Estudios sintéticos sobre la reacción de Povarov, nuevos sustratos y aplicaciones

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A mis padres

Memoria presentada por Esther Vicente García para optar al grado de doctor por la Universidad de Barcelona.

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…Si no hubiera nunca invierno,

no nos daríamos cuenta de la primavera…

Heráclito (535 – 484 a.C.)

Índice

1. Introducción y Objetivos

1. Introducción.

La síntesis orgánica es uno de los campos más importantes dentro del área de la química orgánica. Entre sus funciones destaca la mejora de las metodologías orientadas a la preparación de compuestos orgánicos y la búsqueda de nuevas estructuras útiles para la sociedad. Estos objetivos se pueden afrontar mediante tres estrategias diferentes: *Target-Oriented Synthesis*, para preparar estructuras complejas; *Combinatorial Chemistry*, centrada en la creación de librerías de compuestos que comparten un fragmento estructural común; y *Diversity-Oriented Synthesis*, cuyo objetivo es conseguir un grupo de productos de diversidad elevada (Figura 1).

- *Target-Oriented Synthesis* es la aproximación sintética más antigua, se centra en la síntesis de una molécula diana, esta estrategia se utiliza para la síntesis de productos naturales y de fármacos. Normalmente implica realizar el análisis retrosintético de la molécula objetivo, una vez identificados los fragmentos clave del compuesto; se encadena una secuencia multi-etapa preparativa a partir de reactivos accesibles (a, Figura 1).[1]

- *Combinatorial Chemistry* (b): Consiste en la producción en paralelo de un gran número de compuestos de manera rápida, utilizando la misma aproximación sintética y una gran variedad de sustratos. Esto permite aumentar la diversidad de forma considerable respecto a la aproximación anterior, ya que pasamos de obtener un solo producto a obtener una librería de compuestos con un núcleo estructural común (*scaffold*). En este caso, la diversidad se introduce a partir de las funcionalizaciones de los reactivos de partida o de la diferente reactividad que estos pueden mostrar frente a las mismas condiciones de reacción.[2, 3]

- *Diversity-Oriented Synthesis* (c, Figura 1): Tiene como objetivo la síntesis de una librería de moléculas pequeñas con un alto grado de complejidad estructural y funcional. Permitiendo abarcar una parte relevante del espacio químico involucrado, gracias a la diversidad de la metodología.[2, 4] Esta aproximación se centra en la distinta funcionalización de los precursores comunes, mediante diferentes reacciones para dar lugar a una colección de compuestos.

En los últimos años, los avances en el campo de la síntesis han sido muy notables, permitiendo la preparación de moléculas con alto grado de complejidad, colecciones de millones de compuestos estructuralmente relacionados, así como la obtención de estructuras diversas a partir de productos comunes; A pesar de todos los esfuerzos aún existen limitaciones conceptuales y prácticas muy importantes, siendo necesaria una investigación básica y aplicada para conseguir la preparación de compuestos químicos, especialmente fármacos, de una manera rápida, sencilla, eficaz y barata.

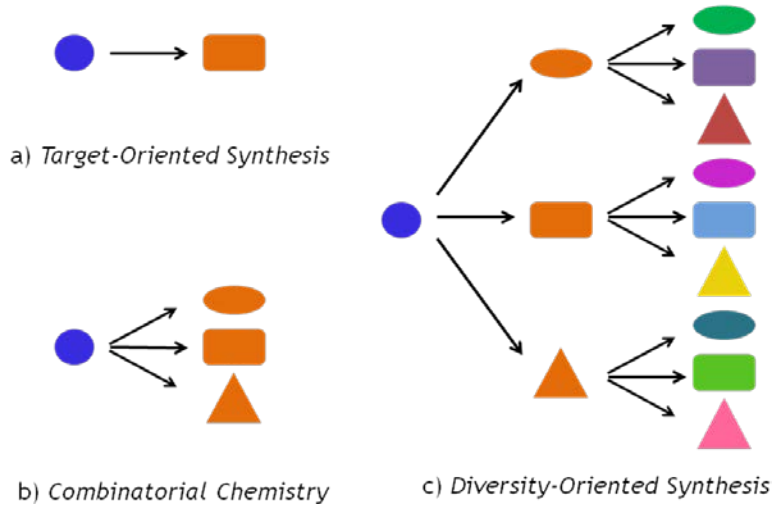


Figura 1. Tipos de aproximaciones sintéticas.

1.1. Reacciones multicomponente.

En el contexto anterior, cabe destacar la importancia de las reacciones multicomponente (RMCs), una metodología especialmente relevante al permitir acceder a una gran versatilidad estructural mediante procesos experimentales muy sencillos. Resultan por tanto, procedimientos ideales para la exploración de nuevos compuestos de utilidad en áreas como la química médica, la agricultura y la ciencia de los materiales.[5]

1.1.1. Definición y características.

Las reacciones multicomponente se definen como, procesos en los que participan 3 o más reactivos que reaccionan en una sola operación para formar un único compuesto, que contiene esencialmente todos los átomos presentes en los precursores (a excepción de los productos de condensación tales como, H_2O, HCl, MeOH, etc.) (Figura 2).[5, 6]

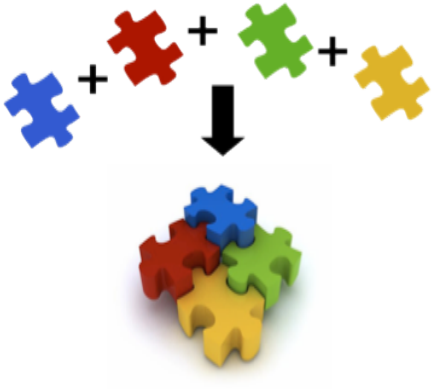


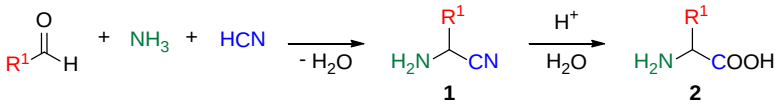
Figura 2. Definición de reacción multicomponente.

Las RMCs se caracterizan por tener propiedades que se ajustan a la definición de síntesis ideal.[7] La principal característica de este tipo de reacciones es su gran poder exploratorio, este concepto hace referencia a reacciones que permiten la obtención de compuestos de alta complejidad a partir de compuestos simples. Pero, a la vez deben ser procesos versátiles que permitan (mediante el cambio de un fragmento de alguno de los reactivos, la variación de éstos o el uso de diferentes condiciones de reacción), la obtención de diferentes tipos estructurales. Existen otras características que definen las RMCs, como su selectividad. Uno de los objetivos de las RMCs es obtener diversidad estructural pero, a la hora de realizar este tipo de reacciones se espera la obtención de un único producto final. Por otro lado, son procesos que mantienen muy elevado el balance de átomos (economía de átomos), esto significa que la pérdida de materia durante la transformación es mínima. Por último, cabe destacar que se trata de procesos altamente convergentes, ayudando a incrementar el rendimiento del proceso sintético, con reducción del número de pasos sintéticos y de este modo las manipulaciones, particularmente los procesos de purificación (Figura 3).[7, 8]

Figura 3. Características de las RMCs.

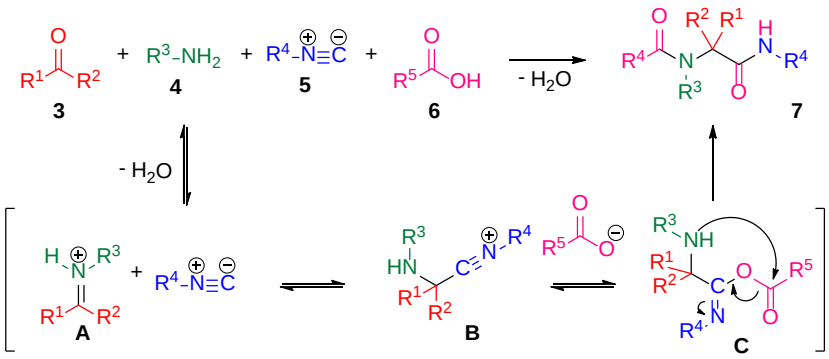
1.1.2. Ejemplos.

A lo largo de la historia se han descrito un gran número de reacciones multicomponente, un ejemplo significativo de este tipo de procesos es la reacción de Strecker, que se considera la primera RCM descrita en la literatura (1850). En este proceso, una molécula de amoniaco, una de aldehído y otra de ácido cianhídrico se combinan formando las α-cianoaminas (**1**), las cuales después de una hidrólisis se convierten en α-aminoácidos (**2**, Esquema 1). [9, 10]



Esquema 1. Reacción de Strecker.

Por otro lado, una de las RMCs más ampliamente conocidas y estudiadas, es la reacción de Ugi (1959), ya que permite la obtención de un conjunto diverso de productos a partir de una extraordinaria variedad de compuestos. En este proceso intervienen 4 componentes: un aldehído o cetona (**3**, Esquema 2), un ácido carboxílico (**6**), una amina (**4**) y un isonitrilo (**5**), para dar lugar a una α-acilamidoamida (**7**). El mecanismo propuesto implica la formación de un intermedio nitrilio **B**, el cual se obtiene a partir de la interacción entre el isonitrilo **5** y el ión iminio (**A**) generado *in situ*. El intermedio **B** es atrapado por el carboxilato, originario de **6** para generar el α-aducto inestable (**C**), que seguidamente sufre una acilación intramolecular denominada transposición de Mumm, dando lugar al producto final **7**. [5, 11]



Esquema 2. Reacción de Ugi.

1.1.3. Estrategias para el desarrollo de nuevas RMCs.

Los aductos obtenidos en reacciones multicomponente son sometidos a reacciones de post-condensación, con el objetivo de aumentar la diversidad estructural. Así, esta metodología auxiliar ha conseguido en los últimos años aumentar la diversidad y complejidad de los productos obtenidos a partir de RMCs. No obstante recientemente han aparecido nuevas estrategias para el desarrollo de nuevas RMCs, con el objetivo de aumentar la variedad estructural sin recurrir a reacciones de post-condensación (Figura 4):[6, 10, 12]

a) Substitución de un reactivo *(Single reactant replacement*, SRR).
b) Secuencias modulares de reacción (*Modular reaction sequences*, MRS).
c) Variación de las condiciones de reacción (*Conditions-based divergence*, CBD).
d) Combinación de RMCs (*Combination of MCRs*, MCR^2).

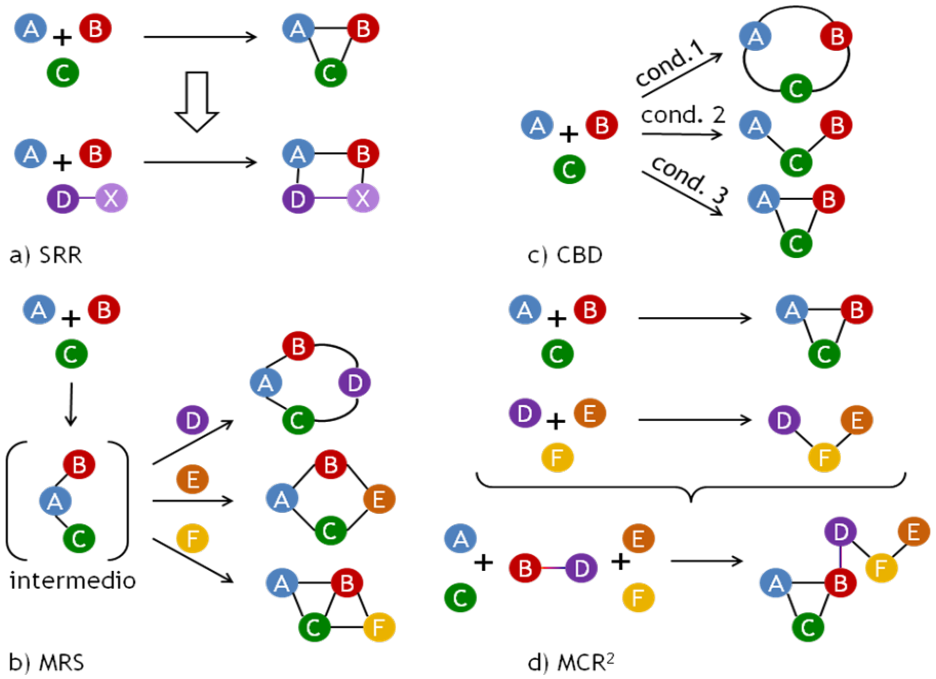


Figura 4. Estrategias para el desarrollo de nuevas RMCs.

El primer método (**SRR**) se basa en el conocimiento de una RMC, su mecanismo y el papel que juega cada uno de los precursores. Así, esta estrategia se centra en remplazar uno de los reactivos (**C**) por otro diferente (**D-X**), el cual reacciona de manera análoga al remplazado, pero permite la obtención de un producto con una estructura diferente a la original (a, Figura 4).

El **MRS** (b) está directamente relacionado con el **SRR**, ya que ahora, a través de una primera RMC se forma un intermedio lo bastante estable como para ser tratado con diferentes tipos de reactivos y de ese modo obtener una diferenciación en la estructura dependiendo del reactivo añadido, aumentando así la variabilidad de la reacción.

La siguiente estrategia, **CBD** (c), se centra en la variación de las condiciones de reacción pero manteniendo constantes los reactivos. Las modificaciones pueden implicar, catalizador, disolvente o aditivos; pudiendo variar el curso de la reacción y de ese modo obtener diferentes tipos de productos. Esta aproximación, tiene sus propias limitaciones, ya que, en muchas ocasiones, el efecto de sus cambios no es obvio. Por ello no se encuentran un gran número de ejemplos sobre este tipo de método.

Por último, la **MCR²** se centra en la unión de dos ó más RMCs. Para ello es necesario que los grupos que se encuentran en los reactivos desde el inicio o se forman durante el proceso, no interfieran en el trascurso de la reacción principal. La variación de las RMCs secundarias permite la obtención de una gran variabilidad de estructuras (d, Figura 4).

Además de estas técnicas para encontrar nuevas RMCs, existen otras maneras de encontrar nuevas reacciones ya sean multicomponentes o no.

El descubrimiento de nuevas reacciones es un campo en el cual la mayoría de hallazgos relevantes tienen lugar por accidente (*serendipity*), como es el caso de la

reducción de Birch, la reacción de Wittig o la hidroboración de Brown, las cuales se hallaron basándose en hipótesis de reactividad erróneas.[13]

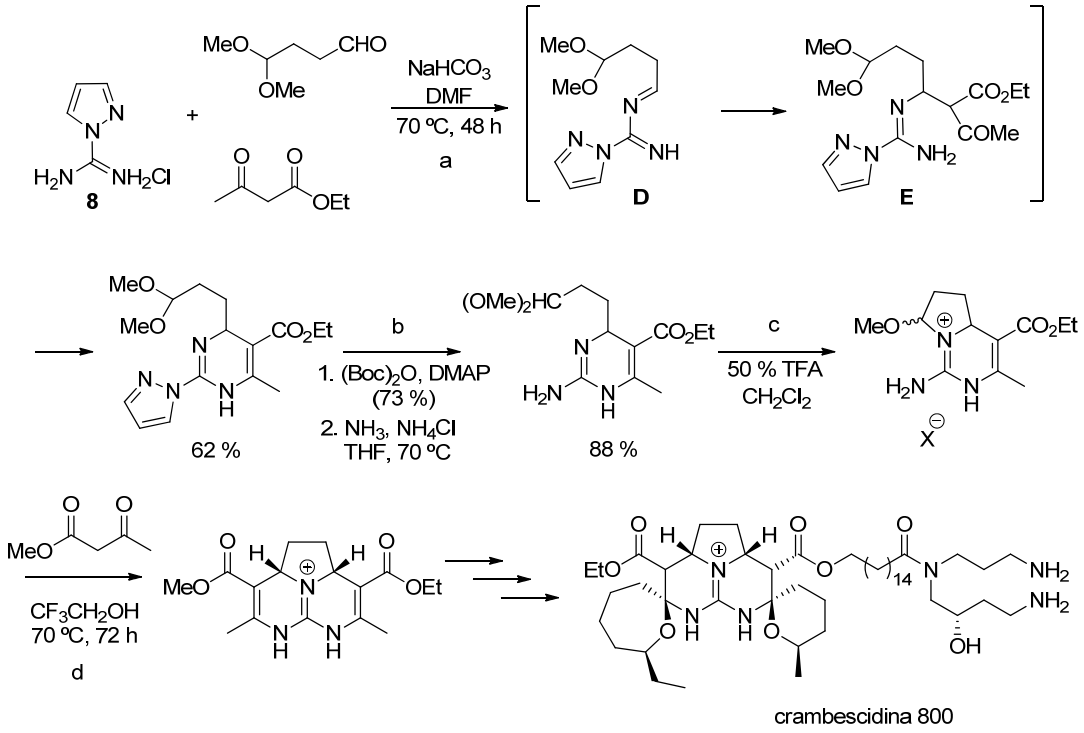
De este modo, se han desarrollado métodos donde la casualidad puede ser inducida y así encontrar nuevas reacciones. Uno de ellos se basa en el anclaje de los reactantes a cadenas de DNA y la posterior hibridación de estas, facilitando la reacción por proximidad de los reactivos. Este método es productivo ya que permite una gran diversificación y una rápida detección de los positivos.[14] Otros métodos se basan en el estudio de diferentes catalizadores disponibles y económicamente viables. De este modo con una combinación de reactivos y variando los catalizadores se puede llegar a descubrir nuevas reacciones.[15] Por último, otro método para encontrar nuevas reacciones se centra en la diversificación a partir de un producto natural de fácil acceso. Este método se basa en la síntesis de librerías de compuestos a partir de una estructura de la cual se conoce su actividad.[16]

1.1.4. Aplicaciones.

1.1.4.1. Síntesis de productos naturales.

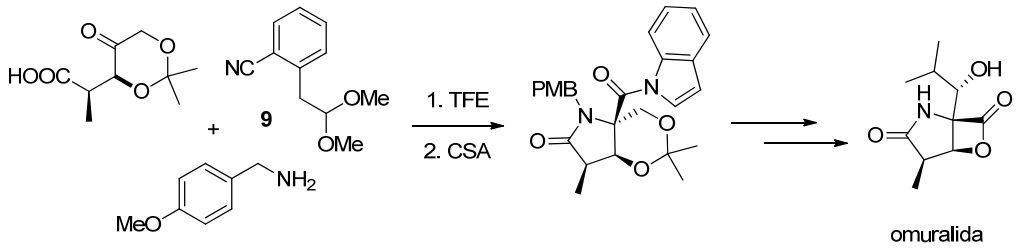
Existe una gran variedad de ejemplos donde las RMCs intervienen como paso clave en síntesis de productos naturales. Esto, además de solucionar un problema sintético, acorta la síntesis y aumenta los rendimientos del proceso global. A continuación se muestran dos casos concretos.

En el primero de ellos, se emplea la reacción de Biginelli (a y d, Esquema 3) para obtener dihidropirimidinonas polisubstituidas, con el objetivo de conseguir la estructura central de la crambescidina 800, [17, 18] citoprotector frente al estrés oxidativo.[19]



Esquema 3. RMCs en la síntesis del producto natural crambescidina 800.

El producto natural omuralida, inhibidor de proteasas, se obtiene a partir de una síntesis corta donde el paso clave de la ruta es una reacción de Ugi[11] para conseguir el intermedio clave de manera esteroselectiva. La reacción multicomponente tiene lugar entre un ácido oxocarboxílico, clave en la síntesis, el isonitrilo **9** y la *p*-metoxibencilamina (Esquema 4).[19]



Esquema 4. RMC en la síntesis de omuralida.

1.1.4.2. Síntesis de productos bioactivos.

Los heterociclos son estructuras que se pueden encontrar en gran variedad de productos con una destacada actividad biológica. Una manera rápida y sencilla de obtener heterociclos son las RMCs, existiendo gran variedad de ejemplos de fármacos sintetizados a partir de este tipo de reacciones.

Un ejemplo es la familia de azaindoles sintetizada a partir de la reacción de Bienaymé-Blackburn-Groebke.[20] Estos compuestos presentan actividad inhibitoria frente a la glutamina sintetasa de *Mycobacterium tuberculosis* (*Mt*GS), enzima que

juega un papel importante en la biosíntensis de las micobacterias y en el metabolismo del nitrógeno.

Se han encontrado compuestos, como el azaindol **10** que muestran una potente actividad inhibitoria del enzima, comparado con los inhibidores más potentes conocidos, MSO y PPT (Figura 5).

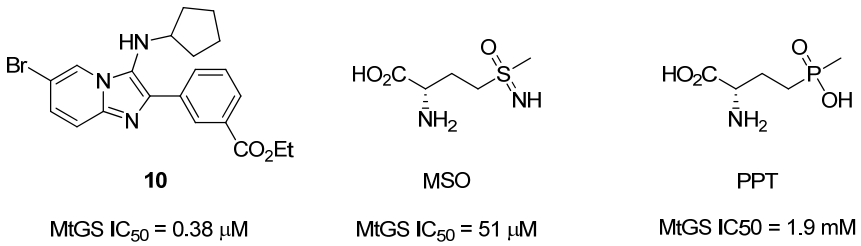
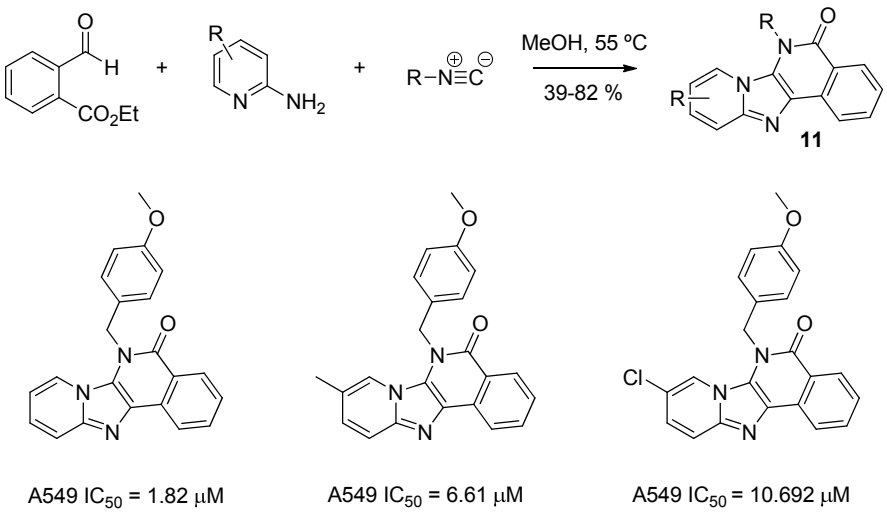


Figura 5. Inhibidores de M*t*GS.

Tomando como patrón el compuesto **10**, se diseñó una estructura a partir de una variación de la reacción de Bienaymé-Blackburn-Groebke entre el ácido *o*-formilbenzoico, 2-aminopiridinas e isonitrilos para obtener las isoquinolinas fusionadas **11** (Esquema 5). Se evaluó la actividad de la quimioteca sintetizada en la línea celular de cáncer de pulmón, y se observó que tres de los compuestos mostraban una actividad interesante. Por otra parte, todos los productos activos presentaban un grupo 4-metoxibencilo en la estructura, lo que podría ser clave para su actividad (Esquema 5).[10] Este ejemplo muestra la idoneidad de las RMC para una rápida evolución de los estudios SAR (estudios de relación estructura-actividad).



Esquema 5. Derivados antitumorales del compuesto **10**.

1.1.4.3. Ciencia de materiales.

La aplicación más importante de las RMCs es la generación de librerías de compuestos con un alto potencial farmacológico. Pero también es posible aprovechar las ventajas de esta metodología para otros campos, como por ejemplo

la ciencia de materiales. En estos últimos años se han estudiado sistemas electrónicos π-extendidos, como los presentes en cromóforos, fluoróforos y electróforos, y el uso de las RMCs para la síntesis de este tipo de compuestos.[10] Para ello se ha desarrollado una metodología *one-pot* que tiene lugar en dos pasos; primero una reacción de Sonogashira, seguida por el ataque nucleófilo al aceptor de Michael generado (Figura 6).[21]

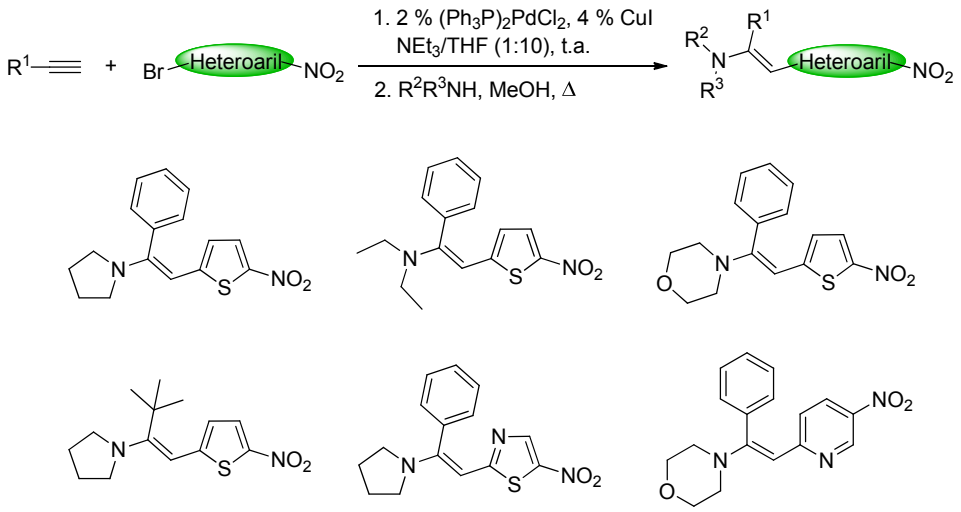
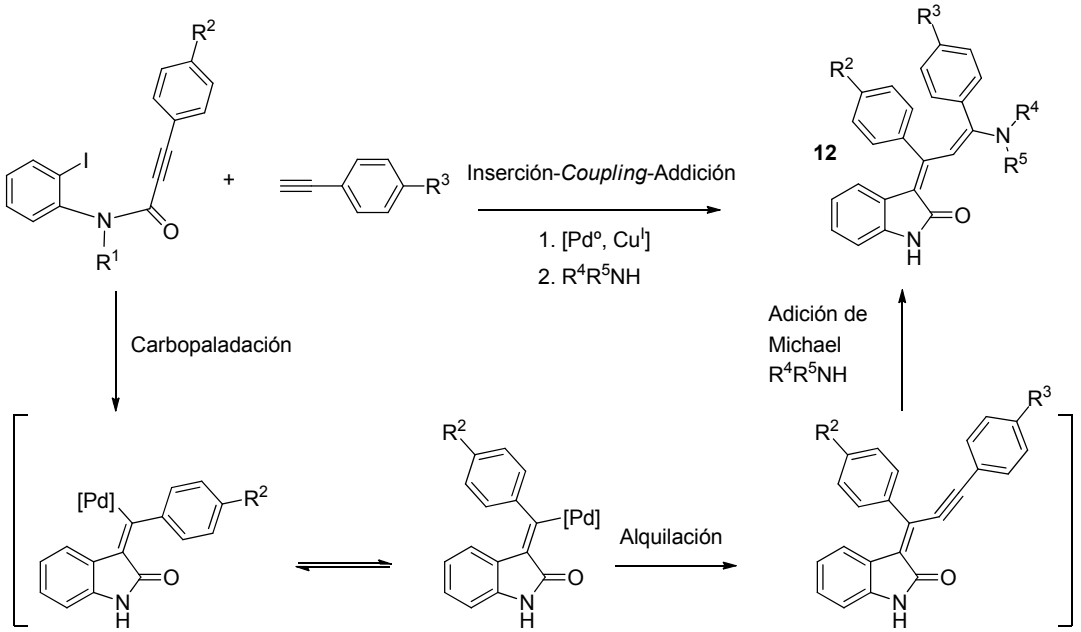


Figura 6. Secuencia Sonogashira-adición de Michael para obtener ß-amino vinil heteroarenos.

Este tipo de estructuras se definen como cromóforos donador-aceptor, y de ellas se han determinado sus propiedades ópticas no lineales y térmicas. Algunos de estos compuestos se han estudiando por calorimetría diferencial de barrido (CDB), dejando ver que este tipo de estructuras poseen una T_g (temperatura de transición vítrea) relativamente baja. Esta propiedad es característica de los compuestos que forman los materiales foto-refractivos (Figura 6). Aplicando la metodología anterior, tras la secuencia de carbopaladación, reacción de Sogashira y por último la adición de Michael con una amina secundaria, se desarrolla una reacción de tres componentes que da lugar a los compuestos **12** (Esquema 6) los cuales presenta características fluorescentes interesantes. [21]



Esquema 6. Secuencia sintética para obtener **12**.

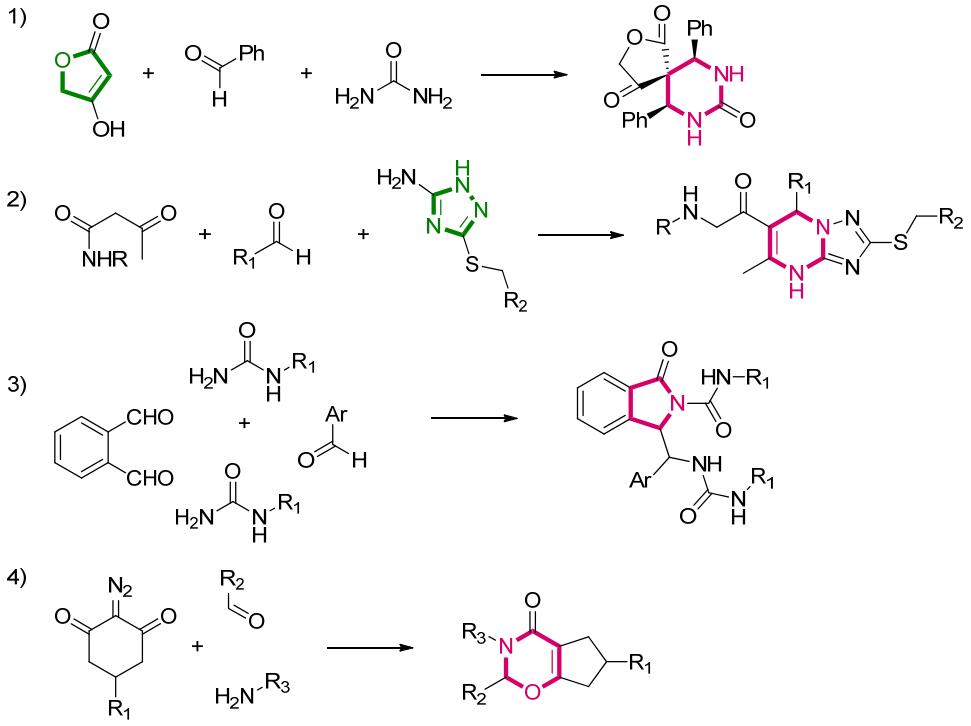
1.2. Heterociclos en procesos multicompoente.

Como ya se ha comentado con anterioridad, los heterociclos son un tipo de estructuras que se encuentran frecuentemente en productos naturales y fármacos, por ello es crucial desarrollar maneras rápidas y eficientes para su síntesis.

En este contexto, las RMCs son de gran utilidad, ya que, en ellas se pueden encontrar estructuras heterocíclicas tanto como reactivos, que como productos. Los heterociclos son de gran ayuda a la hora de diversificar los productos que se obtienen a partir de procesos multicomponente, debido a su reactividad característica. Ésta permite llegar a compuestos con novedosos patrones de conectividad y de esta manera alcanzar compuestos con niveles de complejidad difíciles de obtener por otras metodologías.

El uso de los heterociclos como reactivos de RMCs, hace que los productos obtenidos en este tipo de procesos sean de gran valor estructural.

De este modo, se han desarrollado numerosas librerías de compuestos con gran potencial. Empleando heterociclos como principales reactivos se han obtenido nuevos tipos estructurales con heterociclos de 5, 6 y 7 átomos y con uno o más anillos (1-2, Esquema 7).[22] Adicionalmente, se han desarrollado numerosas RMCs donde el aducto final es de naturaleza heterocíclica y, éste se forma a partir de precursores alicíclicos (3-4, Esquema 7)



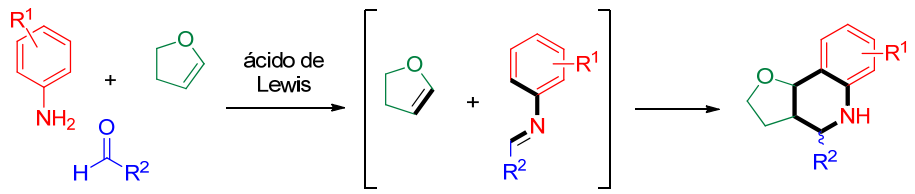
Esquema 7. Rol de los heterociclos en las RMCs.

1.3. Reacción de Povarov.

La reacción de Povarov, es una reacción multicomponente descubierta en la década de los sesenta. Teniendo en cuenta el éxito de este tipo de procesos, el interés sobre esta transformación ha ido en aumento desde su hallazgo.[23]

1.3.1. Definición.

La reacción de Povarov es una reacción multicomponente que tiene lugar entre una anilina, un componente carbonílico (normalmente un aldehído) y una olefina activada, en presencia de un catalizador (ácido de Lewis), dando lugar a tetrahidroquinolinas (THQs) con patrones de substitución interesantes, y esteroquímicas relativas (*cis* y *trans*), ya que el proceso no presenta una elevada estereoselectividad (Esquema 8).[23]



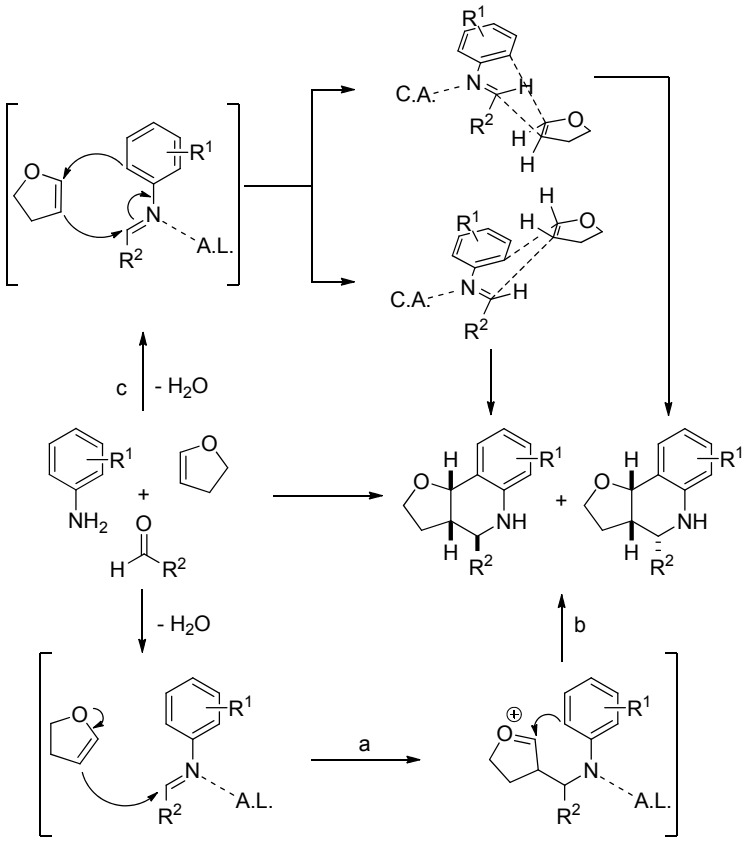
Esquema 8. Reacción de Povarov.

1.3.2. Mecanismo.

En los últimos años el estudio del mecanismo de la reacción de Povarov ha sido un tema de actualidad dentro del campo de las reacciones multicomponente. Pese al esfuerzo realizado, continúa siendo objeto de investigación activa ya que tanto los estudios computacionales como los resultados experimentales parecen apoyar dos hipótesis diferentes.

La primera, defiende que la reacción de Povarov sigue un mecanismo concertado, siendo la olefina activada el dienófilo y la imina, preformada en la reacción, el dieno (Esquema 9). Esta hipótesis, se encuentra apoyada por diversos autores como Batey, R. A. y Jacobsen, E. N.[24] Este último, realizó estudios sobre el efecto isotópico del proceso y de este modo concluye que el mecanismo es concertado. Así, se comprobó que el paso **b** (Esquema 9) es el limitante de la velocidad de la reacción, mientras que los pasos **a** y **c** son mucho más rápidos. El hecho que el paso de la rehibridación (paso **b**) sea el limitante está de acuerdo con que el proceso sea una cicloadición [4+2] asíncrona de tipo imino Diels-Alder (Esquema 9).

La segunda hipótesis plantea la posibilidad que la reacción funciona por pasos cuando el proceso tiene lugar con olefinas activadas con carácter polar. Esta hipótesis se explica con detalle en los últimos trabajos de Zhu y de nuestro grupo de investigación.[25] En estos trabajos se plantea la posibilidad que la reacción funcione a través de un mecanismo por pasos cuando el proceso tiene lugar con olefinas activadas con carácter polar. A partir de aquí se sugiere la idea que cuanto más polar sea la olefina, mas asincrónico será el hipotético proceso concertado. Esto se traduce en que el proceso, en casos extremos, pasa a tener un mecanismo por pasos. En este modelo, primero tiene lugar una reacción tipo Mannich entre la olefina activada y la imina preformada (paso a, Esquema 9), dando lugar a un intermedio catiónico que sufre una ciclación intramolecular de tipo Friedel-Crafts y re-aromatización final (Paso b, Esquema 9). Así, los estudios experimentales y cálculos computacionales realizados hasta la fecha indican que el mecanismo por el cual transcurre el proceso depende de los reactivos, disolvente y catalizador seleccionados, pudiendo ser diferente en cada caso.[24, 25, 26]



Esquema 9. Hipótesis mecanísticas sobre la reacción de Povarov.

1.3.3. Características estereoquímicas de la reacción.

Una de las características más importantes de la reacción de Povarov es su baja estereoselectividad, hecho que contrasta con procesos aparentemente relacionados que se hallan perfectamente estereocontrolados. En la reacción se obtienen cuatro diasteroisomeros. Esto es debido a que en la condensación entre la imina y la olefina se forman tres centros esteregénicos en un solo paso (Figura 7). Aunque los correspondientes a la fusión de ciclos siempre originan estereoquímicas relativas de tipo *cis*.

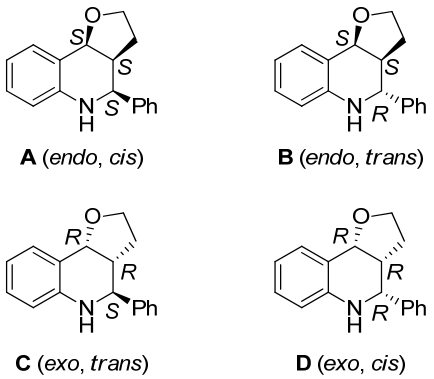


Figura 7. Posibles aductos de la reacción de Povarov.

Por esta razón la búsqueda de catalizadores y condiciones que ayuden a conseguir la reacción de Povarov de forma diastereo- o enantioselectiva ha sido un tema de creciente interés estos últimos años.

Inicialmente, Kobayashi *et. al.* consiguieron el aducto Povarov de manera enantiopura utilizando *o*-hidroxialdiminas como iminas (a, Figura 8). Para conseguirlo, fue necesario el catalizador $Yb(OTf)_3$, (R)-(+)-BINOL, DBU y un derivado de piridina como aditivo. Además del catalizador es necesario un grupo hidroxilo en la anilina, esencial para la estereoselectividad.[27]

Más recientemente Zhu[28] y Jacobsen[24a] han desarrollado una metodología para obtener el producto de la reacción de Povarov de manera enantioselectiva. En el primer caso, la reacción muestra un exceso enantiomérico elevado (92-99% *ee*) cuando la olefina esta activada por un nitrógeno. Éste, se coordina con el catalizador bloqueando una determinada orientación para dar lugar a un solo enantiómero. Por el contrario, en el caso de Jacobsen, el catalizador se coordina con el nitrógeno (b, Figura 8) y el hidrógeno de la imina, bloqueando el acceso a una cara del intermedio, orientando así el ataque sin necesidad de ningún grupo auxiliar (c).

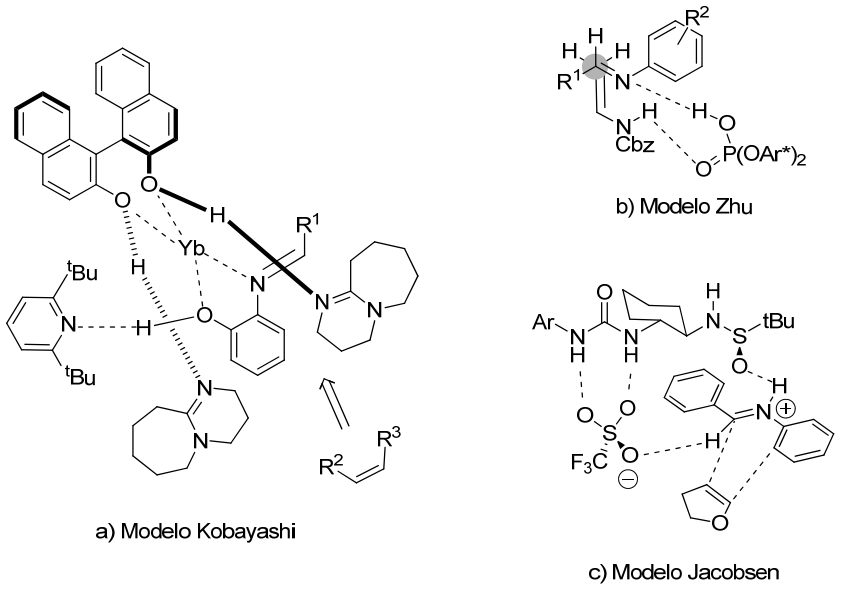


Figura 8. Modelos propuestos para los diferentes catalizadores.

1.3.4. Olefinas activadas.

Las olefinas activadas son el componente más destacado en la reacción de Povarov, ya que permiten aumentar la diversidad estructural del producto final de manera relevante. Por este motivo, gran parte de los estudios realizados sobre la reacción se centran en encontrar nuevos compuestos capaces de actuar en este papel (Figura 9).

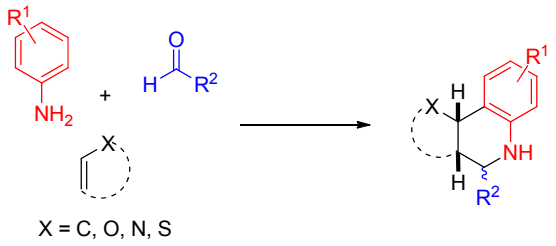
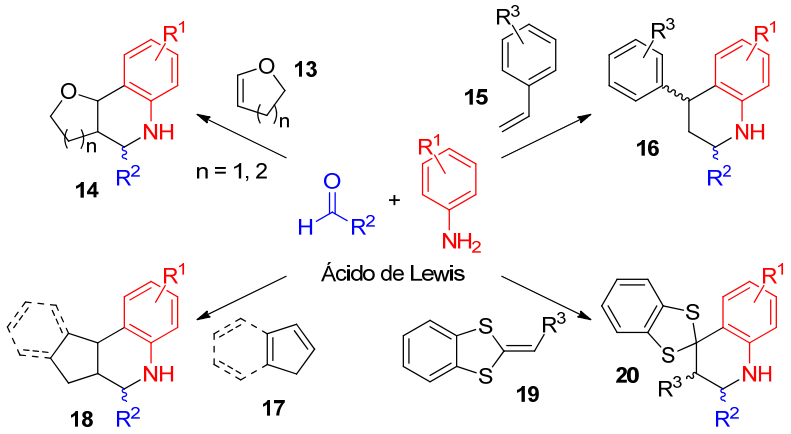


Figura 9. Variabilidad de la olefina activada en procesos Povarov

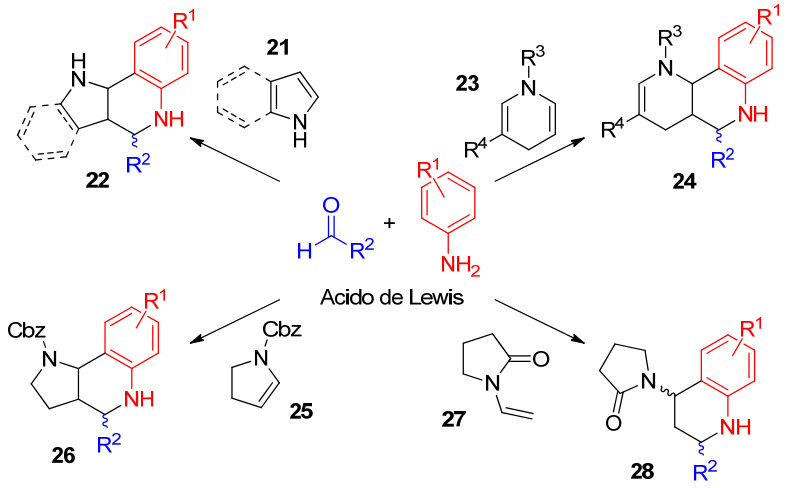
Después de las observaciones realizadas por Povarov en el descubrimiento de la reacción,[23] se han publicado gran cantidad de trabajos centrados en el estudio de diferentes compuestos reactivos como olefina activada. Estos se pueden clasificar atendiendo al átomo o fragmento que activa el doble enlace. Los primeros trabajos publicados describen la reacción con éteres de enol (**13**, Esquema 10) para obtener las tetrahidoquinolinas fusionadas **14**. En este caso el doble enlace es activado por el oxígeno.[23, 29, 30] Se encuentran casos en los que el encargado de activar el doble enlace es otro doble enlace, éste puede ser en forma de anillo aromático o un doble enlace simple, como es el caso del estireno, indeno y el ciclopentadieno (**15** y **17**, Esquema 10).[31, 32, 33] De igual modo, se pueden encontrar olefinas activadas por azufre (**19**).



Esquema 10. Olefinas activadas por O, C y S en la reacción de Povarov

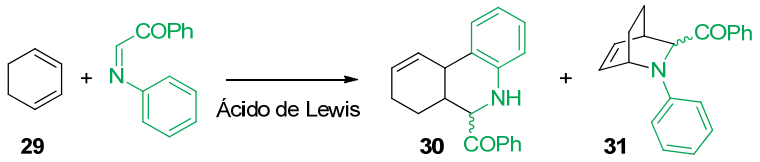
Las olefinas activadas por nitrógeno resultan muy atractivas, ya que las THQs obtenidas a partir de su participación en la reacción de Povarov son interesantes desde el punto de vista de la química médica. Así, en este papel se pueden encontrar estructuras tipo indol y pirrol (**21**, Esquema 11). En el caso del indol, el aducto multicomponente se halla expandido con un ciclo adicional lo cual permite obtener un compuesto final tetracíclico.[32, 33] Por otro lado, dentro del grupo de investigación se estudió la reactividad de las dihidropiridinas (**23**, DHPs) en la reacción de Povarov obteniendo las THQs de manera satisfactoria. En este caso las DHPs permiten la introducción de dos sustituyentes adicionales, sobre el nitrógeno y su posición β.[34, 25b] Por último, las enamidas cíclicas (**25**) y la *N*-vinil-2-pirrolidona

(**27**), que únicamente se diferencian por la posición del doble enlace (*endo*-, ó *exo*-cíclico) dan lugar a THQs de gran valor sintético.



Esquema 11. Olefinas activadas por N en la reacción de Povarov.

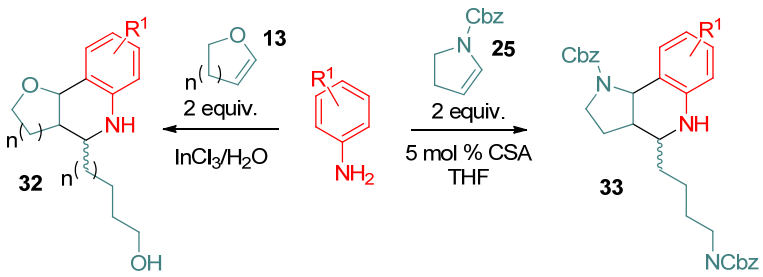
Por otro lado, el ciclohexadieno se comporta de manera diferente bajo las condiciones estándar de reacción de Povarov. Inicialmente, se describió que este compuesto no era reactivo, aún bajo catálisis de triflato de cobre o de yterbio. Más adelante se describió el aducto **30** como el producto de transposición de **31**, el cual es el producto de la reacción de imino Diels-Alder bajo catálisis ácida de $BF_3{\cdot}OEt_2$.[33]



Esquema 12. Ciclohexadieno en condiciones de reacción de Povarov.

1.3.4.1. Otros roles de la olefina activada en la reacción de Povarov.

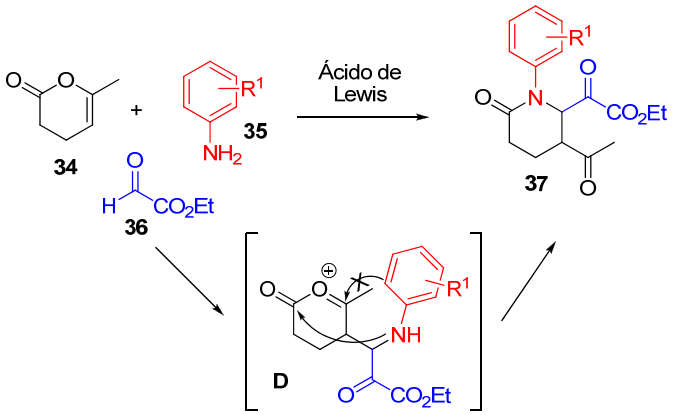
A partir de los estudios realizados con éteres de enol sobre la reacción de Povarov se descubrió que la reactividad de dicho heterociclo depende del catalizador utilizado, y en condiciones adecuadas, los éteres de enol cíclicos pueden actuar como precursores de aldehídos en el proceso multicomponente para obtener **32** (Esquema 13). En el segundo caso, las enaminas cíclicas **25** también son capaces de ejecutar las dos funciones. Esta vez el proceso facilita el acceso a la estructura central tricíclica del alcaloide martinelina. Es relevante anotar que esta aproximación permite la introducción de cadenas alquílicas como sustituyente de la THQ final.[31]



Esquema 13. Roles alternativos de los heterociclos **13** y **25** en la reacción de Povarov.

1.3.4.2. Rutas mecanísticas alternativas.

Teniendo en cuenta la actuación de los éteres de enol cíclicos en procesos de tipo Povarov,[23] nuestro grupo de investigación estudió la reactividad de los ésteres de enol cíclicos. Inicialmente, no se esperaba cambio alguno en la reactividad de estas nuevas olefinas activadas pero, sorprendentemente la reacción entre el éster de enol **34** (Esquema 4), la anilina **35** y el aldehído **36** dio lugar a aductos del tipo *N*-aril lactama (**37**, 25 %).[35] La obtención de este nuevo producto se puede razonar a partir de un mecanismo alternativo al de la reacción de Povarov. Esto se explica ya que los dos procesos comparten un intermedio común. La imina preformada es activada por el catalizador ácido, y posteriormente es atacada por el carbono en ß de la olefina activada, llegando así al intermedio catiónico **D** (Esquema 14). En este punto, la reacción de Friedel-Crafts que termina el proceso Povarov, no tiene lugar, si no que el intermedio **D** progresa vía lactamización, el nitrógeno correspondiente a la anilina ataca al carbonilo activado del intermedio, formando el nuevo heterociclo y liberando el fragmento acetilo. El producto final, **37**, se genera con un 25 % de rendimiento y en una mezcla 3:1 de esteroisómeros, predominando el *cis*.[35]

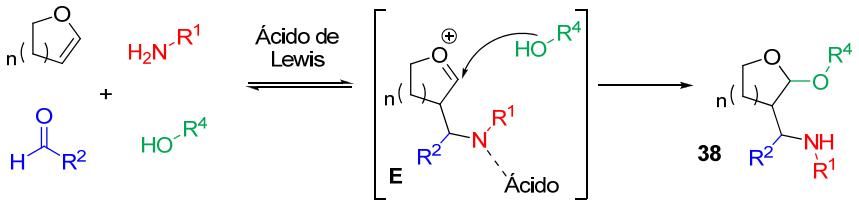


Esquema 14. Reactividad de ésteres de enol cíclicos en condiciones de Povarov.

1.3.5. Introducción de un cuarto componente en la reacción de Povarov.

A partir de las teorías que consideran la reacción de Povarov un proceso por pasos, nuestro grupo de investigación estudió la posibilidad de introducir un nucleófilo externo al proceso, con intención de capturar el posible intermedio carbocatiónico **E** (Esquema 15). Necesitando un compuesto que haga el papel de finalizador de la reacción, para este rol se seleccionaron diferentes tipos de alcoholes (MeOH, EtOH, etc), ya que son lo bastante nucleófilos como para llevar a cabo esta función sin abortar prematuramente el proceso por ataque sobre la imina.

Los experimentos se llevaron a cabo con una variedad de diferentes anilinas, aldehídos y alcoholes, manteniendo los éteres de enol como olefina activada. En todos ellos se obtuvo el producto en que el carbocatión es atrapado por el alcohol, **38** (Esquema 15).[29] Este trabajo demuestra la existencia de un intermedio catiónico en el desarrollo de la reacción de Povarov con estos componentes.



Esquema 15. Reacción de Povarov interrumpida por un nucleófilo externo.

1.3.6. Reacción de Povarov intramolecular.

En varios estudios sobre la reacción de Povarov se ha llegado a desarrollar la versión intramolecular (no multicomponente) de este proceso. Esta nueva adaptación es atractiva, ya que a partir de ella es posible obtener estructuras policíclicas de alta complejidad.

Existen diferentes tipos de reacciones de Povarov intramoleculares, pero uno de ellos es muy interesante y útil en el campo en la síntesis orgánica (Figura 10), debido a la accesibilidad sintética de sus precursores.[32]

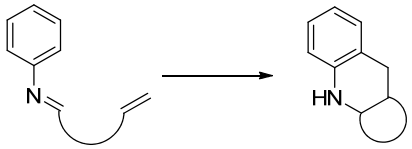
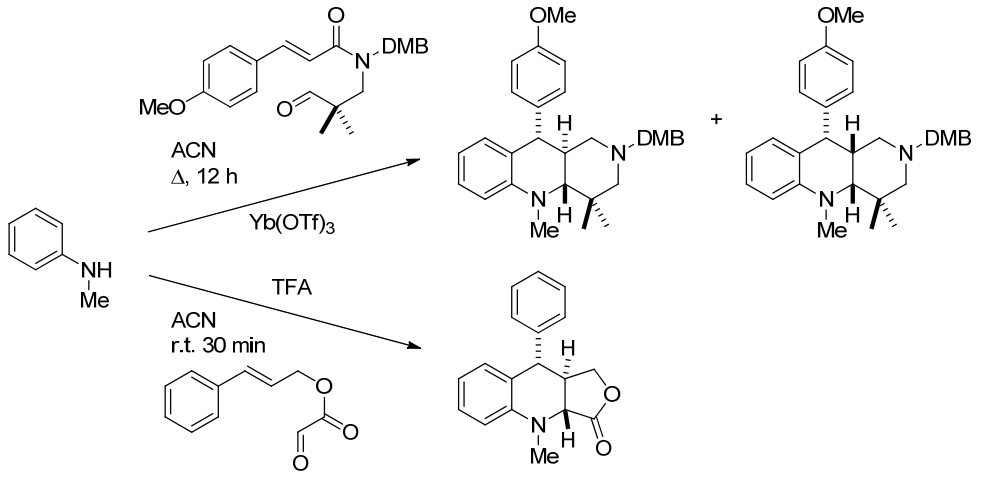


Figura 10. Reacción de Povarov intramolecular.

La reacción de Povarov intramolecular tiene dos ventajas importantes. La primera de ellas es la mejora en el control estereoquímico, mayor normalmente en procesos cíclicos, y la segunda es la formación de un sistema policíclico complejo. Sintéticamente, sólo es necesario un compuesto de tipo aldehído-olefina adecuado. En este contexto se pueden considerar dos grupos, los ω-aldehídos insaturados y los *N*-alquenil aldehídos heteroaromáticos *o*-sustituidos.

Utilizando esta variante de la reacción se ha podido generar diversidad alrededor de la estructura de tetrahidroquinolina con múltiples centros estereogénicos, eso convierte este tipo de estructuras en análogos de productos naturales tipo arilnaftaleno. Ejemplos de esta versión intramolecular de la reacción de Povarov se muestran en el esquema 16.



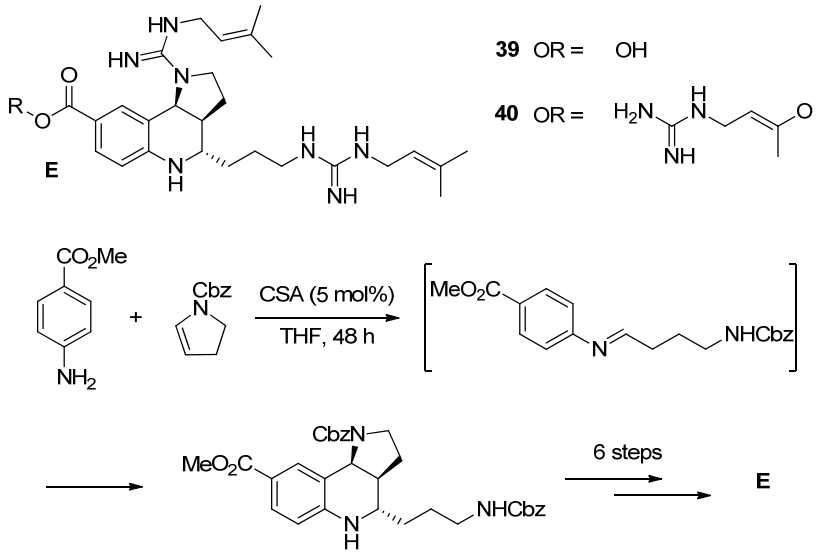
Esquema 16. Ejemplos de la reacción de Povarov intramolecular.

1.3.7. Aplicaciones.

1.3.7.1. Síntesis de productos naturales.

Las RMCs son una herramienta muy útil y popular dentro de la síntesis de productos naturales. En concreto la reacción de Povarov destaca por su aplicación en la síntesis de los alcaloides ácido martinélico (**39**) y de la martinelina (**40**, Esquema 17).

Los extractos de raíz de la *martinella iquitosensis*, una especie vegetal cuyo hábitat natural se encuentra en la selva del Amazonas, son utilizados por los indígenas de la zona para tratar varias enfermedades oculares, incluidas la inflamación y conjuntivitis.[36] Esta actividad está relacionada con la presencia en el extracto de dos alcaloides: el ácido martinélico (**39**) y la martinelina (**40**, Esquema 17), que tienen actividad antibiótica y que son capaces de unirse a la proteína G. El análisis retrosintético de este producto natural realizado por Batey y colaboradores, identifica en la estructura de hexahidropirrol[3,2-*c*]quinolina un fragmento susceptible de ser obtenido mediante la RMC de Povarov. Para que esta propuesta fuera viable, era necesario encontrar el modo en que la aproximación *endo* fuese mayoritaria frente la *exo*. Se ensayaron gran variedad de ácidos próticos y finalmente el catalizador adecuado para obtener el resultado óptimo fue ácido camforsulfónico (CSA).[36]



Esquema 17. Síntesis de los alcaloides ácido martinélico y martinelina.

1.3.7.2. Síntesis de productos bioactivos.

Los inhibidores de POP (*protease propyl oligopeptidase*) son de gran valor para el tratamiento de enfermedades celébrales como la esquizofrenia, el trastorno bipolar y la enfermedad de Alzehimer. Esto es debido a que la enzima POP es una proteasa que hidroliza péptidos pequeños que contienen prolina. Los ensayos *in vivo* sobre la inhibición de esta proteasa confirman su importancia en los procesos que tienen lugar en las enfermedades cerebrales antes mencionadas.

Existen compuestos de origen natural que son potentes inhibidores de esta peptidasa, un ejemplo de este tipo de compuestos es la berberina (a, Figura 11), que procede del extracto *rhizoma coptidis*, y ha sido utilizada en la medicina tradicional China.

Por similitud estructural con este producto natural, se sintetizaron las correspondientes sales de quinolinio de los compuestos de Povarov, producto de la interacción de una variedad de anilinas y aldehídos con éteres de enol cíclicos (b, Figura 11). Estos productos resultaron ser inhibidores moderados, pero mucho más potentes que los respectivos compuestos neutros.[37]

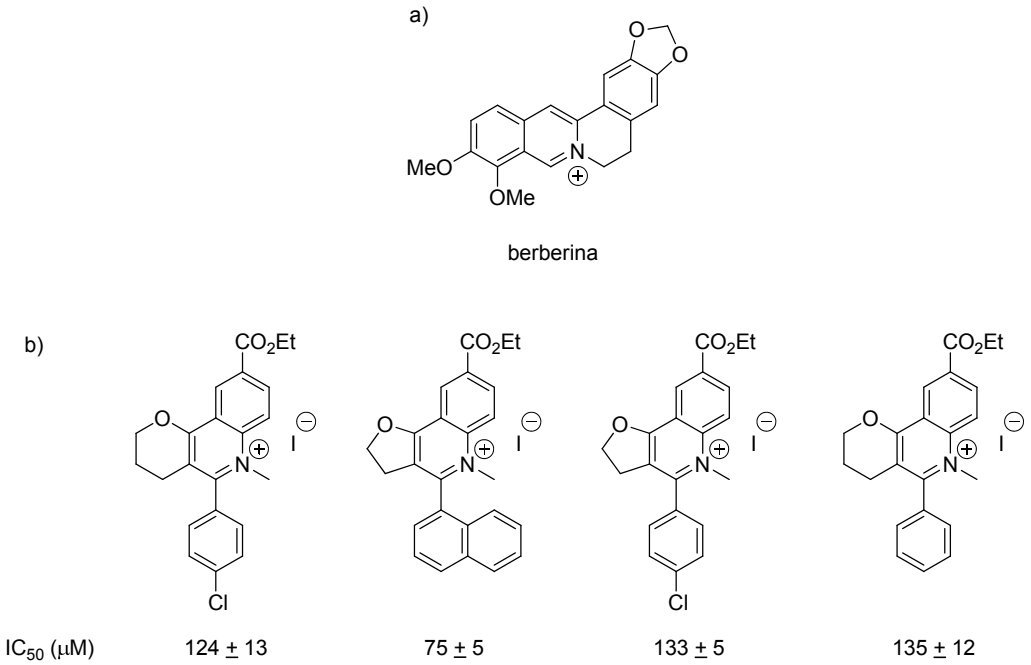


Figura 11. Berberina y productos de la RMC de Povarov inhibidores de POP.

1.4. Oxidación de los aductos Povarov.

Las reacciones de post-condensación son transformaciones que permiten diversificar los productos obtenidos a partir de una primera reacción, como puede ser una RMC, de manera que se pueden obtener nuevos compuestos que mantienen la complejidad introducida por la RMC. Esto permite llegar a compuestos de difícil acceso por una síntesis multietapa.

Existen diferentes tipos de reacciones de post-condensación que se pueden aplicar a los productos obtenidos a partir de la reacción de Povarov, pero la más importante es la reacción de oxidación (Figura 12). A partir de esta trasformación se pueden obtener quinolinas con patrones de substitución complejos. Esta transformación es de gran interés, pese a la pérdida de estereoquímica, ya que las quinolinas son compuestos que pueden encontrarse en gran número de productos naturales y de compuestos bioactivos (Figura 13).[38]

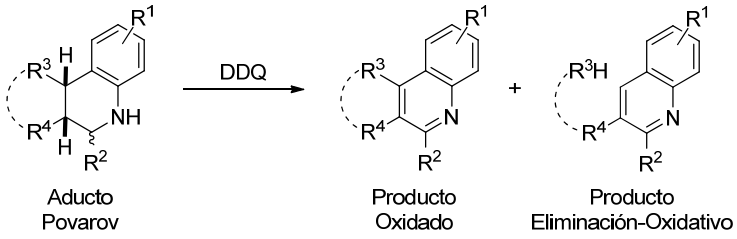


Figura 12. Oxidación de los aductos Povarov.

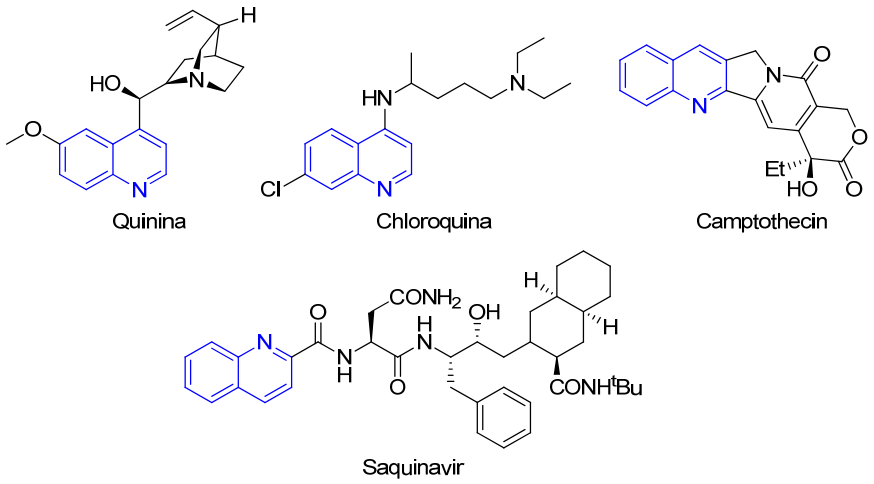


Figura 13. Estructura de quinolina en productos naturales y bioactivos.

Así, en los últimos tiempos se han desarrollado diferentes métodos para oxidar los aductos obtenidos de la reacción de Povarov. Una de las metodologías más populares es la oxidación con DDQ (dicloro-5,6-diciano-1,4-benzoquinona). Este es un procedimiento sencillo y compatible con multitud de grupos funcionales: que presentan como únicos inconvenientes, su difícil purificación y la obtención de un subproducto de eliminación oxidativa (Figura 12). El resto de procedimientos (CAN, nitrobenceno, sulfuro o paladio) presentan diferentes problemáticas, la más importante como en el caso del DDQ es la obtención del subproducto de eliminación oxidativa (Figura 12), pero existen otras como las extremas condiciones de reacción las cuales pueden producir la degradación del aducto Povarov.[30a, 39]

1.5. Enfermedad de Alzheimer y inhibidores de Acetil Colinesterasa.

1.5.1. Definición de enfermedad de Alzheimer.

La enfermedad de Alzheimer, la forma más común de demencia, es un proceso degenerativo que afecta al cerebro, especialmente a las áreas asociativas corticales y parte del sistema límbico.

Los enfermos de Alzheimer se caracterizan por padecer una pérdida neuronal y de sinapsis, y una disminución de la función cognitiva. Estos fenómenos están relacionados con dos patologías; las neurofibrillas, producidas por el plegamiento de las proteínas tau hiperfosforiladas y las placas seniles producto del apilamiento del péptido ß-amiloide (ßA) (Figura 14).[40]

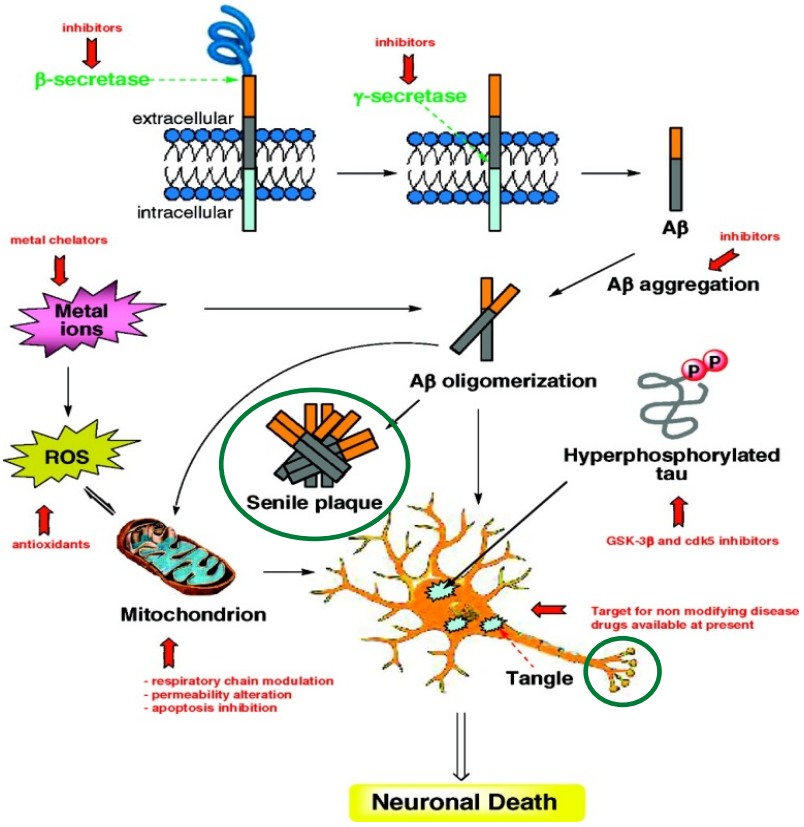


Figura 14. Causa molecular de la enfermedad de Alzheimer.[40]

1.5.2. Área de tratamiento.

Una vez descrita la etiología de la enfermedad, el desarrollo de una terapia anti-Alzheimer se centra en (a) la disminución de la síntesis de ßA y tau, (b) prevenir el plegamiento y la agregación de dichas biomoléculas ó (c) eliminar los agregados o las formas plegadas tóxicas de las proteínas.[41]

De forma complementaria, recientemente se ha desarrollado la hipótesis de la cascada amiloide, la cual da más importancia al péptido ßA como causante de la enfermedad y deja el plegamiento de tau como un efecto secundario ligado a la neurodegeneración (Figura 15).[40, 42]

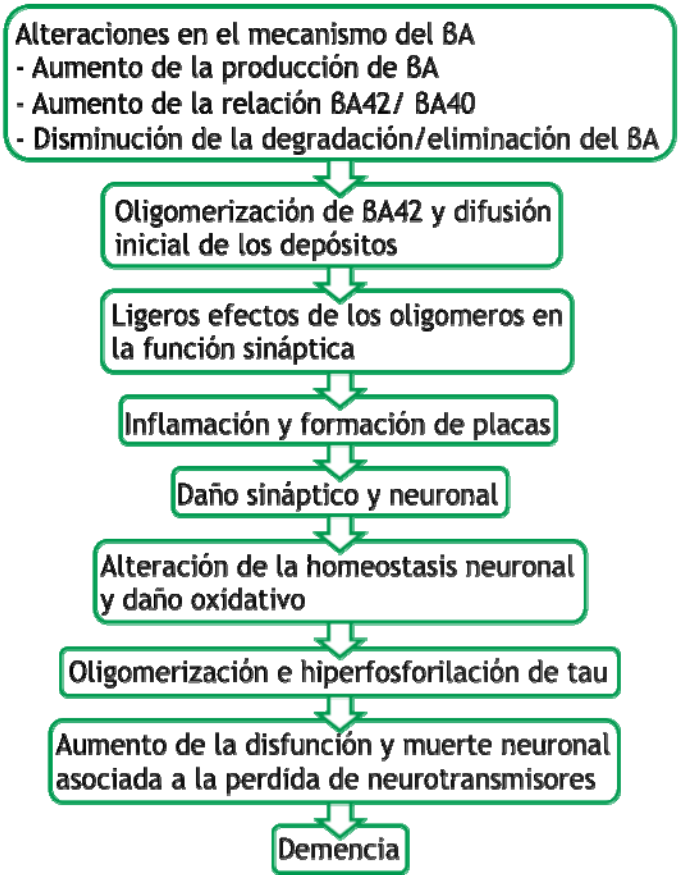


Figura 15. Hipótesis de la cascada amiloide.[43]

La hipótesis de la cascada amiloide sugiere que la acumulación y agregación de los βAs inicia una lenta, pero letal secuencia de acontecimientos que conduce a alteraciones en la sinapsis, modificaciones en la proteína tau y a una pérdida neuronal progresiva.[43]

Por otro lado, hay evidencias de que los oligómeros solubles de βA son realmente los agentes responsables de la sinapto-toxicidad, mientras que las placas seniles que forma este péptido no presentarían tantos efectos nocivos.[41, 44]

Sea una u otra la hipótesis correcta, las dos tienen como protagonista el péptido βA, y esto lo convierte en la diana principal para el tratamiento de la enfermedad. A consecuencia de esta observación, en los últimos años la investigación se ha centrado en frenar la producción y la agregación de este péptido o bien, en su eliminación o metabolismo. En este punto, Inestrosa descubrió que la enzima acetilcolinesterasa (AChE) colocaliza con el βA en las placas seniles, esta enzima puede unirse al βA acelerando su agregación. Pero el AChE no sólo acelera la agregación, sino que también aumenta la neurotoxicidad del βA, ya que el complejo que forman es más tóxico que las propias placas.[45] La función de AChE en el sistema nervioso central (SCN) es la hidrólisis del neurotransmisor acetilcolina (ACh) en el espacio interneuronal (Figura 6).[40b, 42]

En este momento existen cuatro fármacos anti-Alzheimer en el mercado: tacrina, donepecilo, rivastigmina y galantamina (Figura 17). Todos ellos actúan como inhibidores de la AChE. Su efecto inmediato es elevar los niveles disponibles de neurotransmisor a nivel cerebral, lo que conlleva una mejora cognitiva, y

pueden considerarse paliativos, al no estar demostrada su acción anti-degenerativa.

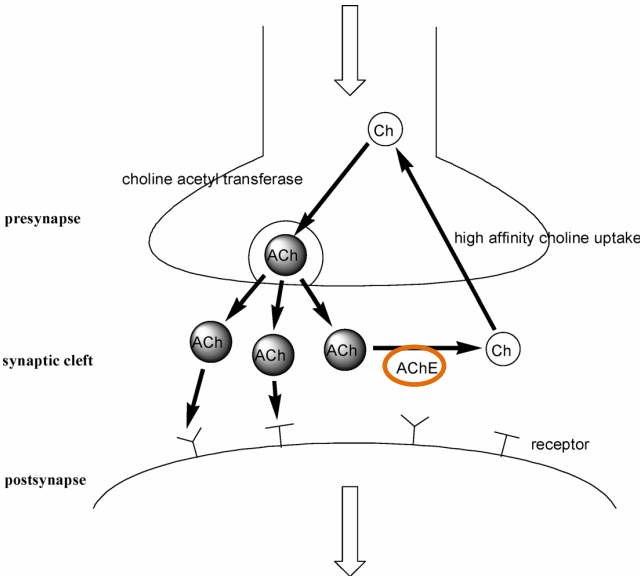


Figura 16. Función de AChE en SNC.[40b]

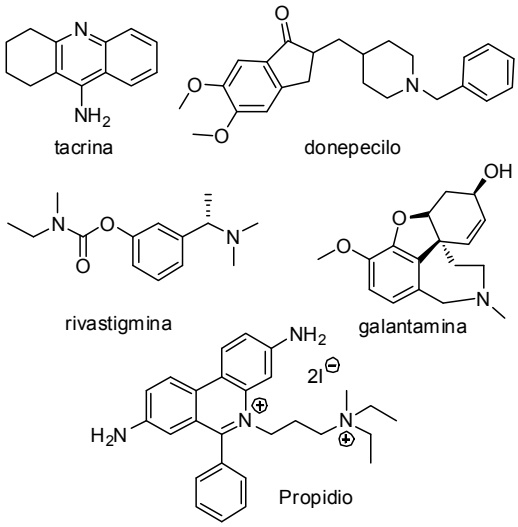


Figura 17. Inhibidores de AChE.

El centro catalítico de la AChE se encuentra en el extremo de una garganta con 20 Å de profundidad, a través de la cual el sustrato (ACh) difunde y es hidrolizado por la tríada catalítica (Ser200-His440-Glu327) (Figura 18). En una zona cercana a la triada, se encuentra el Trp84, amino ácido clave en la interacción con inhibidores coordinándose mediante interacciones π-π. Por otra parte, topológicamente próximos, se encuentran los aminoácidos Phe330, Phe331 y Tyr334 que también presentan interacciones relevantes en la inhibición. Sin embargo, uno de los residuos más importantes es el Trp279 (Figura 18) situado en la entrada de la cavidad formando parte del sitio de unión periférico, clave en el reconocimiento del βA.[46]

Los fármacos anteriormente citados causan inhibición de diferentes tipos, dependiendo de las interacciones moleculares con el enzima. Así por ejemplo, la tacrina (Figura 17) no es selectiva para AChE, sino que también inhibe otros enzimas y bloquea canales transportadores de iones. Actúa sobre la AChE en el fondo de la garganta por interacción π- π con Trp84 y Phe330. Por otro lado, el donepecilo (Figura 17) es mucho más selectivo para AChE, ya que una parte del compuesto interacciona con el Trp279 en el sitio periférico, y la otra interactúa con aminoácidos del fondo de la garganta (Trp84 y Phe330, Figura 18). De este modo el donepecilo ocupa gran parte de la cavidad catalítica y de la garganta.[46] Por otra parte, el prototipo de inhibidor periférico es el propidio (Figura 17), el cual se puede unir a esta zona concreta en dos orientaciones distintas, a partir de interacciónes π-π y π-catión, pero su carácter iónico bloquea el transporte a través de la barrera hematoencefálica (BHE) y presenta además una seria toxicidad, lo que impide su uso terapéutico.[47] La selectividad mostrada por parte del donepecilo sobre AChE ha estimulado el estudio de los inhibidores duales, es decir, que

interaccionan tanto en el fondo de la garganta de la cavidad como en el sitio periférico.[48]

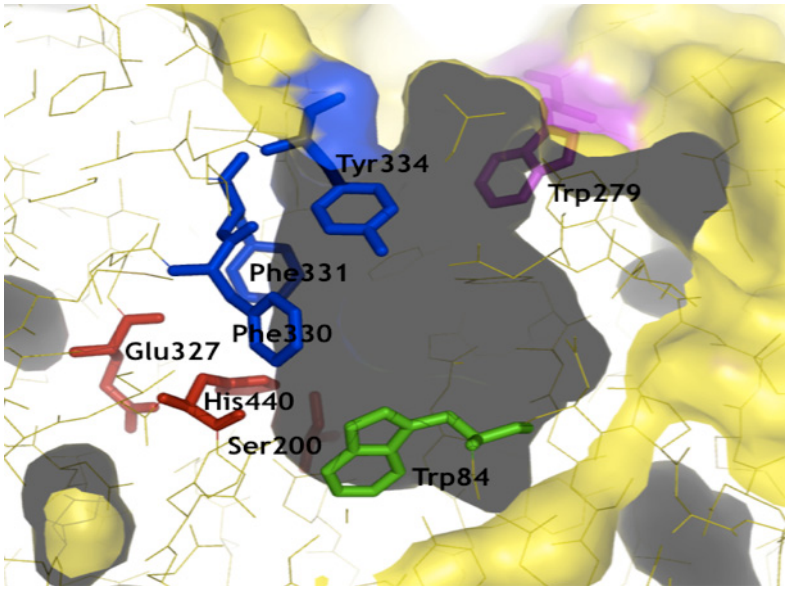


Figura 18. Representación tridimensional de la Acetilcolinesterasa.[34]

1.5.3. Inhibidores duales de AChE conocidos.

Teniendo en cuenta la importancia de los inhibidores duales, dada su potencia y selectividad hacia AChE, en los últimos años se han publicado varios trabajos que evalúan la actividad biológica de derivados de este tipo de compuestos (Figura 19), resultando de interés potencial para el tratamiento de la enfermedad de Alzheimer.[49]

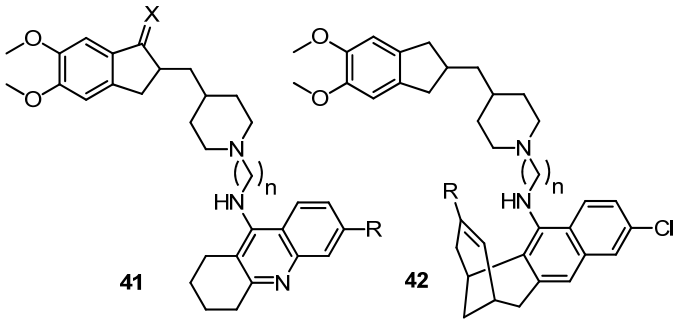


Figura 19. Inhibidores duales de la AChE.

En este contexto y teniendo en cuenta la elevada complejidad molecular de este tipo de compuestos (factor que dificultaba enormemente la síntesis, al implicar secuencias muy largas), en el grupo de investigación se decidió aplicar el uso de las RMCs para su preparación. Así de manera modular, rápida y eficaz se prepararon compuestos muy potentes que actuaban de la manera prevista, y que además mostraron actividad como inhibidores de la agregación del βA tanto espontánea como inducida por AChE. Mediante una variante de la reacción

multicomponente de Povarov desarrollada por nuestro grupo, se hizo reaccionar una anilina, un aldehído y una olefina activada, para dar lugar a compuestos del tipo tetrahidroquinolina polisubstituidas (43), después de la oxidación del aducto (44), éste se unió mediante un conector molecular con la 6-clorotacrina (46, Figura 20). El estudio previo de la posible interacción de este tipo de compuestos con AChE reveló que las quinolinas tipo **44** (Figura 20) a pH fisiológico el nitrógeno presente en el biciclo no estaría protonado, Este carácter más neutro que el propidio le ayudaría a cruzar la barrera hematoencefálica (BHE), y la interacción de esta estructura con el sitio periférico seria del tipo π-π con el Trp279. Estas hipótesis fueron corroboradas experimentalmente.[47]

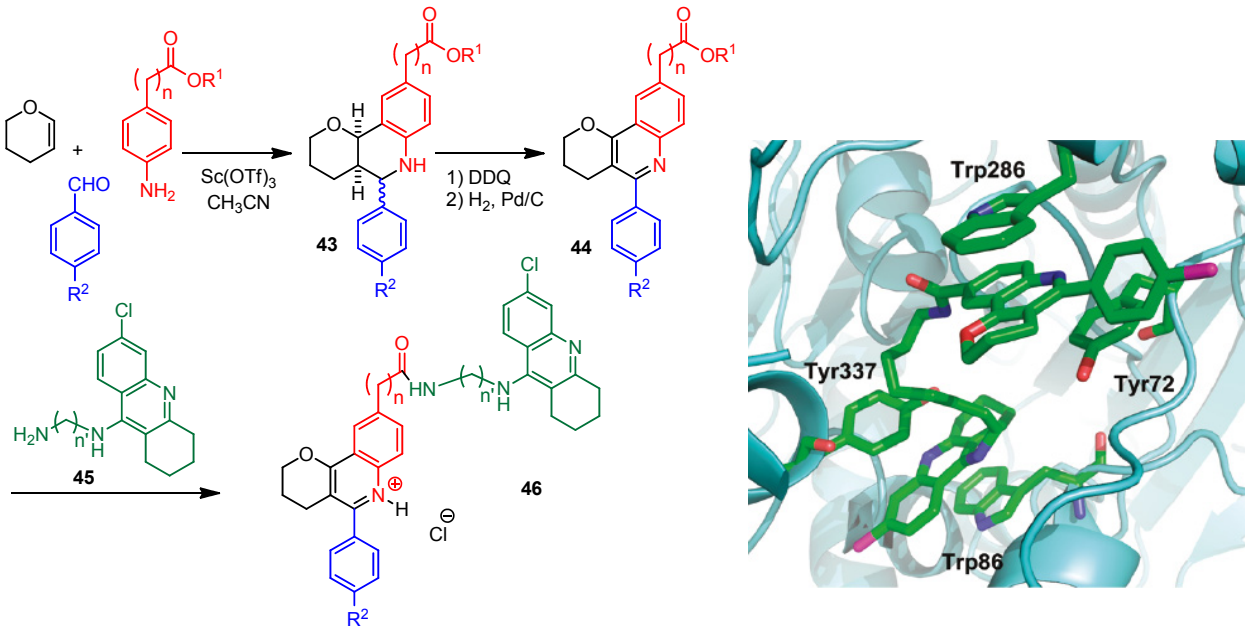


Figura 20. Síntesis de los inhibidores duales de hAChE y modelización de la interacción con el enzima.

2. Objetivos.

La presente tesis doctoral se centra en aumentar la variabilidad del componente olefínico presente en la reacción de Povarov y procesos relacionados, así como en explorar la posible actividad como inhibidores de AChE los productos de oxidación de los aductos Povarov.

i) Capitulo 2.

Explorar la reactividad de lactamas insaturadas como olefinas, con la finalidad de comparar su reactividad con la de los esteres de enol cíclicos los cuales no generan el aducto Povarov. De este modo se pretende la preparación de nuevos aductos con novedosos patrones de sustitución.

ii) Capitulo 3.

Estudiar la reactividad de 1,3-tia-, -oxa- y -imidazolonas, en condiciones de reacción de Povarov para la obtención de tetrahidroquinolinas con patrones originales de sustitución. Estudiar la regioselectividad de la reacción debido a las diferentes posibilidades de ataque a la imina de las citadas olefinas.

iii) Capitulo 4.

Optimizar la reacción de post-condensación oxidativa de los aductos Povarov, realizando un estudio de diferentes oxidantes. Una vez se haya encontrado el oxidante adecuado se realizará la optimización de la reacción para intentar reducir al mínimo la generación de subproductos y facilitar la purificación del producto final.

iv) Capitulo 5.

En nuestro grupo de investigación se ha descubierto una nueva reacción multicomponente a partir de iminas con configuración Z, las cuales en condiciones de reacción de Povarov dan lugar a amidinas cíclicas a través de un proceso Mannich-Ritter. A partir de este hallazgo se planteo el estudio del rango de olefinas para estudiar el efecto que puede tener este componente en el trascurso del nuevo proceso y a partir de los resultados obtenidos estudiar con detalle el mecanismo de la reacción.

v) Capitulo 6.

Se pretende llevar a cabo el análisis de la actividad como inhibidores de acetilcolinesterasa de derivados obtenidos a partir de procesos de tipo Povarov, con lactamas insaturadas y enaminas cíclicas como olefinas activadas. De los productos más activos, se realizará el estudio de *docking* con tal de averiguar la forma en la cual este tipo de compuestos interactúa con el enzima. Y a partir de ahí, diseñar nuevos compuestos potencialmente con mayor actividad.

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2. Lactamas insaturadas como nuevos componentes olefínicos en la reacción de Povarov

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Unsaturated Lactams: New Inputs for Povarov-Type Multicomponent Reactions

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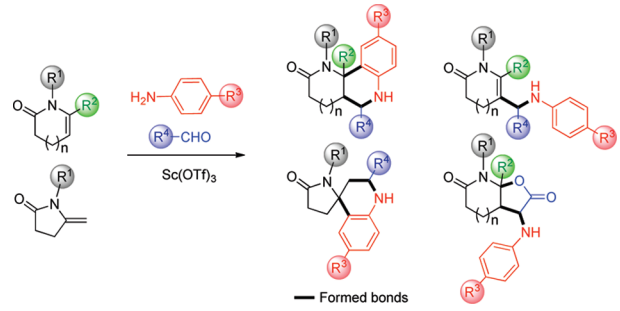
ABSTRACT



Unsaturated lactams with endo- or exocyclic C−C double bonds constitute a set of reactive inputs that serve as the electron-rich olefin component in Povarov reactions. These substrates afford the multicomponent adducts in convenient yields and offer a wide range of structural diversity. Postcondensation transformations allow direct access to a variety of lactam-fused and amide-substituted quinoline derivatives.

Multicomponent reactions (MCRs) constitute a large group of transformations of growing relevance in organic chemistry as they display many features of the ideal synthesis.[1] Among these domino processes, the Povarov MCR, which involves the interaction of a carbonyl compound (normally an aldehyde), an aniline, and an activated alkene to yield a tetrahydroquinoline adduct, is currently the focus of intense research.[2] This transformation links the following three main steps: the generation of an imine, followed by a Mannich-type reaction with the activated olefin, and ending with the intramolecular aromatic electrophilic substitution upon the aniline ring. The presence of tetrahydroquinolines (or oxidized derivatives) in natural products, bioactive compounds, and drugs has recently elicited much interest in this process.

The original protocol has been considerably improved, and recent findings include the possibility to perform catalytic enantioselective versions of this MCR,[3] the introduction of a fourth component to trap the final iminium ion intermediate,[4] and the spatial-temporal control of this MCR to functionalize microelectrodes.[5] With respect to the reactivity range, the process is useful with a broad set of anilines, carbonyl derivatives, and much effort has been devoted to expand the range of activated olefin input. Apart from alkenes

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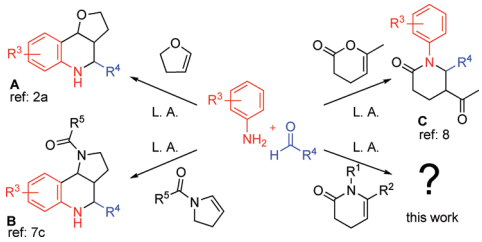
and cyclic enol ethers which have been used widely in this MCR (**A**, Scheme 1), the introduction of enamine-type

Scheme 1. Enol Ethers and Enamides in Povarov MCRs



functional groups has been successfully exploited.[2,6] In this context, cyclic enamides are specially appealing since they allow access to a new set of functionalized tetrahydroquinolines **B**.[7] Importantly, the development of this chemistry by Batey has allowed a straightforward synthesis of the alkaloids Martinelline and Martinellic acid.[7a−c] The MCR adducts in these processes show a normal connectivity pattern, thereby leading to the expected tetrahydroquinolines. In sharp contrast, when cyclic enol esters were tested in Povarov-type conditions, the *N*-aryl lactams **C** were obtained.[8] The origin of these compounds may lie in the intramolecular interception of the activated cationic intermediate by the nucleophilic aniline nitrogen, which overrides the usual aromatic electrophilic substitution. Here we studied the chemistry of unsaturated lactams in Povarov processes to determine their synthetic usefulness and to establish the mechanistic trends of these substrates in the MCR (Scheme 1).

Several unsaturated lactams were prepared by known methods (or modifications thereof), usually from the corresponding N-substituted imides by a reduction−elimination sequence.[9] The set included six- and seven-membered rings, displaying distinct substituents at the nitrogen atom and also at the neighboring position (**1a**−**f**, Figure 1). The pyrrolidone derivative **1g** with an exo double bond was also considered.[10]

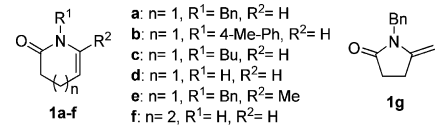
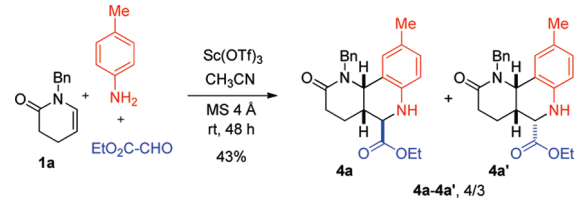


Figure 1. Unsaturated lactams used in this study.

The first experiment involved the interaction of the unsaturated lactam **1a**, with *p*-toluidine and ethyl glyoxalate under $Sc(OTf)_3$ catalysis[11,6b] in the presence of 4 Å molecular sieves in acetonitrile at room temperature. After chromatographic purification, the tetrahydroquinolines **4a** and **4a′** were isolated (isomer ratio 4/3) in 43% overall yield (Scheme 2).

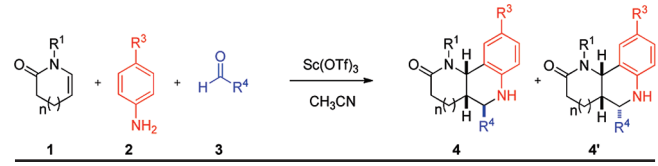
Scheme 2. Povarov MCR with Unsaturated Lactam **1a**



The stereochemical assignment of compounds **4a**−**4a′** was performed by spectroscopical means. The low stereoselectivity observed is the usual outcome in these processes.[2]

Next we examined the scope of the reaction, regarding all the components (Table 1). The aniline input showed

Table 1. Scope of the Povarov MCR with Unsaturated Lactams



entry	n	R^1	R^3	R^4	compound	overall yield (%)	isomer ratio (**4**/**4′**)
1	1	Bn	Me	CO_2Et	**4a**−**4a′**	43	4/3
2	1	Bn	CO_2Et	2-furyl	**4b**	38	1/-
3	1	H	OMe	3-pyridyl	**4c**−**4c′**	42	3/2
4	1	H	F	2-furyl	**4d**	33	1/-
5	1	Bu	OMe	4-CF_3-Ph	**4e**−**4e′**	42	1/1
6	1	Bn	Me	4-Cl-Ph	**4f**−**4f′**	64	1/1
7	1	4-Me-Ph	Me	CO_2Et	**4g**−**4g′**	61	8/5
8	1	H	Me	4-Cl-Ph	**4h**−**4h′**	56	5/8
9	2	H	Me	CO_2Et	**4i**−**4i′**	35	3/2

appropriate reactivity, ranging from deactivated to activated derivatives (entries 1−4). Also, the carbonyl range included

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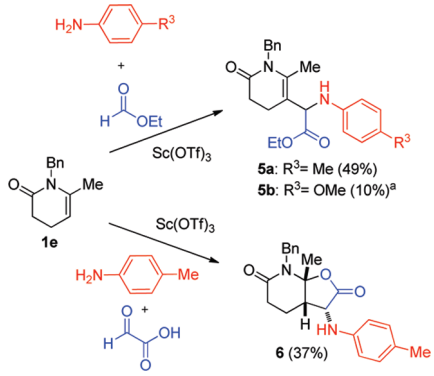
the usual set of aromatic and highly electrophilic aldehydes.[12] Thus, ethyl glyoxalate (entries 1 and 7) and diversely substituted aromatic and heteroaromatic aldehydes (entries 2−6 and 8) afforded the expected adducts. Interestingly, when using 2-furaldehyde in combination with ethyl *p*-aminobenzoate and *p*-fluoroaniline (Table 1, entries 2 and 4), we detected the formation of only the isomers **4b** and **4d**, respectively. Finally, we screened the unsaturated lactams, first studying the substitution pattern at the nitrogen atom (entries 1−8) and looking at the ring size (six- and seven-membered rings, entries 1−8 and 9, respectively). We obtained acceptable yields in all cases.

We explored further variations in the structure of the unsaturated lactams, and alkyl substitution at the α-position was also examined. When derivative **1e** (Scheme 3) was

Scheme 3. α-Substituted Unsaturated Lactam **1e**

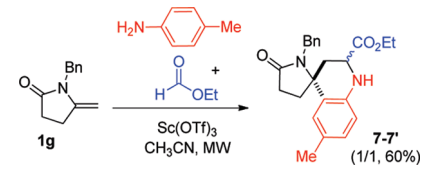


[a] Unoptimized reaction.

reacted with *p*-toluidine or 4-methoxyaniline and ethyl glyoxalate, under the usual conditions, we obtained the Mannich-type products **5a** and **5b**, respectively, in moderate yields. In these cases, the final electrophilic substitution did not take place, probably due to steric reasons. In these reactions, the cationic intermediate evolved via a proton loss at the α-position of the acyliminium moiety to regenerate the unsaturated lactam system. This outcome also differed from the described reactivity of cyclic enol esters, where the aniline nitrogen attacks the carbonyl group of the intermediate.[8] Furthermore, when using glyoxylic acid as the carbonyl component, the carboxylate moiety acts as a nucleophile and captures the final iminium ion intermediate.[4a,13] Thus, adduct **6** (37%) was stereoselectively obtained in this way.

Finally, the pyrrolidone derivative displaying an exo double bond (**1g**) was reacted to afford the spiro-Povarov adduct (Scheme 4). First, the standard conditions were tested affording the MCR adduct in low yield (20%). Performing the reaction under microwave irradiation (MW) resulted in a substantial optimization (**7**−**7′**, 60% overall yield). Barluenga and co-workers recently reported an elegant domino process for the synthesis of related systems by a sequence involving the in situ formation of an exocyclic enol ether,

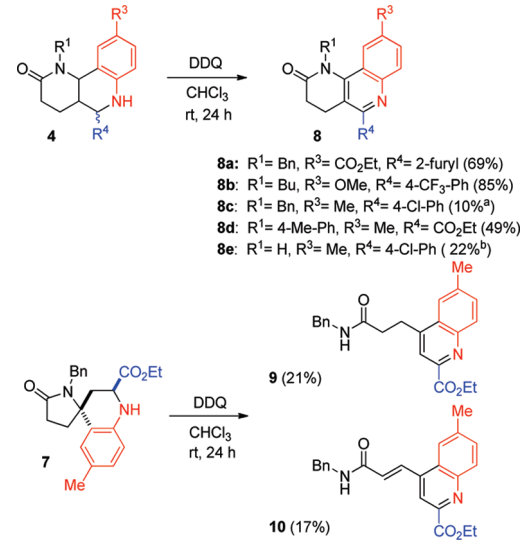
Scheme 4. Spiro-Adduct from Substrate **1g**



via a metal-catalyzed alkoxylation of an ω-hydroxyalkyne, followed by a Povarov reaction.[14]

Next, we explored some postcondensation reactions upon the previously prepared Povarov adducts. Thus, the DDQ-oxidation of the tetrahydroquinolines **4** yielded the corresponding lactam-fused quinolines **8** (Scheme 5).[15,16] The

Scheme 5. DDQ oxidation of Povarov adducts **4** and **7**



[a] Unoptimized result. [b] The overoxidation product **8f** (R^1 = H, R^3 = CHO, R^4 = 4-Cl-Ph) was also isolated in 40% yield.

process was satisfactory and afforded the products in reasonable yields. Adduct **4h** suffered overoxidation, thereby

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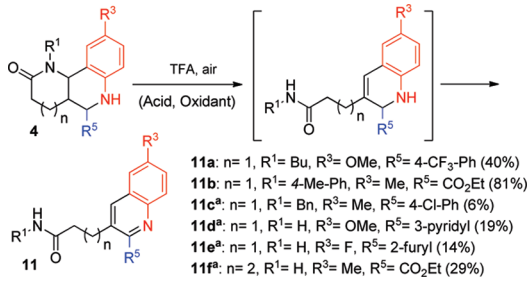
resulting in a mixture of the expected quinoline **8e** (22%), together with the aldehyde derivative **8f** (40%).[16] The treatment of spiro-adduct **7** (Scheme 5) with DDQ gave two compounds arising from an oxidative fragmentation: quinoline **9** (21%) and its dehydrogenated derivative **10** (17%).

In search for variants of this transformation, we tested a TFA treatment to promote an acid-catalyzed elimination[17] of the amide moiety of the Povarov adducts, which would lead to a 1,2-dihydroquinoline prone to spontaneus oxidation to give the 2,3-disubstituted quinoline derivatives (**11a**,**b**). In this way, quinolines **11a** and **11b** were directly prepared from compounds **4e** and **4g**, respectively (Scheme 6). This

Scheme 6. Acid-Catalyzed Fragmentation−Oxidation Process



[a] Isolated as byproduct in Povarov MCRs or in DDQ oxidations of the Povarov adducts **4**.

type of oxidative fragmentation was also observed at a reduced extent in the DDQ-oxidation of adduct **4f**, which allowed the isolation of **11c**. Also in the $Sc(OTf)_3$-catalyzed Povarov reactions, the quinolines **11d**, **11e**, and **11f** were isolated as byproduct (entries 3, 4, and 9, Table 1). These products may have arisen from the full domino sequence.

In conclusion, unsaturated lactams are synthetically useful substrates for Povarov MCRs and allow direct and convenient access to tetrahydroquinoline scaffolds with novel connectivity and functionalization patterns. These adducts are readily converted to a variety of quinoline derivatives in a straightforward manner.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information

Unsaturated Lactams: New Inputs for Povarov-type Multicomponent Reactions.

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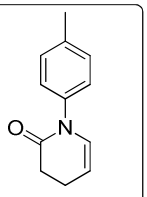
General experimental information.

Unless stated otherwise, all reactions were carried out under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was performed on pre-coated Merk silica gel 60 F254 plates and visualized under a UV lamp. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (at 400 MHz and 100 MHz respectively). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{13}C-NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^{1}H-^{1}H-COSY, ^{1}H-^{13}C-COSY (HSQC: Heteronuclear Single Quantum Coherence) and long-range ^{1}H-^{13}C-COSY (HMBC: Heteronuclear Multiple Bond Connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

Synthesis of unsaturated lactams 1.

The unsaturated lactams **1a** [1], **1b**, **1c**, **1d** [2] and **1f** [3] were prepared from the corresponding imides (according to a reported protocol), [4] following reduction-elimination sequences. In the case of compound **1b** we used DIBAL-H as a reducing agent and MsCl to promote water elimination,[5] and in the other cases $NaBH_4$-*p*-TsOH was employed. [6] The unsaturated lactam **1e** [7] was synthesized with benzylamine addition to 6-methyl-3,4-dihydro-2H-pyran-2-one, following by a water elimination under *p*-TsOH catalyst. The pyrrolidone derivative **1g** was prepared following a reported procedure. [8]

1-(*p*-tolyl)-3,4-dihydropyridin-2(1*H*)-one (1b):

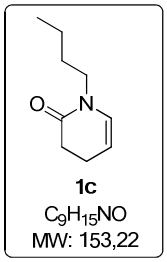


1b
$C_{12}H_{13}NO$
MW: 187,24

Following the reported procedure (using DIBAL-H-MsCl sequence) and after a flash chromatography using hexane/ethyl acetate, compound **1b** was obtained as a brown solid, 20%.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.15-7.04 (m, 4H), 6.17 (dt, *J*= 1.6, 7.7 Hz, 1H), 5.20-5.14 (m, 1H), 2.62 (t, *J*= 8.0 Hz, 2H), 2.40-2.33 (m, 2H), 2.28 (s, 3H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 169.1, 138.1, 136.7, 131.1, 129.6, 125.8, 106.2, 32.1, 21.0, 20.3 ppm. **IR** (film) ν_{max}: 3353, 3027, 2922, 2832, 1694, 1518, 1398, 1348, 1272, 1142, 1117, 811 cm^{-1}. **HRMS**: calcd for $C_{12}H_{14}NO$ 188.1070 ($M+H^+$); found, 188.1064.

[1] Yu, J.; Truc, V.; Riebel, P.; Hierl, E.; Mudryk, B., *Tetrahedron* **2005**, *45*, 4011-4013.
[2] Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N., *Tetrahedron* **1975**, *31*, 1437-1441.
[3] Hu, T.; Li, C., *Org. Lett.* **2008**, *10*, 2035-2038.
[4] (a) Galbo, F. L.; Occhiato, E. G.; Guarna, A.; Faggi, C., *J. Org. Chem.* **2003,** *68*, 6360-6368. (b) Khan, M. M., Melmon, K. L., Egli, M., Lok, S., Goodman, M. *J. Med. Chem.* **1987**, *30*, 2115-2120. (c) Yoshifuji, S., Arakawa, Y., Nitta, Y. *Chem. Pharm. Bull.* **1987**, *35*, 357-363.
[5] Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, C. R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C., *Tetrahedron* **2004,** *60*, 4491-4511.
[6] Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N., *Tetrahedron* **1975,** *31*, 1437-1441.
[7] Zulys, A.; Dochnahl, M.; Hollmann, D.; Löhnwitz, K.; Herrmann, J-S.; Roesky, P. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 7794-7798.
[8] Padwa, A.; Rashatasakhon, P.; Rose, M., *J. Org. Chem.* **2003**, *68*, 5139-5146.

1-butyl-3,4-dihydropyridin-2(1*H*)-one (1c):



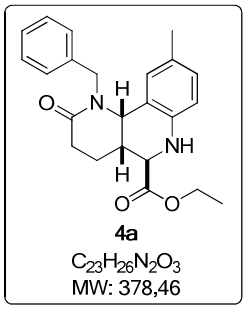
1c
$C_9H_{15}NO$
MW: 153,22

Following the reported procedure (using $NaBH_4$-*p*-TsOH sequence) and after a flash chromatography using hexane/ethyl acetate compound **1c** was obtained as a purple oil, 74%.
^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.05-5.97 (m, 1H), 5.18-5.06 (m,1H), 3.46 (t, *J*= 7.2 Hz, 2H), 2.56-244 (m, 2H), 2.36-2.23 (m, 2H), 1.62-1.20 (m, 4H), 0.93 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 169.1, 129.9, 105.8, 45.8, 31.4, 30.7, 20.3, 19.9, 13.8 ppm. **IR** (film) ν_{max}: 3321, 3065, 2950, 2931, 2873, 1668, 1412, 1399, 1265, 1220, 1201, 1073, 938, 707 cm^{-1}. **HRMS**: calcd for $C_9H_{16}NO$ 154.1226 ($M+H^+$); found, 154.1226.

General procedure A. Synthesis of compounds 4, 5, 6 and 7.

Molecular sieves 4Å (ca. 2g) and a $Sc(OTf)_3$ (0.2 mmol) were added to a solution of aldehyde (1 mmol) and aniline (1 mmol) in dry CH_3CN (4 mL), and the mixture was stirred at room temperature. After 5 min, a solution of the unsaturated lactam (1 mmol) in dry CH_3CN (3 mL) was added, and the resulting suspension was stirred under argon atmosphere at the same temperature for 48 h. An aqueous saturated $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with EtOAc (3×10 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexane- EtOAc) to give the desired products.

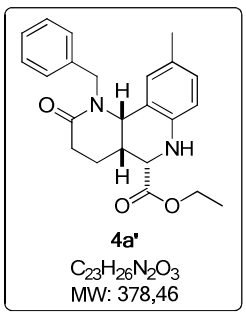
(4a*RS*,5*SR*,10b*RS*)-ethyl 1-benzyl-9-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4a)



4a
$C_{23}H_{26}N_2O_3$
MW: 378,46

Following the general procedure A, the reaction of **1a**, *p*-toluidine and ethyl glyoxalate, afforded compounds **4a**-**4a'** (43%, **4a**/**4a'**, 4:3). This mixture was purified by flash chromatography to afford pure **4a** as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34-7.27 (m, 5H), 6.92 (dd, *J*= 1.7, 8.1 Hz, 1H), 6.84 (s, 1H), 6.54 (d, *J*= 8.1 Hz, 1H), 5.79 (d, *J*= 14.7 Hz, 1H), 4.35 (d, *J*= 4.5 Hz, 1H), 4.06-3.89 (m, 3H), 4.76 (d, *J*= 3.0 Hz, 1H), 2.58-2.37 (m, 3H), 2.23 (s, 3H), 1.95-1.81 (m, 2H), 1.04 (t, *J*= 7.1 Hz, 1H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 172.8, 170.7, 139.3, 137.3, 129.2, 128.5, 128.0, 127.6, 127.4, 126.5, 119.9, 114.4, 61.5, 57.6, 53.6, 51.1, 33.6, 30.2, 22.6, 20.6, 13.9 ppm. **IR**: (film) ν_{max} : 3337, 2936, 1739, 1645, 1508, 1471, 1355, 1299, 1194, 1134, 1027, 814, 702 cm^{-1}. **HRMS**: calcd for $C_{23}H_{27}N_2O_3$ 379.2016 ($M+H^+$); found, 379.2019.

(4a*RS*,5*RS*,10b*RS*)-ethyl 1-benzyl-9-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4a')

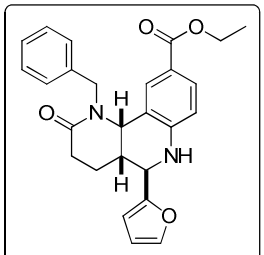


4a'
$C_{23}H_{26}N_2O_3$
MW: 378,46

On further elution, compound **4a'** was obtained as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.21 (m, 5H), 6.82 (dd, *J*= 1.4, 8.1 Hz, 1H), 6.74 (s, 1H), 6.44 (d, *J*= 8.1 Hz, 1H), 5.70 (d, *J*= 14.7 Hz, 1H), 4.56 (d, *J*= 4.5 Hz, 1H), 4.23-4.14 (m, 3H), 4.13 (dd, *J*= 1.6, 3.4 Hz, 1H), 4.05 (d, *J*= 14.7 Hz, 1H), 2.46-2.29 (m, 2H), 2.26-2.15 (m, 1H), 2.14 (s, 3H), 1.68-1.48 (m, 2H), 1.23 (t, *J*= 7.13 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.2, 170.8, 139.6, 137.3, 129.3, 128.8, 128.2, 127.6, 127.5, 126.2,

119.5, 114.2, 61.8, 56.7, 56.3, 51.6, 33.4, 29.8, 20.6, 18.0, 14.2 ppm. **IR**: (film) ν_{max}: 3404, 2917, 1734, 1652, 1507, 1451, 1215, 1169, 1021, 816, 695 cm^{-1}. **HRMS**: calcd for $C_{23}H_{27}N_2O_3$ 379.2016 ($M+H^+$); found, 379.2018.

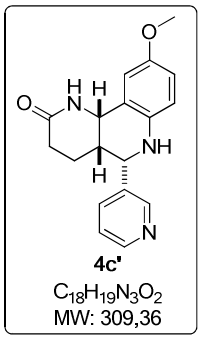
(4a*RS*,5*RS*,10b*RS*)-ethyl 1-benzyl-5-(furan-2-yl)-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-9-carboxylate (4b)



4b
$C_{26}H_{26}N_2O_4$
MW: 430,50

Following the general procedure A, the reaction between **1a**, ethyl 4-aminobenzoate and 2-furaldehyde, and after a flash chromatography afforded compound **4b** as a pink powder (38%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (dd, *J*= 1.9, 8.4 Hz, 1H), 7.67-7.64 (m, 1H), 7.20-7.12 (m, 4H), 7.08-7.02 (m, 2H), 6.44 (d, *J*= 8.4 Hz, 1H), 6.14 (dd, *J*= 1.8,3.2 Hz, 1H), 5.89-5.85 (m, 1H), 5.50 (d, *J*= 14.7 Hz, 1H), 4.70 (br s, 1H), 4.35 (d, *J*= 4.0, 1H), 4.31 (d, *J*= 4.5 Hz, 1H), 4.29-4.21 (m, 2H), 4.01 (d, *J*= 14.8 Hz, 1H), 2.53-2.30 (m, 3H), 1.90-1.78 (m, 1H), 1.70-1.57 (m, 1H), 1.29 (t, *J*= 7.12 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 170.7, 166.4, 154.7, 146.2, 142.4, 137.2, 130.8, 129.6, 128.4, 128.0, 127.3, 119.2, 117.7, 112.9, 110.1, 106.6, 60.4, 53.5, 51.8, 49.8, 34.8, 29.8, 21.9, 14.5 ppm. **IR** (film) ν_{max}: 3321, 2975, 2930, 1700, 1630, 1609, 1521, 1367, 1284, 1252, 1188, 1108, 1009, 765 cm^{-1}. **HRMS**: calcd for $C_{26}H_{27}N_2O_4$, 431.1965 ($M+H^+$); found, 431.1956.

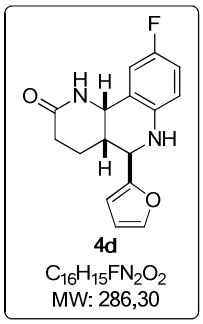
(4a*RS*,5*SR*,10b*RS*)-9-methoxy-5-(pyridin-3-yl)-1,4,4a,5,6,10b-hexahydrobenzo[h]quinolin-2(3*H*)-one (4c')



4c'
$C_{18}H_{19}N_3O_2$
MW: 309,36

Following the general procedure A, the reaction of **1d**, 4-methoxyaniline and nicotinaldehyde, afforded compounds **4c**-**4c'** as yellow powder (42%, **4c**/**4c'**, 3:2). After flash chromatography purification using DCM/MeOH, compound **4c'** was obtained as a yellow powder. On further elution, quinoline **11d** (19%) was isolated (see below).
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.71 (d, *J*= 2.1 Hz, 1H), 8.61 (dd, *J*= 1.6, 4.8 Hz, 1H), 7.83-7.80 (m, 1H), 7.35 (ddd, *J*= 0.5, 4.9, 7.8 Hz, 1H), 7.16 (d, *J*= 4.4 Hz, 1H), 6.81-6.79 (m, 1H), 6.73 (ddd, *J*= 0.6, 2.8, 8.7 Hz, 1H), 6.60 (d, *J*= 8.7 Hz, 1H), 4.96 (t, *J*= 4.8 Hz 1H), 4.80 (d, *J*= 1.8 Hz, 1H), 3.75 (s, 3H), 2.37 (ddd, *J*= 1.8, 6.1, 18.0 Hz, 1H), 2.34-2.28 (m, 1H), 2.26-2.17 (m, 1H), 1.91-1.80 (m, 1H), 1.53-1.46 (m, 1H) ppm. **^{13}C-NMR** (125 MHz, $CDCl_3$) δ: 171.9, 153.3, 149.5, 148.8, 136.5, 136.3, 134.5, 123.5, 122.6, 116.4, 115.2, 112.5, 57. 0, 55.8, 52.7, 38.2, 30.4, 15.8 ppm. **IR** (film) ν_{max}: 3289, 2917, 1662, 1502, 1425, 1300, 1226, 1111, 1004, 804 cm^{-1}. **HRMS**: calcd for $C_{18}H_{20}N_3O_2$, 310.155 ($M+H^+$); found, 310.1548.

(4a*RS*,5*SR*,10b*SR*)-9-fluoro-5-(furan-2-yl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4d)

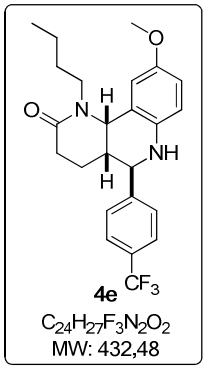


4d
$C_{16}H_{15}FN_2O_2$
MW: 286,30

Following the general procedure A, the reaction of **1d**, 4-fluoroaniline and 2-furaldehyde, afforded compound **4d** as a pink powder (33%) after flash chromatography purification using DCM/MeOH. On further elution, quinoline **11e** (14%) was isolated (see below).
^{1}H-NMR (400 MHz, DMSO) δ: 8.10 (d, *J*= 3.31 Hz, 1H), 7.61 (dd, *J*= 0.7, 1.7Hz, 1H), 7.01 (dd, *J*= 2.9, 10.0 Hz, 1H), 6.83 (td, *J*= 2.9, 8.7 Hz, 1H), 6.60 (dd, *J*= 5.0, 8.9 Hz, 1H), 6.39 (dd, *J*= 1.8, 3.2 Hz, 2H), 6.35 (d, *J*= 2.4 Hz, 2H), 6.24-6.12 (m, 1H), 4.40 (dd, *J*= 2.8, 4.8 Hz,

1H), 4.14 (t, *J*= 4.1 Hz, 1H), 2.43-2-22 (m, 2H), 2.21-2-11 (m, 1H), 1.84-1.74 (m, 1H), 1.55-1.43 (m, 1H), ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 169.6, 155.9, 155.3, 153.0, 142.2, 139.1, 139.1, 121.1, 121.1, 114.7, 114.5, 114.5, 114.3, 114.3, 114.3, 110.2, 106.4, 50.3, 48.2, 33.3, 29.5, 21.8 ppm (Only absortion lines are listed, no multiplicity had been assigned due to high signal overlapping). **IR** (film) ν_{max}: 3327, 3161, 3033, 2956, 2860, 1643, 1501, 1412, 1258, 1015, 765 cm^{-1}. **HRMS**: calcd for $C_{16}H_{16}FN_2O_2$ 287.1190 ($M+H^+$); found, 287.1191..

(4a*RS*,5*SR*,10b*RS*)-1-butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4e)

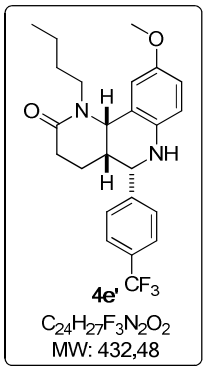


4e
$C_{24}H_{27}F_3N_2O_2$
MW: 432,48

Following the general procedure A, the reaction of **1c**, 4-methoxyaniline and 4-(trifluoromethyl)benzaldehyde, afforded a mixture of compounds **4e**-**4e'** (42%, **4e**/**4e**', 1:1). After flash chromatography purification, pure compound **4e** was obtained as a white powder

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J*= 8.2 Hz, 2H), 7.46 (d, *J*= 8.2 Hz, 2H), 6.75 (dd, *J*= 2.7, 8.6 Hz, 1H), 6.62 (d, *J*= 2.3 Hz, 1H), 6.60 (d, *J*= 8.6 Hz, 1H), 4.36 (d, *J*= 3.8 Hz, 1H), 4.17 (d, *J*= 4.2 Hz, 1H), 4.15-4.07 (m, 1H), 2.89-2.80 (m, 1H), 2.46-2.28 (m, 3H), 1.92-1.82 (m, 1H), 1.77-1.64 (m, 1H), 1.42-1.29 (m, 2H), 1.18-1.03 (m, 2H), 0.74 (t, *J*= 7.3 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 170.2, 152.3, 148.8, 136.5, 129.9 (q, *J*= 32.5 Hz), 126.5, 125.7 (q, *J*= 3.8 Hz), 121.1, 114.9, 114.5, 112.7, 58.4, 55.8, 54.4, 47.7, 39.5, 30.3, 30.0, 23.2, 20.0, 13.6 ppm. **IR** (film) ν_{max}: 3328, 2931, 1636, 1504, 1416, 1326, 1163, 1123, 1067, 1016, 810 cm^{-1}. **HRMS**: calcd for $C_{24}H_{28}F_3N_2O_2$, 433.2097 ($M+H^+$); found, 433.2088.

(4a*RS*,5*RS*,10b*RS*)-1-butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4e')

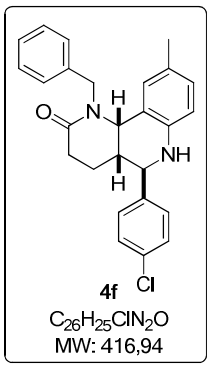


4e'
$C_{24}H_{27}F_3N_2O_2$
MW: 432,48

On further elution, compound **4e'** was isolated as a white powder.

^{1}H-NMR (400MHz, $CDCl_3$) δ: 7.63 (d, *J*= 8.2 Hz, 2H), 7.54 (d, *J*= 8.2 Hz, 2H), 6.71 (dd, *J*= 2.7, 8.6 Hz, 1H), 6.64 (d, *J*= 2.6 Hz, 1H), 6.58 (d, *J*= 8.6 Hz, 1H), 4.94 (d, *J*= 2.7 Hz, 1H), 4.87 (d, *J*= 4.3 Hz, 1H), 4.38 (ddd, *J*= 5.8, 9.4, 13.1 Hz, 1H), 3.74 (s, 3H), 2.97 (ddd *J*= 5.8, 9.4, 13.2 Hz, 1H), 2.35-2.27 (m, 1H), 2.22-2.15 (m, 2H), 1.86-1-53 (m, 3H), 1.45-1.15 (m, 3H), 0.96 (t, *J*= 7.3 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 170.6, 152.8, 145.2, 145.2, 136.8, 130.1 (q, *J*= 32.6 Hz), 127.0, 125.5 (q, J= 3.7 Hz), 122.0, 115.6, 114.4, 112.1, 59.1, 58.7, 55.8, 49.4, 38.9, 30.2, 30.1, 20.3, 16.7, 13.9 ppm. **IR** (film) ν_{max} : 3310, 2958, 1638, 1502, 1416, 1325, 1274, 1164, 1124, 1067, 1017, 851 cm^{-1}. **HRMS**: calcd for $C_{24}H_{28}F_3N_2O_2$, 433.2097 ($M+H^+$); found, 433.2088.

(4a*RS*,5*SR*,10b*RS*)-1-benzyl-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4f)



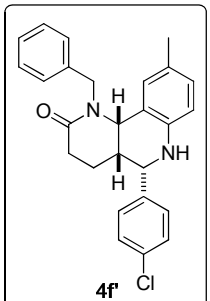
4f
$C_{26}H_{25}ClN_2O$
MW: 416,94

Following the general procedure A, the reaction of **1a**, *p*-toluidine and 4-chlorobenzaldehyde, afforded a mixture of compounds **4f**-**4f'** (64%, **4f**/**4f'**, 1:1). After a flash chromatography purification, compound **4f** was isolated as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.15-7.04 (m, 5H), 7.03-6.98 (m, 2H), 6.96-6.90 (m, 2H), 6.84 (dd, *J*= 1.8, 8.1 Hz, 1H), 6.67 (s, 1H), 6.40 (d, *J*= 8.1 Hz, 1H), 5.38 (d, *J*= 14.6Hz, 1H), 4.14-4-09 (m, 2H), 4.0

(br s, 1H), 3.88 (d, *J*= 14.6 Hz, 1H), 2.48-2.29 (m, 2H), 2.12 (s, 3H), 2.03-1.94 (m, 1H), 1.85-1.34 (m, 1H), 1.66-1.53 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.1, 142.5, 140.5, 137.2, 133.1, 129.5, 128.7, 128.3, 128.0, 127.9, 127.4, 127.2, 126.6, 118.8, 113.4, 57.2, 53.0, 49.7, 38.8, 29.9, 22.5, 20.5 ppm. IR (film) ν_{max}: 3333, 3013, 2911, 2866, 1639, 1508, 1405, 1405, 1354, 1310, 1252, 1149, 1079, 1002, 797 cm^{-1}. **HRMS**: calcd for $C_{26}H_{26}ClN_2O$, 417.1728 ($M+H^+$); found, 417.1723.

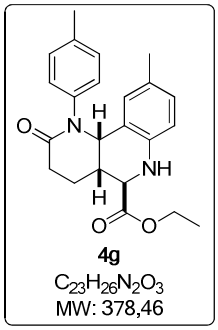
(4a*RS*,5*RS*,10b*RS*)-1-benzyl-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4f')



4f'
$C_{26}H_{25}ClN_2O$
MW: 416,94

On further elution, compound **4f'** was isolated as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.13 (m, 9H), 6.85-6.80 (m, 1H), 6.78 (s, 1H), 6.43 (d, *J*= 8.0Hz, 1H), 5.74 (d, *J*= 14.7 Hz, 1H), 4.73 (d, *J*= 4.3 Hz, 1H), 4.65 (d, *J*= 3.1Hz, 1H), 4.04 (d, *J*= 14.7 Hz, 1H), 3.78 (br s, 1H), 2.25-2.19 (m, 2H), 2.16 (s, 3H), 2.08-1.98 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ:171.3, 140.8, 139.5, 137.4, 133.4, 129.1, 128.7, 128.7, 128.0, 127.9, 127.7, 127.5, 126.6, 120.4, 114.4, 58.0, 57.9, 51.8, 38.6, 30.1, 20.7, 16.9 ppm. **IR** (film) ν_{max}: 3314, 3019, 2918, 1641, 1506, 1278, 1088, 1014, 816, 702 cm^{-1}. **HRMS**: calcd for $C_{26}H_{26}ClN_2O$, 417.1728 ($M+H^+$); found, 417.1723.

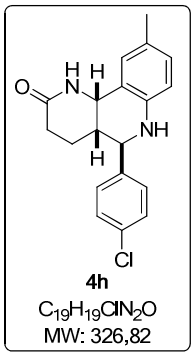
(4a*RS*,5*SR*,10b*RS*)-ethyl 9-methyl-2-oxo-1-(*p*-tolyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4g)



4g
$C_{23}H_{26}N_2O_3$
MW: 378,46

Following the general procedure A, the reaction of **1b**, *p*-toluidine and ethyl glyoxalate solution, afforded a mixture of compounds **4g**-**4g'** (61%, **4g**/**4g'**, 8:5). After a flash chromatography purification, compound **4g** was obtained as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.23-7.19 (m, 2H), 7.12-7.08 (m, 2H), 6.86 (s, 1H), 6.80 (dd, *J*= 1.7, 8.1 Hz, 1H), 6.44 (d, *J*= 8.1 Hz, 1H), 4.87 (d, *J*= 4.7 Hz, 1H), 4.24 (br s, 1H), 4.20-4.06 (m, 2H), 3.87 (d, *J*= 3.5, 1H), 2.92-2.85 (m, 1H), 2.49-2.33 (m, 2H), 2.26 (s, 3H), 2.06 (s, 3H), 2.04-1.85 (m, 2H), 1.19 (t, *J*= 7.13 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.9, 170.8, 140.5, 139.4, 135.9, 129.5, 129.2, 127.6, 127.4, 125.4, 120.4, 114.2, 61.5, 58.0, 57.5, 33.2, 30.7, 22.5, 20.9, 20.5, 14.2 ppm. **IR** (film) ν_{max}: 3347, 2922, 2860, 1734, 1653, 1511, 1436, 1289, 1192, 1137, 1023, 810 cm^{-1}. **HRMS**: calcd for $C_{23}H_{27}N_2O_3$, 379.2016 ($M+H^+$); found, 379.2016.

(4a*RS*,5*SR*,10b*RS*)-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4h)

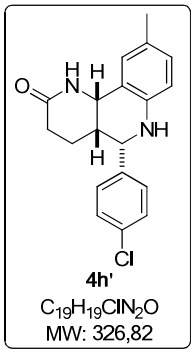


4h
$C_{19}H_{19}ClN_2O$
MW: 326,82

Following the general procedure A, the reaction of **1b**, *p*-toluidine and *p*-chlorobenzaldehyde, afforded a mixture of compounds **4h**-**4h'** (56%, **4h**/**4h'**, 5:8). After a flash chromatography purification using DCM/MeOH, compound **4h** was isolated as a white powder.
^{1}H-NMR (400 MHz, DMSO) δ: 7.90 (d, *J*= 3.1 Hz, 1H), 7.41-7.33 (m, 4H), 6.96 (s, 1H), 6.81 (dd, *J*= 1.7, 8.2 Hz, 1H), 6.54 (d, *J*= 8.1 Hz, 1H), 6.23 (d, *J*= 2.3 Hz, 1H), 5.75 (br s, 1H), 4.32 (dd, *J*= 2.5, 5.5 Hz, 1H), 3.99 (t, *J*= 3.7 Hz, 1H), 2.28-2.08 (m, 6H), 1.85-1.74 (m, 1H), 1.51-1.38 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO) δ: 169.6, 143.2, 140.8, 131.4, 128.9, 128.6, 128.3, 128.2, 123.9, 120.0, 113.1, 54.6,

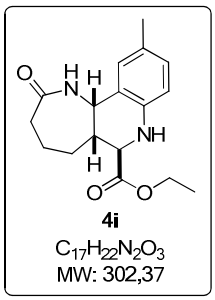
48.0, 36.0, 29.4, 22.3, 20.2 ppm. **IR** (KCl) ν_{max}: 3324, 3205, 3046, 2948, 1649, 1513, 1488, 1408, 1263, 1014, 831, 740, 579 cm^{-1}. **HRMS**: calcd for $C_{19}H_{20}ClN_2O$, 327.1259 ($M+H^+$); found, 327.1261.

