

FACULTAD DE FARMACIA  
DEPARTAMENTO DE QUÍMICA ORGÁNICA Y FARMACÉUTICA



**NUEVAS APLICACIONES SINTÉTICAS DE LA  
REACCIÓN ENTRE VINIL- Y ARILMAGNESIANOS Y  
NITROARENOS**

TESIS DOCTORAL

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Madrid, Abril de 2012

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CERTIFICA:

Que el trabajo contenido en la memoria adjunta, titulada:

**“NUEVAS APLICACIONES SINTÉTICAS DE LA REACCIÓN ENTRE VINIL- Y ARILMAGNESIANOS Y NITROARENOS”**

que presenta **D. Riccardo Egris** como tesis doctoral, ha sido realizado en los laboratorios de este Departamento bajo la dirección de los Dres. D. José Carlos Menéndez Ramos y Dña. Mercedes Villacampa Sanz, Profesores Titulares de este Departamento.

Y para que conste proceda, expido y firmo el presente certificado en Madrid, a 10 de Mayo de dos mil doce.

Fdo. María Teresa Ramos García



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En Madrid, a 10 de Mayo de 2012

Fdo. José Carlos Menéndez Ramos

Fdo. Mercedes Villacampa Sanz

*....Lasciate ogni speranza, voi ch'entrate...*  
(*Inferno*, Canto III, vv. 1-9)

*...Ai miei genitori...*

*Deseo expresar mi agradecimiento:*

*Al Dr. D. José Carlos Menéndez Ramos, Profesor Titular de la Universidad Complutense de Madrid y a la Dra. Dña. Mercedes Villacampa Sanz, directores de este trabajo, por el apoyo, esfuerzo y tiempo que me han dedicado durante estos años.*

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*A M<sup>a</sup> José Saucedo y Pilar Cledera, encargadas del C.A.I. Microanálisis Elemental, a Marisa y Jesús, técnicos del Departamento.*

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*Dopo tanti anni di sforzi, di successi e fallimenti non posso che dedicare questo dottorato ai miei genitori, alla mia famiglia e a Stefano, che “mai” mi hanno abbandonato e hanno sempre saputo tirarmi fuori la forza per andare avanti.*

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## RESUMEN/SUMMARY

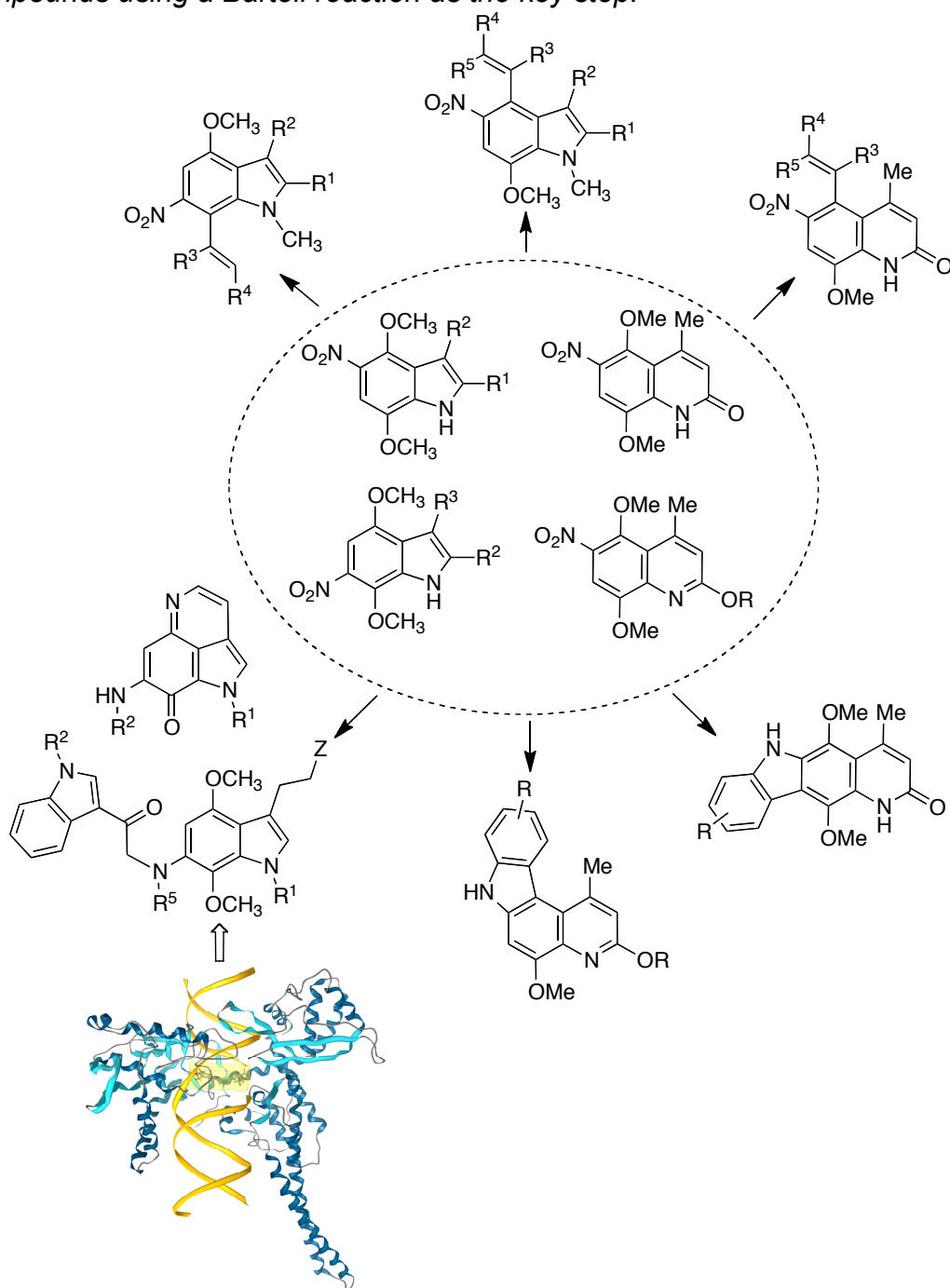
Los principales descubrimientos realizados en el curso de este trabajo pueden resumirse como sigue:

*The main discoveries achieved in the course of this work can be summarized as follows:*

1. Primera síntesis de derivados de nitroindol por medio de reacciones de Bartoli regioselectivas.  
*First synthesis of nitroindoles based on regioselective Bartoli reactions.*
2. Desarrollo de un método de vinilación de derivados de indol en C-4 y C-7, basado en un proceso de adición-eliminación en el que se utilizan vinilmagnesianos como nucleófilos y un grupo metoxi actúa como saliente.  
*Development of a method for C-4 and C-7 indole vinylation, based on an addition-elimination process using a vinylmagnesium reagent as nucleophile and a methoxy substituent as the leaving group.*
3. Extensión de la reacción de vinilación aromática a sustratos no indólicos con estructura de anilida y 2-quinolinona (carbostirilo).  
*Extensión of the aromatic vinylation to non-indolic substrates, including anilides and 2-quinolinones (carbostyrils).*
4. Estudio de la reacción entre magnesianos aromáticos y 5-metoxi-6-nitroquinolinas para acceder, de forma quimiodivergente, a 6-arilamino- o 5-arilquinolinas. Transformación de estos intermedios en carbazoles fusionados tetracíclicos de estructura lineal o angular utilizando procesos de acoplamiento oxidativo promovidas por paladio o reacciones de Cadogan.  
*Study of the reaction between arylmagnesium bromides and 5-methoxy-6-nitroquinolines, which provides chemodivergent access to 6-aryl-amino- or 5-arylquinolines. Transformation of these intermediates into tetracyclic fused linear or angular carbazole systems, using, respectively, palladium-promoted oxidative coupling or Cadogan reactions.*
5. Descubrimiento de un nuevo proceso dominó de ciclodeshidrogenación-desmetilación oxidativa de 6-arilamino-5,8-dimetoxicarbostirilos.  
*Discovery of a new cyclodehydrogenation-oxidative demethylation domino process from 6-aryl-amino-5,8-dimethoxycarbostyrils.*

6. Diseño de una serie de análogos simplificados del antitumoral de origen marino wakayina mediante estudios de docking en la topoisomerasa I y síntesis de estos compuestos utilizando una reacción de Bartoli como etapa clave.

*Design of a library of simplified analogues of the anticancer marine alkaloid wakayin by docking studies on topoisomerase I and synthesis of these compounds using a Bartoli reaction as the key step.*



## **1.- Introducción y objetivos**

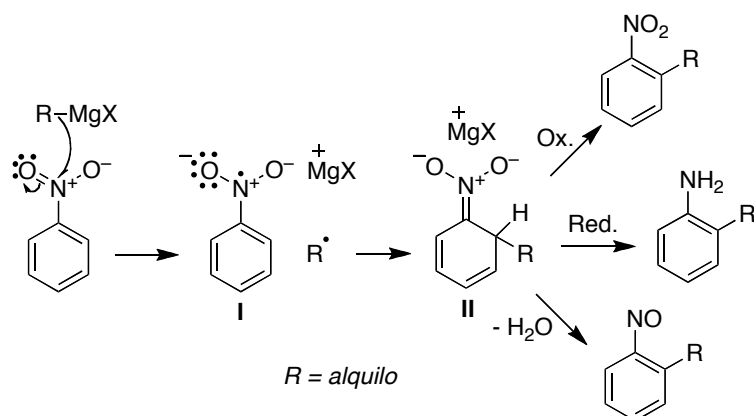


## 1.1.- REACCIÓN ENTRE MAGNESIANOS Y NITROARENOS. ANTECEDENTES

Aunque existían datos aislados desde principios del siglo XX, el primer estudio sistemático de los modos de reactividad de los nitroarenos frente a magnesianos se debe al grupo de Bartoli, en la Universidad de Bolonia.<sup>1</sup> Estos estudios demostraron que la primera etapa de la interacción entre ambos reactivos consiste en un proceso de transferencia de un electrón (*Single Electrón Transfer*, SET) que da una estructura de tipo jaula que contiene un anión radical derivado del nitroareno (I) y un radical correspondiente al reactivo de Grignard. La forma de continuar la reacción depende de la forma de este radical, y así los radicales alquilo simples, que son piramidales, se unen a las posiciones del anillo aromático conjugadas con el grupo nitro para dar aductos II que, dependiendo de las condiciones de reacción, pueden evolucionar por oxidación a nitroarenos sustituidos, por reducción a anilinas o por deshidratación a nitrosoarenos (esquema 1.1).

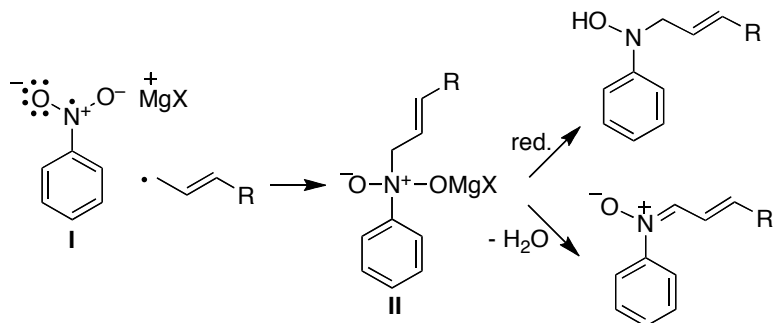
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<sup>1</sup> Revisiones de este trabajo: (a) Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109. (b) Ver también la referencia 7.



Esquema 1.1

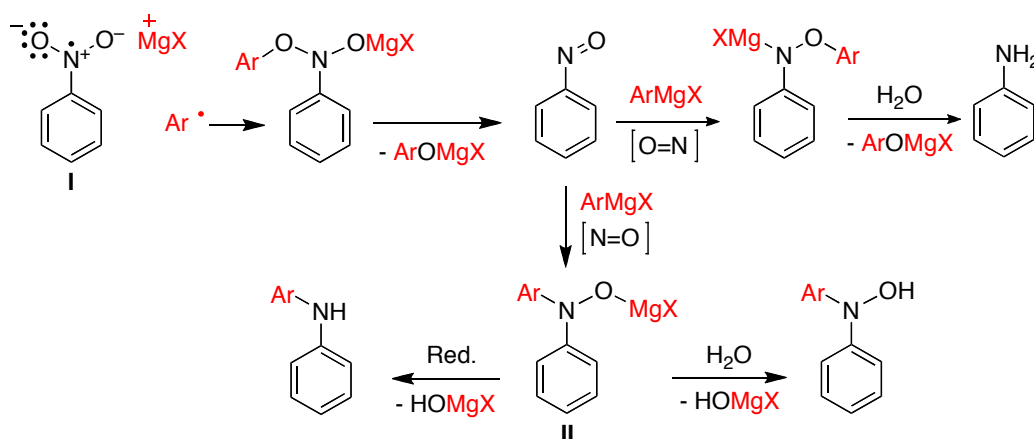
Los radicales alquilo planos, como por ejemplo los derivados de magnesianos alílicos o *terc*-butílicos, tienden a unirse al átomo de nitrógeno del grupo nitro en el catión-radical inicial I, dando intermediarios tetraédricos II, que evolucionan a derivados de hidroxilamina por reducción, o bien a nitronas insaturadas por deshidratación (esquema 1.2).



Esquema 1.2

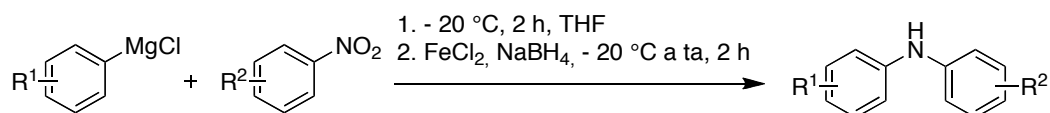
El comportamiento de los magnesianos aromáticos ha sido más difícil de estudiar a causa de la inestabilidad de algunos de los productos de reacción. Los estudios iniciales mostraban la formación de mezclas complejas de productos que incluían hidroxilaminas como componente mayoritario, junto con pequeñas cantidades de diarilaminas y anilinas. Su formación se explica a través del mecanismo resumido en el esquema 1.3, y se inicia con la adición del radical arilo al oxígeno del grupo nitro en I, originando la especie II, que evoluciona a un nitroso

derivado por eliminación de una molécula de fenolato de magnesio. Este nitroso derivado evoluciona por adición de una segunda molécula de magnesiano, que tiene lugar mayoritariamente sobre el átomo de nitrógeno, dando lugar a la especie II, que puede evolucionar a las hidroxilaminas mayoritarias por hidrólisis o a diarilaminas por reducción. Por otra parte, la adición del magnesiano al oxígeno del grupo nitroso seguida de hidrólisis explica el aislamiento de anilinas como producto minoritario (esquema 1.3).



Esquema 1.3

El principal problema encontrado en la aplicación sintética de esta reacción era la reducida estabilidad del derivado de diarilhidroxilamina. Knochel<sup>2</sup> descubrió que era posible su reducción *in situ* por adición de cloruro de hierro(II) y borohidruro sódico (esquema 1.4), dando lugar a una excelente síntesis de diarilaminas, que son intermedios sintéticos muy importantes.<sup>3</sup> Posteriormente, se descubrió que era posible lograr la misma transformación con a partir de nitrosoarenos, confirmando el



Esquema 1.4

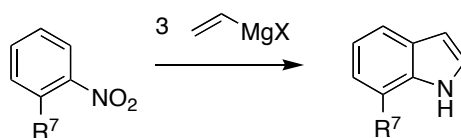
<sup>2</sup> Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390.

<sup>3</sup> Revisión de los métodos de síntesis de diarilaminas: Sapountzis, I.; Knochel, *Angew. Chem. Int. Ed.* **2004**, *43*, 897.

mecanismo propuesto,<sup>4</sup> y también que la reacción entre nitroarenos y arillitios conduce a diarilaminas, aunque el proceso es menos general que el que emplea magnesianos.<sup>5</sup>

En cuanto a la reacción entre nitroarenos sustituidos y reactivos de vinil Grignard, el grupo de Bartoli describió en 1989 que conduce a derivados de indol.<sup>6</sup> Las principales características de esta reacción son:<sup>7</sup>

- Se necesitan al menos tres equivalentes del magnesiano.
- El nitroareno debe estar sustituido en *orto* para que la reacción transcurra con rendimiento aceptable. Como consecuencia, la reacción de Bartoli está restringida, en principio, a la síntesis de indoles sustituidos en la posición 7 (esquema 1.5). No obstante, si se utiliza un átomo de bromo como sustituyente R<sup>7</sup>, es posible su supresión posterior en condiciones radicalarias por tratamiento con hidruro de tributilestaño, como ha sido demostrado por Dobbs.<sup>8</sup>



Esquema 1.5

- El rendimiento de la reacción suele ser moderado (en torno al 50%) y casi nunca supera el 70%.
- El rendimiento depende del tamaño del sustituyente en *orto* respecto al grupo nitro, siendo mayor cuando dicho sustituyente es voluminoso.
- Aunque lo más habitual es el empleo de bromuro de vinilmagnesio, también es posible utilizar alquenilmagnesianos sustituidos. Esto permite el acceso a indoles sustituidos en las posiciones 2 y 3 (esquema 1.6).

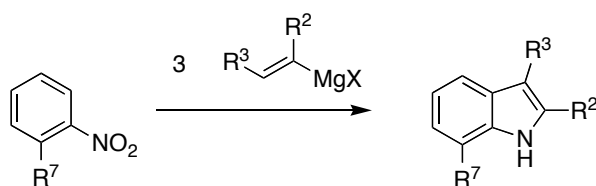
<sup>4</sup> Kopp, F.; Sapountzis, I.; Knochel, P. *Synlett* **2003**, 885.

<sup>5</sup> Yang, T.; Cho, B. P. *Tetrahedron Lett.* **2003**, 40, 7549.

<sup>6</sup> Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, 30, 2129.

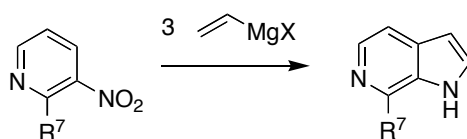
<sup>7</sup> Revisión de la reacción de Bartoli: Dalpozzo, R.; Bartoli, G. *Curr. Org. Chem.* **2005**, 9, 163.

<sup>8</sup> Dobbs, A. *J. Org. Chem.* **2001**, 66, 638.



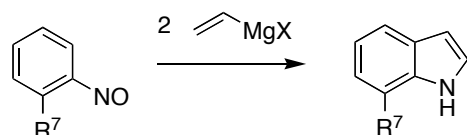
Esquema 1.6

- f) La reacción puede extenderse a nitroheterociclos, como por ejemplo nitropiridinas, resultando derivados de azaindol (esquema 1.7).



Esquema 1.7

- g) La reacción puede llevarse a cabo a partir de nitrosoarenos. En este caso, sólo se necesitan dos equivalentes de magnesiano, lo que sugiere que el primer equivalente de magnesiano se emplea en reducir el grupo nitro a nitroso (esquema 1.8).

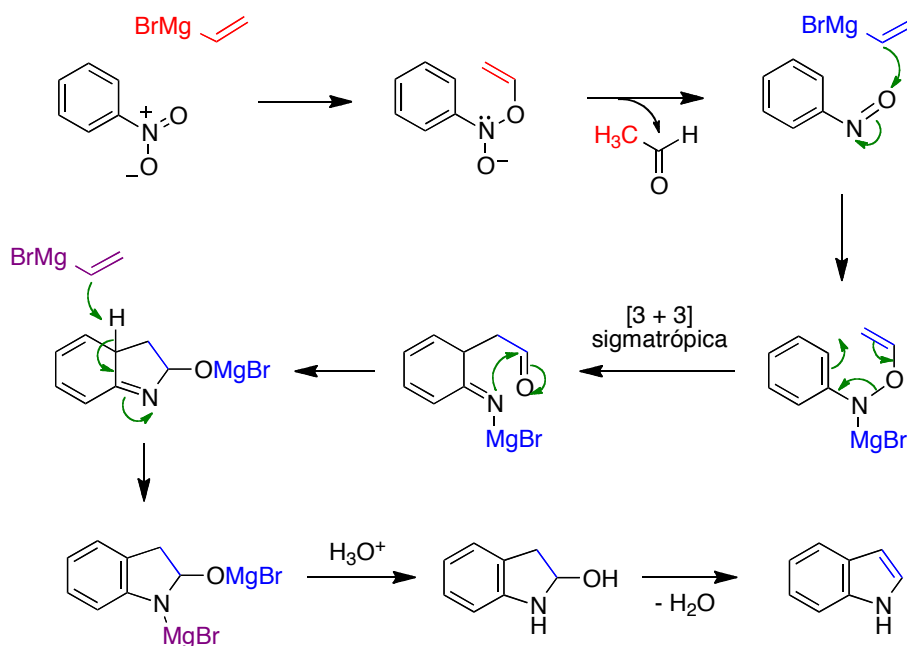


Esquema 1.8

El mecanismo de la reacción de Bartoli no se conoce en todos sus detalles, pero se ha podido establecer sus principales etapas.<sup>9</sup> El primer paso consiste en la adición del magnesiano al átomo de oxígeno del grupo nitro a través del proceso SET habitual seguido de unión del radical vinilo al átomo de oxígeno del grupo nitro y de una rápida descomposición del O-alquenil derivado resultante para dar un nitrosoareno, como se comentó para el caso de los magnesianos aromáticos. El nitroso derivado reacciona con un segundo equivalente de magnesiano, dando una

<sup>9</sup> Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. *J. Chem. Soc. Perkin Trans. 2* **1991**, 657.

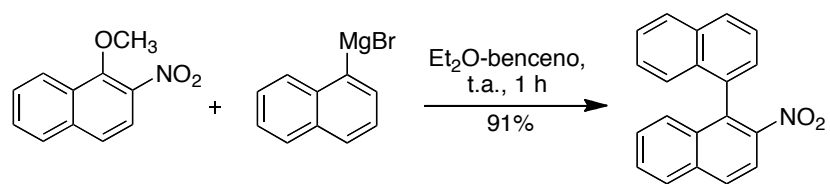
O-alqueniilhidroxilamina, que experimenta una transposición [3+3]-sigmatrópica que conduce a un producto que sufre un ataque nucleófilo intramolecular originando finalmente el esqueleto de indol. Su aromatización final requiere la eliminación del protón en la cabeza de puente por una tercera molécula del magnesiano, seguida de eliminación de una molécula de agua (esquema 1.9).



Esquema 1.9

Un aspecto que ha recibido poca atención, y que cuyo estudio constituye el núcleo de la presente memoria, es la selectividad de reacciones en las que pueden competir la adición de magnesianos vinílicos o arílicos a grupos nitro con procesos de adición-eliminación, facilitados por la presencia de un grupo saliente en posición *orto* o *para* respecto al grupo nitro. Así, existe un ejemplo que demuestra que el 1-metoxi-2-nitronaftaleno reacciona con arilmagnesianos por desplazamiento de su grupo metoxilo (esquema 1.10),<sup>10</sup> pero no se ha extendido este estudio a sustratos más complejos y, además, no se ha investigado una reacción similar con magnesianos vinílicos.

<sup>10</sup> Hattori, T.; Takeda, A.; Yamabe, O.; Miyano, S. *Tetrahedron* **2002**, *58*, 233.

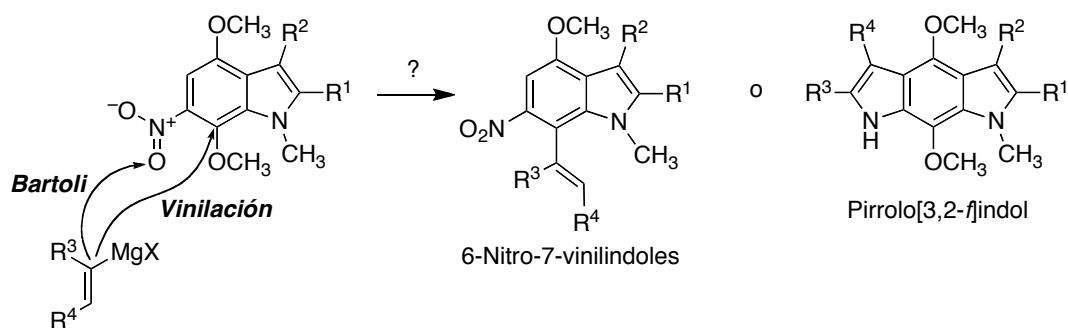


Esquema 1.10

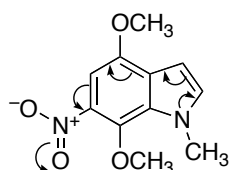
## 1.2. OBJETIVOS

Como se ha mencionado en el apartado 1, la principal finalidad de este trabajo es la de estudiar las aplicaciones sintéticas de la reacción de vinil y aril magnesianos con nitroheteroarenos que presentan un grupo saliente en orto. Los objetivos concretos se pueden resumir como sigue:

1. Estudio de la reacción entre 7-metoxi-6-nitroindoles con vinilmagnesianos, para estudiar la posible competencia entre una reacción de Bartoli o un proceso de adición eliminación con desplazamiento del grupo metoxi.

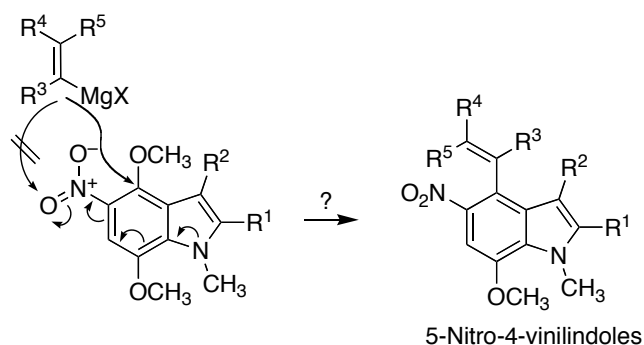


En principio, el producto mayoritario esperado es el de vinilación, debido a que esperábamos que la conjugación existente entre el nitrógeno indólico, fuertemente donador, y el grupo nitro, sumada a la cesión de carga por el metoxilo en *orto*, dificultase la etapa inicial de la reacción de Bartoli, en la que el magnesiano debe atacar al enlace O=N del grupo nitro:

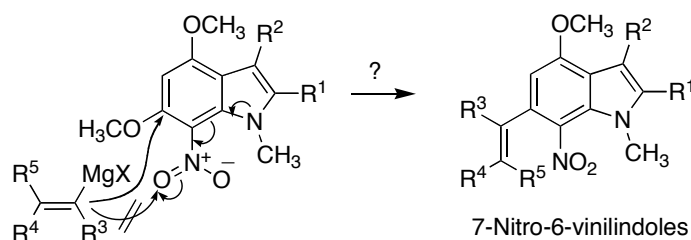


2. Estudio de otras situaciones en las que exista conjugación entre el grupo nitro y el nitrógeno indólico, esperando de nuevo que esta conjugación favorezca el proceso de C-vinilación. Los casos particulares que hemos planteado son los siguientes:

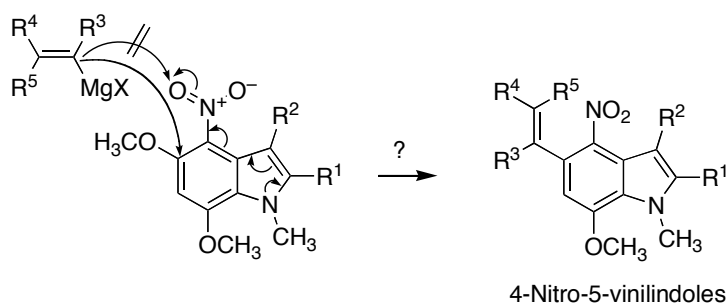
## 2.1. Preparación de 5-nitro-4-vinilindoles a partir de 4-metoxi-5-nitroindoles:



## 2.2. Preparación de 7-nitro-6-vinilindoles a partir de 6-metoxi-7-nitroindoles:

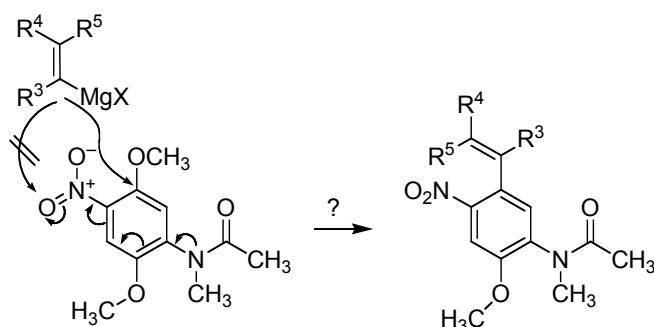


## 2.3. Preparación de 4-nitro-5-vinilindoles a partir de 5-metoxi-4-nitroindoles:

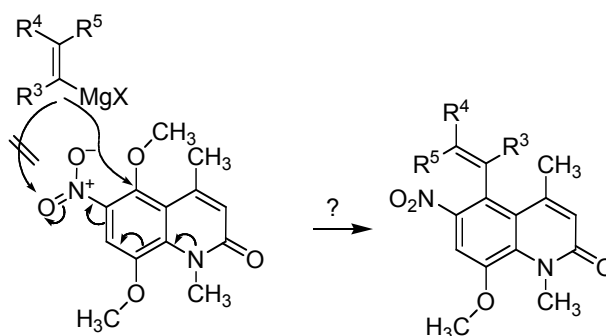


3. Estudios iniciales acerca de extensión del método en sustratos aromáticos diferentes del indol en los que exista también un grupo donador electrónico conjugado con el grupo nitro, además del metoxilo en *orto*:

## 3.1. Anilidas:



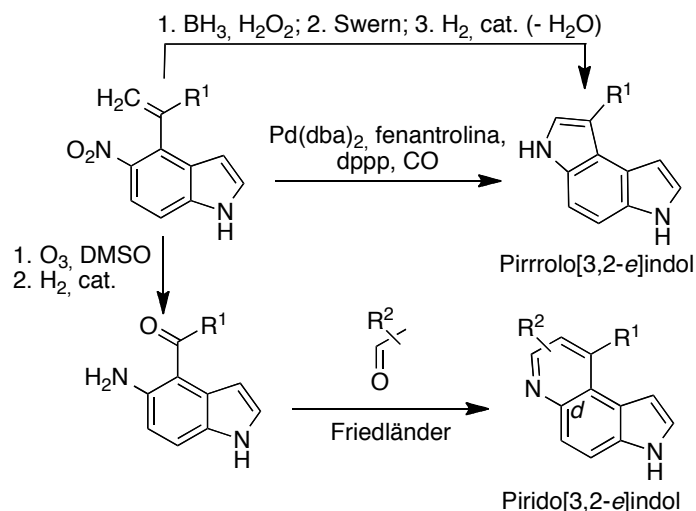
## 3.2. 2-Quinolinonas (carbostirilos):



En caso de tener éxito, este nuevo método de vinilación aromática permitirá el acceso a *o*-vinilnitroarenos que, gracias a la presencia de dos funcionalizaciones vecinas, pueden especialmente útiles en la preparación de heterociclos fusionados. Aunque el estudio detallado de estas posibilidades escapa del alcance del presente trabajo, mencionaremos, como ejemplo, algunas transformaciones sencillas que deben permitir el empleo de derivados de 4-vinil-5-nitroindol como materiales de partida para la preparación de pirrolo[3,2-*e*]indoles y pirido[3,2-*e*]indoles (esquema 1.11). La obtención del primer tipo de compuestos se podría basar en la generación de un sistema de indol por funcionalización oxidativa del extremo del doble enlace vinílico y reducción del grupo nitro, o bien en un proceso de *N*-heteroanulación reductora directa catalizada por paladio.<sup>11</sup> La degradación oxidativa del grupo vinilo

<sup>11</sup> Clawson, R. W.; Deavers, R. E.; Akhmedov, N. G.; Söderberg, B. C. G. *Tetrahedron* **2006**, *62*, 10829.

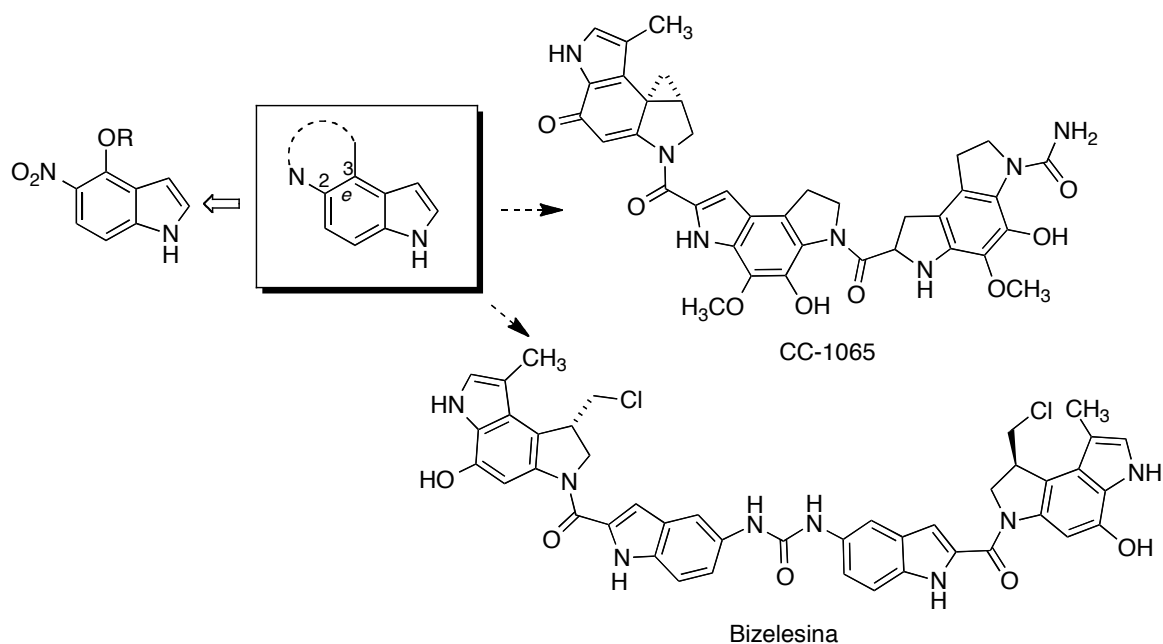
seguida de una reacción de Friedländer permitiría el acceso a derivados de pirido[3,2-*e*]indol.



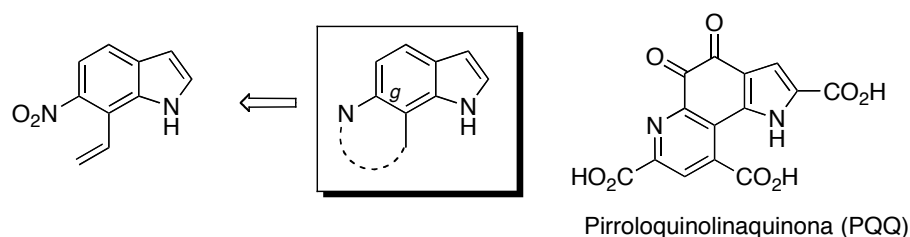
Esquema 1.11

Estos esqueletos son de gran interés por estar presentes en un gran número de compuestos bioactivos. Así, el sistema de pirrolo[3,2-*e*]indol es el principal fragmento estructural de una familia de antitumorales conocidos como ciclopropilindoles, entre los que destacan el producto natural CC-1065 y sus análogos menos tóxicos, como la bizelesina.<sup>12</sup> Estos compuestos se unen específicamente a secuencias adenina-timina del surco menor del ADN, donde posteriormente forman enlaces covalentes con el N-3 de residuos de adenina. Los halometil derivados, como la bizelesina, son profármacos que necesitan activarse a un sistema de ciclopropa[*c*]indol semejante al que existe en el producto natural por medio de una reacción de ciclación promovida por la desprotonación del hidroxilo fenólico.

<sup>12</sup> Schwartz, G. H.; Patnaik, A.; Hammond, L. A.; Rizzo, J.; Berg, K.; von Hoff, D. D.; Rowinsky, E. K. *Ann. Oncol.* **2003**, *14*, 775.



Como ejemplo de una estructura fusionada por la cara *g* del indol, accesible en principio a partir de un derivado de 7-alcoxi-6-nitroindol, mencionaremos la pirroloquinolinaquinona (PQQ). Este compuesto es un cofactor redox aislado inicialmente de bacterias, con numerosas propiedades biológicas asociadas a su capacidad de actuar como inhibidor de radicales libres.<sup>13</sup> Además, la pirroloquinolinaquinona es un nutriente esencial que se ha propuesto como una vitamina en humanos.<sup>14</sup>

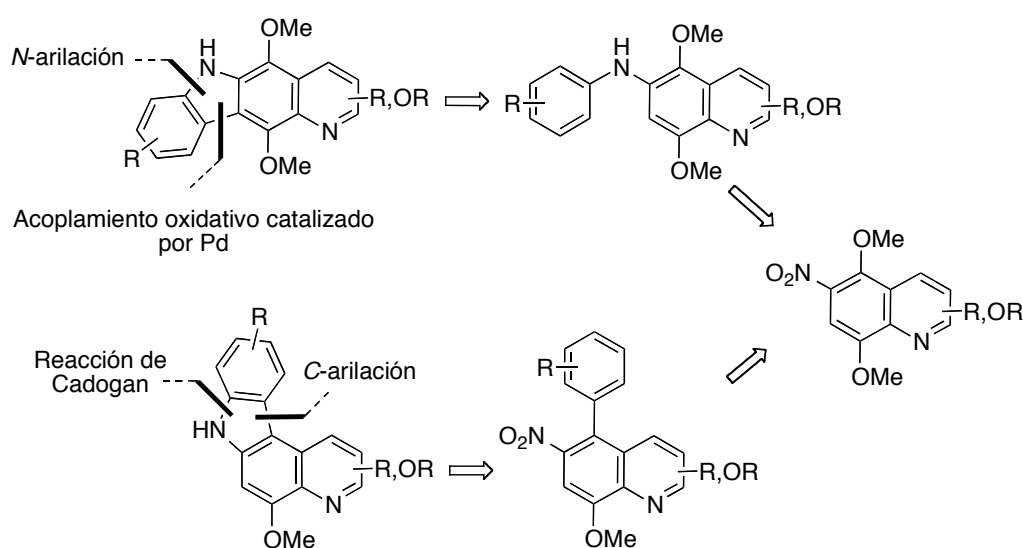


4. Investigación de reacciones de arilmagnesianos con *o*-vinilnitroarenos. Esta parte del trabajo se centró en el uso de 5-metoxi-6-nitrocarbostirilos como sustratos

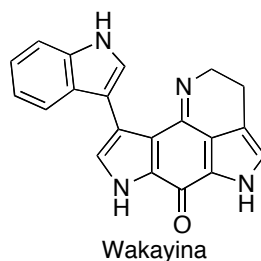
<sup>13</sup> Un ejemplo: Kosano, H.; Setogawa, T.; Nishigori, H.; Kobayashi, K. *Life Sci.* **1995**, *56*, 1707.

<sup>14</sup> (a) Kasahara, T.; Kato, T. *Nature* **2003**, *422*, 832. (b) Rucker, R.; Storms, D.; Sheets, A.; Tchapanian, E.; Fascetti, A. *Nature* **2005**, *433*, E10.

a causa de nuestro interés en la preparación de estructuras híbridas de carbazol/quinolinona, motivado por la actividad antitumoral encontrada en representantes de ambos heterociclos. Nos planteamos el estudio de modificaciones en la estructura de la quinolina de partida mediante la introducción de sustituyentes con diversos tipos de efectos estéricos o electrónicos, orientadas a lograr de forma selectiva los procesos de N- y C-arilación. Esto nos debía permitir acceder a dos tipos de derivados fusionados de carbazol, utilizando un acoplamiento oxidativo catalizado por paladio o la reacción de Cadogan para crear el último anillo.



5. Nuestro último objetivo consiste en aplicar la química de vinilmagnesianos a la preparación de compuestos relacionados con el alcaloide citotóxico wakayina, un inhibidor natural de la topoisomerasa I.





## **2.- Reacción entre nitroarenos y vinilmagnesianos**



## 2.1. ANTECEDENTES BIBLIOGRÁFICOS DE MÉTODOS DE SÍNTESIS DE DERIVADOS DE 2-VINILNITROARENO

Una revisión bibliográfica ha indicado que los derivados de indol sustituidos por grupos nitro y vinilo contiguos que se mencionan en el apartado de objetivos son desconocidos hasta la fecha. Haremos a continuación un breve comentario de los principales métodos que permiten el acceso a derivados de 2-vinilnitrobenceno y que en principio podrían adaptarse a la preparación de indoles. Estos métodos se basan en reacciones de acoplamiento catalizadas por paladio y, a pesar de tratarse de procesos muy extendidos, distan mucho de ser ideales, debido al elevado costo de los catalizadores de paladio y de muchas de las fosfinas necesarias como ligandos. Los más importantes son:

### 2.1.1. Reacción de Heck

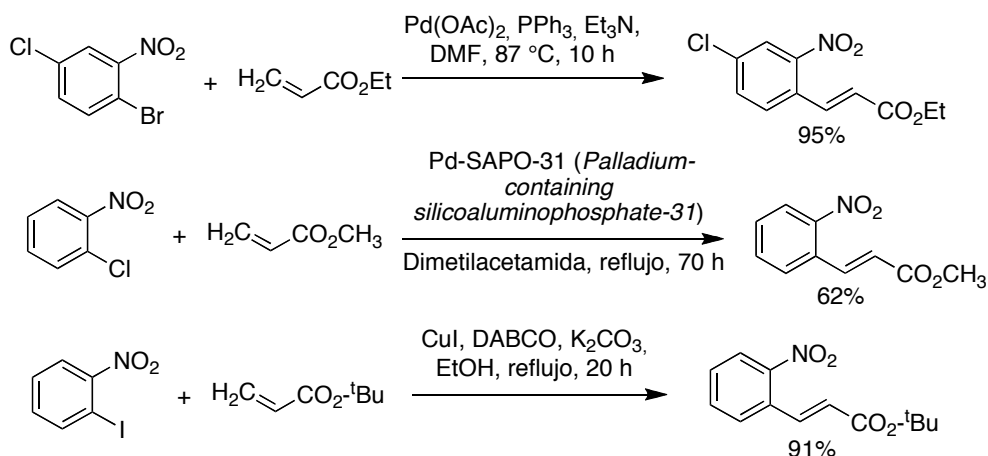
Consiste en la reacción entre haluros de arilo y compuestos olefínicos en presencia de cantidades catalíticas de Pd (0) y ligandos con estructura de aminas impedidas, y desde su descubrimiento en la década de 1970 se ha convertido en una de las reacciones más utilizadas en síntesis orgánica. Los materiales de partida más habituales de la reacción de Heck son bromuros de arilo,<sup>15</sup> ya que los cloruros

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<sup>15</sup> Caron, S.; Vázquez, E.; Stevens, R. W.; Nakao, K.; Koike, H.; Murata, Y. *J. Org. Chem.* **2003**, *68*, 4104.

no han sido tradicionalmente buenos sustratos. Recientemente se han descrito algunos catalizadores que permiten superar esta limitación, aunque se necesitan condiciones drásticas y catalizadores especiales. Un ejemplo es el conocido como Pd-SAPO-31 (palladium-containing silicoaluminophosphate-31).<sup>16</sup> También recientemente se han introducido variantes de la reacción de Heck en las que se emplean catalizadores de cobre, mucho más asequibles que los de paladio. Un ejemplo descrito recientemente es la combinación de yoduro de cobre con 1,4-diazabicyclo[2.2.2]octano (DABCO) como ligando (esquema 2.1).<sup>17</sup>

La principal limitación de la reacción de Heck como método de vinilación aromática en procesos intermoleculares radica en la conveniencia de usar alquenos con grupos aceptores electrónicos.



Esquema 2.1

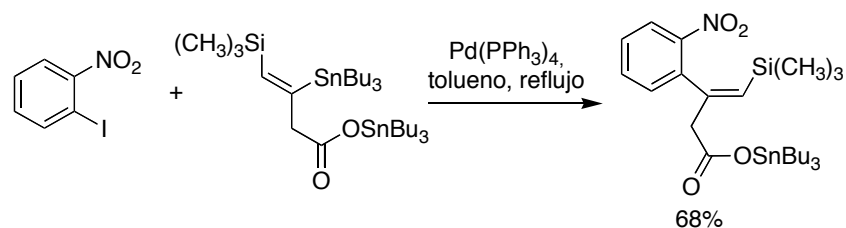
### 2.1.2. Reacción de Stille

Consiste en el acoplamiento catalizado por paladio entre organoestannanos y electrófilos orgánicos, como triflatos o haluros. Aunque suele dar buenos resultados, tiene el inconveniente de que a menudo es necesario sintetizar los estannanos de partida, que son tóxicos, y de que resulta difícil eliminar completamente los restos de estaño de los productos de reacción. A continuación se representa un ejemplo del empleo de esta reacción en una vinilación aromática (esquema 2.2):<sup>18</sup>

<sup>16</sup> Srivastava, R.; Venkatathri, N.; Srinivas, D.; Ratnasamy, P. *Tetrahedron Lett.* **2003**, *44*, 3649.

<sup>17</sup> Li, J.-H.; Wang, D. P.; Xie, Y.-X. *Tetrahedron Lett.* **2005**, *46*, 4941.

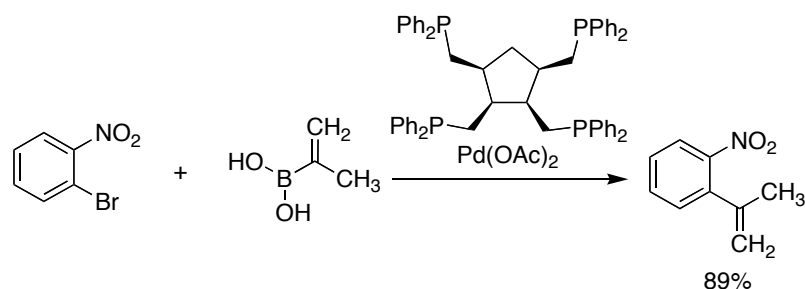
<sup>18</sup> Lunot, S.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L.; Abarbri, M. *Tetrahedron Lett.* **2000**, *41*, 8893.



Esquema 2.2

### 2.1.3. Reacción de Suzuki

Así se conoce normalmente la reacción de acoplamiento catalizada por paladio entre compuestos de organoboro y haluros o triflatos orgánicos. Aunque muchos ácidos borónicos aromáticos son comerciales, no puede decirse lo mismo de los ácidos borónicos vinílicos, lo que limita la utilidad de esta reacción como método de vinilación. Otra desventaja de la reacción de Suzuki en este sentido es la baja reactividad de los haluros aromáticos, aunque recientemente se han empezado a desarrollar ligandos de tipo fosfina que están ayudando a superar esta limitación (esquema 2.3).<sup>19</sup>



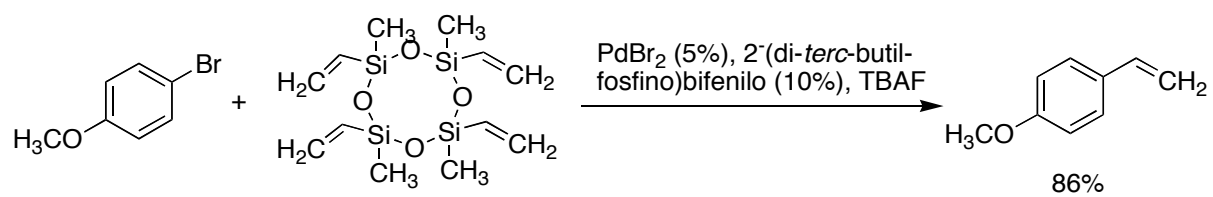
Esquema 2.3

### 2.1.4. Otras reacciones catalizadas por paladio

Se ha descrito la vinilación catalizada por paladio de bromuros o yoduros aromáticos utilizando polisiloxanos como donadores de vinilo y en presencia de fluoruro de tetrabutilamonio como activador del proceso (esquema 2.4).<sup>20</sup>

<sup>19</sup> Lunot, S.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L.; Abarbri, M. *Tetrahedron Lett.* **2000**, 41, 8893.

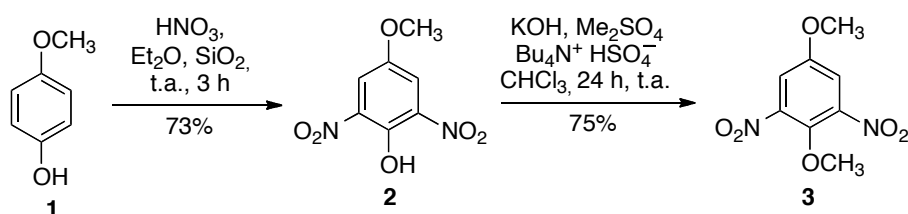
<sup>20</sup> Denmark, S. E.; Butler, C. R. *Org. Lett.* **2006**, 8, 63.



Esquema 2.4

## 2.2. REACCIÓN DE 7-METOXI-6-NITROINDOLES CON MAGNESIANOS VINÍLICOS: SÍNTESIS DE DERIVADOS DE 6-NITRO-7-VINILINDOL

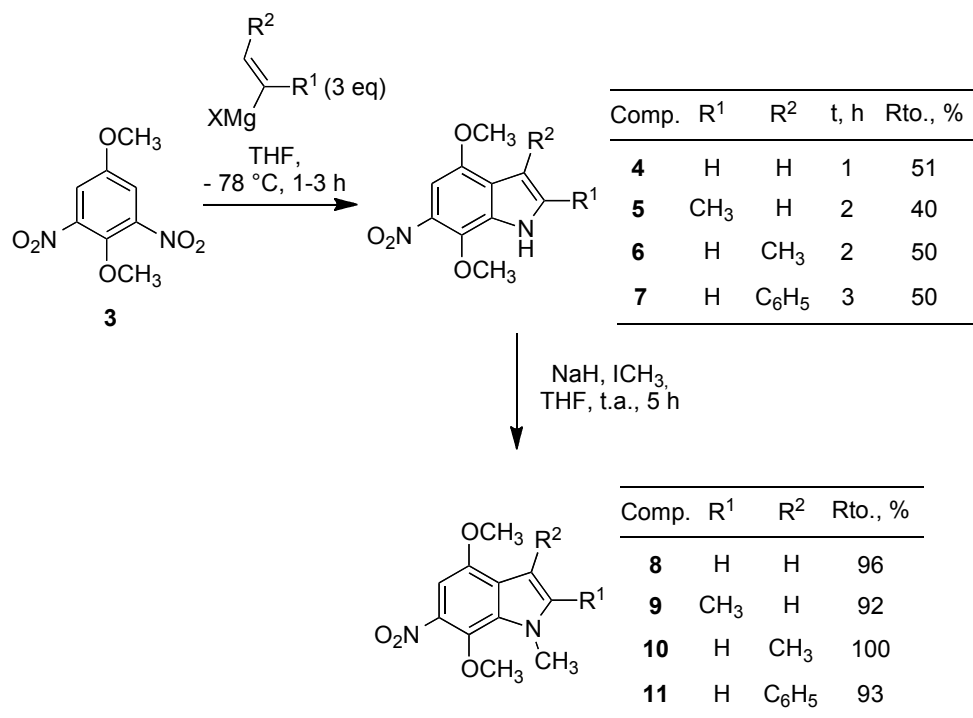
La preparación de los materiales de partida necesarios para esta parte de nuestro estudio se inició con la doble nitración del 4-metoxifenol **1** para dar el compuesto **2**. En los ensayos iniciales, realizados con mezclas de ácido nítrico y éter etílico, esta reacción fue problemática porque proporcionaba mezclas de productos de mono- y dinitración, sin que el rendimiento de este último superase el 35%. Varios intentos de forzar las condiciones incrementando la concentración de ácido nítrico fueron infructuosos, ya que condujeron a mezclas complejas. Experimentos posteriores demostraron las ventajas del empleo de ácido nítrico soportado sobre sílice, que proporciona un 73% de compuesto **2**, que en su mayor parte cristaliza durante el aislamiento y está exento de compuesto de mononitración y de derivados de oxidación o polinitración. La metilación del oxígeno fenólico de **2** se llevó a cabo en condiciones de transferencia de fase y proporcionó el compuesto **3** con un rendimiento del 75% (esquema 2.5). Ambas reacciones pueden realizarse en escalas de varios gramos.



Esquema 2.5

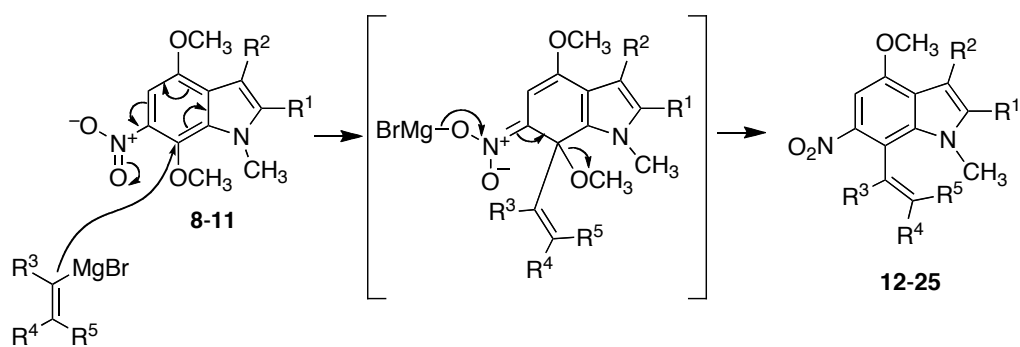
La disponibilidad del compuesto **3** permitió estudiar su transformación en derivados de indol a través de reacciones de Bartoli. Tras varios experimentos iniciales que dieron malos resultados, encontramos que, al menos para el caso del compuesto **3**, la reacción es mucho más reproducible si se lleva a cabo a  $-78\text{ }^\circ\text{C}$  en lugar de  $-50\text{ }^\circ\text{C}$ , que es la temperatura generalmente recomendada para la reacción de Bartoli. Con esta modificación, se obtuvieron rendimientos aceptables de los indoles **4-7**, sustituidos en las posiciones 2 y 3. Para evitar su posible interferencia en reacciones posteriores, se metilaron los nitrógenos indólicos por tratamiento con

hidruro sódico seguido de yoduro de metilo, resultando los compuestos **8-11** (esquema 2.6).



Esquema 2.6

Los resultados del estudio de reactividad de los compuestos **8-11** frente a magnesianos vinílicos se resumen en el esquema 2.7 y en la tabla 2.1. De acuerdo con nuestra predicción inicial, en ninguna de las reacciones se observó la formación de productos tricíclicos procedentes de la adición del magnesiano al enlace  $\text{O}=\text{N}$  del grupo nitro (etapa inicial de la reacción de Bartoli). En todos los casos se obtuvieron únicamente los derivados de vinilación en posición 7 (compuestos **12-25**), normalmente con rendimientos excelentes. La reacción de vinilación parece ligeramente sensible a efectos estéricos, ya que suele dar rendimientos algo inferiores en los casos en los que el magnesiano está sustituido en la posición  $\alpha$  respecto al magnesio ( $\text{R}^3 = \text{CH}_3$ ).

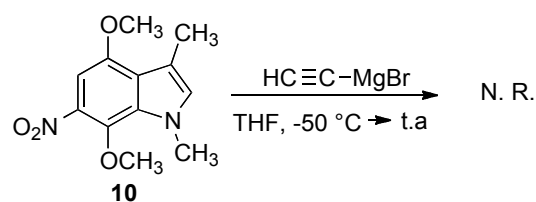


Esquema 2.7

Tabla 2.1

Compuesto	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	t, h	Rto., %
<b>12</b>	H	H	H	H	H	1	91
<b>13</b>	H	H	H	CH <sub>3</sub>	H	1	99
<b>14</b>	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	1	94
<b>15</b>	H	H	H	C <sub>6</sub> H <sub>5</sub>	H	5	98
<b>16</b>	H	H	CH <sub>3</sub>	H	H	1	75
<b>17</b>	H	CH <sub>3</sub>	H	H	H	2	95
<b>18</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H	2	98
<b>19</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	2	72
<b>20</b>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H	2	71
<b>21</b>	CH <sub>3</sub>	H	H	H	H	1	96
<b>22</b>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H	3	97
<b>23</b>	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	2	85
<b>24</b>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	3	81
<b>25</b>	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H	5	98

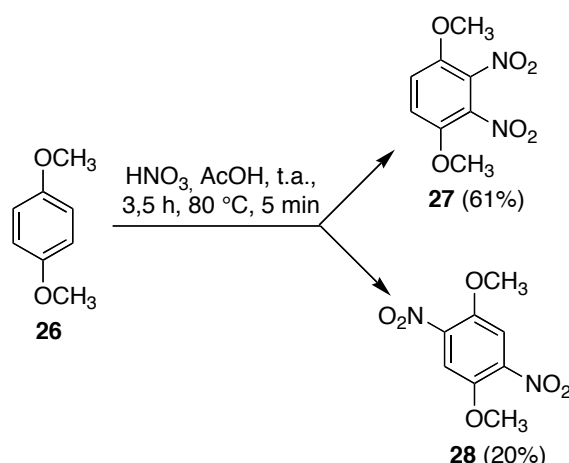
Resultó fallido un intento de llevar a cabo una reacción de etinilación por tratamiento del compuesto **10** con bromuro de etinilmagnesio (esquema 2.8).



Esquema 2.8

### 2.3. REACCIÓN DE 4-METOXI-5-NITROINDOLES CON MAGNESIANOS VINÍLICOS: SÍNTESIS DE DERIVADOS DE 5-NITRO-4-VINILINDOL

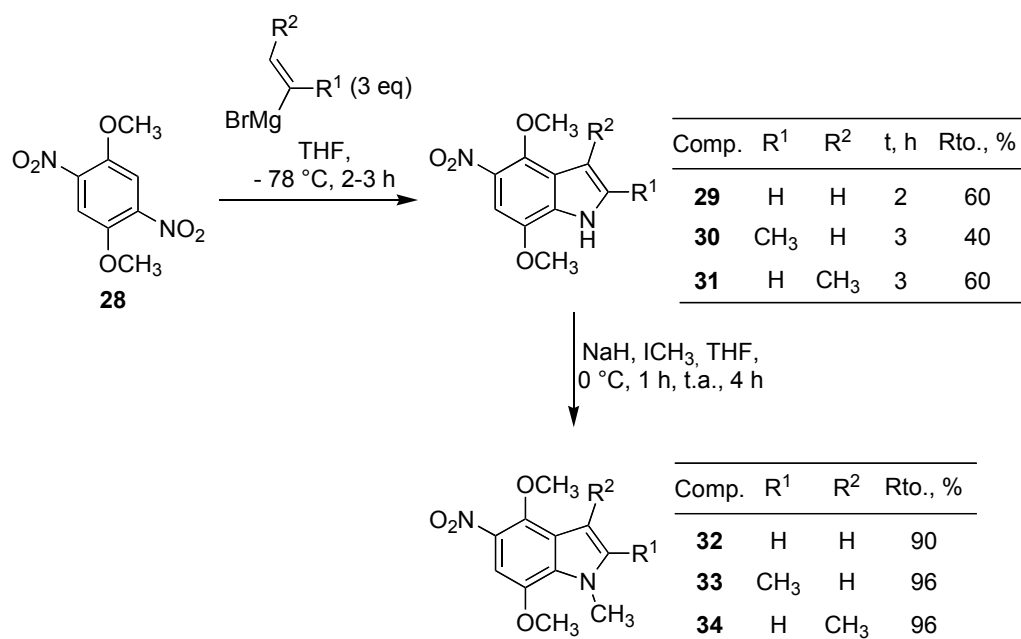
En este caso, el material de partida adecuado para la reacción de Bartoli es el 1,4-dimetoxi-2,5-dinitrobenceno **28**. Este compuesto se obtuvo por nitración del 1,4-dimetoxibenceno **26**, resultando ser el producto minoritario de dicha reacción, en contra de lo descrito en algunas referencias bibliográficas (esquema 2.9).<sup>21</sup> La identificación de los dos isómeros se ha basado en su reactividad posterior, ya que sólo el compuesto **28** dio la reacción de Bartoli mientras que **27** proporcionó una mezcla muy compleja. Esta determinación estructural coincide con la de Suzuki, que ha obtenido el compuesto **28** como producto mayoritario de la reacción del 1,4-dimetoxibenceno con dióxido de nitrógeno en presencia de ozono y lo ha diferenciado del minoritario (**27**) a través de la transformación de éste en un derivado de benzimidazol por reducción a diamina y reacción de Phillips con ácido acético.<sup>22</sup>



Esquema 2.9

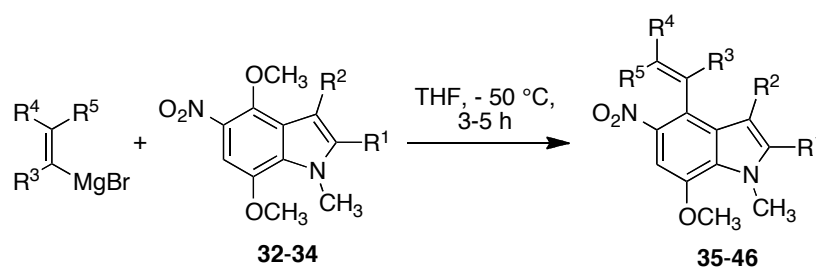
El compuesto **28** dio la reacción de Bartoli en las mismas condiciones previamente establecidas para el caso de **2**. Los derivados de indol **29-31** así obtenidos se transformaron posteriormente en los correspondientes derivados *N*-metilados **32-34** por tratamiento con yoduro de metilo en presencia de hidruro sódico (esquema 2.10).

<sup>21</sup> Lion, C.; Baudry, R.; Hedayatullah, M.; Da Conceição, L.; Genard, S.; Maignan, J. *J. Heterocycl. Chem.* **2002**, *39*, 125.



Esquema 2.10

La reacción de los compuestos **32-34** con varios bromuros de vinilmagnesio proporcionó los correspondientes derivados de 5-nitro-4-vinilindol **35-46** sin especiales problemas y casi siempre con rendimientos superiores al 90% (esquema 2.11 y tabla 2.2). La única excepción fue el caso del compuesto **38**, cuyo rendimiento fue del 60%, lo que probablemente refleja el impedimento estérico asociado a la presencia del grupo R<sup>3</sup> = CH<sub>3</sub> en el magnesiano.



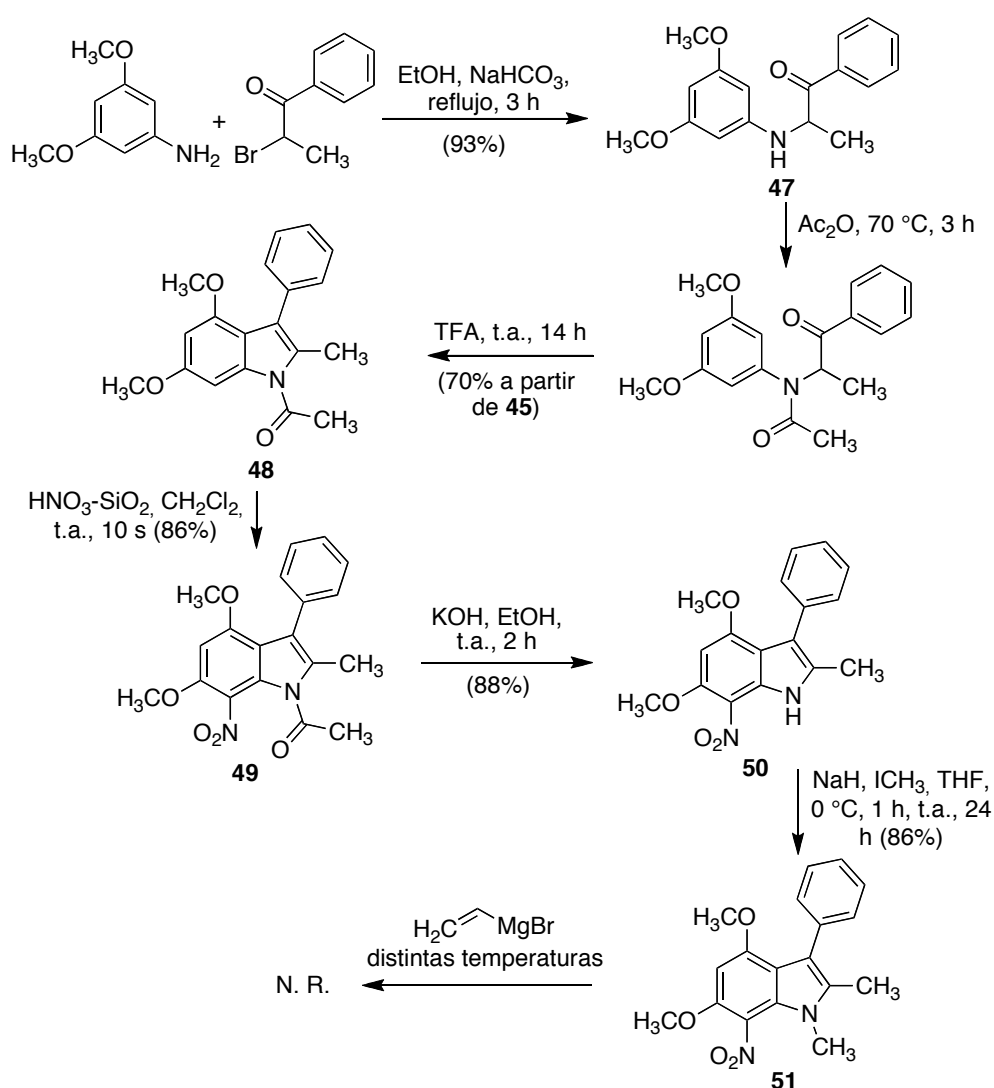
Esquema 2.11

Tabla 2.2

Compuesto	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	t, h	Rto., %
<b>35</b>	H	H	H	H	H	5	95
<b>36</b>	H	H	H	H	CH <sub>3</sub>	5	88
<b>37</b>	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>	4	96
<b>38</b>	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	5	60
<b>39</b>	H	CH <sub>3</sub>	H	H	H	3	90
<b>40</b>	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>	3	90
<b>41</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>	3	94
<b>42</b>	CH <sub>3</sub>	H	H	H	H	3	96
<b>43</b>	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>	5	91
<b>44</b>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>	3	94
<b>45</b>	CH <sub>3</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	H	4	91
<b>46</b>	H	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	4	90

## 2.4. INTENTOS DE SÍNTESIS DE DERIVADOS DE 7-NITRO-6-VINILINDOL Y 4-NITRO-5-VINILINDOL

En el esquema 2.12 resumimos la preparación de un derivado de 6-metoxi-7-nitroindol (compuesto **51**), que se basó en una ligera modificación de un método encontrado en la bibliografía.<sup>23</sup> La *N*-alquilación de la 3,5-dimetoxianilina con  $\alpha$ -bromopropiofenona en presencia de bicarbonato sódico condujo a la amina secundaria **47**, que se cicló al derivado de indol **48** en presencia de ácido trifluoroacético, previa acetilación de su nitrógeno básico. La nitración de la posición

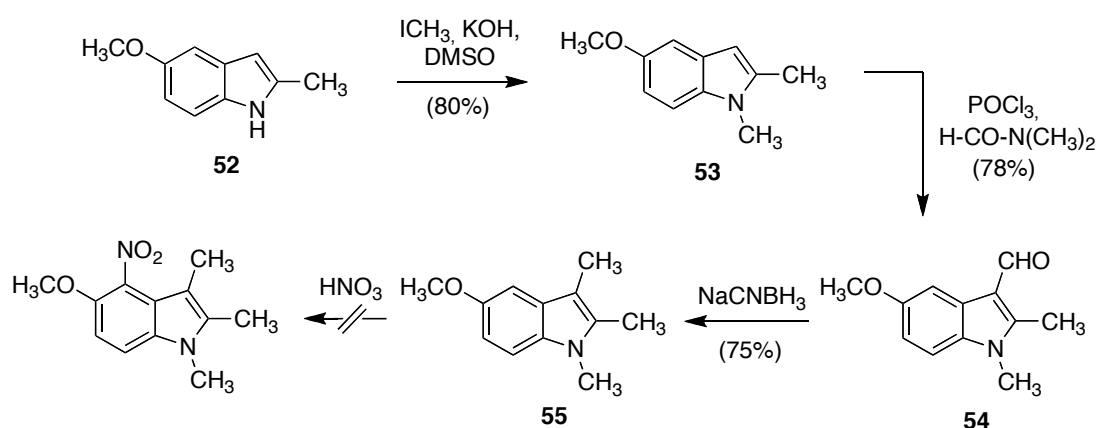


<sup>23</sup> Jones, A. W.; Wahyuningsih, T. D.; Pchalek, K.; Kumar, N.; St. Black, D. *Tetrahedron* **2005**, *61*, 10490.

## Esquema 2.12

7 del anillo de indol de **48** se llevó a cabo por tratamiento con ácido nítrico soportado en gel de sílice, aislándose el compuesto **49**. Su desacetilación por hidrólisis básica dio **50**, cuyo anión fue finalmente metilado para originar **51**. A diferencia de lo observado en los casos anteriores, en esta ocasión fueron infructuosos todos los intentos de utilizar el compuesto **51** como sustrato de reacciones de vinilación aromática (esquema 2.12).

Para concluir esta parte de nuestro estudio, intentamos la preparación de un derivado de 5-metoxi-4-nitroindol, que serviría como precursor potencial de derivados de 4-nitro-5-vinilindol. El compuesto comercial **52** se metiló en condiciones distintas que los otros indoles, utilizando hidróxido pótasio en dimetilsulfóxido como base.<sup>24</sup> Esta reacción condujo a **53**, que se formiló en condiciones de Vilsmeier proporcionando **54**. El tratamiento de este compuesto con cianoborohidruro sódico<sup>25</sup> condujo en un paso a la reducción del grupo formilo a hidroximetilo y a la hidrogenolisis de éste y dio el derivado de trimetilindol **55**, que no ha podido ser nitrado en condiciones encontradas en la bibliografía para un sustrato similar,<sup>26</sup> ni tampoco en otras condiciones ensayadas (esquema 2.13).



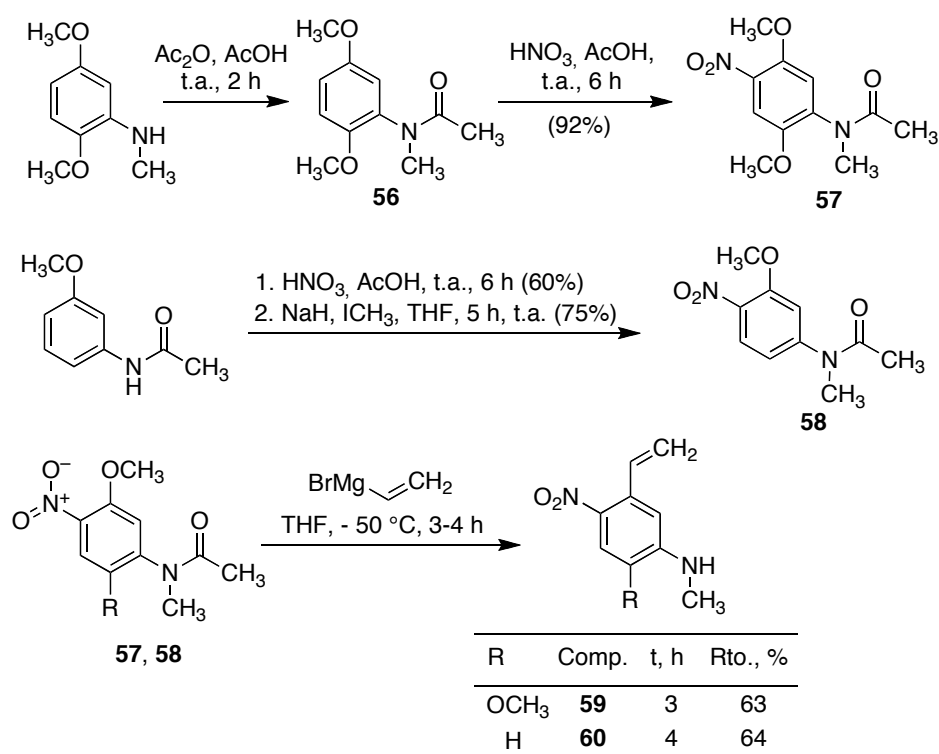
<sup>24</sup> Heaney, H.; Ley, S. V. *Org. Synth.* **1974**, *54*, 58.

<sup>25</sup> Colandrea, V. J.; Rajaraman, S.; Jiménez, L. S. *Org. Lett.* **2003**, *5*, 785.

<sup>26</sup> Everett, S. A.; Naylor, M. A.; Barraja, P.; Swann, E.; Patel, K. B.; Stratford, M. R. L.; Hudnott, A. R.; Vojnovic, B.; Locke, R. J.; Wardman, P.; Moody, C. J. *J. Chem. Soc. Perkin Trans. 2*, **2001**, 843.

## 2.5. VINILACIÓN DE ANILIDAS Y CARBOSTIRILOS

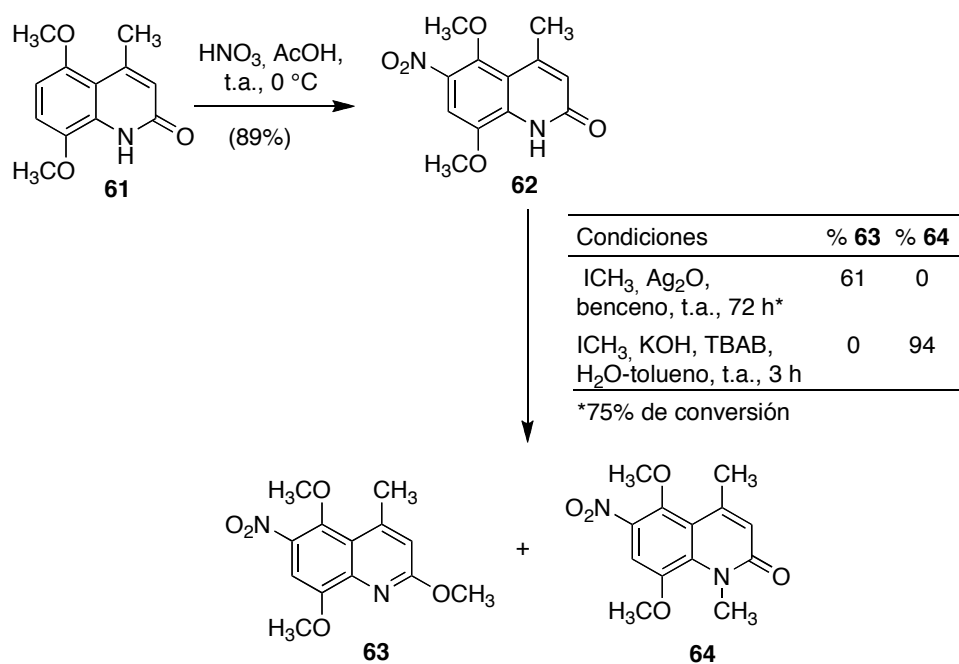
En un intento de explorar la generalidad de nuestro método de vinilación, investigamos brevemente la reacción con vinilmagnesianos de compuestos aromáticos diferentes del indol que fueran portadores de un grupo nitro conjugado con un grupo donador electrónico y un metoxilo en *orto*. Un ejemplo de este tipo de estructura se encuentra en las anilidas **57** y **58**, que se obtuvieron a partir de las correspondientes anilidas utilizando condiciones estándar de nitración y N-metilación.<sup>27</sup> Como se observa en el esquema 2.14, el tratamiento de **57** y **58** con bromuro de vinilmagnesio en las condiciones habituales proporcionó los derivados de vinilación **59** y **60** con rendimientos aceptables, lo que permite concluir que las anilidas son también sustratos adecuados para el proceso de vinilación. Además de la reacción de adición-eliminación, el magnesiano se adicionó al carbonilo de amida, provocando una reacción de desacetilación.



