UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE FARMACIA
Departamento de Química en Ciencias Farmacéuticas

TESIS DOCTORAL

Diversity-oriented synthesis around pyrrole cores

Síntesis orientada a la diversidad basada en núcleos de Pirrol

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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Directores

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FACULTAD DE FARMACIA
DEPARTAMENTO DE QUÍMICA EN CIENCIAS FARMACÉUTICAS

DIVERSITY-ORIENTED SYNTHESIS AROUND PYRROLE CORES

SÍNTESIS ORIENTADA A LA DIVERSIDAD BASADA EN NÚCLEOS DE PIRROL

TESIS DOCTORAL

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Madrid, Enero de 2019

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Resumen

1. Introducción

Uno de los objetivos de la Química Orgánica a los que se atribuye mayor importancia en los últimos tiempos es el desarrollo de nuevas metodologías para la exploración del espacio químico con la finalidad de identificar nuevas entidades químicas bioactivas que sirvan como base para el desarrollo de nuevos fármacos. Esta exploración require nuevos procesos sintéticos, siendo de especial importancia los que permiten la construcción de varios enlaces en una misma operación sintética, como las reacciones multicomponente.

La síntesis orientada a diversidad (Diversity-Oriented Synthesis, DOS) es una aproximación relativamente reciente a la identificación de moléculas orgánicas bioactivas, diseñada para explorer regiones amplias del espacio químico. Pone el énfasis en la generación de esqueletos variados, dando lugar a moléculas con variedad de formas tridimensionales. No está dirigida a la obtención de moleculas específicas, y las quimiotecas derivadas de DOS se utilizan sobre todo para la identificación de nuevos ligandos (*hit*) para dianas biológicas a través de técnicas de cribado de alto rendimiento (*high-throughput screening*) para su aplicación en descubrimiento de fármacos y química biológica.

Una de las estrategias más eficaces en síntesis orientada a diversidad se conoce como construcción/acoplamiento/emparejamiento (*build/couple/pair*), en la que el paso de construcción (*build*) implica sintetizar (o, idealmente, adquirir de fuentes comerciales) compuestos de artida que contengan grupos funcionales que permitan los pasos posteriores. En la etapa de acoplamiento (*couple*) se construye una estructura central, idealmente por medio de una reacción multicomponente, y finalmente en la etapa de emparejamiento (*pair*) se hace reaccionar los grupos funcionales mencionados para generar diversidad y complejidad molecular, principalmente a través de reacciones de ciclación.

2. Objetivos

Esta tesis se basa en el empleo del pirrol, una estructura privilegiada bien conocida, como núcleo central sobre el que construir una serie de quimiotecas basadas en los principios de la síntesis orientada a diversidad mediante la aproximación *build/couple/pair*. Sus objetivos concretos son:

1. Adaptación de una reacción mecanoquímica multicomponente previamente desarrollada por nuestro grupo a la síntesis de derivados de pirrol portadores en sus posiciones N-1, C-2 y C-5 de grupos funcionales adecuados para la generación de complejidad estructural en la etapa de emparejamiento. También fue necesario adaptar la reacción multicomponente a la preparación de moléculas simétricas que contienen dos anillos de pirrol en los extremos de un espaciador.

2. Síntesis de derivados de pirrol fusionados basada en reacciones catalizadas por metals de transición. En particular, se consideraron de interés las siguientes transformaciones:
   a) Síntesis de derivados de pirrolo[1,2-*c*]quinazolina por combinación de procesos de acoplamiento cruzado de C-arilación y N- arilación.
   b) Síntesis de esqueletos de pirrolo[2,1-*a*]isoquinolina and benzo[*c*]pirrolo[1,2-*a*]azepina por medio de reacciones de Heck intramoleculares.
   c) Síntesis de esqueletos de pirrolo[1,2-*a*]azepina and pirrolo[1,2-*a*]azocina por metátesis con cierre de anillo.
3. Síntesis de esqueletos de pirrolo[2,1-*a*]isoindol y pirrolo[2,1-*a*]isoquinolina por medio de reacciones de Diels-Alder intramoleculares.
4. Investigación de procesos de anelación en sustratos pirrólicos mediada por la generación de intermedios de oxonio, con las siguientes posibilidades:
   a) Ciclación del sistema de oxonio sobre un grupo arilo en C-5, utilizando una transformación relacionada con la síntesis de Pommeranz-Fritsch de isoquinolinas.
   b) Ciclación del sistema de oxonio sobre un metileno activo situado en C-2 y vecino a un éster, mediante la transformación de dicha función en un acetal de cetena.
5. Síntesis de macrociclos basada en reacciones de metátesis con cierre de anillo a partir de bis-pirroles simétricos.
6. Síntesis de anillos de tamaño medio por metátesis de cierre de anillo. Los pirroles de partida necesarios procederían de β,δ-dialilaminoenonas, que a su vez procederían de un proceso dominó de formación de enaminona /isomerización /aza Michael.
7. Preparación de basada en una reacción de Hantzsch doble, en la que la formación de uno de los anillos de pirrol constituye la etapa de macrociclación.
8. Estudio de las quimiotecas mencionadas en los apartados anteriores por métodos de cribado de alto rendimiento, a través del programa *Open Innovation in Drug Discovery* (OIDD) de Lilly.
9. Adiestramiento en técnicas sintéticas no convencionales, especialmente mecanoquímica y síntesis en flujo.

3. Resultados y discusión

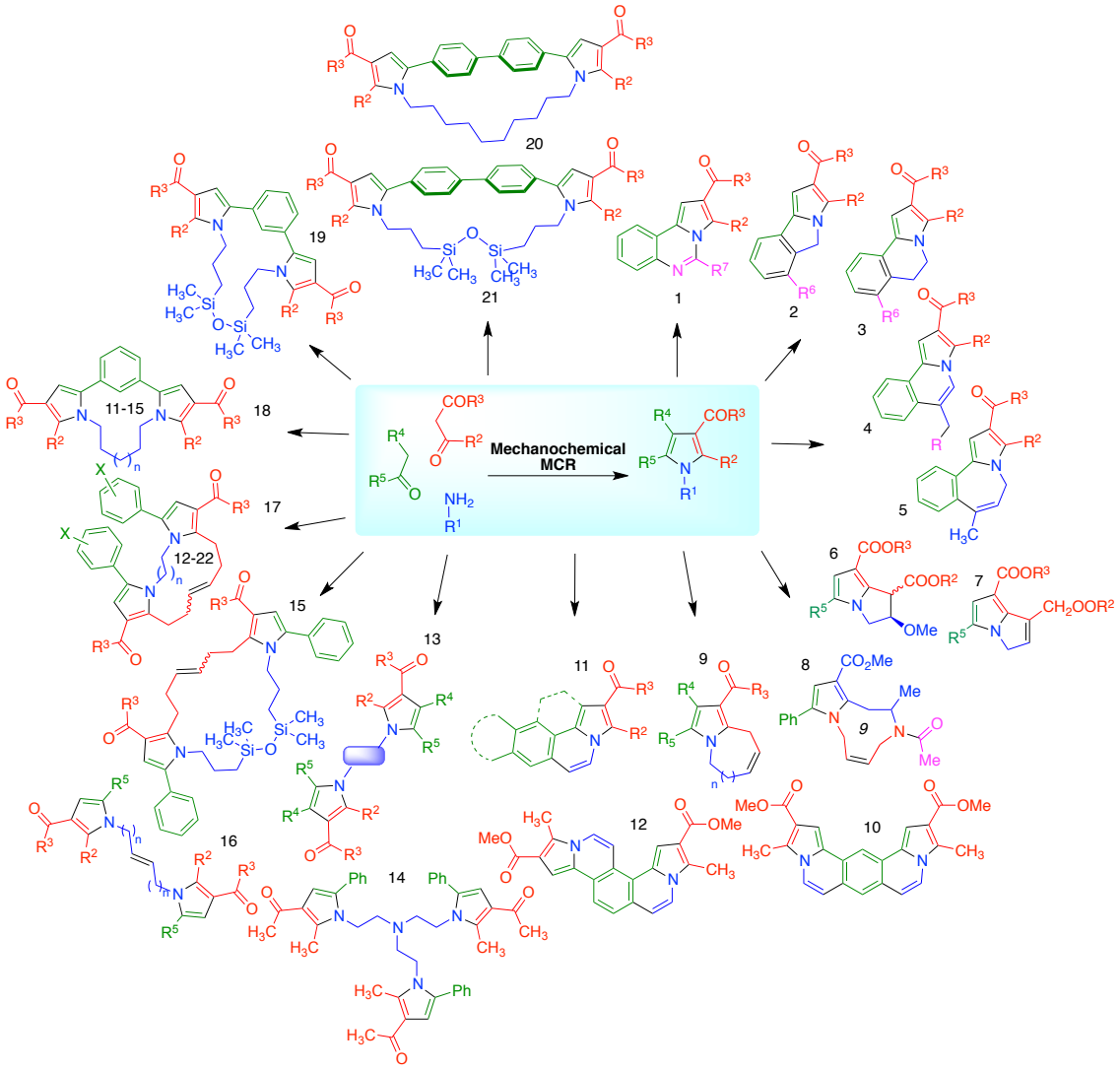
1. La capacidad de sintetizar pirroles de partida portadores de determinados grupos funcionales en las posiciones N-1, C-2 y C-5 de derivados de pirrol era crucial para el desarrollo de nuestro proyecto. Por tanto, fue necesario verificar la adecuación de una síntesis mecanoquímica multicomponente de pirroles previamente desarrollada por nuestro grupo para esta finalidad. Aunque la introducción de algunos de los sustituyentes planificados podía ser en principio problemática por

diversas razones, como impedimento estérico en el caso de grupos 5-(*o*-iodometilo) o baja estabilidad potencial de anillos de furano o grupos acetal en las condiciones de reacción. Sin embargo, no se dieron problemas significativos gracias a la suavidad de nuestro método y los derivados de pirrol deseados pudieron prepararse.

2. Se sintetizaron varios esqueletos heterocíclicos poco habituales a partir de precursores pirrólicos utilizando reacciones catalizadas por metales de transición. Concretamente, se implementaron con éxito los siguientes procesos: (a) Síntesis de of pirrolo[1,2-*c*]quinazolinas por medio de un proceso domino iniciado por una reacción de Ullmann. (b) Síntesis de esqueletos de pirrolo[2,1-*a*]isoquinolina y benzo[*c*]pirrolo[1,2-*a*]azepina por reacciones de Heck intramoleculares. (c) Síntesis de pirrolo[1,2-*a*]azepinas y pirrolo[1,2-*a*]azocinas por reacciones de metátesis con cierre de anillo.
3. Se obtuvieron esqueletos de 5,6-dihidropirrolo[2,1-*a*]isoquinolina y pirrolo[2,1-*a*]isoindol utilizando reacciones intramoleculares Diels-Alder a partir de precursores procedentes de reacciones de metátesis cruzada de 1-alil-5-(2-furil)pirroles.
4. La posibilidad de obtener pirroles portadores de una function acetal en el extreme de una cadena unida al nitrógeno permite generar intermedios de oxonio por tratamiento con ácidos de Brønsted o Lewis. Estos intermedios permitieron crear pirroles fusionados mediante procesos de ciclación sobre sustituyentes adecuados presents en las posiciones C-2 o C-5, proporcionando, respectivamente, esqueletos de pirrolizina y relacionados y esqueletos de pirrolo[2,1-*a*]isoquinolina y relacionados.
5. Se investigó también la síntesis de sistemas macrocíclicos portadores de anillos de pirrol como parte de su estructura. Condcretamente, se ha demostrado la viabilidad de las siguientes estrategias: (a) Síntesis de macrociclos basada en reacciones de metátesis con cierre de anillo, empleando como materiales de partida bis-pirroles simétricos en los que cada anillo de pirrol es portador de un sustituyente homoalílico. (b) Síntesis de anillos de tamaño medio derivados del esqueleto de pirrolo[1,2-*a*][1,5]diazonina por metátesis con cierre de anillo. (c) Macrociclación multicomponente en una sola etapa por medio de reacciones de Hantzch dobles, actuando una de ellas como la etapan de cierre del macrociclo.
6. Las quimiotecas obtenidas se estudiaron por metodologías de cribado de alto rendimiento gracias a una colaboración con Lilly a través del programa *Open Innovation in Drug Discovery* (OIDD).
7. Finalmente, como parte de los requisitos para optar a la mención internacional de la tesis doctoral, llevé a cabo una estancia de tres meses en el laboratoriuo del profesor Steven Ley en el Department of Química de la Universidad de Cambridge, trabajando en el desarrollo de reacciones de homologación fotoquímica para lamobtención de aldehídos alifáticos en condiciones de flujo.

4. Conclusiones

Los principales esqueletos moleculares generados en esta tesis se resumen a continuación. Para su construcción ha sido necesario el desarrollo de nueva metodologia sintética, y su estudio por técnicas de cribado de alto rendimiento ha dado lugar a algunos compuestos interesantes como puntos de partida para una optimización futura.



Summary

1. Introduction

One of the goals of synthetic Organic Chemistry in recent years is the development of new ways to explore chemical space in order to identify new biologically active entities and use them to uncover new therapeutic targets. The exploration of chemical space requires new synthetic processes, ideally allowing the construction of several bonds in a single operation. In this connection, the MCR chemical space, defined as the ensemble of all possible molecules that can be obtained by multicomponent synthetic processes, is of particular interest.

Diversity-Oriented Synthesis (DOS) is a recent approach to the identification of small bioactive molecules that is is designed to explore broader extensions of chemical space, its emphasis being on the generation of diverse scaffolds with varied molecular shapes. It is not directed at a specific biological target, and DOS libraries are used for the fast high-throughput identification of new ligands for varied targets in an effort to locate hit compounds in medicinal chemistry and chemical biology.

One of the most effective strategies for the fast generation of diverse molecular libraries endowed with molecular diversity and complexity is the "*build/couple/pair*" strategy, where the *build* step involves synthesizing or purchasing building blocks that contain suitable functionality for the subsequent steps. In the *couple* step, the desired structural core is constructed, ideally using a multicomponent reaction that is compatible with the presence of the functional groups needed for the complexity-generating event in the final phase. Finally, in the *pair* step, these functional groups react to provide structural complexity and diversity, mainly *via* cyclization reactions.

2. Objectives

This thesis is based on the use of pyrrole, a well-known privileged structure, as the central core on which to build a variety of DOS libraries using the *build-couple-pair* approach. More specifically, the objectives that have been pursued are:

1. Adaptation of a known, in house-developed mechanochemical multicomponent reaction to the preparation of pyrrole derivatives bearing functional groups that allow suitable complexity-generating reactions at the *pair* stage at their N-1, C-2 and C-5 positions. The mechanochemical pyrrole synthesis also needed to be adapted to the preparation of symmetrical molecules containing two pyrrole units at the end of a spacer.
2. Synthesis of fused pyrrole derivatives based on transition metal-catalyzed reactions. In particular, the following transformations were considered of interest:
    a) Synthesis of pyrrolo[1,2-*c*]quinazolines by combination of C-arylation and N-arylation cross-coupling processes.
    b) Synthesis of pyrrolo[2,1-*a*]isoquinoline and benzo[*c*]pyrrolo[1,2-*a*]azepine frameworks by intramolecular Heck reactions.

   c) Synthesis of pyrrolo[1,2-*a*]azepine and pyrrolo[1,2-*a*]azocine frameworks by ring-closing metathesis.
3. Synthesis of pyrrolo[2,1-*a*]isoindole and pyrrolo[2,1-*a*]isoquinoline frameworks by intramolecular Diels-Alder reactions.
4. Investigation of ring-formation processes on pyrrole-derived substrates *via* the generation of oxonium intermediates. Two possibilities were studied:
   a) Cyclization onto a C-5 aryl substituent, using a transformation related to the Pommeranz-Fritsch isoquinoline synthesis.
   b) Cyclization of an oxonium species from an acetal under Noyori-type conditions onto a C-2 active methylene group adjacent to an ester *via* the formation of a ketene acetal intermediate.
5. Synthesis of macrocycles based on ring-closing metathesis reactions, using as starting materials symmetrical bis-pyrrole derivatives.
6. Synthesis of diaza medium-sized rings by ring-closing metathesis. The starting pyrroles would be constructed by the Hantzsch method from β,δ-diallylaminoenones, which would in turn be available *via* an enaminone formation/double bond isomerization/aza Michael domino sequence.
7. Preparation of macrocycles based on a double Hantzsch pyrrole synthesis, with one of these reactions serving as the macrocyclization event.
8. Study of the libraries synthesized by the above methods using high-throughput screening methodologies. These studies were performed thanks to our collaboration with the Lilly Open Innovation in Drug Discovery (OIDD) program.
9. Training in non-conventional synthetic methodologies such as mechanochemistry and synthesis in flow.

3. Results and discussion

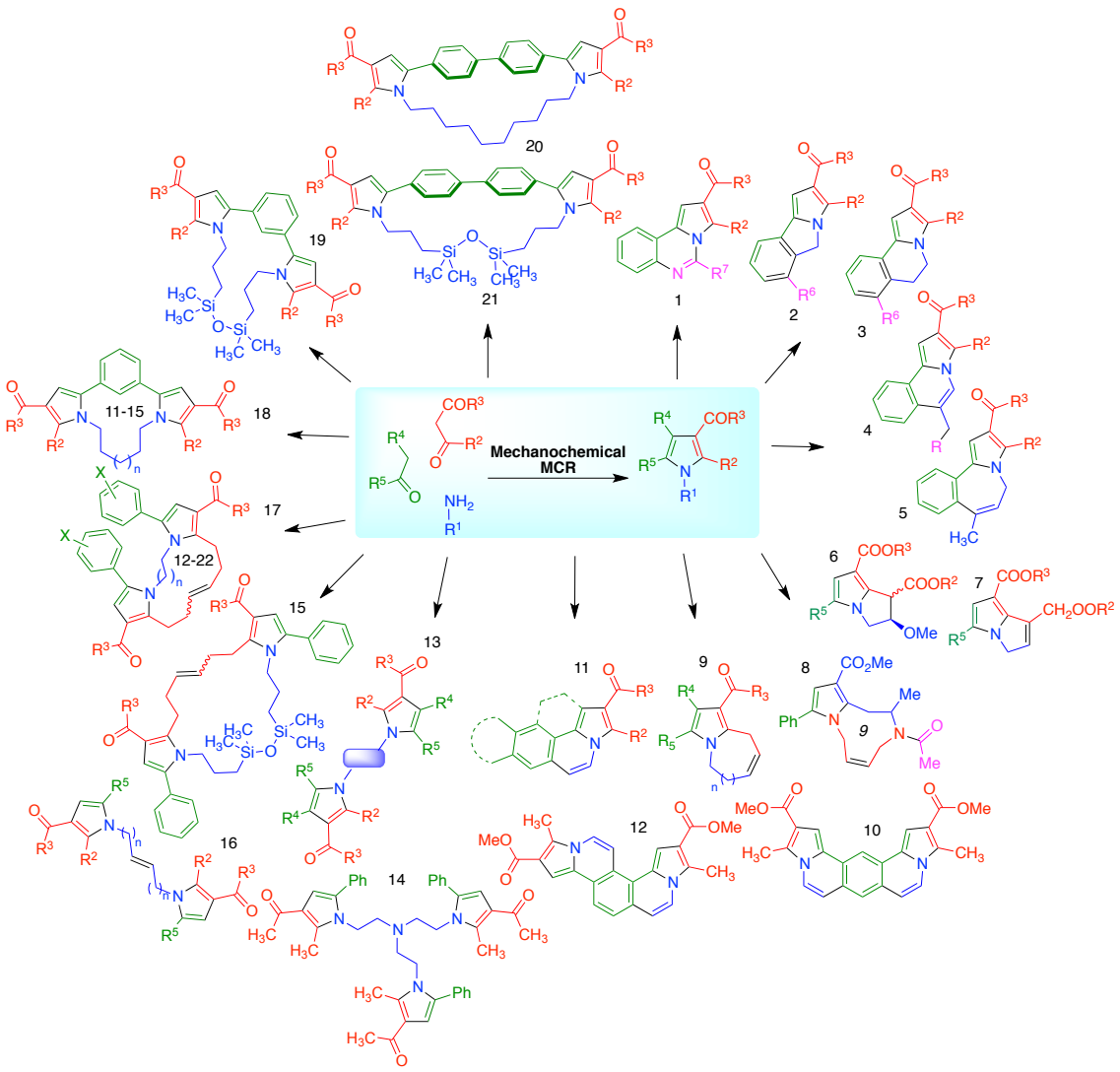
1. The ability to synthesize starting pyrroles bearing suitable functionalities was crucial to the success of our DOS project. Therefore, we needed to verify whether the mechanochemical multicomponent pyrrole synthesis previously developed by our group and based on the Hantzsch reaction was compatible with the functionalities planned to be present at their N-1, C-2 and C-5 positions in order to carry out complexity-generating reactions at the final *pair* stage. The introduction of some of these groups could be in principle troublesome for a variety of reasons such as the steric hindrance due to the *o*-iodophenyl substituent or the potential low stability of the furan ring or the acetal function under the reaction conditions. In the event, these concerns proved to be largely unfounded thanks to the mildness of our method and the usual reaction conditions of our method gave good results, allowing the preparation of a large library of starting pyrroles.
2. A number of unusual fused pyrrole heterocyclic frameworks were synthesisized from suitable pyrrole precursors using transition metal-catalyzed reactions. In

particular, the following processes were successfully implemented: (a) Synthesis of pyrrolo[1,2-*c*]quinazolines by an Ullmann coupling-initiated domino process. (b) Synthesis of pyrrolo[2,1-*a*]isoquinoline and benzo[*c*]pyrrolo[1,2-*a*]azepine frameworks by ring-closing Heck reactions. (c) Synthesis of pyrrolo[1,2-*a*]azepines and pyrrolo[1,2-*a*]azocines by ring-closing metathesis.

3. 5,6-Dihydropyrrolo[2,1-*a*]isoquinoline and pyrrolo[2,1-*a*]isoindole frameworks were obtained using intramolecular Diels-Alder reactions from precursors obtained by cross-metathesis of 1-allyl-5-(2-furyl)pyrroles.
4. The possibility to synthesize pyrrole derivatives with a nitrogen substituent ending in an acetal group opened up the possibility to readily generate oxonium species by treatment with Brønsted or Lewis acids. These intermediates were suitable substrates for ring-creation processes leading to fused pyrrole systems by cyclization onto the C-2 or C-5 substituents, leading respectively, to pyrrolizine and related frameworks or pyrrolo[2,1-*a*]isoquinoline and related frameworks.
5. The synthesis of pyrrole-based macrocyclic structures was also investigated. In particular, the following strategies were successfully explored: (a) Synthesis of macrocycles based on ring-closing metathesis reactions, using as starting materials symmetrical bis-pyrrole derivatives where each of the pyrrole rings bears an homoallyl chain. (b) Synthesis of pyrrole-derived medium-sized rings derived from the pyrrolo[1,2-*a*][1,5]diazonine framework by ring-closing metathesis. (c) One-pot multicomponent macrocyclization application of a one-pot process involving two Hantzch pyrrole syntheses, one of which acts as the macrocyclization event.
6. The DOS libraries obtained were studied by high-throughput screening methodologies, in collaboration with the Lilly Open Innovation in Drug Discovery (OIDD) program.
7. Finally, as part of the requirements for the *International Ph D Label*, I carried out a three-month stay at the group of Professor Steven Ley at the Department of Chemistry, Cambridge University, working on the use of photochemical homologation reactions for the preparation of aliphatic aldehydes under flow chemistry conditions.

4. Conclusions

The main frameworks whose synthesis is described in this thesis are summarized below. Some new synthetic methodology was discovered in the course of this endeavour, and some interesting hit compounds for a number of diseases were identified by high-throughput screening.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COOR3
COOR2
CH2OOR2
OMe
CO2Me
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Ph
MeO
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H3C
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List of Publications

1. **M. Leonardi**, M. Villacampa, J. C. Menéndez. “Mild and general synthesis of pyrrolo[2,1‐*a*]isoquinolines and related polyheterocyclic frameworks from pyrrole precursors derived from a mechanochemical multicomponent reaction” *Journal of Organic Chemistry*, **2017**, *82*, 2570−2578.

2. **M. Leonardi**, M. Villacampa, J. C. Menéndez. “High-speed vibration-milling-promoted synthesis of symmetrical frameworks containing two or three pyrrole units”, *Beilstein Journal of Organic Chemistry* **2017**, *13*, 1957–1962. This article was written by invitation and is is part of the Thematic Series "Mechanochemistry II".

3. **M. Leonardi**, M. Villacampa, J. C. Menéndez. “Multicomponent mechanochemical synthesis”, *Chemical Science*, **2018**, *9*, 2042-2065.

4. Y. Chen, **M. Leonardi**, P. Dingwall, R. Labes, P. Pasau, D. C. Blakemore, S. V. Ley. “Photochemical homologation for the preparation of aliphatic aldehydes in flow”, *Journal of Organic Chemistry*, **2018**, *83*, 15558–15568.

5. **M. Leonardi**, V. Estévez, M. Villacampa, J. C. Menéndez. “The Hantzsch pyrrole synthesis: Non-conventional variations and applications of a neglected classical reaction”, *Synthesis*, **2019**, *51*, DOI: 10.1055/s-0037-1610320.

6. **M. Leonardi**, M. Villacampa, J. C. Menéndez. Mechanochemical synthesis of biologically relevant heterocycles, in R. Ballini (Ed.), Green synthetic processes and procedures. Royal Society of Chemistry, 2019 (in press), written by invitation.

7. **M. Leonardi**, V. Estévez, M. Villacampa, J. C. Menéndez. “Diversity-oriented synthesis of complex pyrrole-based architectures from very simple starting materials”. *Advanced Synthesis and Catalysis*, **2019**, submitted.

8. S. Maiti, **M. Leonardi**, M. Villacampa, J. C. Menéndez. Efficient synthesis and some applications of 1,4-diazepines obtained by a domino process involving the *in situ* generation of an aza-Nazarov reagent. *Journal of Organic Chemistry*, **2019**, in preparation.

1. Introduction

1.1. Diversity-Oriented Synthesis

One of the goals of Organic Chemistry in recent years is the development of new ways to explore chemical space in order to identify new biologically active entities and use them to uncover new therapeutic targets.[1] Chemical space spans all organic compounds having certain pre-defined properties. In the field of drug discovery, some of these parameters are lipophilicity, polarizability, molecular weight, etc. Chemical space is truly astronomic in size, and it has been estimated that the number of existing organic molecules built from the elements normally associated with life (C, H, N, S, O), chemically stable and with certain drug like properties (e.g. molecular weight below 500 Daltons) is over 10^{63},[2] a mind-boggling number that is impossible to conceive and that can be somehow placed in context by bearing in mind that the number of chemical compounds registered in the *Chemical Abstracts* service is $1{,}43.10^{8}$, the age of the Universe is 5.10^{17} seconds and the number of atoms in Earth is in the 10^{50} order of magnitude. Regarding the targets at which these molecules are addressed, although the number of all possible proteic structures has been estimated to be 20^{300},[3] the human proteome comprises only about 250,000 proteins.

The exploration of chemical space requires new synthetic processes, ideally allowing the construction of several bonds in a single operation. In this connection, the MCR chemical space, defined as the ensemble of all possible molecules that can be obtained by multicomponent synthetic processes, is of particular interest.[4]

In order to place Diversity-Oriented Synthesis (DOS) in context, it is useful to compare it with Target-Oriented Synthesis (TOS) and combinatorial synthesis. Regarding TOS, the identification and characterization of natural bioactive entities is usually followed by their total synthesis, which is normally designed using the retrosynthetic approach. Using this approach, a single and defined molecular architecture is obtained, representing a single point in chemical space (Figure 1.1).

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4 (a) Lenci E.; Guarna A.; Trabocchi A., *Molecules* **2014**, *19*, 16506; (b) Bender A., Fergus S., Galloway W. R., Glansdrop F. G., Marsden D. M., Nicholson R. L., Spandl R. J., Thomas G. L., Wyatt E. E., Glen R. C., Spring D. R. *Ernst Shering Res Found Workshop,* **2006**, *58*, 47; (c) Lipinski C.; Hopkins A. *Nature,* **2004** ,*432*, 855. (d) Abdelraheem, E. M. M.; Camacho, C. J.; Dömling, A. *Expert Opin. Drug Discov.* **2015**, 10, 1179. (e) Orru, R.; Ruijter, E. (Eds). *Multicomponent Reactions in Drug Discovery and Medicinal Chemistry*. Elsevier, **2018**.

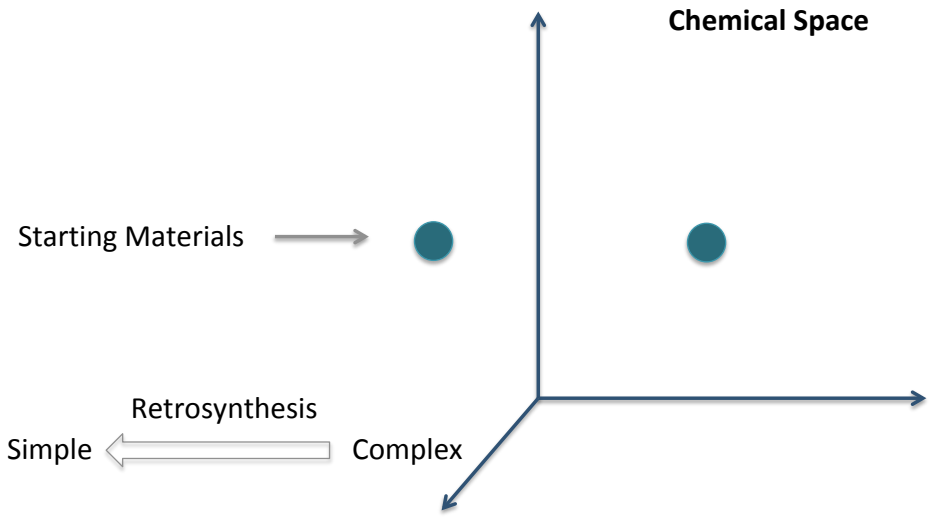

Figure 1.1

Combinatorial chemistry has been widely employed to prepare chemical libraries *via* the generation of structural diversity by modification of functional groups and substituents around a single skeleton. It leads to the exploration of only a small region of chemical space, centered on the point corresponding to the original framework. Retrosynthetic reasoning is still the prevalent form of synthetic design (Figure 1.2).

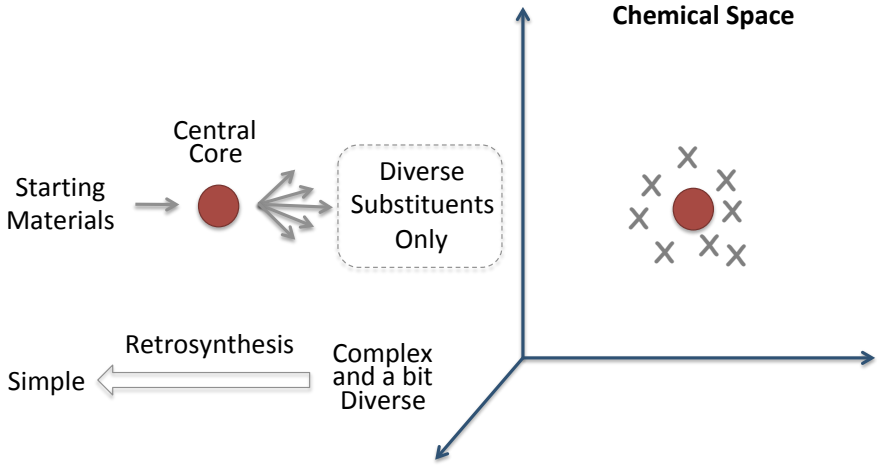

Figure 1.2

Diversity-Oriented Synthesis (DOS) is a more recent approach to the identification of small bioactive molecules that is is designed to explore broader extensions of chemical space, its emphasis being on the generation of diverse scaffolds with varied molecular

shapes.[5] It is not directed at a specific biological target and DOS libraries are used for the fast high-throughput identification of new ligands for varied targets in an effort to locate hit compounds in medicinal chemistry and chemical biology.[6] Because in DOS there is no target molecule, the synthetic planning is prospective rather than retrosynthetic, proceeding from building blocks to to products.[7,8,9] The stringent characteristics of DOS in terms of synthetic efficiency have been a driving force for the advancement of synthetic methodology, in particular in the area of multiple bond-forming processes such as domino and multicomponent reactions (Figure 1.3).

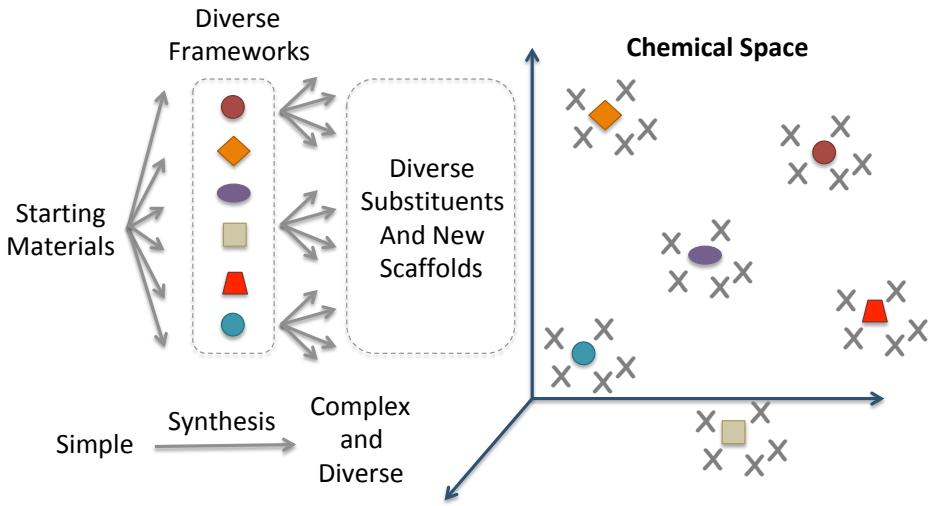

Figure 1.3

One of the most effective strategies for the fast generation of diverse molecular libraries endowed with molecular diversity and complexity is the "*build/couple/pair*"

[5] For a monograph, see: Trabocchi, A.; (ed.). *Diversity-Oriented Synthesis. Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*. *John Wiley & Sons*, Hoboken, **2013**.

[6] (a) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, R. D. *Nat. Comm.*, **2010**, *80*. (b) O'Connell, K. M. G.; Galloway, W. R. J. D.; Spring, D. R in: Trabocchi A. (ed.); *Diversity-Oriented synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*, **2013**, Wiley, *chapter 1*. (c) Medina-Franco, J. L.; Martínez-Mayorga, K.; Meurice, N. *Expert Opin. Drug Discov.* **2014**, *9*, 151. (d) Aliagas, I.; Berger, R.; Goldberg, K.; Nishimura, R. T.; Reilly, J.; Richardson, P.; Richter, D.; Sherer, E. C.; Sparling, B. A.; Bryan, M. C. *J. Med. Chem.* **2017**, *60*, 5955. (f) Kidd, S. L.; Osberger, T. J.; Mateu, N.; Sore, H. F.; Spring, D. R. *Front. Chem.* **2018**, *6*, 460. (g) Gerry, C. J.; Schreiber, S. L. *Nat. Rev. Drug. Discov.* **2018**, *17*, 333. (h) Pavlinov, I.; Gerlach, E. M.; Aldrich, L. N. *Org. Biomol. Chem.* **2018**, Advance Article. (i) Pawar, T. J.; Jiang, H.; Vázquez, M. A.; Villegas-Gómez, C.; Cruz-Cruz, D. *Eur. J. Org. Chem.* **2018**, 1835.

[7] (a) Schreiber S. L. *Science,* **2000**, *287*, 1964; (b) Burke, M. D.; Berger, E. M.; Schreiber, M. L. *Science,* **2003**, *302*, 5645; (c) Burke M. D., Schreiber S. L., *Angew. Chem. Int. Ed*., **2004**, *43*, 46; (d) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F.; Schenk, R. J.; Trippe A. J. *J. Org. Chem.,* **2008** , *73*, 4443; (e) Schreiber, S. L.; *Nature,* **2009**, *457*, 153. (f) Biggs-Houck, J.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.,* **2010**, *14*, 371.

[8] Anoh, V.; Agbo, S.; Swande, P. *Chem. Sci. Rev. Lett.* **2015**, *4*, 1148.

[9] Sahn, J. J.; Granger, A. B.; Martin, S. F. *Org. Biomol. Chem.*, **2014**, *12*, 7659.

strategy,[10] first proposed by Schreiber in 2008[11] and that is increasingly employed as a fast method to yield small molecules with increased probability of success in the discovery[12] and optimization phases of drug-discovery research.

In this strategy, the *build* step involves synthesizing or purchasing building blocks that contain suitable functionality for the subsequent steps. In the *couple* step, the desired structural core is constructed, ideally using a multicomponent reaction that is compatible with the presence of the functional groups needed for the complexity-generating event in the final phase. Finally, in the *pair* step, these functional groups react to provide structural complexity and diversity, mainly *via* cyclization reactions (Figure 1.4). The use of MCRs as a starting point for subsequent reactions that exploit the core connectivity of the components is a powerful approach to achieving efficiency and diversity.

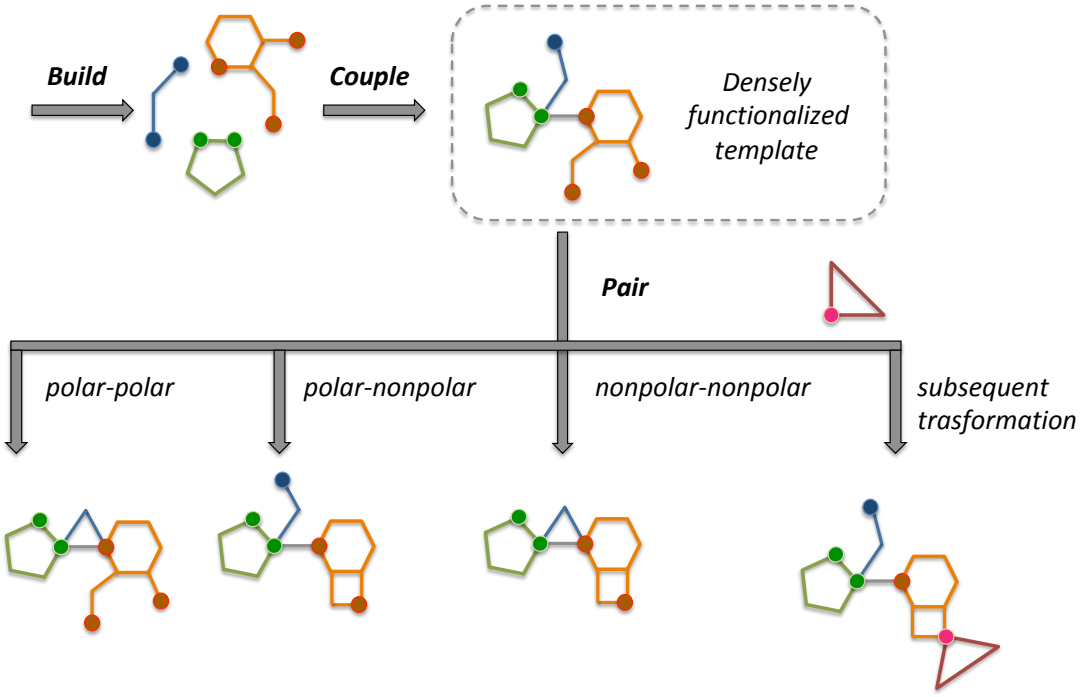

Figure 1.4

As an example of the B/C/P strategy, we will mention the work of Hung *et al.*[13] for the generation of a diverse library of bicyclic derivatives. In the *build* stage, compounds **I** and **II** were obtained from proline, following a literature procedure. In the *couple* stage other reactive appendages were introduced by functionalizing the proline or by

[10] Yi, S.; Varun, B. V.; Choi, Y.; Park, S. B. *Front. Chem.,* **2018***, 6, 507.*

[11] Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.,* **2008**, *47*, 48.

[12] Chauhan, J.; Luthra, T.; Gundla, R.; Ferraro, A.; Holzgrabe, U.; Sen, S. *Org. Biomol. Chem.*, **2017**, *15*, 9108.

[13] Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. *Proc. Natl. Acad. Sci. U.S.A.,* **2011**, *108*, 6799.

coupling the amino group to generate intermediates **III**. The substituents thus introduced can undergo the final *pair* step to generate final bicyclic structures **IV** mostly *via* Ring Closing Metathesis reactions (Figure 1.5). This article contains also an example of a post-pairing modification (defined also subsequent modification), since the authors transformed the architectures initially created *via* a subsequent hydrolysis of the methyl ester and reduction of the alkene groups to give the final derivatives **V**.

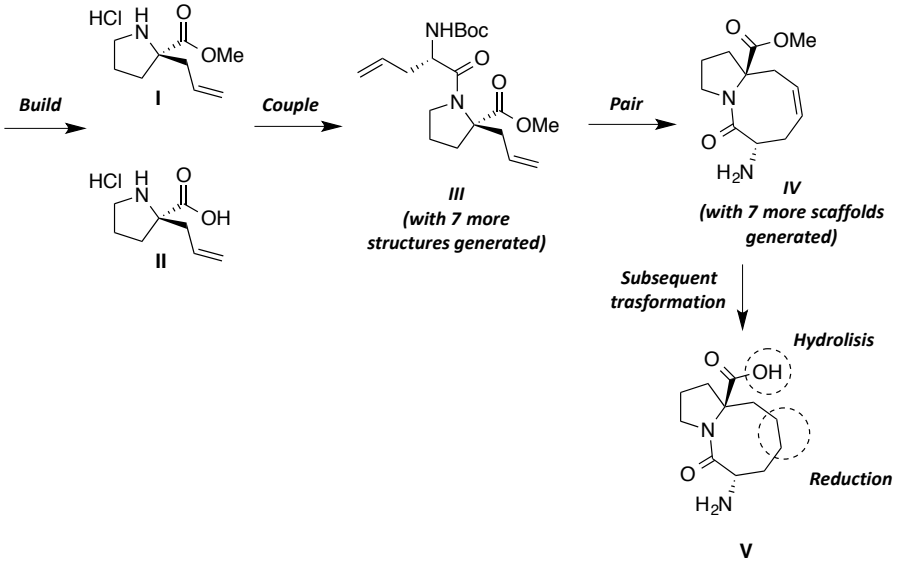

Figure 1.5

Because of the unconceivably large size of chemical space, which makes imposible to even attempt its full exploration, a recent trend is to direct the construction of DOS libraries towards regions of chemical space where compounds have a higher probability of success. One possibility is to use as guidelines the structures of natural products, which can be considered to have been optimized by evolution for interaction with biomolecules.[14] Alternatively, the concept of privileged structure can be used as a guideline.[15] Privileged structures are defined as structural fragments that are common to compounds that are able to interact with varied pharmacological targets, leading to the conclusion that they have a particular affinity for biomolecules.[16]

[14] (a) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.,* **2011**, *50*, 10800; (b) Bon, R. S.; Waldmann, H. *Acc. Chem. Res*., **2010**, *43*, 1103; (c) van Hattum, H.; Waldmann, H. *J. Am. Chem. Soc.,* **2014**, *136*, 11853; (d) Chauhan, I.; Luthra, T.; Gundla R.; Ferraro, A.; Holzgrabe, U.; Sen, S. *Org. Biomol. Chem.,* **2017**, *15*, 9108; (e) Laraia, L.; Robke, L.; Waldmann, H. *Chem* **2018**, *4*, 705.

[15] Kim, J.; Kim, H.; Park, S. B. *J. Am. Chem. Soc.* **2014**, *136*, 14629.

[16] Yet, L. *Privileged Structures in Drug Discovery*. John Wiley & Sons, Hoboken, EEUU **2018**.

1.2. Multicomponent Mechanochemical Synthesis

This thesis is based on the use of a mechanochemical, generalized version of the multicomponent Hantzsch pyrrole synthesis as the *couple* phase of a *build-couple-pair* protocol for the generation of molecular diversity and complexity. In this Section, some background will be given on multicomponent reactions, mechanochemical synthesis and their combined use.

Modern organic synthesis, besides being driven by the classical principles of regio-, chemo- and stereo-selectivity, is based on economic and environmental concerns toward an *ideal synthesis*[17] whose characteristics can be summarized as:

- Use of simple, cheap and easily available starting materials.
- Low environmental impact.
- Simple methodology.
- Possibility of automation.
- Atom economy.
- Alternative sources of energy.
- Quantitative conversion of the starting materials.
- Capacity to generate molecular complexity and diversity.

Multicomponent reactions (MCRs)[18], are an efficient tool towards achieving these goals. They are defined as convergent transformations in which three or more starting materials are combined to generate the final product so that the final product contains significant structural fragments of all reactants.[19]. The transformation may take place *via* a one-step process, when all the starting components are added at the same time, or sequentially, when the addition of the components is not simultaneous. In both cases, but the overall process takes place with no purification of intermediates (Figure 1.6).

[17] Wender, P. A.; Miller, B. L. Nature **2009**, *460*, 197.
[18] Leonardi, M.; Villacampa, M.; Menéndez, J. C. *Chem. Sci.* **2018**, *9*, 2042.
[19] Dömling, A.; Wang, W.; Wang K. *Chem. Rev.* **2012**, *112*, 3083.

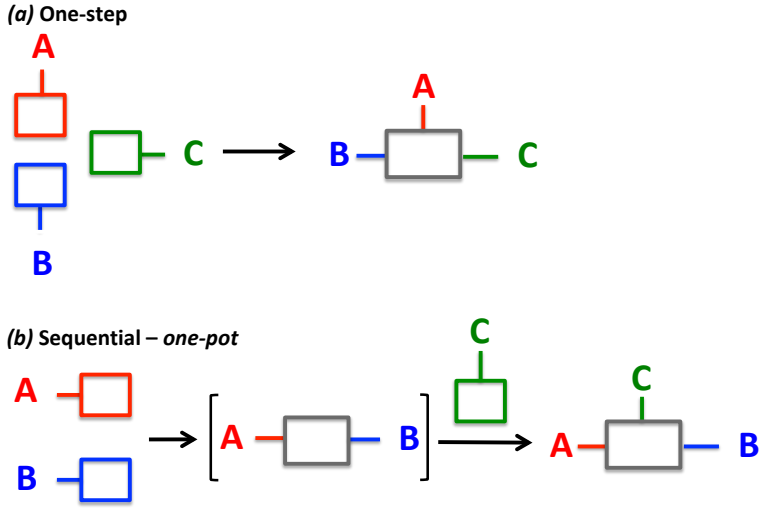

Figure 1.6

This approach to synthetic chemistry has several advantages:

- Several bonds are generated in a single operation, which represents a more effective synthetic strategy if compared with classical multi-step synthesis.[20]
- Because intermediates are not isolated, the number of isolation and purification steps is reduced. This involves reduced waste generation from organic solvents and chromatographic stationary phases.
- It is well suited to the fast and experimentally simple preparation of molecular libraries.

MCRs have been known since the 19th century (Strecker reaction[21], Biginelli reaction[22], Hantzsch dihydropyridine synthesis[23]) (Scheme 1.1). Isocyanide-based multicomponent reactions are widely employed in organic synthesis, mostly in the generation of peptides or peptide mimics. Due to the high reactivity of the isocyanide group, whose carbon atom can act as both a nucleophile of an electrophile, they show a very versatile nature. The first MCRs using isocyanide are the Passerini (3CR) and the Ugi (4CR) reactions, described for the first time in 1921 and 1959, respectively (Scheme 1.2).[24]

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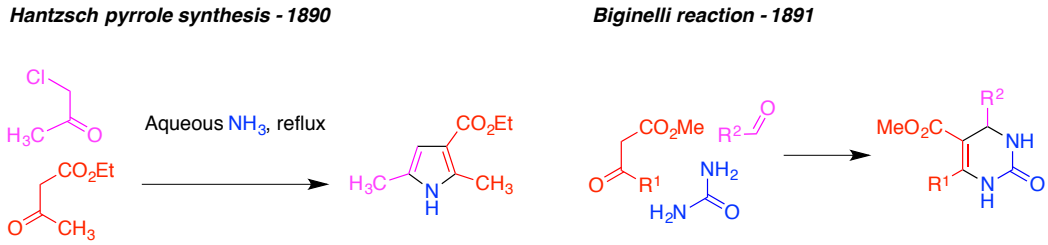
[20] For reviews about multibond forming reactions as a more eco-compatible chemistry, see: (a) Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol, D.; Rodriguez, J. *in Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, **2010**, *Vol. 1, Chapter 9*, 187; (b) Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2013**, *19*, 2218. (c) For a Special Issue on this topic, see: Menéndez, J. C. (ed.), *Curr. Org. Chem*. **2013**, *17*, 1919. (d) Cioc, R. C.; Ruitjer, E.; Orru, R. V. A. *Green Chem*. **2014**, *16*, 2958.

[21] Strecker, A. *Liebigs Ann.* **1850**, *75*, 27.

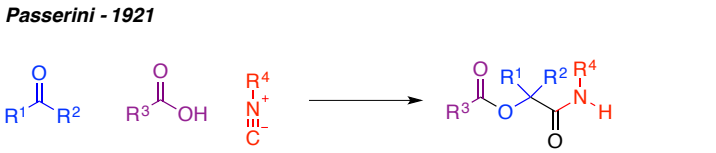
[22] Biginelli, P. *Chem. Ber.* **1891**, *24*, 1317.

[23] Hantzsch, A. *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 1474.

[24] For reviews of isonitrile-based MCRs, see: (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168; (b) Ugi, A. *Pure Appl. Chem.* **2001**, *73*, 187. (c) Ugi, A. *Molecules* **2003**, *8*, 53; Dömling, A.



Scheme 1.1



Scheme 1.2

The widespread application of multicomponent reactions in medicinal chemistry is relatively recent. Their importance and relevance in drug discovery programs and the lead identification process can be correlated to their ability to generate diverse and complex molecular libraries,[25,26,27] both in combinatorial and diversity-oriented contexts. MCRs leading to the formation of heterocyclic products are increasingly

Chem. Rev., **2006**, *106*, 17. (d) Sadjadi, S.; Heravi, M. M.; Nazari, N. *RSC Adv.* **2016**, *6*, 53203. (e) Song, B.; Xu, B. *Chem. Soc. Rev*. **2017**, *46*, 1103.

25 (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (b) Tejedor, D.; González-Cruz, D.; Santos-Exposito, A.; Marrero-Tellado, J. J.; de Armas, P.; García-Tellado, F. *Chem. Eur. J.* **2005**, *11*, 3502; Some reviews on multicomponent reactions for the generation of molecular complexity and diversity: (a) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Curr. Opin. Chem. Biol.* **2010**, *14*, 371; (b) Eckert, H. *Molecules* **2012**, *17*, 1074; (c) van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Synlett* **2013**, *24*, 666; (d) Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948. (e) Rodriguez, J.; Bonne, D. (Eds). *Stereoselective Multiple Bond-Forming Transformations in Organic Synthesis*. John Wiley & Sons, **2015**. (f) Eckert, H. *Molecules*, **2017**, *22*, 349.

26 O' Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev*. **2012,** *41*, 4444.

27 Dömling, A.; Wang, W.; Wang, K. *Chem. Rev*. **2012**, 112, 3083.

common, mostly because more than 60% of drugs and agrochemicals are heterocycles.[28,29]

The IUPAC Compendium of Chemical Technology ("gold book") defines mechanochemical reactions as those induced by the direct absorption of mechanical energy, which may come from shear, friction or compression associated to grinding or milling processes. While ball milling has been widely employed in industry to reduce particle size during the manufacturing of paints, drugs and some other products,[30] the use of mechanical energy in organic synthesis has been historically almost negligible. Nevertheless, in recent times the synthetic community is slowly becoming acquitted with this technique. [31]

Mechanochemical activation is relevant in the context of green chemistry because it allows solvent-free conditions and, in most cases, room temperature processes. Thus, a reduction is achieved of the use of volatile organic solvents, which represent the main waste from synthesis, both at laboratory and industrial scales. Furthermore, under solid state conditions very high concentration of the reactants is achieved and solvation phenomena do not exist, often leading to improved reaction rates.[32]

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[28] For a monograph, see: Ruijter, E.; Orru, R. V. A. *Synthesis of heterocycles via multicomponent reactions,* vols. 1 and 2*,* Springer Verlag, **2010** (*Topics in Heterocyclic Chemistry* series, volumes 23 and 25).

[29] For selected reviews of the synthesis of heterocycles using multicomponent reactions as key steps, see: (a) Sapi, J.; Laronze, J.-Y. *Arkivoc* **2004** (*vii*) 208; (b) D'Souza, D. M.; Mueller, T. J. J. *Chem. Soc. Rev*. **2007**, *36*, 1095; (c) Isambert, N.; Lavilla, R. *Chem. Eur. J.* **2008**, *14*, 8444; (d) Sunderhaus, J. D.; Martin, S.-F. *Chem. Eur. J*. **2009**, *15*, 1300; (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318; (f) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (g) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633; (h) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Res. Chem. Intermediat*. **2016**, *42*, 5147. (i) Haji, M. Beilstein *J. Org. Chem.* **2016**, *12*, 1269. (j) Mamaghani, M.; Hossein-Nia, R. *J. Heterocyclic Chem*. **2017**, *54*, 1700. (k) Ibarra, I. A.; Islas-Jacome, A.; Gonzalez-Zamora, E.; *Org. Biomol. Chem.* **2018**, *16*, 1402.

[30] Kaupp, G. *CrystEngComm*, 2006, **8**, 794.

[31] (a) Rodríguez, B.; Bruckmann, A.; Rantanen, T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 2213. (b) Stolle, A.; Szuppa, T.S.; Leonhardt, E. S.; Ondruschka, B. *Chem. Soc. Rev.* **2011**, *40*, 2317. (c) Stolle, A.; Ondruschka, B.; Krebs, A.; Bolm, C. Catalyzed Organic Reactions in Ball Mills, in P. G. Andersson (Ed.), Innovative Catalysis in Organic Synthesis: Oxidation, Hydrogenation, and C–X Bond Forming Reactions, Wiley-VCH, Weinheim, 2012. (d) James, S. L.C.; Adams, J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, L. A. G.; Parkin, I. P.; Shearouse, W. C.; J. W. Steed, J. W.; Waddell, D. C. *Chem. Soc. Rev*. **2012**, *41*, 413. (e) Bowmaker, G. A. *Chem. Commun*., **2013**, *49*, 334. (f) Wang, G.-W. *Chem. Soc. Rev*. **2013**, *42*, 7688. (g) Claramunt, R. M.; López, C.; Sanz, D.; Elguero, J. *Adv. Heterocycl. Chem*. **2014**, *112*, 117. (h) Hernández, J. G.; Vila-Ortiz, C. G.; Juaristi, E. in Comprehensive Organic Synthesis, Vol. 9, 2nd ed., (Eds. G.A. Molander, P. Knochel), Elsevier, Oxford, **2014**, p. 287. (i) Hernández, J. G.; Friščić, T. *Tetrahedron Lett*. **2015**, *56*, 4253. (j) Do, J. L.; Friščić, T. *ACS Cent. Sci*. **2017**, *3*, 13. (k) Achar, T. K.; A. Bose, A.; Mal, P. *Beilstein J. Org. Chem.* **2017**, *13*, 1907. (l) Tan, D.; Friščić, T. *Eur. J. Org. Chem.* **2017**, 18. (m) D. Margetić and V. Štrukil (Eds.), *Mechanochemical organic synthesis*. Elsevier, 2016. (n) Hernández, J. C. *Beilstein J. Org. Chem*., **2017**, *13*, 2372. (o) Andersen, J.; Mack, J. *Green Chem*. **2018**, *20*, 1435. (p) Howard, J. L.; Cao, Q.; Browne, D. L. *Chem. Sci.* **2018**, *9*, 3080. (q) Leonardi, M.; Villacampa, M.; Menéndez, J. C. *Chem. Sci.* **2018**, *9*, 2042.

[32] Hernández, J. C.; Bolm, C. *J. Org. Chem*. **2017**, *82*, 4007.

The first mechanochemical reaction known in the literature was achieved by grinding reactants together with a mortar and pestle (Figure 1.7a).[33] This approach is sometimes described as "grindstone chemistry" and can easily performed in any laboratory as it does not require specialized equipment. However, it is not easily reproducible because it depends on the physical strength of the operator. More recently, automated ball mills have been introduced for laboratory-scale synthesis. With these instruments it is possible to control the energy input by controlling the milling frequency, safety is improved because the reactions are run in a closed vessel (if compared with the mortar). These instruments can be classified into two main types: planetary ball mills, where the balls and reactants experience two types of movements, namely friction with the inside walls of the jar as a result of the centrifugal force and impact when they lift off and collide with the opposite wall (Figure 1.7b) and mixer (shaker) mills, where the jar is horizontal and swings back and forth to let the balls and reactants collide with the opposite wall of the jar (Figure 1.7c) and is usually described as high-speed vibration milling (HSVM) or high-speed ball milling (HSBM).

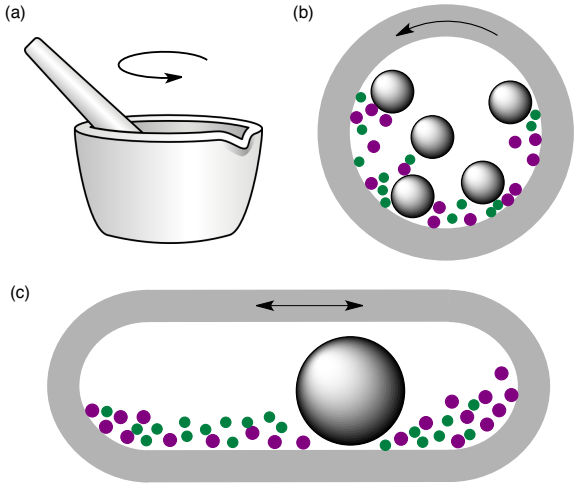
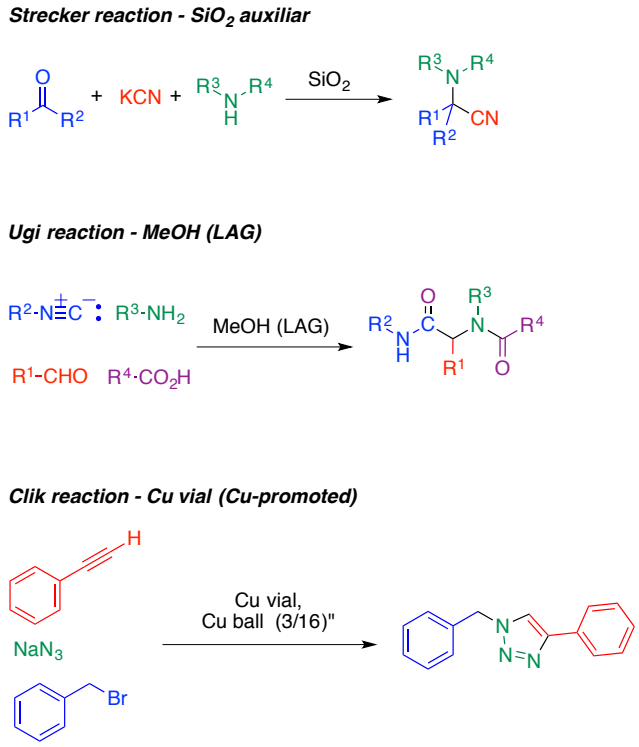


Figure 1.7

Besides the vibration frequency and the type of ball-mill, there are other important parameters to consider when planning a mechanochemical reaction, namely the material of the milling balls and jars, and the number of balls used. The material that makes up the jar or the balls sometimes promotes the reaction because of the release of catalytic particles of metal during milling; one example is the copper ball-promoted *click* reaction for the synthesis of triazoles, Scheme 3.[34] Coadjuvants are often useful to increase reactivity. For liquid starting materials, an inert solid such as NaCl, Al_2O_3 and SiO_2, that allows the transfer of mechanical energy, is normally included to increase

[33] For the historical development of mechanochemistry, see: Takacs, L. *Chem. Soc. Rev*. **2013**, *42*, 7649.
[34] Cook, T. L.; Walker, J. A.; Mack, J. *Green Chem*., **2013**, *15*, 617.

friction. Furthermore, SiO_2, retains water and generates mildly acidic conditions, thereby displacing condensation equilibrium in some cases, as in the case of the Strecker reaction.[35] Small amounts of liquids are also sometimes added to solid starting compounds to accelerate the reaction under solvent-free conditions, a process known as solvent-drop grinding (SDG) or liquid-assisted grinding (LAG); one example is the acceleration of the Ugi reaction by addition of a few drops of methanol.[36] When reaction acceleration is promoted by the use of a ionic liquid, it is defined as "ionic liquid-assisted grinding" (ILAG); polymer-assisted grinding (POLAG) is another recently introduced variation of mechanochemistry when a polymer promotes the reaction (Scheme 1.3).



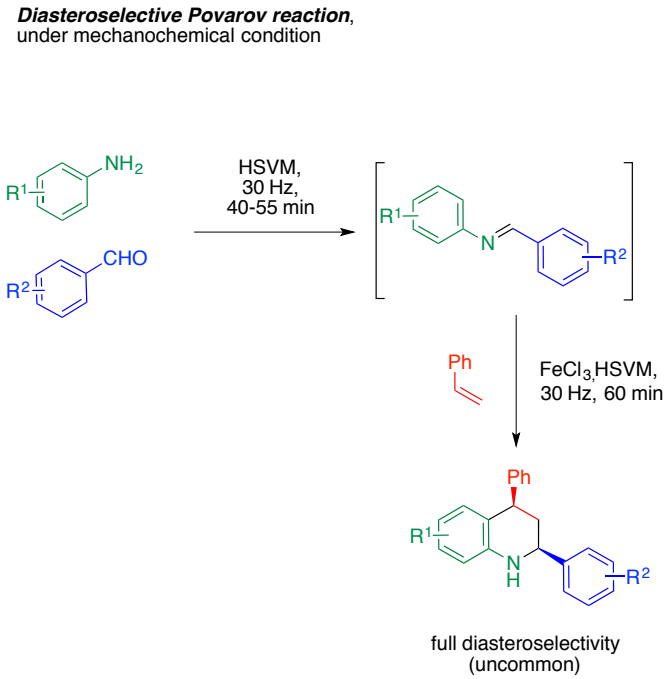
Scheme 1.3

Reactions performed under mechanochemical conditions may show improved selectivities. One example is the mechanochemical Povarov reaction, which furnishes *cis*-2,4-diphenyl-1,2,3,4-tetrahydroquinoline derivatives with complete diastereoselectivity (Scheme 1.4).[37] This full *cis*-selectivity is uncommon when acyclic olefins are employed in batch experiments.

[35] Dabral, S.; Turberg, M.; Wanninger, A.; Bolm, C.; Hernández, J. G. *Molecules*, **2017**, *22*, 146.

[36] Polindara-García, L. A.; Juaristi, E. *Eur. J. Org. Chem.*, **2016**, 1095.

[37] (a) Tan, Y.-J.; Zhang, Z.; Wang, F.-J.; Wu, H.-H.; Li, Q.-H. *RSC Adv.*, **2014**, *4*, 35635. (b) Tan, Y.-J.; Wang, F.-J.; Asirib, A. A.; Marwanib, H. D.; Zhang, Z. *J. Chin. Chem. Soc.*, **2017**, *64*.

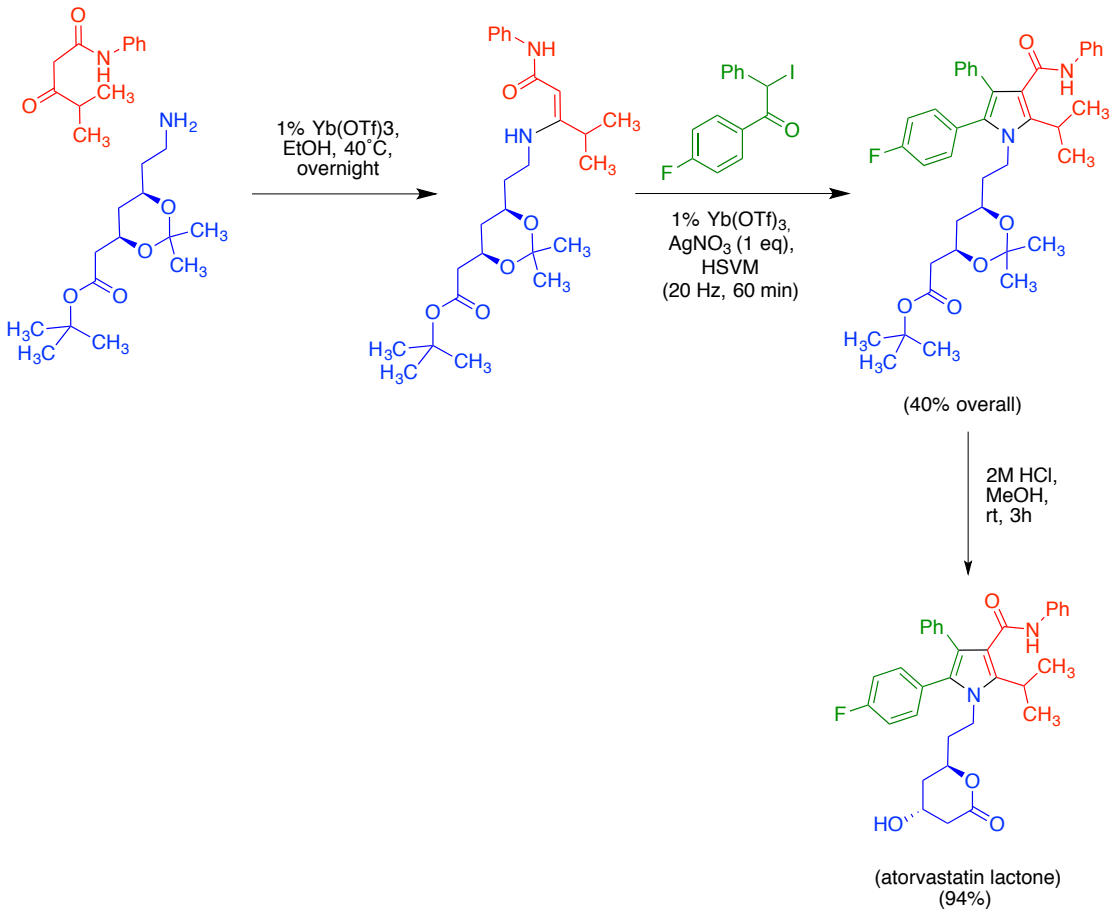


Scheme 1.4

An example of total synthesis with a mechanochemical key step has been published in 2014 by our group and it is involved a mechanochemical Hantzsch pyrrole synthesis as the key step for the preparation of the antihyperlipidemic agent atorvastatin (Scheme 1.5). This compound can be regarded the most important pyrrole-based synthetic molecule, having been the top-selling drug for more than a decade.[38]

[38] Estévez, V.; Villacampa, M.; Menéndez, J. C. *Org. Chem. Front.*, **2014**, *1,* 458.

Mechanochemical-based synthesis of Atorvastatin



Scheme 1.5

In conclusion, we can assert that the synergism of MCRs and mechanochemistry represents an efficient tool for the generation of several bonds in a single operation under sustainable conditions.

1.3. The Hantzsch pyrrole synthesis and its evolution

Pyrrole was first isolated in 1857 from the product of bone pyrolysis and is one of the most important and widespread simple heterocycles in natural products and drugs, being considered a privileged structure in medicinal chemistry.[39] Pyrrole is the central core of some key natural products including heme and chlorophyll, two pigments essential for life.[40] The red pigment prodigiosin, from bacteria belonging to the *Serratia* genus, has antibiotic properties and acts as a transporter of chloride anions and protons across phospholipid membranes thanks to the association of its protonated form with chloride anion, generating a lipophilic species.[41] Several bioactive secondary metabolites bear a pyrrole moiety, including pentabromopseudodiline and pioluteorine from bacterial origin, and some marine natural products that include the lamellarines, halitulin, nakamuric acid and marinopyrrole, the latter of which are important due to their activity against methicillin-resistant *Staphillococcus* strains.[42] A variety of marine organisms contain 3,4-diarylpyrrole compounds and among them storniamide and its O-methylated derivatives have shown activity as inhibitors of the multidrug resistance (MDR) phenomenon,[43] one of the main obstacles to anticancer chemotherapy. Many unnatural pyrrole derivatives showed also antimalarial[44] and antimycobacterial[45] activities and as inhibitors of HIV virus fusion[46] and hepatoprotectors[47]. Marketed pyrrole-based drugs include the anti-inflammatories tolmetin and zomepirac, the antihypercholesterolemic atorvastatin[48] and the anticancer sunitinib (Figure 1.8).

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[39] For reviews, see: (a) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma P.; *RSC Adv.* **2015**, *5*, 15233; (b) Gholap, S. S.; *Eur. J. Med. Chem,* **2016**, *110*, 13.

[40] Domagala, T.; Jarosz, M.; Lapkowski; *Eur. J. Med. Chem.* **2015**, *100*, 176.

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[45] Biava, M.; Porretta, G. C.; Poce, G.; Battilocchio, C.; Alfonso, S.; de Logu, A.; Manetti, F.; Botta, M.; *ChemMedChem,* **2011**, *4*, 593.

[46] Teixeira, C.; Barbault, F.; Rebehmed, J.; Liu, K.; Xie, L.; Lu, H.; Jiang, S.; Fan, B.; Maurel, F.; *Bioorg. Med. Chem.,* **2008**, *16*, 3039.

[47] Chin, Y. W.; Lim, S. W.; Kim, S.-H.; Shin, D.-Y.; Suh, Y.-G.; Kim, Y.-B.; Kim, Y. C.; Kim, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 79-81.

[48] For a review of atorvastatin, see: Roth, B. D. *Progress Med. Chem.* **2002**, *40*, 1-22.

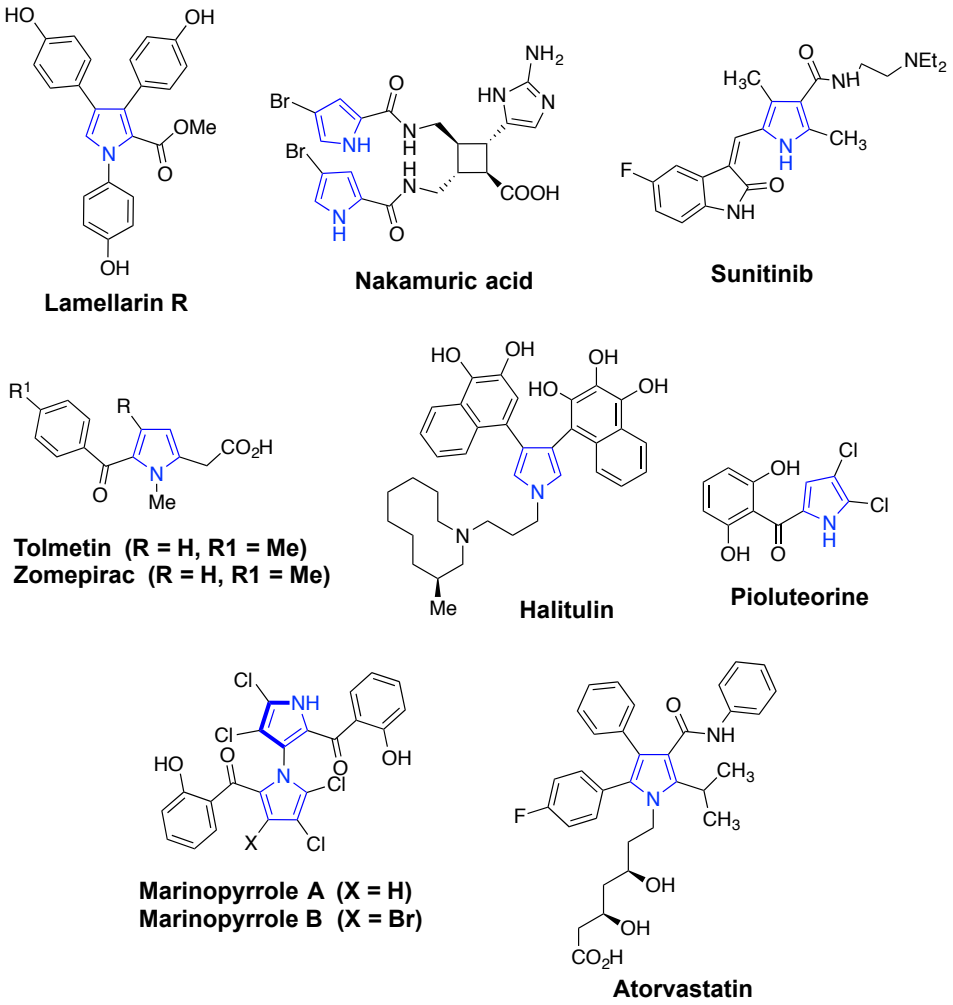


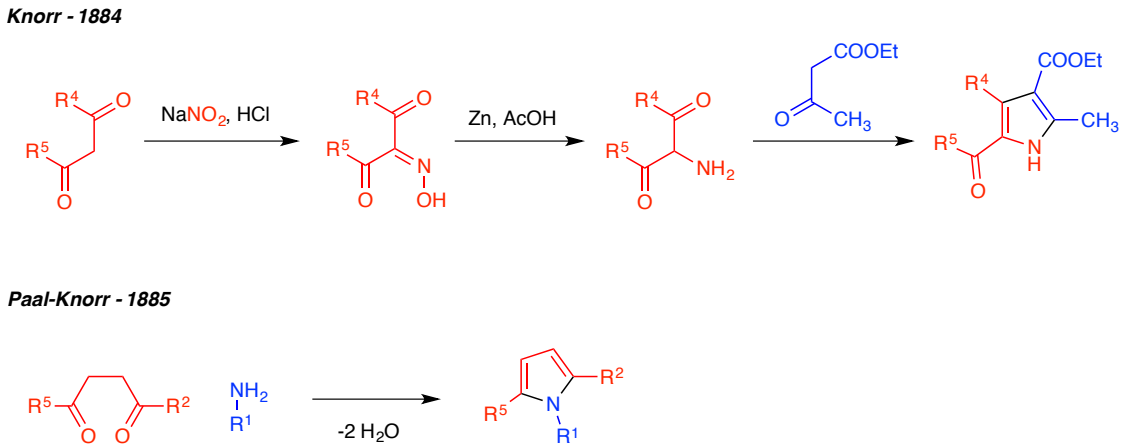
Figure 1.8

Pyrrole has also relevance in materials science and technology.[49] For instance, BODIPYs are an organoboron-derived family of compounds whose most important characteristic is a strong absorption in the UV and the emission of a very intense fluorescence. These derivatives of the 4,4-difluoro-4-boradipyrrin system have been employed as fluorescent dyes, among many other applications.[50]

Pyrrole syntheses are attained by different methodologies such as the classical Knorr and Paal-Knorr reactions (Scheme 1.6), but they are still far from being general and in many cases they stumble on regioselectivity problems and are not suitable for the preparation of polisubstituted derivatives.

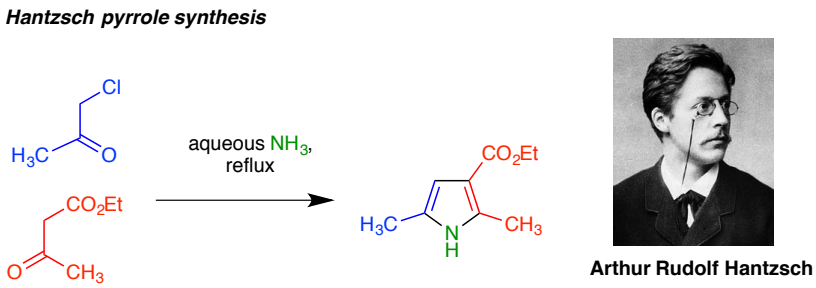
[49] For reviews of pyrrole derivatives in materials science, see: (a) Higgins, S. J. *Chem. Soc. Rev.* **1997**, *26*, 247-273. (b) Maeda, H. *Eur. J. Org. Chem*. **2007**, 5313-5325. (c) Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4981-4932. (d) Berlin, A.; Vercelli, B.; Zotti, G. *Polym. Rev*. **2008**, *48*, 493-530.

[50] For reviews, see: (a) Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4891. (b) Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Lip Yong Chung, L. Y.; Burgess, K. *Chem. Soc. Rev*. **2013**, *42*, 77. (c) Kulyk, B.; Taboukhat, S.; Akdas-Kilig, H.; Fillaut, J.-L.; Karpierz, M.; Sahraoui, B. *Dyes pigments* **2017**, *137*, 507. (d) Yuriy S. Marfin, Y. S.; Solomonov, A. V.; Timin, A. S.; Rumyantsev, E. V. *Curr. Med. Chem*. **2017**, *24*, 2745. (e) Solomonov, A. V.; Marfina, Y. S.; Rumyantsev, E. V. *Dyes pigments* **2019, *162*,** 517**.**



Scheme 1.6

The Hantzsch pyrrole synthesis was first described in 1890 by Arthur Rudolf Hantzsch in a brief note reporting the reaction between ethyl acetoacetate, ammonia and 1-chloropropan-2-one to yield the corresponding pyrrole derivative (Scheme 1.7).[51]

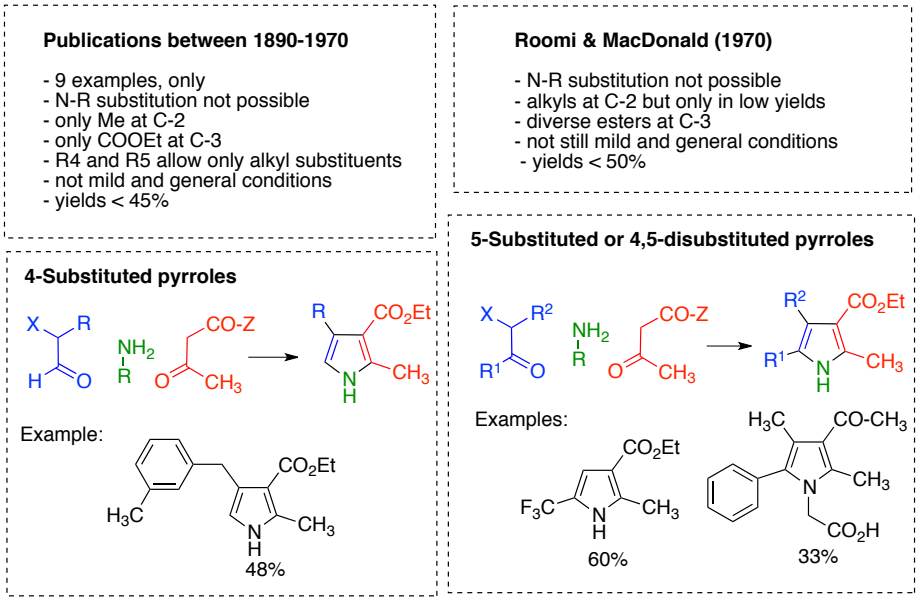


Scheme 1.7

In 1970, Roomi and MacDonald published a paper where they reported to have only been able to find eight additional examples of pyrroles made by the Hantzsch method in the 1890-1970 literature. Additionally, these reactions proceeded with yields below 45% and enabled few structural variations, which were limited to alkyl substituents at C-4 and C-5. The study of Roomi and MacDonald somehow extended the scope of the Hantzsch reaction and they were able to prepare compounds with substituents at C-2 different from methyl, and at C-3 with esters other than ethyl. Unfortunately, yields were still below 50% and the presence of substituents at the N-1 position was still not possible.[52]

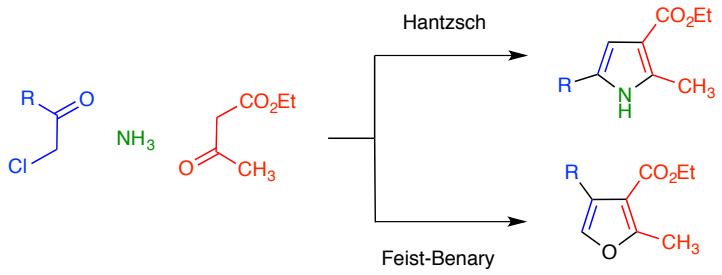
More recent versions of the Hantzsch pyrrole synthesis are still hampered by severe limitations in scope. Again, the yields generated are still moderate and almost never surpass 60%. A graphic summary of these precedents is shown in Scheme 1.8.

[51] Hantzsch, A. *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 1474.
[52] Roomi, M. W.; MacDonald, S. F. *Can. J. Chem*. **1970**, *48*, 1689.



Scheme 1.8

Compounds arising from competing side reactions have not been isolated often, although in some reactions involving the use of α-chlorocarbonyl as one of the starting materials, the Hantzsch reaction competes with a Feist-Benary furan synthesis, with no incorporation of the amine component into the product (Scheme 1.9).



Scheme 1.9

Because of the limitations of the conventional Hantzsch pyrrole synthesis in terms of low yields, harsh reaction conditions and lack of generality, the study and improvement of the Hantzsch pyrrole method is still challenging. A number of non-conventional variations of the reaction have been developed in recent years (Figure 1.9) and will be briefly summarized below.[53]

[53] For a review, see: Leonardi, M.; Estévez, V.; Villacampa, M.; Menéndez, J. C. *Synthesis*, **2019**, *51*, DOI: 10.1055/s-0037-1610320.

Hantzsch pyrrole synthesis, unconventional protocol

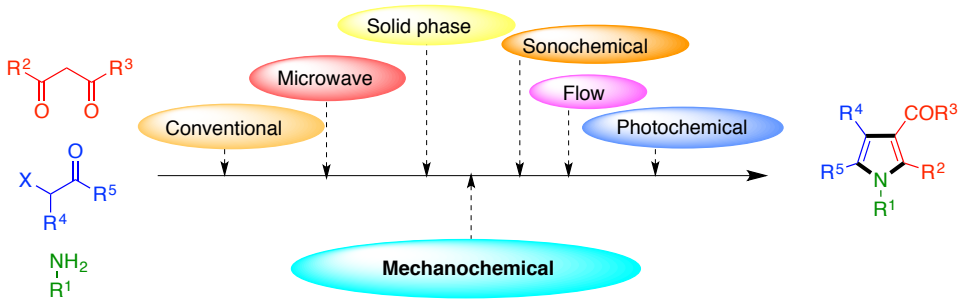
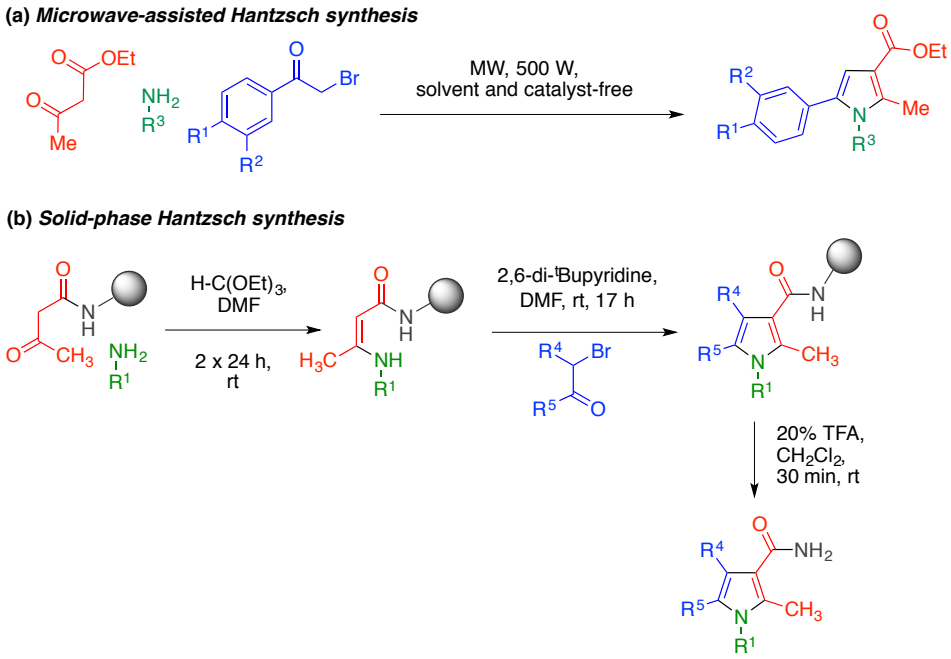


Figure 1.9

Zhao and co-workers in 2015 [54] reported that the irradiation of α-bromoacetophenones, ethyl acetoacetate and primary amines at 500 W in a pressurized microwave vial led to the generation of 5-arylpyrroles in good yields, without the need for any solvent or catalyst (Scheme 1.10a). The main features of the reaction are the tolerance of both electron-withdrawing and electron-releasing groups in the α-bromoacetophenone component and the use of alkyl, aryl and arylmethyl or heteroarylmethyl amines, although its scope was restricted regarding the β-dicarbonyl component.

In 1998 a solid-phase version of the Hantzsch pyrrole synthesis was proposed by Jung, using an acetoacetylated Rink resin (Scheme 1.10b). The reaction of this modified resin with primary amines afforded the corresponding β-enaminoamides. The following step was the reaction with α-halocarbonyl derivative to give desired pyrroles. In the last step the final product so obtained was liberated from the solid support *via* acid hydrolysis. The method only allows the preparation of pyrrole-3-carboxamide derivatives, which were isolated in excellent purities but unfortunately no yields were reported.[55]

[54] Kan, W.; Jing, T.; Zhang, X.-H.; Zheng, Y.-J.; Chen, L.; Zhao, B. *Heterocycles* **2015**, *91*, 2367.
[55] Trautwein, A. W.; Süssmuth, R. D.; Jung, G. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2381-2384

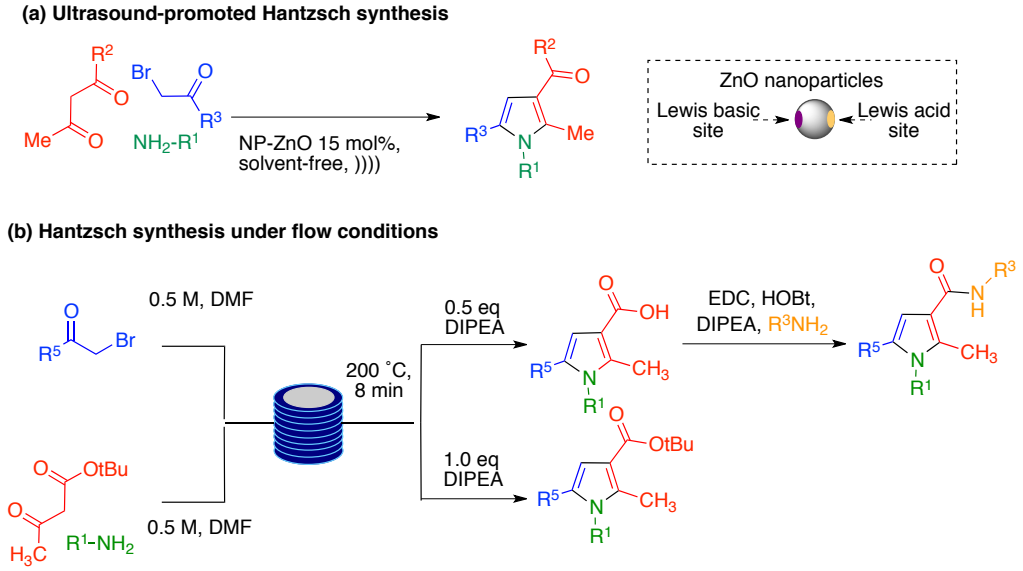


Scheme 1.10

Shahvelayati *et al.* reported an efficient Hantzsch pyrrole synthesis under solvent-free conditions promoted by irradiation using an ultrasonic cleaner (frequency, 60 kHz and intensity, 285 W), and catalysed by ZnO nanoparticles prepared in an ionic liquid (Scheme 11a). The ZnO-NPs employed in this version bring both Lewis acid sites (Zn^{2+}) and Lewis basic sites (O^{2-}) and they can be easily recycled and reused upon three time maintaining the same efficiency.[56]

Cosford showed that a one-pot synthesis of pyrrole-3-carboxylic acid derivatives is possible by reaction of *tert*-butyl acetoacetate, primary amines and 2-bromoketones at 200 °C during 8 min in continuous flow (Scheme 1.11b). The *in situ* hydrolysis of the *tert*-butyl ester groups led to the generation of the corresponding carboxylic acid derivatives that by a subsequent coupling of with diverse amines can easily give pyrrole-3-carboxamide compounds.[57]

[56] Shahvelayati, A. S.; Sabbaghan, M.; Banihashem, S. *Monatsh. Chem.* **2017**, *148*, 1123.
[57] Herath, A.; Cosford, N. D. P. *Org. Lett*. **2010**, *12*, 5182.



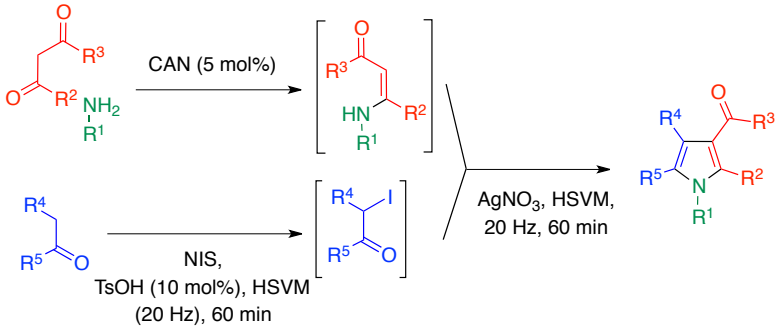
Scheme 1.11

Finally, our group has developed a mechanochemical multicomponent reaction based on the Hantzsch pyrrole synthesis that constitutes the foundation of this thesis. In the context of our interest in the development of new synthetic methodology based on the use of Ce(IV) ammonium nitrate (CAN) as a Lewis acid catalyst,[58] we investigated the Hantzsch reaction in ethanol between β-dicarbonyl compounds, primary amines and α-iodoketones in the presence of CAN and silver nitrate, which was necessary in order to prevent reductive dehalogenation of the starting iodoketones by the HI liberated in the alkylation step. Later, we discovered that the reaction could be also performed in a solvent-free fashion, under high-speed vibration milling conditions (HSVM) in a mixer mill working at 20 Hz with the use of a single zirconium oxide ball 20 mm in diameter. Furthermore, the mechanochemical version of the Hantzsch pyrrole synthesis could be telescoped with the synthesis of the starting α-iodoketone from the corresponding ketone and *N*-iodosuccinimide (NIS). This solvent-free method afforded considerably higher yields of pyrroles than previous versions of the Hantzsch reaction, in spite of comprising an additional step, and was far broader in scope (Scheme 1.12).[59] By starting from cyclic ketones, the reaction was extended to the synthesis of fused pyrrole derivative.[60]

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

[59] Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun.* **2013**, *49*, 591.

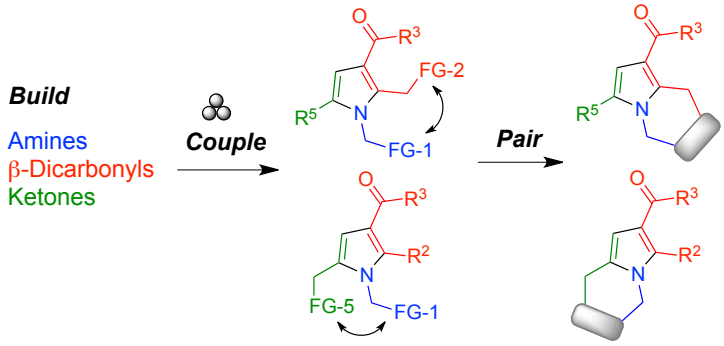
[60] Estévez, V.; Sridharan, V.; Sabaté, S.; Villacampa, M.; Menéndez, J. C. *Asian J. Org. Chem.* **2016**, *5*, 652.


CAN (5 mol%)
NIS,
TsOH (10 mol%), HSVM
(20 Hz), 60 min
AgNO3, HSVM,
20 Hz, 60 min

Scheme 1.12

2. Objectives

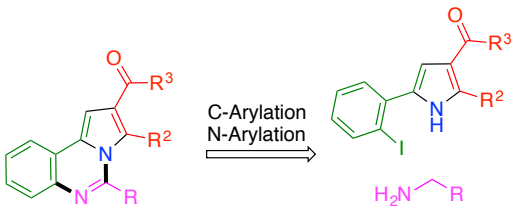
This thesis is based on the use of pyrrole, a well-known privileged structure, as the central core on which to build a variety of DOS libraries using the *build-couple-pair* approach. In this general context, the goals of the first part of the thesis involve the use of a mechanochemical multicomponent reaction as the *couple* phase and a number of cyclization processes as the *pair* phase to generate fused heterocyclic frameworks bearing a bridgehead nitrogen atom. The second part of the thesis is focused on the application of the same principles to the preparation of libraries of medium-sized rings and macrocycles.



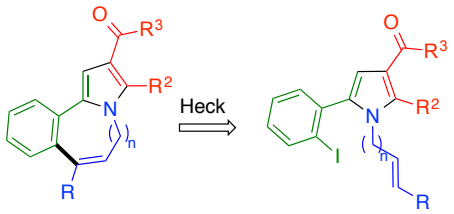
More specifically, the objectives that have been pursued are:

1. Adaptation of a known, in house-developed mechanochemical multicomponent reaction to the preparation of pyrrole derivatives bearing functional groups that allow suitable complexity-generating reactions at the *pair* stage at their N-1, C-2 and C-5 positions. The mechanochemical pyrrole synthesis also needed to be adapted to the preparation of symmetrical molecules containing two pyrrole units at the end of a spacer.

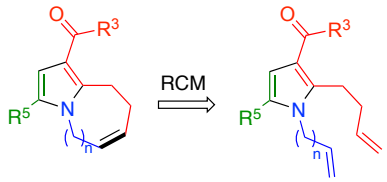
2. Synthesis of fused pyrrole derivatives based on transition metal-catalyzed reactions, including cross-coupling and metathesis. In particular, the following transformations were considered of interest:
    a) Synthesis of pyrrolo[1,2-*c*]quinazolines by combination of C-arylation and N-arylation processes.



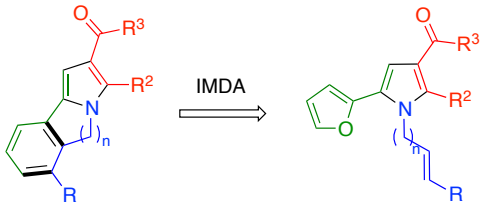
b) Synthesis of benzo[*c*]pyrrolo[1,2-*a*]azepine and frameworks by intramolecular Heck reactions.



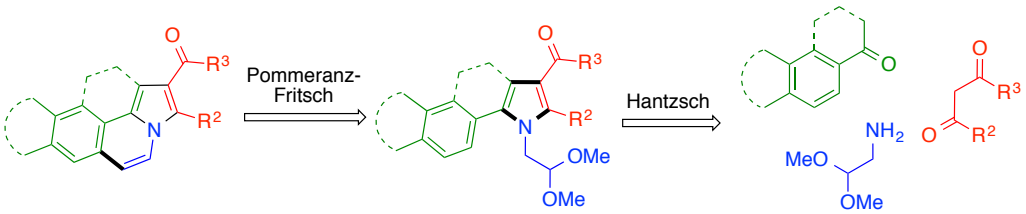
c) Synthesis of pyrrolo[1,2-*a*]azepine and pyrrolo[1,2-*a*]azocine frameworks by ring-closing metathesis.



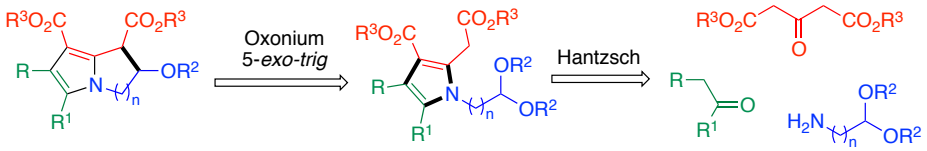
3. Synthesis of pyrrolo[2,1-*a*]isoindole and pyrrolo[2,1-*a*]isoquinoline frameworks by intramolecular Diels-Alder reactions.



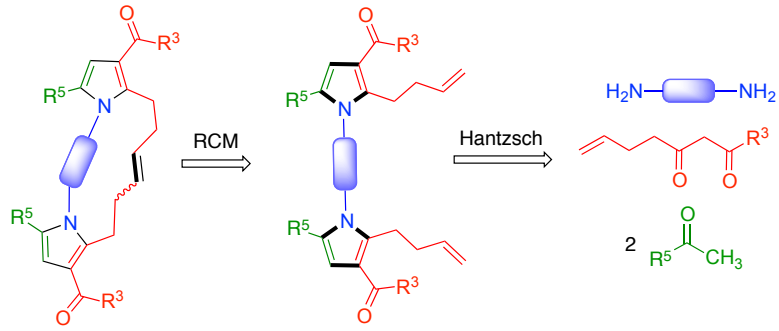
4. Investigation of ring-formation processes on pyrrole-derived substrates *via* the generation of oxonium intermediates. Two possibilities were studied:
   a) Cyclization onto a C-5 aryl substituent, using a transformation related to the Pommeranz-Fritsch isoquinoline synthesis.



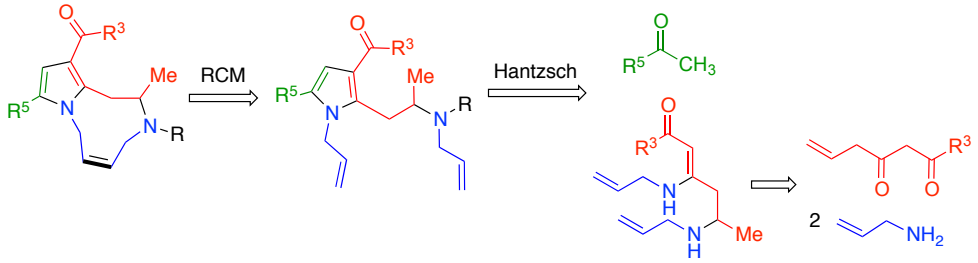
   b) Cyclization of an oxonium species from an acetal under Noyori-type conditions onto a C-2 active methylene group adjacent to an ester *via* the formation of a ketene acetal intermediate.



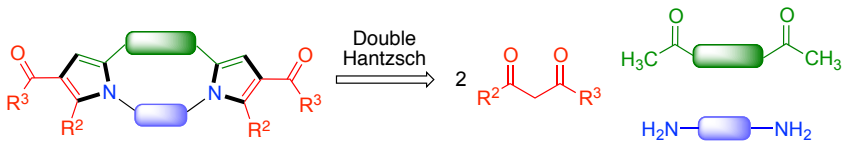
5. Synthesis of macrocycles based on ring-closing metathesis reactions, using as starting materials symmetrical bis-pyrrole derivatives.



6. Synthesis of diaza medium-sized rings by ring-closing metathesis. The starting pyrroles would be constructed by the Hantzsch method from β,δ-diallylaminoenones, which would in turn be available *via* an enaminone formation/double bond isomerization/aza Michael domino sequence.



7. Preparation of macrocycles based on a double Hantzsch pyrrole synthesis, with one of these reactions serving as the macrocyclization event.



8. Study of the libraries synthesized by the above methods using high-throughput screening methodologies. These studies were performed thanks to our collaboration with the Lilly Open Innovation in Drug Discovery (OIDD) program.

9. Finally, as part of the requirements for the *International Ph D Label*, I carried out a three-month stay at the group of Professor Steven Ley at the Department of Chemistry, Cambridge University, working on the use of photochemical homologation reactions for the preparation of aliphatic aldehydes under flow chemistry conditions.

3. The *build* phase: Synthesis of starting pyrroles

3.1. Synthesis of compounds with a single pyrrole ring

The ability to synthesize starting pyrroles bearing suitable functionalities is crucial to the success of our DOS project. Hence, we needed to verify whether the mechanochemical multicomponent pyrrole synthesis developed by our group was compatible with the functionalities planned to be present at their N-1, C-2 and C-5 positions in order to carry out complexity-generating reactions at the final *pair* stage, as summarized in Figure 3.1.

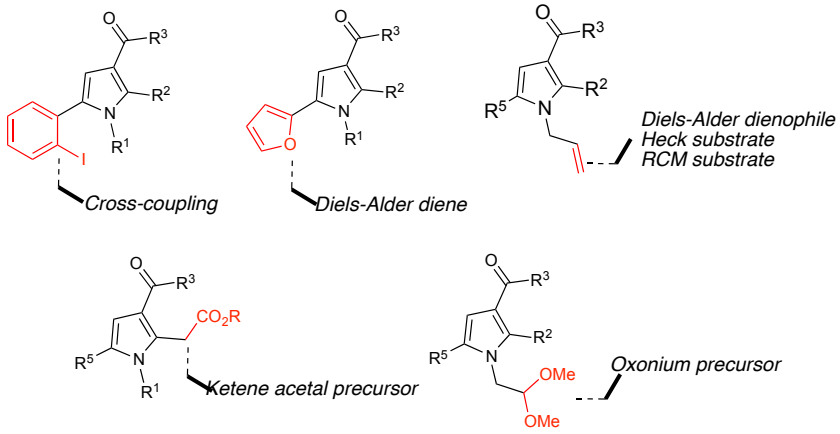


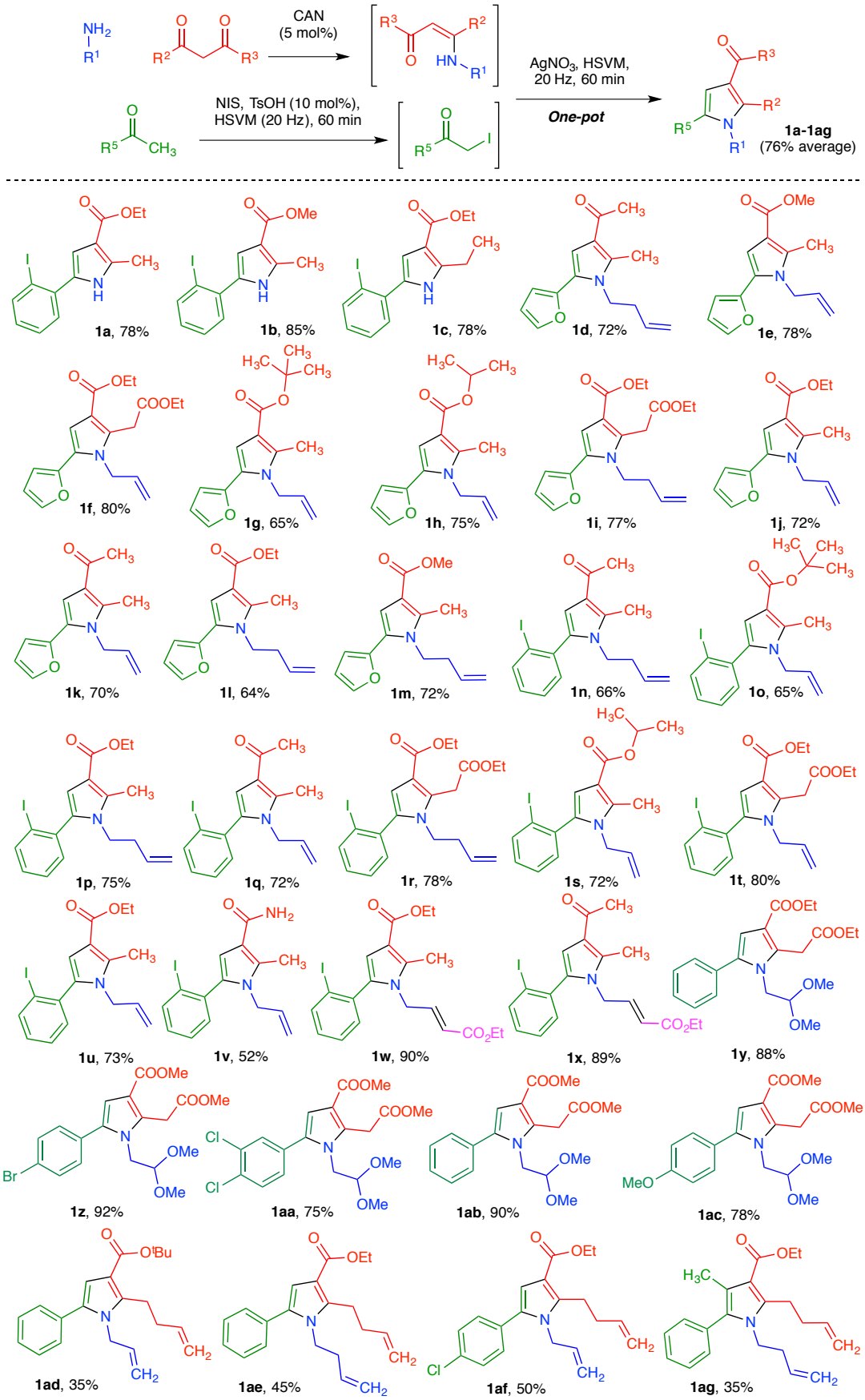
Figure 3.1

The introduction of some of these groups could be in principle troublesome for a variety of reasons such as the steric hindrance due to the *o*-iodophenyl substituent or the potential low stability of the furan ring or the acetal function under the reaction conditions.[61] Fortunately, these concerns proved to be largely unfounded and the usual reaction conditions of our previously established method gave good results. Thus, the primary amine and β-dicarbonyl components were pre-mixed in the presence of Ce(IV) ammonium nitrate or indium trichloride (5%) as catalysts to form the corresponding β-enaminone or β-enaminoester. This mixture was added to a 20 mL milling jar containing the suitable arylcarbonylmethyl iodides, and after addition of an additional amount of catalyst (5%), one equivalent of silver nitrate and one zirconia ball, the mixture was shaken in an horizontal ball mill for 1 hour at 20 Hz, affording the target pyrroles **1a**-**1x**, usually in good yields (Scheme 3.1). In some cases (pyrroles **1y**-**1ag**), the iodides could prepared *in situ* by a mechanochemical method involving the reaction of the corresponding ketones with N-iodosuccinimide in the presence of *p*-toluenesulfonic acid, while for the other examples (pyrroles **1a**-**1x**) the iodide had to be synthesized in a separate step from the ketone, iodine and copper oxide.[62]

---

[61] As an example of such transformations, CAN is an excellent catalyst for the hydrolysis of acetals and ketals. See: Maulide, N.; Vanherck, J.-C.; Gautier, A.; Markó, I. E. *Acc. Chem. Res.*, **2007**, *40*, 381.