(4a*RS*,5*RS*,10b*RS*)-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4h')



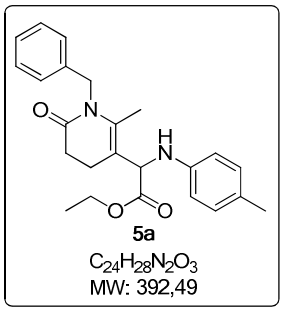
On further elution, compound **4h'** was isolated as a white powder. **^{1}H-NMR** (400 MHz, DMSO) δ: 8.39 (d, *J*= 4.3 Hz, 1H), 7.51-7.40 (m, 4H), 7.10 (s, 1H), 6.79 (d, *J*= 8.0 Hz, 1H), 6.57 (d, *J*= 8.1 Hz, 1H), 5.85 (s, 1H), 4.75 (t, *J*= 3.9 Hz, 1H), 4.70 (s, 1H), 2.21-2.09 (m, 4H), 1.96 (m, 2H), 1.51-1.37 (m, 1H), 1.2-1.12 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, DMSO) δ: 169.9, 141.3, 140.7, 131.4, 128.7, 128.1, 127.9, 127.8, 125.1, 122.0, 114.6, 56.6, 51.2, 37.0, 30.2, 20.3, 15.8 ppm. **IR** (KCl) ν_{max}: 3285, 3185, 3023, 2899, 1654, 1509, 1408, 1311, 1281, 1213, 1009, 819, 662, 541 cm^{-1}. **HRMS**: calcd for $C_{19}H_{20}ClN_2O$, 327.1259 ($M+H^+$); found, 327.1261.

(5a*RS*,6*SR*,11b*SR*)-ethyl 10-methyl-2-oxo-2,3,4,5,5a,6,7,11b-octahydro-1*H*-azepino[3,2-c]quinoline-6-carboxylate (4i)



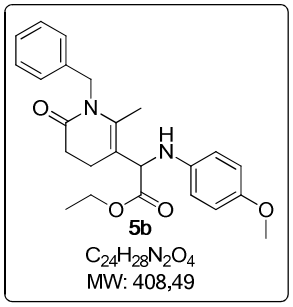
Following the general procedure A, the reaction of **1f**, *p*-toluidine and ethyl glyoxalate solution, afforded a mixture of compounds **4i**-**4i'** (35%, **4i**/**4i'**, 3:2). After flash chromatography purification, compound **4i** (temptative stereochemical assignment, based on analogies with related compounds in this series) was isolated as a white powder. On further elution, quinoline **11f** (29%) was isolated (see below).
^{1}H-NMR (500 MHz, MeOH) δ: 6.91-6.85 (m, 2H), 6.54 (d, *J*= 8.1Hz, 1H), 4.48 (d, *J*= 3.3 Hz, 1H), 4.27-4.16 (m, 2H), 3.86 (d, *J*= 5.8 Hz, 1H), 2.57-2.49 (m, 1H), 2.36-2.28 (m,1H), 2.26-2.16 (m, 4H), 1.92-1.61 (m, 5H), 1.31-1.27 (m, 3H) ppm. **^{13}C-NMR** (125 MHz, MeOH) δ: 180.6, 175.4, 141.9, 130.3, 127.9, 127.4, 120.2, 115.4, 62.4, 59.4, 51.8, 39.2, 37.3, 31.5, 22.0, 20.7, 14.6 ppm. **IR** (film) ν_{max} : 3327, 2924, 2847, 1732, 1656, 1502, 1451, 1361, 1297, 1201, 1028, 810 cm^{-1}. **HRMS**: calcd for $C_{17}H_{23}N_2O_3$, 303.1703 ($M+H^+$); found, 303.1701.

ethyl 2-(1-benzyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-(*p*-tolylamino)acetate (5a)



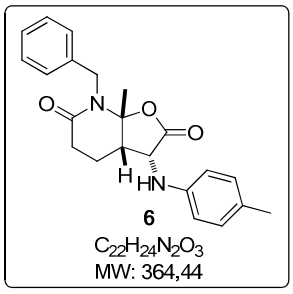
Following the general procedure A, the reaction of **1e**, *p*-toluidine and ethyl glyoxalate solution, afforded compound **5a** as a yellow oil (49%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.23-7.15 (m, 3H), 7.05-7.01 (m, 2H), 6.83 (d, *J*= 8.2 Hz, 2H), 6.34-6.29 (m, 2H), 5.12 (d, *J*= 16.3 Hz, 1H), 4.75-4.67 (m, 2H), 4.48 (br s, 1H), 4.17-4.08 (m, 2H), 2.39-2.29 (m, 2H), 2.16 (s, 3H), 2.11-2.07 (m, 2H), 1.98 (t, *J*= 1.4 Hz, 3H), 1.14 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.5, 170.7, 143.5, 138.0, 134.9, 129.8, 128.7, 127.3, 126.9, 126.1, 115.4, 113.5, 61.8, 57.2, 44.3, 31.8, 20.5, 19.5, 14.6, 14.1 ppm. **IR** (film) ν_{max}: 3368, 2954, 2902, 2821, 1732, 1670, 1513, 1185, 1028 cm^{-1}. **HRMS**: calcd for $C_{24}H_{28}N_2NaO_3$, 415.1992 ($M+Na^+$); found, 415.1983.

ethyl 2-(1-benzyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-((4-methoxyphenyl)amino)acetate (5b)



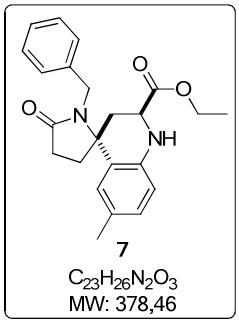
Following the general procedure A, the reaction of **1e**, 4-methoxyaniline and ethyl glyoxalate solution, afforded compound **5b** as a brown solid (10%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.22 (m, 3H), 7.10-7.05 (m, 2H), 6.69-6.64 (m ,2H), 6.44-6.39 (m, 2H), 5.20 (d, *J*= 16.4 Hz, 1H), 4.79-4.71 (m, 2H), 4,41 (br s, 1H), 4.26-4.11 (m, 2H), 3.72 (s, 3H), 2.43-2.35 (m, 2H), 2.19-2.12 (m, 2H), 2.05-2.01 (m, 3H), 1.20 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.5, 170.6, 152.5, 139.9, 138.0, 134.9, 128.7, 126.9, 126.0, 115.5, 114.9, 114.7, 61.7, 57.7, 55.7, 44.3, 31.7, 19.5, 14.5, 14.1 ppm. **IR** (film) ν_{max}: 3398, 2981, 2911, 1725, 1668, 1521, 1187, 803 cm^{-1}. **HRMS**: calcd for $C_{24}H_{28}N_2NaO_4$, 431.1941 (M+Na$^+$); found, 431.1940.

(3*RS*,3a*SR*,7a*RS*)-7-benzyl-3-(*p*-tolylamino)hexahydrofuro[2,3-b]pyridine-2,6-dione (6)



Following the general procedure A, the reaction of **1e**, *p*-toluidine and glyoxylic acid, afforded compound **6** as a yellow solid (37%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27-7.21 (m, 2H), 7.16-7.19 (m, 3H), 6.97 (d, *J*= 8.4 Hz ,2H), 6.51-6.46 (m, 2H), 5.10 (d, *J*= 16.0 Hz, 1H), 4.45 (dd, *J*= 3.0, 7.1 Hz, 1H), 4,38 (d, *J*= 16.0 Hz, 1H), 4.12 (d, *J*= 2.7 Hz, 1H), 2.99-2.80 (m, 1H), 2.53 (dt, *J*= 3.8, 17.1 Hz, 1H), 2.37-2.26 (m, 1H), 2.19 (s, 3H), 1.79-1.71 (m, 1H), 1.64 (s, 3H), 1.5-7-1.51 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.4, 170.1, 143.7, 138.1, 130.0, 128.6, 128.5, 127.0, 126.8, 113.0, 95.7, 57.8, 46.3, 45.7, 30.8, 27.5, 20.4, 18.1 ppm. **IR** (film) ν_{max}: 3372, 3026, 2917, 2853, 1777, 1666, 1521, 1162, 807 cm^{-1}. **HRMS**: calcd for $C_{22}H_{25}N_2O_3$, 365.1860 (M+H$^+$); found, 365.1853.

(2*RS*,2'*SR*)-ethyl 1-benzyl-6'-methyl-5-oxo-2',3'-dihydro-1'H-spiro[pyrrolidine-2,4'-quinoline]-2'-carboxylate (7)



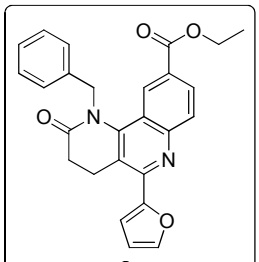
Following the general procedure A, the reaction of **1g**, *p*-toluidine and ethyl glyoxalate solution, afforded compound **7** as yellow powder (20%). Microwave promoted reaction: a solution of unsaturated lactam **1g** (1 mmol), *p*-toluidine (1 mmol), ethyl glyoxalate (1 mmol) and $Sc(OTf)_3$ (0.2 mmol) in dry CH_3CN (2 mL) was placed in sealed tube. The reaction mixture was irradiated in a monomode CEM apparatus for 5 minutes at 80ºC and 100 W. The reaction mixture was diluted with 6 mL of EtOAc, a saturated aqueous $NaHCO_3$ solution (10 mL) was added and the mixture extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The reaction mixture containing spiro adducts **7**-**7'**(60%, **7**/**7**' 1:1) was purified with flash chromatography using hexane/ethyl acetate mixtures and compound **7** was isolated as a yellow powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.22-7.08 (m, 5H), 6.87-6.83 (m, 1H), 6.58 (d, *J*= 1.2 Hz, 1H), 6.51 (d, *J*= 8.1 Hz, 1H), 4.77 (d, *J*= 15.7 Hz, 1H), 4.20 (br s, 1H), 4.13-4.03 (m, 2H), 3.80 (t, *J* = 5.3 Hz, 1H), 3.69 (d, *J*= 15.7 Hz, 1H), 2.58-2.51 (m, 2H), 2.28 (dd, *J*=

5.8, 13 Hz, 1H), 2.13-1.90 (m, 6H), 1.17 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 176.0, 173.2, 141.2, 138.6, 129.8, 128.4, 127.8, 127.4, 127.0, 126.2, 122.1, 115.5, 63.3, 61.4, 52.1, 44.4, 36.1, 35.4, 29.4, 20.6, 14.1 ppm. **IR** (film) ν_{max}: 3319, 2972, 2922, 1734, 1673, 1508, 1026 cm^{-1}. **HRMS**: calcd for $C_{23}H_{27}N_2O_3$, 379.2016 ($M+H^+$); found, 379.2008.

General procedure B. Synthesis of compounds 8, 9 and 10.

To a solution of compound **4** (1 mmol) in 15 mL of $CHCl_3$, DDQ (2 mmol) was added, and the mixture was stirred 24 h in an open vessel at room temperature. An aqueous saturated $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The reaction mixture was purified with flash chromatography (hexane- EtOAc) to afford the desired product.

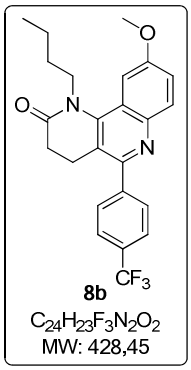
ethyl 1-benzyl-5-(furan-2-yl)-2-oxo-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridine-9-carboxylate (8a)



8a
$C_{26}H_{22}N_2O_4$
MW: 426,46

Following the general procedure B, the oxidation of **4b**, afforded compound **8a** as brownish solid (69%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, *J*= 1.7 Hz, 1H), 8.25 (dd, *J*= 1.7, 8.8 Hz, 1H), 8.19-8.11 (m, 1H), 7.67-7.65 (m, 1H), 7.25-7.16 (m, 4H), 7.12-7.07 (m, 2H), 6.63 (dd, *J*= 1.8, 3.4 Hz, 1H), 5.37 (s, 2H), 4.35 (q, *J*= 7.1 Hz, 2H), 3.34-3.29 (m, 2H), 2.74-2.69 (m, 2H), 1.35 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.6, 166.1, 144.6, 137.2, 130.4, 129.2, 129.2, 128.8, 128.2, 128.0, 127.8, 127.7, 127.4, 126.2, 121.5, 119.3, 114.1, 114.1, 112.3, 61.6, 52.8, 32.5, 22.7, 14.6 ppm. **IR** (film) ν_{max}: 3353, 3110, 2969, 1700, 1566, 1431, 1380, 1265, 1143, 746 cm^{-1}. **HRMS**: calcd for $C_{26}H_{23}N_2O_4$, 427.1652 ($M+H^+$); found, 427.1644.

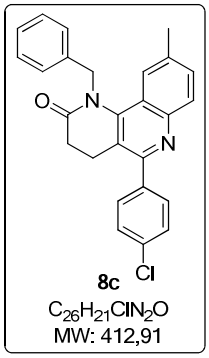
butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8b)



8b
$C_{24}H_{23}F_3N_2O_2$
MW: 428,45

Following the general procedure B, the oxidation of **4e**, afforded compound **8b** as a purple solid (84%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, *J*= 9.2 Hz, 1H), 7.76 (s, 4H), 7.38 (dd, *J*= 2.7, 9.2 Hz, 1H),7.26 (br s, 1H), 7.10 (d, *J*= 2.7 Hz, 1H), 4.25-4.19 (m, 2H), 3.96 (s, 3H), 3.00-2.95 (m, 2H), 2.60-2.54 (m, 2H), 1.67-1.58 (m, 2H), 1.30-1.19 (m, 2H), 0.85 (t, *J*= 7.4 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 173.4, 157.9, 154.2, 145.8, 144.8, 144.8, 143.1, 143.1, 132.2, 131.2, 130.8, 129.8, 125.7, 125.7, 125.6, 122.5, 122.4, 121.5, 101.2, 55.9, 48.2, 33.4, 30.9, 24.0, 20.3, 13.9 ppm (only absortion lines are listed, no multiplicity had been assigned to carbon signals due to severe overlapping). **IR** (film) ν_{max}: 2960, 1688, 1618, 1572, 1495, 1324, 1068, 848, 816. **HRMS**: calcd for $C_{24}H_{24}F_3N_2O_2$, 429.1784 ($M+H^+$); found, 429.1782.

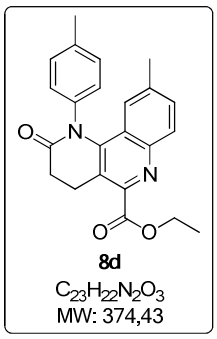
benzyl-5-(4-chlorophenyl)-9-methyl-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8c)



8c
$C_{26}H_{21}ClN_2O$
MW: 412,91

Following the general procedure B, the oxidation of **4f**, afforded compound **8c** as a white solid (10%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, *J*= 8.6 Hz, 1H), 7.65 (s, 1H), 7.56-7.44 (m, 5H), 7.31- 7.23 (m, 3H), 7.17-7.13 (m, 2H), 5.32 (s, 2H), 2.92-2.86 (m, 2H), 2.64-2.58 (m, 2H), 2.42 (s, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 172.9, 156.0, 147.2, 146.3, 137.7, 136.3, 134.9, 131.7, 131.6, 130.5, 130.1, 128.6, 128.5, 127.4, 127.3, 122.0, 121.4, 120.0, 52.3, 32.8, 23.6, 21.9 ppm. **IR** (film) ν_{max}: 3372, 3058, 2917, 1687, 1553, 1482, 1386, 1283, 1194, 1098, 1014, 829, 720 cm^{-1}. **HRMS**: calcd for $C_{26}H_{22}ClN_2O$, 413.1415 ($M+H^+$); found, 413.1410. On further elution, quinoline **11c** (6%) was isolated (see below).

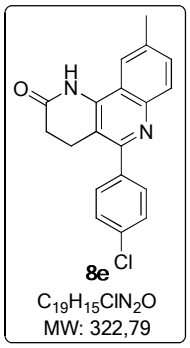
ethyl 9-methyl-2-oxo-1-(*p*-tolyl)-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridine-5-carboxylate (8d)



8d
$C_{23}H_{22}N_2O_3$
MW: 374,43

Following the general procedure B, the oxidation of **4g**, afforded compound **8d** as a yellowish solid (20%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.0 (d *J*= 8.6 Hz, 1H), 7.37 (dd, *J*= 1.6, 8.6 Hz, 1H), 7.19-7.06 (m, 4H), 7.05 (s, 1H), 4.55 (q, *J*= 7.2 Hz, 2H), 3.42-3.35 (m, 2H), 2.86-2.79 (m, 2H), 2.36 (s, 3H), 2.17 (s, 3H); 1.50 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 170.9, 170.8, 165.1, 156.5, 138.0, 137.9, 137.5, 137.3, 132.3, 129.7, 129.1, 127.0, 123.2, 121.5, 120.7, 62.8, 32.5, 22.1, 22.0, 21.1, 14.3 ppm. **IR** (film) ν_{max} 3374, 2915, 1706, 1375, 1050, 926 cm^{-1}. **HRMS**: calcd for $C_{23}H_{23}N_2O_3$, 375.1703 ($M+H^+$); found, 375.1700.

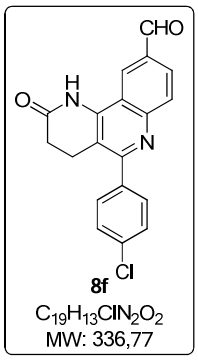
5-(4-chlorophenyl)-9-methyl-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8e)



8e
$C_{19}H_{15}ClN_2O$
MW: 322,79

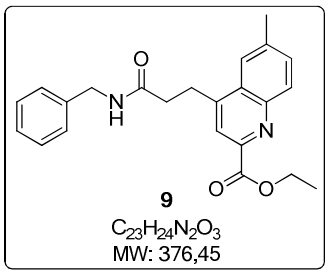
Following the general procedure B, the oxidation of **4h**, afforded compound **8e** as a white solid (22%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.59 (br s, 1H), 8.00 (d, *J*= 8.6 Hz, 1H), 7.59 (s, 1H), 7.55 (dd, *J*= 1.6, 8.7 Hz, 1H), 7.53-7.43 (m, 4H), 3.13-3.06 (m, 2H), 2.71-2.64 (m, 2H), 2.57 (s, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.3, 156.8, 156.8, 146.1, 140.2, 137.2, 134.9, 132.3, 130.5, 130.3, 128.9, 117.9, 116.7, 112.4, 30.8, 23.5, 22.4 ppm. **IR** (film) ν_{max}: 3340, 3212, 2923, 1681, 1597, 1488, 1328, 1207, 1014, 867, 809 cm^{-1}. **HRMS**: calcd for $C_{19}H_{16}ClN_2O$, 323.0946 ($M+H^+$); found, 323.0943.

5-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydrobenzo[h]quinoline-9-carbaldehyde (8f)



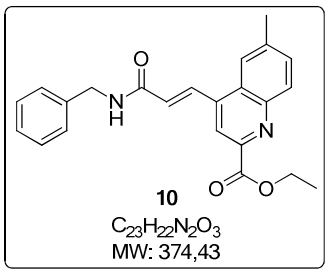
Following the general procedure B, the oxidation of **4h**, afforded compound **8f** as a white solid (40%).
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.24 (s, 1H), 9.49 (br s, 1H), 8.63 (s, 1H), 8.22 (br s, 2H), 7.61-7.50 (m, 4H), 3.25-3.18 (m, 2H), 2.82-2.75 (m, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 191.1, 171.4, 160.3, 149.9, 142.4, 137.7, 135.4, 134.1, 131.5, 130.3, 128.8, 127.4, 125.2, 116.4, 113.3, 30.4, 23.3 ppm. **IR** (film) ν_{max}: 3362, 2910, 2361, 2325, 1704, 1690, 1680, 1596, 1207 cm^{-1}. **HRMS**: calcd for $C_{19}H_{14}ClN_2O_2$, 337.0738 ($M+H^+$); found, 337.0735.

ethyl 4-(3-(benzylamino)-3-oxopropyl)-6-methylquinoline-2-carboxylate (9)



Following the general procedure B, the oxidation of **7**, afforded compound **9** as a yellow powder (21%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, *J*= 8.7 Hz, 1H), 7.91 (s, 1H), 7.78 (s, 1H), 7.52 (dd, *J*= 1.7, 8.7 Hz, 1H), 7.24-7.07 (m, 5H), 5.70 (br s, 1H), 4.45 (q, *J*= 7.1 Hz, 2H), 4.36 (d, *J*= 5.7 Hz, 2H), 3.47-3.39 (m, 2H), 2.65-2.59 (m, 2H), 2.54 (s, 3H), 1.40 (t, J= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.0, 165.6, 147.4, 147.0, 146.3, 139.0, 137.9, 132.2, 131.3, 128.7, 128.3, 127.8, 127.6, 122.1, 120.4, 62.1, 43.8, 36.2, 27.6, 22.1, 14.4 ppm. **IR** (film) ν_{max}: 3302, 3065, 3026, 2911, 2847, 1713, 1636, 1591, 1540, 1367, 1246, 1214, 1021, 823, 784 cm^{-1}. **HRMS**: calcd for $C_{23}H_{25}N_2O_3$ 377.186 ($M+H^+$); found, 377.1854.

ethyl 4-(3-(benzylamino)-3-oxoprop-1-en-1-yl)-6-methylquinoline-2-carboxylate (10)

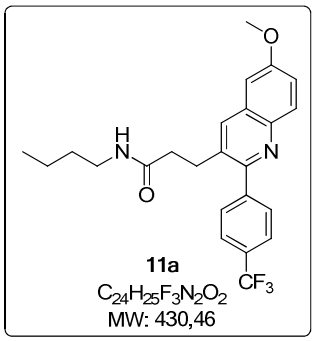


Following the general procedure B, the oxidation of **7**, afforded compound **10** as a yellow powder (17%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.37 (d, *J*= 15.4 Hz, 1H), 8.18 (s, 1H), 8.14 (d, *J*= 8.7, 1H), 7.92 (s, 1H), 7.57 (dd, *J*= 1.7, 8.7 Hz, 1H), 7.31-7.20 (m, 5H), 6.64 (d, *J*= 15.3 Hz, 1H), 6.10 (br s, 1H), 4.57 (d, *J*= 5.78 Hz, 2H), 4.47 (q, *J*= 7.11, 2H), 2.52 (s, 3H), 1.41 (t, *J*= 7.13 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 165.5, 164.5, 147.0, 146.8, 140.9, 139.7, 137.7, 135.9, 132.8, 131.1, 128.8, 128.0, 127.8, 127.3, 127.1, 122.3, 117.9, 62.3, 44.1, 22.1, 14.4 ppm. **IR** (film) ν_{max}: 3276, 3052, 2949, 2917, 1720, 1656, 1617, 1451, 1374, 1258, 1220, 1111, 1015, 977, 816 cm^{-1}. **HRMS**: calcd for $C_{23}H_{23}N_2O_3$, 375.1703 ($M+H^+$); found, 375.1695.

General procedure C. Synthesis of compounds 11a and b.

To a solution of compound **4** (1 mmol) in CH_3CN/H_2O (1:1, 6 mL), TFA (2 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with an aqueous saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue which was purified by flash chromatography (hexane – ethyl acetate) to afford the desired product.

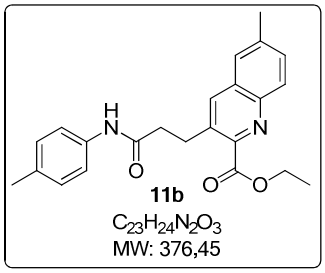
3-(6-methoxy-2-(4-(trifluoromethyl)phenyl)quinolin-3-yl)-*N*-pentylpropanamide (11a)



11a
$C_{24}H_{25}F_3N_2O_2$
MW: 430,46

Following the general procedure C, the treatment of **4e** afforded compound **11a** as a white solid (49%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.97 (d, *J*= 9.2 Hz, 1H), 7.70 (dd, *J*= 8.0, 30.7 Hz, 4H), 7.34 (dd, *J*= 2.8, 9.2 Hz, 1H), 7.07 (d, *J*= 2.8 Hz, 1H), 5.18 (br s, 1H), 3.94 (s, 3H), 3.17-3.10 (m, 4H), 2.28 (t, *J*= 7.5 Hz, 2H), 1.37-1.27 (m, 2H), 1.24-1.13 (m, 2H), 0.82 (t, *J*= 7.3 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$) ppm. δ: 171.1, 158.2, 156.1, 144.3, 142.8, 135.5, 132.0, 130.6, 130.4, 130.1, 129.2, 128.7, 125.5 (q, J= 3.7 Hz), 122.7, 122.4, 104.4, 55.6, 39.2, 36.9, 31.6, 28.5, 19.9, 13.6 ppm. **IR** (film) ν_{max}: 3303, 2962, 2932, 2866, 1641, 1552, 1491, 1324, 1229, 1121, 1067, 853 cm^{-1}. **HRMS**: calcd for $C_{24}H_{26}F_3N_2O_2$, 431.1941 ($M+H^+$); found, 431.1935.

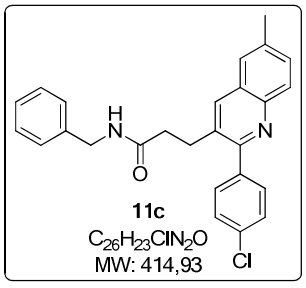
ethyl 6-methyl-3-(3-oxo-3-(*p*-tolylamino)propyl)quinoline-2-carboxylate (11b)



11b
$C_{23}H_{24}N_2O_3$
MW: 376,45

Following the general procedure C, the treatment of **4g** afforded compound **11b** as a white solid (81%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.07-8.03 (m, 2H), 7.59-7.51 (m, 3H), 7.36 (d, *J*= 8.3 Hz, 2H), 7.09 (d, *J*= 8.3 Hz, 2H), 4.55 (q, *J*= 7.1, 2H), 3.40-3.34 (m, 2H), 2.79-2.73 (m, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.49 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 206.9, 170.1, 167.0, 148.0, 144.8, 138.7, 137.5, 135.4, 133.8, 133.0, 132.2, 129.5, 129.4, 125.9, 119.9, 62.3, 39.5, 30.9, 21.8, 20.8, 14.3 ppm. **IR** (film) ν_{max}: 3315, 2962, 2924, 2853, 1720, 1649, 1598, 1534, 1502, 1284, 1233, 1181, 1073, 810 cm^{-1}. **HRMS**: calcd for $C_{23}H_{25}N_2O_3$ 377.1860 ($M+H^+$); found, 377.1866.

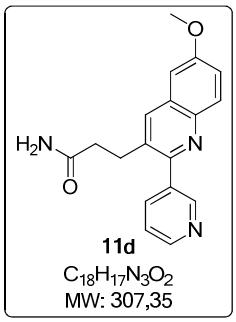
N-benzyl-3-(2-(4-chlorophenyl)-6-methylquinolin-3-yl)propanamide (11c)



11c
$C_{26}H_{23}ClN_2O$
MW: 414,93

Following the general procedure B, during the oxidation of **4f** (see above), under DDQ treatment, compound **11c** was isolated as a white solid (6%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.00 (br s, 2H), 7.54-7.50 (m, 2H), 7.49-7.41 (m, 4H), 7.23-7.17 (m, 3H), 7.09-7.03 (m, 2H), 5.44 (br s, 1H), 4.32 (d, *J*= 5.7 Hz, 2H), 3.17 (t, *J*= 7.5 Hz, 2H), 2.53 (s, 3H), 2.32 (t, *J*= 7.5 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 171.2, 158.1, 145.4, 138.1, 137.0, 136.3, 135.9, 134.7, 132.0, 131.9, 130.4, 128.9, 128.9, 128.5, 127.8, 127.8, 127.7, 126.1, 43.8, 36.9, 28.9, 21.9 ppm. **IR** (film) ν_{max}: 3276, 2923, 1661, 1540, 1431, 1251, 1085, 1008, 835 cm^{-1}. **HRMS**: calcd for $C_{26}H_{24}ClN_2O$, 415.1572 ($M+H^+$); found, 415.1569.

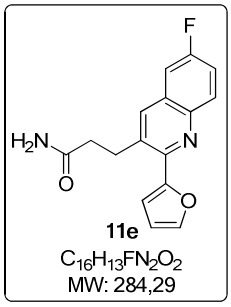
3-(6-methoxy-2-(pyridin-3-yl)quinolin-3-yl)propanamide (11d)



Following the general procedure A, the reaction of **1d**, 4-methoxyaniline and nicotinaldehyde (see above), and after a flash chromatography using DCM/MeOH compound **11d** was isolated as a white powder (19%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 8.72-8.62 (m, 1H), 8.04 (s, 1H), 7.99-7.89 (m, 2H), 7.44 (dd, *J*= 5.0, 7.5 Hz, 1H), 7.35 (dd, *J*= 2.8, 9.2 Hz, 1H), 7.08 (d, *J*= 2.7 Hz, 1H), 5.59 (br s, 1H), 5.48 (br s, 1H), 3.95 (s, 3H), 3.13 (t, *J*= 7.5 Hz, 2H), 2.40 (t, *J*= 7.5 Hz, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 173.5, 158.3, 154.0, 149.3, 148.9, 142.8, 136.8, 136.5, 135.5, 132.2, 130.5, 128.8, 123.5, 122.6, 104.4, 55.6, 35.9, 28.1 ppm. **IR** (film) ν_{max}: 3334, 3167, 2917, 1681, 1617, 1489, 1412, 1342, 1246, 1156, 1028, 912, 829 cm^{-1}. **HRMS**: calcd for $C_{18}H_{18}N_3O2$, 308.1394 ($M+H^+$); found, 308.1392.

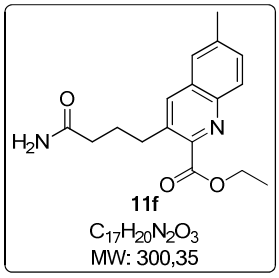
3-(6-fluoro-2-(furan-2-yl)quinolin-3-yl)propanamide (11e)



Following the general procedure A, the reaction of **1d**, *p*-fluoroaniline and 2-furaldehyde (see above), and after a flash chromatography using DCM/MeOH, compound **11e** was isolated as a pink powder (14%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (dd, *J*= 5.3, 9.2 Hz, 1 H), 7.90 (s, 1H), 7.54 (dd, *J*= 0.7, 1.7 Hz, 1H), 7.36-7.30 (m, 1H), 7.26 (dd, *J*= 2.8, 8.8 Hz, 1H), 7.10 (dd, *J*= 0.6, 3.4 Hz, 1H), 6.51 (dd, *J*= 1.8, 3.4 Hz, 1H), 5.24 (br s, 2H), 3.38-3.34 (m, 2H), 2.52-2.46 (m, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ:173.8, 143.8, 143.6, 137.0, 136.9, 131.9, 131.6, 131.5, 119.8, 119.6, 112.2, 112.0, 110.1, 109.9, 36.2, 29.2 ppm. **IR** (film) ν_{max}: 3404, 3359, 3289, 3166, 2924, 2646, 1662, 1623, 1502, 1476, 1406, 1220, 1162, 1002, 900, 823, 746 cm^{-1}. **HRMS**: calcd for $C_{16}H_{14}FN_2O_2$, 285.1034 ($M+H^+$); found, 285.1036.

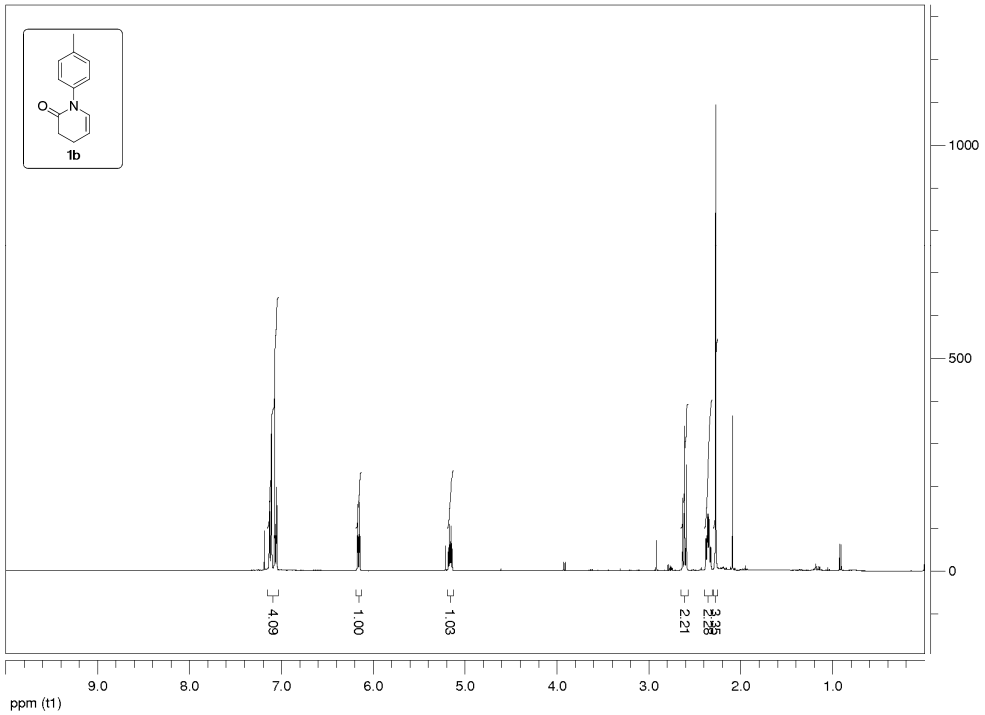
ethyl 3-(4-amino-4-oxobutyl)-6-methylquinoline-2-carboxylate (11f)

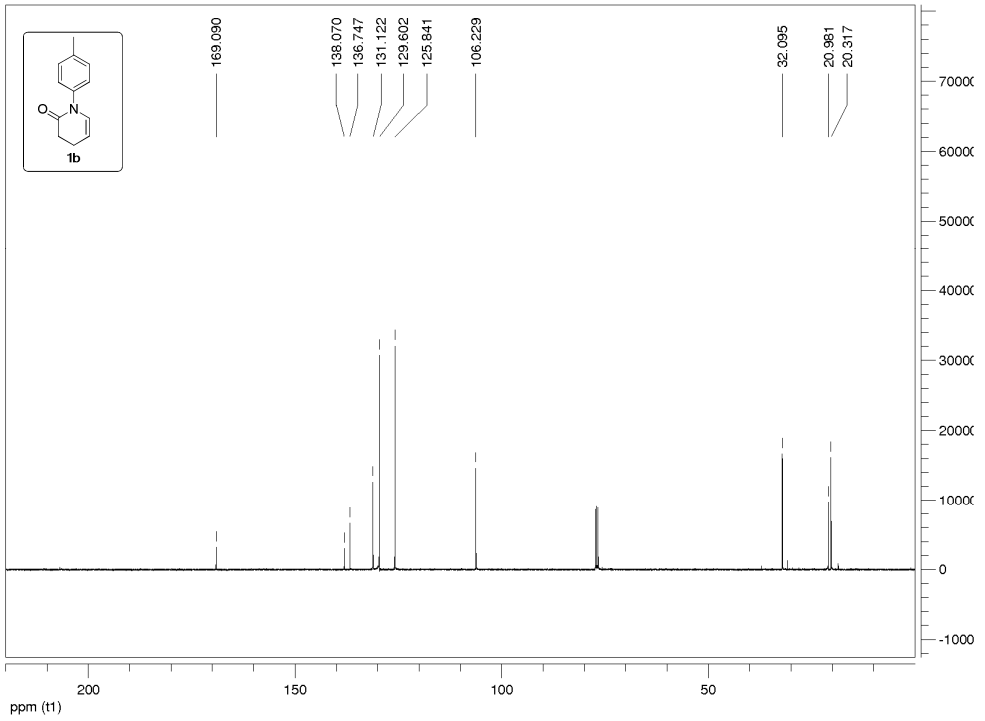


Following the general procedure A, the reaction of **1f**, *p*-toluidine and ethyl glyoxalate solution (see above), and after a flash chromatography, compound **11f** was isolated as a white powder (29%).

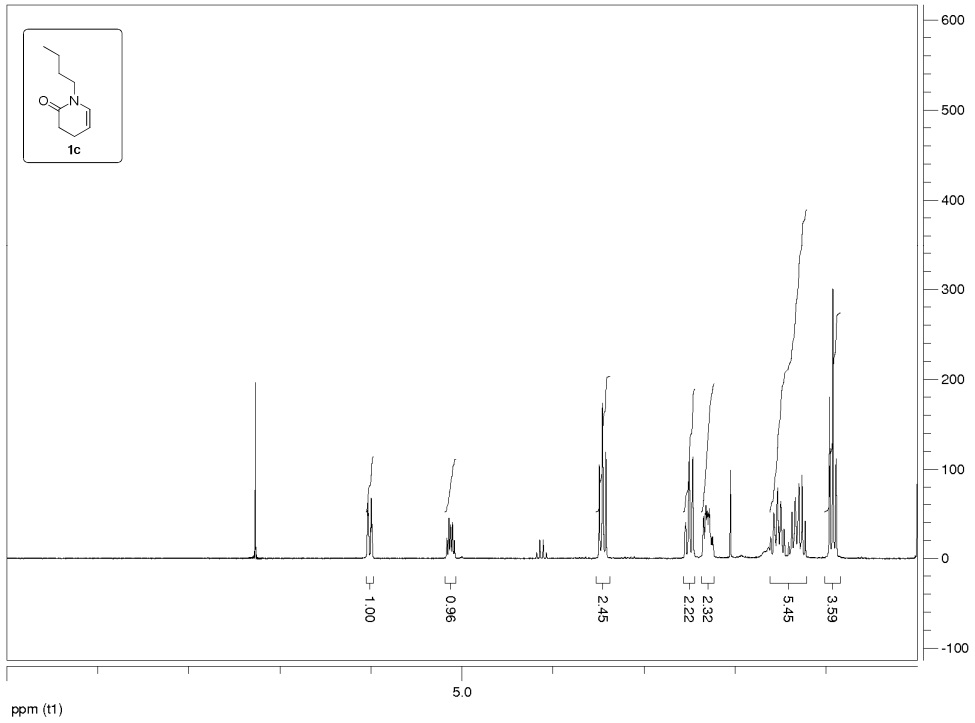
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, *J*= 9.4 Hz, 1H), 8.0 (s, 1H), 7.58-7.53 (m, 2H), 5.61 (br s, 1H), 5.28 (br s, 1H), 4.52 (q, *J*= 7.1 Hz, 2H), 3.07-3.02 (m, 2H), 2.54 (s, 3H), 2.33 (t, *J*= 7.2, 2H), 2.11-2.02 (m, 2H), 1.47 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 174.5, 139.0, 138.2, 138.1, 133.6, 132.8, 129.1, 128.6, 128.6, 128.6, 125.8, 62.5, 35.0, 32.0, 26.7, 21.8, 14.3 ppm. **IR** (film) ν_{max}: 3391, 3302, 3212, 2911, 2811, 2817, 1726, 1656, 1617, 1412, 1297, 1181, 1079, 823 cm^{-1}. **HRMS**: calcd for $C_{17}H_{21}N_2O_3$ 301.1546 ($M+H^+$); found, 301.1540.

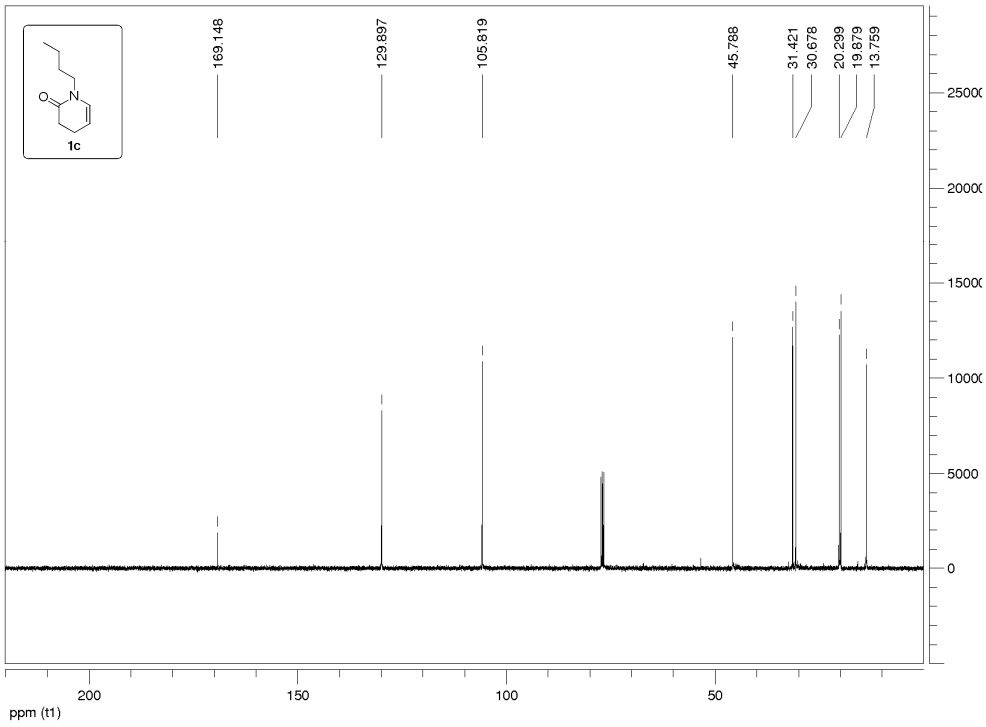
1-(*p*-tolyl)-3,4-dihydropyridin-2(1*H*)-one (1b):



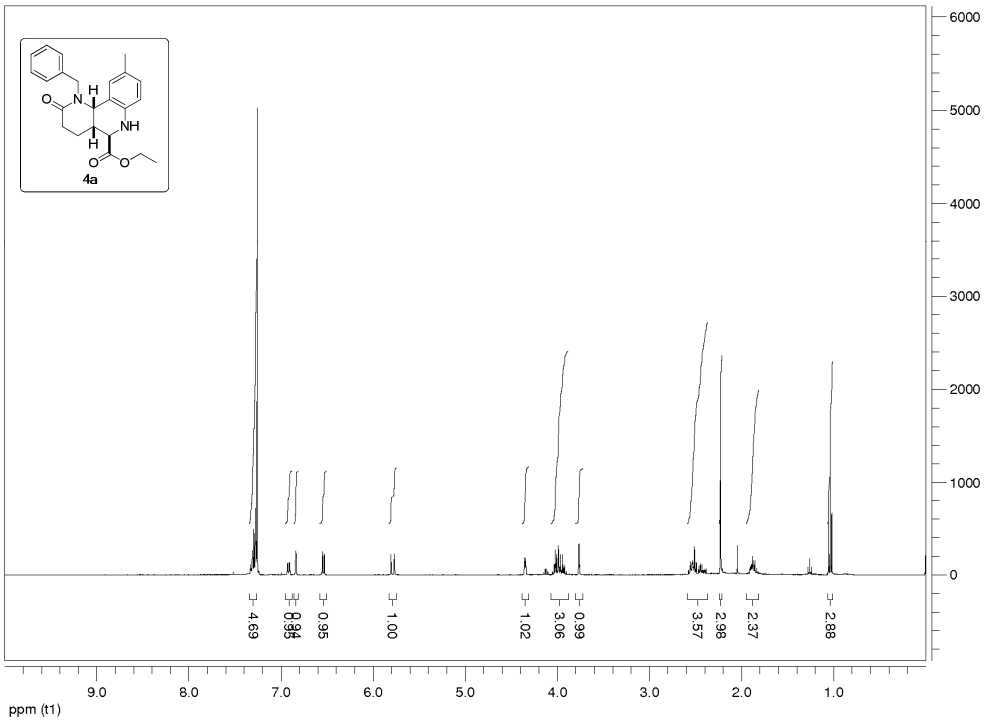


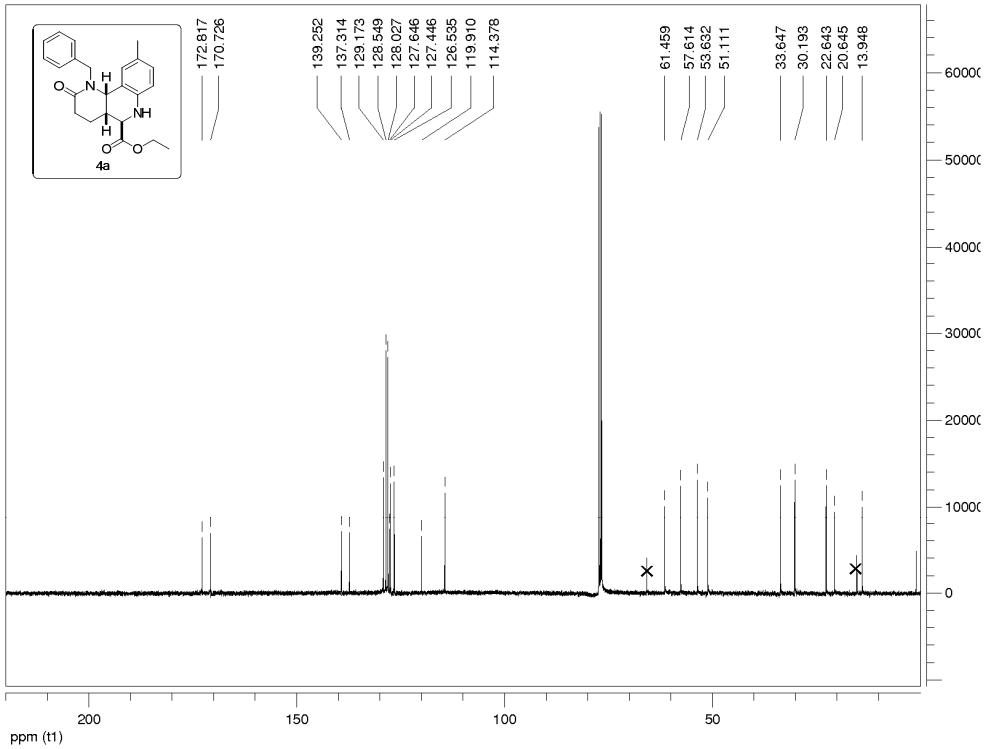
1-butyl-3,4-dihydropyridin-2(1*H*)-one (1c):

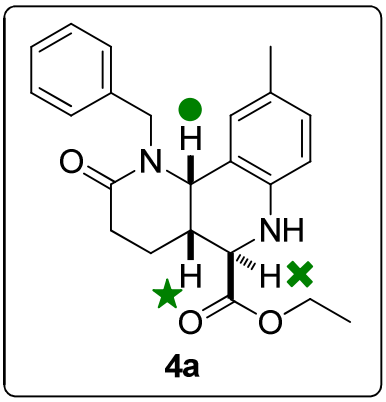




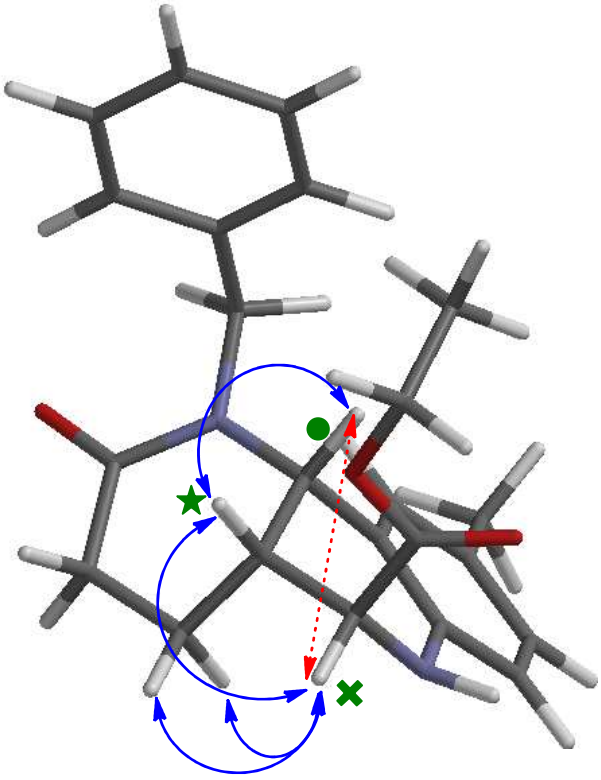
(4a*RS*,5*SR*,10b*RS*)-ethyl 1-benzyl-9-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4a):



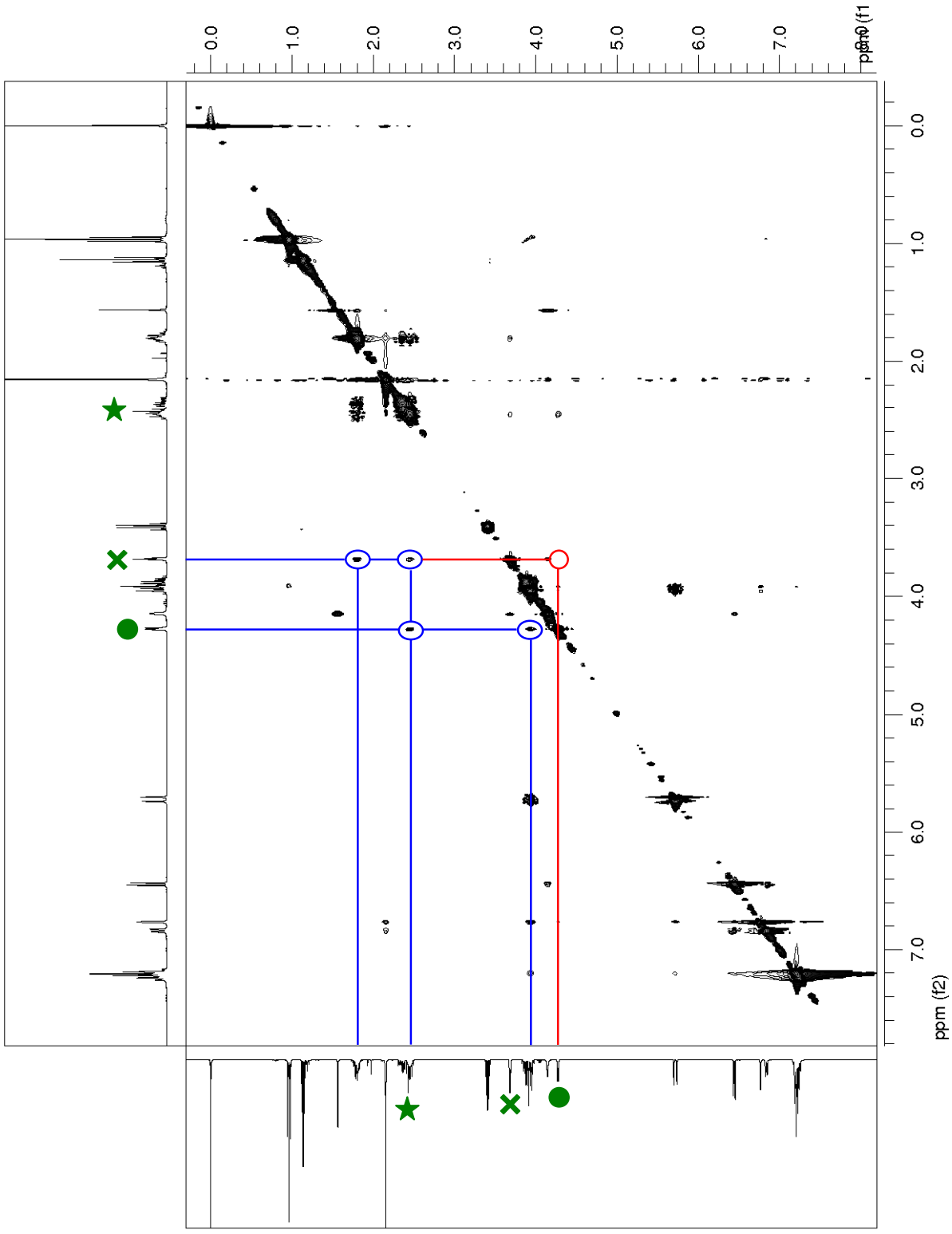




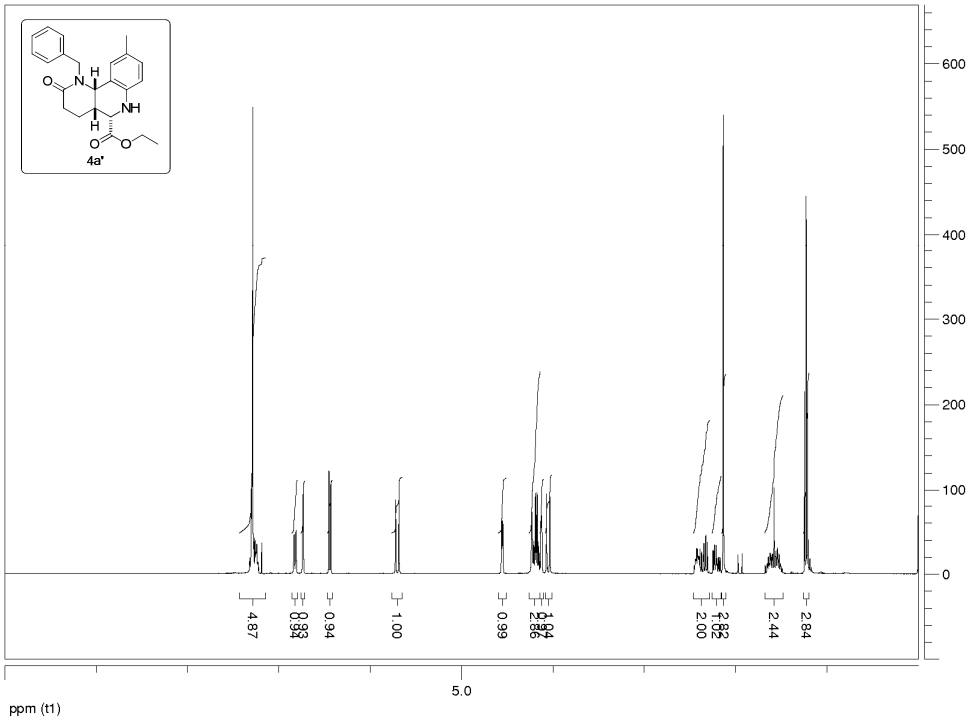
4a

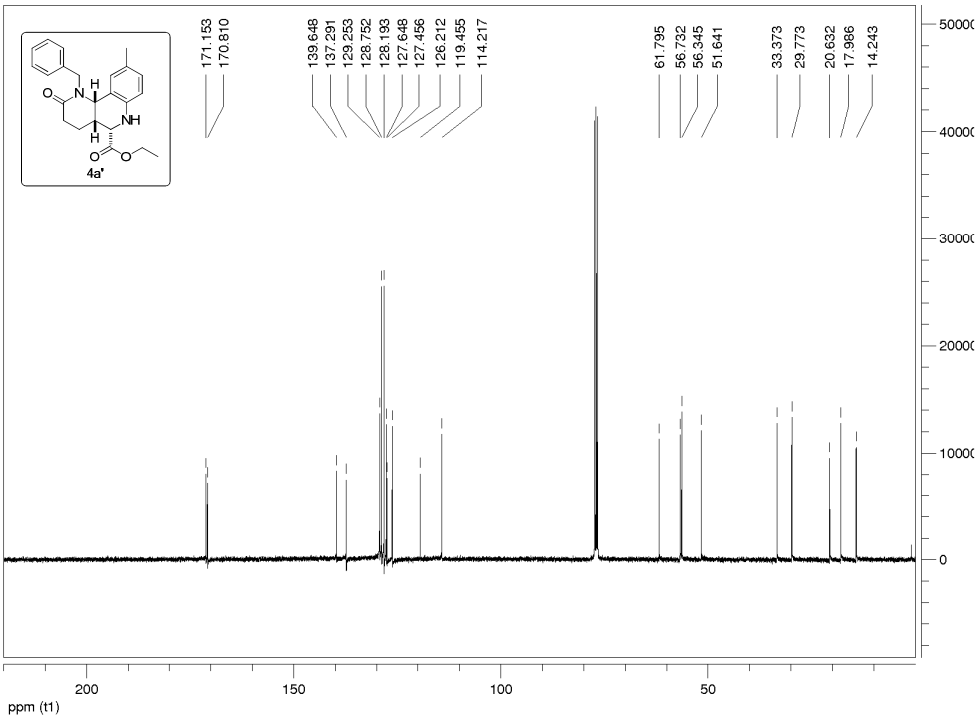


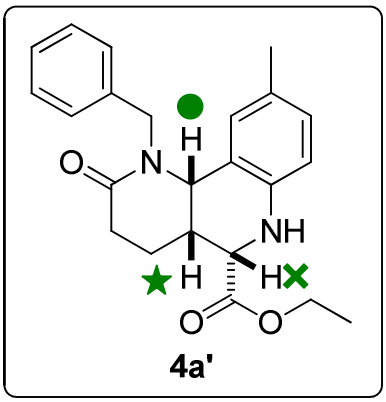
In this 3D optimized structure (MM94F + AM1), the NOE's correlations observed in NMR NOESY experiments are shown (blue arrows). The distance between protons ● and **X** is too long (3.9 Å) to observe a NOE correlation (red arrow), confirming the *trans* -relationship of these nuclei. The blue arrows correspond to shorter distances.


0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (f1)
ppm (f2)

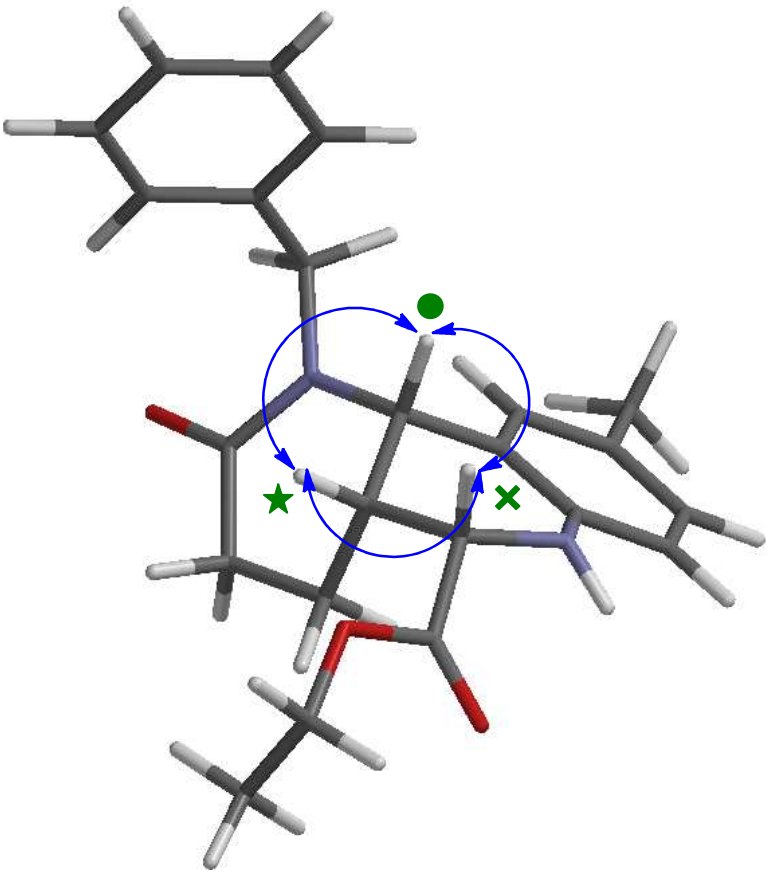
(4a*RS*,5*RS*,10b*RS*)-ethyl 1-benzyl-9-methyl-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4a'):



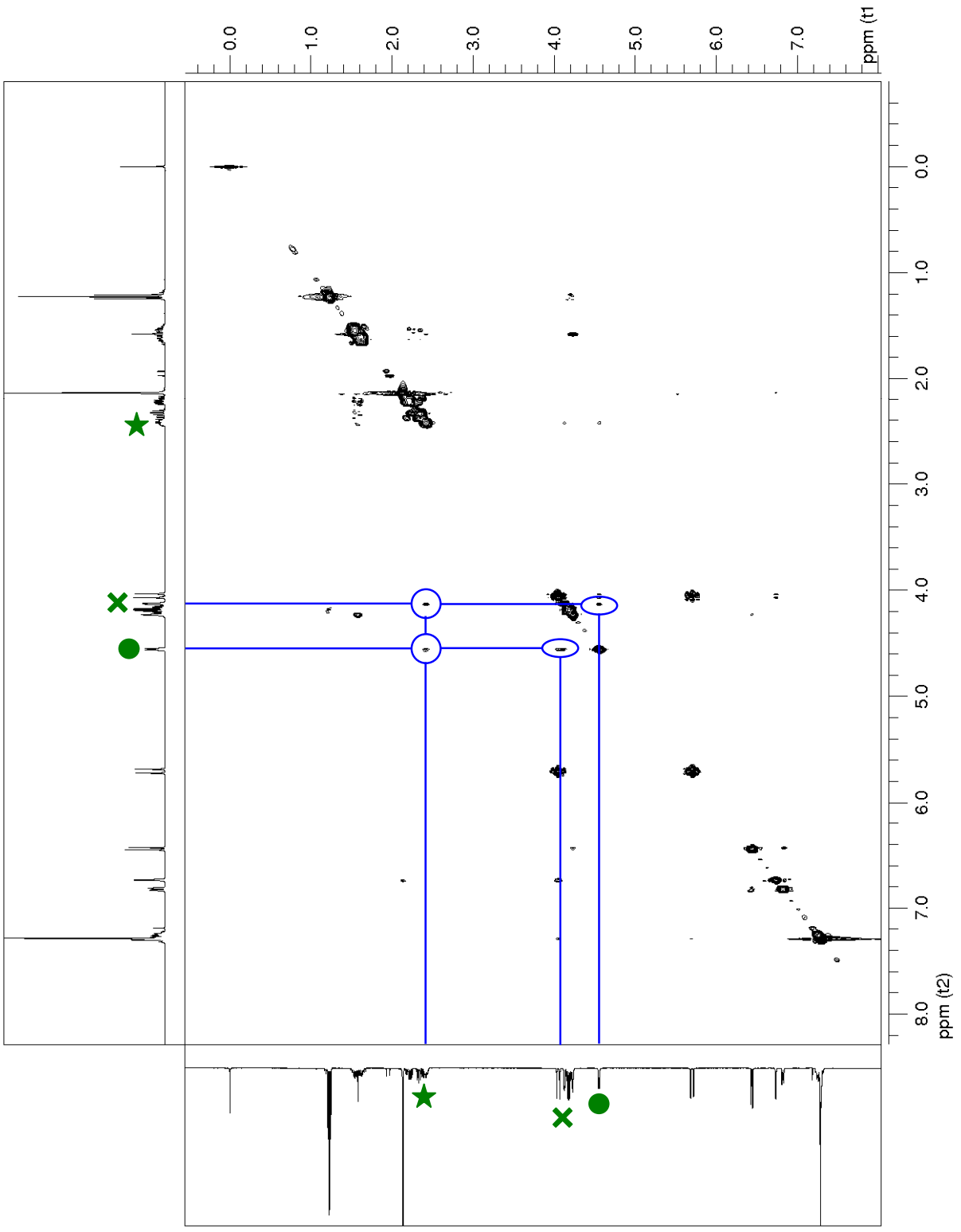




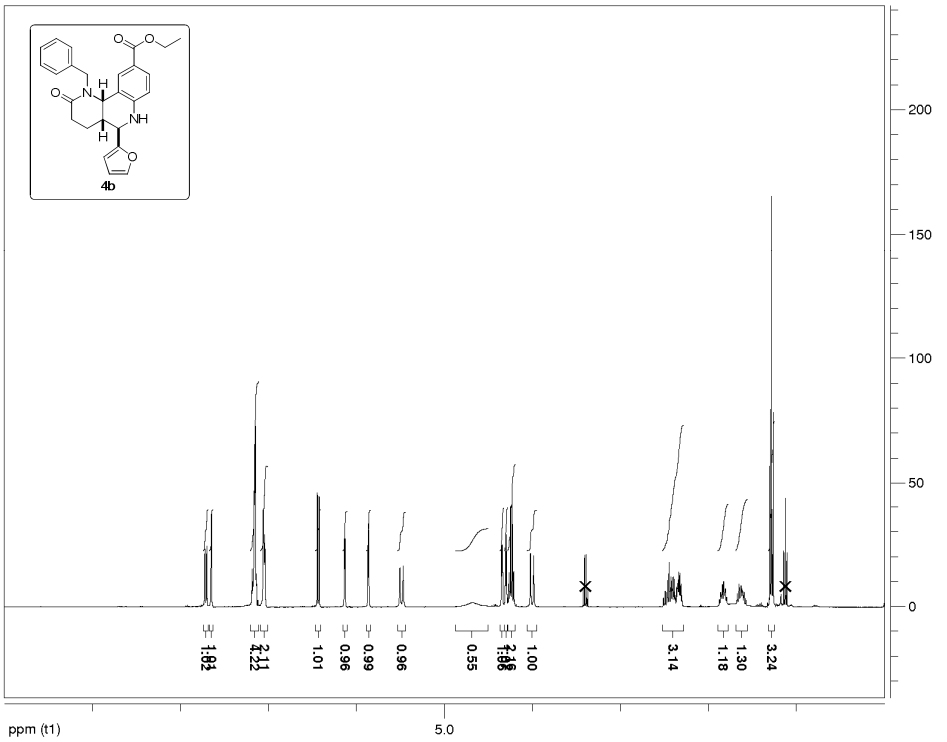
4a'

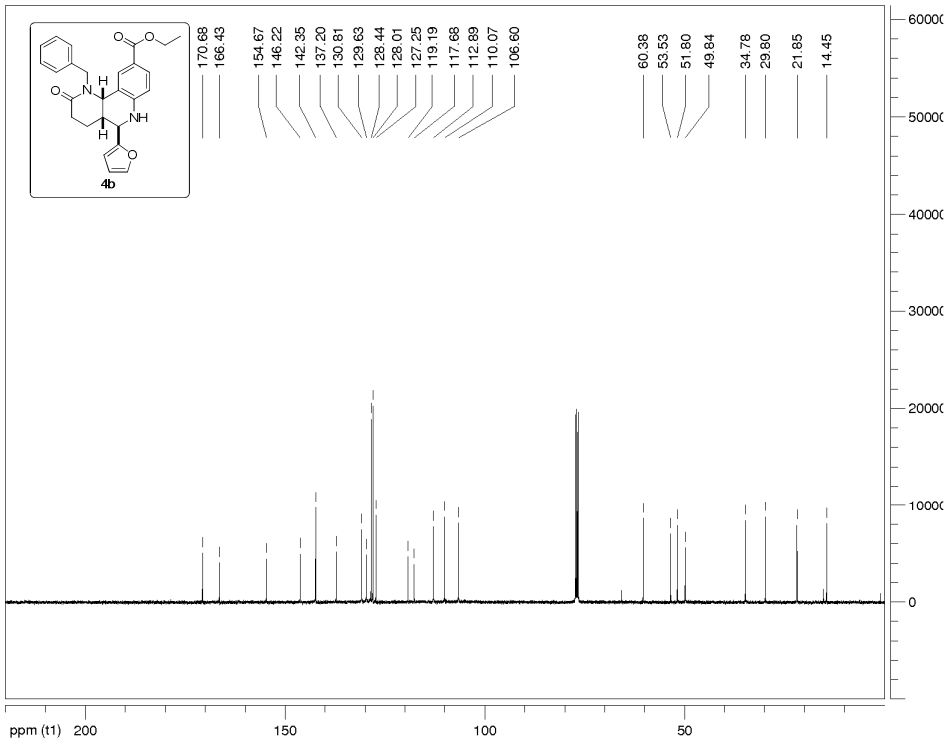


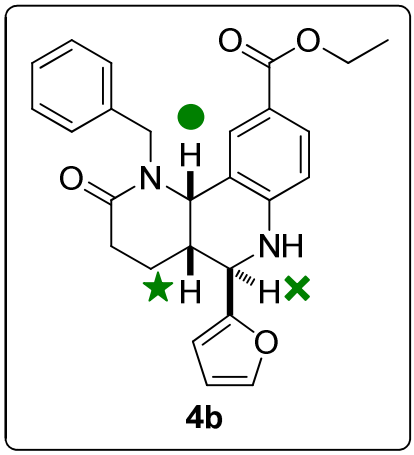
In this 3D optimized structure (MM94F + AM1), the NOE's correlations observed in NMR NOESY experiments are shown (blue arrows). The distance between protons ● and **X** is in this stereoisomer much shorter (2.6 Å) and allows the observation of a NOE correlation (blue arrow), confirming the *cis* -relationship of these nuclei.

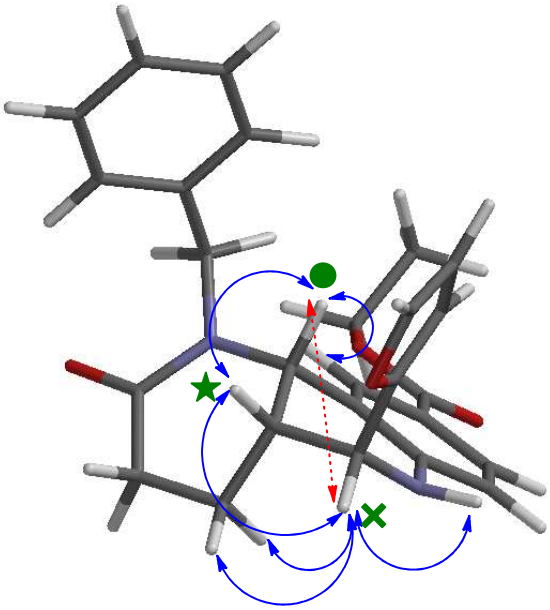

0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t1
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t2)

(4a*RS*,5*RS*,10b*RS*)-ethyl 1-benzyl-5-(furan-2-yl)-2-oxo-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-9-carboxylate (4b):

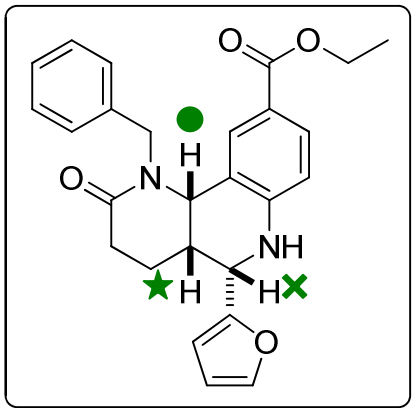


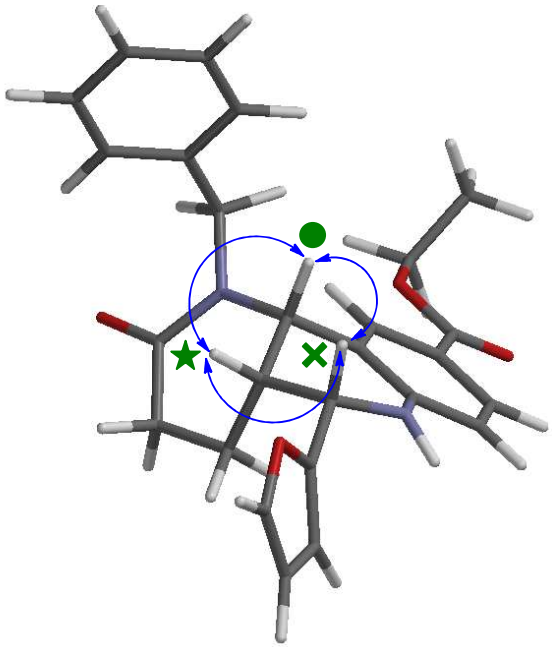




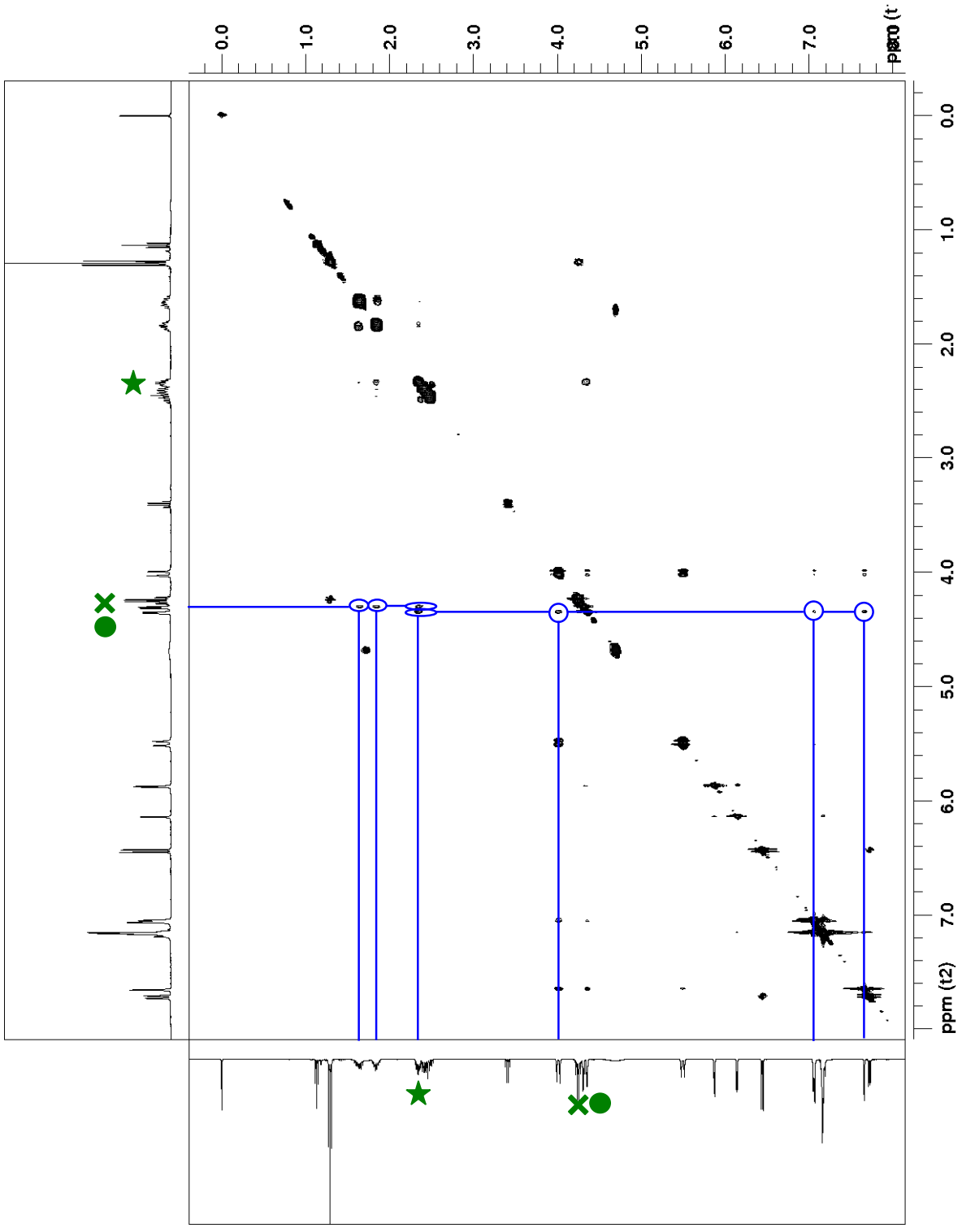


In this 3D optimized structure (MM94F + AM1), the NOE's correlations observed in NMR NOESY experiments are shown (blue arrows). The distance between protons ● and **X** is too long (around 3.9 Å) to observe a NOE correlation (red arrow), confirming the *trans* relationship of these nuclei. The blue arrows correspond to shorter distances. The rest of correlations are in agreement with the proposed stereochemistry.

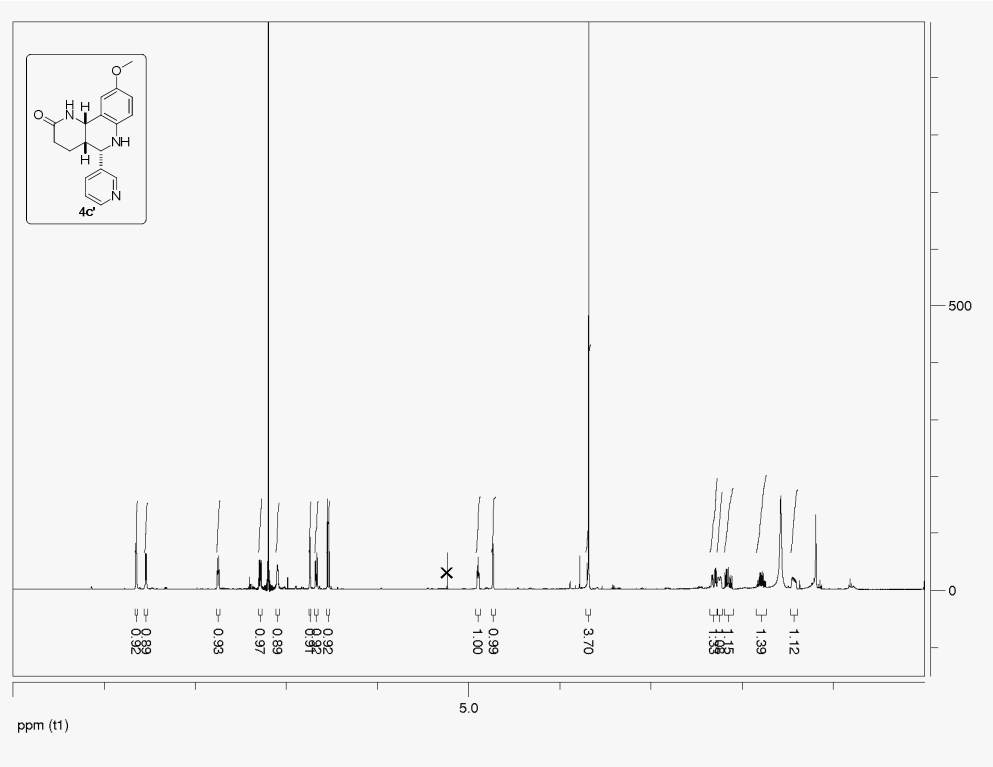


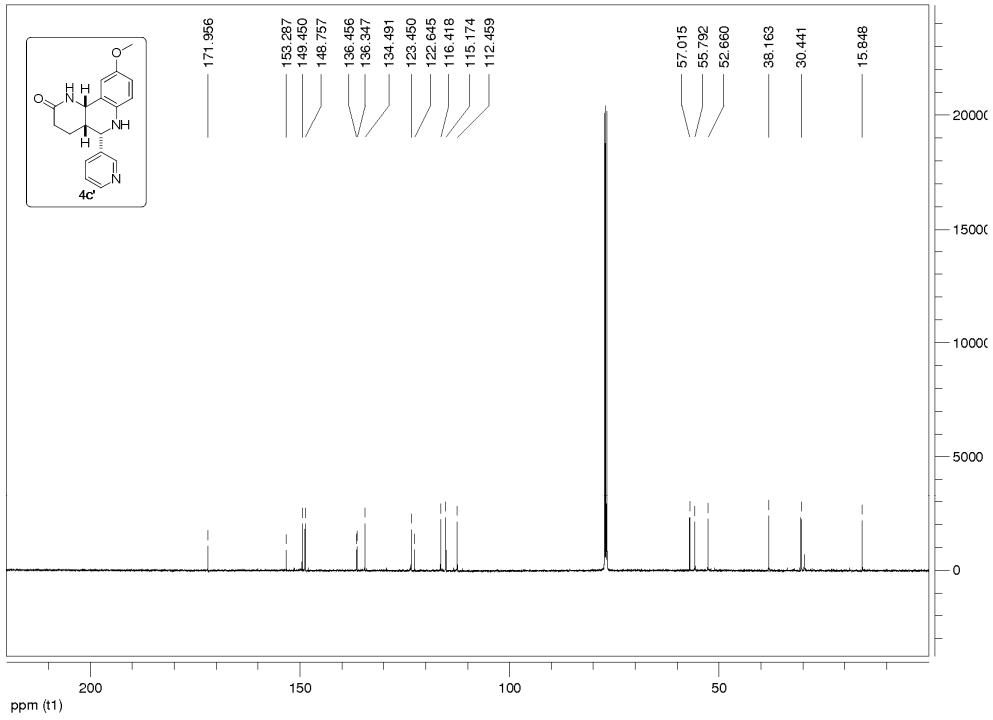


In this 3D optimized structure (MM94F + AM1), corresponding to the *cis* isomer, the expected NOE's correlations in NMR NOESY experiments are shown (blue arrows). The distance between protons ● and **X** is short enough (around 2.6 Å) to allow detection of a NOE correlation (blue arrow), however, such correlation was not observed and therefore, the stereochemical assignment of the *trans* stereochemistry (see above) is done.

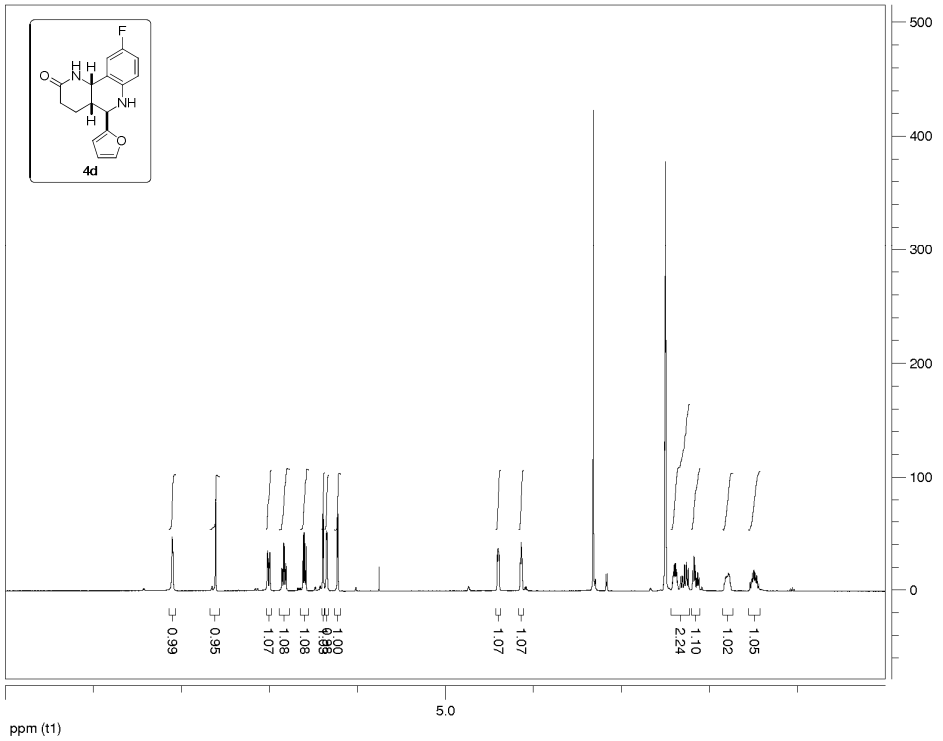

0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
ppm (t2)

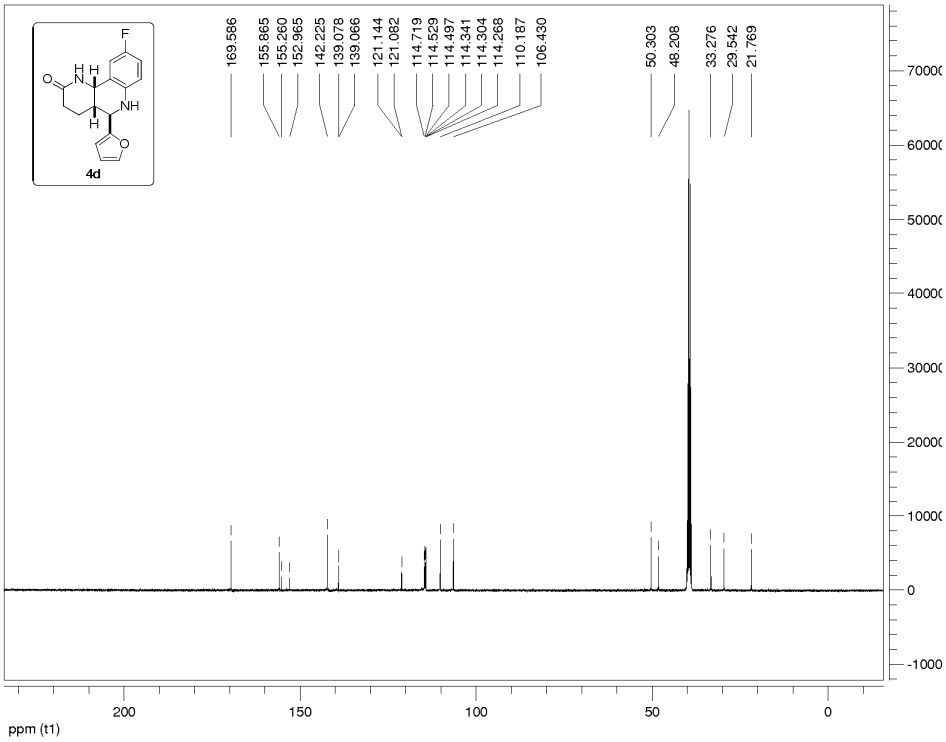
(4a*RS*,5*SR*,10b*RS*)-9-methoxy-5-(pyridin-3-yl)-1,4,4a,5,6,10b-hexahydrobenzo[h]quinolin-2(3*H*)-one (4c'):

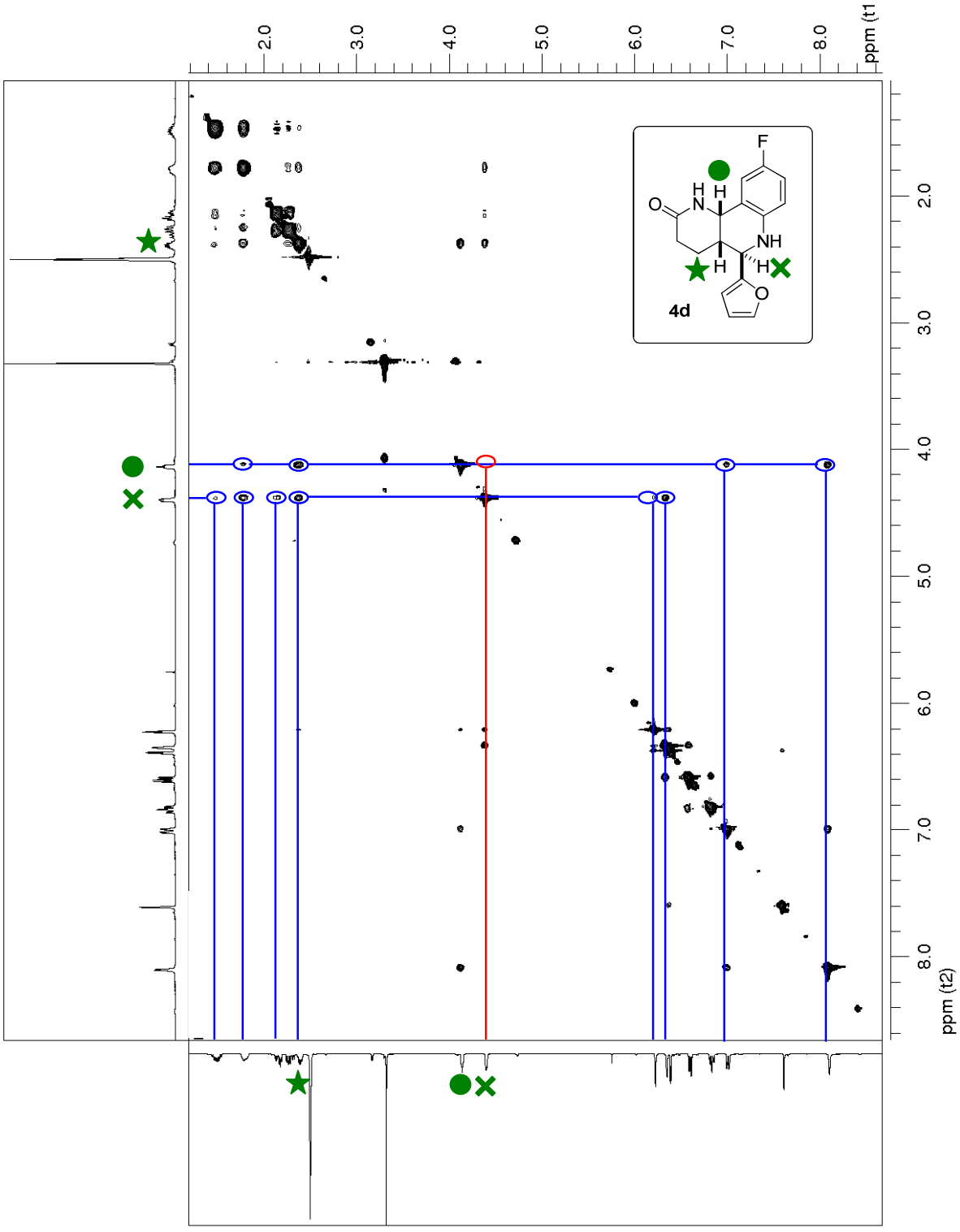




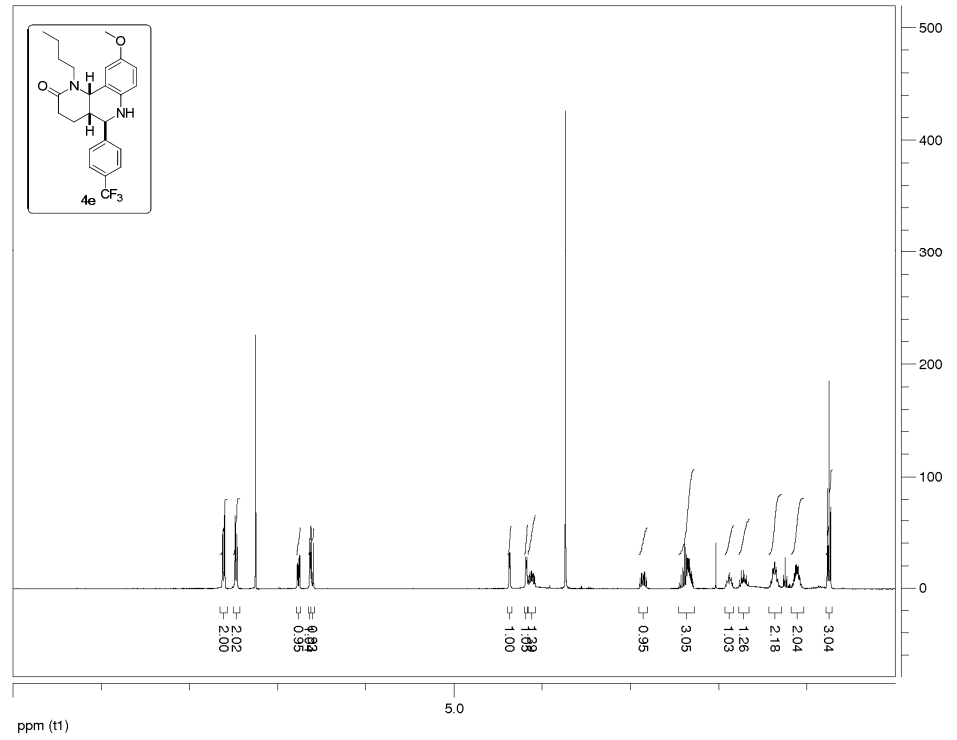
(4a*RS*,5*SR*,10b*SR*)-9-fluoro-5-(furan-2-yl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4d):

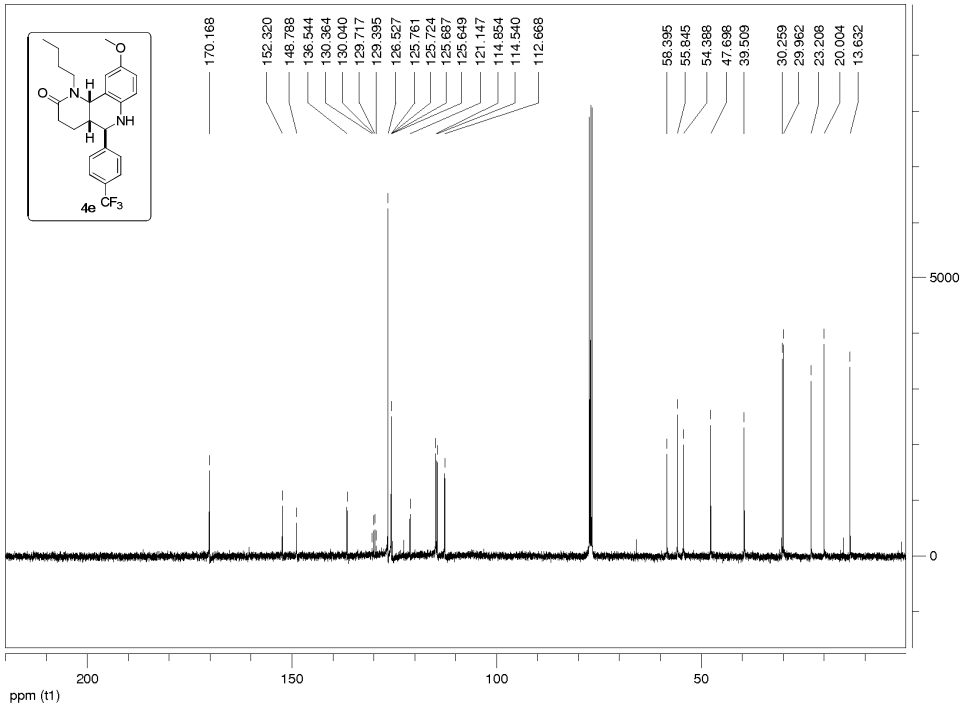




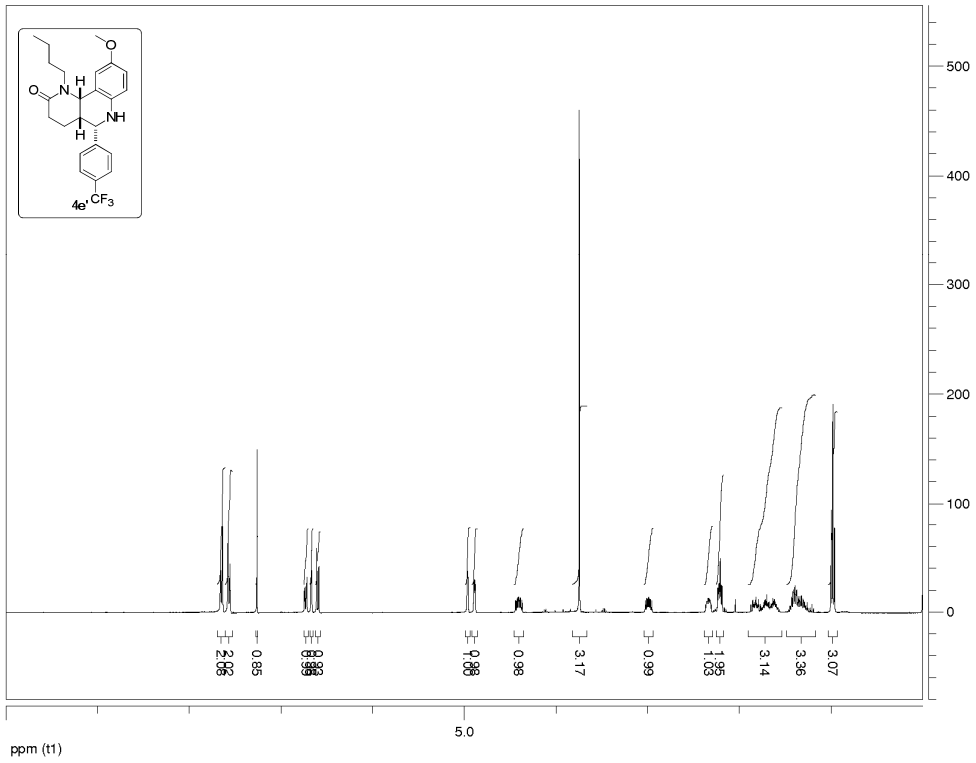

ppm (t1
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t2)
F
H
N
O
H
NH
H
H
O
4d

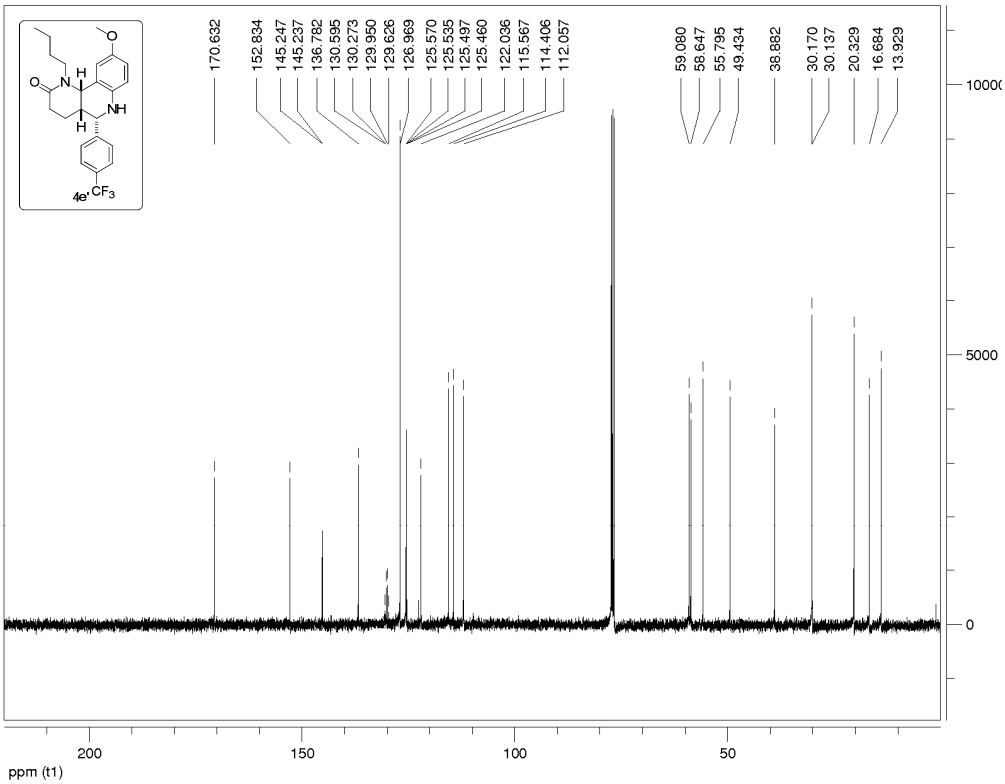
(4a*RS*,5*SR*,10b*RS*)-1-butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4e):



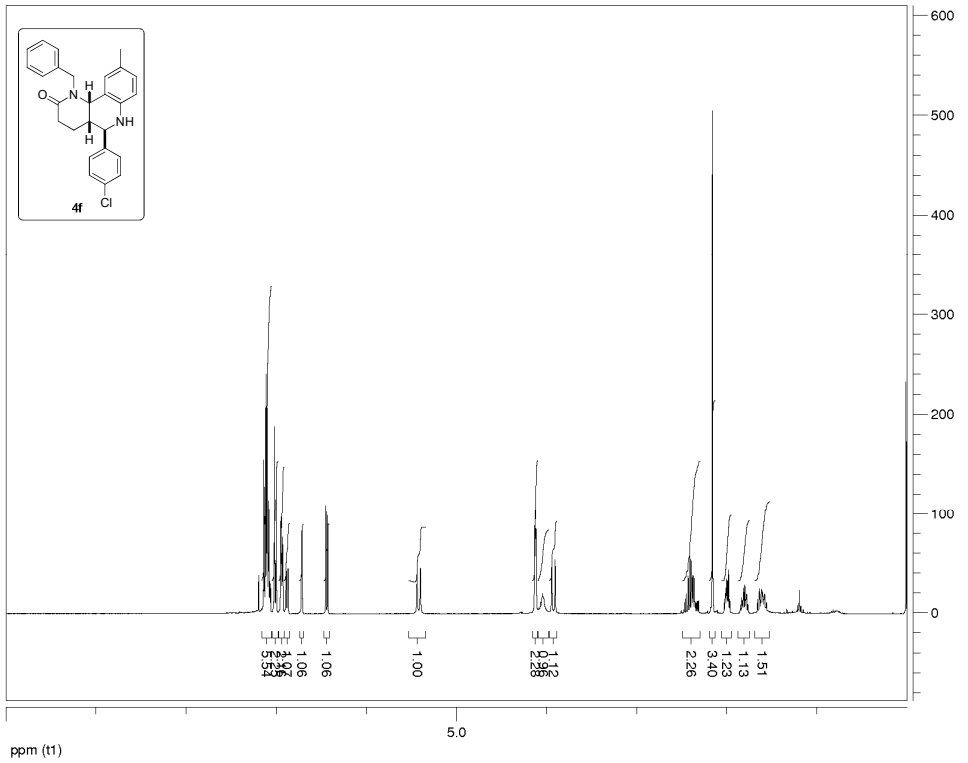


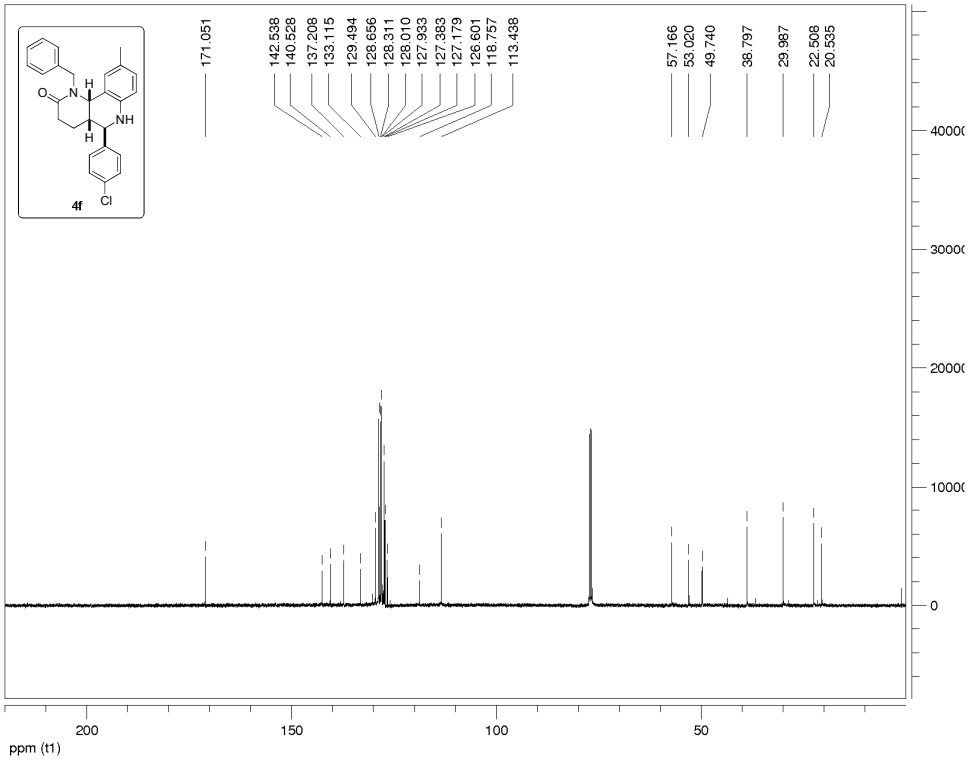
(4a*RS*,5*RS*,10b*RS*)-1-butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4e'):



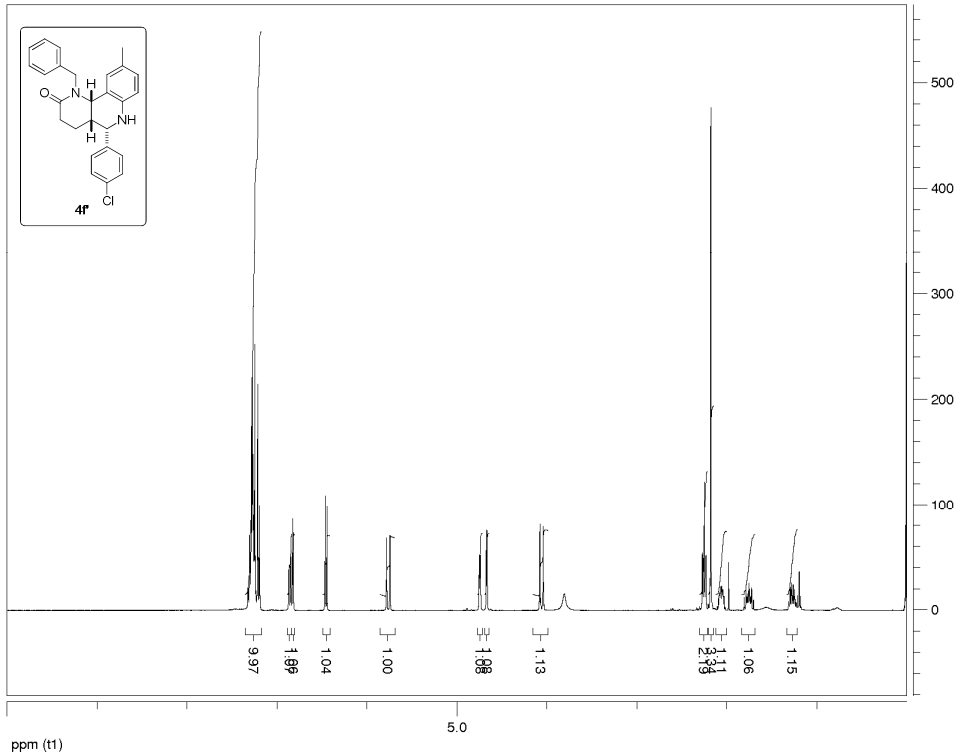


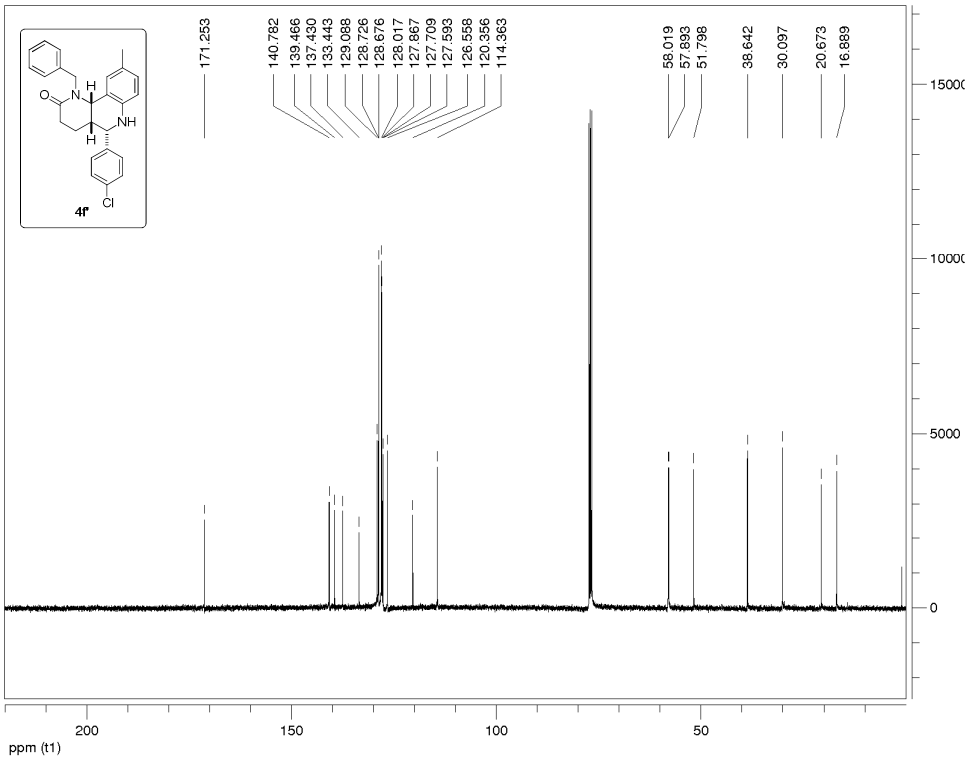
(4a*RS*,5*SR*,10b*RS*)-1-benzyl-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4f):



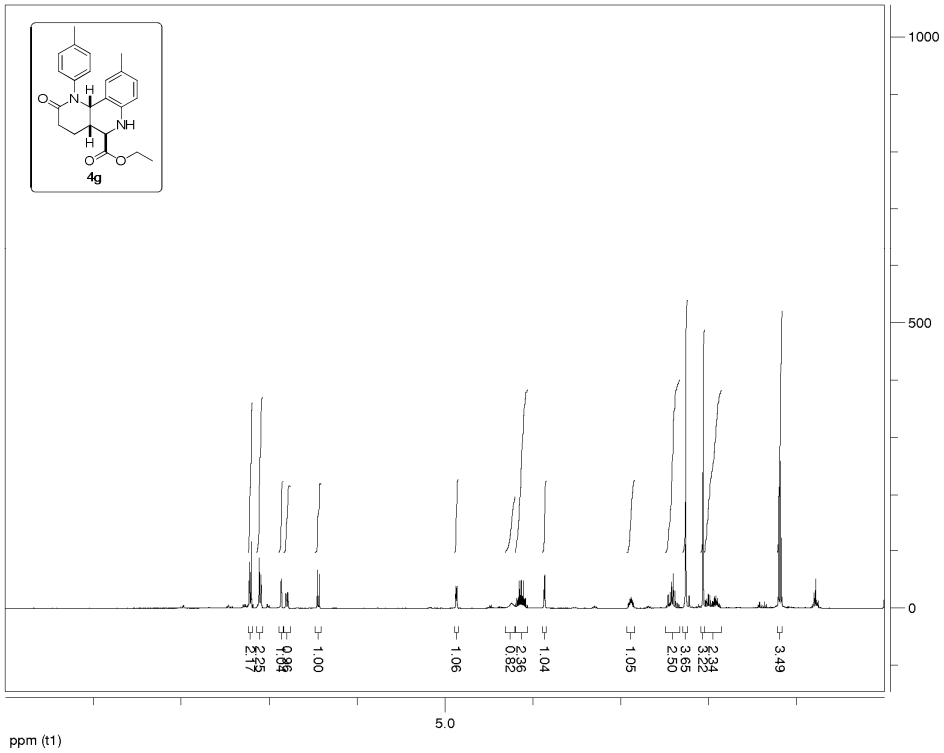


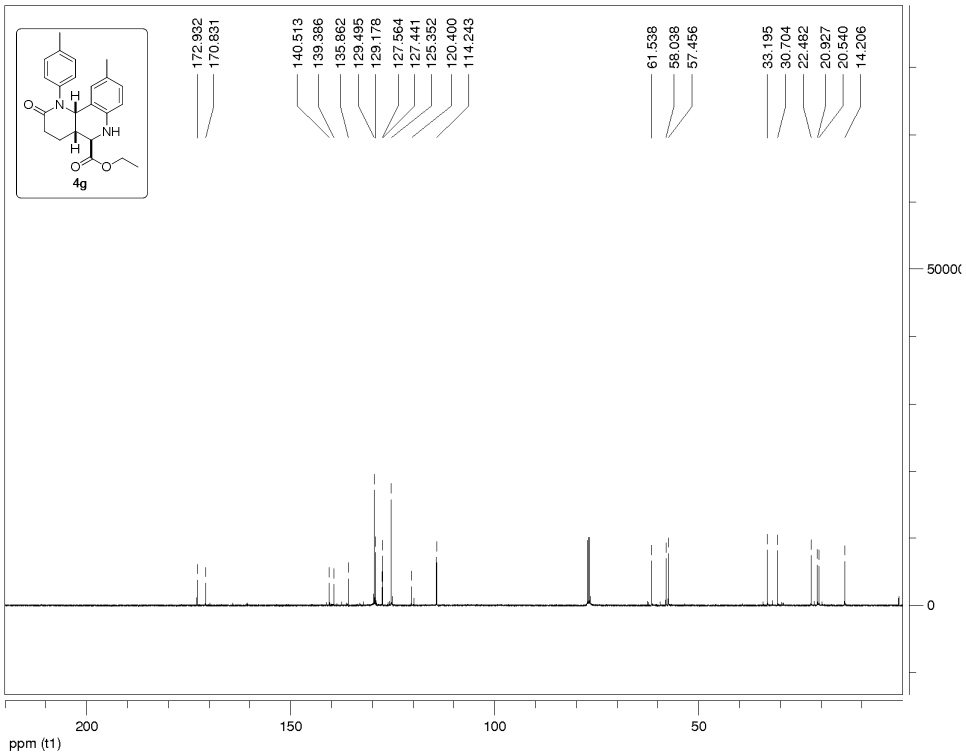
(4a*RS*,5*RS*,10b*RS*)-1-benzyl-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4f'):



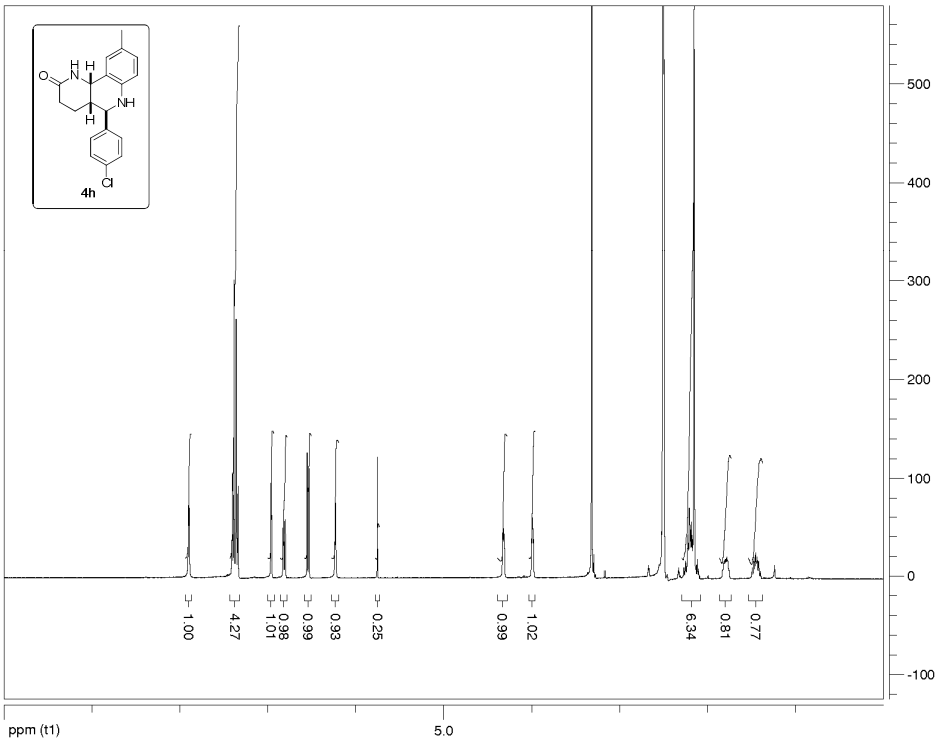


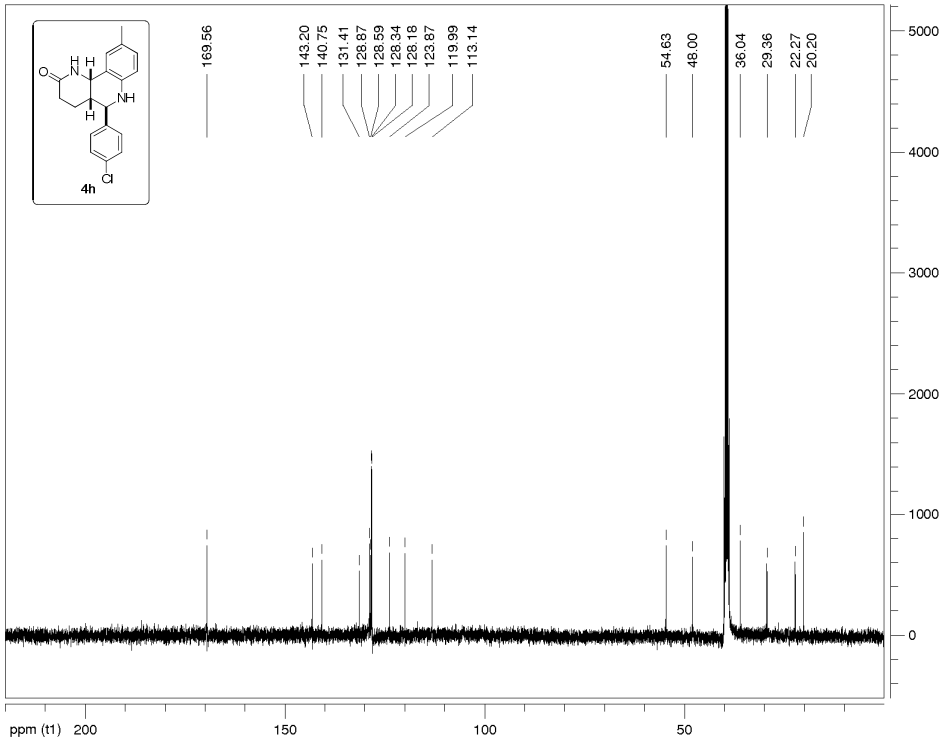
(4a*RS*,5*SR*,10b*RS*)-ethyl 9-methyl-2-oxo-1-(*p*-tolyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[h][1,6]naphthyridine-5-carboxylate (4g):



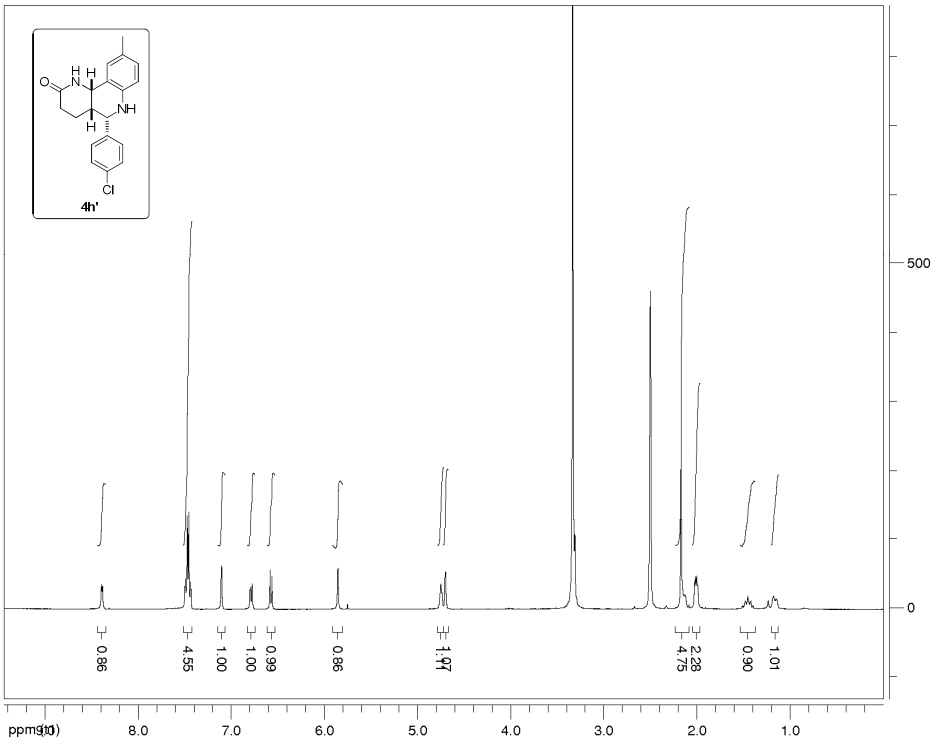


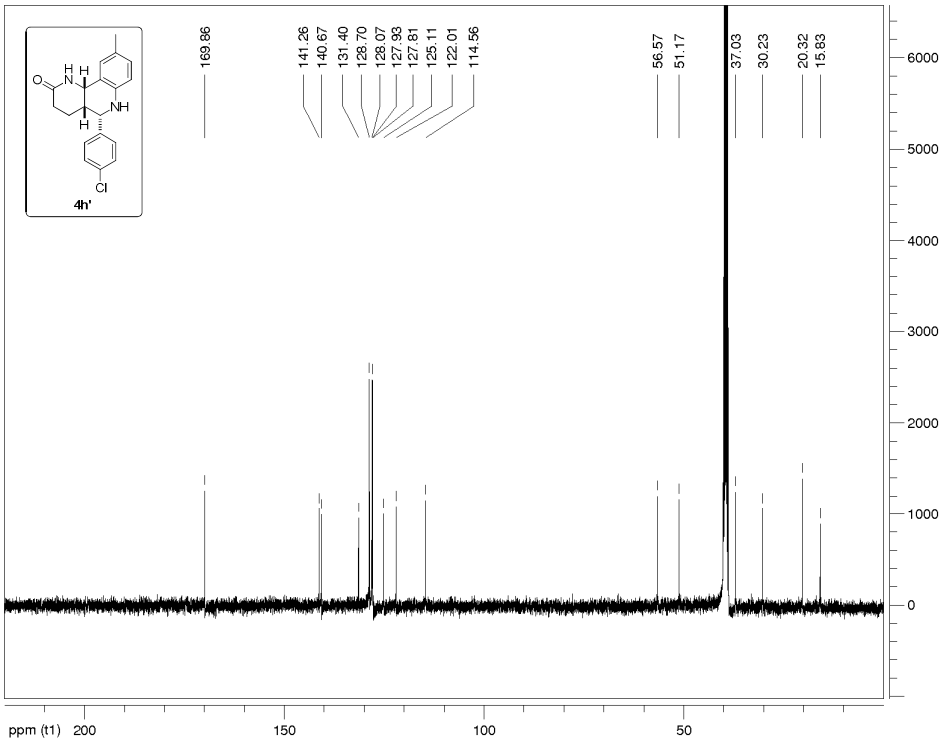
(4a*RS*,5*SR*,10b*RS*)-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4h):



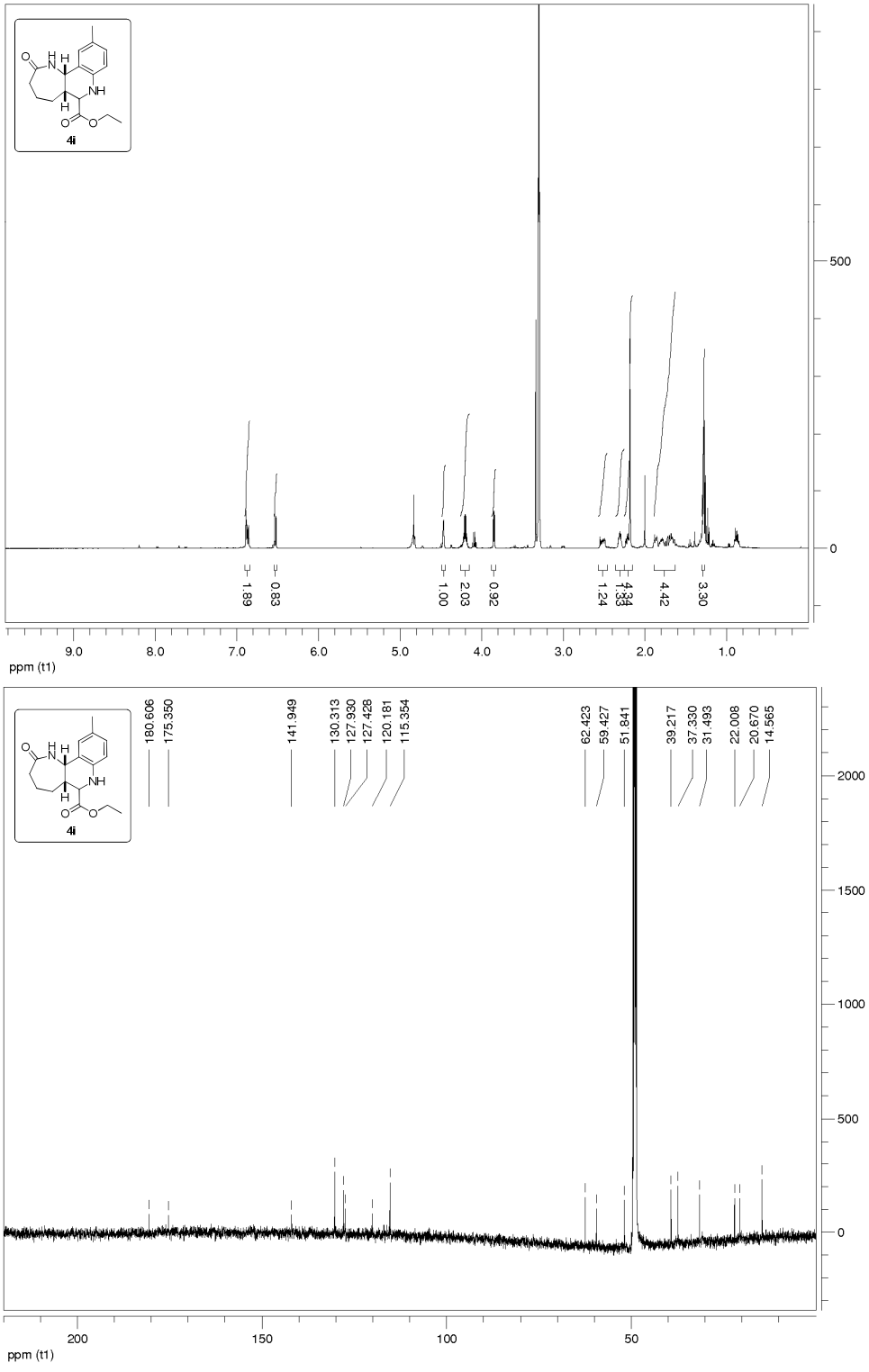


(4a*RS*,5*RS*,10b*RS*)-5-(4-chlorophenyl)-9-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridin-2(3*H*)-one (4h'):

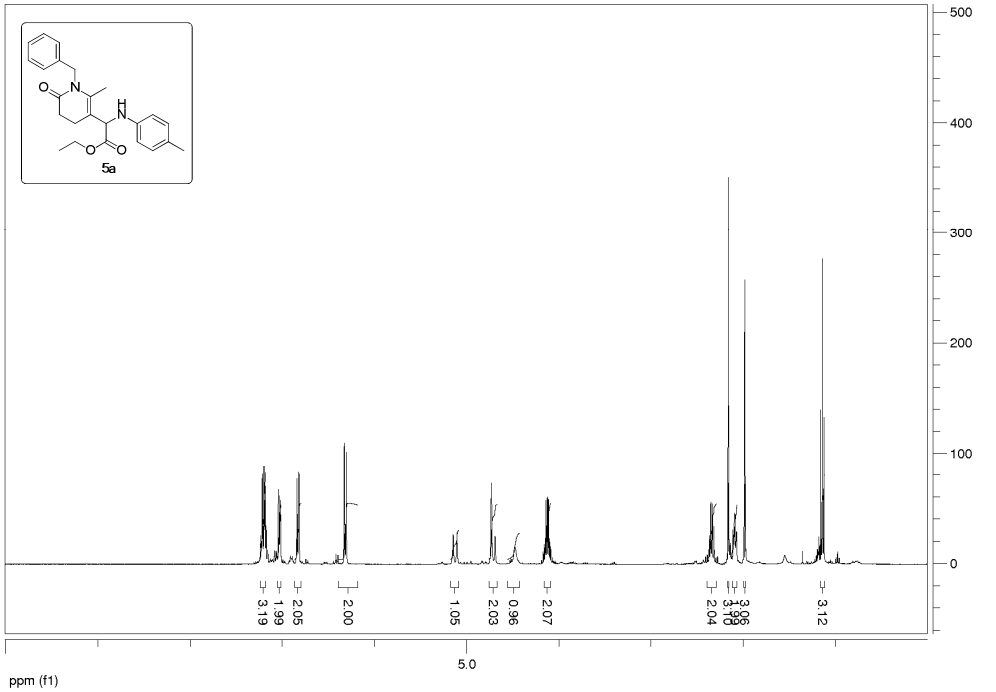


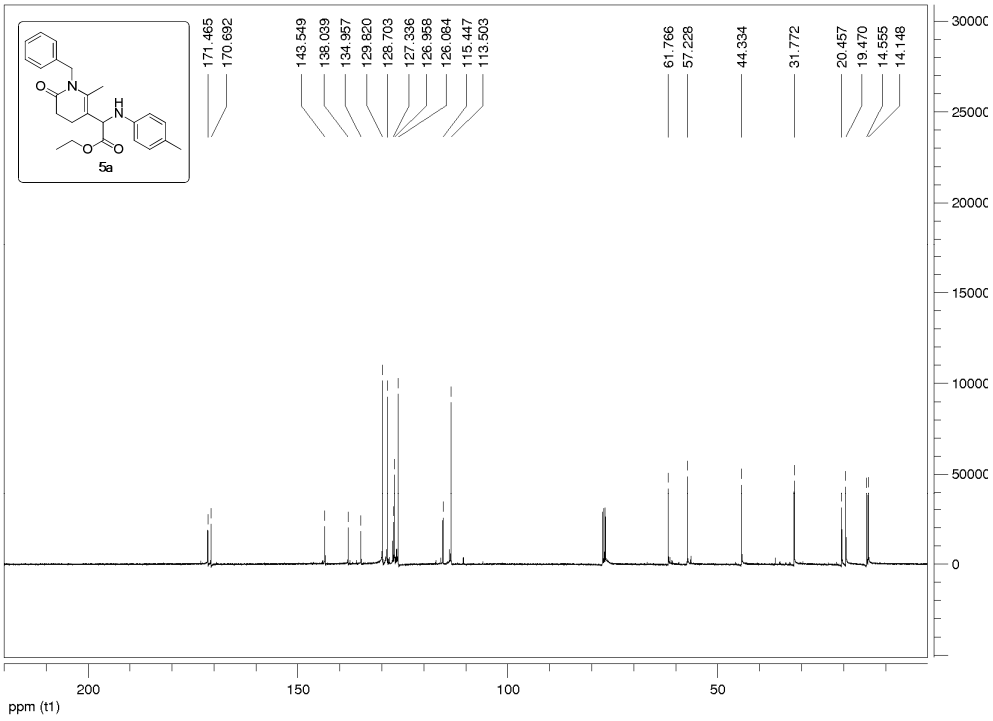


(5a*RS*,6*SR*,11b*SR*)-ethyl 10-methyl-2-oxo-2,3,4,5,5a,6,7,11b-octahydro-1H-azepino[3,2-c]quinoline-6-carboxylate (4i):

