisidine for a better compatibility with the reaction environment. When the reaction was performed under our standard conditions but in the presence of 3 equivalents of *p*-anisidine, the only reaction product was tetrahydroquinoline **6l**, albeit in low yield, and we did not observe the formation of compound **I** or its derivatives (Scheme 4.7).



Scheme 4.7.

We next sought to extend our conditions to the asymmetric synthesis of C-4 functionalized 2-aryl-1,2,3,4-tetrahydroquinolines. To this end, we studied the reaction between compounds **2a**,**b** and several imines **1**, with the results shown in Table 4.5. The products thus obtained (compounds **x**) had again a *cis* relationship between the 2-aryl and 4-dimethylhydrazonomethyl substituents, which must arise from an *endo* orientation during the cycloaddition reaction. This result proves once again the key role of the hydrazone substituent in stabilizing the *endo* transition state, since Jacobsen observed that imines **1**, when reacted with acyclic dienophiles such as 1-vinylpyrrolidin-2-one, give *trans* 2,4-disubstituted tetrahydroquinolines, *via* an *exo* approach of both reagents.

Very long reaction times were required, even at higher temperatures and in the presence of superacids such as triflic acid. This observation underscores the importance of the electron-withdrawing effect of the 2-acyl substituent in accelerating the asymmetric reaction. Comparison of the results obtained with compounds **1** with those from α-ketoimines **4** was possible in some cases (*e.g.* entry 2 in Table 4.4 with entries 3 and 4 in Table 4.5; entry 4 in Table 4.4 with entry 5 in Table 4.5). This comparison shows a better enantiomeric excess for the latter reactions which, as previously mentioned, can be attributed to the fact that the 2-acyl substituent may provide additional interactions with the dienophile in the *endo* transition state, leading to a tighter ternary complex and hence to improved stereochemical results. Furthermore, the low rates of the reactions starting from imines **1** may allow a "racemic" pathway, catalysed solely by the Brønsted acid, to compete with the asymmetric one.



Scheme 4.8.

*Table 4.4. Asymmetric aza-vinylogous Povarov reaction of imines **1***

Entry	**R^2**	**R^3**	**R^4**	**Solvent**	**Acid**	**t (d)**	**T (°C)**	**M**	**Yield (%)**	**ee (%)**
1	H	OCH_3	CH_3	Toluene	(+)CSA(10%)	7	-78 °C	0.08	18[a]	-
2	H	OCH_3	CH_3	$CHCl_3$	(+)CSA (20%)	6	-40 °C	0.16	33	32
3	H	OCH_3	CH_3	CH_2Cl_2	(+)CSA (10%)	7	-78 °C	0.08	70	44
4	H	OCH_3	CH_3	CH_2Cl_2	(+)CSA (20%)	4	-20 °C	0.16	72	79
5	OCH_3	OCH_3	CH_3	CH_2Cl_2	(+)CSA (20%)	4	-20 °C	0.16	75	62
6	OCH_3	OCH_3	CH_3	CH_2Cl_2	TsOH (20%)	4	-40 °C	0.16	35	80
7	H	OCH_3	CH_3	CH_2Cl_2	TfOH (10%)	4	-40 °C	0.16	68	91
8	H	CH_3	CH_3	CH_2Cl_2	TfOH (10%)	4	-40 °C	0.16	40	99
9	OCH_3	OCH_3	CH_3	CH_2Cl_2	TfOH (10%)	4	-40 °C	0.16	86	37
10	H	OCH_3	CH_2CH_3	CH_2Cl_2	TfOH (10%)	4	-40 °C	0.16	72	68
11	Cl	OCH_3	CH_3	CH_2Cl_2	TfOH (10%)	4	-40 °C	0.16	66	72
12	OCH_3	OCH_3	CH_3	CH_2Cl_2	TfOH (20%)	4	-40 °C	0.16	78	47

[a] In this case the major reaction is a transimination process.

5 – Synthesis of 2-acyl and 2-arylquinolines based on the aza-vinylogous Povarov reaction

5.1 - Introduction

In this chapter we will describe a new and efficient synthetic protocol to obtain polysubstituted quinolines.[70]

Quinoline is one of the most important heterocycles, present in a variety of natural products[71] and pharmaceutically relevant compounds with wide range of activities[72], including antimalarial,[73] antitubercular,[74] anti-HIV,[75] anticancer[76] and anti-inflammatory[77] properties. Furthermore, quinoline derivatives also have important applications as agrochemicals, metal-coordinating moieties in new materials such as OLED phosphorescent compounds and structural fragments of ligands useful in organocatalysis[78] (Figure 5.1).

---

[70] A part of this work has been published: Bianchini G., Ribelles P., Becerra D., Ramos M. T., Menéndez J. C. *Org. Chem. Front.*, **2016**, *3*, 412–422.

[71] Michael J.P., *Nat. Prod. Rep.*, **2008**, *25*, 166.

[72] For representative reviews of the importance of quinolines in drug discovery, see: (a) Solomon V.R., Lee H. *Curr. Med. Chem.*, **2011**, *18*, 1488. (b) Marella A., Tanwar O.P., Saha R., Ali M.R., Srivastava S., Akhter M., Shaquiquzzaman M., Alam M.M. *Saudi Pharm. J.*, **2013**, *21*, 1; (c) Pati B., Banerjee S. *J. PharmaSciTech*, **2014**, *3*, 59.

[73] Andrews S., Burgess S.J., Skaalrud D. *J. Med. Chem.*, **2010**, *53*, 916.

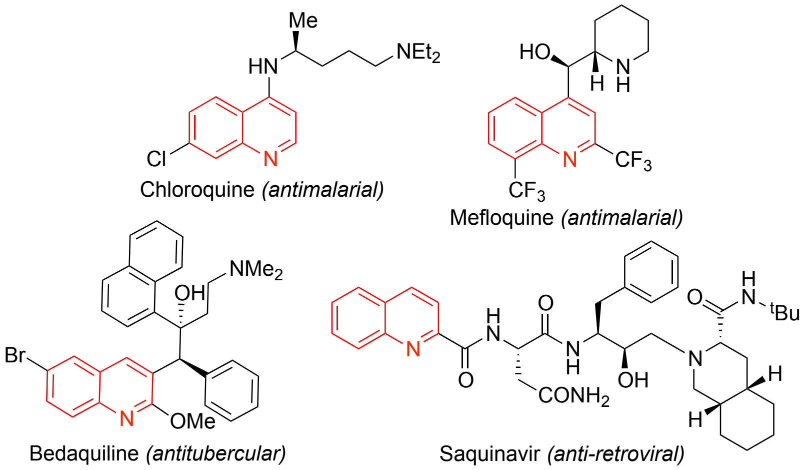
[74] Diacon A.H., et al. *N. Engl. J. Med.,* **2009**, *360*, 2397.

[75] Strekowski L., Mokrosz J.L., Honkan V.A., Czarny A., Cegla M.T., Patterson S.E., *et al. J. Med. Chem.*, **1991**, *34*, 1739.

[76] Bax B.D., Chan P.F., Eggleston D.S., Fosberry A., Gentry D.R., Gorrec F., Giordano I., Hann M.M., Hennessy A., Hibbs M., Huang J., Jones E., Jones J., Brown K.K., Lewis C.J., May E.W., Saunders M.R., Singh O., Spitzfaden C.E., Shen C., Shillings A., Theobald A.J., Wohlkonig A., Pearson N.D., Gwynn M.N. *Nature*, **2010**, *466*, 935.

[77] Chen Y.L., Zhao Y.L., Lu C.M., Tzeng C.C., Wang J.P. *Bioorg. Med. Chem.*, **2006**, *14*, 4373.

[78] (a) Palacio C., Connon S.J. *Org. Lett.*, **2011**, *13*, 1298. (b) Kim J.I., Shin I., Kim H., Lee J. *J. Am. Chem. Soc.*, **2003**, *46*, 1242.



Chloroquine *(antimalarial)*
Mefloquine *(antimalarial)*
Bedaquiline *(antitubercular)*
Saquinavir *(anti-retroviral)*

Figure 5.1: Some representative quinoline-based compounds endowed with relevant pharmacological activity.

Due to its relevance, the synthesis of the quinoline scaffold has been investigated for well over a century.[79] The oldest method is the Skraup[80] reaction discovered in 1880, in which aniline and glycerol are refluxed with an oxidant in concentrated sulfuric acid for several hours, allowing the preparation of 2,3,4-unsubstituted quinolines. The Doebner—Von Miller[81] variation, characterized by the use of α,β-unsaturated aldehydes or ketones in acidic conditions to afford 2,4-disubstituted quinolines, was introduced in 1881. Later in 1887 the Doebner[82] reaction was discovered, furnishing 2-substituted quinoline-4-carboxylic acid derivatives from aniline, aldehydes and pyruvic acid. In the same year another protocol to synthetize quinolines was discovered, known nowadays as Conrad-Limpach reaction,[83] in which anilines and *β*-ketoesters were refluxed in the presence of acid to furnish 2,3-disubstituted 4-hydroxyquinolines. Combes,[84] in 1883, reported that the reaction between unsubstituted anilines and β-diketones in acidic conditions yielded 2,4-disubstituted quinolines (Scheme 5.1). In addition, the Friedländer reaction,[85] which was reported in 1882,

---

[79] For a review of the traditional quinoline syntheses, see: Jones G. *Comprehensive Heterocyclic Chemistry II, ed.* Katritzky A., Rees C.W., Scriven E.F.V. Pergamon Press, **1996**, chapter 5.05, *5*, 167.

[80] Skraup Z.H. *Ber. Dtsch. Chem. Ges.*, **1880**, *13*, 2086.

[81] Doebner O., Miller W. *Ber. Dtsch. Chem. Ges.*, **1881**, *14*, 2812.

[82] Doebner O. *Ann.*, **1887**, 242.

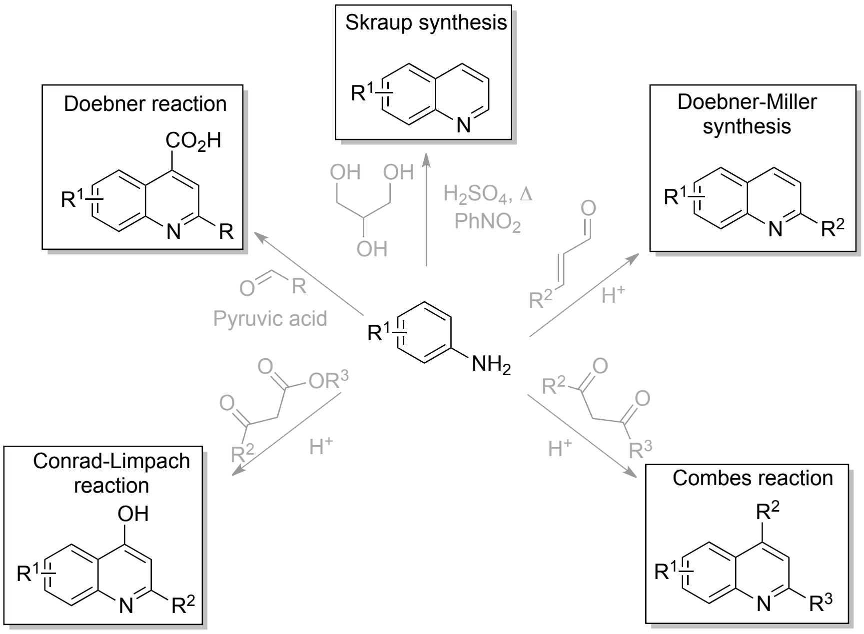
[83] Conrad M. Limpach L. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 944.

[84] Combes A. *Bull. Soc. Chim. Fr.*, **1883**, *49*, 89.

[85] (a) Friedländer P. *Ber. Dtsch. Chem. Ges.*, **1882**, *15*, 2572; (b) For a recent review, see: Marco-Contelles J.L., Pérez- Mayoral E., Samadi A., Carreiras M.C., Soriano E. *Chem. Rev.*, **2009**, *109*, 2652.

involves the treatment of 2-aminobenzaldehydes with carbonyl compounds to obtain 2,3-disubstituted quinolines.

Although these classical methods could appear as simple, efficient and versatile, they often suffer from limitations, including the requirement for large excesses of certain reagents, the use of strong acids as promoters, harsh reaction conditions or complex experimental protocols, besides poor regioselectivities in some cases (*e.g.* the Friedländer reaction from unsymmetrical ketones).



Scheme 5.1.

In recent years, many new approaches have been discovered,[86] most of which are based on transition metal-catalyzed reactions,[87] but the use of expensive and often toxic metal

---

[86] For reviews of recent methods for quinoline synthesis, see: (a) Ramann G.A., Cowen B.J. *Molecules*, **2016**, *21*, 986. (b) Kouznetsov V., Vargas Méndez L.Y., Meléndez Gómez C.M. *Curr. Org. Chem.*, **2005**, *9*, 141. (c) Madapa S., Tusi Z., Batra S. *Curr. Org. Chem.*, **2008**, *12*, 1116. (d) Prajapati S.M., Patel K.D., Vekariya R.H., Panchal S.N., Patel H.D. *RSC Adv.*, **2014**, *4*, 24463.

[87] (a) Li H., Xu X., Yang J., Xie X., Huang H., Li Y. *Tetrahedron Lett.*, **2011**, *52*, 530. (b) Li H., Wang C., Huang H., Xu X., Li Y. *Tetrahedron Lett.*, **2011**, *52*, 1108. (c) Cai S., Zeng J., Bai Y., Liu X. *J. Org. Chem.*, **2012**, *77*, 801. (d) Kuzmina O.M., Steib A.K., Flubacher D., Knochel P. *Org. Lett.*, **2012**, *14*, 4818. (e) Neo M.L., Dhanorkar R.J. *Tetrahedron*, **2015**, *71*, 338. (f) Kong L., Zhou Y., Huang H., Yang Y., Liu Y., Li Y. *J. Org. Chem.*, **2015**, *80*, 1275. (g) Zhou J., Wu G., Zhang M., Jie X., Su W. *Chem. – Eur. J.*, **2012**, *18*, 8032. (h) Zhang X., B. Liu, X. Shu, Y. Gao, H. Lv and J. Zhu, *J. Org. Chem.*, **2012**, *77*, 501. (i) Ji X., Huang H., Li Y., Chen H., Jiang H. *Angew. Chem., Int. Ed.*, **2012**, *51*, 7292.

catalysts can be viewed as a disadvantage. Furthermore, neither the classical nor the modern methods have sufficient generality to provide access to certain types of quinoline derivatives.

In this context, the development of mild and efficient routes to previously inaccessible quinoline frameworks, preferably avoiding the use of transition metals, is still a useful and challenging task. One relevant case is that of quinolines bearing a carbonyl group at C-2, which comprises compounds with a variety of pharmacological activities,[88] but whose preparation with the currently available methodologies either requires multi-step sequences[88d,89] or is low-yielding and/or very restricted in scope, being limited to the case $R^2 = CO_2Et$ or to very few examples (in some cases, a single one) of 2-acyl substituents.[90]

The Povarov reaction, which was briefly reviewed in Chapter 1, is one of the main methods for the synthesis of tetrahydroquinolines. It can be used for the preparation of quinolines by coupling the cycloaddition to an oxidation step,[91] specially when acetylenes are used as dienophiles. However, neither these synthetic procedures nor some more general, transition metal-catalyzed Povarov-like reactions,[87h,i] have been employed for the preparation of quinolines endowed with a C-2 acyl substituent other than an ester group and, furthermore, the use of acetylene dienophiles strategy is restricted in most cases to the synthesis of quinolines with a 4-aryl substituent.[92]

We describe in this chapter general synthetic protocols for the preparation of 2-aryl and 2-acylquinolines from tetrahydroquinolines obtained *via* the aza-vinylogous Povarov reaction, using two alternative strategies summarized in Scheme 5.2.

---

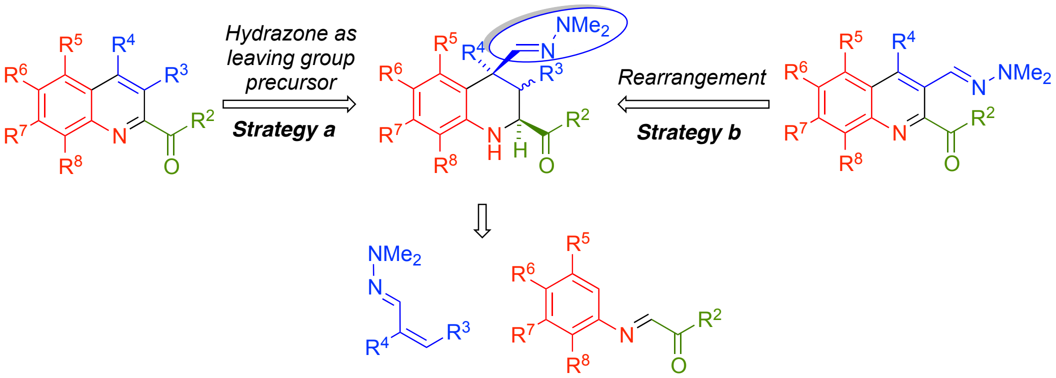
[88] (a) Zhu Y.F., Wang X.C., Connors P., Wilcoxen K., Gao Y.H., Gross R., Strack N., Gross T., McCarthy J.R., Xie Q., Ling N. Chen C. *Bioorg. Med. Chem.*, **2003**, *13*, 1931. (b) Manfredini S., Vertuani S., Pavan B., Vitali F., Scaglianti M., Bortolotti F., Biondi C., Scatturin A., Dalpiaz P.P. *Bioorg. Med. Chem.*, **2004**, *12*, 5453. (c) Horchler C.L., McCauley J.P., Hall J.E., Snyder D.H.A., Moore W.C., Hudzik T.J. Chapdelaine M.J. *Bioorg. Med. Chem.*, **2007**, *15*, 939. (d) Reux B., Nevalainen T., Raitio K.H., Koskinen A.M.P. *Bioorg. Med. Chem.*, **2009**, *17*, 444. (e) McNulty J., Vemula R., Bordón C., Yolke R., Jones-Brando L. *Org. Biomol. Chem.*, **2014**, *12*, 255.

[89] Mao Z., Qu H., Zhao Y., Lin X. *Chem. Commun.*, **2012**, *48*, 9927.

[90] (a) Vicente-García E., Catti F., Ramo R., Lavilla R. *Org. Lett.*, **2010**, *12*, 860. (b) Richter H., Mancheño O.G. *Org. Lett.*, **2011**, *13*, 6066. For two additional reports, describing a single example of the synthesis of 2-alkoxycarbonylquinolines via Friedländer reactions, see: (c) McNaughton B.R., Miller B.L. *Org. Lett.*, **2003**, *5*, 4257. (d) Chen Y., Huang J., Hwang T.L., Li T.J., Cui S., Chan J., Bio M. *Tetrahedron Lett.*, **2012**, *53*, 3237.

[91] For a representative example, see: Sridharan V., Avendaño C., Menéndez J.C. *Tetrahedron*, **2009**, *65*, 2087.

[92] (a) Huang H., Jiang H., Chen K., Liu H. *J. Org. Chem.*, **2009**, *74*, 5476. (b) Li X., Mao Z., Wang Y., Chen W., Lin X. *Tetrahedron*, **2011**, *67*, 3858.



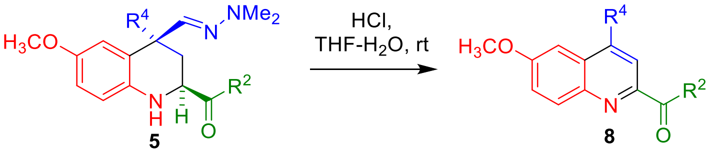
Scheme 5.2.

We have previously described that the indium trichloride-catalyzed reaction between aromatic α-acylimines and α,β-unsaturated *N,N*-dimethylhydrazones affords 2-acyl-1,2,3,4-tetrahydroquinolines bearing a hydrazone function at the quaternary C-4 position via a one-pot diastereoselective process (Chapter 3). For our first strategy (***a***), we deal with the transformation of the dimethylhydrazone moiety at C-4 into a good leaving group and its subsequent elimination with concomitant dehydrogenation, to furnish 2-acylquinolines. In the cases when C-4 was not quaternary, the aromatization was compatible with the retention of a functional group at this position. For strategy ***b***, we have developed conditions that induce a rearrangement process in which the hydrazono substituent is transferred to C-3, allowing aromatization. We also show that both methods can be extended to the preparation of 2-arylquinolines.

5.2 - Development of a protocol for the synthesis of 2-acylquinolines *via* oxidative elimination of the C-4 hydrazone substituent

For the first step of the synthetic process leading to 2-acylquinolines, the aza-vinylogous Povarov reaction has been applied. As previously described, the reaction afforded 2-aryl-1,2,3,4-tetrahydroquinoline **3a**-**h** and 2-acyl-1,2,3,4-tetrahydroquinolines **5a**-**u**, if *N*-arylimines or α-ketoimines are involved respectively. With compounds **3** and **5** in hand, we studied several routes potentially allowing their conversion into quinoline derivatives.

As a first approach, we studied the possibility to hydrolyse in acidic conditions the hydrazine group in representative tetrahydroquinolines in order to obtain the corresponding aldehyde, which we hoped would be amenable to decarboxylative aromatization. Interestingly, as shown in Scheme 5.3, treatment of compounds **5a**–**d** and **5m** with hydrochloric acid in a THF–water reaction medium in an air-open flask afforded directly the corresponding quinolines **8**, although the yields were only moderate in some cases and poor for the compound bearing a bulkier substituent at C-4.

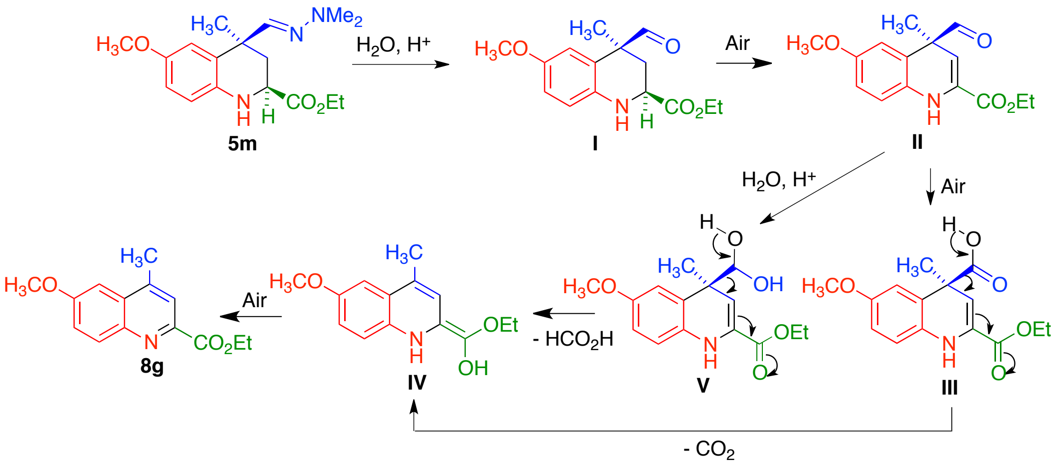


Scheme 5.3.

*Table 5.1. Aromatization of compounds **5** under acidic conditions*

Starting cmpd.	Product	R²	R⁴	Time (h)	Yield (%)
5a	**8a**	C_6H_5	CH_3	24	76
5b	**8b**	4-FC_6H_4	CH_3	7	55
5c	**8c**	4-$OCH_3C_6H_4$	CH_3	24	48
5d	**8d**	C_6H_5	CH_2CH_3	24	25
5m	**8g**	OEt	CH_3	20	95

The mechanism summarized in Scheme 5.4 for the case of **5m** may explain the one-pot conversion of compounds **5** into **8** in the presence of an acid. Thus, acid-promoted hydrolysis of the hydrazone to an aldehyde **I** would be followed by dehydrogenation in the presence of atmospheric oxygen, probably assisted by captodative stabilization[93] of an intermediate C-2 radical due to the presence of the adjacent carbonyl group, to give **II** and the hydrate of aldehyde **II** (intermediate **V**) may also evolve to **IV** by loss of formic acid. Alternatively, the aldehyde may be air-oxidized to a carboxylic acid **III** that would then evolve to the final product by decarboxylation to **IV** followed by keto–enol tautomerism and aromatization by air-promoted dehydrogenation.



Scheme 5.4.

Although we did not carry out a detailed mechanistic study, the above proposal has some experimental support. Thus, the aldehyde derived from **5m** by hydrolyzing the hydrazone function under mild conditions ($CuCl_2$ hydrate at room temperature in THF–water[94]) was isolated and we verified that this compound was readily transformed into **8g** under our reaction conditions. The influence of the C-2 carbonyl substituent in both the dehydrogenation and aromatization steps was confirmed by the fact that an aldehyde similar to **I** but bearing a C-2 phenyl substituent instead of an ester, which is known in the literature,[52] was stable under the same conditions.

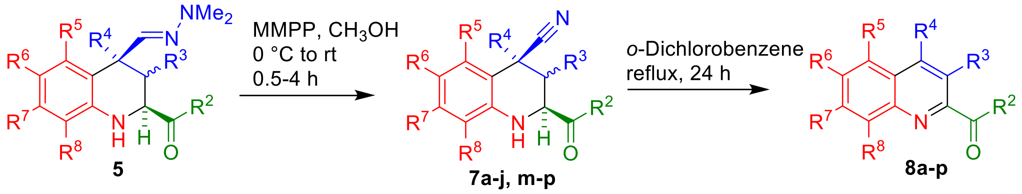
In an effort to improve the yields of our quinoline synthesis, we investigated an alternative aromatization strategy, based on the oxidation of the hydrazone function to a nitrile followed by elimination and dehydrogenation. After some experimentation, we discovered that treatment of compounds **5** with magnesium monoperoxyphthalate

---

[93] For a review of the captodative effect, see: Easton J.C.. *Chem. Rev.*, **1997**, *97*, 53.

[94] (a) Mino T., Fukui S., Yamashita M. *J. Org. Chem.*, **1997**, *62*, 734. (b) Ribelles P., Ramos M.T., Menéndez J.C. *Org. Lett.*, **2012**, *14*, 1402.

hexahydrate (MMPP)[95] in methanol at room temperature allowed the clean preparation of the corresponding nitriles **7**. This transformation proceeds *via* the *N*-oxidation of the dimethylamino group, followed by a Cope-like elimination.[96] Compounds **7** were then transformed into the target quinolines **8** by refluxing them in *o*-dichlorobenzene, via air-induced dehydrogenation with loss of hydrogen cyanide (Scheme 5.5 and Table 5.2). Importantly from the point of view of efficiency and user-friendliness, both the hydrazones **5**



Scheme 5.5.

*Table 5.2. Two-step oxidative aromatization of compounds **5***

Cmpd	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Yield 7(%)	Yield 8(%)
5a	C_6H_5	H	CH_3	H	OCH_3	H	H	72	90
5b	$4\text{-}FC_6H_4$	H	CH_3	H	OCH_3	H	H	70	97
5c	$4\text{-}OCH_3C_6H_4$	H	CH_3	H	OCH_3	H	H	89	88
5d	C_6H_5	H	CH_2CH_3	H	OCH_3	H	H	-[a]	98
5e	C_6H_5	H	CH_3	H	CH_3	H	CH_3	98	95
5f	$4\text{-}FC_6H_4$	H	CH_3	CH_3	H	CH_3	H	93	91
5m	OEt	H	CH_3	H	OCH_3	H	H	60	97
5n	OEt	H	CH_3	H	CH_3	H	CH_3	83	97
5o	OEt	H	CH_2CH_3	H	OCH_3	H	H	63[b]	98
5p	2-furyl	H	CH_3	H	OCH_3	H	H	78	98
5u	C_6H_5	CH_2CH_3	CH_3	H	OCH_3	H	H	69	87
5h	$4\text{-}OCH_3C_6H_4$	H	CH_3	H	CH_3	H	CH_3	70	83
5l	$4\text{-}FC_6H_4$	H	CH_2CH_3	H	CH_3	H	CH_3	-[a]	62
5r	C_6H_5	H	CH_3	CH_3	H	CH_3	H	-[a]	65

[a] Directly converted into the corresponding quinoline. [b] Together with 32% of the corresponding quinoline **8i**.

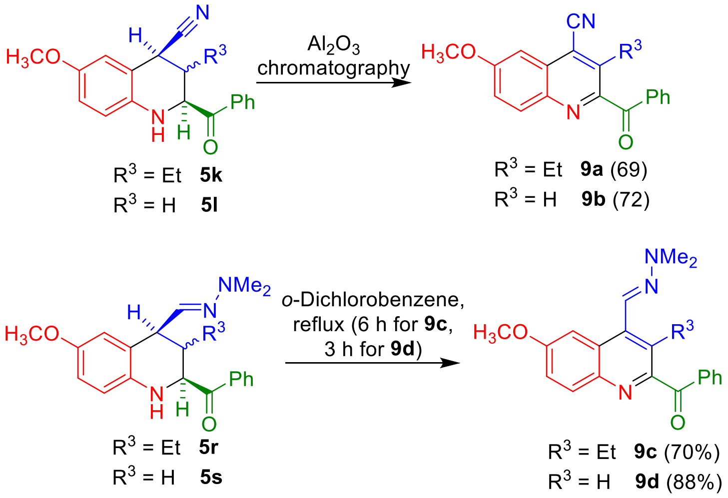
---

[95] Díez E., Fernández R., Gasch C., Lassaletta J.M., Llera J.M., Martín-Zamora E., Vázquez J. *J. Org. Chem.*, **1997**, *62*, 5144.

[96] Fernández R., Gasch C., Lassaletta J.M., Llera J.M., Vázquez J. *Tetrahedron Lett.* **1993**, *34*, 141.

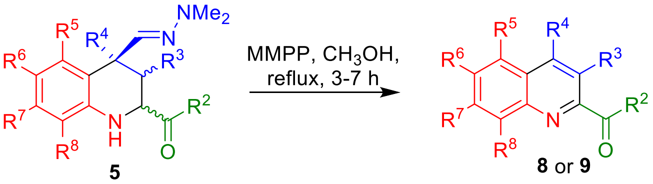
and the nitriles **7** could be employed as *cis–trans* mixtures without any loss in yield of the final quinolines **8**.

Interestingly, for the case R^4 = H an alternative aromatization process took place, which allowed the preparation of quinolines that maintained the C-4 nitrile substituent. Thus, when crude nitriles **7k** and **7l** were subjected to our usual protocol of heating in refluxing *o*-dichlorobenzene, they afforded the quinoline-4-carbonitrile derivatives **9a** and **9b** in excellent yields. We subsequently found that the heating step could be avoided, since simple chromatography of the crude nitriles in basic alumina afforded the quinoline-4-carbonitrile derivatives in similar yields. The peculiar behavior of these compounds can be attributed to the acidity of their H-4 proton, which is simultaneously benzylic and adjacent to the nitrile group. The formation of a C-4 anion in the presence of basic alumina in the chromatographic column may explain their easy dehydrogenation by atmospheric oxygen. In order to increase the structural diversity of the quinolines thus obtained, we also examined the dehydrogenation of hydrazones **5r** and **5s** to furnish quinolines **9c** and **9d**, respectively, and found that it required harsher conditions involving reflux in *o*-dichlorobenzene (Scheme 5.6). This is consistent with the proposed mechanism, in view of the lower acidity of the protons α to a dimethylhydrazone group in comparison with those α to a nitrile.



Scheme 5.6.

The reactions in refluxing *o*-dichlorobenzene were very efficient, but had the disadvantage of requiring high temperatures and a tedious procedure for the elimination of this high-boiling solvent. In an effort to overcome these shortcomings, we examined the use of alternative oxidants for the last step of our sequence. Furthermore, we reasoned that performing both reactions with the same oxidant, besides simplifying the experimental protocol, might set the stage for the development of a method for the transformation of the Povarov products into the target 2-acylquinolines in a single operation. With this goal in mind, we examined the use of MMPP for the aromatization step, eventually discovering that the use of 2 eq. of this reagent in refluxing methanol allowed carrying out the whole procedure in a single operation (Scheme 5.7). This new protocol generally afforded improved overall yields and was experimentally more convenient than the two-step procedure described above.



Scheme 5.7.

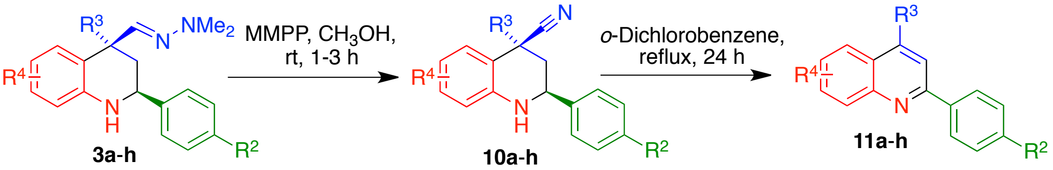
*Table 5.3. One-step aromatization of compounds **5***

Cmpd	Time (h)	Yield (%)
8a	7	74
8b	3	78
8c	4	76
8d	5	79
8e	3	74
8f	5	80
8g	6	75
8h	5	81
8i	4	77
8j	6	85
8m	7	80
9a	7	82
9b	7	78

Finally, we studied the preparation of one of the acylquinolines in a larger scale. Thus, the preparation of compound **8a** was carried out in 40% overall yield for the whole process starting from 4.5 mmol of imine **4a** (compared with a 53% starting with 0.5 mmol). At this scale, an increase in the reaction time from 7 h to 18 h was necessary for the one-pot oxidation process in the presence of MMPP.

5.3. Extension of the elimination-based method to the synthesis of 2-arylquinolines

Compounds bearing 2-arylquinoline structural fragments have a broad range of biological activities that include antiproliferative[97] and antifungal[98] properties, modulation of HIV transcription[99] and inhibition of hepatitis C NS3/4A protease,[100] among many others. For this reason, we examined the application of our method to the synthesis of these compounds from the known 2-aryl Povarov adducts (compounds **3a-h**). As shown in Scheme 5.8, the two-step protocol consisting of the oxidation of the dimethylhydrazones **3** with MMPP at room temperature followed by aromatization of the resulting nitriles (**10a-h**) by prolonged



Scheme 5.8.

Table 5.4. Two-step aromatization of 2-aryl-1,2,3,4-tetrahydroquinolines ***3***

Starting cmpd.	R^2	R^3	R^4	Yield 10 (%)	Yield 11 (%)
3a	H	CH_3	6-OCH_3	70	92
3b	Cl	CH_3	6-OCH_3	97	86
3c	OCH_3	CH_3	6-OCH_3	93	87
3d	CH_3	CH_3	6-OCH_3	86	86
3e	H	CH_3	6,8-$(CH_3)_2$	84	95
3f	OCH_3	CH_3	6-CH_3	98	92
3g	H	CH_2CH_3	6,8-$(CH_3)_2$	77	89
3h	CH_3	CH_3	5,7-$(OCH_3)_2$	62	95

---

[97] Chen Y.-L., Huang C.-J., Huang Z.-Y., Tseng C.-H., Chang F.-S., Yang S.-H., Lin S.-R., Tzeng C.-C., *Bioorg. Med. Chem.*, **2006**, *14*, 3098.

[98] Meléndez Gómez C.M., Kouznetsov V.V., Sortino M.A., Álvarez S.L., Zacchino S.A. *Bioorg. Med. Chem.*, **2008**, *16*, 7908.

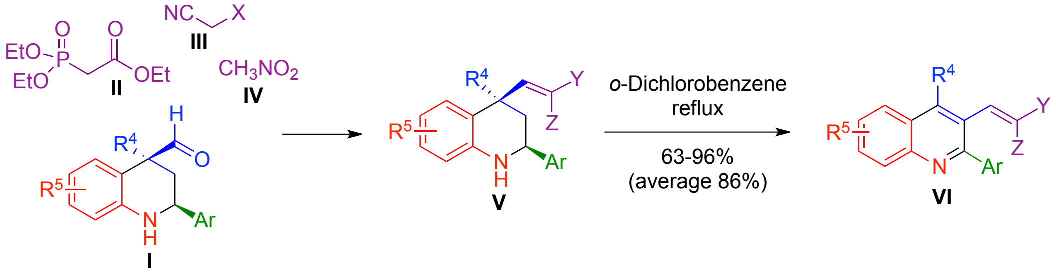
[99] Bedoya L.M., Abad M.J., Calonge E., Astudillo Saavedra L., Gutiérrez M., Kouznetsov V.V., Alcamia J., Bermejo P., *Antiviral Res.*, **2010**, *87*, 338.

[100] Liverton N.J., Holloway M.K., McCauley J.A., Rudd M.T., Butcher J.W., Carroll S.S., DiMuzio J., Fandozzi C., Gilbert K.F., Mao S.S., McIntyre C.J., Nguyen K.T., Romano J.J., Stahlhut M., Wan B.L., Olsen D.B., Vacca J.P., *J. Am. Chem. Soc.*, **2008**, *130*, 4607.

heating in refluxing *o*-dichlorobenzene afforded excellent yields of the target 2-arylquinolines **11a**-**h**. In this case, the one-pot method (heating the starting materials **3a**-**h** with MMPP in refluxing methanol) gave complex mixtures.

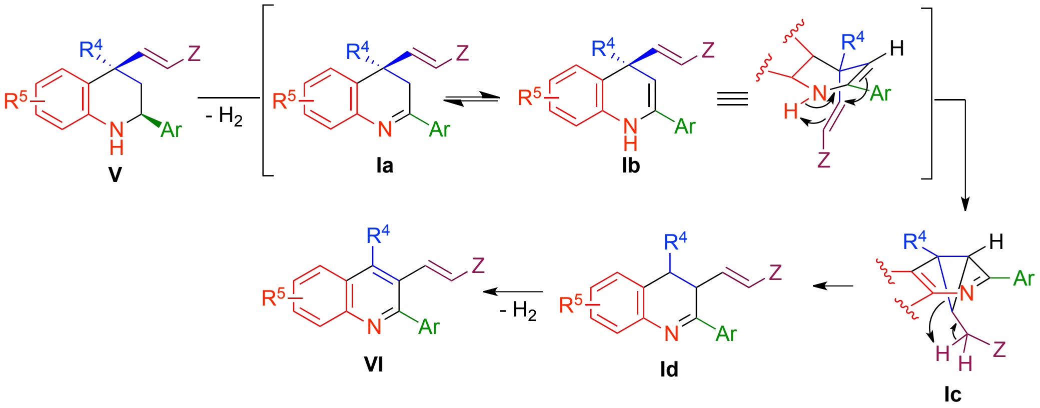
5.4. Synthesis of quinolines via migration of the hydrazone group

The work described in this Section is complementary to previous research developed in our group by Dr. Pascual Ribelles and which is summarized in Scheme 5.9.[101] He showed that tetrahydroquinolines **V**, bearing a vinyl function at C-4 and constructed *via* a variety of olefination methods including Wadsworth-Emmons, Henry and Knoevenagel reactions from the aldehydes **I**, undergo an oxidative rearrangement that leads to quinoline derivatives **VI** when heated in refluxing *o*-dichlorobenzene.



Scheme 5.9.

In order to explain the migration of vinyl function from C-4 to C-3, a mechanism was proposed in which an aza-ene intramolecular reaction takes place in intermediate **Ib**, arising from the air-promoted dehydrogenation of the starting material. The unstable cyclopropane intermediate **Ic** opens to **Id**, and a second dehydrogenation reaction furnishes product **VI** (Scheme 5.10).

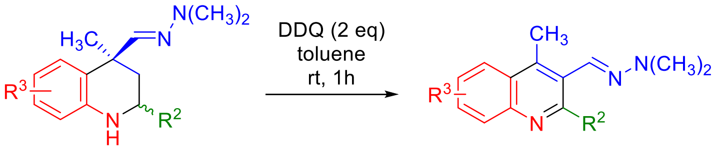


Scheme 5.10.

---

[101] Ribelles P., Ramos M.T., Menéndez J.C. *Org. Lett.*, **2012**, *14*, 1402.

In an effort to extend the scope of this reaction, we became interested in applying the above conditions to additional situations, using as substrates the Povarov-derived hydrazones **3** and **5**. Unfortunately, these compounds failed to react when heated in refluxing *o*-dichlorobenzene open to air. However, during studies aimed at the preparation of intermediates of the mechanism shown in Scheme 5.10 (see a more detailed explanation below), we discovered that when these compounds were submitted to alternative oxidative conditions by exposure to 2 equivalents of DDQ in benzene, quinolines **12a-f** were obtained in acceptable to good yields. The method worked well for 2-aryl and 2-acyltetrahydroquinoline substrates (Scheme 5.11 and Table 5.5).



3 and **5**

12a-f

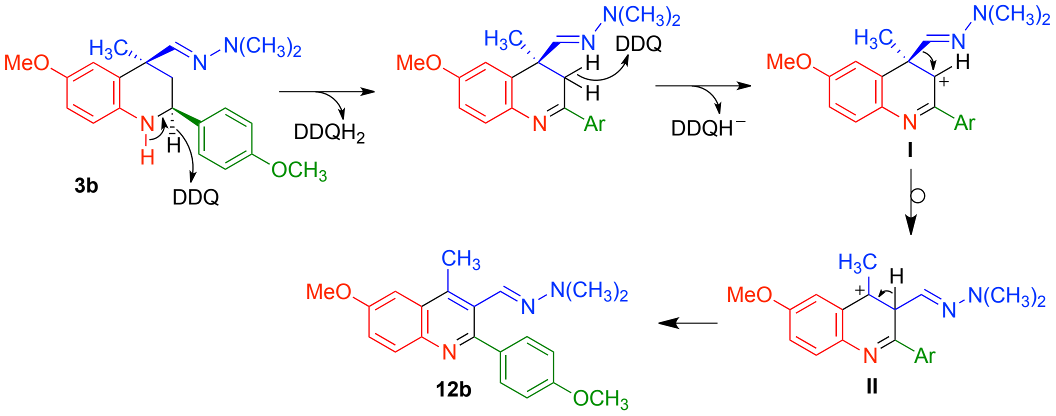
Scheme 5.11.

*Table 5. 5. Oxidative C_4-C_3 migration of the hydrazone substituent of compounds **3** and **5***

Cmpd	R^2	R^3	Yield (%)
12a	4-Cl-C_6H_4	6-OCH_3	57
12b	4-OCH_3-C_6H_4	6-OCH_3	50
12c	C_6H_5CO	6-OCH_3	75
12d	(4-OCH_3-C_6H_4)CO	6-OCH_3	73
12e	(4-F-C_6H_4)CO	6,8-$(CH_3)_2$	59
12f	(4-F-C_6H_4)CO	6-OCH_3	53

This rearrangement takes place under much milder conditions than the previous one, and we propose the mechanism summarized in Scheme 5.12 to explain it, on **3b** as the substrate. The first equivalent DDQ, acting as an hydride acceptor, transforms the starting material into its dehydro derivative **I**, which can in fact be isolated as the only reaction product by employing one equivalent of the oxidant. A second equivalent of DDQ would accept an hydride from the quinoline C-3 position to furnish carbocation **I**, which is stabilized by conjugation with the methoxy group at C-6. A cationic rearrangement to the tertiary cation

II,[102] followed by deprotonation, explains the formation of compound **12b**. The preferential migration of the hydrazonomethyl substituent can be ascribed to the conjugation of the electron-releasing dimethylamino group with the atom involved in the rearrangement, since the increasing migratory ability of more electron-rich R groups is well established.



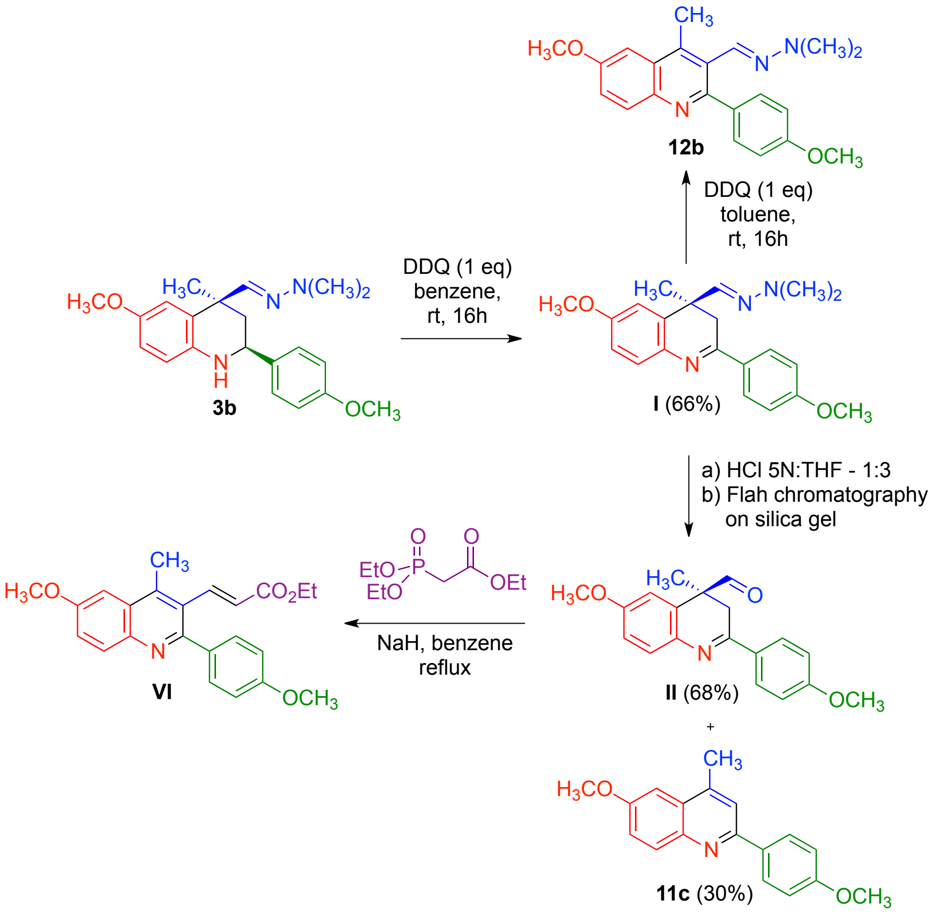
Scheme 5.12

The development of this new method for the oxidative rearrangement provided an opportunity to attempt the isolation of an intermediate of the proposed mechanism, which had not been possible in the previous conditions. Indeed, we found that treatment of compound **3b** with one equivalent of DDQ in benzene at room temperature afforded 3,4-dihydroquinoline **I**, an isomer of the proposed reaction intermediate, which was isolated in 66% yield. When **I** was treated with DDQ under the previously described rearrangement conditions, it afforded compound **12b** in 75% yield.

In order to generalize the mechanistic study, the hydrazone function of dihydroquinoline **I** was converted into an aldehyde by hydrolysis, allowing the isolation of **II** in 68% yield. Interestingly, during the purification of compound **II** by flash chromatography 30% of quinoline **11c** was been isolated, probably because the acidic character of silica gel promotes the elimination of hydrogen cyanide and dimethylamine from **II**. With intermediate **II** in hand, we proceed to carry out the Wadsworth-Emmons reaction, which led to the rearranged compound **VI** in 70% yield (Scheme 6.4).

---

[102] For precedent of a similar rearrangement in a DDQ oxidation, see: Batista V.S., Crabtree R.H., Konezny S.J., Luca O.R., Praetorius J.M. *New J. Chem.*, **2012**, *36*, 1141


H3CO
CH3
N(CH3)2
N
OCH3
12b
DDQ (1 eq)
toluene,
rt, 16h
H3C
3b
DDQ (1 eq)
benzene,
rt, 16h
I (66%)
a) HCl 5N:THF - 1:3
b) Flah chromatography
on silica gel
EtO
OEt
NaH, benzene
reflux
CO2Et
VI
O
II (68%)
+
11c (30%)

Scheme 5.13

6 – 2-Acylquinoline derivatives as multitarget-directed antitubercular agents

6.1 - Tuberculosis: a global plague

Tuberculosis (TB) is an infectious lung disease caused by different species of bacteria, mainly *Mycobacterium tuberculosis*, but also including *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium caprae*, *Mycobacterium canettii*, *Mycobacterium pinnipedii* and *Mycobacterium microti*.

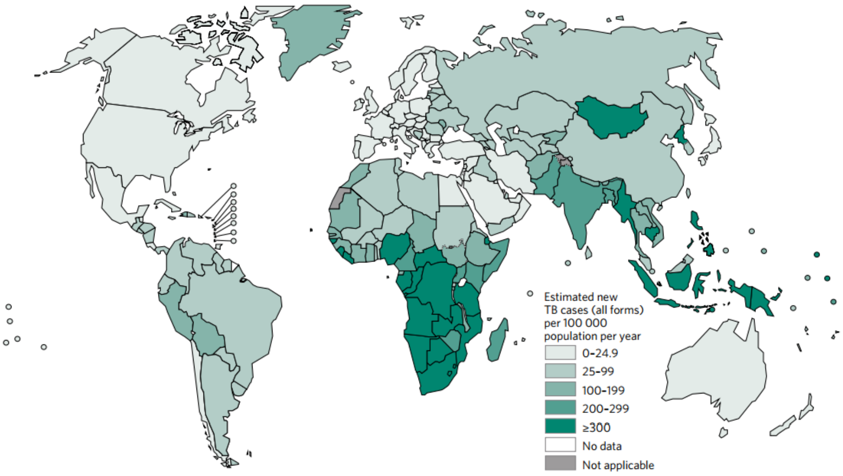


Figure 6.1: Estimated TB incidence rates, 2015 (WHO).

Tuberculosis is the most deadly bacterial disease. The World Health Organization (WHO) reported in October 2016 that tuberculosis is one of the top 10 causes of death worldwide and about one-third of the world's population has latent TB, which means people have been infected by TB bacteria but have not yet developed the disease, nor can they transmit it. In 2015, there were an estimated 10.4 million new cases worldwide, of which there were 480000 new cases of multidrug-resistant TB (MDR-TB) and 100000 new cases of extensively-drug resistant TB (XDR-TB). HIV patients accounted for 1.2 million (11%) of all new TB cases. Over 95% of TB deaths occur in low- and middle-income countries. Six countries account for 60% of the total, with India leading the count, followed by Indonesia, China, Nigeria, Pakistan and South Africa. There were an estimated 1.4 million TB deaths in 2015 and an additional 0.4 million deaths resulting from TB disease among people living with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015.[103]

The treatment of tuberculosis involves first-line drugs including isoniazid (INH), streptomycin, rifampicin (RMP), ethambutol and pyrazinamide. The second-line treatments involve the application of *p*-aminosalicylic acid, ethionamide, cycloserine, azithromycin, clarithromycin and fluoroquinolones. In the case of drug-susceptible tuberculosis (DS)-TB up to 95% of people can be cured during six months with a four-drugs regimen, *i.e.* two drugs of the first line for two months followed by isoniazid and rifamycin in a continuation phase of four months.

The scenario got worse with the appearance of multi- and extensively-drug-resistant tuberculosis (MDR-TB and XDR-TB). MDR-TB is resistant at least to isoniazid and rifampicin, the most important first-line drugs; the treatment for this disease involves combination of eight to ten drugs for 18-24 months. In these cases the cure rates ranges from 50% to 70%, approximatively. The XDR-TB is resistant to isoniazid and rifampicin as well as to any fluoroquinolone or any injectable second line drugs, in these cases the mortality rates are very high. Furthermore, the frequent co-infection of TB in HIV patients complicates the selection of a suitable treatment due to drug-drug interactions, enhanced side effects and decreased patient compliance.[104]

---

[103] Global tuberculosis report of **2016** (http://www.who.int/mediacentre/factsheets/fs104/en/).

[104] Koul A., Arnoult N., Lounis N., Guillemont J., Andries K. *Nature*, **2011**, *469*, 483.

6.2 - Strategies for the development of new tuberculosis treatments

As a consequence of this dramatic scenario, numerous attempts are being undertaken to combat this worldwide killer. Recent advances have been achieved with the availability of the TB genome sequence. This powerful tool allowed the identification of several new targets that may represent a good starting point for the classical rational drug design strategy,[105] but unfortunately this approach has not led to new drug candidates so far. Phenotypic screening of pharmaceutical libraries has met with limited success because of the limited structural diversity of the companies libraries and the fact that antimycobacterial compounds usually do not respect Lipinsky's "rule of 5", which on the other hand is strongly implemented in the construction of the libraries, the reason being the very highly lipophilic nature of the *Mycobacterium* cover, which requires successful compounds to have unusually high lipophilicities.[106] Nevertheless, it is important to note that, previous failures notwithstanding, in the last six years the whole-cell-screening approach has disclosed several interesting molecules. The main one is bedaquiline (Sirturo®),[107] which blocks the main energy source for mycobacteria by interacting with their adenosine triphosphate (ATP) synthase[108] and was approved for multi-drug-resistant TB by the FDA in 2012. Other compounds are nearing phase I clinical trials, as in the case of BTZ043.[109]

In spite of these partial successes, the need for new TB drugs is still unmet. The ideal drug should predominantly: (1) target MDR- and XDR-TB, (2) shorten and simplify treatment to enhance the patient compliance, making more difficult the insurgence of new resistance and (3) be compatible with HIV medications.

---

[105] Cole S.T. et al. *Nature*, **1998**, *393*, 537.

[106] Payne D.J., Gwynn M.N., Holmes D.J., Pompliano D.L. *Nat. Rev. Drug Discov.*, **2007**, *6*, 29.

[107] (a) Andries K., et al. *Science*, **2005**, *307*, 223. (b) Koul A. et al. *Nat. Chem. Biol.*, **2007**, *3*, 323. (c) Diacon AH, Pym A, Grobusch M, et al. *N. Engl. J. Med.*, **2009**, *360*, 2397.

[108] Karl D., Xilin Z., Barry K. *Lancet Infect. Dis.*, **2008**, *8*, 273.

[109] (a) Makarov V. et al. *Science*, **2009**, *324*, 801. (b) Gao C., Peng C., Shi Y., You X., Ran K., Xiong L., Ye T.-H., Zhang L., Wang N., Zhu Y., Liu K., Zuo W., Yu L., Wei Y. *Sci. Rep.*, **2016**, 6, 29717.

6.3 - Quinoline derivatives in tuberculosis therapy. Screening of 2-acylquinolines against *Mycobacterium tuberculosis*

Quinoline has long been considered a privileged structure in drug discovery, i.e., a molecular framework that, following judicious structural modifications, can provide ligands for several types of therapeutic targets.[110] In this connection, many types of quinoline derivatives have shown good antitubercular activities, although their targets are often unknown. In a recent review of this subject,[111] the structures of active compounds have been summarized as shown in Figure 6.2.

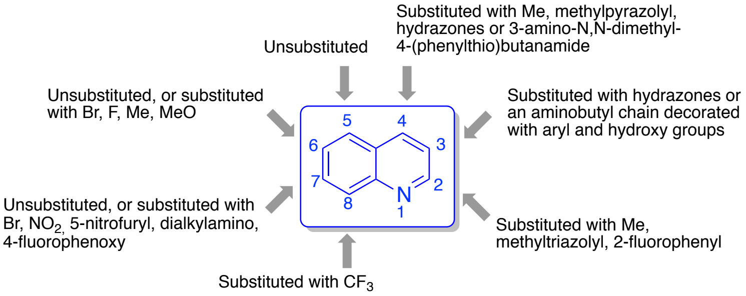


Figure 6.2: Antitubercular quinoline derivatives.

Three specific examples of quinoline-derived molecules endowed with a notable anti-TB activity are shown below, including the previously mentioned betaquiline, approved by the FDA in 2012, and compounds AQCH[112] and DCMQ,[113] which have shown promising activity against drug-sensitive TB and multi-drug-resistant TB (Figure 6.3).

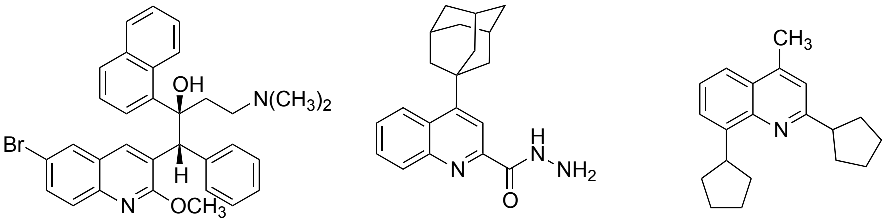
---

[110] For selected reviews of this concept and its usefulness in drug discovery, see: (a) DeSimone R.W., Currie K.S., Mitchell S.A., Darrow J.W., Pippin D.A. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 473. (b) Constantino L., Barlocco D. *Curr. Med. Chem*. **2006**, *13*, 65. (c) Duarte C.D., Barreiro E.J., Fraga C.A. *Mini Rev. Med. Chem.* **2007**, *11*, 1108. (d) Alex A.A., Storer R.I., Drugs and their structural motifs, in Smith D.A. (Ed.), Metabolism, pharmacokinetics and toxicity of functional groups: Impact of the building blocks of medicinal chemistry on ADMET, Chapter 1. Royal Society of Chemistry, 2010. (e) Kim J., Kim H., Park S.B. *J. Am. Chem. Soc.* **2014**, *136*, 14629. For a monograph, see: (f) Bräse S. (Ed.) Privileged scaffolds in Medicinal Chemistry. Design, synthesis, evaluation. Royal Society of Chemistry, 2016.

[111] Keri R.S:, Patil S.A. *Biomed. Pharmacother.* **2014**, *68*, 1161. For an additional review, see: Singh S., Kaur G., Mangla V., Gupta M.K. *J. Enzyme Inhib. Med. Chem*., **2015**, *3*, 492.

[112] Jain R., Vaitilingam R., Nayyar A., Palde P.B. *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 1051.

[113] Monga V., Nayyar A., Vaitilingam B., Palde P.B., Jhamb S.S., Kaur S., Singh P.P., Jain R. *Bioorg. Med. Chem*., **2004**, *12*, 6465.



Bedaquiline

AQCH
4-(1-Adamantyl)-2-quinolinecarbohydrazide

DCMQ
2,8-Dicyclopentyl-4-methylquinoline

Figure 6.3. Some quinoline-derived antitubercular compounds.

Due to the absence of data on the activity of 2-acylquinolines, probably associated to the lack of suitable synthetic methods, we became interested in screening representative compounds from our library, together with some 2-arylquinolines for comparison purposes (figure 6.4). This work was performed by the group of Dr. Arufin Mohammed, at the Center for Drug Discovery, Universiti Sains Malaysia, Penang, and the results obtained are summarized in Table 6.1. All compounds showed antitubercular activity, and one of them (compound **8n**) had a better activity than some established antitubercular drugs such as cycloserine and pyrimethamine. 2-Acylquinolines seem to be more potent than their 2-aryl counterparts (see entries 1 and 8). Importantly, none of the compounds showed significant cytotoxicity in *Mycobacterium tuberculosis* strain $H_{37}Rv$.

These interesting initial data, coupled with the novelty of the structures, prompted us to attempt further optimization.

8a: R^1: 6-OMe; R^2: Ph; R^3: Me
8b: R^1: 6-OMe; R^2: 4-FC_6H_4; R^3: Me
8c: R^1: 6-OMe; R^2: 4-$OMeC_6H_4$; R^3: Me
8d: R^1: 6-OMe; R^2: Ph; R^3: Et
8n: R^1: 6,8-Me_2; R^2: OEt; R^3: Me
8o: R^1: 6-OMe; R^2: OEt; R^3: Et
8p: R^1: 6-OMe; R^2: 2-furyl; R^3: Me

11a: R^1: 6-OMe; R^2: H; R^3: Me
11b: R^1: 6-OMe; R^2: Cl; R^3: Me
11e: R^1: 6,8-Me_2; R^2: H; R^3: Me

Figure 6.4: Compounds used for the initial activity study

Table 6.1. Antitubercular activities in Mycobacterium tuberculosis (H37Rv) and cytotoxicities in Mycobacterium tuberculosis $H_{37}Rv$ cells

Entry	Compound	IC_{50} (μM)	IC_{90} (μM)	MIC (μM)	Cytotoxicity μg/mL
1	**8a**	18.28	36.50	50.00	>6.25
2	**8b**	21.91	47.93	50.00	>6.25
3	**8c**	29.95	41.87	50.00	>6.25
4	**8d**	25.87	44.60	100.00	>6.25
5	**8n**	5.81	16.13	25.00	>6.25
6	**8o**	47.20	66.50	100.00	>6.25
7	**8p**	23.19	45.90	50.00	>6.25
8	**11a**	47.20	66.50	100.00	>6.25
9	**11b**	17.20	35.50	50.00	>6.25
10	**11e**	18.46	36.42	50.00	>6.25
11	Amikacin	0.07	0.08	0.16	>6.25
12	Cycloserine	12.47	13.49	25.00	>6.25
13	Ethambutol	<1.56	32.79	12.50	>6.25
14	Isoniazid	0.18	0.29	0.31	>6.25
15	Pyrimethamine	37.35	74.96	100.00	>6.25

6.4 - A multi-target ligand strategy based on 2-acylquinoline structures

While the “one disease-one target / one-target-one drug” strategy can still be considered the main paradigm in drug discovery, over the last few decades, a new strategy has emerged as effective in multifactorial diseases, especially in diabetes, neurodegenerative, inflammatory, cardiovascular disease and bacterial diseases, especially when complicated by drug resistance: the multi-target directed ligand (MTDL) strategy.[114]

There are three different approaches in the multi-target therapy. Traditionally, when monotherapy is not effective, combination therapy (polypharmacology) is employed. This approach, while very common, presents several drawbacks such as decreased patient compliance and so a more easy development of drug resistance, overlapping side effects, drug-drug interactions; a modification of this approach is the formulation of a dosage form containing two or more drugs together, which allow increased patient compliance but does not solve the other issues. A more innovative approach involves the design of a single chemical entity that interacts with multiple targets, having advantages such as a lower risk of drug-drug interactions and easier clinical assays and formulation, even though a more complex dose optimization phase may be expected (Figure 6.5). The design of these drugs involves the selection of two (or more) pharmacophores and their combination through a linker that can bind, fuse or overlap both fragments.

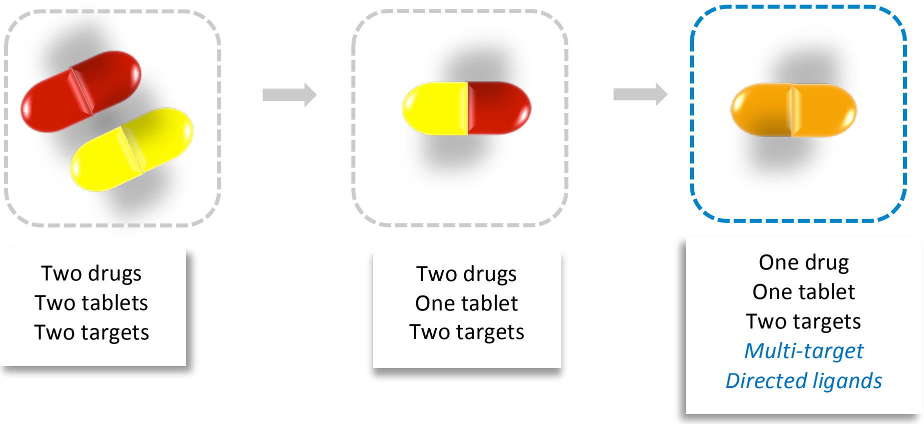
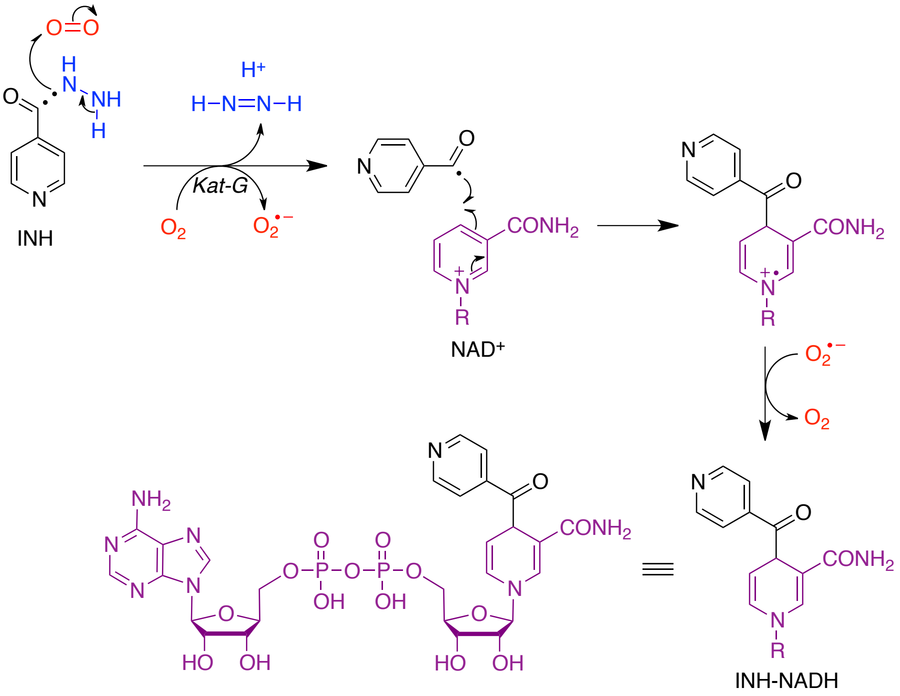


Figure 6.5. A schematic representation of three approaches to therapy addressed at more than one target.

---

[114] Katselou M.G., Matralis A.N., Kourounakis A.P. *Curr. Med. Chem.*, **2014**, *21*, 2743.

In this context, we planned to potentiate the antitubercular activity of our compounds by addition of a second pharmacophore, and to this end we chose isoniazide (INH), one of the first-line antitubercular molecules. Even though this compound was discovered over sixty years ago, its mechanism of action is still to be established in all its details. The main target of INH is enoyl-ACP reductase (InhA), an enzyme involved in the synthesis of mycolic acids, which are the key structural components of the mycobacterial wall. INH is a prodrug, which is activated by the catalase-peroxidase (KatG) enzyme of *Mycobacterium tuberculosis*. Although the precise chemical details of the transformation are still under investigation, it has been hypothesized that the activation of isoniazid leads to an isonicotinoyl acyl radical that then combines with NAD$^+$/NADH to form the isoniazid-NADH adduct (INH-NADH) (Scheme 6.1).[115]



Scheme 6.1.

---

[115] (a) Scior T., Meneses Morales I., Garces Eisele S.J., Domeyer D., Laufer S. *Arch. Pharm. Pharm. Med. Chem.*, **2002**, *11*, 511. (b) Vilcheze C., Jacobs W.R. Jr. *Annu. Rev. Microbiol.*, **2007**, *61*, 35. (c) Slayden R.A., Barry C.E. *Microbes Infect.*, **2000**, *2*, 659.

This species inhibits the InhA enzyme, interacting with the NADH site through several hydrogen bonds and π–π stacking interactions (Figure 6.6). The inhibition of mycolic acid biosynthesis causes the loss of structure in the wall of the pathogen and allows the accumulation of metabolites, leading to the cellular death.[116] In an additional mechanism, the activated INH-NADH adduct can also inhibit the dihydrofolate reductase (DHFR), an enzyme involved in the synthesis of nucleic acids.[117] A further possible target proposed for INH is the β-ketoacyl synthase (KasA).[118]

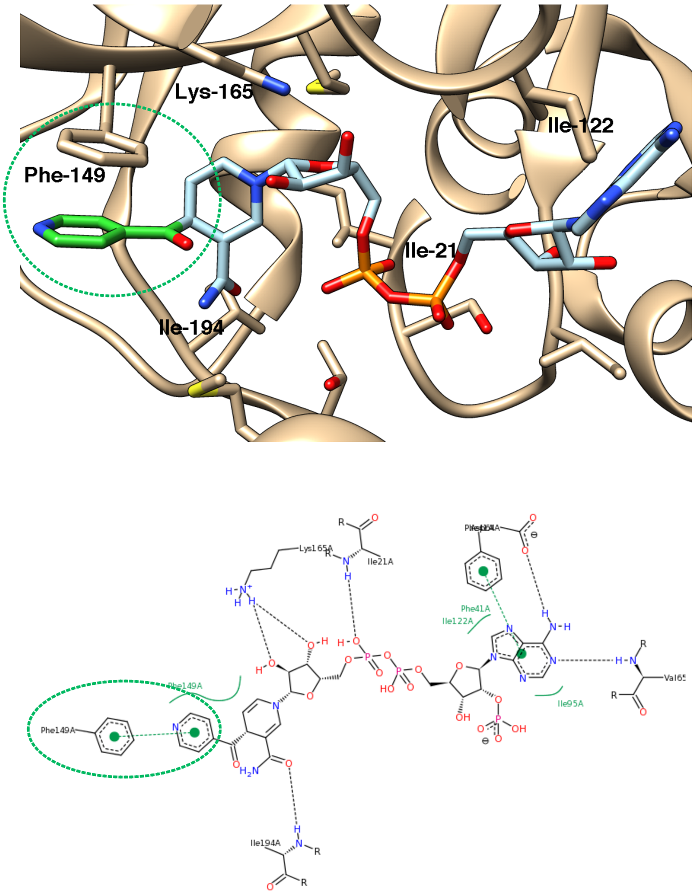


Figure 6.6. Interaction of INH-NADH with the InhA enzyme. The top figure was generated from PDB 1ZID using Chimera 1.10

---

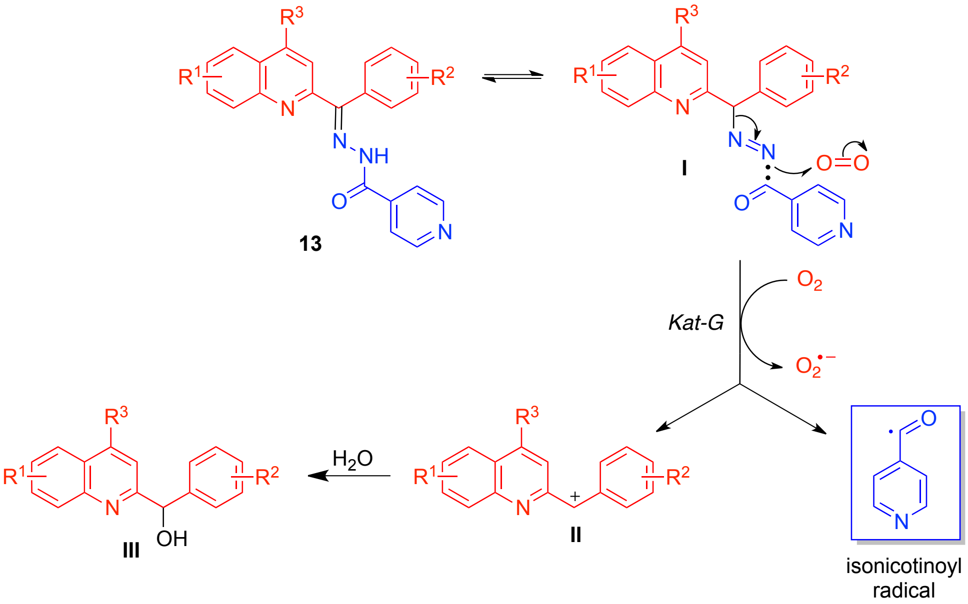
[116] (a) Banerjee A., Dubnau E., Quemard A., Balasubramanian V., Urn K.S., Wilson T., Collins D., de Lisle G., Jacobs W.R. Jr. *Science*, **1994**, *263*, 227. (b) Marrakchi H., Lanéelle G., Quémard A. *Microbiology*, **2000**, *146*, 289.

[117] Argyrou A., Vetting M.W., Aladegbami B., Blanchard J.S. *Struct. & Mol. Biol.*, **2006**, *13*, 408.

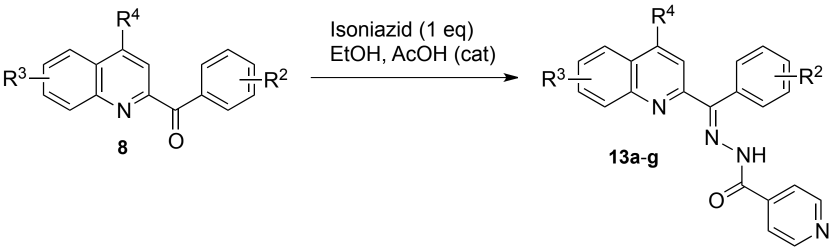
[118] Mdluli K., Slayden R.A., Zhu Y., Ramaswamy S., Pan X., Mead D., Crane D.D., Musser J.M., Barry C.E. *Science*, **1998**, *280*, 1607.

In this context, we planned the combination of our 2-acylquinolines **8** and isoniazide into a single molecular entity, namely the N-acylhydrazones **13**. We propose that, besides acting by the same mechanism as the 2-acyl derivatives, these compounds would undergo the mechanism summarized in Scheme 6.2. Thus, the tautomeric species **I** would serve as a substrate of the Kat-G peroxidase, which would fragment **I** into the isonicotinoyl radical and a doubly benzylic carbocation **II**, which would then presumably be transformed into carbinol **III**. Since **III** may presumably be metabolically oxidized to a 2-acylquinoline, compounds **13** can be viewed as mutual prodrugs aimed at two different targets.

For the synthesis of compounds **13**, 2-acylquinolines **8** were treated with one equivalent of isoniazid in ethanol in the presence of a catalytic amount of acetic acid, at room temperature for 24 h (Scheme 6.3 and Table 6.2).



Scheme 6.2.



Scheme 6.3.

Table 6.2. Synthesis of isonicotinylhydrazides ***13a-g***

Cmpd	R^2	R^3	R^4	Yield (%)
13a	H	5,7-CH_3	CH_3	90
13b	4-OCH_3	6-OCH_3	CH_3	76
13c	4-F	6-OCH_3	CH_3	75
13d	H	6-OCH_3	CH_3	39
13e	H	6-OCH_3	CH_2CH_3	63
13f	4-OCH_3	6,8-CH_3	CH_3	38
13g	4-F	6,8-CH_3	CH_2CH_3	77

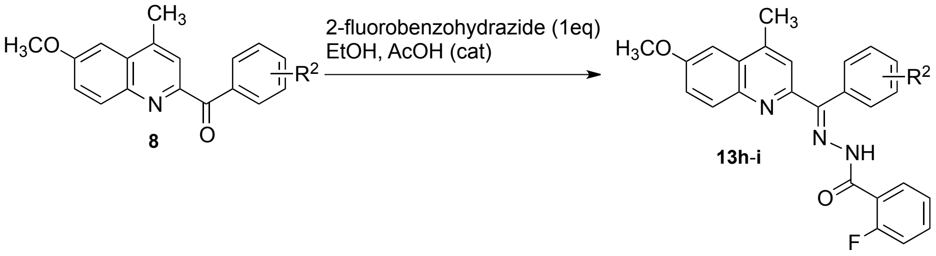
The presence of fluorine as a substituent in hydrazones derived from fluorobenzoic acid hydrazides has been shown to enhance anti-TB activity.[119] In general, it is well known that fluorine's electronegativity, size, and electrostatic interactions can deeply influence chemical reactivity. One of the major effects of fluorination is a modulation of acidity and basicity of the molecule. Fluorination can also aid further interactions between the drug and binding sites of receptors or enzymes. An increase in lipophilicity is also often observed, an important consideration for molecules that are designed to be active in cellular systems. Another established effect of fluorination is a modulation of metabolic stability. In particular, replacing hydrogen with fluorine on aromatic rings is a very effective strategy to slow down significantly the oxidative metabolic step of a given drug by cytochrome P450 monooxygenases.[120]

For this reason, we decided to employ commercially available 2-fluorobenzohydrazide for the synthesis of two additional hydrazones **13h** and **13i**, *via* the previously described method (Scheme 6.4 and Table 6.3).

---

[119] (a) Nayyar A., Malde A., Coutinho E., Jain R. *Bioorg. Med. Chem.*, **2006**, *14*, 7302. (b) Koçyiğit-Kaymakçıoğlu B., Elçin Oruç-Emre E., Unsalan S., Rollas S. *Med. Chem. Res.* **2009**, *18*, 277. (c) Eswaran S., Adhikari A.V., Ajay Kumar R. *Eur. J. Med. Chem.*, **2010**, *45*, 957.

[120] For more details about fluorine in pharmaceuticals see: (a) Müller K., Faeh C., Diederich F. *Science*, **2007**, *317*, 1881. (b) Wang J., Sánchez-Roselló M., Aceña J.-L., del Pozo C., Sorochinsky A.E., Fustero S., Soloshonok V.A., Liu H. *Chem. Rev.*, **2014**, *114*, 2432.



Scheme 6.4

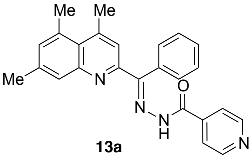
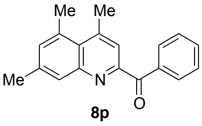
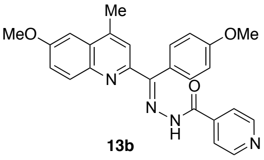
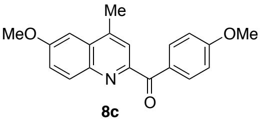
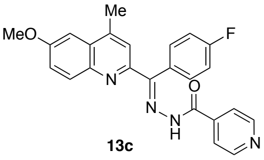
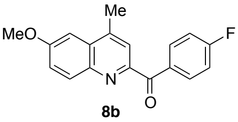
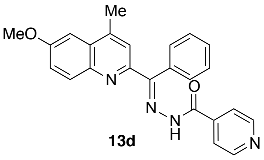
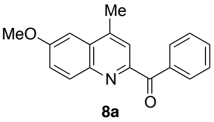
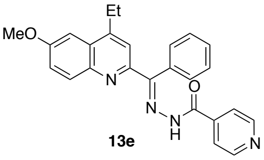
Table 6.3. Synthesis of 2-fluorobenzohydrazides ***13h,i***

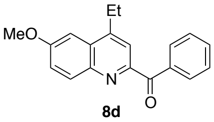
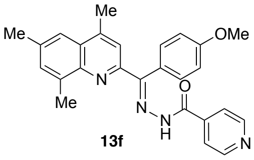
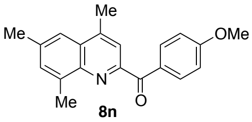
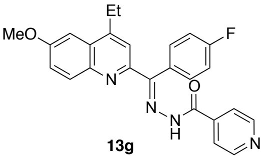
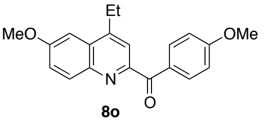
Cmpd	R2	Yield (%)
13h	H	71
13i	4-F	75

Scheme 7.4.

We report in Table 6.4 the results of antimycobacterial activity of compounds **13a-l**, compared with those of the corresponding 2-acylquinolines **8**, analyzed against cultures of *Mycobacterium tuberculosis* H37Rv (Mtb H37Rv). From the comparison of activities, it can be concluded that the presence of the isoniazid fragment increases activity by at least one order of magnitude. In particular, compounds **13c** and **13f** (entries 3 and 11) show a good activity with a MIC of 1.07 and 3.38 μg/mL respectively, which is comparable to that of ethambutol and better than the one obtained for cycloserine and pyrimethamine. Regarding substitution at the quinoline ring itself, the presence of an ethyl group at C-4 rather than a methyl is associated to a decrease in activity (entries 7,9/8,10 and 5,13/6,14). Substitution at other positions of the quinoline ring noes not seem to cause much change in activity. Regarding substitution of the phenyl moiety the best results come from p-fluorine atom, which leads to a considerably increased activity. We hope to acquire a more detailed SAR picture with the remaining microbiological assays (compounds **13h**, **13i**, **8d**, **8e**, **8g**, **8h** and **9b**.)

Table 6.4. Antimycobacterial activity of compounds ***13*** *and the corresponding acylquinolines* ***8***

Entry	Compound[a]	IC_{50} (μM)	IC_{90} (μM)	MIC (μM)	Cytotoxicity μg/mL
1	 **13a**	15.17	27.86	100.00	>6.25
2	 **8p**	23.19	45.90	50.00	>6.25
3	 **13b**	16.30	25.50	100.0	>6.25
4	 **8c**	29.95	41.87	50.00	>6.25
5	 **13c**	1.07	1.98	6.25	>6.25
6	 **8b**	21.91	47.93	50.00	>6.25
7	 **13d**	8.57	14.72	50.00	>6.25
8	 **8a**	18.28	36.50	50.00	>6.25
9	 **13e**	12.87	24.60	50.00	>6.25

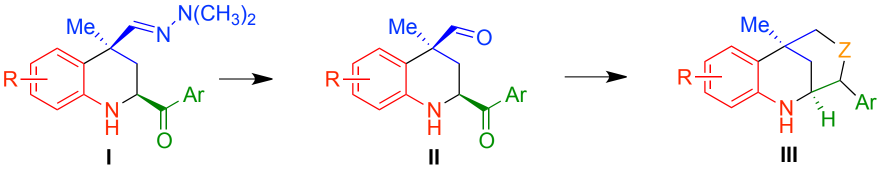
Entry	Compound[a]	IC_{50} (µM)	IC_{90} (µM)	MIC (µM)	Cytotoxicity µg/mL
10	 **8d**	25.87	44.60	100.00	>6.25
11	 **13f**	3.38	06.97	25.00	>6.25
12	 **8n**	5.81	16.13	25.00	>6.25
13	 **13g**	17.20	35.50	50.00	>6.25
14	 **8o**	47.20	66.50	100.00	>6.25
15	Amikacin	0.07	0.08	0.16	>6.25
16	Cycloserine	12.47	13.49	25.00	>6.25
17	Ethambutol	<1.56	32.79	12.50	>6.25
18	Isoniazid	0.18	0.29	0.31	>6.25
19	Pyrimethamine	37.35	74.96	100.00	>6.25

[a] The evaluation of compounds **13h**, **13i**, **8d**, **8e**, **8g**, **8h** and **9b** is in progress.

7 – Synthesis of 2,6-methanobenzo[*e*][1,4] diazocine derivatives and their investigation as neuroprotective agents

7.1 - Introduction

This Chapter is devoted to the synthesis of bridged heterocycles derived from the 2,6-methanobenzo[*e*][1,4]-diazocine system (compounds **III**) using as starting materials the 2-acyl-4-(dimethylhydrazonomethyl)-1,2,3,4-tetrahydroquinolines **I** obtained *via* the aza-vinylogous Povarov reactions described in Chapter 3. Compounds **II**, arising from the hydrolysis of **I,** have two carbonyl groups in a *cis*-1,5 arrangement and are therefore amenable to the generation of a bridged system via reductive amination (leading to Z = NH or NR) or related processes, as summarized in Scheme 7.1. In prior work, our group has studied the direct transformation of compounds **I** into bridged systems **III** where Z is a N-NMe$_2$ group,[121] and hence both methods would be complementary.

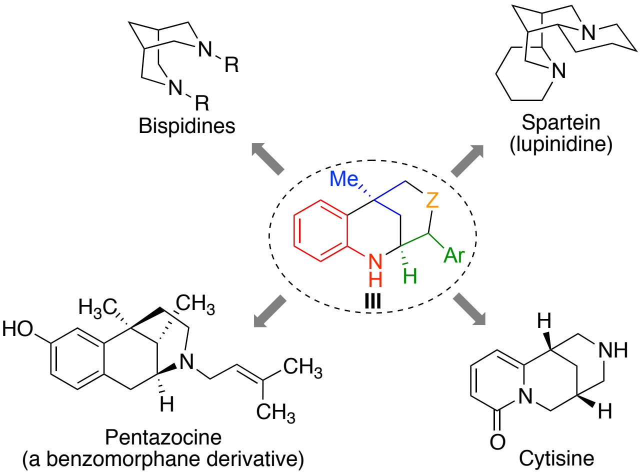


Scheme 7.1

---

[121] (a) Pascual Ribelles, Ph. D. Thesis. Universidad Complutense, 2012. (b) Diana K. Becerra, Ph. D. Thesis, Universidad del Valle, Colombia, 2014.

Compounds **III** are of potential interest in many areas (Scheme 7.2). They show in their structure a cavity similar to that present in the bispidines (compounds **I**), although with a fused aromatic ring and an additional substituent (Ar) that may be used to modulate the size of the cavity. Bispidins are of interest because of their ability to act as rigid, bidentate Lewis bases,[122] allowing them to bind certain ion channels.[123] In this context, it is interesting to note the analogy between compounds **III** and cytisine, an $\alpha_4\beta_2$ acetylcholine nicotinic receptor partial agonist that has been proposed as a smoking cessation aid[124] and has potential interest in neurodegenerative diseases, as will be discussed below in this Chapter. Compounds **III** can also be viewed as aza analogues of benzomorphans, a well-known family of opioid receptor agonists. Indeed, the scarce literature references on the synthesis of 2,6-metanobenzo[*e*][1,4]diazocine derivatives were aimed at their study as opioid analgesics.[125] Interestingly, besides this classical application, some types of opioid receptors are currently under intense scrutiny as targets for neurodegenerative disease.[126] The chelating properties



Scheme 7.2

---

[122] (a) For reviews of the synthesis and applications of the bispidines, see: (a) Breuning M., Steiner M. *Synthesis* **2008**, 2841. (b) Tomassoli I., Gündisch D. *Curr. Top. Med. Chem.* **2016**, *16*, 1314. See also: (c) Wang, Z.; Miller, E. J.; Scalia, S. J. *Org. Lett.* **2011**, *13*, 6540 and references therein.

[123] Antyarrhythmic activity: (a) Garrison G.L., Berlin K.D., Scherlag B.J., Lazzara R., Patterson E., Fazekas T., Sangiah S., Chen C.L., Schubot F.D., van der Helm D. *J. Med. Chem.* **1996**, *39*, 2559. (b) For a presentation summarizing the work of Astra Zeneca in this area, see: http://www.soci.org/News/~/media/Files/Conference%20Downloads/MedChem%20Sept%202011/Annika_Bjore_Presentation_1100_1145.ashx.

[124] Jeong S.H., Newcombe D., Sheridan J., Tigle M. *Drug Test Anal.* **2015**, *7*, 475.

[125] Kametani T.; Kigasawa K.; Hayasaka T. *Chem. Pharm. Bull.* **1965**, *13*, 300.

[126] (a) Pradhan A.A., Befort K., Nozaki C.,Gavériaux-Ruff C., Kieffer B.L. *Trends Pharmacol. Sci.* **2011**, *32*, 581. (b) Schunk E., Aigner C., Stefanova N., Wenning G., Herzog H., Scwarzer C. *Hippocampus* **2012**, *21*, 1010.

of bispidine derivatives make them useful for the transport of radioactive isotopes useful in Positron Emission Tomography (PET) and double imaging procedures.[127]

One final important aspect of the chemistry of bispidins (including the alkaloid spartein) is their use as chiral auxiliaries and catalysts.[128]

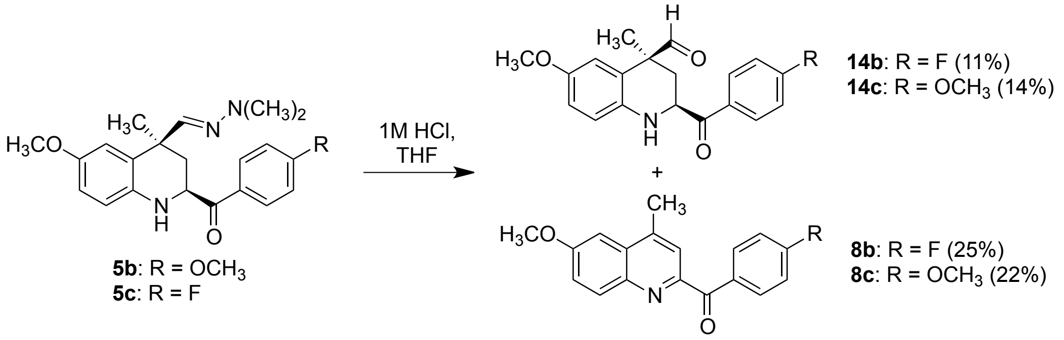
---

[127] (a) Comba P., Hunoldt S., Morgen M., Pietzsch J., Stephan H., Wadepohl H. *Inorg. Chem.* **2013**, *52*, 8131. (b) Stephan H., Walther M,, Fähnemann S., Ceroni P., Molloy J.K., Bergamini G., Heisig F., Müller C.E., Kraus W., Comba P. *Chem. Eur. J.* **2014**, *20*, 17011.

[128] See, for instance: Chuzel, O.; Riant, O. *Top. Organomet. Chem.* **2005**, *15*, 59, in Lemaire M., Mangeney P. (eds.) Chiral diazaligands for asymmetric synthesis, Springer-Verlag, 2005.

7.2 - Synthesis of derivatives of the 2,6-methanobenzo[*e*][1,4]diazocine nucleus

To perform the required hydrolysis of the hydrazone group and thus obtain the starting materials for our study (compounds **14**), we first resorted to methods previously employed by our group on similar substrates bearing an aryl group in C-2,[129] and thus started by investigating Cu(II)-promoted hydrolyses,[130] which unfortunately gave very complex reaction mixtures. We also attempted the use of aqueous HCl solutions[131] but, in spite of studying the effect of several concentrations (5M, 2M, 1M), both at room temperature and at 5 °C, the reactions were not clean and the yields of **14** were low. The major reaction products (compounds **8**) arose from decarbonylative aromatization of the starting materials (Scheme 7.3; see also Scheme 5.4). The lower stability of compounds **14** in comparison to their 2-aryl conterparts must be attributed to the presence of the carbonyl at C-2, which would stabilize radical intermediates of air-promoted dehydrogenation reactions *via* the captodative effect.[132]



Scheme 7.3.

After investigating a number of acidic conditions, we eventually discovered that treatment of tetrahydroquinolines **5** with a 1:1 mixture of 50% aqueous glyoxylic acid and THF at room temperature[133] allowed obtaining the derivatives **14a**-**k** in acceptable to good yields (Scheme 7.4 and Table 7.1).

---

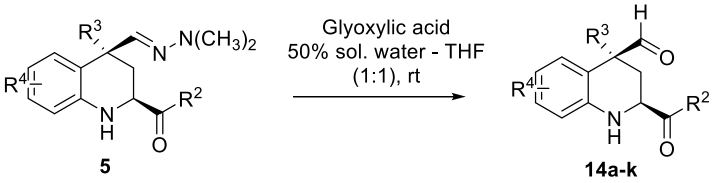
[129] Ribelles P., Ramos M.T., Menéndez J.C. *Org. Lett.*, **2012**, *14*, 1402.

[130] (a) Corey E.J., Knapp S. *Tetrahedron Lett.*, **1976**, *41*, 3667. (b) Mino T., Fukui S., Yamashita M. *J. Org. Chem.*, **1997**, *62*, 734.

[131] Mitra R.B., Reddy G.B. *Synthesis*, **1989**, 694.

[132] (a) Vieh H.J., Janousek Z., Merenyi R., Stella L. *Acc. Chem. Res.*, **1985**, *18*, 148. (b) Easton, C. J. *Chem. Rev.* **1997**, *97*, 53.

[133] Petroski R.J. *Synth. Commun.*, **2006**, *36*, 1727.

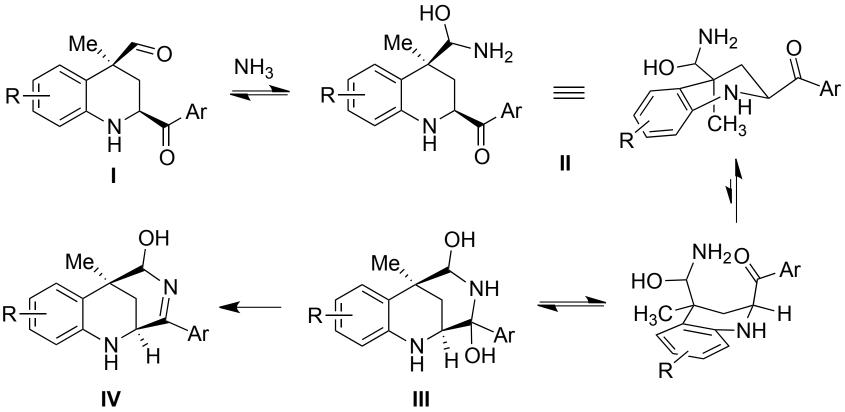


Scheme 7.4.

Table 7.1. Synthesis of dicarbonyl compounds ***14***

Cmpd	R^2	R^3	R^4	t (h)	Yield (%)
14a	C_6H_5	CH_3	6-OCH_3	20	85
14b	4-$OCH_3C_6H_4$	CH_3	6-OCH_3	24	80
14c	4-FC_6H_4	CH_3	6-OCH_3	15	82
14d	C_6H_5	CH_3	6,8-CH_3	22	78
14e	2-furyl	CH_3	6-OCH_3	22	83
14f	2-thienyl	CH_3	6-OCH_3	15	84
14g	C_6H_5	CH_2CH_3	6-OCH_3	22	81
14h	4-$OCH_3C_6H_4$	CH_3	6,8-OCH_3	19	95
14i	C_6H_5	CH_2CH_3	6,8-CH_3	18	83
14j	4-$OCH_3C_6H_4$	CH_3	6-CH_3	18	90
14k	4-$OCH_3C_6H_4$	CH_2CH_3	8-OCH_3	24	85

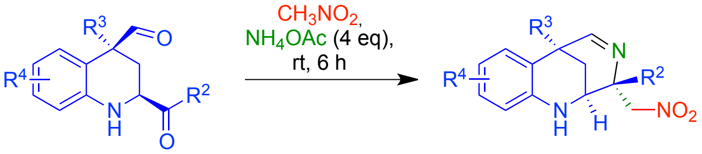
With dicarbonyl compounds **14** in hand, we next studied their transformation into the target structures by examining the reaction between compound **14b** and sources of ammonia, under a variety of conditions. However, we only obtained complex mixtures,



Scheme 7.5.

which we attributed to the low stability of the expected reaction product **IV**, owing to the simultaneous presence of an hydroxy function and an imino nitrogen attached to the same carbon (Scheme 7.5).

In an effort to trap the putative unstable species with a nucleophile, in the hope that the resulting products would sufficiently stable to handle, we run the reaction using as solvent nitromethane and an excess of ammonium acetate. Under these conditions, 2,6-methanobenzo[*e*][1,4]-diazocine derivatives **15** were obtained. This process is a multicomponent reaction, since the products are endowed with fragments of three starting materials: aldehydes **14**, nitromethane and ammonia, released from ammonium acetate. It is relevant to note that in this reaction a new quaternary carbon was generated, namely the former ketone carbon of the starting material **14**, with complete regio- and diastereoselectivity (Scheme 7.6). All reactions were quantitative, and the chromatography-unstable products were used directly for the next step.



Scheme 7.6.

*Table 7.2. Synthesis of 2,6-methanobenzo[e][1,4]diazocine derivatives **15***

Cmpd	R^2	R^3	R^4
15a	C_6H_5	CH_3	8-OCH_3
15b	4-$OCH_3C_6H_4$	CH_3	8-OCH_3
15c	4-FC_6H_4	CH_3	8-OCH_3
15d	C_6H_5	CH_3	8,10-CH_3
15e	2-furyl	CH_3	8-OCH_3
15f	2-thienyl	CH_3	8-OCH_3
15g	C_6H_5	CH_2CH_3	8-OCH_3
15h	4-$OCH_3C_6H_4$	CH_3	8,10-CH_3
15i	C_6H_5	CH_2CH_3	6,8-CH_3
15j	4-$OCH_3C_6H_4$	CH_3	6-CH_3
15k	4-$OCH_3C_6H_4$	CH_2CH_3	8-OCH_3

The structural determination of compounds **15** was performed on **15g** and stems from the presence of two quaternary carbons at 39 and 69 ppm and a signal of an imine function at 169.6 ppm in the ^{13}C-NMR spectrum. In ^{1}H-NMR, the imine proton shows a doublet at 7.84 ppm with a *J* of 1.5 Hz that can be ascribed to a W coupling with a proton of the bridge. The analysis of NOE effects confirmed the stereochemistry of the new quaternary carbon (Figure 7.1).

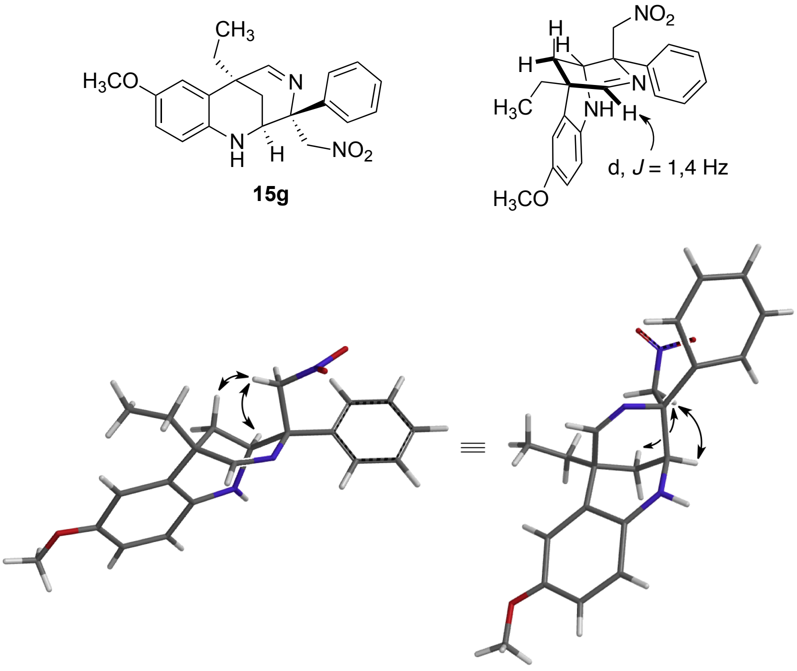
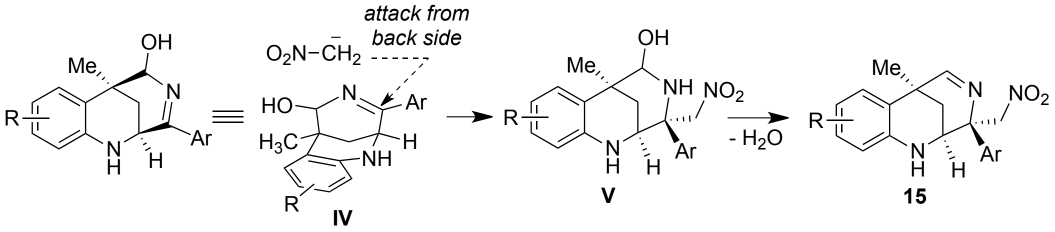


Figure 7.1.

A possible mechanism pathway explaining the generation of compounds **15** is summarized below (Scheme 7.7). It starts with the generation of compound **IV** in Scheme 7.5 by a first attack of ammonia to the aldehyde carbonyl followed by intramolecular cyclization, affording diol intermediate **III** that is converted into **IV** by dehydration. The C=N double bond in **IV** is conjugated with the C-2 aryl substituent, which explains its preferential formation over the other possible imine. Through a nitro-Mannich (aza-Henry) reaction,[134] a molecule of nitromethane, activated by the acetate base, can intervene in this step trapping intermediate **IV** by stereoselective attack from the less hindered side, furnishing intermediate **V**. A final dehydration reaction would afford the observed compounds **15**.

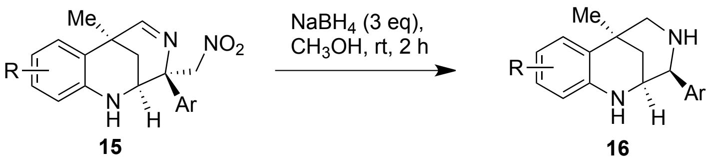
---

[134] For a review of nitro-Mannich reactions, see: Noble A., Anderson J.C. *Chem. Rev.*, **2013**, *113*, 2887.



Scheme 7.7.

In order to increase the stability of compounds **15**, we decided to reduce their imine bond by treatment with sodium borohydride in methanol. Interestingly, these conditions led also to loss of the nitromethyl substituent, presumably through a retro nitro-Mannich reaction, affording compounds, where the R^2 substituent maintains an equatorial orientation (Scheme 7.8 and Table 7.3.



Scheme 7.8.

Table 7.3. Synthesis of compounds ***16***

Cmpd	R^2	R^3	R^4	Yield (%)
16a	C_6H_5	CH_3	8-OCH_3	78
16b	4-$OCH_3C_6H_4$	CH_3	8-OCH_3	75
16c	4-FC_6H_4	CH_3	8-OCH_3	68
16d	C_6H_5	CH_3	8,10-$(CH_3)_2$	64
16e	2-furyl	CH_3	8-OCH_3	73
16f	2-thienyl	CH_3	8-OCH_3	70
16g	C_6H_5	CH_2CH_3	8-OCH_3	91
16h	4-$OCH_3C_6H_4$	CH_3	8,10-$(OCH_3)_2$	89
16i	C_6H_5	CH_2CH_3	8,10-$(CH_3)_2$	80
16j	4-$OCH_3C_6H_4$	CH_3	8-CH_3	76
16k	4-$OCH_3C_6H_4$	CH_2CH_3	8-OCH_3	82

The relative configuration of **16** has been analysed by NOE studies of compound **16b**, which supported an axial position for the C-2 proton (Figure 7.2).

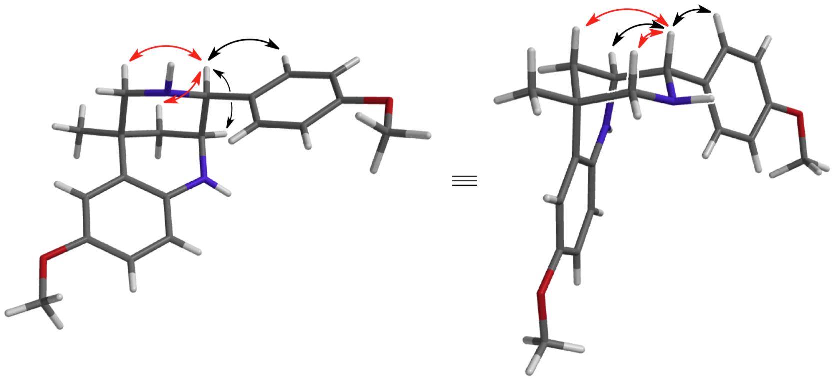
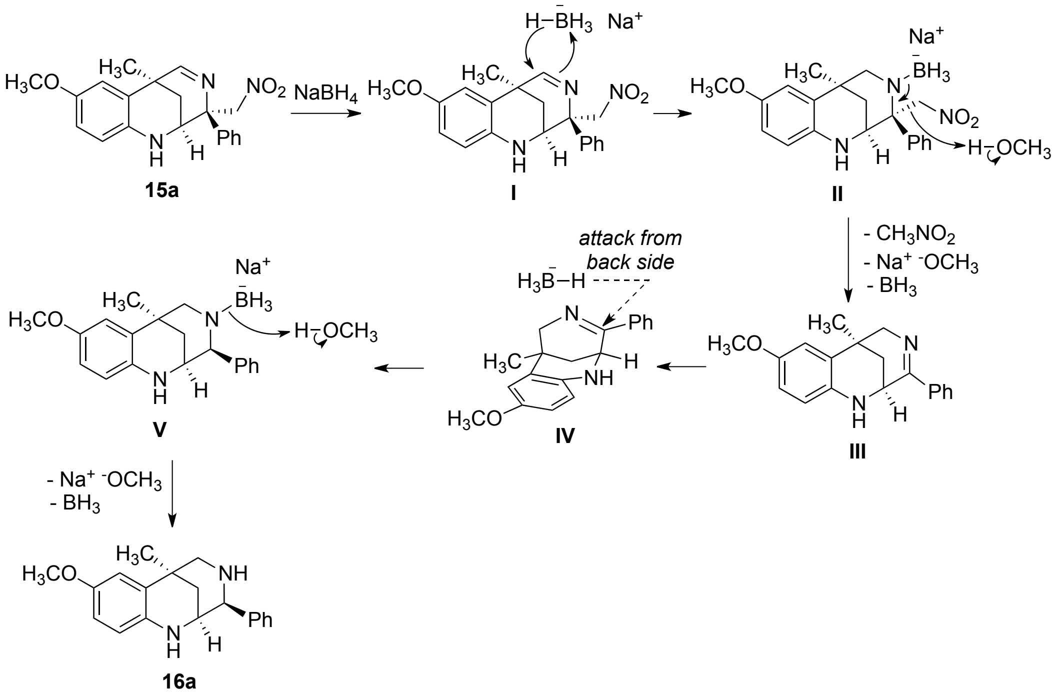


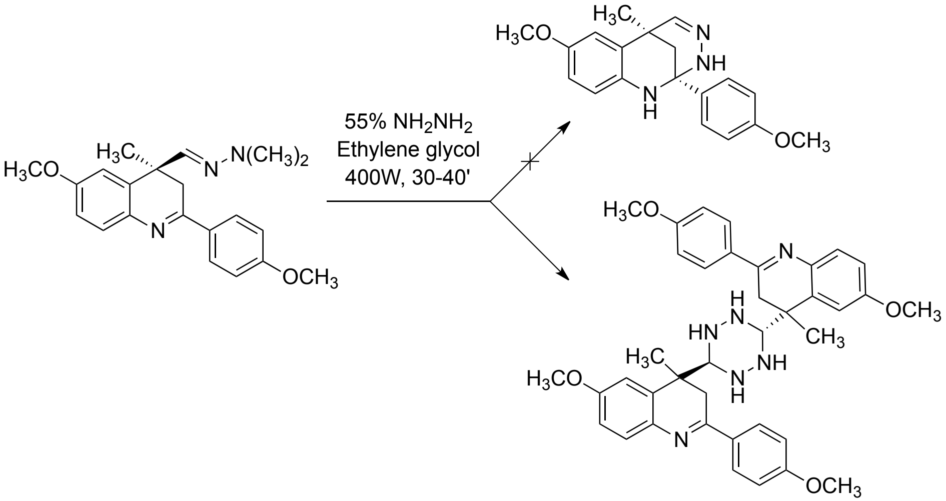
Figure 7.2.

An explanation of the formation of compounds **16** is summarized in Scheme 7.9. The proposed mechanism starts with the initial attack of hydride to the imine carbon, followed by elimination of the nitromethyl group via a retro nitro-Mannich reaction, leading to the formation of conjugated iminic intermediate **III**; a second attack of hydride to the imine function of intermediate **III** from the less hindered side finally leads to compound **16.**



Scheme 7.9

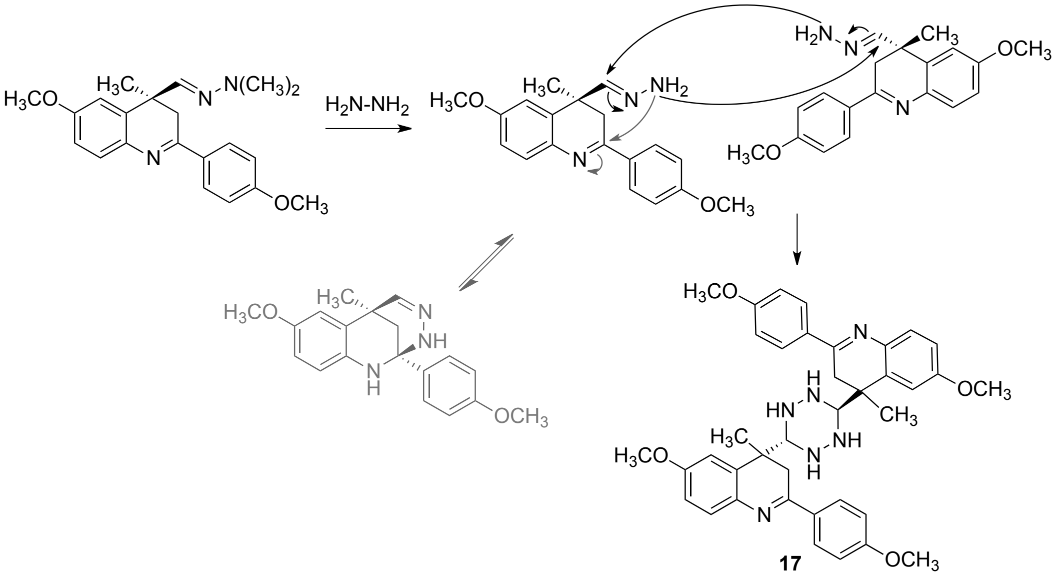
In an attempt to obtain an additional family of cytisine related bicyclic compounds, we examined the reaction of the partially dehydrogenated intermediate **II** described in Chapter 5 with hydrazine, in the hope of achieving a transhydrazonation-nucleophilic addition sequence. However, when the reaction mixture was irradiated in a conventional microwave oven at 400 W for 30-40 seconds it did did not afford the desired product, and yielded instead the dimeric 1,2,4,5-tetrazine derivative **17** in good yield. A characteristic singlet at 4.74 ppm in the ^{1}H-NMR spectrum and a peak at 78.5 ppm in ^{13}C-NMR were assigned to the CH of the tetrazinane ring, and the structure was finally confirmed by mass analysis. We have assumed a *trans* arrangement for the bulky substituents in the central ring, which would allow both of them to be equatorial.