[62] Yin, G.; Gao, M.; She, N.; Hu, S.; Wu, A.; Pan, Y. *Synthesis,* **2007**, 3113.


CAN
(5 mol%)
NIS, TsOH (10 mol%),
HSVM (20 Hz), 60 min
AgNO3, HSVM,
20 Hz, 60 min
One-pot
1a-1ag
(76% average)
1a, 78%
1b, 85%
1c, 78%
1d, 72%
1e, 78%
1f, 80%
1g, 65%
1h, 75%
1i, 77%
1j, 72%
1k, 70%
1l, 64%
1m, 72%
1n, 66%
1o, 65%
1p, 75%
1q, 72%
1r, 78%
1s, 72%
1t, 80%
1u, 73%
1v, 52%
1w, 90%
1x, 89%
1y, 88%
1z, 92%
1aa, 75%
1ab, 90%
1ac, 78%
1ad, 35%
1ae, 45%
1af, 50%
1ag, 35%

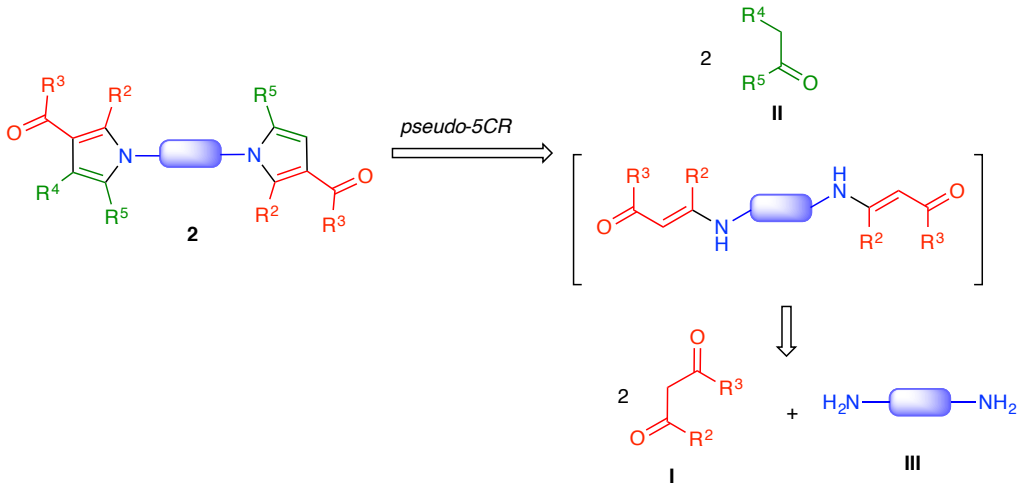
Scheme 3.1

3.2. Synthesis of symmetrical molecules containing two or three pyrrole units via mechanochemical pseudo-five(seven)-component reactions

The mechanochemical pyrrole synthesis also needed to be adapted to the preparation of symmetrical molecules containing two pyrrole units at the end of a spacer, which were necessary for subsequent work on macrocycle synthesis.

Furthermore, we considered such compounds to be of interest in themselves as part of our diversity-oriented synthesis libraries. Indeed, symmetrical molecules consisting of two or more pharmacophoric units joined by a spacer are of relevance in drug discovery, and some examples of therapeutic targets in which such bivalent symmetrical ligands have proved useful include HIV protease,[63] the PrP^c cellular prion protein [64] and the transient receptor potential melastatin 8 (TRPM8) channel receptor.[65] The importance of these molecules can be explained by the existence of many symmetrical drug targets, composed by two or more identical subunits. The development of new efficient synthetic procedures to obtain this class of symmetrical architectures is still challenging and relies, normally, on multistep sequences.[66]

We realized that our pyrrole synthesis could be adapted to this task by applying a pseudo-five component process comprising two concomitant Hantzsch-like reactions starting from two equivalents of β-dicarbonyl compounds **I**, two equivalents of aryl ketones **II** and one equivalent of diamine **III**. The route to bis-pyrrole derivatives **2** by this disconnection is summarized in Scheme 3.2.



Scheme 3.2

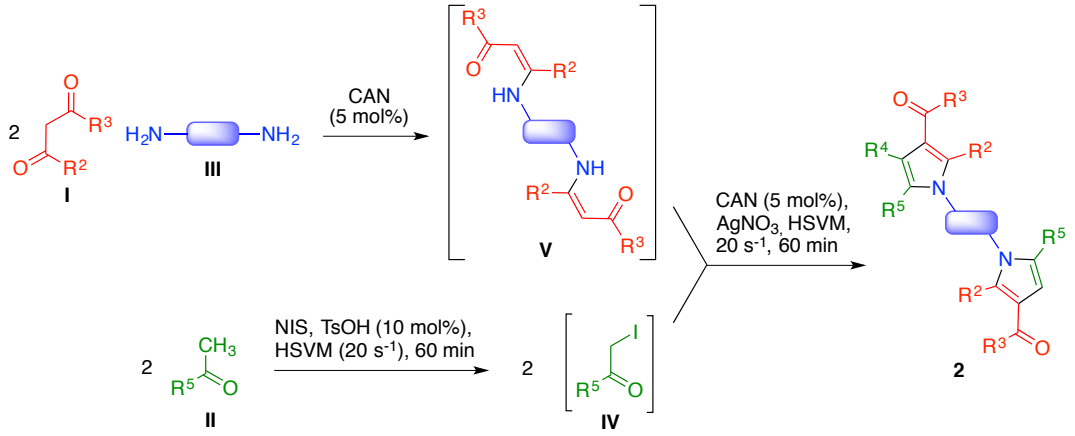
[63] Lv, Z.; Chu, Y.; Wang, Y. *HIV AIDS (Auckl).*, **2015**, *7*, 95.

[64] Staderini, M.; Legname, G.; Bolognesi, M. L.; Menéndez, J. C. *Curr .Top. Med. Chem.*, **2013**, *13*, 2491.

[65] De Petrocellis, L.; Arroyo, F. J.; Orlando, P.; Schiano Moriello, A.; Vitale, R. M.; Amodeo, P.; Sánchez, A.; Roncero, C.; Bianchini, G.; Martín, M. A.; López-Alvarado, P.; Menéndez, J. C. *J. Med. Chem.*, **2016**, *59*, 5661.

[66] Bitzer J.; Streibel M.; Langer H.-J.; Grond S. *Org. Biomol. Chem.*, **2009**, *7*, 444.

As in the case of compounds **1**, containing a single pyrrole ring, our protocol started with the treatment of aromatic ketones **II** with *N*-iodosuccinimide in the presence of toluenesulfonic acid under high-speed vibration milling during 1 h to afford the α-iodoketones **IV** which were not isolated in order to achieve a telescoped procedure. The suitable commercial β-dicarbonyl compound **I** and α,ω-diamine **III** together with a catalytic amount of Ce(IV) ammonium nitrate, which had been pre-mixed for 30-60 min (monitored by TLC) to ensure the complete generation of the intermediate bis-β-enaminones **V**, were added to the milling jar together with an additional 5% of CAN and one equivalent of silver nitrate, and the mixture was again submitted to milling for an additional hour to generate the final products (Scheme 3.3). The proof for the formation of species **IV** and **V** relies on the facts that: (i) they could be isolated by suitably interrupting our process and (ii) they reacted under our usual conditions to give compounds **2**.



Scheme 3.3

In the case of compounds **2d, 2g, 2j, 2l, 2m** and **2o**, it was not possible the iodination promoted by the ball mill and it has been achieved with obtaining the α-iodoketones **IV** by treatment of **II** with I_2 and CuO in a separate step.

The scope of this *pseudo*-5CR is summarized in Figure 3.2. Beyond the simple polymethylene spacers, in order to increase the molecular diversity and we studied the inclusion of spacer chains containing nitrogen atoms (**2a**-**2g**, **2i**). The use of N^1-(2-aminoethyl)ethane-1,2-diamine as the starting material was also possible, without interference from the secondary amino group in spite of its nucleophilicity, to give compound **2h**. Furthermore, some tetramethyldisiloxane derivatives (**2k**-**2o**) were prepared in view of the current interest in silicon-containing compounds for drug discovery applications, which has led to the "silicon switch" approach, also defined as sila-subsitution. It represents a novel source of chemical diversity in drug design. Examples described in literature for the demonstration of the efficiency of the carbon/silicon switch strategy are sila-venlafaxine, disila-bexarotene and sila-

haloperidol, as well as sila-analogues of venlafaxine, a serotonin/noradrenaline reuptake inhibitor, haloperidol, a dopamine antagonist, and bexarotene, a retinoid agonist.[67] Regarding the pyrrole rings, they were generally methyl-substituted at C-2,

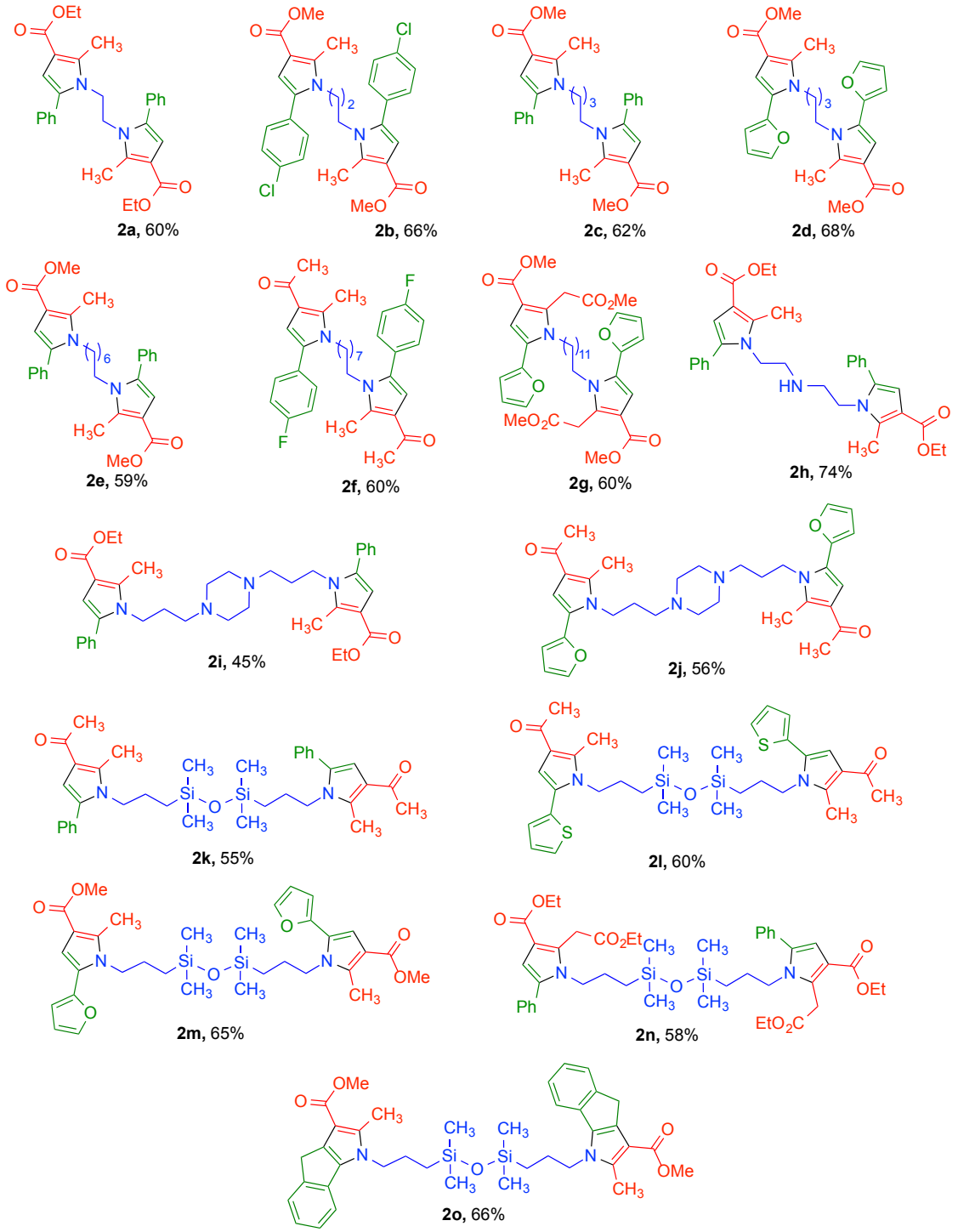
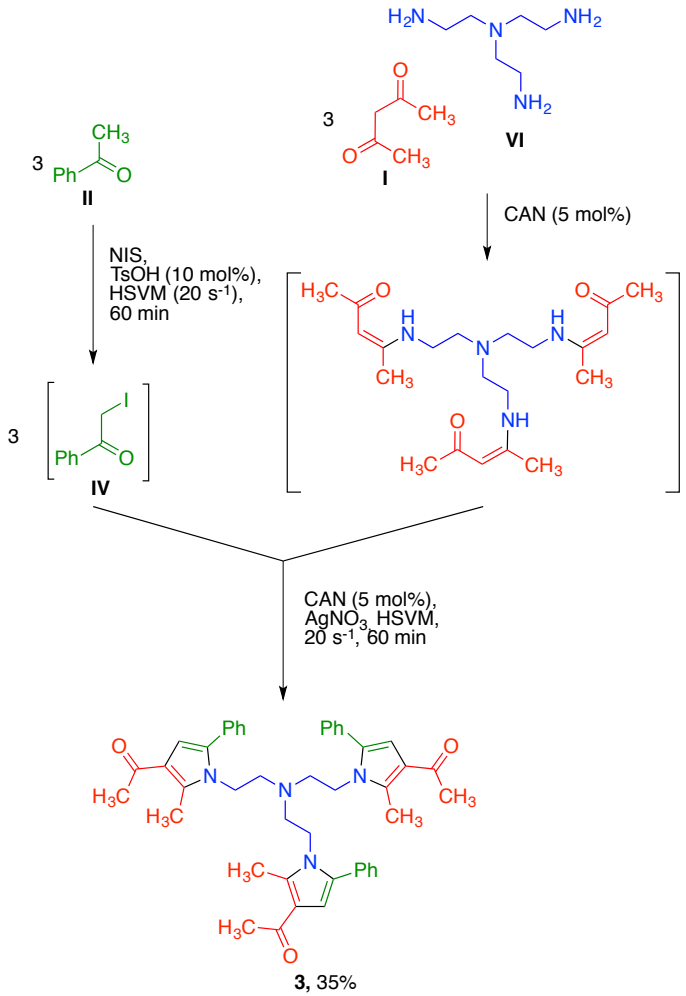


Figure 3.2

[67] For reviews of the "silicon-switch" approach, see: (a) Mills, J. S.; Showell, G. A. *Expert Opin. Investig. Drugs,* **2004**, *13*, 1149; (b) Gately, S.; West, R. *Drug Dev. Res.,* **2007**, *68*, 156; (c) Franz, A. K.; Wilson, S. O.; *J. Med. Chem.,* **2013**, *56*, 388.

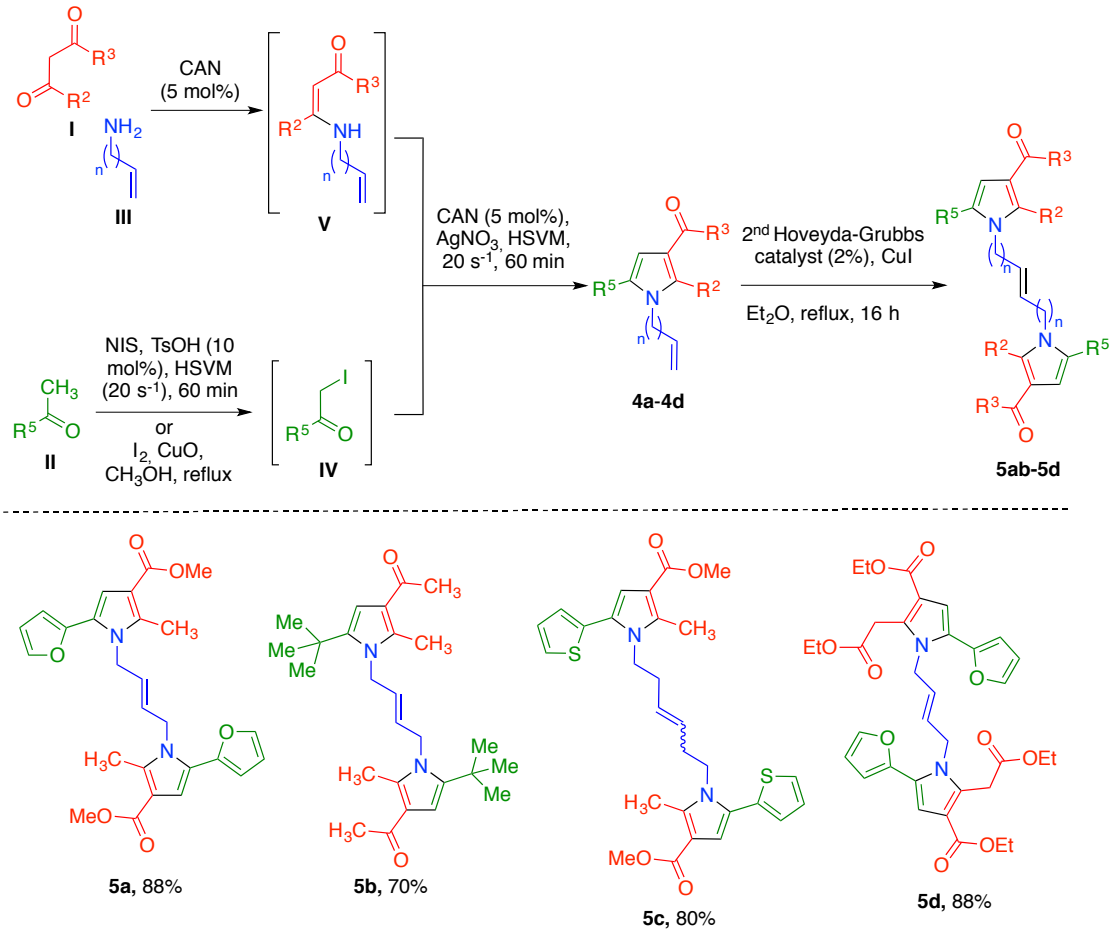
but the attachment of functional groups to the methyl substituent was also possible, as shown by the preparation of compounds **2g** and **2n**. Ketone (compounds **2f** and **2j**-**2l**) and ester functions (compounds **2a**-**2e**, **2g**-**2i** and **2m**-**2o**) could be present at C-3, although an attempt to introduce an amide was unsuccessful. At the C-5 position, a variety of aromatic and heteroaromatic rings were tolerated. Furthermore, the synthesis of compound **2o** from 1-indanone proved the possibility to prepare systems containing two fused pyrrole moieties linked by a spacer.

We also investigated the generation of a *ter*-pyrrole derivative by employing triamine **VI** as the starting material. The synthesis of compound **3** was achieved *via* a *pseudo*-seven-component reaction between **VI**, three equivalents of 1,3-pentanedione and three equivalents of acetophenone, as shown in Scheme 3.4. While the overall yield was only moderate, it has to be taken into account that the preparation of **3** involves 12 individual steps, with a linear sequence comprising 9, and thus the average yield is 89% per step. In view of its high functionalization, compound **3** can be viewed as a potential precursor to heterocyclic dendrimeric structures.



Scheme 3.4

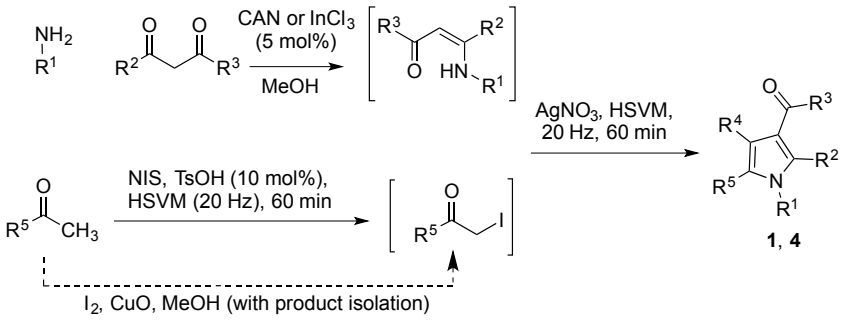
Finally we studied an alternative method for the generation of dimeric pyrrole-based architectures with partially saturated spacers that are not accessible by the previous route. To this end, we planned homodimerization reactions of 2-allyl- and 2-homoallylpyrroles *via* cross-metathesis. The starting materials for this study (compounds **4**) were readily prepared under the conditions for single-ring pyrrole derivatives described in the previous Section and, as shown in Scheme 3.5, they were uneventfully transformed into the target compounds **5**. The dimerization step took place in the presence of the second-generation Hoveyda-Grubbs catalyst and copper(I) iodide (Scheme 3.5). Interestingly, the reactions starting from 1-allylpyrroles gave a single stereoisomer at the central double bond, which was assumed to be *E* (compounds **5a**, **5b** and **5d**), while compound **5c**, obtained from a 1-homoallyl derivative, was isolated as a 1:1 *E*/*Z* mixture that could not be separated.



Scheme 3.5

3.3. Experimental section

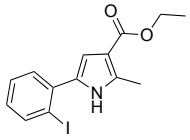
3.3.1. General procedure for the synthesis of pyrroles 1a-1v, 1y-1ag and 4a-d



Method A: The suitable ketone (1 eq.), *N*-iodosuccinimide (NIS, 1 eq.) and *p*-toluenesulphonic acid (PTSA, 10 mol%) were added to a ball mill vessel, along with a zirconium oxide ball. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 s^{-1} for 60 min at room temperature to generate the iodinated product. Then, a mixture of the suitable amine (1.3 eq.), the suitable β-dicarbonyl compound (1 eq.) and $InCl_3$ or CAN (5 mol%), previously stirred at room temperature during 30 min, and silver nitrate (1 eq.) were added to the vessel. The reaction was subjected to the vibratory movement at the same frequency for 60 min. Then, the reaction vessel was cleansed with ethyl acetate and the suspension was filtered to remove the silver iodide precipitate. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate afforded the desired pyrrole derivatives. Compounds **1e** and **1f** were known in the literature.[68]

Method B: In some cases where the mechanochemical protocol did not work (synthesis of pyrroles **1a**-**1x**), the α-iodoketone was prepared under literature[69] conditions, as follows: To a solution of the suitable ketone (1 eq) in anhydrous methanol, iodine (1 eq) and cupper(II) oxide (1 eq) were added. The mixture was stirred at room temperature for 5 min and, then, refluxed until no starting material was detected by TLC. The reaction was cooled, filtered and the solvent was removed. The residue was dissolved in ethyl acetate (10 mL) and washed with a 10% solution of $Na_2S_2O_3$ (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried over anhydrous sodium sulphate and the solvent was evaporated. The a-iodoketones thus obtained were used in the next reaction without further purification.

Ethyl 5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1a)

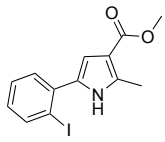


Prepared from *o*-iodoacetophenone (1 mmol) and ethyl 3-aminocrotonate (1.5 mmol); yield: 277 mg (78%); dark orange solid; mp: 109-111 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.65 (br s, 1H), 7.95 – 7.92 (m, 1H), 7.41 – 7.33 (m, 2H), 7.03 – 6.96 (m, 1H), 6.80 (d, *J* = 3.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 140.2, 136.9, 135.5,

[68]For reviews, see: (a) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.,* **2006**, *45*, 6086; (b) Gradillas, A.; Pérez-Castells, J. *Top. Heterocycl. Chem.,* **2015**, *47*, 245.
[69]Yin, G.; Gao, M.; She, N.; Hu, S.; Wu, A.; Pan, Y. *Synthesis,* **2007**, 3113.

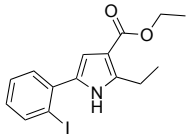
130.4, 130.4, 128.8, 128.3, 112.5, 110.9, 96.2, 59.5, 14.5, 13.4; IR (neat) ν: 3292.2 (N-H), 2977.7 (C-H), 1670.6 (C=O), 1233.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{14}H_{14}INO_2$: C, 47.34; H, 3.97; N, 3.94; found: C, 47.16; H, 3.61, N, 4.65.

Methyl 5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1b)



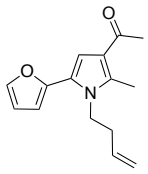
Prepared from *o*-iodoacetophenone (1 mmol) and methyl 3-aminocrotonate (1.5 mmol); yield: 289 mg (85%); dark orange solid; mp: 144-146 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.66 (br s, 1H), 7.95 – 7.92 (m, 1H), 7.39 – 7.36 (m, 2H), 7.03 – 6.96 (m, 1H), 6.79 (d, *J* = 3 Hz, 1H), 3.84 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 165.9, 140.3, 136.8, 135.7, 130.5, 130.3, 128.9, 128.3, 112.2, 110.9, 96.3, 50.9, 13.3; IR (neat) ν: 3298.6, 3292.1 (N-H), 2921.8 (C-H), 1678.9 (C=O), 1233.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{13}H_{12}INO_2$: C, 45.77; H, 3.55; N, 4.11; found: C, 45.89; H, 3.35; N, 4.51.

Ethyl 2-ethyl-5-(2-iodophenyl)-1*H*-pyrrole-3-carboxylate (1c)



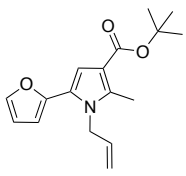
Prepared from *o*-iodoacetophenone (1 mmol), ammonium chloride (4.5 mmol) and ethyl propionylacetate (1.5 mmol); yield: 288 mg (78%); yellowish solid; mp: 78-80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.63 (br s, 1H), 7.96 – 7.93 (m, 1H), 7.46 – 7.35 (m, 2H), 7.05 – 6.98 (m, 1H), 6.80 (d, *J* = 3 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.09 (q, *J* = 7.3 Hz, 2H), 1.42 – 1.33 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3, 141.3, 140.3, 136.9, 130.4, 130.2, 128.8, 128.4, 111.7, 110.9, 95.9, 59.4, 20.6, 14.5, 13.4; IR (neat) ν: 3294.2 (N-H), 2977.3, 2922.5 (C-H), 1670.9, (C=O), 1233.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{16}INO_2$: C, 48.80; H, 4.37; N, 3.79; found: C, 49.00; H, 4.77; N, 3.89.

1-(1-(But-3-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (1d)



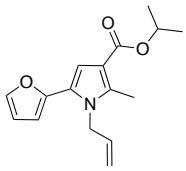
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), butenamine (1.95 mmol) and acetylacetone (1.5 mmol); yield: 175 mg (72%); yellowish solid; mp: 117°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.73 (s, 1H), 6.49 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.42 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.91 – 5.64 (m, 1H), 5.15 – 5.09 (m, 1H), 5.07 – 5.06 (m, 1H), 4.11 – 4.05 (m, 2H), 2.64 (s, 3H), 2.44 (s, 3H), 2.48 – 2.39 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 146.6, 141.8, 136.6, 133.7, 123.0, 120.8, 117.6, 111.1, 110.9, 107.2, 44.0, 34.6, 28.5, 11.8; IR (neat) ν: 1699.7 (C=O), 1236.6 (C-O), 1075.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{17}NO_2$: C 74.05, H 7.04, N 5.76; found: C 73.07, H 7.14, N 5.67.

^{t}Butyl 1-allyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (1g)



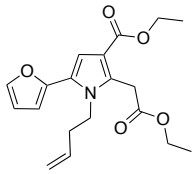
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), allylamine (1.95 mmol) and tert-butyl acetoacetate (1.5 mmol); yield: 186 mg (65%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 1H), 6.77 (s, 1H), 6.45 – 6.43 (m, 1H), 6.38 – 6.36 (m, 1H), 6.00 – 5.89 (m, 1H), 5.20 – 5.16 (m, 1H), 4.90 – 4.82 (m, 1H), 4.64 – 4.60 (m, 2H), 2.55 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 164.9, 146.7, 141.7, 136.9, 133.0, 123.3, 116.4, 113.8, 111.0, 110.4, 106.9, 79.4, 46.9, 28.5, 11.0; IR (neat) ν: 2971.9, 2916.8, 2848.5 (C-H), 1699.3 (C=O), 1247.9, 1235.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; found: C, 70.82; H, 6.99; N, 4.61.

Isopropyl 1-allyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (1h)



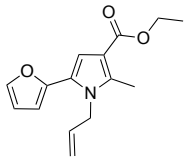
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), allylamine (1.95 mmol) and isopropyl acetoacetate (1.5 mmol); yield: 204 mg (75%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 1H), 6.82 (s, 1H), 6.46 – 6.44 (m, 1H), 6.39 – 6.38 (m, 1H), 6.01 – 5.90 (m, 1H), 5.23 – 5.17 (m, 2H), 4.90 – 4.83 (m, 1H), 4.65 – 4.62 (m, 2H), 2.57 (s, 3H), 1.35 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 146.6, 141.7, 137.2, 133.0, 123.6, 116.4, 112.7, 111.0, 110.2, 106.9, 66.5, 46.9, 22.1, 11.0; IR (neat) ν: 2950.5, 2834.5 (C-H), 1690.7 (C=O), 1247.2, 1188.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12; found: C, 70.67; H, 7.30; N, 5.44.

Ethyl 1-(but-3-en-1-yl)-2-(2-ethoxy-2-oxoethyl)-5-(furan-2-yl)-1*H*-pyrrole-3-carboxylate (1i)



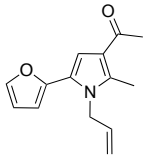
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), butenamine (1.95 mmol) and diethyl 1,3-acetonedicarboxylate (1.5 mmol); yield: 266 mg (77%); white solid; mp: 76-78 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.84 (s, 1H), 6.49 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.44 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.86 – 5.62 (m, 1H), 5.18 – 5.01 (m, 2H), 4.34 – 4.07 (m, 8H), 2.42 (q, *J* = 7.3 Hz, 2H), 1.33 (dt, *J* = 16.2, 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 164.8, 146.6, 141.8, 133.7, 132.4, 124.2, 117.7, 113.7, 111.1, 110.7, 107.5, 61.2, 59.6, 44.7, 34.9, 31.3, 14.4, 14.2; IR (neat) ν: 2979.1, 2977.3 (C-H), 1699.7, 1696.3 (C=O), 1244.2, 1233.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06; found: C, 66.23; H, 6.75; N, 4.33.

Ethyl 1-allyl-5-(2-furyl)-2-methyl-1H-pyrrole-3-carboxylate (1j)



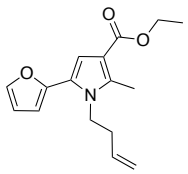
Prepared from 2-iodo-1-(2-furyl)ethanone (236 mg, 1 mmol), allylamine (142 mg, 1.95 mmol), ethyl acetoacetate (195 mg, 1.5 mmol) and InCl3 (11 mg); yield: 186 mg (72%); yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J = 1.8, 0.8 Hz, 1H), 6.82 (s, 1H), 6.45 (dd, J = 3.3, 1.8 Hz, 1H), 6.38 (dd, J =3.3, 0.8 Hz, 1H), 6.03 – 5.88 (m, 1), 5.22 – 5.15 (m, 1H), 4.90 – 4.81 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.66 – 4.62 (m, 2H), 2.57 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); 13C NMR (63 MHz, $CDCl_3$) δ 165.3, 146.6, 141.7, 137.4, 133.0, 123.7, 116.4, 112.3, 111.0, 110.1, 107.0, 59.4, 47.0, 14.5, 11.0; IR (neat) ν: 1700.1 (C=O), 1246.3 (C-O) cm^{-1}; elemental analysis (%) calcd for $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40; found: C 69.39, H 6.55, N 5.34.

1-(1-Allyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (1k)



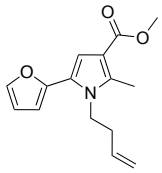
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), allylamine (1.95 mmol) and acetylacetone (1.5 mmol); yield: 160 mg (70%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 1H), 6.77 (s, 1H), 6.48 – 6.46 (m, 1H), 6.41 – 6.39 (m, 1H), 6.02 – 5.89 (m, 1H), 5.24 – 5.18 (m, 1H), 4.91 – 4.82 (m, 1H), 4.66 – 4.62 (m, 2H), 2.60 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.0, 146.4, 141.9, 137.0, 132.7, 123.5, 121.0, 116.6, 111.1, 110.6, 107.1, 46.7, 28.6, 11.5; IR (neat) ν: 1699.4 (C=O), 1249.0 (C-O), 1067.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{14}H_{15}NO_2$: C 73.34, H 6.59, N 6.11; found: C 72.98, H 6.40, N 5.71.

Ethyl 1-(but-3-enyl)-5-(2-furyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1l)



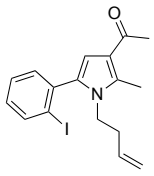
Prepared from 2-iodo-1-(2-furyl)ethanone (236 mg, 1 mmol), 3-butenamine (138 mg, 1.95 mmol), ethyl acetoacetate (195 mg, 1.5 mmol) and $InCl_3$ (11 mg); yield: 176 mg (64%); yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.79 (s, 1H), 6.47 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 0.7 Hz, 1H), 5.84 – 5.66 (m, 1H), 5.14 – 5.09 (m, 1H), 5.06 – 5.05 (m, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.05 (m, 2H), 2.61 (s, 3H), 2.48 – 2.38 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.3, 146.9, 141.6, 137.9, 133.9, 123.2, 117.5, 112.1, 111.1, 110.4, 107.1, 59.4, 44.3, 34.8, 14.5, 11.3; IR (neat) ν: 1699.2 (C=O), 1249.0 (C-O), 1067.2 (C=C-H) cm^{-1}; elemental analysis (%) calcd for $C_{16}H_{19}NO_3$: C 70.31, H 7.01, N 5.12; found: C 70.23, H 6.95, N 5.10.

Methyl 1-(but-3-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (1m)



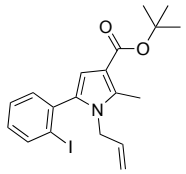
Prepared from 2-iodo-1-(2-furyl)ethanone (1 mmol), butenamine (1.95 mmol) and methyl acetoacetate (1.5 mmol); yield: 187 mg (72%); yellowish oil; mp: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.77 (s, 1H), 6.48 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.04 – 5.56 (m, 1H), 5.11 (dd, *J* = 6.3, 1.3 Hz, 1H), 5.06 (t, *J* = 1.3 Hz, 1H), 4.17 – 4.01 (m, 2H), 3.83 (s, 3H), 2.62 (s, 3H), 2.50 – 2.38 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 146.9, 141.7, 137.2, 133.8, 123.3, 117.5, 111.7, 111.1, 110.4, 107.2, 50.8, 44.4, 34.8, 11.3; IR (neat) ν: 2951.0, 2941.4 (C-H), 1708.7 (C=O), 1244.2, 1182.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40; found: C, 69.12; H, 6.43; N, 5.08.

1-(1-(But-3-en-1-yl)-5-(2-iodophenyl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (1n)



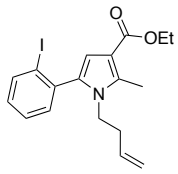
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 98 mg (66%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.47 – 7.35 (m, 2H), 7.17 – 7.10 (m, 1H), 6.44 (s, 1H), 5.63 – 5.46 (m, 1H), 5.00 – 4.91 (m, 2H), 3.84 – 3.69 (m, 2H), 2.66 (s, 3H), 2.44 (s, 3H), 2.21 (br s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 139.1, 138.1, 135.1, 134.0, 133., 132.4, 130.1, 128.0, 120.6, 117.6, 110.8, 103.0, 43.8, 34.7, 28.6, 12.1; IR (neat) ν: 1689.2 (C=O), 1250.0 (C-O), 1077.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{18}INO$: C 53.84, H 4.68, N 3.82; found: C 53.75, H 4.53, N 3.76.

^{t}Butyl 1-allyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1o)



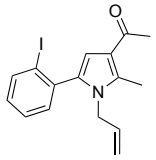
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 111 mg (65%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ ^{1}H NzMR (250 MHz, $CDCl_3$) δ 7.91 – 7.88 (m, 1H), 7.37 – 7.26 (m, 2H), 7.08 – 7.02 (m, 1H), 6.45 (s, 1H), 5.73 – 5.59 (m, 1H), 5.06 – 5.02 (m, 1H), 4.71 – 4.65 (m, 1H), 4.31 – 4.18 (m, 2H), 2.53 (s, 3H), 1.56 (s, 9H); ^{13}NMR (63 MHz, $CDCl_3$) δ 165.1, 138.8, 138.1, 135.3, 134.1, 133.1, 133.0, 132.4, 129.8, 127.7, 116.3, 113.2, 110.2, 102.7, 79.2, 46.7, 28.5, 11.3; IR (neat) ν: 1689.5 (C=O), 1259.1 (C-O), 1068.6 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{22}INO_2$: C 53.91, H 5.24, N 3.31; found: C 53.68, H 5.40, N 3.63.

Ethyl 1-(but-3-en-1-yl)-5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1p)



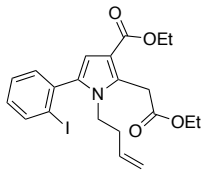
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 122 mg (75%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 1H), 7.45 – 7.33 (m, 2H), 7.15 – 7.08 (m, 1H), 6.50 (s, 1H), 5.63 – 5.46 (m, 1H), 4.99 – 4.90 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.83 – 3.68 (m, 2H), 2.64 (s, 3H), 2.20 (br s, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 139.0, 138.2, 135.5, 134.2, 133.8, 132.4, 129.9, 127.9, 117.5, 111.6, 110.2, 102.9, 59.3, 44.0, 34.8, 14.5, 11.6; IR (neat) ν: 1695.4 (C=O), 1236.8 (C-O), 1070.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for$C_{18}H_{20}INO_2$: C 52.83, H 4.93, N 3.42; found: C 52.63, H 4.84, N 3.44.

1-(1-Allyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (1q)



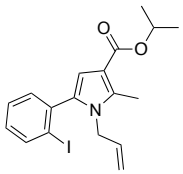
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 105 mg (72%); yellowish solid; mp: 93-95 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 1H), 7.43 – 7.29 (m, 2H), 7.15 – 7.08 (m, 1H), 6.48 (d, *J* = 0.7 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.13 – 5.07 (m, 1H), 4.76 – 4.68 (m, 1H), 4.36 – 4.22 (m, 2H), 2.62 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.2, 139.0, 137.8, 135.6, 134.3, 132.7, 132.3, 130.1, 127.8, 120.6, 116.5, 110.7, 102.8, 46.5, 28.6, 11.8; IR (neat) ν: 1697.7 (C=O), 1234.0 (C-O), 1070.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. For $C_{16}H_{16}INO$: C 52.62, H 4.42, N 3.84; found: C 52.99, H 4.61, N 3.78.

Ethyl 1-(but-3-en-1-yl)-2-(2-ethoxy-2-oxoethyl)-5-(2-iodophenyl)-1*H*-pyrrole-3-carboxylate (1r)



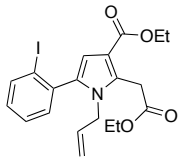
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 150 mg (78%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 1H), 7.46 – 7.39 (m, 2H), 7.15 – 7.09 (m, 1H), 6.56 (s, 1H), 5.60 – 5.44 (m, 1H), 4.98 – 4.88 (m, 2H), 4.27 – 4.17 (m, 6H), 3.82 – 3.68 (m, 2H), 2.20 – 2.14 (m, 2H), 1.38 – 1.26 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0, 165.1, 139.0, 137.9, 135.1, 133.7, 132.4, 131.1, 130.1, 127.9, 117.6, 113.2, 110.6, 102.6, 61.1, 59.5, 44.3, 34.9, 31.6, 14.4, 14.2; IR (neat) ν: 1742.5, 1697.4 (C=O), 1236.0 (C-O), 1070.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{24}INO_4$: C 52.20, H 5.03, N 2.91; found: C 52.01, H 4.94, N 2.78.

Isopropyl 1-allyl-5-(2-iodophenyl)-2-methyl-1H-pyrrole-3-carboxylate (1s)



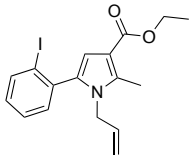
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 118 mg (72%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 1H), 7.23 – 7.12 (m, 2H), 6.95 – 6.88 (m, 1H), 6.37 (s, 1H), 5.59 – 5.46 (m, 1H), 5.08 – 4.98 (m, 1H), 4.93 – 4.89 (m, 1H), 4.58 – 4.50 (m, 1H), 4.18 – 4.04 (m, 2H), 2.42 (s, 3H), 1.18 (d, J = 6.2 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 138.8, 137.9, 135.7, 134.3, 133.0, 132.4, 129.9, 127.7, 116.3, 112.1, 110.1, 102.7, 66.4, 46.6, 22.1, 11.3; IR (neat) ν: 1694.4 (C=O), 1249.9 (C-O), 1067.0 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{20}INO_2$: C 52.82, H 4.93, N 3.42; found: C 52.98, H 4.56, N 3.71.

Ethyl 1-allyl-2-(2-ethoxy-2-oxoethyl)-5-(2-iodophenyl)-1*H*-pyrrole-3-carboxylate (1t)



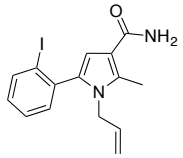
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 149 mg (80%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96 – 7.93 (m, 1H), 7.42 – 7.30 (m, 2H), 7.14 – 7.07 (m, 1H), 6.59 (s, 1H), 5.79 – 5.65 (m, 1H), 5.09 – 5.04 (m, 1H), 4.77 – 4.69 (m, 1H), 4.41 – 4.02 (m, 8H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 165.1, 138.9, 137.7, 135.5, 133.1, 132.4, 131.4, 130.1, 127.8, 116.5, 113.5, 110.3, 102.5, 61.1, 59.6, 47.1, 31.5, 14.4, 14.2; IR (neat) ν: 1736.6, 1688.4 (C=O), 1236.5 (C-O), 1070.1 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{22}INO_4$: C 51.40, H 4.75, N 3.00; found: C 51.22, H 4.88 , N 2.86.

Ethyl 1-allyl-5-(*o*-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1u)



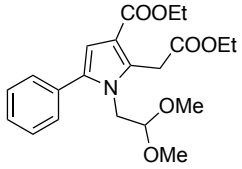
Prepared from 2-iodo-1-(*o*-iodophenyl)ethanone (492 mg, 2 mmol), allylamine (284 mg, 3.9 mmol), ethyl acetoacetate (390 mg, 3 mmol) and CAN (54 mg); yield: 576 mg (73%); orange solid; mp: 51-52 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.41-7.29 (m, 2H), 7.09 (ddd, *J* = 8.0, 7.1, 2.0 Hz, 1H), 6.54 (s, 1H), 5.78-5.63 (m, 1H), 5.08 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.71 (dd, *J* = 17.1, 1.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.34-4.16 (m, 2H), 2.59 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.6, 138.9, 137.9, 136.0, 134.5, 133.0, 132.3, 129.9, 127.8, 116.3, 111.7, 110.0, 102.7, 59.3, 46.7, 14.5, 11.3; IR (neat) ν: 1697.4 (C=O), 1236.6 (C-O), 1070.1 (C=C-H) cm^{-1}; elemental analysis (%) calcd for $C_{17}H_{18}INO_2$: C 51.66, H 4.59, N 3.54; found: C 51.60, H 4.50, N 3.51.

1-Allyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (1v)



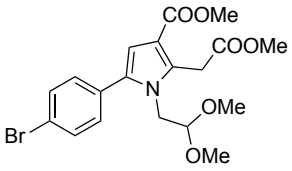
Prepared from *o*-iodoacetophenone (0.40 mmol), allylamine (0.78 mmol) and 3-oxobutanamide (0.60 mmol); yield: 77 mg (52%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 1H), 7.32 – 7.15 (m, 2H), 6.94 – 6.86 (m, 1H), 6.08 (s, 1H), 5.54 (dt, *J* = 6.6, 3.3 Hz, 2H), 5.02 – 4.87 (m, 1H), 4.68 – 4.47 (m, 2H), 4.11 (d, *J* = 29.1 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.2, 139.0, 137.8, 134.9, 134.5, 132.9, 132.25, 130.0, 127.8, 116.4, 113.2, 107.5, 102.7, 46.6, 11.26; IR (neat) ν: 1697.4 (C=O), 1070.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{15}IN_2O$: C 49.20, H 4.13, N 7.65; found: C 49.45, H 4.30, N 7.72.

Ethyl 1-(2,2-dimethoxyethyl)-2-(2-ethoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (1y)



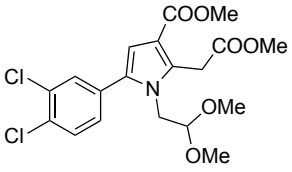
Prepared from 2-iodo-acetophenone (0.5 mmol), 2,2-dimethoxyethan-1-amine (1.0 mmol) and diethyl 3-oxopentanedioate (0.75 mmol); yield: 171 mg (88 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 5H), 6.63 (s, 1H), 4.33 – 4.25 (m, 4H), 4.25 – 4.15 (m, 2H), 4.15 – 4.05 (m, 3H), 3.15 (s, 6H), 1.39 – 1.33 (m, 3H), 1.33 – 1.27 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.2, 164.9, 134.3, 133.1, 132.5, 129.6, 128.4, 127.8, 113.6, 110.2, 104.2, 60.8, 59.4, 55.1, 46.9, 31.4, 14.3, 14.1; IR (neat) ν: 2930.2, 2844.5 (C-H), 1695.2 (C=O), 1257.5 (C-O)cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60; found: C, 64.92; H, 6.76; N, 3.81.

Methyl 5-(4-chlorophenyl)-1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-3-carboxylate (1z)



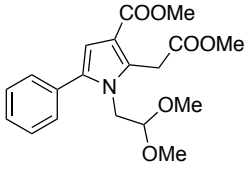
Prepared from *p*-Bromo-2-iodo-acetophenone (0.5 mmol), 2,2-dimethoxyethan-1-amine (1.0 mmol) and dimethyl 3-oxopentanedioate (0.75 mmol); yield: 202 mg (92 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 – 7.35 (m, 2H), 7.12 – 7.08 (m, 4H), 6.41 (s, 1H), 4.09 (s, 2H), 3.96 (d, *J* = 4.6 Hz, 1H), 3.87 (d, *J* = 5.1 Hz, 2H), 3.62 (s, 3H), 3.56 (s, 3H), 2.99 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.5, 165.2, 133.5, 133.3, 131.6, 131.4, 131.1, 122.0, 113.5, 110.5, 104.0, 55.1, 52.1, 50.9, 46.9, 31.1; IR (neat) ν: 3040.0, 2855.2 (C-H), 1675.2 and 1645.0 (C=O), 1244.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{22}BrNO_6$: C, 57.65; H, 5.60; N, 3.54; found: C, 57.28; H, 5.43; N, 3.69.

Methyl 5-(3,4-dichlorophenyl)-1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-3-carboxylate (1aa)



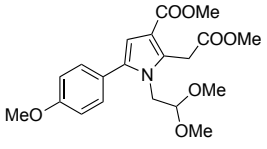
Prepared from 2-iodo-3,4-dichloro-acetophenone (0.5 mmol), 2,2-dimethoxyethan-1-amine (1.0 mmol) and dimethyl 3-oxopentanedioate (0.75 mmol); yield: 161 mg (75 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.08 – 7.04 (m, 1H), 6.41 (s, 1H), 4.07 (s, 2H), 4.04 – 3.97 (m, 1H), 3.85 (d, *J* = 5.1 Hz, 2H), 3.61 (s, 3H), 3.55 (s, 3H), 3.01 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.5, 165.2, 133.9, 132.7, 132.5, 132.3, 132.1, 131.3, 130.5, 128.8, 113.8, 111.2, 104.0, 55.3, 52.2, 51.0, 47.1, 31.3, IR (neat) ν: 3010.0, 2950.2 (C-H), 1705.2 and 1675.0 (C=O), 1254.1 and 1195.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{21}Cl_2NO_6$: C, 53.04; H, 4.92; N, 3.26; found: C, 53.26; H, 4.59; N, 3.06.

Methyl 1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (1ab)



Prepared from 2-iodo-acetophenone (0.5 mmol), 2,2-dimethoxyethan-1-amine (1.0 mmol) and dimethyl 3-oxopentanedioate (0.75 mmol); yield: 162 mg (90 %); transparent oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 5H), 6.61 (s, 1H), 4.31 (s, 2H), 4.10 (q, *J* = 3.7 Hz, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.15 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7, 165.5, 134.6, 133.3, 132.6, 129.8, 128.6, 128.0, 113.4, 110.2, 104.3, 55.3, 52.2, 50.9, 47.0, 31.3; IR (neat) ν: 3110.3, 2959.9 (C-H), 1772.8 and 1682.4 (C=O), 1255.1 and 1176.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.42; N, 3.88; found: C, 63.32; H, 6.21; N, 3.55.

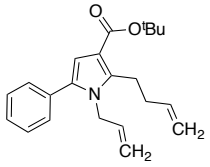
Methyl 1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (1ac)



Prepared from 2-iodo-*p*-methocy-acetophenone (0.5 mmol), 2,2-dimethoxyethan-1-amine (1.0 mmol) and dimethyl 3-oxopentanedioate (0.75 mmol); yield: 152 mg (78 %); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.12 – 7.05 (m, 2H), 6.76 – 6.70 (m, 2H), 6.31 (s, 1H), 4.05 (s, 2H), 3.90 (dd, *J* = 5.7, 4.6 Hz, 1H), 3.80 (d, *J* = 5.1 Hz, 2H), 3.62 (s, 3H), 3.57 (s, 3H), 3.51 (s, 3H), 2.93 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7, 165.5, 159.3, 134.3, 132.8, 131.1, 124.8, 113.9, 113.1, 109.8, 104.2, 55.2, 52.1, 50.8,

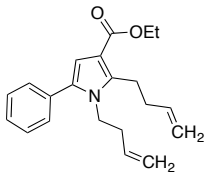
46.9, 31.2; IR (neat) ν: 3050.3, 2955.5 (C-H), 1787.8 and 1680.0 (C=O), 12335.1 and 1129.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58; found: C, 61.12; H, 6.8 N, 3.26.

^{t}Butyl-1-allyl-2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (1ad)



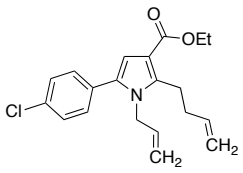
Prepared from acetophenone (0.5 mmol), allylamine (1 mmol) and ^{t}butyl 3-oxohex-5-enoate (0.75 mmol); yield: 59 mg (35%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39 (s, 5H), 6.62 (s, 1H), 5.92 (ddd, *J* = 17.1, 10.4, 1.1 Hz, 2H), 5.33 – 4.94 (m, 3H), 4.85 (dd, 1H), 4.51 (dt, 2H), 3.10 – 2.93 (m, 2H), 2.40 (dt, *J* = 10.7, 6.7 Hz, 2H), 1.60 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.7, 139.4, 137.8, 134.3, 133.5, 132.8, 129.1,128.0, 127.4, 116.5, 115.0, 113.7, 110.3, 79.3, 46.3, 34.1, 28.5, 25.2; IR (neat) ν: 1698.4 (C=O), 1236.7 (C-O), 1074.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15; found: C 77.90, H 7.91, N 4.00.

Ethyl-1,2-di(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate (1ae)



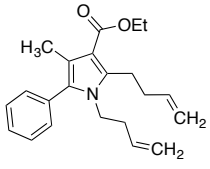
Prepared from acetophenone (0.5 mmol), butenamine (1 mmol) and ethyl 3-oxohex-5-enoate (0.75 mmol); yield: 73 mg (45%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27 – 7.14 (m, 5H), 6.39 (s, 1H), 5.75 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.36 (dd, *J* = 17.0, 10.3 Hz, 1H), 4.97 – 4.69 (m, 4H), 4.11 (t, *J* = 7.1 Hz, 2H), 3.84 – 3.73 (m, 2H), 2.99 – 2.86 (m, 2H), 2.29 – 2.16 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 140.1, 137.7, 133.7, 133.3, 132.8, 129.3, 128.5, 127.5, 117.5, 115.2, 111.8, 110.3, 59.3, 43.6, 35.3, 34.2, 25.3, 14.5; IR (neat) ν: 1699.4 (C=O), 1236.0 (C-O), 1075.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{25}NO_2$: C 77.98, H 7.79, N 4.33; found: C 77.62, H 7.42, N 4.53.

Ethyl-1-allyl-2-(but-3-en-1-yl)-5-(4-chlorophenyl)-1*H*-pyrrole-3-carboxylate (1af)



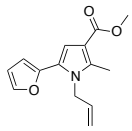
Prepared from *p*-chloroacetophenone (0.5 mmol), allylamine (1 mmol) and ethyl 3-oxohex-5-enoate (0.75 mmol); yield: 86 mg (50%); yellowish solid; mp: 190°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 3H), 6.65 (s, 1H), 6.02 – 5.79 (m, 2H), 5.25 – 4.96 (m, 4H), 4.81 (dd, *J* = 17.1, 0.8 Hz, 1H), 4.50 (dt, *J* = 3.9, 2.0 Hz, 2H), 4.38 – 4.24 (m, 2H), 3.09 – 2.96 (m, 2H), 2.48 – 2.28 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.0, 140.7, 137.6, 134.0, 133.9, 132.4, 131.0, 130.2, 128.6, 116.6, 115.2, 112.2, 110.3, 59.4, 46.3, 34.0, 25.2, 14.5; IR (neat) ν: 1699.4 (C=O), 1236.0 (C-O), 1075.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{22}ClNO_2$: C 69.86, H 6.45, N 4.07; found: C 70.09, H 6.67, N 3.88.

Ethyl-1,2-di(but-3-en-1-yl)-4-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (1ag)



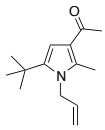
Prepared from acetophenone (0.5 mmol), butenamine (1 mmol) and ethyl 3-oxohex-5-enoate (0.75 mmol); yield: 59 mg (35%); yellowish solid; mp: 190°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.29 (m, 3H), 7.24 – 7.08 (m, 2H), 5.95 – 5.75 (m, 1H), 5.56 – 5.29 (m, 1H), 5.08 – 4.70 (m, 4H), 4.22 (q, 2H), 3.76 – 3.65 (m, 2H), 3.03 – 2.88 (m, 2H), 2.33 (m, 2H), 2.04 (s, 5H), 1.25 (dt, *J* = 7.1, 5.2 Hz, 3H) ppm; ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 139.0, 137.9, 133.9, 132.4, 131.1, 130.9, 128.4, 127.7, 118.5, 117.2, 115.0, 110.7, 59.1, 43.5, 35.3, 34.4, 25.6, 14.5, 11.8 ppm; IR (neat) ν: 1698.9 (C=O), 1237.0 (C-O), 1075.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{27}NO_2$: C 78.30, H 8.06, N 4.15; found: C 77.89, H 8.17, N 3.52.

Methyl 1-allyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (4a)



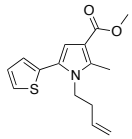
Prepared from 2-furyl methyl ketone (0.5 mmol), allylamine (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 106 mg (87%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 – 7.33 (m, 1H), 6.70 (s, 1H), 6.34 – 6.32 (m, 1H), 6.28 – 6.26 (m, 1H), 5.90 – 5.77 (m, 1H), 5.10 – 5.05 (m, 1H), 4.77 – 4.69 (m, 1H), 4.54 – 4.51 (m, 2H), 3.72 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 146.5, 141.7, 137.5, 132.9, 123.7, 116.3, 111.7, 111.0, 110.0, 107.0, 50.8, 46.9, 10.9; IR (neat) ν: 3124.9, 2947.4 (C-H), 1700.8 (C=O), 1244.1, 1200.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71; found: C, 68.59; H, 6.13; N, 5.76.

1-(1-Allyl-5-(*tert*-butyl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (4b)



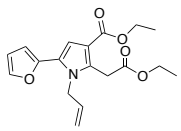
Prepared from 3,3-dimethylbutan-2-one (0.5 mmol), allylamine (1 mmol) and acetylacetone (0.75) ; yield: 65 mg (60%); green oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.28 (s, 1H), 6.02 – 5.77 (m, 1H), 5.24 – 5.16 (m, 1H), 4.76 – 4.62 (m, 3H), 2.50 (s, 3H), 2.41 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 140.3, 137.0, 133.3, 119.5, 116.4, 106.4, 47.1, 31.8, 30.7, 28.6, 11.6; IR (neat) ν: 2964.7, 2869.9 (C-H), 1649.3 (C=O) cm^{-1}; elemental analysis (%) calcd. for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39; found: C, 76.76; H, 9.64; N, 6.37.

Methyl 1-(but-3-en-1-yl)-2-methyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate (4c)



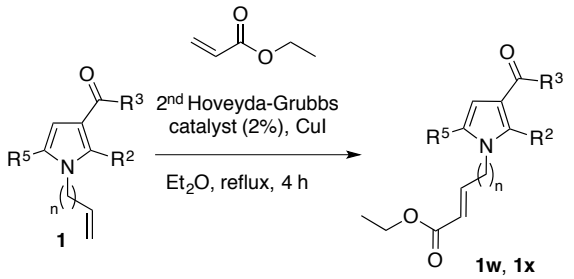
Prepared from 2-acetylthiophene (0.5 mmol), 3-buten-1-amine (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 98 mg (71%); green oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.10 – 7.07 (m, 1H), 6.86 – 6.80 (m, 2H), 6.45 (s, 1H), 5.53 – 5.37 (m, 1H), 4.85 – 4.78 (m, 2H), 3.81 – 3.75 (m, 2H), 3.58 (s, 3H), 2.39 (s, 3H), 2.17 – 2.09 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 137.0, 133.7, 133.4, 127.2, 126.4, 125.6, 126.0, 117.5, 111.6, 111.4, 50.7, 43.5, 34.7, 11.4; IR (neat) ν: 2977.8, 2945.2, 2849.5 (C-H), 1698.0 (C=O), 1240.1, 1188.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; found: C, 65.45; H, 6.29; N, 5.06.

Ethyl 1-allyl-2-(2-ethoxy-2-oxoethyl)-5-(furan-2-yl)-1*H*-pyrrole-3-carboxylate (4d)



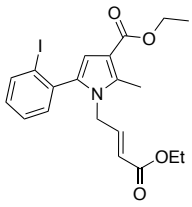
Prepared from 2-furyl methyl ketone (0.5 mmol), allylamine (1 mmol) and diethyl 1,3-acetonedicarboxylate (0.75 mmol); yield: 136 mg (80%); dark orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 (d, *J* = 1.8 Hz, 1H), 6.87 (s, 1H), 6.46 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.41 (d, *J* = 3.3 Hz, 1H), 6.07 – 5.86 (m, 1H), 5.24 – 5.14 (m, 1H), 4.90 – 4.82 (m, 1H), 4.71 – 4.69 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 164.8, 146.3, 141.9, 133.1, 132.7, 124.7, 116.5, 114.0, 111.1, 110.4, 107.5, 61.2, 59.7, 47.2, 31.2, 14.4, 14.1; IR (neat) ν: 2980.5, 2924.4, 2852.3 (C-H), 1734.7, 1704.3 (C=O), 1245.7, 1181.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23; found: C, 65.27; H, 6.34; N, 4.19.

3.3.2. Synthesis of compounds 1w and 1x by cross-metathesis



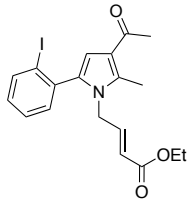
A round-bottomed flask was charged with second generation Hoveyda-Grubbs catalyst (2% mmol), CuI (2% mmol), the suitable pyrrole **1** (0.15 mmol) and ethyl acrylate (0.23 mmol) in dry diethyl ether (2 mL), stirred and heated at 40°C during 4 h. After completion of the reaction (controlled by TLC) the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate, affording the desired pyrroles **1w** and **1x**.

(*E*)-Ethyl 1-(3-ethoxycarbonyl-2-propenyl)-5-(*o*-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (1w)



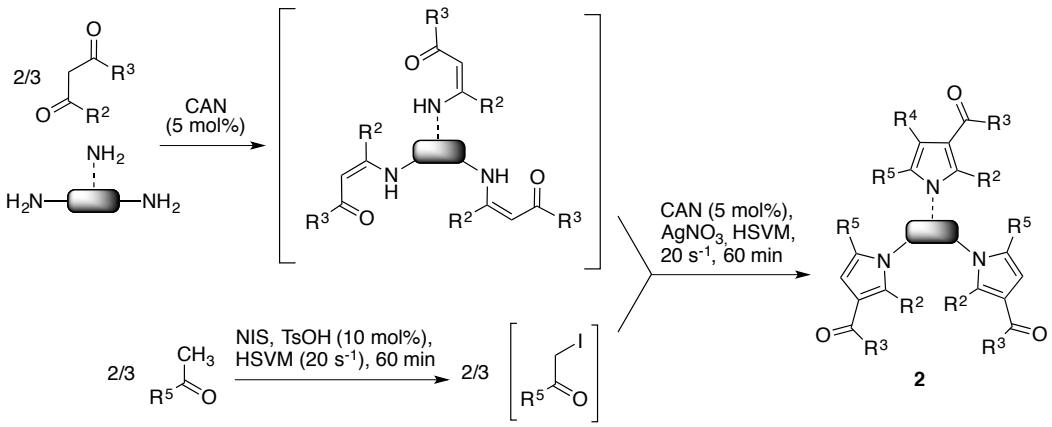
Prepared from pyrrole 119 (79 mg, 0.2 mmol); yield: 84 mg (90%); yellow oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.93 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.36 (ddd, *J* = 7.5, 7.2, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1H); 6.79 (dt, *J* = 15.6, 4.1 Hz, 1H), 6.57 (s, 1H), 5.37 (dt, *J* = 15.6, 2.0 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.59-4.30 (m, 2H), 2.57 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.6, 165.4, 142.7, 139.0, 137.5, 135.6, 134.4, 132.3, 130.2, 128.1, 122.3, 112.3, 110.5, 102.5, 60.6, 59.5, 45.2, 14.5, 14.1, 11.3; IR (neat) ν: 1688.4 (C=O), 1234.6 (C-O), 1072.1 (C=C-H) cm^{-1}; elemental analysis (%) calcd for $C_{20}H_{22}INO_4$: C 51.40, H 4.75, N 3.00; found: C 51.38, H 4.67, N 2.98.

Ethyl (*E*)-4-(3-acetyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrol-1-yl)but-2-enoate (1x)



Prepared from pyrrole xx (0.3 mmol) foolowing the procedure for cross-metathesis derivatives; yield: 78 mg (89%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 1H), 7.30 (td, *J* = 7.4, 1.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.23 – 7.19 (m, 1H), 7.06 – 6.99 (m, 1H), 6.79 (dt, *J* = 15.6, 4.2 Hz, 1H), 6.41 (s, 1H), 5.28 (dt, *J* = 15.6, 2.0 Hz, 1H), 4.43 – 4.28 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.37 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 165.5, 142.3, 139.1, 137.2, 135.1, 134.2, 132.2, 130.3, 128.1, 122.3, 121.0, 111.0, 102.6, 60.6, 44.9, 28.6, 14.1, 11.7; IR (neat) ν: 1697.4 (C=O), 1216.0 (C-O), 1075.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{20}INO_3$: C 52.19, H 4.61, N 3.20; found: C 51.98, H 4.39, N 3.59.

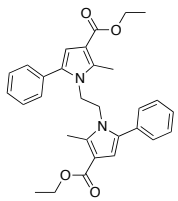
3.3.3. General procedure for the synthesis of symmetrical bispyrrole derivatives 2 and compound 3 under mechanochemical conditions



The suitable ketone (1 mmol), *N*-iodosuccinimide (NIS, 1 mmol) and *p*-toluenesulphonic acid (PTSA, 10 mol%) were added to a milling jar, along with a zirconium oxide ball. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 s^{-1} for 60 min at room temperature. Then, a mixture of the corresponding diamine (0.85 mmol), the suitable b-dicarbonyl compound (1.3 mmol) and cerium(IV) ammonium nitrate (CAN, 10 mol%), previously stirred at room temperature during 30-60 min, and silver nitrate (1 mmol) were added to the vessel. The reaction was subjected to the vibratory movement at the same frequency for 60 min. Then, the reaction vessel was cleansed with ethyl acetate or dichloromethane and the suspension was filtered to remove the silver iodide precipitate. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate afforded the desired pyrrole derivatives. Compounds **2h**, **2i** and **2j** were purified by flash chromatography eluting with a 98/2 dichloromethane/methanol mixture.

For the synthesis of compounds **2d, 2g, 2j, 2l, 2m, 2o**, the required α-iodoketones were prepared in a separate step, according to the following procedure: To a solution of the suitable ketone (1 eq) in anhydrous methanol, iodine (1 eq) and cupper(II) oxide (1 eq) were added. The mixture was stirred at room temperature for 5 min and, then, refluxed until no starting material was detected by TLC. The reaction was cooled, filtered and the solvent was removed. The residue was dissolved in ethyl acetate (10 mL) and washed with a 10% solution of $Na_2S_2O_3$ (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic layers were dried over anhydrous sodium sulphate and the solvent was evaporated. The α-iodoketones thus obtained were used in the next reaction without further purification.

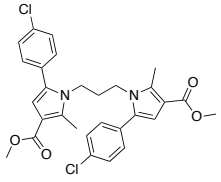
Diethyl 1,1'-(ethane-1,2-diyl)bis(2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate) (2a)



Prepared from acetophenone (1 mmol), ethylenediamine (0.85 mmol) and ethyl acetoacetate (1.30 mmol); yield: 145 mg (60%); white solid; mp: 224-

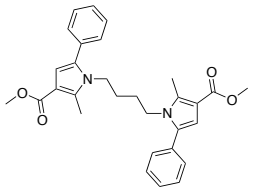
226 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.42-7.36 (m, 6H); 7.20-7.15 (m, 4H); 6.48 (s, 2H); 4.28 (q, *J* = 7.1 Hz, 4H); 3.88 (s, 4H); 1.98 (s, 6H); 1.36 (t, *J* = 7.1 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165, 136.1, 133.0, 132.0, 129.7, 128.6, 128.0, 112.4, 110.3, 59.3, 43.1, 14.5, 10.2 ppm; IR (neat) ν: 1701.6 (C=O), 1242.9 (C-O) cm^{-1}. Elemental analysis (%) calcd for $C_{30}H_{32}N_2O_4$: C 74.36, H 6.66, N 5.78; found: C 74.31, H 6.59, N 5.80.

Dimethyl 1,1'-(propane-1,3-diyl)bis[5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate] (2b)



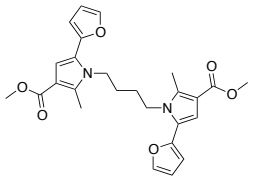
Prepared from 4-chloroacetophenone (1 mmol), propane-1,3-diamine (0.85 mmol) and methyl acetoacetate (1.3 mmol); yield: 178 mg (66%); white solid; mp: 84-86; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 4H), 7.13 – 7.05 (m, 4H), 6.48 (d, *J* = 0.9 Hz, 2H), 3.81 (s, 6H), 3.71 – 3.66 (m, 4H), 2.44 (s, 6H), 1.69 – 1.60 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 136.2, 133.6, 131.6, 130.7, 130.0, 128.7, 112.1, 110.4, 50.7, 40.7, 31.2, 11.2; IR (neat) ν: 2946.4 (C-H), 1689.4 (C=O), 1242.7 (C-O), 1010.9 (C-Cl) cm^{-1}; elemental analysis (%) calcd. for $C_{29}H_{28}Cl_2N_2O_4$: C, 64.57; H, 5.23; N, 5.19; found: C, 64.53; H, 5.20; N, 5.14.

Dimethyl 1,1'-(butane-1,4-diyl)bis(2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate) (2c)



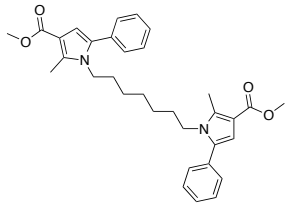
Prepared from acetophenone (1 mmol), butane-1,4-diamine (0.85 mmol) and methyl acetoacetate (1.3mmol); yield: 150 mg (62%); yellowish solid; mp: 156-158 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (m, 6H), 7.02 – 6.93 (m, 4H), 6.27 (s, 2H), 3.59 (s, 6H), 3.46 (m, 4H), 2.27 (s, 6H), 1.01 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 136.2, 133.2, 132.8, 129.2, 128.4, 127.6, 111.6, 109.8, 50.7, 43.0, 27.1, 11.4; IR (neat) ν: 2953.2, 2877.8 (C-H), 1690.5 (C=O), 1243.2, 1211.6 (C-O) cm^{-1}; HRMS (ESI) *m/z* calcd. for $[M+H]^+$ 485.24348, found 485.24568; elemental analysis (%) calcd. for $C_{30}H_{32}N_2O_4$: C, 74.36; H, 6.66; N, 5.78; found: C, 74.31; H, 6.63; N, 5.77.

Dimethyl 1,1'-(propane-1,3-diyl)bis[5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate] (2d)



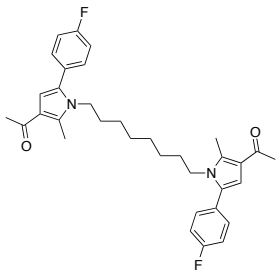
Prepared from 2-furyl methyl ketone (1 mmol), butane-1,4-diamine (0.85 mmol) and methyl acetoacetate (1.3 mmol); yield: 158 mg (68%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 1.9, 0.8 Hz, 2H), 6.74 (s, 2H), 6.47 (dd, *J* = 3.3, 1.9 Hz, 2H), 6.36 (dd, *J* = 3.3, 0.8 Hz, 2H), 3.97 (m, 4H), 3.83 (s, 6H), 2.56 (s, 6H), 1.82 – 1.58 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 146.8, 141.7, 136.9, 123.1, 111.9, 111.2, 110.6, 107.5, 50.9, 44.3, 27.5, 11.2; IR (neat) ν: 2945.0 (C-H), 1700.5 (C=O), 1249.1(C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{26}H_{28}N_2O_6$: C, 67.23; H, 6.08; N, 6.03; found: C, 67.13; H, 6.01; N, 5.99.

Dimethyl 1,1'-(heptane-1,7-diyl)bis(2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate) (2e)



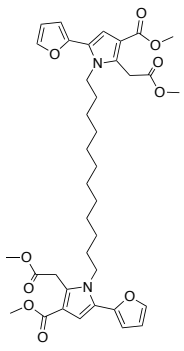
Prepared from acetophenone (1 mmol), heptane-1,7-diamine (0.85 mmol) and methyl acetoacetate (1.3 mmol); yield: 155 mg (59%); yellow solid; mp: 96-98 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 10H), 6.54 (s, 2H), 3.92 – 3.81 (m, 4H), 3.87 (s, 6H), 2.61 (s, 6H), 1.47 –1.41 (m, 4H), 0.99 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 136.4, 133.4, 133.0, 129.3, 128.4, 127.4, 111.5, 109.6, 50.7, 43.8, 30.3, 28.2, 26.1, 11.5; IR (neat) ν: 2935.9, 2900.0 (C-H), 1729.0 (C=O), 1245.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{33}H_{38}N_2O_4$: C, 75.26; H, 7.27; N, 5.32; found: C, 75.26; H, 7.28; N, 5.30.

1,1'-(Octane-1,8-diyl)bis[5-(4-fluorophenyl)-2-methyl-1*H*-pyrrole-1,3-diyl]bis(ethan-1-one) (2f)



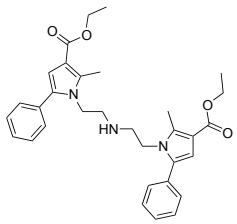
Prepared from 1-(4-fluorophenyl)ethan-1-one (1 mmol), octane-1,8-diamine (0.85 mmol) and acetylacetone (1.3mmol); yield: 163 mg (60%); yellowish solid; mp: 158-160 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24 – 7.09 (m, 4H), 7.02 – 6.88 (m, 4H), 6.29 (s, 2H), 3.79 – 3.54 (m, 4H), 2.45 (s, 6H), 2.26 (s, 6H), 1.29 – 1.25(m, 4H), 0.96 – 0.81 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.0, 162.3 (d, *J* = 252 Hz), 135.7, 131.9, 131.2 (d, *J* = 7.6 Hz), 129.0 (d, *J* = 3.8 Hz), 120.8, 115.4 (d, *J* = 21.4 Hz), 110.5, 43.6, 30.4, 28.7, 28.5, 26.3, 12.0; ^{19}F NMR (235 MHz, $CDCl_3$) δ (-114.31) – (-114.43) (m); IR (neat) ν: 2932.7, 2851.1 (C-H), 1649.2 (C=O), 1242.9, 1215.5 (C-O), 1152.1 (C-F) cm^{-1}; elemental analysis (%) calcd. for $C_{34}H_{38}F_2N_2O_2$: C, 74.97; H, 7.03; N, 5.14; found: C, 74.91; H, 7.00; N, 5.10.

Dimethyl 1,1'-(dodecane-1,12-diyl)bis[5-(furan-2-yl)-2-(2-methoxy-2-oxoethyl)-1*H*-pyrrole-3-carboxylate] (2g)



Prepared from 2-furyl methyl ketone (1 mmol), dodecane-1.12-diamine (0.85 mmol) and 6-methoxy-3,5-dioxohexanoate (1.3 mmol); yield: 207 mg (60%) ; transparent oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H), 6.80 (s, 2H), 6.49 – 6.47 (m, 2H), 6.42 – 6.41 (m, 2H), 4.16 (s, 4H), 4.06 – 3.96 (m, 4H), 3.82 (s, 6H), 3.74 (s, 6H), 1.71 – 1.56 (m, 4H), 1.35 – 1.17 (m, 16H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.3, 165.3, 146.6, 141.8, 132.3, 124.3, 113.2, 111.1, 110.6, 107.6, 52.3, 51.0, 45.4, 31.1, 30.7, 29.5, 29.4, 29.1, 26.6; IR (neat) ν: 2926.0, 2852.6 (C-H), 1740.8, 1703.4 (C=O), 1250.1, 1233.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{38}H_{48}N_2O_{10}$: C, 65.88; H, 6.98; N, 4.04; found: C, 65.89; H, 6.92; N, 4.04.

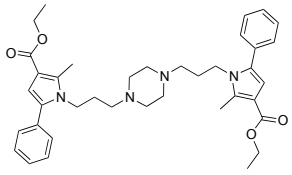
N,N-Bis[2-(3-ethoxycarbonyl-5-phenyl-2-methylpyrrol-1-yl)ethyl]amine (2h)



Prepared from acetophenone (1 mmol), N-(2-aminoethyl)ethane-1,2-diamine (0.85 mmol) and ethyl acetoacetate (1.3 mmol); yield: 183 mg

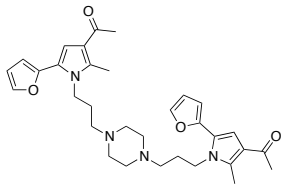
(74%); yellowish oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.15 – 7.00 (m, 10H), 6.36 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 4H), 3.69 (t, *J* = 6.8 Hz, 4H), 2.37 (s, 6H), 2.26 (t, *J* = 6.8 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.5, 136.5, 133.3, 132.8, 129.3, 128.5, 127.6, 112.1, 110.1, 59.3, 48.8, 43.7, 14.5, 11.6; IR (neat) ν: 1650 (C=O), 1250 (C-O) cm^{-1}; Elemental analysis (%) calcd for $C_{32}H_{37}N_3O_4$: C 72.84, H 7.07, N 7.96; C 72.79, H 7.03, N 7.91.

N_1,N_4-Bis[3-(3-ethoxycarbonyl-5-phenyl-2-methylpyrrol-1-yl)propyl]piperazine (2i)



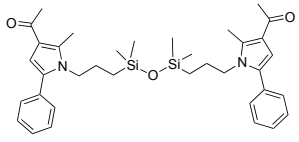
Prepared from acetophenone (1 mmol), 1,4-bis(aminopropyl)piperazine (0.65 mmol) and ethyl acetoacetate (1.3 mmol); yield: 141 mg (45%); yellowish oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.21-7.06 (m, 10H), 6.34 (s, 2H), 4.08 (q, *J* = 7.1 Hz, 4H), 3.73 (m, 4H), 2.41 (s, 6H), 1.97-1.85 (m, 12H), 1.45-1.34 (m, 4H), 1.14 (t, *J* = 7.1, 6H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 166.0, 136.9, 133.6, 133.5, 129.7, 128.8, 127.8, 112.3, 110.3, 59.7, 55.2, 53.1, 42.5, 27.9, 14.9, 11.9; IR (neat) ν: 1650 (C=O), 1250 (C-O) cm^{-1}; elemental analysis (%) calcd for $C_{38}H_{48}N_4O_4$: C 73.05, H 7.74 N, 8.97; found: C 72.97, H 7.70, N 8.90.

N_1,N_4-Bis[3-[3-(methylcarbonyl)-5-(furan-2-yl)-2-methylpyrrol-1-yl]propyl]piperazine (2j)



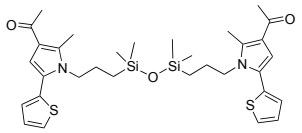
Prepared from 2-furyl methyl ketone (1 mmol), 3,3'-(piperazine-1,4-diyl)bis(propan-1-amine) (0.85 mmol) and acetylacetone (1.3 mmol); yield: 152 mg (56%); light brown oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.9, 0.8 Hz, 2H), 6.63 (s, 2H), 6.39 (dd, *J* = 3.3, 1.9 Hz, 2H), 6.35 (dd, *J* = 3.3, 0.8 Hz, 2H), 4.02 – 3.95 (m, 4H), 2.54 (s, 6H), 2.41 – 2.16 (m, 12H), 2.34 (s, 6H), 1.81 – 1.69 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 146.7, 141.8, 136.8, 123.0, 120.8, 111.1, 111.1, 107.3, 55.1, 53.0, 42.8, 28.5, 27.5, 11.7; IR (neat) ν: 2956.1, 2930.9 (C-H), 1658.9 (C=O), 1256.2 (C-O) cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{32}H_{41}N_4O_4$ $[M+H]^+$ 545.31278, found 545.31720.

1,1'-[[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis(2-methyl-5-phenyl-1*H*-pyrrole-1,3-diyl)]bis(ethan-1-one) (2k)



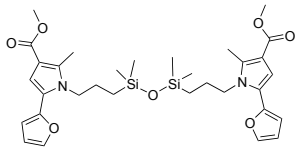
Prepared from acetophenone (1 mmol), 3,3'-(1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propan-1-amine) (0.85 mmol) and acetylacetone (1.3 mmol); yield: 168 mg (55%); yellowish oil; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.46-7.36 (m, 10H), 6.57 (s, 2H), 3.91 (m, 4H), 2.71 (s, 6H), 2.51 (s, 6H), 1.63-1.50 (m, 4H), 0.39-0.32 (m, 4H), 0.00 (s, 12H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 195.0, 135.6, 133.0, 132.9, 129.2, 128.4, 127.5, 120.7, 110.3, 46.6, 28.4, 24.5, 15.0, 12.0, 0.0; IR (neat) ν: 1650 (C=O), 1250 (C-O) cm^{-1}; Elemental analysis (%) calcd for $C_{36}H_{48}N_2O_3Si_2$: C 70.54, H 7.89, N, 4.57; found: C 70.52, H 7.82, N 4.51.

1,1'-[[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis(2-methyl-5-(thiophen-2-yl)-1*H*-pyrrole-1,3-diyl)]bis(ethan-1-one) (2l)



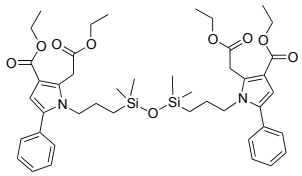
Prepared from 2-acetylthiophene (1 mmol), 1,3-bis(aminopropyl)tetramethyldisiloxane (0.85 mmol) and acetylacetone (1.3 mmol); yield: 187 mg (60%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.09 – 7.06 (m, 2H), 7.03 – 7.01 (m, 2H), 6.63 (s, 2H), 3.92 – 3.86 (m, 4H), 2.62 (s, 6H), 2.43 (s, 6H), 1.67 – 1.54 (m, 4H), 0.45 – 0.38 (m, 4H), 0.00 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 136.3, 133.7, 127.3, 126.7, 125.8, 124.9, 120.8, 112.1, 46.8, 28.5, 24.8, 15.2, 12.0, 0.1; IR (neat) ν: 2952.1, 2926.9 (C-H), 1652.7 (C=O), 1252.5 (C-O) cm^{-1}; HRMS (ESI) *m/z* calcd. for $[M+H]^+$ 625.24101, found 625.24265; elemental analysis (%) calcd. for $C_{32}H_{44}N_2O_3S_2Si_2$: C, 61.50; H, 7.10; N, 4.48; found: C, 61.48; H, 7.06; N, 4.49.

Dimethyl 1,1'-[(1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis[5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate] (2m)



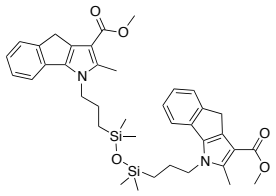
Prepared from 2-furyl methyl ketone (1 mmol), 1,3-bis(aminopropyl)tetramethyldisiloxane (0.85 mmol) and methyl acetoacetate (1.3 mmol); yield: 187 mg (65%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.41 (m, 2H), 6.74 (s, 2H), 6.44 – 6.42 (m, 2H), 6.34 (dd, *J* = 3.3, 0.8 Hz, 2H), 3.97 – 3.90 (m, 4H), 3.81 (s, 6H), 2.57 (s, 6H), 1.69 – 1.56 (m, 6H), 0.47 – 0.40 (m, 4H), 0.00 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 136.3, 133.7, 127.3, 126.7, 125.8, 124.9, 120.8, 112.1, 46.8, 28.5, 24.8, 15.2, 12.0, 0.1; IR (neat) ν: 2950.9 (C-H), 1705.4 (C=O), 1252.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{32}H_{44}N_2O_7Si_2$: C, 61.51; H, 7.10; N, 4.48; found: C, 61.48; H, 7.05; N, 4.48.

Diethyl 1,1'-[(1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis[2-(2-ethoxy-2-oxoethyl)-5-phenyl-1*H*-pyrrole-3-carboxylate] (2n)



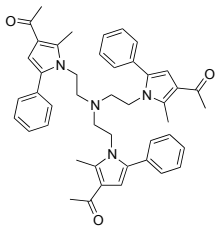
Prepared from acetophenone (0.5 mmol), 1,3-bis(aminopropyl)tetramethyldisiloxane (0.85 mmol) and ethyl 6-ethoxy-3,5-dioxohexanoate (1.3 mmol); yield: 237 mg (58%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 – 7.41 (m, 10H), 6.74 (s, 2H), 4.46 – 4.28 (m, 8H), 4.29 (s, 4H), 4.09 – 3.89 (m, 4H), 1.59 – 1.39 (m, 16H), 0.51 – 0.28 (m, 4H), 0.00 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0, 165.1, 134.1, 132.9, 131.5, 129.2, 128.4, 127.6, 113.4, 110.2, 61.0, 59.4, 47.2, 31.5, 24.8, 15.0, 14.4, 14.1, -0.1; IR (neat) ν: 2953.6, 2933.9, 2900.7 (C-H), 1735.5, 1695.2 (C=O), 1242.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{44}H_{60}N_2O_9Si_2$: C, 64.67; H, 7.40; N, 3.43; found: C, 64.68; H, 7.37; N, 3.40.

Dimethyl 1,1'-[(1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis(2-methyl-1,4-dihydroindeno[1,2-*b*]pyrrole-3-carboxylate) (2o)



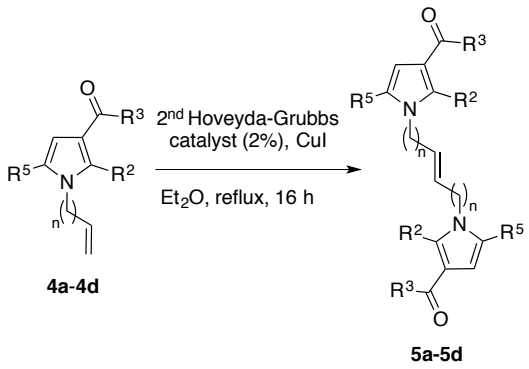
Prepared from 1-indanone (1 mmol), 1,3-bis(aminopropyl)tetramethyldisiloxane (0.85 mmol) and methyl acetoacetate (1.3 mmol); yield: 200 mg (66%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.29 – 7.20 (m, 4H), 7.13 – 7.06 (m, 2H), 4.04 (m, 4H), 3.86 (s, 6H), 3.63 (s, 4H), 2.62 (s, 6H), 1.84 – 1.69 (m, 4H), 0.61 – 0.48 (m, 4H), 0.00 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.2, 146.7, 139.2, 136.4, 135.2, 129.6, 126.3, 125.3, 123.0, 115.7, 107.9, 50.7, 47.8, 32.0, 24.8, 15.2, 11.4, 0.1; IR (neat) ν: 2948.6, 2900.2 (C-H), 1702.0 (C=O), 1280.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{38}H_{48}N_2O_5Si_2$: C, 68.23; H, 7.23; N, 4.19; found: C, 68.17; H, 7.22; N, 4.14.

N,N,N-tris[2-(3-acetyl-5-phenyl-2-methylpyrrol-1-yl)ethyl]amine (3)



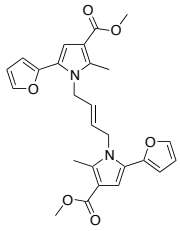
Following the general procedure, prepared from acetophenone (1.8 mmol), N,N-bis(2-aminoethyl)ethane-1,2-diamine (1.2 mmol) and acetylacetone (2.7 mmol). Purification by flash column chromatography on silica gel eluting with a gradient from dichloromethane to 98:02 dichloromethane: methanol afforded 145 mg (35%) of pyrrole **3** as a yellowish oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.42-7.21 (m, 15H), 6.45 (s, 3H), 3.46 (t, 6H, *J* = 7.2 Hz), 2.42 (s, 9H), 2.39 (s, 9H), 2.07 (t, 6H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 194.9, 135.4, 132.8, 132.5, 129.2, 128.6, 128.0, 120.9, 110.6, 54.2, 41.7, 28.5, 11.9; IR (neat) ν: 2973.6, 2927.4 (C-H), 1650.4 (C=O) cm^{-1}; Elemental analysis (%) calcd. for $C_{45}H_{48}N_4O_3$: C 78.00, H 6.98, N 8.09; found: C 77.91, H 6.93, N 8.05.

3.3.4. Preparation of compounds 5 by cross-metathesis reactions



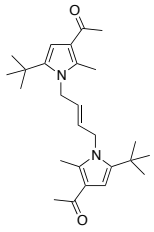
A round-bottomed flask was charged with second generation Hoveyda-Grubbs catalyst (2% mmol), CuI (2% mmol) and the suitable pyrrole 11 (0.15 mmol) in dry diethyl ether (2 mL), stirred and heated at 40°C during 16 (for compounds **5a**, **5c** and **5d**) or 48 hours (for compound **5b**). After completion of the reaction (controlled by TLC) the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate, affording the desired pyrroles **5**.

Dimethyl 1,1'-[(*E*) but-2-ene-1,4-diyl]bis[5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate] (5a)



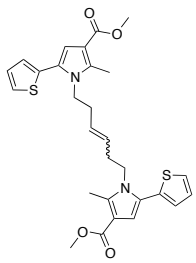
Prepared from compound **14a** (0.25 mmol); yield: 52 mg (88%); dark yellow solid; mp: 170-172 °C; ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 – 7.39 (m, 2H), 6.80 (s, 2H), 6.42 – 6.41 (m, 2H), 6.30 – 6.29 (m, 2H), 5.22 (t, *J* = 1.6 Hz, 2H), 4.55 (d, *J* = 1.6 Hz, 4H), 3.84 (s, 6H), 2.51 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 146.3, 141.7, 137.2, 126.4, 123.6, 112.1, 111.0, 110.1, 107.0, 50.87, 45.6, 10.9; IR (neat) ν: 3011.6, 2944.7, 2849.5 (C-H), 1694.7 (C=O), 1248.4 (C-O), cm^{-1}; HRMS (ESI) *m/z* calcd. for $[M+Na]^+$ 485.16886, found 485.17047; elemental analysis (%) calcd. for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06; found: C, 67.53; H, 5.61; N, 6.03.

(*E*)-1,1'-(But-2-ene-1,4-diyl)bis[5-(*tert*-butyl)-2-methyl-1*H*-pyrrole-1,3-diyl)]bis(ethan-1-one) (5b)



Prepared from compound **4b** (0.25 mmol); yield: 31 mg (70%); green oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.27 (s, 2H), 4.98 (br s, 2H), 4.59 (br s, 4H), 2.44 (s, 6H), 2.41 (s, 6H), 1.32 (s, 18H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.2, 140.3, 136.5, 126.8, 119.7, 106.5, 45.9, 31.8, 30.6, 28.6, 11.4; IR (neat) ν: 2964.4, 2926.1, 2869.9 (C-H), 1650.4 (C=O), 1245.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{26}H_{38}N_2O_2$: 76.06; H, 9.33; N, 6.82; found: C, 76.02; H, 9.26; N, 6.79.

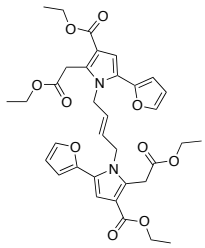
(*E*,*Z*) Dimethyl 1,1'-(hex-3-ene-1,6-diyl)bis[2-methyl-5-(thiophen-2-yl)-1*H*-pyrrole-3-carboxylate] (5c)



The reaction from compound **4c** (0.25 mmol) afforded a 1:1 mixture of the *E* and *Z* isomers; yield: 53 mg (80%); green oil.

Only one of the isomers could be isolated in pure state and its data are given: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 2H), 7.11 – 7.07 (m, 2H), 7.02 – 7.01 (m, 2H), 6.67 (s, 2H), 5.28 – 5.25 (m, 2H), 3.98 – 3.92 (m, 4H), 3.83 (s, 6H), 2.59 (s, 6H), 2.28 – 2.25 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 137.0, 133.8, 128.4, 127.3, 126.6, 125.7, 125.3, 111.8, 111.6, 50.8, 43.7, 33.7, 11.6; IR (neat) ν: 3011.6, 29944.7, 2849.5 (C-H), 1694.7 (C=O), 1241.8 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{28}H_{30}N_2O_4S_2$: C, 64.34; H, 5.79; N, 5.36; found: C, 64.29: H, 5.80: N, 5.39.

Diethyl 1,1'-[(*E*) (but-2-ene-1,4-diyl)]bis[2-(2-ethoxy-2-oxoethyl)-5-(furan-2-yl)-1*H*-pyrrole-3-carboxylate] (5d)

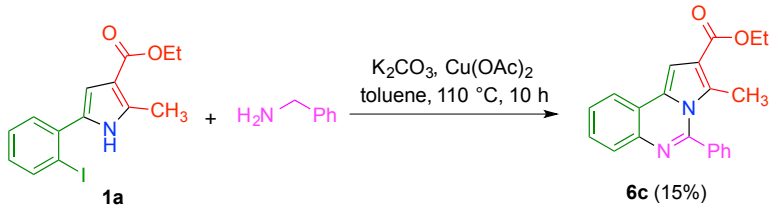


Prepared from compound **4d** (0.25 mmol); yield: 70 mg (88%); dark orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.42 (m, 2H), 6.85 (s, 2H), 6.44 – 6.42 (m, 2H), 6.34 – 6.33 (m, 2H), 5.26 (t, *J* = 1.6 Hz, 2H), 4.60 (br s, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 4.16 (q, *J* = 7.1 Hz, 4H), 4.02 (s, 4H), 1.37 (t, *J* = 7.1 Hz, 6H), 1.28 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7, 164.7, 146.1, 141.9, 132.5, 126.8, 124.6, 114.1, 111.1, 110.4, 107.5, 61.2, 59.7, 45.9, 31.0, 14.4, 14.2; IR (neat) ν: 2973.6, 2927.4 (C-H), 1727.8, 1694.1 (C=O), 1249.8, 1225.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{34}H_{38}N_2O_{10}$: C, 64.34; H, 6.04; N, 4.41; found: C, 64.31; H, 6.00; N, 4.38.

4. Synthesis of fused pyrrole derivatives based on transition metal-catalyzed reactions

4.1. Synthesis of pyrrolo[1,2-*c*]quinazolines by an Ullmann coupling-initiated domino process

The ready availability of the N-unsubstituted 5-(*o*-iodophenyl)pyrroles **1a**-**c** allowed us to examine the creation of a fused pyrrole system by generation of two bonds involving the nitrogen atom and the *o*-position of a C-5 aryl substituent. To this end, we first studied the reaction of compound **1a** with benzylamine in the presence of a Cu(II) salt and potassium carbonate,[70] observing the formation of a low yield of a derivative of the pyrrolo[1,2-*c*]quinazoline framework (compound **6c**), as shown in Scheme 4.1.



Scheme 4.1

The architecture generated is the combination of two privileged structures, namely pyrrole and quinazoline, and is thus of importance in medicinal chemistry.[71] Since currently known methods giving access to this ring system are often multistep in nature and do not always allow the preparation of derivatives of the parent system, we considered this result of interest and undertook a brief optimization study, which is summarized in Table 1.

Table 1. Optimization of the synthesis of **6c**[a]

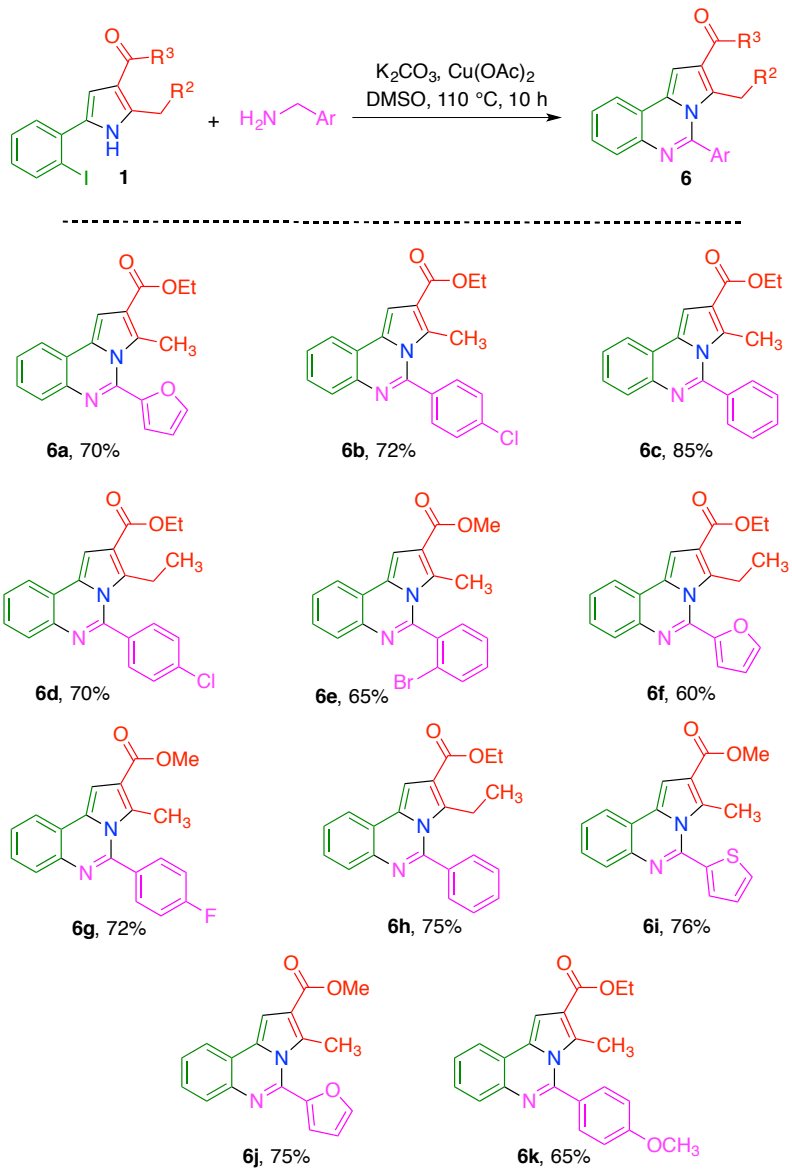
Entry	Catalyst	Base	Solvent	Yield, %
1	$Cu(OAc)_2$	K_2CO_3	toluene	15
2	$Cu(OAc)_2$	K_2CO_3	dioxane	traces
3	$Cu(OAc)_2$	K_2CO_3	DMSO	85
4	$Cu(OAc)_2$	Na_2CO_3	DMSO	62
5	CuI	K_2CO_3	DMSO	42

[a] The reaction conditions were 110 °C, 10 h in all cases.

[70] For precedent of a related domino sequence, see: Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett*., **2012**, *14*, 3894.

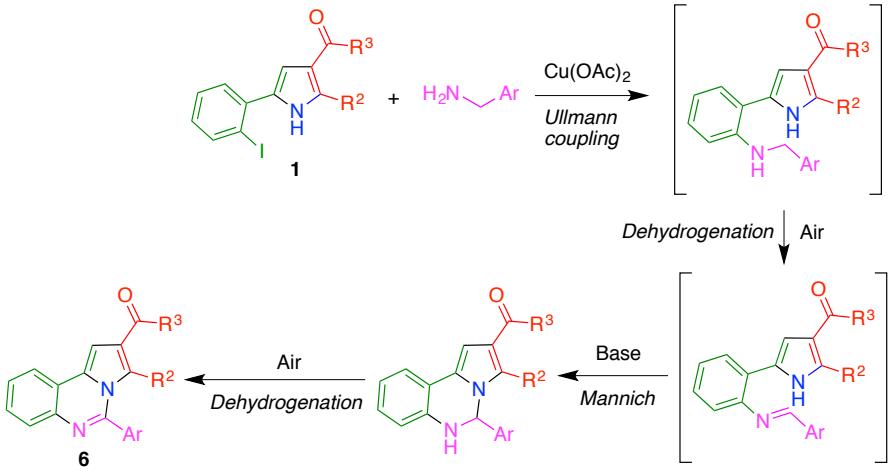
[71] For a review, see: Dumitrascu, F.; Popa, M. M. *Arkivoc,* **2014** (i), 428.

The best conditions found involved the use of Cu(II) acetate as the copper source, K_2CO_3 as the base and DMSO as the reaction medium, and were subsequently applied to the preparation of a library of compounds **6**, as summarized in Scheme 4.2.



Scheme 4.2

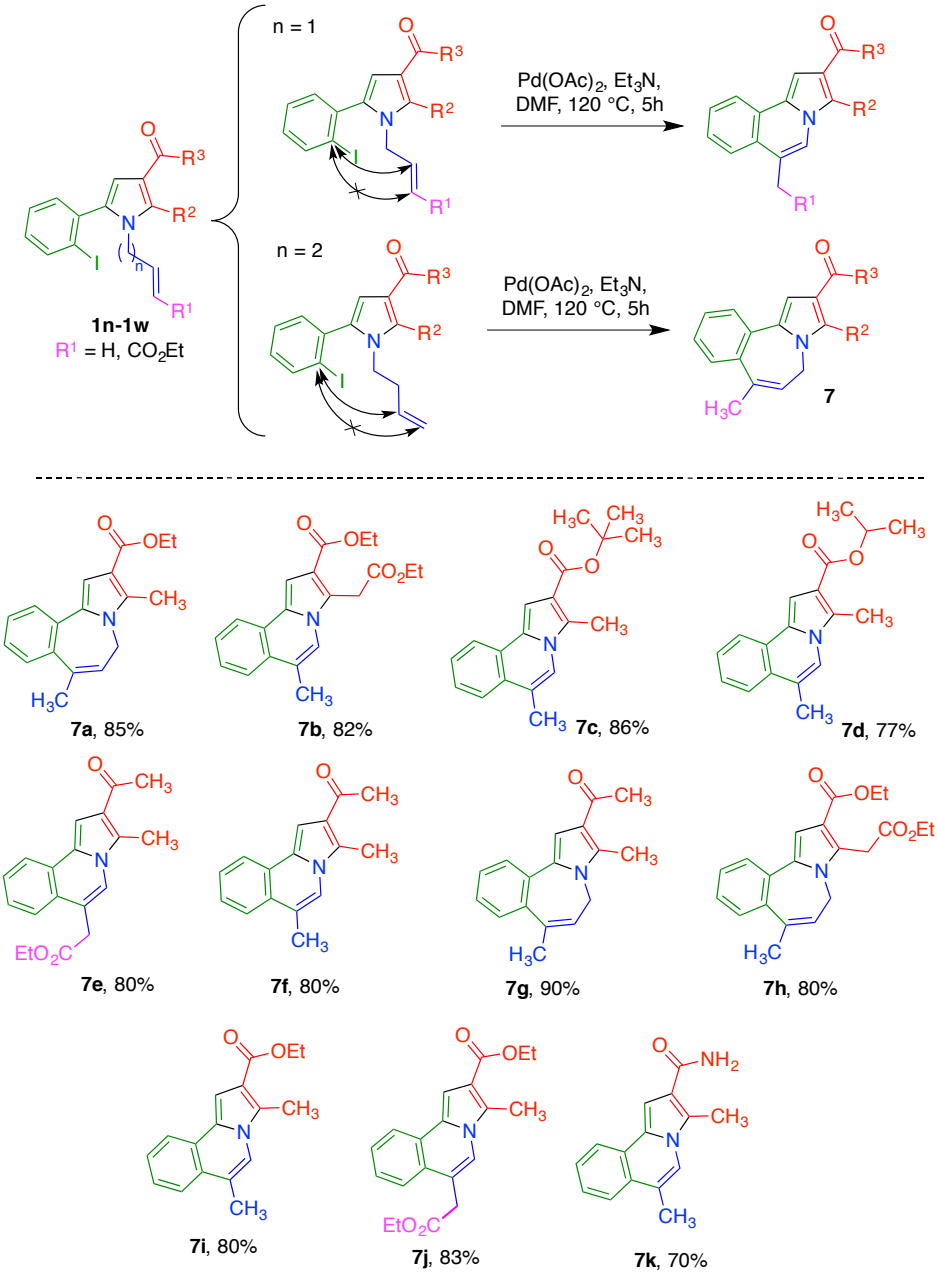
We propose this transformation to take place by a domino process starting with an initial Ullmann coupling, which is followed by an aerobic C-H activation process *via* the dehydrogenation of the arylamine to an imine. This imine next undergoes a base-promoted Mannich-type reaction with the pyrrole nitrogen and, finally, a second aerial dehydrogenation step completes the sequence (Scheme 4.3).


Cu(OAc)2
Ullmann coupling
Dehydrogenation
Air
Base
Mannich
Air
Dehydrogenation
1
6

Scheme 4.3

4.2. Synthesis of pyrrolo[2,1-*a*]isoquinoline and benzo[*c*]pyrrolo[1,2-*a*]azepine frameworks by ring-closing Heck reactions

The availability of pyrrole derivatives decorated both an allyl (or homoallyl) substituent on nitrogen and an *o*-iodophenyl substituent at C-5 (compounds **1n**-**1w**) afforded an opportunity to generate fused pyrrole derivatives *via* their intramolecular Heck cross-coupling reactions.[72] As shown in Scheme 4.4, the transformation was achieved under standard conditions, in the presence of palladium acetate and triethylamine in DMF at



Scheme 4.4

[72] For a precedent of the combination of a multicomponent reaction with Heck intramolecular cross-couplings to generate diverse heterocyclic scaffolds, see: Sunderhaus, J. D.; Dockendorff, C.; Martin, S. F. *Org. Lett*., **2007**, *9*, 4223.

120 °C for 6 h. Depending on the length of the olefin chain, two different scaffolds were obtained with complete regioselectivity, namely pyrrolo[2,1-*a*]isoquinolines (**7b**-**7f**, **7i**, **7j** and **7k**) from the N-allylpyrroles and benzo[*c*]pyrrolo[1,2-*a*]azepine (**7a**, **7g** and **7h**) from the N-homoallylpyrroles. The reaction tolerated well the presence of a variety of substituents at the pyrrole C-3 position, including several esters, ketones and amides. We were also able to functionalize other positions of the final products by including an additional ester group in the β-dicarbonyl component (compounds **7b**, **7h**) or by employing as starting pyrroles the cross-metathesis products **1w** and **1x**, leading to compounds **7e** and **7j**, respectively.

4.3. Synthesis of pyrrolo[1,2-*a*]azepines and pyrrolo[1,2-*a*]azocines by ring-closing metathesis

In order to generate fused heterocyclic moieties with a nitrogen bridgehead atom, we moved to the study of the ring closing metathesis (RCM) reaction, with the aim of generating fused azepine and azocine derivatives. The privileged structure of azepine is contained in several commercial drugs as benazepril, as ACE inhibitor employed for hypertension, or fenoldopam, a selective D_1 agonist. The pyrrolo[1,2-*a*]azepine scaffold is not common but can be found in a number of alkaloids from the *Stemona* and *Stichoneuron* genera (*Stemonaceae*).[73] The pyrrolo[1,2-*a*]azocine scaffold is also represented in nature as a structural fragment of the bioactive polycyclic alkaloids (–)-nakadomarin A and manzamine A.[74] A summary of these structures is represented in Figure 4.1.