Esquema 2.14

<sup>27</sup> Síntesis de este material de partida: Pérez, J. M.; Vidal, L.; Grande, M. T.; Menéndez, J. C.; Avendaño, C. *Tetrahedron* **1994**, *50*, 7923.

Decidimos tratar de extender este resultado a derivados de 2-quinolinona (carbostirilo), que pueden considerarse anilidas cíclicas. Con esta finalidad, transformamos el compuesto **61**<sup>28</sup> en su 6-nitro derivado **62** por tratamiento con ácido nítrico en ácido acético. La metilación de **62** inicialmente proporcionó mezclas de los derivados de *O*-metilación **63** y *N*-metilación **64**. Un estudio de optimización demostró que las condiciones óptimas para la *O*-metilación consisten en el tratamiento con yoduro de metilo en presencia de óxido de plata (61% de **64**), mientras que el tratamiento con yoduro de metilo en condiciones de transferencia de fase condujo a un rendimiento de 94% del *N*-metil derivado **64** como único producto (esquema 2.15). Este compuesto fue el sustrato elegido para estudiar las reacciones con magnesianos.

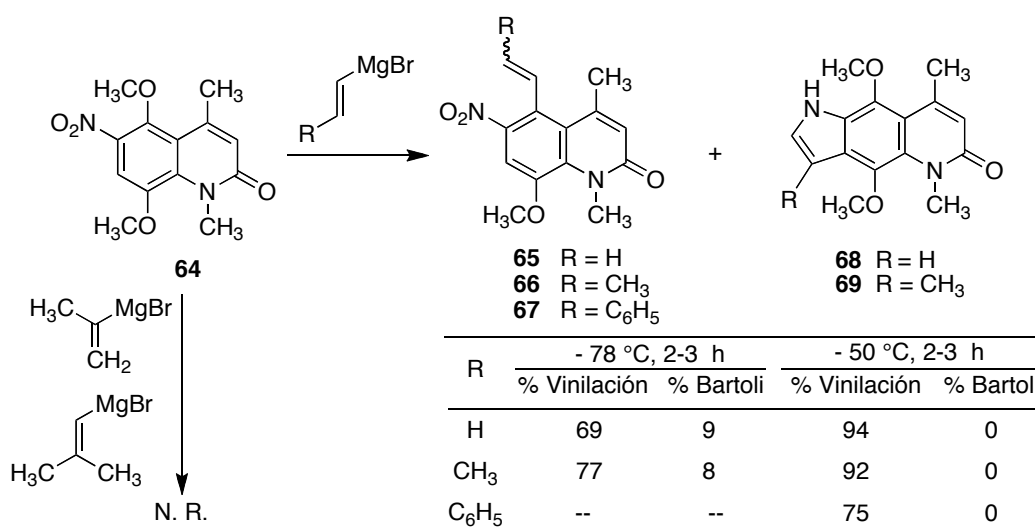


Esquema 2.15

El tratamiento de **64** con varios vinilmagnesianos demostró que la reacción de vinilación también es posible en este caso, aunque con algunas diferencias respecto a lo observado en los sustratos derivados de indol, que se pueden resumir como sigue:

<sup>28</sup> Síntesis de **58**: Avendaño, C.; de la Cuesta, E.; Gesto, C.; *Synthesis* **1991**, 727.

- a) La principal diferencia radica en la imposibilidad de utilizar magnesianos impedidos, como los sustituidos en  $\alpha$  respecto al magnesio o los disustituidos en  $\beta$ . Por otra parte, los vinilmagnesianos no sustituidos o monosustituidos en  $\beta$  dieron de nuevo buenos resultados y proporcionaron los compuestos **65-67**, como se indica en el esquema 2.16.
- b) Otra diferencia respecto a las reacciones llevadas a cabo en indoles fue el aislamiento de pequeñas cantidades de los derivados de pirrolo[2,3-*g*]quinolina **68** y **69**, procedentes de reacciones de Bartoli de **64** con el bromuro de vinilmagnesio y el bromuro de 1-propenilmagnesio, respectivamente. Este producto secundario pudo suprimirse completamente llevando a cabo la reacción a  $-50\text{ }^{\circ}\text{C}$ .



Esquema 2.16



### **3.- Síntesis de carbazoles fusionados basada en la reacción entre nitroarenos y arilmagnesianos**



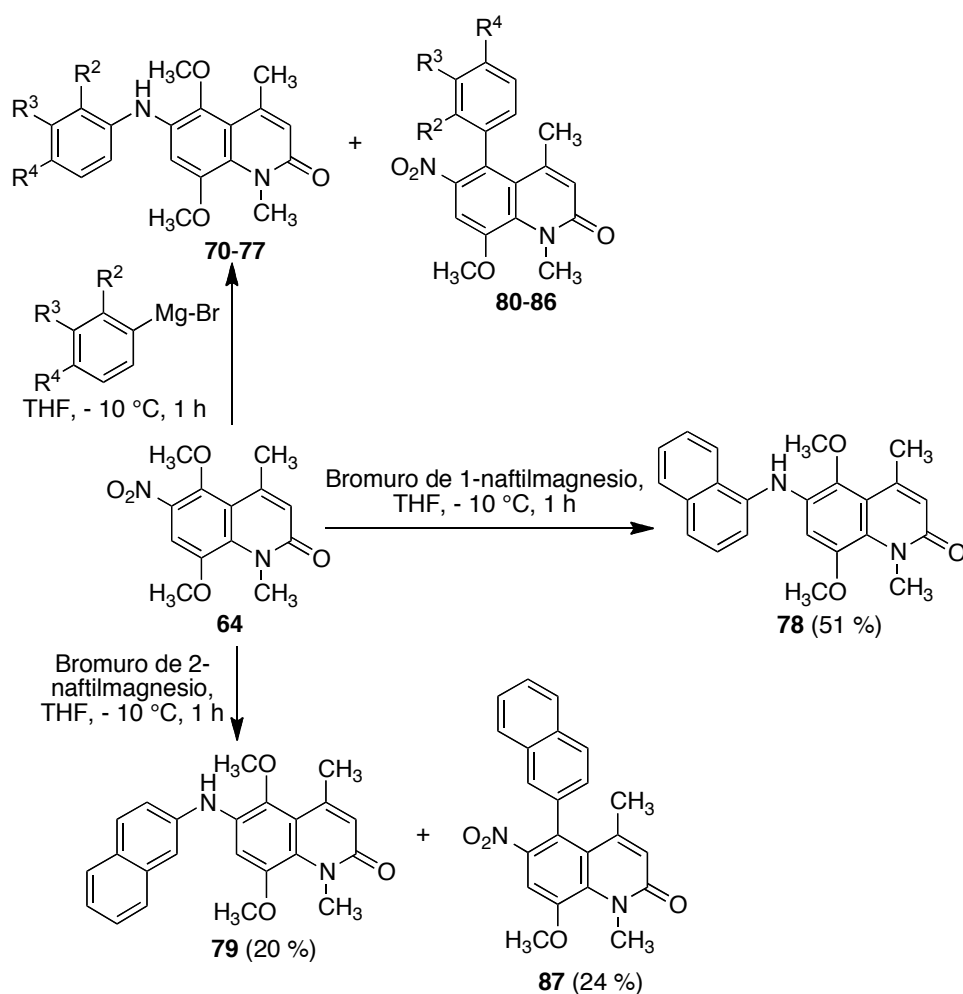
### 3.1. REACCIÓN ENTRE NITROARENOS Y ARILMAGNESIANOS

Estudiamos en primer lugar la reacción entre el derivado de 6-nitrocarbostirilo **64** y varios arilmagnesianos en THF, con los resultados que se recogen en la tabla 4.1 y el esquema 3.1.<sup>29</sup> Contrariamente a lo descrito en los antecedentes del grupo

Tabla 3.1

Producto de N-Arilación	Producto de C-Arilación	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Rto. de N-arilación, %	Rto. de C-arilación, %
<b>70</b>	<b>80</b>	H	H	H	44	18
<b>71</b>	--	CH <sub>3</sub>	H	H	65	0
<b>72</b>	<b>81</b>	H	CH <sub>3</sub>	H	43	2
<b>73</b>	<b>82</b>	H	H	CH <sub>3</sub>	41	13
<b>74</b>	<b>83</b>	H	OCH <sub>3</sub>	H	36	19
<b>75</b>	<b>84</b>	H	H	OCH <sub>3</sub>	38	33
<b>76</b>	<b>85</b>	H	H	Cl	36	31
<b>77</b>	<b>86</b>	H	H	F	42	29
<b>78</b>	--	-CH=CH-CH=CH-		H	51	0
<b>79</b>	<b>87</b>	H	-CH=CH-CH=CH-		20	24

<sup>29</sup> Esta investigación fue iniciada por el Dr. Juan Domingo Sánchez Cebrían durante su estancia postdoctoral, existiendo una comunicación de este trabajo preliminar: Sánchez, J. D.; Avendaño, C.; Menéndez, J. C. *Synlett* **2008**, 1371.

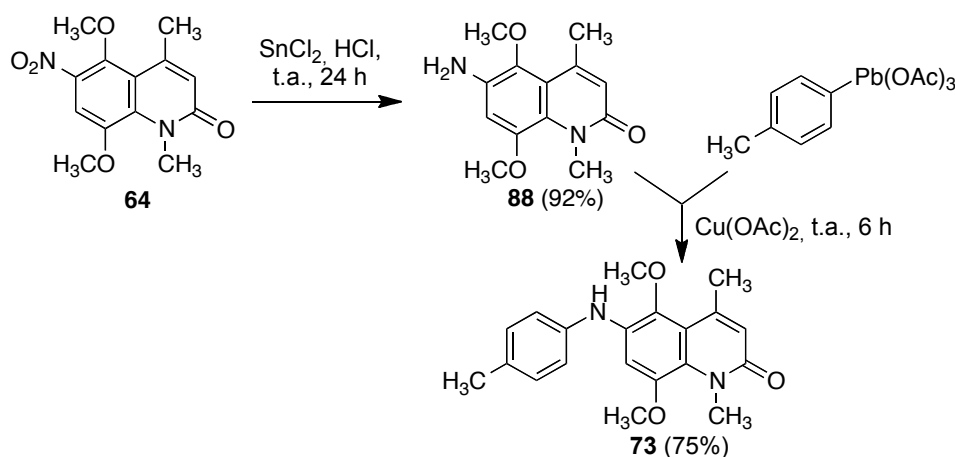


Esquema 3.1

de Miyano para la reacción de 1-metoxi-2-nitronaftaleno con magnesianos aromáticos,<sup>10</sup> los productos mayoritarios fueron las diarilaminas **70-79**, procedentes de un proceso de N-arilación, obteniéndose también pequeñas cantidades de los correspondientes productos de arilación en C-5 (compuestos **80-87**). El curso de la reacción no mostró una dependencia clara hacia el carácter donador o aceptor electrónico de los sustituyentes presentes en el anillo aromático, pero sí hacia efectos estéricos en la proximidad del átomo de magnesio. Así, la reacción con magnesianos sustituidos en *orto*, como el bromuro de *o*-tolilmagnesio condujo exclusivamente a un producto de N-arilación (compuesto **71**). El bromuro de 1-naftilmagnesio reaccionó con una quimioselectividad similar y proporcionó exclusivamente el compuesto **78**, un resultado que puede considerarse significativo

si se tiene en cuenta que la reacción entre el 2-metoxi-2-nitronaftaleno y el mismo magnesiano da 1,1'-binaftilo como único producto.<sup>30</sup> Los magnesianos sustituidos en *meta* y *para* proporcionaron mezclas de productos, en las que en general era mayoritario el de N-arilación (compuestos **72-77** y **79**).

El aislamiento de diarilaminas por reacción entre nitroarenos y arilmagnesianos es casi desconocido en la bibliografía. Ya se ha comentado que el grupo de Knochel ha descrito la preparación de diarilaminas a partir de nitroarenos por adición de reactivos de aril-Grignard al doble enlace O=N del grupo nitro, pero este método requiere la reducción *in situ* de las N,N-diarilhidroxilaminas obtenidas inicialmente por adición de cloruro de hierro(II) y borohidruro sódico.<sup>31</sup> Dada diferencia entre este precedente y nuestro resultado, y a pesar de que la estructura de diarilamina concordaba con todos los datos espectroscópicos y analíticos, consideramos oportuno confirmarla por síntesis independiente (esquema 3.2). Así, la reducción de **64** con cloruro de estaño en ácido clorhídrico acuoso proporcionó la amina **88**, que se transformó en el compuesto **73** por arilación con triacetato de *p*-tolilplomo,<sup>32</sup> en condiciones de Barton.<sup>33</sup> La diarilamina **73** obtenida por este procedimiento resultó idéntica a la procedente de la reacción entre **64** y bromuro de *p*-tolilmagnesio.



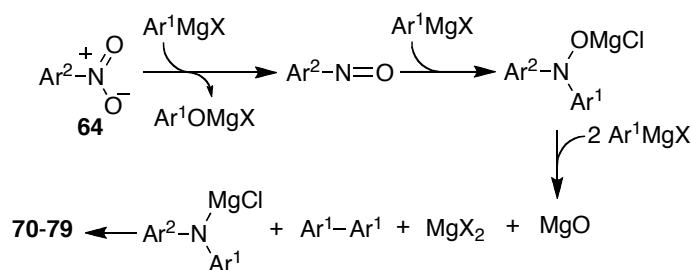
Esquema 3.2

<sup>30</sup> Hattori, T.; Takeda, A.; Yamabe, O.; Miyano, S. *Tetrahedron* **2002**, *58*, 233.

<sup>31</sup> (a) Ver la referencia 2. (b) Puede consultarse un comentario de este trabajo en: Ricci, A.; Fochi, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 1444.

<sup>32</sup> Síntesis de este reactivo: López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *Heterocycles* **1991**, *32*, 1003.

Tras confirmar la estructura de las diarilaminas, se hacía necesario explicar por qué en nuestro caso fue posible su aislamiento directo sin necesidad de una etapa de reducción independiente. Una comparación detallada de nuestras condiciones con las de Knochel revela que difieren principalmente en que nosotros empleamos un mayor exceso de magnesiano. Esto nos lleva a proponer que en nuestro caso tiene lugar el proceso resumido en el esquema 3.3,<sup>34</sup> en el cual el derivado de hidroxilamina reacciona con dos equivalentes de magnesiano para dar la diarilamina y una molécula de biarilo como producto secundario, que de hecho ha sido observado en nuestros crudos de reacción.



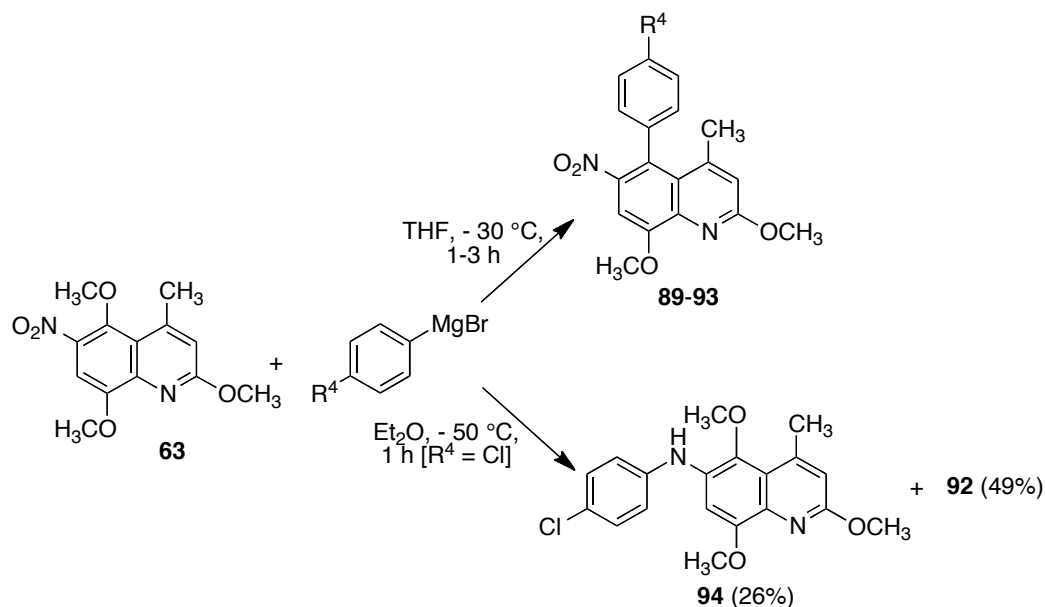
Esquema 3.3

Como siguiente etapa de nuestro estudio, investigamos la reacción entre la 2,5,8-trimetoxi-6-nitroquinolina **63** y magnesianos aromáticos. Como se indica en el esquema 3.4 y en la tabla 3.2, las reacciones en tetrahidrofurano condujeron en esta ocasión a derivados de C<sub>5</sub>-arilación como productos únicos (compuestos **89-93**). Cuando una de las reacciones (con el cloruro de 4-clorofenilmagnesio) se llevó a cabo en éter dietílico, el producto de C-arilación **92** continuó siendo mayoritario (49%), pero se obtuvo una cantidad considerable (26%) del producto de N-arilación **94**. Esta diferencia de comportamiento ha de estar asociada a las diferencias de composición de las disoluciones de magnesianos en distintos disolventes, a través del equilibrio de Schlenk. Así, en éter dietílico los reactivos de Grignard existen

<sup>33</sup> Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2095.

<sup>34</sup> Bartoli, G. *Acc. Chem. Res.* **1984**, *17*, 109.

preferentemente en forma de la especie  $\text{RMgX}$ , mientras que las disoluciones en THF contienen, además,  $\text{R}_2\text{Mg}$  y  $\text{MgX}_2$ .<sup>35</sup>



Esquema 3.4

Tabla 3.2

Comp.	$\text{R}^4$	Rto., %
<b>89</b>	H	57
<b>90</b>	$\text{CH}_3$	60
<b>91</b>	$\text{OCH}_3$	88
<b>92</b>	Cl	62
<b>93</b>	F	60

La diferencia de comportamiento entre los derivados de carbostirilo y los de 2-alcoxiquinolina puede atribuirse a la diferente densidad electrónica del carbono 5 y del enlace  $\text{O}=\text{N}$  del grupo nitro en ambos casos. Una primera inspección revela que en la 2-metoxiquinolina **63** el grupo metoxilo, donador electrónico, está conjugado con el grupo nitro en C-6. En el derivado de carbostirilo **64** coexisten un grupo aceptor electrónico, concretamente un carbonilo  $\alpha,\beta$ -insaturado, conjugado con la posición C-5,

<sup>35</sup> Smith, M. B. Organic Synthesis, 3<sup>a</sup> edición, pp. 636-639. Wavefunction, 2011.

y un donador, el átomo de nitrógeno, que debe ceder carga al grupo nitro. Un estudio computacional *ab initio* llevado a cabo al nivel B3LYP/6-31G dio los resultados cuantitativos que se muestran en la figura 3.1 para las densidades electrónicas de la posición C-5 y el grupo nitro. Se observa que C-5 es más electrófila en el compuesto **63**, lo que explica su mayor tendencia a la C-arilación. Teniendo en cuenta que la reacción de los magnesianos con el grupo nitro comienza por un ataque nucleófilo al enlace O=N, los valores encontrados indica que debe ser más fácil en **64**, en el que el oxígeno es menos negativo. Estos efectos se aprecian de forma más intuitiva en las superficies de potencial electrostático, que se reproducen también en la figura.

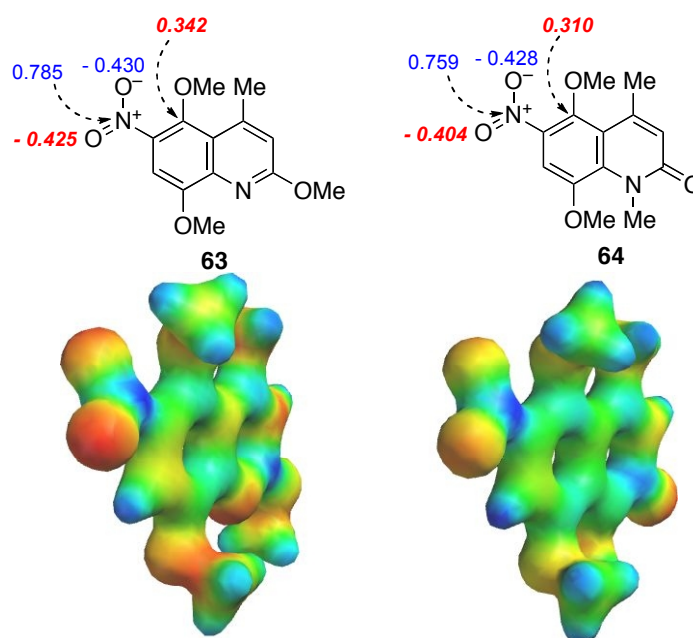
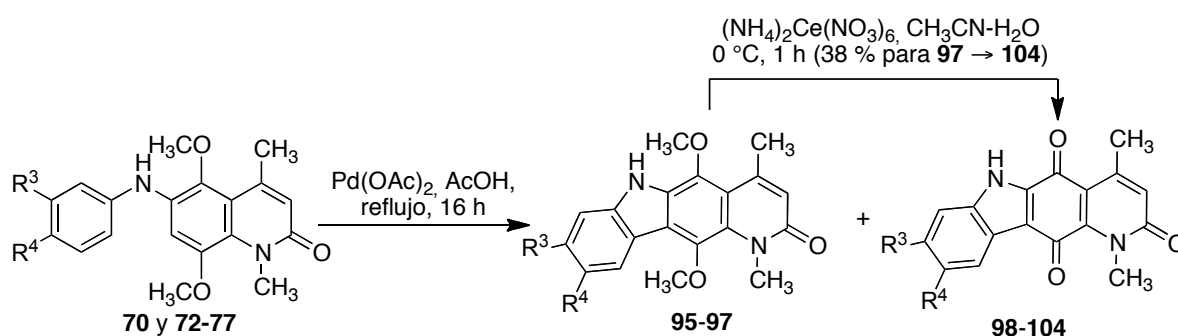


Figura 3.1

### 3.2. SÍNTESIS DE CARBAZOLES FUSIONADOS LINEALES

Una vez disponibles los derivados de arilaminoquinolina, se investigó su transformación en carbazoles fusionados por ciclación oxidativa en presencia de paladio. Cuando se trataron los compuestos **70** y **72-77** con acetato de paladio en ácido acético a reflujo, se obtuvieron en algunos casos los derivados de dimetoxicarbazol esperados (compuestos **95-97**), pero los productos mayoritarios fueron las correspondientes quinonas **98-104**, que se obtuvieron sin necesidad de una etapa independiente de desmetilación oxidativa. Sus estructuras quedaron confirmadas por sus datos espectroscópicos y por la preparación independiente de uno de ellas (compuesto **104**) por tratamiento del dimetoxi derivado **97** con nitrato cérico amónico en las condiciones estándar de desmetilación oxidativa (esquema 3.5 y tabla 3.3).



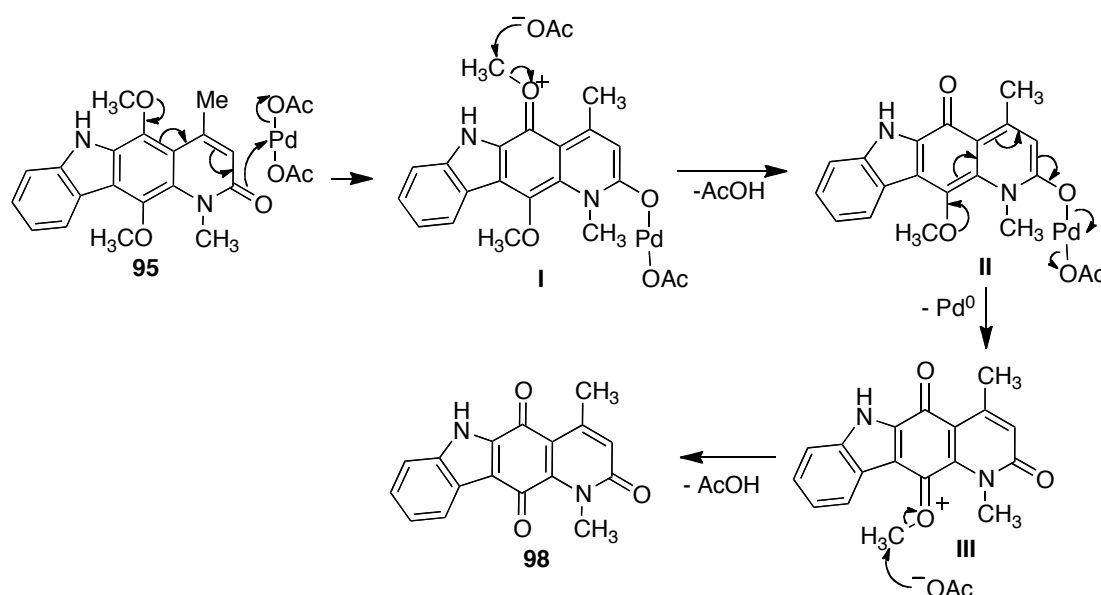
Esquema 3.5

Tabla 3.3

Dimetoxi derivado	Quinona	R <sup>3</sup>	R <sup>4</sup>	Dimetoxi derivado (%)	Quinona (%)
<b>95</b>	<b>98</b>	H	H	25	59
--	<b>99</b>	CH <sub>3</sub>	H	0	25 (52) <sup>a</sup>
--	<b>100</b>	H	CH <sub>3</sub>	0	45 (91) <sup>a</sup>
--	<b>101</b>	OCH <sub>3</sub>	H	0	48
--	<b>102</b>	H	OCH <sub>3</sub>	0	69
<b>96</b>	<b>103</b>	H	Cl	33	29
<b>97</b>	<b>104</b>	H	F	32	47

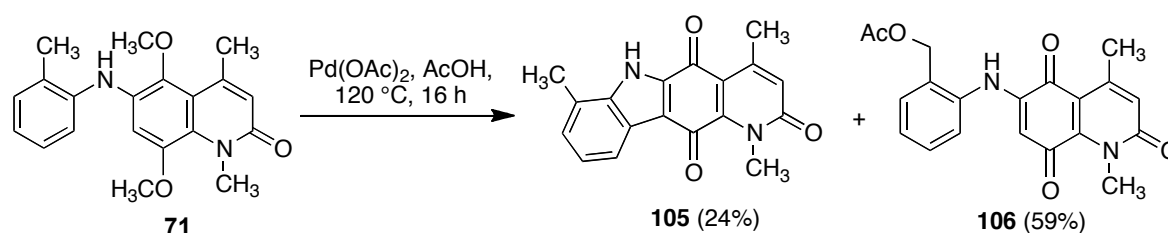
<sup>a</sup> Los rendimientos entre paréntesis se basan en material de partida recuperado

La desmetilación oxidativa por el acetato de paladio resultaba interesante por no existir precedentes bibliográficos. La reacción parece estar restringida a sistemas de carbostirilo, ya que no tuvo lugar cuando se intentó a partir de diarilaminas sencillas. Recientemente se ha descrito que el acetato de paladio puede comportarse como reactivo de N-desmetilación, aunque no de O-desmetilación de éteres fenólicos.<sup>36</sup> Por otra parte, el calentamiento de **72** a reflujo en ácido acético durante 17 h condujo únicamente a material de partida inalterado. Estas observaciones permiten descartar una desmetilación inicial a hidroquinona seguida de oxidación por el aire. Para explicar nuestras observaciones, proponemos el mecanismo resumido en el esquema 3.7, que se inicia por paladación del oxígeno del sistema de carbostirilo con asistencia de uno de los grupos metoxilo, para originar un catión oxonio **I** en el que tiene lugar una primera desmetilación por ataque de un anión acetato que da lugar a **II**. La pérdida de Pd (0) y un anión acetato conduce a un nuevo derivado de oxonio **III**, en el que tiene lugar una segunda desmetilación por ataque de un anión acetato, que proporciona finalmente el compuesto **98** (esquema 3.6).



<sup>36</sup> Carroll, R. J.; Leisch, H.; Scocchera, E.; Hudlicky, T.; Cox, D. P. *Adv. Synth. Catal.* **2008**, *350*, 2984.

En el caso del compuesto **71**, se obtuvo un resultado inesperado adicional ya que, junto a la carbazolquinona **105** (24%), el producto mayoritario fue el compuesto **106**, funcionalizado en el grupo 2-metilo y además oxidado a quinona (esquema 3.7). Esta reacción, por tanto, constituye un ejemplo de un proceso de activación de un enlace C-H.<sup>37</sup>

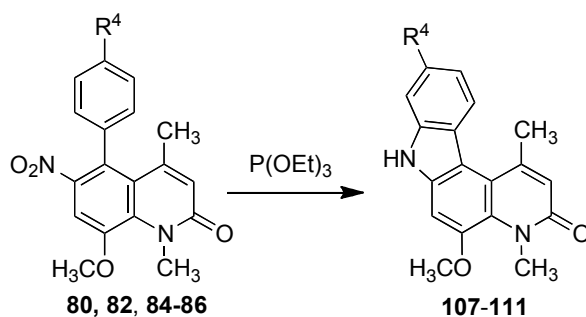


Esquema 3.7

<sup>37</sup> Algunas revisiones de reacciones de activación de enlaces C-H: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (d) Giri, R.; Shi, B.-F.; Engle, K. M.; Mangel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (e) Mkhaliid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

### 3.3. SÍNTESIS DE CARBAZOLES FUSIONADOS ANGULARES

Debido a la presencia de un grupo nitro, los derivados de arilación en posición 5 son adecuados como materiales de partida para la generación de un sistema de carbazol mediante una reacción de Cadogan. Este método transcurre mediante la reducción por un fosfito del grupo nitro a nitreno, que después se adiciona intramolecularmente al anillo aromático adyacente. El tratamiento de los compuestos **80**, **82** y **84-86** con fosfito de trietilo se llevó a cabo en condiciones de reflujo, o bien por irradiación con microondas focalizadas, con los resultados que se indican en el esquema 3.8 y la tabla 3.4. Ambos métodos proporcionaron rendimientos similares, pero las condiciones de irradiación con microondas condujeron, en general, a productos de mayor pureza.



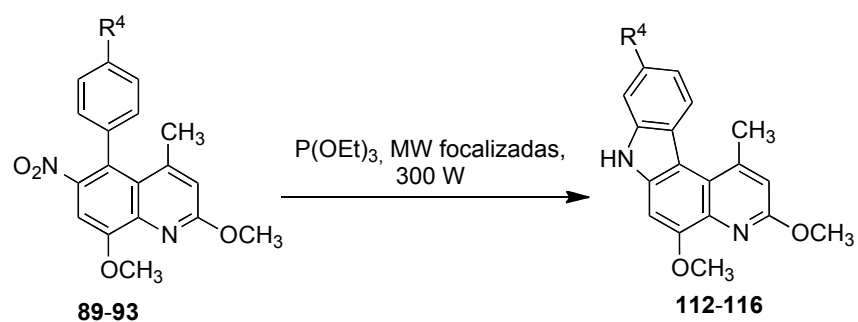
Esquema 3.8

Tabla 3.4

Comp.	R <sup>4</sup>	Método <sup>a</sup>	Rto. (%)
<b>107</b>	H	A	55
<b>108</b>	CH <sub>3</sub>	A	53
		B	50
<b>109</b>	OCH <sub>3</sub>	A	51
		B	56
<b>110</b>	Cl	A	30
<b>111</b>	F	A	39
		B	56

<sup>a</sup> Método A: reflujo, 160 °C, 3 h. Método B: Microondas focalizadas, 300 W, 180 °C, 25 min

Las reacciones de Cadogan de los derivados de 2-metoxiquinolina **89-93** procedieron de forma similar, dando lugar a los compuestos **112-116** (esquema 3.9 y tabla 3.5).

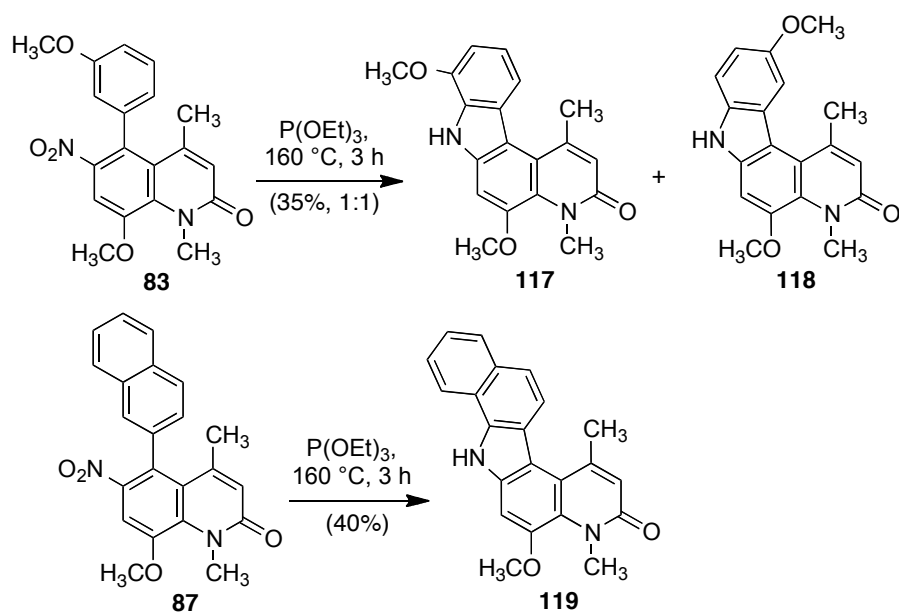


Esquema 3.9

Tabla 3.5

Comp.	R <sup>4</sup>	Rto. (%)
<b>112</b>	H	45
<b>113</b>	CH <sub>3</sub>	55
<b>114</b>	OCH <sub>3</sub>	87
<b>115</b>	Cl	46
<b>116</b>	F	46

También investigamos algunas reacciones de Cadogan en sustratos no simétricos. Como se muestra en el esquema 3.10, cuando partimos del compuesto **83**, obtuvimos cantidades equimoleculares de los dos productos de ciclación posibles (compuestos **117** y **118**), con rendimiento bajo y en forma de una mezcla que no pudo separarse. En cambio, el derivado de naftaleno **87** proporcionó de forma regioselectiva el compuesto **119**, lo que puede interpretarse como una consecuencia de la mayor reactividad de las posiciones  $\alpha$  del naftaleno.



Esquema 3.10

## **4. Síntesis de análogos simplificados de wakayina**



## 4.1. INTRODUCCIÓN

### 4.1.1. Consideraciones generales

La búsqueda de nuevos compuestos antitumorales en organismos de origen marino está experimentando un gran impulso en los últimos años, debido a que la industria farmacéutica necesita urgentemente incrementar el ritmo de descubrimiento de nuevas moléculas (NCE, *New Chemical Entities*).<sup>38</sup> Cabe destacar el papel esencial que puede desempeñar en este sentido la manipulación estructural de modelos naturales, ya que el 61% de las NCE introducidas en el período 1981-2007 son compuestos relacionados con productos naturales, porcentaje que sube hasta el 74% en el caso de los antitumorales.<sup>39·40·41</sup> Debe destacarse que el campo de la búsqueda de sustancias citotóxicas es probablemente el que más se beneficia del uso de modelos naturales, ya que sus estructuras han sido optimizadas en el transcurso de la evolución para servir como

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<sup>38</sup> Paterson, I.; Anderson, E. A. *Science* **2005**, *310*, 451.

<sup>39</sup> Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022.

<sup>40</sup> Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461.

<sup>41</sup> Ravelo, A. G.; Estévez-Braun, A.; Chávez-Orellana, H.; Pérez-Sacau, E.; Mesa-Siverio, D. *Curr. Topics Med. Chem.* **2004**, *4*, 241.

mecanismos de defensa. En este sentido, se ha afirmado que, en el terreno de la quimioterapia del cáncer, “la naturaleza ha hecho ya la química combinatoria”.<sup>42</sup>

A pesar de la tendencia actual a la búsqueda de dianas en los procesos de señalización celular como estrategia en la quimioterapia del cáncer, el ADN continúa siendo el principal objetivo en el diseño de fármacos antitumorales. Por su especial relevancia para las metas de este trabajo, se realizará a continuación un breve comentario de los mecanismos relacionados con la inhibición de topoisomerasas.

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<sup>42</sup> Mann, J. *Nature Rev. Cancer* **2002**, 2, 143.

#### 4.1.2. Inhibición de topoisomerasa I como estrategia en el diseño de nuevos antitumorales

Las topoisomerasas son enzimas que regulan la geometría tridimensional del ADN, permitiendo la relajación de fragmentos de ADN superenrollado, que es una forma de empaquetamiento compacto que hace que ocupe un espacio suficientemente pequeño para poder ser alojado en el núcleo celular. Este proceso es esencial para que tengan lugar los fenómenos de transcripción y replicación. Existen dos tipos principales de topoisomerasas, conocidos como I y II, que actúan, respectivamente, mediante la ruptura transitoria de una o de las dos hebras del ADN, respectivamente. Las topoisomerasas de tipo II son muy conocidas, por ser la diana de las quinolonas antibacterianas y de algunos antitumorales de uso clínico,<sup>43</sup> como las antraciclinas.<sup>44</sup> Sin embargo, desde el punto de vista de la búsqueda de nuevos antitumorales, es mucho más interesante la topoisomerasa I.<sup>45-46-47</sup> Los compuestos que inhiben la topoisomerasa I actúan durante la fase replicativa del ciclo celular (S), mientras los que inhiben la II actúan en la fase de transcripción del

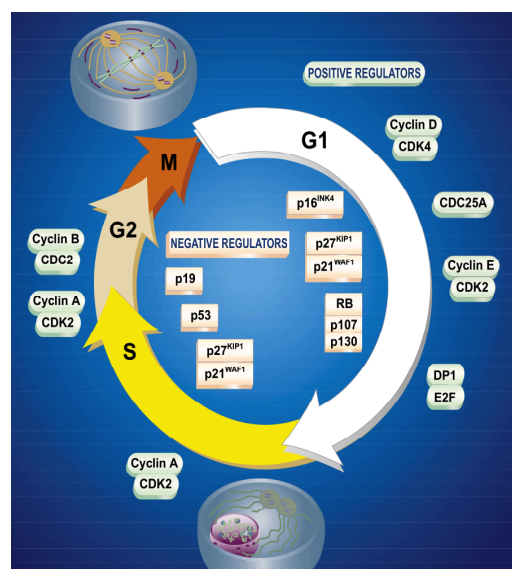


Figura 4.1

<sup>43</sup> Capranico, G.; Zagotto, G.; Palumbo, M. *Curr. Med. Chem.-Anti-Cancer Agents*, **2004**, 4, 335.

<sup>44</sup> Denny, W. A. *Exp. Opin. Emerg. Drugs* **2004**, 9, 105.

<sup>45</sup> Bailly, C. *Curr. Med. Chem.* **2000**, 7, 39.

<sup>46</sup> Meng, L. H.; Liao, Z.-Y.; Pommier, Y. *Curr. Topics Med. Chem.* **2003**, 3, 305.

<sup>47</sup> Denny, W. A.; Baguley, B. C. *Curr. Top. Med. Chem.* **2003**, 3, 339.

RNA, durante casi todo el ciclo celular (fase G2-M, figura 4.1). El estudio de estos compuestos se inició a partir del estudio de la camptotecina, aislada a partir del árbol *Camptotheca acuminata*. El fármaco de este grupo más estudiado en clínica es el irinotecan, utilizado en tumores de colon y recto, solo o en combinación con 5-fluorouracilo;<sup>48</sup> existen otros análogos de interés, como topotecan, lurtotecan y exatecan. A pesar de su introducción en clínica, se han planteado dudas acerca de la seguridad los análogos de camptotecina, y se puede considerar urgente la búsqueda de nuevos compuestos que actúen sobre la topoisomerasa I.

El mecanismo molecular de acción de las topoisomerasas se basa en la formación de un enlace covalente entre un residuo de tirosina de su sitio activo y el ADN. Estos enlaces son reversibles, y por este motivo la estructura que se forma se conoce como complejo hidrolizable (*cleavable complex*). La otra hebra de la molécula de ADN pasa a través del espacio creado por esta rotura y finalmente se regenera la doble hélice. La topoisomerasa I corta un solo fragmento del dúplex del DNA y no necesita cofactores energéticos, mientras que la topoisomerasa II corta los dos filamentos del DNA y es ATP-dependiente.

La topoisomerasa I tiene un peso molecular de 90 kD, con cuatro dominios principales: la región N-terminal, importante para la interacción con otras proteínas nucleares pero no fundamental para el plegamiento proteico, un dominio central, un

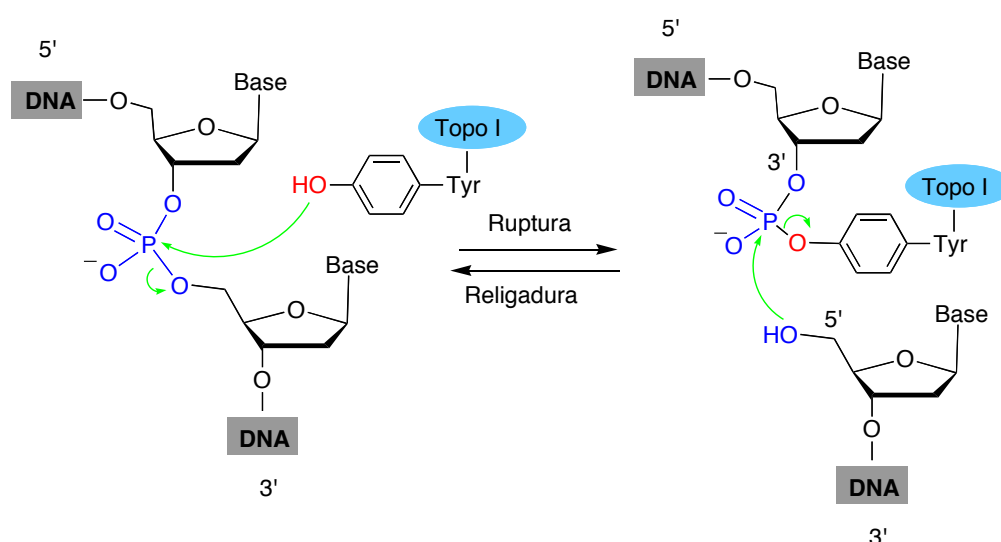


Figura 4.2

<sup>48</sup> Holen, K. D.; Saltz, L. B. *Lancet Oncology*, **2001**, 2, 290-297.

espaciador cargado positivamente y finalmente el dominio C-terminal, donde se encuentra el sitio activo con la tirosina 723. El ciclo catalítico de la topoisomerasa I (figura 4.2) implica dos etapas de transesterificación. La primera ocurre en la etapa de rotura y supone el ataque nucleófilo del grupo hidroxilo de la tirosina a un grupo fosfato perteneciente a un grupo fosfodiéster del esqueleto del ADN. La segunda transesterificación tiene lugar en la etapa de regeneración de la doble hélice y consiste en la reacción entre un grupo hidroxilo de la desoxirribosa y el fosfato de tirosina formado en la primera etapa. Este proceso relaja la tensión debida al superenrollamiento del ADN porque permite reducir en una unidad el número de vueltas que presenta un fragmento de ADN (Figura 4.3).

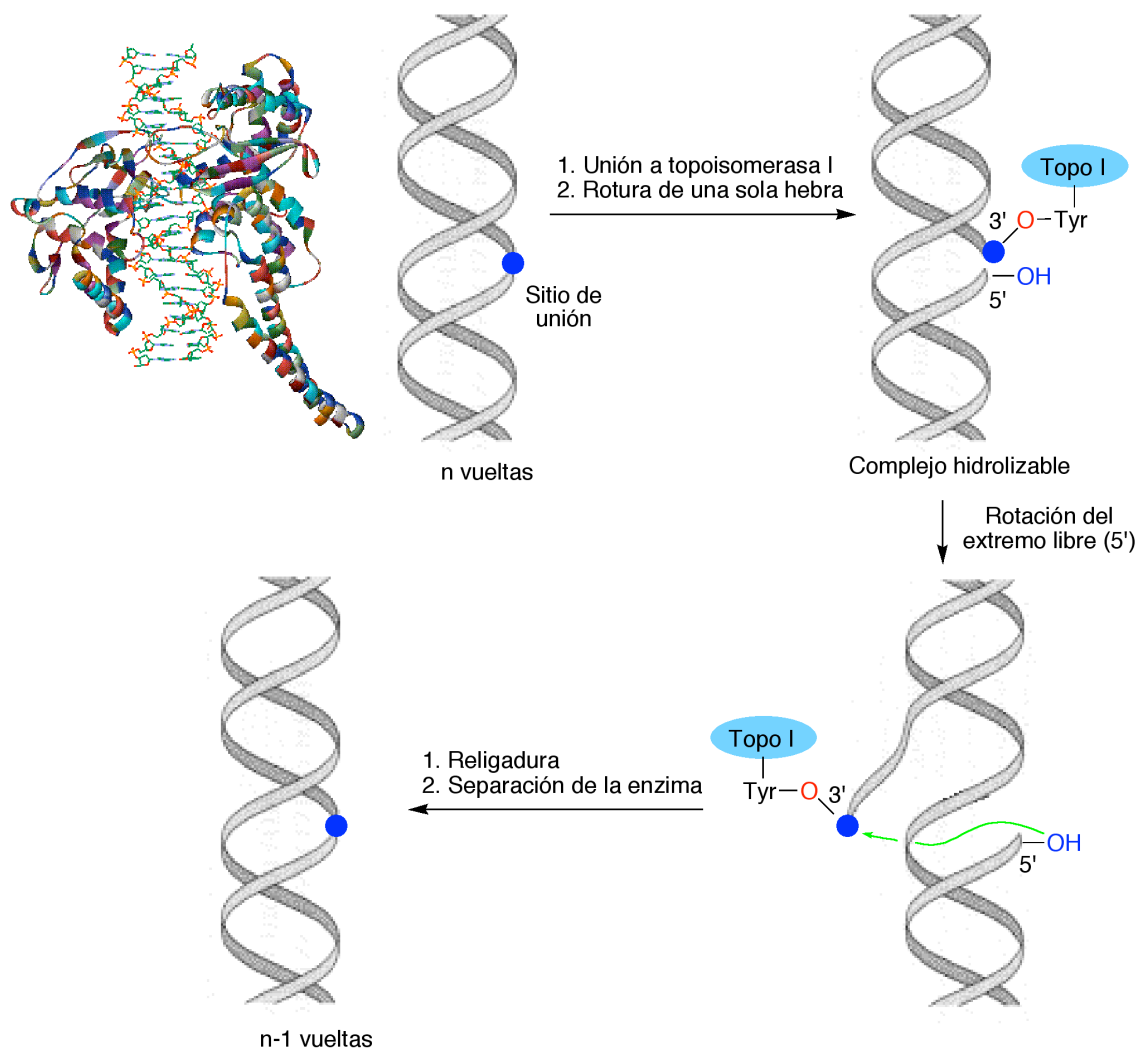


Figura 4.3

La mayor parte de los inhibidores de topoisomerasa I actúan por estabilización del complejo hidrolizable formado por el ADN y la enzima (figura 4.4).

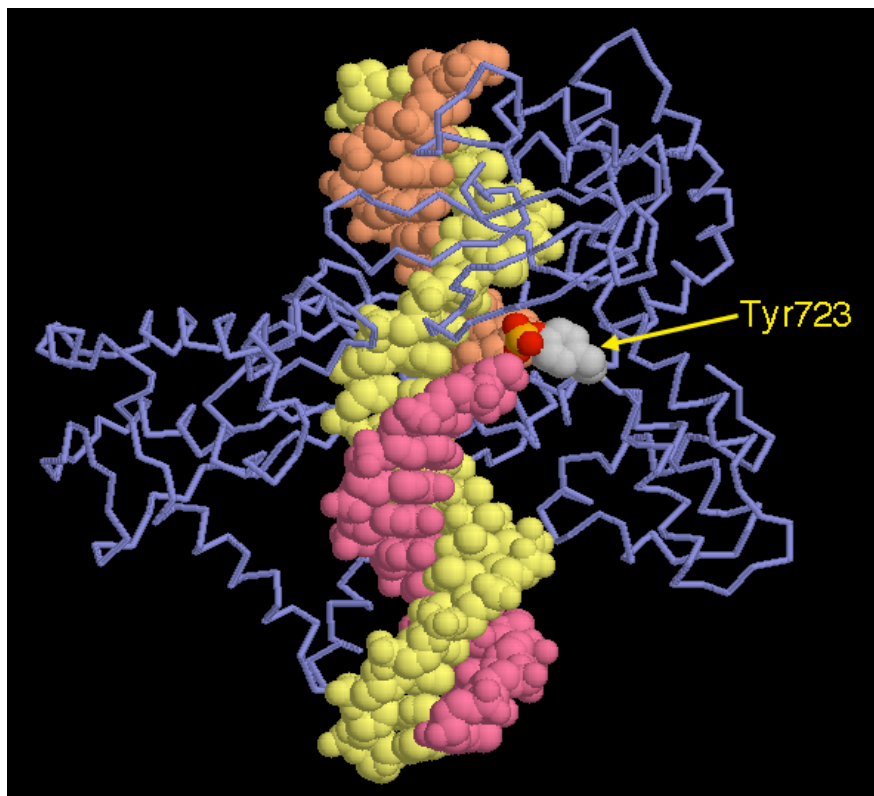


Figura 4.4

### 4.1.3. La wakayina y compuestos relacionados

Algunos alcaloides de origen marino son muy prometedores como cabezas de serie en el campo de la quimioterapia antitumoral a causa de sus perfiles de citotoxicidad poco habituales y del hecho de que algunos de ellos son activos frente a líneas celulares que presentan el fenómeno de resistencia a múltiples fármacos (MDR). Destacaremos, en particular, la familia de las pirroloquinoniminas,<sup>49</sup> un grupo de más de 80 alcaloides que en su mayor parte han sido aislados de esponjas y han mostrado una potente actividad citotóxica. Estos compuestos son de gran interés debido a que su mecanismo de acción consiste en la inhibición de topoisomerasas.<sup>50</sup> Uno de los miembros más interesantes de esta familia es la wakayina, que presenta una elevada citotoxicidad y se comporta como un potente inhibidor de topoisomerasa I que se une a las mismas secuencias que la camptotecina.<sup>51</sup> El estudio de este compuesto ha sido superficial debido a que se encuentra en muy baja concentración en las fuentes naturales, lo que hace imposible disponer de cantidades suficientes para los estudios farmacológicos. Tampoco existen apenas estudios de relaciones estructura-actividad en sus análogos, con la excepción del compuesto abierto **1a**, que ha mostrado una actividad algo inferior a la del modelo,<sup>52</sup> y de los aza análogos **1b** y **1c**, que también han resultado poco activos aunque hay que destacar que carecen del sustituyente indólico.<sup>53</sup> Esta escasez de información se puede atribuir a dificultades sintéticas, que se reflejan en la escasez de publicaciones en este campo<sup>54</sup> y en el hecho de que, a pesar de haber sido aislada en 1991,<sup>55</sup> todavía no se ha publicado una síntesis total de la wakayina, a diferencia de lo sucedido con otras pirroloquinoniminas.

<sup>49</sup> Revisiones: (a) Ding, Q. D.; Chickak, K.; Lown, J. W. *Curr. Med. Chem.* **1999**, *6*, 1. (b) Antunes, E. M.; Copp, B. R.; Davies-Coleman, M. T.; Samaai, T., *Nat. Prod. Rep.* **2005**, *22*, 62. (c) Delfourne, E. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 910.

<sup>50</sup> Matsumoto, S. S.; Haughey, H. M.; Schmehl, D. M.; Venables, D. A.; Ireland, C. M.; Holden, J. A.; Barrows, L. R. *Anti-Cancer Drugs* **1999**, *10*, 39.

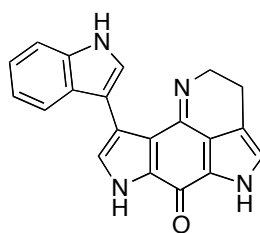
<sup>51</sup> Kokoshka, J. M.; Capson, T. L.; Holden, J. A.; Ireland, C. M.; Barrows, L. R. *Anti-Cancer Drugs* **1996**, *7*, 758.

<sup>52</sup> Bénéteau, V. B.; Pierré, A.; Pfeiffer, B.; Renard, P.; Besson, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2231.

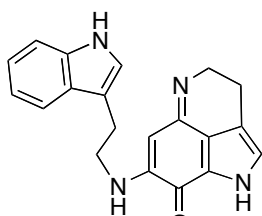
<sup>53</sup> Legentil, L.; Lesur, B.; Delfourne, E. *Bioorg. Med. Chem.* **2006**, *16*, 427.

<sup>54</sup> (a) Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, *40*, 3889. (b) Zhang, L. M.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. *Tetrahedron Lett.* **1998**, *39*, 7677.

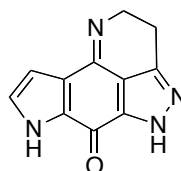
<sup>55</sup> Copp, B. R.; Ireland, C. M.; Barrows, L. R. *J. Org. Chem.* **1991**, *56*, 4596.



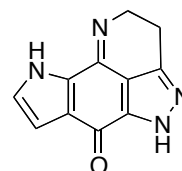
Wakayina



I



II



III

## 4.2. DISEÑO DE ANÁLOGOS SIMPLIFICADOS DE WAKAYINA COMO INHIBIDORES DE TOPOISOMERASA I

### 4.2.1. Introducción

Durante una estancia en el grupo de los profesores Thierry Langer y Gerhard Wolber en la Universidad de Innsbruck, se han llevado a cabo estudios de *docking* destinados a localizar el grupo farmacóforo de la wakayina y utilizar la información obtenida para diseñar análogos simplificados del alcaloide que mantengan su capacidad de interaccionar con la enzima. Debido a que hasta la fecha no se ha cristalizado la topoisomerasa I en presencia de wakayina, ha sido necesario proceder a partir de datos de otros inhibidores cuyos complejos con la enzima pueden encontrarse en el Protein Data Bank. Debido a que la wakayina se une al mismo sitio que la camptotecina, hemos considerado especialmente útil una publicación en la que se comparan los complejos formados por la topoisomerasa I humana con algunos de sus inhibidores como la camptotecina y el topotecan, éste último en su forma abierta y cerrada, utilizando datos cristalográficos.<sup>56</sup>

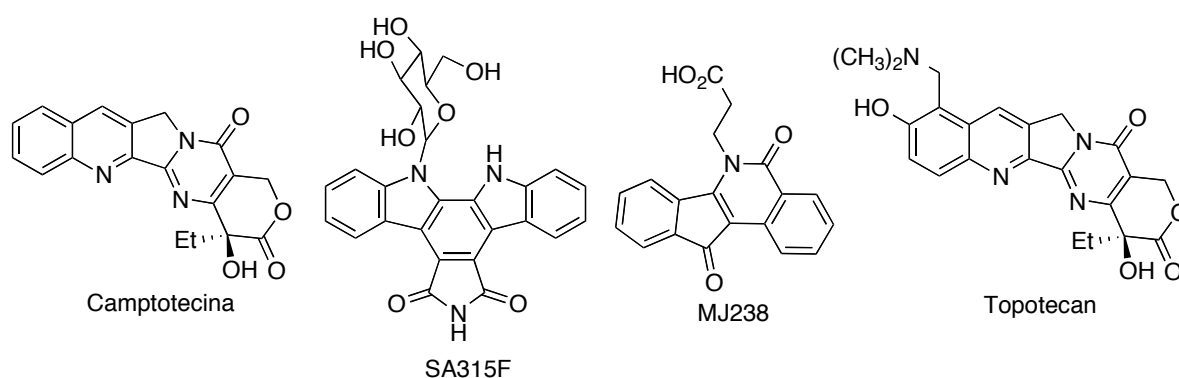


Figura 4.5

La figura 4.6 muestra la superposición de camptotecina (amarillo), SA315F (naranja), MJ238 (magenta) y topotecan (verde) en el centro activo de la topoisomerasa, concluyéndose que existen los siguientes requerimientos estructurales para la unión:

<sup>56</sup> Staker, B. L., Feese, M. D.; Cushman, M.; Pommier, Y.; Zembower, D.; Stewart, L.; Burgin, A. B. *J. Med. Chem.*, **2005**, *48*, 2336.

1. Una estructura heterocíclica plana que se intercala entre los pares de bases de la hebra intacta del ADN.

2. Presencia de un aceptor de enlace de hidrógeno (átomo con un par de electrones libre) orientado hacia el surco menor en la zona de intercalación. Está situada de manera que puede formar un enlace de hidrógeno con un residuo de Arg364. Es la única interacción proteína-inhibidor que se conserva en los tres inhibidores, aunque la naturaleza química del aceptor de enlace de hidrógeno puede ser muy diferente.

3. Presencia de un sustituyente, de naturaleza muy diversa, que se sitúa en el surco mayor, próximo a la cadena lateral de un resto de Asn352 de la enzima.

4. Grupos hidroxilo próximos a un resto de Glu356 en la proximidad de la hebra intacta del ADN.

5. Un anillo E en la zona de la hebra escindida del ADN.

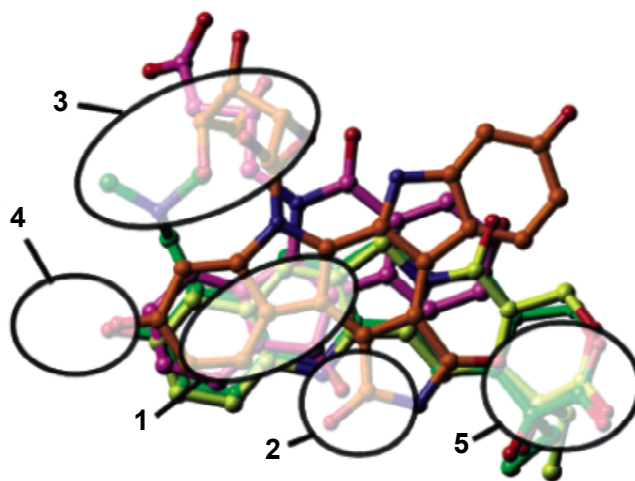


Figura 4.6

### 4.2.2. Validación del protocolo de docking

El objetivo básico de los métodos de docking es identificar la conformación correcta de los ligandos en el bolsillo de unión de la proteína y predecir el grado de afinidad entre el ligando y la proteína. Como compuestos de referencia para validar nuestro estudio de docking antes de aplicarlo a nuestros compuestos, se seleccionaron algunos inhibidores que se muestran en la Figura 4.7, incluyendo la camptotecina y algunos de sus derivados, ya que existe información cristalográfica de su unión a la topoisomerasa I que puede compararse con las predicciones del estudio computacional.

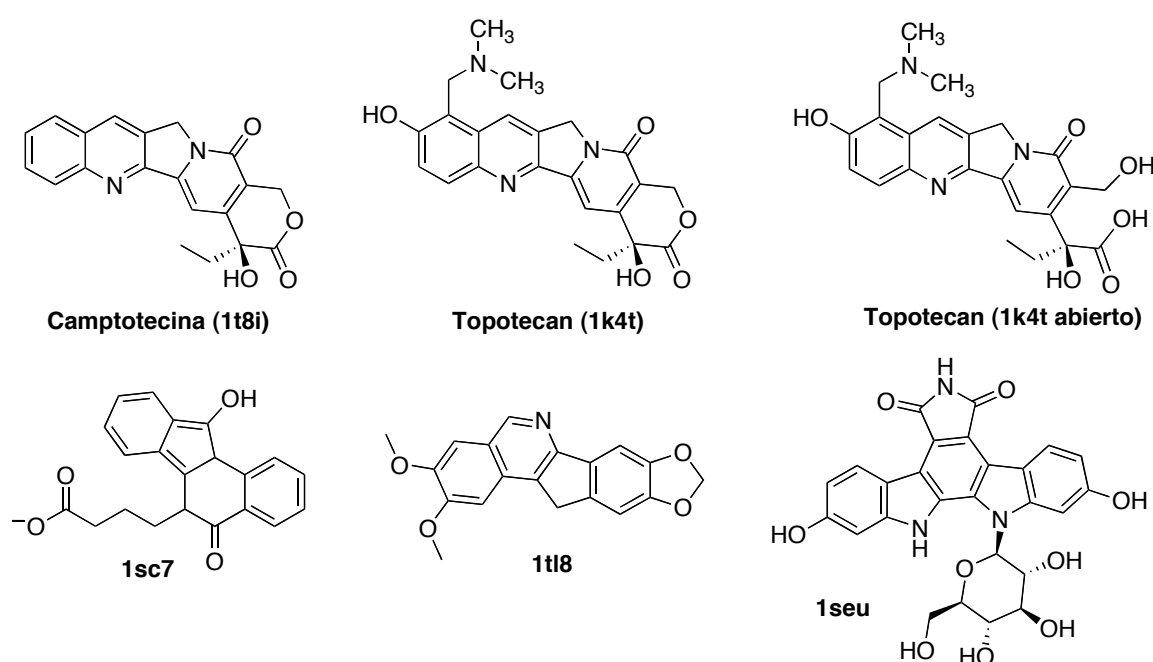


Figura 4.7 (se indican las referencias en el PDB de sus complejos con topoisomerasa I)

Se realizó el docking de todos ellos utilizando tres protocolos diferentes: QPLD (*Quantum Mechanics Polarized Ligand Docking*), Glide y Gold (*Genetic Optimization for Ligand Docking*), con el objetivo de comparar los resultados obtenidos con cada uno de ellos y seleccionar aquel que proporcionara los complejos ligando-topoisomerasa I más semejantes a las estructuras cristalizadas con la enzima para aplicarlo al estudio posterior de la wakayina. Para la comparación de los tres métodos se emplearon los valores de desviación de la media cuadrática (RMSD, de

*Root Mean Square Deviation*), que se indican en la tabla 4.1. Este parámetro se usa para medir la precisión del docking, por comparación con los datos cristalográficos, y es tanto mejor cuanto más se acerca su valor a 0. En general, nuestros valores de RMSD pueden considerarse muy buenos para la camptotecina y sus análogos. En general, se utilizó la estructura de la topoisomerasa cristalizada con topotecan en su forma de hidroxácido. En el caso de 1sc7, los resultados obtenidos de esta manera no fueron buenos, pero mejoraron cuando se partió de los datos cristalográficos de la enzima cristalizada con el propio ligando (datos entre paréntesis), lo que puede justificarse teniendo en cuenta que la cadena lateral de éste obliga a la topoisomerasa a adoptar una conformación distinta a la que presenta en los demás casos. Estos resultados nos llevaron a seleccionar Gold para las etapas posteriores de nuestro trabajo.

Tabla 4.1. Comparación de los tres métodos de docking

Compuesto	RMSD (Root mean square distance)		
	QM-Polarized	Glide	Gold
Topotecan (hidroxácido) 1k4t	1,7	1,61	1,28
Topotecan (lactona) 1k4t	1,61	1,56	0,94
Camptotecina (1t8i)	1,62	0,84	1,06
1sc7	5,82 (5,89)	11,03 (5,87)	7,04 (5,35)
1tl8	4,39	4,49	1,49
1seu	a	a	7,66

<sup>a</sup> No se consiguió el docking

Nuestros resultados de docking mostraron una buena concordancia con los datos cristalográficos pero, además, nuestros datos permiten proponer otro residuo activo (Phe361) que podría intervenir en la inhibición de la enzima e indican, además, que es importante la presencia de tres moléculas de agua estructurales de la proteína (HOH3, HOH28, HOH1002), que forman enlaces hidrógeno y hacen de

puente para la interacción entre el topotecan y el sitio activo. Como ejemplo de las orientaciones adoptadas por los ligandos, se muestra en la Figura 4.8 la superposición de las moléculas de topotecan (naranja) y 1sc7 (amarillo) en el sitio activo.

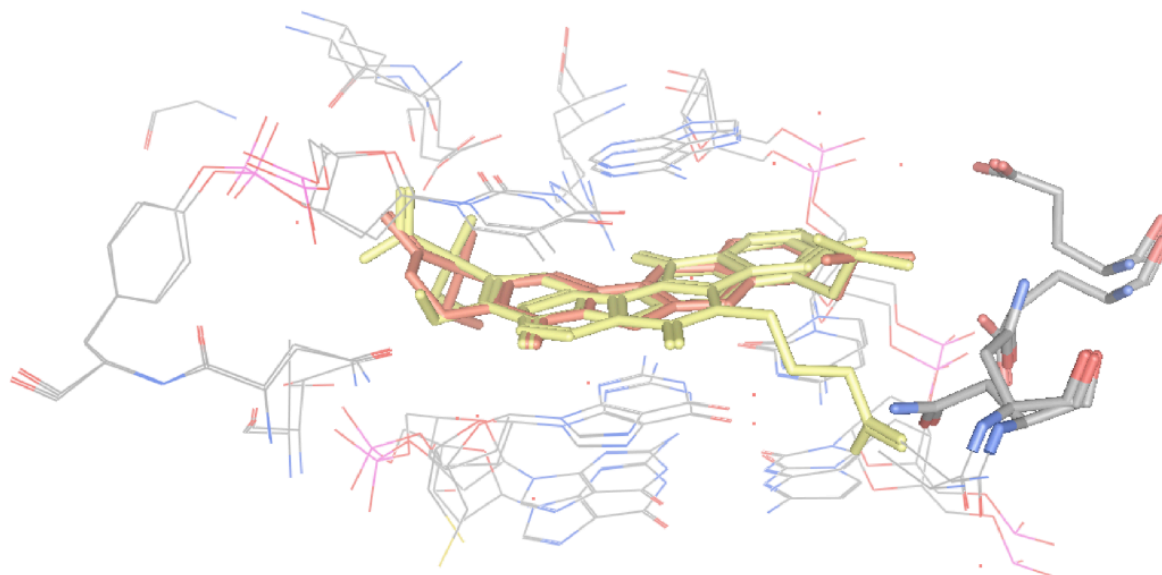


Figura 4.8

### 4.3.3. Docking de la wakayina

A continuación calculamos el docking de la wakayina en la topoisomerasa I utilizando Gold (Figura 4.9). Se observa que las principales interacciones implican el carbonilo del fragmento de iminoquinona, que interacciona con un residuo aminoacídico de la proteína, y el anillo de indol de la cadena lateral, que proporciona una interacción hidrofóbica con el bolsillo. La figura 4.10 muestra la superposición de wakayina, proveniente del docking anterior, con los datos del topotecan cristalizado. Finalmente, a pesar de haber decidido previamente utilizar Gold como opción preferente, estudiamos el docking de la wakayina por los tres métodos disponibles, encontrando una concordancia muy buena entre ellos (Figura 4.11).

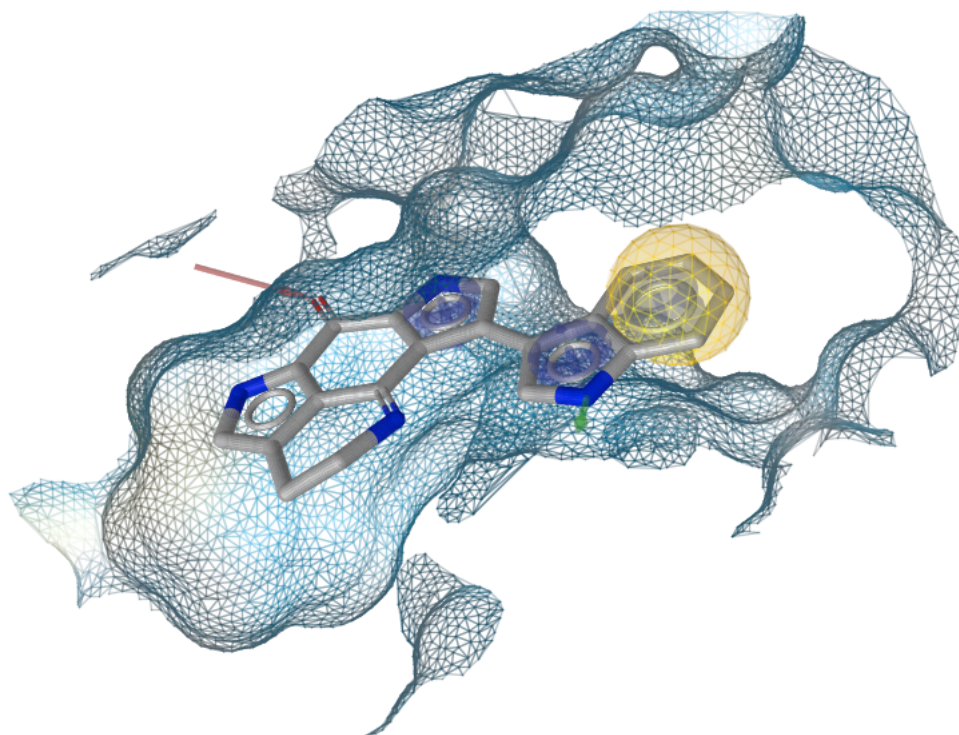


Figura 4.9. Docking de la wakayina (Gold)

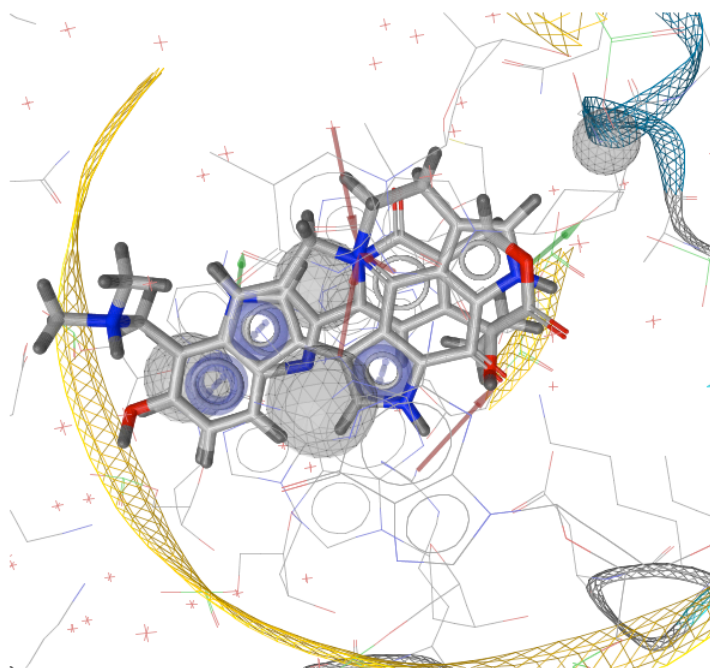


Figura 4.10. Superposición de la wakayina y el topotecan (Gold)

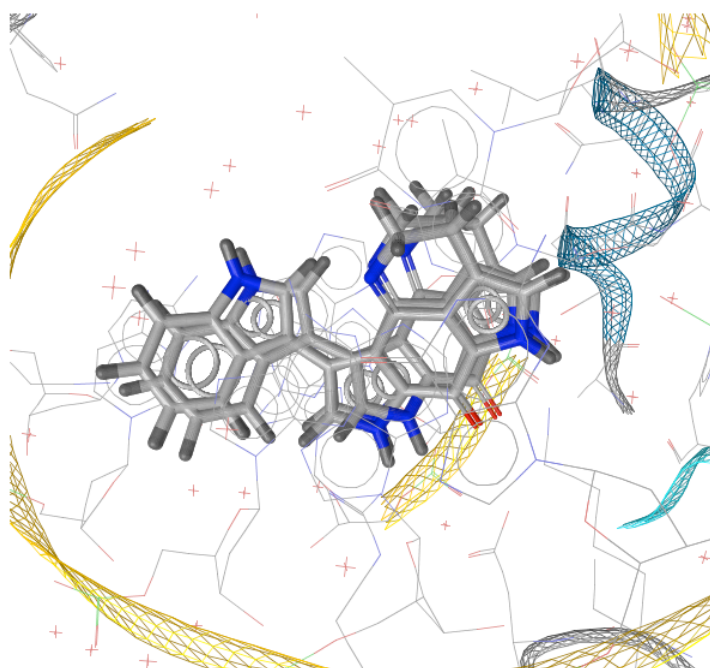


Figura 4.11. Docking de la wakayina por los métodos QM-polarized, Glide y Gold

El último paso del estudio fue el cálculo del farmacóforo de la wakayina, que ha sido posible a partir de los resultados del estudio de docking utilizando Ligand Scout, un programa desarrollado por el grupo de investigación de los profesores Langer y Wolhber. A partir de las estructuras cristalinas procedentes del PDB, utilizamos este método para determinar el farmacóforo de los cinco ligandos de referencia previamente mencionados y así validar nuestro método. Los resultados obtenidos se resumen en las figuras 4.12 a 4.16, y concuerdan bien con los datos bibliográficos.<sup>56</sup>

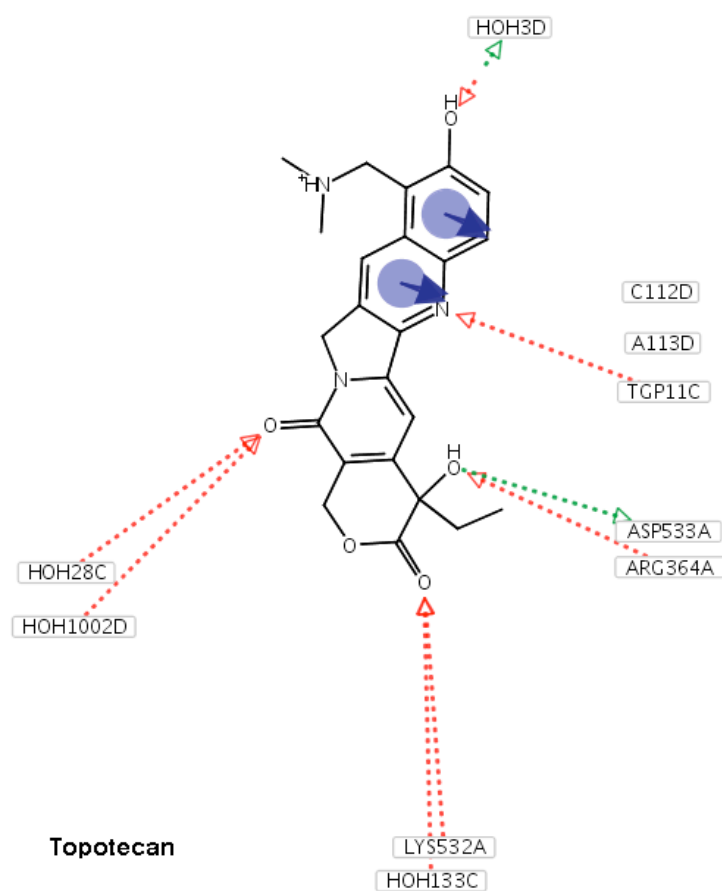


Figura 4.12. Farmacóforo propuesto para el topotecan

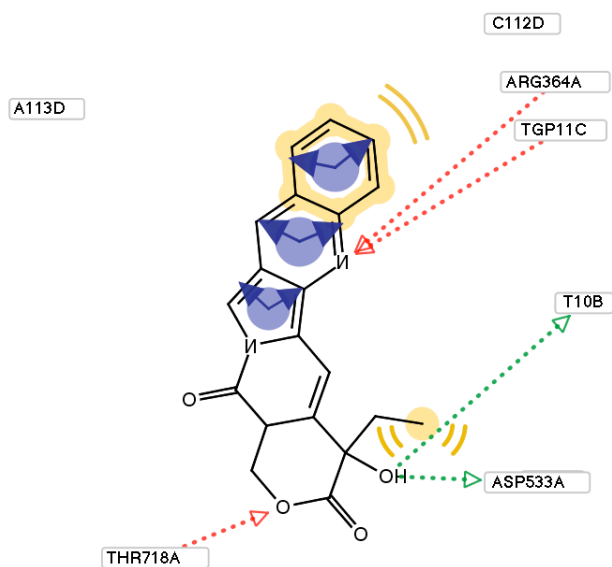


Figura 4.13. Farmacóforo propuesto para la camptotecina

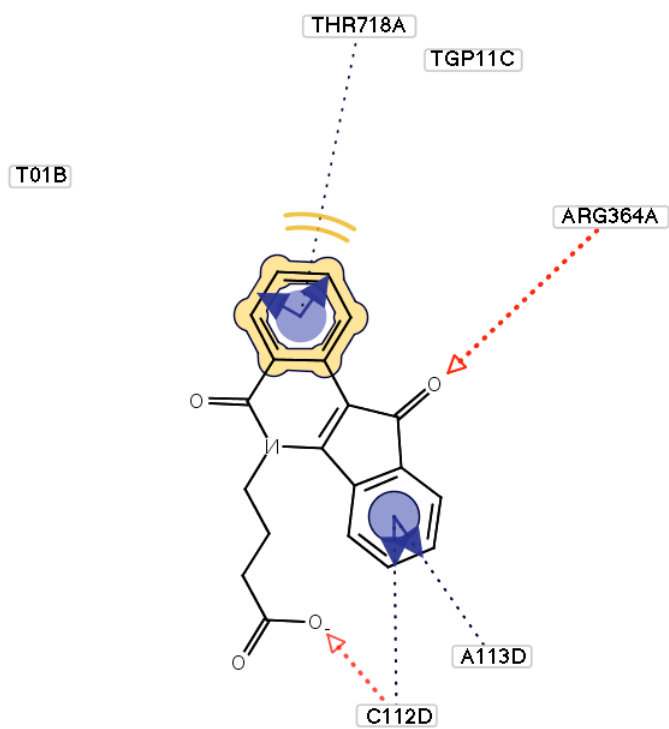


Figura 4.14. Farmacóforo propuesto para 1sc7

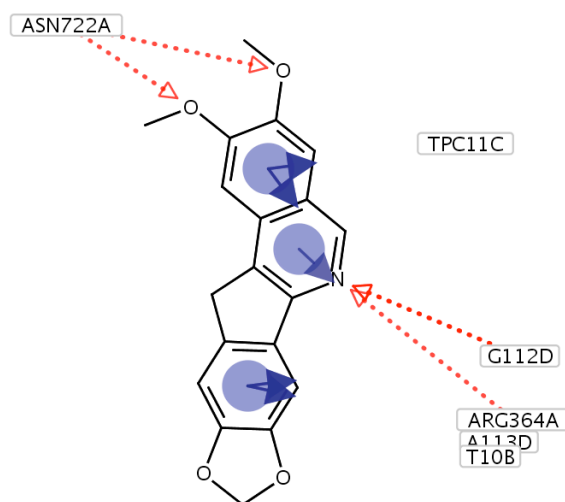


Figura 4.15. Farmacóforo propuesto para 1tl8

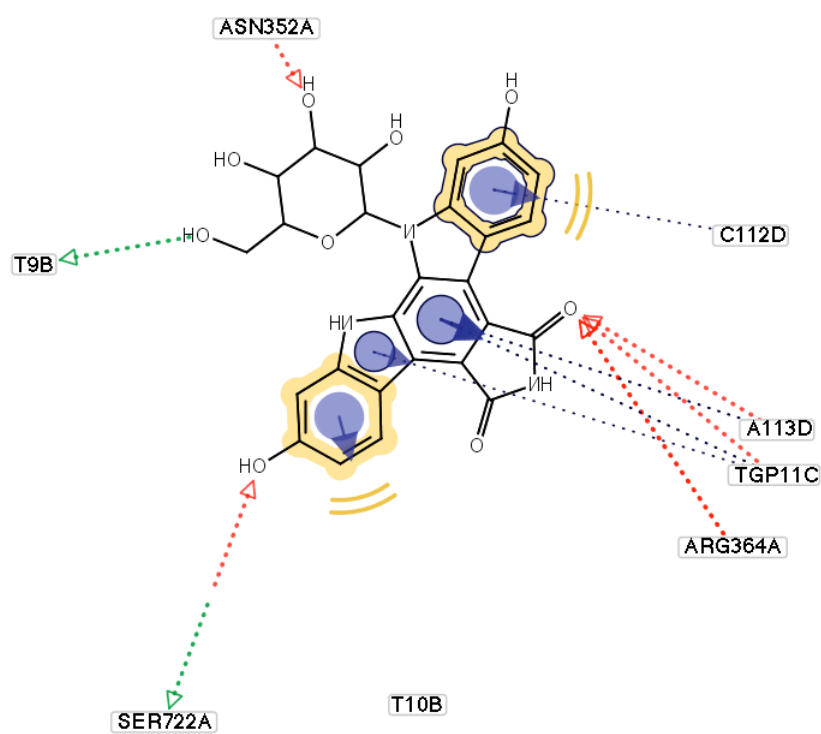


Figura 4.16. Farmacóforo propuesto para 1seu

Finalmente, utilizamos el mismo método para determinar el farmacóforo de la wakayina, que se representa en la figura 4.17. Puede observarse que se mantiene el enlace con la arginina 364, que se considera clave en la inhibición de la

topoisomerasa I, pero que algunas porciones estructurales de la molécula no parecen esenciales.