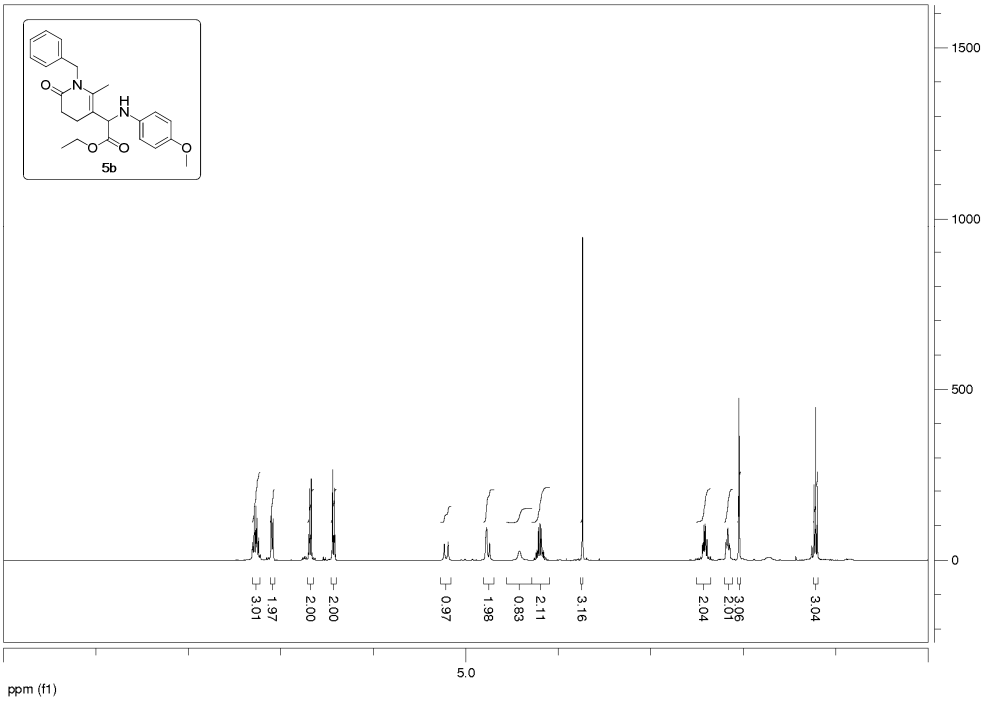


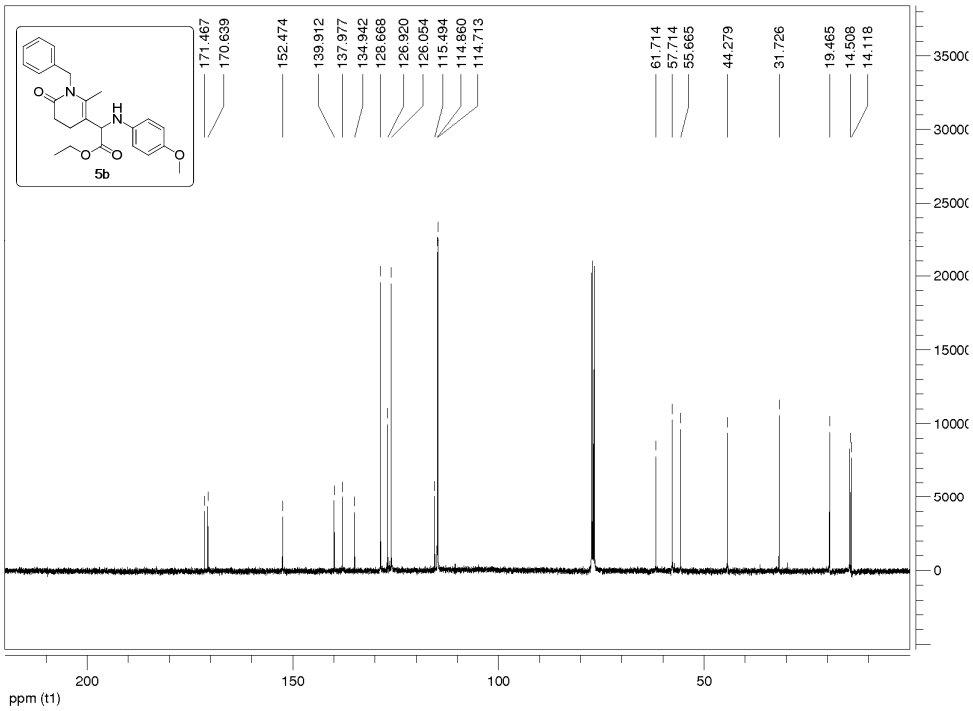
ethyl 2-(1-benzyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-(*p*-tolylamino)acetate (5a):



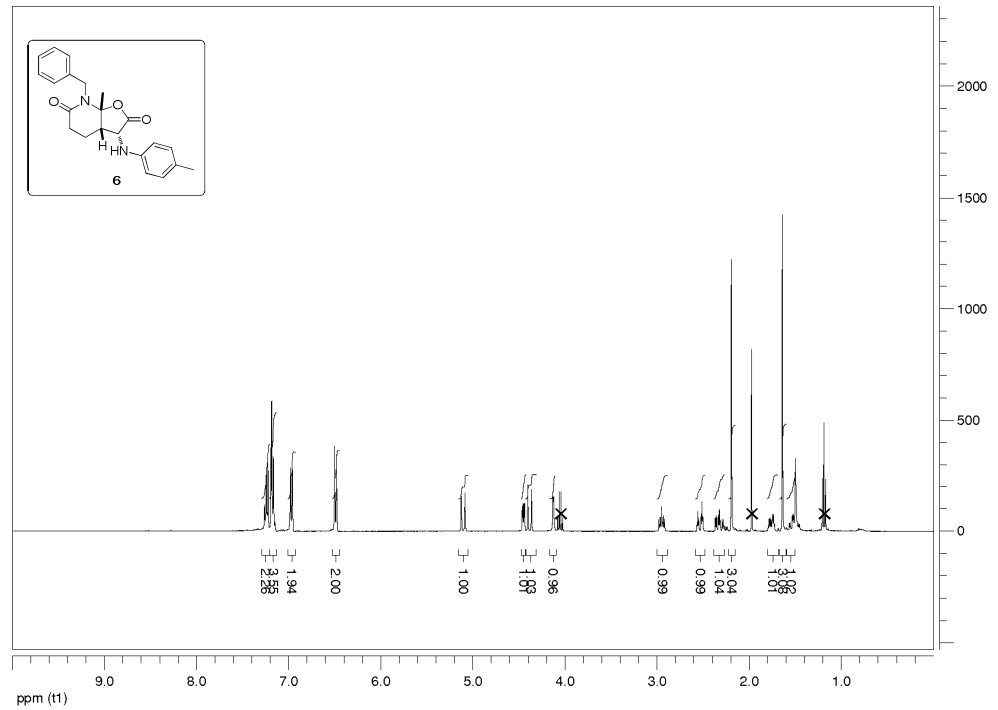


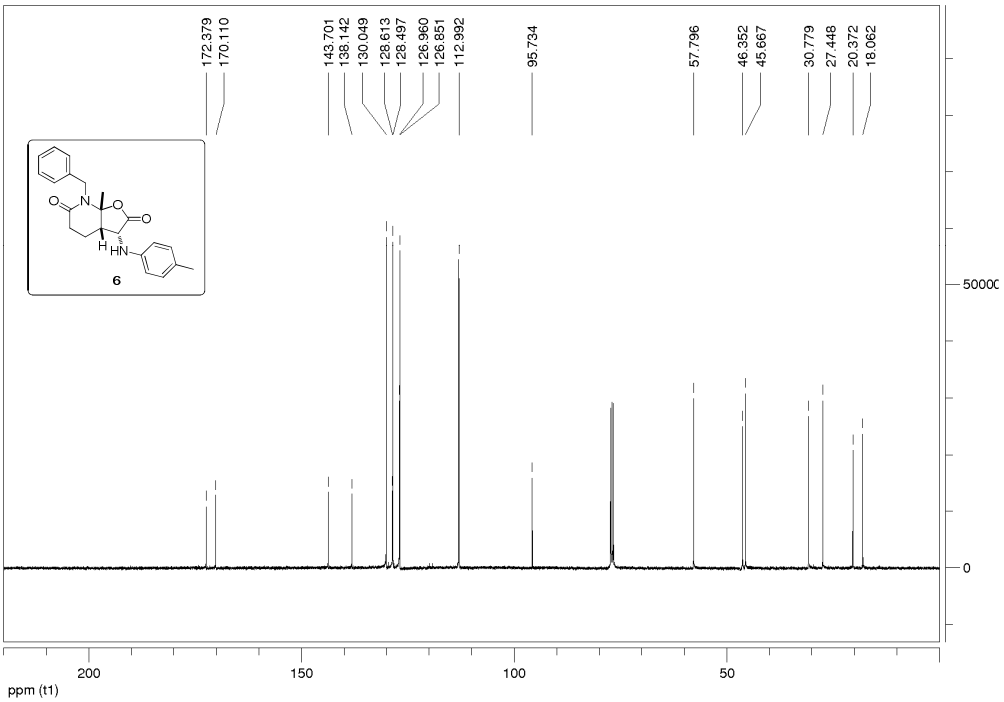
ethyl 2-(1-benzyl-2-methyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-((4-methoxyphenyl)amino)acetate (5b):



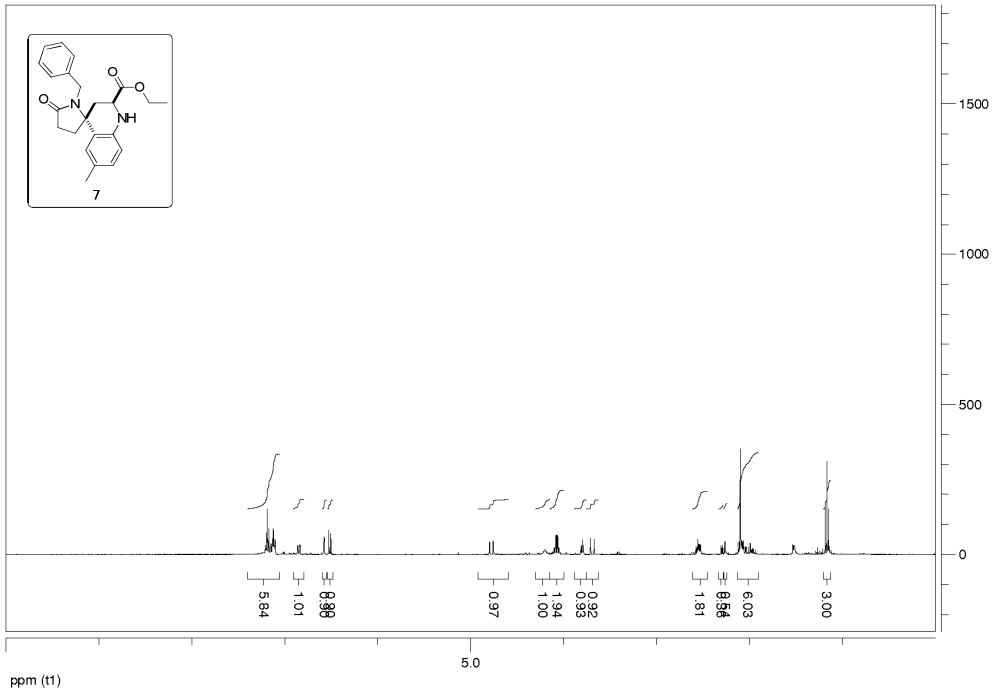


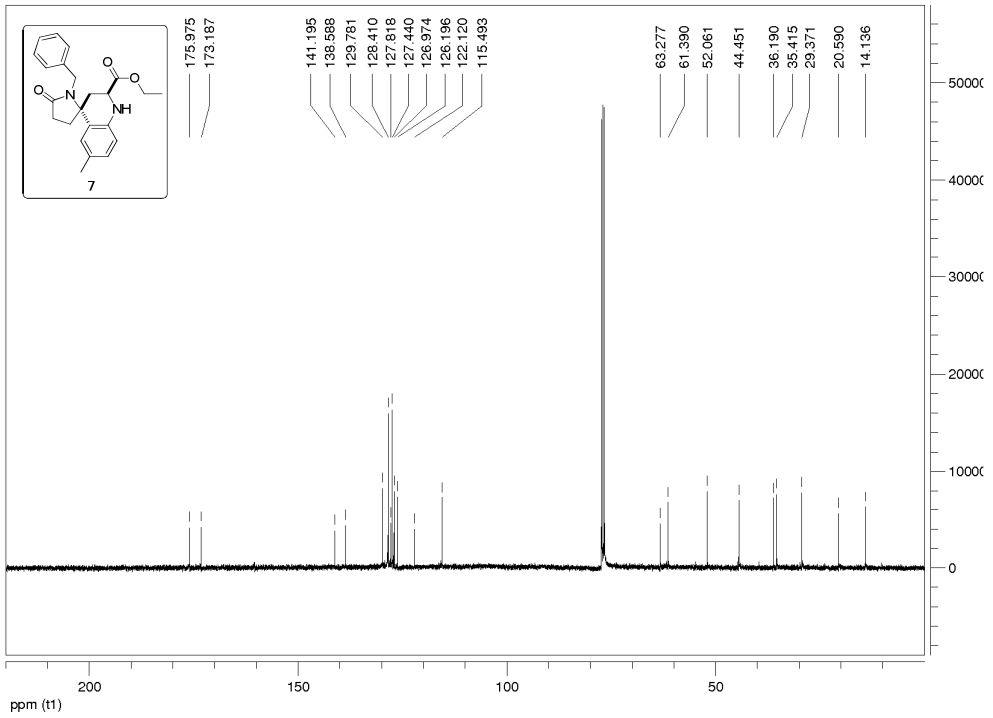
(3*RS*,3a*SR*,7a*RS*)-7-benzyl-3-(p-tolylamino)hexahydrofuro[2,3-b]pyridine-2,6-dione (6):



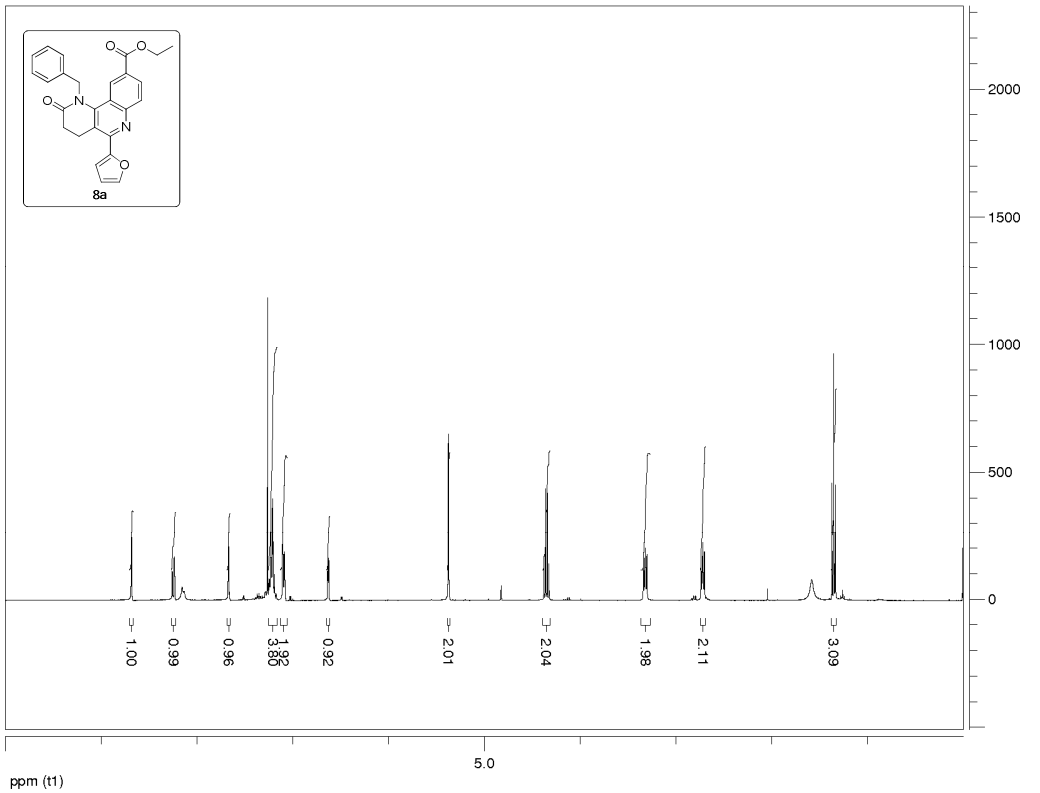


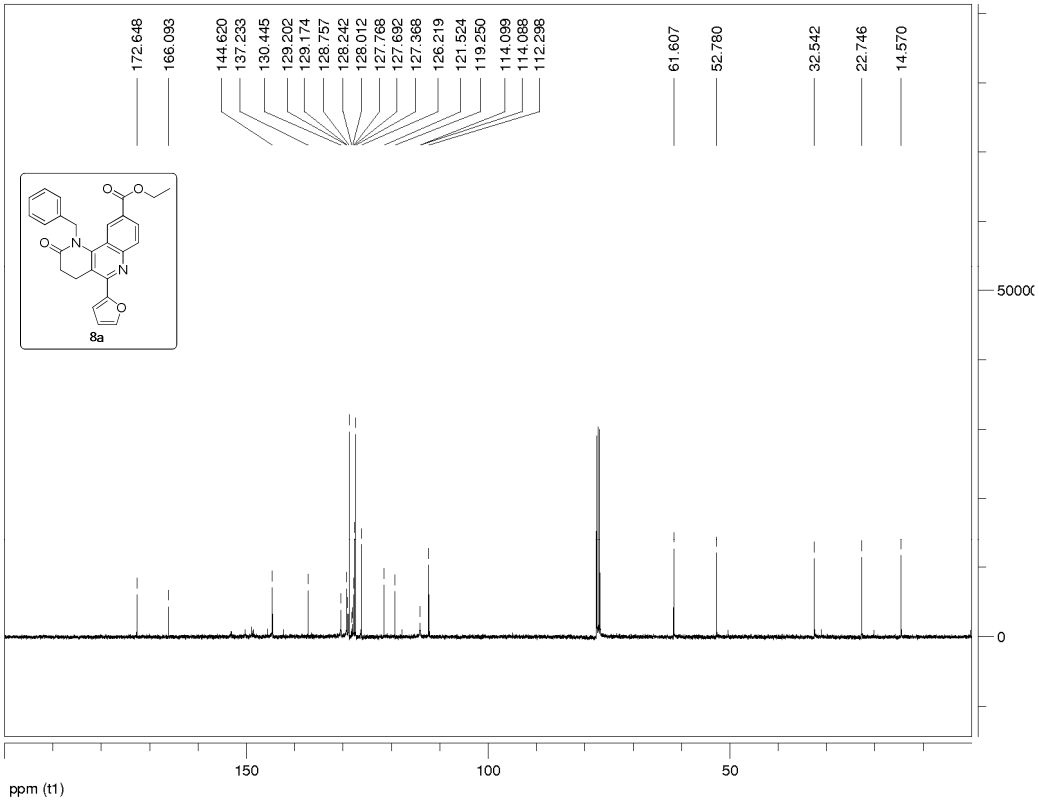
(2*RS*,2'*SR*)-ethyl 1-benzyl-6'-methyl-5-oxo-2',3'-dihydro-1'*H*-spiro[pyrrolidine-2,4'-quinoline]-2'-carboxylate (7):



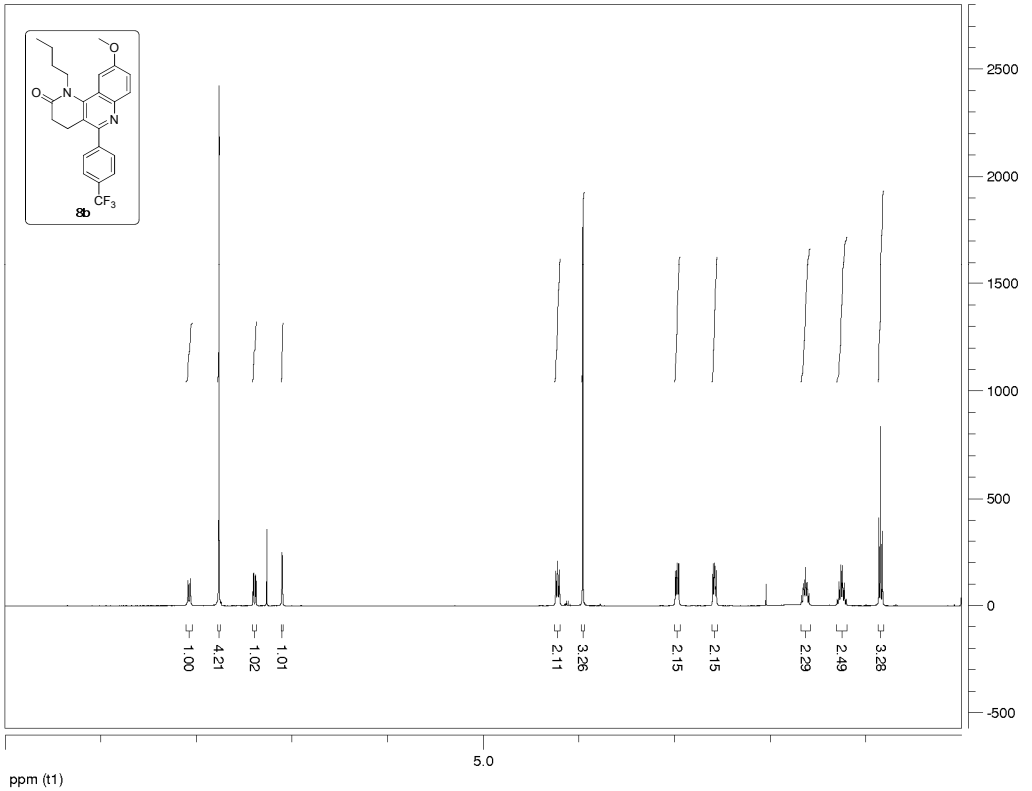


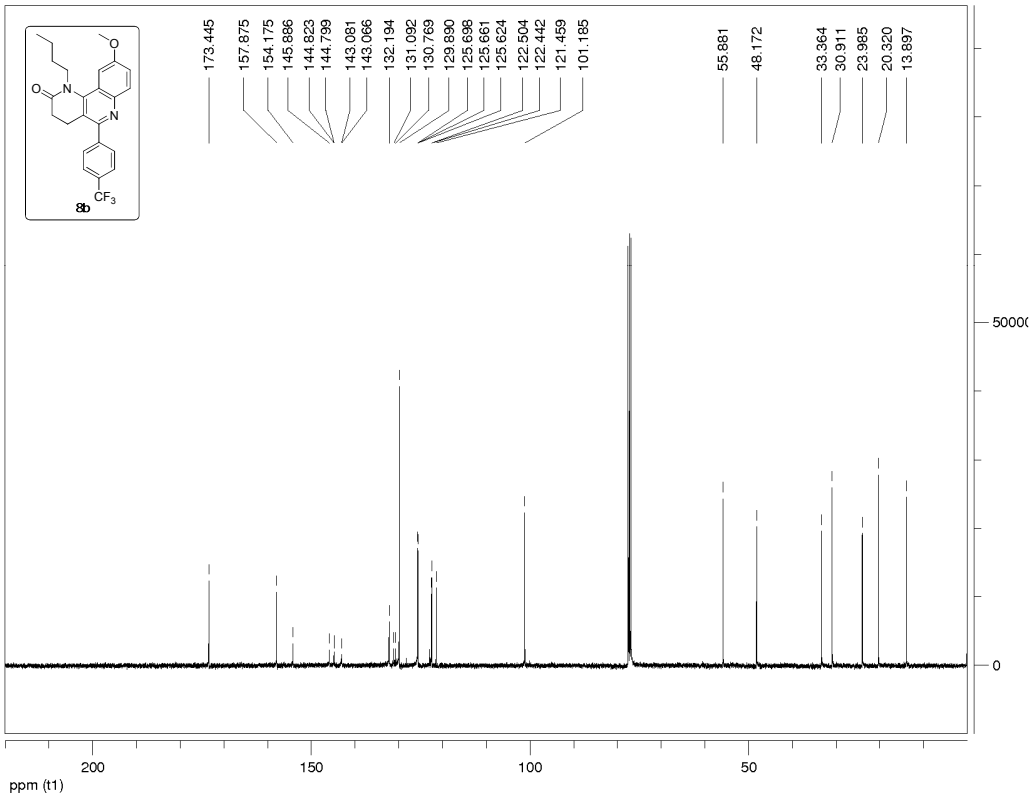
ethyl 1-benzyl-5-(furan-2-yl)-2-oxo-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridine-9-carboxylate (8a):



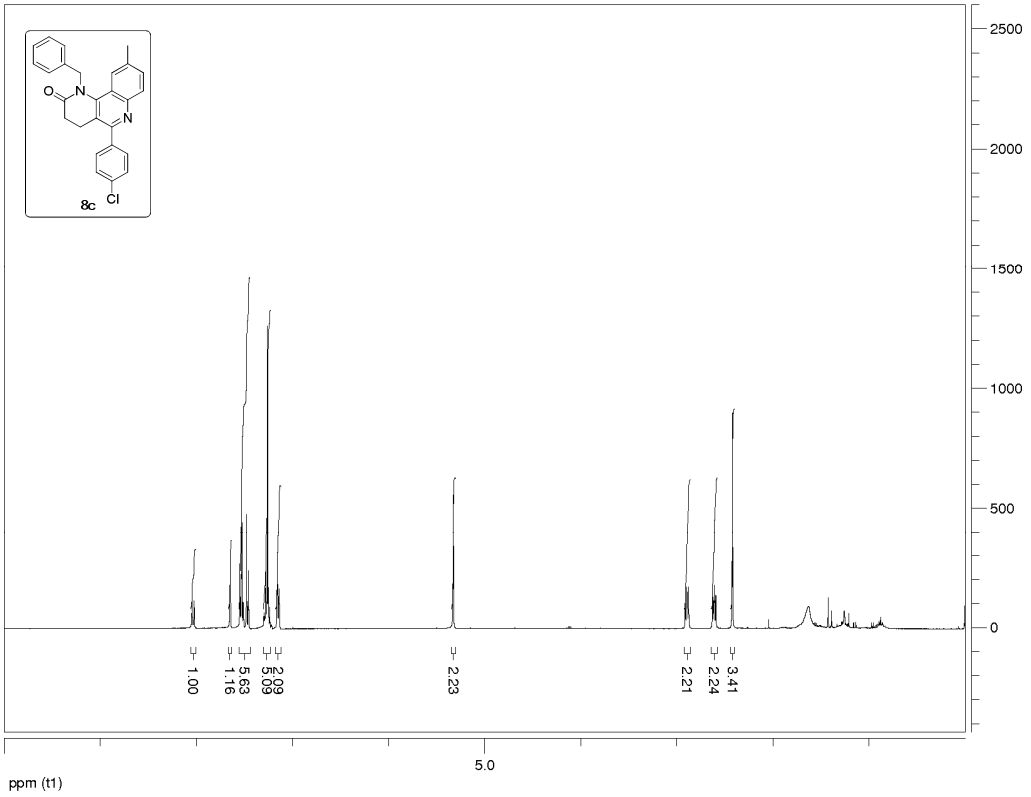


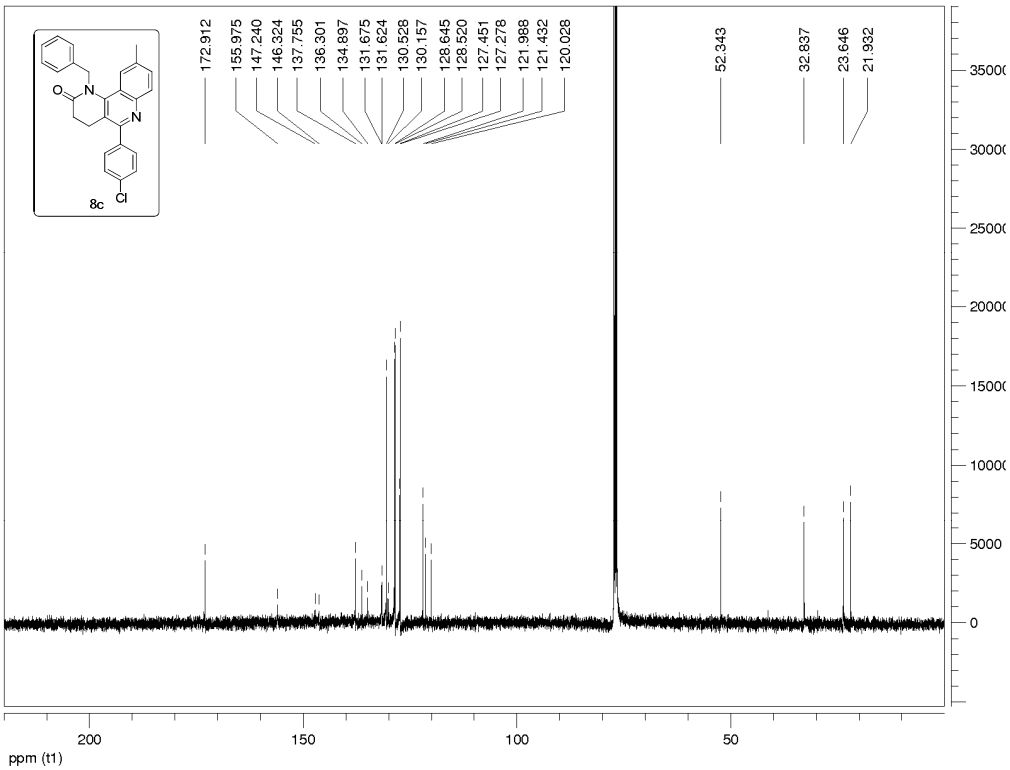
butyl-9-methoxy-5-(4-(trifluoromethyl)phenyl)-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8b):



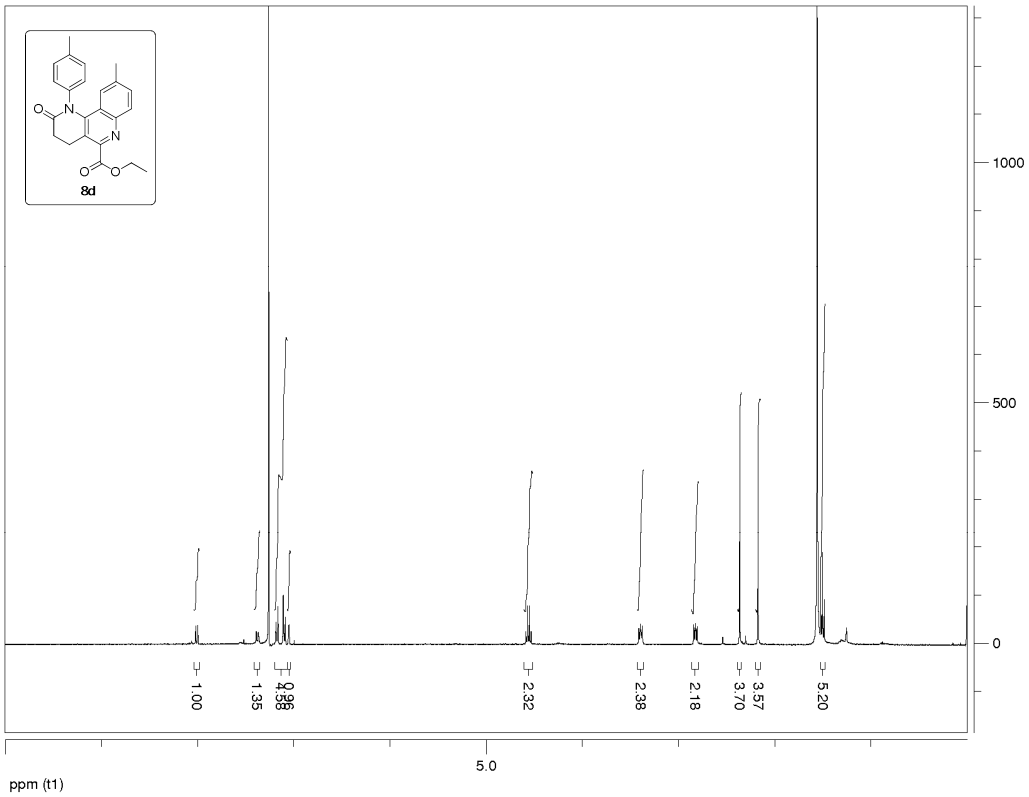


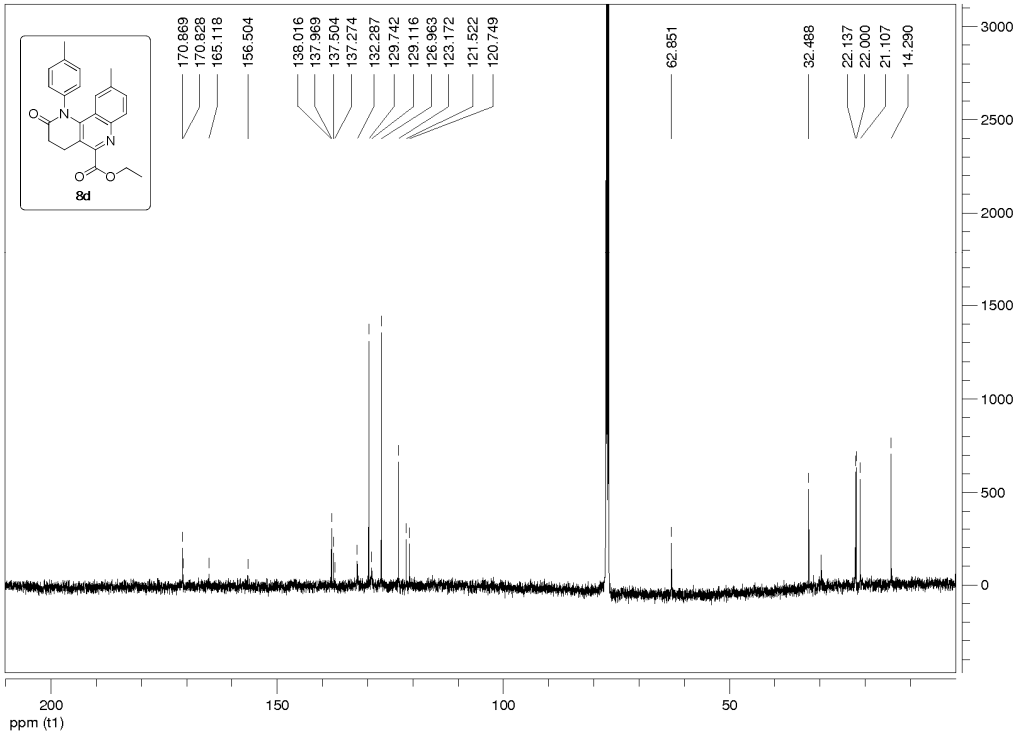
benzyl-5-(4-chlorophenyl)-9-methyl-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8c):



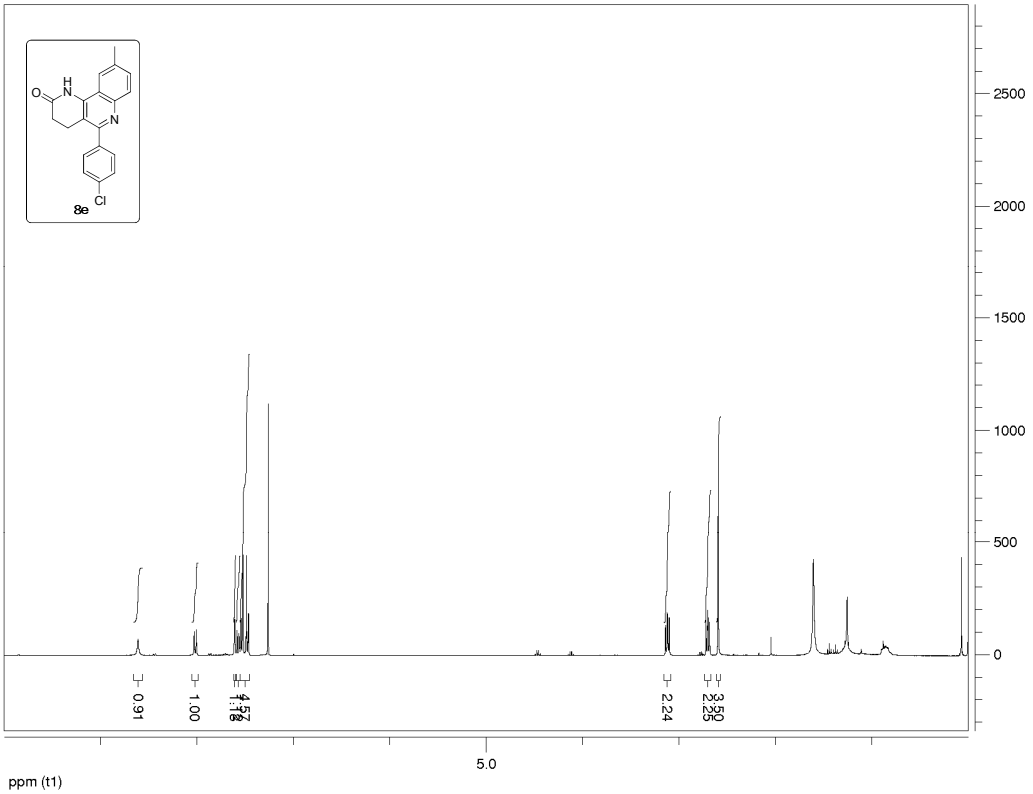


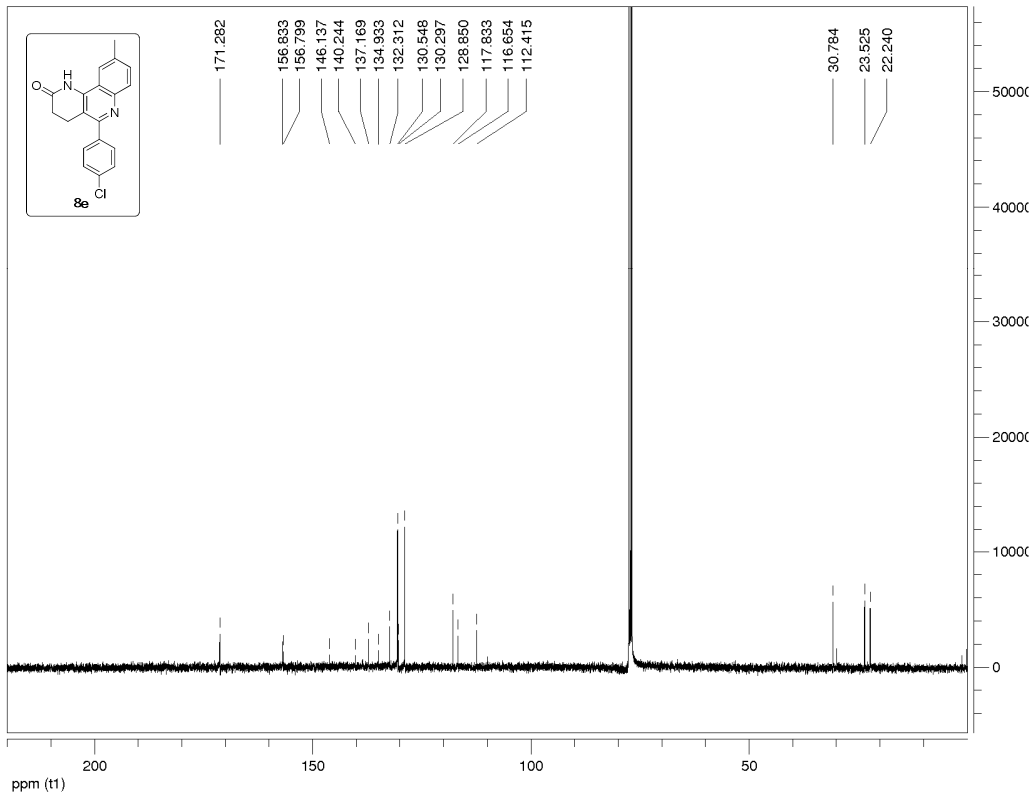
ethyl 9-methyl-2-oxo-1-(*p*-tolyl)-1,2,3,4-tetrahydrobenzo[h][1,6]naphthyridine-5-carboxylate (8d):



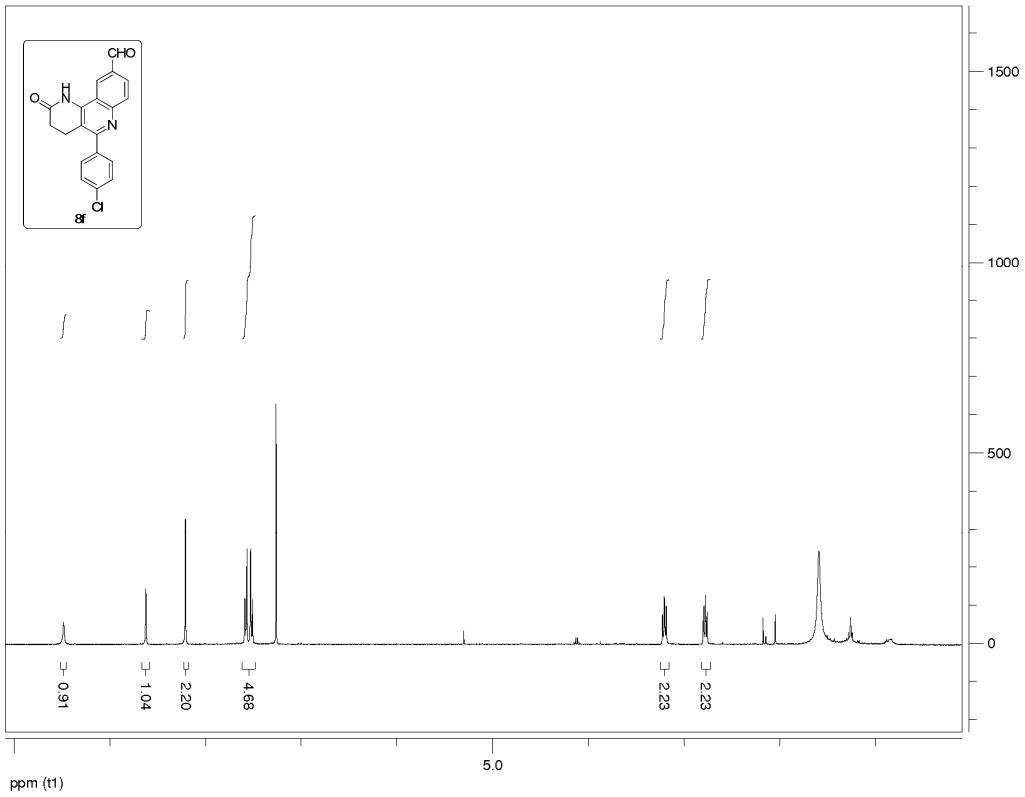


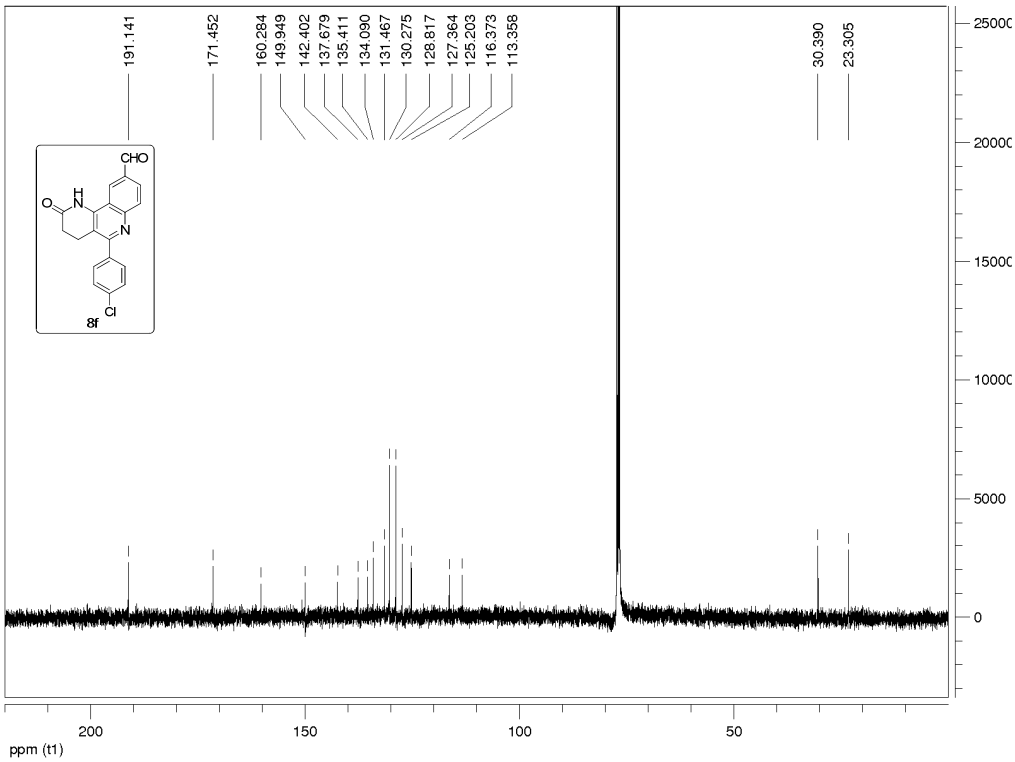
5-(4-chlorophenyl)-9-methyl-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (8e):



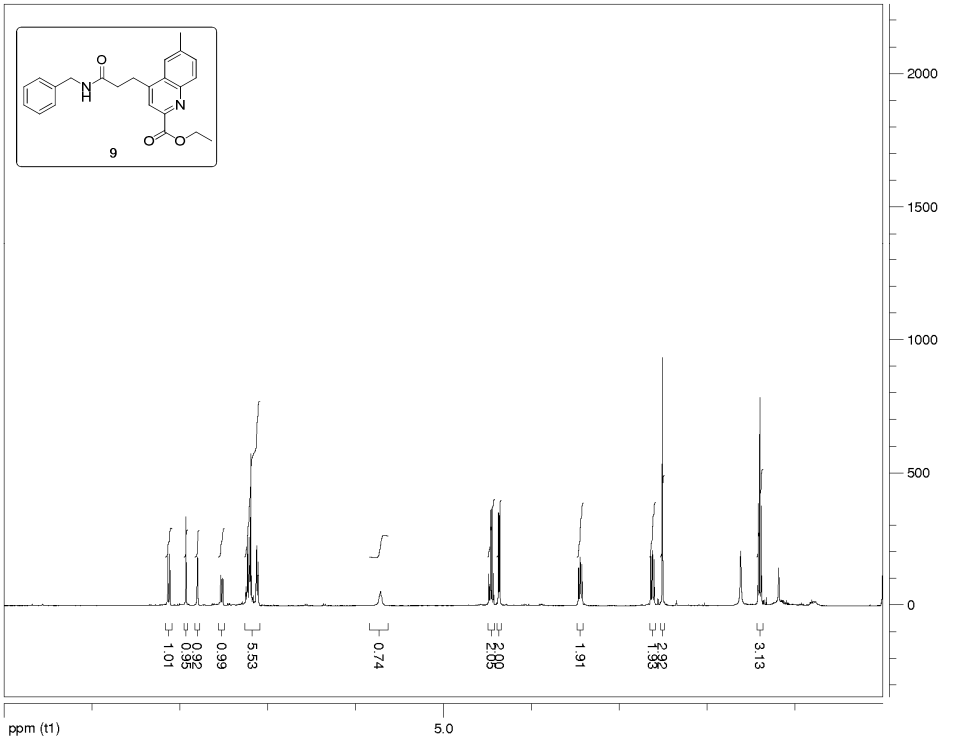


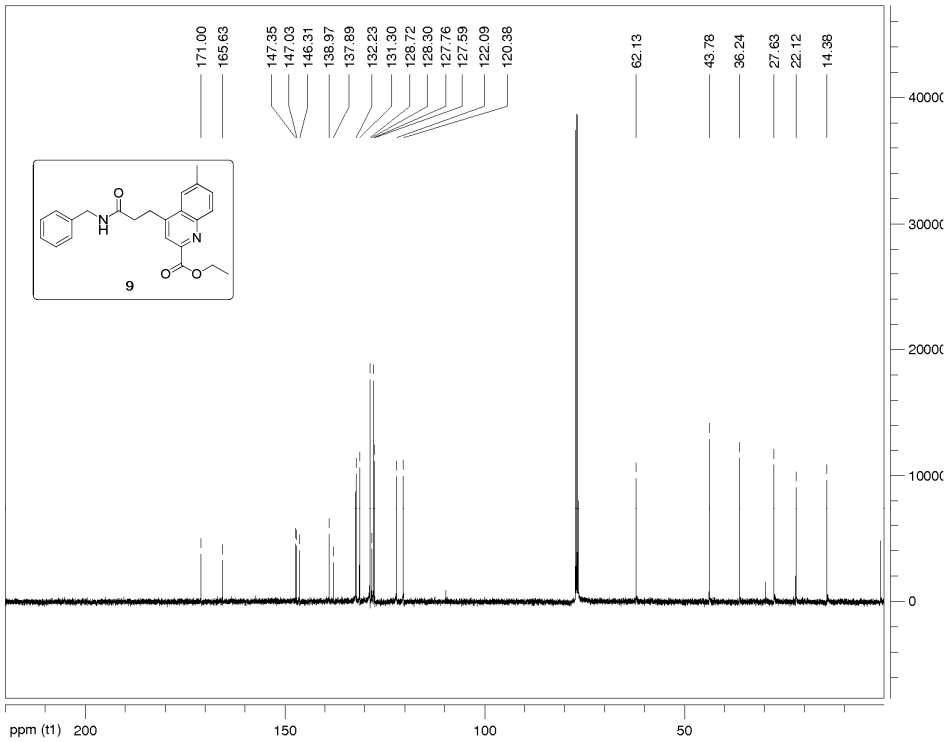
5-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydrobenzo[h]quinoline-9-carbaldehyde (8f):



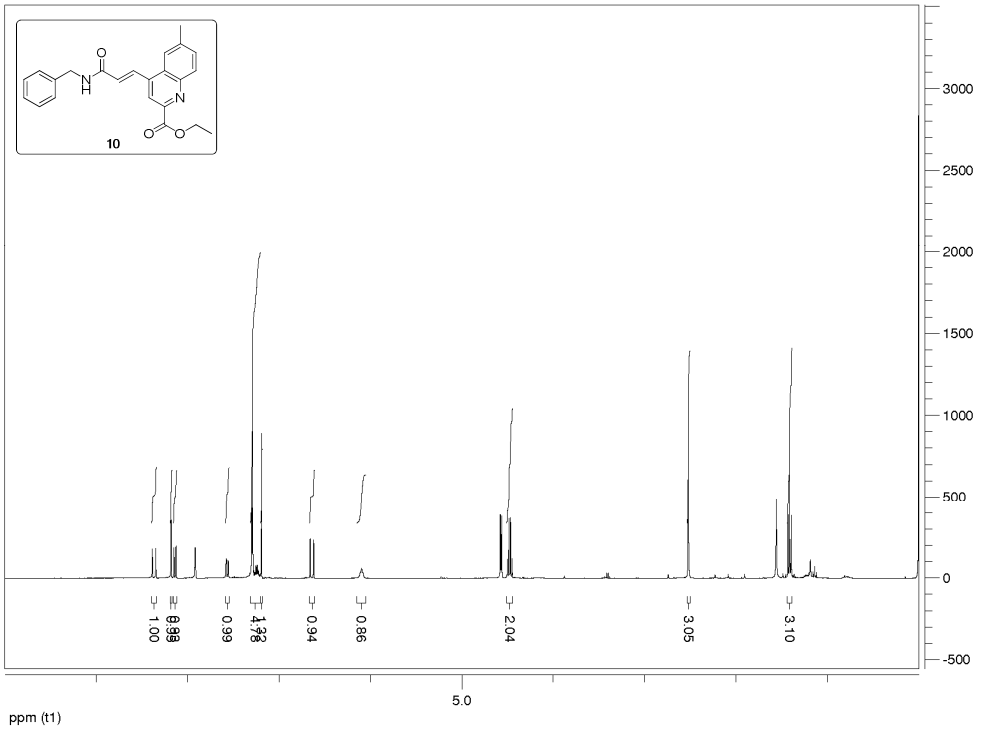


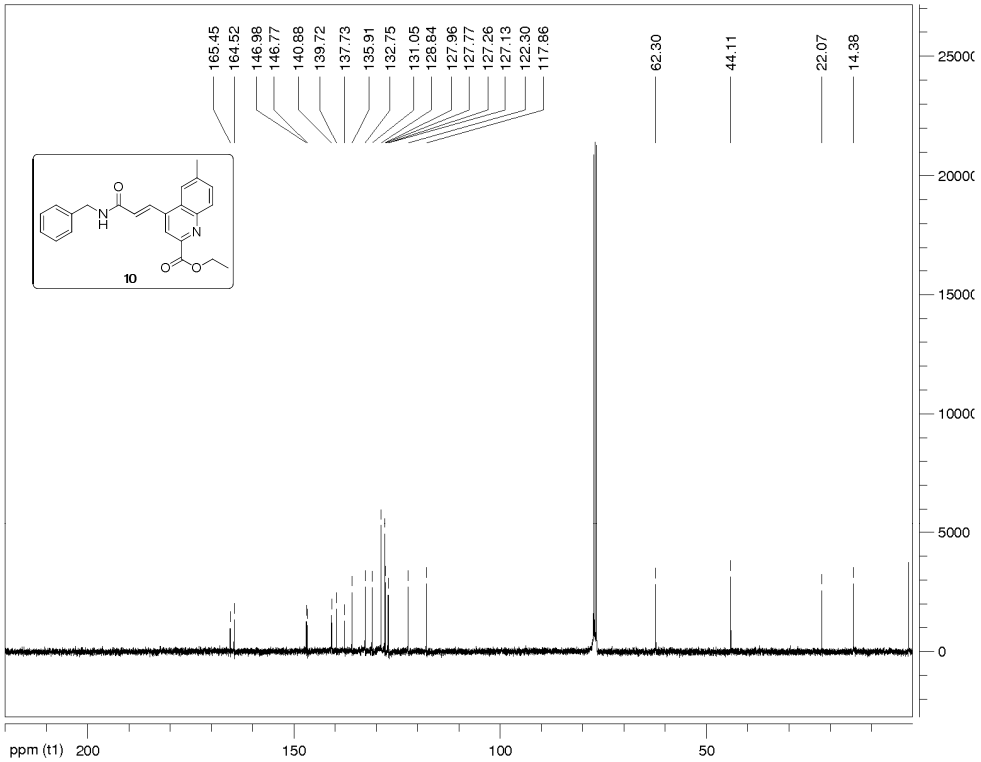
ethyl 4-(3-(benzylamino)-3-oxopropyl)-6-methylquinoline-2-carboxylate (9):



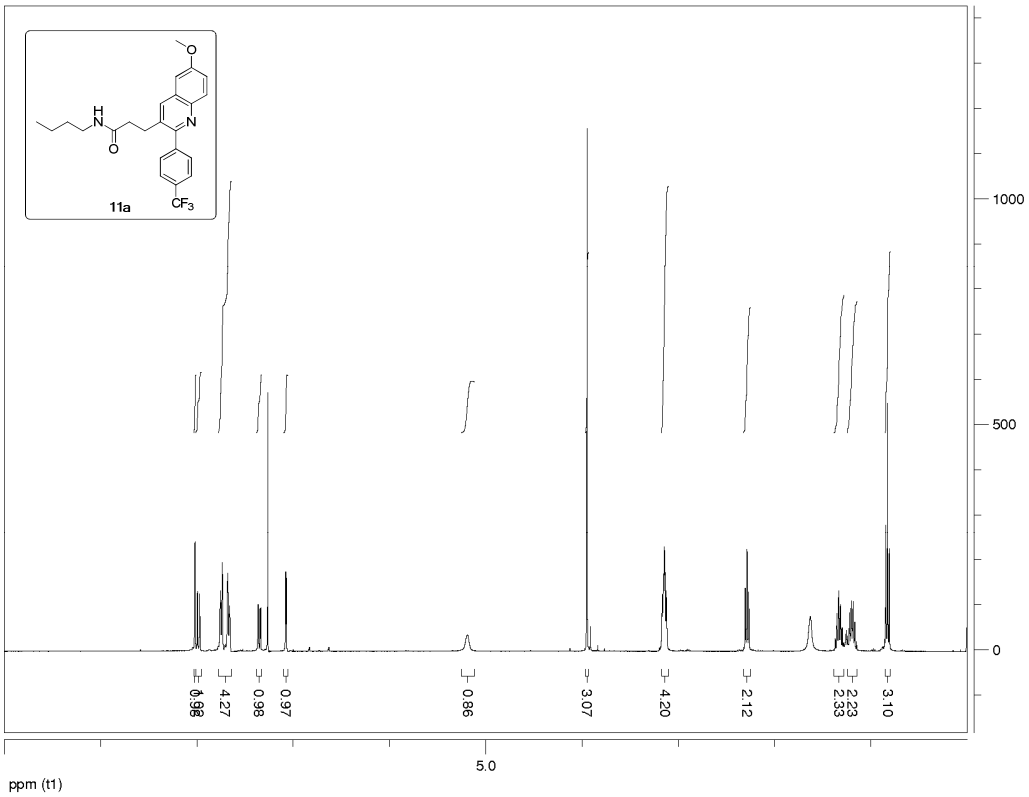


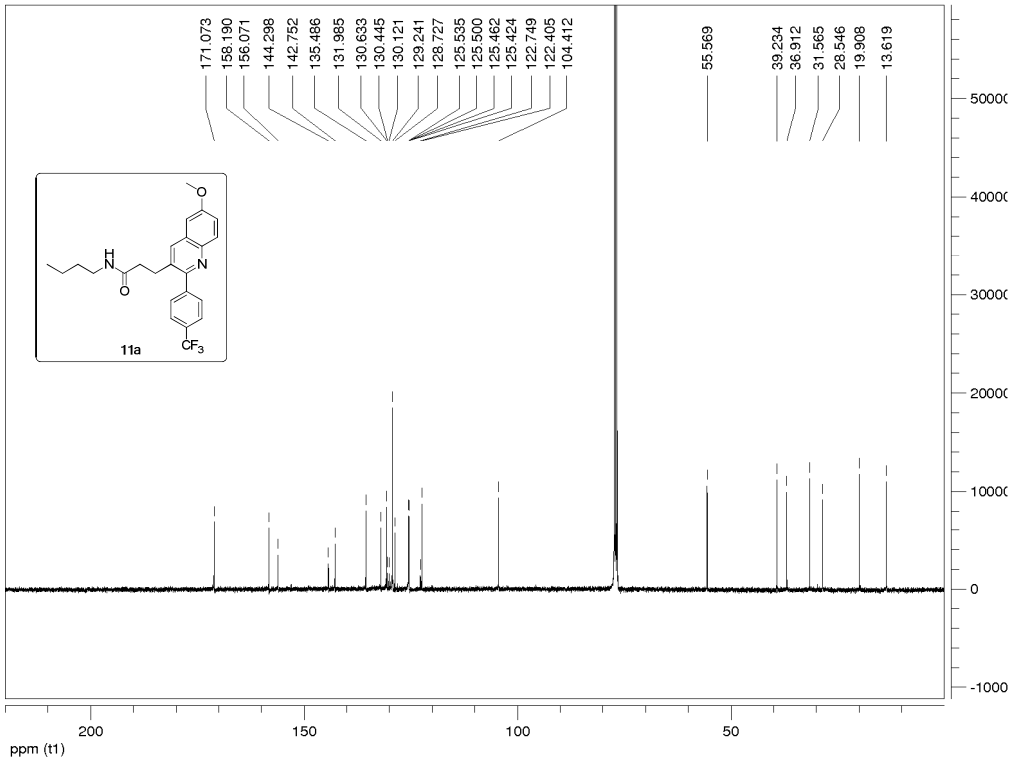
ethyl 4-(3-(benzylamino)-3-oxoprop-1-en-1-yl)-6-methylquinoline-2-carboxylate (10):



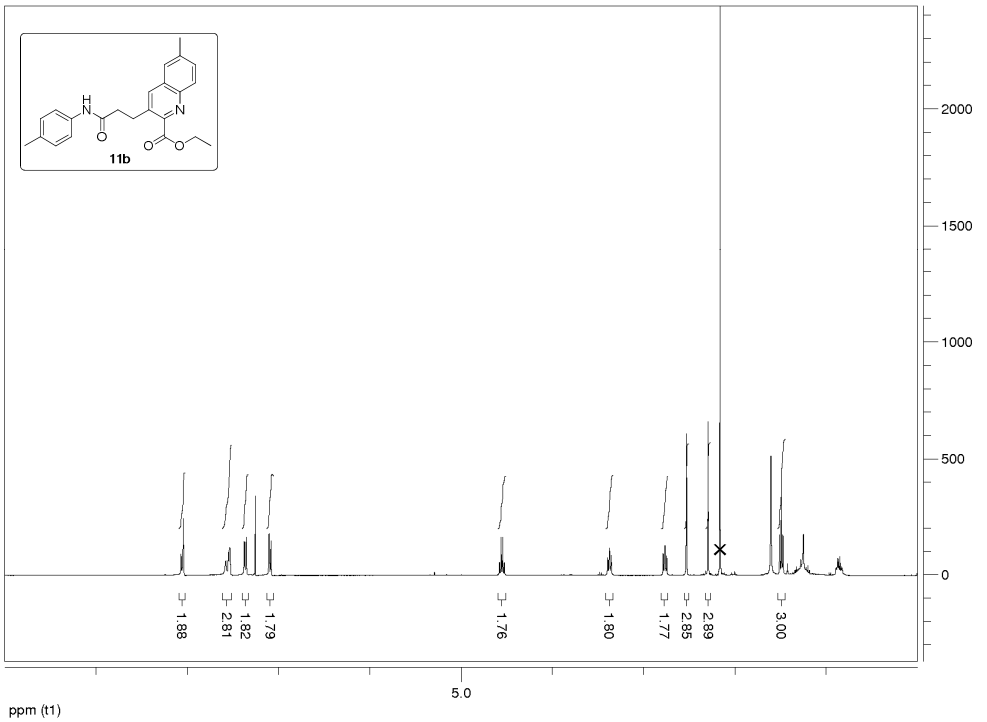


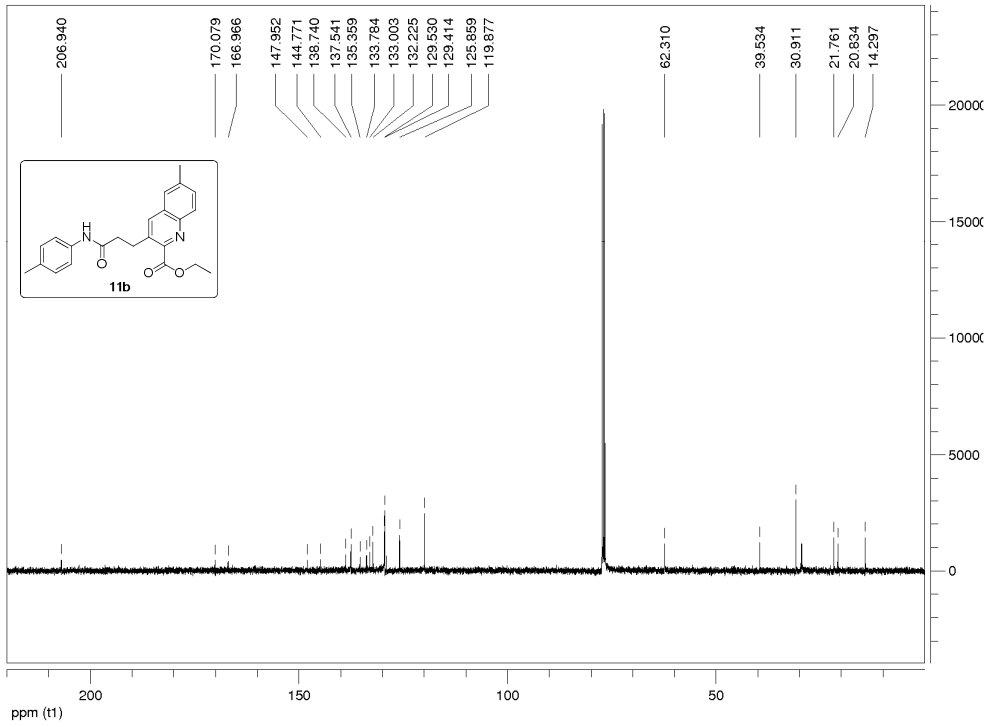
3-(6-methoxy-2-(4-(trifluoromethyl)phenyl)quinolin-3-yl)-*N*-pentylpropanamide (11a):



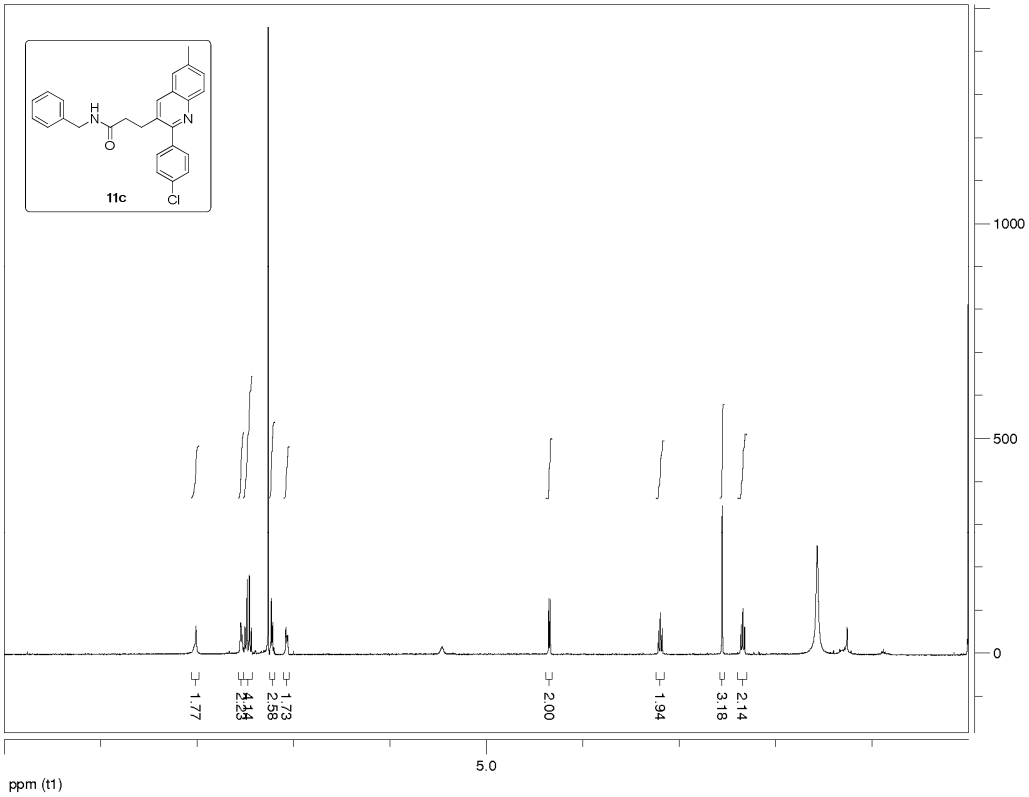


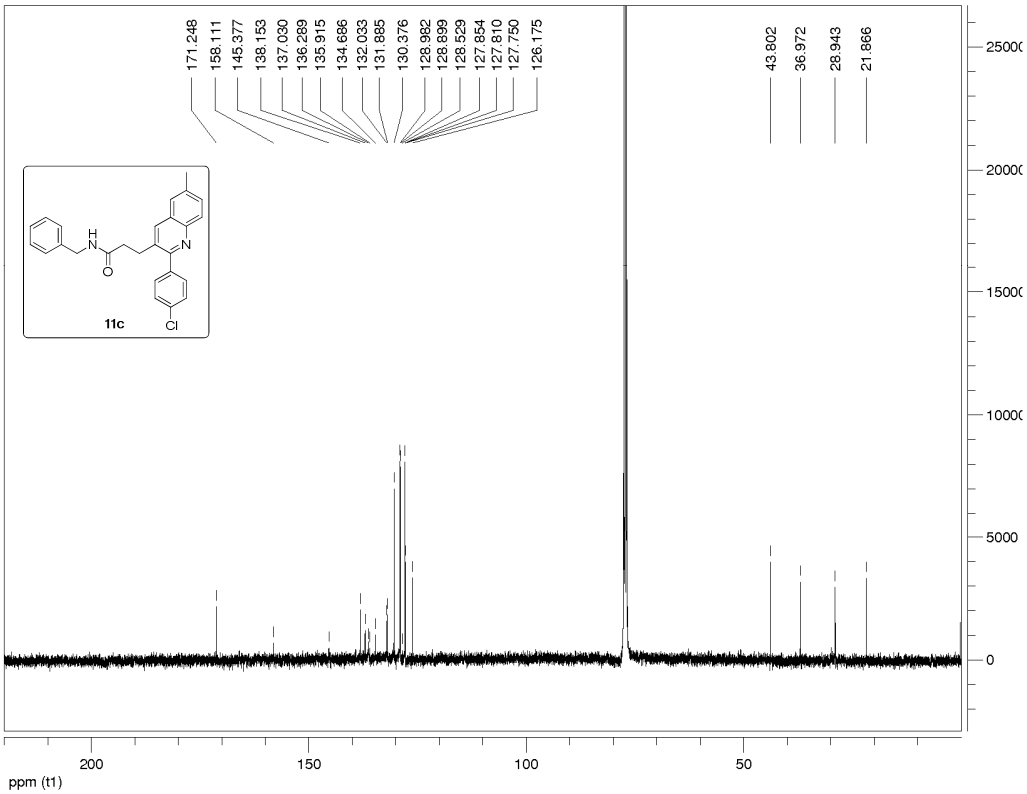
ethyl 6-methyl-3-(3-oxo-3-(*p*-tolylamino)propyl)quinoline-2-carboxylate (11b) :



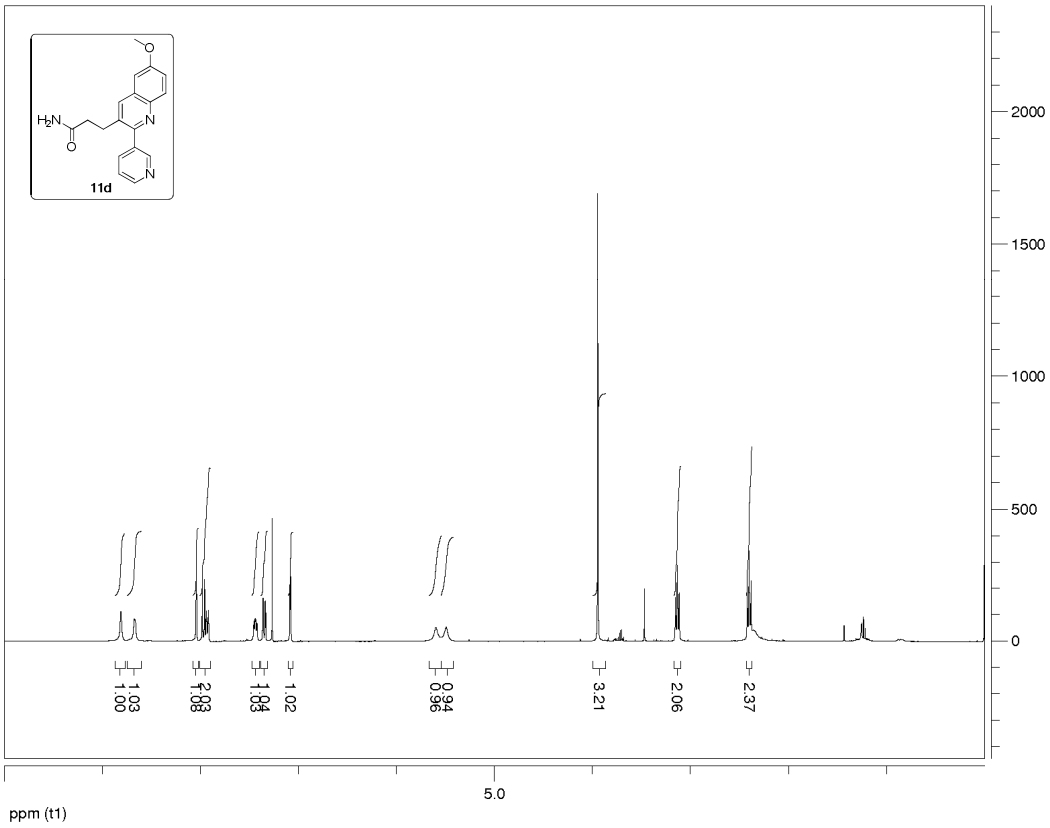


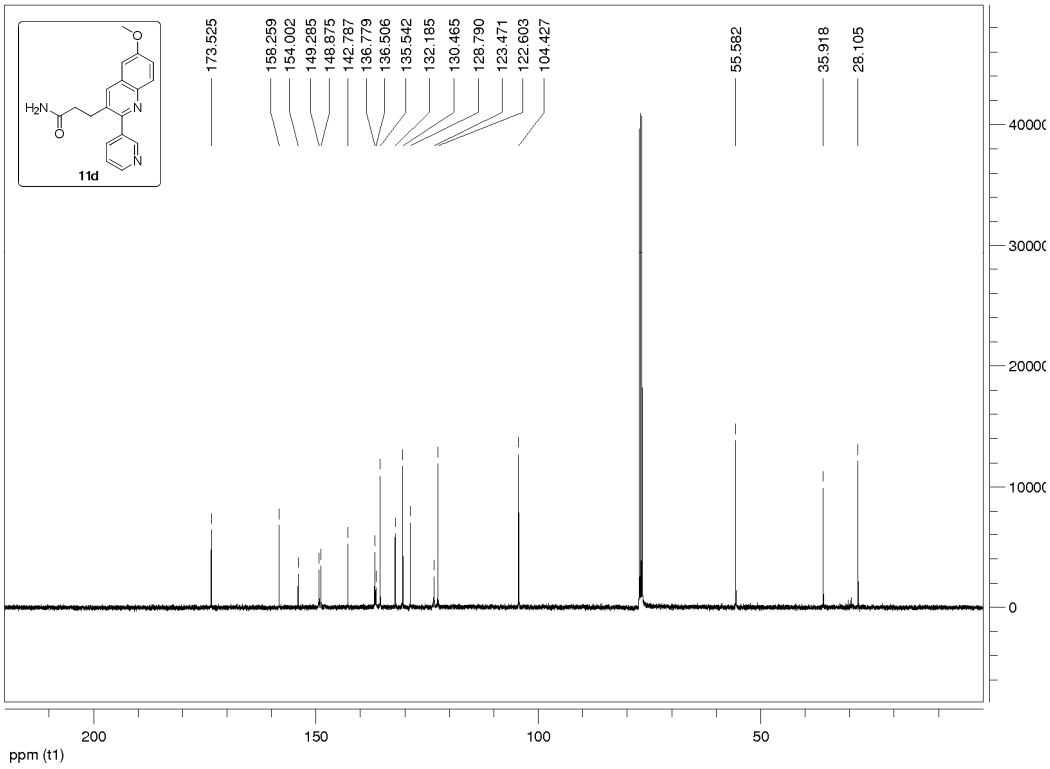
***N*-benzyl-3-(2-(4-chlorophenyl)-6-methylquinolin-3-yl)propanamide (11c):**



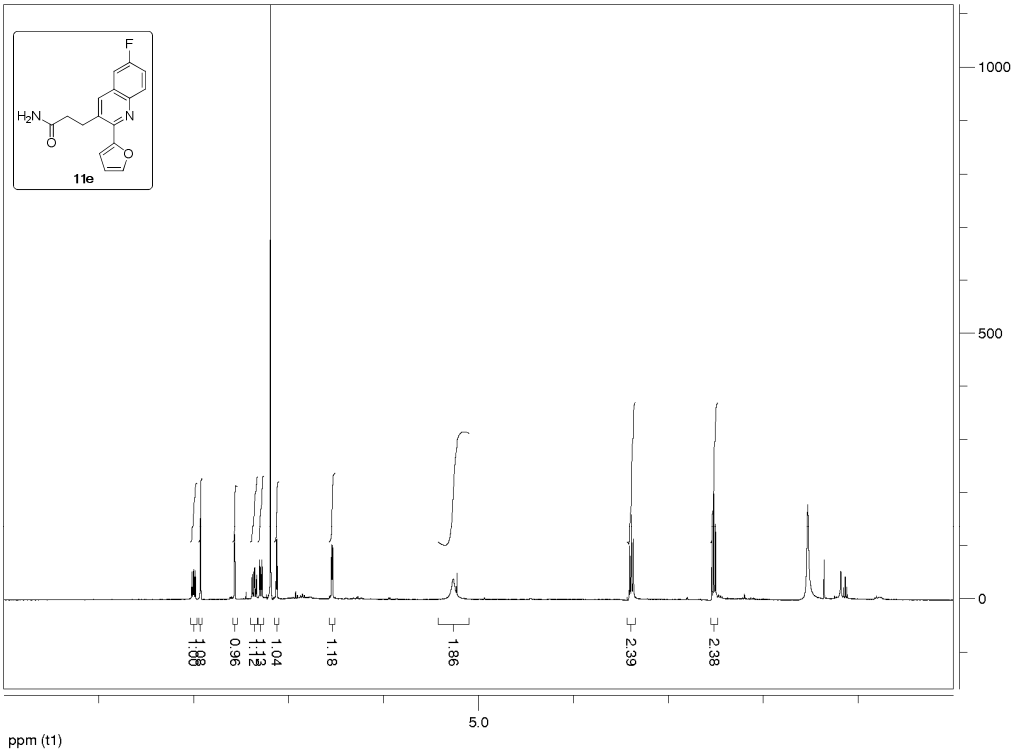


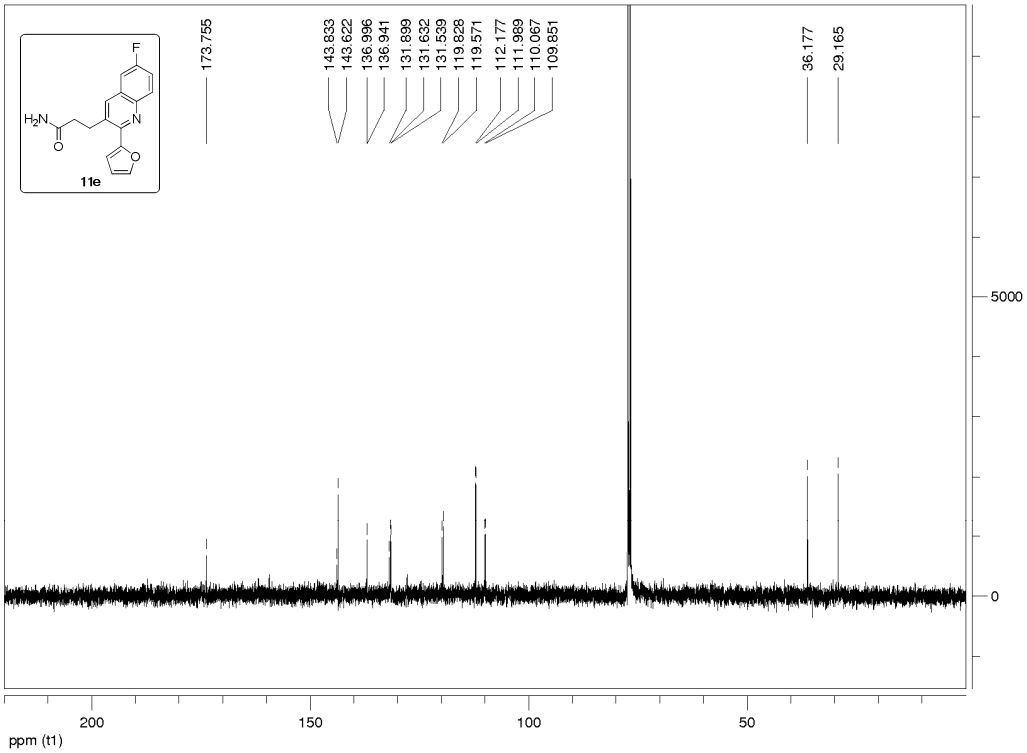
3-(6-methoxy-2-(pyridin-3-yl)quinolin-3-yl)propanamide (11d):



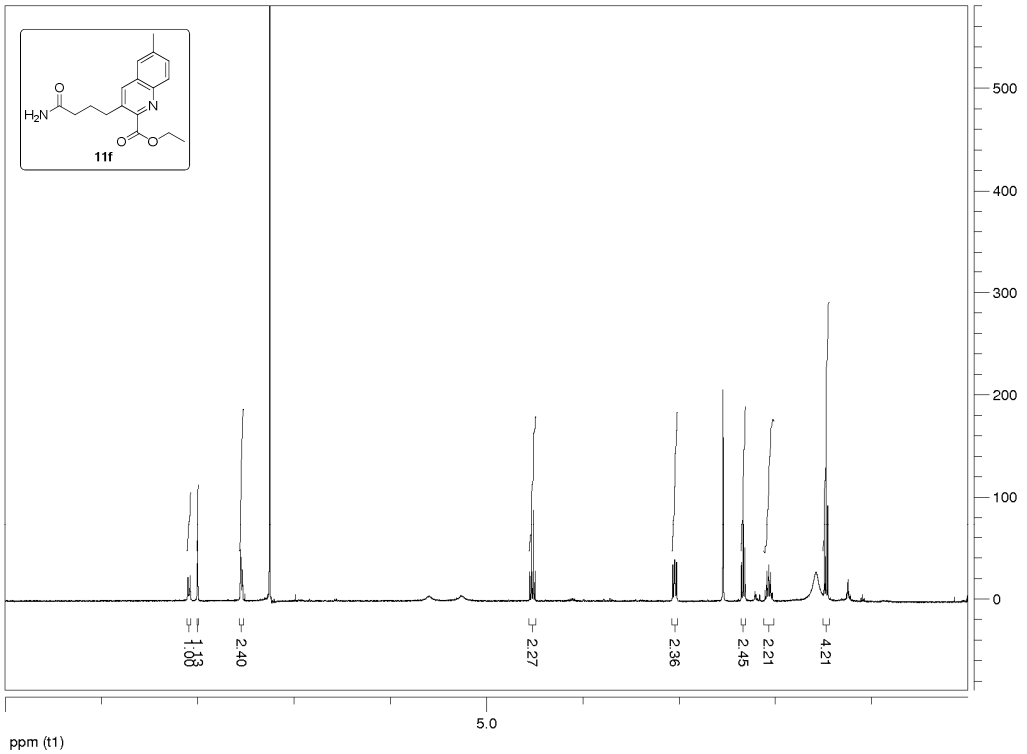


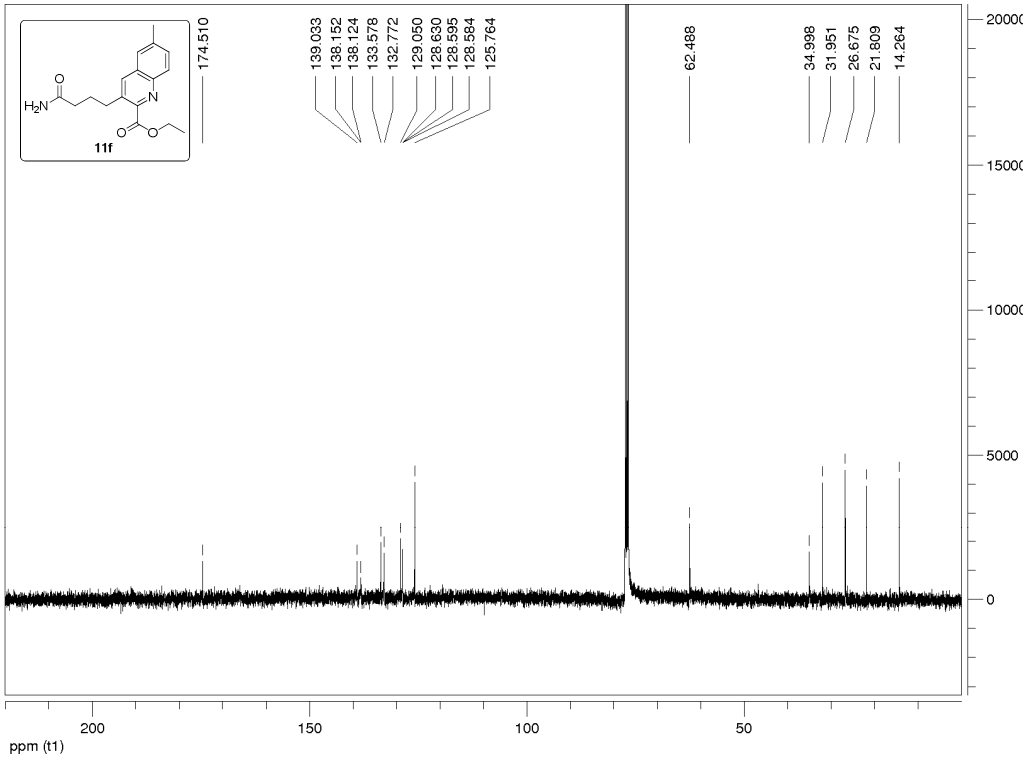
3-(6-fluoro-2-(furan-2-yl)quinolin-3-yl)propanamide (11e):





ethyl 3-(4-amino-4-oxobutyl)-6-methylquinoline-2-carboxylate (11f):





3. Estudio sobre la reactividad de nuevas olefinas heterocíclicas en la reacción de Povarov

New Heterocyclic Inputs for the Povarov Multicomponent Reaction

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

Abstract: Oxa-, thia- and imidazolones are reactive inputs as electron-rich olefin components in Povarov reactions. On interaction with anilines and aldehydes, these substrates afford the corresponding multicomponent adducts in a regioselective manner. Intramolecular processes are also explored. Post-condensation oxidation provides convenient access to a variety of fused quinoline derivatives.

Key words: domino reaction, heterocycles, imines, multicomponent reaction, quinolines

Multicomponent reactions (MCRs) constitute a useful group of transformations of growing impact in organic chemistry. Due to their atom- and step-economy, convergence and exploratory power, they have found numerous applications in organic synthesis, combinatorial chemistry, and medicinal chemistry.[1] On the other hand, heterocycles can be found in a large number of natural products, drugs, and bioactive compounds. Thus, the participation of heterocycles in MCRs as reactants, with their specific reactivity, brings novel avenues of connectivity and nicely complements their classical role as MCR adducts.[2] The Povarov reaction ranks among the most used MCRs.[3] This transformation consists of the interaction of a carbonyl compound, an aniline, and an activated olefin (usually enol ethers or enamine derivatives[4]) to yield, under acid catalysis, a tetrahydroquinoline adduct. The process is assumed to take place in a domino fashion through the intermediacy of the corresponding imine, which once activated by the catalyst suffers the nucleophilic attack of the electron-rich olefin to give a cationic intermediate ready to be trapped by the aromatic ring of the aniline moiety.[5] In this context, our group has reported that a variety of nitrogen heterocycles, such as dihydropyridines[6] and unsaturated lactams,[7] can be used as activated olefin inputs in this MCR. Interestingly, the use of cyclic enol esters in Povarov processes yields, through a mechanistic detour, N-arylated lactams, instead of the usual tetrahydroquinoline adducts.[8]

In order to expand the range of the olefinic components in this MCR, we decided to study the participation of vicinally heteroatom-disubstituted olefins such as 1,3-oxa-, thia-, and imidazol-2-one and related systems (Scheme 1).

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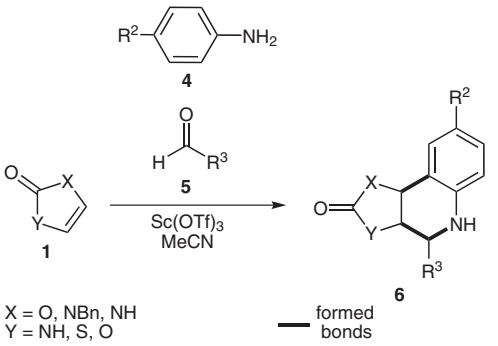
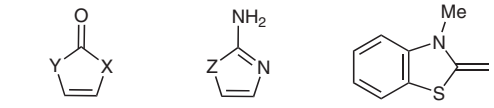
The reactivity of some geminally diheterosubstituted systems was also tackled. Although the putative structures resulting from these MCRs are attractive, only a scattered number of precedents can be found in databases, including ketene dithioacetals,[9] dihydro-1,4-dioxines, and 1,3-dioxoles.[10]



Scheme 1 Povarov reactions with heterocyclic olefinic inputs

The main points to be determined were the stability and reactivity of this class of compounds in Povarov conditions, which involve the presence of water, acidic media, and cross reactivity processes with anilines and aldehydes. Our attention was focused on a large family of structures (Figure 1) with great synthetic potential as versatile building blocks in a variety of transformations, particularly Diels–Alder cycloadditions.[11] The scope of the Povarov MCR was studied with heterocyclic systems **1a–e**, **2a**,**b**, and **3** (Figure 1). Only one of them was commercially available (**1e**) and the rest were synthesized by known methods or modifications thereof.[12] In view of the recently published participation of the 2-aminooxazole **2a** in a somewhat related process,[13] we have included this aromatic compound together with the imidazole **2b**[14] in the reactant list.



1a–e **2** **3**

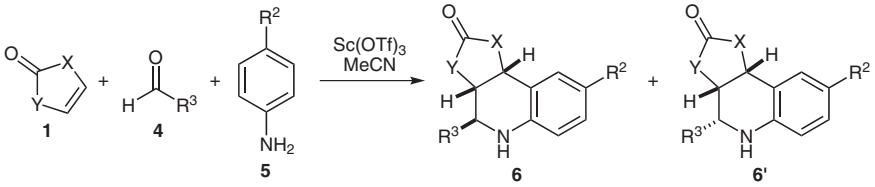
1a: X = NH, Y = NH
1b: X = NBn, Y = O
1c: X = NH, Y = S
1d: X = NBn, Y = S
1e: X = O, Y = O

2a Z = O
2b Z = NH

Figure 1 Novel inputs tested for Povarov MCRs

Initially, all experiments were run under standard conditions for the Povarov reaction, in which the activated olefin interacts with an aniline-aldehyde mixture under $Sc(OTf)_3$ catalysis in the presence of 4 Å molecular sieves, with acetonitrile as the solvent and at room temperature.[3,15] However, in some cases it was necessary to use microwave activation or prolonged heating to achieve useful yields.

Table 1 Scope of the Povarov MCR with 1-Heterosubstituted 3-Azol-2-ones



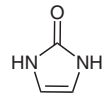
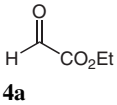
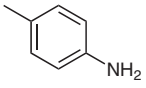
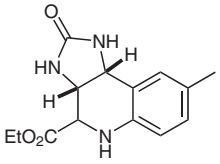
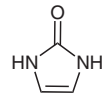
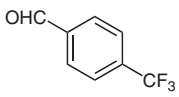
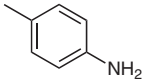
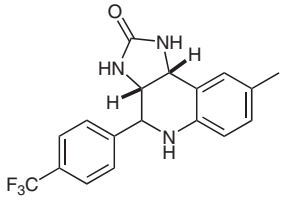
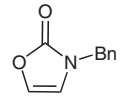
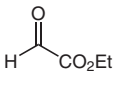
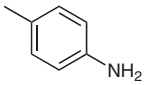
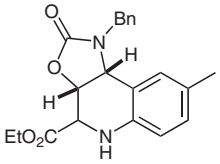
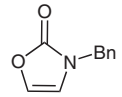
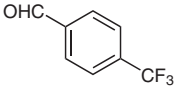
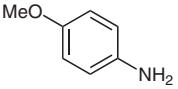
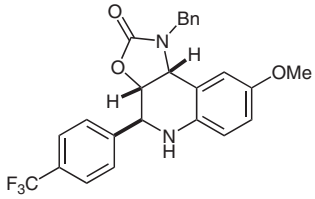
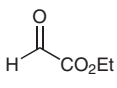
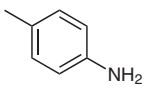
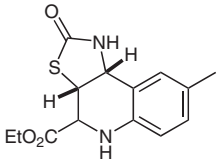
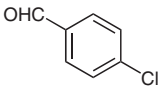
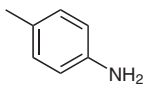
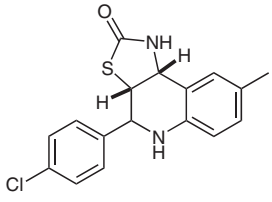
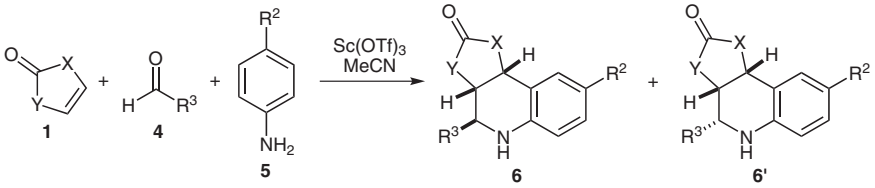
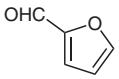
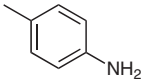
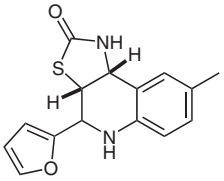
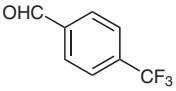
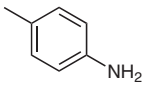
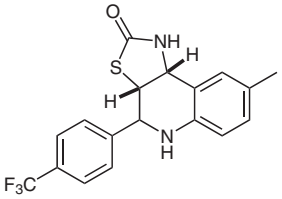
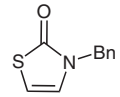
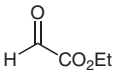
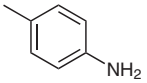
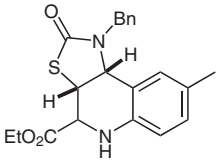
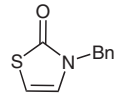
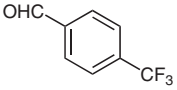
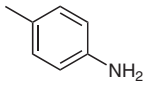
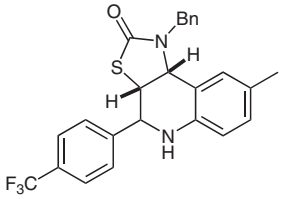
Entry	1	4	5	6/6′	Conditions	Isomer ratio (6/6′)	Yield (%)
1	 **1a**	 **4a**	 **5a**	 **6a/6a′**	50 °C, 12 h	1:1	81
2	 **1a**	 **4b**	 **5a**	 **6b/6b′**	MW, 10 min	1:1	58
3	 **1b**	 **4a**	 **5a**	 **6c/6c′**	r.t., 12 h	3:1	42
4	 **1b**	 **4b**	 **5b**	 **6d**	r.t., 12 h	1:0	35
5	 **1c**	 **4a**	 **5a**	 **6e/6e′**	MW, 10 min	2:1	72
6	 **1c**	 **4c**	 **5a**	 **6f/6f′**	50 °C, 5 d[a]	1:2	44

Table 1 Scope of the Povarov MCR with 1-Heterosubstituted 3-Azol-2-ones (continued)



Entry	1	4	5	6/6′	Conditions	Isomer ratio (6/6′)	Yield (%)
7	 **1c**	 **4d**	 **5a**	 **6g/6g′**	MW, 30 min	1:2	48
8	 **1c**	 **4b**	 **5a**	 **6h/6h′**	50 °C, 5 d	2:1	55
9	 **1d**	 **4a**	 **5a**	 **6i/6i′**	MW, 10 min	5:1[b]	53
10	 **1d**	 **4b**	 **5a**	 **6j/6j′**	MW, 10 min	2:1	84

[a] Two equivalents of components **4** and **5**.
[b] Isomer ratio assigned by analogy with related compounds.

The scope of the reaction was studied by screening all components: the activated olefin input (**1a**–**d**, Table 1), the aniline, and the aldehyde reactants. 1*H*-Imidazol-2(3*H*)-one (**1a**) reacted with ethyl glyoxalate (**4a**) and *p*-toluidine (**5a**) to give the expected adducts **6a/6a′** as a nearly equimolecular mixture of stereoisomers in 81% yield (Table 1, entry 1). As expected, the ring fusion was *cis*, and there was lack of stereoselectivity, which is the usual outcome in this type of MCR. Analogously, the interaction of **1a** with aromatic aldehyde **4b** and aniline **5a** afforded tetrahydroquinolines **6b/6b′** in 58% yield (Table 1, entry 2). In the case of *N*-benzyloxazolone **1b**, the reaction was also productive with aromatic and electrophilic aldehydes, and with activated anilines (4-Me and 4-MeO, **5a** and **5b**, respectively). Remarkably, the reaction displayed a good regioselectivity and only one regioisomer could be detected, **6c/6c′** being produced as the usual stereoisomeric mixture (3:1, 42%, entry 3) and in the case of the interaction with the aromatic aldehyde (Table 1, entry 4), only one racemate was obtained (**6d**, 35%). Next, the reactivity of thiazol-2(3*H*)-one (**1c**) was tested. Thanks to the easier access to this heterocycle, its convenient storage and reluctance to suffer hydrolytic degradation, a broad panel of aldehydes and anilines were reacted against this input. Although requiring different reaction conditions, all kinds of aldehydes gave raise to productive transformations. The reaction was again highly regioselective, and when ethyl glyoxalate was used, a suitable yield of the adduct (**6e/6e′**, 72%, Table 1, entry 5) was obtained. Similar results were observed with aromatic and heteroaromatic aldehydes, ranging from highly activated (4-CF_3, **4b**, entry 8) to less electrophilic derivatives

(4-Cl, **4c**, entry 6; furfural, **4d**, entry 7). The benzylated derivative **1d** also gave satisfactory results, again with high regioselectivities (entries 9 and 10). Interestingly, in the former case, although detected by NMR methods, the crude mixture of adducts **6i/6i′** could not be isolated, as they underwent spontaneous oxidation to the corresponding quinoline derivative **11f** during column chromatography.

The structural assignment of these scaffolds was performed by NMR methods (^{1}H, ^{13}C, COSY, HMBC, HSQC, NOESY), among which the NOE correlations were of diagnostic value and allowed the stereochemical features and regioselectivity of the process to be established (Figure 2). Optimized geometries to crosscheck the observed results were calculated with molecular mechanics, semiempirical, and DFT methods.

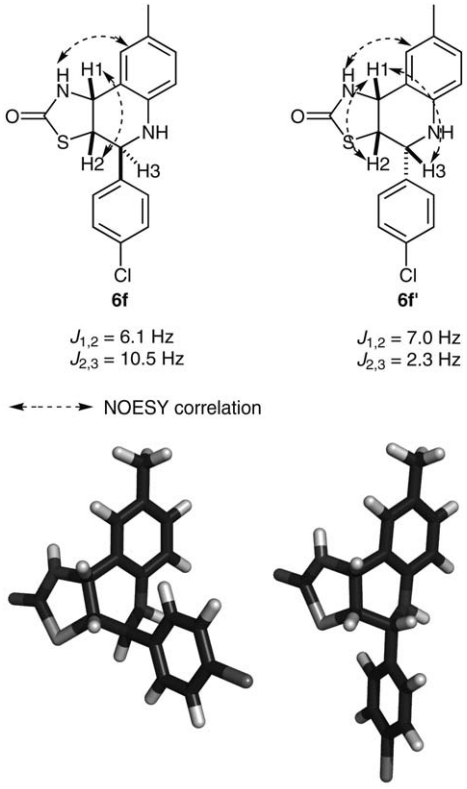
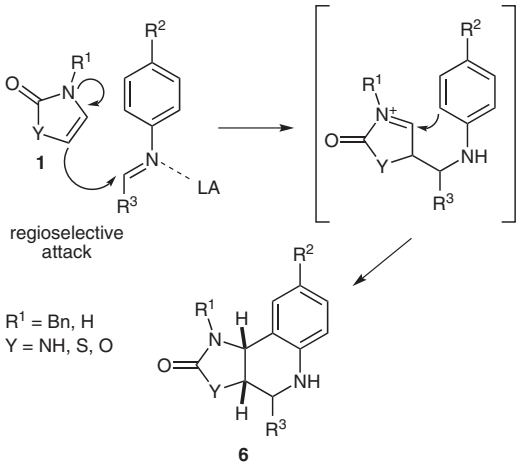


Figure 2 Diagnostic NOESY correlations for **6f/6f′**; comparison with optimized geometries

Taking into account the stepwise nature of the most accepted mechanism for the Povarov reaction (Scheme 2), the low degree of stereoselectivity could be attributed to the feasibility of both facial orientations between the imine and olefin inputs. On the other hand, the regiocontrol seemed to arise from the higher activation exerted by the nitrogen towards its β-carbon, with respect to the corresponding effect of the oxygen or sulfur atoms. Studies to determine the nature of these phenomena are currently being addressed by computational methods. Interestingly, when trying to deactivate the heterocyclic nitrogen in **1c** by acylation, the generated thiazolone proved to be very

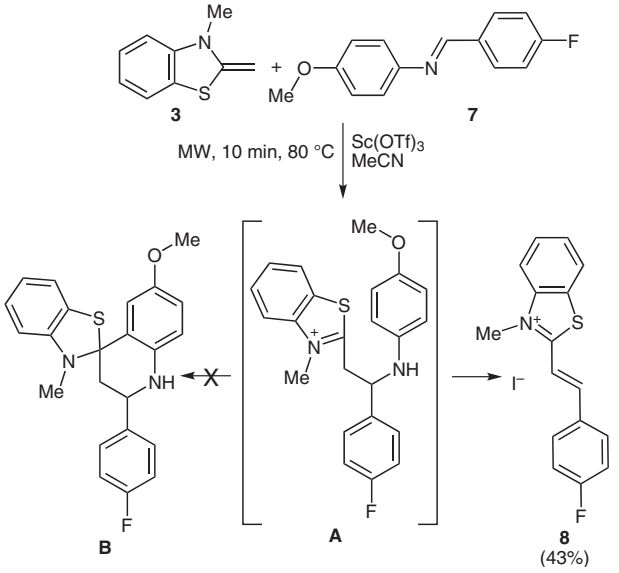


Scheme 2 Mechanistic proposal for the Povarov MCR

sensitive to hydrolysis and did not result in productive MCRs.

No useful reactivity arose from 1,3-dioxol-2-one (**1e**), presumably because of its lability towards hydrolysis. Even when performing the reaction under mild conditions and with preformed imines we were unable to detect the desired adducts or by-products derived from them. Remarkably, 1,3-dioxoles lacking the carbonyl moiety connecting the heterocyclic oxygens have been reported as productive inputs in Povarov processes.[10] Similarly, 2-aminooxazole (**2a**) has been tested in analogous MCRs,[13] although this compound, together with imidazole **2b**,[14] were not productive when reacted under standard conditions in Povarov reactions. Nevertheless, in some cases the formation of the MCR adduct was detected in minute amounts (NMR/MS evidence).

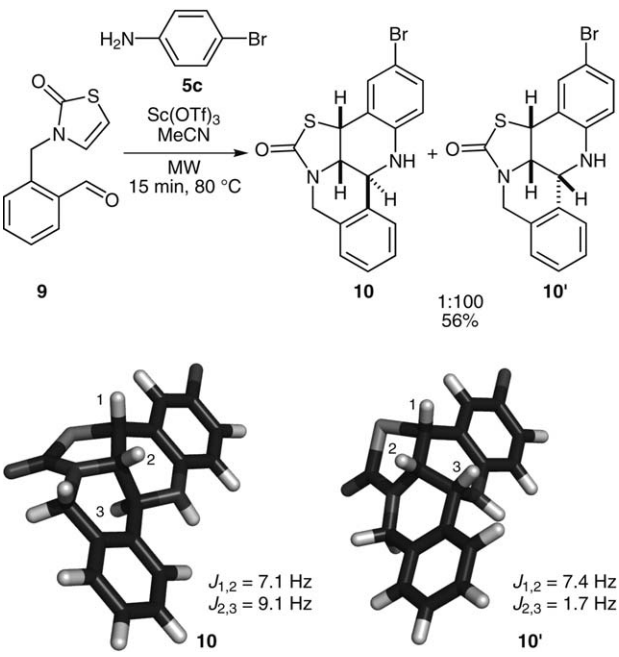
In this context, the reactivity of 2-methylenebenzothiazoline **3** (Scheme 3) was studied next. After some experimentation, it was decided to promote the Povarov reaction with the preformed imines, due to the instability of the activated olefin **3** in the presence of water, and also the literature precedents on the reactivity of this kind of compounds **3** with aldehydes to form styrylmethylbenzothiazolium salts.[16] Therefore, 2,3-dimethylbenzothiazolium iodide was treated with *n*-butyllithium at low temperature to generate in situ the methylenebenzothiazoline **3**, which was reacted with imine **7** using microwave activation conditions. Interestingly, the spiro compound **B** (Scheme 3) was not detected, in sharp contrast with the reactivity described for the structurally similar ketene dithioacetals.[9] The major product in this reaction was the stilbazolium vinylogous salt **8** (43%). Its formation could be the result of the expected addition of the nucleophilic enamine moiety upon the electrophilic imine to generate the putative intermediate **A**, followed by the formal elimination of aniline. To confirm this hypothesis, the reaction between the 4-fluorobenzaldehyde and 2,3-dimethylbenzothiazolium iodide[17] was performed in acetic anhydride as described,[16] to nicely afford compound **8**, thus confirming the initial hypothesis.



Scheme 3 Reactivity study of 2-methylenebenzothiazolines

In order to reverse the observed regiochemistry, it was decided to tackle an intramolecular version of these MCRs.[18] Thus, the olefin-aldehyde input **9**, whose reactive moieties are tethered by a methylene group, was reacted with aniline **5c** (Scheme 4). After unsuccessful attempts at room temperature and reflux conditions, the activation was productive through microwave irradiation, allowing the isolation of the desired pentacyclic products in moderate yield (56%, **10/10′**, 1:100).

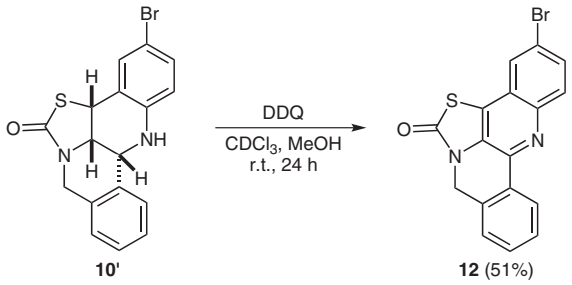
Remarkably, the reaction proceeded with high stereocontrol, with the all-*cis* relative stereochemistry predominating. The stereochemistry of both adducts was determined through the analysis of the diagnostic coupling constants (Scheme 4), which matched the expected values for the



Scheme 4 Intramolecular Povarov reaction

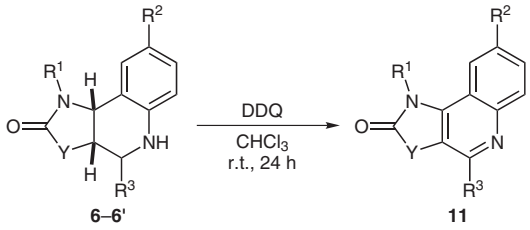
calculated optimized geometries. The origin of such stereoselection, which reverses the natural tendency observed in the intermolecular processes, is under study.

Finally, the MCR adducts were successfully oxidized to the corresponding quinolines through DDQ treatment (Table 2).[19,20] As usual, moderate yields (50–69%) were obtained in these transformations. On other hand, the intramolecular adduct **10′** was successfully oxidized in 51% yield to the corresponding fused quinoline system **12** (Scheme 5).



Scheme 5 Oxidation of the intramolecular Povarov adduct

Table 2 Oxidation of the Povarov Adducts **6/6′**



Entry	Substrate	Y	R^1	R^2	R^3	Product (Yield, %)
1	**6a/6a′**	NH	H	Me	CO_2Et	**11a** (65)
2	**6b/6b′**	NH	H	Me	4-$CF_3C_6H_4$	**11b** (50)
3	**6d**	O	Bn	OMe	4-$CF_3C_6H_4$	**11c** (61)
4	**6e/6e′**	S	H	Me	CO_2Et	**11d** (55)
5	**6g/6g′**	S	H	Me	2-furyl	**11e** (40)
6	**6i/6i′**	S	Bn	Me	CO_2Et	**11f** (quant)[a]
7	**6j/6j′**	S	Bn	Me	4-$CF_3C_6H_4$	**11g** (69)

[a] The Povarov adducts **6i/6i′** were oxidized spontaneously during purification by silica gel chromatography.

In conclusion, a new class of reactive inputs for the Povarov reaction has been described with satisfactory results. A suitable range of heteroatom-substituted olefins participate in the process in a regioselective manner. Remarkably, the intramolecular process involving the thiazolone residue linked to the aldehyde moiety by its nitrogen atom leads to a clean reversal of the natural regioselectivity, affording the tetrahydroquinoline adduct **10′** with high stereocontrol. The obtained MCR adducts were conveniently oxidized to yield the corresponding quino-

lines. This transformation notably expands the structural variability of tetrahydroquinolines and quinolines, which are ubiquitous scaffolds in natural products, biologically active compounds, and drugs.[21,22]

Unless stated otherwise, all reactions were carried out under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. TLC was performed on precoated Merck silica gel 60 F_{254} plates, developed with hexanes–EtOAc (1:1) or CH_2Cl_2–MeOH (95:5) mixtures, and visualized under a UV lamp. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Bruker 500 spectrometer. Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constants (Hz) and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned by means of two-dimensional NMR spectroscopy: ^1H–^1H-COSY, ^1H–^{13}C-COSY (HSQC: Heteronuclear Single Quantum Coherence) and long-range ^1H–^{13}C-COSY (HMBC: Heteronuclear Multiple Bond Connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

Povarov Multicomponent Reaction; General Procedure A

Molecular sieves 4Å (ca. 2 g) and $Sc(OTf)_3$ (0.2 mmol) were added to a solution of aldehyde (1 mmol) and aniline (1 mmol) in anhyd MeCN (4 mL), and the mixture was stirred at r.t. After 5 min, a solution of the olefin (1 mmol) in anhyd MeCN (3 mL) was added. The different reaction conditions are listed below as separate methods. Sat. aq $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography (hexanes–EtOAc) to give the desired products.

Method A: The reaction mixture was stirred at r.t. and the progress of the reaction was controlled by TLC or HPLC until the starting material completely disappeared or no further evolution was observed (if needed, an additional 5% catalyst was added every 24 h).

Method B: The reaction mixture was stirred at 50 °C and the progress of the reaction was controlled by TLC or HPLC until the starting material completely disappeared or no further evolution was observed (if needed, an additional 5% catalyst was added every 24 h).

Method C: $Sc(OTf)_3$ (0.2 mmol) were added to a solution of aldehyde (1 mmol) and aniline (1 mmol) in anhyd MeCN (1–1.5 mL), and the mixture was stirred at r.t. After 5 min, a solution of the olefin (1 mmol) in anhyd MeCN (0.5–1 mL) was added. The reaction vessel was introduced in a microwave apparatus (Discover CEM), and the reaction run at 80 °C and 100 W with Power Max option selected. Cycles of 10 min were carried out until the starting materials completely disappeared or no further evolution was observed.

Oxidation of MCR Adducts to Quinolines; General Procedure B

To a solution of compound **6/6′** or **10′** (1 mmol) in $CHCl_3$ (15 mL) was added DDQ (2 mmol), and the mixture was stirred 24 h in an open vessel at r.t. Sat. aq $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The reaction mixture was purified with flash chromatography (hexanes–EtOAc) to afford the desired product.

Ethyl (3a*RS*,4*SR*,9b*RS*)-8-Methyl-2-oxo-2,3,3a,4,5,9b-hexahydro-1*H*-imidazo[4,5-*c*]quinoline-4-carboxylate (6a′)

Following the general procedure A, method B (12 h), the reaction of **1a**, *p*-toluidine, and ethyl glyoxalate afforded compounds **6a/6a′** (81%, **6a/6a′**, 1:1). This mixture was purified by flash chromatography to afford pure **6a′** as a white powder. Yield: 47 mg (41%).

IR (KBr): 3135, 3001, 2968, 2846, 1713, 1668, 1559, 1463, 1392, 1251, 1187, 1040, 822, 669 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.90–6.86 (m, 1 H), 6.81 (dd, *J* = 8.1, 1.3 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 6.68 (d, *J* = 4.4 Hz, 1 H), 6.42–6.37 (m, 1 H), 5.39 (s, 1 H), 4.73–4.68 (m, 1 H), 4.44–4.38 (m, 1 H), 4.24–4.09 (m, 2 H), 3.87–3.81 (m, 1 H), 2.15 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.6, 162.4, 141.9, 129.6, 128.2, 126.3, 122.8, 115.3, 60.9, 56.2, 53.8, 50.5, 20.3, 13.9.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{17}N_3O_3$ + Na (M + Na^+): 298.1162; found: 298.1160.

(3a*RS*,4*RS*,9b*SR*)-8-Methyl-4-[4-(trifluoromethyl)phenyl]-3,3a,4,5-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2(9b*H*)-one (6b′)

Following the general procedure A, method C (1 cycle of 10 min), the reaction of **1a**, *p*-toluidine, and 4-(trifluoromethyl)benzaldehyde afforded compounds **6b/6b′** (58%, **6b/6b′**, 1:1). This mixture was purified by flash chromatography to afford pure **6b′** as a white powder. Yield: 94 mg (29%).

IR (KBr): 3455, 3263, 3192, 3122, 3077, 2904, 167, 1617, 1508, 1418, 1264, 1168, 1130, 1066, 1014, 829 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.70 (s, 4 H), 7.02–7.00 (m, 1 H), 6.91 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.71 (d, *J* = 8.1 Hz, 1 H), 5.00 (d, *J* = 9.2 Hz, 1 H), 4.42 (dd, *J* = 9.1, 2.6 Hz, 1 H), 4.37 (d, *J* = 2.6 Hz, 1 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 165.8, 145.9, 145.1, 130.98 (q, *J* = 32.2 Hz), 130.6, 130.1, 129.8, 129.3, 127.1, 126.5 (q, *J* = 3.9 Hz), 124.4, 124.1, 121.7, 117.1, 60.1, 59.9, 53.6, 20.7.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{17}F_3N_3O$ (M + H^+): 348.1318; found: 348.1315.

Ethyl (3a*RS*,4*SR*,9b*SR*)-1-Benzyl-8-methyl-2-oxo-1,2,3a,4,5,9b-hexahydrooxazolo[5,4-*c*]quinoline-4-carboxylate (6c)

Following the general procedure A, method A (12 h), the reaction of **1b**, *p*-toluidine, and ethyl glyoxalate afforded compounds **6c/6c′** (42%, **6c/6c′**, 3:1). This mixture was purified by flash chromatography to afford pure **6c** as a white powder. Yield: 81 mg (32%).

IR (KBr): 3365, 3321, 2975, 2917, 1738, 1508, 1431, 1360, 1341, 1232, 1155, 1098, 1053 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 5 H), 6.99 (dd, *J* = 1.6, 8.0 Hz, 1 H), 6.73–6.68 (m, 2 H), 5.41 (dd, *J* = 9.5, 2.6 Hz, 1 H), 4.75 (d, *J* = 15.7 Hz, 1 H), 4.69 (d, *J* = 9.5 Hz, 1 H), 4.41–4.27 (m, 2 H), 3.75 (d, *J* = 2.6 Hz, 1 H), 3.61 (d, *J* = 15.7 Hz, 1 H), 2.25 (s, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1, 157.2, 144.09, 135.9, 130.7, 130.5, 129.2, 128.9, 127.9, 127.9, 119.3, 116.71, 75.8, 62.3, 60.2, 54.1, 45.2, 20.7, 14.3.

HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{23}N_2O_4$ (M + H^+): 367.1652; found: 367.165.

(3a*RS*,4*RS*,9b*SR*)-1-Benzyl-8-methoxy-4-[4-(trifluoromethyl)phenyl]-1,4,5,9b-tetrahydrooxazolo[5,4-*c*]quinolin-2(3a*H*)-one (6d)

Following the general procedure A, method A (12 h), the reaction of **1b**, 4-methoxyaniline, and 4-(trifluoromethyl)benzaldehyde afforded compound **6d** (35%). This crude mixture was purified by

flash chromatography to afford pure **6d** as a pale yellow powder. Yield: 153 mg (35%).

IR (KBr): 3428, 3333, 3071, 3026, 2923, 2832, 1719, 1508, 1431, 1322, 1258, 1117, 1066, 1014 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.80 (d, *J* = 8.2 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 2 H), 7.27 (t, *J* = 7.2 Hz, 1 H), 7.20 (d, *J* = 7.2 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 1 H), 6.76 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.55 (d, *J* = 2.6 Hz, 1 H), 5.80 (s, 1 H), 5.23–5.13 (m, 1 H), 4.85 (d, *J* = 9.3 Hz, 1 H), 4.56 (d, *J* = 16.3 Hz, 1 H), 4.29–4.23 (m, 1 H), 3.92 (d, *J* = 16.2 Hz, 1 H), 3.63 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.7, 152.2, 152.1, 143.3, 142.3, 142.2, 136.2, 128.9, 128.5, 128.2 (q, *J* = 31.7 Hz), 127.2, 126.9, 124.9 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 272.1 Hz), 119.8, 117.5, 117.5, 115.4, 114.4, 77.3, 77.3, 60.3, 60.2, 55.3, 54.2, 44.7.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{22}F_3N_2O_3$ (M + H^+): 455.1577; found: 455.1574.

Ethyl (3a*RS*,4*SR*,9b*RS*)-8-Methyl-2-oxo-1,2,3a,4,5,9b-hexahydrothiazolo[5,4-*c*]quinoline-4-carboxylate (6e)

Following the general procedure A, method C (1 cycle of 10 min), the reaction of **1c**, *p*-toluidine, and ethyl glyoxalate afforded compounds **6e/6e′** (72%, **6e/6e′**, 2:1). This mixture was purified by flash chromatography to afford pure **6e** as a pale yellow powder. Yield: 100 mg (48%).

IR (film): 3334, 3193, 3077, 2917, 2866, 1732, 1694, 1662, 1508, 1329, 1245, 1015, 816 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.92–6.89 (m, 1 H), 6.64 (d, *J* = 8.2 Hz, 1 H), 5.96 (br s, 1 H), 4.98 (d, *J* = 6.2 Hz, 1 H), 4.40 (br s, 1 H), 4.29 (q, *J* = 7.1 Hz, 2 H), 4.10 (d, *J* = 10.1 Hz, 1 H), 3.95 (ddd, *J* = 10.1, 6.2, 0.5 Hz, 1 H), 2.25 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 170.0, 140.4, 130.7, 129.8, 129.2, 117.4, 116.2, 62.4, 56.7, 54.1, 45.5, 20.6, 14.3.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{17}N_2O_3S$ (M + H^+): 293.0954; found: 293.0953.

(3a*RS*,4*RS*,9b*SR*)-4-(4-Chlorophenyl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6f)

Following the general procedure A, method B (5 d), the reaction of **1c**, *p*-toluidine, and 4-chlorobenzaldehyde afforded compounds **6f/6f′** (44%, **6f/6f′**, 1:2). This mixture was purified by flash chromatography to afford pure **6f** as a yellow powder. Yield: 64 mg (15%).

IR (KBr): 3385, 3161, 3071, 2911, 1668, 1617, 1501, 1476, 1341, 1258, 1194, 1085, 1008, 835 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.59 (br s, 1 H), 7.52–7.42 (m, 4 H), 7.05–7.02 (m, 1 H), 6.89 (dd, *J* = 8.3, 1.8 Hz, 1 H), 6.64 (d, *J* = 8.2 Hz, 1 H), 6.25 (br s, 1 H), 4.92 (d, *J* = 6.1 Hz, 1 H), 4.12 (d, *J* = 10.5 Hz, 1 H), 3.92 (dd, *J* = 10.4, 6.0 Hz, 1 H), 2.18 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.5, 143.0, 139.8, 132.6, 130.7, 130.6, 129.3, 128.2, 125.3, 117.0, 114.95, 57.4, 54.6, 50.1, 20.2.

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{16}ClN_2OS$ (M + H^+): 331.0666; found: 331.0669.

(3a*RS*,4*SR*,9b*SR*)-4-(4-Chlorophenyl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6f′)

In the above process, on further elution, compound **6f′** was obtained as a yellow powder. Yield: 125 mg (29%).

IR (KBr): 3385, 3160, 3071, 2911, 1617, 1476, 1341, 1258, 1194, 1085, 1008, 835, 669 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.76 (d, *J* = 1.3 Hz, 1 H), 7.52–7.43 (m, 4 H), 7.06–7.02 (m, 1 H), 6.86 (dd, *J* = 8.2, 1.4 Hz, 1 H), 6.66 (d, *J* = 8.2 Hz, 1 H), 6.01 (br s, 1 H), 5.01 (d, *J* = 7.0 Hz, 1 H), 4.78–4.73 (m, 1 H), 4.67–4.61 (m, 1 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.9, 142.2, 140.2, 132.3, 128.9, 128.5, 128.4, 128.3, 126.4, 120.9, 115.4, 55.1, 53.9, 53.7, 20.3.

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{16}ClN_2OS$ (M + H^+): 331.0666; found: 331.067.

(3a*RS*,4*RS*,9b*RS*)-4-(Furan-2-yl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6g′)

Following the general procedure A, method C (3 cycles of 10 min), the reaction of **1c**, *p*-toluidine, and 2-furaldehyde afforded compounds **6g/6g′** (48%, **6g/6g′**, 1:2). This mixture was purified by flash chromatography to afford pure **6g′** as a brown powder. Yield: 67 mg (32%).

IR (KBr): 3429, 3135, 3096, 2962, 2924, 1668, 1585, 1553, 1502, 1457, 1367, 1265, 1175, 1028, 899, 816, 733 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.51–7.47 (m, 1 H), 7.02–6.98 (m, 1 H), 6.91 (dd, *J* = 8.2, 1.8 Hz, 1 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.43–6.38 (m, 2 H), 5.09 (d, *J* = 7.3 Hz, 1 H), 4.87 (d, *J* = 2.5 Hz, 1 H), 4.79 (d, *J* = 2.4 Hz, 1 H), 2.23 (s, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 177.0, 154.9, 143.5, 142.9, 130.2, 130.0, 129.8, 122.6, 117.1, 111.4, 107.6, 55.5, 52.9, 52.7, 20.7.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{15}N_2O_2S$ (M + H^+): 287.0849; found: 287.0849.

(3a*RS*,4*RS*,9b*SR*)-8-Methyl-4-[4-(trifluoromethyl)phenyl]-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6h)

Following the general procedure A, method B (5 d), the reaction of **1c**, *p*-toluidine, and 4-(trifluoromethyl)benzaldehyde afforded compounds **6h/6h′** (55%, **6h/6h′**, 2:1). This mixture was purified by flash chromatography to afford pure **6h** as a yellow powder. Yield: 92 mg (37%).

IR (KBr): 3397, 3186, 3071, 2917, 2879, 1706, 1617, 1508, 1322, 1258, 1168, 1130, 1066, 1002, 829 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.63 (br s, 1 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 2 H), 7.03–7.07 (m, 1 H), 6.91 (dd, *J* = 8.2, 1.7 Hz, 1 H), 6.65 (d, *J* = 8.2 Hz, 1 H), 6.33 (s, *J* = 14.9 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 1 H), 4.23 (d, *J* = 10.4 Hz, 1 H), 4.00 (dd, *J* = 10.4, 6.0 Hz, 1 H), 2.19 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.4, 145.5, 142.9, 130.8, 129.7, 129.4, 128.7 (d, *J* = 31.7 Hz), 125.4, 125.1 (d, *J* = 3.6 Hz), 124.2 (d, *J* = 272.0 Hz), 117.0, 114.9, 57.7, 54.6, 49.9, 20.2.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{16}F_3N_2OS$ (M + H^+): 365.093; found: 365.0929.

(3a*RS*,4*RS*,9b*SR*)-1-Benzyl-8-methyl-4-[4-(trifluoromethyl)phenyl]-1,4,5,9b-tetrahydrooxazolo[5,4-*c*]quinolin-2(3a*H*)-one (6j)

Following the general procedure A, method C (1 cycle of 10 min), the reaction of **1d**, *p*-toluidine, and 4-(trifluoromethyl)benzaldehyde afforded compounds **6j/6j′** as a diastereomeric mixture (75 mg, overall yield 84%, **6j/6j′**, 2:1). This mixture could not be separated and was directly oxidized to quinoline **11g** following procedure B (see below).

^1H NMR (400 MHz, $CDCl_3$): δ (diagnostic signals from the mixture) = 7.64 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H), 7.43–7.27 (m, 5 H), 6.99 (dd, *J* = 8.0, 1.5 Hz, 1 H), 6.94 (br s, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 5.20 (d, *J* = 15.6 Hz, 1 H), 4.95 (d, *J* = 8.1 Hz, 1 H), 4.59 (d, *J* = 3.1 Hz, 1 H), 4.44 (dd, *J* = 8.1, 3.1 Hz, 1 H), 4.06 (d, *J* = 15.6 Hz, 1 H), 2.27 (s, 3 H).

(*E*)-2-(4-Fluorostyryl)-3-methylbenzo[*d*]thiazol-3-ium Iodide (8)

Following the general procedure A, method C (1 cycle of 10 min), the reaction of **3** and (*E*)-*N*-(4-fluorobenzylidene)-4-methoxyaniline afforded compound **8** (43%). The compound precipitated out as a brown powder from the reaction media, was collected by filtration, and washed with Et_2O (20 mL). Yield: 85 mg (43%).