17 (72%)

Scheme 7.10

A mechanistic proposal to explain the formation of the dimeric species **17** is summarized in Scheme 7.11 below.



Scheme 7.11

7.3 - Derivatives of the 2,6-methanobenzo[*e*][1,4]diazocine nucleus as neuroprotective agents

Neurodegenerative diseases (NDDs) are a heterogeneous group of disorders generally characterized by progressive losses of neurons. Their etiology has not been fully elucidated, and seems to be the result of a complex network of genetic and environmental factors. Nevertheless, some common pathological features have been individuated among different NDDs, which could represent good pharmacological targets. Thus, NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) present as common pathological characteristics an abnormal aggregation of proteins,[135] neuronal apoptosis,[136] inflammation[137] and oxidative stress.[138]

Among these factors, the excessive production of reactive species combined with an insufficient activity of antioxidant defense mechanisms, that lead to a situation of oxidative stress, has been involved in the pathogenesis of many neurodegenerative diseases, even if it is not totally clear if it is a cause or a consequence of neurodegeneration.[139] Because of its high consumption of oxygen and its high lipid content, the brain is particularly vulnerable to damage caused by ROS (reactive oxygen species) and RNS (reactive nitrogen species). These highly reactive species induce changes in the structure and function of cell membranes, proteins, lipoproteins, enzymes and genetic material. In particular, membranes are a primary target for ROS because lipid peroxidation processes lead to the decomposition of polyunsaturated fatty acids and the formation of reactive compounds that react with DNA or protein molecules and modify their structure and functions.[140]

In response to oxidative stress, the cell has different antioxidant systems. One of the major sensors of oxidative stress is the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2), that regulates the expression of genes regulated by Ep-RE (electrophile response elements), also called ARE (antioxidant response elements), whose protein products are

---

[135] Ross C.A., Poirier M.A. *Nat. Rev. Mol. Cell. Biol.*, **2005**, *6*, 891.

[136] (a) Okouchi M., Ekshyyan O., Maracine M., Aw T.Y. *Antioxid. Redox. Signal*, **2007**, *9*, 1059. (b) Radi E., Formichi P., Battisti C., Federico A. *J. Alzheimers. Dis.*, **2014**, *42*, 125.

[137] Zipp F., Aktas O. *Trends Neurosci.*, **2006**, *29*, 518.

[138] For reviews, see: (a) Gandhi S., Abramov A.Y. *Oxidative Medicine and Cellular Longevity*, **2012**, Article ID 428010, doi:10.1155/2012/428010. (b) Kim G.H., Kim J.E., Rhie S.J., Yoon S. *Exp. Neurobiol.*, **2015**, *24*, 325. (c) Niedzielska E., Smaga I., Gawlik M., Moniczewski A., Stankowicz P., Pera J., Filip M. *Mol. Neurobiol.*, **2016**, *53*, 4094. (d) Buendía I., Michalska P., Navarro E., Gameiro I., Egea J., León R. *Pharmacol. Therapeut.*, **2016**, *157*, 84.

[139] Andersen J.K. *Nat. Med.*, **2004**, *10*, 18.

[140] (a) Albarracín S.L., Stab B., Casas Z., Sutachan J.J., Samudio I., González J., Gonzalo L., Capani F., Morales L., Barreto G.E. *Nutr. Neurosci.*, **2012**, *15*, 1. (b) Fritz K.S., Petersen D.R. *Free Radic. Biol. Med.*, **2013**, *59*, 85.

involved in the detoxification and elimination of reactive oxidants and electrophilic agents. These proteins include cytoprotective enzymes such as NAD(P)H quinone oxidoreductase-1 (NQO1), heme oxygenase-1 (HO-1), gluthathione transferase (GST) and gluthathione reductase (GR).[141] Apart from this antioxidant pathway, Nrf2 regulates a wider range of activities like drugs metabolism, inflammation, cell growth and lipid and glucose metabolism.[142] Furthermore, recently it was demonstrated that Nrf2 regulates also different protective proteins such as anti-inflammatory interleukin IL-10[143] and the brain derived neurotrophic factor.[144]

These varied and important biological functions make Nrf2 an extremely interesting pharmaceutical target,[145] with many studies demonstrating its importance in age-related diseases, due to its clear value in the protection pathway.[146]

Under normal conditions, Nrf2 is in the cytoplasm, anchored to a repressor protein known as Kelch-like ECH-associated protein-1 (Keap-1), that prevents the translocation of Nrf2 to the nucleus and thus keeps Nrf2 inactive. Keap-1 is an excellent sensor for oxidative and electrophilic stress owing to the presence of three cysteine residues that undergo chemical modifications in the presence of reactive species, either by alkylation in the presence of electrophiles or by dimerization to cystin by oxidation. These modifications cause a structural change in Keap-1 with the consequent release of Nrf2 that can then migrate into the nucleus. Once in the nucleus, Nrf2 heterodimerizes with other proteins and binds to DNA at the level of Ep-RE. This activation mechanism is known as the "hinge and latch" model (Figure 7.3).[147]

---

[141] (a) de Vries H.E., Witte M., Hondius D., Rozemuller A.J., Drukarch B., Hoozemans J., van Horssen *J. Free Radic. Biol. Med.*, **2008**, *45*, 1375. (b) Nguyen T., Nioi P., Pickett C.B. *J. Biol. Chem.*, **2009**, *284*, 13291.

[142] (a) Kitteringham N.R., Abdullah A., Walsh J., Randle L., Jenkins R.E., Sison R., Goldring C.E., Powell H., Sanderson C., Williams S., Higgins L., Yamamoto M., Hayes J., Park B.K. *Proteomic J. Proteomics*, **2010**, *73*, 1612. (b) Hirotsu Y., Katsuoka F., Funayama R., Nagashima T., Nishida Y., Nakayama K., Engel J.D., Yamamoto M. *Nucleic Acids Res.*, **2012**, *40*, 10228.

[143] Otterbein L.E., Bach F.H., Alam J., Soares M., Lu H.T., Wysk M., Davis R.J., Flavell R.A., Choi A.M. *Nat. Med.*, **2000**, *6*, 422.

[144] Kwak M.K., Wakabayashi N., Greenlaw J.L., Yamamoto M., Kensler T.W. *Mol. Cell. Biol.*, **2003**, *23*, 8786.

[145] (a) Magesh S., Chen Y., Hu L. *Agents. Med. Res. Rev.*, **2012**, *32*, 687. (b) Abed D.A., Goldstein M., Albanyan H., Jin H., Hu L. *Acta Pharm. Sin. B*, **2015**, *5*, 285.

[146] (a) Jaramillo M.C., Zhang D.D. *Genes Dev.*, **2013**, *27*, 2179. (b) Bhakkiyalakshmi E., Sireesh D., Rajaguru P., Paulmurugan R., Ramkumar K.M. *Pharmacol. Res.*, **2015**, *91*, 104.

[147] Tong K.I., Kobayashi A., Katsuoka F., Yamamoto M. *Biol. Chem.*, **2006**, *387*, 1311.

Recently, a new pathway of regulation of Nrf2 involving α_7 nicotinic receptors has been demonstrated.[148] Generally, several kinases are differently involved in the activation of Nrf2

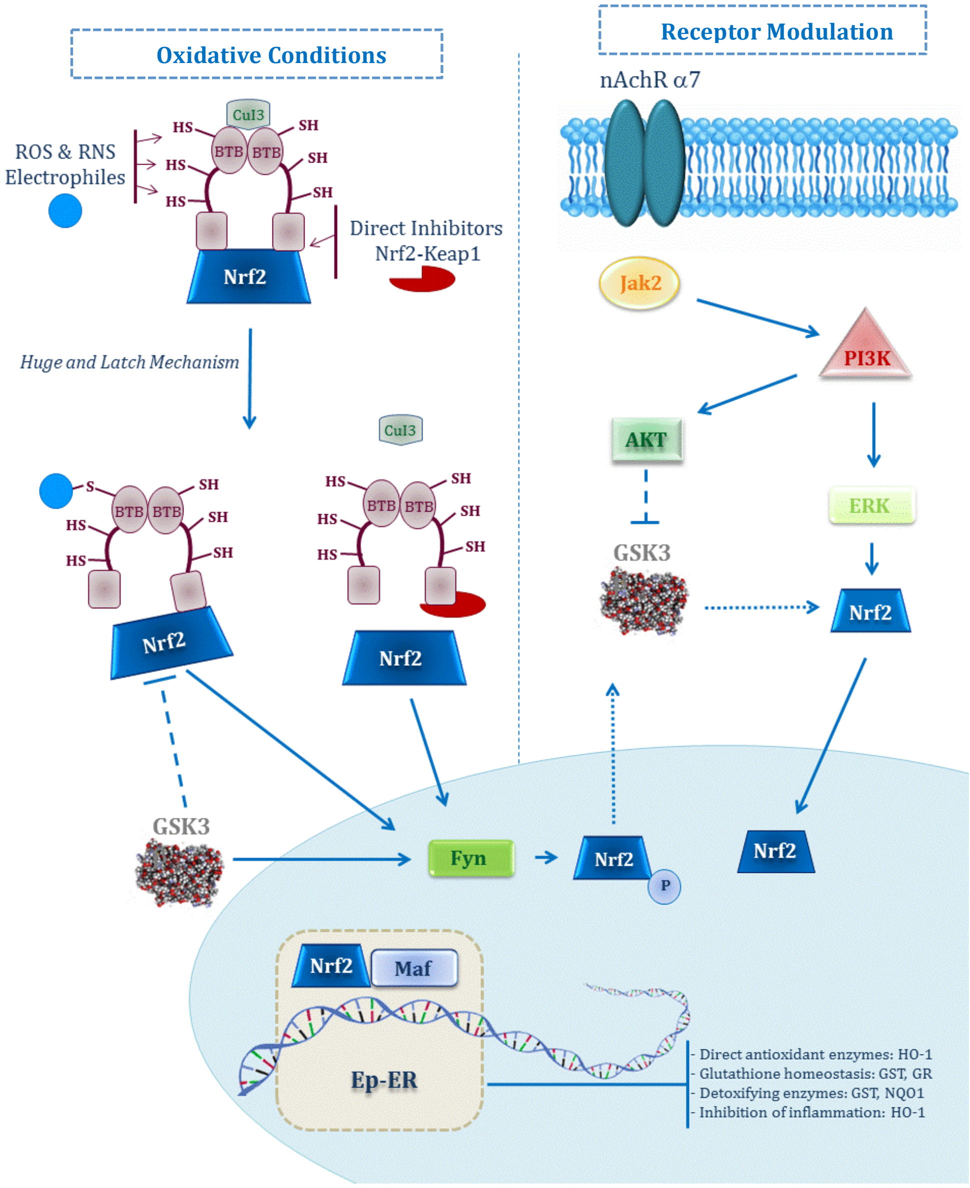


Figure 7.3: Pathway of Nrf2-EpER.

---

[148] (a) Egea J., Rosa A.O., Sobrado M., Gandía L., López M.G., García A.G. *Neuroscience*, **2007**, *145*, 866. (b) Egea J., Rosa A.O., Lorrio S., del Barrio L., Cuadrado A., López M.G. *Pain*, **2009**, *146*, 75. (c) Parada E., Egea J., Buendía I., Negredo P., Cunha A.C., Cardoso S., Soares M.P., López M.G. *Antiox. Redox Sign.* **2013**, *19*. (d) Parada E., Buendía I., León R., Negredo P., Romero A., Cuadrado A., López M.G., Egea J. *J. Pineal. Res.*, **2014**, *56*, 204. (e) Navarro E., Buendía I., Parada E., León R., Jansen-Duerr P., Pircher H., Egea J., López M.G. *Biochem. Pharmacol.*, **2015**, 97, 473.

via specific phosphorylation sites. In this pathway, the activation of α_7 receptors leads to the activation of PI3K (phosphatidylinositide-3-kinases)[149] that then promote the action of Akt, a kinase able to inactivate by phosphorylation GSK3β, a negative regulator of Nrf2. PI3K also activates an extracellularly regulated kinase ERK,[150] that favours Nrf2 migration to the nucleus and thus its binding to the ARE sequence.

To conclude, Nrf2-EpRE system seems to be a very complex and important defence mechanism with a considerable relevance in NDDs where the oxidative stress is a common feature, due to a deregulated pathway and due to the age risk factor present in all NDDs. With these compelling data, the development of compounds able to induce Nrf2-EpRe may represent a strategic approach in the NDDs. One pharmaceutical strategy is the development of electrophile compounds able to interact with the cysteine moieties of Keap1 in order to enhance the releasing of Nrf2 and consequently favour the activation of antioxidant defence; another strategy investigated more recently consist in the preparation of inhibitors of protein-protein interaction between Keap-1 and Nrf2.[151] Finally, the development of α_7 nicotinic agonists has emerged as a new and promising strategy towards Nrf2 activation. In this context, the neuroprotective potential of α_7 nicotinic receptor has been investigated during the last years, and their neuroprotective properties were confirmed in several neurodegenerative models.[152] Besides its role in Nrf2 activation, and based on the role of α_7 nicotinic receptors in the "cholinergic anti-inflammmatory pathway" in the peripheral system,[153] it has been recently suggested that α_7 nAChR also plays a key neuroprotective role in the CNS *via* activation of hemeoxygenase I (HO-1) or regulation of astrocyte apoptosis.[154] Hence, α_7 nAChR agonists can be regarded useful agents able to intervene in these complex cellular pathways, opening up a new opportunity to treat different NDDs.[155,156]

---

[149] Nakaso K., Yano H., Fukuhara Y., Takeshima T., Wada-Isoe K., Nakashima K. *FEBS Lett.*, **2003**, *546*, 181.

[150] Keum Y.S., Yu S., Chang P.P., Yuan X., Kim J.H., Xu C., Han J., Agarwal A., Kong A.N. *Cancer Res.*, **2006**, *66*, 8804.

[151] Jiang Z.-Y., Lu M.-C., You Q.-D. *J. Med. Chem.*, **2016**, *59*, 10837.

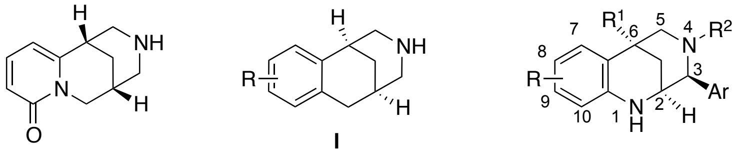
[152] (a) Bencherif M. *Acta Pharmacol. Sin.*, **2009**, *30*, 702. (b) Kawamata J., Shimohama S. *J. Alzheimers Dis.*, **2011**, *24*, 95.

[153] (a) Borovikova L.V., Ivanova S., Zhang M., Yang H., Botchkina G.I., Watkins L.R., Wang H., Abumrad N., Eaton J.W., Tracey K.J. *Nature*, **2000**, *405*, 458. (b) Wang H., Yu M., Ochani M., Amella C.A., Tanovic M., Susarla S., Li J.H., Wang H., Yang H., Ulloa L., Al-Abed Y., Czura C.J., Tracey K.J. *Nature*, **2003**, *421*, 384.

[154] (a) Denga J., Qia X.L., Guana Z.Z., Yana X.M., Huangc Y., Wangc Y.L. *J. Pharm. Pharmacol.*, **2013**, *65*, 1736. (b) Han Z., Li L., Wang L., Degos V., Maze M., Su H. *J. Neurochem.*, **2014**, *131*, 498. (c) Yuan L., Xiaoning Z., Yujian H., Chenlei Z., Jie W., Devin H.T., Juan J., Weimin F., Zuhu H., Jun H. *Neuropharmacol.*, **2015**, *91*, 87. (d) Bordia T., McGregor M., Papke R.L., Decker M.W., McIntosh J.M., Quik M. *Experiment. Neurology*, **2015**, *263*, 277.

[155] For a review of the α_7 nicotinic acetylcholine receptor is a pharmacological target, see: *Int. J. Mol. Sci.* **2012**, *13*, 2219.

Literature precedent demonstrates that many compounds with a diazabicylic nucleus with basic nitrogen atoms show good nicotinic activity. The well-known alkaloid cytisine is a partial agonist of $\alpha_4\beta_2$ nAchRs, used in smoking cessation therapy.[157] It is noteworthy that cytisine is a full agonist of α_7 nAchR, although with low affinity, and could represent a good starting point for further investigations.[158] Thus, O'Neill's group have disclosed a family of all-carbon derivatives of cytisine (compounds **I**), which seems to be promising.[159] Due to the structural similarity between these molecules and our compounds **16**, we decided to study their potential agonistic action towards nicotinic receptors and their potential as neuroprotective agents. We also included in this study the closely related compounds **II**, previously synthesized in our group (Figure 7.4 and Table 7.4).[121] The pharmacological studies were carried by Dr. Izaskun Buendía and Dr. Rafael León at the Instituto-Fundación Teófilo Hernando, Universidad Autónoma, Madrid.



(-)-Cytisine (absolute configuration)

I (relative configuration)

16 (R^2 = H)
II (R^2 = NMe_2)
(relative configuration)

Figure 7.4

---

[156] For a general review of nicotinic receptors: as therapeutic targets in the nervous system, see: Taly A., Corringer P.J., Guedin D., Lestage P., Changeux J.P., *Nature Rev. Drug Discov.* **2009**, *8*, 733.

[157] Tutka P., Zatoński W. *Pharmacol. Rep.*, **2005**, *58*, 777.

[158] Coe J.W., Brooks P.R., Vetelino M.G., Wirtz M.C., Arnold E.P., Huang J., Sands S.B.ThomasI.D., Lorraine A.L., Carol B.F., Shrikhande A., Heym J.H., Schaeffer E., Rollema H., Lu Y., Mansbach R.S., Chambers L.K., Rovetti C.C., Schulz D.W., Tingley F.D., O'Neill B.T. *J. Med. Chem.*, **2005**, *48*, 3474.

[159] Coe J.W., Vetelino M.G., Bashore C.G., Wirtz M.C., Brooks P.R., Arnold E, Lebel L.A., Fox C.B., Sands S.B., Davis T.I, Schulz D.W., Rollema H., Tingley F.D., O'Neill B.T. *Bioorg. Med. Chem. Lett.*, **2005**, *15*, 2974.

Table 7.4. Structures of the compounds assayed

Cmpd	Ar	R	R¹	R²
16a	C_6H_5	8-OCH_3	CH_3	H
16b	4-$OCH_3C_6H_4$	8-OCH_3	CH_3	H
16c	4-FC_6H_4	8-OCH_3	CH_3	H
16d	C_6H_5	8,10-$(CH_3)_2$	CH_3	H
16e	2-furyl	8-OCH_3	CH_3	H
16f	2-thienyl	8-OCH_3	CH_3	H
16g	C_6H_5	8-OCH_3	CH_2CH_3	H
16h	4-$OCH_3C_6H_4$	8,10-$(OCH_3)_2$	CH_3	H
IIa	C_6H_5	8-OCH_3	CH_3	$N(CH_3)_2$
IIb	4-$OCH_3C_6H_4$	8-OCH_3	CH_3	$N(CH_3)_2$
IIc	4-FC_6H_4	8-OCH_3	CH_3	$N(CH_3)_2$
IId	4-FC_6H_5	8,10-$(CH_3)_2$	CH_3	$N(CH_3)_2$
IIe	4-FC_6H_5	7,9-$(CH_3)_2$	CH_3	$N(CH_3)_2$
IIf	2-thienyl	8-OCH_3	CH_3	$N(CH_3)_2$

The ability to induce Nrf2 was evaluated in AREc32 cells, which constitutively express several copies of the ARE sequences followed by the luciferase reporter gene. The activation of ARE sequences, which is proportional to Nrf2 induction, causes an increase in luciferase activity. The activity of each compound is expressed as the concentration necessary to double the basal activity, and therefore the more active agents show lower concentration values. The 4-dimethylamino derivatives showed a better capacity for Nrf2 induction, as shown in Figure 7.4 and Table 7.5. In particular, derivatives **IIa** (1.92 ± 1.03), **IIb** (7.30 ± 0.37), **IIc** (2.38 ± 0.46) and **IIf** (4.21 ± 1.08) were more potent than their N-unsubstituted

Nrf2 induction

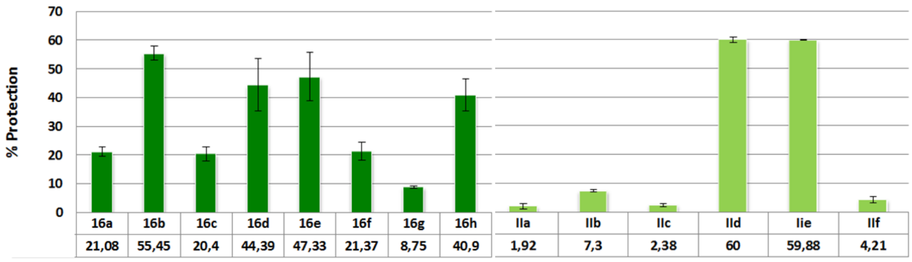


Figure 7.4.

counterparts. In other cases, a direct comparison was not possible due to differences in the additional substituents.

To evaluate the direct antioxidant capacity of compounds, the ORAC (*Oxygen Reactive Absorbance Capacity*) assay was initially employed. The assay measures the oxidative degradation of fluorescein, a highly fluorescent molecule, by peroxyl radicals, produced by free radical generators Antioxidant agents protect fluorescein from the oxidative damage, preserving its fluorescence. The degree of antioxidant activity is quantified using as a standard the antioxidant trolox, a hydrosoluble vitamin E analogue, and therefore the antioxidant ability of a compound is quantified as *trolox equivalent antioxidant capacity*, TEAC. As shown in Figure 7.5, all compounds have good antioxidant activities, with the exception of **IIc** and **IId**. In particular, most compounds of the first series, including **16a**, **16b**, **16c**, **16e**, **16f** and **16g** showed activities above 2 TEAC. Compounds **IIa** and **IIb** were also very potent in this assay.

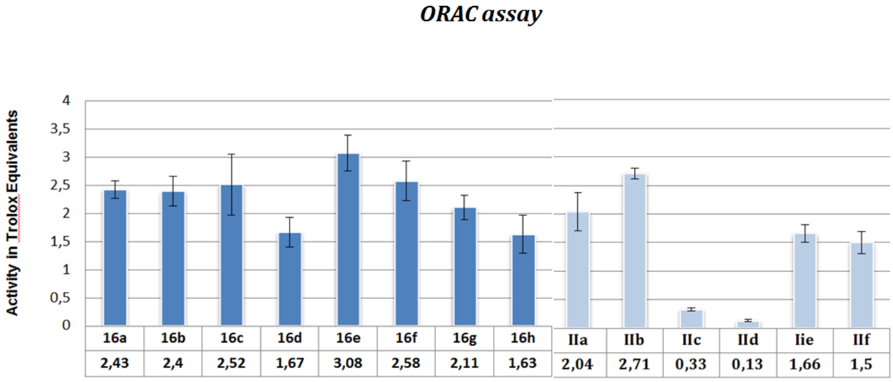


Figure 7.5.

An assay to evaluate neuroprotection in an oxidative stress model was then undertaken (Figure 7.6 and Table 7.6). Rotenone and oligomycin A block complexes I and V, respectively, of the mitochondrial electron transport chain, thus disrupting ATP synthesis. The mixture of rotenone plus oligomycin A (rot/olig) is able to cause oxidative stress, increase α-sinuclein aggregation and formation of Lewy bodies i*n vivo*, constituting a good model to evaluate neuroprotective agents.[160] All our compounds showed some degree of neuroprotection in this model, and in particular compounds **16h** and **16d** provided about 50% protection, and many others showing neuroprotection above 30%.

Rotenone / Oligomycin A Assay

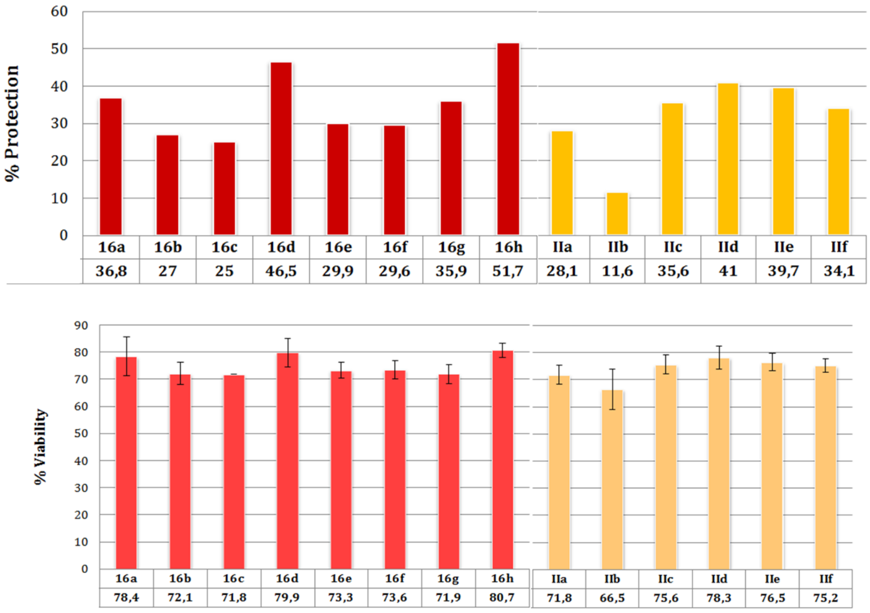


Figure 7.6

Okadaic acid (OKA) is a potent and selective inhibitor of protein phosphatases PP2A and PP1.[161] The inhibition of these protein phosphatases in human brain slices leads to tau hyperphosphorylation.[162] Thus, okadaic acid is able to induce Alzheimer's disease-like symptoms, including cognitive impairment and oxidative stress.[163] It also causes neuronal cell death *in vitro* and *in vivo*.[164] For these reasons, okadaic acid-induced neurotoxicity is a

---

[160] (a) Betarbet R., Sherer T.B., MacKenzie G., Garcia-Osuna M., Panov A.V., Greenamyre J.T. *Nat. Neurosci.*, **2000**, *3*, 1301. (b) González-Muñoz G.C., Arce M.P., López B., Pérez C., Romero A., del Barrio L., Martín de Saavedra M.D., Egea J., León R., Villarroya M., López M.G., García A.G., Conde S., Rodríguez-Franco M.I. *Eur. J. Med. Chem.*, **2011**, *46*, 2224.

[161] Cohen P., Holmes C.F., Tsukitani Y. Trends *Biochem. Sci.*, **1990**, *15*, 98.

[162] Kim Y., Huang J., Cohen P., Matthews H.R. *J. Biolog. Chem.*, **1993**, *268*, 18513.

[163] (a) Tunez I., Muñoz M del C., Feijoo M., Muñoz-Castaneda J.R., Bujalance I., Valdelvira M.E., Montilla López P. *J. Pineal. Res.*, **2003**, *34*, 265. (b) Kamata P.K., Totaa S., Saxenaa G., Shuklaa R., Nath C. *Brain Research*, **2010**, *1309*, 66.

[164] He J., Yamada K., Zou L.B., Nabeshima T. *J. Neural. Transm.*, **2001**, *108*, 1435.

good model of Alzheimer's disease and oxidative stress. As shown in Figure 7.7 and Table 8, most of the compounds under assay, with the sole exception of **IIb**, showed good protective activities. Again in this case, compound **16h**, with *ca.* 50% neuroprotective effect, showed the highest activity.

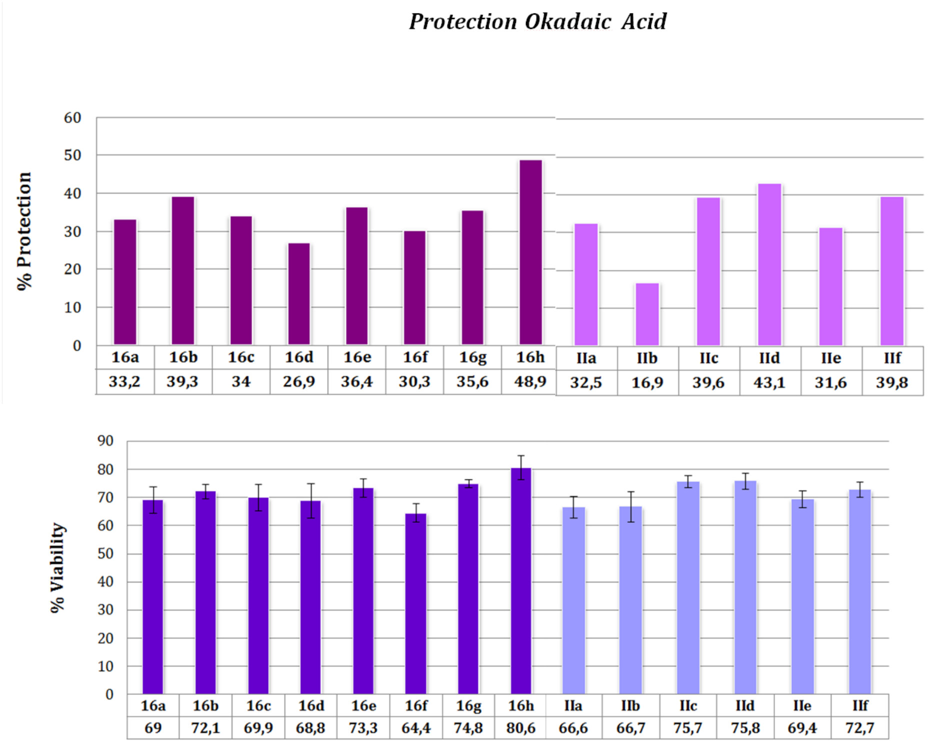


Figure 7.7.

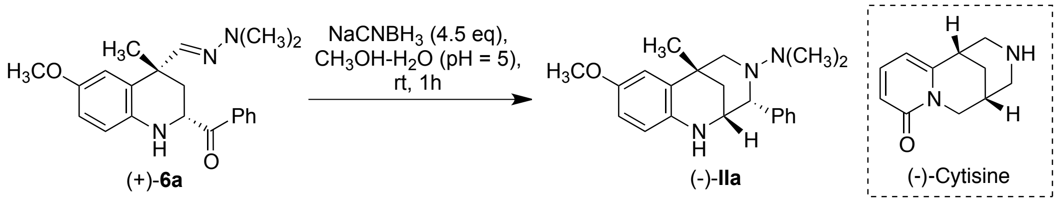
Finally, a preliminary study of the ability of our compounds to antagonize the effects of cytisine was carried out, with the results shown in Table 7.8. It is interesting to note that some of the most potent compounds as neuroprotectors (*e.g.*, compound **16h**) also showed the best activity in this assay.

Table 7.8.

Cmpd	Citysine block (20μM)
16a	44,41 ± 5,167***
16b	32,76 ± 5,296***
16c	35,23 ± 2,105**
16d	45,1 ± 8,04***
16e	29,33 ± 2,746**
16f	31,68 ± 6,661***
16g	41,88 ± 8,558***
16h	64,31 ± 2,581***
IIa	45,59 ± 2,919***
IIb	41,07 ± 2,349***
IIc	41,53 ± 5,862***
IId	19,44 ± 6,339*
IIe	44,26 ± 6,975***
IIf	42,2 ± 2,44***

It can be concluded that our compounds exert neuroprotective effects in two different cellular models, although the correlation between this activity and Nrf2 induction is not clear, and hence the neuroprotection could depend on other cellular pathways, including other routes associated to nicotinic receptors. Further investigations are in progress to establish more clearly the mechanism of action of these compounds.

To conclude this part of the thesis, we examined briefly the synthesis of enantiomerically pure cytisine analogues. It is relevant to note in this regard that the absolute configuration of cytisine corresponds to the one that we obtain for the C-2 and C-4 stereocenters in the tetrahydroquinoline asymmetric synthesis. Thus, we prepared a representative example of compounds **II**, namely (-)-**IIa**, by treating the corresponding enantiopure tetrahydroquinoline **6a** with sodium cyanoborohydride under slightly acidic conditions.[121] Compound **IIa** was isolated in excellent yield via a fully diastereoselective domino process that comprises hydrazine reduction, cyclocondensation and imine reduction steps (Scheme 7.12). The synthetic manipulation did not affect the enantiomeric purity of the product, which was isolated in 97% ee. This result paves the way to the synthesis of enantiomerically pure cytisine analogues, with a view to study their pharmacology in the future


H3CO
H3C
N(CH3)2
N
N
H
Ph
O
(+)-6a
NaCNBH3 (4.5 eq),
CH3OH-H2O (pH = 5),
rt, 1h
H3CO
H3C
N
N(CH3)2
Ph
N
H
H
(-)-IIa
H
NH
N
H
O
(-)-Cytisine

Scheme 7.12.

8 – Molecular docking studies on luotonin analogues

8.1 - Introduction

In this chapter we deal with the use of molecular docking as useful tool to rationalize biological results and address the new design of compounds for a better interaction with a specific target. More specifically, we will describe our contribution to an ongoing project in our group aimed at the optimization of the anticancer activity of the alkaloid luotonin A, a natural topoisomerase I inhibitor. In this case, our contribution was not synthetic and was focused on computational studies to aid compound design and assist the rationalization by computational methods of the cytotoxic activity of three classes of molecules related to luotonin.[165]

---

[165] A part of this work has been published: González-Ruiz V., Pascua I., Fernández-Marcelo T., Ribelles P., Bianchini G., Sridharan V., Iniesta P., Ramos M. T., Olives A. I., Martín M. A., Menéndez J. C. *PLoS ONE*, **2014**, *9*, article e95998, pp. 1-12.

8.2 - Cancer and the camptothecins

Cancer continues to be one of the leading causes of death worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012.[166] The number of new cases is expected to rise by about 70% over the next 2 decades. An appropriate cancer diagnosis is fundamental for an effective treatment because every cancer type requires a specific treatment regimen which includes one or more modalities such as surgery, and/or radiotherapy, and/or chemotherapy. Regarding chemotherapy, the introduction of new active chemical entities is still necessary in order to fight the disease.[167]

Topoisomerases are present in all living organisms and are crucial for relieving torsional tension in supercoiled DNA in the course of DNA replication, transcription and reparation.[168] Topoisomerases, and topoisomerase 1 in particular, are among the most relevant anticancer targets.[169] The camptothecins, specially irinotecan, topotecan and belotecan (Figure 8.1), are the main family of clinically relevant topoisomerase 1 inhibitors.[170] These compounds have a

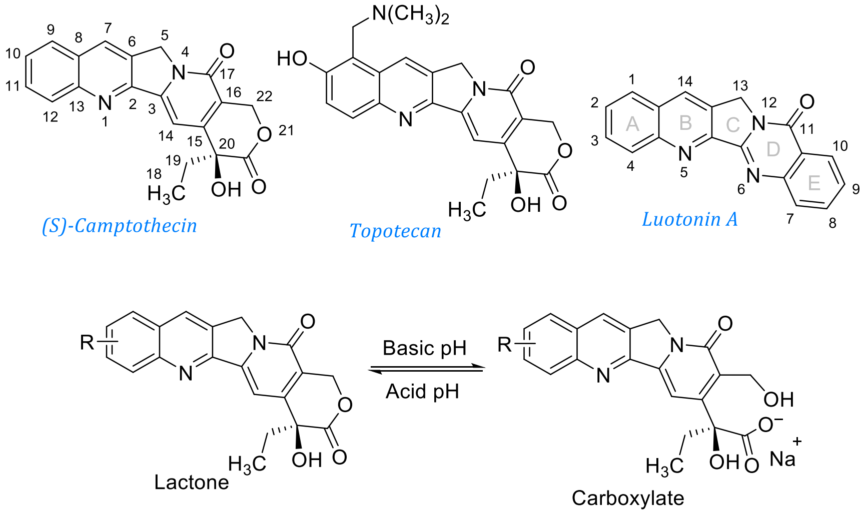


Figure 8.1.

---

[166] World cancer report **2014** (http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014).

[167] For a recent monograph on cancer chemotherapy, see: Avendaño C., Menéndez J.C. Medicinal Chemistry of anticancer drugs, 2nd Edition. Elsevier, 2015.

[168] Chen S.H., Chan N.L., Hsieh T.S. *Ann. Rev. Biochem.*, **2013**, *82*, 139.

[169] (a) Pommier Y. *DNA topoisomerases and cancer. New York: Springer*. **2011**. (b) Pommier Y. *ACS Chem. Biol.,* **2013**, *8*, 82. (c) Ashour M.E., Atteya R., El-Khamisy S.F. *Nature Rev. Cancer*, **2015**, *15*, 1.

[170] Kacprzak K.M., Ramawat K.G., Mérillon J.M. (*Eds.) Natural Products Heidelberg, Berlin: Springer*, **2013**, 643.

planar, pentacyclic core comprising a lactone functional group in ring E and containing a stereocenter at C-20, which must be in the S configuration for camptothecins to be active. Their pharmacologic target is the covalent topoisomerase 1-DNA binary complex, where they can bind non-covalently at the interphase formed between both macromolecules during the enzymatic catalytic cycle. This binding stabilizes the complex and retards its dissociation, finally leading to irreversible DNA damage and cell death.[171]

In spite of their widespread use, they show severe undesired effects, their main dose-limiting toxicities being myelosupression, diarrhea and bone marrow toxicity.[172] Another complication of the camptothecins is their low stability,[173] which is due to the easy opening of its lactone E ring to give an inactive hydroxyl acid form (camptothecin carboxylate) that is sequestered by seric albumin.[174] The lactone-hydroxy acid equilibrium is relevant to bladder toxicity, another problem associated to the clinical use of the camptothecins that is due to accumulation of the active δ-lactone form owing to lactonization at the acidic pH of urine.[175]

Considering these limitations, camptothecin analogues lacking the lactone ring seem attractive, but during decades this structural feature was believed to be essential for activity. The discovery of the stabilization of the human topoisomerase 1-DNA covalent binary complex by the alkaloid luotonin A, closely related to the camptothecins but having an aromatic E ring, brought about a landmark change in this paradigm.[176] Furthermore, luotonin A is achiral, a feature that can be viewed as an advantage in terms of its potential role as a lead compound in drug discovery and development because it simplifies synthetic access to new analogues and their analytical control. In summary, although the potency of luotonin is lower than that of the camptothecins, it does provide an excellent opportunity for the discovery of improved topoisomerase 1 inhibitors.

The low potency of the natural luotonin A has prompted the synthesis and biological evaluation of a considerable number of analogues.[177,178] Nevertheless, these studies have

---

[171] Castelli S., Coletta A., D'Anness I., Fiorani P., Tesauro C., Desideri A. *Biol. Chem.*, **2012**, *393*, 1327.

[172] (a) Venditto V.J., Simanek E.E. *Mol. Pharmaceutics*, **2010**, *7*, 307. (b) Swami U., Goel S., Mani S. *Curr. Drug. Targets*, **2013**, *14*, 777.

[173] Pommier Y. *Chem. Rev.*, **2009**, *109*, 2894.

[174] Marszałł M.P., Buciński A., Kruszewski S., Ziomkowska B. *J. Pharm. Sci.*, **2011**, *100*, 1142.

[175] Pizzolato J.F., Saltz L.B. *Lancet*, **2003**, *361*, 2235.

[176] Cagir A., Jones S.H., Gao R., Eisenhauer B.M.A., Hecht S.M. *J. Am. Chem. Soc.*, **2003**, *125*, 13628.

[177] For representative examples, see: (a) Tseng M.C., Chu Y.W., Tsai H.P., Lin C.M., Hwang J., Chu Y.-H. *Org. Lett.*, **2011**, *13*, 920. (b) Boisse T., Gavara L., Gautret P., Baldeyrou B., Lansiaux A., et al. *Tetrahedron Lett.*, **2011**, *52*, 1592. (c) Golubev A.S., Bogomolov V.O., Shidlovskii A.F., Dezhenkova L.G., Peregudov A.S., et al. *Russ. Chem. Bull., Int. Edition*, **2011**, *59*, 209.

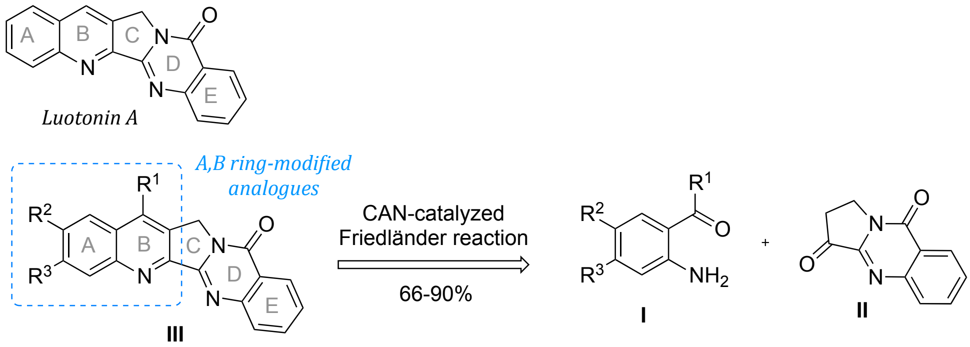
been limited by the constraints found in known synthetic methodologies, specially in terms of A and B ring modification.

---

[178] For reviews of the chemistry and pharmacology of the luotonins, see: Zhongze M., Yoshio H., Taro N. *Heterocycles* **2005**, *65*, 2203. (b) Huang W., Liu J., Wang C. *Chin. J. Org. Chem*. **2009**, *29*, 1533. (c) Liang J.L., Cha H.C., Jahng Y. *Molecules*, **2011**, *16*, 4861.

8.3 - A,B Ring-modified luotonin A analogues

In this context, our group became interested in the analysis of the structure-activity relationship of luotonin A derivatives with modification in the A and B rings with the aim to potentiate their cytotoxic activity. The Friedländer reaction between precursors corresponding to the CDE fragment and aromatic *o*-aminoketones or aldehydes provides, in principle, an excellent opportunity for this type of structural manipulation, but it had previously found no use in this area, presumably due to poor yields. Taking advantage of the discovery of Ce(IV) ammonium nitrate (CAN) as a very efficient Friedländer catalyst,[179] our colleague Pascual Ribelles applied this strategy to the synthesis of a small library of A and B ring-modified luotonin A analogues **III** from o-aminobenzophenones **I** and compound **II**, an oxidized derivative of the alkaloid vasicinone that was prepared using a literature method.[180]



Cmpd	R^1	R^2	R^3
IIIa	H	H	H
IIIb	CH_3	H	H
IIIc	C_6H_5	H	H
IIId	C_6H_5	Cl	H
IIIe	C_6H_5	Br	H
IIIf	3,5-$(CH_3)_2C_6H_3$	H	H
IIIg	3,5-$(CH_3)_2C_6H_3$	H	CH_3

Scheme 8.1.

---

[179] Sridharan V., Ribelles P., Ramos M.T., Menéndez J.C. *J. Org. Chem.*, **2009**, *74*, 5715.

[180] Molina P., Tárraga A., González-Tejero A. *Synthesis*, **2000**, 1523.

An assay of DNA relaxation was undertaken, in collaboration with the groups of Dr. M. Antonia Martín (Department of Analytical Chemistry) and Pilar Iniesta (Department of Biochemistry and Molecular Biology) at our School of Pharmacy. A representative electrophoresis gel showing the separation of DNA topomers after incubation of a plasmid in the presence of human topoisomerase 1 and the inhibitors under assay is shown in Figure 8.2.¡Error! Marcador no definido. Luotonin A (**IIIa**) showed a lower inhibitory activity (++) than CPT, as expected. Interestingly, all the newly synthesized luotonin analogues exhibited an inhibitory activity similar (**IIIb**, **IIIc** and **IIIe**) or better (**IIId**, **IIIf**) than the parent compound. In one case, namely the A ring-methyl, B ring-dimethylphenyl derivative **IIIg**, an excellent DNA poisoning capacity (++++) was observed, which was comparable to that of camptothecin. This level of potency is remarkable in that it has very rarely been found in the inhibition of human topoisomerase by luotonin analogues.[177b]

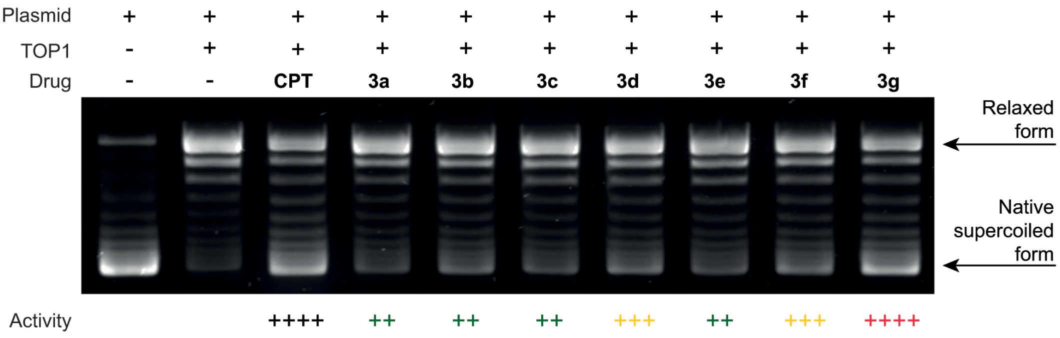


Figure 8.2.

In order to rationalize the high activity as topoisomerase poisons of some of our luotonin analogues, and also with a view of using the information thus obtained for planning improved analogues in the future, we undertook *in silico* studies. To this purpose, the crystal structure of topotecan bounded to the topoisomerase 1-DNA complex was selected and downloaded from Protein Data Band (PDB code 1K4T). This choice was mainly dictated by the fact that topotecan is the only camptothecin in clinical use that has been crystallized in its site of action. Furthermore, it is noteworthy that there is no crystal structure available for the luotonin-DNA-topoisomerase 1 ternary complex and, to the best of our knowledge, this was the first time that docking of luotonin A derivatives onto the DNA topoisomerase 1 complex was carried out.

The crystal structure was prepared for docking: external species (an atom of Hg, PEG and ligands) were eliminated and the Dockprep tool of the UCSF Chimera program was applied.[181] This tool automatically allows the elimination of water molecules, addition of hydrogens to both the enzyme and the DNA, the reparation of truncated side chains (Dunbrack rotamer library[182]) and assignment of Gasteiger charges with the AMBER ff12SB force field.[183] Finally, the input file for docking was generated with AutoDock Tools 1.5.6.[184]

The docking site was defined as a box with dimensions 15x15x20 Å, whose centroid was calculated using the coordinates of the closed lactone form of topotecan (x= 21.377, y= 24.068, z= 28.192). Docking was performed with AutoDock Vina.[185] The best pose for each ligand was selected and analysed. To validate the docking protocol, we docked the closed lactone form of topotecan into the target binding site, after preparing both files as described above. The best resulting pose was compared with the crystal structure, and a RMSD value of 0.492 Å was calculated for the differences between the positions of the atoms in both pentacyclic scaffolds.

To prepare the ligands, individual PDB files of ligands were prepared by *ab initio* energy minimization with Spartan '10 at the 3–21G level. Hydrogens were added to all ligands and the root of torsion tree was detected. The input file for docking was generated with AutoDock Tools 1.5.6.

Our study started with the analysis of the behavior of luotonin A itself (**IIIa**), the lead compound in this series. As shown in Figures 8.3-A and 8.3-B, it stacked between the base pairs (-1) and (+1) and also gave hydrogen bonding interactions between N5 and Arg-364. A comparison between the docking pose of luotonin with the crystal structure of the complex formed by topotecan showed that the orientation of both molecules was the same. For comparison, the docking of compound **IIIc** is also shown (Figure 8.3-C), showing a similar docking pose but a stronger interaction due to hydrogen bonding of its two nitrogen atoms, N5 and N6.

---

[181] Pettersen E.F., Goddard T.D., Huang C.C., Couch G.S., Greenblatt D.M., Meng E.C., Ferrin T.E. *J. Comput. Chem.*, **2004**, *25*, 1605.

[182] Dunbrack Jr R.L. *Curr. Opin. Struct. Biol.*, **2002**, *12*, 431.

[183] Wang J., Wang W., Kollman P.A., Case D.A. *J. Mol. Graph. Modelling*, **2006**, *25*, 247.

[184] Morris G.M., Huey R., Lindstrom W., Sanner M.F., Belew R.K., Goodsell D.S., Olson A.J. *J. Comput. Chem.*, **2009**, *16*, 2785.

[185] Trott O., Olson A.J. *J. Comput. Chem.*, **2010**, *31*, 455.

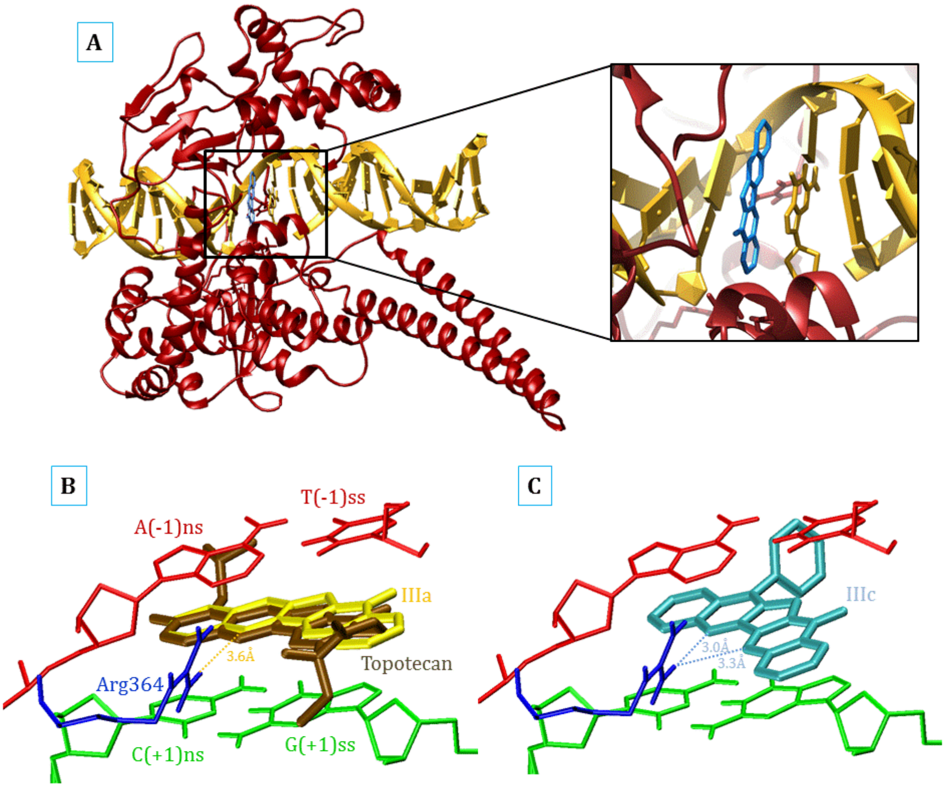


Figure 8.3.

The affinity of the examined molecules was quantified as the free-energy difference between the binary DNA-top1 complex and the ternary complexes formed upon binding of the drugs (the "scores" obtained are shown in Table 8.1). Importantly, a good correlation was found between the ability of the molecules to stabilize the binary complex and their *in vitro* topoisomerase 1 inhibitory effects, as shown in Table 8.1. Thus, the two compounds bearing 3,5-dimethylphenyl substituents (**IIIf** and **IIIg**), which were the most potent of the series, were also the ones showing the highest scores.

Table 8.1.

Cmpd	R^1	R^2	R^3	Score (kcal/mol)	Inhibitory activity
IIIa	H	H	H	-11.4	++
IIIb	CH_3	H	H	-11.7	++
IIIc	C_6H_5	H	H	-11.8	++
IIId	C_6H_5	Cl	H	-12.0	+++
IIIe	C_6H_5	Br	H	-11.7	++
IIIf	$3,5\text{-}(CH_3)_2C_6H_5$	H	H	-13.3	+++
IIIg	$3,5\text{-}(CH_3)_2C_6H_5$	H	CH_3	-13.7	++++
Camptothecin	-	-	-	-12.4	++++
Topotecan	-	-	-	-12.1	Not assayed

Our docking studies revealed that the binding modes of the molecules under study could be grouped into two different types. Derivatives **IIIa–IIIe** bound the target site in the same fashion as the original crystallographic topotecan. All these compounds stacked between the (-1) and (+1) base pairs, perpendicular to the DNA main axis and with the two nitrogens at positions 5 and 6 facing the minor groove of the DNA. The aromatic rings in the pentacyclic structure established π–π stacking interactions, within a 3.6 Å range, with the four DNA bases flanking the molecule. A single direct protein-drug interaction was detected through hydrogen bonding between the Arg-364 residue and the two basic nitrogen atoms in the molecule. Only in the case of halogenated compounds **IIId** and **IIIe** a third class of interaction was found, as halogen bonding was possible between the chlorine or bromine atoms and the Glu-356 side chain. This type of bonding is nowadays widely recognized[186] and can play a significant role in molecular recognition in biological environments, as often evidenced by crystallographic studies of ligand binding site interactions.[187] All compounds in this group pointed their E rings towards the scissile strand, although in the case of compound **IIIb**, another pose was found with a similar score (211.7 *vs.* 211.6 kcal/mol) that stacks the opposite way, with the ring A on the scissile strand side. As mentioned above, the more potent compounds **IIIb–IIIe** showed in all cases a better affinity ("score") than luotonin itself in our computational studies. Upon examination of the 3D docking models, this was attributed to the fact that luotonin binds to the Arg-364 residue by a single hydrogen bond

---

[186] For a review about the halogen bond see: Cavallo G., Metrangolo P., Milani R., Pilati T., Priimagi A., Resnati G., Terraneo G. *Chem. Rev.*, **2016**, *116*, 2478.

[187] For representative examples of halogen bonds in biomolecular complex see: (a) Bartelena L., Robbins J. *Clin. Lab. Med.*, **1993**, *13*, 583. (b) Auffinger P., Hays F.A., Westhof E., Ho P.S. *Proc. Natl. Acad. Sci. U.S.A.*, **2004**, *101*, 16789. (c) Wilcken R., Liu X., Zimmermann M.O., Rutherford T.J., Fersht A.R., Joerger A.C., Boeckler F.M. *J. Am. Chem. Soc.*, **2012**, *134*, 6810.

by the nitrogen belonging to its quinoline fragment, while in the other cases the quinoline and quinazoline fragments are both within hydrogen bonding distance of Arg364.

An overlay of all five compounds at their binding sites (Figure 8.4-A) clearly shows that the docking pose of luotonin A (**IIIa**) is different from the others. This difference may be attributed to the steric effect of the R^1 substituent in compounds **IIIb–IIIe**, which would give repulsive interactions with Asn-352 if their binding poses were superimposable with that of luotonin A, and this effect induces a rotation in the poses of **IIIb-e** (Figures 8.4-B and 8.4-C).

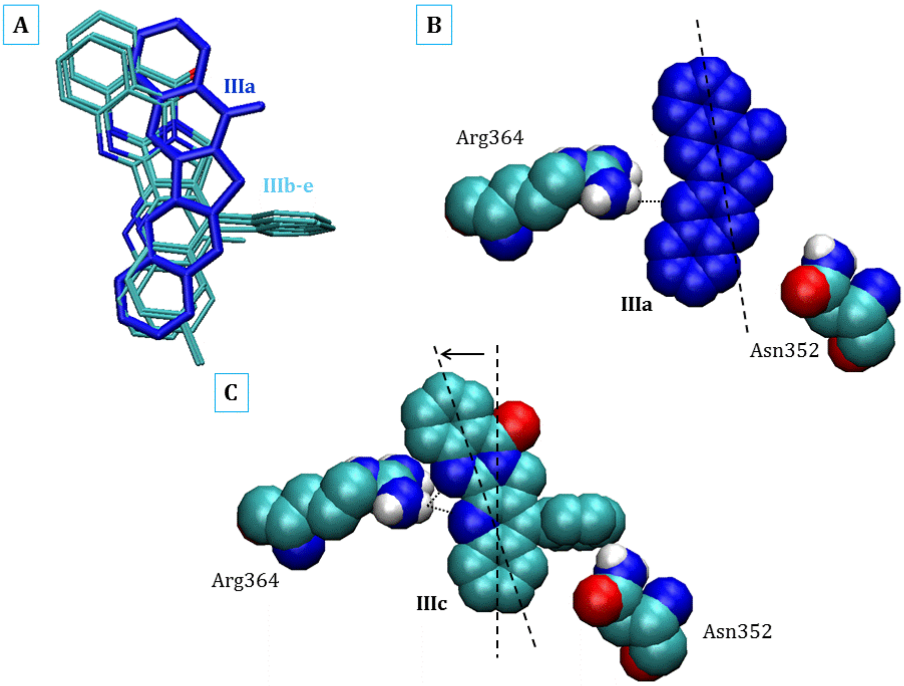


Figure 8.4.

On the other hand, compounds **IIIf** and **IIIg** showed a different binding mode with molecules stacked between the (-1) and (+1) base pairs, but with a modified ring orientation (Figure 8.5-A,B). Both molecules bear a 3,5-dimethylphenyl substituent at the C-14 position of ring B that confers them a high lipophilicity.[188] Although the topotecan-like binding mode previously described allows the accommodation of large groups on position 14 of the luotonin B ring,[189] nevertheless such substituents would remain exposed to the highly polar

---

[188] Mussardo P., Corda E., González-Ruiz V., Rajesh L., Girotti S., Martín S.M., Olives A.I. *J. Sep. Sci.*, **2010**, *33*, 2086.
[189] Verma R.P., Hansch C. *Chem. Rev.*, **2009**, *109*, 213.

environment. In this regard, it is worth noting that solvent accessible surface area for compounds **IIIf** (530.45 Å^2) and **IIIg** (562.76 Å^2) is at least 10% higher than the values calculated for the other luotonin derivatives. The binding mode found for **IIIf** and **IIIg** almost completely shields the hydrophobic dimethylphenyl moiety from the aqueous environment by burying it between the base pairs of the scissile strand and the surface of the protein, more specifically between Arg-364 and the deoxyriboses belonging to G(+1) and T(-1). This minimizes the entropic effect of an ordered layer of water molecules covering the dimethylphenyl moiety[190] and enhances the stability of the ternary complex (Figure 8.5-C).

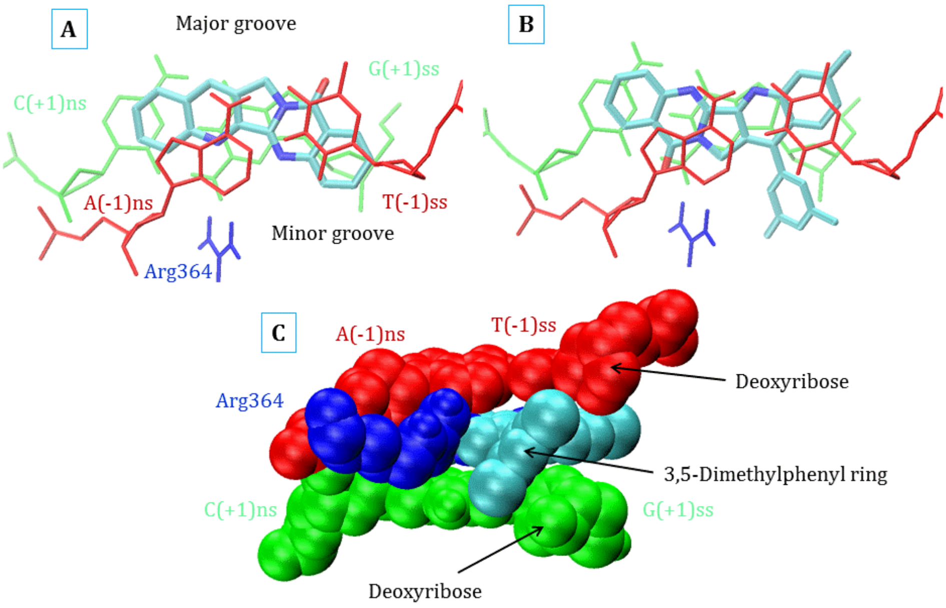


Figure 8.5.

As a consequence of this binding mode, the hydrogen bonds between the basic nitrogens and Arg-364 are lost. Nevertheless, this is compensated by the formation of a new, shorter hydrogen bond between the D-ring carbonyl and the basic amino acid. The dimethylphenyl group ceases to be orthogonal to the pentacyclic system in order to achieve a better fit with this binding pocket.

---

[190] Wadkins R.M., Bearss D., Manikumar G., Wani M.C., Wall M.E., Von Hoff D.D. *Curr. Med. Chem.-Anti- Cancer Agents*, **2004**, *4*, 327.

The main ligand-binding site interactions found in our docking studies are summarized in Table 8.2.

Table 8.2. Main ligand-binding site interactions found for compounds ***III***

Cmpd	H-bond	Stacking Interactions	Halogen bond
IIIa	N5/Arg-364 (3.6 Å)	Ring D,E/G+1 (3.6 Å)	-
IIIb	N5/Arg-364 (2.5 Å) N6/Arg-364 (2.7 Å)	Ring D,E/A-1 (3.4 Å) Ring D,E/G+1 (3.5 Å)	-
IIIc	N5/Arg-364 (3.0 Å) N6/Arg-364 (3.3 Å)	Ring A,B/G+1 (3.6 Å)	-
IIId	N5/Arg-364 (3.0 Å) N6/Arg-364 (3.4 Å)	Ring A,B/A-1 (3.6 Å) Ring A,B/G+1 (3.5 Å)	Cl-Glu356 (3.1 Å)
IIIe	N5/Arg-364 (3.1 Å) N6/Arg-364 (3.5 Å)	Ring A,B/A-1 (3.6 Å) Ring A,B/G+1 (3.5 Å)	Br-Glu356 (3.1 Å)
IIIf	Carbonyl/Arg-364 (1.9 Å)	Ring A,B/T-1 (3.6 Å) Ring A,B/G+1 (3.4 Å) Ring D,E/A-1 (3.5 Å) Ring D,E/C+1 (3.6 Å)	-
IIIg	Carbonyl/Arg-364 (1.9 Å)	Ring A,B/T-1 (3.6 Å) Ring A,B/G+1 (3.4 Å) Ring D,E/A-1 (3.5 Å) Ring D,E/C+1 (3.6 Å)	-

Finally, the *in vitro* cytotoxic activity of the studied compounds was analyzed from the percentage of cell growth observed when several cell cultures were exposed to 25 μM drug concentration, normalized with regard to the negative control (DMSO-treated), with the results shown in Figure 8.6. In the case of HeLa cells, all the derivatives except **IIIc** (91.2 ± 4.9%, p= 0.038) showed a higher cytotoxicity than luotonin A, being particularly remarkable the results of compounds **IIIf** (37.1 ± 3.4%, $p < 0.001$) and **IIIg** (49.3 ± 3.1%, $p < 0.001$). A similar profile was obtained in the case of lung adenocarcinoma A549 cells. All compounds, including luotonin A (56.2 ± 4.0%), showed a higher inhibitory effect in this culture than in HeLa cells. Compound **IIIc** was again the one with the lowest inhibitory activity (83.8 ± 6.8%, p =0.004). On the other hand, compound **IIIf** continued to be the most cytotoxic molecule, leading to a cell growth as low as 11.4 ± 4.1% ($p < 0.001$). Interestingly, the tested compounds showed a different inhibition pattern in the case of SW480 (colon adenocarcinoma) cells. In this cell line, the largest inhibitory effect was exerted by compounds **IIId** (24.2 ± 4.9%), **IIIe** (7.3 ± 4.3%) and **IIIg** (31.8 ± 2.9%), all of them with a value of $p < 0.001$ with respect to luotonin A (73.02 ± 4.9%). Taken in the aggregate, these results unveil a selectivity inhibitory activity pattern of the halogenated derivatives **IIId** and **IIIe** against the colon adenocarcinoma cell line and of compound **IIIf** against the lung adenocarcinoma cell line. This is an interesting feature, since a high potency against all cell lines is usually regarded as a proof of indiscriminate toxicity and therefore as an undesirable property. The fact that the topoisomerase inhibition data showed a less than perfect correlation with the cytotoxicity results can be attributed to the participation in the latter of physicochemical characteristics and pharmacokinetic phenomena such as solubility and transport across membranes.

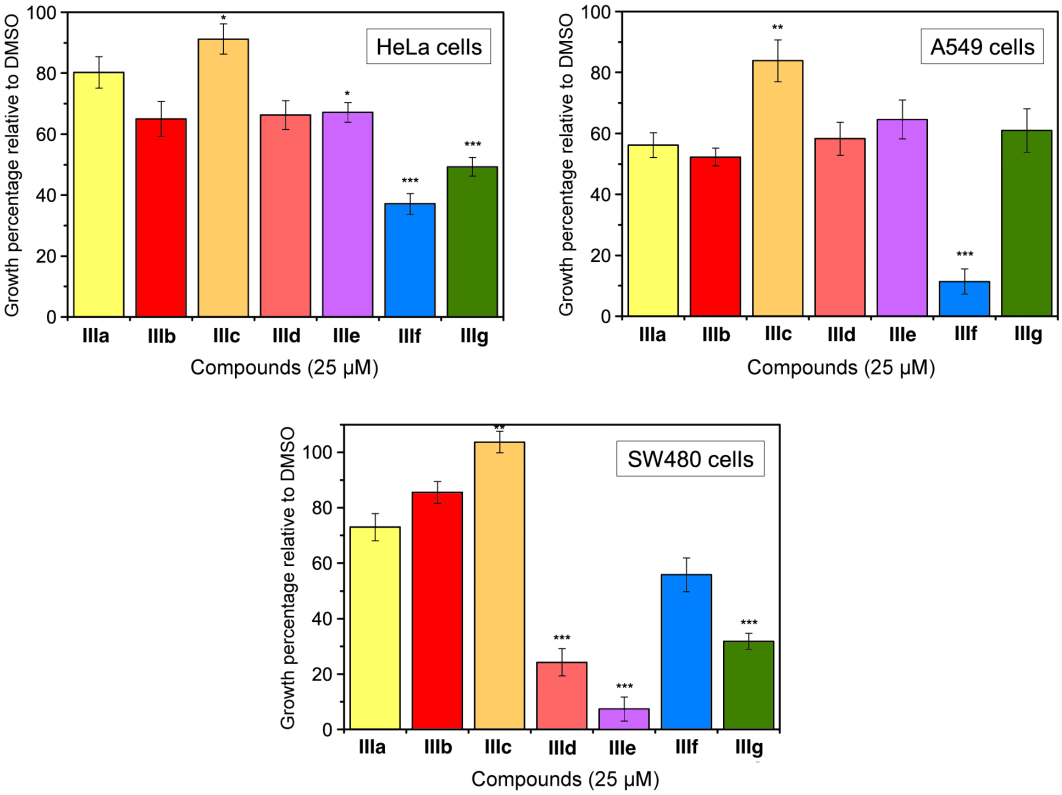
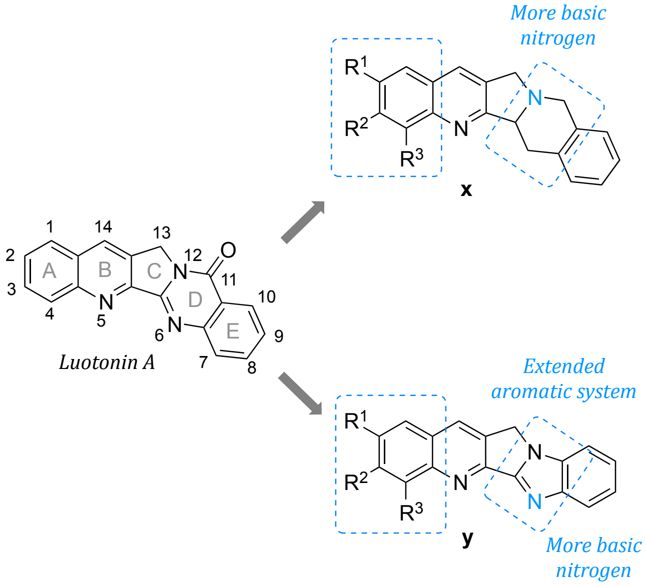


Figure 8.6.

It can be concluded that compounds **IIIf** and **IIIg** are the most promising therapeutic candidates, showing a much higher potency than the reference luotonin A in the three cell lines assayed. Also compounds **IIId** and **IIIe**, in spite of showing only a moderate activity in the topoisomerase 1 inhibition experiments, have been revealed as interesting alternatives, with good results in the colon adenocarcinoma cell line. The high selectivity of these chloro- and bromo- derivatives towards SW480 cells is remarkable and may be the subject of further research.

8.4 - D Ring-modified luotonin A analogues

As part of a collaborative project between our group and the one headed by Professor Abdulrahman I. Almansour at King Saud University, two new families of luotonin A analogues were designed, with the aim of manipulating the basicity of the nitrogen atoms at ring D. In the first of them (compounds **x**), this was achieved by the replacement of the quinazolinone ring by a tetrahydroisoquinoline, which led to the presence of a tertiary amine at the 12 position. In the second strategy, the quinazolinone fragment was replaced by a benzimidazole with the aim of increasing the planarity and the aromaticity of the scaffold to favour stacking interactions and on the other hand introducing a new basic nitrogen as possible H-bond acceptor, leading to decarbonyl luotonins **y** (Scheme 8.2). Both families were synthesized by Drs. Arumugam Natarajan and Raju Suresh Kumar, at King Saud University, by a strategy based on the use of intramolecular Povarov reactions as key steps.



Cmpd.	R^1	R^2	R^3
xa	H	H	H
xb	H	H	Cl
xc	H	H	Me
xd	H	H	OMe
xe	H	Me	H
xf	H	OMe	H
xg	Cl	H	H
xh	Me	H	H
xi	OMe	H	H

Cmpd.	R^1	R^2	R^3
ya	H	H	H
yb	Br	H	H
yc	Cl	H	H
yd	Me	H	H
ye	H	Me	H
yf	H	H	Me
yg	OMe	H	H
yh	H	OMe	H
yi	H	H	OMe

Scheme 8.2

Docking studies were performed on compounds **x** and **y**, employing the same procedure described above and starting from the same crystal structure of the topoisomerase 1-DNA complex. In the case of compounds **x**, it can be concluded from the scores obtained (Table 9.5) that a substituent in C-4 4 generally seems to be unsuitable to stabilize the topoisomerase 1-DNA complex. In the case of derivatives **Xc** and **Xd**, the steric effect of the substituent forces the compound into a position that leads to a loss of interaction between the nitrogen of quinoline fragment and Arg364, and less efficient stacking interactions with bases pairs are also observed. This leads to a low stability for the ternary complex in spite of the presence of two additional interactions, namely a cation-π interaction between the protonated nitrogen at position 12 and cytosine or thymine and an anion-π interaction[191] between ring E, which is electron-poor owing to the presence of adjacent protonated nitrogen, and Glu356. On the other hand, the 4-Cl-substituted derivative **Xb** presents a good ability to stabilize the complex, with better stacking interactions with the bases pairs, although the H-bond with Arg364 is lost.

A substituent in the position 3, such as in the case of derivatives **Xe** and **Xf**, forces the compounds to assume the same orientation of compounds **Xc** and **Xd**, with the quinoline nitrogen in the opposite side respect to Arg364, maybe due for a repulsion effect between the substituent in the position 3 and Thr718 and rings D and E with deoxyribose (figure 8.7).

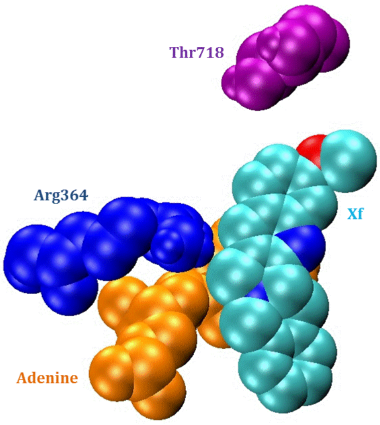


Figure 8.7.

Finally, a substituent in the position 2, as in derivatives **Xg**, **Xh**, **Xi**, seems to promote a stabilization of the topoisomerase 1-DNA. The main favorable interaction seems to be the H-bond between the nitrogen of quinoline and Arg364. Furthermore, all these derivatives present good stacking interactions and a weak H-bond between the hydrogen of protonated

---

[191] Wang D.-Z., Wang M.-X. *J. Am. Chem. Soc.*, **2013**, *135*, 892.

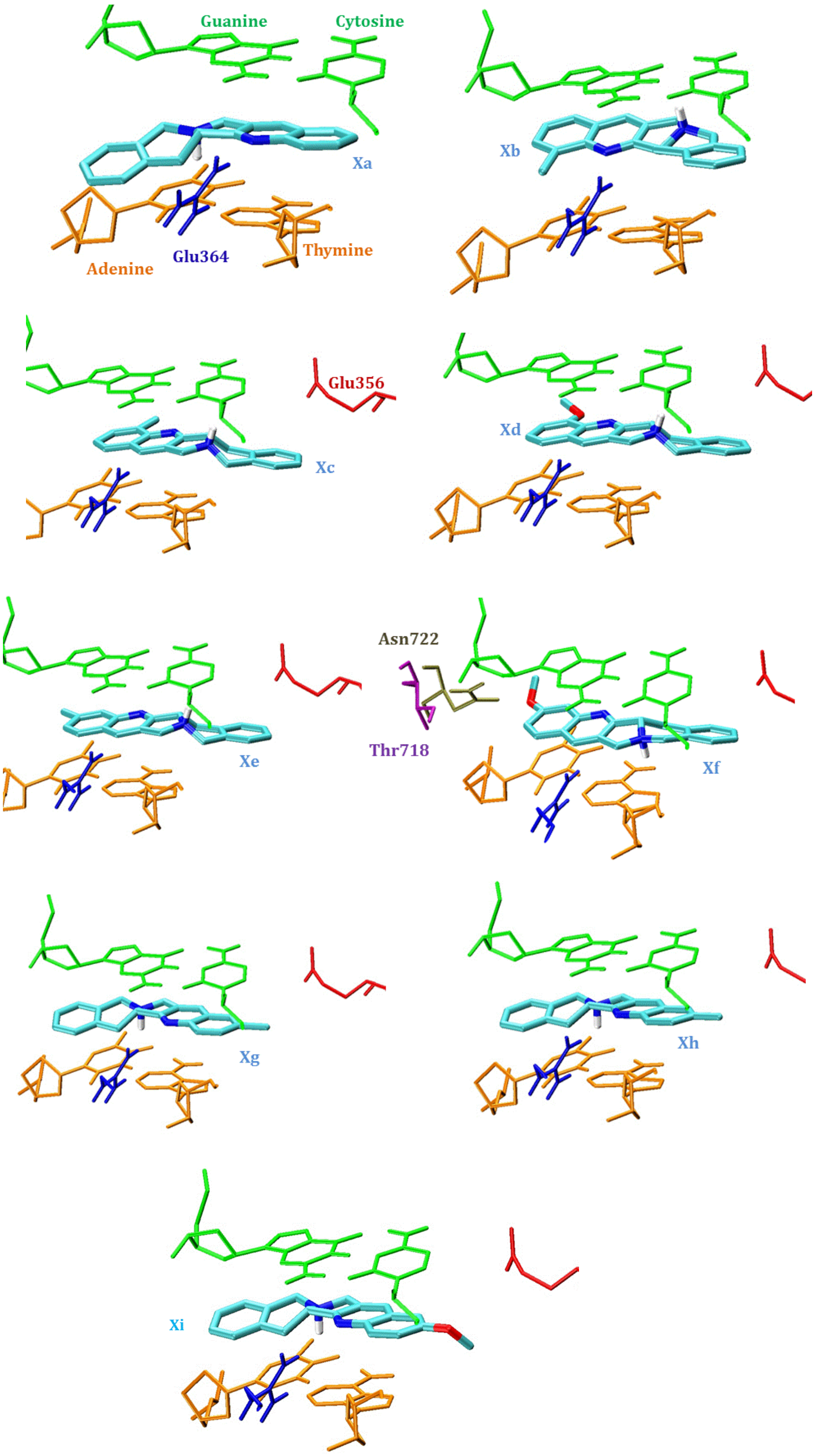

Guanine
Cytosine
Xa
Xb
Adenine
Glu364
Thymine
Glu356
Xc
Xd
Asn722
Thr718
Xe
Xf
Xg
Xh
Xi

Figure 8.7.

nitrogen and the carbonyl of thymine. The best ability to stabilize the complex is exhibited by compound **Xg**, that in addition shows a halogen-bond with Glu364.

The best docking poses for all compounds **x** are shown in Figure 8.8, and the main computed interactions are summarized in Table 9.5.

*Table 9.5. Main interactions calculated for compounds **x***

Cmpd	Score (kcal/mol)	R	N-Arg364	Stacking interactions	Additional interactions
Xa	-10.2	H	2.73	Ring A,B/A-1 (3.6 Å) Ring B/G+1 (3.5 Å)	-
Xb	-10.3	4-Cl	-	Ring A/T-1 (3.9 Å) Ring B/G+1 (3.7 Å) Ring E/C+1 (3.7 Å)	-
Xc	-9.7	4-CH_3	-	Ring A,B/G+1 (3.4 Å) Ring B/A-1 (3.6 Å)	Cation-π/C+1 (2.3 Å) Anion-π/Glu356-ringE (3.7 Å)
Xd	-9.5	4-OCH_3	-	Ring A,B/G+1 (3.4 Å) Ring B/A-1 (3.6 Å)	Cation-π/C+1 (2.4 Å) Anion-π/Glu356-ringE (3.6 Å)
Xe	-9.9	3-CH_3	-	Ring A,B/G+1 (3.4 Å) Ring B/A-1 (3.5 Å)	Cation-π/C+1 (2.3 Å) Anion-π/Glu356-ringE (3.6 Å)
Xf	-10.0	3-OCH_3	-	Ring A/T-1 (3.9 Å) Ring A,B/G+1 (3.5 Å) Ring E/G+1 (3.9 Å)	Cation-π/A-1 (2.5 Å) H-bond/OCH_3-Asn722 (2.9 Å)
Xg	-10.9	2-Cl	3.4 Å	Ring A/C+1 (3.8 Å) Ring B/G+1 (4.0 Å) Ring A,B/A-1 (3.8 Å) Ring E/T-1 (3.8 Å)	Cl-Glu364 (3.5 Å) Cation/T-1(C=O) weak (2.3 Å)
Xh	-10.9	2-CH_3	3.4 Å	Ring A/C+1 (3.8 Å) Ring B/G+1 (4.0 Å) Ring A,B/A-1 (3.8 Å) Ring E/T-1 (3.8 Å)	Cation/T-1(C=O) weak (2.4 Å)
Xi	-10.4	2-OCH_3	3.4 Å	Ring A/C+1 (3.8 Å) Ring B/G+1 (4.0 Å) Ring A,B/A-1 (3.9 Å) Ring E-T-1 (3.8 Å)	Cation/T-1(C=O) weak (2.4 Å)

Topoisomerase I inhibitory activities are not yet available for compounds **x**, and therefore their correlation with docking studies is not possible at this stage.

Regarding the "decarbonyl" analogues of luotonin (compounds **y**), their initial design was based on enthropic considerations. A relevant structural factor that has received little attention while designing compounds of the camptothecin family is the very deep penetration of camptothecins into their binding site, which leads to an uncommonly large enthropic component for binding free energy due to the release of a large number of molecules of hydration water.[190] Bearing in mind that, according to our computational data mentioned above, the luotonin carbonyl substituent does not seem to have an important role in its interaction with the topoisomerase 1-DNA complex, we reasoned that its removal would provide compounds with an increased electron density at the N-6 atom, thereby facilitating their interaction with the Arg-364 residue at the camptothecin binding site. Furthermore, the proposed transformation should lead to a more compact molecule with an enhanced ability to displace deeply buried water molecules, thereby increasing the enthropic contribution to binding free energy. In order to test these ideas computationally, we compared the docking of luotonin A and its analog lacking the carbonyl substituent onto the topoisomerase 1-DNA complex. As shown in Figure 8.9.A, the decarbonyl analogue of luotonin A was predicted to interact with the topoisomerase 1-DNA complex by a

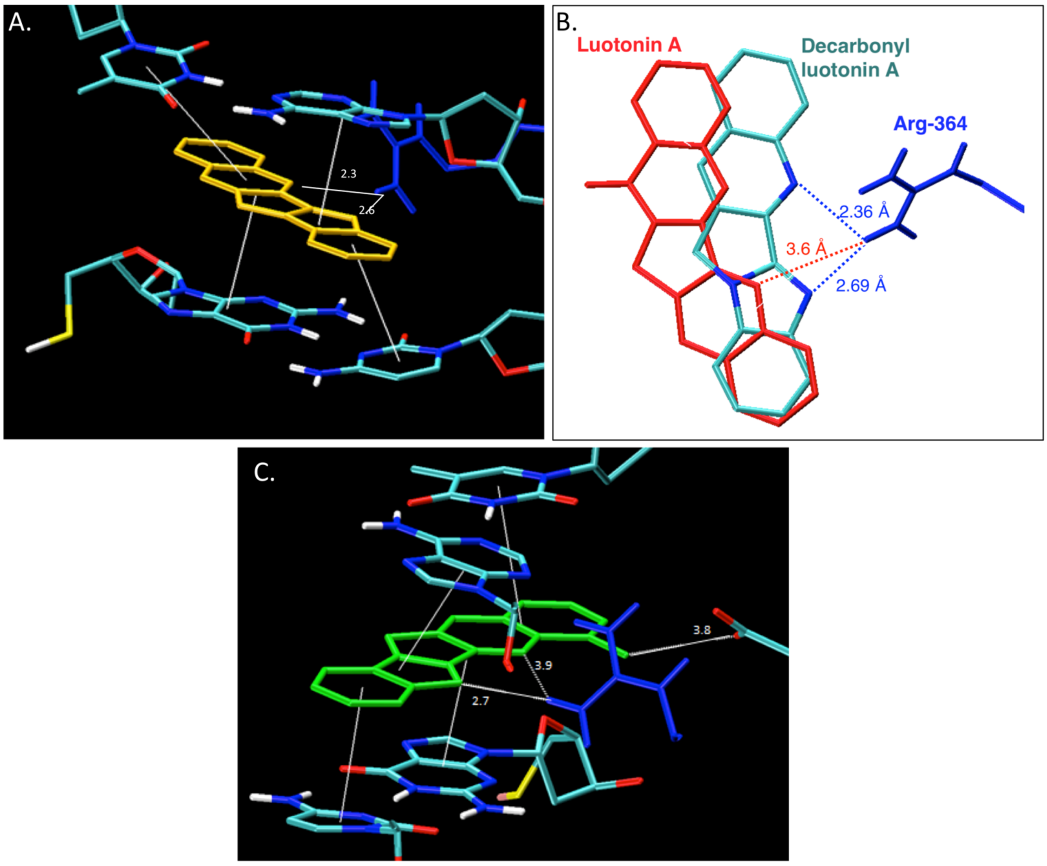


Figure 8.9.

combination of stacking interactions with the base pairs (-1) and (**+**1) and a key hydrogen bond with the Arg-364 residue. Interestingly, the latter bond was predicted to be more efficient than that of luotonin, as shown by the presence of two binding contacts at shorter distances, compared with a single interaction for luotonin (Figure 8.9.B). One final conclusion is that ring orientation is flipped 180 °C with respect to that of luotonin, and this brings ring A close to polar residues that are not involved in binding to known camptothecin or luotonin derivatives. Thus, the proximity of the Asp-533 residue to the C-7 position of our compounds offers opportunities for achieving additional bonding interactions, *e.g. via* halogen bonding, as shown in Figure 8.9.C.

This initial study was extended to the whole library, and in all cases the synthetized derivatives showed a position closer to Arg364, showing a stronger interaction through two strong H-bonds, while luotonin A is involved in only one H-bond. Furthermore a good intercalation between base pairs (-1) and (+1), often better than luotonin A, was observed. The compounds could be grouped into two classes (Figure 8.10). The first group, including derivatives **XVb**,**c**,**d**,**g** and **i**, showed a pose similar to Arg364 when compared to luotonin A. Derivatives **XVb**,**c**,**d** and **g**, with a substituent in the position 2, cannot get closer to arginine due steric hindrance with Asp533, that interacts with the halogen substituent of derivatives **XVb** and **XVc**. Compound **XVi**, with a methoxy group at position 4, exhibited a rotated arrangement, presumably due to interactions with Asn722 and Thr718 that hampered the usual pose (Figure 8.11).

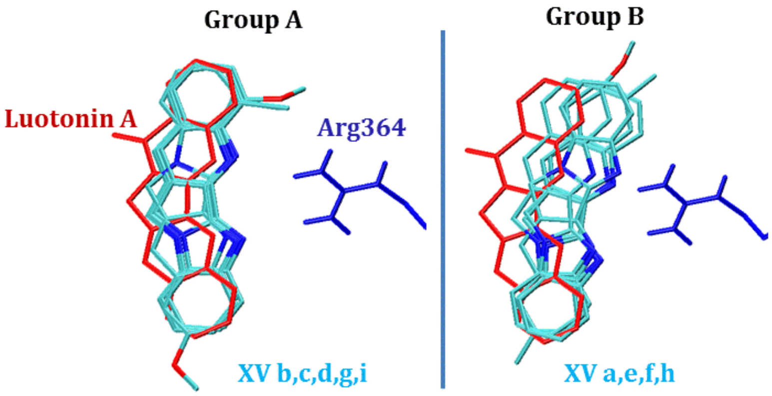


Figure 8.10.

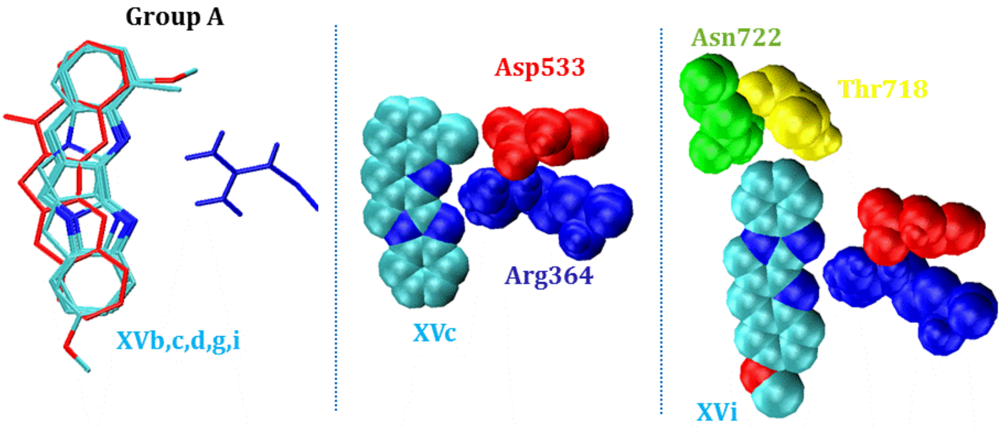


Figure 8.11.

The second group of compounds (**XVa**,**e**,**f** and **h**) showed a pose closer to Arg364 (Figure 8.12). Also in this group the compound with a substituent at position 4 (**XVf**) presented a rotated pose, such as in the case of **XVi**. The best score was calculated for derivative **XVh**, involved in an additional H-bond with Thr718 that highly stabilizes the complex.

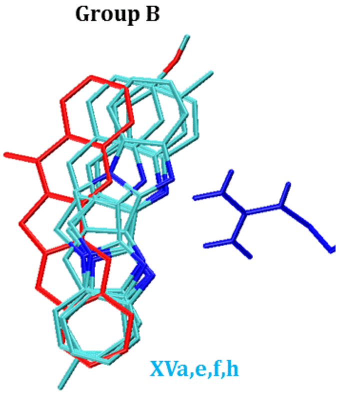


Figure 8.12.

In conclusion, derivatives with a substituent in the position 4 do not show a good affinity for the binding pocket, showing a rotated pose due to steric repulsions with Thr718 and Asn720. Groups at position 2 do not allow the proper stabilization of the ternary complex, except halogens that seem to be involved in a halogen-bond with Asp533. Finally, a substituent at position 3 is well tolerated, especially if they are able to undertake a further interaction like **XVh**. In the following table (Table 9.6) all interactions are summarized.

Table 9.6. Main interactions of compounds ***y***

Cmpd	R	Score (kcal/mol)	N5-Arg364 H-bond (Å)	N6-Arg364 H-bond (Å)	Additional interaction
XVa	H	-10.8	2.69	2.36	-
XVb	2-Br	-11.1	4.02	2.79	Br-Asp533 (3.59 Å)
XVc	2-Cl	-11.1	3.93	2.70	Cl-Asp533 (3.66 Å)
XVd	2-CH_3	-11.1	3.95	2.70	-
XVe	3-CH_3	-11.0	2.85	2.23	-
XVf	4-CH_3	-10.9	2.99	2.38	-
XVg	2-OCH_3	-11.0	3.90	2.48	-
XVh	3-OCH_3	-11.4	3.53	2.35	OCH_3/Thr718(3.4Å)
XVi	4-OCH_3	-10.7	3.95	3.10	-
Luotonin A	--	-11.4	3.60	--	-

The topoisomerase I inhibition data of compounds **y** are still pending, and therefore the docking data have not yet been correlated with activities.

9 – Development of a general and scalable flow protocol for peptide synthesis

9.1 - Flow chemistry

In the last 20 years the way to practice chemistry saw a revolutionary combination with automated technologies, allowing to the chemist the possibility to devote more time and energies to project new processes. Actually, organic chemists spend much of their of time on the optimization of synthetic routes. The best pathways need to be chosen, and reaction conditions must be optimized and finally the purification could require much time and effort. Once a product is successful, the scale-up is required, so the whole synthesis process needs to be revised again and readjusted for larger batch sizes.

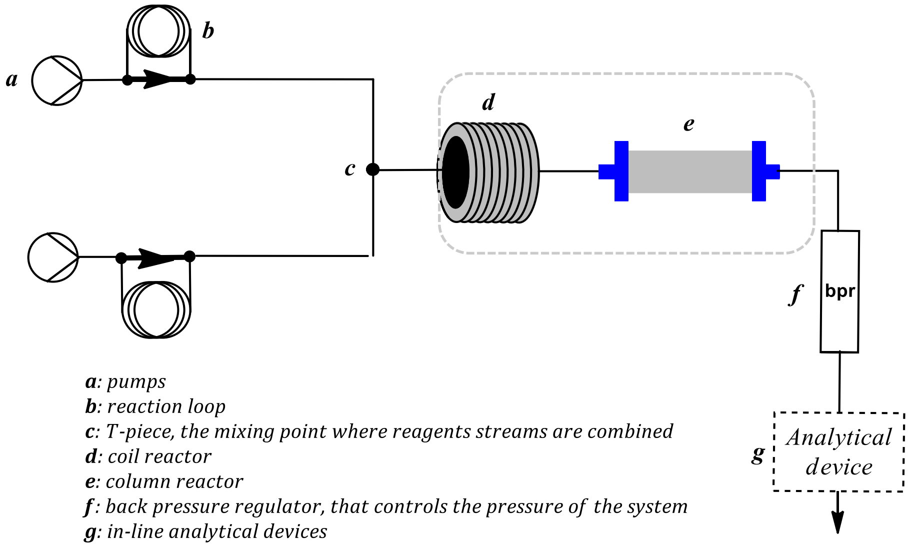
Whereas internet-based software systems are investigated as innovative methods to monitor and control chemical reactions from any location in the world,[192] the chemistry laboratory has not changed for several decades, and at the present time is still based on batch methodology employing glassware. Flow processes may provide an innovative opportunity for renovation in this area. “Flow chemistry” involves chemical processes that occur in a continuous flowing stream, conventionally taking place in a reactor zone. The reagents are introduced into a tube through small reaction loops, in a small-scale reaction, or directly using pumps, in a large-scale reaction. When the tubes of each reagent come together in a reactor, a specific reaction takes place. The most common types of reactors are coil reactors and column reactors packed with solid reagents, catalysts or scavengers. Furthermore, more specific and sophisticated reactors can be employed such as photo-reactors, electrochemical reactors, microwave-reactors etc.

Finally, flow chemistry allows in-line work-up, by solid phase scavenging, chromatographic separation or liquid/liquid extraction, and an analytical instrument can be

---

[192] Fitzpatrick D.E., Battilocchio C., Ley S.V. *Org. Process Res. Dev.*, **2016**, *20*, 386.

integrated to accurately monitor the reaction such as a mini mass spectrometer, a HPLC machine, a nuclear magnetic resonance devise or, as in our case, a FlowIR system (Figure 10.1).[193,194]



a: *pumps*
b: *reaction loop*
c: *T-piece, the mixing point where reagents streams are combined*
d: *coil reactor*
e: *column reactor*
f: *back pressure regulator, that controls the pressure of the system*
g: *in-line analytical devices*

Figure 9.1.

The main advantages of flow chemistry technology compared to standard batch chemistry methods are:

- Improved heat transfer and accurate control of temperature, due to the high surface area-to-volume ratio (thereby, endothermal and exothermal reactions can be easily thermostated)
- Improved mass transfer/mixing
- Reduced reaction time
- Reproducibility
- Scale-up and automation over a 24/ 7 working regime
- Reduction of waste
- Extreme reaction conditions can be applied (high/low temperature, high pressure)

---

[193] For summaries of flow chemistry technology, see: (a) Ley S.V. *Chem. Rec.*, **2012**, *12*, 378. (b) Ley S.V., Fitzpatrick D.E., Ingham R.J., Myers R.M. *Angew. Chem. Int. Ed.*, **2015**, *54*, 3449. (c) Ley S.V., Fitzpatrick D.E., Myers R.M., Battilocchio C., Ingham R.J. *Angew. Chem. Int. Ed.*, **2015**, *54*, 10122.

[194] Darvas F., Dorman G., Hessel V. *Flow chemistry*, volume 1: Fundamentals. **2014**. De Gruyter Textbook.

- Improved safety (managing hazardous reagents and intermediates)
- Adaptable to multistep processes (reaction telescoping), which can be especially beneficial if intermediate compounds are unstable, toxic, or sensitive to air
- In-line downstream processing

Furthermore, there are significant differences between batch and flow processes with respect to the parameters of the reactions. Batch reaction time is determined by the time a vessel is stirred under a set of fixed conditions, whereas the concept of reaction time in a flow process is expressed by the *residence time*, which is the time that reagents spend in the reactor zone. Residence time is determined by the reactor volume and the bulk flow rate.

While in batch mode, the main parameters to be considered are the concentrations of reagents and the ratio of their molar quantities, while under flow conditions the concentration of reagents and the ratio of their flow rates are to be considered. Finally, if we consider the steady state in batch mode, it has uniform concentration at each position of the vessel in a particular moment, but in a flow reactor it has steady but different concentrations at each position of the length of the reactor.

9.2 - Peptide synthesis

Peptides are involved in a wide range of biochemical processes, showing physiological activities as hormones, neurotransmitters, growth factors, signalling molecules and antibiotics. On this basis, peptides represent an interesting class of molecules for the pharmaceutical market, especially after the revolution of the "omics" technologies such as genomics or proteomics. In fact, several diseases such as some forms of cancer, diabetes, osteoporosis or inflammation, as representative examples, can be treated with peptidic drugs.[195] Actually, peptides could represent an alternative to the small molecule drugs and to the biopharmaceuticals, showing a possibility to overcome the bottleneck that affects the new drug discovery processes generated in the last decades. During the past decade, peptides have gained a wide range of applications in medicine and biotechnology, and research into therapeutic peptides has also been intensified.

In comparison to most small-molecule drugs, peptides are endowed with some advantages such as higher potency and selectivity, fewer side-effects and, consequently, tolerability and predictability in vivo, absence of toxic degradation products and drug-drug interactions and, finally, the possibility to interfere with protein-protein interactions as a new type of mechanism of action. Nevertheless, peptide therapies show some drawbacks such as low metabolic stability, short circulating half-life, mainly parenteral administration, and expensive synthesis, even though peptidic compounds present a lower complexity and production costs compared with biopharmaceuticals.[196]

Peptides and proteins could be available, in principle, through native isolation, recombinant techniques or chemical synthesis. However, only chemical synthesis allows the introduction of unnatural aminoacids and the production of large quantities of pure peptide. Traditionally, peptide synthesis has been performed with two main approaches: the liquid-phase synthesis and the solid-phase synthesis.[197] The former is the classical synthetic approach that has been mostly replaced by the solid-phase mode, although it remains useful in large-scale peptide production. Automated solid-phase synthesis is the most frequently method employed in peptide synthesis. However, this technique presents several drawbacks

---

[195] (a) Vlieghe P., Lisowski V., Martinez J., Khrestchatisky M. *Drug Discovery Today*, **2010**, *15*, 40. (b) Bellmann-Sickert K., Beck-Sickinger A.G. *Trends Pharmacol. Sci.*, **2010**, *31*, 434.

[196] Craik D.J., Fairlie D.P., Liras S., Price D. *Chem. Biol. Drug Des.*, **2013**, *81*, 136.

[197] Kimmerlin T., Seebach D. *J. Pept. Res.*, **2005**, *65*, 229.

such as the requirement for a large stoichiometric excess of reagents and limited possibilities for scale-up.[198]

In this context, developing a new scalable, automated and effective synthetic protocol for peptide synthesis constitutes a big challenge for the scientific community. Flow chemistry is a promising technology to develop an automatic, scalable synthesis, which offers the opportunity to perform an excellent heat and mixing control, limiting side reactions. In this chapter we present our work towards a general and scalable syntheses of peptides in flow, as well as the application of this technique to the synthesis of the bioactive natural cyclic hexapeptide segetalin A. This work was carried out during a three-month stay at the Department of Chemistry, Cambridge University, under the supervision of Professor Steven V. Ley, as part of the requirements for the European Ph. D. Mention.

---

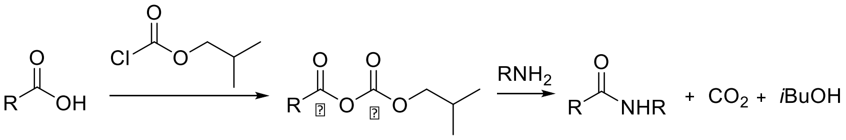
[198] (a) Merrifield R.B. *J. Am. Chem. Soc.*, **1963**, *85*, 2149. (b) Merrifield B. *Biopolymers*, **1995**, *37*, 3. (c) Mäde V., Els-Heindl S., Beck-Sickinger A.G. *Beilstein J. Org. Chem.*, **2014**, *10*, 1197.

9.3 - Precedents to our work

In the group of Professor Ley at the Department of Chemistry in Cambridge University, several projects of peptide coupling in flow have been investigated,[199] and recently, a new synthetic protocol is under study.[200] .Other groups have also recently contributed to this area.[201]

The controlled formation of a peptidic bond entails the protection of the amino group belonging to the carboxy component and of the carboxy group of the amino acid which is the amino component, followed by the proper step of amide bond formation with the aid of an acid activating group, and finally, the deprotection or removal of the protecting groups.

A large variety of activating agents are available, and some of them present drawbacks such as poor atom economy, or formation of by-products that are difficult to remove. For this project, the mixed anhydride method was selected. This activating method was first reported by Vaughan,[202] and then reinvestigated by Anderson[203] and involves acid activation by reaction with an alkyl chloroformate to form a mixed carbonic anhydride. The amine is subsequently added to the reaction mixture and the amide bond is formed with the only by-products being CO_2 and the corresponding alcohol, which are environmentally friendly and easy to remove (Scheme 9.1).



Scheme 9.1.

A tertiary amine is also required, to deprotonate the acid and to release the amine from its salt. Generally, steric hindered amines give low yields and an excess could cause

---

[199] (a) Baxendale I.R., Ley S.V., Smith C.D., Tranmer G.K. *Chem. Commun.*, **2006**, 4835. (b) Baumann M., Baxendale I.R., Brasholz M., Hayward J.J., Ley S.V., Nikbin N. *Synlett*, **2011**, 1375. (c) Fernández A., Levine Z.G., Baumann M., Sulzer-Mossé S., Sparr C., Schläger S., Metzger A., Baxendale I.R., Ley S.V. *Synlett*, **2013**, 514. (d) Lìcke D., Dalton T., Ley S.V., Wilson Z.E. *Chem. Eur. J.*, **2016**, *22*, 4206.

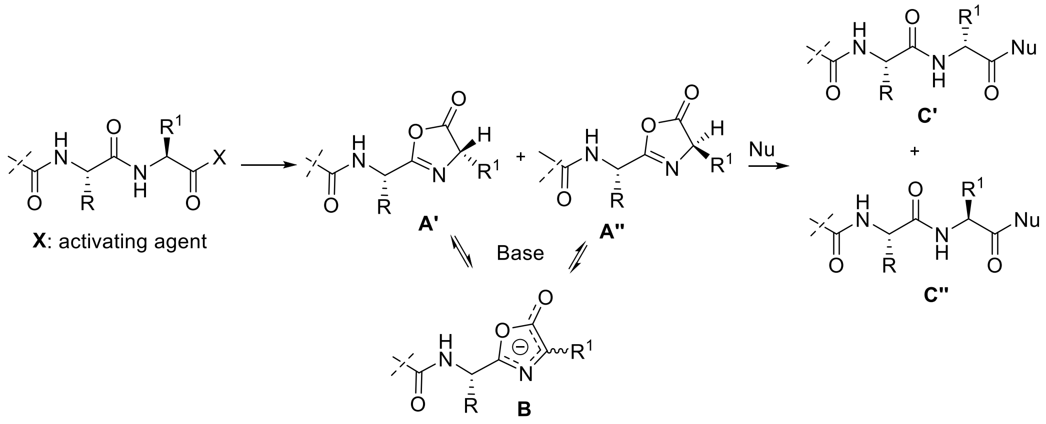
[200] Floden N., Charis Y., Wilson Z., personal communication.

[201] (a) Simon M.D.,Heider P.L. Adamo A.,Vinogradov A.A.,Mong S.K., Li X. Berger T.,Policarpo R.L.,Zhang C., Zou Y., Liao X., Spokoyny A.M., Jensen K.F.,Pentelute B.L. *ChemBioChem* **2014**, *15*, 713. (b) Mándity I.M., Olasz B., Ötvös S.B., Fülöp F. *ChemSusChem* **2014**, *7*, 3172.

[202] Vaughan J., Osato R.L. *J. Am. Chem. Soc.*, **1952**, *74*, 676.

[203] Anderson G.W., Zimmermann E., Callahan F.M. *J. Am. Chem. Soc.*, **1967**, *89*, 5012.

racemization. A classical racemization mechanism implies the formation of oxazolone **A**, which under mild basic conditions, undergoes racemization via the formation of conjugated anionic intermediate **B**. The resulting oxazolone **A’** and **A”** mixture reacts then with a nucleophile, explaining the loss of chirality of the product **C** (Scheme 10.2).[204]



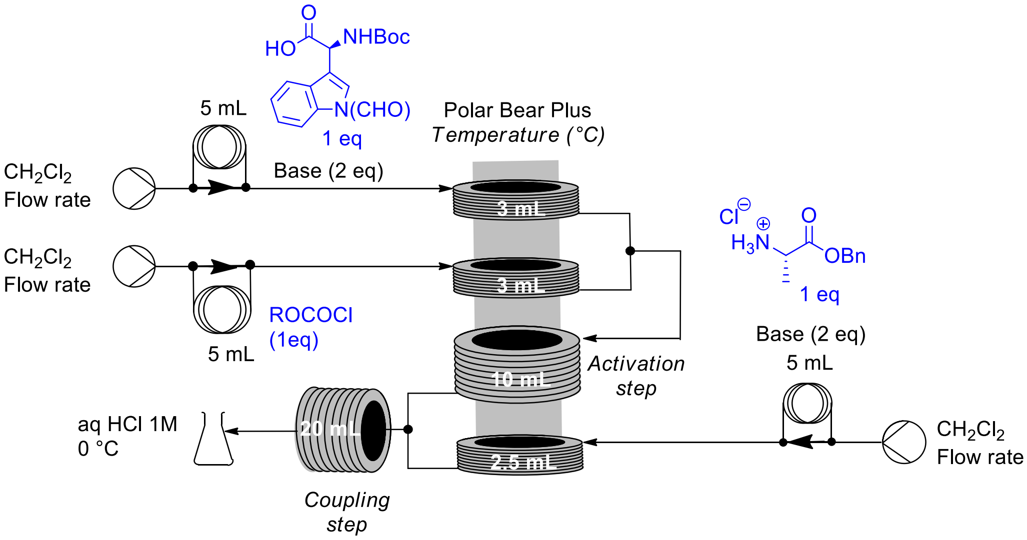
Scheme 9.2.

---

[204] Montalbetti C.A.G.N., Falque V. *Tetrahedron,* **2005**, *61*, 10827.

9.4 - Optimization of mixed anhydride activation under flow conditions

Using this activation method, flow reaction conditions had been previously investigated for the coupling of Boc-L-Trp(CHO)-OH and L-Ala-OBn as starting amino acids. The best results were achieved employing *N*-methylmorfoline as base, dichloromethane as solvent, a flow rate of 1 mL/min and isobutyl chloroformate as activating agent (summarized in Scheme 9.3 and Table 9.1, entry 7). The activation step was carried out at low temperature and the reaction was then allowed to warm to room temperature, to avoid side reactions leading to the formation of urethane species from the attack of the amine to the β carbonyl instead of the α carbonyl. Finally the effect of solvent was also studied, with the conclusion that better yields were obtained in dichlomethane than in THF or CH_3CN (Table 9.1). These studies were performed on a Polar Bear Plus® machine, which allows performing the experiments at low temperatures.



Scheme 9.3.