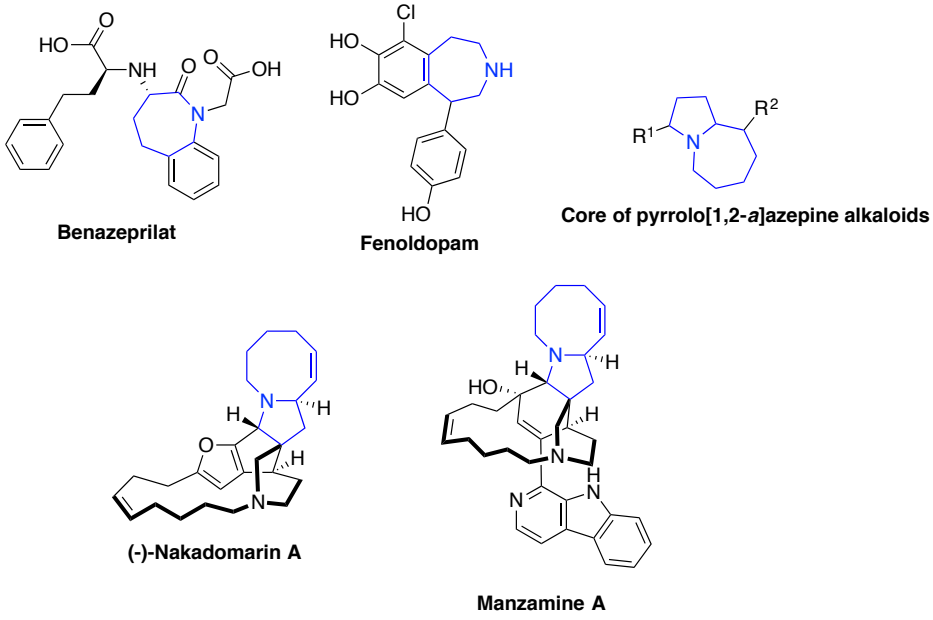


Figure 4.1

The starting pyrroles (compounds **1ad-1ag**) needed to have suitable olefinic substituents both on niytrogen and in its C-1 position. This was achieved by use of allylamine and homoallylamine as the primary amine building blocks, and ethyl-3-oxohept-6-enoate as the β-dicarbonyl component, which was obtained following a procedure previously reported by our group.[75] Exposure of these pyrroles (compounds **1ad-1ag**) to the Grubbs first generation catalyst afforded the target heterocycles **8a-d**, in acceptable to excellent yields under mild conditions at room temperature, with the liberation of a molecule of ethylene (Scheme 4.5).

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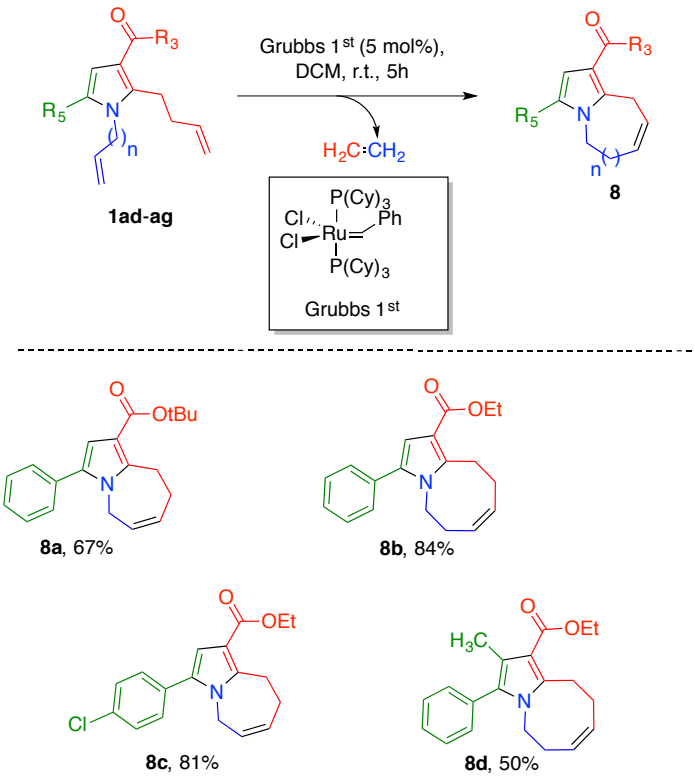
[73] Schinnerl, J.; Kaltenegger, E.; Pacher, T.; Vajrodaya S.; Hofer, O.; Greger, H. *Monatsh. Chem.*, **2005,** *136*, 1671.

[74] Bonazzi, S.; Cheng, B.; Wzorek, J. S.; Evans, D. A. *J. Am. Chem. Soc.*, **2013,** (*25*), 9338.

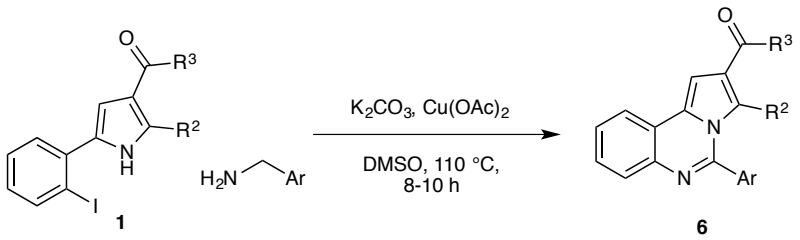
[75] Tenti, G.; Ramos, M. T.; Méndez, J. C. *Curr. Org. Synth.,* **2013**, *10*, 645.


Grubbs 1st (5 mol%),
DCM, r.t., 5h
H2C:CH2
P(Cy)3
Cl
Ru
Ph
Cl
P(Cy)3
Grubbs 1st
1ad-ag
8
OtBu
8a, 67%
OEt
8b, 84%
OEt
Cl
8c, 81%
H3C
OEt
8d, 50%

Scheme 4.5

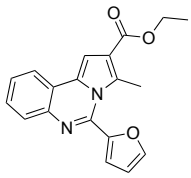
4.4. Experimental section

4.4.1. General procedure for the synthesis of pyrrolo[1,2-c]quinazoline derivatives 6a-6k by an Ullmann-initiated domino process



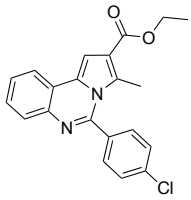
A solution of the suitable pyrrole derivative **1a**-**1c** (0.2 mmol), the suitable benzylamine derivative (0.4 mmol), K_2CO_3 (0.6 mmol) and $Cu(OAc)_2$ (10% mmol) in DMSO (10 mL/mmol) was stirred at 110 °C for 10 h. The cooled reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous NaCl (20 mL). The organic layer was separated and the aqueous one was extracted two additional times with EtOAc (2 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel using a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate as eluent.

Ethyl 5-(furan-2-yl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6a)



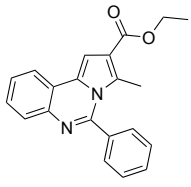
Prepared from pyrrole **1a** (0.2 mmol); yield: 45 mg (70%); dark yellow solid; mp: 151-153 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.00 – 7.97 (m, 1H), 7.84 – 7.81 (m, 1H), 7.64 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.39 (s, 1H), 6.95 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.66 (dd, *J* = 3.4, 1.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 147.1, 143.1, 138.6, 136.7, 130.9, 129.8, 128.7, 128.4, 127.6, 121.4, 121.2, 118.2, 112.9, 111.8, 101.9, 60.3, 14.4, 11.7; IR (neat) ν: 2983.5, 2931.7 (C-H), 1709.0 (C=O), 1241.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74; found: C, 70.91; H, 5.40; N, 8.82.

Ethyl 5-(4-chlorophenyl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6b)



Prepared from pyrrole **1a** (0.2 mmol); yield: 52 mg (72%); white solid; mp: 181-183 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 – 7.98 (m, 1H), 7.82 – 7.78 (m, 1H), 7.58 – 7.43 (m, 6H), 7.41 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 146.5, 136.9, 136.1, 134.6, 130.1, 129.9, 129.8, 128.7, 128.2, 128.0, 127.6, 121.2, 120.8, 118.5, 101.8, 60.3, 15.2, 14.4; IR (neat) ν: 2979.6, 2978.4 (C-H), 1706.2 (C=O), 1239.2 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{21}H_{17}ClN_2O_2$: 364.0979, found: 364.0984.

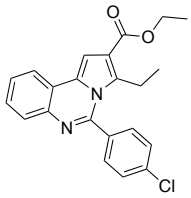
Ethyl 3-methyl-5-phenylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6c)



Prepared from pyrrole **1a** (0.2 mmol); yield: 56 mg (85%); yellow solid; mp: 144-146 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 1H), 7.85 – 7.81 (m, 1H), 7.59 – 7.50 (m, 7H), 7.41 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3, 147.7, 137.0, 136.2, 130.6, 130.0, 129.9, 128.5, 128.4, 128.0, 127.6, 121.2, 120.9, 118.4, 101.7,

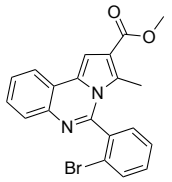
60.3, 14.9, 14.4; IR (neat) ν: 2978.0, 2935.9 (C-H), 1705.6 (C=O), 1237.9 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{21}H_{18}N_2O_2$: 330.1368, found: 330.1376.

Ethyl 5-(4-chlorophenyl)-3-ethylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6d)



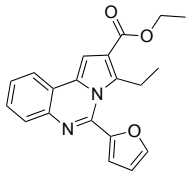
Prepared from pyrrole **1c** (0.2 mmol); yield: 53 mg (70%); yellowish solid; mp: 98-100 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 1H), 7.82 – 7.79 (m, 1H), 7.62 – 7.46 (m, 6H), 7.45 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.82 (q, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 146.4, 136.9, 136.9, 136.2, 134.6, 130.4, 129.6, 128.8, 128.3, 128.0, 127.6, 121.2, 121.0, 117.8, 102.3, 60.3, 19.6, 14.7, 14.4; IR (neat) ν: 2977.2, 2931.9, 2928.6 (C-H), 1708.0 (C=O), 1233.7, 1225.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.06; N, 7.39; found: C, 69.38; H, 5.13; N, 7.63.

Methyl 5-(2-bromophenyl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6e)



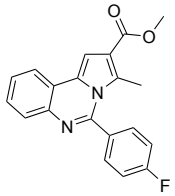
Prepared from pyrrole **1b** (0.2 mmol); yield: 51 mg (65%); yellowish solid; mp: 74-76 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 1H), 7.86 – 7.82 (m, 1H), 7.75 – 7.71 (m, 1H), 7.63 – 7.45 (m, 5H), 7.42 (s, 1H), 3.92 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 146.1, 137.4, 136.7, 132.7, 131.4, 130.7, 130.2, 129.5, 128.4, 128.2, 127.7, 127.6, 123.0, 121.3, 121.1, 117.8, 101.8, 51.5, 12.8; IR (neat) ν: 2945.4, 2943.4 (C-H), 1712.3 (C=O), 1237.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{15}BrN_2O_2$: C, 60.78; H, 3.83; N, 7.09; found: C, 61.09; H, 4.10; N, 7.33.

Ethyl 3-ethyl-5-(furan-2-yl)pyrrolo[1,2-*c*]quinazoline-2-carboxylate (6f)



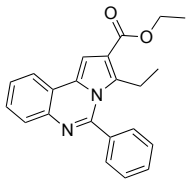
Prepared from pyrrole **1c** (0.2 mmol); yield: 40 mg (60%); yellowish solid; mp: 85-87 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 1H), 7.84 – 7.81 (m, 1H), 7.60 – 7.57 (m, 1H), 7.53 – 7.47 (m, 2H), 7.44 (s, 1H), 7.43 – 7.41 (m, 1H), 7.20 – 7.17 (m, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.91 (q, *J* = 7.3 Hz, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 141.7, 137.5, 136.8, 136.1, 130.6, 129.1, 128.4, 128.1, 127.9, 127.6, 126.7, 121.2, 121.1, 117.8, 102.3, 60.3, 19.7, 15.2, 14.4; IR (neat) ν: 2976.1, 2975.2, 2878.6 (C-H), 1708.9 (C=O), 1231.8, 1226.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38; found: C, 71.49; H, 5.03; N, 8.63.

Methyl 5-(4-fluorophenyl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6g)



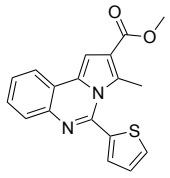
Prepared from pyrrole **1b** (0.2 mmol); yield: 48 mg (72%); yellowish solid; mp: 202-204 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01 – 7.98 (m, 1H), 7.83 – 7.79 (m, 1H), 7.63 – 7.58 (m, 2H), 7.53 – 7.48 (m, 2H), 7.40 (s, 1H), 7.29 – 7.21 (m, 2H), 3.92 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 163.6 (d, *J* = 252 Hz), 146.7, 136.9, 132.3 (d, *J* = 3.6), 130.6 (d, *J* = 8.3), 130.2 (d, *J* = 18.9 Hz), 128.2, 128.0, 127.7, 121.2, 120.8, 118.2, 115.8, 115.5, 101.7, 51.5, 15.1; ^{19}F NMR (235 MHz, $CDCl_3$) δ (-110.11) – (-110.22) (m); IR (neat) ν: 3031.7, 2932.7 (C-H), 1712.1 (C=O), 1239.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{15}FN_2O_2$: C, 71.85; H, 4.52; N, 8.38; found: C, 71.51; H, 4.23; N, 7.98.

Ethyl 3-ethyl-5-phenylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6h)



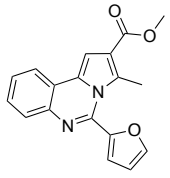
Prepared from pyrrole **1c** (0.2 mmol); yield: 52 mg (75%); yellowish solid; mp: 103-105 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.60 (dd, *J* = 7.4, 2.2 Hz, 2H), 7.56 – 7.43 (m, 5H), 7.39 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.71 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 148.0, 137.7, 137.4, 136.6, 130.8, 130.4, 129.0, 128.6, 128.5, 128.4, 128.0, 121.6, 121.5, 118.0, 102.5, 60.7, 30.1, 20.0, 15.3, 14.8; IR (neat) ν: 2923.4, 2852.4 (C-H), 1730.2 (C=O), 1232.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13; found: C, 76.91; H, 5.63; N, 7.97.

Methyl 3-methyl-5-(thiophen-2-yl)pyrrolo[1,2-*c*]quinazoline-2-carboxylate (6i)



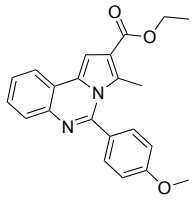
Prepared from pyrrole **1b** (0.2 mmol); yield: 49 mg (76%); dark yellowish solid; mp: 129-130 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01 – 7.98 (m, 1H), 7.85 – 7.81 (m, 1H), 7.60 – 7.48 (m, 3H), 7.41 (s, 1H), 7.35 – 7.33 (m, 1H), 7.21 – 7.18 (m, 1H), 3.93 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 141.8, 136.9, 135.9, 131.0, 130.3, 129.9, 128.4, 128.2, 127.9, 127.6, 126.8, 121.2, 120.9, 118.2, 101.8, 51.5, 14.1; IR (neat) ν: 2921.0, 2918.8, 2851.3 (C-H), 1728.7 (C=O), 1221.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69; found: C, 66.80; H, 3.99; N, 8.34.

Methyl 5-(furan-2-yl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6j)



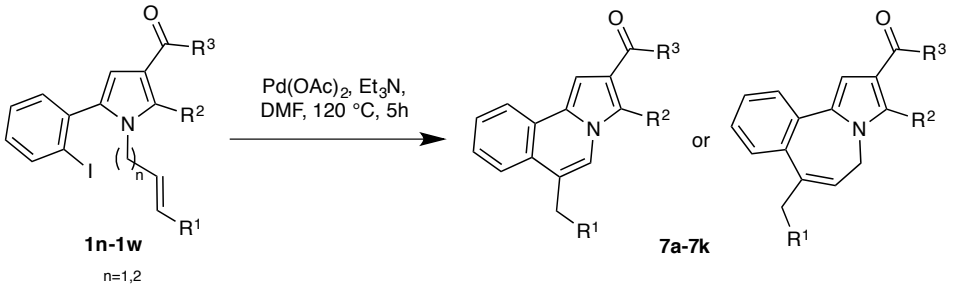
Prepared from pyrrole **1b** (0.2 mmol); yield: 46 mg (75%); dark yellowish solid; mp: 174-176 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 – 7.95 (m, 1H), 7.84 – 7.81 (m, 1H), 7.65 – 7.64 (m, 1H), 7.55 – 7.38 (m, 2H), 7.38 (s, 1H), 6.96 – 6.95 (m, 1H), 6.68 – 6.66 (m, 1H), 3.93 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 147.0, 143.1, 138.5, 136.7, 131.1, 129.9, 128.7, 128.4, 127.6, 121.3, 121.2, 117.8, 113.0, 111.9, 101.8, 51.5, 11.7; IR (neat) ν: 2943.9, 2946.4, 2889.7 (C-H), 1712.3 (C=O), 1244.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.15; found: C, 70.29; H, 4.31; N, 9.54.

Ethyl 5-(4-methoxyphenyl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6k)



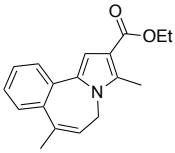
Prepared from pyrrole **1a** (0.2 mmol); yield: 47 mg (65%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 – 7.89 (m, 1H), 7.73 – 7.69 (m, 1H), 7.45 – 7.35 (m, 4H), 7.19 (s, 1H), 6.97 – 6.94 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.15 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 161.3, 148.1, 137.6, 131.2, 130.5, 130.4, 129.0, 128.4, 128.3, 128.0, 121.6, 121.3, 118.7, 114.3, 102.1, 60.7, 56.0, 15.6, 14.9; IR (neat) ν: 2920.8, 2859.2 (C-H), 1709.6 (C=O), 1219.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{20}N_2O_3$: C, 73.32; H, 5.59; N, 7.77; found: C, 73.51; H, 5.78; N, 7.53.

4.4.2. Preparation of compounds 7a-7k by intramolecular Heck reactions



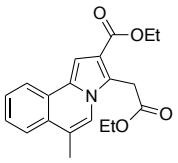
A mixture of compound **1n**-**1x** (0.2 mmol), triethylamine (Et_3N, 0.5 mmol) and palladium(II) acetate (5 mol%) in dimethylformamide (1 mL) was refluxed for 6 h and monitored by TLC. The solvent was removed under reduced pressure and the purification of the residue by flash column chromatography on silica gel, eluting with a gradient from petroleum ether to 8:2 petroleum ether−ethyl acetate, afforded the desired compounds **7a**-**7k**.

Ethyl 3,7-dimethyl-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepine-2-carboxylate (7a)



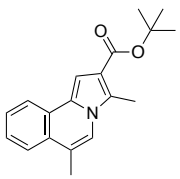
Prepared from pyrrole **1p** (0.2 mmol); yield: 48 mg (85%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 1H), 7.54 – 7.50 (m, 1H), 7.38 – 7.35 (m, 2H), 6.81 (s, 1H), 6.10 – 6.04 (m, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.16 (d, *J* = 7.2 Hz, 2H), 2.63 (s, 3H), 2.18 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 141.1, 136.2, 134.0, 132.8, 131.9, 129.3, 127.8, 127.3, 126.7, 122.9, 112.4, 108.4, 59.3, 40.2, 23.1, 14.6, 11.1; IR (neat) ν: 1669.0 (C=O), 1236.0 (C-O), 1066.0 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{19}NO_2$; C 76.84, H 6.81, N 4.98; found: C 77.03, H 7.01, N 4.76.

Ethyl 3-(2-ethoxy-2-oxoethyl)-6-methylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (7b)



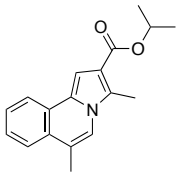
Prepared from pyrrole **1t** (0.2 mmol); yield: 56 mg (82%); yellowish solid; Mp: 115-117 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 1H), 7.71 – 7.68 (m, 1H), 7.53 – 7.43 (m, 3H), 7.38 (s, 1H), 4.44 (s, 2H), 4.44 – 4.35 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 2.20 (s, 2H), 1.44 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7, 165.4, 129.2, 127.8, 127.5, 126.2, 123.8, 122.8, 122.4, 119.3, 119.0, 115.8, 101.0, 61.2, 60.0, 30.7, 16.8, 14.4, 14.2; IR (neat) ν: 1697.4, 1669.0 (C=O), 1236.0 (C-O) cm^{-}1; elemental analysis (%) calcd. for $C_{20}H_{21}NO_4$: C 69.78, H 6.94, N 5.63; found: C 69.57, H 7.00, N 3.50. HRMS (MALDI TOF) calcd. for $C_{20}H_{21}NO_4$: 339,1471, found: 339.145.

^{t}Butyl 3,6-dimethylpyrrolo[2,1-a]isoquinoline-2-carboxylate (7c)



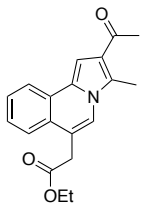
Prepared from pyrrole **1o** (0.2 mmol); yield: 51 mg (86%); yellowish solid; mp: 86-88 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 1H), 7.69 – 7.66 (m, 1H), 7.51 – 7.40 (m, 3H), 7.27 (s, 1H), 2.77 (s, 3H), 2.47 (s, 3H), 1.66 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 127.9, 127.6, 127.3, 126.7, 126.4, 125.8, 123.7, 122.2, 119.0, 118.4, 116.0, 100.8, 79.9, 28.5, 16.8, 10.5; IR (neat) ν: 1702.4 (C=O), 1247.9 (C-O), 1077.7 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74; found: C 76.98, H 6.87, N 4.51.

Isopropyl 3,6-dimethylpyrrolo[2,1-*a*]isoquinoline-2-carboxylate (7d)



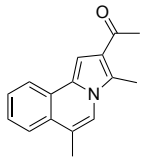
Prepared from pyrrole **1s** (0.2 mmol); yield: 43 mg (77%); yellowish solid; mp: 85-87 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 1H), 7.44 – 7.40 (m, 1H), 7.27 – 7.18 (m, 3H), 7.08 (s, 1H), 5.08 (p, *J* = 6.3 Hz, 1H), 2.53 (s, 3H), 2.20 (d, *J* = 1.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 128.1, 127.5, 127.3, 127.0, 126.3, 125.8, 123.7, 122.1, 118.8, 118.5, 114.8, 100.5, 66.9, 22.6, 16.7, 10.4; IR (neat) ν: 1690.4 (C=O), 1269.0 (C-O), 1100.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{19}NO_2$: C 76.84, H 6.81, N 4.98; found: C 76.94, H 6.49, N 5.21. HRMS (MALDI TOF) calcd. for $C_{18}H_{19}NO_2$: 281.1416, found: 281.1412.

Ethyl 2-(2-acetyl-3-methylpyrrolo[2,1-*a*]isoquinolin-6-yl)acetate (7e)



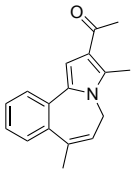
Prepared from pyrrole **1x** (0.1 mmol); yield: 27 mg (80%); white solid; mp: 135-137 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 – 8.05 (m, 1H), 7.67 – 7.64 (m, 1H), 7.61 (br s, 1H), 7.56 – 7.40 (m, 2H), 7.25 (s, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 2H), 2.81 (s, 3H), 2.63 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.4, 171.0, 128.2, 128.0, 126.9, 126.6, 126.2, 123.7, 122.9, 122.2, 121.2, 116.7, 100.9, 61.3, 36.8, 29.1, 14.2, 10.7; IR (neat) ν: 1699.4, 1689.0 (C=O), 1236.0 (C-O), 1066.0 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{19}NO_3$: C 73.77, H 6.19, N 4.53; found: C 72.99, H 6.39, N 4.67.

1-(3,6-Dimethylpyrrolo[2,1-*a*]isoquinolin-2-yl)ethan-1-one (7f)



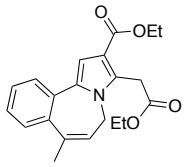
Prepared from pyrrole **1q** (0.2 mmol); yield: 38 mg (80%); yellowish solid; mp: 172-174 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 – 8.04 (m, 1H), 7.71 – 7.68 (m, 1H), 7.56 – 7.42 (m, 3H), 7.24 (s, 1H), 2.80 (s, 3H), 2.63 (s, 3H), 2.47 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.4, 128.1, 127.8, 127.4, 126.5, 126.4, 126.0, 123.9, 122.5, 122.0, 119.3, 118.8, 100.7, 29.1, 16.8, 10.7; IR (neat) ν: 1689.0 (C=O), 1064.5 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{16}H_{15}NO$: C 80.98, H 6.37, N 5.90; found: C 80.59, H 6.40, N 5.84.

1-(3,7-Dimethyl-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepin-2-yl)ethan-1-one (7g)



Prepared from pyrrole **1n** (0.2 mmol); yield: 45 mg (90%); white solid; mp: 91-93 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 1H), 7.55 – 7.52 (m, 1H), 7.40 – 7.37 (m, 2H), 6.74 (s, 1H), 6.08 (t, J = 7.2 Hz, 1H), 4.17 (d, J = 7.2 Hz, 2H), 2.66 (s, 3H), 2.47 (s, 3H), 2.19 (s, 3H);^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 141.2, 136.3, 133.7, 132.7, 131.7, 129.2, 127.9, 127.4, 126.9, 122.9, 121.4, 108.9, 39.9, 28.5, 23.1, 11.5; IR (neat) ν:1702.4 (C=O), 1239.0 (C-O), 1087.6(C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{17}NO$: C 81.24, H 6.82, N 5.57; found: C 81.05, H 6.88, N 5.65.

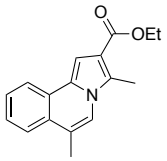
Ethyl 3-(2-ethoxy-2-oxoethyl)-7-methyl-5*H*-benzo[*c*]pyrrolo[1,2-*a*]azepine-2-carboxylate (7h)



Prepared from pyrrole **1r** (0.2 mmol); yield: 56 mg (80%); yellowish solid; mp: 87-89 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 1H), 7.54 – 7.51 (m, 1H), 7.38 – 7.36 (m, 2H), 6.85 (s, 1H), 6.10 – 6.03 (m, 1H), 4.35 – 4.16 (m, 8H), 2.18 (d, *J* = 1.4 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 165.2, 140.9, 136.3, 133.9, 131.7, 129.4, 129.4, 127.8, 127.3, 126.9, 123.3, 113.7, 108.7, 61.2, 59.5, 41.1,

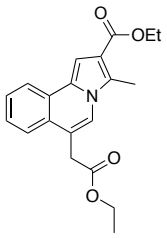
31.0, 23.0, 14.5, 14.2; IR (neat) ν: 1689.4, 1669.0 (C=O), 1236.0 (C-O), 1066.0 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{23}NO_4$; C 71.37, H 6.56, N 3.96; found: C 71.60, H 6.43, N 4.01.

Ethyl 3,6-dimethyl-pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (7i)



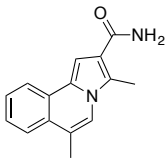
Prepared from pyrrole **1u** (100 mg, 0.25 mmol); yield: 53 mg (80%); orange solid; mp: 86-89 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.06 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.55-7-40 (m, 3H), 7.32 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.79 (s, 3H), 2.47 (d, *J* = 1.2 Hz, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.9, 128.2, 127.7, 127.3, 127.2, 126.4, 125.9, 123.7, 122.2, 118.9, 118.7, 114.5, 100.6, 59.8, 16.8, 14.5, 10.4; IR (neat) ν: 1699.9 (C=O), 1249.9 (C-O), 1066.9 (C=C-H) cm^{-1}; elemental analysis (%) calcd for $C_{17}H_{17}NO_2$: C 76.38, H 6.41, N 5.24; found: C 76.20, H 6.37, N 5.20.

Ethyl 6-ethoxycarbonylmethyl-3-methyl-pyrrolo[2,1-*a*]isoquinoline-2-carboxylate (7j)



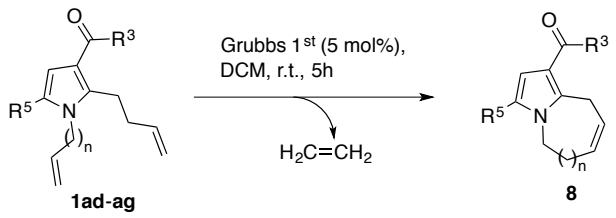
Prepared from pyrrole **1w** (100 mg, 0.21 mmol); yield: 60 mg (83%); yellowish solid; mp: 111-114 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.06 (td, *J* = 7.2, 1.3 Hz, 1H), 7.64 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.60 (s, 1H), 7.50 (td, *J* = 7.8, 1.3 Hz, 1H), 7.41 (td, *J* = 7.2, 1.3 Hz, 1H), 7.33 (d, *J* = 0.6 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (d, *J* = 0.6 Hz, 2H), 2.81 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 171.1, 165.7, 128.3, 127.9, 127.2, 126.6, 126.2, 126.1, 122.4, 121.4, 116.1, 115.1, 100.8, 61.2, 59.9, 36.8, 14.5, 14.2, 10.4; IR (neat) ν: 1728.8, 1701.6 (C=O), 1248.8, 1209.2 (C-O) cm^{-1}; elemental analysis (%) calcd for $C_{20}H_{21}NO_4$: C 70.78, H 6.24, N 4.13; found: C 70.72, H 6.18, N 4.02.

3,6-Dimethylpyrrolo[2,1-*a*]isoquinoline-2-carboxamide (7k)



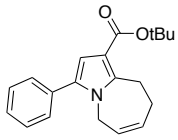
Prepared from pyrrole **1v** (0.2 mmol); yield: 33 mg (70%); yellowish solid; mp: 171-173 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 1H), 7.72 – 7.69 (m, 1H), 7.54 – 7.42 (m, 3H), 7.03 (s, 1H), 5.80 (br s, 2H), 2.81 (s, 3H), 2.48 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.1, 128.3, 127.6, 127.5, 126.1, 126.0, 123.9, 121.9, 119.0, 118.5, 116.3, 99.5, 97.5, 16.8, 10.4; IR (neat) ν: 1689.0 (C=O), 1236.0 (C-O) cm^{-1}, 1066.0 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{14}N_2O$: C 75.61, H 5.92, N 11.76; found: C 75.30, H 5.80, N 11.89.

4.4.3. Preparation of compounds 8 by ring-closing-metathesis



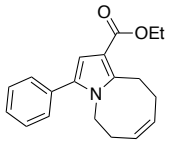
To a solution of pyrrole (0.5 mmol) in dry dichloromethane, first generation Grubbs catalyst (5% mmol) was added. The mixture was stirred for 5 h and, then, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using petroleum ether- ethyl acetate (9:1) as solvent, giving the desired compound **8a**-**8d**.

^{t}Butyl-3-phenyl-8,9-dihydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate (8a)



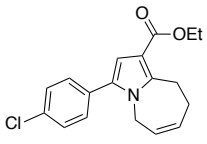
Prepared from pyrrole **1ad** (0.2 mmol); yield: 52 mg (67%); yellowish solid; mp: 87.2°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 – 7.17 (m, 5H), 6.50 (s, 1H), 5.90 – 5.69 (m, 2H), 4.53 (m, 2H), 3.60 – 3.38 (m, 2H), 2.49 (br s, 2H), 1.59 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.0, 141.1, 134.0, 132.9, 132.5, 129.0, 128.5, 127.2, 122.4, 112.3, 108.9, 79.3, 42.1, 28.4, 22.3; IR (neat) ν: 1699.4 (C=O), 1236.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53; found: C 77.38, H 7.64, N 4.22.

Ethyl-3-phenyl-5,6,9,10-tetrahydropyrrolo[1,2-*a*]azocine-1-carboxylate (8b)



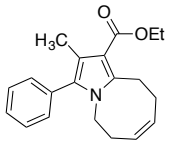
Prepared from pyrrole **1ae** (0.2 mmol); yield: 73 mg (84%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 – 7.31 (m, 5H), 6.56 (s, 1H), 5.73 (m, 1H), 5.47 (m, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.20 (t, *J* = 6.8 Hz, 2H), 3.53 (t, *J* = 7.1 Hz, 2H), 2.63 (q, *J* = 6.8 Hz, 2H), 2.52 (q, *J* = 6.7 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.48, 141.2, 133.0, 132.9, 131.9, 129.5, 128.4, 127.4, 125.7, 110.8, 109.7, 59.2, 44.3, 29.0, 27.0, 24.7, 14.5; IR (neat) ν: 1689.4 (C=O), 1246.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{21}NO_2$: C 77.26, H 7.17, N 4.74; found: C 75.45, H 7.46, N 4.35.

Ethyl-3-(4-chlorophenyl)-8,9-dihydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate (8c)



Prepared from pyrrole **1af** (0.2 mmol); yield: 65 mg (81%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68 – 7.26 (m, 4H), 6.70 (s, 1H), 6.50 (m, 4H), 5.94 – 5.62 (m, 2H), 5.16 – 4.89 (m, 2H), 4.17 – 3.55 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 142.0, 134.2, 133.3, 131.9, 130.8, 130.1, 128.7, 122.0, 110.8, 109.0, 59.3, 42.2, 28.3, 22.3, 14.5; IR (neat) ν: 1696.4 (C=O), 1238.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{18}ClNO_2$: C 68.46, H 5.75, N 4.44; found: C 68.08, H 5.96, N 4.12.

Ethyl-2-methyl-3-phenyl-5,6,9,10-tetrahydropyrrolo[1,2-*a*]azocine-1-carboxylate (8d)



Prepared from pyrrole **1ag** (0.2 mmol); yield: 36 mg (50%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (tdd, *J* = 6.5, 5.5, 2.6 Hz, 3H), 7.20 – 7.11 (m, 2H), 5.80 – 5.48 (m, 1H), 5.43 – 5.22 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.94 (t, *J* = 6.8 Hz, 2H), 3.39 (t, *J* = 7.0 Hz, 2H), 2.53 (q, 2H), 2.41 – 2.22 (q, 2H), 2.02 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.3, 140.1, 132.4, 131.6, 131.2, 130.5, 128.3, 127.6, 125.7, 117.9, 110.0, 59.0, 44.0, 29.2, 27.4, 24.8, 14.5, 12.1; IR (neat) ν: 1699.4 (C=O), 1236.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53; found: C 77.25, H 7.34, N 4.25.

5. Ring creation based on intramolecular Diels-Alder reactions

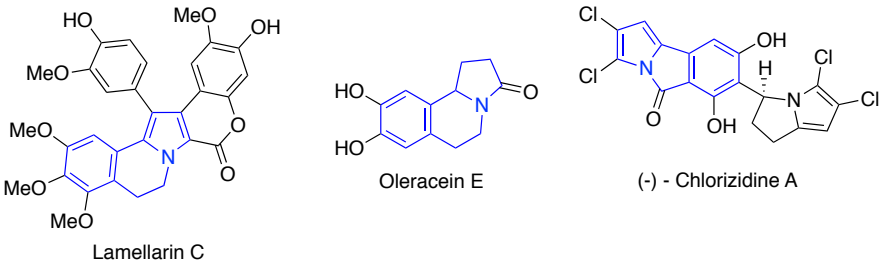
5.1. Introduction

Polyheterocyclic derivatives with a ring-fusion nitrogen atom are interesting compounds in drug discovery programs. For this reason, new synthetic methods for the fast generation of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline and 5*H*-pyrrolo[2,1-*a*]isoindole (Figure 5.1) are of relevance..

5,6-dihydropyrrolo[2,1-*a*]isoquinoline 5*H*-pyrrolo[2,1-*a*]isoindole

Figure 5.1

These scaffolds are important structural fragments in alkaloids and pharmacologically active compounds (Figure 5.2).[76] Lamellarine C is a member of the well-known lamellarine family of anticancer marine pyrrole alkaloids. Oleracein E is a neuroprotective tetrahydroisoquinoline.[77] (⁻)-Chlorizidine A, a pyrrolo[2,1-*a*]isoindole derivative, is known for its cytotoxic activity.[78]



Lamellarin C Oleracein E (-) - Chlorizidine A

Figure 5.2

In general the synthesis of these compounds relies on multistep procedures, involving the use of metals and harsh reaction conditions. Even if many entries are known into this ring system, the preparation of functionalized derivatives, particularly at C-7, is not trivial and has been possible in our method.

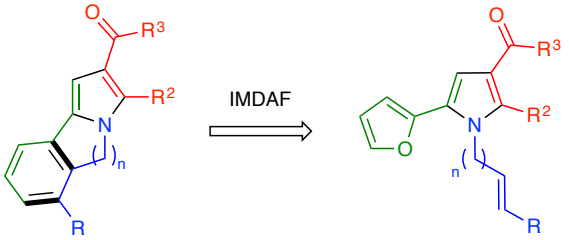
[76](a) Mikhailovskii, G.; Shklyaev, V. S. *Chem. Heterocycl. Compd*., **1997**, *33*, 243; (b) Nelina-Nemtseva, J. I.; Gulevskaya, A. V.; Pozharskii, A. F.; Nguyen, H. T. L.; Filatova, E. A. *Tetrahedron,* **2016**, *72*, 2327; (c) Wiest, J. M.; Pöthig, A.; Bach, T. *Org. Lett*., **2016**, *18*, 852.

[77]Sun, H.; He, X.; Liu, C.; Li, L.; Zhou, R.; Jin, T.; Yue, S.; Feng, D.; Gong, J.; Sun, J.; Ji, J.; Xiang, L. *ACS Chem Neurosci.*, **2017**, *18*;8(1), 155.

[78]Alvarez-Mico, X.; Jensen, P. R.; Fenicial, W.; Hughes, C. C. *Org. Lett.*, **2013**, *15* (5), 988.

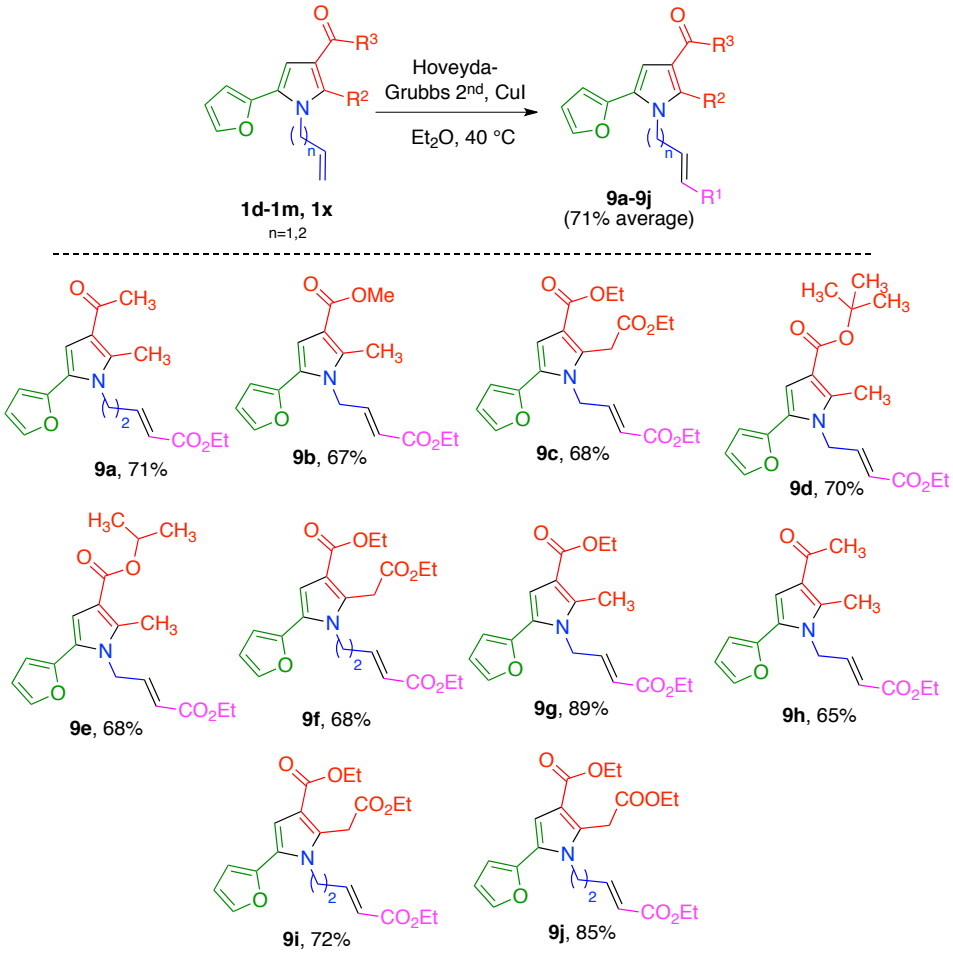
5.2. Synthesis of pyrrole substrates

As previously mentioned, one of our objectives was the exploration of the intramolecular Diels-Alder strategy as a route towards pyrrole-based polycyclic nitrogen heterocycles using the IMDAF (*Intramolecular Diels–Alder Cycloaddition of Furans*) strategy,[79] as shown in Scheme 5.1.



Scheme 5.1

As summarized in Scheme 5.2, the 1-allyl (homoallyl)-5-(2-furyl) pyrroles **1d**-**1m** previously synthesized were used as starting materials for this study but, in order to increase the reactivity of the olefin as a dienophile, we first incorporated an



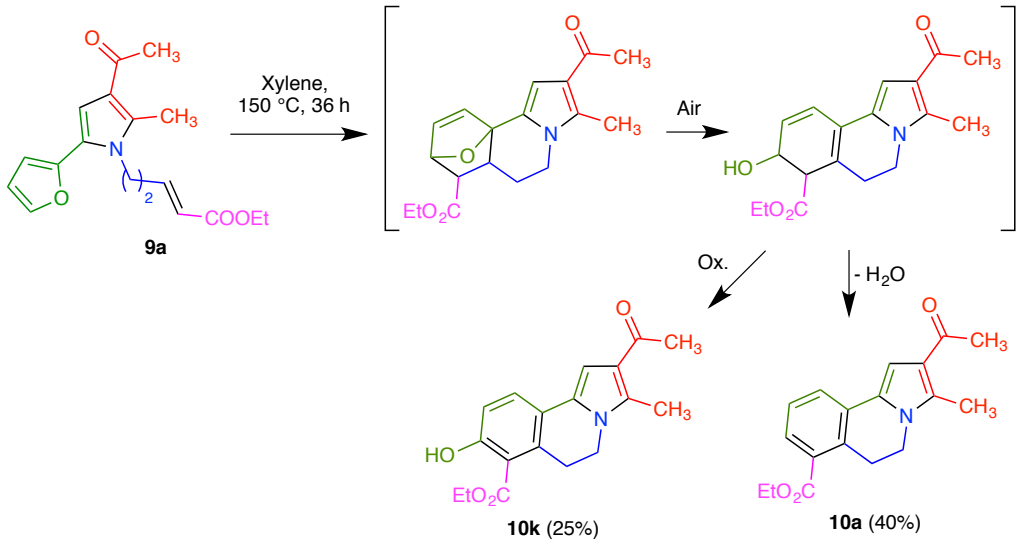
Scheme 5.2

[79] For a review, see: Padwa, A.; Flick, A. C. *Adv. Heterocycl. Chem.*, **2013**, *110*, 1.

unsaturated ester unit at its end by a cross-metathesis reaction in the presence of the Hoveyda-Grubbs second-generation catalyst and CuI in diethyl ether to furnish compounds **9**.

5.3. Intramolecular furan Diels–Alder cycloadditions

During our first experiments of the IMDAF reaction, which involved heating compound **9a** in refluxing xylene, we obtained a mixture of **10a** (40%) and its 7-hydroxy derivative **10k (**25%), probably due to the existence of oxidative and dehydrative competing pathways for the evolution of the initial Diels-Alder adduct (Scheme 5.3).

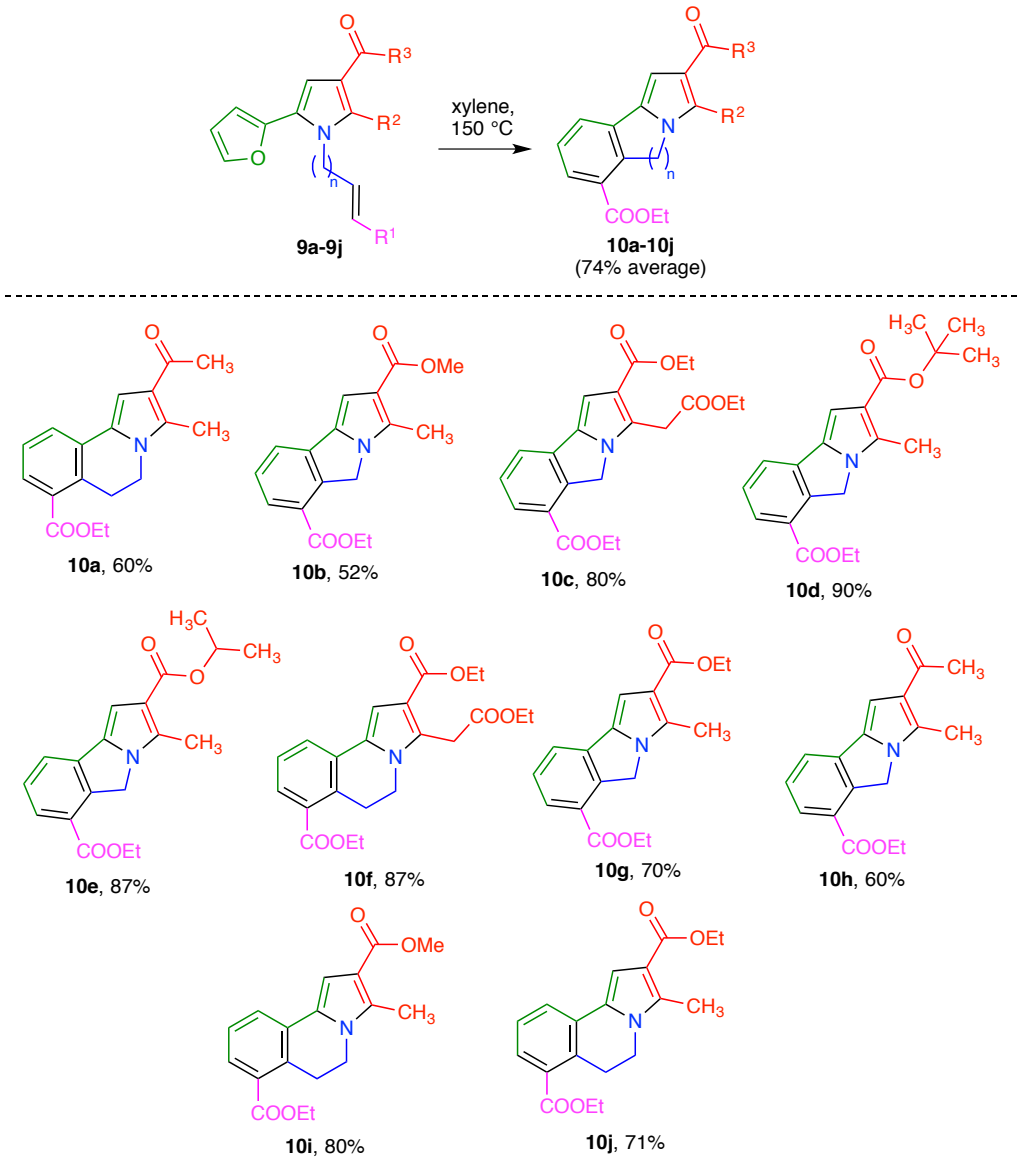


Scheme 5.3

For this reason, we carried out the experiment under an argon atmosphere and obtained compound **9a** as a single product in 60% yield. Using these conditions, we carried out a number of additional intramolecular Diels-Alder reactions, with the results summarized in Scheme 5.4. These studies led, on one hand, to pyrrolo[2,1-*a*]isoindoles **10b**-**10e** and **10g**,**h**, with a good degree of structural variability and normally in good to excellent yields. This framework has received little attention in the literature, with only a few scattered examples having being described.[80] On the other hand, by starting from N-homoallyl pyrroles we also obtained the pyrrolo[2,1-*a*]isoquinoline derivatives **10a**,**f**,**i**,**j**; this framework represents an important group of

[80] For selected more recent work, see: (a) Jin, R.-Z.; Zhang, W.-T.; Zhou, Y.-J.; Wang, X.-S. *Tetrahedron Lett.,* **2016**, *57*, 2515 (b) Zhang, W.-T.; Qiang, W.-W.; Yao, C.-S.; Wang, X.-S. *Tetrahedron,* **2016**, *72*, 2178; (c) Reddy, S. B. V.; Reddy, B. P.; Reddy, V. G. P.; Siriwardena, A. *Org. Biomol. Chem*., **2016**, *14*, 4276; (d) Kazemi, S. S.; Keivanloo, A.; Nasr-Isfahani, H.; Bamoniri, A. *RSC Adv.,* **2016**, *6*, 92663; (e) Acosta, P.; Ortiz, A.; Insuasty, B.; Abonia, R.; Quiroga, J. *Monatsh. Chem*., **2017**, *148*, 237; (f) Fekete, B.; Palkó, M.; Haukka, M.; Fülöp. F. *Molecules,* **2017**, *22*, 613.

pharmacologically active compounds[81] and natural products.[82] Even if several entries are known into this ring system,[83] the preparation of functionalized derivatives, particularly at C-7, is not trivial.



Scheme 5.4

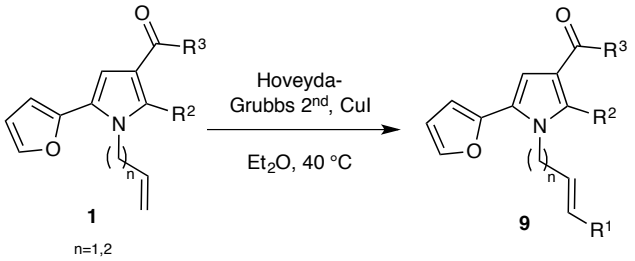
[81] For representative examples, see: (a) Maryanoff, B. E.; Maryanoff, C. A.; McComsey, D. F.; Sorgi, K. L.; U.S. Patent, 4,837,328, 1989. (b) Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc.*, **1990**, *112*, 3567; (c) Goodman, M. M.; Shi, B. Z.; U.S. Patent, 6,162,417, 2000; (d) Pla, D.; Albericio, F.; Álvarez, M. *MedChemComm,* **2011**, *2*, 689.

[82] Pa̋ssler, U.; Knölker, H.-J. *Alkaloids Chem. Biol.,* **2011**, *70*, 79.

[83] For a review, see: (a) Mikhailovskii, G.; Shklyaev, V. S. *Chem. Heterocycl. Compd.*, **1997**, *33*, 243; For selected more recent methods, see: (b) Su, S.; Porco, J. A. *J. Am. Chem. Soc.*, **2007**, *129*, 7744; (c) Naskar, S.; Banerjee, M.; Hazra, A.; Mondal, S.; Maity, A.; Paira, R.; Sahu, K. B.; Saha, P.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett.,* **2011**, *52*, 1527; (d) Nelina-Nemtseva, J. I.; Gulevskaya, A. V.; Pozharskii, A. F.; Nguyen, H. T. L.; Filatova, E. A. *Tetrahedron,* **2016**, *72*, 2327; (e) Xu, X.-M.; Zhao, L.; Zhu, J.; Wang, M.-X. *Angew. Chem. Int. Ed.,* **2016**, *55*, 3799; (f) Wiest, J. M.; Pöthig, A.; Bach, T. *Org. Lett.*, **2016**, *18*, 852.

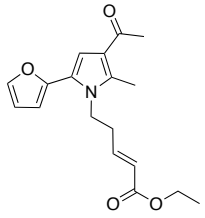
5.4. Experimental section

5.4.1. Preparation of compounds 9a-9j by cross-metathesis



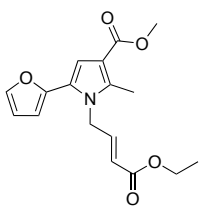
A round-bottomed flask was charged with second-generation Hoveyda-Grubbs catalyst (2 mol%), CuI (2 mol%) and the suitable pyrrole **1** (0.2 mmol) in dry diethyl ether (2 mL). Then, ethyl acrylate (0.3 mmol) was added to the mixture, stirred and heated at 40 °C for 3h. After completion, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate afforded the desired derivatives. These derivatives need to be stored in a fridge due to their low stability and should be used within a short time.

Ethyl (*E*)-5-(3-acetyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-1-yl)pent-2-enoate (9a)



Prepared from pyrrole **1d** (0.5 mmol); yield: 110 mg (71%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.87 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.72 (s, 1H), 6.50 – 6.48 (m, 1H), 6.43 – 6.42 (m, 1H), 5.86 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.26 – 4.11 (m, 4H), 2.63 (s, 3H), 2.66 – 2.55 (m, 2H), 2.44 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 165.9, 146.4, 143.3, 142.0, 136.4, 123.8, 122.9, 121.1, 111.2, 107.7, 60.4, 43.1, 33.1, 28.5, 14.2, 11.7; IR (neat) ν: 1699.4, 1640.7 (C=O), 1216.0 (C-O), 1065.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 67.63, H 6.90, N 4.33.

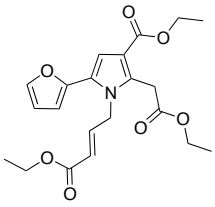
Methyl (*E*)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (9b)



Prepared from pyrrole **1e** (0.5 mmol); yield: 106 mg (67%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.44 (m, 1H), 7.06 (dt, *J* = 15.6, 4.0 Hz, 1H), 6.82 (s, 1H), 6.46 – 6.44 (m, 1H), 6.38 – 6.36 (m, 1H), 5.47 (dt, *J* = 15.6, 2.1 Hz, 1H), 4.81 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.55 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63

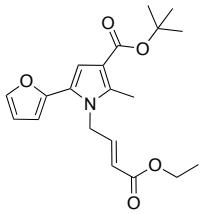
MHz, $CDCl_3$) δ 166.2, 166.0, 146.6, 143.1, 142.4, 137.6, 124.1, 122.7, 112.9, 111.6, 110.8, 107.9, 61.1, 51.4, 46.1, 14.6, 11.4; IR (neat) ν: 2930.8, 2859.8 (C-H), 1712.1 (C=O), 1247.0, 1177.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41; found: C, 64.11; H, 6.23; N, 4.65.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethyl)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-1*H*-pyrrole-3-carboxylate (9c)



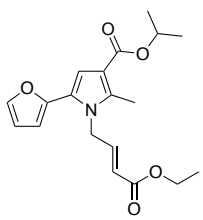
Prepared from pyrrole **1f** (0.5 mmol); yield: 142 mg (68%); yellowish oil; ^1H NMR (250 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 1H), 6.96 (dt, *J* = 15.7, 4.0 Hz, 1H), 6.78 (s, 1H), 6.38 – 6.34 (m, 1H), 6.33 – 6.29 (m, 1H), 5.40 (dt, *J* = 15.6, 2.1 Hz, 1H), 4.79 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.13 – 4.06 (m, 4H), 3.99 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.21 – 1.15 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.1, 166.1, 165.1, 146.3, 143.1, 142.6, 132.8, 125.1, 122.8, 115.0, 111.6, 111.1, 108.3, 61.8, 61.1, 60.3, 46.3, 31.6, 14.8, 14.6 (x2C); IR (neat) ν: 2979.0, 2835.4 (C-H), 1670.2, 1667.7 (C=O), 1244.2, 1182.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47; found: C, 62.23; H, 6.65; N, 3.73.

^{t}Butyl (*E*)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (9d)



Prepared from pyrrole **1g** (0.5 mmol); yield: 126 mg (70%); yellowish oil; ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 – 7.43 (m, 1H), 7.04 (dt, *J* = 15.6, 4.0 Hz, 1H), 6.77 (s, 1H), 6.44 – 6.43 (m, 1H), 6.36 – 6.35 (m, 1H), 5.50 (dt, *J* = 15.6, 2.1 Hz, 1H), 4.79 (dd, *J* = 4.0, 2.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.52 (s, 3H), 1.59 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 164.6, 146.4, 142.7, 141.9, 136.4, 123.3, 122.3, 114.4, 111.1, 110.9, 107.3, 79.6, 60.6, 45.5, 28.4, 14.1, 11.0; IR (neat) ν: 2976.2, 2929.9 (C-H), 1696.1 (C=O), 1251.8, 1258.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90; found: C, 66.57; H, 6.90; N, 3.62.

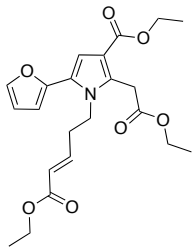
Isopropyl (*E*)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (9e)



Prepared from pyrrole **1h** (0.5 mmol); yield: 117 mg (68%); yellowish oil; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.43 (m, 1H), 7.06 (ddd, *J* = 15.8, 4.4, 3.4 Hz, 1H), 6.83 (s, 1H), 6.56 – 6.44 – 6.43 (m, 1H), 6.38 – 6.36 (m, 1H), 5.53 – 5.45 (m, 1H), 5.26 – 5.16 (m, 1H), 4.82 – 4.79 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H, 2H), 2.54 (s, 3H), 1.36 (d, *J* = 6.2 Hz, 6H),

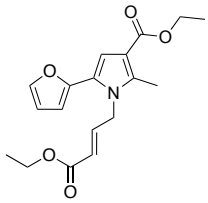
1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 164.7, 146.2, 142.7, 141.9, 136.8, 123.5, 122.2, 113.3, 111.1, 110.6, 107.3, 66.7, 60.7, 45.6, 22.1, 14.1, 11.0; IR (neat) ν: 2944.0, 2869.9 (C-H), 1699.74 (C=O), 1274.2, 1162.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06; found: C, 65.83; H, 6.35; N, 4.33.

Ethyl (*E*)-2-(2-ethoxy-2-oxoethyl)-1-(5-ethoxy-5-oxopent-3-en-1-yl)-5-(furan-2-yl)-1*H*-pyrrole-3-carboxylate (9f)



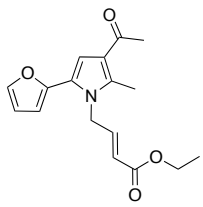
Prepared from pyrrole **1i** (0.5 mmol); yield: 142 mg (68%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 1H), 6.90 – 6.76 (m, 2H), 6.49 – 6.41 (m, 2H), 5.82 (dt, *J* = 15.7, 1.4 Hz, 1H), 4.23 (dd, *J* = 20.5, 7.1 Hz, 10H), 2.63 – 2.48 (m, 2H), 1.36 – 1.26 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7, 165.8, 164.6, 146.3, 143.2, 141.9, 132.1, 124.0, 123.7, 114.0, 111.2, 110.9, 107.9, 61.2, 60.3, 59.6, 43.6, 33.2, 31.1, 14.3, 14.1, 14.1; IR (neat) ν: 2980.6, 2978.3 (C-H), 1714.4, 1709.8 (C=O), 1249.1, 1237.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36; found: C, 62.91; H, 6.75; N, 3.62.

Ethyl (*E*)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (9g)



Prepared from pyrrole **1j** (52 mg, 0.2 mmol); yield: 59 mg (89%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.83 (s, 1H), 6.44 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.37 (dd, *J* = 3.3, 0.7 Hz, 1H), 7.05 (dt, *J* = 15.6, 4.0 Hz, 1H), 5.48 (dt, *J* = 15.6, 2.1 Hz, 1H), 4.31 (q, 2H, *J* = 7.1 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.81 (dd, *J* = 4.0, 2.1 Hz, 2H), 2.55 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 165.7, 165.1, 146.2, 142.7, 141.9, 137.0, 122.3, 123.6, 112.9, 111.1, 110.5, 107.4, 60.7, 59.6, 45.6, 14.5, 14.1, 11.0; IR (neat) ν: 1710.1 (C=O), 1246.0 (C-O), 1556.0 (C-H, furyl), 1070.7 (C=C-H), 773.8 (C-H, furyl) cm^{-1}; elemental analysis (%) calcd for $C_{18}H_{21}NO_5$: C 65.24, H 6.39, N 4.23; found: C 65.00, H 6.24, N 4.03.

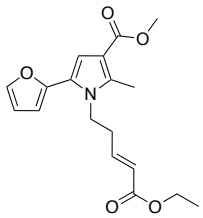
Ethyl (*E*)-4-(3-acetyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-1-yl)but-2-enoate (9h)



Prepared from pyrrole **1k** (0.5 mmol); yield: 98 mg (65%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.45 (m, 1H), 7.05 (dt, *J* = 15.6, 4.0 Hz, 1H), 6.78 (s, 1H), 6.47 – 6.45 (m, 1H), 6.38 – 6.37 (m, 1H), 5.48 (dt, *J* = 15.6, 2.0 Hz, 1H), 4.80 (dd, *J* = 4.0, 2.0 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 2.47 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63

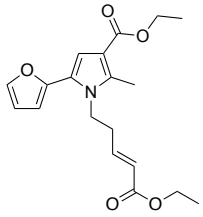
MHz, $CDCl_3$) δ 195.2, 165.9, 141.5, 134.2, 133.0, 128.6, 126.7, 126.1, 124.8, 122.9, 100.3, 61.3, 50.2, 28.4, 14.3, 12.6; IR (neat) ν: 2947.0, 2835.4 (C-H), 1695.7 (C=O), 1244.2, 1182.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{19}NO_4$: C 67.76, H 6.36, N 4.65; found: C 67.63, H 6.10, N 4.31.

Methyl (*E*)-1-(5-ethoxy-5-oxopent-3-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (9i)



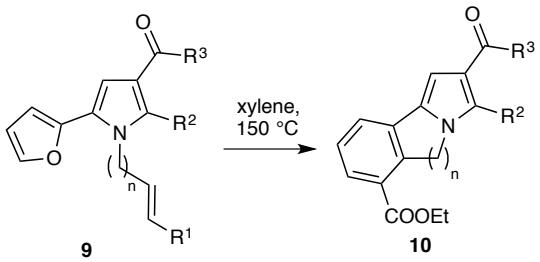
Prepared from pyrrole **1m** (0.5 mmol); yield: 120 mg (72%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.84 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.73 (s, 1H), 6.48 – 6.42 (m, 1H), 6.38 (dd, *J* = 3.3, 0.8 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.26 – 4.06 (m, 4H), 3.80 (s, 3H), 2.57 (s, 5H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 165.6, 146.6, 143.5, 141.9, 137.0, 123.8, 123.2, 112.0, 111.2, 110.6, 107.6, 60.4, 50.9, 43.4, 33.2, 14.2, 11.2; IR (neat) ν: 2950.4, 2946.0 (C-H), 1705.7 (C=O), 1244.2, 1182.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23; found: C, 64.91; H, 6.73; N, 4.12.

Ethyl (*E*)-1-(5-ethoxy-5-oxopent-3-en-1-yl)-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (9j)



Prepared from pyrrole **1l** (55 mg, 0.2 mmol); yield: 59 mg (85%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.77 (s, 1H), 6.47 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 0.7 Hz, 1H), 6.87 (dt, *J* = 15.7, 7.2 Hz, 1H), 5.86 (dt, *J* = 15.7, 1.4 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.17 – 4.11 (m, 2H), 2.60 (s, 3H), 2.64 – 2.53 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 166.0, 165.2, 146.7, 143.5, 141.8, 136.7, 123.7, 123.1, 112.4, 111.2, 110.7, 107.6, 60.4, 59.5, 43.4, 33.3, 14.5, 14.2, 11.2; IR (neat) ν: 1707.2 and 1606.8 (C=O), 1250.6 and 1194.2 (C-O), 1067.2 (C=C-H) cm^{-1}; elemental analysis (%) calcd for $C_{19}H_{23}NO_5$: C 66.07, H 6.71, N 4.06; found: C 66.32, H 6.38, N 3.80.

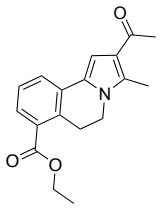
5.4.2. Preparation of compounds 10a-10k by intramolecular Diels Alder reactions



9 **10**

A solution of the suitable compound **9a**-**9j** (0.2 mmol) in xylene (1 mL) was refluxed for 36 h under argon atmosphere. The solvent was removed under reduced pressure. Purification of the residue by flash column chromatography on silica gel, eluting with a gradient from petroleum ether to 8:2 petroleum ether−ethyl acetate, afforded the desired compounds **10**.

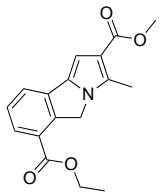
Ethyl 2-acetyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-7-carboxylate (10a)



Prepared from pyrrole **9a** (0.2 mmol); yield: 36 mg (60%); yellowish solid; mp: 151-153 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.80 – 7.71 (m, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.88 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.99 (t, *J* = 6.6, Hz, 2H), 3.54 (t, *J* = 6.6 Hz, 2H), 2.63 (s, 3H), 2.49 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 167.4, 135.2, 131.7, 130.0, 129.6, 128.3, 127.8, 126.8, 126.2, 121.7, 105.7, 61.0, 39.9, 28.6, 26.0, 14.3, 11.4; IR (neat) ν: 1678.9 (C=O), 1234.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{19}NO_3$: C 72.71 H 6.44, N 4.71; found: C 73.03, H 6.58, N 4.57.

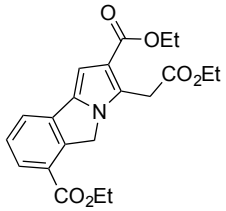
When the reaction from **9a** was performed in a flask open to air, it afforded 40% of compound **10a** and 25% of compound **10k**.

6-Ethyl 2-methyl 3-methyl-5*H*-pyrrolo[2,1-*a*]isoindole-2,6-dicarboxylate (10b)



Prepared from pyrrole **9b** (0.2 mmol); yield: 31 mg (52%); yellowish solid; mp: 165-167 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 6.73 (s, 1H), 5.16 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 2.62 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 165.9, 141.6, 134.4, 134.3, 133.4, 128.6, 126.5, 126.0, 123.0, 115.3, 100.1, 61.2, 50.8, 50.4, 14.3, 12.0; IR (neat) ν: 3056.1, 2949.4 (C-H), 1696.4 (C=O), 1211.1, 1202.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68; found: C, 67.94; H, 5.99; N, 4.86.

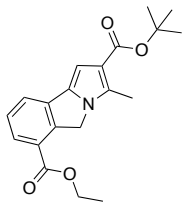
Diethyl 3-(2-ethoxy-2-oxoethyl)-5*H*-pyrrolo[2,1-*a*]isoindole-2,6-dicarboxylate (10c)



Prepared from pyrrole **9c** (0.2 mmol); yield: 62 mg (80%); yellowish solid; mp: 137-139 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.80 (s, 1H), 5.27 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.24 – 4.19 (m, 4H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.40 (d, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.3, 165.8, 165.2, 141.6,

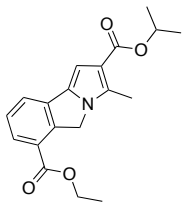
135.7, 134.1, 128.6, 128.5, 126.8, 125.9, 123.1, 117.2, 100.4, 61.2, 59.7, 50.9, 32.0, 14.4, 14.3, 14.2.; IR (neat) ν: 2980.8, 2934.1 (C-H), 1714.3, 1710.1 (C=O), 1244.2, 1222.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63; found: C, 65.21; H, 6.32; N, 3.96.

2-(^{t}Butyl) 6-ethyl 3-methyl-5*H*-pyrrolo[2,1-a]isoindole-2,6-dicarboxylate (10d)



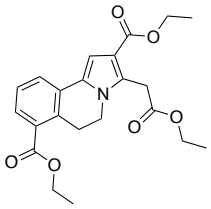
Prepared from pyrrole **9d** (0.2 mmol); yield: 62 mg (90%); yellowish solid; mp: 175-177 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.69 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 5.17 (s, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 1.62 (s, 9H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 165.1, 141.6, 134.6, 134.1, 132.6, 128.5, 126.3, 126.0, 122.9, 117.4, 100.4, 79.4, 61.2, 50.3, 28.5, 14.4, 12.0; IR (neat) ν: 2972.8, 2924.1 (C-H), 1686.3 (C=O), 1280.9, 1278.3 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{20}H_{23}NO_4$: 341.16271, found: 341.1611.

6-Ethyl 2-isopropyl 3-methyl-5*H*-pyrrolo[2,1-*a*]isoindole-2,6-dicarboxylate (10e)



Prepared from pyrrole **9e** (0.2 mmol); yield: 56 mg (87%); yellowish solid; Mp: 143-145 °C; ^{1}H NMR (250 MHz, $CDCl_{3z}$) δ 7.88 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.69 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.58 – 7.40 (m, 1H), 6.76 (s, 1H), 5.28 – 5.20 (m, 1H), 5.18 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.38 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 165.2, 141.6, 134.5, 134.3, 133.1, 128.6, 126.4, 126.0, 122.9, 116.1, 100.2, 66.5, 61.2, 50.3, 22.2, 14.4, 12.0; IR (neat) ν: 2947.0, 2835.4 (C-H), 1695.0 (C=O), 1270.7, 1234.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28; found: C, 69.43; H, 6.75; N, 4.61.

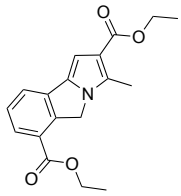
Diethyl 3-(2-ethoxy-2-oxoethyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2,7-dicarboxylate (10f)



Prepared from pyrrole **9f** (0.2 mmol); yield: 70 mg (87%); yellowish solid; Mp: 131-133 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 2H), 7.37 – 7.29 (m, 1H), 6.99 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 4.25 – 4.16 (m, 4H), 4.01 (t, *J* = 6.6 Hz, 2H), 3.55 (t, *J* = 6.6 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.7, 167.3, 165.0, 131.8, 130.7, 129.9, 129.5, 129.0, 128.4, 126.7, 126.5, 114.2, 105.7, 61.2, 61.0, 59.6, 40.8, 30.8, 26.0, 14.4, 14.3, 14.2; IR (neat) ν: 2980.2, 2978.1 (C-H), 1706.7, 1702.1 (C=O), 1234.2, 1182.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51; found: C,

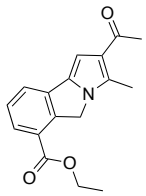
65.95; H, 6.75; N, 3.17. HRMS (MALDI TOF) calcd. for $C_{22}H_{25}NO_6$: 399.16819, found: 399.1695.

Diethyl 3-methyl-5*H*-pyrrolo[2,1-*a*]isoindole-2,6-dicarboxylate (10g)



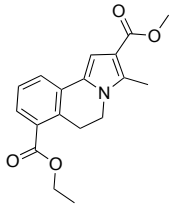
Prepared from pyrrole **9g** (52 mg, 0.2 mmol); yield: 44 mg (70%); white solid; mp: 162-164 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.7Hz, 1H), 6.76 (s, 1H), 5.18 (s, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 165.6, 141.6, 134.4, 134.3, 133.2, 128.5, 126.4, 126.0, 122.9, 115.6, 100.2, 61.2, 59.4, 50.3, 14.5, 14.3, 12.0; IR (neat) ν: 1678.9 (C=O), 1233.9 (C-O) cm^{-1}; elemental analysis (%) calcd for $C_{18}H_{19}NO_4$: C 69.00, H 6.11, N 4.47; found: C 68.76, H 6.00, N 4.25.

Ethyl 2-acetyl-3-methyl-5*H*-pyrrolo[2,1-*a*]isoindole-6-carboxylate (10h)



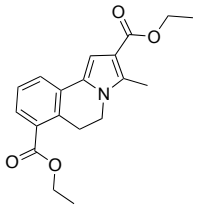
Prepared from pyrrole **9h** (0.2 mmol); yield: 34 mg (60%); yellowish solid; mp: 133-135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 5.19 (s, 2H), 4.46 (q, *J* = 7.1 Hz, 2H), 2.66 (s, 3H), 2.49 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 165.9, 141.5, 134.3, 134.2, 132.9, 128.6, 126.6, 126.0, 124.8, 122.9, 100.3, 61.3, 50.2, 28.4, 14.3, 12.6; IR (neat) ν: 1689.0 (C=O), 1236.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94; found: C 73.03, H 6.26, N 4.55.

7-Ethyl 2-methyl 3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2,7-dicarboxylate (10i)



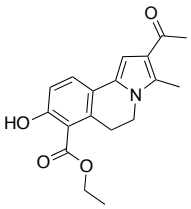
Prepared from pyrrole **9i** (0.2 mmol); yield: 50 mg (80%); yellowish solid; mp: 113-115 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.25 – 7.18 (m, 1H), 6.83 (s, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 3.88 (t, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 3.44 (t, *J* = 6.6 Hz, 2H), 2.50 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.4, 165.8, 135.7, 131.5, 130.1, 129.5, 128.1, 128.0, 126.7, 126.3, 112.4, 105.4, 61.0, 50.8, 40.1, 26.0, 14.3, 10.9; IR (neat) ν: 2980.6, 2974.7 (C-H), 1701.8 (C=O), 1222.2, 1189.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47; found: C, 69.37; H, 6.49; N, 4.69.

Diethyl 3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2,7-dicarboxylate (10j)



Prepared from pyrrole **9j** (55 mg, 0.2 mmol); yield: 46 mg (71%); yellow solid; mp: 89-92°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.95 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.61 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.4, 165.5, 135.5, 131.5, 130.2, 129.6, 128.0, 128.1, 126.4, 126.7, 112.9, 105.5, 61.0, 59.4, 40.1, 26.1, 14.5, 14.3, 10.9; IR (neat) ν: 1695.2 (C=O), 1228.2 (C-O) cm^{-1}; elemental analysis (%) calcd for $C_{19}H_{21}NO_4$: C 69.71, H 6.47, N 4.28; found: C 69.65, H 6.39, N 4.25.

Ethyl 2-acetyl-8-hydroxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-7-carboxylate (10k)

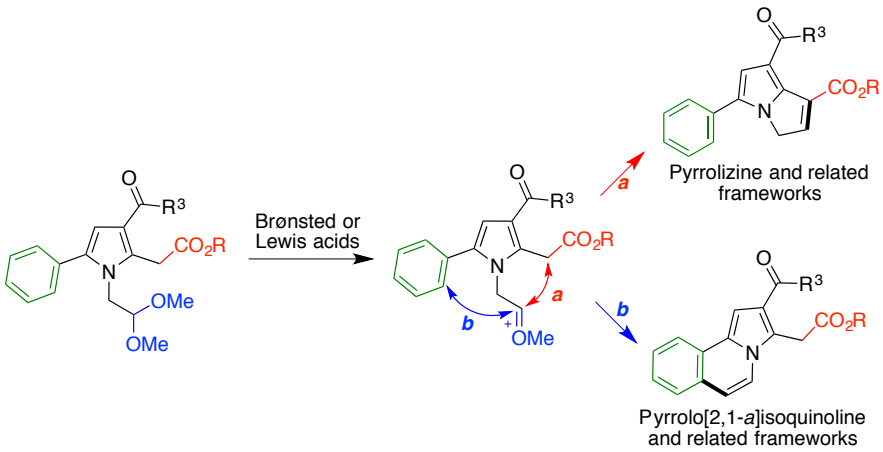


Prepared from pyrrole **9a** (0.2 mmol) under air; yield: 25 mg (25 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.99 (br s, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.72 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 3.96 (t, *J* = 6.6 Hz, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 2.61 (s, 3H), 2.47 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.0, 170.8, 160.8, 134.2, 132.3, 129.6, 128.0, 121.9, 121.6, 117.1, 112.0, 103.9, 62.1, 39.8, 28.6, 27.8, 14.2, 11.3 ;IR (neat) ν: 1689.0 (C=O, 1231.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{19}NO_4$: C 68.99, H 6.11, N 4.47; found: C 69.05, H 6.56, N 4.26.

6. Ring creation *via* oxonium intermediates

6.1 Introduction

The possibility to synthesize pyrrole derivatives with a nitrogen substituent ending in an acetal group opens up the possibility to readily generate oxonium species by treatment with Brønsted or Lewis acids. These intermediates can be suitable substrates for ring-creation processes leading to fused pyrrole systems by cyclization onto the C-2 or C-5 substituents, leading respectively, to pyrrolizine and related frameworks (route ***a*** in Scheme 6.1) or pyrrolo[2,1-*a*]isoquinoline and related frameworks (route ***b***).



Scheme 6.1

6.2. Cyclization onto a C-2 active methylene. Synthesis of the pyrrolizine framework from pyrrole precursors

6.2.1. A brief outline of pyrrolizine and pyrrolizidine derivatives

Alkaloids derived from the pyrrolizine, dihydropyrrolizine and pyrrolizidine ring systems (Figure 6.1) are very abundant in the *Asteraceae, Boraginaceae* and *Fabaceae* families. They probably serve a role as plant chemical defense against insects and grazing animals.[84]

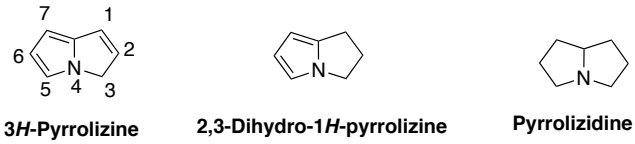


Figure 6.1

As shown in Figure 6.2, some other more complex alkaloids as for example the antitumor antibiotic mitomycin C[85] contain the structural core of pyrrolizidine. The dihydropyrrolizine moiety has been employed for the generation of arylacetic acids with analgesic, antipyretic and anti-inflammatory activities.[86] For instance, ketorolac is a non-selective inhibitor of isoforms 1 and 2 of cyclooxygenase and licofelone (ML-3000) is the precursor of a family of dual inhibitors of COX and lipooxogenase.[87] Some selective inhibitors of COX-2 containing a dihydropyrrolizine core are also known, such as compound **I**.[88]

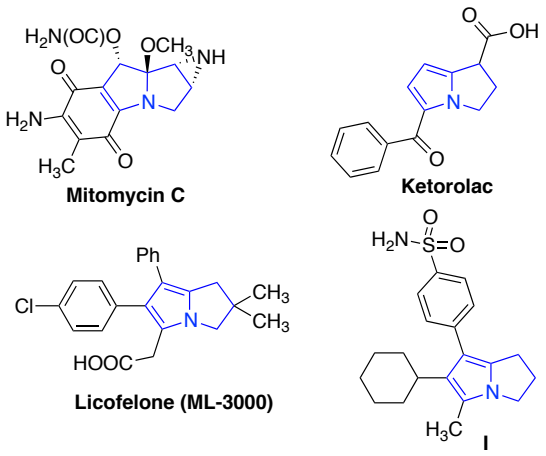


Figure 6.2

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[84] (a) Wiedenfeld, H. *Food Addit. Contam.,* **2011**, *28*, 282; (b) Flitsch, W. *Adv. Heterocycl. Chem.* **1984**, 37, 1.

[85] (a) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc.*, **1989**, *111* , 8303; (b) Kovalchuk, A.; Kolb, B. *Cell Cycle* **2017**, *16*, 1345.

[86] For a review, see: Gouda, A. M.; Abdelazeem, A. H. *Eur. J. Med. Chem*., **2016**, *114*, 257.

[87] Laufer, S.; Striegel, H.-G.; Neher, K.; Zechmeister, P.; Donat, C.; Stolingwa, K.; Baur, S.; Tries, S.; Kammermeier, T.; Dannhardt, G.; Kiefer, W. *Arch. Pharm*., **1997**, *330*, 307.

[88] Striegel, H. G.; Laufer, S.; Tollmann, K.; Tries, S.; European Patent EP 1246825 A1 (9 Oct 2002).

The most commonly employed methods for the synthesis of pyrrolizine or dihydropyrrolizine[89] are based on the formation of the 1-2 bond by intramolecular anion alkylation reactions, or by intramolecular Wittig reactions. Other strategies involve the creation of the 4-5 bond by intramolecular condensation reactions (Figure 6.3). In all cases, the preparation of the starting pyrrole derivative is carried out by a sequence of several steps, and the routes do not represent general and versatile synthetic methods.

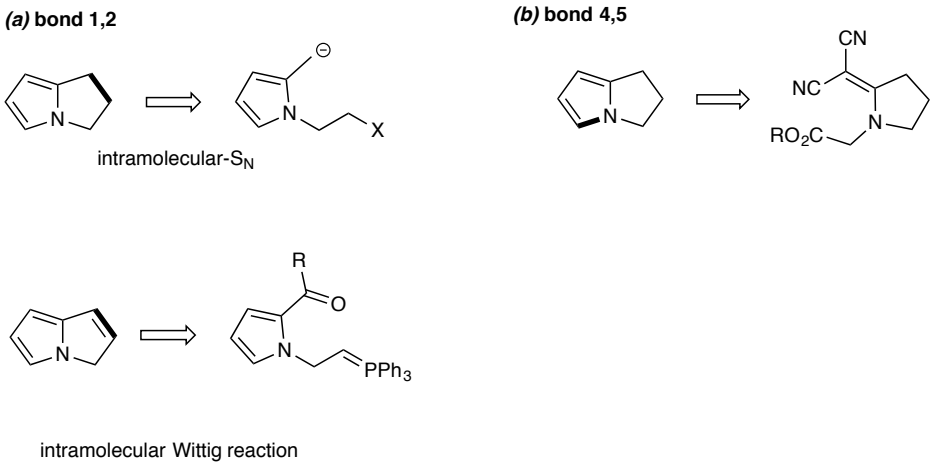
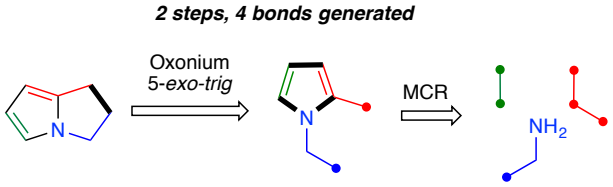


Figure 6.3

6.2.2. Synthesis of the pyrrolizine ring system from pyrrole precursors

The work presented in this thesis represents the generation of the pyrrolizine framework in two steps and is based on the formation of four bonds and two rings as summarized in Scheme 6.2.

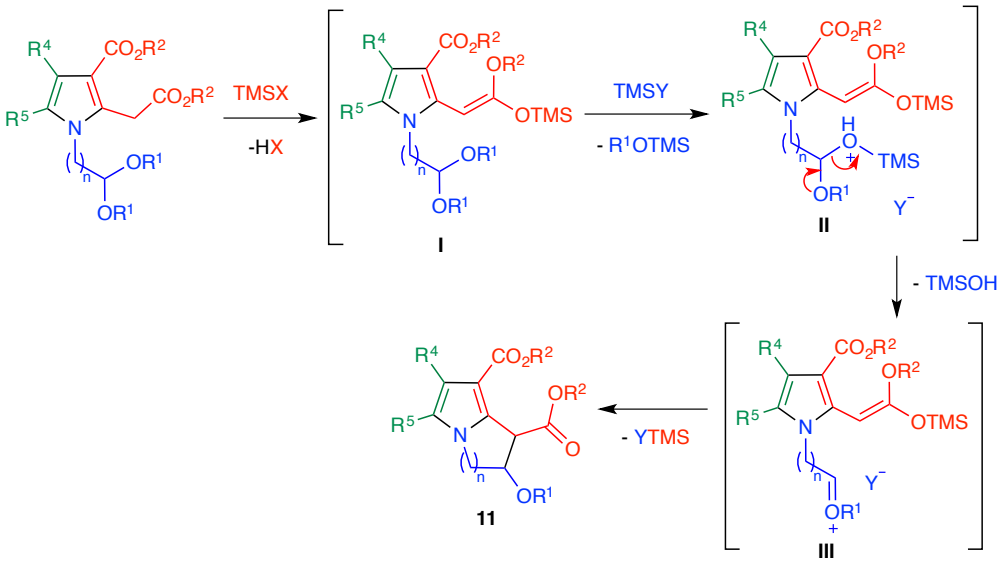


Scheme 6.2

In our approach, the final stage is based on a 5-*exo-trig* cyclization of an oxonium intermediate, generated from a starting acetal. The preparation of suitable starting pyrroles has been previously described using under our mechanochemical three-component pyrrole synthesis from dialkoxyalkylamines, a ketone and a symmetrical 1,3,5-tricarbonyl compound. To achieve the desrired cyclization, we studied the activation of the aliphatic position at C-2, neighboring the ester group as a nucleophile,

[89] (a) Flitsch, W. *Adv. Heterocycl. Chem.*, **1984**, *37*, 1; (b) Hall, G.; Sugden, J. K.; Waghela M. B. *Synthesis*, **1987**, *1*, 10; (c) Gilchrist, L. T.; Lemos, A. *Tetrahedron,* **1992**, *48*, 7655.

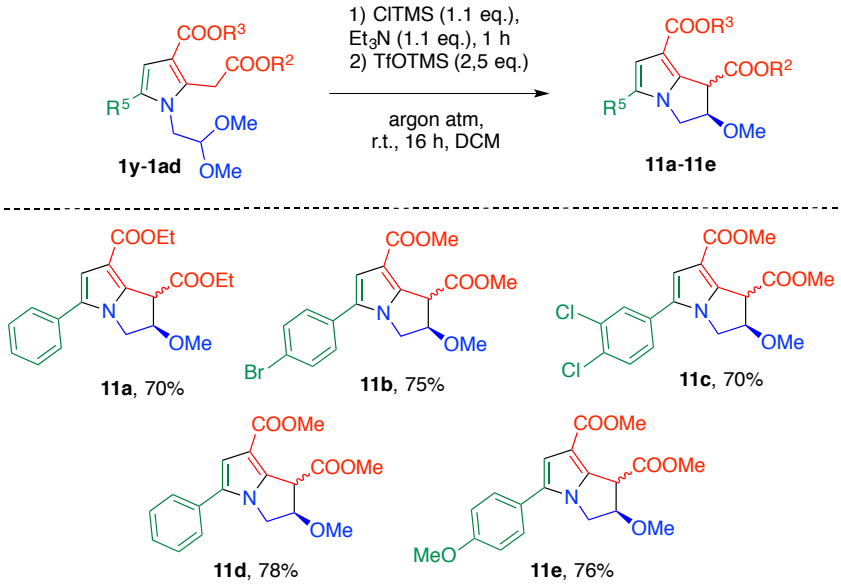
by formation of the corresponding trimethylsilyl enol ether with trimethylsilyl chloride, and the simultaneous generation of an oxonium cation by treatment of the acetal function with trimethylsilyl triflate, under Noyori conditions The planned domino process proceeds through the intermediacy of species **I**, **II** and **III** (Scheme 6.3).



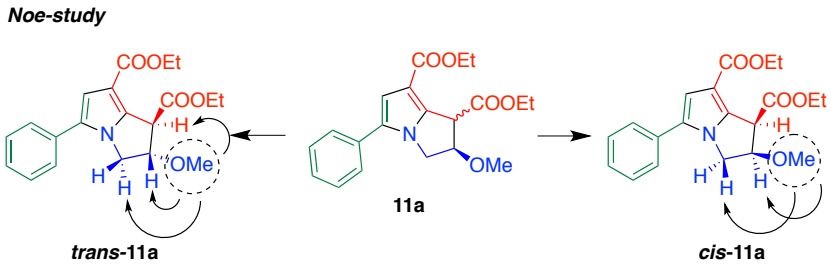
Scheme 6.3

Our initial attempts were carried out from pyrrole derivative **1y** using 2.5 equivalents of trimethylsilyl chloride (X = Y = Cl) and triethylamine, with no success. We changed the conditions to combine trimethylsilyl chloride (X = Cl) to generate intermediate **I**, followed by a catalytic amount (0.2 to 0.4 equivalents) of trimethylsilyl triflate (Y = OTf), but again these attempts were unsuccessful. Finally we found that the use of trimethylsilyl chloride (X = Cl) followed by an over-stoichiometric amount of trimethylsilyl triflate (X = Y = OTf) led to the desired cyclization. It is important to note that the order of addition of the reagents needs to be as follows: first the trimethylsilyl chloride and the triethylamine are added and, at least one hour later to ensure the formation of intermediate **II**, trimethylsilyl triflate is added and the reaction left to continue for 16 hours.

Using these conditions, we obtained a small library of compounds **11**, summarized in Scheme 6.4. All these derivatives were obtained as a 1:1 mixture of the two possible diasteroisomers, which were separated and characterized by NOE experiments for the case of **11a** as a representative example (Scheme 6.5). Some attempts were made to run the reaction at lower temperatures, but the ratio of diasteroisomers did not significantly change. Work on this reaction is ongoing in order to increase its scope.

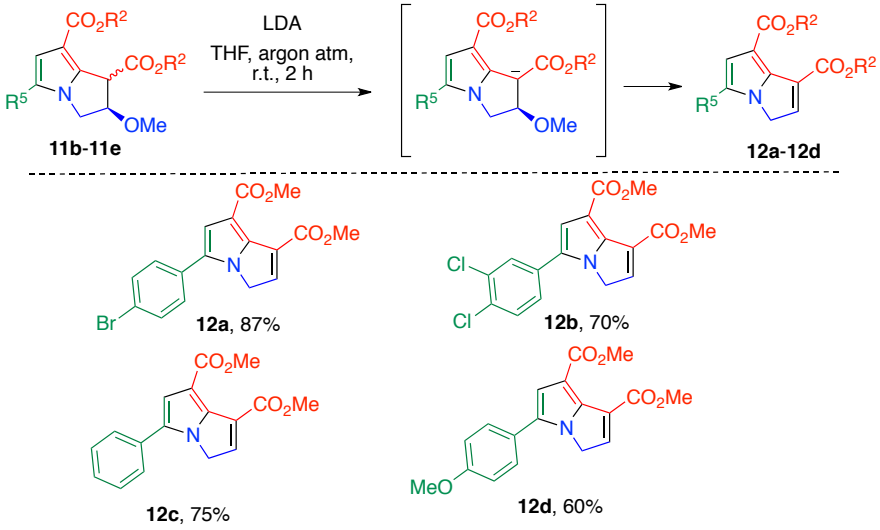


Scheme 6.4



Scheme 6.5

Treatment of the crude compounds **11** with 1.2 equivalents of LDA at room temperature for 2 h in THF, under an argon atmosphere, led to the isolation of the corresponding pyrrolizine derivatives **12** *via* a base-promoted elimination of methanol, as shown in Scheme 6.6.



Scheme 6.6

6.3. Cyclization onto a C-5 aryl substituent. Synthesis of pyrrolo[2,1-*a*]isoquinoline and related frameworks

6.3.1. Introduction

Polyheterocyclic scaffolds, and in particular heterocycles with a ring-fusion nitrogen atom, are increasingly attractive in drug discovery programs[90] and there is therefore a demand for synthetic methods allowing their rapid and efficient construction from simple starting materials.[91] Among these ring systems, the pyrrolo[2,1-*a*]isoquinoline scaffold constitutes the structural core of a large family of alkaloids,[92] including lamellarine D, a potent topoisomerase I inhibitor,[93] annosqualine, crispine A, antitumor alkaloids, and trolline,[94] known in the traditional Chinese medicine for having effect against respiratory infections (Figure 6.4). Its unnatural derivatives have shown interesting pharmacological properties such as antidepressant,[95] cardiotonic[96] and serotonin uptake modulating activities.[97]

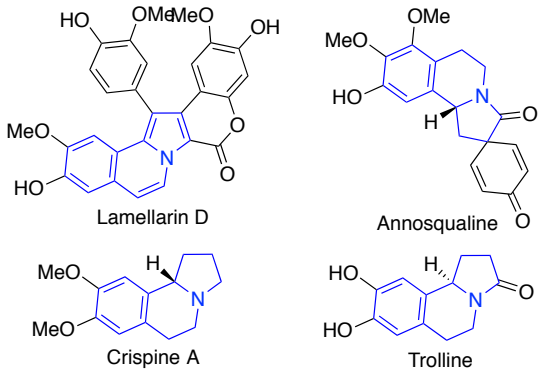


Figure 6.4

Despite the existence of several synthetic approaches to the fully unsaturated pyrrolo[2,1-*a*]isoquinoline system, most published methods involve multi-step

---

90 For representative examples, see: (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*., **2003**, *103*, 893. (b) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippoin, D. A. *Comb. Chem. High Throughput Screen*., **2004**, *7*, 473. (c) Oh, S.; Park, S. B. *Chem. Commun.,* **2011**, *47*, 12754. (d) Collins, I.; Jones, A. M. *Molecules,* **2014**, *19*, 17221. (e) Lenci, E.; Guarna, A.; Trabocchi, A. *Molecules,* **2014**, *19*, 16506. (f) Wang, S.; Fang, F.; Dong, G.; Chen, S.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng, C. *J. Med. Chem.,* **2015**, *58*, 6678.

91 For representative examples, see: (a) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett*., **2012**, *14*, 3894. (b) Suryavanshi, P. A.; Sridharan, V.; Menéndez, J. C. *Chem. Eur. J.,* **2013**, *19*, 13207. (c) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nature Chem.,* **2014**, *6*, 57. (d) Zheng, L.; Bin, Y.; Wang, Y.; Hua, R. *J. Org. Chem.,* **2016**, *81*, 8911. For representative reviews, see: (e) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Nat. Prod. Rep*., **2008**, *25*, 719. (f) García-Castro, M.; Zimmermann, S.; Sankar, M. G.; Kumar, K. *Angew. Chem. Int. Ed.,* **2016**, *55*, 7586.

92 Pässler, U.; Knölker, H.-J. *The Alkaloids,* **2011**, *70*, 79.

93 For reviews, see: (a) Fukuda, T.; Ishibashi, F.; Iwao, M. *Heterocycles,* **2011**, *83*, 491. (b) Pla, D.; Albericio, F.; Álvarez, M. *Med. Chem. Commun*., **2011**, *2*, 689.

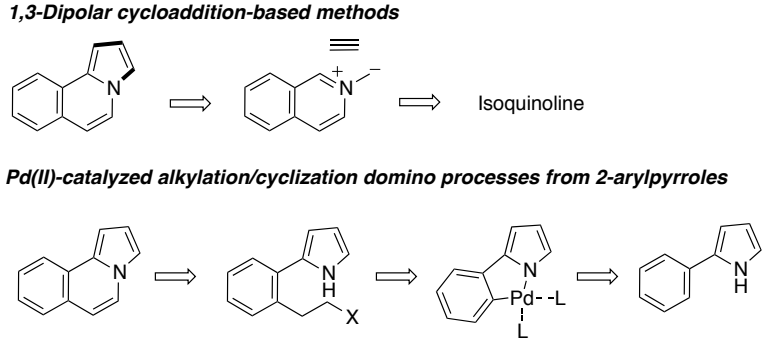
94 Zhao Y.-X.; Ding X.-B. *Yaoxue Xuebao*, **2004,** *39*, 598.

95 Sorgi, K. L.; Maryanoff, C. A.; McComsey, D. F.; Graden, D. W.; Maryanoff, B. E. *J. Am. Chem. Soc*., **1990**, *112*, 3567.

96 Maryanoff, B. E.; Maryanoff, C. A.; McComsey, D. F.; Sorgi, K. L. U.S. Patent, 4,837,328 (Jan 31, 1989).

97 Goodman, M. M.; Shi, B. Z. U.S. Patent, 6,162,417 (Dec 19, 2000).

strategies and normally require harsh reaction conditions.[98] Among them, the most general method is based on 1,3-dipolar cycloadditions between isoquinolinium N-ylides and alkynes[99], or a Pd(II)-catalyzed protocol for the alkylation of the phenyl ring 2-phenylpyrroles, followed by allylation and a "Pd-induced pyrrole addition" (Scheme 6.7).[100] Lamellarin precursors or derivatives are usually synthesized by multistep procedures starting from suitable methyl pyrrole-2-carboxylate derivatives, including N-alkylation/intramolecular Heck reaction/ dehydrogenation[101] or N-alkylation/triflic acid-promoted Pomeranz-Fritsch[102] sequences (Scheme 6.7).

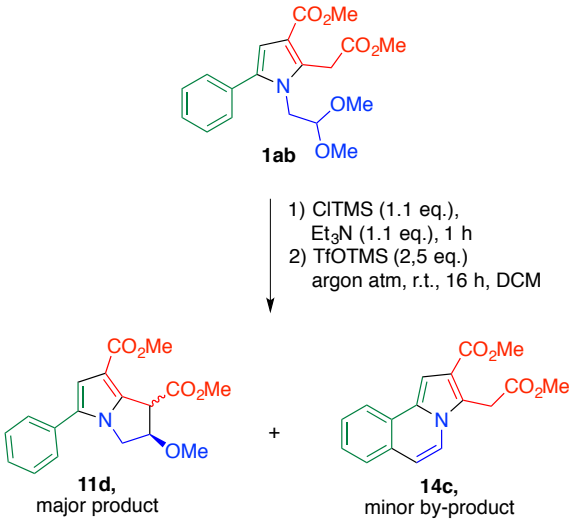


Scheme 6.7

[98] For a review, see: Mikhailovskii, G.; Shklyaev, V. S. *Chem. Heterocycl. Compd*., **1997**, *33*, 243.
[99] Dumitrascu, F.; Georgescu, E.; Georgescu, F.; Popa, M. M.; Dumitrescu, D. *Molecules,* **2013**, *18*, 2635.
[100] Wiest, J. M.; Pöthig, A.; Bach, T. *Org. Lett.,* **2016**, *18*, 852.
[101] Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Álvarez, M. *J. Org. Chem*., **2005**, *70*, 8231.
[102] Dialer, C.; Imbri, D.; Hansen, S. P.; Opatz, T. *J. Org. Chem*., **2015**, *80*, 11605.

6.3.2. Preparation of pyrrolo[2,1-a]isoquinolines and related frameworks

During the study for the optimization of the reaction to obtain the pyrrolizine derivative **10a**, the generation of a minor by-product, later identified as arising from a Pomeranz-Fritsch cyclization and having the structure **14d** was detected (Scheme 6.8).



Scheme 6.8

In an effort to deviate the reaction towards **14a**, we carried out a similar experiment with only TMSOTf as catalyst in a large excess of 1.5 equivalents and observed the presence of **14a** as the only significant component of the reaction crude. On this basis, we undertook an optimization study that is summarized in Table 6.1. The usual conditions for the Pomeranz-Fritsch isoquinoline synthesis require the use of strong Brønsted acids but, because of the success of the experiment with TMSOTf and the potential low stability of pyrrole derivatives under such harsh conditions, we sought to perform our transformation in the presence of Lewis acids. Thus, the preparation of model compound **14a** from the corresponding pyrrole **1y** was assayed in the presence of a large excess of aluminium trichloride in dichloroethane,[103] with modest yields (Table 6.1, entries 1 and 2). In the presence of excess boron trifluoride etherate in 1,4-dioxane,[104] the reaction failed at room temperature (entry 3) but afforded **14a** in 69% yield at 120 °C. In an effort to improve this result, we resorted to the previously employed trimethylsilyl triflate, which is well known to activate acetals via the formation of oxonium species[105] but has received very little attention for cyclization reactions leading to heterocyclic systems, and not always acts as a catalyst in the few examples known.[106] In our initial experiment, **1y** had been transformed into **14a** in an

[103] Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. G. *J. Org. Chem.,* **1980**, *45*, 1950.
[104] Hewlins, M. J. E.; Salter, R. *Synthesis,* **2007**, 2157.
[105] Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron,* **1988**, *44*, 4259.
[106] (a) Pictet-Spengler-type reaction: González, J. F.; Salazar, L.; de la Cuesta, E.; Avendaño, C. *Tetrahedron,* **2005**, *61*, 7447 (using stoichiometric TMSOTf). (b) Intramolecular Pummerer reaction:

excellent 90% yield in the presence of TfOTMS (1.5 eq.) in dry dichloromethane under an argon atmosphere. The reaction was very fast, and was complete in only 5 min at room temperature (entry 5). Subsequent experiments proved that the reaction could be carried out open to the air (entry 6) and in the presence of catalytic amounts of trimethylsilyl triflate (entry 7) without loss in yield. The optimal conditions involved the use of 15% of the catalyst (entry 8).

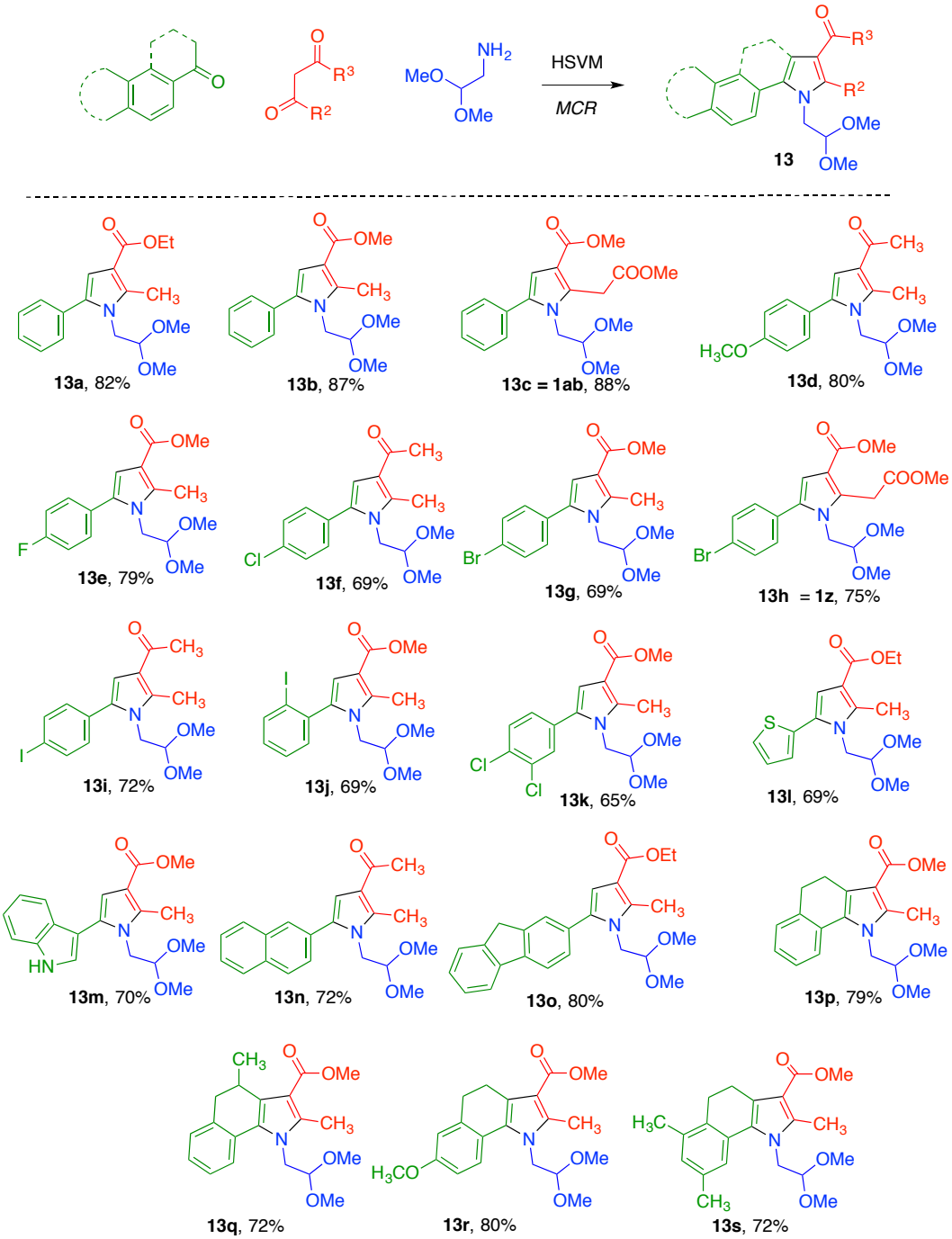
Table 6.1. Optimization of the Pommeranz-Fritzsh-type cyclization leading to compound 14a

Entry	Catalyst (%)	Conditions	Yield, %
1	$AlCl_3$ (400)	DCE, rt, 8 h (Ar)	30
2	$AlCl_3$ (400)	DCE, rt, 24 h (Ar)	50
3	$BF_3.Et_2O$ (500)	Dioxane, rt, 4 h (Ar)	0
4	$BF_3.Et_2O$ (500)	Dioxane, 120 °C, 0.5 h (Ar)	69
5	TfOTMS (150)	DCM, rt, 5 min (Ar)	90
6	TfOTMS (100)	DCM, rt, 5 min (air)	89
7	TfOTMS (50)	DCM, rt, 5 min (air)	88
8	TfOTMS (15)	DCM, rt, 5 min (air)	89

In order to study the scope of this transformation, we needed a library of pyrroles bearing a 2,2-dimethoxyethyl substituent on nitrogen (compounds **13**), which were prepared under our usual conditions (Scheme 6.9). It is interesting to highlight that, as previously mentioned, the mildness of the reaction conditions and the absence of solvent under our mechanochemical conditions prevented CAN-promoted side reactions at the acetal functional group.[107]

Komatsubara, M.; Umeki, T.; Fukuda, T.; Iwao, M. *J. Org. Chem*., **2014**, *79*, 529 (requires a separate oxidative step for aromatization). (c) Tang, E.; Zhao, Y.; Li, W.; Wang, W.; Zhang, M.; Dai, X. *Org. Lett.,* **2016**, *18*, 912.

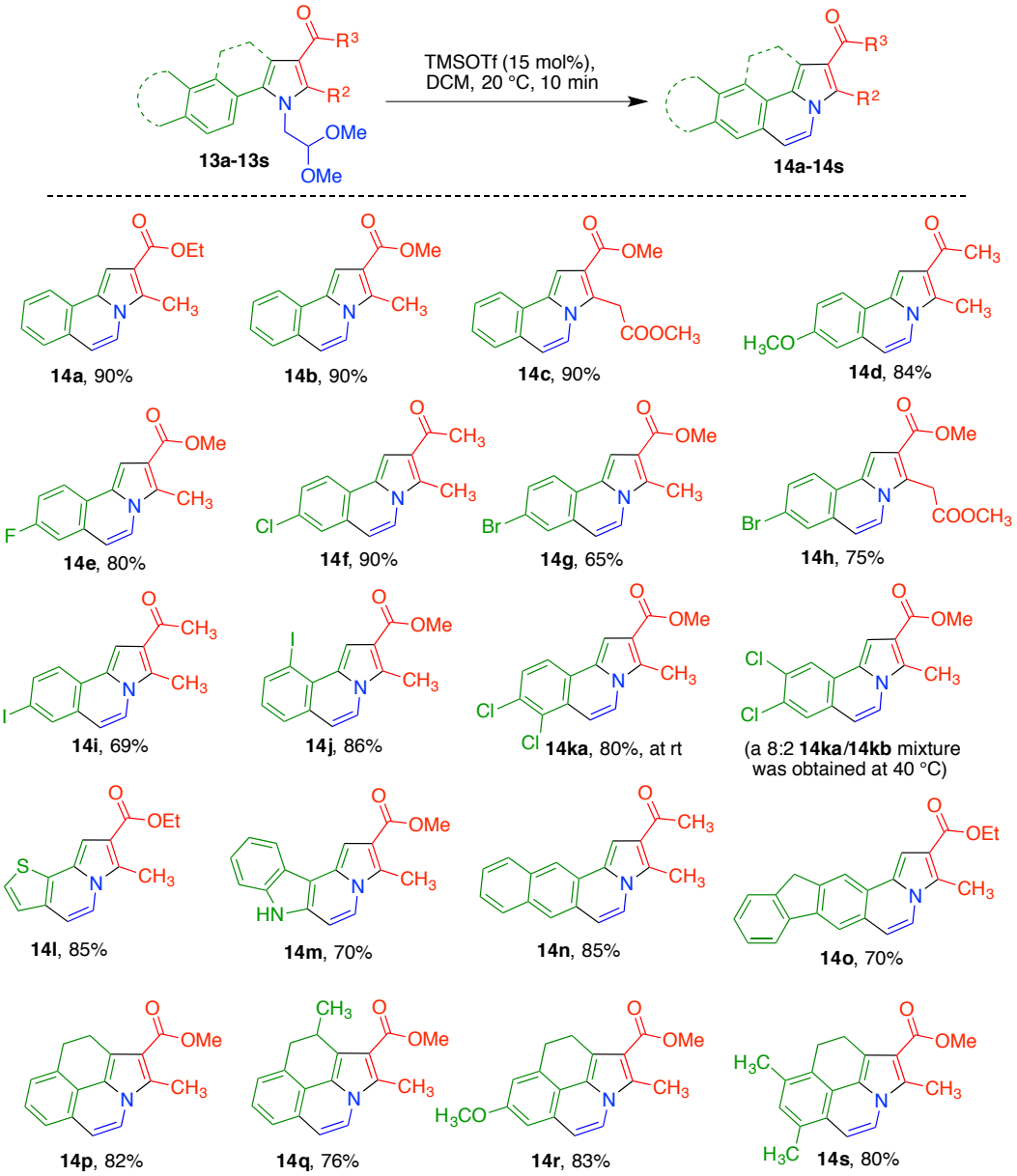
[107] As an example of such transformations, CAN is an excellent catalyst for the hydrolysis of acetals and ketals. See: Maulide, N.; Vanherck, J.-C.; Gautier, A.; Markó, I. E. *Acc. Chem. Res.,* **2007**, *40*, 381.