IR (KBr): 3423, 3045, 2994, 1617, 1591, 1508, 1450, 1418, 1328, 1232, 1155, 829, 752 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.45 (d, *J* = 7.8 Hz, 1 H), 8.29–8.21 (m, 2 H), 8.20–8.13 (m, 2 H), 8.03 (d, *J* = 15.9 Hz, 1 H), 7.93–7.86 (m, 1 H), 7.84–7.76 (m, 1 H), 7.44 (t, *J* = 8.8 Hz, 1 H), 4.37 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.9, 165.6, 163.1, 147.1, 142.0, 132.3, 132.3, 130.8, 129.4, 128.5, 127.9, 124.3, 116.9, 116.5, 116.3, 113.9, 36.5.

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{13}FNS$ ($M + H^+$): 270.0747; found: 270.0747.

(4b*RS*,4b^1*SR*,12b*SR*)-3-Bromo-4b^1,8,12b,13-tetrahydrodibenzo[*b*,*h*]thiazolo[5,4,3*de*][1,5]naphthyridin-6(4b*H*)-one (10)

Following the general procedure A, method C (1 cycle of 15 min), the reaction of **9** (see Supporting Information) and 4-bromoaniline afforded compounds **10**/**10′** (56%, **10**/**10′**, 1:100). The precipitated major stereoisomer **10′** was filtered and washed with Et_2O (20 mL) to afford **10′** as a white powder. Yield: 7 mg (1%).

The resulting filtrate was concentrated and the residual solid was purified by flash chromatography to afford **10** as a white powder. Yield: 762 mg (55%).

IR (KBr): 3429, 3372, 2930, 2846, 1649, 1482, 1450, 1405, 1328, 1245, 1213, 822, 752, 733, 662, 547 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.78–7.76 (m, 1 H), 7.39–7.25 (m, 5 H), 6.99 (d, *J* = 8.6 Hz, 1 H), 6.82 (br s, 1 H), 5.50 (d, *J* = 5.50 Hz, 1 H), 5.05 (d, *J* = 17.5 Hz, 1 H), 4.48–4.40 (m, 2 H), 3.98 (dd, *J* = 7.1, 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.4, 144.6, 134.1, 132.5, 131.5, 131.3, 127.2, 126.6, 126.2, 125.0, 120.65, 118.6, 108.8, 57.8, 47.8, 44.0, 41.0.

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{14}BrN_2OS$ ($M + H^+$): 373.0005; found: 373.0014.

(4b*RS*,4b^1*SR*,12b*RS*)-3-Bromo-4b^1,8,12b,13-tetrahydrodibenzo[*b*,*h*]thiazolo[5,4,3-*de*][1,5]naphthyridin-6(4b*H*)-one (10′)

IR (KBr): 3423, 3308, 3064, 3026, 2962, 2911, 2859, 1649, 1597, 1482, 1437, 1380, 1296, 1258, 1162, 931, 809, 758, 713, 630 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.50–7.27 (m, 5 H), 7.13 (dd, *J* = 2.3, 8.6 Hz, 1 H), 6.65 (dd, *J* = 1.7, 8.6 Hz, 1 H), 6.04 (br s, 1 H), 5.26 (d, *J* = 7.38 Hz, 1 H), 4.66 (d, *J* = 17.4 Hz, 1 H), 4.51 (d, *J* = 17.4 Hz, 1 H), 4.41 (dt, *J* = 1.8, 7.42 Hz, 1 H), 4.39–4.36 (m, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 143.7, 133.8, 132.2, 131.7, 130.3, 129.7, 128.6, 126.9, 126.8, 124.5, 117.1, 108.5, 57.8, 52.1, 44.9, 41.6.

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{14}BrN_2OS$ ($M + H^+$): 373.0005; found: 373.0003.

Ethyl 8-Methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinoline-4-carboxylate (11a)

Following the general procedure B, the oxidation of **6a′** afforded compound **11a** as a yellow powder. Yield: 34 mg (65%).

IR (KBr): 3385, 3135, 2975, 2923, 2853, 2750, 1700, 1674, 1629, 1476, 1341, 1296, 1226, 1200, 1111, 1066, 989, 822 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.5 (br s, 1 H), 11.04 (br s, 1 H), 7.93 (d, *J* = 8.8 Hz, 1 H), 7.91–7.88 (m, 1 H), 7.50 (dd, *J* = 8.8, 1.9 Hz, 1 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 2.51 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 154.9, 141.2, 137.5, 132.3, 130.3, 129.9, 129.8, 122.8, 119.8, 115.31, 61.2, 21.6, 14.3.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{14}N_3O_3$ ($M + H^+$): 272.103; found: 272.1028.

8-Methyl-4-[4-(trifluoromethyl)phenyl]-1*H*-imidazo[4,5-*c*]quinolin-2(3*H*)-one (11b)

Following the general procedure B, the oxidation of **6b′** afforded compound **11b** as a pale yellow powder. Yield: 5 mg (50%).

IR (KBr): 2893, 1713, 1655, 1629, 1437, 1367, 1322, 1168, 1098, 1066, 893, 662 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 12.10 (br s, 1 H), 11.32 (br s, 1 H), 8.17 (d, *J* = 8.1 Hz, 2 H), 7.90 (dd, *J* = 12.0, 8.4 Hz, 4 H), 7.48 (dd, *J* = 8.8, 1.7 Hz, 1 H), 2.51 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.8, 142.4, 141.6, 139.9, 136.2, 132.0, 130.2, 129.8, 129.7, 129.5 (q, *J* = 31.7 Hz), 125.9 (q, *J* = 3.9 Hz), 120.7, 120.3, 114.7, 102.8, 21.9.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{13}N_3O$ ($M + H^+$): 344.1005; found: 344.1000.

1-Benzyl-8-methoxy-4-[4-(trifluoromethyl)phenyl]oxazolo[5,4-*c*]quinolin-2(1*H*)-one (11c)

Following the general procedure B, the oxidation of **6d** afforded compound **11c** as a white powder. Yield: 30 mg (61%).

IR (KBr): 3519, 3417, 3116, 3007, 2936, 2834, 1764, 1604, 1559, 1508, 1476, 1444, 1322, 1232, 1162, 1117, 1066, 1027, 1002, 938, 854 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 8.52 (d, *J* = 8.1 Hz, 2 H), 8.01 (dd, *J* = 8.8, 2.1 Hz, 3 H), 7.49 (d, *J* = 7.4 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.37–7.32 (m, 2 H), 7.06 (d, *J* = 2.7 Hz, 1 H), 5.63 (s, 2 H), 3.63 (s, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.6, 154.3, 140.9, 138.8, 136.3, 135.9, 134.6, 132.5, 131.8, 129.6 (q, *J* = 31.8 Hz), 129.0, 128.7, 127.8, 126.0, 125.7 (q, *J* = 3.4 Hz), 124.2 (q, *J* = 272.1 Hz), 121.7, 115.7, 99.4, 55.5, 46.7.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{18}F_3N_2O_3$ ($M + H^+$): 451.1264; found: 451.126.

Ethyl 8-Methyl-2-oxo-1,2-dihydrothiazolo[5,4-*c*]quinoline-4-carboxylate (11d)

Following the general procedure B, the oxidation of **6e** afforded compound **11d** as a white powder. Yield: 28 mg (55%).

IR (KBr): 3135, 3000, 2968, 2846, 1713, 1668, 1559, 1463, 1392, 1251, 1187, 1040, 822, 771, 669 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 13.13 (br s, 1 H), 8.11–8.08 (m, 1 H), 8.01 (d, *J* = 8.7 Hz, 1 H), 7.66 (dd, *J* = 8.8, 1.8 Hz, 1 H), 4.48 (q, *J* = 7.1 Hz, 2 H), 2.53 (s, 1 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 172.5, 164.6, 143.4, 140.6, 138.9, 138.7, 132.3, 129.9, 120.9, 115.8, 115.5, 62.1, 21.6, 14.1.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{13}N_2O_3S$ ($M + H^+$): 289.0641; found: 289.064.

4-(Furan-2-yl)-8-methylthiazolo[5,4-*c*]quinolin-2(1*H*)-one (11e)

Following the general procedure B, the oxidation of **6g′** afforded compound **11e** as a brown powder. Yield: 10 mg (40%).

IR (KBr): 3432, 3130, 2913, 2847, 1665, 1581, 1556, 1502, 1363, 1183, 1074, 1014, 899, 815, 728 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.14 (br s, 1 H), 8.08 (d, *J* = 20.0 Hz, 2 H), 7.92 (d, *J* = 8.6 Hz, 1 H), 7.62 (dd, *J* = 8.6, 1.3 Hz, 1 H), 7.34 (d, *J* = 3.0 Hz, 1 H), 6.83–6.77 (m, 1 H), 2.51 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 151.9, 145.3, 144.1, 140.5, 139.9, 136.2, 132.0, 128.8, 121.0, 119.1, 114.4, 112.8, 111.1, 21.4.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_8N_2O_3S$ (M + H$^+$): 283.0536; found: 283.0536.

Ethyl 1-Benzyl-8-methyl-2-oxo-1,2-dihydrothiazolo [5,4-*c*]quinoline-4-carboxylate (11f)

Following the general procedure A, method C (1 cycle of 10 min), the reaction of **1c**, *p*-toluidine, and ethyl glyoxalate afforded compounds **6i/6i′** (**6i/6i′**, 5:1). This mixture was purified by flash chromatography to afford pure **11f** as a yellow powder. Yield: 109 mg (53%).

IR (film): 3064, 2984, 2911, 1706, 1674, 1553, 1495, 1444, 1424, 1367, 1264, 1053, 829, 713 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.7 Hz, 1 H), 7.89 (s, 1 H), 7.50 (dd, *J* = 8.7, 1.5 Hz, 1 H), 7.41–7.33 (m, 2 H), 7.32–7.22 (m, 3 H), 5.73 (s, 2 H), 4.63 (q, *J* = 7.1 Hz, 2 H), 2.36 (s, 3 H), 1.54 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 165.4, 145.4, 140.9, 139.4, 139.2, 135.4, 131.7, 131.7, 129.4, 128.1, 125.8, 120.7, 117.1, 115.7, 63.2, 49.0, 22.3, 14.5.

HRMS (ESI+): *m*/*z* calcd for $C_{21}H_{19}N_2O_3S$ (M + H$^+$): 379.1111; found: 379.1106.

1-Benzyl-8-methyl-4-[4-(trifluoromethyl)phenyl]thiazolo[5,4-*c*]quinolin-2(1*H*)-one (11g)

Following the general procedure B, the oxidation of **6j** afforded compound **11g** as a white powder. Yield: 25 mg (69%).

IR (film): 3340, 3026, 2911, 1681, 1540, 1495, 1399, 1162, 1123, 1066, 841, 726 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 8.3, 5.5 Hz, 3 H), 7.87 (s, 1 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 7.48 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.34–7.28 (m, 3 H), 5.74 (s, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 150.1, 146.3, 142.5, 139.8, 137.2, 135.4, 131.7 (q, *J* = 32.7 Hz), 131.5, 130.9, 129.4, 128.8, 128.1, 124.1 (q, *J* = 272.4 Hz), 126.1 (q, *J* = 3.7 Hz), 125.9, 120.7, 115.6, 113.43, 49.4, 29.5.

HRMS (ESI+): *m*/*z* calcd for $C_{25}H_{18}F_3N_2OS$ (M + H$^+$): 451.1086; found: 451.1084.

3-Bromodibenzo[*b*,*h*]thiazolo[5,4,3-*de*][1,5]naphthyridin-6(8*H*)-one (12)

Following the general procedure B, the oxidation of **10′** afforded compound **12** as a brownish solid. Yield: 66 mg (51%).

IR (KBr): 3051, 2923, 1706, 1585, 1495, 1463, 1341, 1296, 1258, 1207, 1066, 950, 816, 790, 720 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.51 (d, *J* = 7.0 Hz, 1 H), 8.14 (d, *J* = 2.0 Hz, 1 H), 8.02 (d, *J* = 8.9 Hz, 1 H), 7.84–7.79 (m, 1 H), 7.63–7.49 (m, 3 H), 5.35 (s, 2 H).

^{13}C NMR: The ^{13}C NMR spectrum could not be recorded due to the extreme insolubility of compound **12** in all solvents tested.

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_9BrN_2OS$ (M + H$^+$): 368.9692; found: 368.9696.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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SYNTHESIS Journal of Synthetic organic Chemistry SUPPORTING INFORMATION

Supporting Information
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Supporting Information

New Heterocyclic Inputs for Povarov Multicomponent Reaction.

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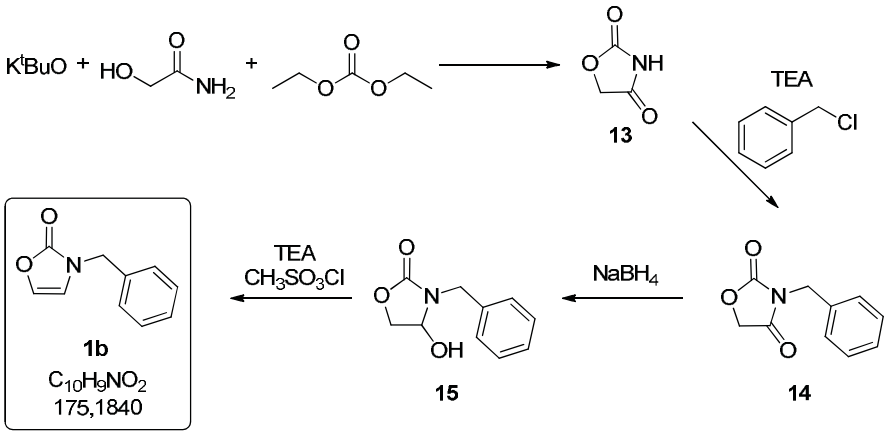
Synthesis of 3-benzyloxazol-2(3*H*)-one (1b).[1]



A solution of potassium tert-butoxide (32.9 mmol, 3.69 g), glycolamide (32.9 mmol, 2.47 g) and diethyl carbonate (39.5 mmol, 4.8 mL) in anhydrous methanol (31 mL) under argon atmosphere was refluxed for 18 hours. After the reaction was complete, the solvent was removed *in vacuo* and the resulting residue was washed with brine (15 mL). The solution was acidified to pH 2 with HCl 6N, and extracted with EtOAc (3×20 mL). The organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*, yielding the desired compound (**13**) as a white solid (74%) which was used for the next step without further purification.

A solution of **13** (6.92 mmol, 700 mg) and triethylamine (6.92 mmol, 0.96 mL) in $CHCl_3$ (8 mL) was stirred under argon atmosphere at room temperature for 30 minutes. Then, (chloromethyl)benzene (6.92 mmol, 0.8 mL) was added and the mixture was stirred at 60 ºC for 3 days. After the reaction was complete, EtOAc (200 mL) was added to the solution, the organic layers were washed with H_2O (3×75 mL) and brine (2×75 mL). The resulting organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*, to afford compound **14** as a white solid (72%), which was used for the next step without further purification.

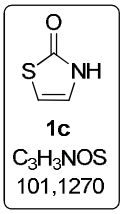
A solution of **14** (3.98 mmol, 800 mg) in MeOH (16 mL) was cooled at 0 ºC. Then, sodium borohydride (17.88 mmol, 676 mg) was added slowly and the mixture was stirred at this temperature for 30 minutes. The reaction was warmed to room temperature and stirred for 2 hours. Finally, the reaction was quenched with acetone (5 mL) and the solvent was removed *in vacuo*. The residue was diluted in H_2O and extracted with $CHCl_3$ (3×10 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent were removed *in vacuo*. The desired compound (**15**) was obtained as a white solid (92%) and used for the next step without further purification.

A mixture of **15** (3.9 mmol, 746 mg) and triethylamine (7.72 mmol, 1.1 mL) in CH_2Cl_2 (8 mL) was cooled at 0 ºC. Then, mesyl chloride (5.79 mmol, 0.6 mL) was added and the resulting solution was stirred for 12 hours. After the reaction was complete, the crude was diluted in H_2O (8 mL) and extracted with $CHCl_3$ (3×10 mL). The organic layer was washed with HCl 0.5 M (10 mL) and aqueous $NaHCO_3$ 5% solution (10 mL) and brine (10 mL). The resulting organic layer was dried over Na_2SO_4, filtered and the solvent

[1] (a) Matsuura, T.; Kuneida, T.; Takizawa, T. *Chem. Pharm. Bull.* **1977**, *25*, 1225-1229. (b) Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. *J. Med. Chem.* **1991***, 5,* 1538-1544. (c) Dow, R. L.; Hulin, B.; Clark, D. A. U.S. **1996** US 5498621 A 19960312. *Chem. Abstr.* **1996**, *125*, 10797. (d) Casadei, M. A.; Cesa, S.; Inesi, A. *Tetrahedron* **1995***, 20,* 5891-5900. (e) Fearnley, S. P.; Thongsornkleeb, C. *J. Org. Chem.* **2010***, 3,* 933-936.

was removed *in vacuo*. The desired product, 3-benzyloxazol-2(3H)-one, was isolated as a white solid (90%).

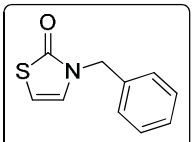
Synthesis of thiazol-2(3*H*)-one (1c).[2]



1c
C_3H_3NOS
101,1270

A mixture of 2-bromothiazole (20 mmol, 1.8 mL) and sodium hydroxide (60 mmol, 2.4 g) in tert-butyl alcohol (20 mL) was refluxed for 2 days. After the reaction was complete, the solvent was removed in *vacuo*. The residue was dissolved in water (30 mL), acidified to pH 2 adding HCl (1 M) and extracted with EtOAc (3×30 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes – EtOAc) to yield the desired compound as a brown solid (80%).

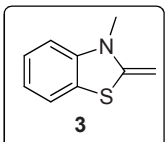
Synthesis of 3-benzylthiazol-2(3*H*)-one (1d).[3]



1d
$C_{10}H_9NOS$
191,2496

A mixture of thiazol-2(3H)-one (**1c**) (9.9 mmol, 1.0 g) and potassium hydroxide (44.5 mmol, 2.5 g) in DMF (5 mL) was stirred under argon atmosphere for 5 minutes. Then, chloromethylbenzene (11.4 mmol, 1.4 mL) was added. And the resulting mixture was stirred at room temperature for 1 hour. After the reaction was complete, EtOAc (5 mL) was added. The organic layer was washed with HCl 1N (3×5 mL) and brine (5 mL). The resulting organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes – EtOAc) to yield the desired product as a brown oil (90%).

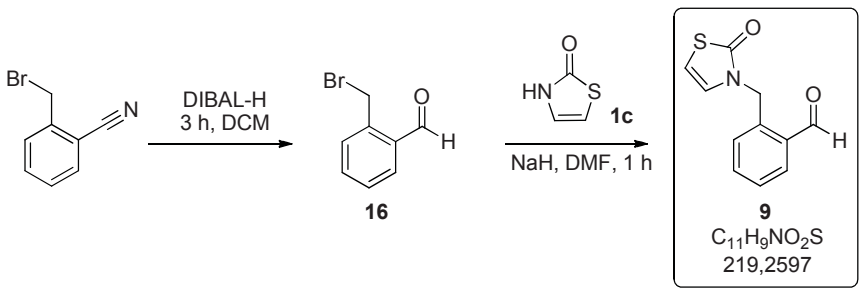
Synthesis of 3-methyl-2-methylene-2,3-dihydrobenzo[*d*]thiazole (3).



3
C_9H_9NS
163,2395

A solution of 3-substituted-2-methylbenzothiazolium iodide[4] (0.5 mmol, 150 mg) in THF (2 mL), under argon, was cooled at -78 ^{o} C, and *n*-BuLi (0.5 mmol, 0.2 mL, 2.5 M solution in hexanes) was added dropwise at this temperature. Then the mixture was warmed to 0 ^{o}C and stirred for 1 hour. The resulting mixture was used for the multicomponent reaction.

Synthesis of 2-((2-oxothiazol-3(2*H*)-yl)methyl)benzaldehyde (9).



[2] (a) Cornwell, S. P.; Kaye, P. T.; Kent, A. G.; Meakins, G. D. *J. Chem. Soc. , Perkin Trans. 1* **1981**, 2340-2343. (b) Hoshimoto,S.; Matsunaga, H.; Kunieda, T. *Chem. Pharm. Bull.* **2000**, *10*, 1541-1544.
[3] (a) Rokach, J.; Hamel, P. *J. Chem. Soc., Chem. Commun.* **1979***, 18,* 786-787. (b) Fei, J.; Basu, A.; Xue, F.; Palmore, G. T. *Org. Lett.* **2006***, 1,* 3-6.
[4] Josel, H-P.; Heindl, D.; Irlinger, B.; Weilke, C. PCT Int. Appl. WO2008052742, **2008**; *Chem. Abstr.* **2008**, *148*, 539881.

The synthesis of **16** was described in the literature.[5] To a solution of **1c** (0.5 mmol, 50 mg) in DMF (2 mL) was added sodium hydride (60% oil dispersion, 0.6 mmol, 23.5 mg) under ice-cooling, the mixture was stirred at room temperature for 20 minutes. Then **16** (0.5 mmol, 97 mg) was added, diluted in DMF (1 mL), dropwise, and the mixture was stirred for 1 hour at same temperature. After the reaction was complete, EtOAc (5 mL). The organic layer was washed with water (5 mL) and saturated brine (5 mL).[6] The resulting organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to afford aldehyde **9** as a dark brown solid (86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.14 (s, 1H), 7.60 (td, *J* = 7.5, 1.5 Hz, 1H), 7.54 (td, *J* = 7.4, 1.1 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 5.4 Hz, 1H), 6.14 (d, *J* = 5.4 Hz, 1H), 5.38 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.7, 172.4, 137.4, 135.6, 134.5, 133.5, 129.4, 128.6, 125.1, 101.6, 46.1 ppm.

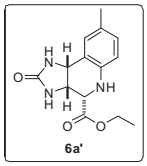
IR (film): 3148, 3110, 2917, 2853, 2744, 1700, 1662, 1572, 1451, 1342, 1233, 1194, 1085, 861, 752 cm^{-1}.

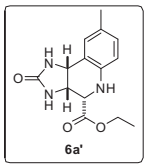
MS (ESI+): *m*/*z* 219.7 (M^+).

[5] Shah. J. R.; Mosier, P. D.; Reddi, S.; Roth, B. L.; Westkaeper, R. B. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 935-938.

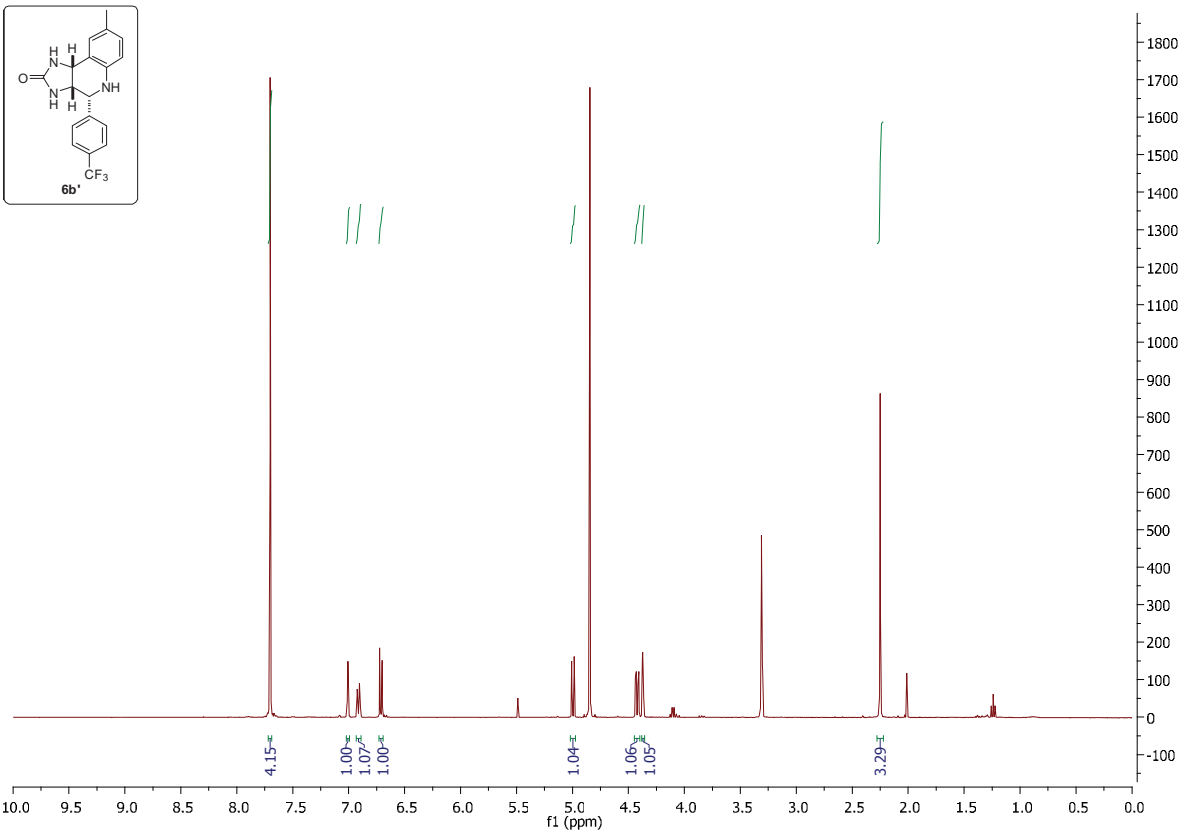
[6] Azukizawa, S.; Kasai, M.; Takahashi, K.; Miike, T.; Kunishiro,K.; Kanda, M.; Mukai, C.; Shirahase, H. *Chem. Pharm. Bull.* **2008**, *56*, 335-345.

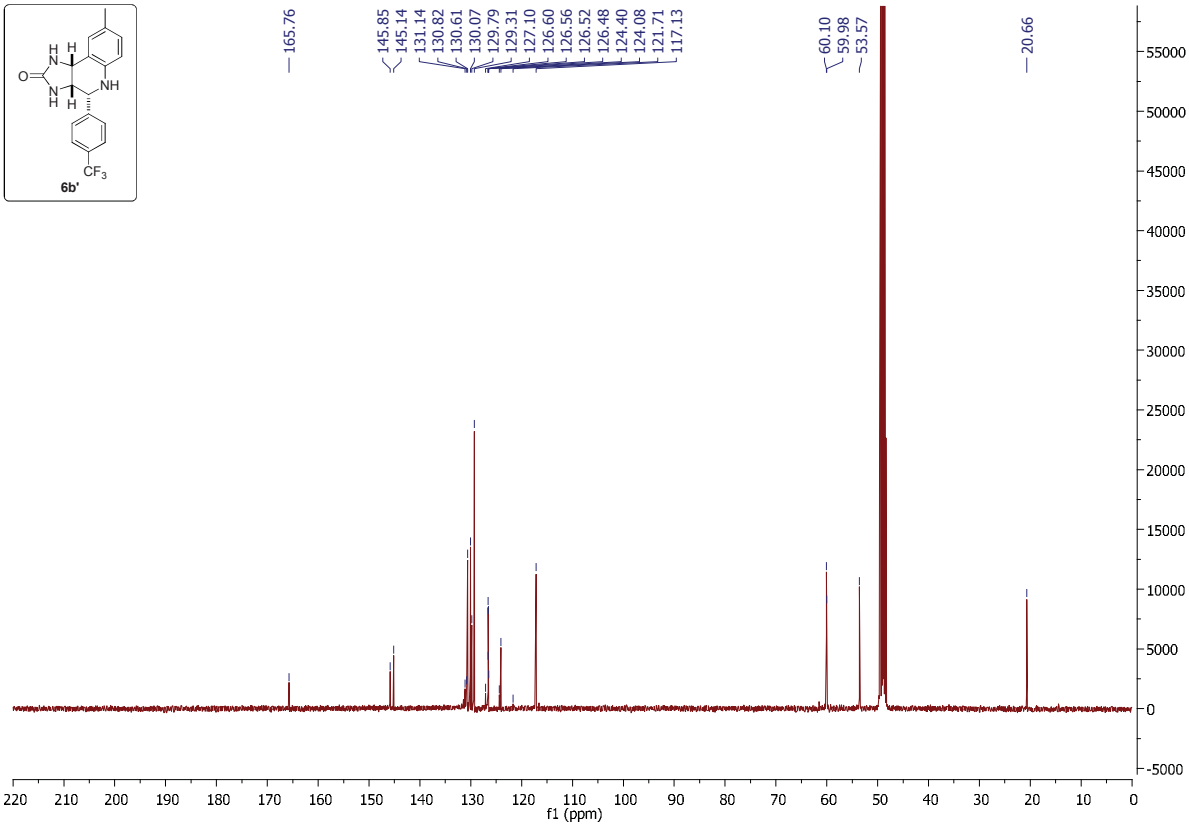
(3a*RS*,4*SR*,9b*RS*)-Ethyl8-methyl-2-oxo-2,3,3a,4,5, 9b-hexahydro-1*H*-imidazo[4,5-*c*]quinoline-4-carboxylate (6a')



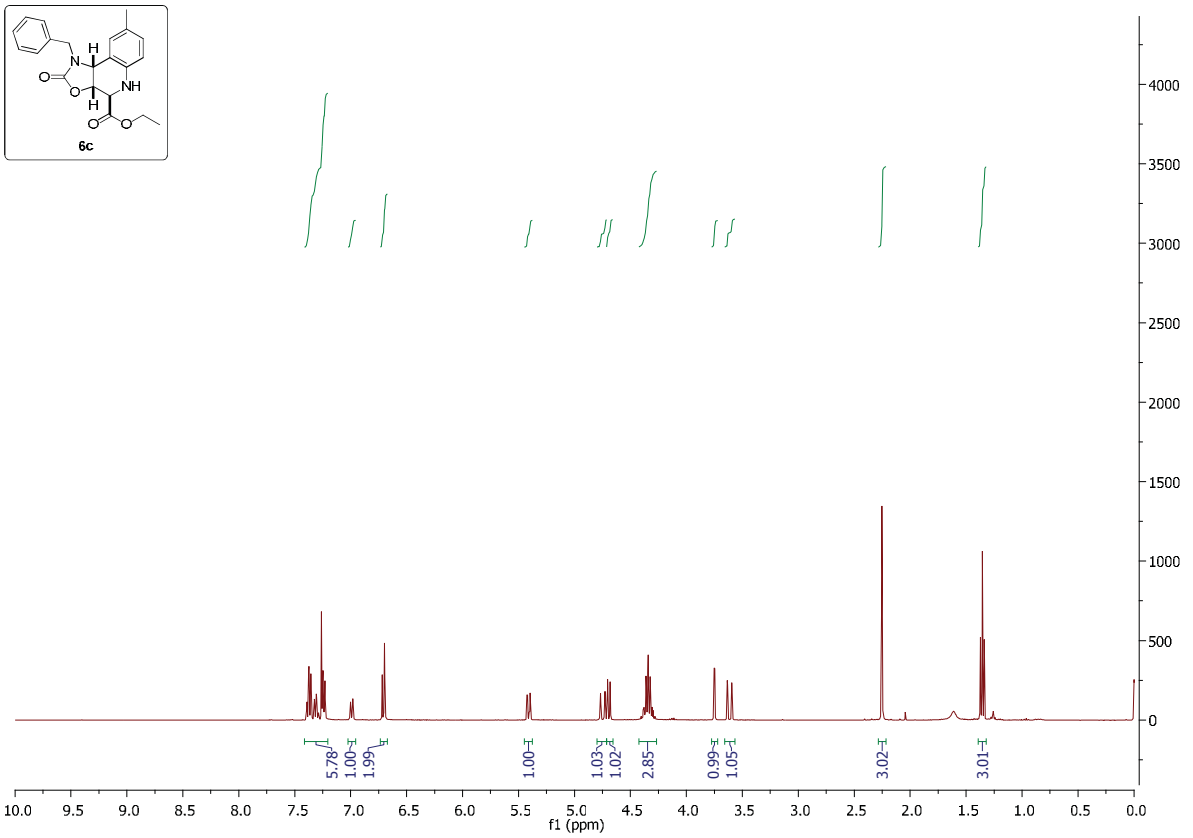


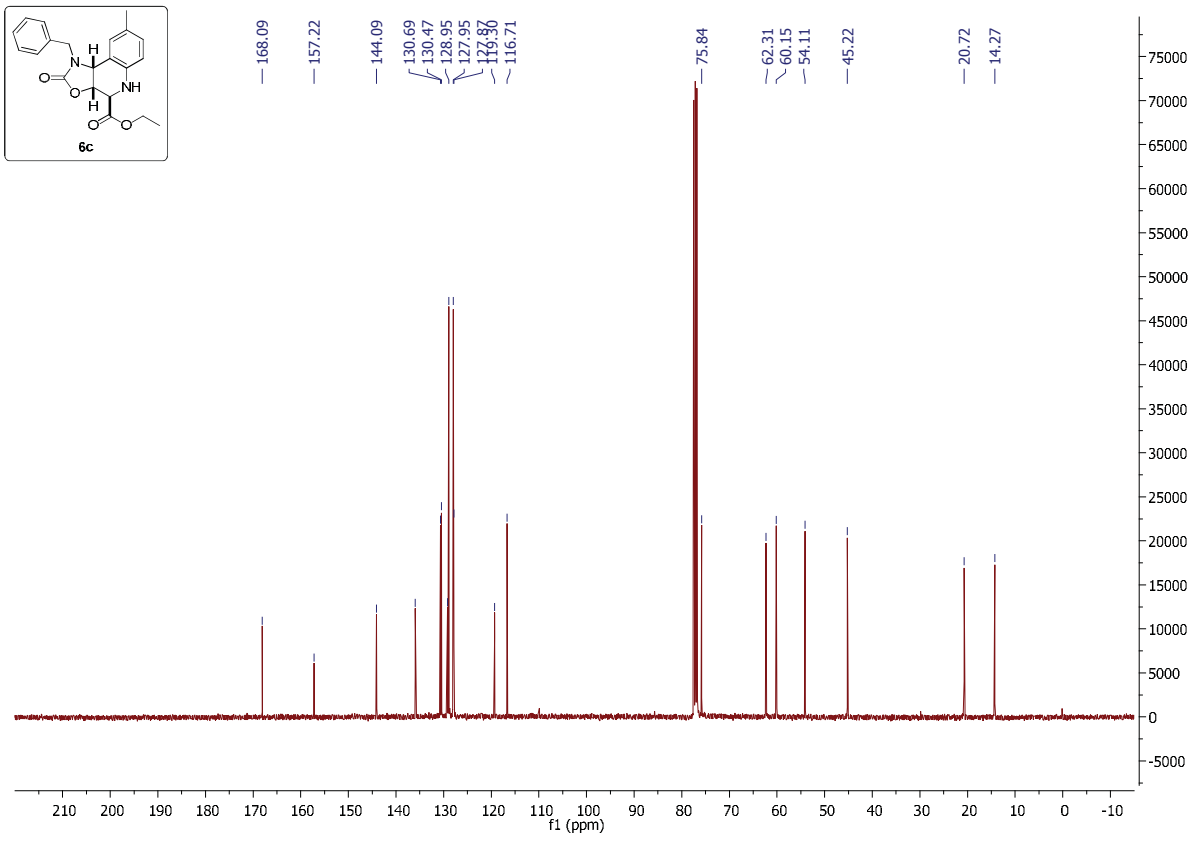
(3a*RS*,4*RS*,9b*SR*)-8-Methyl-4-[4-(trifluoromethyl) phenyl]-3,3a,4,5-tetrahydro-1*H*-imidazo[4,5-*c*] quinolin-2(9b*H*)-one (6b')



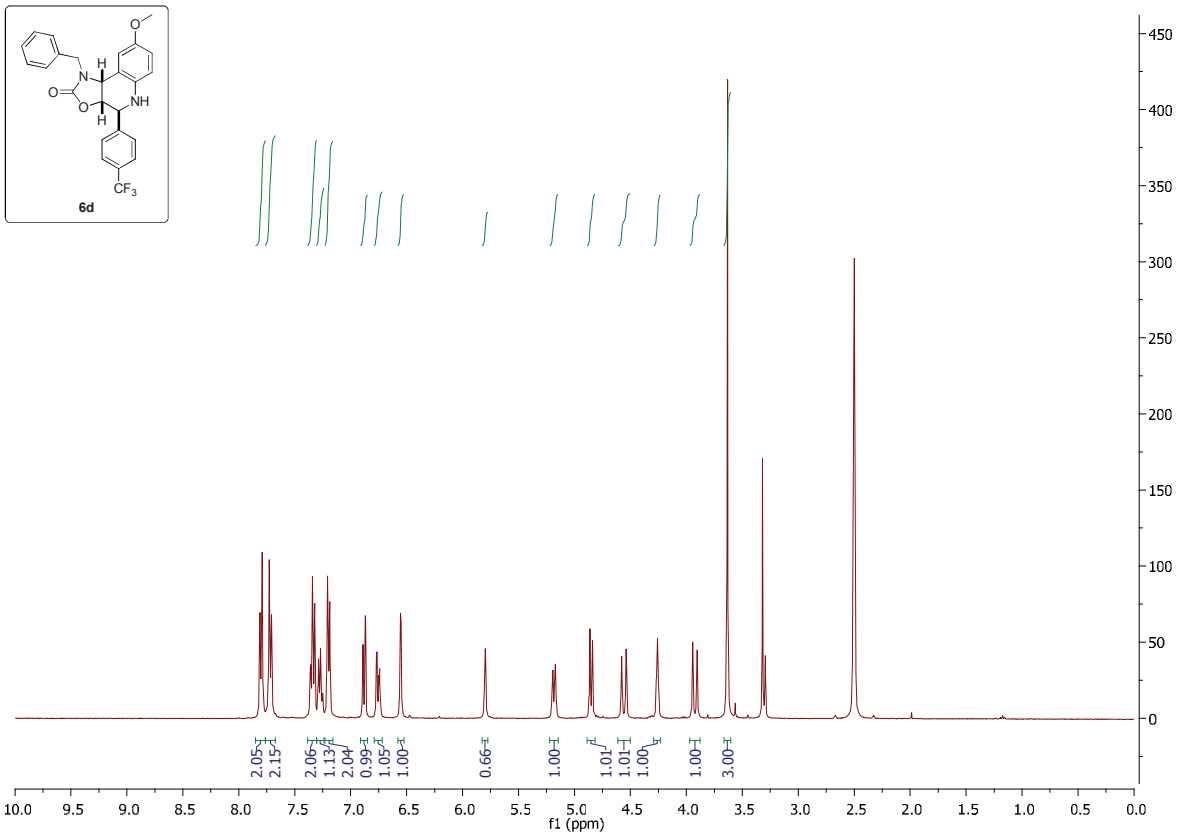


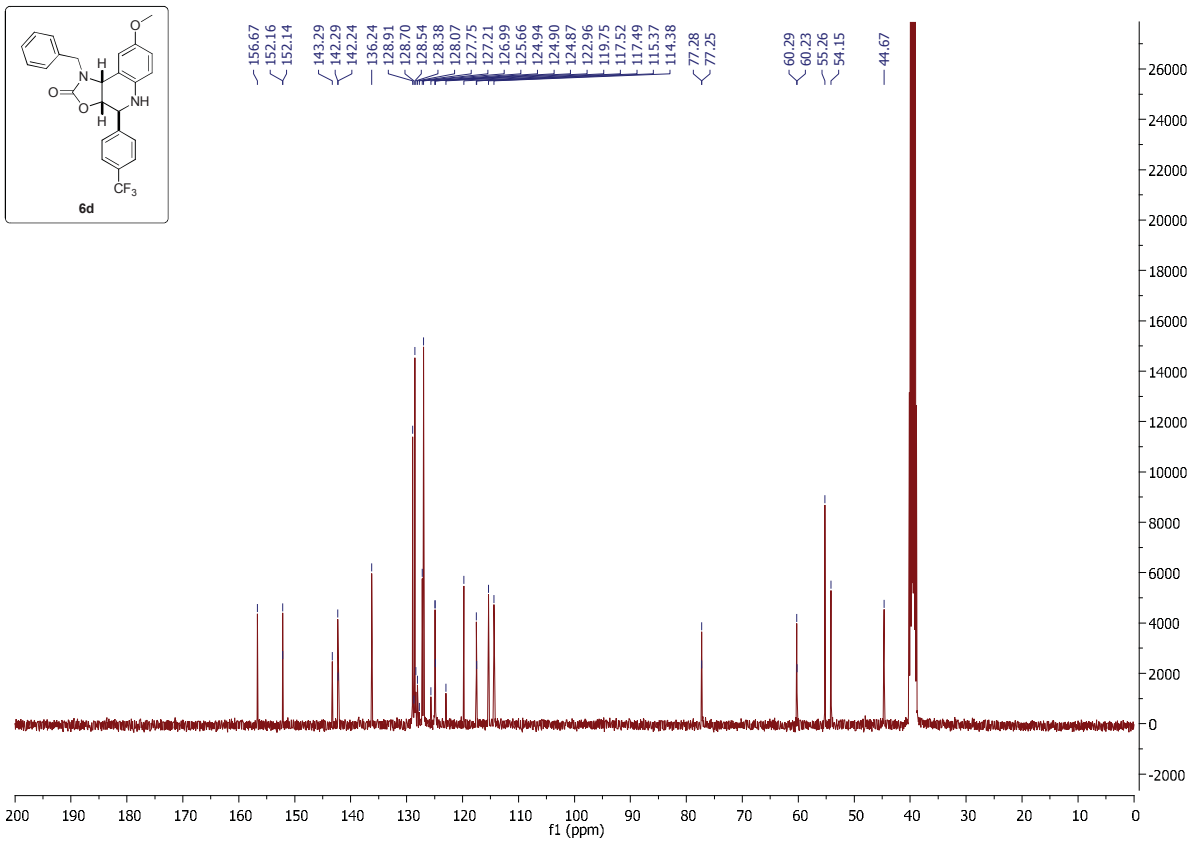
(3a*RS*,4*SR*,9b*SR*)-Ethyl 1-benzyl-8-methyl-2-oxo-1,2,3a,4,5,9b-hexahydrooxazolo[5,4-*c*]quinoline-4-carboxylate (6c)



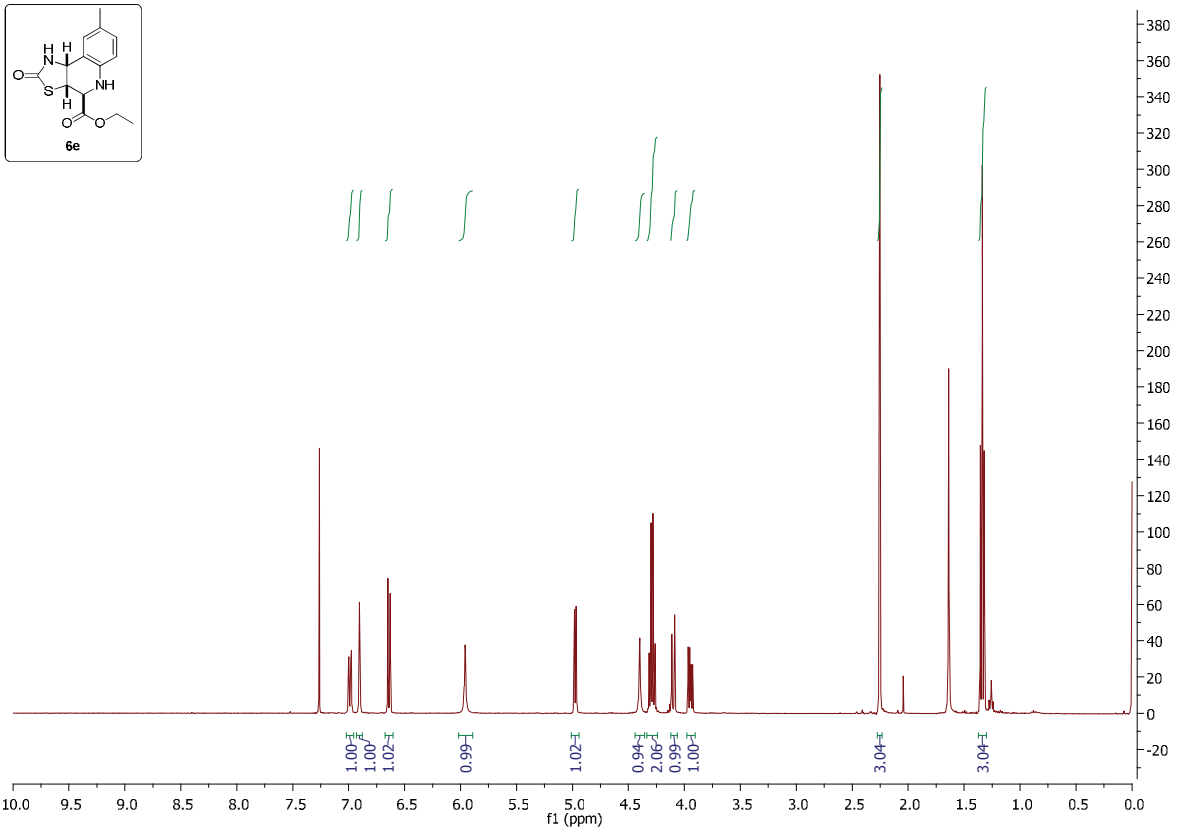


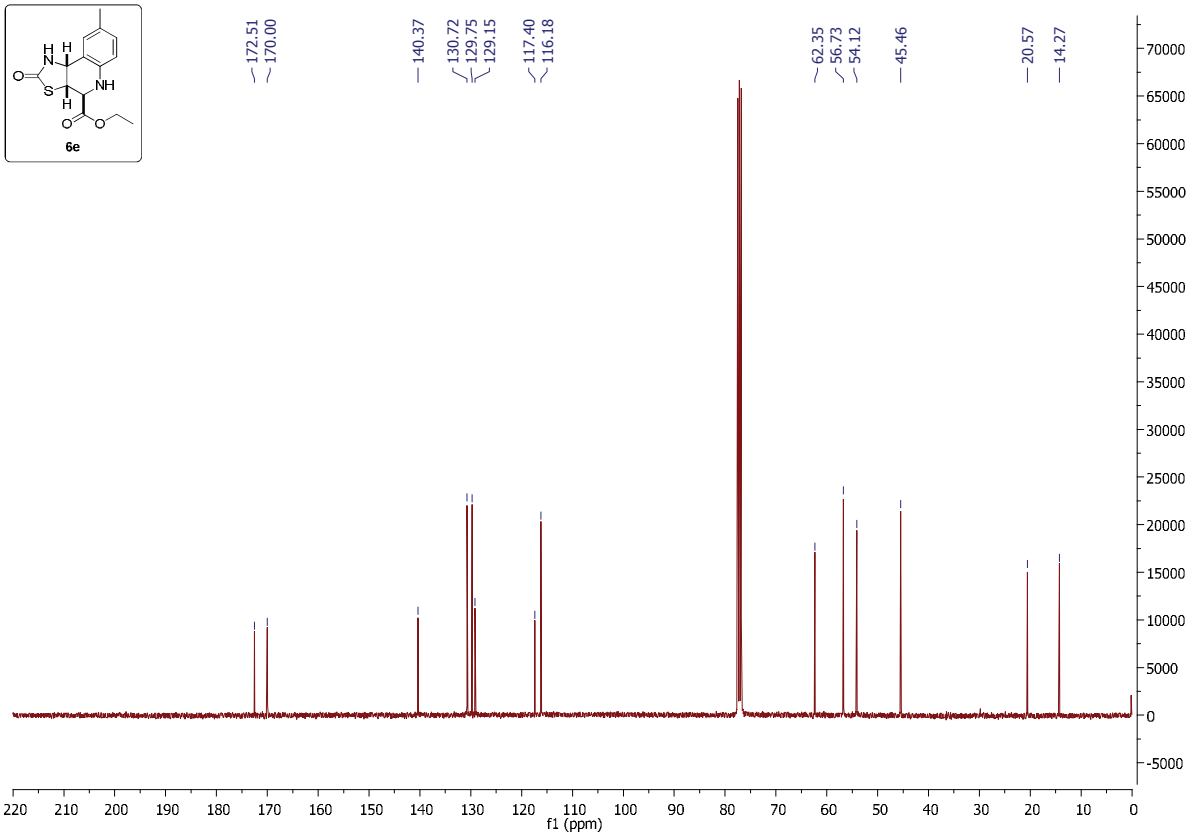
(3a*RS*,4*RS*,9b*SR*)-1-Benzyl-8-methyl-4-[4-(trifluoromethyl)phenyl]-1,4,5,9b-tetrahydrooxazolo[5,4-*c*]quinolin-2(3a*H*)-one (6d)

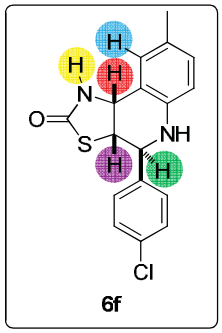




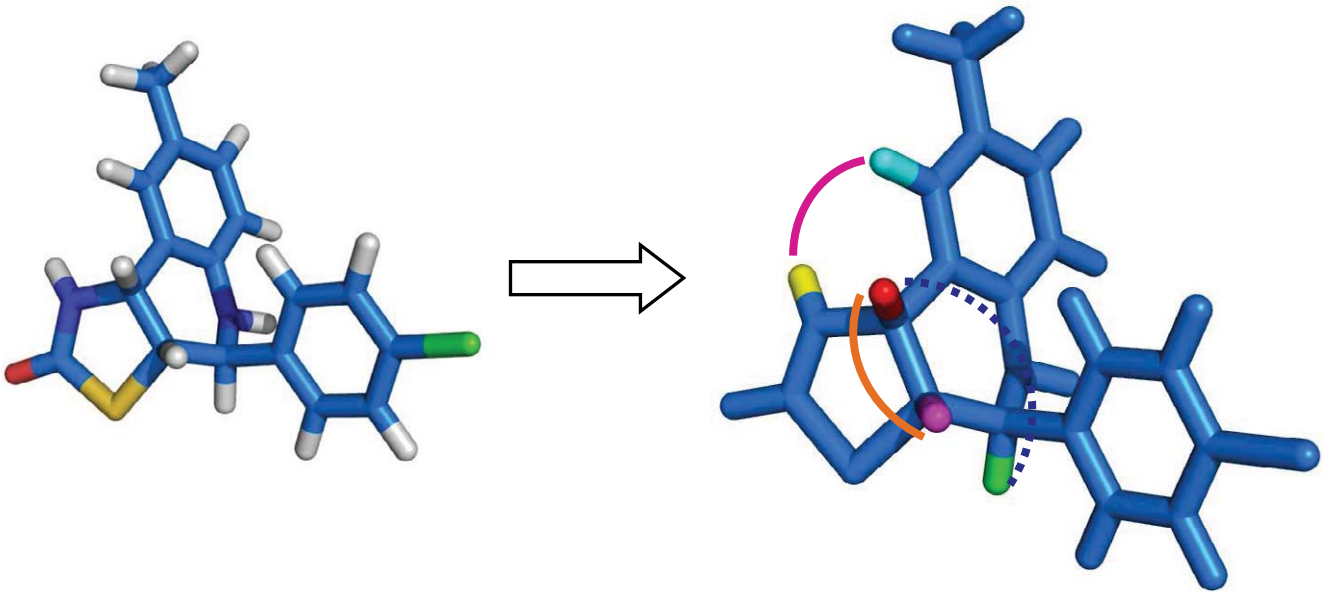
(3a*RS*,4*SR*,9b*RS*)-Ethyl 8-methyl-2-oxo-1,2,3a,4,5, 9b-hexahydrothiazolo[5,4-*c*]quinoline-4-carboxylate (6e)



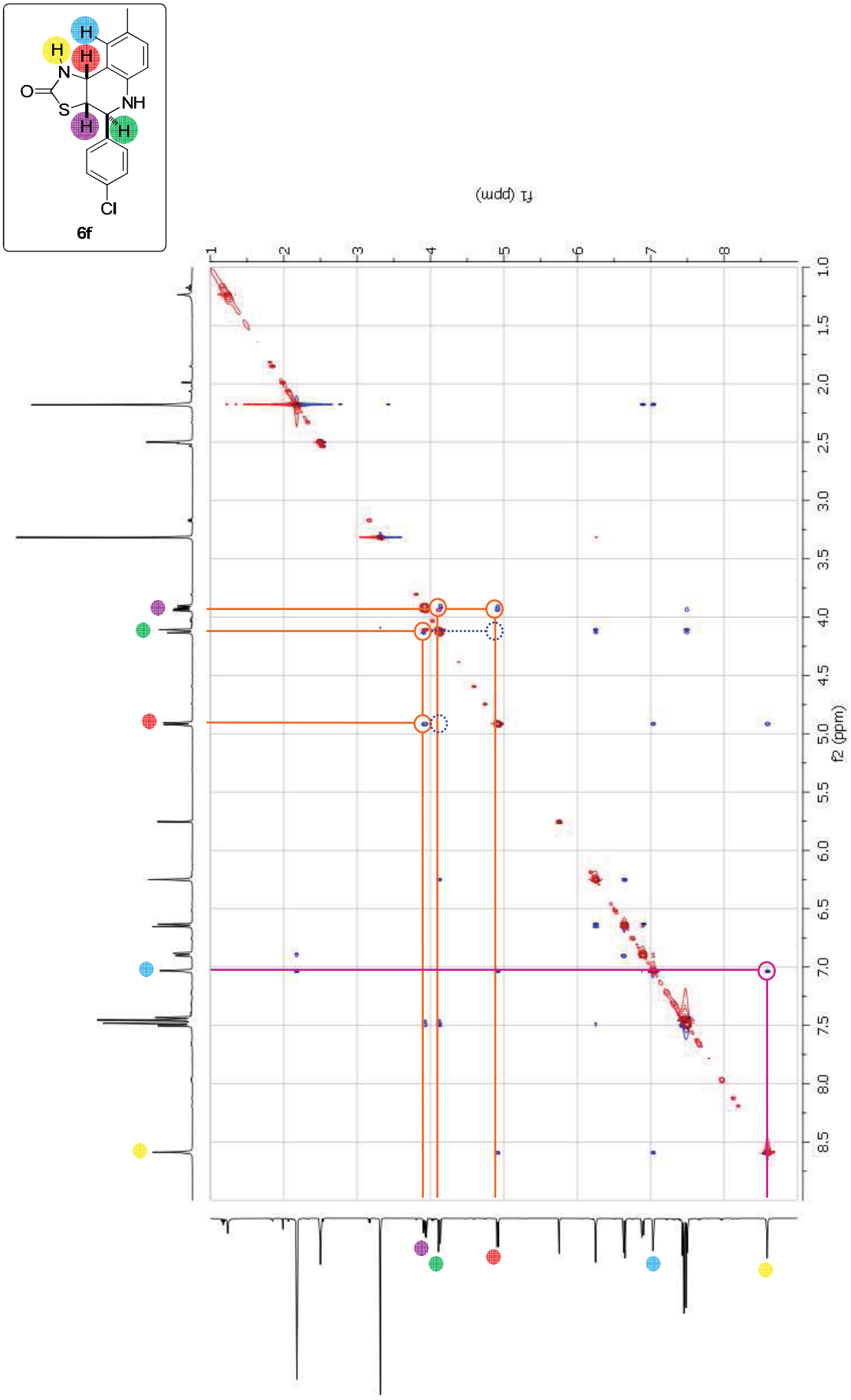




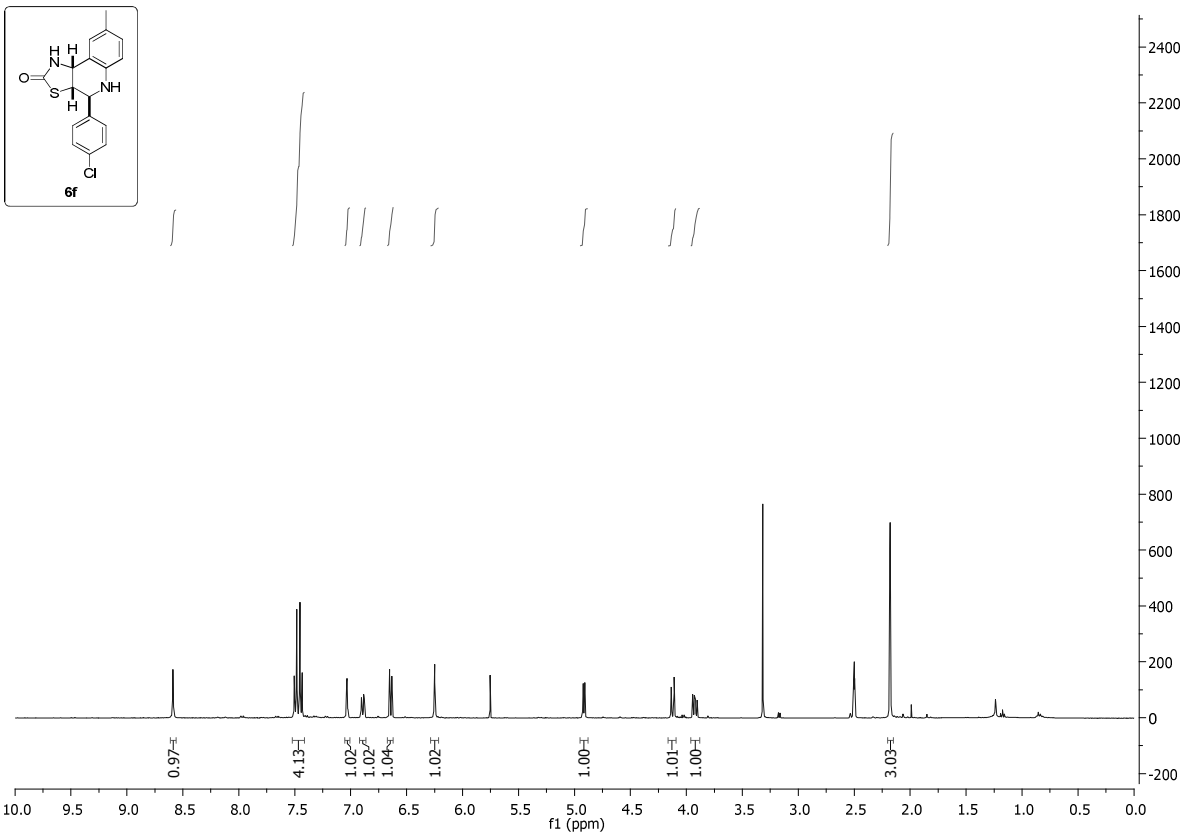
6f

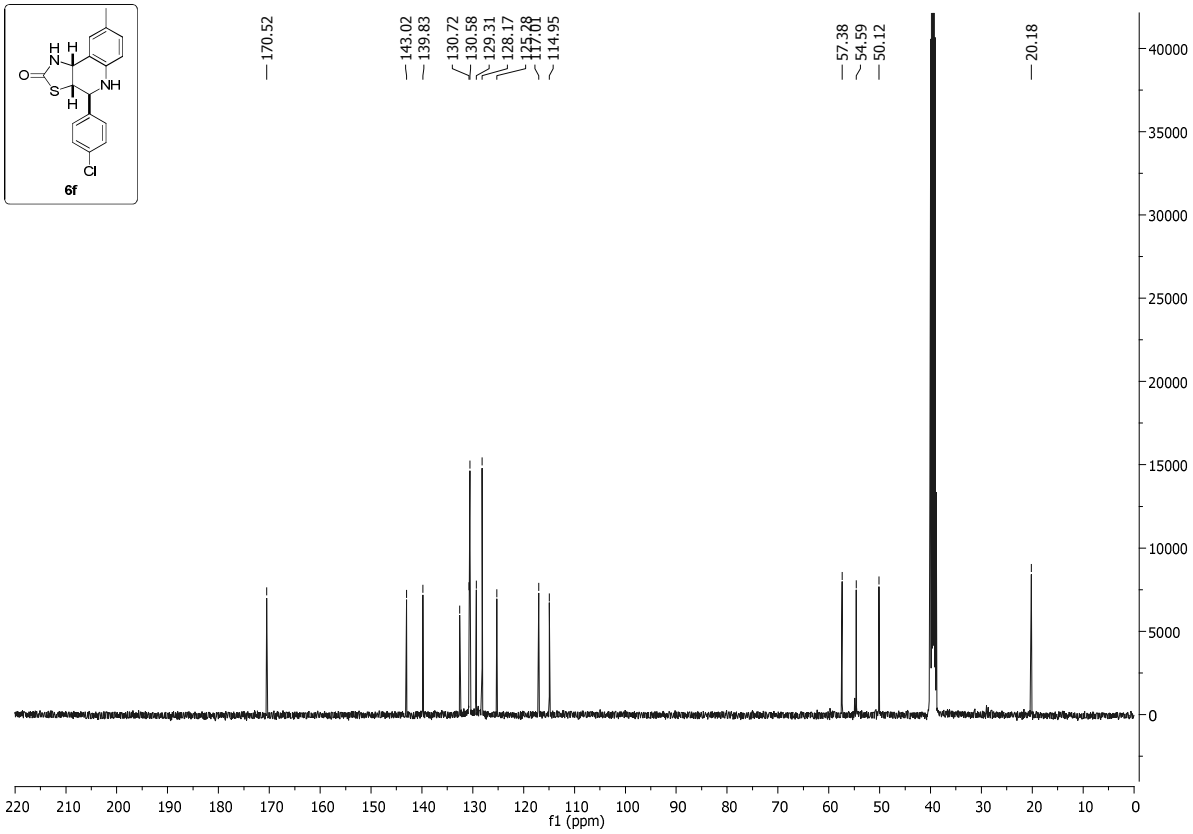


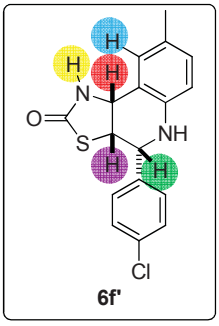
In this 3D optimized structure for **6f**, the NOE interactions observed in the NMR experiments are shown (orange and pink lines). The distance between protons H and H is too big to produce a NOE signal (discontinuous blue line), in agreement with the anti-relationship between these nuclei. On the other hand, the regiochemistry is secured by the Noesy correlation detected H and H (pink line).


H
H
H
N
O
S
NH
H
H
Cl
6f
f1 (ppm)
f2 (ppm)

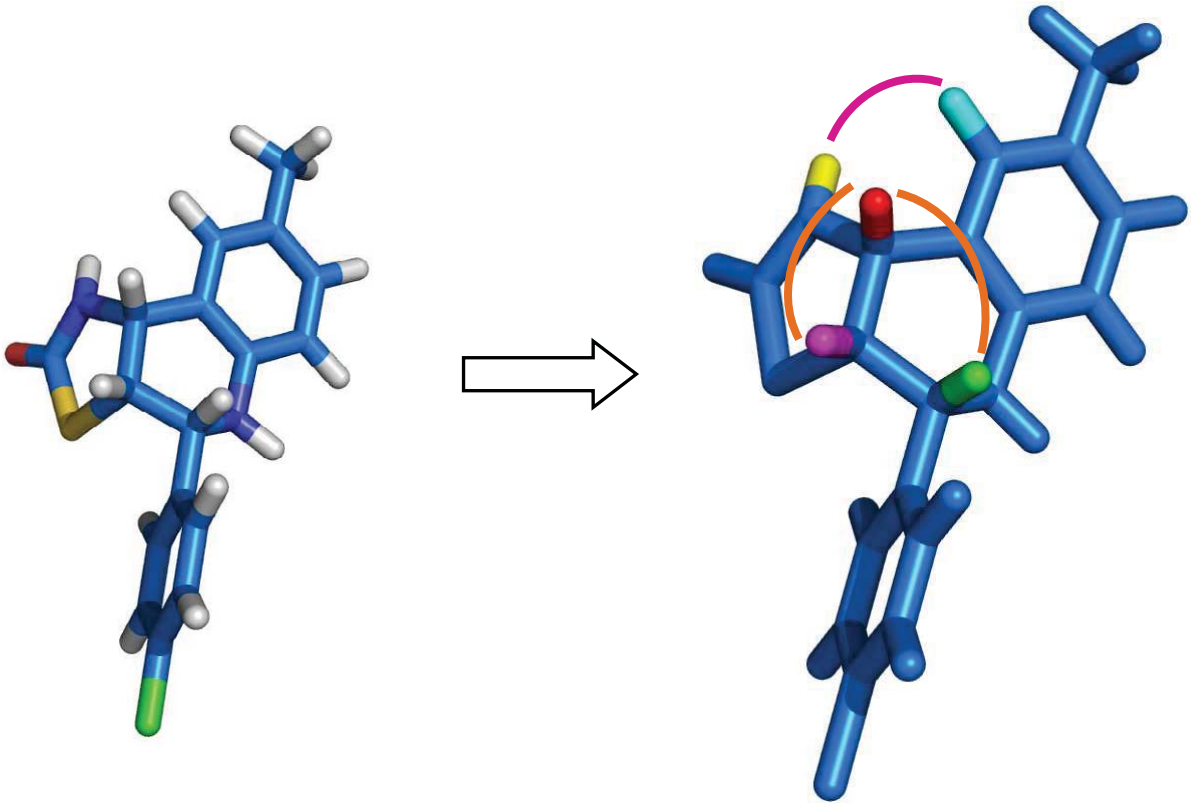
(3a*RS*,4*RS*,9b*SR*)-4-(4-Chlorophenyl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6f)



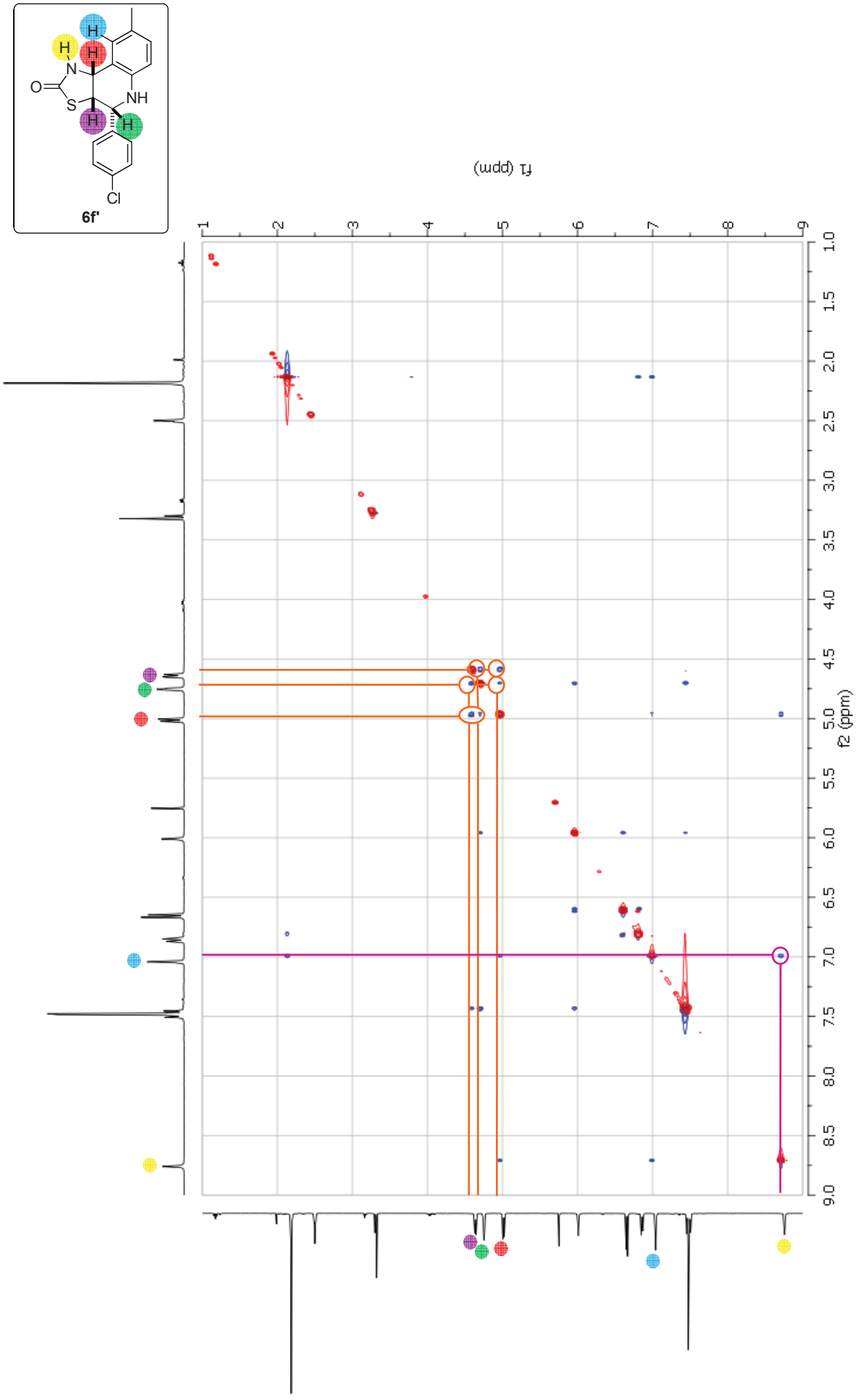




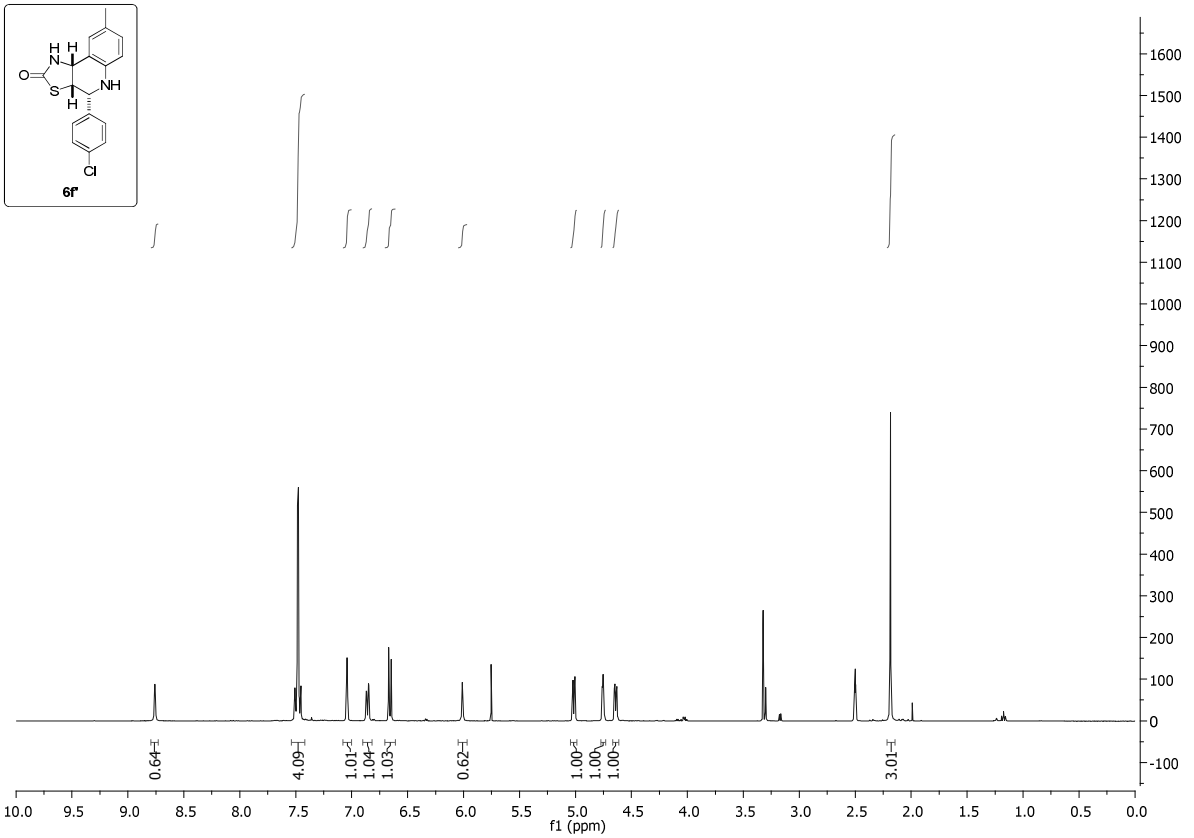
6f'

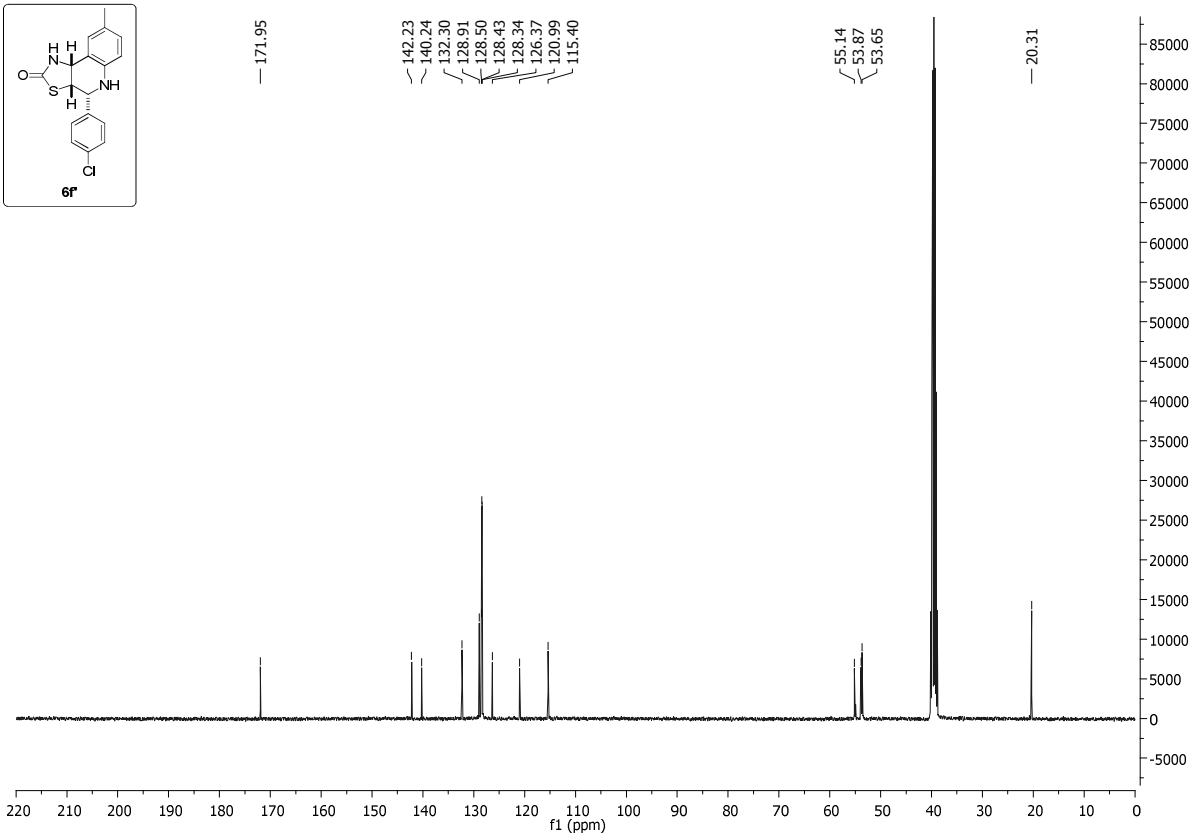


In this 3D optimized structure for **6f'**, the NOE interactions observed in NMR experiments are shown (orange and pink lines). See page S10 for comments.

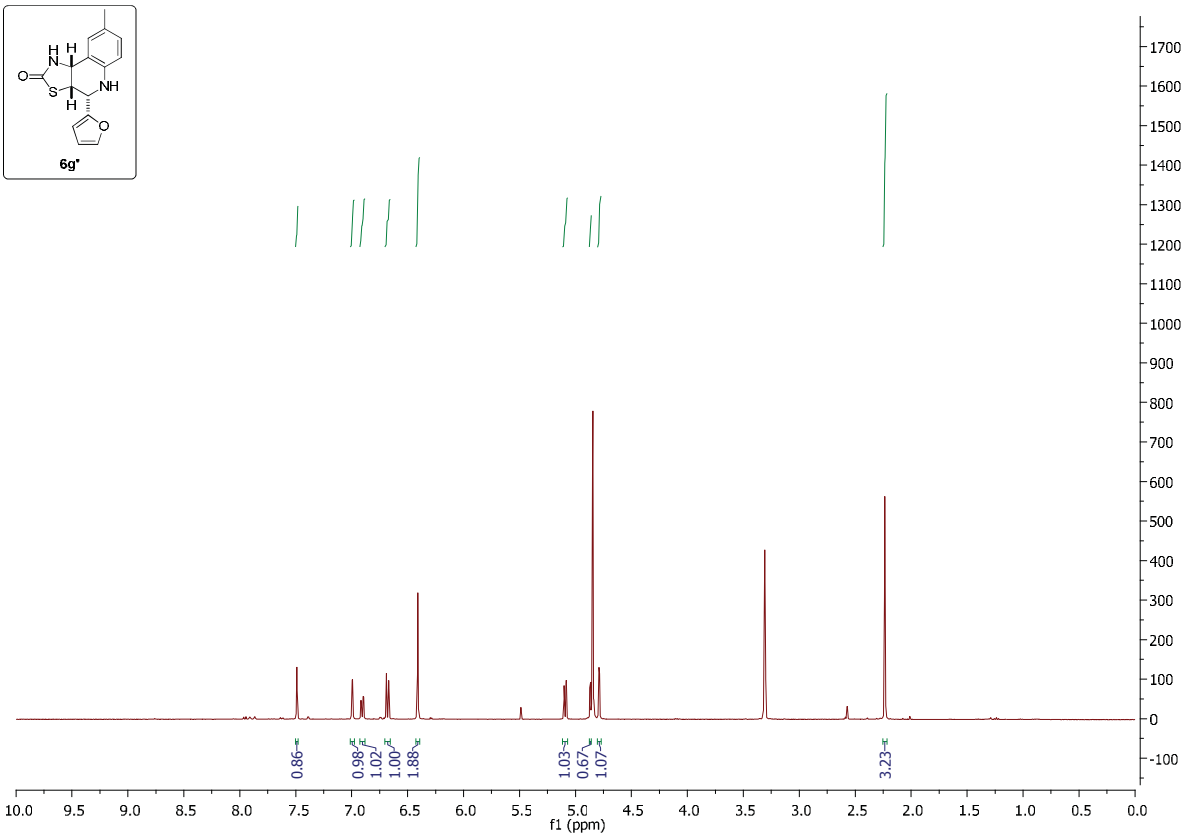

H
H
H
N
O
S
NH
H
H
Cl
6f'
f1 (ppm)
f2 (ppm)

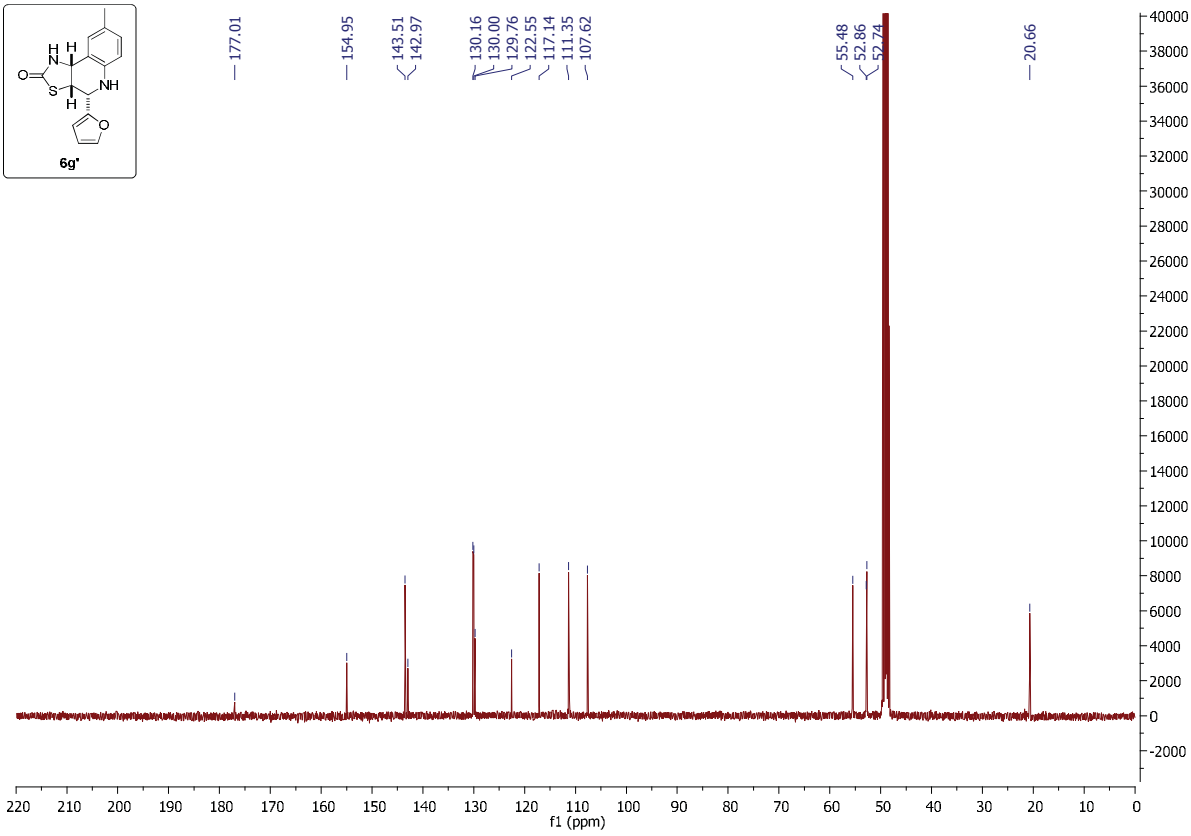
(3a*RS*,4*SR*,9b*SR*)-4-(4-Chlorophenyl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6f')



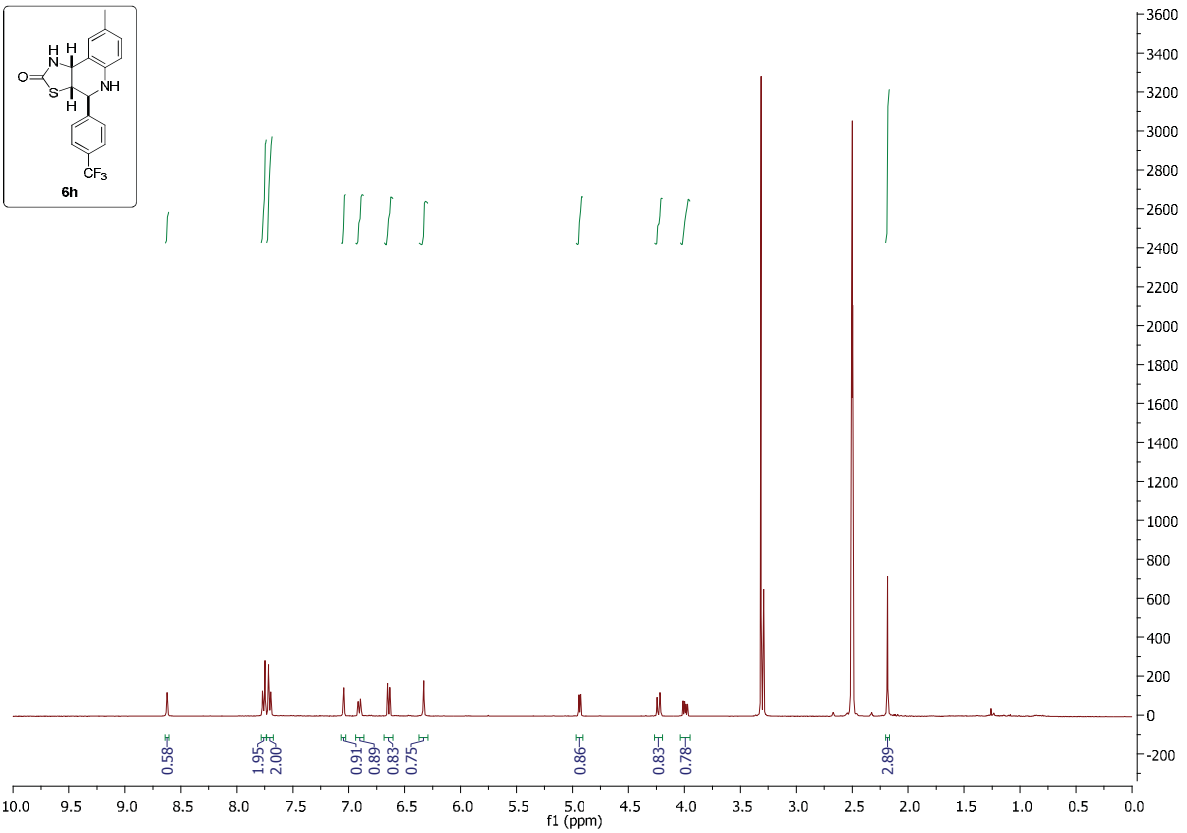


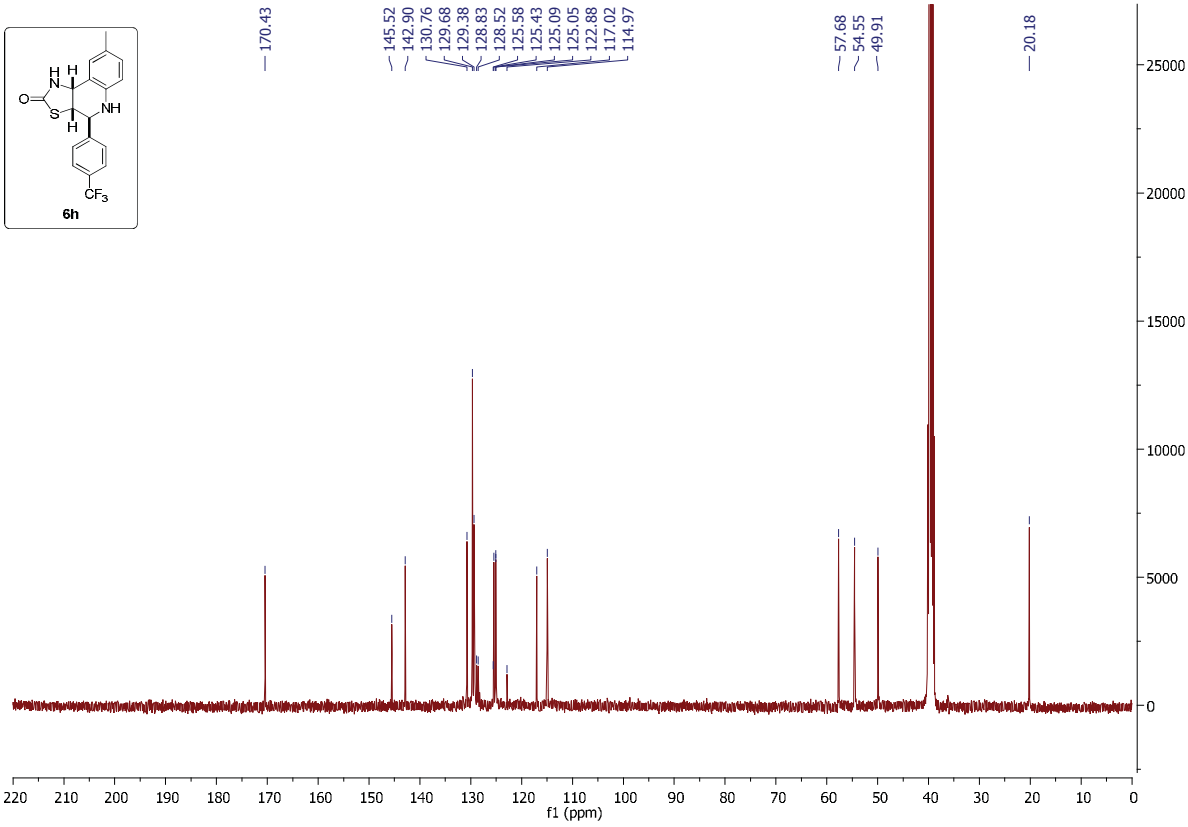
(3a*RS*,4*RS*,9b*RS*)-4-(Furan-2-yl)-8-methyl-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6g')



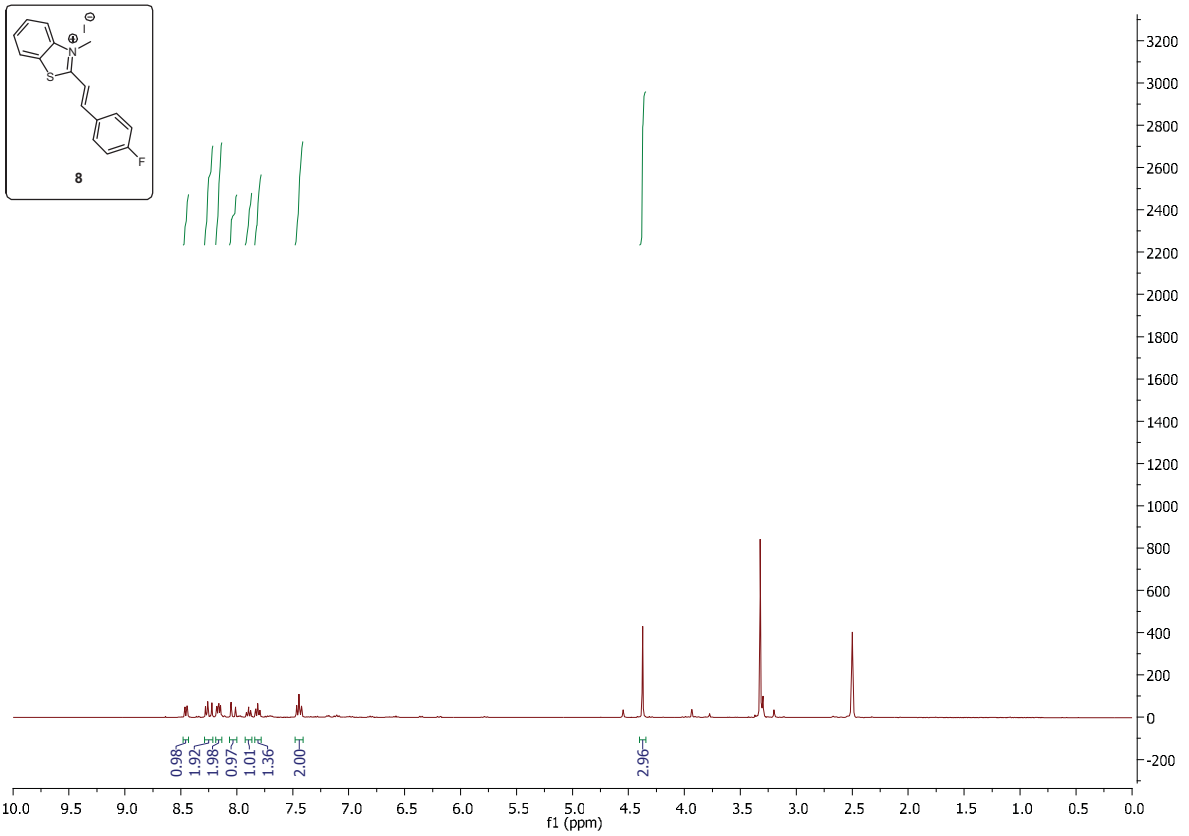


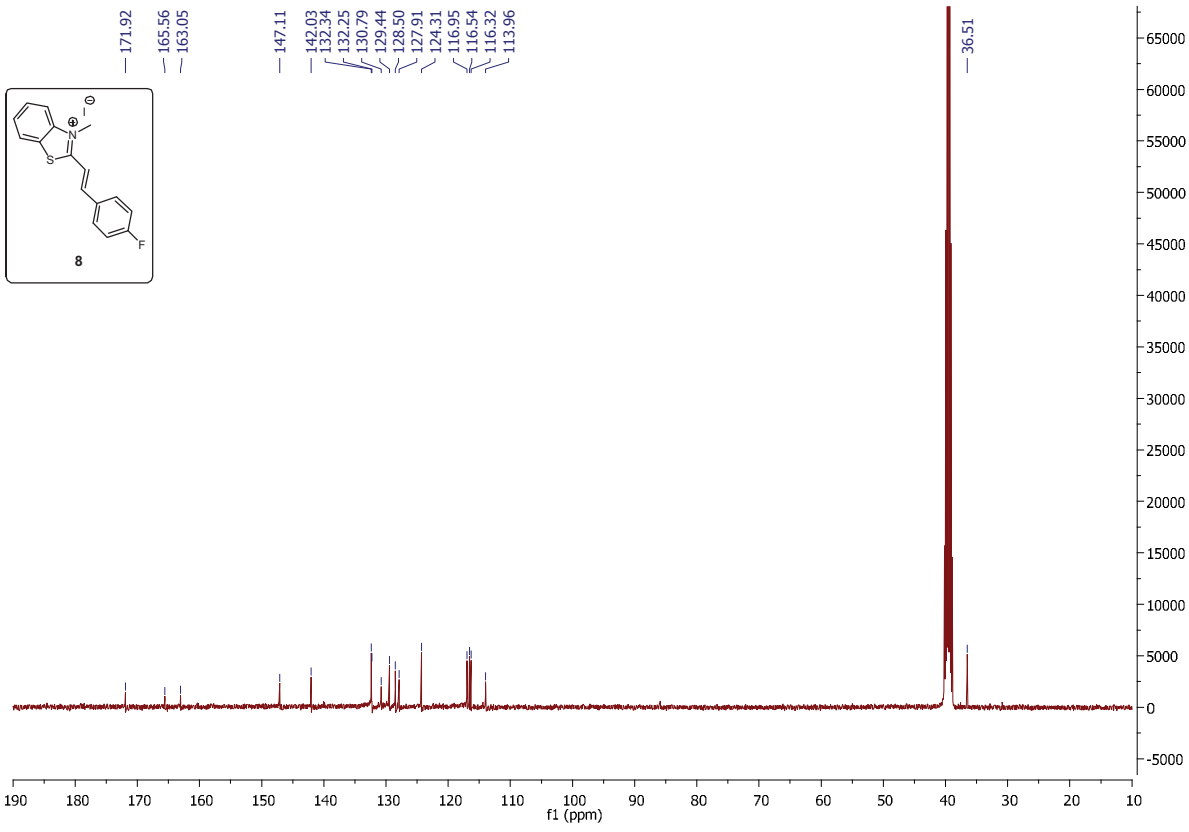
(3a*RS*,4*RS*,9b*SR*)-8-Methyl-4-[4-(trifluoromethyl) phenyl]-1,4,5,9b-tetrahydrothiazolo[5,4-*c*]quinolin-2(3a*H*)-one (6h)



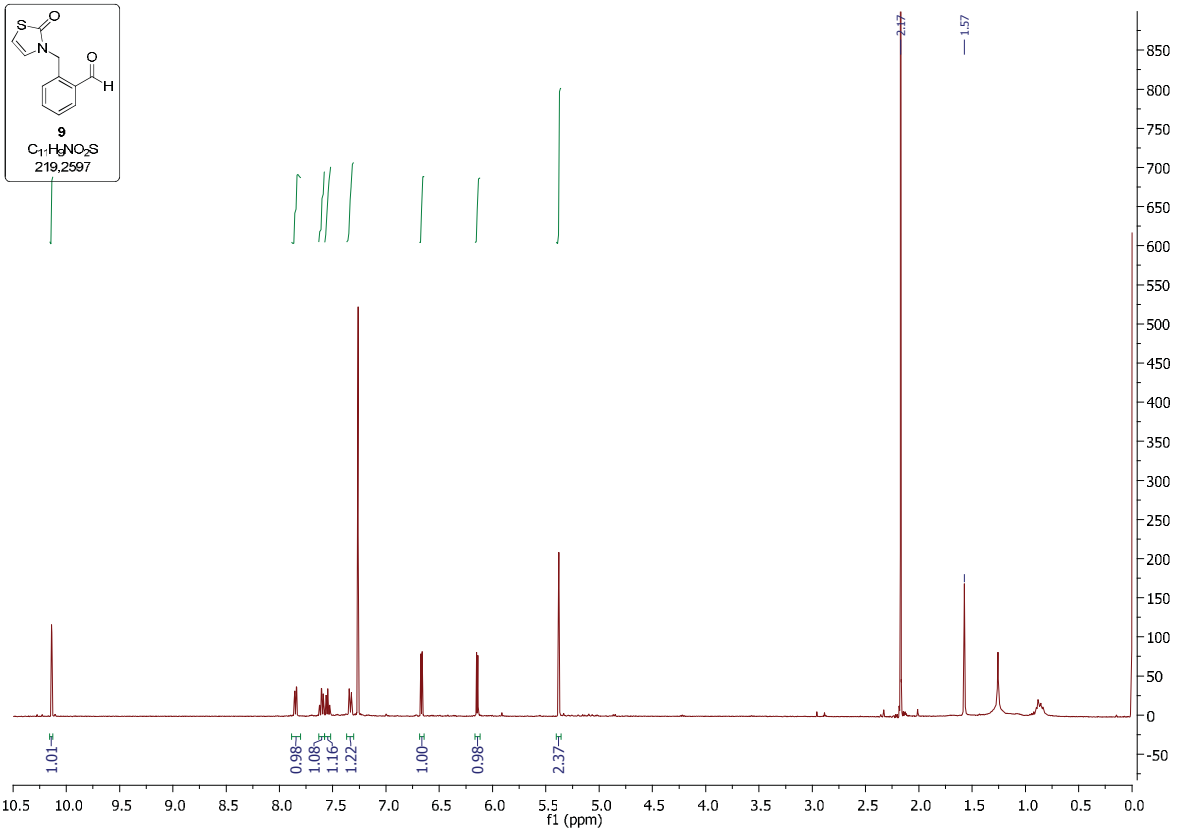


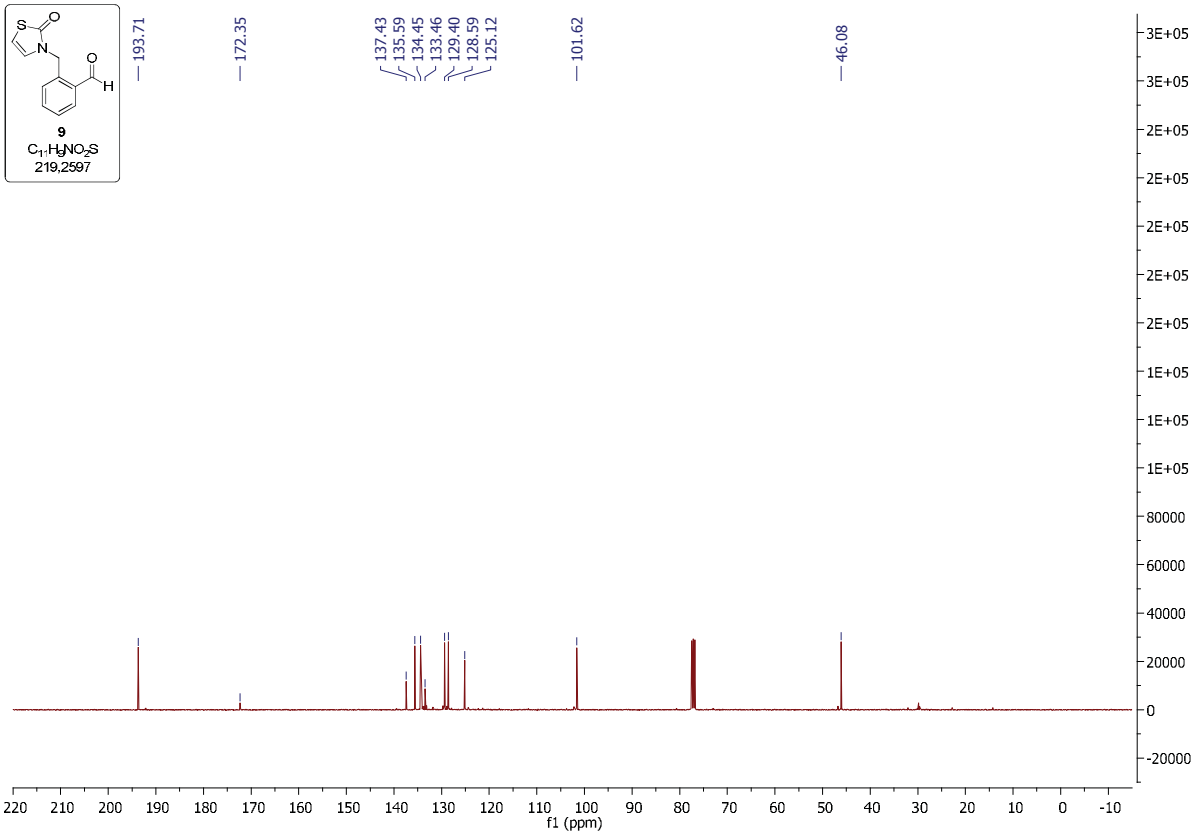
(*E*)-2-(4-Fluorostyryl)-3-methylbenzo[*d*]thiazol-3-ium iodide (8)



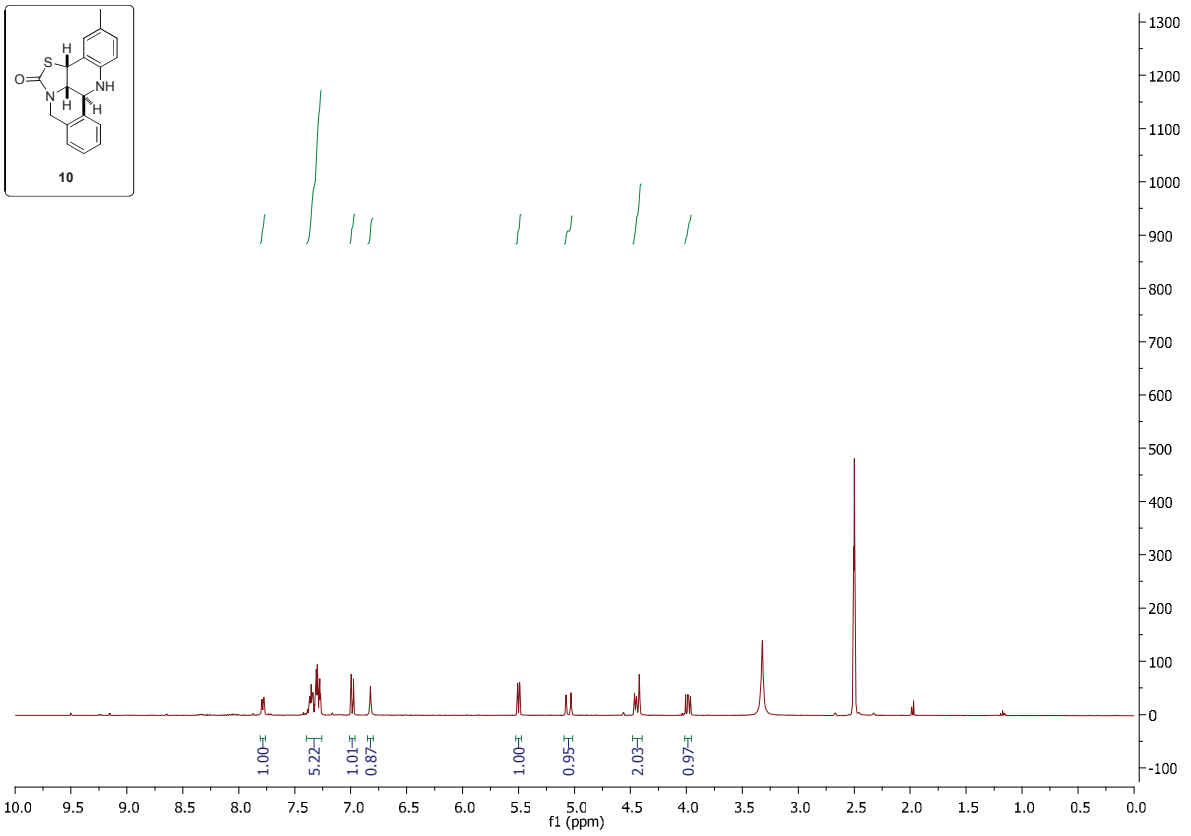


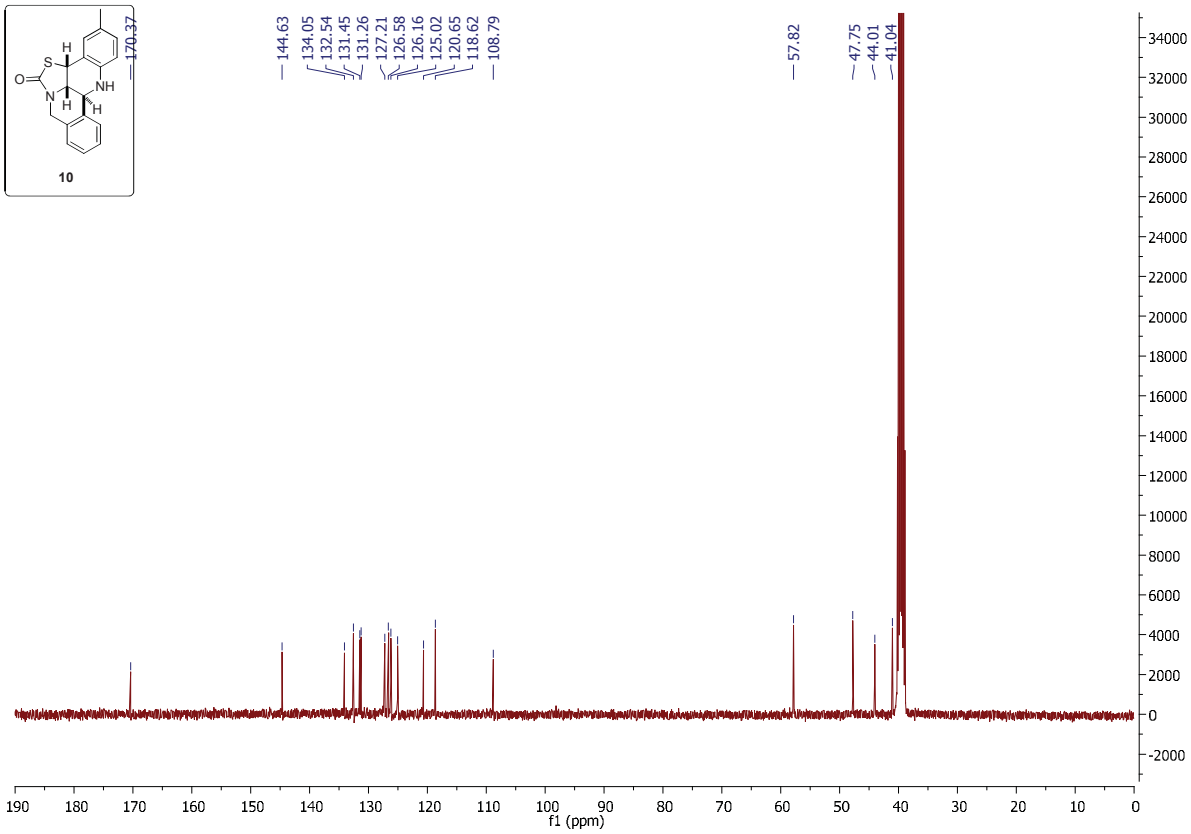
2-[(2-Oxothiazol-3(2*H*)-yl)methyl]benzaldehyde (9)



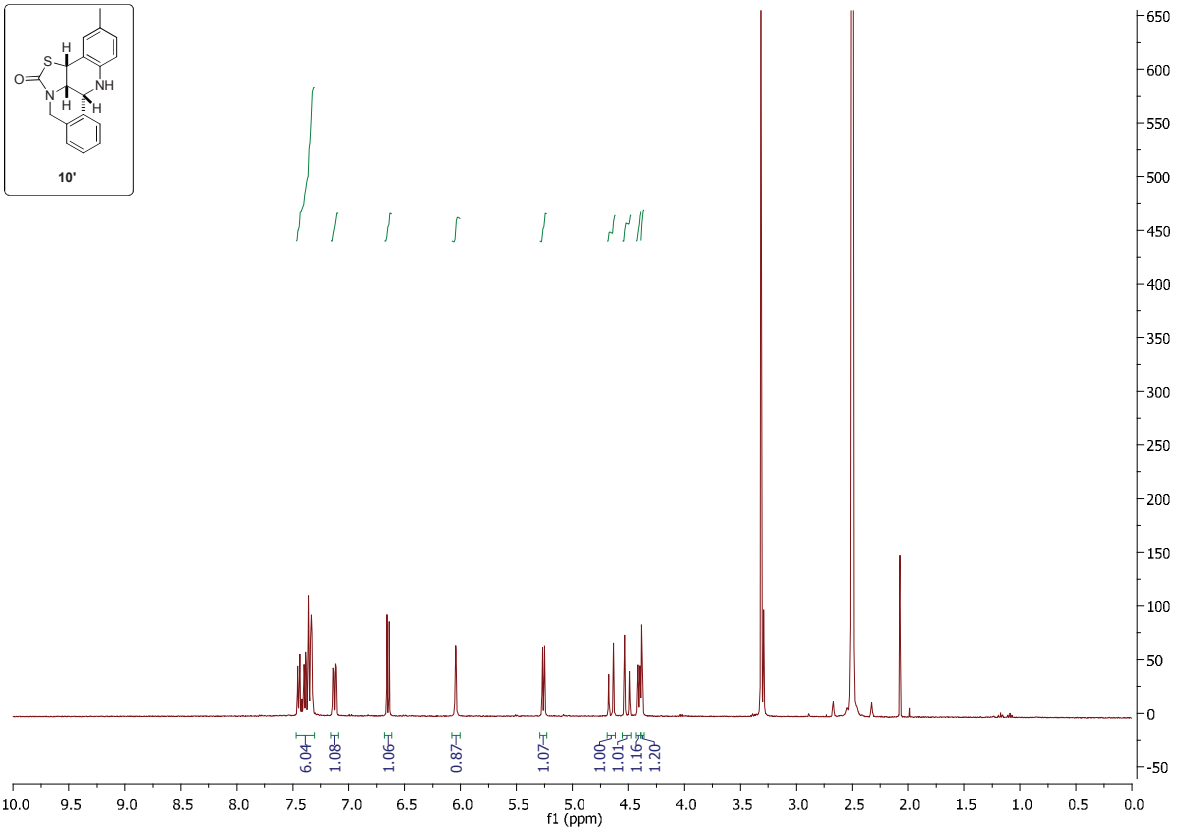


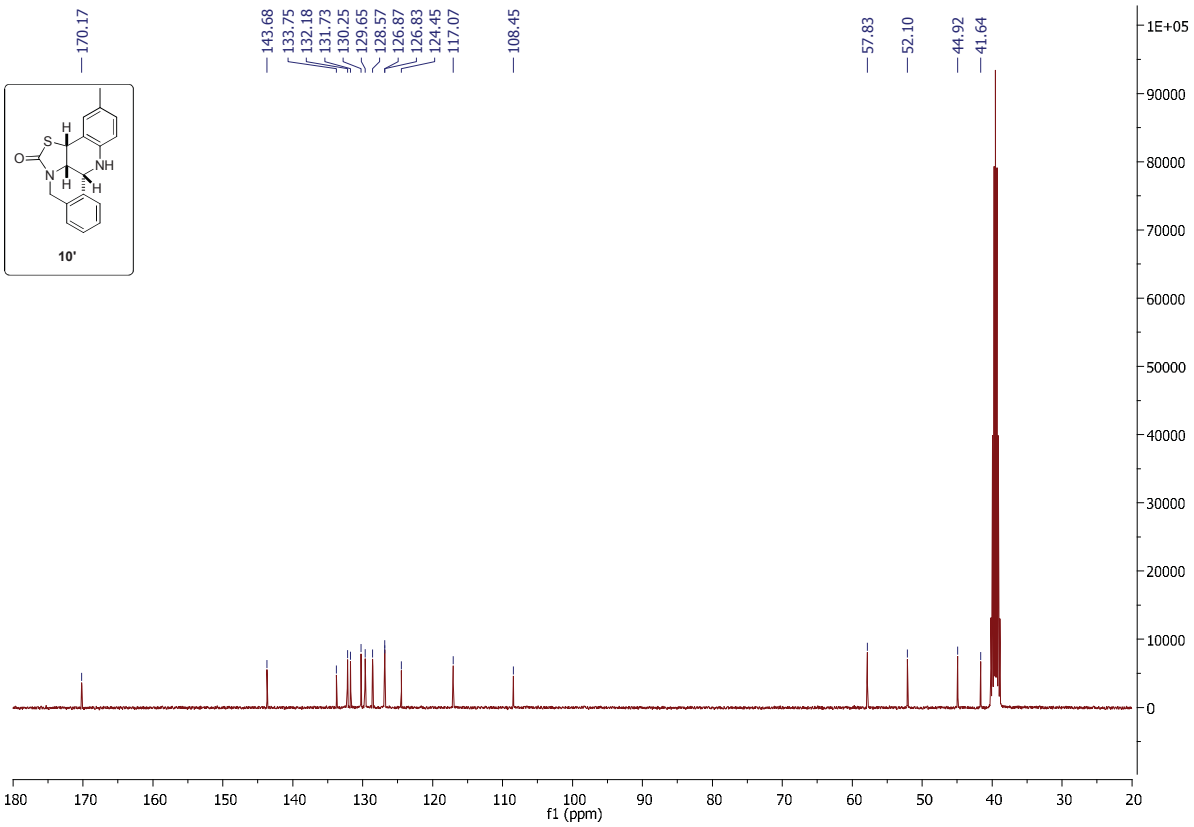
(4b*RS*,4b^1*SR*,12b*SR*)-3-Bromo-4b^1,8,12b,13-tetrahydrodibenzo[*b*,*h*]thiazolo[5,4,3*de*][1,5]naphthyridin-6(4b*H*)-one (10)



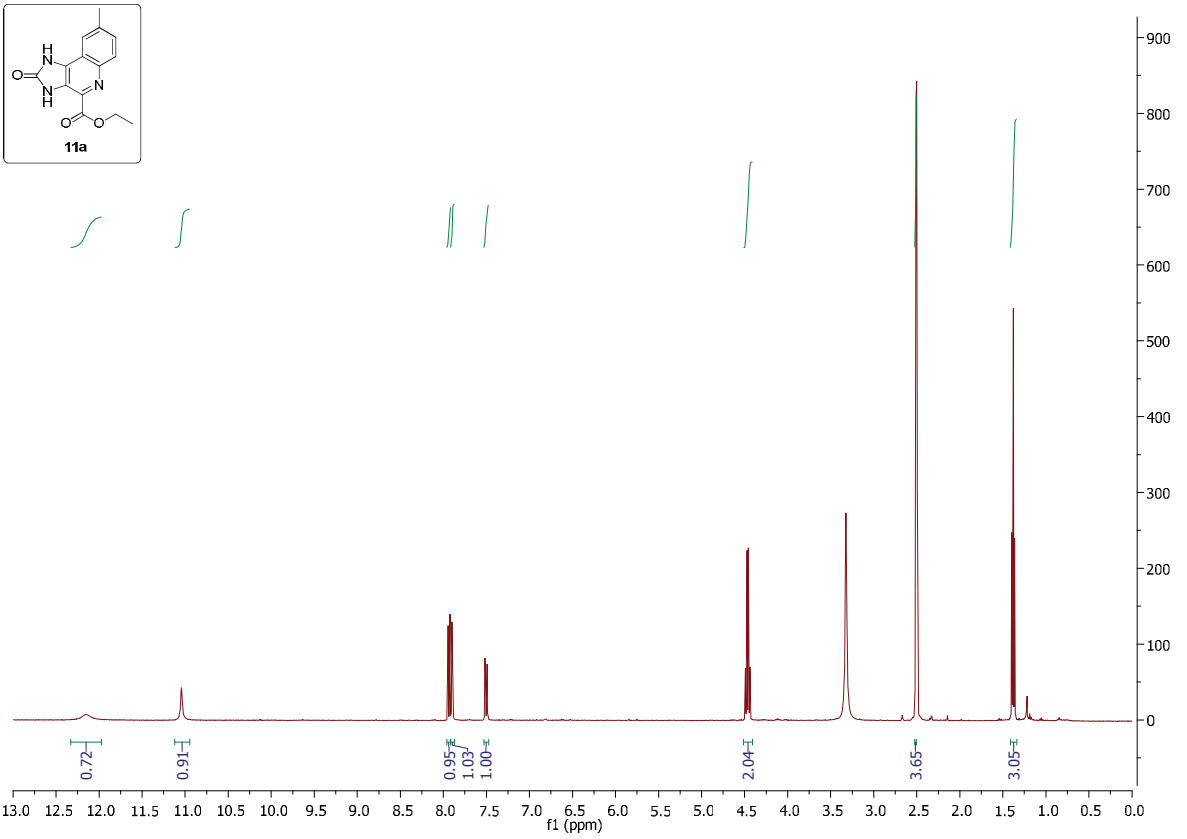


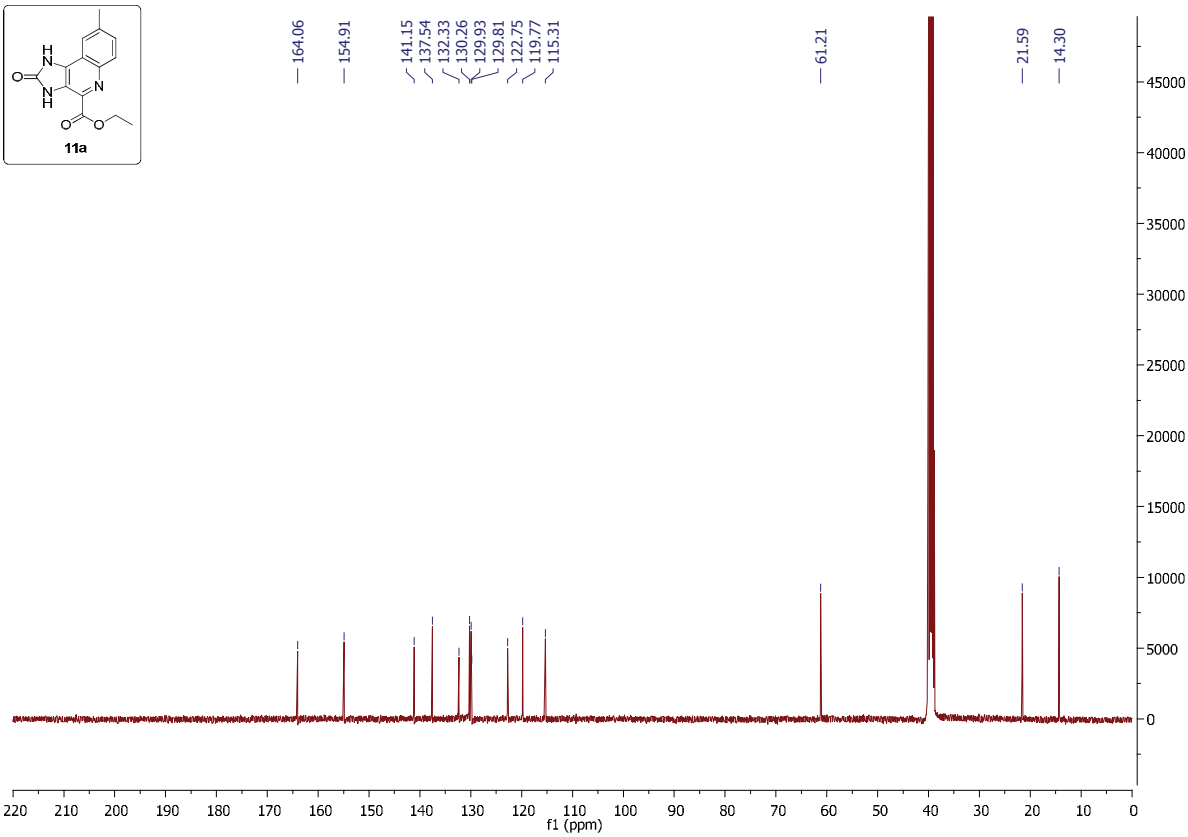
(4b*RS*,4b^1*SR*,12b*RS*)-3-Bromo-4b^1,8,12b,13-tetrahydrodibenzo[*b*,*h*]thiazolo[5,4,3-*de*][1,5]naphthyridin-6(4b*H*)-one (10')



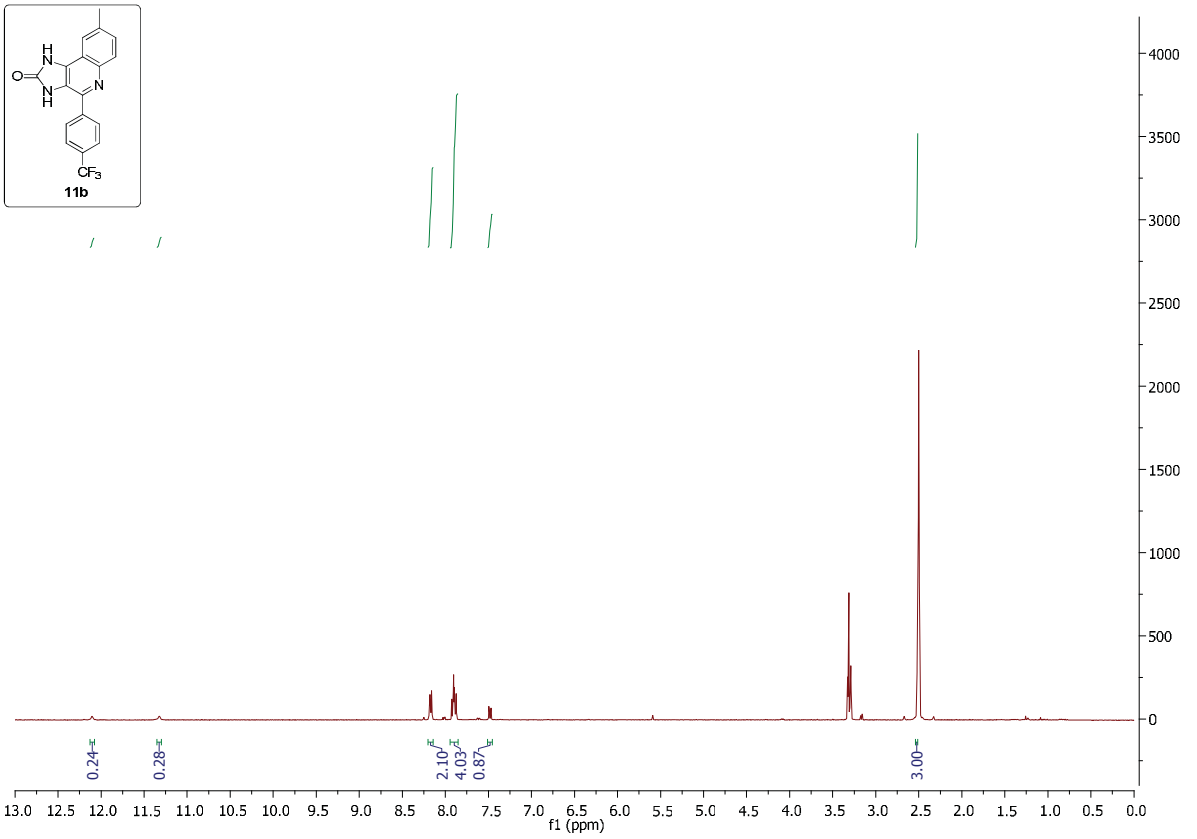


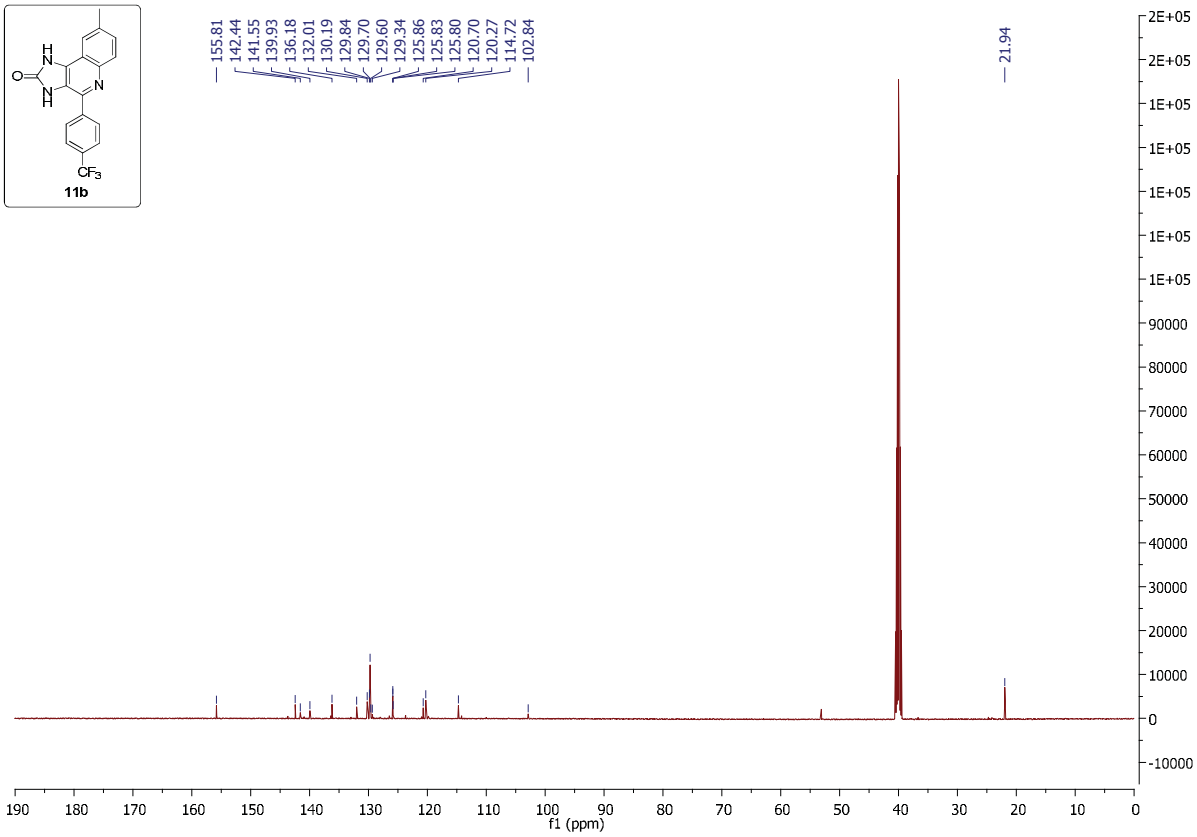
Ethyl 8-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*c*]quinoline-4-carboxylate (11a)