Table 9.1. Temperature and flow rate optimization

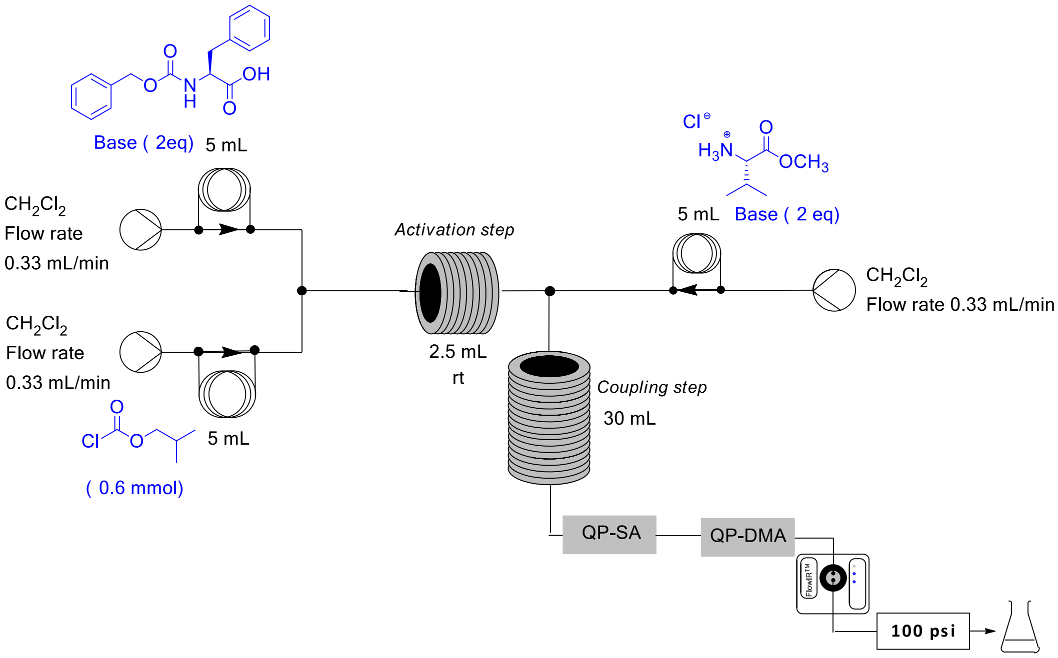
Entry	**Reagent**	**Base**	**Flow rate (mL/min)**	**T (° C)**	**M**	**Yield (%)**
1	EtOCOCl	DIPEA	1	-10	0.01	64
2	EtOCOCl	NMM	1	-10	0.01	85
3	EtOCOCl	NMM	1	-20	0.01	73
4	EtOCOCl	NMM	1	0	0.01	67
5	EtOCOCl	NMM	1	10	0.01	76
6	EtOCOCl	NMM	1	20	0.01	99
7	*i*BuOCOCl	NMM	1	-10	0.01	99
8	*i*BuOCOCl	NMM	2	-10	0.01	99
9	*i*BuOCOCl	NMM	1	-10	0.02	68
10	*i*BuOCOCl	NMM	1	-10	0.05	67
11	*i*BuOCOCl	NMM	1	-10	0.1	62
12	*i*BuOCOCl	NMM	1	-10	0.01	62

Using the coupling of Cbz-L-Phe-OH and L-Val-OMe as a new model reaction, it was found subsequently that the activation step could be carried out in a coil of 2.5 mL at room temperature without affecting yield, contrary to the low temperature necessitated by the batch conditions. For the coupling step, a coil of 30 mL volume at room temperature gave the best results (Scheme 9.4 and Table 9.2, entry 15). A flow rate of 0.33 mL/min was selected. Furthermore, an attempt at in-line purification was been carried out on this reaction using solid-supported reagents. A first column was loaded with the sulfonic acid resin QP-SA, to capture the base and any remaining Ala-OBn. A second column was loaded with the basic resin-supported dimethylamine (QP-DMA) to scavenge any unreacted carboxylic acid.[205]
In addition, a FlowIR was used to monitor the reaction. The characteristic peak of amide (approx. 1660 cm^{-1}), present in the product but not in the reagents, was used to monitor the progress of the reaction. The reaction product was collected during the steady phase, as judged by the absorption observed in the IRspectra detector.

---

[205] QP-SA and QP-DMA resins are commercially available from Johnson Matthey. Website: http://www.matthey.com/.

Unfortunately, the above-described conditions were found not to be general and further optimization studies were deemed necessary. This was the problem that we set out to solve.

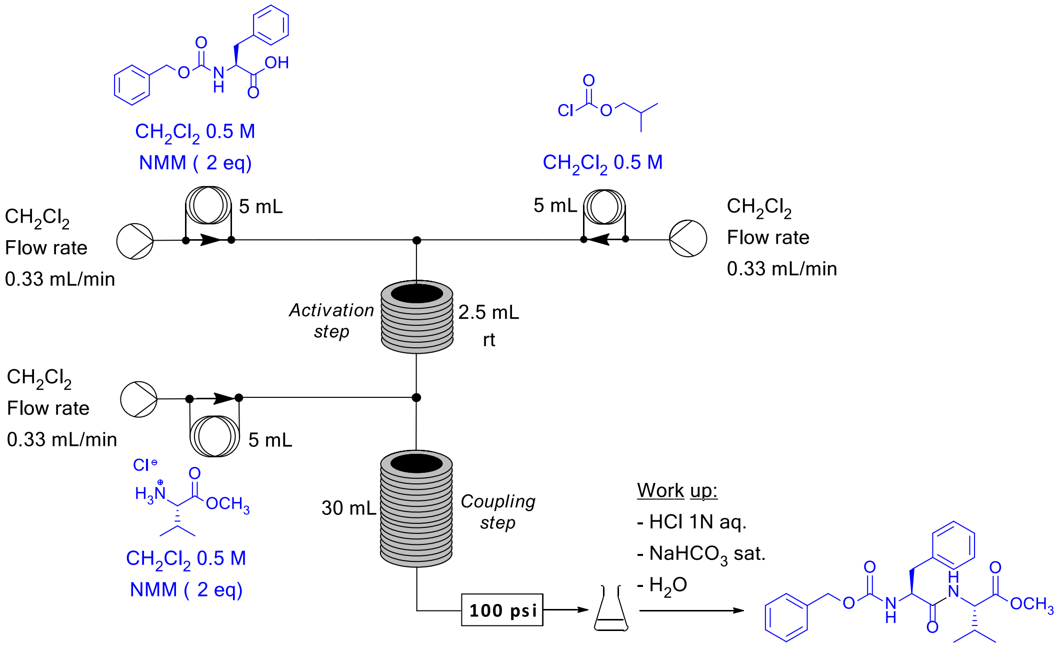


Scheme 9.4.

Table 9.2. Conditions not requiring low temperatures.

Entry	Reactor volume for coupling reaction (mL)	Base	Flow rate (mL/min)	T (°C)	Yield (%)
13	20	DIPEA	1	rt	60
14	20	NMM	0.33	rt	83
15	30	NMM	0.33	rt	98
16	20	NMM	0.33	40	92

For additional optimization, an improvement of the flow design was introduced (Scheme 9.5), by use of two Vapourtec R2plus/R4 flow systems, each one equipped with two HPLC pumps. Using this new setup, the use of triethylamine as base and dichloromethane-acetonitrile (1:1) as solvent mixture was tested, without improving the yield. Finally, the reaction conditions described in the entry 20 of the Table 9.3 were selected as optimal, since they afforded the desired dipeptide in a 99% yield.



Scheme 9.5.

Table 9.3. Additional optimization of the synthesis of Cbz-Phe-Val-OMe using the modified flow system

Entry	Base	Solvent	T (°C)	M	Scale, mmol	Yield (%)
1	Et_3N (4 eq)	CH_2Cl_2	rt	0.1	0.5	73
2	Et_3N (4 eq)	CH_2Cl_2-CH_3CN	rt	0.1	0.5	59
3	NMM (4 eq)	CH_2Cl_2	50	0.1	0.5	77
4	NMM (4 eq)	CH_2Cl_2	rt	0.1	0.5	99
5	NMM (4 eq)	CH_2Cl_2-CH_3CN	rt	0.1	0.5	73

[a] Isolated yields after column chromatography

9.5 - Scope of the mixed anhydride activation method under flow conditions

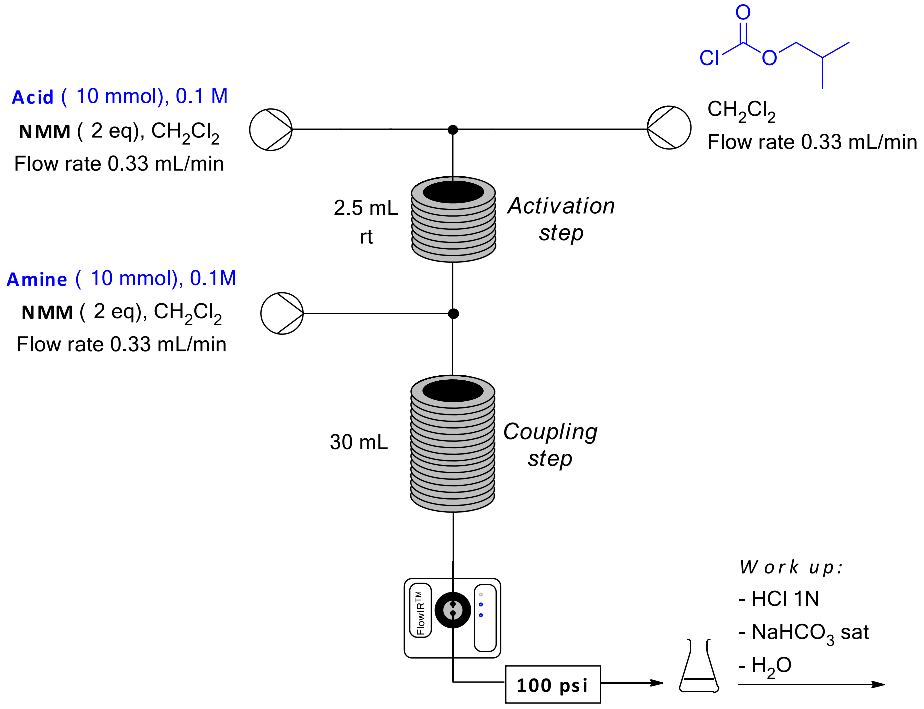
The optimized reaction conditions were applied to the obtention of several Cbz, Boc and Fmoc protected peptides. All aminoacids used are natural and belong to the L series, and the target peptides were isolated in moderate to excellent yields (44-99 %). The lower yields correspond to reactions involving side chain-unprotected amino acids, such as

Table 9.4. Scope of the mixed anhydride activation method under flow conditions

Entry	Product	M	Yield (%)
	Cbz Protected Peptides		
1	Cbz-Phe-Val-OMe	0.1	99
2	Cbz-Pro-Ile-OMe	0.1	96
3	Cbz-Thr-Phe-OMe	0.1	63
4	Cbz-Thr(Bzl)-Phe-OMe	0.1	68
5	Cbz-Ser-Pro-OMe	0.1	57
6	Cbz-Ser(*t*Bu)-Pro-OMe	0.1	67
	Boc Protected Peptides		
7	Boc-Gly-Val-OBn	0.1	98
8	Boc-L-Ala-Val-OBn	0.1	98
9	Boc-D-Ala-Val-OBn	0.1	96
10	Boc-Pro-Val-OBn	0.1	83
11	Boc-Trp(CHO)-Ala-OBn	0.1	78
12	Boc-Trp(H)-Ala-OBn	0.1	85
	Fmoc Protected Peptides		
13	Fmoc-Leu-Ile-OMe	0.1	92
14	Fmoc-Ala-Ile-OMe	0.1	81
15	Fmoc-Tyr-Ala-OBn	0.1	44
16	Fmoc-Tyr(O*t*Bu)-Ala-OBn	0.1	81

Cbz-Thr-Phe-OMe (entry 3, 63% yield), Cbz-Ser-Pro-OMe (entry 5, 57%), Boc-Trp(H)-Ala-OBn (entry 12, 85%) and Fmoc-Tyr-Ala-OBn (entry 15, 44%). In these cases, the use of doubly protected amino acids gave better yields (entries 4, 6, 11 and 16) (Table 10.4).

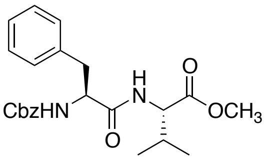
All this work was carried out on a 0.5 mmol scale. In order to obtain proof of concept for scaled-up conditions, we performed four of the reactions on a 10 mmol scale with very good yields, obtaining 2-4 grams of each peptide in just 5 hours (Scheme 9.6 and Table 9.5).



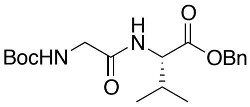
Scheme 9.6.

Table 9.5. Dipeptide syntheses at 10 mmol-scale (0.1 M concentration in all cases)

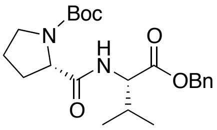
Entry	Product	Yield (%)
1	Cbz-Phe-Val-OMe	75
2	Boc-Gly-Val-OBn	93
3	Boc-Pro-Val-OBn	84
4	Boc-Trp(H)-Ala-OBn	85



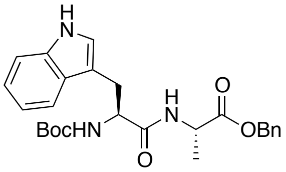
Cbz-L-Phe-L-ValOMe
3.8 g



Boc-Gly-L-ValOBn
3.1 g



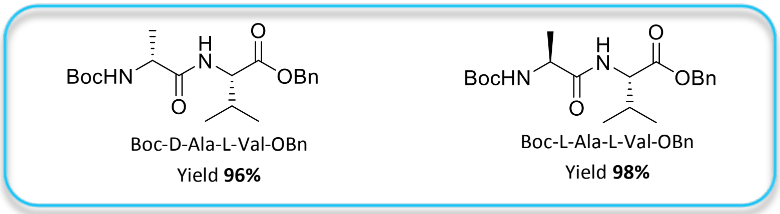
Boc-L-Pro-L-ValOBn
2.8 g

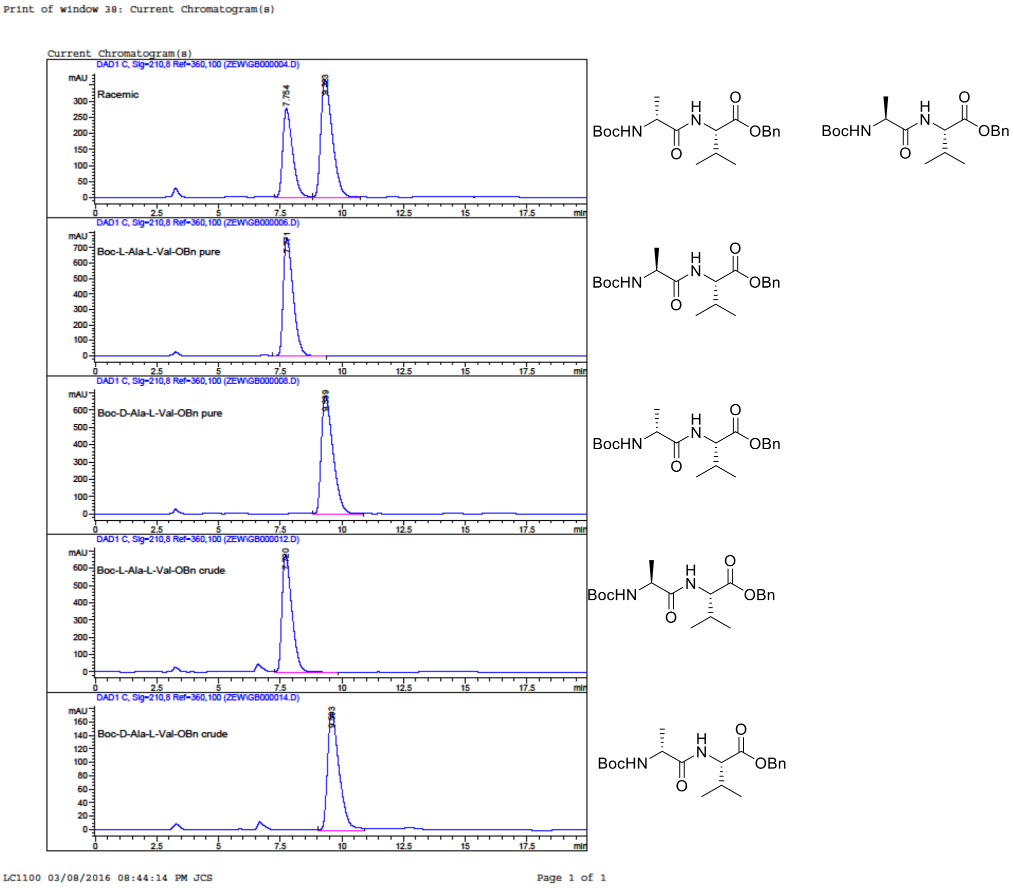


Boc-L-Trp(H)-L-AlaOBn
3.5 g

9.6 - Studies on stereocenter integrity

In order to study whether a racemization process had taken place during the flow synthetic protocol, we selected dipeptides Boc-D-Ala-L-Val-OBn and Boc-L-Ala-L-Val-OBn for our study. We analyzed by HPLC the reaction crudes and the dipeptides after purification, using a racemic as reference, to conclude that our conditions respected the integrity of stereocenters during the synthesis of these two dipeptides (Figure 9.2).




Print of window 38: Current Chromatogram(s)

LC1100 03/08/2016 08:44:14 PM JCS Page 1 of 1

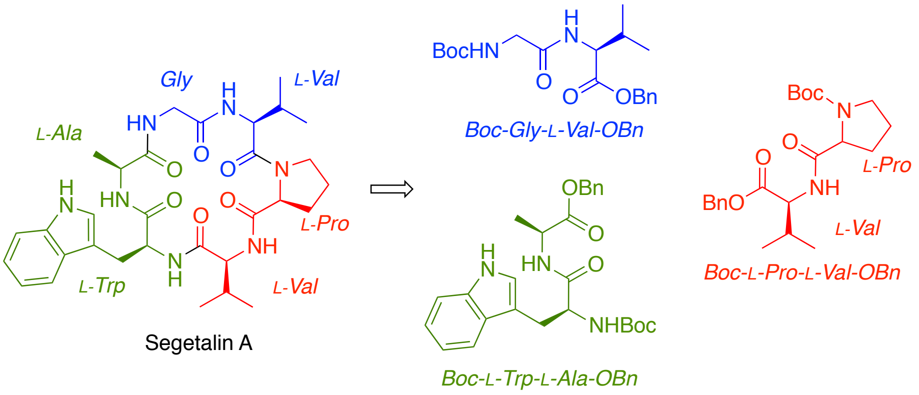
Figure 9.2.

9.7 - Towards the synthesis of segetalin A, a bioactive natural cyclic peptide

Cyclic peptides represent an interesting class of naturally occurring molecules, which exhibit a wide range of biological activities.[206] Their cyclic nature often offers more lipophilicity and membrane permeability, because of reduced zwitterionic character. In addition, restricted bond rotation promotes rigidity in the backbone conformation with more affinity and selectivity for binding proteins.[207]

Segetalin A was isolated in 1994[208] from the seeds of *Vaccaria segetalis* (*Caryophyllaceae*), a plant that has been used to activate blood flow, promote milk secretion and to treat amenorrhea and breast infections in China.[209] Segetalin A is endowed with a potent estrogen-like activity. Based on these considerations, Segetalin A could represent an interesting starting point to study the estrogenic activity of other cyclic peptides in order to improve their activity.

In this context, we decided to apply our recently developed flow synthetic methodology to the synthesis of Segetalin A. Structurally, it is a cyclohexapeptide formed by natural aminoacids, and its immediate precursor is a linear hexapeptide. Strategically, it seems prudent to avoid proline as either *N*- or *C* terminal amino acid of this linear precursor, since



Scheme 9.7.

---

[206] Itokawa H., Takeya K., Hitotsuyanagi Y., Morita H. *The Alkaloids*, **1997**, *49*, 301.

[207] Sakai R., Rinehart K.L., Kishore V., Kundu B., Faircloth G., Gloer J.B., Carney J.R., Namikoshi M., Sun F., Hughes R.G., Grávalos D.G., Quesada T.G., Wilson G.R., Heid R.M. *J. Med. Chem.*, **1996**, *39*, 2819.

[208] Morita H., Yun Y.S., Takeya K., Itokawa H. *Tetrahedron Lett.*, **1994**, *35*, 9593.

[209] Huang K.C. *The Pharmacology of Chinese Herbs*, CRC Press: London and Tokyo, **1994**, 254.

it makes cyclization more difficult and increases the risk of racemization. The synthesis of the linear precursor was planned in a convergent fashion by the coupling of three dipeptides, which should be more efficient than the sequential incorporation of aminoacids to elongate the chain until reaching the required number of six. A disconnection along these lines is proposed in Scheme 9.7.

The synthesis of the three dipeptide precursors was described in section 9.5. The coupling of two these dipeptides to afford a tetrapeptide requires that the Boc and Bn protecting groups of the amine and the acid, respectively, be removed. The *tert*-butyloxycarbonyl group of Boc-Pro-Val-OBn was removed by treatment with an anhydrous solution of HCl in dioxane (2M), in quantitative yield, and the product went directly into the next step. Benzyl ester protection of Boc-Gly-Val-OBn was removed by simple hydrogenolysis. Flow hydrogenation has been previously carried out in an HCube® flow hydrogenator.[199d,210] The starting dipeptide was hydrogenated at 1 mL/min over a CatCart of $Pd(OH)_2$ 20% on carbon at 50 °C in dichloromethane affording the acid in quantitative yield. The acid was directly employed for the next reaction without purification.

We assayed several combinations between the three dipeptides to afford three tetrapeptides (Table 9.6). We selected Boc-Gly-Val-Pro-Val-OBn (entry 3), obtained in 57 % yield, as our first tetrapeptide intermediate for the synthesis of Segetalin A.

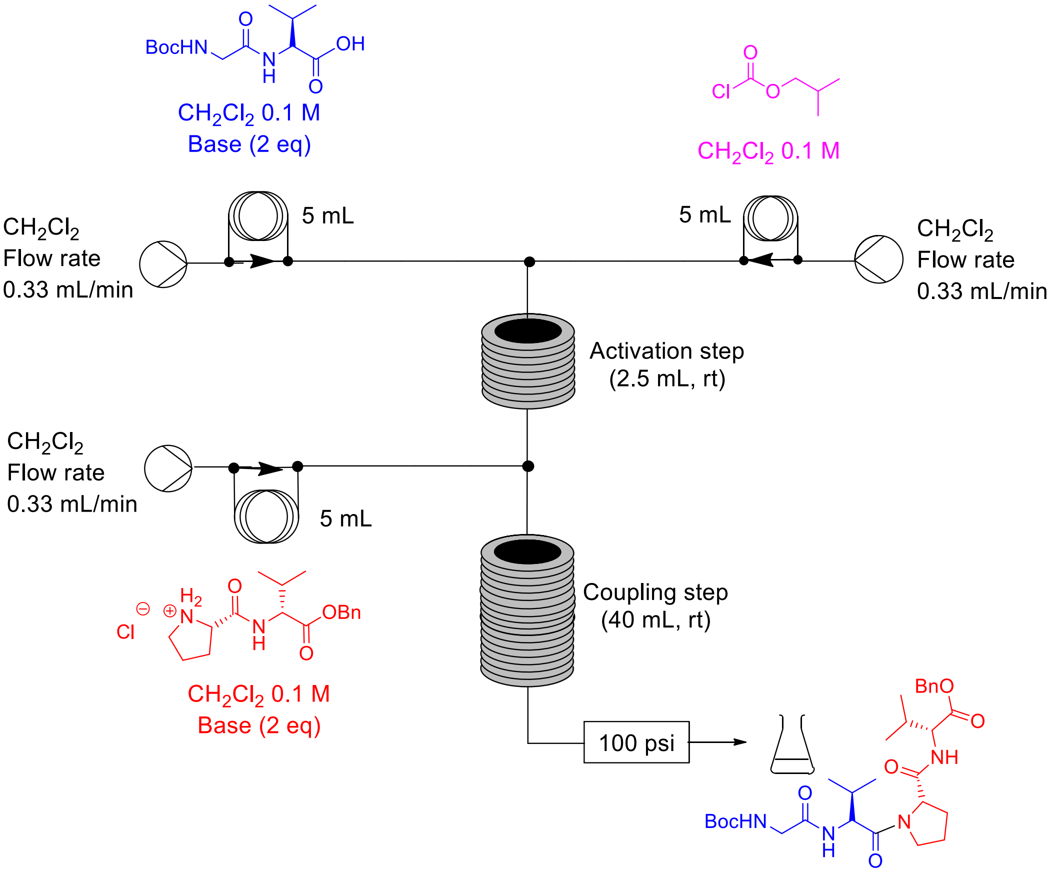
Table 9.6. Synthesis of potential tetrapeptide intermediates.

Entry	Product	M	mmol	Yield (%)
1	Boc-Trp(H)-Ala-Gly-Val-OBn	0.1	0.5	42
2	Boc-Pro-Val-Trp(H)-Ala-OBn	0.1	0.5	54
3	Boc-Gly-Val-Pro-Val-OBn	0.1	0.5	57

In an effort to improve the yield of Boc-Gly-Val-Pro-Val-OBn, the flow rate was reduced and the residence time of the activation step was increased, with no noticeable improvements being observed. However, a slightly improved yield was achieved by increasing the residence time of the coupling step from 30 to 40 minutes (Scheme 9.7 and Table 9.7).

---

[210] For examples of the use of H-Cube flow hydrogenation see: (a) Saaby S., Knudsen K.R., Ladlow M., Ley S.V. *Chem Commun.*, **2005**, *23*, 2909. (b) Franckevicius V., Knudsen K.R., Ladlow M., Longbottom D.A., Ley S.V. *Synlett*, **2006**, *6*, 889. (c) Knudsen K.R., Ladlow M., Bandpey Z., Ley S.V. *J. Flow Chem.*, **2014**, *4*, 18.



Scheme 9.7.

Table 9.7. Residence time optimization in the tetrapeptide synthesis

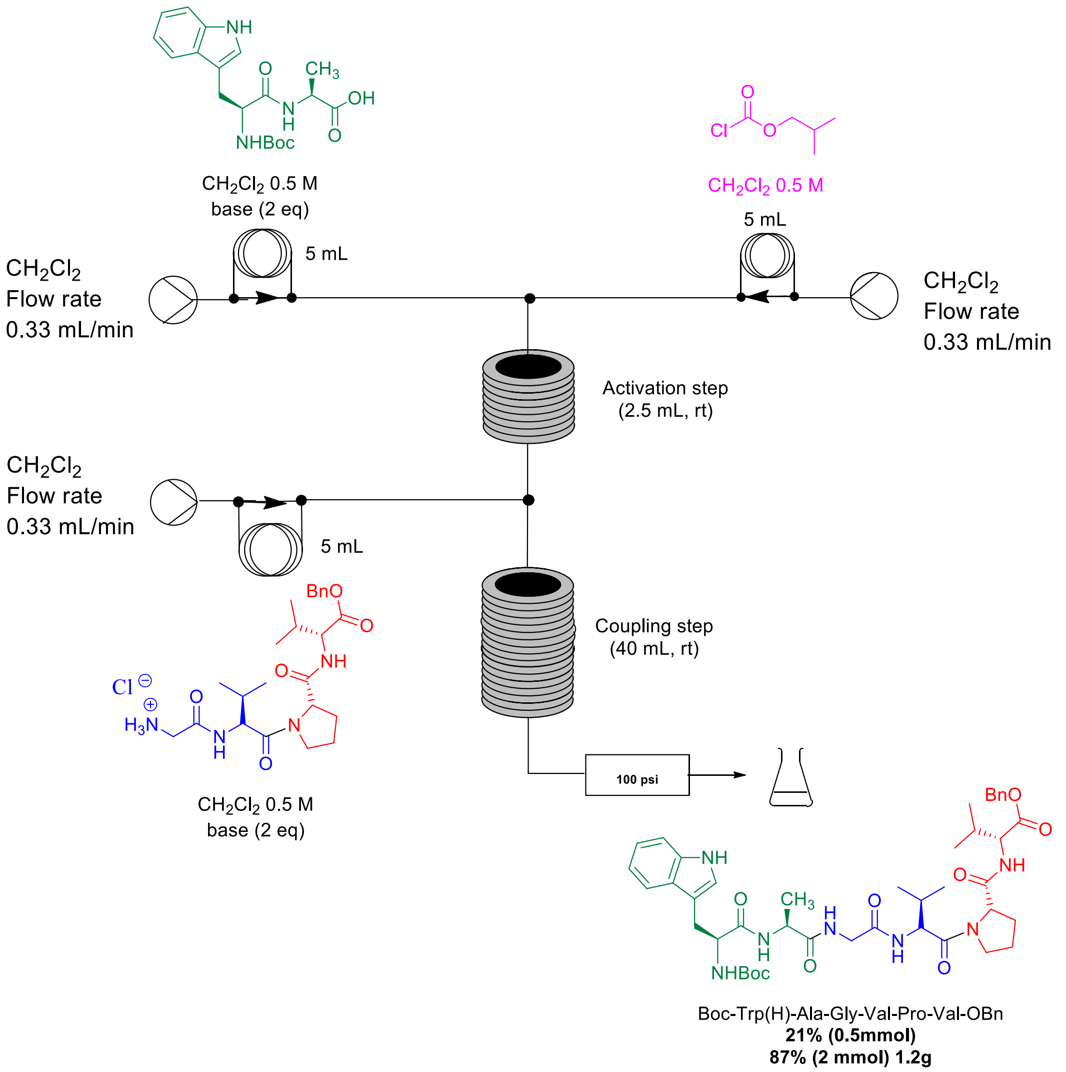
Entry	Product	Activation step coil (mL)	Coupling step coil (mL)	Flow rate (mL/min)	mmol	Yield (%)
1	Boc-Gly-Val-Pro-Val-OBn	2.5	30	1	0.5	57
2	Boc-Gly-Val-Pro-Val-OBn	10	30	1	0.5	34
3	Boc-Gly-Val-Pro-Val-OBn	2.5	30	0.45	0.5	55
4	Boc-Gly-Val-Pro-Val-OBn	2.5	40	1	0.5	58
5	Boc-Gly-Val-Pro-Val-OBn	2.5	40	1	6	35

Furthermore, an assay for scale up conditions has been attempted employing an E-series machine (Figure 9.3), obtaining the desired product in 35% yield (entry 5 of Table 9.7).

Figure 9.3. – E-series machine.

With the tetrapeptide in hand, we proceeded to its coupling with Boc-Trp(H)-Ala-OBn. As in previous cases, the Boc-Gly-Val-Pro-Val-OBn tetrapeptide was previously treated with a anhydrous solution of HCl in dioxane (2M) to remove the Boc group, and the Boc- Trp-Ala-OBn dipeptide was carboxyl-deprotected by hydrogenolysis under the same conditions described above. After coupling, the desired hexapeptide was obtained in 21% yield on a 0.5 mmol scale. Also in this case we scaled up the reaction obtaining the desired product in an excellent yield of 87% in a 2 mmol scale (Scheme 9.8).

The efficient preparation of the linear hexapeptide sets the stage for the last step of the synthesis, involving the final macrocyclic construction. Although this step could not be investigated due to lack of time, the synthesis will hopefully be completed soon by other members of the Ley group.


NH
O
CH3
OH
NHBoc
O
CH2Cl2 0.5 M
base (2 eq)
Cl
O
O
CH2Cl2 0.5 M
5 mL
CH2Cl2
Flow rate
0.33 mL/min
5 mL
CH2Cl2
Flow rate
0.33 mL/min
Activation step
(2.5 mL, rt)
CH2Cl2
Flow rate
0.33 mL/min
5 mL
BnO
O
NH
O
Cl ⊖
⊕
H3N
O
N
H
N
O
Coupling step
(40 mL, rt)
100 psi
CH2Cl2 0.5 M
base (2 eq)
BnO
O
NH
O
NH
O
CH3
H
N
O
N
H
N
H
N
O
NHBoc
O
Boc-Trp(H)-Ala-Gly-Val-Pro-Val-OBn
21% (0.5mmol)
87% (2 mmol) 1.2g

Scheme 9.8.

10 – Experimental section

10.1. General experimental information

All air-and/or moisture sensitive reactions were carried out under an argon atmosphere in oven-dried glassware. Solvents and reagents were transferred by syringe or via cannula through rubber septa.

Solvents and reagents: All reagents that are commercially available (Aldrich, Alfa-Aesar, Fluka, Merck, Panreac, Probus, Scharlau) were used directly without further purification. When required, solvents were dried using standard procedures.

TLC and preparative chromatography: Analytical thin layer chromatography (TLC) was carried out using commercially available aluminium-backed plates coated with silica gel (ScharlauCf530 or Macherey-Nagel AlugramSil G/UV254) or neutral aluminium oxide 60F254 (UV254), with fluorescent indicator and visualized under ultra-violet light Camag UV-II lamp cabinet (at 254 and 366 nm), staining with iodine vapor or by inmersion in suitable stain solutions which were prepared by standard reported procedure. Flash column chromatography was performed using silica gel SDS 60 ACC or Scharlau Ge 048 or neutral aluminium oxide Merck 90 standardized (0.063-0.200 mM, 70-230 mesh ASTM) and the eluent indicated in each case. Automated flash chromatography was performed in a Combiflash RF 200 system.

HPLC: The enantiomeric excess analysis has been conducted in a HPLC Agilent 1220 Infinity LC with a chiral column ULTRON ES-OVM analytical 4.6mm x 150mm, whose particles are silica-based, nominally 5 µm in diameter with 120 Å pores. A chiral-recognition protein, ovomucoid, is chemically bonded to the silica support.

Melting point: Melting points were determined either in a Stuart Scientific apparatus SMP3 Model or a Kofler-type heating platine microscope from Reichert, 723 Model and are uncorrected.

IR spectroscopy: Infrared spectra (IR) were taken using a Perkin-Elmer FTIR Paragon 1000 spectrometer. Samples were prepared as thin films on sodium chloride windows, or as pellets (potassium bromide).

NMR spectroscopy: NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 and 62.9 MHz for ^{1}H and ^{13}C NMR spectra, respectively (CAI de Resonancia Magnética Nuclear, Universidad Complutense) with the signal of the residual non-deuterated solvent as an internal standard. All coupling constants are given in Hz and the multiplicities of ^{1}H signals indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m complex (complex multiplet), bs (broad singlet). Uncertain ^{13}C-NMR assignments have been marked with *.

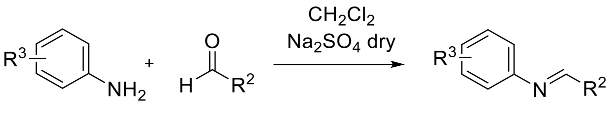
Elemental analysis: Quantitative combustion elemental analysis for carbon, hydrogen and nitrogen were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS microanalyzer.

Mass spectrometry: Gas chromatography mass spectra (GC-MS) were taken with different ionization methods, as Electronic Impact (EI) or Electrospray Ionization (ESI) in both the positive and negative ion mode were carried out by the CAI de Espectometría de Masas from Universidad Complutense Madrid (Spain).

10.2 - Synthesis of racemic 1,2,3,4-tetrahydroquinolines *via* $InCl_3$-catalysed Povarov reactions

10.2.1 - Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines

10.2.1.1 - Synthesis of arylimines 1a-g



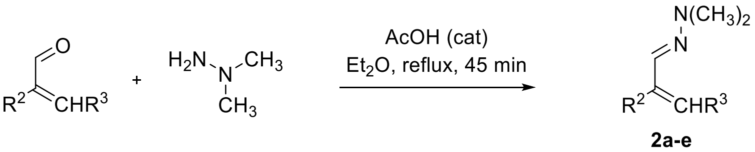
1a-g

General procedure

Prepared as described previuosly in our group. ^{1}H-NMR and ^{13}C-NMR data were identical to those previously reported.**¡Error! Marcador no definido.**

Cmpd	R^2	R^3
1a	C_6H_5	4-OCH_3
1b	4-ClC_6H_4	4-OCH_3
1c	4-$OCH_3C_6H_4$	4-OCH_3
1d	4-$CH_3C_6H_4$	4-OCH_3
1e	C_6H_5	2,4-$(CH_3)_2$
1f	4-$OCH_3C_6H_4$	4-CH_3
1g	4-$CH_3C_6H_4$	3,5-$(OCH_3)_2$

10.2.1.2 - Synthesis of *α,β*-unsaturated *N,N*-dimethylhydrazones 2a-e

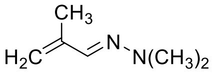


2a-e

Hydrazone	R2	R3	Yield (%)
2a	CH_3	H	95
2b	CH_2CH_3	H	90
2c	H	H	95
2d	H	CH_2CH_3	95
2e	CH_3	CH_2CH_3	90

To a stirred solution of the corresponding acrolein derivative (1 eq, 60 mmol) in diethyl ether (50 mL) was added *N,N*-dimethylhydrazine (2 eq, 120 mmol) and acetic acid (1 mL) dropwise and the resulting yellow solution was reflux for 45 minutes. After cooling at room temperature, it was washed successively with saturated $NaHCO_3$ (2 x 50 mL) and water (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated on a water bath keeping the temperature below 60°C, to avoid volatilization of the resulting hydrazone. The crude product thus obtained was used in subsequent reactions with no further purification.

1,1-Dimethyl-2-(2-methylallylidene)hydrazine[211] (2a)



2a

Prepared from methacrolein (4.9 mL, 60 mmol) and *N,N*-dimethylhydrazine (9.1 mL, 120 mmol).

Yield: 6.39 g (95 %). Yellow liquid.

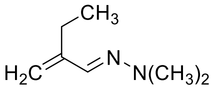
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.91 (s, 3H, CH_3); 2.85 (s, 6H, $N(CH_3)_2$); 5.02 (s, 1H, CH_2); 5.10 (s, 1H, CH_2); 7.03 (s, 1H, CH=N).

---

[211] Gómez-Bengoa E., Echavarren A.M. *J. Org. Chem.*, **1991**, *56*, 3497.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 17.2 (CH_3); 42.0 ($N(CH_3)_2$); 114.3 (CH_2); 135.7 (CH=N); 142.1 (C-2) ppm.

1,1-Dimethyl-2-(2-ethylallylidene)hydrazine[211] (2b)

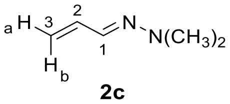


2b

Prepared from 2-ethylacrolein (5.9 mL, 60 mmol) and *N,N*-dimethylhydrazine (9.1 mL, 120 mmol).
Yield: 6.81 g (90 %). Yellow liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.08 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); 2.34 (q, *J* = 7.4 Hz, 2H, CH_2CH_3); 2.81 (s, 6H, $N(CH_3)_2$); 5.01 (d, *J* = 0.6 Hz, 1H, $=CH_2$); 5.08 (d, *J* = 1.1 Hz, 1H, $=CH_2$); 6.98 (s, 1H, CH=N) ppm.
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 13.1 (CH_3); 24.3 (CH_2); 42.9 ($N(CH_3)_2$); 113.7 (CH_2); 136.4 (CH=N); 148.7 (C-2) ppm.

2-Allylidene-1,1-dimethylhydrazine[211] (2c)

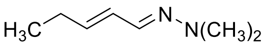


2c

Prepared from acrolein (1.3 mL, 20 mmol) and *N,N*-dimethylhydrazine (3.0 mL, 40 mmol).
Yield: 1.86 g (95 %). Yellow liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.84 (s, 6H, $N(CH_3)_2$); 5.21 (d, *J* = 9.9 Hz, 1H, H-3a); 5.26 (d, *J* = 16.8 Hz, 1H, H-3b); 6.45 (ddd, *J* = 17.3, 10.3, 9.0 Hz, 1H, H-2); 6.96 (d, *J* = 8.9 Hz, 1H, H-1) ppm.
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 42.7 ($N(CH_3)_2$); 116.7 (C3); 135.7 (C2); 135.8 (C1) ppm.

1,1-Dimethyl-2-(pent-2-enylidene)hydrazine[211] (2d)



2d

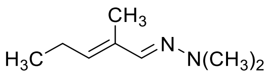
Prepared from 2-pentenal (0.98 mL, 10 mmol) and *N,N*-dimethylhydrazine (1.52 mL, 20 mmol).

Yield: 1.2 g (95 %). Orange liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.04 (t, J = 7.4 Hz, 3H, CH_2CH_3); 2.14 (quint, J = 7.4 Hz, 2H, CH_2CH_3); 2.80 (s, 6H, $N(CH_3)_2$); 5.01 (dt, J = 15.6, 6.4 Hz, 1H, CH_2-C*H*=CH); 6.18 (m, 1H, C*H*-CH=N); 7.01 (d, J = 8.8 Hz, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 13.7 (CH_3); 26.0 (CH_2); 43.4 ($N(CH_3)_2$); 128.3 (C-2); 137.6 (CH=N); 137.8 (C-3) ppm.

1,1-Dimethyl-2-(2-methylpent-2-enylidene)[212,213] (2e)



2e

Prepared from 2-methyl-2-pentenal (1.14 mL, 10 mmol) and *N,N*-dimethylhydrazine (1.52 mL, 20 mmol). Yield: 1.26 g (90%). Yellow liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.00 (t, J = 7.5 Hz, 3H, CH_2CH_3); 1.82 (s, 3H, CH_3); 2.18 (quint, J = 7.5 Hz, 2H, CH_2CH_3); 2.79 (s, 6H, $N(CH_3)_2$); 5.54 (t, J = 7.3 Hz, 1H, CH_2-C*H*=); 7.02 (s, 1H, CH=N) ppm.

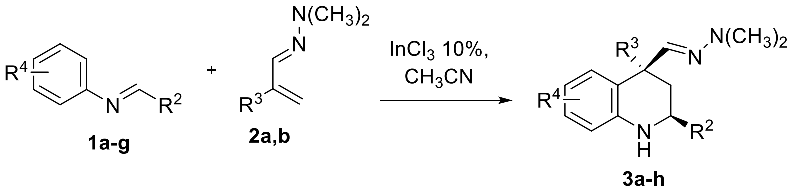
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 11.6 (CH_3); 14.1 (CH_3); 21.5 (CH_2); 43.3 ($N(CH_3)_2$); 133.8 (C-2); 135.1 (CH=N); 140.6 (C-3) ppm.

---

[212] Waldner A. *Helv. Chim. Acta*, **1988**, *71*, 486.

[213] Pérez J.M., Avendaño C., Menéndez J.C. *Tetrahedron*, **1995**, *51*, 6573.

10.2.1.3 - Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolines 3a-h



To a stirred solution of imine **1** (1 eq, 1.0 mmol) and $InCl_3$ (10 mol %) in acetonitrile (20 mL) was added hydrazone **2** (1.2 eq, 1.2 mmol). Stirring was continued for the time period specified in the compound data sheet and after completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (4 x 10 mL), dried and evaporated. The resulting crude was purified by silica gel flash chromatography eluting with petroleum ether : ethyl acetate (9:1, v/v).

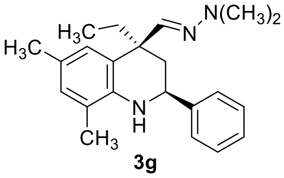
Starting imine	Cmpd	R^2	R^3	R^4	Yield (%)
1a	**3a**[a]	C_6H_5	CH_3	6-OCH_3	90
1b	**3b**[a]	4-ClC_6H_4	CH_3	6-OCH_3	87
1c	**3c**[a]	4-$OCH_3C_6H_4$	CH_3	6-OCH_3	80
1d	**3d**[a]	4-$CH_3C_6H_4$	CH_3	6-OCH_3	93
1e	**3e**[a]	C_6H_5	CH_3	6,8-$(CH_3)_2$	80
1f	**3f**[a]	4-$OCH_3C_6H_4$	CH_3	6-CH_3	72
1e	**3g**	C_6H_5	CH_2CH_3	6,8-$(CH_3)_2$	61
1g	**3h**[a]	4-$CH_3C_6H_4$	CH_3	5,7-$(OCH_3)_2$	72

[a] Compounds described in literature; their NMR spectra were identical those previously reported.[214]

---

[214] (a) Sridharan V., Perumal P.T., Avendaño C., Menéndez J.C. *Org. Biomol. Chem.*, **2007**, **5**, 1351. (b) Sridharan V., Ribelles P., Estévez V., Villacampa M., Ramos M.T., Perumal P.T., Menéndez J.C. *Chem. Eur. J.*, **2012**, *18*, 5056.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-4-ethyl-6,8-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline (3g)



3g

Prepared from imine **1e** (0.272 g, 1.3 mmol) and hydrazone **2b** (0.180 g, 1.4 mmol).

Reaction time: 3 h.

Yield: 0.266 g (61%). Yellow solid, mp: 121-123 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 0.97 (t, *J* = 7.3 Hz, 3H, CH_3); 1.99-2.11 (m, 7H, CH_3, H-3eq, H-3ax and CH_2); 2.23 (s, 3H, CH_3); 2.75 (s, 6H, $N(CH_3)_2$); 3.84 (s, 1H, NH); 4.57 (dd, *J* = 11.1, 2.7 Hz, 1H, H-2); 6.63 (s, 1H, H-7); 6.80 (s, 2H, H-5 and CH=N); 7.32-7.51 (m, 5H, H-2', H-3', H-4', H-5' and H-6') ppm.

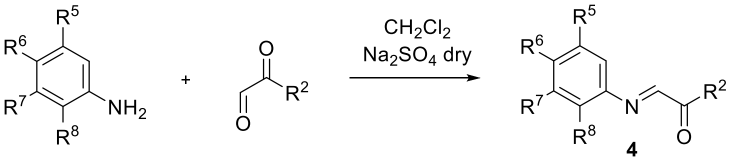
^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 8.8 ($CH_2\mathit{C}H_3$); 17.7 ($ArCH_3$); 20.7 ($ArCH_3$); 32.2 ($\mathit{C}H_2CH_3$); 40.2 (C-3); 43.6 ($N(CH_3)_2$); 43.7 (C-4); 53.0 (C-2); 121.4 (C-4a); 125.4 (C-8); 125.8 (C-6); 126.8 (C-2' and C-6'); 127.0 (C-5); 127.7 (C-4'); 128.8 (C-3' and C-5'); 129.5 (C-7); 139.7 (C-8a); 143.6 (CH=N); 145.2 (C-1') ppm.

IR (NaCl) *ν*: 3401.2 (N-H), 2958.6 (C-H), 1604.1 (C=C), 1251.2 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{29}N_3$ (M = 335.49): C, 78.76; H, 8.71; N, 12.53. Found: C, 78.35; H, 8.68; N, 12.56.

10.2.2 - Synthesis of 2-acyl-1,2,3,4-tetrahydroquinolines

10.2.2.1 - Synthesis of α-ketoimines 4a-q



Cmpd	R^2	R^5	R^6	R^7	R^8
4a	C_6H_5	H	OCH_3	H	H
4b	$4\text{-}FC_6H_4$	H	OCH_3	H	H
4c	$4\text{-}OCH_3C_6H_4$	H	OCH_3	H	H
4d	C_6H_5	H	CH_3	H	CH_3
4e	$4\text{-}FC_6H_4$	CH_3	H	CH_3	H
4f	$4\text{-}FC_6H_4$	H	CH_3	H	CH_3
4g	$4\text{-}OCH_3C_6H_4$	H	CH_3	H	CH_3
4h	$4\text{-}OCH_3C_6H_4$	H	CH_3	H	H
4i	OEt	H	OCH_3	H	H
4j	OEt	H	CH_3	H	CH_3
4k	2-furyl	H	OCH_3	H	H
4l	2-thienyl	H	OCH_3	H	H
4m	OEt	H	CH_3	H	H
4n	C_6H_5	H	CH_3	H	H
4o	C_6H_5	CH_3	H	CH_3	H
4p	$4\text{-}FC_6H_4$	H	CH_3	H	H
4q	C_6H_5	H	H	H	H

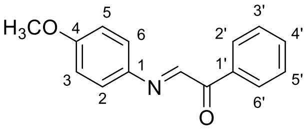
A solution of the suitable aniline (1 eq) and glyoxal derivative[215] (1 eq) in CH_2Cl_2 (5 mL) was stirred vigorously in the presence of anhydrous Na_2SO_4 (5 g) for 30 minutes and then, the reaction mixture was filtrated and the solvent evaporated under vacuum to afford the

---

[215] Some commercially available glyoxals (4-methoxyphenyl and 4-fluorophenyl) are available as hydrates containing an unknown amount of water so the amount of aldehyde used had to be optimized by gradual addition until no aniline was detected by ^1H-NMR.

desired acylimines **4a-q**, that were used without further purification in the following reactions. In all cases the yields were quantitative.

2-(4-Methoxyphenylimino)-1-phenylethanone (4a)[216]



4a

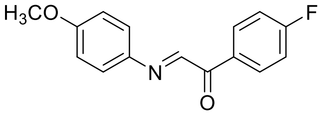
Prepared from *p*-anisidine (162 mg, 1.31 mmol) and phenylglyoxal hydrate (200 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 3.84 (s, 3H, OCH_3); 6.96 (d, J = 9.0 Hz, 2H, H-3 and H-5); 7.40 (d, J = 9.0 Hz, 2H, H-2 and H-6); 7.49-7.58 (m, 2H, H-3´ and H-5´); 7.62 (m, 1H, H-4´); 8.27-8.31 (m, 2H, H-2´ and H-6´); 8.35 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 55.8 (OCH_3); 114.9 (C-3 and C-5); 123.8 (C-2 and C-6); 128.6 (C-2´ and C-6´); 130.9 (C-3´ and C-5´); 133.7 (C-4´); 135.8 (C-1´); 141.9 (C-1); 154.4 (CH=N); 160.8 (C-4); 191.1 (CO) ppm.

IR (NaCl) *ν*: 1653.7 (C=O), 1595.9 (C=N) cm^{-1}.

1-(4-Fluorophenyl)-2-(4-methoxyphenylimino)ethanone (4b)[216]



4b

Prepared from *p*-anisidine (162 mg, 1.31 mmol) and 4-fluorophenylglyoxal hydrate (402 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 3.86 (s, 3H, OCH_3); 6.97 (d, J = 9.0 Hz, 2H, H-3 and H-5); 7.17 (t, J = 8.8 Hz, 2H, H-3´ and H-5´); 7.40 (d, J = 9.0 Hz, 2H, H-2 and H-6); 8.31 (s, 1H, CH=N); 8.39 (dd, J = 9.0, 5.6 Hz, 2H, H-2´ and H-6´) ppm.

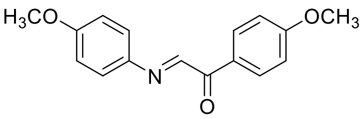
^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 55.9 (OCH_3); 115.0 (C-3 and C-5); 115.9 (d, J = 23.5 Hz, C-3´ and C-5´); 123.9 (C-2 and C-6); 132.1 (d, J = 3.4 Hz, C-1'); 133.8 (d, J = 9.6 Hz, C-2´ and C-6´); 141.7 (C-1); 154.4 (CH=N); 161.0 (C-4); 166.4 (d, J = 280.4 Hz, C-4´); 189.6 (CO) ppm.

IR (NaCl) *ν*: 1654.9 (C=O), 1599.5 (C=N) cm^{-1}.

---

[216] Kunzi S.A. Morandi B., Carreira E.M. *Org. Lett.*, **2012**, *14*, 1900.

1-(4-Methoxyphenyl)-2-(4-methoxyphenylimino)ethanone (4c)[216]



4c

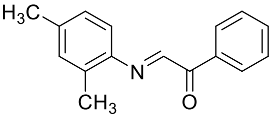
Prepared from *p*-anisidine (162 mg, 1.31 mmol) and 4-methoxyphenylglyoxal hydrate (214 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 3.85 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 6.96 (d, J = 9.0 Hz, 2H, H-3 and H-5); 6.98 (d, J = 9.1 Hz, 2H, H-3´ and H-5´); 7.39 (d, J = 9.0 Hz, 2H, H-2 and H-6); 8.33 (s, 1H, CH=N); 8.35 (d, J = 9.1 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 55.8 (OCH_3); 55.8 (OCH_3); 114.0 (C-3´ and C-5´); 114.9 (C-3 and C-5); 123.7 (C-2 and C-6); 128.7 (C-1´); 133.4 (C-2´ and C-6´); 142.1 (C-1); 155.1 (CH=N); 160.6 (C-4); 164.3 (C-4´); 189.3 (CO) ppm.

IR (NaCl) ν: 1670.1 (C=O), 1597.7 (C=N) cm^{-1}.

2-(2,4-Dimethylphenylimino)-1-phenylethanone (4d)



4d

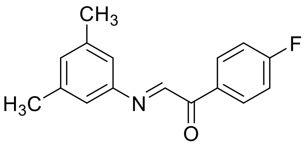
Prepared from 2,4-dimethylaniline (159 mg, 1.31 mmol) and phenylglyoxal hydrate (200 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.36 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 7.00 (d, J = 8.0 Hz, 1H, H-6); 7.03-7.13 (m, 2H, H-3 and H-5); 7.47-7.54 (m, 2H, H-3’ and H-5’); 7.61 (m, 1H, H-4’); 8.23 (s, 1H, CH=N); 8.33-8.36 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 18.3 (CH_3); 21.2 (CH_3); 116.9 (C-6); 127.7 (C-5); 128.4 (C-3’ and C-5’); 130.8 (C-2’ and C-6’); 131.7 (C-3); 133.5 (C-4’); 134.3 (C-2); 135.5 (C-1’); 138.8 (C-4); 145.7 (C-1); 155.6 (CH=N); 191.2 (C=O) ppm.

IR (NaCl) ν: 2924.7 (C-H), 1649.3 (C=O), 1580.8 (C=N) cm^{-1}.

2-(3,5-Dimethylphenylimino)-1-(4-fluorophenyl)ethanone (4e)



4e

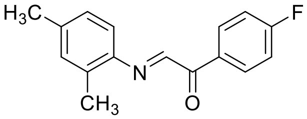
Prepared from 3,5-dimethylaniline (220 mg, 1.80 mmol) and 4-fluorophenylglyoxal hydrate (548 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.37 (s, 6H, 2 x CH_3); 6.96 (s, 2H, H-2 and H-6); 7.01 (s, 1H, H-4); 7.18 (t, *J* = 8.7 Hz, 2H, H-3′ and H-5′); 8.26 (s, 1H, CH=N); 8.40 (d, *J* = 9.0 Hz, 2H, H-2′ and H-6′) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 21.6 (2 x CH_3); 116.0 (d, *J* = 24.1 Hz, C-3′ and C-5′); 119.5 (C-2 and C-6); 130.7 (C-4); 131.8 (d, *J* = 3.4 Hz, C-1′); 133.8 (d, *J* = 10.3 Hz, C-2′ and C-6′); 139.5 (C-3 and C-5); 149.3 (C-1); 157.0 (CH=N); 166.4 (d, *J* = 281.5 Hz, C-4'); 189.4 (C=O) ppm.

IR (NaCl) *ν*: 1654.4 (C=O), 1598.0 (C=N) cm^{-1}.

2-(2,4-Dimethylphenylimino)-1-(4-fluorophenyl)ethanone (4f)



4f

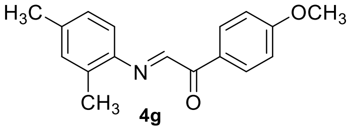
Prepared from 2,4-dimethylaniline (0.220 g, 1.80 mmol) and 4-fluorophenylglyoxal hydrate (0.548 g).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.36 (s, 3H, CH_3); 2.40 (s, 3H, CH_3); 7.00 (d, *J* = 8.0 Hz, 1H, H-6); 7.06 (d, *J* = 8.0 Hz, 1H, H-5); 7.11 (s, 1H, H-3); 7.18 (t, *J* = 8.7 Hz, 2H, H-3′ and H-5′); 8.20 (s, 1H, CH=N); 8.44 (dd, *J* = 9.0, 5.6 Hz, 2H, H-2′ and H-6′) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 18.5 (CH_3); 21.4 (CH_3); 115.8 (d, *J* = 23.4 Hz, C-3′ and C-5′); 117.0 (C-6); 127.9 (C-5); 132.0 (d, *J* = 3.4 Hz, C-1′); 132.0 (C-3); 133.8 (d, *J* = 10.3 Hz, C-2′ and C-6′); 134.5 (C-2); 139.2 (C-4); 145.7 (C-1); 155.7 (CH=N); 166.5 (d, *J* = 280.8 Hz, C-4′); 189.6 (CO) ppm.

IR (NaCl) *ν*: 1655.1 (C=O), 1595.7 (C=N) cm^{-1}.

2-((2,4-Dimethylphenyl)imino)-1-(4-methoxyphenyl)ethanone (4g)



4g

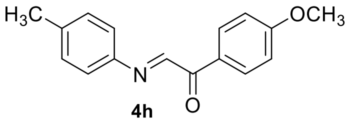
Prepared from 2,4-dimethylaniline (159 mg, 1.31 mmol) and 4-methoxyphenylglyoxal hydrate (214 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.36 (s, 3H, CH$_3$); 2.41 (s, 3H, CH$_3$); 3.90 (s, 3H, OCH$_3$); 6.97 (d, *J* = 8.0 Hz, 1H, H-6); 6.94-7.02 (m, 2H, H-3' and H-5'); 7.03-7.12 (m, 2H, H-5 and H-3); 8.20 (s, 1H, CH=N); 8.36-8.47 (m, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 18.3 (CH$_3$); 21.2 (CH$_3$); 55.6 (OCH$_3$); 113.8 (C-3´ and C-5´); 116.9 (C-6); 127.6 (C-5); 128.3 (C-1'); 131.6 (C-3); 133.3 (C-2' and C-6'); 133.9 (C-2); 138.4 (C-4); 146.0 (C-1); 156.3 (CH=N); 164.1 (C-4´); 189.3 (CO) ppm.

IR (NaCl) *ν*: 1668.2 (C=O), 1598.8 (C=N) cm^{-1}.

1-(4-methoxyphenyl)-2-(p-tolylimino)ethanone (4h)



4h

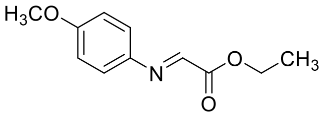
Prepared from *p*-toluidine (140 mg, 1.31 mmol) and 4-methoxyphenylglyoxal hydrate (214 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.19 (s, 3H, CH$_3$); 3.69 (s, 3H, OCH$_3$); 6.78 (d, *J* = 9.0 Hz, 2H, H-3' and H-5'); 7.05 (s, 4H, H-2, H-3, H-5 and H-6); 8.10 (s, 1H, CH=N); 8.16 (d, *J* = 9.0 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 21.3 (CH$_3$); 55.6 (OCH$_3$); 113.9 (C-3´ and C-5´); 121.6 (C-2 and C-6); 128.3 (C-1'); 130.2 (C-3 and C-5); 133.2 (C-2´ and C-6´); 138.8 (C-4); 146.8 (C-1); 156.7 (CH=N); 164.2 (C-4´); 189.1 (CO) ppm.

IR (NaCl) *ν*: 1672.1 (C=O), 1595.9 (C=N) cm^{-1}.

Ethyl 2-(4-methoxyphenylimino)acetate (4i)[216]



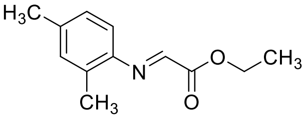
4i

Prepared from *p*-anisidine (162 g, 1.31 mmol) and ethyl glyoxal monohydrate (136 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.35 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H$_3$*); 3.77 (s, 3H, OCH$_3$); 4.35 (q, *J* = 7.1 Hz, 2H, OC*H$_2$*CH$_3$); 6.88 (d, *J* = 8.9 Hz, 2H, H-3 and H-5); 7.32 (d, *J* = 8.9 Hz, 2H, H-2 and H-6); 7.89 (CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 15.5 ($OCH_2\mathit{C}H_3$); 55.8 (OCH_3); 62.2 ($O\mathit{C}H_2CH_3$); 114.8 (C-3 and C-5); 124.0 (C-2 and C-6); 141.6 (C-1); 148.3 (CH=N); 160.9 (C-4); 163.9 (CO_2Et) ppm.
IR (NaCl) *ν*: 2838.4 (C-H), 1740.1 (C=O), 1622.5 (C=N) cm^{-1}.

Ethyl 2-(2,4-dimethylphenylimino)acetate (4j)



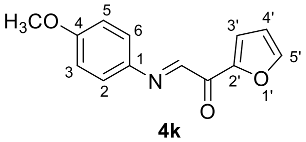
4j

Prepared from 2,4-dimethylaniline (158 mg, 1.31 mmol) and ethyl glyoxal monohydrate (136 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.41 (t, *J* = 7.1 Hz, 3H, $OCH_2\mathit{CH_3}$); 2.33 (s, 3H, CH_3); 2.35 (s, 3H, CH_3); 4.41 (q, *J* = 7.1 Hz, 2H, $O\mathit{CH_2}CH_3$); 6.83 (d, *J* = 8.0 Hz, 1H, H-6); 7.00 (m, 1H, H-5); 7.06 (s, 1H, H-3); 7.81 (s, 1H, CH=N) ppm.
^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 14.3 (CH_3); 17.9 (CH_3); 21.2 (CH_3); 63.0 ($O\mathit{C}H_2CH_3$); 117.2 (C-6); 127.4 (C-5); 131.6 (C-3); 133.4 (C-6); 138.3 (C-4); 146.0 (C-1); 150.1 (CH=N); 163.5 (C=O) ppm.
IR (NaCl) *ν*: 2922.4 (C-H), 1741.8 (C=O), 1624.3 (C=N) cm^{-1}.

1-(2-Furyl)-2-(4-methoxyphenylimino)ethanone (4k)

The required 2-furylglyoxal was prepared as follows: 2-Acetylfuran (1.10 g, 10 mmol) was added to a solution of SeO_2 (1.11 g, 10 mmol) in dioxane (6 mL) and water (0.2 mL) prepared at 50-55 °C. The mixture was refluxed for 5 h and then allowed to stand for an hour. The precipitated selenium was removed by filtration. The filtrate was concentrated and the residue was purified by column chromatography on silica gel eluting with a petroleum ether:ethyl acetate mixture (3:1, v/v). Some starting material eluted first and then, 2-furylglyoxal was obtained as a red oil (495 mg, 40%), containing the aldehyde (characterized by a singlet at 9.56 ppm) also the hydrated form. The compound was used with no additional manipulation.



4k

Prepared from *p*-anisidine (370 mg, 3 mmol) and 2-furylglyoxal (372 mg, 3 mmol).

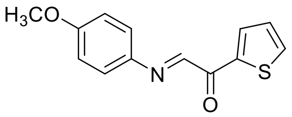
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 3.89 (s, 3H, OCH$_3$); 6.65 (dd, *J* = 3.6, 1.7 Hz, 1H, H-4´); 7.01 (d, *J* = 9.0 Hz, 2H, H-3 and H-5); 7.44 (d, *J* = 9.0 Hz, 2H, H-2 and H-6); 7.78 (dd, *J* = 1.6, 0.7 Hz, 1H, H-5´); 8.00 (dd, *J* = 3.5, 0.7 Hz, 1H, H-3´); 8.29 (s, 1H, CH=N) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 55.5 (OCH$_3$); 112.5 (C-4´); 114.6 (C-3 and C-5); 123.1 (C-3´); 123.7 (C-2 and C-6); 141.3 (C-1); 147.9 (C-5´); 150.6 (C-2´); 153.0 (CH=N); 160.7 (C-4); 177.6 (CO) ppm.

IR (NaCl) ν: 2854.3 (C-H), 1642.4 (C=O); 1578.2 (C=N) cm^{-1}.

2-(4-Methoxyphenylimino)-1-(2-thienyl)ethanone (4l)

2-Thienylglyoxal was prepared by oxidation of 2-acetylthiophene following the procedure described for 2-furylglyoxal under **4k**.



4l

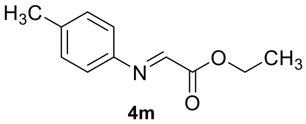
Prepared from *p*-anisidine (88 mg, 0.71 mmol) and 2-thienylglyoxal (154 mg, 1.10 mmol).

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 3.85 (s, 3H, OCH$_3$); 6.97 (d, *J* = 9.0 Hz, 2H, H-3 and H-5); 7.18 (dd, *J* = 5.0, 3.9 Hz, 1H, H-4´); 7.43 (d, *J* = 9.1 Hz, 2H, H-2 and H-6); 7.74 (dd, *J* = 5.0, 1.2 Hz, 1H, H-5´); 8.22 (s, 1H, CH=N); 8.36 (dd, *J* = 3.9, 1.2 Hz, 1H, H-3´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 55.9 (OCH$_3$); 115.0 (C-3 and C-5); 124.1 (C-2 and C-6); 128.0 (C-4´); 136.1 (C-5´); 136.7 (C-3´); 139.5 (C-2´); 141.1 (C-1); 153.6 (CH=N); 161.1 (C-4); 182.8 (CO) ppm.

IR (NaCl) ν: 1669.3 (C=O), 1631.7 (C=N) cm^{-1}.

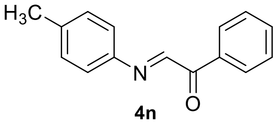
Ethyl 2-(*p*-tolylimino)acetate (4m)[217]


4m

Prepared from *p*-toluidine (140 g, 1.31 mmol) and ethyl glyoxal monohydrate (136 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.40 (t, J = 7.4 Hz, 3H, CH$_2$CH_3); 2.37 (s, 3H, ArCH$_3$); 4.41 (q, J = 7.4 Hz, 2H, CH_2CH$_3$), 7.25-7.18 (m, 4H, H-2, H-3, H-5 and H-6), 7.92 (s, 1H, CH=N) ppm.

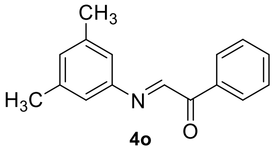
1-Phenyl-2-(*p*-tolylimino)ethan-1-one (4n)


4n

Prepared from *p*-toluidine (140 mg, 1.31 mmol) and phenylglyoxal hydrate (200 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.38 (s, 3H, CH$_3$); 7.25-7.26 (m, 4H, H-2, H-3, H-5 and H-6); 7.46-7.52 (m, 2H, H-3' and H-5'); 7.59 (m, 1H, H-4'); 8.29-8.32 (m, 3H, CH=N, H-2' and H-6') ppm.

2-((3,5-Dimethylphenyl)imino)-1-phenylethan-1-one (4o)


4o

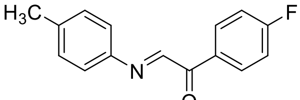
Prepared from 2,4-dimethylaniline (159 mg, 1.31 mmol) and phenylglyoxal hydrate (200 mg).

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.38 (s, 6H, 2 x CH$_3$); 6.98-7.01 (m, 3H, H-2, H-4, and H-6); 7.48-7.54 (m, 2H, H-3' and H-5'); 7.61 (m, 1H, H-4'); 8.31-8.34 (m, 3H, CH=N, H-2' and H-6') ppm.

---

[217] Zhu S., Dong J., Fu S., Jiang H., Zeng W. J. *Org. Lett.,* **2011**, 13, 4914.

1-(4-Fluorophenyl)-2-(*p*-tolylimino)ethan-1-one (4p)

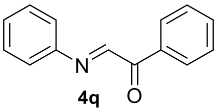


4p

Prepared from *p*-toluidine (0.193 g, 1.80 mmol) and 4-fluorophenylglyoxal hydrate (0.548 g).

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.51 (s, 3H, CH_3); 7.28 (m, 2H, H-3´ and H-5´); 7.38 (m, 4H, H-2, H-3, H-5 and H-6); 8.40 (s, 1H, CH=N); 8.51 (dd, *J* = 8.6, 5.6 Hz, 2H, H-2´ and H-6´) ppm.
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 21.3 (CH_3); 115.6 (d, *J* = 21.7 Hz, C-3´ and C-5´); 121.7 (C-2 and C-6); 130.2 (C-3 and C-5); 131.6 (d, *J* = 2.8 Hz, C-1´); 133.6 (d, *J* = 9.3 Hz, C-2´ and C-6´); 139.3 (C-4); (C-2); 146.3 (C-1); 156.0 (CH=N); 166.1 (d, *J* = 256.6 Hz, C-4´); 189.2 (CO) ppm.

1-Phenyl-2-(phenylimino)ethan-1-one (4q)

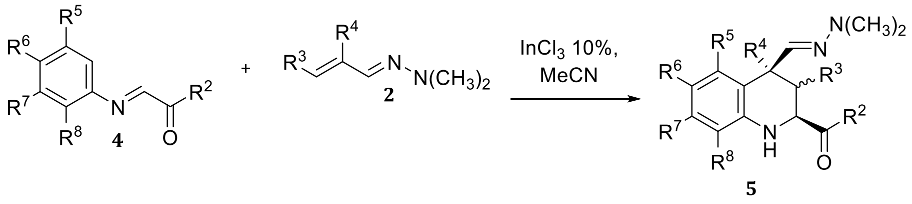


4q

Prepared from aniline (122 mg, 1.31 mmol) and phenylglyoxal hydrate (200 mg).

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 7.36-7.67 (m, 8H, H-3', H-4', H-5', H-2, H-3, H-4, H-5 and H-6); 8.34-8.38 (m, 3H, H-2', H-6' and CH=N) ppm.

10.2.2.2 - Synthesis of 2-acyl-1,2,3,4-tetrahydroquinolines 5a-u

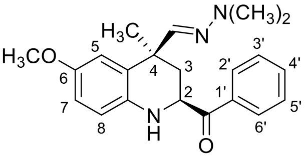


Cmpd	R²	R³	R⁴	R⁵	R⁶	R⁷	R⁸	Yield (%)	*Cis* : *Trans*
5a	C_6H_5	H	CH_3	H	OCH_3	H	H	72	82 : 18[a]
5b	4-FC_6H_4	H	CH_3	H	OCH_3	H	H	75	84 : 16[a]
5c	4-$OCH_3C_6H_4$	H	CH_3	H	OCH_3	H	H	70	83 : 17[a]
5d	C_6H_5	H	CH_2CH_3	H	OCH_3	H	H	63	91 : 09[a]
5e	C_6H_5	H	CH_3	H	CH_3	H	CH_3	95	98 : 02[a]
5f	4-FC_6H_4	H	CH_3	CH_3	H	CH_3	H	50[c]	55 : 45[a]
5g	4-FC_6H_4	H	CH_3	H	CH_3	H	CH_3	68	83 : 17
5h	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	CH_3	72	86 : 14
5i	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	H	30	88 : 22
5j	C_6H_5	H	CH_2CH_3	H	CH_3	H	CH_3	56	80 : 20
5k	4-$OCH_3C_6H_4$	H	CH_2CH_3	H	OCH_3	H	H	56	79 : 21
5l	4-FC_6H_4	H	CH_2CH_3	H	CH_3	H	CH_3	55	81 : 19
5m	OEt	H	CH_3	H	OCH_3	H	H	88	100 : 0[a]
5n	OEt	H	CH_3	H	CH_3	H	CH_3	86	84 : 16[a]
5o	OEt	H	CH_2CH_3	H	OCH_3	H	H	74	87 : 13[a]
5p	2-furyl	H	CH_3	H	OCH_3	H	H	88	100 : 0[a]
5q	2- thienyl	H	CH_3	H	OCH_3	H	H	72	90 : 10
5r	C_6H_5	H	CH_3	CH_3	H	CH_3	H	63	52 : 48
5s	C_6H_5	CH_2CH_3	H	H	OCH_3	H	H	66[c]	50 : 50[b]
5t	C_6H_5	H	H	H	OCH_3	H	H	72	100 : 0[a]
5u	C_6H_5	CH_2CH_3	CH_3	H	OCH_3	H	H	73[c]	57 : 43[b]

[a] *Cis*:*trans* diastereoselection in 2,4-disubstituted compounds determined by ^{1}H-NMR of the crude before column chromatography. [b] The C-2 and C-4 substituents are *cis*, and the group at C-3 can be *cis* or *trans* with regard to them with no selectivity. [c] Overall yields for the combination of *cis* and *trans* tetrahydroquinolines.

To a stirred solution of imine **4** (1 eq, 1.0 mmol) and $InCl_3$ (10 mol %) in acetonitrile (20 mL) was added hydrazone **2** (1.2 eq, 1.2 mmol). Stirring was continued for the time period specified in the compound data sheet and after completion of the reaction, indicated by TLC, the reaction mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (4 X 10 mL), dried and evaporated. The resulting crude was purified by silica gel column chromatography using the suitable mixture of solvents.

(±)-(2*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (5a)



5a

Prepared from imine **4a** (0.313 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (10:1, v/v).

Yield: 0.331 g (72%). Yellow solid, mp: 130-131 °C.

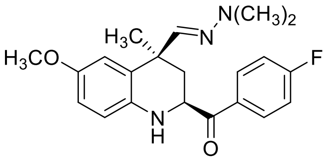
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.65 (s, 3H, CH_3); 1.73 (t, *J* = 12.6 Hz, 1H, H-3ax); 2.07 (dd, *J* = 13.0, 2.8 Hz, 1H, H-3eq); 2.72 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 4.60 (bs, 1H, NH); 5.09 (dd, *J* = 12.2, 2.7 Hz, 1H, H-2); 6.53 (s, 1H, CH=N); 6.65 (m, 1H, H-5); 6.70-6.73 (m, 2H, H-7 and H-8); 7.49 (t, *J* = 7.4 Hz, 2H, H-3´ and H-5´); 7.61 (t, *J* = 7.4 Hz, 1H, H-4´); 7.92-7.98 (m, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 26.6 (CH_3); 39.2 (C-3); 41.4 (C-4); 43.6 ($N(CH_3)_2$); 54.6 (C-2); 56.1 (OCH_3); 113.8 (C-5); 113.9 (C-7); 117.4 (C-8); 128.5 (C-4a); 128.6 (C-2´ and C-6´); 129.2 (C-3´ and C-5´); 133.9 (C-4´); 135.0 (C-1´); 136.8 (C-8a); 143.6 (CH=N); 152.5 (C-6); 199.9 (CO) ppm.

IR *ν*: 3370.9 (N-H), 2954.1 (C-H), 1685.3 (C=O), 1597.0 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{25}N_3O_2$ (M = 351.44): C, 71.77; H, 7.17; N, 11.96. Found: C, 71.48; H, 7.03; N, 11.80.

(±)-(2S*,4S*)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (5b)



5b

Prepared from imine **4b** (0.337 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.363 g (75%). Yellow solid, mp: 121-122 °C.

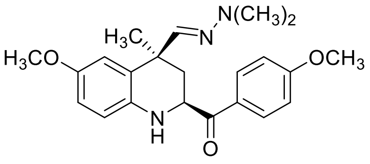
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.63 (s, 3H, CH_3); 1.74 (t, J = 12.6 Hz, 1H, H-3ax); 2.04 (dd, J = 13.0, 2.8 Hz, 1H, H-3eq); 2.72 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 5.04 (dd, J = 12.2, 2.8 Hz, 1H, H-2); 6.53 (s, 1H, CH=N); 6.64-6.66 (m, 1H, H-5); 6.70-6.72 (m, 2H, H-7 and H-8); 7.17 (t, J = 8.6 Hz, 2H, H-3´ and H-5´); 7.98 (dd, J = 8.8, 5.4 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 26.7 (CH_3); 39.3 (C-3); 41.3 (C-4); 43.6 ($N(CH_3)_2$); 54.6 (C-2); 56.1 (OCH_3); 113.9 (C-5); 114.0 (C-7); 116.4 (d, J = 24.1 Hz, C-3´ and C-5´); 117.5 (C-8); 128.6 (C-4a); 131.3 (d, J = 10.2 Hz, C-2´ and C-6´); 131.3 (d, J = 3.6 Hz, C-1´); 136.7 (C-8a); 143.1 (CH=N); 152.6 (C-6); 166.2 (d, J = 280.8 Hz, C-4´); 198.3 (CO) ppm.

IR ν: 3358.2 (N-H), 2960.2 (C-H), 1686.1 (C=O), 1597.4 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{24}FN_3O_2$ (M = 369.43): C, 68.27; H, 6.55; N, 11.37. Found: C, 68.53; H, 6.29; N, 10.98.

(±)-(2S*,4S*)-4-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-2-(4-methoxybenzoyl)-4-methyl-1,2,3,4-tetrahydroquinoline (5c)



5c

Prepared from imine **4c** (0.352 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.350 g (70%). Yellow solid, mp: 127-128 °C.

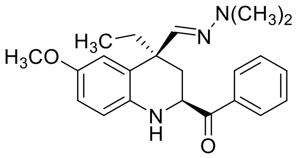
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.64 (s, 3H, CH_3); 1.72 (t, *J* = 12.7 Hz, 1H, H-3ax); 2.06 (dd, *J* = 13.0, 2.8 Hz, 1H, H-3eq); 2.73 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 4.58 (bs, 1H, NH); 5.04 (dd, *J* = 12.3, 2.7 Hz, 1H, H-2); 6.53 (s, 1H, CH=N); 6.65 (m, 1H, H-5); 6.69-6.73 (m, 2H, H-7 and H-8); 6.96 (d, *J* = 9.0 Hz, 2H, H-3´ and H-5´); 7.94 (d, *J* = 9.0 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 26.5 (CH_3); 39.5 (C-3); 41.4 (C-4); 43.6 ($N(CH_3)_2$); 54.1 (C-2); 55.9 (OCH_3); 56.1 (OCH_3); 113.9 (C-5); 113.9 (C-7); 114.4 (C-3´ and C-5´); 117.5 (C-8); 127.8 (C-1´); 128.6 (C-4a); 131.0 (C-2´ and C-6´); 137.0 (C-8a); 143.4 (CH=N); 152.5 (C-6); 164.1 (C-4´); 198.2 (CO) ppm.

IR *ν*: 3375.9 (N-H), 2960.7 (C-H), 1676.3 (C=O), 1600.5 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{27}N_3O_3$ (M = 381.47): C, 69.27; H, 7.13; N, 11.02. Found: C, 68.90; H, 6.90; N, 10.77.

(±)-(2*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-4-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline (5d)



5d

Prepared from imine **4a** (0.313 g, 1.31 mmol) and hydrazone **2b** (0.177 g, 1.4 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.302 g (63%). Orange oil.

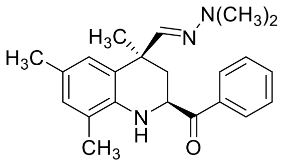
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.00 (t, *J* = 7.3 Hz, 3H, $CH_2\mathit{CH_3}$); 1.71 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.06 (q, *J* = 7.3 Hz, 2H, $\mathit{CH_2}CH_3$); 2.23 (dd, *J* = 13.3, 3.3 Hz, 1H, H-3eq); 2.69 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 5.05 (dd, *J* = 12.4, 3.3 Hz, 1H, H-2); 6.51 (s, 1H, CH=N); 6.68 (m, 3H, H-5, H-7 and H-8); 7.45-7.51 (m, 2H, H-3’ and H-5’); 7.57(m, 1H, H-4’); 7.93 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 9.3 ($CH_2\mathit{C}H_3$); 30.8 ($\mathit{C}H_2CH_3$); 35.2 (C-3); 43.3 ($N(CH_3)_2$); 43.8 (C-4); 54.1 (C-2); 56.0 (OCH_3); 113.3 (C-5); 114.5 (C-7); 116.8 (C-8); 127.4 (C-4a); 128.3 (C-2’ and C-6’); 129.0 (C-3’ and C-5’); 133.6 (C-4’); 135.2 (C-1’); 136.9 (C-8a); 141.2 (CH=N); 151.8 (C-6); 200.4 (C=O) ppm.

IR *ν*: 3375 (N-H), 2925 (C-H), 1620 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{27}N_3O_2$ (M= 365.47): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.01; H, 7.23; N, 11.25.

(±)-(2*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline (5e)



5e

Prepared from imine **4d** (0.427 g, 1.8 mmol) and hydrazone **2a** (0.222 g, 1.9 mmol).

Reaction time: 4 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.598 g (95%). White solid, mp: 136-138 °C.

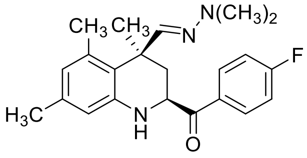
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.64-1.74 (m, 4H, CH_3 and H-3ax); 2.06 (dd, *J* = 12.9, 2.9 Hz, 1H, H-3eq); 2.21 (s, 3H, CH_3); 2,22 (s, 3H, CH_3); 2.73 (s, 6H, $N(CH_3)_2$); 4.57 (s, 1H, NH); 5.13 (d, *J* = 12.4 Hz, 1H, H-2); 6.55 (s, 1H, CH=N); 6.75 (s, 1H, H-7); 6.82 (s, 1H, H-5); 7.47-7.51 (m, 2H, H-3' and H-5'); 7.57 (m, 1H, H-4'); 7.94-7.97 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 17.7 (CH_3); 20.6 (CH_3); 26.3 (CH_3); 39.0 (C-3); 41.1 (C-4); 43.5 ($N(CH_3)_2$); 54.4 (C-2); 123.4 (C-4a); 126.2 (C-5); 126.4 (C-8); 126.4 (C-6); 128.5 (C-3' and C-5'); 129.0 (C-2' and C-6'); 129.7 (C-7); 133.7 (C-4'); 134.8 (C-1'); 138.2 (C-8a); 143.9 (CH=N); 199.7 (C=O) ppm.

IR *ν*: 3346.8 (N-H), 2918.2 (C-H), 1627.5 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{27}N_3O$ (M= 349.47): C, 75.61; H, 7.79; N, 12.02. Found: C, 75.31; H, 7.79; N, 11.90.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-4,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (5f)



5f

Prepared from imine **4e** (0.459 g, 1.8 mmol) and hydrazone **2a** (0.222 g, 1.9 mmol).

Reaction time: 5 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.150 g (25%). Yellow solid, mp: 145-147 °C.

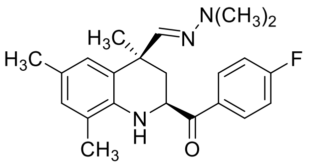
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.66 (t, J = 12.6 Hz, 1H, H-3ax); 1.72 (s, 3H, CH_3); 1.91 (dd, J = 12.8, 2.5 Hz, 1H, H-3eq); 2.21 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 2.71 (s, 6H, $N(CH_3)_2$); 4.99 (dd, J = 12.2, 2.6 Hz, 1H, H-2); 6.37 (s, 1H, H-8); 6.47 (s, 1H, H-6); 6.62 (s, 1H, CH=N); 7.18 (t, J = 8.6 Hz, 2H, H-3′ and H-5′); 7.99 (dd, J = 8.8, 5.4 Hz, 2H, H-2′ and H-6′) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 21.1 (CH_3); 22.2 (CH_3); 23.4 (CH_3); 41.3 (C-4); 42.2 (C-3); 43.5 ($N(CH_3)_2$); 53.9 (C-2); 114.8 (C-8); 116.4 (d, J = 24.0 Hz, C-3′ and C-5′); 121.5 (C-4a); 122.9 (C-6); 131.2 (d, J = 2.8 Hz, C-1′); 131.3 (d, J = 10.1 Hz, C-2′ and C-6′); 137.6 (C-7); 137.7 (C-5); 143.5 (C-8a); 145.3 (CH=N); 166.2 (d, J = 280.6 Hz, C-4′); 197.9 (CO) ppm.

IR ν: 3332.4 (N-H), 2961.6 (C-H), 1686.9 (C=O), 1596.8 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{26}FN_3O$ (M = 367.46): C, 71.91; H, 7.13; N, 11.44. Found: C, 71.79; H, 6.88; N, 11.05.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline (5g)



5g

Prepared from imine **4f** (0.261 g, 1.02 mmol) and hydrazone **2a** (0.126 g, 1.12 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (10:1, v/v).

Yield: 0.255 g (68%). Yellow viscous liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.64 (s, 3H, CH_3); 1.71 (t, J = 12.6 Hz, 1H, H-3ax); 2.04 (dd, J = 12.8, 2.9 Hz, 1H, H-3eq); 2.22 (s, 6H, 2 x CH_3); 2.74 (s, 6H, $N(CH_3)_2$); 4.52 (bs, 1H, NH); 5.10 (dd, J = 12.4, 2.8 Hz, 1H, H-2); 6.57 (s, 1H, CH=N); 6.75 (s, 1H, H-7); 6.83 (s, 1H, H-5); 7.18 (t, J = 8.6 Hz, 2H, H-3′ and H-5′); 8.00 (dd, J = 8.9, 5.3 Hz, 2H, H-2′ and H-6′) ppm.

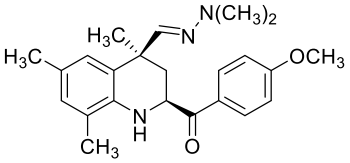
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 17.8 (CH_3); 20.8 (CH_3); 26.5 (CH_3); 39.2 (C-3); 41.2 (C-4); 43.7 ($N(CH_3)_2$); 54.5 (C-2); 116.4 (d, J = 24.0 Hz, C-3′ and C-5′); 123.6 (C-4a); 126.4 (C-5); 126.5

(C-8); 126.7 (C-6); 130.0 (C-7); 131.3 (d, *J* = 10.3 Hz, C-2´ and C-6´); 131.3 (d, *J* = 3.5 Hz, C-1´); 138.3 (C-8a); 144.1 (CH=N); 166.2 (d, *J* = 280.7 Hz, C-4´); 198.3 (CO) ppm.

IR (NaCl) *ν*: 3381.8 (N-H), 2923.3 (C-H), 1685.7 (C=O), 1597.6 (C=N) cm^{-1}.

Elemental analysis: Calc. for $C_{22}H_{26}FN_3O$ (M = 367.46): C, 71.91; H, 7.13; N, 11.44. Found: C, 71.67; H, 6.88; N, 11.19.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-methoxybenzoyl)-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline (5h)



5h

Prepared from imine **4g** (0.350 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.264 g (72%). Yellow solid, mp: 137-140 °C.

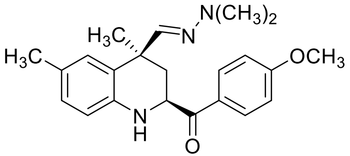
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.66 (s, 3H, CH_3); 1.70 (t, *J* = 12.7 Hz, 1H, H-3ax); 2.07 (dd, *J* = 13.0, 2.8 Hz, 1H, H-3eq); 2.21 (s, 6H, 2 x CH_3); 2.74 (s, 6H, $N(CH_3)_2$); 3.90 (s, 3H, OCH_3); 4.55 (bs, 1H, NH); 5.10 (dd, *J* = 12.5, 2.8 Hz, 1H, H-2); 6.57 (s, 1H, CH=N); 6.76 (s, 1H, H-7); 6.83 (s, 1H, H-5); 6.95-7.01 (m, 2H, H-3´ and H-5´); 7.91-8.05 (m, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 17.6 (CH_3); 20.6 (CH_3); 26.2 (CH_3); 39.3 (C-3); 41.0 (C-4); 43.5 ($N(CH_3)_2$); 53.9 (C-2); 55.7 (OCH_3); 114.2 (C-3´ and C-5´) 123.5 (C-4a); 126.2 (C-5); 126.3 (C-8*); 126.4 (C-6*); 127.6 (C-1’); 129.7 (C-7); 130.8 (C-2´ and C-6´); 138.4 (C-8a); 144.2 (CH=N); 163.9 (C-4´); 198.0 (CO) ppm.

IR *ν*: 3365.9 (N-H), 2954.7 (C-H), 1669.2 (C=O), 1611.2 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{23}H_{29}N_3O_2$ (M = 379.50): C, 72.79; H, 7.70; N, 11.07. Found: C, 72.51; H, 7.34; N, 11.36.

(±)-(2*S**,4*S**)-4,6-Dimethyl-4-[(2,2-dimethylhydrazono)methyl]-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroquinoline (5i)



5i

Prepared from imine **4h** (0.332 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.185 g (30%). Yellow solid, mp: 118-121 °C.

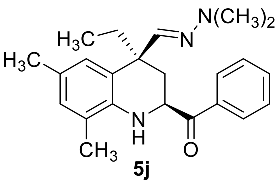
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.64 (s, 3H, CH$_3$); 1.74 (t, *J* = 12.8 Hz, 1H, H-3ax); 2.07 (dd, *J* = 13.0, 2.8 Hz, 1H, H-3eq); 2.23 (s, 3H, ArCH$_3$); 2.75 (s, 6H, N(CH$_3$)$_2$); 3.89 (s, 3H, OCH$_3$); 4.71 (bs, 1H, NH); 5.06 (d, *J* = 11.7 Hz, 1H, H-2); 6.56 (s, 1H, CH=N); 6.68 (d, *J* = 8.0 Hz, 1H, H-8); 6.78-7.15 (m, 4H, H-5, H-7, H-3’ and H-5’); 7.96 (d, *J* = 8.7 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 20.6 (ArCH$_3$); 26.3 (CH$_3$); 39.3 (C-3); 40.9 (C-4); 43.4 (N(CH$_3$)$_2$); 53.8 (C-2); 55.6 (OCH$_3$); 114.1 (C-3´ and C-5´) 116.0 (C-8); 126.8 (C-4a); 126.9 (C-6); 127.6 (C-1’); 128.4 (C-5 and C-7); 130.7 (C-2´ and C-6´); 140.4 (C-8a); 143.6 (CH=N); 163.9 (C-4´); 197.9 (CO).

IR *ν*: 3356.2 (N-H), 2961.2 (C-H), 1668.2 (C=O), 1601.3 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{27}N_3O_2$ (M = 365.48): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.17; H, 7.31; N, 11.27.

(±)-(2*S**,4*S**)-2-Benzoyl-6,8-dimethyl-4-[(2,2-dimethylhydrazono)methyl]-4-ethyl-1,2,3,4-tetrahydroquinoline (5j)



5j

Prepared from imine **4d** (0.427 g, 1.8 mmol) and hydrazone **2b** (0.240 g, 1.9 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (40:1, v/v).

Yield: 0.366 g (56%). Yellow oil.

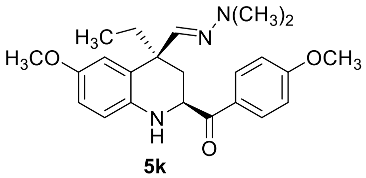
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.16 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$); 1.79 (t, *J* = 12.9 Hz, 1H, H-3ax); 2.20 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$); 2.36 (s, 7H, 2 x CH$_3$ and H-3eq); 2.83 (s, 6H, N(CH$_3$)$_2$); 4.74 (bs, 1H, NH); 5.24 (d, *J* = 12.4 Hz, 1H, H-2); 6.67 (s, 1H, CH=N); 6.88 (s, 1H, H-7); 6.95 (s, 1H, H-5); 7.60 (t, *J* = 7.3 Hz, 2H, H-3´ and H-5´); 7.70 (m, 1H, H-4’); 8.08 (d, *J* = 7.4 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 9.1 (CH$_2$CH$_3$); 17.6 (ArCH$_3$); 20.6 (ArCH$_3$); 30.5 (CH$_2$*C*H$_3$); 35. 0 (C-3); 43.2 (C-4); 43.6 (N(CH$_3$)$_2$); 54.0 (C-2); 122.9 (C-4a) 125.4 (C-8*); 125.5 (C-6*); 126.4 (C-5); 128.2 (C-3’ and C-5’); 128.8 (C-2’ and C-6’); 129.5 (C-7); 133.4 (C-4’); 135.0 (C-1’); 138.2 (C-8a); 141.9 (CH=N); 200.1 (CO) ppm.

IR *ν*: 3363.7 (N-H), 2952.5 (C-H), 1670.2 (C=O), 1612.3 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{23}H_{29}N_3O$ (M = 363.51): C, 76.00; H, 8.04; N, 11.56. Found: C, 75.81; H, 7.84; N, 11.36.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-4-ethyl-6-methoxy-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroquinoline (5k)



5k

Prepared from imine **4c** (0.352 g, 1.31 mmol) and hydrazone **2b** (0.177 g, 1.4 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (30:1, v/v).

Yield: 0.290 g (56%). Yellow solid, mp: 139-141 °C.

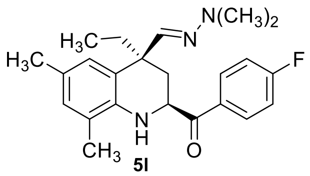
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.01 (t, *J* = 7.3 Hz, 3H, CH$_2$C*H*$_3$); 1.69 (t, *J* = 12.9 Hz, 1H, H-3ax); 2.07 (q, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$); 2.22 (dd, *J* = 13.3, 3.2 Hz, 1H, H-3eq); 2.71 (s, 6H, N(CH$_3$)$_2$); 3.73 (s, 3H, OCH$_3$); 3.89 (s, 3H, OCH$_3$); 4.60 (bs, 1H, NH); 5.01 (dd, *J* = 12.5, 3.0 Hz, 1H, H-2); 6.51 (s, 1H, CH=N); 6.66 (m, 1H, H-5); 6.70-6.71 (m, 2H, H-7 and H-8); 6.97 (d, *J* = 8.9 Hz, 2H, H-3´ and H-5´); 7.95 (d, *J* = 8.9 Hz, 2H, H-2´ and H-6´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 9.3 (CH$_2$*C*H$_3$); 30.8 (*C*H$_2$CH$_3$); 35.6 (C-3); 43.3 (N(CH$_3$)$_2$); 43.8 (C-4); 53.7 (C-2); 55.6 (OCH$_3$); 55.9 (OCH$_3$); 113.3 (C-5); 114.1 (C-3´ and C-5´); 114.4 (C-7); 116.9 (C-8); 127.4 (C-4a); 127.9 (C-1’); 130.7 (C-2´ and C-6´); 137.0 (C-8a); 141.3 (CH=N); 151.8 (C-6); 163.9 (C-4´); 198.6 (CO) ppm.

IR *ν*: 3375.9 (N-H), 2960.7 (C-H), 1676.3 (C=O), 1600.5 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{23}H_{29}N_3O_3$ (M = 395.50): C, 69.85; H, 7.39; N, 10.62. Found: C, 69.70; H, 7.10; N, 10.47.

(±)-(2*S**,4*S**)-6,8-Dimethyl-4-[(2,2-dimethylhydrazono)methyl]-4-ethyl-2-(4-fluorobenzoyl)-1,2,3,4-tetrahydroquinoline (5l)



5l

Prepared from imine **4f** (0. g, 1.31 mmol) and hydrazone **2b** (0.177 g, 1.4 mmol).

Reaction time: 3h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (30:1, v/v).

Yield: 0.274 g (55%). Yellow oil.

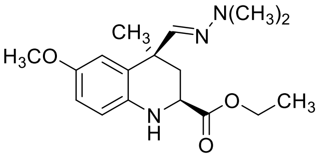
^{1}**H-NMR** ($CDCl_3$, 250 MHz) *δ*: 1.01 (t, *J* = 7.3 Hz, 3H, $\mathrm{CH_2C}\mathit{H}_3$); 1.68 (t, *J* = 12.9 Hz, 1H, H-3ax); 2.05 (q, *J* = 7.3 Hz, 2H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); 2.17-2.22 (m, 7H, 2 x Ar-CH_3 and H-3eq); 2.71 (s, 6H, $N(CH_3)_2$); 4.53 (bs, 1H, NH); 5.07 (d, *J* = 11.4 Hz, 1H, H-2); 6.55 (s, 1H, CH=N); 6.74 (s, 1H, H-7); 6.83 (s, 1H, H-5); 7.10-7.24 (m, 2H, H-3´ and H-5´); 7.85-8.12 (m, 2H, H-2´ and H-6´) ppm.

^{13}**C-NMR** ($CDCl_3$, 63 MHz) *δ*: 9.3 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$); 17.8 ($CH_3$); 20.7 ($CH_3$); 30.7 ($\mathit{C}\mathrm{H_2CH_3}$); 35.2 (C-3); 43.4 ($N(CH_3)_2$); 43.7 (C-4); 54.1 (C-2); 116.2 (d, *J* = 126 Hz, C-3’ and C-5’); 123.1 (C-4a); 125.5 (C-8); 125.9 (C-6); 126.6 (C-5); 129.7 (C-7); 131.0 (d, *J* = 9 Hz, C-2’ and C-6’); 131.4 (d, *J* = 2.9 Hz, C-1’); 138.2 (C-8a); 142.0 (CH=N); 166.0 (d, *J* = 252 Hz, C-4’); 198.8 (CO) ppm.

IR *ν*: 3370.9 (N-H), 2964.5 (C-H), 1673.1 (C=O), 1603.3 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{23}H_{28}FN_3O$ (M = 381.50): C, 72.41; H, 7.40; N, 11.01. Found: C, 72.10; H, 7.10; N, 10.57.

(±)-(2*S**,4*S**)-Ethyl 4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (5m)[218]



5m

Prepared from imine **4i** (0.271 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 2 h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield: 0.368 g (88%). Pale yellow viscous liquid.

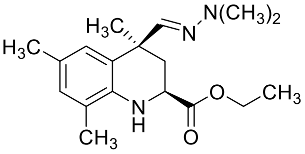
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.34 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); 1.52 (s, 3H, CH_3); 1.98 (t, *J* = 12.0 Hz, 1H, H-3ax); 2.12 (dd, *J* = 12.9, 3.3 Hz, 1H, H-3eq); 2.80 (s, 6H, $N(CH_3)_2$); 3.74 (s, 3H, OCH_3); 4.14 (dd, *J* = 11.6, 3.2 Hz, 1H, H-2); 4.28 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3); 4.29 (bs, 1H, NH); 6.60-6.73 (m, 4H, H-5, H-7, H-8 and CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.1 (OCH_2CH_3); 26.9 (CH_3); 37.3 (C-3); 40.3 (C-4); 43.3 ($N(CH_3)_2$); 51.1 (C-2); 55.7 (OCH_3); 61.3 (OCH_2CH_3); 113.4 (C-7)*; 113.7 (C-8)*; 116.0 (C-5); 127.9 (C-4a); 136.4 (C-8a); 143.5 (CH=N); 152.1 (C-6); 173.2 (CO_2Et) ppm.

IR *ν*: 3388.0 (N-H), 2977.8 (C-H), 2828.9 (C-H), 1737.3 (C=O); 1603.1 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{17}H_{25}N_3O_3$ (M = 319.40): C, 63.93; H, 7.89; N, 13.16. Found: C, 63.94; H, 7.63; N, 13.03.

(±)-(2*S**,4*S**)-Ethyl 4-[(2,2-dimethylhydrazono)methyl]-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (5n)



5n

Prepared from imine **4j** (0.269 g, 1.31 mmol) and hydrazone **2a** (0.161 g, 1.4 mmol).

Reaction time: 2 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (10:1, v/v).

Yield: 0.357 g (86%). Yellow oil.

---

[218] Sridharan V., Ribelles P., Estévez V., Villacampa M., Ramos M.T., Perumal P.T., Menéndez J.C.. *Chem. Eur. J.*, **2012**, *18*, 5056.

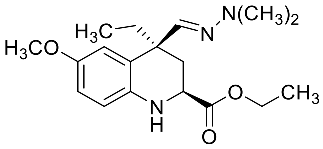
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.34 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); 1.51 (s, 3H, CH_3); 1.93 (t, *J* = 12.4 Hz, 1H, H-3ax); 2.10 (dd, *J* = 13.2, 4.0 Hz, 1H, H-3eq); 2.18 (s, 3H, CH_3); 2.21 (s, 3H, CH_3); 2.79 (s, 6H, $N(CH_3)_2$); 4.19 (m, 1H, H-2); 4.24-4.32 (m, 3H, OCH_2CH_3 and NH); 6.64 (s, 1H, CH=N); 6.75 (s, 1H, H-7); 6.79 (s, 1H, H-5) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.3 (OCH_2CH_3); 17.4 (CH_3); 20.5 (CH_3); 26.8 (CH_3); 37.3 (C-3); 40.2 (C-4); 43.5 ($N(CH_3)_2$); 51.1 (C-2); 61.5 (OCH_2CH_3); 122.2 (C-4a); 126.1 (C-8); 126.3 (C-6); 126.4 (C-5); 129.6 (C-7); 138.1 (C-8a); 144.3 (CH=N); 173.6 (C=O) ppm.

IR *ν*: 3405 (N-H), 2930 (C-H), 1730 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{27}N_3O_2$ (M= 317.43): C, 68.11; H, 8.57; N, 13.24. Found: C, 67.98; H, 8.32; N, 12.99.

(±)-(2*S**,4*S**)-Ethyl 4-[(2,2-dimethylhydrazono)methyl]-4-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate (5o)



5o

Prepared from imine **4i** (0.271 g, 1.31 mmol) and hydrazone **2b** (0.177 g, 1.4 mmol).

Reaction time: 2 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (10:1, v/v).

Yield: 0.323 g (74%). Orange oil.

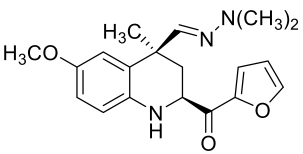
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.30 (t, *J* = 7.1 Hz, 6H, 2 x CH_3); 1.81-2.0 (m, 3H, CH_2CH_3 and H-3ax); 2.29 (dd, *J* = 13.3, 3.6 Hz, 1H, H-3eq); 2.75 (s, 6H, $N(CH_3)_2$); 3.71 (s, 3H, OCH_3); 4.08 (dd, *J* = 11.9, 3.6 Hz, 1H, H-2); 4.23 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3); 6.55-6.68 (m, 4H, H-5, H-7, H-8 and CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 8.8 (CH_2CH_3); 14.3 (OCH_2CH_3); 33.4 (C-3 and CH_2CH_3); 43.1 (C-4); 43.4 ($N(CH_3)_2$); 51.0 (OCH_3); 55.9 (C-2); 61.5 (OCH_2CH_3); 113.2 (C-5*); 114.3 (C-7*); 115.9 (C-8*); 127.3 (C-4a); 136.6 (C-8a); 141.8 (CH=N); 151.8 (C-6); 173.8 (C=O) ppm.

IR *ν*: 3395.4 (N-H), 2927.3 (C-H), 1743.8 (C=O), 1117.3 (C-O) cm^{-1}.

This compound was contaminated with *ca.* 13% of the corresponding quinoline **8i** and could not be purified further.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-2-(2-furylcarbonyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (5p)[218]



5p

Prepared from imine **4k** (0.343 g, 1.5 mmol) and hydrazone **2a** (0.185 g, 1.65 mmol).

Reaction time: 3 h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield: 0.450 g (88%). Yellow solid, mp: 113-114 °C.

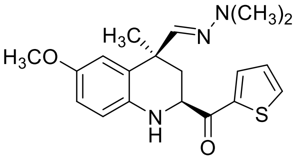
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.64 (s, 3H, CH$_3$); 1.86 (t, *J* = 12.3, 1H, H-3ax); 2.22 (dd, *J* = 12.7, 3.0 Hz, 1H, H-3eq); 2.77 (s, 6H, N(CH$_3$)$_2$); 3.75 (s, 3H, OCH$_3$); 4.87 (dd, *J* = 11.9, 2.9 Hz, 1H, H-2); 6.58-6.62 (m, 2H, H-4′ and CH=N); 6.66-6.73 (m, 3H, H-5, H-7 and H-8); 7.34 (dd, *J* = 3.6, 0.5 Hz, 1H, H-3′); 7.65 (dd, *J* = 1.6, 0.7 Hz, 1H, H-5′) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 26.2 (CH$_3$); 38.3 (C-3); 40.6 (C-4); 43.2 (N(CH$_3$)$_2$); 54.7 (C-2); 55.7 (OCH$_3$); 112.3 (C-4′); 113.4 (C-7)*; 113.5 (C-8)*; 116.8 (C-5); 118.2 (C-3′); 128.1 (C-4a); 136.3 (C-8a); 143.0 (CH=N); 146.5 (C-5′); 150.9 (C-2′); 152.1 (C-6); 188.5 (CO) ppm.

IR *ν*: 3378.0 (N-H), 2956.3 (C-H), 1675.8 (C=O), 1568.2 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for C$_{19}$H$_{23}$N$_3$O$_3$ (M = 341.40): C, 66.84; H, 6.79; N, 12.31. Found: C, 66.59; H, 6.56; N, 12.63.

(±)-(2*S**,4*S**)-4-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-4-methyl-2-(2-thienylcarbonyl)-1,2,3,4-tetrahydroquinoline (5q)



5q

Prepared from **4l** (175.1 mg, 0.71 mmol) and hydrazone **2a** (93.0 mg, 0.83 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: dichloromethane.

Yield: 183.8 mg (72%). Brown solid, mp: 107-108 °C.

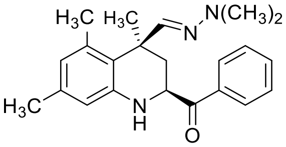
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.62 (s, 3H, CH_3); 1.92 (t, *J* = 12.4 Hz, 1H, H-3ax); 2.14 (dd, *J* = 13.0, 3.1 Hz, 1H, H-3eq); 2.73 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 4.90 (dd, *J* = 12.1, 3.0 Hz, 1H, H-2); 6.56 (s, 1H, CH=N); 6.65 (m, 1H, H-5); 6.68-6.71 (m, 2H, H-7 and H-8); 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H, H-4´); 7.68 (dd, *J* = 5.0, 1.1 Hz, 1H, H-3´); 7.82 (dd, *J* = 3.8, 1.1 Hz, 1H, H-5´) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 26.8 (CH_3); 40.2 (C-3); 41.2 (C-4); 43.6 ($N(CH_3)_2$); 56.0 (C-2); 56.1 (OCH_3); 113.9 (C-5 and C-7); 117.3 (C-8); 128.6 (C-4a and C-4´); 132.7 (C-3´); 134.4 (C-5´); 136.6 (C-8a); 141.1 (C-2´); 143.2 (CH=N); 152.6 (C-6); 192.9 (CO) ppm.

IR (NaCl) *ν*: 3367.8 (N-H), 2957.3 (C-H), 1661.8 (C=O), 1597.0 (C=N) cm^{-1}.

Elemental analysis: Calc. for $C_{19}H_{23}N_3O_2S$ (M = 357.47): C, 63.84; H, 6.49; N, 11.75; S, 8.97. Found: C, 63.65; H, 6.22; N, 11.59; S, 8.92.

(±)-(2*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-4,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (5r)



5r

Prepared from imine **4o** (0.310 g, 1.31 mmol) and hydrazone **2a** (0.160 g, 1.4 mmol).

Reaction time: 3 h.

Purification of *cis* isomer: petroleum ether:ethyl acetate (40:1, v/v).

Yield: 288.4 mg (63%). White solid, mp: 153-154 °C.

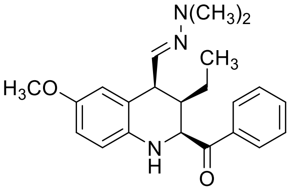
^{1}H-NMR (250 MHz) δ: 1.65 (t, *J* = 12.5 Hz, 1H, H-3ax); 1.73 (s, 3H, CH_3); 1.94 (dd, *J* = 12.8, 2.5 Hz, 1H, H-3eq); 2.21 (s, 3H, $ArCH_3$); 2.22 (s, 3H, $ArCH_3$); 2.70 (s, 6H, $N(CH_3)_2$); 4.86 (bs, 1H, NH); 5.03 (dd, *J* = 12.3, 2.5 Hz, 1H, H-2); 6.36 (s, 1H, H-6); 6.47 (s, 1H, H-8); 6.60 (s, 1H, CH=N); 7.50 (t, *J* = 7.4 Hz, 2H, H-3’ and H-5’); 7.61 (t, *J* = 7.3 Hz, 1H, H-4’); 7.95 (d, *J* = 7.1 Hz, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR (63 MHz) δ: 21.0 (CH_3); 22.1 ($ArCH_3$); 23.1 ($ArCH_3$); 41.2 (C-4); 41.9 (C-3); 43.3 ($N(CH_3)_2$); 53.8 (C-2); 114.6 (C-8); 121.4 (C-4a); 122.7 (C-6); 128.5 (C-3’ and C-5’); 129.0 (C-2’ and C-6’); 133.7 (C-4’); 134.7 (C-7*); 137.4 (C-5*); 137.6 (C-1’*); 143.5 (C-8a); 145.2 (CH=N); 199.3 (CO) ppm.

IR *ν*: 3333.7 (NH), 2918.9 (C-H), 1682.9 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $C_{22}H_{27}N_3O$ (M = 349,48): C, 75.61; H, 7.79; N, 12.02. Found: C, 75.58; H, 8.01; N, 12.21.

(±)-(2*S**,3*R**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-3-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline (5s')



5s'

Prepared from imine **4a** (0.313 g, 1.31 mmol) and hydrazone **2d** (0.177 g, 1.4 mmol).

Reaction time: 1.5 h.

Purification of the all-*cis* isomer: flash chromatography with petroleum ether:ethyl acetate (97:3, v/v).

Yield: 0.163 g (34%). Yellow solid, mp: 79-81 °C.