Scheme 6.9

Using the optimized conditions, we studied the scope of the TMSOTf-promoted Pommeranz-Fritzsch reaction on these structurally varied substrates, which allowed us to study the influence of the nature of the substituents on the C-5 aromatic ring on the electrophilic aromatic substitution step. We found that the reaction allowed a wide range of substitutions working well with unsubstituted phenyl derivatives (**14a**-**14c**) and also when electron-releasing groups were present on the C-5 substituent (**14d**). Interestingly, the presence of electron-withdrawing groups did not hamper the reaction, allowing the preparation of fluoro- (**14e**), chloro- (**14k**), bromo- (**14g**, **14h**)

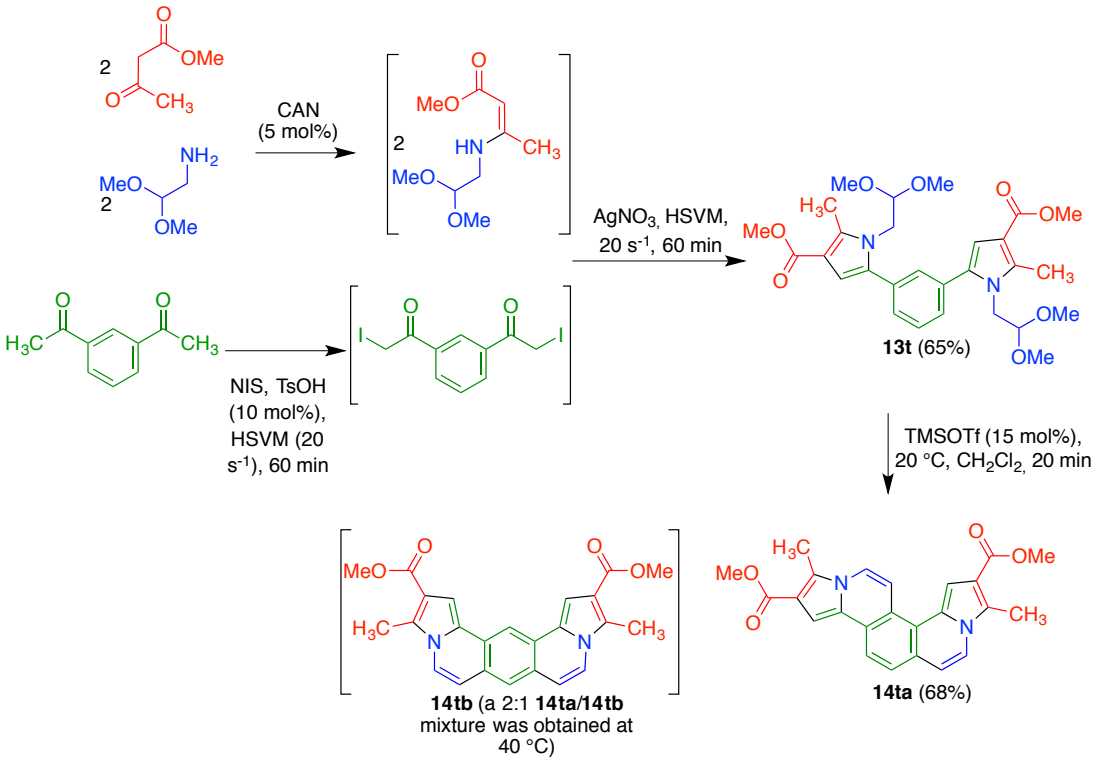
and iodo- (**14i**, **14j**) derivatives. These substituents are synthetically relevant because they represent potential synthetic handles for additional functionalization of these compounds using cross-coupling chemistry. The presence of two Cl substituents in the C-5 aryl ring was also well tolerated in terms of reactivity. Under the usual conditions at 20 °C this reaction afforded exclusively the 7,8-dichloro derivative **14ka**, while a higher temperature (40 °C) led to an 8:2 **14ka**/**14kb** mixture. Replacement of the 5-phenyl by other aromatic substituents such as 2-thienyl, 3-indolyl, 2-naphthyl and 2-fluorenyl was represented by compounds **14l**, **14m**, **14n** and **14o**, respectively, and took place with no loss in efficiency and yields. Literature precedent for these frameworks is very scarce (**14l**, **14m**) or non-existent (**14n**, **14o**). The use of 1-tetralone as the ketone component



Scheme 6.10

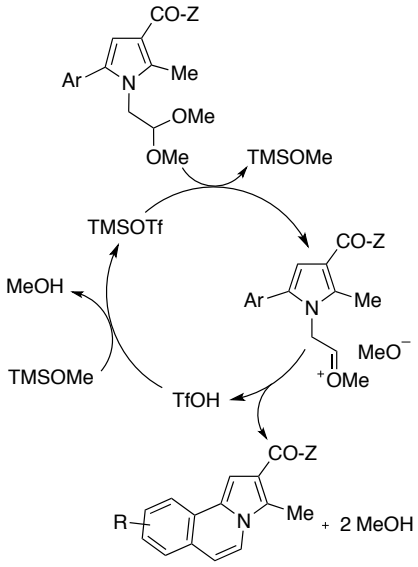
allowed the synthesis of compounds **14p**-**14s**, derived from the hitherto unknown benzo[*de*]pyrrolo[3,2,1-*ij*]quinoline framework.

As a final effort to increase the structural complexity in the final architecture and expand the scope of the method, we examined double TMSOTf-promoted cyclizations. The required starting material **13t** was prepared *via* a pseudo-five component reaction from 1,3-diacetylbenzene, and the cyclization proceeded uneventfully and yielded the angular pentacyclic compound **14ta** when the reaction was performed at 20 °C, and a 2:1 mixture of **14ta** and its linear regioisomer **14tb** at 40 °C (Scheme 6.11). Again, derivatives **14ta** and **14tb** represent previously unknown frameworks.



Scheme 6.11

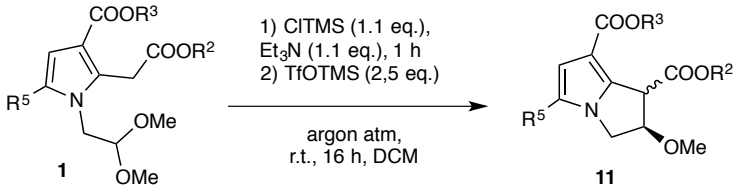
The cyclization reaction is assumed to proceed by the mechanism proposed in Scheme 6.12. The reaction starts with the activation of the acetal by the TMSOTf catalyst. The acetal so activated can easily undergo the attack of the aromatic ring in position C-5 to produce the final cyclization product with loss of two molecules of methanol and the generation of triflic acid. The acid thus regenerates the TMSOTf catalyst from TMSOMe and starts another catalytic cycle.


CO-Z
Ar
N
Me
OMe
OMe
TMSOMe
TMSOTf
CO-Z
MeOH
Ar
N
Me
MeO⁻
TMSOMe
+OMe
TfOH
CO-Z
R
N
Me
+ 2 MeOH

Scheme 6.12

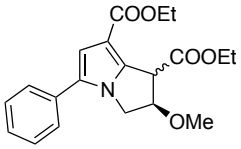
6.4. Experimental section

6.4.1. General procedure for the synthesis of 1,2-dihydro-3H-pyrrolizine derivatives 11a-11e



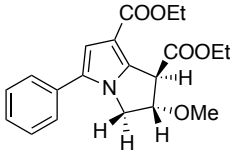
The required amount of the chosen pyrrole **1y**-**1ac** (1 eq) is added to a round bottom flask under argon atmosphere. Then 1 ml of anhydrous DCM was added and was followed by TMS chloride (1.1 eq) and Et_3N (1.1 eq), in this order. The reaction was stirred for 1 h at room temperature and, then, TfOTMS (2.5 eq). The stirring is maintained for additional 16 h, after which the reaction is controlled by TLC using ether phase as mobile phase ethyl acetate 8:2. When the reaction was finished, the mixture was washed with $KHCO_3$. The aqueous phase was extracted with chloroform, this process will be repeated as many times as necessary until it is well extracted. Finally, the organic phase are dried with anhydrous sodium sulphate and concentrated under *vacuum*. The product obtained is purified by flash column using hexane: ethyl acetate as the mobile phase. For compounds **11b**-**11e** only the work-up has been done because the crude undergoes directly to the subsequent reaction of elimination in order to lead to only one regioisiomer.

Diethyl 2-methoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,7-dicarboxylate (11a)



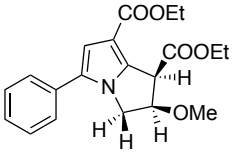
Prepared from compound **1y** (0.3 mmol); yield: 78 mg (70 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 – 7.30 (m, 10H), 6.85 (s, 1H), 6.83 (s, 1H), 4.78 – 4.49 (m, 4H), 4.37 – 4.12 (m, 12H), 3.55 (s, 3H), 3.48 (s, 3H), 1.39 – 1.25 (m, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6, 168.7, 164.3, 138.7, 138.3, 132.0, 131.9, 130.6, 130.1, 128.8, 128.8, 128.3, 127.0, 126.9, 126.1, 126.1, 111.8, 110.9, 110.3, 110.1, 86.9, 83.4, 61.5, 61.1, 59.7, 59.6, 58.8, 57.2, 53.1, 51.0, 50.9, 48.2, 14.5, 14.3, 14.2; IR (neat) ν: 3099.9 (C-H), 1766.5 and 1733.6 (C=O), 1205.1 cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; found: C, 67.43; H, 6.80; N, 3.59.

***Trans*-Diethyl 2-methoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,7-dicarboxylate (11aa)**



Isolated from compound **11a** by chromatography 1:1:0.1 DCM/Ex/MeOH; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.75 (s, 1H), 4.54 (dt, *J* = 5.6, 2.2 Hz, 1H), 4.44 (dd, *J* = 11.4, 5.6 Hz, 1H), 4.27 – 3.98 (m, 6H), 3.38 (s, 3H), 1.28 – 1.19 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6, 164.3, 138.7, 132.0, 130.1, 128.8, 126.9, 126.0, 111.9, 110.1, 86.9, 61.4, 59.6, 57.2, 53.1, 51.0, 14.5, 14.1; IR (neat) ν: 3140.2, 2955.5 (C-H), 1655.2 and 1625.2 (C=O), 1229.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; found: C, 67.44; H, 6.23; N, 3.65.

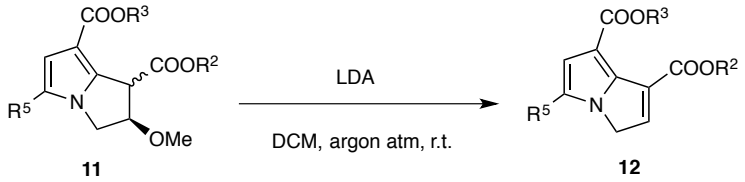
***Cis*-Diethyl 2-methoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,7-dicarboxylate (11ab)**



Isolated from compound **11a** by chromatography 1:1:0.1 DCM/Ex/MeOH; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 – 7.33 (m, 5H), 6.83 (s, 1H), 4.72 (q, *J* = 7.6 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 4.42 (dd,

J = 10.3, 7.1 Hz, 1H), 4.34 – 4.19 (m, 5H), 3.55 (s, 3H), 1.34 (dd, *J* = 12.2, 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.7, 164.3, 138.3, 132.0, 130.6, 128.8, 127.0, 126.1, 110.9, 110.3, 83.4, 61.2, 59.7, 58.9, 50.9, 48.2, 14.4, 14.3, IR (neat) ν: 2993.0 (C-H), 1677.2 and 1645.2 (C=O), 1234.0 (C-O) cm^{-1}.

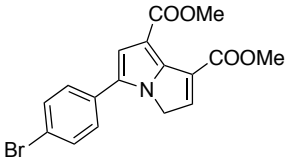
6.4.2. General procedure for the base-promoted elimination affording derivatives 12a-12d



11 12

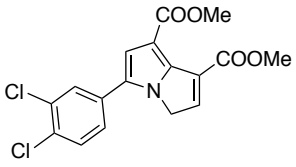
The required amount of the starting pyrrole **11c**-**11f** (0.1 mmol) is added to a round bottom flask under argon atmosphere with THF and then LDA (1.2 equivalents) are added. The mixture is stirred for 1 hour and then controlled by TLC. The product **12** obtained is purified by flash column using 8:2 hexane: ethyl acetate as the mobile phase.

Dimethyl 5-(4-bromophenyl)-3*H*-pyrrolizine-1,7-dicarboxylate (12a)



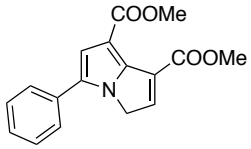
Prepared from compound **11c** (0.1 mmol), formed from **1z**; yield: 33 mg (87 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 0.9 Hz, 1H), 6.89 – 6.86 (m, 1H), 4.77 (d, *J* = 2.1 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.2, 141.2, 133.1, 132.1, 131.8, 130.8, 130.3, 126.3, 120.9, 112.5, 107.7, 52.9, 52.5, 51.3; IR (neat) ν: 3140.2, 2955.5 (C-H), 1655.2 and 1625.2 (C=O), 1229.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{14}BrNO_4$: C, 54.28; H, 3.75; N, 3.72; found: C, 54.11; H, 3.92; N, 3.44.

Dimethyl 5-(3,4-dichlorophenyl)-3*H*-pyrrolizine-1,7-dicarboxylate (12b)



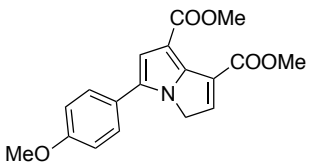
Prepared from compound **11d** (0.1 mmol), formed from **1aa**; yield: 26 mg (70 %); transparent oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.1 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.01 (d, *J* = 0.8 Hz, 1H), 6.93 – 6.87 (m, 1H), 4.79 (d, *J* = 2.1 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.1, 141.6, 133.3, 133.1, 131.7, 131.3, 130.9, 130.8, 129.4, 126.2, 123.9, 113.7, 107.9, 53.0, 52.5, 51.3; IR (neat) ν: 3111.3, 2923.1 (C-H), 1698.2 and 1675.3 (C=O), 1264.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{13}Cl_2NO_4$: C, 55.76; H, 3.58; N, 3.83; found: C, , 55.34; H, 3.22; N, 3.98.

Dimethyl 5-phenyl-3*H*-pyrrolizine-1,7-dicarboxylate 12c)



Prepared from compound **11e** (0.1 mmol), formed from **1ab**; yield: 23 mg (75 %); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 3H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 4.79 (d, *J* = 1.9 Hz, 2H), 3.96 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.4, 140.9, 132.9, 131.9, 131.7, 131.4, 128.9, 127.2, 124.9, 112.0, 107.5, 52.9, 52.5, 51.2; IR (neat) ν: 2899.9 (C-H), 1777.9 and 1732.5 (C=O), 1255.5 cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71; found: C, 68.43; H, 5.33; N, 4.39.

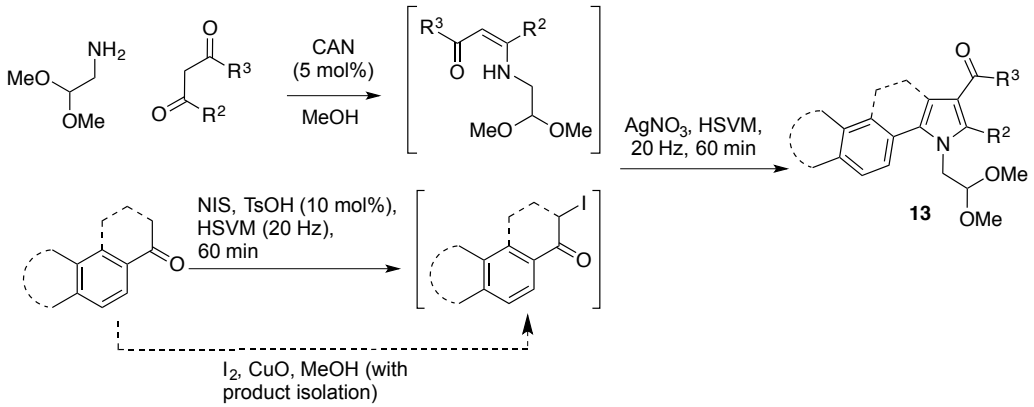
Dimethyl 5-(4-methoxyphenyl)-3*H*-pyrrolizine-1,7-dicarboxylate (12d)



Prepared from compound **11f** (0.1 mmol), formed from **1ac**; yield: 20 mg (60 %); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.89 – 6.84 (m, 2H), 4.76 (d, *J*

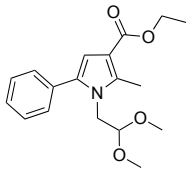
= 2.1 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H) ;^{13}C NMR (63 MHz, $CDCl_3$) δ 164.5, 158.8, 132.5, 131.9, 131.8, 128.6, 126.4, 124.2, 114.4, 114.3, 111.0, 107.3, 55.4, 52.7, 52.5, 51.2, 31.0; IR (neat) ν: 2988.3 (C-H), 1722.4 and 1677.0 (C=O), 1235.1 and 1122.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28; found: C, 66.35; H, 5.60; N, 4.02.

6.4.3. General procedure for the synthesis of pyrrole derivatives 6 under solvent-free high-speed vibration milling (HSVM) conditions



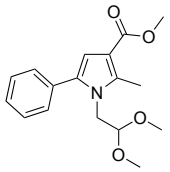
The suitable ketone (0.5 mmol), *N*-iodosuccinimide (NIS, 0.5 mmol) and *p*-toluenesulphonic acid (PTSA, 10 mol%) were added to a ball mill vessel, along with a zirconium oxide ball. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 s^{-1} for 60 min at room temperature. Then, a mixture of aminoacetaldehyde dimethyl acetal (1.0 mmol), the suitable β-dicarbonyl compound (0.75 mmol) and cerium(IV) ammonium nitrate (CAN, 5 mol%), previously stirred at room temperature during 30 min, and silver nitrate (0.5 mmol) were added to the vessel. The reaction was subjected to the vibratory movement at the same frequency for 60 min. Then, the reaction vessel was cleansed with ethyl acetate and the suspension was filtered to remove the silver iodide precipitate. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate afforded the desired pyrrole derivatives **13**. Compounds 6l-6o were prepared from isolated α-iodoketones, obtained by treatment of the corresponding ketones with iodine in the presence of CuO.

Ethyl 1-(2,2-dimethoxyethyl)-2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (13a)



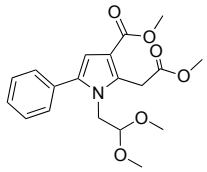
Prepared from acetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and ethyl acetoacetate (0.75 mmol); yield: 130 mg (82%); dark orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 – 7.35 (m, 5H), 6.59 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.15 (t, *J* = 4.8 Hz, 1H), 4.07 (d, *J* = 4.8 Hz, 2H), 3.16 (s, 6H), 2.67 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 137.7, 133.5, 132.9, 129.5, 128.4, 127.6, 112.0, 110.0, 104.1, 59.3, 55.1, 46.4, 14.4, 11.8; IR (neat) ν: 3013.5, 2982.2, 2835.5 (C-H), 1687.1 (C=O), 1241.9, 1196.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41; found: C, 68.09; H, 7.25; N, 4.35.

Methyl 1-(2,2-dimethoxyethyl)-2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (13b)



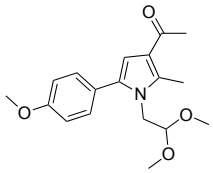
Prepared from acetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 132 mg (87%); yellowish oil; 1H NMR (250 MHz, CDCl3) δ 7.43 – 7.30 (m, 5H), 6.57 (s, 1H), 4.17 – 4.13 (m, 1H), 4.06 (d, *J* = 5.2 Hz, 2H), 3.82 (s, 3H), 3.15 (s, 6H), 2.67 (s, 3H); 13C NMR (250 MHz, CDCl3) δ 165.8, 137.7, 133.6, 132.7, 129.4, 128.4, 127.5, 111.6, 109.9, 104.0, 55.0, 50.5, 46.4, 11.7; IR (neat) ν: 2947.0 and 2835.4 (C-H), 1695.7 (C=O), 1244.2 and 1182.6 (C-O) cm^{1}; elemental analysis (%) calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62; found: C, 67.01; H, 6.75; N, 4.63.

Methyl 1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (13c)



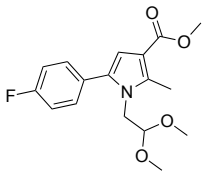
Prepared from acetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and dimethyl-1,3-acetonedicarboxylate (0.75 mmol); yield: 159 mg (88%); yellowish solid; mp: 78-80 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 5H), 6.61 (s, 1H), 4.31 (s, 2H), 4.10 (m, 3H), 3.83 (s, 3H), 3.76 (s, 3H), 3.15 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.7, 165.5, 134.6, 133.3, 132.6, 129.8, 128.6, 127.9, 113.4, 110.2, 104.3, 55.3, 52.2, 50.9, 47.0, 31.3; IR (neat) ν: 2942.3, 2923.1, 2848.1 (C-H), 1748.9, 1695.6 (C=O), 1248.5, 1222.9 1194.9, 1163.6 (C-O) cm^{-1}; ESI-MS: (*m/z*) 320.1 (M^{+}+Na); elemental analysis (%) calcd. for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.42; N, 3.88; found: C, 63.41; H, 6.77; N, 3.63.

1-(1-(2,2-Dimethoxyethyl)-5-(4-methoxyphenyl)-2-methyl-1H-pyrrol-3-yl)ethan-1-one (13d)



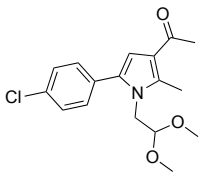
Prepared from 4-methoxyacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and acetylacetone (0.75 mmol); yield: 126 mg (80%); orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 7.00 – 6.92 (m, 2H), 6.44 (s, 1H), 4.19 (t, *J* = 5.1 Hz, 1H), 4.01 (d, *J* = 5.1 Hz, 2H), 3.85 (s, 3H), 3.17 (s, 6H), 2.65 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 159.1, 136.6, 133.1, 130.9, 124.9, 120.6, 113.8, 110.1, 103.8, 55.1, 54.9, 46.0, 28.4, 12.2; IR (neat) ν: 3006.1, 2936.7, 2836.5 (C-H), 1648.3 (C=O), 1287.3, 1246.1 (C-O) cm^{-1}; ESI-MS: (*m/z*) 318.2 (M^{+}+H); elemental analysis (%) calcd. for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41; found: C, 68.07: H, 7.27: N, 4.43.

1-(1-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-2-methyl-1H-pyrrol-3-yl)ethan-1-one (13e)



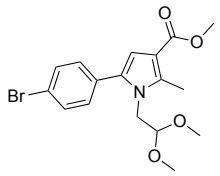
Prepared from 4′-fluoroacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and acetylacetone (0.75 mmol); yield: 127 mg (79%); orange solid; mp: 106-108 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 2H), 7.23 – 7.05 (m, 2H), 6.53 (s, 1H), 4.17 (t, *J* = 5.3 Hz, 1H), 4.02 (d, *J* = 5.3 Hz, 2H), 3.82 (s, 3H), 3.18 (s, 6H), 2.65 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 164.2 – 160.3 (d, *J* = 248.2 Hz), 137.6, 132.6, 131.4 – 131.3 (d, *J* = 8.12 Hz), 128.9 – 128.8 (d, *J* = 3.1 Hz), 115.6 – 115.2 (d, *J* = 21.4 Hz), 111.7, 110.1, 104.0, 55.2, 50.7, 46.4, 11.7; IR (neat) ν: 2972.8, 2945.2, 2840.1 (C-H), 1691.3 (C=O), 1242.5, 1192.0 (C-O), 1129.1 (C-F) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{20}FNO_4$: C, 63.54; H, 6.27; N, 4.36; found: C, 63.32; H, 6.19; N, 4.29.

1-(5-(4-Chlorophenyl)-1-(2,2-dimethoxyethyl)-2-methyl-1H-pyrrol-3-yl)ethan-1-one (13f)



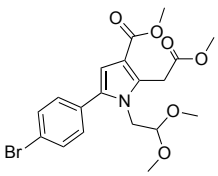
Prepared from 4′-chloroacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and acetylacetone (0.75 mmol); yield: 111 mg (69%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 6.50 (s, 1H), 4.23 (t, *J* = 5.3 Hz, 1H), 4.03 (d, *J* = 5.3 Hz, 2H), 3.19 (s, 6H), 2.67 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 137.2, 133.6, 132.3, 131.2, 130.8, 128.7, 121.0, 110.9, 103.7, 55.1, 46.2, 28.5, 12.3; IR (neat) ν: 2994.0, 2933.2, 2834.4 (C-H), 1652.6 (C=O), 1245.2 (C-O), 1011.8 (C-Cl) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{20}ClNO_3$: C, 63.45; H, 6.26; N, 4.35; found: C, 63.35; H, 6.20; N, 4.29.

Methyl 5-(4-bromophenyl)-1-(2,2-dimethoxyethyl)-2-methyl-1H-pyrrole-3-carboxylate (13g)



Prepared from 4′-bromoacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 131 mg (69%); white solid; mp: 91-93 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.61 – 7.53 (m, 2H), 7.33 – 7.26 (m, 2H), 6.56 (s, 1H), 4.19 (t, *J* = 5.3 Hz, 1H), 4.04 (d, *J* = 5.3 Hz, 2H), 3.83 (s, 3H), 3.20 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 138.1, 132.5, 131.8, 131.7, 131.0, 121.8, 110.4, 103.9, 55.2, 50.8, 46.6, 11.8; IR (neat) ν: 2999.2, 2947.7, 2839.3 (C-H), 1691.4 (C=O), 1242.1, 1212.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{20}BrNO_4$: C, 53.42; H, 5.27; N, 3.66; found: C, 53.35; H, 5.22; N, 3.56.

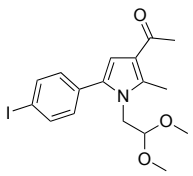
Methyl 5-(4-bromophenyl)-1-(2,2-dimethoxyethyl)-2-(2-methoxy-2-oxoethyl)-1H-pyrrole-3-carboxylate (13h)



Prepared from 4′-bromoacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and dimethyl-1,3-acetonedicarboxylate (0.75 mmol); yield: 165 mg (75%); yellowish solid; mp: 59-61 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 2H), 7.29 – 7.26 (m, 2H), 6.58 (s, 1H), 4.27 (s, 2H), 4.15 (t, *J* = 5.1 Hz, 1H), 4.04 (d, *J* = 5.1 Hz, 2H), 3.80 (s, 3H), 3.73 (s,

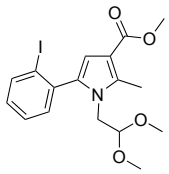
3H), 3.17 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.5, 165.1, 133.4, 133.3, 131.6, 131.4, 131.1, 122.0, 113.5, 110.5, 103.9, 55.1, 52.0, 50.8, 46.9, 31.1; IR (neat) ν: 2982.1, 2952.6, 2905.6 (C-H), 1756.5, 1703.4 (C=O), 1245.1, 1226.3, 1182.5, 1149.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{22}BrNO_6$: C, 51.83; H, 5.04; N, 3.18; found: C, 51.79; H, 4.99; N, 3.18.

1-(1-(2,2-dimethoxyethyl)-5-(4-iodophenyl)-2-methyl-1H-pyrrol-3-yl)ethan-1-one (13i)



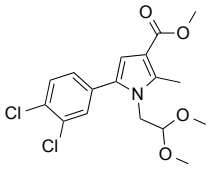
Prepared from 4-iodoacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and acetylacetone (0.75 mmol); yield: 149 mg (72%); orange solid; mp: 121-123 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.81 – 7.70 (m, 2H), 7.23 – 7.11 (m, 2H), 6.50 (s, 1H), 4.23 (t, *J* = 5.3 Hz, 1H), 4.04 (d, *J* = 5.3 Hz, 2H), 3.20 (s, 6H), 2.66 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.9, 137.6, 137.3, 132.4, 132.2, 131.2, 121.0, 110.9, 103.7, 93.3, 55.1, 46.2, 28.5, 12.3; IR (neat) ν: 2989.4, 2931.4, 2834.6 (C-H), 1649.4 (C=O), 1247.6, 1207.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{20}INO_3$: C, 49.41; H, 4.88; N, 3.39; found: C, 49.39; H, 4.80; N, 3.37.

Methyl 1-(2,2-dimethoxyethyl)-5-(2-iodophenyl)-2-methyl-1H-pyrrole-3-carboxylate (13j)



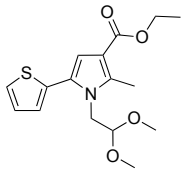
Prepared from 2-iodoacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 148 mg (69%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.10 (m, 1H), 6.51 (s, 1H), 4.13 (t, *J* = 5.3 Hz, 1H), 3.95 – 3.71 (m, 5H), 3.16 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 139.1, 137.9, 137.2, 134.4, 132.4, 129.9, 127.9, 111.3, 110.4, 104.2, 102.7, 55.1, 50.6, 46.7, 11.6; IR (neat) ν: 2992.4, 2946.7, 2834.6 (C-H), 1697.2 (C=O), 1234.8, 1196.9 (C-O), 1067.3 (C-I) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{20}INO_4$: C, 47.57; H, 4.70; N, 3.26; found: C, 47.49; H, 4.65; N, 3.18.

Methyl 5-(3,4-dichlorophenyl)-1-(2,2-dimethoxyethyl)-2-methyl-1H-pyrrole-3-carboxylate (13k)



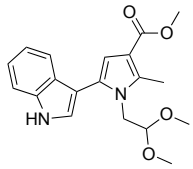
Prepared from 3,4-dichloroacetophenone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 120 mg (65%); yellowish oil; ^{1}H NMR (250 MHz, CDCl3) δ 7.55 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.27 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.58 (s, 1H), 4.25 (t, *J* = 5.3 Hz, 1H), 4.04 (d, *J* = 5.3 Hz, 2H), 3.83 (s, 3H), 3.22 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 138.3, 132.8, 132.5, 131.7, 131.4, 131.1, 130.4, 128.6, 112.2, 111.0, 103.8, 55.2, 50.8, 46.7, 11.8; IR (neat) ν: 2992.8, 2848.0, 2835.9 (C-H), 1699.4 (C=O), 1241.3, 1196.5 (C-O) cm^{-1}; ESI-MS: (*m/z*) 394.1 (M^++Na); elemental analysis (%) calcd. for $C_{17}H_{19}Cl_2NO_4$: C, 54.85; H, 5.15; N, 3.76; found: C, 54.73; H, 5.10; N, 3.75.

Ethyl 1-(2,2-dimethoxyethyl)-2-methyl-5-(thiophen-2-yl)-1H-pyrrole-3-carboxylate (13l)



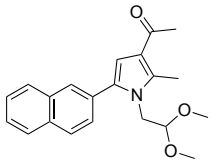
Prepared from 2-acetylthiophene (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and ethyl acetoacetate (0.75 mmol); yield: 111 mg (69%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 – 7.34 (m, 1H), 7.14 – 7.08 (m, 2H), 6.72 (s, 1H), 4.38 – 4.25 (m, 3H), 4.12 (d, *J* = 5.4 Hz, 2H), 3.27 (s, 6H), 2.66 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.3, 138.4, 133.7, 127.3, 127.1, 125.8, 125.5, 112.2, 111.9, 104.2, 59.4, 55.4, 46.8, 14.4, 11.8; IR (neat) ν: 2934.1, 2834.3 (C-H), 1693.6 (C=O), 1287.3, 1246.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33; found: C, 59.38; H, 6.49; N, 4.35.

Methyl 1-(2,2-dimethoxyethyl)-5-(1H-indol-3-yl)-2-methyl-1H-pyrrole-3-carboxylate (13m)



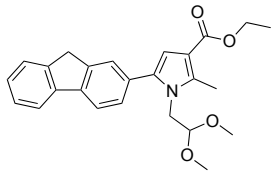
Prepared from 3-acetylindole (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 120 mg (70%); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (brs, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.32 – 7.14 (m, 2H), 6.71 (s, 1H), 4.27 (t, *J* = 5.3 Hz, 1H), 4.07 (d, *J* = 5.3 Hz, 2H), 3.88 (s, 3H), 3.17 (s, 6H), 2.72 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.3, 137.3, 135.7, 127.6, 126.2, 124.1, 122.5, 120.2, 119.5, 111.6, 111.2, 110.6, 108.1, 104.3, 55.2, 50.7, 46.8, 11.9; IR (neat) ν: 3322.9 (N-H), 2911.2, 2853.7 (C-H), 1679.8 (C=O), 1224.8, 1135.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18; found: C, 66.57; H, 6.39; N, 8.15.

1-(1-(2,2-Dimethoxyethyl)-2-methyl-5-(naphthalen-2-yl)-1H-pyrrol-3-yl)ethan-1-one (13n)



Prepared from 2-acetylnaphtalene (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and acetylacetone (0.75 mmol); yield: 121 mg (72%); white solid; mp: 97-99 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 – 7.88 (m, 4H), 7.66 – 7.48 (m, 3H), 6.63 (s, 1H), 4.30 – 4.21 (m, 1H), 4.16 (m, 2H), 3.16 (s, 6H), 2.73 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.0, 137.3, 133.4, 133.2, 132.4, 130.1, 128.4, 128.1, 127.9, 127.6, 127.3, 126.4, 126.2, 121.0, 111.0, 103.8, 55.0, 46.3, 28.6, 12.3; IR (neat) ν: 2998.9, 2836.2, 2836.3 (C-H), 1648.0 (C=O), 1200.0, 1200.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15; found: C, 74.71; H, 6.80; N, 4.10.

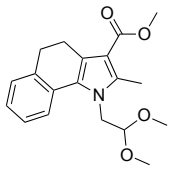
Ethyl 1-(2,2-dimethoxyethyl)-5-(9H-fluoren-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (13o)



Prepared from 2-acetylfluorene (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and ethyl acetoacetate (0.75 mmol); yield: 162 mg (80%); yellowish solid; mp: 89-91 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84 (m, 3.3 Hz, 2H), 7.60 (m, 2H), 7.48 – 7.32 (m, 3H), 6.66 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.25 – 4.17 (m, 1H), 4.14 (m, 2H), 3.97 (s, 2H), 3.17 (s, 6H), 2.71 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.5, 143.4, 143.2, 141.1, 141.0, 137.7, 133.9, 131.2, 128.2, 126.9, 126.8, 126.0, 125.0, 119.9, 119.8,

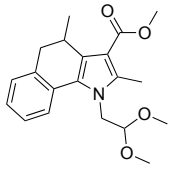
112.0, 110.1, 104.1, 59.2, 55.1, 46.5, 36.8, 14.4, 11.8; IR (neat) ν: 2962.2, 2918.0, 2838.2 (C-H), 1681.9 (C=O), 1246.3, 1194.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45; found: C, 73.98; H, 6.65; N, 3.38.

Methyl 1-(2,2-dimethoxyethyl)-2-methyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (13p)



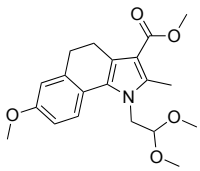
Prepared from α-tetralone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 130 mg (79%); orange solid; mp: 60-62 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 10.6, 4.7 Hz, 2H), 7.13 (dd, *J* = 11.6, 4.2 Hz, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 4.36 (d, *J* = 5.2 Hz, 2H), 3.86 (s, 3H), 3.36 (s, 6H), 3.02 – 2.90 (m, 2H), 2.90 – 2.79 (m, 2H), 2.68 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.5, 139.1, 136.7, 129.3, 128.5, 128.1, 126.6, 125.1, 123.9, 120.3, 109.8, 104.3, 55.4, 50.5, 48.1, 30.8, 21.6, 12.1; IR (neat) ν: 2935.2, 2899.4, 2834.5 (C-H), 1695.7 (C=O), 1255.0, 1225.2, 1194.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25; found: C, 69.22; H, 6.98; N, 4.23.

Methyl 1-(2,2-dimethoxyethyl)-2,4-dimethyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (13q)



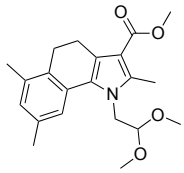
Prepared from 4-methyl-1-tetralone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 123 mg (72%); green oil; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.57 (d, *J* = 7.7 Hz, 1H), 7.22 (m, 3H), 4.58 (t, *J* = 5.1 Hz, 1H), 4.37 (d, *J* = 5.1 Hz, 2H), 3.85 (s, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 3.10 – 2.80 (m, 3H), 2.67 (s, 3H), 1.26 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (250 MHz, $CDCl_3$) d 166.5, 141.3, 139.2, 128.4, 127.3, 127.1, 126.3, 125.3, 122.3, 120.5, 110.3, 104.3, 55.5, 55.4, 50.5, 48.0, 34.3, 29.1, 19.8, 12.1; IR (neat) ν: 2947.9, 2835.7 (C-H), 1690.8 (C=O), 1271.7, 1248.5, 1217.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08; found: C, 69.89; H, 7.28; N, 4.04.

Methyl 1-(2,2-dimethoxyethyl)-7-methoxy-2-methyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (13r)



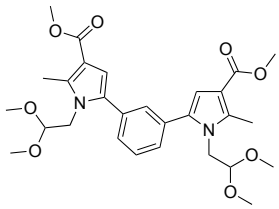
Prepared from 7-methoxy-1-tetralone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 144 mg (80%); dark orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.6 Hz, 1H), 6.96 – 6.73 (m, 2H), 4.59 (d, *J* = 5.1 Hz, 1H), 4.32 (d, *J* = 5.1 Hz, 2H), 3.84 (s, 6H), 3.36 (s, 6H), 2.99 – 2.90 (m, 2H), 2.83 (m, 2H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.5, 157.0, 138.9, 138.1, 128.0, 122.5, 121.9, 121.5, 114.8, 110.9, 109.6, 104.3, 55.4, 55.1, 50.5, 48.0, 31.3, 21.6, 12.0; IR (neat) ν: 2940.4, 2905.5, 2834.4 (C-H), 1694.5 (C=O), 1245.4, 1239.2, 1188.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90; found: C, 66.76; H, 6.97; N, 3.89.

Methyl 1-(2,2-dimethoxyethyl)-2,6,8-trimethyl-4,5-dihydro-1H-benzo[g]indole-3-carboxylate (13s)



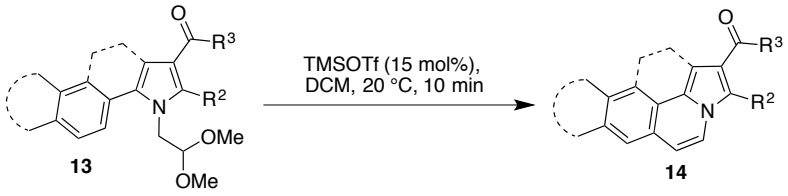
Prepared from 5,7-Dimethyl-1-tetralone (0.5 mmol), aminoacetaldehyde dimethyl acetal (1 mmol) and methyl acetoacetate (0.75 mmol); yield: 129 mg (72%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.88 (s, 1H), 4.63 (t, *J* = 5.0 Hz, 1H), 4.37 (d, *J* = 5.0 Hz, 2H), 3.88 (s, 3H), 3.39 (s, 6H), 2.95 (m, 2H), 2.81 – 2.78 (m, 2H), 2.70 (s, 3H), 2.37 (d, *J* = 2.5 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.4, 139.0, 135.3, 134.8, 131.7, 129.0, 128.3, 128.0, 123.5, 119.2, 109.4, 104.4, 55.2, 50.4, 48.00, 25.5, 21.4, 21.2, 20.3, 12.00; IR (neat) ν: 2946.8, 2832.2 (C-H), 1694.9 (C=O), 1260.7, 1226.0, 1194.4 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92; found: C, 70.51; H, 7.55; N, 3.92.

Dimethyl 5,5'-(1,3-phenylene)bis(1-(2,2-dimethoxyethyl)-2-methyl-1H-pyrrole-3-carboxylate) (13t)



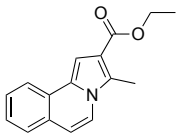
Prepared from 1,3-diacetylbenzene (0.5 mmol), aminoacetaldehyde dimethyl acetal (2 mmol) and methyl acetoacetate (1.5 mmol); yield: 171 mg (65%); yellowish solid; mp= 122-124 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 – 7.39 (m, 2H), 6.60 (s, 1H), 4.20 (d, *J* = 5.0 Hz, 1H), 4.11 (d, *J* = 5.0 Hz, 2H), 3.84 (s, 3H), 3.18 (s, 6H), 2.68 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 138.0, 133.2, 130.6, 128.7, 128.5, 111.9, 110.3, 104.1, 55.1, 50.7, 46.6, 11.8; IR (neat) ν: 2920.2, 2843.3 (C-H), 1695.5 (C=O), 1245.8, 1213.5 (C-O) cm^{-1}; HRMS calcd. for $C_{28}H_{36}N_2O_8$ (M^++Na): 551.2363, found: 551.2390; elemental analysis (%) calcd. for $C_{28}H_{36}N_2O_8$: C, 63.62; H, 6.86; N, 5.30; found: C, 63.56; H, 6.85; N, 5.25.

6.4.4. General procedure for the Pommeranz-Fritsch synthesis of pyrrolo[2,1-a]isoquinoline-related frameworks 14a-14t



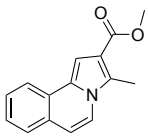
To a round bottom flask was added the corresponding pyrrole derivative **13** (1.0 eq), trimethylsilyl trifluoromethanesulfonate (0.15-0.3 eq) and DCM as solvent (4 mL/mmol). The reaction was stirred at room temperature for 10-20 min and monitored for conversion by TLC. At the end of the reaction, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate and final compound **14** is obtained.

Ethyl 3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14a)



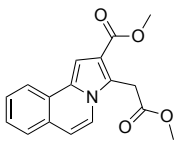
Prepared from pyrrole **13a** (0.2 mmol); yield: 41,5 mg (82%); dark yellow solid; mp: 113-115 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (d, J = 8 Hz, 1H), 7.64 – 7.45 (m, 3H), 7.39 (dd, J = 7.5, 1.2 Hz, 1H), 7.35 (m, 1H), 6.83 (d, J = 7.5 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.79 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 128.4, 127.8, 127.7, 126.9, 126.4, 126.3, 126.0, 122.0, 120.9, 114.9, 112.7, 100.7, 59.9, 14.5, 10.4; IR (neat) ν: 3052.8, 2980.5, 2937.8 (C-H), 1689.9 (C=O), 1296.0, 1226.7 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; found: C, 75.80; H, 5.89; N, 5.50.

Methyl 3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14b)



Prepared from pyrrole **13b** (0.2 mmol); yield: 43 mg (90%); green solid; mp: 133-135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 1H), 7.60 – 7.44 (m, 3H), 7.39 (dd, J = 7.5, 1.3 Hz, 1H), 7.35 – 7.29 (m, 1H), 6.81 (d, J = 7.6 Hz, 1H), 3.94 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.1, 128.5, 127.8, 127.8, 126.9, 126.4, 126.3, 126.0, 121.9, 120.8, 114.6, 112.8, 100.6, 51.1, 10.3; IR (neat) ν: 2992.7, 2946.6 (C-H), 1696.8 (C=O), 1230.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85; found: C, 75.21; H, 5.47; N, 5.82.

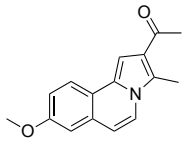
Methyl 3-(2-methoxy-2-oxoethyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate (14c)



Prepared from pyrrole **13c** (0.2 mmol); 53 mg (90%); yellowish solid; mp: 171-173 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.43 (dd, J = 7.5, 1.2 Hz, 1H), 7.38 (s, 1H), 6.88 (d, J = 7.5 Hz, 1H), 4.47 (s, 2H), 3.94 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.0, 165.7, 129.5, 128.0, 127.0, 126.5, 126.4, 126.2, 123.3, 122.1, 121.0, 115.9, 113.4, 101.1,

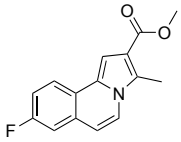
52.4, 51.4, 30.4; IR (neat) ν: 2994.3, 2948.8, 2843.1 (C-H), 1725.5, 1695.5 (C=O), 1239.9, 1197.1 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71; found: C, 68.59; H, 5.03; N, 4.63.

1-(8-Methoxy-3-methylpyrrolo[2,1-a]isoquinolin-2-yl)ethan-1-one (14d)



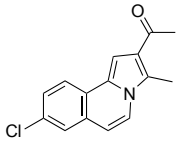
Prepared from pyrrole **13d** (0.2 mmol); yield: 43 mg (84%); dark orange solid; mp: 126-128 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.00 (d, J = 2.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.78 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.5, 158.0, 128.6, 127.8, 126.3, 123.4, 122.8, 121.3, 120.3, 116.8, 113.0, 108.9, 99.1, 55.4, 29.1, 10.7; IR (neat) ν: 2993.8, 2899.5, 2837.9 (C-H), 1656.0 (C=O), 1259.3, 1223.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; found: C, 75.78; H, 5.91; N, 5.44.

Methyl 8-fluoro-3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14e)



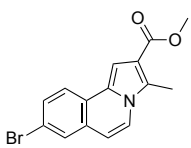
Prepared from pyrrole **13e** (0.2 mmol); yield: 41 mg (80%); yellowish solid; mp: 82-84 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.28 – 7.18 (m, 3H), 6.79 (d, J = 7.6 Hz, 1H), 3.93 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) d 166.1, 161.0 (d, J = 245.7 Hz), 128.0 (d, J = 16.4 Hz), 124.0 (d, J = 8.2 Hz), 123.0 , 122.1, 116.3, 115.9, 114.9, 112.3, 112.0, 111.9, 100.2, 51.2, 10.4; ^{19}F NMR (235 MHz, $CDCl_3$) δ -115.67, -115.72, -115.75, -115.78, -115.81; IR (neat) ν: 2954.9, 2855.8 (C-H), 1708.6 (C=O), 1255.5 (C-O), 1140.5 (C-F) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{12}FNO_2$: C, 70.03; H, 4.70; N, 5.44; found: C, 69.91; H, 4.63; N, 5.39.

1-(8-Chloro-3-methylpyrrolo[2,1-a]isoquinolin-2-yl)ethan-1-one (14f)



Prepared from pyrrole **13f** (0.2 mmol); yield: 46 mg (90%); yellowish solid; mp: 179-181 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.5, 2.0 Hz, 1H), 7.20 (s, 1H), 6.74 (d, J = 7.6 Hz, 1H), 2.78 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.2, 131.5, 128.1, 127.6, 127.6, 127.2, 126.3, 124.8, 123.2, 123.1, 121.8, 112.1, 101.1, 29.1, 10.7; IR (neat) ν: 3116.5, 3058.0, 3000.5 (C-H), 1653.3 (C=O), 1088.4 (C-Cl) cm^{-1}; ESI-MS: (m/z) 280.0 (M^++Na); elemental analysis (%) calcd. for $C_{15}H_{12}ClNO$: C, 69.91; H, 4.69; N, 5.44; found: C, 69.88; H, 4.65; N, 5.38.

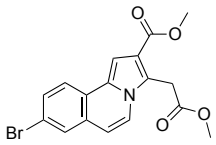
Methyl 8-bromo-3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14g)



Prepared from pyrrole **13g** (0.2 mmol); yield: 41 mg (65%); white solid; mp: 158-160 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.57 (dd, J = 8.5, 1.9 Hz, 1H), 7.32 (s, 1H), 6.75 (d, J = 7.6 Hz, 1H), 3.93 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ

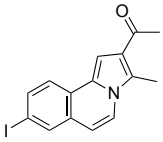
166.0, 130.9, 129.3, 128.2, 128.0, 127.9, 125.2, 123.6, 122.0, 119.4, 115.0, 111.6, 101.2, 51.3, 10.4; IR (neat) ν: 2922.4, 2852.6 (C-H), 1705.0 (C=O), 1231.9 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{12}BrNO_2$: C, 56.63; H, 3.80; N, 4.40; found: C, 56.56; H, 3.71; N, 4.34.

8-Bromo-3-(2-methoxy-2-oxoethyl)pyrrolo[2,1-a]isoquinoline-2-carboxylate (14h)



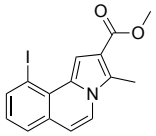
Prepared from pyrrole **13h** (0.2 mmol); yield: 56 mg (75%); white solid; mp: 199-201 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 1.8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.60 (dd, J = 8.5, 1.8 Hz, 1H), 7.38 (s, 1H), 6.80 (d, J = 7.6 Hz, 1H), 4.47 (s, 2H), 3.94 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.9, 165.5, 131.0, 129.3, 128.9, 128.1, 125.0, 123.7, 123.7, 122.1, 119.9, 116.3, 112.2, 101.5, 52.5, 51.5, 30.4; IR (neat) ν: 3059.8, 2951.9 (C-H), 1704.1 (C=O), 1229.4, 1198.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{14}BrNO_4$: C, 54.28; H, 3.75; N, 3.72; found: C, 54.15; H, 3.75; N, 3.71.

1-(8-Iodo-3-methylpyrrolo[2,1-a]isoquinolin-2-yl)ethan-1-one (14i)



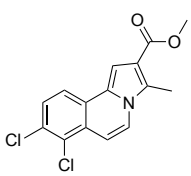
Prepared from pyrrole **13i** (0.2 mmol); yield: 48 mg (69%); yellowish solid; mp: 219-221 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79 – 7.67 (m, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.23 (s, 1H), 6.72 (d, J = 7.6 Hz, 1H), 2.78 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.2, 136.4, 135.5, 128.2, 127.7, 127.4, 125.6, 123.4, 123.1, 121.6, 111.9, 101.4, 90.5, 29.1, 10.7; IR (neat) ν: 3111.1, 3001.0 (C-H), 1655.9 (C=O), 1073.8 (C-I) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{12}INO$: C, 51.60; H, 3.46; N, 4.01; found: C, 51.55; H, 3.45; N, 4.00.

Methyl 10-iodo-3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14j)



Prepared from pyrrole **13j** (0.2 mmol); yield: 63 mg (86%); dark orange solid; mp: 155-157 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.11 (dd, J = 8, 1.3 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.45 (dd, J = 7.8, 1.3 Hz, 1H), 6.95 (m, 1H), 6.67 (d, J = 7.5 Hz, 1H), 3.94 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 141.8, 128.9, 128.6, 128.1, 127.5, 127.3, 126.3, 121.2, 113.9, 113.1, 106.5, 89.6, 51.2, 10.5; IR (neat) ν: 3079.2, 2946.4, 2909.7 (C-H), 1697.4 (C=O), 1231.1 (C-O), 1056.6 (C-I) cm^{-1}; elemental analysis (%) calcd. for $C_{15}H_{12}INO_2$: C, 49.34; H, 3.31; N, 3.84; found: C, 49.32; H, 3.30; N, 3.81.

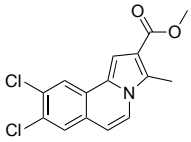
Methyl 7,8-dichloro-3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate (14ka)



Prepared from pyrrole **13k** (0.2 mmol); yield: 49 mg (80%); yellow solid; mp: 179-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.6 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.6 Hz, 1H), 7.34 (s, 1H), 7.29 (m, 2H), 3.94 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.8, 130.2, 129.4, 129.1, 128.3,

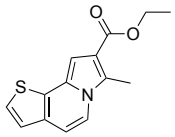
127.3, 126.2, 125.7, 122.8, 121.3, 115.7, 108.8, 101.9, 51.3, 10.4; IR (neat) ν: 2922.4, 2853.2 (C-H), 1694.7 (C=O), 1237.8 (C-O) cm^{-1}; ESI-MS: (m/z) 330.0 (M^++Na); elemental analysis (%) calcd. for $C_{15}H_{11}Cl_2NO_2$: C, 58.47; H, 3.60; N, 4.55; found: C, 58.42; H, 3.54; N, 4.49.

When the reaction was carried out at 40°C, a 8:2 mixture of **14ka** and a second regioisomer (**14kb**) was detected. Isomer **14kb** (*methyl 8,9-dichloro-3-methylpyrrolo[2,1-a]isoquinoline-2-carboxylate*) could not be isolated in pure state. Its NMR data, obtained from the mixture, are given below:



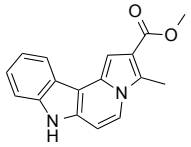
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.60 – 7.57 (m, 2H), 7.26 (s, 1H), 6.69 (d, 1H), 3.94 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 131.7, 130.1, 129.6, 129.0, 128.7, 128.2, 128.0, 127.2, 126.6, 126.1, 125.9, 125.9, 125.6, 123.4, 122.1, 121.2, 115.3, 111.0, 109.8, 108.7, 101.9, 101.9, 51.3, 51.3, 10.4.

Ethyl 7-methylthieno[3,2-g]indolizine-8-carboxylate (14l)



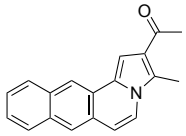
Prepared from pyrrole **13l** (0.2 mmol); yield: 65 mg (85%); green solid; mp: 93-95 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, J = 8 Hz, 1H), 7.68 – 7.46 (m, 3H), 7.41 (dd, J = 7.5, 1.2 Hz, 1H), 7.36 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 2.82 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 130.5, 130.2, 126.5, 126.3, 124.3, 123.1, 119.6, 115.6, 108.2, 98.1, 59.9, 14.4, 10.6; IR (neat) ν: 3112.4, 2971.5, 2909.8, 2858.4 (C-H), 1691.2 (C=O), 1228.4, 1203.8 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.36; found: C, 64.80; H, 5.03; N, 5.39; S, 12.30.

Methyl 3-methyl-7H-indolizino[7,8-b]indole-2-carboxylate (14m)



Prepared from pyrrole **13m** (0.2 mmol); yield: 39 mg (70%); green solid; mp: 237-239 °C; ^{1}H NMR (250 MHz, Acetone-d) δ 10.70 (br s, 1H), 8.12 (dd, J = 7.9, 1.1 Hz, 1H), 8.01 (d, J = 7.6 Hz, 2H), 7.64 – 7.55 (m, 1H), 7.33 – 7.13 (m, 2H), 7.07 (s, 1H), 3.87 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (63 MHz, Acetone-d) δ 166.9, 139.2, 132.4, 128.7, 125.8, 124.7, 123.3, 123.0, 121.3, 121.1, 116.2, 112.5, 109.2, 103.1, 96.4, 51.4, 10.9; IR (neat) ν: 2962.5, 2915.9, 2839.3 (C-H), 1682 (C=O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07; found: C, 73.33; H, 5.06; N, 9.99.

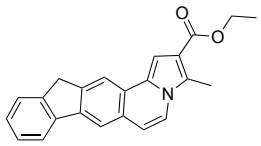
1-(3-Methylbenzo[g]pyrrolo[2,1-a]isoquinolin-2-yl)ethan-1-one (14n)



Prepared from pyrrole **13n** (0.2 mmol); yield: 46 mg (85%); yellowish solid; mp: 217-219 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.81 (d, J = 7.8 Hz, 1H), 7.71 – 7.53 (m, 3H), 7.32 (s, 1H), 2.84 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 196.6, 131.9, 129.5, 129.2, 128.8, 128.7, 127.1, 126.1, 125.8, 124.4, 123.5, 122.4, 121.5, 120.9, 120.7, 108.3, 100.5, 29.2, 10.7; IR (neat) ν: 2996.0, 2918.6, 2852.4 (C-H), 1654.4 (C=O), 1224.4 (C-O) cm^{-1};

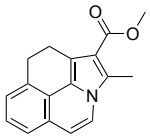
elemental analysis (%) calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12; found: C, 83.42; H, 5.51; N, 5.07.

Ethyl 3-methyl-12H-indeno[1,2-g]pyrrolo[2,1-a]isoquinoline-2-carboxylate (14o)



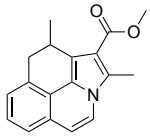
Prepared from pyrrole **13o** (0.2 mmol); yield: 41 mg (70%); dark yellow solid; mp: 189-191 °C; 1H NMR (250 MHz, CDCl3) δ 7.59 – 7.55 (m, 2H), 7.33 – 7.28 (m, 2H), 6.57 (s, 1H), 4.20 (t, J = 5.3 Hz, 1H), 4.05 (d, J = 5.3 Hz, 2H), 3.84 (s, 3H), 3.20 (s, 6H), 2.66 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.8, 143.4, 143.3, 141.1, 140.2, 128.9, 127.6, 127.0, 126.9, 125.6, 125.5, 125.1, 120.4, 119.9, 118.1, 117.6, 114.9, 113.2, 100.5, 59.8, 36.8, 14.5, 10.5; IR (neat) ν: 2924.3, 2854.3 (C-H), 1695.6 (C=O), 1232.0 (C-O) cm^{-1}; HRMS calcd for $C_{23}H_{19}NO_2$ (M^++H): 342.1488, found 342.1519; elemental analysis (%) calcd. for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10; found: C, 80.84; H, 5.60; N, 4.07.

Methyl 2-methyl-9,10-dihydrobenzo[de]pyrrolo[3,2,1-ij]quinoline-1-carboxylate (14p)



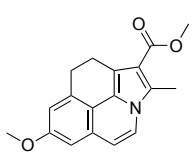
Prepared from pyrrole **13p** (0.2 mmol); yield: 43 mg (82%); red solid; mp: 73-75 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 1H), 7.38 – 7.29 (m, 3H), 6.78 (d, J = 7.6 Hz, 1H), 3.95 (s, 3H), 3.33 – 3.27 (m, 4H), 2.80 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 131.7, 127.7, 126.6, 126.1, 125.7, 124.4, 123.4, 123.0, 120.7, 112.5, 112.4, 112.1, 50.9, 27.9, 22.2, 10.4; IR (neat) ν: 2913.5, 2853.2 (C-H), 1687.1 (C=O), 1252.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28; found: C, 76.91; H, 5.70; N, 5.27.

Methyl 2,10-dimethyl-9,10-dihydrobenzo[de]pyrrolo[3,2,1-ij]quinoline-1-carboxylate (14q)



Prepared from pyrrole **13q** (0.2 mmol); yield: 42 mg (76%); dark yellow solid; mp: 77-79 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (d, J = 7.6 Hz, 1H), 7.40 – 7.30 (m, 3H), 6.75 (d, J = 7.6 Hz, 1H), 3.93 (s, 3H), 3.51 – 3.33 (m, 2H), 3.03 – 2.95 (m, 1H), 2.77 (s, 3H), 1.47 (d, J = 6.7 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 136.7, 127.6, 126.1, 125.8, 124.8, 123.6, 123.3, 123.2, 120.6, 112.6, 111.5, 50.8, 33.1, 30.6, 21.0, 10.4; IR (neat) ν: 3057.8, 2881.8, 2835.3 (C-H), 1690.3 (C=O), 1217.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01; found: C, 77.35; H, 6.08; N, 5.00.

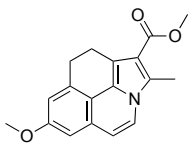
Methyl 7-methoxy-2-methyl-9,10-dihydrobenzo[de]pyrrolo[3,2,1-ij]quinoline-1-carboxylate (14r)



Prepared from pyrrole **13r** (0.2 mmol); yield: 49 mg (83%); dark yellow solid; mp: 114-116 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 (d, J = 7.6 Hz, 1H), 6.97 – 6.86 (m, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.34 – 3.12 (m, 4H), 2.73 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.9, 158.3, 133.5, 126.8, 126.7, 123.9, 121.1, 118.5, 115.2, 112.3, 112.2, 109.6, 105.6, 55.4, 50.8, 28.0, 22.1, 10.3; IR (neat) ν: 2935.7, 2885.4, 2843.9 (C-H), 1694.4 (C=O), 1255.3 (C-O)

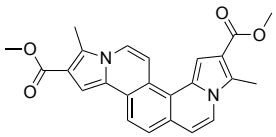
cm^{-1}; elemental analysis (%) calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74; found: C, 73.19; H, 5.73; N, 4.76.

Methyl 2,6,8-trimethyl-9,10-dihydrobenzo[*de*]pyrrolo[3,2,1-ij]quinoline-1-carboxylate (14s)



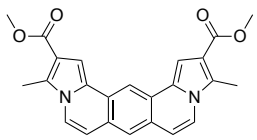
Prepared from pyrrole **13s** (0.2 mmol); yield: 47 mg (80%); dark orange solid; mp: 215-217 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 1H), 6.97 (s, 1H), 6.84 (d, J = 7.5 Hz, 1H), 3.93 (s, 3H), 3.31 (m, 2H), 3.13 (m, 2H), 2.77 (s, 3H), 2.49 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.0, 134.6, 130.7, 129.2, 127.1, 126.8, 124.2, 120.2, 119.3, 112.1, 111.9, 109.6, 50.8, 24.5, 21.9, 19.0, 18.1, 10.4; IR (neat) ν: 2914.4, 2860.4 (C-H), 1688.4 (C=O), 1256.4 (C-O), 1056.6 (C-I) cm^{-1}; ESI-MS: (m/z) 316.1 (M^++Na); elemental analysis (%) calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77; found: C, 77.73; H, 6.49; N, 4.74.

Dimethyl 4,10-dimethyldipyrrolo[2,1-a:2',1'-i][2,8]phenanthroline-5,11-dicarboxylate (14ta)



Prepared from pyrrole **13t** (0.2 mmol); yield: 55 mg (68%); green solid; mp: 255-257 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98 (t, J = 8.2 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.68 (m, 2H), 7.61 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 2.83 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.1, 166.0, 128.9, 127.5, 127.3, 127.3, 127.2, 126.6, 125.7, 122.6, 121.4, 120.9, 120.7, 120.4, 115.2, 115.2, 113.5, 110.2, 105.9, 101.1, 51.3, 51.3, 10.6, 10.4; IR (neat) ν: 2929.4, 2918.6 (C-H), 1709.9 (C=O), 1237.3, 1231.2 (C-O) cm^{-1}; HRMS calcd. for $C_{24}H_{20}N_2O_4$ (M^++H): 401.1496, found 401.1549; elemental analysis (%) calcd. for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00; found: C, 71.90; H, 4.97; N, 6.98.

When the reaction was carried out at 40°C, a 2:1 mixture of **14ta** and a second regioisomer (**14tb**) was detected. Isomer **14tb** (*dimethyl 3,11-dimethylindolizino[7,8-g]pyrrolo[2,1-a]isoquinoline-2,12-dicarboxylate*) could not be isolated in pure state. Its NMR data, obtained from the mixture, are given below:



^{1}H NMR (250 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.91 (dd, J = 12.4, 8.2 Hz, 1H), 7.73 - 7.45 (m, 2H), 7.33 (s, 2H), 6.80 (d, 7.5 Hz, 2H), 3.95 (s, 3H), 2.79 - 2.75 (d, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 128.8, 128.0, 127.5, 125.9, 124.9, 124.6, 114.6, 114.1, 112.4, 102.0, 51.2, 10.6.

7. Synthesis of pyrrole-based macrocycles

7.1. Introduction

Drug discovery is a highly inefficient process, as shown by the fact that only 4% of research programs in pharmaceutical industry eventually end with a drug placed in the market. Furthermore, the efficiency of drug discovery is declining in terms of the ratio between the number of new drugs approved each year and the ever-increasing costs of pharmaceutical development. This decline has been attributed to a number of causes, and there seems to be a consensus among experts that an improved selection of targets is the most important factor that may accelerate and increase the efficiency of the drug discovery process. In this context, it is relevant to mention that known drugs act on about 500 targets, while the number of proteins that may potentially serve as therapeutic targets has been recently estimated to be about 4,500.[108] Only a fraction of these targets are considered "druggable", *i.e*., amenable to manipulation with small molecules complying with Lipinsky's rule of 5 (Ro5) and are therefore considered as likely to be cell permeable and orally bioavailable. Less explored targets, in particular protein−protein and protein-nucleic acid interactions, that are "undruggable" using conventional small molecules, are expected to provide many additional opportunities for drug discovery. Such non-conventional targets contain binding sites that are large, flexible, often endowed with extreme polarity values (either highly lipophilic or highly polar) but normally lacking features that are key in conventional drug design such as sites involved in hydrogen bonding. The realization of these problems has led to the concept of exploring the chemical space that lies "beyond Ro5" (bRo5), also known as "middle space", which is expected to yield compounds that are aimed at these traditionally intractable targets while retaining significant oral bioavailability.[109]

Macrocycles[110] are very attractive in this regard because they are pre-organized and sufficiently rigid to position substituents and functional groups in specific regions for

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[108] Finan C., Gaulton A., Kruger F. A., Lumbers T., Shah T., Engmann J., Galver L., Kelley R., Karlsson A., Santos R., Overington J. P., Hingorani A. D., Casas J. P., *Sci. Transl. Med.,* **2017**, *9*, article eaag1166.

[109] (a) Terrett N., *MedChemComm* **2013**, *4*, 474; (b) Doak B. C., Over B., Giordanetto F., Kihlberg J., *Chem. Biol.,* **2014**, *21*, 1115; (c) Whitty A., Zhou L., *Future Med*. *Chem*., **2015**, *7*, 1093; (d) Doak B. C., Zheng J., Dobritzsch D., Kihlberg J., *J. Med. Chem*., **2016**, *59*, 2312.

[110] For representative reviews, see: (a) Diggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K.; *Nat. Rev. Drug Disc.,* **2008**, *7*, 608; (b) Terrett, N. K.; *Drug Disc. Today: Technologies,* **2010**, *7*, 97; (c) Levin, J.; (Ed.), *Macrocycles in Drug Discovery*, Royal Society of Chemistry, **2014**. (d) Mallinson, J.; Collins, I.; *Fut. Med. Chem*., **2012**, *4*, 1409; (e) Yu, X.; Sun, D.; *Molecules*, **2013**, *18*, 6230; (f) Giordanetto, F.; Kihlberg, J.; *J. Med. Che.,* **2014**, *57*, 278; (g) Yudin, A. K.; *Chem. Sci.,* **2015**, *6*, 30; (h) Raboisson, P. C.; Wermuth, D.; Aldous, P.; Raboisson, D.; Rognan, D.; (Eds.). *The practice of medicinal chemistry*, 4th Ed., **Ch. 10**, Wiley, 2015. (i) You, L. R.; Liang, K.; Cui, B.; Wang, X.; *Curr. Pharm. Des.,* **2016**, *22*, 4086; (j) Paterson, M. L.; https://www.americanpharmaceuticalreview.com/Featured-Articles/343609-The-Evolution-of-Macrocycles-in-Drug-Discovery-From-Technologies-to-Drugs/. (k) Marsault, E.; Peterson, M. L.; (Eds.). *Practical Medicinal Chemistry with Macrocycles*. Wiley, **2017**.

target interaction, while maintaining sufficient flexibility to allow binding to the extended, shallow surfaces that characterize the interaction between biomolecules. Furthermore, their higher surface area in comparison to small molecules and the associated increased entropic factor leads to a higher affinity to flat protein surfaces.[111]

Macrocycles thus cover a unique region of the chemical space that is intermediate between small molecules and biological drugs (Figure 7.1). Furthermore, macrocycles have the possibility to adopt different conformations, allowing them to change their physical characteristics in order to gain cell permeability in spite of their high molecular weight.

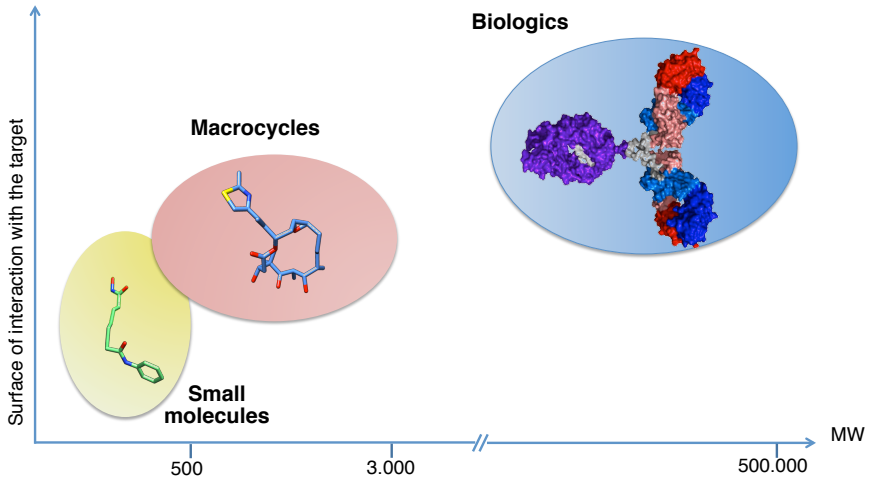


Figure 7.1

Many macrocyclic natural products are employed as therapeutic agents in spite of representing only about 3% of natural products,[112] and their mechanisms of action usually involve interference with the interactions between biomolecules. Representative examples include antibacterials such as the macrolide antibiotics (*e.g.* erythromycin) and rifampicin, the epothilones, a family of anticancer compounds interfering with tubulin. Fully synthetic macrocycles such as the antiviral simeprevir, used for the treatment of chronic hepatitis C, are also increasingly important (Figure 7.2).

[111] Villar, E. A.; Beglov, D.; Chennamadhavuni, S.; Porco Jr, J. A.; Kozakov, D.; Vajda, S.; Whitty, A. *Nat. Chem. Biol.* **2014**, *10*, 723.

[112] Wessjohann L. A., Ruijter E., García-Rivera D., Brandt W., *Mol. Divers*. **2005**, *9*, 171.

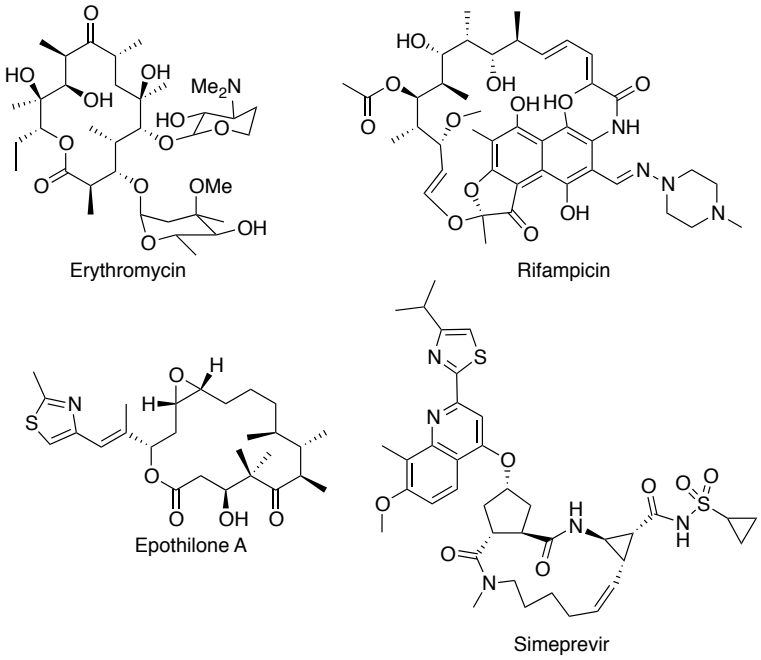


Figure 7.2

Despite their unique characteristics, medicinal chemists have underexplored this class of compounds because of challenges found in development of synthetic methods that are fast and efficient and allow the fine-tuning of their properties (Figure 7.3).[113]

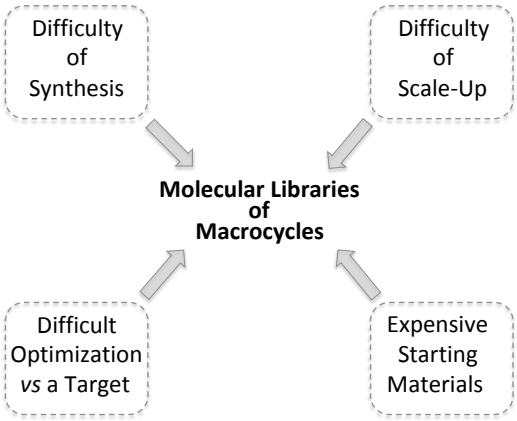


Figure 7.3

Some examples of diversity-oriented libraries of macrocycles are known,[114] but DOS

[113] Whitty A.; Zhou L.; *Future Med. Chem*. **2015**, *7,* 1093.

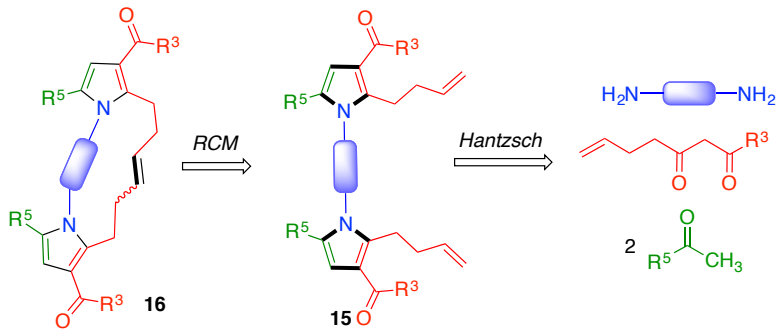
[114] a) S. Kota, K. Singh, *Eur. J. Med. Chem*. **2007**, 5909–5916. b) A. Isidro-Llobet, T. Murillo, P. Bello, A. Cilibrizzi, J. T. Hodgkinson, W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6793–6798. c) F. Kopp, C. F. Stratton, L. B. Akella, D. S. Tan, *Nat. Chem. Biol*. **2012**, *8*, 358–365. d) A. Guarnieri-Ibáñez, F. Medina, C. Besnard, S. L. Kidd, D. R. Spring, J. Lacour, *Chem. Sci*. **2017**, *8*, 5713-5720. e) M. Dow, F. Marchetti, K. A. Abrahams, L. Vaz, G. S. Besra, S. Warriner, A. Nelson, *Chem. Eur. J.* **2017**, *23*, 7207-7211.

libraries of macrocyclic structures with embedded privileged heterocyclic frameworks are rare.[115] Due to the very high potential of macrocycles in drug discovery and their under-representation in currently available molecular libraries, we decided to study the preparation of pyrrole-based macrocycles by application of our mechanochemical pyrrole synthesis.

[115] H. S. G. Beckmann, F. Nie, C. E. Hagerman, H. Johansson, Y. S. Tan, D. Wilcke, D. R. Spring, *Nat. Chem.* **2013**, *5*, 861–867.

7.2. Synthesis of pyrrole-derived macrocycles by ring-closing metathesis

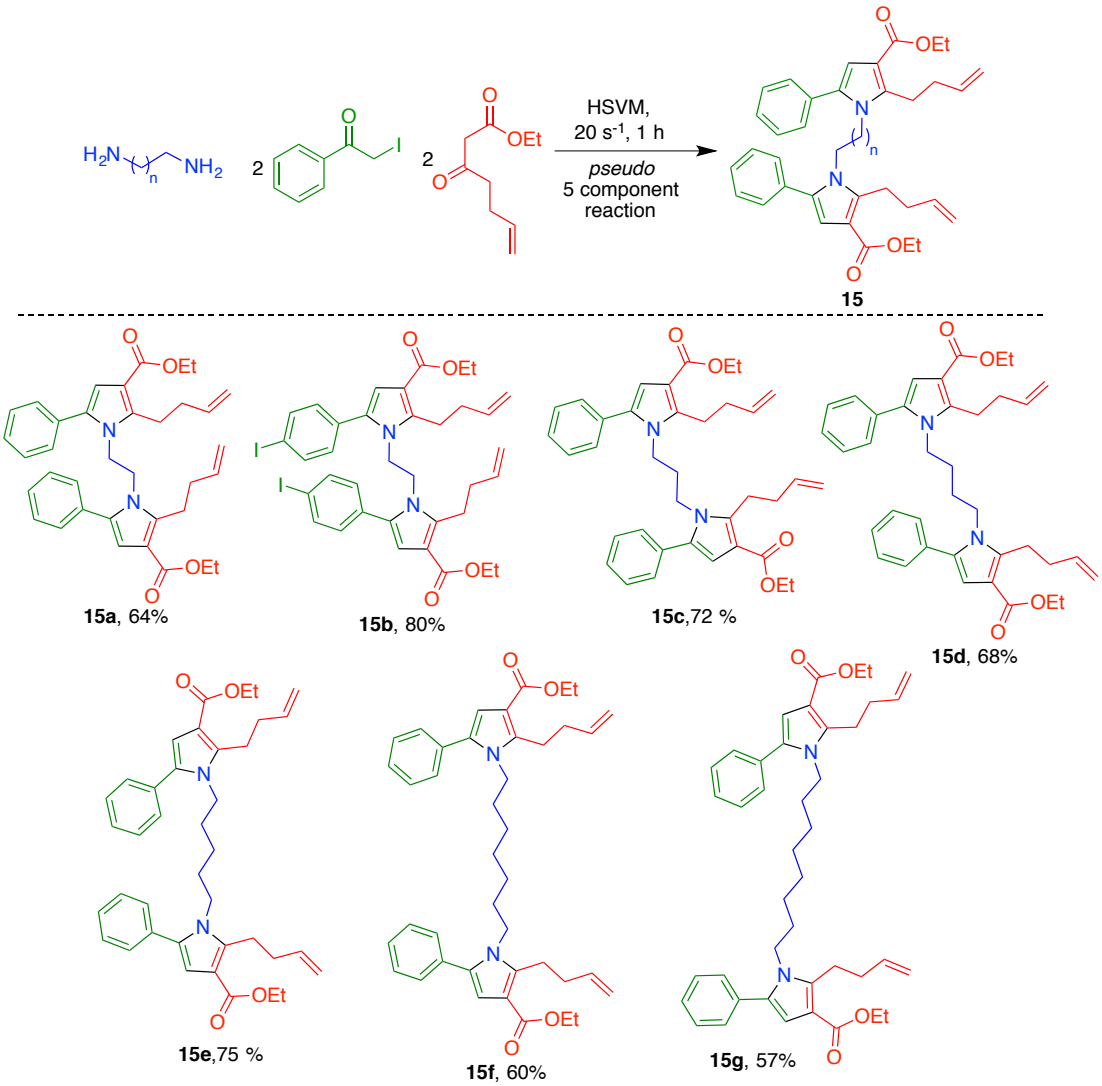
Our first approach to macrocycles is based on the use of ring-closing metathesis for the creation of the macrocycle,[116] as shown in Scheme 7.1



Scheme 7.1

The pyrrole derivatives required as starting materials are characterized by a dimeric architecture with two pyrrole rings connected by a bridge represented by the diamine and two homoallyl substituents attached to their C-2 positions. For the preparation of these compounds (**15**), we employed the pseudo five-component reaction described in Section 3.2, in this case involving as starting materials a diamine, two equivalents of a phenacyl iodide and two equivalents of ethyl 3-oxo-6-heptenoate as the β-dicarbonyl component. The results obtained are summarized in Scheme 7.2.

[116] For reviews, see: (a) Gradillas, A.; Pérez-Castells, J.; *Angew. Chem. Int. Ed.,* **2006**, *45*, 6086; (b) Gradillas, A.; Pérez-Castells, J.; *Top. Heterocycl. Chem.,* **2015**, *47*, 245.



Scheme 7.2

The ring-closing metathesis reaction was optimized on substrate **15a**, as shown in Table 7.1. Although the yields were not very different in the various conditions assayed, the best result corresponded to the use of high dilution conditions, which were achieved by slow injection of the substrate *via* syringe pump to a dichloromethane solution of the catalyst, at room temperature under an argon

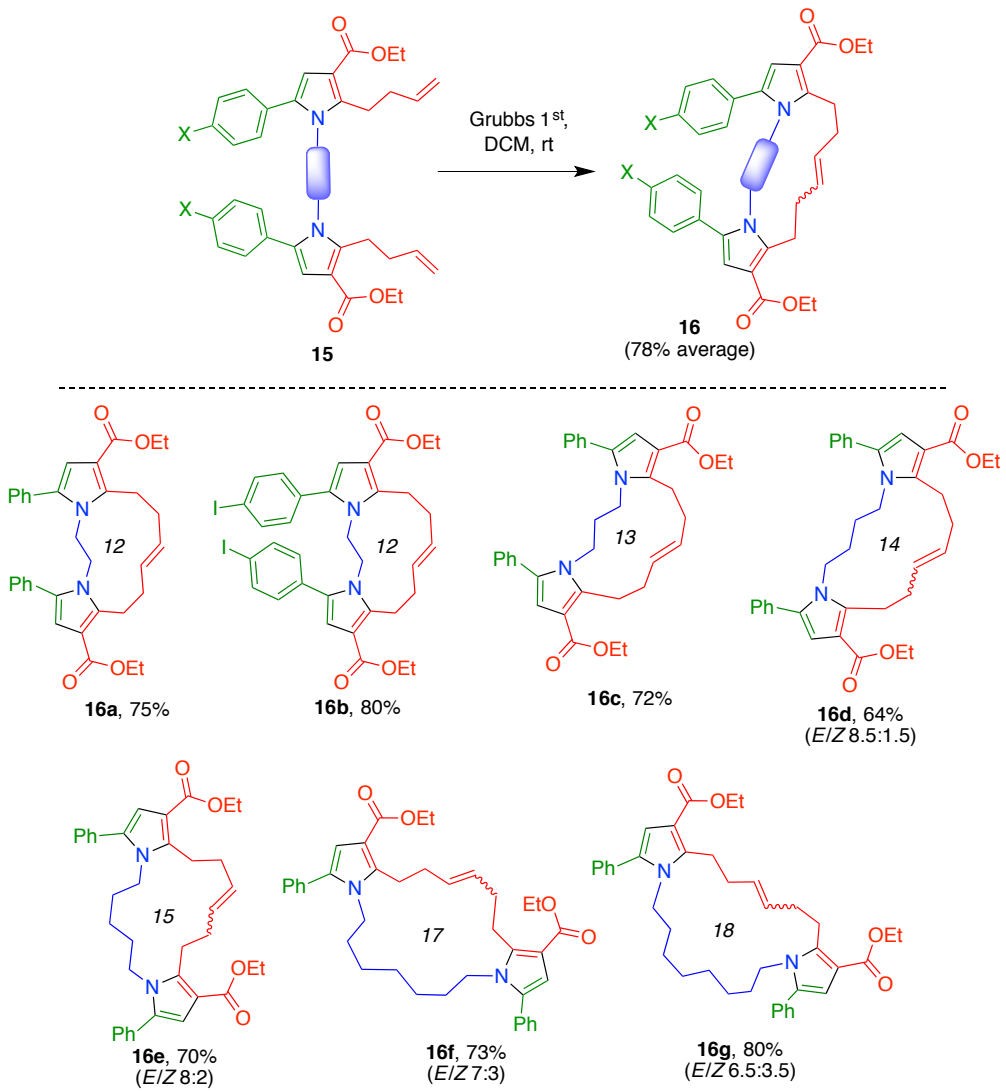
Table 7.1

Entry	DCM (mL)/mmol	% Grubbs 1st	T (°C)	Atmosphere	% Yield
1	10	5	r.t.	air	65
2*	15	5	r.t.	air	65
3*	20	10	r.t.	air	65
4*	30	20	35	argon	60
5	10	10-15	r.t.	argon	75

*Slow injection of the pyrrole substrate to the solution of the catalyst in DCM

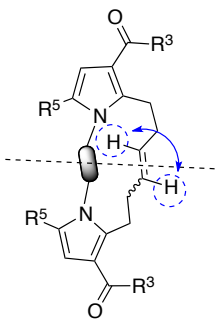
with a syringe pump over 1 h.

atmosphere and in the presence of 10-15% of the Grubbs first generation catalyst, depending on the substrate (entry 5). Using these conditions, the macrocyclic compounds summarized in Scheme 7.3 were synthesized. Ring sizes varied between 12-membered and 18-membered rings. For the systems with a smaller size (12 and 13-membered rings, compounds **16a**-**c**), a single isomer was obtained, but in the other cases (14, 15, 17 and 18-membered rings, compounds **16d**-**16g**) mixtures of *E* and *Z* isomers were obtained.



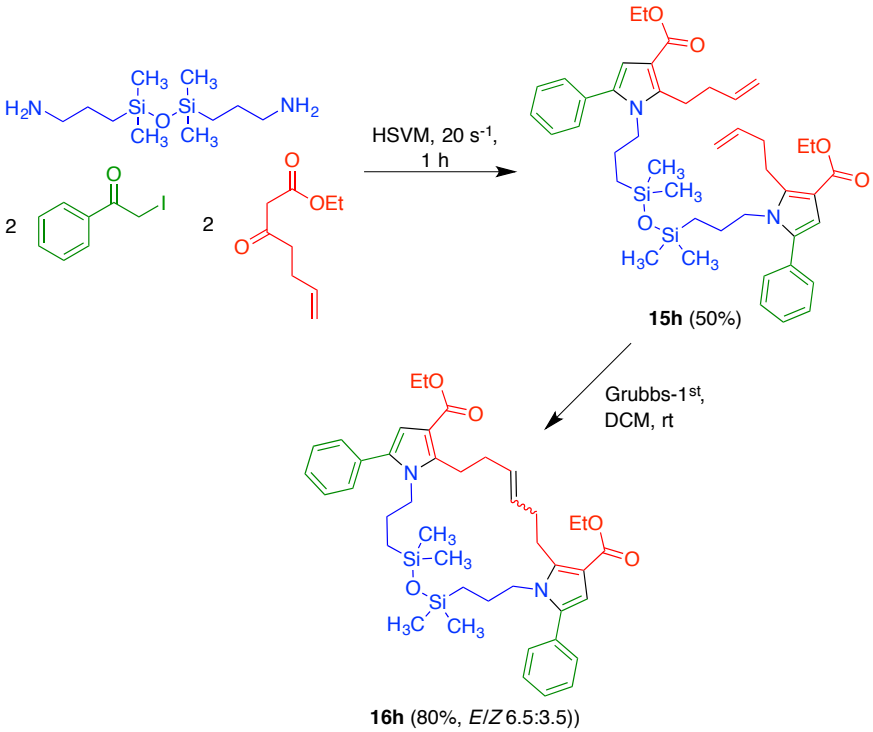
Scheme 7.3

Owing to the symmetry of our systems, both olefinic protons are equivalent and for this reason the double bond geometry cannot be assessed by determining the value of the coupling constant. Furthermore, none of the compounds was sufficiently crystalline to allow single crystal X-Ray studies. We assumed that the



predominant isomer would be *E*, which is the most common behaviour observed in macrocycles due to the thermodynamic bias in RCM reactions, and in order to confirm this assumption we carried out a DFT computational study of both isomers of compound **16a**, which showed that its *E* isomer is 26.7 kJ/mol more stable than the corresponding *Z* species.

Using the same method, we prepared compound **15h**, bearing a silicon atom at the spacer between the two pyrroles, and the corresponding 18-membered, unusual macrocycle **16h** (Scheme 7.4). As previously mentioned, the so-called "silicon-switch" strategy represents an interesting recent trend in medicinal chemistry.

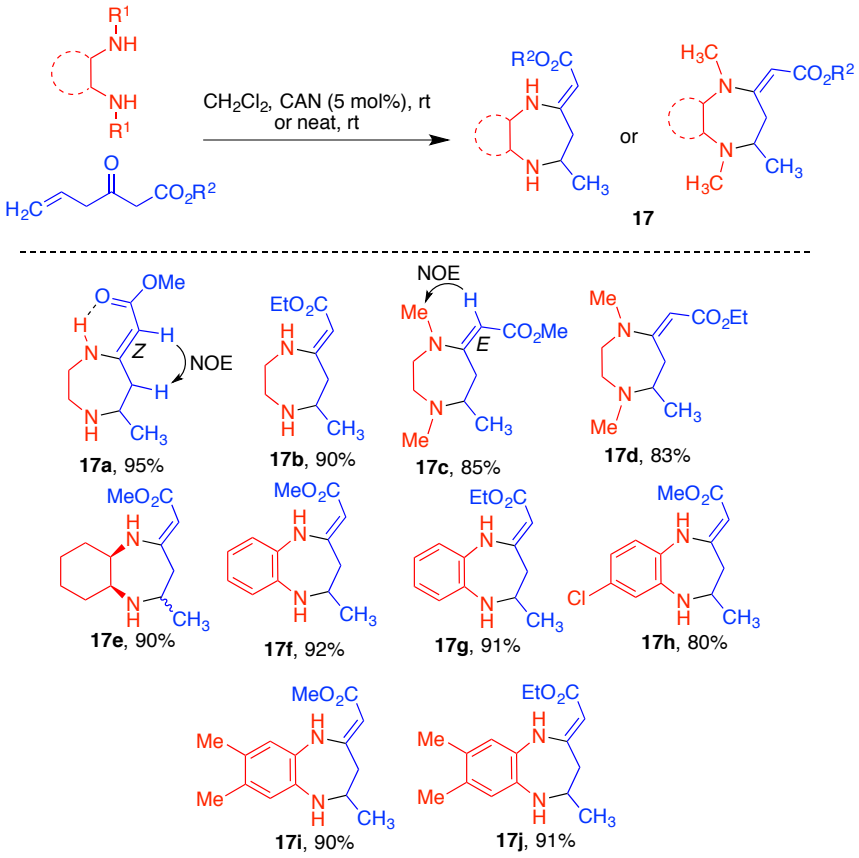


Scheme 7.4

7.3. Synthesis of pyrrole-derived medium-sized rings by ring-closing metathesis

The objective of this part of the thesis was to complete the study of a new domino reaction that allows the synthesis of 1,4-diazepines containing an embedded β-aneminoester moiety from 1,2-diamines and alkyl 3-oxo-5-hexenoates *via* the generation of an intermediate aza-Nazarov reagent that was discovered by Dr. Swarupananda Maiti during his postdoctoral stay in our group. In a second stage, the conditions were established for employing this reaction as the initial step of a synthesis of pyrrole-based medium-sided rings, and some failed attempts were made to use the heterocyclic β-aneminoesters as starting materials for the synthesis of fused pyrroles.

As shown in Scheme 7.5, the reaction between 1,2-diamines and alkyl 3-oxo-5-hexenoates was initially performed in the presence of a catalytic amount of CAN in dichloromethane solution, but it was subsequently discovered that it could also be carried out in the absence of any solvent and catalyst. This reaction afforded the functionalized 1,4-diazepines **17a**-**m**, normally in good to excellent yields.[117] The geometry of the enaminoester unit was normally *Z*, as shown by NOE studies in **17a**, but became *E* for the N-substituted compounds (e.g. **17c**). A reaction starting from a

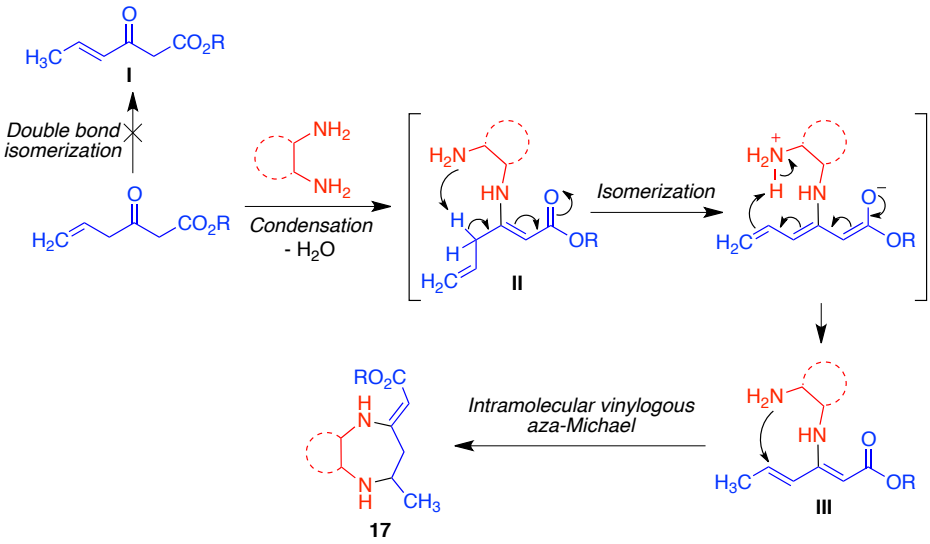


Scheme 7.5

[117] Compounds **17** were synthesized exclusively by Dr. Maiti, but are shown here for completeness.

ketone (1-phenyl-4-penten-2-one) afforded compound **17n**, with an endocyclic C=N bond, and the use of urea as the dinucleophile, which required reflux conditions in ethanol, gave the pyrimidine derivatives **17o** and **17p**.

A mechanistic proposal to account for the formation of compounds **17** is summarized in Scheme 7.6. The starting β-ketoester was found to be stable at room temperature as an isolated product and in $CDCl_3$ solution, with or without the presence of CAN. Therefore, the mechanism does not start with the isomerization of its double bond to give *in situ* the conjugated system **I**. Instead, we propose that the domino sequence is initiated by the condensation of one of the amino groups with the ketone to give enaminone **II**. This intermediate then undergoes a double bond isomerization, assisted by the second amino group of the diamine, to give intermediate **III**. A final intramolecular vinylogous aza-Michael reaction completes the formation of the diazapine ring.



Scheme 7.6

The *in situ* generation of intermediate **III** is of interest, since it can be regarded as an aza-Nazarov reagent. The Nazarov reagent (methyl or ethyl 3-oxo-4-pentenoate)[118] is a densely functionalized building block that has found widespread application in synthesis, especially in annelation reactions, thanks to the presence of a vinyl ketone unit that is activated as a β-keto ester.[119] The Nazarov and related reagents[120] have some limitations, as their preparation normally requires multi-step protocols and they sometimes show low stability. For this reason, the design of domino processes

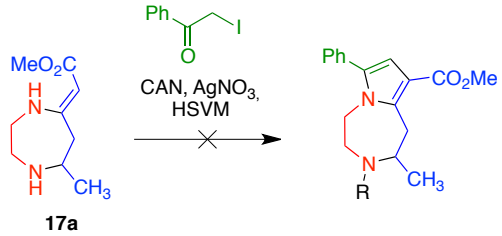
[118] Zibuck, R.; Streiber, J. *Org. Syntheses* **1993**, *71*, 236.

[119] For a review, see: Audran, G.; Brémond, P.; Feuerstein, M.; Marque, S. R. A.; Santelli, M. *Tetrahedron* **2013**, *69*, 8325.

[120] For a synthetic equivalent to the Nazarov reagent, see: Amat, M.; Arioli, F.; Pérez, M.; Molins, E.; Bosch, J. *Org. Lett*. **2013**, *15*, 2470.

involving the generation of such reagents from simple precursors, followed by their *in situ* transformation, would have considerable advantages, although this approach has received very little attention in the literature. Furthermore, aza-Nazarov reagents, which should be very useful for the preparation of nitrogen heterocycles, are almost unknown.

Since most compounds **17** contain a β-enaminoester structural fragment, they could be potential precursors of the pyrrolo[1,2-*d*][1,4]diazepine framework. However, all our attempts to carry out a mechanochemical Hantzsch reaction using **17a** as a substrate were unsuccessful (Scheme 7.7).



17a

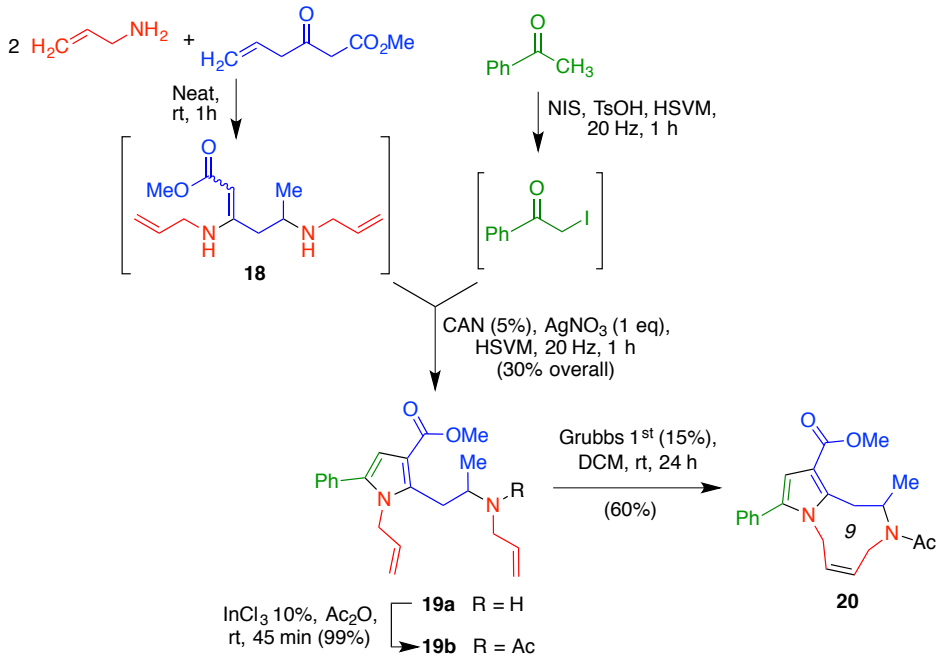
Scheme 7.7

We next examined a reaction involving as starting materials two molecules of allylamine rather than a diamine, aiming at the generation of a ring-closing metathesis precursor. When we mixed methyl 3-oxo-5-hexenoate and diallylamine in the absence of solvent at room temperature, the expected β-enaminone **18** was obtained in quantitative yield, as a 1:1 mixture of *Z* and *E* isomers. This transformation can be regarded a chemo-differentiating ABB' multicomponent reaction, since the final product arises from one molecule of one the components and two molecules of the other, which have different roles in the reaction.[121] The crude **18** was added to a milling jar where we had previously reacted acetophenone and N-iodosuccinimide in the presence of toluenesulfonic acid under high-speed vibration milling conditions for 1 h, and the mixture was treated with CAN (5%) and silver nitrate (1 eq) and submitted to the same mechanochemical conditions for 1 h. This reaction afforded the desired pyrrole derivative **19a**, although in moderate yield. An attempt to cyclize **19a** by ring closing metathesis was unsuccessful, which was attributed to catalyst inactivation by the basic nitrogen.[122] Therefore, we acetylated **19a** with acetic anhydride in the presence of indium trichloride to furnish the non-basic pyrrole **19b**, which gave the desired ring-closing metathesis reaction uneventfully in the presence of the Grubbs first generation catalyst in dichloromethane at room temperature. The resulting

[121] Tejedor, D.; García-Tellado, F. *Chem. Soc. Rev*. **2007**, *36*, 484.

[122] For discussions of the problems found in olefin metathesis of compounds containing basic nitrogen atoms, see: (a) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829. (b) Lafaye, K.; Bosset, C.; Nicolas, L.; Guérinot, A.; Cossy, J. *Beilstein J. Org. Chem.* **2015,** *11,* 2223. See also: (c) Stoianova, D. http://allthingsmetathesis.com/metathesis-of-amine-containing-compounds/.

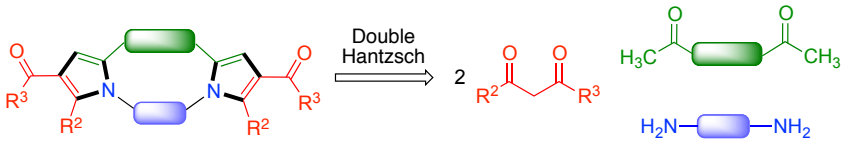
product **20** is a derivative of the previously unknown pyrrolo[1,2-*a*][1,5]diazonine framework.



Scheme 7.8

7.4. One-pot multicomponent macrocyclization

As an aditional approach to macrocyclic structures, we decided to investigate the application of a one-pot process involving two Hantzch pyrrole syntheses, one of which acts as the macrocyclization event (Scheme 7.9).



Scheme 7.9

In our first experiments, treatment of 1,3-diacetylbenzene with N-iodosuccinimide under our previously described mechanochemical conditions (ball milling at 20 Hz in the presence of TsOH for 1 h), followed by addition of 1,4-butanediamine and two equivalents of methyl acetoacetate (which had been premixed in the presence of $InCl_3$), silver nitrate and additional ball milling afforded only a 5% yield of the target macrocycle **21a**, the main isolated products being **22** and **23** (Figure 7.4). These compounds arose from the formation of one or two pyrrole rings, respectively, followed by a subsequent reductive dehalogenation of the second α-iodophenacyl moiety, as previously observed by us in cases where the Hantzsch reaction is slow.[123]

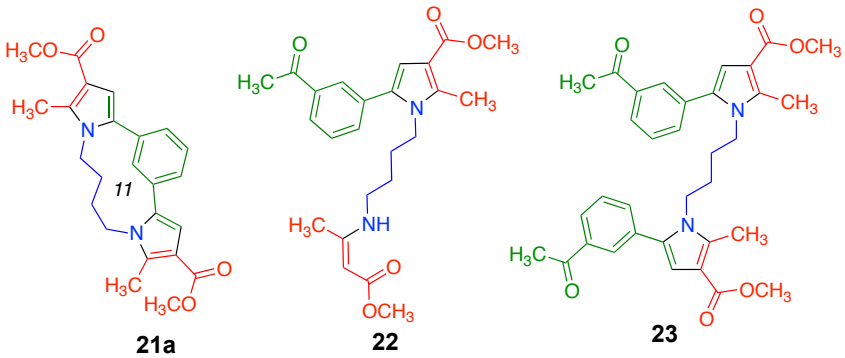


Figure 7.4

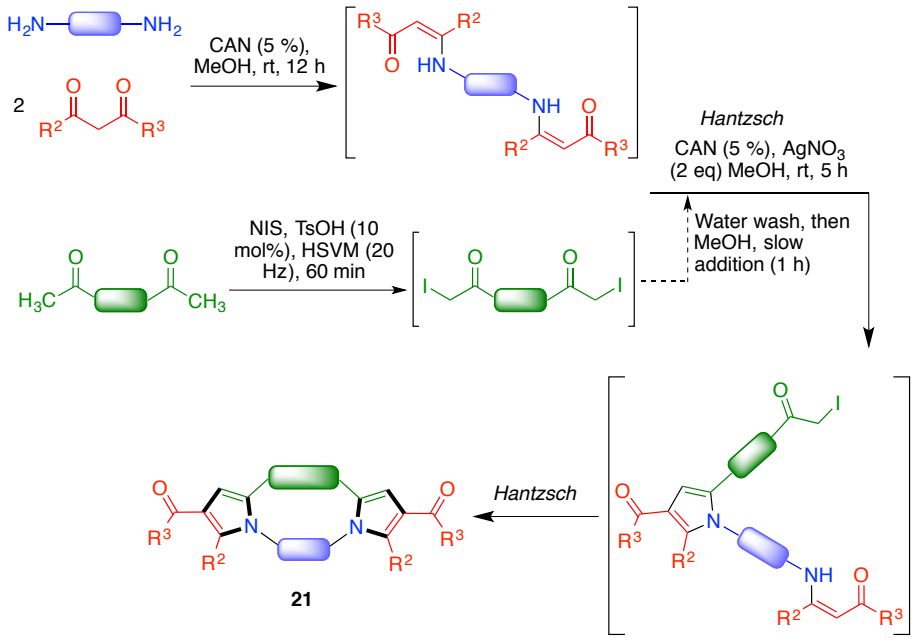
We reasoned that this result was due to the fact that the high reactant concentrations that are prevalent under the solvent-free mechanochemical conditions did not favour the macrocyclization stage. For this reason, we resorted to a more conventional methodology, carrying out a slow addition of the iodoketone to a solution containing the *in situ*-prepared β-enaminone, the CAN catalyst and silver nitrate in order to achieve high dilution conditions. The optimization of this process was carried out for the case of **21a** and is summarized in Table 7.2.

[123] Estévez, V.; Sridharan, V.; Sabaté, S.; Villacampa, M.; Menéndez, J. C. *Asian J. Org. Chem*. **2016**, *6*, 526.