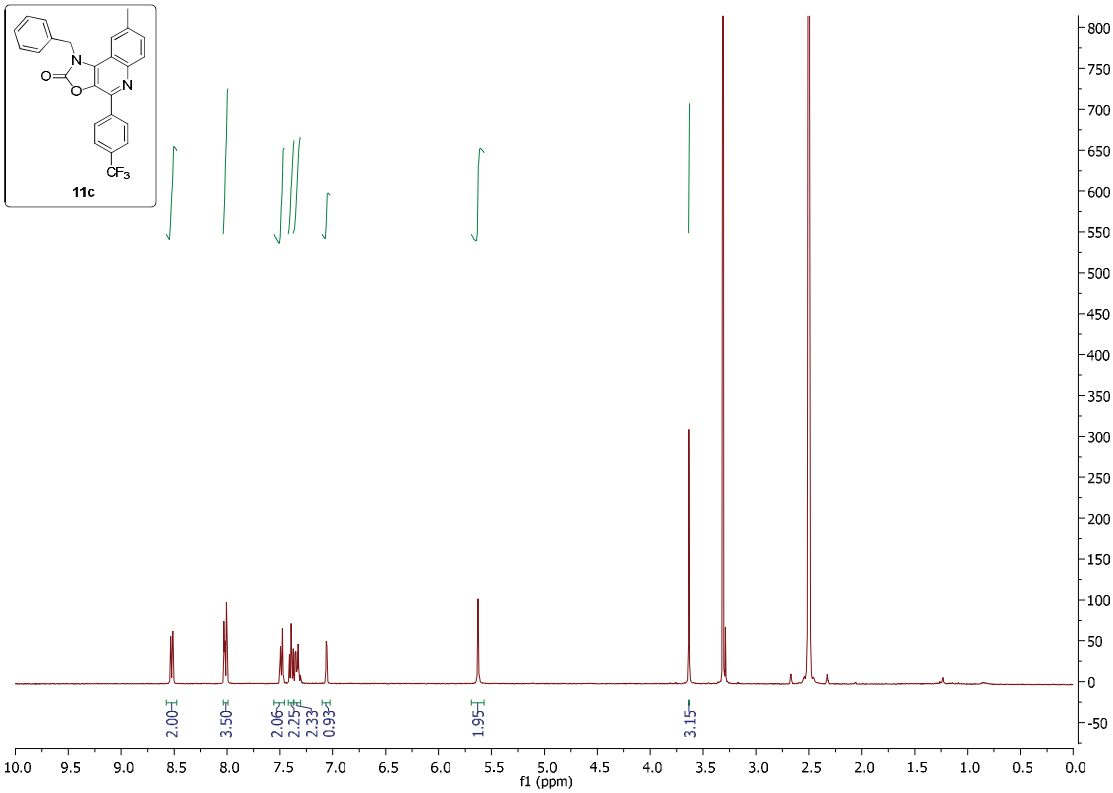


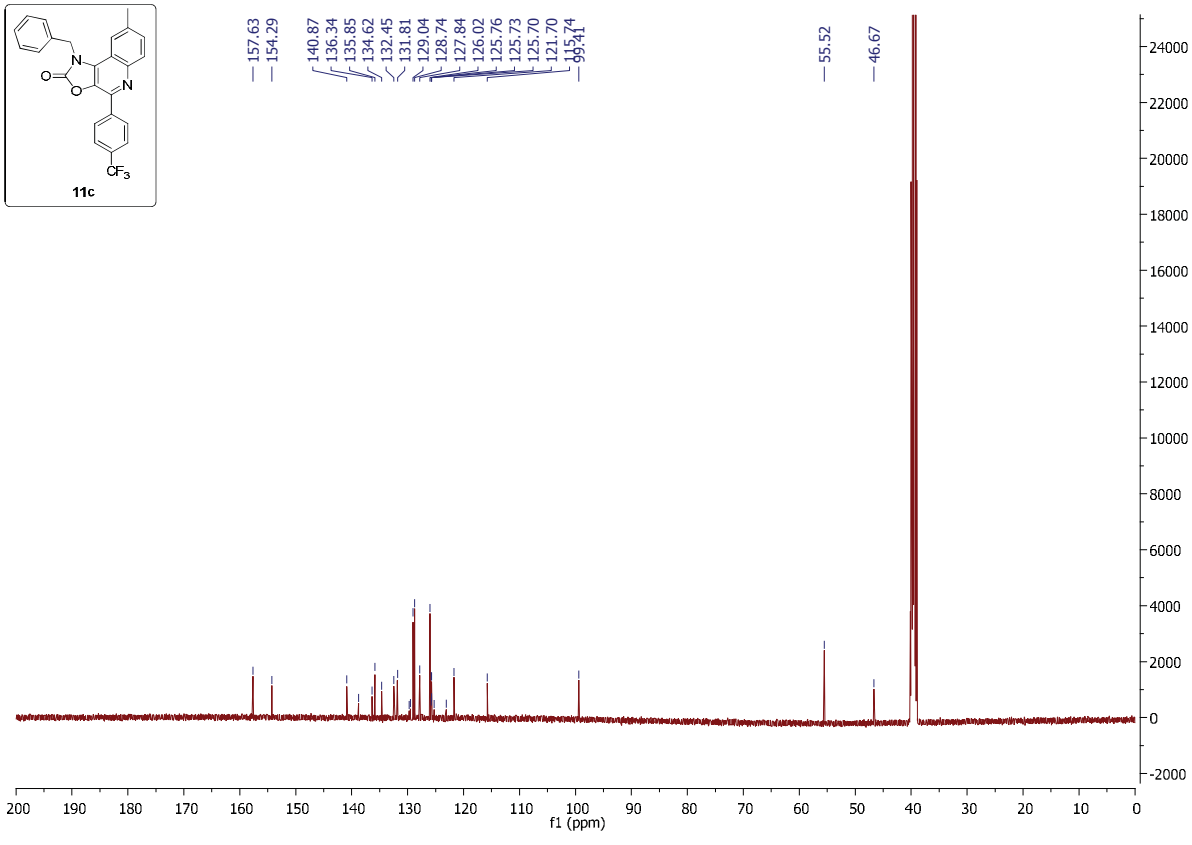
8-Methyl-4-[4-(Trifluoromethyl)phenyl]-1*H*-imidazo[4,5-*c*]quinolin-2(3*H*)-one (11b)



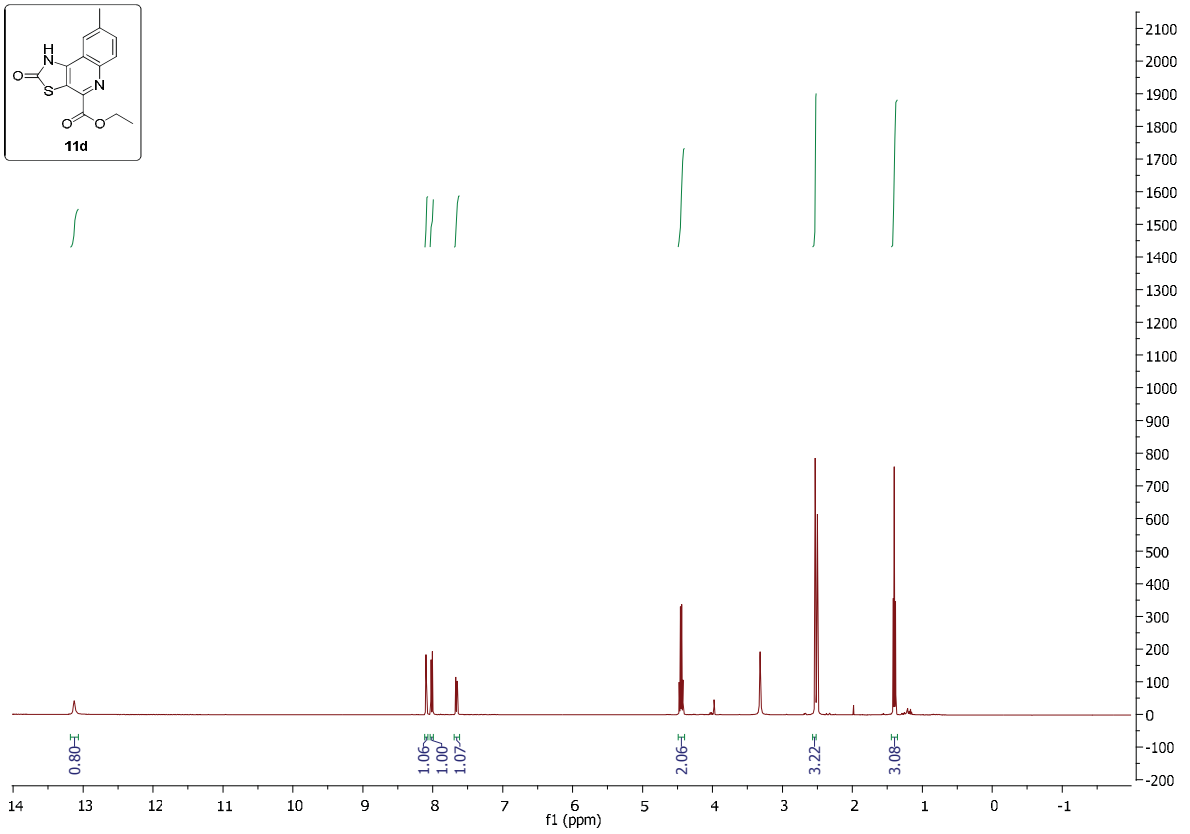


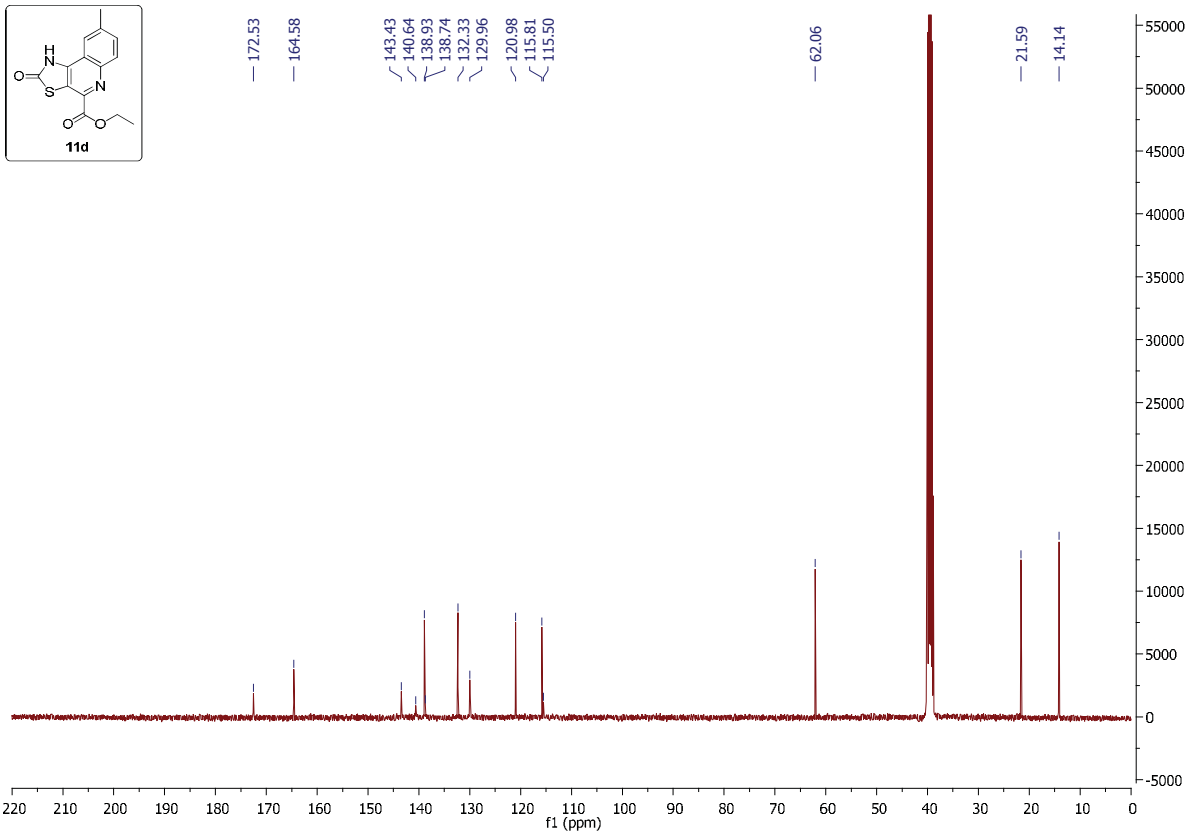
1-Benzyl-8-methoxy-4-[4-(trifluoromethyl)phenyl] oxazolo[5,4-*c*]quinolin-2(1*H*)-one (11c)



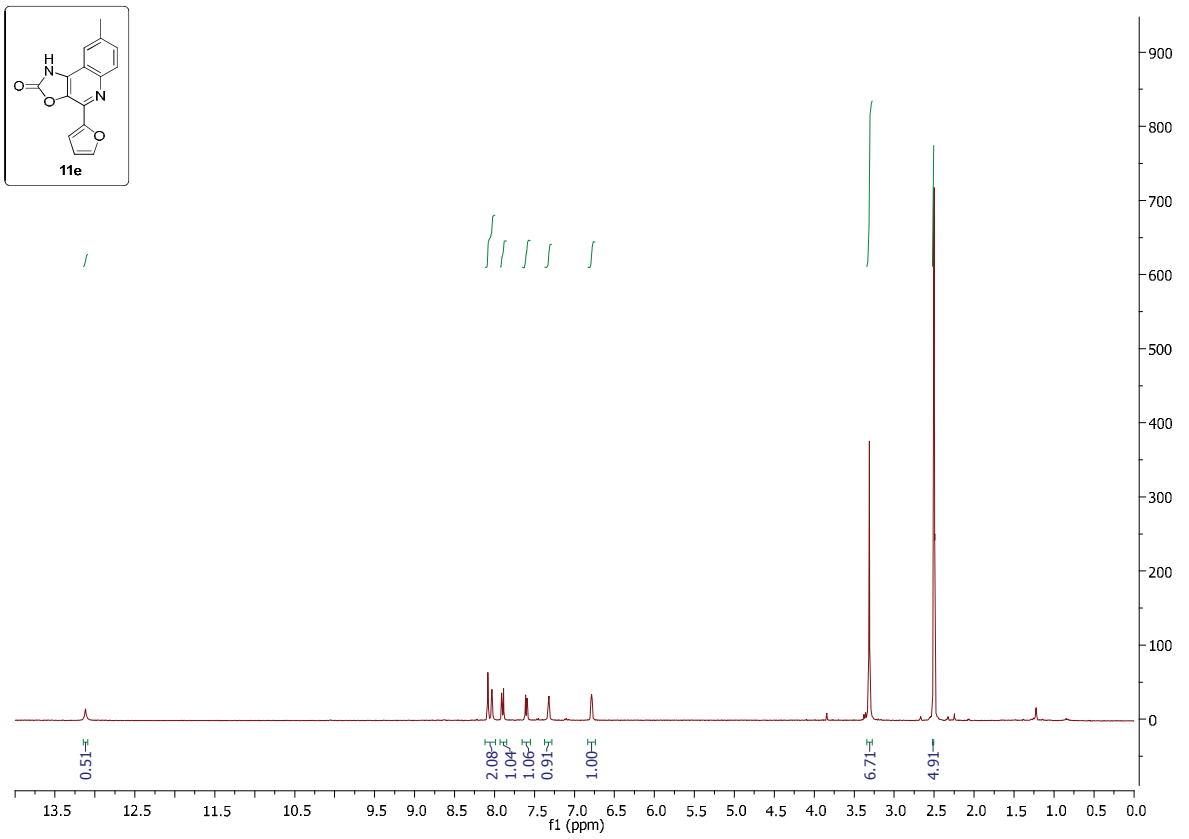


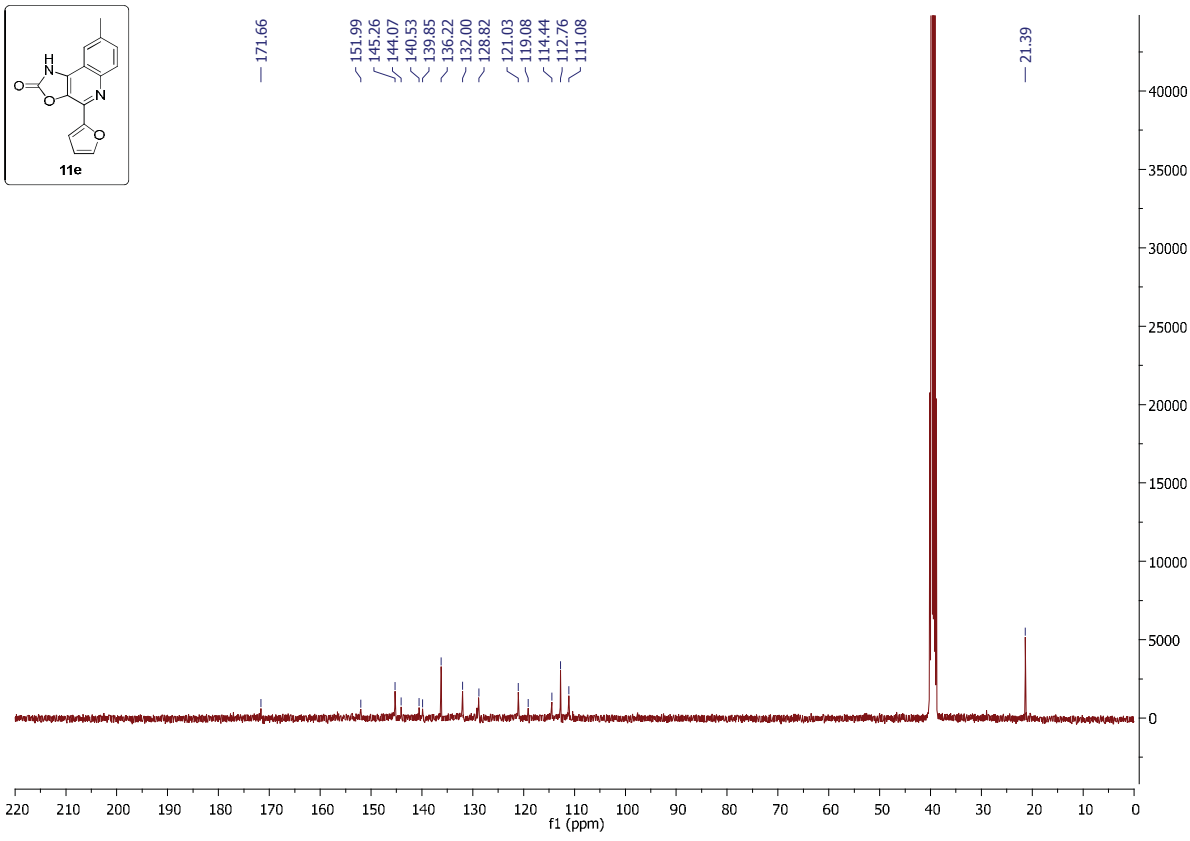
Ethyl 8-methyl-2-oxo-1,2-dihydrothiazolo[5,4-*c*] quinoline-4-carboxylate (11d)



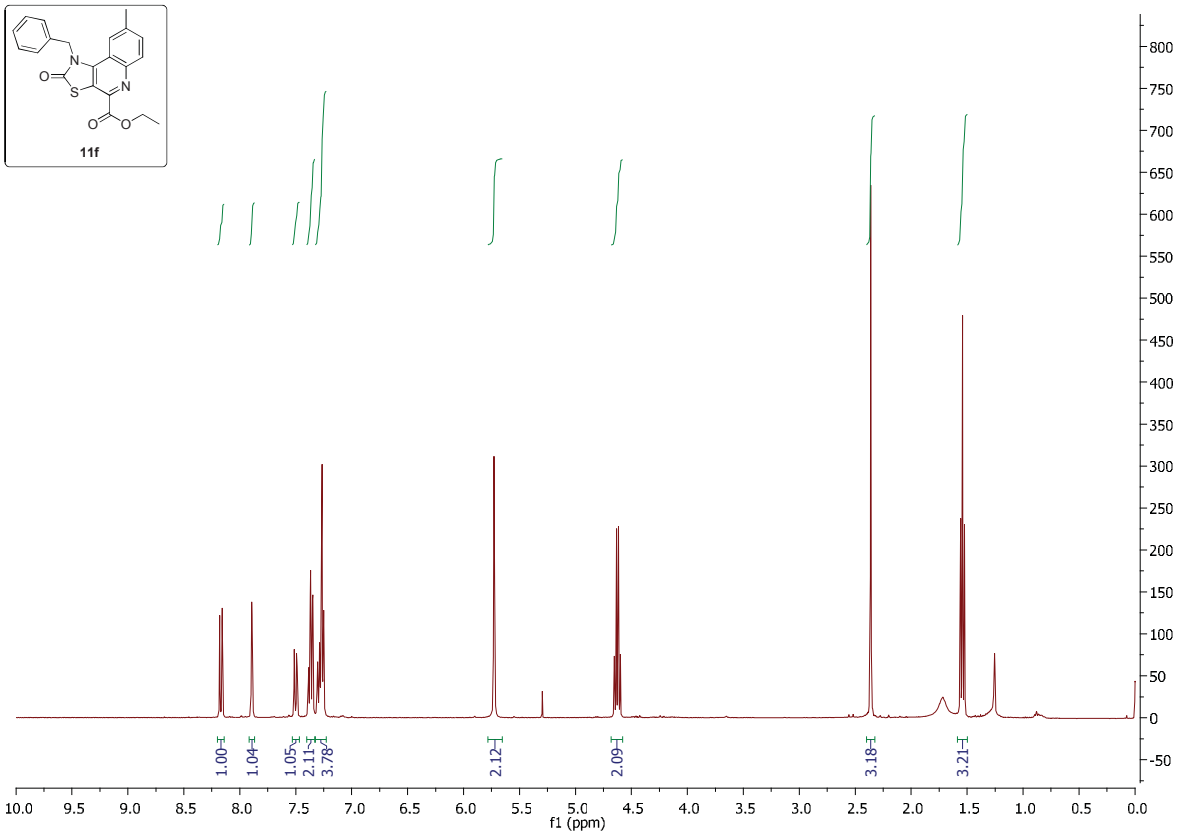


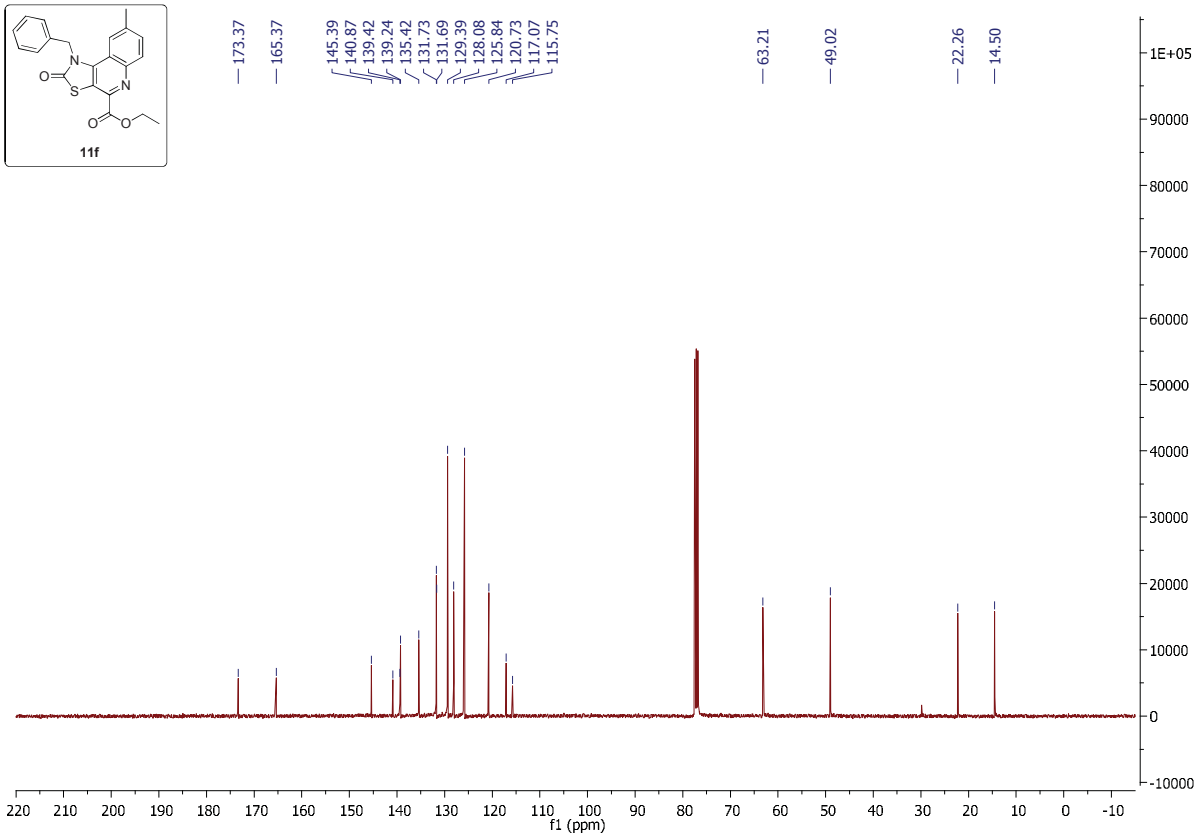
4-(Furan-2-yl)-8-methylthiazolo[5,4-*c*]quinolin-2(1*H*)-one (11e)



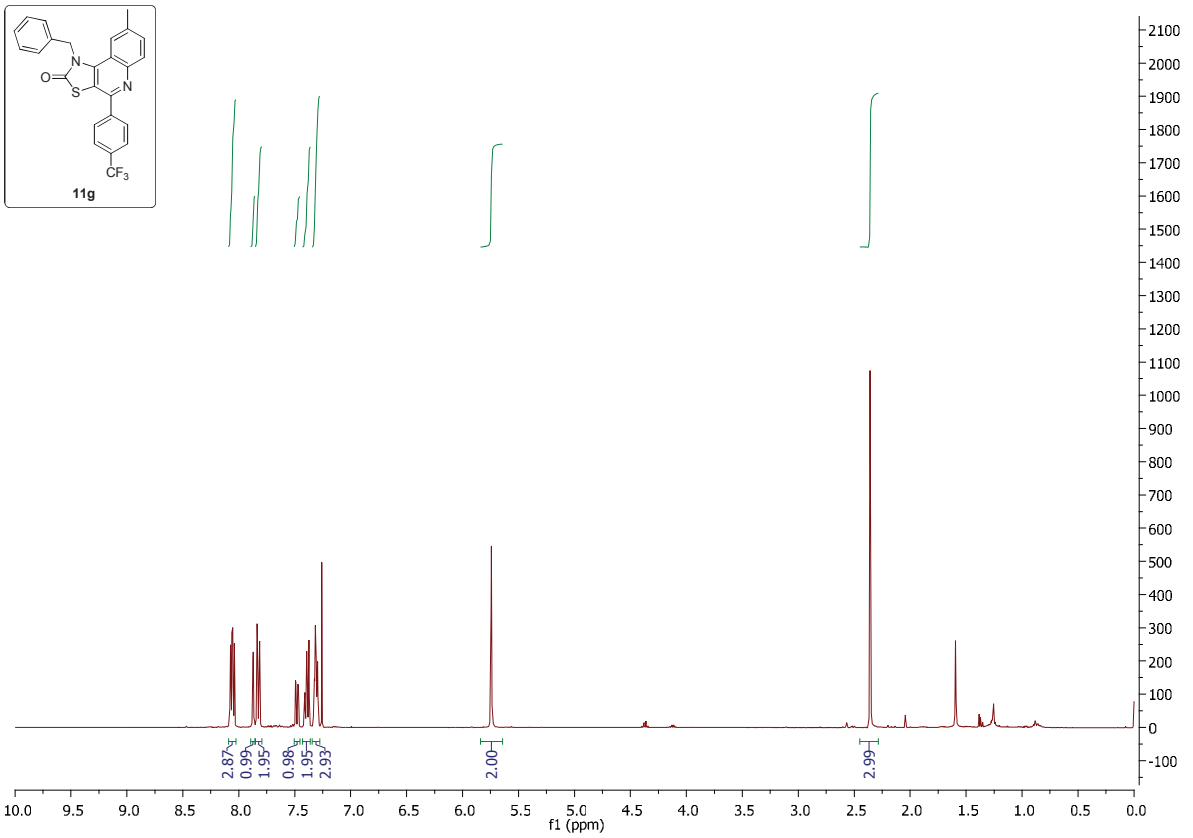


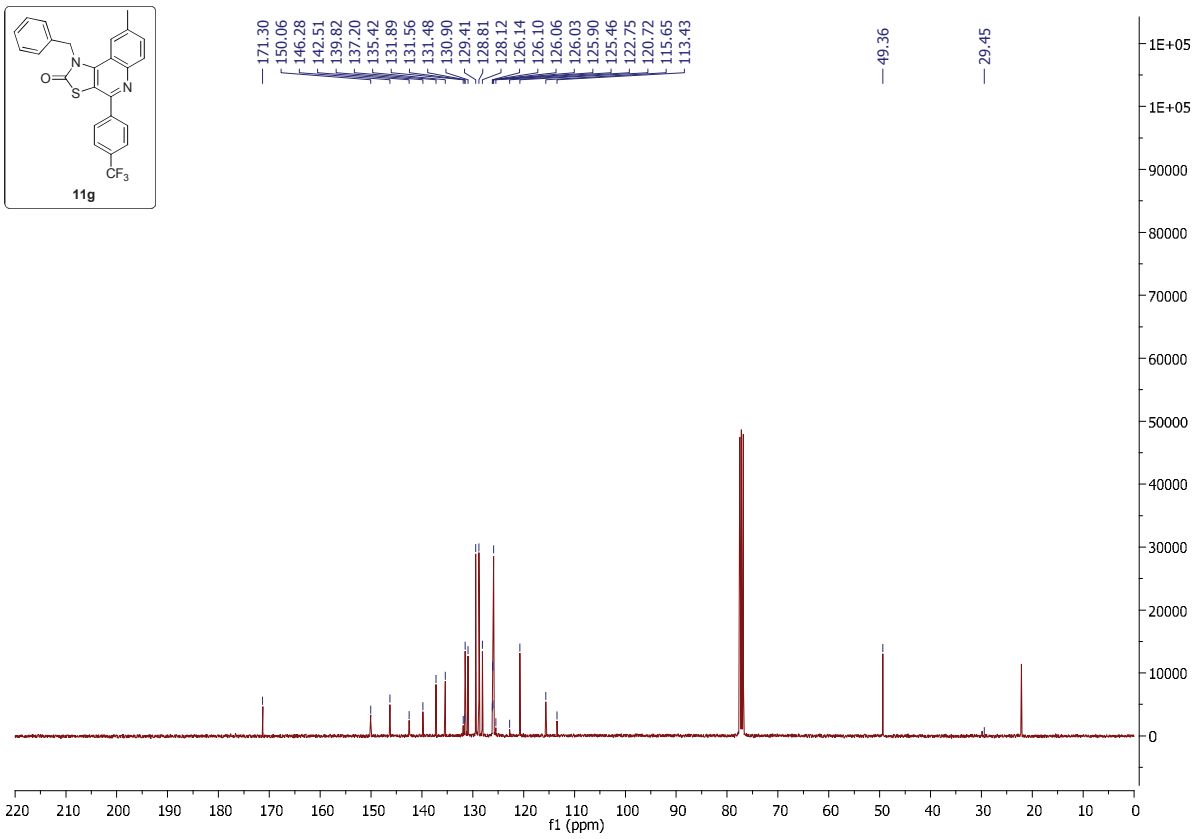
Ethyl 1-benzyl-8-methyl-2-oxo-1,2-dihydrothiazolo [5,4-*c*] quinoline-4-carboxylate (11f)



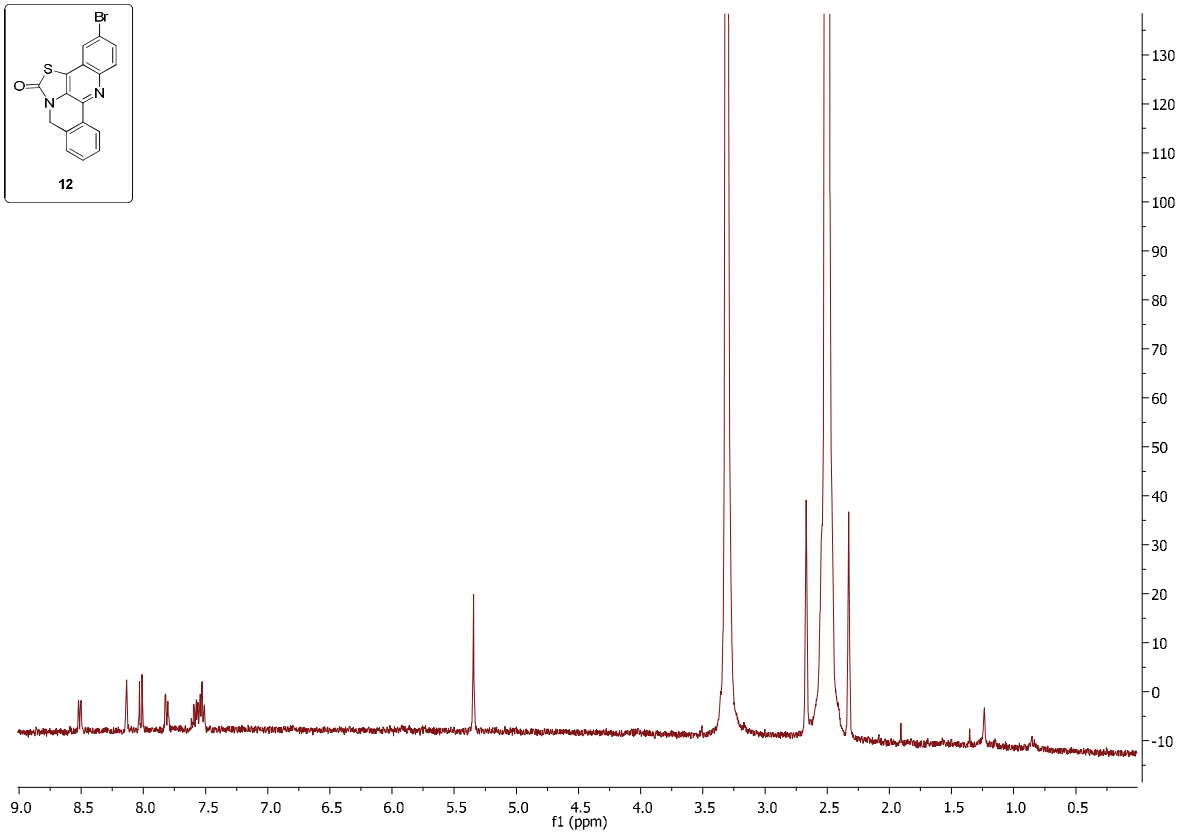


1-Benzyl-8-methyl-4-[4-(trifluoromethyl)phenyl] thiazolo[5,4-*c*]quinolin-2(1*H*)-one (11g)





3-Bromodibenzo[*b*,*h*]thiazolo[5,4,3-*de*][1,5]naphthyridin-6(8*H*)-one (12)



4. Nueva metodología para la oxidación de los aductos Povarov a quinolinas

Beilstein Journal of Organic Chemistry

Multicomponent reaction access to complex quinolines via oxidation of the Povarov adducts

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Abstract

The tetrahydroquinolines obtained through the Povarov multicomponent reaction have been oxidized to the corresponding quinoline, giving access to a single product through a two-step sequence. Several oxidizing agents were studied and manganese dioxide proved to be the reagent of choice, affording higher yields, cleaner reactions and practical protocols.

Introduction

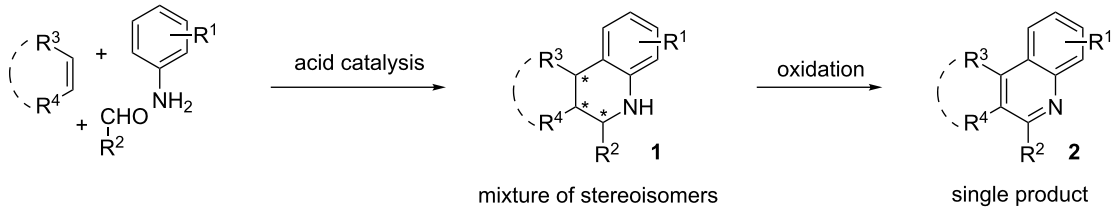
Heterocycles are ubiquitous scaffolds in pharmaceuticals, natural products and biologically active compounds. Quinoline systems in particular constitute a privileged substructure and are present in a large number of compounds with remarkable biological activity [1]. Although a variety of methods are used to prepare these heterocyclic compounds, the synthetic access to polysubstituted-polyfunctionalized derivatives remains a serious challenge [2]. Multistep sequences are widespread in the literature, but even in these cases the preparation of some substitution patterns and functional group combinations is particularly difficult. The recent introduction of multicomponent reactions (MCRs) into this field has brought interesting features typical of the ideal reaction, such as atom- and step economy, convergence, and exploratory power, together with new avenues in connectivity, leading to the straightforward synthesis of previously unobtainable scaffolds [3]. In this context, it is possible to obtain a wide variety of complex tetrahydroquinolines through the Povarov MCR (the interaction of anilines, aldehydes and activated olefin inputs under acid catalysis) [4-8]. Interestingly, this process allows cyclic enol ethers and enamines to be used as electron-rich alkenes, leading to heterocycle-fused tetrahydroquinolines, usually as a mixture of stereoisomers [9-13]. Unfortunately, no general methods for enantioselective Povarov reactions have been developed (for examples of catalytic enantioselective transformations operating in particular systems, see [14,15]), and this constitutes a serious drawback in the use

of this reaction for library preparation, as one reaction affords several products, when ideally it should give only one. However, these adducts can be subjected to oxidation, which will lead to the corresponding quinolines, preserving the substituents and functionalization already introduced in the preceding MCR. Despite the loss of all stereochemical information, in this way it would be feasible to obtain a single product from a multicomponent process (Scheme 1).

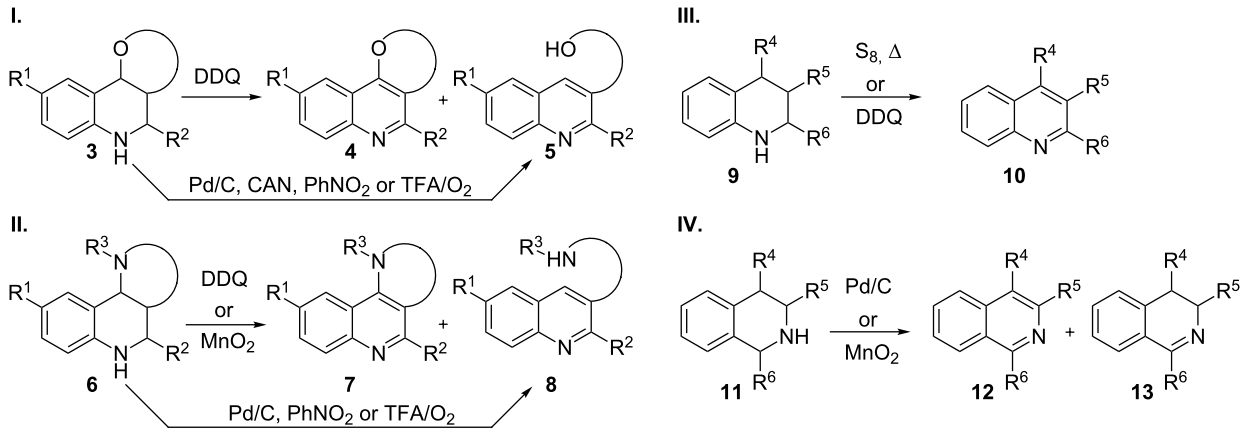
The oxidation step itself is challenging as it involves the formal removal of four hydrogens from a tetrahydropyridine moiety to reach the fully aromatic species. The literature contains scattered reports of the use of oxidants for this transformation: 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), ceric ammonium nitrate (CAN), nitrobenzene, elemental sulfur, palladium and manganese dioxide among others, all of them far from being ideally suited for these substrates.

One of the most commonly used is DDQ, which affords quinolines in acceptable yields. The main advantages of this oxidizing agent lie in its chemoselectivity and a requirement for relatively mild conditions, allowing it to be used in the presence of a wide range of substituents of the starting tetrahydroquinoline, such as O-, N- and C-linked residues (Scheme 2) [8,9,12,13,16-18]. Unfortunately, the alternative oxidation–elimination products (**5** and **8**) are often observed, therefore suggesting an acid catalyzed process. This would account for the elimination of alcohol and amine moieties, leading to dihydroquinoline intermediates that, after spontaneous oxidation in air, provide the final fragmented quinolines. The ability of DDQ to act as a Lewis acid and promote this alternative pathway has some precedent in the literature [19]. Furthermore, TFA treatment of Povarov adducts in oxygenated atmospheres also affords the oxidation–elimination products **5** and **8** (Scheme 2) [8,12,20].

The alternative oxidation–elimination pathway is predominant in some CAN-promoted oxidations of different Povarov adducts **3**. Incidentally, this reagent is also used as a catalyst in the Povarov MCR without oxidative interference [18]. The same trend (oxidation–fragmentation) can be observed using nitrobenzene [21] as the oxidant. Analogously, elemental sulfur and palladium, although requiring drastic conditions, also lead to the fragmented quinolines when the substrates bear O- and N-substituents [22-25] (for related isoquinoline oxidations, see [26,27]).



Scheme 1: Povarov oxidation access to substituted quinolines.



Scheme 2: Tetrahydroquinoline oxidation.

Related oxidative processes involve, for instance, a cascade Povarov–hydrogen transfer reaction using Tf_2NH as a catalyst and the imine as an oxidant, as recently described [28]. In addition, Povarov adducts resulting from the reaction between 3-aminocoumarin, aldehydes and cyclic enol ethers have been oxidized with different types of reagents, such as bromide, palladium, DDQ, sodium periodate, manganese dioxide or CAN, but in all cases the main product was the elimination–oxidation compound [29].

Finally, chemical manganese dioxide (CMD) has been widely used in this type of transformations, and already in 1982 the oxidation of tetrahydroisoquinoline (**11**, Scheme 2) was reported to yield the corresponding isoquinoline **12**, the intermediate dihydroisoquinoline **13** being obtained as a by-product [26]. Later, Thompson et al. described the oxidation of fused pyrrolohydroquinolines (type **6**) using MnO_2 obtained from batteries. A kinetic competition between two processes was observed, and the desired double oxidation to the corresponding fused quinoline **7** took place, along with the oxidation–elimination sequence leading to **8**. A large excess of oxidant was required in order to obtain the desired quinoline **7** as the major product (Scheme 2) [30,31].

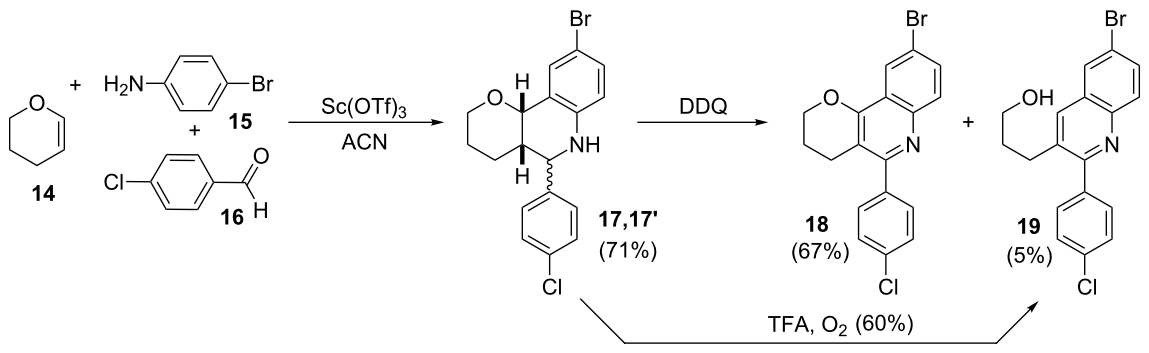
Results and Discussion

Experiments were performed with the goal of developing a general and practical protocol for the oxidation of Povarov adducts to furnish the corresponding fused quinolines, avoiding elimination by-products. After unsuccessful attempts using palladium on carbon (decomposition), CuCl (partial oxidative elimination), Fremy's salt (unreactive) and IBX (a complex reaction leading to unknown compounds), we focused our attention on MnO_2 as the oxidant of choice. A literature search revealed different reactivity patterns depending on the type and origin of the reagent, with the commercial source being particularly important [32-36]. A systematic study was therefore conducted to determine the influence of different reaction conditions, commercial reagents and additives on the oxidation of an elimination-prone Povarov tetrahydroquinoline substrate.

In this way, tetrahydroquinolines **17**,**17'** were synthesized as a mixture of isomers from the enol ether **14**, *p*-bromoaniline (**15**) and *p*-chlorobenzaldehyde (**16**) under $Sc(OTf)_3$ catalysis using standard reaction conditions (Scheme 3) [9]. Subsequently, these adducts **17**,**17'** were oxidized with DDQ by the standard protocol [9], to isolate the desired quinoline **18** and its fragmented derivative **19**, and they could also be subjected to an acid treatment to obtain selectively the latter product [8]. All compounds were purified and unequivocally characterized by NMR and HPLC methods.

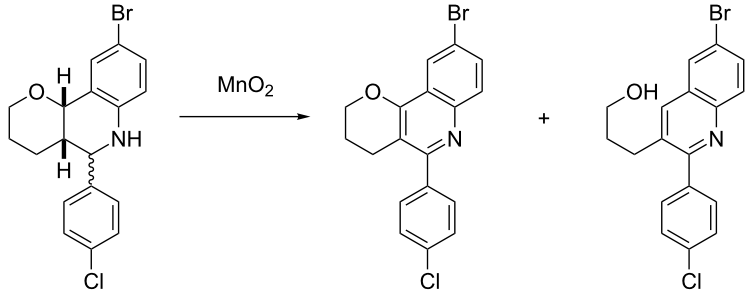
Taking into account that the oxidation of thiazolidines to thiazoles with MnO_2 (25 equiv) in toluene (55 °C) in the presence of pyridine (1.25 equiv) is a clean and efficient method [35], a first experiment was set up to test these conditions with an old (≈40 years) MnO_2 sample of unknown origin (particle size 11.46 μm, see below). A promising result was obtained, achieving a 39% conversion to the desired product **18**, albeit with a high ratio of the elimination–oxidation compound **19**. Next, the equivalents of oxidant and pyridine were increased to 100 and 6, respectively, and under these optimized conditions, a 72% isolated yield of quinoline **18** was obtained, and no starting material or elimination–oxidation compound was detected.

Unfortunately, we were not able to reproduce the above results when using brand new samples of MnO_2. It was decided to test different commercially available MnO_2 sources (Aldrich, Acros and Wako) of distinct activation degrees (particle size, powder or activated reagent, Table 1) in order to find a suitable reagent leading to comparable results.



Scheme 3: Synthesis of the Povarov adducts and their oxidation products.

Table 1: Survey of different MnO_2 reagents.



17,17' **18** **19**

entry	MnO_2 trademark, characteristics (reagent code)	particle size (median diameter, d_{50}, μm)[a]	reaction conditions	product ratios (**17**,**17'**)/**18**/**19**
1	Aldrich, reagent grade (310700)	4.3	25 equiv of oxidant	54/3/43
2	Aldrich, reagent grade (310700)	4.3	pyridine (50 equiv)	48/8/44
3	Aldrich, reagent grade (310700)	4.3	25 equiv of oxidant K_2CO_3 (6 equiv)	37/6/57
4	Aldrich, reagent grade (310700)	4.3	55 °C for 14 h	37/13/50
5	Aldrich, reagent grade (310700)	4.3	rt for 48 h	51/0/49
6	Aldrich, reagent plus (243442)	138.4	general conditions[b]	100/0/0
7	Aldrich, reagent plus (243442)	138.4	110 °C for 14 h	61/0/39
8	Aldrich, activated (217646)	4.2	general conditions[b]	8/14/78
9	Acros, powder (213490010)	7.6	general conditions[b]	75/0/25
10	Wako, 1st grade powder (138-09675)	25.7	general conditions[b]	0/100/0

[a]All manganese dioxide samples were analyzed with a LS™ 13 320 series Laser diffraction particle size analyzer. For more details, see Supporting Information File 1. [b]Unless otherwise stated, the reactions were performed in toluene as the solvent, using 100 equiv of oxidant, 6 equiv of pyridine at 55 °C for 2 h.

Aldrich MnO_2 (reagent grade) did not afford the desired quinoline **18** (entry 1, Table 1), the main products being the fragmented quinoline **19** and starting material. Modifications including the use of a greater excess of pyridine, the addition of K_2CO_3 as a heterogeneous base (entries 2 and 3), and adjustment of the reaction time or temperature (entries 4 and 5) did not substantially change the outcome. MnO_2 (Aldrich, reagent plus) was completely inefficient at 55 °C (entry 6), and on heating to 110 °C for 14 h it promoted a 39% conversion but led exclusively to the elimination product (entry 7). On the other hand, using activated MnO_2 (Aldrich), some oxidized quinoline **18** was observed, although again the predominant product was the fragmentation compound **19** (entry 8). Next, the reagents from Acros (entry 9) and Wako (entry 10) were tested, the latter being selective in the formation of the desired oxidation product, completely avoiding the elimination pathway. The results were reproducible, allowing the isolation of quinoline **18** in 66% yield in gram scale quantities.

In an attempt to improve the reaction conditions, Et_3N was tested as a base, and molecular sieves (4 Å) and $MgSO_4$ were introduced as dehydrating agents, but no meaningful changes were observed in any case. As the elimination–oxidation product **19** is thought to be generated by the acid characteristics of the oxidation reagents, an activated MnO_2 sample was treated with an aqueous basic ($NaCO_3$) solution, in an attempt to neutralize the acidic impurities, but the ratio of the elimination–oxidation product did not decrease. We then analysed the particle size of all samples using a laser diffraction technique (see Supporting Information File 1). Although a straightforward conclusion is not evident, it seems that all samples with a small (around 4 μm) or large particle size (138

μm) were inefficient in promoting the desired oxidation. On the other hand, medium size samples (Wako and the old sample of unknown origin) were the most selective oxidants (see Supporting Information File 1).

Using this reliable reagent, different reaction conditions were tested in order to optimize the process, especially regarding reagent consumption (Figure 1). The effects of varying the amounts of Wako MnO_2 (from 10 to 100 equiv) and pyridine (from 2 to 20 equiv) in the standard solvent (toluene), reaction time and temperature (2 h, 55 °C) were studied. The gradual increment in the amount of oxidant resulted in a progressive increase in the yield of compound **18** and the simultaneous decrease of the elimination quinoline **19**. No productive transformation to quinoline **18** was observed using 10 equiv of oxidant, the fragmented compound **19** being the predominant species. It is worth noting that the conversion of the starting material was only complete when at least 80 equiv of MnO_2 were used, but even in these conditions the elimination pathway could not be completely avoided, despite the huge excess of pyridine (up to 20 equiv). As such large amounts of pyridine were not beneficial, the use of 6 equiv of this reagent was a practical compromize, leading to the same essential outcome. In an attempt to disaggregate the Wako MnO_2 powder, and in this way reduce the amount of reagent, the reaction was performed in an ultrasonic bath under the general conditions, but no improvement was observed in the reaction profile.

The optimized oxidation conditions were applied to another class of tetrahydroquinolines, which contain a fused lactam ring (**20**,**20'**, Scheme 4) [12]. These new substrates were prepared through the Povarov MCR from the corresponding unsaturated lactam, aldehyde and aniline. The oxidation and elimination products (**21** and **22**, respectively) were independently prepared with DDQ under acid catalysis in an oxygenated atmosphere (O_2-TFA), and characterized by NMR and HPLC methods. The optimized conditions with the Wako reagent were productive and selectively afforded the corresponding quinolines **21** in high yields, and the elimination product **22** was not detected. The processes were slower (5–8 h) than those involving the pyran-

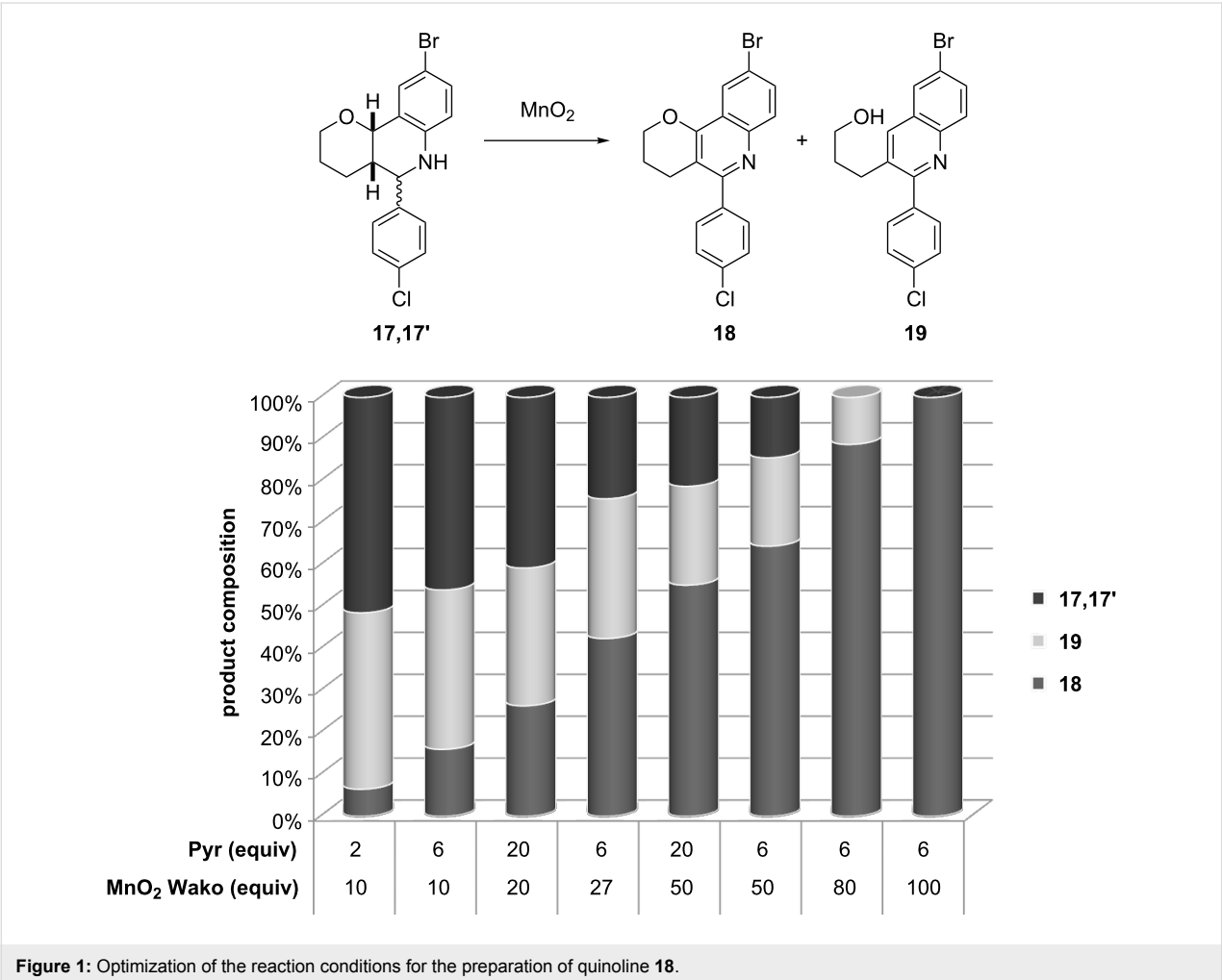
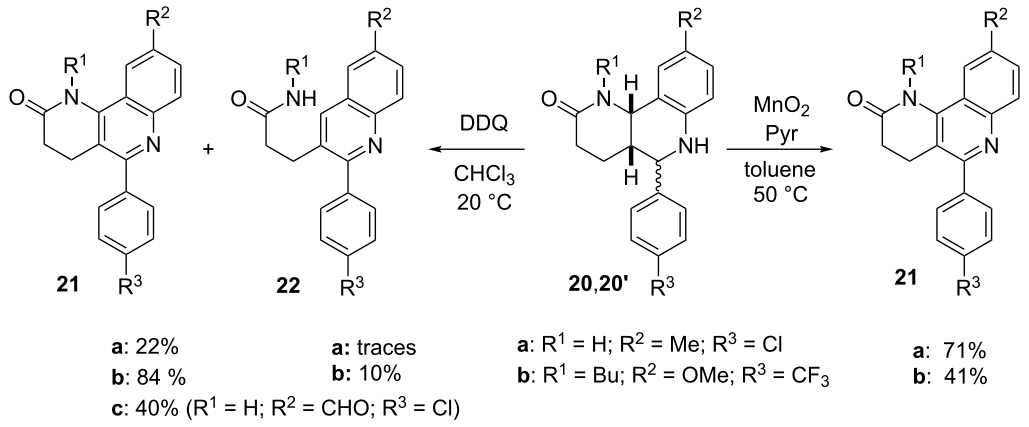


Figure 1: Optimization of the reaction conditions for the preparation of quinoline **18**.



Scheme 4: Oxidation of lactam-fused tetrahydroquinolines **20**,**20'**.

fused substrates **17**,**17'** (Scheme 3). Interestingly, although DDQ is also capable of promoting these transformations, it is not as selective as Wako MnO_2, and apart from yielding the fragmented quinolines **22**, it also oxidizes the benzylic hydrogens (**a** series, R^2 = Me) leading to the corresponding aldehyde derivative **21c** [12]. Studies are ongoing to expand this set of transformations to fused oxygenated and nitrogenated 5-membered ring systems.

Conclusion

In conclusion, we have described a fast, practical and reliable methodology to oxidize complex polysubstituted tetrahydroquinolines, arising from Povarov MCRs, to the corresponding quinolines, using MnO_2. The influence of the reagent source, stoichiometry, additives and reaction conditions has been determined. Wako CMD is the oxidant of choice and the presence of pyridine is critical to avoid the fragmentation pathway, a side reaction often found in this type of transformation. This process enables the selective preparation of heterocycle-fused quinolines arising from a single combination of aldehydes, anilines and activated alkenes in a short sequence, involving Povarov MCR and oxidation steps.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Unless otherwise stated, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H NMR spectra are reported as follows: Chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned by means of two-dimensional NMR spectroscopy: ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-COSY (HSQC: heteronuclear single quantum coherence) and long-range ^{1}H,^{13}C-COSY (HMBC: heteronuclear multiple bond connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

General procedure A [9,12]

To a solution of compound **17**,**17'** or **20**,**20'** (1 mmol) in 15 mL of $CHCl_3$, DDQ (2 mmol) was added and the mixture was stirred for 24 h in an open vessel at room temperature. An aqueous saturated $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The reaction mixture was purified by flash chromatography (hexane–EtOAc) to afford the desired product.

General procedure B [9,12]

To a solution of compound **17**,**17'** or **20**,**20'** (1 mmol) in CH_3CN/H_2O or $CHCl_3/H_2O$ (1:1, 6 mL), TFA (2 mmol) was added. The reaction mixture was stirred for 24 h at room temperature, quenched with an aqueous saturated $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue which was purified by flash chromatography (hexane–ethyl acetate) to afford the desired product.

General procedure C

To a solution of compound **17**,**17'** or **20**,**20'** (1 mmol) in 50 mL of toluene, pyridine (6 mmol) and MnO_2 Wako (100 mmol) were added and the mixture was stirred in an open vessel at 55 °C. The progress of the reaction was controlled by TLC or HPLC, until the starting material completely disappeared or no evolution was observed. The crude mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The reaction

mixture was purified by flash chromatography (hexane–EtOAc) to afford the desired product.

9-bromo-5-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinoline (18)

Following the general procedure A, the oxidation of **17**,**17'** afforded compound **18** as a white solid (68%). Following the general procedure C for 2 h with Wako MnO_2, the oxidation of **17**,**17'** afforded compound **18** as a white solid (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.2 Hz, 1H), 7.85 (d, J = 8.9 Hz, 1H), 7.70 (dd, J = 2.3, 8.9 Hz, 1H), 7.53–7.48 (m, 2H), 7.45–7.40 (m, 2H), 4.46–4.39 (m, 2H), 2.72 (t, J = 6.3 Hz, 2H), 2.03–1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.91, 156.71, 145.86, 138.58, 134.58, 132.71, 130.76, 130.24, 128.54, 123.91, 121.18, 119.46, 111.35, 67.21, 23.80, 21.75; IR (film): 3319, 3058, 2987, 2949, 2917, 2859, 1905, 1585, 1476, 1392, 1348, 1322, 1162, 1123, 1085, 989 cm^{-1}; HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{14}BrClNO$, 373.9942; found, 373.9933.

3-(6-bromo-2-(4-chlorophenyl)quinolin-3-yl)propan-1-ol (19)

Following the general procedure B, the oxidation of **17**,**17'** afforded compound **19** as a white solid (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.87 (m, 3H), 7.67 (dd, J = 2.2, 8.9 Hz, 1H), 7.44–7.37 (m, 4H), 3.51 (t, J = 6.2 Hz, 2H), 2.85–2.77 (m, 2H), 1.75–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 145.2, 139.0, 135.3, 134.8, 134.3, 132.8, 131.2, 130.3, 129.2, 128.9, 128.9, 120.8, 62.0, 33.3, 29.4; IR (film): 3353, 2924, 2847, 1783, 1732, 1598, 1476, 1431, 1393, 1258, 1188, 1085, 1059, 1009, 919, 823 cm^{-1}; HRMS (ESI+, *m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{16}BrClNO$, 376.0098; found, 376.0090.

Supporting Information

Supporting information features the characterization data of compounds **18**, **19**, **21** and **22,** copies of their ^{1}H NMR and ^{13}C NMR spectra, and the particle size analyses of MnO_2 samples.

Supporting Information File 1

Experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-110-S1.pdf]

Acknowledgements

This work was supported by DGICYT – Spain (project BQUCTQ2009-07758), Generalitat de Catalunya (project 2009SGR 1024) and Barcelona Science Park. Grupo Ferrer (Barcelona, Spain) is thanked for financial support. We thank Dr. Pedro Grima (Grupo Ferrer, R+D center, Barcelona) for useful comments.

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License and Terms

Supporting Information

for

Multicomponent reaction access to complex quinolines via oxidation of the Povarov adducts

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Experimental details

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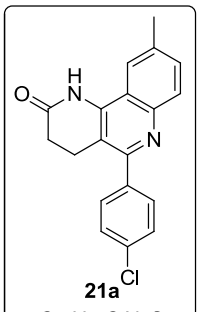
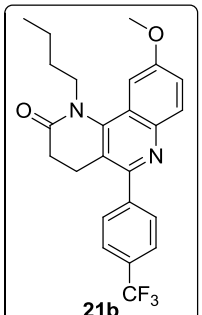
5-(4-Chlorophenyl)-9-methyl-3,4-dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (21a)



21a
$C_{19}H_{15}ClN_2O$
MW: 322,79

Following the general procedure A, the oxidation of **20a**,**20a'**, afforded compound **21a** as a white solid (22%).
Following the general procedure C for 5h with Wako MnO_2, the oxidation of **20a**,**20a'**, afforded compound **21a** as a white solid (71%). The spectroscopic data for this compound perfectly matches the published data [12].

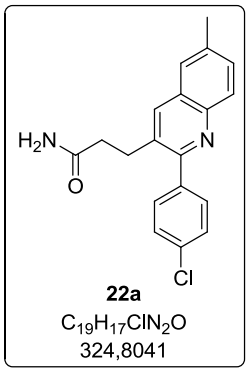
Butyl-9-methoxy-5-[4-(trifluoromethyl)phenyl]-3,4 dihydrobenzo[h][1,6]naphthyridin-2(1*H*)-one (21b)



21b
$C_{24}H_{23}F_3N_2O_2$
MW: 428,45

Following the general procedure A, the oxidation of **20b**,**20b'**, afforded compound **21b** as a purple solid (84%).
Following the general procedure C for 8h with Wako MnO_2, the oxidation of **20b**,**20b'**, afforded compound **21b** as a purple solid (41%). The spectroscopic data for this compound perfectly matches the published data [12].

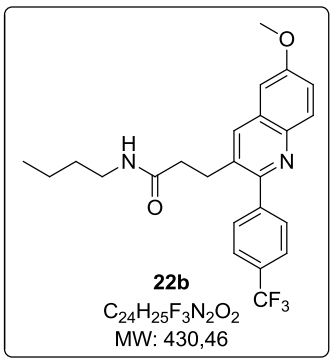
3-[2-(4-Chlorophenyl)-6-methylquinolin-3-yl]propanamide (22a)



22a
$C_{19}H_{17}ClN_2O$
324,8041

Following the general procedure B, the treatment of **20a**,**20a'** afforded compound **22a** as a white solid (49%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.93 (m, 2H), 7.55 (s, 1H), 7.51 (dd, *J*= 8.6, 1.9 Hz, 1H), 7.48–7.40 (m, 4H), 5.49 (br s, 1H), 5.39 (br s, 1H), 3.14–3.08 (m, 2H), 2.54 (s, 3H), 2.36–2.31 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.7, 158.1, 145.4, 139.2, 136.9, 135.9, 134.5, 131.9, 131.8, 130.3, 128.9, 128.8, 127.7, 126.0, 36.0, 28.5, 21.8 ppm. **IR** (film) ν_{max}: 3353, 3186, 3051, 2911, 2847, 1662, 1617, 1482, 1437, 1405, 1373, 1296, 1085, 1002, 918, 822, 133 cm^{-1}. **HRMS**: calcd for $C_{19}H_{18}ClN_2O$, 325.1102 ($M+H^+$); found, 325.1101.

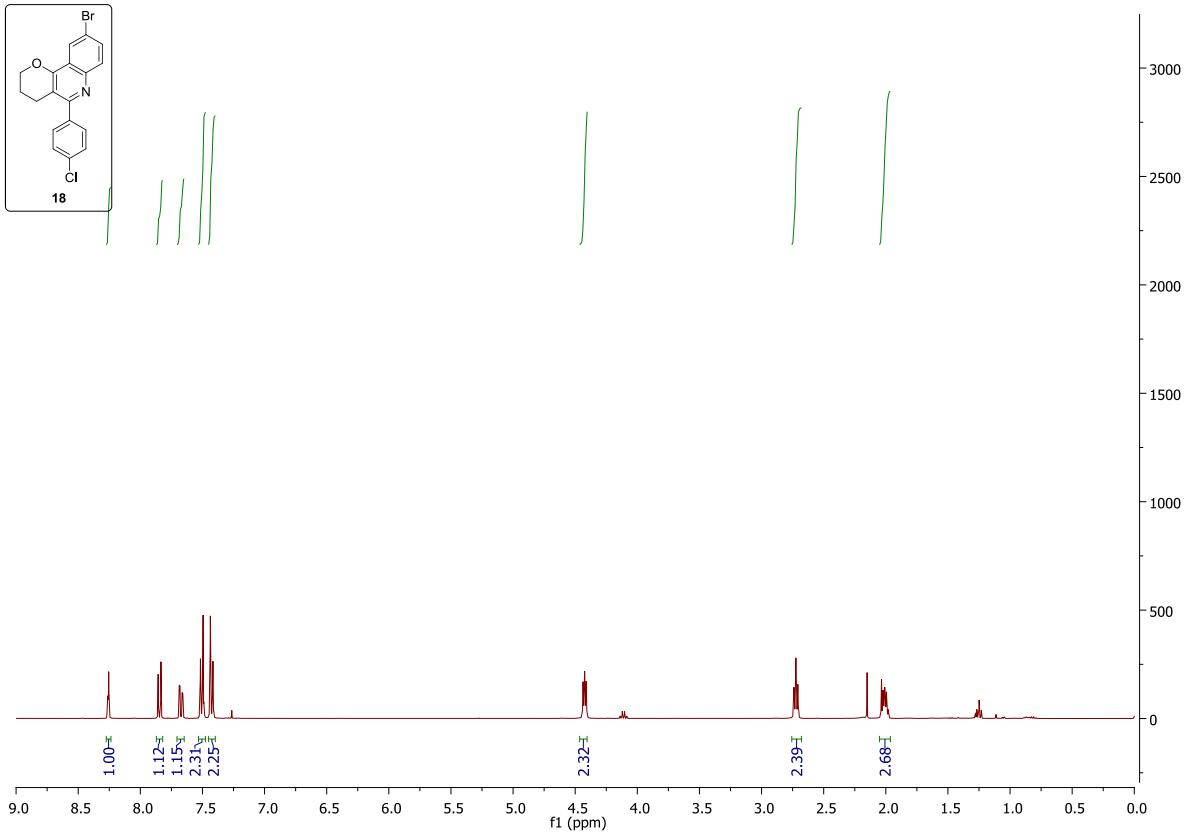
3-[6-Methoxy-2-{4-(trifluoromethyl)phenyl}quinolin-3-yl]-*N*-pentylpropanamide (22b)

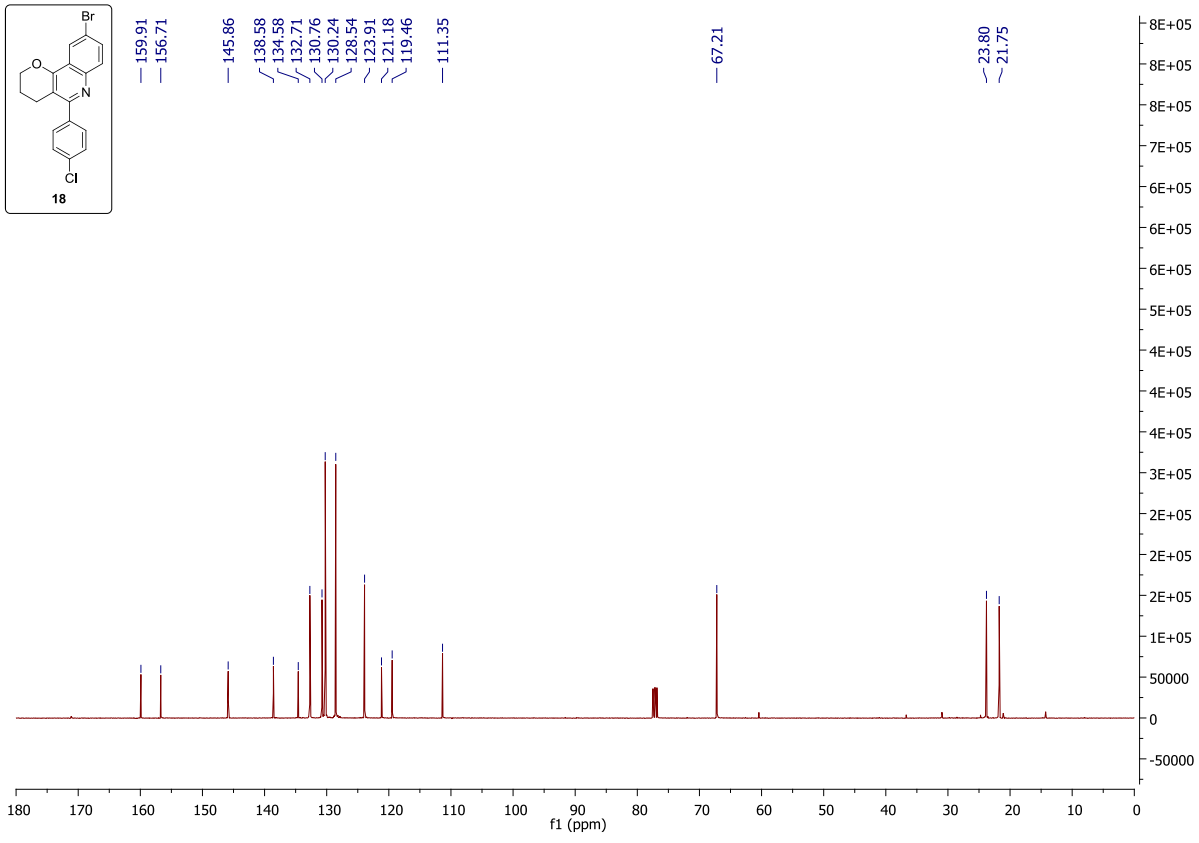


22b
$C_{24}H_{25}F_3N_2O_2$
MW: 430,46

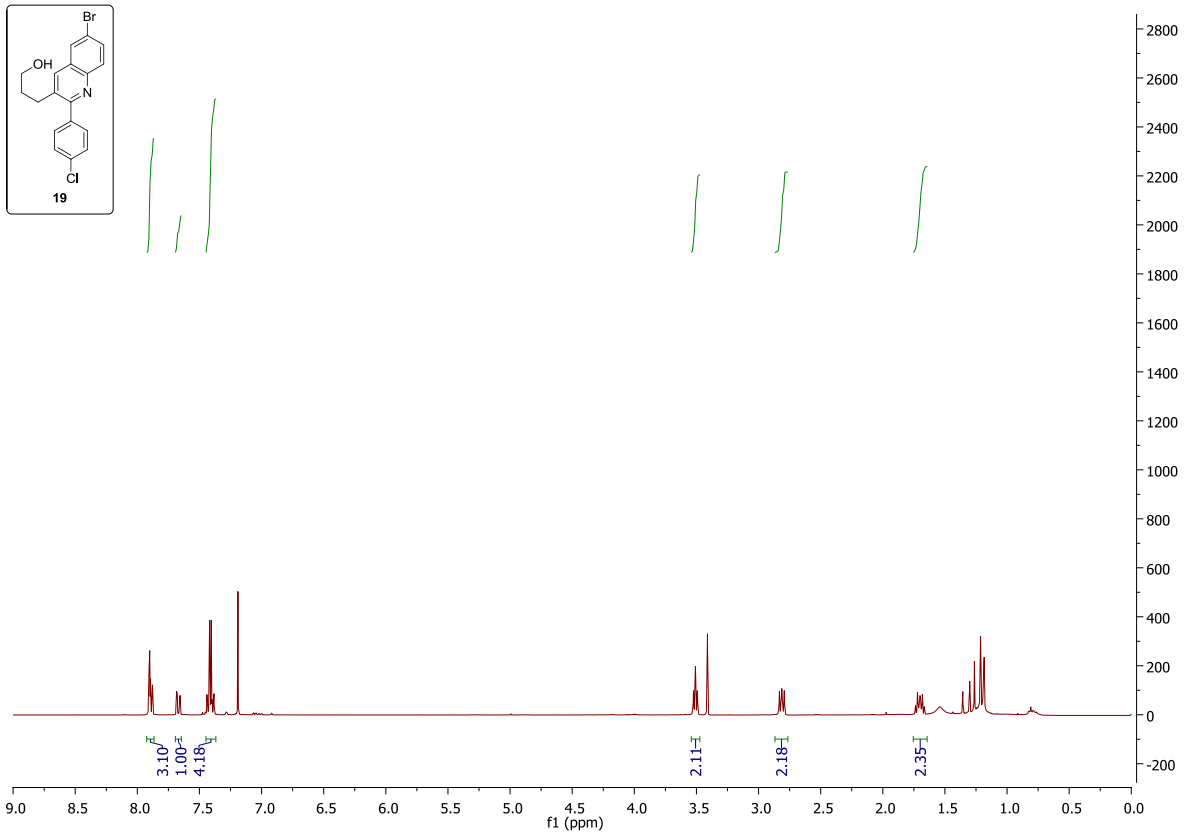
Following the general procedure B, the treatment of **20b**,**20b'** afforded compound **22b** as a white solid (49%). The spectroscopic data for this compound perfectly matches the published data [12].

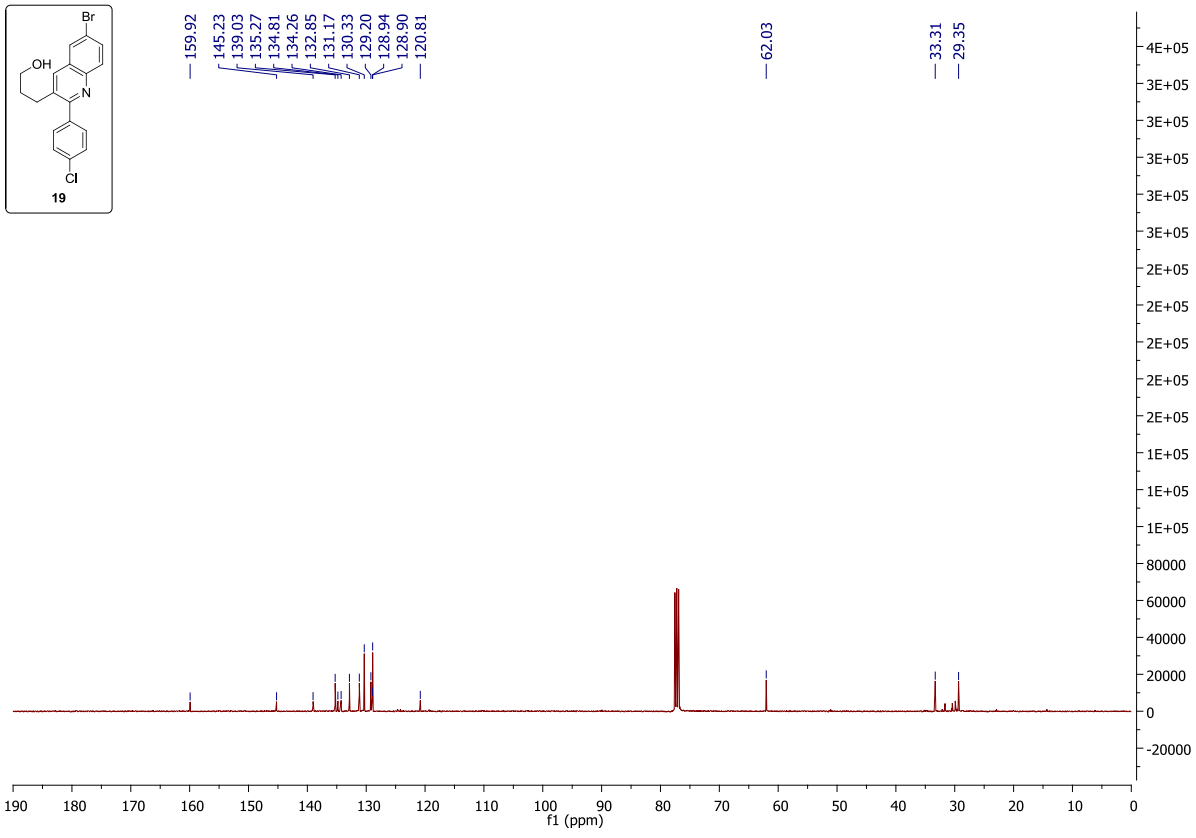
9-Bromo-5-(4-chlorophenyl)-3,4-dihydro-2H-pyrano[3,2-c]quinoline (18)



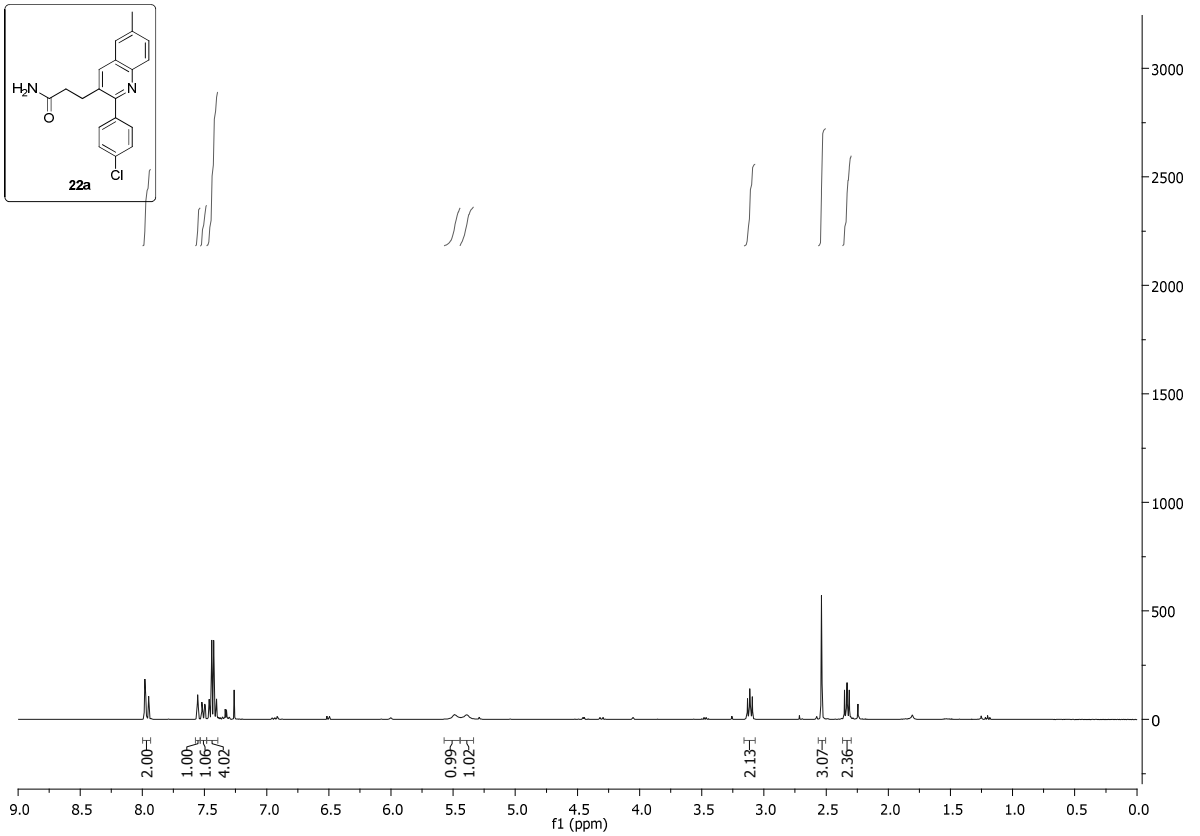


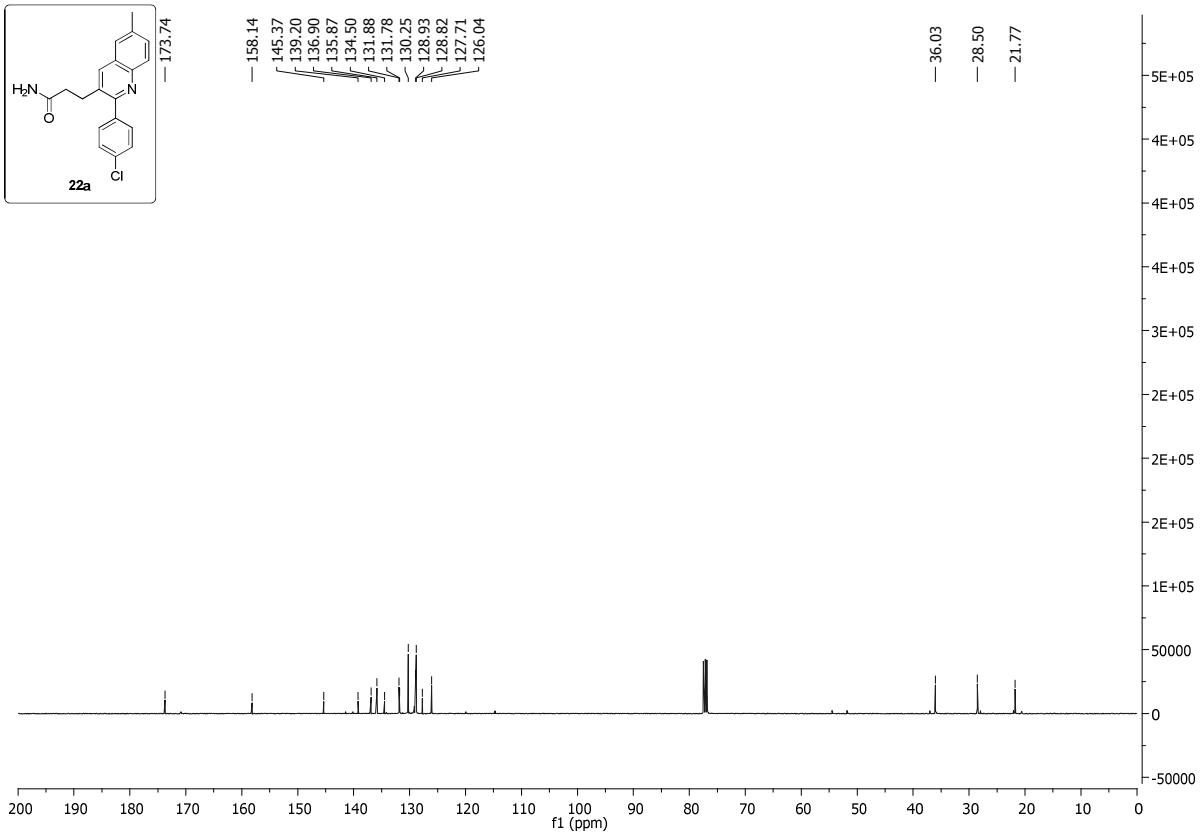
3-(6-Bromo-2-(4-chlorophenyl)quinolin-3-yl)propan-1-ol (19)





3-[2-(4-Chlorophenyl)-6-methylquinolin-3-yl]propanamide (22a)





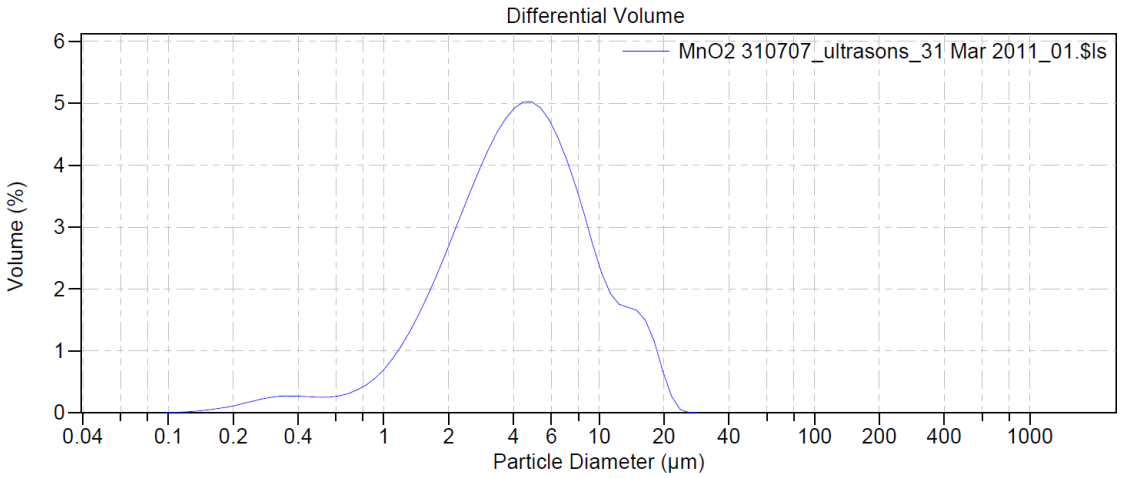
MnO_2 Particle size study:

All the manganese dioxide samples were analyzed with a LS™ 13 320 series Laser diffraction particle size analyzer to determine the particle size.

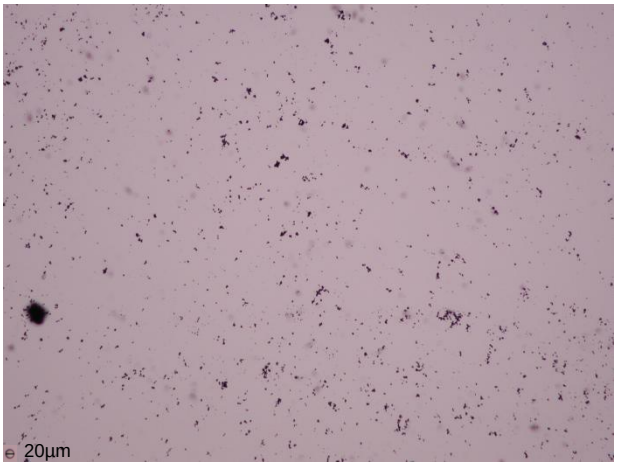
Reagent code	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)	<75%	<95%	<10 µm (%)
310700	1.475	4.302	11.16	7.022	14.53	87.5
243442	77.66	138.4	173.2	156.8	183.2	1.57
217646	0.577	4.240	16.04	9.583	19.69	75.3
213490010	1.509	7.555	37.30	18.16	51.39	57.3
138-09675	2.743	25.70	63.10	44.77	73.05	21.6
Old Sample	0.932	11.46	47.78	24.40	66.57	47.7

d_{xx} (µm) indicates the size of particle below which XX% of the sample lies (50% - median diameter)

Aldrich (310700):

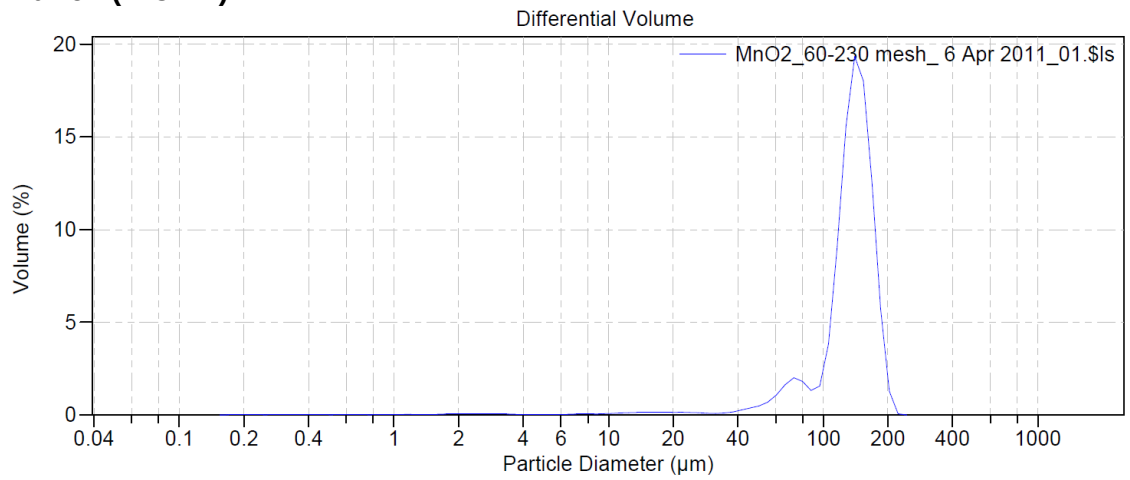


d_{10}: 1.475 µm d_{50}: 4.302 µm d_{90}: 11.16 µm
<75% 7.022 µm <95% 14.53 µm
<10 µm 87.5%

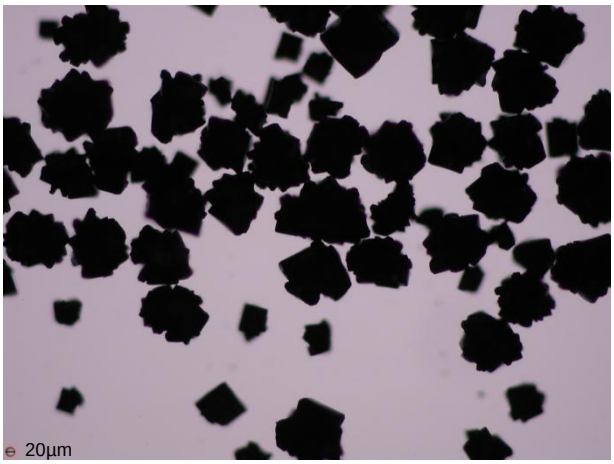


10x

Aldrich (243442):



d_{10}: 77.66 µm d_{50}: 138.4 µm d_{90}: 173.2 µm
<75% 156.8 µm <95% 183.2 µm
<10 µm 1.57%



10x

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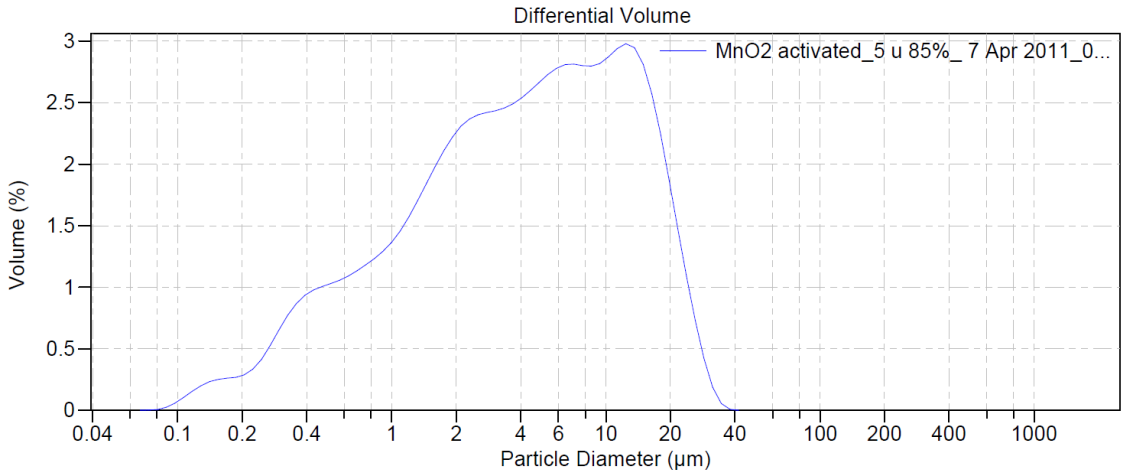
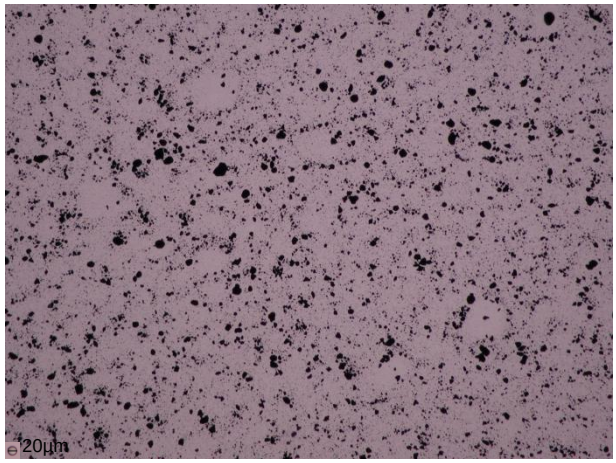


d_{10}: 0.577 µm d_{50}: 4.240 µm d_{90}: 16.04 µm
<75% 9.883 µm <95% 19.69 µm
<10 µm 75.3%



10x

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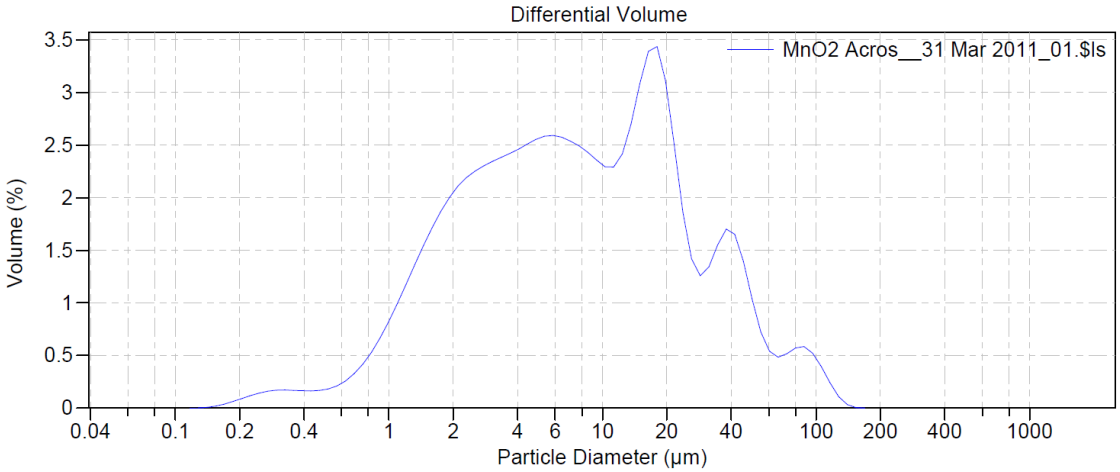
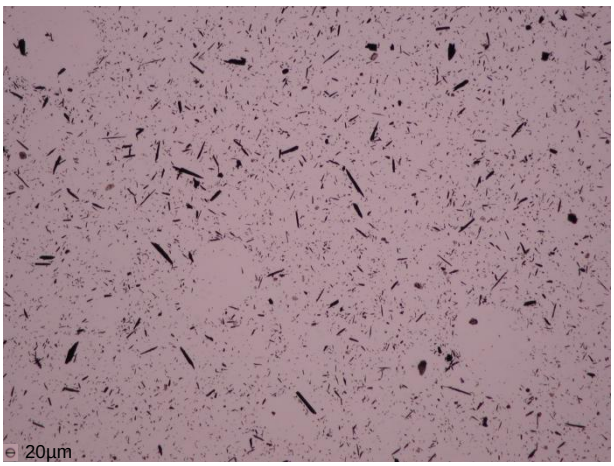


d_{10}: 1.509 µm d_{50}: 7.555 µm d_{90}: 37.30 µm
<75% 18.16 µm <95% 51.39 µm
<10 µm 57.3%



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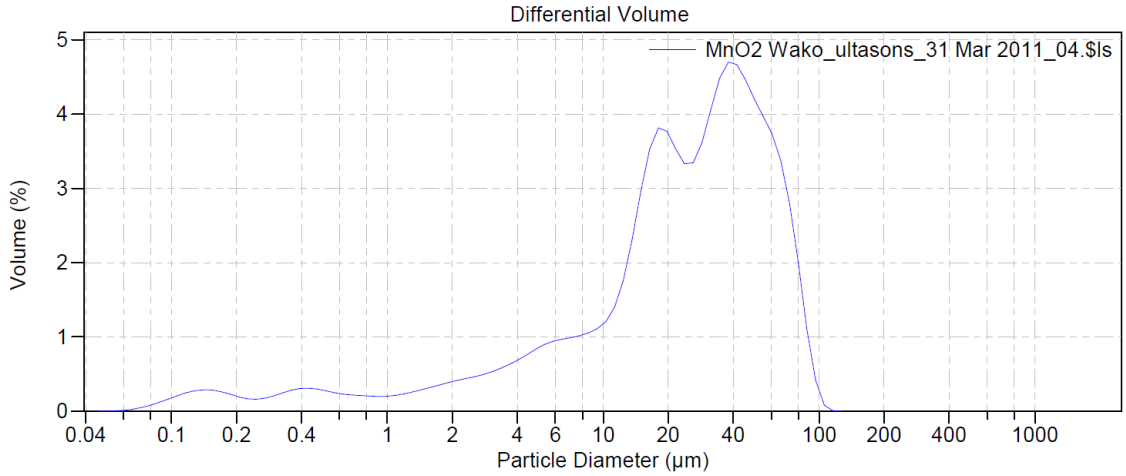
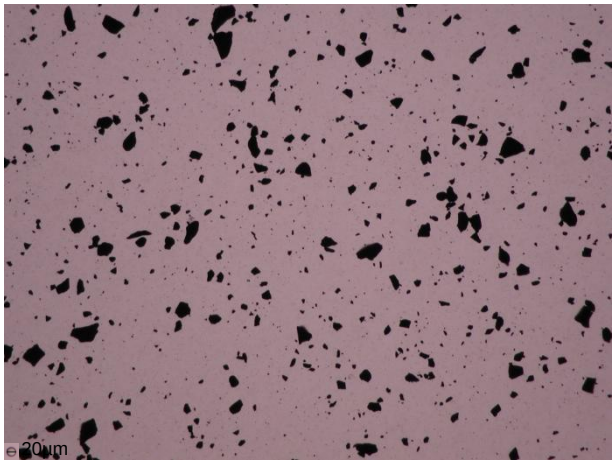


d_{10}: 2.743 µm d_{50}: 25.70 µm d_{90}: 63.10 µm
<75% 44.77 µm <95% 73.05 µm
<10 µm 21.6%



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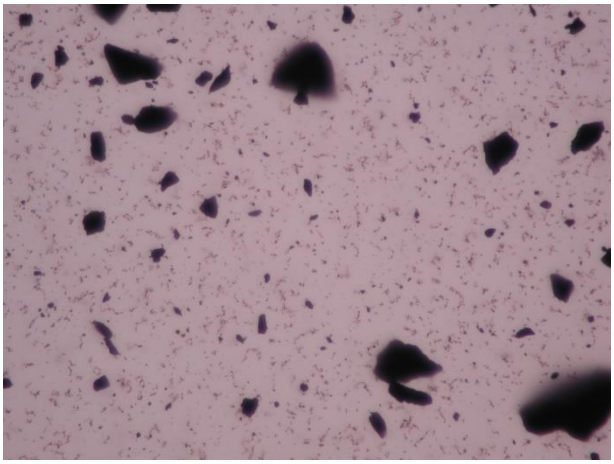
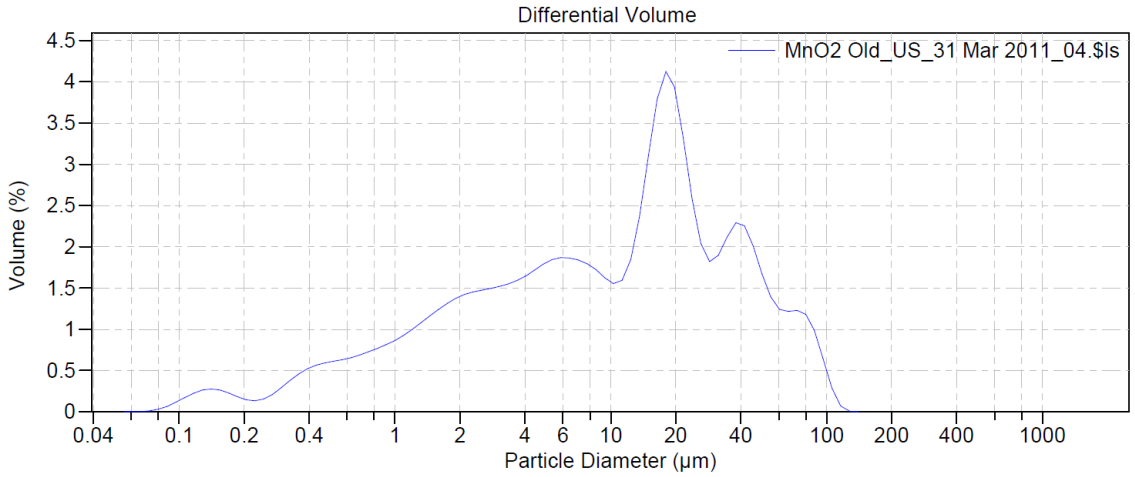
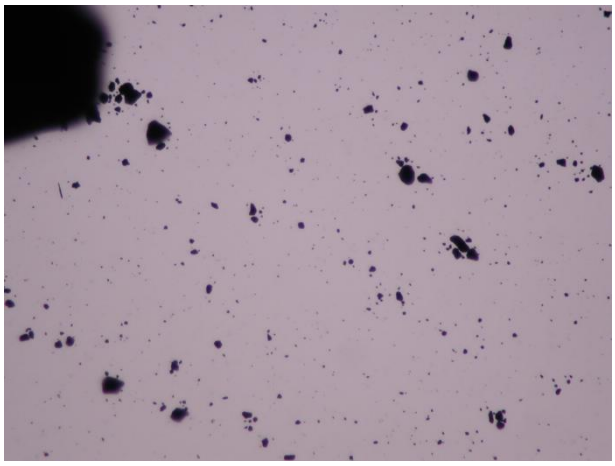


40x

MnO_2 Old Sample:



d_{10}: 0.932 µm d_{50}: 11.46 µm d_{90}: 47.78 µm
<75% 24.40 µm <95% 66.57 µm
<10 µm 47.7%



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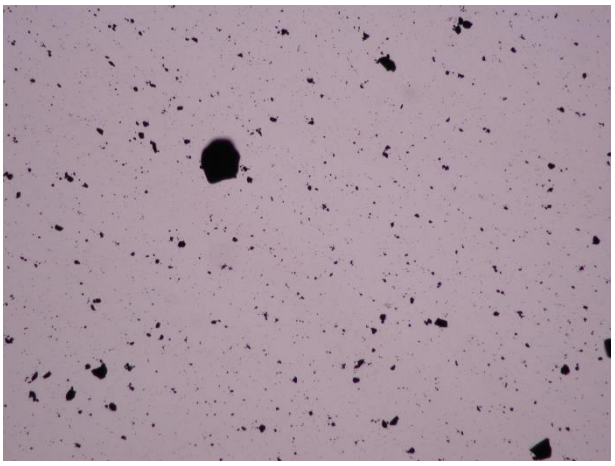


40x

5. Estudio de la reactividad de diferentes olefinas en la RMC de tipo Mannich-Ritter y sus consecuencias mecanísticas

Multicomponent Reactions

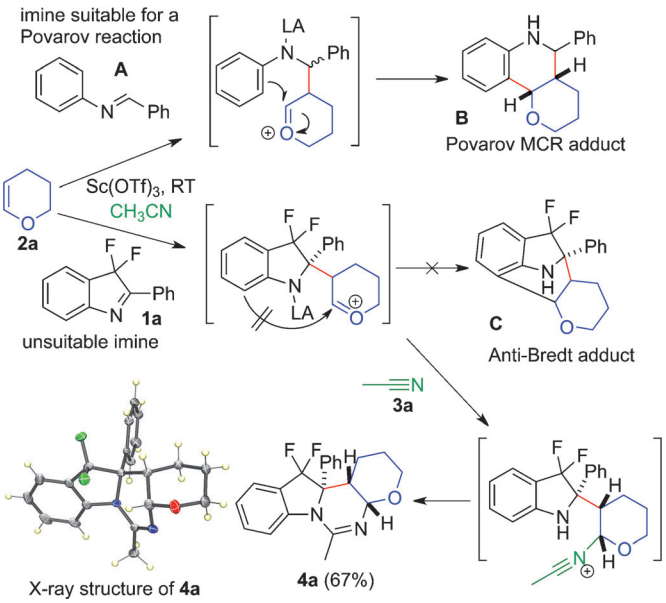
DOI: 10.1002/anie.201202927

Exploration of Forbidden Povarov Processes as a Source of Unexpected Reactivity: A Multicomponent Mannich–Ritter Transformation**

*Sara Preciado, Esther Vicente-García, Salomé Llabrés, F. Javier Luque, and Rodolfo Lavilla**

The ideal synthesis constitutes the ultimate challenge in organic transformations.[1] In this context, multicomponent reactions (MCRs) have enormous conceptual and practical advantages,[2] especially for the exploitation of molecular diversity based on heterocycles,[3] as these substructures are widely present in natural products, bioactive compounds, and drugs. This is exemplified by the Povarov reaction,[4] which provides highly convenient access to the ubiquitous tetrahydroquinoline scaffold. This transformation features the interaction of an aniline, a carbonyl compound, and an electron-rich olefin (under acid catalysis) to generate the MCR adduct **B** through the intermediacy of an imine **A** (Scheme 1).[5,6] In this process, the olefin should be amenable to bond formation with the imine carbon and one unsubstituted *ortho* position of the aniline ring (Scheme 1). We report here the results of exploratory chemistry we carried out on systems in which this pathway is geometrically or electronically infeasible.[7]

The cyclic imine **1a**[8] was reacted with 2*H*-dihydropyran (**2a**) under standard conditions with $Sc(OTf)_3$ catalysis[9] in acetonitrile (**3a**) at room temperature. The Povarov product (**C**, Scheme 1) was not formed as it would feature a highly strained anti-Bredt moiety.[10] Instead, the Mannich process was followed by a sequential Ritter step and completed by amidine formation through trapping of the nitrilium ion by the aniline nitrogen,[11] yielding the three-component-reaction adduct **4a** (67%) in a stereoselective manner (Scheme 1). The structure of **4a** was unequivocally determined by X-ray structure analysis.[12] The stereochemical features of this product reflect the expected patterns of interaction between



Scheme 1. Suitable and unsuitable imines for Povarov MCRs. L.A. = Lewis acid.

the two π systems to generate a C–C bond,[4–6] followed by the nitrile addition to the cyclic oxocarbenium ion to yield a *cis*-fused pyran ring.[13] This finding sparked a series of experiments to determine the usefulness of the new reaction. Its scope was investigated by systematically scanning all the components.

α-Substituted difluorinated indolenines **1b–d** afforded the corresponding adducts **4b–d** (Table 1, entries 1–4). The carbonyl analogue **1e** was also productive (Table 1, entry 5), whereas the dimethylindolenine **1f** (entry 6) failed to react, probably because of steric hindrance or lack of activation. Interestingly, the N- and O-heterocyclic derivatives **1g** and **1h** (Table 1, entries 7 and 8) yielded **4g** and **4h**, respectively, the latter being isolated after MeOH quenching. However, the phenyl-substituted derivative **1i** gave only traces of the MCR adduct. In these reactions, *N*-alkylimines were almost unreactive.[14] Analogous restrictions were found for *o*,*o*′-disubstituted aromatic imines such as **1j** (Table 1, entry 9). The latter substrates did not undergo the Mannich–Ritter process, except in trace amounts, reflecting the practical limits of the reaction. In contrast, the highly electrophilic *m*-dinitroaniline derivative afforded the *trans* tetrahydropyran **4k** (16% unoptimized yield; Table 1, entry 10), presumably after spontaneous epimerization. This is a remarkable example of

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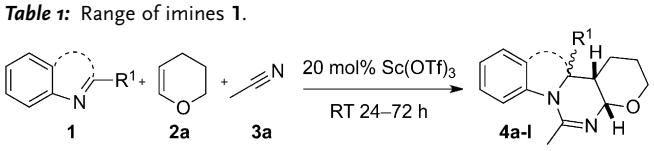
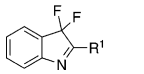
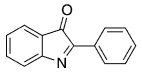
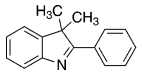
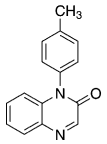
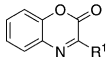
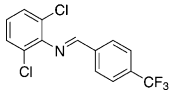
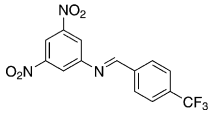
Table 1: Range of imines **1**.



Entry[a]	Imine	1	Yield [%][b]	Prod.
1		**1a**, R^1 = Ph	67[c]	**4a**
2		**1b**, R^1 = 4-OMe-C_6H_4	32[c]	**4b**
3		**1c**, R^1 = 3,4-$(MeO)_2$-C_6H_3	25[c]	**4c**
4		**1d**, R^1 = CO_2Et	44	**4d**
5		**1e**	60	**4e**
6		**1f**	–	–
7		**1g**	63	**4g**
8		**1h**, R^1 = H	26[d]	**4h**
		1i, R^1 = Ph	traces[e]	**4i**
9		**1j**	traces[e]	**4j**
10		**1k**	16	**4k**

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (excess), $Sc(OTf)_3$ (0.20 mmol), RT, 24–72 h, Ar. [b] Yields of isolated products. Isomer ratio > 96:4. [c] Traces of the carbonyl analogue of the final adduct were detected, which formed by hydrolysis of the starting difluorinated imine. [d] After MeOH quenching. [e] Stereochemistry not assigned.

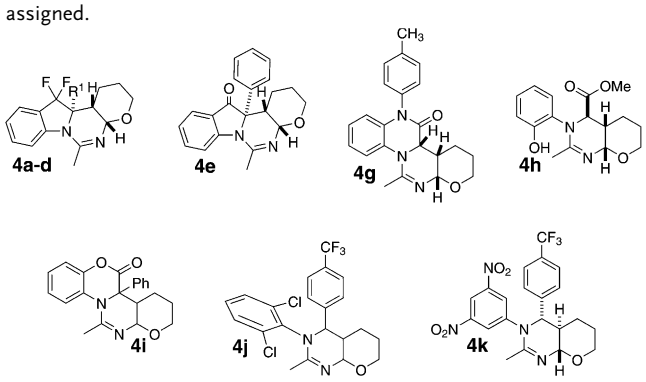
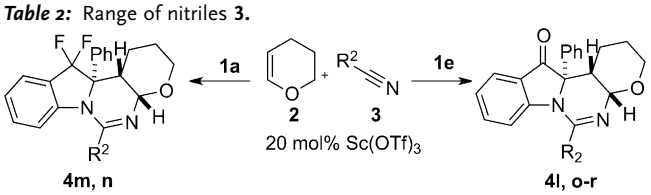
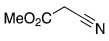


Table 2: Range of nitriles **3**.



Entry[a]	Imine	Nitrile	3	Yield[%][b]	4
1	**1e**		**3b**	69	**4l**, R^2 = Pr
2	**1a**		**3c**	59	**4m**, R^2 = *i*Pr
3	**1a**		**3d**	–	–
4	**1a**		**3e**	40	**4n**, R^2 = Bn
5	**1e**		**3f**	41	**4o**, R^2 = (*E*)-1-propenyl
6	**1e**		**3g**	53	**4p**, R^2 = vinyl
7	**1e**		**3h**	44	**4q**, R^2 = Ph
8	**1e**		**3i**	49[c]	**4r**, R^2 = 2-hydroxy-2-methoxyvinyl

[a] See footnote [a] in Table 1. [b] Yields of isolated products. [c] A stoichiometric amount of **3i** was used and **3d** served as the solvent.

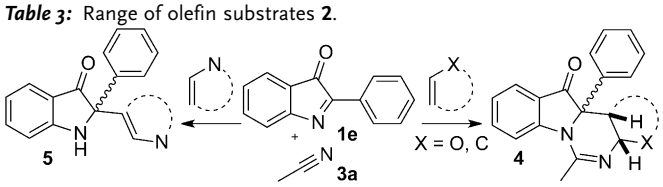
the new MCR, which may formally give rise to standard Povarov adducts, owing to the free *ortho* positions on the aniline precursor.

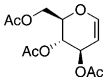
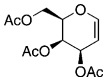
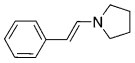
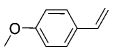
The range of nitriles was studied next using imines **1a** and **1e** as probes, and enol ether **2a** as the olefin component (Table 2). In addition to acetonitrile **3a** (Table 1, entry 1), linear, branched alkyl, benzyl, and allyl cyanides worked very well (Table 2, entries 1, 2, 4, and 5), although the latter adduct presumably isomerized afterwards under acid catalysis to the conjugated amidine **4o**. On the other hand, *tert*-butylcyanide (**3d**) was completely unreactive (Table 2, entry 3). Acrylo- and benzonitrile were suitable substrates for these transformations (Table 2, entries 6 and 7). A functionalized nitrile such as methyl cyanoacetate (**3i**) afforded the corresponding MCR product (**4r**; Table 2, entry 8) isolated as the enol tautomer. The main restriction in this process is the requirement of a large excess of nitrile **3**.[11,15] However, when the "inert" *tert*-butylcyanide served as the solvent it was possible to use only one equivalent of the desired nitrile to achieve comparable yields (Table 2, entry 8). This is particularly interesting, since the most useful catalyst, $Sc(OTf)_3$, performs best in nitrile solvents.[16,17]

Once the range of imines and nitriles was defined, attention was focused on the activated olefin component. Distinct types of enol ethers (Table 3, entries 1–4) afforded the MCR adducts under modified reaction conditions. Thus, 2,3-dihydrofuran (**2b**) and glucal **2c** reacted at higher temperatures, whereas galactal **2d** required microwave irradiation. The reaction with vinyl acetate (**2e**) yielded the hydrolyzed MCR product (**4v**) after chromatographic purification. In the case of N-activated olefins (Table 3, entries 5–8), the main product arose from a Mannich interaction, in sharp contrast with the outcome observed in standard Povarov reactions.[18] In this way, the unsaturated lactam **2f** afforded adduct **5a**. Analogously, enamide **2g** and thiazolone **2h** (Table 3, entries 6 and 7) yielded **5b** and **5c**, respectively, whereas enamine **2i** gave, after the addition process, the hydrolyzed aldehyde **5d** (entry 8). Conjugated olefins such as styrene **2j** (Table 3, entry 9) yielded the expected adduct as a 4:5 mixture of stereoisomers.

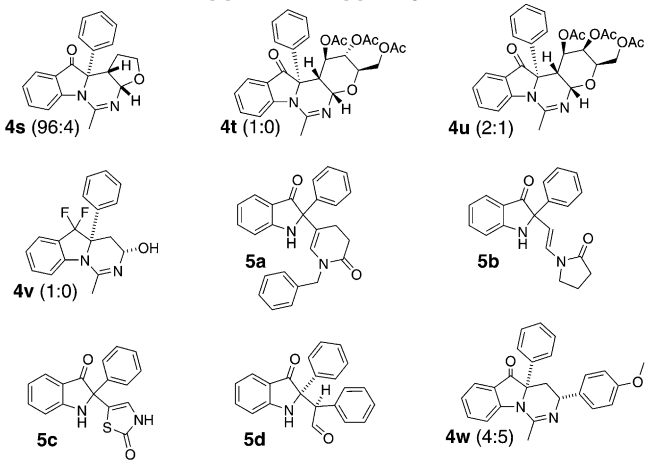
Finally, under standard conditions the sterically hindered imine **1l** afforded the 4-quinolone adduct **6** together with fluoropyridine **7** (Scheme 2). The former compound was

Table 3: Range of olefin substrates **2**.



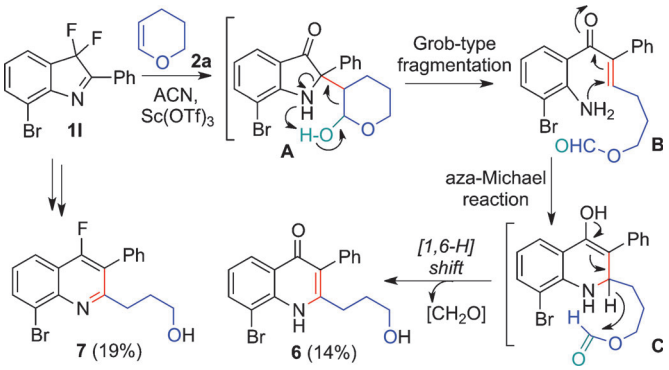
Entry[a]	Olefin substr.	2	Yield [%][b]	Product
1		**2b**	38	**4s**
2		**2c**	17	**4t**[c]
3		**2d**	47	**4u**[d]
4		**2e**	49	**4v**[e]
5		**2f**	64	**5a**
6		**2g**	21	**5b**
7		**2h**	59	**5c**
8		**2i**	49	**5d**
9		**2j**	25	**4w**

[a] See footnote [a] in Table 1. [b] Yields of isolated products. [c] 10 min, 80 °C, MW irradiation. [d] 60 °C, 12 h. [e] Using **1a** as the imine.



unequivocally identified by X-ray structure analysis.[12] The quinolone derivative[19] may arise from a complex sequence involving a Grob-type fragmentation,[20] an aza-Michael process, and a 1,6-hydride shift[21] with concomitant elimination of a formaldehyde equivalent. The fluoropyridine **7** was produced in an analogous manner. This represents a very unusual outcome in a Mannich process involving a cyclic enol ether, where its α-carbon is lost, leading to a substituted quinolone.

Since the nature of the olefin plays a major role in determining the outcome of Povarov MCRs, quantum mechanical computations (MP2/aug-cc-pVDZ; see the Supporting Information) were carried out to examine the energetics for the addition of acetonitrile to the carbenium



Scheme 2. New pathways for hindered imine **1l**.

intermediate generated upon C–C bond formation with indolenine **1e**. Calculations were performed for two olefins that behave in different ways: dihydropyran (**2a**) (which yielded 60% MCR adduct) and cyclic enamide **2f** (0%). Owing to the large size of the intermediate, computations were performed using a mimic where the bound cyclic imine was replaced by a methyl group. The energy profiles indicate that the attack of acetonitrile *cis* to the methyl group is the preferred route, as expected from the greater stability of the chairlike transition state (TS) compared to the boatlike TS formed by *trans* addition (Figure 1).[13] The absence of the MCR adduct for enamide **2f** is explained by the higher

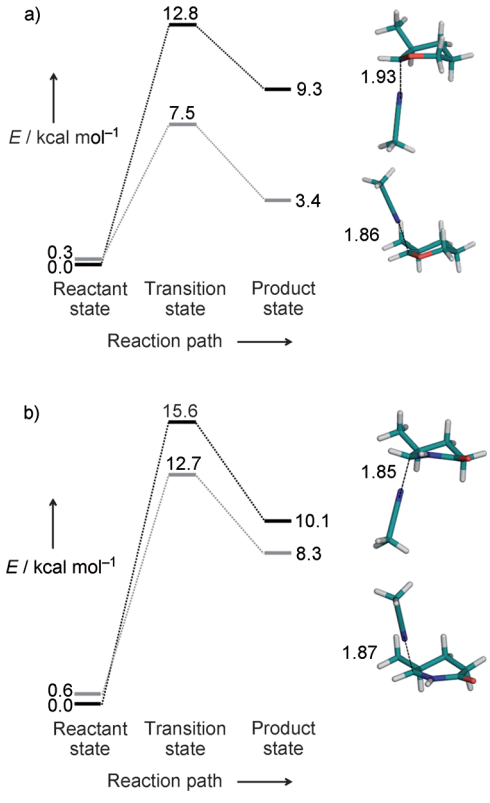


Figure 1. Energy profile (kcal mol^{-1}) for the *cis* (gray) and *trans* (black) addition of acetonitrile to the carbenium intermediate formed from dihydropyran **2a** (a) and cyclic enamide **2f** (b), and representation of the chair- and boatlike transition states formed in the *cis* and *trans* additions (the length of the forming bond is given in Å).

barrier of the *cis* addition (12.7 kcal mol^{-1}) compared to that for **2a** (7.5 kcal mol^{-1}), which can be attributed to the greater conformational strain introduced by the planarity of the amide group in the chairlike TS (Figure S1 in the Supporting Information).

In conclusion, the use of restricted imines in Povarov-type processes has led to the discovery of a new MCR providing cyclic amidines. This finding is complemented by the description of alternative pathways for the formation of these complex systems, including the production of Mannich and interrupted Povarov adducts. The new reaction involves three different inputs, three bonds are formed in a stereoselective manner, and complex and diverse products are produced in competitive yields. The different synthetic outcomes mainly reflect the balance of the reactivity and torsional strain of the olefins. Overall, the results indicate that the systematic exploration of uncharted reactivity space related to formally forbidden processes can be useful in the search for new MCRs, since a blocked step may enable unexpected bond-formation events within the same reactant mixture.[22]

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Supporting Information

69451 Weinheim, Germany

Exploration of Forbidden Povarov Processes as a Source of Unexpected Reactivity: A Multicomponent Mannich–Ritter Transformation**

*Sara Preciado, Esther Vicente-García, Salomé Llabrés, F. Javier Luque, and Rodolfo Lavilla**

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Supporting Information

General experimental information.

Unless stated otherwise, all reactions were carried out under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was performed on pre-coated Merk silica gel 60 F254 plates and visualized under a UV lamp. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (at 400 MHz, 376 MHz and 100 MHz respectively). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{19}F-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{13}C-NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^{1}H-^{1}H-COSY, ^{1}H-^{13}C- COSY (HSQC: Heteronuclear Single Quantum Coherence) and long-range ^{1}H-^{13}C-COSY (HMBC: Heteronuclear Multiple Bond Connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in frequency of absortion (cm^{-1}). High Resolution Mass Spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

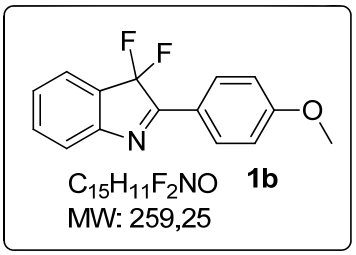
Procedures and characterization data

Synthesis of starting materials

The imines **1a**[1], **1e**[2] and **1i**[3] and the activated olefins **2f**[4], **2g**[5], **2i**[6] and **2j**[7] were prepared according to a reported protocol.

General procedure A. Synthesis of difluorinated imines 1a-1d and 1g

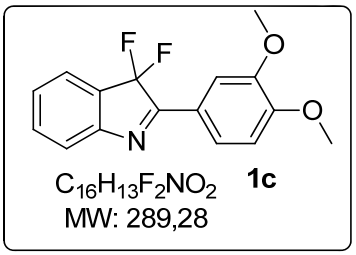
To a solution of indole (1 mmol) in anhydrous ACN (20 mL) and $Na_2CO_{3\ (s)}$ (1 g), was added at 0 ºC the fluorinating reagent Selectfluor® (2.2 mmol). The mixture was stirred at room temperature. When the reaction was complete, Et_2O (30 mL) was added and the mixture washed with H_2O (3 x 15 mL), sat. aq. $NaHCO_3$ (3 x 15 mL) and brine (3 x 15 mL). The organic extracts were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to give the desired product.



$C_{15}H_{11}F_2NO$ **1b**
MW: 259,25

3,3-difluoro-2-(4-methoxyphenyl)-3*H*-indole (1b)

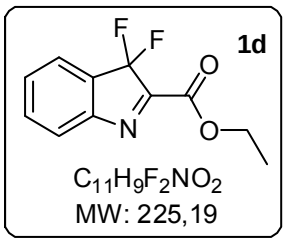
Following the general procedure A (10 minutes), the reaction of 2-(4-methoxyphenyl)-1*H*-indole[8] afforded compound **1b** as a yellow solid (73% yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.16 (d, *J* = 8.7 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 4.1 Hz, 1H), 7.33 – 7.24 (m, 1H), 7.08 – 7.01 (m, 1H), 3.90 (s, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -115.54 (s) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 168.87 (t, *J* = 24.7 Hz), 163.40 (s), 153.20 (t, *J* = 9.8 Hz), 133.47 (s), 130.81 (s), 128.99 (t, *J* = 24.1 Hz), 127.10 (s, *J* = 27.7 Hz), 123.42 (t, *J* = 256.2 Hz), 123.20 (s), 121.85 (t, *J* = 2.8 Hz), 121.68 (s), 114.66 (s), 55.70 (s) ppm. **HRMS** (ESI): calcd for ($M+H^+$) $C_{15}H_{12}F_2NO$: 260.0809; found, 260.0882.



$C_{16}H_{13}F_2NO_2$ **1c**
MW: 289,28

2-(3,4-dimethoxyphenyl)-3,3-difluoro-3H-indole (1c)

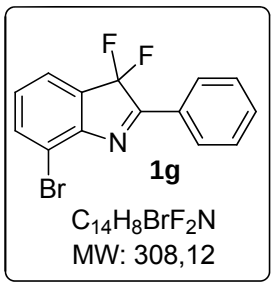
Following the general procedure A (10 minutes), the reaction of 2-(3,4-dimethoxyphenyl)-1*H*-indole[8] afforded compound **1c** as a yellow solid (43% yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.30 – 7.26 (m, 1H), 7.25 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -114.72 ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 168.9 (t, *J* = 24.6 Hz), 153.3, 153.0 (t, *J* = 9.9 Hz), 149.7, 133.5, 129.1 (t, *J* = 24.1 Hz), 127.2, 123.6 (t, *J* = 2.6 Hz), 123.3 (t, *J* = 256.2 Hz), 123.2, 122.1 (t, *J* = 2.8 Hz), 121.7, 110.9, 110.3, 56.3, 56.3 ppm. **HRMS** (ESI): calcd for ($M+H^+$) $C_{16}H_{14}F_2NO_2$: 290.0914; found, 290.0990.



$C_{11}H_9F_2NO_2$
MW: 225,19

Ethyl 3,3-difluoro-3*H*-indole-2-carboxylate (1d)

Following the general procedure A (4 h), the reaction of 2-ethoxycarbonylindole afforded compound **1d** as an orange solid (47% yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): 7.43 (d, *J* = 7.7 Hz, 1H), 7.39 – 7.33 (m, 1H), 6.94 (dd, *J* = 12.7, 5.2 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 4.40 – 4.33 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -125.28 (s) ppm. **IR** (film) ν_{max}: 3372, 2994, 2911, 2841, 1739, 1630, 1470, 1265, 1092, 1066, 1028, 932, 752 cm^{-1}. **HRMS** (ESI): calcd for ($M+H^+$) $C_{11}H_{10}F_2NO_2$: 226.0601; found, 226.0680.