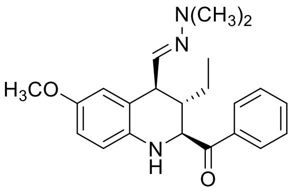
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 0.67 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); 0.97-1.05 (m, 2H, CH_2CH_3); 2.80-2.87 (m, 7H, $N(CH_3)_2$ and H-3); 3.61 (bs, 1H, H-4); 3.77 (s, 3H, OCH_3); 4.69 (bs, 1H, NH); 5.17 (d, *J* = 2.7 Hz, 1H, H-2); 6.72-6.73 (m, 3H, H-7, H-8 and H-5); 6.85 (d, *J* = 3.5 Hz, 1H, CH=N); 7.49 (t, *J* = 7.4 Hz, 2H, H-3' and H-5'); 7.58-7.61 (m, 1H, H-4'); 8.20 (d, *J* = 7.2 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 11.9 (CH_3); 19.9 (CH_2); 37.8 (C-3); 43.4 ($N(CH_3)_2$); 44.2 (C-4); 55.9 (OCH_3); 57.6 (C-2); 114.1 (C-5*); 115.5 (C-7*); 116.6 (C-8*); 121.0 (C-4a); 128.7 (C-3' and C-5'); 128.8 (C-2' and C-6'); 133.5 (C-4'); 135.0 (C-1'); 136.9 (C-8a); 140.3 (CH=N); 152.1 (C-6); 200.1 (C=O) ppm.

IR ν: 3375.5 (N-H), 2914.7 (C-H), 1677.2 (C=O), 1502.2 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{27}N_3O_2$ (M = 365.47): C, 72.30; H, 7.45; N, 11.50. Found: C, 72.42; H, 7.29; N, 11.29.

(±)-(2*S**,3*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-3-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline (5s'')



5s''

In the above reaction, additional fractions could be isolated in the column chromatography corresponding to isomer **5s''**.

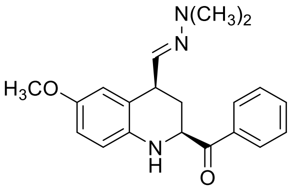
Yield: 0.153 g (32%). Yellow solid. $C_{22}H_{27}N_3O_2$ (M = 365.47).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.09 (t, *J* = 7.4 Hz, 3H, $CH_2C\mathit{H}_3$); 1.62 (m, 2H, $C\mathit{H}_2CH_3$); 2.49 (s, 6H, $N(CH_3)_2$); 2.59 (m, 1H, H-3); 3.43 (dd, *J* = 6.1, 3.8 Hz, 1H, H-4); 3.72 (s, 3H, OCH_3); 4.74 (d, *J* = 3.7 Hz, 1H, H-2); 6.26 (d, *J* = 6.3 Hz, 1H, H-8); 6.59 (d, *J* = 2.6 Hz, 1H, H-5); 6.68-6.70 (m, 2H, H-7 and CH=N); 7.45-7.46 (m, 2H, H-3' and H-5'); 7.53 (m, 1H, H-4'); 7.90-7.94 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 12.2 (CH_3); 26.9 (CH_2); 42.1 (C-3); 43.2 ($N(CH_3)_2$); 45.3 (C-4); 56.1 (OCH_3); 59.1 (C-2); 114.3 (C-5*); 115.3 (C-7*); 116.2 (C-8*); 121.4 (C-4a); 128.6 (C-3' and C-5'); 128.9 (C-2' and C-6'); 133.4 (C-4'); 135.6 (C-1'); 137.1 (C-8a); 140.2 (CH=N); 152.4 (C-6); 202.0 (C=O) ppm.

IR *ν*: 3375.2 (N-H), 2929.1 (C-H), 1682.8 (C=O), 1501.4 (C=N) cm^{-1}.

(±)-(2*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-1,2,3,4-tetrahydroquinoline (5t)



5t

Prepared from imine **4a** (0.313 g, 1.31 mmol) and hydrazone **2c** (0.137 g, 1.4 mmol).

Reaction time: 1 h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield: 0.318 g (72%). Red solid, mp: 95-97 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.64 (q, *J* = 12.5 Hz, 1H, H-3ax); 2.39 (ddd, *J* = 2.7, 5.5, 12.7 Hz, 1H, H-3eq); 2.77 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 3.96 (m, 1H, H-4); 4.61 (bs, 1H, NH); 5.0

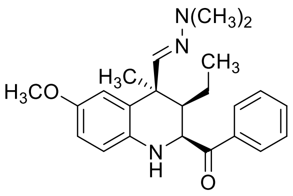
(dd, *J* = 12.0, 2.7 Hz, 1H, H-2); 6.42 (d, *J* = 7.3 Hz, 1H, H-8); 6.66 (m, 1H, H-5); 6.72-6.73 (m, 2H, H-7 and CH=N); 7.43-7.55 (m, 2H; H-3' and H-5'); 7.61 (m, 1H, H-4'); 7.93-7.96 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 33.0 (C-3); 41.9 (C-4); 43.3 ($N(CH_3)_2$); 56.0 (OCH_3); 57.0 (C-2); 114.0 (C-5*); 114.1 (C-7*); 117.1 (C-8*); 123.1 (C-4a); 128.5 (C-3' and C-5'); 129.0 (C-2' and C-6'); 133.7 (C-4'); 134.7 (C-1'); 137.4 (C-8a*); 139.1 (CH=N); 152.3 (C-6); 199.3 (C=O) ppm.

IR *ν*: 3300.5 (N-H), 2949.1 (C-H), 1683.1 (C=O), 1503.0 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{23}N_3O_2$ (M = 337.42): C, 71.19; H, 6.87; N, 12.45. Found: C, 70.86; H, 6.57; N, 12.25.

(±)-(2*S**,3*R**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-3-ethyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (5u')



5u'

Prepared from imine **4a** (0.313 g, 1.31 mmol) and hydrazone **2e** (0.196 g, 1.4 mmol).

Reaction time: 1.30 h.

Purification: petroleum ether:ethyl acetate (20:1, v/v).

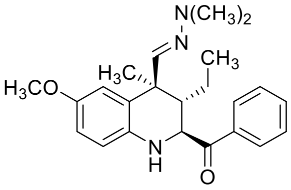
Yield: 0.198 g (41%). Orange oil.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 0.47 (t, *J* = 7.6 Hz, 3H, CH_2CH_3); 1.09 (m, 2H, CH_2CH_3); 1.68 (s, 3H, CH_3); 1.98 (m, 1H, H-3); 2.80 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 5.23 (d, *J* = 2.6 Hz, 1H, H-2); 6.62 (m, 1H, H-8); 6.71-6.72 (m, 2H, H-7 and H-5); 6.83 (s, 1H, CH=N); 7.46-7.52 (m, 2H, H-3' and H-5'); 7.60 (m, 1H, H-4'); 7.93 (d, *J* = 7.0 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 14.8 (CH_2CH_3); 18.8 (CH_2CH_3); 28.8 (CH_3); 43.4 ($N(CH_3)_2$); 44.7 (C-3); 47.6 (C-4); 55.9 (OCH_3); 58.7 (C-2); 113.2 (C-5*); 114.3 (C-7*); 116.1 (C-8*); 128.2 (C-3' and C-5'); 129.0 (C-2' and C-6'); 131.2 (C-4'); 133.5 (C-4a); 135.5 (C-8a); 136.6 (CH=N); 152.0 (C-6), 200.2 (C=O) ppm.

IR *ν*: 3383.9 (N-H), 2925.7 (C-H), 1679.0 (C=O), 1501.5 (C=N) cm^{-1}.

(±)-(2*S**,3*S**,4*S**)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-3-ethyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (5u'')



5u''

In the above reaction, additional fractions could be isolated in the column chromatography corresponding to isomer **5u''**.

Purification: petroleum ether:ethyl acetate (20:1, v/v).

Yield: 0.149 g (32%). Orange oil.

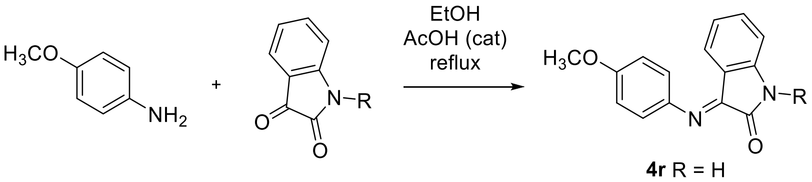
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 0.73 (t, *J* = 7.5 Hz, 3H, $CH_2\mathit{CH_3}$); 0.86 (m, 2H, $\mathit{CH_2}CH_3$); 1.41 (s, 3H, CH_3); 2.21 (m, 1H, H-3); 2.67 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 4.77 (d, *J* = 8.6 Hz, 1H, H-2); 6.47 (s, 1H, CH=N); 6.58 (dd, *J* = 7.9, 1.1 Hz, 1H, H-7); 6.66-6.70 (m, 2H, H-5 and H-8); 7.45-7.51 (m, 2H, H3' and H-5'); 7.57-7.63 (m, 1H, H-4'); 8.07 (d, *J* = 7.0 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.5 ($CH_2\mathit{CH_3}$); 21.3 ($\mathit{C}H_2CH_3$); 22.1 (CH_3); 43.6 ($N(CH_3)_2$); 44.8 (C-4); 46.1 (C-3); 56.2 (OCH_3); 59.3 (C-2); 113.4 (C-5*); 113.9 (C-7*); 116.5 (C-8*); 128.8 (C-3' and C-5'); 129.1 (C-2' and C-6'); 129.6 (C-4a); 133.6 (C-4'); 136.3 (C-1'); 136.5 (C-8a); 143.7 (CH=N); 152.6 (C-6); 201. 3 (C=O) ppm.

IR *ν*: 3358.6 (N-H), 2928.2 (C-H), 1671.6 (C=O), 1503.0 (C=N) cm^{-1}.

10.2.3 - Synthesis of spiro[indolin-3,2'-quinoline]compounds

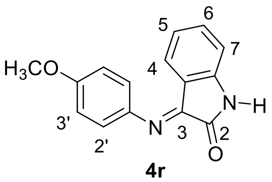
10.2.3.1 - Synthesis of α-ketoimines 4r-s



4r R = H
4s R = Bn

A solution of *p*-anisidine (1 eq) and the corresponding isatin derivative (1 eq) in EtOH and acetic acid (0.2 mL) was refluxed until the starting materials disappeared. The reaction mixture was kept at room temperature overnight. The resulting solid was filtrated and washed with cold ethanol affording imines **4r** and **4s**.

3-(4-Methoxyphenylimino)indolin-2-one (4r)[219]



4r

Prepared from *p*-anisidine (110 mg, 0.9 mmol) and isatin (132 mg, 0.9 mmol) in 2 mL of ethanol and acetic acid (1 drop).

Reaction time: 3 h.

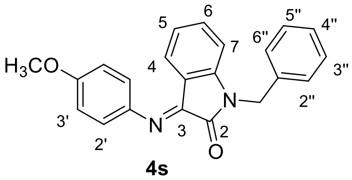
Yield: 95%

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 3.90 (s, 3H, OCH_3); 6.82 (t, J = 7.7 Hz, 1H, H-5); 6.91-7.16 (m, 6H, H-2', H-3', H-5', H-6', H-4 and H-7); 7.29-7.38 (t, J = 7.7 Hz, 1H, H-6); 9.28 (s, 1H, NH) ppm.

---

[219] Khan K.M., Mughal U.R., Perveen S.S., Choudhary M.I. *Lett. Drug Design Discov.*, **2008**, *5*, 243.

1-Benzyl-3-(4-methoxyphenylimino)indolin-2-one (4s)



4s

Prepared from *p*-anisidine (110 mg, 0.9 mmol) and N-benzylisatin (213 mg).

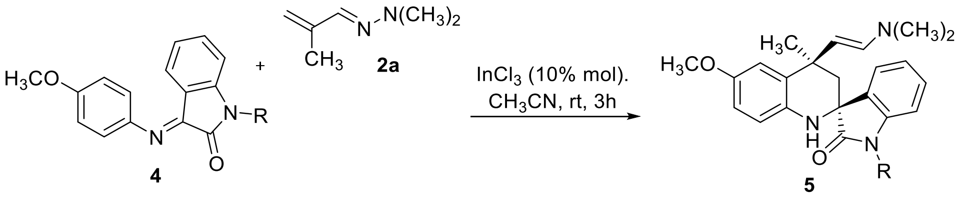
Reaction time: 2 h.

Yield: 88%

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 3.87 (s, 3H, OCH_3); 5.02 (s, 2H, CH_2); 6.69-6.80 (m, 2H, H-5 and H-7); 6.93-7.03 (m, 3H, H-3’, H-5’ and H-4); 7.04-7.09 (m, 2H, H-2’ and H-6’); 7.23-7.42 (m, 6H, H-6, H-2’’, H-3’’, H-4’’, H-5’’ and H-6’’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 44.1 (CH_2); 55.6 (OCH_3); 110.4 (C-7); 114.7 (C-3’ and C-5’); 116.1 (C-3a); 120.4 (C-2’ and C-6’); 122.7 (C-5); 125.8 (C-4); 127.6 (C-3’’ and C-5’’); 128.0 (C-4’’); 129.0 (C-2’’ and C-6’’); 133.9 (C-6); 135.3 (C-1’’); 143.2 (C-1’); 147.1 (C-7a); 153.8 (C-4’); 158.0 (C-3); 163.7 (CO) ppm.

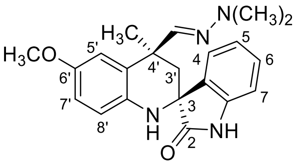
10.2.3.2 - Synthesis of spiro[indolin-3,2'-quinoline] derivatives 5v and 5w



The reaction conditions described in the section 10.2.2.2 were followed to obtain compounds **5v** and **5w**.

Cmpd	R	Yield (%)	dr
5v	H	51	1:0
5w	Bn	44	1:0

(±)-(2'*S**,4'*S**)-4'-[(-(2,2-Dimethylhydrazono)-methyl]-6'-methoxy-4'-methyl-3',4'-dihydro-1'*H*-spiro[indoline-3,2'-quinolin]-2-one (5v)



5v

Prepared from imine **4r** (0.240 g, 0.9 mmol) and hydrazone **2a** (0.111 g, 0.99 mmol).

Reaction time: 3h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield : 0.167 g (51%). Orange solid, mp: 168-170 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.58 (s, 3H, CH_3); 2.25 (d, *J* = 14.0 Hz, 1H, H-3'); 2.60 (s, 6H, $N(CH_3)_2$); 2.61 (d, *J* = 15.0 Hz, 1H, H-3'); 3.78 (s, 3H, OCH_3); 3.91 (bs, 1H, NH); 6.57 (d, *J* = 8.6 Hz, 1H, H-8'); 6.68 (dd, *J* = 8.6, 2.8 Hz, 1H, H-7'); 6.71 (s, 1H, HC=N); 6.84-6.89 (m, 3H, H-5', H-5 and H-7); 7.07 (d, *J* = 7.1 Hz, 1H, H-4); 7.16 (t, *J* = 7.7 Hz, 1H, H-6); 8.58 (s, 1H, NHCO) ppm.

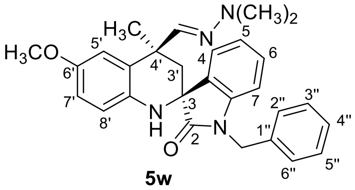
^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 29.3 (CH_3); 39.6 (C-4'); 43.2 ($N(CH_3)_2$); 43.6 (C-3'); 55.8 (OCH_3); 60.9 (C-3); 110.2 (C-7); 113.1 (C-7'); 113.9 (C-5'); 116.7 (C-8'); 122.4 (C-5); 125.6 (C-4);

128.9 (C-4’a); 129.0 (C-6); 133.3 (C-8’a); 136.4 (C-7a); 139.9 (C-3a); 143.7 (CH=N); 153.2 (C-6’); 181.1 (C=O) ppm.

IR *ν*: 3177.1 (N-H), 2920.9 (C-H), 1713.5 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{24}N_4O_2$ (M = 364.44): C, 69.21; H, 6.64; N, 15.37. Found: C, 68.89; H, 6.39; N, 15.01.

(±)-(2'*S**,4'*S**)-1-Benzyl-4'-[(2,2-dimethylhydrazono)methyl]-6'-methoxy-4'-methyl-3',4'-dihydro-1'*H*-spiro[indoline-3,2'-quinolin]-2-one (5w)



5w

Prepared from imine **4s** (0.320 g, 0.9 mmol) and hydrazone **2a** (0.111 g, 0.99 mmol).

Reaction time: 3h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield: 0.180 g (44%). Orange solid, mp: 173-174 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.60 (s, 3H, CH_3); 2.30 (d, *J* = 13.6 Hz, 1H, H-3’); 2.59 (s, 6H, $N(CH_3)_2$); 2.64 (d, *J* = 13.6 Hz, 1H, H-3’); 3.79 (s, 3H, OCH_3); 3.87 (bs, 1H, NH); 4.70 (d, *J* = 15.6 Hz, 1H, CH_2-Ph); 5.09 (d, *J* = 15.6 Hz, 1H, CH_2-Ph); 6.58 (d, *J* = 8.6 Hz, 1H, H-8’); 6.67-6.74 (m, 3H, HC=N, H-7 and H-7’); 6.85-6.89 (m, 2H, H-5’ and H-5); 7.07-7.12 (m, 2H, H-4 and H-6); 7.30-7.33 (m, 5H, H-2’’, H-3’’, H-4’’, H-5’’ and H-6’’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 29.3 (CH_3); 39.6 (C-4’); 43.2 ($N(CH_3)_2$); 43.9 (C-3’ and CH_2Ph); 55.9 (OCH_3); 60.7 (C-3); 109.3 (C-7’); 113.1 (C-7); 114.0 (C-5’); 116.8 (C-8’); 122.4 (C-5); 125.2 (C-4); 127.4 (C-3’’ and C-5’’); 127.8 (C-4’’); 128.9 (C-6); 129.0 (C-2’’ and C-6’’); 132.9 (C-4’a); 136.0 (C-8a’); 136.5 (C-7a); 141.9 (C-3a); 143.7 (CH=N); 145.2 (C-1’’); 153.2 (C-6’); 178.8 (C=O) ppm.

IR (NaCl) *ν*: 3332.1 (N-H), 2927.0 (C-H), 1709.6 (C=O) cm^{-1}.

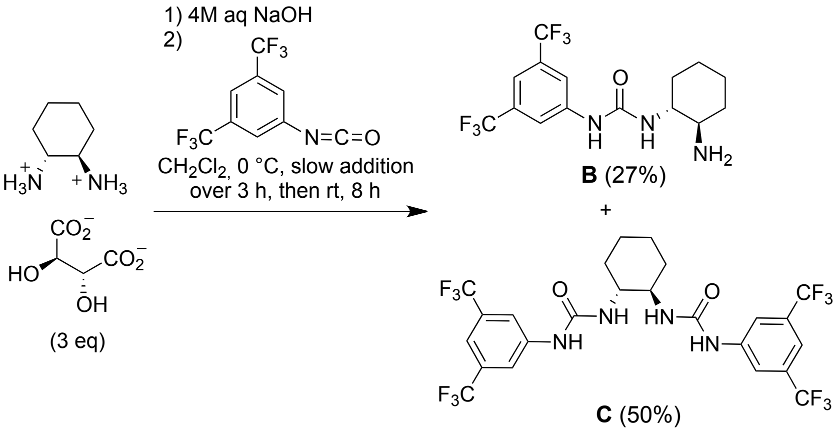
Elemental analysis (%): Calc. for $C_{28}H_{30}N_4O_2$ (M = 454.56): C, 73.98; H, 6.65; N, 12.33. Found: C, 73.58; H, 6.38; N, 12.09.

10.3 - Synthesis of enantiopure 2-acyl-1,2,3,4-tetrahydroquinolines *via* chiral urea-catalyzed Povarov reaction

10.3.1 - Synthesis of chiral urea catalyst A

The preparation of **A** has been previously described in the literature[220] and here we report a slightly modified protocol. In all cases, ^{1}H-NMR analysis confirmed the isolation of the desired products.

a) Preparation of 1-[(1*R*,2*R*)-2-aminocyclohexyl]-3-[3,5-bis-(trifluoromethyl)phenyl]-urea (B)



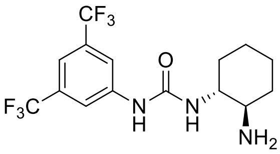
To a solution of 7.77 g (29.4 mmol) of (*R,R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate in 20 mL of dichloromethane in a 125-mL Erlenmeyer flask, 4M sodium hydroxide solution (40 mL) was added and the biphasic mixture was stirred with a magnetic stirring bar for 10 min. The two phases were separated in a 250-mL separatory funnel and then, the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate (10 g) and filtered through a funnel lined with filter paper. The filtrate was concentrated in a 250-mL round-bottom flask under vacuum to

---

[220] Tan K.L., Jacobsen E.N. *Angew. Chem. Int. Ed.*, **2007**, *46*, 1315.

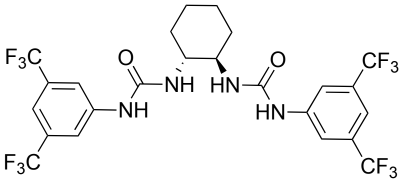
obtain (*R,R*)-1,2-diaminocyclohexane as a free base. This compound was dissolved in dichloromethane (40 mL) and the solution was cooled to 0 °C. A solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (2.5 g, 9.8 mmol) in dichloromethane (10 mL) was added using a syringe pump (2 mL/h). After completion of the addition, the solution was stirred at room temperature (23 °C) for 3 h, and then concentrated under vacuum. A chromatography column (4.0 cm inner diameter (i.d.) × 16 cm length) with silica gel (100 g) was packed using a mixture of dichloromethane/methanol/aqueous ammonia (95:5:1, vol/vol/vol) as eluent. The crude product was dissolved in the eluent (4 mL) and loaded to the column. The column was eluted using the mixture of DCM/methanol/aqueous ammonia (gradient from 95:5:1 to 90:10:1, vol/vol/vol), and the contents of the collected fractions were analyzed by TLC (DCM/methanol/aqueous ammonia, 90:10:1, vol/vol/vol). The first product eluted is the dimeric derivative **C** (50%, 1.413 g), the second one is the desired urea derivative (27%, 0.954 g), and the last product is the starting material. The combined fractions containing the product were dried with anhydrous sodium sulfate (50 g), filtered and concentrated by rotary evaporation to yield the product, which was dried under high vacuum.

Data of Urea B:



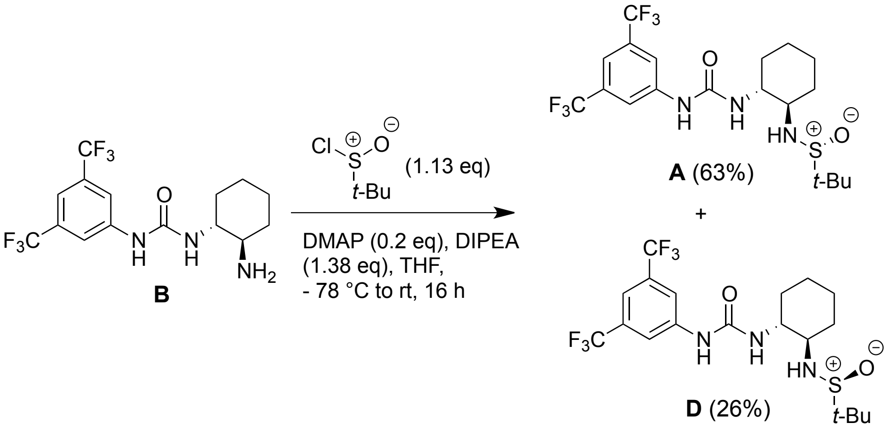
^{1}H-NMR (CD_3OD, 250 MHz) δ: 1.08-1.51 (m, 4H, 2 x CH_2); 1.74-1.77 (m, 2H, CH_2); 1.87-2.09 (m, 2H, CH_2); 2.47 (dt, *J* = 10.3, 3.7 Hz, 1H, H-2); 3.37 (dt, *J* = 10.4, 3.7 Hz, 1H, H-1); 7.48 (s, 1H, H-4); 8.01 (s, 2H, H-2 and H-6) ppm.

Data of bisurea C:[221]



^{1}H-NMR (CD_3OD, 250 MHz) δ: 1.38-1.40 (m, 4H, 2 x CH_2); 1.81 (bs, 2H, 2 x CH); 2.01-2.03 (m, 2H, 2 x CH); 3.57 (bs, 2H, 2 x CH-1); 7.32 (s, 2H, 2 x H-4); 7.84 (s, 4H, 2 x H-2 and H-6) ppm.

b) Synthesis of chiral sulfinamidoureas A and D



A solution of 1-[(1*R*,2*R*)-2-aminocyclohexyl]-3-[3,5-bis-(trifluoromethyl)phenyl]urea **B** (0.60 g, 1.63 mmol) and 4-(dimethylamino)pyridine (40 mg, 0.33 mmol) in THF (50 mL) in a 250-mL round-bottom flask was cooled to −78 °C. Then, *N,N*-diisopropylethylamine (0.39 mL, 2.25 mmol) and racemic *tert*-butylsulfinyl chloride (0.23 mL, 1.84 mmol) were added slowly *via* syringe. The reaction mixture was stirred at −78 °C for 4 h, and then warmed it up to room temperature slowly over a period of 12 h.

After quenching the reaction with methanol (5 mL), the solvent was removed under vacuum, the residue was dissolved in ethyl acetate (20 mL), and the organic layer was washed with

---

[221] Sohtome Y., Tanatani A., Hashimoto Y., Nagasawa K. *Chem. Pharm. Bull.*, **2004**, *52*, 477.

1M HCl (20 mL) and saturated $NaHCO_3$ aqueous solution (20 mL). The organic layer was dried with anhydrous sodium sulfate (10 g), filtered with a filter funnel, and the solvent was removed under vacuum. A chromatography column (4.0 cm i.d. × 16 cm length) was prepared with silica gel (100 g), using a mixture of DCM/methanol (99.25:0.75, vol/vol) as eluent. The crude product was dissolved in eluent (2 mL), loaded onto the column, and eluted using mixtures of DCM/methanol (gradient from 99.25:0.75 to 97:3, vol/vol).

The collected fractions were analyzed by TLC (DCM/methanol, 95:5, vol/vol). The desired chiral urea catalyst **A** elutes first off the column (63%, 0.503 g), followed by its diastereoisomer **D** (26%, 0.207 g) and recovered starting material **B**.

The combined fractions containing the product were concentrated using a rotary evaporator. The product was dried under high vacuum. It is bench-stable and it can be stored at room temperature in a desiccator indefinitely.

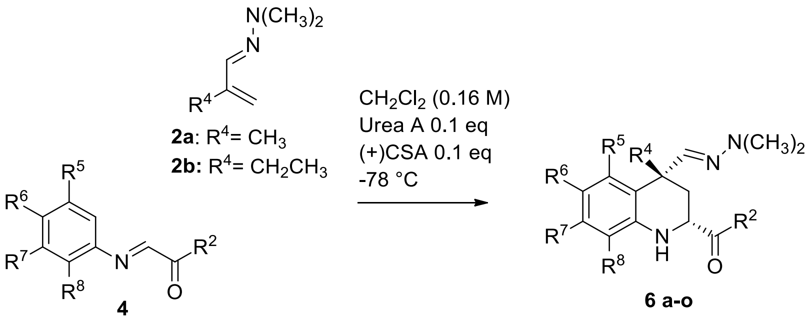
Compound A

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.28 (m, 13H, *t*Bu and 2 x CH_2); 1.79-2.19 (m, 4H, 2 x CH_2); 2.89 (m, 1H, H-2); 3.58 (s, 1H, H-1); 6.12 (s, 1H, NH); 6.47 (d, J = 6.3 Hz, 1H, NH); 7.13 (s, 1H, H-4); 7.57 (s, 2H, H-2 and H-6); 8.89 (s, 1H, NH) ppm.

Compound D:

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.21-1.62 (m, 13H, *t*-Bu and 2 x CH_2); 1.75-1.85 (m, 2H, CH_2); 2.05-2.10 (m, 2H, CH_2); 2.97 (bs, 1H, CH); 3.52 (m, 1H, CH); 4.19 (bs, 1H, NH); 7.40 (s, 1H, H-4); 7.94 (s, 2H, H-2 and H-6) ppm.

10.3.2 - Synthesis of enantiomerically pure 2-acyl-1,2,3,4-tetrahydroquinoline compounds 6a-o



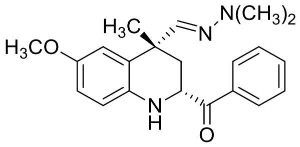
A 10 mL oven-dried round bottom flask was charged with urea catalyst A (0.04 mmol), (+)CSA (0.04 mmol) and activated molecular sieve powder (40 mg) under argon atmosphere. The flask was cooled to -78 °C and a solution of imine **4** (0.4 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred for 10 minutes. The corresponding hydrazone **2** (0.44 mmol) was added dropwise with a syringe and the suspension was stirred at -78 °C until the starting material disappeared (see the reaction times in the data sheet). The reaction was quenched with Et_3N (0.14 mL, 1 mmol) at -78°C and the resulting mixture was stirred for 10 minutes. The suspension was filtered to eliminate the molecular sieve powder and the residue was washed with ethyl acetate. The filtrate was concentrated under vacuum. The resulting crude was purified by flash chromatography using a Combiflash Teledyne automated chromatograph, eluting with a gradient from neat petroleum ether to 9:1 petroleum ether-ethyl acetate.

The enantiomeric excess values were measured in a HPLC Agilent 1220 Infinity LC equipped with a UV-Vis detector set at 204 nm, employing a chiral ULTRON ES-OVM column purchased from Agilent, and eluting with a solution of 30% methanol and 70% 20 mM phosphate buffer (pH 4.3) in a flow rate of 1.0 mL/min.

Imine	Cmpd	R^2	R^4	R^5	R^6	R^7	R^8	Yield (%)	dr (*cis*: *trans*)[b]	ee *cis* (%)[c]
4a	**6a**[a]	C_6H_5	CH_3	H	OCH_3	H	H	75	98:02	95
4a	**6b**[a]	C_6H_5	CH_2CH_3	H	OCH_3	H	H	82	100:0	97
4b	**6c**[a]	4-FC_6H_4	CH_3	H	OCH_3	H	H	95	96:04	90
4c	**6d**[a]	4-$OCH_3C_6H_4$	CH_3	H	OCH_3	H	H	95	100:0	95
4d	**6e**	C_6H_5	CH_3	H	CH_3	H	CH_3	57	100:0	51
4h	**6f**	4-$OCH_3C_6H_4$	CH_3	H	CH_3	H	H	68	96:04	94
4i	**6g**[a]	OCH_2CH_3	CH_3	H	OCH_3	H	H	56	100:0	83
4k	**6h**	2-furyl	CH_2CH_3	H	OCH_3	H	H	93	97:03	94
4l	**6i**	2-thienyl	CH_2CH_3	H	OCH_3	H	H	91	96:04	97
4l	**6j**[a]	2-thienyl	CH_3	H	OCH_3	H	H	93	100:0	94
4m	**6k**	OCH_2CH_3	CH_3	H	CH_3	H	H	52	100:0	91
4n	**6l**	C_6H_5	CH_2CH_3	H	CH_3	H	H	95	97:03	99
4o	**6m**	C_6H_5	CH_3	CH_3	H	CH_3	H	72	77:23	90
4p	**6n**	4-FC_6H_4	CH_3	H	CH_3	H	H	70	97:3	85
4q	**6o**	C_6H_5	CH_3	H	H	H	H	43	100:0	97

[a] The characterization data of these compounds are in total agreement with the data for the racemic compounds. We report as an example the ^{1}H-NMR spectrum of compound (+)-**6a**. [b] The diastereoseletivities were determined by integration of suitable signals in the ^{1}H spectra of the crude reaction products. [c] Enantiomeric excesses were determined by HPLC, using a ULTRON ES-OVM chiral column.

(+)-(2*R*,4*R*)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (6a)



6a

Prepared from imine **4a** (0.095 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

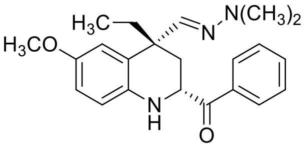
Yellow solid, mp: 130-131 °C.

Reaction time: 5 h.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.65 (s, 3H, CH_3); 1.73 (t, *J* = 12.7 Hz, 1H, H-3ax); 2.07 (dd, *J* = 12.7, 2.9 Hz, 1H, H-3eq); 2.73 (s, 6H, $N(CH_3)_2$); 3.73 (s, 3H, OCH_3); 4.62 (bs, 1H, NH); 5.09 (dd, *J* = 12.3, 2.8 Hz, 1H, H-2); 6.53 (s, 1H, CH=N); 6.66 (s, 1H, H-5); 6.71 (m, 2H, H-7 and H-8); 7.42-7.56 (m, 2H, H-3' and H-5'); 7.60 (m, 1H, H-4'); 7.94 (d, *J* = 7.1 Hz, 2H, H-2' and H-6') ppm.

$[\alpha]_D^{20}$: +66.96 (C = 1.2 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-4-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline (6b)



6b

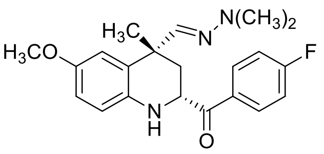
Prepared from imine **4a** (0.095 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2b** (0.055 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Orange oil.

Reaction time: 5 h.

$[\alpha]_D^{20}$: +62.00 (C = 1 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-4-[(2,2-Dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline (6c)



6c

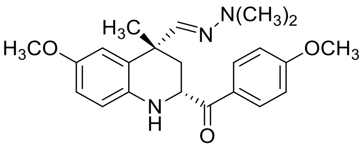
Prepared from imine **4b** (0.103 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 121-122 °C.

Reaction time: 5 h.

$[\alpha]_D^{20}$: +18.33 (C = 1.2 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-4-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-2-(4-methoxybenzoyl)-4-methyl-1,2,3,4-tetrahydroquinoline (6d)



6d

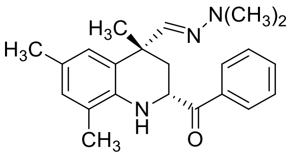
Prepared from imine **4c** (0.107 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 127-128 °C.

Reaction time: 3 h.

$[\alpha]_D^{20}$: +79.00 (C = 1 mg/mL, $CHCl_3$).

(2*R*,4*R*)- and (2*S*,4*S*)-4-[(2,2-Dimethylhydrazono)methyl]-4,6-dimethyl-2-benzoyl-1,2,3,4-tetrahydroquinoline (6e)



6e

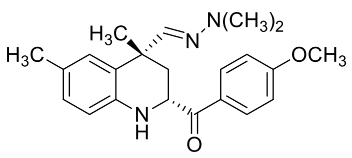
Prepared from imine **4d** (0.107 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 147-149 °C.

Reaction time: 3 h.

In this case the $[\alpha]_D^{20}$ value was measured because of the very low ee (51%).

(+)-(2*R*,4*R*)-4,6-Dimethyl-4-[(2,2-dimethylhydrazono)methyl]-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroquinoline (6f)



6f

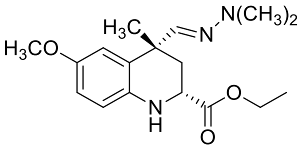
Prepared from imine **4h** (0.108 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.044 mmol) in 2 mL of CH_2Cl_2.

White solid, mp: 133-135 °C.

Reaction time: 4 h.

$[\alpha]_D^{20}$: -131.76° (C = 0.85 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-Ethyl 4-[(2,2-dimethylhydrazono)methyl]-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (6g)



6g

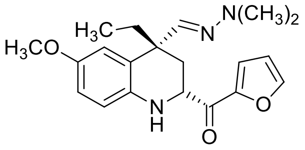
Prepared from imine **4i** (0.059 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Pale yellow viscous liquid.

Reaction time: 5 h.

$[\alpha]_D^{20}$: -11.77° (C = 1.3 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-4-[(2,2-Dimethylhydrazono)methyl]-4-ethyl-2-(2-furylcarbonyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (6h)



6h

Prepared from imine **4k** (0.091 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2b** (0.055 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 95-96 °C.

Reaction time: 3 h.

^{1}H-NMR ($\mathrm{CDCl_3}$, 250 MHz) δ: 1.02 (t, *J* = 7.3 Hz, 3H, $\mathrm{CH_2C}\mathit{H}_3$); 1.80 (t, *J* = 12.6 Hz, 1H, H-3ax); 1.97-2.04 (m, 2H, $\mathit{CH_2}\mathrm{CH_3}$); 2.42 (dd, *J* = 13.1, 3.3 Hz, 1H, H-3eq); 2.72 (s, 6H, $\mathrm{N(CH_3)_2}$); 3.72 (s, 3H, $\mathrm{OCH_3}$); 4.46 (bs, 1H, NH); 4.81 (dd, *J* = 12.0, 3.3 Hz, 1H, H-2); 6.55-6.58 (m, 2H, H-4' and CH=N); 6.67 (m, 3H, H-5, H-7 and H-8); 7.30 (d, *J* = 3.5 Hz, 1H, H-3'); 7.60 (d, *J* = 1.2 Hz, 1H, H-5') ppm.

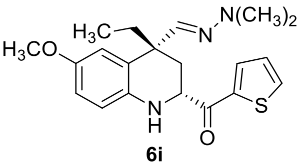
^{13}C-NMR ($\mathrm{CDCl_3}$, 63 MHz) δ: 8.9 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$); 30.9 ($\mathit{C}\mathrm{H_2CH_3}$); 34.1 (C-3); 43.3 ($\mathrm{N(CH_3)_2}$); 43.4 (C-4); 54.6 (C-2); 55.8 ($\mathrm{OCH_3}$); 112.5 (C-4'); 113.1 (C-5); 114.0 (C-7); 116.6 (C-8); 118.1 (C-3'); 127.6 (C-4a); 136.6 (C-8a); 141.3 (CH=N); 146.5 (C-5'); 151.3 (C-2'); 151.8 (C-6); 189.1 (CO) ppm.

IR (NaCl) ν: 3413.9 (NH), 2956.3 (C-H), 1670.3 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $\mathrm{C_{20}H_{25}N_3O_3}$ (M = 355,44): C, 67.58; H, 7.09; N, 11.82. Found: C, 67.22; H, 6.95; N, 11.61.

$[\alpha]_D^{20}$: + 44.24° (C = 1.65 mg/mL, $\mathrm{CHCl_3}$)

(+)-(2*R*,4*R*)-4-[(2,2-Dimethylhydrazono)methyl]-4-ethyl-2-(2-thienylcarbonyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (6i)



6i

Prepared from imine **4l** (0.098 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2b** (0.055 g, 0.44 mmol) in 2 mL of $\mathrm{CH_2Cl_2}$.

Orange solid, mp: 90-91 °C.

Reaction time: 3 h.

^{1}H-NMR ($\mathrm{CDCl_3}$, 250 MHz) δ: 1.01 (t, *J* = 7.4 Hz, 3H, $\mathrm{CH_2C}\mathit{H}_3$); 1.90 (t, *J* = 12.8 Hz, 1H, H-3ax); 2.04 (q, *J* = 7.4 Hz, 2H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); 2.33 (dd, *J* = 13.3, 3.3 Hz, 1H, H-3eq); 2.72 (s, 6H, $\mathrm{N(CH_3)_2}$); 3.73 (s, 3H, $\mathrm{OCH_3}$); 4.44 (bs, 1H, NH); 4.86 (dd, *J* = 12.2, 3.2 Hz, 1H, H-2); 6.54 (s, 1H, CH=N); 6.67 (m, 1H, H-5); 6.69-6-70 (m, 2H, H-7 and H-8); 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H, H-4'); 7.68 (dd, *J* = 4.9, 1.1 Hz, 1H, H-3'); 7.84 (dd, *J* = 3.8, 1.0 Hz, 1H, H-5') ppm.

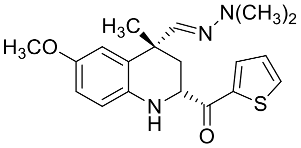
^{13}C-NMR ($\mathrm{CDCl_3}$, 63 MHz) δ: 9.2 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$); 31.1 ($\mathit{C}\mathrm{H_2CH_3}$); 36.0 (C-3); 43.3 ($\mathrm{N(CH_3)_2}$); 43.6 (C-4); 55.7 (C-2); 56.0 ($\mathrm{OCH_3}$); 113.3 (C-5); 114.3 (C-7); 116.8 (C-8); 127.5 (C-4a); 128.4 (C-4'), 132.4 (C-3'), 134.1 (C-5'); 136.6 (C-8a); 141.1 (C=N and C-2'); 152.0 (C-6); 193.3 (CO) ppm.

IR *ν*: 3362.0 (NH), 2957.0 (C-H), 1659.1 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $C_{20}H_{25}N_3O_2S$ (M = 371,50): C, 64.66; H, 6.78; N, 11.31; S, 8.63. Found: C, 64.53; H, 6.64; N, 11.15; S, 8.49.

$[\alpha]_D^{20}$: -19.17 (C = 1.2 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-4-[(2,2-Dimethylhydrazono)methyl]-6-methoxy-4-methyl-2-(2-thienylcarbonyl)-1,2,3,4-tetrahydroquinoline (6j)



6j

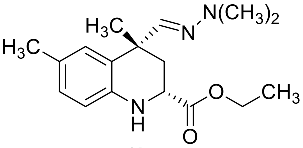
Prepared from imine **4l** (0.098 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Brown solid, mp: 107-108 °C.

Reaction time: 3 h.

$[\alpha]_D^{20}$: +50.00 (C = 1 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-Ethyl 4,6-dimethyl-4-[(2,2-dimethylhydrazono)methyl]-1,2,3,4-tetrahydroquinoline-2-carboxylate (6k)



6k

Prepared from imine **4m** (0.052 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow oil.

Reaction time: 4 h.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.32 (t, *J* = 7.1 Hz, 3H, CH_2CH_3); 1.48 (s, 3H, CH_3); 1.94 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.09 (dd, *J* = 12.9, 3.4 Hz, 1H, H-3eq); 2.21 (s, 3H, $ArCH_3$); 2.78 (s, 6H, $N(CH_3)_2$); 4.13 (dd, *J* = 11.7, 3.4 Hz, 1H, H-2); 4.26 (q, *J* = 7.0 Hz, 2H, CH_2CH_3); 4.36 (bs, 1H, NH); 6.56 (d, *J* = 7.9 Hz, 1H, H-8); 6.61 (s, 1H, CH=N); 6.82-6.87 (m, 2H, H-7 and H-5) ppm.

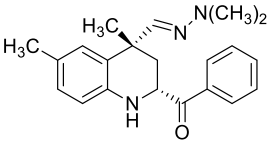
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.3 (OCH_2CH_3); 20.6 (CH_3); 27.0 ($ArCH_3$); 37.4 (OCH_2CH_3); 40.2 (C-4); 43.5 ($N(CH_3)_2$); 51.1 (C-2); 61.5 (C-3); 115.1 (C-8); 126.6 (C-4a); 127.1 (C-6); 128.3 (C-5); 128.6 (C-7); 140.1 (C-8a); 143.9 (CH=N); 173.3 (CO) ppm.

IR ν: 3389.7 (NH), 2919.5 (C-H), 1732.3 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $C_{17}H_{25}N_3O_2$ (M = 303,41): C, 67.30; H, 8.31; N, 13.85. Found: C, 67.07; H, 8.07; N, 13.80.

$[\alpha]_D^{20}$: -61.05 (C = 0.95 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-2-Benzoyl-4,6-dimethyl-4-[(2,2-dimethylhydrazono)methyl]-1,2,3,4-tetrahydroquinoline (6l)



6l

Prepared from imine **4n** (0.103 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 104-105 °C.

Reaction time: 3 h.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.64 (s, 3H, CH_3); 1.73 (t, *J* = 12.6 Hz, 1H, H-3ax); 2.07 (dd, *J* = 12.9, 2.9 Hz, 1H, H-3eq); 2.23 (s, 3H, $ArCH_3$); 2.74 (s, 6H, $N(CH_3)_2$); 5.10 (dd, *J* = 12.3, 2.8 Hz, 1H, H-2); 6.55 (s, 1H, CH=N); 6.68 (d, *J* = 8.0 Hz, 1H, H-8); 6.84 (s, 1H, H-5); 6.90 (dd, *J* = 8.0, 1.8 Hz, 1H, H-7); 7.44-7.56 (m, 2H, H-3’ and H-5’); 7.60 (m, 1H, H-4’); 7.96 (d, *J* = 7.5 Hz, 2H, H-2’ and H-6’) ppm.

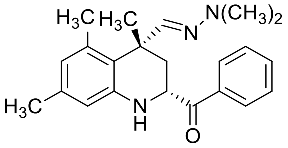
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 20.7 (CH_3); 26.3 ($ArCH_3$); 39.0 (C-3); 40.9 (C-4); 43.4 ($N(CH_3)_2$); 54.3 (C-2); 115.9 (C-8); 126.8 (C-4a); 127.0 (C-6); 128.4 (C-5, C-3’ and C-5’); 129.0 (C-7, C-2’ and C-6’); 133.7 (C-4’); 134.8 (C-1’); 140.3 (C-8a); 143.6 (CH=N); 199.6 (CO) ppm.

IR ν: 3378.8 (NH), 2853.6 (C-H), 1683.9 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $C_{21}H_{25}N_3O$ (M = 335,44): C, 75.19; H, 7.51; N, 12.53. Found: C, 75.36; H, 7.44; N, 12.48.

$[\alpha]_D^{20}$: +55.55 (C = 0.9 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-4,5,7-trimethyl-1,2,3,4-tetrahydroquinoline (6m)



6m

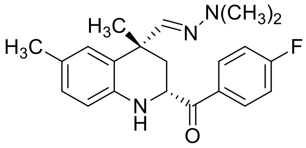
Prepared from imine **4o** (0.095 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

White solid, mp: 153-154 °C.

Reaction time: 3 h.

$[\alpha]_D^{20}$: +42.00 (C = 1 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-4,6-Dimethyl-4-[(2,2-dimethylhydrazono)methyl]-2-(4-fluorobenzoyl)-1,2,3,4-tetrahydroquinoline (6n)



6n

Prepared from imine **4p** (0.096 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 111-113 °C.

Reaction time: 5 h.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.64 (s, 3H, CH_3); 1.76 (t, J = 12.6 Hz, 1H, H-3ax); 2.04 (dd, J = 12.9, 2.9 Hz, 1H, H-3eq); 2.23 (s, 3H, $ArCH_3$); 2.75 (s, 6H, $N(CH_3)_2$); 4.68 (bs, 1H, NH); 5.06 (dd, J = 12.2, 2.9 Hz, 1H, H-2); 6.55 (s, 1H, CH=N); 6.67 (d, J = 8.0 Hz, 1H, H-8); 6.86 (s, 1H, H-5); 6.90 (dd, J = 8.0, 1.8 Hz, 1H, H-7); 7.12-7.23 (m, 2H, H-3' and H-5'); 7.90-8.04 (m, 2H, H-2' and H-6') ppm.

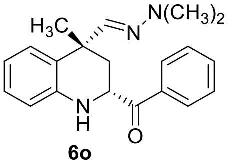
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 20.7 (CH_3); 26.4 ($ArCH_3$); 39.0 (C-3), 40.8 (C-4); 43.4 ($N(CH_3)_2$); 54.3 (C-2); 115.9 (C-8); 116.2 (d, J = 22 Hz, C-3' and C-5'); 126.8 (C-4a); 127.1 (C-6); 128.5 (C-7 and C-5); 131.0 (d, J = 9.3 Hz, C-2' and C-6'); 131.1 (C-1'); 140.1 (C-8a); 140.3 (CH=N); 165.9 (d, J = 256 Hz, C-4'); 198.0 (CO) ppm.

IR ν: 3311.3 (NH), 2953.9 (C-H), 1686.1 (C=O) cm^{-1}.

Elemental analysis (%) calc. for $C_{21}H_{24}FN_3O$ (M = 353,43): C, 71.36; H, 6.84; N, 11.89. Found: C, 71.07; H, 6.71; N, 11.64.

$[\alpha]_D^{20}$: +40.00 (C = 1.05 mg/mL, $CHCl_3$)

(+)-(2*R*,4*R*)-2-Benzoyl-4-[(2,2-dimethylhydrazono)methyl]-1,2,3,4-tetrahydroquinoline (6o)



6o

Prepared from imine **4q** (0.103 g, 0.4 mmol), urea catalyst (0.019 g, 0.04 mmol), (+)-CSA (0.009 g, 0.04 mmol) and hydrazone **2a** (0.051 g, 0.44 mmol) in 2 mL of CH_2Cl_2.

Yellow solid, mp: 95-98 °C.

Reaction time: 5 h.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.65 (s, 3H, CH_3); 1.75 (t, J = 12.7 Hz, 1H, H-3ax); 2.10 (dd, J = 12.9, 2.8 Hz, 1H, H-3eq); 2.74 (s, 6H, $N(CH_3)_2$); 4.87 (s, 1H, NH); 5.13 (d, J = 12.2 Hz, 1H, H-2); 6.55 (s, 1H, CH=N); 6.59-6.84 (m, 2H, H-6 and H-8); 6.94-7.13 (m, 2H, H-5 and H-7); 7.50 (t, J = 7.4 Hz, 2H, H-3' and H-5'); 7.62 (t, J = 7.3 Hz, 1H, H-4'); 7.95 (d, J = 7.4 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 26.3 (CH_3); 38.7 (C-3); 40.8 (C-4); 43.4 ($N(CH_3)_2$); 54.2 (C-2); 115.6 (C-8); 117.7 (C-6); 126.7 (C-4a); 127.7 (C-5); 128.1 (C-7); 128.4 (C-3' and C-5'); 129.0 (C-2' and C-6'); 133.7 (C-4'); 134.8 (C-1'); 142.7 (C-8a); 143.2 (CH=N); 199.5 (CO) ppm.

IR ν: 3388.7 (NH), 2955.9 (C-H), 1680.3 (C=O) cm^{-1}.

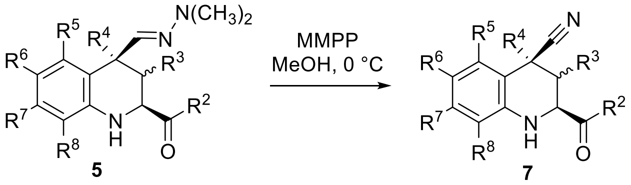
Elemental analysis (%) calc. for $C_{20}H_{23}N_3O$ (M = 321,42): C, 74.74; H, 7.21; N, 13.07. Found: C, 74.59; H, 7.09; N, 12.99.

$[\alpha]_D^{20}$: +108.87 (C = 1.15 mg/mL, $CHCl_3$)

10.4 - Synthesis of highly functionalized quinolines

10.4.1 - Synthetic procedure to obtain 2-acylquinolines

10.4.1.1 - Synthesis of 2-acyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile derivatives 7a-c,e-n

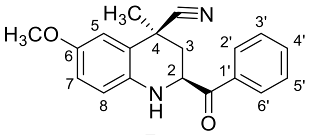


Cmpd	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Yield (%)
7a	C_6H_5	H	CH_3	H	OCH_3	H	H	72
7b	4-FC_6H_4	H	CH_3	H	OCH_3	H	H	70[a]
7c	4-$OCH_3C_6H_4$	H	CH_3	H	OCH_3	H	H	89
7d	C_6H_5	H	CH_2CH_3	H	OCH_3	H	H	[b]
7e	C_6H_5	H	CH_3	H	CH_3	H	CH_3	98
7f	4-FC_6H_4	H	CH_3	CH_3	H	CH_3	H	93[c]
7g	OEt	H	CH_3	H	OCH_3	H	H	60
7h	OEt	H	CH_3	H	CH_3	H	CH_3	83
7i	OEt	H	CH_2CH_3	H	OCH_3	H	H	63[d]
7j	2-furyl	H	CH_3	H	OCH_3	H	H	78
7k	C_6H_5	CH_2CH_3	H	H	OCH_3	H	H	[e]
7l	C_6H_5	H	H	H	OCH_3	H	H	[e]
7m'	C_6H_5	CH_2CH_3	CH_3	H	OCH_3	H	H	69
7m''	C_6H_5	CH_2CH_3	CH_3	H	OCH_3	H	H	69
7n	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	CH_3	70
7o	4-FC_6H_4	H	CH_2CH_3	H	CH_3	H	CH_3	[b]
7p	C_6H_5	H	CH_3	CH_3	H	CH_3	H	[b]

[a] Together with 14% of compound **8b**; [b] Compounds **7d**, **7o** and **7p** were not isolated because they were oxidized to **8d**, **8o** and **8p**, respectively, in the reaction conditions; [c] Isolated as a *ca.* 1:1 *cis*/*trans* mixture. [d] Together with 32% of compound **8i**; [e] Compounds **7k** and **7l** were isolated but they could not be fully characterized because of aromatization to **9a** and **9b** respectively during the purification process.

To a solution of hydrazone **5** (0.5 mmol, 1 eq) in methanol (10 mL) was added dropwise a suspension of MMPP·6H_2O (0.62 mmol, 1.25 eq) in methanol (5 mL) at 0 °C. The mixture was stirred at room temperature until consumption of the starting material. The mixture was then diluted with water (20 mL) and extracted with CH_2Cl_2 (3 X 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried (Na_2SO_4), concentrated and the residue was purified by flash chromatography on silica gel eluting with a mixture of petroleum ether:ethyl acetate (9:1, v/v).

(±)-(2*S**,4*S**)-2-Benzoyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7a)



7a

Prepared from tetrahydroquinoline **5a** (0.300 g, 0.85 mmol) and MMPP·6H_2O (0.523 g, 1.06 mmol).

Reaction time: 2 h.

Yield: 0.200 g (72%). Yellow oil.

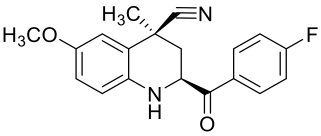
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.87 (s, 3H, CH_3); 2.07 (t, *J* = 12.7 Hz, 1H, H-3ax); 2.50 (dd, *J* = 13.0, 3.2 Hz, 1H, H-3eq); 3.78 (s, 3H, OCH_3); 4.97 (dd, *J* = 12.5, 3.2 Hz, 1H, H-2); 6.72 (d, *J* = 8.7 Hz, 1H, H-8); 6.80 (dd, *J* = 8.8, 2.7 Hz, 1H, H-7); 6.97 (d, *J* = 2.6 Hz, 1H, H-5); 7.48-7.59 (m, 2H, H-3' and H-5'); 7.62-7.72 (m, 1H, H-4'); 7.87-7.96 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 28.6 (CH_3); 35.6 (C-4); 36.7 (C-3); 52.9 (C-2); 56.0 (OCH_3); 112.2 (C-7); 116.5 (C-5); 117.8 (C-8); 120.6 (CN); 123.7 (C-4a); 128.8 (C-3' and C-5'); 129.3 (C-2' and C-6'); 134.2 (C-4'); 134.4 (C-8a); 135.2 (C-1'); 152.7 (C-6); 198.0 (C=O) ppm.

IR (NaCl) *v*: 3373.4 (NH), 2926.2 (C-H), 2235.0 (CN), 1691.6 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{18}N_2O_2$ (M = 306,36): C, 74.49; H, 5.92; N, 9.14. Found: C, 74.23; H, 5.75; N, 8.98.

(±)-(2*S**,4*S**)-2-(4-Fluorobenzoyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7b)



7b

Prepared from tetrahydroquinoline **5b** (0.320 g, 0.86 mmol) and MMPP·$6H_2O$ (0.533 g, 1.08 mmol).

Reaction time: 2 h.

Yield: 0.195 g (70%). Yellow solid, mp: 119-120 °C.

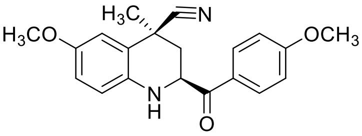
^{1}H-NMR ($CDCl_3$, 250 MHz) δ:: 1.86 (s, 3H, CH_3); 2.10 (t, J = 12.5 Hz, 1H, H-3ax); 2.46 (dd, J = 13.0, 3.2 Hz, 1H, H-3eq); 3.78 (s, 3H, OCH_3); 4.58 (s, 1H, NH); 4.92 (m, 1H, H-2); 6.71 (d, J = 8.8 Hz, 1H, H-8); 6.80 (dd, J = 8.8, 2.7 Hz, 1H, H-7); 6.96 (d, J = 2.7 Hz, 1H, H-5); 7.22 (t, J = 8.6 Hz, 2H, H-3' and H-5'); 7.92-7.99 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 28.7 (CH_3); 35.5 (C-4); 36.8 (C-3); 52.9 (C-2); 56.0 (OCH_3); 112.2 (C-7); 116.4 (d, J = 12.7 Hz, C-3' and C-5'); 116.8 (C-5); 117.9 (C-8); 120.5 (CN); 123.7 (C-4a); 130.7 (d, J = 3.1 Hz, C-1'); 131.1 (d, J = 9.4 Hz, C-2' and C-6'); 135.1 (C-8a); 152.8 (C-6); 166.5 (d, J = 257.3 Hz, C-4'); 196.4 (C=O) ppm.

IR (NaCl) ν: 3345.2 (N-H), 2923.1 (C-H), 2232.1 (CN), 1684.4 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{17}FN_2O_2$ (M = 324,35): C, 70.36; H, 5.28; N, 8.64. Found: C, 70.12; H, 5.03; N, 8.45.

(±)-(2S*,4S*)-6-Methoxy-2-(4-methoxybenzoyl)-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7c)



7c

Prepared from tetrahydroquinoline **5c** (0.340 g, 0.89 mmol) and MMPP·$6H_2O$ (0.550 g, 1.11 mmol).

Reaction time: 2 h.

Yield: 0.266 g (89%). Yellow oil.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.87 (s, 3H, CH_3); 2.07 (t, J = 12.8 Hz, 1H, H-3ax); 2.48 (dd, J = 13.0, 3.1 Hz, 1H, H-3eq); 3.78 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.91 (dd, J = 12.5, 3.0 Hz, 1H, H-2); 6.71 (d, J = 8.7 Hz, 1H, H-8); 6.79 (dd, J = 8.8, 2.7 Hz, 1H, H-7); 6.96-7.02 (m, 3H, H-5, H-3' and H-5'); 7.90-7.93 (m, 2H, H-2' and H-6') ppm.

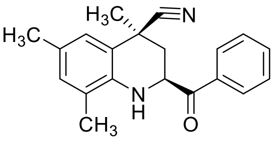
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.1 (CH_3); 35.9 (C-4); 37.3 (C-3); 52.7 (C-2); 56.0 (OCH_3); 56.3 (OCH_3); 112.4 (C-7*); 114.8 (C-3' and C-5'); 116.7 (C-5*); 118.2 (C-8*); 120.9 (CN); 124.1 (C-

4a); 127.4 (C-1’); 131.0 (C-2’ and C-6’); 135.7 (C-8a); 153.0 (C-6); 164.6 (C-4’); 196.4 (C=O) ppm.

IR (NaCl) *v*: 3362.8 (N-H), 2924.9 (C-H), 2234.4 (CN), 1680.4 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{20}N_2O_3$ (M = 336,38): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.23; H, 5.78; N, 8.17.

(±)-(2*S**,4*S**)-2-Benzoyl-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7e)



7e

Prepared from tetrahydroquinoline **5e** (0.400 g, 1.14 mmol) and MMPP·6H_2O (0.705 g, 1.4 mmol).

Reaction time: 0.5 h.

Yield: 0.340 g (98%). Orange solid, mp: 113-115 °C.

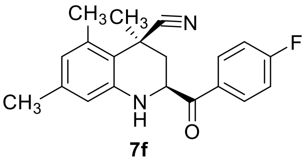
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.87 (s, 3H, CH_3); 2.04 (t, *J* = 12.8 Hz, 1H, H-3ax); 2.21 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 2.51 (dd, *J* = 12.9, 3.2 Hz, 1H, H-3eq); 4.61 (s, 1H, NH); 5.01 (d, *J* = 12.6 Hz, 1H, H-2); 6.90 (s, 1H, H-7); 7.13 (s, 1H, H-5); 7.51-7.58 (m, 2H, H-3’ and H-5’); 7.67 (m, 1H, H-4’); 7.91-7.94 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 17.5 ($ArCH_3$); 20.5 ($ArCH_3$); 28.7 (CH_3); 35.6 (C-4); 36.7 (C-3); 52.9 (C-2); 119.2 (CN*); 123.8 (C-4a*); 124.1 (C-8); 125.6 (C-6); 127.3 (C-5); 128.3 (C-3’ and C-5’); 129.3 (C-2’ and C-6’); 131.3 (C-7); 134.2 (C-4’); 134.4 (C-1’); 136.9 (C-8a); 198.0 (C=O) ppm.

IR (NaCl) *v*: 3386.3 (N-H), 2921.7 (C-H), 2234.8 (CN), 1680.4 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{20}N_2O$ (M = 304,39): C, 78.92; H, 6.62; N, 9.20. Found: C, 78.67; H, 6.45; N, 9.01.

(±)-(2*S**,4*S**)-2-(4-Fluorobenzoyl)-4,5,7-trimethyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7f)



7f

Prepared from tetrahydroquinoline **5f** (0.430 g, 1.17 mmol) and MMPP·6H_2O (0.720 g, 1.46 mmol).

Reaction time: 1 h.

Yield: 0.350 g (93%), as a 1:1 diastereomer mixture. Orange oil.

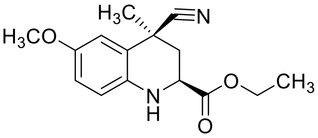
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.76 (s, 3H, CH_3); 1.88 (s, 3H, CH_3); 1.98 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.21-2.22 (m, 7H, $ArCH_3$, $ArCH_3$ and H-3ax); 2.52-2.56 (m, 7H, $ArCH_3$, $ArCH_3$ and H-3eq); 2.73 (dd, *J* = 13.4, 1.9 Hz, 1H, H-3eq); 4.87 (dd, *J* = 12.6, 2.6 Hz,1H, H-2); 5.03 (dd, *J* = 11.7, 1.9 Hz, 1H, H-2); 6.42-6.45 (m, 4H, H-6 and H-8); 7.19-7.25 (m, 4H, H-3' and H-5'); 7.97 (dd, *J* = 8.9; 5.3 Hz, 2H, H-2' and H-6'); 8.07 (dd, *J* = 8.9, 5.3 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 20.9; 21.0; 21.0; 22.1; 26.4 and 26.5 (6 x CH_3); 33.5 and 33.8 (C-4); 40.0 and 44.0 (C-3); 52.2 and 54.9 (C-2); 114.2 and 115.8 (C-4a); 115.0 and 115.3 (C-8); 116.6 (d, *J* = 25.2 Hz, C-3' and C-5'); 123.1 and 123.8 (C-6); 124.0 (CN); 130.5 (d, *J* = 3.1 Hz, C-1'); 130.6 (d, *J* = 3.2 Hz, C-1'); 131.1 (d, *J* = 9.4 Hz, C-2' and C-6'); 131.3 (d, *J* = 9.4 Hz, C-2' and C-6'); 137.0 and 138.1 (C-7); 138.9 and 139.0 (C-5); 142.0 and 143.7 (C-8a); 166.2 and 166.3 (d, *J* = 254 Hz, C-4'); 195.7 and 196.0 (C=O) ppm.

IR (NaCl) ν: 3361.5 (N-H), 2923.4 (C-H), 2237.1 (CN), 1689.3 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{19}FN_2O$ (M = 322,38): C, 74.51; H, 5.94; N, 8.69. Found: C, 74.23; H, 5.75; N, 8.44.

(±)-(2*S**,4*S**)-Ethyl 4-cyano-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (7g)



7g

Prepared from tetrahydroquinoline **5m** (0.350 g, 1.1 mmol) and MMPP·$6H_2O$ (0.675 g, 1.36 mmol).

Reaction time: 1 h.

Yield: 0.181 g (60%). Orange oil.

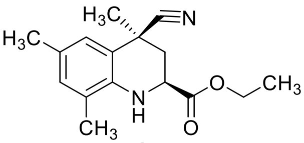
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.32 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); 1.73 (s, 3H, CH_3); 2.34 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.48 (dd, *J* = 13.1, 3.8 Hz, 1H, H-3eq); 3.76 (s, 3H, OCH_3); 4.02 (dd, *J* = 10.9, 3.8 Hz, 1H, H-2); 4.27 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3); 6.59 (d, *J* = 8.8 Hz, 1H, H-8); 6.74 (dd, *J* = 8.8, 2.8 Hz, 1H, H-7); 6.91 (d, *J* = 2.8 Hz, 1H, H-5) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.3 (OCH_2CH_3); 29.0 (CH_3); 34.6 (C-4); 35.6 (C-3); 50.1 (C-2); 56.0 (OCH_3); 62.1 (OCH_2CH_3); 112.4 (C-7*); 116.3 (C-5*); 116.9 (C-8*); 120.3 (CN); 123.9 (C-4a); 135.3 (C-8a); 152.7 (C-6); 171.8 (C=O) ppm.

IR (NaCl) ν: 3341.3 (N-H), 2922.7 (C-H), 2231.5 (CN), 1738.9 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{15}H_{18}N_2O_3$ (M = 274,32): C, 65.68; H, 6.61; N, 10.21. Found: C, 65.36; H, 6.43; N, 10.02.

(±)-(2*S**,4*S**)-Ethyl 4-cyano-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (7h)



7h

Prepared from tetrahydroquinoline **5n** (0.340 g, 1.1 mmol) and MMPP·6H$_2$O (0.660 g, 1.34 mmol).

Reaction time: 2 h.

Yield: 0.250 g (83%). Yellow oil.

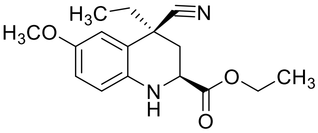
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.34 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); 1.72 (s, 3H, CH$_3$); 2.15 (s, 3H, ArCH$_3$); 2.24 (s, 3H, ArCH$_3$); 2.31 (t, *J* = 10.0 Hz, 1H, H-3ax); 2.50 (dd, *J* = 13.3, 3.6 Hz, 1H, H-3eq); 4.08 (dd, *J* = 11.5, 3.7 Hz, 1H, H-2); 4.33 (q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$ and NH); 6.86 (s, 1H, H-7); 7.08 (s, 1H, H-5) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 14.3 (OCH$_2$CH$_3$); 17.3 (CH$_3$); 20.5 (CH$_3$); 29.0 (CH$_3$); 34.7 (C-4); 35.4 (C-3); 50.0 (C-2); 62.2 (O*C*H$_2$CH$_3$); 119.0 (CN); 122.7 (C-4a); 124.2 (C-8); 125.7 (C-5); 127.2 (C-6); 131.3 (C-7); 136.9 (C-8a); 172.0 (C=O) ppm.

IR (NaCl) *ν*: 3348.9 (N-H), 2921.4 (C-H), 2241.9 (CN), 1733.2 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{16}H_{20}N_2O_2$ (M = 272,34): C, 70.56; H, 7.40; N, 10.29. Found: C, 70.43; H, 7.18; N, 10.12.

(±)-(2*S**,4*S**)-Ethyl 4-cyano-4-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate (7i)



7i

Prepared from tetrahydroquinoline **5o** (0.300 g, 0.9 mmol) and MMPP·6H$_2$O (0.554 g, 1.12 mmol).

Reaction time: 1 h.

Yield: 0.163 g (63%). Orange oil.

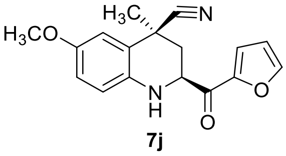
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.17 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$); 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$); 1.93 (m, 2H, C*H*$_2$CH$_3$); 2.19 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.60 (dd, *J* = 13.2, 3.9 Hz, 1H, H-3eq); 3.76 (s, 3H, OCH$_3$); 4.01 (dd, *J* = 11.8, 3.9 Hz, 1H, H-2); 4.27 (2 q, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$); 6.59 (d, *J* = 8.7 Hz, 1H, H-8); 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H, H-7); 6.89 (d, *J* = 2.8 Hz, 1H, H-5) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 9.3 (CH$_2$*C*H$_3$); 14.3 (OCH$_2$*C*H$_3$); 32.3 (*C*H$_2$CH$_3$); 32.9 (C-3); 40.2 (C-4); 49.9 (C-2); 56.0 (OCH$_3$); 62.1 (O*C*H$_2$CH$_3$); 112.9 (C-7*); 116.2 (C-5*); 116.6 (C-8); 119.5 (CN); 122.6 (C-4a); 135.2 (C-8a); 152.3 (C-6); 172.1 (C=O) ppm.

IR (NaCl) *ν*: 3350 (N-H), 2910 (C-H), 1739 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{16}H_{20}N_2O_3$ (M = 288,34): C, 66.65; H, 6.99; N, 9.72. Found: C, 66.42; H, 6.78; N, 9.59.

(±)-(2*S**,4*S**)-2-(2-Furylcarbonyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7j)



7j

Prepared from tetrahydroquinoline **5p** (0.430 g, 1.25 mmol) and MMPP·6H$_2$O (0.775 g, 1.6 mmol).

Reaction time: 0.4 h.

Yield: 0.289 g (78%). Yellow solid, mp: 101-102 °C.

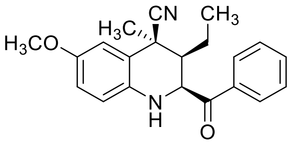
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.87 (s, 3H, CH$_3$); 2.15 (t, *J* = 12.5, 1H, H-3ax); 2.71 (dd, *J* = 12.7, 3.2 Hz, 1H, H-3eq); 3.81 (s, 3H, OCH$_3$); 4.57 (bs, 1H, NH); 4.76 (dd, *J* = 12.3, 3.0 Hz, 1H, H-2); 6.66 (dd, *J* = 3.6, 1.7 Hz, 1H, H-4´); 6.72 (d, *J* = 8.7 Hz, 1H, H-8); 6.81 (dd, *J* = 8.8, 2.7 Hz, 1H, H-7); 6.99 (d, *J* = 2.7 Hz, 1H, H-5); 7.41 (dd, *J* = 3.6, 0.6 Hz, 1H, H-3´); 7.69 (dd, *J* = 1.7, 0.6 Hz, 1H, H-5´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 28.4 (CH$_3$); 35.3 (C-4); 35.7 (C-3); 53.3 (C-2); 55.8 (OCH$_3$); 111.9 (C-4´); 112.8 (C-7); 116.2 (C-5); 117.5 (C-8); 118.9 (C-3´); 120.4 (CN); 123.7 (C-4a); 134.9 (C-8a); 146.8 (C-5´); 150.8 (C-2´); 152.5 (C-6); 186.5 (CO) ppm.

IR (NaCl) *ν*: 3370.3 (N-H), 2932.8 (C-H), 2232.4 (C≡N), 1676.1 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{17}H_{16}N_2O_3$ (M = 296.32): C, 68.91; H, 5.44; N, 9.45. Found: C, 68.65; H, 5.45; N, 9.39.

(±)-(2*S**,3R*,4*S**)-2-Benzoyl-3-ethyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7m')



7m'

Prepared from tetrahydroquinoline **5u'** (0.150 g, 0.393 mmol) and MMPP·$6H_2O$ (0.242 g, 0.490 mmol).

Reaction time: 4 h.

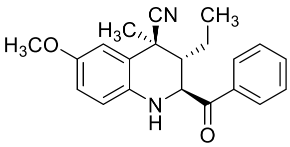
Yield: 0.090 g (69%). Yellow oil.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 0.64 (t, *J* = 7.6 Hz, 3H, $CH_2\mathit{CH_3}$); 0.81-0.89 (m, 2H, $C\mathit{H_2}CH_3$); 1.92 (s, 3H, CH_3); 2.24-2.29 (m, 1H, H-3); 3.78 (s, 3H, OCH_3); 4.84 (bs, 1H, NH); 5.07-5.10 (m, 1H, H-2); 6.70 (d, *J* = 8.8 Hz, 1H, H-8); 6.79 (dd, *J* = 8.8, 2.7 Hz, 1H, H-7); 7.00 (d, *J* = 2.7 Hz, 1H, H-5); 7.51-7-57 (m, 2H, H-3' and H-5'); 7.63-7.66 (m, 1H, H-4'); 7.89-7.90 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.1 ($CH_2\mathit{C}H_3$); 20.9 ($\mathit{C}H_2CH_3$); 30.7 (CH_3); 42.8 (C-4); 44.4 (C-3); 55.8 (C-2); 56.0 (OCH_3); 112.8 (C-7*); 116.2 (C-5*); 116.9 (C-8*); 119.2 (CN); 123.4 (C-4a); 128.1 (C-3' and C-5'); 129.3 (C-2' and C-6'); 134.1 (C-4'); 135.0 (C-1' and C-8a); 152.4 (C-6); 198.4 (C=O) ppm.

Elemental analysis (%): Calc. for $C_{21}H_{22}N_2O_2$ (M = 334,41): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.03; H, 6.38; N, 8.02.

(±)-(2*S**,3*S**,4*S**)-2-Benzoyl-3-ethyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7m'')



7m''

Prepared from tetrahydroquinoline **5u''** (0.150 g, 0.393 mmol) and MMPP·$6H_2O$ (0.242 g, 0.490 mmol).

Reaction time: 4 h.

Yield: 0.090 g (69%). Yellow oil.

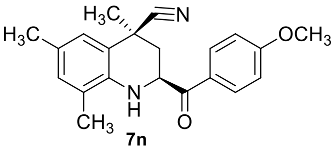
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 0.91 (t, *J* = 7.6 Hz, 3H, $CH_2\mathit{CH_3}$); 1.07-1.14 (m, 2H, $C\mathit{H_2}CH_3$); 1.66 (s, 3H, CH_3); 2.56 (td, *J* = 8.6, 3.9 Hz, 1H, H-3); 3.78 (s, 3H, OCH_3); 4.64 (d, *J* = 9.0 Hz, 1H, H-2); 6.54 (d, *J* = 8.7 Hz, 1H, H-8); 6.74 (dd, *J* = 8.7, 2.8 Hz, 1H, H-7); 7.01 (d, *J* = 2.8 Hz, 1H, H-5);

7.52 (t, *J* = 7.4 Hz, 2H, H-3’ and H-5’); 7.64 (t, *J* = 7.3 Hz, 1H, H-4’); 8.02-8.05 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 13.4 ($CH_2\mathit{C}H_3$); 22.5 (CH_3); 22.9 ($\mathit{C}H_2CH_3$); 40.0 (C-4); 43.6 (C-3); 56.0 (OCH_3); 58.3 (C-2); 112.0 (C-7*); 115.9 (C-5*); 117.0 (C-8*); 123.0 (CN); 123.4 (C-4a); 129.1 (C-3’ and C-5’); 129.2 (C-2’ and C-6’); 134.0 (C-4’); 134.6 (C-1’*); 135.6 (C-8a*); 153.1 (C-6); 198.5 (C=O) ppm.

Elemental analysis (%): Calc. for $C_{21}H_{22}N_2O_2$ (M = 334,42): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.11; H, 6.41; N, 8.11.

(±)-(2*S**,4*S**)-2-(4-Methoxybenzoyl)-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (7n)


7n

Prepared from tetrahydroquinoline **5h** (0.200 g, 0.527 mmol) and MMPP·$6H_2O$ (0.325 g, 0.658 mmol).

Reaction time: 3 h.

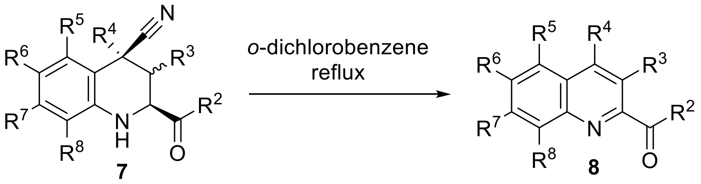
Yield: 0.123 g (70%). Yellow solid, mp: 119-121 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.87 (s, 3H, CH_3); 2.04 (t, *J* = 12.8 Hz, H-3ax); 2.20 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 2.51 (dd, *J* = 12.9, 3.1 Hz, H-3eq); 3.91 (s, 3H, OCH_3); 4.59 (s, 1H, NH); 4.96 (dd, *J* = 12.6, 2.9 Hz, 1H, H-2); 6.90 (s, 1H, H-7); 6.98-7.05 (m, 2H, H-3’ and H-5’); 7.13 (s, 1H, H-5); 7.89-7.98 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 17.5 (CH_3); 20.5 (CH_3); 28.7 (CH_3); 35.6 (C-3); 37.0 (C-4); 52.4 (C-2); 55.8 (OCH_3); 114.5 (C-3’ and C-5’); 119.2 (C-4a); 123.9 (CN); 124.2 (C-6); 125.6 (C-5); 127.1 (C-1’); 127.2 (C-8); 130.7 (C-2’ and C-6’); 131.3 (C-7); 137.1 (C-8a); 164.3 (C-4’); 196.2 (C=O) ppm.

Elemental analysis (%): Calc. for $C_{21}H_{22}N_2O_2$ (M = 334,42): C, 75.42; H, 6.63; N, 8.38. Found: C, 75.08; H, 6.33; N, 8.22.

10.4.1.2 - Synthesis of 2-acylquinoniles 8a-j and 8m-o

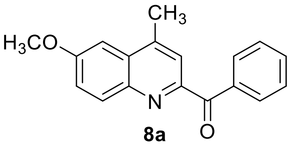


Cmpd	**R²**	**R³**	**R⁴**	**R⁵**	**R⁶**	**R⁷**	**R⁸**	**Yield (%)**
8a	C_6H_5	H	CH_3	H	6-OCH_3	H	H	90
8b	4-FC_6H_4	H	CH_3	H	6-OCH_3	H	H	97
8c	4-$OCH_3C_6H_4$	H	CH_3	H	6-OCH_3	H	H	88
8d	C_6H_5	H	CH_2CH_3	H	6-OCH_3	H	H	98[a]
8e	C_6H_5	H	CH_3	H	CH_3	H	CH_3	95
8f	4-FC_6H_4	H	CH_3	CH_3	H	CH_3	H	91
8g	OEt	H	CH_3	H	6-OCH_3	H	H	97
8h	OEt	H	CH_3	H	CH_3	H	CH_3	97
8i	OEt	H	CH_2CH_3	H	6-OCH_3	H	H	98
8j	2-furyl	H	CH_3	H	6-OCH_3	H	H	98
8m	C_6H_5	CH_2CH_3	CH_3	H	6-OCH_3	H	H	87
8n	4-$OCH_3C_6H_4$	H	CH_3	H	CH_3	H	CH_3	83
8o	4-FC_6H_4	H	CH_2CH_3	H	CH_3	H	CH_3	62[b]
8p	C_6H_5	H	CH_3	CH_3	H	CH_3	H	65[c]

[a] Overall yield from tetrahydroquinoline **5d**. [b] Overall yield from tetrahydroquinoline **5l**. [c] Overall yield from tetrahydroquinoline **5r**.

Solutions of compounds **7** (0.4 mmol) in *o*-dichlorobenzene (5 mL) were refluxed for 24 h. The reaction mixtures were allowed to reach room temperature and were then concentrated under reduced pressure. The oily residues were purified by flash column chromatography, eluting with mixtures of petroleum ether and ethyl acetate, to give the desired products **8**.

2-Benzoyl-6-methoxy-4-methylquinoline (8a)



8a

Prepared from nitrile derivative **7a** (0.180 g, 0.593 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.150 g (90%). Yellow solid, mp: 117-119 °C.

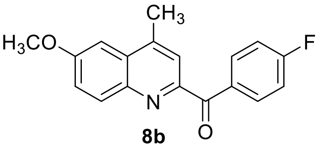
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.75 (s, 3H, CH_3); 4.00 (s, 3H, OCH_3); 7.24 (m, 1H, H-5); 7.42 (dd, *J* = 9.2, 2.4 Hz, 1H, H-7); 7.50 (t, *J* = 7.4 Hz, 2H, H-3' and H-5'); 7.61 (t, *J* = 7.3 Hz, 1H, H-4'); 7.96 (s, 1H, H-3); 8.09 (d, *J* = 9.2 Hz, 1H, H-8); 8.22 (d, *J* = 7.3 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 19.3 (CH_3); 55.8 (OCH_3); 101.8 (C-5); 121.9 (C-3); 122.4 (C-7); 128.2 (C-3' and C-5'); 130.4 (C-4a); 131.6 (C-2' and C-6'); 132.9 (C-8); 132.9 (C-4'); 136.6 (C-1'); 142.7 (C-4); 143.8 (C-8a); 152.1 (C-2); 159.4 (C-6); 194.2 (C=O) ppm.

IR (NaCl) *ν*: 2924.3 (C-H), 1657.9 (C=O), 1619.8 cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{15}NO_2$ (M = 277.32): C, 77.96; H, 5.45; N, 5.05. Found: C, 77.69; H, 5.41; N, 4.95.

2-(4-Fluorobenzoyl)-6-methoxy-4-methylquinoline (8b)



8b

Prepared from nitrile derivative **7b** (0.180 g, 0.553 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.158 g (97%). Pale yellow solid, mp: 143-144 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.75 (s, 3H, CH_3); 4.00 (s, 3H, OCH_3); 7.14-7.21 (m, 2H, H-3' and H-5'); 7.24 (d, *J* = 2.7 Hz, 1H, H-5); 7.42 (dd, *J* = 9.2, 2.7 Hz, 1H, H-7); 7.97 (s, 1H, H-3); 8.08 (d, *J* = 9.2 Hz, 1H, H-8); 8.29-8.35 (m, 2H, H2' and H-6') ppm.

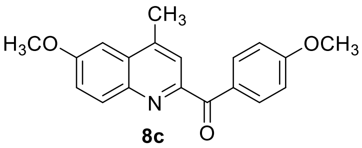
^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 19.3 (CH_3); 55.8 (OCH_3); 101.8 (C-5); 115.2 (d, *J* = 21.7 Hz, C-3' and C-5'); 121.9 (C-3*); 122.5 (C-7*); 130.5 (C-4a); 132.8 (C-8); 132.9 (d, *J* = 2.9 Hz, C-1');

134.3 (d, *J* = 9.2 Hz, C-2' and C-6'); 142.6 (C-4*); 144.0 (C-8a*); 151.9 (C-2); 159.5 (C-6); 165.8 (d, *J* = 254.8 Hz, C-4'); 192.4 (C=O) ppm.

IR (NaCl) *ν*: 2921.4 (C-H), 1657.1 (C=O), 1620.8 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{14}FNO_2$ (M = 295.31): C, 73.21; H, 4.78; N, 4.74. Found: C, 73.13; H, 5.00; N, 4.49.

6-Methoxy-2-(4-methoxybenzoyl)-4-methylquinoline (8c)



8c

Prepared from nitrile derivative **7c** (0.250 g, 0.743 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.200 g (88%). White solid, mp: 142-144 °C.

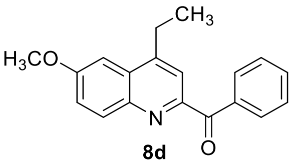
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.77 (s, 3H, CH_3); 3.93 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 7.02 (d, *J* = 8.7 Hz, 2H, H-3' and H-5'); 7.28 (d, *J* = 2.2 Hz, 1H, H-5); 7.44 (dd, *J* = 9.2, 2.2 Hz, 1H, H-7); 7.94 (s, 1H, H-3); 8.12 (d, *J* = 9.2 Hz, 1H, H-8); 8.31 (d, *J* = 8.7 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 19.3 (CH_3); 55.6 (OCH_3); 55.8 (OCH_3); 101.8 (C-5); 113.6 (C-3' and C-5'); 122.0 (C-3*); 122.3 (C-7*); 129.4 (C-4a*); 130.3 (C-1'*); 132.7 (C-8); 134.0 (C-2' and C-6'); 142.6 (C-4*); 143.8 (C-8a*); 152.8 (C-2); 159.2 (C-6); 163.7 (C-4'); 192.7 (C=O) ppm.

IR (NaCl) *ν*: 2922.1 (C-H), 1646.5 (C=O), 1620.4 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{17}NO_3$ (M = 307.34): C, 74.25; H, 5.58; N, 4.56. Found: C, 74.08; H, 5.84; N, 4.31.

2-Benzoyl-4-ethyl-6-methoxyquinoline (8d)



8d

Prepared from tetrahydroquinoline **5d** (0.250 g, 0.684 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.195 g (98%). Yellow solid, mp: 116-118 °C.

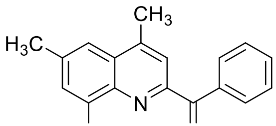
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.47 (t, J = 7.5 Hz, 3H, CH_2CH_3); 3.15 (q, J = 7.6 Hz, 2H, CH_2CH_3); 3.99 (s, 3H, OCH_3); 7.30 (d, J = 2.7 Hz, 1H, H-5); 7.41 (dd, J = 9.2, 2.8 Hz, 1H, H-7); 7.44-7.53 (m, 2H, H-3' and H-5'); 7.61 (m, 1H, H-4'); 7.98 (s, 1H, H-3); 8.11 (d, J = 9.2 Hz, 1H, H-8); 8.20-8.24 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 13.6 (CH_3); 25.5 (CH_2); 55.8 (OCH_3); 101.5 (C-5); 119.8 (C-3*); 122.2 (C-7*); 128.2 (C-3' and C-5'); 128.6 (C-4a); 130.3 (C-8); 131.6 (C-2' and C-6'); 132.9 (C-4'); 133.0 (C-1'); 142.9 (C-8a); 149.3 (C-4); 152.3 (C-2); 159.4 (C-6); 194.3 (C=O) ppm.

IR (NaCl) ν: 2868.5 (C-H), 1647.8 (C=O), 1619.7 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{17}NO_2$ (M = 291.34): C, 78.33; H, 5.88; N, 4.81. Found: C, 78.01; H, 6.04; N, 4.59.

2-Benzoyl-4,6,8-trimethylquinoline (8e)



8e

Prepared from nitrile derivative **7e** (0.320 g, 1.051 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.275 g (95%). Orange solid, mp: 119-120 °C.

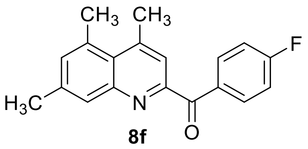
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.55 (s, 3H, CH_3); 2.73 (s, 3H, CH_3); 2.75 (s, 3H, CH_3); 7.47-7.53 (m, 3H, H-5, H-3' and H-5'); 7.62 (m, 1H, H-4'); 7.66 (s, 1H, H-7); 8.00 (s, 1H, H-3); 8.33-8.37 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 18.4 (CH_3); 19.4 (CH_3); 22.3 (CH_3); 120.7 (C-3*); 121.2 (C-5*); 127.9 (C-3' and C-5'); 129.2 (C-4a); 131.9 (C-2' and C-6'); 132.2 (C-4'*); 132.7 (C-7*); 136.9 (C-1'*); 138.3 (C-6*); 139.1 (C-8*); 144.4 (C-4); 144.8 (C-8a); 151.9 (C-2); 194.0 (C=O) ppm.

IR (NaCl) ν: 2920.5 (C-H), 1657.5 (C=O), 1619.8 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{17}NO$ (M = 275.34): C, 82.88; H, 6.22; N, 5.09. Found: C, 82.56; H, 6.28; N, 5.00.

2-(4-Fluorobenzoyl)-4,5,7-trimethylquinoline (8f)



8f

Prepared from nitrile derivative **7f** (0.320 g, 0.993 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.270 g (91%). Orange solid, mp: 128-131 °C.

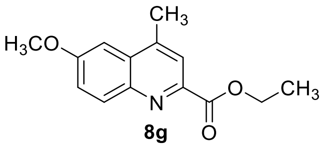
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.49 (s, 3H, CH_3); 2.91 (s, 3H, CH_3); 2.98 (s, 3H, CH_3); 7.17 (t, *J* = 8.7 Hz, 2H, H-3’ and H-5’); 7.26 (s, 1H, H-3); 7.79 (s, 1H, H-8); 7.81 (s, 1H, H-6); 8.29-8.35 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 21.3 (CH_3); 25.5 (2 x CH_3); 115.3 (d, *J* = 21.7 Hz, C-3’ and C-5’); 122.8 (C-3); 127.5 (C-4a); 129.2 (C-8); 132.7 (d, *J* = 3.1 Hz, C-1’); 133.9 (C-6); 134.3 (d, *J* = 9.2 Hz, C-2’ and C-6’); 135.3 (C-5*); 139.3 (C-7*); 146.9 (C-4); 149.0 (C-8a); 153.4 (C-2); 165.9 (d, *J* = 255.2 Hz, C-4’); 192.4 (C=O) ppm.

IR (NaCl) *v*: 2925.0 (C-H), 1660.4 (C=O), 1623.8 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{16}FNO$ (M = 293.33): C, 77.80; H, 5.50; N, 4.77. Found: C, 77.96; H, 5.33; N, 4.59.

Ethyl 6-methoxy-4-methylquinoline-2-carboxylate (8g)



8g

Prepared from nitrile derivative **7g** (0.150 g, 0.547 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.135 g (97%). Yellow solid, mp: 131-133 °C.

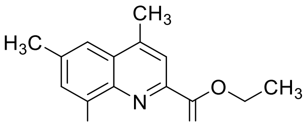
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.48 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3); 2.71 (s, 3H, CH_3); 3.97 (s, 3H, OCH_3); 4.53 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3); 7.18 (d, *J* = 2.7 Hz, 1H, H-5); 7.41 (dd, *J* = 9.3, 2.8 Hz, 1H, H-7); 8.01 (s, 1H, H-3); 8.20 (d, *J* = 9.3 Hz, 1H, H-8) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 14.5 (OCH$_2$*C*H$_3$); 19.2 (CH$_3$); 55.7 (OCH$_3$); 62.2 (O*C*H$_2$CH$_3$); 101.5 (C-5); 122.2 (C-3*); 122.6 (C-7*); 130.7 (C-4a); 133.1 (C-8); 143.5 (C-8a*); 144.0 (C-4*); 145.5 (C-2); 159.4 (C-6); 165.9 (C=O) ppm.

IR (NaCl) *v*: 2920.6 (C-H), 1731.8 (C=O), 1107.6 (C-O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{14}H_{15}NO_3$ (M = 245.27): C, 68.56; H, 6.16; N, 5.71. Found: C, 68.24; H, 5.98; N, 5.62.

Ethyl 4,6,8-trimethylquinoline-2-carboxylate (8h)



8h

Prepared from nitrile derivative **7h** (0.230 g, 0.844 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.201 g (97%). Yellow solid, mp: 125-127 °C.

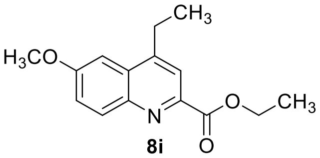
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.48 (t, *J* = 7.1 Hz, 3H, OCH$_2$CH$_3$); 2.53 (s, 3H, CH$_3$); 2.71 (s, 3H, CH$_3$); 2.85 (s, 3H, CH$_3$); 4.50 (q, *J* = 7.1 Hz, 2H, OCH$_2$CH$_3$); 7.45 (s, 1H, H-5); 7.61 (s, 1H, H-7); 7.96 (s, 1H, H-3) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 14.5 (OCH$_2$*C*H$_3$); 18.2 (CH$_3$); 19.3 (CH$_3$); 22.2 (CH$_3$); 61.9 (O*C*H$_2$CH$_3$); 120.6 (C-3*); 121.6 (C-5*); 129.5 (C-4a); 132.4 (C-7); 138.2 (C-6*); 139.0 (C-8*); 144.8 (C-4); 145.3 (C-8a); 145.8 (C-2); 166.2 (C=O) ppm.

IR (NaCl) *v*: 2929.7 (C-H), 1704.5 (C=O), 1118.0 (C-O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{15}H_{17}NO_2$ (M = 243.30): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.72; H, 6.83; N, 6.06.

Ethyl 4-ethyl-6-methoxyquinoline-2-carboxylate (8i)



8i

Prepared from nitrile derivative **7i** (0.150 g, 0.520 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.132 g (98%). Orange oil.

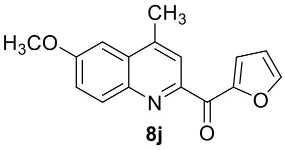
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.43 (t, J = 7.5 Hz, 3H, CH$_2$CH$_3$); 1.48 (t, J = 7.1 Hz, 3H, OCH$_2$CH$_3$); 3.11 (q, J = 7.6 Hz, 2H, CH$_2$CH$_3$); 3.97 (s, 3H, OCH$_3$); 4.54 (q, J = 7.1 Hz, 2H, OCH$_2$CH$_3$); 7.25 (d, J = 2.7 Hz, 1H, H-5); 7.40 (dd, J = 9.3, 2.8 Hz, 1H, H-7); 8.03 (s, 1H, H-3); 8.21 (d, J = 9.3 Hz, 1H, H-8) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 13.6 (OCH$_2$*C*H$_3$); 14.5 (CH$_2$*C*H$_3$); 25.4 (*C*H$_2$CH$_3$); 55.7 (OCH$_3$); 62.2 (O*C*H$_2$CH$_3$); 101.3 (C-5); 120.1 (C-3); 122.4 (C-7); 130.0 (C-4a); 133.2 (C-8); 143.8 (C-8a); 145.7 (C-4); 149.5 (C-2); 159.4 (C-6); 166.1 (C=O) ppm.

IR (NaCl) ν: 2927.4 (C-H), 1715.7 (C=O), 1111.1 (C-O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{15}H_{17}NO_3$ (M = 259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.23; H, 6.42; N, 5.21.

2-(2-Furylcarbonyl)-6-methoxy-4-methylquinoline (8j)



8j

Prepared from nitrile derivative **7j** (0.260 g, 0.877 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.230 g (98%). Yellow solid, mp: 150-152 °C.

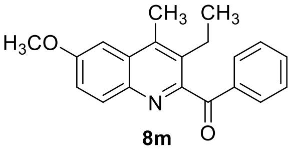
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.75 (s, 3H, CH$_3$); 4.01 (s, 3H, OCH$_3$); 6.67 (dd, J = 3.5, 1.7 Hz, 1H, H-4´); 7.23 (d, J = 2.7 Hz, 1H, H-5); 7.45 (dd, J = 9.2, 2.7 Hz, 1H, H-7); 7.79 (dd, J = 1.6, 0.7 Hz, 1H, H-5´); 8.09 (s, 1H, H-3); 8.13 (d, J = 9.2 Hz, 1H, H-8); 8.29 (dd, J = 3.5, 0.7 Hz, 1H, H-3´) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 19.0 (CH$_3$); 55.6 (OCH$_3$); 101.6 (C-5); 112.4 (C-4´); 120.8 (C-3); 122.3 (C-7); 124.4 (C-3´); 130.6 (C-4a); 132.5 (C-8); 142.7 (C-4); 143.6 (C-8a); 147.5 (C-5´); 150.8 (C-2); 151.2 (C-2´); 159.3 (C-6); 179.6 (CO) ppm.

IR (NaCl) ν: 2939.4 (C-H), 1620.4 (C=N) cm^{-1}.

Elemental analysis (%): Calc. For $C_{16}H_{13}NO_3$ (M = 267.28): C, 71.90; H, 4.90; N, 5.24. Found: C, 71.76; H, 4.87; N, 5.14.

2-Benzoyl-3-ethyl-6-methoxy-4-methylquinoline (8m)



8m

Prepared from nitrile derivative **7m'** and **7m''** (0.080 g, 0.24 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.064 g (87%). White solid, mp: 125-128 °C.

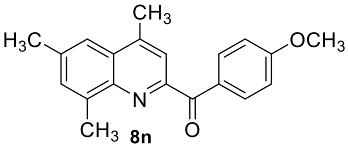
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.19 (t, J = 7.5 Hz, 3H, CH_2CH_3); 2.68 (s, 3H, CH_3); 2.81 (q, J = 7.5 Hz, 2H, CH_2CH_3); 3.98 (s, 3H, OCH_3); 7.25 (d, J = 2.6 Hz, 1H, H-5); 7.34 (dd, J = 9.2, 2.7 Hz, 1H, H-7); 7.44 (t, J = 7.5 Hz, 2H, H-3' and H-5'); 7.59 (m, 1H, H-4'); 7.90 (d, J = 7.0 Hz, 2H, H-2' and H-6'); 7.96 (d, J = 9.2 Hz, 1H, H-8) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.2 (CH_3); 15.3 (CH_3); 23.0 (CH_2); 55.7 (OCH_3); 101.9 (C-5); 121.3 (C-7); 128.6 (C-3' and C-5'); 129.6 (C-4a); 130.8 (C-2' and C-6'); 131.8 (C-8); 132.8 (C-3); 133.8 (C-4'); 136.5 (C-1'*); 141.1 (C-4* and C-8a*); 154.8 (C-2); 158.6 (C-6); 196.3 (CO) ppm.

IR (NaCl) ν: 2921.9 (C-H), 1674.0 (C=O); 1616.6 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{19}NO_2$ (M = 305.37): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.32; H, 6.01; N, 4.27.

2-Methoxybenzoyl-4,6,8-trimethylquinoline (8n)



8n

Prepared from nitrile derivative **7n** (0.100 g, 0.299 mmol).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

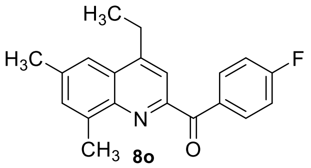
Yield: 0.075 g (83%). White solid, mp: 126-128 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.56 (s, 3H, CH_3); 2.75 (s, 3H, CH_3); 2.76 (s, 3H, CH_3); 3.91 (s, 3H, OCH_3); 6.99 (dd, J = 7.0, 2.0 Hz, 2H, H-3' and H-5'); 7.47 (s, 1H, H-7); 7.66 (s, 1H, H-5); 7.96 (s, 1H, H-3); 8.43 (dd, J = 7.0, 2.0 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 18.5 (CH_3); 19.4 (CH_3); 22.3 (CH_3); 55.6 (OCH_3); 113.3 (C-3' and C-5'); 120.7 (C-3); 121.3 (C-5); 129.1 (C-4a); 129.6 (C-1'); 132.2 (C-7); 134.3 (C-2' and C-6'); 138.0 (C-6); 138.9 (C-8); 144.3 (C-4); 144.7 (C-8a); 152.5 (C-2); 163.4 (C-4'); 192.4 (C=O) ppm.

Elemental Analysis: Calc. for $C_{20}H_{19}NO_2$ (M = 305,38): C, 78.66; H, 6.27; N, 4.59. Found: C, 78.39; H, 6.01; N, 4.44.

4-Ethyl-6,8-dimethyl-2-(4-fluorobenzoyl)quinoline (8o)



8o

Prepared from tetrahydroquinoline **5l** (0.100 g, 0.299 mmol) and MMPP·6H_2O (0.185 g).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

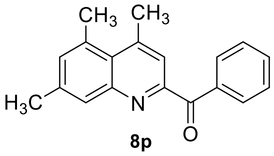
Yield: 0.075 g (62%). Yellow solid, mp: 133-135 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.44 (t, J = 7.5 Hz, 3H, CH_2CH_3); 2.56 (s, 3H, CH_3); 2.74 (s, 3H, CH_3); 3.16 (q, J = 7.5 Hz, 2H, CH_2CH_3); 7.12-7.24 (m, 2H, H-3' and H-5'); 7.47 (s, 1H, H-7); 7.71 (s, 1H, H-5); 8.03 (s, 1H, H-3); 8.41-8.47 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.2 (CH_2CH_3); 18.5 (CH_3); 22.3 (CH_3); 25.6 (CH_2CH_3); 115.0 (d, J = 22.5 Hz, C-3' and C-5'); 119.2 (C-3); 120.3 (C-5); 128.4 (C-4a); 132.2 (C-7); 133.2 (d, J = 3.0 Hz, C-1'); 134.5 (d, J = 9.0 Hz, C-2' and C-6'); 138.4 (C-6); 139.1 (C-8); 144.6 (C-4); 150.5 (C-8a); 151.9 (C-2); 165.7 (d, J = 252.0 Hz, C-4'); 192.3 (C=O) ppm.

Elemental Analysis: Calc. for $C_{20}H_{18}FNO$ (M = 307.37): C, 78.15; H, 5.90; N, 4.56. Found: C, 77.95; H, 5.74; N, 4.32.

2-Benzoyl-4,5,7-trimethylquinoline (8p)



8p

Prepared from tetrahydroquinoline **5r** (0.100 g, 0.286 mmol) and MMPP·6H_2O (0.176 g).

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

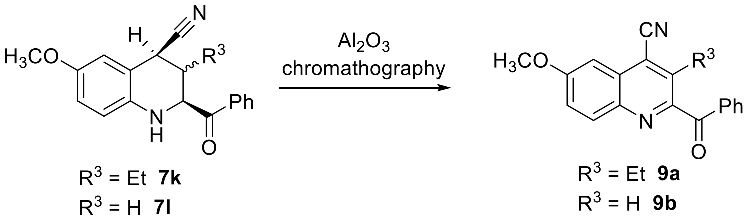
Yield: 0.052 g (65%). White solid, mp: 133-135 °C.

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.56(s, 3H, CH$_3$); 2.74 (s, 3H, CH$_3$); 2.76 (s, 3H, CH$_3$); 7.47-7.66 (m, 5H, H-3', H-4', H-5', H-6 and H-8); 8.00 (s, 1H, H-3); 8.35 (d, J = 7.4 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 21.3 (CH$_3$); 25.5 (2 x CH$_3$); 122.8 (C-3); 127.5 (C-4a); 128.2 (C-3' and C-5'); 129.2 (C-8); 131.6 (C-2' and C-6'); 133.1 (C-6); 133.8 (C-4'); 135.3 (C-5); 136.4 (C-1'); 139.2 (C-4); 146.8 (C-7); 149.1 (C-8a); 153.6 (C-2); 194.3 (C=O) ppm.

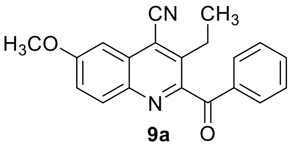
Elemental Analysis: Calc. for $C_{19}H_{17}NO$ (M = 275.35): C, 82.88; H, 6.22; N, 5.09. Found: C, 82.55; H, 6.04; N, 4.91.

10.4.2 - Synthesis of 2-acylquinoline-4-carbonitriles 9a-b



The crude nitriles **7k,l** obtained by the general method described in the section 10.4.1.1, were dissolved in CH_2Cl_2 (5 mL), to which alumina (100 mg) was added. The solvent was evaporated and the resulting solid was loaded onto a cartridge that was attached to the flash chromatography system. Chromatography on alumina furnished quinolines **9a** and **9b**, respectively.

2-Benzoyl-3-ethyl-6-methoxyquinoline-4-carbonitrile (9a)



9a

Prepared from tetrahydroquinoline **5s** (0.070 g, 0.191 mmol) and MMPP (0.118 g).

Reaction time: 4 h.

Purification: flash chromatography of crude **7k** on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.041 g (69%). White solid, mp: 138-141 °C.

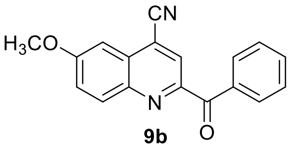
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.34 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); 3.10 (q, *J* = 7.5 Hz, 2H, CH_2CH_3); 4.03 (s, 3H, OCH_3); 7.37-7.53 (m, 4H, H-3', H-5', H-5 and H-7); 7.63 (m, 1H, H-4'); 7.91 (d, *J* = 7.1 Hz, 2H, H-2' and H-6'); 8.02 (d, *J* = 9.1 Hz, H-8) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 15.9 (CH_3); 25.2 (CH_2); 56.2 (OCH_3); 102.1 (C-5); 115.1 (C-4); 117.6 (CN); 124.2 (C-7); 128.5 (C-4a); 128.7 (C-3' and C-5'); 130.9 (C-2' and C-6'); 132.1 (C-8*); 134.2 (C-4'); 135.9 (C-3*); 140.8 (C-1'*); 141.3 (C-8a*); 153.2 (C-2); 161.1 (C-6); 193.8 (CO) ppm.

IR (NaCl) ν: 2927.5 (C-H), 2225.1 (CN), 1664.8 (C=O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{16}N_2O_2$ (M = 316.35): C, 75.93; H, 5.10; N, 8.86. Found: C, 75.75; H, 5.31; N, 8.52.

2-Benzoyl-6-methoxyquinoline-4-carbonitrile (9b)



9b

Prepared from tetrahydroquinoline **5t** (0.060 g, 0.178 mmol) and MMPP (0.110 g).

Reaction time: 2 h.

Purification: flash chromatography of crude **7l** on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.037 g (72%). Yellow solid, mp: 140-142 °C.

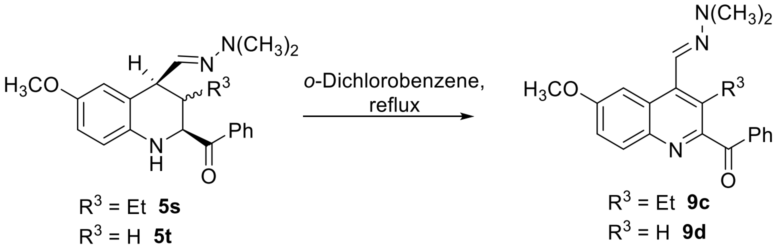
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 3.99 (s, 3H, OCH_3); 7.38 (d, *J* = 2.7 Hz, 1H, H-5); 7.41-7.51 (m, 3H, H-3', H-5' and H-7); 7.59 (m, 1H, H-4'); 8.14 (m, 3H, H-2', H-6' and H-8); 8.40 (s, 1H, H-3) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 56.3 (OCH_3); 102.3 (C-5); 115.8 (C-4); 118.0 (CN); 125.3 (C-7*); 125.6 (C-3*); 128.4 (C-3' and C-5'); 128.6 (C-4a); 131.5 (C-2' and C-6'); 133.2 (C-8*); 133.5 (C-4'*); 135.7 (C-1'); 142.9 (C-8a); 151.3 (C-2); 161.8 (C-6); 191.8 (CO) ppm.

IR (NaCl) ν: 2920.4 (C-H), 2229.9 (CN), 1664.4 (C=O) cm^{-1}.

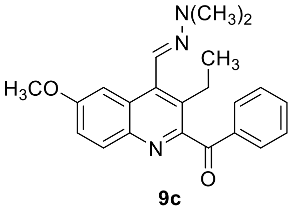
Elemental analysis (%): Calc. for $C_{18}H_{12}N_2O_2$ (M = 288.30): C, 74.99; H, 4.20; N, 9.72. Found: C, 74.82; H, 4.02; N, 9.64.

10.4.3 - Synthesis of 2-acyl-4-(dimethylhydrazonomethyl)quinolines 9c,d



A solution of the suitable hydrazones **5s** or **5t** in *o*-dichlorobenzene (5 mL) was refluxed until no starting material was detected by TLC. The reaction mixture was allowed to reach room temperature and the solvent was evaporated under reduced pressure. The oily residue was purified by flash column chromatography, eluting with a 9:1 (v/v) mixture of petroleum ether and ethyl acetate, to give compounds **9c**,**d**.

2-Benzoyl-4-((2,2-dimethylhydrazono)methyl)-3-ethyl-6-methoxyquinoline (9c)



9c

Prepared from tetrahydroquinoline **5s** (0.070 g, 0.191 mmol).

Reaction time: 6 h.

Yield: 0.048 g (70%). Yellow solid, mp: 109-111 °C.

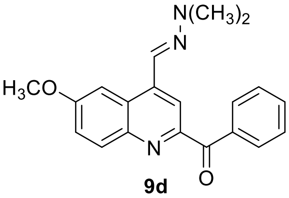
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.21 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$); 2.87 (q, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_3$); 3.17 (s, 6H, N(CH$_3$)$_2$); 3.95 (s, 3H, OCH$_3$); 7.32 (dd, *J* = 9.2, 2.8 Hz, 1H, H-7); 7.43 (d, *J* = 7.3 Hz, 2H, H-3' and H-5'); 7.56 (m, 1H, H-4'); 7.63 (s, 1H, CH=N); 7.88-7.95 (m, 3H, H-2', H-6' and H-8); 8.28 (d, *J* = 2.8 Hz, 1H, H-5) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 15.5 (CH$_3$); 22.7 (CH$_2$); 42.7 (N(CH$_3$)$_2$); 55.5 (OCH$_3$); 104.5 (C-5); 121.5 (C-7); 127.1 (C-4a); 127.4 (CH=N); 128.6 (C-3' and C-5'); 130.8 (C-2' and C-6'); 131.4 (C-8); 131.9 (C-3*); 133.8 (C-4'); 136.5 (C-4*); 137.4 (C-1'*); 142.4 (C-8a); 154.9 (C-2); 158.9 (C-6); 196.2 (CO) ppm.