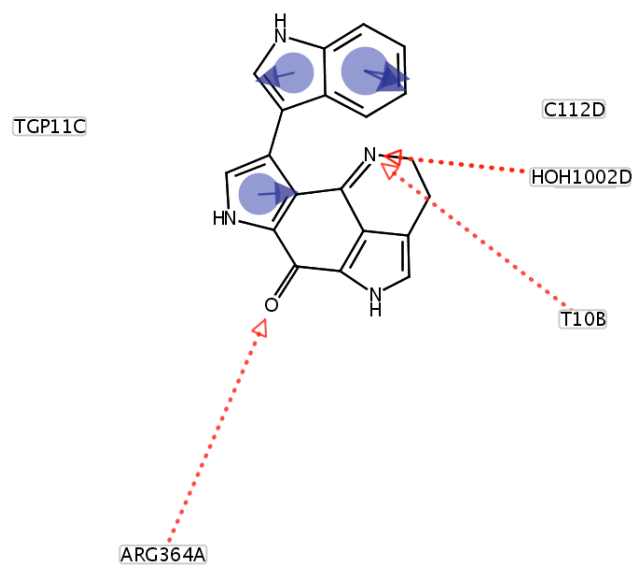


Figura 4.17. Farmacóforo propuesto para la wakayina

#### 4.3.4. Docking de análogos simplificados de wakayina

Puesto que la unión del producto natural a su diana parecía tener lugar sin la intervención de porciones significativas de la molécula, se consideró factible encontrar actividad en análogos simplificados. De hecho, existen algunos productos naturales de origen marino que presentan actividad antitumoral y pueden considerarse análogos ligeramente simplificados de la wakayina, como las tsitsikamaminas, que tienen un anillo de benceno en lugar de indol, las zizzyanonas A, que carecen del anillo de iminoquinona y en su lugar presentan una cadena de etilamina, y algunas de las makaluvaminas, que carecen del sistema de de bis-pirrol. Todos estos compuestos presentan citotoxicidad, y para algunos de ellos se ha demostrado actividad inhibidora de la topoisomerasa I (Figura 4.18).

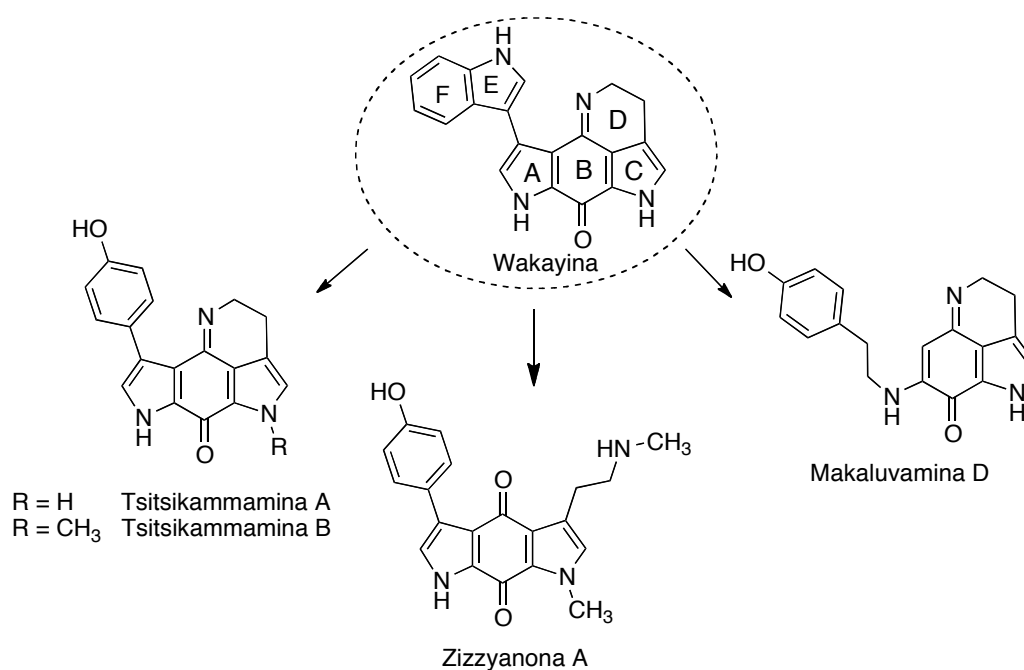


Figura 4.18

Teniendo en cuenta los resultados del estudio de docking y considerando también la accesibilidad sintética y la probable necesidad de utilizar grupos protectores, se diseñó una serie de compuestos en la que se fue simplificando progresivamente la estructura del compuesto de referencia (Figura 4.19). Se

procedió a su docking y a investigar la estructura de sus farmacóforos, con los resultados indicados en las figuras 4.20 y 4.21.

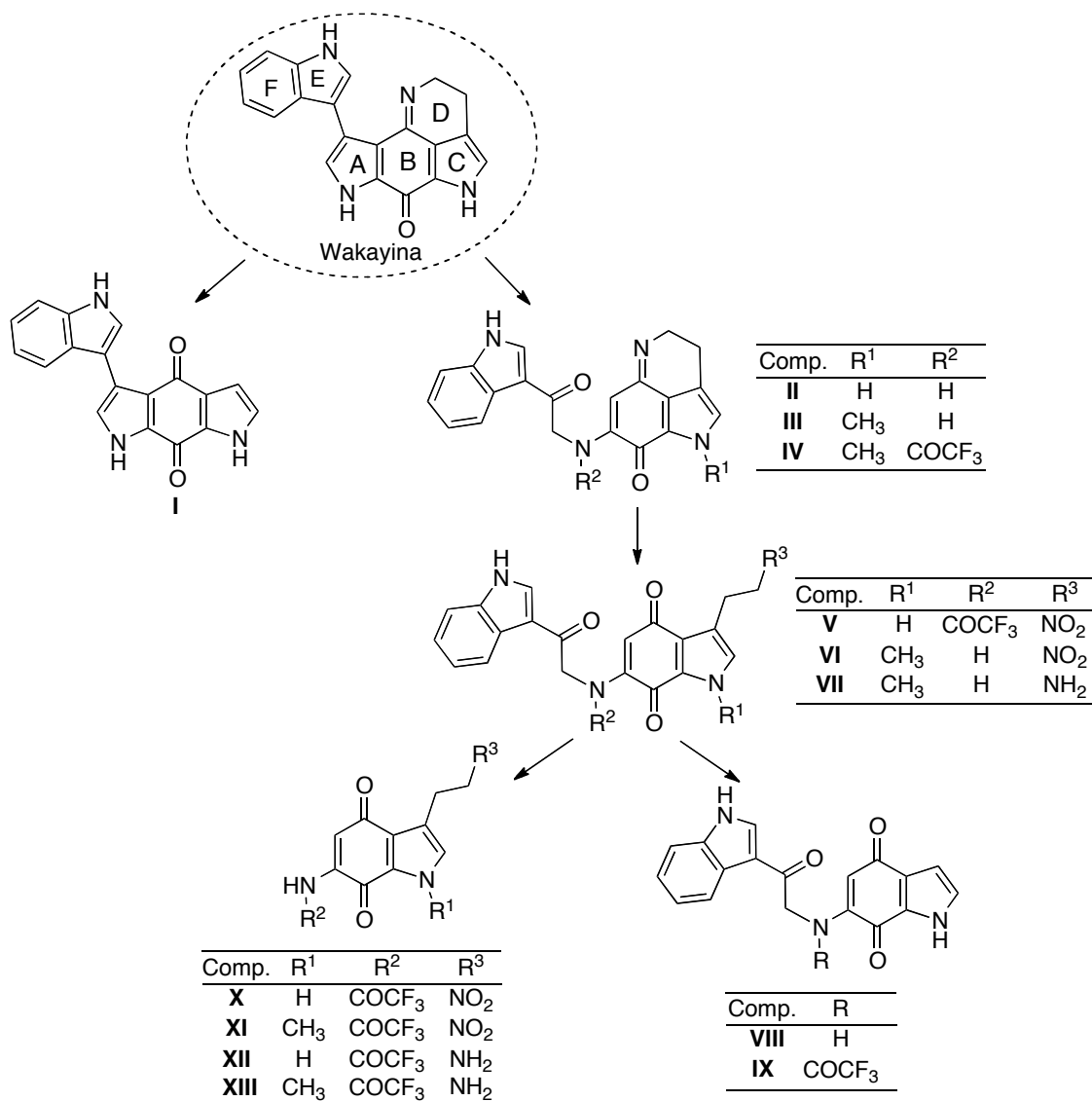


Figura 4.19

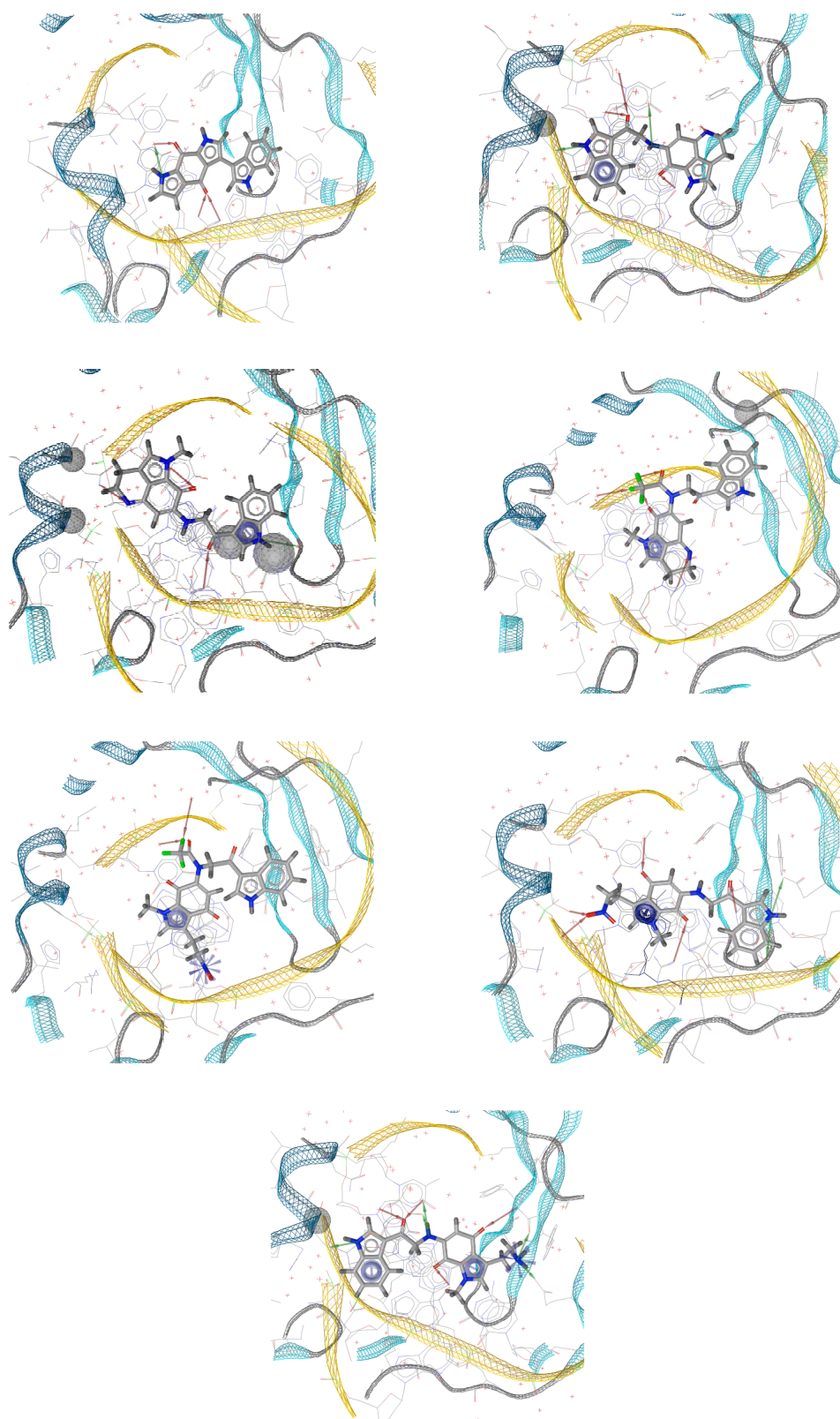


Figura 4.20. Docking de los compuestos I-VII

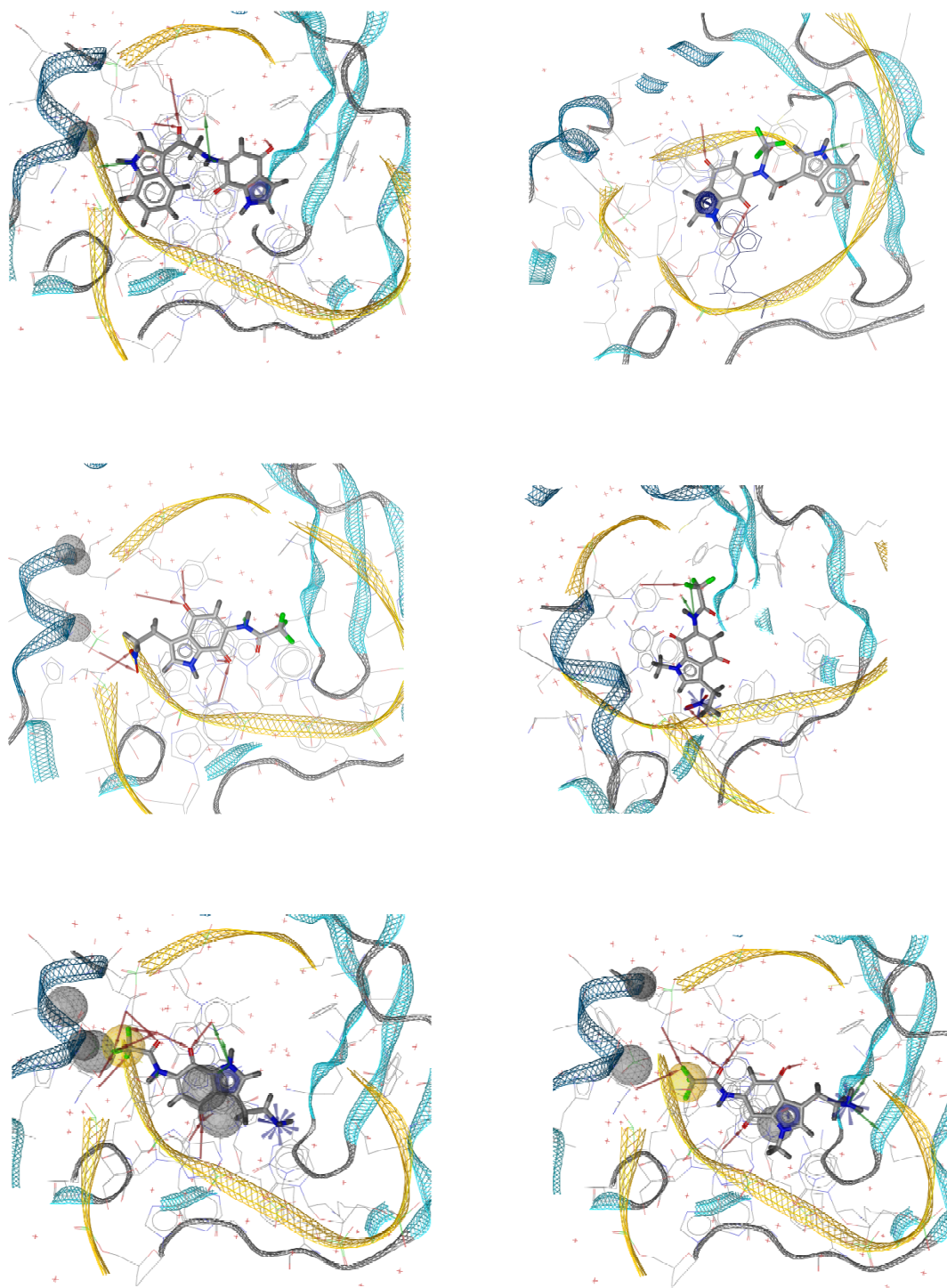


Figura 4.26. Docking de los compuestos VIII-XIII

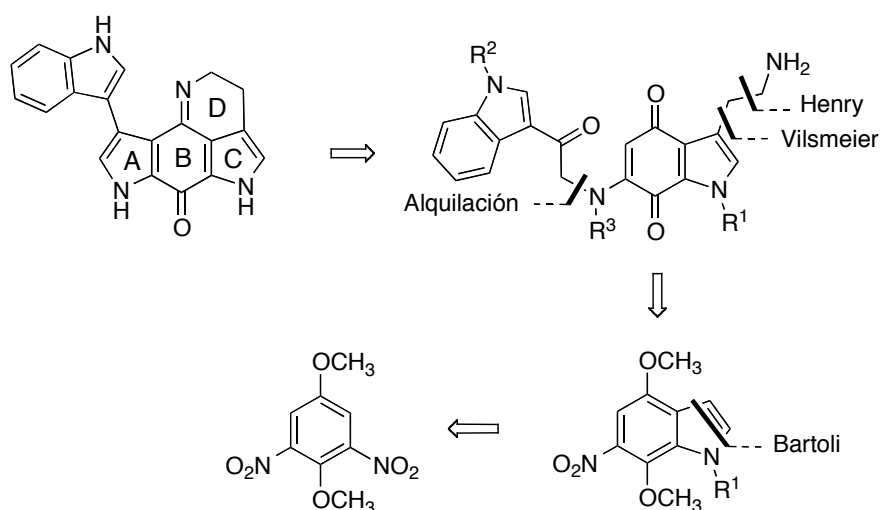
La comparación de los datos obtenidos para la wakayina y sus análogos simplificados lleva a las conclusiones que se resumen a continuación, que nos animaron a iniciar la preparación de dichos análogos:

1. Para la interacción con la topoisomerasa no es fundamental el anillo D del producto natural, que contiene la función de iminoquinona.
2. El nitrógeno del anillo de indol puede estar libre o llevar una cadena de hasta 2 átomos de carbono.
3. Es fundamental la presencia de un grupo carbonilo o algún otro átomo capaz de actuar como aceptor de hidrógeno.
4. El segundo anillo de indol puede ser sustituido por otro grupo aromático más sencillo.
5. La forma abierta del anillo de bis-pirrol puede imitar la estructura de su forma cerrada.

### 4.3. SÍNTESIS DE ANÁLOGOS SIMPLIFICADOS DE WAKAYINA

#### 4.3.1. Introducción

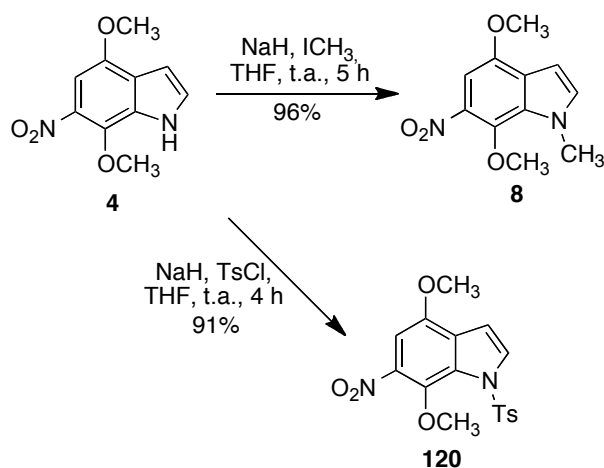
Para la preparación de los esqueletos propuestos en el apartado anterior se planeó la ruta retrosintética que se resume en el esquema 4.1. Se inicia con la construcción de un anillo de indol correspondiente a los anillos B y C mediante una reacción de Bartoli. La incorporación de la cadena que contiene los restantes átomos del anillo D se plantea por introducción de un grupo formilo mediante una secuencia de reacciones de Vilsmeier y Henry. La presencia de un grupo nitro en el derivado de indol inicial permite proponer la incorporación de una cadena lateral correspondiente al sustituyente indólico, que puede originar, finalmente, el anillo A por ciclación de B sobre un grupo carbonilo.



Esquema 4.1

#### 4.3.2. Obtención de materiales de partida

La obtención del derivado de 6-nitroindol **4** por medio de una reacción de Bartoli, así como su metilación para dar **8**, se ha descrito en el apartado 2.3. El compuesto **4** se transformó también en su N-tosil derivado (**120**) por tratamiento con cloruro de tosilo en presencia de hidruro sódico (esquema 4.2).

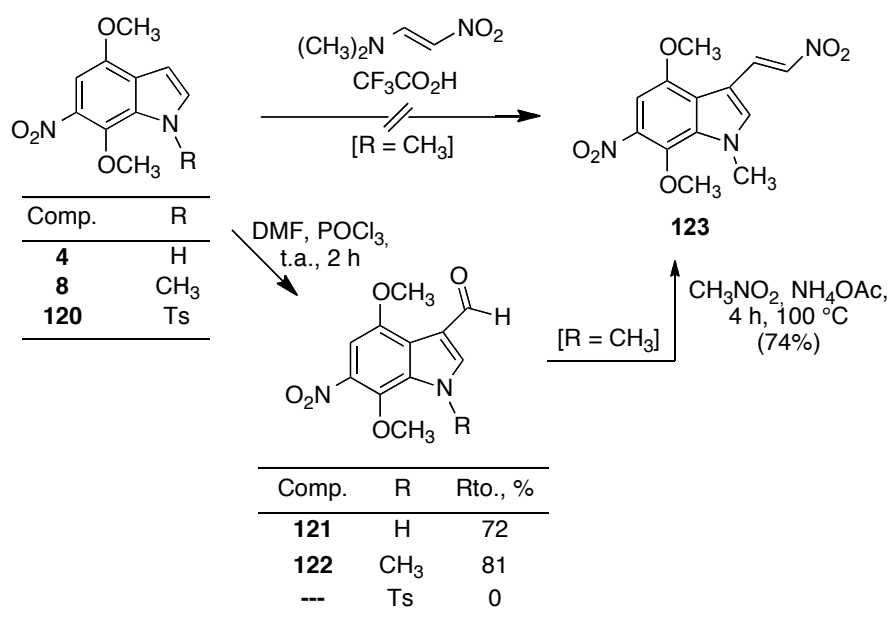


Esquema 4.2

#### 4.3.3. Síntesis de derivados del fragmento BC de la wakayina

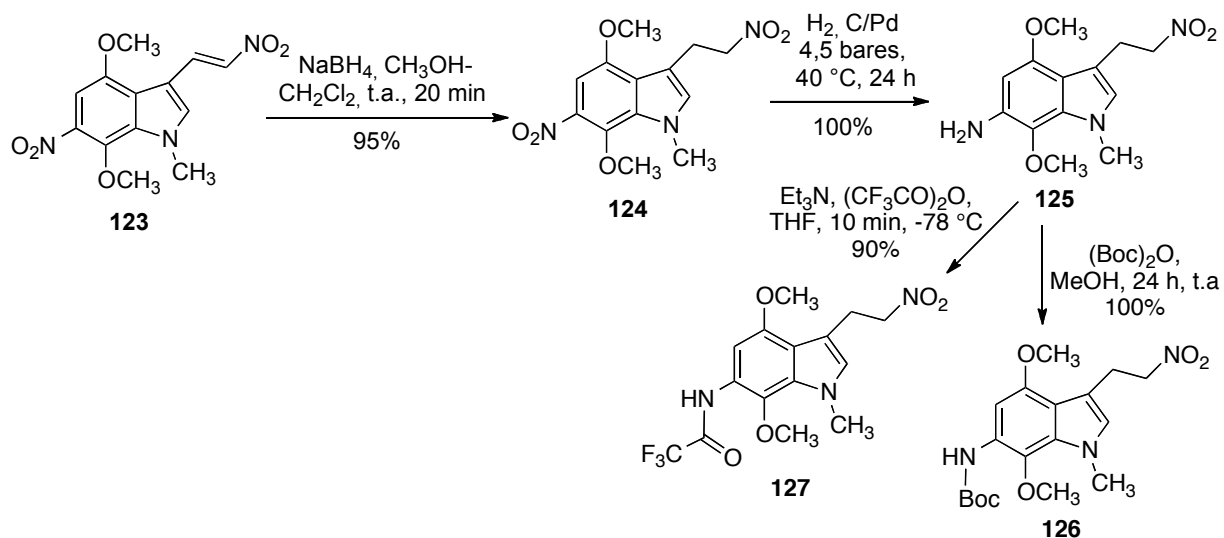
Para la introducción de la cadena de la posición 3, se ensayó, sin éxito, un método directo basado en el empleo de 1-dimetilamino-2-nitroetileno (DMANE) en ácido trifluoroacético.<sup>57</sup> El fracaso de este intento se puede atribuir a la presencia de un grupo nitro, fuertemente aceptor, en la posición 6 del indol, conjugada con la que se desea funcionalizar. Por ese motivo, decidimos recurrir a un protocolo alternativo basado en un reacción de Henry (nitroaldólica) a partir del 3-formilindol y nitrometano. Por tanto, investigamos la formilación de Vilsmeier en la posición 3 de los derivados de 6-nitroindol disponibles, los compuestos **4**, **8** y **120**. La reacción tuvo lugar en los dos primeros casos (R = H, CH<sub>3</sub>), pero no así en el tercero (R = Ts), a causa del efecto combinado de los dos grupos aceptores. A causa de la baja estabilidad del compuesto N-no sustituido **121**, decidimos realizar las reacciones posteriores a partir del N-metil derivado **122**, que resultó algo más manejable. El tratamiento de **121** con nitrometano, en presencia de acetato amónico dio lugar a la reacción de Henry esperada y condujo al compuesto **123** (esquema 4.3).

<sup>57</sup> Büchi, G.; Mak, C. P. *J. Org. Chem* **1977**, *42*, 1784.



Esquema 4.3

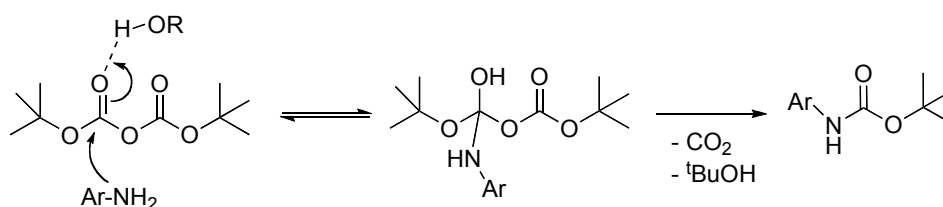
En etapas posteriores, se redujo el doble enlace de **123** por adición conjugada de borohidruro sódico, que condujo a **124**, y a continuación se procedió a la hidrogenación quimiosselectiva del grupo nitro aromático para dar **125**. Se realizaron algunos intentos de llevar a cabo las dos etapas de reducción simultáneamente, pero sin buenos resultados. El grupo amino del compuesto **125** se protegió en forma



Esquema 4.4

de carbamato (Boc) y de trifluoroacetamida, dando lugar a los compuestos **126** y **127** (esquema 4.4). La finalidad de las reacciones de protección era la de disminuir la densidad electrónica del anillo de indol para poder proceder a su transformación en quinona, ya que existen precedentes bibliográficos que demuestran que derivados de anilina portadores de varios sustituyentes donadores se descomponen en presencia de todo tipo de agentes oxidantes.<sup>58</sup>

El método seleccionado para la introducción del grupo Boc requiere un breve comentario, ya que los métodos clásicos, que implican el empleo de bases y disolventes apróticos, dieron malos resultados, que se atribuyeron a la baja estabilidad del indol en las condiciones ácidas necesarias para la extracción de los productos de reacción. Esto nos indujo a emplear un protocolo en el que la reacción se lleva a cabo en un disolvente prótico como el metanol sin añadir ninguna base<sup>59</sup> y sin necesidad de ningún tipo de purificación ni extracción en medio ácido o básico. En estas condiciones, la preparación de **126** tuvo lugar con un rendimiento del 100 %. Se ha propuesto que, en estas condiciones, la reacción de protección tiene lugar según el mecanismo representado en el esquema 4.5, en el cual el metanol activa el grupo carbonilo por formación de un enlace de hidrógeno, lo que facilita el ataque de la amina.



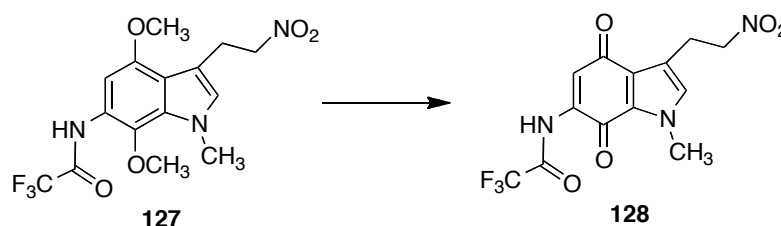
Esquema 4.5

#### 4.3.4. Síntesis de derivados del fragmento BCD de la wakayina

La transformación de **127** en la quinona **128** (esquema 4.6) se ensayó inicialmente en las condiciones estándar, empleando nitrato cérico amónico (CAN) como reactivo en acetonitrilo-agua (1:1), pero se observó únicamente la descomposición del material de partida. Esto nos indujo a emplear condiciones

<sup>58</sup> Pascual-Alfonso, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron Lett.* **2003**, *44*, 6003.

previamente utilizadas por nuestro grupo para la preparación de una quinona en un sistema de alta densidad electrónica,<sup>58</sup> utilizando trifluoruro de cobalto para la reacción de desmetilación oxidativa. Aunque el rendimiento obtenido fue bueno (80%), la reacción fue difícil de escalar y, además, presentaba dificultades de manejo a causa de la baja estabilidad del trifluoruro de cobalto. Se ensayó, infructuosamente, el empleo de otros métodos suaves de desquilación oxidativa, tales como la N-bromosuccinimida<sup>60</sup> y el reactivo de Koser (hidroxi tosiloxi iodobenceno).<sup>61</sup> Estos resultados nos indujeron a examinar de nuevo el empleo de nitrato cérico amónico bajo condiciones modificadas. El uso de catálisis por transferencia de fase fue inadecuado, pero un estudio de optimización de las condiciones tradicionales condujo finalmente a un protocolo reproducible. Los mejores resultados se obtuvieron utilizando como disolvente una mezcla de acetonitrilo/agua 2:1 y tiempos de reacción muy cortos (15 minutos) tras realizar la adición del CAN a 0 °C (Tabla 4.1).



Esquema 4.6

Tabla 4.1

Oxidante	Disolvente	Temp.	Tiempo	Rendimiento %
CoF <sub>3</sub>	Dioxano/H <sub>2</sub> O (10 eq)	t. a.	1 h	80
NBS	THF/H <sub>2</sub> O/H <sub>2</sub> SO <sub>4</sub>	t. a.	5 h	0
Reactivo de Koser	CH <sub>3</sub> CN	90 °C	1 h	
Reactivo de Koser	DCM	40 °C	1 h	
CAN	DCM/TBAB/H <sub>2</sub> O	t. a.	7 h	0
CAN	CH <sub>3</sub> CN/H <sub>2</sub> O (2:1)	t. a.	15 min	90-95

<sup>59</sup> Vilaivan, T. *Tetrahedron Lett.* **2006**, 47, 6739.

<sup>60</sup> Kim, D. W.; Choi, H. Y.; Lee, K.-J.; Chi, D. Y. *Org. Lett.* **2001**, 3, 445.

<sup>61</sup> Ortín, I.; González, J. F.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **2010**, 66, 646.

Existían precedentes bibliográficos de la formación de estructuras de quinonimina por reducción de compuestos portadores de subestructuras de quinona y nitroareno, que probablemente suponían la reducción de la quinona a hidroquinona y del grupo nitro a amina, explicándose la formación de la quinonimina final por regeneración posterior de la quinona debido a la acción del oxígeno del aire durante el proceso de aislamiento.<sup>62</sup> Debido a la existencia de estos antecedentes, intentamos la reducción del grupo nitro alifático de la cadena lateral del compuesto **129**, pero todas las condiciones ensayadas condujeron únicamente a productos de descomposición. Se decidió, por tanto, invertir el orden de los dos últimos pasos, llevando a cabo primero la reducción del grupo nitro y después la formación de la quinona. Sin embargo, la mayor parte de las condiciones bibliográficas ensayadas condujeron únicamente a la recuperación del material de partida, incluyendo la hidrogenación catalítica en presencia de Pd-C, empleando hidrógeno o formiato amónico, zinc en ácido acético, hidrazina,<sup>63</sup> indio en presencia de cloruro amónico,<sup>64</sup> y borohidruro sódico en presencia de tetracloruro de circonio.<sup>65</sup> Las únicas condiciones capaces de reducir el grupo nitro de la trifluoroacetamida **127** afectaron también al grupo protector, proporcionando la diamina **129**, y consistieron en la reacción con hidruro de litio y aluminio seguida de tratamiento con tartrato sódico potásico (sal de Rochelle)<sup>66</sup> para deshacer las emulsiones de sales de aluminio formadas durante el aislamiento.<sup>67</sup>

A pesar de que, según la experiencia previa de nuestro grupo, era dudosa la posibilidad de realizar una desmetilación oxidativa de un sistema de tan elevada densidad electrónica como el compuesto **129**, hicimos algunos intentos de preparar la correspondiente quinona, pero en todos los casos obtuvimos únicamente mezclas complejas de productos de descomposición (esquema 4.7).

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<sup>62</sup> De la Fuente, J. A.; Martín, M. J.; Blanco, M. M.; Pascual-Alfonso, E.; Avendaño, C.; Menéndez, J. C. *Bioorg. Med. Chem.* **2001**, *9*, 1807.

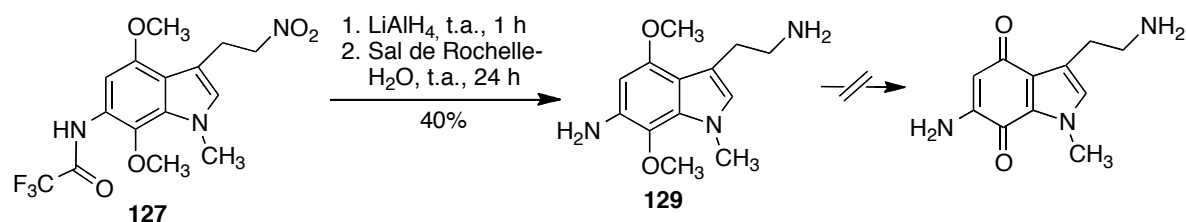
<sup>63</sup> Gowda, S.; Kempe Gowda, B. K.; Channe Gowda, D. *Synth. Commun.* **2003**, *33*, 231.

<sup>64</sup> Moody, Pitts, M. R. *Synlett* **1998**, 1028.

<sup>65</sup> Chare, K. P.; Ram, S. R.; Iyengar, D. S. *Synlett* **2000**, 683.

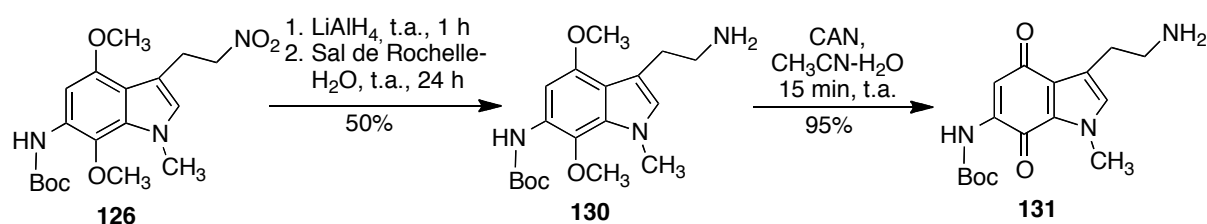
<sup>66</sup> Un ejemplo reciente de aplicación de estas condiciones: Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. *J. Am. Chem. Soc.* **2009**, *131*, 10796.

<sup>67</sup> Fallaron otros tratamientos habituales, como la adición de agua seguida de sulfato sódico, o bien de bicarbonato sódico.



Esquema 4.7

Estas observaciones nos indujeron a ensayar la misma secuencia de reacciones a partir del Boc derivado **126**. La reducción de su grupo nitro por acción del hidruro de litio y aluminio condujo al compuesto **130**, que en este caso se transformó fácilmente en la correspondiente quinona (compuesto **131**) por tratamiento con nitrato cérico amónico en las condiciones previamente establecidas durante la preparación de **128** (esquema 4.8).

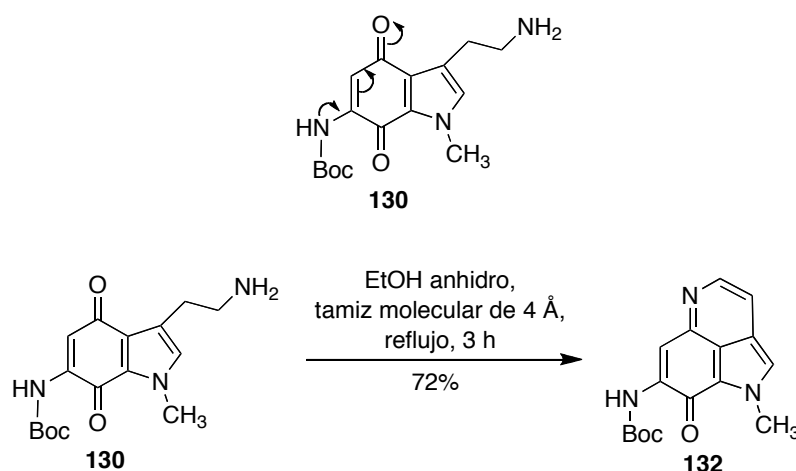


Esquema 4.8

Es interesante destacar que normalmente no es posible aislar aminoquinonas relacionadas con **131**, ya que ciclan espontáneamente para dar las correspondientes quinoniminas.<sup>68</sup> La razón de la especial estabilidad del compuesto **131** debe buscarse en el efecto donador electrónico del nitrógeno del grupo carbamato, que disminuye la reactividad del carbonilo de quinona que debería participar en la formación de la imina. Por este motivo, para lograr la formación de la imina fue necesario calentar el compuesto **131** en presencia de tamiz molecular, y en estas condiciones se observó la formación de la imina y, además, la aromatización del anillo de dihidropiridina inicialmente generado, dando lugar al compuesto **132**

<sup>68</sup> Algunas revisiones de la síntesis de pirroloiminoquinonas: (a) Antunes, E. M.; Copp, B. R.; Davies-Coleman, M. T.; Samaai, T. *Nat. Prod. Rep.* **2005**, *22*, 62. (b) Delfourne, E. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 910.

(esquema 4.9). Esta reacción de deshidrogenación se debe indudablemente a la acción del oxígeno del aire, pero no fue posible evitarla llevando a cabo la reacción en atmósfera inerte. El compuesto **132** tiene interés por tratarse del Boc-derivado del producto natural makaluvamina B.

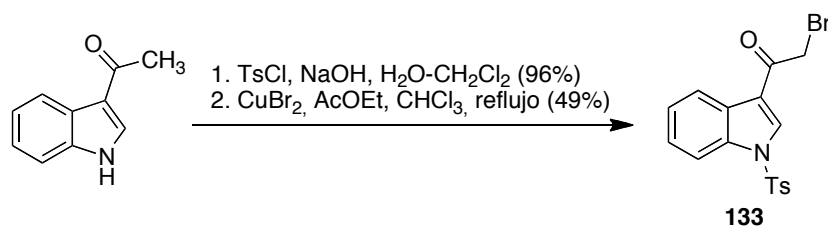


Esquema 4.9

#### 4.3.5. Incorporación de los anillos F y G

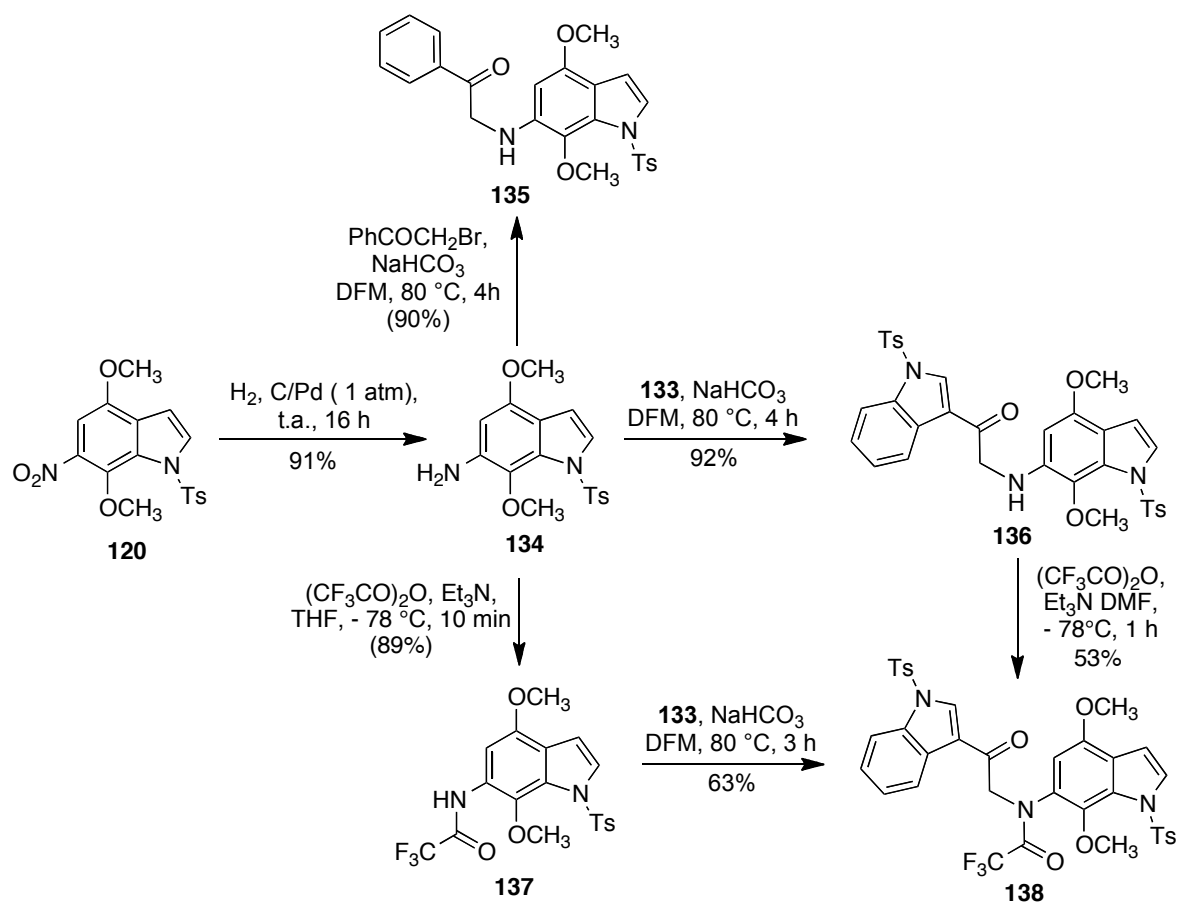
Se preparó 3-bromoacetil-1-tosilindol (**133**) por bromación del 3-acetil-1-tosilindol con bromuro de cobre(II) en cloroformo-acetato de etilo, empleando una modificación de un método bibliográfico (esquema 4.10).<sup>69</sup> El rendimiento aislado de **133** fue moderado (49%) porque fue necesario interrumpir la reacción a una conversión del 70% para evitar la formación de cantidades sustanciales del derivado de dibromación, que es muy difícil de separar cromatográficamente del producto deseado. Se ensayaron también las condiciones de reacción tradicionales para la halogenación en  $\alpha$  de cetonas, basadas en el empleo de bromo en ácido acético, pero proporcionaron una mezcla compleja.

<sup>69</sup> Jiang, B.; Gu, X-H. *Bioorg. Med. Chem.* **2000**, *8*, 363.



Esquema 4.10

Para estudiar la preparación de compuestos portadores de los anillos BC y FG de la welwistatina, estudiamos la reacción de alquilación de la amina **134**, preparada por hidrogenación catalítica de **120**, con el haluro **133**. Ensayamos inicialmente el calentamiento de cantidades equimoleculares de los los materiales de partida a 85 °C, en ausencia de disolvente, pero en estas condiciones no conseguimos llevar a término la reacción. El empleo de 2-3 equivalentes de la amina **134** permitía que la reacción concluyera, pero esta reacción no era completamente reproducible y, además, la separación cromatográfica del producto deseado y el exceso de **134** era difícil. Finalmente, utilizando como modelo la reacción con bromuro de fenacilo, encontramos las condiciones idóneas, consistentes en el tratamiento de cantidades equimoleculares de la amina y el haluro en metanol que contiene bicarbonato sódico en suspensión para atrapar el bromuro de hidrógeno liberado. Esta reacción proporcionó un 90% de **135**, y las mismas condiciones resultaron adecuadas para la obtención del compuesto **136**, con un rendimiento del 92%, a partir de **133** y **134**. Con vistas a facilitar su posterior desmetilación oxidativa, se llevó a cabo la trifluoroacetilación de **136** con anhídrido trifluoroacético en presencia de bicarbonato sódico, resultando el compuesto **138**. Debido al rendimiento moderado el último paso, se investigó un método alternativo en el que los pasos de alquilación y acilación se llevaban a cabo en el orden contrario. Así, se preparó la trifluoroacetamida **137** por tratamiento de **134** con anhídrido trifluoroacético, y se llevó a cabo a continuación su alquilación con el haluro **133**. El rendimiento global obtenido en este caso fue ligeramente superior y, sobre todo, la ruta alternativa conduce al compuesto **138** con buena pureza y sin necesidad de purificación cromatográfica (esquema 4.11).

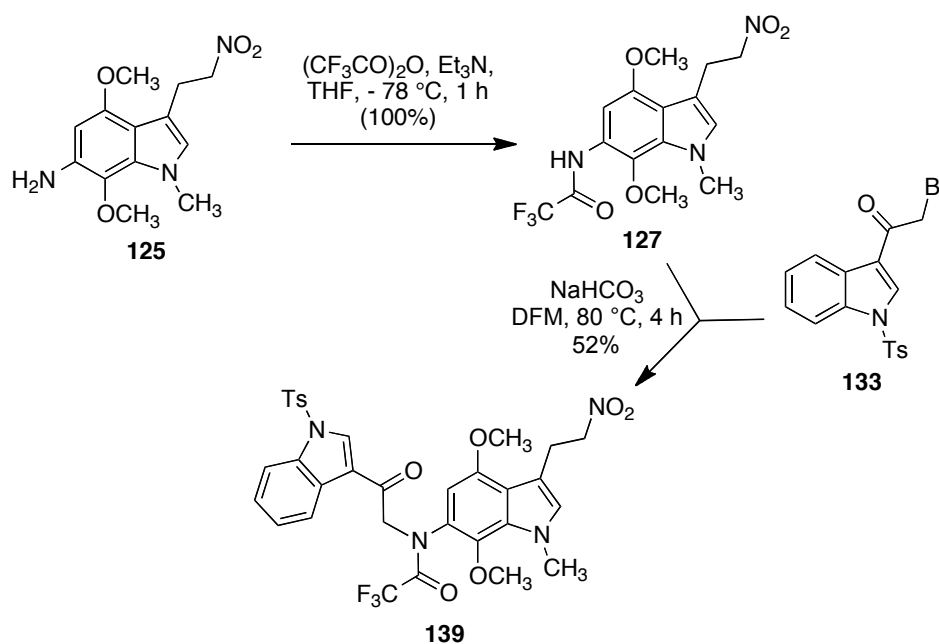


Esquema 4.11

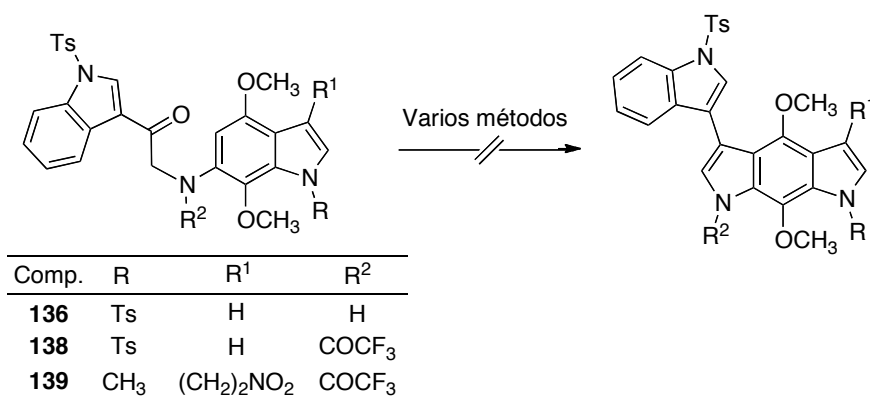
Los resultados anteriores se extendieron a la preparación de compuestos portadores de la cadena lateral que corresponde al anillo D. Así, el tratamiento de la amina **127** con el haluro **133**, en las condiciones previamente optimizadas, condujo al compuesto **139**, que fue transformado posteriormente en su derivado de N-trifluoroacetilación **140** (esquema 4.12).

Se realizaron varios intentos de crear el anillo C por ciclación de los compuestos **136**, **138** y **139** en presencia de varios ácidos de Lewis, incluyendo trifluoruro de boro y tricloruro de aluminio,<sup>70</sup> pero todos resultaron infructuosos (esquema 4.13).

<sup>70</sup> Galons, H.; Girardeau, J.-F.; Farnoux, C.C.; Miocque, M. *J. Heterocycl. Chem.* **1981**, *18*, 561.



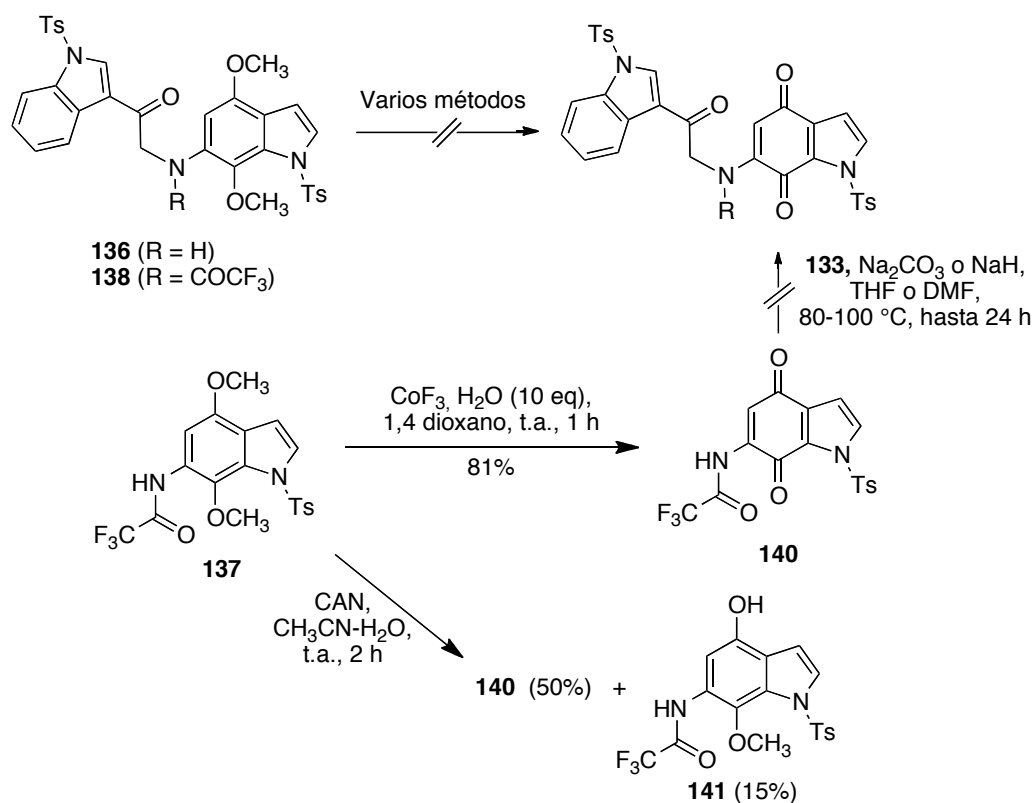
Esquema 4.12



Esquema 4.13

Sobre la base de datos bibliográficos, se consideró que una quinona podría ser un sustrato más adecuado para la ciclación deseada. De hecho, Cava ha descrito que los derivados de 2-(2'-aril-2'-oxoetilamino)naftoquinona no son aislables, por ciclarse espontáneamente generando un anillo de pirrol similar al anillo C de la wakayina a través de una adición de Michael intramolecular del sistema de enamina contenido en la estructura de aminoquinona sobre el grupo carbonilo de la cadena

lateral,<sup>71</sup> y posteriormente se demostró un efecto parecido en derivados de indol-4,7-quinona relacionados con nuestros sustratos.<sup>72</sup> En un intento de aprovechar esta reactividad, investigamos la transformación de los compuestos **136** y **138** en quinonas, aprovechando la experiencia previamente adquirida durante nuestros estudios preliminares resumidos en la tabla 4.1. Sin embargo, en esta ocasión no fue posible lograr la transformación deseada. Por otra parte, fue imposible lograr la N-alquilación de la quinona **140**, preparada en esta ocasión por tratamiento de **137** con trifluoruro de cobalto debido a que la reacción con CAN conduce a una mezcla del compuesto deseado y el derivado de desmetilación parcial **141** (esquema 4.14).

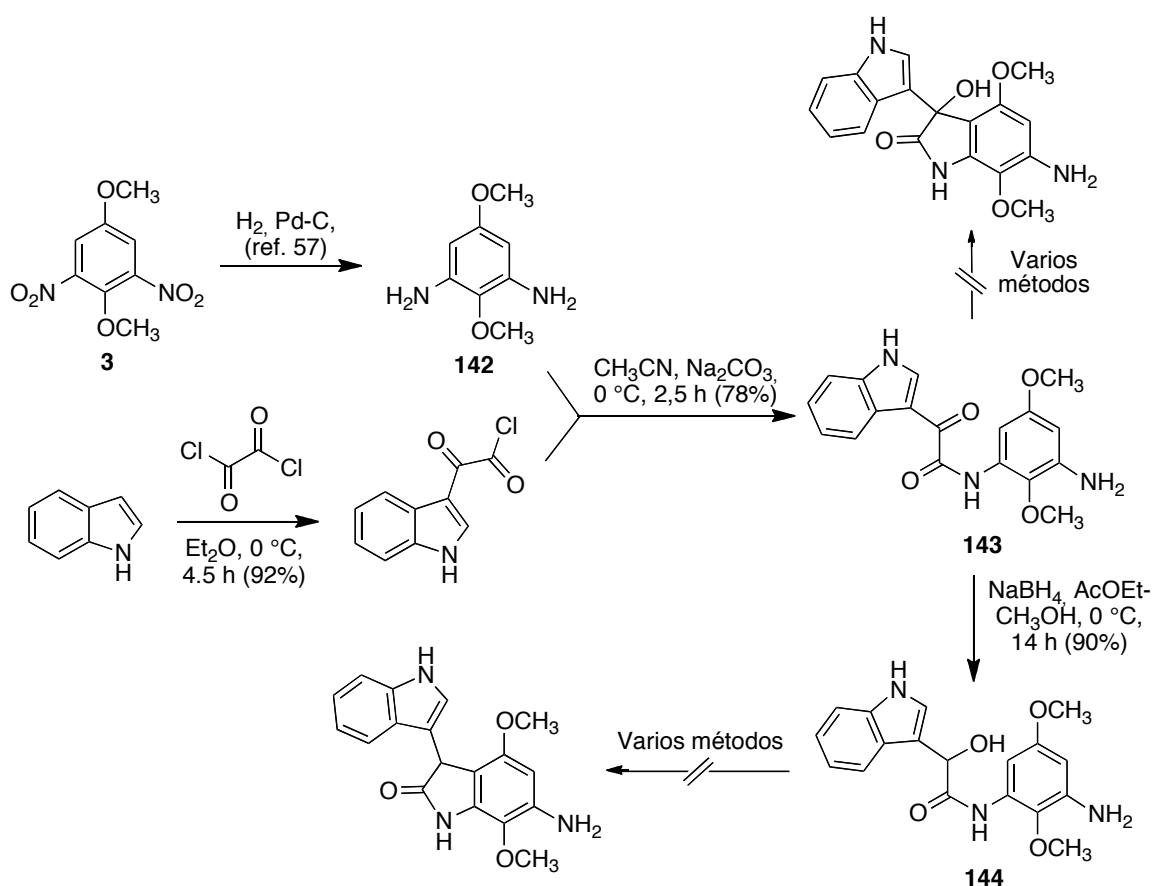


Esquema 4.14

<sup>71</sup> Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. *Tetrahedron Lett.* **1998**, 39, 7677.

<sup>72</sup> Barret, R.; Roue, N. *Tetrahedron Lett.* **1999**, 40, 3889.

En paralelo con los estudios anteriores, se estudiaron otros precursores potenciales del anillo C. Se obtuvo cloruro de 3-indoliloxalilo por tratamiento de indol con cloruro de oxalilo,<sup>73</sup> y su reacción con la 2,5-dimetoxi-1,3-fenilenodiamina **142**<sup>74</sup> proporcionó el compuesto **143**, junto con pequeñas cantidades del producto de doble acilación. Sin embargo, fracasaron los intentos de ciclación de este compuesto en condiciones encontradas en la bibliografía para sistemas relacionados, incluyendo el tratamiento con trifluoruro de boro en diclorometano o tolueno,<sup>70</sup> cloruro de zinc<sup>75</sup> y triflato de disprosio en metanol.<sup>76</sup> También fallaron todos los intentos de ciclar en medio ácido el alcohol **144**, procedente de la reducción de **143** con borohidruro sódico (esquema 4.15).



Esquema 4.15

<sup>73</sup> Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.

<sup>74</sup> Burger, A.; Fitchett, G. T. *J. Am. Chem. Soc.* **1953**, *75*, 1359.

<sup>75</sup> Brown, F.; Mann, F. G. *J. Chem. Soc.* **1948**, 847.

<sup>76</sup> Zhang, W; Wang, P. G. *J. Org. Chem.* **2000**, *65*, 4732.



## **5. Experimental section**



#### 4.1 General experimental information

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received, or purified and dried by standard procedures when needed. The expression “petroleum ether” refers to the fraction boiling at 40–60 °C.

Grignard reagents were used as commercially available solutions in THF,<sup>77</sup> except the styryl and naphthyl Grignard reagents that were prepared from the corresponding bromide and magnesium, following a standard procedure. 1-Propenylmagnesium bromide was purchased in the form of an *E*, *Z* isomer mixture, which results in the obtention of two isomeric vinylation products, in a variable *E/Z* ratio, as indicated in each case.<sup>78</sup>

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<sup>77</sup> Vinyl Grignard reagents were purchased as 0.5 M solutions in THF, except vinylmagnesium bromide (1 M in THF). Aryl Grignard reagents were purchased as 1 M solutions in THF, except 4-chlorophenylmagnesium chloride, which was obtained as a solution in diethyl ether. When a THF solution was needed, the ether was evaporated under a stream of argon and the suitable amount of THF was then added.

<sup>78</sup> This ratio depends on the manufacturing batch of the commercial Grignard reagent used.

Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40-63  $\mu\text{m}$ ).

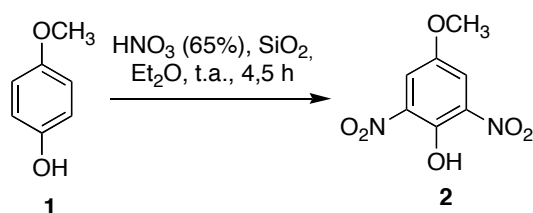
Reactions under microwave irradiation were carried out in a CEM Discover focused microwave reactor.

Melting points were measured on a Reichert 723 hot stage microscope, and are uncorrected.

Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined as thin films on NaCl disks or as KBr pellets.

NMR spectra were obtained on Bruker Avance 250 and 500 spectrometers operating at 250 or 500 MHz for  $^1\text{H}$  and 63 or 125 MHz for  $^{13}\text{C}$ , respectively (CAI de Resonancia Magnética Nuclear, Universidad Complutense).

Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

**4-METHOXY-2,6-DINITROPHENOL (2)**

To a solution of 4-methoxyphenol **1** (15 g, 120 mmol) in ethyl ether (240 mL) cooled at 0 °C and with stirring, was added 65% nitric acid (15 mL). The reaction was stirred at rt for 30 min and, then, silica gel (10 g) was added and stirred for one more hour. The mixture was again cooled at 0 °C and nitric acid was added (15 mL) into 2 equal portions, leaving one hour elapse between additions and bringing to room temperature after each addition. Stirring was continued for 1.5 h.

The silica gel was filtered out and extracted with ethyl ether (2x100 mL) and the combined organic layers were washed with water (75 mL) to remove the excess of nitric acid. Since compound **2** is soluble in water, the aqueous layer was extracted with ether (3x75 mL) and the organic extracts were combined, dried over anhydrous sodium sulfate and the volume of solvent was reduced *in vacuo* until to 100 mL. The ethereal solution was cooled in an ice bath and the yellow precipitate was collected by filtration and washed twice with ethyl ether previously cooled, yielding 16 g (62%) of the desired product **2**.

The residue was purified by flash chromatography on silica gel eluting with petroleum ether / ethyl acetate (2:1), affording an additional 15% of compound **2**.

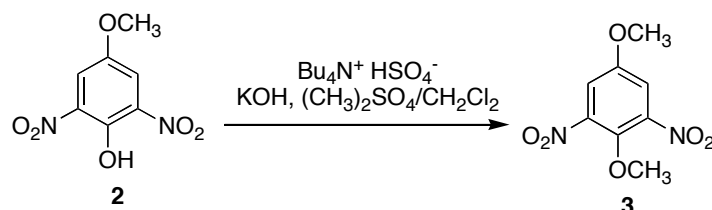
Melting point: 86-90 °C

Elemental analysis calc. (%) for C<sub>7</sub>H<sub>6</sub>N<sub>2</sub>O<sub>6</sub>: C 39.25, H 2.80, N 13.08; found C 39.25, H 2.95, N 12.99.

IR (NaCl)  $\nu$ : 3318 (OH), 1532, 1357 (NO<sub>2</sub>), 1238 (OCH<sub>3</sub>) cm<sup>-1</sup>.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  = 11.03 (s, 1H, OH), 7.86 (s, 2H, H<sub>3</sub> and H<sub>5</sub>), 3.90 (s, 3H, OCH<sub>3</sub>) ppm.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 63 MHz):  $\delta$  = 150.7 (C<sub>4</sub>); 144.1 (C<sub>1</sub>); 137.8 (C<sub>2</sub> and C<sub>6</sub>); 116.9 (C<sub>3</sub> and C<sub>5</sub>); 56.6 (OCH<sub>3</sub>) ppm.

**2,5-DIMETHOXY-1,3-DINITROBENZENE (3)**

To a solution of 4-methoxy-1,3-dinitrophenol **2** (4.28 g, 20 mmol) in dichloromethane (50 mL) at 0 °C was added tetrabutylammonium hydrogen sulfate (2 g, 5.9 mmol), potassium hydroxide (1.12 g, 20 mmol) and, after 10 min, dimethyl sulfate (2.52 g, 20 mmol). The reaction was kept at 0 °C for 1 h, stirred at room temperature overnight and, then, quenched with water (30 mL). The organic layer was washed with water (30 mL), dried over anhydrous sodium sulfate and the solvent was removed under vacuum. The yellow solid obtained was recrystallized from ethanol, yielding 3.4 g (75%) of compound **3**.

Melting point 98-100 °C.

Elemental analysis calc. (%) for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>6</sub>: C 42.10, H 3.50, N 12.28; found C 42.17, H 3.56, N 12.00.

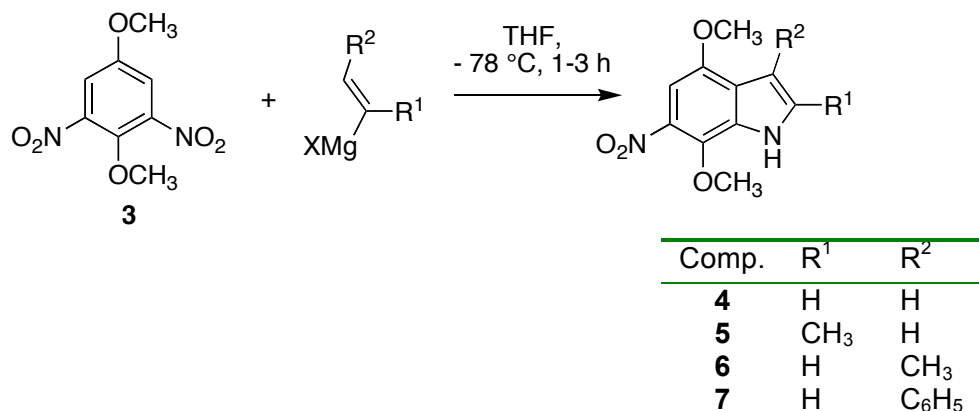
IR (NaCl)  $\nu$ : 1546, 1352 (NO<sub>2</sub>), 1230 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 7.59 (s, 2H, H<sub>3</sub> and H<sub>5</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>) ppm.

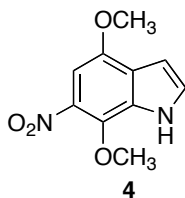
<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz) =  $\delta$  = 154.8 (C<sub>2</sub> and C<sub>6</sub>), 145.5 (C<sub>4</sub>), 141.3 (C<sub>1</sub>), 114.7 (C<sub>3</sub> and C<sub>5</sub>), 64.7 (OCH<sub>3</sub>), 56.6 (OCH<sub>3</sub>) ppm.

## PREPARATION OF 4,7-DIMETHOXY-6-NITROINDOLE DERIVATES 4-7

### General procedure:



The suitable vinylmagnesium reagent (30 mmol, as a commercially available solution in THF) was added dropwise to a cooled (-78 °C) solution of 2,5-dimethoxy-1,3-dinitrobenzene **3** (10 mmol) in dry THF (150 mL), under an argon atmosphere. The reaction mixture was stirred at the same temperature for 1-3 h and was, then, poured onto a saturated NH<sub>4</sub>Cl aqueous solution (75 mL), which was extracted with AcOEt (3 x 50 mL). The combined organic extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with a 5:1 petroleum ether-ethyl acetate mixture.

**4,7-DIMETHOXY-6-NITROINDOLE (4)****Reaction data:**

2,5-Dimethoxy-1,3-dinitrobenzene: 3 g (13.2 mmol).

Vinylmagnesium bromide: 50 mL (39.6 mmol).

Reaction time: 1 h

Yield: 1.13 g, 51% (yellow solid).

**Data for compound 4:**

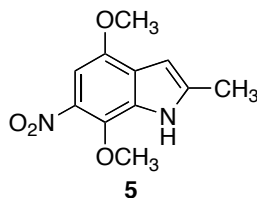
Melting point: 138-140 °C

Elemental analysis calc. (%) for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C 54.05, H 4.50, N 12.61; found: C 54.46, H 4.73, N 12.32.

IR (NaCl)  $\nu$ : 1519 and 1315 (NO<sub>2</sub>), 1284 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 8.81 (s, 1H, NH), 7.39 (dd, 1H,  $J$  = 2.9 and 2.7 Hz, H<sub>2</sub>), 7.17 (s, 1H, H<sub>5</sub>), 6.74 (dd, 1H,  $J$  = 2.9 and 2.3 Hz, H<sub>3</sub>), 4.08 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 148.9 (C<sub>4</sub>), 137.8 (C<sub>7</sub>), 136.1 (C<sub>6</sub>), 130.5 (C<sub>7a</sub>), 128.1 (C<sub>2</sub>), 125.2 (C<sub>3a</sub>), 102.2 (C<sub>3</sub>), 96.5 (C<sub>5</sub>), 62.8 (OCH<sub>3</sub>), 56.3 (OCH<sub>3</sub>) ppm.

**2-METHYL-4,7-DIMETHOXY-6-NITROINDOLE (5)****Reaction data:**

2,5-Dimethoxy-1,3-dinitrobenzene: 2.5 g (10.96 mmol).

Isopropenylmagnesium bromide: 51.12 mL (32.9 mmol).

Reaction time: 2 h

Yield: 1.06 g, 45 % (yellow solid).

**Data for compound 5:**

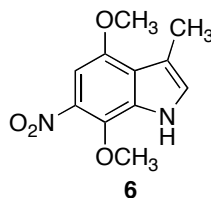
Melting point: 128-130 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C 55.96, H 5.08, N 11.86; found: C 56.15, H 5.24, N 11.52.

IR (NaCl): 3394 (NH), 1519 and 1315 (NO<sub>2</sub>), 1284 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>): δ = 8.92 (s, 1H, NH), 7.16 (s, 1H, H<sub>5</sub>), 6.38 (dd, 1H, J = 2.3 and 0.7 Hz, H<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 2.50 (d, 3H, J = 0.7 Hz, C<sub>2</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): δ = 147.5 (C<sub>4</sub>), 139.7 (C<sub>7</sub>), 136.9 (C<sub>2</sub>), 134.4 (C<sub>6</sub>), 129.7 (C<sub>7a</sub>), 125.9 (C<sub>3a</sub>), 99.7 (C<sub>3</sub>), 96.2 (C<sub>5</sub>), 62.2 (OCH<sub>3</sub>), 55.7 (OCH<sub>3</sub>), 13.8 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**3-METHYL-4,7-DIMETHOXY-6-NITROINDOLE (6)****Reaction data:**

2,5-Dimethoxy-1,3-dinitrobenzene: 2.4 g (10.57 mmol).

1-propenylmagnesium bromide: 48.5 mL (31.7 mmol).

Reaction time: 2 h

Yield: 1.3 g, 52 % (yellow solid).

**Data for compound 6:**

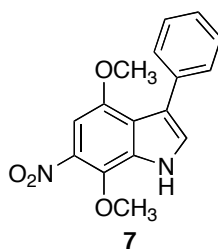
Melting point: 147-149 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C 55.96, H 5.08, N 11.86; found: C 55.85, H 5.05, N 11.67.