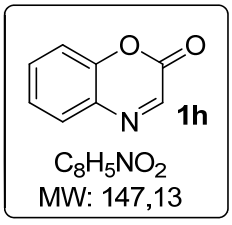
1g

$C_{14}H_8BrF_2N$

MW: 308,12

7-bromo-3,3-difluoro-2-phenyl-3H-indole (1l)

Following the general procedure A (24 h), the reaction of 7-bromo-2-phenyl-1*H*-indole[9] afforded compound **1l** as a yellow solid (66% yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.25 (d, *J* = 7.4 Hz, 2H), 7.66 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.55 – 7.49 (m, 3H), 7.20 – 7.15 (m, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -115.25 (s) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 169.8 (t, *J* = 24.4 Hz), 150.9 (t, *J* = 9.4 Hz), 136.8 (t, *J* = 1.2 Hz), 132.9 (s), 130.8 (t, *J* = 24.8 Hz), 128.9 (t, *J* = 1.5 Hz), 128.9 (s), 128.7 (t, *J* = 1.5 Hz), 128.5 (t, *J* = 2.8 Hz), 123.4 (t, *J* = 258.0 Hz), 122.3 – 120.8 (m, *J* = 109.7 Hz), 116.3 (s), 109.9 (s) ppm. **IR** (film) ν_{max}: 3417, 3052, 2911, 2853, 1547, 1451, 1425, 1354, 1265, 1207, 1073, 906, 752, 695, 663 cm^{-1}. **HRMS** (ESI): calcd for ($M+H^+$) $C_{14}H_9BrF_2N$: 307.9808; found, 307.9872.



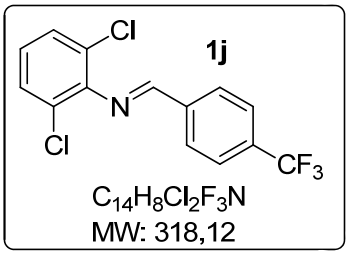
1h

$C_8H_5NO_2$

MW: 147,13

2*H*-benzo[*b*][1,4]oxazin-2-one (1h)

To a solution of *o*-aminophenol (200 mg, 1.79 mmol) in dry pyridine was added ethylglyoxalate (427 µL). The mixture was stirred al 120 ºC for 24 h. When the reaction was complete, the crude was evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to give 138 mg of compound **1h** as a pale solid (53% yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H) ppm.



1j

$C_{14}H_8Cl_2F_3N$

MW: 318,12

(**E)-2,6-dichloro-*N*-(4-(trifluoromethyl)benzylidene) aniline (1j)**

To a solution of 2,6-dichloroaniline (200 mg, 1.21 mmol). in anhydrous MeOH (4 mL) was added 4-(trifluoromethyl)benzaldehyde (330 µL, 2.42 mmol). The mixture was stirred at 80 ºC for 72 h. Then, the crude was dried over Na_2SO_4, filtered and evaporated under reduced pressure, obtaining 308 mg of compound **1j** as a pale oil (80 % yield). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.43 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.32 (m, 2H), 7.03 (t, *J* = 8.1 Hz, 1H) ppm.

General procedure B. Synthesis of compounds 4a-4x

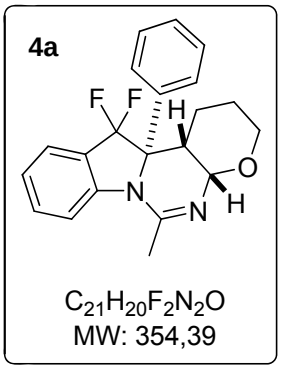
$Sc(OTf)_3$ (0.2 mmol) was added to a solution of imine **1** (1 mmol) and olefin **2** (1 mmol) in the corresponding nitrile **3** (5 mL), and the mixture was stirred under argon atmosphere. The different reaction conditions are listed below as separate methods. When the reaction was complete sat. aq. $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers

were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane–EtOAc) to give the desired products.

Method A: The reaction mixture was stirred at room temperature and the progress of the reaction was controlled by TLC or HPLC until the starting material completely disappeared or no further evolution was observed (if needed, an additional 5% catalyst was added every 24 h).

Method B: The reaction mixture was stirred at 60 °C and the progress of the reaction was controlled by TLC or HPLC until the starting material completely disappeared or no further evolution was observed (if needed, an additional 5% catalyst was added every 24 h).

Method C: $Sc(OTf)_3$ (0.2 mmol) was added to a solution of imine **1** (1 mmol) and olefin **2** (1 mmol) in the corresponding nitrile **3** (1–1.5 mL). The reaction vessel was introduced in a microwave apparatus (Discover CEM), and the reaction irradiated at the nitrile boiling point temperature and 100 W with Power Max option selected. Cycles of 10 min were carried out until the starting materials completely disappeared or no further evolution was observed.

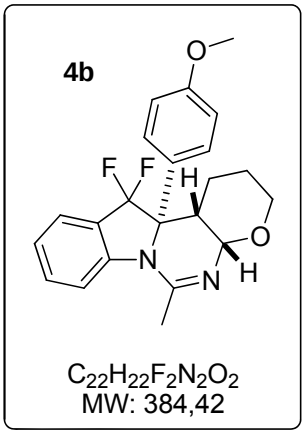


$C_{21}H_{20}F_2N_2O$
MW: 354,39

(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-6-methyl-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole (4a)

Following the general procedure B, method A (72 h), the reaction of **1a** and 3,4-dihydro-2*H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4a**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 6:4) to afford pure **4a** as a white solid (67% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.37 (m, 1H), 7.37 – 7.31 (m, 3H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.27 – 7.18 (m, 3H), 7.01 (t, *J* = 7.4 Hz, 1H), 5.41 (s, 1H), 3.90 (td, *J* = 11.7, 2.6 Hz, 1H), 3.66 – 3.60 (m, 1H), 3.06 (dt, *J* = 12.3, 4.3 Hz, 1H), 2.55 (d, *J* = 1.9 Hz, 3H), 1.67 – 1.54 (m, 1H), 1.41 (dd, *J* = 9.1, 4.4 Hz, 1H), 1.17 – 1.08 (m, 1H), 1.00 (ddd, *J* = 25.8, 12.6, 4.0 Hz, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -93.18 (d, *J* = 239.5 Hz), -125.37 (d, *J* = 239.4 Hz) ppm. **^{13}C-RMN**($CDCl_3$, 100 MHz): δ 152.6, 145.0 (dd, *J* = 7.3, 4.7 Hz), 136.1, 136.1, 132.7 (d, *J* = 2.8 Hz), 128.9 (d, *J* = 4.4 Hz), 128.5 – 123.1 (m), 127.9, 127.0 (dd, *J* = 27.4, 24.1 Hz), 124.1, 124.1 (d, *J* = 2.1 Hz), 115.9, 82.6 (d, *J* = 12.6 Hz), 74.5 (dd, *J* = 24.4, 20.1 Hz), 60.6, 38.3, 25.6 , 25.5, 22.7 ppm. **IR** (film) ν_{max}: 3404, 3058, 2924, 2873, 1643, 1617, 1476, 1444, 1271, 1111, 1066, 1034, 759, 701 cm^{-1}. **HRMS**: calcd for $C_{21}H_{20}F_2N_2O$ 355.1544 ($M+H^+$); found, 355.1625.

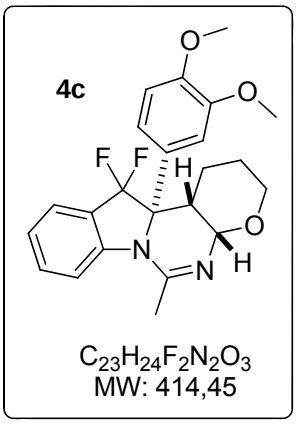


$C_{22}H_{22}F_2N_2O_2$
MW: 384,42

(4a*R*S,12a*R*S,12b*R*S)-12,12-difluoro-12a-(4-methoxyphenyl)-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole (4b)

Following the general procedure B, method A (48 h), the reaction of **1b** and 3,4-dihydro-2*H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4b**. The crude was purified by flash chromatography (SiO_2, DCM/MeOH 95:5) to afford pure **4b** as a pale solid (32% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.42 – 7.36 (m, 1H), 7.31 (dd, *J* = 7.1, 5.4 Hz, 2H), 7.26 (d, *J* = 3.0 Hz, 1H), 7.24 (d, *J* = 3.4 Hz, 1H), 7.06 – 6.98 (m, 1H), 6.81 – 6.73 (m, 2H), 5.40 (d, *J* = 19.2 Hz, 1H), 3.89 (td, *J* = 11.5, 2.7 Hz, 1H), 3.73 (s, 3H), 3.62 (dd, *J* = 16.5, 6.9 Hz, 1H), 3.01 (dt, *J* = 11.9, 4.3 Hz, 1H), 2.54 (d, *J* = 1.9 Hz, 3H), 1.67 – 1.51 (m, 1H), 1.45 – 1.37 (m, 1H), 1.21 – 1.12 (m, 1H), 1.05 (ddd, *J* = 25.5, 12.2, 4.0 Hz, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -93.35 (d, *J* = 239.4 Hz), -125.83 (d, *J* = 239.2 Hz) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 159.1, 152.8, 144.7 (dd, *J* = 7.3, 4.6 Hz), 132.5 (d, *J* = 2.8 Hz), 129.9 (d, *J* = 5.0 Hz), 128.3, 127.6 (d, *J* = 6.5 Hz), 127.0 (dd, *J* = 27.3, 24.1 Hz), 125.7 124.9, 124.0 (m), 123.2, 122.6, 82.4 (d, *J* = 12.1 Hz), 74.1 (dd, *J* = 24.4, 20.3 Hz), 60.9, 55.2, 38.0, 25.3, 22.6 ppm. **IR** (film) ν_{max}: 3366, 3058, 2937, 2866, 1707, 1649, 1617, 1515, 1469, 1386, 1278, 1258, 1187, 1117, 1079, 1031, 970, 868, 829, 804, 759, 733 cm^{-1}. **HRMS**: calcd for $C_{22}H_{22}F_2N_2O_4$ 385.1649 ($M+H^+$); found, 385.1719.

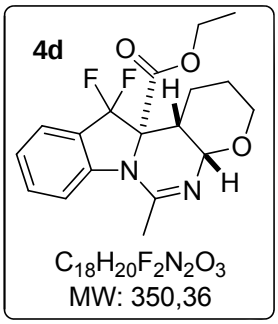


$C_{23}H_{24}F_2N_2O_3$
MW: 414,45

(4a*RS*,12a*R*S,12b*R*S)-12a-(3,4-dimethoxyphenyl)-12,12-difluoro-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole (4c)

Following the general procedure B, method A (48 h), the reaction of **1c** and 3,4-dihydro-2*H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4c**. The crude was purified by flash chromatography (SiO_2, DCM/MeOH 95:5) to afford pure **4c** as a pale solid (25% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.92 – 6.87 (m, 2H), 6.75 – 6.69 (m, 1H), 5.37 (s, 1H), 3.88 (td, *J* = 11.3, 2.8 Hz, 1H), 3.81 (d, *J* = 4.5 Hz, 6H), 3.66 – 3.60 (m, 1H), 3.01 (dt, *J* = 11.5, 4.4 Hz, 1H), 2.56 (d, *J* = 1.7 Hz, 3H), 1.56 (ddd, *J* = 15.8, 6.9, 4.3 Hz, 1H), 1.43 – 1.36 (m, 1H), 1.20 – 1.10 (m, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -93.07 (d, *J* = 234.0 Hz), -125.54 (d, *J* = 239.0 Hz) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 153.1, 148.8, 148.4, 132.6 (d, *J* = 2.7 Hz), 128.1, 128.1, 127.7 – 126.7 (m), 125.8, 124.4, 124.2, 121.2 (d, *J* = 4.1 Hz), 116.0, 112.8 (d, *J* = 7.4 Hz), 110.4, 82.5, 82.3, 75.1 – 74.2 (m), 61.1, 56.2, 55.9, 37.8, 25.2, 22.6 ppm. **IR** (film) ν_{max}: 3429, 2943, 2841, 1643, 1611, 1521, 1469, 1271, 1149, 1117, 1073, 1034, 880, 809, 759 cm^{-1}. **HRMS**: calcd for $C_{23}H_{25}F_2N_2O_3$ 415.1755 ($M+H^+$); found, 415.1819.

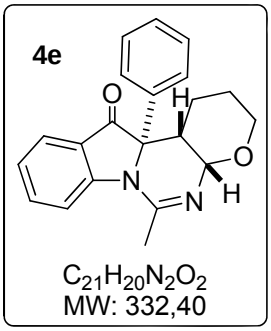


$C_{18}H_{20}F_2N_2O_3$
MW: 350,36

(4a*RS*,12a*RS*,12b*RS*)ethyl 12,12-difluoro-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido [1,6-*a*]indole-12a-carboxylate (4d)

Following the general procedure B, method A (48 h), the reaction of **1d** and 3,4-dihydro-*2H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4d**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 1:9) to afford pure **4d** as a white solid (44% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.55 – 7.44 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 4.96 (s, 1H), 4.32 – 4.23 (m, 2H), 3.71 – 3.62 (m, 2H), 3.04 (dt, *J* = 12.5, 4.5 Hz, 1H), 2.58 (d, *J* = 1.6 Hz, 3H), 1.89 (d, *J* = 13.1 Hz, 1H), 1.44 (d, *J* = 13.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.08 (td, *J* = 12.9, 4.7 Hz, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -80.32 (d, *J* = 262.9 Hz), -93.00 (d, *J* = 263.0 Hz) ppm. **^{13}C-RMN** ($CDCl_3$, 151 MHz): δ 166.9 (s), 151.5 (s), 133.7 (s), 133.7 (d, *J* = 99.6 Hz), 124.6 (s), 124.1 (d, *J* = 8.5 Hz), 122.5 (s), 121.1 (s), 112.9 (s), 112.5 (d, *J* = 60.2 Hz), 80.8 (s), 63.0 (s), 60.4 (s), 33.8 (s), 24.9 (s), 24.0 (s), 19.3 (s), 13.9 (s) ppm. **IR** (film) ν_{max}: 3359, 2969, 2917, 2853, 1745, 1719, 1617, 1483, 1438, 1374, 1297, 1258, 1092, 1028, 791 cm^{-1}. **HRMS**: calcd for $C_{18}H_{21}F_2N_2O_3$ 351.1442 ($M+H^+$); found, 351.1519.

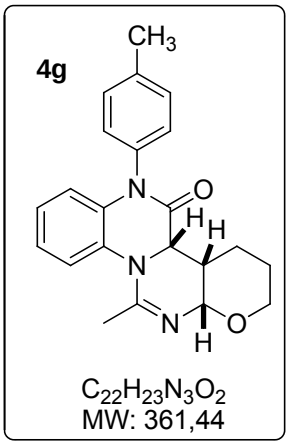


$C_{21}H_{20}N_2O_2$
MW: 332,40

(4a*RS*,12a*RS*,12b*RS*)-6-methyl-12a-phenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indol-12(4a*H*)-one (4e)

Following the general procedure B, method A (72 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4e**. The crude was purified by flash chromatography (SiO_2, DCM/MeOH, 95:5) to afford pure **4e** as a pale solid (60% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.66 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.57 (s, 1H), 7.52 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.27 (m, 3H), 7.07 (s, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 3.81 (d, *J* = 3.5 Hz, 1H), 3.55 (s, 1H), 2.79 – 2.74 (m, 1H), 2.72 (d, *J* = 1.5 Hz, 3H), 1.97 – 1.86 (m, 1H), 1.44 – 1.31 (m, 2H), 1.23 – 1.19 (m, 1H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 200.5, 153.9, 153.3, 136.9, 136.0, 128.4, 128.2, 127.1, 127.1, 125.6, 124.3, 123.4, 115.9, 82.9, 72.9, 63.3, 39.4, 25.8, 23.5, 21.2 ppm. **IR** (film) ν_{max}: 3347, 3058, 2962, 2917, 2873, 1719, 1643, 1611, 1476, 1386, 1316, 1258, 1111, 1034, 970, 906, 765, 727, 695 cm^{-1}. **HRMS**: calcd for $C_{21}H_{21}N_2O_3$ 333.1525 ($M+H^+$); found, 333.1598.

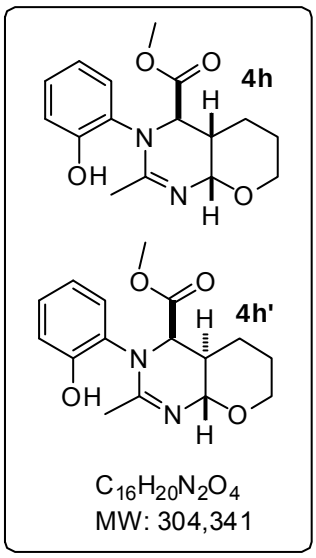


$C_{22}H_{23}N_3O_2$
MW: 361,44

(4a*RS*,4b*RS*,13a*RS*)-12-methyl-6-(*p*-tolyl)-2,3,4,4a,6,13a-hexahydropyrano[2',3':4,5]pyrimido[1,6-*a*]quinoxalin-5(4bH)-one (4g)

Following the general procedure B, method A (72 h), the reaction of **1g** and 3,4-dihydro-*2H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **4g**. The crude was purified by flash chromatography (SiO_2, DCM/MeOH 98:2) to afford pure **4g** as a pale solid (63% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36 – 7.29 (m, 3H), 7.14 – 7.07 (m, 4H), 6.63 – 6.57 (m, 1H), 5.03 (d, *J* = 3.1 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.87 (d, *J* = 4.1 Hz, 1H), 3.69 (dt, *J* = 10.9, 4.1 Hz, 1H), 2.88 (td, *J* = 8.6, 4.3 Hz, 1H), 2.42 (s, 3H), 2.28 (d, *J* = 0.7 Hz, 3H), 1.88 (m, 1H), 1.81 – 1.62 (m, 3H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 167.7, 153.5, 138.9, 135.5, 134.5, 130.8, 128.4, 126.8, 124.9, 123.6, 118.7, 79.3, 62.5, 59.4, 30.1, 24.1, 24.0, 22.4, 21.4 ppm. **IR** (film) ν_{max}: 3353, 2956, 2917, 2853, 1662, 1604, 1508, 1457, 1374, 1258, 1079, 1015, 868, 797 cm^{-1}. **HRMS**: calcd for $C_{22}H_{23}N_3O_2$ 362.1790 ($M+H^+$); found, 362.1861.

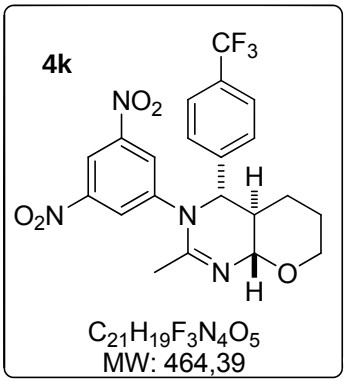


$C_{16}H_{20}N_2O_4$
MW: 304,341

(4*RS*,4a*RS*,8a*RS*)-methyl 3-(2-hydroxyphenyl)-2-methyl-4,4a,5,6,7,8a-hexahydro-3*H*-pyrano[2,3-*d*]pyrimidine-4-carboxylate (4h)

Following the general procedure B, method B (24 h), the reaction of **1h** and 3,4-dihydro-*2H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compounds **4h/4h'** after addition of MeOH (4 mL) and TFA (1 mL) and heating at 50 ºC for 24 h. The crude was purified by flash chromatography (SiO_2, DCM/MeOH 98:2) to afford a mixture of estereoisomers **4h**:**4h'** in a 1:0.7 ratio (26% overall yield), which could not be separated. The minor isomer is probably the trans fused compound (**4h'**).

^{1}H-NMR (**4*RS*,4a*RS*,8a*RS***, major stereoisomer): 7.25 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.83 (m, 1H), 5.15 (d, *J* = 4.2 Hz, 1H), 4.21 (d, *J* = 2.5 Hz, 1H), 3.77 (s, 3H), 3.75-3.70 (m, 2H), 2.50 (m, 1H), 2.20 (s, 3H), 1.90 (m, 2H), 1.67 (m, 2H) ppm. **IR** (film) ν_{max}: 3231, 3078, 2956, 2930, 2847, 1745, 1675, 1617, 1457, 1290, 1246, 1207, 1130, 1028, 759 cm^{-1}. **HRMS**: calcd for $C_{16}H_{21}N_2O_4$ 305.1423 ($M+H^+$); found, 305.1493.

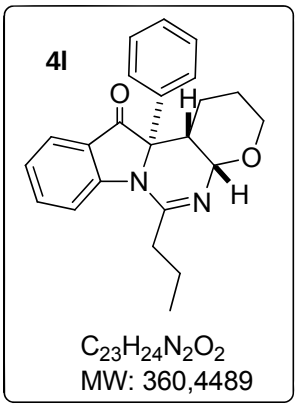


$C_{21}H_{19}F_3N_4O_5$
MW: 464,39

(4*RS*,4a*SR*,8a*RS*)-3-(3,5-dinitrophenyl)-2-methyl-4-(4-(trifluoromethyl)phenyl)-4,4a,5,6,7,8a-hexahydro-3*H*-pyrano[2,3-*d*]pyrimidine (4k)

To a solution of 3,5-dinitroaniline (250 mg, 1.33 mmol) in anhydrous acetonitrile (7.4 mL) and molecular sieves 4 Å was added under argon atmosphere 4-(trifluoromethyl)benzaldehyde (205.2 µL, 1.47 mmol). The mixture was stirred for 10 minutes at room temperature and then, $Sc(OTf)_3$ (133 mg, 0.27 mmol) was added. After 5 min, 3,4-dihydro-2*H*-pyran (**2a**) was added, and the resulting suspension was stirred under argon atmosphere for 24 h. When the reaction was complete, an aqueous saturated $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with EtOAc (3×10 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, DCM/MeOH 98:2) to give compound **4k** as a pale solid (16% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.71 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 4.61 (dd, *J* = 9.1, 1.5 Hz, 1H), 4.38 (d, *J* = 10.8 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.59 (d, *J* = 3.1 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.53 (m, 2H), 1.41 (d, *J* = 13.0 Hz, 1H), 1.22 – 1.17 (m, 1H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 152.4, 148.8, 145.9, 141.9, 131.4 (q, *J* = 32.9 Hz), 128.4, 128.4, 126.9, 126.5 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.3 Hz). 117.1, 87.7, 68.0, 67.5, 43.9, 26.5, 25.4, 23.9 ppm. **IR** (film) ν_{max}: 3340, 3109, 2917, 2853, 1636, 1540, 1457, 1419, 1354, 1329, 1258, 1175, 1124, 1073, 1015, 855, 733 cm^{-1}. **HRMS**: calcd for $C_{21}H_{19}F_3N_4O_5$ 465.1308 ($M+H^+$); found, 465.1380.

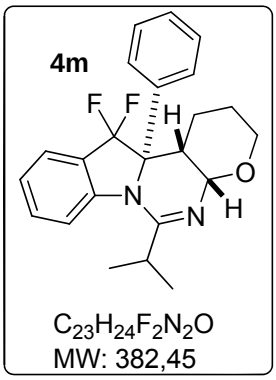


$C_{23}H_{24}N_2O_2$
MW: 360,4489

(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-propyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4aH)-one (4l)

Following the general procedure B, method A (72 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in butyronitrile (**3b**) as solvent, afforded compound **4l**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 6:4) to afford pure **4l** as a pale solid (69% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.60 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.54 – 7.50 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31 – 7.17 (m, 4H), 7.10 – 6.97 (m, 1H), 4.85 – 4.69 (m, 1H), 3.92 (td, *J* = 11.1, 2.6 Hz, 1H), 3.69 – 3.55 (m, 1H), 3.02 (dt, *J* = 11.0, 4.4 Hz, 1H), 2.97 – 2.76 (m, 2H), 2.12 – 1.96 (m, 2H), 1.66 – 1.50 (m, 1H), 1.41 – 1.35 (m, 2H), 1.20 – 1.09 (m, 4H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 201.8, 157.2, 154.6, 137.1, 136.8, 128.6, 128.2, 126.7, 125.6, 124.8, 123.3, 115.9, 82.3, 74.3, 61.7, 40.9, 40.5, 24.9, 21.5, 20.5, 14.3 ppm. **IR** (film) ν_{max}: 3365, 2956, 2917, 2866, 2847, 1719, 1681, 1604, 1598, 1444, 1380, 1290, 1130, 1079, 957, 752, 701 cm^{-1}. **HRMS**: calcd for $C_{23}H_{24}N_2O_2$ 361.1838 ($M+H^+$); found, 361.1902.

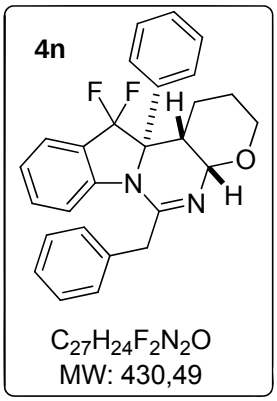


$C_{23}H_{24}F_2N_2O$
MW: 382,45

(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-6-isobutyl-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido [1,6-a]indole (4m)

Following the general procedure B, method A (48 h), the reaction of **1a** and 3,4-dihydro-*2H*-pyran (**2a**) in isobutyronitrile (**3c**) as solvent, afforded compound **4m**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **4m** as a pale solid (59% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.44 – 7.26 (m, 5H), 7.23 (dd, *J* = 10.9, 7.2 Hz, 3H), 7.03 (d, *J* = 7.4 Hz, 1H), 5.51 (s, 1H), 3.97 (t, *J* = 10.9 Hz, 1H), 3.64 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.23 – 3.14 (m, 1H), 3.08 (dt, *J* = 12.9, 4.1 Hz, 1H), 1.71 – 1.57 (m, 1H), 1.52 (d, *J* = 6.9 Hz, 3H), 1.43 (d, *J* = 12.8 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 10.0 Hz, 1H), 0.88 (tt, *J* = 13.0, 6.6 Hz, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -91.69 (d, *J* = 239.6 Hz), -123.27 (d, *J* = 239.8 Hz) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 160.1, 145.1 (dd, *J* = 7.4, 4.8 Hz), 136.2 (d, *J* = 6.4 Hz), 132.8 (d, *J* = 2.7 Hz), 129.1, 129.0, 128.9, 128.6, 128.1, 127.9, 127.8, 126.9 (dd, *J* = 27.3, 24.3 Hz), 125.9, 124.2, 123.8 (d, *J* = 2.2 Hz), 115.6, 84.9, 82.1 (d, *J* = 14.2 Hz), 74.1 (dd, *J* = 23.7, 20.0 Hz), 67.1, 60.0, 38.9, 34.6, 25.8, 22.6, 22.4, 20.0 ppm. **IR** (film) ν_{max}: 3359, 3065, 2969, 2930, 2873, 1732, 1649, 1611, 1483, 1393, 1303, 1284, 1214, 1117, 1085, 1047, 977, 861, 759, 701, 643 cm^{-1}. **HRMS**: calcd for $C_{23}H_{24}F_2N_2O$ 383.1857 ($M+H^+$); found, 383.1923.

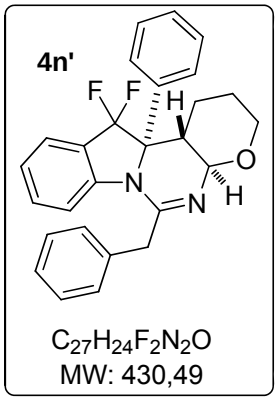


$C_{27}H_{24}F_2N_2O$
MW: 430,49

(4a*RS*,12a*RS*,12b*RS*)-6-benzyl-12,12-difluoro-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido [1,6-a]indole (4n)

Following the general procedure B, method A (48 h), the reaction of **1a** and 3,4-dihydro-*2H*-pyran (**2a**) in 2-phenylacetonitrile (**3e**) as solvent, afforded compound **4n**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **4n** as a pale solid (40% yield).

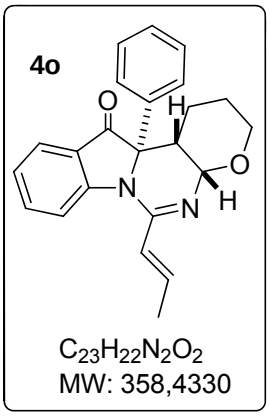
^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.46 (d, *J* = 7.2 Hz, 3H), 7.42 – 7.30 (m, 7H), 7.13 – 6.99 (m, 4H), 5.58 (s, 1H), 4.24 – 4.06 (m, 2H), 3.98 (t, *J* = 10.9 Hz, 1H), 3.69 (dd, *J* = 11.3, 4.5 Hz, 1H), 3.10 (dt, *J* = 12.8, 4.2 Hz, 1H), 1.79 – 1.55 (m, 4H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -93.07 (d, *J* = 239.6 Hz), -124.57 (d, *J* = 239.5 Hz) ppm.



$C_{27}H_{24}F_2N_2O$
MW: 430,49

(4a*RS*,12a*SR*,12b*SR*)-6-benzyl-12,12-difluoro-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido [1,6-a]indole (4n')

Repurification of compound **4n** (SiO_2, hexane:EtOAc, 9:1) afford pure **4n'**. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.47 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.30 (m, 6H), 7.28 – 7.25 (m, 2H), 7.23 – 7.18 (m, 2H), 6.95 (t, *J* = 7.1 Hz, 1H), 4.27 (d, *J* = 15.8 Hz, 1H), 4.16 – 4.09 (m, 2H), 4.05 – 3.98 (m, 1H), 3.37 (tt, *J* = 11.0, 5.5 Hz, 1H), 2.46 – 2.30 (m, 2H), 1.84 (tt, *J* = 15.1, 4.8 Hz, 1H), 1.70 – 1.59 (m, 2H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -87.46 (d, *J* = 240.5 Hz), -121.00 (d, *J* = 240.2 Hz) ppm. **^{13}C-RMN**($CDCl_3$, 100 MHz): δ 150.6, 142.9, 136.2, 134.2, 132.4, 129.1, 128.6, 128.1, 127.1, 126.4, 125.9, 124.6, 123.7, 122.1, 116.7, 84.8, 74.6, 74.3, 74.1, 67.1, 41.6, 39.5, 29.9, 25.9, 24.9 ppm. **IR** (film) ν_{max}: 3334, 3058, 3026, 2949, 2847, 1681, 1617, 1476, 1438, 1380, 1303, 1258, 1124, 1092, 1047, 989, 957, 855, 752, 714, 701 cm^{-1}. **HRMS**: calcd for $C_{27}H_{24}F_2N_2O$ 431.1857 ($M+H^+$); found, 431.1929.

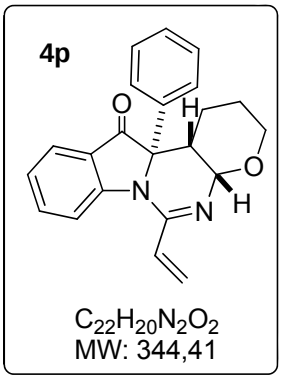


$C_{23}H_{22}N_2O_2$
MW: 358,4330

(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-(*E*)-prop-1-en-1-yl)-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4a*H*)-one (4o)

Following the general procedure B, method A (72 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in but-3-enenitrile (**3f**) as solvent, afforded compound **4o**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 8:2) to afford pure **4o** as a pale solid (41% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.62 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.49 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.26 – 7.22 (m, 1H), 6.99 (t, *J* = 7.7 Hz, 2H), 6.51 (dd, *J* = 15.7, 1.7 Hz, 1H), 4.76 (d, *J* = 3.7 Hz, 1H), 3.98 (td, *J* = 11.9, 2.6 Hz, 1H), 3.66 (ddd, *J* = 11.4, 2.8, 1.6 Hz, 1H), 3.11 (d, *J* = 12.3 Hz, 1H), 2.17 – 2.06 (m, 3H), 1.74 – 1.58 (m, 1H), 1.50 – 1.40 (m, 1H), 1.13 (dd, *J* = 12.8, 3.9 Hz, 1H), 1.05 (ddd, *J* = 13.3, 8.8, 4.2 Hz, 1H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 202.3, 156.1, 154.8, 139.9, 137.3, 136.9, 129.3, 128.5, 128.1, 126.8, 125.4, 122.9, 122.3, 114.5, 82.7, 74.1, 61.1, 44.4, 25.5, 22.1, 18.8 ppm. **IR** (film) ν_{max}: 3429, 2924, 2847, 1719, 1649, 1559, 1540, 1457, 1271, 1105, 1034, 752 cm^{-1}. **HRMS**: calcd for $C_{23}H_{22}N_2O_2$ 359.1681 ($M+H^+$); found, 359.1751.

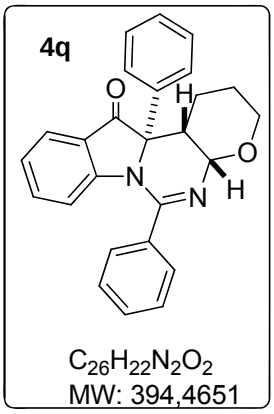


$C_{22}H_{20}N_2O_2$
MW: 344,41

(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-vinyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4a*H*)-one (4p)

Following the general procedure B, method A (72 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in acrylonitrile (**3g**) as solvent, afforded compound **4p**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 6:4) to afford pure **4p** as a pale solid (53% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.57 – 7.51 (m, 3H), 7.45 – 7.38 (m, 1H), 7.32 – 7.28 (m, 1H), 7.20 (m, *J* = 8.5, 7.0, 4.6, 2.2 Hz, 3H), 6.95 – 6.91 (m, 1H), 6.77 – 6.69 (m, 1H), 6.38 (dt, *J* = 17.5, 0.9 Hz, 1H), 5.98 (dt, *J* = 10.7, 1.0 Hz, 1H), 4.72 (t, *J* = 6.6 Hz, 1H), 3.91 (td, *J* = 11.9, 2.6 Hz, 1H), 3.64 – 3.56 (m, 1H), 3.10 – 3.02 (m, 1H), 1.62 – 1.53 (m, 1H), 1.44 – 1.33 (m, 1H), 1.10 – 0.94 (m, 2H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): 202.2, 155.9, 155.2, 137.4, 136.9, 135.0, 128.5, 128.2, 126.8, 125.5, 123.1, 122.6, 114.7, 82.8, 74.1, 61.2, 44.4, 25.5, 22.1 ppm. **IR** (film) ν_{max}: 3353, 3052, 2937, 2846, 1700, 1623, 1489, 1463, 1322, 1156, 1079, 1041, 887, 733, 695 cm^{-1}. **HRMS**: calcd for $C_{22}H_{20}N_2O_2$ 345.1525 ($M+H^+$); found, 345.1597.

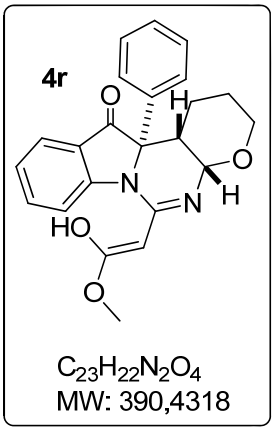


$C_{26}H_{22}N_2O_2$
MW: 394,4651

(4a*RS*,12a*RS*,12b*RS*)-6,12a-diphenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4a*H*)-one (4q)

Following the general procedure B, method B (24 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in benzonitrile (**3h**) as solvent, afforded compound **4q**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **4q** as a pale solid (44% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.17 – 8.08 (m, 2H), 7.65 (dd, *J* = 5.3, 3.4 Hz, 2H), 7.60 – 7.49 (m, 4H), 7.28 – 7.23 (m, 2H), 7.23 – 7.16 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 4.86 (d, *J* = 3.9 Hz, 1H), 3.97 (td, *J* = 11.7, 2.5 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.13 (dt, *J* = 12.4, 4.3 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.36 (dd, *J* = 7.7, 4.1 Hz, 1H), 1.24 (dd, *J* = 10.1, 7.3 Hz, 1H), 1.06 – 0.97 (m, 1H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 202.2, 155.9, 155.8, 137.1, 136.8, 136.1, 131.9, 129.5, 129.2, 128.6, 128.2, 126.9, 125.4, 123.7, 122.9, 115.4, 83.1, 74.4, 66.1, 61.4, 43.9, 25.4, 21.9 ppm. **IR** (film) ν_{max}: 3385, 3058, 2956, 2930, 2873, 1713, 1591, 1469, 1322, 1278, 1162, 1117, 964, 778, 727, 695 cm^{-1}. **HRMS**: calcd for $C_{26}H_{22}N_2O_2$ 395.4651 ($M+H^+$); found, 395.1752.

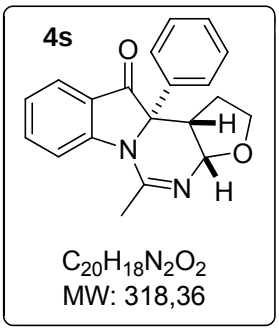


$C_{23}H_{22}N_2O_4$
MW: 390,4318

(4a*RS*,12a*RS*,12b*RS*)-6-((E)-2-hydroxy-2-methoxyvinyl)-12a-phenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4a*H*)-one (4r)

Following the general procedure B, method A (72 h), the reaction of **1e** and 3,4-dihydro-*2H*-pyran (**2a**) in methyl 2-cyanoacetate (**3i**) as solvent, afforded compound **4r**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **4r** as a pale solid (49% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.79 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.75 – 7.68 (m, 2H), 7.61 – 7.56 (m, 1H), 7.39 – 7.33 (m, 1H), 7.31 – 7.27 (m, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 5.01 (bs, 1H), 4.79 (d, *J* = 3.6 Hz, 1H), 3.77 (d, *J* = 2.0 Hz, 3H), 3.68 – 3.60 (m, 1H), 3.45 – 3.37 (m, 1H), 2.76 – 2.64 (m, 1H), 2.47 – 2.37 (m, 1H), 1.61 (ddd, *J* = 16.6, 11.4, 5.8 Hz, 2H), 1.26 – 1.18 (m, 2H) ppm. **^{13}C-RMN** ($CDCl_3$, 100 MHz): δ 198.9, 171.4, 154.0, 153.6, 137.7, 135.6, 128.7, 128.4, 128.3, 127.7, 127.1, 125.6, 122.7, 114.0, 79.8, 64.7, 50.8, 38.9, 31.7, 30.4, 29.9, 21.9, 20.4 ppm. **IR** (film) ν_{max}: 3346, 2962, 2917, 2853, 1713, 1617, 1502, 1463, 1322, 1258, 1156, 1079, 1028, 759, 701 cm^{-1}. **HRMS**: calcd for $C_{23}H_{22}N_2O_4$ 391.1580 ($M+H^+$); found, 391.1644.

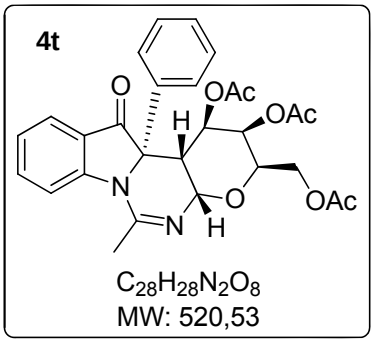


$C_{20}H_{18}N_2O_2$
MW: 318,36

(3a*RS*,11a*RS*,11b*RS*)-5-methyl-11a-phenyl-1,3a,11a,11b-tetrahydrofuro[2',3':4,5]pyrimido[1,6-*a*]indol-11(2*H*)-one (4s)

Following the general procedure B, method B (16 h), the reaction of **1e** and 2,3-dihydrohydrofuran (**2b**), in acetonitrile (**3a**) as solvent, afforded compound **4s**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **4s** as a yellow pale solid (38% yield).

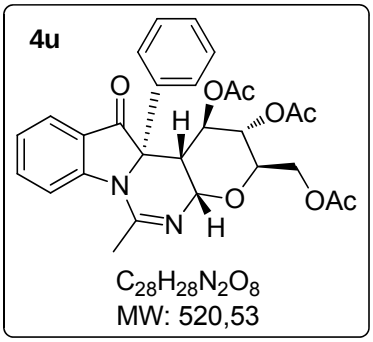
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.74-7.70 (m, 1H), 7.62–7.54 (m, 3H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.32-7.22 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.01 (dd, *J* = 5.2, 1.0 Hz, 1H), 3.66-3.58 (m, 1H), 2.93 (q, *J* = 8.0 Hz, 1H), 2.78 (d, *J* = 1.2 Hz, 3H), 2.68 (ddd, *J* = 8.4, 5.2, 3.5 Hz, 1H), 2.46 (dddd, *J* = 13.3, 8.3, 4.9, 3.7 Hz, 1H), 2.24-2.13 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 199.7, 152.4, 152.2, 137.5, 134.3, 128.5, 128.3, 127.4, 125.9, 122.8, 122.4, 114.4, 87.9, 68.8, 64.9, 42.1, 27.2, 26.2 ppm. **IR** (film) ν_{max}: 3359, 3058, 2930, 2879, 1707, 1604, 1470, 1386, 1316, 1271, 1194, 1111, 1053, 1021, 944, 752 cm^{-1}. **HRMS**: calcd for $C_{20}H_{19}N_2O_2$, 319.1441 ($M+H^+$); found, 319.1446.



(1*R*,2*R*,3*R*,4a*S*,12a*S*,12b*R*)-3-(acetoxymethyl)-6-methyl-12-oxo-12a-phenyl-2,3,4a,12,12a,12b-tetrahydro-1*H*-pyrano [2',3':4,5]pyrimido[1,6-*a*]indole-1,2-diyl diacetate (4t)

Following the general procedure B, method C (1 cycle of 10 min), the reaction of **1e** and 2,3- (2R,3R,4R)-2-(acetoxymethyl)-3,4-dihydro-2*H*-pyran-3,4-diyl diacetate (**2c**) in acetonitrile (**3a**) as solvent, afforded compound **4t**. The crude was purified by flash cromatography (SiO_2, hexane: EtOAc, 1:1) compound **4t** was obtained as a white solid (37% yield, isomer ratio 2/1).

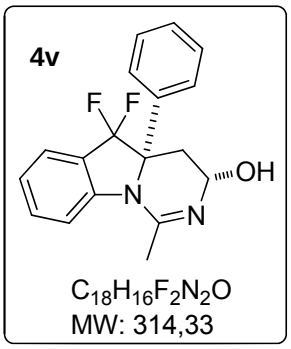
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.68-7.64 (m, 1H), 7.54 (ddd, *J* = 8.5, 7.3, 1.4 Hz, 1H), 7.44–7.39 (m, 2H), 7.34-7.30 (m, 1H), 7.26-7.17 (m, 3H), 7.09-7.03 (m, 1H), 5.20 (dd, *J* = 3.3, 1.4 Hz, 1H), 5.08 (dd, *J* = 11.3, 3.3 Hz, 1H), 4.93 (dd, *J* = 4.1, 1.9 Hz, 1H), 4.50 (td, *J* = 6.0, 1.0 Hz, 1H), 4.18-4.09 (m, 2H), 3.58 (dd, *J* = 11.3, 4.4 Hz, 1H), 2.66 (d, *J* = 1.9 Hz, 3H), 2.14 (s, 3H), 2.02 (s, 3H), 1.34 (s, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 199.82, 170.7, 170.5, 169.6, 155.9, 153.3, 137.3, 136.2, 128.7, 128.5, 127.0, 125.9, 124.4, 123.6, 115.5, 82.1, 73.1, 67.8, 66.7, 66.5, 61.9, 41.2, 25.4, 20.9, 20.9, 20.2 ppm. **IR** (film) ν_{max}: 3379, 3058, 2956, 2923, 1739, 1649, 1604, 1470, 1374, 1309, 1226, 1137, 1098, 1047, 765 cm^{-1}. **HRMS**: calcd for $C_{28}H_{29}N_2O_8$, 521.1918 ($M+H^+$); found, 521.192.



(1*R*,2*S*,3*R*,4a*S*,12a*S*,12b*R*)-3-(acetoxymethyl)-6-methyl-12-oxo-12a-phenyl-2,3,4a,12,12a,12b-tetrahydro-1*H*-pyrano [2',3':4,5]pyrimido[1,6-*a*]indole-1,2-diyl diacetate (4u)

Following the general procedure B, method B (16 h), the reaction of **1e** and 2-(acetoxymethyl)-3,4-dihydro-*2H*-pyran-3,4-diyl diacetate (**2d**) in acetonitrile (**3a**) as solvent, afforded compound **4u**. The crude was purified by HPLC preparative purification chromatography to afford pure **4u** as a white solid (17% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.78-7.73 (m, 1H), 7.71-7.65 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.45-7.39 (m, 2H), 7.37-7.25 (m, 4H), 5.83 (dd, *J* = 9.6, 4.7 Hz, 1H), 5.64 (d, *J* = 2.7 Hz, 1H), 5.42 (t, *J* = 10.0 Hz, 1H), 3.89 (d, *J* = 2.7 Hz, 2H), 3.01 (s, 3H), 2.99-2.91 (m, 2H), 2.00 (s, 3H), 1.97 (s, 3H), 1.90 (s, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 193.9, 171.0, 169.9, 169.8, 160.4, 148.9, 137.6, 130.6, 129.9, 129.2, 127.9, 127.7, 126.6, 125.3, 117.9, 75.4, 71.7, 71.4, 67.6, 67.0, 62.5, 43.5, 21.9, 20.9, 20.7, 20.6 ppm. **IR** (film) ν_{max}: 3404, 3071, 2924, 2853, 1745, 1674, 1630, 1598, 1457, 1367, 1226, 1194, 1130, 1041, 983, 912, 797, 765, 714 cm^{-1}. **HRMS**: calcd for $C_{28}H_{29}N_2O_8$, 521.1918 ($M+H^+$); found, 521.1928.

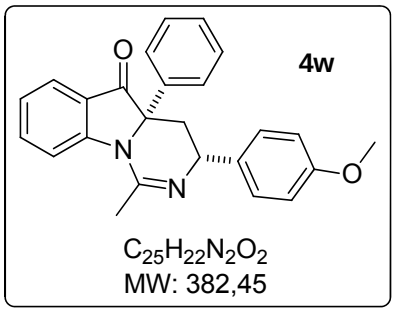


$C_{18}H_{16}F_2N_2O$
MW: 314,33

(3*RS*,4a*RS*)-5,5-difluoro-1-methyl-4a-phenyl-3,4,4a,5-tetrahydropyrimido[1,6-a]indol-3-ol (4v)

Following the general procedure B, method B (24 h), the reaction of **1a** and vinyl acetate (**2e**) in acetonitrile (**3a**) as solvent, afforded compound **4v**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford the hydrolyzed pure **4v** as a pale solid (49% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.52 (t, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.25 – 7.20 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.53 (d, *J* = 10.4 Hz, 1H), 2.99 (dd, *J* = 13.0, 3.9 Hz, 1H), 2.57 (d, *J* = 1.1 Hz, 3H), 2.22 (ddd, *J* = 12.9, 10.5, 2.4 Hz, 1H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -84.24 (d, *J* = 239.9 Hz), -115.49 (d, *J* = 240.1 Hz) ppm. **^{13}C-RMN**($CDCl_3$, 100 MHz): δ 150.9, 136.0, 133.2, 128.9, 128.8, 127.0, 126.9, 125.2, 124.5, 115.7, 72.5, 72.3, 72.0, 33.9, 33.8, 23.7 ppm. **IR** (film) ν_{max}: 3333.81, 3058.36, 2923.84, 2846.98, 1713.17, 1674.73, 1617.08, 1476.16, 1450.53, 1296.80, 1155.87, 1085.41, 1027.76, 758.72, 707.47 cm^{-1}. **HRMS**: calcd for $C_{18}H_{16}F_2N_2O$ 315.1231 ($M+H^+$); found, 315.1303.

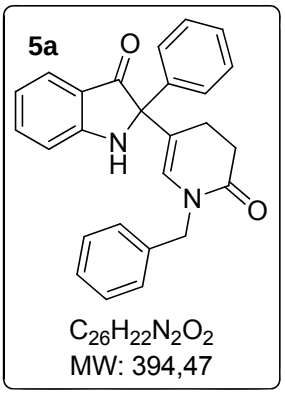


$C_{25}H_{22}N_2O_2$
MW: 382,45

(3*RS*,4a*SR*)-3-(4-methoxyphenyl)-1-methyl-4a-phenyl-4,4*a*-dihydropyrimido[1,6-*a*]indol-5(3*H*)-one (4w)

Following the general procedure B, method A (72 h), the reaction of **1e** and 1-methoxy-4-vinylbenzene (**2k**) in acetonitrile (**3a**) as solvent, afforded compound **4w**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 0:1) to afford pure **4w** as a white solid (25% yield, isomer ratio 4/5).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.62-7.53 (m, 3H), 7.05-6.95 (m, 3H), 6.92-6.85 (m, 3H), 6.63-6.57 (m, 2H), 6.41-6.35 (m, 2H), 4.77 (d, *J* = 6.9 Hz, 1H), 3.60 (s, 3H), 3.10 (dd, *J* = 13.7, 1.3 Hz, 1H), 2.78 (d, *J* = 1.5 Hz, 2H), 2.32 (dd, *J* = 13.7, 7.1 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 198.3, 157.5, 153.2, 150.9, 137.6, 134.9, 134.9, 128.3, 127.6, 127.5, 126.4, 125.7, 122.8, 121.4, 114.5, 113.2, 68.9, 55.8, 55.4, 36.8, 26.1 ppm. **IR** (film) ν_{max}: 3366, 3052, 2988, 2962, 2930, 2841, 1713, 1604, 1508, 1463, 1444, 1380, 1335, 1239, 1162, 1028, 906, 759 cm^{-1}. **HRMS**: calcd for $C_{25}H_{23}N_2O_2$, 383.1754 ($M+H^+$); found, 383.1765.

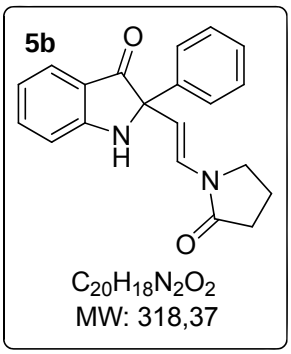


$C_{26}H_{22}N_2O_2$
MW: 394,47

2-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-phenylindolin-3-one (5a)

Following the general procedure B, method A (72 h), the reaction of **1e** and 1-benzyl-3,4-dihydropyridin-2(1*H*)-one (**2f**) in acetonitrile (**3a**) as solvent, afforded compound **5a**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 4:6) to afford pure **5a** as a white solid (64% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.62-7.58 (m, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.39–7.34 (m, 2H), 7.33-7.22 (m, 6H), 7.22-7.16 (m, 2H), 6.88-6.81 (m, 2H), 6.31 (s, 1H), 4.92 (br s, 1H), 4.73 (d, *J* = 15.0 Hz, 1H), 4.55 (d, *J* = 15.0 Hz, 1H), 2.55-2.47 (m, 2H), 2.46-2.35 (m, 1H), 2.22-2.12 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 199.7, 169.2, 159.8, 138.2, 137.8, 137.2, 129.0, 128.8, 128.4, 128.4, 127.7, 127.6, 126.8, 125.5, 120.2, 119.8, 118.4, 112.6, 73.7, 49.6, 31.5, 21.7 ppm. **IR** (film) ν_{max}: 3327, 3065, 3026, 2937, 2853, 1675, 1617, 1489, 1399, 1329, 1271, 1214, 1149, 1085, 1028, 906, 759, 727, 701 cm^{-1}. **HRMS**: calcd for $C_{26}H_{23}N_2O_2$, 395.1754 ($M+H^+$); found, 395.175.

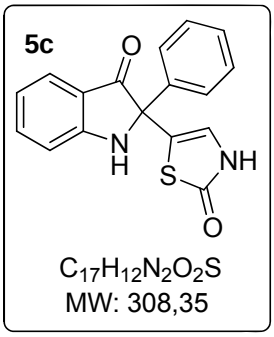


$C_{20}H_{18}N_2O_2$
MW: 318,37

(*E*)-2-[2-(2-oxopyrrolidin-1-yl)vinyl]-2-phenylindolin-3-one (5b)

Following the general procedure B, method A (72 h), the reaction of **1e** and 1-vinylpyrrolidin-2-one (**2h**) in acetonitrile (**3a**) as solvent, afforded compound **5b**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 1:1) to afford pure **5b** as a white solid (21% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.64-7.60 (m, 1H), 7.49 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.45–7.38 (m, 3H), 7.36-7.28 (m, 4H), 6.95-6.92 (m, 1H), 6.89-6.84 (m, 1H), 5.46 (d, *J* = 14.4 Hz, 1H), 5.02 (br s, 1H), 3.63-3.52 (m, 2H), 2.52-2.45 (m, 2H), 2.18-2.06 (m, 2H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 200.9, 173.7, 160.2, 140.2, 137.8, 129.0, 128.3, 126.4, 125.7, 124.7, 119.8, 119.3, 112.7, 111.4, 71.9, 45.6, 31.3, 17.6 ppm. **IR** (film) ν_{max}: 3321, 3065, 2962, 2911, 2847, 1681, 1649, 1610, 1489, 1470, 1406, 1329, 1297, 1265, 1028, 893, 797 cm^{-1}. **HRMS**: calcd for $C_{20}H_{19}N_2O_2$, 319.1441 ($M+H^+$); found, 319.1438.



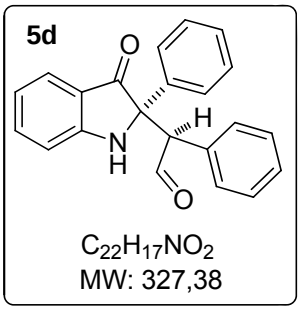
$C_{17}H_{12}N_2O_2S$
MW: 308,35

5-(3-oxo-2-phenylindolin-2-yl)thiazol-2(3*H*)-one (5c)

Following the general procedure B, method A (72 h), the reaction of **1e** and thiazol-2(3*H*)-one (**2i**) in acetonitrile (**3a**) as solvent, afforded compound **5c**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 4:6) to afford pure **5c** as a white solid (59% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.15 (brs, 1H), 7.59-7.55 (m, 1H),

7.46 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.42–7.36 (m, 2H), 7.31-7.22 (m, 3H), 6.91-6.82 (m, 2H), 6.55 (d, *J* = 2.7 Hz, 1H), 5.19 (brs, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 197.9, 174.6, 160.1, 138.3, 137.9, 129.1, 128.9, 126.7, 125.9, 121.3, 120.6, 119.2, 119.1, 113.0, 70.9 ppm. **IR** (film) ν_{max}: 3308, 3058, 3020, 2969, 2924, 2847, 1649, 1604, 1489, 1463, 1444, 1329, 1290, 1092, 1034, 906, 733 cm^{-1}. **HRMS**: calcd for C17H17N2O_2S, 309.0692 ($M+H^+$); found, 309.0691.

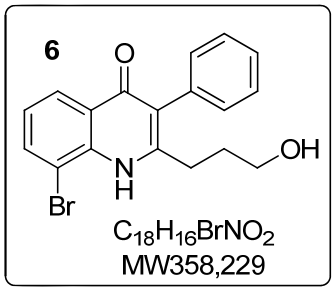


$C_{22}H_{17}NO_2$
MW: 327,38

2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetaldehyde (5d)

Following the general procedure B, method A (72 h), the reaction of **1e** and (*E*)-1-styrylpyrrolidine (**2j**) in acetonitrile (**3a**) as solvent, afforded compound **5d**. The crude was purified by flash chromatography (SiO_2, hexane:EtOAc, 9:1) to afford pure **5d** as a white solid (49% yield).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.60 (d, *J* = 0.6 Hz, 1H), 7.66-7.60 (m, 2H), 7.33-7.06 (m, 10H), 6.77–6.76 (m, 1H), 6.51-6.45 (m, 1H), 6.04 (br s, 1H), 5.00 (s, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 199.4, 198.8, 160.5, 138.2, 137.6, 131.3, 129.2, 128.9, 128.7, 128.6, 127.9, 125.7, 125.2, 118.7, 118.6, 111.1, 72.4, 63.9 ppm. **IR** (film) ν_{max}: 3436, 3398, 3052, 3019, 2930, 2841, 2738, 1713, 1675, 1617, 1585, 1483, 1463, 1399, 1316, 1271, 1194, 1066, 1021, 746, 695 cm^{-1}. **HRMS**: calcd for $C_{22}H_{18}NO_2$, 328.1332 ($M+H^+$); found, 328.1335.

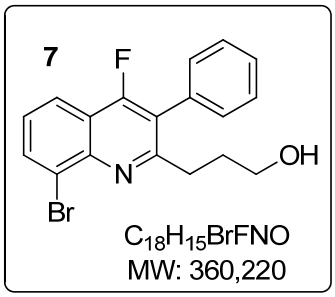


$C_{18}H_{16}BrNO_2$
MW358,229

8-bromo-2-(3-hydroxypropyl)-3-phenylquinolin-4(1*H*)-one (6)

Following the general procedure, method B (72 h), the reaction of **1l** and 3,4-dihydro-2*H*-pyran (**2a**) in acetonitrile (**3a**) as solvent, afforded compound **6**. This mixture was purified by flash chromatography (SiO_2, hexane:EtOAc, 6:4) to afford pure **6** as a pale solid (19% yield). Further elution afforded 3-(8-bromo-4-fluoro-3-phenylquinolin-2-yl)propan-1-ol (**7**), which was isolated as a pale oil (14% yield).

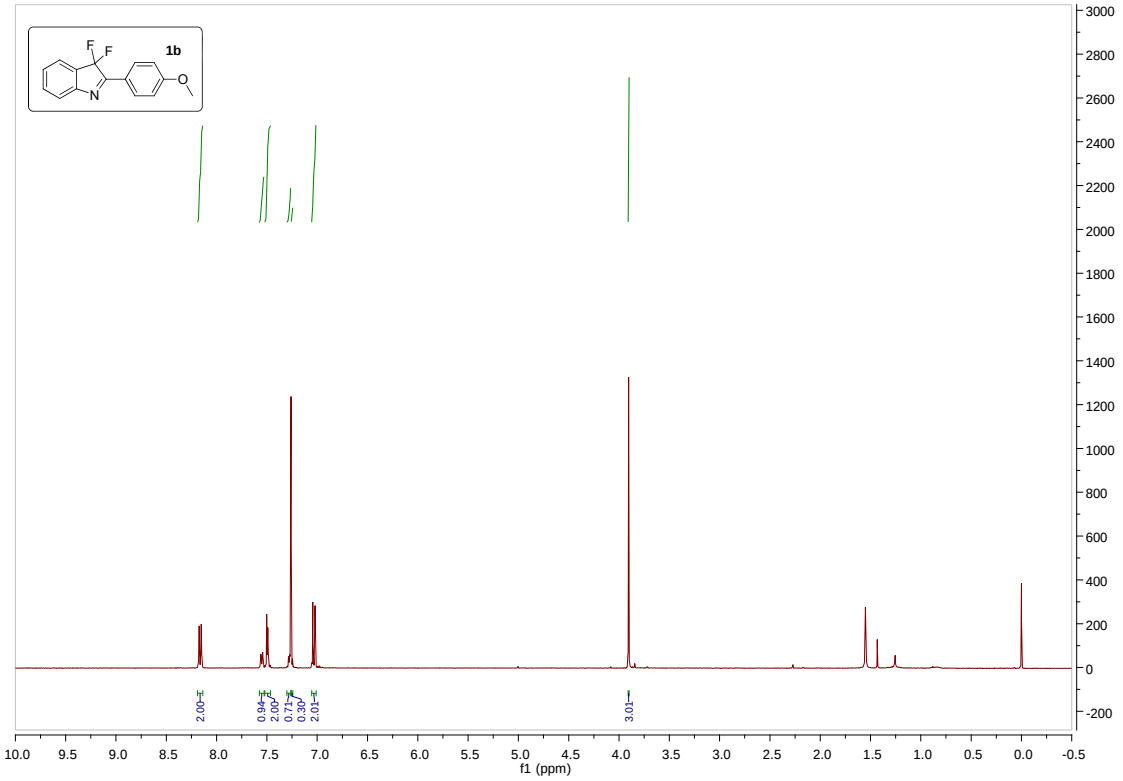
Data for quinolone **6**: **^{1}H-NMR** (DMSO, 400 MHz): δ 8.09 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.31 (dd, *J* = 8.6, 6.1 Hz, 1H), 7.25 – 7.18 (m, 3H), 3.36 (t, *J* = 6.3 Hz, 2H), 3.28 (s, 1H), 2.65 (t, *J* = 7.3 Hz, 2H), 1.68 (p, *J* = 6.4 Hz, 2H) ppm. **^{13}C-NMR** (DMSO, 151 MHz): δ 174.9, 151.5, 135.7, 135.2, 130.8, 127.9, 126.8, 125.9, 125.4, 123.7, 121.8, 60.2, 31.3, 28.6 ppm. **IR** (film) ν_{max}: 3359, 2917, 2841, 2258, 1719, 1623, 1598, 1553, 1521, 1438, 1073, 1034, 759, 727, 695 cm^{-1}. **HRMS**: calcd for $C_{18}H_{17}BrNO_2$, 358.0364 ($M+H^+$); found, 358.0432.

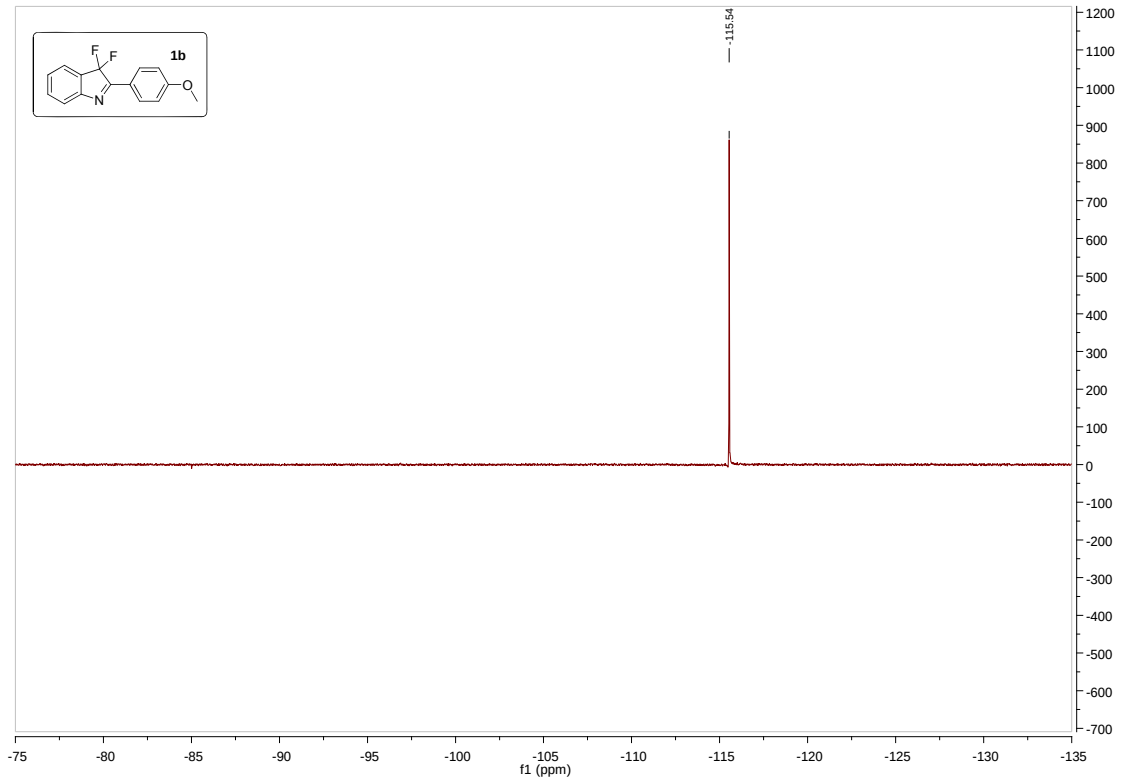


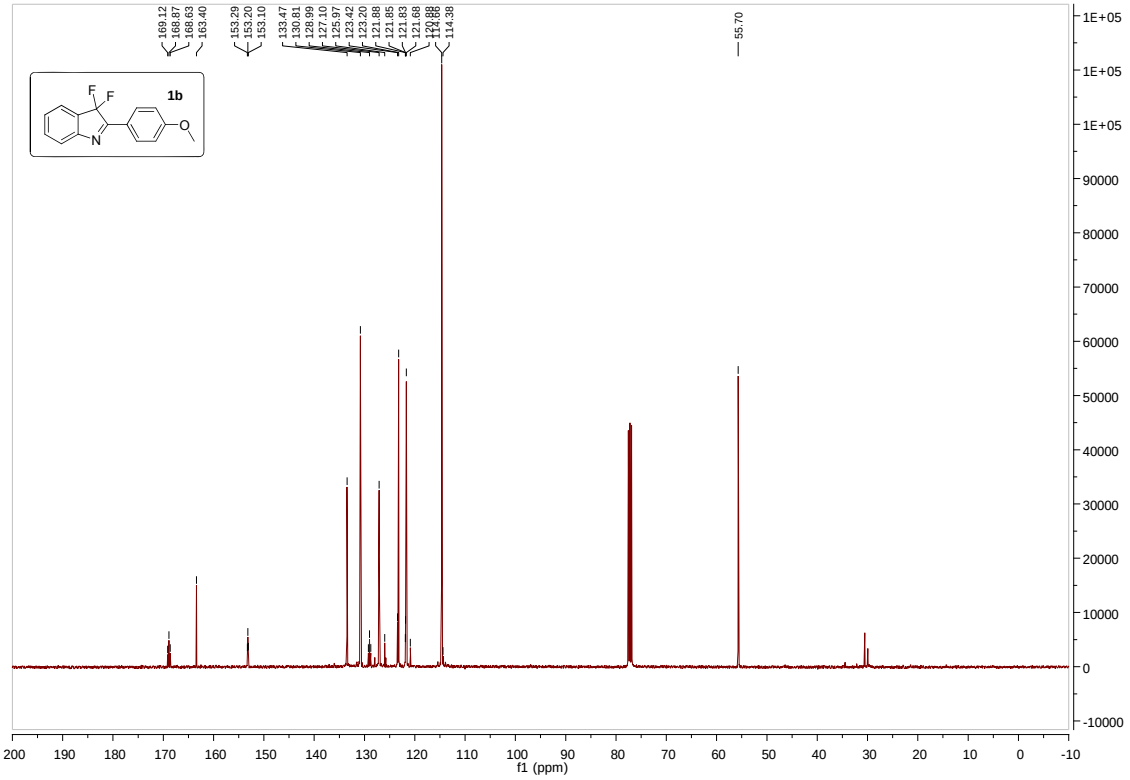
Data for quinoline **7**: **^{1}H-NMR** ($CDCl_3$, 400 MHz): 8.07 (ddd, *J* = 9.5, 7.9, 1.3 Hz, 2H), 7.53 – 7.50 (m, 2H), 7.46 – 7.39 (m, 2H), 7.36 – 7.33 (m, 2H), 3.96 (s, 1H), 3.72 (d, *J* = 5.4 Hz, 2H), 3.10 – 3.01 (m, 2H), 2.00 (dd, *J* = 11.7, 6.1 Hz, 2H) ppm. **^{19}F-RMN** ($CDCl_3$, 376 MHz): δ -112.98 (s) ppm. **^{13}C-NMR** ($CDCl_3$, 151 MHz): δ 163.8, 161.7 (d, *J* = 265.8 Hz), 134.2, 131.9, 129.8, 129.2, 128.8, 128.6, 126.9, 123.9, 120.5 (d, *J* = 5.3 Hz), 19.2, 62.0, 33.4, 33.4, 30.0, 29.7 ppm. **IR** (film) ν_{max}: 3385, 3065, 2930, 2847, 1713, 1623, 1591, 1476, 1438, 1380, 1265, 1162, 1066, 1028, 880, 772, 695 cm^{-1}.

Copies of NMR Spectra

3,3-difluoro-2-(4-methoxyphenyl)-3*H*-indole (1b)



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168.87
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153.10
133.47
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127.10
125.97
123.42
123.20
121.88
121.85
121.83
121.68
120.88
120.66
114.38
55.70
1b
F
F
N
O
1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
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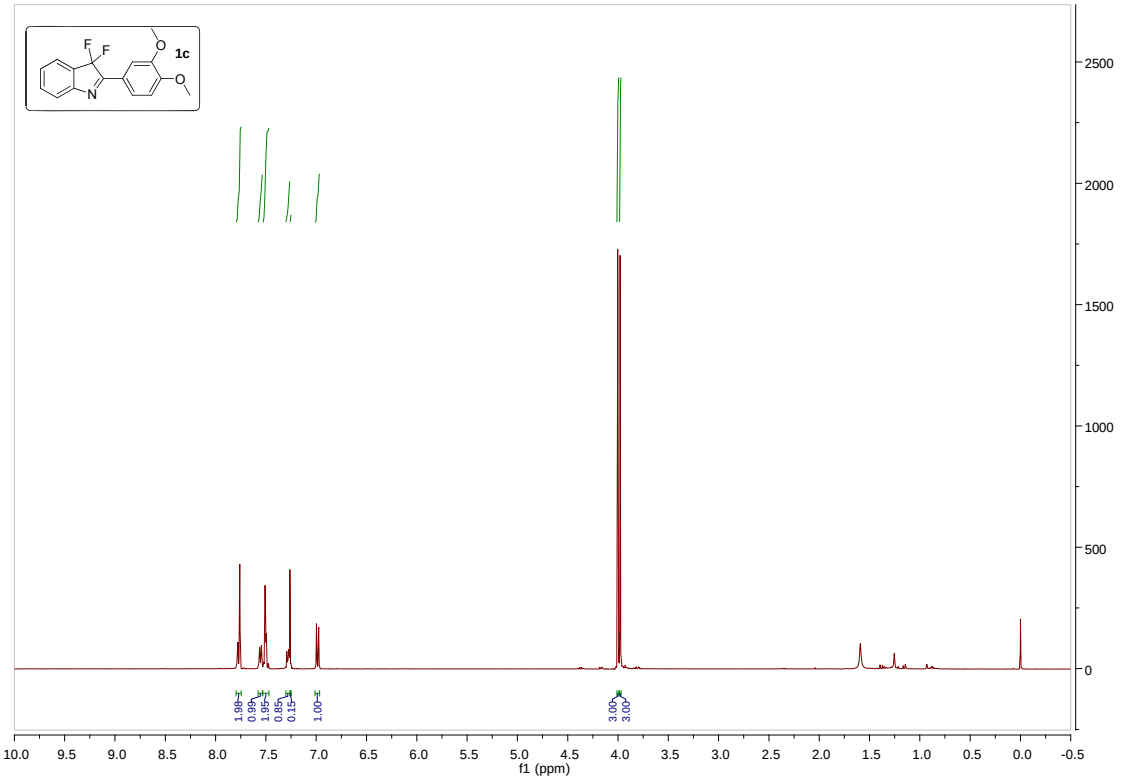
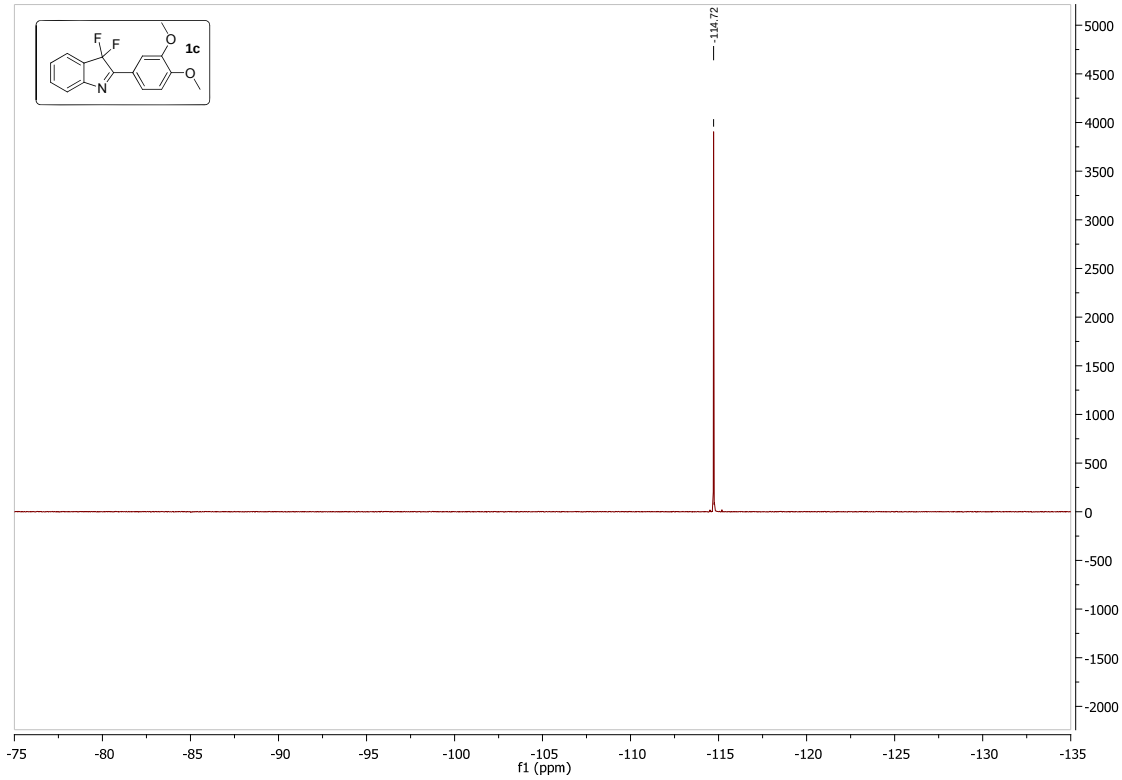
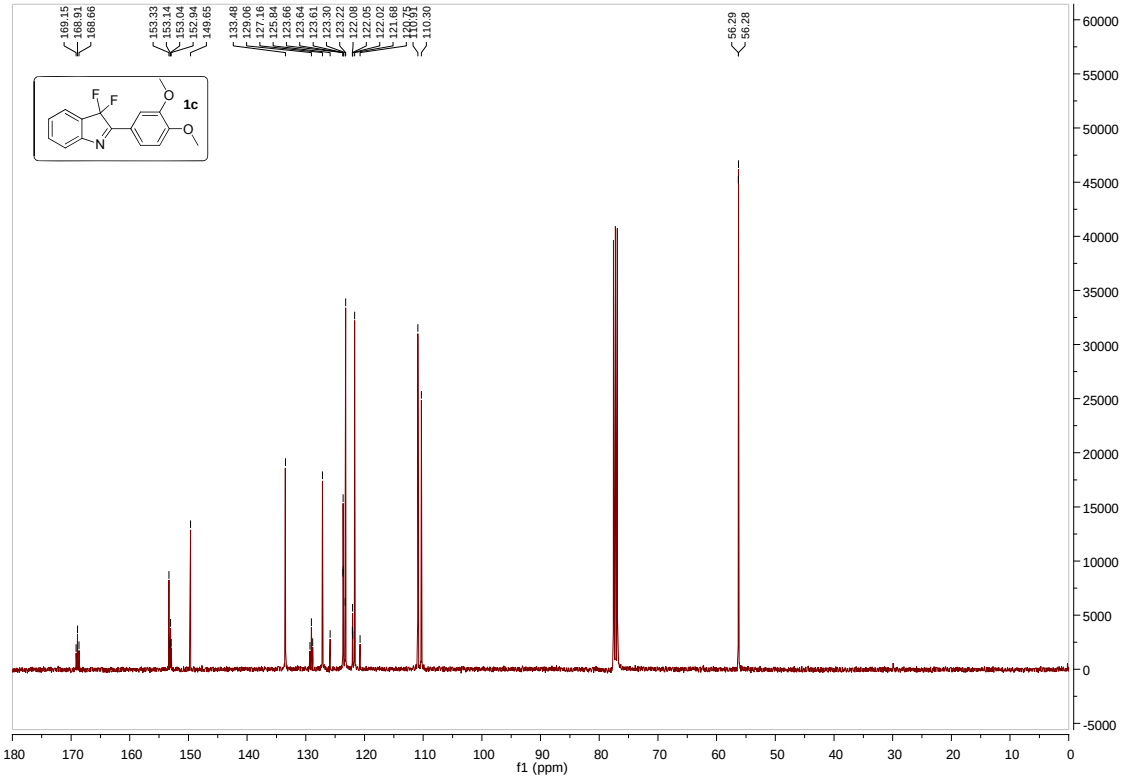
40
30
20
10
0
-10
f1 (ppm)

2-(3,4-dimethoxyphenyl)-3,3-difluoro-3*H*-indole (1c)






169.15
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153.14
153.04
152.94
148.65
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125.84
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123.64
123.61
123.30
123.22
122.08
122.05
122.02
121.68
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110.30
56.29
56.28
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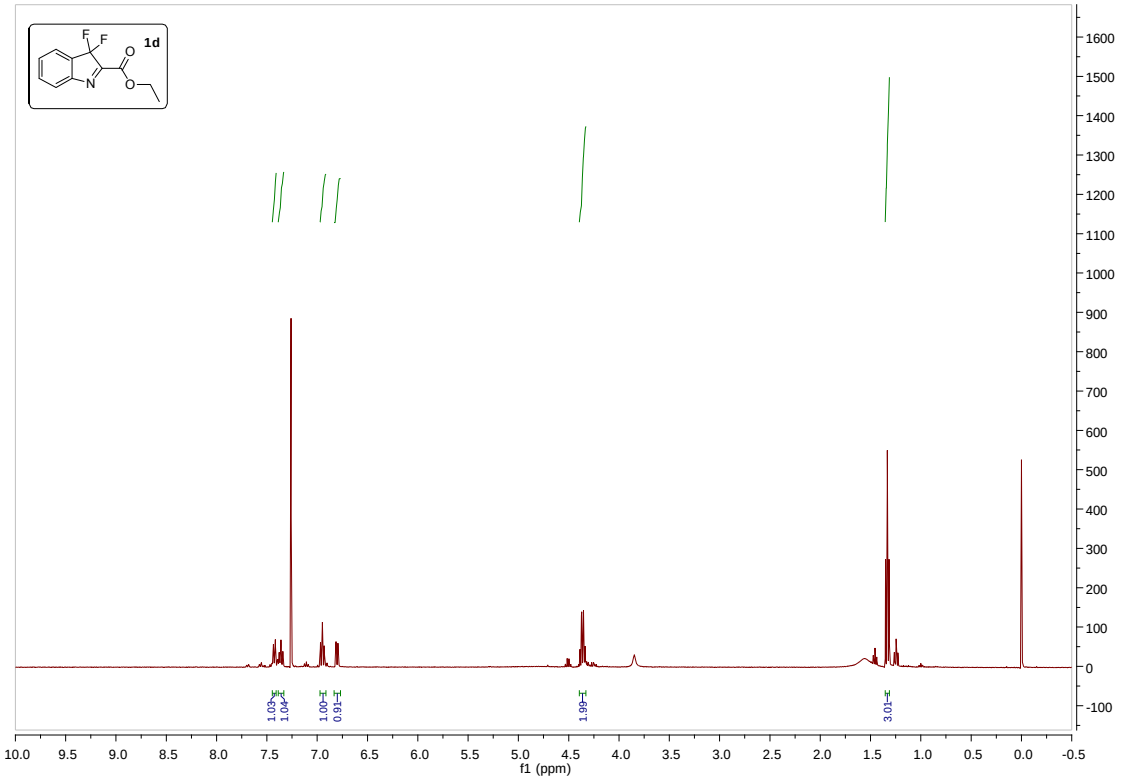
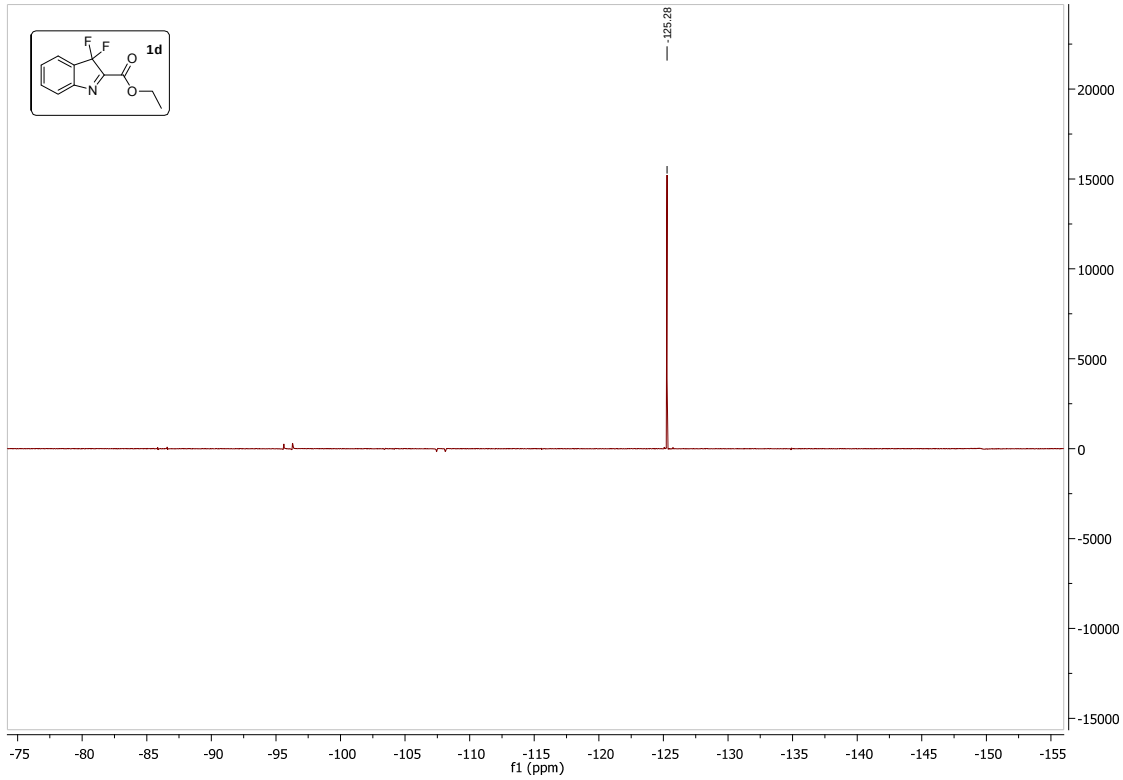
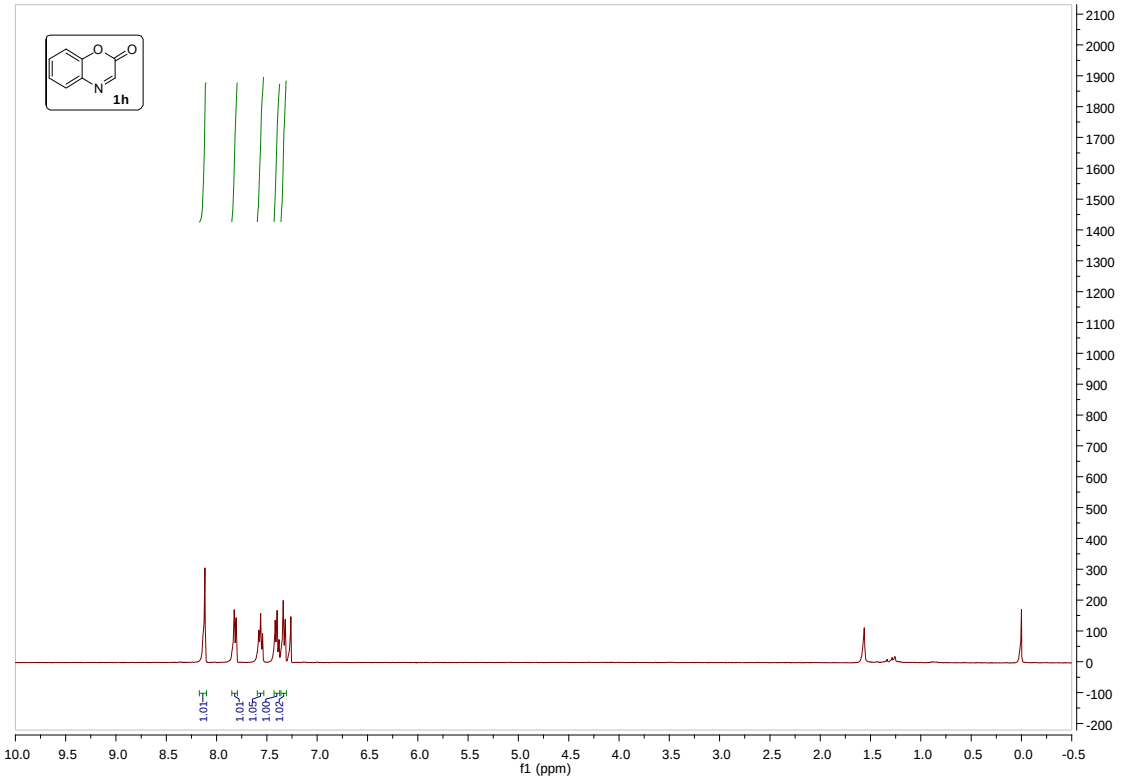
F
O
O
N
1c
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Ethyl 3,3-difluoro-3*H*-indole-2-carboxylate (1d)

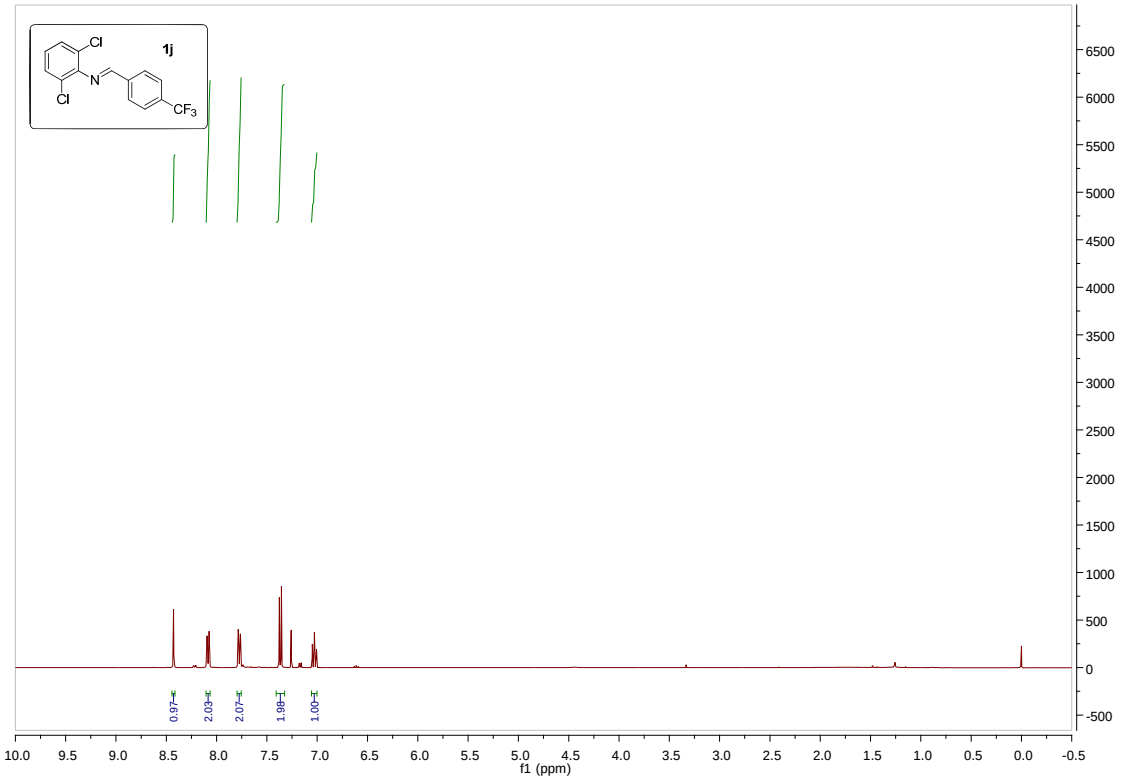




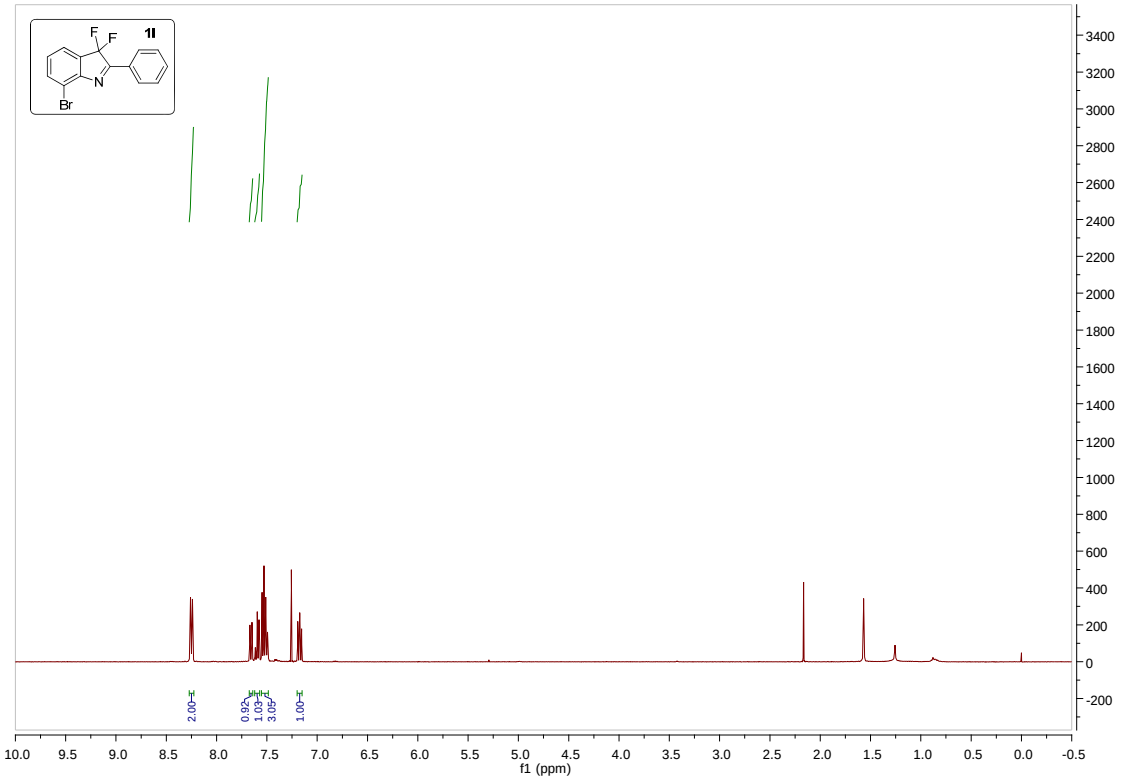
2H-benzo[b][1,4]oxazin-2-one (1h)

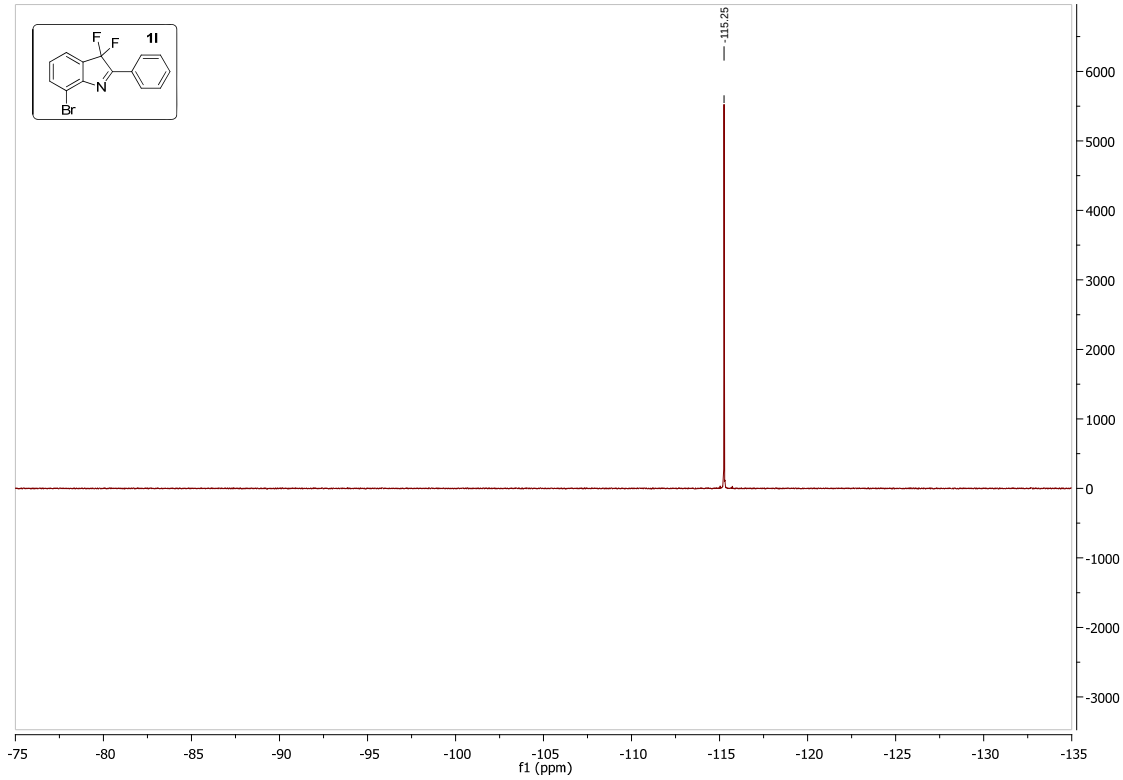


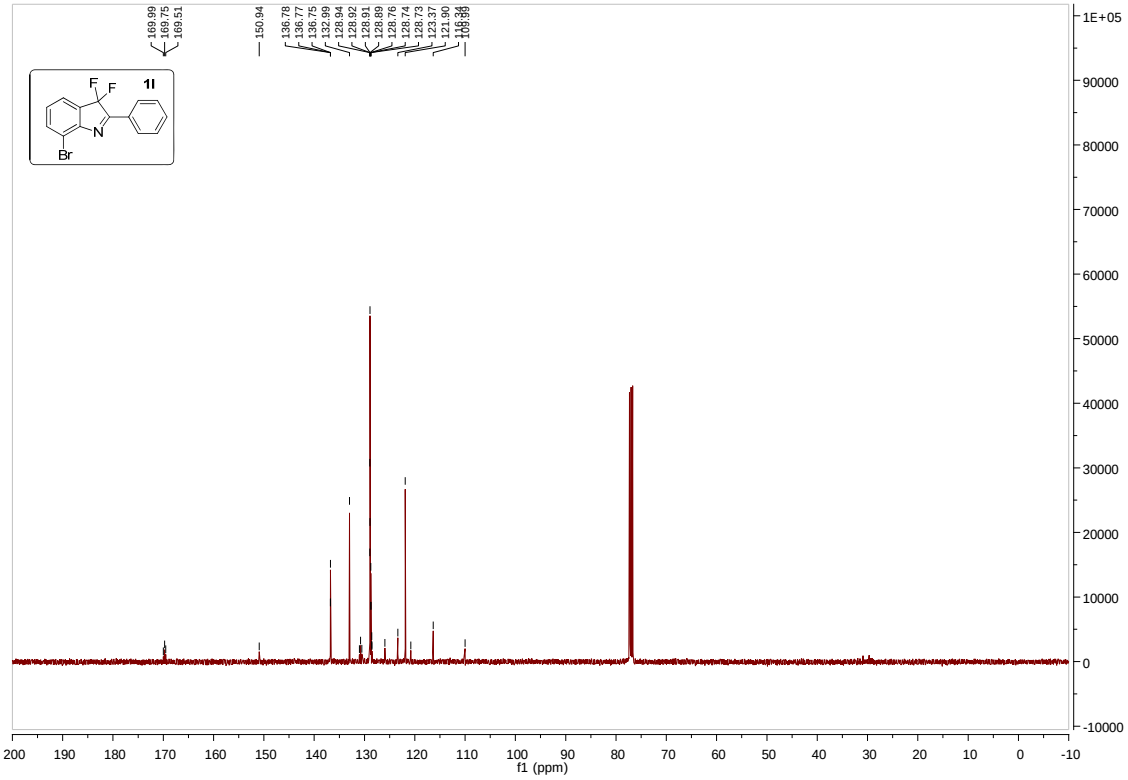
(E)-2,6-dichloro-*N*-(4-(trifluoromethyl)benzylidene)aniline (1j)



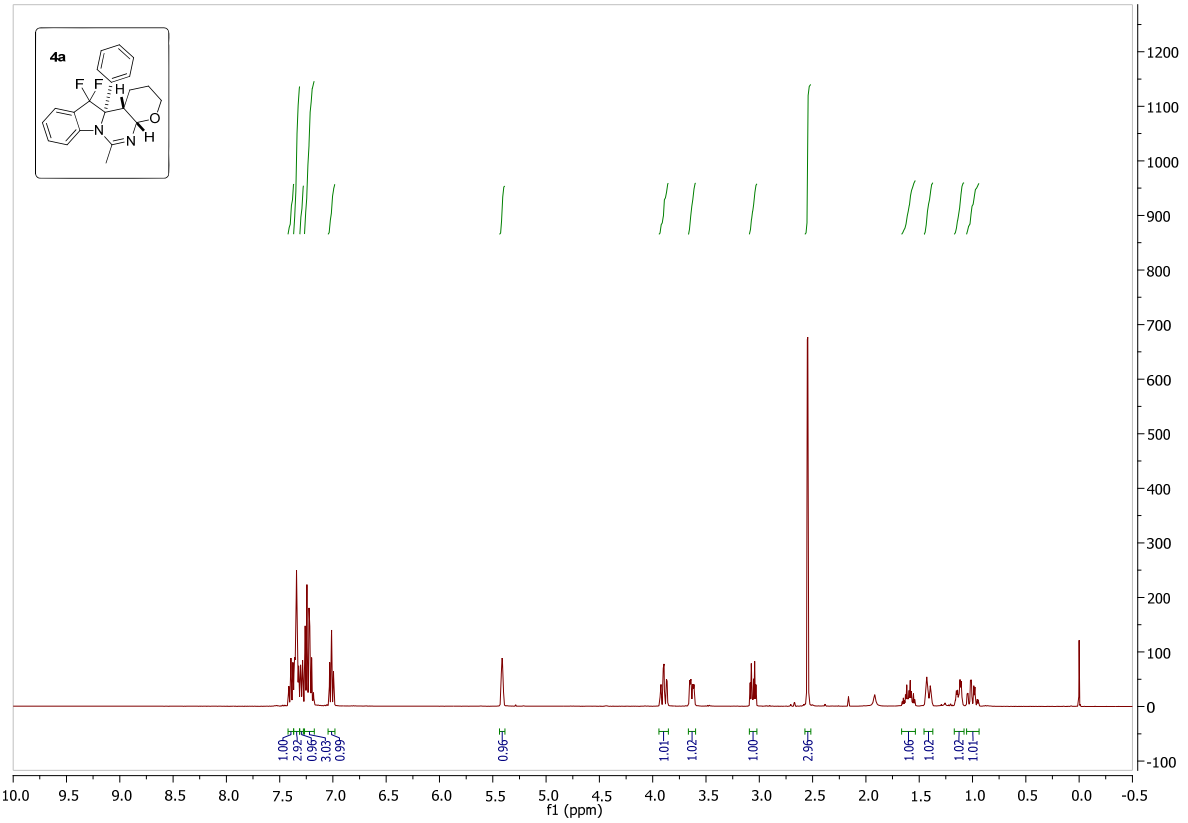
7-bromo-3,3-difluoro-2-phenyl-3H-indole (1l)

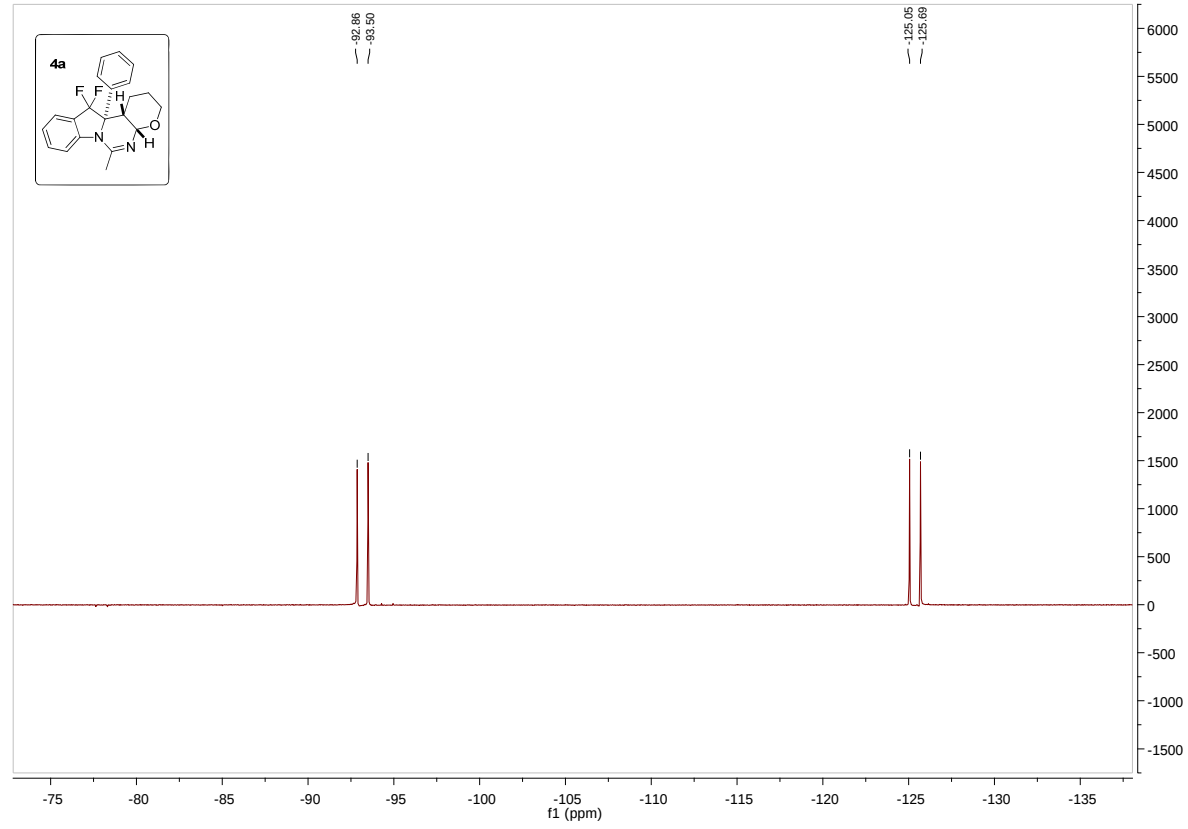


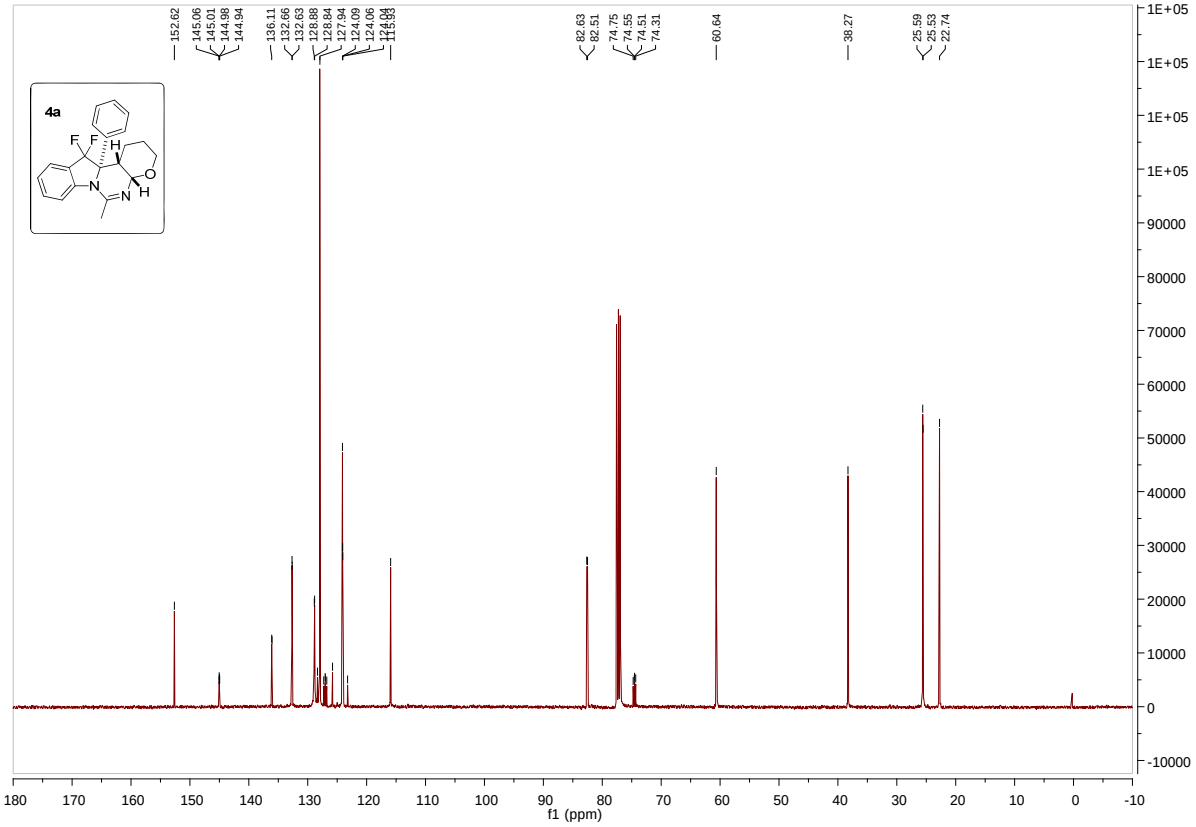



169.99
169.75
169.51
150.94
136.78
136.77
136.75
132.99
128.94
128.92
128.91
128.89
128.76
128.74
123.73
123.37
121.90
116.34
116.09
1l
F
F
N
Br
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

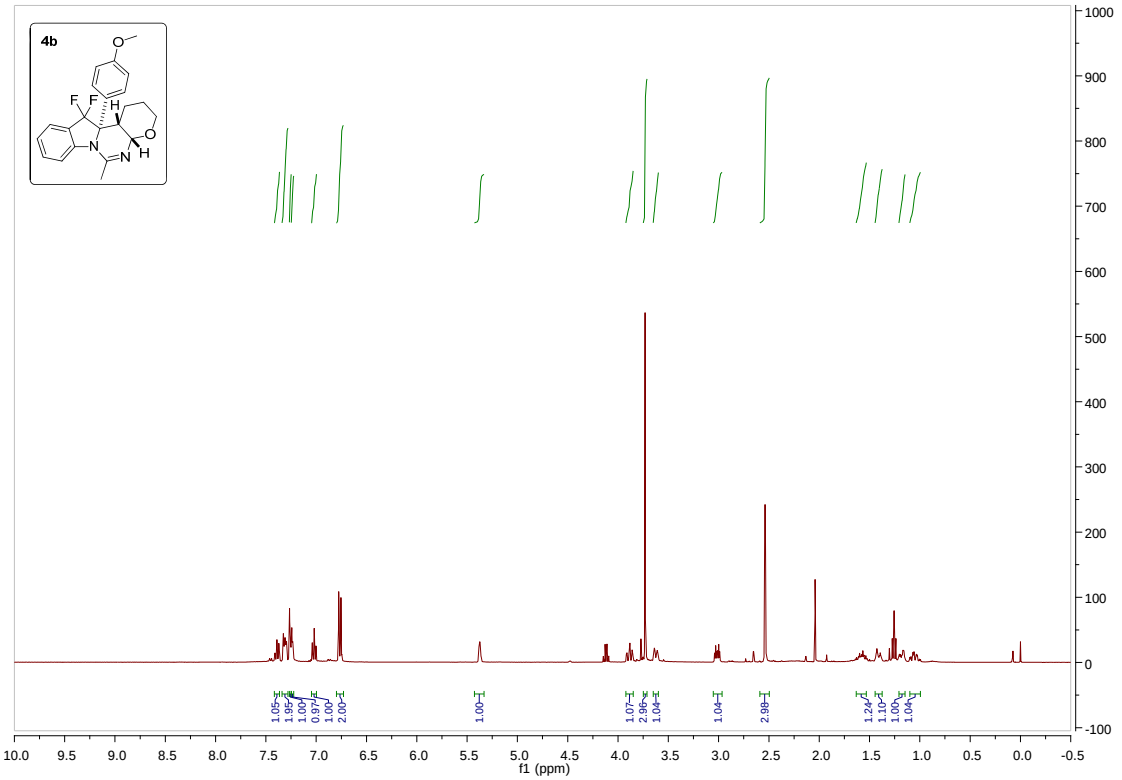
(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-6-methyl-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole (4a)

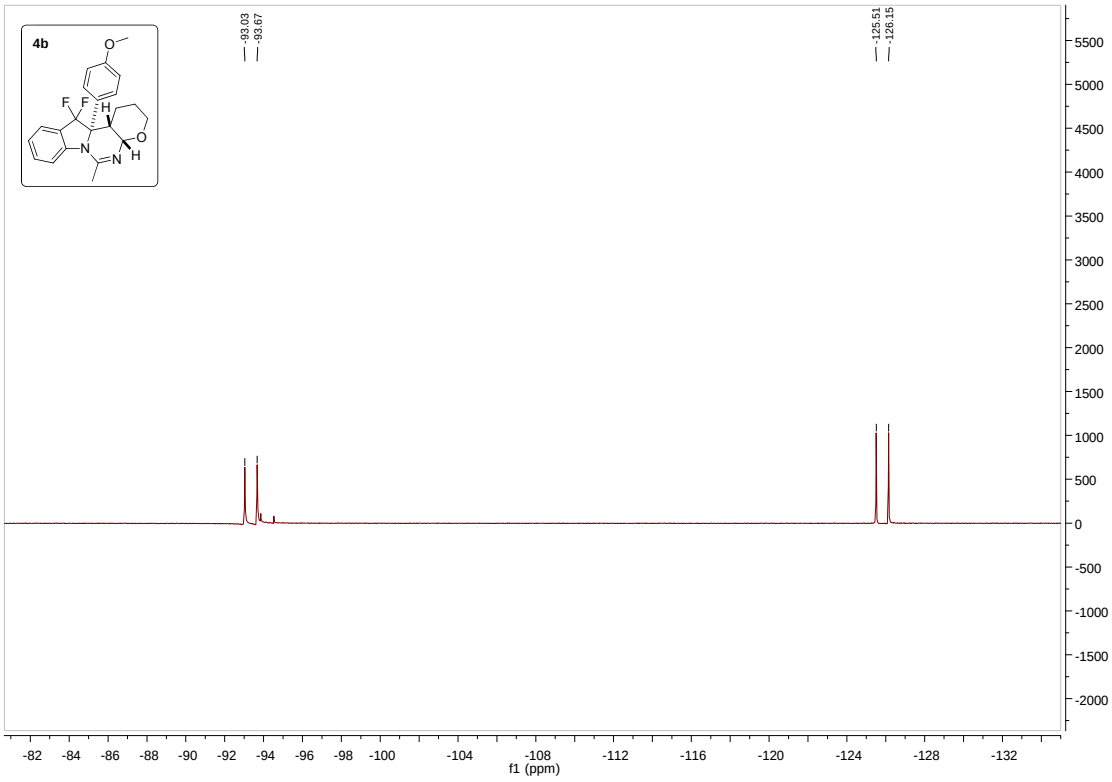


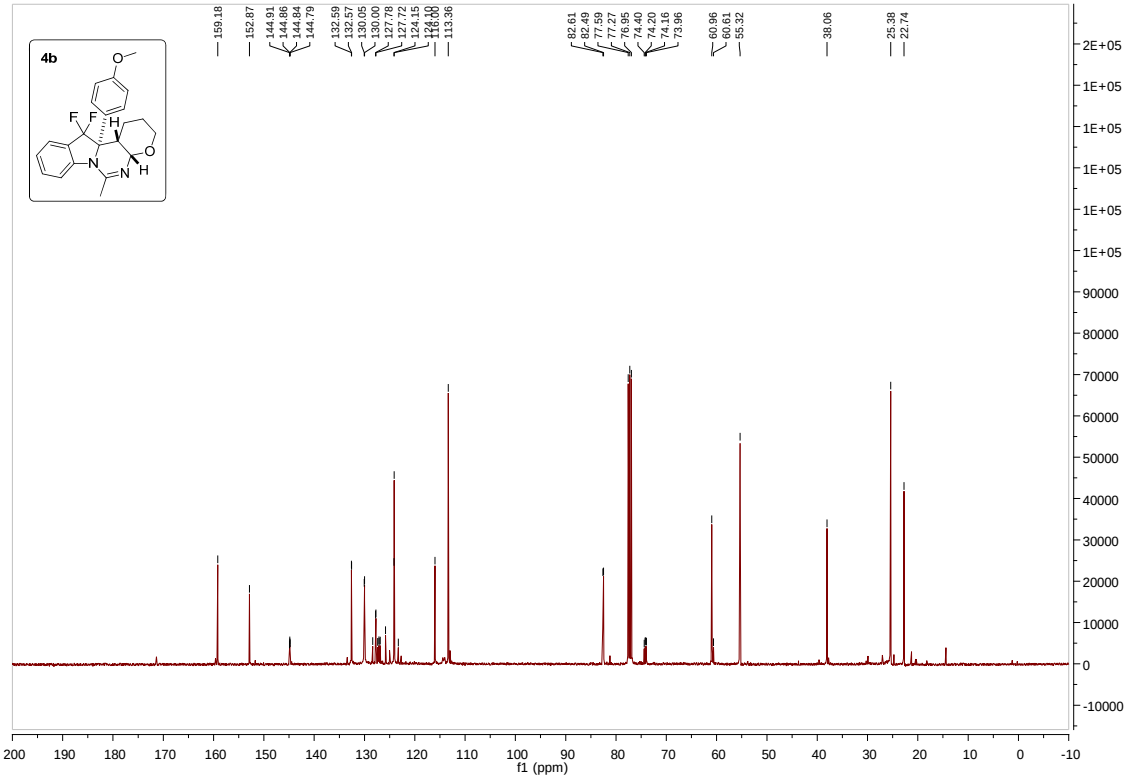



4a
F
F
H
N
O
H
N
152.62
145.06
145.01
144.98
144.94
136.11
132.66
132.63
128.88
128.84
127.94
124.09
124.06
82.63
82.51
74.75
74.55
74.51
74.31
60.64
38.27
25.59
25.53
22.74
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

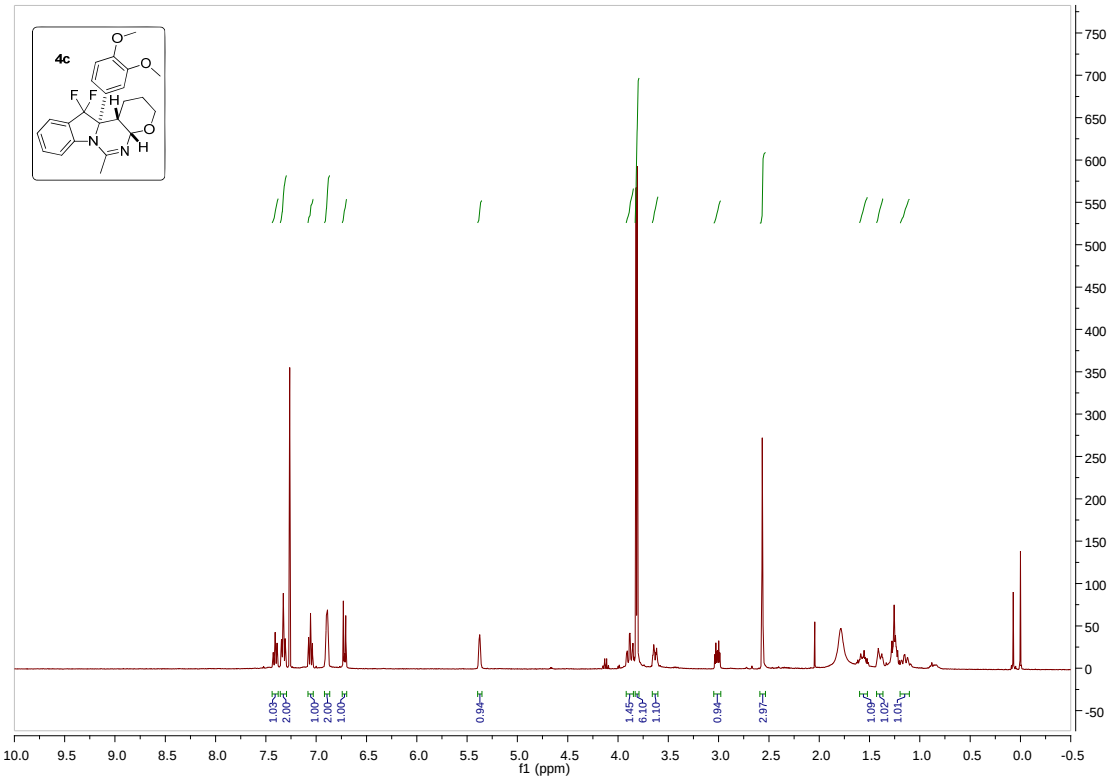
(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-12a-(4-methoxyphenyl)-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole (4b)

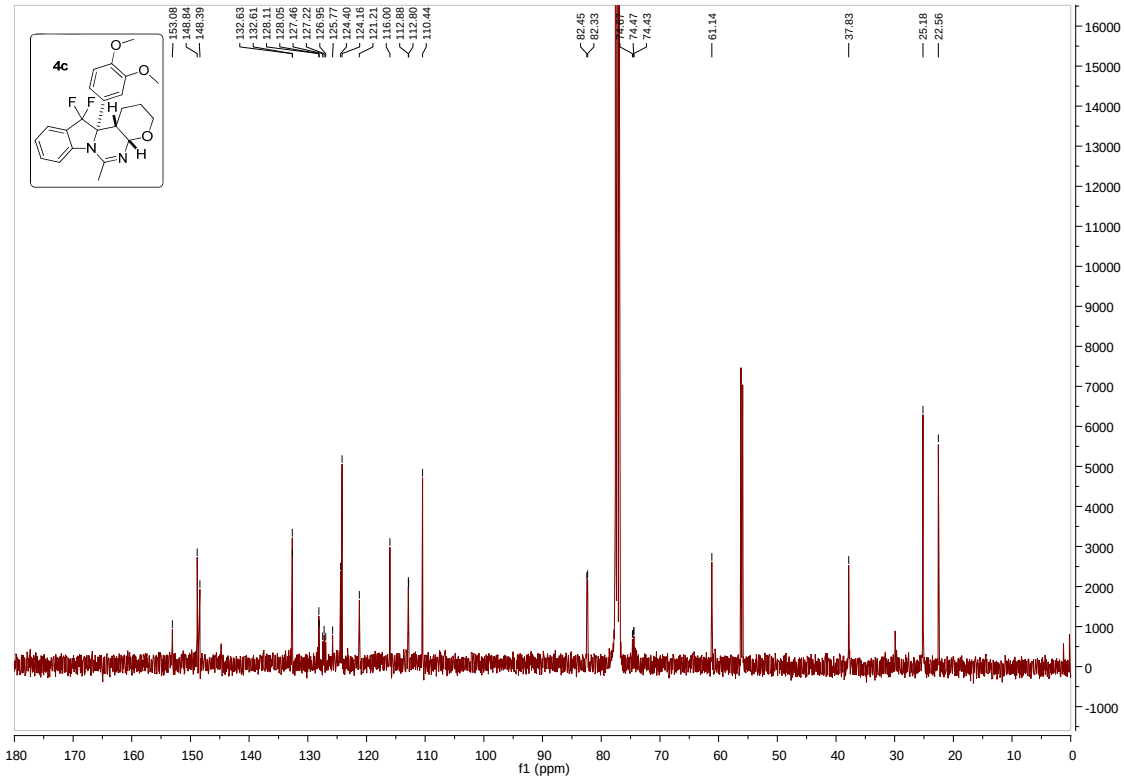




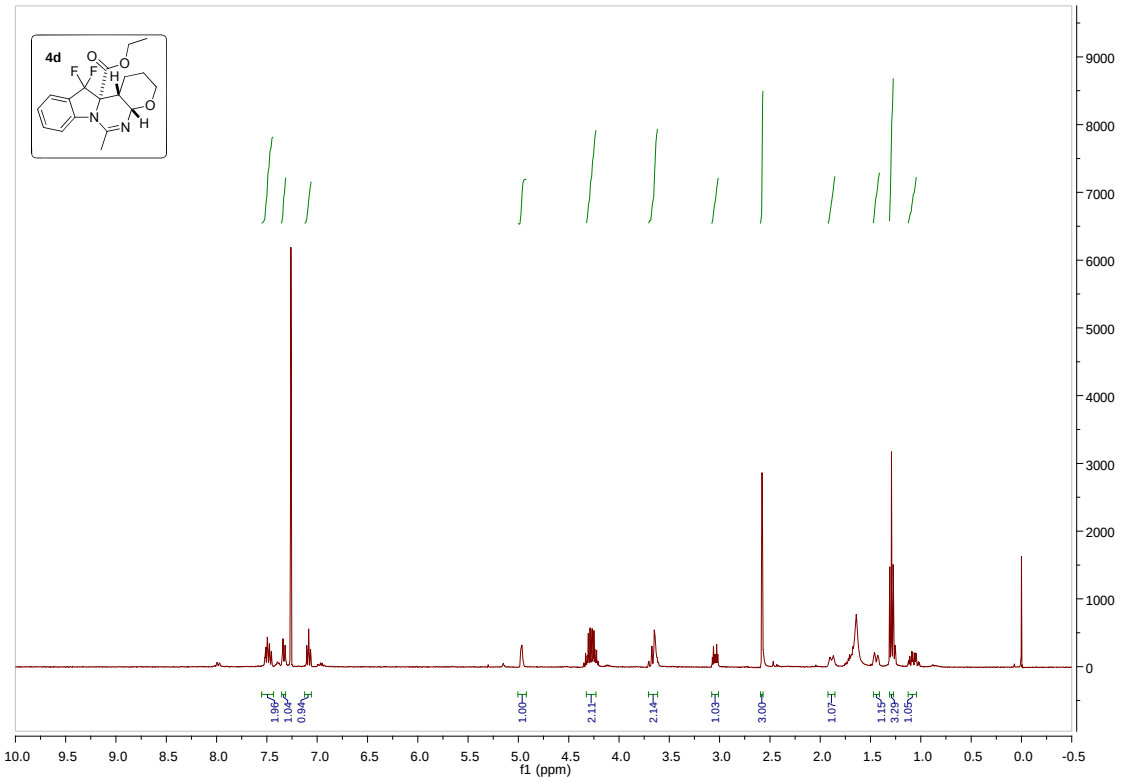

4b
159.18
152.87
144.91
144.86
144.84
144.79
132.59
132.57
130.05
130.00
127.78
127.72
124.15
124.10
124.00
113.36
82.61
82.49
77.59
77.27
76.95
74.40
74.20
74.16
73.96
60.96
60.61
55.32
38.06
25.38
22.74
f1 (ppm)

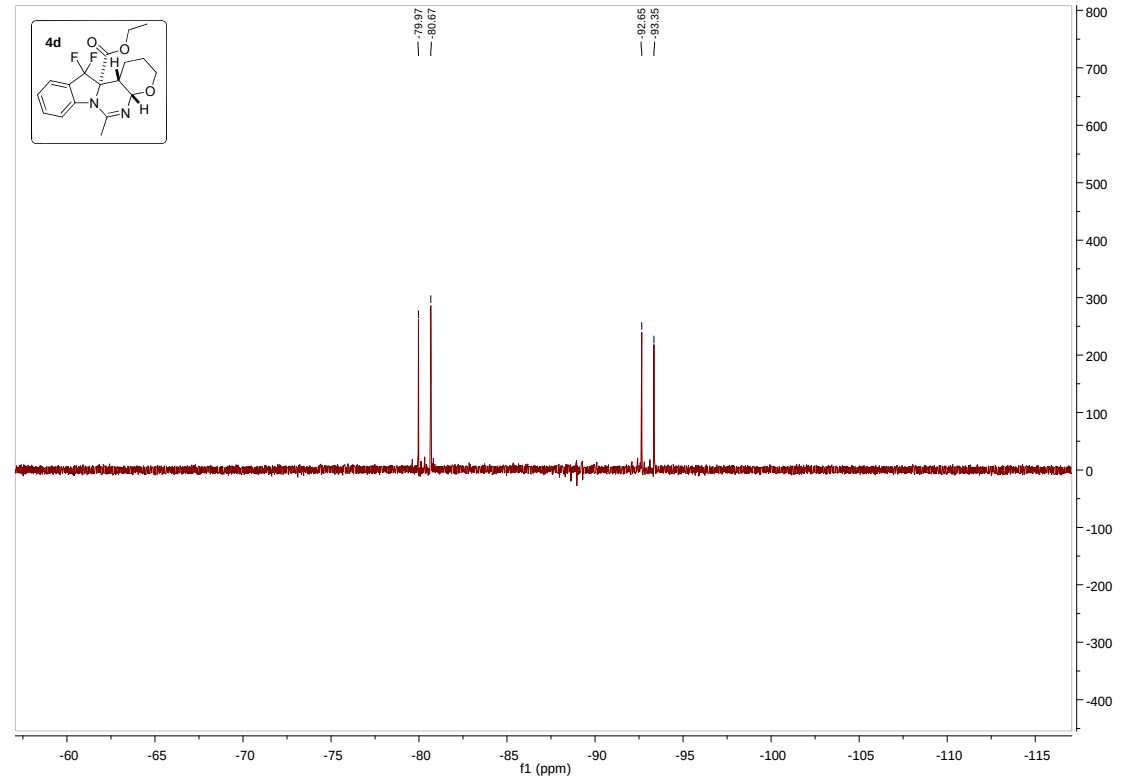
(4a*RS*,12a*RS*,12b*RS*)-12a-(3,4-dimethoxyphenyl)-12,12-difluoro-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole (4c)