IR (NaCl) ν: 2920.9 (C-H), 1669.6 (C=O); 1616.3 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{23}N_3O_2$ (M = 361.44): C, 73.11; H, 6.41; N, 11.63. Found: C, 73.27; H, 6.61; N, 11.34.

2-Benzoyl-4-((2,2-dimethylhydrazono)methyl)-6-methoxyquinoline (9d)



9d

Prepared from tetrahydroquinoline **5t** (0.070 g, 0.207 mmol).

Reaction time: 3 h.

Yield: 0.060 g (88%). Yellow oil.

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 3.19 (s, 6H, N(CH$_3$)$_2$); 3.99 (s, 3H, OCH$_3$); 7.40 (dd, *J* = 9.3, 2.8 Hz, 1H, H-7); 7.50 (t, *J* = 7.3 Hz, 2H, H-3' and H-5'); 7.58-7.61 (m, 2H, H-4' and CH=N); 8.08 (d, *J* = 9.2 Hz, 1H, H-8); 8.20-8.24 (m, 3H, H-2', H-6' and H-3); 8.27 (d, *J* = 2.8 Hz, 1H, H-5) ppm.

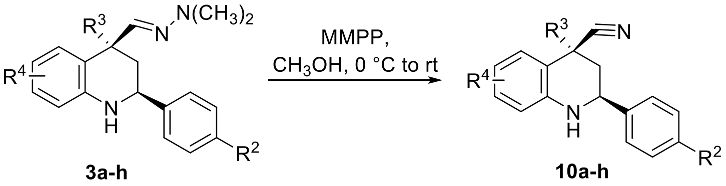
^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 42.7 (N(CH$_3$)$_2$); 55.6 (OCH$_3$); 103.5 (C-5); 118.8 (C-3); 122.1 (C-7); 127.0 (C-4a); 127.5 (CH=N); 128.2 (C-3' and C-5'); 131.6 (C-2' and C-6'); 132.6 (C-8); 132.9 (C-4'); 136.7 (C-4*); 139.9 (C-1'*); 144.0 (C-8a); 152.3 (C-2); 159.6 (C-6); 194.4 (CO) ppm.

IR (NaCl) ν: 2922.8 (C-H), 1653.9 (C=O); 1616.3 (C=N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{19}N_3O_2$ (M = 333.38): C, 72.05; H, 5.74; N, 12.60. Found: 72.10; H, 5.86; N, 12.83.

10.4.4 - Synthesis of 2-arylquinolines

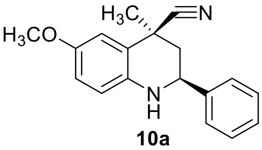
10.4.4.1 - Synthesis of 2-aryl-1,2,3,4-tetrahydroquinolin-4-carbonitrile derivatives 10a-h



Nitriles **10a-h** were prepared from compounds **3a-h** following the procedure described in section 10.4.1.1**.**

Cmpd	R^2	R^3	R^4	Yield (%)
10a	H	CH_3	6-OCH_3	70
10b	Cl	CH_3	6-OCH_3	97
10c	OCH_3	CH_3	6-OCH_3	93
10d	CH_3	CH_3	6-OCH_3	86
10e	H	CH_3	6,8-$(CH_3)_2$	84
10f	OCH_3	CH_3	6-CH_3	98
10g	H	CH_2CH_3	6,8-$(CH_3)_2$	77
10h	CH_3	CH_3	5,7-$(OCH_3)_2$	62

(±)-(2*S,4*S**)-6-Methoxy-4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10a)**



10a

Prepared from tetrahydroquinoline **3a** (0.323 g, 1 mmol) and MMPP·6H_2O (0.618 g, 1.25 mmol).

Reaction time: 0.4 h.

Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.195 g (70%). Yellow solid, mp: 115-117 °C.

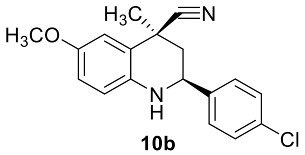
$C_{18}H_{18}N_2O$ (M = 278.36)

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.82 (s, 3H, CH_3); 2.22 (dd, *J* = 13.1, 2.8 Hz, 1H, H-3eq); 2.45 (t, *J* = 12.9 Hz, 1H, H-3ax); 3.79 (s, 3H, OCH_3); 3.95 (s, 1H, NH); 4.40 (dd, *J* = 11.8, 2.8 Hz, 1H, H-2); 6.54 (d, *J* = 8.7 Hz, 1H, H-8); 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H, H-7); 6.97 (d, *J* = 2.8 Hz, 1H, H-5); 7.34-7.44 (m, 5H, H-2', H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 30.7 (CH_3); 35.4 (C-4); 42.1 (C-3); 52.2 (C-2); 56.0 (OCH_3); 112.9 (C-7*); 116.2 (C-5*); 116.4 (C-8*); 120.6 (CN); 124.6 (C-4a); 126.9 (C-2' and C-6'); 128.4 (C-4'); 129.0 (C-3' and C-5'); 137.2 (C-8a); 142.2 (C-1'); 152.5 (C-6) ppm.

IR (Nujol) *ν*: 3380 (N-H), 2665 (C-H), 1715 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-2-(4-Chlorophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10b)



10b

Prepared from tetrahydroquinoline **3b** (0.357 g, 1 mmol) and MMPP·$6H_2O$ (0.618 g, 1.25 mmol).

Reaction time: 1 h.

Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.303 g (97%). Yellow solid, mp: 158-159 °C.

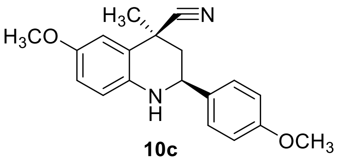
$C_{18}H_{17}ClN_2O$ (M = 312.80)

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.81 (s, 3H, CH_3); 2.18 (dd, *J* = 13.2, 2.8 Hz, 1H, H-3eq); 2.39 (t, *J* = 12.4 Hz, 1H, H-3ax); 3.78 (s, 3H, OCH_3); 4.38 (dd, *J* = 11.7, 2.8 Hz, 1H, H-2); 6.56 (d, *J* = 8.8 Hz, 1H, H-8); 6.75 (dd, *J* = 8.8, 2.8 Hz, 1H, H-7); 6.96 (d, *J* = 2.8 Hz, 1H, H-5); 7.36 (s, 4H, H-2', H-3', H-5' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 30.7 (CH_3); 35.4 (C-4); 42.1 (C-3); 51.6 (C-2); 56.0 (OCH_3); 112.9 (C-7*); 116.2 (C-5*); 116.5 (C-8*); 120.6 (CN); 124.4 (C-4a); 128.3 (C-2' and C-6'); 129.1 (C-3' and C-5'); 134.0 (C-4'); 136.9 (C-8a); 140.8 (C-1'); 152.6 (C-6) ppm.

IR (Nujol) *ν*: 3260 (N-H), 2660 (C-H), 2000 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-6-Methoxy-2-(4-methoxyphenyl)-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10c)

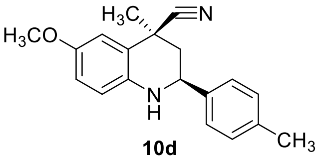


10c

Prepared from tetrahydroquinoline **3c** (0.353 g, 1 mmol) and MMPP·6H_2O (0.618 g, 1.25 mmol).
Reaction time: 1 h.
Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).
Yield: 0.286 g (93%).Yellow solid, mp: 144-145 °C.
$C_{19}H_{20}N_2O_2$ (M = 308.37)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.81 (s, 3H, CH_3); 2.18 (dd, J = 13.1, 2.8 Hz, 1H, H-3eq); 2.43 (t, J = 12.8 Hz, 1H, H-3ax); 3.79 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 3.90 (s, 1H, NH); 4.34 (dd, J = 11.8, 2.7 Hz, 1H, H-2); 6.52 (d, J = 8.7 Hz, 1H, H-8); 6.74 (dd, J = 8.8, 2.8 Hz, 1H, H-7); 6.93 (m, 2H, H-3’ and H-5’); 6.96 (d, J = 2.8 Hz, 1H, H-5); 7.34 (m, 2H, H-2’ and H-6’) ppm.
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 30.7 (CH_3); 35.5 (C-4); 42.1 (C-3); 51.6 (C-2); 55.5 (OCH_3); 56.1 (OCH_3); 112.9 (C-7*); 114.3 (C-3’ and C-5’); 116.2 (C-5*); 116.3 (C-8*); 120.6 (CN); 124.7 (C-4a); 128.0 (C-2’ and C-6’); 134.3 (C-4’*); 137.3 (C-8a*); 152.4 (C-1’); 159.6 (C-6) ppm.
IR (NaCl) ν: 3368.2 (N-H), 2927.4 (C-H), 2232.5 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-6-Methoxy-2-(4-methylphenyl)-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10d)



10d

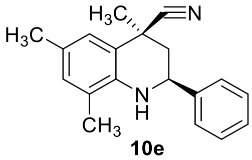
Prepared from tetrahydroquinoline **3d** (0.337 g, 1 mmol) and MMPP·6H_2O (0.618 g, 1.25 mmol).
Reaction time: 1 h.
Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).
Yield: 0.251 g (86%). Yellow solid, mp: 147-149 °C.
$C_{19}H_{20}N_2O$ (M = 292.37)

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.82 (s, 3H, CH$_3$); 2.19 (d, J = 12.4 Hz, 1H, H-3eq); 2.38 (s, 3H, CH$_3$); 2.43 (t, J = 12.9 Hz, 1H, H-3ax); 3.79 (s, 3H, OCH$_3$); 3.94 (s, 1H, NH); 4.37 (d, J = 9.8 Hz, 1H, H-2); 6.53 (d, J = 8.7 Hz, 1H, H-8); 6.75 (dd, J = 8.7, 2.8 Hz, 1H, H-7); 6.98 (d, J = 2.8 Hz, 1H, H-5); 7.20 (d, J = 8.1 Hz, 2H, H3' and H-5'); 7.31 (d, J = 8.1 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ:: 21.2 (CH$_3$); 30.6 (ArCH$_3$); 35.4 (C-4); 42.0 (C-3); 51.8 (C-2); 56.0 (OCH$_3$); 112.9 (C-7*); 116.3 (C-5*); 116.5 (C-8*); 120.6 (CN); 124.7 (C-4a); 126.8 (C-2' and C-6'); 129.6 (C-3' and C-5'); 137.2 (C-4'*); 138.1 (C-8a*); 139.2 (C-1'); 152.3 (C-6) ppm.

IR (NaCl) ν: 3393.7 (N-H), 2918.2 (C-H), 2229.6 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-4,6,8-Trimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10e)



10e

Prepared from tetrahydroquinoline **3e** (0.321 g, 1 mmol) and MMPP·6H$_2$O (0.618 g, 1.25 mmol).

Reaction time: 2 h.

Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yieold: 0.232 g (84%). Yellow solid, mp: 142-143 °C.

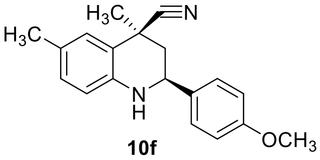
$C_{19}H_{20}N_2$ (M = 276.38)

^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.83 (s, 3H, CH$_3$); 2.10 (s, 3H, Ar-CH$_3$); 2.23 (m, 1H, H-3eq); 2.29 (s, 3H, ArCH$_3$); 2.46 (t, J = 12.5 Hz, 1H, H-3ax); 3.90 (s, 1H, NH); 4.47 (dd, J = 11.9, 2.8 Hz, 1H, H-2); 6.89 (s, 1H, H-7); 7.16 (s, 1H, H-5); 7.38-51 (m, 5H, H-2',H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 17.4 (CH$_3$); 20.5 (CH$_3$); 30.6 (CH$_3$); 35.4 (C-4); 42.0 (C-3); 52.2 (C-2); 119.3 (CN); 122.2 (C-4a); 124.9 (C-8); 126.3 (C-4'); 126.9 (C-2', C-6' and C-6); 128.5 (C-5); 129.1 (C-3' and C-5'); 131.1 (C-7); 138.7 (C-8a); 142.6 (C-1') ppm.

IR (NaCl) ν: 3391.5 (N-H), 2960.0 (C-H), 2232.8 (CN), cm^{-1}.

(±)-(2*S**,4*S**)-2-(4-Methoxyphenyl)-4,6-dimethyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10f)



10f

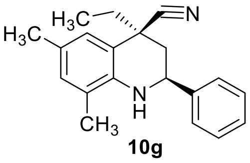
Prepared from tetrahydroquinoline **3f** (0.337 g, 1 mmol) and MMPP·6H_2O (0.618 g, 1.25 mmol).
Reaction time: 2 h.
Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).
Yield: 0.286 g (98%). Yellow solid, mp: 136-137 °C.
$C_{19}H_{20}N_2O$ (M = 292,38).

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*:: 1.79 (s, 3H, CH_3); 2.18 (dd, *J* = 13.1, 2.9 Hz, 1H, H-3eq); 2.28 (s, 3H, CH_3); 2.42 (t, *J* = 12.8 Hz, 1H, H-3ax); 3.83 (s, 3H, OCH_3); 4.01 (s, 1H, NH); 4.37 (dd, *J* = 11.8, 2.8 Hz, 1H, H-2); 6.48 (d, *J* = 8.1 Hz, 1H, H-8); 6.91-6.94 (m, 3H, H-7, H-3' and H-5'); 7.23 (d, *J* = 1.1 Hz, 1H, H-5); 7.32-7.36 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*:: 20.5 (CH_3); 30.6 ($ArCH_3$); 35.2 (C-4); 42.1 (C-3); 51.4 (C-2); 55.5 (OCH_3); 114.3 (C-3' and C-5'); 115.1 (C-8); 119.7 (CN); 124.8 (C-4a); 127.6 (C-6); 128.0 (C-2' and C-6'); 128.5 (C-7); 129.9 (C-5); 134.2 (C-1'); 140.7 (C-8a); 159.6 (C-4') ppm.

IR (NaCl) *ν*: 3368.8 (N-H), 2926.6 (C-H), 2232.8 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-4-Ethyl-6,8-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10g)



10g

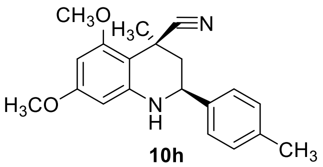
Prepared from tetrahydroquinoline **3g** (0.335 g, 1 mmol) and MMPP·6H_2O (0.618 g, 1.25 mmol).
Reaction time: 2 h.
Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).
Yield: 0.223 g (77%). Yellow solid, mp: 145-147 °C.
$C_{20}H_{22}N_2$ (M = 290.40)

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.23 (t, *J* = 7.4 Hz, 3H, $CH_2C\mathit{H_3}$); 2.06 (dd, *J* = 7.4, 2.9 Hz, 1H, H-3eq); 2.11 (s, 3H, $ArCH_3$); 2.26-2.43 (m, 6H, $ArCH_3$, H-3ax and $C\mathit{H_2}CH_3$); 3.89 (s, 1H, NH); 4.49 (dd, *J* = 11.4, 3.9 Hz, 1H, H-2); 6.90 (s, 1H, H-5); 7.13 (s, 1H, H-7); 7.38-7.51 (m, 5H, H2', H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 9.2 ($CH_2\mathit{C}H_3$); 17.5 ($ArCH_3$); 20.5 ($ArCH_3$); 34.2 ($\mathit{C}H_2CH_3$); 38.4 (C-3); 40.8 (C-4); 52.0 (C-2); 118.5 (CN); 121.8 (C-4a*); 123.5 (C-8*); 126.3 (C-6); 126.6 (C-4'); 126.8 (C-2' and C-6'); 128.4 (C-5); 129.1 (C-3' and C-5'); 131.1 (C-7); 138.3 (C-8a); 143.0 (C-1') ppm.

IR (NaCl) *ν*: 3360 (N-H), 2930 (C-H), 2250 (CN) cm^{-1}.

(±)-(2*S**,4*S**)-5,7-Dimethoxy-4-methyl-2-(4-methylphenyl)-1,2,3,4-tetrahydroquinoline-4-carbonitrile (10h)



10h

Prepared from tetrahydroquinoline **3h** (0.367 g, 1 mmol) and MMPP·$6H_2O$ (0.618 g, 1.25 mmol).

Reaction time: 2 h.

Purification: flash chromatography on alumina with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.198 g (62%). Yellow solid, mp: 147-150 °C.

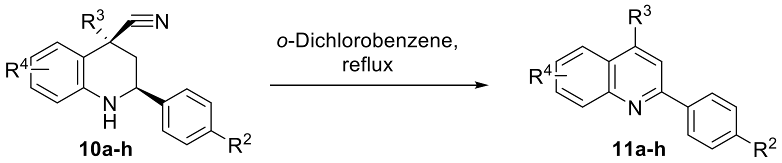
$C_{20}H_{22}N_2O_2$ (M = 322.40)

^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.76 (s, 3H, CH_3); 2.19 (dd, *J* = 13.1, 2.3 Hz, 1H, H-3eq); 2.37-2.49 (m, 4H, H-3ax and $ArCH_3$); 3.74 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.13 (bs, 1H, NH); 4.26 (dd, *J* = 11.8, 2.1 Hz, 1H, H-2); 5.75 (d, *J* = 2.3 Hz, 1H, H-8); 5.96 (d, *J* = 2.3 Hz, 1H, H-6); 7.20 (d, *J* = 7.9 Hz, 2H, H-3' and H-5'); 7.30 (d, *J* = 8.0 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 21.3 (CH_3); 27.6 ($ArCH_3$); 31.7 (C-4); 44.5 (C-3); 51.8 (C-2); 55.3 (OCH_3); 55.7 (OCH_3); 90.0 (C-6*); 90.2 (C-8*); 101.3 (C-4a); 124.9 (CN); 126.8 (C-2' and C-6'); 129.7 (C-3' and C-5'); 138.2 (C-4'*); 138.9 (C-1'*); 145.6 (C-8a); 159.5 (C-7*); 161.0 (C-5*) ppm.

IR (NaCl) *ν*: 3368.8 (N-H), 2931.1 (C-H), 2231.9 (CN) cm^{-1}.

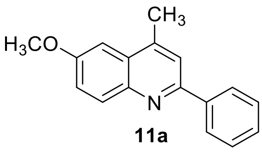
10.4.4.2 - Synthesis of 2-arylquinolines 11a-h



Quinolines **11a-h** were prepared from compounds **10a-h** following the reaction conditions described in section 10.4.1.2.

Cmpd	R^2	R^3	R^4	Yield (%)
11a	H	CH_3	6-OCH_3	92
11b	Cl	CH_3	6-OCH_3	86
11c	OCH_3	CH_3	6-OCH_3	87
11d	CH_3	CH_3	6-OCH_3	86
11e	H	CH_3	6,8-$(CH_3)_2$	95
11f	OCH_3	CH_3	6-CH_3	92
11g	H	CH_2CH_3	6,8-$(CH_3)_2$	89
11h	CH_3	CH_3	5,7-$(OCH_3)_2$	95

6-Methoxy-4-methyl-2-phenylquinoline (11a)[222,223]



11a

Prepared from nitrile derivative **10a** (0.150 g, 0.538 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.123 g (92%). White solid, mp: 128-129 °C.

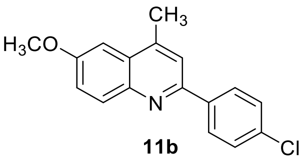
---

[222] Cornforth J.W., *J. Chem. Soc.* **1948**, 93.

[223] Xiao F., Chen W., Liao Y., Deng G.-J. *Org. Biomol. Chem.*, **2012**, *10*, 8593.

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.72 (s, 3H, CH$_3$); 3.96 (s, 3H, OCH$_3$); 7.19 (d, *J* = 2.7 Hz, 1H, H-5); 7.38 (dd, *J* = 9.2, 2.7 Hz, 1H, H-7); 7.43-7.54 (m, 3H, H-3', H-5'and H-4'); 7.68 (s, 1H, H-3); 8.10-8.13 (m, 3H, H-8, H-2' and H-6') ppm.

2-(4-Chlorophenyl)-6-methoxy-4-methylquinoline (11b)



11b

Prepared from nitrile derivative **10b** (0.150 g, 0.48 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether:ethyl acetate (9:1, v/v).

Yield: 0.117 g (86%). White solid, mp: 119-122 °C.

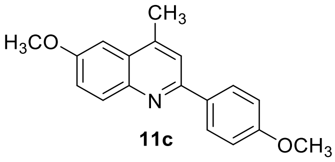
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.72 (s, 3H, CH$_3$); 3.97 (s, 3H, OCH$_3$); 7.20 (d, *J* = 2.8 Hz, 1H, H-5); 7.38 (dd, *J* = 9.2, 2.8 Hz, 1H, H-7); 7.45-7.49 (m, 2H, H-3' and H-5'); 7.65 (s, 1H, H-3); 8.04-8.09 (m, 3H, H-8, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 19.4 (CH$_3$); 55.7 (OCH$_3$); 102.0 (C-5); 119.7 (C-3); 121.8 (C-7); 128.3 (C-4a); 128.6 (C-2' and C-6'); 129.0 (C-3' and C-5'); 131.9 (C-8); 135.1 (C-4'); 138.4 (C-1'); 143.6 (C-8a); 144.2 (C-4); 153.5 (C-2); 157.8 (C-6) ppm.

IR (NaCl) *v*: 2918.0 (C-H), 1624.6 (C=N), 717.2 (C-Cl) cm^{-1}.

Elemental analysis (%): Calc. for $C_{17}H_{14}ClNO$ (M= 283.75): C, 71.96; H, 4.97; N, 4.94. Found: C, 72.08; H, 5.27; N, 5.00.

6-Methoxy-2-(4-methoxyphenyl)-4-methylquinoline (11c)[224]



11c

Prepared from nitrile derivative **10c** (0.150 g, 0.486 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

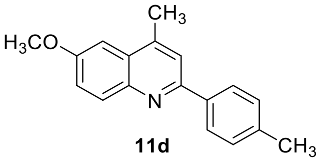
Yield: 0.118 g (87%). White solid, mp: 109-111 °C.

---

[224] Swenson R.E., Sowin T.J., Zhang H.Q.. *J. Org. Chem.* **2002**, *67*, 9182.

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.71 (s, 3H, CH$_3$); 3.88 (s, 3H, OCH$_3$); 3.96 (s, 3H, OCH$_3$); 6.98-7.08 (m, 2H, H-3’ and H-5’); 7.19 (d, *J* = 2.7 Hz, 1H, H-5); 7.36 (dd, *J* = 9.2, 2.8 Hz, 1H, H-7); 7.65 (s, 1H, H-3); 8.02-8.13 (m, 3H, H-8, H-2’ and H-6’) ppm.

6-Methoxy-4-methyl-2-(4-methylphenyl)quinoline (11d)



11d

Prepared from nitrile derivative **10d** (0.150 g, 0.513 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.116 g (86%). White solid, mp: 124-127 °C.

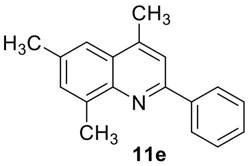
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.43 (s, 3H, CH$_3$); 2.70 (s, 3H, CH$_3$); 3.96 (s, 3H, OCH$_3$); 7.19 (d, *J* = 2.7 Hz, 1H, H-5); 7.27-7.41 (m, 3H, H-5, H-3’ and H-5’); 7.66 (s, 1H, H-3); 7.99-8.04 (m, 3H, H-8, H-2’ and H-6’) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 19.4 (CH$_3$); 21.5 (CH$_3$); 55.7 (OCH$_3$); 102.0 (C-5); 120.0 (C-3*); 121.5 (C-7*); 127.2 (C-2’ and C-6’); 128.1 (C-4a); 129.6 (C-3’ and C-5’); 131.8 (C-8); 135.4 (C-4’*); 137.2 (C-1’*); 143.3 (C-8a*); 144.2 (C-4*); 154.9 (C-2); 157.5 (C-6) ppm.

IR (NaCl) *v*: 3058.7 (C-H), 1603.8 (C=C), 1030.2 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{17}NO$ (M = 263.33): C, 82.10; H, 6.51; N, 5.32. Found: 81.90; H, 6.32; N, 5.12.

4,6,8-Trimethyl-2-phenylquinoline (11e)



11e

Prepared from nitrile derivative **10e** (0.150 g, 0.542 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.127 g (95%). Yellow solid, mp: 121-123 °C.

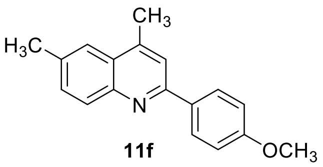
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.54 (s, 3H, CH$_3$); 2.73 (s, 3H, CH$_3$); 2.90 (s, 3H, CH$_3$); 7.43 (s, 1H, H-5); 7.45-7.57 (m, 3H, H-3', H-4' and H-5'); 7.60 (s, 1H, H-7); 7.71 (s, 1H, H-3); 8.24-8.28 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 18.4 (CH$_3$); 19.5 (CH$_3$); 22.0 (CH$_3$); 119.1 (C-3); 120.6 (C-5); 127.2 (C-4a); 127.4 (C-2' and C-6'); 128.8 (C-3' and C-5'); 129.0 (C-4'); 131.8 (C-7); 135.4 (C-6); 137.8 (C-8); 140.2 (C-1'); 144.1 (C-4*); 145.7 (C-8a*); 154.3 (C-2) ppm.

IR (NaCl) ν: 3058.7 (C-H), 1603.8 (C=C), 1030.2 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{17}N$ (M = 247.33): C, 87.41; H, 6.93; N, 5.66. Found: C, 87.45; H, 6.82; N, 5.94.

2-(4-Methoxyphenyl)-4,6-dimethylquinoline (11f)[224]



11f

Prepared from nitrile derivative **10f** (0.150 g, 0.513 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.124 g (92%). Yellow solid, mp: 127-129 °C.

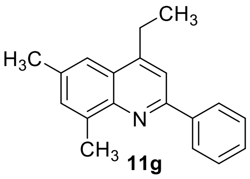
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.56 (s, 3H, CH$_3$); 2.73 (s, 3H, CH$_3$); 3.88 (s, 3H, OCH$_3$); 7.00-7.05 (m, 2H, H-3' and H-5'); 7.53 (dd, J = 8.6, 1.9 Hz, 1H, H-7); 7.64 (s, 1H, H-5); 7.73 (s, 1H, H-3); 8.04 (d, J = 8.6 Hz, 1H, H-8); 8.08-8.12 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 19.2 (CH$_3$); 22.0 (CH$_3$); 55.5 (OCH$_3$); 114.3 (C-3' and C-5'); 119.5 (C-3); 122.8 (C-5); 127.1 (C-4a); 128.9 (C-2' and C-6'); 129.9 (C-8*); 131.6 (C-7*); 132.6 (C-1'*); 135.6 (C-6*); 144.0 (C-8a); 146.7 (C-4); 155.9 (C-2); 160.7 (C-4') ppm.

IR (NaCl) ν: 2922.4 (C-H), 1607.5 (C=C), 1033.3 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{18}H_{17}NO$ (M = 263.33): C, 82.10; H, 6.51; N, 5.32. Found: C, 81.84; H, 6.43; N, 5.12.

4-Ethyl-6,8-dimethyl-2-phenylquinoline (11g)



11g

Prepared from nitrile derivative **10g** (0.150 g, 0.516 mmol).

Reaction time: 24 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.120 g (89%). White solid, mp: 90-93 °C.

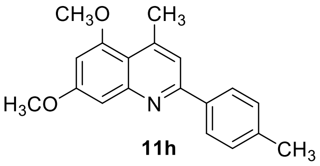
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 1.44 (t, *J* = 7.5 Hz, 3H, CH_2CH_3); 2.53 (s, 3H, CH_3); 2.87 (s, 3H, CH_3); 3.14 (q, *J* = 7.3 Hz, 2H, CH_2CH_3); 7.41 (s, 1H, H-5); 7.44-7.56 (m, 3H, H-3', H-4' and H-5'); 7.65 (s, 1H, H-7); 7.73 (s, 1H, H-3); 8.23-8.27 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 14.5 (CH_3); 18.5 (CH_3); 22.1 (CH_3); 25.8 (CH_2); 117.2 (C-3); 120.2 (C-5); 126.4 (C-4a); 127.5 (C-2' and C-6'); 128.8 (C-3' and C-5'); 129.0 (C-4'); 131.7 (C-7); 135.4 (C-6*); 138.0 (C-8*); 140.4 (C-1'); 146.0 (C-4); 149.8 (C-8a); 154.5 (C-2) ppm.

IR (NaCl) *ν*: 2917.4 (C-H), 1596.8 (C-C), 1029.1 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{19}N$ (M = 261.36): C, 87.31; H, 7.33; N, 5.36. Found: C, 87.06; H, 7.35; N, 5.51.

5,7-Dimethoxy-4-methyl-2-(4-methylphenyl)quinoline (11h)



11h

Prepared from nitrile derivative **10h** (0.150 g, 0.451).

Reaction time: 48 h.

Purification: flash chromatography with petroleum ether : ethyl acetate (9:1, v/v).

Yield: 0.125 g (95%). Yellow solid, mp: 130-133 °C.

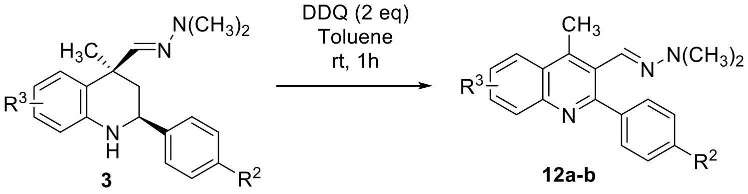
^{1}H-NMR ($CDCl_3$, 250 MHz) *δ*: 2.42 (s, 3H, CH_3); 2.87 (s, 3H, CH_3); 3.92 (s, 3H, OCH_3); 3.95 (s, 3H, OCH_3); 6.47 (d, *J* = 2.4 Hz, 1H, H-6); 7.11 (d, *J* = 2.4 Hz, 1H, H-8); 7.30 (d, *J* = 7.9 Hz, 2H, H-3' and H-5'); 7.41 (s, 1H, H-3); 8.01 (d, *J* = 8.2 Hz, 2H, H-2' and H-6') ppm.

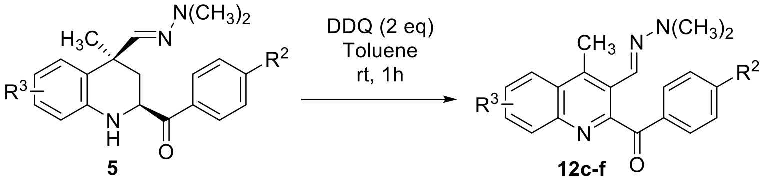
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 21.5 (CH_3); 24.7 (CH_3); 55.6 (OCH_3); 55.7 (OCH_3); 98.3 (C-6*); 101.1 (C-8*); 115.6 (C-4a); 119.1 (C-3); 127.4 (C-3’ and C-5’); 129.6 (C-2’ and C-6’); 136.9 (C-4’); 139.2 (C-1’); 146.3 (C-4); 151.9 (C-8a); 157.3 (C-5*); 158.7 (C-7*); 160.6 (C-2) ppm.

IR (NaCl) ν: 2928.3 (C-H), 1620.1 (C-C), 1135.4 (C-O) cm^{-1}.

Elemental analysis (%): Calc. for $C_{19}H_{19}NO_2$ (M = 293.36): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.78; H, 6.71; N, 4.87.

10.4.5 – Synthesis of quinolines *via* C4-C3 migration of the hydrazone substituent

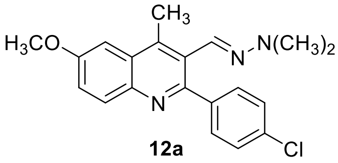




To a stirred solution of 2-aryltetrahydroquinoline **3** or 2-acyltetrahydroquinolines **5** (0.3 mmol) in toluene (10 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.6 mmol) slowly. The solution was stirred at room temperature until the starting material disappeared as confirmed by TLC (1 h). The solvent was evaporated under reduced pressure. The solid residue was purified by flash column chromatography, eluting with a 8:2 (v/v) mixture of petroleum ether and ethyl acetate, to give compounds **12a-f**.

Starting material	**Cmpd**	**R^2**	**R^3**	**Yield (%)**
3b	**12a**	Cl	6-OCH_3	57
3c	**12b**	OCH_3	6-OCH_3	50
5a	**12c**	H	6-OCH_3	75
5c	**12d**	OCH_3	6-OCH_3	73
5g	**12e**	F	6,8-$(CH_3)_2$	59
5b	**12f**	F	6-OCH_3	53

2-(4-Chlorophenyl)-3-((2,2-dimethylhydrazono)methyl)-6-methoxy-4-methylquinoline (12a)



12a

Prepared from tetrahydroquinoline **3b** (0.100 g, 0.279 mmol) and DDQ (0.127 g, 0.560 mmol). Yield: 0.056 g (57%). Yellow solid, mp: 140-142 °C.

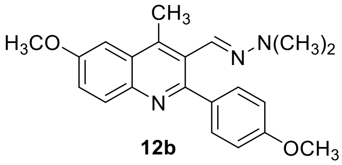
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 2.83 (s, 3H, CH$_3$); 2.89 (s, 6H, N(CH$_3$)$_2$); 3.98 (s, 3H, OCH$_3$); 7.15 (s, 1H, CH=N); 7.30 (d, *J* = 2.7 Hz, 1H, H-5); 7.36-7.40 (m, 3H, H-3', H-5' and H-7); 7.52 (d, *J* = 6.2 Hz, 2H, H-2' and H-6'); 8.04 (d, *J* = 9.1 Hz, 1H, H-8) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 16.3 (CH$_3$); 42.8 (N(CH$_3$)$_2$); 55.7 (OCH$_3$); 102.8 (C-5); 121.9 (C-7); 127.6 (C-3); 128.4 (C-2' and C-6'); 129.1 (C-4a); 130.7 (C-8); 131.2 (CH=N); 131.4 (C-3' and C-5'); 134.5 (C-4'); 138.8 (C-1'); 141.4 (C-4); 142.4 (C-8a); 155.0 (C-2); 158.3 (C-6) ppm.

IR (NaCl) *v*: 2932.2 (C-H), 1618.7 (CH=N), 1217.2 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{20}H_{20}ClN_3O$ (M = 353.85): C, 67.89; H, 5.70; N, 11.88. Found: C, 67.67; H, 5.99; N, 11.60.

3-((2,2-Dimethylhydrazono)methyl)-6-methoxy-2-(4-methoxyphenyl)-4-methylquinoline (12b)



12b

Prepared from tetrahydroquinoline **3c** (0.100g, 0.283 mmol) and DDQ (0.128 g, 0.566 mmol). Yield: 0.049 g (50%). Yellow viscous liquid.

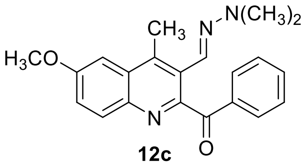
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.43 (s, 3H, CH$_3$); 2.62 (s, 6H, N(CH$_3$)$_2$); 3.83 (s, 3H, OCH$_3$); 3.86 (s, 3H, OCH$_3$); 6.47 (s, 1H, CH=N); 6.78-6.89 (m, 2H, H-5 and H-7); 6.91-7.00 (m, 2H, H-3' and H-5'); 7.44 (d, *J* = 8.4 Hz, 1H, H-8); 7.96-8.06 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 16.2 (CH$_3$); 43.0 (N(CH$_3$)$_2$); 55.5 (OCH$_3$); 55.7 (OCH$_3$); 102.9 (C-5); 113.5 (C-3' and C-5'); 121.4 (C-7); 127.5 (C-3); 128.8 (C-4a); 131.1 (C-8); 131.4 (C-2' and C-6'); 133.2 (CH=N and C-1'*); 134.2 (C-4*); 134.7 (C-8a*); 156.3 (C-2); 157.9 (C-6); 159.7 (C-4') ppm.

IR (NaCl) ν: 2923.8 (C-H), 1620.5 (C=N), 1222.4 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{23}N_3O_2$ (M = 349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 71.93; H, 6.85; N, 11.88.

3-((2,2-Dimethylhydrazono)methyl)-6-methoxy-4-methylquinolin-2-yl(phenyl)methanone (12c)



12c

Prepared from tetrahydroquinoline **5a** (0.100 g, 0.284 mmol) and DDQ (0.130 g, 0.570 mmol). Yield: 0.074 g (75%). Yellow solid, mp: 180-182 °C.

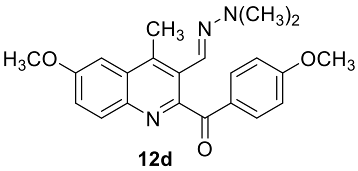
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.61 (s, 9H, $N(CH_3)_2$ and CH_3); 3.87 (s, 3H, OCH_3); 7.16 (d, J = 2.7 Hz, 1H, H-5); 7.21 (dd, J = 9.1, 2.7 Hz, 1H, H-7); 7.26-7.32 (m, 3H, H-3', H-5' and CH=N); 7.40 (m, 1H, H-4'); 7.76 (d, J = 8.3 Hz, 2H, H-2' and H-6'); 7.87 (d, J = 9.1, 1H, H-8) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.5 (CH_3); 42.0 ($N(CH_3)_2$); 55.7 (OCH_3); 102.2 (C-5); 121.1 (C-7); 125.2 (C-4'); 127.0 (C-3); 128.3 (C-2' and C-6'); 129.0 (C-4a); 130.0 (C-3' and C-6'); 131.9 (C-8); 132.6 (CH=N); 137.3 (C-1'); 138.7 (C-4); 141.3 (C-8a); 154.3 (C-2); 158.6 (C-6); 195.8 (C=O) ppm.

IR (NaCl) ν: 2914.4 (C-H), 1712.8 (C=O), 1676.7 (C=N), 1226.2 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{21}N_3O_2$ (M = 347.42): C, 72.60; H, 6.09; N, 12.10. Found: C, 72.25; H, 6.13; N, 11.95.

3-((2,2-Dimethylhydrazono)methyl)-6-methoxy-4-methylquinolin-2-yl(4-methoxyphenyl)methanone (12d)



12d

Prepared from tetrahydroquinoline **5c** (0.100 g, 0.262 mmol) and DDQ (0.120 g, 0.525 mmol). Yield: 0.072 g (73%). Yellow solid, mp: 173-174 °C.

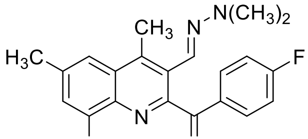
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.72 (s, 3H, CH$_3$); 2.74 (s, 6H, N(CH$_3$)$_2$); 3.84 (s, 3H, OCH$_3$); 3.97 (s, 3H, OCH$_3$); 6.77-6.94 (m, 2H, H-3' and H-5'); 7.26 (d, *J* = 2.7 Hz, 1H, H-5); 7.32 (dd, *J* = 9.1, 2.7 Hz, 1H, H-7); 7.37 (s, 1H, CH=N); 7.78-7.87 (m, 2H, H-2' and H-6'); 7.98 (d, *J* = 9.0, 1H, H-8) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 14.7 (CH$_3$); 42.1 (N(CH$_3$)$_2$); 55.6 (OCH$_3$); 55.7 (OCH$_3$); 102.2 (C-5); 113.5 (C-3' and C-5'); 121.1 (C-7); 125.6 (C-3); 127.1 (C-8); 129.1 (C-4a*); 130.4 (C-1'*); 131.7 (CH=N); 132.3 (C-2' and C-6'); 139.1 (C-4); 141.0 (C-8a); 154.4 (C-2); 158.6 (C-6); 163.3 (C-4'); 195.7 (C=O) ppm.

IR (NaCl) *ν*: 2906.4 (C-H), 1743.8 (C=O), 1649.3 (C=N), 1226.5 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{23}N_3O_3$ (M = 377.44): C, 70.01; H, 6.14; N, 11.13. Found: C, 69.86; H, 6.07; N, 10.96.

3-((2,2-Dimethylhydrazono)methyl)-4,6,8-trimethylquinolin-2-yl (4-fluorophenyl)-methanone (12e)



12e

Prepared from tetrahydroquinoline **5g** (0.100 g, 0.272 mmol) and DDQ (0.124 g, 0.544 mmol).

Yield: 0.058 g (59%). Orange solid, mp: 149-152 °C.

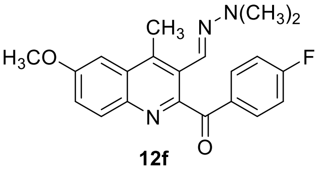
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.45 (s, 3H, CH$_3$); 2.71 (s, 6H, N(CH$_3$)$_2$); 2.91 (s, 6H, CH$_3$); 7.03-7.10 (m, 2H, H-3' and H-5'); 7.22 (s, 1H, H-5); 7.35 (s, 1H, CH=N); 7.72 (s, 1H, H-7); 7.85-7.91 (m, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 19.9 (CH$_3$); 21.3 (CH$_3$); 26.2 (CH$_3$); 42.1 (N(CH$_3$)$_2$); 115.3 (d, *J* = 22.0 Hz, C-3' and C-5'); 125.9 (C-5); 127.0 (C-3); 127.5 (C-4a); 127.9 (C-7); 132.6 (d, *J* = 9.3 Hz, C-2' and C-6'); 133.6 (d, *J* = 2.9 Hz, C-1'); 133.8 (CH=N); 135.0 (C-6); 139.9 (C-4); 142.8 (C-8); 146.8 (C-8a); 155.2 (C-2); 165.6 (d, *J* = 254.4 Hz, C-4'); 194.0 (C=O) ppm.

IR (NaCl) *ν*: 2914.4 (C-H), 1689.4 (C=O), 1595.3 (C=N), 1226.1 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{22}H_{22}FN_3O$ (M = 363.44): C, 72.71; H, 6.10; N, 11.56. Found: C, 72.77; H, 5.91; N, 11.65.

3-((2,2-Dimethylhydrazono)methyl)-6-methoxy-4-methylquinolin-2-yl)(4-fluorophenylmethanone (12f)



12f

Prepared from tetrahydroquinoline **5b** (0.100 g, 0.270 mmol) and DDQ (0.123 g, 0.541 mmol).

Yield: 0.052 g (53%). Yellow solid, mp: 151-154 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.73 (s, 3H, CH_3); 2.74 (s, 6H, $N(CH_3)_2$); 3.98 (s, 3H, OCH_3); 7.03-7.13 (m, 2H, H-3' and H-5'); 7.27 (d, *J* = 2.7 Hz, 1H, H-5); 7.33 (dd, *J* = 9.1, 2.7 Hz, 1H, H-7); 7.38 (s, 1H, CH=N); 7.84-7.95 (m, 2H, H-2' and H-6'); 7.97 (d, *J* = 9.1, 1H, H-8) ppm.

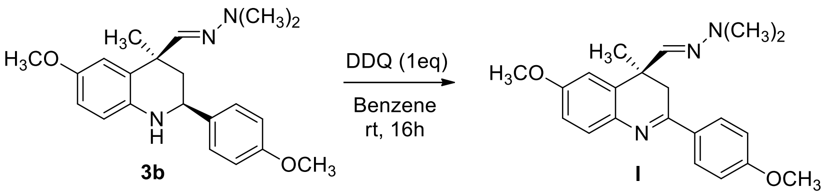
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 14.6 (CH_3); 42.1 ($N(CH_3)_2$); 55.7 (OCH_3); 102.2 (C-5); 115.4 (d, *J* = 22.0 Hz, C-3' and C-5'); 121.2 (C-7); 125.2 (C-8); 127.0 (C-3); 129.1 (C-4a); 131.9 (CH=N); 132.6 (d, *J* = 9.4 Hz, C-2' and C-6'); 133.9 (d, *J* = 2.5 Hz, C-1'); 138.8 (C-4); 141.2 (C-8a); 153.9 (C-2); 158.7 (C-6); 165.5 (d, *J* = 254.0 Hz, C-4'); 194.3 (CO) ppm.

IR (NaCl) ν: 2923.8 (C-H), 1673.9 (C=O), 1600.0 (C=N), 1230.6 (C-N) cm^{-1}.

Elemental analysis (%): Calc. for $C_{21}H_{20}FN_3O_2$ (M = 365.41): C, 69.03; H, 5.52; N, 11.50. Found: C, 68.83; H, 5.34; N, 11.23.

10.5 - Mechanistic study

10.5.1 - Synthesis of intermediate I

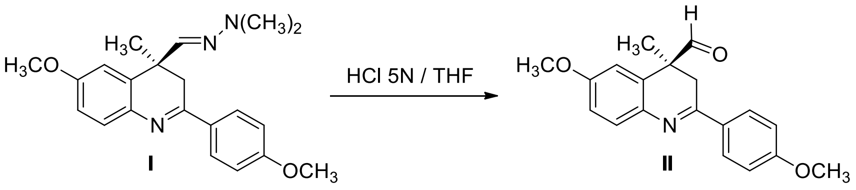


To a solution of the tetrahydroquinoline **3b** (0.6 mmol) in benzene (5 mL) an equimolar amount of DDQ was added, and the mixture was stirred at room temperature for 16 hours. Then, the reaction was washed with water (2 mL), with brine (2 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under vacuum. The obtained residue was purified by flash chromatography on silica gel eluting with petroleum ether : ethyl acetate, allowed the isolation of compound **I**, as a yellow viscous liquid, in 66% yield.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.46 (s, 3H, CH_3); 2.57 (d, *J* = 16.1 Hz, 1H, H-3eq); 2.66 (s, 6H, $N(CH_3)_2$); 3.22 (d, *J* = 16.0, 1H, H-3ax); 3.86 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 6.50 (s, 1H, CH=N); 6.86 (dd, *J* = 8.4, 2.5 Hz, H-7); 6.91 (d, *J* = 2.5 Hz, 1H, H-5); 6.98 (d, *J* = 8.9 Hz, 2H, H-3' and H-5'); 7.46 (d, *J* = 8.4 Hz, 1H, H-8); 8.05 (d, *J* = 8.9 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 24.4 (CH_3); 35.9 (C-2); 39.7 (C-4); 43.4 ($N(CH_3)_2$); 55.7 (OCH_3); 55.8 (OCH_3); 111.3 (C-5); 111.9 (C-7); 114.0 (C-3' and C-5'); 128.9 (C-8); 129.0 (C-2' and -6'); 132.6 (C-1'); 135.0 (C-8a); 138.6 (C-4a); 139.5 (CH=N); 158.7 (C-2); 161.5 (C-6); 163.9 (C-4') ppm.

10.5.2 - Synthesis of intermediate II

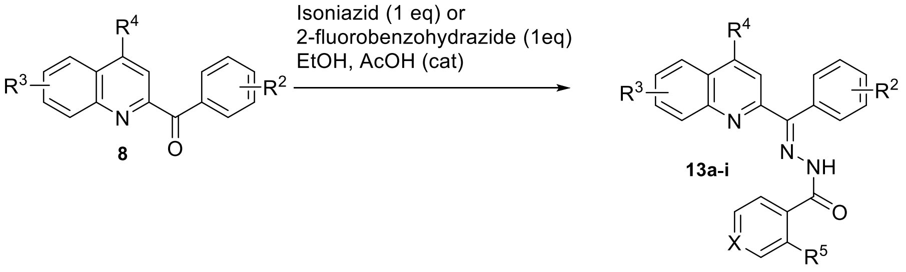


To a solution of compound **I** in THF (15 mL), 5N HCl (5 mL) was added dropwise and the mixture was vigorously stirred at room temperature for 5 hours. The reaction mixture was quenched with 3M aqueous NH_4OH. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed under vacuum and the obtained residue was purified by flash chromatography on silica gel eluting with petroleum ether : ethyl acetate, gaving the aldehyde **II**, as yellow oil in 68% yield.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.41 (s, 3H, CH_3); 2.60 (d, *J* = 16.4 Hz, 1H, H-3eq); 3.22 (d, *J* = 16.4, 1H, H-3ax); 3.84 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3); 6.77 (d, *J* = 2.7 Hz, H-5); 6.91 (dd, *J* = 8.6, 2.8 Hz, H-7); 6.96 (d, *J* = 8.9 Hz, 2H, H-3’ and H-5’); 7.47 (d, *J* = 8.6 Hz, 1H, H-8); 7.99 (d, *J* = 8.9 Hz, 2H, H-2’ and H-6’); 9.48 (s, 1H, HC=O) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 20.1 (CH_3); 31.7 (C-3); 48.4 (C-4); 55.8 (OCH_3); 55.9 (OCH_3); 112.0 (C-5); 113.4 (C-7); 114.2 (C-3’ and C-5’); 127.8 (C-8); 128.8 (C-2’ and -6’); 129.5 (C-4a); 131.8 (C-8a); 138.9 (C-1’); 159.1 (C-2); 161.7 (C-6); 161.9 (C-4’); 199.9 (C=O) ppm.

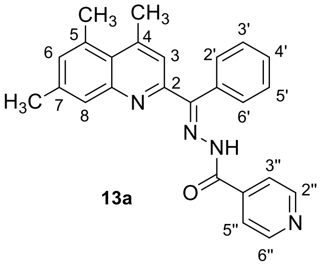
10.6 - Synthesis of antitubercular hybrid quinolines 13a-i



To a stirred solution of quinoline **8** (0.3 mmol) in ethanol (5 mL) and two drops of acetic acid was added isoniazid or 2-fluorobenzohydrazide (0.3 mmol). The solution was refluxed until the starting material disappeared as confirmed by TLC (24 h). The solvent was evaporated under reduced pressure. The solid residue was purified by flash column chromatography, eluting with a 7:3 (v/v) mixture of petroleum ether : ethyl acetate, to give compounds **13a-i**.

Cmpd	R^2	R^3	R^4	R^5	X	Yield (%)
13a	H	$5,7\text{-}(CH_3)_2$	CH_3	H	N	90
13b	$4\text{-}OCH_3$	$6\text{-}OCH_3$	CH_3	H	N	76
13c	4-F	$6\text{-}OCH_3$	CH_3	H	N	75
13d	H	$6\text{-}OCH_3$	CH_3	H	N	39
13e	H	$6\text{-}OCH_3$	CH_2CH_3	H	N	63
13f	$4\text{-}OCH_3$	$6,8\text{-}(CH_3)_2$	CH_3	H	N	38
13g	4-F	$6,8\text{-}(CH_3)_2$	CH_2CH_3	H	N	77
13h	H	$6\text{-}OCH_3$	CH_3	F	CH	71
13i	4-F	$6\text{-}OCH_3$	CH_3	F	CH	75

N'-[Phenyl(4,5,7-trimethylquinolin-2-yl)methylene]isonicotinohydrazide (13a)



13a

Prepared from quinoline **8p** (0.080g, 0.290 mmol) and isoniazid (0.040 g, 0.290 mmol).

Reaction time: 24 h.

Yield: 0.103 g (90%). Yellow solid, mp: 213-215 °C.

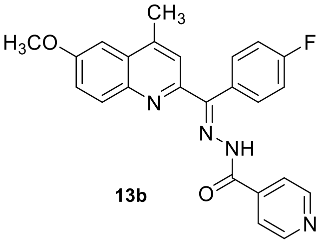
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.55 (s, 3H, CH$_3$); 2.86 (s, 3H, CH$_3$); 2.90 (s, 3H, CH$_3$); 7.13 (s, 1H, H-8); 7.30 (s, 1H, H-6); 7.46-7.48 (m, 3H, H-3', H-4' and H-5'); 7.66-7.72 (m, 3H, H-3, H-2' and H-6'); 7.90 (d, *J* = 5.9 Hz, 2H, H-3'' and H-5''); 8.85 (d, *J* = 5.8 Hz, 2H, H-2'' and H-6'') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 21.6 (CH$_3$); 25.5 (CH$_3$); 25.7 (CH$_3$); 121.6 (C-3'' and C-5''); 125.6 (C-3); 126.3 (C-4a); 127.0 (C-5); 128.6 (C-3' and C-5'); 129.5 (C-4'); 129.6 (C-2' and -6'); 134.0 (C-7); 135.8 (C-8); 137.6 (C-1'); 140.6 (C-6); 141.5 (C-4); 147.8 (C-1''); 148.0 (C-8a); 149.7 (C-2); 150.8 (C-2'' and C-6''); 151.7 (C=N-NH); 162.9 (C=O) ppm.

IR (NaCl) *ν*: 3377.1 (N-H), 2950.0 (C-H), 1690.5 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{25}H_{22}N_4O$ (M = 394.48): C, 76.12; H, 5.62; N, 14.20. Found: C, 75.83; H, 5.41; N, 14.02.

N'-[(4-Fluorophenyl)-(6-methoxy-4-methylquinolin-2-yl)methylene] isonicotinohydrazide (13b)



13b

Prepared from quinoline **8b** (0.090 g, 0.305 mmol) and isoniazid (0.042 g, 0.305 mmol).

Reaction time: 24h.

Yield: 0.096 g (76%). Yellow solid, mp: 229-231 °C.

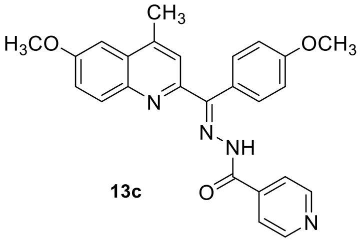
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.66 (s, 3H, CH$_3$); 4.01 (s, 3H, OCH$_3$); 7.16 (t, *J* = 8.7 Hz, 2H, H-3' and H-5'); 7.23-7.24 (m, 2H, H-3 and H-5); 7.53 (dd, *J* = 9.2, 2.7 Hz, 1H, H-7); 7.67 (dd, *J* = 8.7, 5.4 Hz, 2H, H-2’ and H-6’); 7.86 (d, *J* = 6.0 Hz, 2H, H-3’’ and H-5’’); 7.99 (d, *J* = 9.2 Hz, 1H, H-8); 8.85 (d, *J* = 5.9 Hz, 2H, H-2’’ and H-6’’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 19.5 (CH_3); 55.9 (OCH_3); 102.1 (C-5); 115.7 (d, *J* = 21.7 Hz, C-3’ and C-5’); 121.5 (C-3’’ and C-5’’); 123.8 (C-7*); 124.3 (C-3*); 129.2 (C-4a); 130.5 (C-8); 131.5 (d, *J* = 8.4 Hz, C-2’ and C-6’); 133.9 (d, *J* = 3.1 Hz, C-1’); 141.4 (C-1’’*); 141.7 (C-8a*); 145.0 (C-4); 149.0 (C-2); 149.9 (C=N-NH); 150.9 (C-4’’ and C-6’’); 159.6 (C-6); 162.9 (C=O); 163.6 (d, *J* = 249.5 Hz, C-4’) ppm.

IR (NaCl) ν: 3357.2 (N-H), 2974.7 (C-H), 1687.8 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{24}H_{19}FN_4O_2$ (M **=** 414.44): C, 69.55; H, 4.62; N, 13.52. Found: C, 69.40; H, 4.44; N, 13.31.

N'-[(6-Methoxy-4-methylquinolin-2-yl)(4-methoxyphenyl)methylene] isonicotinohydrazide (13c)



Prepared from quinoline **8c** (0.080g, 0.260 mmol) and isoniazid (0.036 g, 0.260 mmol).

Reaction time: 24h.

Yield: 0.083 g (75%). Orange solid, mp: 206-208 °C.

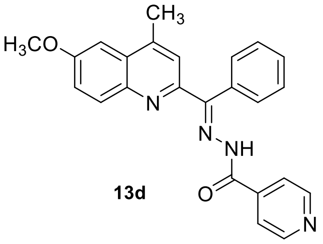
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.65 (s, 3H, CH_3); 3.87 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 6.97 (d, *J* = 8.7 Hz, 2H, H-3’ and H-5’); 7.23 (d, *J* = 2.6 Hz, 1H, H-5); 7.29 (s, 1H, H-3); 7.51 (dd, *J* = 9.2, 2.7 Hz, 2H, H-7); 7.62 (d, *J* = 8.7 Hz, 2H, H-2’ and H-6’); 7.84 (d, *J* = 4.6 Hz, 2H, H-3’’ and H-5’’); 7.99 (d, *J* = 9.2 Hz, 1H, H-8); 8.84 (d, *J* = 5.9 Hz, 2H, H-2’’ and H-6’’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 19.4 (CH_3); 55.5 (OCH_3); 55.9 (OCH_3); 102.1 (C-5); 113.9 (C-3’ and C-5’); 121.4 (C-3’’ and C-5’’); 123.6 (C-7*); 124.6 (C-3*); 129.1 (C-4a); 130.1 (C-1’); 130.5 (C-8); 131.0 (C-2’ and C-6’); 141.5 (C-1’’*); 141.7 (C-8a*); 144.8 (C-4); 150.1 (C-2*); 150.1 (C=N-NH*); 150.8 (C-2’’ and C-6’’); 159.5 (C-6); 160.7 (C-4’); 162.6 (C=O) ppm.

IR (NaCl) ν: 3356.3 (N-H), 2921.9 (C-H), 1680.5 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{25}H_{22}N_4O_3$ (M = 426.48): C, 70.41; H, 5.20; N, 13.14. Found: C, 70.30; H, 5.14; N, 12.91.

N'-[(6-Methoxy-4-methylquinolin-2-yl)(phenyl)methylene]isonicotinohydrazide (13d)



13d

Prepared from quinoline **8a** (0.090 g, 0.324 mmol) and isoniazid (0.045 g, 0.324 mmol).

Reaction time: 24 h.

Yield: 0.050 g (39%). White solid, mp: 208-209 °C.

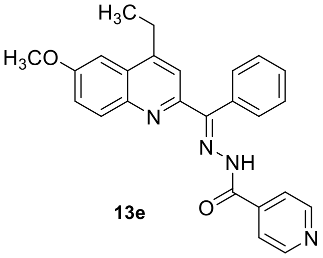
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.64 (s, 3H, CH_3); 4.01 (s, 3H, OCH_3); 7.23 (d, *J* = 2.6 Hz, 1H, H-5); 7.39-7.55 (m, 5H, H-3', H-4', H-5', H-3 and H-7); 7.65-7.69 (m, 2H, H-2' and H-6'); 7.88 (d, *J* = 5.9 Hz, 2H, H-3'' and H-5''); 7.98 (d, *J* = 9.1 Hz, 1H, H-8); 8.85 (d, *J* = 5.9 Hz, 2H, H-2'' and H-6'') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 19.4 (CH_3); 55.9 (OCH_3); 102.1 (C-5); 121.5 (C-3'' and C-5''); 123.7 (C-7*); 124.5 (C-3*); 128.6 (C-3' and C-5'); 129.1 (C-4a); 129.4 (C-8); 129.6 (C-2' and C-6'); 130.5 (C-4'); 137.8 (C-1'); 141.5 (C-1''*); 141.6 (C-8a*); 144.8 (C-4); 150.0 (C-2*); 150.1 (C=N-NH*); 150.8 (C-2'' and C-6''); 159.5 (C-6); 162.9 (C=O) ppm.

IR (NaCl) ν: 3349.0 (N-H), 2937.9 (C-H), 1683.9 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{24}H_{20}N_4O_2$ (M = 396.45): C, 72.71; H, 5.09; N, 14.13. Found: C, 72.52; H, 4.84; N, 13.91.

N'-[(4-Ethyl-6-methoxyquinolin-2-yl)(phenyl)methylene]isonicotinohydrazide (13e)



13e

Prepared from quinoline **8d** (0.100 g, 0.343 mmol) and isoniazid (0.047 g, 0.343 mmol).

Reaction time: 24 h.

Yield: 0.074 g (53%). Orange solid, mp: 140-141 °C.

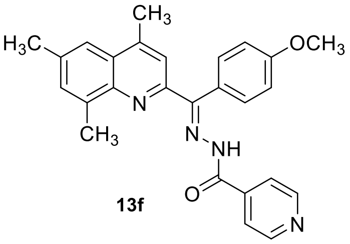
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.29 (t, *J* = 7.5 Hz, 3H, $\mathrm{CH_2C}\mathit{H_3}$); 3.03 (q, *J* = 7.5 Hz, 2H, $\mathrm{C}\mathit{H_2}\mathrm{CH_3}$); 4.00 (s, 3H, OCH$_3$); 7.26-7.29 (m, 2H, H-5 and H-3); 7.40-7.55 (m, 4H, H-3', H-4', H-5' and H-7); 7.66 (dd, *J* = 6.5, 2.8 Hz, 2H, H-2' and H-6'); 7.87 (d, *J* = 5.9 Hz, 2H, H-3'' and H-5''); 7.99 (d, *J* = 9.2 Hz, 1H, H-8); 8.85 (d, *J* = 5.8 Hz, 2H, H-2'' and H-6'') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 13.8 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$); 25.6 ($\mathit{C}\mathrm{H_2CH_3}$); 55.9 (OCH$_3$); 101.8 (C-5); 121.5 (C-3'' and C-5''); 122.7 (C-7*); 123.5 (C-3*); 128.3 (C-4a); 128.5 (C-3' and C-5'); 129.5 (C-8); 129.6 (C-2' and C-6'); 130.7 (C-4'); 137.7 (C-1'); 141.5 (C-3'', C-4'' and C-5''); 141.8 (C-8a); 150.2 (C-4*); 150.3 (C-2*); 150.4 (C=N-NH*); 150.8 (C-2'' and C-6''); 159.5 (C-6); 162.9 (C=O) ppm.

IR (NaCl) *ν*: 3384.0 (N-H), 2920.2 (C-H), 1689.4 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{25}H_{22}N_4O_2$ (M **=** 410.48): C, 73.15; H, 5.40; N, 13.65. Found: C, 72.95; H, 5.46; N, 13.43.

N'-[(4-Methoxyphenyl)(4,6,8-trimethylquinolin-2-yl)methylene] isonicotinohydrazide (13f)



13f

Prepared from quinoline **8n** (0.070 g, 0.230 mmol) and isoniazid (0.032 g, 0.230 mmol).

Reaction time: 24 h.

Yield: 0.035 g (38%). White solid, mp: 189-190 °C.

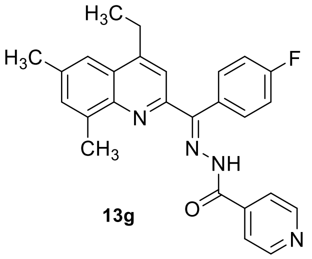
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 2.52 (s, 3H, CH$_3$); 2.57 (s, 3H, CH$_3$); 2.66 (s, 3H, CH$_3$); 3.86 (s, 3H, OCH$_3$); 6.96 (d, *J* = 8.8 Hz, 2H, H-3' and H-5'); 7.25 (s, 1H, H-3); 7.42-7.54 (m, 2H, H-5 and H-7); 7.62-7.67 (m, 4H, H-2', H-6', H-3'' and H-5''); 8.73 (d, *J* = 5.2 Hz, 2H, H-2'' and H-6'') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 18.6 (CH$_3$); 19.5 (CH$_3$); 22.2 (CH$_3$); 55.5 (OCH$_3$); 113.9 (C-3' and C-5'); 121.1 (C-3); 121.7 (C-5); 124.0 (C-7); 128.0 (C-1'); 130.1 (C-4a); 130.9 (C-3'' and C-5''); 133.3 (C-2' and C-6'); 136.5 (C-6); 138.2 (C-8); 141.8 (C-4''); 143.8 (C-4); 145.9 (C-8a); 150.2 (C-2); 150.6 (C-2'' and C-6''); 151.2 (C=N-NH); 160.8 (C-4'); 163.6 (C=O) ppm.

IR (NaCl) *ν*: 3344.1 (N-H), 2920.2 (C-H), 1678.2 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{26}H_{24}N_4O_2$ (M = 424.50): C, 73.56; H, 5.70; N, 13.20. Found: C, 73.36; H, 5.74; N, 12.98.

N'-[(4-Fluorophenyl)(4,6,8-trimethylquinolin-2-yl)methylene] isonicotinohydrazide (13g)



13g

Prepared from quinoline **8o** (0.100 g, 0.325 mmol) and isoniazid (0.047 g, 0.325 mmol).

Reaction time: 24 h.

Yield: 0.052 g (77%). Yellow solid, mp: 177-180 °C.

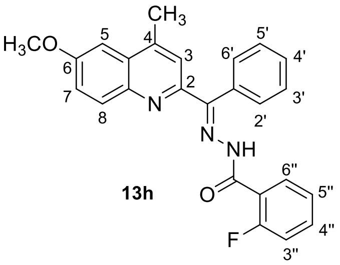
^{1}H-NMR (DMSO, 250 MHz) *δ*: 1.21 (t, *J* = 6.8 Hz, 3H, $CH_2C\mathit{H_3}$); 2.42 (s, 3H, $ArCH_3$); 3.06-3.08 (m, 2H, $C\mathit{H_2}CH_3$); 7.28-7.90 (m, 9H, H-3, H-5, H-7, H-2', H-3', H-5', H-6', H-3'' and H-5''); 8.79 (s, 2H, H-2'' and H-6''); 11.13 (s, 1H, NH) ppm.

^{13}C-NMR (DMSO, 63 MHz) *δ*: 14.3 ($CH_2\mathit{C}H_3$); 18.1 ($ArCH_3$); 21.6 ($ArCH_3$); 24.8 ($\mathit{C}H_2CH_3$); 115.6 (d, *J* = 21.8 Hz, C-3' and C-5'); 120.7 (C-3); 121.4 (C-3'' and C-5''); 124.0 (C-5); 126.7 (d, *J* = 3.5 Hz, C-1'); 131.0 (d, *J* = 8.4 Hz, C-2' and C-6'); 132.8 (C-7); 136.3 (C-4a); 137.7 (C-6); 141.8 (C-8); 144.0 (C-4''); 148.1 (C-4); 149.5 (C-8a); 149.8 (C-2'' and C-6''); 150.1 (C-2); 151.5 (C=N-NH); 162.9 (C=O); 166.2 (d, *J* = 264.6 Hz, C-4') ppm.

IR (NaCl) *ν*: 3358.1 (N-H), 3034.2 (C-H), 1687.0 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{26}H_{23}FN_4O$ (M = 426,50): C, 73.22; H, 5.44; N, 13.14. Found: C, 73.02; H, 5.27; N, 12.93.

2-Fluoro-N'-[(6-methoxy-4-methylquinolin-2-yl)(phenyl)methylene] benzohydrazide (13h)



13h

Prepared from quinoline **8a** (0.080g, 0.288 mmol) and 2-fluorobenzohydrazide (0.044 g, 0.288 mmol).

Reaction time: 24 h.

Yield: 0.085. g (71%). White solid, mp: 154-156 °C.

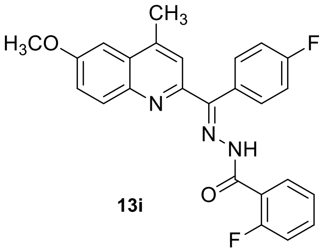
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.43 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.97-7.14 (m, 4H, H-3'',H-5'', H-7 and H-5); 7.20-7.39 (m, 5H, H-3, H-8, H-3', H-4' and H-5'); 7.45-7.56 (m, 2H, H-2' and H-6'); 7.94 (d, *J* = 9.2, 1.4 Hz, 1H, H-6''); 8.03 (td, *J* = 7.7, 1.8 Hz, 1H, H-4'') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 19.3 (CH_3); 55.8 (OCH_3); 101.8 (C-5); 116.1 (d, *J* = 23.8 Hz, C-3''); 121.2 (d, *J* = 12.8 Hz, C-1''); 123.0 (C-7); 124.0 (C-3); 124.9 (d, *J* = 3.3 Hz, C-6''); 128.4 (C-3' and C-5'); 129.0 (C-4a); 129.3 (C-8); 129.5 (C-2' and C-6'); 131.3 (C-8); 131.4 (C-4'); 131.7 (d, *J* = 2.5 Hz, C-5''); 133.7 (d, *J* = 9.0 Hz, C-4''); 138.2 (C-1'); 142.3 (C-8a); 144.3 (C-4); 149.8 (C-2); 159.2 (C=N-NH); 160.5 (d, *J* = 250.1 Hz, C-2''); 161.0 (C-6); 161.0 (C=O) ppm.

IR (NaCl) *v*: 3332.5 (N-H), 3052.1 (C-H), 1677.6 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{25}H_{20}FN_3O_2$ (M = 413,45): C, 72.63; H, 4.88; N, 10.16. Found: C, 72.36; H, 4.98; N, 10.11.

2-Fluoro-N'-[(4-fluorophenyl)(6-methoxy-4-methylquinolin-2-yl)methylene] benzohydrazide (13i)



13i

Prepared from quinoline **8b** (0.070 g, 0.237 mmol) and 2-fluorobenzohydrazide (0.036 g, 0.237 mmol).

Reaction time: 24 h.

Yield: 0.077. g (75%). White solid, mp: 189-190 °C.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 2.74 (s, 3H, CH_3); 4.10 (s, 3H, OCH_3); 7.18-7.44 (m, 6H, H-3, H-5, H-3', H-5', H-3'' and H-5''); 7.57-7.63 (m, 2H, H-7 and C-8); 7.73-7.85 (m, 2H, C-2' and C-6'); 8.23 (dd, *J* = 9.2, 1.4 Hz, 1H, H-6''); 8.32 (td, *J* = 7.7, 1.8 Hz, 1H, H-4'') ppm.

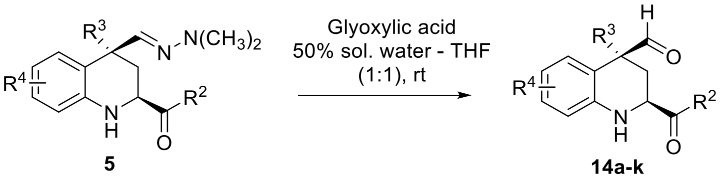
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 19.4 (CH_3); 55.8 (OCH_3); 101.8 (C-5); 115.5 (d, *J* = 21.4 Hz, C-3' and C-5'); 116.1 (d, *J* = 23.9 Hz, C-3''); 121.0 (d, *J* = 12.8 Hz, C-1''); 123.1 (C-7); 123.7 (C-3); 125.0 (d, *J* = 3.2 Hz, C-6''); 129.0 (C-4a); 131.3 (C-2' and C-6'); 131.5 (C-8); 132.7 (d, *J* = 2.4 Hz, C-5''); 133.7 (d, *J* = 9.0 Hz, C-4''); 134.2 (d, *J* = 3.3 Hz, C-1'); 142.3 (C-8a); 144.4 (C-4); 148.8 (C-2); 149.5 (C-2a); 159.2 (C-6); 160.0 (d, *J* = 189.1 Hz, C-2''); 161.0 (d, *J* = 2.9 Hz, C=O); 164.0 (d, *J* = 188.7 Hz, C-4') ppm.

IR (NaCl) *v*: 3346.7 (N-H), 3042.1 (C-H), 1663.8 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{25}H_{19}F_2N_3O_2$ (M **=** 431,44): C, 69.60; H, 4.44; N, 9.74. Found: C, 69.67; H, 4.48; N, 9.59.

10.7 - Synthesis of benzo-fused bicyclic systems

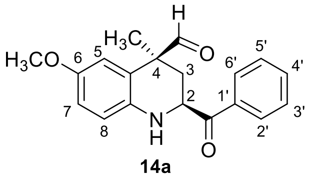
10.7.1 - Synthesis of aldehydes 14a-k



To a stirred solution of tetrahydroquinoline **5** (0.6 mmol) in THF (4 mL), 2 mL of glyoxylic acid solution (50 wt% in water) was added. The mixture was stirred at room temperature until the starting material disappeared as indicated by TLC (the reaction times are indicated in the table). After this time, the THF was removed under reduced pressure, the solution was neutralized with a saturated solution of $NaHCO_3$ and finally the aqueous suspension was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with a gradient from neat petroleum ether to 9 : 1 petroleum ether–ethyl acetate.

Cmpd	R^4	R^3	R^2	t (h)	Yield (%)
14a	6-OCH_3	CH_3	C_6H_5	20	85
14b	6-OCH_3	CH_3	4-$OCH_3C_6H_4$	24	80
14c	6-OCH_3	CH_3	4-FC_6H_4	15	82
14d	6,8-$(CH_3)_2$	CH_3	C_6H_5	22	78
14e	6-OCH_3	CH_3	2-furyl	22	83
14f	6-OCH_3	CH_3	2-thienyl	15	84
14g	6-OCH_3	CH_2CH_3	C_6H_5	22	81
14h	6,8-$(OCH_3)_2$	CH_3	4-$OCH_3C_6H_4$	19	95
14i	6,8-$(CH_3)_2$	CH_2CH_3	C_6H_5	18	83
14j	6-CH_3	CH_3	4-$OCH_3C_6H_4$	18	90
14k	6-OCH_3	CH_2CH_3	4-$OCH_3C_6H_4$	24	85

(±)-(2*S**,4*S**)-2-Benzoyl-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14a)



14a

Prepared from tetrahydroquinoline **5a** (0.200 g, 0.626 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 20 h.

Yield: 0.164 g (85%). Pale yellow solid.

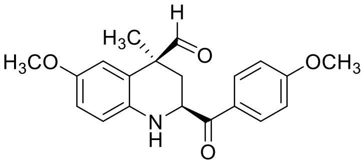
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.60 (s, 3H, CH_3); 1.79-2.06 (m, 2H, H-3); 3.72 (s, 3H, OCH_3); 4.81 (bs, 1H, NH); 4.97 (dd, *J* = 11.4, 3.0 Hz, 1H, H-2); 6.40 (s, 1H, H-5); 6.79 (m, 2H, H-7 and H-8); 7.52 (t, *J* = 7.5 Hz, 2H, H-3’ and H-5’); 7.64 (t, *J* = 7.3 Hz, 1H, H-4’); 7.94 (d, *J* = 7.4 Hz, 2H, H-2’ and H-6’); 9.31 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.4 (CH_3); 33.9 (C-3); 49.8 (C-4); 53.1 (C-2); 55.9 (OCH_3); 113.2 (C-5); 115.6 (C-7); 118.1 (C-8); 121.1 (C-4a); 128.4 (C-3’ and C-5’); 129.2 (C-2’ and C-6’); 134.1 (C-4’); 134.5 (C-1’); 137.1 (C-8a); 152.7 (C-6); 198.8 (C=O); 201.2 (CHO) ppm.

IR ν: 3391.2 (N-H), 2930.9 (C-H), 1702.9 (C=O), 1681.8 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{19}H_{19}NO_3$ (M = 309.37): C, 73.77; H, 6.19; N, 4.53. Found: C. 73.45; H, 5.98; N, 4.32.

(±)-(2*S**,4*S**)-6-Methoxy-2-(4-methoxybenzoyl)-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14b)



14b

Prepared from tetrahydroquinoline **5c** (0.210 g, 0.601 mmol) in 4 mL of THF and 2 mL of glyoxylic acid in 50% of water.

Reaction time: 24 h.

Yield: 0.162 g (80%). Yellow solid.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.60 (s, 3H, CH_3); 1.77-2.06 (m, 2H, H-3); 3.73 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.63 (bs, 1H, NH); 4.92 (dd, *J* = 11.3, 3.0 Hz, 1H, H-2); 6.40 (s, 1H, H-5);

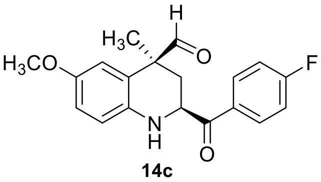
6.78 (m, 2H, H-7 and H-8); 6.99 (d, *J* = 8.9 Hz, 2H, H-3' and H-5'); 7.94 (d, *J* = 8.9 Hz, 2H, H-2' and H-6'); 9.30 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.3 (CH_3); 34.2 (C-3); 49.9 (C-4); 52.7 (C-2); 55.7 (OCH_3); 55.9 (OCH_3); 113.2 (C-5); 114.4 (C-3' and C-5'); 115.6 (C-7); 118.2 (C-8); 121.2 (C-4a); 127.3 (C-1'); 130.8 (C-2' and C-6'); 137.3 (C-8a); 152.7 (C-6); 164.2 (C-4'); 197.1 (C=O); 201.3 (CHO) ppm.

IR *ν*: 3386.5 (N-H), 2923.7 (C-H), 1716.8 (C=O), 1669.2 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{20}H_{21}NO_4$ (M = 339.39): C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55: H, 6.01; N, 3.96.

(±)-(2*S**,4*S**)-2-(4-Fluorobenzoyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14c)



14c

Prepared from tetrahydroquinoline **5b** (0.200 g, 0.540 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 15 h.

Yield: 0.146 g (82%). Orange solid.

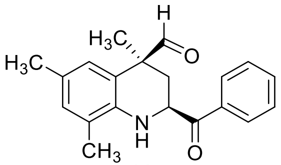
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.59 (s, 3H, CH_3); 1.83-2.02 (m, 2H, H-3); 3.73 (s, 3H, OCH_3); 4.93 (dd, *J* = 10.3, 4.1 Hz, 1H, H-2); 6.41 (bs, 1H, H-5); 6.79 (bs, 2H, H-8 and H-7); 7.20 (d, *J* = 8.6 Hz, 2H, H-3' and H-5'); 7.99 (dd, *J* = 8.6, 5.3 Hz, 2H, H-2' and H-6'); 9.32 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.5 (CH_3); 33.9 (C-3); 49.7 (C-4); 53.1 (C-2); 55.9 (OCH_3); 113.2 (C-5); 115.5 (C-7); 116.5 (d, *J* = 22.0 Hz, C-3' and C-5'); 118.1 (C-8); 121.1 (C-4a); 131.0 (d, *J* = 3.0 Hz, C-1'); 131.2 (d, *J* = 9.4 Hz, C-2' and C-6'); 137.0 (C-8a); 152.8 (C-6); 166.2 (d, *J* = 256.9 Hz, C-4'); 197.3 (C=O); 201.1 (CHO) ppm.

IR *ν*: 3393.2 (N-H), 2964.8 (C-H), 1707.6 (C=O), 1688.9 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{19}H_{18}FNO_3$ (M = 327.36): C, 69.71; H, 5.54; N, 4.28. Found: C, 69.54; H, 5.35; N, 4.16.

(±)-(2*S**,4*S**)-2-Benzoyl-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14d)



14d

Prepared from tetrahydroquinoline **5e** (0.200 g, 0.630 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 22 h.

Yield: 0.171 g (78%). Yellow solid.

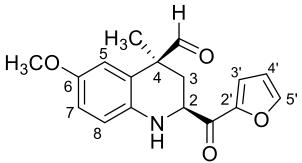
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.60 (s, 3H, CH$_3$); 1.83 (t, *J* = 12.3 Hz, 1H, H-3ax); 2.00 (dd, *J* = 12.8, 2.7 Hz, 1H, H-3eq); 2.22 (s, 3H, ArCH$_3$); 2.23 (s, 3H, ArCH$_3$); 4.62 (bs, 1H, NH); 5.02 (dd, *J* = 11.8, 3.0 Hz, 1H, H-2); 6.53 (s, 1H, H-7); 6.90 (s, 1H, H-5); 7.53 (t, *J* = 7.4 Hz, 2H, H-3' and H-5'); 7.64 (t, *J* = 7.3 Hz, 1H, H-4'); 7.96 (d, *J* = 7.1 Hz, 2H, H-2' and H-6'); 9.28 (s, 1H, CHO) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 17.5 (CH$_3$); 20.5 (ArCH$_3$); 23.3 (ArCH$_3$); 33.9 (C-3); 49.7 (C-4); 53.1 (C-2); 119.5 (C-4a); 124.2 (C-8); 126.4 (C-5); 127.1 (C-6); 128.4 (C-3' and C-5'); 129.2 (C-2' and C-6'); 130.9 (C-7); 134.1 (C-4'); 134.5 (C-1'); 138.8 (C-8a); 198.9 (C=O); 201.5 (CHO) ppm.

IR *ν*: 3407.9 (N-H), 2921.1 (C-H), 1705.7 (C=O), 1684.6 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{20}H_{21}NO_2$ (M = 307.39): C, 78.15; H, 6.89; N, 4.56. Found: C, 77.88; H, 6.67; N, 4.43.

(±)-(2*S**,4*S**)- 2-(2-Furylcarbonyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14e)



14e

Prepared from tetrahydroquinoline **5p** (0.200 g, 0.585 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 22 h.

Yield: 0.147 g (83%). Orange solid.

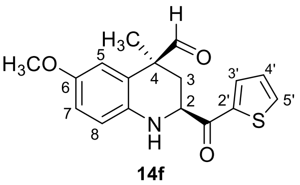
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.56 (s, 3H, CH$_3$); 1.97 (t, *J* = 12.5 Hz, 1H, H-3ax); 2.12 (dd, *J* = 12.7, 2.9 Hz, 1H, H-3eq); 3.71 (s, 3H, OCH$_3$); 4.53 (bs, 1H, NH); 4.73 (dd, *J* = 11.4, 2.9 Hz, 1H, H-2); 6.39 (d, *J* = 2.5 Hz, 1H, H-5); 6.60 (dd, *J* = 3.6, 1.7 Hz, 1H, H-4’); 6.69-6.79 (m, 2H, H-7 and H-8); 7.34 (dd, *J* = 3.6, 0.5 Hz, 1H, H-3’); 7.64 (dd, *J* = 1.6, 0.6 Hz, 1H, H-5’); 9.34 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.3 (CH_3); 33.3 (C-3); 49.5 (C-4); 53.7 (C-2); 55.9 (OCH_3); 112.8 (C-4’); 113.2 (C-5); 115.4 (C-7); 117.9 (C-8); 118.8 (C-3’); 121.1 (C-4a); 137.0 (C-8a); 147.0 (C-5’); 151.0 (C-2’); 152.7 (C-6); 187.7 (C=O); 201.3 (CHO) ppm.

IR ν: 3392.0 (N-H), 2920.9 (C-H), 1702.3 (C=O), 1676.5 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{17}H_{17}NO_4$ (M = 299.33): C, 68.21; H, 5.72; N, 4.68. Found: C, 67.98; H, 5.43; N, 4.32.

(±)-(2*S**,4*S**)- 6-Methoxy-4-methyl-2-(2-thienylcarbonyl)-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14f)



14f

Prepared from tetrahydroquinoline **5q** (0.200 g, 0.559 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 15 h.

Yield: 0.147 g (84%). Yellow solid.

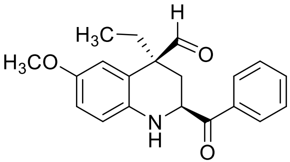
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.58 (s, 3H, CH_3); 2.01-2.12 (m, 2H, H-3); 3.72 (s, 3H, OCH_3); 4.53 (bs, 1H, NH); 4.78 (dd, *J* = 8.3, 6.1 Hz, 1H, H-2); 6.41 (s, 1H, H-5); 6.70-6.83 (m, 2H, H-7 and H-8); 7.20 (dd, *J* = 4.9, 3.9 Hz, 1H, H-4’); 7.73 (dd, *J* = 5.0, 1.1 Hz, 1H, H-5’); 7.82 (dd, *J* = 3.8, 1.1 Hz, 1H, H-3’); 9.33 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 23.5 (CH_3); 34.8 (C-3); 49.7 (C-4); 54.6 (C-2); 55.9 (OCH_3); 113.2 (C-5); 115.6 (C-7); 118.1 (C-8); 121.2 (C-4a); 128.6 (C-4’); 132.7 (C-3’); 134.7 (C-5’); 136.9 (C-8a); 140.7 (C-2’); 152.9 (C-6); 191.8 (C=O); 201.1 (CHO) ppm.

IR ν: 3391.4 (N-H), 2926.9 (C-H), 1702.4 (C=O), 1656.8 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{17}H_{17}NO_3S$ (M= 315.39): C, 64.74; H, 5.43; N, 4.44. Found: C, 64.51; H, 5.34; N, 4.21.

(±)-(2*S**,4*S**)-2-(Benzoyl)-4-ethyl-6-methoxy-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14g)



14g

Prepared from tetrahydroquinoline **5d** (0.200 g, 0.599 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 22 h.

Yield: 0.156 g (81%). Yellow oil.

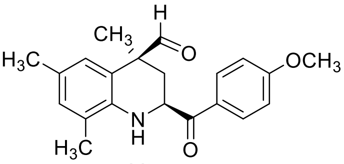
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.00 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); 1.85 (t, *J* = 12.5 Hz, 1H, H-3ax); 1.97-2.13 (m, 2H, CH_2CH_3); 2.19 (dd, *J* = 13.2, 3.1 Hz, 1H, H-3eq); 3.73 (s, 3H, OCH_3); 4.61 (bs, 1H, NH); 4.94 (dd, *J* = 11.6, 3.1 Hz, 1H, H-2); 6.47 (bs, 1H, H-5); 6.77-6.78 (m, 2H, H-7 and H-8); 7.52 (t, *J* = 7.5 Hz, 2H, H-3' and H-5'); 7.63 (t, *J* = 7.4 Hz, 1H, H-4'); 7.86-7.99 (m, 2H, H-2' and H-6'); 9.32 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 9.4 (CH_2CH_3); 28.8 (CH_2CH_3); 30.5 (C-3); 52.8 (C-4); 53.2 (C-2); 56.0 (OCH_3); 113.9 (C-5); 115.2 (C-7); 117.7 (C-8); 119.8 (C-4a); 128.3 (C-3' and C-5'); 129.2 (C-2' and C-6'); 133.9 (C-4'); 134.9 (C-1'); 137.6 (C-8a); 152.3 (C-6); 199.5 (C=O); 201.4 (CHO) ppm.

IR *ν*: 3395.4 (N-H), 2922.1 (C-H), 1720.1 (C=O), 1694.3 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{20}H_{21}NO_3$ (M = 323.39): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.01; H, 6.34; N, 4.12.

(±)-(2*S**,4*S**)-2-(4-Methoxybenzoyl)-4,6,8-trimethyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14h)



14h

Prepared from tetrahydroquinoline **5h** (0.250 g, 0.659 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 19 h.

Yield: 0.211 g (95%). Yellow solid.

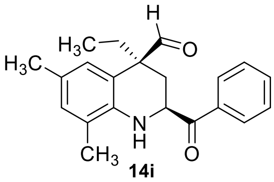
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.59 (s, 3H, CH_3); 1.82 (t, *J* = 12.8 Hz, 1H, H-3ax); 1.98 (dd, *J* = 12.8, 2.8 Hz, 1H, H-3eq); 2.21 (s, 6H, 2 x CH_3); 3.90 (s, 3H, OCH_3); 4.97 (dd, *J* = 12.8, 2.8 Hz, 1H, H-2); 6.51 (s, 1H, H-7); 6.89 (s, 1H, H-5); 6.93-7.04 (m, 2H, H-3' and H-5'); 7.89-7.99 (m, 2H, H-2' and H-6'); 9.26 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 17.6 (Ar-CH_3); 20.5 (Ar-CH_3); 23.3 (CH_3); 34.1 (C-3); 49.8 (C-4); 52.6 (C-2); 55.7 (OCH_3); 114.4 (C-3' and C-5'); 119.5 (C-4a); 124.3 (C-8); 126.4 (C-5); 127.0 (C-6); 127.2 (C-1'); 130.8 (C-7 and C-2' and C-6'); 138.9 (C-8a); 164.2 (C-4'); 197.2 (C=O); 201.6 (CHO) ppm.

IR *ν*: 3386.8 (N-H), 2919.2 (C-H), 1717.4 (C=O), 1668.5 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{21}H_{23}NO_3$ (M = 337.42): C, 74.75; H, 6.87; N, 4.15. Found: C, 74.43; H, 6.66; N, 3.89.

(±)-(2*S**,4*S**)-2-Benzoyl-6,8-dimethyl-4-ethyl-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14i)



14i

Prepared from tetrahydroquinoline **5j** (0.150 g, 0.412 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 18 h.

Yield: 0.112 g (83%). Yellow oil.

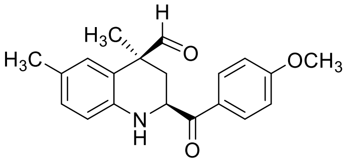
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.02 (t, *J* = 7.4 Hz, 3H, $CH_2\mathit{CH_3}$); 1.80 (m, 1H, H-3ax); 1.97-2.35 (m, 9H, H-3eq, 2 x CH_3 and $C\mathit{H_2}CH_3$); 4.63 (s, 1H, NH); 5.02 (dd, *J* = 11.9, 2.7 Hz, 1H, H-2); 6.58 (s, 1H, H-7); 6.91 (bs, 1H, H-5); 7.47-7.74 (m, 3H, H-3', H-4' and H-5'); 7.96 (d, *J* = 8.0 Hz, 2H, H-2' and H-6'); 9.30 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 9.4 ($CH_2\mathit{C}H_3$); 17.6 (Ar-CH_3); 20.6 (Ar-CH_3); 28.6 ($\mathit{C}H_2CH_3$); 30.4 (C-3); 52.8 (C-4); 53.1 (C-2); 118.1 (C-4a); 123.8 (C-8); 126.5 (C-6); 126.8 (C-5); 128.3 (C-3' and C-5'); 129.1 (C-2' and C-6'); 130.8 (C-7); 133.9 (C-4'); 134.8 (C-1'); 139.0 (C-8a); 199.4 (C=O); 201.6 (CHO) ppm.

IR *ν*: 3385.3 (N-H), 2921.1 (C-H), 1704.3 (C=O), 1660.5 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{21}H_{23}NO_2$ (M = 321.42): C, 78.47; H, 7.21; N, 4.36. Found: 78.23; H, 7.04; N, 4.12.

(±)-(2*S**,4*S**)-4,6-Dimethyl-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14j)



14j

Prepared from tetrahydroquinoline **5i** (0.150 g, 0.410 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 18 h.

Yield: 0.117 g (90%). Yellow solid.

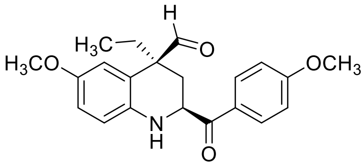
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.58 (s, 3H, CH_3); 1.78-2.06 (m, 2H, H-3); 2.22 (s, 3H, $ArCH_3$); 3.89 (s, 3H, OCH_3); 4.92 (dd, *J* = 11.4, 3.0 Hz, 1H, H-2); 6.62 (s, 1H, H-5); 6.72 (d, *J* = 8.2 Hz, 1H, H-8); 6.88-7.06 (m, 3H, H-3’, H-5’ and H-7); 7.93 (d, *J* = 8.9 Hz, 2H, H-2’ and H-6’); 9.27 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 20.5 (Ar-CH_3); 23.3 (CH_3); 34.0 (C-3); 49.5 (C-4); 52.5 (C-2); 55.7 (OCH_3); 114.3 (C-3’ and C-5’); 116.6 (C-8); 119.8 (C-4a); 127.2 (C-6); 127.5 (C-1’); 128.7 (C-5); 129.6 (C-7); 130.7 (C-2’ and C-6’); 141.0 (C-8a); 164.1 (C-4’); 197.0 (C=O); 201.5 (CHO) ppm.

IR *ν*: 3361.2 (N-H), 2966.5 (C-H), 1688.0 (C=O), 1594.1 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{20}H_{21}NO_3$ (M = 323.39): C, 74.28; H, 6.55; N, 4.33. Found: C, 74.01; H, 6.23; N, 4.12.

(±)-(2*S**,4*S**)-4-Ethyl-6-methoxy-2-(4-methoxybenzoyl)-1,2,3,4-tetrahydroquinoline-4-carbaldehyde (14k)



14k

Prepared from tetrahydroquinoline **5k** (0.150 g, 0.380 mmol) in 4 mL of THF and 2 mL of glyoxylic acid solution (50 wt% in water).

Reaction time: 18 h.

Yield: 0.115 g (85%). Yellow oil.

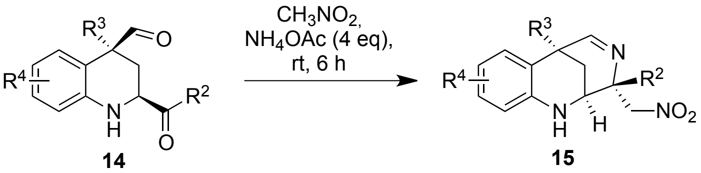
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.01 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); 1.83 (t, *J* = 12.8 Hz, 1H, H-3ax); 1.95-2.14 (m, 2H, CH_2CH_3); 2.18 (dd, *J* = 13.3, 3.1 Hz, 1H, H-3eq); 3.73 (s, 3H, OCH_3); 3.89 (s, 3H, OCH_3); 4.90 (dd, J = 11.7, 3.1 Hz, 1H, H-2); 6.46 (m, 1H, H-5); 6.75-6.79 (m, 2H, H-7 and H-8); 6.97-7.01 (m, 2H, H-3' and H-5'); 7.88-8.01 (m, 2H, H-2' and H-6'); 9.32 (s, 1H, CHO) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 9.5 ($CH_2\mathit{C}H_3$); 28.8 ($\mathit{C}H_2CH_3$); 30.8 (C-3); 52.7 (C-4); 52.9 (OCH_3); 55.7 (C-2); 56.0 (OCH_3); 113.9 (C-5); 114.3 (C-3' and C-5'); 115.2 (C-7); 117.9 (C-8); 119.8 (C-4a); 127.5 (C-1'); 130.7 (C-2' and C-6'); 137.6 (C-8a); 152.3 (C-6); 164.2 (C-4'); 197.7 (C=O); 201.5 (CHO) ppm.

IR ν: 3383.1 (N-H), 2921.0 (C-H), 1713.6 (C=O), 1662.9 (C=O) cm^{-1}.

Elemental Analysis: Calc. for $C_{21}H_{23}NO_4$ (M = 353.42): C, 71.37; H, 6.56; N, 3.96. Found: C, 71.12; H, 6.43; N, 3.75.

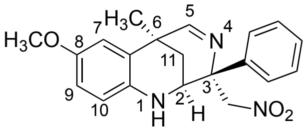
10.7.2 - Synthesis of 1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4] diazocine derivatives 15a-k



Cmpd	R^2	R^3	R^4
15a	C_6H_5	CH_3	8-OCH_3
15c	4-FC_6H_4	CH_3	8-OCH_3
15d	C_6H_5	CH_3	8,10-$(CH_3)_2$
15e	2-furyl	CH_3	8-OCH_3
15f	2-thienyl	CH_3	8-OCH_3
15g	C_6H_5	CH_2CH_3	8-OCH_3
15h	4-$OCH_3C_6H_4$	CH_3	8,10-$(CH_3)_2$
15i	C_6H_5	CH_2CH_3	8,10-$(CH_3)_2$
15j	4-$OCH_3C_6H_4$	CH_3	8-CH_3
15k	4-$OCH_3C_6H_4$	CH_2CH_3	8-OCH_3

A mixture of the corresponding aldehyde **14a-k** (1.00 mmol), ammonium acetate (4.00 mmol) and nitromethane (5 mL) was stirred at room temperature for 6 h, filtered and concentrated. The oily obtained residue was dissolved in Cl_2CH_2 (10 mL), washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of the solvent provided the products that were used directly for the next step without purification. ^{1}H-NMR and ^{13}C-NMR spectra have been recorded in the case of compounds **15a-k** to confirm the chemical structure of these intermediates.

(±)-(2*S**,3*S**,6*S**)-8-Methoxy-6-methyl-3-nitromethyl-3-phenyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15a)



15a

Prepared from aldehyde **14a** (0.095 g, 0.307 mmol) in 2 mL of nitromethane and ammonium acetate (0.095 g).

Yield: 0.108 g (quantitative). Pale yellow oil.

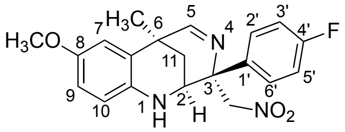
$C_{20}H_{21}N_3O_3$ (M = 351.41)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.64 (s, 3H, CH_3); 1.96 (d, J = 3.0 Hz, 2H, H-11); 3.60 (bs, 1H, NH); 3.72 (s, 3H, OCH_3); 4.10 (t, J = 3.0 Hz, 1H, H-2); 4.72 (d, J = 10.8 Hz, 1H, CH_2NO_2); 4.87 (d, J = 10.8 Hz, 1H, CH_2NO_2); 6.05 (d, J = 8.7 Hz, 1H, H-10); 6.52 (dd, J = 8.7, 2.8 Hz, H-9); 6.72 (d, J = 2.8 Hz, 1H, H-7); 7.27-7.43 (m, 5H, H-2', H-3', H-4', H-5' and H-6'); 7.90 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 22.0 (CH_3); 29.5 (C-11); 35.3 (C-6); 50.1 (C-2); 56.0 (OCH_3); 68.8 (C-3); 83.0 (CH_2NO_2); 110.9 (C-7); 113.6 (C-9); 114.1 (C-10); 122.2 (C-6a); 126.2 (C-2' and C-6'); 127.8 (C-4'); 129.1 (C-3' and C-5'); 136.2 (C-1'); 140.7 (C-10a); 151.7 (C-8); 169.5 (CH=N) ppm.

IR ν: 3409.5 (N-H), 2927.6 (C-H), 1646.8 (C=N), 1548.4 (NO_2), 1375.0 (NO_2) cm^{-1}.

(±)-(2*S**,3*S**,6*S**)-3-(4-Fluorophenyl)-8-methoxy-6-methyl-3-nitromethyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15c)



15c

Prepared from aldehyde **14c** (0.080 g, 0.244 mmol) in 2 mL of nitromethane and ammonium acetate (0.075 g).

Yield: 0.092 g (quantitative). Yellow oil.

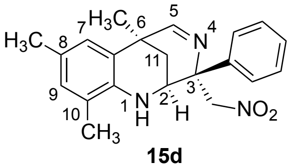
$C_{20}H_{20}FN_3O_3$ (M = 369.40)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.64 (s, 3H, CH_3); 1.97 (d, J = 2.6 Hz, 2H, H-11); 3.72 (s, 3H, OCH_3); 4.09 (m, 1H, H-2); 4.68 (d, J = 10.8 Hz, 1H, CH_2NO_2); 4.82 (d, J = 10.8 Hz, 1H, CH_2NO_2); 6.10 (d, J = 8.6 Hz, 1H, H-10); 6.54 (dd, J = 8.6, 2.8 Hz, H-9); 6.71 (d, J = 2.8 Hz, 1H, H-7); 7.08 (dd, J = 11.9, 5.4 Hz, 2H, H-3' and H-5'); 7.23-7.35 (m, 2H, H-2' and H-6'); 7.87 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 22.0 (CH_3); 29.5 (C-11); 35.4 (C-6); 50.1 (C-2); 56.0 (OCH_3); 68.3 (C-3); 82.9 (CH_2NO_2); 111.0 (C-7); 113.7 (C-9); 114.1 (C-10); 116.0 (d, *J* = 21.4 Hz, C-3' and C-5'); 122.1 (C-6a); 128.1 (d, *J* = 8.0 Hz, C-2' and C-6'); 136.1 (C-10a); 136.5 (d, *J* = 3.4 Hz, C-1'); 151.8 (C-8); 162.1 (d, *J* = 247.6 Hz, C-4'); 169.5 (CH=N) ppm.

IR *ν*: 2926.5 (C-H), 1599.2 (C=N), 1553.1 (NO_2), 1375.2 (NO_2) cm^{-1}.

(±)-(2*S**,3*S**,6*S**)-6,8,10-trimethyl-3-nitromethyl-3-phenyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15d)



15d

Prepared from aldehyde **14d** (0.085 g, 0.276 mmol) in 2 mL of nitromethane and ammonium acetate (0.085 g).

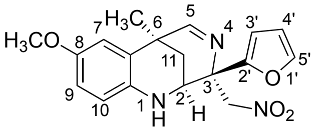
Yield: 0.096 g (quantitative). Yellow oil.

$C_{21}H_{23}N_3O_2$ (M = 349.43)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.46 (s, 3H, CH_3); 1.67 (s, 3H, CH_3); 1.96-2.04 (m, 2H, H-11); 2.23 (s, 3H, CH_3); 3.44 (s, 1H, NH); 4.11 (m, 1H, H-2); 4.79 (d, *J* = 10.8 Hz, 1H, CH_2NO_2); 4.95 (d, *J* = 10.8 Hz, 1H, CH_2NO_2); 6.65 (s, 1H, H-9); 6.84 (s, 1H, H-7); 7.24-7.45 (m, 5H, H-2', H-3', H-4', H-5' and H-6'); 7.95 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 16.4 ($ArCH_3$); 20.6 ($ArCH_3$); 22.3 (CH_3); 29.5 (C-11); 34.9 (C-6); 50.4 (C-2); 69.0 (C-3); 82.7 (CH_2NO_2); 120.4 (C-6a); 122.9 (C-7); 125.7 (C-10); 126.0 (C-4'); 126.9 (C-8); 127.7 (C-2' and C-6'); 129.0 (C-3' and C-5'); 129.7 (C-1'); 137.5 (C-9); 140.8 (C-10a); 170.4 (CH=N) ppm.

(±)-(2*S**,3*S**,6*S**)-3-(2-Furyl)-8-methoxy-6-methyl-3-nitromethyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15e)



15e

Prepared from aldehyde **14e** (0.070 g, 0.234 mmol) in 2 mL of nitromethane and ammonium acetate (0.072 g).

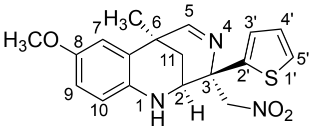
Yield: 0.085 g (quantitative). Yellow oil.

$C_{18}H_{19}N_3O_4$ (M = 341.37)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.62 (s, 3H, CH_3); 1.78-1.98 (m, 2H, H-11); 3.71 (s, 3H, OCH_3); 3.82 (bs, 1H, NH); 4.17 (s, 1H, H-2); 4.62 (d, *J* = 10.3 Hz, 1H, CH_2NO_2); 4.84 (d, *J* = 10.3 Hz, 1H, CH_2NO_2); 6.16-6.25 (m, 2H, H-10 and H-3'); 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H, H-4'); 6.56 (dd, *J* = 8.7, 2.8 Hz, 1H, H-9); 6.71 (d, *J* = 2.8 Hz, 1H, H-7); 7.46 (bs, 1H, H-5'); 7.80 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 22.0 (CH_3); 28.7 (C-11); 35.5 (C-6); 49.1 (C-2); 55.9 (OCH_3); 67.5 (C-3); 81.1 (CH_2NO_2); 109.7 (C-3'); 110.9 (C-7*); 111.0 (C-4'*); 113.7 (C-9); 113.9 (C-10); 121.7 (C-6a); 136.4 (C-10a); 142.2 (C-5'); 151.5 (C-8); 153.3 (C-2'); 170.6 (CH=N) ppm.

(±)-(2*S**,3*S**,6*S**)-8-Methoxy-6-methyl-3-nitromethyl-3-(2-thienyl)-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15f)



15f

Prepared from aldehyde **14f** (0.070 g, 0.221 mmol) in 2 mL of nitromethane and ammonium acetate (0.068 g).

Yield: 0.084 g (quantitative). Yellow oil.

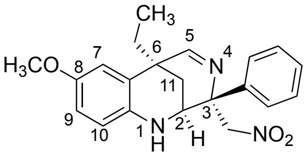
$C_{18}H_{19}N_3O_3S$ (M = 357.47)

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.61 (s, 3H, CH_3); 1.78-2.08 (m, 2H, H-11); 3.71 (s, 3H, OCH_3); 3.99 (bs, 1H, NH); 4.31 (s, 1H, H-2); 4.64 (d, *J* = 11.0 Hz, 1H, CH_2NO_2); 4.72 (d, *J* = 10.9 Hz, 1H, CH_2NO_2); 6.21 (d, *J* = 8.6 Hz, 1H, H-10); 6.56 (dd, *J* = 8.6, 2.7 Hz, 1H, H-9); 6.70 (d, *J* = 2.7 Hz, 1H, H-7); 6.91 (d, *J* = 3.6 Hz, 1H, H-3'); 7.06 (d, *J* = 5.0, 3.7 Hz, 1H, H-4'); 7.29 (d, *J* = 5.1 Hz, 1H, H-5'); 7.71 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 21.6 (CH_3); 28.8 (C-11); 35.9 (C-6); 49.7 (C-2); 56.0 (OCH_3); 67.7 (C-3); 82.7 (CH_2NO_2); 110.7 (C-7); 113.7 (C-9); 114.0 (C-10); 121.9 (C-6a); 122.7 (C-3'); 125.8 (C-5'*); 127.5 (C-4'*); 136.7 (C-10a); 145.8 (C-2'); 151.6 (C-8); 169.3 (CH=N) ppm.

IR ν: 3394.1 (N-H), 2921.9 (C-H), 1640.7 (C=N), 1547.5 (NO_2), 1374.3 (NO_2) cm^{-1}.

(±)-(2*S**,3*S**,6*S**)-6-Ethyl-8-methoxy-3-nitromethyl-3-phenyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15g)



15g

Prepared from aldehyde **14g** (0.071 g, 0.219 mmol) in 2 mL of nitromethane and ammonium acetate (0.068 g).

Yield: 0.087 g (quantitative). Yellow oil.

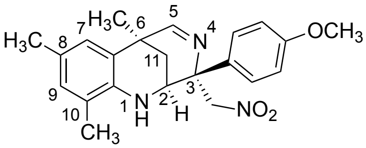
$C_{21}H_{23}N_3O_3$ (M = 365.43)

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.04 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); 1.25 (m, 1H, CH_2CH_3); 1.42 (m, 1H, CH_2CH_3); 1-91-2.13 (m, 2H, H-11); 3.71 (s, 3H, OCH_3); 4.12 (bs, 1H, H-2); 4.72 (d, *J* = 10.8 Hz, 1H, CH_2NO_2); 4.85 (d, *J* = 10.8 Hz, 1H, CH_2NO_2); 6.05 (d, *J* = 8.7 Hz, 1H, H-10); 6.50 (dd, *J* = 8.7, 2.8 Hz, H-9); 6.69 (d, *J* = 2.8 Hz, 1H, H-7); 7.24-7.38 (m, 5H, H-2', H-3', H-4', H-5' and H-6'); 7.84 (bs, 1H, CH=N) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 7.9 (CH_2CH_3); 25.2 (CH_2CH_3); 26.9 (C-11); 38.9 (C-6); 50.0 (C-2); 55.9 (OCH_3); 68.9 (C-3); 83.0 (CH_2NO_2); 111.0 (C-7); 113.4 (C-9); 114.4 (C-10); 120.5 (C-6a); 126.2 (C-2' and C-6'); 127.8 (C-4'); 129.1 (C-3' and C-5'); 136.9 (C-1'); 140.7 (C-10a); 151.7 (C-8); 169.6 (CH=N) ppm.

IR ν: 3419.4 (N-H), 2923.4 (C-H), 1648.4 (C=N), 1550.3 (NO_2), 1374.5 (NO_2) cm^{-1}.

(±)-(2*S**,3*S**,6*S**)-3-(4-Methoxyphenyl)-3-nitromethyl-6,8,10-trimethyl-1,2,3,6-tetrahydro-2,6-methanobenzo[*e*][1,4]diazocine (15h)



15h

Prepared from aldehyde **14h** (0.190 g, 0.563 mmol) in 5 mL of nitromethane and ammonium acetate (0.173 g).

Yield: 0.233 g (quantitative). Yellow oil.