IR (NaCl)  $\nu$ : 3340 (NH), 1515 and 1312 (NO<sub>2</sub>), 1228 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 8.57 (s, 1H, NH), 7.11 (d, 1H,  $J$  = 1.1 Hz, H<sub>2</sub>), 7.10 (s, 1H, H<sub>5</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 2.46 (d, 3H,  $J$  = 1.1 Hz, C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.2 (C<sub>4</sub>), 137.2 (C<sub>7</sub>), 135.2 (C<sub>6</sub>), 130.7 (C<sub>7a</sub>), 125.6 (C<sub>2</sub>), 123.8 (C<sub>3a</sub>), 114.2 (C<sub>3</sub>), 95.5 (C<sub>5</sub>), 62.2 (OCH<sub>3</sub>), 55.7 (OCH<sub>3</sub>), 11.5 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**4,7-DIMETHOXY-6-NITRO-3-PHENYLINDOLE (7)****Reaction data:**

2,5-Dimethoxy-1,3-dinitrobenzene: 1.8 g (7.89 mmol).

Styrylmagnesium bromide: 29.51 mL (23.55 mmol).

Reaction time: 3 h

Yield: 1.5 g, 51 % (pale brown solid).

**Data for compound 7:**

Melting point: 132-134 °C

Elemental analysis calc. (%) for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C 64.42, H 4.69, N 9.39; found: C 64.10, H 4.92, N 9.52.

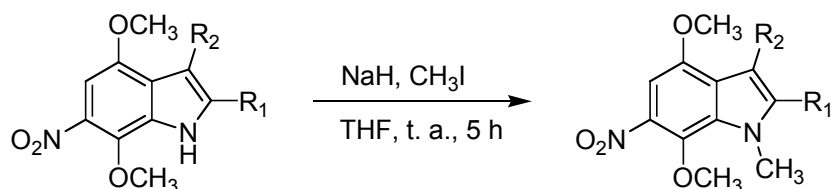
IR (NaCl)  $\nu$ : 3338(NH), 1520 and 1318 (NO<sub>2</sub>), 1220 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 9.97 (s, 1H, NH), 7.65-7.62 (m, 2H, Ar-H), 7.48-7.33 (m, 4H, Ar-H and H<sub>2</sub>), 7.20 (s, 1H, H<sub>5</sub>), 4.07 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.1 (C<sub>4</sub>), 138.2 (C<sub>7</sub>), 137.1 (C<sub>6</sub>), 135.6 (C<sub>1'</sub>), 133.8 (C<sub>2</sub>), 129.7 (C<sub>7a</sub>), 129.2 and 128.0 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5</sub> and C<sub>6'</sub>), 126.8 (C<sub>4'</sub>), 123.1 (C<sub>3a</sub>), 117.7 (C<sub>3</sub>), 96.9 (C<sub>5</sub>), 63.4 (OCH<sub>3</sub>), 56.7 (OCH<sub>3</sub>) ppm.

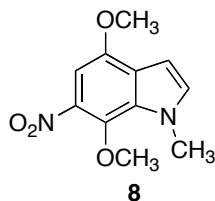
## PREPARATION OF 4,7-DIMETHOXY-1-METHYL-6-NITROINDOLE DERIVATIVES 8-11

### General procedure:



Comp.	R <sup>1</sup>	R <sup>2</sup>
<b>8</b>	H	H
<b>9</b>	CH <sub>3</sub>	H
<b>10</b>	H	CH <sub>3</sub>
<b>11</b>	H	C <sub>6</sub> H <sub>5</sub>

A 60% suspension of sodium hydride in mineral oil (10 mmol) was washed twice with dry petroleum ether (10 mL), under an argon atmosphere. Dry THF (10 mL) was added, and the resulting suspension was cooled to 0 °C, while magnetically stirred. To this suspension was added a solution of the suitable 4,7-dimethoxy-6-nitroindole (5.0 mmol) in dry THF (50 mL), and the mixture was stirred at 0 °C for 1 h. Methyl iodide (11 mmol) was added and stirring was maintained for 4 h, allowing the reaction to reach room temperature. The reaction mixture was poured on ice (20 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated, affording the desired methylindoles **8-11**.

**4,7-DIMETHOXY-1-METHYL-6-NITROINDOLE (8)****Reaction data:**

4,7-Dimethoxy-6-nitroindole: 1 g (4.50 mmol).

Sodium hydride (60% in mineral oil): 355 mg (9 mmol).

Methyl iodide: 1.42 g (10 mmol).

Reaction time: 5 h

Yield: 1.13 g, 96 % (pale brown solid).

**Data for compound 8:**

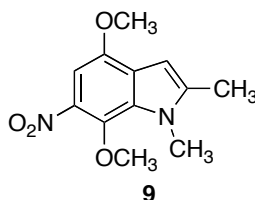
Melting point: 111-113 °C

Elemental analysis calc. (%) for  $C_{11}H_{12}N_2O_4$ : C 55.93, H 5.08, N 11.86; found: C 55.57, H 4.88, N 12.16.

IR (NaCl)  $\nu$ : 1522 and 1337 ( $NO_2$ ), 1213 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR (250 MHz  $CDCl_3$ ):  $\delta$  = 7.11 (d, 1H,  $J$  = 3 Hz,  $H_2$ ), 7.07 (s, 1H,  $H_5$ ), 6.57 (d, 1H,  $J$  = 3 Hz,  $H_3$ ), 4.07 (s, 3H,  $OCH_3$ ), 3.99 (s, 3H,  $OCH_3$ ), 3.95 (s, 3H, N- $CH_3$ ) ppm.

$^{13}C$ -NMR (63 MHz,  $CDCl_3$ ):  $\delta$  = 148.6 ( $C_4$ ), 139.3 ( $C_7$ ), 135.0 ( $C_6$ ), 134.2 ( $C_2$ ), 129.6 ( $C_{7a}$ ), 126.6 ( $C_{3a}$ ), 100.2 ( $C_3$ ), 96.4 ( $C_5$ ), 64.0 ( $OCH_3$ ), 56.2 ( $OCH_3$ ), 36.4 (N- $CH_3$ ) ppm.

**4,7-DIMETHOXY-1,2-DIMETHYL 6-NITROINDOLE (9)****Reaction data:**

4,7-Dimethoxy-2-methyl-6-nitroindole: 380 mg (1.61 mmol).

Sodium hydride (60% in mineral oil): 138 mg (3.45 mmol).

Methyl iodide: 493 mg (3.5 mmol).

Reaction time: 5 h

Yield: 370 mg, 92 % (pale brown solid).

**Data for compound 9:**

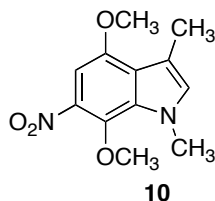
Melting point: 128-130 °C

Elemental analysis calc. (%) for  $C_{12}H_{14}N_2O_4$ : C 57.59, H 5.64, N 11.19; found: C 57.81, H 5.79, N 10.85.

IR (NaCl): 1515 and 1330 ( $NO_2$ ), 1209 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR (250 MHz  $CDCl_3$ ):  $\delta$  = 7.14 (s, 1H,  $H_5$ ), 6.41 (d, 1H,  $J$  = 0.8 Hz,  $H_3$ ), 4.00 (s, 6H,  $OCH_3$  and  $N-CH_3$ ), 3.97 (s, 3H,  $OCH_3$ ), 2.45 (d, 3H,  $J$  = 0.8 Hz,  $C_2-CH_3$ ) ppm.

$^{13}C$ -NMR (63 MHz,  $CDCl_3$ ):  $\delta$  = 147.3 ( $C_4$ ), 141.9 ( $C_2$ ), 138.4 ( $C_7$ ), 135.4 ( $C_6$ ), 129.3 ( $C_{7a}$ ), 125.4 ( $C_{3a}$ ), 99.1 ( $C_3$ ), 96.2 ( $C_5$ ), 63.4 ( $OCH_3$ ), 55.8 ( $OCH_3$ ), 31.8 ( $N-CH_3$ ), 13.1 ( $C_2-CH_3$ ) ppm.

**4,7-DIMETHOXY-1,3-DIMETHYL-6-NITROINDOLE (10)****Reaction data:**

4,7-Dimethoxy-3-methyl-6-nitroindole: 444 mg (1.83 mmol).

Sodium hydride (60% in mineral oil): 157 mg (3.92 mmol).

Methyl iodide: 564 mg (4 mmol).

Reaction time: 5 h

Yield: 465 mg, 100 % (pale yellow solid).

**Data for compound 10:**

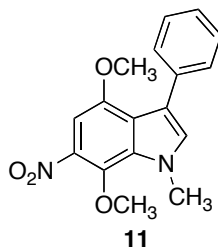
Melting point: 83-85 °C

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C 57.59, H 5.64, N 11.19; found: C 57.65, H 5.71, N 10.87.

IR (NaCl)  $\nu$ : 1515 and 1336 (NO<sub>2</sub>), 1193 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 6.97 (s, 1H, H<sub>5</sub>), 6.79 (d, 1H,  $J$  = 0.7 Hz, H<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, N-CH<sub>3</sub>), 2.36 (d, 3H,  $J$  = 0.7 Hz, C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 149.8 (C<sub>4</sub>), 138.5 (C<sub>7</sub>), 135.4 (C<sub>6</sub>), 132.3 (C<sub>2</sub>), 129.4 (C<sub>7a</sub>), 124.8 (C<sub>3a</sub>), 111.8 (C<sub>3</sub>), 95.0 (C<sub>5</sub>), 63.2 (OCH<sub>3</sub>), 55.3 (OCH<sub>3</sub>), 35.4 (N-CH<sub>3</sub>), 11.2 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**4,7-DIMETHOXY-1-METHYL-6-NITRO-3-PHENYLINDOLE (11)****Reaction data:**

4,7-Dimethoxy-6-nitro-3-phenylindole: 514 mg (1.72 mmol).

Sodium hydride (60% in mineral oil): 186 mg (4.6 mmol).

Methyl iodide: 564 mg (4 mmol).

Reaction time: 5 h

Yield: 499 mg, 93 % (pale reddish solid).

**Data for compound 11:**

Melting point: 105-107 °C

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C 65.38, H 5.12, N 8.97; found: C 65.19, H 4.98, N 8.72.

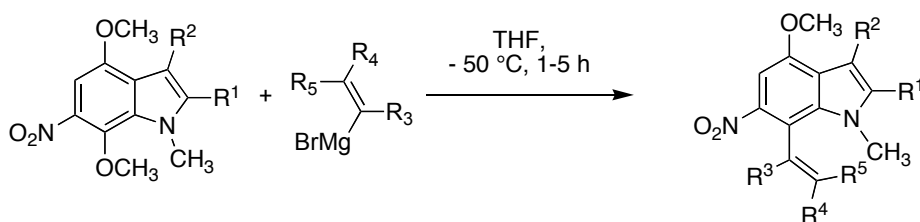
IR (NaCl)  $\nu$ : 1513 and 1338 (NO<sub>2</sub>), 1201 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.56-7.52 (m, 2H, Ar-H), 7.44-7.30 (m, 4H, Ar-H and H<sub>2</sub>), 7.16 (s, 1H, H<sub>5</sub>), 4.15 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 149.5 (C<sub>4</sub>), 138.7 (C<sub>7</sub>), 136.7 (C<sub>6</sub>), 134.3 (C<sub>1'</sub>), 133.2 (C<sub>2</sub>), 130.1 (C<sub>7a</sub>), 129.6 and 127.6 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5'</sub>, C<sub>6'</sub>), 126.3 (C<sub>4'</sub>), 122.5 (C<sub>3a</sub>), 118.5 (C<sub>3</sub>), 96.5 (C<sub>5</sub>), 63.6 (OCH<sub>3</sub>), 55.5 (OCH<sub>3</sub>), 36.3 (N-CH<sub>3</sub>) ppm.

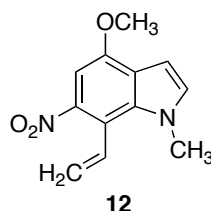
**PREPARATION OF 4-METHOXY-1-METHYL-6-NITRO-7-VINYLIINDOLE  
DERIVATIVES 12-25.**

**General procedure:**



Comp.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
<b>12</b>	H	H	H	H	H
<b>13</b>	H	H	H	CH <sub>3</sub>	H
<b>14</b>	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>
<b>15</b>	H	H	H	C <sub>6</sub> H <sub>5</sub>	H
<b>16</b>	H	H	CH <sub>3</sub>	H	H
<b>17</b>	H	CH <sub>3</sub>	H	H	H
<b>18</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	H
<b>19</b>	H	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>
<b>20</b>	H	CH <sub>3</sub>	CH <sub>3</sub>	H	H
<b>21</b>	CH <sub>3</sub>	H	H	H	H
<b>22</b>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H
<b>23</b>	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H
<b>24</b>	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>
<b>25</b>	H	C <sub>6</sub> H <sub>5</sub>	H	CH <sub>3</sub>	H

A commercial THF solution of the suitable Grignard reagent (1.5 mmol) was added dropwise to a cooled (−50 °C) solution of the adequate 4,7-dimethoxy-1-methyl-6-nitroindole (0.5 mmol) in dry THF (20 mL), under an inert atmosphere. The reaction mixture was stirred at −50 °C for 1-5 h, poured onto a saturated NH<sub>4</sub>Cl aqueous solution (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 5:1 petroleum ether-ethyl acetate.

**4-METHOXY-1-METHYL-6-NITRO-7-VINYLIINDOLE (12)****Reaction data:**

4,7-Dimethoxy-1-methyl-6-nitroindole: 100 mg (0.42 mmol).

Vinylmagnesium bromide: 1.68 mL (1.26 mmol).

Reaction time: 1 h

Yield: 89 mg, 91% (yellow solid).

**Data for compound 12:**

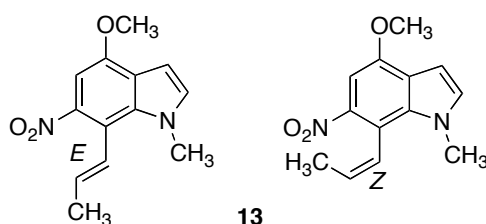
Melting point: 108-110 °C

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C 62.10, H 5.20, N 12.05; found: C 62.36, H 4.95, N 11.80.

IR (NaCl)  $\nu$ : 1519 and 1313 (NO<sub>2</sub>), 1233 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.33 (dd, 1H,  $J$  = 17.5 Hz and 11.0 Hz, CH=CH<sub>2</sub>), 7.14 (s, 1H, H<sub>5</sub>), 7.12 (d, 1H,  $J$  = 3.0 Hz, H<sub>2</sub>), 6.65 (d, 1H,  $J$  = 3.0 Hz, H<sub>3</sub>), 5.62 (dd, 1H,  $J$  = 11.0 Hz and 1.5 Hz, CH=CH<sub>2</sub>), 5.28 (dd, 1H,  $J$  = 17.5 Hz and 1.5 Hz, CH=CH<sub>2</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.0 (C<sub>4</sub>), 143.0 (C<sub>6</sub>), 134.1 (C<sub>2</sub>), 133.0 (C<sub>7a</sub>), 131.0 (CH=CH<sub>2</sub>), 123.9 (C<sub>3a</sub>), 121.0 (CH=CH<sub>2</sub>), 115.0 (C<sub>7</sub>), 99.0 (C<sub>3</sub>), 95.9 (C<sub>5</sub>), 55.0 (OCH<sub>3</sub>), 38.0 (N-CH<sub>3</sub>) ppm.

**(E/Z)-1-METHYL-4-METHOXY-6-NITRO-7-(1-PROPENYL)INDOLE (13)****Reaction data:**

4,7-Dimethoxy-1-methyl-6-nitroindole: 100 mg (0.42 mmol).

1-Propenylmagnesium bromide: 1,93 mL (1.26 mmol).

Reaction time: 1 h

Yield: 102 mg, 99% (yellow solid), corresponding to a *E/Z* = 1.3/1 mixture.

**Data for compound 13:**

Melting point: 80-82 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.68, H 5.84, N 11.04.

IR (NaCl)  $\nu$ : 1518 and 1311 (NO<sub>2</sub>), 1230 (OCH<sub>3</sub>) cm<sup>-1</sup>.

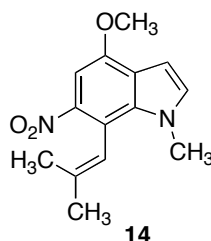
<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 7.11 (d, 1H, *J* = 3.2 Hz, H<sub>2</sub>), 7.08 (s, 1H, H<sub>5</sub>), 6.87 (m, 1H, HC=CH-CH<sub>3</sub>), 6.61 (d, 1H, *J* = 3.2 Hz, H<sub>3</sub>), 5.65 (dq, 1H, *J* = 15.9 and 6.6 Hz, HC=CH-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, N-CH<sub>3</sub>), 1.94 (dd, 3H, *J* = 6.6 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 7.15 (s, 1H, H<sub>5</sub>), 7.09 (d, 1H, *J* = 3.2 Hz, H<sub>2</sub>), 6.92 (m, 1H, HC=CH-CH<sub>3</sub>), 6.64 (d, 1H, *J* = 3.2 Hz, H<sub>3</sub>), 6.01 (dq, 1H, *J* = 11.0 and 6.8 Hz, HC=CH-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, N-CH<sub>3</sub>), 1.40 (dd, 3H, *J* = 6.8 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 151.0 (C<sub>4</sub>), 144.5 (C<sub>6</sub>), 134.1 (C<sub>7a</sub>, overlapped with the same signal of the *Z* isomer), 133.7 (C<sub>2</sub>), 131.6 (HC=CH-CH<sub>3</sub>),

123.6 (C<sub>3a</sub>), 123.3 (HC=CH-CH<sub>3</sub>), 114.8 (C<sub>7</sub>), 98.6 (C<sub>3</sub>, overlapped with the same signal of the *Z* isomer), 95.6 (C<sub>5</sub>), 55.4 (OCH<sub>3</sub>), 38.1 (N-CH<sub>3</sub>), 18.3 (CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 151.2 (C<sub>4</sub>), 144.4 (C<sub>6</sub>), 134.1 (C<sub>7a</sub>, overlapped with the same signal of the *E* isomer), 133.7 (C<sub>2</sub>), 129.7 (HC=CH-CH<sub>3</sub>), 123.6 (C<sub>3a</sub>), 123.7 (C<sub>3</sub> and HC=CH-CH<sub>3</sub>), 112.5 (C<sub>7</sub>), 98.6 (C<sub>3</sub>, overlapped with the same signal of the *E* isomer), 95.8 (C<sub>5</sub>), 55.4 (OCH<sub>3</sub>), 36.9 (N-CH<sub>3</sub>), 14.2 (CH<sub>3</sub>) ppm.

**4-METHOXY-1-METHYL-7-(2-METHYL-1-PROPENYL)-6-NITROINDOLE (14)****Reaction data:**

4,7-Dimethoxy-1-methyl-6-nitroindole: 100 mg (0.42 mmol).

2-Methyl-1-propenylmagnesium bromide: 2.1 mL (1.26 mmol).

Reaction time: 1 h

Yield: 103 mg, 94% (brown solid).

**Data for compound 14:**

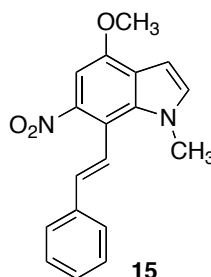
Melting point: 45 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 65.00, H 6.34, N 10.43.

IR (NaCl)  $\nu$ : 1500 and 1333 (NO<sub>2</sub>), 1230 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.11 (s, 1H, H<sub>5</sub>), 7.09 (d, 1H, *J* = 3.0 Hz, H<sub>2</sub>), 6.62 (d, 1H, *J* = 3.0 Hz, H<sub>3</sub>), 6.58-6.57 (m, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, N-CH<sub>3</sub>), 1.96 (d, 3H, *J* = 1.3 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.37 (d, 3H, *J* = 1.0 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.0 (C<sub>4</sub>), 144.6 (C<sub>6</sub>), 137.8 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 134.1 (C<sub>7a</sub>), 133.6 (C<sub>2</sub>), 123.2 (C<sub>3a</sub>), 117.9 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 113.9 (C<sub>7</sub>), 98.6 (C<sub>3</sub>), 95.7 (C<sub>5</sub>), 55.5 (OCH<sub>3</sub>), 36.7 (N-CH<sub>3</sub>), 24.9 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 19.2 (HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

**4-METHOXY-1-METHYL-6-NITRO-7-STYRYLINDOLE (15)****Reaction data:**

4,7-Dimethoxy-1-methyl-6-nitroindole: 50 mg (0.21 mmol).

Styrylmagnesium bromide: 1.12 mL (0.63 mmol).

Reaction time: 5 h

Yield: 64 mg, 98% (brown solid).

**Data for compound 15:**

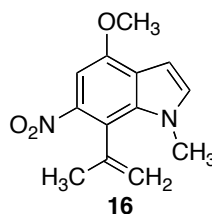
Melting point: 141-143 °C

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 70.12, H 5.19, N 9.09; found: C 70.52, H 5.36, N 8.91.

IR (NaCl)  $\nu$ : 1520 and 1324 (NO<sub>2</sub>), 1232 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.65 (d, 1H,  $J$  = 16.3 Hz, HC=CH-C<sub>6</sub>H<sub>5</sub>), 7.57-7.53 (m, 2H, Ph), 7.46-7.29 (m, 3H, Ph), 7.24 (s, 1H, H<sub>5</sub>), 7.15 (d, 1H,  $J$  = 3.0 Hz, H<sub>2</sub>), 6.69 (d, 1H,  $J$  = 3.0 Hz, H<sub>3</sub>), 6.53 (d, 1H,  $J$  = 16.3 Hz, HC=CH-C<sub>6</sub>H<sub>5</sub>), 4.04 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.9 (C<sub>4</sub>), 144.7 (C<sub>6</sub>), 136.9 (C<sub>1'</sub>), 135.3 (C<sub>2</sub>), 134.8 (C<sub>7a</sub>), 134.7 (HC=CH-C<sub>6</sub>H<sub>5</sub>), 129.0 and 128.8 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5'</sub> and C<sub>6'</sub>), 128.9 (C<sub>4'</sub>), 124.4 (C<sub>3a</sub>), 122.5 (HC=CH-C<sub>6</sub>H<sub>5</sub>), 115.3 (C<sub>7</sub>), 99.5 (C<sub>3</sub>), 96.6 (C<sub>5</sub>), 56.1 (OCH<sub>3</sub>), 39.0 (N-CH<sub>3</sub>) ppm.

**7-ISOPROPENYL-1-METHYL-4-METHOXY-6-NITROINDOLE (16)****Reaction data:**

4,7-Dimethoxy-1-methyl-6-nitroindole: 100 mg (0.42 mmol).

Isopropenylmagnesium bromide: 1.96 mL (1.26 mmol).

Reaction time: 1 h

Yield: 78 mg, 75% (brown solid).

**Data for compound 16:**

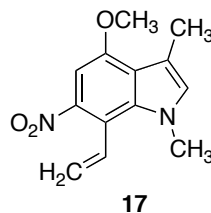
Melting point: 87-89 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.70, H 5.82, N 11.15.

IR (NaCl)  $\nu$ : 1522 and 1315 (NO<sub>2</sub>), 1223 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.14-7.12 (m, 2H, H<sub>2</sub> and H<sub>5</sub>), 6.66 (d, 1H,  $J$  = 3.0 Hz, H<sub>3</sub>), 5.42-5.40 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 5.04-5.03 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, N-CH<sub>3</sub>), 2.27 (dd, 3H,  $J$  = 1.3 Hz and 0.8 Hz, H<sub>2</sub>C=C-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 151.2 (C<sub>4</sub>), 139.7 (C<sub>6</sub> and H<sub>2</sub>C=C-C-CH<sub>3</sub>), 133.8 (C<sub>2</sub>), 123.8 (C<sub>7a</sub>), 118.9 (C<sub>3a</sub>), 117.7 (H<sub>2</sub>C=C-C-CH<sub>3</sub>), 98.9 (C<sub>3</sub>), 95.8 (C<sub>5</sub>), 55.6 (OCH<sub>3</sub>), 36.1 (N-CH<sub>3</sub>), 25.9 (H<sub>2</sub>C=C-C-CH<sub>3</sub>) ppm.

**4-METHOXY-1,3-DIMETHYL-6-NITRO-7-VINYLINDOLE (17)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

Vinylmagnesium bromide: 0.8 mL (0.6 mmol).

Reaction time: 2 h

Yield: 47 mg, 95% (pale brown solid).

**Data for compound 17:**

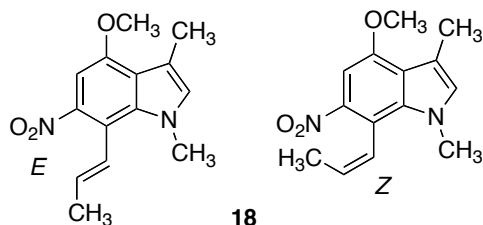
Melting point: 57-59 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.26, H 5.90, N 11.04.

IR (NaCl)  $\nu$ : 1515 and 1315 (NO<sub>2</sub>), 1234 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.30 (dd, 1H,  $J$  = 17.5 Hz and 11.0 Hz, HC=CH<sub>2</sub>), 7.07 (s, 1H, H<sub>5</sub>), 6.83 (s, 1H, H<sub>2</sub>), 5.59 (dd, 1H,  $J$  = 11.0 Hz and 1.5 Hz, HC=CH<sub>2</sub>), 5.23 (dd, 1H,  $J$  = 17.5 Hz and 1.5 Hz, HC=CH<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, N-CH<sub>3</sub>), 2.44 (d, 3H,  $J$  = 0.8 Hz C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.3 (C<sub>4</sub>), 144.0 (C<sub>6</sub>), 134.4 (C<sub>7a</sub>), 132.4 (HC=CH<sub>2</sub>), 131.4 (C<sub>2</sub>), 122.5 (C<sub>3a</sub>), 120.4 (HC=CH<sub>2</sub>), 115.0 (C<sub>7</sub>), 111.2 (C<sub>3</sub>), 95.4 (C<sub>5</sub>), 55.5 (OCH<sub>3</sub>), 38.0 (N-CH<sub>3</sub>), 11.6 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**(E,Z)-4-METHOXY-1,3-DIMETHYL-6-NITRO-7-(1-PROPENYL)INDOLE (18)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-6-nitroindole: 70 mg (0.28 mmol).

1-Propenylmagnesium bromide: 1.3 mL (0.84 mmol).

Reaction time: 2 h

Yield: 71 mg, 98% (yellow solid), corresponding to a *E/Z* = 1.3/1 mixture.

**Data for compound 18:**

Melting point: 85-87 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 64.29, H 6.48, N 10.52.

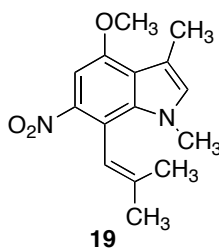
IR (NaCl)  $\nu$ : 1510 and 1329 (NO<sub>2</sub>), 1232 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 7.02 (s, 1H, H<sub>5</sub>), 6.91-6.86 (m, 1H, HC=CH-CH<sub>3</sub>), 6.81 (d, 1H, *J* = 0.9 Hz, H<sub>2</sub>), 5.61 (dq, 1H, *J* = 15.8 Hz and 6.6 Hz, HC=CH-CH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 3H, N-CH<sub>3</sub>), 2.43 (d, 3H, *J* = 0.9 Hz, C<sub>3</sub>-CH<sub>3</sub>), 1.93 (dd, 3H, *J* = 6.6 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 7.09 (s, 1H, H<sub>5</sub>), 6.85-6.81 (m, 1H, HC=CH-CH<sub>3</sub>), 6.83 (d, 1H, *J* = 0.9 Hz, H<sub>2</sub>), 5.98 (dq, 1H, *J* = 11.0 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, N-CH<sub>3</sub>), 2.45 (d, 3H, *J* = 0.9 Hz, C<sub>3</sub>-CH<sub>3</sub>), 1.37 (dd, 3H, *J* = 6.8 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

$^{13}\text{C}$ -NMR (63 MHz,  $\text{CDCl}_3$ ): *E* isomer:  $\delta = 152.9$  ( $\text{C}_4$ ),  $144.3$  ( $\text{C}_6$ ),  $134.8$  ( $\text{C}_{7a}$ ),  $132.2$  ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ),  $131.3$  ( $\underline{\text{H}}\text{C}=\text{CH}-\text{CH}_3$ ),  $123.9$  ( $\text{C}_2$ ),  $122.3$  ( $\text{C}_{3a}$ , overlapped with the same signal of the *Z* isomer),  $114.7$  ( $\text{C}_7$ , overlapped with the same signal of the *Z* isomer),  $111.0$  ( $\text{C}_3$ , overlapped with the same signal of the *Z* isomer),  $95.3$  ( $\text{C}_5$ ),  $55.4$  ( $\text{OCH}_3$ ),  $37.8$  ( $\text{N}-\text{CH}_3$ ),  $18.3$  ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ ),  $11.6$  ( $\text{C}_3-\text{CH}_3$ , overlapped with the same signal of the *Z* isomer) ppm.

*Z* isomer:  $\delta = 153.1$  ( $\text{C}_4$ ),  $144.2$  ( $\text{C}_6$ ),  $134.5$  ( $\text{C}_{7a}$ ),  $132.3$  ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ),  $129.5$  ( $\underline{\text{H}}\text{C}=\text{CH}-\text{CH}_3$ ),  $124.0$  ( $\text{C}_2$ ),  $122.3$  ( $\text{C}_{3a}$ , overlapped with the same signal of the *E* isomer),  $114.7$  ( $\text{C}_7$ , overlapped with the same signal of the *E* isomer),  $111.0$  ( $\text{C}_3$ , overlapped with the same signal of the *E* isomer),  $95.5$  ( $\text{C}_5$ ),  $55.4$  ( $\text{OCH}_3$ ),  $36.6$  ( $\text{N}-\text{CH}_3$ ),  $14.2$  ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ ),  $11.6$  ( $\text{C}_3-\text{CH}_3$ , overlapped with the same signal of the *E* isomer) ppm.

**4-METHOXY-1,3-DIMETHYL-7-(2-METHYL-1-PROPENYL)-6-NITROINDOLE (19)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

2-Methyl-1-propenylmagnesium bromide: 1 mL (0.6 mmol).

Reaction time: 2 h

Yield: 41 mg, 72% (yellow solid).

**Data for compound 19:**

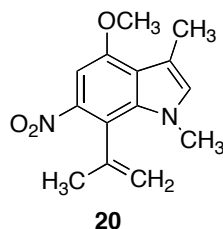
Melting point: 55-57 °C

Elemental analysis calc. (%) for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 65.69, H 6.57, N 10.21; found: C 65.30, H 6.21, N 9.94.

IR (NaCl)  $\nu$ : 1516 and 1329 (NO<sub>2</sub>), 1236 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.06 (s, 1H, H<sub>5</sub>), 6.82 (br s, 1H, H<sub>2</sub>), 6.56 (br s, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, N-CH<sub>3</sub>), 2.44 (br s, 3H, C<sub>3</sub>-CH<sub>3</sub>), 1.95 (br s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.36 (br s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.9 (C<sub>4</sub>), 145.0 (C<sub>6</sub>), 137.7 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 135.0 (C<sub>7a</sub>), 132.4 (C<sub>2</sub>), 124.3 (C<sub>3a</sub>), 118.1 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 113.9 (C<sub>7</sub>), 111.2 (C<sub>3</sub>), 95.9 (C<sub>5</sub>), 55.9 (OCH<sub>3</sub>), 36.9 (N-CH<sub>3</sub>), 25.4 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 19.2 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 11.9 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**7-ISOPROPENYL-4-METHOXY-1,3-DIMETHYL-6-NITROINDOLE (20)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

Isopropenylmagnesium bromide: 0.93 mL (0.6 mmol).

Reaction time: 2 h

Yield: 40 mg, 71% (yellow solid).

**Data for compound 20:**

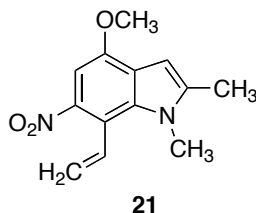
Melting point: 75-77 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 65.01, H 6.06, N 10.87.

IR (NaCl)  $\nu$ : 1510 and 1316 (NO<sub>2</sub>), 1232 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.07 (s, 1H, H<sub>5</sub>), 6.85 (d, 1H,  $J$  = 0.8 Hz, H<sub>2</sub>), 5.39-5.37 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 5.01-5.00 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>), 3.90 (s, 3H, N-CH<sub>3</sub>), 2.45 (d, 3H,  $J$  = 0.8 Hz, C<sub>3</sub>-CH<sub>3</sub>), 2.31 (t, 3H,  $J$  = 1.2 Hz, H<sub>2</sub>C=C-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.1 (C<sub>4</sub>), 143.4 (C<sub>6</sub>), 140.1 (H<sub>2</sub>C=C-CH<sub>3</sub>), 133.3 (C<sub>7a</sub>), 132.3 (C<sub>2</sub>), 122.8 (C<sub>3a</sub>), 118.8 (C<sub>7</sub>), 117.7 (H<sub>2</sub>C=C-CH<sub>3</sub>), 111.4 (C<sub>3</sub>), 95.4 (C<sub>5</sub>), 55.7 (OCH<sub>3</sub>), 35.9 (N-CH<sub>3</sub>), 26.2 (H<sub>2</sub>C=C-CH<sub>3</sub>), 11.7 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**4-METHOXY-1,2-DIMETHYL-6-NITRO-7-VINYLINDOLE (21)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

Vinylmagnesium bromide: 0.8 mL (0.6 mmol).

Reaction time: 1 h

Yield: 47 mg, 96% (dark green solid).

**Data for compound 21:**

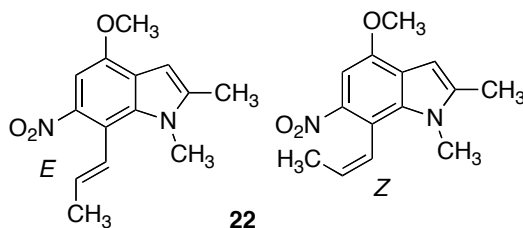
Melting point: 65-67 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.21, H 5.32, N 11.09.

IR (NaCl)  $\nu$ : 1515 and 1315 (NO<sub>2</sub>), 1234 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.30 (dd, 1H,  $J$  = 17.5 Hz and 11.0 Hz, HC=CH<sub>2</sub>), 7.14 (s, 1H, H<sub>5</sub>), 6.44 (s, 1H, H<sub>3</sub>), 5.59 (dd, 1H,  $J$  = 11.0 Hz and 1.5 Hz, HC=CH<sub>2</sub>), 5.23 (dd, 1H,  $J$  = 17.5 Hz and 1.5 Hz, HC=CH<sub>2</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, N-CH<sub>3</sub>), 2.43 (s, 3H, C<sub>2</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 152.7 (C<sub>4</sub>), 143.1 (C<sub>6</sub>), 132.8 (C<sub>2</sub>), 132.2 (C<sub>7a</sub>), 131.7 (HC=CH<sub>2</sub>), 123.5 (C<sub>3a</sub>), 121.0 (C<sub>7</sub>), 119.3 (HC=CH<sub>2</sub>), 112.2 (C<sub>3</sub>), 96.0 (C<sub>5</sub>), 56.7 (OCH<sub>3</sub>), 37.5 (N-CH<sub>3</sub>), 12.2 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**4-METHOXY-1,2-DIMETHYL-6-NITRO-7-(1-PROPENYL)INDOLE (22)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-6-nitroindole: 50 mg (0,2 mmol).

1-Propenylmagnesium bromide: 0,9 mL (0,6 mmol).

Reaction time: 3 h

Yield: 50 mg, 97% (brown solid), corresponding to a *E/Z*= 1.3/1 mixture.

**Data for compound 22:**

Melting point: 68-70 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 64.55, H 6.33, N 10.57.

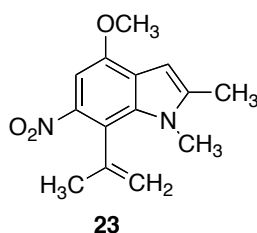
IR (NaCl)  $\nu$ : 1517 and 1326 (NO<sub>2</sub>), 1225 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 7.10 (s, 1H, H<sub>5</sub>), 6.93-6.88 (m, 1H, HC=CH-CH<sub>3</sub>), 6.42 (d, 1H, *J* = 0.8 Hz, H<sub>3</sub>), 5.61 (dq, 1H, *J* = 15.9 Hz and 6.6 Hz, HC=CH-CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, N-CH<sub>3</sub>), 2.43 (d, 3H, *J* = 0.8 Hz, C<sub>2</sub>-CH<sub>3</sub>, partially overlapped with the same signal of the *Z* isomer), 1.94 (dd, 3H, *J* = 6.6 Hz and 1.8 Hz, HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 7.16 (s, 1H, H<sub>5</sub>), 6.97-6.94 (m, 1H, HC=CH-CH<sub>3</sub>), 6.44 (d, 1H, *J* = 0.9 Hz, H<sub>3</sub>), 5.99 (dq, 1H, *J* = 11.0 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 3.80 (s, 3H, N-CH<sub>3</sub>), 2.44 (d, 3H, *J* = 0.9 Hz, C<sub>2</sub>-CH<sub>3</sub>, partially overlapped with the same signal of the *E* isomer), 1.39 (dd, 3H, *J* = 6.8 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

$^{13}\text{C}$ -NMR (63 MHz,  $\text{CDCl}_3$ ): *E* isomer:  $\delta$  = 150.1 ( $\text{C}_4$ ), 143.9 ( $\text{C}_6$ , overlapped with the same signal of the *Z* isomer), 141.3 ( $\text{C}_2$ ), 135.0 ( $\text{C}_{7a}$ ), 131.2 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 124.3 ( $\underline{\text{H}}\text{C}=\text{CH}-\text{CH}_3$ ), 114.7 ( $\text{C}_7$ ,  $\text{C}_{3a}$ ), 98.2 ( $\text{C}_3$ , overlapped with the same signal of the *Z* isomer), 96.0 ( $\text{C}_5$ ), 55.5 ( $\text{OCH}_3$ ), 33.9 ( $\text{NCH}_3$ ), 18.4 ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ ), 13.6 ( $\text{C}_2-\text{CH}_3$ , overlapped with the  $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$  signal of the *Z* isomer) ppm.

*Z* isomer:  $\delta$  = 150.3 ( $\text{C}_4$ ), 143.9 ( $\text{C}_6$ , overlapped with the same signal of the *E* isomer), 141.4 ( $\text{C}_2$ ), 134.5 ( $\text{C}_{7a}$ ), 129.4 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 122.7 ( $\underline{\text{H}}\text{C}=\text{CH}-\text{CH}_3$ ), 112.3 ( $\text{C}_7$ ,  $\text{C}_{3a}$ ), 98.2 ( $\text{C}_3$ , overlapped with the same signal of the *E* isomer), 96.2 ( $\text{C}_5$ ), 55.5 ( $\text{OCH}_3$ ), 32.7 ( $\text{N}-\text{CH}_3$ ), 13.6 ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ , overlapped with the  $\text{C}_2-\text{CH}_3$  signal of the *E* isomer), 14.2 ( $\text{C}_2-\text{CH}_3$ ) ppm.

**7-ISOPROPENYL-4-METHOXY-1,2-DIMETHYL-6-NITROINDOLE (23)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

Isopropenylmagnesium bromide: 0.93 mL (0.6 mmol).

Reaction time: 2 h

Yield: 44 mg, 85% (yellow solid).

**Data for compound 23:**

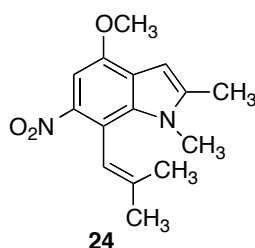
Melting point: 155-157 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 64.34, H 6.14, N 10.45.

IR (NaCl)  $\nu$ : 1515 and 1314 (NO<sub>2</sub>), 1219 OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.13 (s, 1H, H<sub>5</sub>), 6.46 (d, 1H, *J* = 0.8 Hz, H<sub>2</sub>), 5.41-5.38 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 5.03-5.01 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.87 (s, 3H, N-CH<sub>3</sub>), 2.45 (d, 3H, *J* = 0.8 Hz, C<sub>2</sub>-CH<sub>3</sub>), 2.34 (t, 3H, *J* = 1.1 Hz, H<sub>2</sub>C=C-CH<sub>3</sub>) ppm.

<sup>3</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.9 (C<sub>4</sub>), 143.4 (C<sub>6</sub>), 142.1 (H<sub>2</sub>C=C-CH<sub>3</sub>), 140.8 (C<sub>2</sub>), 134.2 (C<sub>7a</sub>), 123.6 (C<sub>3a</sub>), 119.1 (C<sub>7</sub>), 117.9 (H<sub>2</sub>C=C-CH<sub>3</sub>), 98.7 (C<sub>3</sub>), 96.4 (C<sub>5</sub>), 56.0 (OCH<sub>3</sub>), 32.2 (N-CH<sub>3</sub>), 26.5 (H<sub>2</sub>C=C-CH<sub>3</sub>), 14.1 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**4-METHOXY-1,2-DIMETHYL-7-(2-METHYL-1-PROPENYL)-6-NITROINDOLE (24)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-6-nitroindole: 50 mg (0.2 mmol).

2-Methyl-1-propenylmagnesium bromide: 1 mL (0.6 mmol).

Reaction time: 3 h

Yield: 45 mg, 81% (yellow solid).

**Data for compound 24:**

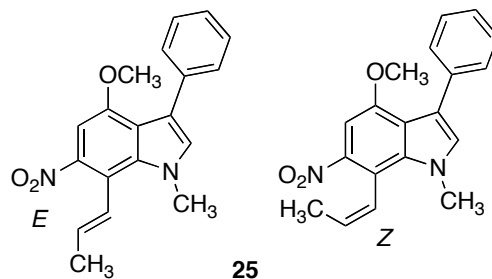
Melting point: 98-100 °C

Elemental analysis calc. (%) for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 65.69, H 6.57, N 10.21; found: C 65.75, H 6.47, N 9.94.

IR (NaCl)  $\nu$ : 1515 and 1302 (NO<sub>2</sub>), 1230 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.13 (s, 1H, H<sub>5</sub>), 6.61-6.59 (m, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 6.43 (d, 1H,  $J$  = 0.8 Hz, H<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, N-CH<sub>3</sub>), 2.43 (d, 3H,  $J$  = 0.8 Hz, C<sub>2</sub>-CH<sub>3</sub>), 1.97 (d, 3H,  $J$  = 1.3 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.36 (d, 3H,  $J$  = 1.0 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.1 (C<sub>4</sub>), 144.0 (C<sub>6</sub>), 141.4 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 137.4 (C<sub>2</sub>), 134.8 (C<sub>7a</sub>), 122.5 (C<sub>3a</sub>), 118.4 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 113.6 (C<sub>7</sub>), 98.1 (C<sub>3</sub>), 96.1 (C<sub>5</sub>), 55.5 (OCH<sub>3</sub>), 32.4 (N-CH<sub>3</sub>), 24.8 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 19.2 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 13.7 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**(E/Z) 4-METHOXY-1-METHYL-6-NITRO-3-PHENYL-7-(1-PROPENYL)INDOLE (25)****Reaction data:**

4,7-Dimethoxy-1-methyl-3-phenyl-6-nitroindole: 50 mg (0.16 mmol).

1-Propenylmagnesium bromide: 0.73 mL (0.48 mmol).

Reaction time: 5 h

Yield: 50 mg, 98% (dark red solid), corresponding to a *E/Z* = 1.3/1 mixture.

**Data for compound 25:**

Melting point: 53-55 °C

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.79, H 5.63, N 8.69; found: C 70.62, H 6.01, N 8.04.

IR (NaCl)  $\nu$ : 1517 and 1340 (NO<sub>2</sub>), 1203 (OCH<sub>3</sub>) cm<sup>-1</sup>.

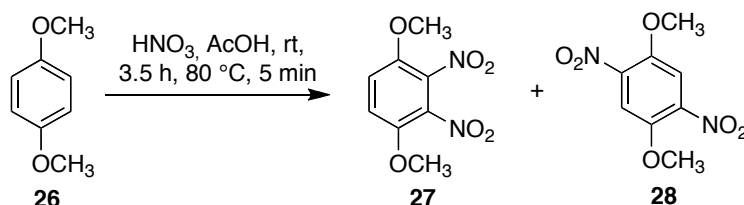
<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 7.47-7.41 (m, 2H, Ph, overlapped with the same signal of the *Z* isomer), 7.33-7.21 (m, 3H, Ph, overlapped with the same signal of the *Z* isomer), 7.18 (s, 1H, H<sub>5</sub> overlapped with the same signal of the *Z* isomer), 7.05 (s, 1H, H<sub>2</sub>, overlapped with the same signal of the *Z* isomer), 6.92-6.91 (m, 1H, HC=CH-CH<sub>3</sub>), 5.59 (dq, 1H, *J* = 15.8 Hz and 6.6 Hz, HC=CH-CH<sub>3</sub>), 4.04 (s, 3H, N-CH<sub>3</sub>), 3.75 (s, 3H, O-CH<sub>3</sub>), 1.86 (dd, 3H, *J* = 6.6 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 7.47-7.41 (m, 2H, Ph, overlapped with the same signal of the *E* isomer), 7.33-7.21 (m, 3H, Ph, overlapped with the same signal of the *E* isomer),

7.18 (s, 1H, H<sub>5</sub>, overlapped with the same signal of the *E* isomer), 7.05 (s, 1H, H<sub>2</sub>, overlapped with the same signal of the *E* isomer), 6.97-6.95 (m, 1H, HC=CH-CH<sub>3</sub>), 5.94 (dq, 1H, *J* = 11.0 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 3.82 (s, 3H, N-CH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 1.35 (dd, 3H, *J* = 6.8 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 152.6 (C<sub>4</sub>), 149.4 (C<sub>6</sub>), 138.6 (C<sub>7a</sub>), 134.2 (C<sub>1'</sub>), 133.2 (C<sub>2</sub>), 130.1 (HC=CH-CH<sub>3</sub>), 129.7 and 127.5 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5'</sub> and C<sub>6'</sub>), 126.3 (HC=CH-CH<sub>3</sub>), 123.7 (C<sub>4'</sub>, overlapped with the same signal of the *Z* isomer), 119.8 (C<sub>3a</sub>), 117.5 (C<sub>3</sub>), 112.3 (C<sub>7</sub>), 96.4 (C<sub>5</sub>), 55.3 (OCH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 14.4 (HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 152.4 (C<sub>4</sub>), 144.6 (C<sub>6</sub>), 136.0 (C<sub>7a</sub>), 134.8 (C<sub>1'</sub>), 133.1 (C<sub>2</sub>) 131.8 (HC=CH-CH<sub>3</sub>), 129.6 and 127.6 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5'</sub> and C<sub>6'</sub>), 126.1 (HC=CH-CH<sub>3</sub>), 123.7 (C<sub>4'</sub>, overlapped with the same signal of the *E* isomer), 122.5 (C<sub>3a</sub>), 118.5 (C<sub>3</sub>), 114.6 (C<sub>7</sub>), 96.3 (C<sub>5</sub>), 55.5 (OCH<sub>3</sub>), 36.3 (N-CH<sub>3</sub>), 18.4 (HC=CH-CH<sub>3</sub>) ppm.

**1,4-DIMETHOXY-2,5-DINITROBENZENE (28)**

To a solution of 1,4-dimethoxybenzene **26** (10 g, 72.46 mmol) in acetic acid (250 mL) was added 65% nitric acid (125 mL) and was stirred at room temperature for 1.5 h. Then, nitric acid (125 mL) was again added and the stirring was kept for 2 h. Finally, the reaction was heated to 70-80 °C for 5 min. The reaction mixture was cooled in an ice bath, poured onto water (500 mL) and the yellow precipitate was filtered and washed with water (50 mL), affording 13,73 g of a mixture of compounds **27** and **28**. Purification by flash chromatography on silica gel, eluting with 2:1 petroleum ether-ethyl acetate gave 9.98 g (61%) of **27** and 3.37 g (20%) of the desired compound **28**.

**Data for compound 27:**

Melting point: 190-192 °C

Elemental analysis calc. (%) for C<sub>8</sub>H<sub>8</sub>N<sub>2</sub>O<sub>6</sub> (%): C 42.10, H 3.50, N 12.28; found: C 42.01, H 3.53, N 12.44

IR (NaCl)  $\nu$ : 1515 and 1333 (NO<sub>2</sub>); 1220 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz):  $\delta$  = 7.32 (s, 2H, H<sub>5</sub>, H<sub>6</sub>), 3.95 (s, 6H, OCH<sub>3</sub>, C<sub>1</sub>, C<sub>4</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz):  $\delta$  = 145.2 (C<sub>1</sub>, C<sub>4</sub>), 134.1 (C<sub>2</sub>, C<sub>3</sub>), 116.6 (C<sub>5</sub>, C<sub>6</sub>), 57.4 (OCH<sub>3</sub>) ppm.

**Data for compound 28:**

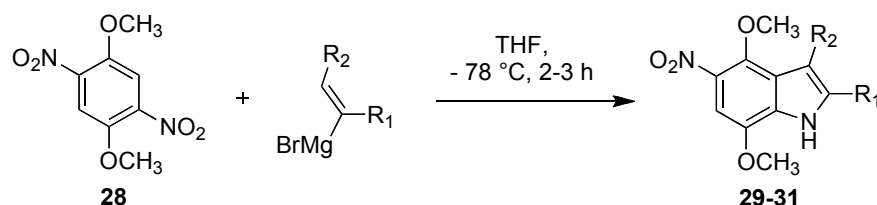
Melting point: 208-210 °C

Elemental analysis calc. (%) for  $C_8H_8N_2O_6$  (%): C 42.10, H 3.50, N 12.28; found: C 42.05, H 3.45, N 12.32.

IR (NaCl)  $\nu$ : 1520 y 1330 ( $NO_2$ ); 1223 ( $OCH_3$ )  $cm^{-1}$ .

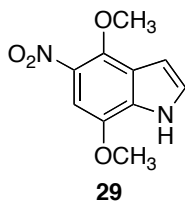
$^1H$ -NMR ( $CDCl_3$ , 250 MHz):  $\delta$  = 7.59 (s, 2H,  $H_2$ ,  $H_5$ ), 4.01 (s, 6H,  $OCH_3$ ) ppm.

$^{13}C$ -NMR ( $CDCl_3$ , 63 MHz):  $\delta$  = 146.4 ( $C_2$ ,  $C_5$ ), 141.9 ( $C_1$ ,  $C_4$ ), 111.2 ( $C_3$ ,  $C_6$ ), 57.4 ( $OCH_3$ ) ppm.

**PREPARATION OF 4,7-DIMETHOXY-5-NITROINDOLE DERIVATIVES 29-31****General procedure:**

Comp.	R <sup>1</sup>	R <sup>2</sup>
<b>29</b>	H	H
<b>30</b>	CH <sub>3</sub>	H
<b>31</b>	H	CH <sub>3</sub>

The suitable vinylmagnesium reagent (30 mmol, as a commercially available solution in THF) was added dropwise to a cooled (-78 °C) solution of 1,4-dimethoxy-2,5-dinitrobenzene **28** (10 mmol) in dry THF (150 mL), under an argon atmosphere. The reaction mixture was stirred at the same temperature for 2-3 h and was then poured onto a saturated aqueous NH<sub>4</sub>Cl solution (75 mL), which was extracted with AcOEt (3 x 50 mL). The combined organic extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 5:1 petroleum ether-ethyl acetate.

**4,7-DIMETHOXY-5-NITROINDOLE (29)****Reaction data:**

1,4-Dimethoxy-2,5-dinitrobenzene: 200 mg (0.88 mmol).

Vinylmagnesium bromide: 3,53 mL (2.64 mmol).

Reaction time: 2 h

Yield: 118 mg, 60% (yellow solid).

**Data for compound 29:**

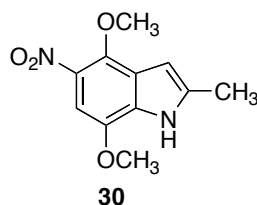
Melting point: 86-88 °C

Elemental analysis calc. (%) for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>: C 54.05, H 4.54, N 12.61; found: C 54.35, H 4.32, N 12.39.

IR (NaCl)  $\nu$ : 1523 and 1339 (NO<sub>2</sub>), 1197 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 8.84 (s, 1H, NH); 7.30-7.27 (m, 1H, H<sub>2</sub>), 7.24 (s, 1H, H<sub>6</sub>), 6.83 (dd, 1H,  $J$  = 3.2 Hz and 2.3 Hz, H<sub>3</sub>), 4.15 (s, 3H, OCH<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.4 (C<sub>4</sub>), 141.3 (C<sub>7</sub>), 134.5 (C<sub>5</sub>), 130.4 (C<sub>7a</sub>), 125.1 (C<sub>2</sub>), 122.1 (C<sub>3a</sub>), 103.3 (C<sub>3</sub>), 98.6 (C<sub>6</sub>), 62.1 (OCH<sub>3</sub>), 55.9 (OCH<sub>3</sub>) ppm.

**4,7-DIMETHOXY-2-METHYL-5-NITROINDOLE (30)****Reaction data:**

1,4-Dimethoxy-2,5-dinitrobenzene: 200 mg (0.88 mmol).

Isopropenylmagnesium bromide: 4.1 mL (2.64 mmol).

Reaction time: 3 h

Yield: 97 mg, 47% (yellow solid).

**Data for compound 30:**

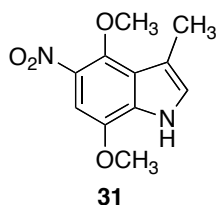
Melting point: 129-131 °C

Elemental analysis calc. (%) for  $C_{11}H_{12}N_2O_4$ : C 55.93, H 5.08, N 11.86; found: C 56.06, H 5.09, N 11.52.

IR (NaCl)  $\nu$ : 3396 (NH), 1515 and 1305 ( $NO_2$ ), 1223 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR (250 MHz  $CDCl_3$ ):  $\delta$  = 8.70 (s, 1H, NH), 7.17 (s, 1H,  $H_6$ ), 6.47-6.46 (m, 1H,  $H_3$ ), 4.01 (s, 1H,  $OCH_3$ ), 3.93 (s, 3H,  $OCH_3$ ), 2.46 (s, 3H,  $CH_3$ ) ppm.

$^{13}C$ -NMR (63 MHz,  $CDCl_3$ ):  $\delta$  = 143.7 ( $C_4$ ), 140.7 ( $C_7$ ), 136.4 ( $C_2$ ), 134.0 ( $C_5$ ), 130.5 ( $C_{7a}$ ), 122.8 ( $C_{3a}$ ), 100.6 ( $C_3$ ), 97.9 ( $C_6$ ), 61.8 ( $OCH_3$ ), 55.8 ( $OCH_3$ ), 13.4 ( $C_2-CH_3$ ) ppm.

**4,7-DIMETHOXY-3-METHYL-5-NITROINDOLE (31)****Reaction data:**

1,4-Dimethoxy-2,6-dinitrobenzene: 200 mg (0.88 mmol).

1-Propenylmagnesium bromide: 4 mL, (2.64 mmol).

Reaction time: 3 h

Yield: 125 mg , 60 % (yellow solid).

**Data for compound 31:**

Melting point: 108-110 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C 55.93, H 5.08, N 11.86; found: C 56.29, H 5.17, N 11.68.

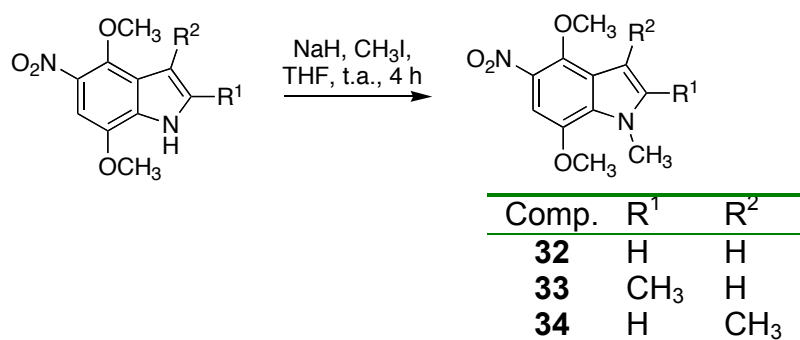
IR (NaCl)  $\nu$ : 3339 (NH), 1515 and 1315 (NO<sub>2</sub>), 1223 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 8.43 (s, 1H, NH), 7.27 (s, 1H, H<sub>6</sub>), 7.00 (s, 1H, H<sub>2</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 2.51 (s, 3H, CH<sub>3</sub>) ppm.

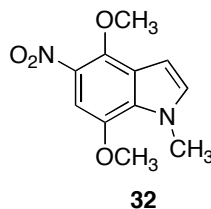
<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 146.1 (C<sub>4</sub>), 141.6 (C<sub>7</sub>), 134.4 (C<sub>5</sub>), 131.2 (C<sub>7a</sub>), 123.2 (C<sub>2</sub>), 122.2 (C<sub>3a</sub>), 114.9 (C<sub>3</sub>), 98.7 (C<sub>6</sub>), 63.4 (OCH<sub>3</sub>), 57.4 (OCH<sub>3</sub>), 11.3 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

## PREPARATION OF 1-METHYL-4,7-DIMETHOXY-5-NITROINDOLE DERIVATIVES 32-34

### General procedure:



A 60% suspension of sodium hydride in mineral oil (10 mmol) was washed twice with dry petroleum ether (10 mL), under an argon atmosphere. Dry THF (10 mL) was added, and the resulting suspension was cooled to 0 °C, while magnetically stirred. To this suspension was added a solution of the suitable 4,7-dimethoxy-5-nitroindole (5.0 mmol) in dry THF (50 mL), and the mixture was stirred at 0 °C for 1 h. Methyl iodide (11 mmol) was added and stirring was maintained for 4 h, allowing the reaction to reach room temperature. The reaction mixture was poured on ice (20 mL) and was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, affording the methylindoles **32-34**.

**4,7-DIMETHOXY-1-METHYL-5-NITROINDOLE (32)****Reaction data:**

4,7-Dimethoxy-5-nitroindole: 100 mg (0.45 mmol)

Sodium hydride (60% in mineral oil): 47.3 mg (0.9 mmol).

Methyl iodide: 141 mg (1 mmol).

Reaction time: 4 h

Yield: 92 mg, 90 % (pale brown solid).

**Data for compound 32:**

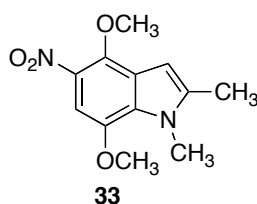
Melting point: 102-104 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C 55.93, H 5.08, N 11.86; found: C 55.60, H 5.23, N 12.02.

IR (NaCl)  $\nu$ : 1519 and 1324 (NO<sub>2</sub>), 1226 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.23 (s, 1H, H<sub>6</sub>), 7.0 (d, 1H,  $J$  = 3.1 Hz, H<sub>2</sub>), 6.70 (d, 1H,  $J$  = 3.1 Hz, H<sub>3</sub>), 4.08 (s, 3H, OCH<sub>3</sub>), 4.07 (s, 3H, N-CH<sub>3</sub>), 3.96 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 144.3 (C<sub>4</sub>), 143.2 (C<sub>7</sub>), 133.7 (C<sub>5</sub>), 131.3 (C<sub>2</sub>), 130.1 (C<sub>8</sub>), 124.1 (C<sub>9</sub>), 101.6 (C<sub>3</sub>), 98.5 (C<sub>6</sub>), 64.2 (OCH<sub>3</sub>), 55.9 (OCH<sub>3</sub>), 36.5 (N-CH<sub>3</sub>) ppm.

**4,7-DIMETHOXY-1,2-DIMETHYL-5-NITROINDOLE (33)****Reaction data:**

2-Methyl-4,7-dimethoxy-5-nitroindole: 200 mg (0.85 mmol).

Sodium hydride (60% in mineral oil): 94 mg (1.7 mmol).

Methyl iodide: 280 mg (2 mmol).

Reaction time: 4 h

Yield: 205 mg, 96 % (pale yellow solid).

**Data for compound 33:**

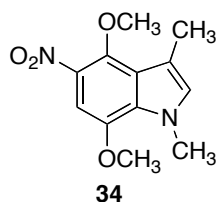
Melting point: 128-129 °C

Elemental analysis calc. (%) for  $C_{12}H_{14}N_2O_4$ : C 57.60, H 5.60, N 11.20; found: C 57.39, H 5.34, N 11.31.

IR (NaCl)  $\nu$ : 1524 and 1319 ( $NO_2$ ), 1220 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR (250 MHz  $CDCl_3$ ):  $\delta$  = 7.19 (s, 1H,  $H_6$ ), 6.50 (d, 1H,  $J$  = 0.9 Hz,  $H_3$ ), 4.06 (s, 3H,  $OCH_3$ ), 3.98 (s, 3H,  $OCH_3$ ), 3.97 (s, 3H,  $N-CH_3$ ), 2.42 (d, 3H,  $J$  = 0.9 Hz,  $C_2-CH_3$ ) ppm.

$^{13}C$ -NMR (63 MHz,  $CDCl_3$ ):  $\delta$  = 143.7 ( $C_4$ ), 142.7 ( $C_7$ ), 139.3 ( $C_2$ ), 133.4 ( $C_5$ ), 130.5 ( $C_{7a}$ ), 123.4 ( $C_{3a}$ ), 100.3 ( $C_3$ ), 98.3 ( $C_6$ ), 61.9 ( $OCH_3$ ), 56.2 ( $OCH_3$ ), 32.7 ( $N-CH_3$ ), 12.9 ( $C_2-CH_3$ ) ppm.

**1,3-DIMETHYL-4,7-DIMETHOXY-5-NITROINDOLE (34)****Reaction data:**

4,7-Dimethoxy-3-methyl-5-nitroindole: 230 mg (0.97 mmol).

Sodium hydride (60% in mineral oil): 118 mg (2 mmol).

Methyl iodide: 282 mg (2 mmol).

Reaction time: 4 h

Yield: 233 mg, 96 % (pale yellow solid).

**Data for compound 34:**

Melting point: 64-66 °C

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C 57.60, H 5.60, N 11.20; found: C 57.42, H 5.41, N 11.55.

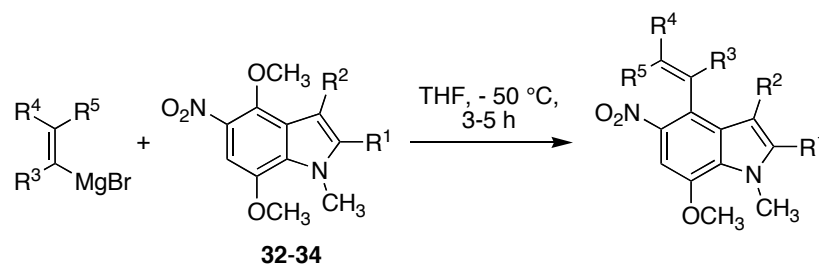
IR (NaCl)  $\nu$ : 1518 and 1323 (NO<sub>2</sub>), 1216 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.21 (s, 1H, H<sub>6</sub>), 6.73 (s, 1H, H<sub>2</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, N-CH<sub>3</sub>), 2.45 (d, 3H, *J* = 0.9 Hz, C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 146.2 (C<sub>4</sub>), 143.2 (C<sub>7</sub>), 133.4 (C<sub>5</sub>), 130.8 (C<sub>7a</sub>), 129.9 (C<sub>2</sub>), 123.4 (C<sub>3a</sub>), 113.4 (C<sub>3</sub>), 98.7 (C<sub>6</sub>), 63.1 (OCH<sub>3</sub>), 55.8 (OCH<sub>3</sub>), 36.1 (N-CH<sub>3</sub>), 11.2 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

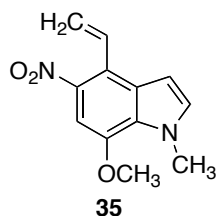
**PREPARATION OF 1-METHYL-7-METHOXY-5-NITRO-4-VINYLLINDOLE.  
DERIVATIVES 35-46**

**General procedure:**



Comp.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
35	H	H	H	H	H
36	H	H	H	H	CH <sub>3</sub>
37	H	H	H	CH <sub>3</sub>	CH <sub>3</sub>
38	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H
39	H	CH <sub>3</sub>	H	H	H
40	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>
41	H	CH <sub>3</sub>	H	CH <sub>3</sub>	CH <sub>3</sub>
42	CH <sub>3</sub>	H	H	H	H
43	CH <sub>3</sub>	H	H	H	CH <sub>3</sub>
44	CH <sub>3</sub>	H	H	CH <sub>3</sub>	CH <sub>3</sub>
45	CH <sub>3</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	H
46	H	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H

A commercial THF solution of the suitable Grignard reagent (1.5 mmol) was added dropwise to a cooled (−50 °C) solution of the adequate 4,7-dimethoxy-1-methyl-5-nitroindole (0.5 mmol) in dry THF (20 mL), under an inert atmosphere. The reaction mixture was stirred at −50 °C for 1-5 h, poured onto a saturated NH<sub>4</sub>Cl aqueous solution (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 5:1 petroleum ether-ethyl acetate.

**1-METHYL-7-METHOXY-5-NITRO-4-VINYLIINDOLE (35)****Reaction data:**

4,7-Dimethoxy-1-methyl-5-nitroindole: 50 mg (0.21 mmol).

Vinylmagnesium bromide: 0.84 mL (0.63 mmol).

Reaction time: 5 h

Yield: 47 mg, 95% (pale yellow solid).

**Data for compound 35:**

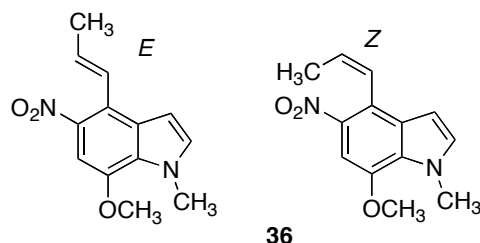
Melting point: 118-120 °C

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C 62.06, H 5.21, N 12.06; found: C 61.78, H 5.32, N 11.74.

IR (NaCl)  $\nu$ : 1513 and 1330 (NO<sub>2</sub>), 1215 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.41 (s, 1H, H<sub>6</sub>), 7.33-7.22 (m, 1H, HC=CH<sub>2</sub>), 7.06 (d, 1H, *J* = 3.0 Hz, H<sub>2</sub>), 6.79 (d, 1H, *J* = 3.0 Hz, H<sub>3</sub>), 5.69 (s, 1H, HC=CH<sub>2</sub>), 5.65-5.61 (m, 1H, HC=CH<sub>2</sub>), 4.11 (s, 3H, N-CH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 146.5 (C<sub>7</sub>), 140.2 (C<sub>5</sub>), 132.8 (HC=CH<sub>2</sub>), 132.1 (C<sub>2</sub>), 128.9 (C<sub>7a</sub>), 128.8 (C<sub>3a</sub>), 123.4 (C<sub>4</sub>), 119.3 (HC=CH<sub>2</sub>), 104.3 (C<sub>3</sub>), 98.9 (C<sub>6</sub>), 55.8 (N-CH<sub>3</sub>), 36.9 (OCH<sub>3</sub>) ppm.

**(E/Z)-7-Methoxy-1-methyl-5-nitro-4-(1-propenyl)indole (36)****Reaction data:**

4,7-Dimethoxy-1-methyl-5-nitroindole: 50 mg (0.21 mmol).

1-Propenylmagnesium bromide: 0.96 mL (0.63 mmol).

Reaction time: 5 h

Yield: 47 mg, 88% (pale yellow solid), corresponding to a *Z/E* = 3:1 mixture.

**Data for compound 36:**

Melting point: 93-95 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.80, H 6.00, N 11.04.

IR (NaCl)  $\nu$ : 1518 and 1320 (NO<sub>2</sub>), 1227 (OCH<sub>3</sub>) cm<sup>-1</sup>.

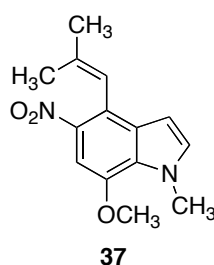
<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *Z* isomer:  $\delta$  = 7.47 (s, 1H, H<sub>6</sub>), 7.04 (d, 1H, *J* = 3.0 Hz, H<sub>2</sub>, partially overlapped with the same signal of the *E* isomer), 6.84 (dq, 1H, *J* = 11.2 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>), 6.47 (d, 1H, *J* = 3.0 Hz, H<sub>3</sub>), 5.98 (dq, 1H, *J* = 11.2 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 4.10 (s, 3H, N-CH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 1.50 (dd, 3H, *J* = 6.8 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>) ppm.

*E* isomer:  $\delta$  = 7.37 (s, 1H, H<sub>6</sub>), 7.01 (d, 1H, *J* = 3.0 Hz, H<sub>2</sub>, partially overlapped with the same signal of the *Z* isomer), 6.98 (dq, 1H, *J* = 15.8 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>, partially overlapped with the H<sub>2</sub> signal), 6.73 (d, 1H, *J* = 3.0 Hz, H<sub>3</sub>), 6.15 (dq, 1H, *J*

= 15.8 Hz and 6.5 Hz, HC=CH-CH<sub>3</sub>), 4.09 (s, 3H, N-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 2.02 (dd, 3H, *J* = 6.5 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): *Z* isomer: δ = 145.9 (C<sub>7</sub>), 140.3 (C<sub>5</sub>, overlapped with the same signal of the *E* isomer), 131.8 (C<sub>2</sub>), 131.2 (C<sub>7a</sub>, overlapped with the same signal of the *E* isomer), 129.2 (C<sub>3a</sub>), 127.4 (HC=CH-CH<sub>3</sub>), 125.3 (HC=CH-CH<sub>3</sub>), 122.1 (C<sub>4</sub>, overlapped with the same signal of the *E* isomer), 104.7 (C<sub>3</sub>), 98.8 (C<sub>6</sub>, overlapped with the same signal of the *E* isomer), 55.7 (OCH<sub>3</sub>, overlapped with the same signal of the *E* isomer), 36.6 (N-CH<sub>3</sub>), 15.1 (HC=CH-CH<sub>3</sub>) ppm.

*E* isomer: δ = 145.8 (C<sub>7</sub>), 140.3 (C<sub>5</sub>, overlapped with the same signal of the *Z* isomer), 131.7 (C<sub>2</sub>), 131.2 (C<sub>7a</sub>, overlapped with the same signal of the *Z* isomer), 129.0 (C<sub>3a</sub>), 128.0 (HC=CH-CH<sub>3</sub>), 126.2 (HC=CH-CH<sub>3</sub>), 122.1 (C<sub>4</sub>, overlapped with the same signal of the *Z* isomer), 104.4 (C<sub>3</sub>), 98.8 (C<sub>6</sub>, overlapped with the same signal of the *Z* isomer), 55.7 (OCH<sub>3</sub>, overlapped with the same signal of the *Z* isomer), 36.7 (N-CH<sub>3</sub>), 18.9 (HC=CH-CH<sub>3</sub>) ppm.

**7-METHOXY-1-METHYL-4-(2-METHYL-1-PROPENYL)-5-NITROINDOLE (37)****Reaction data:**

4,7-Dimethoxy-1-methyl-5-nitroindole: 50 mg (0.21 mmol).

2-Methyl-1-propenylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 4 h

Yield: 52 mg, 96% (pale yellow solid).

**Data for compound 37:**

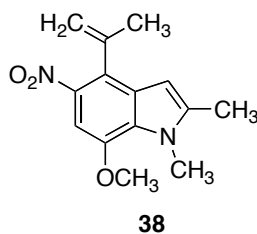
Melting point: 116-118 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.76; found: C 64.60, H 6.61, N 10.33.

IR (NaCl)  $\nu$ : 1518 and 1320 (NO<sub>2</sub>), 1227 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.41 (s, 1H, H<sub>6</sub>), 7.03 (d, 1H,  $J$  = 3.0 Hz, H<sub>2</sub>), 6.58-6.56 (m, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 6.43 (d, 1H,  $J$  = 3.0 Hz, H<sub>3</sub>), 4.09 (s, 3H, N-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 2.01 (d, 3H,  $J$  = 1.3 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.48 (d, 3H,  $J$  = 1.0 Hz, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.7 (C<sub>7</sub>), 14.5 (C<sub>5</sub>), 136.1 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 131.6 (C<sub>2</sub>), 129.7 (C<sub>7a</sub>), 128.0 (C<sub>3a</sub>), 123.2 (C<sub>4</sub>), 119.9 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 104.7 (C<sub>3</sub>), 98.8 (C<sub>6</sub>), 55.8 (OCH<sub>3</sub>), 36.6 (N-CH<sub>3</sub>), 25.6 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 20.1 (HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

**4-ISOPROPENYL-7-METHOXY-1,2-DIMETHYL-5-NITROINDOLE (38)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

Isopropenylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 5 h

Yield: 36 mg, 70% (pale yellow solid).

**Data for compound 38:**

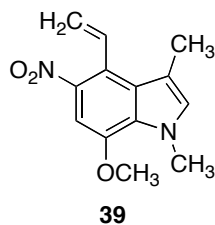
Melting point: 38-40 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.60, H 6.20, N 10.76; found: C 65.03, H 5.95, N 11.00.

IR (NaCl)  $\nu$ : 1518 and 1320 (NO<sub>2</sub>), 1260 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.36 (s, 1H, H<sub>6</sub>), 6.36 (d, 1H,  $J$  = 0.8 Hz, H<sub>3</sub>), 5.32-5.30 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 4.90-4.88 (m, 1H, H<sub>2</sub>C=C-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 4.00 (s, 3H, N-CH<sub>3</sub>), 2.41 (d, 3H,  $J$  = 0.8 Hz, C<sub>2</sub>-CH<sub>3</sub>), 2.17-2.16 (m, 3H, H<sub>2</sub>C=C-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.2 (C<sub>7</sub>), 142.7 (C<sub>2</sub>), 142.2 (H<sub>2</sub>C=C-CH<sub>3</sub>), 139.9 (C<sub>2</sub>), 131.9 (C<sub>7a</sub>), 128.3 (C<sub>3a</sub>), 127.0 (C<sub>4</sub>), 113.9 (H<sub>2</sub>C=C-CH<sub>3</sub>), 102.6 (C<sub>3</sub>), 98.4 (C<sub>6</sub>), 55.7 (OCH<sub>3</sub>), 30.9 (NCH<sub>3</sub>), 23.3 (H<sub>2</sub>C=C-CH<sub>3</sub>), 12.8 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**1,3-DIMETHYL-7-METHOXY-5-NITRO-4-VINYLINDOLE (39)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

Vinylmagnesium bromide: 0.8 mL (0.63 mmol).

Reaction time: 3 h

Yield: 42 mg, 90% (yellow solid).

**Data for compound 39:**

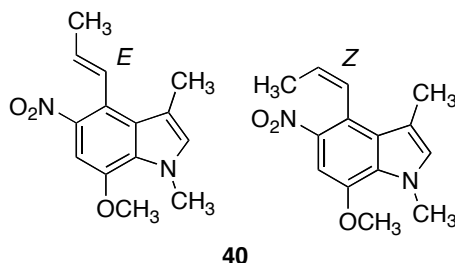
Melting point: 113-115 °C

Elemental analysis calc. (%) for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 63.41, H 5.69, N 11.38; found: C 63.89, H 6.06, N 11.04.