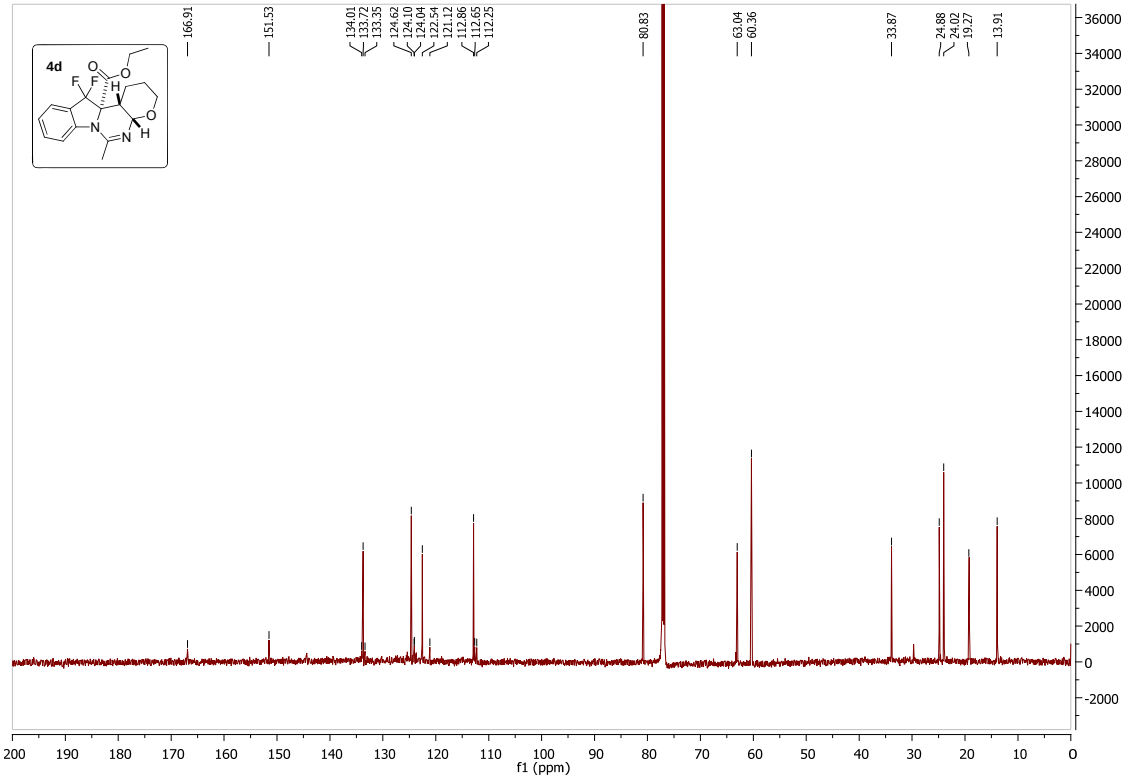




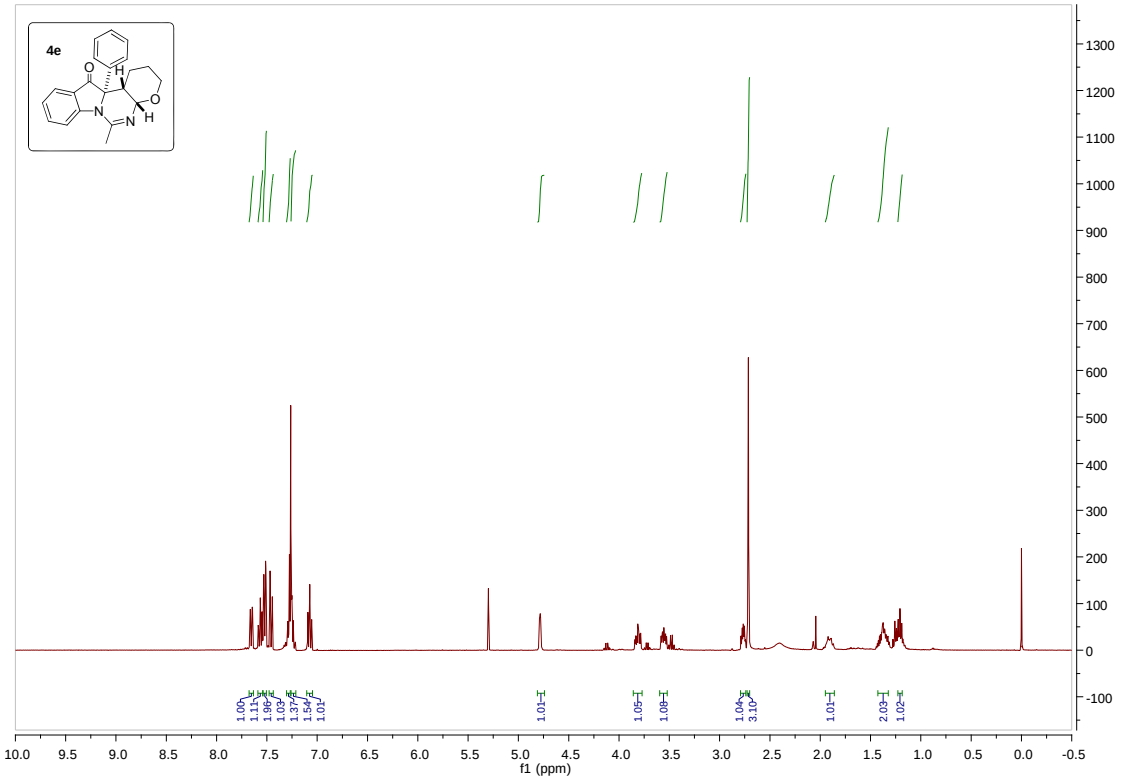
(4a*RS*,12a*RS*,12b*RS*)ethyl 12,12-difluoro-6-methyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole-12a-carboxylate (4d)

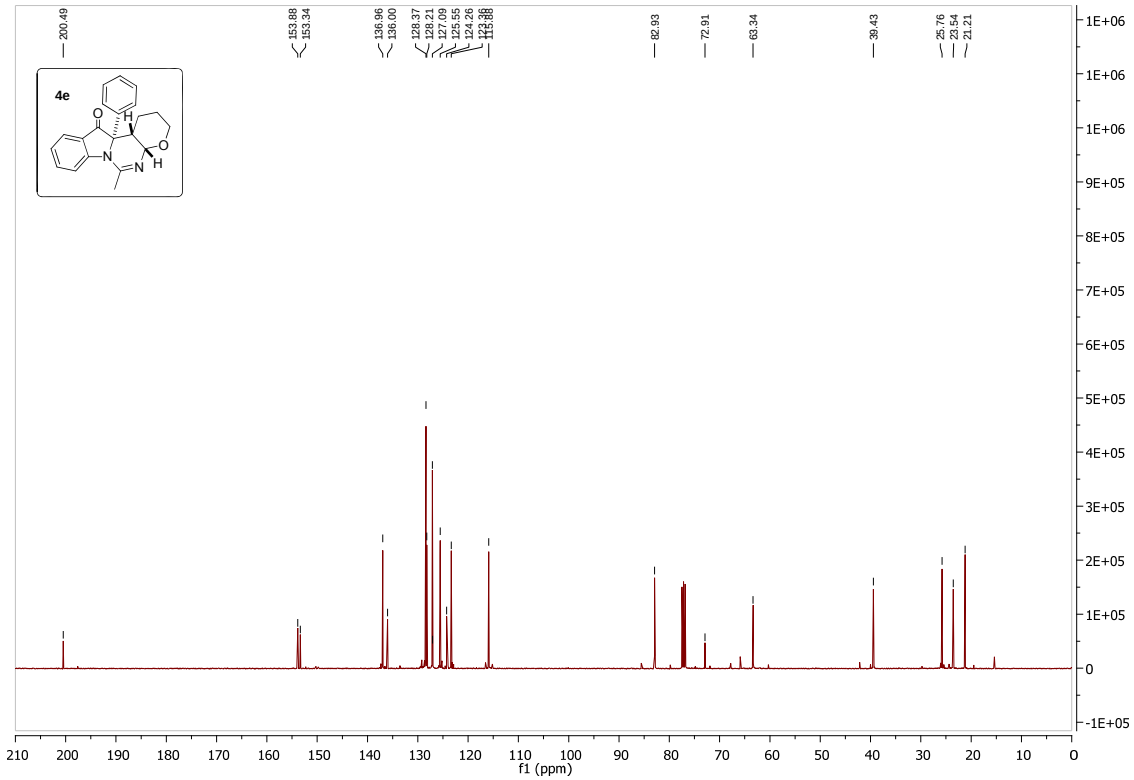




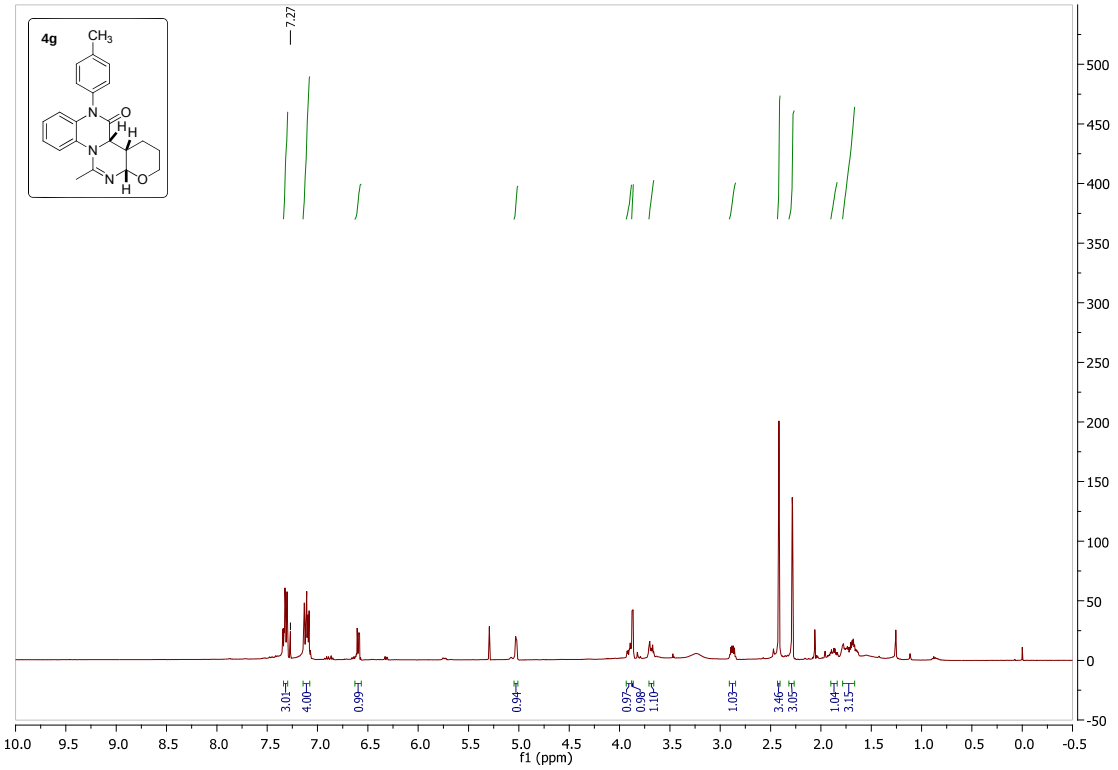

4d
166.91
151.53
134.01
133.72
133.35
124.62
124.10
124.04
122.54
121.12
112.86
112.65
112.25
80.83
63.04
60.36
33.87
24.88
24.02
19.27
13.91
f1 (ppm)

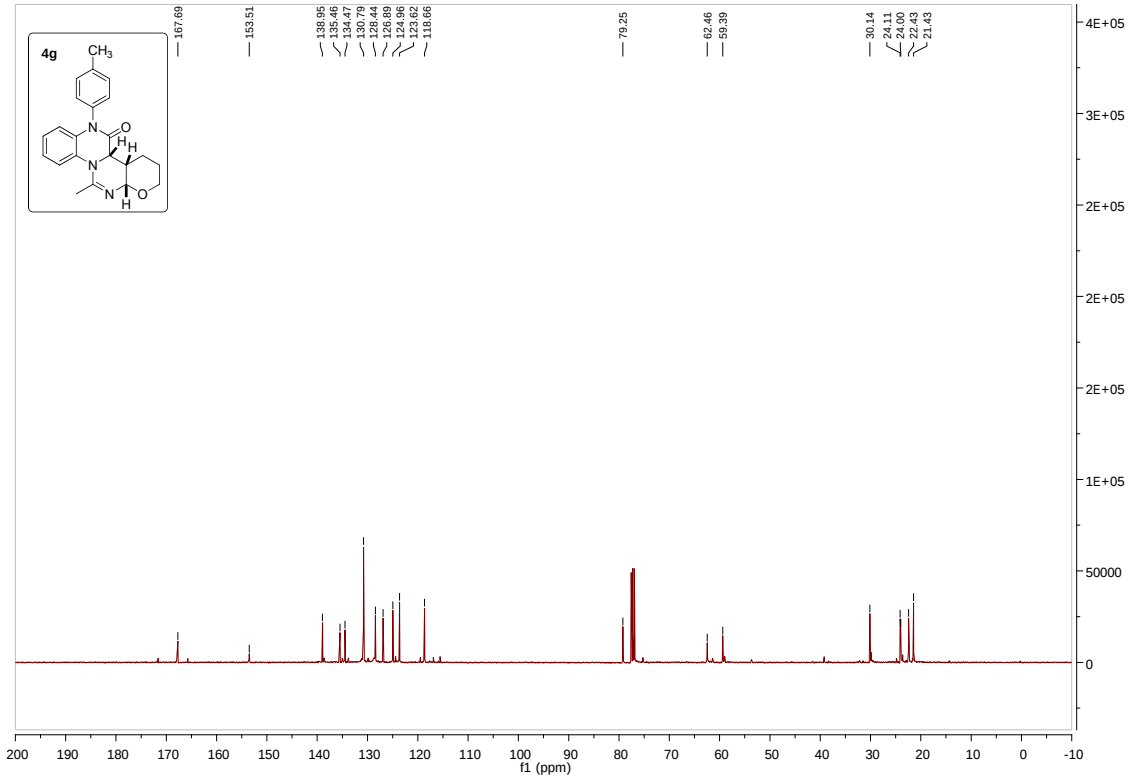
(4a*RS*,12a*RS*,12b*RS*)-6-methyl-12a-phenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4aH)-one (4e)



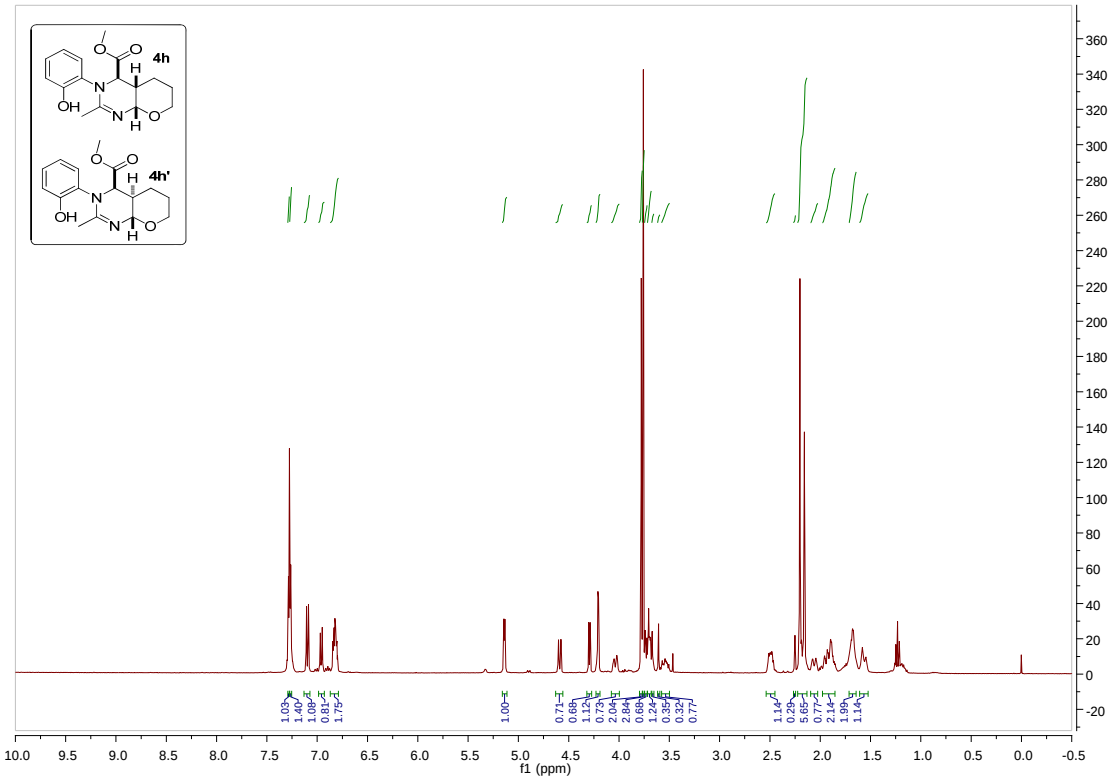


(4a*RS*,4b*RS*,13a*RS*)-12-methyl-6-(*p*-tolyl)-2,3,4,4a,6,13a-hexahydropyrano[2',3':4,5]pyrimido[1,6-*a*]quinoxalin-5(4b*H*)-one (4g)

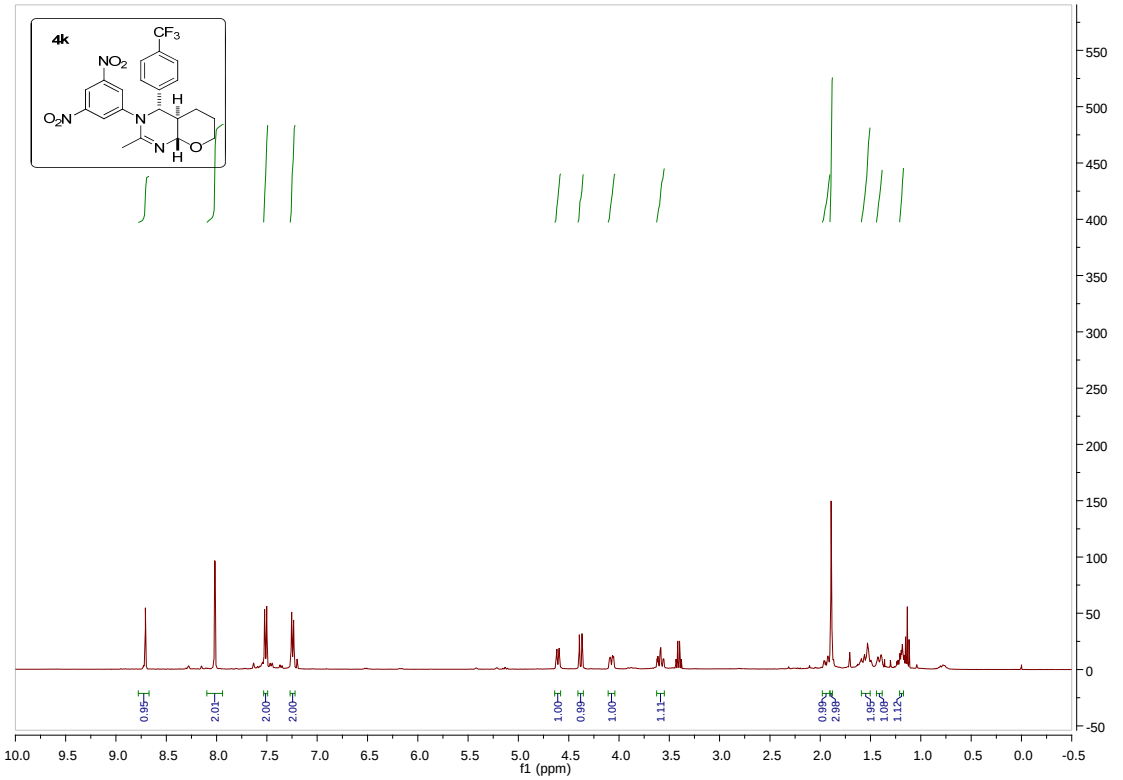


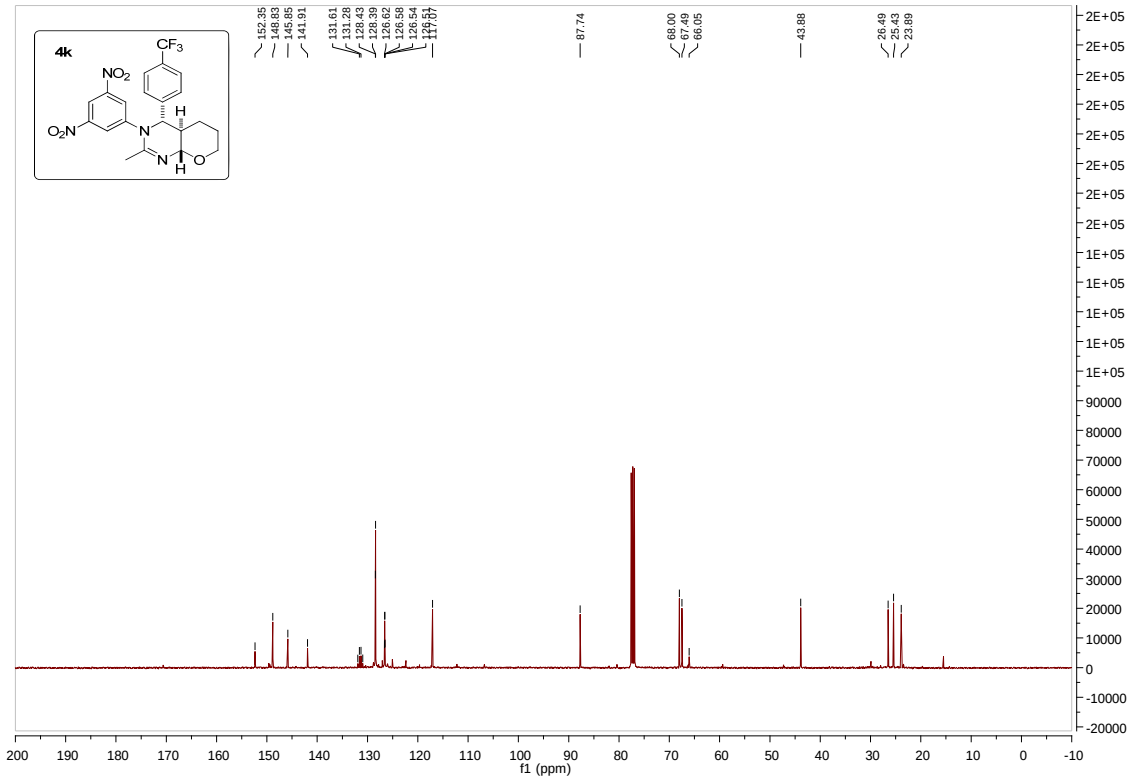


(4*RS*,4a*RS*,8a*RS*)-methyl 3-(2-hydroxyphenyl)-2-methyl-4,4a,5,6,7,8a-hexahydro-3*H*-pyrano[2,3-d]pyrimidine-4-carboxylate (4h)

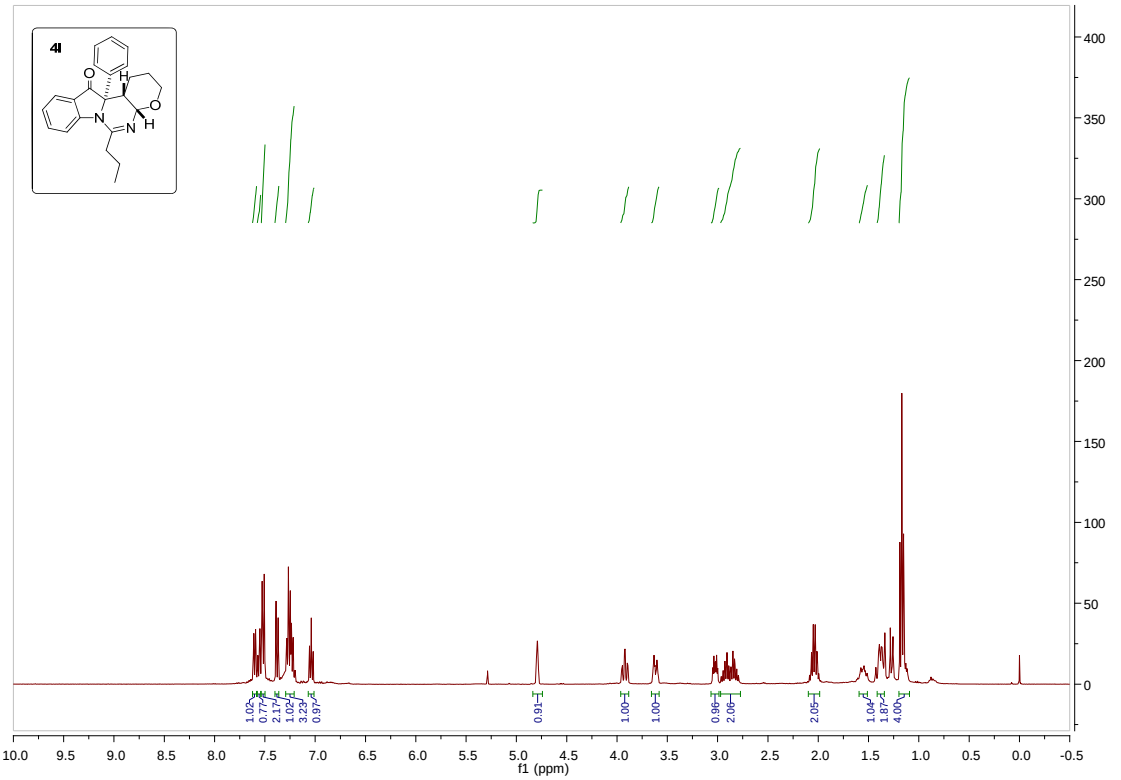


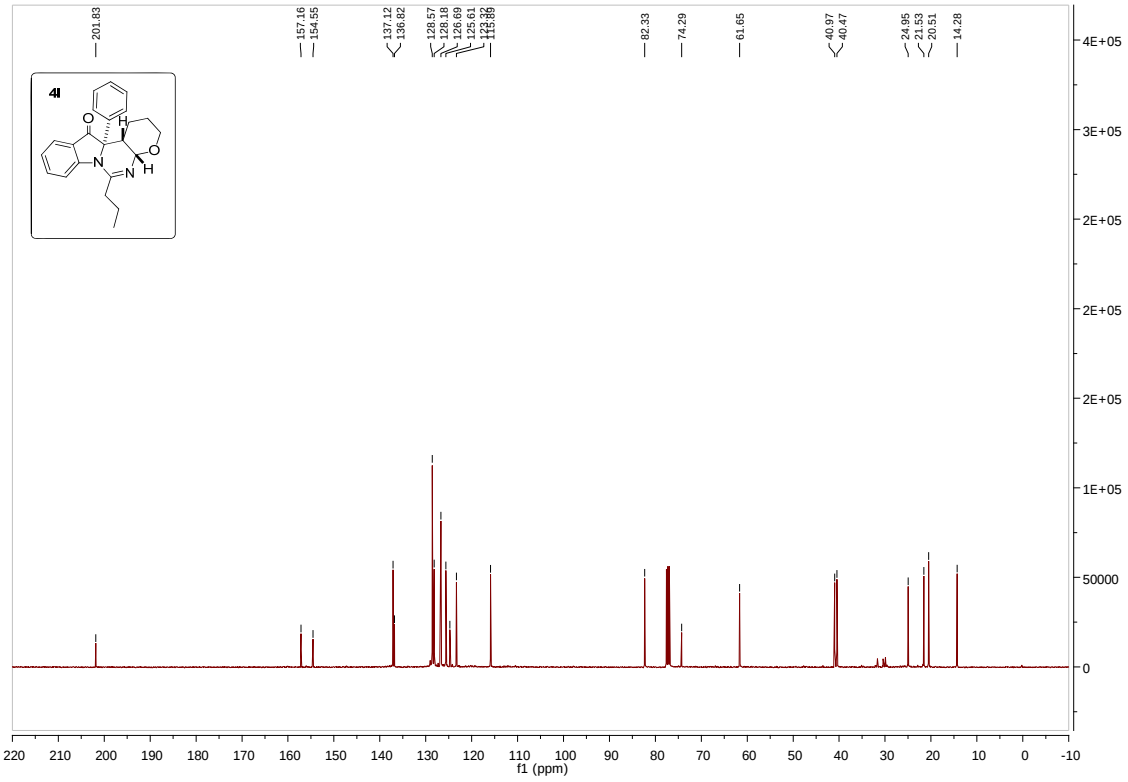
(4*RS*,4a*SR*,8a*RS*)-3-(3,5-dinitrophenyl)-2-methyl-4-(4-(trifluoromethyl)phenyl)-4,4a,5,6,7,8a-hexahydro-3*H*-pyrano[2,3-*d*]pyrimidine (4k)



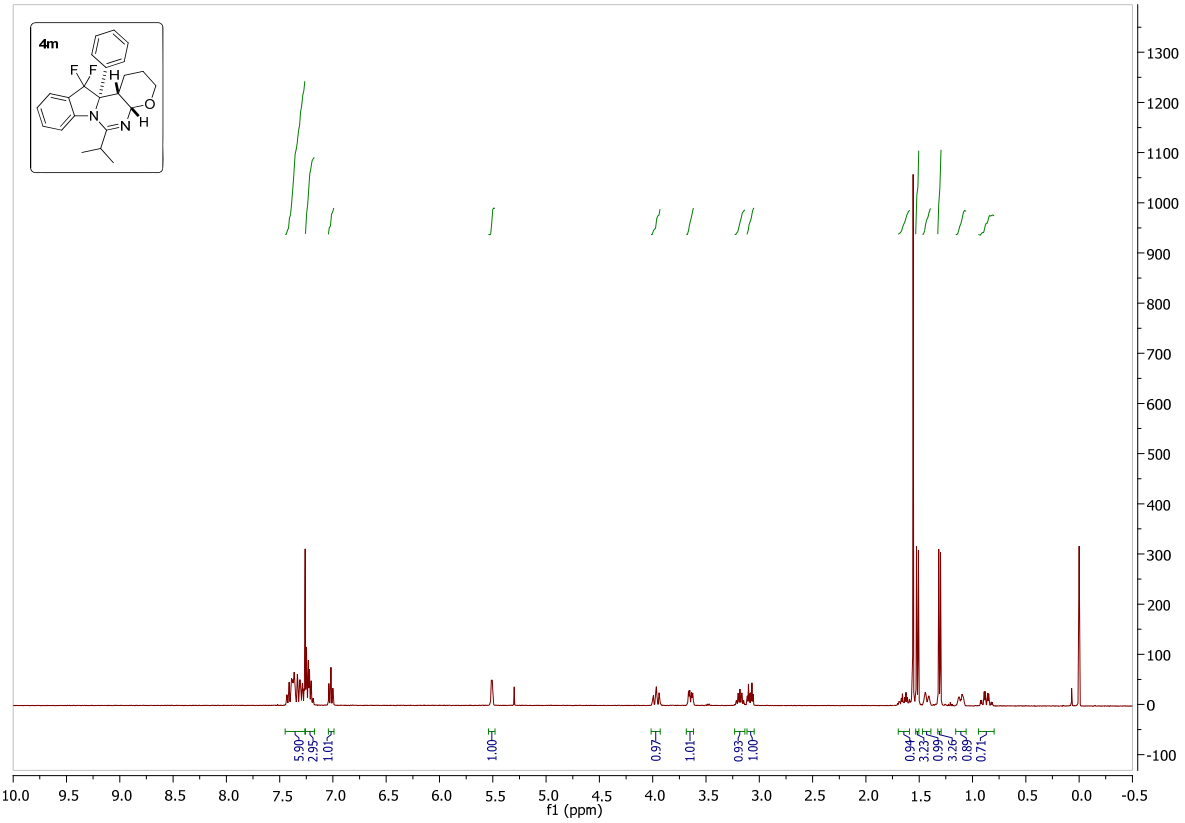


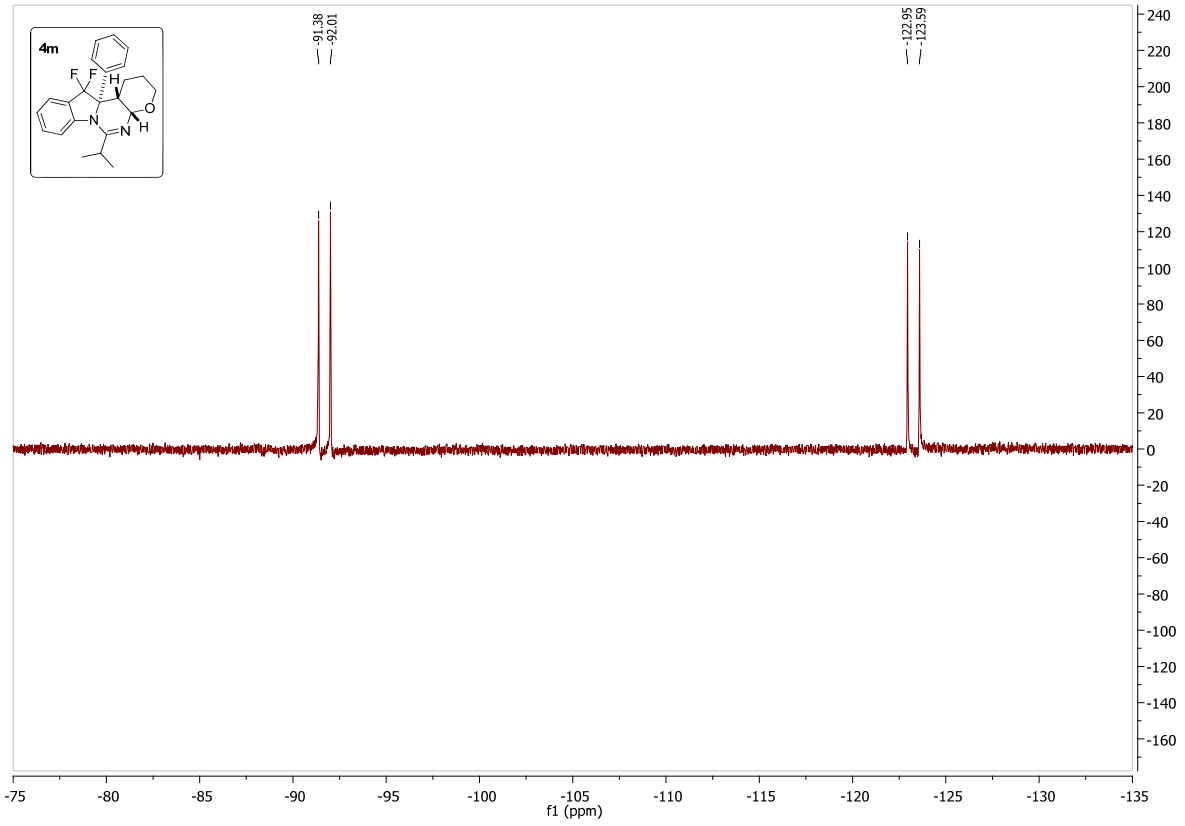
(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-propyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indol-12(4a*H*)-one (4l)

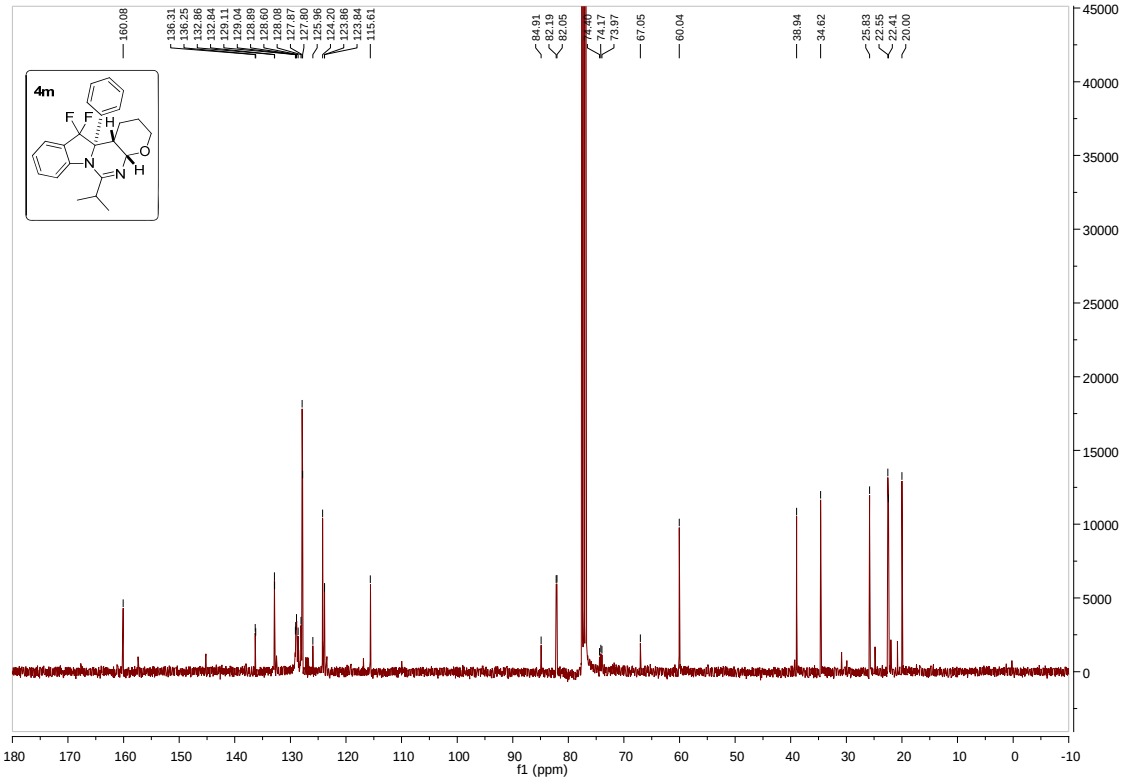




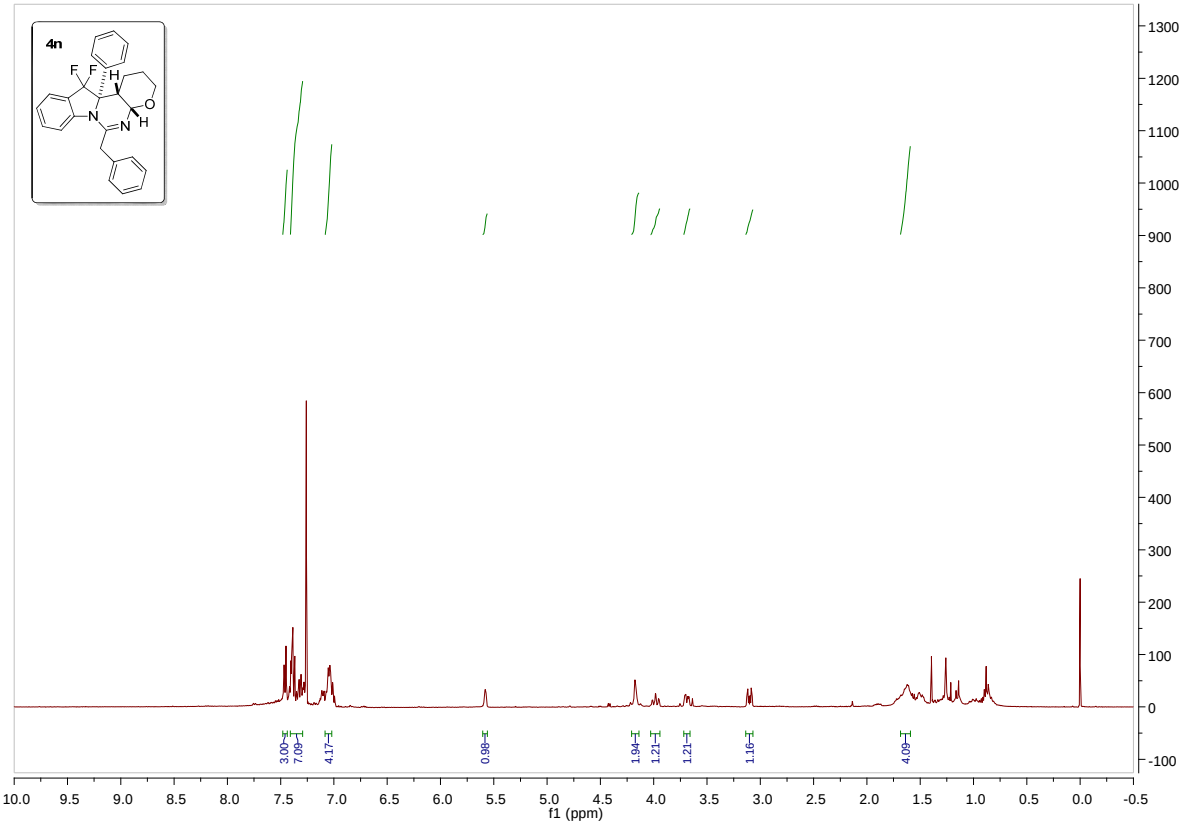
(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-6-isobutyl-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole (4m)

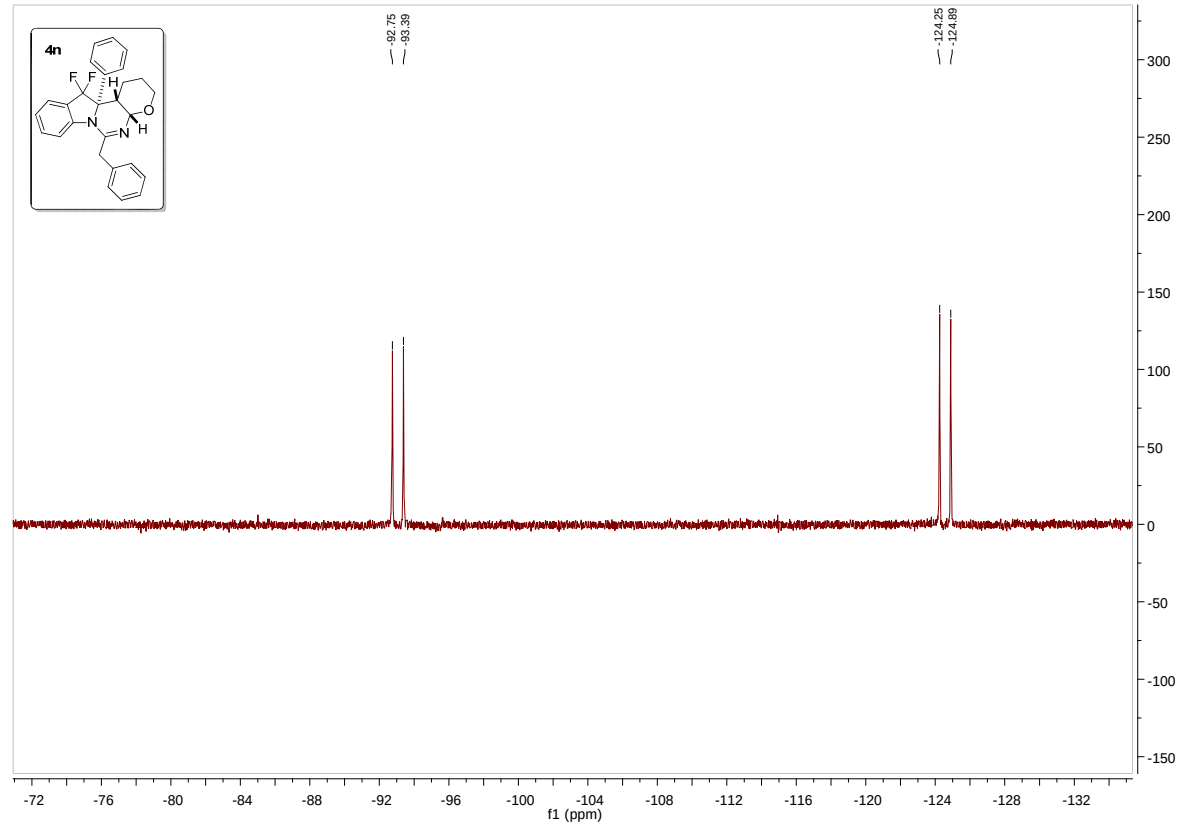




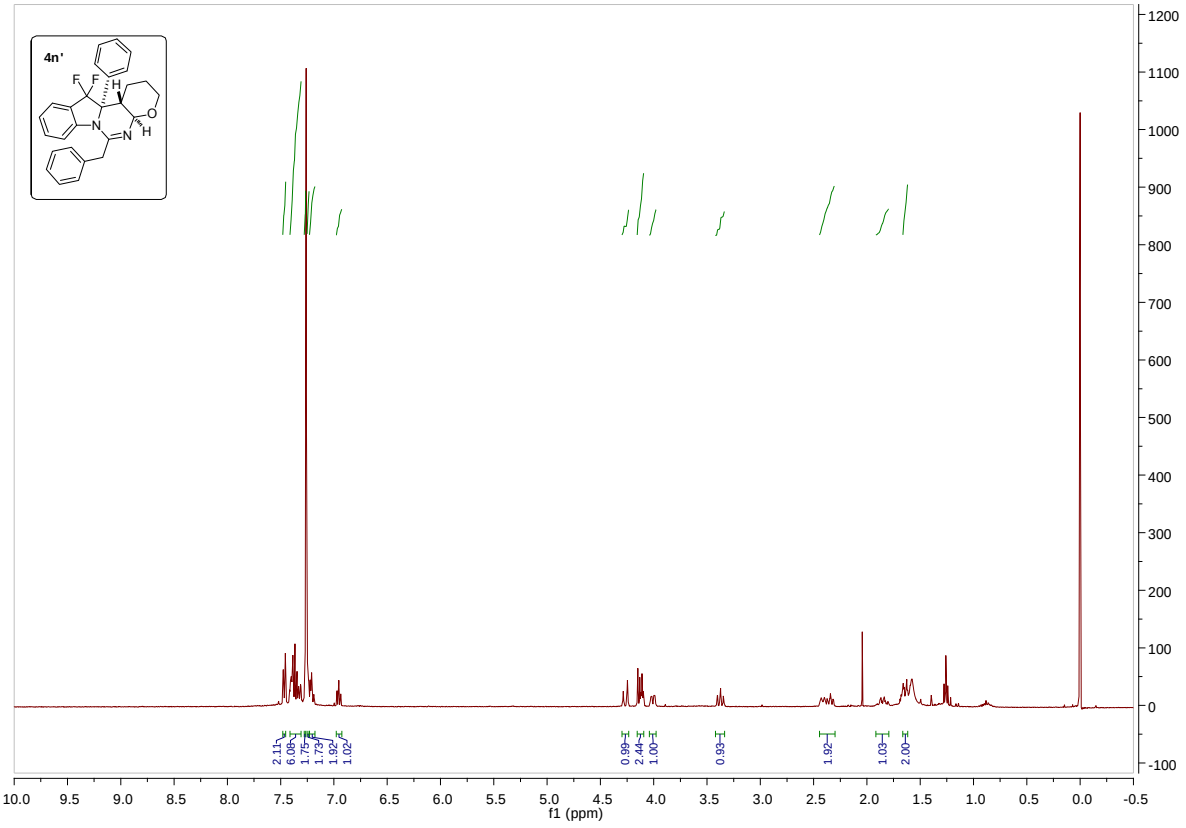

4m
160.08
136.31
136.25
132.86
132.84
129.11
129.04
128.89
128.60
128.08
127.87
127.80
125.96
124.20
123.86
123.84
115.61
84.91
82.19
82.05
74.40
74.17
73.97
67.05
60.04
38.94
34.62
25.83
22.55
22.41
20.00
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

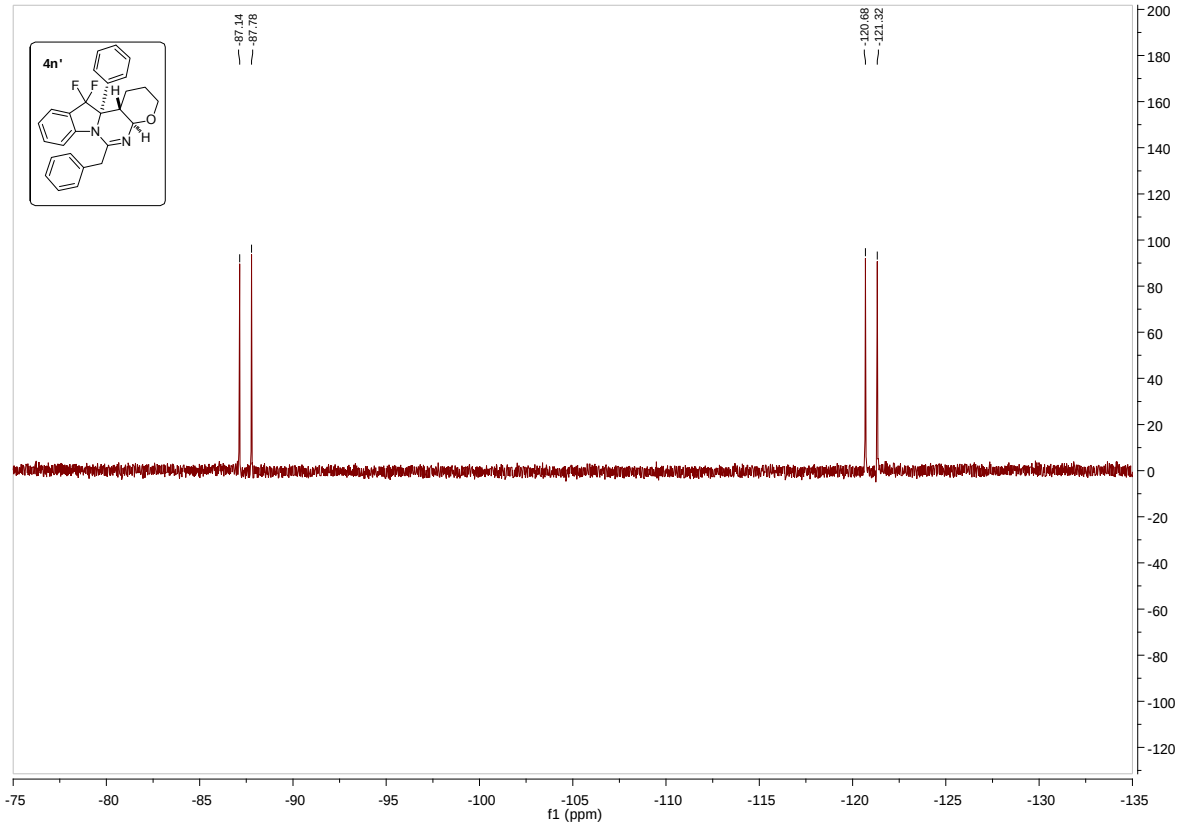
(4a*RS*,12a*RS*,12b*RS*)-6-benzyl-12,12-difluoro-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole (4n)

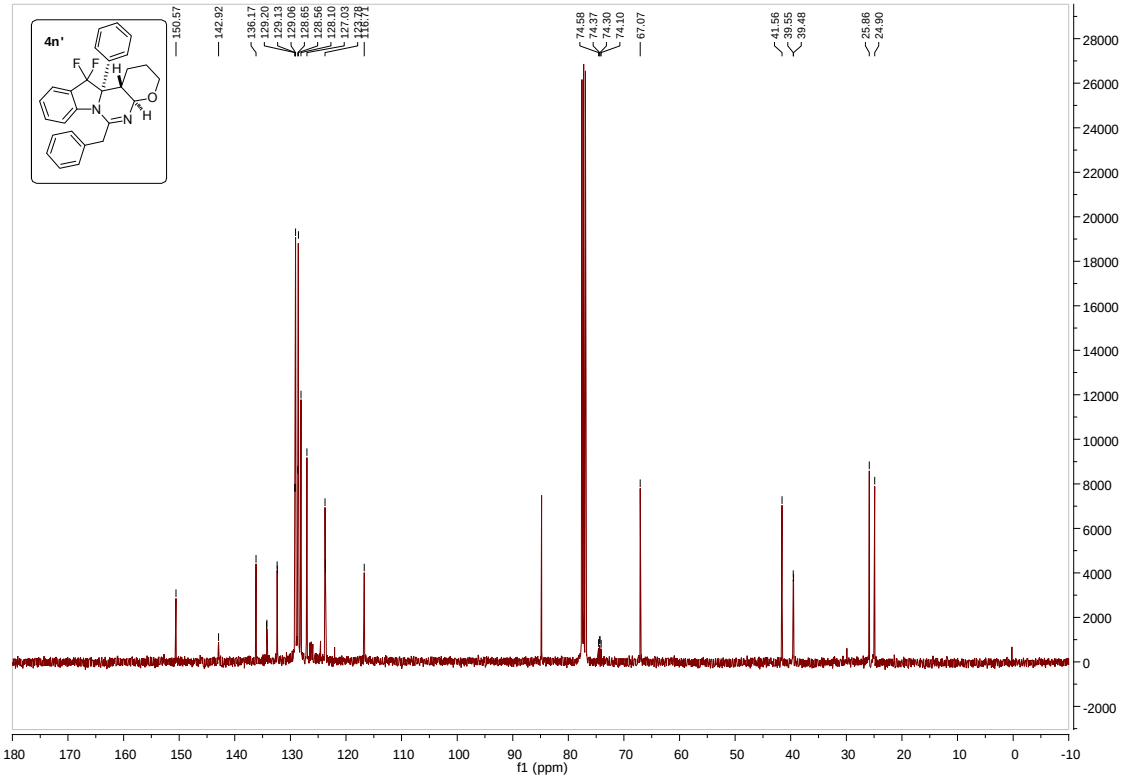




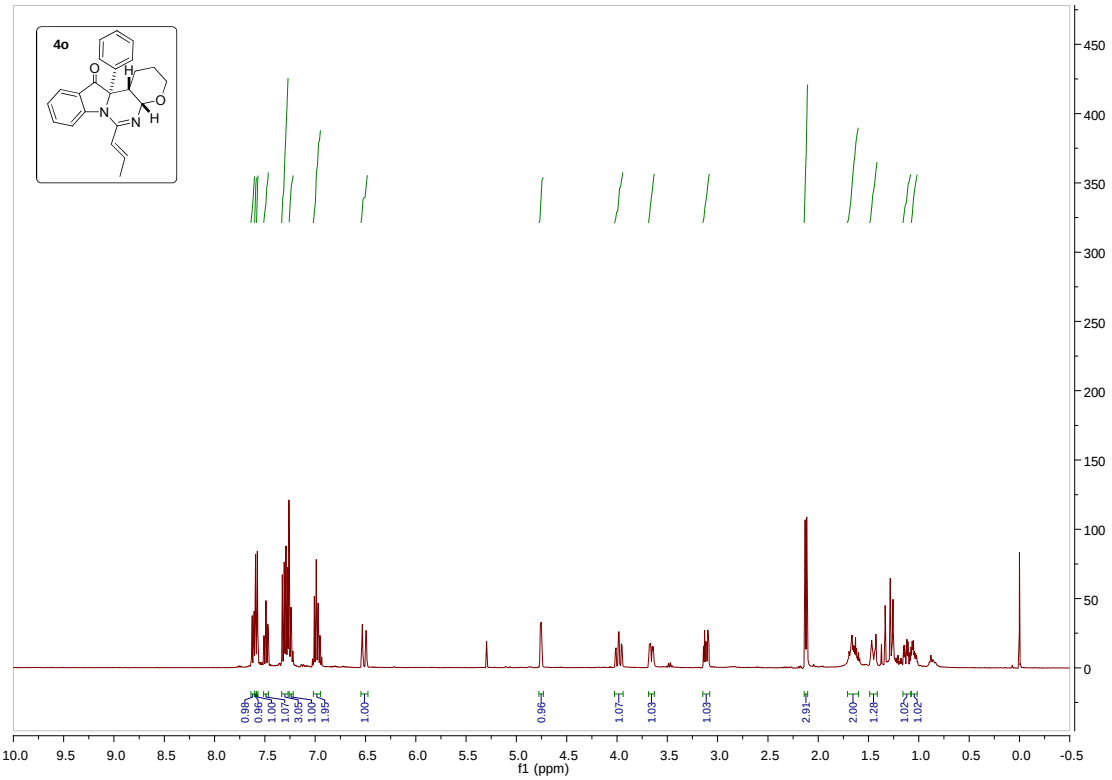
(4a*RS*,12a*SR*,12b*SR*)-6-benzyl-12,12-difluoro-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]índole (4n')

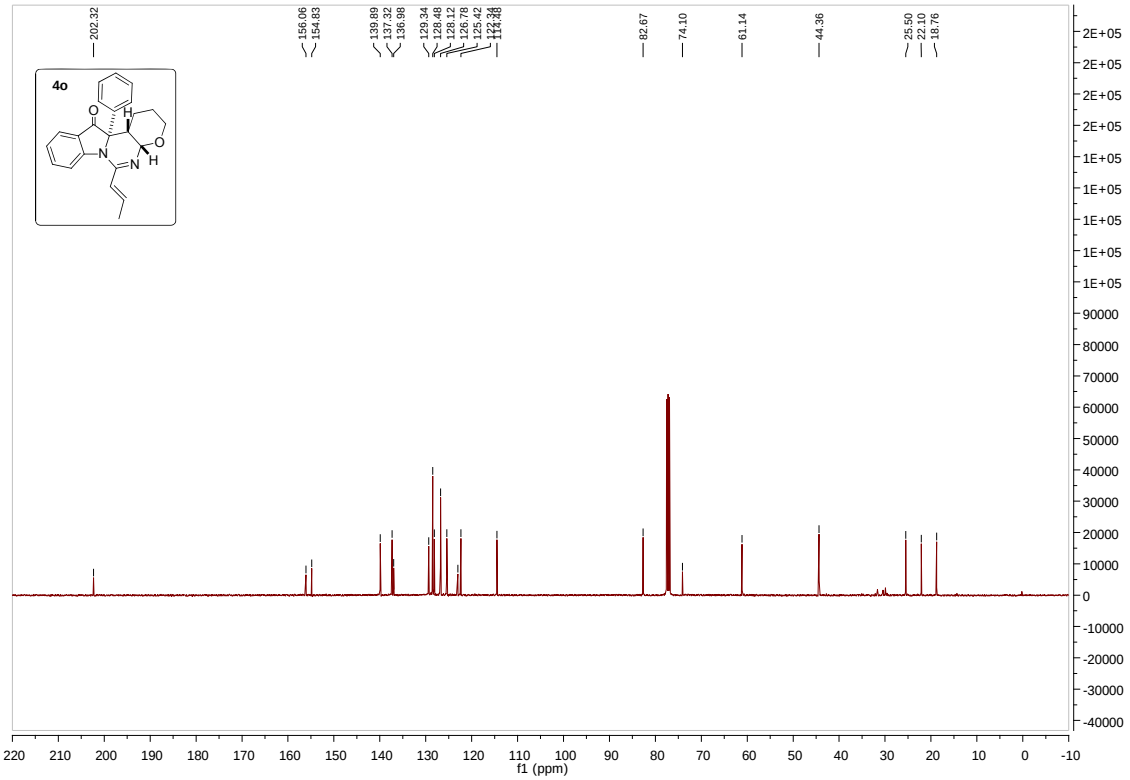




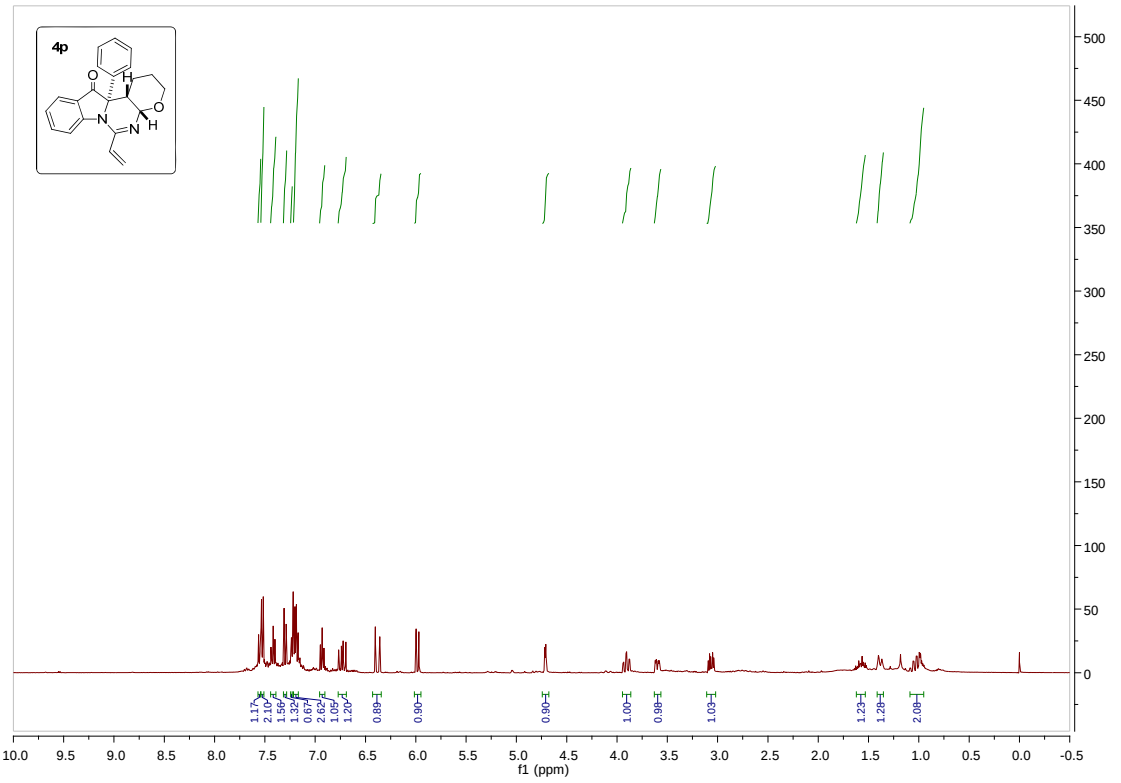

4n'
F
F
H
N
N
H
O
150.57
142.92
136.17
129.20
129.13
129.06
128.65
128.56
128.10
127.03
123.78
116.71
74.58
74.37
74.30
74.10
67.07
41.56
39.55
39.48
25.86
24.90
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

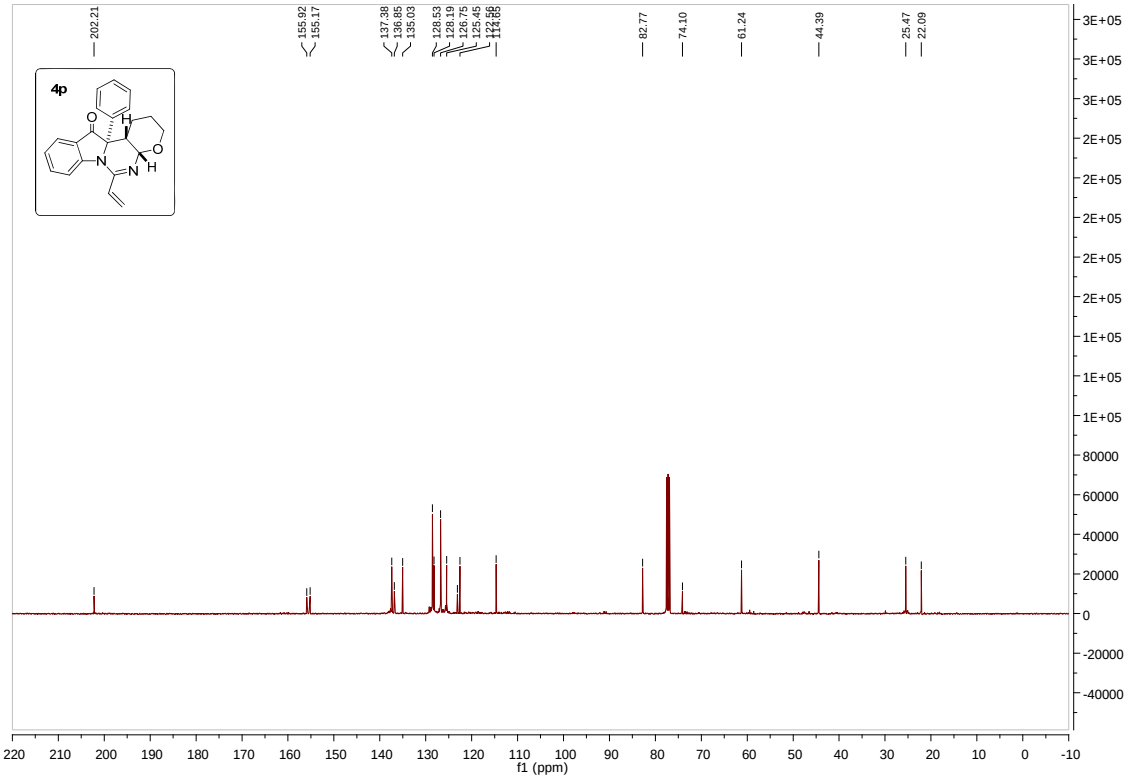
(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-((E)-prop-1-en-1-yl)-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4aH)-one (4o)



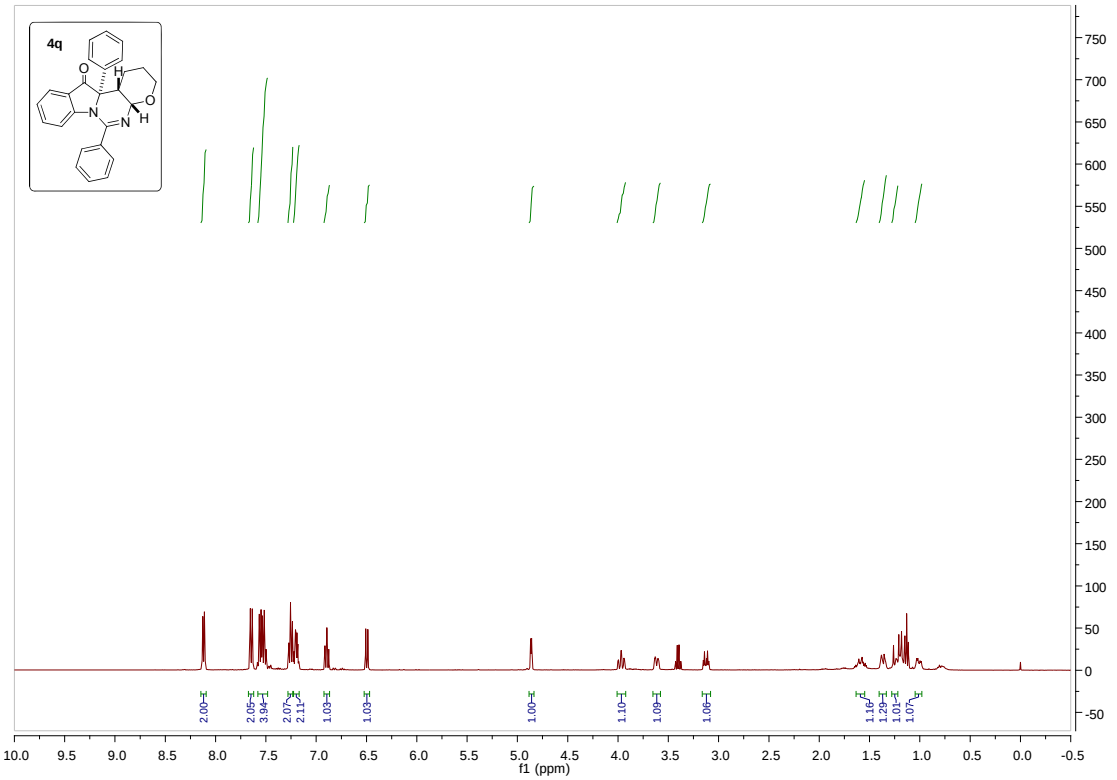


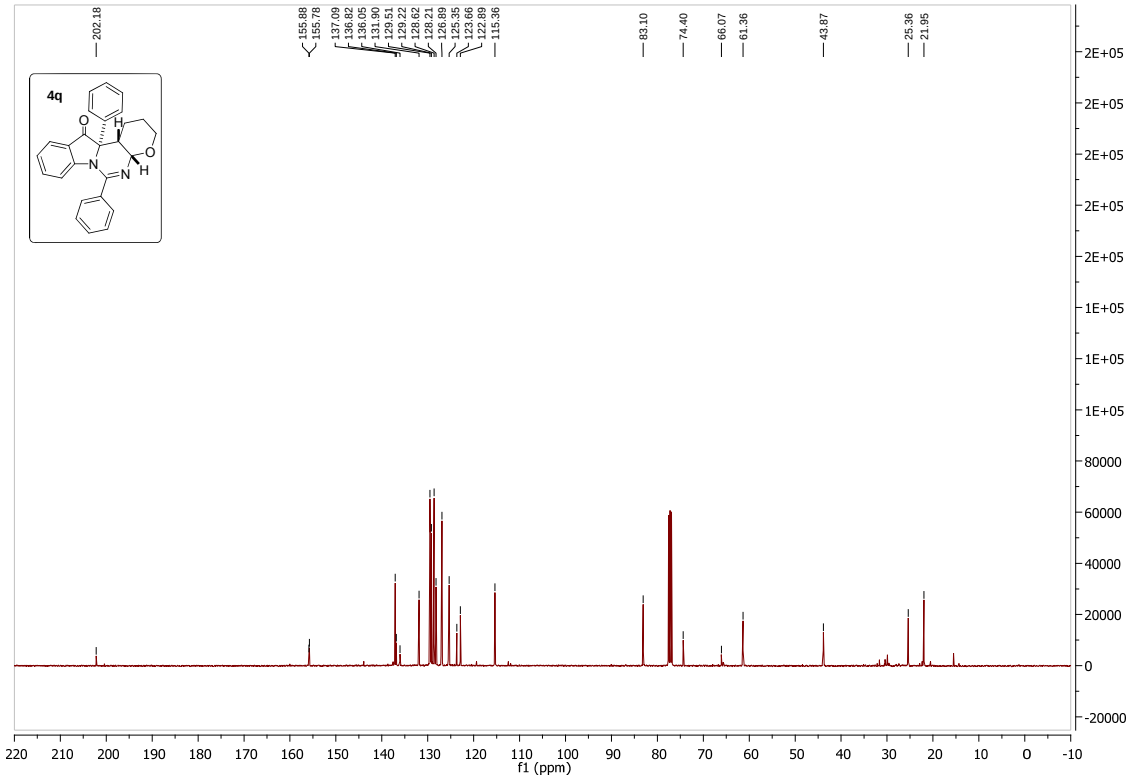
(4a*RS*,12a*RS*,12b*RS*)-12a-phenyl-6-vinyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4aH)-one (4p)



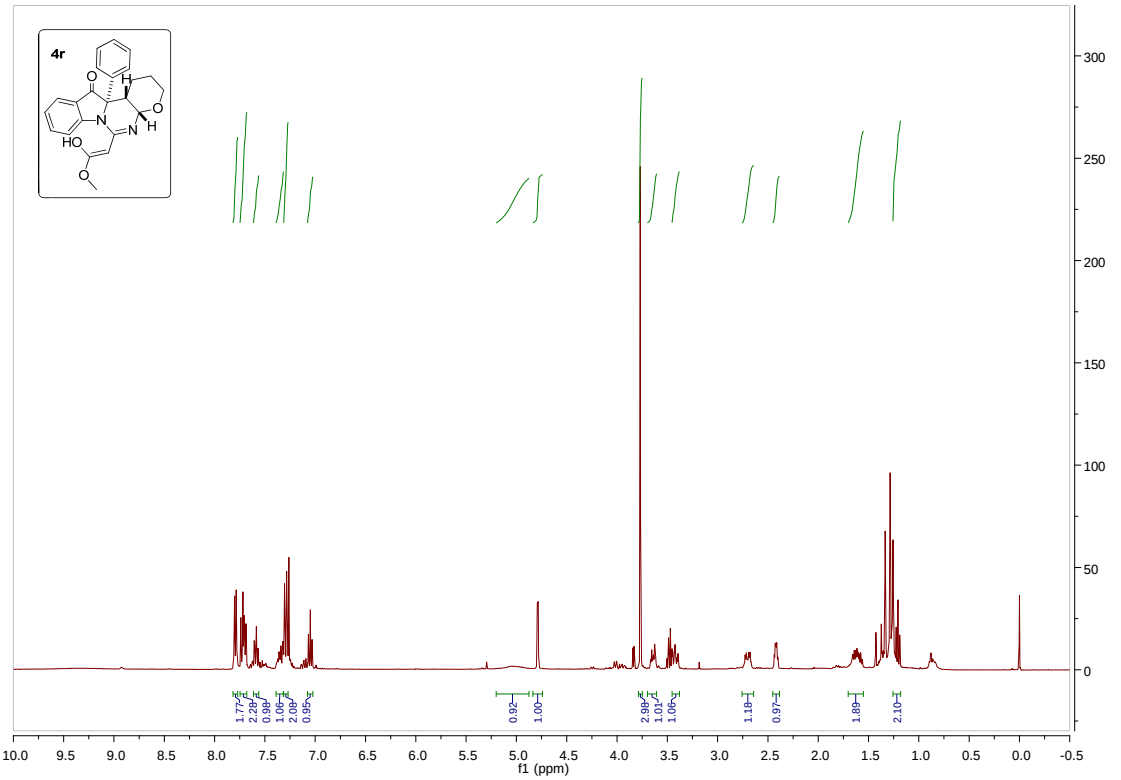


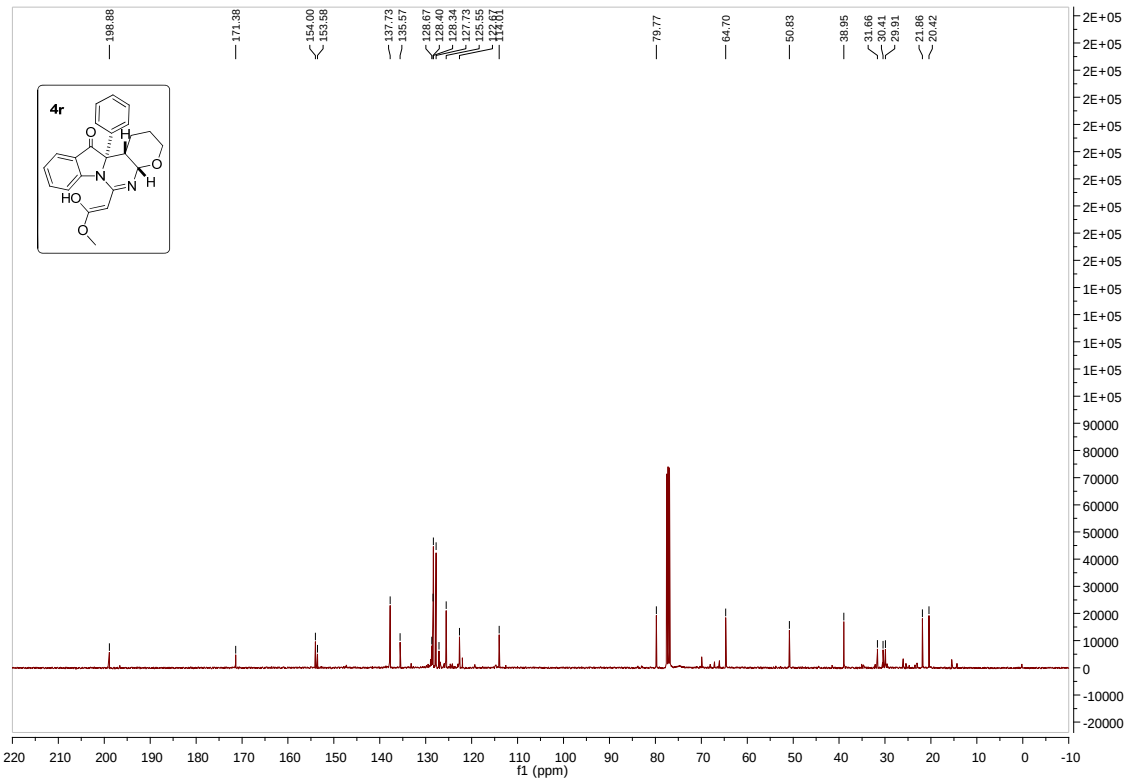
(4a*RS*,12a*RS*,12b*RS*)-6,12a-diphenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4aH)-one (4q)



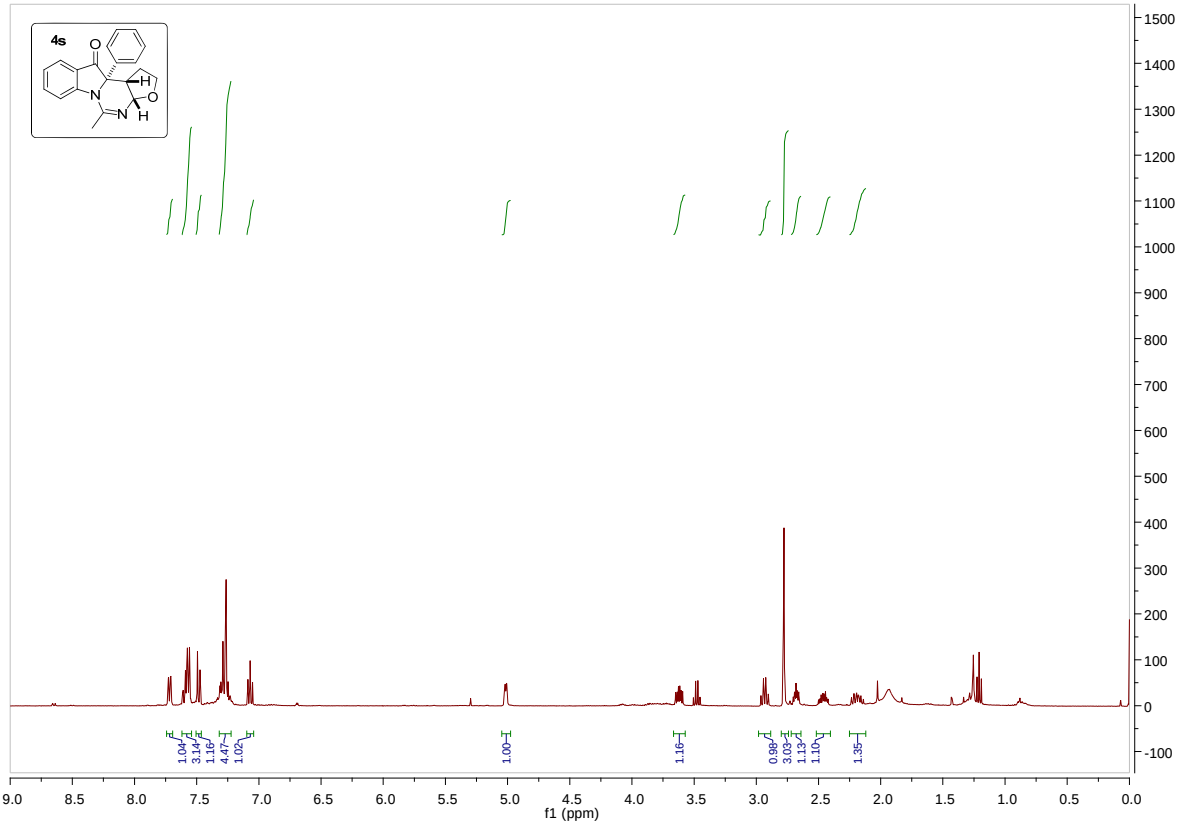


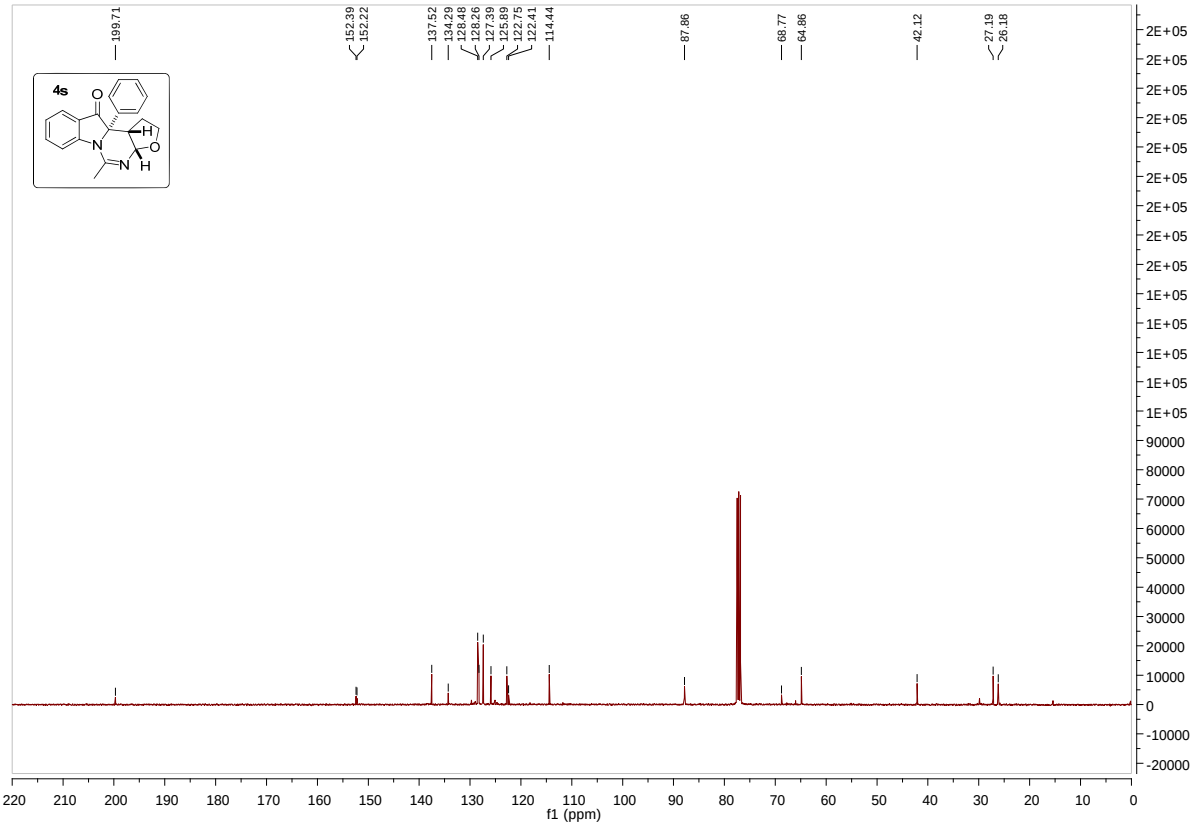
(4a*RS*,12a*RS*,12b*RS*)-6-((E)-2-hydroxy-2-methoxyvinyl)-12a-phenyl-2,3,12a,12b-tetrahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indol-12(4a*H*)-one (4r)



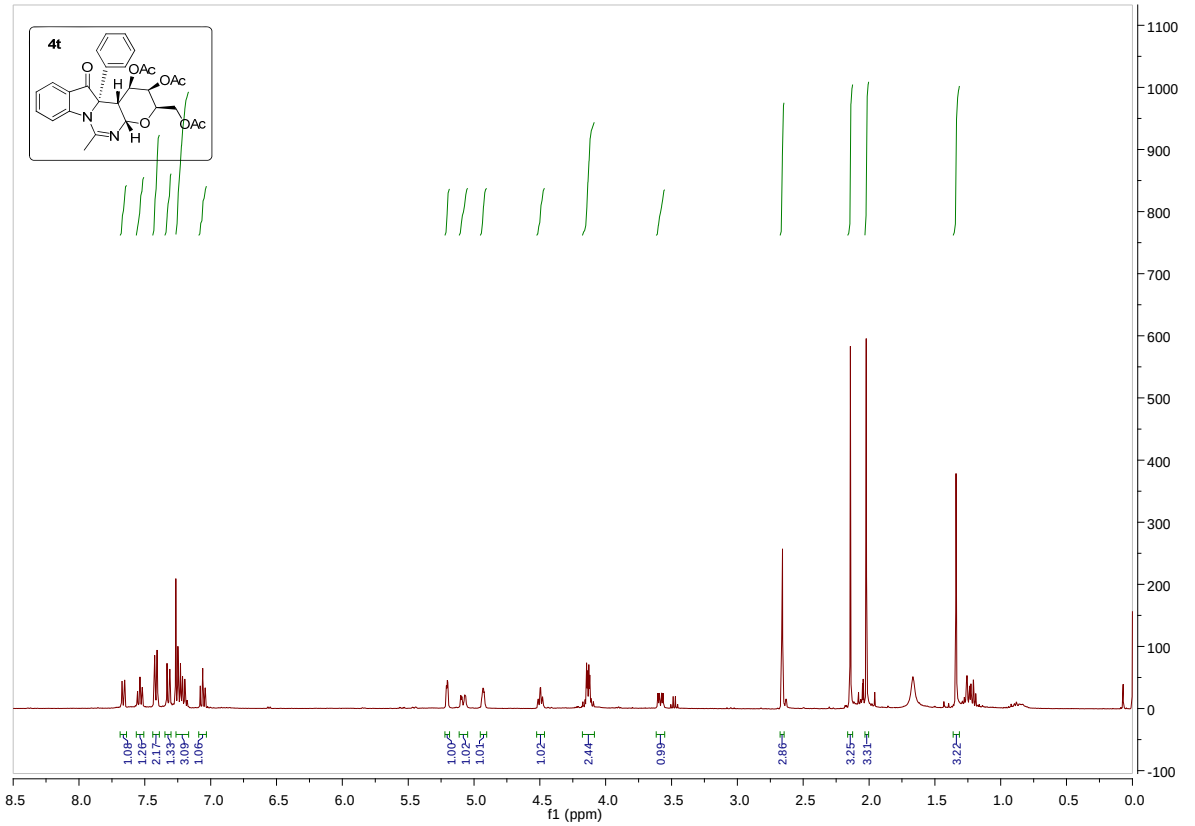


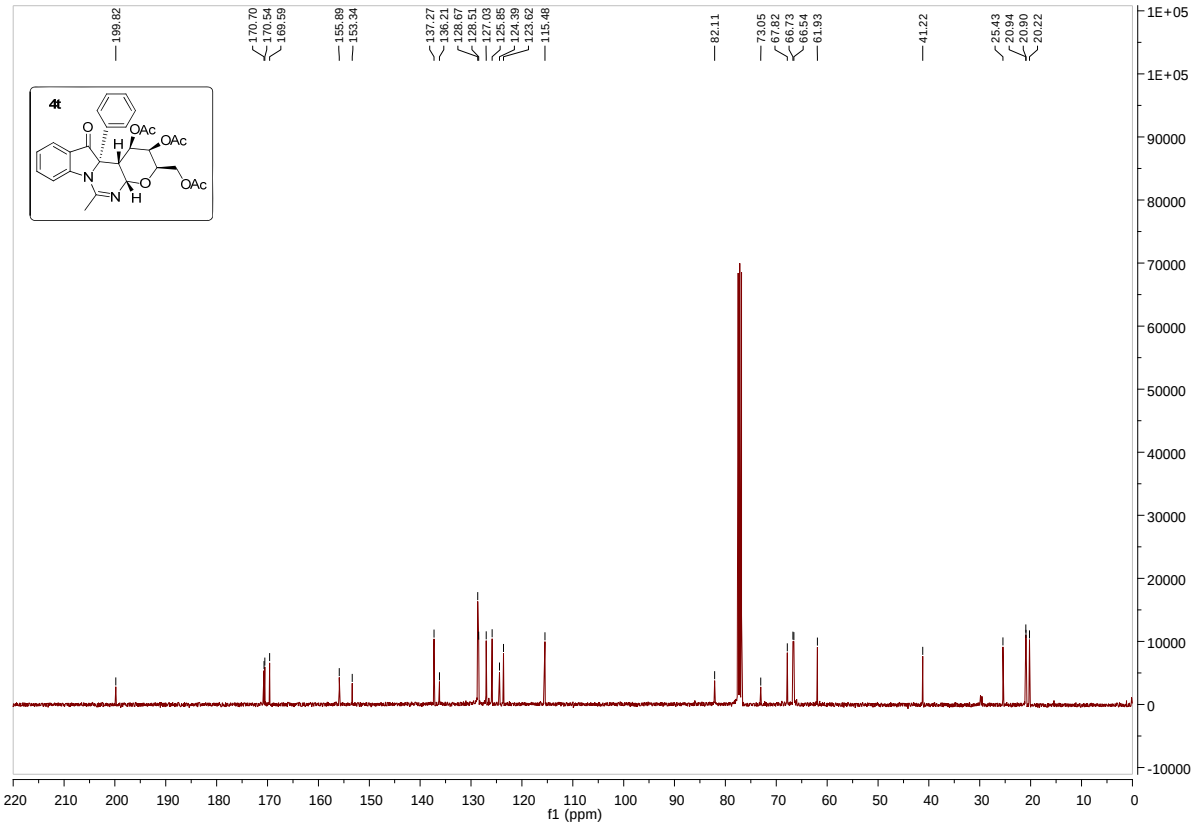
(3a*RS*,11a*RS*,11b*RS*)-5-methyl-11a-phenyl-1,3a,11a,11b-tetrahydrofuro[2',3':4,5]pyrimido[1,6-*a*]indol-11(2*H*)-one (4s)



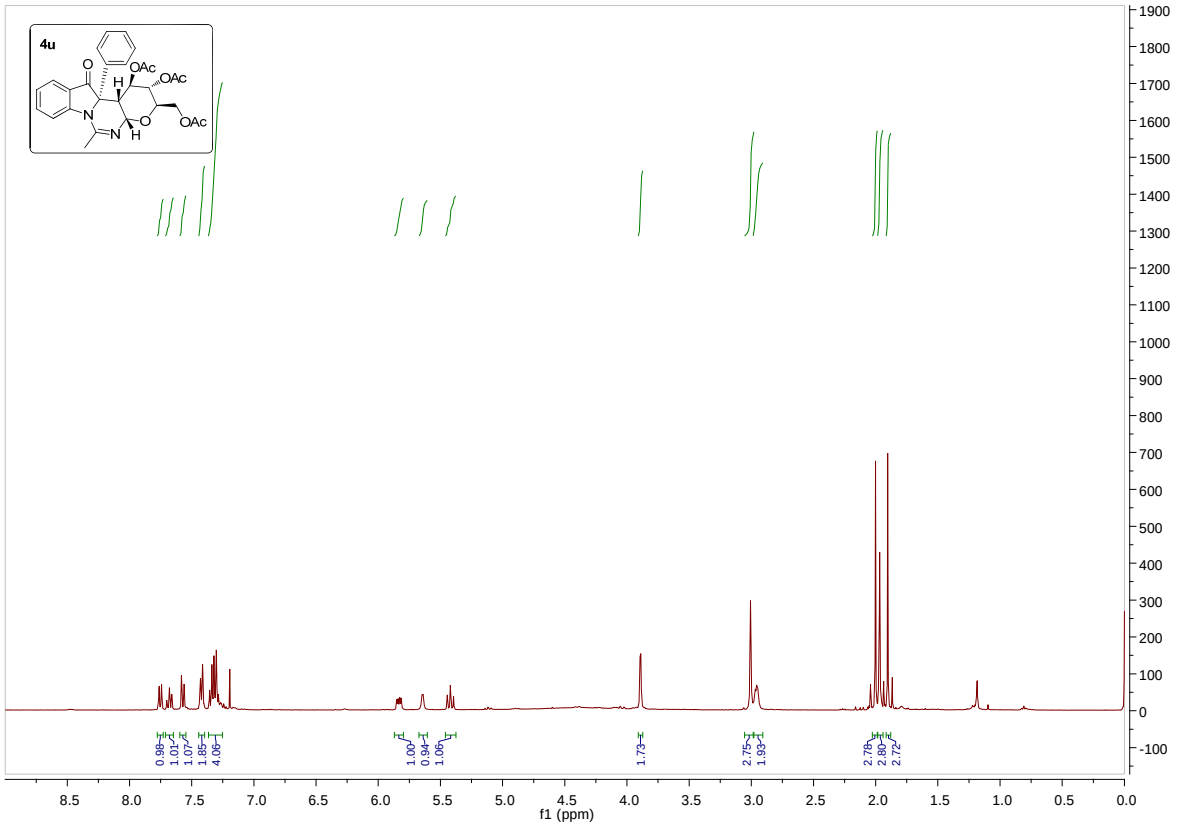


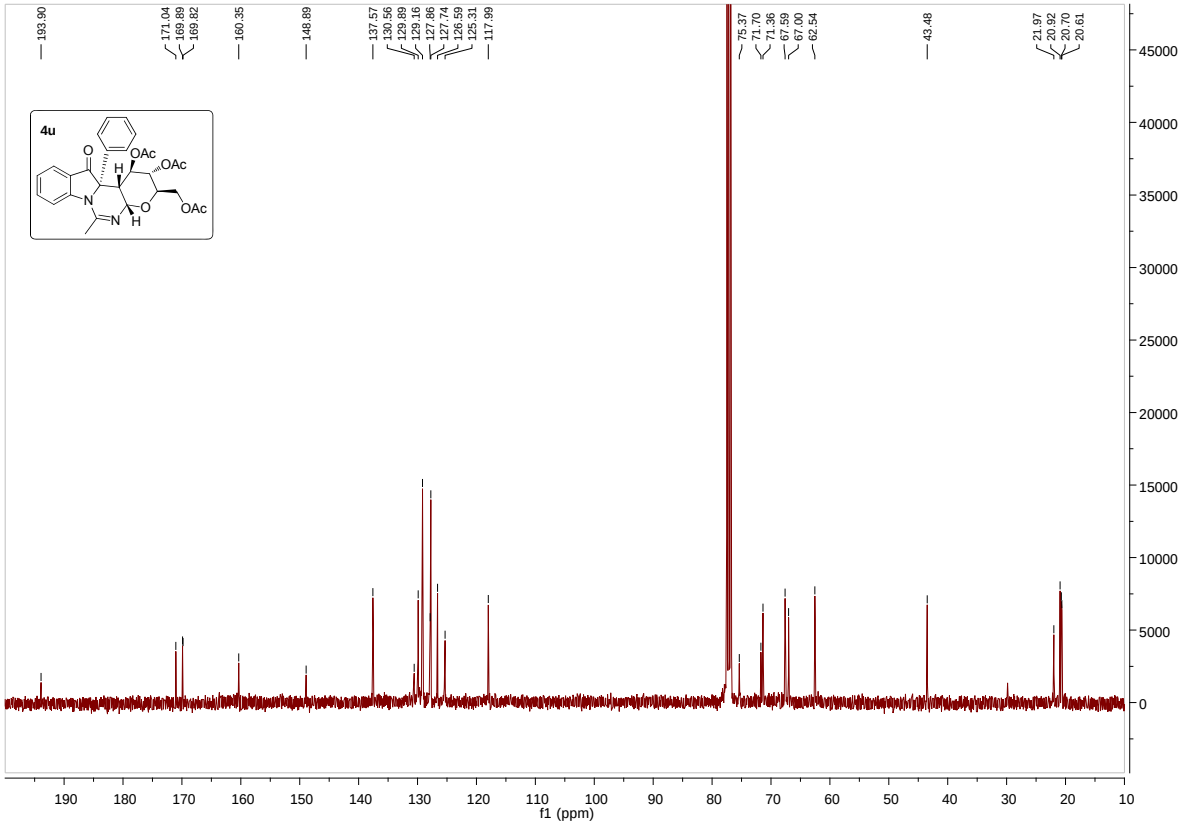
(1*R*,2*R*,3*R*,4a*S*,12a*S*,12b*R*)-3-(acetoxymethyl)-6-methyl-12-oxo-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole-1,2-diyl diacetate (4t)



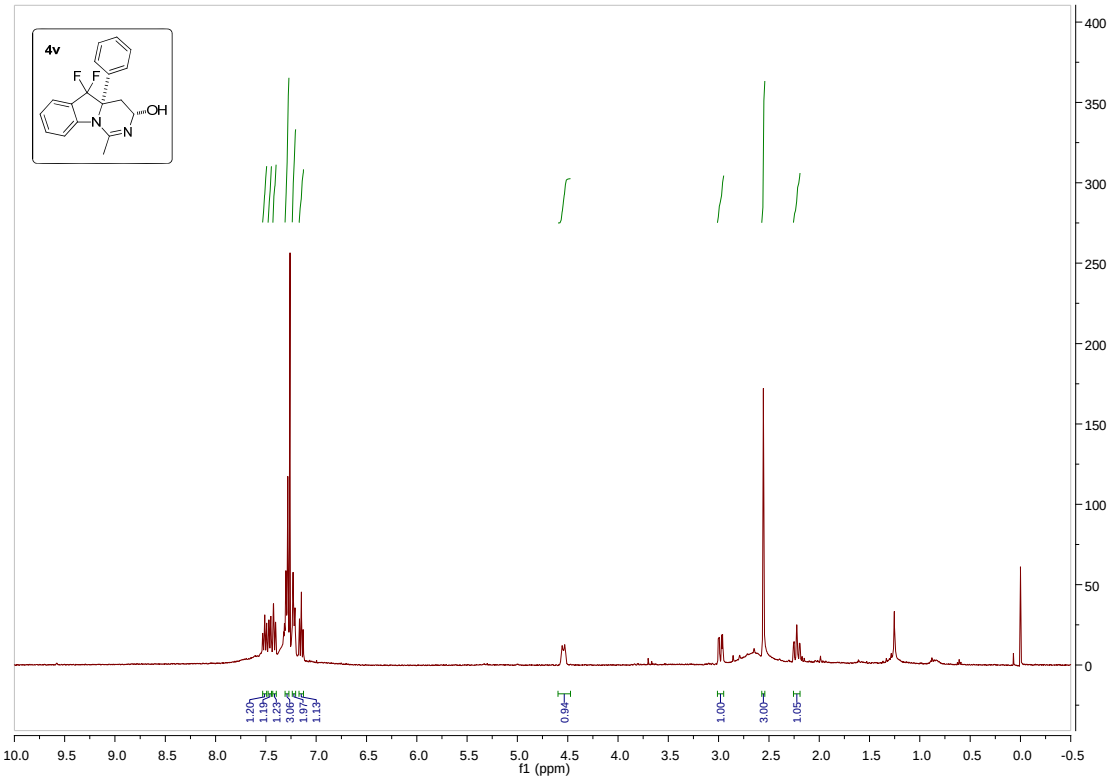


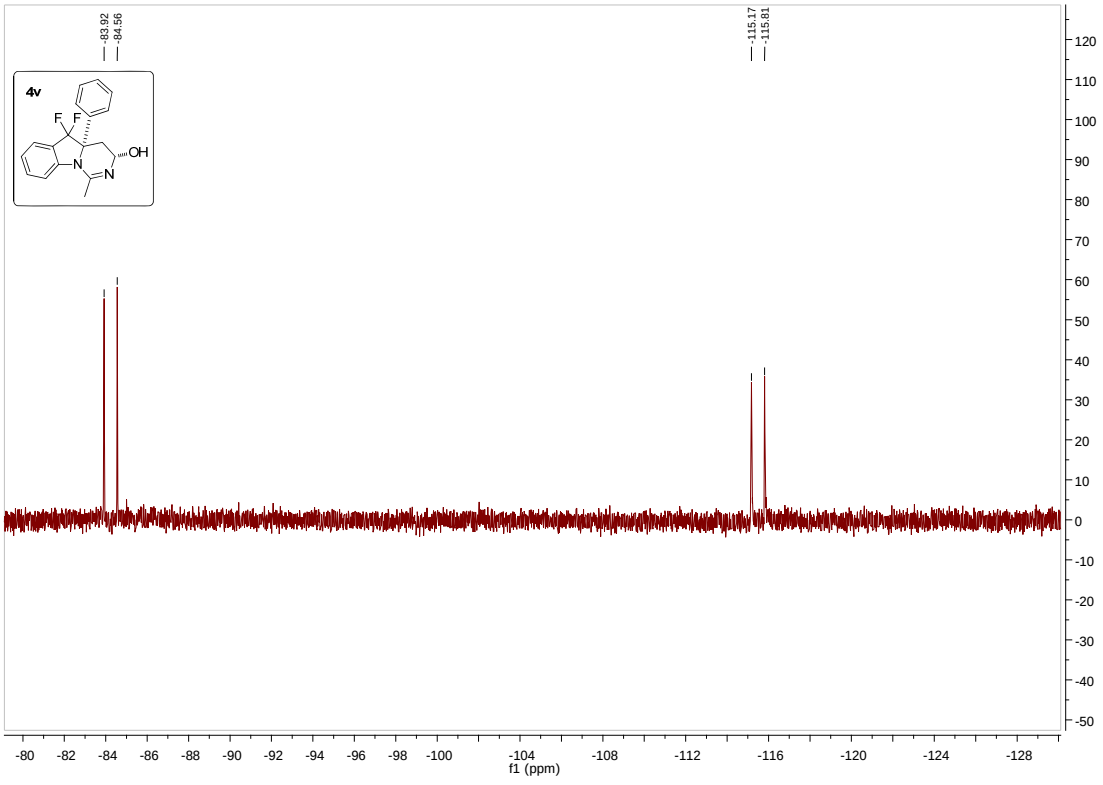
(1*R*,2*S*,3*R*,4a*S*,12a*S*,12b*R*)-3-(acetoxymethyl)-6-methyl-12-oxo-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1H-pyrano[2',3':4,5]pyrimido[1,6-*a*]indole-1,2-diyl diacetate (4u)

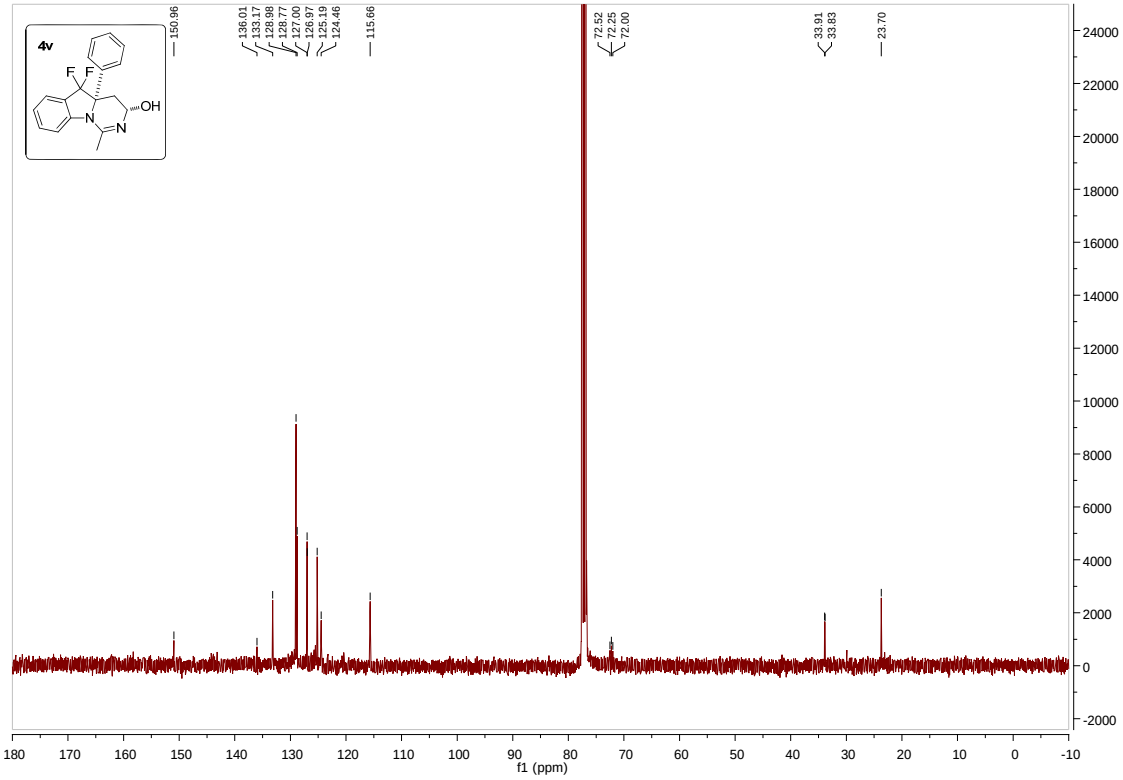




(3*RS*,4a*RS*)-5,5-difluoro-1-methyl-4a-phenyl-3,4,4a,5-tetrahydropyrimido[1,6-a]indol-3-ol (4v)



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N
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136.01
133.17
128.98
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127.00
126.97
125.19
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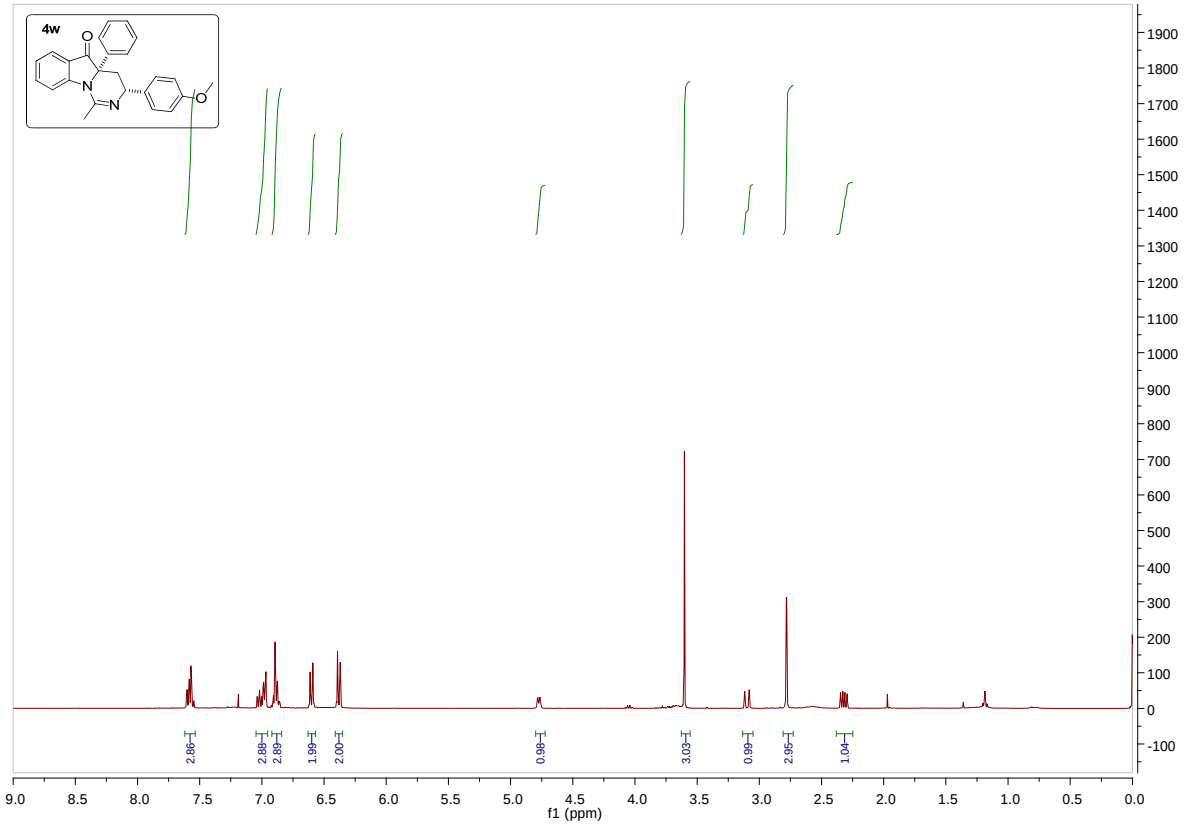
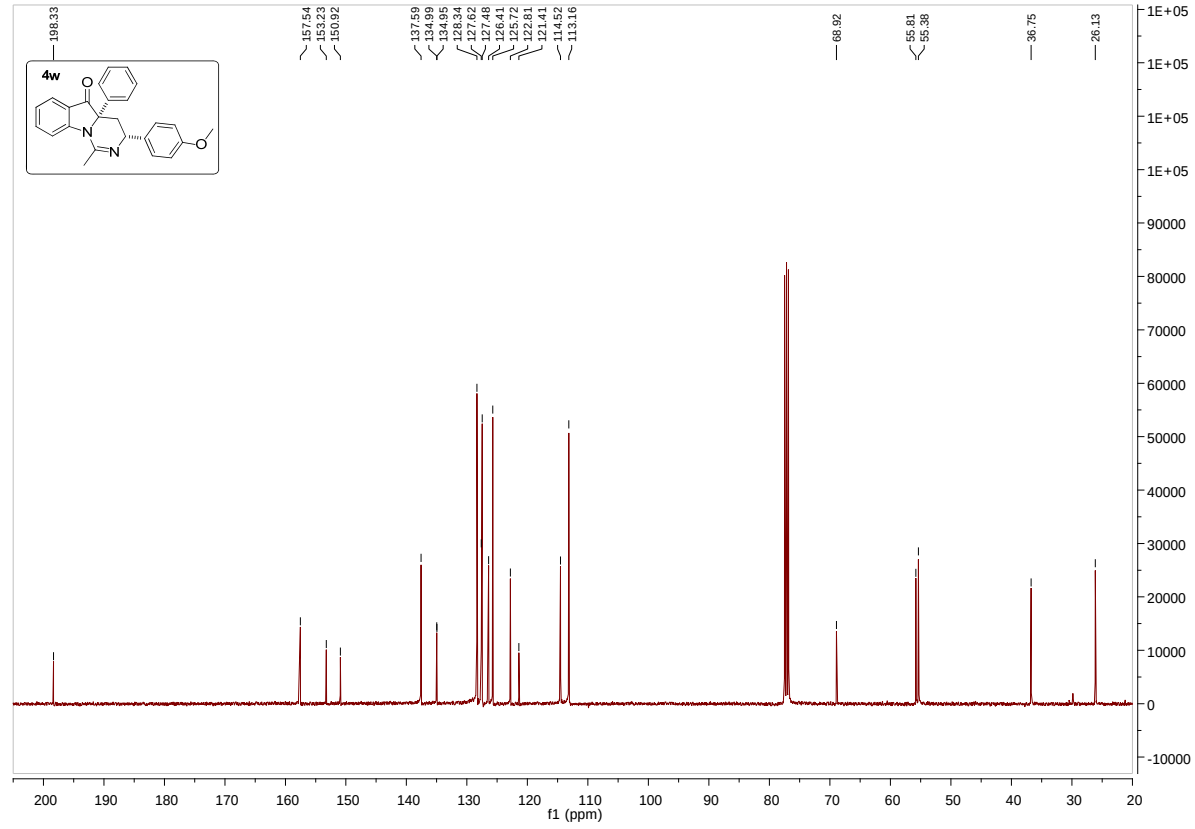
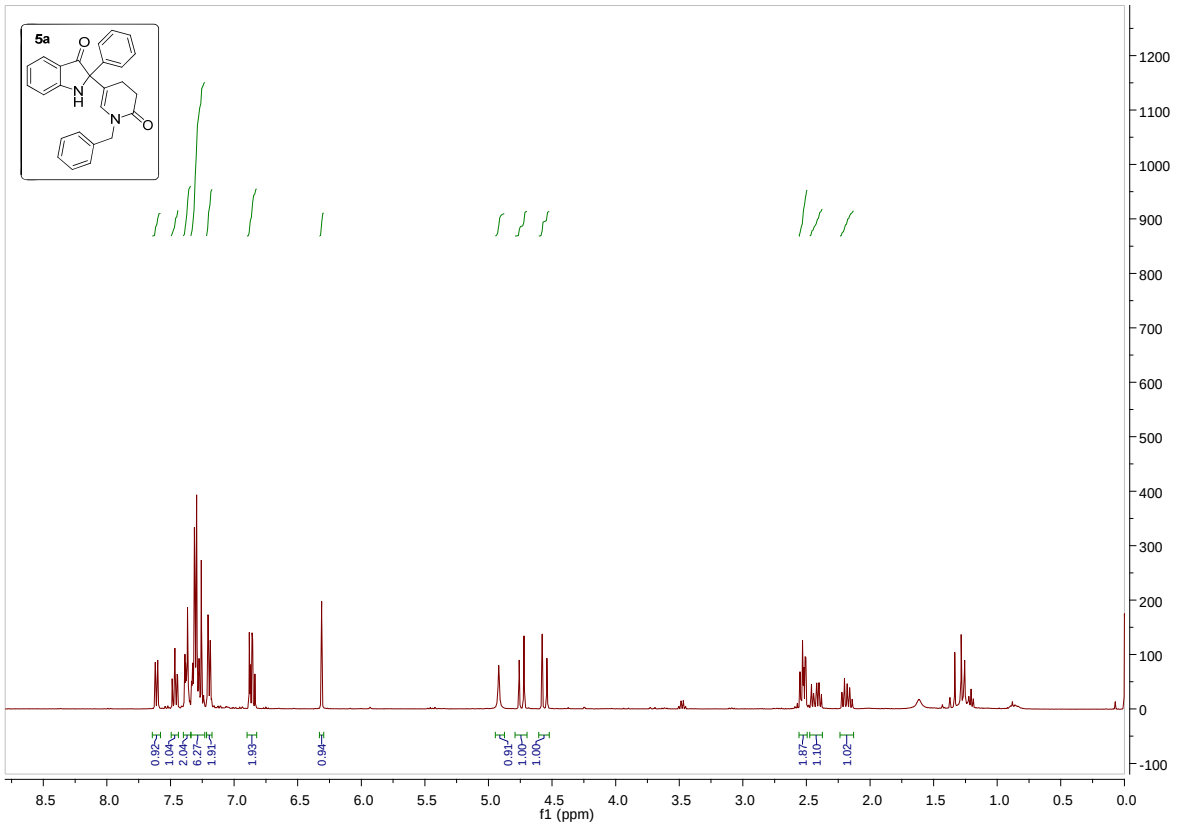
115.66
72.52
72.25
72.00
33.91
33.83
23.70
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

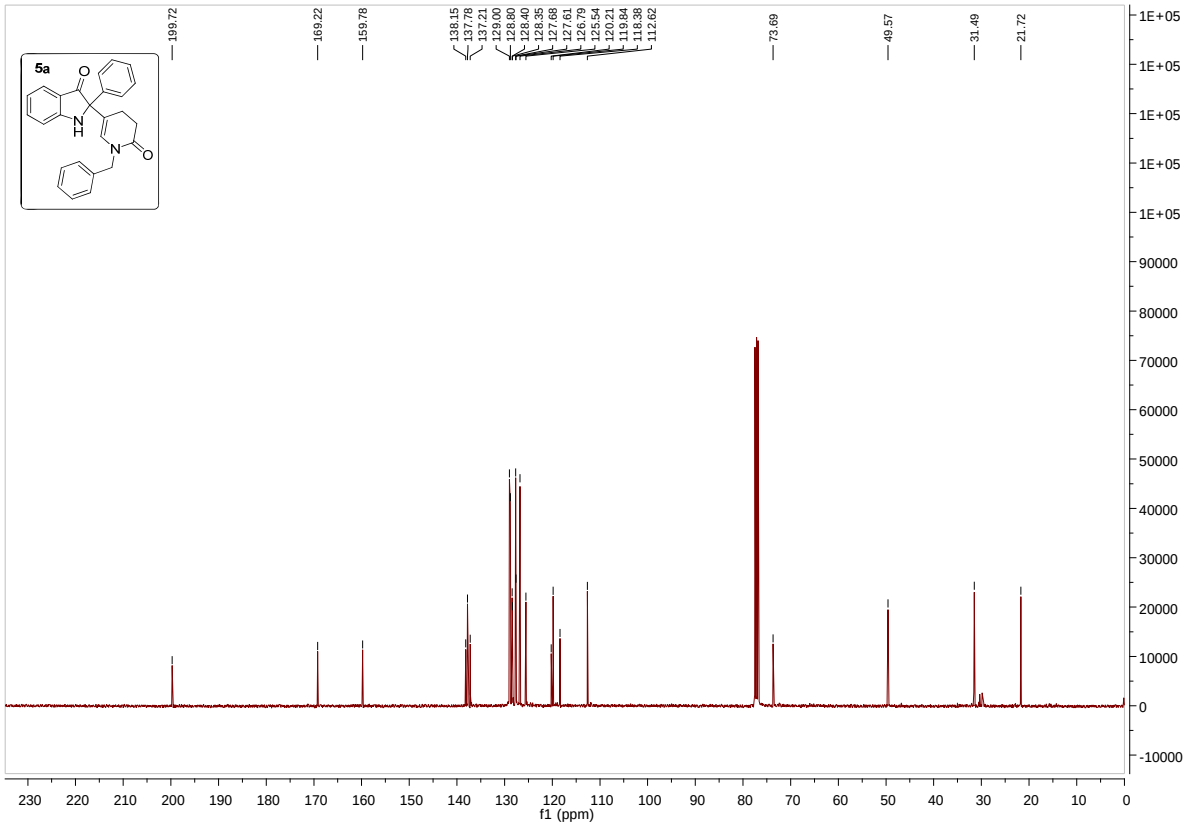
(3*RS*,4a*SR*)-3-(4-methoxyphenyl)-1-methyl-4a-phenyl-4,4a-dihydropyrimido[1,6-a]indol-5(3*H*)-one (4w)



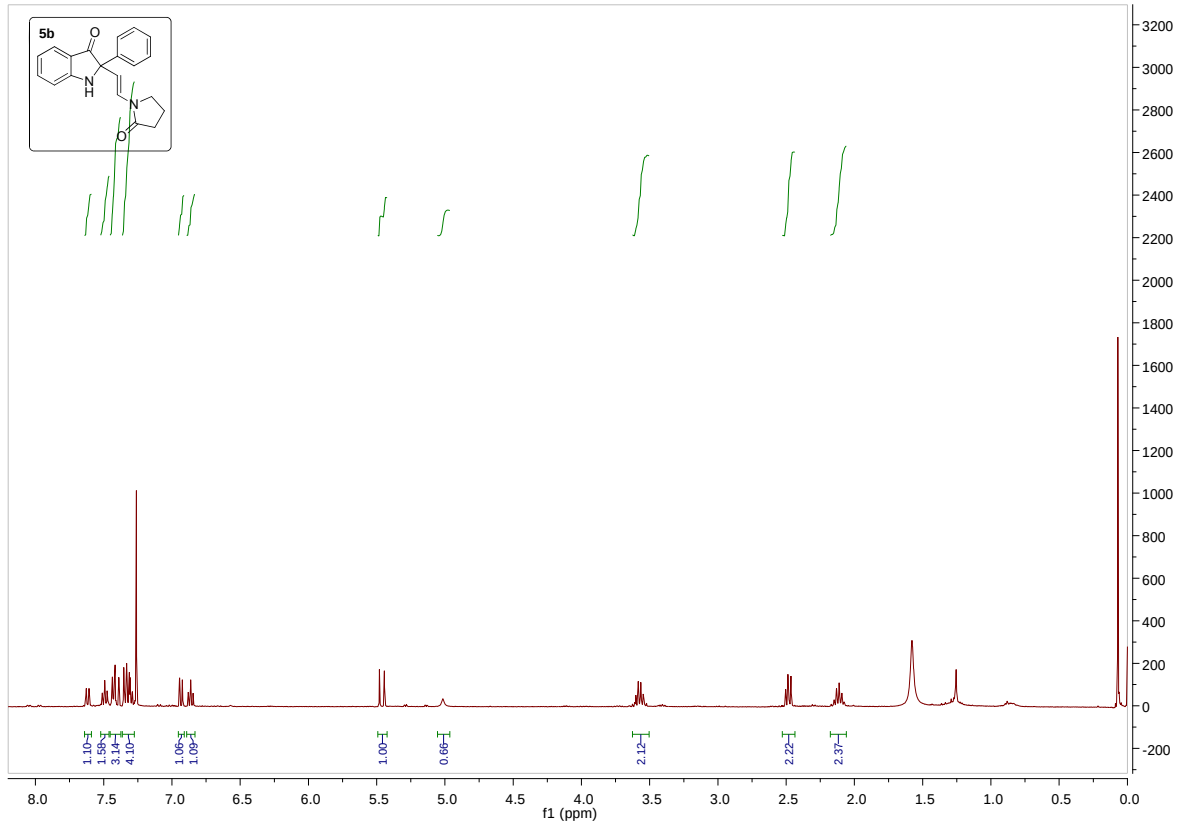


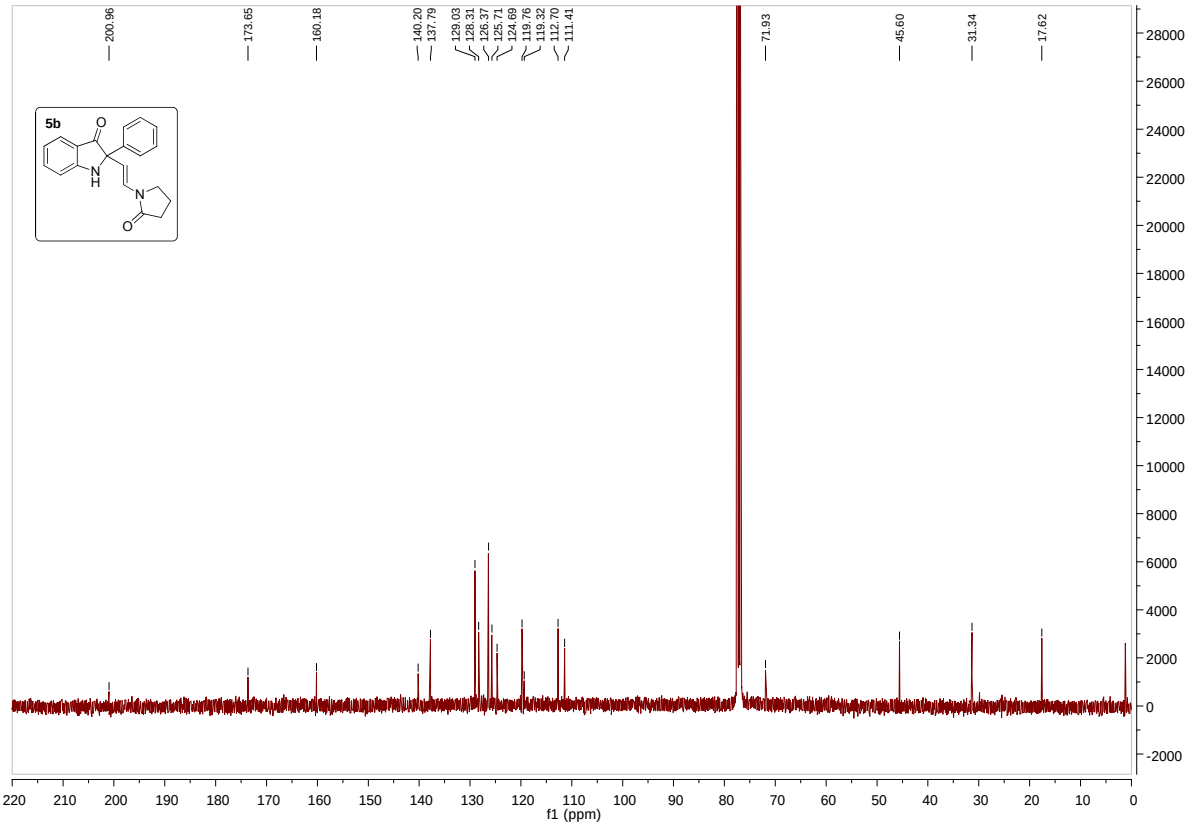
2-(1-benzyl-6-oxo-1,4,5,6-tetrahydropyridin-3-yl)-2-phenylindolin-3-one (5a)



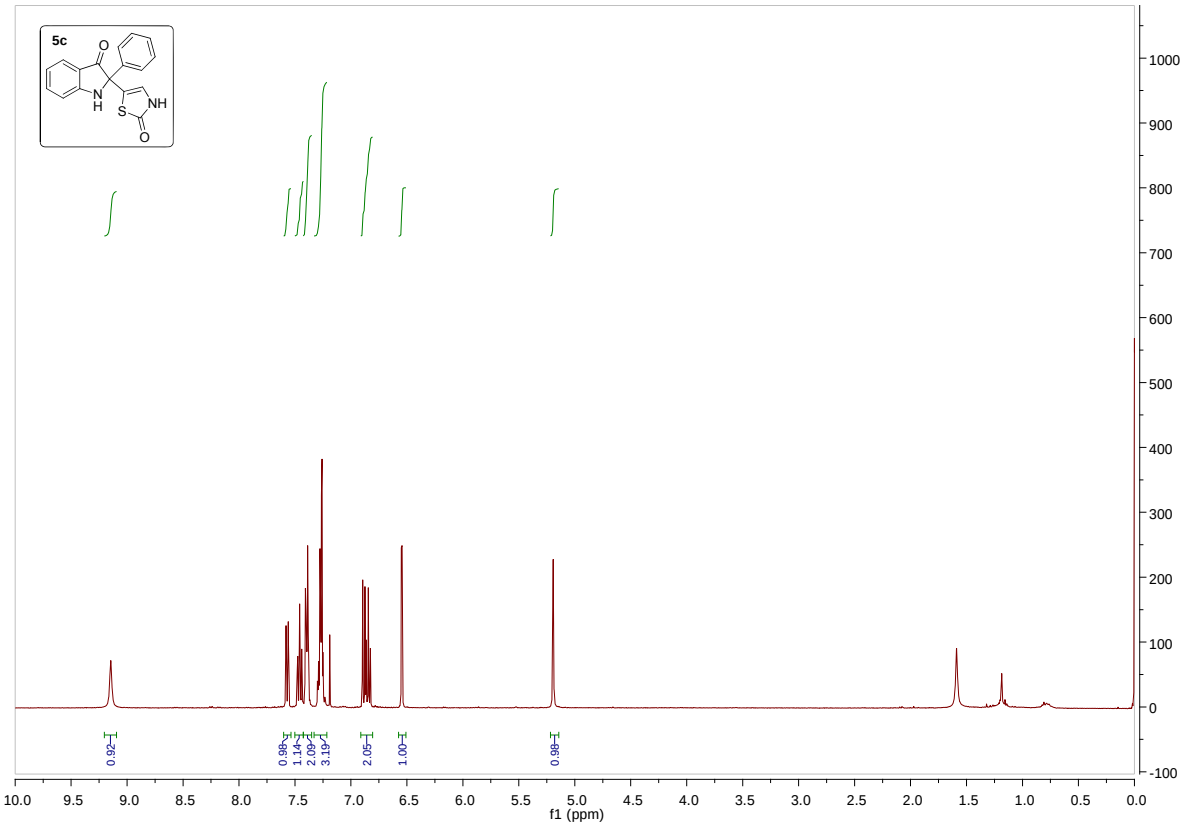


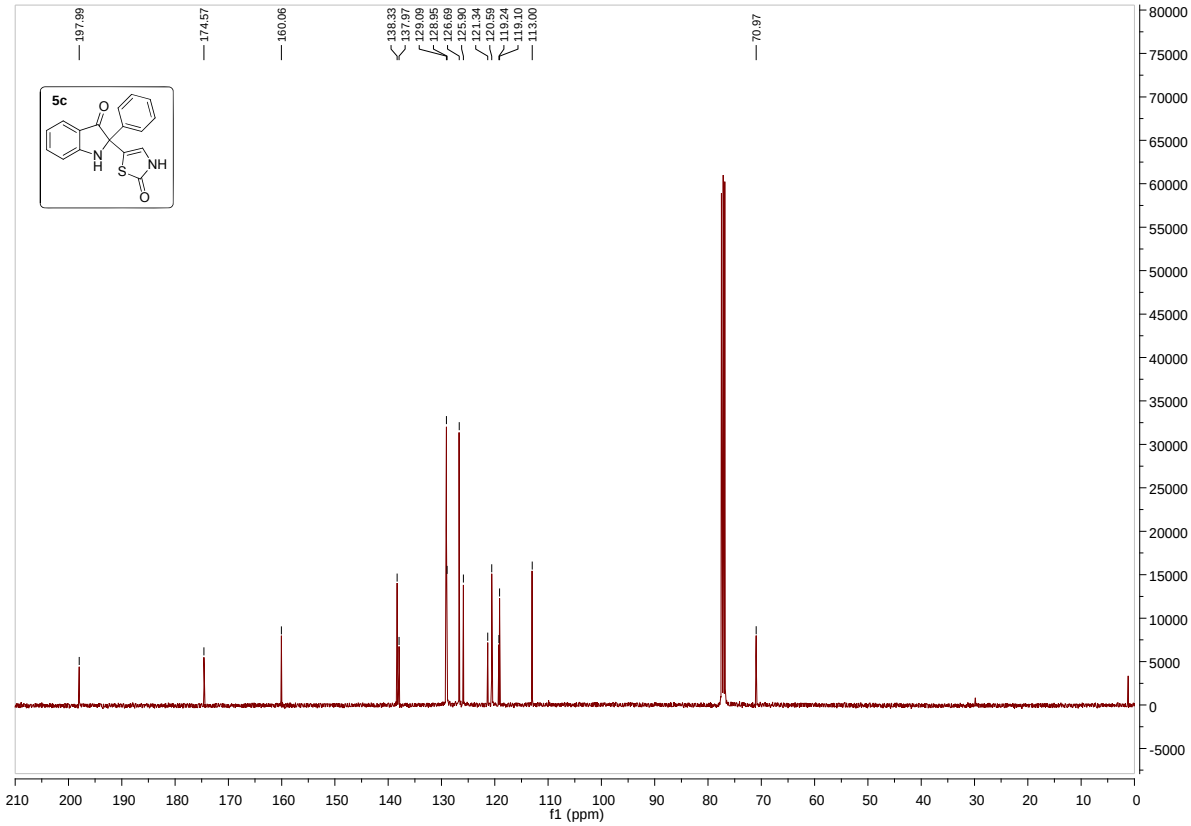
(*E*)-2-(2-(2-oxopyrrolidin-1-yl)vinyl)-2-phenylindolin-3-one (5b)