Table 7.2: optimization of the reaction condition

Vol MeOH (mL/mmol)	Eq. Lewis acid	Eq. $AgNO_3$	Injection time (h)	Yield (%)
10	0,1	2	6	25
10	0,1	2	2	25
20	0,1	2	2	traces
15	2	2	2	traces
15	0,1	2	2	52

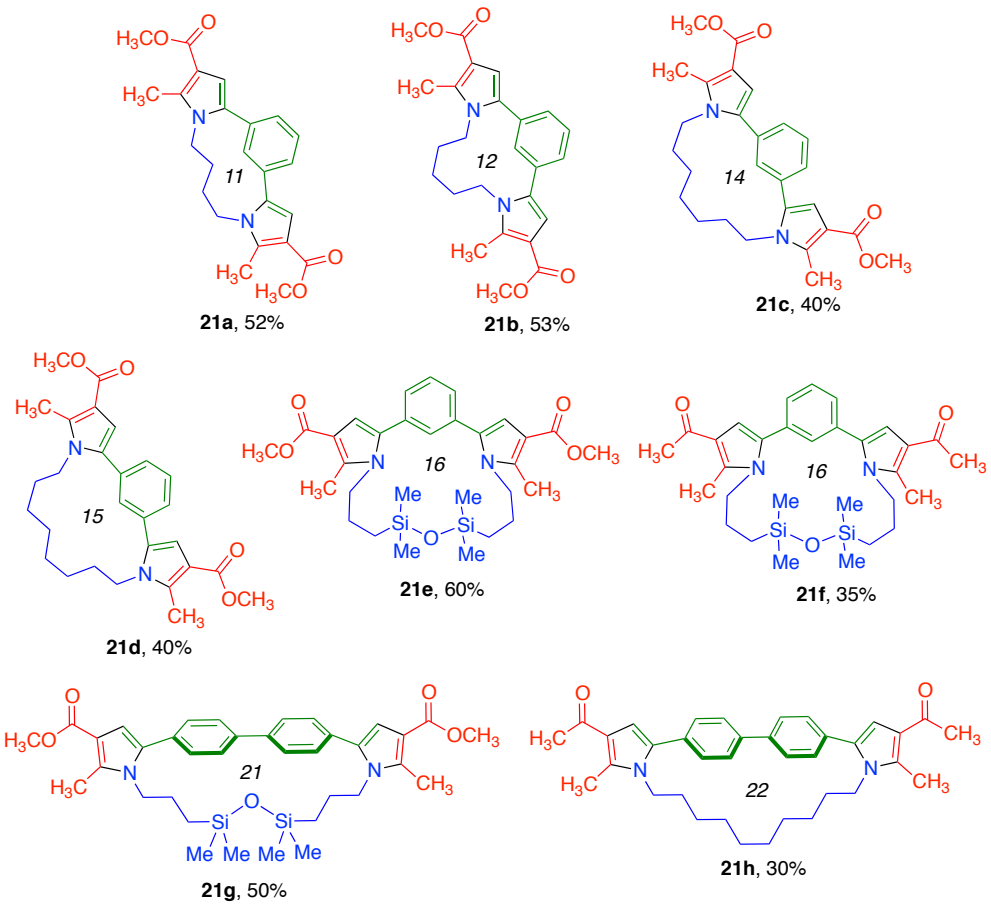
This reaction can be viewed as a double Hantzsch pyrrole synthesis telescoped with the preparation of the α-haloketone starting material. This reaction achieves the creation of six bonds in a single operation and has as the key step the formation of a macrocyclic scaffold during the formation of the second pyrrole ring (Scheme 7.10). To our knowledge, this is the first example of the construction of macrocyclic systems by one-pot generation of two heterocyclic rings.



Scheme 7.10

The optimized conditions were used to prepare a library of compounds **21**, which cover a very unusual region of chemical space corresponding to macrocyclic cyclophanes that contain *ter*- or *quater*-aryl structural fragments (Figure 7.5). Although yields were 60% or below, it has to be taken into account that this pseudo four-component process involves the creation of two rings and six bonds, comprising up to 11 individual steps. In most cases, both pyrrole nitrogens were connected *via* a polymethylene chain, but in the cases of compounds **21e**-**21g** we employed a spacer

containing a tetramethyldisiloxane moiety.



21a, 52% **21b**, 53% **21c**, 40%

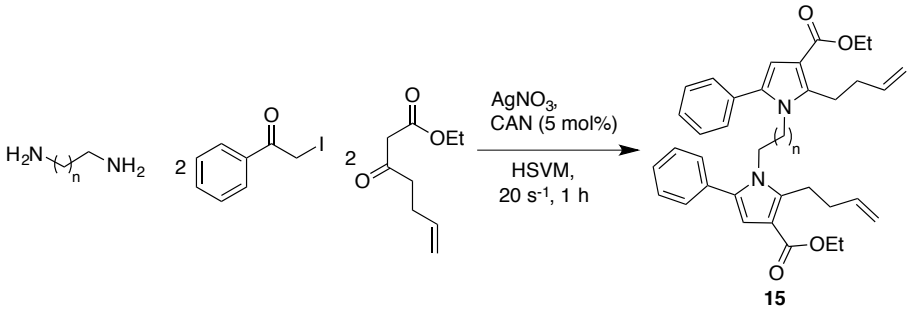
21d, 40% **21e**, 60% **21f**, 35%

21g, 50% **21h**, 30%

Scheme 7.11

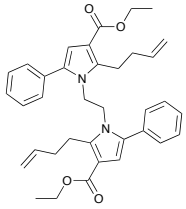
7.5. Experimental section

7.5.1. Mechanochemical synthesis of bis-pyrroles bearing two terminal alkenes.



The suitable acetophenone derivative (0.4 mmol), N-iodosuccinimide (0.4 mmol) and *p*-toluenesulfonic acid (10 mol%) was placed in a 20 mL milling jar together with a 20 mm zirconium oxide ball. The ball mill was set to vibrate at a frequency of 20 s^{-1} for 60 min at room temperature. To this reaction vessel was added a mixture of the suitable diamine (0.2 mmol), ethyl-3-oxohept-6-enoate,[124] (0.4 mmol) and CAN (5 mol%), which had been premixed at room temperature during 240 min. Silver nitrate (0.4 mmol) and additional CAN (5 mol%) were added and the ball mill was set to vibrate at a 20 s^{-1} frequency for 80 min at room temperature. Then, the reaction vessel was cleansed with ethyl acetate or dichloromethane and the suspension was filtered to remove the silver iodide precipitate. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate and compounds **15a**-**15h** are obtained.

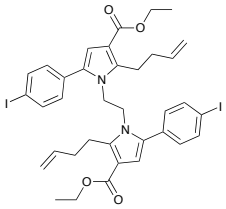
Diethyl-1,1'-(ethane-1,2-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15a)



Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), diaminoethane (0.2 mmol) and acetophenone (0.4 mmol); yield: 72 mg (64%); yellowish solid; mp: 134-135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 – 7.31 (m, 6H), 7.19 – 7.14 (m, 4H), 6.41 (s, 2H), 5.62 – 5.46 (m, 2H), 4.88 – 4.80 (m, 4H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.74 (s, 4H), 2.21 – 2.15 (m, 4H), 2.03 – 1.94 (m, 4H), 1.26 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, CDCl3) δ 157.9, 133.0, 130.1, 125.9, 125.2, 122.5, 121.9, 121.1, 108.5, 105.3, 103.8, 52.4, 36.7, 27.1, 16.7, 7.5; IR (neat) ν: 1699.4, 1640.7 (C=O), 1216.0 (C-O), 1065.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{36}H_{40}N_2O_4$ C, 76.57; H, 7.14; N, 4.96; found: C 76.45, H 7.26, N 4.62.

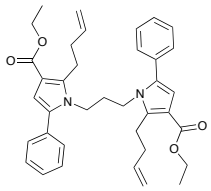
[124] Tenti, G.; Ramos, M. T.; Menéndez, J. C.; *Curr. Org. Synth.* **2013**, *10*, 645.

Diethyl-1,1'-(ethane-1,2-diyl)bis(2-(but-3-en-1-yl)-5-(4-iodophenyl)-1*H*-pyrrole-3-carboxylate) (15b)



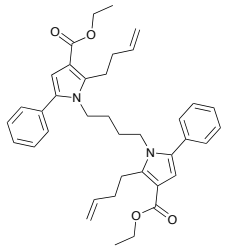
Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), 1,2-diaminoetane (0.2 mmol) and acetophenone (0.4 mmol); yield: 131 mg (80%); yellowish solid; mp: 116-118 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 4H), 6.91 (d, *J* = 8.3 Hz, 4H), 6.49 (s, 2H), 5.78 – 5.62 (m, 2H), 5.03 – 4.94 (m, 4H), 4.29 (q, *J* = 7.1 Hz, 4H), 3.86 (br s, 4H), 2.43 – 2.37 (m, 4H), 2.20 – 2.10 (m, 4H), 1.36 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.64, 140.23, 137.87, 136.9, 131.7, 131.4, 131.0, 115.7, 112.7, 111.3, 93.8, 59.6, 43.8, 34.0, 24.0, 14.5; IR (neat) ν: 1698.2 (C=O), 1221.7 (C-O), 1114.6 (C=C-H) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{36}H_{38}I_2N_2NaO_4$:, 839,0818 found: 839.0835.

Diethyl-1,1'-(propane-1,3-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15c)



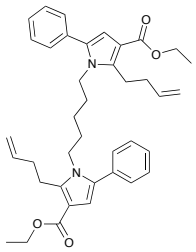
Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), diaminoethane (0.2 mmol) and acetophenone (0.4 mmol); yield: 83 mg (72%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 6H), 7.14 – 7.10 (m, 4H), 6.43 (s, 2H), 5.81 – 5.65 (m, 2H), 4.98 – 4.85 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 4H), 3.63 – 3.56 (m, 4H), 2.79 – 2.66 (m, 4H), 2.20 – 2.10 (m, 4H), 1.57 – 1.42 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.0, 139.7, 137.3, 133.1, 132.6, 129.0, 128.6, 127.7, 115.3, 112.2, 110.5, 59.4, 41.0, 34.1, 32.4, 25.0, 14.5; IR (neat) ν: 1699.4 (C=O), 1216.0 (C-O), 1065.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{37}H_{42}N_2O_4$: C, 76.79; H, 7.32; N, 4.84; found: C 76.53, H 7.28, N 4.67.

Diethyl-1,1'-(butane-1,4-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15d)



Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), diaminoethane (0.2 mmol) and acetophenone (0.4 mmol); yield: 80 mg (68%); yellowish solid; mp: 116-118 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 6H), 7.25 – 7.20 (m, 4H), 6.53 (s, 2H), 5.97 – 5.81 (m, 2H), 5.11 – 5.01 (m, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 3.70 (br s, 4H), 3.00 – 2.93 (m, 4H), 2.33 – 2.27 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 6H), 1.21 (br s, 4H); ^{13}C NMR (63 MHz, CDCl3) δ 165.1, 139.8, 137.6, 133.2, 133.0, 129.2, 128.5, 127.6, 115.2, 111.9, 110.4, 59.4, 43.2, 34.2, 27.8, 25.2, 14.5; IR (neat) ν: 1699.0 (C=O), 1216.0 (C-O), 1065.8 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{38}H_{44}N_2O_4$: C, 77.00; H, 7.48; N, 4.73; found: C 76.83, H 7.38, N 4.66.

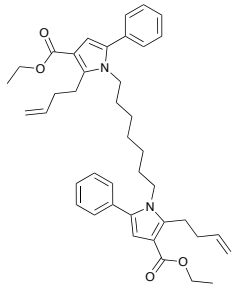
Diethyl-1,1'-(pentane-1,5-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15e)



Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), 1,5-diaminopentane (0.2 mmol) and acetophenone (0.4 mmol); yield: 91 mg (75%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 6H), 7.30 – 7.27 (m, 4H), 6.55 (s, 2H), 6.00 – 5.84 (m, 2H), 5.13 – 5.02 (m, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 3.83 – 3.74 (m, 4H), 3.05 – 2.99 (m, 4H), 2.41 – 2.32 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 6H),

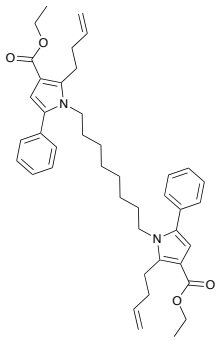
1.33 – 1.19 (m, 6H), 0.93 – 0.80 (m, 2H); ^{13}C NMR (63 MHz, CDCl3) δ 165.1, 139.9, 137.6, 133.2, 133.1, 129.2, 128.4, 127.5, 115.2, 111.8, 110.3, 59.3, 43.7, 34.2, 30.5, 25.3, 23.3, 14.5; IR (neat) ν: 1702.0 (C=O), 1216.2 (C-O), 1064.3 (C=C-H) cm^{-1}; elemental analysis (%) calcd. for $C_{39}H_{46}N_2O_4$: C, 77.20; H, 7.64; N, 4.62; found: C 72.53, H 7.28, N 4.36.

Diethyl-1,1'-(pentane-1,5-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15f)



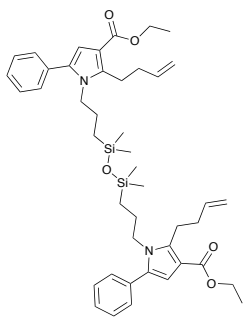
Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), 1,7-diaminoepthane (0.2 mmol) and acetophenone (0.4 mmol); yield: 76 mg (60%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.33 (m, 10H), 6.57 (s, 2H), 6.03 – 5.87 (m, 2H), 5.16 – 5.03 (m, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 3.87 – 3.81 (m, 4H), 3.11 – 3.04 (m, 4H), 2.45 – 2.37 (m, 4H), 1.42 – 1.29 (m, 10H), 0.96 (br s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 139.9, 137.7, 133.3, 133.2, 129.3, 128.4, 127.5, 115.1, 111.7, 110.2, 59.3, 50.7, 43.9, 34.2, 31.0, 28.3, 26.2, 25.3, 14.5; IR (neat) ν: 1689.0 (C=O), 1211.2 (C-O), 1104.3 (C=C-H) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{41}H_{50}N_2O_4Na$:, 657,3668 found: 657.3654.

Diethyl-1,1'-(octane-1,8-diyl)bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (16g)



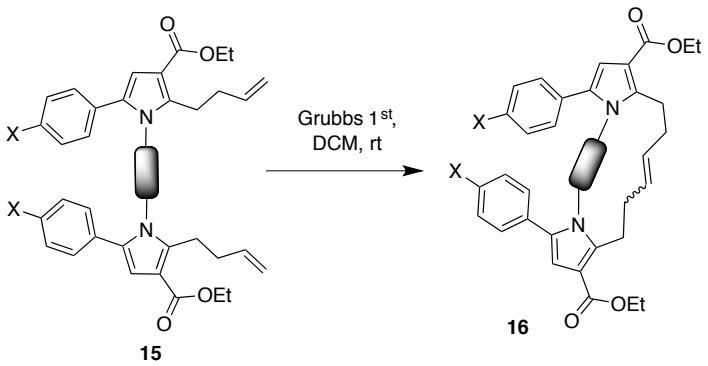
Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), 1,8-diaminooctane (0.2 mmol) and acetophenone (0.4 mmol); yield: 74 mg (57%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 10H), 6.57 (s, 2H), 6.03 – 5.87 (m, 2H), 5.16 – 5.03 (m, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 3.89 – 3.83 (m, 5H), 3.12 – 3.05 (m, 4H), 2.46 – 2.37 (m, 4H), 1.48 – 1.34 (m, 3H), 1.37 (t, *J* = 7.1 Hz, 6H), 0.99 (br s, 8H); ^{13}C NMR (63 MHz, CDCl3) δ 165.2, 140.0, 137.8, 133.4, 133.2, 129.3, 128.4, 127.4, 115.1, 111.7, 110.1, 59.3, 44.0, 34.2, 31.1, 28.6, 26.3, 25.3, 14.5; IR (neat) ν: 1700.2 (C=O), 1222.7 (C-O), 1094.6 (C=C-H) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{42}H_{52}N_2O_4Na$:, 671,3824 found: 671.3810.

Diethyl-1,1'-((1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl))bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15h)



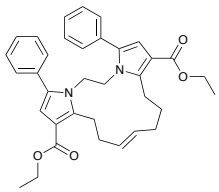
Prepared from ethyl-3-oxohept-6-enoate, (0.4 mmol), 1,3-bis(aminopropyl)tetramethyldisiloxane (0.2 mmol) and acetophenone (0.4 mmol); yield: 73 mg (50 %); dark yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 10H), 6.58 (s, 2H), 6.03 – 5.87 (m, 2H), 5.16 – 5.02 (m, 4H), 4.30 (q, *J* = 7.1 Hz, 4H), 3.88 – 3.81 (m, 4H), 3.12 – 3.05 (m, 4H), 2.46 – 2.37(m, 4H), 1.37 (t, *J* = 7.1 Hz, 6H), 1.40 – 1.34 (m, 4H), 0.28 – 0.21 (m, 4H), -0.12 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 140.0, 137.7, 133.3, 133.2, 129.3, 129.2, 128.4, 127.5, 115.2, 111.6, 110.2, 59.3, 47.0, 34.3, 25.3, 25.24, 15.1, 14.5, 0.0; IR (neat) n: 1703.2 (C=O), 1223.7 (C-O), 1111.6 (C=C-H) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{44}H_{60}N_2NaO_5Si_2$:, 775,3938 found: 775,3972.

7.5.2. General procedure of pyrrole-based macrocycles 16a-16h by RCM reaction



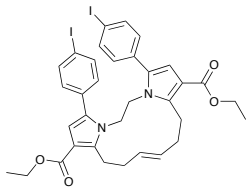
To a solution of the suitable pyrrole **15a**-**15h** (0.15 mmol) in dry dichloromethane (10 mL) under argon atmosphere, Grubbs 1st generation catalyst (5-10 mmol%) was added. The mixture was stirred for 4-12 h at room temperature. Upon completion, as judged by TLC, the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate affording the desired macrocycle derivatives **16a**-**16h**.

Diethyl-(*E*)-1,12-diphenyl-4,5,8,9,14,15-hexahydrodipyrrolo[1,2-*d*:2',1'-*l*][1,4]diazacyclododecine-3,10-dicarboxylate (16a)



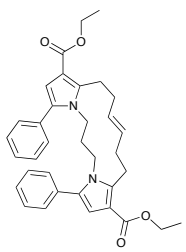
Prepared from pyrrole **15a** (0.1 mmol); yield: 40 mg (75%); yellowish solid; mp: 177-179 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.13 – 7.05 (m, 4H), 6.96 – 6.93 (m, 4H), 6.39 (s, 2H), 5.93 – 5.80 (m, 2H), 4.25 – 4.17 (m, 8H), 3.16 (br s, 4H), 2.44 (br s, 4H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 139.5, 133.9, 131.8, 130.9, 129.1, 128.6, 127.8, 112.8, 110.6, 59.5, 44.4, 27.7, 27.1, 14.4; IR (neat) ν: 1699.4 (C=O), 1236.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{34}H_{36}N_2O_4$: C, 76.09; H, 6.76; N, 5.22; found: C 75.95, H 6.84, N 5.16.

Diethyl-(*Z*)-1,12-bis(4-iodophenyl)-4,5,8,9,14,15-hexahydrodipyrrolo[1,2-*d*:2',1'-*l*][1,4]diazacyclododecine-3,10-dicarboxylate (16b)



Prepared from pyrrole **15b** (0.1 mmol); yield: 71 mg (90%); yellowish solid; mp: 124-126 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 4H), 6.80 (d, *J* = 7.9 Hz, 4H), 6.48 (s, 2H), 6.02 – 5.89 (m, 2H), 4.30 (q, *J* = 7.1 Hz, 4H), 4.18 (br s, 4H), 3.22 (br s, 4H), 2.52 (br , 4H), 1.37 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 140.2, 138.1, 133.0, 131.7, 131.3, 131.2, 113.5, 111.4, 94.5, 60.1, 44.8, 28.2, 27.4, 14.9; IR (neat) ν: 1702.4 and 1699.9 (C=O), 1276.0 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{34}H_{34}I_2N_2O_4$:, 788,0607 found: 788,0622.

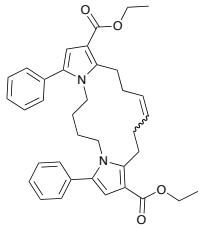
Diethyl-(*Z*)-1,12-diphenyl-4,5,8,9,15,16-hexahydro-14*H*-dipyrrolo[1,2-*e*:2',1'-*m*][1,5]diazacyclotridecine-3,10-dicarboxylate (16c)



Prepared from pyrrole **15c** (0.1 mmol); yield: 48 mg (88%); white solid; Mp: 199-201 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 5H), 7.36 – 7.29 (m, 5H), 6.61 (s, 2H), 5.86 – 5.73 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 4H), 3.85 – 3.74 m,

4H), 2.99 (br s, 4H), 2.62 – 2.37 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 164.9, 140.0, 133.7, 132.7, 129.4, 129.2, 128.6, 127.8, 112.2, 109.6, 59.5, 41.7, 34.1, 27.9, 27.9, 14.5; IR (neat) ν: 1696.4, 1689.9 (C=O), 1266.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{35}H_{38}N_2O_4$: C, 76.34; H, 6.96; N, 5.09; found: C 76.47, H 7.01, N 4.99.

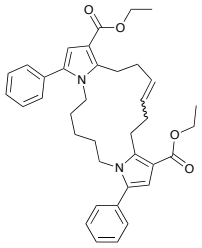
Diethyl 1,12-diphenyl-4,5,8,9,14,15,16,17-octahydrodipyrrolo[1,2-*f*:2',1'-*n*][1,6]diazacyclotetradecine-3,10-dicarboxylate (16d)



This compound is a mix of isomer A and isomer B (as 8.5:1.5).
Prepared from pyrrole **15d** (0.5 mmol); yield: 36 mg (64%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 6H, isomer A+B), 7.33 – 7.30 (m, 4H, isomer A+B), 6.58 (s, 2H, isomer B), 6.57 (s, 2H, isomer A), 5.80 – 5.68 (m, 2H, isomer A), 5.53 – 5.49 (m, 2H, isomer B), 4.31 (q, *J* = 7.1 Hz, 4H, isomer A+B), 3.89 (br s, 4H, isomer A+B), 3.12 – 3.05 (m, 4H), 2.62 – 2.44 (m, 4H, isomer A+B), 1.52 (br s, 4H, isomer A+B), 1.29 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 139.9, 133.2, 133.0, 129.4, 129.1 (129.0 isomer B), 128.5, 127.6, 112.2 (112.1 isomer B), 110.3, 59.4, 44.1, 28.9, 27.9 (29.7 isomer B), 26.2, 14.5; IR (neat) ν: 1699.4, 1689.0 (C=O), 1236.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{36}H_{40}N_2O_4$: C, 76.57; H, 7.14; N, 4.96; found: C 76.21, H 6.81, N 4.58.

Diethyl 3,11-diphenyl-6,7,8,9,14,15,18,19-octahydro-5*H*-dipyrrolo[1,2-*g*:2',1'-*o*][1,7]diazacyclopentadecine-1,13-dicarboxylate (16e)

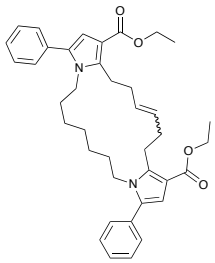
This compound is a mix of isomer A and isomer B (as 8:2).



Prepared from pyrrole **15e** (0.5 mmol); yield: 40 mg (70%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 10H, isomer A+B), 6.59 (s, 2H, isomer A+B), 5.79 – 5.66 (m, 2H, isomer A), 5.60 – 5.57 (m, 2H, isomer B), 4.36 – 4.27 (m, 4H, $CH_3C\mathbf{H_2}OCO$-, isomer A+B), 3.96 – 3.84 (m, 4H, isomer A+B), 3.11 – 3.05 (m, 4H, isomer A+B), 2.60 – 2.43 (m, 4H, isomer A+B), 1.82 – 1.58 (m, 4H, isomer A+B), 1.41 – 1.34 (m, 6H, $C\mathbf{H_3}CH_2OCO$-, isomer A+B), 1.18 – 1.10 (m, 2, isomer A+B); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.1, 165.0 (isomer B), 133.3, 133.4 (isomer B), 133.0, 133.1 (isomer B), 111.7, 110.3, 110.1 (isomer B), 59.4, 50.8 (isomer B), 43.5, 32.6 (isomer B), 30.9 (isomer B), 29.9, 28.2, 26.6, 22.8, 14.5; IR (neat) ν: 1701.4, 1689.2 (C=O), 1233.8 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{37}H_{42}N_2O_4$: C, 76.79; H, 7.32; N, 4.84; found: C 76.49, H 6.98, N 4.58.

Diethyl 3,13-diphenyl-6,7,8,9,10,11,16,17,20,21-decahydro-5*H*-dipyrrolo[1,2-*i*:2',1'-*q*][1,9]diazacycloheptadecine-1,15-dicarboxylate (16f)

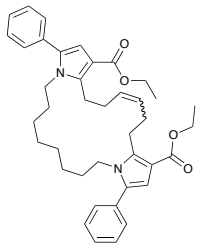
This compound is a mix of isomer A and isomer B (as 1:1).



Prepared from pyrrole **15f** (0.5 mmol); yield: 44 mg (73%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 10H, isomer A+B), 6.60 (s, 2H, isomer A), 6.59 (s, 2H, isomer **A**), 5.72 – 5.66 (m, 2H, isomer A+B), 4.36 – 4.27 (m, 4H, $CH_3C\mathbf{H_2}OCO$-, isomer A+B), 3.94 – 3.84 (m, 4H, isomer A+B), 3.15 – 3.05 (m, 4H, isomer A+B), 2.47 (br s, 4H, isomer A+B), 1.68 – 1.61 (m, 2H, isomer A), 1.41 – 1.21 (m, 12H, isomer A+B); ^{13}C NMR (63 MHz, $CDCl_3$) δ all the picks refer to isomer A and B: 165.2, 165.1, 140.2, 140.1, 133.2, 133.1, 130.7, 129.5, 129.3, 129.2, 128.4, 127.5, 127.5, 111.8, 111.6,

110.4, 110.1, 59.3, 59.3, 50.7, 44.0, 43.9, 32.7, 30.2, 30.1, 28.3, 26.9, 26.4, 26.1, 26.0, 25.6, 24.9, 14.5, 14.5; IR (neat) ν: 1698.4, 1687.2 (C=O), 1237.6 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{39}H_{46}N_2O_4Na$: 629,3355 found: 629,3333.

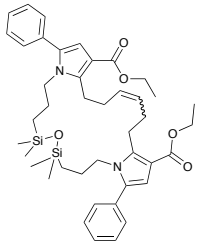
Diethyl 3,14-diphenyl-5,6,7,8,9,10,11,12,17,18,21,22-dodecahydrodipyrrolo[1,2-*a*:2',1'-*i*][1,10]diazacyclooctadecine-1,16-dicarboxylate (16g)



This compound is a mix of isomer A and isomer B (as 6.5:3.5).
Prepared from pyrrole **15g** (0.5 mmol); yield: 49 mg (80%); yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 10H, isomer A+B), 6.60 (s, 2H, isomer A), 6.60 (s, 2H, isomer **A+B**), 5.70 – 5.67 (m, 2H, isomer A), 5.62 – 5.59 (m, 2H, isomer B), 4.31 (t, *J* = 7.1 Hz, 4H, $CH_3C\mathbf{H_2}OCO$-, isomer A+B), 3.94 – 3.83 (m, 4H, isomer A+B), 3.12 – 3.06 (m, 4H, isomer A+B), 2.49 (br s, 4H, isomer A+B), 1.72 – 1.50 (m, 4H, isomer A), 1.40 – 1.21 (m, 14H, isomer A+B); ^{13}C NMR (63 MHz, $CDCl_3$) δ all the picks refer to isomer A and when they refer to isomr B is indicated: ^{13}C NMR (63 MHz, $CDCl_3$) d 165.5 (isomer B), 165.1, 140.6 (isomer B), 140.3, 140.0, 133.4 (isomer B), 133.3, 133.2, 133.1, 133.1, 133.0 (isomer B), 130.4, 129.6, 129.3, 129.2, 128.4, 127.5 (isomer B), 127.5, 111.7, 111.6, 110.2, 109.9, 59.3, 50.8 (isomer B), 44.3, 44.0 (isomer B), 32.6, 30.4 (isomer B), 30.1, 28.2 (isomer B), 27.1 (isomer B), 27.0, 26.1, 25.8, 25.4 (isomer B), 14.5; IR (neat) ν: 1702.1, 1698.0 (C=O), 1198.9 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{40}H_{48}N_2O_4Na$: 643,3512 found: 643,3506.

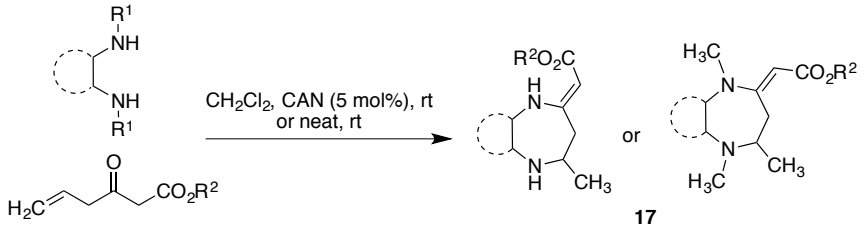
Diethyl 8,8,10,10-tetramethyl-3,15-diphenyl-5,6,7,8,10,11,12,13,18,19,22,23-dodecahydrodipyrrolo[1,2-*f*:2',1'-*n*][1]oxa[6,15]diaza[2,19]disilacyclononadecine-1,17-dicarboxylate (16h)

This compound is a mix of isomer A and isomer B (as 6.5:3.5)



Prepared from pyrrole **15h** (0.5 mmol); yield: 58 mg (80%); white solid; Mp: 134-135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 10H, isomer A+B), 6.60 (s, 2H, isomer B), 6.58 (s, 2H, isomer **A**), 5.69 – 5.64 (m, 2H, isomer A+B), 4.31 (t, *J* = 7.1 Hz, 4H, $CH_3C\mathbf{H_2}OCO$-, isomer A+B), 3.93 – 3.79 (m, 4H, isomer A+B), 2.43 (mbr s, 4H, isomer A+B), 1.70 – 1.53 (m, 4H, isomer A), 1.37 (t, *J* = 7.1 Hz, 6H, $C\mathbf{H_3}CH_2OCO$-, isomer A+B), 0.44 – 0.37 (m, 4H), -0.01 (s, 12H, isomer A), -0.08 (s, 12H, isomer B); ^{13}C NMR (63 MHz, $CDCl_3$) d all the picks refer to isomer A and when they refer to isomr B is indicated: ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.2, 140.1, 133.2, 133.2, 130.5, 129.3, 128.4, 127.5, 111.6, 109.9, 59.3, 47.2, 32.7, 26.4, 25.6, 15. 7, 14.5, 0.3, -0.02 (isomer B); IR (neat) ν: 1700.8, 1699.8 (C=O), 1089.9 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{42}H_{56}N_2O_5Si_2$: 724,3728 found: 724,3742.

7.5.3. General experimental procedure for the synthesis of pyrrole-derived medium-sized rings by ring-closing metathesis

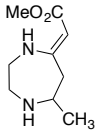


17

Procedure A: CAN (5 mol%) was added to a solution of 1,2 diamine derivative (1 mmol) and the suitable allyl ketone or allyl ketoester (1 mmol) in CH_2Cl_2 (5 ml) at room temperature under argon. The solution was stirred until completion of the reaction, as checked by TLC. The reaction mixture was diluted with 15 ml CH_2Cl_2 and washed with water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography using as the stationary phase neutral Al_2O_3 (activity grade IV), using 1:10 ethyl acetate:petroleum ether as mobile phase.

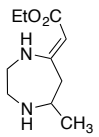
Procedure B: The same procedure was applied without solvent, by adding the suitable allyl ketone or allyl ketoester (1 mmol) onto the suitable 1,2-diamine (1 mmol) at room temperature.

Methyl (*Z*)-2-(7-methyl-1,4-diazepan-5-ylidene)acetate (17a)



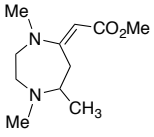
Procedure A was followed using ethane-1,2-diamine (60 mg, 1 mmol) and methyl 3-oxohex-5-enoate (142 mg ,1 mmol). Compound **17a** is obtained as a white solid (175 mg, 95%); mp 62 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.80 (s, 1H), 4.39 (s, 1H), 3.57 (s, 3H), 3.51 – 3.19 (m, 2H), 3.01 (m, 1H), 2.92 – 2.60 (m, 2H), 2.42 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.16 (dt, *J* = 14.4, 1.4 Hz, 1H), 1.82 (s, 1H), 1.12 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3, 166.1, 82.1, 52.8, 50.4, 50.1, 47.0, 45.8, 24.1; IR (film, neat) ν: 3309.1, 2950.2, 1651.3, 1606.0, 1506.0, 1306.4, 1240.3, 1172.9, 1050.3, 784.1 cm^{-1}; Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.57; H, 8.41; N, 15.01.

Ethyl (7-methyl-[1,4]-diazepan-5-ylidene)acetate (17b)



Procedure A was followed using ethane-1,2-diamine (60 mg, 1 mmol) and ethyl 3-oxohex-5-enoate (156 mg ,1 mmol). Compound **17b** is obtained as a white solid (178 mg, 90%), mp 46 °C ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.86 (br s, 1H), 4.44 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.28-3.49 (m, 2H), 3.03-3.10 (m, 1H), 2.74-2.93 (m, 2H), 2.48 (dd, *J* = 14.4 and 9.0 Hz, 1H), 2.21 (d, *J* = 14.8 Hz, 1H), 1.77 (br s, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6, 165.6, 82.1, 58.4, 52.4, 49.6, 46.5, 45.4, 23.7, 14.6; IR (film, neat) ν: 3306.0, 2973.3, 1651.5, 1606.0, 1505.6, 1304.2, 1238.4, 1173.1, 1103.9, 1052.4, 783.8 cm^{-1}; Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.23; H, 9.32; N, 14.29.

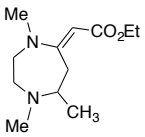
Methyl (*E*)-2-(1,4,7-trimethyl-1,4-diazepan-5-ylidene)acetate (17c)



Procedure A was followed using *N,N*-dimethylethane-1,2-diamine (88 mg, 1 mmol) and methyl 3-oxohex-5-enoate (142 mg ,1 mmol). Compound **17c** is obtained as a colourless, viscous liquid (180 mg, 85%); ^{1}H NMR (250 MHz,

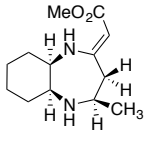
$CDCl_3$) δ 4.84 (br. S, 1H), 4.50 (s, 1H), 3.61 (s, 3H), 3.59 – 3.42 (m, 3H), 3.42 – 3.20 (m, 1H), 2.93 (s, 3H), 2.77 (m, 2H), 2.58 – 2.40 (m, 1H), 2.34 (s, 3H), 2.24 (s, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 169.8, 164.7, 84.8, 57.2, 55.0, 54.3, 50.5, 43.5, 41.2, 34.6; IR (film, neat) ν: 2931.3, 2797.8, 1682.0, 1580.1, 1450.0, 1407.9, 1144.3, 1052.9, 796.4 cm^{-1}; Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.01; H, 9.13; N, 9.39.

Ethyl (*E*)-2-(1,4,7-trimethyl-1,4-diazepan-5-ylidene)acetate (17d)



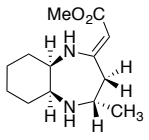
Procedure A was followed using *N,N*-dimethylethane-1,2-diamine (88 mg, 1 mmol) and Ethyl 3-oxohex-5-enoate (156 mg ,1 mmol). Compound **17d** is obtained as a colourless, viscous liquid (188 mg, 83%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.47 (s, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.58 - 3.51 (m, 3H), 3.49 – 3.27 (m, 1H), 2.90 (s, 3H), 2.78 - 2.73 (m, 2H), 2.72 - 2.38 (m, 1H), 2.31 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 168.9, 164.0, 84.7, 58.2, 56.8, 54.5, 53.8, 43.0 (2c), 34.0, 14.5; IR (neat) ν: 2972.3, 2930.6, 1679.4, 1578.9, 1449.5, 1409.8, 1140.2, 1054.3, 796.5 cm^{-1}; Anal. Calcd for $C_{12}H_{22}N_2O_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.39; H, 9.45; N, 12.66.

Methyl (*Z*)-2-((4*R*,5a*S*,9a*R*)-4-methyldecahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17ea)



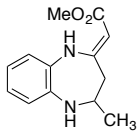
^{1}H NMR (250 MHz, $CDCl_3$) δ 8.88 (br s, 1H), 4.34 (d, *J* = 1.7 Hz, 1H), 3.60 (d, *J* = 2.0 Hz, 4H), 3.01 (q, *J* = 6.3 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.64 (dd, *J* = 14.8, 5.1 Hz, 1H), 2.18 (dd, *J* = 14.9, 6.4 Hz, 1H), 2.12 – 1.98 (m, 1H), 1.73 – 1.20 (m, 9H), 1.13 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3, 164.3, 82.6, 57.6, 54.9, 50.4, 49.2, 44.5, 31.6, 28.6, 25.3, 23.5, 22.8; IR (film, neat) ν: 3290.8, 2932.1, 2856.0, 1651.3, 1607.1, 1445.3, 1243.3, 1173.8, 1108.7, 1046.7, 786.0 cm^{-1}; Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 63.87; H, 9.66; N, 11.44.

Methyl (*Z*)-2-((4*S*,5a*S*,9a*R*)-4-methyldecahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17eb)



^{1}H NMR (250 MHz, $CDCl_3$) δ 8.64 (br s, 1H), 4.40 (s, 1H), 4.05 – 3.84 (m, 1H), 3.63 (s, 3H), 3.04 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.84 (m, 1H), 2.43 (dd, *J* = 14.3, 9.3 Hz, 1H), 2.10 (d, *J* = 14.3 Hz, 1H), 2.02 – 1.73 (m, 3H), 1.73 – 1.47 (m, 4H), 1.47 – 1.22 (m, 2H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.6, 165.6, 81.5, 58.2, 55.0, 50.4, 46.5, 46.1, 32.3, 27.2, 26.1, 24.9, 20.2; IR (film, neat) ν: 3290.8, 2932.1, 2856.0, 1651.3, 1607.1, 1445.3, 1243.3, 1173.8, 1108.7, 1046.7, 786.0 cm^{-1}; Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.30; N, 11.75. Found: C, 63.87; H, 9.66; N, 11.44.

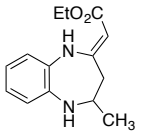
Methyl (*Z*)-2-(4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17f)



Procedure A was followed using benzene-1,2-diamine (108 mg, 1 mmol) and Methyl 3-oxohex-5-enoate (142 mg, 1 mmol). Compound **17f** is obtained as a colourless, viscous liquid (139 mg, 60 %) or procedure B was followed using benzene-1,2-diamine (108 mg, 1 mmol) and Methyl 3-oxohex-5-enoate (142 mg , 1 mmol). Compound **17f** is obtained as a colourless, viscous liquid (213 mg, 92 %); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.29 - 6.87 (m, 3H), 6.78 (d, *J* = 7.6 Hz, 1H), 4.72 (s, 1H), 3.97 - 3.89 (m, 1H), 3.72 (s, 3H), 2.79 (br s, 1H), 2.51 (dd, *J* = 13.8 and 4.7 Hz, 1H), 2.26 (dd, *J* = 13.8

and 7.1 Hz, 1H), 1.31 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.9, 159.8, 138.5, 130.7, 125.2, 122.8, 122.1, 121.4, 84.3, 56.3, 50.7, 39.8, 23.6; IR (film, neat) ν: 3346.0, 2966.0, 1651.6, 1614.6, 1588.4, 1497.8, 1309.5, 1163.6, 1041.8, 750.2 cm^{-1}; Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.71; H, 6.49; N, 12.42.

Ethyl (*Z*)-2-(4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17g)

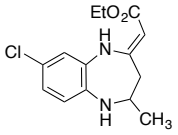


Procedure B was followed using benzene-1,2-diamine (108 mg, 1 mmol) and Ethyl 3-oxohex-5-enoate (156 mg , 1 mmol). Compound **17g** is obtained as a colourless, viscous liquid (224 mg, 91 %); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.24 (br s, 1H), 7.00 - 6.90 (m, 3H), 6.76 (d, *J* = 7.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.96 - 3.89 (m, 1H), 3.45 (br s, 1H), 2.50 (dd, *J* = 13.6 and 4.3 Hz, 1H), 2.26 (dd, *J* = 13.7 and 7.0 Hz, 1H), 1.32 (t, *J* = 6.5 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.6, 159.7, 138.5, 130.7, 125.2, 122.7, 122.0, 121.4, 84.7, 59.2, 56.3, 39.8, 23.9, 15.0; IR (film, neat) ν: 3346.8, 2973.6, 1651.2, 1614.3, 1497.3, 1307.0, 1273.8, 1158.9, 1044.8, 751.5 cm^{-1}; Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.97; H, 7.11; N, 10.99.

Ethyl (*Z*)-2-(7-chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17h)

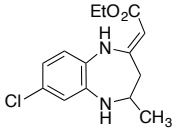
Procedure B was followed using 4-chlorobenzene-1,2-diamine (142 mg, 1 mmol) and Ethyl 3-oxohex-5-enoate (156 mg , 1 mmol). Compound **17h**is obtained as 3:1 mixture (**17ha**:**17hb**) (244 mg, 87 %) of diasteroisomers that has been possible to separate with column chromatography.

Ethyl (*Z*)-2-(8-chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17ha)



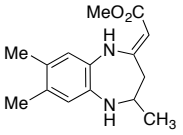
White solid, m.p 87 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.22 (br s, 1H), 6.84 (d, *J* = 1.0 Hz, 2H), 6.76 (s, 1H), 4.72 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.97 - 3.85 (m, 1H), 2.49 (dd, *J* = 13.9 and 4.1 Hz, 1H), 2.27 (dd, *J* = 13.8 and 7.2 Hz, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.29 (d, *J* = 7.1 Hz, 3H). One NH proton missing; ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.6, 159.2, 139.4, 129.7, 128.9, 123.6, 121.5, 120.6, 85.2, 59.4, 55.8, 39.7, 23.9, 14.9; IR (film, neat) ν: 3353.7, 2974.8, 1651.0, 1614.4, 1493.5, 1307.1, 1274.9, 1229.7, 1160.7, 1044.4 cm^{-1}; Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.56; H, 5.88; N, 10.16.

Ethyl (*Z*)-2-(7-chloro-4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17hb)



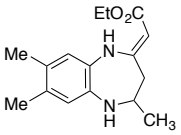
Colourless viscous liquid; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.21 (br s, 1H), 6.94-6.83 (m, 2H), 6.67 (d, *J* = 8.2 Hz, 1H), 4.73 (s, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.95-3.85 (m, 1H), 3.38 (br s, 1H), 2.49 (dd, *J* = 13.9 and 4.4 Hz, 1H), 2.23 (dd, *J* = 13.8 and 7.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.5. 158.9, 136.9, 131.8, 126.6, 124.4, 122.4, 122.2, 85.8, 59.4, 56.1, 39.7, 23.8, 14.9; IR (neat) ν: 3354.0, 2972.6, 1651.4, 1621.3, 1494.9, 1366.3, 1305.5, 1268.8, 1162.6, 1044.4 cm^{-1}; Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C, 59.89; H, 6.10; N, 9.98. Found: C, 60.07; H, 6.54; N, 10.22.

Methyl (*Z*)-2-(4,7,8-trimethyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17i)



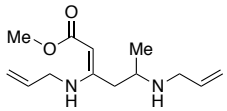
Procedure B was followed using 4,5-dimethylbenzene-1,2-diamine-1,2-diamine (136 mg, 1 mmol) and methyl 3-oxohex-5-enoate (142 mg, 1 mmol). Compound **17i** is obtained as a colourless viscous liquid (234 mg, 90 %); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.13 (br s, 1H), 6.70 (s, 1H), 6.54 (s, 1H), 4.90 (br s, 1H), 4.68 (s, 1H), 3.88 - 3.81 (m, 1H), 3.69 (s, 3H), 2.54 – 2.40 (m, 1H), 2.22 - 2.15 (m, 7H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.2, 159.5, 135.4, 132.8, 129.6, 127.8, 123.1, 122.1, 83.0, 55.9, 50.0, 39.1, 23.1, 18.8, 18.6; IR (film, neat) ν: 3344.8, 2966.2, 1651.7, 1614.3, 1515.6, 1311.4, 1244.5, 1165.7, 1037.4, 783.7 cm^{-1}; Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.47; H, 7.91; N, 10.36.

Ethyl (*Z*)-2-(4,7,8-trimethyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,4]diazepin-2-ylidene)acetate (17j)



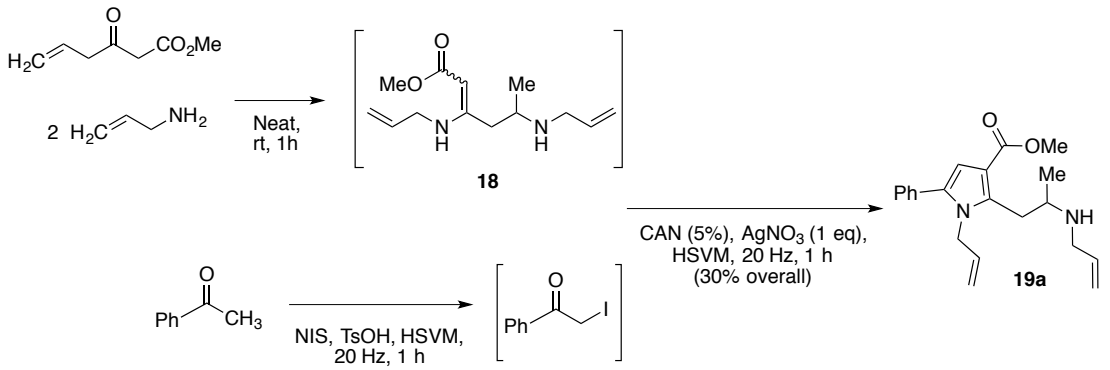
Procedure B was followed using 4,5-dimethylbenzene-1,2-diamine-1,2-diamine (136 mg, 1 mmol) and methyl 3-oxohex-5-enoate (142 mg, 1 mmol). Compound **17j** is obtained as a colourless viscous liquid (247 mg, 91 %); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 10.16 (br s, 1H), 6.74 (s, 1H), 6.58 (s, 1H), 4.68 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.92-3.85 (m, 1H), 2.46 (dd, *J* = 13.7 and 4.4 Hz, 1H), 2.26-2.18 (m, 1H), 2.18 (s, 7H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.28 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 170.6, 159.9, 135.9, 133.4, 130.4, 128.6, 123.8, 122.7, 84.2, 59.2, 56.5, 39.9, 23.8, 19.5, 19.2, 15.0; IR (neat) ν: 3342.0, 2970.2, 1651.3, 1613.4, 1514.5, 1308.5, 1242.5, 1163.8, 1046.3, 782.9 cm^{-1}; Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.71; H, 7.77; N, 9.94.

Methyl 3,5-bis(allylamino)hex-2-enoate (18)



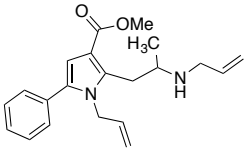
Procedure B was followed using allylamine (228 mg, 4 mmol) and methyl 3-oxohex-5-enoate (284 mg, 2 mmol). Compound **18** is obtained as a 3:1 mixture of diasteroisomers, yellowish viscous liquid in a full conversion that has not been purified and used for the subsequent step as a crude; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.57 (br s, 1H), 5.87 – 5.62 (m, 2H), 5.25 – 4.88 (m, 4H), 4.40 (s, 1H), 3.88 – 3.66 (m, 2H), 3.48 (s, 3H), 3.26 – 2.99 (m, 2H), 2.88 – 2.68 (m, 1H), 2.26 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.01 (dd, *J* = 13.9, 6.7 Hz, 1H), 1.00 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.4, 162.5, 136.3, 134.4, 115.6, 115.5, 83.0, 50.7, 49.6, 49.4, 44.7, 39.5, 20.0.

7.5.4. Mechanochemical synthesis of compound 19a and its N-acetylation to 19b



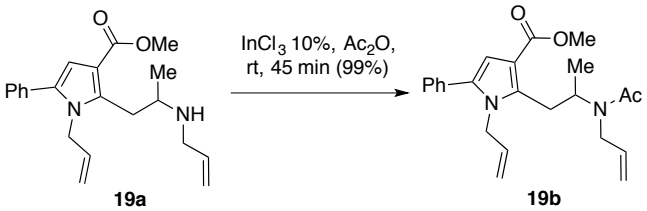
Acetophenone (0.5 mmol), *N*-iodosuccinimide (NIS, 0.5 mmol) and *p*-toluenesulphonic acid (PTSA, 10 mol%) were added to a ball mill vessel, along with a zirconium oxide ball. The vessel was fitted to one of the horizontal vibratory arms of the ball mill, while the other arm was occupied with an empty vessel. The ball mill was set to vibrate at a frequency of 20 s^{-1} for 60 min at room temperature. Then, a mixture of prop-2-en-1-amine (2.0 mmol), methyl 3-oxohex-5-enoate (0.75 mmol) and cerium(IV) ammonium nitrate (CAN, 5 mol%), previously stirred at room temperature during 30 min, and silver nitrate (0.5 mmol) were added to the vessel. The reaction was subjected to the vibratory movement at the same frequency for 60 min. Then, the reaction vessel was cleansed with ethyl acetate and the suspension was filtered to remove the silver iodide precipitate. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel eluting with a gradient from petroleum ether to 8:2 petroleum ether-ethyl acetate afforded the desired pyrrole derivatives **19a**.

Methyl 1-allyl-2-(2-(allylamino)propyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (19a)



Prepared from acetophenone (0.5 mmol) and compound **18** (0.75 mmol) and obtained as a yellowish oil (84 mg , 50%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38 (s, 6H), 6.63 (s, 1H), 6.07 – 5.70 (m, 2H), 5.40 – 5.04 (m, 5H), 4.85 – 4.43 (m, 3H), 3.83 (s, 4H), 3.56 – 2.93 (m, 5H), 2.00 (s, 1H), 1.17 (d, *J* = 6.0 Hz, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 137.9, 135.1, 134.2, 133.9, 132.4, 129.0, 128.3, 127.6, 116.9, 116.1, 112.5, 110.0, 53.1, 50.8, 49.2, 46.4, 32.2, 19.4; IR (film, neat) ν: 3252.2, 3113.5, 2951.5, 1711.3, 1667.9, 1647.0, 1237.6, 1157.3 cm^{-1}; Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.90; H, 7.99; N, 8.02.

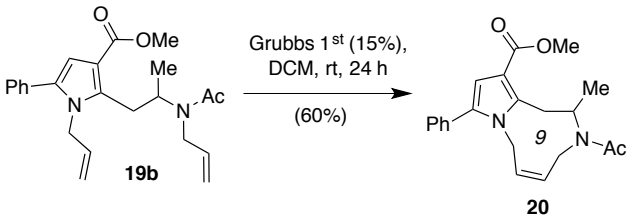
Methyl 1-allyl-2-(2-(N-acetylallylamino)propyl)-5-phenyl-1*H*-pyrrole-3-carboxylate 19b



Pyrrole **19a** (68 mg, 0.2 mmol) was treated with Ac2O (0.03 mL, 0.3 mmol) at room temperature for 30 min under magnetic stirring in the presence of InCl3 (10% mol).[125] No solvent was used. The reaction was monitored by TLC. The crude mixture was extracted with Et2O to afford final product in a full conversión monitored by 1H-NMR. The mixture was employed with no further purification for the subsequent reaction.

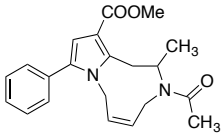
[125] Chakraborti, A. K.; Gulhane, R.; *Tetrahedron Letters*, **2003,** 44, 6749.

7.5.5. Synthesis of compound 20 by ring closing metathesis reaction



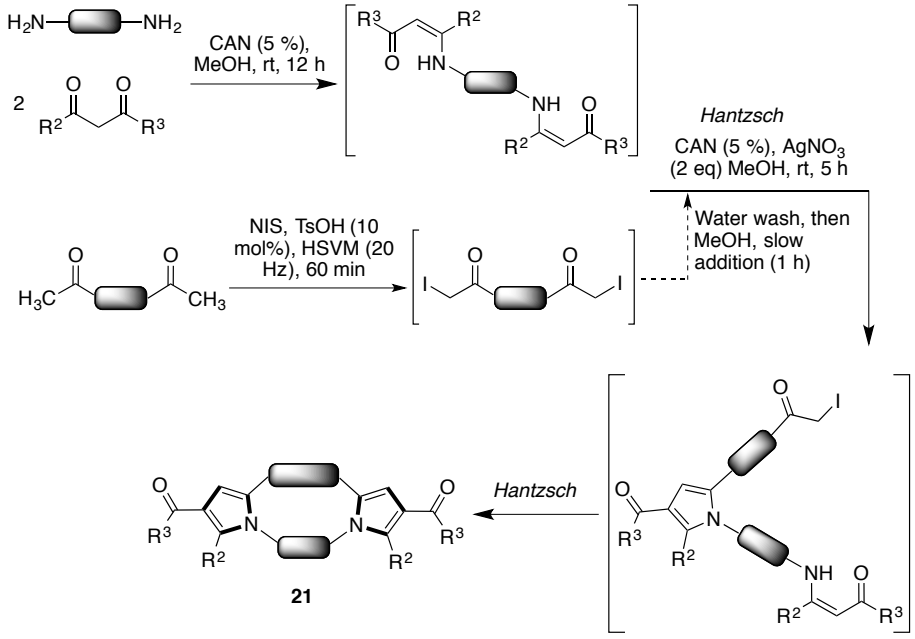
To a solution of compound **19b** (0.15 mmol) in dry dichloromethane, first generation Grubbs catalyst (5% mmol) was added. The mixture was stirred for 24 h and, then, the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography on silica gel using 9:1 petroleum ether-ethyl acetate as solvent.

Methyl 1-allyl-2-(2-(*N*-allylacetamido)propyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (20)



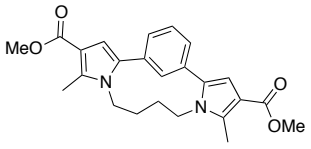
Final compound **20** is obtained giving the desired compound as a dark yellow oil; yield: 38 mg (50 %) ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 3.9, 2.5 Hz, 6H), 6.51 (s, 1H), 6.26 (dt, *J* = 9.8, 7.6 Hz, 1H), 5.49 – 5.21 (m, 1H), 4.73 (ddd, *J* = 23.4, 13.0, 7.4 Hz, 2H), 4.26 (dd, *J* = 14.8, 7.2 Hz, 1H), 3.84 (s, 4H), 3.74 (d, *J* = 7.3 Hz, 2H), 3.57 (dd, *J* = 15.0, 4.5 Hz, 1H), 3.41 – 3.08 (m, 1H), 1.92 (s, 3H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.3, 166.2, 136.6, 134.4, 133.8, 133.1, 130.5, 128.7, 128.4, 127.0, 112.23, 110.4, 54.5, 51.3, 39.3, 37.4, 31.5, 22.5, 20.3; IR (neat) ν: 3102.3 (CAr), 1702.2 (C=O), 1236.0 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{21}H_{26}N_2O_2$: 338.1994, found: 338.1985.

7.5.6. General procedure of pyrrole-based macrocycles 21a-21h by two concomitant Hantzsch pyrrole syntheses



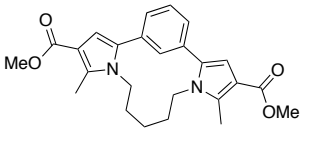
A mixture of the corresponding diamine (0.33 mmol), the suitable dicarbonyl compound (0.66 mmol) and CAN (5 mol%) in methanol (10 mL/mmol of diamine) was stirred at room temperature for 12 h. A solution of the suitable a-iodoketone (0.23 mmol) in methanol (5 mL/mmol), silver nitrate (0.5 mmol) and indium trichloride ($InCl_3$, 5 mol%) were slowly added by 1 hour injection to the flask containing the non-isolated enaminone, and stirred for additional 5 h. Then, washed with water and dry with Na_2SO_4. Purification by flash column chromatography on silica gel eluting with a gradient from dichloromethane to 9.5:0.5 dichloromethane-methanol afforded the desired macrocycle derivatives **21a**-**21h**.

Dimethyl 3,10-dimethyl-5,6,7,8-tetrahydro-13,17-(metheno)dipyrrolo[1,2-*f*:2',1'-*m*][1,6]diazacyclotridecine-2,11-dicarboxylate (21a)



Prepared from 1,3-diacetylbenzene, (0.23 mmol), methyl acetoacetate (0.66 mmol) and 1,4-diaminobutane (0.33 mmol); yield: 50 mg (52%); white solid; mp > 210 °C; ^{1}H NMR (250 MHz,$CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.38 – 7.35 (m, 2H), 6.70 (s, 2H), 3.85 (s, 10H), 2.68 (s, 6H), 2.32 – 2.14 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.9, 139.1, 134.9, 131.7, 131.6, 129.7, 126.3, 111.8, 107.8, 50.9, 41.8, 26.7, 12.0; IR (neat) ν: 2958.7 and 2943.4 (Ar C-H), 1699.4 (C=O), 1231.6 and 1177.5 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89; found: C, 70.61; H, 6.15; N, 6.57.

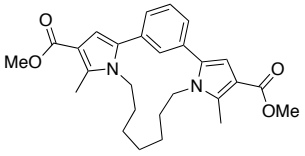
Dimethyl 1^5,3^5-dimethyl-1^1*H*,3^1*H*-1,3(2,1)-dipyrrola-2(1,3)-benzenacyclooctaphane-1^4,3^4-dicarboxylate (21b)



Prepared from 1,3-diacetylbenzene (0.23 mmol), methyl acetoacetate (0.66 mmol) and 1,5-diaminopentane (0.33 mmol); yield: 53 mg (53%); white solid; mp > 210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.63 (br s, 1H), 7.43 – 7.42 (m, 3H), 6.82 (s, 2H), 4.03 (d, *J* = 8.5 Hz, 4H), 3.85 (s, 6H), 2.66 (s, 6H), 2.06 (s, 4H), 1.62 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) d

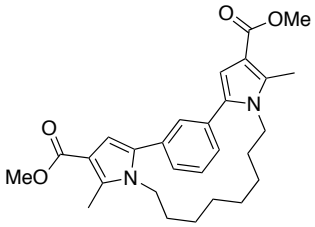
165.8, 137.2, 132.4, 132.3, 129.6, 127.6, 124.7, 111.6, 109.5, 50.8, 43.6, 21.6, 11.5; IR (neat) ν: 2945.8 (Ar C-H), 1699.2.6 (C=O), 1232.0 and 1177.6 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{25}H_{28}N_2O_4$: C, 71.41; H, 6.71; N, 6.66; found: C, 71.09; H, 6.38; N, 6.24.

Dimethyl 1^5,3^5-dimethyl-1^1*H*,3^1*H*-1,3(2,1)-dipyrrola-2(1,3)-benzenacyclodecaphane-1^4,3^4-dicarboxylate (21c)



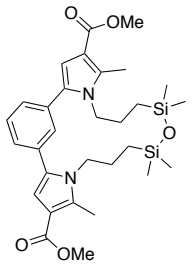
Prepared from 1,3-diacetylbenzene (0.23 mmol), methyl acetoacetate (0.66 mmol) and 1,7-diaminoheptane (0.33 mmol); yield: 43 mg (40%); light yellow solid; mp = 182-184 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.53 – 7.42 (m, 2H), 7.33 – 7.25 (m, 2H), 6.57 (s, 2H), 3.84 – 3.78 (m, 10H), 2.61 (s, 6H), 1.62 – 1.46 (m, 4H), 0.98 (br s, 4H), 0.69 – 0.57 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 136.0, 133.8, 133.6, 133.3, 129.9, 128.0, 111.6, 108.4, 50.7, 42.1, 29.2, 26.4, 24.4, 11.6; IR (neat) ν: 2931.7 and 2855.5 (Ar C-H), 1698.1 (C=O), 1438.9 and 1234.0 and 1193.5 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{27}H_{32}N_2O_4$: 448,2362, found: 448.2368.

Dimethyl 1^5,3^5-dimethyl-1^1*H*,3^1*H*-1,3(2,1)-dipyrrola-2(1,3)-benzenacycloundecaphane-1^4,3^4-dicarboxylate (21d)



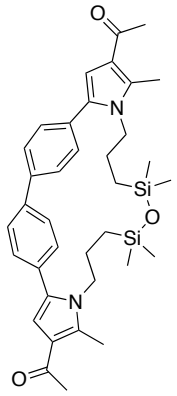
Prepared from 1,3-diacetylbenzene (0.23 mmol), methyl acetoacetate (0.66 mmol) and 1,8-diaminooctane (0.33 mmol); yield: 44 mg (40%); yellow solid; mp = 148-150 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 2H), 7.30 – 7.18 (m, 2H), 6.48 (s, 2H), 3.89 – 3.83 (m, 4H), 3.73 (s, 6H), 2.53 (s, 6H), 1.48 – 1.28 (m, 4H), 1.11 – 0.83 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 136.5, 133.5, 132.8, 130.5, 129.1, 128.5, 111.6, 109.7, 50.8, 43.1, 28.7, 26.0, 24.6, 11.5; IR (neat) ν: 2924.7 and 2851.5 (Ar C-H), 1700.4 (C=O), 1440.8 and 1192.3 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06; found: C, 72.31; H, 7.20; N, 5.85.

Dimethyl 1^5,3^5,7,7,9,9-hexamethyl-1^1*H*,3^1*H*-8-oxa-7,9-disila-1,3(2,1)-dipyrrola-2(1,3)-benzenacyclododecaphane-1^4,3^4-dicarboxylate (21e)



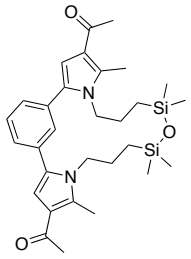
Prepared from 1,3-diacetylbenzene (0.23 mmol), methyl acetoacetate (0.66 mmol) and 1,3-bis(aminopropyl)tetramethyldisiloxane (0.33 mmol); yield: 81 mg (60%); white solid; mp > 210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 2H), 7.38 – 7.31 (m, 2H), 6.60 (s, 2H), 3.98 (t, *J* = 7.3 Hz, 4H), 3.84 (s, 6H), 2.63 (s, 6H), 1.43 – 1.28 (m, 4H), 0.26 – 0.14 (m, 4H), -0.07 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 136.6, 133.8, 132.7, 130.9, 128.2, 127.9, 111.5, 110.1, 50.7, 46.6, 24.3, 15.2, 11.5, 0.2; IR (neat) ν: 2948.5 (Ar C-H), 1701.9 (C=O), 1438.8 and 1253.1 and 1207.6 and 1069.0 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{30}H_{42}N_2O_5Si_2$: C, 63.57; H, 7.47; N, 4.94; found: C, 63.19; H, 7.09; N, 4.58.

1,1'-(1^5,4^5,8,8,10,10-hexamethyl-1^1*H*,4^1*H*-9-oxa-8,10-disila-1,4(2,1)-dipyrrola-2(1,3),3(1,4)-dibenzenacyclotridecaphane-1^4,4^4-diyl)bis(ethan-1-one) (21f)



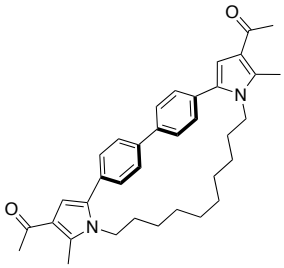
Prepared from 4,4'-diacetylbiphenyl (0.23 mmol), acetylacetone (0.66 mmol) and 1,3-bis(aminopropyl)tetramethyldisiloxane (0.33 mmol); yield: 51 mg (35%); white solid; mp > 210 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 4H), 7.48 (d, *J* = 8.3 Hz, 4H), 6.70 (s, 2H), 3.85 (s, 6H), 3.78 (t, *J* = 7.8 Hz, 4H), 2.60 (s, 6H), 1.07 – 0.95 (m, 4H), 0.17 – 0.08 (m, 4H), -0.25 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 166.0, 138.4, 136.1, 132.5, 132.4, 130.6, 126.2, 110.9, 108.6, 50.8, 47.2, 24.0, 16.2, 11.3, -0.1; IR (neat) ν: 3095.5 and 2965.1 (Ar C-H), 1700.3 (C=O), 1248.6 and 1203.2 (C-O) cm^{-1}; elemental analysis (%) calcd. for $C_{36}H_{46}N_2O_3Si_2$: C, 70.77; H, 7.59; N, 4.59; found: C, 70.49; H, 7.25; N, 4.35.

1,1'-(1^5,3^5,7,7,9,9-hexamethyl-1^1*H*,3^1*H*-8-oxa-7,9-disila-1,3(2,1)-dipyrrola-2(1,3)-benzenacyclododecaphane-1^4,3^4-diyl)bis(ethan-1-one) (21g)



Prepared from 1,3-diacetylbenzene (0.23 mmol), acetylacetone (0.66 mmol) and 1,3-bis(aminopropyl)tetramethyldisiloxane (0.33 mmol); yield: 64 mg (50%); white solid; mp: 164-166 °C; ^{1}H NMR (250 MHz, $CDCl_3$) d 7.54 (br s, 2H), 7.45 – 7.35 (m, 2H), 6.63 (s, 2H), 4.04 (t, *J* = 7.0 Hz, 4H), 2.72 (s, 6H), 2.53 (s, 6H), 1.44 (s, 4H), 0.36 – 0.21 (m, 4H), -0.00 (s, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 136.0, 133.8, 132.4, 131.0, 128.4, 128.2, 120.8, 110.8, 46.4, 28.6, 24.3, 15.2, 12.0, 0.2; IR (neat) ν: 2955.2 (Ar C-H), 1711.6 (C=O), 1252.6 and 1090.9 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{30}H_{42}N_2O_3Si_2$: 534,2734, found: 534.2744.

1,1'-(1^5,4^5-dimethyl-1^1*H*,4^1*H*-1,4(2,1)-dipyrrola-2(1,3),3(1,4)-dibenzenacyclotetradecaphane-1^4,4^4-diyl)bis(ethan-1-one) (21h)

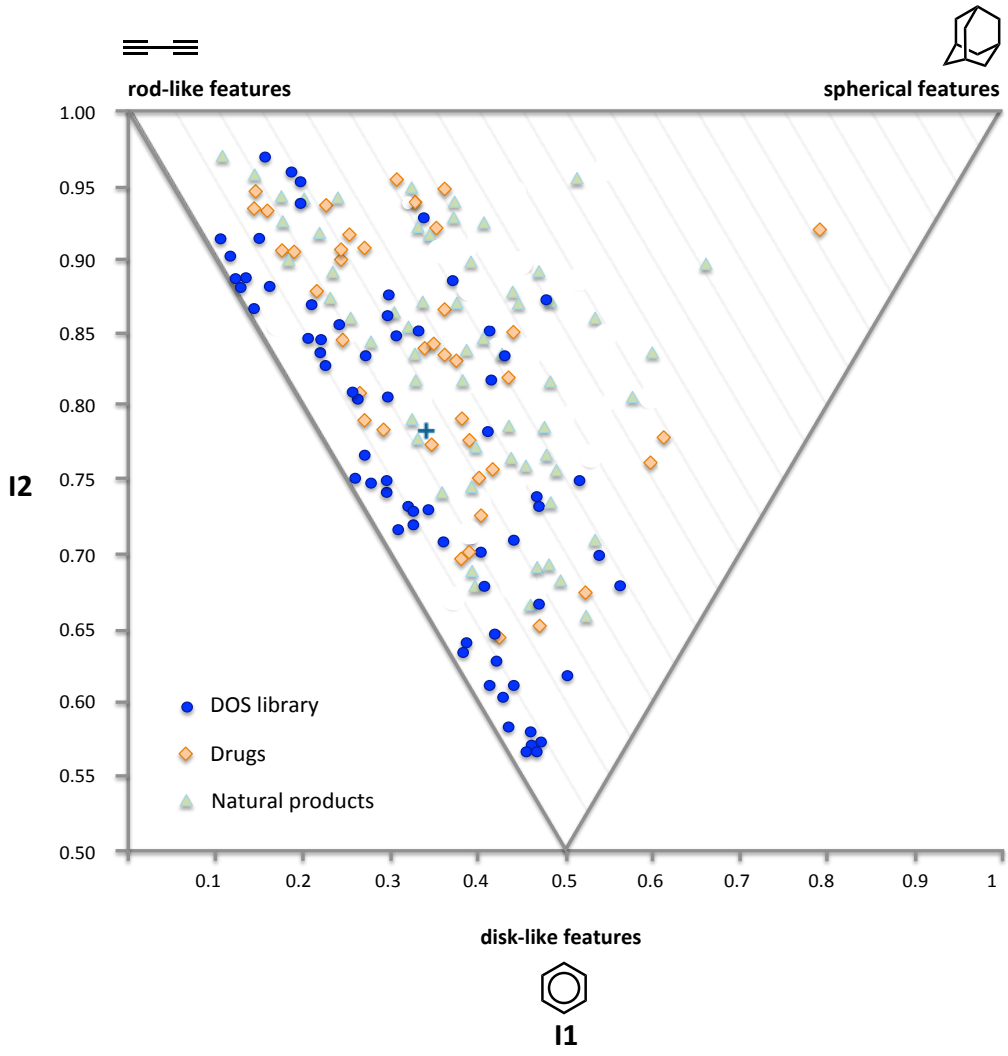


Prepared from 4,4'-diacetylbiphenyl (0.23 mmol), acetylacetone (0.66 mmol) and 1,10-diaminodecane (0.33 mmol); yield: 38 mg (30%); yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 4H), 7.49 (d, *J* = 8.3 Hz, 4H), 6.63 (s, 2H), 3.81 – 3.75 (m, 4H), 2.64 (s, 6H), 2.49 (s, 6H), 1.31 – 1.20 (m, 6H), 1.01 (br s, 4H), 0.62 (br s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 195.1, 139.0, 135.6, 132.3, 131.0, 126.4, 120.4, 109.3, 76.5, 42.9, 30.4, 29.0, 28.7, 28.6, 26.5, 11.8; IR (neat) ν: 2924.3 and 2852.2 (Ar C-H), 1679.4 and 1602.5 (C=O), 1422.5 and 1265.5 and 1179.9 (C-O) cm^{-1}; HRMS (MALDI TOF) calcd. for $C_{36}H_{42}N_2O_2$: 534.3246, found: 534.3235.

8. Chemometric study and high-throughput screening of the libraries synthesized

8.1. Chemometric study

We also undertook a brief chemoinformatic study of our compounds in order to assess their diversity in terms of molecular shape, as judged by the distribution of their principal moments of inertia for each molecule in its minimum energy conformer. The study was carried out with the open-access LLAMA platform for Diversity-Oriented Synthesis from the University of Leeds (UK).[126,127] This study showed (Figure 8.1) that the DOS library has a broad shape distribution that was comparable to a library formed by 60 structurally diverse natural products and another of 40 high-selling drugs that are summarized in Figure 8.2.



126 Colomer, I.; Empson, C. J.; Craven, P.; Owen, Z.; Doveston, R. G.; Churcher, I.; Marsden, S. P.; Nelson, A. *Chem. Commun*. **2016**, *52*, 7209.

127 The address of the LLAMA web site is: https://llama.leeds.ac.uk.

Figure 8.1

Reference compounds for the Principal Moments of Inertia (PMI) study

Natural products

1.Rapamycin
2.Mizoribine
3.Penicillin G
4.Erythromycin A
5.Discodermolide
6.Streptomycin
7.Validamycin
8.Actinonin
9.Echinocandin B
10.Sperguallin
11.Calyculin A
12.Taxol
13.Coformycin
14.Monensin
15.Arglabin
16.Ginkgolide B
17.Staurosporine
18.Vancomycin
19.Forskolon
20.Amphotericin B
21.SQ 26180
22.Radicicol
23.Cephamycin C
24.Salicylihalamide A
25.Telomestatin
26.Rifamycin B
27.Thienamycin
28.Avermectin B1a
29.FK506
30.Phorbolmyristate acetate
31.Apoptolidin
32.Cyclosporin A
33.Adriamycin
34.Trapoxin B
35.Vincristine
36.Colchicine
37.Bleomycin A2
38.Fumagillin
39.Midecamycin A1
40.Spongistatin 1
41.Talaromycin B
42.Zaragozic acid A
43.Brevetoxin B
44.Compactin
45.Mycobactin S
46.Duocarmycin A
47.Quinine
48.Trichostatin A
49.Calicheamicin ÔÅß1
50.Brefeldin A
51.Pseudomonic acid A
52.Cytochalasin B
53.Daptomycin
54.Epothilone A
55.Bestatin
56.Artemisinin
57.Plaunotol
58.Lipstatin
59.Geldanamycin
60. Lactacystin

Drugs

1.Montelukast (Singulair®)
2.Esomeprazole (Nexium®)
3.Simvastatina (Zocor®)
4.Fluticasona (Flonase®)
5.Salmeterol (Servent®)
6.Atorvastatin (Lipitor®)
7.Zolpidem (Ambien®)
8.Clopidogrel (Plavix®)
9.Lansoprazol (Prevacid®)
10.Amlodipine (Norvasc®)
11.Bupropion (Wellbutrin®)
12.Quetiapine (Seroquel®)
13.Pantoprazole (Protonix®)
14.Venlafaxine (Effexor®)
15.Pioglitazone (Actos®)
16.Sertraline (Zoloft®)
17.Escitalopram (Lexapro®)
18.Rosiglitazone (Avandia®)
19.Risperidone (Risperdal®)
20.Olanzapine (Zyprexa®)
21.Fenofibrate (Tricor®)
22.Topiramate (Topomax®)
23.Metoprolol (Toprol®)
24.Benazepril (Benazepril®)
25.Alendronic acid (Fosamax®)
26.Aripiprazol (Abilify®)
27.Levofloxacin (Levaquin®)
28.Lamotrigine (Lamictal®)
29.Colecoxib (Celebrex®)
30.Ezetimibe (Zetia®)
31.Cetirizine (Zyrtec®)
32.Valsartan (Diovan®)
33.Valaciclovir (Valtrex®)
34.Amphetamine (four salts of its two enantiomers) (Adderall®)
35.Rabeprazole (Aciphex®)
36.Sumatriptan (Imitrex®)
37.Rosuvastatin (Crestor®)
38.Carvedilol (Coreg®)
39.Bupropion (Wellbutrin®)
40.Duloxetine (Cymbalta®)

Figure 8.2

8.2. Introduction to the OIDD program

The high-throughput study of our libraries was done in collaboration with Lilly *via* its Open Innovation Drug Discovery (OIDD) Program. This is a platform to facilitate the collaboration between big pharma and academic researchers for early drug discovery. The main advantage of this collaboration for academic research group is the possibility to access to cutting-edge research tools and data aimed at improving their scientific work for the discovery of novel therapeutics for, possibly, novel targets. Participants of the OIDD, to specify, can be universities (as our case), research institutes and small biotechnology companies.

Once affiliated, registered and accepted the agreement, participants have to upload molecular structures to Lilly's web page for an initial *in silico* evaluation. At this point, molecular descriptors are created by the program and a first evaluation of the molecular parameters is done (as metabolic stability, structural novelty, drug-likeness properties, molecular weight…) to identify which compounds are eligible for the second step of biological evaluation. If a compound is chosen and approved, the OIDD program provides vials as an in-kind service to participants. The whole process is driven in a structure-blinded fashion, where the results of the *in silico* analysis are considered and become available to Lilly or Elanco. Compounds accepted for biological evaluation can belong to fragment-like molecules, small molecules, natural products, larger molecules or small peptides. The following step, when the physical samples have been received, is the beginning of the biological evaluation in several different assays modules for different therapeutic diseases using High Throughput Screening (HTS) technology. All the biological results are provided to the researcher through their personal OIDD account. All the accepted compounds will further undergo *in vitro* screening in both Lilly active and emerging projects, neglected and tropical disease screening (summary of all diseases considered in the OIDD program in Figure 8.3). The OIDD team may decide to discuss further steps with investigator for specific compounds with a promising profile.

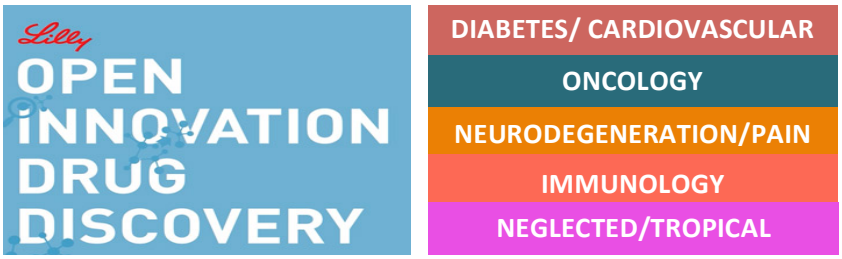


Figure 8.3

In vitro screening process consists of a primary screening assay followed by secondary biochemical and/or cell-based follow-up screen to define the activity profile of the compound. In this phase both phenotypic and target-based approaches are employed. For

In the first case, complex cellular systems are required instead of specific targets of the target-based approaches. Finally the biological results are provided to the participating investigators and they are allowed to export results to create personalized reports, as the case of this thesis. Data reported include the single point (SP) of concentration at which the compound was tested to a specific assay to measure biological activity, plus the results associated with the subsequent concentration-response curve (CRC), where applicable. In addition, the exportable report includes molecular properties such as the atomic molecular weight (AMW), a measure of the compound's lipophilicity (cLogP), and heavy atom count (HA).

8.3. Biological results of our DOS libraries

Following the initial *in silico* testing, the majority of our molecules were been accepted and approved for biological screening. The structures of all the compounds assayed is given in Figure 8.4, with the codes used in this thesis and also with the code assigned by OIDD.

Figure 8.4

The results obtained are reported below, organized by targets and diseases.

1-**Protein Translation Inhibition for Alzheimer's disease**: neurodegeneration and pain scope.

The accumulation in the extracellular space of amyloid plaques and intracellular formation of neurofibrillary tangles (NFTs) it basically features the Alzheimer's pathology, also defined as Alzheimer's disease (AD). Amyloid plaques are composed of Aβ protein and the NFTs of tau protein. Modern strategies for the AD treatment are to target this association of proteins by preventing their accumulation and, or, their removal once deposited. For this reason, acting at the level of protein translation could regulate or inhibit the expression of such proteins as a new possible valid target.

In the following all the biological results that, in some cases, have shown promising preliminary activity, are reported.

Neuroscience:
Tau
Primary assays:
- Tau target-based reporter inhibition assay Huh7 SP (% Inhibition) CRC(IC_{50})
- Profiling Target-based reporter inhibition assay Huh7 SP
- Target-less reporter assay Huh7 CRC Inhibition (IC_{50})

This assays have been done in Huh7 cell-line, widely employed in laboratory due to its facility condition growth. Their origin is from human liver, derived from a well-differentiated hepatocyte-derived carcinoma cell-line. With the intention of interpret all the data furnish by Lilly, we have to introduce the role of the targets studied in these assays:

- ANGPTL8 (also known as lipasin or Betatrophin) is a protein encoded in humans by the C19orf80 gene (gene 19). Human betatrophine, olso the one from mice, is not able to increase beta-cell division. Deletion of betatrophin/Angptl8 does not seem

to impact glucose and insulin tolerance in mice.[128] This protein is able to inhibit the enzyme Lipoprotein lipase (LPL) and consequently, when overexpressed, an increment of circulating triglyceride levels is detected.[129]

- APOC3 or apolipoprotein C-III (known also as apo-CIII) is a human protein encoded by APOC3 gene. Its secretion is at level of liver and small intestine. Its role is to inhibit lipoprotein and hepatic lipase and, for example, it blocks the uptake of triglyceride rich particles. When apoC-III levels increases, hypertriglyceridemia is produced.[130]
- $Na_v1.7$ is a voltage-gated sodium ion channel encoded by SCN94 gene in humans. Its expression is at neuronal level: in the sympathetic ganglion neurons in the involuntary nervous system and in the nociceptive (pain) neurons at level of dorsal root ganglion (DRG).[131] $Na_v1.7$ is located at the pain-sensing nerves, the nociceptors, close to the region where the impulse is initiated. This channel is relevant in the early phases of neuronal electrogenesis and its acts by a transition of the channel into an inactive state when it is depolarized also under little electric changes. It is relevant in several diseases as primary erythromelalgia, paroxysmal extreme pain disorder, congenital insensitivity to pain, clinical analgesics and itch.
- PCSK9 will be further discussed.
-

The Lilly assay oriented to targets different from hTau are employed as reference in order to find selective TAU-inhibition. All the targets described before are proteins overexpressed in the Huh7 cell-line and, for these reason, evaluated in this experiment as controls.

Cmpd	OIDD ID	Primary SP				
		hTau Huh7 TT Inhib SP	hAngptl8 Huh7 TT Inhib SP	hAPOC3 Huh7 TT Inhib SP	hNav1.7 Huh7 TT Inhib SP	hPCSK9 Huh7 TT Inhib SP
		%Inhib @40μM	%Inhib@ 40μM	%Inhib@ 40μM	%Inhib@ 40μM	%Inhib@ 40μM
	2351663277	63,06	77,21	52,36	60,05	49,06
	2351663279	62,51	57,3	34,06	36,16	39,62
	2351663280	-259,6	38,24	20,68	-22,55	7,541
	2351663281	85,52	85,7	78,74	71,81	73,58
	2351663285	93,33	98,51	90,66	85,76	72,46

[128] Wang Y.; Quagliarini F.; Gusarova V.; Gromada J.; Valenzuela D. M.; Cohen J. C.; Hobbs H. H.; *Proc. Natl. Acad. Sci. U.S.A.,* **2013**, *110,* 16109.

[129] Zhang R.; *Biochem. Biophys. Res. Commun.,* **2012**, *424,* 786.

[131] Rush A.M.; Dib-Hajj S. D.; Liu S.; Cummins T. R.; Black J. A.; Waxman S. G.; *Proc. Natl. Acad. Sci. U.S.A.* **2006,** *103*, 8245.

Cmpd	OIDD ID	Primary SP				
		hTau Huh7 TT Inhib SP	hAngptl8 Huh7 TT Inhib SP	hAPOC3 Huh7 TT Inhib SP	hNav1.7 Huh7 TT Inhib SP	hPCSK9 Huh7 TT Inhib SP
		%Inhib @40µM	%Inhib@ 40µM	%Inhib@ 40µM	%Inhib@ 40µM	%Inhib@ 40µM
	2351663286	-100,3	24,36	12,46	7,08	8,571
	2351663287	20,75	22,76	31,88	-33,47	29,76
	2351663288	-38,62	-41,67	-14,32	-29,6	-3,39
	2351663289	12,45	19,24	13,2	-14,71	20,24
	2351663291	99,43	97,56	98,62	96,66	94,34
	2351663292	90,28	99,25	82,87	91,44	77,36
	2351663341	-64,16	-1,764	2,086	-2,828	12,86
	2351663342	-19,17	-0,8819	3,493	-1,471	-2,857
	2351663343	28,34	51,22	16,73	13,35	28,3
	2351663344	-13,55	0	-13,54	-3,055	-2,143
	2351663345	60,12	-749,5	44,53	15,99	40,48
	2351663348	99,53	96,95	98,62	101,1	98,11
	2351663349	2,643	14,55	18,73	-15,95	8,571
	2351663350	98,15	97,07	95,58	80,38	94,75
	2351663368	58,06	49,86	35,43	48,07	43,4
	2351663369	61,35	62,79	58,71	42,88	50
	2351663370	32,78	-152,6	25,28	-22,97	21,43
	2351663371	74,09	-749	68,7	51,89	64,15
	2351663372	68,22	70,28	58,35	49,68	67,86
	2351663373	-1,833	16,23	13,72	-18,55	27,38
	2351663375	17,5	32,62	29,53	18,4	18,87
	2351663376	-33,79	-1,764	12,18	-27,04	-12,14
	2351663378	9,553	-12,88	21,18	32,62	28,57
	2351663379	10,56	39,72	41,34	28,51	37,74
	2351663381	61,42	43,43	42,42	42,81	65,25
	2351663388	-3,889	55,27	24,61	17,68	30,19
	2351663390	21,55	-34,19	40,58	37,25	40,95
	2351663391	-71,43	-24,95	5,966	-56,34	8,571
	2351663393	66,1	66,6	53,16	39,87	88,1

2-**PCSK9-inhibition**: cardiovascular and endocrine scope.

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a proteinase K belonging to the family of secretory proteases. Its major role is in the regulation of cholesterol homeostasis and, specifically, this protein drives LDL receptor (LDL-R) to lysosomal degradation in order to regulate plasma LDL-cholesterol (LDL-C). When mutated, PCSK9 provokes hyperlipidemia and premature coronary artery disease (CAD) in humans. Its important to highlight that if this proporotein is absent of mutation, it lows LDL levels and acts as protector from CAD. As therapy, antibodies have recently been approved by FDA and have shown to be impressive efficient in lowering LDL levels, in some cases, in combination with statins. Small molecules able to inhibit PCSK9 are now being studied. The expression of protein PCSK9 is strictly regulated at level of transcription and post transcription. PCSK9 SI is a phenotypic module employed in the identification of organic molecules able to inhibit expression of this protein in multiple cell systems (including human hepatoma cell lines Huh7, Hela cells and primary hepatocytes). In Lilly's screen also all the compounds inhibiting PCSK9 protein secretion with no suppression of cell viability and Apo-A1 protein secretion, will be considered of interest.

Endocrine/Cardiovascular: PCSK9 Inhibition

PCSK9 Alphalisa
Viabily VellTiter-Glo
Huh7
SP/CRC

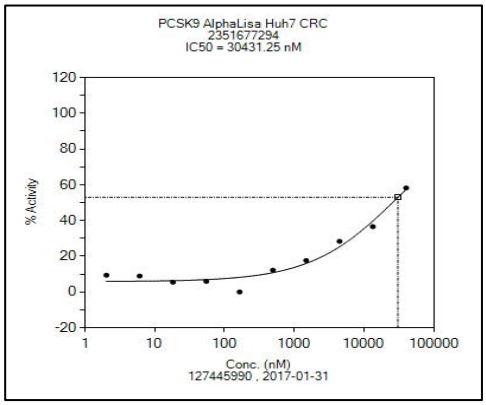
Primary assays

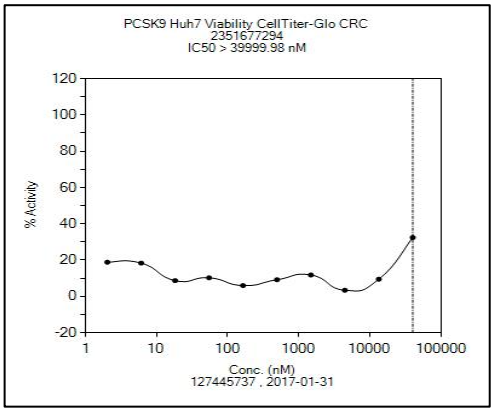
- PCSK9 Alphalisa Huh7 SP/CRC (% Inhibition/IC_{50})
- PCSK9 Viability CellTiter-Glo SP/CRC (% Inhibition/IC_{50})

Cmpd	OIDD ID	Primary SP		Primary CRC	
		PCSK9 AlphaLisa Huh7 SP	PCSK9 Huh7 Viability CellTiter-Glo SP	PCSK9 AlphaLisa Huh7 CRC	PCSK9 Huh7 Viability CellTiter Glo CRC
		%Inhib@ 5mM	%Inhib@ 5mM	Rel IC50 (mM)	Rel IC50 (mM)
	2351663277	-1,304	-3,942		
	2351663279	-34,93	-0,5383		
	2351663280	-41,87	-1,434		
	2351663281	-39,32	-3,283		
	2351663285	-55,43	0,4058		
	2351663286	-29,52	-14,83		

Cmpd	OIDD ID	Primary SP		Primary CRC	
		PCSK9 AlphaLisa Huh7 SP	PCSK9 Huh7 Viability CellTiter-Glo SP	PCSK9 AlphaLisa Huh7 CRC	PCSK9 Huh7 Viability CellTiter Glo CRC
		%Inhib@ 5mM	%Inhib@ 5mM	Rel IC50 (mM)	Rel IC50 (mM)
	2351663287	-38,66	-7,866		
	2351663288	-25,54	3,125		
	2351663289	-18,73	0,5016		
	2351663291	-49,02	-9,354		
	2351663292	-24,46	-1,556		
	2351663341	-16,88	6,037		
	2351663342	-25,61	0,3128		
	2351663343	-6,146	5,744		
	2351663344	-10,69	3,458		
	2351663345	-38,92	-1,07		
	2351663348	-32,28	4,072		
	2351663349	-30,6	2,449		
	2351663350	-8,828	-5,803		
	2351663368	-63,61	-1,31		
	2351663369	-29,34	0,2424		
	2351663370	-16,36	-14,18		
	2351663371	-9,555	-1,093		
	2351663372	-24,59	3,424		
	2351663373	-33,94	-2,3		
	2351663375	-20,01	-2,68		
	2351663376	-34,35	0,6228		
	2351663378	-14,79	1,733		
	2351663379	-17,89	1,091		
	2351663381	-6,583	-1,682		
	2351663388	-17,33	-2,739		
	2351663390	-23,71	-1,009		
	2351663391	-33,24	-0,3974		
	2351663393	-28,86	-5,535		
	2351677024	-74,09	2,97		
	2351677025	75,6	36,7		
	2351677124	31,39	29,61		
	2351677125	-20,11	32,61		
	2351677126	-2,254	-6,219		

Cmpd	OIDD ID	Primary SP		Primary CRC	
		PCSK9 AlphaLisa Huh7 SP	PCSK9 Huh7 Viability CellTiter-Glo SP	PCSK9 AlphaLisa Huh7 CRC	PCSK9 Huh7 Viability CellTiter Glo CRC
		%Inhib@ 5mM	%Inhib@ 5mM	Rel IC50 (mM)	Rel IC50 (mM)
	2351677128	44,66	23,81		
	2351677148	-44,62	-2,247		
	2351677149	-41,39	1,303		
	2351677151	-64,93	3,32		
	2351677152	-52,35	4,029		
	2351677153	-40,78	3,89		
	2351677271	-58,4	0,1916		
	2351677274	-74,57	42,27		
	2351677276	-33,54	-5,759		
	2351677278	-36,98	-8,298		
	2351677280	22,03	24,56		
	2351677282	46,05	28,8		
	2351677284	-39,45	-15,64		
	2351677286	-68,69	-2,654		
	2351677287	74,23	30,62		
	2351677289	-19,5	-12,25		
	2351677290	37,68	27,44		
	2351677291	44,83	35,53		
	2351677292	-73,44	19,76		
	2351677293	-47,19	6,961		
	2351677294	75,65	21,82	30,43	>40.0
	2351677295	-67,26	-6,597		
	2351677296	-37,78	31,48		
	2351677304	-101,6	30,4		
	2351692808	-65,82	36,08		





Compound	OIDD ID	Primary SP
		hPCSK9 Huh7 TT Inhib SP
		%Inhib@ 40mM
	2351663277	49,06
	2351663279	39,62
	2351663280	7,541
	2351663281	73,58
	2351663285	72,46
	2351663286	8,571
	2351663287	29,76
	2351663288	-3,39
	2351663289	20,24
	2351663291	94,34
	2351663292	77,36
	2351663341	12,86
	2351663342	-2,857
	2351663343	28,3
	2351663344	-2,143
	2351663345	40,48
	2351663348	98,11
	2351663349	8,571
	2351663350	94,75
	2351663368	43,4
	2351663369	50
	2351663370	21,43
	2351663371	64,15

	2351663372	67,86
	2351663373	27,38
	2351663375	18,87
	2351663376	-12,14
	2351663378	28,57
	2351663379	37,74
	2351663381	65,25
	2351663388	30,19
	2351663390	40,95
	2351663391	8,571
	2351663393	88,1

3-**Arginase:** oncology scope.

Arginase is an enzyme placed in the intracellular space. Its role is to hydrolyse L-arginine to ornithine and urea. The Arginase isoenzymes are characteristic of mammals and their difference is related in their location: ARG1 is cytoplasmic and RG2 is mitochondrial. The major activity of Arginase is at the level of immune response. When high ARG1 levels are detected, its activity is expressed in both M2 macrophages and myeloid-derived suppressor cells (MDSC). The reason why Arginase is a target of interest for oncology is to stimulate the same immune system when used in combination with checkpoint inhibitors.

Oncology:
Arginase Inhibition

- hArginase LC-MS SP
- hArginase LC-MC CRC

Primary assays

- Human Arginase LC-MS SP (% Inhibition)
- Human Arginase LC-MC CRC (% Inhibition)

Compound	OIDD ID	Primary SP
		hARG1 MassSpec_No Metal or BSA_384 SP
		%Inhib@100mM
	2351663277	35,49
	2351663279	13,92
	2351663280	28,12
	2351663281	
	2351663285	38,23
	2351663286	22,64

Compound	OIDD ID	Primary SP
		hARG1 MassSpec_No Metal or BSA_384 SP
		%Inhib@100mM
	2351663287	19,64
	2351663288	49,65
	2351663289	10,04
	2351663291	40,61
	2351663292	56,65
	2351663341	3,496
	2351663342	16,58
	2351663343	
	2351663344	6,946
	2351663345	7,179
	2351663348	0,9942
	2351663349	
	2351663350	35,76
	2351663368	31,4
	2351663369	
	2351663370	12,18
	2351663371	17
	2351663372	-0,4162
	2351663373	25,57
	2351663375	14,46
	2351663376	7,302
	2351663378	6,174
	2351663379	26,67
	2351663381	-11,53
	2351663388	10,17
	2351663390	2,035
	2351663391	13,64
	2351663393	1,875
	2351677024	15,31
	2351677025	8,392
	2351677124	3,589
	2351677125	-13,11
	2351677126	-13,09
	2351677128	16,84
	2351677148	17,57
	2351677149	40,15

Compound	OIDD ID	Primary SP
		hARG1 MassSpec_No Metal or BSA_384 SP
		%Inhib@100mM
	2351677151	49,08
	2351677152	52,24
	2351677153	37,48
	2351677271	15,57
	2351677274	0,9057
	2351677276	1,341
	2351677278	-7,016
	2351677280	55,32
	2351677282	14,6
	2351677284	-15,7
	2351677286	3,211
	2351677287	-1,025
	2351677289	73,1
	2351677290	52,97
	2351677291	50,19
	2351677292	83,03
	2351677293	47,43
	2351677294	32,46
	2351677295	54,43
	2351677296	52,46
	2351677304	27,6
	2351692808	30,56

4-**IL-17 Protein Protein Interaction:** immunology and inflammation scope.

IL-17A is an proinflammatory cytokine produced by activated T cells (a subset called Th17) at inflammatory site. This IL acts in three different manners: first, as host defense against extracellular bacteria and fungi; secondly, as promoter of neutrophil homeostasis; thirdly, it has a role in the chronic pathogenic inflammation. The IL-17A can exists as a homodimer A/A or heterodimer A/F with IL-17F. Cells able to respond to the local production of IL-17A are that ones that express the IL-17A receptors (IL-17RC and IL-17RC). Its mechanism is to stimulate the cytokine and chemokine cascade that are able to recruit and activate neutrophils and memory T cells to maintain a proinflammatory state. In some cases, IL-17A produce pathogenic T cells which are responsible of pathogenesis and autoimmune diseases (psoriasis, psoriatic arthritis, rheumatoid arthritis and anklyosing spondylitis). Efficient treatment for patients with plaques psoriasis is, demonstrated, the employment of neutralizing antibodies.
In Lilly assay is evaluated the ability of our molecules to inhibit the protein-protein interaction in order to avoid the dimer formation A/A or A/F.

Autoimmune:
IL-17A

- IL-17A Alphalisa SP
- IL-17A Alphalisa

IL 17_IL17R TR-FRET CRC

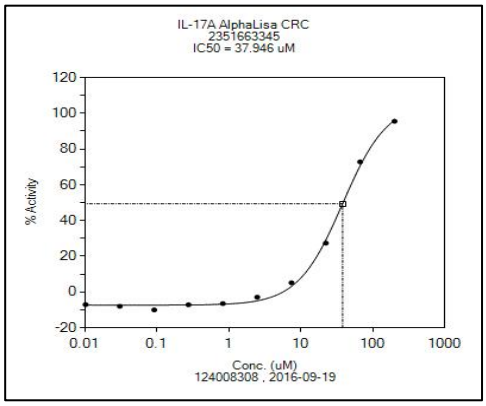
Primary assays

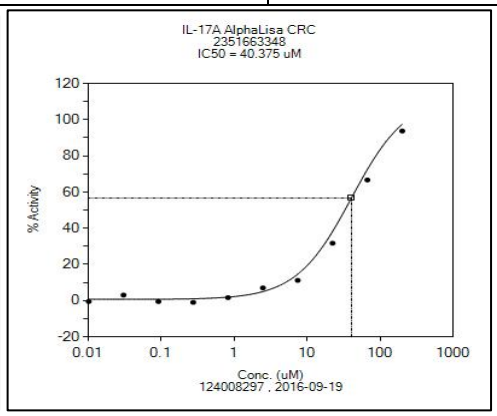
- IL-17A Alphalisa SP/CRC (% Inhibition/IC_{50})
- IL-17_IL17R TR-FRET Inhibition CRC (IC_{50})

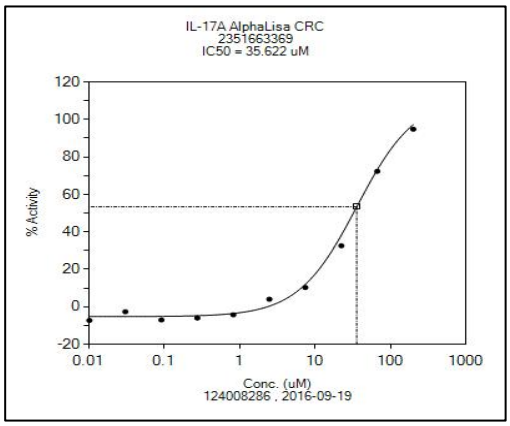
Compound	OIDD ID	Primary SP	Primary CRC
		IL-17A AlphaLisa SP	IL-17A AlphaLisa CRC
		%Inhib@100mM	Abs IC50 (mM)
	2351663277	62,34	
	2351663279	36,1	
	2351663280	3,144	
	2351663281	45,49	
	2351663285	4,259	
	2351663286	38,39	
	2351663287	15,15	
	2351663288	40,43	
	2351663289	28,46	
	2351663291	32,44	
	2351663292	63,57	

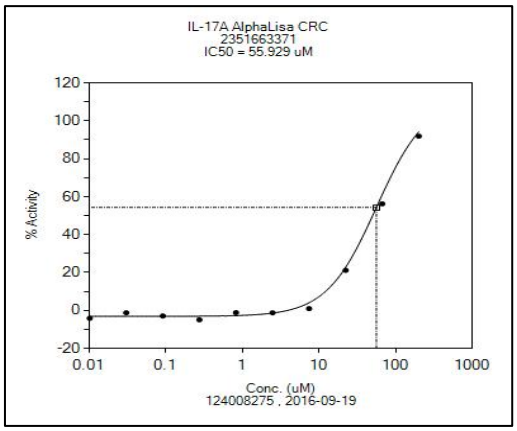
Compound	OIDD ID	Primary SP	Primary CRC
		IL-17A AlphaLisa SP	IL-17A AlphaLisa CRC
		%Inhib@100mM	Abs IC50 (mM)
	2351663341	49,46	
	2351663342	24,26	
	2351663343	51,77	
	2351663344	15,96	
	2351663345	73,53	37,95
	2351663348	73,89	40,37
	2351663349	31,93	
	2351663350	67,28	
	2351663368	65,44	
	2351663369	74,04	35,62
	2351663370	69,49	
	2351663371	71	55,93
	2351663372	49,27	
	2351663373	11,2	
	2351663375	18,2	
	2351663376	50,78	
	2351663378	31,38	
	2351663379	48,96	
	2351663381	24,61	
	2351663388	39,19	
	2351663390	36,31	
	2351663391	49,55	
	2351663393	29,43	
	2351677024	47,33	
	2351677025	76,06	45,77
	2351677124	-17,63	
	2351677125	-1,197	
	2351677126	36,34	
	2351677128	34,17	
	2351677148	13,6	
	2351677149	22,2	
	2351677151	7,943	
	2351677152	23,07	
	2351677153	14,69	
	2351677271	67,03	

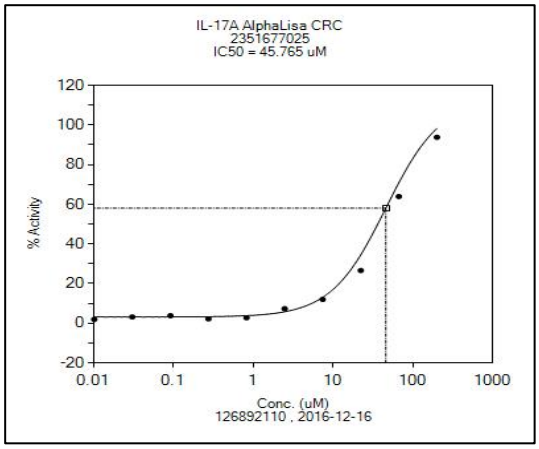
Compound	OIDD ID	Primary SP	Primary CRC
		IL-17A AlphaLisa SP	IL-17A AlphaLisa CRC
		%Inhib@100mM	Abs IC50 (mM)
	2351677274	32,54	
	2351677276	-6,638	
	2351677278	-0,7617	
	2351677280	37,87	
	2351677282	16,32	
	2351677284	24,37	
	2351677286	0,9793	
	2351677287	26,44	
	2351677289	55,71	
	2351677290	46,35	
	2351677291	67,9	

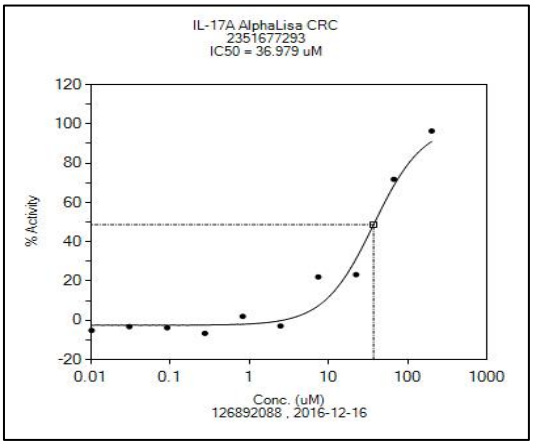


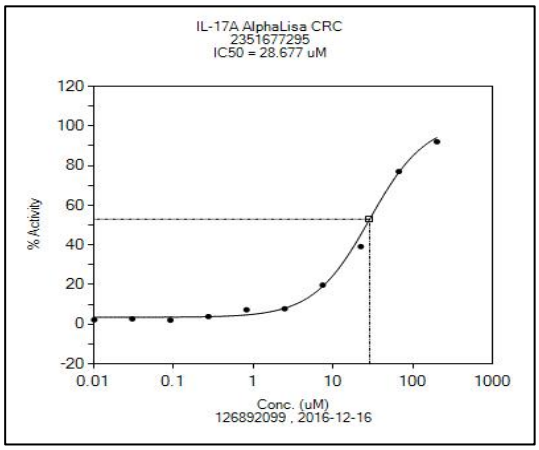


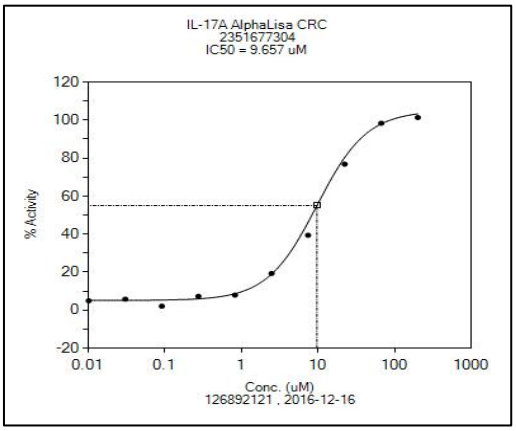





IL-17A AlphaLisa CRC
2351677025
IC50 = 45.765 uM
% Activity
Conc. (uM)
126892110 , 2016-12-16


IL-17A AlphaLisa CRC
2351677293
IC50 = 36.979 uM
% Activity
Conc. (uM)
126892088 , 2016-12-16


IL-17A AlphaLisa CRC
2351677295
IC50 = 28.677 uM
% Activity
Conc. (uM)
126892099 , 2016-12-16

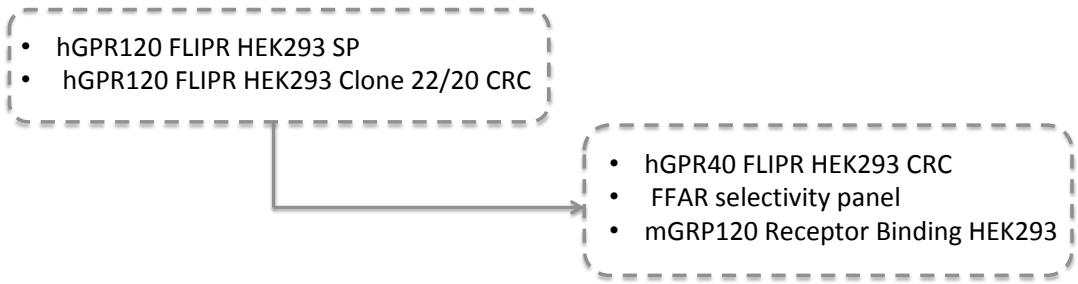

IL-17A AlphaLisa CRC
2351677304
IC50 = 9.657 uM
% Activity
Conc. (uM)
126892121 , 2016-12-16

5-**GPR120 Agonist:** endocrine and cardiovascular scope.

GPR120 is a receptor for long-chain fatty acids, Omega-3 included. Its expression is related in all the tissues affected by metabolic disease and diabetes, including pancreas, adipose tissue, gastrointestinal tract and the pituitary gland. When GPR120 is activated it acts with the important role to regulate body weight and glucose homeostasis. For example in human the R270H mutation of GPR120 is correlated with obesity and high glucose levels. GPR120 knockout mice are obese and insulin resistant and intolerant to glucose. In recent years have been discovered small molecules able to act as GPR120 agonists and so able to low glucose levels, improving insulin sensitivity and reduction the inflammation in obese people. For this reason, the activation of this receptor is seen as a new frontier in the treatment of this class of diseases.
Lilly assay is made in HEK293 cell-line that are human embryonic kidney. Calcium mobilization FLIPR test is able to determine concentration-depending changes of calcium levels through a fluorescent detection. More exactly, calcium-extracellular level is evaluated.