IR (NaCl)  $\nu$ : 1516 and 1322 (NO<sub>2</sub>), 1220 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.30 (dd, 1H,  $J$  = 17.6 and 11.2 Hz HC=CH<sub>2</sub>), 7.28 (s, 1H, H<sub>6</sub>), 6.81 (br s, 1H, H<sub>2</sub>), 5.55 (dd, 1H,  $J$  = 11.2 Hz and 1.7 Hz, HC=CH<sub>2</sub>), 5.21 (dd, 1H,  $J$  = 17.6 and 1.7 Hz, HC=CH<sub>2</sub>), 4.02 (s, 3H, N-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 2.28 (d, 3H,  $J$  = 0.8 Hz, C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.9 (C<sub>7</sub>), 140.5 (C<sub>5</sub>), 132.2 (HC=CH<sub>2</sub>), 131.3 (C<sub>2</sub>), 128.9 (C<sub>7a</sub>), 126.9 (C<sub>3a</sub>), 124.3 (C<sub>4</sub>), 119.3 (HC=CH<sub>2</sub>), 114.0 (C<sub>3</sub>), 98.6 (C<sub>6</sub>), 55.7 (N-CH<sub>3</sub>), 36.4 (OCH<sub>3</sub>), 13.9 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**(E/Z) 7-METHOXY-1,3-DIMETHYL-5-NITRO-4-(1-PROPENYL)INDOLE (40)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

1-Propenylmagnesium bromide: 0.8 mL (0.63 mmol).

Reaction time: 3 h

Yield: 42 mg, 90% (yellow solid), corresponding to a *Z/E* = 3/1 mixture.

**Data for compound 40:**

Melting point: 89-91 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.41, H 6.15, N 10.77; found: C 64.09, H 6.29, N 10.46.

IR (NaCl)  $\nu$ : 1518 and 1320 (NO<sub>2</sub>), 1227 (OCH<sub>3</sub>) cm<sup>-1</sup>.

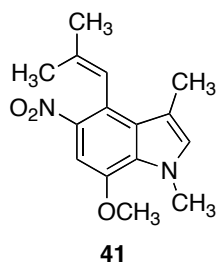
<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *Z* isomer:  $\delta$  = 7.30 (s, 1H, H<sub>6</sub>), 6.86 (dq, 1H, *J* = 11.2 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>, partially overlapped with the same signal of the *E* isomer), 6.79 (br s, 1H, H<sub>2</sub>, overlapped with the same signal of the *E* isomer), 5.90 (dq, 1H, *J* = 11.2 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 4.02 (s, 3H, N-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 2.29 (d, 3H, *J* = 0.8 Hz, C<sub>3</sub>-CH<sub>3</sub>), 1.40 (dd, 3H, *J* = 6.8 Hz and *J* = 1.5 Hz, HC=CH-CH<sub>3</sub>) ppm.

*E* isomer:  $\delta$  = 7.25 (s, 1H, H<sub>6</sub>), 6.91 (dq, 1H, *J* = 15.8 Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>, partially overlapped with the same signal of the *Z* isomer), 6.79 (br s, 1H, H<sub>2</sub>,

overlapped with the same signal of the *Z* isomer), 5.59 (dq, 1H,  $J = 15.8$  Hz and 6.5 Hz, HC=CH-CH<sub>3</sub>), 4.00 (s, 3H, N-CH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 2.25 (d, 3H,  $J = 0.8$  Hz, C<sub>3</sub>-CH<sub>3</sub>), 1.94 (dd, 3H,  $J = 6.5$  Hz and 1.7 Hz, HC=CH-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): *Z* isomer:  $\delta = 145.7$  (C<sub>7</sub>), 141.1 (C<sub>5</sub>), 130.9 (C<sub>2</sub>), 128.6 (C<sub>7a</sub>), 127.7 (HC=CH-CH<sub>3</sub>), 127.3 (C<sub>3a</sub>), 125.3 (HC=CH-CH<sub>3</sub>), 122.2 (C<sub>4</sub>), 114.3 (C<sub>3</sub>), 98.5 (C<sub>6</sub>, overlapped with the same signal of the *E* isomer), 55.6 (OCH<sub>3</sub>, overlapped with the same signal of the *E* isomer), 36.3 (N-CH<sub>3</sub>, overlapped with the same signal of the *E* isomer), 14.1 (HC=CH-CH<sub>3</sub>), 12.5 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

*E* isomer:  $\delta = 145.5$  (C<sub>7</sub>), 140.9 (C<sub>5</sub>), 131.0 (HC=CH-CH<sub>3</sub>), 130.6 (C<sub>2</sub>), 130.1 (C<sub>7a</sub>), 128.9 (C<sub>3a</sub>), 125.1 (HC=CH-CH<sub>3</sub>), 124.9 (C<sub>4</sub>), 114.3 (C<sub>3</sub>), 98.5 (C<sub>6</sub>, overlapped with the same signal of the *Z* isomer), 55.6 (OCH<sub>3</sub>, overlapped with the same signal of the *Z* isomer), 36.3 (N-CH<sub>3</sub>, overlapped with the same signal of the *Z* isomer), 18.3 (HC=CH-CH<sub>3</sub>), 13.8 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**7-METHOXY-1,3-DIMETHYL-4-(2-METHYL-1-PROPENYL)- 5-NITROINDOLE (41)****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

2-Methyl-1-propenylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 3 h

Yield: 51 mg, 94% (yellow solid).

**Data for compound 41:**

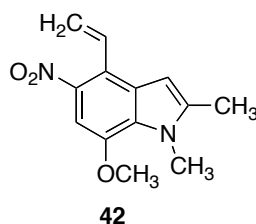
Melting point: 71-73 °C

Elemental analysis calc. (%) for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 65.69, H, 6.57, N 10.21; found: C 65.60, H 6.61, N 10.02.

IR (NaCl)  $\nu$ : 1520 and 1330 (NO<sub>2</sub>), 1227 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.27 (s, 1H, H<sub>6</sub>), 6.77 (br s, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 6.55 (br s, 1H, H<sub>2</sub>), 4.01 (s, 3H, N-CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 2.23 (s, 3H, C<sub>3</sub>-CH<sub>3</sub>), 1.94 (s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.36 (s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.6 (C<sub>7</sub>), 141.2 (C<sub>5</sub>), 135.5 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 130.7 (C<sub>2</sub>), 128.6 (C<sub>7a</sub>), 127.9 (C<sub>3a</sub>), 123.6 (C<sub>4</sub>), 119.8 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 114.6 (C<sub>3</sub>), 98.5 (C<sub>6</sub>), 57.0 (OCH<sub>3</sub>), 36.3 (N-CH<sub>3</sub>), 25.0 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 19.1 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 12.5 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**7-METHOXY-1,2-DIMETHYL-5-NITRO-4-VINYLINDOLE (42)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

Vinylmagnesium bromide: 0.8 mL (0.63 mmol).

Reaction time: 3 h

Yield: 47 mg, 95% (yellow solid).

**Data for compound 42:**

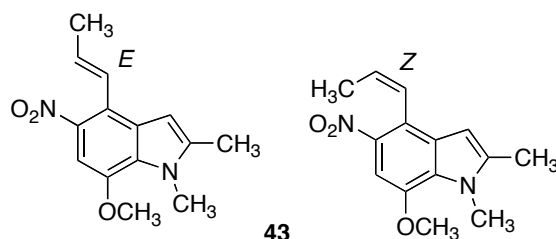
Melting point: 118-120 °C

Elemental analysis calc. (%) for  $C_{13}H_{14}N_2O_3$ : C 63.41, H 5.69, N 11.38; found: C, 63.08, H 5.42, N 11.64.

IR (NaCl)  $\nu$ : 1515 and 1315 ( $NO_2$ ), 1297 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR (250 MHz  $CDCl_3$ ):  $\delta$  = 7.39 (s, 1H,  $H_6$ ), 7.33-7.22 (m, 1H,  $HC=CH_2$ ), 6.58 (s, 1H,  $H_3$ ), 5.66 (s, 1H,  $HC=CH_2$ ), 5.62-5.59 (m, 1H,  $HC=CH_2$ ), 4.02 and 4.01 (2s, 6H, N- $CH_3$  and  $OCH_3$ ), 2.42 (s, 3H,  $C_2-CH_3$ ) ppm.

$^{13}C$ -NMR (63 MHz,  $CDCl_3$ ):  $\delta$  = 145.6 ( $C_7$ ), 139.9 ( $C_5$ ), 135.7 ( $HC=CH_2$ ), 133.2 ( $C_2$ ), 129.5 ( $C_{7a}$ ), 127.9 ( $C_{3a}$ ), 124.2 ( $C_4$ ), 118.9 ( $HC=CH_2$ ), 103.7 ( $C_3$ ), 98.8 ( $C_6$ ), 56.1 ( $OCH_3$ ) 32.8 (N- $CH_3$ ), 12.9 ( $C_2-CH_3$ ) ppm.

**(E/Z) 1,2-DIMETHYL-7-METHOXY-5-NITRO-4-(1-PROPENYL)INDOLE (43)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

1-Propenylmagnesium bromide: 0.8 mL (0.63 mmol).

Reaction time: 5 h

Yield: 41 mg, 91% (yellow solid), corresponding to a *Z/E* = 3/1 mixture.

**Data for compound 43:**

Melting point: 97-99 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C 64.61, H 6.15, N 10.77; found: C 65.00, H 6.53, N 10.46.

IR (NaCl)  $\nu$ : 1518 and 1318 (NO<sub>2</sub>), 1220 (OCH<sub>3</sub>) cm<sup>-1</sup>.

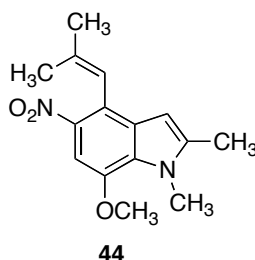
<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>): *Z* isomer:  $\delta$  = 7.44 (s, 1H, H<sub>6</sub>), 6.80 (dq, 1H, *J* = 11.2 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>), 6.26 (d, 1H, *J* = 0.8 Hz, H<sub>3</sub>), 5.95 (dq, 1H, *J* = 11.2 Hz and 6.8 Hz, HC=CH-CH<sub>3</sub>), 4.01-3.99 (m, 6H, OCH<sub>3</sub> and N-CH<sub>3</sub>, overlapped with the same signal of the *E* isomer), 2.42 (d, 3H, *J* = 0.8 Hz, C<sub>2</sub>-CH<sub>3</sub>, overlapped with the same signal of the *E* isomer), 1.50 (dd, 3H, *J* = 6.8 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>) ppm.

*E* isomer:  $\delta$  = 7.35 (s, 1H, H<sub>6</sub>), 6.94 (dq, 1H, *J* = 15.8 Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>), 6.52 (d, 1H, *J* = 0.8 Hz, H<sub>3</sub>), 6.10 (dq, 1H, *J* = 15.8 Hz and 6.5 Hz HC=CH-CH<sub>3</sub>), 4.01-3.99 (m, 6H, OCH<sub>3</sub> and N-CH<sub>3</sub>, overlapped with the same signal of the *Z*

isomer), 2.42 (d, 3H,  $J = 0.8$  Hz, C<sub>2</sub>-CH<sub>3</sub>, overlapped with the same signal of the Z isomer), 2.02 (dd, 3H,  $J = 6.5$  Hz and 1.5 Hz, HC=CH-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>): Z isomer:  $\delta = 145.2$  (C<sub>7</sub>), 139.9 (C<sub>5</sub>), 139.5 (C<sub>2</sub> and C<sub>7a</sub>), 128.3 (C<sub>3a</sub>), 127.1 (HC=CH-CH<sub>3</sub>), 125.5 (HC=CH-CH<sub>3</sub>), 121.0 (C<sub>4</sub>), 103.5 (C<sub>3</sub>), 98.6 (C<sub>6</sub>, overlapped with the same signal of the E isomer), 55.7 (OCH<sub>3</sub>, overlapped with the same signal of the E isomer), 32.7 (N-CH<sub>3</sub>, overlapped with the same signal of the E isomer), 15.1 (HC=CH-CH<sub>3</sub>), 12.9 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

E isomer:  $\delta = 145.1$  (C<sub>7</sub>), 139.4 (C<sub>5</sub>), 135.2 (C<sub>2</sub>), 130.8 (HC=CH-CH<sub>3</sub>), 128.4 (C<sub>3a</sub>), 126.3 (HC=CH-CH<sub>3</sub>), 122.4 (C<sub>4</sub>), 103.3 (C<sub>3</sub>), 98.6 (C<sub>6</sub>, overlapped with the same signal of the Z isomer), 55.7 (OCH<sub>3</sub>, overlapped with the same signal of the Z isomer), 32.7 (N-CH<sub>3</sub>, overlapped with the same signal of the Z isomer), 18.9 (HC=CH-CH<sub>3</sub>), 12.8 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**7-METHOXY-1,2-DIMETHYL-4-(2-METHYL-1-PROPENYL)-5-NITROINDOLE (44)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

2-Methyl-1-propenylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 3 h

Yield: 51 mg, 90% (yellow solid).

**Data for compound 44:**

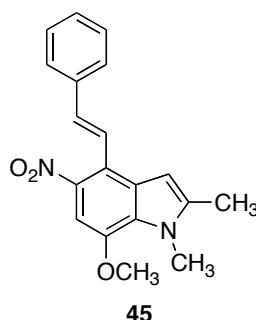
Melting point: 124-126 °C

Elemental analysis calc. (%) for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 65.69, H 6.56, N 10.21; found: C 65.32, H 6.91, N 10.45.

IR (NaCl)  $\nu$ : 1518 (NO<sub>2</sub>), 1297 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.39 (s, 1H, H<sub>6</sub>), 6.55 (br s, 1H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 6.22 (s, 1H, H<sub>3</sub>), 4.00 (m, 6H, OCH<sub>3</sub> and N-CH<sub>3</sub>), 2.41 (s, 3H, C<sub>2</sub>-CH<sub>3</sub>), 2.01 (s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>), 1.47 (s, 3H, HC=C(CH<sub>3</sub>)<sub>2</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.0 (C<sub>7</sub>), 140.2 (C<sub>5</sub>), 139.3 (C<sub>2</sub>), 135.7 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 128.8 (C<sub>7a</sub>), 128.3 (C<sub>3a</sub>), 122.1 (C<sub>4</sub>), 120.0 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 103.5 (C<sub>3</sub>), 98.5 (C<sub>6</sub>), 55.7 (OCH<sub>3</sub>), 32.7 (N-CH<sub>3</sub>), 25.5 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 20.1 (HC=C(CH<sub>3</sub>)<sub>2</sub>), 12.9 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**7-METHOXY-1,2-DIMETHYL-5-NITRO-4-STYRYLINDOLE (45)****Reaction data:**

4,7-Dimethoxy-1,2-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

Styrylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 4 h

Yield: 51 mg, 90% (yellow solid).

**Data for compound 45:**

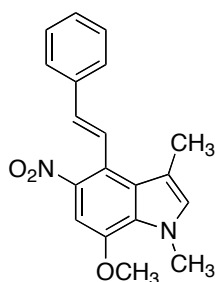
Melting point: 136-138°C

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.80, H 5.60, N 8.69; found: C 71.40, H 5.61, N 8.47.

IR (NaCl)  $\nu$ : 1514 and 1299 (NO<sub>2</sub> and OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.73 (d, 1H, -CH=CH-C<sub>6</sub>H<sub>5</sub>,  $J$  = 16.3 Hz), 7.64-7.60 (m, 2H, H<sub>2'</sub> and H<sub>6'</sub>), 7.45 (s, 1H, H<sub>6</sub>), 7.46-7.33 (m, 2H, H<sub>3'</sub> H<sub>4'</sub> and H<sub>5'</sub>), 7.01 (d, 1H, -CH=CH-C<sub>6</sub>H<sub>5</sub>,  $J$  = 16.3 Hz), 6.64 (d, 1H, H<sub>3</sub>,  $J$  = 0.8 Hz), 4.03 (s, 3H, OCH<sub>3</sub>), 4.02 (s, 3H, N-CH<sub>3</sub>), 2.43 (d, 3H, C<sub>2</sub>-CH<sub>3</sub>,  $J$  = 0.8 Hz) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 145.4 (C<sub>7</sub>), 140.0 (C<sub>5</sub>), 139.9 (C<sub>2</sub>), 137.3 (C<sub>1'</sub>), 133.6 (-CH=CH-C<sub>6</sub>H<sub>5</sub>), 129.0 (C<sub>7a</sub>), 128.5 (C<sub>3'</sub> and C<sub>5'</sub>), 127.9 (C<sub>3a</sub>), 127.8 (C<sub>4'</sub>), 126.6 (C<sub>2'</sub> and C<sub>6'</sub>), 124.8 (-CH=CH-C<sub>6</sub>H<sub>5</sub>), 121.8 (C<sub>4</sub>), 103.3 (C<sub>3</sub>), 98.9 (C<sub>6</sub>), 55.7 (OCH<sub>3</sub>), 32.8 (N-CH<sub>3</sub>), 12.90 (C<sub>2</sub>-CH<sub>3</sub>) ppm.

**7-METHOXY-1,3-DIMETHYL-5-NITRO-4-STYRYLINDOLE(46)****46****Reaction data:**

4,7-Dimethoxy-1,3-dimethyl-5-nitroindole: 50 mg (0.21 mmol).

Styrylmagnesium bromide: 1 mL (0.63 mmol).

Reaction time: 4 h

Yield: 51 mg, 90% (yellow solid).

**Data for compound 46:**

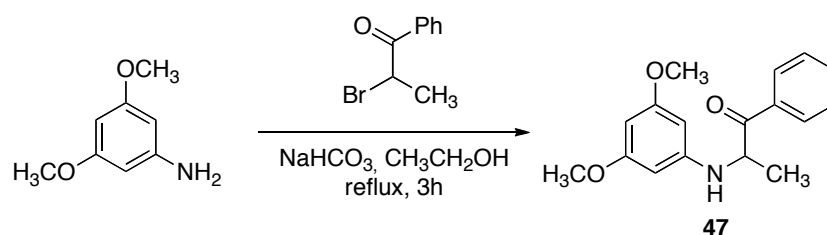
Melting point: 135-137 °C

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.80, H 5.60, N 8.69; found: C 70.80, H 5.62, N 8.36.

IR (NaCl)  $\nu$ : 1517 and 1319 (NO<sub>2</sub>), 1229 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.68 (d, 1H, -CH=CH-C<sub>6</sub>H<sub>5</sub>,  $J$  = 16.3 Hz), 7.57-7.54 (m, 2H, H<sub>2'</sub> and H<sub>6'</sub>), 7.44-7.30 (m, 4H, H<sub>6</sub>, H<sub>3'</sub>, H<sub>4'</sub> and H<sub>5'</sub>), 6.84 (br s, 1H, H<sub>2</sub>), 6.50 (d, 1H, -CH=CH-C<sub>6</sub>H<sub>5</sub>,  $J$  = 16.3 Hz), 4.05 (s, 3H, N-CH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 2.26 (d, 3H,  $J$  = 0.8 Hz, C<sub>3</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 146.0 (C<sub>7</sub>), 140.8 (C<sub>5</sub>), 137.0 (C<sub>1'</sub>), 134.2 (-CH=CH-C<sub>6</sub>H<sub>5</sub>), 131.5 (C<sub>2</sub>), 129.2 (C<sub>7a</sub>), 128.6 (C<sub>3'</sub> and C<sub>5'</sub>), 127.7 (C<sub>4'</sub>), 127.6 (C<sub>3a</sub>), 126.5 (C<sub>2'</sub> and C<sub>6'</sub>), 124.0 (C<sub>4</sub>), 123.7 (-CH=CH-C<sub>6</sub>H<sub>5</sub>), 114.3 (C<sub>3</sub>), 98.9 (C<sub>6</sub>), 55.8 (OCH<sub>3</sub>), 36.5 (N-CH<sub>3</sub>), 14.1 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**$\alpha$ -(3,5-DIMETHOXYPHENYLAMINO)PROPIOFENONE (47)**

To a solution of 3,5-dimethoxyaniline (3 g, 19.6 mmol) in ethanol (50 mL), were added 2-bromo-1-phenylpropanone (4.17 g, 19.6 mmol) and  $\text{NaHCO}_3$  (3.3 g, 39.2 mmol). The mixture was stirred at reflux for 3 h. After this time the reaction was cooled in an ice bath and the yellow solid that precipitated was filtered and washed with water (30 mL), affording 5.19 g (93%) of the expected compound **47**.

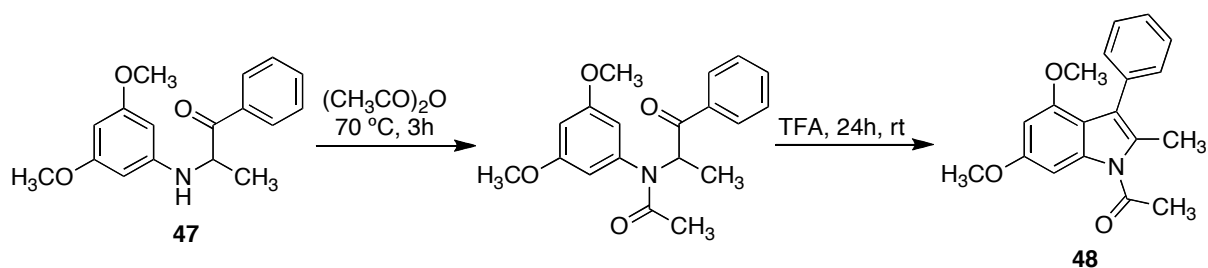
Melting point: 118-119 °C

Elemental analysis calc. (%) for  $\text{C}_{17}\text{H}_{19}\text{NO}_3$ : C 71.57, H 6.66, N 4.91; found: C 71.25, H 6.46, N 4.82.

IR (NaCl)  $\nu$ : 3379 (NH); 1613 (CO); 1203 ( $\text{OCH}_3$ )  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $\delta$ : 8.05-8.02 (m, 2H, Ar-H), 7.63-7.62 (m, 1H, Ar-H), 7.57-7.51 (m, 2H, Ar-H), 5.93-5.89 (m, 3H,  $\text{H}_2$ ,  $\text{H}_4$ ,  $\text{H}_6$ ), 5.12 (q, 1H,  $J = 14.5$  Hz y  $J = 7.2$  Hz, HN-CH- $\text{CH}_3$ COPh), 4.81 (d, 1H,  $J = 7.7$  Hz, NH), 3.77 (s, 6H,  $\text{OCH}_3$ ), 1.50 (d, 3H,  $J = 6.9$  Hz, HN-CH- $\text{CH}_3$ COPh) ppm.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 63 MHz)  $\delta$ : 200.4 (C=O), 161.6 ( $\text{C}_3$  and  $\text{C}_5$ ), 148.3 ( $\text{C}_1$ ), 134.5 (Ar-CPh), 133.7 (Ar-CH), 128.9 (Ar-CH), 128.5 (Ar-CH), 92.2 ( $\text{C}_2$  and  $\text{C}_6$ ), 89.9 ( $\text{C}_4$ ), 55.2 (2  $\text{OCH}_3$ ), 53.2 (HN-CH- $\text{CH}_3$ COPh), 18.6 (HN-CH- $\text{CH}_3$ COPh) ppm.

**1-ACETYL-4,6-DIMETHOXY-2-METHYL-3-PHENYLINDOLE (48)**

A suspension of compound **47** (4 g, 16.13 mmol) in acetic anhydride (30 mL) was heated at  $70\text{ }^\circ\text{C}$  for 3 h. Then, the mixture was cooled in an ice bath and water (1 mL) was added dropwise, heated at  $50\text{--}60\text{ }^\circ\text{C}$  a few minutes and, then, cooled at room temperature. The reaction was extracted with ethyl acetate (3 x 30 mL), the combined organic layers were washed with water to neutral pH and washed with saturated  $\text{NaHCO}_3$  solution and brine, subsequently. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Trifluoroacetic acid (100 mL) was added directly to the residue and the mixture was stirred at room temperature for 24 h. After this time, ice water was added and the precipitate was filtered and washed with water (20 mL). The product was recrystallized in EtOH, giving 3.5 g (70%) of compound **48** as a grey solid.

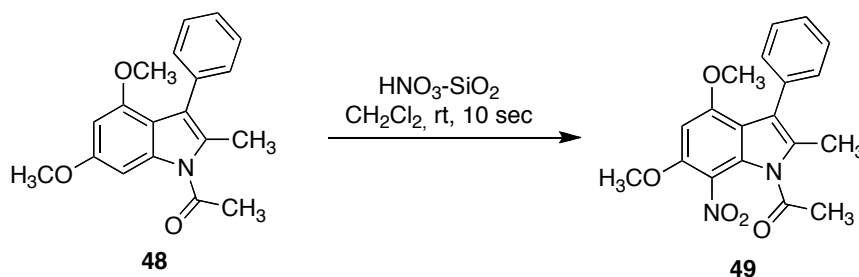
Melting point:  $146\text{--}148\text{ }^\circ\text{C}$ .

Elemental analysis calc. (%) for  $\text{C}_{19}\text{H}_{19}\text{NO}_3$ : C 73.78, H 6.14, N 4.53; found: C 73.42, H 5.91, N 4.42.

IR (NaCl):  $\nu$ : 1700 (CO); 1287 ( $\text{OCH}_3$ )  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz)  $^{\text{TM}}$ : 7.48–7.35 (m, 6H,  $\text{H}_7$ , Ar-H), 6.38 (d,  $J = 1.9\text{ Hz}$ , 1H,  $\text{H}_5$ ), 3.91 (s, 3H,  $\text{OCH}_3$ ), 3.64 (s, 3H,  $\text{OCH}_3$ ), 2.76 (s, 3H,  $\text{CO-CH}_3$ ), 2.46 (s, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ , 63 MHz)  $^{\text{TM}}$ : 171.1 (C=O), 158.8 ( $\text{C}_6$ ), 153.4 ( $\text{C}_4$ ), 137.7 ( $\text{C}_{7a}$ ), 135.0 (Ar-C), 130.9 (Ar-CH), 129.6 ( $\text{C}_2$ ), 127.2 (Ar-CH), 126.7 (Ar-CH), 122.1 ( $\text{C}_{3a}$ ), 112.9 ( $\text{C}_3$ ), 95.1 ( $\text{C}_7$ ), 92.7 ( $\text{C}_5$ ), 55.8 ( $\text{OCH}_3$ ), 55.3 ( $\text{OCH}_3$ ), 27.5 (CO- $\text{CH}_3$ ), 15.1 ( $\text{CH}_3$ ) ppm.

**1-ACETYL-4,6-DIMETHOXY-2-METHYL-7-NITRO-3-PHENYLINDOLE (49)**

To a solution of 1-acetyl-4,6-dimethoxy-2-methyl-3-phenylindole **48** (1 g, 3.24 mmol) in dichloromethane (60 mL) was added nitric acid supported on silica gel (1 g) and stirred at room temperature for 10 sec. The mixture was filtered and the solvent was concentrated *in vacuo*. The residue was recrystallized in ethanol to give 980 mg (86%) of **49** as a green solid.

*Preparation of nitric acid supported on silica gel:* A suspension of silica gel (60 g) in 65% nitric acid (140 mL) was stirred at room temperature for 2 h. The suspension was filtered, the silica gel allowed to dry for 1 week and then, stored in an airtight flask. Nitric acid content is about 20%.

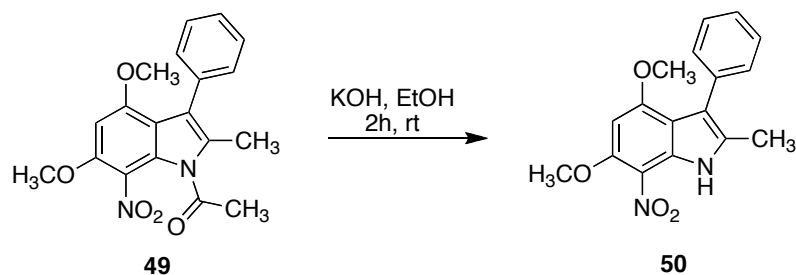
Melting point: 190-191 °C

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C 64.40, H 5.08, N 7.90; found: C 64.86, H 5.26, N 7.37.

IR (NaCl):  $\nu$  = 1734 (CO); 1557 y 1320 (NO<sub>2</sub>); 1269 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz):  $\tau^m$  = 7.43-7.31 (m, 5H, Ar-H), 6.35 (s, 1H, H<sub>5</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 2.62 (s, 3H, CO-CH<sub>3</sub>), 2.40 (s, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz):  $\tau^m$  = 171.7 (C=O), 156.9 (C<sub>4</sub>), 152.2 (C<sub>6</sub>), 134.2 (C<sub>2</sub>), 131.4 (C<sub>7a</sub>), 130.8 (Ar-CH), 129.2 (Ar-C), 127.5 (Ar-CH), 126.8 (Ar-CH), 122.2 (C<sub>3a</sub>), 119.0 (C<sub>3</sub>), 114.3 (C<sub>7</sub>), 90.7 (C<sub>5</sub>), 57.5 (OCH<sub>3</sub>), 55.6 (OCH<sub>3</sub>), 26.7 (CO-CH<sub>3</sub>), 13.4 (CH<sub>3</sub>) ppm.

**4,6-DIMETHOXY-2-METHYL-7-NITRO-3-PHENYLINDOLE (50)**

To a solution of compound **49** (700 mg, 2 mmol) in ethanol (50 mL) potassium hydroxide (1.12 g, 20 mmol) was added and was stirred at room temperature for 2 h. The orange precipitate was filtered to afford 550 mg (88%) of the desired compound **50**.

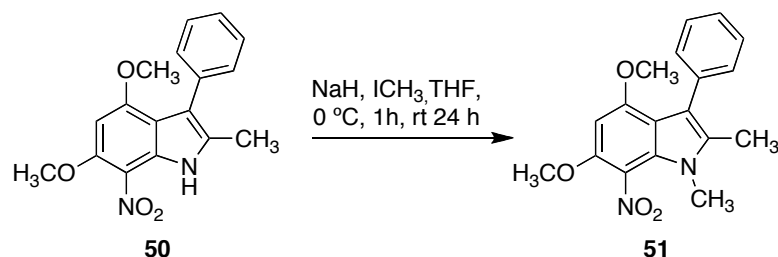
Melting point: 218-220 °C

Elemental analysis calc. (%) for  $C_{17}H_{16}N_2O_4$ : C 65.38, H 5.16, N 8.97; found: C 65.06, H 5.26, N 8.57.

IR (NaCl):  $\nu = 3367$  (NH); 1569 y 1325 ( $NO_2$ ); 1225 ( $OCH_3$ )  $cm^{-1}$ .

$^1H$ -NMR ( $CDCl_3$ , 250 MHz):  $\tau^M = 10.10$  (s, 1H, NH), 7.41-7.31 (m, 5H, Ar-H), 6.23 (s, 1H, H<sub>5</sub>), 4.09 (s, 3H,  $OCH_3$ ), 3.86 (s, 3H,  $OCH_3$ ), 2.41 (s, 3H,  $CH_3$ ) ppm.

$^{13}C$ -NMR ( $CDCl_3$ , 63 MHz):  $\tau^M = 159.7$  ( $C_4$ ), 156.0 ( $C_6$ ), 134.6 (Ar-C), 131.9 ( $C_2$ ), 131.0 ( $C_{7a}$ ), 130.7 (Ar-CH), 127.4 (Ar-CH), 126.2 (Ar-CH), 119.6 ( $C_3$ ), 115.3 ( $C_{3a}$ ), 112.9 ( $C_7$ ), 87.9 ( $C_5$ ), 57.2 ( $OCH_3$ ), 55.6 ( $OCH_3$ ), 12.0 ( $CH_3$ ) ppm.

**4,6-DIMETHOXY-1,2-DIMETHYL-7-NITRO-3-PHENYLINDOLE (51)**

A solution of compound **50** (100 mg, 0.32 mmol) in anhydrous THF (15 mL) was added to a suspension of sodium hydride (38 mg, 0.64 mmol) in anhydrous THF (5 mL) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 1 h. After this time methyl iodide (99 mg, 0.7 mmol) was added and the stirring was maintained at room temperature for 24 h. After cooling in ice bath, water (20 mL) was added and the mixture was then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 90 mg (86%) of the expected compound **51** as a pale brown solid.

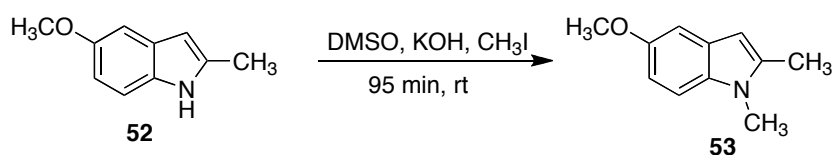
Punto de fusión: 142-144 °C

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 66.25, H 5.52, N 8.59; found: C 65.91, H 5.94, N 8.46.

IR (NaCl):  $\nu$  = 1516 y 1316 (NO<sub>2</sub>); 1217 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) <sup>TM</sup>: 7.42-7.32 (m, 5H, C<sub>6</sub>H<sub>5</sub>), 6.24 (s, 1H, H<sub>5</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.57 (s, 3H, N-CH<sub>3</sub>), 2.32 (s, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz) <sup>TM</sup>: 155.6 (C<sub>4</sub>), 149.7 (C<sub>6</sub>), 135.4 (C<sub>1'</sub>), 134.0 (C<sub>2</sub>), 131.0 (Ar-CH), 129.0 (C<sub>7a</sub>), 127.2 (Ar-CH), 126.0 (Ar-CH), 122.5 (C<sub>7</sub>), 114.5 (C<sub>3</sub>), 112.9 (C<sub>3a</sub>), 87.6 (C<sub>5</sub>), 57.6 (OCH<sub>3</sub>), 55.4 (OCH<sub>3</sub>), 31.3 (N-CH<sub>3</sub>), 11.0 (CH<sub>3</sub>) ppm.

**5-METHOXY-1,2-DIMETHYLINDOLE (53)**

To a solution of KOH (909 mg, 16.24 mmol) in DMSO (10 mL), stirred at room temperature for 5 min, was added a solution of compound **52** (654 mg, 4.06 mmol) in DMSO (15 mL). The mixture was stirred at room temperature for 45 min and, then, dimethyl sulfate (1.02 g, 8.12 mmol) was added and the stirring was maintained at room temperature for another 45 min. The reaction was poured onto water (20 mL) and extracted with ethyl ether (3 x 30 mL). The combined organic layers were washed with water (3 x 15 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to dryness, affording 565 mg (80%) of the desired compound **53** as a grey solid.

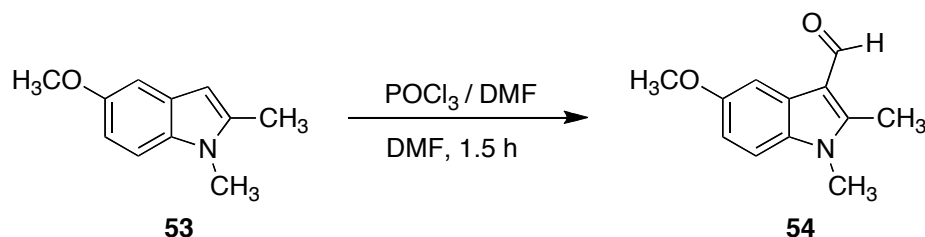
Melting point: 67-68 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>13</sub>NO: C 75.42, H 7.42, N 8.00; found: C 75.01, H 7.20, N 7.77.

IR (NaCl):  $\nu = 1488$  (CH);  $1214$  (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) <sup>TM</sup>: 7.25 (d,  $J = 8.7$  Hz, 1H, H<sub>7</sub>), 7.19 (d,  $J = 2.4$  Hz, 1H, H<sub>4</sub>), 6.98 (dd,  $J = 8.8$  Hz and  $J = 2.5$  Hz, 1H, H<sub>6</sub>), 6.33 (t,  $J = 0.8$  Hz, 1H, H<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 3.67 (s, 3H, NCH<sub>3</sub>), 2.51 (d,  $J = 0.8$  Hz, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz) <sup>TM</sup>: 153.9 (C<sub>5</sub>), 137.4 (C<sub>2</sub>), 132.6 (C<sub>7a</sub>), 128.1 (C<sub>3a</sub>), 110.0 (C<sub>7</sub>), 109.3 (C<sub>4</sub>), 101.8 (C<sub>6</sub>), 99.1 (C<sub>3</sub>), 55.9 (OCH<sub>3</sub>), 29.5 (NCH<sub>3</sub>), 12.1 (CH<sub>3</sub>) ppm.

**5-METHOXY-1,2-DIMETHYLINDOLE-3-CARBALDEHYDE (54)**

A solution of POCl<sub>3</sub> (877 mg, 5.72 mmol) and DMF (10 mL) was cooled at 0 °C and stirred for 30 min under an inert atmosphere. Then, a solution of compound **53** (500 mg, 2.86 mmol) in DMF (10 mL) was added and the mixture was stirred at room temperature for 45 min. The reaction was again cooled to 0 °C and water (8 mL) and 20% NaOH solution (pH > 8) were added and it was stirring for 30 min. The mixture was filtered and the solid product was dissolved in CHCl<sub>3</sub>, dried over anhydrous sodium sulfate and concentrated under vacuum to obtain 450 mg (78%) of compound **54** as a pale brown solid.

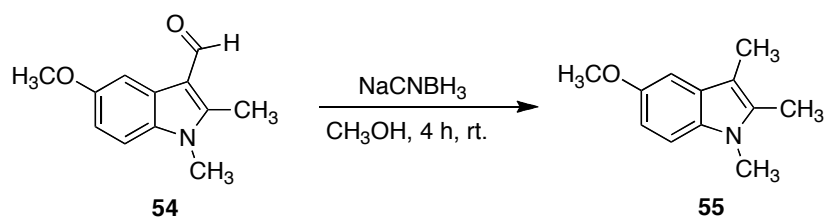
Melting point: 138 °C

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>: C 70.90, H 6.40, N 6.89; found: C 70.62, H 6.21, N 7.04.

IR (NaCl):  $\nu$  = 1636 (CO); 1262 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) <sup>TM</sup>: 10.16 (s, 1H, CHO), 7.83 (d, *J* = 2.5 Hz, 1H, H<sub>4</sub>), 7.23 (d, *J* = 8.8 Hz, 1H, H<sub>7</sub>), 6.94 (dd, *J* = 8.8 Hz y *J* = 2.5 Hz, 1H, H<sub>6</sub>), 3.92 (s, 3H, OCH<sub>3</sub>), 3.72 (s, 3H, NCH<sub>3</sub>), 2.71 (d, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz) <sup>TM</sup>: 183.8 (OCH), 156.5 (C<sub>5</sub>), 147.8 (C<sub>2</sub>), 131.7 (C<sub>7a</sub>), 126.1 (C<sub>3a</sub>), 114.1 (C<sub>3</sub>), 112.8 (C<sub>7</sub>), 109.9 (C<sub>6</sub>), 102.7 (C<sub>4</sub>), 55.7 (OCH<sub>3</sub>), 29.7 (NCH<sub>3</sub>), 10.4 (CH<sub>3</sub>) ppm.

**5-METHOXY-1,2,3-TRIMETHYLINDOLE (55)**

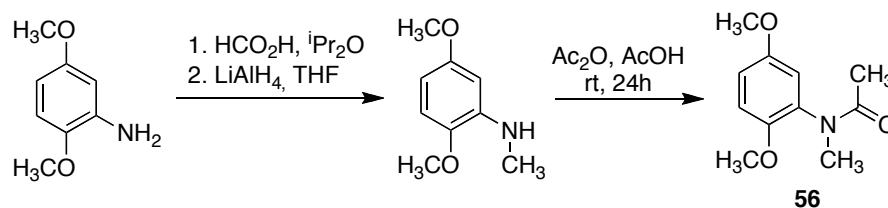
To a solution of compound **54** (100 mg, 0.49 mmol) in methanol (20 mL) were added NaCNBH<sub>3</sub> (77.3 mg, 1.23 mmol) and 10% HCl methanolic solution. The reaction was stirred at room temperature for 4 h and, then, the solvent was evaporated to dryness. Purification of the residue by flash chromatography on silica gel, eluting with 3:1 petroleum ether/ethyl acetate, gave 70 mg (75%) of compound **55** as a brown solid.

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>15</sub>NO: C 76.19, H 7.93, N 7.40; found: C 75.91, H 7.60, N 7.77.

IR (NaCl):  $\nu = 1201$  (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz) <sup>TM</sup>: 7.16 (d, *J* = 8.7 Hz, 1H, H<sub>7</sub>), 6.98 (d, *J* = 2.3 Hz, 1H, H<sub>4</sub>), 6.83 (dd, *J* = 8.7 Hz y *J* = 2.5 Hz, 1H, H<sub>6</sub>), 3.90 (s, 3H, OCH<sub>3</sub>), 3.65 (s, 3H, NCH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 2.26 (s, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz) <sup>TM</sup>: 153.5 (C<sub>5</sub>), 133.4 (C<sub>2</sub>), 131.8 (C<sub>7a</sub>), 128.5 (C<sub>3a</sub>), 110.1 (C<sub>7</sub>), 109.1 (C<sub>6</sub>), 105.8 (C<sub>3</sub>), 100.2 (C<sub>4</sub>), 56.0 (OCH<sub>3</sub>), 29.6 (NCH<sub>3</sub>), 10.2 (CH<sub>3</sub>), 8.9 (CH<sub>3</sub>) ppm.

***N*-(2,5-DIMETHOXYPHENYL)-*N*-METHYLACETAMIDE (56)**

To a suspension of 2,5-dimethoxyaniline<sup>79</sup> (2 g, 13 mmol) in dry isopropyl ether (40 mL) was heated at 60 °C until complete dissolution and, then, was added dropwise acid formic (2.3 g, 50 mmol) and the mixture was stirred at 80 °C for 90 min. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with dichloromethane/ethyl acetate (4:1), affording 2.3 g (98%) of *N*-(2,5-dimethoxyphenyl)formamide as a viscous oil.

A solution of this amide (2.3 g, 12.8 mmol) in anhydrous ethyl ether (50 mL) was added dropwise to a suspension of LiAlH<sub>4</sub> (2.24 g, 64 mmol) in anhydrous ethyl ether (100 mL) at 0 °C and the reaction was stirred at room temperature for 4 h. After cooling at 0 °C, ethyl acetate (10 mL) was added dropwise and the mixture was then extracted with ethyl ether (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum. The residue was purified by chromatography on silica gel eluting with 1:1 ethyl ether/petroleum ether, yielding 1.71 g (80%) of the expected amine.<sup>80</sup>

To a solution of this amine (91 mg, 0.54 mmol) in acetic acid (10 mL) was added dropwise acetic anhydride (83.7 mg, 0.54 mmol) and the reaction mixture was stirred at room temperature for 3 h. Then, the mixture was extracted with ethyl acetate and the organic layer washed with water (30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*, giving the expected product **56** as a yellow oil. Yield: 110 mg (97%).

<sup>79</sup> The commercial 2,5-dimethoxyaniline was purified by filtration through silica gel, eluting with ethyl ether.

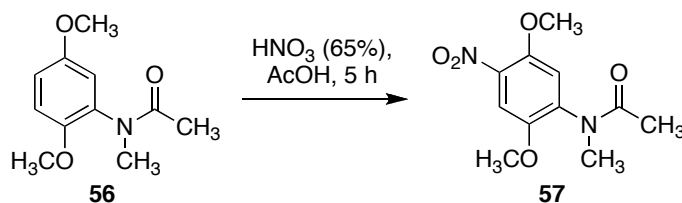
<sup>80</sup> Pérez, J. M.; Vidal, L.; Grande, M. T.; Menéndez, J. C.; Avendaño, C. *Tetrahedron* **1994**, *50*, 7923.

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>15</sub>NO<sub>3</sub>: C 63.15, H 7.17, N 6.69; found: C 62.91, H 7.14, N 6.63.

IR (NaCl):  $\nu$  = 1660 (CO); 1218 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 250 MHz):  $\tau^m$  = 6.86 (s, 1H, H<sub>6</sub>), 6.84 (d,  $J$  = 2.7 Hz, 1H, H<sub>3</sub>), 6.72 (d,  $J$  = 2.7 Hz, 1H, H<sub>4</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 3.14 (s, 3H, NCH<sub>3</sub>), 1.8 (s, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (CDCl<sub>3</sub>, 63 MHz):  $\tau^m$  = 171.4 (CO), 153.5 (C<sub>5</sub>), 148.9 (C<sub>2</sub>), 133.1 (C<sub>1</sub>), 114.0 (C<sub>3</sub>), 113.5 (C<sub>4</sub>), 112.5 (C<sub>6</sub>), 55.8 (OCH<sub>3</sub>), 55.6 (OCH<sub>3</sub>), 38.2 (NCH<sub>3</sub>), 21.5 (COCH<sub>3</sub>) ppm.

***N*-(2,5-DIMETHOXY-4-NITROPHENYL)-*N*-METHYLACETAMIDE (57)**

To a solution of *N*-(2,5-dimethoxyphenyl)-*N*-methylacetamide (105 mg, 0.5 mmol) in acetic acid (10 mL) at 0 °C was added dropwise 65% nitric acid (0.3 mL). The reaction was stirred at 0 °C for 1 h and at rt for 4 h. Then, the mixture was cooled at 0 °C, poured onto cold water (100 mL) and the yellow solid that precipitated was collected by filtration and washed with water (20 mL), yielding 117 mg (92%) of **57**.

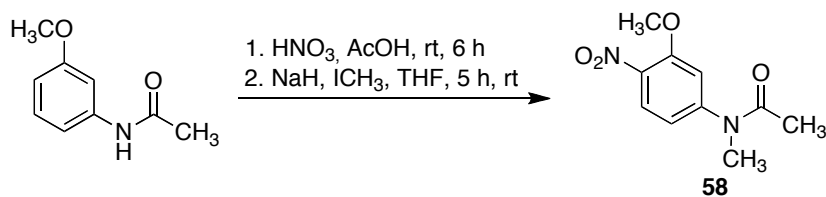
Melting point: 125 °C

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C 51.97, H 5.55, N 11.02; found: C 51.60, H 5.32, N 10.81

IR (NaCl):  $\nu$  = 1667 (N-C=O), 1523 and 1346 (NO<sub>2</sub>), 1210 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.52 (s, 1H, H<sub>3</sub>), 6.98 (s, 1H, H<sub>6</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.19 (s, 3H, N-CH<sub>3</sub>), 1.86 (s, 3H, CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 170.6 (C=O), 148.3 (C<sub>5</sub>), 147.5 (C<sub>2</sub>), 138.1 (C<sub>4</sub>), 137.8 (C<sub>1</sub>), 114.7 (C<sub>3</sub>), 109.2 (C<sub>6</sub>), 57.1 (OCH<sub>3</sub>), 56.2 (OCH<sub>3</sub>), 35.9 (N-CH<sub>3</sub>), 21.6 (CO-CH<sub>3</sub>) ppm.

***N*-(3-METHOXY-4-NITROPHENYL)-*N*-METHYLACETAMIDE (58)**

To a solution of *N*-(3-methoxyphenyl)acetamide (500 mg, 3.03 mmol) in acetic acid (15 mL) at 0 °C was added dropwise 65% nitric acid (1.8 mL). The reaction was stirred at 0 °C for 1 h and at rt for 4 h. Then, the mixture was cooled to 0 °C, poured onto cold water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>), evaporated and the residue was purified by flash chromatography on silica gel, eluting with 1:1 petroleum ether-ethyl acetate, affording 380 mg (60%) of *N*-(3-methoxy-4-nitrophenyl)acetamide.

A solution of this compound (130 mg, 0.72 mmol) in THF (15 mL) was added to a suspension of NaH (83 mg, 2.07 mmol), previously washed with dry petroleum ether, in THF (10 mL) at 0 °C under an argon atmosphere and stirred at 0 °C for 1 h. Then, methyl iodide (257 mg, 1.82 mmol) was added and the reaction was allowed to warm to rt for 4 h. The mixture was cooled at 0 °C, poured onto cold water (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated. The residue was washed with hexane to afford 120 mg (75%) of the desired compound **58** as a yellow solid.

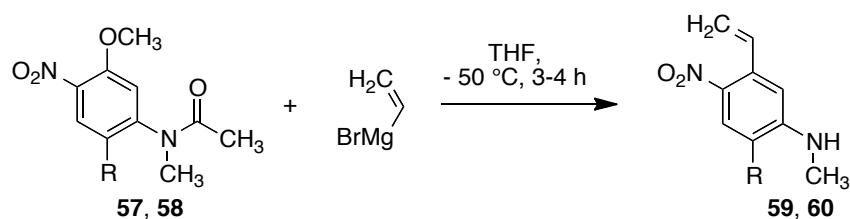
Melting point: 78-80 °C

Elemental analysis calc. (%) for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>: C 53.57, H 5.39, N 12.49; found: C 53.94, H 5.76, N 12.22.

IR (NaCl):  $\nu$  = 1663 (C=O), 1517 and 1348 (NO<sub>2</sub>), 1238 (OCH<sub>3</sub>) cm<sup>-1</sup>.

$^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.91 (d, 1H,  $J$  = 8.5 Hz,  $\text{H}_5$ ), 6.97 (m, 1H,  $\text{H}_2$ ), 6.89 (dd, 1H,  $J$  = 8.5 and 2.0 Hz,  $\text{H}_6$ ), 3.87 (s, 3H,  $\text{OCH}_3$ ), 3.31 (s, 3H,  $\text{N-CH}_3$ ), 2.02 (br s, 3H,  $\text{CO-CH}_3$ ) ppm.

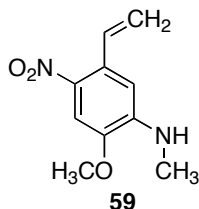
$^{13}\text{C-NMR}$  (63 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 169.8 (CO), 153.7 ( $\text{C}_3$ ), 149.4 ( $\text{C}_1$ ), 137.8 ( $\text{C}_4$ ), 126.8 ( $\text{C}_5$  and  $\text{C}_6$ ), 111.9 ( $\text{C}_2$ ), 56.6 ( $\text{OCH}_3$ ), 37.2 ( $\text{N-CH}_3$ ), 29.5 ( $\text{CO-CH}_3$ ) ppm.

**PREPARATION OF N-METHYL-N-(4-NITROVINYLPHENYL)ANILINES 59-60**

Comp.	R
<b>59</b>	OCH <sub>3</sub>
<b>60</b>	H

**General procedure**

A commercial THF solution of vinylmagnesium bromide (1.5 mmol) was added dropwise to a cooled (-50 °C) solution of compound **57** or **58** (0.5 mmol) in dry THF (20 mL), under an inert atmosphere. The reaction mixture was stirred at -50 °C for 3-4 h, poured onto a saturated NH<sub>4</sub>Cl aqueous solution (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried (anhydrous Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 5:1 petroleum ether-ethyl acetate.

***N*-(2,5-DIMETHOXY-4-NITRO-5-VINYLPHENYL)-*N*-METHYLANILINE (59)****Reaction data:**

*N*-(2,5-dimethoxy-4-nitrophenyl)-*N*-methylacetamide **57**: 150 mg (0.6 mmol).

Vinylmagnesium bromide: 2.35 mL (1.8 mmol).

Reaction time: 3 h

Yield: 79 mg, 63% (yellow solid).

**Data for compound 59:**

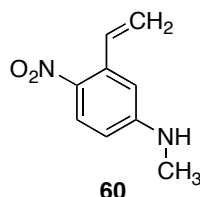
Melting point: 55-57 °C

Elemental analysis calc. (%) for C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C 57.68, H 5.81, N 13.45; found: C 57.42, H 5.59, N 13.23.

IR (NaCl):  $\nu = 1538$  and  $1312$  (NO<sub>2</sub>),  $1217$  (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 7.60$  (s, 1H, H<sub>3</sub>);  $7.45$  (dd, 1H,  $J = 17.2$  and  $10.8$  Hz, HC=CH<sub>2</sub>);  $6.54$  (s, 1H, H<sub>6</sub>);  $5.62$  (dd, 1H,  $J = 17.2$  and  $1.3$  Hz, HC=CH<sub>2</sub>);  $5.40$  (dd, 1H,  $J = 10.8$  and  $1.3$  Hz, HC=CH<sub>2</sub>);  $5.04$  (br s, 1H, NH),  $3.94$  (s, 3H, OCH<sub>3</sub>);  $3.00$  (d, 3H,  $J = 5.2$  Hz, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta = 144.9$ . (C<sub>2</sub>),  $144.1$  (C<sub>1</sub>),  $135.5$  (HC=CH<sub>2</sub>),  $131.6$  (C<sub>4</sub>),  $130.8$  (C<sub>5</sub>),  $116.5$  (HC=CH<sub>2</sub>),  $106.4$  (C<sub>3</sub>),  $105.8$  (C<sub>6</sub>),  $55.9$  (OCH<sub>3</sub>),  $29.6$  (N-CH<sub>3</sub>) ppm.

**N-METHYL-N-(4-NITRO-3-VINYLPHENYL)ANILINE (60)****Reaction data:**

*N*-(3-methoxy-4-nitrophenyl)-*N*-methylacetamide **58**: 135 mg (0.6 mmol).

Vinylmagnesium bromide: 2.35 mL (1.8 mmol).

Reaction time: 4 h

Yield: 71 mg, 64% (yellowish green solid).

**Data for compound 60:**

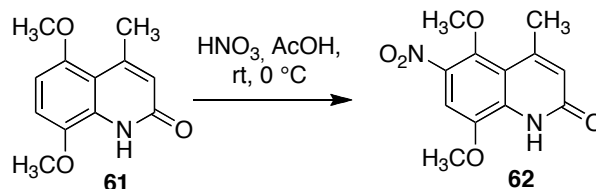
Melting point: 66-68 °C

Elemental analysis calc. (%) for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C 60.66, H 5.66, N 15.72; found: C 60.97, H 5.84, N 15.37.

IR (NaCl):  $\nu$  = 1579 and 1309 (NO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.07 (d, 1H,  $J$  = 9.0 Hz, H<sub>5</sub>), 7.40 (dd, 1H,  $J$  = 17.2 and 10.8 Hz, CH=CH<sub>2</sub>), 6.58 (d, 1H,  $J$  = 2,6 Hz, H<sub>2</sub>), 6.51 (dd, 1H,  $J$  = 9.0 and 2.6 Hz, H<sub>6</sub>), 5.62 (dd, 1H,  $J$  = 17.2 and 1.0 Hz, CH=CH<sub>2</sub>), 5.42 (dd, 1H,  $J$  = 10.8 and 1.0 Hz, CH=CH<sub>2</sub>), 4.50 (br s, 1H, NH), 2.97 (d, 3H,  $J$  = 2.8 Hz, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 153.2 (C<sub>1</sub>), 137.8 (C<sub>3</sub>), 137.1 (C<sub>4</sub>), 135.5 (CH=CH<sub>2</sub>), 127.9 (C<sub>5</sub>), 117.3 (CH=CH<sub>2</sub>), 110.5 (C<sub>2</sub> and C<sub>6</sub>), 30.1 (N-CH<sub>3</sub>) ppm.

**5,8-DIMETHOXY-4-METHYL-6-NITROQUINOLIN-2(1H)-ONE (62)**

To a solution of 5,8-dimethoxy-4-methylquinolin-2(1H)-one<sup>81</sup> **61** (5 g, 22.8 mmol) in acetic acid (40 mL) at 0 °C, 65% nitric acid (12.5 mL) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. Then, the reaction was poured onto cold water (200 mL) and the yellow precipitate was collected by filtration and washed with water, yielding 6.5 g (100%) of compound **62**.

Melting point: 261 °C (acetone)

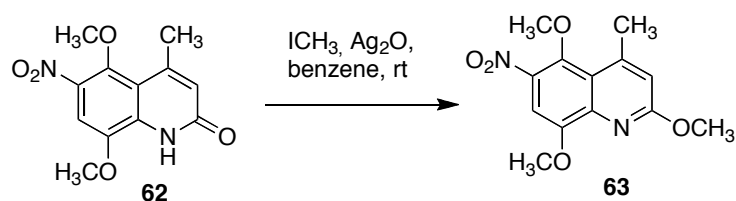
Elemental analysis calc. (%) for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>: C 54.55, H 4.58, N 10.60; found: C 54.27, H 4.54, N 10.73.

IR (NaCl):  $\nu$  3600 (NH), 1664 (N-C=O), 1564 and 1352 (NO<sub>2</sub>), 1255 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.55 (s, 1H, H<sub>7</sub>), 6.60 (d, 1H, *J* = 0.9 Hz, H<sub>3</sub>), 4.06 (s, 3H, OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 2.73 (d, 3H, *J* = 0.9 Hz, C<sub>4</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 162.0 (C=O), 150.4 (C<sub>4</sub>), 148.6 (C<sub>5</sub>), 142.0 (C<sub>8</sub>), 137.3 (C<sub>6</sub>), 134.1 (C<sub>8a</sub>), 124.9 (C<sub>3</sub>), 115.7 (C<sub>4a</sub>), 106.8 (C<sub>7</sub>), 64.0 (OCH<sub>3</sub>), 57.1 (OCH<sub>3</sub>), 23.9 (C<sub>4</sub>-CH<sub>3</sub>) ppm.

<sup>81</sup> Avendaño, C., de la Cuesta, E., Gesto, C. *Synthesis* **1991**, 727.

**2,5,8-TRIMETHOXY-4-METHYL-6-NITROQUINOLINE (63)**

To a solution of 5,8-dimethoxy-4-methyl-6-nitroquinolin-2(1H)-one **62** (1.2 g, 4.56 mmol) in dry benzene (100 mL) was added silver oxide (1.1 g, 4.56 mmol) and methyl iodide (3.4 g, 24 mmol, divided into three parts that were added every 24 h). The mixture was stirred at room temperature for 72 h, protected from light and humidity. The resultant suspension was filtered and the organic layer was evaporated to dryness. The residue was chromatographed on silica gel, eluting with an ethyl acetate/petroleum ether gradient (8:2 to 1:1), yielding 775 mg (61%) of **63**, as a yellow solid, together with 250 mg (25%) of recovered starting material.

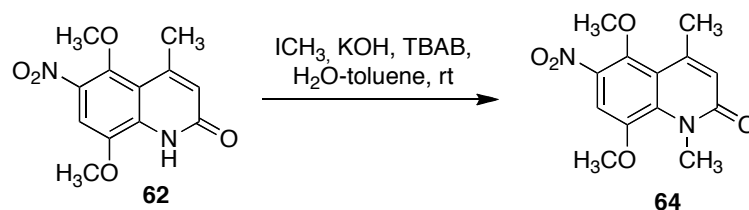
Melting point: 155-156 °C

Elemental analysis calc. (%) for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_5$ : C 56.11, H 5.07, N 10.07; found C 56.21, H 4.98, N 10.22.

IR (KBr):  $\nu = 1581$  and  $1323$  ( $\text{NO}_2$ ),  $1165$   $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 2.86$  (d,  $J = 0.9$  Hz, 3H, 4- $\text{CH}_3$ ), 3.92 (s, 3H, 5- $\text{OCH}_3$ ), 4.08 (s, 3H, 8- $\text{OCH}_3$ ), 4.14 (s, 3H, 2- $\text{OCH}_3$ ), 6.84 (d,  $J = 0.9$  Hz, 1H, 3-H), 7.49 (s, 1H, 7-H) ppm.

$^{13}\text{C-NMR}$  (63 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 23.3$  (4- $\text{CH}_3$ ), 53.6 (2- $\text{OCH}_3$ ), 56.7 (8- $\text{OCH}_3$ ), 63.5 (5- $\text{OCH}_3$ ), 103.9 (C-7), 116.7 (C-3), 120.9 (C-4a), 137.8 (C-6), 142.9 (C-8a), 147.4 (C-5), 149.3 (C-4), 150.7 (C-8), 163.6 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-NITROQUINOLIN-2(1H)-ONE (64)**

Tetrabutylammonium bisulphate (770 mg, 2.27 mmol) and 50% potassium hydroxide solution (820 mg, 20.5 mmol) were added to a solution of **62** (3 g, 11.36 mmol) in toluene (100 mL) and stirred for 15 min. Then, methyl iodide (2.1 g, 14.8 mmol) was added and the reaction mixture was stirred at room temperature for 3 h and water (30 mL) was then added. The organic layer was dried (anhydrous  $\text{Na}_2\text{SO}_4$ ) and evaporated, and the residue was washed with acetone, affording 2.99 g (94%) of 5,8-dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**.

Melting point: 157 °C

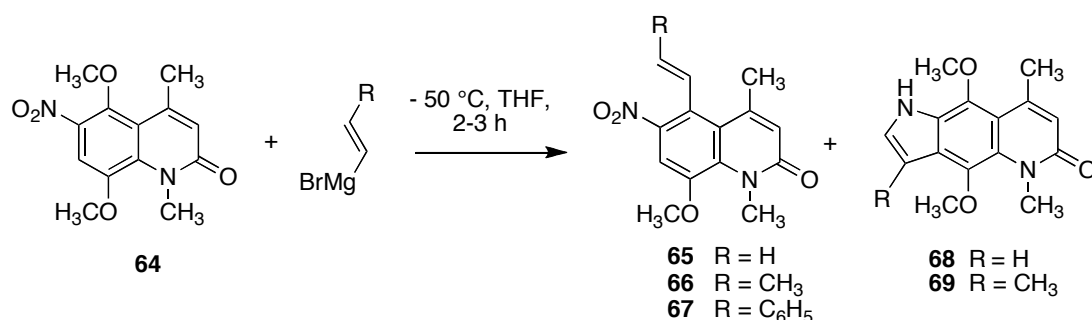
Elemental analysis calc. (%) for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_5$ : C 56.11, H 5.07, N 10.07; found: C 56.23, H 5.10, N 10.19.

IR (NaCl):  $\nu = 1667$  (N-C=O), 1572 and 1324 ( $\text{NO}_2$ ), 1283 ( $\text{OCH}_3$ )  $\text{cm}^{-1}$ .

$^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.62$  (s, 1H,  $\text{H}_7$ ), 6.62 (d, 1H,  $J = 1$  Hz,  $\text{H}_3$ ), 3.97 (s, 3H,  $\text{OCH}_3$ ), 3.88 (s, 3H,  $\text{OCH}_3$ ), 3.87 (s, 3H,  $\text{NCH}_3$ ), 2.67 (d, 3H,  $J = 1$  Hz,  $\text{C}_4\text{-CH}_3$ ) ppm.

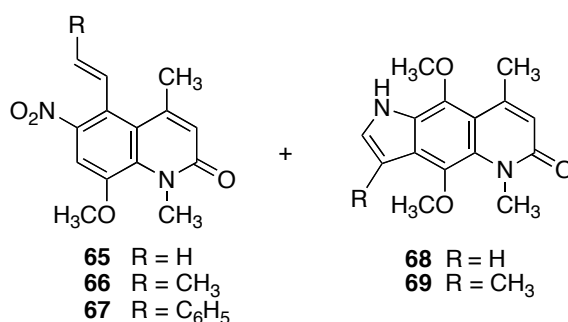
$^{13}\text{C-NMR}$  (63 MHz,  $\text{CDCl}_3$ ):  $\delta = 162.9$  ( $\text{C}_2$ ), 148.4 ( $\text{C}_5$ ), 146.9 ( $\text{C}_8$ ), 144.8 ( $\text{C}_4$ ), 138.1 ( $\text{C}_{8a}$ ), 137.0 ( $\text{C}_6$ ), 124.6 ( $\text{C}_3$ ), 118.4 ( $\text{C}_{4a}$ ), 109.0 ( $\text{C}_7$ ), 63.99 and 57.2 (2  $\text{OCH}_3$ ), 36.5 ( $\text{N-CH}_3$ ), 24.9 ( $\text{C}_4\text{-CH}_3$ ) ppm.

## REACTION OF COMPOUND 64 WITH VINYL GRIGNARD REAGENTS

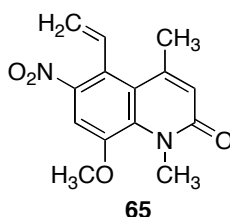


### General procedure:

To a cooled ( $-78\text{ }^\circ\text{C}$  or  $-50\text{ }^\circ\text{C}$ ) solution of 5,8-dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1*H*)-one **64** (0.5 mmol) in dry THF (20 mL), under an inert atmosphere was added dropwise a commercial THF solution of the suitable vinyl Grignard reagent (1.5 mmol). The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  or  $-50\text{ }^\circ\text{C}$  for 2-3 h, poured onto a saturated  $\text{NH}_4\text{Cl}$  aqueous solution (15 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 5:1 petroleum ether/ethyl acetate. Yields are summarized below.



R	$-78\text{ }^\circ\text{C, 2-3 h}$		$-50\text{ }^\circ\text{C, 2-3 h}$	
	% Vinylation	% Bartoli	% Vinylation	% Bartoli
H	69	9	94	0
CH <sub>3</sub>	77	8	92	0
C <sub>6</sub> H <sub>5</sub>	--	--	75	0

**8-METHOXY-1,4-DIMETHYL-6-NITRO-5-VINYLSQUINOLIN-2(1H)-ONE (65)****Reaction data:**

5,8-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 140 mg (0.5 mmol)

Vinylmagnesium bromide: 3 mL (1.5 mmol)

Yield: 129 mg (94 %). Yellow solid.

**Data for compound 65:**

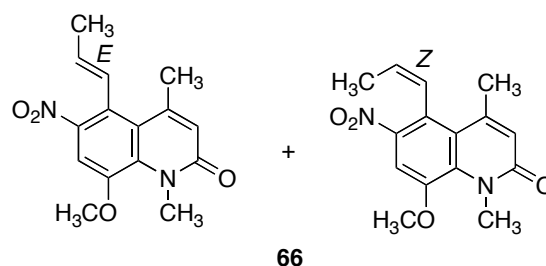
Melting point: 117-118 °C

Elemental analysis calc. (%) for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O: C 61.31, H 5.14, N 10.21; found C 61.43, H 5.25, N 10.09.

IR (KBr):  $\nu$  = 1663 (N-C=O), 1524 and 1328 (NO<sub>2</sub>), 1296 (OCH<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.45 (s, 1H, H<sub>7</sub>), 7.30 (dd, 1H,  $J$  = 17.6 Hz and 11.1 Hz, HC=CH<sub>2</sub>), 6.61 (s, 1H, H<sub>3</sub>), 5.42 (d, 1H,  $J$  = 11.1 Hz, HC=CH<sub>2</sub>), 5.07 (d, 1H,  $J$  = 17.6 Hz, HC=CH<sub>2</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, N-CH<sub>3</sub>), 2.48 (s, 3H, C<sub>4</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.0 (C<sub>2</sub>), 148.2 (C<sub>8</sub>), 147.9 (C<sub>4</sub>), 136.3 (C<sub>6</sub>), 134.7 (HC=CH<sub>2</sub> and H<sub>8a</sub>), 126.8 (C<sub>4a</sub>), 125.4 (C<sub>3</sub>), 123.5 (C<sub>5</sub>), 120.7 (HC=CH<sub>2</sub>), 107.3 (C<sub>7</sub>), 56.9 (OCH<sub>3</sub>), 37.1 (N-CH<sub>3</sub>), 27.1 (C<sub>4</sub>-CH<sub>3</sub>) ppm.

**(E/Z) 8-METHOXY-1,4-DIMETHYL-6-NITRO-5-(1-PROPENYL)QUINOLIN-2(1H)-ONE (66)****Reaction data:**

5,8-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 140 mg (0.5 mmol)

Propenylmagnesium bromide: 3 mL (1.5 mmol)

Yield: 133 mg (92%), corresponding to an *E/Z* = 1.3/1 mixture.

**Data for compound 65:**

Elemental analysis calc. (%) for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C 62.49, H 5.59, N 9.72; found: C 62.84, H 5.88, N 9.55.

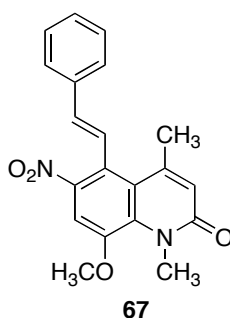
MS (EI, *m/z*): 288 (M<sup>+</sup>, 39%), 245 (M-43, 100%).

IR (KBr):  $\nu$  = 1662 (N-C=O), 1515 and 1335 (NO<sub>2</sub>), 1271 (OCH<sub>3</sub>) cm<sup>-1</sup>

<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>): *E* isomer:  $\delta$  = 7.41 (s, 1H, H<sub>7</sub>), 6.83-6.81 (m, 1H, HC=CH-CH<sub>3</sub>), 6.60-6.58 (m, 1H, H<sub>3</sub>, overlapped with the same signal of the *Z* isomer), 5.38 (dd, 1H, *J* = 15.8 Hz and 6.6 Hz, HC=CH-CH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, N-CH<sub>3</sub>), 2.42 (d, 3H, *J* = 1.0 Hz, C<sub>4</sub>-CH<sub>3</sub>), 1.85 (dd, 3H, *J* = 6.6 Hz and 1.8 Hz, HC=CH-CH<sub>3</sub>) ppm.

*Z* isomer:  $\delta$  = 7.44 (s, 1H, H<sub>7</sub>), 6.89-6.85 (m, 1H, HC=CH-CH<sub>3</sub>), 6.60-6.58 (m, 1H, H<sub>3</sub>, overlapped with the same signal of the *E* isomer), 5.84 (dd, 1H, *J* = 11.2 Hz and 6.9 Hz, HC=CH-CH<sub>3</sub>), 3.97 (s, 3H, OCH<sub>3</sub>), 3.84 (s, 3H, N-CH<sub>3</sub>), 2.47 (d, 3H, *J* = 1.0 Hz, C<sub>4</sub>-CH<sub>3</sub>), 1.28 (dd, 3H, *J* = 6.9 Hz and 1.8 Hz, HC=CH-CH<sub>3</sub>) ppm.

$^{13}\text{C}$ -NMR (63 MHz,  $\text{CDCl}_3$ ): *E* isomer:  $\delta$  = 163.1 ( $\text{C}_2$ ), 148.3 ( $\text{C}_8$ ), 147.9 ( $\text{C}_4$ , overlapped with the same signal for the *Z* isomer), 145.9 ( $\text{C}_6$ ), 136.3 ( $\text{C}_{8a}$ ), 131.8 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 127.5 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 126.5 ( $\text{C}_{4a}$ , overlapped with the same signal for the *Z* isomer), 125.3 ( $\text{C}_3$ ), 123.9 ( $\text{C}_5$ ), 107.3 ( $\text{C}_7$ ), 56.9 ( $\text{OCH}_3$ , overlapped with the same signal for the *Z* isomer), 37.1 ( $\text{N}-\text{CH}_3$ ), 26.8 ( $\text{C}_4-\text{CH}_3$ ), 18.9 ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ ) ppm; *Z* isomer:  $\delta$  = 163.0 ( $\text{C}_2$ ), 148.2 ( $\text{C}_8$ ), 147.9 ( $\text{C}_4$ , overlapped with the same signal for the *E* isomer), 146.1 ( $\text{C}_6$ ), 136.1 ( $\text{C}_{8a}$ ), 129.9 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 127.0 ( $\text{HC}=\underline{\text{C}}\text{H}-\text{CH}_3$ ), 126.5 ( $\text{C}_{4a}$ , overlapped with the same signal for the *E* isomer), 125.3 ( $\text{C}_3$ ), 124.0 ( $\text{C}_5$ ), 107.5 ( $\text{C}_7$ ), 56.9 ( $\text{OCH}_3$ , overlapped with the same signal for the *E* isomer), 37.2 ( $\text{N}-\text{CH}_3$ ), 26.4 ( $\text{C}_4-\text{CH}_3$ ), 14.2 ( $\text{HC}=\text{CH}-\underline{\text{C}}\text{H}_3$ ) ppm.

**8-METHOXY-1,4-DIMETHYL-6-NITRO-5-STYRYLQUINOLIN-2(1H)-ONE (67)****Reaction data:**

5,8-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 140 mg (0.5 mmol)

Propenylmagnesium bromide: 3 mL (1.5 mmol)

Yield: 132 mg (75%).

**Data for compound 67:**

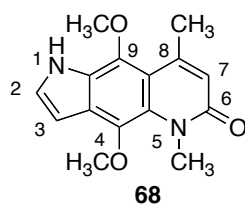
Melting point: 98-100 °C.

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 68.56, H 5.18, N 8.00; found: C 68.26, H 5.02, N 7.65.

IR (KBr):  $\nu$  = 1662 (N-C=O), 1519 and 1329 (NO<sub>2</sub>), 1289 (OCH<sub>3</sub>) cm<sup>-1</sup>.

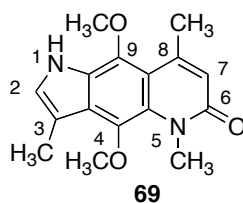
<sup>1</sup>H-NMR (250 MHz CDCl<sub>3</sub>):  $\delta$  = 7.66 (s, 1H, H<sub>7</sub>), 7.62 (d, 1H, *J* = 16.2 Hz, HC=CH-Ph), 7.53-7.31 (m, 5H, Ph), 6.95 (s, 1H, H<sub>3</sub>), 6.37 (d, 1H, *J* = 16.3 Hz, Hz, HC=CH-Ph), 4.09 (s, 3H, OCH<sub>3</sub>), 4.07 (s, 3H, N-CH<sub>3</sub>), 2.62 (d, 3H, *J* = 0.9 Hz, C<sub>4</sub>-CH<sub>3</sub>) ppm.

<sup>13</sup>C-NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 162.5 (C<sub>2</sub>), 147.7 (C<sub>8</sub>), 147.6 (C<sub>4</sub>), 144.9 (C<sub>6</sub>), 136.5 (C<sub>8a</sub>), 136.1 (C<sub>1'</sub>), 134.6 (HC=CH-Ph), 128.8 and 126.6 (C<sub>2'</sub>, C<sub>3'</sub>, C<sub>5'</sub> and C<sub>6'</sub>), 128.4 (C<sub>4'</sub>), 128.0 (C<sub>4a</sub>), 126.0 (C<sub>5</sub>), 125.0 (HC=CH-Ph), 124.9 (C<sub>3</sub>), 107.1 (C<sub>7</sub>), 56.5 (OCH<sub>3</sub>), 36.6 (N-CH<sub>3</sub>), 26.6 (C<sub>4</sub>-CH<sub>3</sub>) ppm.

**4,9-DIMETHOXY-5,8-DIMETHYL-1*H*-PIRROLO[2,3-*g*]QUINOLIN-6(5*H*)-ONE (68)**

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  = 8.56 (br s, 1H, NH), 7.34 (dd, 1H,  $J$  = 2.5 and 3.1 Hz,  $\text{H}_2$ ), 6.69 (dd, 1H,  $J$  = 2.5 and 3.1 Hz,  $\text{H}_3$ ), 6.42 (d, 1H,  $J$  = 1 Hz,  $\text{H}_7$ ), 3.95 (s, 3H,  $\text{OCH}_3$ ), 3.90 (s, 3H,  $\text{OCH}_3$ ), 3.85 (s, 3H,  $\text{N-CH}_3$ ), 2.68 (d, 3H,  $J$  = 1 Hz,  $\text{C}_8\text{-CH}_3$ ) ppm.