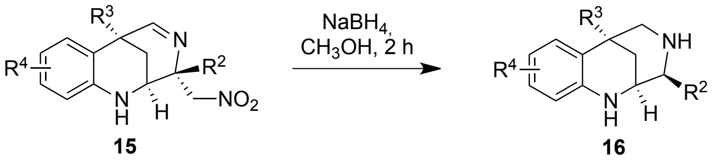
$C_{22}H_{25}N_3O_3$ (M = 379.46)

^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.53 (s, 3H, CH_3); 1.65 (s, 3H, CH_3); 1.96-1.99 (m, 2H, H-11); 2.21 (s, 3H, CH_3); 3.47 (bs, 1H, NH); 3.80 (s, 3H, OCH_3); 4.09 (s, 1H, H-2); 4.75 (d, *J* = 10.7 Hz, 1H, CH_2NO_2); 4.89 (d, *J* = 10.7 Hz, 1H, CH_2NO_2); 6.65 (s, 1H, H-9); 6.83 (s, 1H, H-7); 6.90 (d, *J* = 8.9 Hz, 2H, H-3’ and H-5’); 7.19 (d, *J* = 8.9 Hz, 2H, H-2’ and H-6’); 7.90 (s, 1H, CH=N) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) *δ*: 16.6 ($ArCH_3$); 20.6 ($ArCH_3$); 22.3 (CH_3); 29.5 (C-11); 34.9 (C-6); 50.4 (C-2); 55.4 (OCH_3); 68.5 (C-3); 82.8 (CH_2NO_2); 114.3 (C-3’, C-5’ and C-7); 120.5 (C-6a); 120.8 (C-1’); 122.9 (C-9); 125.7 (C-10); 127.2 (C-2’*); 129.7 (C-6’*); 132.6 (C-10a); 137.6 (C-4’); 158.9 (CH=N) ppm.

IR *ν*: 3426.7 (NH), 2918.3 (C-H), 1600.3 (C=N), 1547.9 (NO_2), 1375.5 (NO_2) cm^{-1}.

10.7.3 - Synthesis of 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[e][1,4] diazocine products 16a-k

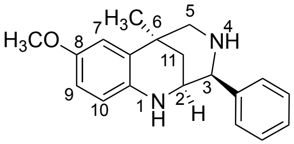


Cmpd	R^2	R^3	R^4	Yield (%)
16a	C_6H_5	CH_3	8-OCH_3	78
16b	4-$OCH_3C_6H_4$	CH_3	8-OCH_3	75
16c	4-FC_6H_4	CH_3	8-OCH_3	68
16d	C_6H_5	CH_3	8,10-$(CH_3)_2$	64
16e	2-furyl	CH_3	8-OCH_3	73
16f	2-thienyl	CH_3	8-OCH_3	70
16g	C_6H_5	CH_2CH_3	8-OCH_3	91
16h	4-$OCH_3C_6H_4$	CH_3	8,10-$(CH_3)_2$	89
16i	C_6H_5	CH_2CH_3	8,10-$(CH_3)_2$	80
16j	4-$OCH_3C_6H_4$	CH_3	8-CH_3	76
16k	4-$OCH_3C_6H_4$	CH_2CH_3	8-OCH_3	82

To a stirred solution of compounds **15a**-**k** (1 eq, 0.200 mmol approx) in methanol (5 mL), $NaBH_4$ (3 eq) was added. The reaction mixture was stirred at rt for 2 h until the starting material disappeared. Then water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, and then the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel eluting with a gradient from neat petroleum ether to 1 : 1 petroleum ether–ethyl acetate.

Data of compounds **16a**-**k**, and the experimental conditions employed for their syntheses are indicated below.

(±)-(2*S,3*S**,6*S**)-8-Methoxy-6-methyl-3-phenyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16a)**



16a

Prepared from crude imine **15a** (0.108 g, 0.307 mmol) in 5 mL of methanol and sodium borohydride powder (0.035 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.070 g (78%). Yellow solid, mp: 119-121 °C.

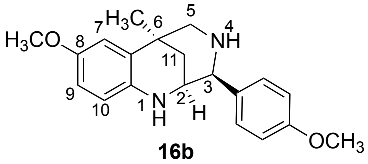
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.35 (s, 3H, CH_3); 1.95 (dd, *J* = 12.4, 2.7 Hz, 1H, H-11); 2.10 (m, 1H, H-11); 2.89 (m, 2H, H-5); 3.42 (bs, 1H, H-2); 3.76 (s, 3H, OCH_3); 3.99 (bs, 1H, H-3); 6.42 (d, *J* = 8.6 Hz, 1H, H-10); 6.64 (dd, *J* = 8.6, 2.8 Hz, 1H, H-9); 6.77 (d, *J* = 2.8 Hz, 1H, H-7); 7.33 (m, 5H, H-2', H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 24.0 (CH_3); 32.5 (C-6); 37.6 (C-11); 51.1 (C-2); 56.0 (OCH_3); 61.5 (C-5); 66.4 (C-3); 111.7 (C-7); 112.7 (C-9); 113.3 (C-10); 126.7 (C-2' and C-6'); 127.2 (C-4'); 128.6 (C-3' and C-5'); 128.8 (C-6a); 140.0 (C-10a); 142.0 (C-1'); 151.5 (C-8) ppm.

IR ν: 3389.8 (N-H), 2923.3 (C-H), 1552.4 (N-H), 1499.5 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{19}H_{22}N_2O$ (M = 294.39): C, 77.52; H, 7.53; N, 9.52. Found: C, 77.51; H, 7.32; N, 9.27.

(±)-(2*S**,3*S**,6*S**)-8-Methoxy-3-(4-methoxyphenyl)-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16b)



16b

Prepared from crude imine **15b** (0.103 g, 0.303 mmol) in 5 mL of methanol and sodium borohydride powder (0.034 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.073 g (75%). Orange paste.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.35 (s, 3H, CH_3); 1.93 (dd, *J* = 12.4, 2.6 Hz, 1H, H-11); 2.09 (m, 1H, H-11); 2.78-2.96 (m, 2H, H-5); 3.37 (s, 1H, H-2); 3.76 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.94 (s, 1H, H-3); 6.43 (d, *J* = 8.6 Hz, 1H, H-10); 6.64 (dd, *J* = 8.6, 2.8 Hz, 1H, H-9); 6.76 (d, *J* =

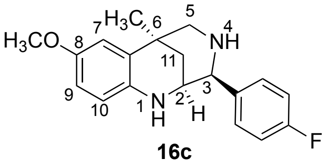
2.8 Hz, 1H, H-7); 6.89 (d, *J* = 8.6 Hz, 2H, H-3’ and H-5’); 7.19 (d, *J* = 8.6 Hz, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 24.0 (CH_3); 32.4 (C-6); 37.5 (C-11); 51.1 (C-2); 55.4 (OCH_3); 56.0 (OCH_3); 61.5 (C-5); 65.7 (C-3); 111.7 (C-7); 112.7 (C-9); 113.3 (C-10); 114.0 (C-3’ and C-5’); 127.7 (C-2’ and C-6’); 128.9 (C-6a); 134.1 (C-10a); 140.0 (C-1’); 151.5 (C-8); 159.7 (C-4’) ppm.

IR *ν*: 3397.4 (N-H), 2921.5 (C-H), 1607.8 (N-H), 1497.4 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{20}H_{24}N_2O_2$ (M = 324.42): C, 74.05; H, 7.46; N, 8.63. Found: C, 73.98; H, 7.30; N, 8.35.

(±)-(2*S**,3*S**,6*S**)-3-(4-Fluorophenyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16c)



16c

Prepared from crude imine **15c** (0.092 g, 0.244 mmol) in 5 mL of methanol and sodium borohydride powder (0.028 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.052 g (68%). Orange paste.

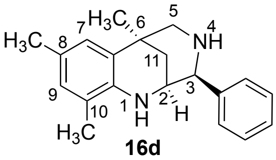
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.40 (s, 3H, CH_3); 1.98 (dd, *J* = 12.5, 2.7 Hz, 1H, H-11); 2.13 (m, 1H, H-11); 2.86-3.01 (m, 2H, H-5); 3.43 (t, *J* = 3.9 Hz, 1H, H-2); 3.80 (s, 3H, OCH_3); 4.01 (bs, 1H, H-3); 6.47 (d, *J* = 8.6 Hz, 1H, H-10); 6.69 (dd, *J* = 8.6, 2.8 Hz, 1H, H-9); 6.81 (d, *J* = 2.8 Hz, 1H, H-7); 7.03-7.15 (m, 2H, H-3’ and H-5’); 7.22-7.37 (m, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 24.0 (CH_3); 32.4 (C-6); 37.5 (C-11); 51.1 (C-2); 56.0 (OCH_3); 61.4 (C-5); 65.7 (C-3); 111.8 (C-7); 112.8 (C-9); 113.3 (C-10); 115.4 (d, *J* = 21.1 Hz, C-3’ and C-5’); 128.3 (d, *J* = 7.8 Hz, C-2’ and C-6’); 128.8 (C-6a); 137.7 (d, *J* = 3.1 Hz, C-1’); 139.8 (C-10a); 151.6 (C-8); 162.0 (d, *J* = 245.6 Hz, C-4’) ppm.

IR *ν*: 3401.2 (N-H), 2921.1 (C-H), 1601.1 (N-H), 1495.1 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{19}H_{21}FN_2O$ (M = 312.38): C, 73.05; H, 6.78; N, 8.97. Found: C, 72.88; H, 6.64; N, 8.68.

(±)-(2*S**,3*S**,6*S**)-6,8,10-Trimethyl-3-phenyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16d)



16d

Prepared from crude imine **15d** (0.096 g, 0.275 mmol) in 5 mL of methanol and sodium borohydride powder (0.031 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.051 g (64%). Orange oil.

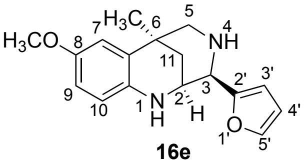
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.25 (s, 3H, CH$_3$); 1.58 (s, 1H, NH); 1.81-1.85 (m, 4H, CH$_3$ and H-11eq); 1.98 (t, J = 13.0 Hz, 1H, H-11ax); 2.14 (s, 3H, CH$_3$); 2.69-2.83 (m, 2H, H-5); 3.34 (bs, 1H, H-2); 3.46 (s, 1H, H-3); 3.88 (s, 1H, NH); 6.66 (s, 1H, H-9); 6.76 (s, 1H, H-7); 7.07-7.28 (m, 5H, H-2', H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 17.5 (ArCH$_3$); 20.8 (ArCH$_3$); 24.2 (CH$_3$); 32.2 (C-6); 37.7 (C-11); 51.5 (C-2); 61.7 (C-5); 66.4 (C-3); 119.6 (C-10); 123.5 (C-7); 125.0 (C-8); 126.7 (C-2' and C-6'); 127.1 (C-6a); 127.2 (C-4'); 128.5 (C-3' and C-5'); 129.2 (C-9); 141.3 (C-10a); 142.1 (C-1') ppm.

IR ν: 3424.3 (N-H), 2914.7 (C-H), 1612.0 (N-H), 1484.0 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{20}H_{24}N_2$ (M = 292.43): C, 82.15; H, 8.27; N, 9.58. Found: C, 81.90; H, 8.06; N, 9.32.

(±)-(2*S**,3*S**,6*S**)-3-(2-Furyl)-8-methoxy-6-methyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16e)



16e

Prepared from crude imine **15e** (0.085 g, 0.234 mmol) in 5 mL of methanol and sodium borohydride powder (0.028 g).

Purification: petroleum ether: ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.048 g (73%). Orange solid, mp: 90-93 °C.

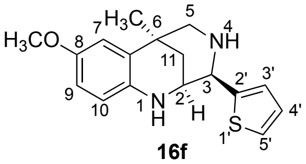
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.32 (s, 3H, CH$_3$); 1.86 (dd, *J* = 12.6, 2.6 Hz, 1H, H-11eq); 2.05 (ddd, *J* = 12.6, 3.8, 2.5 Hz, 1H, H-11ax); 2.76-2.90 (m, 2H, H-5); 3.69 (s, 1H, H-2); 3.74 (s, 3H, OCH$_3$); 4.01 (s, 1H, H-3); 6.19 (dt, *J* = 3.2, 0.9 Hz, 1H, H-3’); 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H, H-4’); 6.44 (d, *J* = 8.6 Hz, 1H, H-10); 6.62 (dd, *J* = 8.6, 2.8 Hz, 1H, H-9); 6.73 (d, *J* = 2.8 Hz, 1H, H-7); 7.37 (d, *J* = 1.5 Hz, 1H, H-5’) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 24.0 (CH$_3$); 32.5 (C-6); 36.5 (C-11); 48.6 (OCH$_3$); 56.0 (C-2); 61.1 (C-5); 61.5 (C-3); 106.0 (C-7); 110.4 (C-3’*); 111.7 (C-4’*); 112.9 (C-9); 113.6 (C-10); 128.3 (C-6a); 139.7 (C-10a); 141.6 (C-5’); 151.6 (C-8); 155.5 (C-1’) ppm.

IR *ν*: 3235.8 (N-H), 2921.0 (C-H), 1585.4 (N-H), 1498.4 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{17}H_{20}N_2O_2$ (M = 284.36): C, 71.81; H, 7.09; N, 9.85. Found: C, 71.66; H, 7.10; N, 9.62.

(±)-(2*S**,3*S**,6*S**)-8-Methoxy-6-methyl-3-(2-thienyl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16f)



16f

Prepared from crude imine **15f** (0.084 g, 0.221 mmol) in 5 mL of methanol and sodium borohydride powder (0.027 g).

Purification: petroleum ether: ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.046 g (70%). Yellow solid, mp: 101-103 °C.

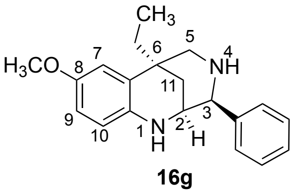
^{1}H-NMR (CDCl$_3$, 250 MHz) *δ*: 1.34 (s, 3H, CH$_3$); 1.90 (dd, *J* = 12.6, 2.7 Hz, 1H, H-11-eq); 2.09 (d, *J* = 12.4 Hz, 1H, H-11ax); 2.76-3.00 (m, 2H, H-5); 3.57 (s, 1H, H-2); 3.75 (s, 3H, OCH$_3$); 4.21 (s, 1H, H-3); 6.46 (d, *J* = 8.6 Hz, 1H, H-10); 6.63 (dd, *J* = 8.6, 2.8 Hz, 1H, H-9); 6.74 (d, *J* = 2.8 Hz, 1H, H-7); 6.94 (d, *J* = 3.4 Hz, 1H, H-3’); 7.02 (m, 1H, H-4’); 7.24 (m, 1H, H-5’) ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) *δ*: 24.0 (CH$_3$); 32.5 (C-6); 37.0 (C-11); 50.7 (OCH$_3$); 56.0 (C-2); 61.5 (C-5); 63.1 (C-3); 111.7 (C-7); 112.9 (C-9); 113.7 (C-10); 123.2 (C-4’); 124.3 (C-3’*); 127.0 (C-5’*); 128.6 (C-6a); 139.5 (C-1’*); 145.9 (C-10a*); 151.7 (C-8) ppm.

IR *ν*: 3404.7 (N-H), 2921.9 (C-H), 1498.1 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{17}H_{20}N_2OS$ (M = 300.42): C, 67.97; H, 6.71; N, 9.32; S, 10.67. Found: C, 67.71; H, 6.53; N, 9.13; S, 10.44.

(±)-(2*S**,3*S**,6*S**)-6-Ethyl-8-methoxy-3-phenyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16g)



16g

Prepared from crude imine **15g** (0.087 g, 0.219 mmol) in 5 mL of methanol and sodium borohydride powder (0.027 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.061 g (91%). Yellow paste.

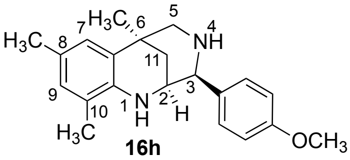
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 0.95 (t, J = 7.4 Hz, 3H, CH$_2$C*H$_3$*); 1.54 (m, 1H, *CH$_2$*CH$_3$); 1.85 (dd, *J* = 12.4, 2.8 Hz, 1H, H-11eq); 2.03 (dq, *J* = 14.8, 7.5 Hz, 1H, *CH$_2$*CH$_3$); 2.27 (m, 1H, H-11ax); 2.79-2.86 (m, 2H, H-5); 3.44 (s, 1H, H-2); 3.78 (s, 3H, OCH$_3$); 4.04 (s, 1H, H-3); 6.45 (d, *J* = 8.5 Hz, 1H, H-10); 6.65 (dd, *J* = 8.5, 2.8 Hz, 1H, H-9); 6.71 (d, *J* = 2.8 Hz, 1H, H-7); 7.26-7.42 (m, 5H, H-2', H-3', H-4', H-5' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 7.8 (CH$_2$CH$_3$); 28.6 (*C*H$_2$CH$_3$); 33.3 (C-11); 36.0 (C-6); 50.9 (OCH$_3$); 56.0 (C-2); 61.6 (C-5); 66.9 (C-3); 112.1 (C-7); 112.5 (C-9); 113.6 (C-10); 126.7 (C-2' and C-6'*); 127.2 (C-4'); 128.6 (C-3' and C-5'*); 140.9 (C-6a); 142.0 (C-10a); 151.6 (C-8) ppm.

IR *ν*: 3399.9 (N-H), 2921.1 (C-H), 1495.3 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{20}H_{24}N_2O$ (M = 308.43): C, 77.89; H, 7.84; N, 9.08. Found: C, 77.63; H, 8.03; N, 8.89.

(±)-(2*S**,3*S**,6*S**)-3-(4-Methoxyphenyl)-6,8,10-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16h)



16h

Prepared from crude imine **15h** (0.230 g, 0.562 mmol) in 15 mL of methanol and sodium borohydride powder (0.069 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.160 g (89%). Yellow solid, mp: 128-130 °C.

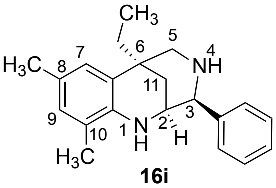
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.37 (s, 3H, CH_3); 1.92-2.04 (m, 5H, ArCH_3, H-11eq and NH); 2.13 (m, 1H, H-11ax); 2.25 (s, 3H, ArCH_3); 2.80-2.94 (m, 2H, H-5); 3.42 (s, 1H, H-2); 3.60 (bs, 1H, NH); 3.82 (s, 3H, OCH_3); 3.97 (s, 1H, H-3); 6.78 (s, 1H, H-9); 6.87-6.91 (m, 3H, H-7, H-3’ and H-5’); 7.17 (d, J = 8.5 Hz, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 17.6 (CH_3); 20.8 (CH_3); 24.3 (CH_3); 32.2 (C-6); 37.6 (C-11); 51.5 (OCH_3); 55.4 (C-2); 61.7 (C-5); 65.8 (C-3); 113.9 (C-3’ and C-5’); 119.7 (C-10); 123.6 (C-7); 125.1 (C-8); 127.1 (C-6a); 127.8 (C-2’ and C-6’); 129.3 (C-9); 134.2 (C-1’); 141.3 (C-10a); 158.8 (C-4’) ppm.

IR ν: 3439.2 (N-H), 2907.5 (C-H), 1607.9 (N-H), 1491.4 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{21}H_{26}N_2O$ (M = 322.45): C, 78.22; H, 8.13; N, 8.69. Found: C, 78.03; H, 7.91; N, 8.41.

(±)-(2_S_*,3_S_*,6_S_*)-8,10-Dimethyl-6-ethyl-3-phenyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[_e_][1,4]diazocine (16i)



16i

Prepared from crude imine **15i** (0.080 g, 0.216 mmol) in 5 mL of methanol and sodium borohydride powder (0.069 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.053 g (80%). Yellow oil.

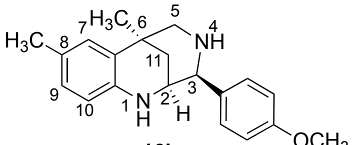
^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 0.96 (t, J = 7.4 Hz, 3H, CH_2CH_3); 1.57 (m, 1H, CH_2CH_3); 1.80-2.18 (m, 6H, CH_3, H-11eq, NH and CH_2CH_3); 2.20-2.41 (m, 4H, CH_3 and H-11ax); 2.80 (dd, J = 12.2, 2.4 Hz, 1H, H-5); 2.95 (d, J = 12.2 Hz, 1H, H-5); 3.50 (s, 1H, H-2); 3.59 (bs, 1H, NH); 4.06 (s, 1H, H-3); 6.79 (s, 1H, H-9); 8.82 (s, 1H, H-7); 7.20-7.45 (m, 5H, H-2’, H-3’, H-4’, H-5’ and H-6’) ppm.

^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 7.9 (CH_2CH_3); 17.6 (CH_3); 20.9 (CH_3); 28.7 (CH_2CH_3); 33.4 (C-11); 35.7 (C-6); 51.3 (C-2); 61.8 (C-5); 66.9 (C-3); 119.8 (C-10); 123.9 (C-7); 124.8 (C-8); 125.1 (C-6a); 126.7 (C-2’ and C-6’); 127.2 (C-4’); 128.5 (C-3’ and C-5’); 129.1 (C-9); 142.1 (C-10a); 142.2 (C-1’) ppm.

IR ν: 3421.8 (N-H), 2909.7 (C-H), 1611.8 (N-H), 1483.0 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{21}H_{26}N_2$ (M = 306.45): C, 82.31; H, 8.55; N, 9.14. Found: C, 82.12; H, 8.30; N, 8.98.

(±)-(2*S**,3*S**,6*S**)-6,8-Dimethyl-3-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16j)



16j

Prepared from crude imine **15j** (0.080 g, 0.216 mmol) in 5 mL of methanol and sodium borohydride powder (0.025 g).

Purification: petroleum ether: ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.050 g (76%). Yellow oil.

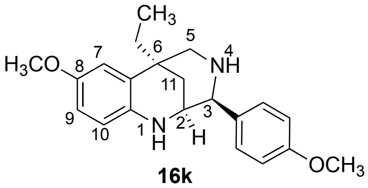
^{1}H-NMR (CDCl$_3$, 250 MHz) δ: 1.35 (s, 3H, CH$_3$); 1.92 (dd, *J* = 12.4, 2.5 Hz, 2H, H-11eq and NH); 2.08 (d, *J* = 12.3 Hz, 1H, H-11ax); 2.25 (s, 3H, ArCH$_3$); 2.76-2.97 (m, 2H, H-5); 3.39 (s, 1H, H-2); 3.81 (s, 4H, OCH$_3$ and NH); 3.94 (s, 1H, H-3); 6.40 (d, *J* = 8.0 Hz, 1H, H-10); 6.78-6.99 (m, 4H, H-7, H-9, H-3' and H-5'); 7.19 (d, *J* = 8.6 Hz, 2H, H-2' and H-6') ppm.

^{13}C-NMR (CDCl$_3$, 63 MHz) δ: 20.9 (CH$_3$); 24.0 (ArCH$_3$); 32.2 (C-6); 37.7 (C-11); 51.2 (OCH$_3$); 55.4 (C-2); 61.6 (C-5); 65.7 (C-3); 112.7 (C-10); 113.9 (C-3' and C-5'); 125.7 (C-8); 125.8 (C-9); 127.5 (C-6a); 127.7 (C-2' and C-6'); 128.0 (C-7); 134.1 (C-1'); 143.4 (C-10a); 158.7 (C-4') ppm.

IR *ν*: 3407.6 (N-H), 2918.7 (C-H), 1610.0 (N-H), 1502.1 (C-C) cm^{-1}.

Elemental analysis calc. for $C_{20}H_{24}N_2O$ (M = 308.43): C, 77.89; H, 7.84; N, 9.08. Found: C, 77.90; H, 7.92; N, 9.05.

(±)-(2*S**,4*S**)-4-Ethyl-6-methoxy-2-(4-methoxyphenyl)-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4]diazocine (16k)



16k

Prepared from crude imine 15**k** (0.058 g, 0.153 mmol) in 5 mL of methanol and sodium borohydride powder (0.069 g).

Purification: petroleum ether:ethyl acetate (from 9:1 to 4:1, v/v).

Yield: 0.042 g (82%). Yellow oil.

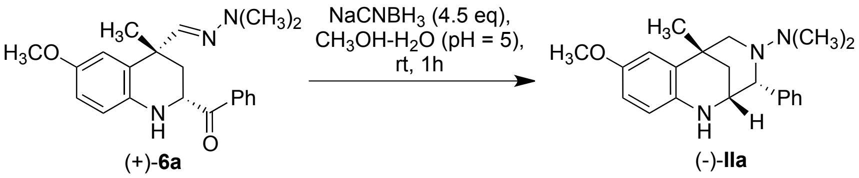
^{1}H-NMR ($\mathrm{CDCl_3}$, 250 MHz) δ: 0.92 (t, J = 7.4 Hz, 3H, $\mathrm{CH_2C}\mathit{H}_3$); 1.54 (m, 1H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); 1.81 (dd, J = 12.4, 2.6 Hz, 1H, H-11eq); 2.00 (m, 1H, $\mathrm{C}\mathit{H}_2\mathrm{CH_3}$); 2.24 (m, 1H, H-11ax); 2.75-2.93 (m, 2H, H-5); 3.38 (s, 1H, H-2); 3.75 (s, 3H, $\mathrm{OCH_3}$); 3.82 (s, 4H, NH and $\mathrm{OCH_3}$); 3.98 (s, 1H, H-3); 6.44 (d, J = 8.5 Hz, 1H, H-10); 6.63 (dd, J = 8.5, 2.8 Hz, 1H, H-9); 6.68 (d, J = 2.8 Hz, 1H, H-7); 6.89 (d, J = 8.6 Hz, 2H, H-3’ and H-5’); 7.18 (d, J = 8.6 Hz, 2H, H-2’ and H-6’) ppm.

^{13}C-NMR ($\mathrm{CDCl_3}$, 63 MHz) δ: 7.9 ($\mathrm{CH_2}\mathit{C}\mathrm{H_3}$); 28.6 ($\mathit{C}\mathrm{H_2CH_3}$); 33.2 (C-6); 36.0 (C-11); 50.9 ($\mathrm{OCH_3}$); 55.4 ($\mathrm{OCH_3}$); 56.0 (C-2); 61.6 (C-5); 66.2 (C-3); 112.1 (C-7); 112.6 (C-9); 113.6 (C-10); 114.0 (C-3’ and C-5’); 126.8 (C-2’ and C-6’); 127.7 (C-6a); 134.0 (C-10a); 140.9 (C-1’); 151.6 (C-8); 158.8 (C-4’) ppm.

IR ν: 3400.3 (N-H), 2921.7 (C-H), 1600.9 (N-H), 1497.1 (C-C) $\mathrm{cm^{-1}}$.

Elemental analysis calc. for $\mathrm{C_{21}H_{26}N_2O_2}$ (M = 338.45): C, 74.53; H, 7.74; N, 8.28. Found: C, 74.32; H, 7.58; N, 8.01.

10.7.4 - Synthesis of an enantiomerically pure 1,2,3,4,5,6-hexahydro-2,6-methanobenzo[*e*][1,4] diazocine, compound (-)-IIa



To a stirred solution of tetrahydroquinoline (+)-**6a** (300 mg, 0.854 mmol) in methanol (9 mL) at room temperature, was added dropwise an HCl-MeOH solution (pH 3) to adjust the pH of the mixture at 4-5. Then, $NaBH_3CN$ (11 mg, 1 eq) was added in a portion, stirring was continued for 10 min, and the pH was again adjusted to 4-5. This process was repeated until 55 mg (5 eq) of $NaBH_3CN$ were employed and pH was 5. Then, solvent was evaporated and the residue was dissolved in Cl_2CH_2 (10 mL), washed with water (1 x 5 mL) and brine (1 x 5 mL). The aqueous layer was extracted with Cl_2CH_2 (3 × 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated. The resulting residue was purified by a silica gel column chromatography, eluting with 8:2 petroleum ether:ethyl acetate.

^{1}H-NMR ($CDCl_3$, 250 MHz) δ: 1.45 (s, 3H, CH_3); 1.80 (dd, *J* = 12.4, 3.1 Hz, 1H, H-11); 2.13 (bs, 7H, $N(CH_3)_2$ and H-11); 2.46 (d, *J* = 9.7 Hz, 1H, H-5); 2.88 (dd, *J* = 9.7, 2.2 Hz, 1H, H-5); 3.26 (bs, 1H, H-2); 3.82-3.84 (m, 4H, OCH_3 and H-3); 6.40 (d, *J* = 8.5 Hz, 1H, H-10); 6.67 (dd, *J* = 8.5, 2.8 Hz, 1H, H-9); 6.81 (d, *J* = 2.8 Hz, 1H, H-8); 7.26-7.42 (m, 5H, Ar) ppm.

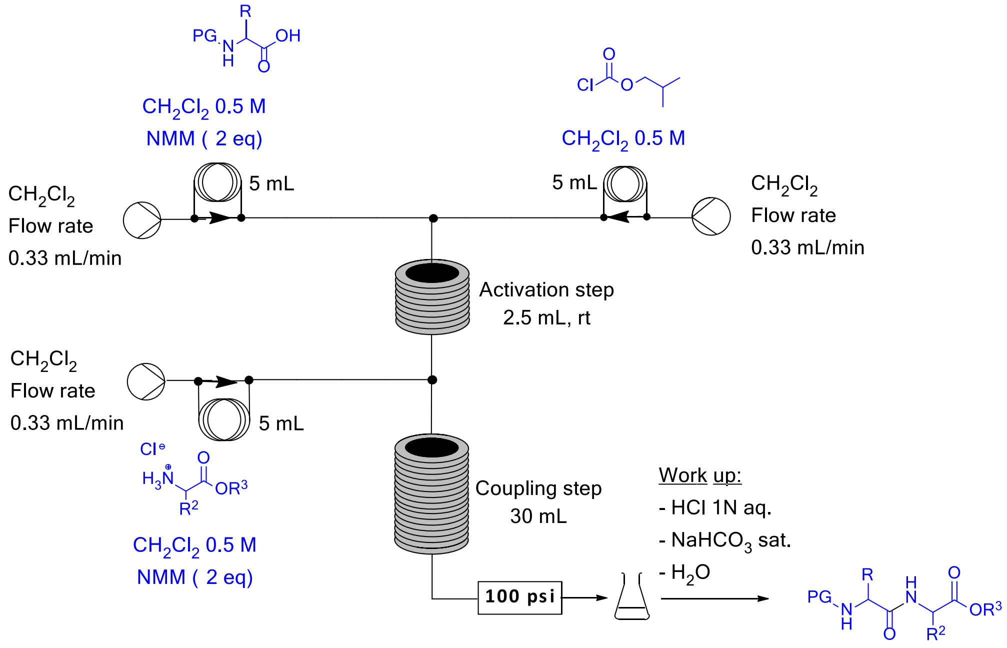
^{13}C-NMR ($CDCl_3$, 63 MHz) δ: 25.0 (CH_3); 33.8 (C-6); 37.8 (C-11); 38.9 ($N(CH_3)_2$); 53.2 (C-2); 56.2 (OCH_3); 56.5 (C-5); 71.5 (C-3); 111.8 (C-7); 112.0 (C-9); 113.0 (C-10); 127.0 (C-4´); 128.1 (C-2´ and C-6´); 128.3 (C-3´ and C-5´); 130.7 (C-6a); 140.2 (C-10a); 142.9 (C-1´); 151.6 (C-8).

IR (NaCl) *ν*: 3406.2 (N-H), 2935.4 (C-H), 2810.9 (C-H), 1503.4 (C=C) cm^{-1}.

10.8 - Peptide synthesis

10.8.1 - Flow synthesis of dipeptides at a 0.5 mmol scale

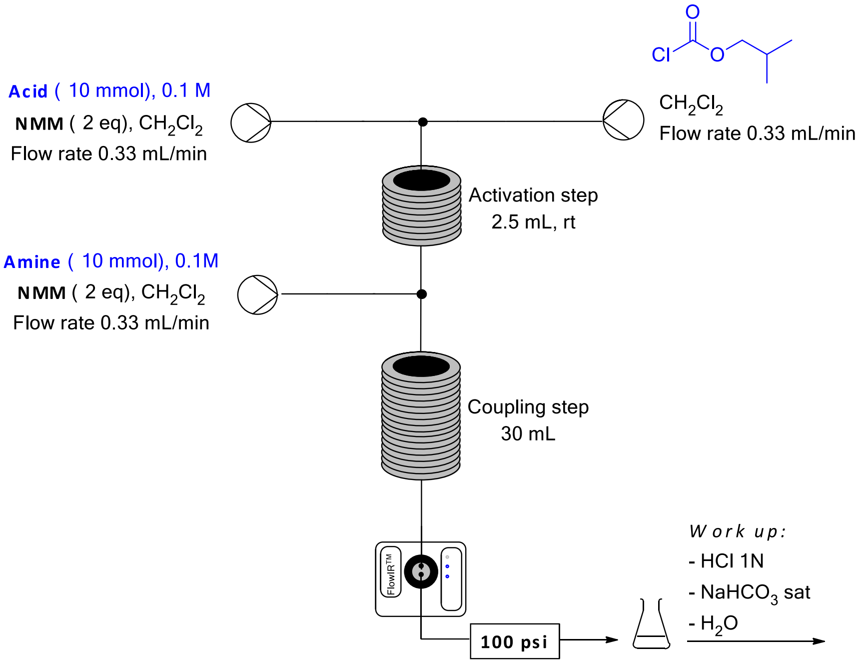
The flow machine was set up according to the scheme described below. A solution of the corresponding protected aminoacid (0.5 mmol) and *N*-methylmorfoline (0.11 mL, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was loaded onto a 5 mL sample loop. A solution of isobutyl chloroformate (0.065 mL, 0.5 mmol) in dry CH_2Cl_2 was loaded onto another 5 mL sample loop. The two loops were switched inline at a flow rate of 0.33 mL/min, the two streams mixed at a T-piece and the mixed stream passed through a 2.5 mL coil at rt. Meanwhile, a solution of the corresponding aminoester (0.5 mmol) and *N*-methylmorfoline (0.11 mL, 1.0 mmol) in dry CH_2Cl_2 (5 mL) was loaded onto a 5 mL sample loop and switched inline at a flow rate of 0.33 mL/min to run with the previously mixed stream at a second T-piece, after which the reaction stream was passed through a 30 mL coil at rt. The stream was then directed through a FlowIR and finally through a 100 psi back-pressure regulator before being collected. The FlowIR readings were used to inform the timings for product collection. The collected organic solvent was washed with a 1M aqueous HCl (30 mL), aqueous saturated sodium bicarbonate (30 mL) and finally with water (30 mL). The organic phase was dried over $MgSO_4$. Finally the crude reaction was concentrated under vacuum and the residue was purified by flash chromatography.



Flow set-up for dipeptide synthesis at a 0.5 mmol scale.

10.8.2 - Flow peptide synthesis at a 10 mmol scale

The flow machine was set up according to scheme described below. A solution of the corresponding acid (10 mmol) and *N*-methylmorfoline (2.2 mL, 20.0 mmol) in dry CH_2Cl_2 (100 mL) was prepared in a 100 mL flask. A solution of isobutyl chloroformate (1.426 mL, 11 mmol) in dry CH_2Cl_2 (100 mL) was prepared in another 100 mL flask. The two were switched inline at a flow rate of 0.33 mL/min, the two streams mixed at a T-piece and the mixed stream passed through a 2.5 mL coil at rt. Meanwhile a solution of the corresponding amine (10 mmol) and *N*-methylmorfoline (2.2 mL, 20.0 mmol) in dry CH_2Cl_2 (100 mL) was prepared in a 100 mL flask, and switched inline at a flow rate of 0.33 mL/min to run with the previously mixed stream at a second T-piece, after which the reaction stream was passed through a 30 mL coil at rt. The stream was then directed through a FlowIR and finally through a 100 psi back-pressure regulator before being collected. The FlowIR readings were used to inform the timings for product collection. The collected organic solvent was washed with a 1M aqueous HCl (300 mL), aqueous saturated sodium bicarbonate (300 mL) and finally with water (300 mL). The organic phase was dried over $MgSO_4$. Finally the crude reaction was concentrated under vacuum, and purification by flash chromatography was performed.

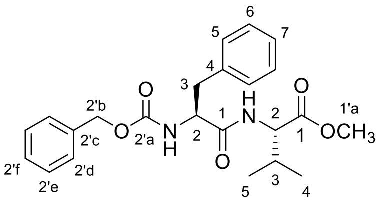


Flow set-up for dipeptide synthesis on a 10 mmol scale.

Entry	Product	M	Mmol	Yield (%)
	Cbz Protected Peptide			
1	Cbz-Phe-Val-OMe[a]	0.1	0.5	99
2	Cbz-Pro-Ile-OMe	0.1	0.5	96
3	Cbz-Thr-Phe-OMe	0.1	0.5	63
4	Cbz-Thr(Bn)-Phe-OMe	0.1	0.5	68
5	Cbz-Ser-Pro-OMe	0.1	0.5	57
6	Cbz-Ser(*t*Bu)-Pro-OMe	0.1	0.5	67
	Boc Protected Peptide			
7	Boc-Gly-Val-OBn[a]	0.1	0.5	98
8	Boc-L-Ala-Val-OBn	0.1	0.5	98
9	Boc-D-Ala-Val-OBn	0.1	0.5	96
10	Boc-Pro-Val-OBn[a]	0.1	0.5	83
12	Boc-Trp(CHO)-Ala-OBn[a]	0.1	0.5	78
13	Boc-Trp(H)-Ala-OBn[a]	0.1	0.5	85
	Fmoc Protected Peptide			
14	Fmoc-Leu-Ile-OMe	0.1	0.5	92
15	Fmoc-Ala-Ile-OMe	0.1	0.5	81
16	Fmoc-Tyr-Ala-OBn	0.1	0.5	44
17	Fmoc-Tyr(O*t*Bu)-Ala-OBn	0.1	0.5	81

[a] Previously characterized in the Ley group. In these cases, only the ^{1}H-NMR is reported.

Cbz-Phe-Val-OMe[225]



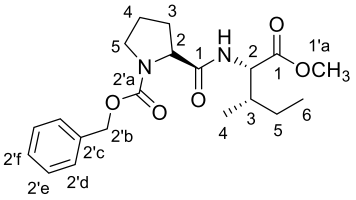
Prepared from Cbz-Phe-OH (0.149 g, 0.5 mmol) and Val-OMe·HCl (0.084 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{23}H_{28}N_2O_5$ (M = 412,49)

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.82 (d, *J* = 7.5 Hz, 3H, Val-C4$\underline{H}_3$); 0.84 (d, *J* = 7.0 Hz, 3H, Val-C5$\underline{H}_3$); 2.08 (m, 1H, Val-C3$\underline{H}$); 3.08 (m, 2H, Phe-C3$\underline{H}_2$); 3.69 (s, 3H, Val-C1'a$\underline{H}_3$); 4.45 (m, 2H, Val-C2$\underline{H}$ and Phe-C2$\underline{H}$); 4.98-5.17 (m, 2H, Phe-C2'b$\underline{H}_2$); 5.31 (d, *J* = 6.3 Hz, 1H, Phe-N$\underline{H}$); 6.23 (d, *J* = 7.8 Hz, 1H, Val-N$\underline{H}$); 7.08-7.48 (m, 10H, 2 x Phe-C5$\underline{H}$, 2 x Phe-C6$\underline{H}$, Phe-C7$\underline{H}$, 2 x Phe-C2'd$\underline{H}$, 2 x Phe-C2'e$\underline{H}$ and Phe-C2'f$\underline{H}$) ppm.

Cbz-Pro-Ile-OMe[226]



Prepared from Cbz-Pro-OH (0.125 g, 0.5 mmol) and Ile-OMe·HCl (0.091 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{20}H_{28}N_2O_5$ (M = 376,45)

^{1}H-NMR (600 MHz, DMSO, T: 100 °C) δ: 0.82 (t, *J* = 6.8 Hz, 6H, Ile-C4$\underline{H}_3$ and Ile-C6$\underline{H}_3$); 1.16 (m, 1H, Ile-C5$\underline{H}$); 1.40 (m, 1H, Ile-C5$\underline{H}$); 1.77-1.90 (m, 4H, Pro-C4$\underline{H}_2$, Ile-C3$\underline{H}$ and Pro-C3$\underline{H}$); 2.12 (m, 1H, Pro-C3$\underline{H}$); 3.37-3.49 (m, 2H, Pro-C5$\underline{H}_2$); 3.62 (s, 3H, Ile-C1'a$\underline{H}_3$); 4.25 (dd, *J* = 8.1, 6.2 Hz, 1H, Pro-C2$\underline{H}$); 4.37 (bs, 1H, Ile-C2$\underline{H}$); 5.05 (q, *J* = 12.9 Hz, 2H, Pro-C2'b$\underline{H}_2$); 7.21-7.38 (m, 5H, 2 x Pro-C2'd$\underline{H}$, 2 x Pro-2'e$\underline{H}$ and Pro-C2'f$\underline{H}$); 7.72 (d, *J* = 7.5 Hz, 1H, Pro-N$\underline{H}$) ppm.

^{13}C-NMR (151 MHz, DMSO, T = 100 °C) δ: 10.4 (Ile-$\underline{C}$4*); 14.9 (Ile-$\underline{C}$6*); 22.8 (Pro-$\underline{C}$4 and Pro-$\underline{C}$3); 24.4 (Ile-$\underline{C}$5); 36.0 (Ile-$\underline{C}$3); 46.4 (Pro-$\underline{C}$5); 50.8 (Ile-$\underline{C}$1'a); 56.0 (Ile-$\underline{C}$2); 58.9 (Pro-$\underline{C}$2);

---

[225] Zhao D.Y., Zhang M.-X., Dong X.-W., Hu Y.-Z., Dai X.-Z., Wei X., Hider R.C., Zhang J.-C., Zhou T. *Bioorg. Med. Chem. Lett.*, **2016**, *26*, 3103.

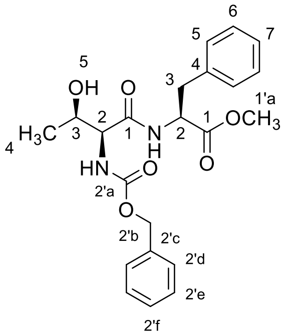
[226] Liu J., West K.R., Bondy C.R., Sanders J.K.M. *Org. Biomol. Chem.*, **2007**, *5*, 778.

65.5 (Pro-C2'b); 126.7 (2 x Pro-C2'd); 127.0 (Pro-C2'f); 127.7 (2 x Pro-C2'e); 136.6 (Pro-C2'c); 153.7 (Pro-C2'a); 171.2 (Pro-C1); 171.6 (Ile-C1) ppm.

IR (neat) *ν*: 3322 (NH); 2963 (Ar); 1740 (CO ester); 1668 (CO amide) cm^{-1}.

HRMS (ESI) = found 377.2065; $[M + H]^+$ $C_{20}H_{29}N_2O_5$ requires 377.2071; D = -1.6 ppm.

Cbz-Thr-Phe-OMe



Prepared from Cbz-Thr-OH (0.126 g, 0.5 mmol) and Phe-OMe·HCl (0.108 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{22}H_{26}N_2O_6$ (M = 414,46)

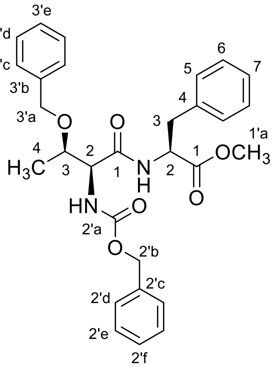
^{1}H-NMR (600 MHz, $CDCl_3$) *δ:* 1.04 (d, *J* = 6.5 Hz, 3H, Thr-C4$\underline{H}_3$); 2.92 (dd, *J* = 14.0, 7.1 Hz, 1H, Phe-C3$\underline{H}$H); 3.06 (dd, *J* = 13.9, 5.4 Hz, 2H, Phe-C3H$\underline{H}$ and Thr-O$\underline{H}$); 3.63 (s, 3H, Phe-C1'a$\underline{H}_3$); 4.05 (m, 1H, Thr-C2$\underline{H}$); 4.19 (d, *J* = 4.9 Hz, 1H, Thr-C3$\underline{H}$); 4.76 (dd, *J* = 13.2, 7.2 Hz, 1H, Phe-C2$\underline{H}$); 5.00 (q, *J* = 12.1 Hz, 2H, Thr-C2'b$\underline{H}_2$); 5.65 (d, *J* = 7.7 Hz, 1H, NH); 6.94 (d, *J* = 7.7 Hz, 1H, NH); 7.0 (d, *J* = 7.1 Hz, 2H, 2 x Phe-C5$\underline{H}$); 7.11 (m, 1H, Phe-C7$\underline{H}$); 7.13-7.17 (m, 2H, 2 x Phe-C6$\underline{H}$); 7.21-7.29 (m, 5H, Thr-Ar) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$) *δ:* 18.1 (Thr-C4); 37.8 (Phe-C3); 52.6 (Phe-C1'a); 53.4 (Phe-C2); 58.5 (Thr-C2); 66.9 (Thr-C3); 67.4 (Thr-C2'b); 127.3 (Phe-C7); 128.1 (2 x Thr-C2'd); 128.4 (Thr-C2'f); 128.7 (2 x Thr-C2'e); 128.7 (2 x Phe-C6); 129.3 (2 x Phe-C5); 135.8 (Phe-C4); 136.1 (Thr-C2'c); 156.9 (Thr-C2'a); 170.7 (Phe-C1); 171.8 (Thr-C1) ppm.

IR (neat) *ν*: 3300 (NH); 2964 (Ar); 1739 (CO ester); 1696 (CO carbamate); 1644 (CO amide) cm^{-1}.

HRMS (ESI) = found 415.1874; $[M + H]^+$ $C_{22}H_{27}N_2O_6$ requires 415.1863; D = 2.6 ppm.

Cbz-Thr(Bzl)-Phe-OMe



Prepared from Cbz-Thr(Bzl)-OH (0.172 g, 0.5 mmol) and Phe-OMe·HCl (0.107 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{29}H_{32}N_2O_6$ (M = 504,58)

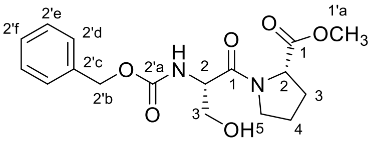
^{1}H-NMR (600 MHz, $CDCl_3$) *δ:* 1.19 (d, *J* = 6.4 Hz, 3H, Thr-C4H_3); 3.04 (dd, *J* = 13.8, 6.0 Hz, 2H, Phe-C3H_2); 3.68 (s, 3H, Phe-C1'aH_3); 4.14 (s, 1H, Thr-C3H); 4.35 (d, *J* = 2.8 Hz, 1H, Thr-C2H); 4.52-4.63 (m, 2H, Thr-C3'aH_2); 4.81 (dd, *J* = 12.9, 6.6 Hz, 1H, Phe-C2H); 5.01-5.21 (m, 2H, Thr-C2'bH_2); 5.76 (d, *J* = 5.8 Hz, 1H, Thr-NH); 6.95-7.03 (m, 2H, 2 x Phe-C5H); 7.13-7.18 (m, 4H, 2 x Phe-C6H*, Phe-C7H* and Phe-NH); 7.27-7.42 (m, 10H, 2 x Thr2'dH, 2 x Thr-2'eH, Thr-C2'fH, 2 x Thr-C3'cH, 2 x Thr-C3'dH and Thr-C3'eH) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$) *δ:* 14.7 (Thr-C4); 37.9 (Phe-C3); 52.3 (Phe-C1'a); 53.6 (Phe-C2); 57.5 (Thr-C2); 67.2 (Thr-C2'b); 71.5 (Thr-C3'a); 74.6 (Thr-C3); 127.2 (Phe-C7*); 127.9 (Thr-C2'f); 127.9 (Thr-C3'e); 128.1 (2 x Thr-C3'c); 128.3 (2 x Thr-C2'd); 128.5 (2 x Thr-C2'e); 128.7 (2 x Phe-C6); 128.7 (2 x Thr-C3'd); 129.2 (2 x Phe-C5); 135.8 (Thr-C2'c); 136.2 (Phe-C4); 137.9 (Thr-C3'b); 156.3 (Thr-C2'a); 169.2 (Phe-C1); 171.6 (Thr-C1) ppm.

IR (neat) *ν*: 3238 (NH); 2925 (Ar); 1746 (CO ester); 1716 (CO carbamate); 1663 (CO amide) cm^{-1}.

HRMS (ESI) = found 505.2320; $[M + H]^+$ $C_{29}H_{33}N_2O_6$ requires 505.2333; D = -2.5 ppm.

Cbz-Ser-Pro-OMe



Prepared from Cbz-Ser-OH (0.119 g, 0.5 mmol) and Pro-OMe·HCl (0.083 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{17}H_{22}N_2O_6$ (M = 350.37)

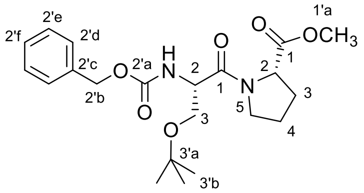
^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 1.99 (s, 3H, Pro-C4H$_2$ and Pro-C3HH); 2.24 (s, 1H, Pro-C3HH); 3.23 (s, 1H, Ser-OH); 3.63-3.68 (m, 5H, Pro-C1'aH$_3$, Pro-C5HH and Ser-C3H); 3.83 (s, 1H, Pro-C5HH); 3.92 (s, 1H, Ser-C3HH); 4.57 (d, *J* = 4.2 Hz, 1H, Pro-C2H); 4.67 (s, 1H, Ser-C2H); 5.09 (s, 2H, Ser-C2'bH$_2$); 5.81 (s, 1H, Ser-NH); 7.33 (s, 5H, Ser-Ar) ppm.

^{13}C NMR (151 MHz, CDCl$_3$) *δ*: 24.9 (Pro-C4); 29.0 (Pro-C3); 47.4 (Pro-C5); 52.8 (Pro-C1'a); 53.9 (Ser-C2); 59.0 (Pro-C2); 64.2 (Ser-C3); 67.1 (Ser-C2'a); 128.1 (2 x Ser-C2'd); 128.3 (Ser-C2'f); 128.6 (2 x Ser-C2'e); 136.3 (Ser-C2'c); 156.2 (Ser-C2'a); 170.0 (Ser-C1); 173.0 (Pro-C1) ppm.

IR (neat) *v*: 3270 (NH); 2954 (Ar); 1734 (CO ester); 1712 (CO carbamate); 1627 (CO amide) cm^{-1}.

HRMS (ESI) = found 351.1546; [M + H]$^+$ $C_{17}H_{23}N_2O_6$ requires 351.1550; D = -1.1 ppm.

Cbz-Ser(*t*Bu)-Pro-OMe



Prepared from Cbz-Ser(*t*Bu)-OH (0.147 g, 0.5 mmol) and Pro-OMe·HCl (0.083 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{21}H_{30}N_2O_6$ (M = 406.48)

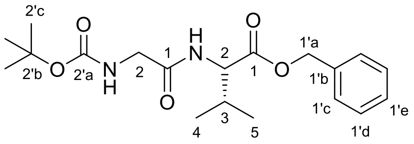
^{1}H-NMR (600 MHz, DMSO) *δ:* 1.14 (s, 9H, 3 x Ser-C3'bH$_3$); 1.85-1.93 (m, 3H, Pro-C4H$_2$ and Pro-C3HH); 2.14 (m, 1H, Pro-C3HH); 2.87 (bs, 2H, Pro-C5H$_2$); 3.41-3.51 (m, 3H, Pro-C2H and Ser-C3H$_2$); 3.62 (s, 3H, Pro-C1'aH$_3$); 4.40 (s, 1H, Ser-C2H); 5.03 (t, *J* = 8.3 Hz, 2H, Ser-C2'bH$_2$); 6.58 (s, 1H, Ser-NH); 7.23-7.42 (m, 5H, Ser-Ar) ppm.

^{13}C-NMR (151 MHz, DMSO) *δ:* 17.9 (Pro-C4); 26.5 (Ser-C3'b); 26.9 (Pro-C3); 45.8 (Pro-C5); 50.8 (Pro-C1'a); 52.7 (Pro-C2); 58.0 (Ser-C3); 65.1 (Ser-C2'b); 70.0 (Ser-C2); 72.2 (Ser-C3'a); 126.8 (2 x Ser-C2'd); 126.9 (Ser-C2'f); 127.5 (2 x Ser-C2'e); 136.4 (Ser-C2'c); 154.8 (Ser-C2'a); 168.4 (Ser-C1); 171.3 (Pro-C1) ppm.

IR (neat) *v*: 3293 (NH); 2972 (Ar); 1712 (CO carbamate); 1640 (CO amide) cm^{-1}.

HRMS (ESI) = found; [M + H]$^+$ $C_{21}H_{31}N_2O_6$ requires 407.2176; D = -3.1 ppm.

Boc-Gly-Val-OBn[227]



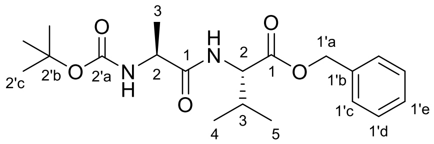
Prepared from Boc-Gly-OH (0.122 g, 0.5 mmol) and Val-OBn·HCl (0.088 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{19}H_{28}N_2O_5$ (M = 364.44)

^{1}H-NMR (400 MHz, $CDCl_3$) *δ:* 0.82 (d, *J* = 7.0 Hz, 3H, Val-C4$\underline{H}_3$*); 0.88 (d, *J* = 6.9 Hz, 3H, Val-C5$\underline{H}_3$*); 1.41 (s, 9H, 3 x Gly-C2'c$\underline{H}_3$); 2.15 (dd, *J* = 12.0, 6.8 Hz, 1H, Val-C3$\underline{H}$); 3.80 (s, 2H, Gly-C2$\underline{H}_2$); 4.57 (dd, *J* = 8.4, 4.8 Hz, 1H, Val-C2$\underline{H}$); 5.08 (d, *J* = 12.3 Hz, 1H, Val-C1'aH$\underline{H}$); 5.15 (d, *J* = 12.2 Hz, 1H, Val-C1'aH$\underline{H}$); 5.61 (s, 1H, Val-N$\underline{H}$); 7.01 (s, 1H, Gly-N$\underline{H}$); 7.27-7.33 (m, 5H, Val-Ar) ppm.

Boc-L-Ala-L-Val-OBn[228]



Prepared from Boc-L-Ala-OH (0.095 g, 0.5 mmol) and Val-OBn·HCl (0.088 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

Transparent oil. $C_{20}H_{30}N_2O_5$ (M = 378.47)

^{1}H NMR (600 MHz, $CDCl_3$) *δ:* 0.84 (d, *J* = 6.9 Hz, 3H, Val-C4$\underline{H}_3$*); 0.89 (d, *J* = 6.9 Hz, 3H, Val-C5$\underline{H}_3$*); 1.32 (d, *J* = 6.9 Hz, 3H, Ala-C3$\underline{H}_3$); 1.42 (s, 9H, 3 x Ala-C2'c$\underline{H}_3$); 2.17 (dd, *J* = 12.2, 6.5 Hz, 1H, Val-C3$\underline{H}$); 4.21 (s, 1H, Ala-C2$\underline{H}$); 4.56 (dd, *J* = 8.7, 4.8 Hz, 1H, Val-C2$\underline{H}$); 5.00-5.35 (m, 3H, Ala-N$\underline{H}$ and Val-C1'a$\underline{H}_2$); 6.82 (s, 1H, Val-N$\underline{H}$); 7.20-7.43 (m, 5H, Val-Ar) ppm.

^{13}C-NMR (151 MHz, $CDCl_3$) *δ:* 17.6 (Val-$\underline{C}$4*); 17.9 (Ala-$\underline{C}$3); 19.0 (Val-$\underline{C}$5*); 28.4 (Ala-$\underline{C}$2'c); 31.3 (Val-$\underline{C}$3); 50.0 (Ala-$\underline{C}$2); 57.1 (Val-$\underline{C}$2); 67.0 (Val-$\underline{C}$1'a); 80.0 (Ala-$\underline{C}$2'b); 128.4 (2 x Val-

---

[227] Wu F.-C., Da C.-S., Du Z.-X., Guo Q.-P., Li W.-P., Yi L., Jia Y.-N., Ma X. *J. Org. Chem.*, **2009**, *74*, 4812.

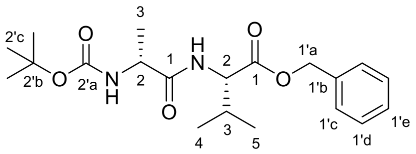
[228] Fustero S., García Sancho A., Chiva G., Sanz-Cervera J.F., del Pozo C., Aceña J.L. *J. Org. Chem.*, **2006**, 71, 3299.

C1’c); 128.5 (Val-C1’e); 128.6 (2 x Val-C1’d); 135.4 (Val-C1’b); 155.6 (Ala-C2’a); 171.7 (Ala-C1); 172.8 (Val-C1) ppm.

IR (neat) *v*: 3322 (NH); 2969 (Ar); 1661 (CO carbamate) cm^{-1}.

HRMS (ESI) = found 379.2217; $[M + H]^+$ $C_{20}H_{31}N_2O_5$ requires 379.2227; D = -2.6 ppm.

Boc-D-Ala-L-Val-OBn[228]



Prepared from Boc-D-Ala-OH (0.095 g, 0.5 mmol) and Val-OBn·HCl (0.088 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{20}H_{30}N_2O_5$ (M = 378.47)

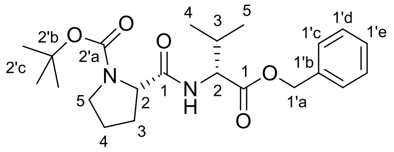
^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 0.85 (d, *J* = 6.9 Hz, 3H, Val-C4H$_3$*); 0.92 (d, *J* = 6.9 Hz, 3H, Val-C5H$_3$*); 1.36 (d, *J* = 7.1 Hz, 3H, Ala-C3H$_3$); 1.44 (s, 9H, 3 x Ala-C2’cH$_3$); 2.19 (m, 1H, Val-C3H); 4.22 (s, 1H, Ala-C2H); 4.57 (dd, *J* = 8.8, 4.7 Hz, 1H, Val-C2H); 5.00 (s, 1H, Ala-NH); 5.11 (dd, *J* = 12.2 Hz, 1H, Val-C1’aHH); 5.19 (dd, *J* = 12.2 Hz, 1H, Val-C1’aHH); 6.78 (s, 1H, Val-NH); 7.28-7.44 (m, 5H, Val-Ar) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$) *δ:* 17.5 (Val-C4*); 18.2 (Ala-C3); 19.1 (Val-C5*); 28.4 (Ala-C2’c); 31.3 (Val-C3); 50.3 (Ala-C2); 57.0 (Val-C2); 67.1 (Val-C1’a); 80.3 (Ala-C2’b); 128.5 (2 x Val-C1’c); 128.5 (Val-C1’e); 128.7 (2 x Val-C1’d); 135.5 (Val-C1’b); 155.6 (Ala-C2’a); 171.8 (Ala-C1); 172.7 (Val-C1) ppm.

IR (neat) *v*: 3333 (NH); 2971(Ar); 1736 (CO ester); 1686 (CO carbamate); 1653 (CO amide) cm^{-1}.

HRMS (ESI) = found 379.2226; $[M + H]^+$ $C_{20}H_{31}N_2O_5$ requires 379.2227; D = -0.2 ppm.

Boc-Pro-Val-OBn



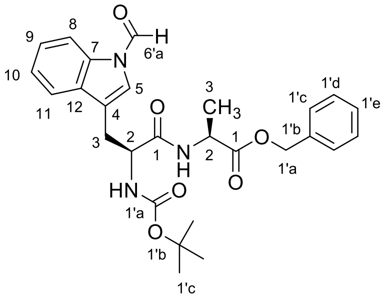
Prepared from Boc-Pro-OH (0.107 g, 0.5 mmol) and Val-OBn·HCl (0.122 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether: ethyl acetate.

White solid. C$_{22}$H$_{32}$N$_2$O$_5$ (M = 404.51)

^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 0.83 (d, *J* = 5.7 Hz, 3H, Val-C4$\underline{H}_3$*); 0.87 (d, *J* = 6.9 Hz, 3H, Val-C5$\underline{H}_3$*); 1.45 (s, 9H, 3 x Pro-C2'c$\underline{H}_3$); 1.99-170 (m, 3H, Val-C3$\underline{H}$ and Pro-C4$\underline{H}_2$); 2.15 (s, 2H, Pro-C3$\underline{H}_2$); 3.17-3.59 (m, 2H, Pro-C5$\underline{H}_2$); 4.28 (m, 1H, Val-C2$\underline{H}$); 4.53 (m, 1H, Pro-C2$\underline{H}$); 5.11-5.17 (m, 2H, Val-C1'a$\underline{H}_2$); 7.17-7.42 (m, 5H, 2 x Val-C1'c$\underline{H}$, 2 x Val-C1'd$\underline{H}$ and Val-C1'e$\underline{H}$); 7.56 (d, *J* = 8.3 Hz, 1H, Val-N$\underline{H}$) ppm.

Boc-Trp(CHO)-Ala-OBn



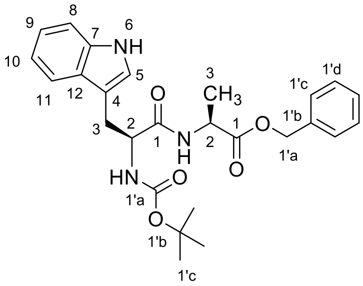
Prepared from Boc-Trp(CHO)-OH (0.166 g, 0.5 mmol) and Ala-OBn·HCl (0.107 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. C$_{27}$H$_{31}$N$_3$O$_6$ (M = 493.56)

^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 1.26-1.39 (m, 12H, Ala-C3$\underline{H}_3$ and 3 x Trp-C1'c$\underline{H}_3$); 2.99-3.31 (m, 2H, Trp-C3$\underline{H}_2$); 4.40-4.66 (m, 2H, Ala-C2$\underline{H}$ and Trp-C2$\underline{H}$); 4.99-5.21 (m, 2H, Ala-C1'a$\underline{H}_2$); 5.50 (d, *J* = 8.1 Hz, 1H, Trp-N$\underline{H}$); 6.90 (s, 1H, Ala-N$\underline{H}$); 7.10-7.40 (m, 7H, Trp-C9$\underline{H}$, Trp-C5$\underline{H}$, 2 x Ala-C1'c$\underline{H}$, 2 x Ala-C1'd$\underline{H}$, Ala-C1'e$\underline{H}$); 7.57 (s, 2H, Trp-C11$\underline{H}$ and Trp-C8$\underline{H}$); 8.33 (d, *J* = 7.9 Hz, 1H, Trp-C10$\underline{H}$); 8.89 (s, 1H, Trp-NH); 9.25 (s, 1H, CHO) ppm.

Boc-Trp(H)-Ala-OBn



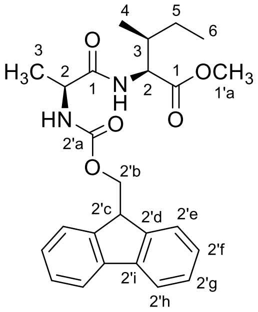
Prepared from Boc-Trp(H)-OH (0.152 g, 0.5 mmol) and Ala-OBn·HCl (0.108 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{26}H_{31}N_3O_5$ (M = 465.55)

^{1}H-NMR (600 MHz, $CDCl_3$) *δ:* 1.27 (d, *J* = 6.9 Hz, 3H, Ala-C3$\underline{H}_3$); 1.43 (s, 9H, 3 x Trp-C1’c$\underline{H}_3$); 3.21 (m, 2H, Trp-C3$\underline{H}_2$); 4.45-4.52 (m, 2H, Trp-C2$\underline{H}$ and Ala-C2$\underline{H}$); 5.08 (s, 2H, Ala-C1’a$\underline{H}_2$); 5.21 (s, 1H, Trp-N$\underline{H}$); 6.36 (d, *J* = 7.1 Hz, 1H, Ala-N$\underline{H}$); 7.02 (s, 1H, Trp-C5$\underline{H}$); 7.11 (t, *J* = 7.4 Hz, 1H, Trp-C10$\underline{H}$); 7.18 (t, *J* = 7.4 Hz, 1H, Trp-C9$\underline{H}$); 7.28-7.41 (m, 6H, Trp-C8$\underline{H}$, 2 x Ala-C1’c$\underline{H}$, 2 x Ala-C1’d$\underline{H}$, Ala-C1’e$\underline{H}$); 7.65 (d, *J* = 7.7 Hz, 1H, Trp-C11$\underline{H}$); 8.14 (bs, 1H, Trp-N6$\underline{H}$) ppm.

Fmoc-Ala-Ile-OMe



Prepared from Fmoc-Ala-OH (0.155 g, 0.5 mmol) and Ile-OMe·HCl (0.091 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{25}H_{30}N_2O_5$ (M = 438.52)

^{1}H-NMR (600 MHz, $CDCl_3$) *δ:* 0.84-0.94 (m, 6H, Ile-C4$\underline{H}_3$ and Ile-C6$\underline{H}_3$); 1.16 (dd, *J* = 13.9, 7.6 Hz, 1H, Ile-C5$\underline{H}$H); 1.33-1.49 (m, 4H, Ile-C5H$\underline{H}$ and Ala-C3$\underline{H}_3$); 1.89 (s, 1H, Ile-C3$\underline{H}$); 3.73 (s, 3H, Ile-C1’a$\underline{H}_3$); 4.22 (t, *J* = 7.1 Hz, 1H, Ala-C2’c$\underline{H}$); 4.32 (s, 1H, Ala-C2$\underline{H}$); 4.39 (d, *J* = 6.6 Hz, 2H, Ala-C2’b$\underline{H}_2$); 4.58 (dd, *J* = 8.6, 4.9 Hz, 1H, Ile-C2$\underline{H}$); 5.46 (d, *J* = 6.0 Hz, 1H, Ala-N$\underline{H}$); 6.57 (d, *J* = 6.7 Hz, 1H, Ile-N$\underline{H}$); 7.31 (t, *J* = 7.4 Hz, 2H, 2 x Ala-C2’f$\underline{H}$); 7.40 (t, *J* = 7.4 Hz, 2H, 2 x Ala-C2’g$\underline{H}$); 7.58 (d, *J* = 7.3 Hz, 2H, 2 x Ala-C2’e$\underline{H}$); 7.76 (d, *J* = 7.5 Hz, 2H, 2 x Ala-C2’h$\underline{H}$) ppm.

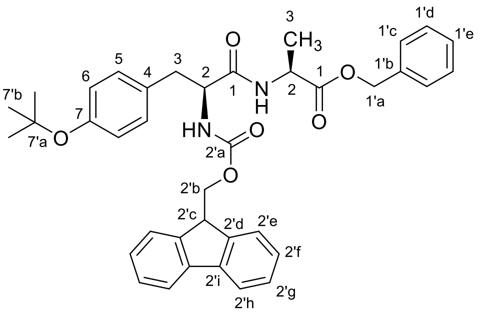
^{13}C-NMR (151 MHz, $CDCl_3$) *δ:* 11.7 (Ile-$\underline{C}$6*); 15.6 (Ile-$\underline{C}$4*); 18.7 (Ala-$\underline{C}$3); 25.2 (Ile-$\underline{C}$5); 38.0 (Ile-$\underline{C}$3); 47.2 (Ala-$\underline{C}$2’c); 50.6 (Ala-$\underline{C}$2); 52.3 (Ile-$\underline{C}$1’a); 56.6 (Ile-$\underline{C}$2); 67.3 (Ala-$\underline{C}$2’b); 120.1

(Ala-C2’h); 125.2 (Ala-C2’e); 127.2 (Ala-C2’g); 127.9 (Ala-C2’f); 141.4 (Ala-C2’i); 143.9 (Ala-C2’d); 156.1 (Ala-C2’a); 172.1 (Ile-C1); 172.3 (Ala-C1) ppm.

IR (neat) *v*: 3298 (NH); 2964 (Ar); 1734 (CO ester); 1691 (CO carbamate); 1653 (CO amide) cm^{-1}.

HRMS (ESI) = found 439.2231; [M + H]$^+$ $C_{25}H_{31}N_2O_5$ requires 439.2231; D = 0.9 ppm.

Fmoc-O*t*Bu-Tyr-Ala-OBn



Prepared from Fmoc-O*t*Bu-Tyr-OH (0.229 g, 0.5 mmol) and Ala-OBn·HCl (0.107 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{38}H_{40}N_2O_6$ (M = 620.75)

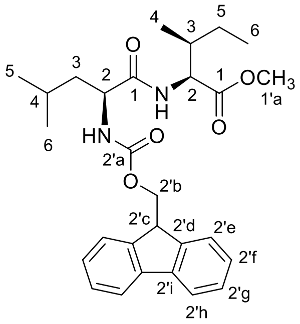
^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 1.31-1.35 (m, 12H, 3 x Tyr-C7’bH_3 and Ala-C3H_3); 2.99-3.07 (m, 2H, Tyr-C3H_2); 4.18 (t, *J* = 6.9 Hz, 1H, Tyr-C2’cH); 4.32 (s, 1H, Tyr-C2H); 4.39-4.45 (m, 2H, Tyr-C2’bH_2); 4.55 (m, 1H, Ala-C2H); 5.15 (s, 2H, Ala-C1’aH_2); 5.48 (d, *J* = 5.1 Hz, 1H, Tyr-NH); 6.44 (s, 1H, Ala-NH); 6.89 (d, *J* = 8.0 Hz, 2H, 2 x Tyr-C6H); 7.08 (s, 2H, 2 x Tyr-C5H); 7.28-7.44 (m, 9H, 2 x Tyr-C2’fH, 2 x Tyr-C2’eH, 2 x Ala-C1’cH, 2 x Ala-C1’dH and Ala-1’eH); 7.56 (t, *J* = 7.6 Hz, 2H, 2 x Tyr-C2’gH); 7.76 (dd, *J* = 7.4 Hz, 2H, 2 x Tyr-C2’hH) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$) *δ:* 18.4 (Ala-C3); 28.9 (Tyr-C7’b); 38.1 (Tyr-C2’c); 47.2 (Ala-C2); 48.4 (Tyr-C2); 56.2 (Tyr-C3); 67.2 (Tyr-C2’b); 67.3 (Ala-C1’a); 78.5 (Tyr-C7’a); 120.1 (2 x Tyr-C6); 124.4 (2 x Tyr-C2’g); 125.2 (2 x Tyr-C2’f*); 127.2 (2 x Tyr-C2’e*); 127.8 (2 x Tyr-C2’h); 128.3 (2 x Ala-C1’c); 128.6 (Ala-C1’e); 128.7 (2 x Ala-C1’d); 129.9 (2 x Tyr-C5); 135.4 (Tyr-C4); 141.4 (Ala-C1’b); 143.8 (2 x Tyr-C2’i); 143.9 (2 x Tyr-C2’d); 154.6 (Tyr-C7); 156.0 (Tyr-C2’a); 170.6 (Ala-C1); 172.3 (Tyr-C1) ppm.

IR (neat) *v*: 3303 (NH); 2976 (Ar); 1733 (CO ester); 1689 (CO carbamate); 1653 (CO amide) cm^{-1}.

HRMS (ESI) = found 621.2962; [M + H]$^+$ $C_{38}H_{41}N_2O_6$ requires 621.2959; D = 0.4 ppm.

Fmoc-Leu-Ile-OMe



Prepared from Fmoc-Leu-OH (0.176 g, 0.5 mmol) and Ile-OMe·HCl (0.091 g, 0.5 mmol).

Purification: flash chromatography 3:1 petroleum ether : ethyl acetate.

White solid. $C_{28}H_{36}N_2O_5$ (M = 480.61)

^{1}H-NMR (600 MHz, CDCl$_3$) *δ:* 0.87-0.94 (m, 6H, Ile-C4H$_3$ and Ile-C6H$_3$); 0.95 (s, 6H, Leu-C5H$_3$ and Leu-C6H$_3$); 1.16 (m, 1H, Ile-C5H); 1.41 (m, 1H, Ile-C5H); 1.55 (m, 1H, Leu-C4H); 1.63-1.71 (m, 2H, Leu-C3H$_2$); 1.89 (s, 1H, Ile-C3H); 3.73 (s, 3H, Ile-C1’aH$_3$); 4.22 (t, *J* = 7.0 Hz, 2H, Leu-C2H and Leu-C2’cH); 4.40 (p, *J* = 10.6 Hz, 2H, Leu-C2’bH$_2$); 4.58 (dd, *J* = 8.6, 4.9 Hz, 1H, Ile-C2H); 5.22 (d, *J* = 7.9 Hz, 1H, Leu-NH); 6.44 (d, *J* = 7.9 Hz, 1H, Ile-NH); 7.31 (t, *J* = 7.5 Hz, 2H, 2 x Leu-C2’fH); 7.40 (t, *J* = 7.5 Hz, 2H, 2 x Leu-C2’gH); 7.58 (d, *J* = 7.4 Hz, 2H, 2 x Leu-C2’eH); 7.76 (d, *J* = 7.6 Hz, 2H, 2 x Leu-C2’hH) ppm.

^{13}C-NMR (151 MHz, CDCl$_3$) *δ:* 11.7 (Ile-C4*); 15.6 (Ile-C6*); 22.2 (Leu-C5*’); 23.0 (Leu-C6*’); 24.8 (Leu-C3); 25.2 (Ile-C5); 38.0 (Ile-C3); 41.5 (Leu-C4); 47.3 (Leu-C2’c); 52.3 (Ile-C1’a); 53.6 (Leu-C2); 56.6 (Ile-C2); 67.2 (Leu-C2’b); 120.1 (2 x Leu-C2’h); 125.2 (2 x Leu-C2’e); 127.2 (2 x Leu-C2’f); 127.9 (2 x Leu-C2’g); 141.4 (2 x Leu-C2’i); 143.9 (Leu-C’2’d); 144.0 (Leu-C2’d); 156.3 (Leu-C2’a); 172.0 (Leu-C1); 172.2 (Ile-C1) ppm.

IR (neat) *ν*: 3307 (NH); 2957 (Ar); 1743 (CO ester); 1697 (CO carbamate); 1656 (CO amide) cm^{-1}.

HRMS (ESI) = found 481.2703; [M + H]$^+$ $C_{28}H_{37}N_2O_5$ requires 481.2697; D = 1.2 ppm.

10.8.3 - Procedure for the synthesis of linear precursors to segetalin A

The deprotection steps of the acid and amine functions were performed as follows:

Deprotection of the acid

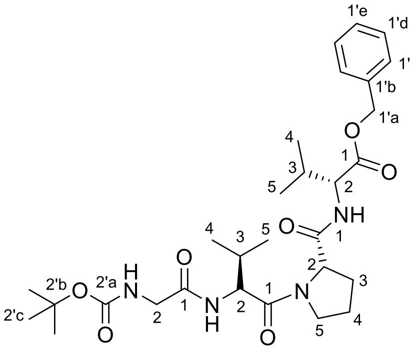
Flow hydrogenation was performed in an HCube© flow hydrogenator. The procedure conditions were previuosly optimised in the group.[229] The R-AA-OBn (0.5 mmol) was solved in CH_2Cl_2 (3 mL) and a hydrogen current at 1 mL/min over a CatCart of $Pd(OH)_2$ 20% on carbon at 50 °C to remove the benzyl protectin group. The resulting organic layer was collected and the solvent was removed at rotavapor and the crude reaction was directly used in the coupling reaction without further purification.

Deprotection of the amino group

The Boc-AA-R was treated with a solution of anhydrous dioxane HCl (2N) in batch for 3h at room temperature to remove the *tert*-butyloxycarbonyl group. When the reaction finished, as indicated by the TLC, the crude was concentrated at rotavapor and directly employed in the coupling step.

For the coupling step the same reaction condition described above were applied.

Boc-Gly-Val-Pro-Val-OBn



Prepared from Boc-Gly-Val-OBn (0.182 g, 0.5 mmol) and Boc-Pro-Val-OBn (0.202 g, 0.5 mmol).

Purification: flash chromatography 9:1 dichlorometane : methanol.

Yellow solid. $C_{29}H_{44}N_4O_7$ (M = 560.69)

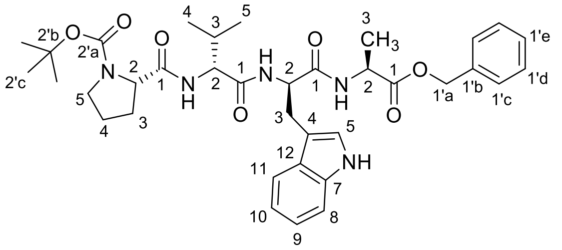
HRMS (ESI) = found 583.3135; $[M + H]^+$ $C_{29}H_{45}N_4O_7Na$ requires 583.3108; D = 4.6 ppm.

IR (neat) v/cm^{-1} = 3307 (NH); 2967 (Ar); 1671 (CO carbamate); 1626 (CO amide).

---

[229] For examples of the use of H-Cube flow hydrogenation, see: (a) Saaby S., Knudsen K.R., Ladlow M., Ley S.V. *Chem Commun.*, **2005**, *23*, 2909. (b) Franckevicius V., Knudsen K.R., Ladlow M., Longbottom D.A., Ley S.V. *Synlett.*, **2006**, *6*, 889. (c) Knudsen K.R., Ladlow M., Bandpey Z., Ley S.V. *J. Flow Chem.*, **2014**, *4*, 18.

Boc-Pro-Val-Trp(H)-Ala-OBn



Prepared from Boc-Pro-Val-OBn (0.202 g, 0.5 mmol) and Boc-Trp(H)-Ala-OBn (0.233 g, 0.5 mmol).

Purification: flash chromatography in dichloromethane with 8% of methanol.

Yellow solid. $C_{36}H_{47}N_5O_7$ (M = 661,80)

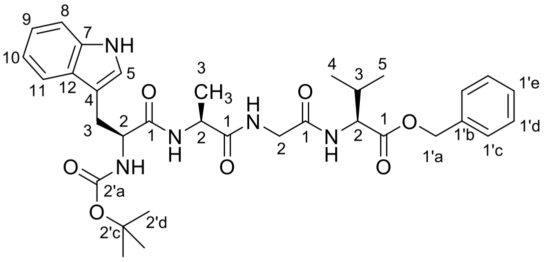
^{1}H-NMR (600 MHz, DMSO, T = 120 °C) *δ:* 0.83 (s, 6H, Val-C4H$_3$ and Val-C5H$_3$); 1.27 (d, *J* = 7.0 Hz, 3H, Ala-C3H$_3$); 1.37 (s, 9H, 3 x Pro-C2'cH$_3$); 1.76-1.77 (m, 3H, Pro-C4H$_2$ and Pro-C3H); 1.97-1.98 (m, 2H, Val-C3H and Pro-C3H); 3.01 (dd, *J* = 7.6, 14.8 Hz, 1H, Trp-C3H); 3.15 (dd, *J* = 5.6, 14.8 Hz, 1H, Trp-C3H); 3.33 (t, *J* = 6.6 Hz, 2H, Pro-C5H$_2$); 4.12 (m, 1H, Val-C2H); 4.19 (m, 1H, Ala-C2H); 4.38 (m, 1H, Pro-C2H); 4.64 (dd, *J* = 7.4, 13.6 Hz, 1H, Trp-C2H); 5.11 (s, 2H, Ala-C1'aH$_2$); 6.95 (t, *J* = 7.3 Hz, 1H, Trp-C10H); 7.04 (t, *J* = 7.3 Hz, 1H, Trp-C9H); 7.08 (s, 1H, Trp-C5H); 7.27-7.34 (m, 6H, Trp-C8H, Trp-C11H, 2 x Ala-C1'dH, Ala-C1'eH and NH); 7.52 (d, *J* = 7.4 Hz, 2H, 2 x Ala-C1'cH); 7.75 (s, 1H, Trp-C11H); 10.41 (s, 1H, Trp-N6H) ppm.

^{13}C-NMR (151 MHz, DMSO, T = 120 °C) *δ:* 16.3 (Val-C4*); 17.2 (Val-C5*); 18.4 (Ala-C3); 22.8 (Pro-C4); 27.1 (Pro-C3); 27.5 (3 x Pro-C2'c); 29.3 (Trp-C3); 29.8 (Val-C3); 46.0 (Pro-C5); 47.3 (Ala-C2); 52.6 (Trp-C2); 57.5 (Val-C2); 59.1 (Pro-C2); 65.3 (Ala-C1'a); 78.3 (Pro-C2'b); 109.4 (Trp-C4); 110.6 (Trp-C8); 117.6 (Trp-C10); 117.6 (Trp-C11); 120.2 (Trp-C9); 122.8 (Trp-C5); 126.9 (2 x Ala-C1'd); 127.0 (Trp-C12); 127.2 (Ala-C1'e); 127.6 (2 x Ala-C1'c); 135.5 (Ala-C1'b); 135.8 (Trp-C7); 153.3 (Pro-C2'a); 169.9 (Val-C1*); 170.4 (Ala-C1*); 171.2 (Trp-C1*); 171.5 (Pro-C1) ppm.

IR (neat) *ν*: 3298 (NH); 2976 (Ar); 1733 (CO ester); 1689 (CO carbamate); 1653 (CO amide) cm^{-1}.

HRMS (ESI) = found 662.3538; $[M + H]^+$ $C_{36}H_{48}N_5O_7$ requires 661.3548; D = 1.5 ppm.

Boc-Trp(H)-Ala-Gly-Val-OBn



Prepared from Boc-Trp(H)-Ala-OBn (0.233 g, 0.5 mmol) and Boc-Gly-Val-OBn (0.182 g, 0.5 mmol).

Purification: flash chromatography in dichloromethane with 8% of methanol.

Yellow solid. $C_{33}H_{43}N_5O_7$ (M = 621.74)

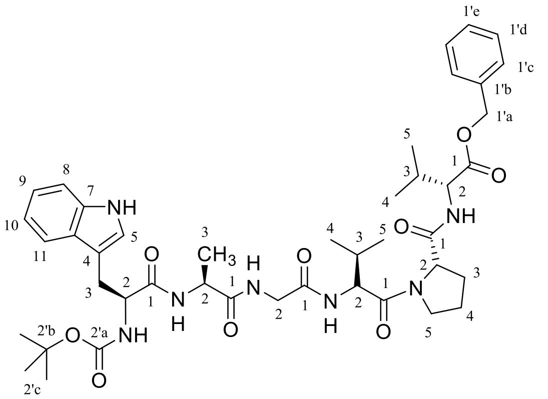
^{1}H-NMR (500 MHz, DMSO, T = 100 °C) *δ:* 0.90 (d, *J* = 6.8 Hz, 6H, Val-C4H_3 and Val-C5H_3); 1.26 (d, *J* = 7.0 Hz, 3H, Ala-C3H_3); 1.33 (s, 9H, 3 x Trp-C2'cH_3); 2.11 (dd, *J* = 13.5, 6.7 Hz, 1H, Val-C3H); 2.99 (m, 1H, Trp-C3H); 3.18 (dd, *J* = 14.7, 5.0 Hz, 1H, Trp-C3H); 3.71-3.89 (m, 2H, Gly-C2H_2); 4.22-4.42 (m, 3H, Ala-C2H, Trp-C2H and Val-C2H); 5.16 (s, 2H, Val-C1'aH_2); 6.28 (s, 1H, Trp-NH*); 6.98 (t, *J* = 7.4 Hz, 1H, Trp-C10H); 7.06 (t, *J* = 7.5 Hz, 1H, Trp-C9H); 7.12 (s, 1H, Trp-C5H); 7.26-7.43 (m, 6H, Val-Ar and Trp-C8H); 7.58 (d, *J* = 7.8 Hz, 1H, Trp-C11H); 7.63-7.73 (m, 2H, Val-NH *and Ala-NH*); 7.77 (s, 1H, Gly-NH*); 10.5 (s, 1H, Trp-N6H) ppm.

^{13}C-NMR (151 MHz, DMSO, T = 100 °C) *δ:* 17.5 (Val-C4*); 17.5 (Val-C5*); 18.3 (Ala-C3); 27.3 (Trp-C3); 27.7 (3 x Trp-C2'd); 29.6 (Val-C3); 41.8 (Gly-C2); 48.1 (Ala-C2); 55.1 (Trp-C2); 57.2 (Val-C2); 65.5 (Val-C1'a); 109.8 (Trp-C4); 110.7 (Trp-C8); 117.7 (Trp-C10); 117.9 (Trp-C11); 120.3 (Trp-C9); 123.1 (Trp-C5); 127.2 (Trp-C12); 127.4 (2 x Val-C1'c); 127.5 (Val-C1'e); 127.8 (2 x Val-C1'd); 135.5 (Val-C1'b); 135.9 (Trp-C7); 154.6 (Trp-C2'a); 168.4 (Gly-C1); 170.5 (Trp-C1); 171.1 (Ala-C1); 171.9 (Val-C1) ppm.

IR (neat) *v*: 3311 (NH); 2976 (Ar); 1733 (CO ester); 1689 (CO carbamate); 1653 (CO amide) cm^{-1}.

HRMS (ESI) = found 622.3239; $[M + H]^+$ $C_{33}H_{44}N_5O_7$ requires 622.3235; D = -0.6 ppm.

Boc-Trp(H)-Ala-Gly-Val-Pro-Val-OBn



Prepared from Boc-Gly-Val-Pro-Val-OBn (0.280 g, 0.5 mmol) and Boc-Trp(H)-Ala-OBn (0.233 g, 0.5 mmol).

Purification: flash chromatography in dichloromethane with 8% of methanol.

Pink pale solid. $C_{43}H_{59}N_7O_9$ (M = 817.99)

^{1}H-NMR (600 MHz, DMSO, T = 120°C) *δ:* 0.78-1.02 (m, 12H, 2 x Val-C4H_3 and 2 x Val-C5-H_3); 1.27 (s, 3H, Ala-C3H_3); 1.33 (s, 9H, 3 x Trp-C2’cH_3); 1.80-2.11 (m, 6H, 2 x Val-C3H, Pro-C4H_2 and Pro-C3H_2); 2.99 (dd, *J* = 14.7, 8.3 Hz, 1H, Trp-C3HH); 3.18 (dd, *J* = 14.6, 5.0 Hz, 1H, Trp-C3HH); 3.52-3.86 (m, 5H, Pro-C5H_2, Gly-C2H_2 and NH); 4.21-4.31 (m, 2H, Trp-C2H and Val-C2H); 4.35 (m, 1H, Ala-C2H); 4.42 (m, 1H, Val-C2H); 4.52 (m, 1H, Pro-C2H); 5.14 (q, *J* = 12.5 Hz, 2H, Val-C1’aH_2); 6.20 (s, 1H, NH); 6.97 (t, *J* = 7.4 Hz, 1H, Trp-C10H); 7.06 (t, *J* = 7.5 Hz, 1H, Trp-C9H); 7.11 (s, 1H, Trp-C5H); 7.30-7.40 (m, 5H, Val-Ar); 7.56-7.68 (m, 3H, Trp-C8H, Trp-C11H and NH); 10.43 (s, 1H, Trp-N6H) ppm.

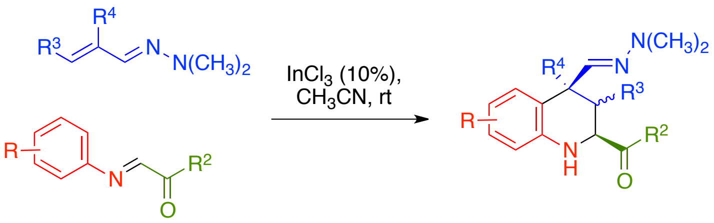
^{13}C-NMR (151 MHz, DMSO, T = 120°C) *δ:* 18.4 (Ala-C3); 18.5 (Val-C4); 18.5 (Val-C4); 19.2 (Val-C5); 19.5 (Val-C5); 24.8 (Pro-C4); 28.3 (Trp-C3); 28.6 (Trp-C2’c); 28.9 (Pro-C3); 30.5 (Val-C3); 30.9 (Val-C3); 42.9 (Pro-C5); 47.6 (Gly-C2); 49.0 (Ala-C2); 56.0 (Val-C2); 58.2 (Trp-C2); 59.7 (Pro-C2); 66.4 (Val-C1’a); 70.7 (Val-C2); 78.9 (Trp-C2’b); 110.8 (Trp-C4); 111.7 (Trp-C8); 118.7 (Trp-C10); 118.8 (Trp-C11); 121.2 (Trp-C9); 124.0 (Trp-C5); 128.2 (Trp-C12); 128.3 (2 x Val-C1’c); 128.4 (Val-C1’e); 128.7 (2 x Val-C1’d); 136.5 (Val-C1’b); 136.9 (Trp-C7); 155.5 (Trp-C2’a); 168.8 (Gly-C1); 169.1 (Pro-C1); 170.5 (Val-C1); 171.4 (Ala-C1); 171.9 (Trp-C1); 172.8 (Val-C1) ppm.

IR (neat) *ν*: 3293 (NH); 2967 (Ar); 1624 (CO amide) cm^{-1}.

HRMS (ESI) = found 818.4420; $[M + H]^+$ $C_{43}H_{60}N_7O_9$ requires 818.4447; D = 3.3 ppm.

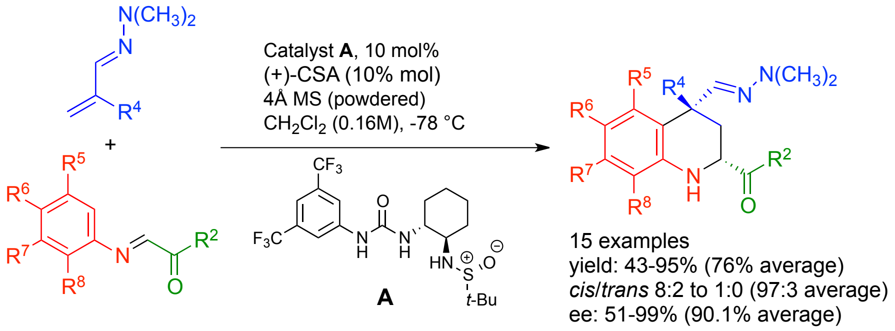
11 – Conclusions

1. The indium trichloride-catalyzed aza-vinylogous Povarov reaction between α,β-unsaturated *N*,*N*-dimethylhydrazones and *α*-ketoimines affords 2-acyl-4-(dimethylhydrazonomethyl)-1,2,3,4-tetrahydroquinolines. The reaction highly favours a *cis* relationship between the C-2 and C-4 substituents and generates a quaternary stereocenter at the C-4 position. The generality of the method was underscored by the preparation of compounds substituted at all carbons of the tetrahydroquinoline system. 2-Spiro tetrahydroquinolines were also accessible by using isatin-derived imines as the diene component.



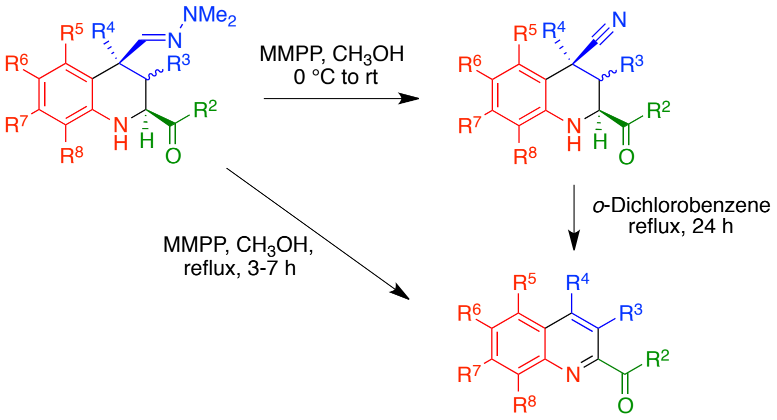
2. An asymmetric, organocatalytic version of the aza-vinylogous Povarov reaction was developed by treating *N*,*N*-dimethylhydrazones and *α*-ketoimines in the presence of a combination of Jacobsen's chiral urea catalyst and camphorsulfonic acid at – 78 °C in dichloromethane containing 4 Å molecular sieves. This is a challenging transformation in that there is no precedent for asymmetric Povarov reactions in which both the diene and the dienophile bear basic nitrogen atoms. Furthermore, the use of acyclic dienophiles is unprecedented in the presence of urea or thiourea-derived catalysts. The reaction

generates a quaternary stereocenter, which is an important synthetic goal that has been rarely achieved in Povarov chemistry.



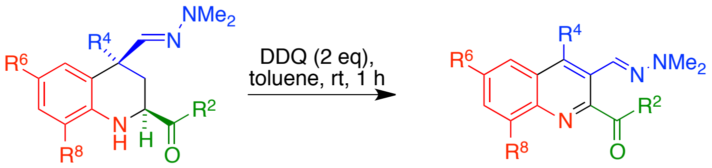
15 examples
yield: 43-95% (76% average)
cis/*trans* 8:2 to 1:0 (97:3 average)
ee: 51-99% (90.1% average)

3. The products of the aza-vinylogous Povarov reactions were identified as suitable precursors of 2-acylquinolines, which is a relevant finding due to the scarcity of literature procedures for their preparation and the great importance of quinoline derivatives. In our first approach, this goal was achieved by oxidation of the dimethylhydrazone group to a nitrile with magnesium monoperoxyphthalate, followed by elimination of hydrogen cyanide and dehydrogenation under thermal conditions. Alternatively, the whole transformation could be carried out in a single operation by treatment of the starting materials with magnesium monoperoxyphthalate in refluxing methanol.

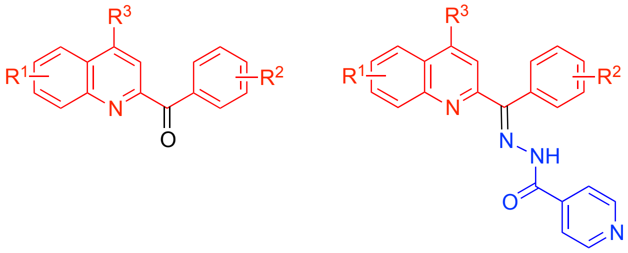


4. In an alternative approach, 2-acylquinolines were also obtained by treatment of the aza-vinylogous Povarov reaction products with DDQ at room temperature. These condicions

indiced migration of the dimethylhydrazonomethyl moiety to the quinoline C-3 position with concomitant aromatization.

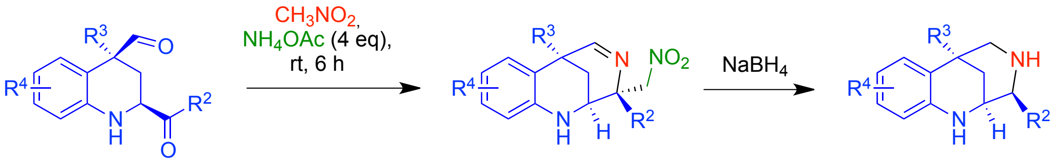


5. Quinoline can be viewed as a privileged structure in the development of antitubercular compounds. However, data on the activity of 2-acylquinolines were absent due to the lack of suitable synthetic methods. For this reason, we screened representative compounds from our recently synthesized library, with promising results. N-acylhydrazones of these 2-acylquinolines, designed to liberate the same active species as the antitubercular drug isoniazide upon oxidative metabolism, showed good antitubercular activities.

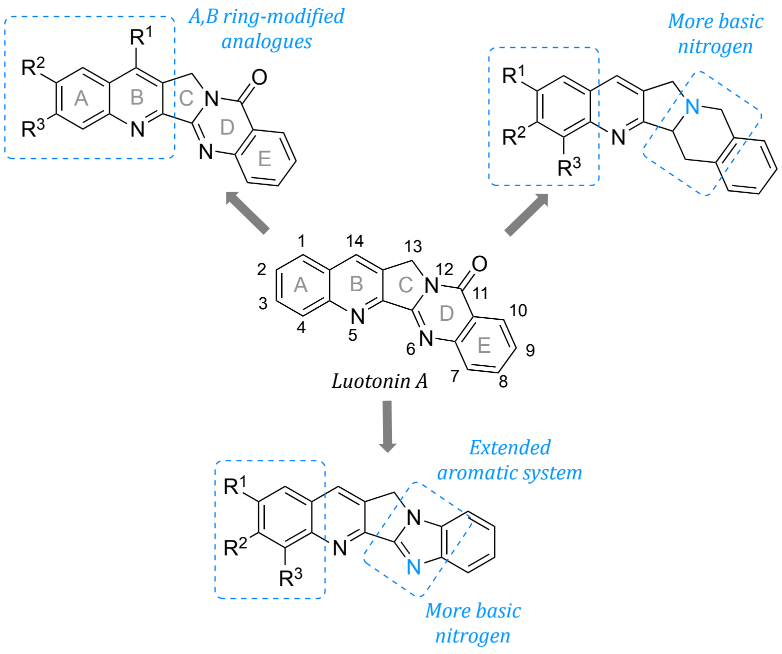


6. The combined presence of carbonyl and hydrazone functions at the tetrahydroquinoline C-2 and C-4 positions, coupled with their *cis* arrangement, allowed their use as starting materials for the generation of additional rings. Thus, a three-component reaction between 1,5-dicarbonyl compounds derived from the hydrolysis of the hydrazones obtained in the Povarov reaction, nitromethane and ammonium acetate furnished derivatives of the 2,6-methanobenzo[e][1,4]diazocine framework, with the fully diastereoselective generation of a new quaternary stereocenter. The sodium borohydride reduction of these compounds via a reduction/retro aza-Mannich/reduction sequence was again diastereoselective, and involved loss of the nitromethyl group.
Owing to the analogy between these structures and that of cytisine, an $\alpha_4\beta_2$ acetylcholine nicotinic receptor partial agonist that has potential interest in neurodegenerative

diseases, the pharmacological study of these compounds as neuroprotective agents was performed, with very interesting results.

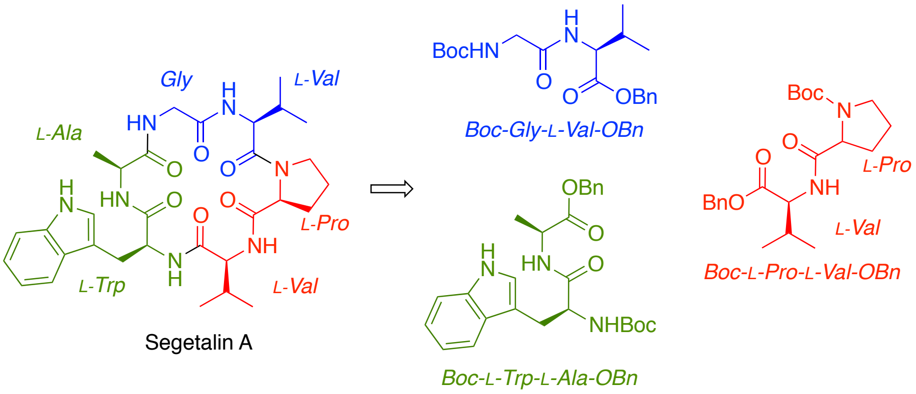


7. As a contribution to the work of our group in the development of new luotonin A-inspired topoisomerase I inhibitors as anticancer agents, one of the objectives of this thesis was the computational study of the interaction of three families of luotonin analogues with the topoisomerase I-DNA complex. This study has been used to assist the rationalization of the topoisomerase inhibition and cytotoxic activity of these molecules and to aid new compound design.

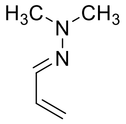


8. During a three-month stay at the Department of Chemistry, Cambridge University, under the supervision of Professor Steven V. Ley, in partial fulfillment of the requirements for the European Ph. D. label, the development of a new method for peptide synthesis under

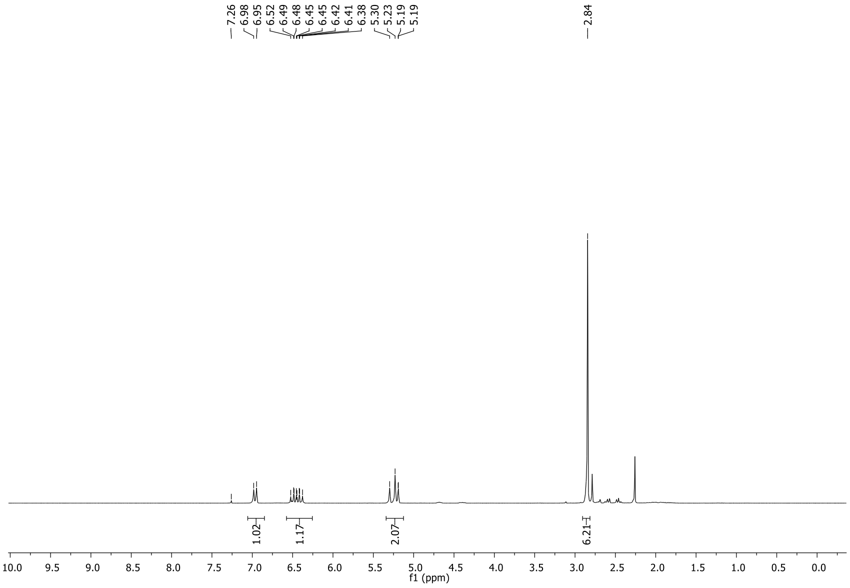
flow conditions, based on carboxyl activation by mixed anhydride generation, was developed. In order to underscore the flexibility of the method, its application to the synthesis of the bioactive natural peptide segetalin A was also investigated.