Endocrine/Cardiovascular:
GPR120 Agonist
Primary assays:
- hGPR120, Calcium Mobilization FLIPR, HEK293 Clone 22, SP (% Inhibition)
- Calcium Mobilization FLIPR, HEK293 un-transfected, SP (% Inhibition)
- hGPR120, Calcium Mobilization FLIPR, HEK293 cells, Clone 20/22 cells, CRC (IC_{50})

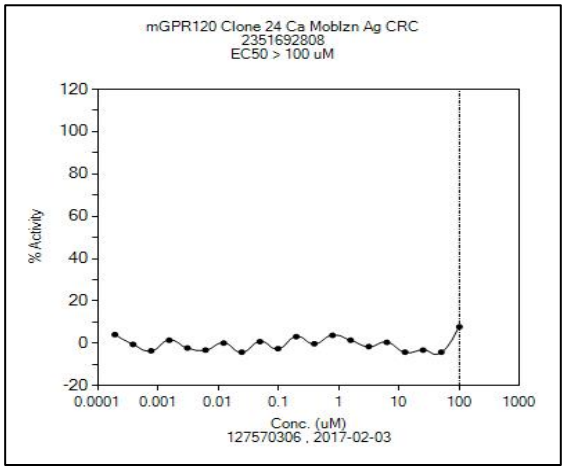
Secondary assays:
- hGPR40, hGPR120, Calcium Mobilization FLIPR, HEK293 cells, CRC (IC_{50})
- FFAR selectivity, CRC (IC_{50})
- mGPR120, Receptor Binding, CRC (IC_{50})

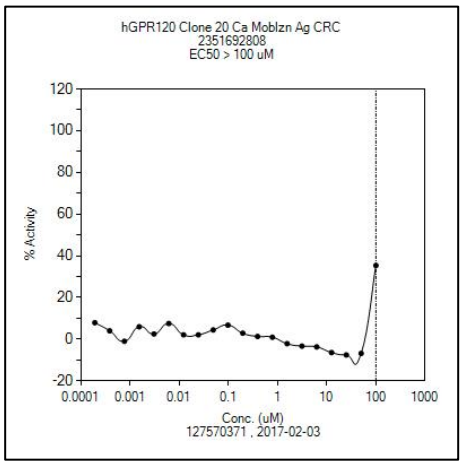


Cmpd	OIDD ID	Primary SP		Primary CRC	Secondary
		hGPR120 Clone 22 Ca Moblzn Ag SP	HEK293 Ca Moblzn Ag SP	hGPR120 Clone 20 Ca Moblzn Ag CRC	mGPR120 Clone 24 Ca Moblzn Ag CRC
		%Stim@ 30mM	%Stim@ 30mM	Rel EC50 (mM)	Rel EC50 (mM)
	2351663277	7,064			
	2351663279	0,3347			
	2351663280	0,7606			
	2351663281	0,3955			
	2351663285	0,9431			
	2351663286	-0,213			
	2351663287	0,3955			
	2351663288	1,917			
	2351663289	20,35			
	2351663291	2,221			
	2351663292	0,03042			
	2351663341	1,917			
	2351663342	0,3955			
	2351663343	1,1			
	2351663344	0,4563			
	2351663345	13,17			
	2351663348	14,21			
	2351663349	0,03042			
	2351663350	1,065			
	2351663368	0,6997			
	2351663369	28,81			
	2351663370	3,803			
	2351663371	0,4563			
	2351663372	4,837			
	2351663373	1,065			
	2351663375	7,758			
	2351663376	0,6389			
	2351663378	3,438			
	2351663379	0,9431			
	2351663381	1,917			
	2351663388	0,3955			
	2351663390	0,8823			

Cmpd	OIDD ID	Primary SP		Primary CRC	Secondary
		hGPR120 Clone 22 Ca Moblzn Ag SP	HEK293 Ca Moblzn Ag SP	hGPR120 Clone 20 Ca Moblzn Ag CRC	mGPR120 Clone 24 Ca Moblzn Ag CRC
		%Stim@ 30mM	%Stim@ 30mM	Rel EC50 (mM)	Rel EC50 (mM)
	2351663391	0,1521			
	2351663393	1,004			
	2351677024	3,653			
	2351677025	4,566			
	2351677124	-1,37			
	2351677125	-5,023			
	2351677126	7,763			
	2351677128	9,589			
	2351677148	10,5			
	2351677149	2,74			
	2351677151	3,653			
	2351677152	-2,74			
	2351677153	5,479			
	2351677271	3,196			
	2351677274	3,196			
	2351677276	10,5			
	2351677278	-3,653			
	2351677280	0			
	2351677282	-10,96			
	2351677284	5,936			
	2351677286	-3,196			
	2351677287	4,11			
	2351677289	-0,9132			
	2351677290	14,16			
	2351677291	0,4566			
	2351677292	-7,763			
	2351677293	1,826			
	2351677294	-1,826			
	2351677295	2,74			
	2351677296	10,96			
	2351677304	7,306			
	2351692808	73,52	0	>100.0 EC50 is not	>100.0 EC50 is not

Cmpd	OIDD ID	Primary SP		Primary CRC	Secondary
		hGPR120 Clone 22 Ca Moblzn Ag SP	HEK293 Ca Moblzn Ag SP	hGPR120 Clone 20 Ca Moblzn Ag CRC	mGPR120 Clone 24 Ca Moblzn Ag CRC
		%Stim@ 30mM	%Stim@ 30mM	Rel EC50 (mM)	Rel EC50 (mM)
				reached till 100mM	reached till 100mM





Compound	OIDD ID	Primary SP
		hPCSK9 Huh7 TT Inhib SP
		%Inhib@40mM
	2351663277	49,06
	2351663279	39,62
	2351663280	7,541
	2351663281	73,58
	2351663285	72,46
	2351663286	8,571
	2351663287	29,76
	2351663288	-3,39
	2351663289	20,24
	2351663291	94,34
	2351663292	77,36
	2351663341	12,86
	2351663342	-2,857
	2351663343	28,3
	2351663344	-2,143
	2351663345	40,48
	2351663348	98,11
	2351663349	8,571
	2351663350	94,75
	2351663368	43,4
	2351663369	50
	2351663370	21,43
	2351663371	64,15
	2351663372	67,86
	2351663373	27,38
	2351663375	18,87
	2351663376	-12,14
	2351663378	28,57
	2351663379	37,74
	2351663381	65,25
	2351663388	30,19
	2351663390	40,95
	2351663391	8,571
	2351663393	88,1

6-**Tuberculosis (TB):** is an infectious disease caused by *Mycobacterium tuberculosis* (MTB) bacteria and generally affects the lungs. In the Lilly's screen is tested the ability ot new compounds to prevent the growth of a virulent strain of *Mycobacterium tuberculosis* (H37Rv) in liquid medium. More specifically, the primary assay tests, at a single concentration, compound by their inhibition against a genetically-modified and fluorescent reporter strain of the bacteria.

Tuberculosis-
Primary assays:
Whole cellular activity H37Rv cells at SP (% Inhibition)

Compound	OIDD ID	Primary SP
		TB MIC SP IDRI OIDD
		%Inhib@20mM
	2351663277	15.3 5.5
	2351663279	2.2 -16.7
	2351663280	7.0 -0.8
	2351663281	2.7 0.2
	2351663285	11.5 2.9
	2351663286	6.3 -6.3
	2351663287	10.0 -1.7
	2351663288	-2.7 -9.5
	2351663289	1.2 4.4
	2351663291	10.0 10.5
	2351663292	72.7 74.3

Compound	OIDD ID	Primary SP
		TB MIC SP IDRI OIDD
		%Inhib@20mM
	2351663341	4.5
		5.5
	2351663342	3.8
		6.1
	2351663343	3.6
		-15.8
	2351663344	3.3
		3.8
	2351663345	2.2
		0.8
	2351663348	1.6
		-1.3
	2351663349	4.9
		3.9
	2351663350	22.3
		15.8
	2351663368	11.8
		6.9
	2351663369	26.6
		5.0
	2351663370	-9.2
		-5.4
	2351663371	2.5
		3.5
	2351663372	4.7
		4.7
	2351663373	6.1
		2.3
	2351663375	9.7
		6.3
	2351663376	5.2
		4.3
	2351663378	4.1
		0.7
	2351663379	2.3
		-17.2

Compound	OIDD ID	Primary SP
		TB MIC SP IDRI OIDD
		%Inhib@20mM
	2351663381	20.9
		20.0
	2351663388	5.2
		0.8
	2351663390	5.6
		3.4
	2351663391	3.3
		2.2
	2351663393	13.9
		6.9
	2351677024	4.9
		-8.1
	2351677025	-0.9
		-0.9
	2351677124	9.4
		5.1
	2351677125	10.9
		-2.1
	2351677126	9.4
		9.8
	2351677128	11.1
		8.8
	2351677148	-1.9
		-8.5
	2351677149	11.5
		5.8
	2351677151	8.3
		11.5
	2351677152	2.6
		2.8
	2351677153	6.4
		-4.4
	2351677271	1.1
		6.2
	2351677274	8.7
		12.0

Compound	OIDD ID	Primary SP
		TB MIC SP IDRI OIDD
		%Inhib@20mM
	2351677276	7.2 15.3
	2351677278	4.4 -3.3
	2351677280	11.1 14.0
	2351677282	4.2 -9.4
	2351677284	7.4 11.1
	2351677286	-15.2 0.5
	2351677287	10.7 -0.6
	2351677289	12.6 -2.7
	2351677290	4.4 -1.0
	2351677291	7.6 0.2
	2351677292	21.4 15.3
	2351677293	10.4 -0.8
	2351677294	5.8 -7.2
	2351677295	12.6 -4.8
	2351677296	12.0 3.9
	2351677304	13.4 4.2
	2351692808	12.0 -7.2
	2351786662	2,46
	2351786663	-4,15

Compound	OIDD ID	Primary SP
		TB MIC SP IDRI OIDD
		%Inhib@20mM
	2351786664	-1,22
	2351786669	-1,58
	2351786670	5,23
	2351786671	5,76
	2351791156	3,73
	2351798652	0,62
	2351798653	-0,48
	2351798654	3,56
	2351798655	-1,22
	2351798657	6,5
	2351798658	0,99

7-**Leishmania:** *Leishmania* parasite is the responsible of the so-called kala-azar disease. The global disease reported by Neglected Tropical Diseases (NTDs) is always higher. The World Health Organization (WHO) reports that half a billion people are at risk of contracting Chagas disease, African trypanosomiasis and several different forms of lehismaniasis (almost 20 million persons are infected and every year a number around 95 thousands deaths are registered). Kinetoplastid therapies are far from being efficient and safe. In 2012 these three diseases have been included in the London Declaration of private and public partners to focus the attention in 10 NTDs, as new perspective for WHO.

The disease is presented with cutaneous, mucocutaneous or visceral manifestations. The parasites are flagellated protozoans and are characterized by the presence of a DNA-containing region called kinetoplast in the mitochondrion (only one present). When hosted in a vehicle they undergo morphological changes during their all life cycle. Its genomes encode for several proteins that are not contained in human proteome. For this reason researcher think about the possibility to identify and target this different proteins in order to find a more efficient therapy.

In Lilly assay is tested and so evaluated the ability to inhibit the growth of the parasite.

Leishmania-
Primary assays:

- *L.donovani* Axenic Assay growth Inhibition SP/CRC (% Inhibition/IC_{50})
- *L.donovani Imaging CRC,* infected THP-1 macrophage intracellular Imaging assay.
- HepG2 cytotoxicity Assay CRC (IC_{50}).

Compound	OIDD ID	Primary SP	Primary CRC			
		Viability L. donovani Cytotox SP	NV-Basal_Viability L. donovani Cytotox CRC Tres Cantos	NV-L. donovani THP-1 FBS Dead Cells CRC Tres Cantos	NV-L. donovani THP-1 FBS Parasites per Cell CRC Tres Cantos	NV-L. donovani THP-1 FBS Infected Cells CRC Tres Cantos
		%Inhib@ 5uM	pIC50 (M)	pIC50 (M)	pIC50 (M)	pIC50 (M)
	2351663277	1,78				
	2351663279	-18,9				
	2351663280	-5,27				

Compound	OIDD ID	Primary SP	Primary CRC			
		Viability L. donovani Cytotox SP	NV-Basal_Viability L. donovani Cytotox CRC Tres Cantos	NV-L. donovani THP-1 FBS Dead Cells CRC Tres Cantos	NV-L. donovani THP-1 FBS Parasites per Cell CRC Tres Cantos	NV-L. donovani THP-1 FBS Infected Cells CRC Tres Cantos
		%Inhib@ 5uM	pIC50 (M)	pIC50 (M)	pIC50 (M)	pIC50 (M)
	2351663281	-0,07				
	2351663285	13,04				
	2351663286	-7,76				
	2351663287	-0,65				
	2351663288	23,01				
	2351663289	10,97				
	2351663291	95,99	4.43 4.43	<4.3 4.34	<4.3 <4.3	<4.3 <4.3
	2351663292	-5,86				
	2351663341	12,62				
	2351663342	-34,84				
	2351663343	-23,89				
	2351663344	10,71				
	2351663345	0,88				
	2351663348	-42,27				
	2351663349	7,31				
	235166335	-12,45				

Compound	OIDD ID	Primary SP	Primary CRC			
		Viability L. donovani Cytotox SP	NV-Basal_Viability L. donovani Cytotox CRC Tres Cantos	NV-L. donovani THP-1 FBS Dead Cells CRC Tres Cantos	NV-L. donovani THP-1 FBS Parasites per Cell CRC Tres Cantos	NV-L. donovani THP-1 FBS Infected Cells CRC Tres Cantos
		%Inhib@ 5uM	pIC50 (M)	pIC50 (M)	pIC50 (M)	pIC50 (M)
	0					
	2351663368	1,64				
	2351663369	-0,04				
	2351663370	-6,37				
	2351663371	7,45				
	2351663372	-10,65				
	2351663373	-11,54				
	2351663375	10,8				
	2351663376	3,72				
	2351663378	-5,2				
	2351663379	12,84				
	2351663381	-17				
	2351663388	-12,63				
	2351663390	-8,93				
	2351663391	-4,91				
	2351663393	5,42				

Compound	OIDD ID	Primary SP	Primary CRC			
		Viability L. donovani Cytotox SP	NV-Basal_Viability L. donovani Cytotox CRC Tres Cantos	NV-L. donovani THP-1 FBS Dead Cells CRC Tres Cantos	NV-L. donovani THP-1 FBS Parasites per Cell CRC Tres Cantos	NV-L. donovani THP-1 FBS Infected Cells CRC Tres Cantos
		%Inhib@ 5uM	pIC50 (M)	pIC50 (M)	pIC50 (M)	pIC50 (M)
	2351677024	-3,56				
	2351677025	3,56				
	2351677124	-4,87				
	2351677125	-0,36				
	2351677126	-0,26				
	2351677128	-1,66				
	2351677148	4,58				
	2351677149	10,57				
	2351677151	8,4				
	2351677152	6,52				
	2351677153	0,03				
	2351677271	4,25				
	2351677274	-23,18				
	2351677276	-13,84				
	2351677278	-4,38				
	235167728	0,41				

Compound	OIDD ID	Primary SP	Primary CRC			
		Viability L. donovani Cytotox SP	NV-Basal_Viability L. donovani Cytotox CRC Tres Cantos	NV-L. donovani THP-1 FBS Dead Cells CRC Tres Cantos	NV-L. donovani THP-1 FBS Parasites per Cell CRC Tres Cantos	NV-L. donovani THP-1 FBS Infected Cells CRC Tres Cantos
		%Inhib@ 5uM	pIC50 (M)	pIC50 (M)	pIC50 (M)	pIC50 (M)
	0					
	2351677282	-3,5				
	2351677284	-16,03				
	2351677286	0,26				
	2351677287	5,37				
	2351677289	4,17				
	2351677290	-17,67				
	2351677291	2,82				
	2351677292	-11,71				
	2351677293	-34,98				
	2351677294	5,77				
	2351677295	-31,07				
	2351677296	-6,36				
	2351677304	2,21				
	2351692808	-9,38				

8-**Chagas Disease:** known as American trypanosomiasis, is a tropical parasitic disease. Spread by blood-sucking insects called Triatominae or kissing bug. Symptoms are different during the infection: at the begining no or mild symptoms as fever, are shown. At the stage of 8-12 weeks the chronic phase is detected. In the succesive cases two different behaviours can be presented: for the 60-70% of the cases the patient never presents the symptoms, and on the other side, the resting 30-40% sill develop further symptoms in the next 10-30 years.

Chagas Disease-
Primary assays:

- T. cruzi NIH-3T3 growth inhibition assay SP/CRC (% Inhibition/IC_{50})
- T. cruzi H9C2 intracellular Imaging assay CRC (IC_{50})
- Trypomastigote luciferin-based assay (IC_{50})
- HepG2 cytotoxicity Assays CRC (IC_{50})

Cmpd	OIDD ID	Primary SP				
		T.cruzi Growth Inhibition SP	NV-Basal_Viability T.cruzi CTG Inhib SP Tres Cantos	NV-T.cruzi myocardiocyte Dead Cells SP Tres Cantos	NV-T.cruzi myocardiocyte Parasites per Cell SP Tres Cantos	NV-T.cruzi myocardiocyte Infected Cells SP Tres Cantos
		%Inhib @ 5mM	%Inhib@ 5mM	%Inhib@ 5mM	%Inhib@ 5NA	%Inhib@ 5mM
	2351663277	6,03				
	2351663279	2.3 2.3				
	2351663280	-20.78 -20.78				
	2351663281	6,79				
	2351663285	9,76				
	2351663286	3,88				
	2351663287	5,32				
	2351663288	9.36 9.36				
	2351663289	8.03 8.03				

Cmpd	OIDD ID	Primary SP				
		T.cruzi Growth Inhibition SP	NV-Basal_Viability T.cruzi CTG Inhib SP Tres Cantos	NV-T.cruzi myocardiocyte Dead Cells SP Tres Cantos	NV-T.cruzi myocardiocyte Parasites per Cell SP Tres Cantos	NV-T.cruzi myocardiocyte Infected Cells SP Tres Cantos
		%Inhib @ 5mM	%Inhib@ 5mM	%Inhib@ 5mM	%Inhib@ 5NA	%Inhib@ 5mM
	2351663291	8.18 8.18				
	2351663292	-17.31 -17.31				
	2351663341	6.47 6.47				
	2351663342	2.9 2.9				
	2351663343	0.11 0.11				
	2351663344	4.76 4.76				
	2351663345	-7.53 -7.53				
	2351663348	-7.41 -7.41				
	2351663349	-7.23 -7.23				
	2351663350	-8.18 -8.18				
	2351663368	-13,26				
	2351663369	-3,52				
	2351663370	-1,21				
	2351663371	0,22				
	2351663372	-24,26				
	2351663373	2,76				
	2351663375	-0,53				
	2351663376	8,92				
	2351663378	-6,79				
	2351663379	10,56				

Cmpd	OIDD ID	Primary SP				
		T.cruzi Growth Inhibition SP	NV-Basal_Viability T.cruzi CTG Inhib SP Tres Cantos	NV-T.cruzi myocardiocyte Dead Cells SP Tres Cantos	NV-T.cruzi myocardiocyte Parasites per Cell SP Tres Cantos	NV-T.cruzi myocardiocyte Infected Cells SP Tres Cantos
		%Inhib @ 5mM	%Inhib@ 5mM	%Inhib@ 5mM	%Inhib@ 5NA	%Inhib@ 5mM
	2351663381	6,13				
	2351663388	-0,76				
	2351663390	18,67				
	2351663391	-1,75				
	2351663393	-7,02				
	2351677024	-18.87 -18.87				
	2351677025	2.64 2.64				
	2351677124	-2.79 -2.79				
	2351677125	9.98 9.98				
	2351677126	8.69 8.69				
	2351677128	-13.77 -13.77				
	2351677148	16.92 16.92				
	2351677149	4.41 4.41				
	2351677151	-5.87 -5.87				
	2351677152	-6.4 -6.4				
	2351677153	-4.49 -4.49				
	2351677271	-8.26 -8.26				

Cmpd	OIDD ID	Primary SP				
		T.cruzi Growth Inhibition SP	NV-Basal_Viability T.cruzi CTG Inhib SP Tres Cantos	NV-T.cruzi myocardiocyte Dead Cells SP Tres Cantos	NV-T.cruzi myocardiocyte Parasites per Cell SP Tres Cantos	NV-T.cruzi myocardiocyte Infected Cells SP Tres Cantos
		%Inhib @ 5mM	%Inhib@ 5mM	%Inhib@ 5mM	%Inhib@ 5NA	%Inhib@ 5mM
	2351677274	7.22 7.22				
	2351677276	16.08 16.08				
	2351677278	5.11 5.11				
	2351677280	19.93 19.93				
	2351677282	1.83 1.83				
	2351677284	-9.61 -9.61				
	2351677286	4.55 4.55				
	2351677287	-1.32 -1.32				
	2351677289	16.86 16.86				
	2351677290	2.87 2.87				
	2351677291	-11.72 -11.72				
	2351677292	-40.37 -40.37				
	2351677293	-13.17 -13.17				
	2351677294	8.24 8.24				
	2351677295	0.53 0.53				

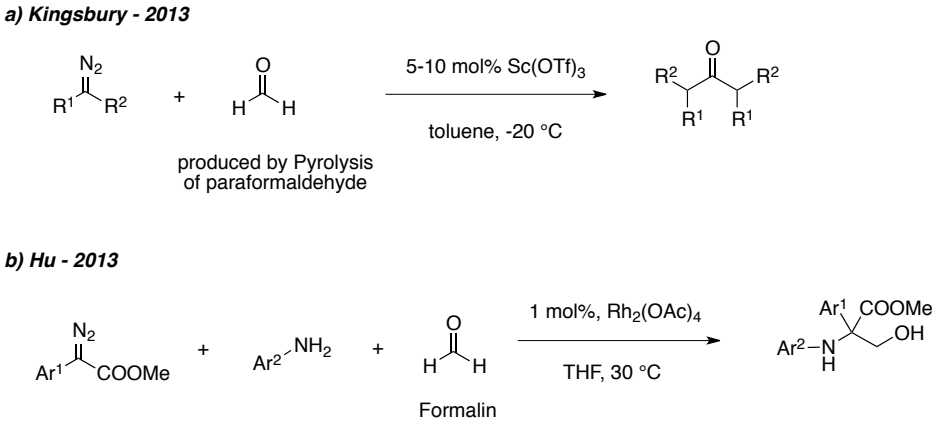
Cmpd	OIDD ID	Primary SP				
		T.cruzi Growth Inhibition SP	NV-Basal_Viability T.cruzi CTG Inhib SP Tres Cantos	NV-T.cruzi myocardiocyte Dead Cells SP Tres Cantos	NV-T.cruzi myocardiocyte Parasites per Cell SP Tres Cantos	NV-T.cruzi myocardiocyte Infected Cells SP Tres Cantos
		%Inhib @ 5mM	%Inhib@ 5mM	%Inhib@ 5mM	%Inhib@ 5NA	%Inhib@ 5mM
	2351677296	-0.28 -0.28				
	2351677304	15.0 15.0				
	2351692808	82.96 82.96 81.97 83.36	55.35 57.63	8.78 12.55	5.94 40.05	-1.91 18.4

9. Mild and versatile synthesis of aliphatic aldehydes in a photochemical-promoted process in flow

9.1. Introduction

The reactions between carbonyl compounds and diazo compounds have been extensively studied [132] since the description of the Buchner-Curtius-Schlotterbeck reaction,[133] almost a century ago.

This type of reactivity represents an efficient synthetic tool for the generation of C-C bond, which have been mostly employed for the construction of ketones or fro the extenxion of carbon chains.[134] However, the controlled formation of aldehydes using diazo chemistry does not represent an easy task due to the high coupling reactivity of diazo compounds with carbonyl groups. Kingsbury reported a double homologation reaction catalyzed by a Lewis acid which combines *ex-situ* prepared diazo compounds and the flash-pyrolyzed preparation of anhydrous formaldehyde (Scheme 9.1, *a*)[135] and Hu described an interesting three-component coupling of aryldiazoacetate, aniline and aqueous formaldehyde (Scheme 9.1, *b*).[136] In both cases, the authors were unable to stop the reaction at the aldehyde-generating step on the way to a final product either the doubly homologated ketone or the α-aryl serine derivative.



Scheme 9.1

[132] (a) Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem. Rev.,* **2016**, *116*, 2937; (b) Guttenberger, N.; Breinbauer, R. *Tetrahedron,* **2017**, *73*, 6815.

[133] (a) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.,* **1885**, *18*, 2377. (b) Schlotterbeck, F. *Ber. Dtsch. Chem. Ges.,* **1885**, *40*, 1826.

[134] (a) Mock, W. L.; Hartman, M. E. *J. Org. Chem.,* **1977**, *42*, 459; (b) Allwood, D. M.; Blakemore, D. C.; Ley, S. V. *Org. Lett.* **2014**, *16*, 3064; (c) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.,* **2009**, *131*, 878.

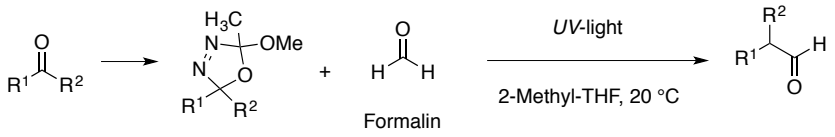
[135] Wommack, A. J.; Kingsbury, J. S. *J. Org. Chem.,* **2013**, *78*, 10573.

[136] Wang, C.; Liu, S.; Xing, D.; Wang, X.; Wu, X.; Hu, W. *Tetrahedron,* **2013**, *69*, 11203.

Based on the previous experience in the Ley group on the use of oxadiazolines as benchstable, nonstabilized diazo compound precursors under flow conditions,[137] we set up to study the controlled homologation of diazo compounds generated from bench-stable precursors in flow to form aldehydes and their derivatives.

9.2. Synthesis of aliphatic aldehydes and their corresponding alcohols and benzimidazoles derivatives

Due to the lack of a general method for the preparation of aliphatic aldehydes, we were encouraged to further investigate this kind of transformation by controlling the aldehyde formation step and with no use of protecting group chemistry. The planned synthetic strategy is described in Scheme 9.2.



Scheme 9.2

We selected 2-tetralone oxadiazoline as the reference compound for the optimization study and we combined it with different sources of formaldehyde under UV irradiation (Table 9.1). Formaldehyde surrogates trioxane and dioxolane, which are usually employed as formaldehyde source, gave only traces of desired aldehyde **22a** although almost all the oxadiazoline starting material was converted into the diazo specie (entries 1 and 2).[138]

The use of a stock solution of monomeric formaldehyde, generated *via* thermolysis of paraformaldehyde,[139] gave a 55% yield of the desired aldehyde (entry 3) but the tendency of the stock solution to polymerize without warning on warming above -78 °C, made this strategy no worthy. Then, we attempted the reaction with formalin, a 37% aqueous solution of formaldehyde, and the target aldehyde **22a** was obtained in a modest 48% yield (entry 4). After several modifications of the reaction conditions, we found an improvement of the conversion (87%) and the yield (60%) when the reaction was carried out with 0.4 mmol of oxadiazoline, 0.4 mmol of formalin (0.3 mL, 37 wt%) in 2-methyltetrohydrofuran (4 mL) and elongating the residence time up to 80, with an (entry 7). Other ajustments such as formaldehyde ratio changes or switching to tetrahydrofuran or dichloromethane were ineffective (entry 8, 9, 10 and 11).

---

[137] (a) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.,* **2016**, *45*, 4892; (b) Greb, A.; Poh, J. S.; Greed, S.; Battilocchio, C.; Pasau, P.; Blakemore, D. C.; Ley, S. V. *Angew. Chem. Int. Ed.,* **2017**, *56*, 16602; (c) Dingwall, P.; Greb, A.; Crespin, L. N. S.; Labes, R.; Musio, B.; Poh, J.S.; Pasau, P.; Blakemore D. C.; Ley S. V. *Chem. Comm.,* **2018**, *54*, 11685; (d) Chen, Y.; Blakemore, D.C.; Pasau P.; Ley S.V. *Org. Lett.*, **2018**, *20*, 6569.

[138] Hamilton, J. Y.; Morandi, B.; Carreira, E. M. *Synthesis,* **2013**, *45*, 1857.

[139] Gilman, H.; Catlin, W. E. *Org. Synth.,* **1926**, *6*, 22.

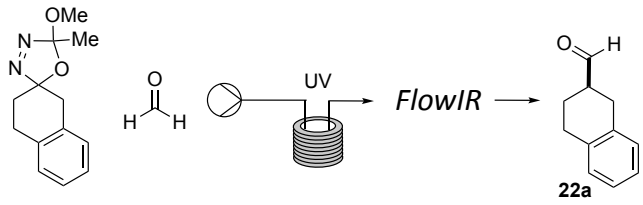


Table 9.1: optimization of the reaction conditions.

Entry[a]	Fomaldehyde source	Ox./M	t_R/min	T/°C	Conv.	Yield
1	Dioxolane	0.1	40	20	99%	0%
2	Trioxane	0.1	40	20	96%	2%
3	Thermolysed Paraformaldheyde	0.1	40	20	67%	55%
4	37% aq	0.1	40	20	78%	48%
5	37% aq	0.1	40	10	72%	41%
6	37% aq	0.05	40	10	80%	39%
7	37% aq	0.1	80	20	87%	60% (50%)[b]
8[c]	37% aq	0.1	80	20	86%	58%
9[d]	37% aq	0.1	80	20	87%	56%
10[e]	37% aq	0.1	80	20	78%	41%
11[f]	37% aq	0.1	80	20	79%	12%

[a]NMR yields calculated with 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]100 equiv. of formaldehyde was used. [d]5.0 equiv. of formaldehyde was used. [e]Tetrahydrofuran was used instead of 2-methyltetrahydrofuran. [f]Dichloromethane was used instead of 2-methyltetrahydrofuran.

It is interesting to remark that even if the conversion of the oxadiazoline increased, the aldehyde was recovered only in 50% yield after column chromatography. A carefully study of the crude sample showed that a significant amount of the aldehyde hydrate form was also present, but no more than 10% of the doubly homologated ketone.

The formation of the hydrate derivative could be due to the presence of large amount of water in the reaction media, that acts as an *in situ* protecting group. This fact, together with a very low concentration of diazo compound during the progression of the reaction, hinder double homologation. It was also observed in same cases, over an extended period of time, the presence of the corresponding carboxylic acid, probably proceeding from an aerobic oxidation process.

In order to better handle the unstable aldehydes, we explored two methods to trap the desired products. The first one was to reduce the crude mixture reaction with a solution of sodium borohydride ($NaBH_4$) to convert the aldehyde into the corresponding alcohol. This strategy can be also considered a way to store unstable aldehydes, which can be used again *via* a secondary oxidation. The second one

consisted in subjecting the crude mixture reaction to an oxidative condensation with *o*-phenylenediamine, based on a modified procedure originally reported by Jiao *et. al.*[140] The scope of the aldehyde synthesis and their derivatization to alcohols and benzimidazoles is summarized in Table 9.2.

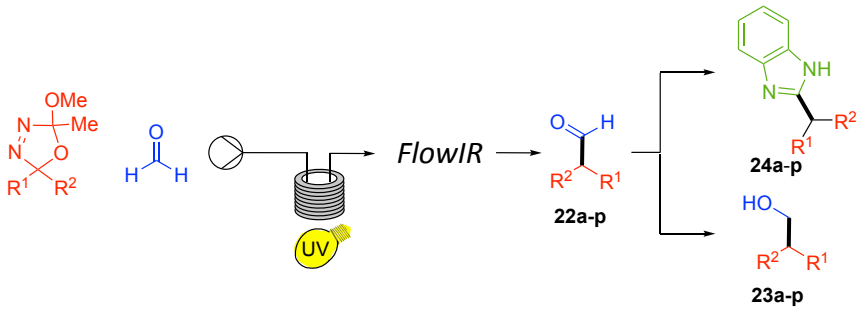
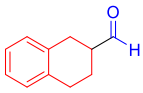
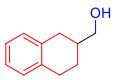
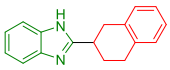
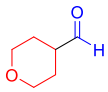
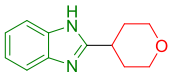
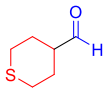
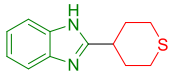
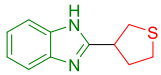
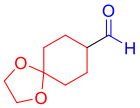
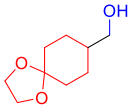
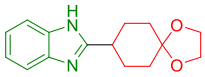
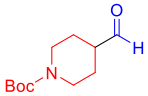
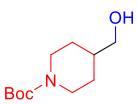
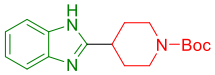
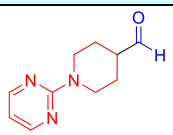
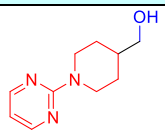
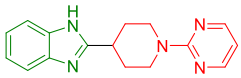
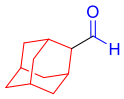
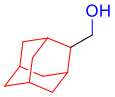
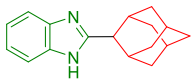
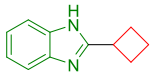
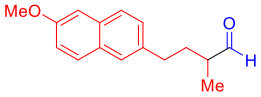
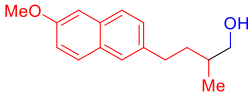
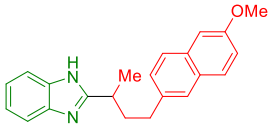
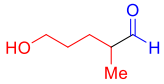
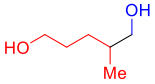
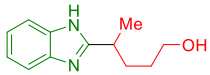
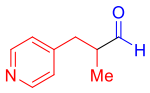
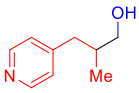
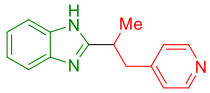
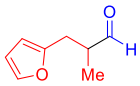
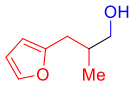
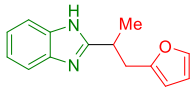
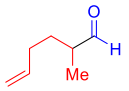
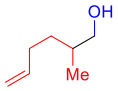
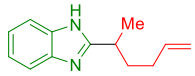
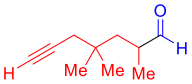
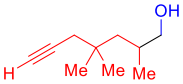
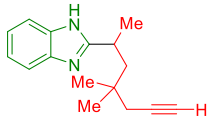
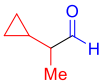
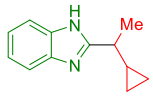


Table 9.2: Scope of the aldehyde synthesis and their derivatization into alcohols and benzimidazoles

Entry	Aldehyde **22a – p**[a]	Alcohol **23a – p**[b]	Benzimidazole **24a – p**[c]
1	 **22a**, 60%[d] (50%)	 **23a**, 60%	 **24a**, 72%
2	 **22b**, 48%	 **23b**, 53%	 **24b**, 76%
3	 **22c**, 56%	 **23c**, 72%	 **24c**, 55%
4	 **22d**, 85%[d] (75%)	 **23d**, 89%[d] (77%)	 **24d**, 60%
5	 **22e**, 65%	 **23e**, 75%	 **24e**, 80%
6	 **22f**, 58%[d] (49%)	 **23f**, 53%	 **24f**, 49%

[140]Zhang, C.; Zhang, L.; Jiao, N. *Green Chem.*, **2012**, *14*, 3273.

Entry	Aldehyde **22a – p**[a]	Alcohol **23a – p**[b]	Benzimidazole **24a – p**[c]
7	 **22g**, 55%[d]	 **23g**, 68%[d]	 **24g**, 72%
8	 **22h**, 68%	 **23h**, 75%	 **24h**, 79%
9	 **22i**, n.d.[e]	 **23i**, n.d.[e]	 **24i**, 59%
10	 **22j**, 57%	 **23j**, 75%	 **24j**, n.d.[e]
11	 **22k**, 85%[f]	 **23k**, 66%	 **24k**, n.d.[e]
12	 **22l**, 35%[d]	 **23l**, 50%	 **24l**, 48%
13	 **22m**, 25%[d]	 **23m**, 60%	 **24m**, 75%
14	 **22n**, 58%[d]	 **23n**, 88%[d] (69%)	 **24n**, 73%
15	 **22o**, 18%[d]	 **23o**, n.d.[e]	 **24o**, 39%
16	 **22p**, 8%[d]	 **23p**, 58%[d]	 **24p**, 69%

[a]Reaction conditions: oxadiazoline (1.0 equiv., 0.1 M), formaldehyde (10 equiv., 37 wt% in H_2O, 1.0 M) in 2-methyltetrahydrofuran. [b]Aldehyde reduced directly with $NaBH_4$ (10 equiv., 0.5 M) in ethanol. [c]Aldehyde reacted with *o*-phenylenediamine (1.5 equiv., 0.075 M) in toluene. [d]NMR yield, calculated using 1,3,5-trimethoxybenzene as an internal standard. [e]Not determined due to volatility or product contamination. [f]81% of the product identified as the hydrated form.

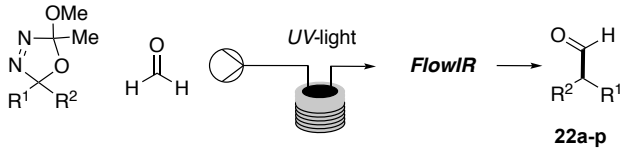
In general, yields of compounds **23** and **24** are better than the isolated yields of **22**, reflecting that the aldehyde was present in the crude mixture reaction. The obtention of benzimidazole derivatives in much higher isolated yields represents a proof of the robustness of the method and of the good production of the desired aliphatic aldehydes, and their stability problems make difficult their isolation. Functional groups as alkene, alkyne, nitrogen-based functional groups, Boc-protected amine and bulky substituents were well tolerated. For compounds **22i** and **23i** isolated yields were not determined due to their volatility, a common problem with these low molecular weight molecules. Even thought, the formation of 2-cyclobutylbenzimidazole was possible in 59% yield (**24i**) as a proof for the aldehyde formation. Generally, α-methyl aldehydes displayed a tendency towards hydration or aerobic oxidation, resulting in low crude NMR yields and difficulty in their isolation their isolation, being this behaviour known for similar materials.

Many of these products can be thought of as branched or iso aldehydes, which would be difficult to prepare through traditional methods such as hydroformylation, particularly in the presence of an alkene or alkyne

We can conclude that have developed a mild, operationally straightforward procedure for the homologation of ketones and aryl aldehydes *via* non-stabilised diazo compounds in flow avoiding expensive and reactive transition metal catalysts and uses formalin as a cheap and readily available homologation reagent.

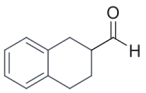
9.3. Experimental section

9.3.1. General procedure A: synthesis of aliphatic aldehydes 22



A solution of the appropriate oxadiazoline (1.0 equiv., 0.05 mmol/mL) and formaldehyde (10 equiv. aqueous solution, 37% w/w) in 2-MeTHF (0.5 mol/mL) was pumped (0.125 mL min^{-1}, t_R = 80 min) through a Vapourtec UV-150 photochemical reactor (10 mL, FEP tubing) while irradiate by a 310 nm UV lamp (output power: 9W) held at 20 °C. The reactor output was monitored using a Mettler Toledo FlowIR® instrument (SiComp head, bands of interest: C=O stretch signal at 1750-1700 cm^{-1} for methyl acetate, generated by the decomposition of oxadiazoline). Once the FlowIR® detector showed the signal of the reaction slug, the output stream was collected in a sealed sample vial containing a biphasic solution of dichloromethane and brine with stirring to separate excess formaldehyde and other potential impurities. The collected material was rested, and the organic phase was separated and con- centrated under reduced pressure. The remaining residue was purified *via* flash silica gel column chromatography with appropriate eluent combination to give the desired product.

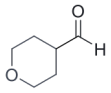
1,2,3,4-Tetrahydronaphthalene-2-carbaldehyde (22a)



General procedure A was followed using 5'-methoxy-5'-methyl-3,4-dihydro-1*H*,5'*H*-spiro(naphthalene-2,2'-[1,3,4]oxadiazole) (92 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H2O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 - 20% EtOAc in petroleum ether) to give the titled product as a transparent oil (32 mg, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (d, *J* = 1.2 Hz, 1H, *H*CO), 7.13 (dt, *J* = 6.3, 3.5 Hz, 3H, H_{Ar}), 7.10 (q, *J* = 4.1, 3.5 Hz, 1H, H_{Ar}), 3.04 – 2.95 (m, 2H, Ar$CH_2$$CH_2$), 2.94 – 2.82 (m, 2H, ArCH_2), 2.75 – 2.68 (m, 1H, HCOC*H*), 2.26 – 2.19 (m, 1H, ArCH_a), 1.84 – 1.75 (m, 1H, Ar$CH_{a'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.9 (H*C*O), 136.1 (C_{Ar}), 134.4(C_{Ar}), 129.4(C_{Ar}H), 129.0(C_{Ar}H), 126.2(C_{Ar}H), 126.1(C_{Ar}H), 47.0 (HCO*C*H), 28.6 (Ar*C*$H_2$$CH_2$), 28.2 (Ar*C*$H_2$CH), 23.1 (*C*a). HRMS (ESI) calcd for $C_{11}H_{12}ONa^+$ $[M+Na]^+$ 183.0780, found 183.0775. IR max (film) ν: 2904, 2851, 1723, 1702, 1432, 1110, 1042 cm^{-1}. The data presented are consistent with literature precedent.[141]

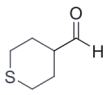
[141]Shi, Z.-C.; Devasagayaraj, A.; Gu, K.; Jin, H.; Marinelli, B.; Samala, L.; Scott, S.; Stouch, T.; Tunoori, A.; Wang, Y.; Zang, Y.; Zhang, C.; Kimball, S. D.; Main, A. J.; Sun, W.; Yang, Q.; Nouraldeen, A.; Yu, X.-Q.; Buxton, E.; Patel, S.; Nguyen, N.; Swaffield, J.; Powell, D. R.; Wilson, A.; Liu, Q. *J. Med. Chem.,* **2008**, *51*, 3684.

Tetrahydro-2*H*-pyran-4-carbaldehyde (22b)



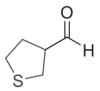
General procedure A was followed using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]- dec-1-ene (74 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (0−15% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (23 mg, 48%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.68 (d, J = 1.0 Hz, 1H, HCO), 4.00− 3.92 (m, 2H, OCH_a+OCH_b), 3.48 (ddd, J = 11.5, 10.7, 2.6 Hz, 2H, $OCH_{a'}$ + $OCH_{b'}$), 2.55−2.36 (m, 1H, HCOCH), 1.89−1.83 (m, 2H, OCH_c + OCH_d), 1.70 (dtd, J = 13.7, 10.7, 4.2 Hz, 2H, $OCH_{c'}$ + $OCH_{d'}$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 203.0 (HCO), 66.8 (C_a+C_b), 46.9 (HCOCH), 25.8 (C_c+C_d); LRMS (ESI, m/z) 115.2 ([M + H]$^+$, 100); IR max (film) ν: 2968, 1879, 1720, 1279, 1201, 1135, 1080, 924 cm−1. The data presented are consistent with literature precedent.[142]

Tetrahydro-2*H*-thiopyran-4-carbaldehyde (22c)



General procedure A was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H2O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (29 mg, 56%). ^{1}H NMR (600 MHz, CDCl3) δ 9.59 (s, 1H, *H*CO), 2.67 (dt, *J* = 10.2, 3.6 Hz, 4H, SC*H*$_2$), 2.34 – 2.22 (m, 3H, HCOC*H* + C*H*$_a$ + C*H*$_b$), 1.75 (dtd, *J* = 14.3, 10.2, 4.5 Hz, 2H, C*H*$_{a'}$+ C*H*$_{b'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.3 (H*C*O), 49.3 (HCOC*H*), 27.6 (S*C*H$_2$), 27.2 (*C*$_a$ + *C*$_b$); HRMS (ESI) calcd for $C_6H_{11}OS^+$ [M+H]$^+$: 131.0528, found 131.0531. IR max (film) ν: 2918, 2849, 2369, 1724, 1239, 1130, 1088, 983 cm-1. The data presented are consistent with literature precedent.[143]

Tetrahydrothiophene-3-carbaldehyde (22d)



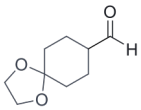
General procedure A was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 eq.) and formaldehyde (0.16 mL, 37 wt% in H_2O, 2.0 mmol, 10 eq.). A NMR 85% yield was calculated using 1,3,5-trimethoxybenzene (11mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified via flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless volatile oil (17 mg, 75%) with less than 10% of dichloromethane. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (d, J = 1.3 Hz, 1H, HCO), 3.16 (dd, J = 10.9, 5.0 Hz, 1H, SCH_cCH), 3.09 – 3.04 (m, 1H, HCOCH), 2.98 (dd, J = 10.9, 7.0 Hz, 1H, SCH_cCH), 2.91 – 2.85 (m, 1H, SCH_bCH2) J = 12.7, 5.9 Hz, 1H, $CHCH_a$), 2.12 (dq, J = 13.4, 6.9 Hz, 1H, $CHCH_{a'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 201.3 (H*C*O), 55.1 (HCO*C*H), 31.1 (*C*$_c$), 30.9 (*C*$_b$), 30.5 (*C*$_a$). LRMS (ESI, m/z) 117.1

[142] Kazem Shiroodi, R.; Dudnik, A. S.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 6928.

[143] Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. *Angew. Chem. Int. Ed.,* **2017**, *56*, 11958.

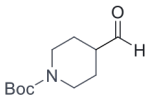
([M+H]$^+$, 100%). IR max (film) ν: 2944, 1720, 1416, 1235, 1028, 956 cm-1. The data presented are consistent with literature precedent.[144]

1,4-Dioxaspiro[4.5]decane-8-carbaldehyde (22e)



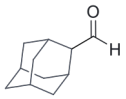
General procedure A was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.48.25]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 eq.) and formaldehyde (0.3 mL, 37 wt% in H2O, 4 mmol, 10 eq.). The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless volatile oil (44 mg, 65%) ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.3 Hz, 1H, *H*CO), 3.94 (dd, *J* = 5.3, 3.4 Hz, 4H, OCH_2CH_2O), 2.25 (ttd, *J* = 9.7, 4.1, 1.4 Hz, 1H, HCOC*H*), 1.97 – 1.91 (m, 2H, CH_c + CH_d), 1.80 – 1.71 (m, 4H, C$H_{c'}$ + C$H_{d'}$ + CH_e + CH_f), 1.61 – 1.56 (m, 2H, CH_e + CH_f); ^{13}C NMR (151 MHz, $CDCl_3$) δ 204.2 (H*C*O), 108.2 (O*C*O), 64.5 (C_a), 64.5 (C_b), 48.4 (HCO*C*H), 33.5 (C_c + C_d), 23.4 (C_e + C_f). LRMS (ESI, m/z) 171.4 ([M+H]$^+$, 100%). IR max (film) ν: 2949, 1722, 1447, 1362, 1239, 1142, 1104, 1033, 948, 881 cm-1. The data presented are consistent with literature precedent.[145]

^{t}Butyl 4-formylpiperidine-1-carboxylate (22f)



General procedure A was followed using *tert*-butyl 3-meth-oxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 eq.) and formaldehyde (0.16 mL, 37 wt% in H_2O, 2.0 mmol, 10 eq.). A NMR 58% yield was calculated using 1,3,5-trimethoxybenzene (11mg, 0.066 mmol, 0.33 eq.) as an internal standard. The crude mixture was purified *via* flash column chromatography (0 – 20% EtOAc in petroleum ether) to give the titled product as a colourless oil (21 mg, 49%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (s, 1H, *H*CO), 3.97 (br s, 2H, NCH_c + NCH_d), 3.02 – 2.81 (m, 2H, NC$H_{c'}$ + NC$H_{d'}$), 2.47 – 2.36 (m, 1H, HCOC*H*), 1.98 – 1.80 (m, 2H, CH_a + CH_b), 1.59 – 1.50 (m, 2H, C$H_{a'}$ + C$H_{b'}$), 1.44 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.1 (H*C*O), 154.8 (N*C*OO), 79.8 (*C*(CH$_3$)$_3$), 48.1 (HCO*C*H), 43.0 (br, C_c + C_d), 28.5 (C(*C*H$_3$)$_3$), 25.3 (C_a + C_b). LRMS (ESI, m/z) 214.3 ([M+H]$^+$, 100%). IR max (film) ν: 2927, 1726, 1688, 1418, 1365, 1273, 1232, 1168, 1128, 958, 864, 769 cm-1. The data presented are consistent with literature precedent.[146]

Adamantane-2-carbaldehyde (22h)



General procedure A was followed using 5′ -methoxy-5′ -methyl-5′ H-spiro[adamantane-2,2′ - [1,3,4]oxadiazole] (94 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (0 − 20% EtOAc in petroleum ether) to give the

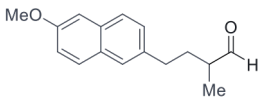
[144] Boehm, J., Charles; Busch-Petersen, J.; Fu, W.; Jin, Q.; Kerns, J. K.; Li, H.; Lin, G.; Lin, X.; Neipp, C. E. *Indole Carboxamides as IKK2 Inhibitors. WO2008118724 (A1)*, **2008**.

[145] Tseng, C.-C.; Noordali, H.; Sani, M.; Madhani, M.; Grant, D. M.; Frenneaux, M. P.; Zanda, M.; Greig, I. R. *J. Med. Chem*., **2017**, *60*, 2780.

[146] Vallone, A.; D'Alessandro, S.; Brogi, S.; Brindisi, M.; Chemi, G.; Alfano, G.; Lamponi, S.; Lee, S. G.; Jez, J. M.; Koolen, K. J. M.; Dechering, K. J.; Saponara, S.; Fusi, F.; Gorelli, B.; Taramelli, D.; Parapini, S.; Caldelari, R.; Campiani, G.; Gemma, S.; Butini, S. *Eur. J. Med. Chem.,* **2018**, *150*, 698.

titled product as a white solid (45 mg, 68%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.73 (s, 1H, HCO), 2.44−2.37 (m, 3H, HCOCH + HCOCHCH), 2.01−1.67 (m, 12H, CH_b + CH_c + CH_d); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.1 (HCO), 56.7 (HCOCH), 38.0 (C_b), 37.2 (C_d), 33.7 ($C_{b'}$), 28.3 (C_a), 28.0 (C_c), 27.6 ($C_{c'}$); HRMS (ESI) calcd for $C_{11}H_{17}O^+$ $[M + H]^+$ 165.1274, found 165.1271; IR max (film) ν: 2936, 2896, 1752, 1463, 1190, 1076, 912 cm^{-1}; mp 164−166 °C. The data presented are consistent with literature precedent.[147]

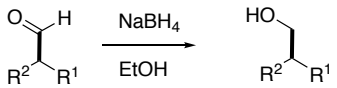
4-(6-Methoxynaphthalen-2-yl)-2-methylbutanal (22j)



General procedure A was followed using 2-methoxy-5-(2-(6-methoxynaph-thalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (126 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (0 − 20% EtOAc in petroleum ether) to give the titled product as a transparent oil (55 mg, 57%) together with 7% of oxidized carboxylic acid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (d, J = 1.8 Hz, 1H, HCO), 7.68 (dd, J = 8.5, 3.4 Hz, 2H, H_{Ar}), 7.55 (d, J = 1.8 Hz, 1H, H_{Ar}), 7.30 (dd, J = 8.4, 1.8 Hz, 1H, H_{Ar}), 7.16−7.10 (m, 2H, H_{Ar}), 3.92 (s, 3H, OCH_3), 2.88−2.75 (m, 2H, HCOCH + $ArCH_a$), 2.41 (qd, J = 6.9, 1.8 Hz, 1H, $ArCH_{a'}$), 2.19−2.10 (m, 1H, $ArCH_2CH_b$), 1.78−1.70 (m, 1H, $ArCH_2CH_{b'}$), 1.18 (d, J = 7.1 Hz, 3H, $CHCH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 205.0 (HCO), 157.4 (C_{Ar}), 136.6 (C_{Ar}), 133.2 (C_{Ar}), 129.2 (C_{Ar}), 129.0 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 119.0 ($C_{Ar}H$), 105.8 ($C_{Ar}H$), 55.3 (OCH_3), 45.6 (HCOCH), 33.0 (C_a), 32.1 (C_b), 13.4 ($CHCH_3$); HRMS (ESI) calcd for $C16H19O2^+$ $[M + H]^+$ 243.1385, found 243.1386; IR max (film) ν: 2933, 1721, 1634, 1606, 1483, 1390, 1264, 1229, 1031, 850 cm^{-1}.

[147]Madder, A.; Sebastian, S.; Van Haver, D.; De Clercq, P. J.; Maskill, H. *J. Chem. Soc.,* Perkin Trans. 2 **1997**, *2*, 2787.

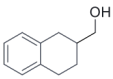
9.3.2. General procedure B: synthesis of alcohol derivatives 23



23a-p

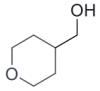
The reaction slug from general procedure A was directly collected into a round-bottom flask containing $NaBH_4$ (10 equiv) in EtOH (0.5 mmol/mL) and stirred for a further 1 h. The resulting mixture was then quenched with ice−water, extracted with ethyl acetate (2 × 20 mL), and washed with brine (2 × 20 mL). The organic phase was combined, dried over MgSO4, filtered, and concentrated under reduced pressure. The remaining residue was purified via flash column chromatography with appropriate eluents to give the desired alcohol.

(1,2,3,4-Tetrahydronaphthalen-2-yl)methanol (23a)



General procedure B was followed using 5-methoxy-5-methyl-3,4-dihydro-1H,5′H-spiro[naphthalene-2,2-[1,3,4]oxadiazole] (92 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (39 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (app. p, J = 2.2 Hz, 4H, H_{Ar}), 3.69−3.59 (m, 2H, $HOCH_2$), 2.93−2.79 (m, 3H, $ArCH_2CH$ + $ArCH_a$), 2.52 (dd, J = 16.3, 10.7 Hz, 1H, $ArCH_{a'}$), 2.06−1.95 (m, 2H, $ArCH_2CH_2$), 1.55− 1.39 (m, 2H, $HOCH_2CH$ + CH_2OH); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.8 (C_{Ar}), 136.0 (C_{Ar}), 129.3 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 67.8 ($HOCH_2$), 37.1 ($HOCH_2CH$), 32.5 ($ArCH_2$), 28.8 (C_a), 26.0 ($ArCH_2CH_2$); HRMS (ESI) calcd for $C_{11}H_{14}ONa^+$ $[M + Na]^+$ 185.0937, found 185.0931; IR max (film) ν: 3370, 2918, 1494, 1453, 1436, 1065, 1022, 900 cm^{-1}. The data presented are consistent with literature precedent.[148]

(Tetrahydro-2H-pyran-4-yl)methanol (23b)

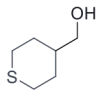


General procedure B was followed using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]-dec-1-ene (74 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (25 mg, 53%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.99 (ddt, J = 11.5, 4.6, 1.1 Hz, 2H, OCH_a + OCH_b), 3.51 (d,J=6.5Hz,2H,$HOCH_2$),3.41(td,J=11.5,2.1Hz,2H, $OCH_{a'}$ + $OCH_{b'}$), 1.79−1.73 (m, 1H, $HOCH_2CH$), 1.68−1.64 (m, 2H, CH_c + CH_d), 1.38−1.32 (m, 2H, $CH_{c'}$ + $CH_{d'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 68.1 ($HOCH_2$), 67.8 (C_a + C_b), 37.7 ($HOCH_2CH$), 29.4 (C_c + C_d); LRMS (ESI, m/z) 115.3 ($[M - H]^-$,

[148] Jones, G. B.; Wright, J. M.; Plourde, G. W.; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc,.* **2000**, *122*, 1937.

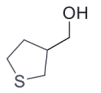
100); IR max (film) ν: 3368, 2918, 2847, 1652, 1443, 1235, 1140, 1031, 1012, 984, 849 cm^{-1}. The data presented are consistent with literature precedent.[149]

(Tetrahydro-2H-thiopyran-4-yl)methanol (23c)



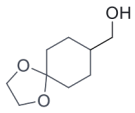
General procedure B was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (38 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.47 (d, J = 6.4 Hz, 2H, $HOCH_2$), 2.70 (ddd, J = 14.3, 11.9, 2.6 Hz, 2H, SCH_a + SCH_b), 2.64−2.58 (m, 2H, $SCH_{a'}$ + $SCH_{b'}$), 2.07 (dd, J = 13.5, 3.5 Hz, 2H, CH_c + CH_d), 1.59 (br s, 1H, OH), 1.57−1.48 (m, 1H, $HOCH_2CH$), 1.39 (dtd, J = 13.1, 11.8, 3.5 Hz, 1H, $CH_{c'}$ + $CH_{d'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 68.4 ($HOCH_2$), 40.2 ($HOCH_2CH$), 30.8 (C_a + C_b), 28.3 (C_c + C_d); HRMS (ESI) calcd for $C_6H_{13}O_{32}S^+$ $[M + H]^+$ 133.0682, found 133.0681; IR max (film) ν: 3584, 2924, 1454, 1422, 1273, 1036 cm^{-1}. The data presented are consistent with literature precedent.[150]

(Tetrahydrothiophene-3-yl)methanol (23d)



General procedure B was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). An 89% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. The crude mixture was purified via flash column chromatography (0 − 40% EtOAc in petroleum ether) to give the titled product as a colorless oil (18 mg, 77%) with less than 5% of ethyl acetate: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.64 (dt, J = 6.8, 3.5 Hz, 2H, $HOCH_2$), 2.94 (dd, J = 10.6, 6.8 Hz, 1H, SCH_cCH), 2.87 (ddd, J = 7.2, 5.9, 1.6 Hz, 2H, SCH_bCH_2 + $SCH_{b'}$ CH_2), 2.65 (dd, J = 10.6, 7.2 Hz, 1H, $SCH_{c'}$ CH), 2.44 (dpd, J = 8.3, 6.8, 5.5 Hz, 1H, $HOCH_2CH$), 2.12 (dq, J = 11.9, 5.7 Hz, 1H, $CHCH_a$), 1.85−1.71 (m, 2H, OH + $CHCH_{a'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 64.8 ($HOCH_2$), 46.7 ($HOCH_2CH$), 33.8 (C_c), 33.4 (C_d), 30.9 (C_a); LRMS (ESI, m/z) 117.3 ($[M - H]^-$, 100); IR max (film) ν: 3336, 2928, 2860, 2355, 1438, 1264, 1210, 1079, 1049, 1028, 967, 945, 885, 684 cm^{-1}. The data presented are consistent with literature precedent.[151]

(1,4-Dioxaspiro[4.5]decan-8-yl)metanol (23e)



General procedure B was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.48.25]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium

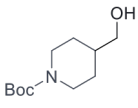
[149] Kazem Shiroodi, R.; Dudnik, A. S.; Gevorgyan, V. *J. Am. Chem. Soc.,* **2012**, *134*, 6928.

[150] Callahan, J. F.; Kerns, J. K.; Li, P.; Li, T.; McCleland, B. W.; Nie, H.; Pero, J. E.; Davies, T. G.; Grazia Carr, M.; Griffiths-Jones, C. M.; Heightman, T. D.; Norton, D.; Verdonk, M. L.; Woolford, A. J.- A.; Willems, H. M. G. *Biaryl Pyrazoles as NRF2 Regulators. WO2017/60854*, **2017**.

[151] Della, E. W.; Graney, S. D. *J. Org. Chem.,* **2004**, *69*, 3824.

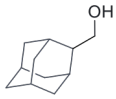
borohydride (152 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (52 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09−3.78 (m, 4H, OCH_2CH_2O), 3.46 (d, J = 6.5 Hz, 2H, $HOCH_2$), 1.86 (br s, 1H, HO), 1.78−1.73 (m, 4H, CH_c + CH_d), 1.52 (td, J = 13.5, 12.8, 4.6 Hz, 3H, $HOCH_2CH$ + $OCCH_a$ + $OCCH_b$), 1.26 (dtd, J = 13.5, 12.8, 11.7, 4.0 Hz, 2H, $OCCH_{a'}$ + $OCCH_{b'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 109.1 (OCO), 67.8 ($HOCH_2$), 64.2 (OCH_2CH_2O), 39.2 ($HOCH_2CH$), 34.2 (C_a + C_b), 26.7 (C_c + C_d); HRMS (ESI) calcd for $C_9H_{16}O_3Na^+$ $[M + Na]^+$ 195.0992, found 195.0987; IR max (film) ν: 3460, 2928, 2863, 1106, 1032, 928, 890 cm^{-1}. The data presented are consistent with literature precedent.[152]

^{t}Butyl 4-(Hydroxymethyl)piperidine-1-carboxylate (23f)



General procedure B was followed using tert-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10− 50% EtOAc in petroleum ether) to give the titled product as a colorless oil (23 mg, 53%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12 (br s, 2H, NCH_c + NCH_d), 3.56−3.44 (m, 2H, $HOCH_2CH$), 2.69 (br s, 2H, $NCH_{c'}$ + $NCH_{d'}$), 1.75−1.68 (m, 2H, CH_a + NCH_b), 1.66−1.59 (m, 1H, $HOCH_2CH$), 1.45 (s, 9H, $C(CH_3)_3$), 1.20−1.05 (m, 2H, $CH_{a'}$ + $CH_{b'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.0 (NCOO), 79.5 ($C(CH_3)_3$), 67.8 ($HOCH_2$), 43.8 (br, C_c + C_d), 39.0 ($HOCH_2CH$), 28.7 (br, C_a + C_b), 28.6 ($C(CH_3)_3$); HRMS (ESI) calcd for C11H22O3N+ $[M + H]^+$ 216.1594, found 216.1591; IR max (film) ν: 3455, 2974, 2924, 2857, 2355, 1693, 1669, 1424, 1366, 1313, 1274, 1247, 1168, 1087, 1039, 962, 864, 769 cm^{-1}. The data presented are consistent with literature precedent.[153]

(Adamantan-2-yl)methanol (23h)



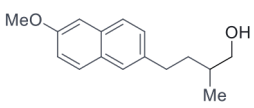
General procedure B was followed using 5-methoxy-5-methyl-5′H-spiro[adamantane-2,2-[1,3,4]oxadiazole] (94 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (50 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, J = 7.1 Hz, 2H, $HOCH_2$), 1.94−1.90 (m, 1H, $HOCH_2CH$), 1.89−1.84 (m, 4H, CH_b), 1.83−1.79(m, 3H, $CH_{b'}$ + CH_a), 1.79−1.77 (m, 1H, $CH_{a'}$), 1.75−1.72 (m, 2H, $CH_{b''}$), 1.57 (br s, 1H, CH_c), 1.55 (br s, 3H, $CH_{c'}$ + CH_d), 1.25 (br s, 1H, HO); ^{13}C NMR (151 MHz, $CDCl_3$) δ 65.3 ($HOCH_2$), 47.3 ($HOCH_2CH$), 39.1 (C_b), 38.2 (C_d), 31.9 ($C_{b'}$), 29.2 (C_a), 28.4 (C_c), 27.9 ($C_{c'}$); HRMS (ESI) calcd for $C_{11}H_{18}ONa+$ $[M + Na]^+$ 189.1250,

[152] Kitbunnadaj, R.; Hoffmann, M.; Fratantoni, S. A.; Bongers, G.; Bakker, R. A.; Wieland, K.; Jilali, A. e.; De Esch, I. J. P.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. *Bioorg. Med. Chem.*, **2005**, *13*, 6309.

[153] Renou, J.; Dias, J.; Mercey, G.; Verdelet, T.; Rousseau, C.; Gastellier,A.-J.;Arboleás,M.;Touvrey-Loiodice,M.;Baati,R.;Jean, L.; Nachon, F.; Renard, P.-Y. *RSC Adv.,* **2016**, *6*, 17929.

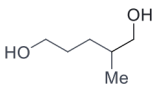
found 189.1247; IR max (film) ν: 3260, 2861, 2849, 1466, 1452, 1066, 1033, 1007, 971 cm^{-1}. The data presented are consistent with literature precedent.[154]

4-(6-Methoxynaphthalen-2-yl)-2-methylbutan-1-ol (23j)



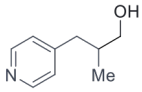
General procedure B was followed using 2-methoxy-5-(2-(6-methoxynaph-thalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (98 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a yellow oil (73 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.55 (s, 1H, H_{Ar}), 7.33 (dd, J = 8.3, 1.8 Hz, 1H, H_{Ar}), 7.14−7.09 (m, 2H, H_{Ar}), 3.91 (s, 3H, OCH_3), 3.56 (br s, 1H, $HOCH_c$), 3.54−3.51 (m, 1H, $HOCH_{c'}$), 2.89−2.79 (m, 1H, $ArCH_a$), 2.78−2.68 (m, 1H, $ArCH_{a'}$), 1.91−1.80 (m, 1H, CH_b), 1.76−1.66 (m, 1H, $CH_{b'}$), 1.61−1.50 (m, 2H, $HOCH_2CH$ + OH), 1.02 (d, J = 6.7 Hz, 3H, $CHCH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.3 (C_{Ar}), 137.9 (C_{Ar}), 133.1 (C_{Ar}), 129.2 (C_{Ar}), 129.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 118.6 ($C_{Ar}H$), 105.6 ($C_{Ar}H$), 68.2 (C_c), 55.3 (OCH_3), 35.3 (C_a), 34.9 (C_b), 33.2 ($HOCH_2CH$), 16.5 ($CHCH_3$); HRMS (ESI) calcd for $C_{16}H_{20}O_2^+$ $[M + H]^+$ 244.1467, found 244.1463; IR max (film) ν: 3342, 2961, 2926, 2850, 1634, 1604, 1484, 1462, 1391, 1263, 1228 cm^{-1}.

2-Methylpentane-1,5-diol (23k)



General procedure B was followed using 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)-propan-1-ol (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (2% MeOH in dichloromethane) to give the titled product as a colorless oil (16 mg, 66%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60 (t, J = 6.1 Hz, 2H, $HOCH_2CH_2$), 3.48−3.36 (m, 2H, $HOCH_2CH$), 3.16 (br s, 2H, OH), 1.66−1.56 (m, 2H, $HOCH_2CH_2$), 1.54−1.45 (m, 2H, $CH_2CH_2CHCH_3$), 1.16−1.06 (m, 1H, $CHCH_3$), 0.88 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 67.8 ($HOCH_2CH_2$), 62.8 ($HOCH_2CH$), 35.4 ($HOCH_2CH_2$), 29.7 ($CH_2CH_2CHCH_3$), 29.1 ($CHCH_3$), 16.7 (CH_3); HRMS (ESI) calcd for $C_6H_{15}O_2^+$ $[M + H]^+$ 119.1067, found 119.1066; IR max (film) ν: 3291, 2932, 2869, 1652, 1455, 1418, 1377, 1104, 1038, 940, 897, 731 cm^{-1}. The data presented are consistent with literature precedent.[155]

2-Methyl-3-(pyridin-4-yl)propan-1-ol (23l)

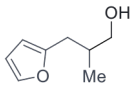


General procedure B was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (88 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column

[154] Kawamoto, T.; Fukuyama, T.; Ryu, I. *J. Am. Chem. Soc.*, **2012**, *134*, 875.
[155] Jackson, W.; Moffat, M.; Perlmutter, P.; Tasdelen, E. *J. Chem.,* **1992**, *45*, 823.

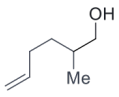
chromatography (30 − 70% EtOAc in petroleum ether) to give the titled product as a transparent oil (30 mg, 50%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (br s, 2H, H_{Ar}), 7.12 (d, J = 4.9 Hz, 2H, H_{Ar}), 3.51 (dd, J = 5.9, 1.0 Hz, 2H, $HOCH_2$), 2.81 (dd, J = 13.4, 6.0 Hz, 1H, CH_a), 2.40 (dd, J = 13.4, 8.4 Hz, 1H, $CH_{a'}$), 2.03−1.93 (m, 1H, $HOCH_2CH$), 1.75 (br s, 1H, OH), 0.91 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2 ($C_{pyridine}H$), 149.6 ($C_{pyridine}H$), 124.8 ($C_{pyridine}H$), 67.2 (HOCH), 39.0 (Ca), 7.2 ($HOCH_2CH$), 16.4 ($CHCH_3$); HRMS (ESI) calcd for $C_9H_{14}NO^+$ $[M + H]^+$ 152.1071, found 152.1075; IR max (film) ν: 3353, 2924, 2348, 2185, 1605, 1043 cm^{-1}. The data presented are consistent with literature precedent.[156]

3-(Furan-2-yl)-2-methylpropan-1-ol (23m)



General procedure B was followed using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (84 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (152 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (34 mg, 60%): ^{1}H NMR (600 MHz, CDCl3) δ 7.31 (dd, J = 1.9, 0.9 Hz, 1H,H_{Furan}),6.29(dd,J=3.2,1.9Hz,1H, H_{Furan}), 6.02(dd,J=3.2, 0.9 Hz, 1H, H_{Furan}), 3.50 (d, J = 6.0 Hz, 2H, $HOCH_2$), 2.73 (dd, J = 14.9, 6.4 Hz, 1H, CH_a), 2.54 (dd, J = 14.9, 7.4 Hz, 1H, $CH_{a'}$), 2.03 (dq, J = 13.2, 6.4 Hz, 1H, $HOCH_2CH$), 1.46 (br s, 1H, OH), 0.94 (d, J = 6.8 Hz, 3H, $CHCH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.7 (C_{Furan}), 141.2 ($C_{Furan}H$), 110.3 ($C_{Furan}H$), 106.3 ($C_{Furan}H$), 67.6 ($HOCH_2$), 35.4 (C_a), 31.5 ($HOCH_2CH$), 16.5 ($CHCH_3$); HRMS (ESI) calcd for $C_8H_{11}O_2^-$ $[M - H]^-$ 139.0754, found 139.0753; IR max (film) ν: 3342, 2919, 1595, 1507, 1460, 1381, 1146, 1033, 927 cm^{-1}. The data presented are consistent with literature precedent.[157]

2-Methylhex-5-en-1-ol (23n)

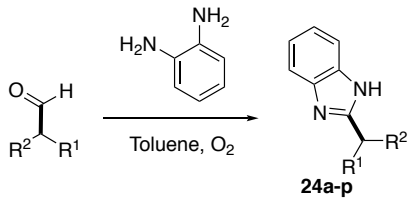


General procedure B was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-ox-adiazole (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). An 88% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. The crude mixture was purified via flash column chromatography (0 − 40% EtOAc in petroleum ether) to give the titled product as a colorless oil (16 mg, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H, CH_2=CH), 5.02 (dd, J = 17.0, 1.9 Hz, 1H, H_b), 4.95 (dd, J = 10.2, 1.9 Hz, 1H, H_a), 3.48 (ddd, J = 45.3, 10.5, 6.1 Hz, 2H, $CHCH_2OH$), 2.18−2.09 (m, 1H, CH2=$CHCH_c$), 2.09−1.99 (m, 1H, CH2=$CHCH_{c'}$), 1.70−1.60 (m, 1H, $CH_2CHdCHCH_3$), 1.58−1.47 (m, 1H, $CH_2CH_{d'}$ $CHCH_3$), 1.33 (br s, 1H, OH), 1.28−1.16 (m, 1H, $CHCH_3$), 0.93 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.0 (CH_2=CH), 114.6 (CH_2=CH), 68.3 ($CHCH_2OH$), 35.4 (C_c), 32.4 (C_d), 31.3 ($CHCH_3$),

[156] Nacsa, E. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.,* **2018**, *140*, 3322.
[157] Harmata, M.; Gamlath, C. B.; Barnes, C. L.; Jones, D. E. *J. Org. Chem.,* **1995**, *60*, 5077.

16.6 (CH_3); LRMS (ESI, m/z) 113.5 ([M + H]$^+$, 100); IR max (film) ν: 3436, 2969, 2355, 2316, 1448, 1329, 1046 cm^{-1}. The data presented are consistent with literature precedent.[158]

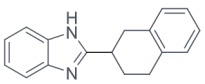
9.3.3. General procedure C: synthesis of benzimidazoles derivatives 24



24a-p

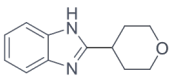
The reaction slug from general procedure A was collected into a round-bottom flask containing a biphasic solution of brine and toluene with stirring. Upon resting, the toluene phase was syringed out and injected into another open round-bottom flask charged with freshly activated 4 Å molecular sieves. The mixture was stirred for another 1 min before o-phenylenediamine (1.5 equiv) was added. The reaction mixture was then bubbled with one O_2 balloon and stirred at room temperature (30 °C) for 12 h. Molecular sieves were filtered over filter paper, and the filtrate was concentrated under vacuum before being purified via flash chromatography with appropriate eluent combinations to afford the final benzimidazole derivatives.

2-(1,2,3,4-Tetrahydronaphthalen-2-yl)-1H-benzimidazole (24a)



General procedure C was followed using 5-methoxy-5-methyl-3,4-dihydro-1H,5′ H-spiro[naphthalene-2,2-[1,3,4]oxadiazole] (46 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (36 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.06 (br s, 1H, NH), 7.76 (br s, 1H, H_{Ar}), 7.40 (br s, 1H, H_{Ar}), 7.24 (d, J = 5.5 Hz, 2H, H_{Ar}), 7.29−7.13 (m, 4H, H_{Ar}), 3.41 (tdd, J = 10.3, 5.5, 3.1 Hz, 1H, CCH), 3.35−3.20 (m, 2H, $ArCH_2CH$), 2.97 (qp, J = 10.3, 5.5 Hz, 2H, $ArCH_2CH_2$), 2.48− 2.37 (m, 1H, $CHCH_{a'}$), 2.14 (dtd, J = 13.0, 10.3, 6.2 Hz, 1H, $CHCH_{c'}$); ^{13}C NMR (151 MHz, methanol-d_4) δ 159.8 (C_{Ar}), 136.8 (C_{Ar}), 136.1 (C_{Ar}), 130.0 ($C_{Ar}H$), 129.9 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 123.3 ($C_{Ar}H$), 115.4 (br, $C_{Ar}H$), 36.7 (CCH), 35.4 ($ArCH_2CH$), 30.0 ($ArCH_2CH_2$), 29.6 (C_a); One aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{17}H_{17}N_2^+$ [M + H]$^+$ 249.1387, found 249.1392; IR max (film) ν: 2921, 1423, 1275, 1009, 993, 932, 743 cm^{-1}. mp: 239−241 °C.

2-(Tetrahydro-2H-pyran-4-yl)-1H-benzimidazole (24b)

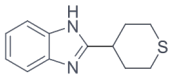


General procedure C was followed using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]dec-1-ene (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o- phenylenediamine (32 mg,

[158] Peram, P. S.; Vences, M.; Schulz, S. *Org. Biomol. Chem.,* **2017**, *15*, 6967.

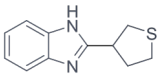
0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a transparent oil (31 mg, 76%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.51 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 7.19 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 4.06 (dt, J = 11.5, 3.3 Hz, 2H, OCH_c + OCH_d), 3.65−3.53 (m, 2H, $OCH_{c'}$ + $OCH_{d'}$), 3.24−3.15 (m, 1H, CCH), 2.04−1.92 (m, 4H, CH_a + OCH_b); ^{13}C NMR (151 MHz, Methanol-d_4) δ 159.0 (C_{Ar}), 123.3 (C_{Ar}H), 115.2 (br, C_{Ar}H), 68.6 (C_c + C_d), 36.8 (CCH), 32.4 (C_a + C_b); one aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{12}H_{15}N_2O^+$ $[M + H]^+$ 203.1181, found 203.1184; IR max (film) ν: 2958, 2922, 2852, 1457, 1427, 1128, 739 cm^{-1}. mp: 225−227 °C.

2-(Tetrahydro-2H-thiopyran-4-yl)-1H-benzimidazole (24c)



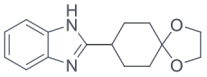
General procedure C was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (40 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o- phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (24 mg, 55%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.51 (br s, 2H, H_{Ar}), 7.20 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 4.59 (s, 1H, NH), 3.00 (ddd, J = 12.0, 8.7, 3.3 Hz, 1H, CCH), 2.92−2.85 (m, 2H, SCH_c + SCH_d), 2.73 (d, J = 14.0 Hz, 2H, $SCH_{c'}$ + $SCH_{b'}$), 2.37 (dd, J = 13.6, 3.1 Hz, 2H, CH_a + CH_b), 2.06 (qd, J = 12.5, 3.2 Hz, 2H, CH_a + CH_b); ^{13}C NMR (151 MHz, methanol-d_4) δ 159.7 (C_{Ar}), 123.3 (br, C_{Ar}H), 39.5 (CCH), 33.8 (C_a + C_b), 29.2 (C_c + C_d); two aromatic carbons are not seen in the ^{13}C NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{12}H_{15}N_2S^+$ $[M + H]^+$ 219.0956, found 219.0955; IR max (film) ν: 3394, 2924, 1709, 1432, 1274, 1047, 951, 744 cm^{-1}; mp 220−222 °C.

2-(Tetrahydrothiophene-3-yl)-1H-benzimidazole (24d)



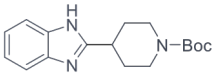
General procedure C was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (38 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o- phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 72%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.55−7.38 (m, 2H, H_{Ar}), 7.21−7.13 (m, 2H, H_{Ar}), 3.60 (ddd, J = 15.8, 9.7, 6.3 Hz, 1H, CCH), 3.23 (dd, J = 10.4, 6.9 Hz, 1H, $CCHCH_a$), 3.14 (dd, J = 10.4, 9.3 Hz, 1H, $CCHCH_{a'}$), 2.98 (dd, J = 8.4, 5.0 Hz, 2H, SCH_2CH_2), 2.52 (dt, J = 10.4, 5.1 Hz, 1H, $CCHCH_b$), 2.36−2.26 (m, 1H, $CCHCH_{b'}$); ^{13}C NMR (151 MHz, methanol-d_4) δ 156.4 (C_{Ar}), 123.4 (C_{Ar}H), 115.4 (br, C_{Ar}H), 45.0 (CCH), 37.0 (C_b), 36.0 (C_a), 31.2 (SCH_2CH_2); one aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{11}H_{13}N_2S^+$ $[M + H]^+$ 205.0805, found 205.0799; IR max (film) ν: 2923, 2356, 2348, 2158, 2034, 1420, 740 cm^{-1}; mp 242−244 °C.

2-(1,4-Dioxaspiro[4.5]decan-8-yl)-1H-benzimidazole (24e)



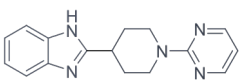
General procedure C was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.48.25]tetradec-1-ene (51 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (41 mg, 80%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2H, H_{Ar}), 7.20 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 4.01–3.90 (m, 4H, OCH_2CH_2O), 3.02 (tt, J = 11.8, 3.7 Hz, 1H, CCH), 2.21–2.13 (m, 2H, $CHCH_a$ + $CHCH_b$), 2.07–1.97 (m, 2H, $CHCH_{a'}$ + $CHCH_{b'}$), 1.90–1.83 (m, 2H, CCH_c + CCH_d), 1.68 (td, J = 13.2, 4.3 Hz, 2H, $CCH_{c'}$ + $CCH_{d'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.9 (C_{Ar}), 122.4 ($C_{Ar}H$), 114.8 (br, $C_{Ar}H$), 108.1 (OCO), 64.5 (C_e), 64.4 (C_f), 37.3 (CCH), 34.4 (C_c + C_d), 29.2 (C_a + C_b); one aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2^+$ $[M + H]^+$ 259.1457, found 259.1447; IR max (film) ν: 2988, 2945, 1678, 1588, 1402, 1344, 1249, 1219, 1089, 1013, 967, 838, 735 cm^{-1}; mp 230–232 °C.

^{t}Butyl 4-(1H-Benzimidazol-2-yl)piperidine-1-carboxylate (24f)



General procedure C was followed using tert-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (30 mg, 49%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (br s, 1H, NH), 7.71 (br s, 1H, H_{Ar}), 7.41 (br s, 1H, H_{Ar}), 7.22 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 4.23 (br s, 2H, NCH_c + NCH_d), 3.10 (tt, J = 11.8, 3.8 Hz, 1H, CCH), 2.89 (br s, 2H, $NCH_{c'}$ + $NCH_{d'}$), 2.13–2.04 (m, 2H, CH_a + CH_b), 1.85 (qd, J = 12.2, 4.3 Hz, 2H, $CH_{a'}$ + $CH_{b'}$), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.0 (C_{Ar}), 154.9 ($NCOOC(CH_3)_3$), 143.2 (br, C_{Ar}), 122.5 (br, $C_{Ar}H$), 119.1 (br, $C_{Ar}H$), 110.7 (br, $C_{Ar}H$), 80.0 ($C(CH_3)_3$), 44.1 (br, C_c + C_d), 37.1 (CCH), 30.9 (br, C_a + C_b), 28.6 ($C(CH_3)_3$); HRMS (ESI) calcd for $C_{17}H_{24}O_2N_3^+$ $[M + H]^+$ 302.1869, found 302.1869; IR max (film) ν: 2976, 1692, 1536, 1425, 1366, 1272, 1231, 1166, 1123, 980, 861, 768, 742 cm^{-1}; mp 226–228 °C.

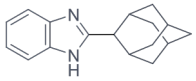
2-[1-(Pyrimidin-2-yl)piperidin-4-yl]-1H-benzimidazole (24g)



General procedure C was followed using 3-methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (55 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 – 40% EtOAc in petroleum ether) to give the titled product as a white solid (40 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (br s, 1H, NH), 8.30 (d, J = 4.6 Hz, 2H, $H_{pyrimidine}$), 7.54 (br s, 2H, H_{Ar}), 7.22 (dd, J = 5.9, 3.1 Hz, 2H, H_{Ar}), 6.47 (t, J = 4.6 Hz, 1H, $H_{pyrimidine}$), 4.86 (d, J = 13.5 Hz, 2H, NCH_c + NCH_d), 3.22 (tt, J = 11.8, 3.7 Hz, 1H, CCH), 3.10–2.99 (m, 2H, $NCH_{c'}$ + $NCH_{d'}$), 2.19 (d, J = 11.3 Hz, 2H, CH_a + CH_b), 1.92 (qd, J = 12.4, 3.9 Hz, 2H, $CH_{a'}$ + $CH_{b'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.7 ($C_{pyrimidine}$), 157.9 ($C_{pyrimidine}H$),

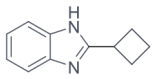
157.2 (C_{Ar}), 122.6 (br, $C_{Ar}H$), 110.0 ($C_{pyrimidine}H$), 43.9 (C_c + C_d), 37.3 (CCH), 30.7 (C_a + C_b); two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{16}H_{18}N_5^+$ $[M + H]^+$ 280.1557, found 280.1546; IR max (film) ν: 2936, 2346, 1982, 1584, 1541, 1518, 1481, 1456, 1426, 1358, 1304, 1272, 1233, 1105, 1050, 977, 798, 741 cm^{-1}; mp 222−224 °C.

2-(Adamantan-2-yl)-1H-benzimidazole (24h)



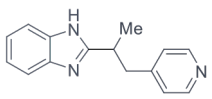
General procedure C was followed using 5-methoxy-5-methyl-5′ H-spiro[adamantane-2,2-[1,3,4]oxadiazole] (47 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a dark yellow solid (40 mg, 79%): ^1H NMR (600 MHz, $CDCl_3$) δ 7.57 (br s, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 3.27 (s, 1H, CCH), 2.66−2.59 (m, 2H, CH_a), 2.08−1.94 (m, 7H, CH_c + C_b), 1.87−1.86 (m, 1H, $CH_{c'}$), 1.83 (br s, 2H, C_d), 1.77−1.70 (m, 2H, C_b); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.2 (C_{Ar}), 122.3 ($C_{Ar}H$), 44.6 (CCH), 38.4 (C_b), 37.6 (C_d), 33.1 ($C_{b'}$), 31.0 (C_a), 27.8 (C_c), 27.7 ($C_{c'}$); two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{17}H_{21}N_2^+$ $[M + H]^+$ 253.1705, found 253.1700; IR max (film) ν: 2922, 1422, 1275, 1009, 993, 743 cm^{-1}; mp 244−246 °C.

2-Cyclobutyl-1H-benzimidazole (24i)



General procedure C was followed using 7-methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (31 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (20 mg, 59%): ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, J = 6.0, 3.2 Hz, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 3.80 (p, J = 8.7 Hz, 1H, CCH), 2.58−2.47 (m, 2H, CH_a + CH_b), 2.47−2.38 (m, 2H, $CH_{a'}$ + $CH_{b'}$), 2.14−2.01 (m, 1H, CH_c), 1.99−1.91 (m, 1H, $CH_{c'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.1 (C_{Ar}), 138.6 (br, C_{Ar}), 122.3 ($C_{Ar}H$), 114.8 (br, $C_{Ar}H$), 34.3 (CCH), 28.2 (C_a + C_b), 18.8 (C_c); HRMS (ESI) calcd for $C_{11}H_{13}N_2^+$ $[M + H]^+$ 173.1073, found 173.1069; IR max (film) ν: 2942, 1537, 1455, 1419, 1328, 1272, 982, 740 cm^{-1}; mp 186−188 °C. The data presented are consistent with literature precedent.[159]

2-[1-(Pyridin-4-yl)propan-2-yl]-1H-benzimidazole (24l)

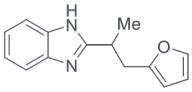


General procedure C was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (44 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and

[159] Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M. *Org. Lett*., **2018**, *20,* 3229.

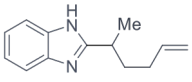
o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 100% EtOAc in petroleum ether) to give the titled product as a yellow solid (23 mg, 48%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (br s, 1H, NH), 8.40−8.36 (m, 2H, $H_{Pyridine}$), 7.73 (br s, 1H, H_{Ar}), 7.34 (br s, 1H, H_{Ar}), 7.23 (s, 2H, H_{Ar}), 7.00−6.98 (m, 2H, $H_{Pyridine}$), 3.35 (p, J = 7.0 Hz, 1H, CCH), 3.28 (dd, J = 13.4, 7.5 Hz, 1H, $CHCH_a$), 3.00 (dd, J = 13.4, 6.8 Hz, 1H, $CHCH_{a'}$), 1.47 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.3 (C_{Ar}), 149.5 ($C_{Pyridine}H$), 148.8 ($C_{Pyridine}$), 143.1 (br, C_{Ar}), 124.5 ($CP_{yridine}H$), 122.3 (br, $C_{Ar}H$), 110.5 (br, $C_{Ar}H$), 41.8 (C_a), 35.9 (CCH), 19.4 (CH_3). HRMS (ESI) calcd for $C_{15}H_{16}N_3^+$ $[M + H]^+$ 238.1344, found 238.1344; IR max (film) ν: 3051, 2969, 1603, 1559, 1535, 1484, 1454, 1419, 1328, 1272, 1219, 1110, 1070, 1043, 993, 907, 843, 795, 768, 747 cm^{-1}; mp 188− 190 °C.

2-[1-(Furan-2-yl)propan-2-yl]-1H-benzimidazole (24m)



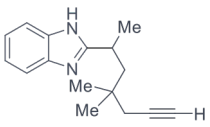
General procedure C was followed using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (42 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 2 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (34 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 7.30−7.27 (m, 1H, H_{Furan}), 7.23−7.18 (m, 2H, H_{Ar}), 6.24 (dd, J = 3.2, 1.9 Hz, 1H, H_{Furan}), 5.96 (d, J = 3.2 Hz, 1H, H_{Furan}), 3.51 (h, J = 7.1 Hz, 1H, CCH), 3.24 (dd, J = 15.0, 7.2 Hz, 1H, $CHCH_a$), 3.06 (dd, J = 15.0, 7.2 Hz, 1H, $CHCH_{a'}$), 1.48 (d, J = 7.0 Hz, 3H, $CHCH_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.1 (C_{Furan}), 153.3 (C_{Ar}), 141.5 ($C_{Furan}H$), 122.4 ($C_{Ar}H$), 115.1 (br, $C_{Ar}H$), 110.5 ($C_{Furan}H$), 107.1($C_{Furan}H$), 34.6 (C_a), 34.1 (CCH), 19.3 (CH_3); one aromatic carbon is not seen in the $^{13}C\{^{1}H\}$ NMR spectrum; HRMS (ESI+): m/z calcd for $C_{14}H_{15}N_2O^+$ $[M + H]^+$ 227.1177, found 227.1184; IR max (film) ν: 2921, 1423, 1275, 1009, 993, 932, 743 cm^{-1}; mp 180−182 °C.

2-(Hex-5-en-2-yl)-1H-benzimidazole (24n)



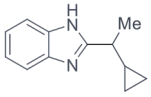
General procedure C was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv) and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.18 (br s, 1H, NH), 7.55 (br s, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 5.75 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H, CH_2=CH), 4.97 (dd, J = 17.0, 1.8 Hz, 1H, H_a), 4.93 (dd, J = 10.2, 1.8 Hz, 1H, H_b), 3.14 (h, J = 7.0 Hz, 1H, CCH), 2.14−2.05 (m, 2H, CH_2=$CHCH_2$), 2.04−1.97 (m, 1H, $CCHCH_c$), 1.85−1.77 (m, 1H, $CCHCH_{c'}$), 1.45 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3 (C_{Ar}), 137.9 (CH_2=CH), 122.3 ($C_{Ar}H$), 115.3 (CH_2CH), 35.6 (C_c), 34.2 (CCH), 31.6 (CH_2=$CHCH_2$), 19.8 (CH_3); two aromatic carbons are not seen in the ^{13}C NMR spectrum; HRMS (ESI) calcd for $C_{13}H_{17}N_2^+$ $[M + H]^+$ 201.1386, found 201.1379; IR max (film) ν: 3074, 2968, 2932, 2736, 1818, 1640, 1538, 1454, 1426, 1330, 1272, 989, 906, 745, 729 cm^{-1}; mp 182−185 °C.

2-(4,4-Dimethylhept-6-yn-2-yl)-1H-benzimidazole (24o)



General procedure C was followed using 2-(2,2-dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (45 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10 − 40% EtOAc in petroleum ether) to give the titled product as a white solid (19 mg, 39%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.68 (br s, 1H, NH), 7.71 (br s, 1H, H_{Ar}), 7.38 (br s, 1H, H_{Ar}), 7.21 (dd, J = 6.2, 2.9 Hz, 2H, H_{Ar}), 3.29−3.21 (m, 1H, $CCHCH_3$), 2.12 (dd, J = 14.4, 8.9 Hz, 1H, $CHCCH_b$), 2.07 (dd, J = 16.2, 3.2 Hz, 1H, $CHCCH_a$), 2.02−1.93 (m, 2H, $CHCCH_2$ + $CHCCH_{a'}$), 1.72 (dd, J = 14.4, 4.0 Hz, 1H, $CHCCH_{b'}$), 1.44 (d, J = 7.1 Hz, 3H, $CHCH_3$), 0.92 (d, J = 17.9 Hz, 6H, $C(CH_3)_2$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7 (C_{Ar}), 122.3 (br, $C_{Ar}H$), 110.7 (br, $C_{Ar}H$), 82.6 ($CHCCH_2$), 70.5 ($CHCCH_2$), 47.1 (C_b), 34.0 ($C(CH_3)_2$), 31.9 (C_a), 31.2 ($CCHCH_3$), 27.3 ($C(CH_3)_2$), 27.1 ($C(CH_3)_2$), 23.3 ($CCHCH_3$); one aromatic carbon is not seen in the ^{13}C NMR spectrum; HRMS (ESI) calcd for $C_{16}H_{21}N_2^+$ $[M + H]^+$ 241.1699, found 241.1690; IR max (film) ν: 3311, 2965, 2752, 2367, 1538, 1453, 1424, 1335, 1269, 994, 746 cm^{-1}; mp 191−192 °C.

2-(1-Cyclopropylethyl)-1H-benzimidazole (24p)

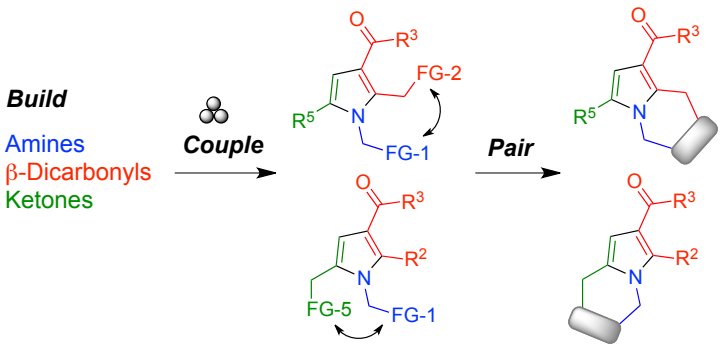


General procedure C was followed using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (34 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (26 mg, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.49 (br s, 1H, NH), 7.73 (br s, 1H, H_{Ar}), 7.41 (br s, 1H, H_{Ar}), 7.22 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 2.36 (dq, J = 9.6, 7.0 Hz, 1H, CCH), 1.56 (d, J = 7.0 Hz, 3H, CH_3), 1.10 (dddd, J = 13.0, 9.6, 8.0, 4.9 Hz, 1H, $CHCHCH_2$), 0.71−0.63 (m, 2H, CH_a + $CH_{a'}$), 0.44−0.38 (m, 1H, CH_b), 0.36−0.30 (m, 1H, $CH_{b'}$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.7 (C_{Ar}), 143.4 (br, C_{Ar}), 133.5 (br, C_{Ar}), 122.3 ($C_{Ar}H$), 119.4 (br, $C_{Ar}H$), 110.4 (br, $C_{Ar}H$), 39.5 (CCH), 19.0 (CH_3), 16.6 (CCHCH), 4.8 (C_a), 4.4 (C_b); HRMS (ESI) calcd for $C_{12}H_{15}N_2^+$ $[M + H]^+$ 187.1230, found 187.1221; IR max (film) ν: 2969, 2317, 2135, 1456, 1414, 1274, 1076, 744 cm^{-1}; mp 187−189 °C.

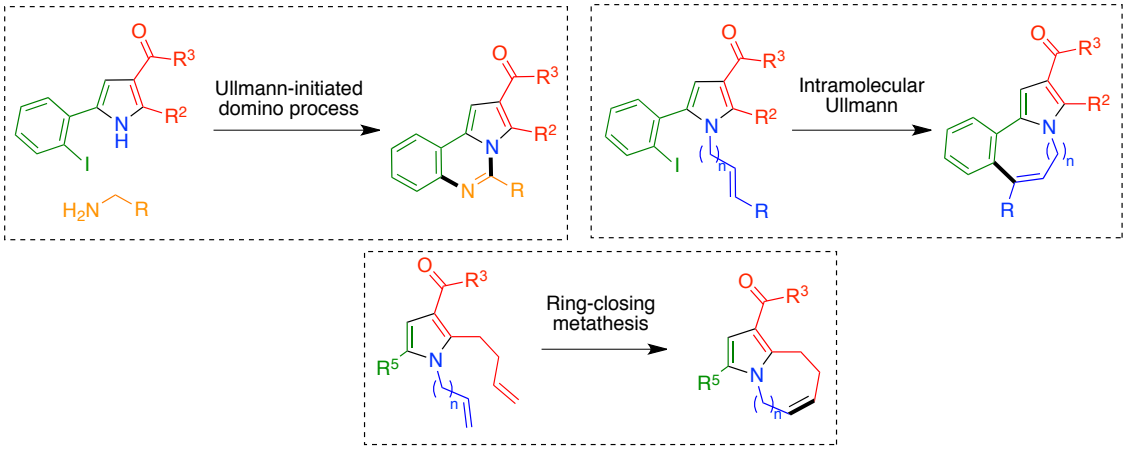
10. Conclusions

1. As a general conclusion, this thesis has proved that the *build-couple-pair* approach is suitable to construct DOS libraries using pyrrole, a well-known privileged structure, as the central core on which to generate molecular diversity and complexity.

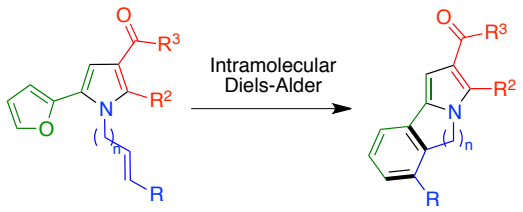
2. A mechanochemical multicomponent pyrrole synthesis related to the Hantzsch reaction is suitable for the preparation of pyrrole derivatives bearing at their N-1, C-2 and C-5 positions functional groups allowing suitable complexity-generating reactions at a later (*pair*) stage. The mechanochemical pyrrole synthesis was also suitable for the preparation of symmetrical molecules containing two pyrrole units at the end of a spacer.



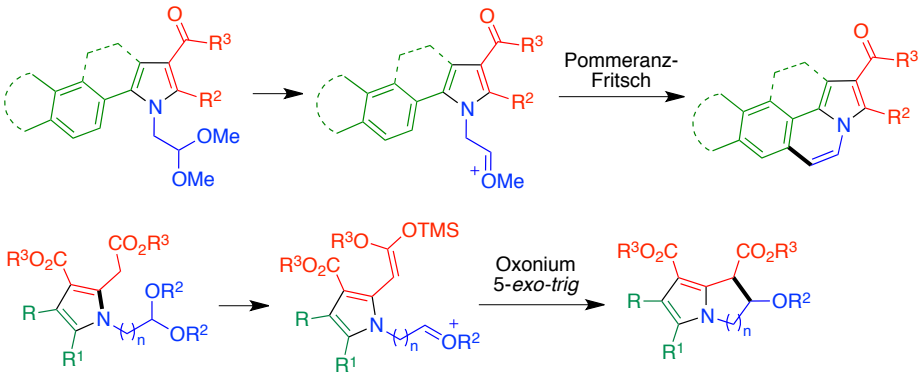
3. Some transition metal-catalyzed reactions were suitable to generate rings at the *pair* stage of our strategy, giving rise to pyrrolo[1,2-*c*]quinazoline, pyrrolo[2,1-*a*]isoquinoline and benzo[*c*]pyrrolo[1,2-*a*]azepine frameworks by application of an Ullmann-initiated domino process, ring-closing Heck reactions and ring-closing metathesis reactions, respectively.



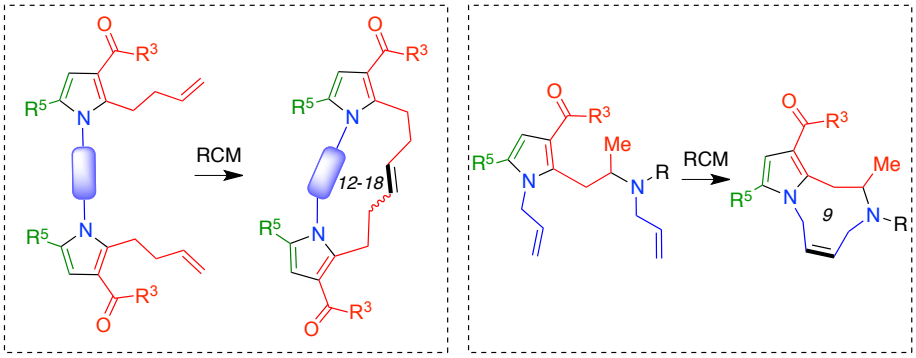
4. Pyrrolo[2,1-*a*]isoindole and pyrrolo[2,1-*a*]isoquinoline frameworks are readily available by intramolecular Diels-Alder reactions from 1-allyl(homoallyl)-5-(2-furyl)pyrroles.



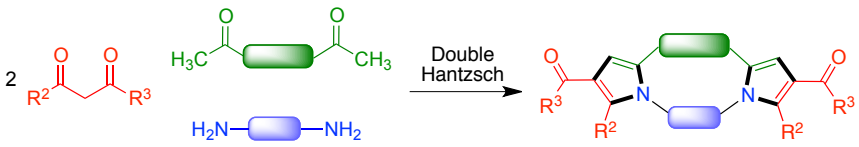
5. The generation of intermediate oxonium species from acetals *via* their treatment with Brønsted or Lewis acids is a good strategy to generate fused pyrroles by Pommeranz-Fritsch type cyclizations onto C-5 aryl substituents or by attack of a ketene acetal function concomitantly generated at C-2.



6. Ring-closing metathesis reactions, using as starting materials symmetrical bis-pyrrole derivatives bearing homoallyl chains or 1-allyl-2-allylaminoethylpyrroles allow the efficient construction of pyrrole-derived macrocycles or medium-sided rings.



7. Structurally unusual pyrrole-related macrocycles, including cyclophane structural fragments, are also readily available by means of double Hantzsch pyrrole syntheses, where one of these reactions serves as the macrocyclization event.



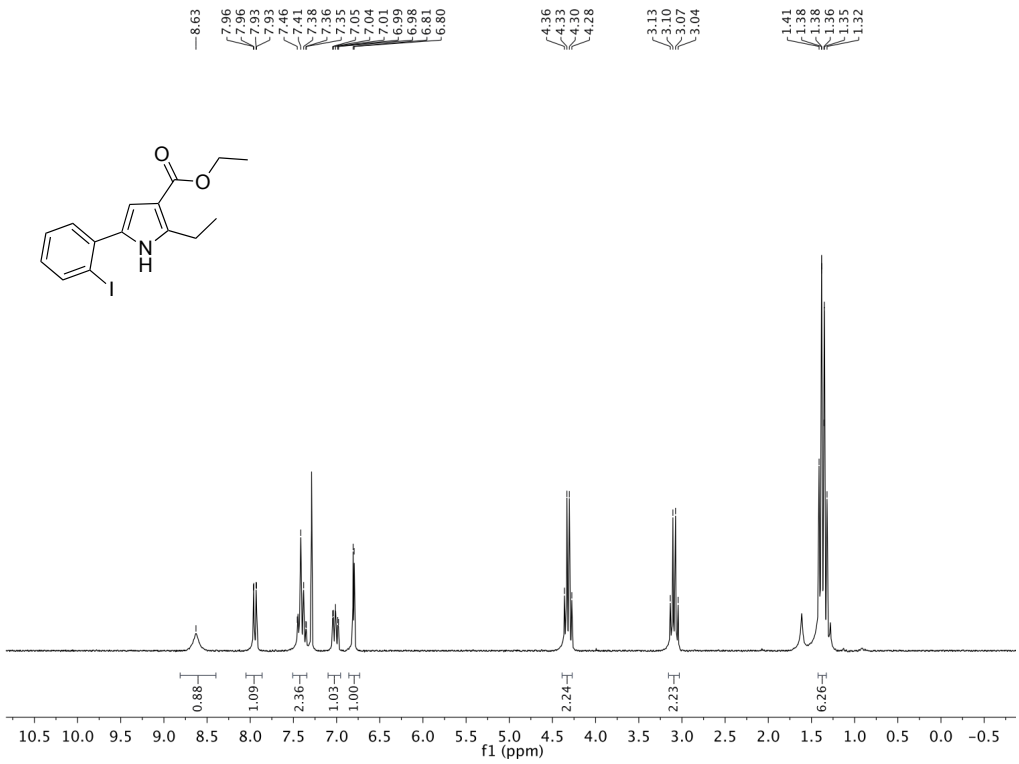
8. The DOS libraries synthesized by the above methods were assayed using high-throughput screening methodologies *via* the Lilly Open Innovation in Drug Discovery (OIDD) program and generated some interesting hit compounds that will be further studied in the future.

9. Photochemical homologation reactios under flow conditions are suitable for the synthesis of aliphatic aldehydes, This part of the thesis was carried at the laboratory of Professor Steven Ley at the Department of Chemistry, Cambridge University.