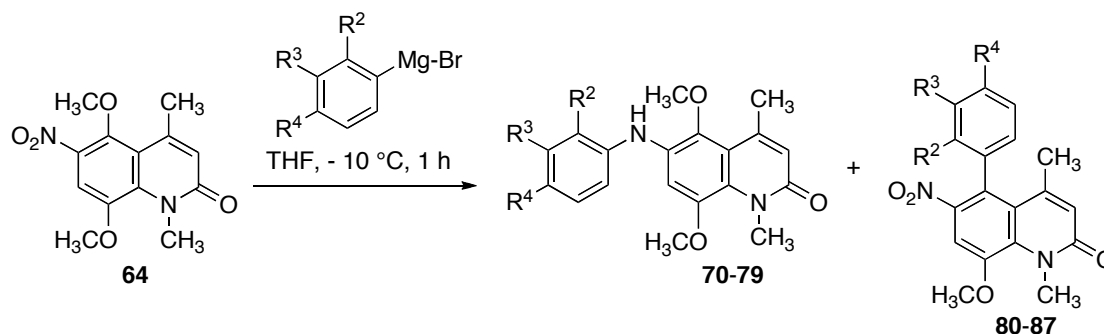
$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 63 MHz):  $\delta$  = 164.7 ( $\text{C=O}$ ), 145.0 ( $\text{C}_8$ ), 140.0 ( $\text{C}_4$ ), 137.5 ( $\text{C}_9$ ), 127.6 ( $\text{C}_{9a}$ ), 127.6 ( $\text{C}_7$ ), 126.4 ( $\text{C}_{3a}$ ), 121.4 ( $\text{C}_2$ ), 114.1 ( $\text{C}_{4a}$ ), 111.3 ( $\text{C}_{8a}$ ), 101.1 ( $\text{C}_3$ ), 62.6 ( $\text{OCH}_3$ ), 62.2 ( $\text{OCH}_3$ ), 35.9 ( $\text{N-CH}_3$ ), 23.7 ( $\text{C}_8\text{-CH}_3$ ) ppm.

**3,5,8-TRIMETHYL-4,9-DIMETHOXY-1*H*-PIRROLO[2,3-*g*]QUINOLIN-6(5*H*)-ONE (69)**

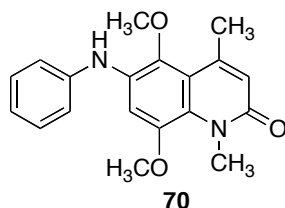
$^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  = 8.15 (br s, 1H, NH), 7.05 (d, 1H,  $J$  = 1 Hz, H<sub>2</sub>), 6.43 (d, 1H,  $J$  = 1.2 Hz, H<sub>7</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, OCH<sub>3</sub>), 3.70 (s, 3H, N-CH<sub>3</sub>), 2.67 (s, 3H, C<sub>8</sub>-CH<sub>3</sub>), 2.51 (s, 3H, C<sub>3</sub>-CH<sub>3</sub>) ppm.

$^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 63 MHz):  $\delta$  = 164.1 (C=O), 146.6 (C<sub>4</sub>), 139.8 (C<sub>8</sub>), 138.7 (C<sub>9</sub>), 128.7 (C<sub>9a</sub>), 126.8 (C<sub>3a</sub>), 125.7 (C<sub>2</sub>), 121.3 (C<sub>4a</sub>), 121.2 (C<sub>7</sub>), 113.0 (C<sub>8a</sub>), 112.3 (C<sub>3</sub>), 63.0 (OCH<sub>3</sub>), 62.5 (OCH<sub>3</sub>), 36.3 (N-CH<sub>3</sub>), 23.6 (C<sub>8</sub>-CH<sub>3</sub>), 11.8 (C<sub>3</sub>-CH<sub>3</sub>) ppm.

**REACTION OF COMPOUND 64 WITH ARYL GRIGNARD REAGENTS.  
COMPOUNDS 70-87**



To a solution of 5,8-dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64** (1 eq) in dry THF (50 mL) was added the suitable arylmagnesium bromide (3 eq, as a commercially available solution in THF; the naphthyl Grignard reagents were prepared from the corresponding bromide and magnesium). The reaction mixture was stirred at -10 °C for 1 h and poured onto a saturated aqueous solution of NH<sub>4</sub>Cl (15 mL), which was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a petroleum ether/ethyl acetate mixture (2:1).

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(PHENYLAMINO)QUINOLIN-2(1H)-ONE (70)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

Phenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 51 mg, 44% (yellow solid).

**Data for compound 70:**

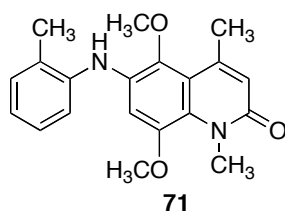
Melting point: 85-86 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>: C 70.35, H 6.21, N 8.64; found C 70.12, H 6.11, N 8.59.

IR (KBr):  $\nu$  = 3387, 2921, 1648, 1601 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 2.62 (s, 3H, 4-CH<sub>3</sub>), 3.68 (s, 3H, N-CH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 6.00 (br s, 1H, NH), 6.52 (s, 1H, 3-H), 6.97 (t, *J* = 7.4 Hz, 1H, 4'-H), 7.07-7.12 (m, 3H, 7-H, 2'-H, 6'-H), 7.34-7.27 (m, 2H, 5'-H, 3'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 23.7 (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 62.1 (OCH<sub>3</sub>), 106.7 (C-7), 117.7 (C-2', C-6'), 118.8 (C-4a), 121.5 (C-4'), 123.9 (C-3), 127.8 (C-8a), 130.0 (C-3', C-5'), 131.7 (C-6), 141.8 (C-5), 143.5 (C-8), 145.9, 146.0 (C-4, C-1') 163.2 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(O-TOLYLAMINO)QUINOLIN-2(1H)-ONE (71)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*o*-Tolylmagnesium bromide: 0.6 mL (1.08 mmol).

Yield: 81 mg, 65% (pale brown oil).

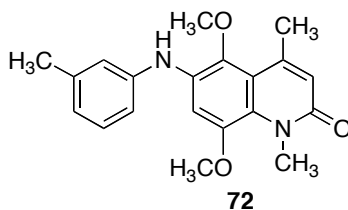
**Data for compound 71:**

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 70.99, H 6.55, N, 8.28; found C 71.05, H 6.60, N, 8.18.

IR (NaCl):  $\nu = 3392, 2936, 1651, 1599 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.32$  (s, 3H, 2'-CH<sub>3</sub>), 2.64 (d,  $J = 0.8$  Hz, 3H, 4-CH<sub>3</sub>), 3.70 (s, 3H, N-CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 5.72 (br s, 1H, NH), 6.53 (d,  $J = 0.8$  Hz, 1H, 3-H), 6.93 (s, 1H, 7-H), 6.94-6.99 (m, 1H, 6'-H), 7.18-7.24 (m, 3H, 3'-H, 4'-H, 5'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 18.3$  (2'-CH<sub>3</sub>), 23.7 (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.6 (OCH<sub>3</sub>), 61.9 (OCH<sub>3</sub>), 106.5 (C-7), 117.8 (C-6'), 118.7 (C-4a), 122.3 (C-4'), 124.0 (C-3), 127.4 (C-5'), 127.5 (C-8a), 128.4 (C-2'), 131.5 (C-3'), 132.4 (C-6), 141.3 (C-1'), 141.5 (C-5), 145.8 (C-8), 146.0 (C-4), 163.2 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(*m*-TOLYLAMINO)QUINOLIN-2(1*H*)-ONE (72)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1*H*)-one **64**: 100 mg (0.36 mmol).

*m*-Tolylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 52 mg, 43% (pale brown oil).

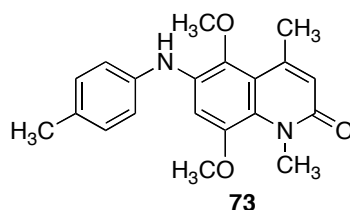
**Data for compound 72:**

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 70.99, H 6.55, N, 8.28; found C 70.75, H6.50, N, 8.13.

IR (NaCl):  $\nu = 3413, 2935, 1645, 1601 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.47$  (s, 3H, 3'-CH<sub>3</sub>), 2.74 (s, 3H, 4-CH<sub>3</sub>), 3.81 (s, 3H, N-CH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 6.14 (br s, 1H, NH), 6.23 (s, 1H, 3-H), 6.92 (d,  $J = 7.6$  Hz, 4'-H), 7.03-7.06 (m, 2H, 7-H, 5'-H), 7.28-7.39 (m, 2H, 2'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 22.0$  (3'-CH<sub>3</sub>), 23.7 (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 62.0 (OCH<sub>3</sub>), 106.8 (C-7), 114.7 (C-6'), 118.5 (C-4'), 118.8 (C-4a), 122.4 (C-2'), 123.8 (C-3), 127.6 (C-8a), 129.8 (C-5'), 131.8 (C-6), 139.9 (C-3'), 141.8 (C-5), 143.5 (C-1'), 145.9 (C-8), 146.1 (C-4), 163.3 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(*p*-TOLYLAMINO)QUINOLIN-2(1*H*)-ONE (73)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1*H*)-one **64**: 100 mg (0.36 mmol).

*p*-Tolylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 50 mg, 41% (pale brown oil).

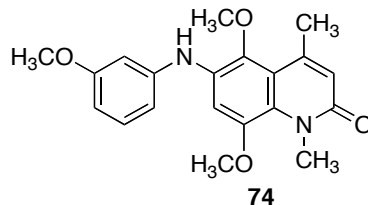
**Data for compound 73:**

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 70.99, H 6.55, N, 8.28; found C 70.75, H 6.50, N 8.30.

IR (NaCl):  $\nu = 3365, 2922, 1646, 1599 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.26$  (s, 3H, 4'-CH<sub>3</sub>), 2.61 (d,  $J = 0.9$  Hz, 3H, 4-CH<sub>3</sub>), 3.67 (s, 3H, N-CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 5.98 (br s, 1H, NH), 6.50 (d,  $J = 0.9$  Hz, 1H, 3-H), 7.01 (d,  $J = 8.3$  Hz, 2H, 3'-H, 5'-H), 7.06 (s, 1H, 7-H), 7.12 (d,  $J = 8.3$  Hz, 2'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 21.1$  (4'-CH<sub>3</sub>), 23.7 (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 61.9 (OCH<sub>3</sub>), 105.9 (C-7), 118.6 (C-2', C-6'), 118.7 (C-4a), 123.8 (C-3), 127.2 (C-8a), 130.5 (C-3', C-5'), 131.3 (C-6), 132.6 (C-4'), 140.7 (C-5), 141.2 (C-1'), 145.9 (C-4, C-8), 163.2 (C-2) ppm.

**5,8-DIMETHOXY-6-(3-METHOXYPHENYLAMINO)-1,4-DIMETHYLQUINOLIN-2(1H)-ONE (74)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*m*-Methoxyphenylmagnesium bromide: 1.8 mL (1.08 mmol).

Yield: 46 mg, 36% (pale brown oil).

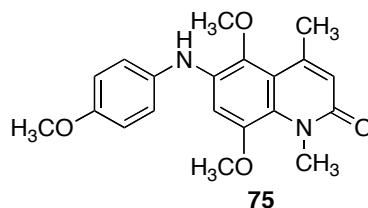
**Data for compound 74:**

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C 67.78, H 6.26, N, 7.90; found C 67.58, H 6.33, N 7.92.

IR (NaCl):  $\nu = 3433, 1645, 1607 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.55$  (s, 3H, 4-CH<sub>3</sub>), 3.62 (s, 3H, N-CH<sub>3</sub>), 3.73 (s, 3H, OCH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.77 (s, 3H, OCH<sub>3</sub>), 6.16 (br s, 1H, NH), 6.44 (d,  $J = 0.9$  Hz, 1H, 3-H), 6.45-6.47 (m, 1H, 2'-H), 6.60-6.71 (m, 2H, 4'-H, 5'-H), 7.11-7.19 (m, 2H, 7-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.7$  (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 55.6 (3'-OCH<sub>3</sub>), 57.4 (OCH<sub>3</sub>), 62.0 (OCH<sub>3</sub>), 103.1 (C-2'), 106.3 (C-7), 107.5 (C-6'), 109.9 (C-4'), 118.7 (C-4a), 123.7 (C-3), 127.9 (C-8a), 130.7 (C-5'), 131.4 (C-6), 142.3 (C-5), 145.1 (C-1'), 145.8 (C-8), 146.1 (C-4), 161.2 (C-3'), 163.2 (C-2) ppm.

**5,8-DIMETHOXY-6-(4-METHOXYPHENYLAMINO)-1,4-DIMETHYLQUINOLIN-2(1H)-ONE (75)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol)

*p*-Methoxyphenylmagnesium bromide: 1.08 mL (1.08 mmol)

Yield: 48 mg, 38% (yellow oil)

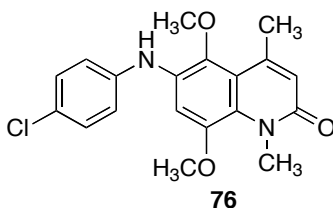
**Data for compound 75:**

Elemental analysis calc. (%) for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>: C 67.78, H 6.26, N 7.90; found C 67.63, H 6.17, N 7.83.

IR (NaCl):  $\nu = 3139, 2923, 1646, 1599 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.61$  (d,  $J = 0.6$  Hz, 3H, 4-CH<sub>3</sub>), 3.69 (s, 3H, N-CH<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.81 (s, 3H, OCH<sub>3</sub>), 5.87 (br s, 1H, NH), 6.77 (s, 1H, 3-H), 6.89 (d,  $J = 8.9$  Hz, 2H, 3'-H, 5'-H, partially overlapped with 7-H signal), 6.91 (s, 1H, 7-H), 7.08 (d,  $J = 8.9$  Hz, 2H, 2'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.6$  (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 56.0 (4'-OCH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 61.9 (OCH<sub>3</sub>), 104.6 (C-7), 115.3 (C-3', C-5'), 118.8 (C-4a), 122.1 (C-2', C-6'), 123.9 (C-3), 126.5 (C-8a), 134.0 (C-6), 135.9 (C-1'), 140.0 (C-5), 145.9 (C-8), 146.1 (C-4), 155.7 (C-4'), 163.1 (C-2) ppm.

**6-(4-CHLOROPHENYLAMINO)-5,8-DIMETHOXY-1,4-DIMETHYLQUINOLIN-2(1H)-ONE (76):****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Chlorophenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 46 mg, 36% (yellow solid).

**Data for compound 76:**

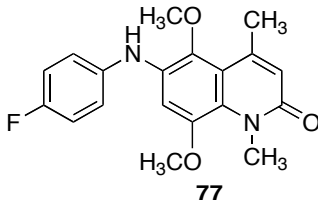
Melting point: 110-112 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub>Cl: C 63.60, H 5.34, N 7.81; found C 63.51, H 5.25, N 7.72.

IR (KBr):  $\nu = 3433, 2926, 1655, 1601 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.62$  (d,  $J = 0.9$  Hz, 3H, 4-CH<sub>3</sub>), 3.67 (s, 3H, N-CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 5.93, (br s, 1H, NH), 6.53 (d,  $J = 0.9$  Hz, 1H, 3-H), 7.01 (d,  $J = 8.8$  Hz, 2H, 3'-H, 5'-H), 7.04 (s, 1H, 7-H), 7.26 (d,  $J = 8.8$  Hz, 2H, 2'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.7$  (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 62.1 (OCH<sub>3</sub>), 106.7 (C-7), 118.7 (C-2', C-6'), 118.8 (C4a), 123.6 (C-4'), 124.1 (C-3), 126.1 (C-8a), 129.9 (C-3', C-5'), 131.1 (C-6), 142.1, 142.2 (C-5, C-1'), 145.8 (C-8), 146.0 (C-4), 163.2 (C-2) ppm.

**6-(4-FLUOROPHENYLAMINO)-5,8-DIMETHOXY-1,4-DIMETHYLQUINOLIN-2(1H)-ONE  
(77)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Fluorophenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 52 mg, 42% (pale brown solid).

**Data for compound 77:**

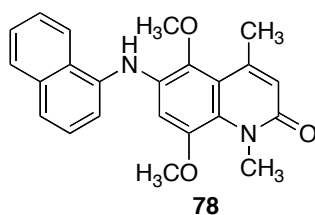
Melting point: 110-112 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>19</sub>FN<sub>2</sub>O<sub>3</sub>: C 66.66, H 5.59, N, 8.18; found C 66.46, H 5.61, N 8.21.

IR (KBr):  $\nu = 3317, 2935, 1654, 1600 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.59$  (s, 3H, 4-CH<sub>3</sub>), 3.66 (s, 3H, N-CH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 6.01 (br s, 1H, NH), 6.48 (s 1H, 3-H), 6.95 (s, 1H, 7-H), 6.99-7.08 (m, 4H, 2'-H, 3'-H, 5'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.6$  (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 61.9 (OCH<sub>3</sub>), 105.8 (C-7), 116.5 (d,  $J = 22.6$  Hz, C-3', C-5'), 118.8 (C-4a), 120.3 (d,  $J = 7.7$  Hz, C-2', C-6'), 123.9 (C-3), 127.4 (C-8a), 132.5 (C-6), 139.5 (d,  $J = 2.4$  Hz, C-1'), 141.3 (C-5), 145.8 (C-8), 146.0 (C-4), 158.4 (d,  $J = 240$  Hz, C-4'), 163.1 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(1-NAPHTHYLAMINO)QUINOLIN-2(1H)-ONE (78):****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

1-Naphthylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 69 mg, 51% (yellow oil).

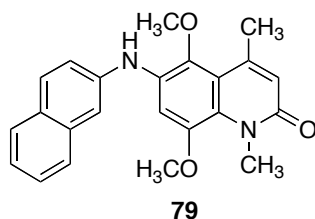
**Data for compound 78:**

Elemental analysis calc. (%) for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 73.78, H 5.92, N 7.48; found C 73.81, H 6.02, N 7.43.

IR (NaCl):  $\nu = 3321, 2932, 1646, 1603, 1576, 1513, 1482 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.67$  (s, 3H, 4-CH<sub>3</sub>), 3.67 (s, 3H, N-CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 3.84 (s, 3H, OCH<sub>3</sub>), 6.34 (br s, 1H, NH), 6.55 (br s, 1H, 3-H), 6.93 (s, 1H, 7-H), 7.26-7.40 (m, 1H, 2'-H), 7.43-7.61 (m, 4H, 3'-H, 4'-H, 6'-H, 7'-H), 7.89-7.93 (m, 1H, 5'-H), 8.07-8.11 (m, 1H, 8'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.7$  (4-CH<sub>3</sub>), 36.4 (N-CH<sub>3</sub>), 57.4 (OCH<sub>3</sub>), 62.3 (OCH<sub>3</sub>), 106.7 (C-7), 114.5 (C-2'), 121.9 (C-4', C-8'), 123.1 (C-4a), 124.0 (C-3), 126.3 (C-7'), 126.5 (C-4'a, C-6'), 126.8 (C-3'), 127.7 (C-8a), 129.1 (C-5'), 133.1 (C-6), 135.1 (C-8'a), 139.3 (C-1'), 141.4 (C-5), 145.9 (C-8), 146.1 (C-4), 163.3 (C-2) ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-6-(2-NAPHTHYLAMINO)QUINOLIN-2(1H)-ONE (79)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

Phenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 28 mg, 21% (pale brown solid).

**Data for compound 79:**

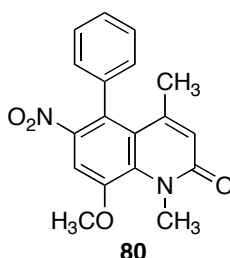
Melting point: 174-176 °C.

Elemental analysis calc. (%) for C<sub>23</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>: C 73.78, H 5.92, N 7.48; found C 73.66, H 5.90, N 7.41.

IR (KBr):  $\nu = 3326, 2932, 1648, 1603 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.64$  (d,  $J = 1.0$  Hz, 3H, 4-CH<sub>3</sub>), 3.71 (s, 3H, N-CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 6.18 (br s, 1H, NH), 6.54 (d,  $J = 1.0$  Hz, 1H, 3-H), 7.22 (s, 1H, 7-H), 7.25-7.36 and 7.40-7.47 (2m, 4H, Ar-H), 7.67 (d,  $J = 8.0$  Hz, 1H, 4'-H), 7.76-7.82 (m, 2H, Ar-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 23.7$  (4-CH<sub>3</sub>), 36.5 (N-CH<sub>3</sub>), 57.5 (OCH<sub>3</sub>), 62.2 (OCH<sub>3</sub>), 107.3 (C-7), 111.3 (C-1'), 118.8 (C-4a), 120.1 (C-3'), 124.0 (C-3), 124.1 (C-6'), 126.8 (C-8'), 127.1 (C-7'), 128.1 (C-5'), 128.2 (C-8a), 129.6 (C-4'a), 129.9 (C-4'), 131.5 (C-6), 135.0 (C-8'a), 141.4 (C-5), 142.4 (C-2'), 145.9 (C-8), 146.0 (C-4), 163.2 (C-2) ppm.

**8-METHOXY-1,4-DIMETHYL-6-NITRO-5-PHENYLQUINOLIN-2(1H)-ONE (80)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

Phenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 21 mg, 18% (pale brown solid).

**Data for compound 80:**

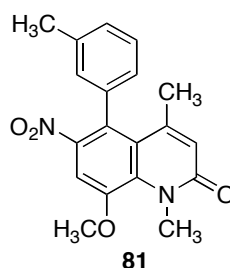
Melting point: 172-174 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C 66.66, H 4.97, N 8.64; found C 66.57, H 5.05, N 8.61.

IR (KBr):  $\nu = 3142, 2960, 1648, 1600, 1554 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 1.60$  (d,  $J = 1.0$  Hz, 3H, 4-CH<sub>3</sub>), 3.86 (s, 3H, N-CH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 6.52 (d,  $J = 1.0$  Hz, 1H, 3-H), 7.27-7.29 (m, 2H, Ph), 7.37-7.43 (m, 4H, 7-H, Ph) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 24.9$  (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.0 (OCH<sub>3</sub>), 106.9 (C-7), 125.8 (C-3, C-5), 127.1 (C-4a), 128.5 (C-2', C-6'), 129.2 (C-4'), 130.6 (C-3', C-5'), 136.1, 136.2 (C-1', C-8a), 146.6 (C-6), 148.0 (C-4), 148.5 (C-8), 162.9 (C-2) ppm.

**8-METHOXY-1,4-DIMETHYL-6-NITRO-5-(*M*-TOLYL)QUINOLIN-2(1*H*)-ONE (81)**

Yield: 24 mg, 2% (pale brown solid)

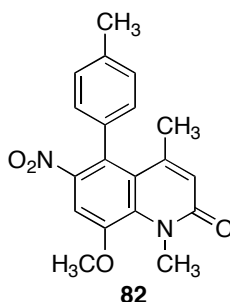
**Data for compound 81:**

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 67.44, H 5.36, N, 8.28; found C 67.52, H 5.41, N 8.30.

IR (KBr):  $\nu = 2922, 1660, 1572, 1523, 1051 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 1.63$  (s, 3H, 3'-CH<sub>3</sub>), 2.37 (s, 3H, 4-CH<sub>3</sub>), 3.86 (s, 3H, N-CH<sub>3</sub>), 4.00 (s, 3H, OCH<sub>3</sub>), 6.53 (s, 1H, 3-H), 7.06-7.08 and 7.25-7.27 (2m, 4H, 2'-H, 4'-H, 5'-H, 6'-H), 7.38 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 21.8$  (3'-CH<sub>3</sub>), 24.9 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.0 (OCH<sub>3</sub>), 106.8 (C-7), 123.0 (C-5), 125.7 (C-3), 127.1 (C-4a), 127.8 (C-6'), 128.4 (C-4'), 129.9 (C-2'), 131.2 (C-5'), 136.0, 136.1 (C-1', C-8a), 138.2 (C-3'), 146.3 (C-6), 148.2 (C-4), 148.4 (C-8), 163.0 (C-2) ppm.

**8-METHOXY-1,4-DIMETHYL-6-NITRO-5-(*p*-TOLYL)QUINOLIN-2(1*H*)-ONE (82)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1*H*)-one **64**: 100 mg (0.36 mmol)

*p*-Tolylmagnesium bromide: 1.08 mL (1.08 mmol)

Yield: 16 mg, 13% (pale brown solid)

**Data for compound 82:**

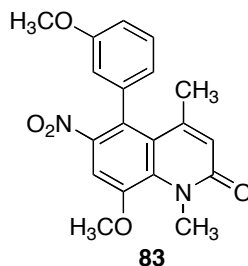
Melting point: 181-183 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 67.44, H 5.36, N 8.28; found C 67.40, H 5.31, N 8.19.

IR (KBr):  $\nu = 3141, 1665, 1607, 1567, 1522 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 1.63$  (d,  $J = 0.9$  Hz, 3H, 4-CH<sub>3</sub>), 2.41 (s, 3H, 4'-CH<sub>3</sub>), 3.85 (s, 3H, N-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 6.52 (d,  $J = 0.9$  Hz, 1H, 3-H), 7.12-7.21 (m, 4H, 2'-H, 3'-H, 5'-H, 6'-H), 7.36 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 21.8$  (4'-CH<sub>3</sub>), 24.9 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.0 (OCH<sub>3</sub>), 106.8 (C-7), 123.2 (C-5), 125.6 (C-3), 126.9 (C-4a), 129.3 (C-2', C-6'), 130.5 (C-3', C-5'), 133.1 (C-4'), 136.2 (C-8a), 139.2 (C-1'), 146.4 (C-6), 148.2 (C-4), 148.4 (C-8), 163.0 (C-2) ppm.

**8-METHOXY-5-(3-METHOXYPHENYL)-1,4-DIMETHYL-6-NITROQUINOLIN-2(1H)-ONE  
(83)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Methoxyphenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 24 mg, 19% (pale brown solid).

**Data for compound 83:**

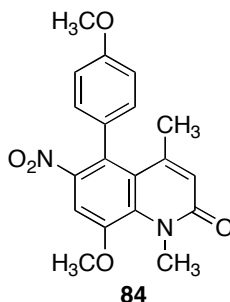
Melting point: 160-161 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C 64.40, H 5.12, N, 7.91; found C 64.36, H 5.18, N 7.86.

IR (KBr):  $\nu$  = 3057, 2941, 1659, 1607, 1570, 1524, 1048 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.69 (s, 3H, 4-CH<sub>3</sub>), 3.79 (s, 3H, N-CH<sub>3</sub>), 3.84 (s, 3H, 3'-OCH<sub>3</sub>), 3.99 (s, 3H, 8-OCH<sub>3</sub>), 6.52 (s, 1H, 3-H), 6.77-6.79 (m, 1H, 2'-H), 6.86-6.83 and 6.93-6.97 (2m, 2H, 4'-H, 6'-H), 7.29 (dd, *J* = 8.1 and 7.7 Hz, 1H, 5'-H), 7.37 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.6 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 55.7 (3'-OCH<sub>3</sub>), 57.0 (8'-OCH<sub>3</sub>), 106.8 (C-7), 114.5 (C-4'), 116.6 (C-2'), 122.9 (C-5), 123.3 (C-6'), 125.7 (C-3), 126.8 (C-4a), 129.6 (C-5'), 136.2 (C-8a), 137.3 (C-1'), 146.3 (C-6), 148.1 (C-4), 148.5 (C-8), 159.6 (C-3'), 162.9 (C-2) ppm.

**8-METHOXY-5-(4-METHOXYPHENYL)-1,4-DIMETHYL-6-NITROQUINOLIN-2(1H)-ONE (84):****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol)

*p*-Tolylmagnesium bromide: 1.08 mL (1.08 mmol)

Yield: 42 mg, 33% (pale brown oil)

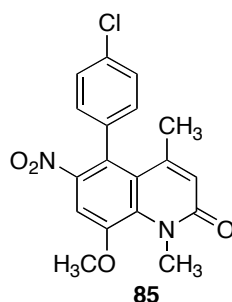
**Data for compound 84:**

Elemental analysis calc. (%) for (C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>): C 64.40, H 5.12, N 7.91; found C 64.34, H 5.17, N 7.79.

IR (NaCl):  $\nu$  = 3139, 1646, 1599, 1513, 1494 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.64 (d, *J* = 0.9 Hz, 3H, 4-CH<sub>3</sub>), 3.84 (s, 3H, N-CH<sub>3</sub>), 3.85 (s, 3H, 4'-OCH<sub>3</sub>), 3.98 (s, 3H, 8-OCH<sub>3</sub>), 6.53 (d, *J* = 0.9 Hz, 1H, 3-H), 6.91 (d, *J* = 8.8 Hz, 2H, 3'-H, 5'-H), 7.14 (d, *J* = 8.8 Hz, 2H, 2'-H, 6'-H), 7.35 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 25.0 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 55.6 (4'-OCH<sub>3</sub>), 57.0 (8-OCH<sub>3</sub>), 106.8 (C-7), 114.0 (C-3', C-5'), 123.4 (C-4a), 125.5 (C-3), 126.8 (C-5), 127.9 (C-1'), 131.7 (C-2', C-6'), 136.0 (C-8a), 146.6 (C-6), 148.4 (C-4), 148.5 (C-8), 160.3 (C-4'), 163.1 (C-2) ppm.

**5-(4-CHLOROPHENYL)-8-METHOXY-1,4-DIMETHYL-6-NITROQUINOLIN-2(1H)-ONE (85)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Chlorophenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 40 mg, 31% (yellow solid).

**Data for compound 85:**

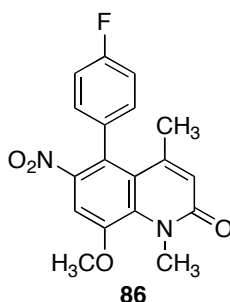
Melting point: 139-141 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>Cl: C 60.26, H 4.21, N 7.81; found C 60.25, H 4.18, N 7.74.

IR (KBr):  $\nu$  = 2926, 1663, 1623, 1606, 1517 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.64 (d, *J* = 1.0 Hz, 3H, 4-CH<sub>3</sub>), 3.86 (s, 3H, N-CH<sub>3</sub>), 4.01 (s, 3H, OCH<sub>3</sub>), 6.54 (d, *J* = 1.0 Hz, 1H, 3-H), 7.21 (d, *J* = 8.4 Hz, 2H, 3'-H, 5'-H), 7.38 (d, *J* = 8.4 Hz, 2H, 2'-H, 6'-H, partially overlapped with 7-H signal), 7.40 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 25.4 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.1 (OCH<sub>3</sub>), 107.0 (C-7), 122.9 (C-4a), 125.8 (C-5), 126.1 (C-3), 128.9 (C-2', C-6'), 132.0 (C-3', C-5'), 134.8 (C-1', C-4'), 136.4 (C-8a), 146.4 (C-6), 147.6 (C-4), 148.8 (C-8), 162.9 (C-2) ppm.

**5-(4-FLUOROPHENYL)-8-METHOXY-1,4-DIMETHYL-6-NITROQUINOLIN-2(1H)-ONE (86)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Fluorophenylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 36 mg, 29% (yellow solid).

**Data for compound 86:**

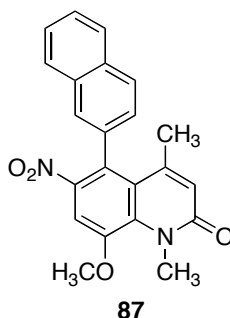
Melting point: 106-108 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>4</sub> (342): C 63.15, H 4.42, N, 8.18; found C 63.23, H 4.50, N 8.21.

IR (KBr):  $\nu$  = 2937, 2853, 1665, 1605, 1575, 1522, 1443 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.60 (s, 3H, 4-CH<sub>3</sub>), 3.83 (s, 3H, N-CH<sub>3</sub>), 3.98 (s, 3H, OCH<sub>3</sub>), 6.52 (s, 1H, 3-H), 7.07 (m, 2H, 3'-H, 5'-H), 7.24 (m, 2H, 2'-H, 6'-H), 7.38 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 25.2 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.0 (OCH<sub>3</sub>), 106.9 (C-7), 115.8 (d, *J* = 21.8 Hz, C-3', C-5'), 123.1 (C-5), 125.9 (C-4a), 126.0 (C-3), 132 (d, *J* = 2.7 Hz, C-1'), 132.4 (d, *J* = 8.2 Hz, C-2', C-6'), 136.3 (C-8a), 146.5 (C-6), 147.7 (C-4), 148.7 (C-8), 162.9 (C-2), 166.6 (d, *J* = 239.4 Hz, C-4') ppm.

**8-METHOXY-1,4-DIMETHYL-5-(NAPHTHALEN-2-YL)-6-NITROQUINOLIN-2(1H)-ONE (87)****Reaction data:**

5,6-Dimethoxy-1,4-dimethyl-6-nitroquinolin-2(1H)-one **64**: 100 mg (0.36 mmol).

*p*-Tolylmagnesium bromide: 1.08 mL (1.08 mmol).

Yield: 33 mg, 24% (brown solid).

**Data for compound 87:**

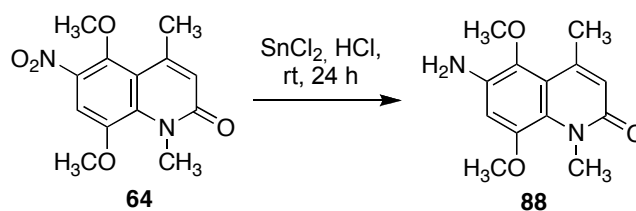
Melting point: 143-145 °C.

Elemental analysis calc. (%) for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 70.58, H 4.85, N 7.48; found C 70.49, H 4.77, N 7.41.

IR (KBr):  $\nu$  = 2934, 2836, 1661, 1605, 1570, 1518, 1449 cm<sup>-1</sup>.

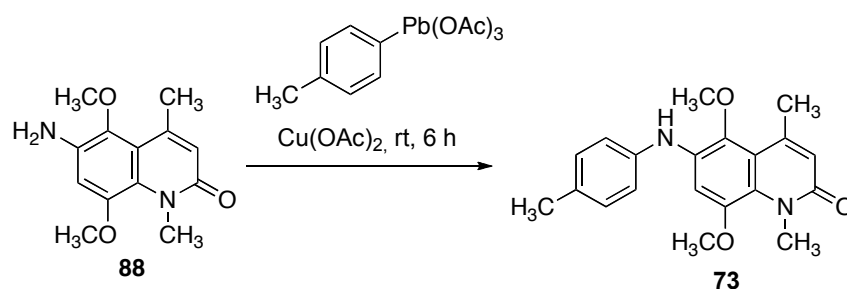
<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.56 (d, *J* = 1.0 Hz, 3H, 4-CH<sub>3</sub>), 3.89 (N-CH<sub>3</sub>), 4.08 (OCH<sub>3</sub>), 6.52 (d, *J* = 1.0 Hz, 1H, 3-H), 7.43 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 3'-H), 7.44 (s 1H, 7-H), 7.51-7.60 (m, 2H, 6'-H, 7'-H), 7.70 (s, 1H, 2'-H), 7.78-7.82 (m, 1H, 4'-H), 7.86-7.91 (m, 2H, 5'-H, 8'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 25.2 (4-CH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 57.0 (OCH<sub>3</sub>), 107.0 (C-7), 123.3 (C-5), 125.8 (C-3), 127.1 (C-4a), 127.2, 127.3, 128.1, 128.2, 128.5, 128.6, 129.5, 133.0 (C-4'a), 133.4 (C-8'a), 133.7 (C-2'), 136.3 (C-8a), 146.6 (C-6), 148.1 (C-4), 148.6 (C-8), 162.9 (C-2) ppm.

**6-AMINO-5,8-DIMETHOXY-1,4-DIMETHYLQUINOLIN-2(1H)-ONE (88)**

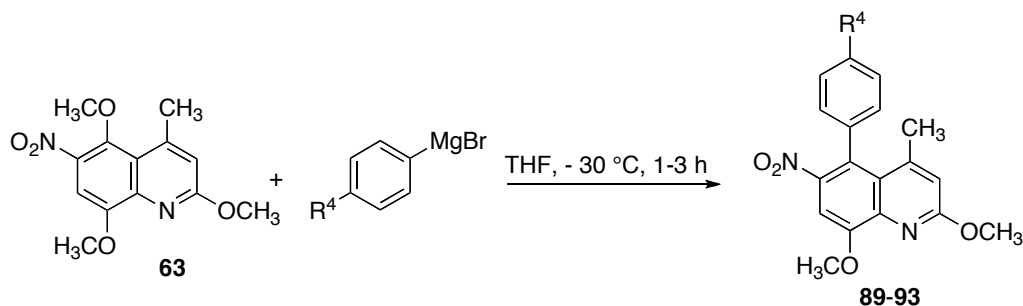
To a suspension of the nitro compound **64** (278 mg, 1 mmol) in 35% aqueous hydrochlorid acid (7 mL) was added stannous chloride dihydrate (1.12 g, 50 mmol of SnCl<sub>2</sub>). The reaction was stirred for 24 h at rt and was then basified to pH 10 with a 20% aqueous solution of sodium hydroxide, which was extracted with chloroform (4 x 30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated, yielding 228 mg (92%) of compound **88**.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C): δ = 2.58 (d, *J* = 0.9 Hz, 3H, 4-CH<sub>3</sub>), 3.67 (s, 3H, OCH<sub>3</sub>), 3.78 (s, 6H, OCH<sub>3</sub> and N-CH<sub>3</sub>), 3.9 (br s, 2H, NH<sub>2</sub>), 6.45 (d, *J* = 0.9 Hz, 3-H), 6.62 (s, 1H, 7-H) ppm. <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C): δ = 22.9 (4-CH<sub>3</sub>), 35.8 (N-CH<sub>3</sub>), 56.7 (8-OCH<sub>3</sub>), 60.3 (5-OCH<sub>3</sub>), 104.3 (C-7), 118.1 (C-4a), 123.1 (C-3), 125.1 (C-8a), 135.1 (C-6), 137.5 (C-5), 145.2 (C-4), 145.6 (C-8), 162.5 (C-2) ppm.

**SYNTHESIS OF COMPOUND 73 BY N-ARYLATION OF 88**

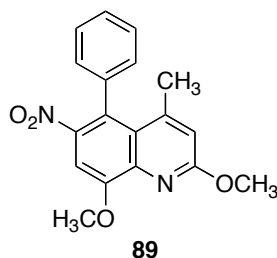
A solution of amine **88** (225 mg, 0.9 mmol), *p*-tolyllead triacetate (0.56 g, 1.17 mmol) and copper(II) acetate (20 mg) in dichloromethane (10 mL) was stirred at room temperature for 6 h. The reaction mixture was filtered through a layer of alumina, which was washed with dichloromethane (2 x 20 mL). The combined organic layers were evaporated and the residue was purified by column chromatography on silica gel, eluting with a gradient from 8:2 to 1:1 petroleum ether-ethyl acetate, affording 228 mg (75%) of compound **73**, which was identical in all respects to the sample obtained by the alternative method described above, starting from nitro derivative **64**.

**REACTION OF COMPOUND 63 WITH ARYL GRIGNARD REAGENTS.  
SYNTHESIS OF COMPOUNDS 89-93**



**General procedure:**

To a solution of 2,5,8-trimethoxy-4-methyl-6-nitroquinoline **63** (100 mg, 0.36 mmol) in THF (10 mL) was added the suitable arylmagnesium bromide (1.1 mmol, as a commercially available solution in THF). The reaction mixture was stirred at -30 °C for 1-3 h and poured onto a saturated aqueous solution of NH<sub>4</sub>Cl (15 mL), which was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a petroleum ether/ethyl acetate mixture (3:1).

**5-PHENYL-2,8-DIMETHOXY-4-METHYL-6-NITROQUINOLINE (89)****Reaction data:**

2,5,8-Trimethoxy-4-methyl-6-nitroquinoline **63**: 150 mg (0.54 mmol)

Phenylmagnesium bromide: 2.92 mL (1.62 mmol)

Reaction time: 3 h

Yield: 100 mg, 57% (brownish solid)

**Data for compound 89:**

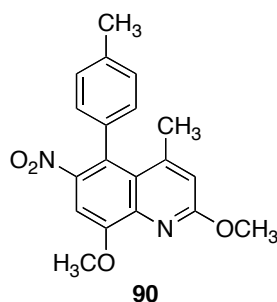
Melting point: 184-186 °C

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: C 66.66, H 4.97, N 8.64; found C 66.58, H 5.04, N 8.60.

IR (NaCl):  $\nu = 1582, 1504, 1322 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 1.74$  (s, 3H, 4-CH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 6.67 (s, 1H, 3-H), 7.17-7.26 (m, 3H), 7.26-7.33 (m, 3H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 24.2, 53.4, 56.7, 102.6, 117.4, 124.6, 125.3, 127.9, 128.4, 130.4, 136.5, 140.7, 147.1, 150.1, 154.5, 162.6$  ppm.

**5-(4-METHYLPHENYL)-2,8-DIMETHOXY-4-METHYL-6-NITROQUINOLINE (90)****Reaction data:**

2,5,8-Trimethoxy-4-methyl-6-nitroquinoline **63**: 150 mg (0.54 mmol).

*p*-Tolylmagnesium bromide: 3.15 mL (1.62 mmol).

Reaction time: 2 h

Yield: 109 mg, 60% (yellow solid).

**Data for compound 90:**

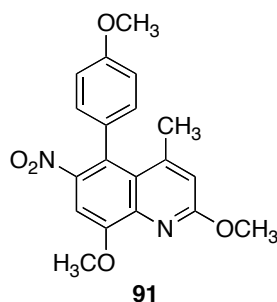
Melting point: 203-205 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C 67.44, H 5.36, N 8.28; found C 67.46, H 5.39, N 8.23

IR (NaCl):  $\nu = 1608, 1505 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 1.88$  (d,  $J = 0.9$  Hz, 3H, 4-CH<sub>3</sub>), 2.45 (s, 3H, 4'-CH<sub>3</sub>), 4.13 (s, 3H, 8-OMe), 4.15 (s, 3H, 2-OMe), 6.78 (d,  $J = 0.9$  Hz, 1H, 3-H) 7.22 (br s, 4H, 2'-H, 3'-H, 5'-H, 6'-H), 7.28 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 21.3$  (4'-CH<sub>3</sub>), 24.3 (4-CH<sub>3</sub>), 53.4 (2-OCH<sub>3</sub>), 56.6 (8-OCH<sub>3</sub>), 102.5 (C-7), 117.3 (C-3), 124.7 and 125.3 (C-4a, C-5), 128.6 (C-3', C-5'), 130.1 (C-2', C-6'), 133.3 (C-1'), 138.3, 140.6 and 147.3 (C-6, C-8a and C-4'), 150.3 (C-4), 154.3 (C-8), 162.6 (C-2) ppm.

**5-(4-METHOXYPHENYL)-2,8-DIMETHOXY-4-METHYL-6-NITROQUINOLINE (91)****Reaction data:**

2,5,8-Trimethoxy-4-methyl-6-nitroquinoline **63**: 150 mg (0.54 mmol).

*p*-Methoxyphenylmagnesium bromide: 3.58 mL (1.62 mmol).

Reaction time: 3 h

Yield: 168 mg, 88% (yellow solid).

**Data for compound 91:**

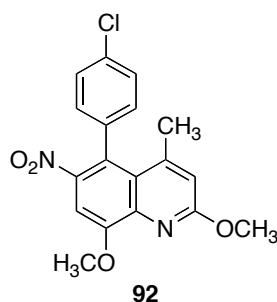
Melting point: 200-202 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>: C 64.40, H 5.12, N 7.91; found C 64.38, H 5.19, N 7.83.

IR (NaCl):  $\nu = 1605, 1582, 1504 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 1.90 (d, *J* = 0.7 Hz, 3H, 4-CH<sub>3</sub>), 3.89 (s, 3H, 4'-OCH<sub>3</sub>), 4.12 (s, 3H, 8-OCH<sub>3</sub>), 4.15 (s, 3H, 2-OCH<sub>3</sub>), 6.78 (d, *J* = 0.7 Hz, 1H, 3-H), 6.95 (d, *J* = 8.8 Hz, 2H, 3'-H, 5'-H), 7.23 (d, *J* = 8.8 Hz, 2H, 2'-H, 6'-H), 7.27 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 24.4 (4-CH<sub>3</sub>), 53.4 (4'-OCH<sub>3</sub>), 55.2 (8-OCH<sub>3</sub>), 56.6 (2-OCH<sub>3</sub>), 102.4 (C-7), 113.4 (C-3', C-5'), 114.7 (C-5), 117.3 (C-3), 124.9 (C-4a), 128.3 (C-1'), 131.4 (C-2', C-6'), 140.5 (C-6), 147.5 (C-8a), 150.2 (C-4), 154.3 (C-8), 159.7 (C-4'), 162.6 (C-2) ppm.

**5-(4-CHLOROPHENYL)-2,8-DIMETHOXY-4-METHYL-6-NITROQUINOLINE (92)****Reaction data:**

2,5,8-Trimethoxy-4-methyl-6-nitroquinoline **63**: 150 mg (0.54 mmol).

*p*-Chlorophenylmagnesium bromide: 3.94 mL (1.62 mmol).

Reaction time: 3 h

Yield: 120 mg, 62% (yellow solid).

**Data for compound 92:**

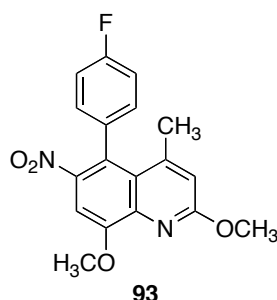
Melting point: 169-171 °C

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>Cl: C 60.26, H 4.21, N 7.81; found: C 60.38, H 4.44, N 7.75.

IR (NaCl):  $\nu = 1518, 1320 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) <sup>TM</sup> = 1.90 (s, 3H, CH<sub>3</sub>), 4.15 (s, 3H, OCH<sub>3</sub>), 4.17 (s, 3H, OCH<sub>3</sub>), 6.82 (s, 1H), 7.30-7.33 (m, 3H), 7.43 (d, *J* = 8.3 Hz, 1H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) <sup>TM</sup> = 24.7, 53.5, 56.7, 102.5, 117.7, 123.9, 124.4, 128.2, 131.7, 134.7, 135.0, 140.7, 147.1, 149.7, 154.7, 162.7 ppm.

**5-(4-FLUOROPHENYL)-2,8-DIMETHOXY-4-METHYL-6-NITROQUINOLINE (93)****Reaction data:**

2,5,8-Trimethoxy-4-methyl-6-nitroquinoline **63**: 150 mg (0.54 mmol)

*p*-Fluorophenylmagnesium bromide: 3.16 mL (1.62 mmol)

Reaction time: 3 h

Yield: 115 mg, 60% (yellow solid)

**Data for compound 89:**

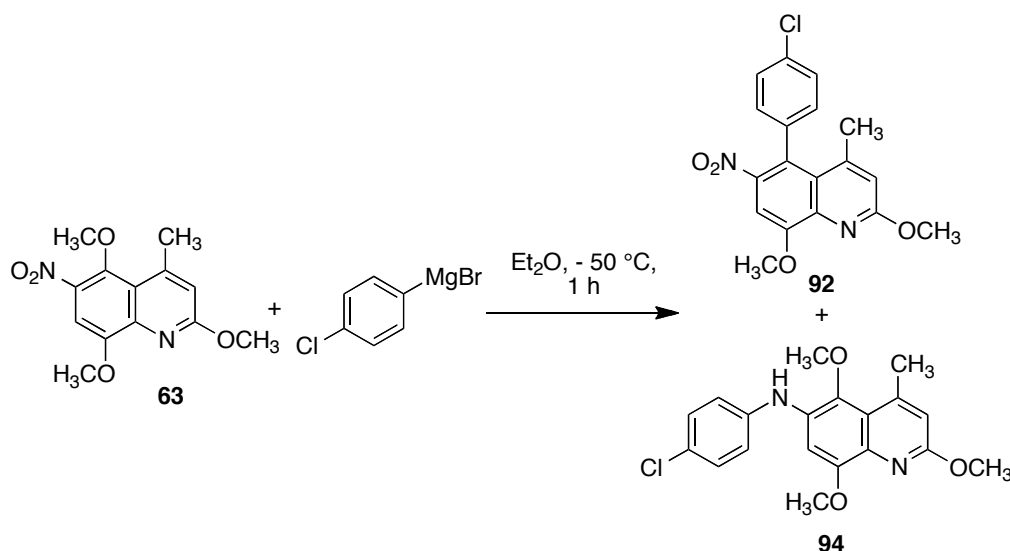
Melting point: 168-170 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>F: C 63.15, H 4.42, N 8.18; found C 63.11, H 4.45, N 8.13.

IR (NaCl):  $\nu = 1580, 1520, 1330 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>) <sup>TM</sup> = 1.86 (d, *J* = 0.9 Hz, 3H, 4-CH<sub>3</sub>), 4.13 (s, 3H, 2-OCH<sub>3</sub>), 4.15 (s, 3H, 8-OCH<sub>3</sub>), 6.79 (d, *J* = 0.9 Hz, 1H, 3-H), 7.10–7.16 (m, 2H, 3'-H, 5'-H), 7.30 (s, 1H, 7-H, partially overlapped with 2'-H and 6'-H signal), 7.28-7.33 (m, 2H, 2'-H, 6'-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>) <sup>TM</sup> = 24.5 (4-CH<sub>3</sub>), 53.5 (2-OCH<sub>3</sub>), 56.6 (8-OCH<sub>3</sub>), 102.5 (C-7), 115.1 (d, *J* = 21.7 Hz, C-3', C-5'), 117.6 (C-3), 124.1 (C-5), 124.6 (C-4a), 132.1 (d, *J* = 8.1 Hz, C-2', C-6'), 132.3 (d, *J* = 3.7 Hz, C-1'), 140.7, and 147.3 (C-6 and C-8a), 149.8 (C-4), 154.7 (C-8), 162.7 (C-2), 162.9 (d, *J* = 248.9 Hz, C-4'), ppm.

**REACTION BETWEEN COMPOUND 63 AND 4-CHLOROPHENYLMAGNESIUM CHLORIDE IN ETHER**

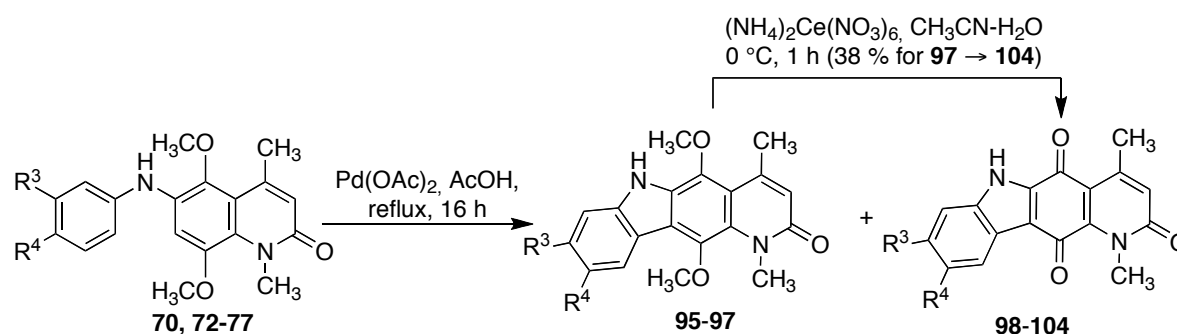
To a solution of 2,5,8-trimethoxy-4-methyl-6-nitroquinoline **63** (100 mg, 0.36 mmol) in THF (10 mL) was added 4-chlorophenylmagnesium chloride (1.1 mmol, as a commercially available 1M solution in Et<sub>2</sub>O). The reaction mixture was stirred at -50 °C for 1 h and poured onto a saturated aqueous solution of NH<sub>4</sub>Cl (15 mL), which was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with a petroleum ether/ethyl acetate mixture (3:1), giving a mixture of compounds **92** (49%) and **94** (26%), which could not be separated.

**Data for compound 94:**

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)<sup>TM</sup> = 2.20 (s, 3H, 4-CH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>); 4.06 (s, 3H, OCH<sub>3</sub>), 4.12 (s, 3H, 2-OCH<sub>3</sub>), 6.21 (s, 1H, NH); 6.84 (d, *J* = 0.8 Hz, 1H, 3-H), 6.77 (d, *J* = 8.4 Hz, 2H, 2'-H, 6'-H); 7.15 (d, *J* = 8.4 Hz, 2H, 3'-H, 5'-H), 7.48 (s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)<sup>TM</sup> = 163.6, 154.6, 150.6, 149.3, 147.4, 142.8, 137.7, 134.7, 129.3, 125.0, 120.9, 116.7, 116.1, 103.9, 63.2, 56.6, 53.6, 23.3 ppm.

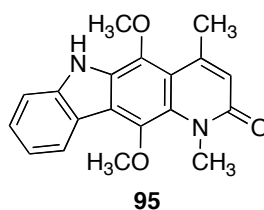
## SYNTHESIS OF TETRACYCLIC LINEARLY FUSED CARBAZOLES 95-104



Dimethoxy derivative	Quinone	R <sup>3</sup>	R <sup>4</sup>
<b>95</b>	<b>98</b>	H	H
--	<b>99</b>	CH <sub>3</sub>	H
--	<b>100</b>	H	CH <sub>3</sub>
--	<b>101</b>	OCH <sub>3</sub>	H
--	<b>102</b>	H	OCH <sub>3</sub>
<b>96</b>	<b>103</b>	H	Cl
<b>97</b>	<b>104</b>	H	F

**General procedure:**

A solution of the suitable 5,8-dimethoxy-1,4-dimethyl-6-(1-arylamino)quinolin-2(1H)-one (1 eq) and Pd(OAc)<sub>2</sub> (2 eq) in acetic acid (15 mL) was heated at 120 °C for 16 h, under an argon atmosphere. The reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel, eluting with an ethyl acetate/petroleum ether 3:1, to give compounds **95-97** and/or **98-104**.

**5,11-DIMETHOXY-1,4-DIMETHYL-1*H*-PYRIDO[3,2-*b*]CARBAZOL-2(6*H*)-ONE (95)**

Yield: 29 mg, 25% (orange solid).

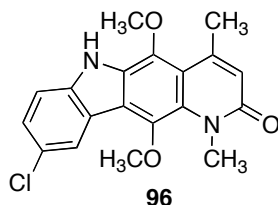
Melting point: 270-272 °C.

Elemental analysis calc. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.79, H 5.63, N, 8.69; found C 70.82, H 5.71, N, 8.60.

IR (KBr):  $\nu$  = 3202, 2930, 1635, 1587, 1550, 1484, 1437, 1230 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 2.74 (s, 3H, 4-CH<sub>3</sub>), 3.85 (s, 3H, 1-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 6.54 (s, 1H, 3-H), 7.28-7.34 (m, 1H, 9-H), 7.51-7.52 (m, 2H, 7-H, 8-H), 8.31 (d, *J* = 7.9 Hz, 1H, 10-H), 8.34 (br s, 1H, 6-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 23.7, 36.1, 61.8, 62.3, 111.2, 116.5, 120.6, 121.4, 122.3, 122.5, 124.0, 127.8, 128.9, 130.7, 139.1, 140.3, 141.2, 146.4, 163.8 ppm.

**9-CHLORO-5,11-DIMETHOXY-1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOL-2(6H)-ONE (96)**

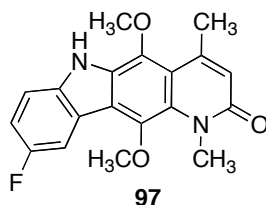
Yield: 32 mg, 33% (yellow solid).

Elemental analysis calc. for  $C_{19}H_{17}N_2O_3Cl$ : C 63.96, H 4.80, N, 7.85; found C 64.01, H 4.89, N, 7.77.

IR (KBr):  $\nu = 3429, 2929, 1650, 1494 \text{ cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 2.73$  (d,  $J = 1.1$  Hz, 3H, 4- $\text{CH}_3$ ), 3.85 (s, 3H, 1- $\text{CH}_3$ ), 3.97 (s, 3H,  $\text{OCH}_3$ ), 3.99 (s, 3H,  $\text{OCH}_3$ ), 6.55 (d,  $J = 1.1$  Hz, 1H, 3-H), 7.43-7.46 (m, 2H, 7-H, 8-H), 8.27 (d,  $J = 1.9$  Hz, 1H, 10-H), 8.33 (br s, 1H, 6-H) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 23.7, 36.0, 61.9, 62.4, 104.9, 112.2, 122.9, 123.4, 125.9, 127.8, 129.1, 130.6, 131.2, 139.2, 139.5, 139.9, 140.2, 146.3, 163.7$  ppm.

**9-FLUORO-5,11-DIMETHOXY-1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOL-2(6H)-ONE (97)**

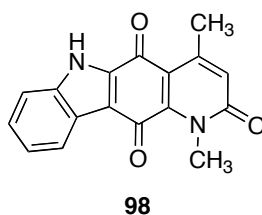
Yield: 30 mg, 32% (brownish solid).

Melting point: 170-172 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>17</sub>N<sub>2</sub>O<sub>3</sub>F: C 67.05, H 5.03, N 8.23; found C 67.16, H 5.05, N 8.19.

IR (KBr):  $\nu$  = 3417, 2918, 2849, 1653, 1599, 1571, 1450 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 2.73 (s, 3H, 4-CH<sub>3</sub>), 3.83 (s, 3H, 1-CH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 3.94 (s, 3H, OCH<sub>3</sub>), 6.56 (s, 1H, 3-H), 7.43-7.49 (m, 2H, 7-H, 10-H), 7.96 (dd, *J* = 8.9 and 2.5 Hz, 1H, 8-H), 8.29 (br s, 1H, 6-H) ppm.

**1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOLE-2,5,11(6H)-TRIONE (98)**

Yield: 64 mg, 59% (red solid).

Melting point > 300 °C.

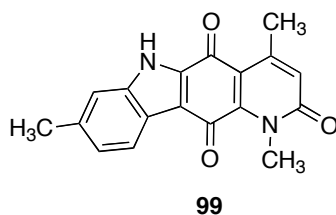
Elemental analysis calc. (%) for C<sub>17</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C 69.86, H 4.14, N 9.58; found C 69.93, H 4.17, N 9.49.

MS: m/z, 292 (M<sup>+</sup>), 264, 263.

IR (KBr):  $\nu$  = 3500-2500, 1647 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.56 (s, 3H, 4-CH<sub>3</sub>), 3.84 (s, 3H, 1-CH<sub>3</sub>), 6.58 (s, 1H, 3-H), 7.30-7.40 (m, 2H, 8-H, 9-H), 7.56 (d, J = 7.5 Hz, 1H, 7-H), 8.06 (d, J = 7.5 Hz, 1H, 10-H), 12.94 (br s, 1H, 6-H) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 30.6, 34.5, 113.8, 114.8, 116.0, 121.8, 122.4, 123.6, 123.9, 126.4, 136.2, 137.7, 145.8, 149.1, 161.3, 177.3, 178.0 ppm.

**1,4,8-TRIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOLE-2,5,11(6H)-TRIONE (99)**

Yield: 45 mg, 25% (dark red solid).

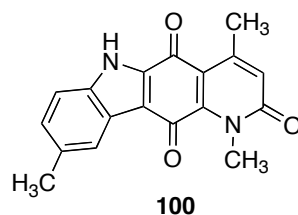
Melting point > 300 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 70.58, H 4.61, N 9.15; found C 70.61, H 4.55, N 8.97.

MS: m/z, 306 (M<sup>+</sup>), 278, 277.

IR (KBr):  $\nu$  = 3500-2500, 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.36 (s, 3H, 8-CH<sub>3</sub>), 2.56 (s, 3H, 4-CH<sub>3</sub>), 3.83 (s, 3H, 1-CH<sub>3</sub>), 6.57 (s, 3H, 3-H), 7.17 (d, *J* = 8.8 Hz, 1H, 9-H), 7.32 (s, 1H, 7-H), 7.93 (d, *J* = 8.8 Hz, 1H, 10-H), 12.81 (br s, 1H, 1-H) ppm.

**1,4,9-TRIMETHYL-1H-PYRIDO[3,2-b]CARBAZOLE-2,5,11(6H)-TRIONE (100)**

Yield: 52 mg, 45% (dark red solid).

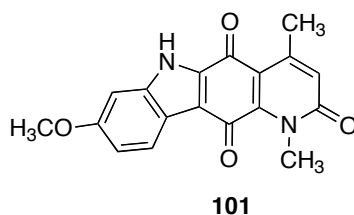
Melting point > 300 °C.

Elemental analysis calc. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C 70.58, H 4.61, N 9.15; found C 70.57, H 4.58, N 9.07.

MS: m/z, 306 (M<sup>+</sup>), 77.

IR (KBr):  $\nu$  = 3500-2500, 1650 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.44 (s, 3H, 9-CH<sub>3</sub>), 2.57 (s, 3H, 4-CH<sub>3</sub>), 3.84 (s, 3H, 1-CH<sub>3</sub>), 6.59 (s, 1H, 3-H), 7.24 (d, *J* = 8.7 Hz, 1H, 8-H), 7.45 (d, *J* = 8.7 Hz, 1H, 7-H), 7.87 (s, 1H, 10-H) 12.86 (br s, 1H, 6-H) ppm.

**8-METHOXY-1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOLE-2,5,11(6H)-TRIONE (101)**

Yield: 44 mg, 48% (brownish solid).

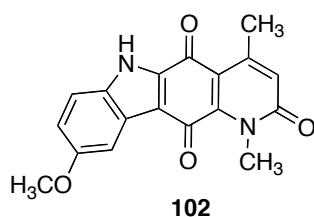
Melting point: 272-275 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C 67.07, H 4.38, N 8.69; found C 67.12, H 4.41, N 8.60.

MS: m/z, 322 (M<sup>+</sup>), 294, 293.

IR (KBr):  $\nu = 3500-2500, 1651 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO)  $\delta = 2.56$  (s, 3H, 4-CH<sub>3</sub>), 3.79 (s, 6H, 1-CH<sub>3</sub>, 8-OCH<sub>3</sub>), 6.57 (s, 1H, 3-H), 6.97 (d,  $J = 8.6$  and 2.2 Hz, 2H, 7-H, 9-H), 7.92 (dd,  $J = 8.6$  Hz, 1H, 10-H), 12.75 (br s, 1H, 6-H) ppm.

**9-METHOXY-1,4-DIMETHYL-1H-PYRIDO[3,2-b]CARBAZOLE-2,5,11(6H)-TRIONE (102)**

Yield: 82 mg, 69% (red solid).

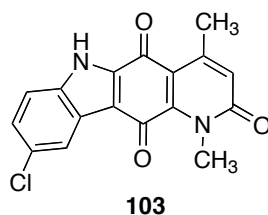
Melting point > 300 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> (322): C 67.07, H 4.38, N, 8.69; found C 66.99, H 4.31, N 8.57.

MS: m/z, 322 (M<sup>+</sup>), 294, 293.

IR (KBr):  $\nu$  = 3500-2500, 1646 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO)  $\delta$  = 2.56 (s, 3H, 4-CH<sub>3</sub>), 3.83 and 3.84 (2s, 6H, 1-CH<sub>3</sub>, 9-OCH<sub>3</sub>), 6.57 (s, 3H, 3-H), 7.03 (m, 1H, 8-H), 7.45 (m, 2H, 7-H, 10-H).

**9-CHLORO-1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOLE-2,5,11(6*H*)-TRIONE (103)**

Yield: 26 mg, 29% (red solid).

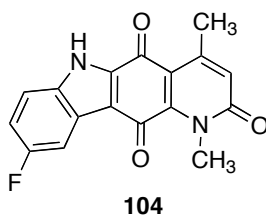
Melting point > 300 °C.

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>Cl: C 62.49, H 3.39, N 8.57; found C 62.44, H 3.41, N 8.51.

MS: m/z, 326 (M<sup>+</sup>), 298, 297.

IR (KBr):  $\nu$  = 3500-2500, 1664, 1649 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.55 (s, 3H, 4-CH<sub>3</sub>), 3.83 (1s, 3H, 1-CH<sub>3</sub>), 6.58 (s, 1H, 3-H), 7.24-7.32 (m, 1H, 8-H), 7.55-7.59 (m, 1H, 7-H), 7.69-7.72 (m, 1H, 10-H) ppm.

**9-FLUORO-1,4-DIMETHYL-1H-PYRIDO[3,2-*b*]CARBAZOLE-2,5,11(6H)-TRIONE (104)**

Yield: 42 mg, 47% (red solid).

Melting point > 300 °C.

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>F: C 65.81, H 3.57, N 9.03; found C 65.90, H 3.63, N 8.99.

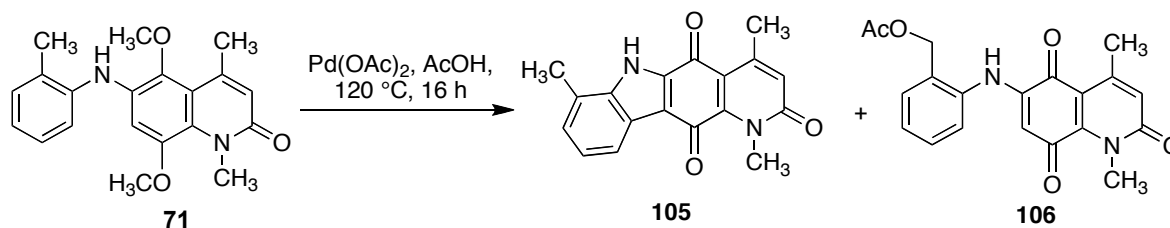
MS: m/z, 310 (M<sup>+</sup>), 282, 281.

IR (KBr):  $\nu$  = 3500-2500, 1662, 1640 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.55 (s, 3H, 4-CH<sub>3</sub>), 3.83 (1s, 3H, 1-CH<sub>3</sub>), 6.58 (s, 1H, 3-H), 7.43 (m, 1H, 8-H), 7.58 (m, 1H, 7-H), 7.69-7.72 (m, 1H, 10-H) ppm.

**Preparation of compound 104 from 97:**

Ceric ammonium nitrate (384 mg, 0.70 mmol) was added to a solution of compound **97** (100 mg, 0.30 mmol) in 2:1 CH<sub>3</sub>CN/H<sub>2</sub>O (30 mL) and the reaction was stirred at 0 °C for 1h. The mixture was, then, extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL), the combined organic layers were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was concentrated *in vacuo* to give 35 mg (38%) of compound **104** as a red solid.

**6-(2-ACETOXYMETHYLPHENYLAMINO)-1,4-DIMETHYLQUINOLINE-2(1H),5,8-TRIONE (106)**

Yield: 13 mg, 35% (red solid).

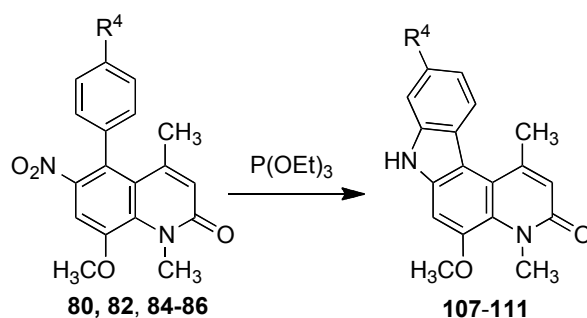
Melting point: 254-256 °C.

Elemental analysis calc. (%) for  $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_5$ : C 65.57, H 4.95, N 7.65; found C 65.61, H 4.98, N 7.61.

IR (KBr):  $\nu = 3500\text{-}2500, 1740, 1654\text{ cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ )  $\delta$  = 2.16 (s, 3H,  $\text{CH}_3\text{-CO}$ ), 2.57 (br s, 3H, 4- $\text{CH}_3$ ), 3.90 (s, 3H, N- $\text{CH}_3$ ), 5.07 (s, 2H,  $\text{OCH}_2\text{Ph}$ ), 6.01 (s, 1H, 7-H), 6.58 (s, 1H, 3-H), 7.25-7.50 (m, 4H, Ph), 8.56 (br s, 1H, NH) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ,  $25\text{ }^\circ\text{C}$ ):  $\delta = 21.3, 23.6, 35.3, 63.6, 101.1, 115.1, 123.6, 124.5, 127.0, 127.5, 130.1, 130.4, 132.3, 136.8, 144.9, 149.9, 162.8, 171.8, 180.6, 180.9$  ppm.

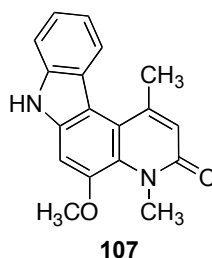
**SYNTHESIS OF TETRACYCLIC ANGULAR FUSED CARBAZOLES 107-111**

Comp.	R <sup>4</sup>
<b>107</b>	H
<b>108</b>	CH <sub>3</sub>
<b>109</b>	OCH <sub>3</sub>
<b>110</b>	Cl
<b>111</b>	F

**General procedure:**

**Method A.** A solution of the suitable compound **80, 82 or 84-86** (50 mg) in triethyl phosphite (1-2 mL) was refluxed at 160 °C for 3 h. The reaction mixture was cooled to rt and the solid that precipitated was filtered and washed with ethyl ether.

**Method B.** A solution of the suitable compound **80, 82 or 84-86** (50 mg) in triethyl phosphite (1-2 mL) was heated under microwave irradiation in a CEM Discover focused microwave reactor at 300 W and 180 °C for 25 min. The reaction mixture was worked up as in *Method A*.

**5-METHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-c]CARBAZOL-3-ONE (107)**

Yield: 24 mg, 55% (method A). Orange solid.

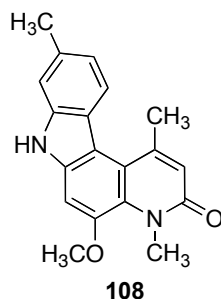
Melting point: 223-225 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C 73.95, H 5.52, N, 9.58; found C 73.77, H 5.46, N, 9.51.

IR (KBr):  $\nu = 3420, 2960, 1648, 1600, 1553, 1453 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.87$  (s, 3H, 1-CH<sub>3</sub>), 3.88 (s, 3H, 4-CH<sub>3</sub>), 3.98 (s, 3H, 5-OCH<sub>3</sub>), 6.73 (s, 1H, 2-H), 7.17 (s, 1H, 6-H), 7.22-7.25 (m, 1H, 10-H), 7.35-7.41 (m, 1H, 9-H), 7.50 (d,  $J = 8.1$  Hz, 1H, 8-H), 8.15 (d,  $J = 8.1$  Hz, 1H, 11-H), 8.87 (br s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 24.6, 37.5, 56.8, 97.3, 111.2, 111.7, 119.5, 120.8, 121.6, 123.5, 124.6, 124.9, 129.5, 136.9, 140.1, 146.5, 149.6, 163.1$  ppm.

**5-METHOXY-1,4,9-TRIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-c]CARBAZOL-3-ONE  
(108)**

Yield: 67 mg, 53% (method A) or 63 mg, 50% (method B). Yellow solid.

Melting point: 253-255 °C.

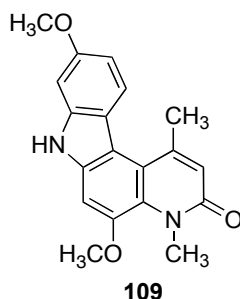
Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C 74.49, H 5.92, N, 9.14; found C 74.37, H 5.97, N, 9.09.

IR (KBr):  $\nu = 3210, 2998, 1655, 1602, 1508, 1450 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.52$  (s, 3H, 9-CH<sub>3</sub>),  $2.86$  (s, 3H, 1-CH<sub>3</sub>),  $3.87$  (s, 3H, 4-CH<sub>3</sub>),  $3.94$  (s, 3H, OCH<sub>3</sub>),  $6.73$  (s, 1H, 2-H),  $7.05$  (dd,  $J = 8.5$  and  $1.2$  Hz, 1H, 10-H),  $7.15$  (s, 1H, 6-H),  $7.28$  (s, 1H, 8-H),  $8.03$  (d,  $J = 8.5$  Hz, 1H, 11-H),  $8.37$  (br s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO, 25 °C):  $\delta = 20.7, 23.2, 36.0, 56.0, 97.3, 109.7, 110.4, 118.3, 119.4, 119.5, 119.6, 123.5, 128.1, 132.7, 136.0, 139.7, 145.2, 147.4, 160.7$  ppm.

**5,9-DIMETHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-c]CARBAZOL-3-ONE**  
**(109)**



Yield: 90 mg, 51% (method A) or 99 mg, 56% (method B). Yellow solid.

Melting point: 251-253 °C.

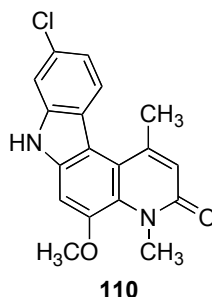
Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.79, H 5.63, N 8.69; found C 70.83, H 5.59, N 8.54.

IR (KBr):  $\nu = 3419, 3151, 2934, 1646, 1602, 1560, 1508 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta = 2.85$  (s, 3H, 1-CH<sub>3</sub>), 3.86 (s, 3H, 4-CH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>), 3.95 (s, 3H, OCH<sub>3</sub>), 6.72 (s, 1H, 2-H), 6.85 (dd,  $J = 9.0$  and 2.2 Hz, 1H, 10-H), 6.97 (d,  $J = 2.2$  Hz, 1H, 8-H), 7.14 (s, 1H, 6-H), 8.03 (d,  $J = 9.0$  Hz, 1H, 11-H), 8.53 (br s, 1H, 7-H) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO, 25 °C):  $\delta = 24.9, 52.4, 55.0, 55.7, 94.1, 96.0, 107.6, 107.7, 112.5, 117.1, 122.1, 124.2, 135.0, 136.9, 140.2, 145.5, 152.4, 156.0, 158.1$  ppm.

**9-CHLORO-5-METHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-c]CARBAZOL-3-ONE (110)**

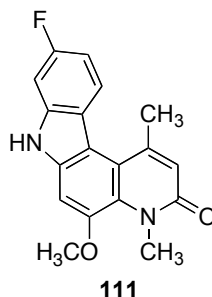


Yield: 50 mg, 30% (method A). Pale brown solid.

Elemental analysis calc. (%) for  $C_{18}H_{15}N_2O_2$  Cl: C 66.16, H 4.63, N 8.57; found C 66.23, H 4.65, N 8.46.

IR (KBr):  $\nu = 3426, 2923, 1645, 1601, 1556, 1455 \text{ cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 2.83$  (s, 3H, 1- $\text{CH}_3$ ), 3.87 (s, 3H, 4- $\text{CH}_3$ ), 4.00 (s, 3H,  $\text{OCH}_3$ ), 6.75 (s, 1H, 2-H), 7.14 (s, 1H, 6-H), 7.19 (dd,  $J = 8.9$  and 1.9 Hz, 1H, 10-H), 7.47 (d,  $J = 1.9$  Hz, 1H, 8-H), 8.04 (d,  $J = 8.9$  Hz, 1H, 11-H), 8.43 (br s, 1H, 7-H) ppm.

**9-FLUORO-5-METHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-c]CARBAZOL-3-ONE (111)**

Yield: 66 mg, 39% (method A) or 95 mg, 56% (method B). Yellow solid.