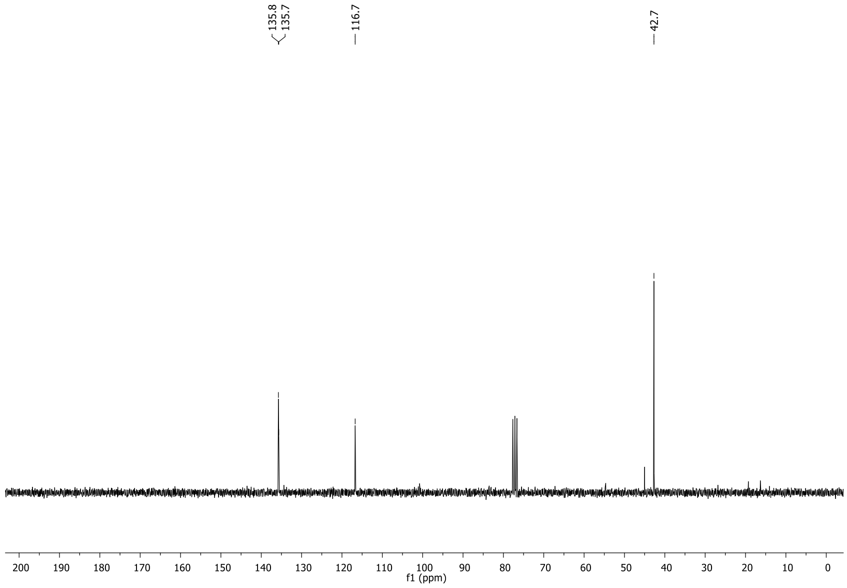


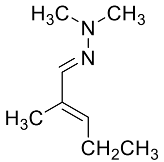
Appendix: Selected spectra


H3C
N
CH3
N

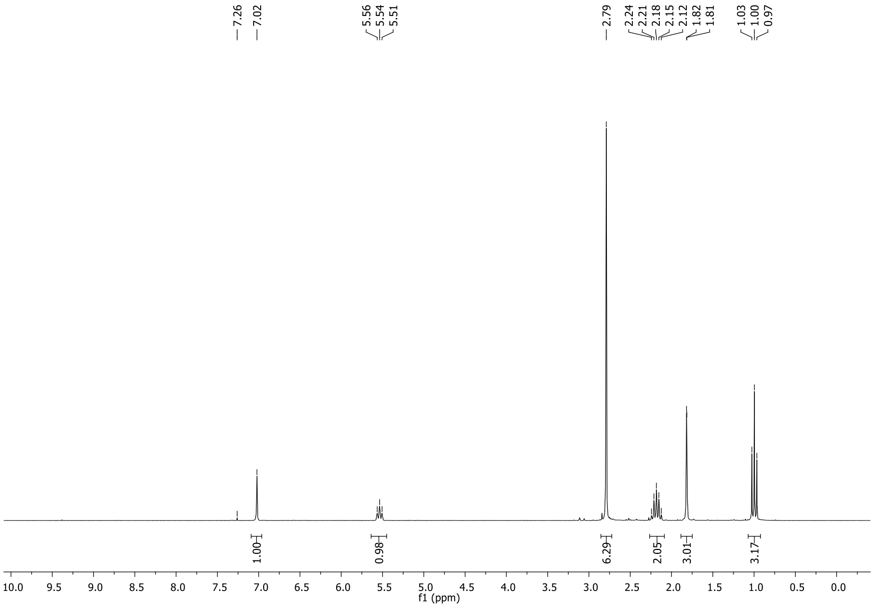
2c

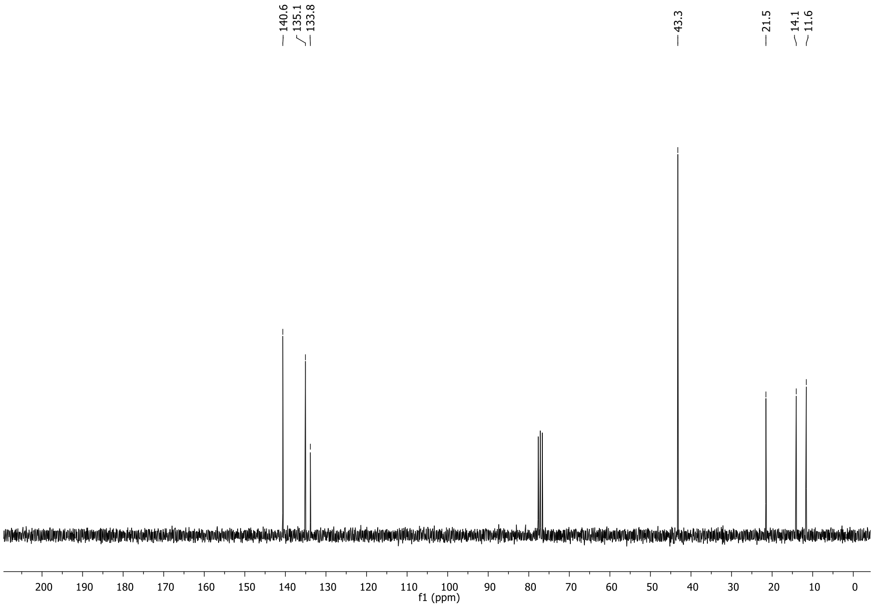

7.26
6.98
6.95
6.52
6.49
6.48
6.45
6.45
6.42
6.41
6.38
5.30
5.23
5.19
5.19
2.84
1.02
1.17
2.07
6.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

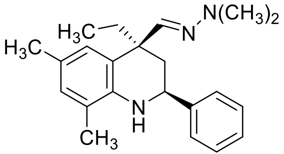

135.8
135.7
116.7
42.7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



2e

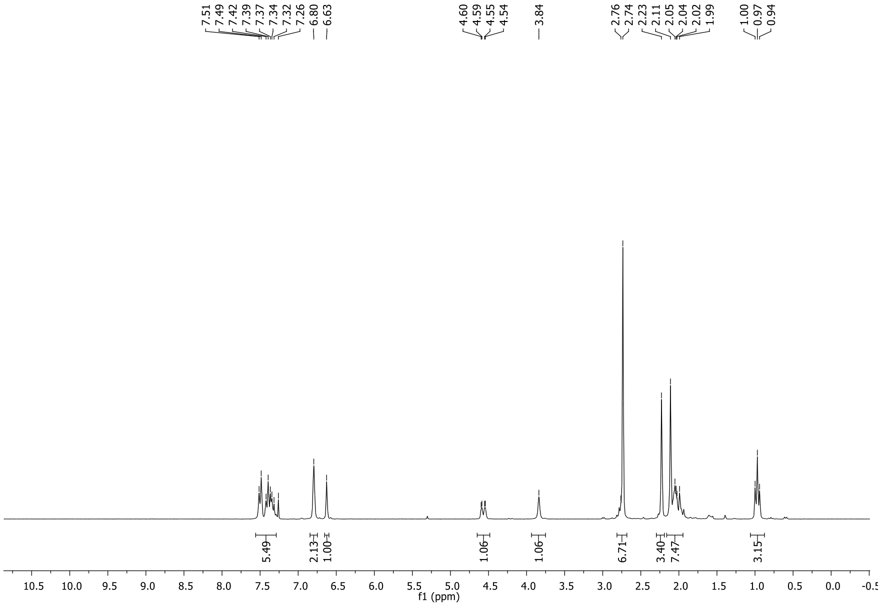

7.26
7.02
5.56
5.54
5.51
2.79
2.24
2.21
2.18
2.15
2.12
1.82
1.81
1.03
1.00
0.97
1.00
0.98
6.29
2.05
3.01
3.17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


140.6
135.1
133.8
43.3
21.5
14.1
11.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

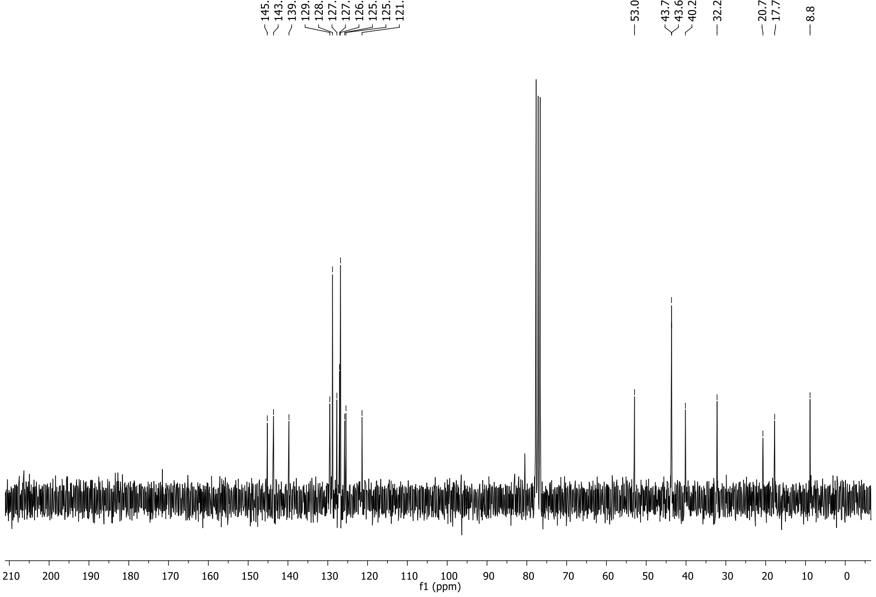


N(CH3)2
H3C
N
H3C
N
H
CH3

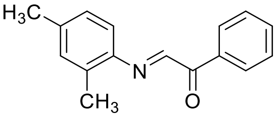
8g



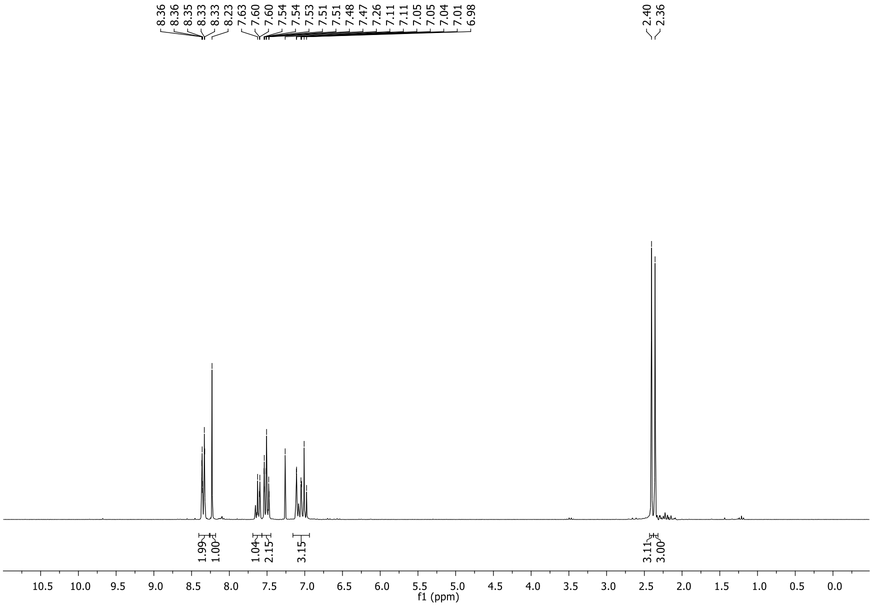
7.51
7.49
7.42
7.39
7.37
7.34
7.32
7.26
6.80
6.63
4.60
4.59
4.55
4.54
3.84
2.76
2.74
2.23
2.11
2.05
2.04
2.02
1.99
1.00
0.97
0.94
5.49
2.13
1.00
1.06
1.06
6.71
3.40
7.47
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

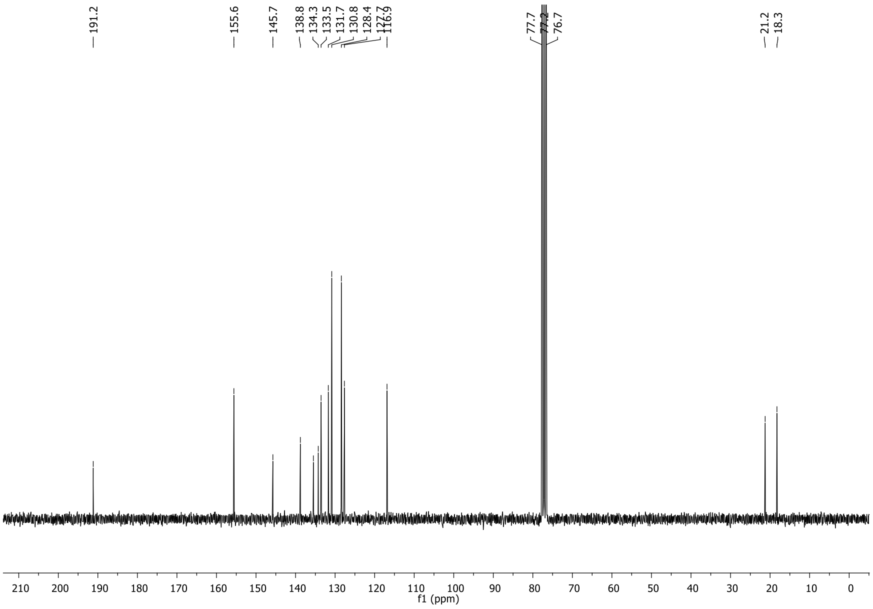


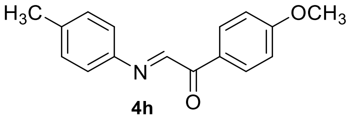
145.2
143.6
139.7
129.5
128.8
127.7
127.0
126.8
125.8
125.4
121.4
53.0
43.7
43.6
40.2
32.2
20.7
17.7
8.8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
N
O
CH3

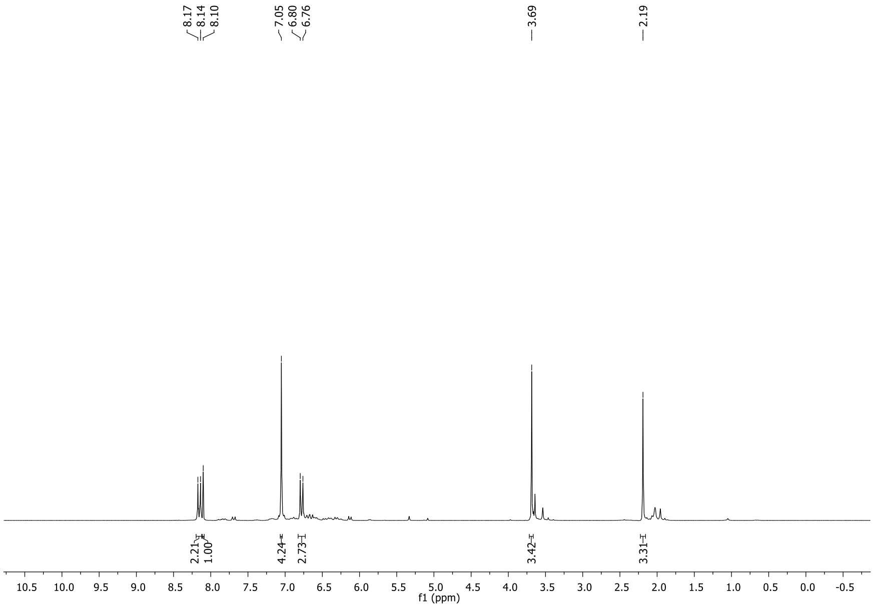
4d

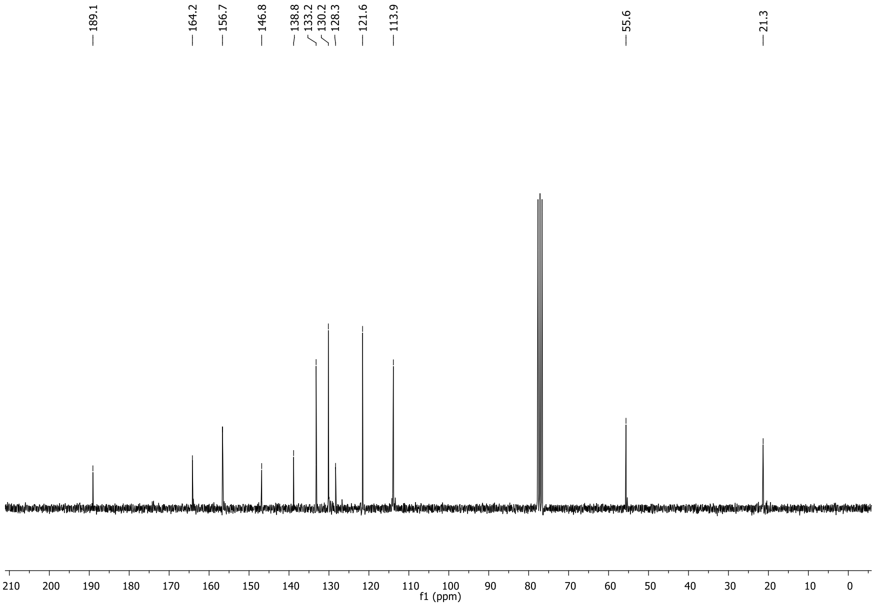

8.36
8.36
8.35
8.33
8.33
8.23
7.63
7.60
7.60
7.54
7.54
7.53
7.51
7.51
7.48
7.47
7.26
7.11
7.11
7.05
7.05
7.04
7.01
6.98
2.40
2.36
1.99
1.00
1.04
2.15
3.15
3.11
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

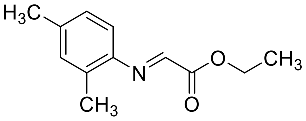

191.2
155.6
145.7
138.8
134.3
133.5
131.7
130.8
128.4
127.7
116.9
77.7
77.2
76.7
21.2
18.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
N
O
OCH3

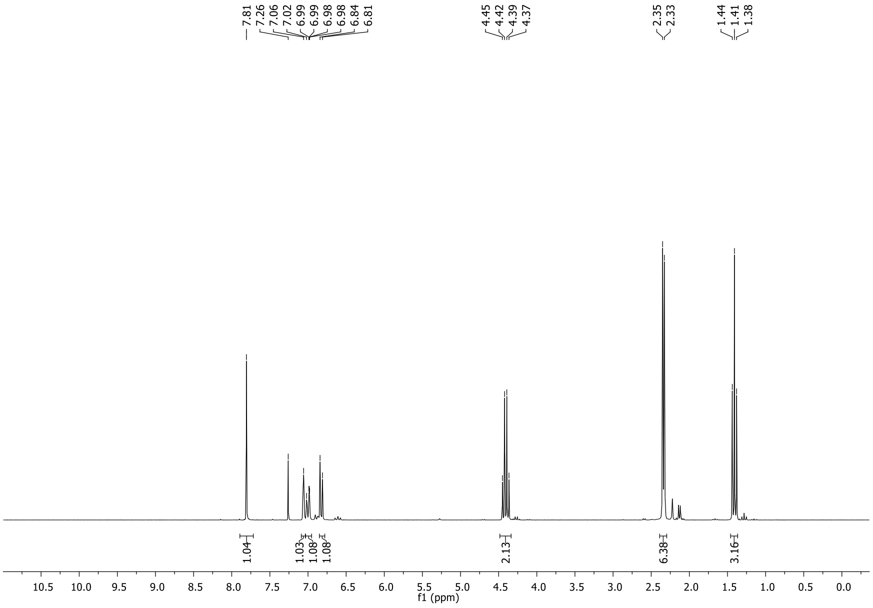
4h

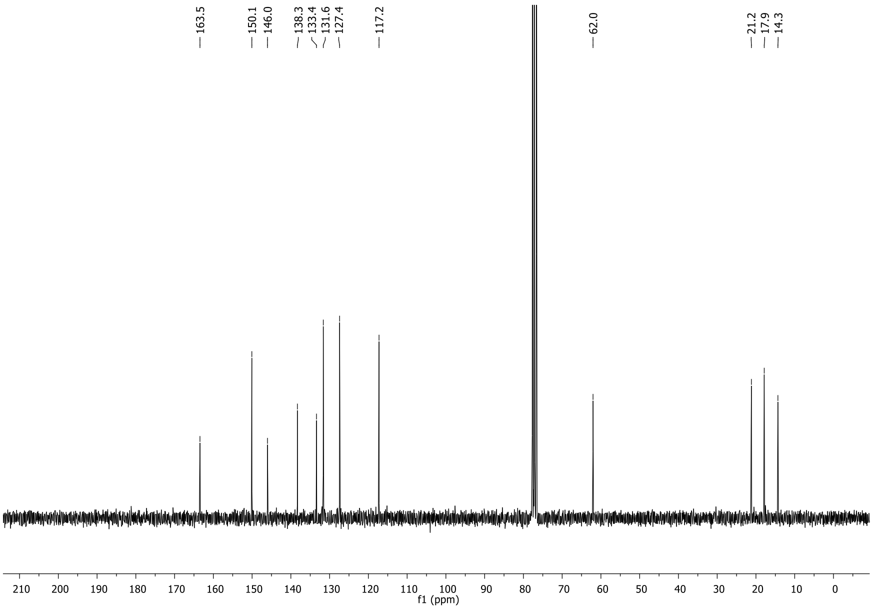

8.17
8.14
8.10
7.05
6.80
6.76
3.69
2.19
2.21
1.00
4.24
2.73
3.42
3.31
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

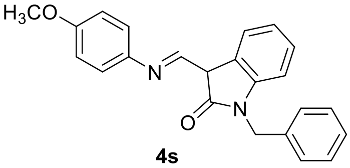

189.1
164.2
156.7
146.8
138.8
133.2
130.2
128.3
121.6
113.9
55.6
21.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
N
O
CH3
O
CH3

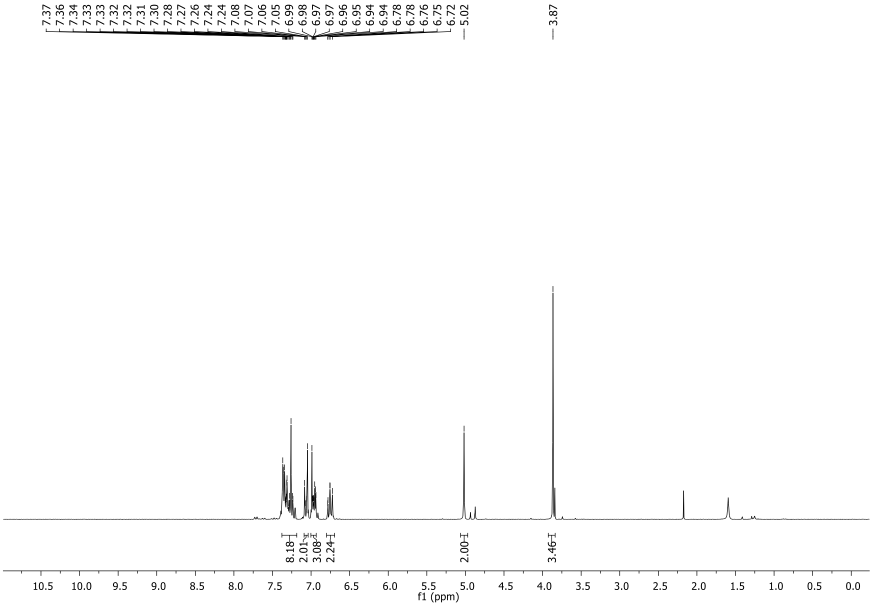
4j

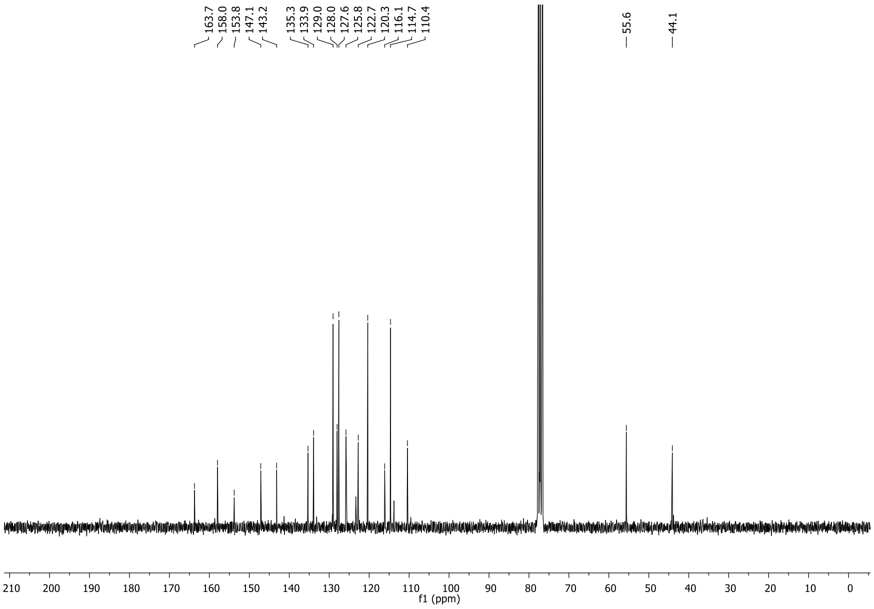

7.81
7.26
7.06
7.02
6.99
6.99
6.98
6.98
6.84
6.81
4.45
4.42
4.39
4.37
2.35
2.33
1.44
1.41
1.38
1.04
1.03
1.08
1.08
2.13
6.38
3.16
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

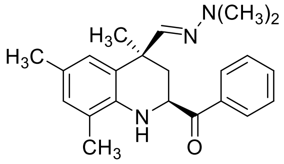

163.5
150.1
146.0
138.3
133.4
131.6
127.4
117.2
62.0
21.2
17.9
14.3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


H$_3$CO
N
O
N

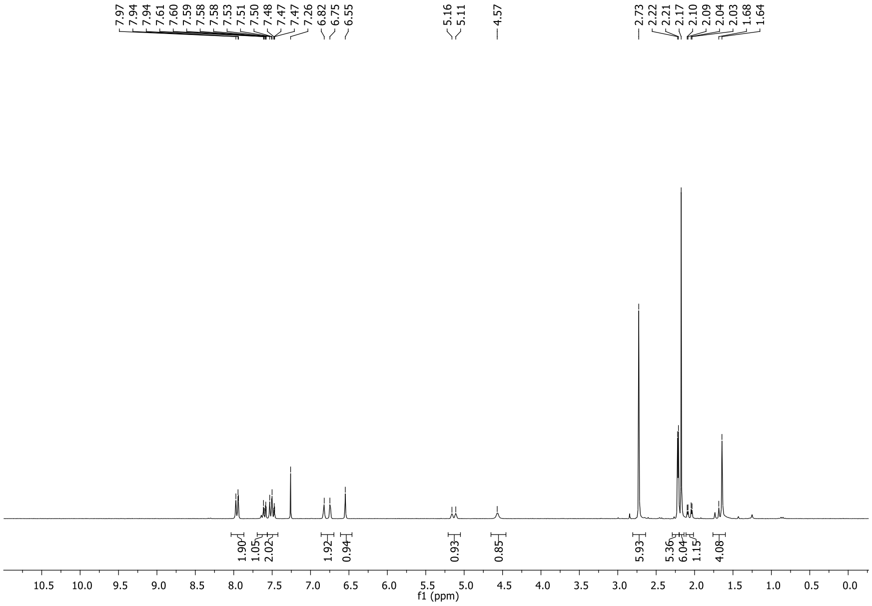
4s

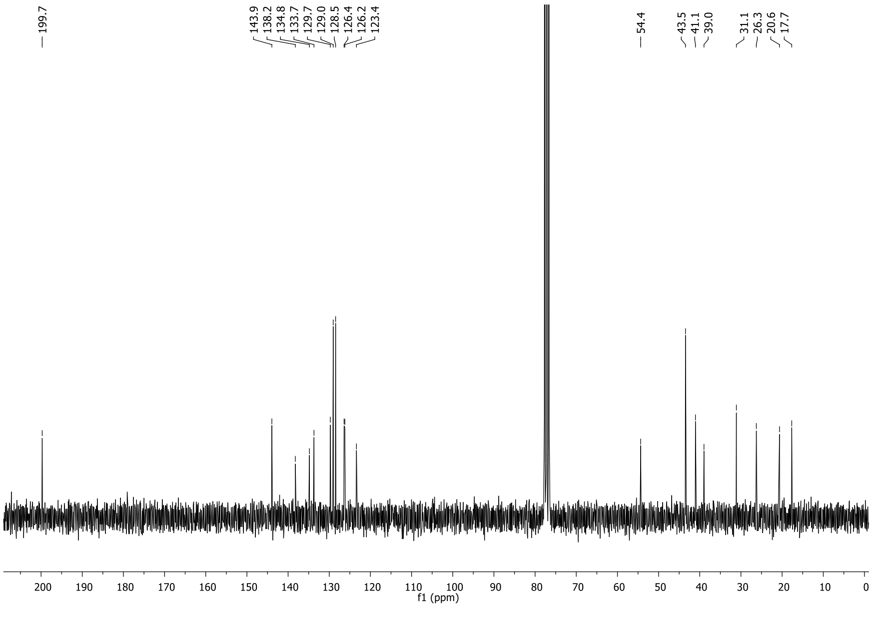

7.37
7.36
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.28
7.27
7.26
7.24
7.24
7.08
7.07
7.06
7.05
6.99
6.98
6.97
6.97
6.96
6.95
6.94
6.94
6.78
6.78
6.76
6.75
6.72
5.02
3.87
8.18
2.01
3.08
2.24
2.00
3.46
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

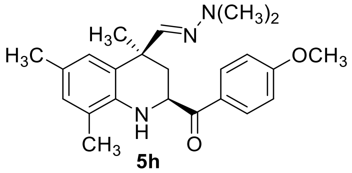

163.7
158.0
153.8
147.1
143.2
135.3
133.9
129.0
128.0
127.6
125.8
122.7
120.3
116.1
114.7
110.4
55.6
44.1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH$_3$)$_2$
H$_3$C
H$_3$C
N
H
CH$_3$
O

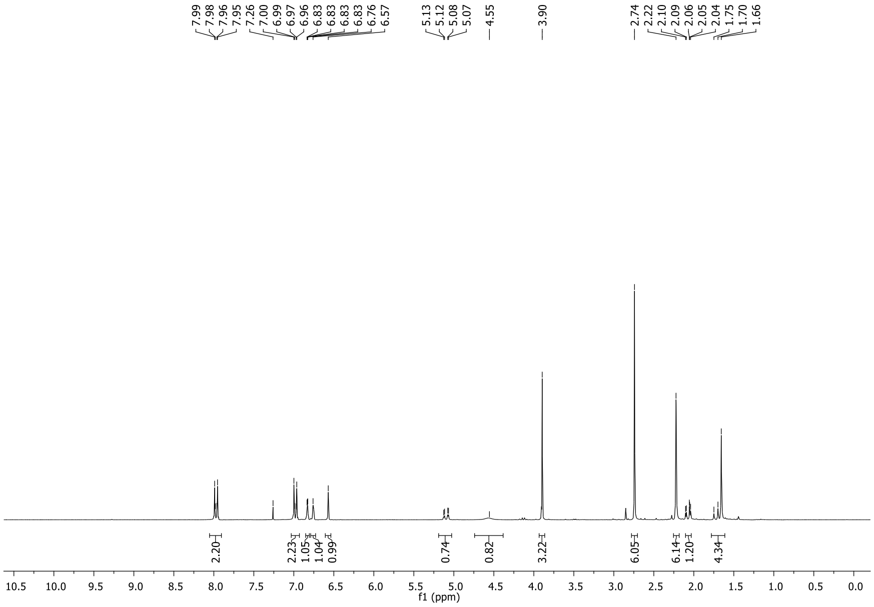
5e

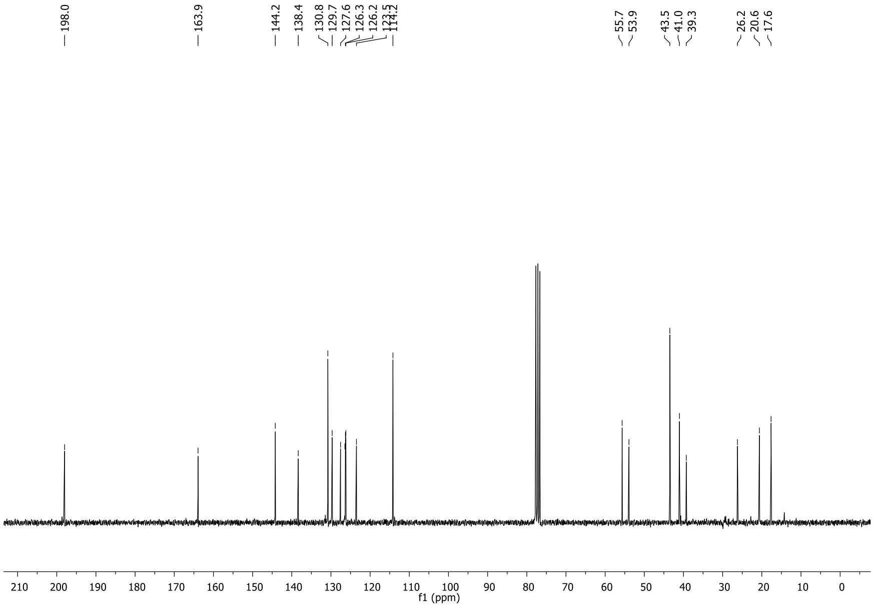

7.97
7.94
7.94
7.61
7.60
7.59
7.58
7.58
7.53
7.51
7.50
7.48
7.47
7.47
7.26
6.82
6.75
6.55
5.16
5.11
4.57
2.73
2.22
2.21
2.17
2.10
2.09
2.04
2.03
1.68
1.64
1.90
1.05
2.02
1.92
0.94
0.93
0.85
5.93
5.36
6.04
1.15
4.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

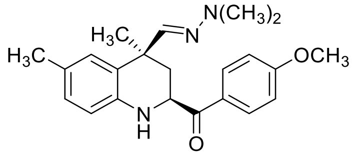

199.7
143.9
138.2
134.8
133.7
129.7
129.0
128.5
126.4
126.2
123.4
54.4
43.5
41.1
39.0
31.1
26.3
20.6
17.7
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH3)2
H3C
N
H3C
OCH3
N
H
CH3
O

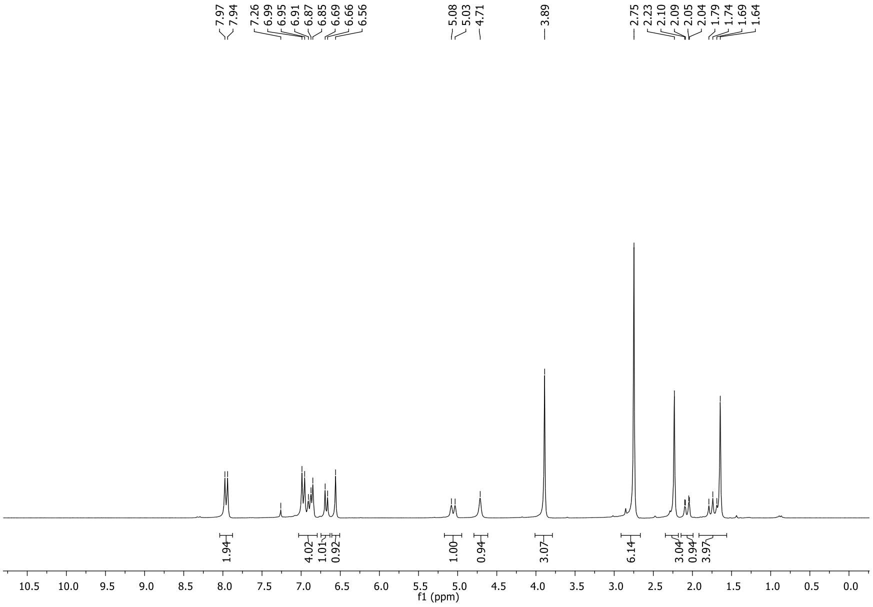
5h

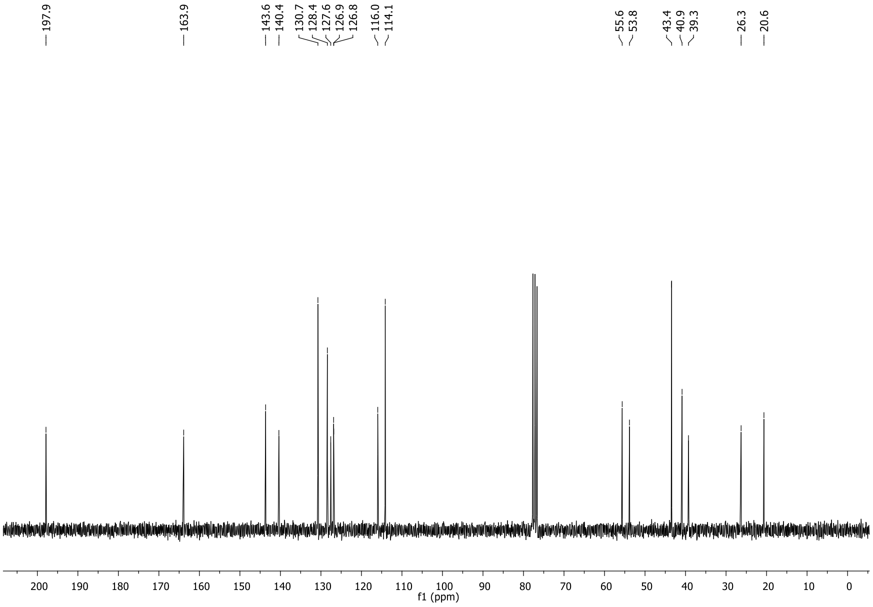

7.99
7.98
7.96
7.95
7.26
7.00
6.99
6.97
6.96
6.83
6.83
6.83
6.83
6.76
6.57
5.13
5.12
5.08
5.07
4.55
3.90
2.74
2.22
2.10
2.09
2.06
2.05
2.04
1.75
1.70
1.66
2.20
2.23
1.05
1.04
0.99
0.74
0.82
3.22
6.05
6.14
1.20
4.34
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

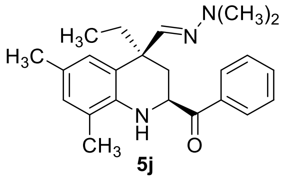

198.0
163.9
144.2
138.4
130.8
129.7
127.6
126.3
126.2
123.5
114.2
55.7
53.9
43.5
41.0
39.3
26.2
20.6
17.6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH3)2
H3C
N
H3C
OCH3
N
H
O

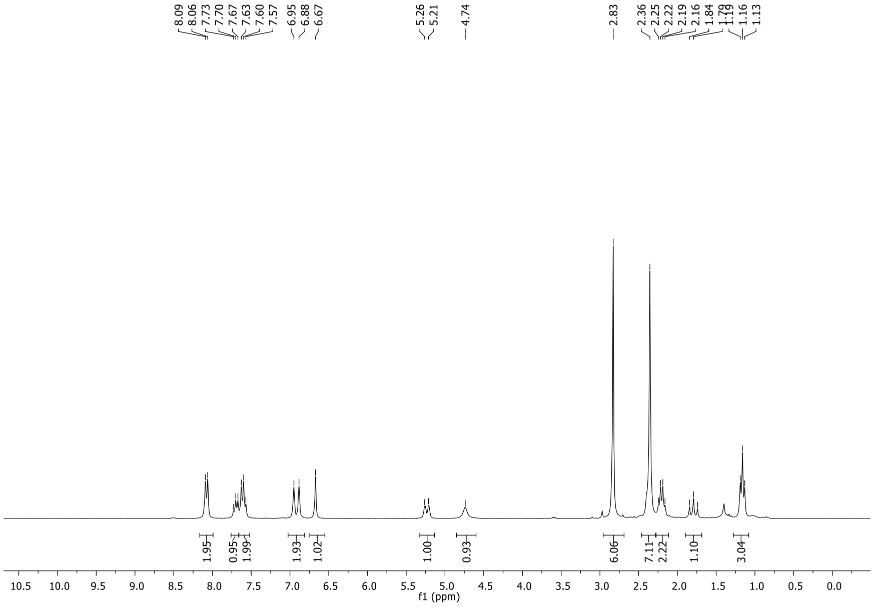
5i

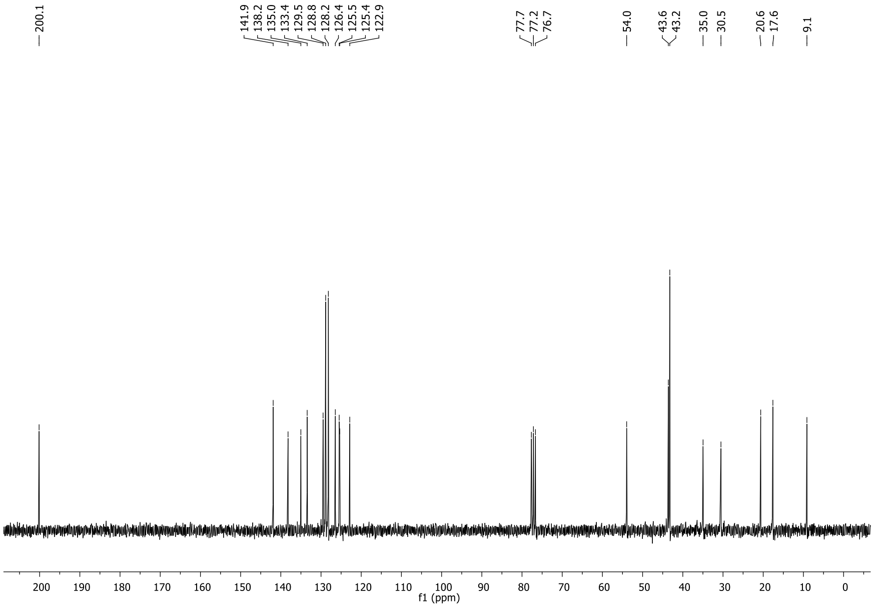

7.97
7.94
7.26
6.99
6.95
6.91
6.87
6.85
6.69
6.66
6.56
5.08
5.03
4.71
3.89
2.75
2.23
2.10
2.09
2.05
2.04
1.79
1.74
1.69
1.64
1.94
4.02
1.01
0.92
1.00
0.94
3.07
6.14
3.04
0.94
3.97
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

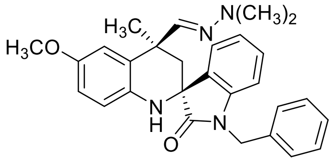

197.9
163.9
143.6
140.4
130.7
128.4
127.6
126.9
126.8
116.0
114.1
55.6
53.8
43.4
40.9
39.3
26.3
20.6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH3)2
H3C
N
H3C
N
H
O
CH3

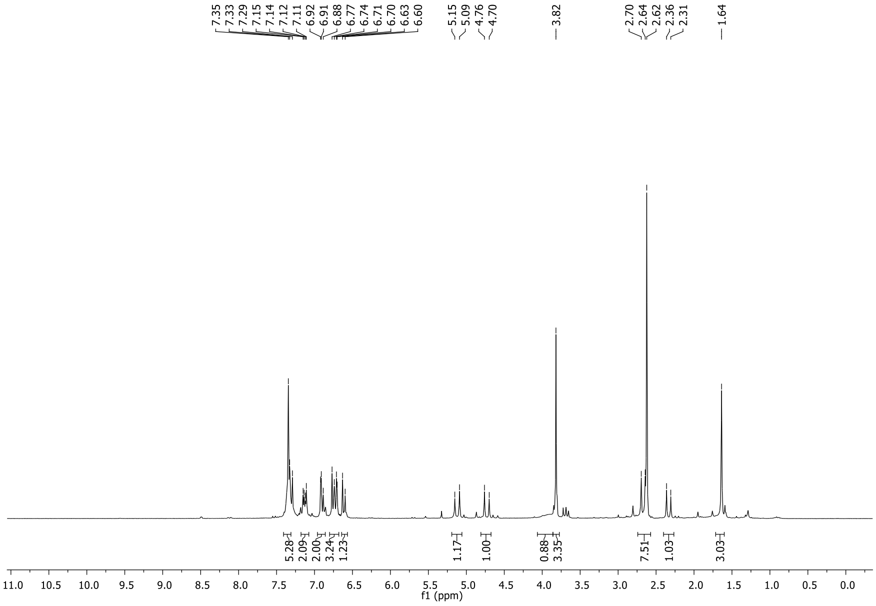
5j

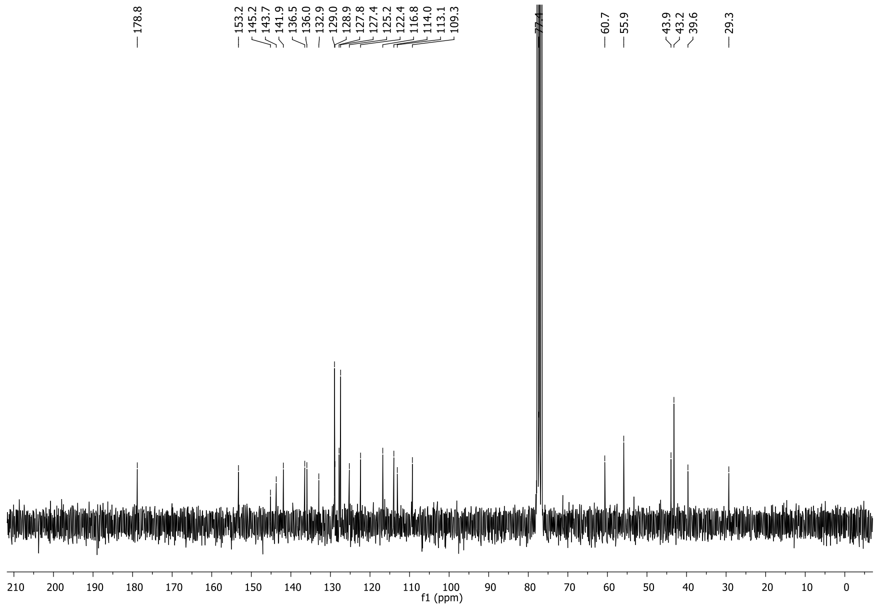

8.09
8.06
7.73
7.70
7.67
7.63
7.60
7.57
6.95
6.88
6.67
5.26
5.21
4.74
2.83
2.36
2.25
2.22
2.19
2.16
1.84
1.79
1.19
1.16
1.13
1.95
0.95
1.99
1.93
1.02
1.00
0.93
6.06
7.11
2.22
1.10
3.04
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200.1
141.9
138.2
135.0
133.4
129.5
128.8
128.2
126.4
125.5
125.4
122.9
77.7
77.2
76.7
54.0
43.6
43.2
35.0
30.5
20.6
17.6
9.1
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

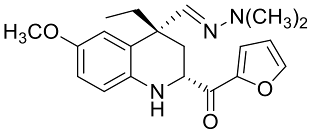

H3CO
H3C
N(CH3)2
N
N
H
O
N

5v


7.35
7.33
7.29
7.15
7.14
7.12
7.11
6.92
6.91
6.88
6.77
6.74
6.71
6.70
6.63
6.60
5.15
5.09
4.76
4.70
3.82
2.70
2.64
2.62
2.36
2.31
1.64
5.28
2.09
2.00
3.24
1.23
1.17
1.00
0.88
3.35
7.51
1.03
3.03
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

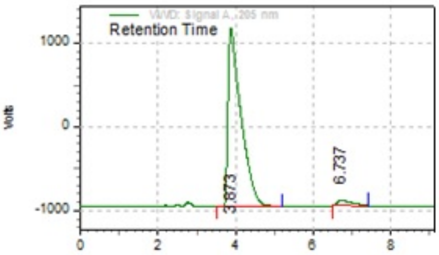

178.8
153.2
145.2
143.7
141.9
136.5
136.0
132.9
129.0
128.9
127.8
127.4
125.2
122.4
116.8
114.0
113.1
109.3
77.4
60.7
55.9
43.9
43.2
39.6
29.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Derivative 6h:



6h

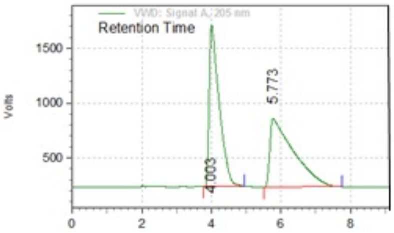
-ee: 94 %



VWD: Signal A,
205 nm Results

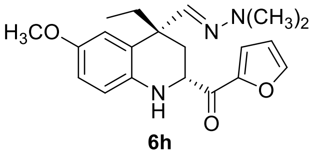
Retention Time	Area	Area %	Height	Height %
3.873	826196869	96.76	35707444	97.21
6.737	27681837	3.24	1024499	2.79
Totals	853878706	100.00	36731943	100.00

Racemic sample:

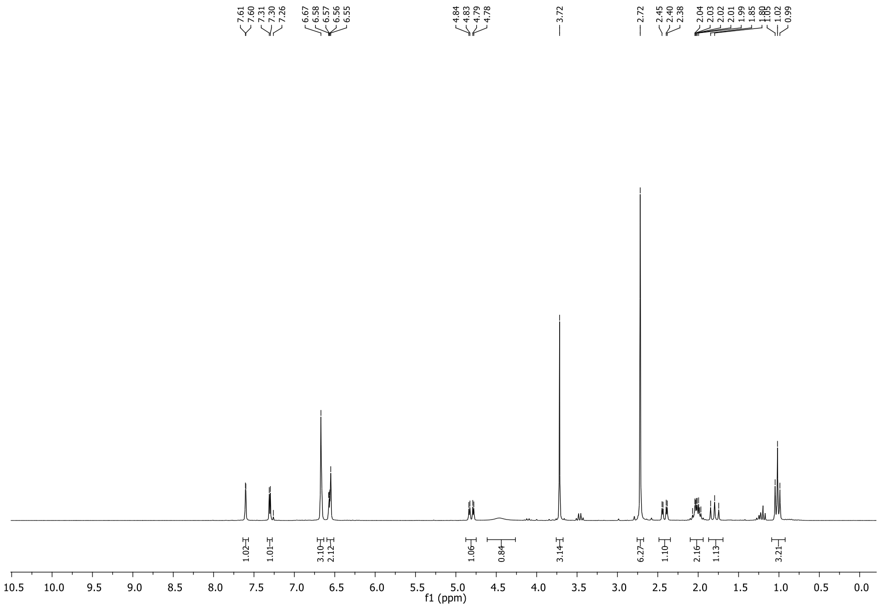


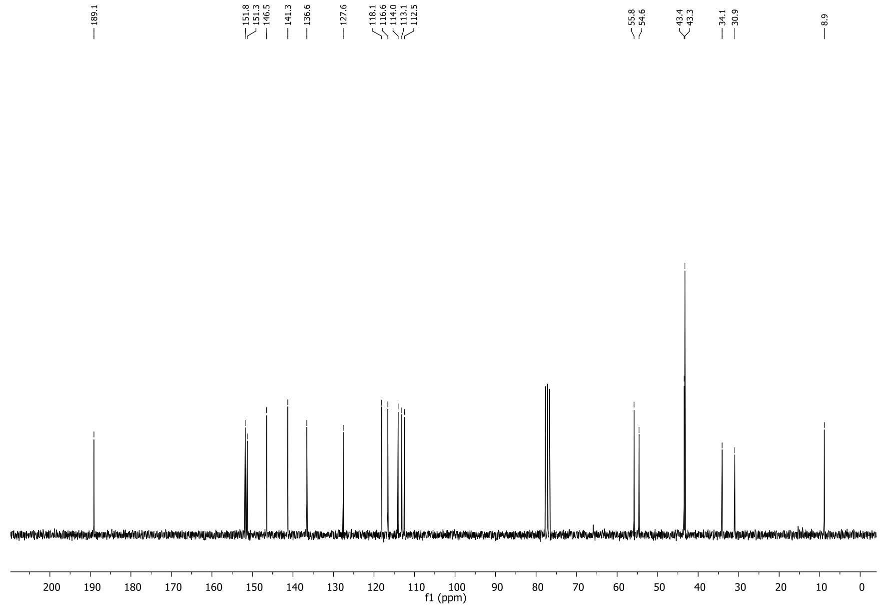
VWD: Signal A,
205 nm Results

Retention Time	Area	Area %	Height	Height %
4.003	492957311	49.96	24688780	70.25
5.773	493714870	50.04	10456236	29.75
Totals	986672181	100.00	35145016	100.00


H3CO
N(CH3)2
N
N
H
O
O

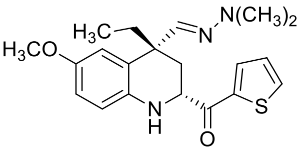
6h


7.61
7.60
7.31
7.30
7.26
6.67
6.58
6.57
6.56
6.55
4.84
4.83
4.79
4.78
3.72
2.72
2.45
2.40
2.38
2.04
2.03
2.02
2.01
1.99
1.85
1.80
1.05
1.02
0.99
1.02
1.01
3.10
2.12
1.06
0.84
3.14
6.27
1.10
2.16
1.13
3.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

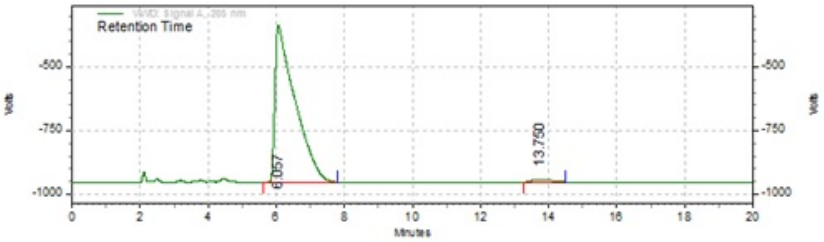

189.1
151.8
151.3
146.5
141.3
136.6
127.6
118.1
116.6
114.0
113.1
112.5
55.8
54.6
43.4
43.3
34.1
30.9
8.9
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Derivative 6i:

- ee: 97%



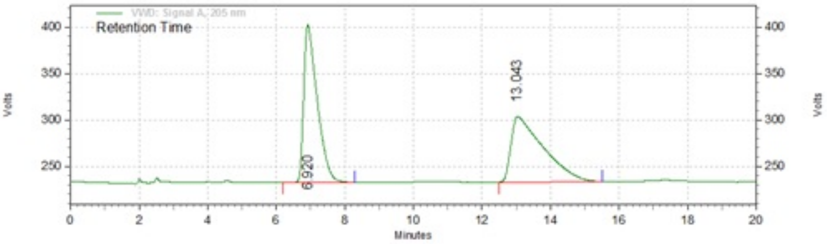
6i



**VWD: Signal A,
205 nm Results**

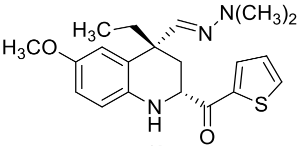
Retention Time	Area	Area %	Height	Height %
6.057	422859660	98.35	10348975	98.30
13.750	7105485	1.65	178722	1.70
Totals	429965145	100.00	10527697	100.00

Racemic sample:

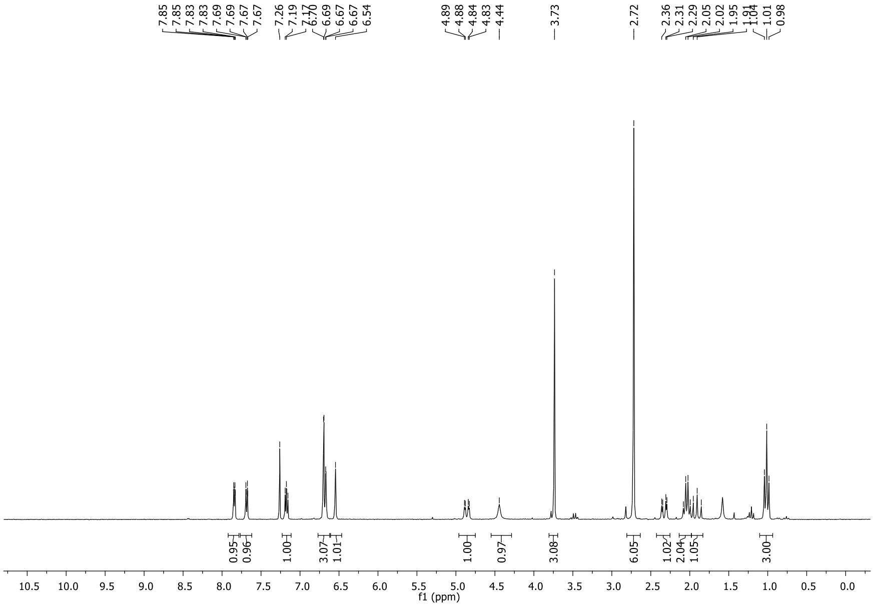


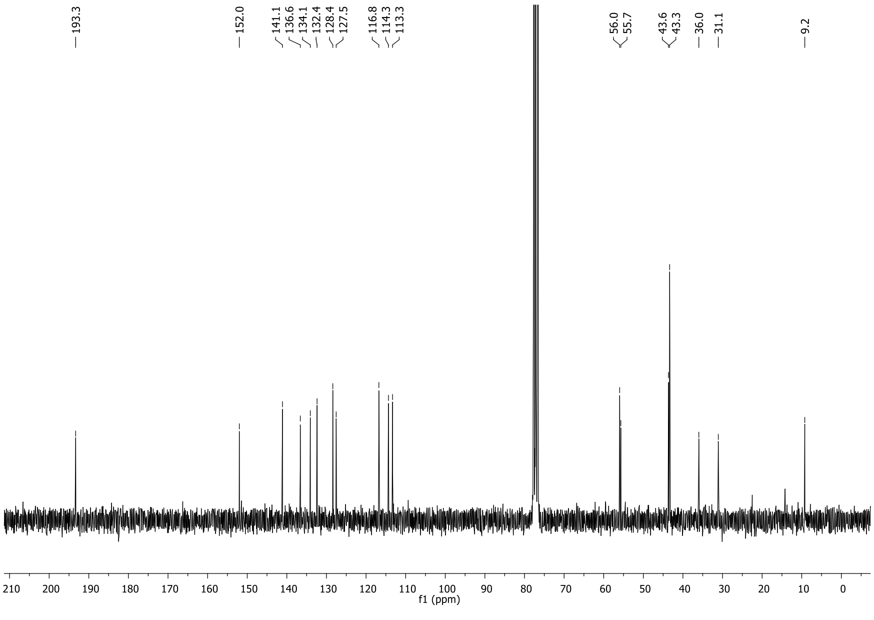
**VWD: Signal A,
205 nm Results**

Retention Time	Area	Area %	Height	Height %
6.920	77997992	50.29	2842340	70.58
13.043	77099600	49.71	1184865	29.42
Totals	155097592	100.00	4027205	100.00

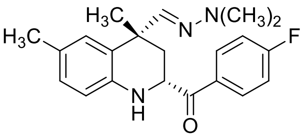

H3CO
H3C
N(CH3)2
N
S
N
H
O

6i


7.85
7.85
7.83
7.83
7.69
7.69
7.67
7.67
7.26
7.19
7.17
6.70
6.69
6.67
6.67
6.54
4.89
4.88
4.84
4.83
4.44
3.73
2.72
2.36
2.31
2.29
2.05
2.02
1.95
1.91
1.04
1.01
0.98
0.95
0.96
1.00
3.07
1.01
1.00
0.97
3.08
6.05
1.02
2.04
1.05
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

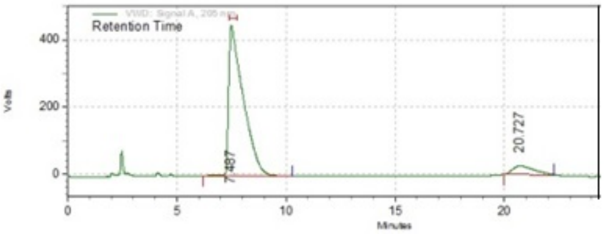

193.3
152.0
141.1
136.6
134.1
132.4
128.4
127.5
116.8
114.3
113.3
56.0
55.7
43.6
43.3
36.0
31.1
9.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

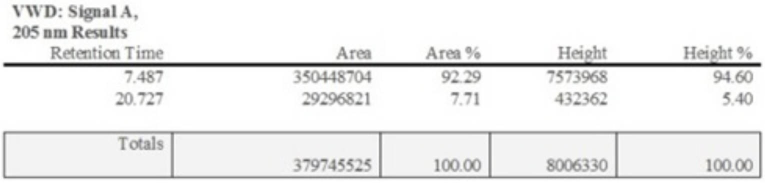
Derivative 6n:



6n

- ee: 85%

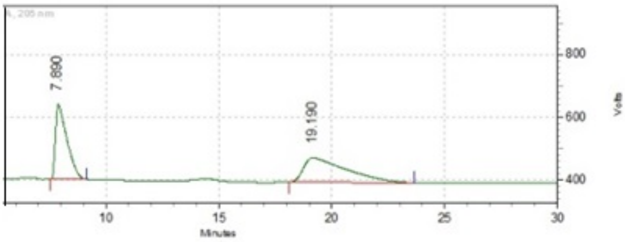


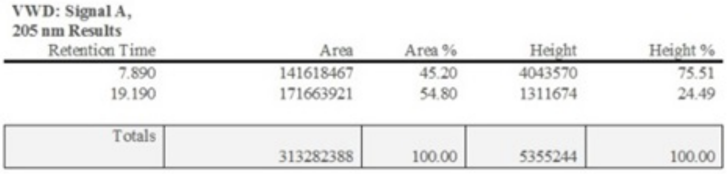


**VWD: Signal A,
205 nm Results**

Retention Time	Area	Area %	Height	Height %
7.487	350448704	92.29	7573968	94.60
20.727	29296821	7.71	432362	5.40
Totals	379745525	100.00	8006330	100.00

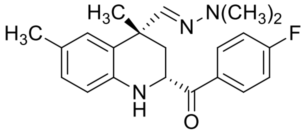
Racemic sample:



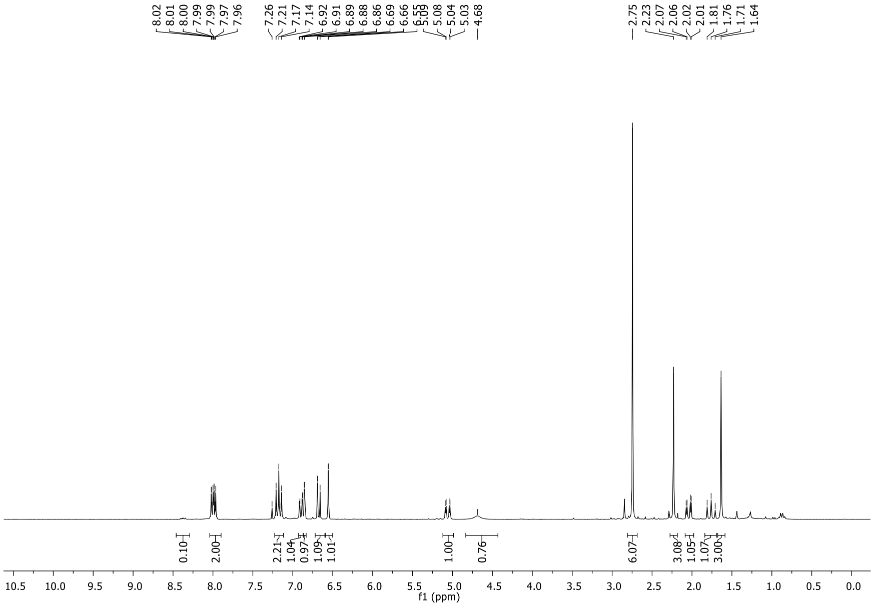


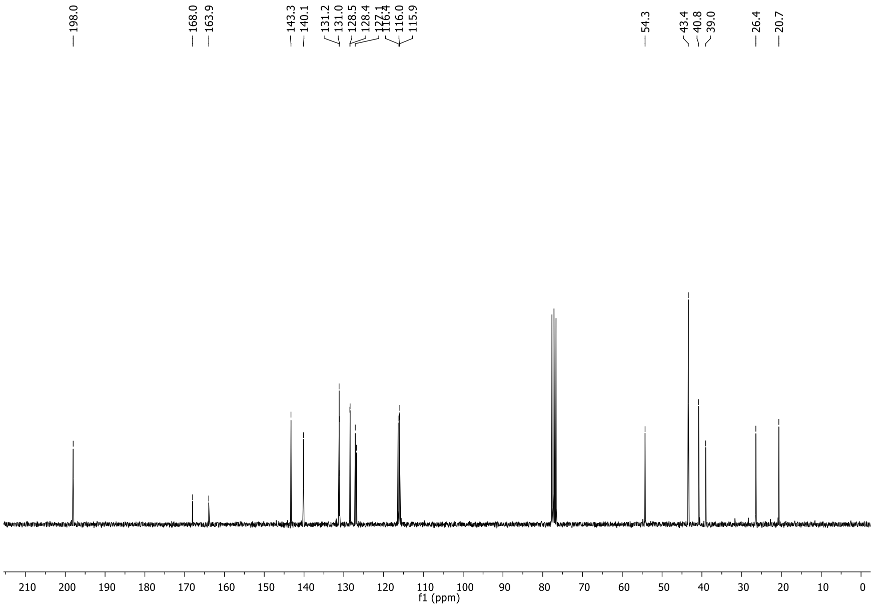
**VWD: Signal A,
205 nm Results**

Retention Time	Area	Area %	Height	Height %
7.890	141618467	45.20	4043570	75.51
19.190	171663921	54.80	1311674	24.49
Totals	313282388	100.00	5355244	100.00


H3C
H3C
N(CH3)2
N
F
N
H
O

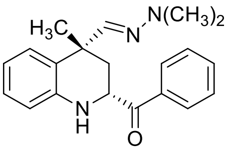
6n


8.02
8.01
8.00
7.99
7.99
7.97
7.96
7.26
7.21
7.17
7.14
6.92
6.91
6.89
6.88
6.86
6.69
6.66
6.55
5.09
5.08
5.04
5.03
4.68
2.75
2.23
2.07
2.06
2.02
2.01
1.81
1.76
1.71
1.64
0.10
2.00
2.21
1.04
0.97
1.09
1.01
1.00
0.76
6.07
3.08
1.05
1.07
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

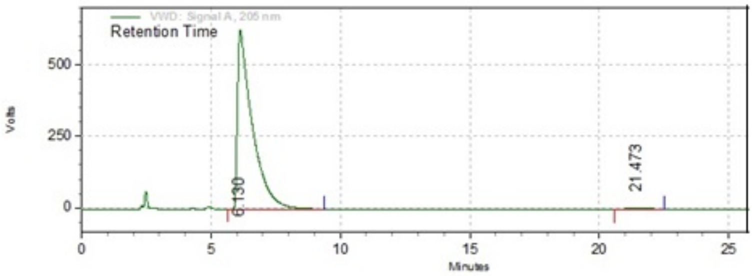

198.0
168.0
163.9
143.3
140.1
131.2
131.0
128.5
128.4
127.1
116.4
116.0
115.9
54.3
43.4
40.8
39.0
26.4
20.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Derivative 6o:

- ee: 97%



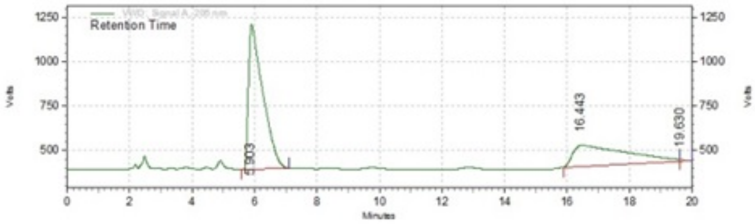
6o



**VWD: Signal A,
205 nm Results**

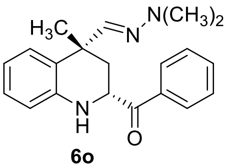
Retention Time	Area	Area %	Height	Height %
6.130	418818641	98.64	10519098	99.03
21.473	5791588	1.36	102854	0.97
Totals	424610229	100.00	10621952	100.00

Racemic sample:

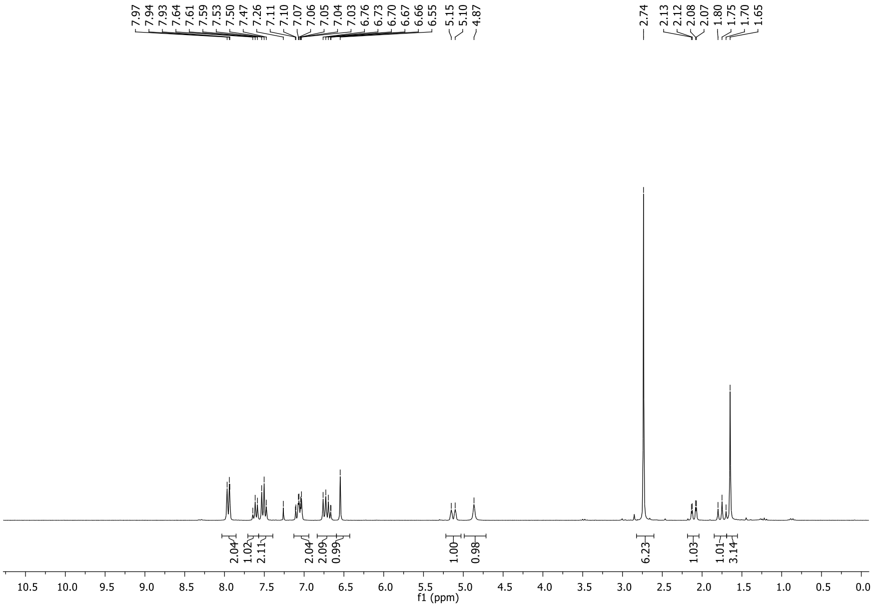


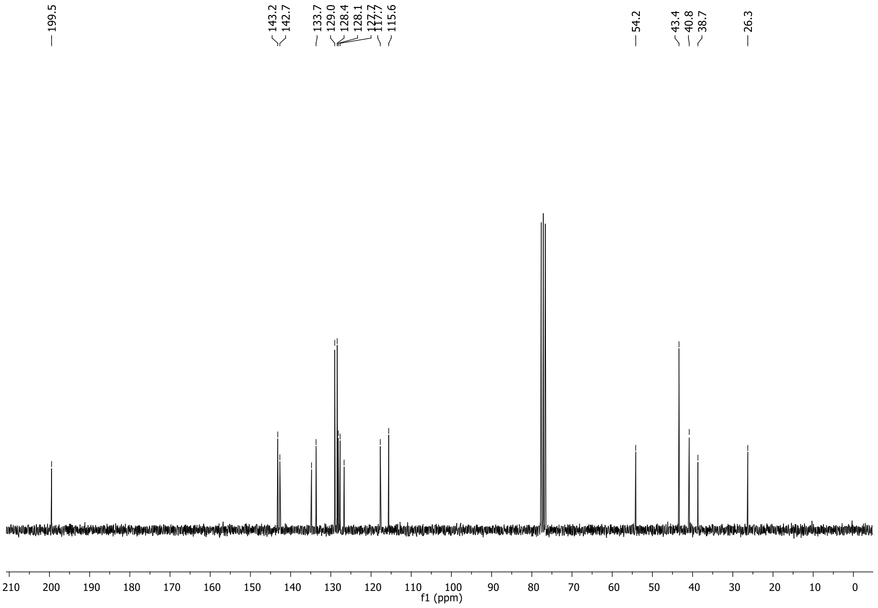
**VWD: Signal A,
205 nm Results**

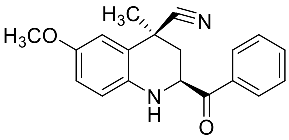
Retention Time	Area	Area %	Height	Height %
5.903	432615920	64.44	13729364	86.14
16.443	236629629	35.25	2020802	12.68
19.630	2058637	0.31	188375	1.18
Totals	671304186	100.00	15938541	100.00


H3C
N(CH3)2
N
N
H
O

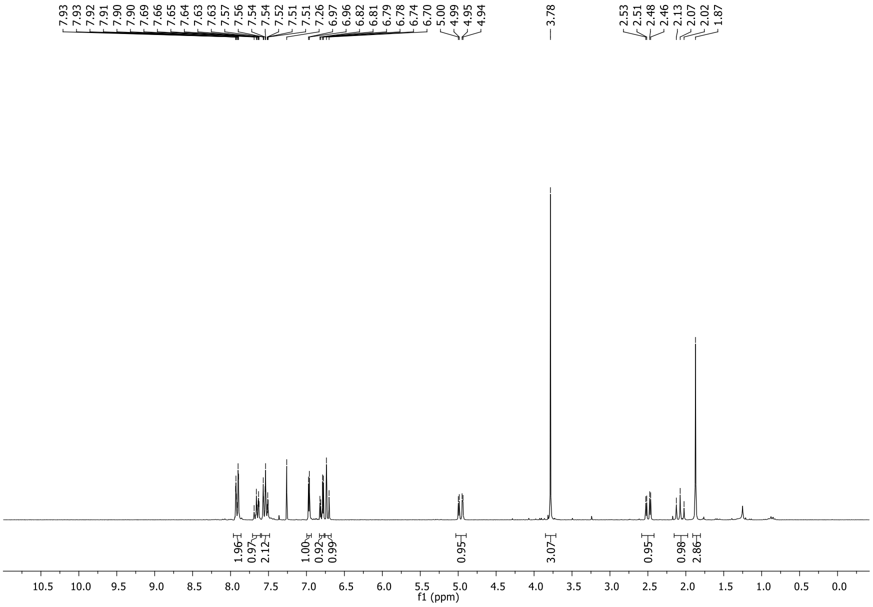
6o

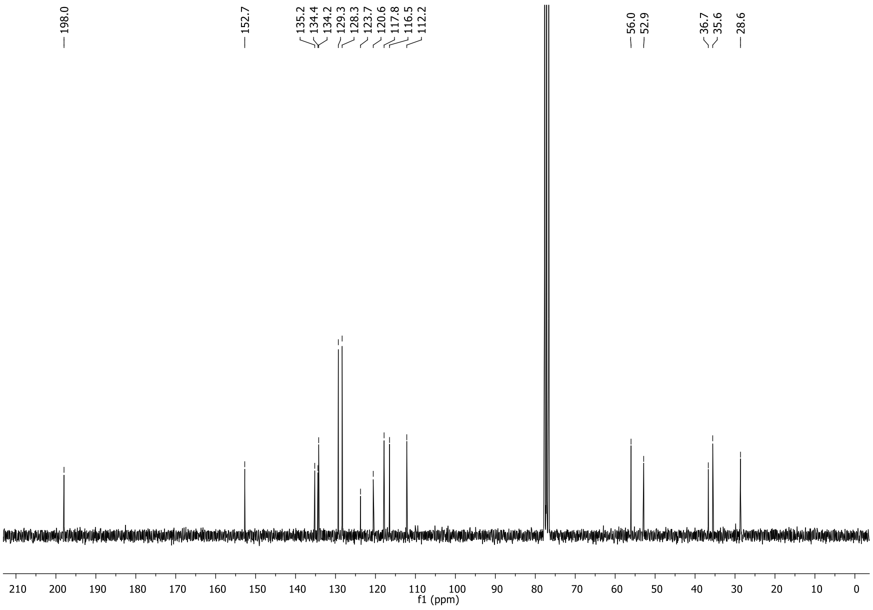

7.97
7.94
7.93
7.64
7.61
7.59
7.53
7.50
7.47
7.26
7.11
7.10
7.07
7.06
7.05
7.04
7.03
6.76
6.73
6.70
6.67
6.66
6.55
5.15
5.10
4.87
2.74
2.13
2.12
2.08
2.07
1.80
1.75
1.70
1.65
2.04
1.02
2.11
2.04
2.09
0.99
1.00
0.98
6.23
1.03
1.01
3.14
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

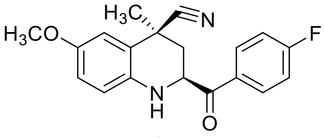

199.5
143.2
142.7
133.7
129.0
128.4
128.1
127.7
117.7
115.6
54.2
43.4
40.8
38.7
26.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
H3C
N
N
H
O

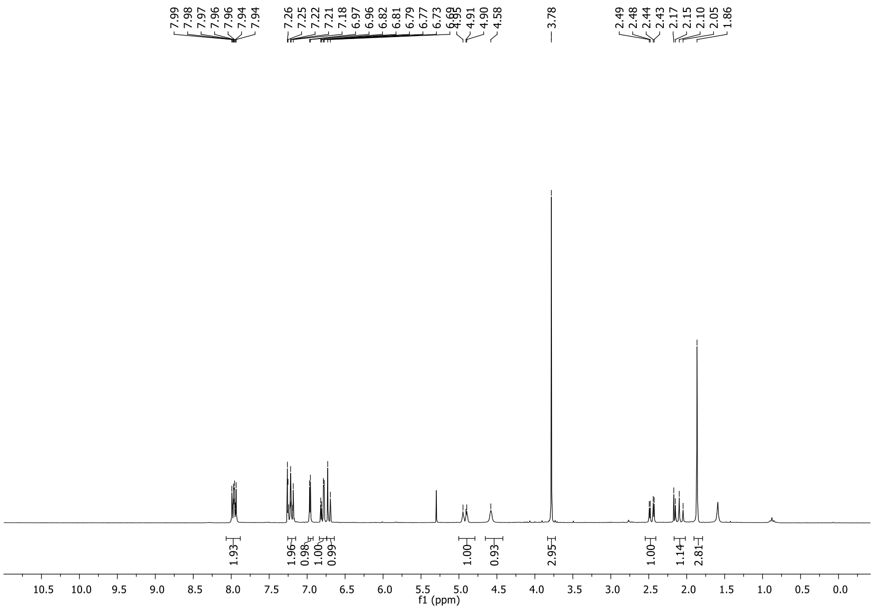
7a

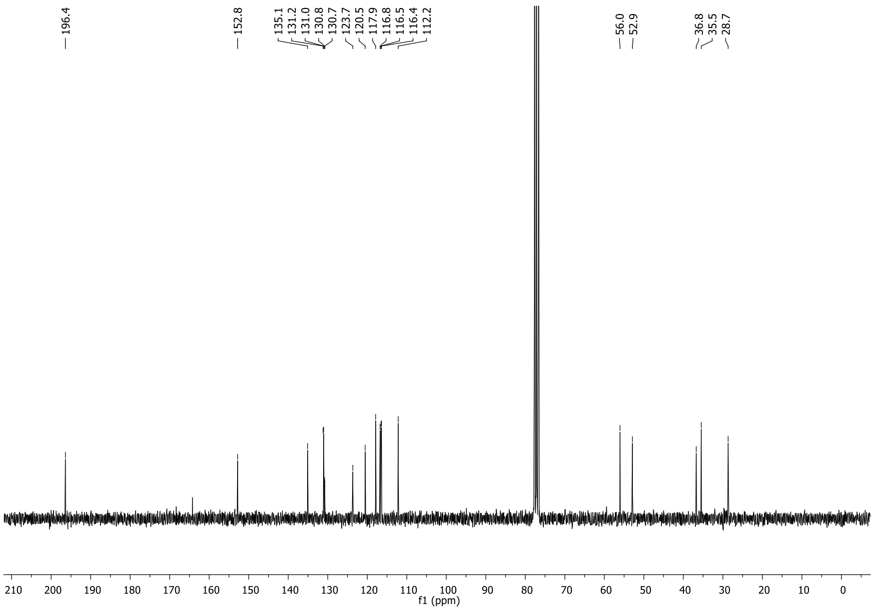

7.93
7.93
7.92
7.91
7.90
7.90
7.69
7.66
7.65
7.64
7.63
7.63
7.57
7.56
7.54
7.54
7.52
7.51
7.51
7.26
6.97
6.96
6.82
6.81
6.79
6.78
6.74
6.70
5.00
4.99
4.95
4.94
3.78
2.53
2.51
2.48
2.46
2.13
2.07
2.02
1.87
1.96
0.97
2.12
1.00
0.92
0.99
0.95
3.07
0.95
0.98
2.86
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

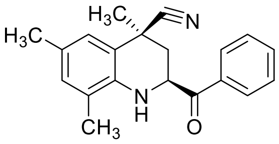

198.0
152.7
135.2
134.4
134.2
129.3
128.3
123.7
120.6
117.8
116.5
112.2
56.0
52.9
36.7
35.6
28.6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
N
H3CO
F
N
H
O

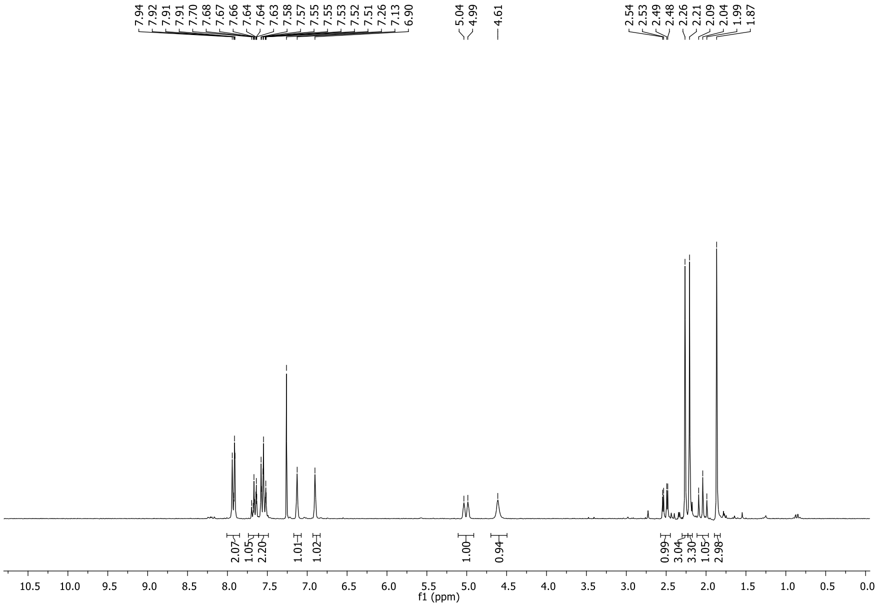
7b

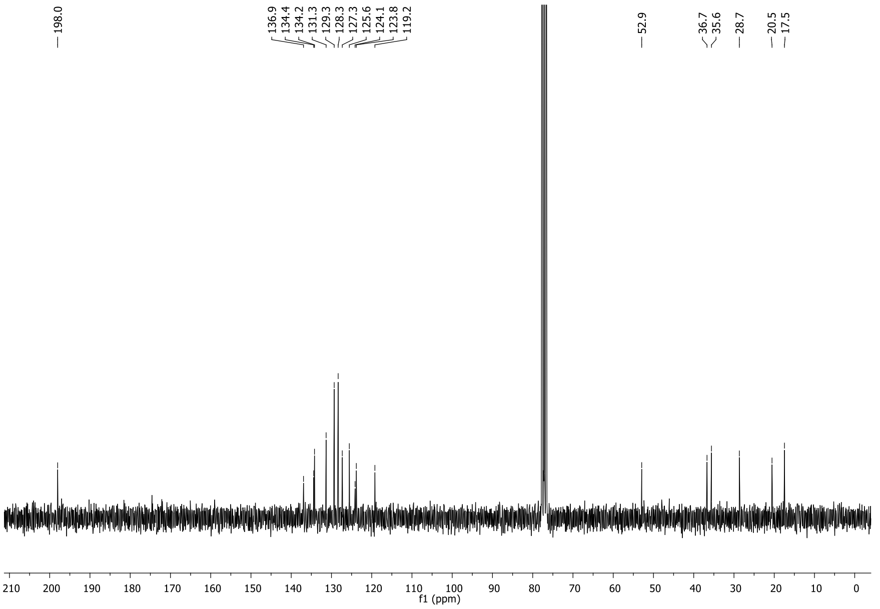

7.99
7.98
7.97
7.96
7.96
7.94
7.94
7.26
7.25
7.22
7.21
7.18
6.97
6.96
6.82
6.81
6.79
6.77
6.73
6.69
4.95
4.91
4.90
4.58
3.78
2.49
2.48
2.44
2.43
2.17
2.15
2.10
2.05
1.86
1.93
1.96
0.98
1.00
0.99
1.00
0.93
2.95
1.00
1.14
2.81
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

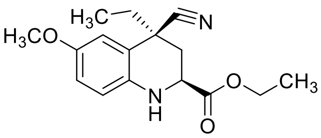

196.4
152.8
135.1
131.2
131.0
130.8
130.7
123.7
120.5
117.9
116.8
116.5
116.4
112.2
56.0
52.9
36.8
35.5
28.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
H3C
N
N
H
CH3
O

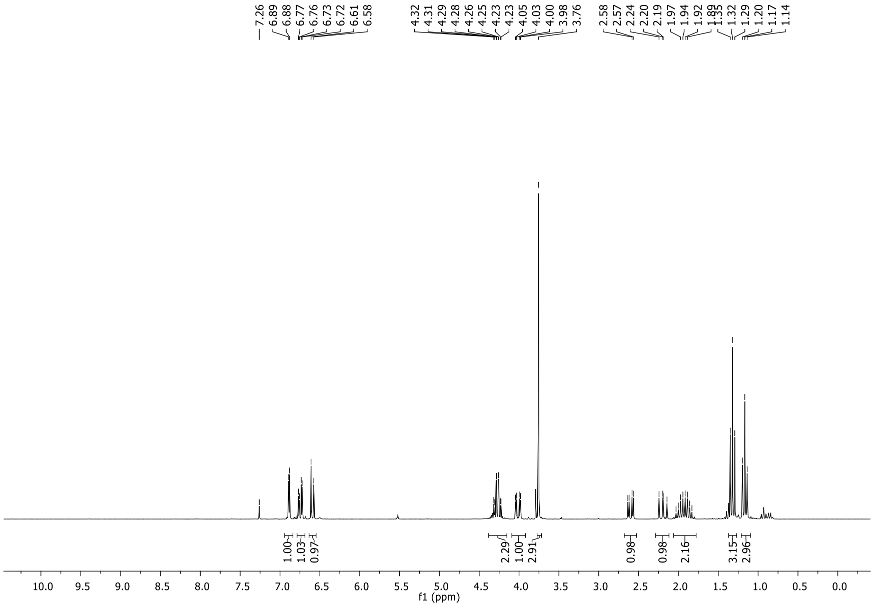
7e

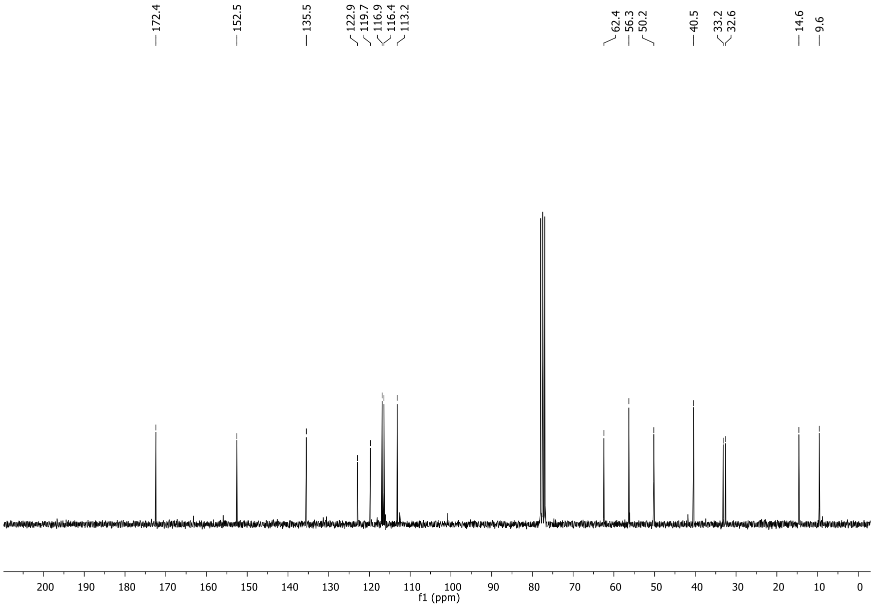

7.94
7.92
7.91
7.91
7.70
7.68
7.67
7.66
7.64
7.64
7.63
7.58
7.57
7.55
7.55
7.53
7.52
7.51
7.26
7.13
6.90
5.04
4.99
4.61
2.54
2.53
2.49
2.48
2.26
2.21
2.09
2.04
1.99
1.87
2.07
1.05
2.20
1.01
1.02
1.00
0.94
0.99
3.04
3.30
1.05
2.98
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

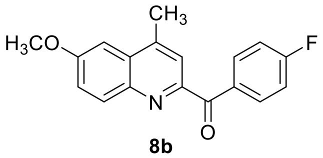

198.0
136.9
134.4
134.2
131.3
129.3
128.3
127.3
125.6
124.1
123.8
119.2
52.9
36.7
35.6
28.7
20.5
17.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H$_3$C
N
H$_3$CO
O
CH$_3$
N
H
O

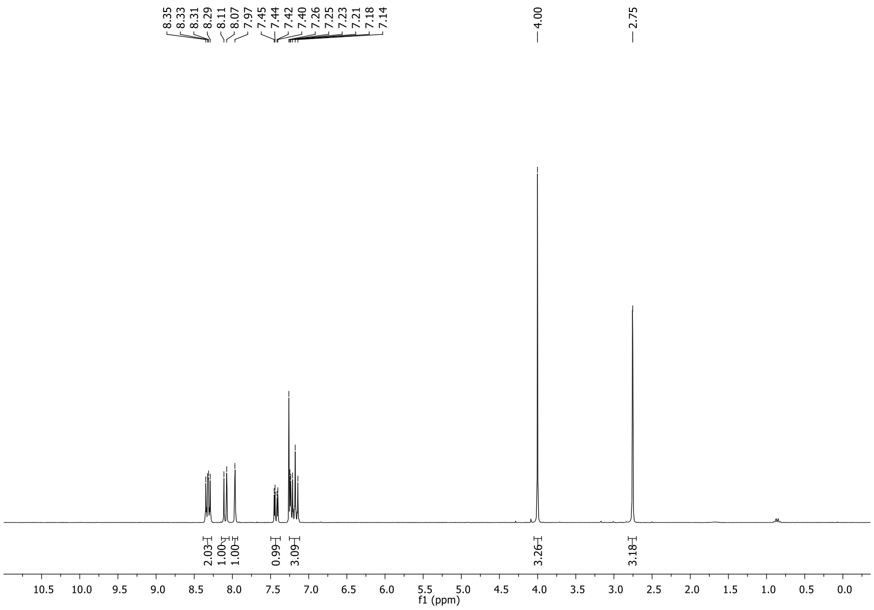
7i

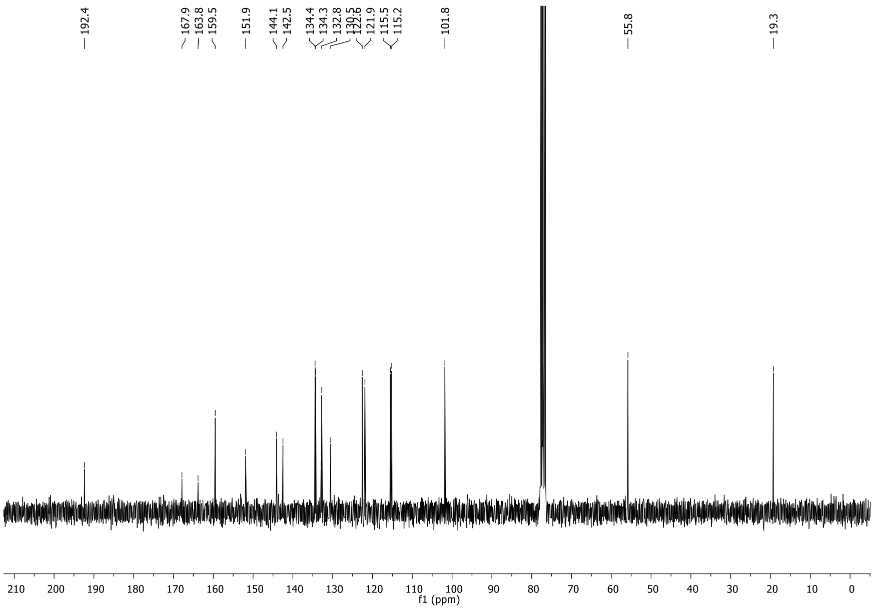

7.26
6.89
6.88
6.77
6.76
6.73
6.72
6.61
6.58
4.32
4.31
4.29
4.28
4.26
4.25
4.23
4.23
4.05
4.03
4.00
3.98
3.76
2.58
2.57
2.24
2.20
2.19
1.97
1.94
1.92
1.89
1.35
1.32
1.29
1.20
1.17
1.14
1.00
1.03
0.97
2.29
1.00
2.91
0.98
0.98
2.16
3.15
2.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

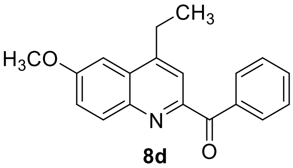

172.4
152.5
135.5
122.9
119.7
116.9
116.4
113.2
62.4
56.3
50.2
40.5
33.2
32.6
14.6
9.6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3CO
N
O
F

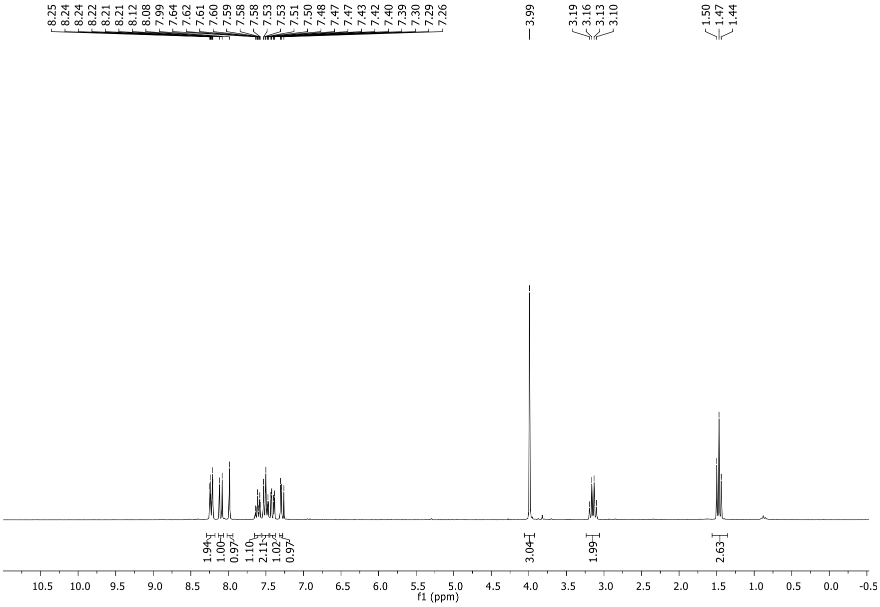
8b

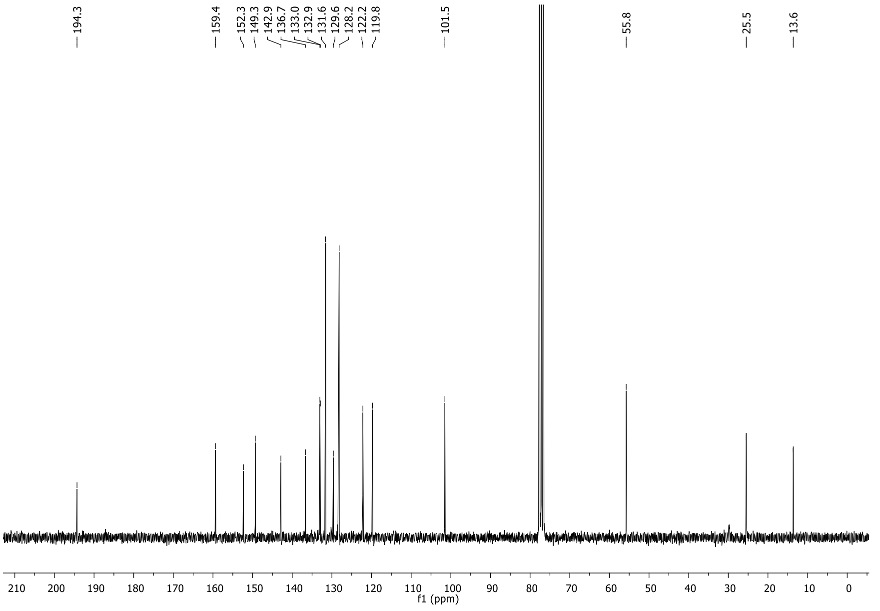

8.35
8.33
8.31
8.29
8.11
8.07
7.97
7.45
7.44
7.42
7.40
7.26
7.25
7.23
7.21
7.18
7.14
4.00
2.75
2.03
1.00
1.00
0.99
3.09
3.26
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

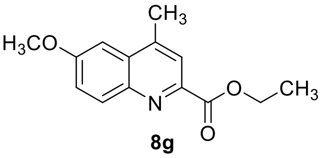

192.4
167.9
163.8
159.5
151.9
144.1
142.5
134.4
134.3
132.8
130.5
122.6
121.9
115.5
115.2
101.8
55.8
19.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3CO
N
O

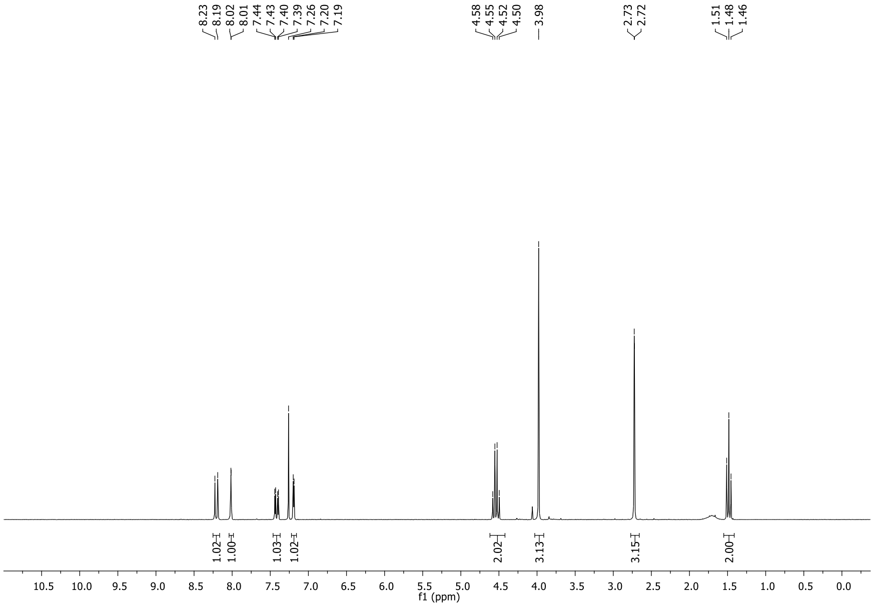
8d

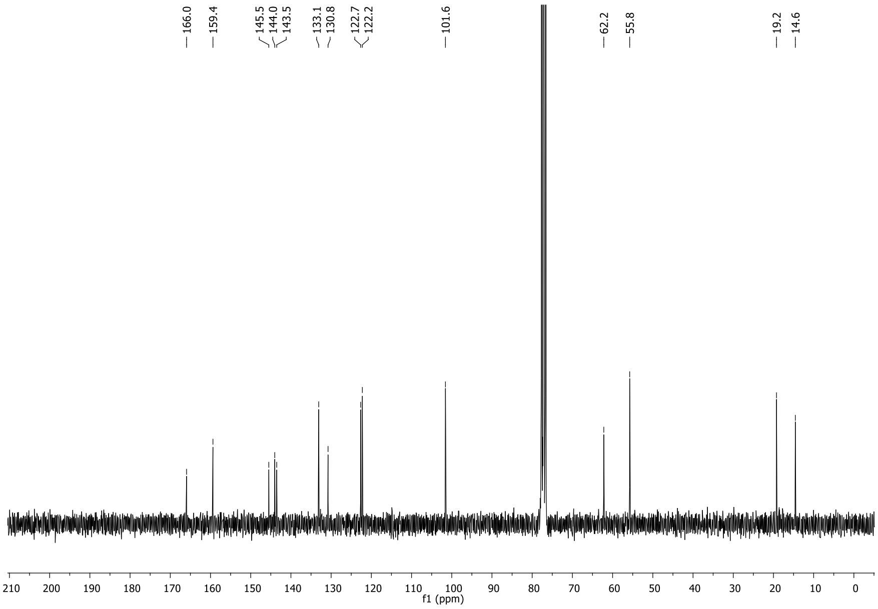

8.25
8.24
8.24
8.22
8.21
8.21
8.12
8.08
7.99
7.64
7.62
7.61
7.60
7.59
7.58
7.58
7.53
7.53
7.51
7.50
7.48
7.47
7.47
7.43
7.42
7.40
7.39
7.30
7.29
7.26
3.99
3.19
3.16
3.13
3.10
1.50
1.47
1.44
1.94
1.00
0.97
1.10
2.11
1.02
0.97
3.04
1.99
2.63
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

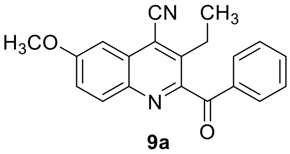

194.3
159.4
152.3
149.3
142.9
136.7
133.0
132.9
131.6
129.6
128.2
122.2
119.8
101.5
55.8
25.5
13.6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



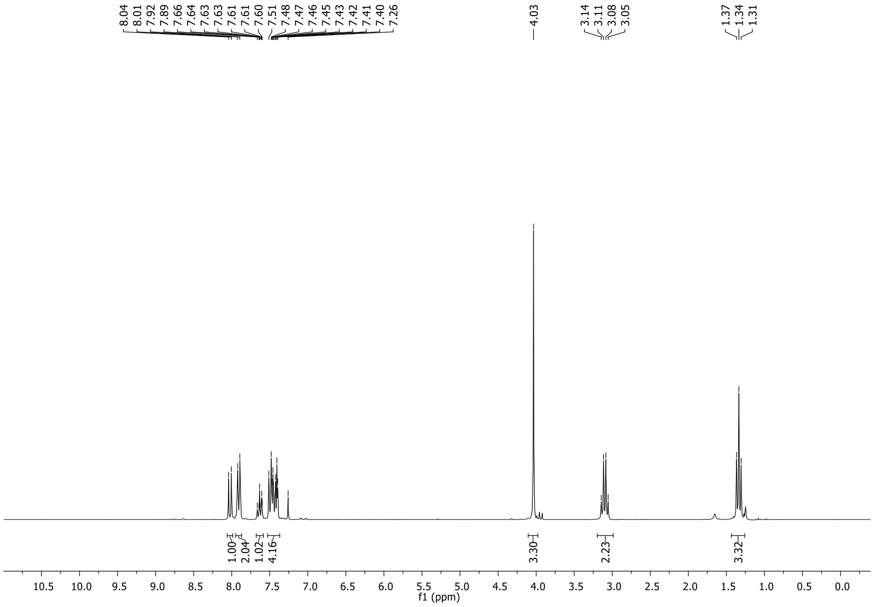
8g

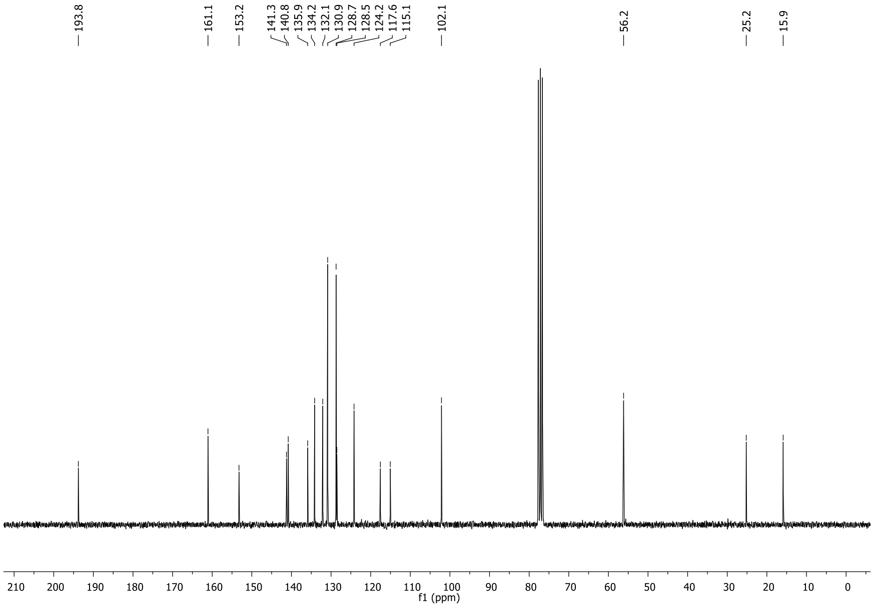

8.23
8.19
8.02
8.01
7.44
7.43
7.40
7.39
7.26
7.20
7.19
4.58
4.55
4.52
4.50
3.98
2.73
2.72
1.51
1.48
1.46
1.02
1.00
1.03
1.02
2.02
3.13
3.15
2.00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

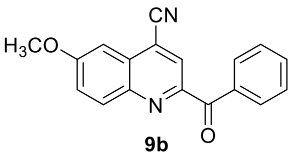

166.0
159.4
145.5
144.0
143.5
133.1
130.8
122.7
122.2
101.6
62.2
55.8
19.2
14.6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CN
CH3
H3CO
N
O

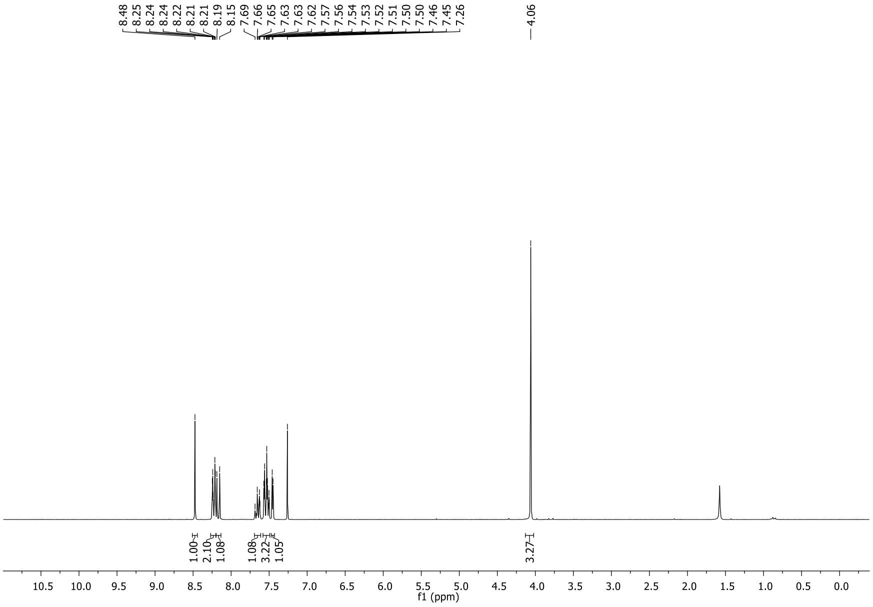
9a

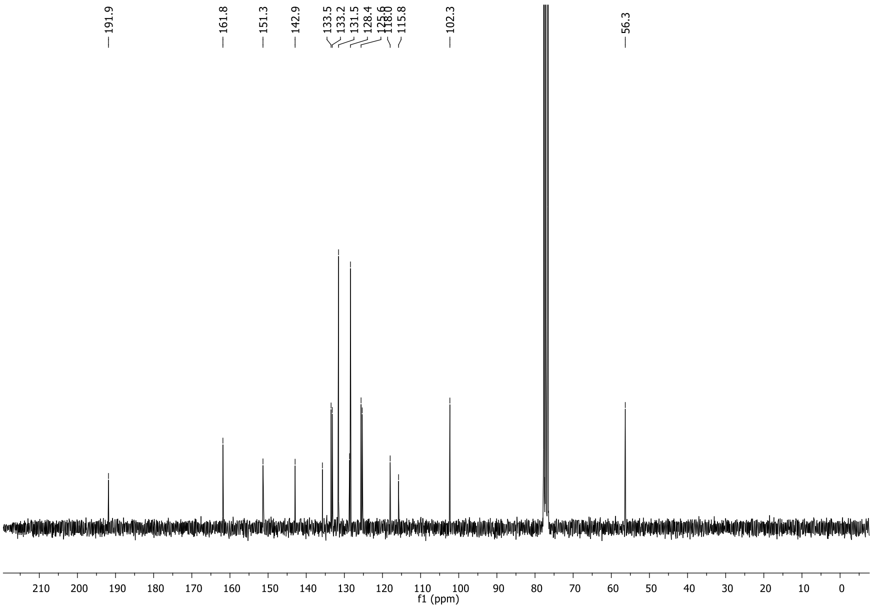

8.04
8.01
7.92
7.89
7.66
7.64
7.63
7.63
7.61
7.61
7.60
7.51
7.48
7.47
7.46
7.45
7.43
7.42
7.41
7.40
7.26
4.03
3.14
3.11
3.08
3.05
1.37
1.34
1.31
1.00
2.04
1.02
4.16
3.30
2.23
3.32
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

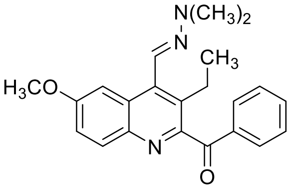

193.8
161.1
153.2
141.3
140.8
135.9
134.2
132.1
130.9
128.7
128.5
124.2
117.6
115.1
102.1
56.2
25.2
15.9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CN
H3CO
N
O

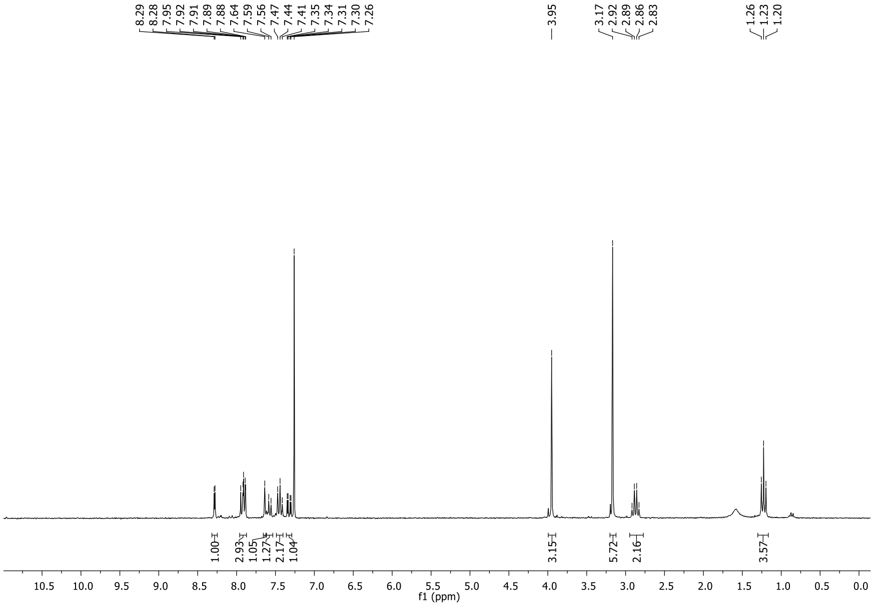
9b

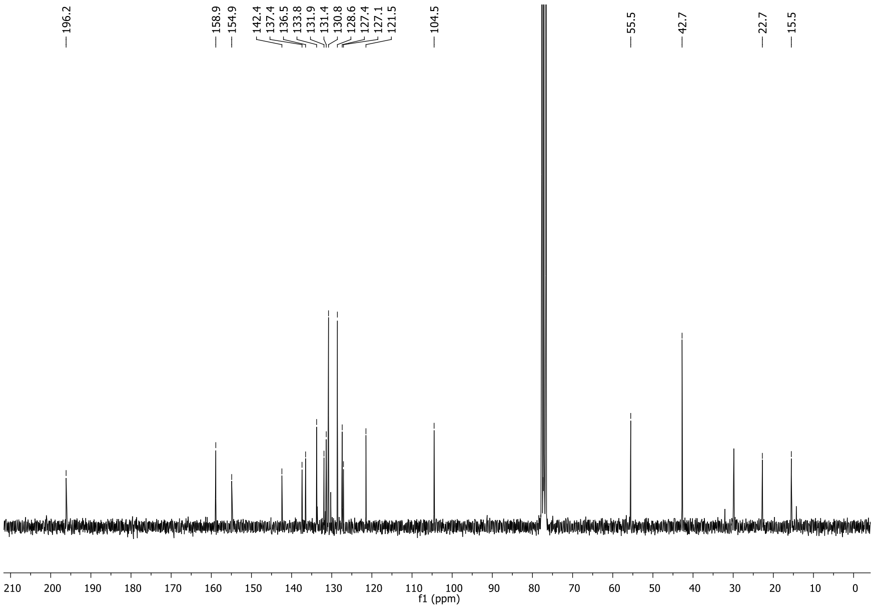

8.48
8.25
8.24
8.24
8.22
8.21
8.21
8.19
8.15
7.69
7.66
7.65
7.63
7.63
7.62
7.57
7.56
7.54
7.53
7.52
7.51
7.50
7.46
7.45
7.26
4.06
1.00
2.10
1.08
1.08
3.22
1.05
3.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

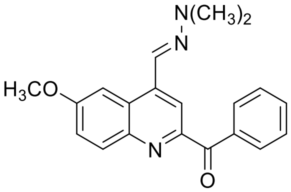

191.9
161.8
151.3
142.9
133.5
133.2
131.5
128.4
125.6
118.0
115.8
102.3
56.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH3)2
N
CH3
H3CO
N
O