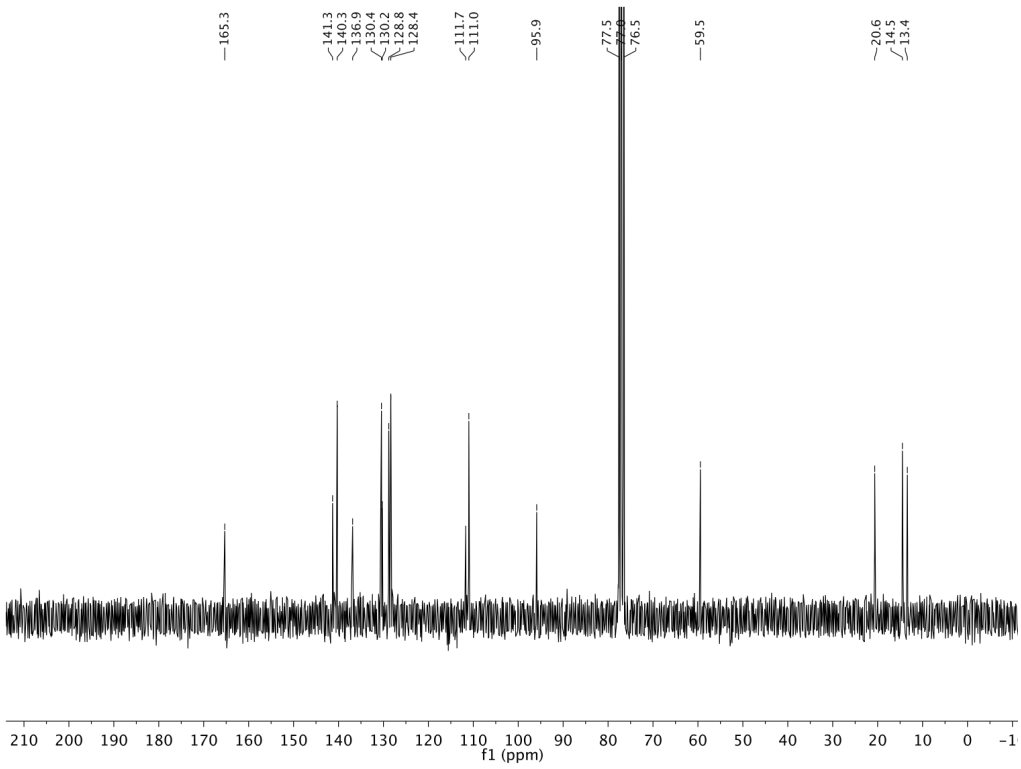
11. Representative spectra

Ethyl 2-ethyl-5-(2-iodophenyl)-1*H*-pyrrole-3-carboxylate (1c)

^{1}H NMR (250 MHz, $CDCl_3$)

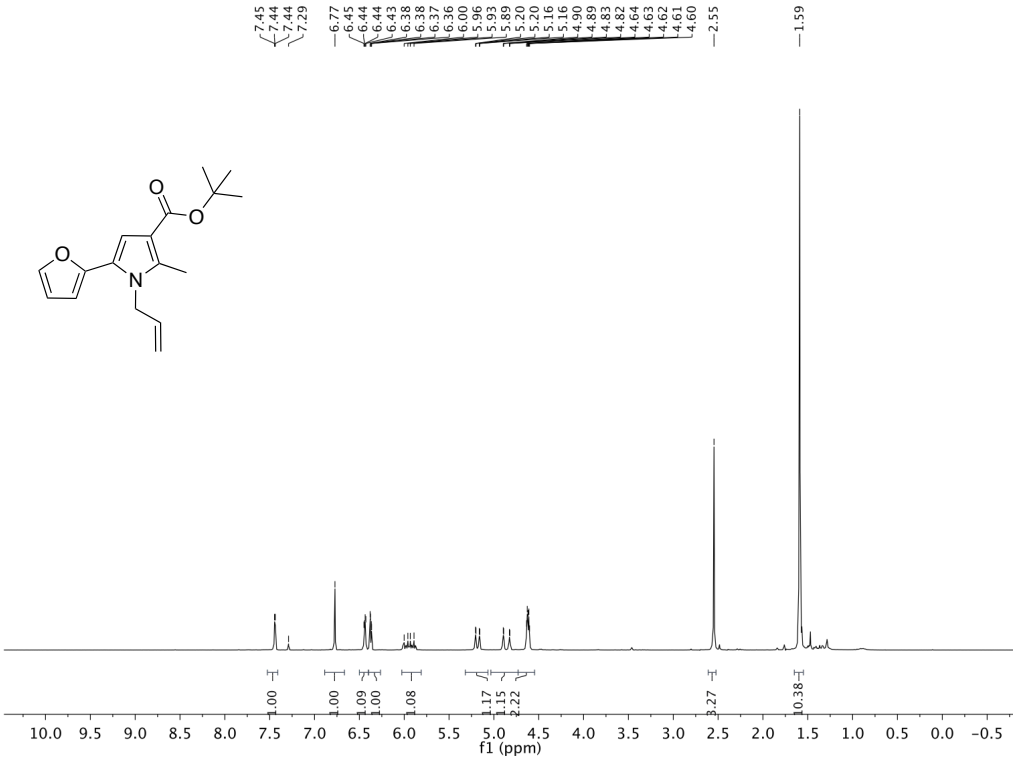


^{13}C NMR (63 MHz, $CDCl_3$)

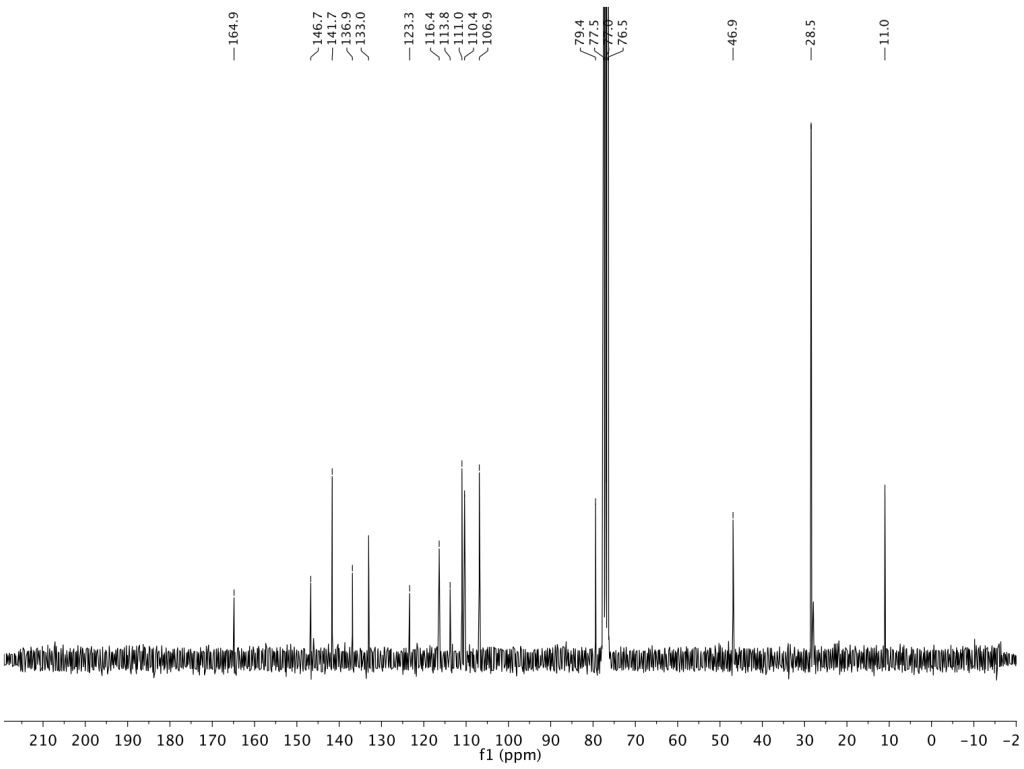


^{t}Butyl 1-allyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrole-3-carboxylate (1g)

^{1}H NMR (250 MHz, $CDCl_3$)

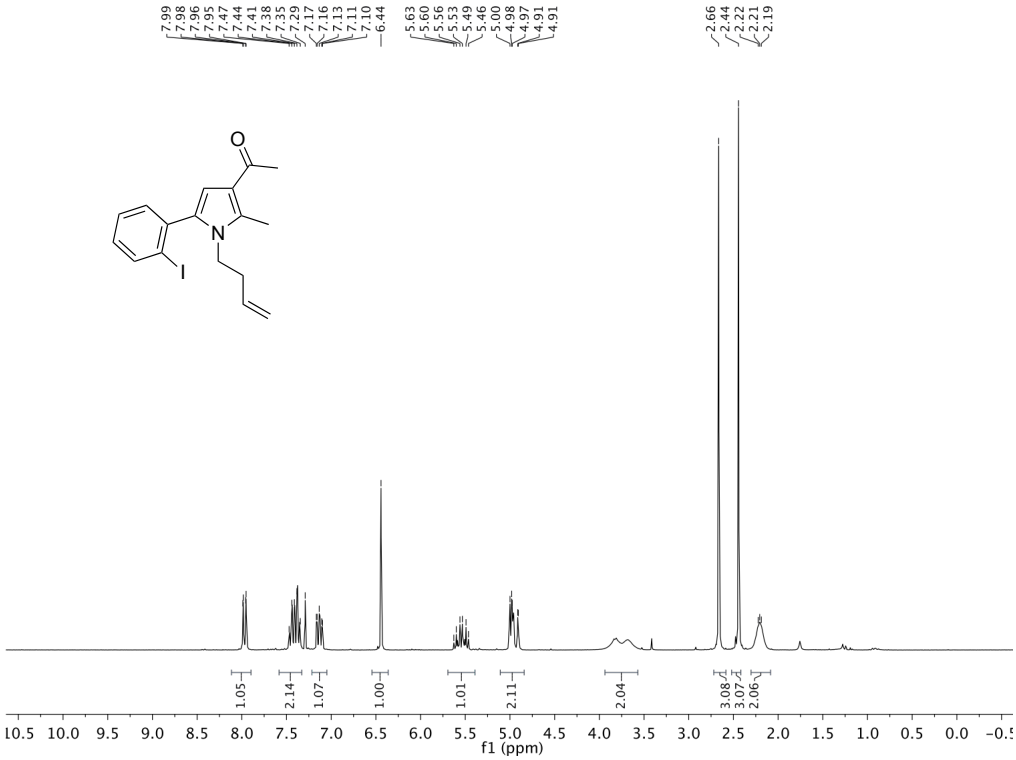


^{13}C NMR (63 MHz, $CDCl_3$)

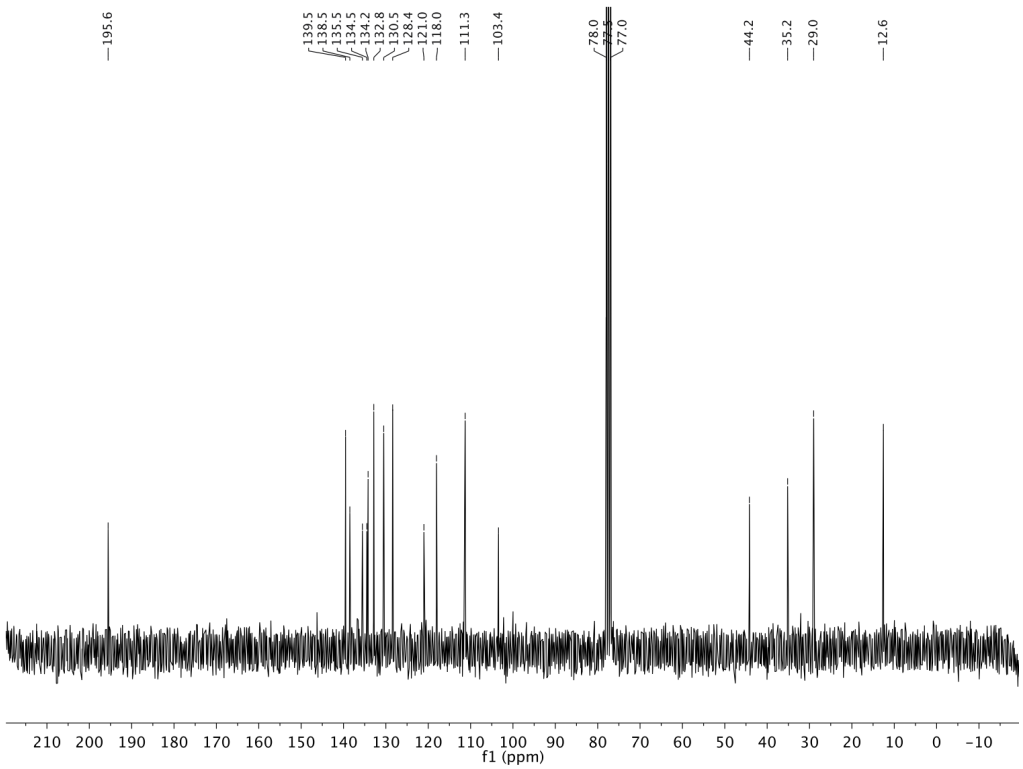


1-(1-(but-3-en-1-yl)-5-(2-iodophenyl)-2-methyl-1*H*-pyrrol-3-yl)ethan-1-one (1n)

^{1}H NMR (250 MHz, $CDCl_3$)

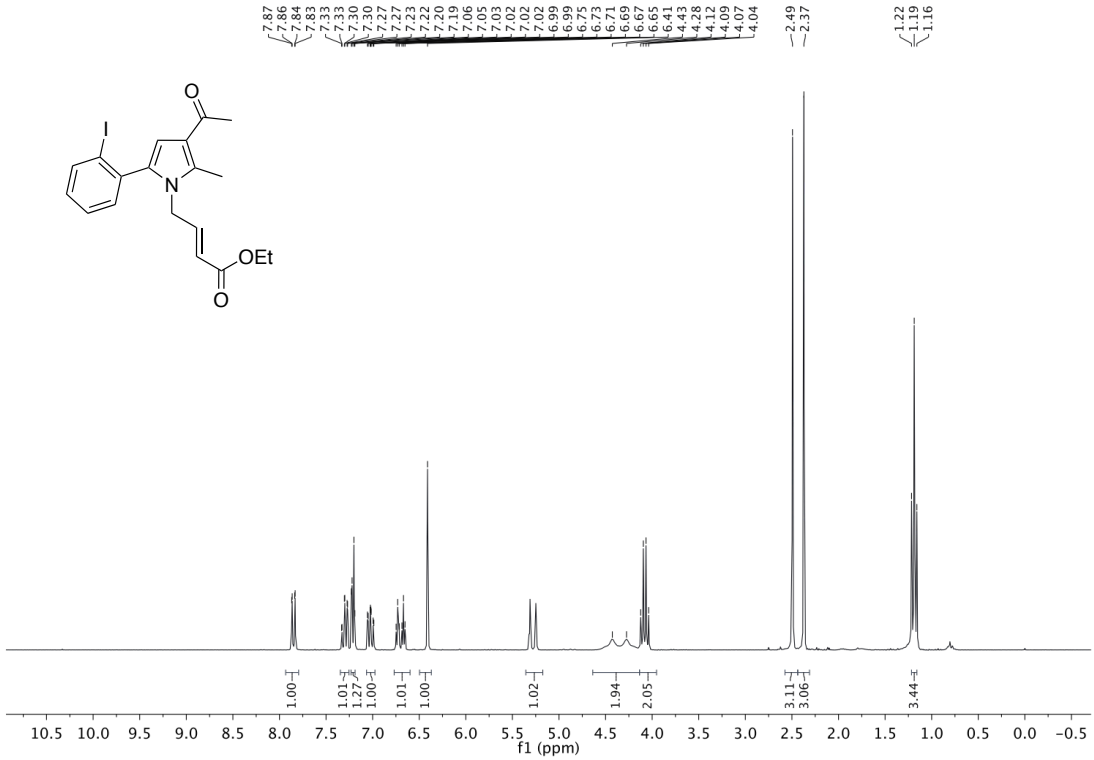


^{13}C NMR (63 MHz, $CDCl_3$)

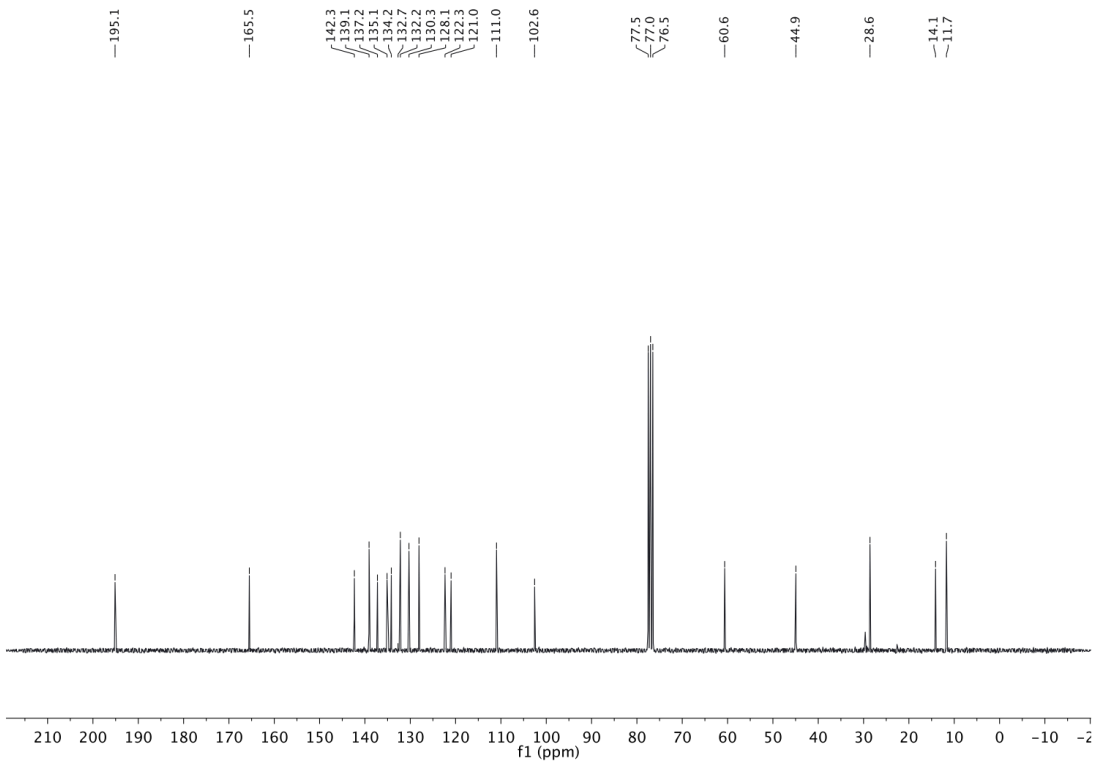


Ethyl (*E*)-4-(3-acetyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrol-1-yl)but-2-enoate (1x)

^{1}H NMR (250 MHz, $CDCl_3$)

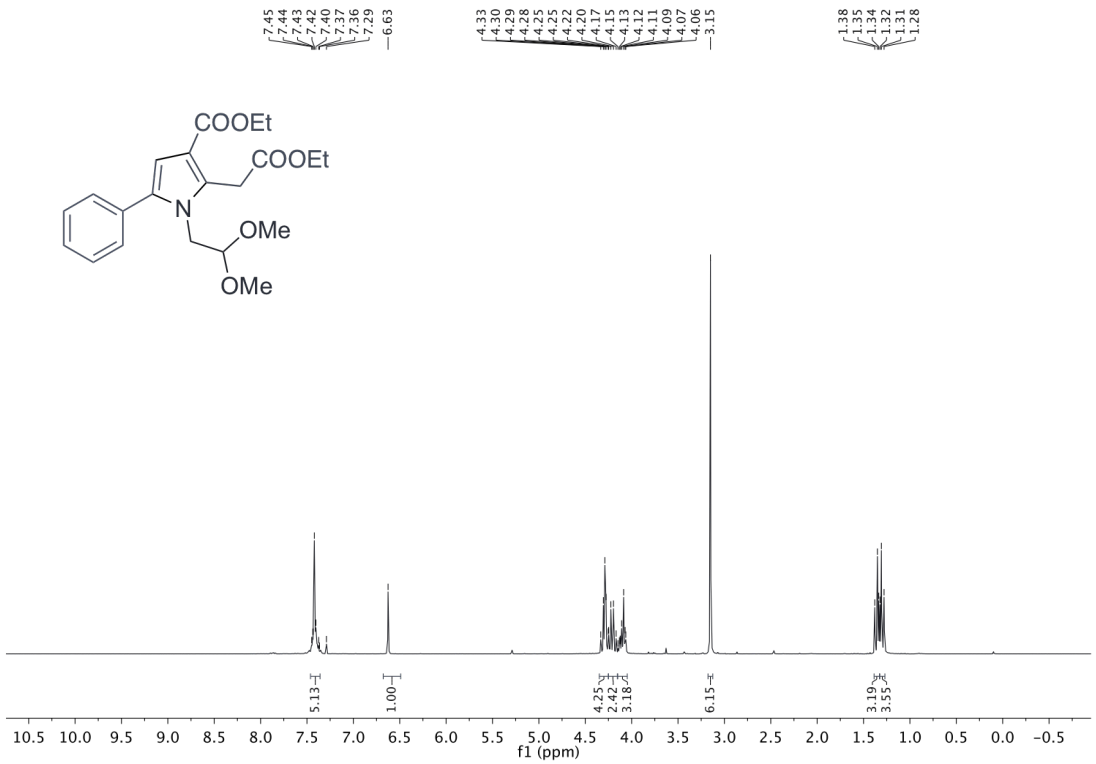


^{13}C NMR (63 MHz, $CDCl_3$)

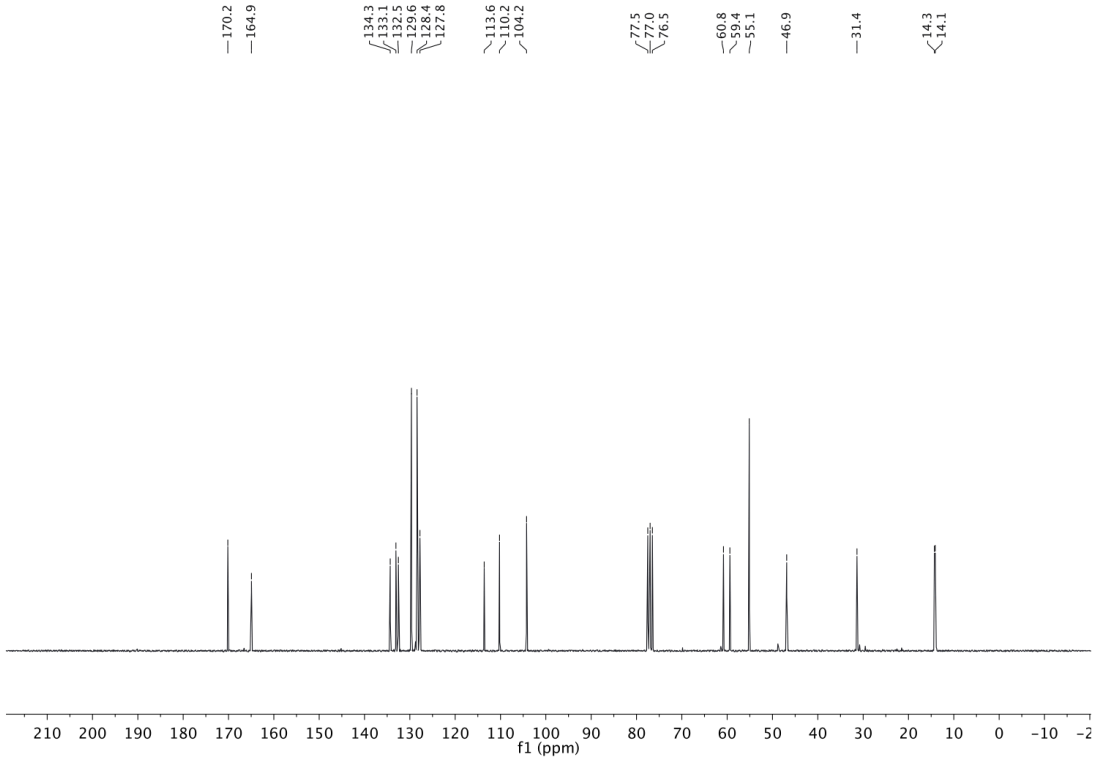


Ethyl 1-(2,2-dimethoxyethyl)-2-(2-ethoxy-2-oxoethyl)-5-phenyl-1H-pyrrole-3-carboxylate (1y)

^{1}H NMR (250 MHz, $CDCl_3$)

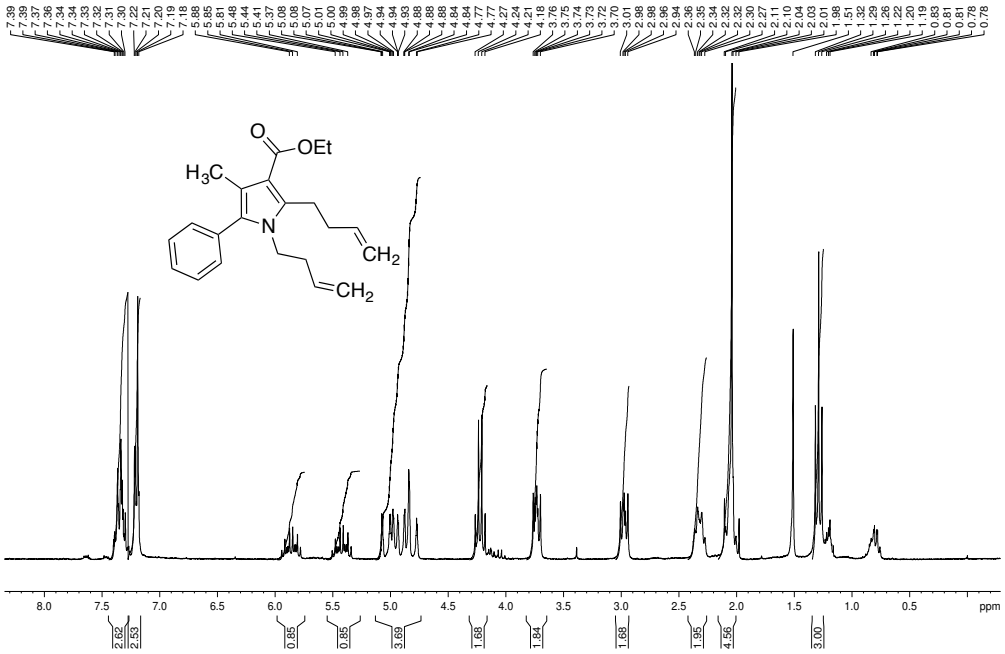


^{13}C NMR (63 MHz, $CDCl_3$)

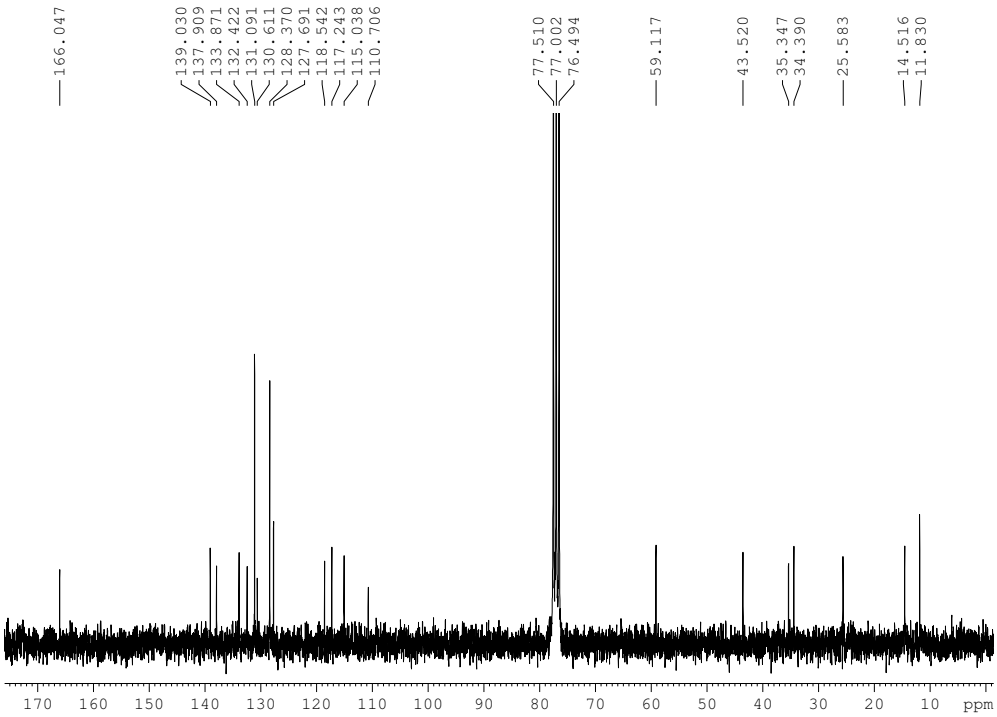


Ethyl-1,2-di(but-3-en-1-yl)-4-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (1ag)

^{1}H NMR (250 MHz, $CDCl_3$)

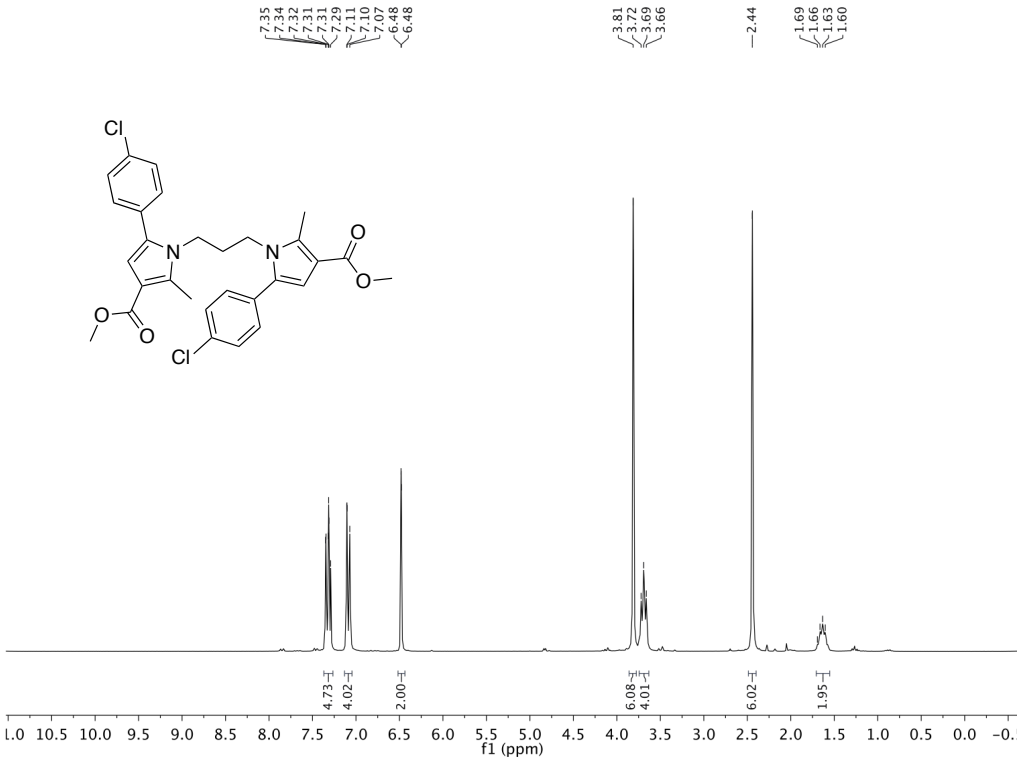


^{13}C NMR (63 MHz, $CDCl_3$)

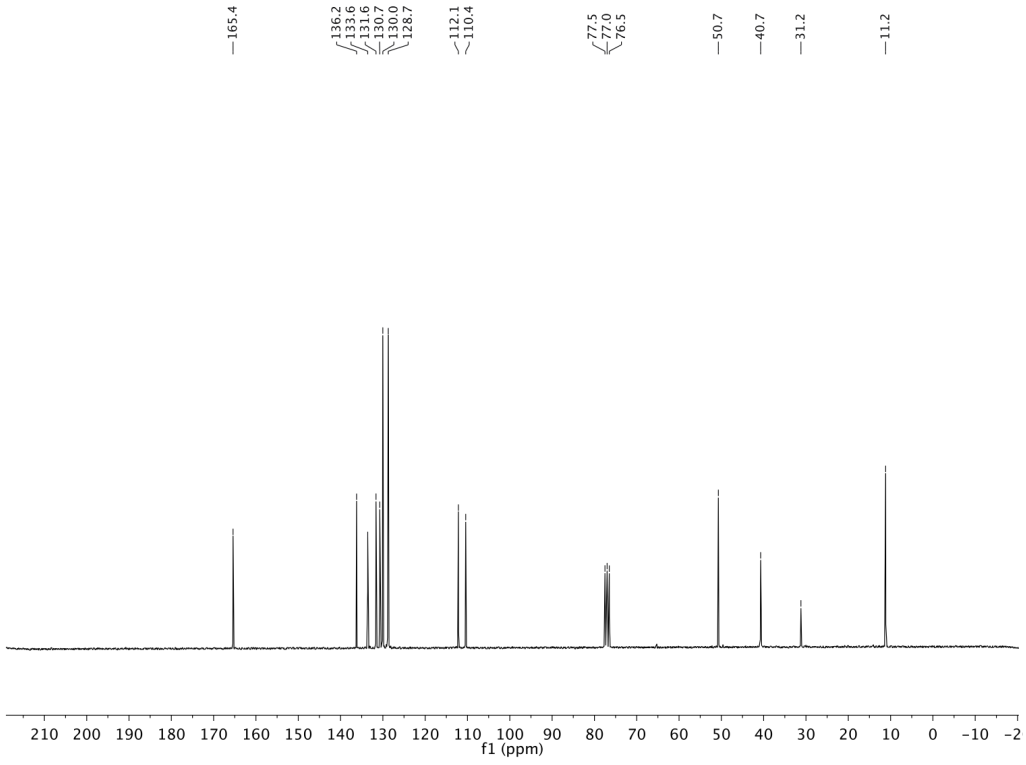


Dimethyl 1,1'-(propane-1,3-diyl)bis[5-(4-chlorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate] (2b)

^{1}H NMR (250 MHz, $CDCl_3$)

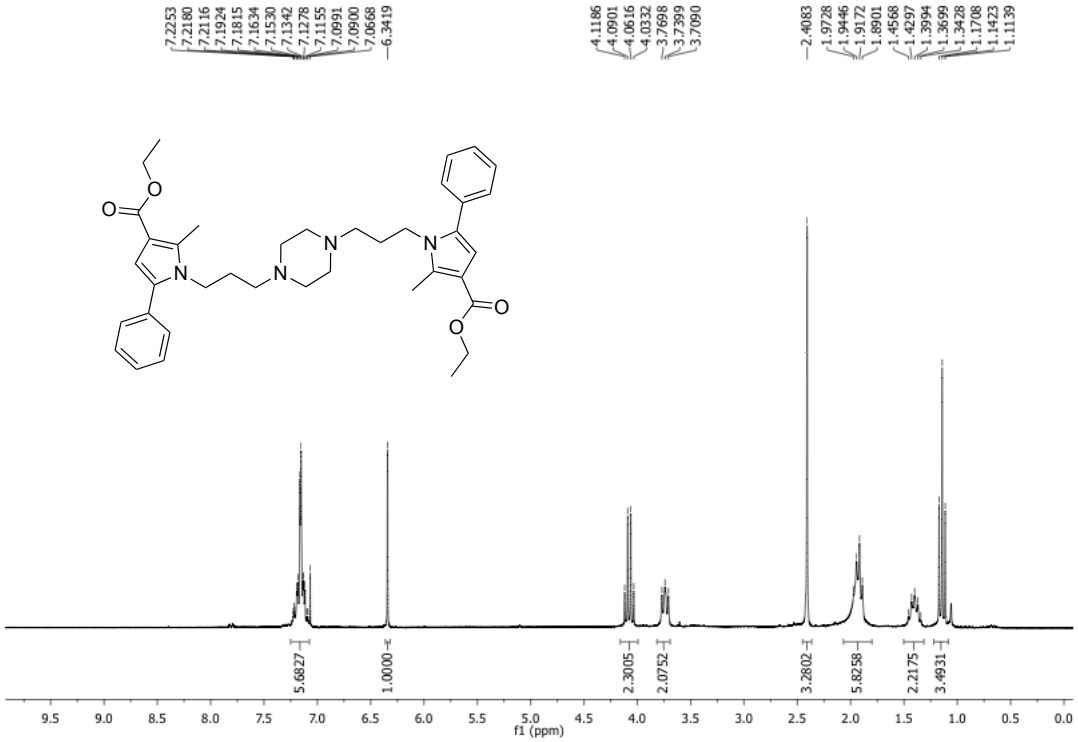


^{13}C NMR (63 MHz, $CDCl_3$)

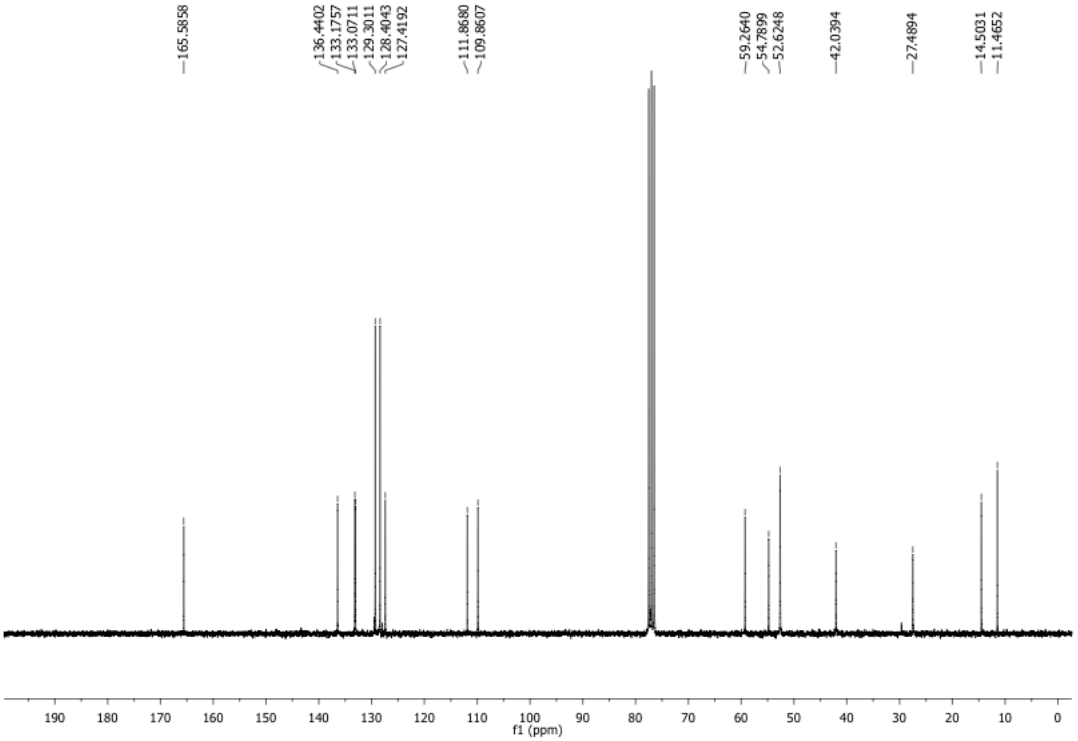


N_1,N_4-Bis[3-(3-ethoxycarbonyl-5-phenyl-2-methylpyrrol-1-yl)propyl]piperazine (2i)

^{1}H NMR (250 MHz, $CDCl_3$)

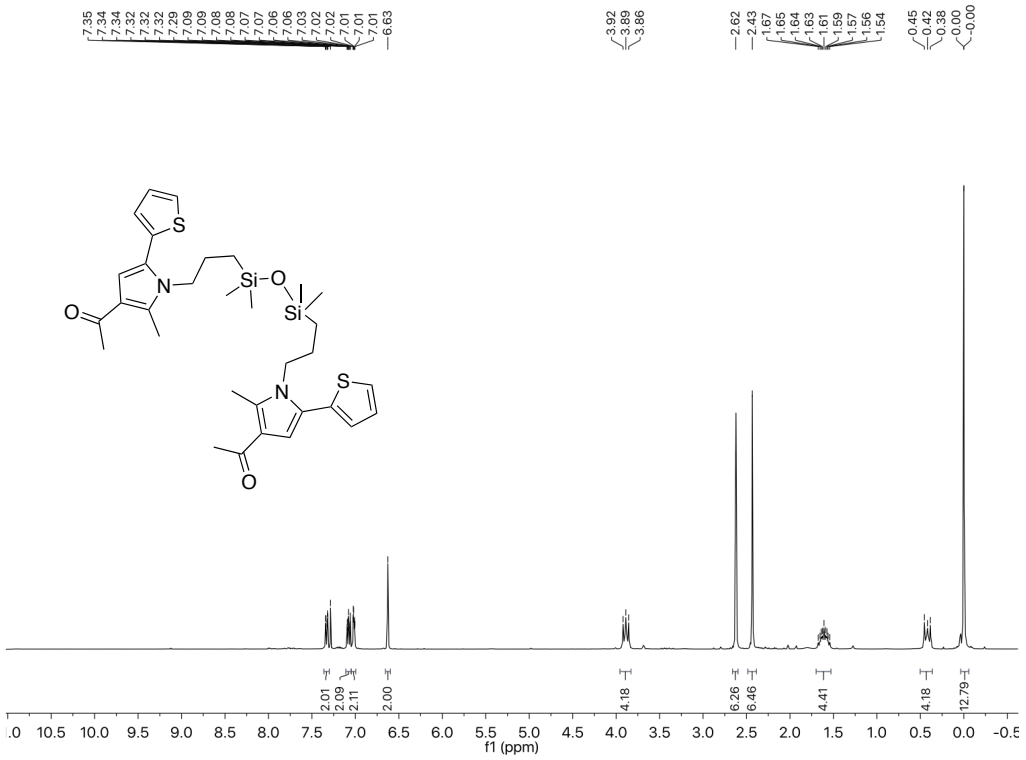


^{13}C NMR (63 MHz, $CDCl_3$)

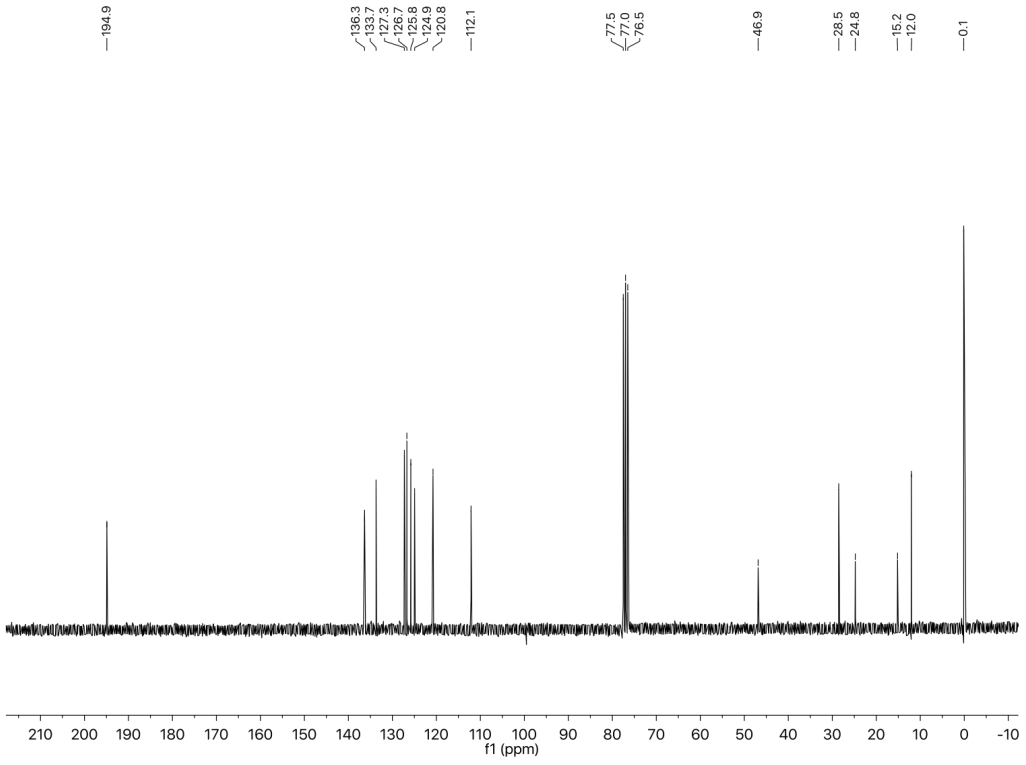


1,1'-[[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl)]bis(2-methyl-5-(thiophen-2-yl)-1*H*-pyrrole-1,3-diyl)]bis(ethan-1-one) (2l)

^{1}H NMR (250 MHz, $CDCl_3$)

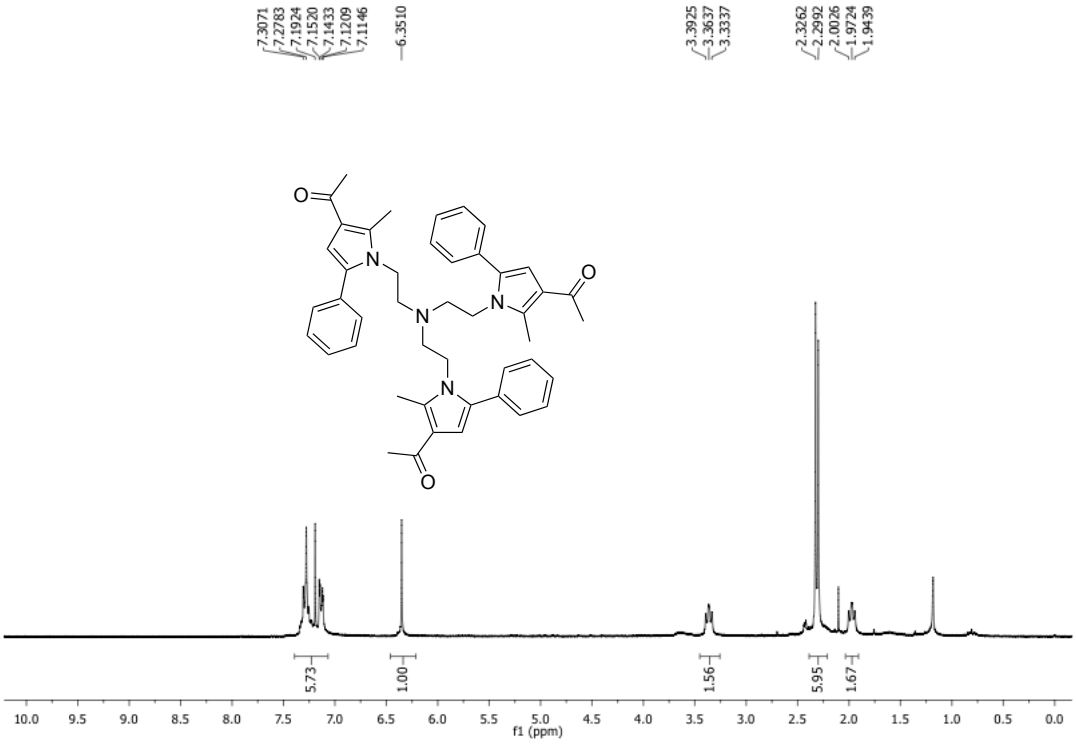


^{13}C NMR (63 MHz, $CDCl_3$)

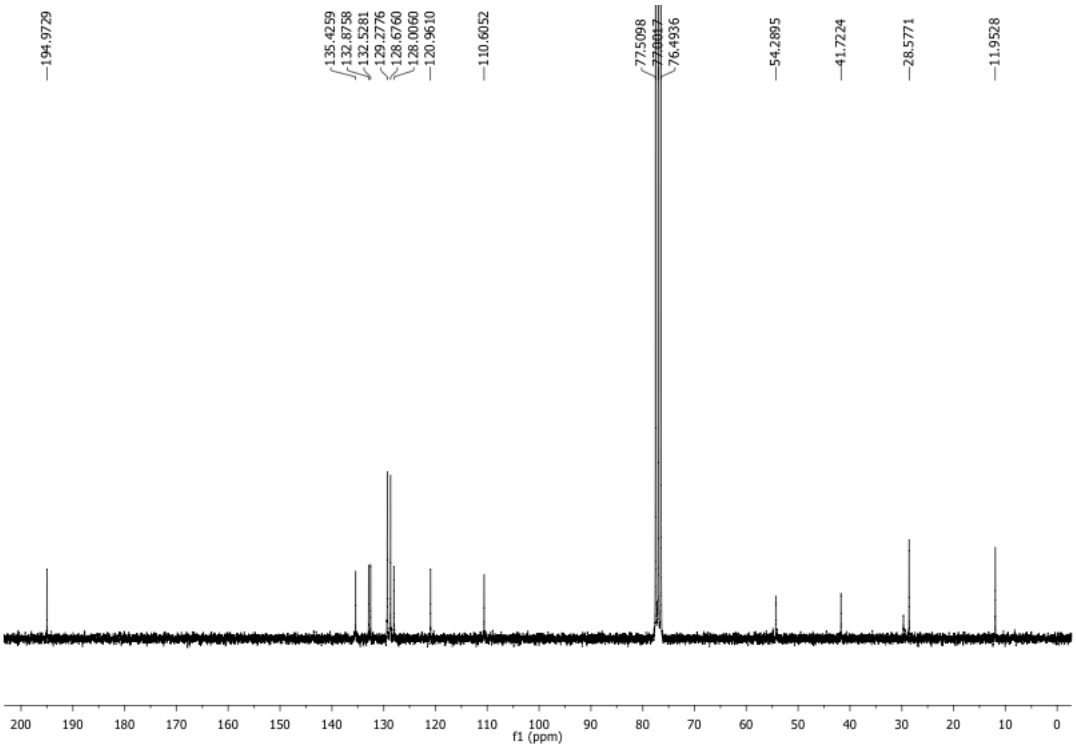


N,N,N-Tris[2-(3-acetyl-5-phenyl-2-methylpyrrol-1-yl)ethyl]amine (3)

^{1}H NMR (250 MHz, $CDCl_3$)

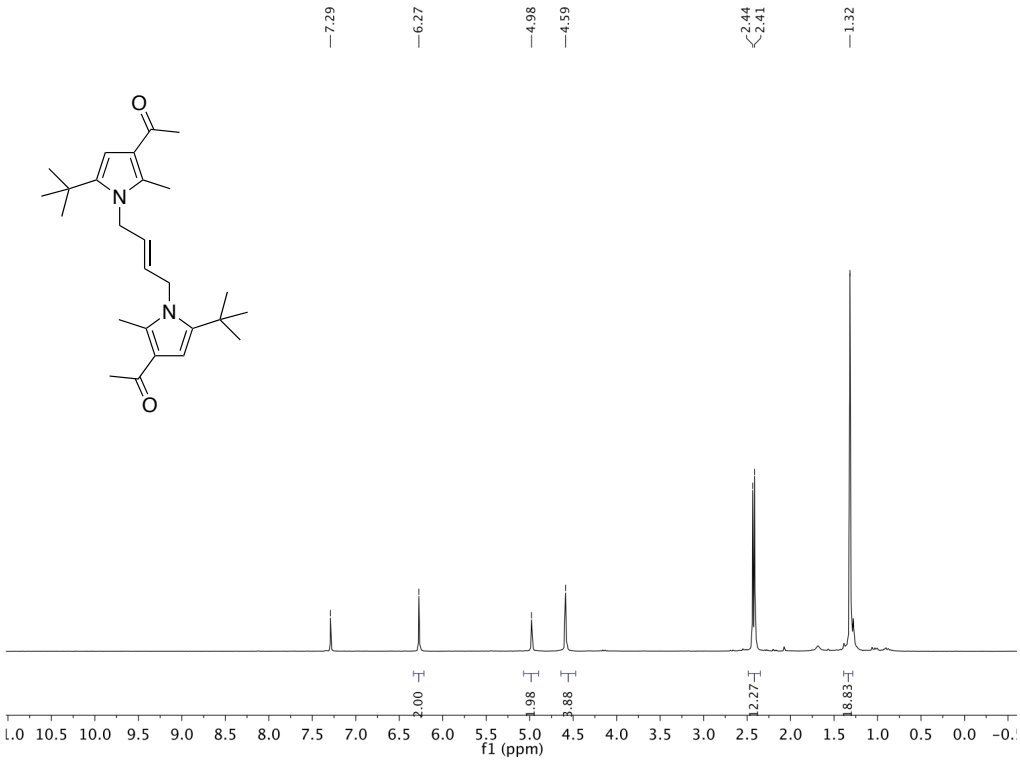


^{13}C NMR (63 MHz, $CDCl_3$)

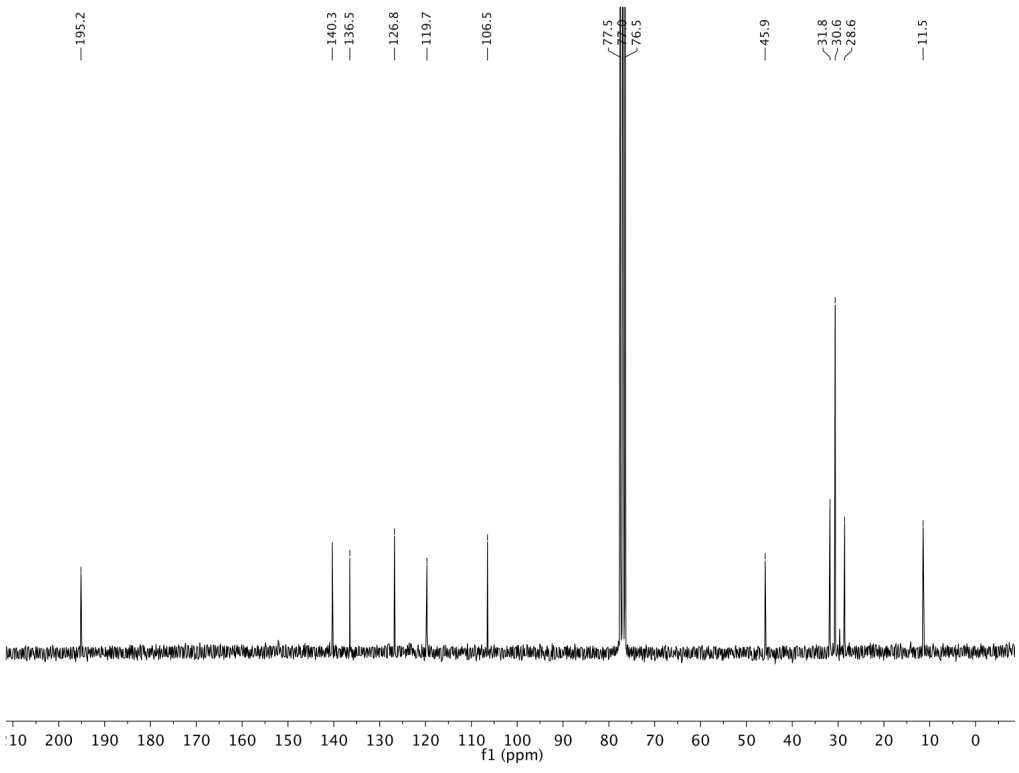


(*E*)-1,1'-(But-2-ene-1,4-diyl)bis[5-(*tert*-butyl)-2-methyl-1*H*-pyrrole-1,3-diyl)]bis(ethan-1-one) (5b)

^{1}H NMR (250 MHz, $CDCl_3$)

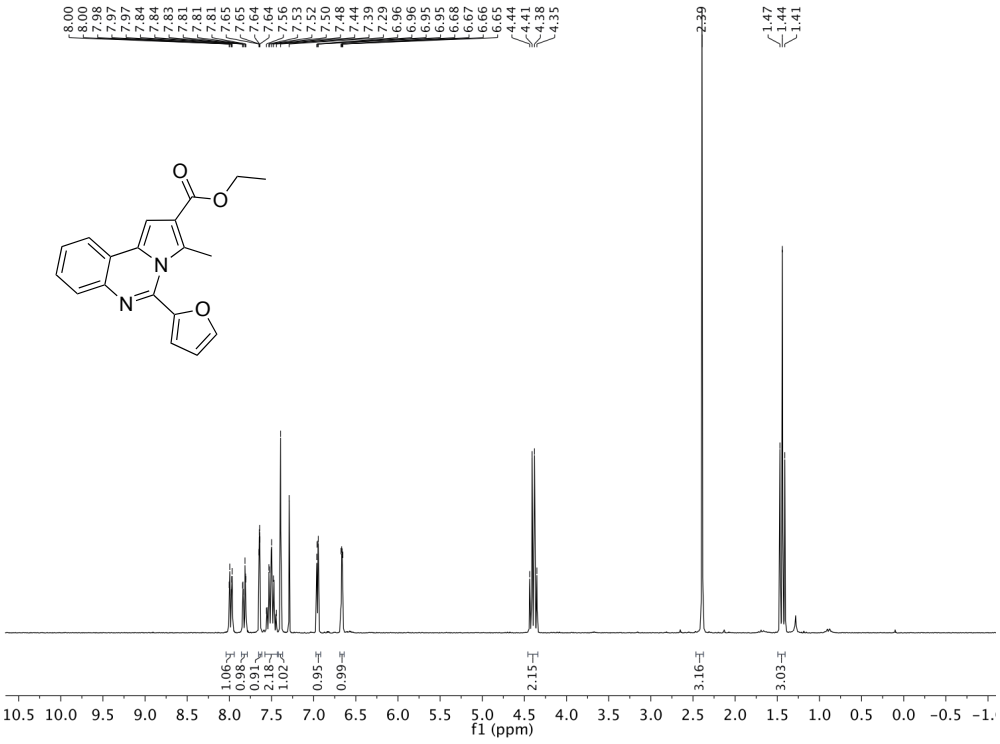


^{13}C NMR (63 MHz, $CDCl_3$)

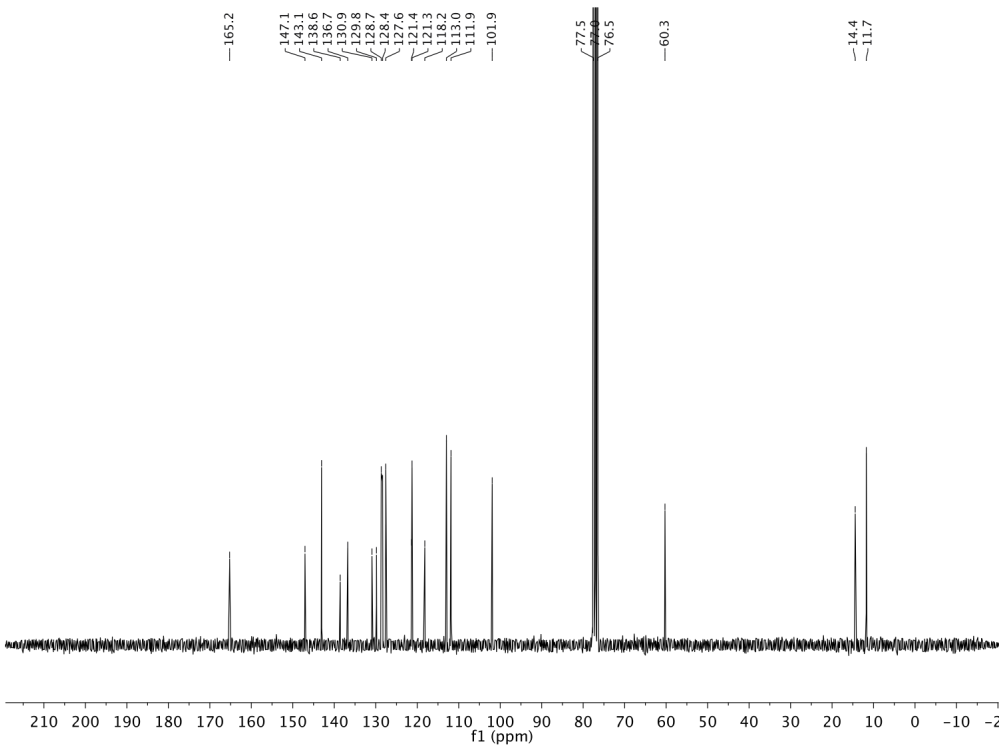


Ethyl 5-(furan-2-yl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6a)

^{1}H NMR (250 MHz, $CDCl_3$)

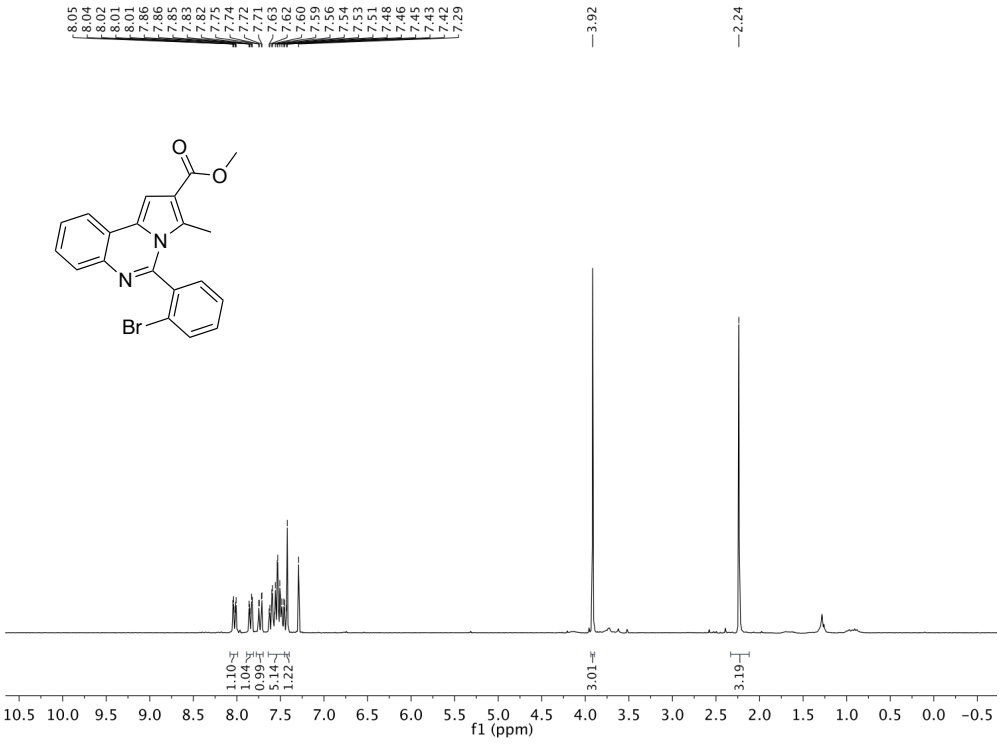


^{13}C NMR (63 MHz, $CDCl_3$)

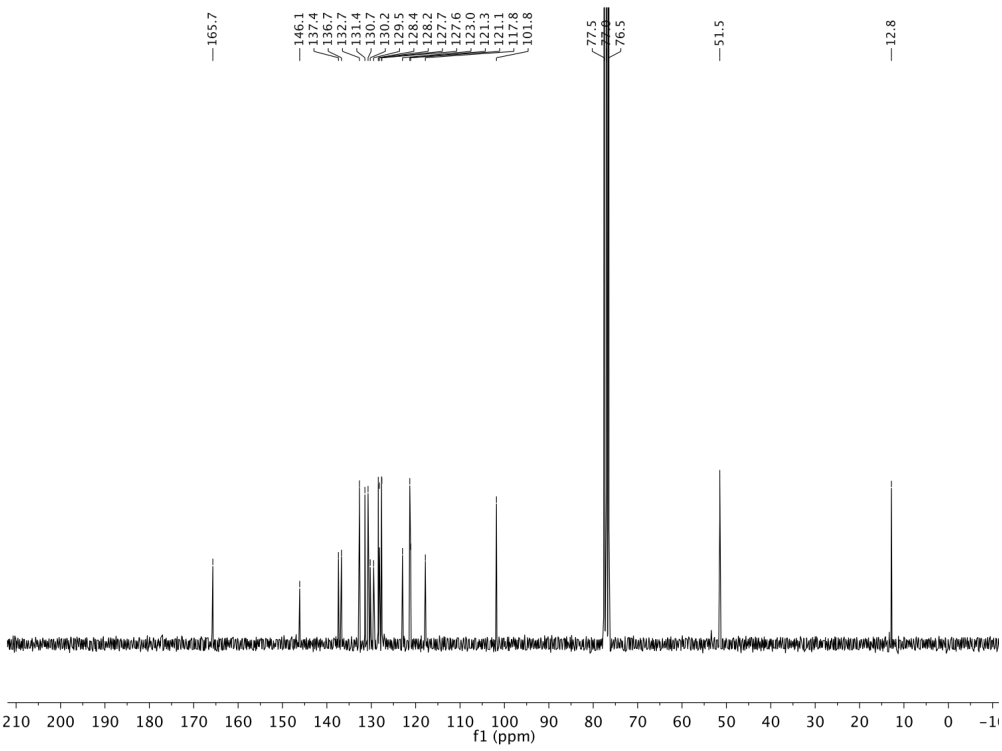


Methyl 5-(2-bromophenyl)-3-methylpyrrolo[1,2-*c*]quinazoline-2-carboxylate (6e)

^{1}H NMR (250 MHz, $CDCl_3$)

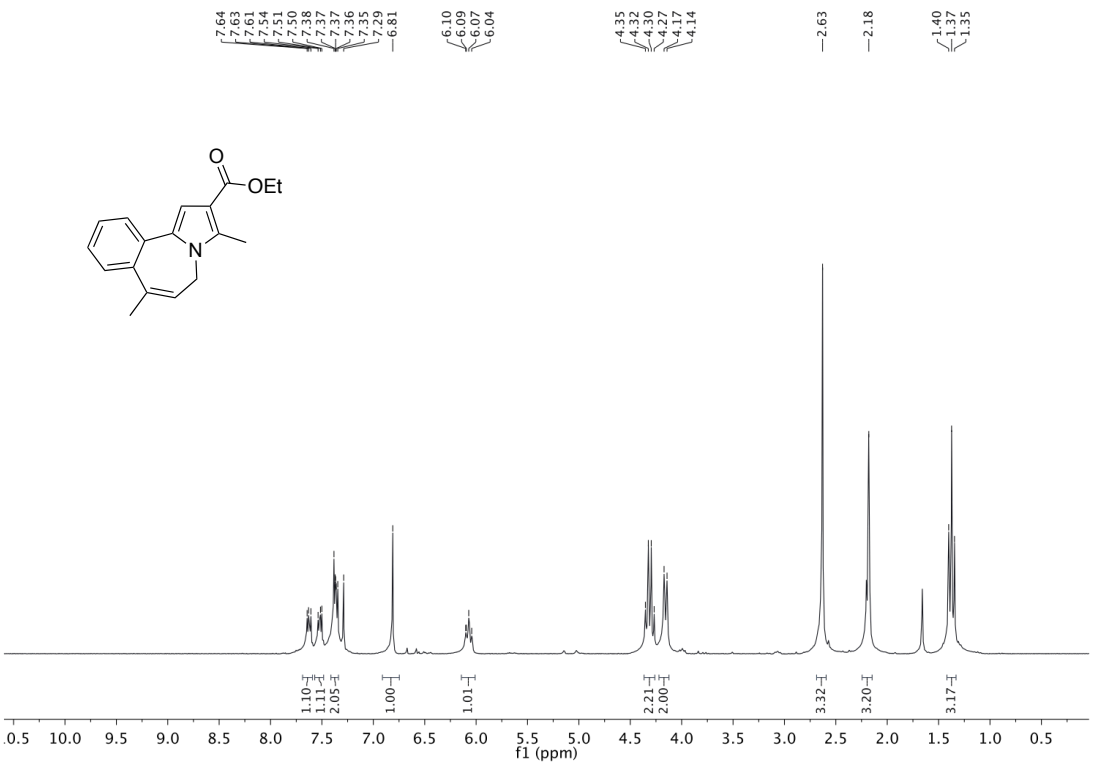


^{13}C NMR (63 MHz, $CDCl_3$)

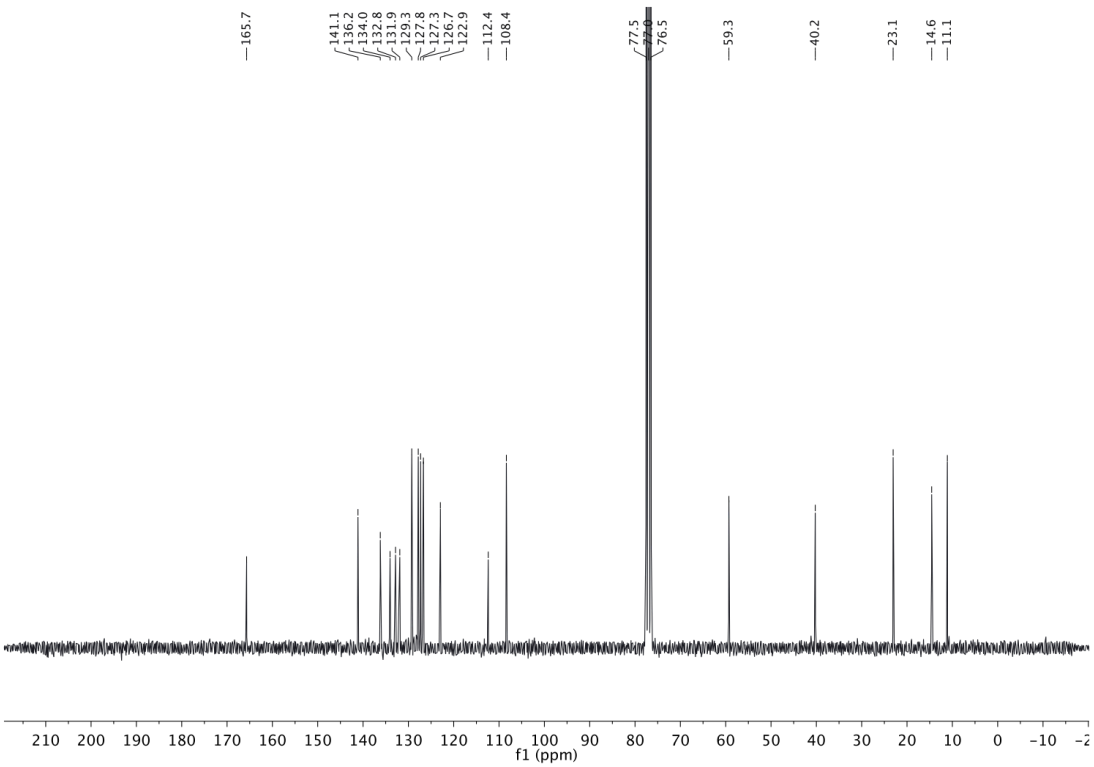


1-allyl-5-(2-iodophenyl)-2-methyl-1*H*-pyrrole-3-carboxamide (5a)

^{1}H NMR (250 MHz, $CDCl_3$)

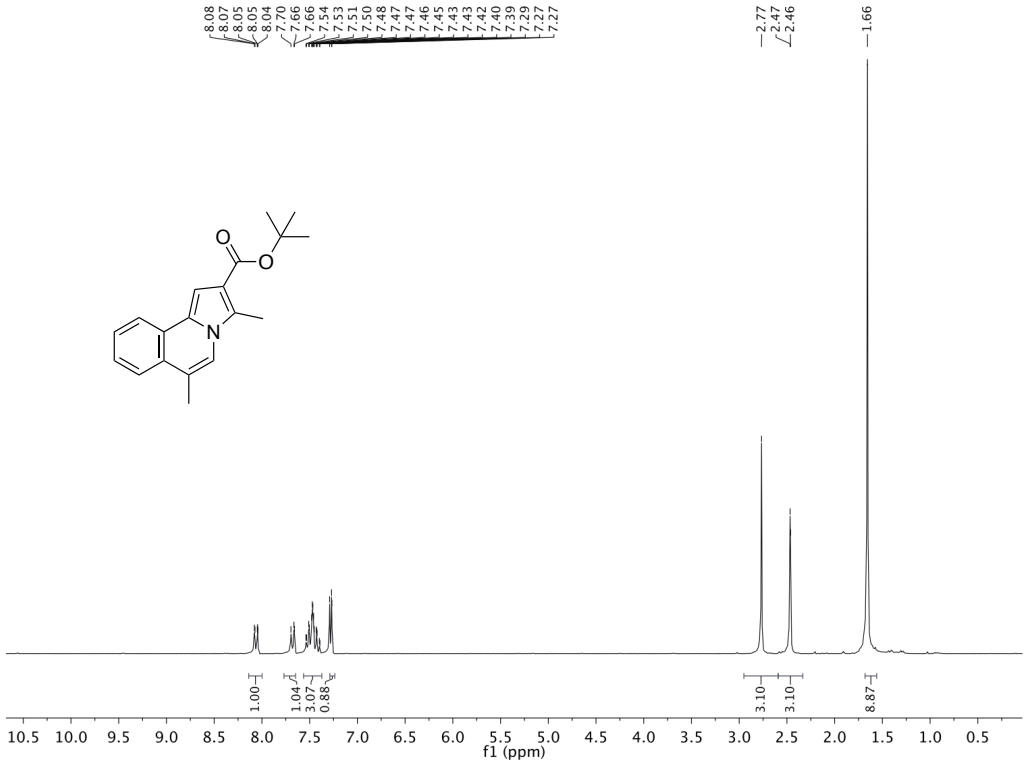


^{13}C NMR (63 MHz, $CDCl_3$)

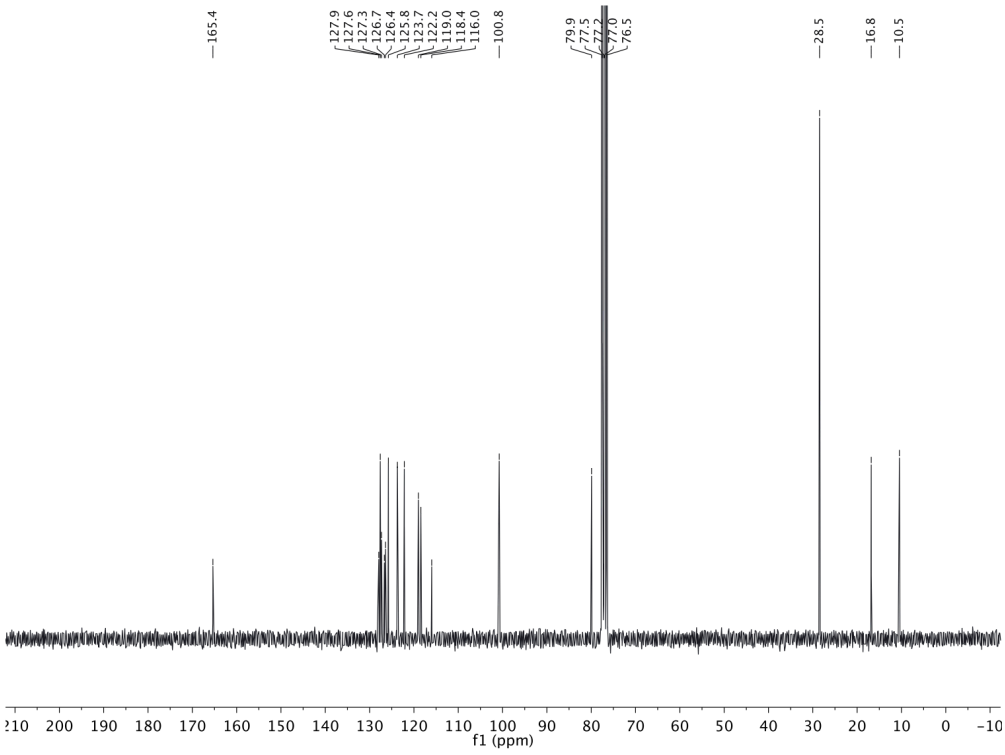


^{t}butyl 3,6-dimethylpyrrolo[2,1-a]isoquinoline-2-carboxylate (7c)

^{1}H NMR (250 MHz, $CDCl_3$)

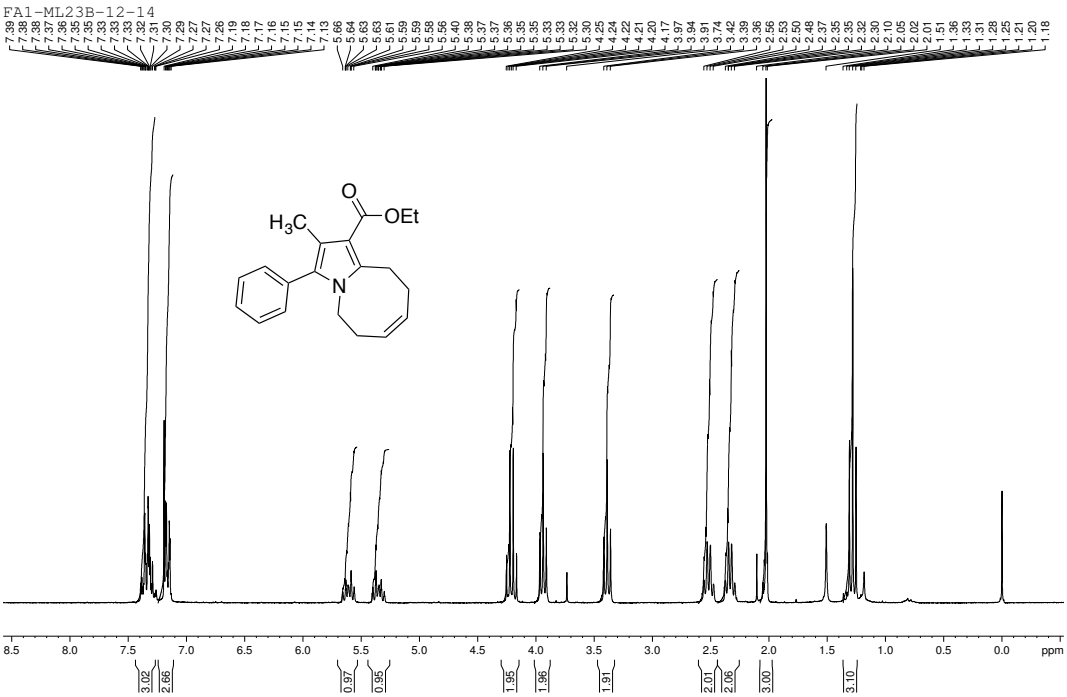


^{13}C NMR (63 MHz, $CDCl_3$)

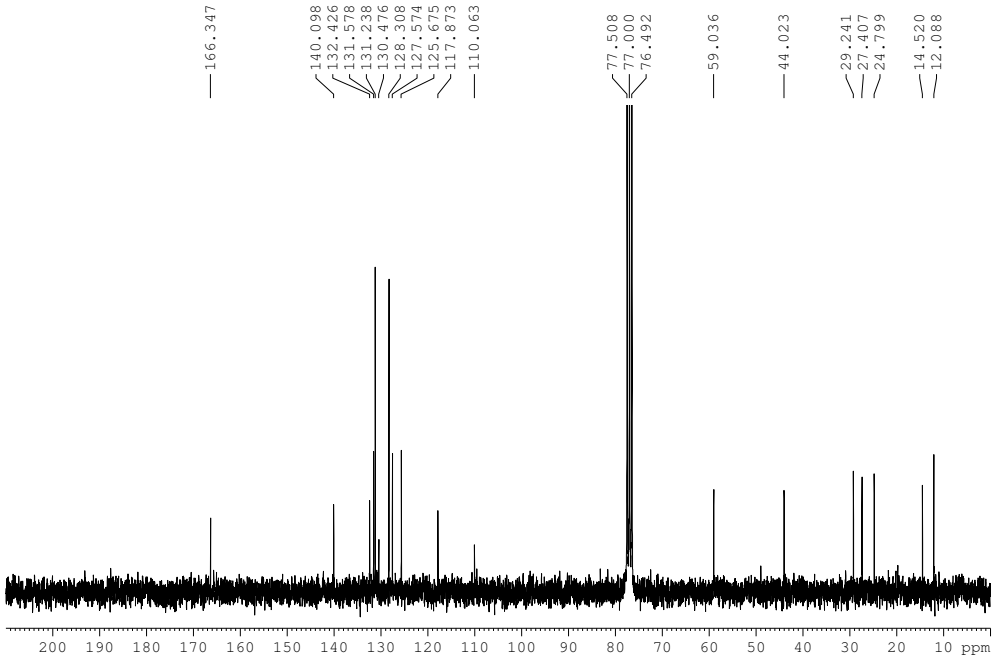


Ethyl-2-methyl-3-phenyl-5,6,9,10-tetrahydropyrrolo[1,2-*a*]azocine-1-carboxylate (8d)

^{1}H NMR (250 MHz, $CDCl_3$)

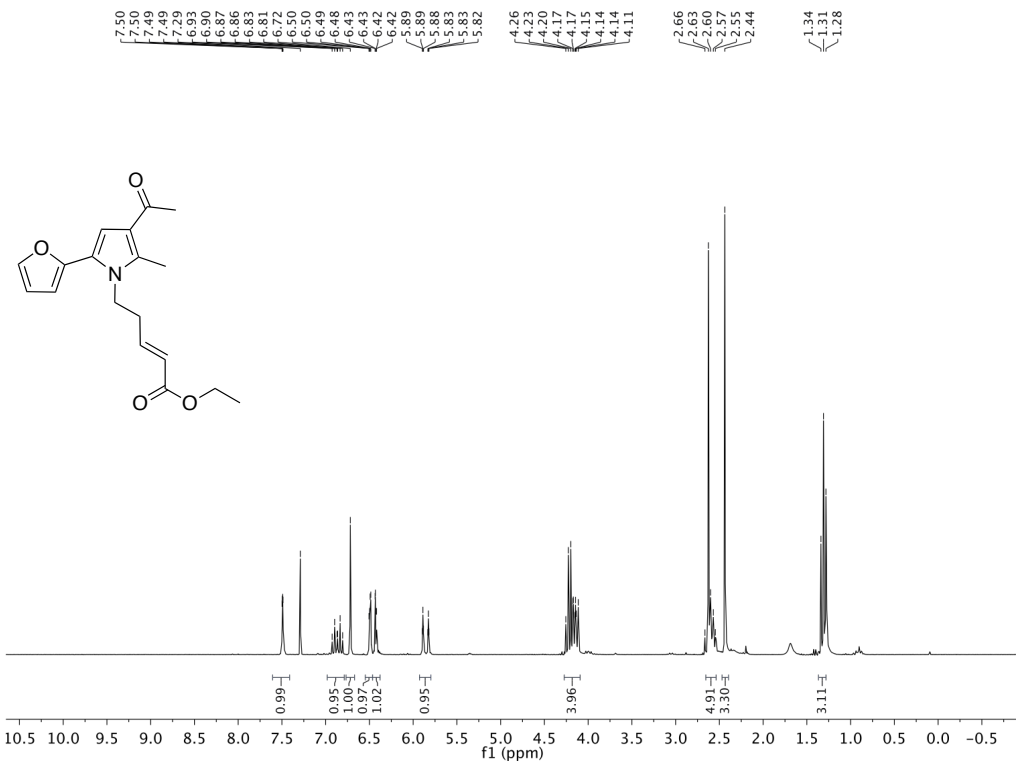


^{13}C NMR (63 MHz, $CDCl_3$)

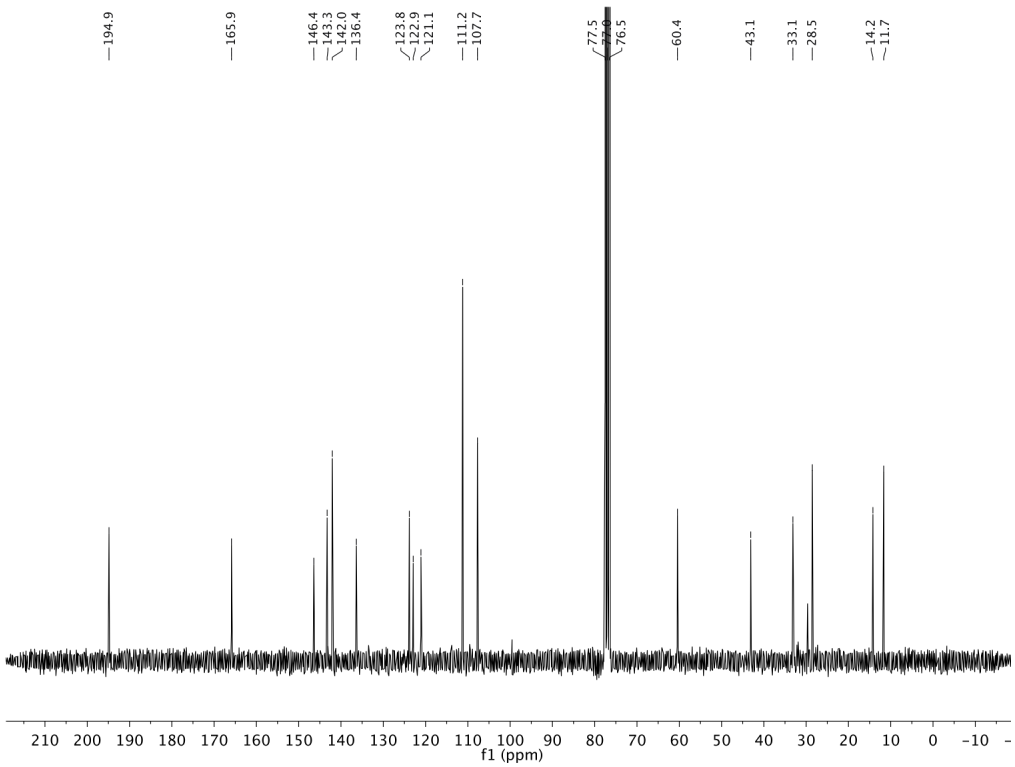


Ethyl (*E*)-5-(3-acetyl-5-(furan-2-yl)-2-methyl-1*H*-pyrrol-1-yl)pent-2-enoate (9a)

^{1}H NMR (250 MHz, $CDCl_3$)

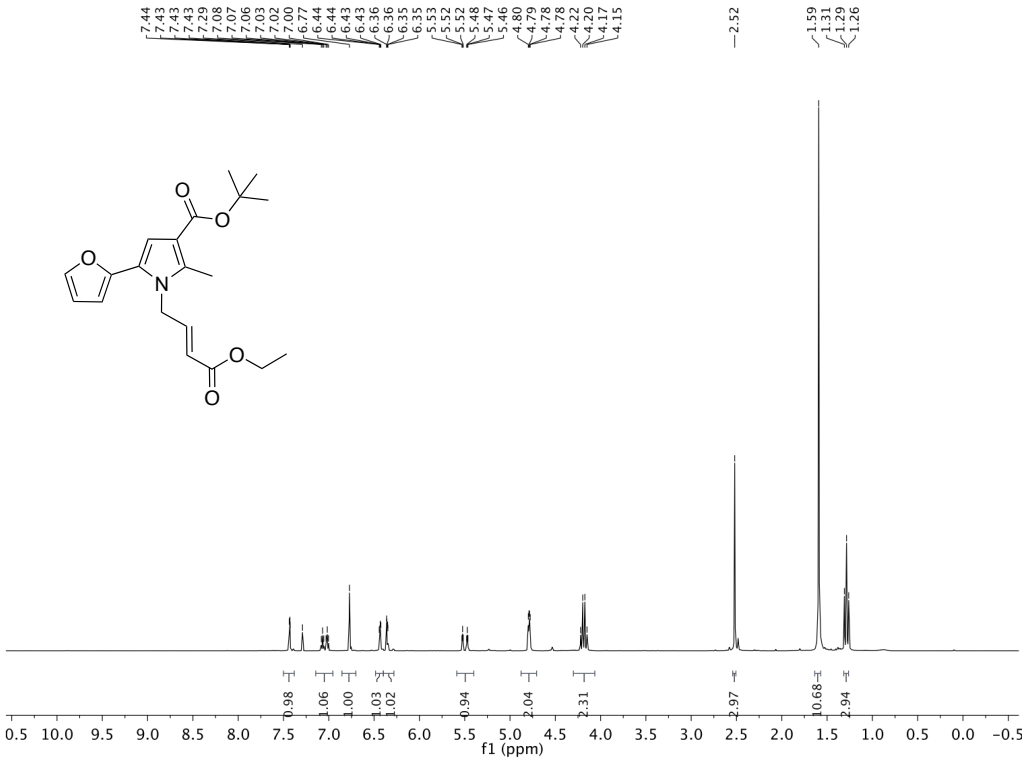


^{13}C NMR (63 MHz, $CDCl_3$)

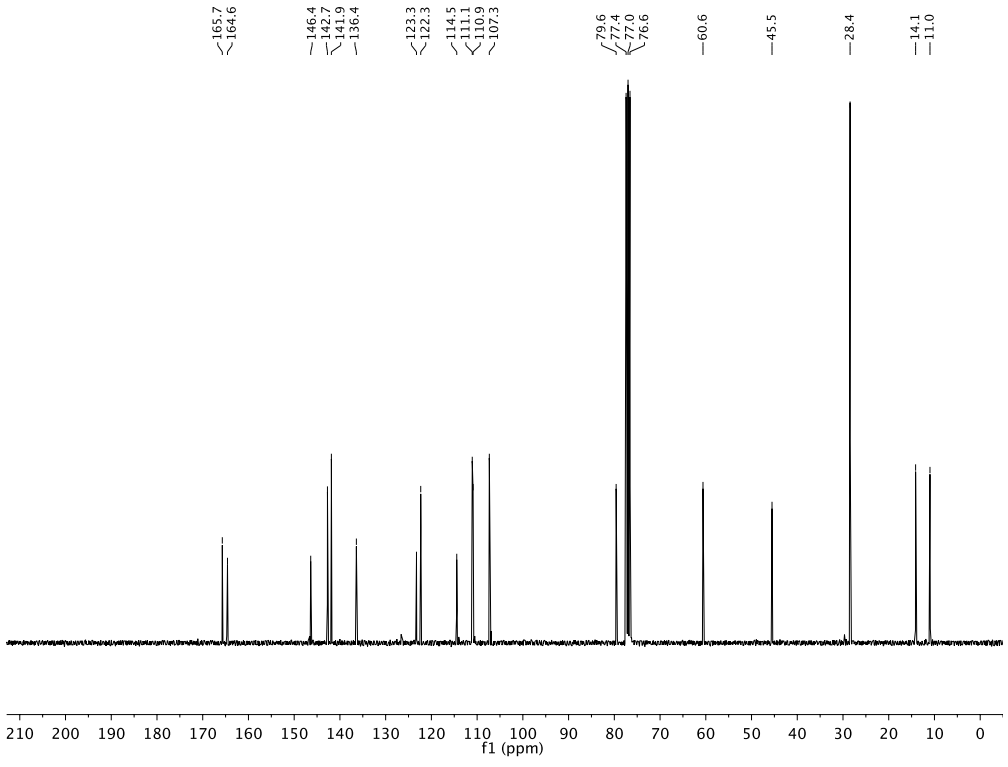


^{t}Butyl (E)-1-(4-ethoxy-4-oxobut-2-en-1-yl)-5-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (3d)

^{1}H NMR (250 MHz, $CDCl_3$)

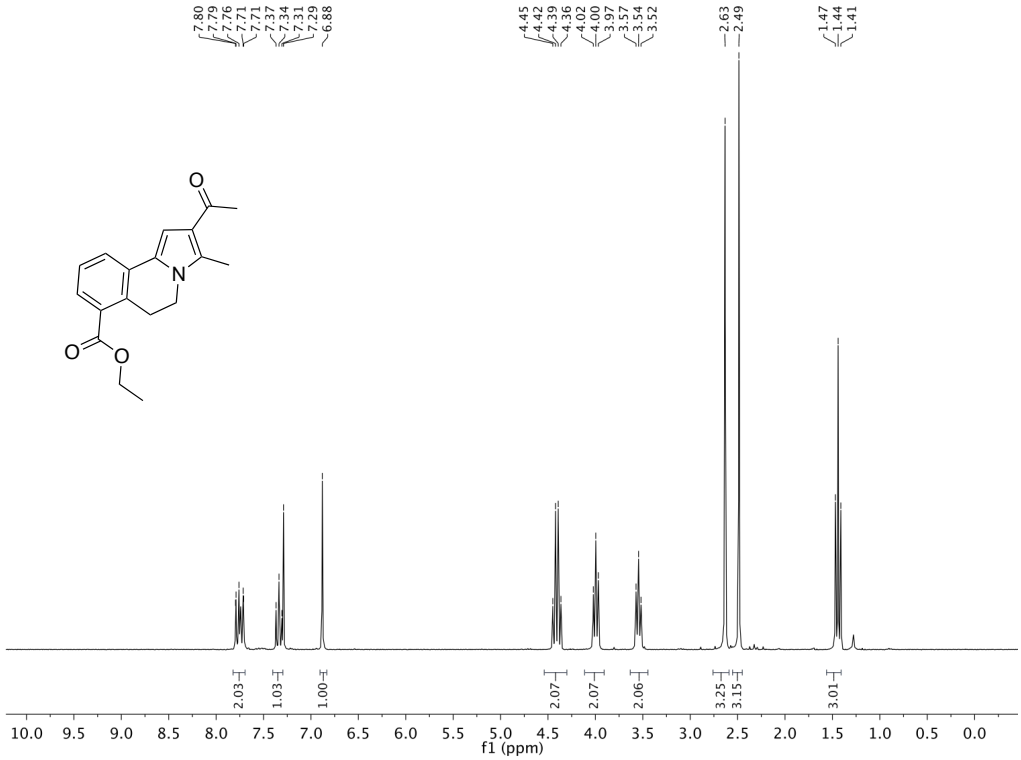


^{13}C NMR (63 MHz, $CDCl_3$)

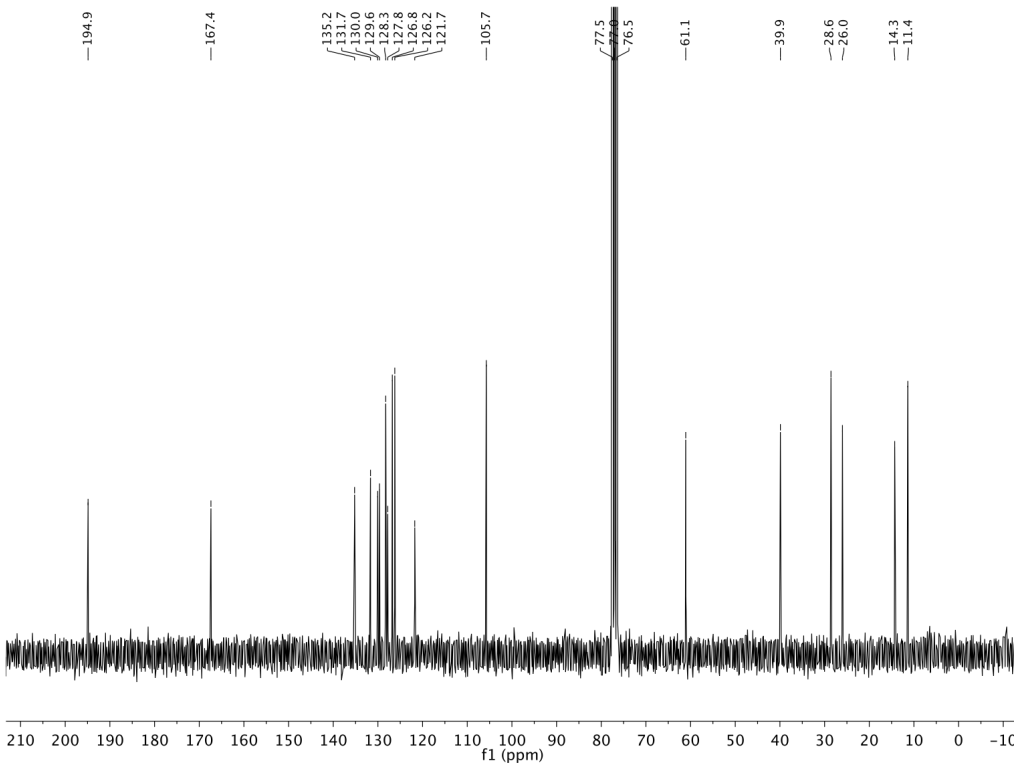


Ethyl 2-acetyl-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-7-carboxylate (10a)

^{1}H NMR (250 MHz, $CDCl_3$)

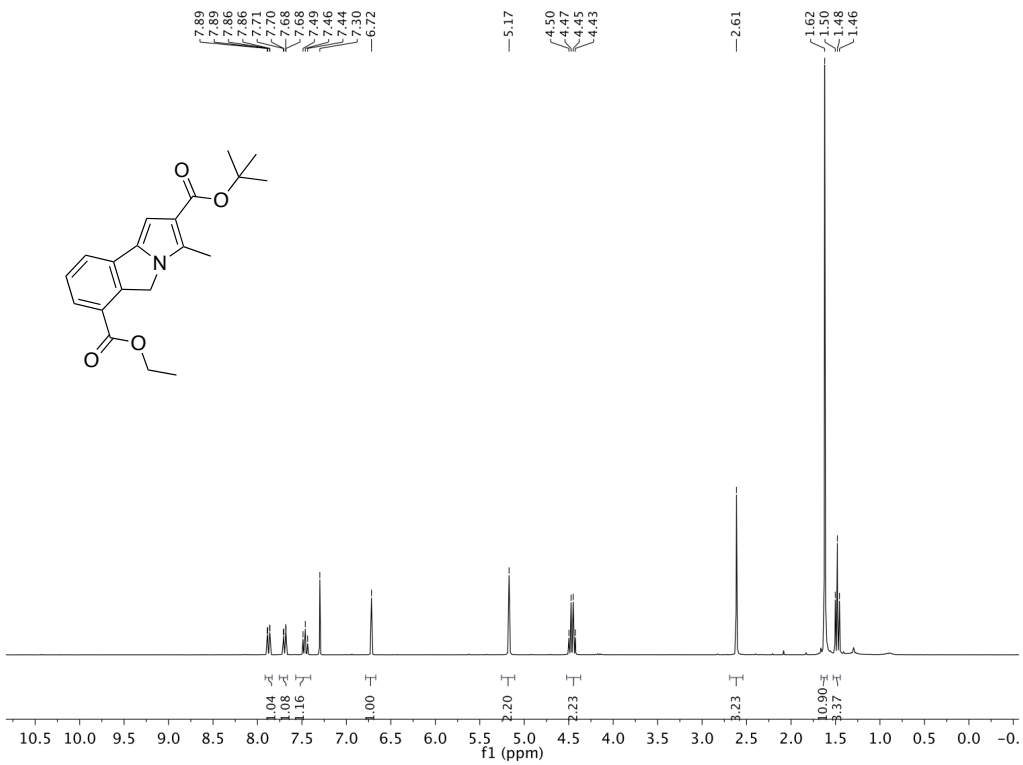


^{13}C NMR (63 MHz, $CDCl_3$)

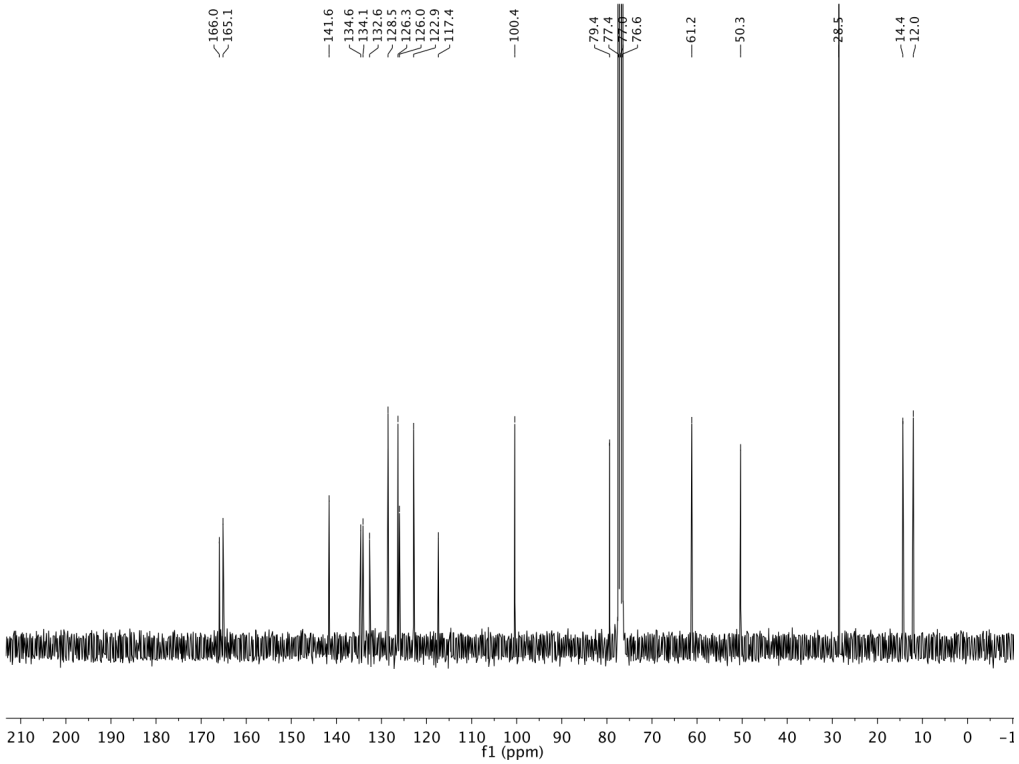


2-(^{t}Butyl) 6-ethyl 3-methyl-5H-pyrrolo[2,1-a]isoindole-2,6-dicarboxylate (4d)

^{1}H NMR (250 MHz, $CDCl_3$)

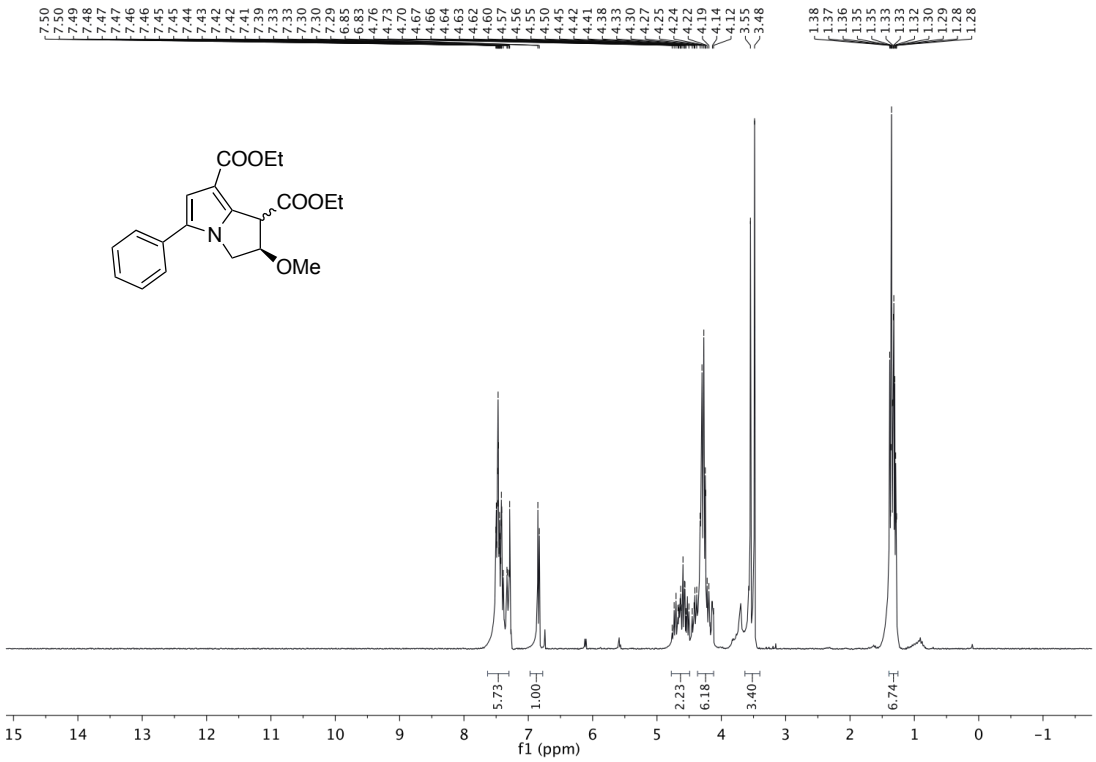


^{13}C NMR (63 MHz, $CDCl_3$)

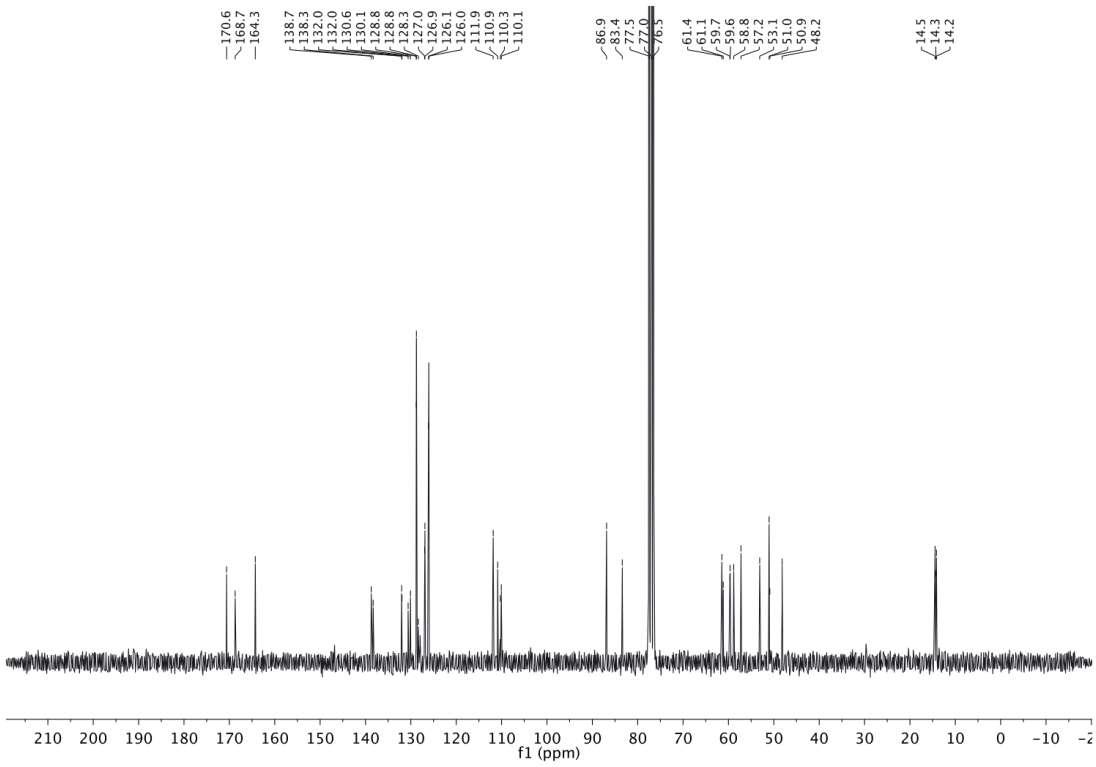


Diethyl 2-methoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,7-dicarboxylate (11a)

^{1}H NMR (250 MHz, $CDCl_3$)

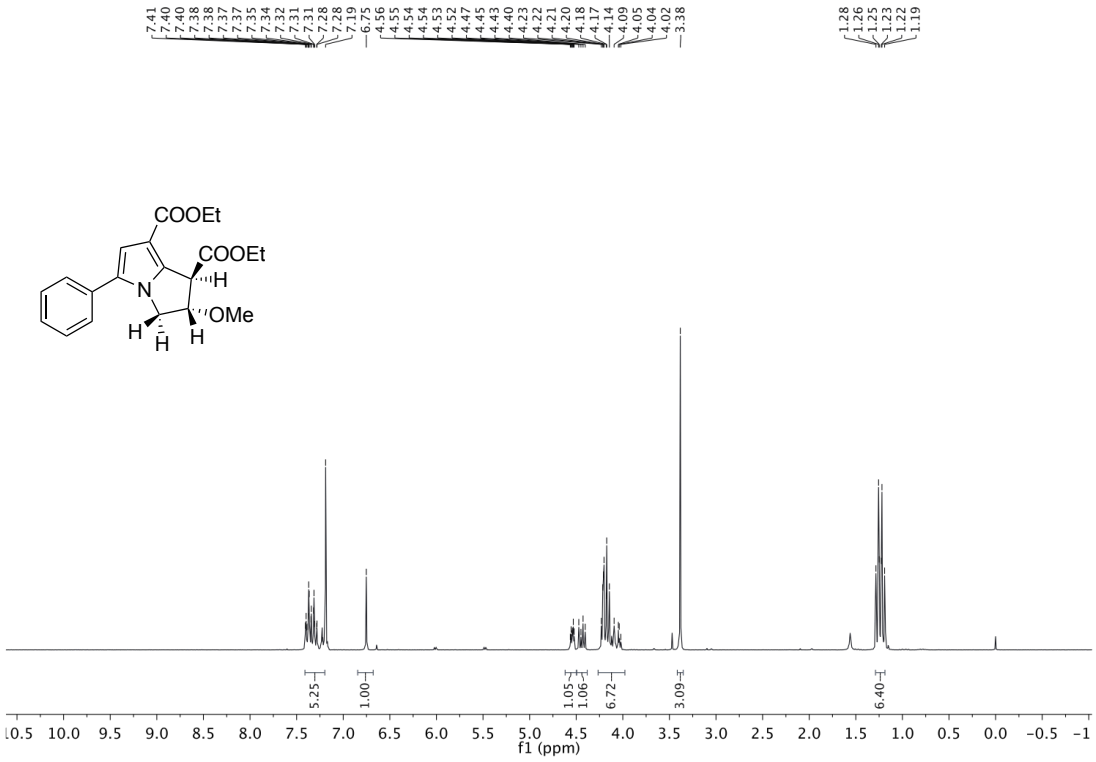


^{13}C NMR (63 MHz, $CDCl_3$)