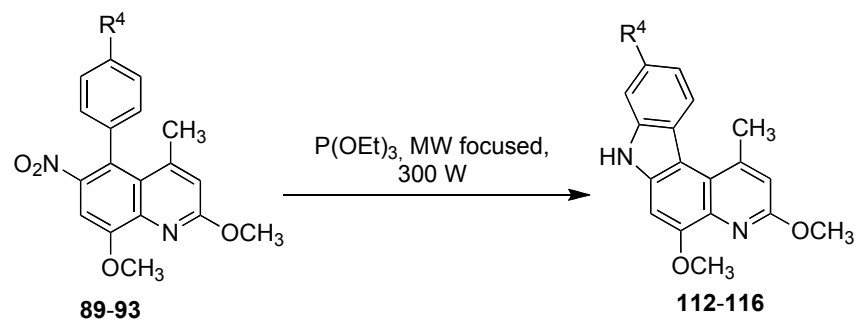
Melting point: 272-274 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>F: calc. C 69.67, H 4.87, N 9.03; found C 69.59, H 4.93, N 8.97.

IR (KBr):  $\nu$  = 3212, 2916, 1653, 1600, 1507, 1429, 1393 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 2.84 (d, *J* = 0.7 Hz, 3H, 1-CH<sub>3</sub>), 3.87 (s, 3H, 4-CH<sub>3</sub>), 3.99 (s, 3H, OCH<sub>3</sub>), 6.72 (d, *J* = 0.7 Hz, 1H, 2-H) 6.96 (td, *J* = 9.1 and 2.5 Hz, 10-H), 7.16 (s, 1H, 6-H), 7.17 (dd, *J* = 9.1 and 2.5 Hz, 8-H), 8.07 (dd, *J* = 9.1 and 5.4 Hz, 11-H), 8.75 (br s, 1H, 7-H) ppm.

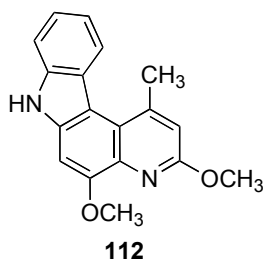
<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.5 (1-CH<sub>3</sub>), 37.5 (4-CH<sub>3</sub>), 56.9 (OCH<sub>3</sub>), 97.3 (C-6), 97.6 (d, *J* = 25.8 Hz, C-10), 107.8 (d, *J* = 23.9 Hz, C-8), 111.5 (C-11c), 120.3 (d, *J* = 13.0 Hz, C-11a), 121.8 (C-2), 125.9 (d, *J* = 10.1 Hz, C-11), 130.2 (C-11b), 137.2 (C-6a), 140.4 (C-4a), 140.6 (C-7a), 146.2 (C-1), 149.0 (C-5), 159.1 (d, *J* = 241.3 Hz, C-9), 163.0 (C-3) ppm.

**SYNTHESIS OF TETRACYCLIC ANGULAR FUSED CARBAZOLES 102-119**

Comp.	R <sup>4</sup>	Rto. (%)
<b>112</b>	H	45
<b>113</b>	CH <sub>3</sub>	55
<b>114</b>	OCH <sub>3</sub>	87
<b>115</b>	Cl	46
<b>116</b>	F	46

**General procedure:**

A solution of the suitable compound **89-93** (50 mg) in triethyl phosphite (1-2 mL) was heated under microwave irradiation in a CEM Discover focused microwave reactor at 300 W and 180 °C for 25 min. The reaction mixture was cooled to rt and the solid that precipitated was filtered and washed with ethyl ether.

**3,5-DIMETHOXY-1-METHYL-7H-PYRIDO[2,3-c]CARBAZOLE (112)**

Yield: 20 mg, 45% (yellow solid).

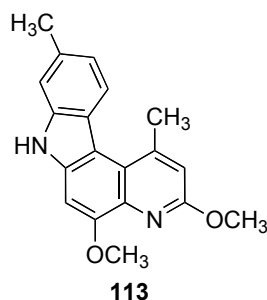
Melting point: 252-254 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>: C 73.95, H 5.52, N, 9.58; found C 74.07, H 5.57, N, 9.54.

IR (NaCl):  $\nu = 3421, 3266, 1593, 1342 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 2.51 (s, 3H, CH<sub>3</sub>), 3.99 (s, 3H, 5-OCH<sub>3</sub>), 4.04 (s, 3H, 3-OCH<sub>3</sub>), 7.00 (s, 1H, 2-H), 7.09–7.36 (m, 3H, 6-H, 9-H, 10-H), 7.57 (d, *J* = 7.9 Hz, 1H, 8-H), 8.35 (d, *J* = 8.3 Hz, 1H, 11-H), 11.74 (s, 1H, NH) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 25.1, 52.7, 55.91, 95.9, 107.6, 111.1, 118.5, 122.6, 122.7, 123.2, 123.6, 135.5, 137.5, 138.9, 145.6, 153.6, 158.5 ppm.

**3,5-DIMETHOXY-1,9-DIMETHYL-7H-PYRIDO[2,3-c]CARBAZOLE (113)**

Yield: 25 mg, 55% (method B). Light yellow solid.

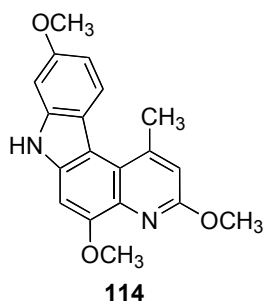
Melting point: 226-228 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>: C 74.49, H 5.92, N, 9.14; found C 74.54, H 5.86, N, 9.10.

IR (NaCl):  $\nu = 3329, 2922, 1593, 1356 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-acetone) <sup>TM</sup> = 2.50 (s, 3H, 9-CH<sub>3</sub>), 3.18 (d, *J* = 0.6 Hz, 3H, 1-CH<sub>3</sub>), 4.05 (s, 3H, 5-OCH<sub>3</sub>), 4.07 (s, 3H, 3-OCH<sub>3</sub>), 6.95 (d, *J* = 0.7 Hz, 1H, 2-H), 7.03 (dd, *J* = 8.5, 1.2 Hz, 1H, 10-H), 7.39 (s, 2H, 8-H, 6-H), 8.30 (d, *J* = 8.5 Hz, 1H, 11-H), 10.66 (s, 1H, NH) ppm.

<sup>13</sup>C NMR (63 MHz d<sub>6</sub>-acetone) <sup>TM</sup> = 22.7, 26.9, 54.2, 57.7, 98.1, 113.0, 114.9, 122.3, 123.8, 124.9, 125.6, 134.5, 141.9, 144.6, 147.4, 147.7, 153.3, 156.1, 160.9 ppm.

**3,5,9-TRIMETHOXY-1-METHYL-7H-PYRIDO[2,3-c]CARBAZOLE (114)**

Yield: 40 mg, 87% (method B). Yellow solid.

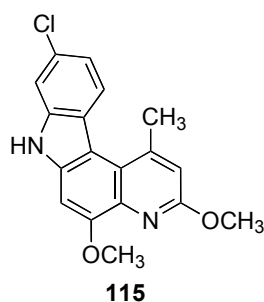
Melting point: 238-240 °C.

Elemental analysis calc. (%) for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C 70.79, H 5.63, N 8.69; found C 70.83, H 5.59, N 8.54.

IR (NaCl):  $\nu = 3341, 1699, 1683, 1457 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 3.09 (s, 3H, CH<sub>3</sub>), 3.86 (s, 3H, 9-OCH<sub>3</sub>), 3.98 (s, 3H, 5-OCH<sub>3</sub>), 4.02 (s, 3H, 3-OCH<sub>3</sub>), 6.78 (dd, *J* = 9.1, 2.3 Hz, 1H, 10-H), 6.96 (s, 1H, 2-H), 7.06 (d, *J* = 2.2 Hz, 1H, 8-H), 7.31 (s, 1H, 6-H), 8.23 (d, *J* = 9.1 Hz, 1H, 11-H), 11.58 (s, 1H, NH) ppm.

<sup>13</sup>C NMR (63 MHz, d<sub>6</sub>-DMSO) <sup>TM</sup> = 25.5 (1-CH<sub>3</sub>), 52.9 (9-OCH<sub>3</sub>), 55.5 (5-OCH<sub>3</sub>), 56.2 (3-OCH<sub>3</sub>), 94.6 (C-8), 96.5 (C-6), 108.1 (C-6a), 108.3 (C-10), 112.9 (C-2), 117.6 (C-9), 122.6 (C-11c), 124.7 (C-8), 135.6 (C-5), 137.4 (C-11), 140.7 (C-11a), 145.9 (C-1), 152.9 (C-11b), 156.5 (C-8a), 158.6 (C-3) ppm.

**9-CHLORO-3,5-DIMETHOXY-1-METHYL-7H-PYRIDO[2,3-c]CARBAZOLE (115)**

Yield: 21 mg, 46% (method B). Yellow solid.

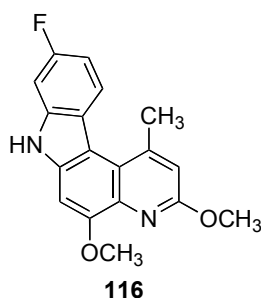
Melting point: 133-135 °C.

Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> Cl: C 66.16, H 4.63, N 8.57; found C 66.26, H 4.65, N 8.51.

IR (NaCl):  $\nu = 3400, 1636 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, MeOD):  $\tau^M = 2.94$  (s, 3H, CH<sub>3</sub>), 3.97 (s, 3H, 5-OCH<sub>3</sub>), 4.09 (s, 3H, 3-OCH<sub>3</sub>), 7.00 (dd,  $J = 9.0, 2.1$  Hz, 1H, 10-H), 7.06 (s, 1H, 2-H), 7.16 (s, 1H, 6-H), 7.36 (d,  $J = 2.0$  Hz, 1H, 8-H), 8.00-8.03 (m, 2H, NH, 11-H) ppm.

<sup>13</sup>C NMR (125 MHz, MeOD):  $\tau^M = 27.6$  (CH<sub>3</sub>), 57.5 (3-OCH<sub>3</sub>), 57.8 (5-OCH<sub>3</sub>), 99.5 (C-6), 109.7 (C-11c), 112.6 (C-2), 112.7 (C-8), 121.2 (C-10), 123.4 (C-11a), 124.0 (C-6a, C-7a), 126.7 (C-11), 131.3 (C-11b), 140.6 (C-4a), 142.1 (C-9), 152.2 (C-5), 155.0 (C-1), 160.6 (C-3) ppm.

**9-FLUORO-3,5-DIMETHOXY-1-METHYL-7H-PYRIDO[2,3-*c*]CARBAZOLE (116)**

Yield: 19 mg, 46% (method B). Yellow solid.

Melting point: 179-181 °C.

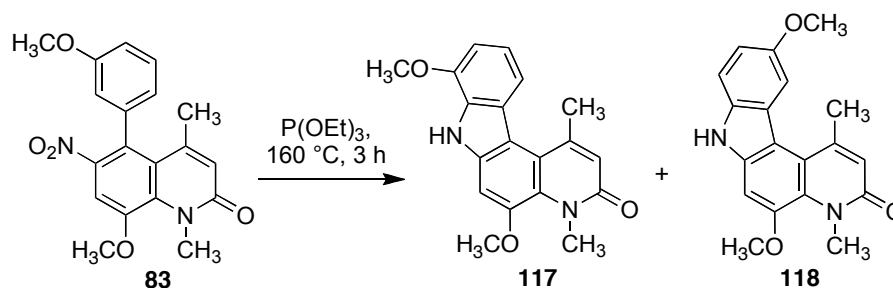
Elemental analysis calc. (%) for C<sub>18</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>F: C 69.67, H 4.87, N 9.03; found C 69.70, H 4.93, N 8.97.

IR (KBr):  $\nu = 3410, 1733, 1506, 1457 \text{ cm}^{-1}$ .

<sup>1</sup>H NMR (250 MHz, MeOD)  $\delta$  = 3.07 (s, 3H, CH<sub>3</sub>), 4.02 (s, 3H, OCH<sub>3</sub>), 4.09 (s, 3H, OCH<sub>3</sub>), 6.86 (td,  $J = 9.2$  and  $2.6$  Hz, 1H, 10-H), 7.11-7.16 (m, 2H, 8-H, 2-H), 7.30 (s, 1H, 6-H), 8.18 (dd,  $J = 9.2$  and  $5.2$  Hz, 1H, 11-H) ppm.

<sup>13</sup>C NMR (126 MHz, MeOD)  $\delta$  = 34.5, 62.2, 65.5, 105.5, 106.6 (d,  $J = 25.4$  Hz), 115.9 (d,  $J = 23.3$  Hz), 116.9, 122.5, 126.7 (d,  $J = 3.7$  Hz), 129.7, 131.9, 134.3 (d,  $J = 10.4$  Hz), 145.1, 148.9 (d,  $J = 12.1$  Hz), 155.2, 162.9, 167.9 (d,  $J = 243.7$  Hz), 168.1 ppm.

**5,8-DIMETHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-*c*]CARBAZOL-3-ONE (117) AND 5,10-DIMETHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-PYRIDO[2,3-*c*]CARBAZOL-3-ONE (118)**



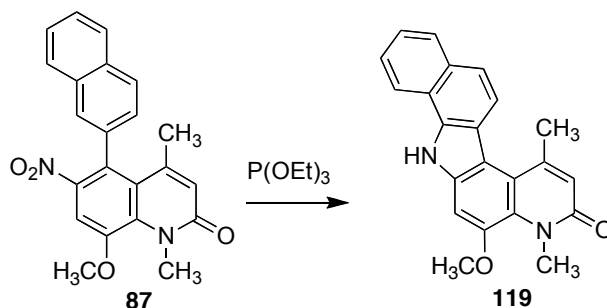
Yield, 16 mg (35%), as a 1:1 mixture from which only compound **117** could be purified.

**Data for compound 117**

Elemental analysis calc. (%) for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$ : C 70.80, H 5.59, N 8.69; found C 70.29, H 5.60, N 8.46.

IR (KBr):  $\nu = 3420, 3149, 2922, 1650, 1607, 1558\text{ cm}^{-1}$ .

$^1\text{H-NMR}$  (250 MHz,  $\text{CDCl}_3$ ): 2.87 (d,  $J = 0,7\text{ Hz}$ , 3H,  $\text{CH}_3\text{-C}_1$ ); 3.87 (s, 3H,  $\text{CH}_3\text{-N}$ ); 3.89 (s, 3H,  $\text{CH}_3\text{O-C}_{10}$ ); 4.02 (s, 3H,  $\text{CH}_3\text{O-C}_5$ ); 6.72 (d, 1H,  $J = 0,7\text{ Hz}$ ,  $\text{C}_2\text{-H}$ ); 6.86 (d, 1H,  $J = 7,6\text{ Hz}$ ,  $\text{C}_{10}\text{-H}$ ); 6.97 (d, 1H,  $J = 7,6\text{ Hz}$ ,  $\text{C}_9\text{-H}$ ); 7.13 (t, 1H,  $J = 8,3\text{ Hz}$ ,  $\text{C}_{10}\text{-H}$ ); 7.16 (s, 1H,  $\text{C}_6\text{-H}$ ); 7.76 (d, 1H,  $J = 8,4\text{ Hz}$ ,  $\text{C}_{11}\text{-H}$ ); 8.74 (br s, 1H, NH) ppm.

**5-METHOXY-1,4-DIMETHYL-4,7-DIHYDRO-3H-BENZO[A]PYRIDO[3,2-*g*]CARBAZOL-3-ONE (119)**

Yield: 26 mg, 40% (method A). Yellow solid.

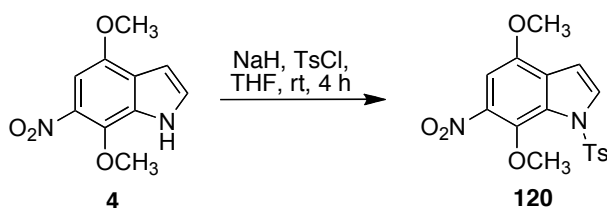
Melting point  $>300$  °C.

Elemental analysis calc. (%) for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$ : C 77.17, H 5.30, N 8.18; found C 77.09, H 5.32, N 8.11.

IR (KBr):  $\nu = 3427, 3139, 2935, 1645, 1604, 1565, 1447, 1381$   $\text{cm}^{-1}$ .

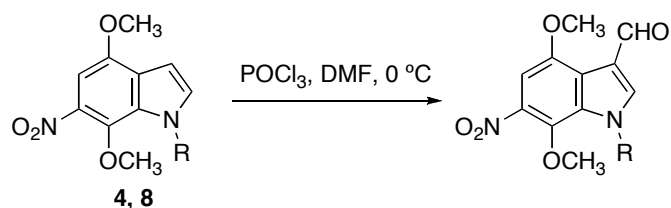
$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 6.82$  (s, 1H, 2-H), 7.35 (s, 1H, 6-H), 7.50-7.70 (m, 2H, 9-H, 10-H), 7.62 (d,  $J = 8.2$  Hz, 1H, 12-H, overlapped with 9-H and 10-H signal), 8.00 (d,  $J = 8.2$  Hz, 1H, 13-H), 8.19 (d,  $J = 9.1$  Hz, 1H, 11-H, partially overlapped with 8-H signal), 8.23 (d,  $J = 9.4$  Hz, 1H, 8-H, partially overlapped with 11-H signal), 9.42 (br s, 1H, 7-H) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{d}_6$ -DMSO, 25 °C):  $\delta = 24.1, 36.8, 57.3, 98.3, 111.9, 118.8, 119.1, 119.2, 120.3, 121.8, 123.8, 124.0, 125.5, 125.8, 128.3, 130.1, 130.9, 136.7, 136.8, 146.8, 148.5, 162.1$  ppm.

**4,7-DIMETHOXY-6-NITRO-1-TOSYLINDOLE (120)**

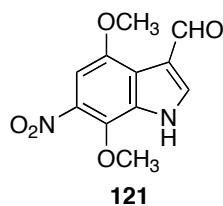
To a solution of 4,7-dimethoxy-6-nitroindole **4** (600 mg, 2.7 mmol) in dry THF (15 mL) at 0 °C under an argon atmosphere, sodium hydride (213 mg, 60% in mineral oil) was added slowly and the solution was stirred for 1 h. Then, *p*-toluenesulfonyl chloride (670 mg, 5.9 mmol) was added and the reaction mixture was stirred for 4 h and allowed to warm to room temperature. Then, the reaction was poured onto water and extracted with ethyl acetate (6 x 30 mL). The combined organic layers were dried over anhydrous sodium sulphate and the solvent was concentrated *in vacuo* to give 980 mg (100%) of the expected compound **120**, which was used without further purification.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>, 25 °C): δ = 7.97 (d, *J* = 3.6 Hz, 1H, H<sub>2</sub>), 7.73 (d, *J* = 8.2 Hz, 2H, H<sub>2'</sub>), 7.27 (d, *J* = 8.2 Hz, 2H, H<sub>3'</sub>), 7.16 (s, 1H, H<sub>5</sub>), 6.82 (d, *J* = 3.6 Hz, 1H, H<sub>3</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 2.40 (s, 3H, C<sub>4</sub>-CH<sub>3</sub>) ppm

**4,7-DIMETHOXY-6-NITROINDOLE-3-CARBALDEHYDES 121 and 122**

Comp.	R
<b>121</b>	H
<b>122</b>	CH <sub>3</sub>

A solution of indole **4** or **8** (1 eq) in dimethylformamide (4 mL) was added to a solution of POCl<sub>3</sub> (2.1 eq) in DMF (8 eq) cooled at 0 °C, under an argon atmosphere, and stirred for 30 min. The mixture was then stirred at room temperature for 45 min and cooled again to 0°C. Water (8 mL) was added and the reaction was basified with 20% NaOH solution and stirred for 30 min. The mixture was filtered and the solid was dissolved in CHCl<sub>3</sub>, the solution was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum.

**4,7-DIMETHOXY-6-NITROINDOLE-3-CARBALDEHYDE (121)**

Yield: 500 mg, 72 % (pale brown solid)

**Data for compound 121:**

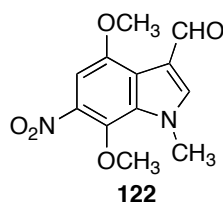
Melting point: 235 °C.

Elemental analysis calc. (%) for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>: C 52.80, H 4.03, N 11.20; found: C 51.92, H 4.02, N 10.91.

IR (NaCl):  $\nu = 1670$  (CHO),  $1552$  (NO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, DMSO):  $\tau^m = 10.29$  (s, 1H, CHO),  $8.30$  (s, 1H, H<sub>2</sub>),  $7.22$  (s, 1H, H<sub>5</sub>),  $3.98$  (s, 3H, C<sub>7</sub>-OCH<sub>3</sub>),  $3.97$  (s, 3H, C<sub>4</sub>-OCH<sub>3</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, DMSO):  $\tau^m = 186.3$  (CHO),  $149.2$  (C<sub>4</sub>),  $137.3$  (C<sub>7</sub>),  $136.7$  (C<sub>6</sub>),  $134.04$  (C<sub>2</sub>),  $130.8$  (C<sub>7a</sub>),  $121.7$  (C<sub>3</sub>),  $119.4$  (C<sub>3a</sub>),  $98.2$  (C<sub>5</sub>),  $63.2$  (C<sub>7</sub>-OCH<sub>3</sub>),  $56.5$  (C<sub>4</sub>-OCH<sub>3</sub>) ppm.

**4,7-DIMETHOXY-1-METHYL-6-NITROINDOLE-3-CARBALDEHYDE (122)**

Yield: 2.960 g, 81% (yellow solid).

**Data for compound 122:**

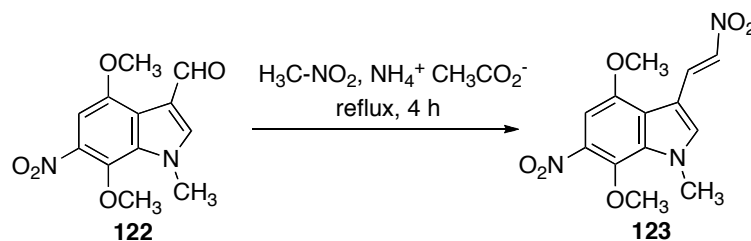
Melting point: 166-167 °C.

Elemental analysis calc. (%) for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub>: C 54.55, H 4.58, N 10.60; found C 54.66, H 4.73, N 11.02.

IR (NaCl):  $\nu$  = 1661 (CHO), 1527 (NO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 10.43 (s, 1H, CHO), 7.90 (s, 1H, H<sub>2</sub>), 7.31 (s, 1H, H<sub>5</sub>), 4.18 (s, 3H, C<sub>7</sub>-OCH<sub>3</sub>), 4.06 (s, 3H, C<sub>4</sub>-OCH<sub>3</sub>), 4.05 (s, 3H, N-CH<sub>3</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, DMSO):  $\tau^m$  = 187.0 (CHO), 149.3 (C<sub>4</sub>), 138.9 (C<sub>7</sub>), 137.0 (C<sub>2</sub>), 137.0 (C<sub>7a</sub>), 130.1 (C<sub>3a</sub>), 123.3 (C<sub>6</sub>), 118.3 (C<sub>3</sub>), 99.0 (C<sub>5</sub>), 63.9 (C<sub>7</sub>-OCH<sub>3</sub>), 56.0 (C<sub>4</sub>-OCH<sub>3</sub>), 37.3 (N-CH<sub>3</sub>) ppm.

**(E)-4,7-DIMETHOXY-1-METHYL-6-NITRO-3-(2-NITROVINYL)INDOLE (123)**

To a suspension of indole **122** (1,150 g, 4.35 mmol) in nitromethane (50 mL) was added ammonium acetate (0.335 g, 4.35 mmol). The mixture was stirred at reflux for 4h. After cooling a light brown solid precipitated which was filtered and recrystallized in MeOH, yielding 0.985 g (74 %).

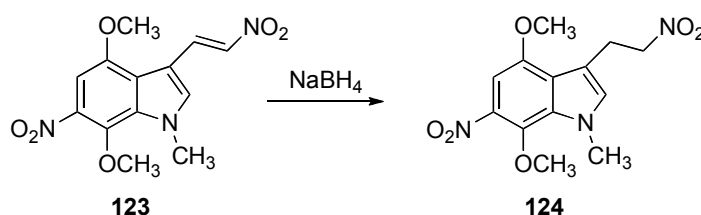
Melting point: 268-269 °C.

Elemental analysis calc. (%) for  $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_6$ : C 50.82, H 4.26, N 13.68; found C 50.57, H 4.30, N 13.54.

IR (NaCl):  $\nu = 1624$  (C=C),  $1547$  ( $\text{NO}_2$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz, DMSO):  $\tau^m = 8.57$ - $8.51$  (m, 3H,  $\text{H}_2$ ,  $\text{CH}_2\text{-NO}_2$ ),  $8.05$  (d,  $J = 13.5$  Hz, 1H,  $\text{CH}_2\text{-CH}_2\text{-NO}_2$ ),  $7.28$  (s, 1H,  $\text{H}_5$ ),  $4.10$  (s, 3H,  $\text{OCH}_3$ ),  $4.02$  (s, 3H,  $\text{OCH}_3$ ),  $3.95$  (s, 3H,  $\text{N-CH}_3$ ) ppm.

$^{13}\text{C}$  NMR (63 MHz, DMSO):  $\tau^m = 149.2$  ( $\text{C}_4$ ),  $139.3$  ( $\text{C}_2$ ),  $138.3$  ( $\text{C}_{7a}$ ),  $137.6$  ( $\text{C}_7$ ),  $134.1$  ( $\text{CH}=\text{CH-NO}_2$ ),  $133.5$  ( $\text{CH}=\text{CH-NO}_2$ ),  $130.6$  ( $\text{C}_6$ ),  $122.6$  ( $\text{C}_{3a}$ ),  $107.3$  ( $\text{C}_3$ ),  $99.1$  ( $\text{C}_5$ ),  $64.4$  ( $\text{C}_7\text{-OCH}_3$ ),  $56.7$  ( $\text{C}_4\text{-OCH}_3$ ),  $37.3$  ( $\text{N-CH}_3$ ) ppm.

**4,7-DIMETHOXY-1-METHYL-6-NITRO-3-(2-NITROETHYL)INDOLE (124)**

To a solution of indole **123** (0.900 g, 2.93 mmol) in  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  (50:50) was added  $\text{NaBH}_4$  (0.330 g, 8.79 mmol) and the reaction was stirred at room temperature for 20 min. Then, the solvent was concentrated *in vacuo* and the residue was dissolved in dichloromethane and washed with water and brine. The aqueous phase was treated with 2N HCl to neutral pH and was extracted with dichloromethane (2 x 30 mL). The organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give 0.890 g (100%) of the desired compound **124**.

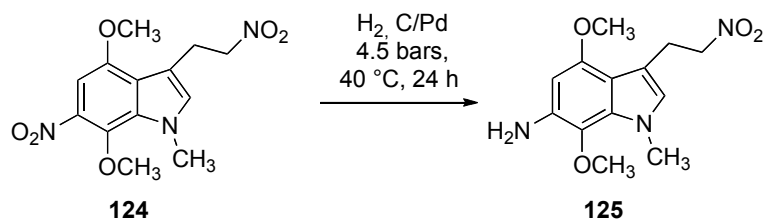
Melting point: 176-178 °C.

Elemental analysis calc. (%) for  $\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}_6$ : C 50.49, H 4.89, N 13.59; found C 50.27, H 4.94, N 12.44.

IR (NaCl):  $\nu = 1517, 1304.4$  ( $\text{NO}_2$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\tau^{\text{M}}$  = 7.11 (s, 1H,  $\text{H}_2$ ), 6.97 (s, 1H,  $\text{H}_3$ ), 4.70 (t,  $J = 6.8$  Hz, 2H,  $\text{CH}_2\text{-CH}_2\text{-NO}_2$ ), 4.04 (s, 3H,  $\text{OCH}_3$ ), 4.00 (s, 3H,  $\text{OCH}_3$ ), 3.98 (s, 3H,  $\text{N-CH}_3$ ), 3.50 (t,  $J = 6.8$  Hz, 2H,  $\text{CH}_2\text{-CH}_2\text{-NO}_2$ ) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\tau^{\text{M}}$  = 148.9 ( $\text{C}_4$ ), 138.6 ( $\text{C}_7$ ), 136.1 ( $\text{C}_{7a}$ ), 133.1 ( $\text{C}_2$ ), 129.8 ( $\text{C}_{3a}$ ), 123.6 ( $\text{C}_6$ ), 109.9 ( $\text{C}_3$ ), 95.8 ( $\text{C}_5$ ), 76.5 ( $\text{CH}_2\text{-CH}_2\text{NO}_2$ ), 63.5 ( $\text{OCH}_3$ ), 55.6 ( $\text{OCH}_3$ ), 35.8 ( $\text{N-CH}_3$ ), 24.4 ( $\text{CH}_2\text{CH}_2\text{NO}_2$ ) ppm.

**4,7-DIMETHOXY-1-METHYL-3-(2-NITROETHYL)INDOL-6-AMINE (125)**

To a solution of compound **124** (0.825 g, 2.66 mmol) in ethyl acetate (50 mL) was added 10% palladised charcoal (165 mg) and the solution was hydrogenated at 40 °C and 4.5 bares for 24 h. The mixture was filtered over celite and the filtrate was concentrated *in vacuo*, affording 0.740 g (100%) of the expected product **125** as a dark green solid.

Melting point: 131-133 °C.

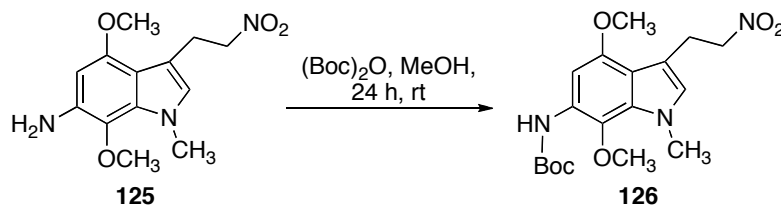
Elemental analysis calc. (%) for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C 55.91, H 6.14, N 15.05; found C 55.93, H 6.09, N 14.32.

IR (NaCl):  $\nu$  = 3356 (NH<sub>2</sub>), 1548 (NO<sub>2</sub>), 1231 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 6.53 (s, 1H, H<sub>2</sub>), 6.03 (s, 1H, H<sub>5</sub>), 4.70 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 3.82 (s, 3H, N-CH<sub>3</sub>), 3.46 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 150.1 (C<sub>4</sub>), 134.4 (C<sub>6</sub>), 131.3 (C<sub>7a</sub>), 127.1 (C<sub>7</sub>), 125.6 (C<sub>2</sub>), 112.0 (C<sub>3a</sub>), 108.8 (C<sub>3</sub>), 91.5 (C<sub>5</sub>), 76.6 (CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>), 60.7 (OCH<sub>3</sub>), 54.8 (OCH<sub>3</sub>), 34.2 (N-CH<sub>3</sub>), 24.9 (CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>) ppm.

**TERT-BUTYL-4,7-DIMETHOXY-1-METHYL-3-(2-NITROETHYL)INDOL-6-  
YLCARBAMATE (126)**



To a solution of compound **125** (1.1 g, 3.94 mmol) in dry CH<sub>3</sub>OH (70 mL) was added di-*tert*-butyl dicarbonate (0.944 g, 4.33 mmol). The mixture was stirred at 30 °C for 24 h. Removal of the solvent under reduced pressure gave 1.490 g (100%) of compound **126** as a grey solid.

Melting point: 87-89 °C.

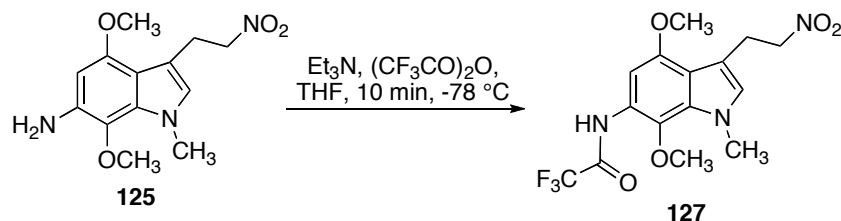
Elemental analysis calc. (%) for C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub>: C 56.98, H 6.64, N 11.08; found C 56.65, H 6.11, N 10.73.

IR (NaCl):  $\nu$  = 3360 (NH), 1623 (CO), 1522 (NO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 6.96 (s, 1H, H<sub>5</sub>), 6.61 (s, 1H, H<sub>2</sub>), 4.68 (t, *J* = 7.0 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>), 3.93 (s, 3H, OCH<sub>3</sub>), 3.88 (s, 3H, N-CH<sub>3</sub>), 3.78 (s, 3H, OCH<sub>3</sub>), 3.45 (t, *J* = 7.0 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>), 1.58 (s, 9H, (C(CH<sub>3</sub>)<sub>3</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 153.1 (CO), 149.9 (C<sub>4</sub>), 146.6 (C<sub>7a</sub>), 130.2 (C<sub>7</sub>), 129.6 (C<sub>6</sub>), 127.4 (C<sub>3</sub>), 126.2 (C<sub>2</sub>), 115.1 (C<sub>3a</sub>), 109.2 (C<sub>5</sub>), 85.1 (C(CH<sub>3</sub>)<sub>3</sub>), 80.2 (C(CH<sub>3</sub>)<sub>3</sub>), 76.8 (CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>), 62.3 (C<sub>7</sub>-OCH<sub>3</sub>), 55.3 (C<sub>4</sub>-OCH<sub>3</sub>), 34.6 (N-CH<sub>3</sub>), 28.3 (C(CH<sub>3</sub>)<sub>3</sub>), 27.3 (C(CH<sub>3</sub>)<sub>3</sub>) (rotamero), 25.1 (CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>).

***N*-(4,7-DIMETHOXY-1-METHYL-3-(2-NITROETHYL)INDOL-6-YL)-2,2,2-TRIFLUOROACETAMIDE (127)**



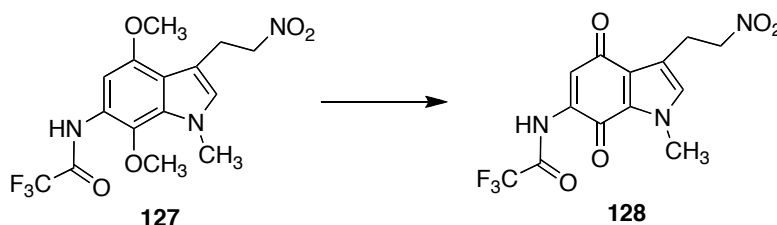
To a solution of indole **125** (150 mg, 0.537 mmol) in dry THF (5 mL) at  $-78^\circ\text{C}$  was added dropwise dry triethylamine (27.1 mg, 0.268 mmol) and trifluoroacetic anhydride (225.5 mg, 1.074 mmol) and the mixture was stirred for 15 min. Then, a saturated  $\text{NaHCO}_3$  solution (5 mL) was added and the reaction was allowed to warm to room temperature. The solution was extracted with  $\text{Et}_2\text{O}$  (2 x 20 mL), the combined organic layers were washed with brine and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was concentrated *in vacuo*, affording 202 mg (100%) of **127** as a grey solid.

Elemental analysis calc. (%) for  $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_5$ : C 48.00, H 4.30, N 11.20; found: C 47.78, H 4.25, N 11.14.

IR (NaCl):  $\nu = 3335$  (NH), 1718 (CO), 1150 ( $\text{NO}_2$ ), 1204 and 1161 ( $\text{CF}_3$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 8.52$  (s, 1H, NH), 7.38 (s, 1H,  $\text{H}_2$ ), 6.74 (s, 1H,  $\text{H}_3$ ), 4.69 (t,  $J = 6.9$  Hz, 2H,  $\text{CH}_2\text{-NO}_2$ ), 3.93 (s, 6H,  $\text{OCH}_3$   $\text{C}_4$  y  $\text{C}_7$ ), 3.84 (s, 3H,  $\text{NCH}_3$ ), 3.47 (t,  $J = 6.9$  Hz, 2H,  $\text{CH}_2\text{-CH}_2\text{-NO}_2$ ) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 154.5$  (dd,  $J = 58.2, 21.4$  Hz, CO), 150.2 ( $\text{C}_4$ ), 131.2 ( $\text{C}_6$ ), 129.7 ( $\text{C}_{7a}$ ), 128.8 ( $\text{C}_2$ ), 125.5 ( $\text{C}_7$ ), 117.5 ( $\text{C}_{3a}$ ), 115.8 (d,  $J = 288.1$  Hz,  $\text{CF}_3$ ), 109.9 ( $\text{C}_3$ ), 93.6 ( $\text{C}_5$ ), 77.3 ( $\text{CH}_2\text{NO}_2$ ), 67.9 (4- $\text{OCH}_3$ ), 62.9 (7- $\text{OCH}_3$ ), 34.8 ( $\text{NCH}_3$ ), 29.6 ( $\text{CH}_2\text{CH}_2\text{NO}_2$ ) ppm.

**2,2,2-TRIFLUORO-N-(1-METHYL-3(2-NITROETHYL)-4,7-DIHYDRO-1H-INDOL-6-YL)ACETAMIDE (128)**

To a solution of compound **127** (450 mg, 1.2 mmol) in 2:1 CH<sub>3</sub>CN-H<sub>2</sub>O (30 mL) CAN (1.9 g, 3.6 mmol) was added and the reaction was stirred at room temperature for 1 h. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL) and the organic layers were dried over anhydrous sodium sulphate. Removal of the solvent in vacuo afforded 336 mg (81%) of compound **128** as a pale brown solid.

Melting point: 150-152 °C.

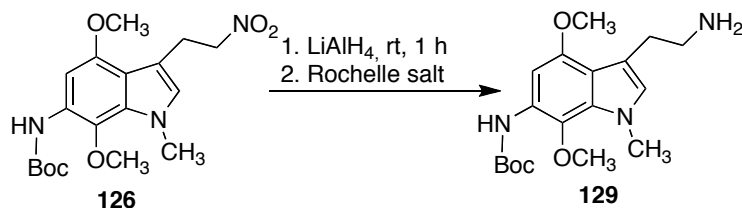
Elemental analysis calc. (%) for C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>: C 45.23, H 2.92, F 16.51; N, 12.17; found: C 46.01, H 2.78, F 16.95; N, 11.81

IR (NaCl):  $\nu$  = 3340 (NH), 1734 and 1647 (quinone and COCF<sub>3</sub>), 1551 (NO<sub>2</sub>), 1209 and 1165 (CF<sub>3</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 9.06 (s, 1H, NH), 7.37 (s, 1H, H<sub>2</sub>), 6.89 (s, 1H, H<sub>5</sub>), 4.77-4.61 (m, 2H, CH<sub>2</sub>-NO<sub>2</sub>), 3.96 (s, 3H, N-CH<sub>3</sub>), 3.37-3.35 (m, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 184.2 (C<sub>4</sub>), 170.9 (C<sub>7</sub>), 155.2 (dd,  $J$  = 58.2, 21.4 Hz, CO), 137.5 (C<sub>6</sub>), 133.2 (C<sub>2</sub>), 127.4 (C<sub>7a</sub>), 124.8 (C<sub>3a</sub>), 120.8 (C<sub>3</sub>), 118.1 (C<sub>5</sub>), 115.3 (d,  $J$  = 288.1 Hz, CF<sub>3</sub>), 74.9 (CH<sub>2</sub>-NO<sub>2</sub>), 37.0 (NCH<sub>3</sub>), 23.9 (CH<sub>2</sub>-CH<sub>2</sub>-NO<sub>2</sub>) ppm.

**TERT-BUTYL-3-(2-AMINOETHYL)-4,7-DIMETHOXY-1-METHYL-1H-INDOL-6YLCARBAMATE (129)**



To a solution of indole **126** (0.343 g, 0.90 mmol) in dry THF (10 mL), at 0 °C and under an argon atmosphere, was added dropwise 1M LiAlH<sub>4</sub> in THF (3.6 mL, 3.6 mmol) and the mixture was stirred at room temperature for 1 h. Then, the reaction was cooled at 0 °C and water (7 mL), ethyl ether (40 mL) and Rochelle salt (20 mL) were added in turn. The stirring was continued at room temperature for 24 h. The organic layer was treated with a 1M HCl solution (2 x 15 mL). This solution was basified with 3M KOH to basic pH. The mixture was then extracted with Et<sub>2</sub>O (3 x 30 mL), dried with Na<sub>2</sub>SO<sub>4</sub> anhydrous and concentrated *in vacuo* to give 155 mg (49%) of **129** as a brown solid.

Melting point: 120-122 °C.

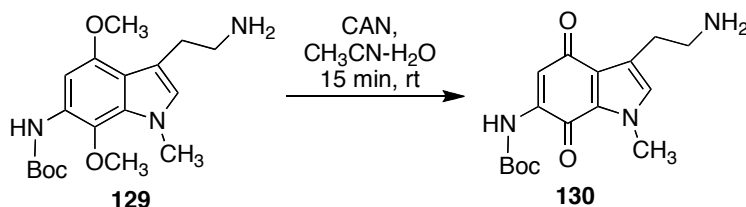
Elemental analysis calc. (%) for C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub>: C 61.87, H 7.79, N 12.03; found C 62.20, H 7.38, N 10.76.

IR (NaCl):  $\nu$  = 3435 and 3425 (NH<sub>2</sub> and NH), 1722 (CO), 1713 (COOt-but) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 7.25 (s, 1H, H<sub>5</sub>), 6.94 (s, 1H, NH), 6.60 (s, 1H, H<sub>2</sub>), 3.92 (s, 6H, 4-OCH<sub>3</sub> and NCH<sub>3</sub>) 3.80 (s, 3H, 7-OCH<sub>3</sub>), 2.95 (t, *J* = 3.4 Hz, 4H, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 1.57 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 153.1 (CO), 150.5 (C<sub>4</sub>), 130.1 (C<sub>7a</sub>), 129.6 (C<sub>7</sub>), 126.7 (C<sub>2</sub>), 125.6 (C<sub>6</sub>), 115.8 (C<sub>3a</sub>), 113.1 (C<sub>3</sub>), 93.1 (C<sub>5</sub>), 79.9 (C(CH<sub>3</sub>)<sub>3</sub>), 62.1 (7-OCH<sub>3</sub>), 55.2 (4-OCH<sub>3</sub>), 42.9 (CH<sub>2</sub>-NH<sub>2</sub>), 34.4 (NCH<sub>3</sub>), 30.6 (CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 28.2 (C(CH<sub>3</sub>)<sub>3</sub>) ppm.

**TERT-BUTYL 3-(2-AMINOETHYL)-1-METHYL-4,7-DIOXO-4,7-DIHYDRO-1H-INDOL-6-YLCARBAMATE (130)**



Ceric ammonium nitrate (1.890 g, 3.45 mmol) was added to a solution of compound **129** (400 mg, 1.15 mmol) in 2:1 CH<sub>3</sub>CN/H<sub>2</sub>O (60 mL) and the reaction was stirred at room temperature for 15 min. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL), the combined organic layers were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was concentrated *in vacuo* to give 335 mg (91 %) of compound **130** as a brown solid.

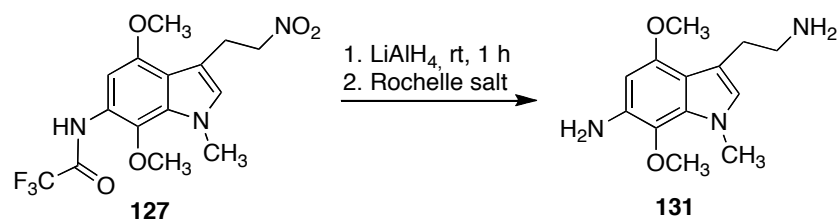
Melting point: 195-197 °C.

Elemental analysis calc. (%) for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C 60.17, H 6.63, N 13.16; found C 59.76, H 6.40, N 12.65

IR (NaCl):  $\nu$  = 3340 (NH<sub>2</sub>), 1727 and 1659 (quinone), 1633 (CO Boc) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, MeOD):  $\tau^m$  = 7.13 (s, 1H, H<sub>2</sub>), 6.92 (s, 1H, H<sub>5</sub>), 3.95 (s, 3H, NCH<sub>3</sub>), 3.20 (t, *J* = 7.0 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 3.04 (t, *J* = 6.9 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 1.53 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.

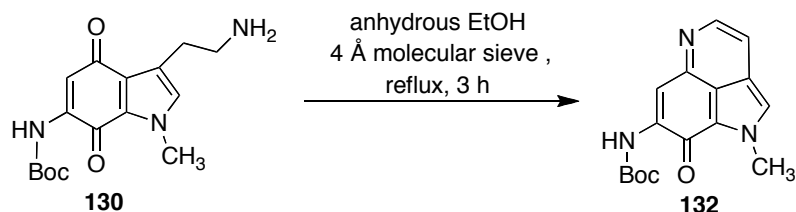
<sup>13</sup>C NMR (63 MHz, MeOD):  $\tau^m$  = 186.8 (C<sub>4</sub>), 172.8 (C<sub>7</sub>), 153.2 (CO), 142.3 (C<sub>6</sub>), 133.7 (C<sub>2</sub>), 129.0 (C<sub>7a</sub>), 125.3 (C<sub>3a</sub>), 120.8 (C<sub>3</sub>), 112.8 (C<sub>5</sub>), 83.1 (C(CH<sub>3</sub>)<sub>3</sub>), 40.6 (CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 36.8 (NCH<sub>3</sub>), 28.3 (C(CH<sub>3</sub>)<sub>3</sub>), 24.7 (CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>) ppm.

**3-(2-AMINOETHYL)-4,7-DIMETHOXY-1-METHYLINDOL-6-AMINE(131)**

To a solution of indole **127** (113 mg, 0.3 mmol) in dry THF (10 mL), at 0 °C and under an argon atmosphere, was added dropwise 1M LiAlH<sub>4</sub> in THF (1.2 mL, 1.2 mmol) and the mixture was stirred at room temperature for 1 h. Then, the reaction was cooled at 0 °C and water (4 mL), ethyl ether (20 mL) and Rochelle salt (10 mL) were added in turn. The stirring was continued at room temperature for 24 h. The organic layer was treated with a 1M HCl solution (2 x 15 mL). This solution was basified with 3M KOH to basic pH. The mixture was then extracted with Et<sub>2</sub>O (3 x 30 mL), dried with Na<sub>2</sub>SO<sub>4</sub> anhydrous and concentrated *in vacuo* to give 30 mg (40%) of **129** as a brown solid.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 6.50 (s, 1H, H<sub>5</sub>), 5.99 (s, 1H, H<sub>2</sub>), 3.90 (s, 3H, 4-OCH<sub>3</sub>) 3.83 (s, 3H, NCH<sub>3</sub>), 3.81 (s, 3H, 7-OCH<sub>3</sub>), 3.11 (t, *J* = 5.5 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 2.92 (t, *J* = 5.5 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 150.8 (C<sub>4</sub>), 137.8 (C<sub>7a</sub>), 134.1 (C<sub>2</sub>), 127.3 (C<sub>7</sub>), 124.8 (C<sub>6</sub>), 113.7 (C<sub>3a</sub>), 110.6 (C<sub>3</sub>), 91.1 (C<sub>5</sub>), 61.2 (7-OCH<sub>3</sub>), 55.7 (4-OCH<sub>3</sub>), 40.2 (CH<sub>2</sub>-NH<sub>2</sub>), 33.5 (NCH<sub>3</sub>), 26.3 (CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>) ppm.

**TERT-BUTYL 1-METHYL-8-OXO-1,8-DIHYDROPYRROLO[4,3,2-d,e]QUINOLIN-7-YLCARBAMATE (132)**

To a solution of compound **130** (125 mg, 0.39 mmol) in deoxygenated EtOH (20 mL) was added 4 Å molecular sieve and the mixture was stirred at reflux for 3 h. After filtration, the solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 4:1 ethyl acetate-petroleum ether, affording 70 mg (60 %) of compound **132** as a yellow solid.

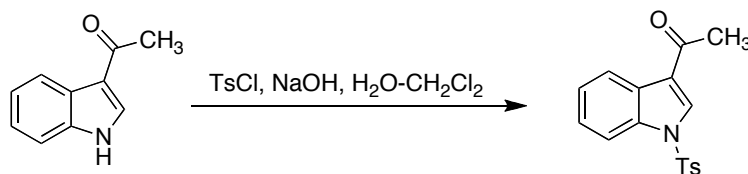
Melting point: 181-183 °C.

Elemental analysis calc. (%) for C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>: C 64.20, H 5.72, N 14.04; found C 64.98, H 5.45, N 14.71

IR (NaCl):  $\nu$  = 3345 (NH<sub>2</sub>), 1721 (CO), 1650 (C=N) 1609 (CO) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, MeOD):  $\tau^m$  = 8.16 (d, *J* = 5.8 Hz, 1H, H<sub>4</sub>), 7.89 (s, 1H, H<sub>2</sub>), 7.82 (s, 1H, H<sub>6</sub>), 7.46 (d, *J* = 5.8 Hz, 1H, H<sub>3</sub>), 4.16 (s, 3H, N-CH<sub>3</sub>), 1.49 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.

<sup>13</sup>C NMR (63 MHz, MeOD):  $\tau^m$  = 165.6 (C<sub>8</sub>), 152.7 (CO), 146.5 (C<sub>5a</sub>), 142.3 (C<sub>4</sub>), 140.9 (C<sub>7</sub>), 132.5 (C<sub>2</sub>), 124.4 (C<sub>2a</sub>), 119.5 (C<sub>8b</sub>), 119.1 (C<sub>8a</sub>), 115.6 (C<sub>3</sub>), 110.9 (C<sub>6</sub>), 81.5 (C(CH<sub>3</sub>)<sub>3</sub>), 37.3 (N-CH<sub>3</sub>), 27.8 (C(CH<sub>3</sub>)<sub>3</sub>) ppm.

**3-ACETYL-N-TOSYLINDOLE.**

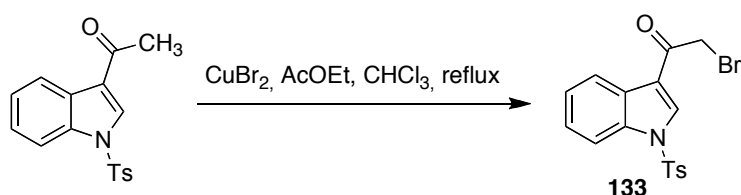
To a stirred suspension of 3-acetylindole (0.796 g, 5 mmol) in dichloromethane (30 mL) and cooled in ice bath, powdered sodium hydroxide (0.4 g) was added in one portion, stirred at 0 °C for 1 h and at room temperature for 5 h. Then the reaction mixture was cooled in the ice bath for 30 min. and solid p-toluenesulfonyl chloride (1.14 g, 6 mmol) was added and the reaction mixture stirred for 15 h. during which the ice bath was allowed to warm up to the room temperature. Then the mixture was poured into water (100 mL) to which additional dichloromethane (100 mL) was added. The organic layer was separated and washed with water (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and the solvent removed. Yield 1.5 g (96%).

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub>S: C 65.16, H 4.82, N 4.47, S, 10.23; found C 65.35, H 4.78, N 4.67, S, 10.81

IR (NaCl):  $\nu$  = 1651.2 (CO), 1120.9 (SO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 8.32 (m, 1H, H<sub>7</sub>), 8.20 (s, 1H, H<sub>2</sub>), 7.97-7.94 (m, 1H, H<sub>4</sub>), 7.85 (d, 2H, J = 8.5 Hz, tosyl group), 7.40-7.20 (m, 4H, H<sub>5</sub>, H<sub>6</sub> and tosyl group), 2.57 (s, 3H, CH<sub>3</sub>CO), 2.37 (s, 3H, CH<sub>3</sub> tosyl group) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 182.3 (CO), 146.3 (CH<sub>3</sub>-C-Ph), 134.6 (SO<sub>2</sub>-C-Ph), 134.1 (C<sub>7a</sub>), 133.3 (C<sub>2</sub>), 130.4 (CH tosyl group), 127.8 (C<sub>3a</sub>), 127.3 (CH tosyl group), 126.2 (C<sub>5</sub> or C<sub>6</sub>), 125.2 (C<sub>5</sub> or C<sub>6</sub>), 123.1 (C<sub>4</sub>), 113.6 (C<sub>3</sub>), 113.2 (C<sub>7</sub>), 39.9 (COCH<sub>3</sub>), 21.7 (CH<sub>3</sub> tosyl group) ppm.

**3-BROMOACETYL-N-TOSYLINDOLE (133)**

To a suspension of copper(II) bromide (4.63 g, 20.67 mmol) in ethyl acetate (25 mL) was added a solution of 3-acetyl-N-tosylindole (2.19 g, 7 mmol) in chloroform (25 mL) and the mixture was refluxed overnight. Then, the reaction was cooled to room temperature and the solid was filtered off. After the removal of the solvent from the filtrate *in vacuo*, the crude product was purified by column chromatography on silica gel eluting with 3:1 petroleum ether/ethyl acetate to give the pure product. Yield 1.34 g (49%).

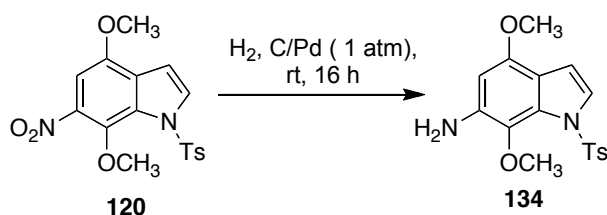
Melting point: 126-127 °C.

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>14</sub>BrNO<sub>3</sub>S: C 52.05, H 3.60, N 3.57, S 8.17; found C 52.32, H 3.25, N 3.81, S 7.97

IR (NaCl):  $\nu$  = 1666 (CO), 1175 (SO<sub>2</sub>), 570 (C-Br) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 8.34 (s, 1H, H<sub>2</sub>), 8.33-8.28 (m, 1H, H<sub>7</sub>), 7.96-7.93 (m, 1H, H<sub>4</sub>), 7.84 (d, 2H, tosyl group, J = 8.4 Hz), 7.41-7.36 (m, 2H, H<sub>5</sub> and H<sub>6</sub>), 7.30 (d, 2H, tosyl group, J = 8.4 Hz), 4.39 (s, 2H, CH<sub>2</sub>Br), 2.38 (s, 3H, CH<sub>3</sub> tosyl) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 188.4 (CO), 146.9 (CH<sub>3</sub>-C-Ph), 135.2 (C<sub>7a</sub>), 134.6 (SO<sub>2</sub>-C-Ph) 134.5 (C<sub>2</sub>), 130.4 (CH tosyl group), 127.9 (C<sub>3a</sub>), 127.5 (CH tosyl group), 125.9 (C<sub>4</sub>), 125.0 (C<sub>5</sub> or C<sub>6</sub>), 122.7 (C<sub>5</sub> or C<sub>6</sub>), 118.2 (C<sub>3</sub>), 113.4 (C<sub>3</sub>), 31.8 (CH<sub>2</sub>Br), 20.5 (CH<sub>3</sub> tosyl group) ppm.

**4,7-DIMETHOXY-1-TOSYL-1H-INDOL-6-AMINE (134)**

To a solution of nitroindole **120** (150 mg, 0.39 mmol) in ethyl acetate (50 mL) was added 10% palladised charcoal (20 mg) and the mixture was hydrogenated at r. t., 3 bars for 24 h. The mixture was filtered over celite and the filtrate was concentrated *in vacuo*, affording 135 mg (100%) of **134** as a green solid.

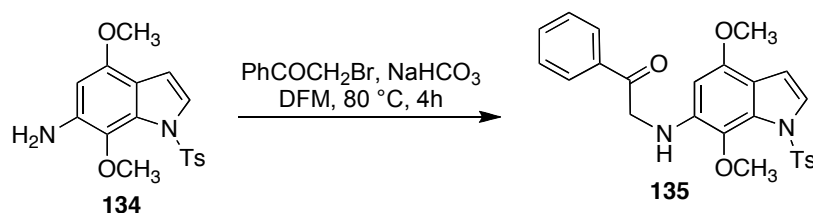
Melting point: 167-169 °C.

Elemental analysis calc. (%) for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: C 58.94, H 5.24, N 8.09, S 9.26; found: 57.61, H 5.18, N 8.45, S 9.01.

IR (NaCl):  $\nu = 3333$  (NH<sub>2</sub>), 1506 cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m = 7.75$  (d,  $J = 8.4$  Hz, 2H, tosyl group), 7.51 (d,  $J = 3.7$  Hz, 1H, H<sub>2</sub>), 7.22 (d,  $J = 8.4$  Hz, 2H, tosyl group), 7.65 (d,  $J = 3.7$  Hz, 1H, H<sub>3</sub>), 6.15 (s, 1H, H<sub>5</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 3.74 (s, 3H, OCH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub> tosyl group) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\tau^m = 149.5$  (C<sub>4</sub>), 144.7 (Ph-C-CH<sub>3</sub>), 138.6 (C<sub>7</sub>), 136.4 (Ph-C-SO<sub>2</sub>), 129.9 (CH tosyl group), 129.6 (C<sub>7a</sub>), 128.9 (C<sub>6</sub>), 127.8 (CH tosyl group), 125.7 (C<sub>2</sub>), 115.9 (C<sub>3a</sub>), 105.7 (C<sub>3</sub>), 95.8 (C<sub>5</sub>), 60.1 (7-OCH<sub>3</sub>), 55.8 (4-OCH<sub>3</sub>), 21.9 (CH<sub>3</sub> tosyl group) ppm.

**2-(4,7-DIMETHOXY-1-TOSYL-INDOL-6-YLAMINO)-1-PHENYLETHANONE (135)**

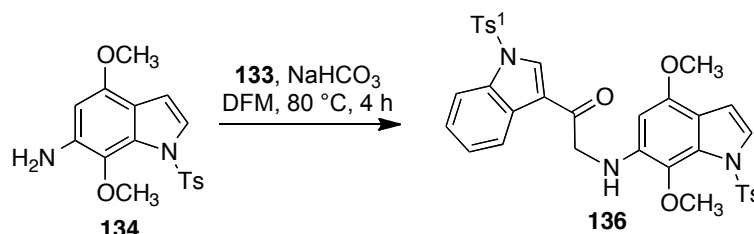
A solution of compound **134** (100 mg, 0.3 mmol), 3-bromoacetyl-acetophenone (51.74 mg, 0.26 mmol) and sodium carbonate (22 mg, 0.26 mmol) in DMF (2 mL) was heated in an oil bath at 85 °C for 35 min. Then the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (300 mL). The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 3:1 petroleum ether-ethyl acetate, affording 121 mg (87%) of compound **135** as a brown solid.

Elemental analysis calc. (%) for C<sub>25</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S: C 64.64, H 5.21, N 6.03, S 6.90; found: 64.41, H 5.13, N 5.85, S 7.04

IR (NaCl):  $\nu = 3325$  (NH<sub>2</sub>), 1656 (CO), 1212 (SO<sub>2</sub>) cm<sup>-1</sup>

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (s, 1H, H<sub>5</sub>), 7.65 (bs, 1H, NH), 7.52 (d, 2H, *J* = 8.4 Hz, tosyl group), 7.45 (d, 1H, *J* = 3.7 Hz, H<sub>2</sub>), 7.34 – 7.20 (m, 6H, Ph), 7.18 (d, 1H, *J* = 1.1 Hz, H<sub>4</sub>'), 7.02 (d, 2H, *J* = 8.1 Hz, tosyl group), 6.59 (d, 1H, *J* = 3.7 Hz, H<sub>3</sub>), 3.72 (s, 3H, OCH<sub>3</sub>), 3.67 (s, 2H, CH<sub>2</sub>), 3.26 (s, 3H, OCH<sub>3</sub>), 2.19 (s, 3H, CH<sub>3</sub> tosyl group) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)  $\delta$  175.6 (CO), 169.2 (C<sub>4</sub>), 148.6 (Ph-C-CH<sub>3</sub>), 144.4 (SO<sub>2</sub>-C-Ph), 135.1 (Ph-C-CO), 134.2 (C<sub>6</sub>), 133.5 (C<sub>7</sub>), 130.8 (C<sub>7a</sub>), 129.4 (CH Ph), 129.3 (CH tosyl group), 129.2 (CH Ph), 129.1 (CH Ph), 128.4 (C<sub>2</sub>), 127.6 (CH Ph), 127.5 (CH Ph), 127.2 (CH tosyl group), 119.7 (C<sub>3a</sub>), 105.5 (C<sub>3</sub>), 98.0 (C<sub>5</sub>), 61.3 (7-OCH<sub>3</sub>), 55.5 (4-OCH<sub>3</sub>), 45.0 (COCH<sub>2</sub>NH), 21.4 (CH<sub>3</sub> tosyl group) ppm..

**2-(4,7-DIMETHOXY-1-TOSYLINDOL-6-YLAMINO)-1-(1-TOSYLINDOL-3-YL)ETHANONE (136)**

A solution of compound **134** (100 mg, 0.3 mmol), 3-bromoacetyl-N-tosylindole (100 mg, 0.26 mmol) and sodium carbonate (22 mg, 0.26 mmol) in DMF (2 mL) was heated in an oil bath at  $85\text{ }^\circ\text{C}$  for 35 min. Then the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (500 mL). The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 3:1 petroleum ether-ethyl acetate, affording 100 mg (57%) of compound **136** as a yellow solid.

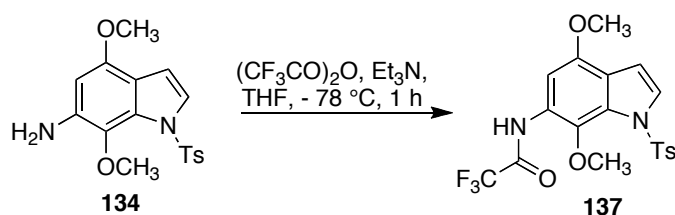
Melting point:  $111\text{--}113\text{ }^\circ\text{C}$ .

Elemental analysis calc. (%) for  $\text{C}_{34}\text{H}_{31}\text{N}_3\text{O}_7\text{S}_2$ : C 62.08; H 4.75; N 6.39; S 9.75; found: C 59.15; H 4.53; N 6.43; S 8.92.

IR (NaCl):  $\nu = 3334.1$  (NH),  $1655.4$  (CO),  $1121.2$  ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz, MeOD):  $\tau^m = 8.33$  (s, 1H,  $\text{H}_2^1$ ), 8.24–8.21 (m, 1H,  $\text{H}_4^1$ ), 7.84–7.81 (m, 1H,  $\text{H}_7^1$ ), 7.68 (d,  $J = 7$  Hz, 2H, tosyl group), 7.64 (d,  $J = 7$  Hz, 2H, tosyl group), 7.38 (d,  $J = 3.1$  Hz, 1H,  $\text{H}_2$ ), 7.28–7.23 (m, 2H,  $\text{H}_5^1$  and  $\text{H}_6^1$ ), 7.10 (d,  $J = 6.7$  Hz, tosyl group), 7.03 (d,  $J = 6.7$  Hz, 2H, tosyl group), 6.54 (d,  $J = 3.1$  Hz, 1H,  $\text{H}_3$ ), 6.04 (s, 1H,  $\text{H}_5$ ), 4.44 (s, 2H,  $\text{COCH}_2$ ), 3.78 (s, 3H,  $\text{OCH}_3$ ), 3.70 (s, 3H,  $\text{OCH}_3$ ), 2.22 (s, 3H,  $\text{CH}_3$  tosyl group), 2.16 (s, 3H,  $\text{CH}_3$  tosyl group) ppm.

$^{13}\text{C}$  NMR (63 MHz, MeOD):  $\delta$  = 186.1 ( $\underline{\text{C}}\text{OCH}_2$ ), 167.7 ( $\text{C}_4$ ), 158.9 ( $\text{CH}_3\text{-}\underline{\text{C}}\text{-Ph}$ ), 158.3 ( $\text{C}_{7a}^1$ ), 154.5 ( $\text{CH}_3\text{-}\underline{\text{C}}\text{-Ph}^1$ ), 146.1 ( $\text{C}_6$ ), 145.9 ( $\text{SO}_2\text{-}\underline{\text{C}}\text{-Ph}$ ), 144.6 ( $\text{SO}_2\text{-}\underline{\text{C}}\text{-Ph}^1$ ), 134.8 ( $\text{C}_7$ ), 134.4 ( $\text{C}_{7a}$ ), 133.1 ( $\text{C}_2^1$ ), 130.3 (CH tosyl group), 130.2 (CH tosyl group), 129.6 ( $\text{C}_2$ ), 128.9 ( $\text{C}_{3a}^1$ ), 127.7 ( $\text{C}_3^1$ ), 127.3 (CH tosyl group), 127.1 (CH tosyl group), 125.4 ( $\text{C}_5^1$  or  $\text{C}_6^1$ ), 125.2 ( $\text{C}_{3a}$ ), 124.4 ( $\text{C}_5^1$  or  $\text{C}_6^1$ ), 122.1 ( $\text{C}_7^1$ ), 113.8 ( $\text{C}_3$ ), 99.1 ( $\text{C}_5$ ), 63.7 ( $\text{OCH}_3$ ), 60.1 ( $\text{OCH}_3$ ), 51.6 ( $\underline{\text{C}}\text{H}_2\text{CO}$ ), 21.6 ( $\text{CH}_3$  tosyl group), 21.5 (tosyl group) ppm.

***N*-(4,7-DIMETHOXY-1-TOSYLINDOL-6-YL)-2,2,2-TRIFLUOROACETAMIDE (137)**

To a solution of compound **134** (500 mg, 1.44 mmol) in dry THF (30 mL) at  $-78\text{ }^\circ\text{C}$  was added dropwise dry triethylamine (72.72 mg, 0.72 mmol) and trifluoroacetic anhydride (605 mg, 2.88 mmol). The mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 1 h. Then, saturated  $\text{NaHCO}_3$  solution (15 mL) was added and the reaction was allowed to warm to room temperature. The mixture was extracted with  $\text{Et}_2\text{O}$  (2 x 40 mL), the combined organic layers were washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Removal of solvent under reduced pressure gave 565 mg (89%) of the desired compound **137** as a light grey solid.

Melting point  $>300$

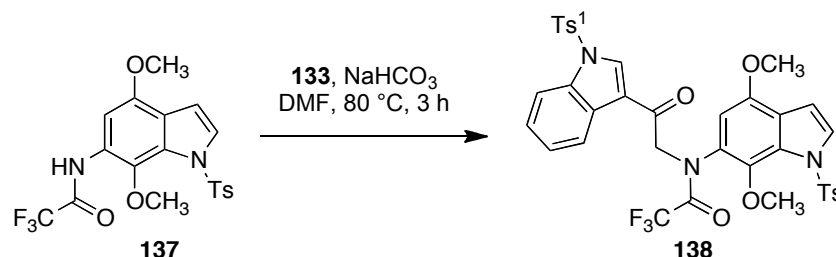
Elemental analysis calc. (%) for  $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_5\text{S}$ : C 51.58, H 3.87, N 6.33; S, 7.25; found C 52.00, H 4.12; N 6.67; S, 7.71

IR (NaCl):  $\nu = 3395$  (NH), 1731 (CO), 1175 ( $\text{CF}_3$ ), 1126 ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 8.48$  (s, 1H, NH), 7.71-7.68 (m, 3H,  $\text{H}_1^1$  Tos group and  $\text{H}_2$ ), 7.25 (d,  $J = 8.2$  Hz, 2H,  $\text{H}_2^1$  Tos group), 6.79 (d,  $J = 3.7$  Hz, 1H,  $\text{H}_3$ ), 3.92 (s, 3H,  $\text{OCH}_3$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 2.39 (s, 3H,  $\text{CH}_3$  Tos group) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 154.4$  (c,  $J = 37.5$  Hz, C=O), 149.0 ( $\text{C}_4$ ), 144.8 (Ph-C- $\text{CH}_3$ ), 135.1 ( $\text{SO}_2$ -C-Ph), 131.9 ( $\text{C}_7$ ), 129.6 (CH Tos), 128.5 ( $\text{C}_2$ ), 127.4 ( $\text{C}_{7a}$ ), 127.3 (CH Tos), 126.4 ( $\text{C}_6$ ), 121.6 ( $\text{C}_{3a}$ ), 105.6 ( $\text{C}_5$ ), 97.9 ( $\text{C}_3$ ), 62.3 ( $\text{OCH}_3$ ), 55.7 ( $\text{OCH}_3$ ), 21.5 ( $\text{CH}_3$  Tos) ppm.

***N*-(4,7-DIMETHOXY-1-TOSYLINDOL-6-YL)-2,2,2-TRIFLUORO-*N*-(2-OXO-2-(1-TOSYLINDOL-3-YL)ETHYL)ACETAMIDE (138)**



A solution of compound **137** (237 mg, 0.54 mmol), 3-bromoacetyl-*N*-tosylindole (185 mg, 0.54 mmol) and sodium carbonate (90 mg, 1.07 mmol) in DMF (10 mL) was heated in an oil bath at 85 °C for 35 min. Then the reaction mixture was poured onto water (25 mL) and extracted with ethyl acetate (50 mL). The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 4:1 petroleum ether-ethyl acetate, affording 254 mg (63%) of compound **138** as a yellow solid.

Melting point: 140-142 °C.

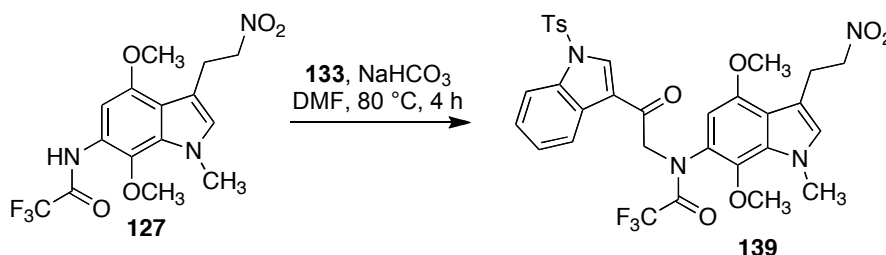
Elemental analysis calc. (%) for C<sub>36</sub>H<sub>30</sub>F<sub>3</sub>N<sub>3</sub>O<sub>8</sub>S<sub>2</sub>: C 57.36, H 4.01, N 5.57, S 8.51; found: C 57.05, H 4.27, N 5.65, S 8.19.

IR (NaCl):  $\nu$  = 1689 (COCF<sub>3</sub>), 1650 (COCH<sub>2</sub>), 1176 (CF<sub>3</sub>), 1125 (SO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 8.29 (s, 1H, H<sub>2</sub><sup>1</sup>), 8.27-8.25 (m, partially overlap with H<sub>2</sub><sup>1</sup>, 1H, H<sub>4</sub><sup>1</sup>), 7.92 (dd, *J* = 1.67 and *J* = 6.9 Hz, 1H, H<sub>7</sub><sup>1</sup>), 7.87 (d, *J* = 8.4 Hz, 2H, tosyl group), 7.78 (d, *J* = 3.7 Hz, 1H, H<sub>2</sub>), 7.70 (d, *J* = 8.4 Hz, 2H, tosyl group), 7.41-7.37 (m, 2H, H<sub>5</sub><sup>1</sup> and H<sub>6</sub><sup>1</sup>), 7.35 (d, *J* = 8.1 Hz, 2H, tosyl group), 7.22 (d, *J* = 8.1 Hz, 2H, tosyl group), 6.89 (s, 1H, H<sub>5</sub>), 6.79 (d, *J* = 3.7 Hz, 1H, H<sub>3</sub>), 5.64 (d, *J* = 16.9 Hz, 1H, COCH<sub>2</sub>), 4.43 (d, *J* = 16.9 Hz, 1H, COCH<sub>2</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 3.86 (s, 3H, OCH<sub>3</sub>), 2.40 (s, 3H, CH<sub>3</sub> tosyl group), 2.31 (s, 3H, CH<sub>3</sub> tosyl group) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 187.3 ( $\text{C}=\text{OCH}_2$ ), 158.5 (d,  $J = 36.6$  Hz,  $\text{C}=\text{OCF}_3$ ), 148.9 ( $\text{C}_4$ ), 146.7 ( $\text{CH}_3\text{-C-Ph}$ ), 145.4 ( $\text{CH}_3\text{-C-Ph}^1$ ), 137.7 ( $\text{C}_{7a}^1$ ), 136.1 ( $\text{SO}_2\text{-C-Ph}$ ), 134.9 ( $\text{C}_7$ ), 134.5 ( $\text{SO}_2\text{-C-Ph}^1$ ), 131.7 ( $\text{C}_2^1$ ), 130.8 (CH tosyl group), 130.4 ( $\text{C}_3^1$ ), 130.2 ( $\text{C}_6$ ), 129.9 (CH tosyl group), 129.0 ( $\text{C}_{3a}^1$ ), 128.8 ( $\text{C}_{7a}$ ), 127.8 (CH tosyl group), 127.7 (CH tosyl group), 126.5 ( $\text{C}_2$ ), 125.5 ( $\text{C}_4^1$ ), 125.2 ( $\text{C}_5^1$  or  $\text{C}_6^1$ ), 123.3 ( $\text{C}_5^1$  or  $\text{C}_6^1$ ), 118.8 ( $\text{C}_{3a}$ ), 116.6 (d,  $J = 288.2$  Hz,  $\text{CF}_3$ ), 113.5 ( $\text{C}_5$ ), 105.9 ( $\text{C}_7^1$ ), 105.3 ( $\text{C}_3$ ), 62.3 ( $\text{OCH}_3$ ), 58.3 ( $\text{COCH}_2$ ), 56.4 ( $\text{OCH}_3$ ), 22.1 ( $\text{CH}_3$  tosyl group), 21.9 ( $\text{CH}_3$  tosyl group) ppm.

***N*-(4,7-DIMETHOXY-1-METHYL-3-(2-NITROETHYL)INDOL-6-YL)-2,2,2-TRIFLUORO-*N*-(2-OXO-2-(1-TOSYLINDOL-3-YL)ETHYL)ACETAMIDE (139)**



A mixture of compound **127** (180 mg, 0.48 mmol), 3-bromoacetyl-*N*-tosylindole (166 mg, 0.48 mmol) and sodium carbonate (80.7 mg, 0.96 mmol) in DMF (7 mL) was heated in an oil bath at 85 °C for 4 h. Then, the reaction mixture was poured onto water (20 mL) and extracted with AcOEt (50 mL). The solvent was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 3:1 petroleum ether-ethyl acetate, affording 170 mg (52%) of compound **139** as a yellow solid.

Melting point: 143-145 °C.