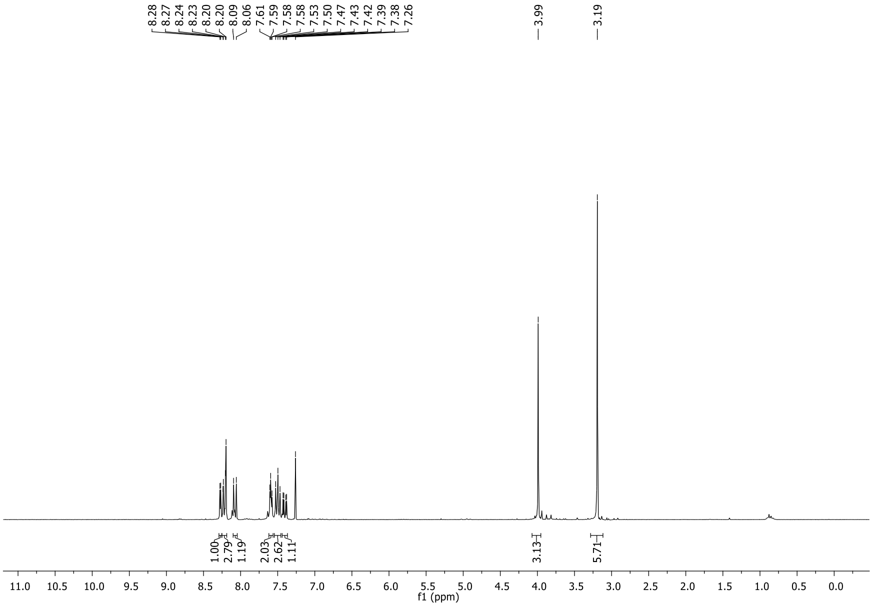
9c

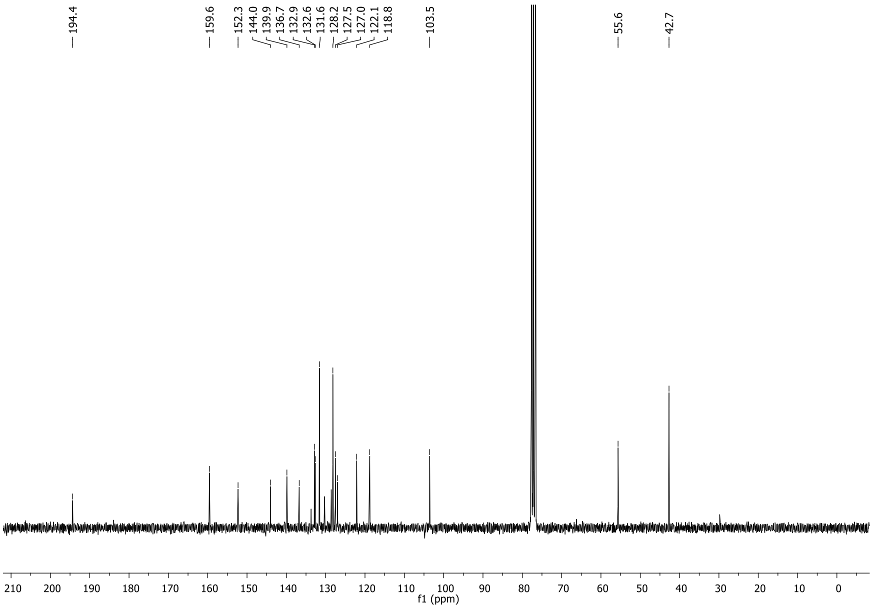

8.29
8.28
7.95
7.92
7.91
7.89
7.88
7.64
7.59
7.56
7.47
7.44
7.41
7.35
7.34
7.31
7.30
7.26
3.95
3.17
2.92
2.89
2.86
2.83
1.26
1.23
1.20
1.00
2.93
1.05
1.27
2.17
1.04
3.15
5.72
2.16
3.57
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

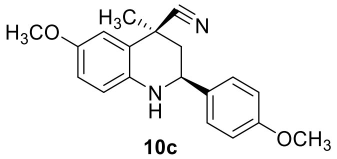

196.2
158.9
154.9
142.4
137.4
136.5
133.8
131.9
131.4
130.8
128.6
127.4
127.1
121.5
104.5
55.5
42.7
22.7
15.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


N(CH3)2
N
H3CO
N
O

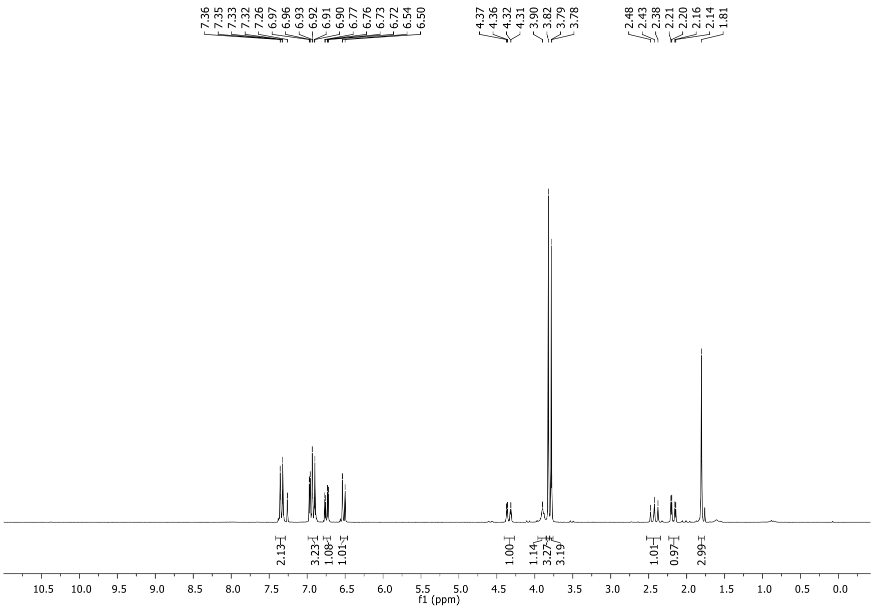
9d

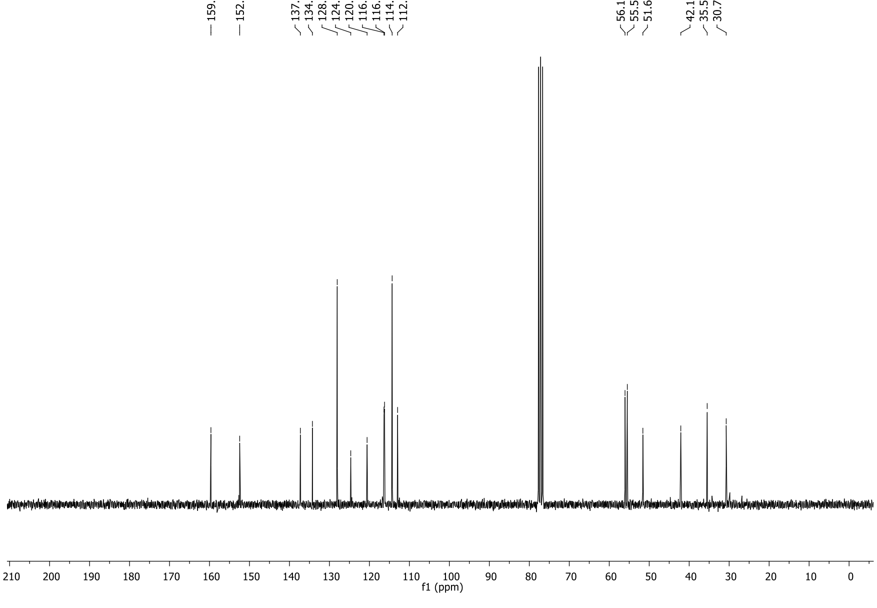

8.28
8.27
8.24
8.23
8.20
8.20
8.09
8.06
7.61
7.59
7.58
7.58
7.53
7.50
7.47
7.43
7.42
7.39
7.38
7.26
3.99
3.19
1.00
2.79
1.19
2.03
2.62
1.11
3.13
5.71
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

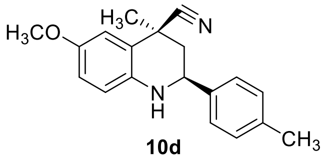

194.4
159.6
152.3
144.0
139.9
136.7
132.9
132.6
131.6
128.2
127.5
127.0
122.1
118.8
103.5
55.6
42.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
H3C
N
N
H
OCH3

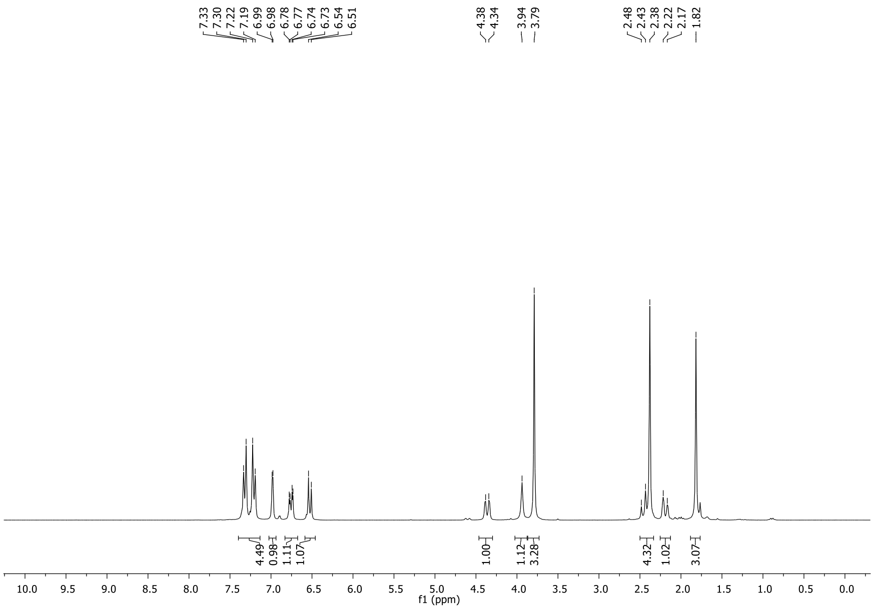
10c

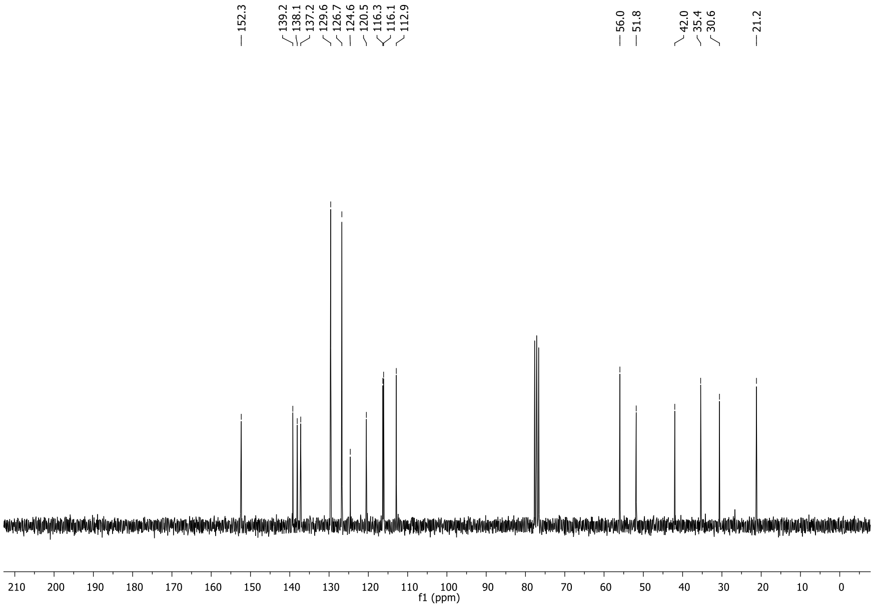

7.36
7.35
7.33
7.32
7.26
6.97
6.96
6.93
6.92
6.91
6.90
6.77
6.76
6.73
6.72
6.54
6.50
4.37
4.36
4.32
4.31
3.90
3.82
3.79
3.78
2.48
2.43
2.38
2.21
2.20
2.16
2.14
1.81
2.13
3.23
1.08
1.01
1.00
1.14
3.27
3.19
1.01
0.97
2.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

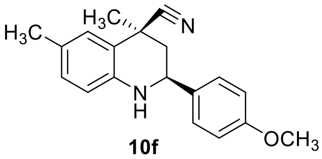

159.6
152.4
137.3
134.3
128.0
124.7
120.6
116.3
116.2
114.3
112.9
56.1
55.5
51.6
42.1
35.5
30.7
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
H3C
N
N
H
CH3

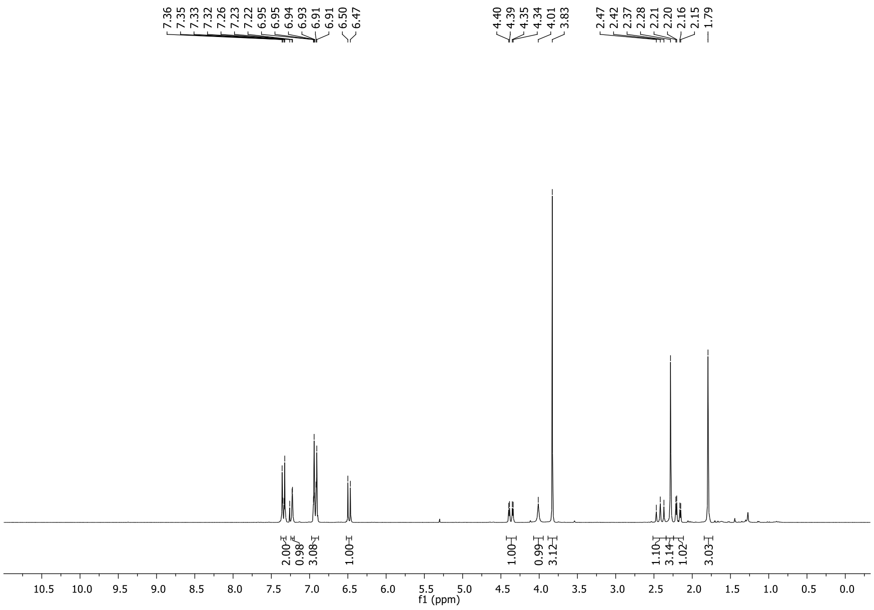
10d

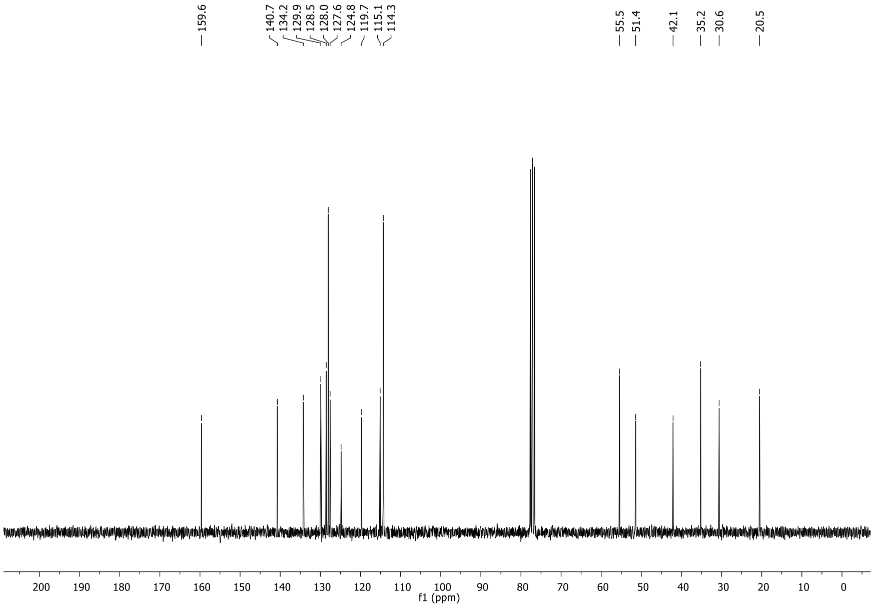

7.33
7.30
7.22
7.19
6.99
6.98
6.78
6.77
6.74
6.73
6.54
6.51
4.38
4.34
3.94
3.79
2.48
2.43
2.38
2.22
2.17
1.82
4.49
0.98
1.11
1.07
1.00
1.12
3.28
4.32
1.02
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

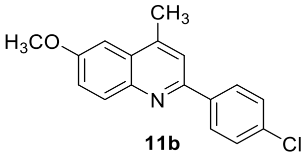

152.3
139.2
138.1
137.2
129.6
126.7
124.6
120.5
116.3
116.1
112.9
56.0
51.8
42.0
35.4
30.6
21.2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
H3C
N
N
H
OCH3

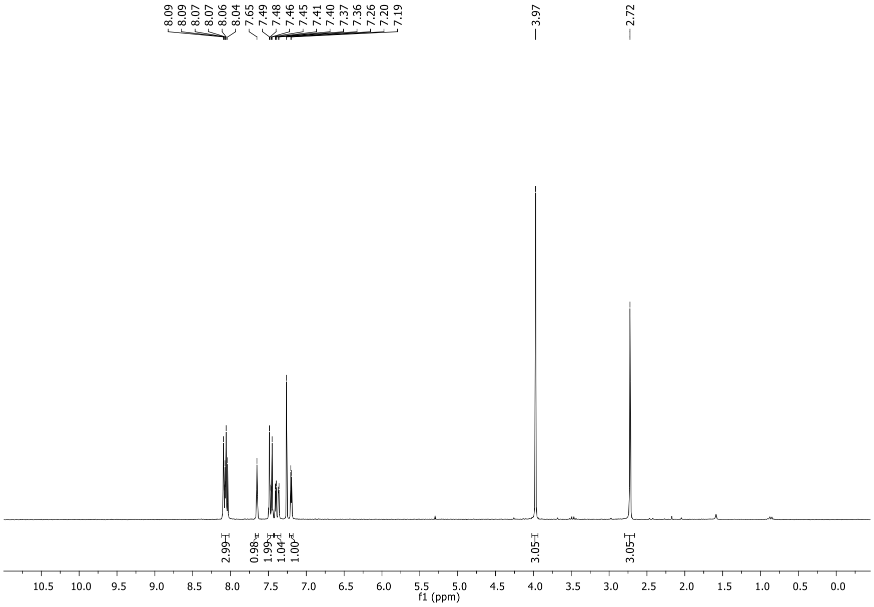
10f

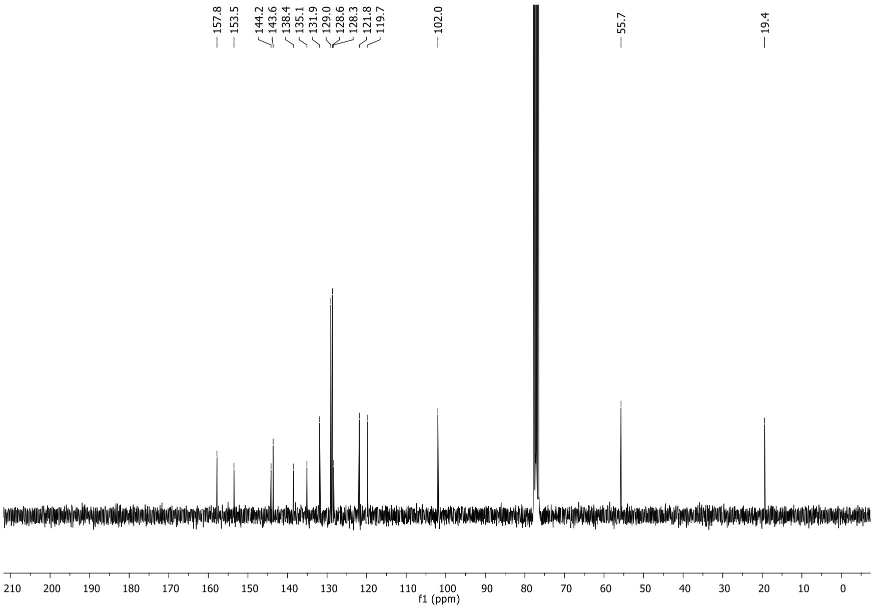

7.36
7.35
7.33
7.32
7.26
7.23
7.22
6.95
6.95
6.94
6.93
6.91
6.91
6.50
6.47
4.40
4.39
4.35
4.34
4.01
3.83
2.47
2.42
2.37
2.28
2.21
2.20
2.16
2.15
1.79
2.00
0.98
3.08
1.00
1.00
0.99
3.12
1.10
3.14
1.02
3.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

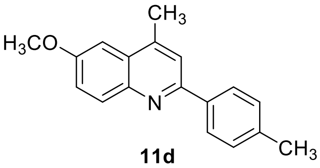

159.6
140.7
134.2
129.9
128.5
128.0
127.6
124.8
119.7
115.1
114.3
55.5
51.4
42.1
35.2
30.6
20.5
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH$_3$
H$_3$CO
N
Cl

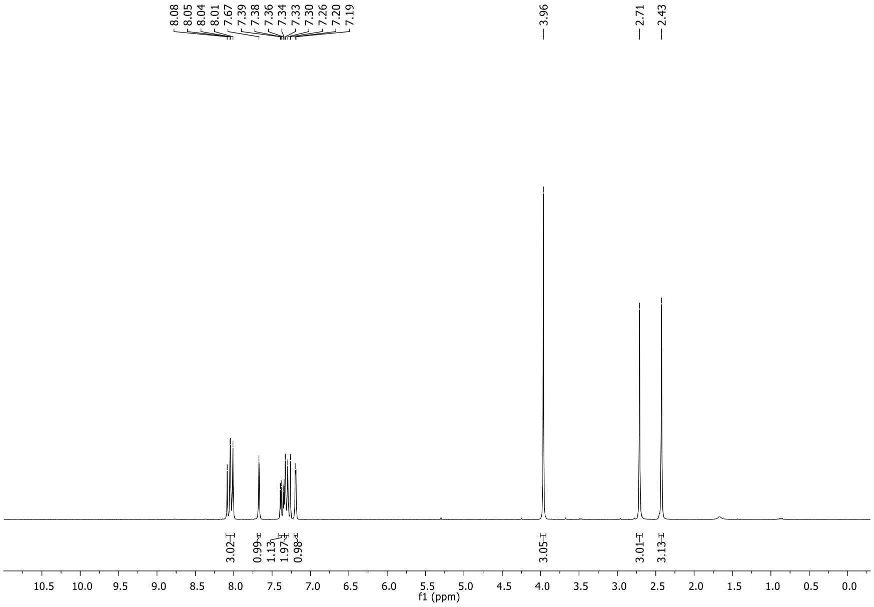
11b

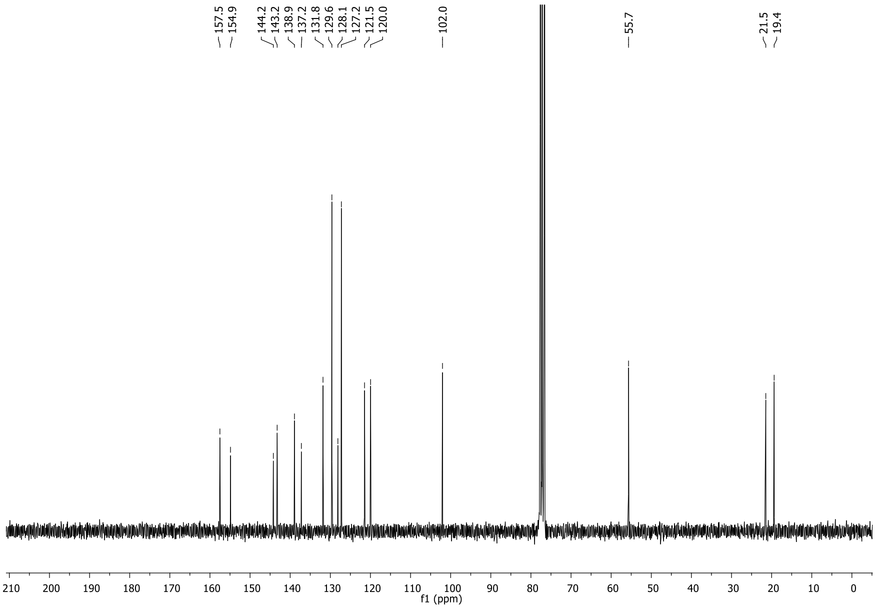

8.09
8.09
8.07
8.07
8.06
8.04
7.65
7.49
7.48
7.46
7.45
7.41
7.40
7.37
7.36
7.26
7.20
7.19
3.97
2.72
2.99
0.98
1.99
1.04
1.00
3.05
3.05
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

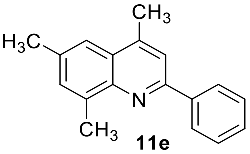

157.8
153.5
144.2
143.6
138.4
135.1
131.9
129.0
128.6
128.3
121.8
119.7
102.0
55.7
19.4
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3
H3CO
N
CH3

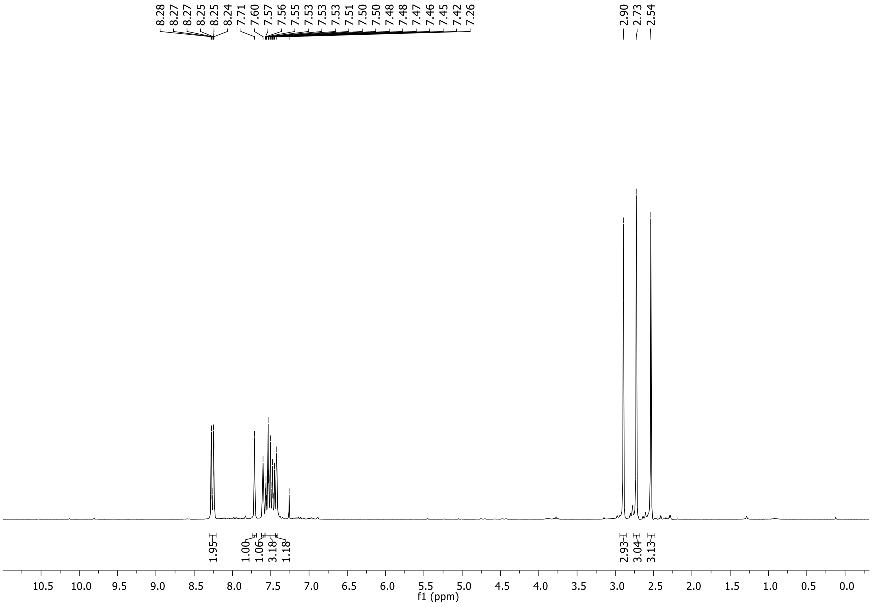
11d

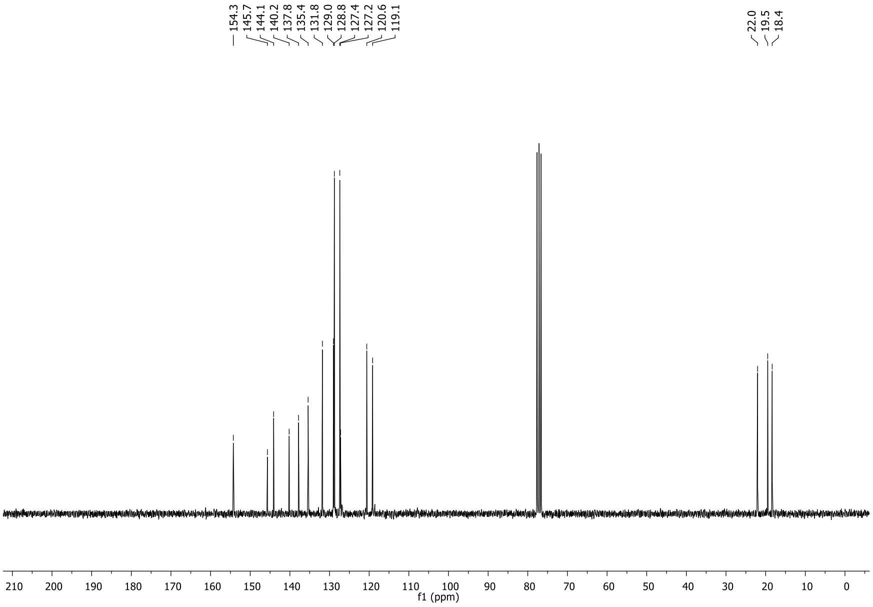

8.08
8.05
8.04
8.01
7.67
7.39
7.38
7.36
7.34
7.33
7.30
7.26
7.20
7.19
3.96
2.71
2.43
3.02
0.99
1.13
1.97
0.98
3.05
3.01
3.13
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

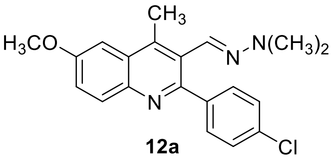

157.5
154.9
144.2
143.2
138.9
137.2
131.8
129.6
128.1
127.2
121.5
120.0
102.0
55.7
21.5
19.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3C
N
CH3

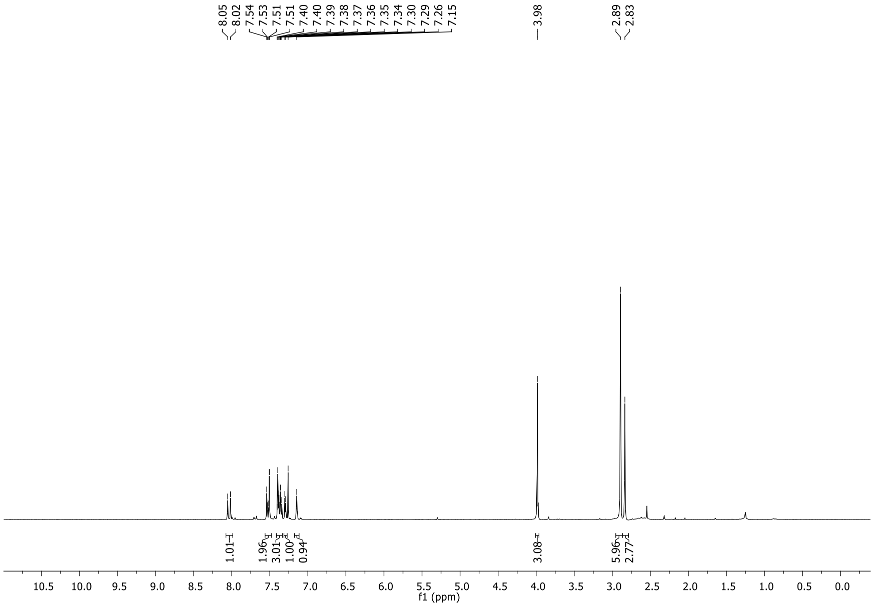
11e

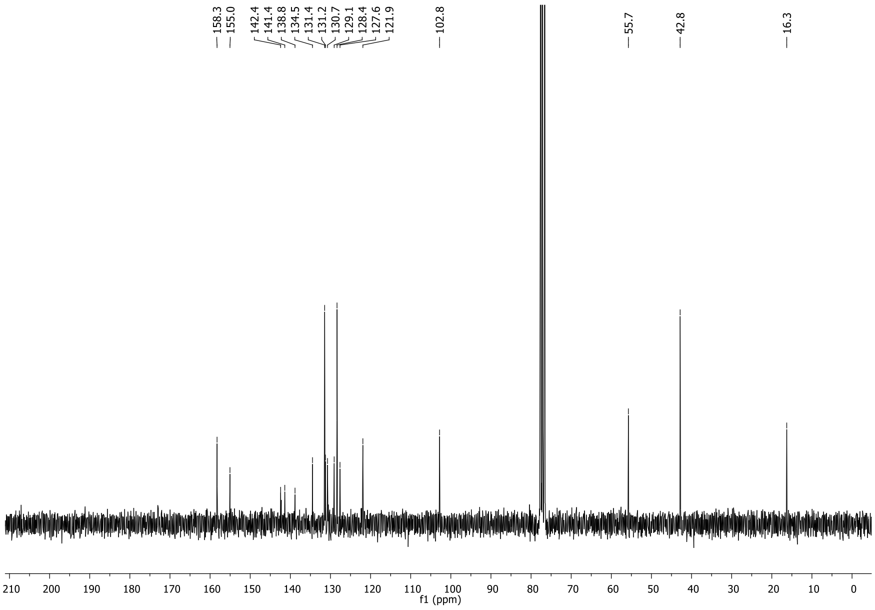

8.28
8.27
8.27
8.25
8.25
8.24
7.71
7.60
7.57
7.56
7.55
7.53
7.53
7.53
7.51
7.50
7.50
7.48
7.48
7.47
7.46
7.45
7.42
7.26
2.90
2.73
2.54
1.95
1.00
1.06
3.18
1.18
2.93
3.04
3.13
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

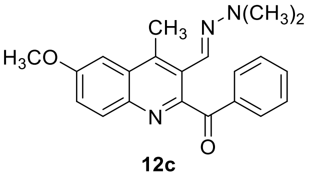

154.3
145.7
144.1
140.2
137.8
135.4
131.8
129.0
128.8
127.4
127.2
120.6
119.1
22.0
19.5
18.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3CO
N(CH3)2
N
N
Cl

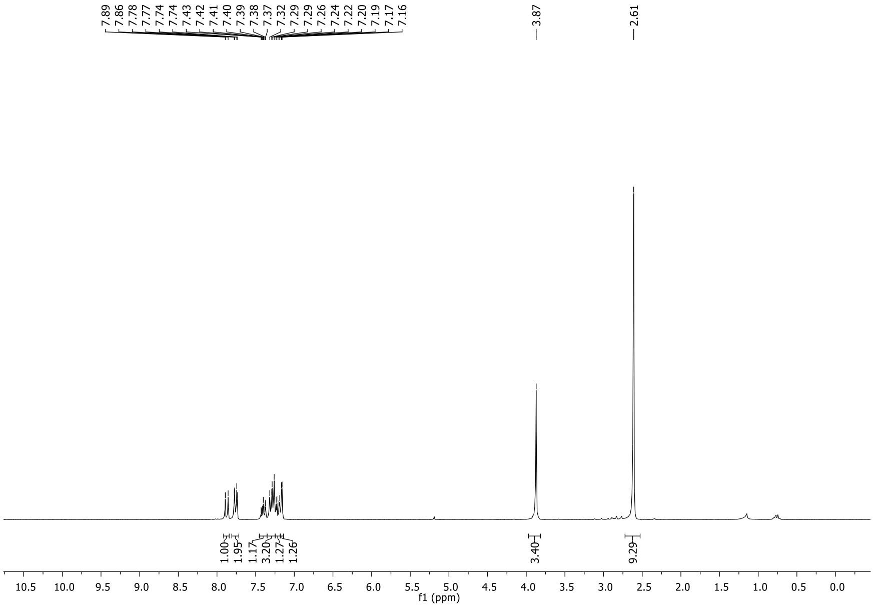
12a

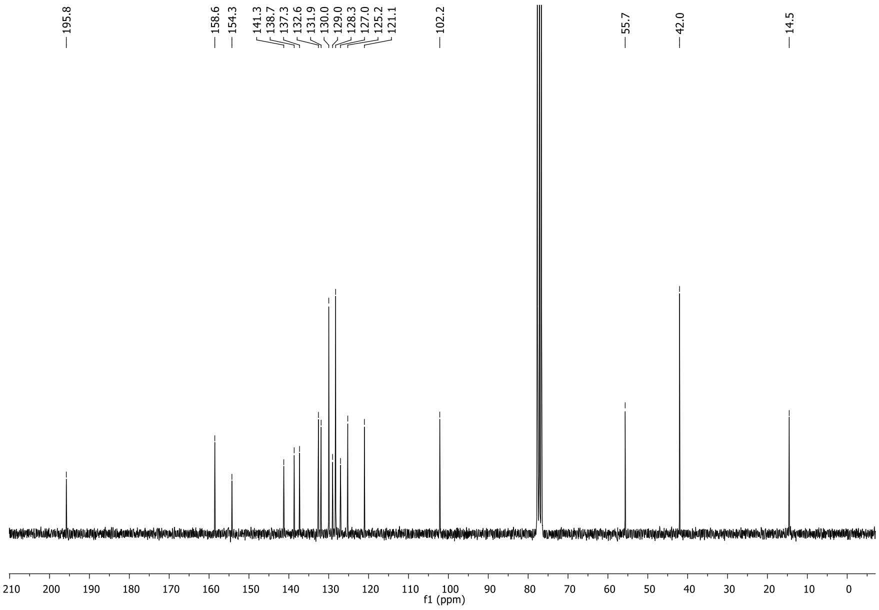

8.05
8.02
7.54
7.53
7.51
7.51
7.40
7.40
7.39
7.38
7.37
7.36
7.35
7.34
7.30
7.29
7.26
7.15
3.98
2.89
2.83
1.01
1.96
3.01
1.00
0.94
3.08
5.96
2.77
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

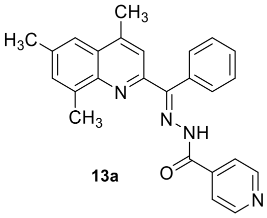

158.3
155.0
142.4
141.4
138.8
134.5
131.4
131.2
130.7
129.1
128.4
127.6
121.9
102.8
55.7
42.8
16.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
N(CH3)2
N
H3CO
N
O

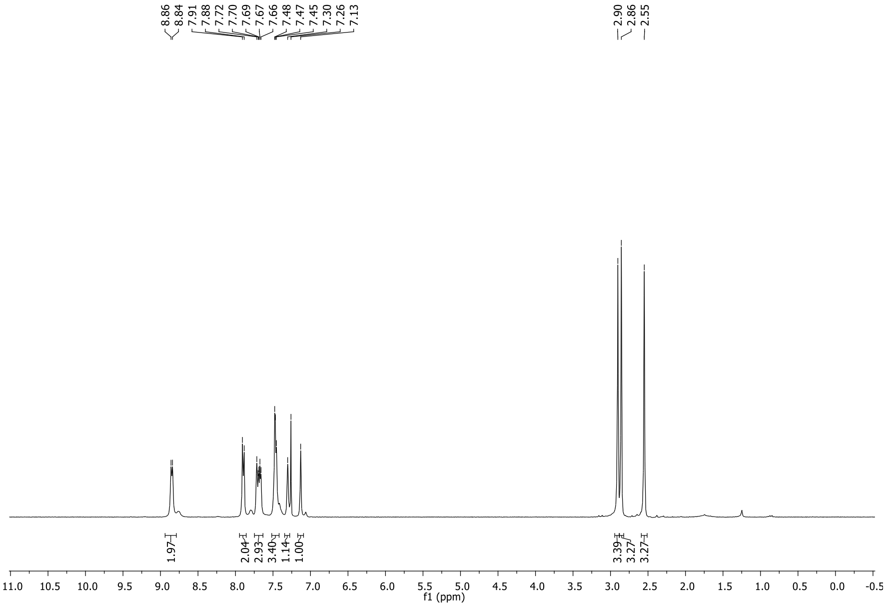
12c

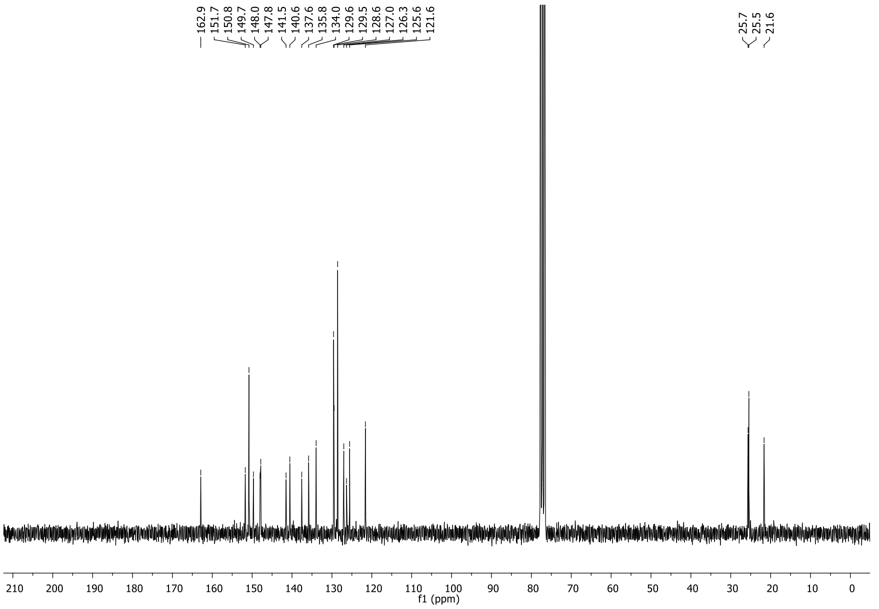

7.89
7.86
7.78
7.77
7.74
7.74
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.32
7.29
7.29
7.26
7.24
7.22
7.20
7.19
7.17
7.16
3.87
2.61
1.00
1.95
1.17
3.20
1.27
1.26
3.40
9.29
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

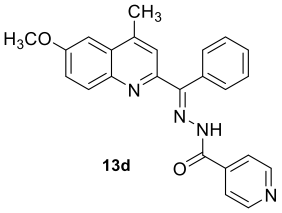

195.8
158.6
154.3
141.3
138.7
137.3
132.6
131.9
130.0
129.0
128.3
127.0
125.2
121.1
102.2
55.7
42.0
14.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3C
CH3
N
N
NH
O
N

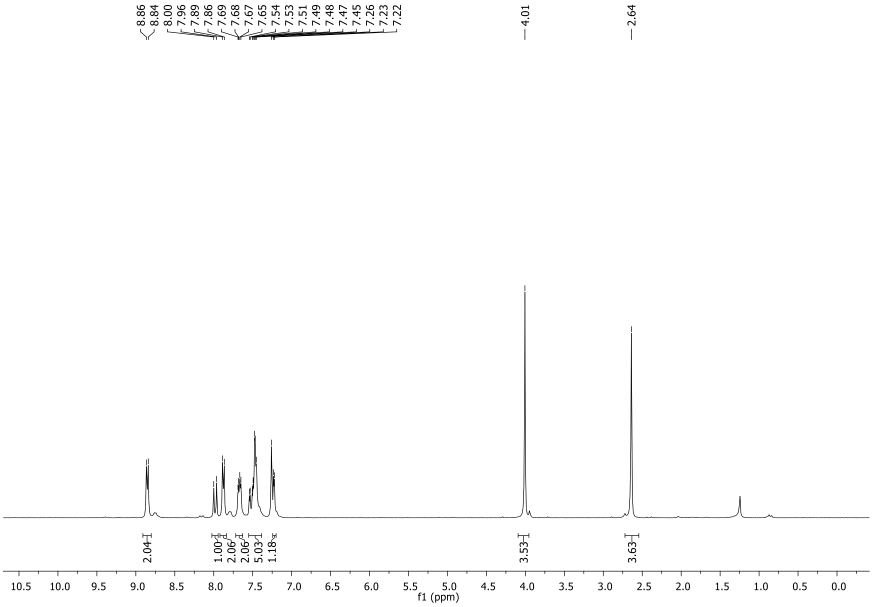
13a

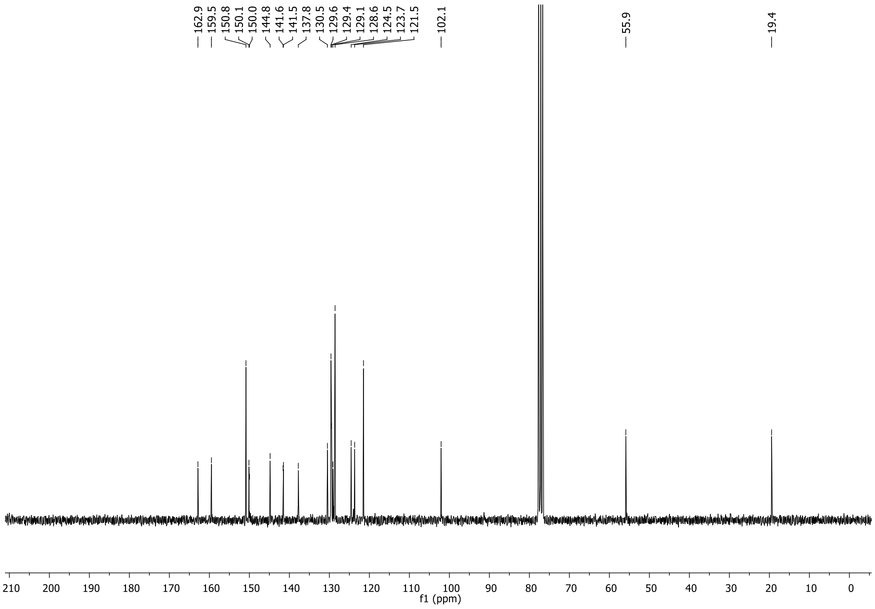

8.86
8.84
7.91
7.88
7.72
7.70
7.69
7.67
7.66
7.48
7.47
7.45
7.30
7.26
7.13
2.90
2.86
2.55
1.97
2.04
2.93
3.40
1.14
1.00
3.39
3.27
3.27
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

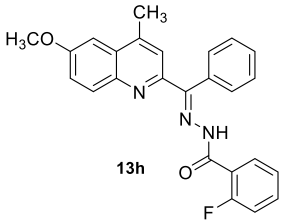

162.9
151.7
150.8
149.7
148.0
147.8
141.5
140.6
137.6
135.8
134.0
129.6
129.5
128.6
127.0
126.3
125.6
121.6
25.7
25.5
21.6
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3CO
N
N
NH
O
N

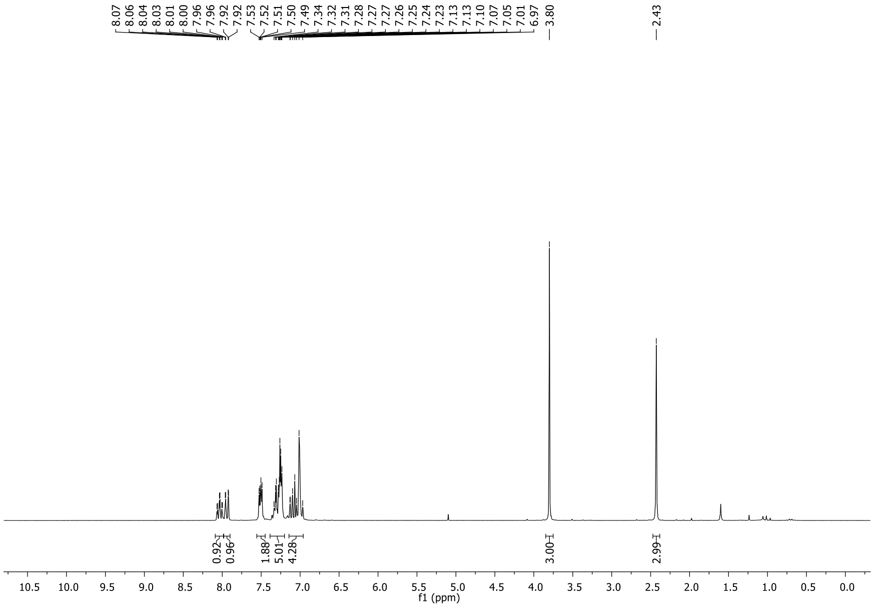
13d

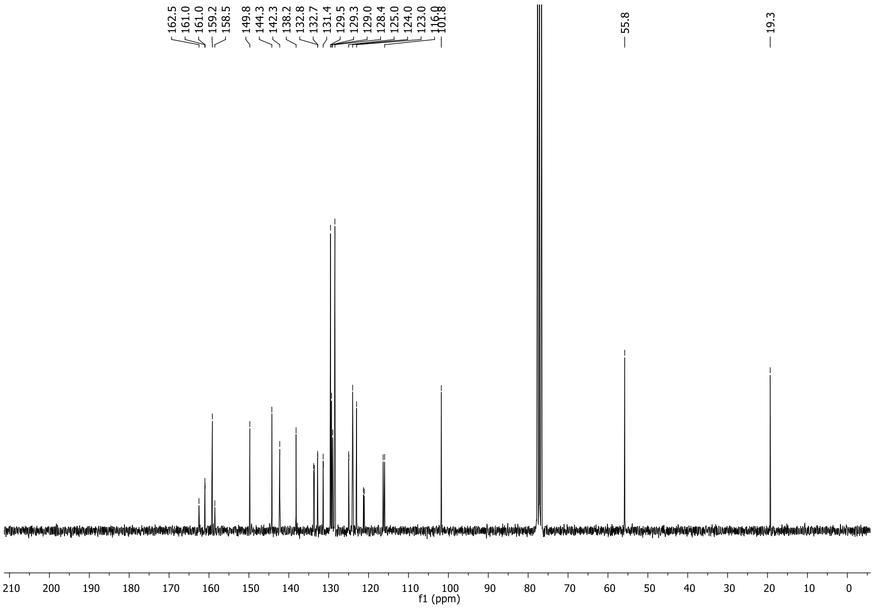

8.86
8.84
8.00
7.96
7.89
7.86
7.69
7.68
7.67
7.65
7.54
7.53
7.51
7.49
7.48
7.47
7.45
7.26
7.23
7.22
4.01
2.64
2.04
1.00
2.06
2.06
5.03
1.18
3.53
3.63
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

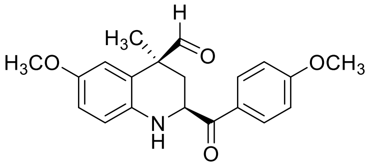

162.9
159.5
150.8
150.1
150.0
144.8
141.6
141.5
137.8
130.5
129.6
129.4
129.1
128.6
124.5
123.7
121.5
102.1
55.9
19.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CH3
H3CO
N
N
NH
O
F

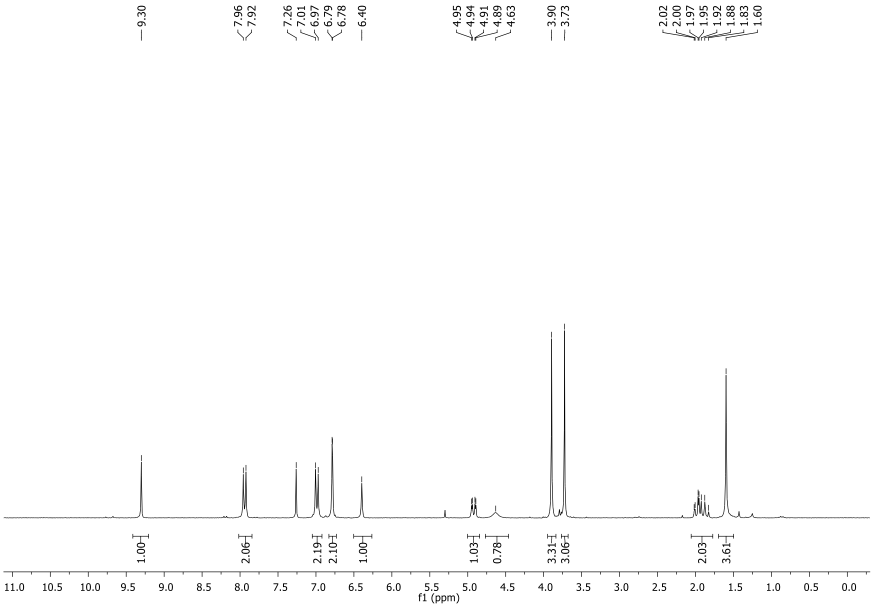
13h

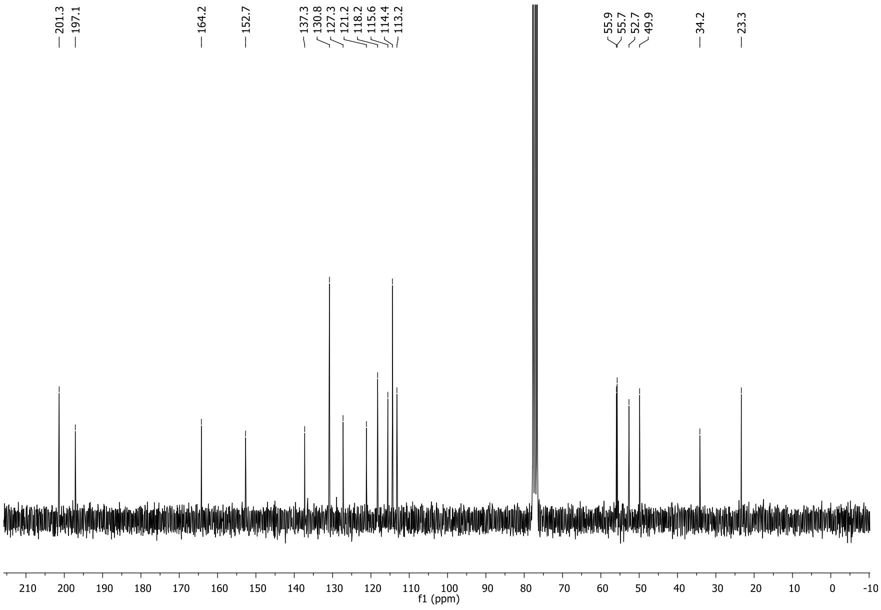

8.07
8.06
8.04
8.03
8.01
8.00
7.96
7.96
7.92
7.92
7.53
7.52
7.51
7.50
7.49
7.34
7.32
7.31
7.28
7.27
7.27
7.26
7.25
7.24
7.23
7.13
7.13
7.10
7.07
7.05
7.01
6.97
3.80
2.43
0.92
0.96
1.88
5.01
4.28
3.00
2.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

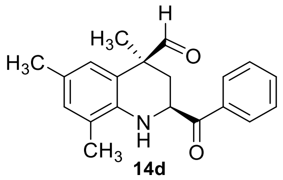

162.5
161.0
161.0
159.2
158.5
149.8
144.3
142.3
138.2
132.8
132.7
131.4
129.5
129.3
129.0
128.4
125.0
124.0
123.0
116.0
101.8
55.8
19.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H$_3$C
O
H$_3$CO
OCH$_3$
N
H
O

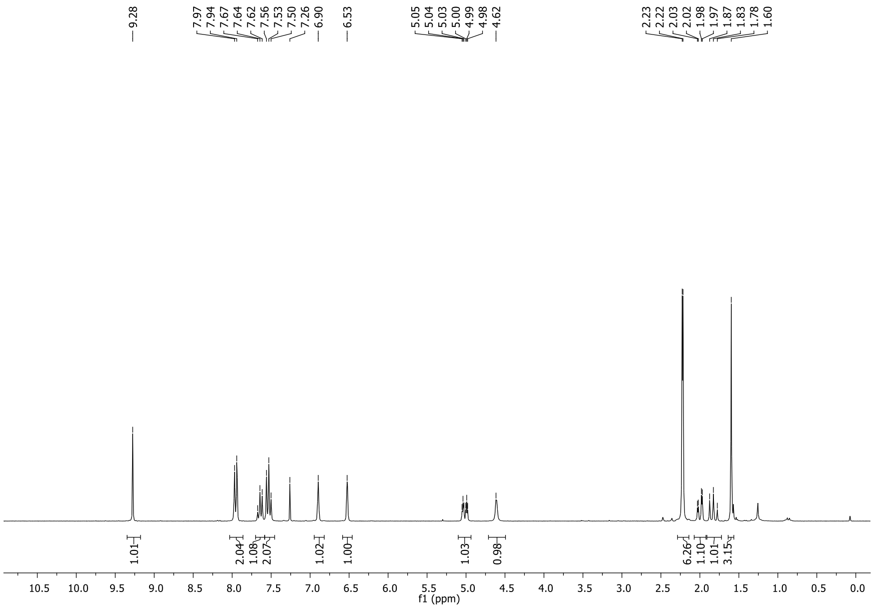
14b

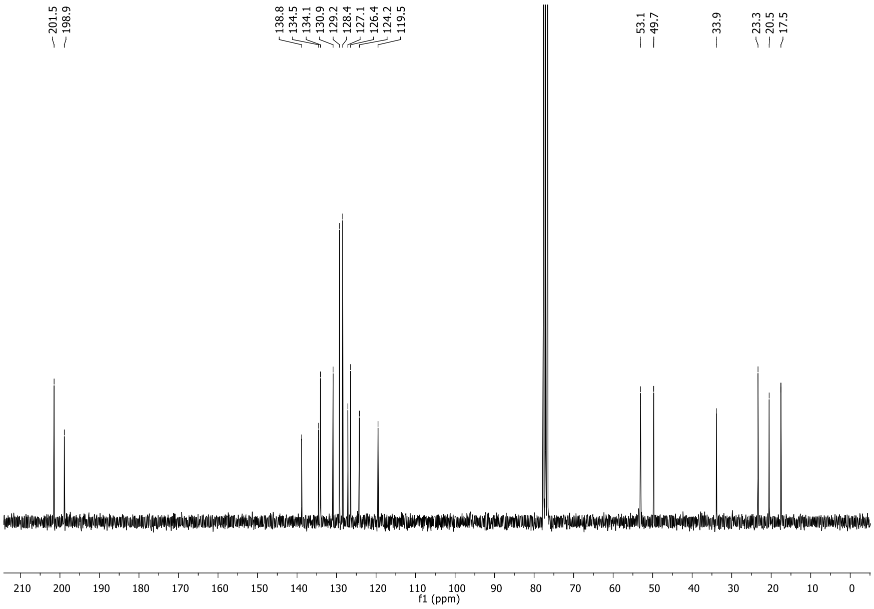

9.30
7.96
7.92
7.26
7.01
6.97
6.79
6.78
6.40
4.95
4.94
4.91
4.89
4.63
3.90
3.73
2.02
2.00
1.97
1.95
1.92
1.88
1.83
1.60
1.00
2.06
2.19
2.10
1.00
1.03
0.78
3.31
3.06
2.03
3.61
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

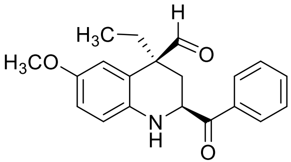

201.3
197.1
164.2
152.7
137.3
130.8
127.3
121.2
118.2
115.6
114.4
113.2
55.9
55.7
52.7
49.9
34.2
23.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
H3C
O
H3C
N
H
CH3
O

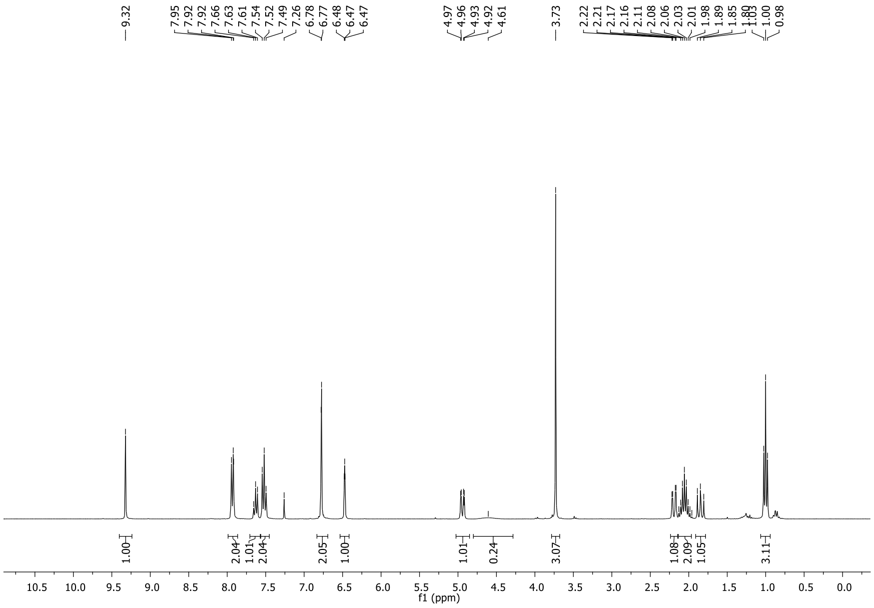
14d

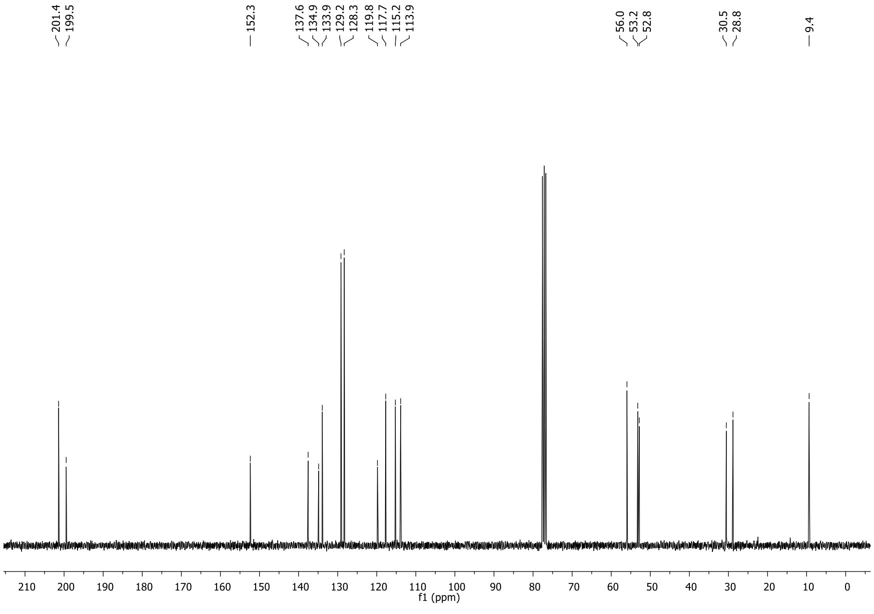

9.28
7.97
7.94
7.67
7.64
7.62
7.56
7.53
7.50
7.26
6.90
6.53
5.05
5.04
5.03
5.00
4.99
4.98
4.62
2.23
2.22
2.03
2.02
1.98
1.97
1.87
1.83
1.78
1.60
1.01
2.04
1.08
2.07
1.02
1.00
1.03
0.98
6.26
1.10
1.01
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

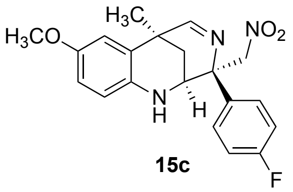

201.5
198.9
138.8
134.5
134.1
130.9
129.2
128.4
127.1
126.4
124.2
119.5
53.1
49.7
33.9
23.3
20.5
17.5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H
H3C
H3CO
O
N
H
O

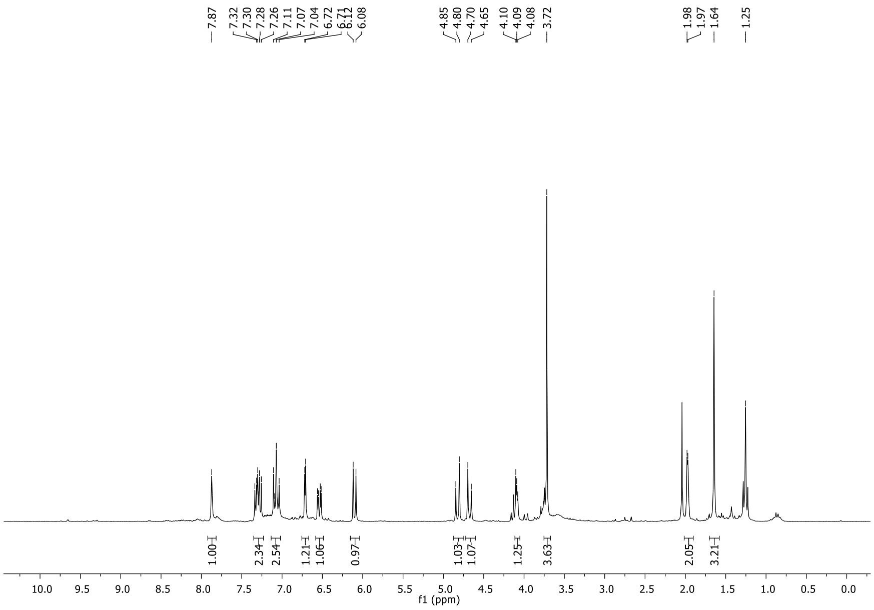
14g

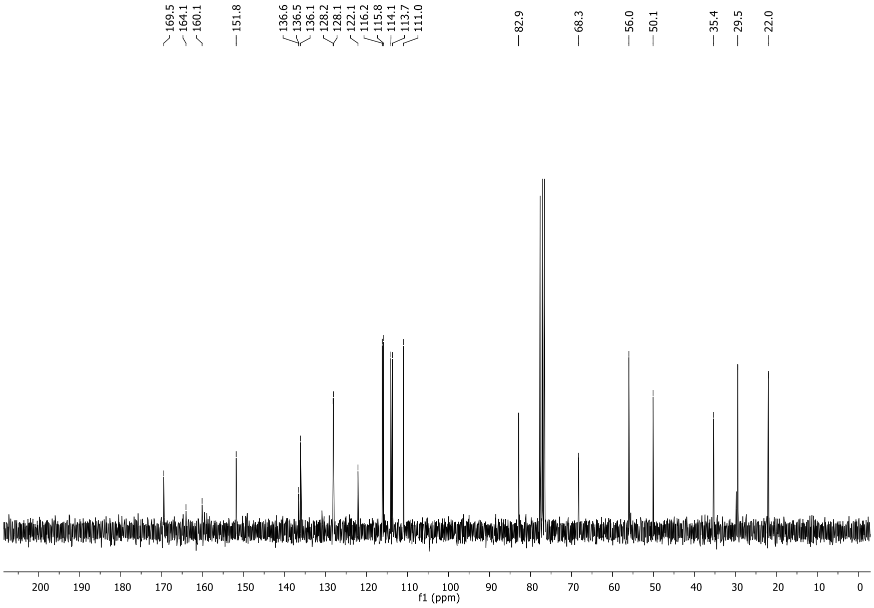

9.32
7.95
7.92
7.92
7.66
7.63
7.61
7.54
7.52
7.49
7.26
6.78
6.77
6.48
6.47
6.47
4.97
4.96
4.93
4.92
4.61
3.73
2.22
2.21
2.17
2.16
2.11
2.08
2.06
2.03
2.01
1.98
1.89
1.85
1.80
1.03
1.00
0.98
1.00
2.04
1.01
2.04
2.05
1.00
1.01
0.24
3.07
1.08
2.09
1.05
3.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

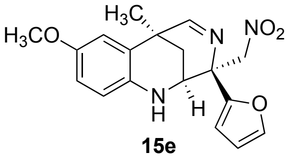

201.4
199.5
152.3
137.6
134.9
133.9
129.2
128.3
119.8
117.7
115.2
113.9
56.0
53.2
52.8
30.5
28.8
9.4
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H$_3$CO
H$_3$C
N
NO$_2$
N
H
H
F

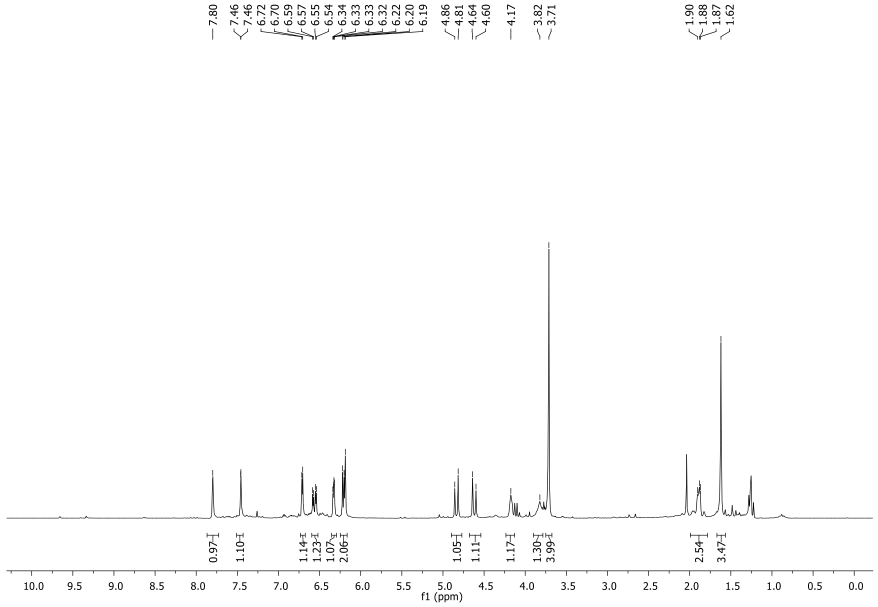
15c

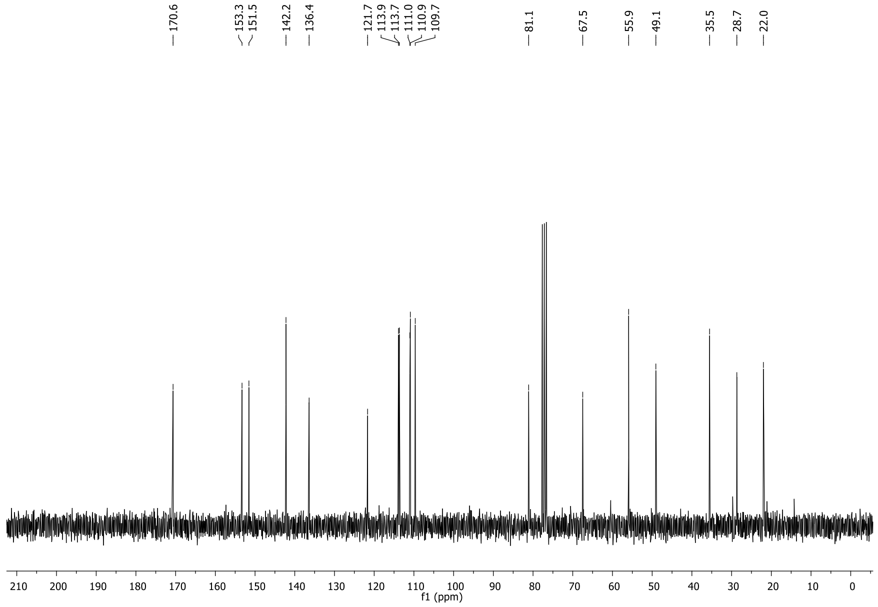

7.87
7.32
7.30
7.28
7.26
7.11
7.07
7.04
6.72
6.71
6.12
6.08
4.85
4.80
4.70
4.65
4.10
4.09
4.08
3.72
1.98
1.97
1.64
1.25
1.00
2.34
2.54
1.21
1.06
0.97
1.03
1.07
1.25
3.63
2.05
3.21
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

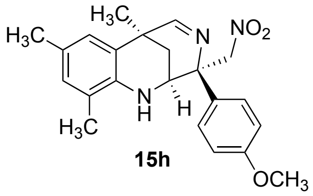

169.5
164.1
160.1
151.8
136.6
136.5
136.1
128.2
128.1
122.1
116.2
115.8
114.1
113.7
111.0
82.9
68.3
56.0
50.1
35.4
29.5
22.0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
H3C
N
NO2
N
H
H
O

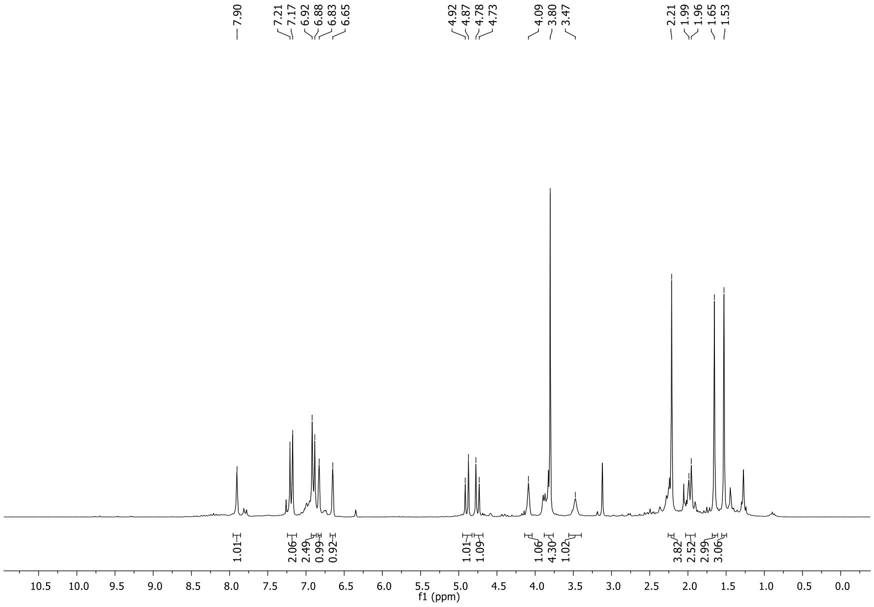
15e

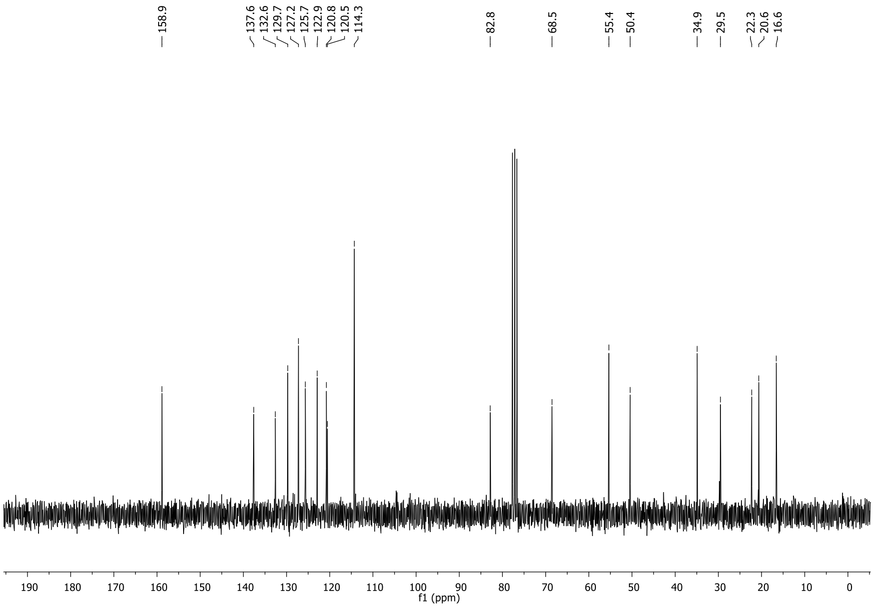

7.80
7.46
7.46
6.72
6.70
6.59
6.57
6.55
6.54
6.34
6.33
6.33
6.32
6.22
6.20
6.19
4.86
4.81
4.64
4.60
4.17
3.82
3.71
1.90
1.88
1.87
1.62
0.97
1.10
1.14
1.23
1.07
2.06
1.05
1.11
1.17
1.30
3.99
2.54
3.47
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

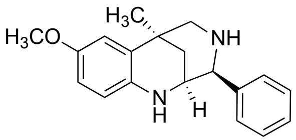

170.6
153.3
151.5
142.2
136.4
121.7
113.9
113.7
111.0
110.9
109.7
81.1
67.5
55.9
49.1
35.5
28.7
22.0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H$_3$C
H$_3$C
NO$_2$
N
N
H
H
H$_3$C
OCH$_3$

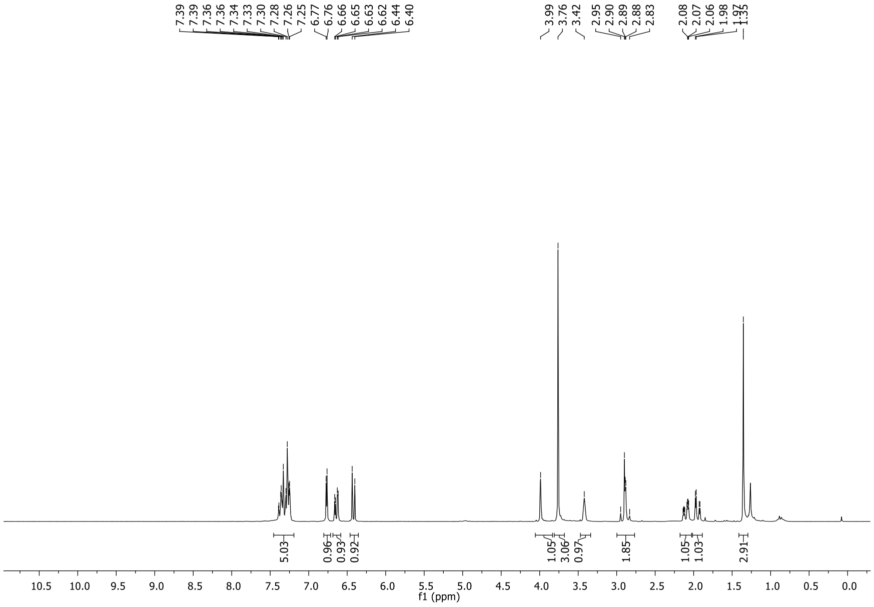
15h

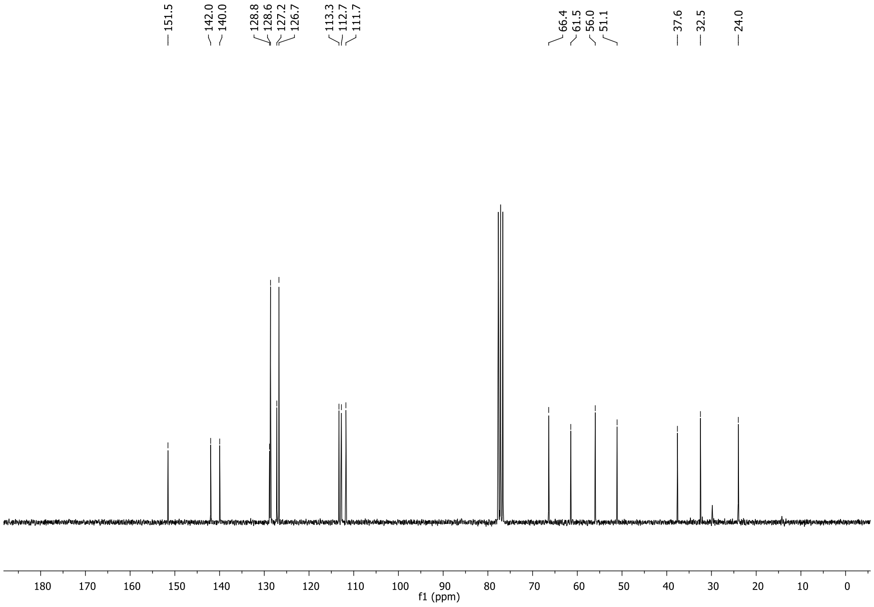

7.90
7.21
7.17
6.92
6.88
6.83
6.65
4.92
4.87
4.78
4.73
4.09
3.80
3.47
2.21
1.99
1.96
1.65
1.53
1.01
2.06
2.49
0.99
0.92
1.01
1.09
1.06
4.30
1.02
3.82
2.52
2.99
3.06
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

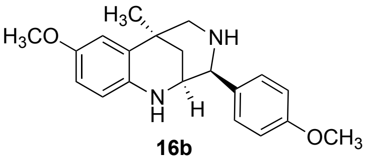

158.9
137.6
132.6
129.7
127.2
125.7
122.9
120.8
120.5
114.3
82.8
68.5
55.4
50.4
34.9
29.5
22.3
20.6
16.6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
H3CO
NH
N
H
H

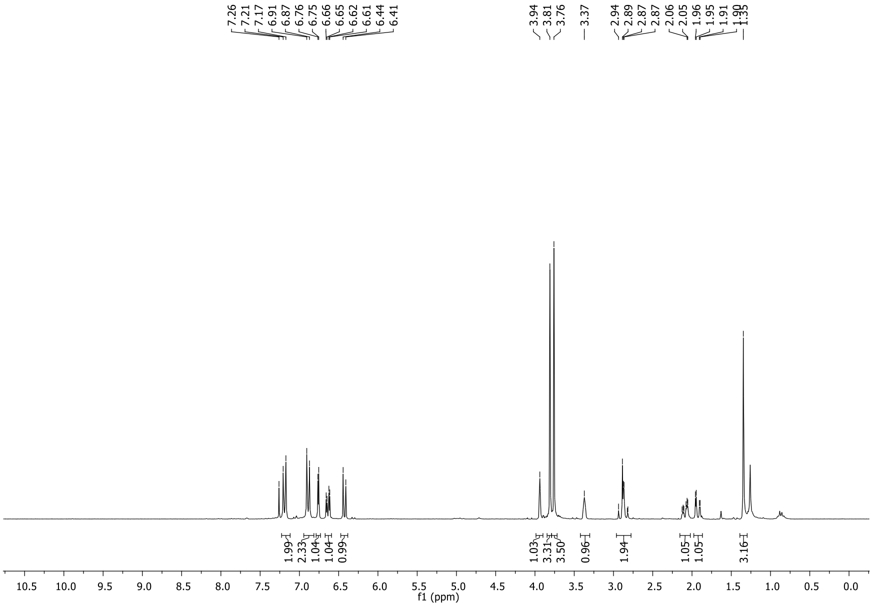
16a

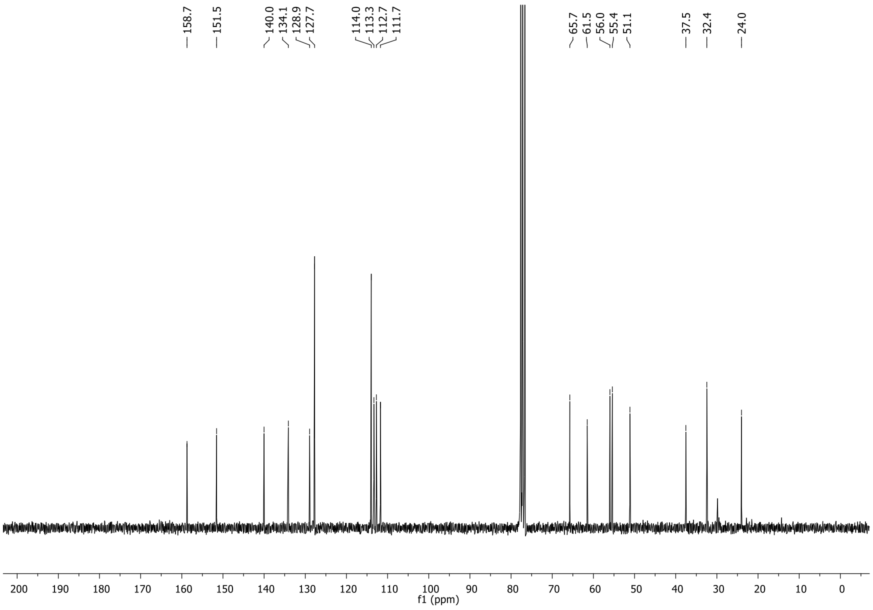

7.39
7.39
7.36
7.36
7.34
7.33
7.30
7.28
7.26
7.25
6.77
6.76
6.66
6.65
6.63
6.62
6.44
6.40
3.99
3.76
3.42
2.95
2.90
2.89
2.88
2.83
2.08
2.07
2.06
1.98
1.97
1.35
5.03
0.96
0.93
0.92
1.05
3.06
0.97
1.85
1.05
1.03
2.91
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

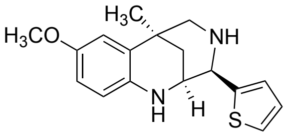

151.5
142.0
140.0
128.8
128.6
127.2
126.7
113.3
112.7
111.7
66.4
61.5
56.0
51.1
37.6
32.5
24.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
H3CO
NH
N
H
H
OCH3

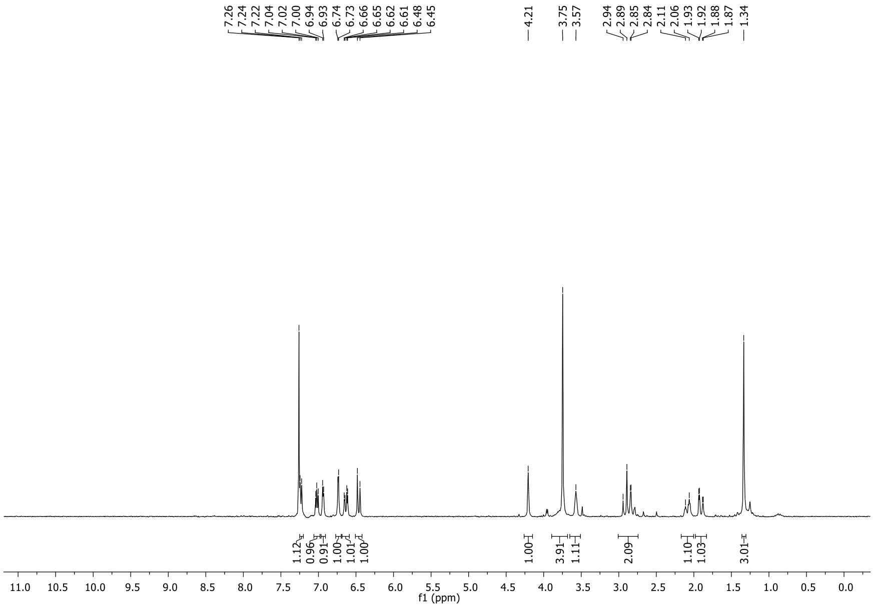
16b

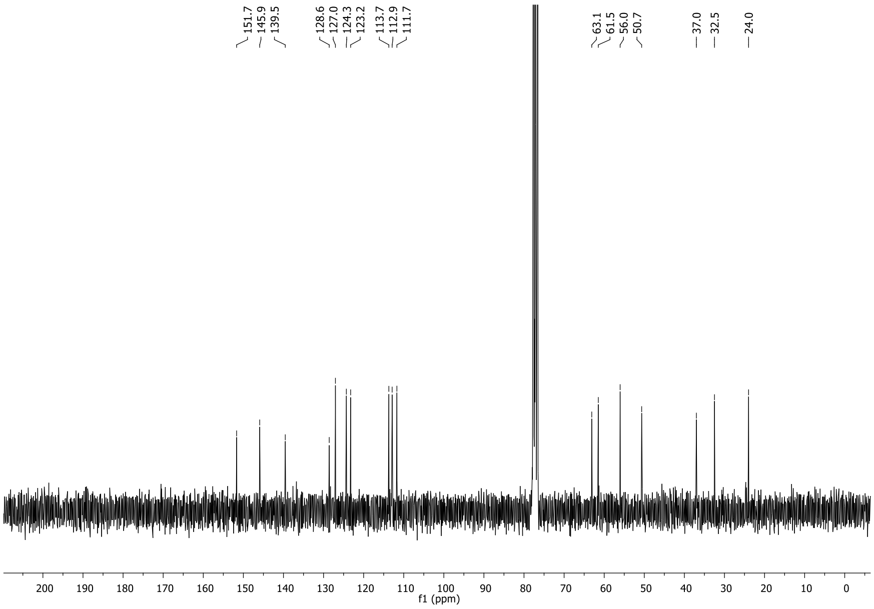

7.26
7.21
7.17
6.91
6.87
6.76
6.75
6.66
6.65
6.62
6.61
6.44
6.41
3.94
3.81
3.76
3.37
2.94
2.89
2.87
2.87
2.06
2.05
1.96
1.95
1.91
1.90
1.35
1.99
2.33
1.04
1.04
0.99
1.03
3.31
3.50
0.96
1.94
1.05
1.05
3.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

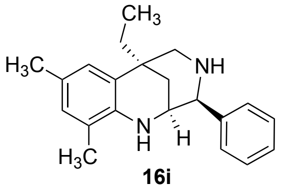

158.7
151.5
140.0
134.1
128.9
127.7
114.0
113.3
112.7
111.7
65.7
61.5
56.0
55.4
51.1
37.5
32.4
24.0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
H3C
NH
N
H
H
S

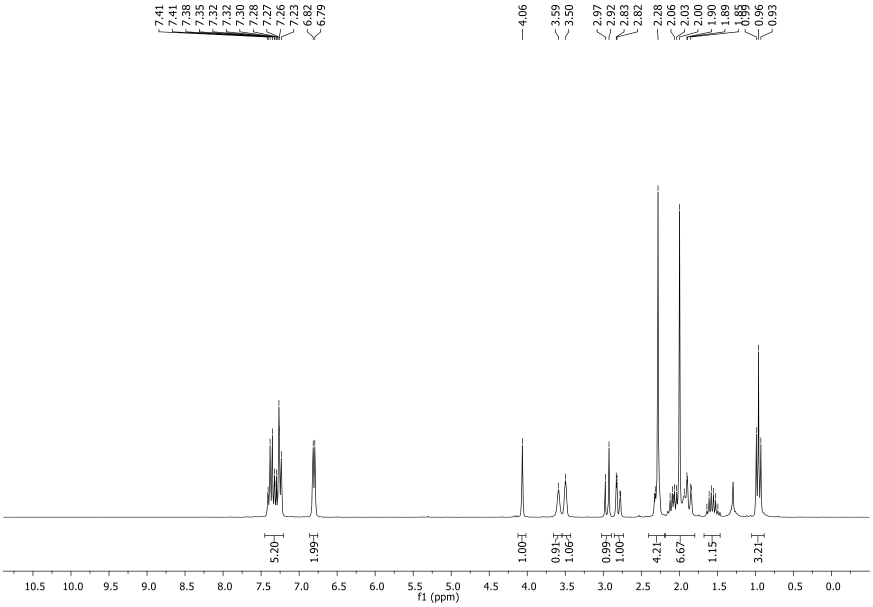
16f

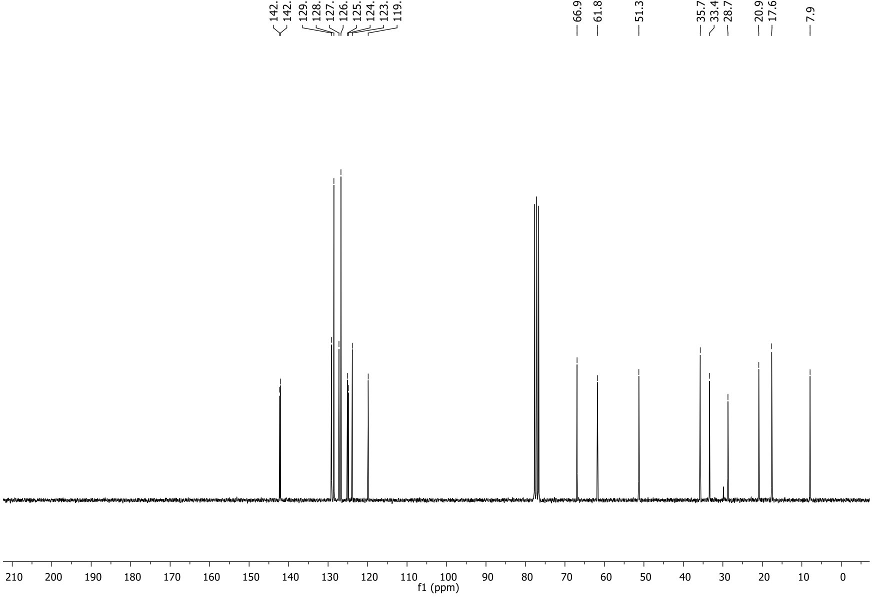

7.26
7.24
7.22
7.04
7.02
7.00
6.94
6.93
6.74
6.73
6.66
6.65
6.62
6.61
6.48
6.45
4.21
3.75
3.57
2.94
2.89
2.85
2.84
2.11
2.06
1.93
1.92
1.88
1.87
1.34
1.12
0.96
0.91
1.00
1.01
1.00
1.00
3.91
1.11
2.09
1.10
1.03
3.01
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

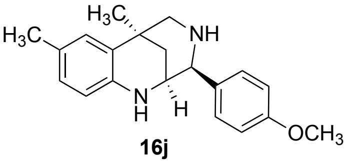

151.7
145.9
139.5
128.6
127.0
124.3
123.2
113.7
112.9
111.7
63.1
61.5
56.0
50.7
37.0
32.5
24.0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


CH3
H3C
NH
N
H
H
H3C

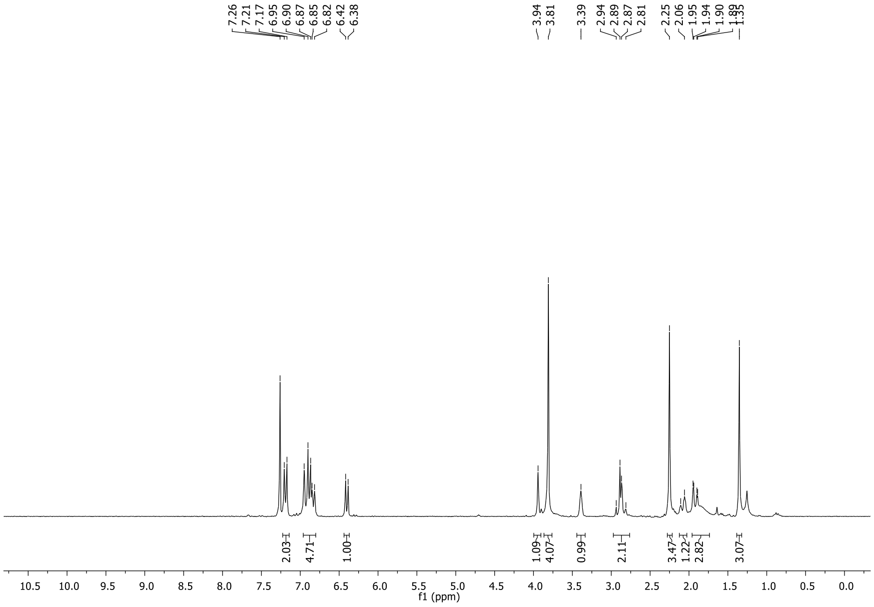
16i

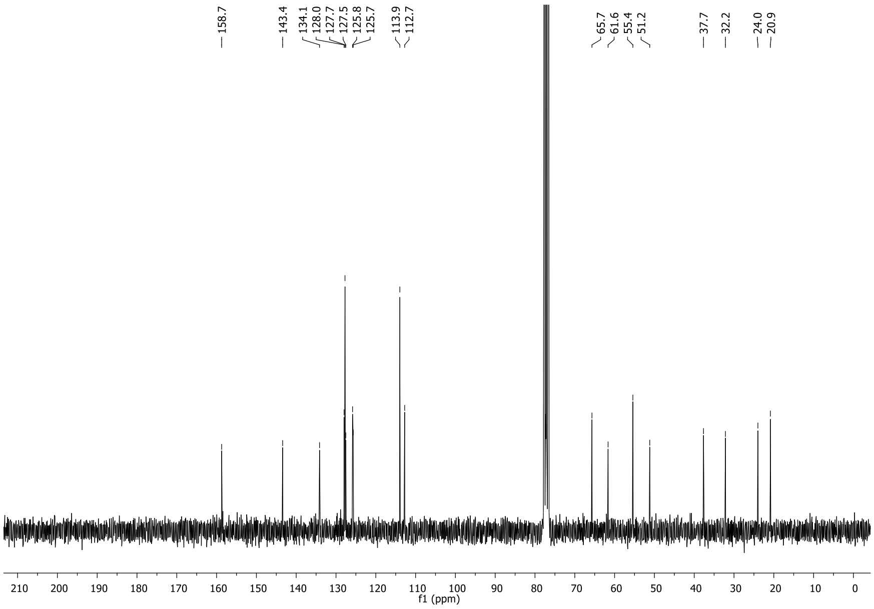

7.41
7.41
7.38
7.35
7.32
7.32
7.30
7.28
7.27
7.26
7.23
6.82
6.79
4.06
3.59
3.50
2.97
2.92
2.83
2.82
2.28
2.06
2.03
2.00
1.90
1.89
1.85
0.99
0.96
0.93
5.20
1.99
1.00
0.91
1.06
0.99
1.00
4.21
6.67
1.15
3.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

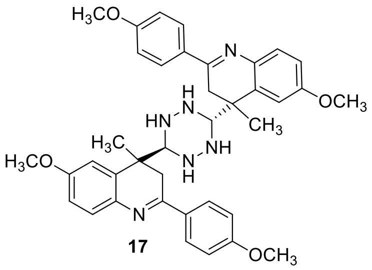

142.2
142.1
129.1
128.5
127.2
126.7
125.1
124.8
123.9
119.8
66.9
61.8
51.3
35.7
33.4
28.7
20.9
17.6
7.9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3C
H3C
NH
N
H
H
OCH3

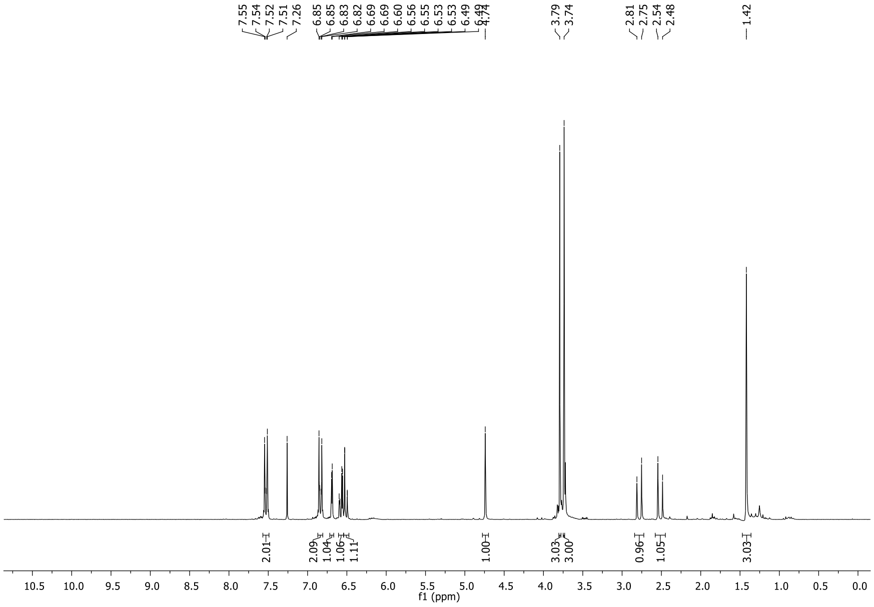
16j

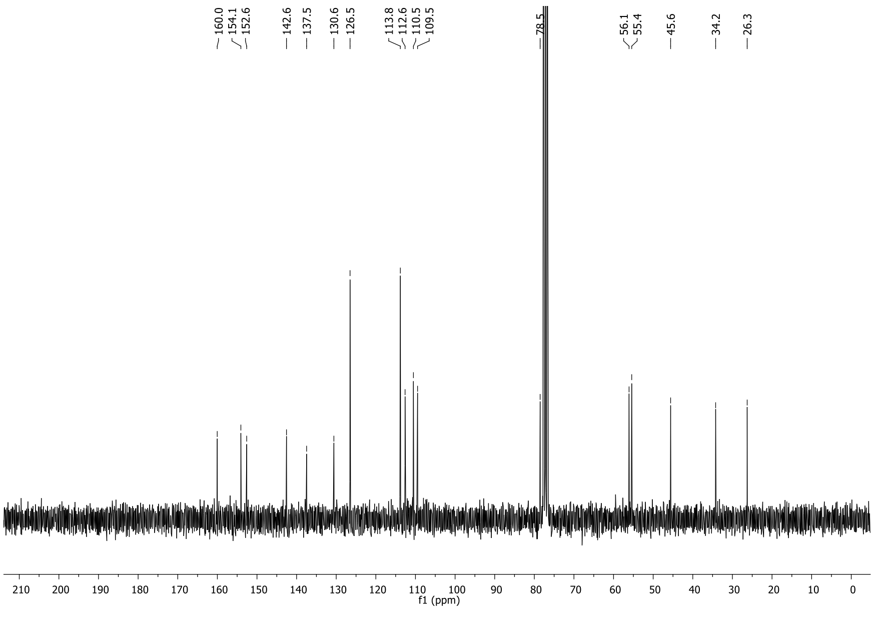

7.26
7.21
7.17
6.95
6.90
6.87
6.85
6.82
6.42
6.38
3.94
3.81
3.39
2.94
2.89
2.87
2.81
2.25
2.06
1.95
1.94
1.90
1.89
1.35
2.03
4.71
1.00
1.09
4.07
0.99
2.11
3.47
1.22
2.82
3.07
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

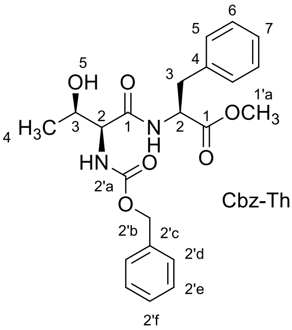

158.7
143.4
134.1
128.0
127.7
127.5
125.8
125.7
113.9
112.7
65.7
61.6
55.4
51.2
37.7
32.2
24.0
20.9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H$_3$CO
N
H
HN
N
CH$_3$
OCH$_3$
H$_3$C
NH
N
H
H$_3$CO
N
OCH$_3$

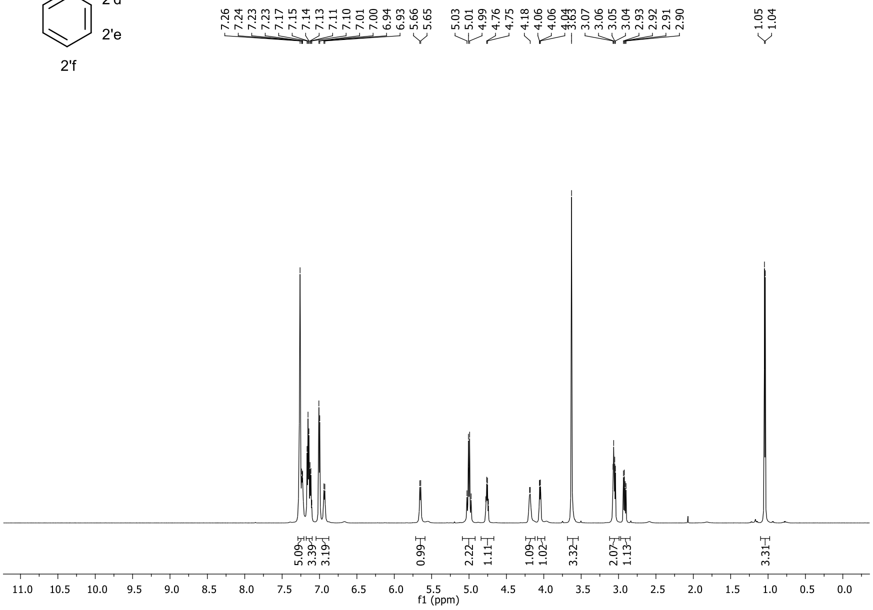
17

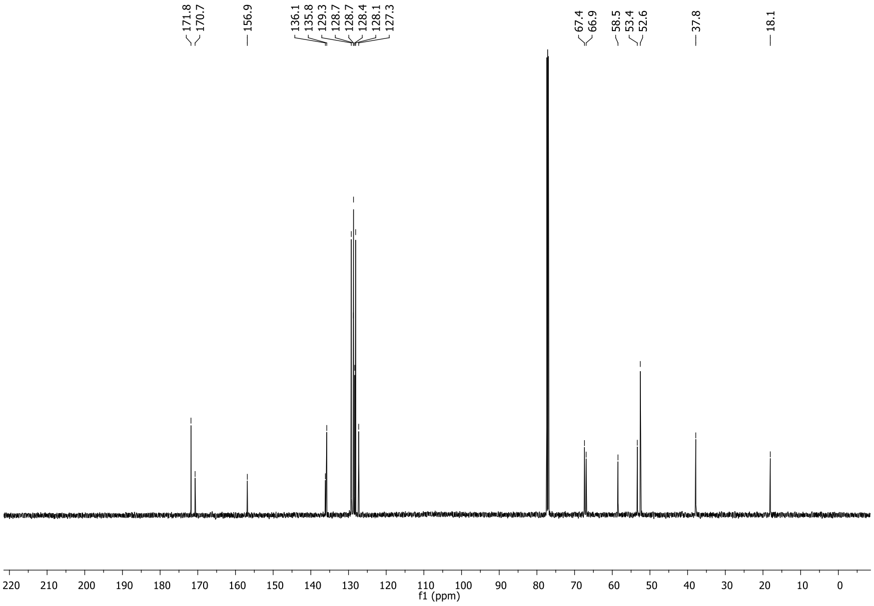

7.55
7.54
7.52
7.51
7.26
6.85
6.85
6.83
6.82
6.69
6.69
6.60
6.56
6.55
6.53
6.53
6.49
6.49
4.74
3.79
3.74
2.81
2.75
2.54
2.48
1.42
2.01
2.09
1.04
1.06
1.11
1.00
3.03
3.00
0.96
1.05
3.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

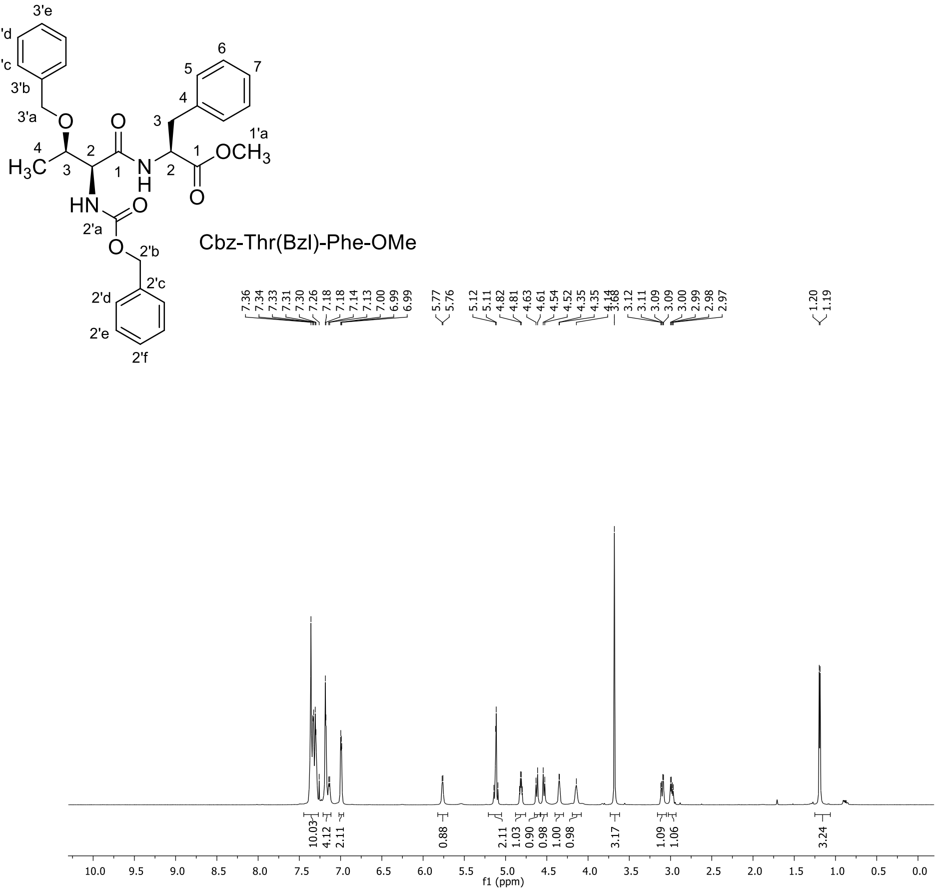

160.0
154.1
152.6
142.6
137.5
130.6
126.5
113.8
112.6
110.5
109.5
78.5
56.1
55.4
45.6
34.2
26.3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



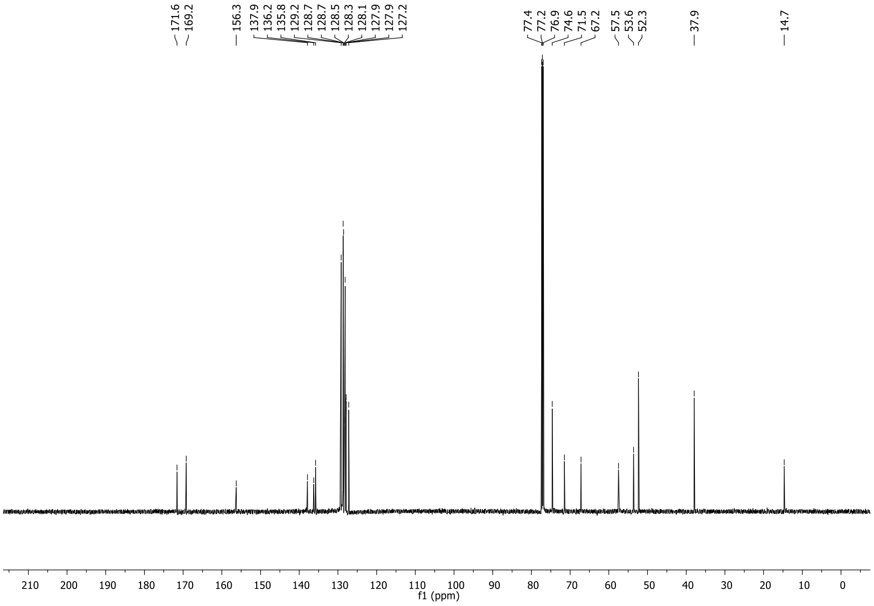
Cbz-Thr-Phe-OMe

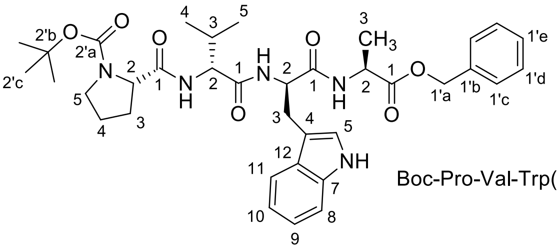






Cbz-Thr(Bzl)-Phe-OMe





Boc-Pro-Val-Trp(H)-Ala-OBn