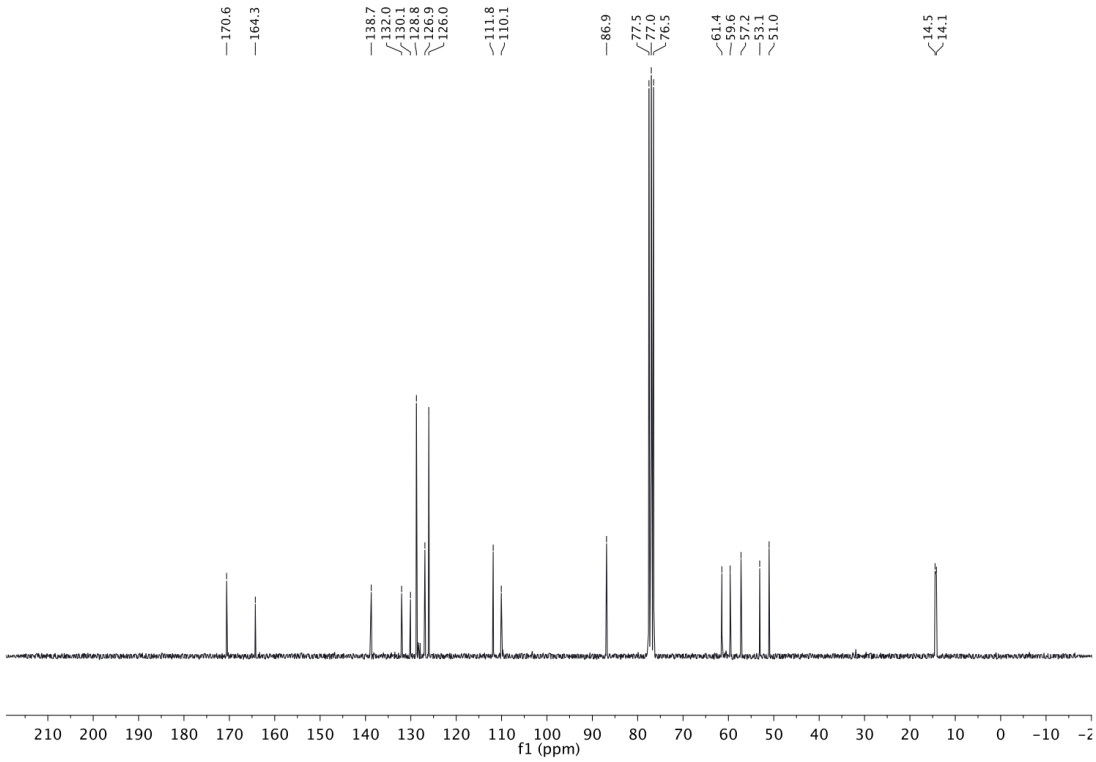


Trans-Diethyl 2-methoxy-5-phenyl-2,3-dihydro-1*H*-pyrrolizine-1,7-dicarboxylate (11aa)

^{1}H NMR (250 MHz, $CDCl_3$)

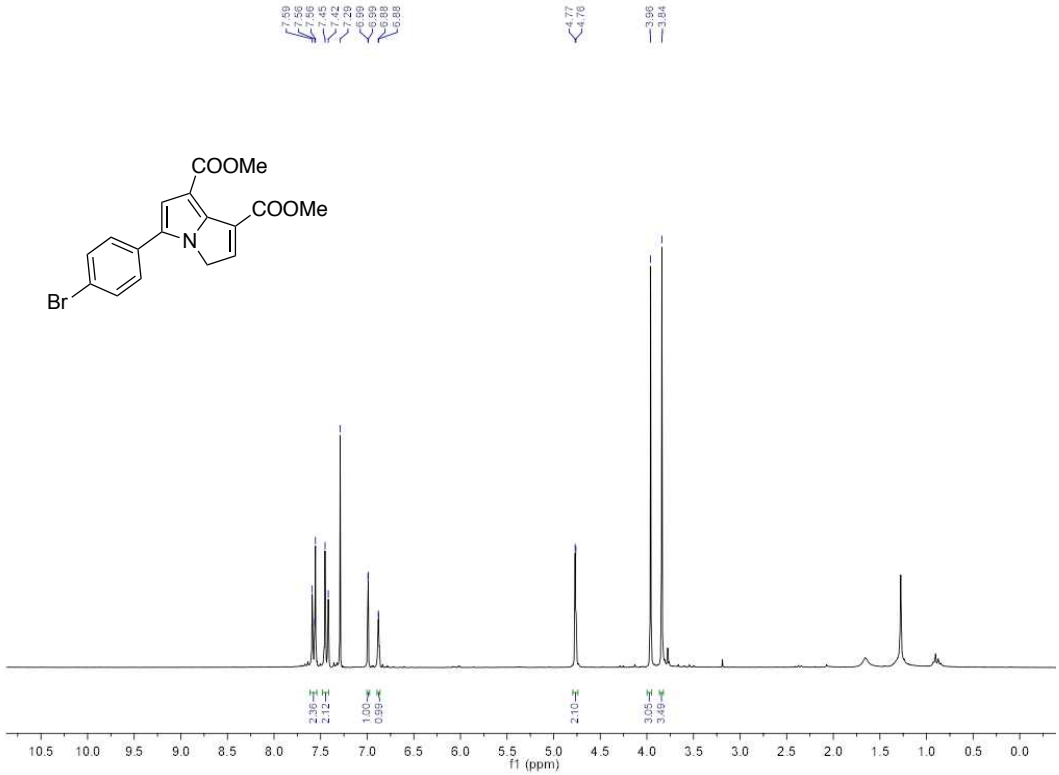


^{13}C NMR (63 MHz, $CDCl_3$)

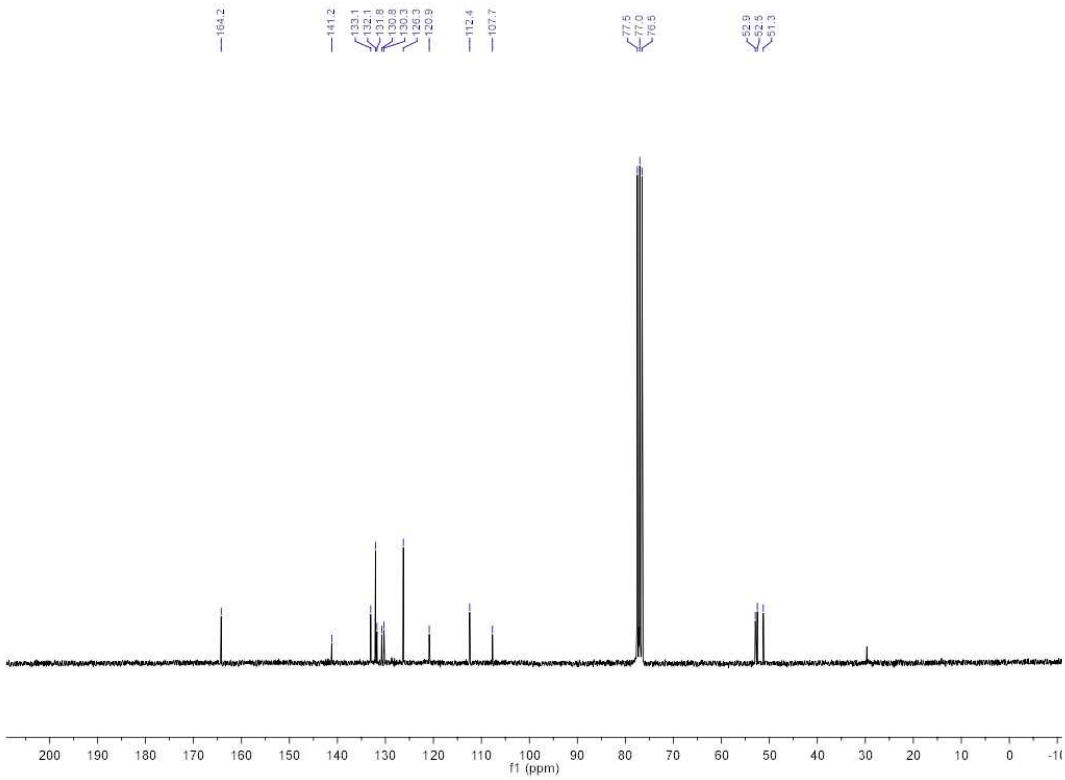


Dimethyl 5-(4-bromophenyl)-3*H*-pyrrolizine-1,7-dicarboxylate (12a)

^{1}H NMR (250 MHz, $CDCl_3$)

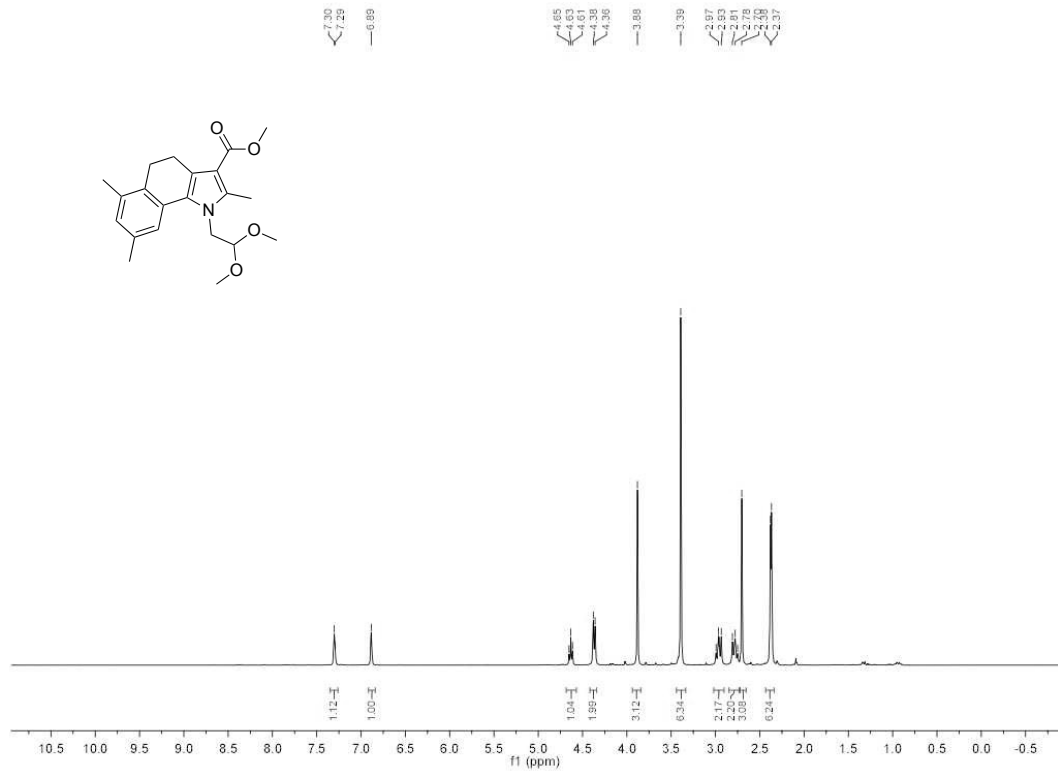


^{13}C NMR (63 MHz, $CDCl_3$)

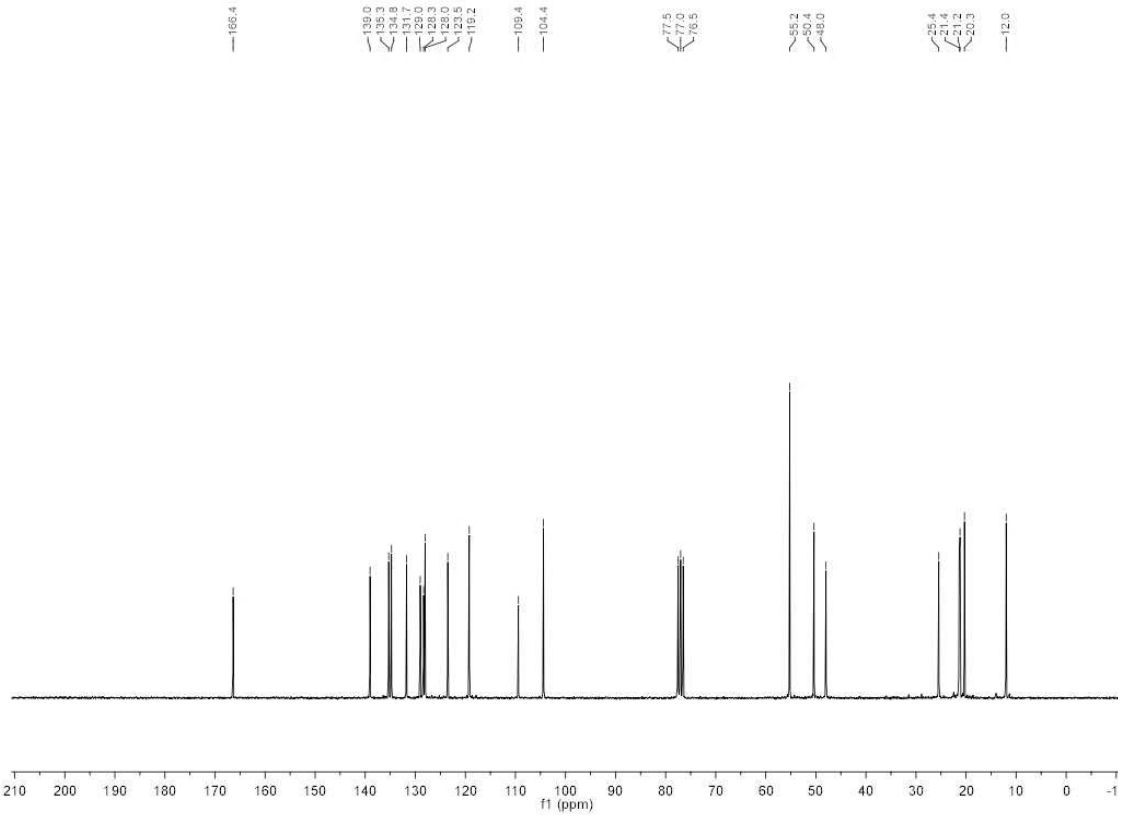


Methyl 1-(2,2-dimethoxyethyl)-2,6,8-trimethyl-4,5-dihydro-1*H*-benzo[*g*]indole-3-carboxylate (13s)

^{1}H NMR (250 MHz, $CDCl_3$)

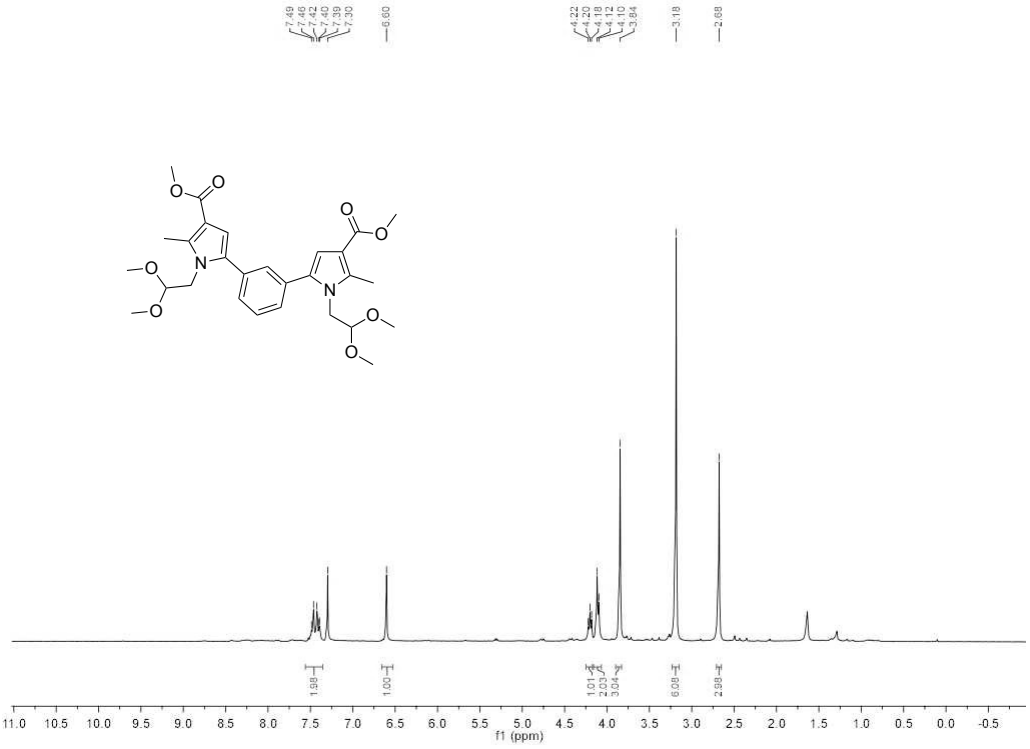


^{13}C NMR (63 MHz, $CDCl_3$)

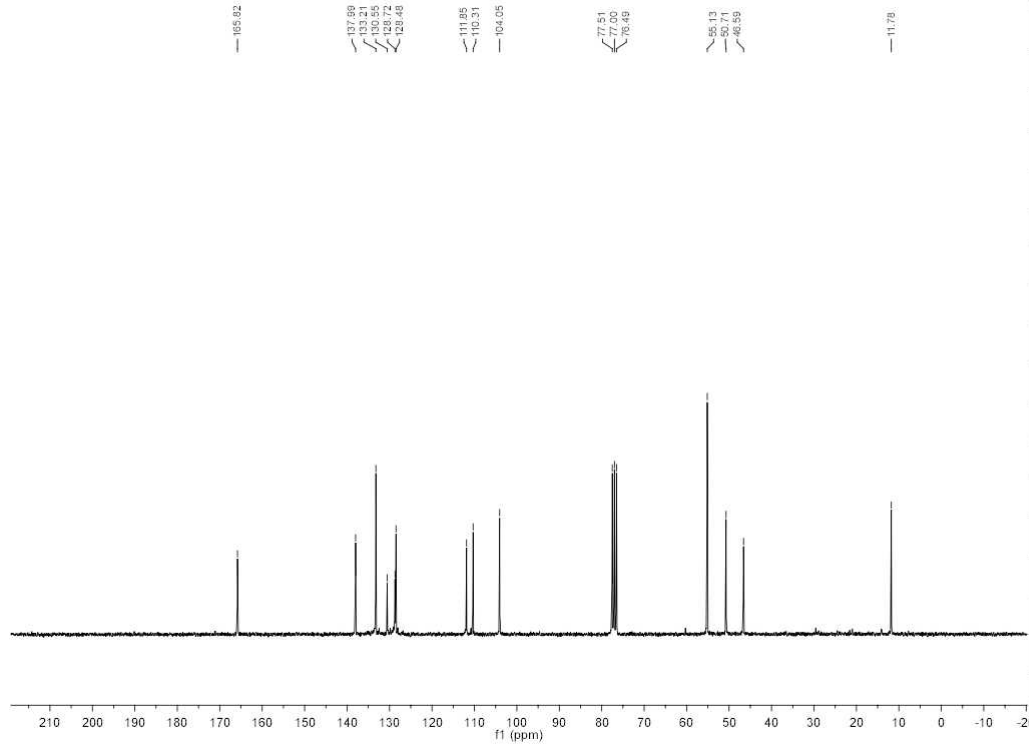


Dimethyl 5,5'-(1,3-phenylene)bis(1-(2,2-dimethoxyethyl)-2-methyl-1*H*-pyrrole-3-carboxylate) (6t)

^{1}H NMR (250 MHz, $CDCl_3$)

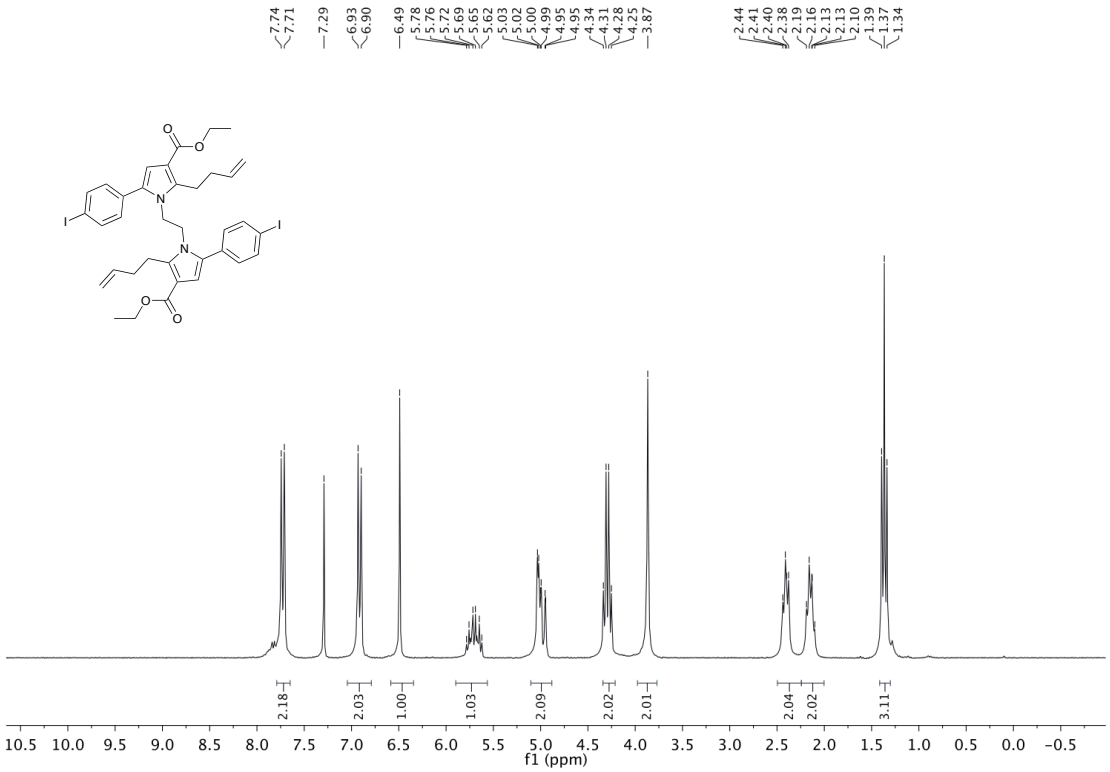


^{13}C NMR (63 MHz, $CDCl_3$)

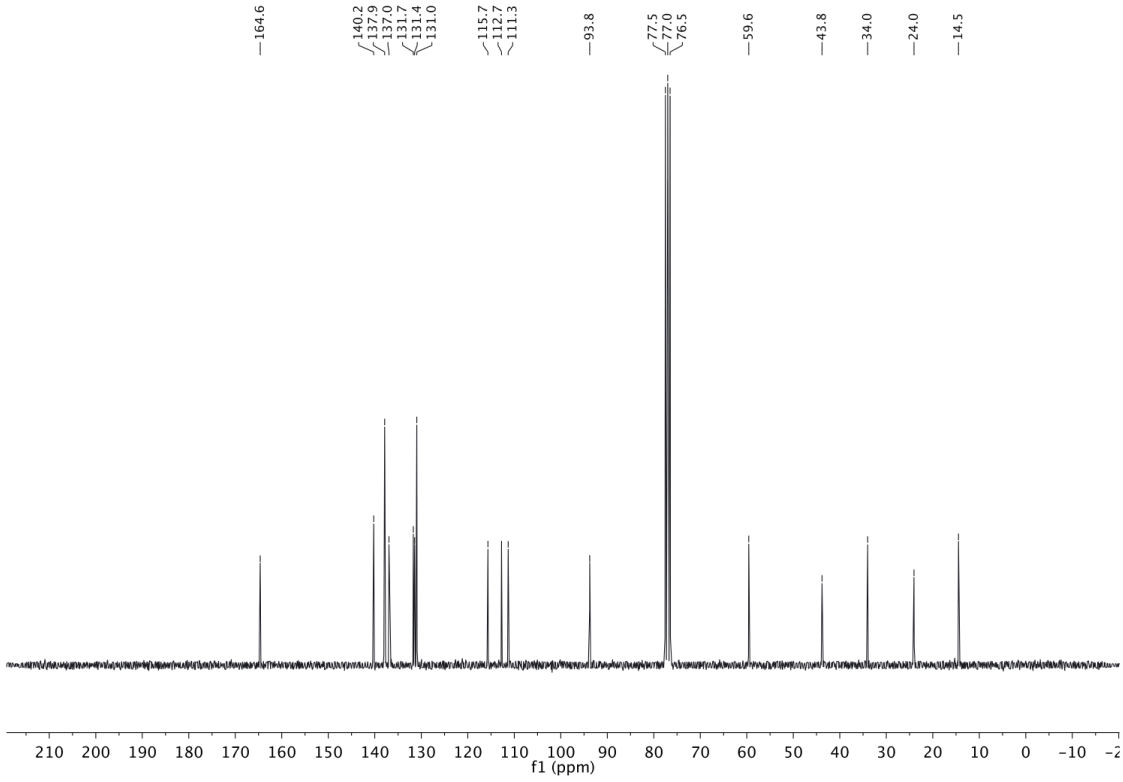


Diethyl-1,1'-(ethane-1,2-diyl)bis(2-(but-3-en-1-yl)-5-(4-iodophenyl)-1*H*-pyrrole-3-carboxylate) (15b)

P^1H NMR (250 MHz, $CDCl_3$)

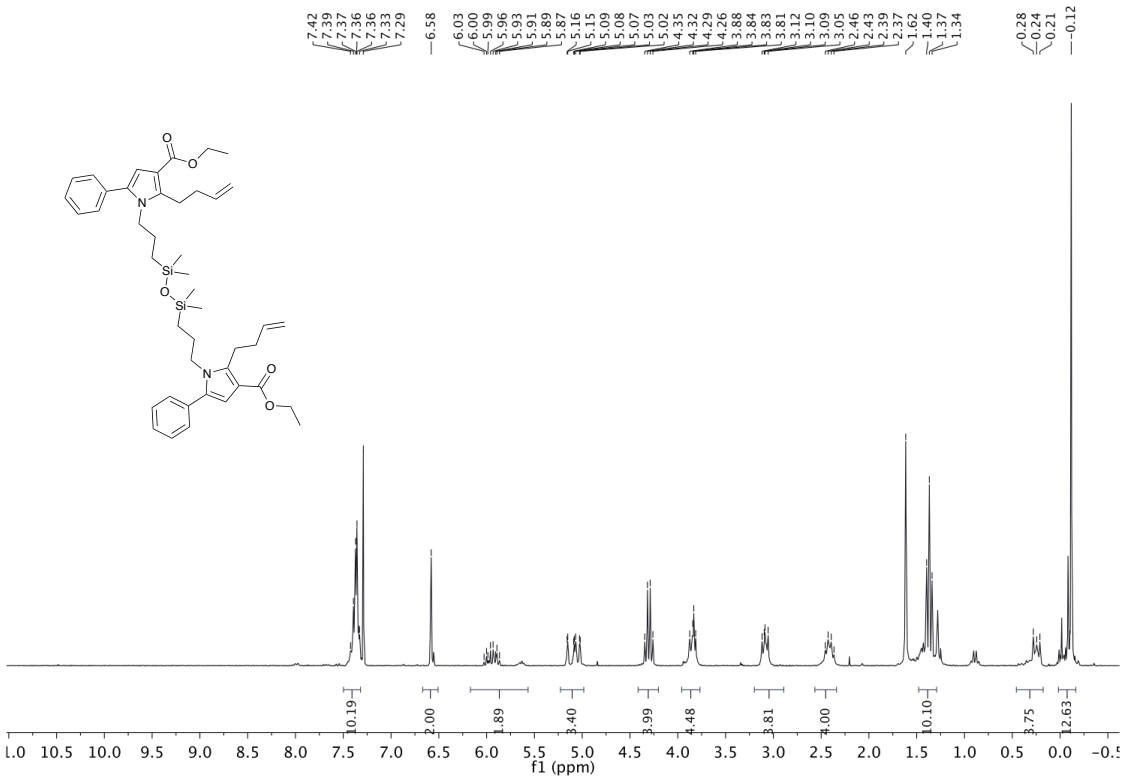


^{13}C NMR (63 MHz, $CDCl_3$)

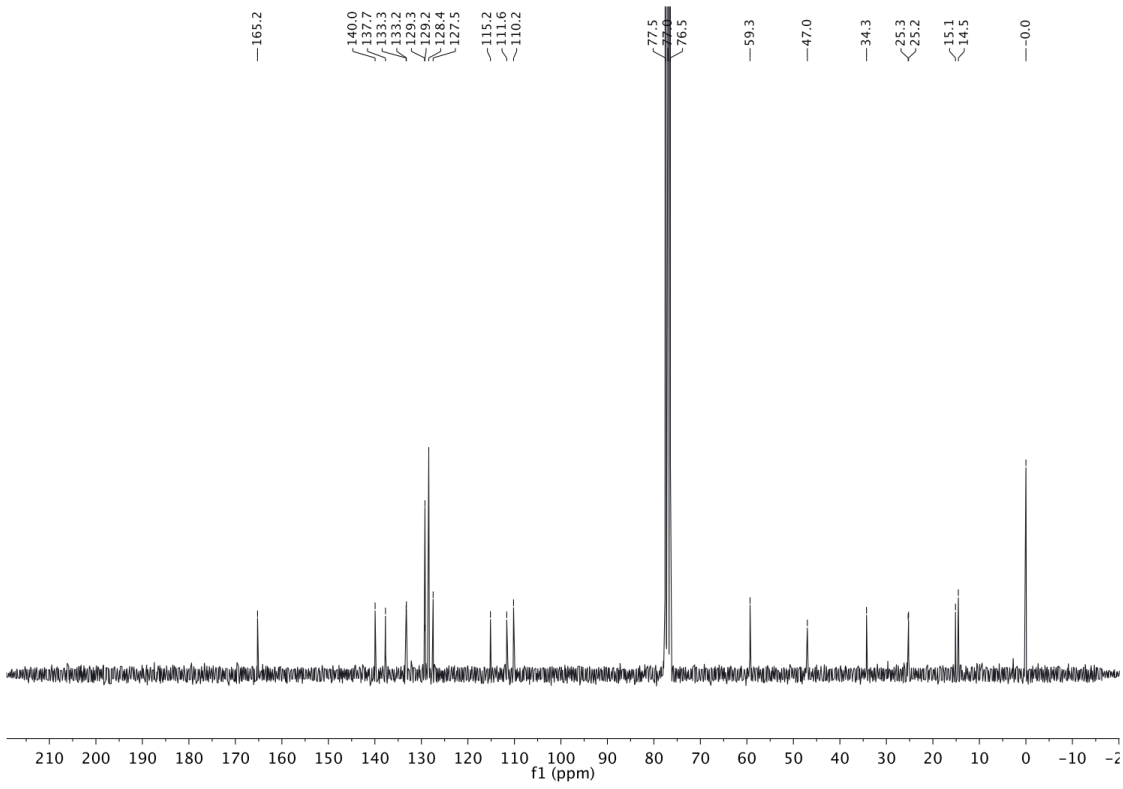


Diethyl-1,1'-((1,1,3,3-tetramethyldisiloxane-1,3-diyl)bis(propane-3,1-diyl))bis(2-(but-3-en-1-yl)-5-phenyl-1*H*-pyrrole-3-carboxylate) (15h)

^{1}H NMR (250 MHz, $CDCl_3$)

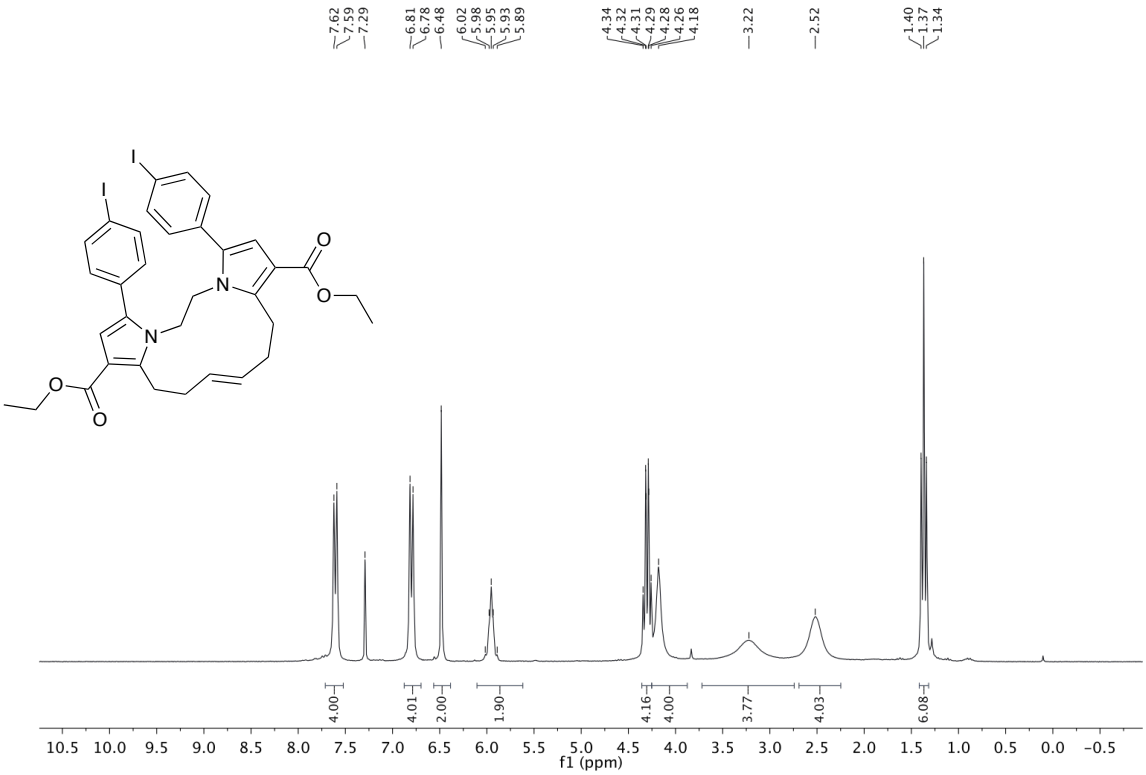


^{13}C NMR (63 MHz, $CDCl_3$)

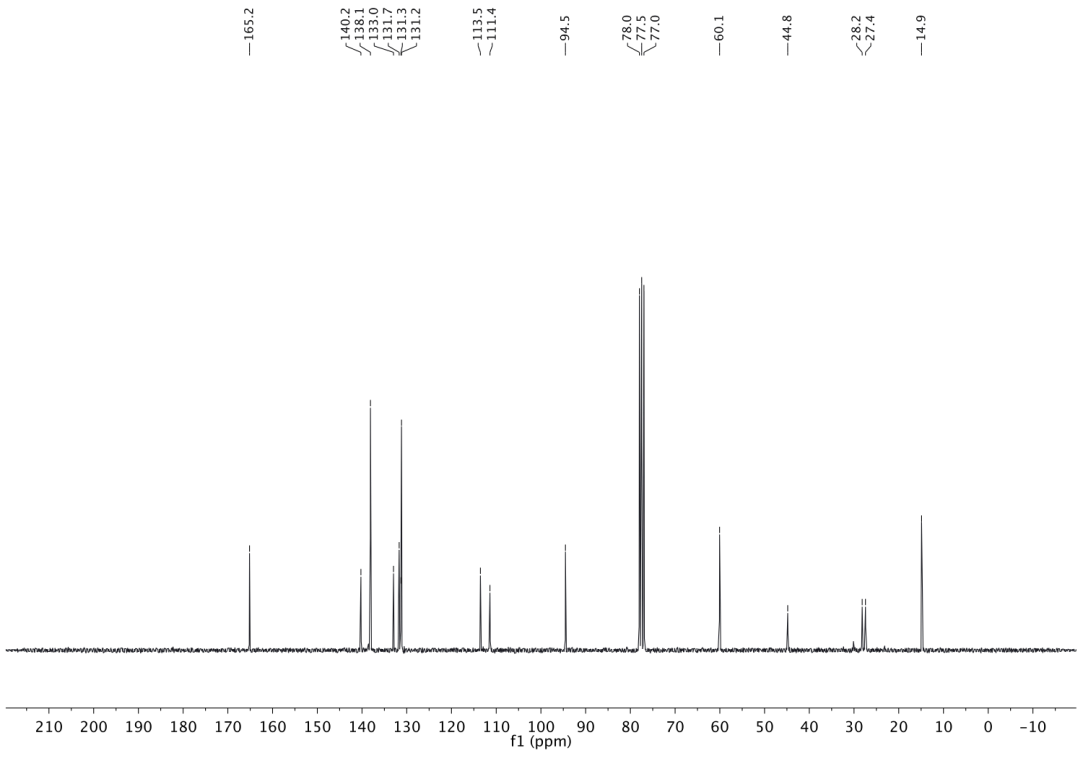


Diethyl-(*Z*)-1,12-bis(4-iodophenyl)-4,5,8,9,14,15-hexahydrodipyrrolo[1,2-*d*:2',1'-*l*][1,4]diazacyclododecine-3,10-dicarboxylate (16b)

^{1}H NMR (250 MHz, $CDCl_3$)



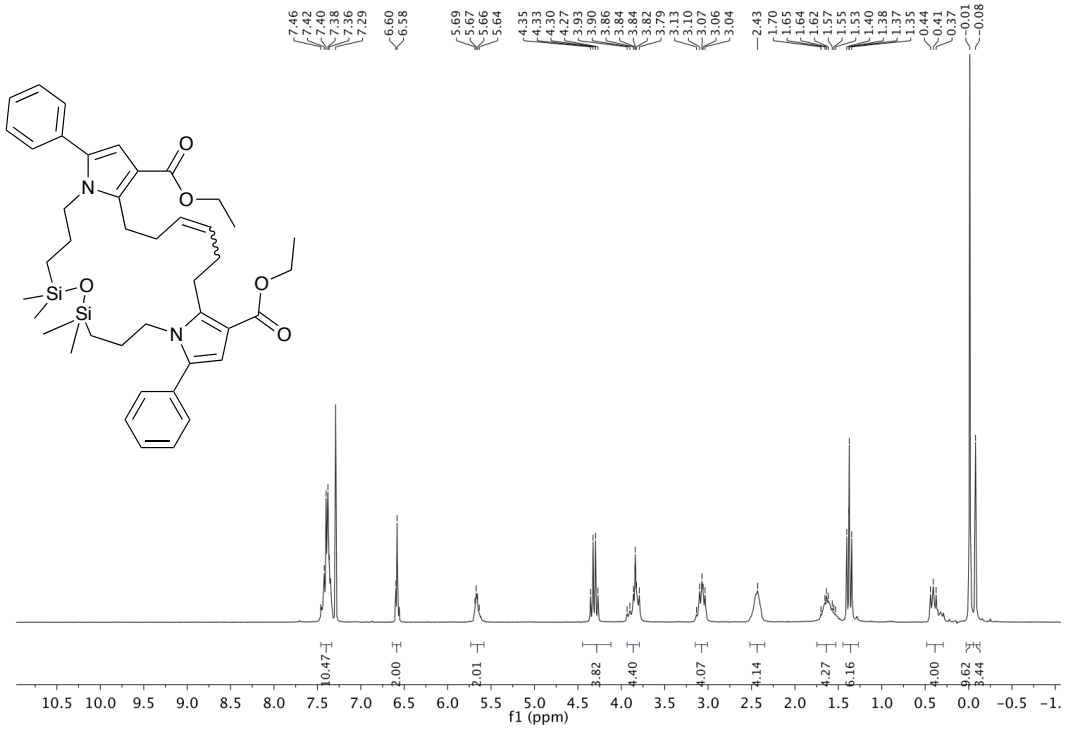
^{13}C NMR (63 MHz, $CDCl_3$)



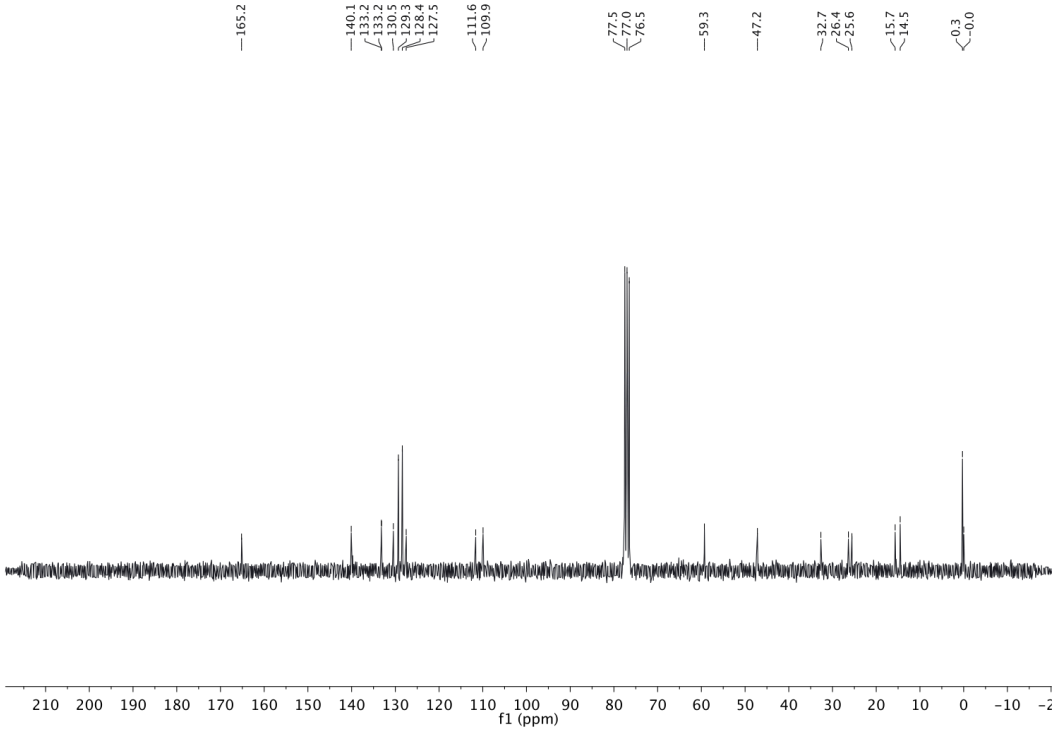
Diethyl 8,8,10,10-tetramethyl-3,15-diphenyl-5,6,7,8,10,11,12,13,18,19,22,23-dodecahydrodipyrrolo[1,2-*f*:2',1'-*n*][1]oxa[6,15]diaza[2,19]disilacyclononadecine-1,17-dicarboxylate (16h)

This compound is a mix of isomer A and isomer B (as 6.5:3.5)

^{1}H NMR (250 MHz, $CDCl_3$)

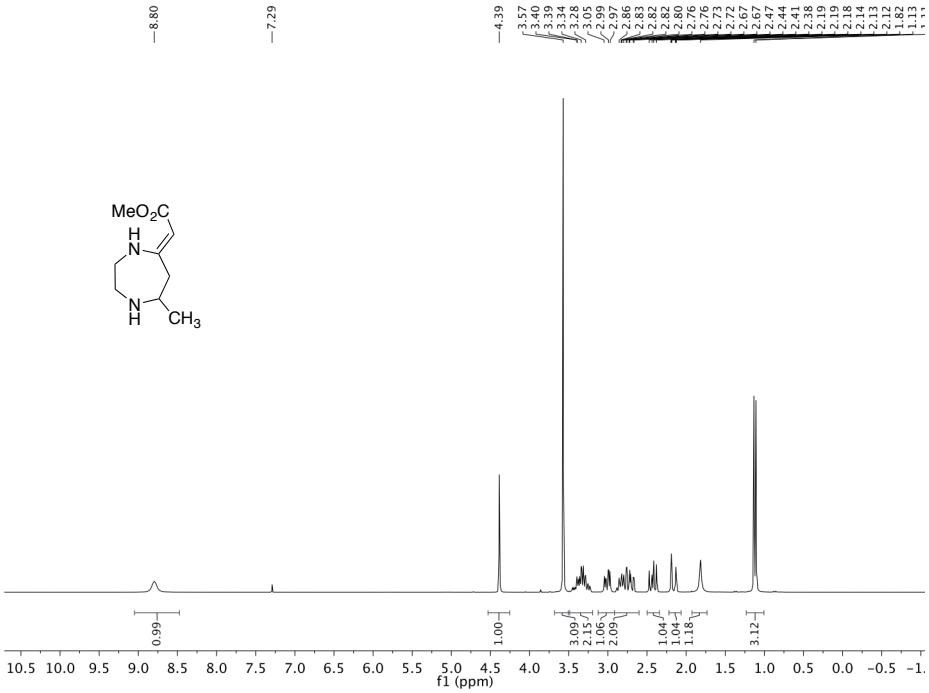


^{13}C NMR (63 MHz, $CDCl_3$)

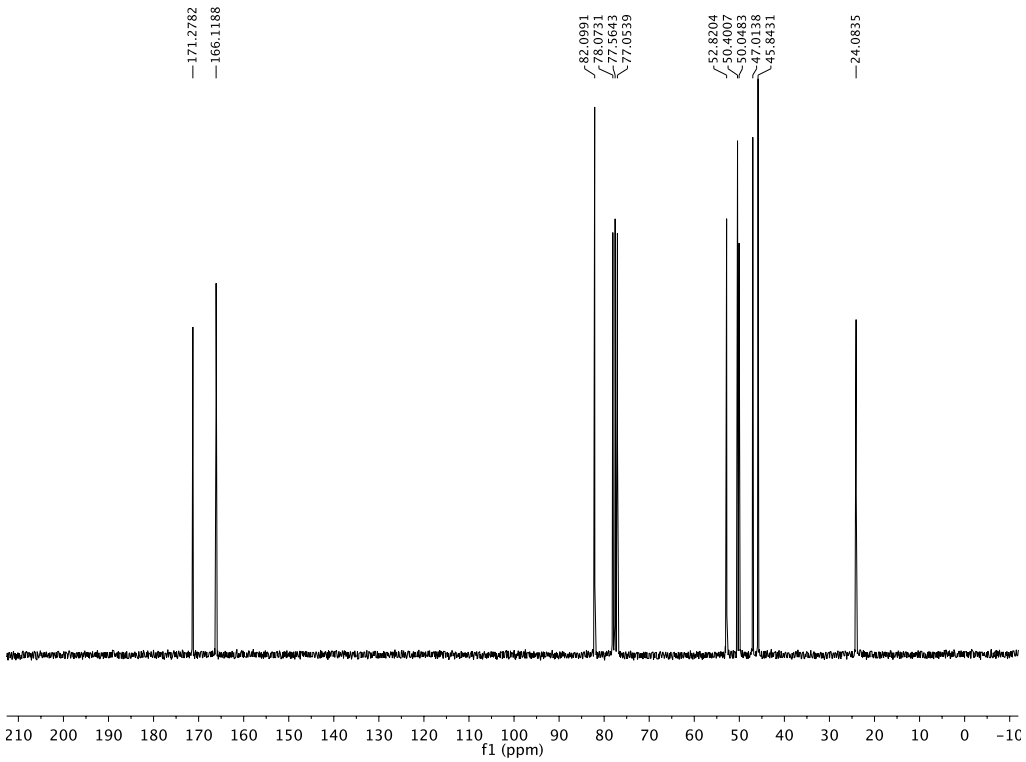


Methyl (*Z*)-2-(7-methyl-1,4-diazepan-5-ylidene)acetate (17a)

^{1}H NMR (250 MHz, $CDCl_3$)

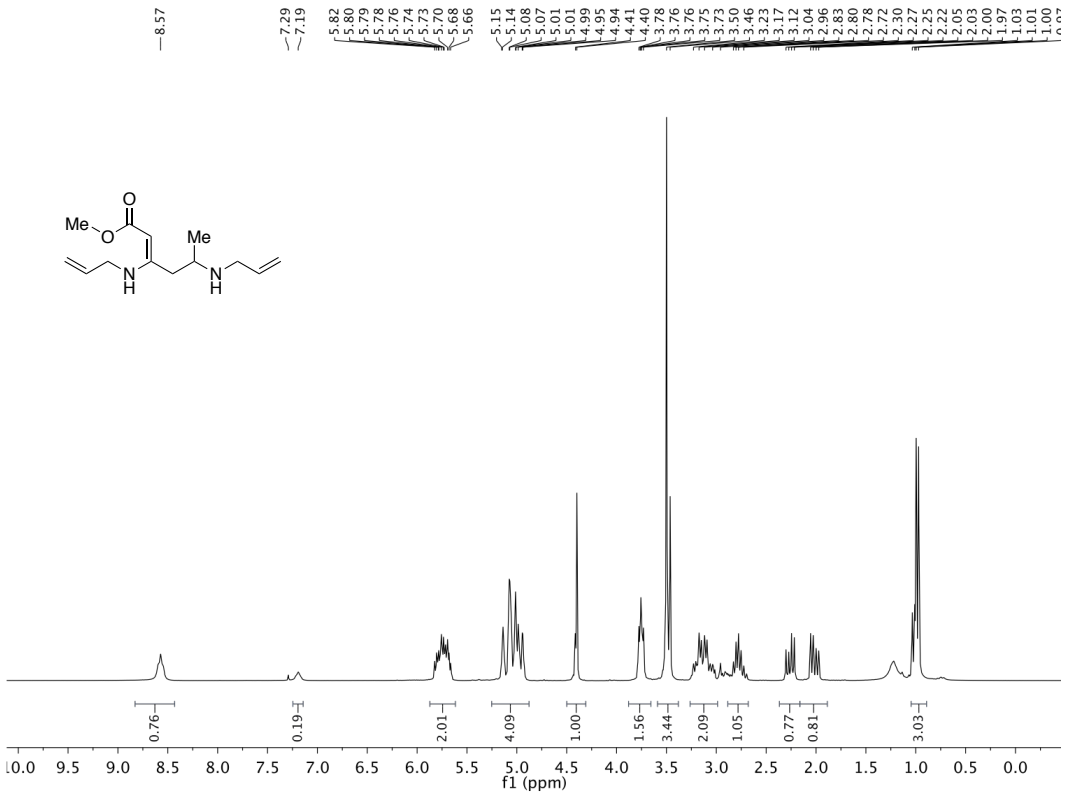


^{13}C NMR (63 MHz, $CDCl_3$)

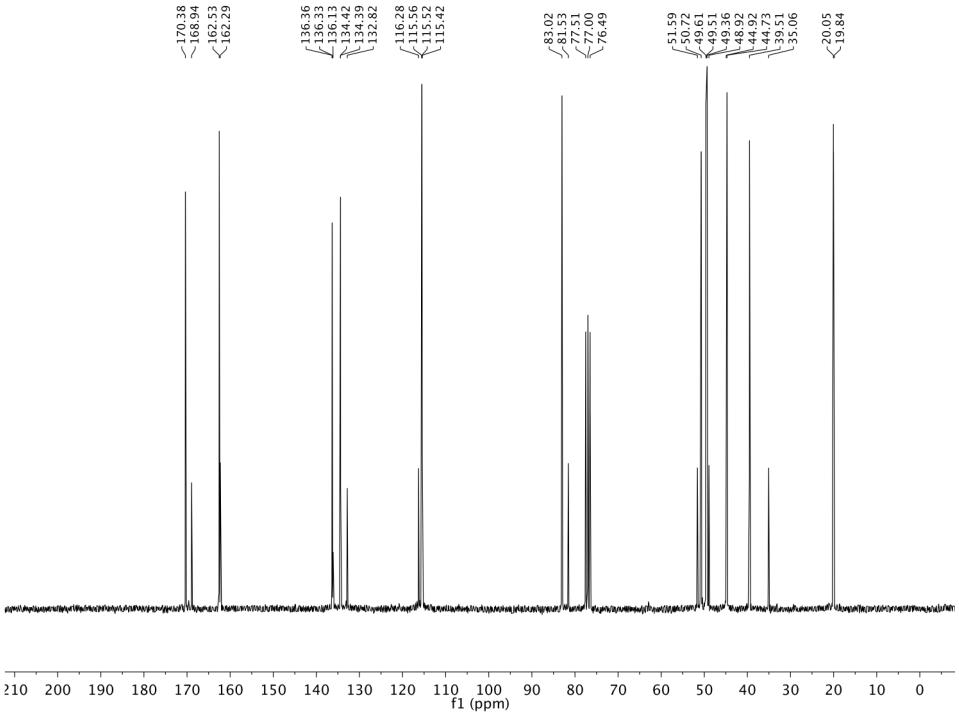


Methyl 3,5-bis(allylamino)hex-2-enoate (18)

^{1}H NMR (250 MHz, $CDCl_3$)

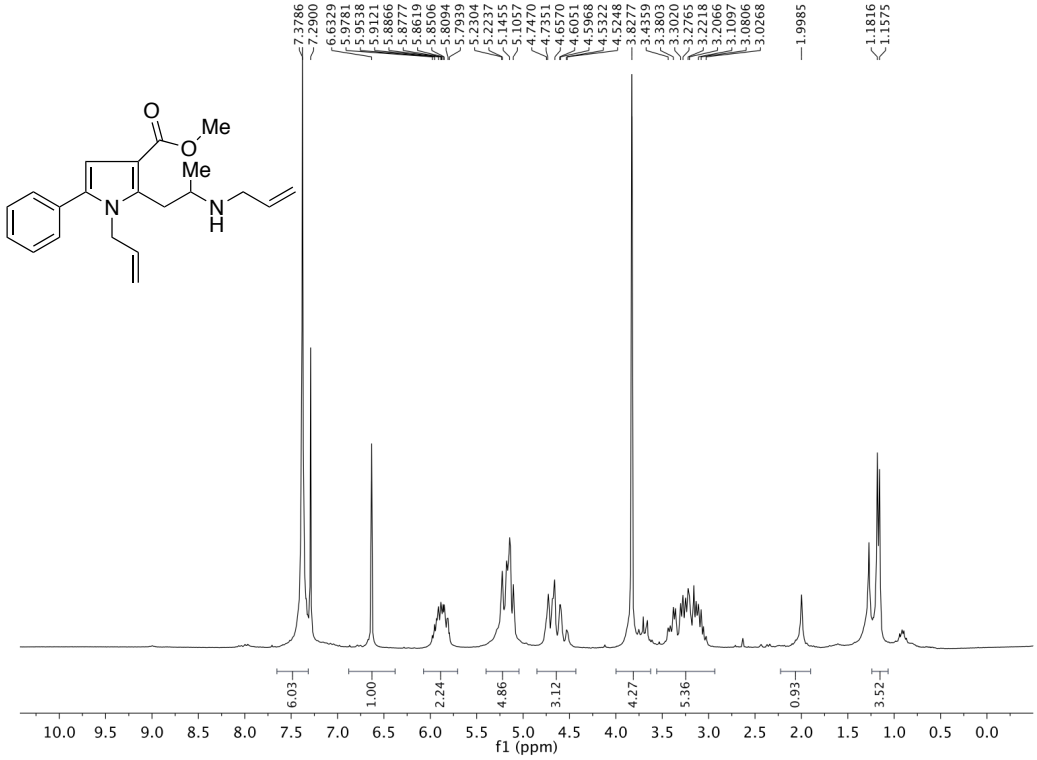


^{13}C NMR (63 MHz, $CDCl_3$)

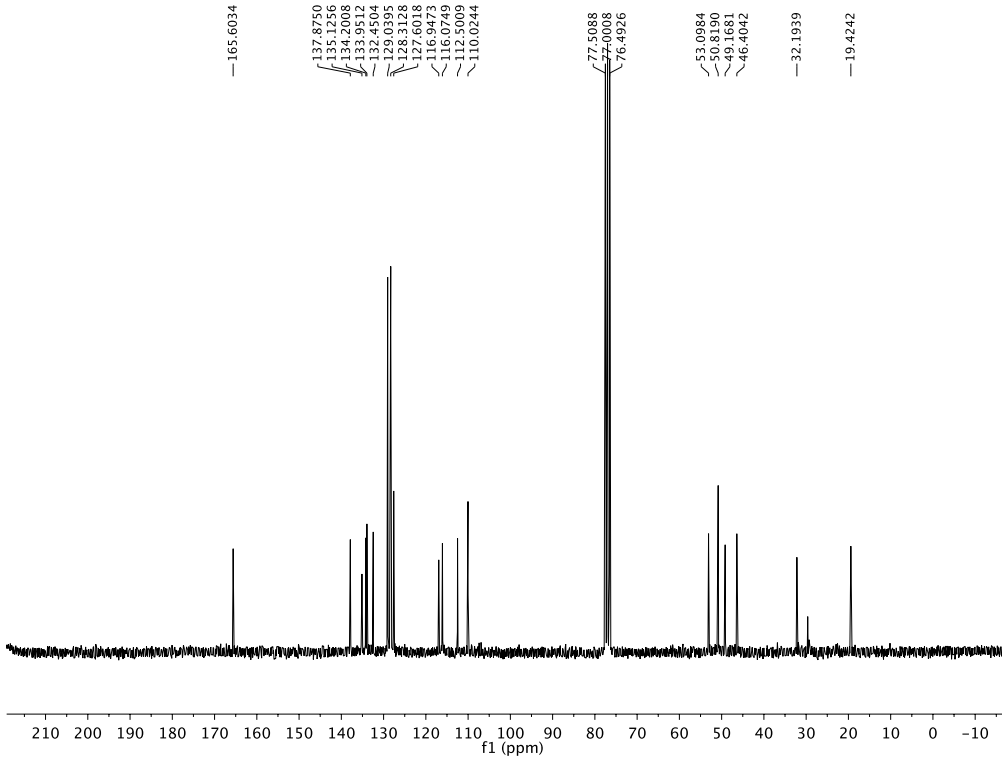


Methyl 1-allyl-2-(2-(allylamino)propyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (19a)

^{1}H NMR (250 MHz, $CDCl_3$)

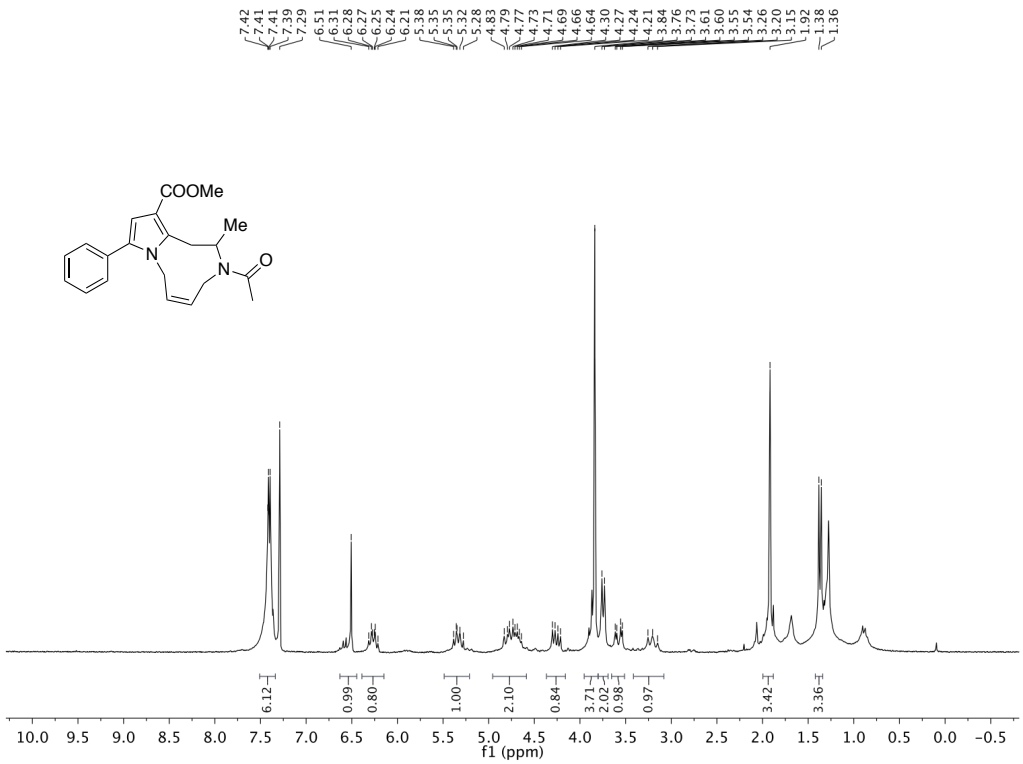


^{13}C NMR (63 MHz, $CDCl_3$)

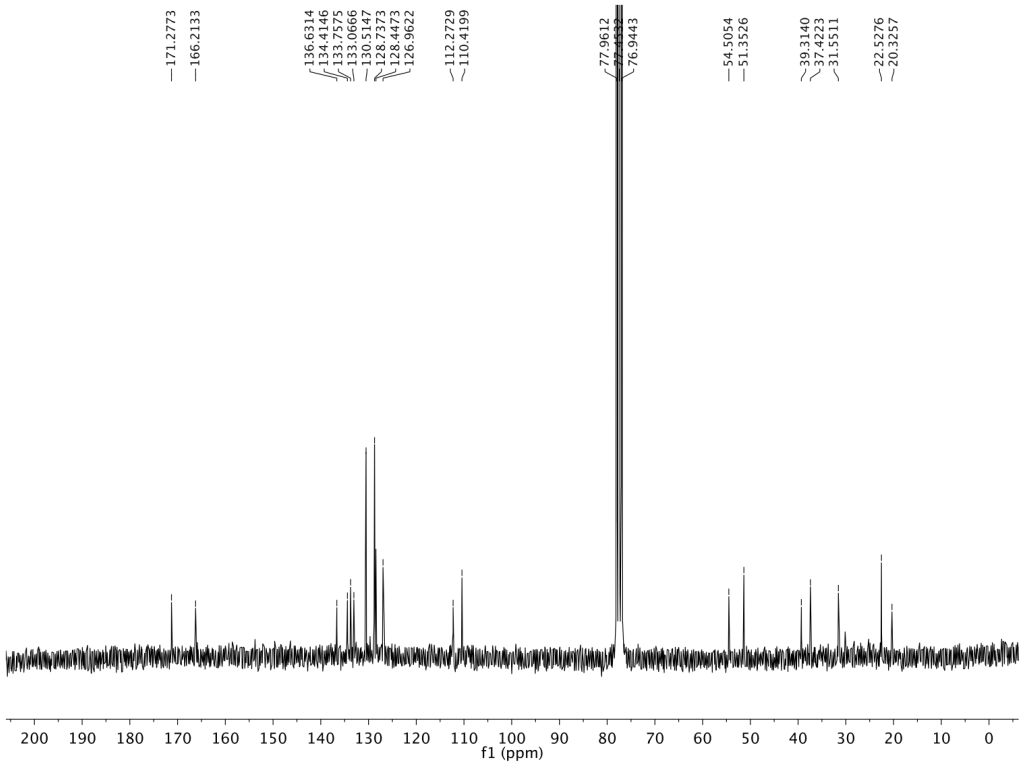


Methyl (*Z*)-3-acetyl-2-methyl-9-phenyl-2,3,4,7-tetrahydro-1*H*-pyrrolo[1,2-*a*][1,5]diazonine-11-carboxylate (20)

^{1}H NMR (250 MHz, $CDCl_3$)

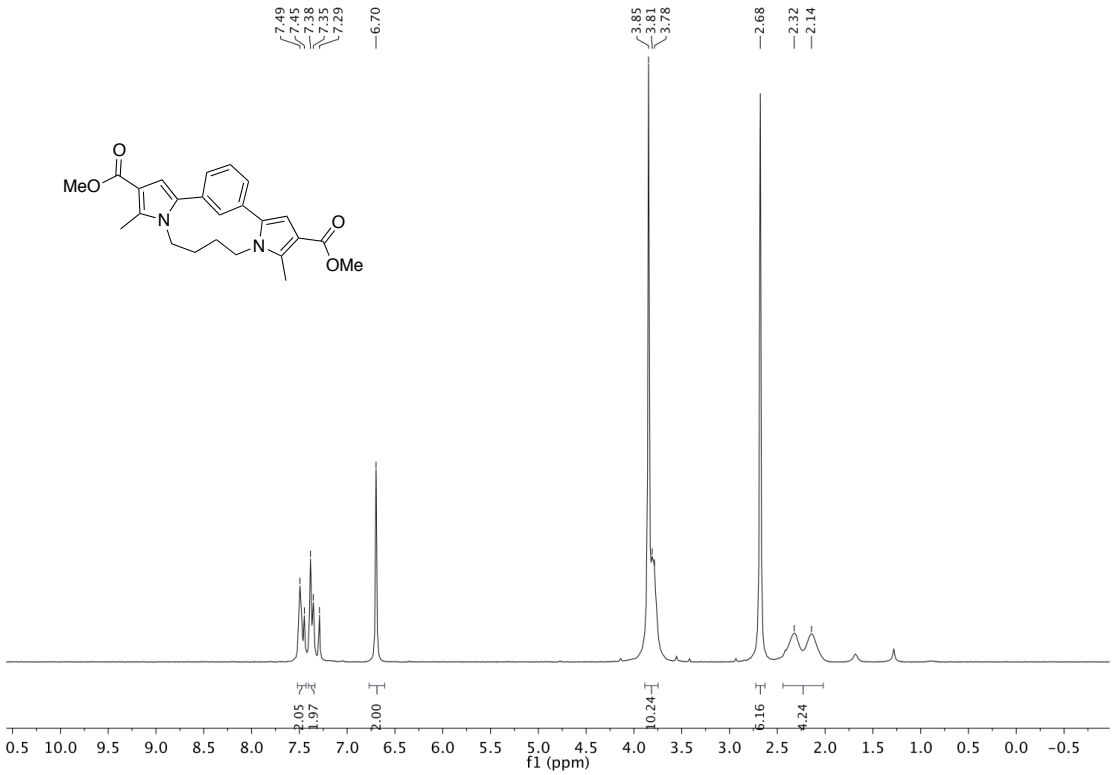


^{13}C NMR (63 MHz, $CDCl_3$)

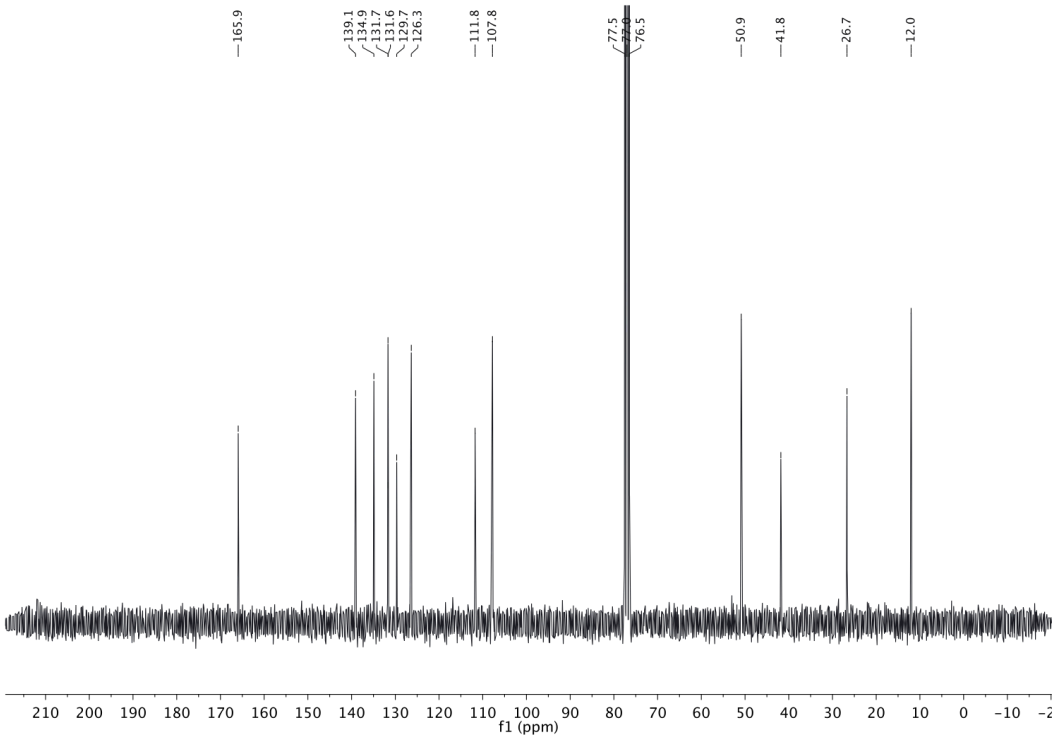


Dimethyl-3,10-dimethyl-5,6,7,8-tetrahydro-13,17-(metheno)dipyrrolo[1,2-*f*:2',1'-*m*][1,6]diazacyclotridecine-2,11-dicarboxylate (21a)

^{1}H NMR (250 MHz, $CDCl_3$)

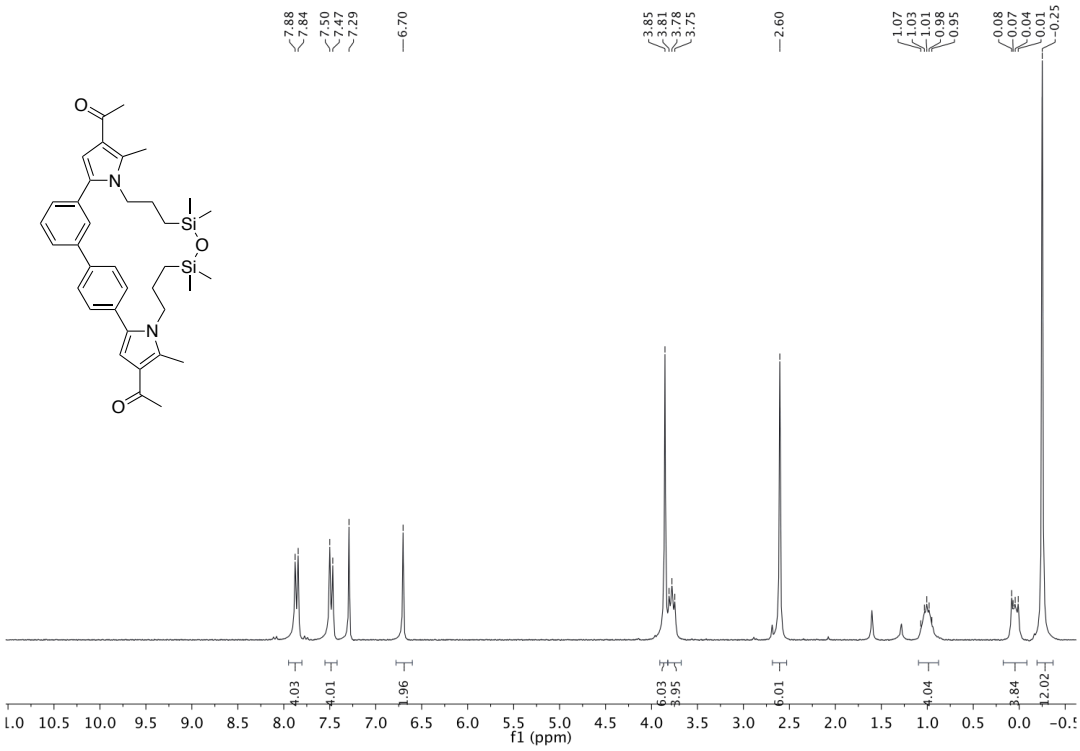


^{13}C NMR (63 MHz, $CDCl_3$)

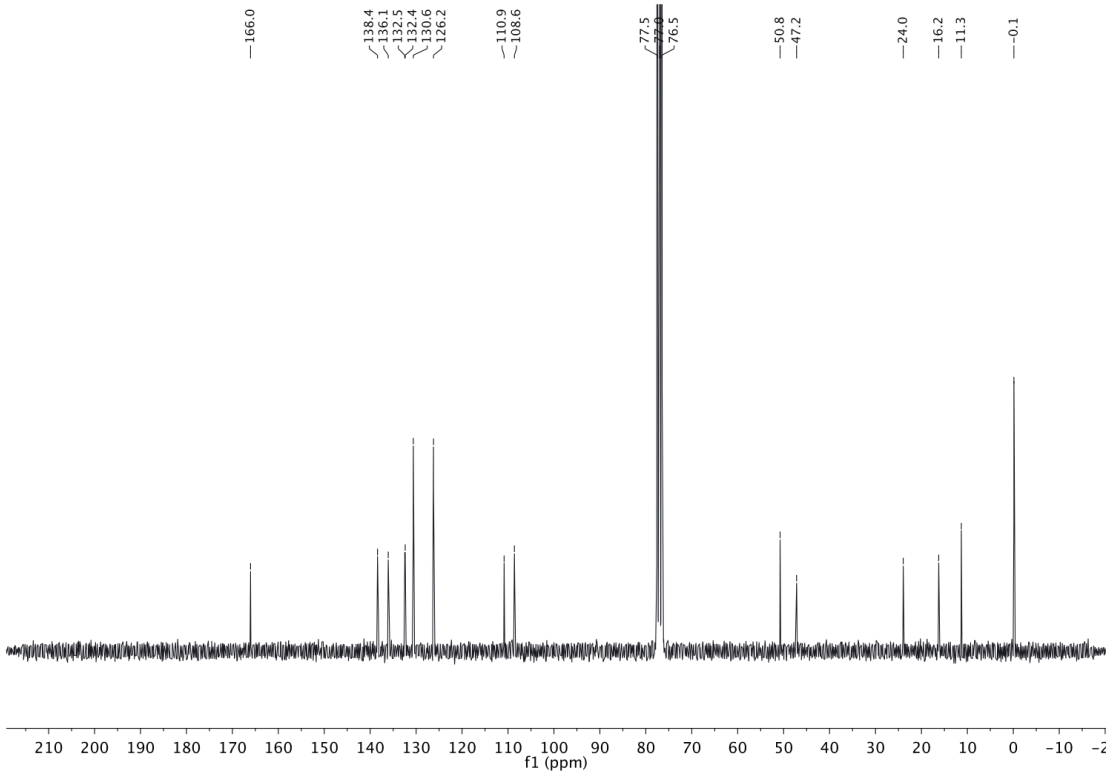


1,1'-(1^5,4^5,8,8,10,10-hexamethyl-1^1*H*,4^1*H*-9-oxa-8,10-disila-1,4(2,1)-dipyrrola-2(1,3),3(1,4)-dibenzenacyclotridecaphane-1^4,4^4-diyl)bis(ethan-1-one) (21f)

^{1}H NMR (250 MHz, $CDCl_3$)

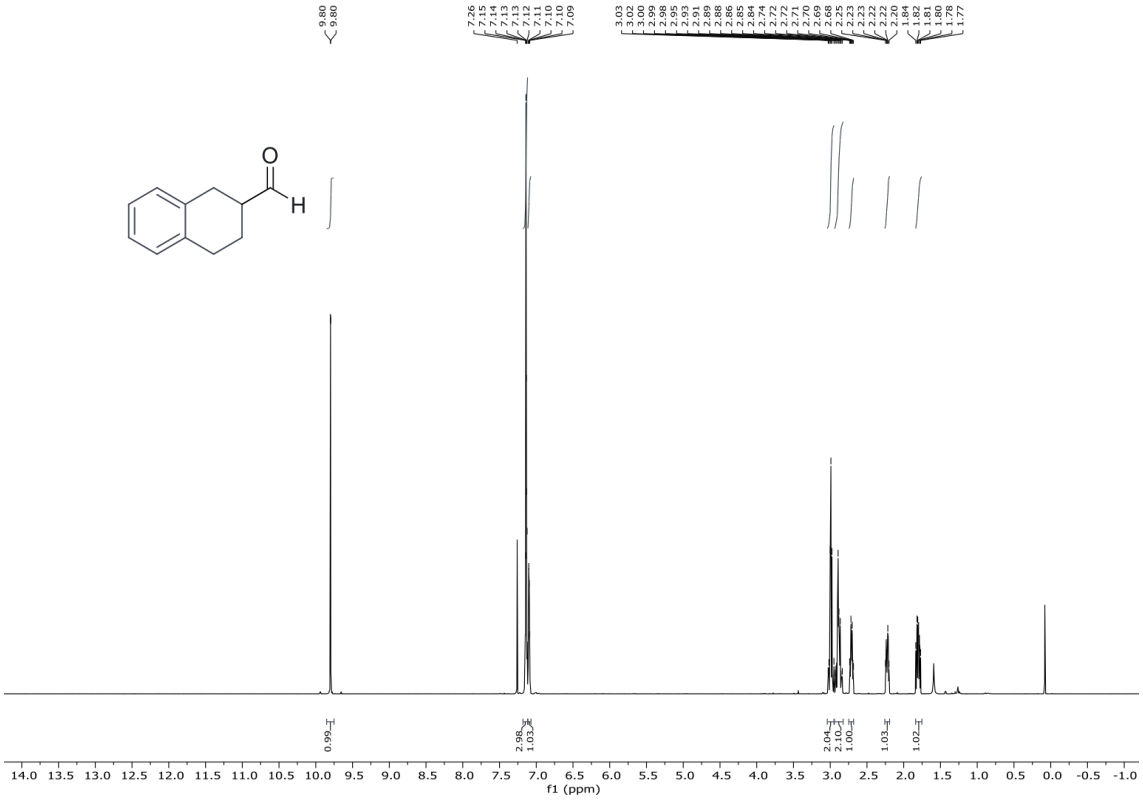


^{13}C NMR (63 MHz, $CDCl_3$)

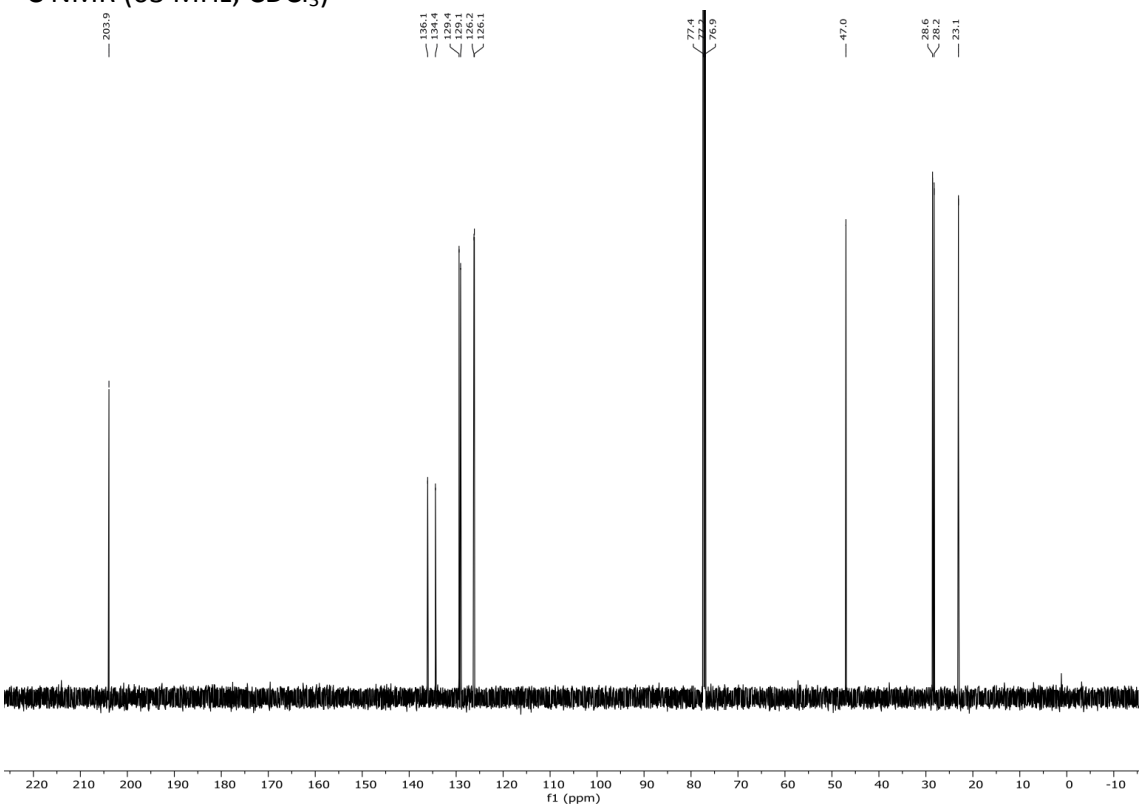


1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (22a)

^{1}H NMR (250 MHz, $CDCl_3$)

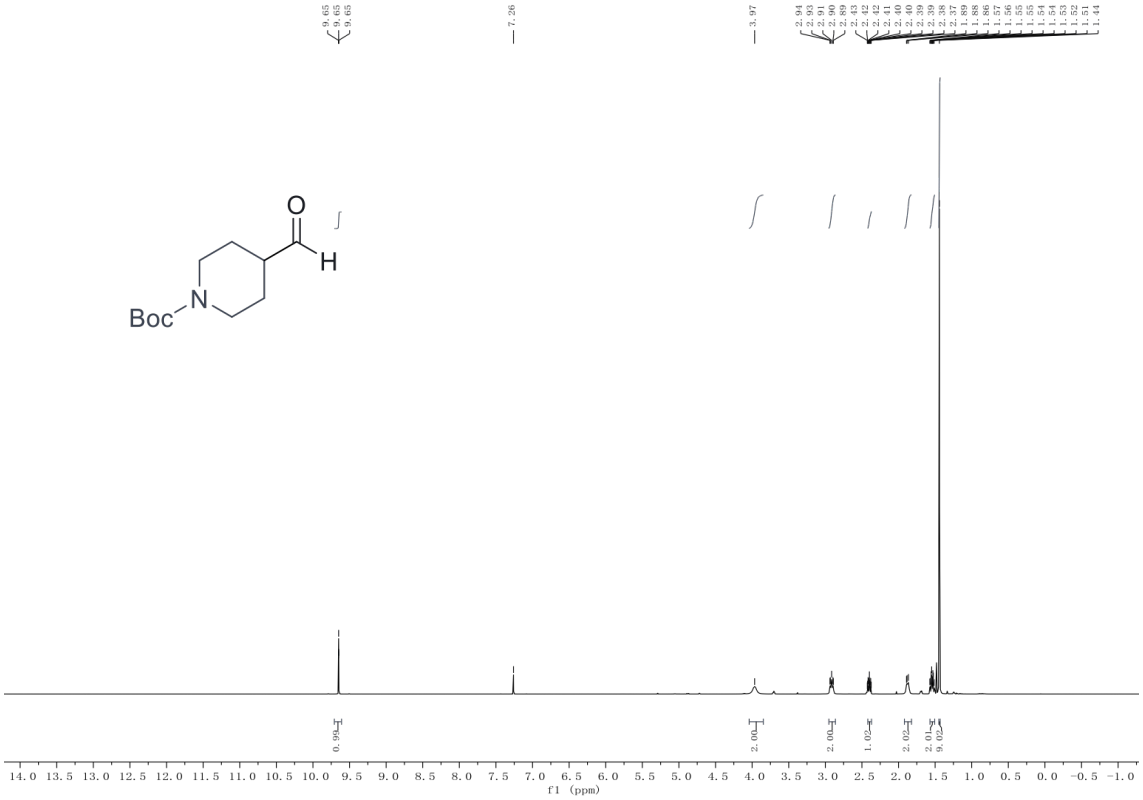


^{13}C NMR (63 MHz, $CDCl_3$)

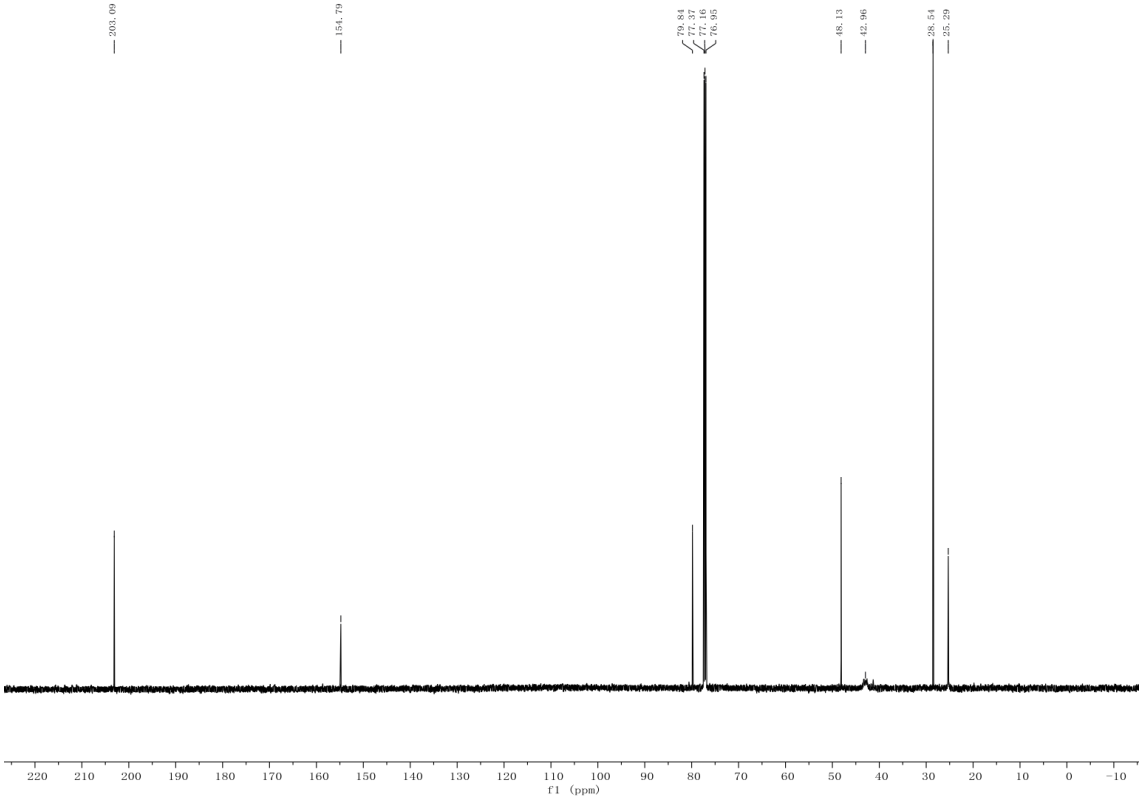


^{t}butyl 4-formylpiperidine-1-carboxylate (22f)

^{1}H NMR (250 MHz, $CDCl_3$)

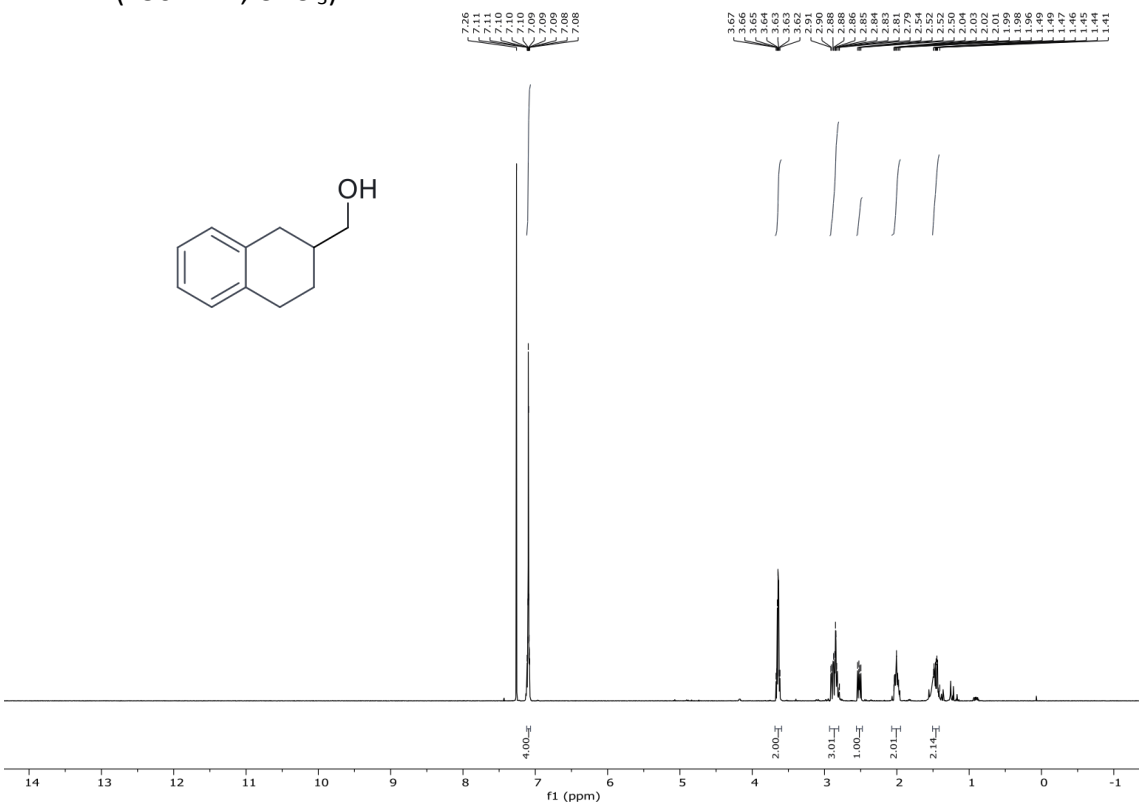


^{13}C NMR (63 MHz, $CDCl_3$)

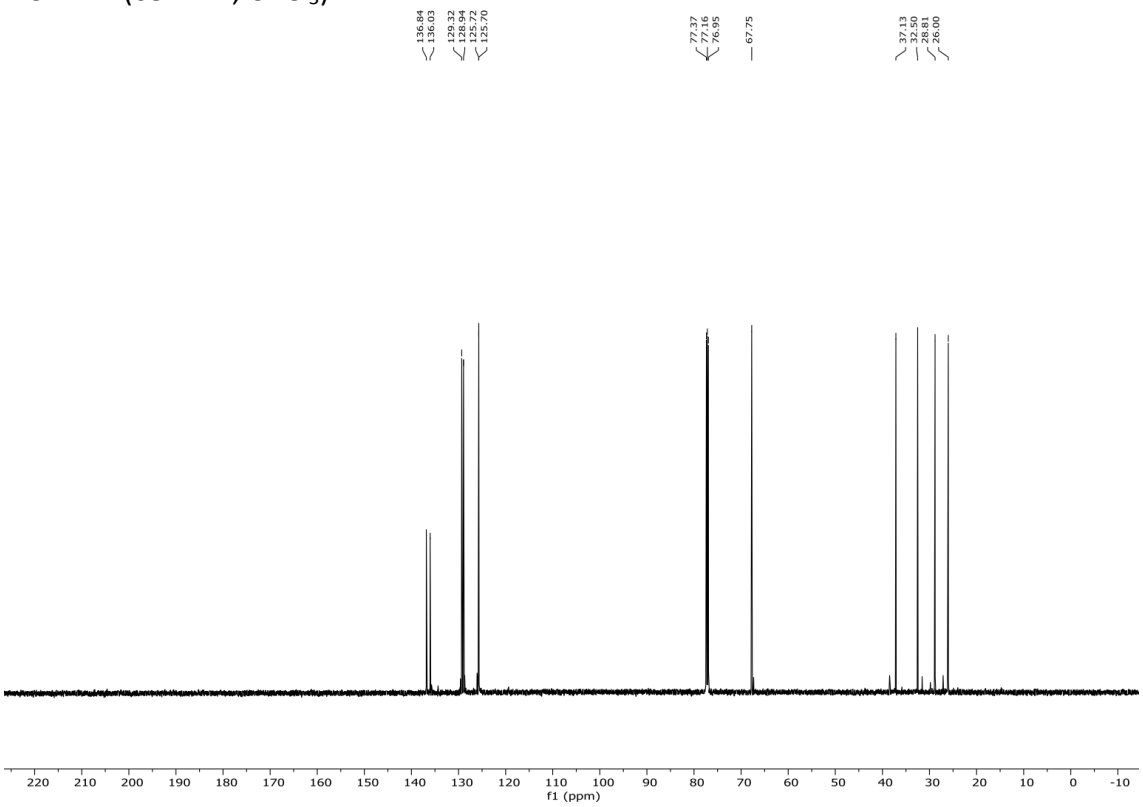


(1,2,3,4-tetrahydronaphthalen-2-yl)metanol (23a)

^{1}H NMR (250 MHz, $CDCl_3$)

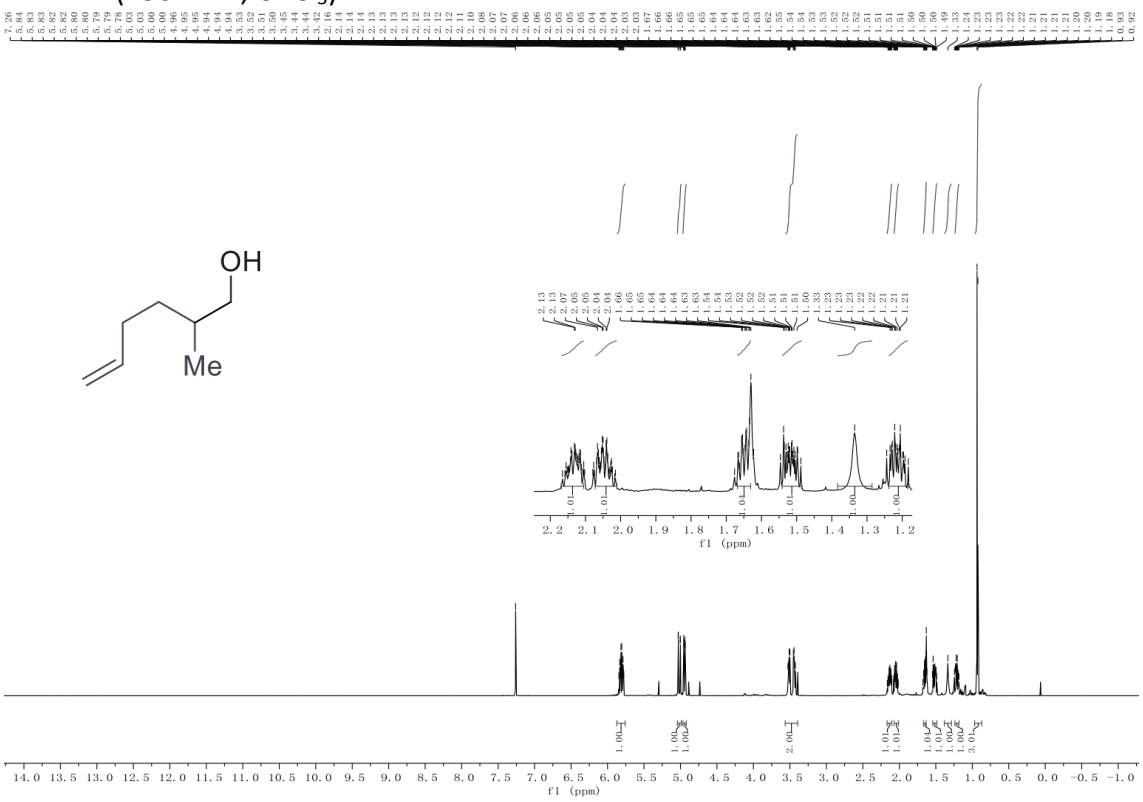


^{13}C NMR (63 MHz, $CDCl_3$)

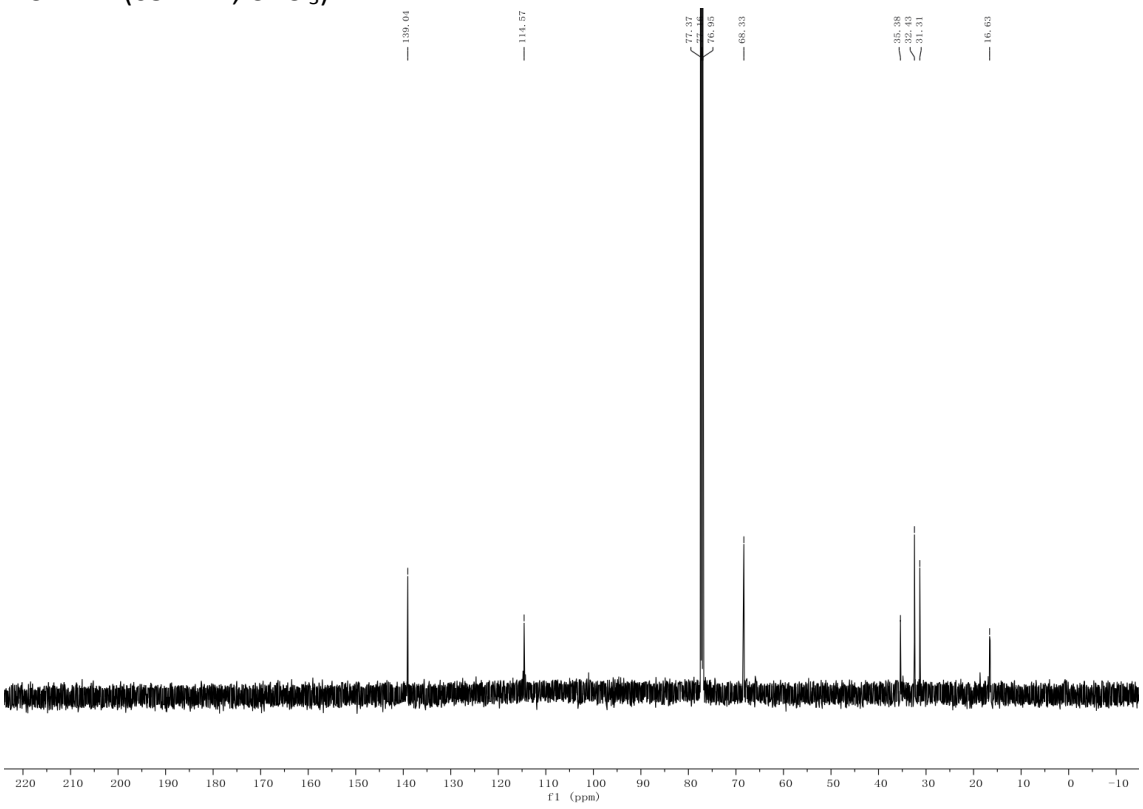


2-methylhex-5-en-1-ol (23n)

^{1}H NMR (250 MHz, $CDCl_3$)

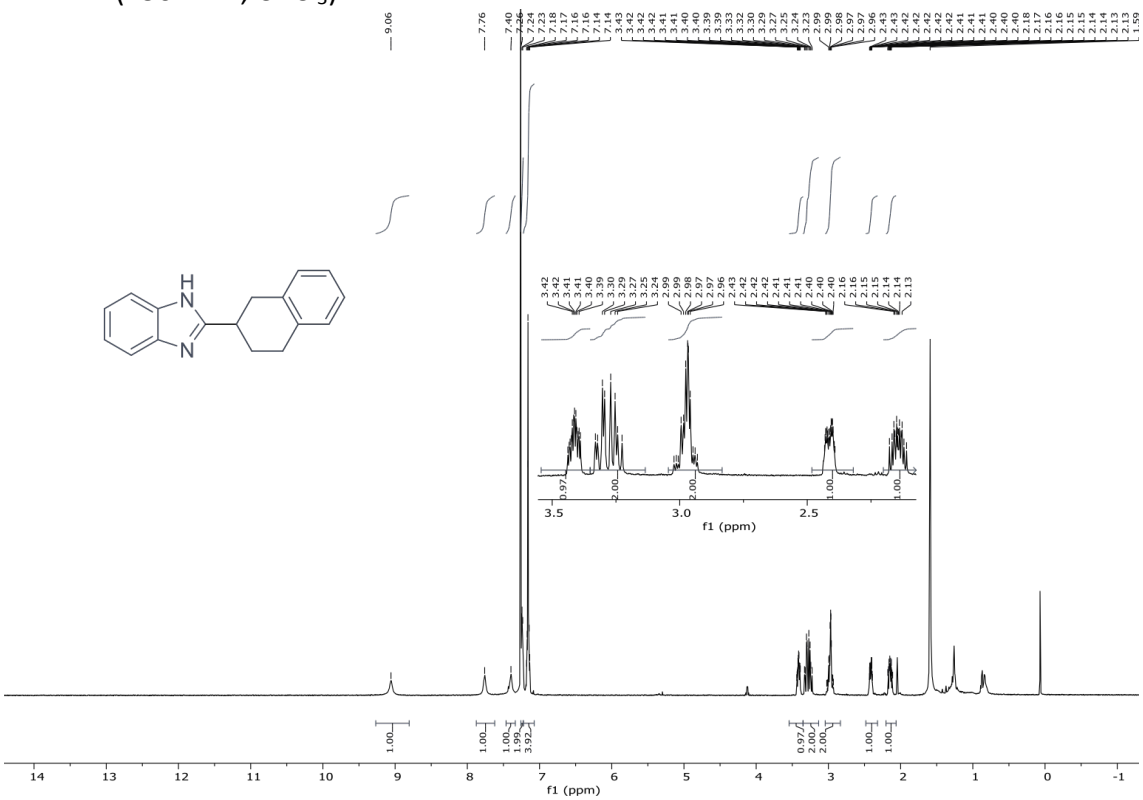


^{13}C NMR (63 MHz, $CDCl_3$)

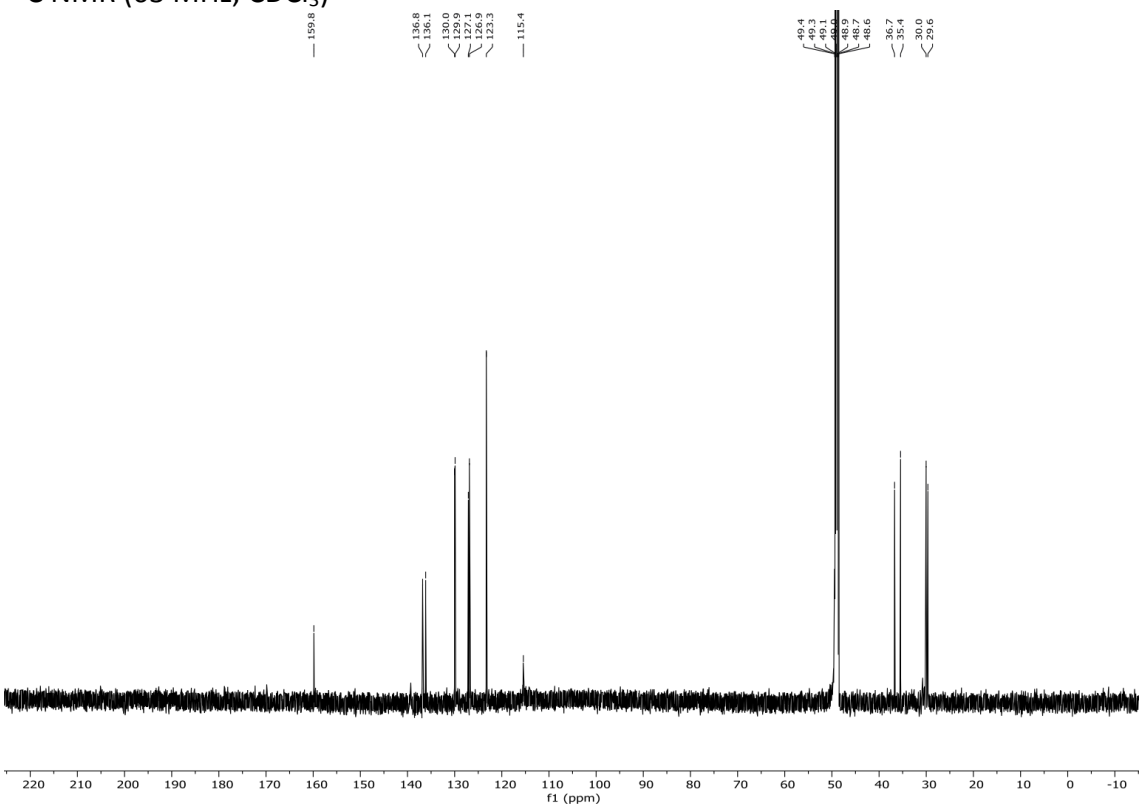


2-(1,2,3,4-tetrahydronaphthalen-2-yl)-1*H*-benzimidazole (24a)

^{1}H NMR (250 MHz, $CDCl_3$)

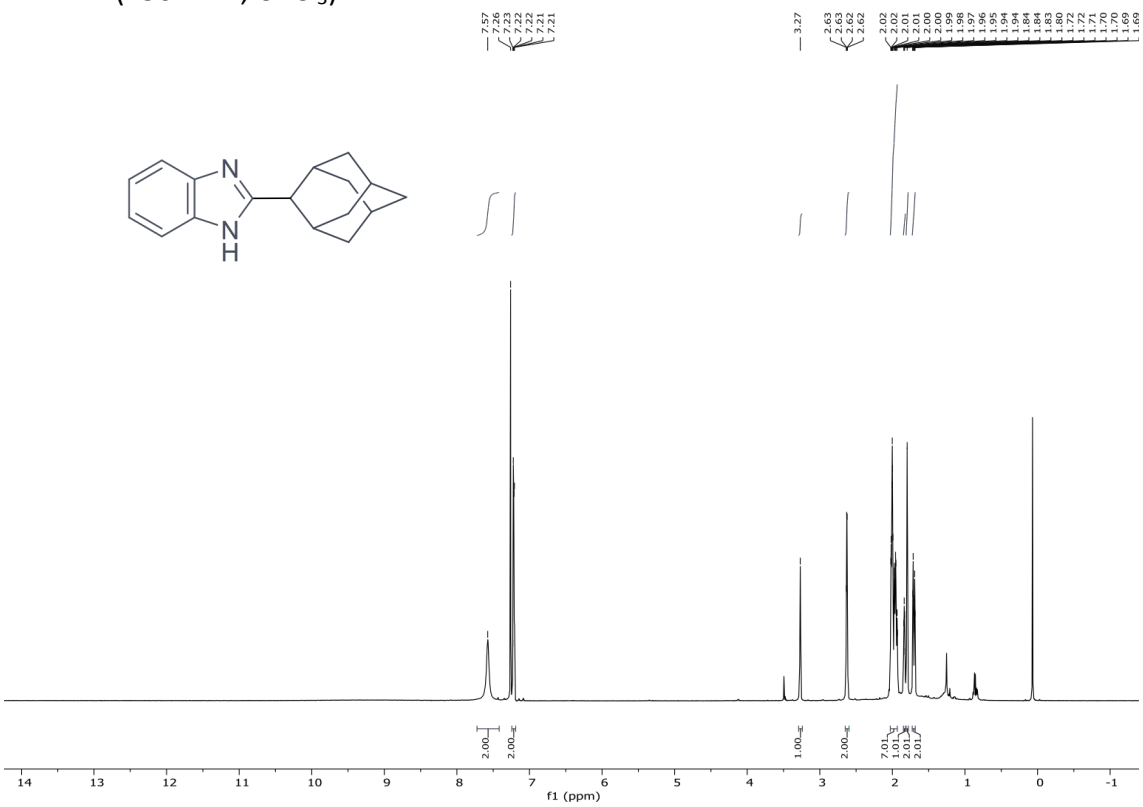


^{13}C NMR (63 MHz, $CDCl_3$)



2-(adamantan-2-yl)-1*H*-benzimidazole (24h)

^{1}H NMR (250 MHz, $CDCl_3$)



^{13}C NMR (63 MHz, $CDCl_3$)