Elemental analysis calc. (%) for C<sub>32</sub>H<sub>29</sub>F<sub>3</sub>N<sub>4</sub>O<sub>8</sub>S: C 55.97; H 4.26; N 8.16; S 4.67; found C 55.46; H 4.00; N 7.78; S 5.01

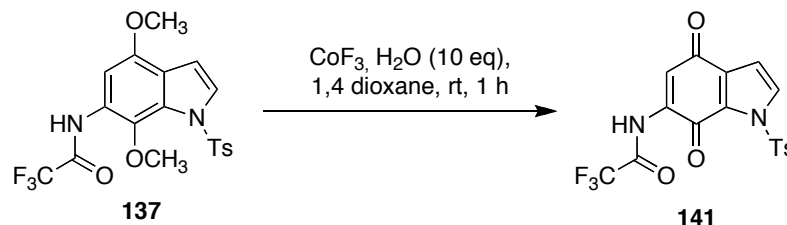
IR (NaCl):  $\nu$  = 1729 (COCF<sub>3</sub>), 1673 (COCH<sub>2</sub>), 1548 (NO<sub>2</sub>), 1321 (NO<sub>2</sub>), 1170 (CF<sub>3</sub>), 1140 and 1130 (SO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\tau^m$  = 8.36-8.25 (m, 2H, H<sub>4</sub><sup>1</sup> and H<sub>2</sub><sup>1</sup>), 7.97-7.89 (m, 1H, H<sub>7</sub><sup>1</sup>), 7.86 (d, *J* = 8.4 Hz, 2H, tosyl group), 7.39 (dd, *J* = 6.4, 5.4, 3.6 Hz, 2H, H<sub>5</sub><sup>1</sup> and H<sub>6</sub><sup>1</sup>), 7.31 (d, *J* = 9.0 Hz, 2H, tosyl group), 6.80 (s, 1H, H<sub>5</sub>), 6.68 (d, *J* = 0.9 Hz, 1H, H<sub>2</sub>), 5.66 (d, *J* = 17.0 Hz, 1H, CH<sub>2</sub>CO), 4.73-4.66 (m, 3H, CH<sub>2</sub>NO<sub>2</sub> and CH<sub>2</sub>CO),

3.98 (s, 3H, NCH<sub>3</sub>), 3.92 (s, 6H, OCH<sub>3</sub> C<sub>4</sub> and C<sub>7</sub>), 3.49 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>CH<sub>2</sub>NO<sub>2</sub>), 2.40 (s, 3H, CH<sub>3</sub> tosyl group) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\delta$  = 186.8 (CH<sub>2</sub>C=O), 158.2 (CF<sub>3</sub>C=O), 149.6 (C<sub>4</sub>), 146.2 (CH<sub>3</sub>-C-Ph), 136.3 (C<sub>7a</sub>), 134.5 (C<sub>7a</sub><sup>1</sup>), 134.2 (SO<sub>2</sub>-C-Ph), 131.2 (C<sub>2</sub><sup>1</sup>), 130.3 (CH tosyl), 129.7 (C<sub>5</sub>), 127.3 (C<sub>6</sub>), 127.2 (CH tosyl), 126.9 (C<sub>3a</sub><sup>1</sup>), 125.9 (C<sub>5</sub><sup>1</sup> or C<sub>6</sub><sup>1</sup>), 124.9 (C<sub>6</sub><sup>1</sup> or C<sub>5</sub><sup>1</sup>), 122.9 (C<sub>4</sub><sup>1</sup>), 120.2 (C<sub>3a</sub>), 118.5 (C<sub>3</sub><sup>1</sup>), 113.0 (C<sub>7</sub><sup>1</sup>), 109.6 (C<sub>3</sub>), 101.1 (C<sub>2</sub>), 76.8 (CH<sub>2</sub>CH<sub>2</sub>NO<sub>2</sub>), 62.4 (4-OCH<sub>3</sub>), 58.1 (COCH<sub>2</sub>), 55.7 (7-OCH<sub>3</sub>), 35.2 (NCH<sub>3</sub>), 24.9 (CH<sub>2</sub>CH<sub>2</sub>NO<sub>2</sub>), 21.6 (CH<sub>3</sub> tosyl group) ppm.

**N-(4,7-DIOXO-1-TOSYL-4,7-DIHYDROINDOL-6-YL)-2,2,2-TRIFLUOROACETAMIDE (141)**



To a solution of compound **137** (30 mg, 0.067 mmol) in dry dioxane (3 mL)  $\text{CoF}_3$  (31.1 mg, 0.268 mmol) and water (12  $\mu\text{L}$ , 10 eq) were added and the mixture was stirred at room temperature for 1 h. Then, water (5 mL) was added and the reaction was extracted with ethyl acetate (3 x 10 mL). The organic layer was dried over sodium sulphate and the solvent removed *in vacuo* to give 20 mg (76%) of compound **141** as a brown solid.

Melting point: 188-190 °C.

Elemental analysis calc. (%) for  $\text{C}_{17}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_5\text{S}$ : C 49.52, H 2.69, N 6.79, S 7.78; found: C 48.72, H 3.05, N 6.72, S 7.19.

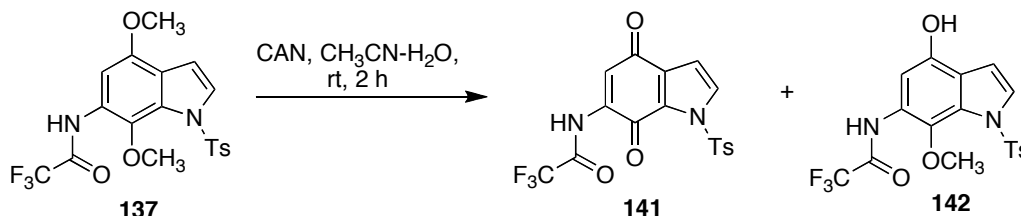
IR (NaCl):  $\nu = 3336$  (NH), 1732 (CO), 1678 and 1659 (quinone), 1177 ( $\text{CF}_3$ ), 1135 ( $\text{SO}_2$ )  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 8.98$  (s, 1H, NH), 8.05 (d,  $J = 8.5$  Hz, 2H, H Tos), 7.93 (d,  $J = 3.2$  Hz, 1H,  $\text{H}_2$ ), 7.53 (s, 1H,  $\text{H}_5$ ), 7.42 (d,  $J = 8.1$  Hz, 2H, H Tos), 6.83 (d,  $J = 3.2$  Hz, 1H,  $\text{H}_3$ ), 2.49 (s, 3H,  $\text{CH}_3$ ) ppm.

$^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ ):  $\tau^m = 182.8$  ( $\text{C}_7$ ), 168.9 ( $\text{C}_4$ ), 155.7 (dd,  $J = 75.7$  and 36.5 Hz, CO), 147.3 ( $\text{CH}_3\text{-C-Ph}$ ), 137.7 ( $\text{C}_6$ ), 133.6 ( $\text{SO}_2\text{-C-Ph}$ ), 132.7 ( $\text{C}_{3a}$ ), 132.4 ( $\text{C}_2$ ), 130.5 ( $\text{C}_3^1$  and  $\text{C}_3^2$ ), 130.1 ( $\text{C}_4^1$ ), 129.5 ( $\text{C}_2^1$  and  $\text{C}_2^2$ ), 126.8 ( $\text{C}_{7a}$ ), 117.0 ( $\text{C}_5$ ), 109.2 ( $\text{C}_3$ ), 22.3 ( $\text{CH}_3$  tosyl) ppm.



**N-(4-HYDROXY-7-METHOXY-1-TOSYL-1H-INDOL-6-YL)-2,2,2-TRIFLUOROACETAMIDE (142)**



Ceric ammonium nitrate (476.7 mg, 0.87 mmol) was added to a solution of compound **137** (130 mg, 0.37 mmol) in 2:1 CH<sub>3</sub>CN/H<sub>2</sub>O (15 mL) and the reaction was stirred at room temperature for 2 h. The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), the combined organic layers were washed with water and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was concentrated *in vacuo* to give 114 mg (75 %) of a mixture of compounds **140** and **141**. Purification by flash chromatography on silica gel eluting with 1:2 petroleum ether-ethyl acetate afforded 76 mg (50%) of **141** and 25 mg (15%) of **142**.

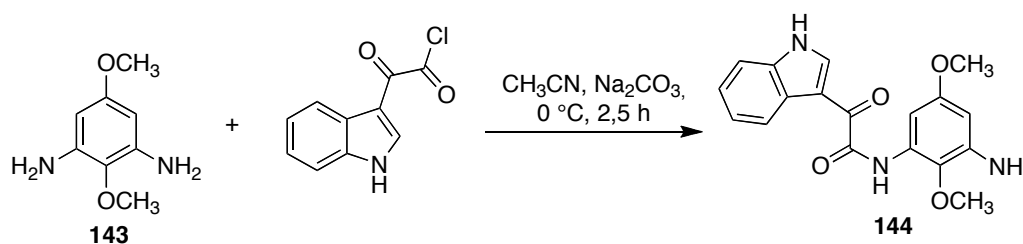
Yield (15 %)

Elemental analysis

IR (NaCl):  $\nu = 3320$  (OH), 1657 (CO), 1175 (CF<sub>3</sub>), 1138.4 (SO<sub>2</sub>) cm<sup>-1</sup>.

<sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta = 8.11$  (d, 2H,  $J = 8.5$  Hz, tosyl), 7.83 (d, 1H,  $J = 3.1$  Hz, H<sub>2</sub>), 7.37 (d, 2H,  $J = 8.4$  Hz, tosyl), 7.29 (s, 1H, H<sub>5</sub>), 6.58 (d, 1H,  $J = 3.1$  Hz, H<sub>3</sub>), 5.59 (s, 1H, OH), 3.93 (s, 3H, OCH<sub>3</sub>), 2.45 (s, 3H, CH<sub>3</sub> tosyl) ppm.

<sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>):  $\delta = 182.8$  (C<sub>7</sub>), 168.9 (C<sub>4</sub>), 155.7 (dd,  $J = 75.7, 36.5$  Hz, CO), 147.3 (CH<sub>3</sub>-C-Ph), 137.7 (C<sub>6</sub>), 133.6 (SO<sub>2</sub>-C-Ph), 132.7 (C<sub>3a</sub>), 132.4 (C<sub>2</sub>), 130.4 (C<sub>3</sub>), 130.1 (C<sub>4</sub>), 129.5 (C<sub>2</sub>), 126.8 (C<sub>7a</sub>), 117.0 (C<sub>5</sub>), 109.2 (C<sub>3</sub>), 22.3 (CH<sub>3</sub> tosyl).

***N*-(3-AMINO-2,5-DIMETHOXYPHENYL)-2-(INDOL-3-YL)-2-OXOACETAMIDE (144)**

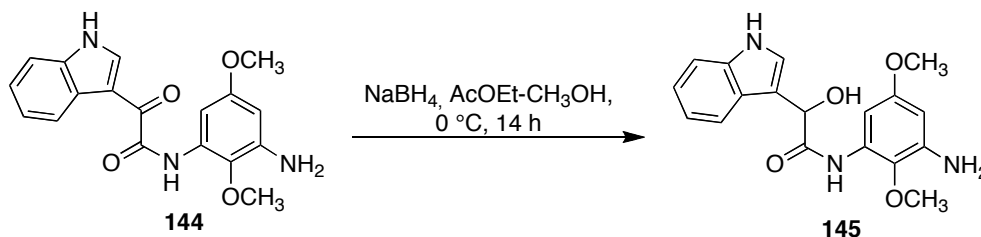
To a mixture of the diamine **143**<sup>82</sup> (240 mg, 0.087 mmol) and sodium bicarbonate (40 mg) in acetonitrile (10 mL) at 0 °C, a suspension of 3-indoleoxalyl chloride<sup>83</sup> (59 mg, 0.284 mmol) in acetonitrile (10 mL) was added in one lot and stirred at 0 °C for 2 h. Then, saturated sodium bicarbonate solution (5 mL) was added and the reaction mixture stirred for 0.5 h. The product was extracted with ethyl acetate and the solvent removed. The residue, consisting of a mixture of mono and diamide (81 % and 19 % respectively) was purified by flash column chromatography eluting with petroleum ether/ethyl acetate (1.5:1) to afford 100 mg (78 %) of compound **144**.

<sup>1</sup>H-RMN (DMSO-d<sub>6</sub>, 250 MHz):  $\tau^m$  = 12.50 (br s, 1H, NH indole), 9.89 (br s, 1H, NHCO), 9.01 (d, 1H, *J* = 3.0 Hz, H<sub>2</sub>), 8.30-25 (m, 1H, H<sub>4</sub>), 7.67-53 (m, 1H, H<sub>7</sub>), 7.30-7.20 (m, 3H, H<sub>5</sub>, H<sub>6</sub> and H<sub>6'</sub>), 6.12 (s, 1H, H<sub>4'</sub>), 5.13 (br s, 2H, NH<sub>2</sub>), 3.36 (s, 6H, 2 OCH<sub>3</sub>) ppm.

<sup>82</sup> R.T. Nelly, J. A. Field, Q. Li, *Tetrahedron Lett.* **1988**, 29, 3545.

<sup>83</sup> N. K. Garg, R. Sarpong, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, 124, 13179.

***N*-(3-AMINO-2,5-DIMETHOXYPHENYL)-2-HYDROXY-2-(INDOL-3-YL)ACETAMIDE  
(145)**



A solution of the monoamide **144** (20 mg, 0.059 mmol) in ethyl acetate (6 mL) and methanol (2 mL) at  $0\text{ }^\circ\text{C}$  was treated with sodium borohydride (2 mg, 0.053 mmol). After the reaction was over, the reaction mixture was treated with a solution of sodium bicarbonate (10 mg in 2 mL), extracted with ethyl acetate (3 X 15 mL), dried over anhydrous sodium sulphate and the solvent removed. Yield: 18 mg (90 %).

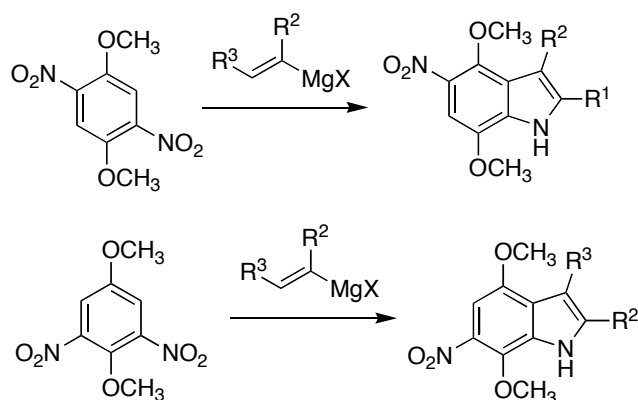
$^1\text{H-RMN}$  ( $\text{DMSO-d}_6$ , 250 MHz):  $\tau^{\text{M}}$  = 11.1 (br s, 1H, NH indole), 9.45 (bs, 1H,  $J = 7.8$  Hz,  $\text{H}_7$ ), 7.50 (m, 2H,  $\text{H}_4$  and  $\text{H}_6'$ ), 7.10-6.80 (m, 3H,  $\text{H}_2$ ,  $\text{H}_5$  and  $\text{H}_6$ ), 6.52 (s, 1H, OH), 6.02 (s, 1H,  $\text{H}_4'$ ), 5.32 (s, 1H,  $\text{H}_4$ ), 5.10 (br s, 2H,  $\text{NH}_2$ ), 3.62 (s, 3H,  $\text{OCH}_3$ ), 3.56 (s, 3H,  $\text{OCH}_3$ ) ppm.

## **6. Conclusiones**



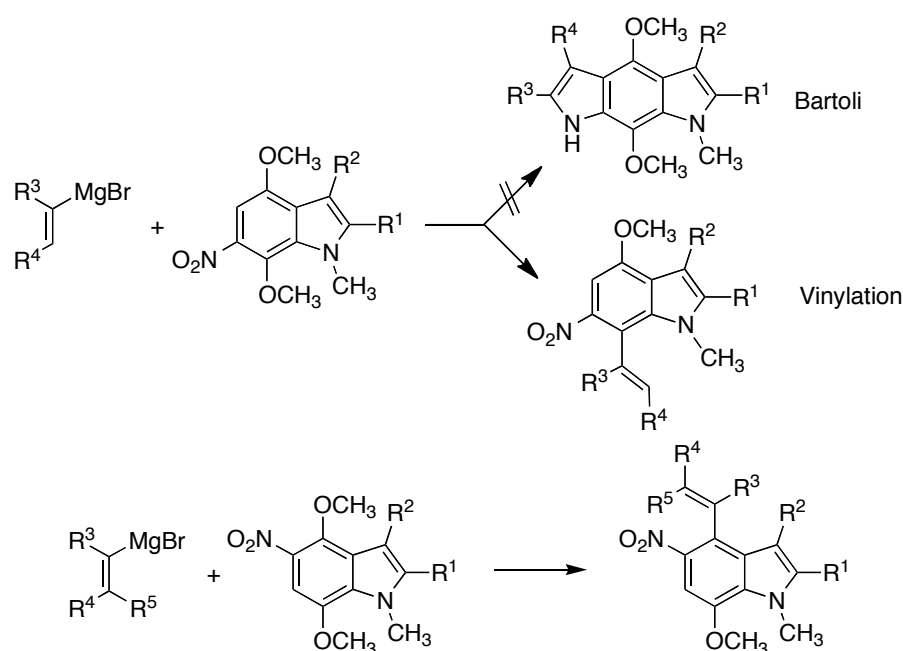
6. La reacción de Bartoli de derivados de 1,4-dimetoxi-2,5- y 2,6-dinitrobenzeno es el método de elección para la síntesis de derivados de 5-nitro- y 6-nitro-4,7-dimetoxiindol, respectivamente. Para el acceso a otros derivados indólicos con grupos metoxilo y nitro vecinos es preferible el empleo de métodos más convencionales, basados en la nitración aromática.

*The Bartoli reaction between 1,4-dimethoxy-2,5- and 2,6-dinitrobenzenes is the method of choice for the synthesis of 5-nitro- and 6-nitro-4,7-dimethoxyindoles, respectively. Access to other indoles bearing adjacent methoxy and nitro substituents is best achieved by conventional methods involving aromatic nitration*



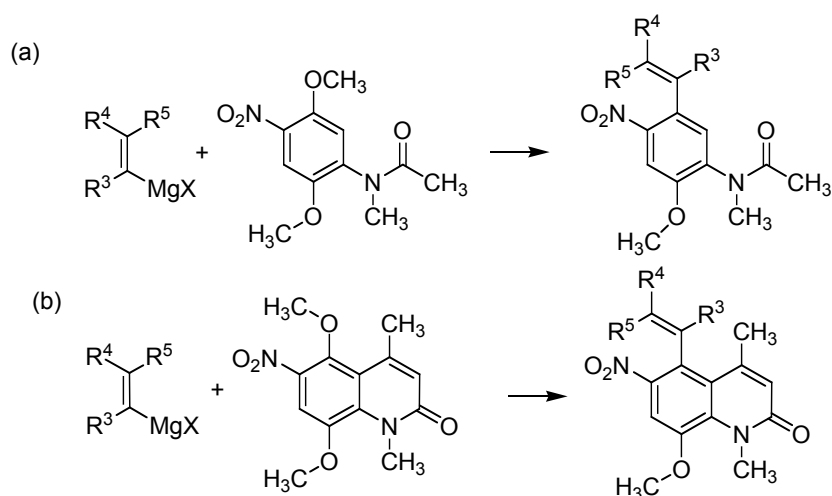
7. El tratamiento de derivados de 4,7-dimetoxi-6-nitroindol con vinilmagnesianos no conduce a una reacción de Bartoli, como cabría esperar, sino a una reacción de vinilación aromática en C-7, en la que el magnesiano desplaza al grupo metoxilo en *orto* respecto al nitro a través de un mecanismo de adición-eliminación. Análogamente, la reacción de derivados de 4,7-dimetoxi-5-nitroindol con vinilmagnesianos proporciona productos de vinilación en la posición C-4 del indol.

*Treatment of 4,7-dimethoxy-6-nitroindoles with vinylmagnesium reagents does not lead, as expected, to Bartoli products. Instead, an aromatic vinylation at C-7 is observed involving displacement of the methoxy group ortho to the nitro substituent via an addition-elimination mechanism. A similar result was obtained for the reaction between 4,7-dimethoxy-5-nitroindoles and vinyl Grignard reagents, which afforded C<sub>4</sub>-vinyl indoles.*



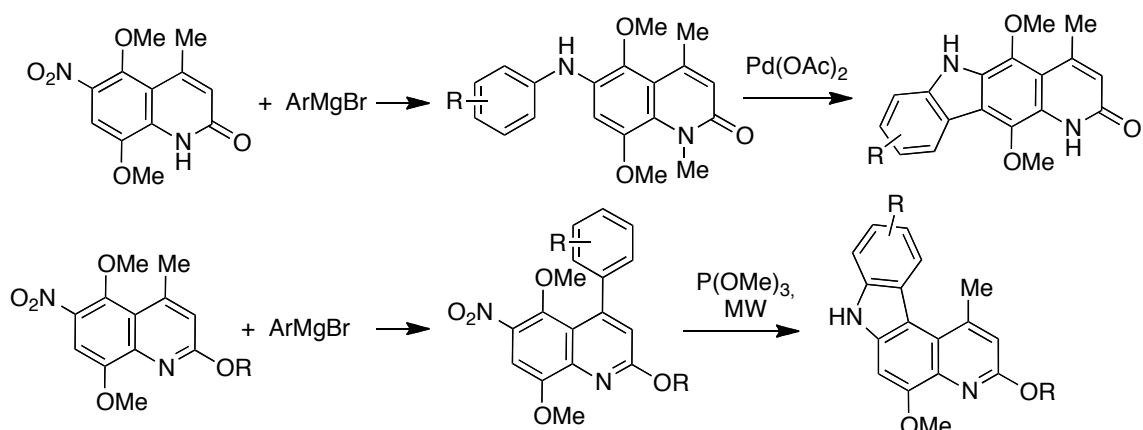
8. La reacción de vinilación puede extenderse a sustratos no indólicos en los que existan un metoxilo y un nitro en *orto* entre sí y un nitrógeno de tipo amida en *para* respecto al nitro. Los compuestos de este tipo que se han estudiado incluyen anilidas y derivados de 2-quinolinona (carbostirilo).

*This method for aromatic vinylation can be extended to substrates different from indole which bear adjacent methoxy and nitro groups and an amide-like nitrogen para to the nitro, including anilides and 2-quinolinones (carbostyrils).*



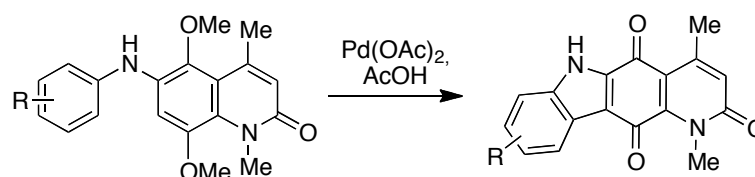
9. La reacción entre magnesianos aromáticos y 5-metoxi-6-nitroquinolinas permite acceder, de forma quimiodivergente, a 6-amilamino- o 5-amilquinolinas dependiendo de la presencia de grupos aceptores o donadores electrónicos, respectivamente, en el sistema de quinolina. Estos intermedios permiten un acceso rápido a carbazoles fusionados tetracíclicos de estructura lineal o angular mediante el uso de reacciones de acoplamiento oxidativo intramolecular promovidas por paladio o reacciones de Cadogan, respectivamente.

*The reaction of arylmagnesium bromides with 5-methoxy-6-nitroquinolines provides chemodivergent access to 6-arylmino- or 5-arylquinolines, depending on the presence of electron-withdrawing or electron-releasing substituents on the heterocyclic ring, respectively. These synthetic intermediates allow an efficient entry into tetracyclic fused linear or angular carbazole systems, using, respectively, palladium-promoted oxidative coupling or Cadogan reactions.*



10. En el curso de los estudios de arilación se descubrieron reacciones inesperadas, incluyendo un nuevo método de desmetilación oxidativa de 6-arylaminio-5,8-dimetoxicarboestirilos con acetato de paladio, que da lugar a un proceso dominó junto con la ciclodeshidrogenación inicial del sistema.

*Some unexpected modes of reactivity were uncovered in the course of the arylation work, including an unprecedented domino cyclodehydrogenation-oxidative demethylation of 6-arylaminio-5,8-dimethoxycarboestiril systems by palladium acetate.*

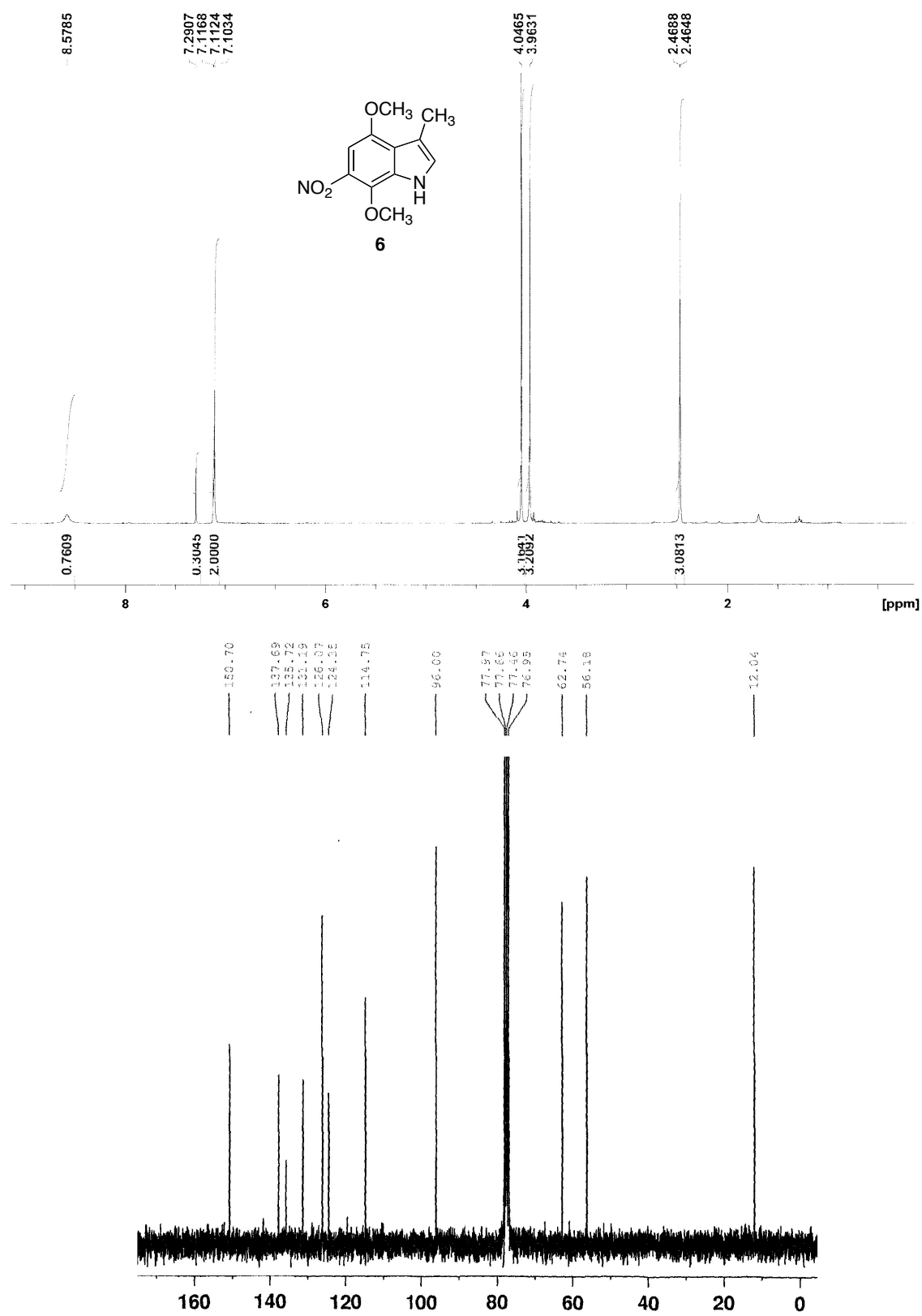


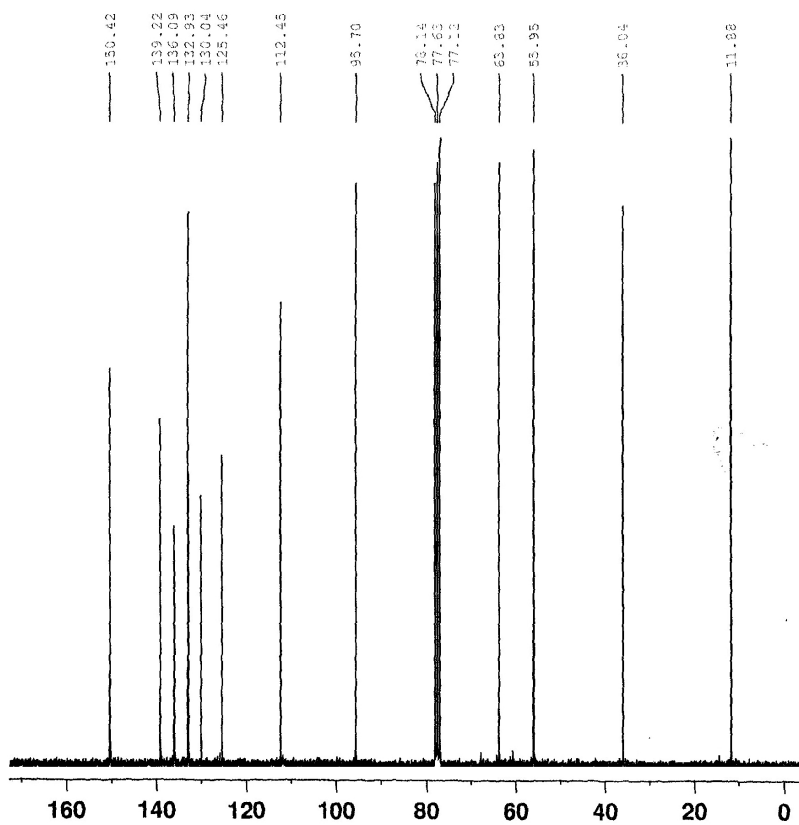
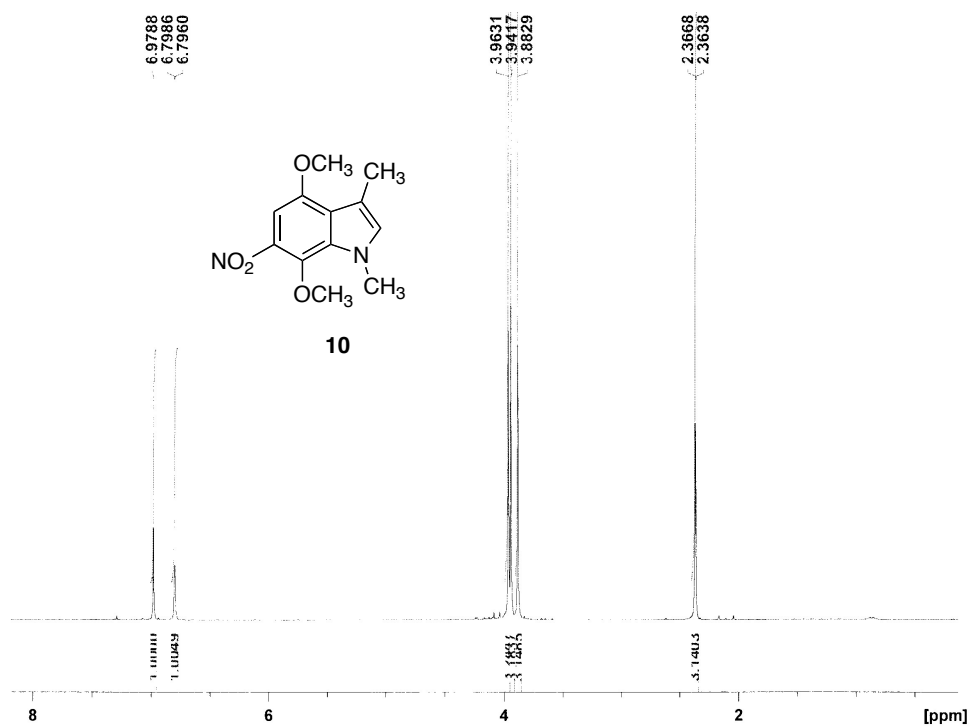
6. Se ha sintetizado una serie de análogos simplificados del alcaloide antitumoral de origen marino wakayina, utilizando una reacción de Bartoli como etapa clave. Estos compuestos se diseñaron mediante estudios de docking en la enzima topoisomnerasa I.

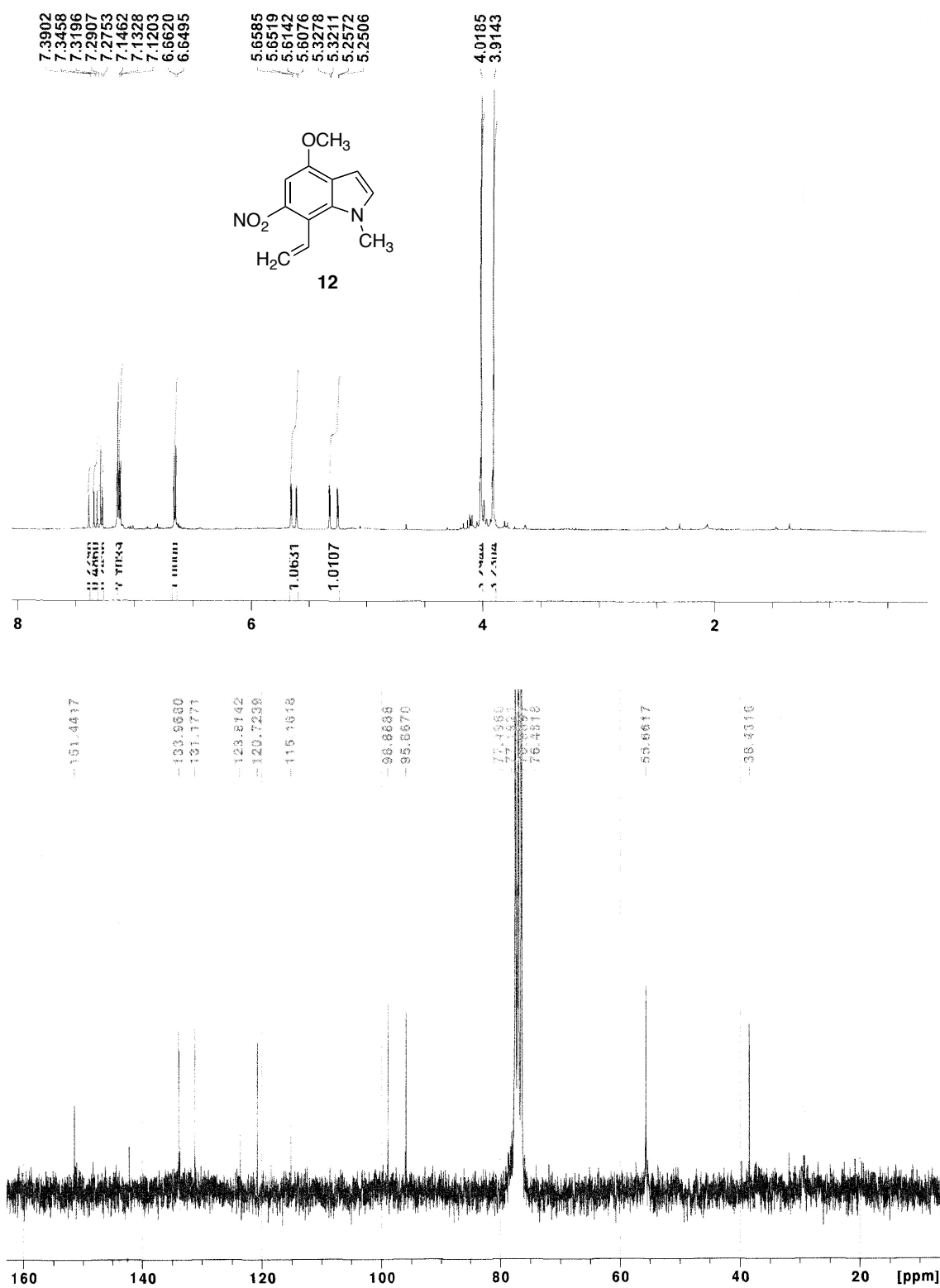
*A library of simplified analogues of the anticancer marine alkaloid wakayin was synthesized, using a Bartoli reaction as the key step. This library was designed by docking studies on the enzyme topoisomnerasa I.*

## **7. Apéndice: Espectros representativos**

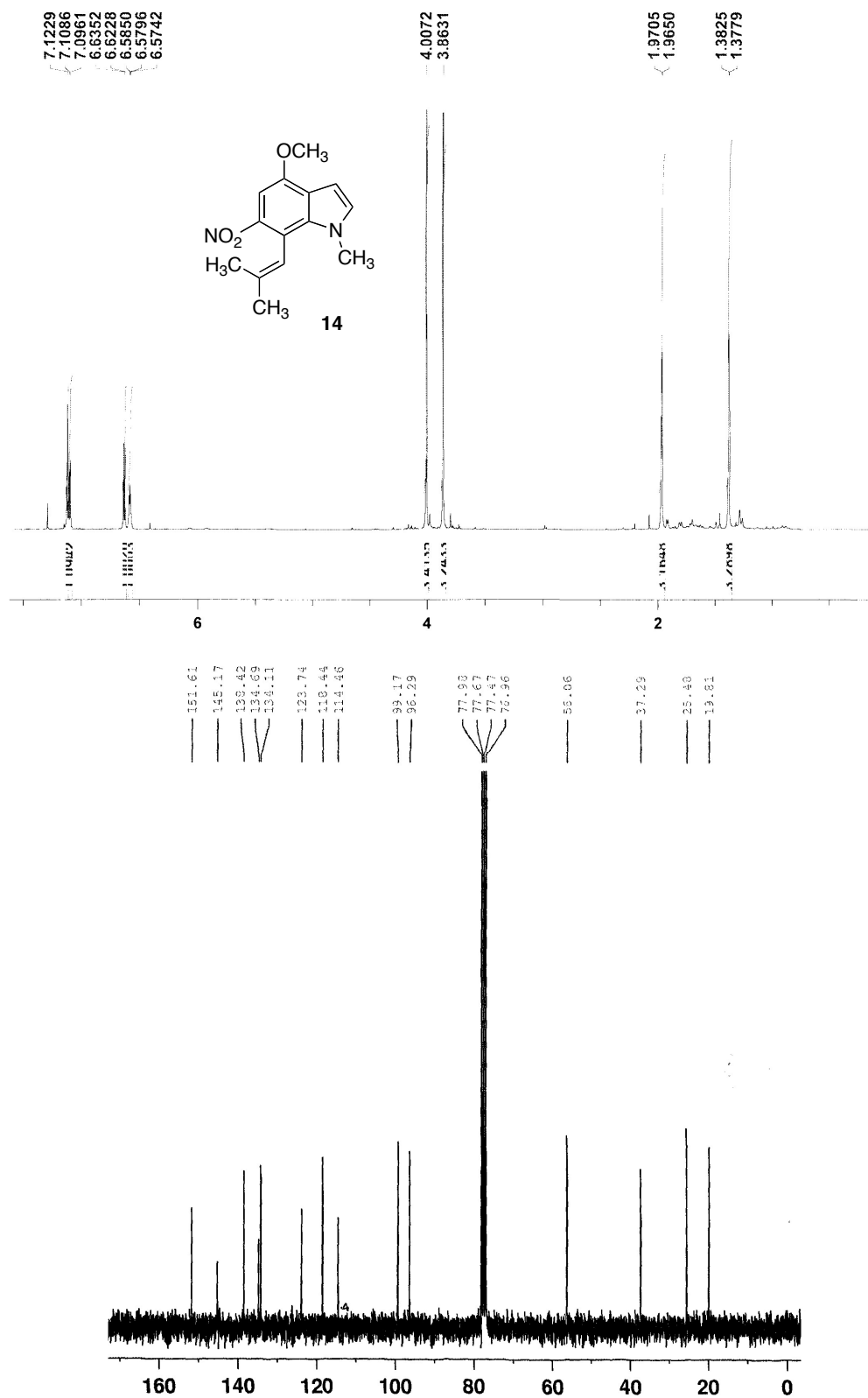


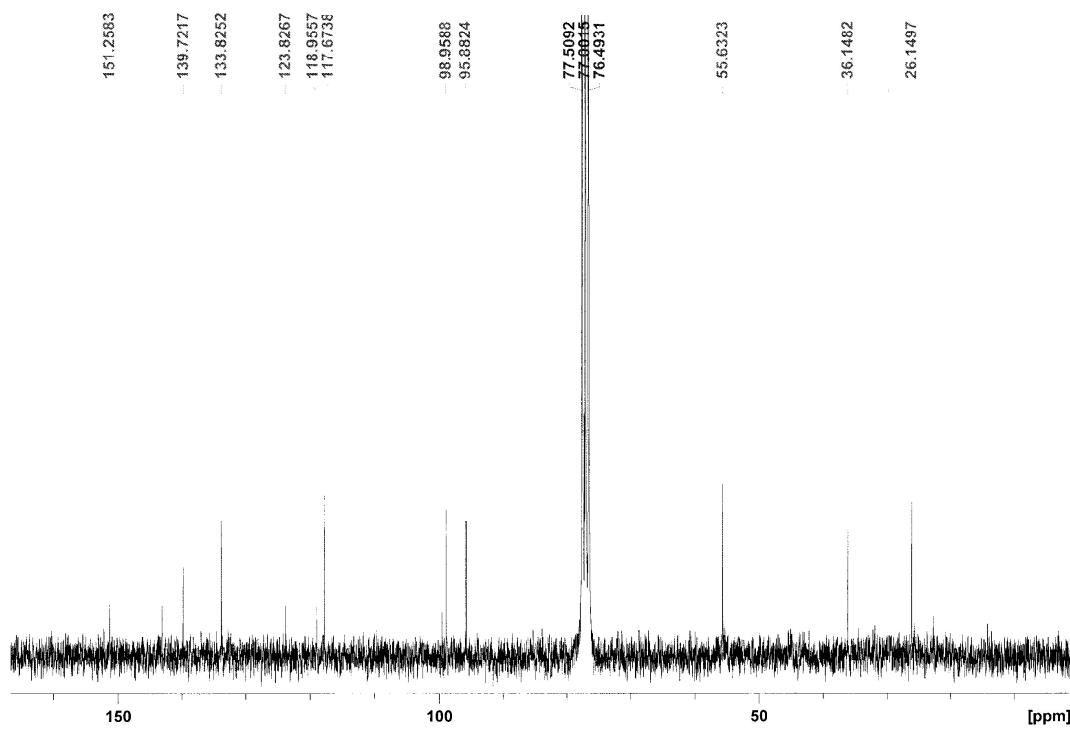
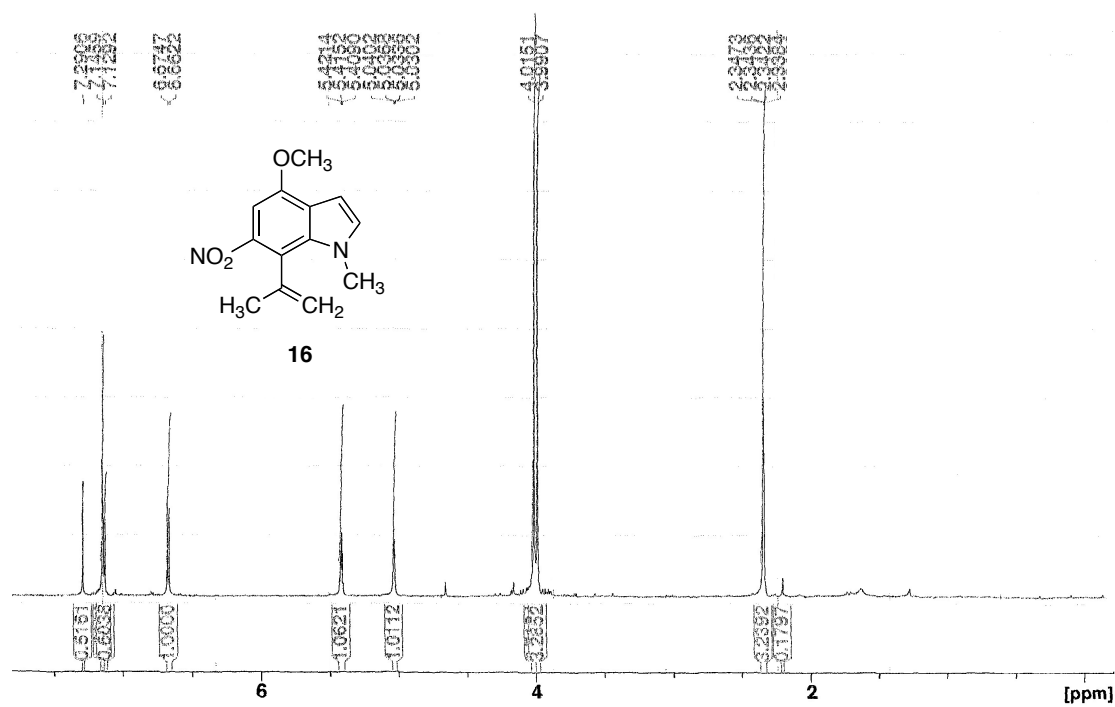




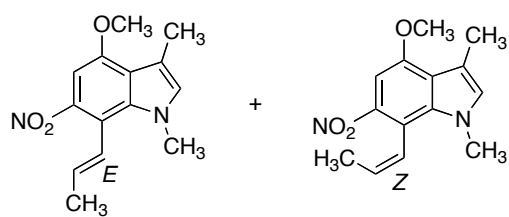
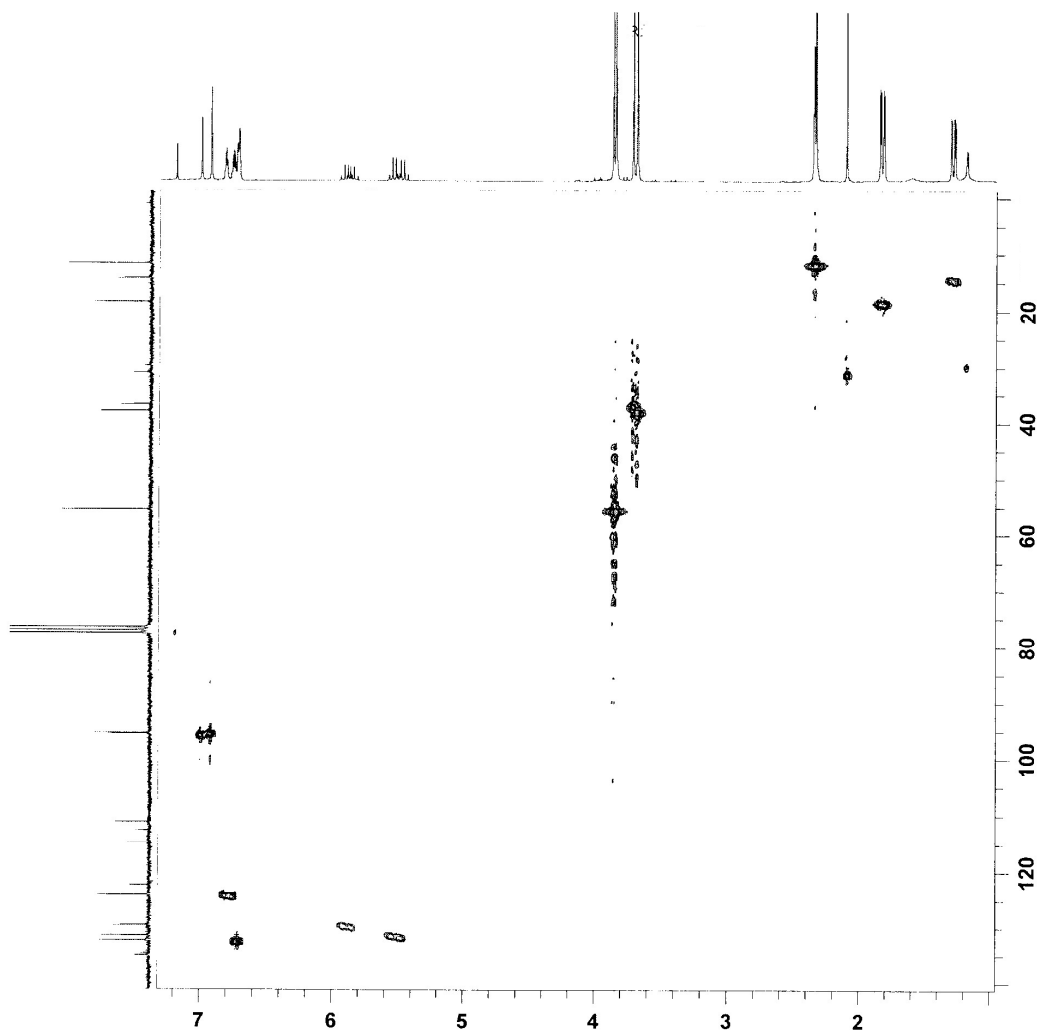


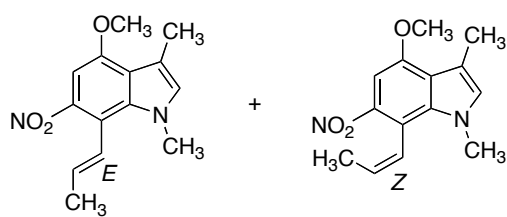




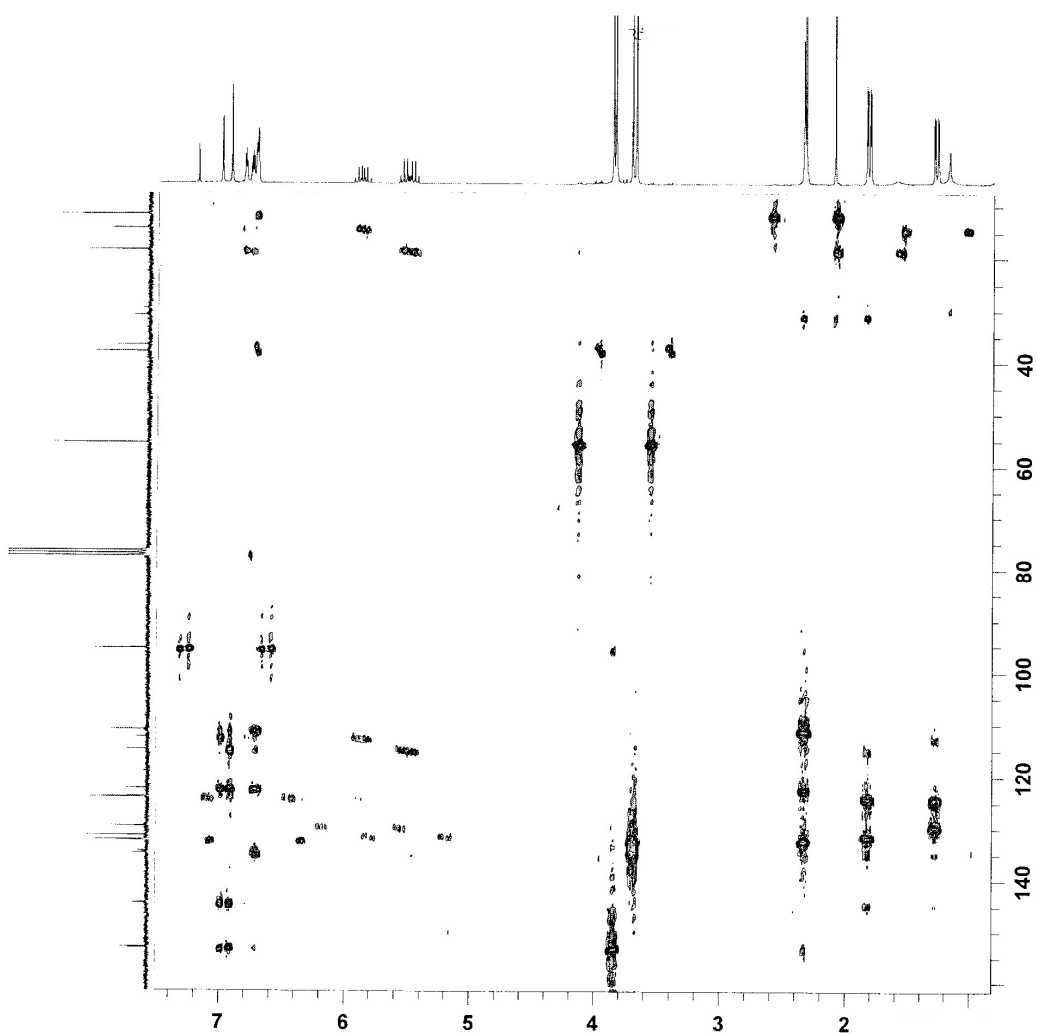


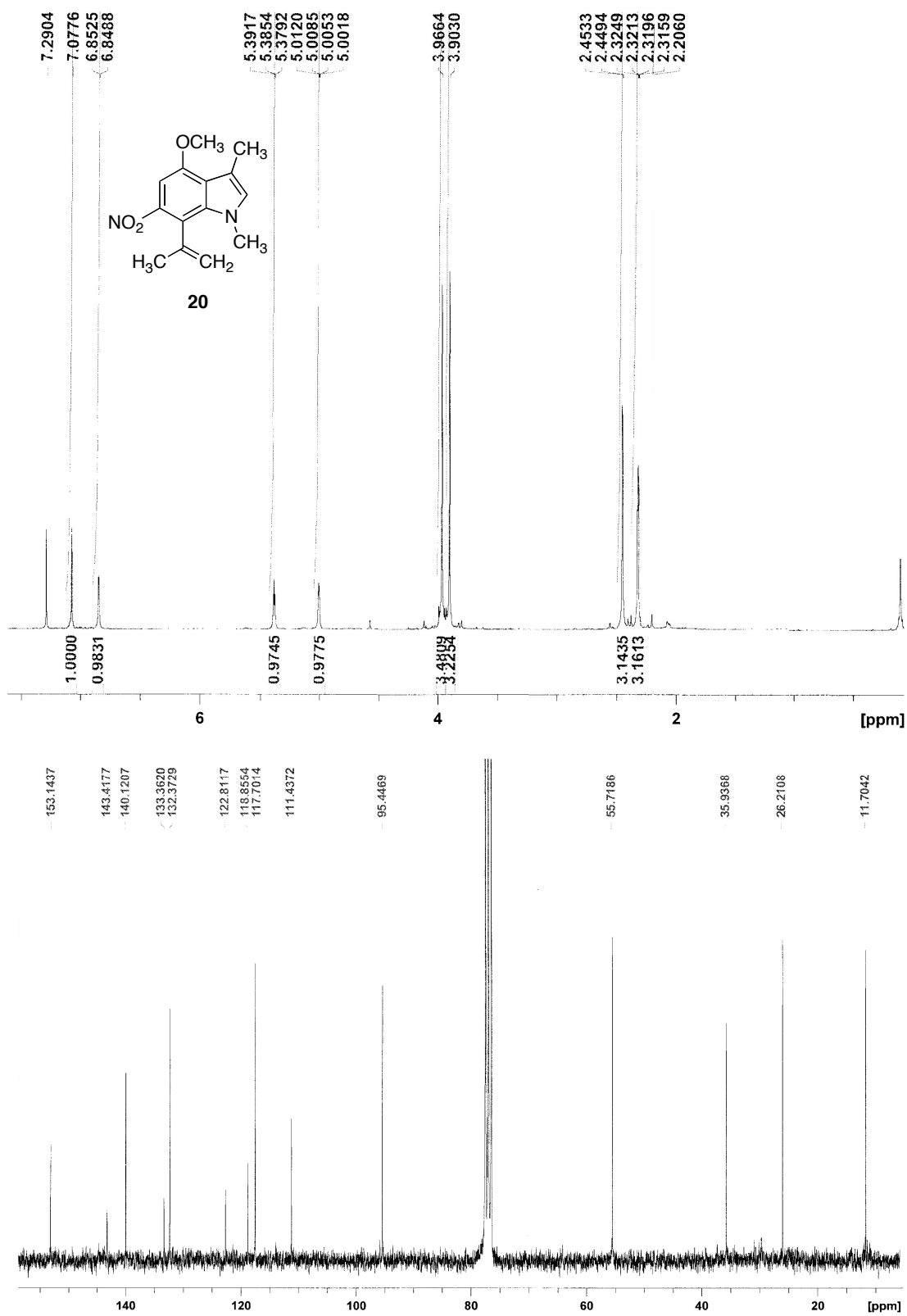


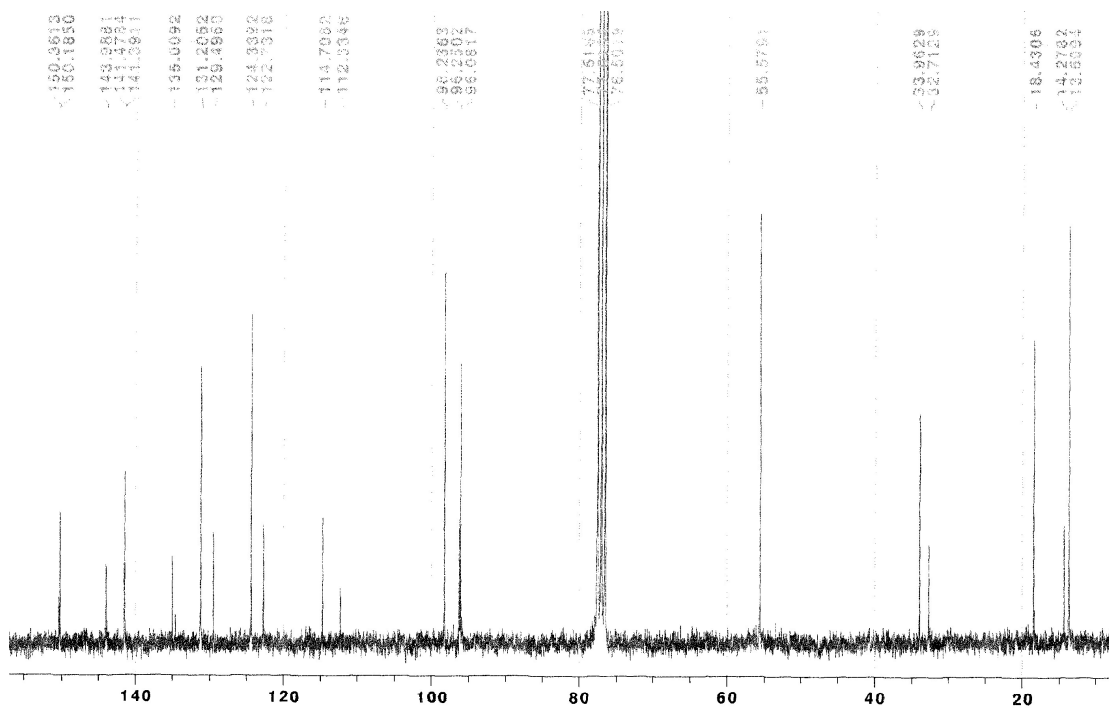
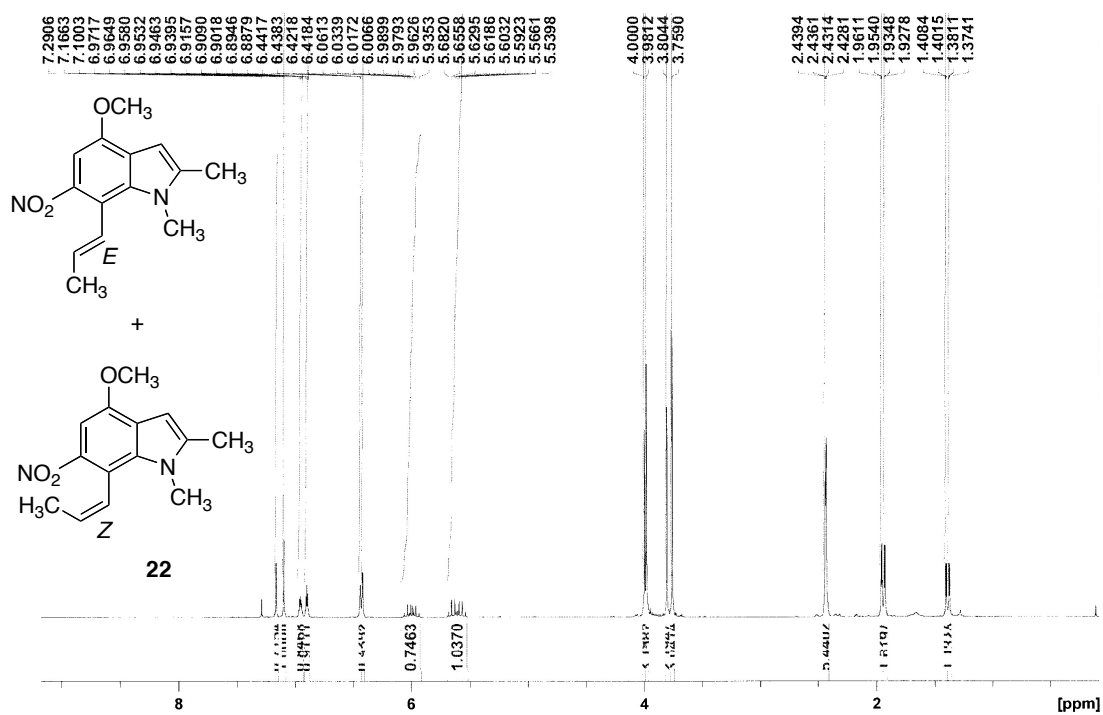
**18**

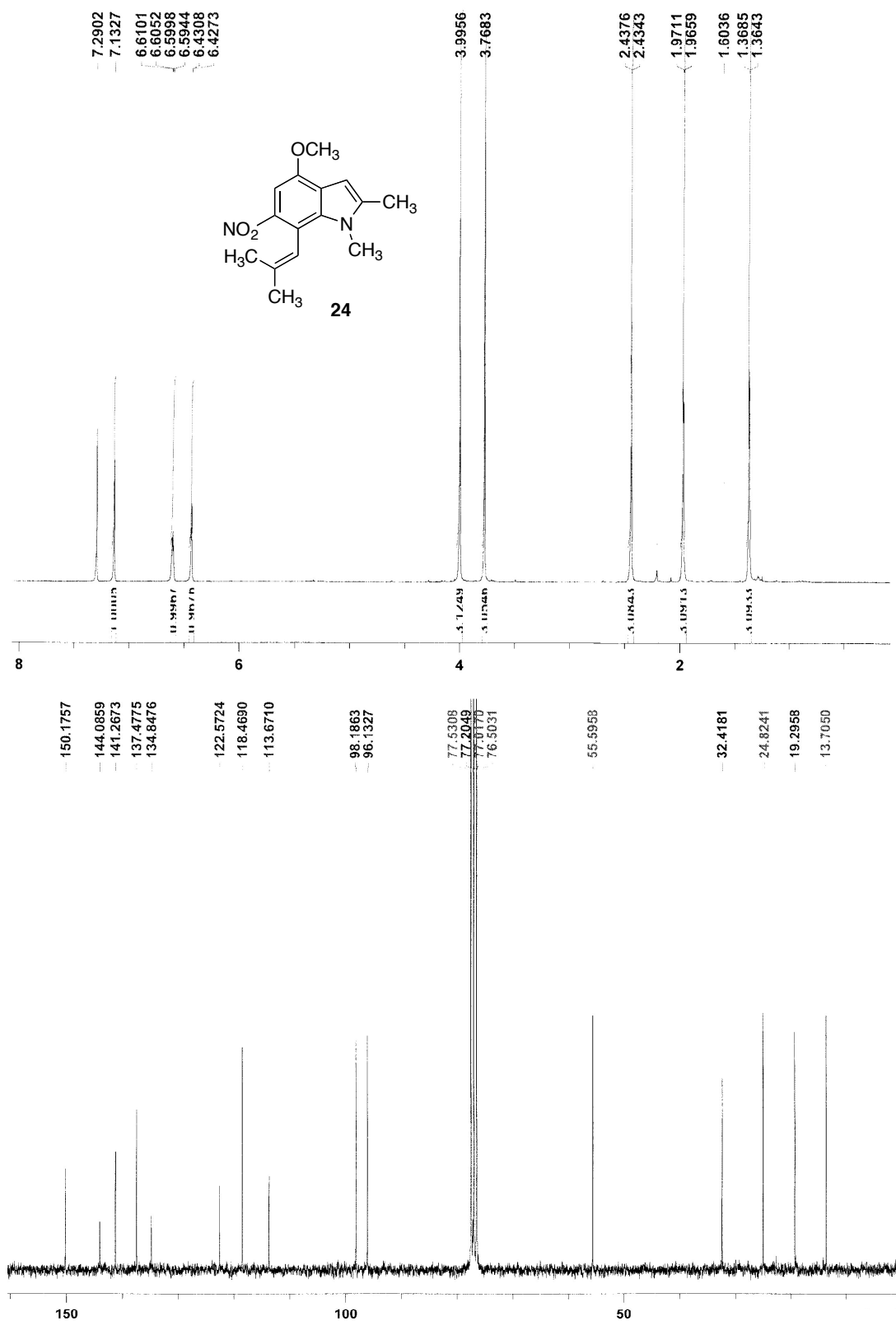


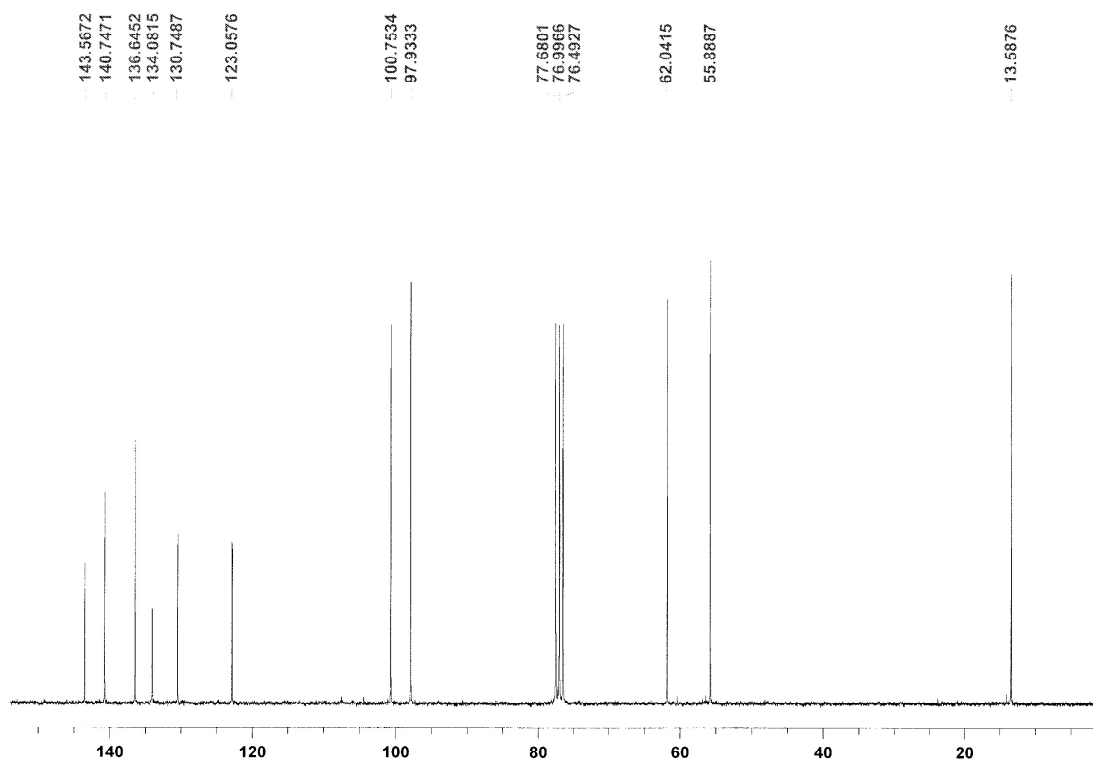
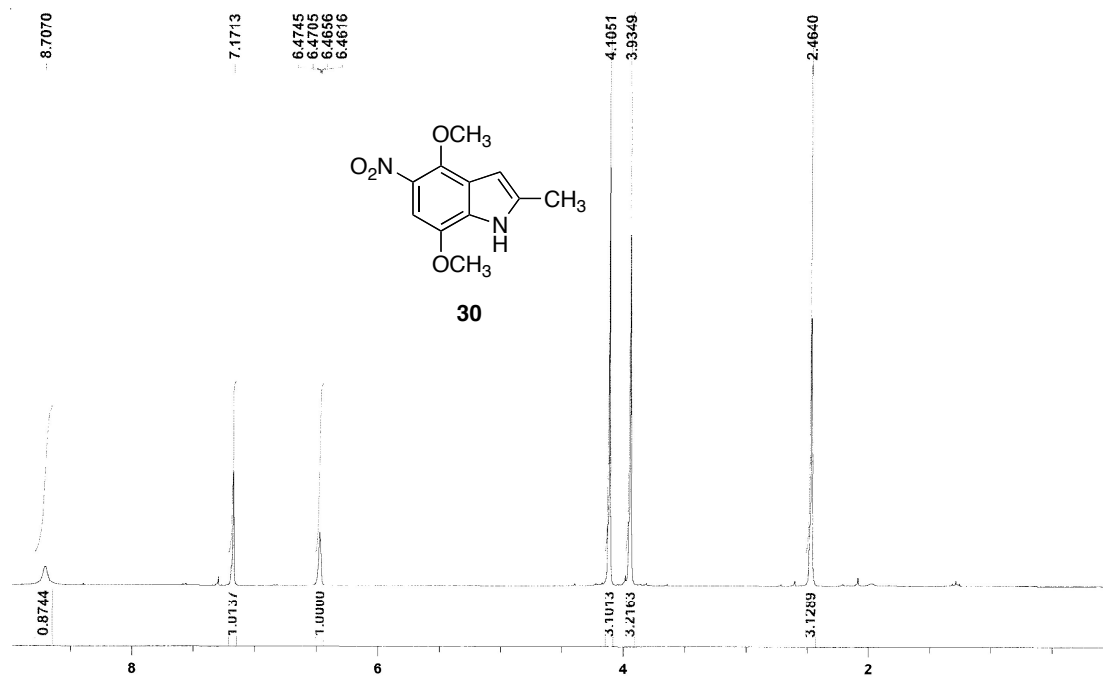
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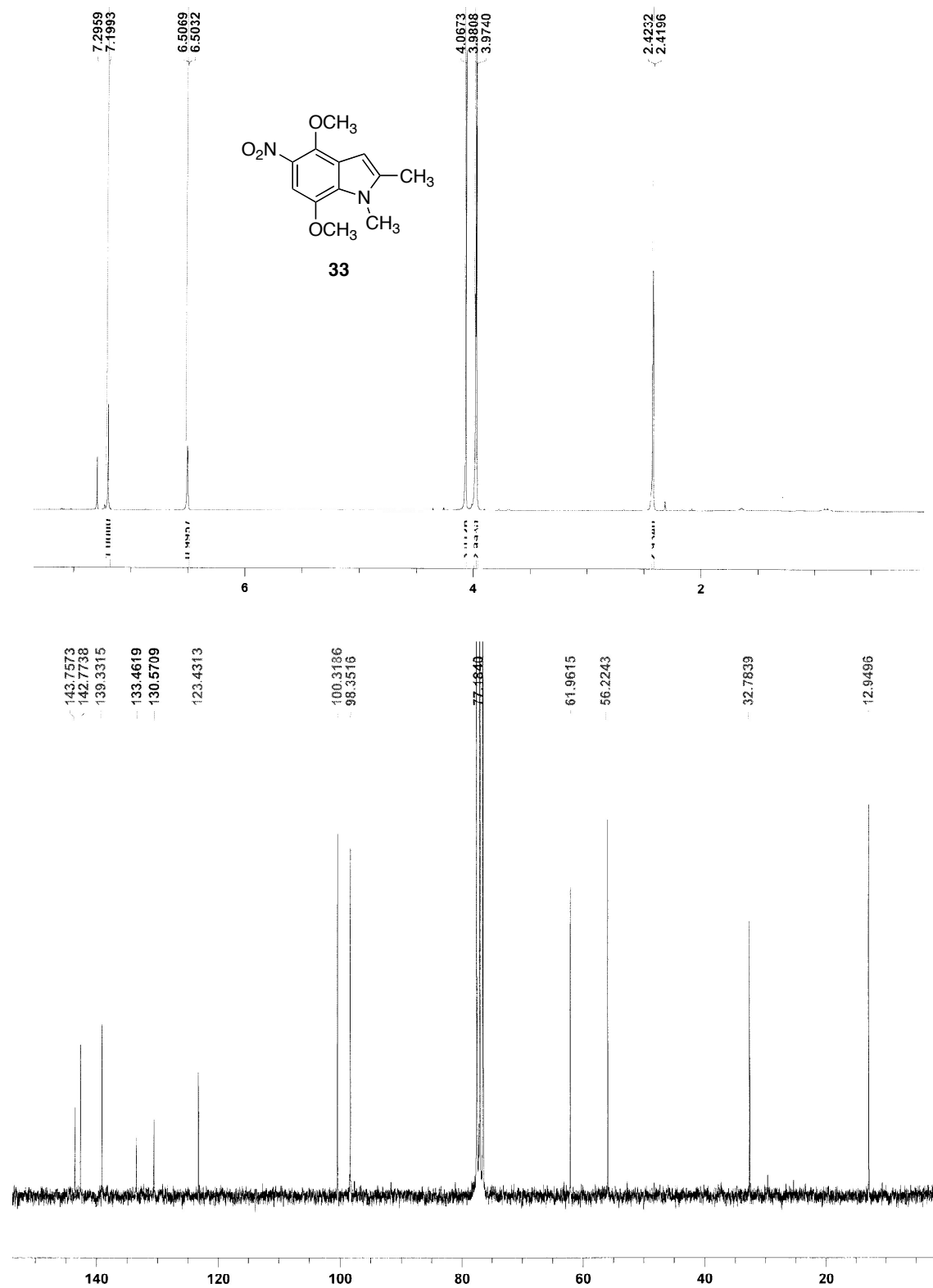


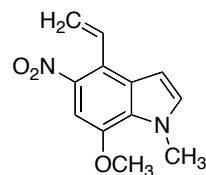
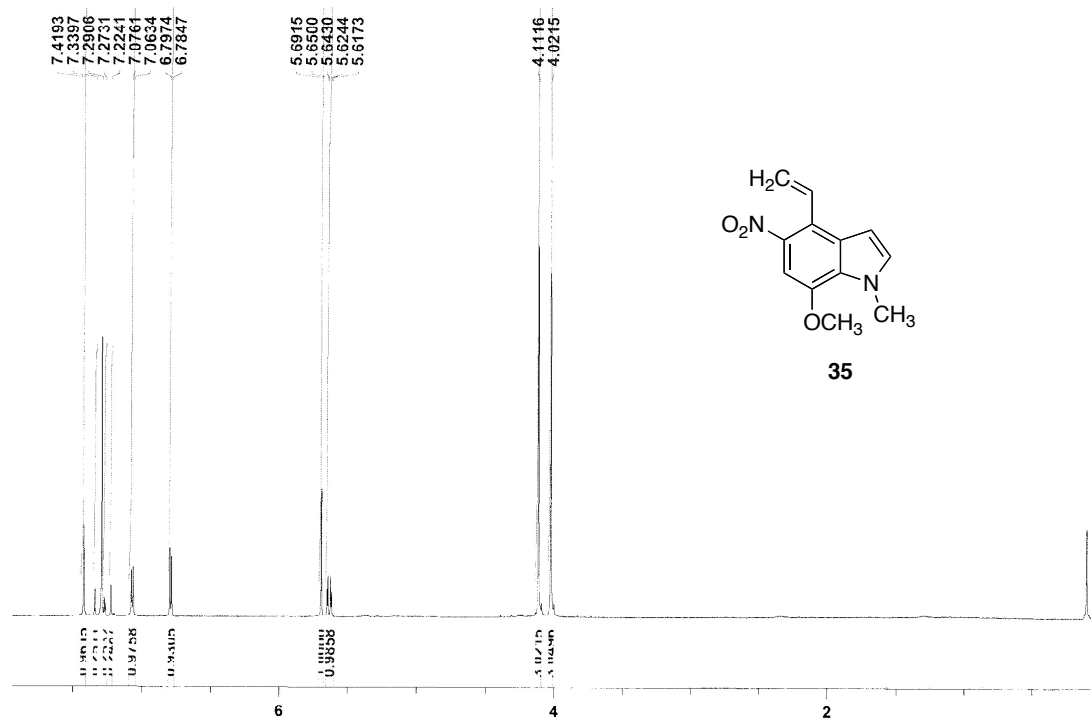












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