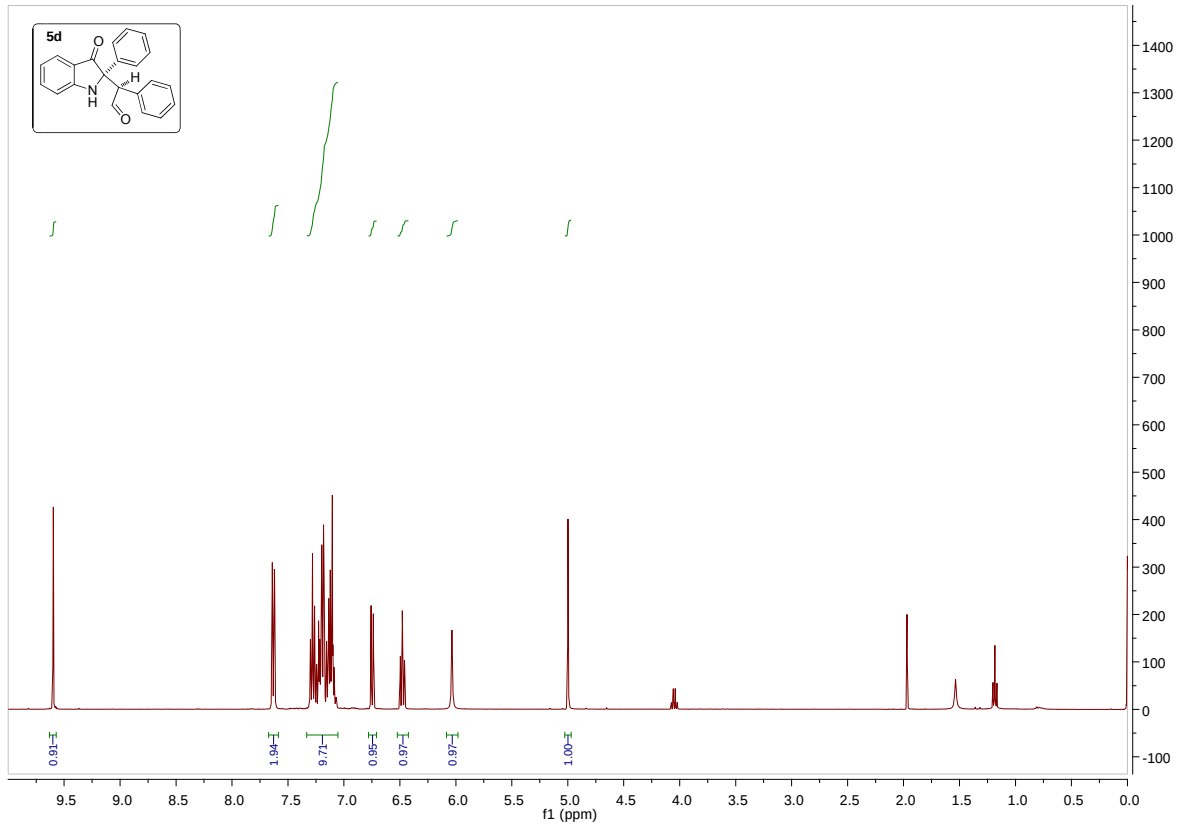


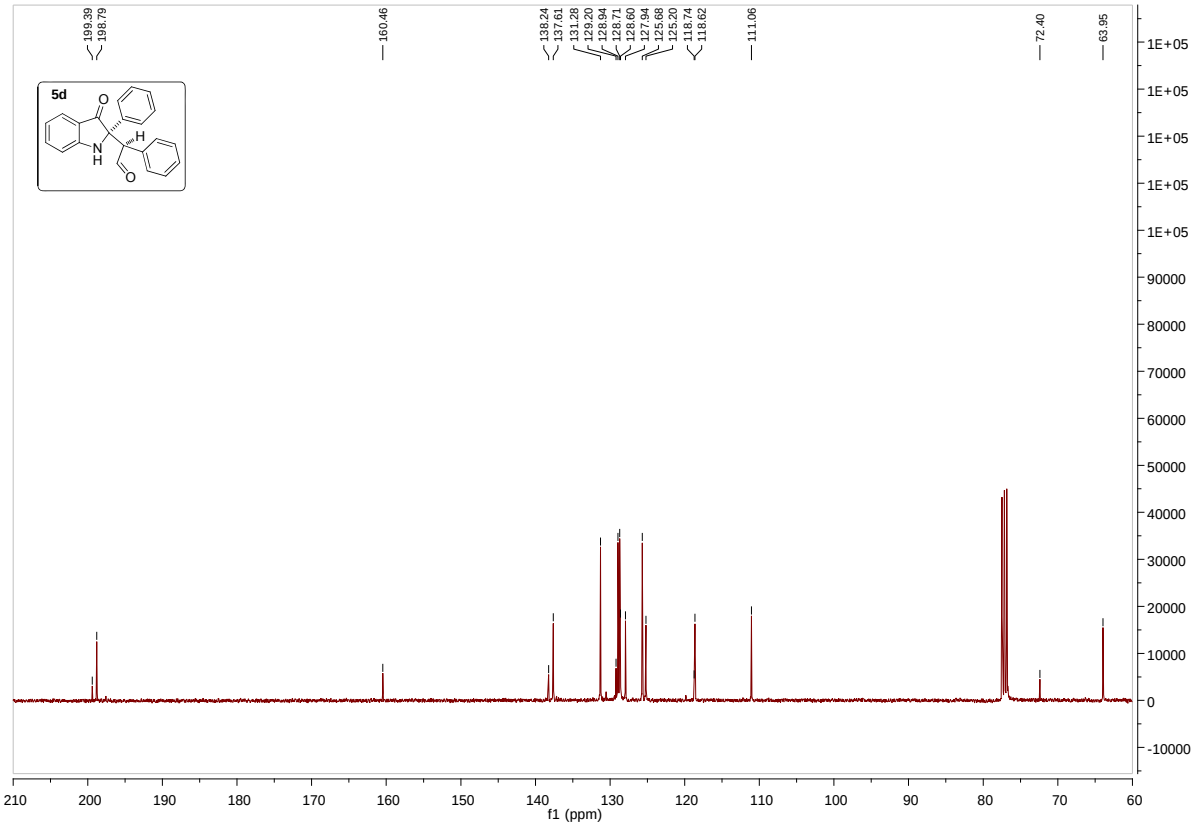
5-(3-oxo-2-phenylindolin-2-yl)thiazol-2(3*H*)-one (5c)



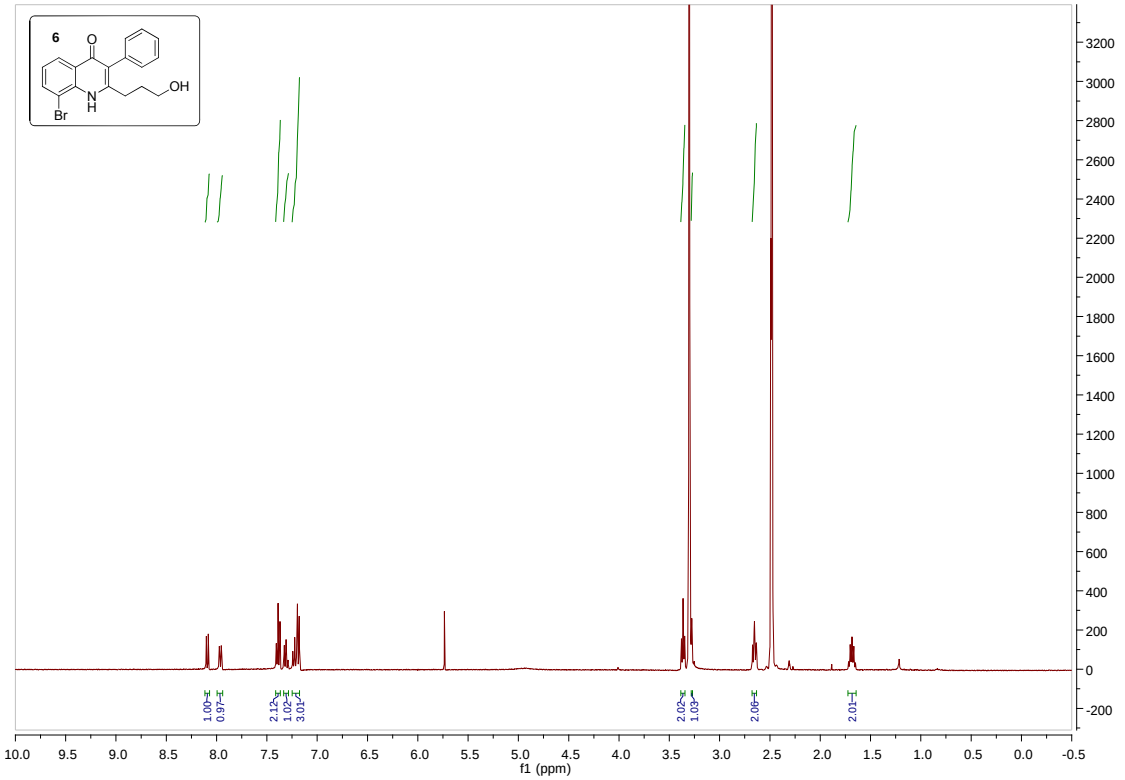


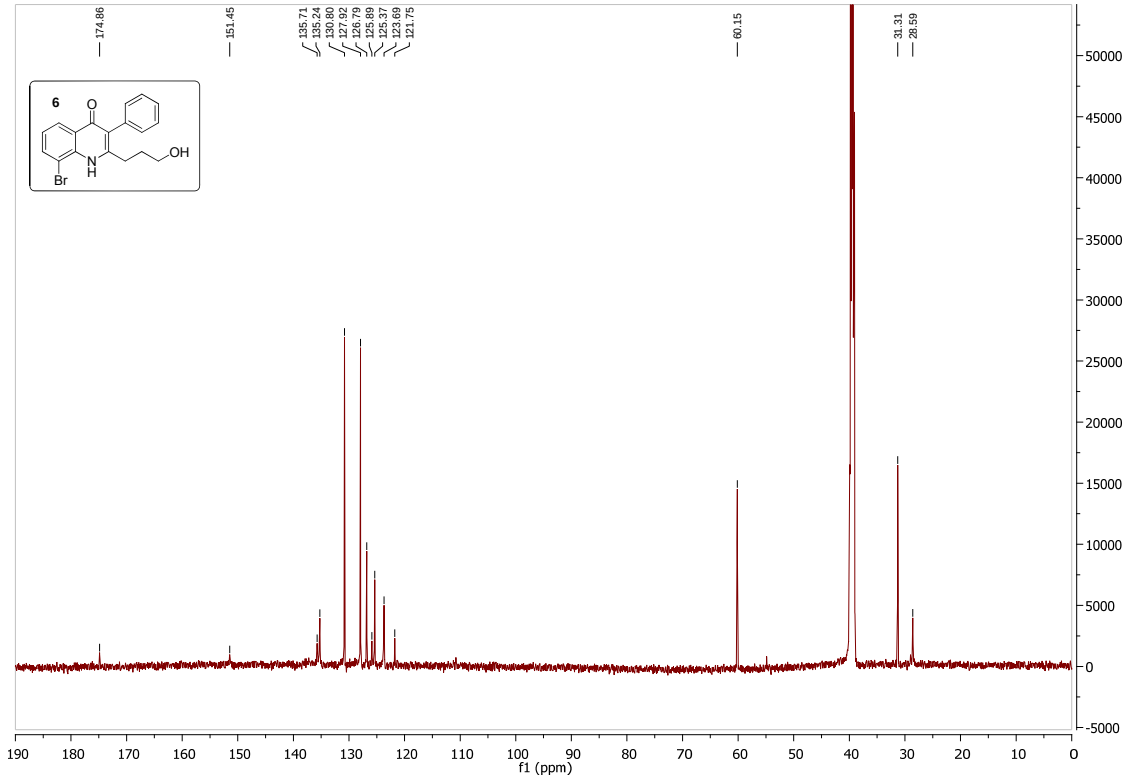
2-(3-oxo-2-phenylindolin-2-yl)-2-phenylacetaldehyde (5d)



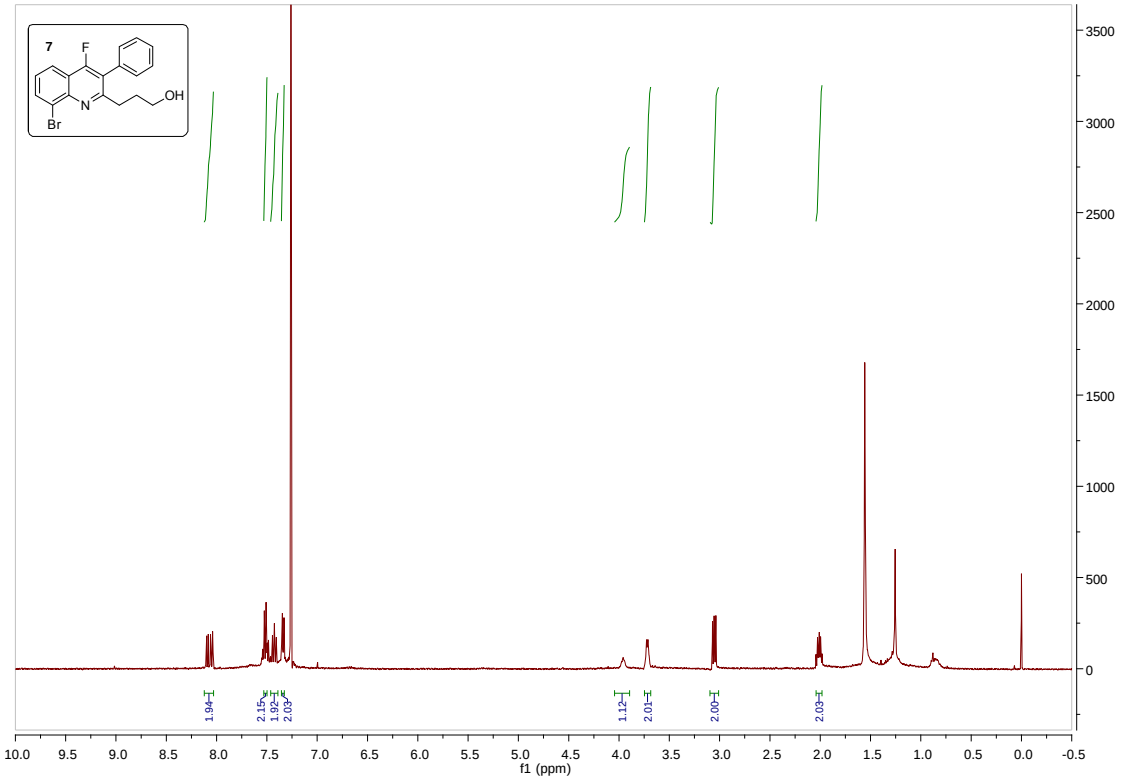


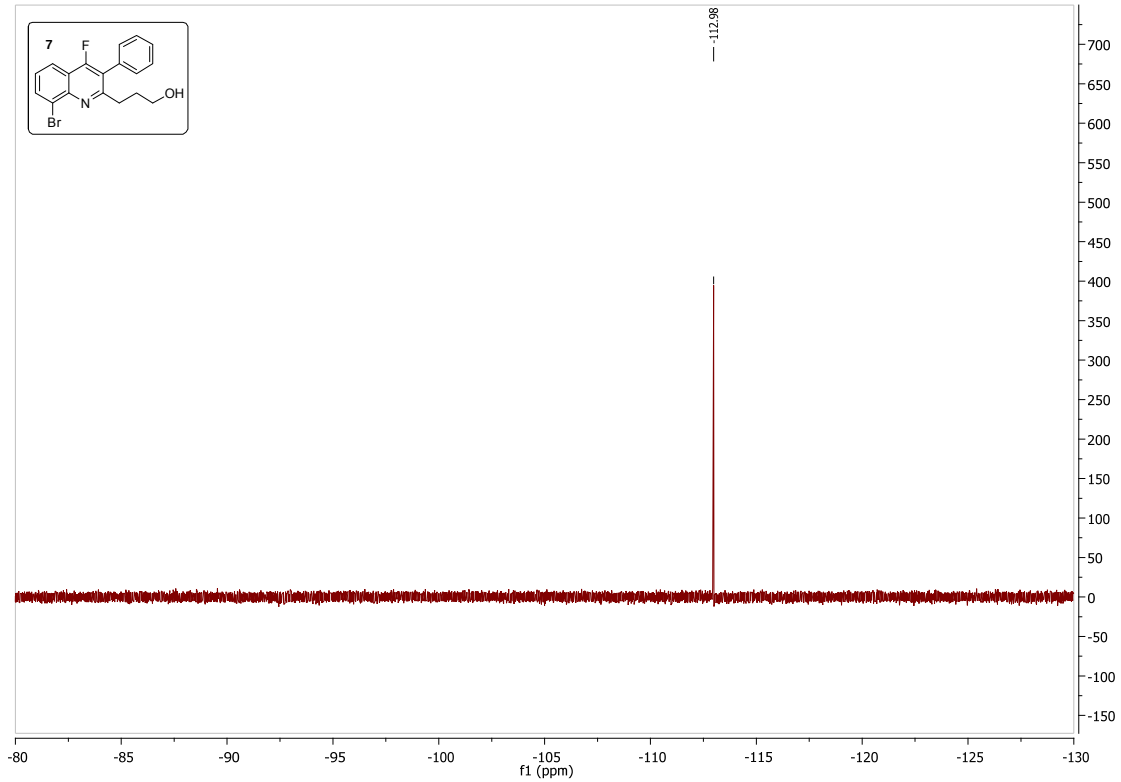
8-bromo-2-(3-hydroxypropyl)-3-phenylquinolin-4(1*H*)-one (6)

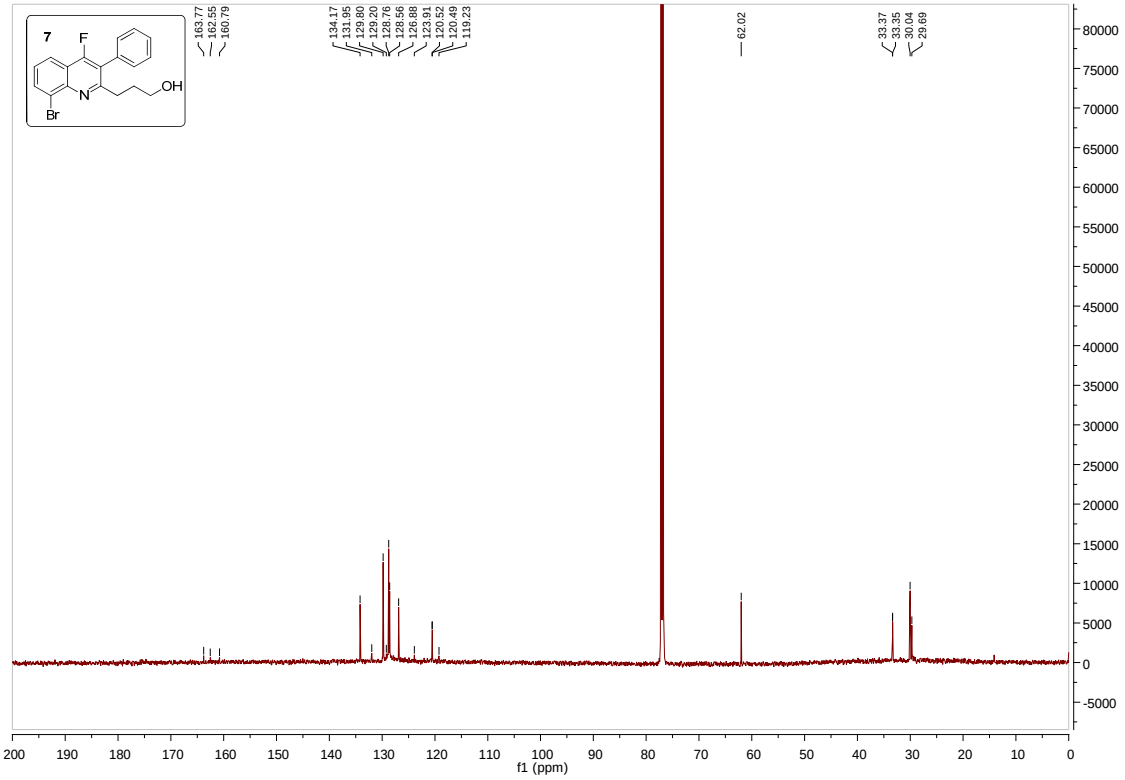




3-(8-bromo-4-fluoro-3-phenylquinolin-2-yl)propan-1-ol (7)

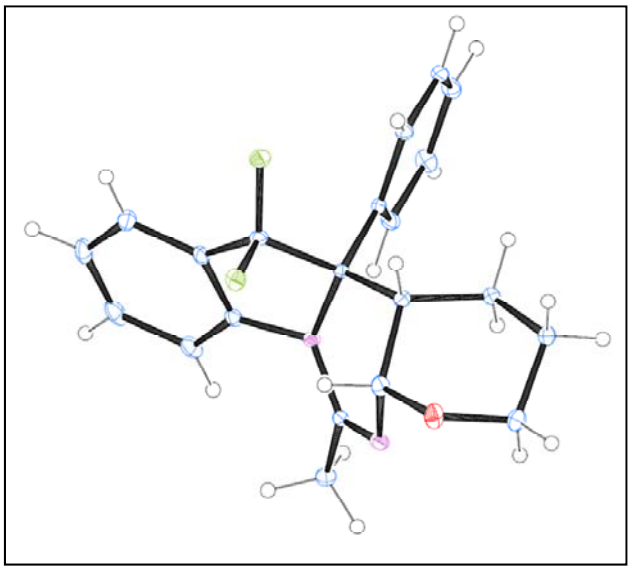





7
F
N
OH
Br
163.77
162.55
160.79
134.17
131.95
129.80
129.20
128.76
128.56
126.88
123.91
120.52
120.49
119.23
62.02
33.37
33.35
30.04
29.69
f1 (ppm)

X ray structures of compounds 4a and 6

(4a*RS*,12a*RS*,12b*RS*)-12,12-difluoro-6-methyl-12a-phenyl-2,3,4a,12,12a,12b-hexahydro-1*H*-pyrano[2',3':4,5]pyrimido[1,6-a]indole (4a)



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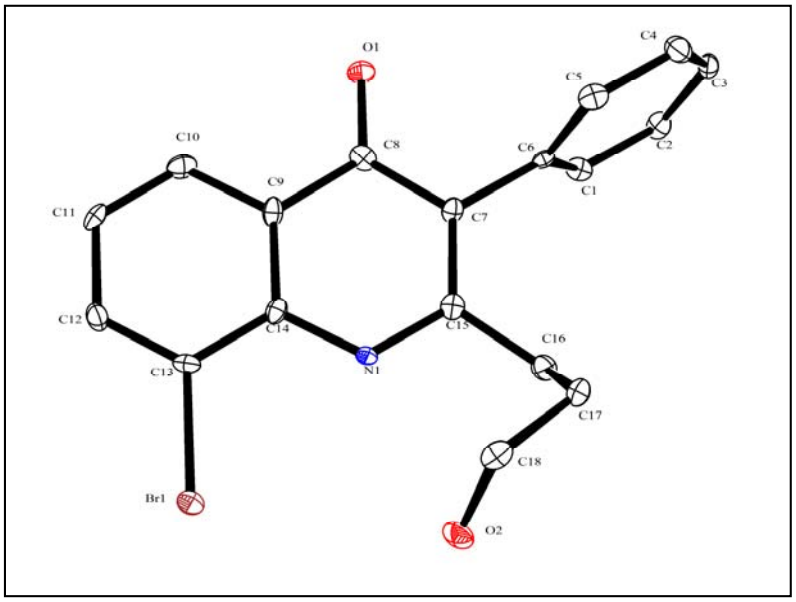
8-bromo-2-(3-hydroxypropyl)-3-phenylquinolin-4(1*H*)-one (6)



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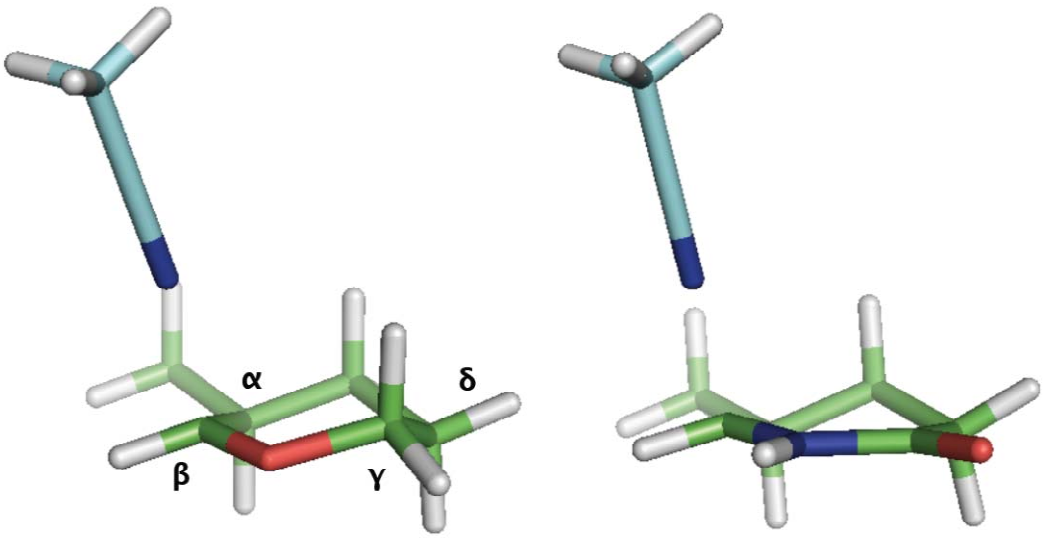
Computational Methods

Full geometry optimizations were performed with the B3LYP[10] density functional method using the 6-31G(d) basis set and taking account solvent effects by means of the SMD version of the IEFPCM model.[11] The nature of the stationary points was verified by inspection of the vibrational frequencies within the harmonic oscillator approximation. Intrinsic reaction coordinate calculations[12] were carried out to confirm the connection between the transition state and the minimum energy structures of pre-reactant complex and product. The suitability of this computational scheme is supported from the results determined for reactive processes in vinyl oxocarbenium ions.[13] Finally, single-point MP2/aug-cc-pVDZ calculations were performed using the B3LYP/6-31G(d) geometries to estimate the energy differences between pre-reactant complex, transition state and product. Calculations were performed using Gaussian 09.[14]

Figure S1. Representation of the chair-like transition state associated with the *cis* addition of acetonitrile to the carbenium intermediate formed from (left) dihydropyran **2a** and (right) cyclic enamide **2f**. The values of selected torsion angles in the pre-reactant complex, TS and product are indicated.

Dihydropyran **2a** Cyclic enamide **2f**



	Dihydropyran **2a**		Cyclic enamide **2f**	
	Cα-Cβ-O-Cγ	Cβ-O-Cγ-Cδ	Cα-Cβ-N-C	Cβ-N-C-Cδ
Pre-reactant	12.3	-27.6	1.8	-6.2
Transition state	33.9	-41.2	21.1	-11.5
Product	50.3	-53.2	27.1	-13.0

In the addition to dihydropyran **2a** the dihedral angles in the transition state facilitate the adoption of a chair-like arrangement. However, in the case of cyclic enamide **2f** the lower deformability of the amide bond impedes the adoption of a chair-like arrangement, which destabilizes the transition state.

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A Divergent Process Leading to Diels-Alder and Mannich-Ritter Adducts. Computational and Mechanistic Evidences of a Cationic Common Intermediate.

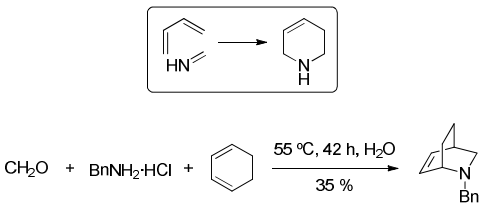
Salomé Llabrés,[a] Esther Vicente-García,[b] Sara Preciado,[b] Cristina Guiu,[b] Rodolfo Lavilla* [b], [c] and F. Javier Luque* [a]

Abstract

Studies on the Lewis acid-catalyzed imino Diels–Alder reaction between cyclohexadiene and 2-phenyl-indol-3-one, show that the reaction proceeds via a stepwise pathway. Experimental and computational data reveal that the transformation takes place through a nucleophilic addition of the diene upon the activated imine to furnish a stabilized cation. These species suffer the capture by the indole-nitrogen atom or by an external nucleophile. The reaction pathway is computationally analyzed and the putative intermediates are described.

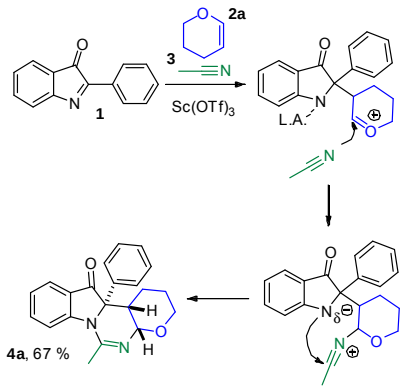
The hetero Diels-Alder (DA) reactions are important as they permit to prepare complex heterocyclic systems and natural products. This type of transformations comprises a wide family of processes involving polarized substrates. Among them, of particular importance are the imino-DA reaction dealing with imines.[1] In spite, a part of the high impact of these transformations in Organic Synthesis, there is an open question on the mechanistic details related with the concerted or stepwise character of these interactions.[2] Recent studies have focused on computational approaches on polarized cycloadditions, have reported the involvement of polar stepwise features in DA type reactions.[1b], [3] At this point, the Grieco reaction can be regarded as the standard model, involving the acid-catalyzed interaction of an in situ generated imine with a diene, to yield a tetrahydropyridine adduct (Scheme 1), in a multicomponent reaction (MCR).[4] These transformations constitute an emerging field in organic chemistry, as MCRs bring together many features of the ideal synthesis: convergency, atom and step economy, synthetic versatility, selectivity, etc.[5] Being intrinsically complex processes (due to the coexistence of 3 or more reactants), few detailed mechanistic studies are known for many MCRs. [6]

Scheme 1. Imino Diels-Alder reaction.



In this context, we have recently published a Povarov-type MCR involving activated imines (**1**, Scheme 2), nucleophilic alkenes (**2a**) and nitriles (**3**) in a Mannich-Ritter cascade process yielding cyclic amidines (Scheme 2).[7] Interestingly, in these conditions, cyclohexadiene (**2b**, Scheme 3) affords the Mannich-Ritter adduct as the minor component (**4b**, 7%),[8] the main product being the imino DA cycloaddition (**5**, 68%, Scheme 3). Interestingly, **5** did not evolve to **4b** under reaction conditions nor with $BF_3{\cdot}Et_2O$ treatment. [9]

Scheme 2. New Mannich-Ritter MCR. [7]



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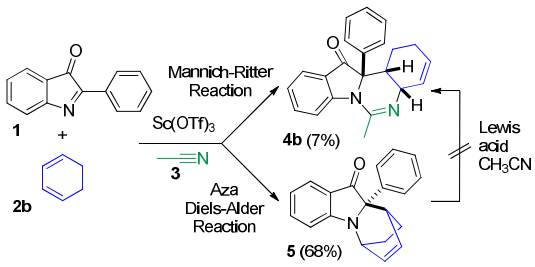
Supporting Information contains the NMR spectra of the new compounds and computational data.



Scheme 3. Imino Diels-Alder reaction.

The structural elucidation of the obtained compounds was performed in a standard manner with spectroscopical methods (^{1}H and ^{13}C, COSY, HMBS, HSQC and NOESY NMR experiments) and the aid of geometry optimization studies (MM94F, AM1 and B3LYP density functional calculations in a Spartan suite). The stereochemistries assigned for the two compounds (Figure 1) are in agreement with the observed trends for the previously reported results on this MCR.[7] Interestingly, the spatial disposition of the substituents connecting C_a (indole) with C_b (cyclohexyl) is different in the two substances, ruling out a common precursor (Figure 1).

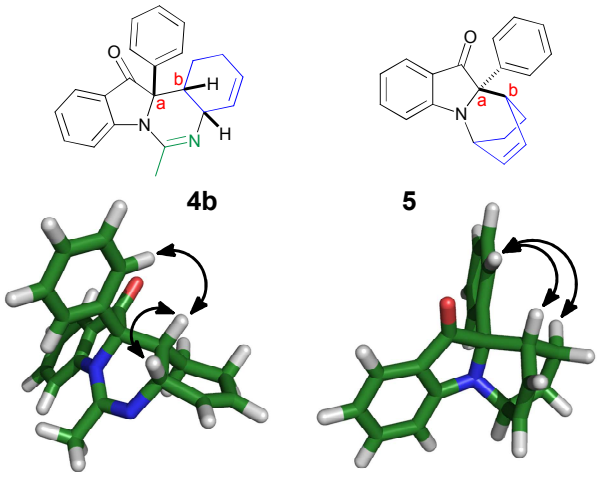


Figure 1. Diagnostic n.O.e's. and optimized geometries for compounds **4b** and **5**.

From these facts, a fundamental question arises: have the DA and MCR processes a common reaction pathway or not? A plausible explanation is that the first reaction could be concerted and the second one might evolve via the usual stepwise mechanism (Figure 2). The pivotal point of the concerted or stepwise character of the imino DA process is deeply rooted in this reaction mechanism, meaning that the interaction may proceed through a concerted TS (**B**) leading to the adduct (**5**) or evolving to a polar intermediate (**A**), then collapsing to the DA adduct or being intercepted by acetonitrile to yield the Mannich-Ritter compound (**4b**). Alternatively, the early stages of the process may involve the approach of one end of the diene to the activated imine to give the charged species **A**. In addition, the distinct stereochemical approaches can dramatically influence the mechanistic outcome.

These reasons prompted us to study the mechanistic features of the process, and in this way a series of experiments were planned. First of all, we screened the range of catalysts that allow the transformation. A part from $Sc(OTf)_3$, an usual Lewis acid for the Povarov and other imine-based MCRs (entry 1).[10] $BF_3{\cdot}Et_2O$ was also efficient, yielding a similar ratio of products **4b**/**5** although in a slightly increased overall yield under the usual conditions (rt, 20% of the catalyst, entry 2). Whereas $Mg(ClO_4)_2$ needs a full equivalent and warming at 60 ºC to achieve total conversion (entry 5); the use of lower amounts at rt, even with prolonged reaction times leaves the starting material almost intact (entries 3, 4). $LiClO_4$ is even less reactive (entries 6, 7) and the transformation does not work in absence of catalysts (entries 8, 9). The product ratio seems to be conserved in all productive cases.

Figure 2. Mechanistic hypothesis on the formation of DA (**5**) and MCR (**4b**) adducts.

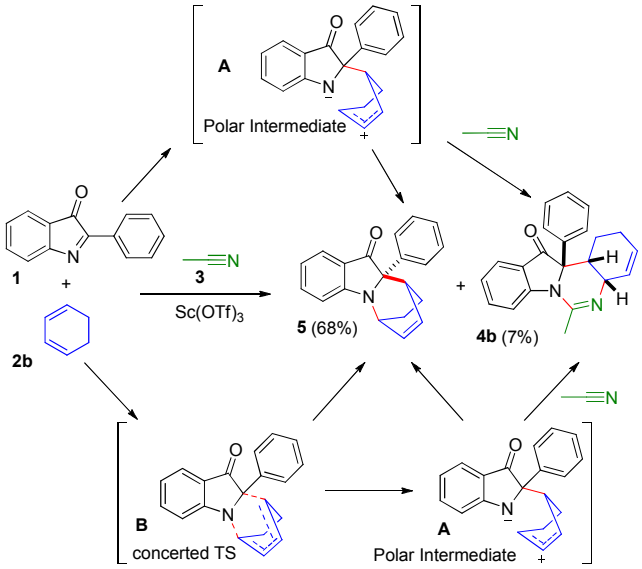
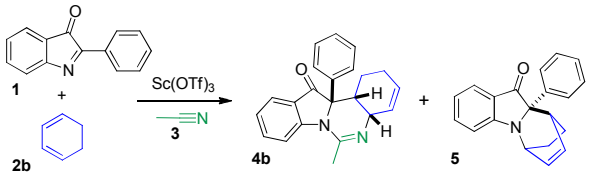


Table 1. Catalyst screen for the reaction of cyclohexadiene (**2b**) with imine **1** in acetonitrile.

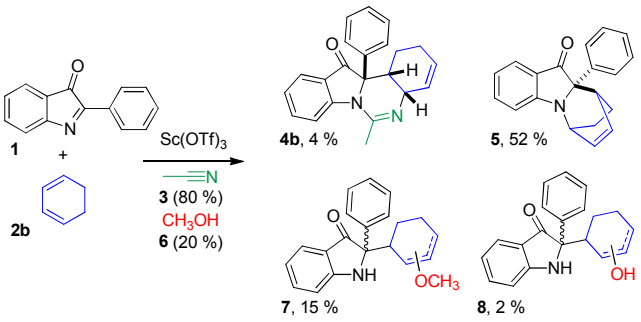


Entry[a]	Catalyst	Conditions	**1** (%)	**4b** (%)	**5** (%)
1	$Sc(OTf)_3$ 20%	rt, 18 h	-	7	68
2	$BF_3{\cdot}OEt_2$ 20%	rt, 18 h	-	13	87
3	$Mg(ClO_4)_2$ 20%	rt, 96 h	98	-	2
4	$Mg(ClO_4)_2$ 100%	rt, 18 h	96	Traces	3
5	$Mg(ClO_4)_2$ 100%	60 ºC, 18 h	-	10	90
6	$LiClO_4$ 20%	rt, 96 h	94	-	6
7	$LiClO_4$ 100%	60 ºC, 96 h	82	Traces	17
8	-	rt, 18 h	>90	-	-
9	-	60 ºC, 96 h	>90	-	-

[a] All reactions were performed using 1 mmol of the imine, 1 mmol of the cyclohexadiene in 5 mL of acetonitrile under inert atmosphere, with the stated catalyst. The reaction crudes were analyzed by HPLC/MS and the products were positively identified with pure control samples.

To gain more knowledge about the reaction, we planned additional experiments. In particular we examined the putative existence of a polar (cationic) intermediate that may evolve by ring closure with the indole nitrogen to afford the DA-adduct **4b** or, alternatively suffer the acetonitrile trapping to yield amidine **5**. Interestingly, a related process in the presence of MeOH (20% v/v in CH_3CN), afforded a complex mixture of compounds, containing the DA adduct **5** (52%), the Ritter-type product **4b** (4%), together with mixtures of stereo-/regio-isomers of the MeOH and H_2O trapping products (**7** and **8**, 17% overall yield, identified by HPLC/MS methods). This result enforces the hypothesis that an intermediate carbonium ion is involved in the reaction mechanism.

Scheme 3. MCR in the presence of MeOH.



Computational Section

In order to realize the origin of the different outcome between DA and MCR processes, M062X/6-31+G(d) calculations were performed to localize the transition state (TS) involved in the addition of cyclohexadiene to **1**. Calculations were performed taking into account the coordination of BF_3 to the indole nitrogen. In addition, the approach of cyclohexadiene can occur by adopting either *endo* or *exo* arrangements.

In the two TSs, the most stable configuration places the diene system interacting with the indol ring of **1**, as expected from the stabilizing contribution of dispersive forces between the π-electron density of cyclohexadiene and indol units. In the *exo* TS, the indol nitrogen atom is located above the cyclohexadiene carbon atom at position gamma (Cγ), leading to a configuration that would favour the cyclization with the indol nitrogen (Figure 2). In fact, intrinsic reaction calculations (IRC) confirm that the *exo* TS leads directly to the DA addition. In contrast, the TS found for the *endo* approach locates such a carbon atom below the carbonyl oxygen, leading to a configuration that precludes the cyclization with the indol nitrogen. Thus, IRC calculations yield an intermediate where the carbon atom Cγ is exposed to the solvent, which in turn can be further stabilized by coordination with an acetonitrile molecule, which might subsequently evolve to the MCR adduct. Interestingly, M062X calculations predict that the *exo* TS is around 2.6 kcal/mol more stable than the *endo* TS, which is in agreement with the experimental outcome found for this reaction.

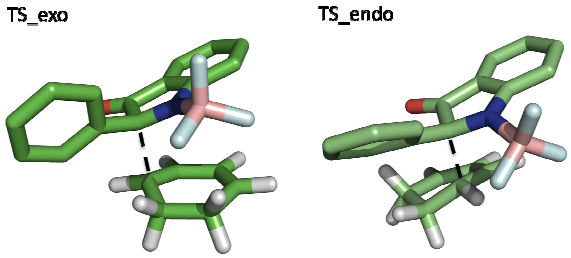


Figure 2. Representation of the transition state geometries for the *exo* and *endo* additions of cyclohexadiene

Experimental Section

General procedure

$Sc(OTf)_3$ (0.2 mmol) was added to a solution of imine **1** (1 mmol) and olefin **2** (1 mmol) in the corresponding nitrile **3** (5 mL), and the mixture was stirred under argon atmosphere at room temperature and the progress of the reaction was controlled by TLC or HPLC until the starting material completely disappeared or no further evolution was observed. When the reaction was complete sat. aq. $NaHCO_3$ (10 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane–EtOAc) to give the desired products.

(4a*RS*,12a*SR*,12b*SR*)-6-methyl-12a-phenyl-1,4a,12a,12b-tetrahydroindolo[1,2-c]quinazolin-12(2*H*)-one (4b)

Following the general procedure (16 h), the reaction of **1** and cyclohexa-1,3-diene (**2b**) in acetonitrile (**3**) as solvent, afforded compound **4b**. The crude was purified by flash chromatography (SiO_2, DCM:MeOH, 3:1) to afford pure **4b** as a minor product as a yellow solid (7% yield). In this reaction compound **5** was obtained as a major product (see below).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72-7.68 (m, 1H), 7.66-7.58 (m, 2H), 7.50-7.45 (m, 2H), 7.38-7.28 (m, 3H), 7.12-7.07 (m, 1H), 5.97-5.91 (m, 1H), 5.87-5.81 (m, 1H), 3.51-3.45 (m, 1H), 2.90 (ddd, *J* = 13.1, 5.1, 2.8 Hz, 1H), 2.75 (d, *J* = 1.7 Hz, 3H), 2.20-2.06 (m, 2H), 1.63-1.55 (m, 1H), 1.24-1.12 (m, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 198.6, 153.5, 147.7, 137.6, 136.8, 129.4, 129.3, 128.6, 127.7, 125.9, 125.3, 123.1, 122.7, 114.3, 74.0, 50.4, 41.2, 25.5, 25.2, 18.9 ppm. **IR** (film) ν_{max}: 3404, 3026, 2924, 2853, 1707, 1604, 1463, 1438, 1380, 1329, 1265, 1163, 1034, 925, 868, 752 cm^{-1}. **HRMS**: calcd for $C_{25}H_{21}N_2O$, 329.1648 ($M+H^+$); found, 329.1656.

(9a*RS*)-9a-phenyl-9,9*a*-dihydro-6,9-ethanopyrido[1,2-a]indol-10(6*H*)-one (5)

Following the general procedure (16 h), the reaction of **1** and cyclohexa-1,3-diene (**2b**) in acetonitrile (**3**) as solvent, afforded compound **5**. After a flash chromatography (SiO_2, hexane: EtOAc, 1:9) compound **5** was obtained as a yellow oil (68% yield). On further elution (DCM:MeOH, 3:1) compound **4b** was obtained as a minor product (see above).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.84-7.79 (m, 2H), 7.51 (ddd, *J* = 8.3, 1.4 Hz, 3H), 7.48-7.45 (m, 1H), 7.32-7.20 (m, 4H), 6.96-6.89 (m, 1H), 6.31 (ddd, *J* = 8.0, 6.6, 1.3 Hz, 1H), 5.98 (s, *J* = 8.0, 5.2, 1.1 Hz, 1H), 4.62-4.57 (m, 1H), 3.52-3.45 (m, 1H), 2.12-2.01 (m, 1H), 1.52-1.35 (m, 2H), 1.09 (dddd, *J* = 12.5, 11.7, 5.5, 2.5 Hz, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$) δ: 205.7, 165.5, 139.3, 136.7, 132.4, 131.5, 128.5, 127.6, 126.5, 126.4, 124.8, 121.9, 116.6, 75.0, 54.3, 39.2, 23.5, 19.4 ppm. **IR** (film) ν_{max}: 3385, 3065, 2962, 2872, 1707, 1604, 1470, 1329, 1303, 1252, 1201, 1162, 1105, 1021, 938, 752, 688 cm^{-1}. **HRMS**: calcd for $C_{20}H_{18}NO$, 288.1383 ($M+H^+$); found, 288.1382.

Acknowledgements

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Keywords: Computational chemistry • Diels-Alder • Imine • Mannich • Reaction Mechanism

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[8] Analogously, the reaction of imine **1** and cyclopentadiene in acetonitrile afforded the corresponding Diels-Alder and Mannich-Ritter adducts, although in lower yields. However, the use of thiophene as diene gave a very complex reaction crude, where many high molecular weight species were detected.

[9] In contrast with a related process where a [4+2] imine-cyclohexadiene adduct was converted into the Povarov isomer, see: V. Lucchini, M. Prato, G. Scorrano, P. Tecilla, *J. Org. Chem.* **1988**, *53*, 2251-2258

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Supporting information

A Divergent Process Leading to Diels-Alder and Mannich-Ritter Adducts. Computationals and Mechanistics Evidences of Cationic Common Intermediate.

Salomé Llabrés, Esther Vicente-García, Sara Preciado, Rodolfo Lavilla, F. Javier Luque

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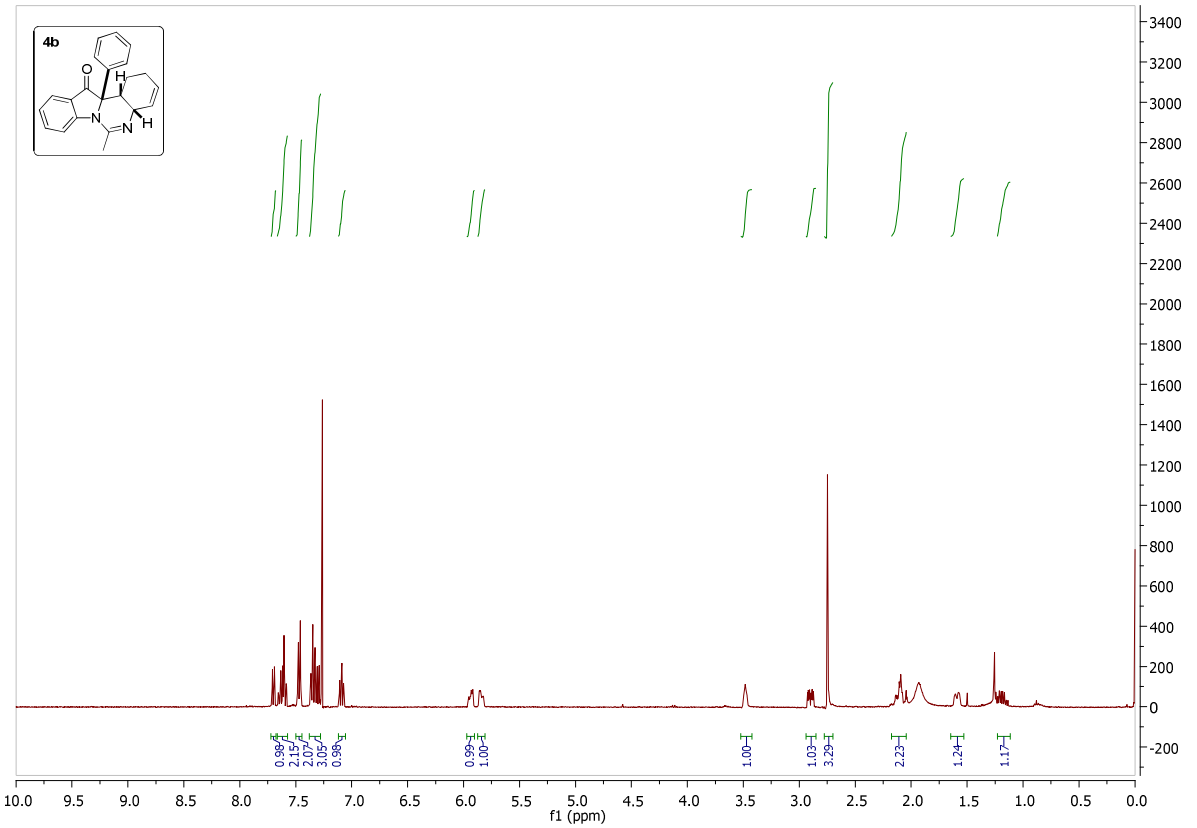
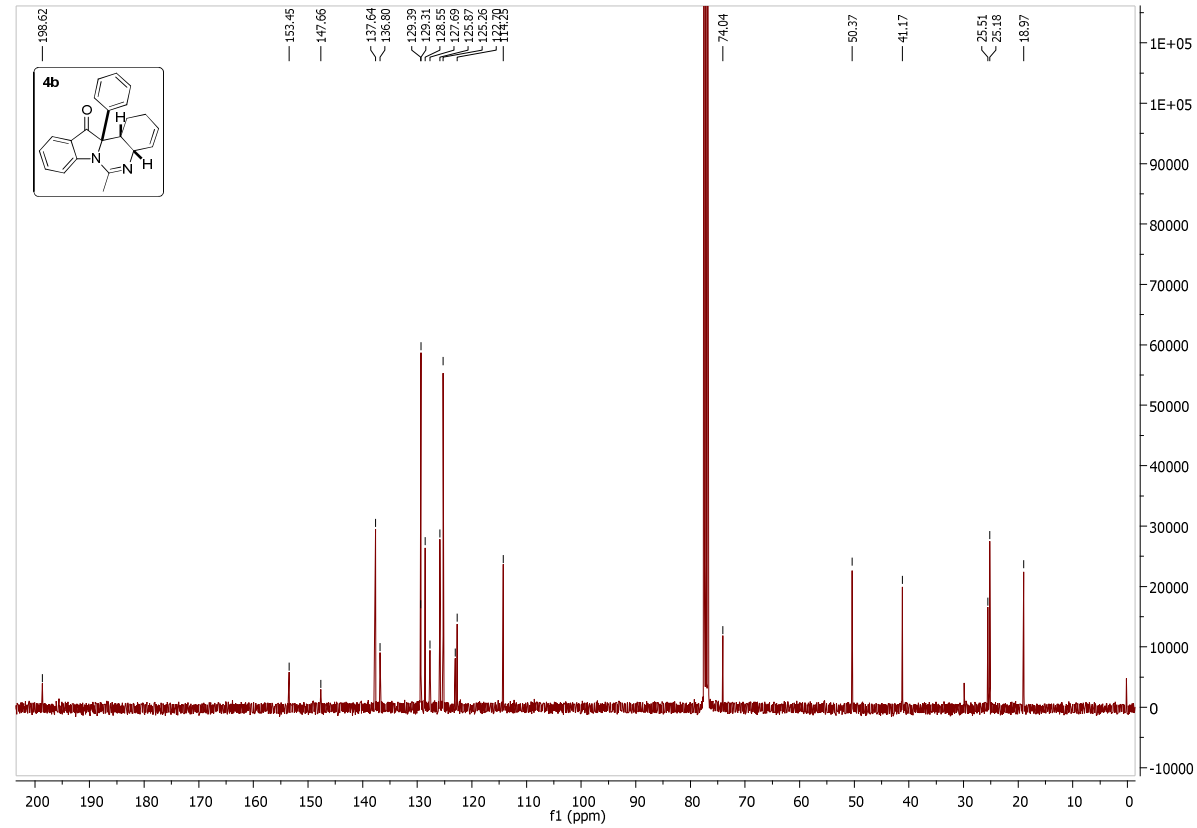
General experimental information

Unless stated otherwise, all reactions were carried out under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was performed on pre-coated Merk silica gel 60 F_{254} plates and visualized under a UV lamp. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (at 400 MHz and 100 MHz respectively). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{13}C-NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^{1}H-^{1}H-COSY, ^{1}H-^{13}CCOSY (HSQC: Heteronuclear Single Quantum Coherence) and long-range ^{1}H-^{13}CCOSY (HMBC: Heteronuclear Multiple Bond Connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in frequency of absortion (cm^{-1}). High Resolution Mass Spectrometry was performed by the University of Barcelona Mass Spectrometry Service.

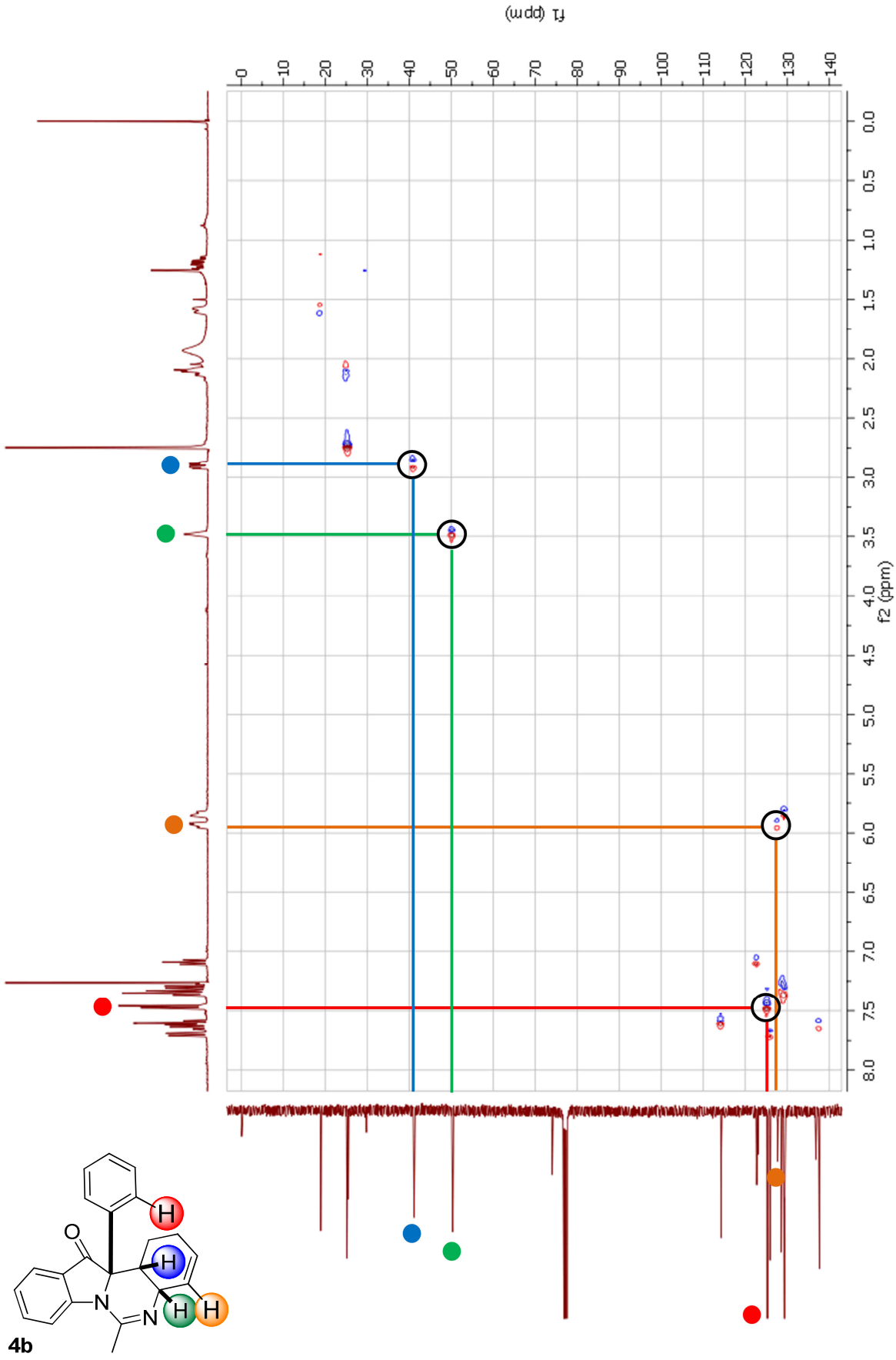
(4a*RS*,12a*SR*,12b*SR*)-6-methyl-12a-phenyl-1,4a,12a,12b-tetrahydroindolo[1,2-c]quinazolin-12(2*H*)-one (4b)

^{1}HNMR and ^{13}CNMR of **4b**

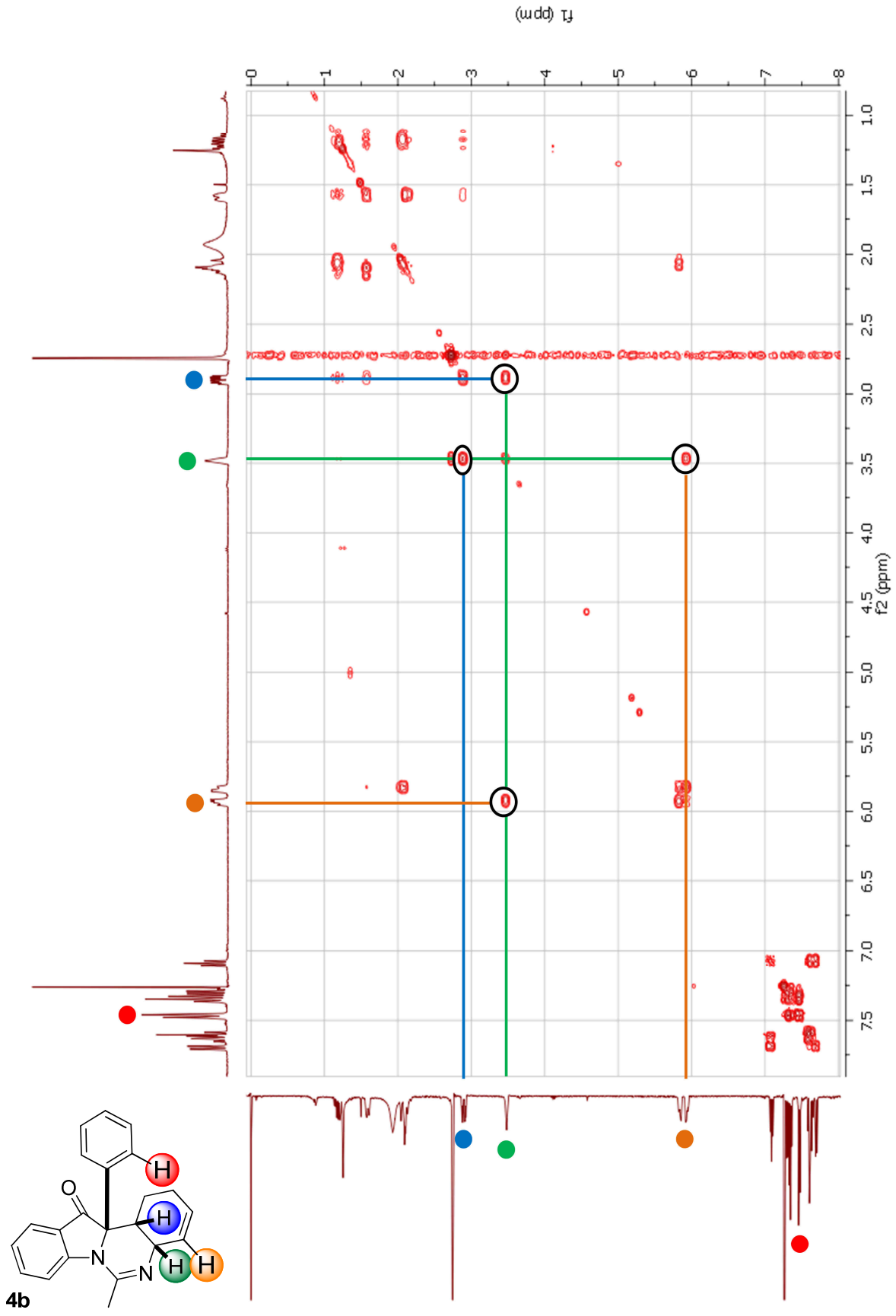




HSQC (Heteronuclear Single Quantum Correlation) of **4b**

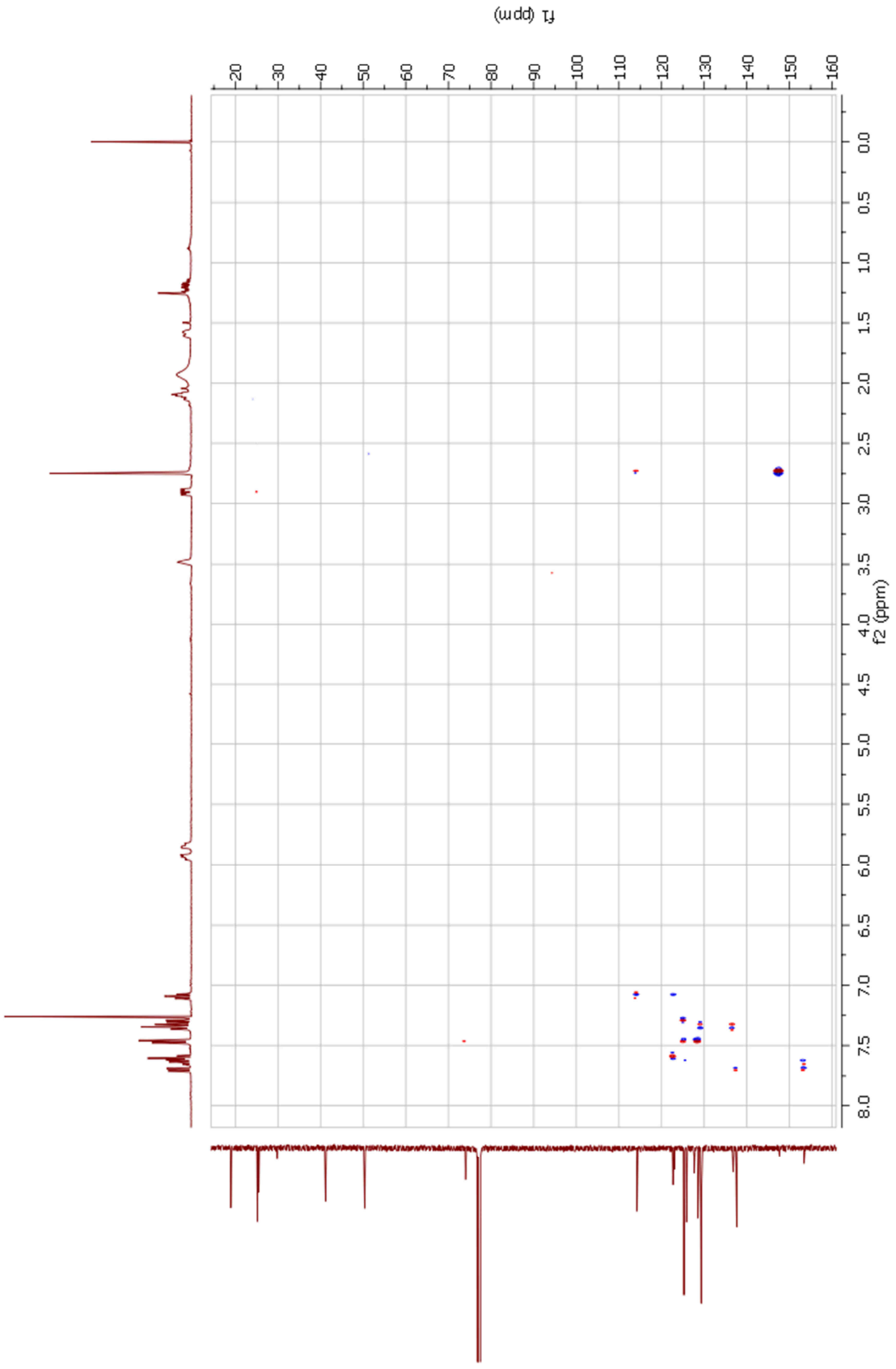


COSY (Correlation Spectroscopy) of **4b**

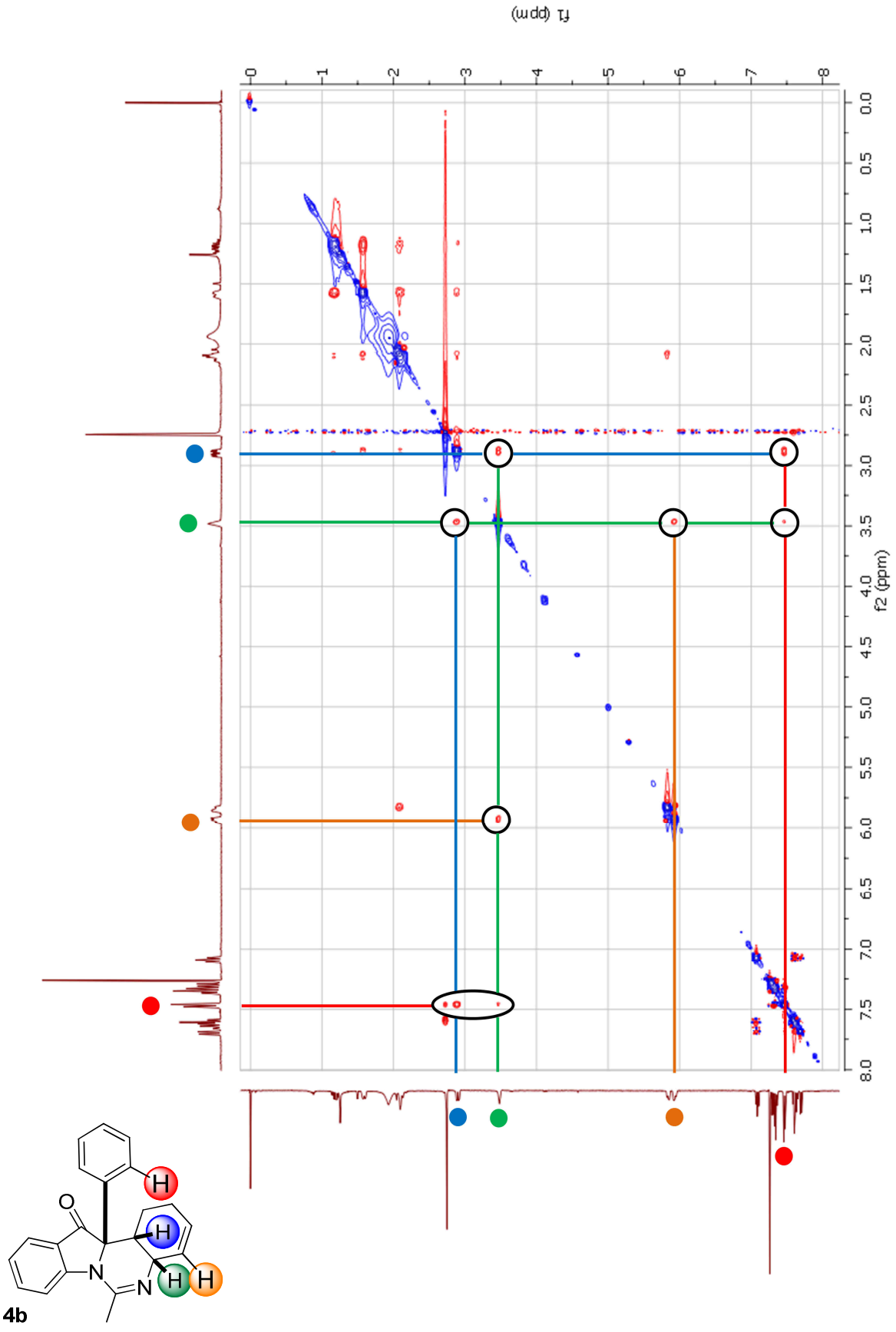


4b

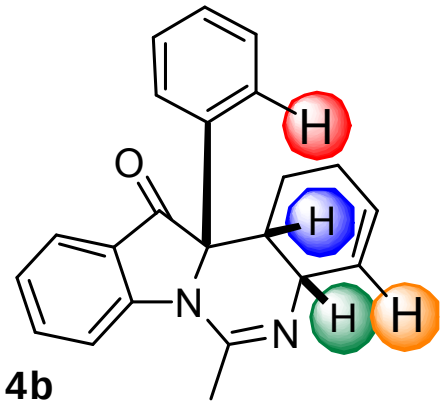
HMBC (Heteronuclear Multiple Bond Correlation) of **4b**



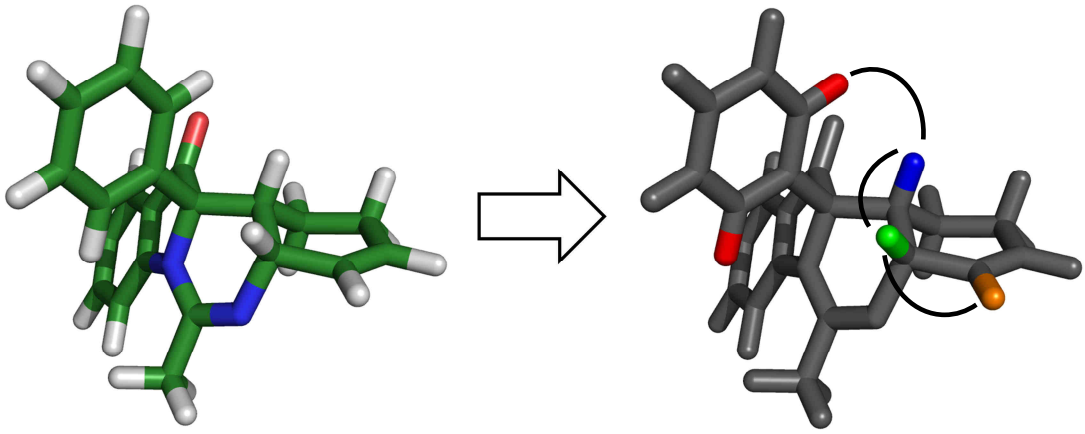
NOESY (Nuclear Overhauser Enhancement Spectroscopy) of **4b**



4b



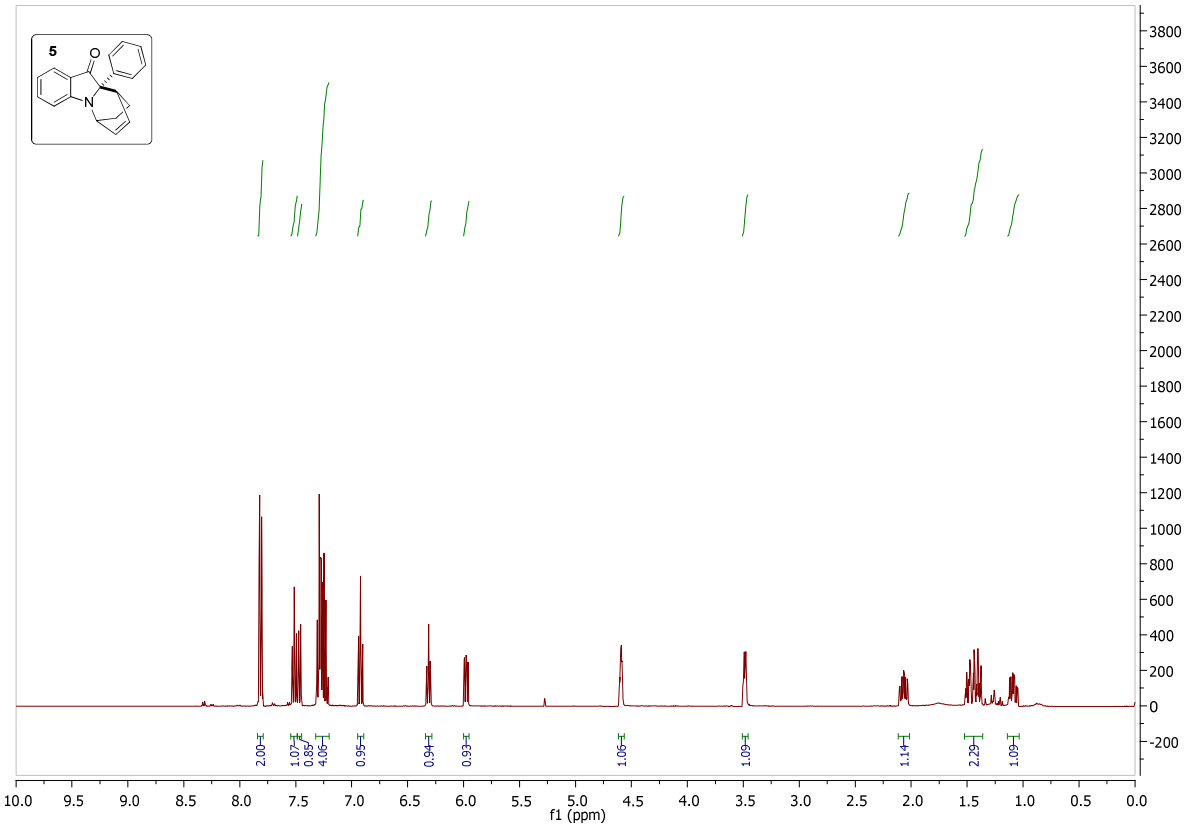
4b

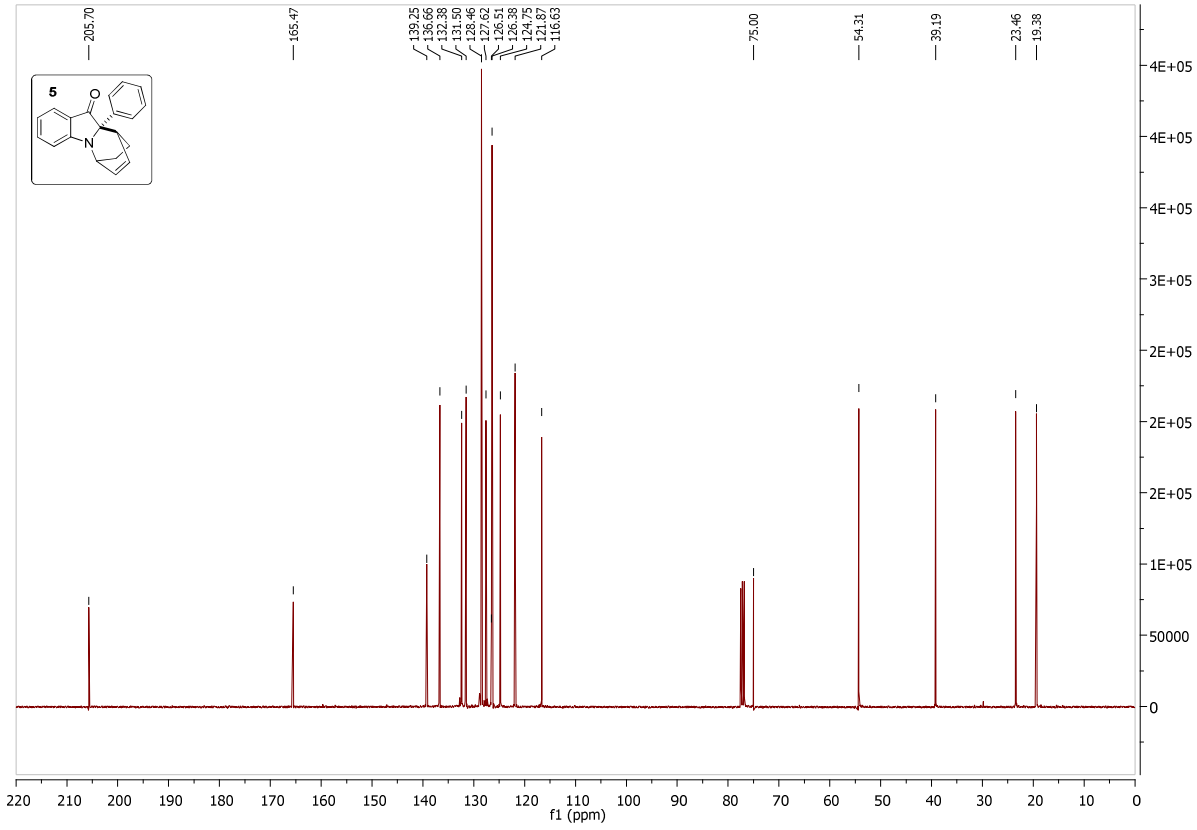


In this 3D optimized structure for **4b**, the NOE interactions observed in NMR experiments are shown in black lines. The distance between protons H ans H confirms the stereochemistry.

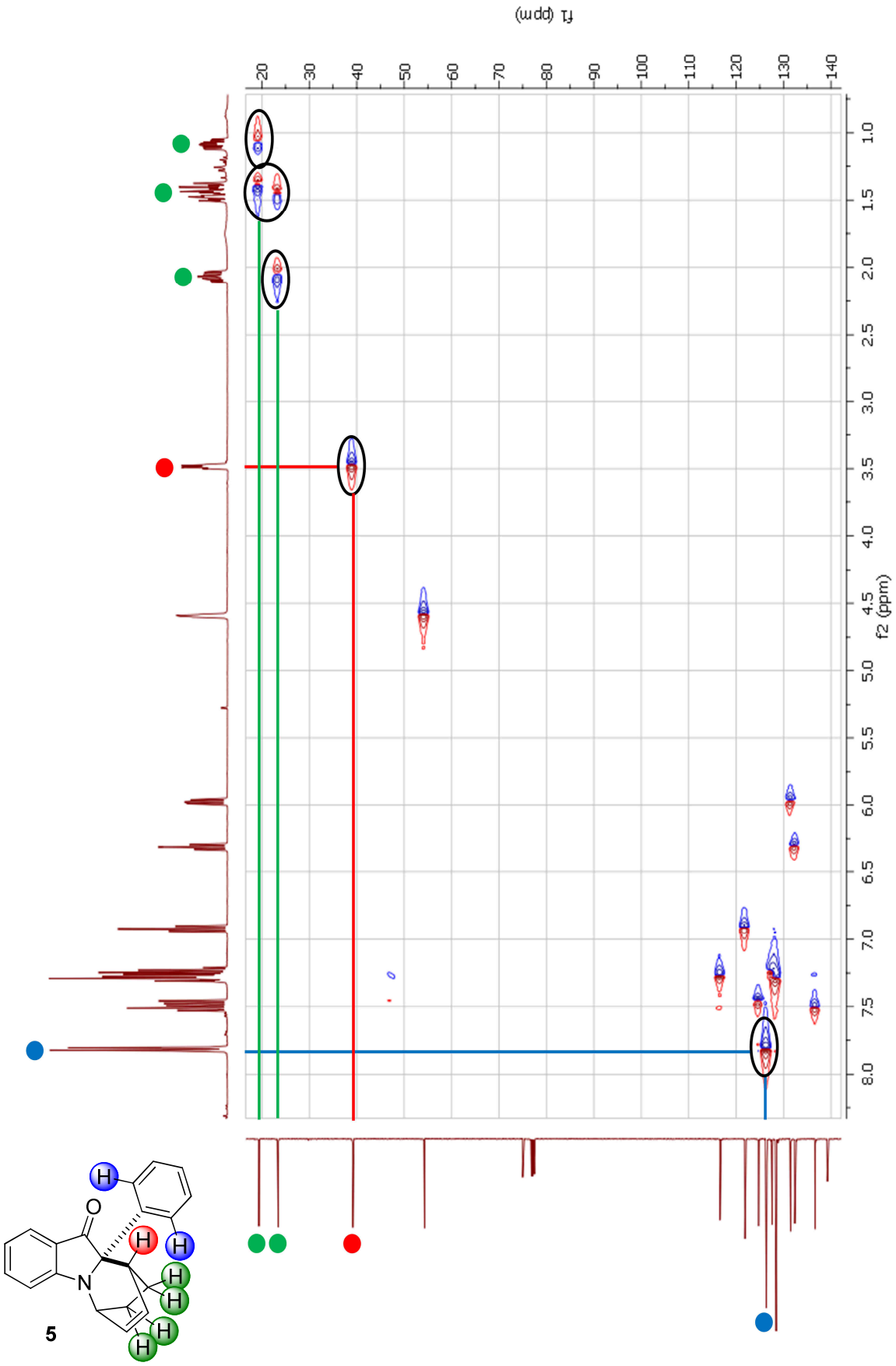
(9a*RS*)-9a-phenyl-9,9*a*-dihydro-6,9-ethanopyrido[1,2-a]indol-10(6H)-one (5)

^{1}HNMR and ^{13}CNMR of **5**

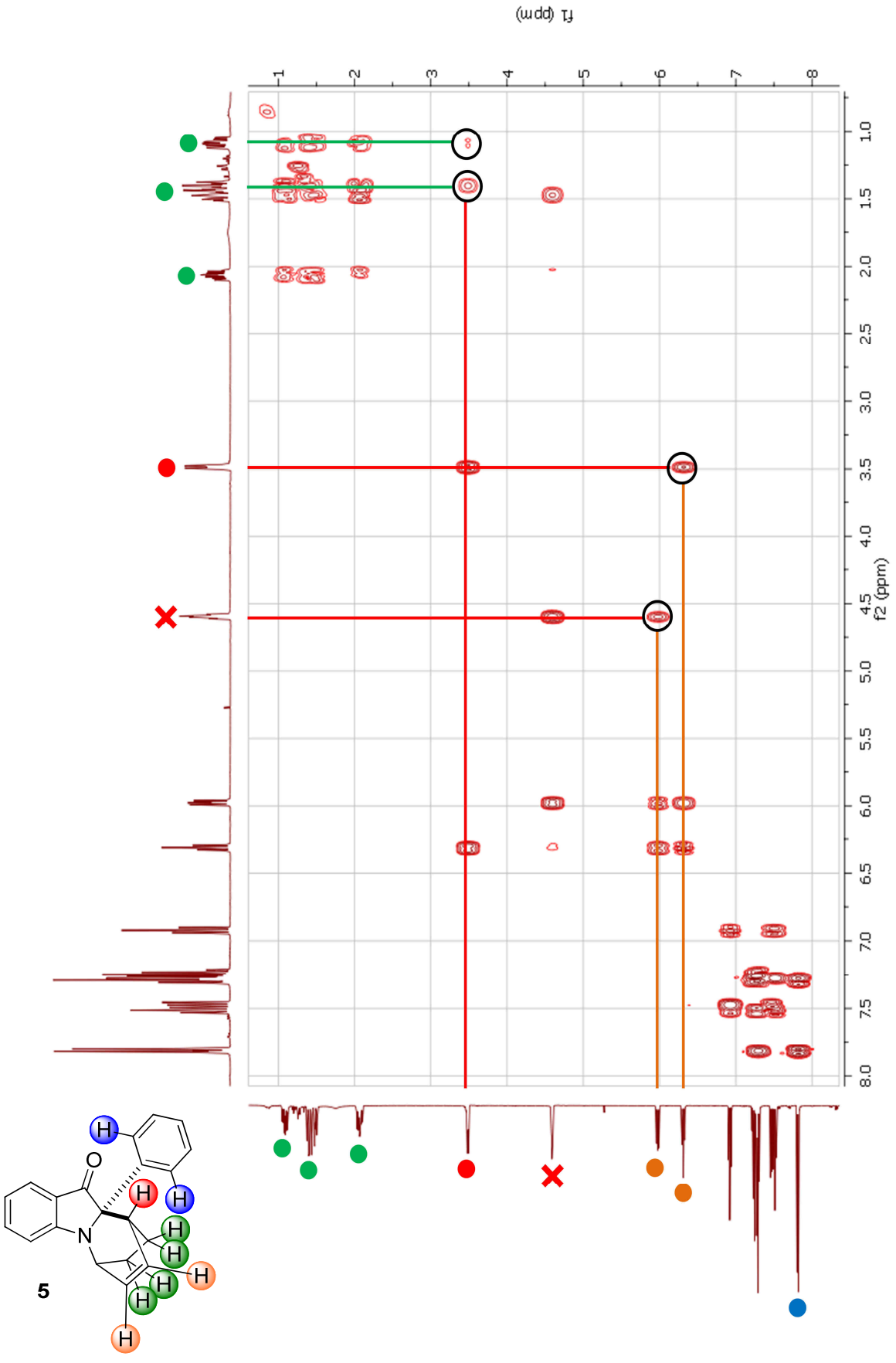




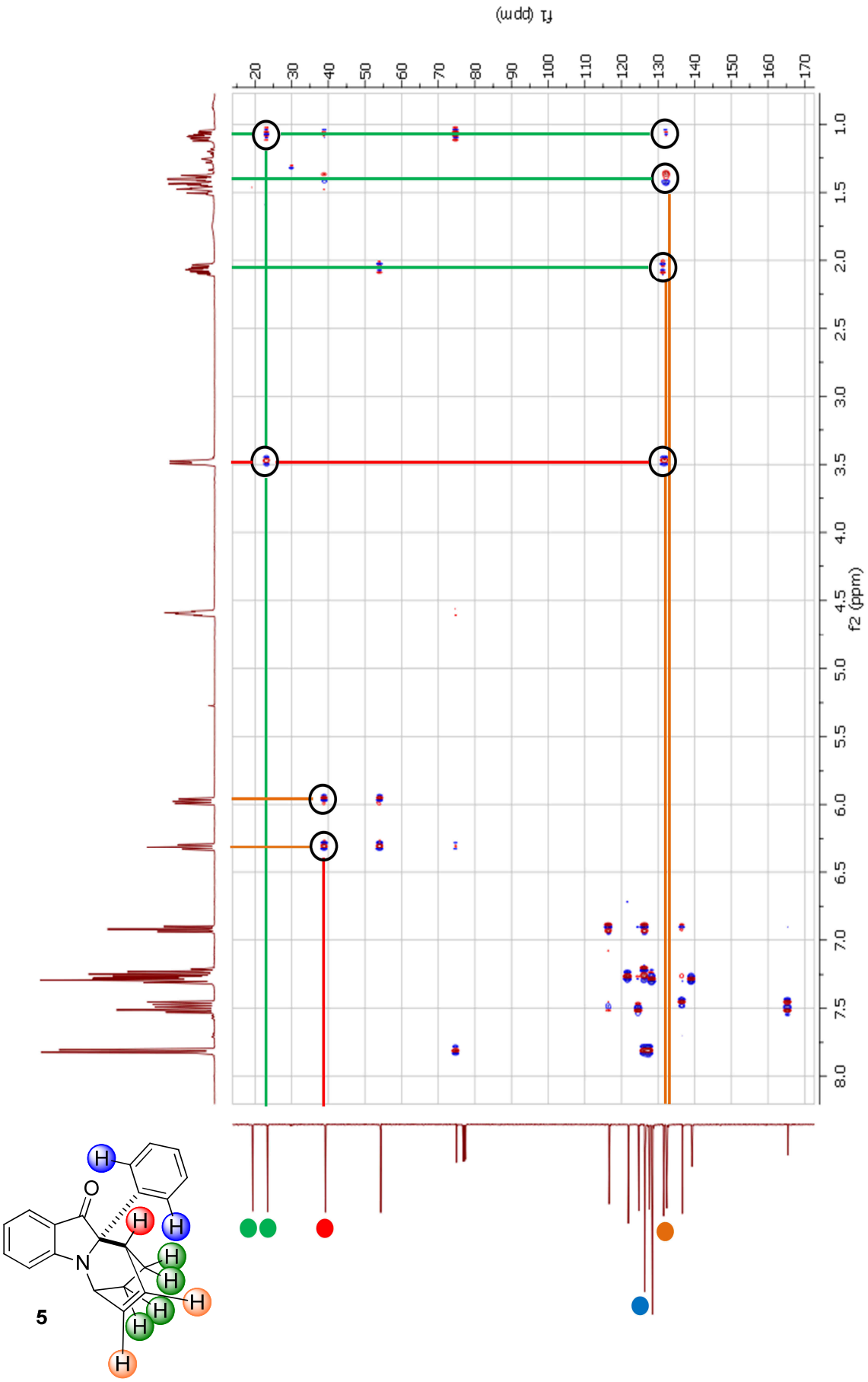
HSQC (Heteronuclear Single Quantum Correlation) of **5**



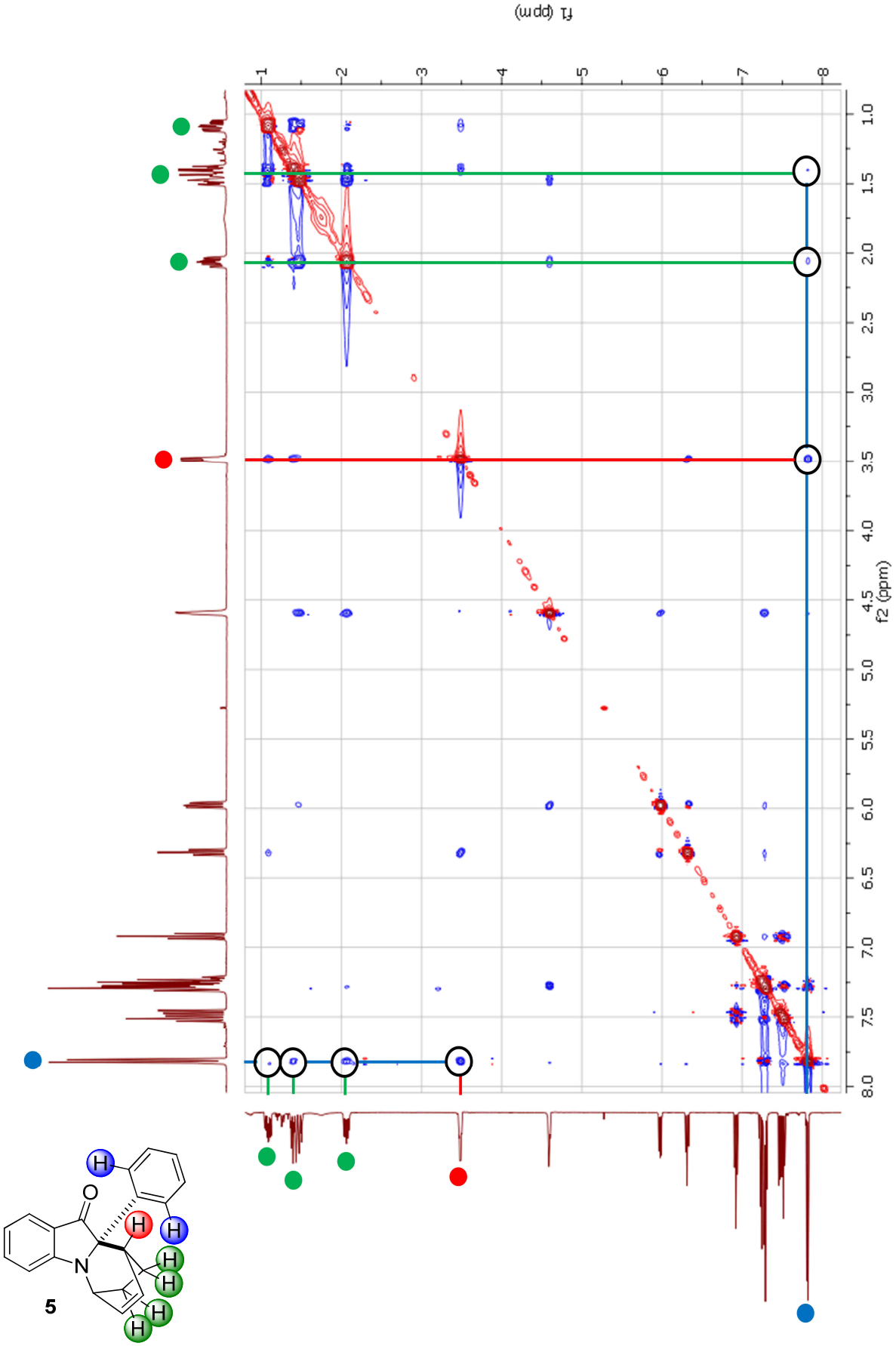
COSY (Correlation Spectroscopy) of **5**

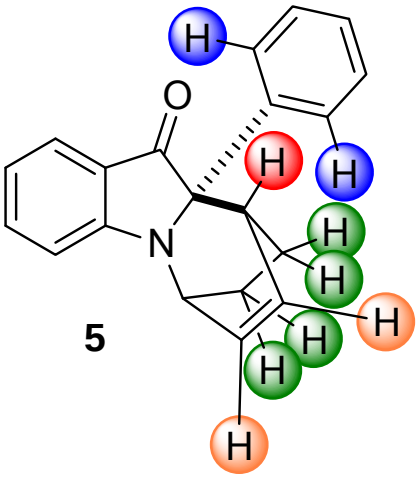


HMBC (Heteronuclear Multiple Bond Correlation) of **5**

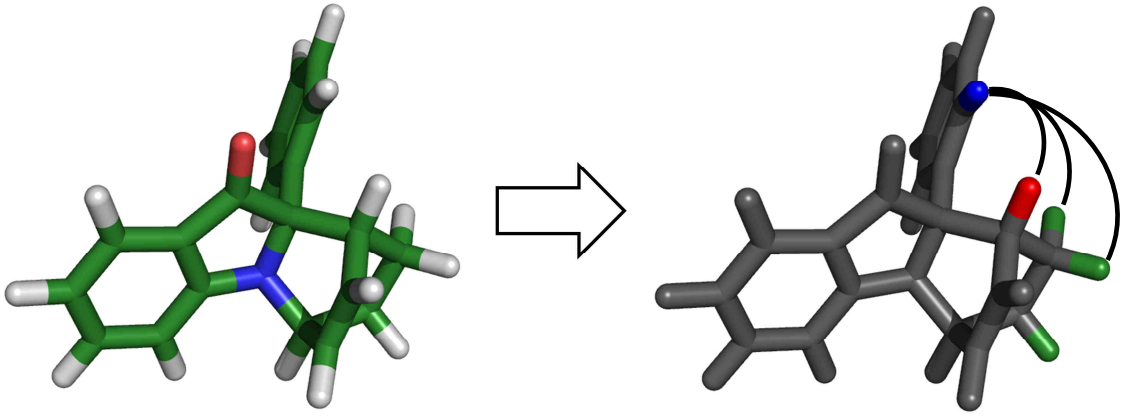


NOESY (Nuclear Overhauser Enhancement Spectroscopy) of **5**





5



In this 3D optimized structure for **5**, the NOE interactions observed in NMR experiments are shown in black lines. The distance between protons H and H confirms the stereochemistry.

6. Aplicación como inhibidores de AChE de derivados de la reacción de Povarov con lactamas insaturadas y enaminas cíclicas

Povarov MCR Derivatives as Novel Peripheric AChE Inhibitors

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KEYWORDS: Acetylcholinesterase, Alzheimer, Inhibitors, Povarov, Quinoline

ABSTRACT: A series of Povarov MCR derivatives have been designed, synthesized and evaluated as inhibitors of acetylcholinesterase (AChE), and self-induced β-amyloid (Aβ) aggregation. Molecular modeling suggests that these new pyridoquinolines interact with AChE filling the middle of the gorge and the peripheral site of the enzyme. These adducts reach nanomolar potencies and good selectivity against AChE, being almost inactive in front of butyrylcholinesterase.

Introduction

Multicomponent reactions (MCRs) have become a useful methodology for the synthesis of complex and structurally diverse compounds libraries, being suitable for medicinal chemistry purposes. This area of research provides an interesting, fast and modern way to discover novel drugs.[1]

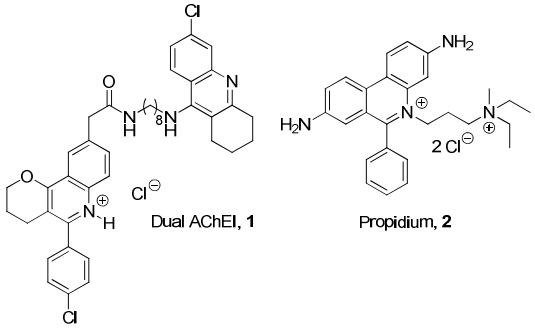
During the last years, we have published studies on the application of Povarov MCR to the efficient synthesis of a key fragment of potent dual binding site acetylcholinesterase enzyme inhibitors (AChEI) (**1**, Chart 1).[2] As acetylcholinesterase (AChE) is a crucial agent in Alzheimer's disease (AD), we plan to prepare a new set of Povarov adducts as AChEI to explore their anti-Alzheimer activities.

AD is one of the main causes of senile dementia. This illness was described in 1906 and nowadays affects millions of people and constitutes one of the most important health problems in the Western countries.[3] Recent studies show that AChE plays a key role in the early stages of AD by promoting the β-amyloid peptide (Aβ) aggregation.[4,5] The peripheral site of the enzyme is the moiety involved in the Aβ recognition, presumably triggering the initial formation of the neurotoxic micro-fibrils.[4] This discovery prompted the study and development of dual binding site inhibitors, affecting both the active and peripheral site (**1**, Chart 1) as a way to inhibit the Aβ aggregation.[2]

The peripheral-site inhibitors interact with Trp286 [human AChE (hAChE) numbering], presumably through cation-π interactions established between a positively charged nitrogen atom (quaternary nitrogen or basic nitrogen atom, protonated of physiological pH), and the indole moiety of the enzyme. Also, π-π stacking interactions with Trp286, reinforce the binding. The prototype of peripheral site AChEI is propidium (**2**, Chart 1), because it display a high potency and its position in the peripheral site has been elucidated by X-ray crystallography (PDB entry 1N5R).[6]

Herein, we report the synthesis, pharmacological evaluation, and molecular modeling of a family of potent peripheral AChEIs derivatives from Povarov – oxidation[7] processes. The pharmacological evaluation of these novel compounds includes AChE, butyrylcholinesterase (BChE) and self-induced Aβ aggregation inhibition.

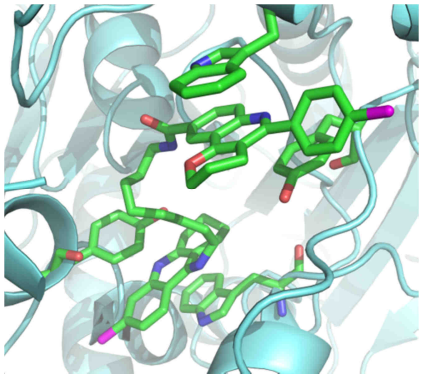
Chart 1. Active compounds as, dual binding site AChEI (**1**) and AChE peripheral inhibitor (**2**)



Recent results with the dual binging site AChEIs, have shown that pyranoquinolines **3** have potent interactions with the peripheral site of the enzyme and that the pyranoquinole unit stacks against the Trp286 and Tyr72 residues (Figure 1).[2] Accordingly, was thought that increasing the basicity of the Povarov adducts might enhance the affinity of the new structure for the AChE peripheral site, thereby extending the aromatic intercalation with π-cation interactions. Ideally, these new types of compounds, if potent enough, would not need the active site binder for their inhibitory activity.

Taking into account this goal, it becomes evident that the replacement of the heterocyclic O atom (in **3**) with a basic N, as in compound **4**, (Figure 1) would allow to reach a suitable basicity.

Figure 1. Representation of the binding mode of the pyranoquinoline inhibitor **1** with AChE,[2] and related quinolines **3** and **4**.

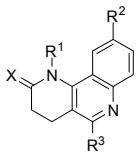


Chemistry

A combinatorial set with a common core was designed with a selection of substituents in all the accessible diversity points (R^1- R^3, Chart 2), trying to explore the related chemical space and find potent inhibitors targeting the enzyme peripheral site. Importantly, thanks to the convergent character of the Povarov MCR, these substituents are already present in the 3 reactants: the cyclic enamine, the aniline and the aldehyde. Then, a chemical library (Chart 2) was readily prepared following a synthetic methodology reported in our group.[8]

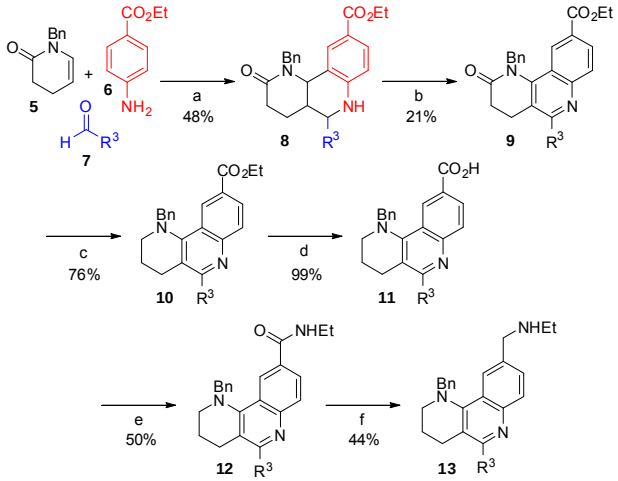
The synthesis starts with a Povarov MCR[7] (Scheme 1) among the corresponding unsaturated lactam **5** (as the activated olefin), aniline **6** and aldehydes **7**, under Lewis acid catalysis. This reaction afforded the tetrahydroquinoline adducts **8**, as a mixture of the *cis* and *trans* isomers. Without separation, the adducts were oxidized, using our recently reported Wako MnO_2-pyridine method,[9] to the corresponding quinolines **9**. Next, it is necessary to reduce the lactam carbonyl in a selective way, as a carboxylic ester is present in the structures. Beller recently reported a selective amide reduction[10] using zinc acetate and triethoxysilane, which allows this type of transformations. In this way, compounds **10** were conveniently prepared; the hydrolysis of the ester moiety afforded the corresponding carboxylic acids **11** which are converted to amides **12** by activation with chloroformate and amine coupling (Scheme 1). Finally, a standard amide reduction yields the desired amines **13**.

Chart 2. Combinatorial set of pyridoquinoline derivatives



Entry	Prod	X	R^1	R^2	R^3
1	**9a**	O	Bn	CO_2Et	*p*-Cl-Ph
2	**9b**	O	Bn	CO_2Et	*p*-CO_2Me-Ph
3	**9c**	O	Bn	CO_2Et	3-pyridyl
4	**10a**	2H	Bn	CO_2Et	*p*-Cl-Ph
5	**10b**	2H	Bn	CO_2Et	*p*-CO_2Me-Ph
6	**10c**	2H	Bn	CO_2Et	3-pyridyl
7	**12**	2H	Bn	CONHEt	*p*-Cl-Ph
8	**13**	2H	Bn	CH_2NHEt	*p*-Cl-Ph
9	**17a**	2H	H	CO_2Et	*p*-Cl-Ph
10	**17b**	2H	H	CO_2Et	3-pyridyl
11	**18**	2H	4-MeO-Bn	CO_2Et	*p*-Cl-Ph
12	**20**	2H	H	CONHEt	*p*-Cl-Ph
13	**21a**	2H	H	CH_2NHEt	*p*-Cl-Ph
14	**21b**	2H	H	CH_2NHEt	3-pyridyl

Scheme 1. Synthesis of quinoline derivatives **8-13**

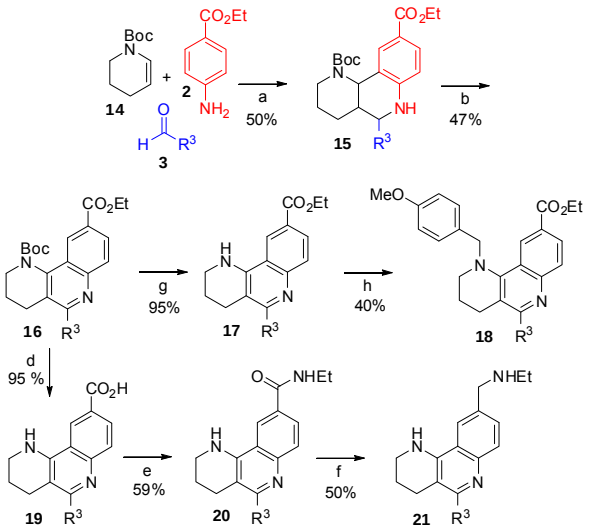


a) $Sc(OTf)_3$, ACN, rt, 24 h. b) MnO_2, Toluene, 55 ºC 2 h. c) $Zn(OAc)_2$, $(EtO)_3SiH$, THF, 65 ºC, 2 h. d) 1. KOH, MeOH, 65 ºC, 24 h; 2. HCl, Et_2O. e) 1. Et_3N, $ClCO_2Et$, DCM; 0 ºC, 30 min; 2. $EtNH_2$, DCM, rt, 72 h. f) $LiAlH_4$, THF, 66 ºC, 15 h.

Regarding the introduction of diversity in the piperidine nitrogen atom, a modified synthesis using *N*-Boc cyclic enamine **14** was performed. As before, the Povarov MCR takes place among the corresponding precursors, obtaining the tetrahydroquinoline adducts **15**, as a mixture of stereoisomers, these were oxidized with MnO_2 to yield the quinolines **16** (Scheme 2). Deprotection of the *N*-Boc in compounds **16** was performed with mild acidic conditions to yield the piperidine derivatives **17**, next alkylation of the secondary amine group with a benzyl halide, afforded the piperidine

derivatives **18**. Alternatively, a vigorous acid treatment of quinolines **16** cursed with simultaneous ester hydrolysis and, in this way, the deprotected amines **19** were conveniently obtained. From these carboxylic acids, amide formation (to yield compounds **20**), and $LiAlH_4$ reduction afforded the final compounds **21** (Scheme 2).

Scheme 2. Synthesis of quinolines derivatives **15-21**



a) $Sc(OTf)_3$, ACN, rt, 24 h. b) MnO_2, Toluene, 55 ºC 2 h. d) 1. KOH, MeOH; 65 ºC, 24 h. 2. HCl, Et_2O. e) 1. Et_3N, $ClCO_2Et$, DCM; 0 ºC. 30 min; 2. $EtNH_2$, DCM, rt, 72 h f) $LiAlH_4$, THF, 66 ºC, 24 h. g) HCl/dioxane 4 N, rt, 18 h. h) 1-(chloromethyl)-4-methoxybenzene, NaH, DMSO, rt, 18 h**.**

Pharmacology and Molecular Modeling.

Cholinesterase Inhibition. **AChE Inhibition.** The AChE inhibitory activity of compounds **9a-c**, **10a-c**, **12**, **13**, **17a-b, 18**, **20** and **21a-b** was determined using the method of Ellman *et al.*[11] on AChE from electric eel (eeAChE) (Table 1). The mentioned quinolines are potent inhibitors, with IC_{50} values on the nanomolar and low nanomolar range in most cases. Compound **20** was the most active (Chart 2, Table 1). Remarkably, this compound has no substitution in the fused piperidino N, the R^2 substituent being an amide and the R^3 a *p*-chlorophenyl group. The rest of compounds that display low nanomolar activity are **13**, **17a-b** and **21a**. Although the structural features seem to be a little divergent, they have in common the presence of, at least, one basic nitrogen capable of hydrogen bonding. The rest of compounds show a micromolar activity or no activity. The exhibited inhibition is somewhat lower than the best dual binding site inhibitors,[12] but exceedingly high for such small molecules.

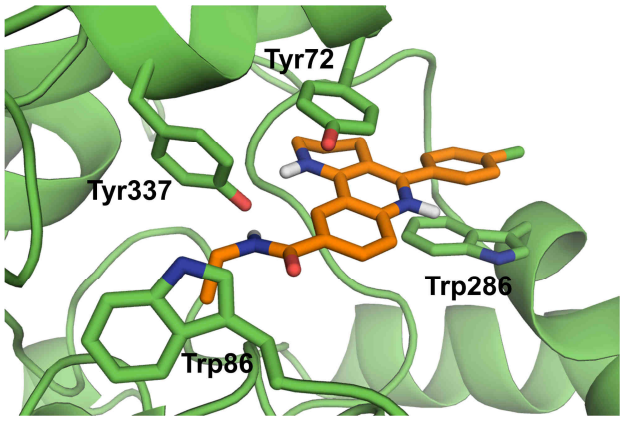
Molecular Modeling Studies. To gain insight into the molecular determinants that modulate the eeAChE inhibitory activity of the novel compounds, the binding mode of the more active product **20** was investigated by means of docking calculations. The conformation of the active site and the gorge appears to be highly conserved in different X-ray crystallographic structures, whereas slight modifications are found in the peripheral site residues, mainly affecting Trp286. However, due to the chemical similarity with propidium, the binding mode of the amino quinoline unit of our compounds can be inferred form the X-ray crystallographic structure of the enzyme complex with propidium.[12]

Table 1. eeAChE Inhibition.

Entry	Compd	IC_{50} (eeAChE) μM	IC_{50} (hBChE) μM
1	**9a**	5.21	>100
2	**9b**	13.6	>100
3	**9c**	>10	>100
4	**10a**	6.33	>100
5	**10b**	6.62	>100
6	**10c**	1.97	nd
7	**12**	5.48	>100
8	**13**	0.147	nd
9	**17a**	0.281	>100
10	**17b**	0.148	nd
11	**18**	>10	>100
12	**20**	0.046	0.92
13	**21a**	0.532	1.37
14	**21b**	2.15	2.59

After removing the propidium unit from the complex, the quinoline **20** was docked on it and the most stable binding mode was determined (Figure 2). Inspection of the model reveals that interaction of the π system protonated quinoline nitrogen atom of the inhibitor with the aromatic moieties of Trp286 and Tyr72 takes place, together with H-bonding of the lateral amide with Tyr337 (Figure 2). The balance of these attractive interactions can account for the high affinity of this compound for its receptor site. On the other hand, compared to propidium, which fills the peripheral site, compound **20** is more deeply inserted into the gorge, which likely contributes to explain its better inhibitory activity (Figure 3).

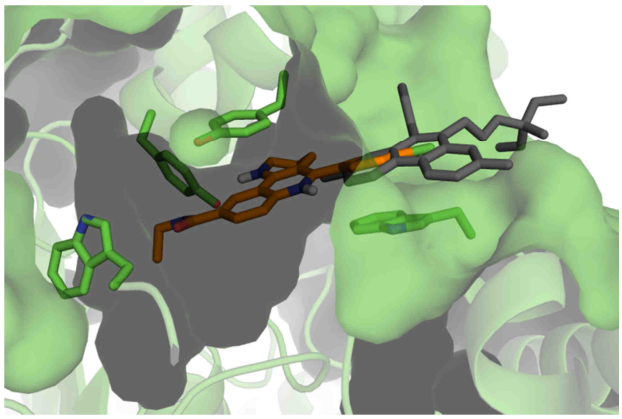
Figure 2. Representation of the most favorable binding mode of quinoline **20** with the AChE (detail).



Butyryl Cholinesterase Inhibition. Recent evidence has shown that inhibition of butyryl cholinesterase (BChE) might be valuable in the search for anti-Alzheimer agents,[13] but selective interaction of AChE in front of BChE has been also reported to reduce cholinergic side effects, as the latter is

mainly expressed outside the central nervous system. Interestingly, the best compounds against AChE display much lower inhibition potency upon BChE (see Table 1).

Figure 3. Comparison between the most favorable binding modes of quinoline **20** (colored) and propidium (grey) within the AChE gorge (detail).



Inhibition of Spontaneous Aβ Aggregation. The novel compound herein described exhibit a mild but significant inhibitory activity on Aβ self-aggregation (see Table 2). Studies regarding the AChE-mediated Aβ aggregation, including propidium displacement,[14] are currently being carried out.

Table 2. β-Amyloid self-aggregation Inhibition

Entry	Compd	Aβ self-induced aggregation (%)	Entry	Compd	Aβ self-induced aggregation (%)
1	**9a**	5.0	6	**10c**	8.0
2	**9b**	4.2	7	**12**	10.5
3	**9c**	5.2	8	**13**	3.6
4	**10a**	0.5	9	**17a**	5.7
5	**10b**	10.5	11	**18**	1.9

Conclusions

A series of novel small molecule inhibitors designed to bind the peripheral site of AChE have been designed, synthesized and tested. The new chemotype of these compounds consists in a fused pyrido-quinoline unit decorated with a diverse combination of substituents at several positions. Remarkably, the synthesis of such compounds is very straightforward using a Povarov MCR which efficiently engages the three reactants directly leading to the desired substitution pattern. Potent (low nanomolar) inhibition is achieved for some compounds, and a mild activity decreasing the Aβ peptide aggregation is observed for some of them. Molecular modeling studies show binding modes compatible with the determined inhibition, and are in agreement with their action upon the peripheral site.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral and analytical data of synthesized compounds. Pharmacological experiments, tables and figures with additional data of docking, molecular dynamics. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

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ABBREVIATIONS

Acetylcholinesterase enzyme (AChE), Acetylcholinesterase enzyme inhibitors (AChEI), Alzheimer disease (AD), Butyryl Cholinesterase (BChE), AChE from electric eel (eeAChE), β-amyloid (Aβ), Multicomponent reaction (MCR), human acetylcholinesterase enzyme (hAChE)

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Supporting information

Povarov MCR Derivatives as Novel Peripheric AChE Inhibitors

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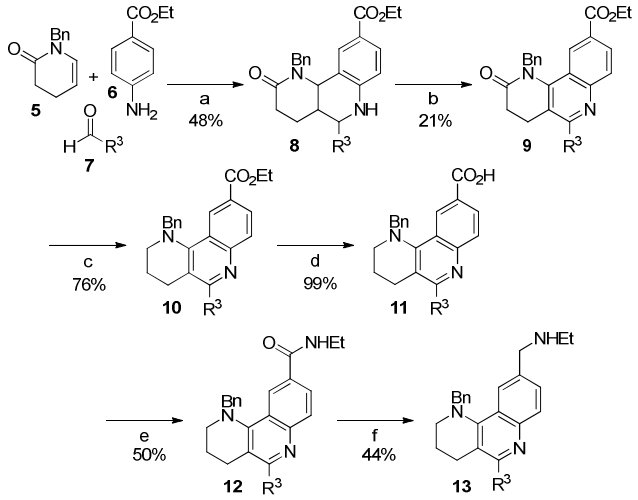
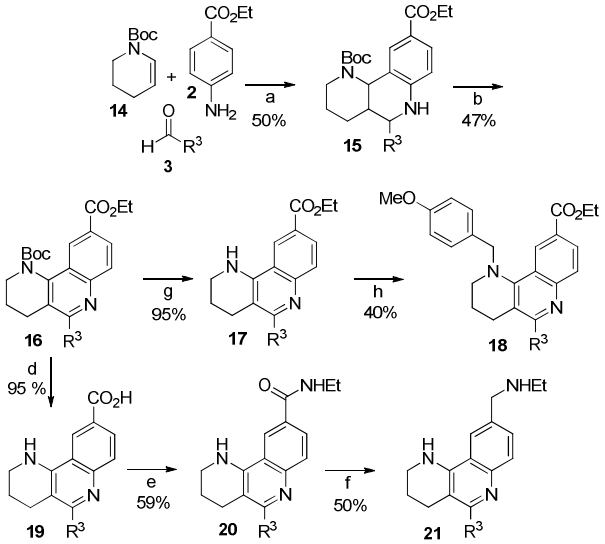
General experimental information

Unless stated otherwise, all reactions were carried out under argon atmosphere in dried glassware. Commercially available reactants were used without further purification. Thin-layer chromatography was performed on pre-coated Merk silica gel 60 F_{254} plates and visualized under a UV lamp. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (at 400 MHz and 100 MHz respectively). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$ solution with TMS as an internal reference. Data for ^{1}H-NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, integration and coupling constants (Hz). Data for ^{13}C-NMR spectra are reported in terms of chemical shift (δ ppm). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^{1}H-^{1}H-COSY, ^{1}H-^{13}CCOSY (HSQC: Heteronuclear Single Quantum Coherence) and long-range ^{1}H-^{13}CCOSY (HMBC: Heteronuclear Multiple Bond Connectivity). IR spectra were recorded using a Thermo Nicolet Nexus spectrometer and are reported in frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry was performed by the University of Barcelona Mass Spectrometry Service.



Scheme 1. Synthesis of quinolines derivatives **8**-**13**



Scheme 2. Synthesis of quinolines derivatives **15**-**21**

General procedure A: Synthesis of tetrahydroquinolines 8 and 15

Molecular sieves 4Å (ca. 2g) and a $Sc(OTf)_3$ (0.2 mmol) were added to a solution of aldehyde **7** (1 mmol) and aniline **6** (1 mmol) in dry CH_3CN (4 mL), and the mixture was stirred at room temperature. After 5 min, a solution of the activated olefin **5** or **14** (1 mmol) in dry CH_3CN (3 mL) was added, and the resulting suspension was stirred under argon atmosphere at the same temperature. When the reaction was complete an aqueous saturated $NaHCO_3$ solution (10 mL) was added, and the resulting mixture was extracted with EtOAc (3×10 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexane- EtOAc) to give the desired products.

General procedure B: Synthesis of quinolines 9 and 16

To a solution of compound **8** or **15** (1 mmol) in 50 mL of toluene, pyridine (6 mmol) and MnO2 Wako (100 mmol) were added and the mixture was stirred in an open vessel at 55 ºC. The progress of the reaction was controlled by TLC or HPLC-MS, until the starting material completely disappeared or no evolution was observed. The crude mixture was filtered through Celite and wash with MeOH, finally the filtrate was concentrated in vacuo. The reaction mixture was purified by flash chromatography (hexane–EtOAc) to afford the desired product.

General procedure C: Synthesis of quinoline 10

In a oven dried schlenk tube with zinc acetate (0.1 mmol) and triethoxysilane (2.2 mmol), dry THF (2 mL) was added after purging the schlenk tube with argon. The resulting mixture was stirred for 30 minutes at room temperature. Then the respective amide-quinoline **9** (1 mmol) in dry THF (1mL) was transferred to the solution under argon. The mixture was stirred at 65 ºC for 2-3h and monitored by TLC or HPLC-MS. After complete disappearance of the substrates, the reaction mixture was vigorously stirred with 3 mL (1M) NaOH solution for 10 minutes and then extracted with EtOAc (3x5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography using EtOAc / hexane to afford the pure desired product.

General procedure D: Synthesis of acids 11 and 19

A suspension of ester **10** or **18** (1 mmol) and KOH (3 mmol) was prepared in MeOH (25 mL). The reaction mixture was stirred under reflux for 24 h. The resulting mixture was cooled down at room temperature and concentrated under reduced pressure. The solid residue was treated with a 0.5 M $HCl{\cdot}Et_2O$ solution (40 mL) and the resulting suspension was concentrated under reduced pressure to give the desired product. It was used in the next step as crude.

General procedure E: Synthesis of amide 12 and 20

To a solution of **11** (1 mmol, of the pure starting material as a maximum) in dry DCM (5 mL) under inert atmosphere was prepared, cooled to 0 ºC in an ice bath and treated with Et_3N (4 mmol) and $ClCO_2Et$ (1 mmol) was added, and the reaction mixture was stirred at room temperature for 72 h. The resulting mixture was treated with a 10 % Na_2CO_3 aqueous solution (200 mL). The phase was separated and the aqueous one was again extracted with DCM (3×100 mL). The combined organic extracts were washed with H_2O (2×100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude that was purified by flash chromatography to afford the desired product.

General procedure F: Synthesis of amine 13 and 21

A solution of the amide **12** (1 mmol) in anhydrous THF (20 mL) was cooled to 0 ºC in an ice bath and $LiAlH_4$ (3 mmol) was added in portions. The resulting suspension was stirred under reflux for 15 h, then cooled to 0 ºC in an ice bath and treated with a 1 N NaOH aqueous solution (14 mL). The resulting mixture was partitioned between H_2O (35 mL) and EtOAc (35 mL), the phases were separated and the aqueous phase was again extracted with EtOAc (2×35 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography to afford the pure desired compound.

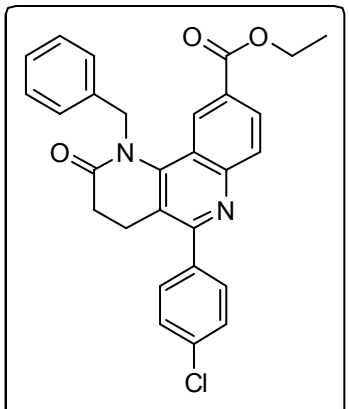
General procedure G: Synthesis of quinoline 17

Compound **16** (1 mmol) was dissolved in 40 mL of a 4 M HCl/dioxane solution at 0 ºC. The resulting mixture was stirred at room temperature for 18 h (control by TLC). After completion of the reaction, the reaction mixture was concentrated under reduced pressure. Water was added to the residue, and the pH of the resultant mixture was adjusted to 9 with a saturated sodium carbonate solution. The mixture was extracted with a 10 % MeOH/$CHCl_3$ mixture, dried over Na_2SO_4 and concentrated under reduced pressure. No further purification was carried out due to the high purity of the final product.

General procedure H: Synthesis of quinoline 18

The alkylation of **17** was carried out using 1-(chloromethyl)-4-methoxybenzene as alkylating agent (1.1 mmol) and NaH (1.1 mmol) in DMSO at room temperature for 18 h (monitored by HPLC-MS). After the completion of the reaction, the quench was performed at 0 ºC with HCl aq. solution to neutralize the NaOH formed during the quench. The pH was adjusted to pH 7-8 with an aqueous sodium bicarbonate. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under *vacuo*. Purification by column chromatography yielded the desire compound.

Ethyl 1-benzyl-5-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (9a)

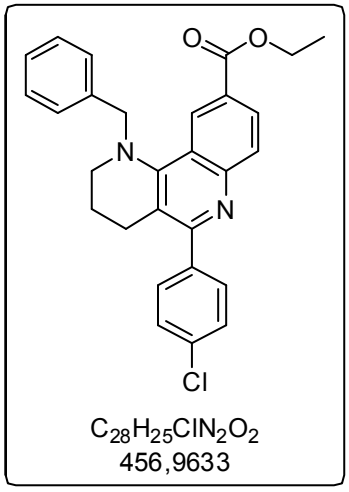


$C_{28}H_{23}ClN_2O_3$
470,9468

Following the general procedure B, the reaction oxidation of **8a**, afforded compound **9a** (21% of the oxididation - 10% of 2 steps from the MCR) after flash chromatography as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 1.6 Hz, 1H), 8.27 (dd, *J*= 8.8, 1.7 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.59-7.54 (m, 2H), 7.52-7.46 (m, 2H), 7.27-7.22 (m, 3H), 7.16-7.11 (m, 2H), 5.41 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.99-2.93 (m, 2H), 2.68-2.63 (m, 2H), 1.35 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 172.6, 166.0, 159.1, 150.4, 148.1, 137.8, 137.2, 135.5, 130.9, 130.6, 129.0, 128.9, 128.7, 128.0, 127.7, 127.3, 126.2, 122.1, 119.4, 61.6, 52.7, 32.8, 23.8, 14.5 ppm. **IR** (film) ν_{max}: 3459, 2981, 1693, 1567, 1442, 1272, 1196, 1090, 1011, 836, 746. **HRMS**: calcd for $C_{28}H_{24}ClN_2O_3$ 471.1470 ($M+H^+$); found, 471.1473.

Ethyl 1-benzyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (10a)

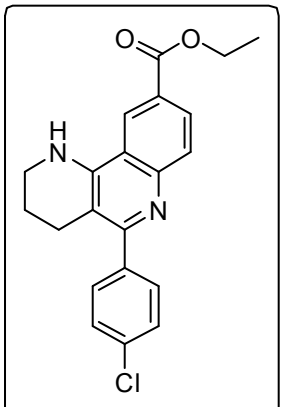


$C_{28}H_{25}ClN_2O_2$
456,9633

Following the general procedure C, the amide reduction of **9a**, afforded compound **10a** (76% of the reduction - 8% of 3 steps form de MCR) after flash chromatography as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.70 (d, *J* = 1.7 Hz, 1H), 8.08 (dd, *J*= 8.8, 1.8 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.52-7.36 (m, 8H), 7.33-7.27 (m, 1H), 4.60 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.25-3.19 (m, 2H), 2.67 (t, *J* = 6.3 Hz, 2H), 1.84-1.76 (m, 2H), 1.04 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 166.5, 160.8, 153.9, 150.1, 139.6, 138.0, 134.5, 130.3, 130.3, 129.0, 128.7, 128.4, 127.7, 127.1, 126.6, 126.2, 120.8, 117.3, 61.1, 60.9, 49.1, 27.2, 19.3, 14.2 ppm. **IR** (film) ν_{max}: 3385, 2969, 2930, 2841, 1713, 1611, 1561, 1494, 1438, 1322, 1265, 1090, 1028, 842, 727. **HRMS**: calcd for $C_{28}H_{26}ClN_2O_2$ 457.1677 ($M+H^+$); found, 457.1680.

Ethyl 5-(4-chlorophenyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (17a)

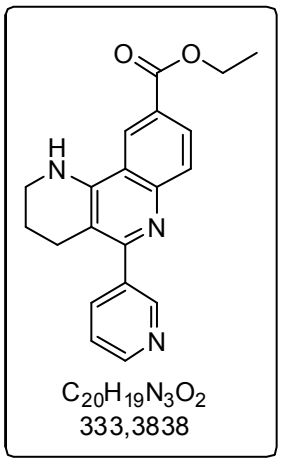


$C_{21}H_{19}ClN_2O_2$
366,8408

Following the general procedure G, the deprotection of the corresponding adduct **16** afforded compound **17a** (97% of the deprotection - 53% from the MCR) after flash chromatography as a white powder.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.45 (d, *J* = 1.4 Hz, 1H), 8.06 (dt, *J*= 20.7, 10.4 Hz, 1H), 7.85 (t, *J* = 9.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.72 (bs, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.51-3.37 (m, 2H), 2.64 (t, *J* = 6.1 Hz, 2H), 1.91-1.73 (m, 2H), 1.31 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 166.6, 160.4, 149.1, 147.7, 139.5, 134.2, 130.3, 129.9, 128.4, 128.3, 125.8, 122.8, 116.4, 108.1, 61.2, 41.6, 25.6, 20.8, 14.5 ppm. **HRMS**: calcd for $C_{21}H_{20}ClN_2O_2$ 367.67 ($M+H^+$); found, 367.1208.

Ethyl 5-(pyridin-3-yl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (17b)

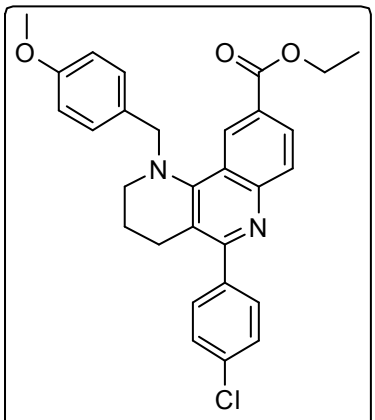


$C_{20}H_{19}N_3O_2$
333,3838

Following the general procedure G, the deprotection of the corresponding adduct **16** afforded compound **17b** (95% of the deprotection - 22% from the MCR) after flash chromatography as a white powder.

^{1}H-NMR (400 MHz, MeOD) δ: 9.30 (s, 1H), 9.11 (s, 1H), 9.05 (d, *J* = 1.5 Hz, 1H), 8.84 (d, *J* = 8.0 Hz, 1H), 8.40 (dd, *J* = 8.8, 1.5 Hz, 1H), 8.25 (dd, *J* = 7.7, 5.8 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.79-3.68 (m, 2H), 2.84-2.74 (m, 2H), 2.09-1.96 (m, 2H), 1.46 (t, *J*= 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, MeOD) δ: 166.3, 156.2, 146.7, 146.5, 145.9, 145.3, 141.2, 134.2, 132.5, 129.8, 128.2, 126.2, 121.3, 116.3, 111.2, 62.9, 43.2, 24.6, 19.7, 14.6 ppm. **HRMS**: calcd for $C_{20}H_{19}N_3O_2$ 334.1550 ($M+H^+$); found, 334.1558.

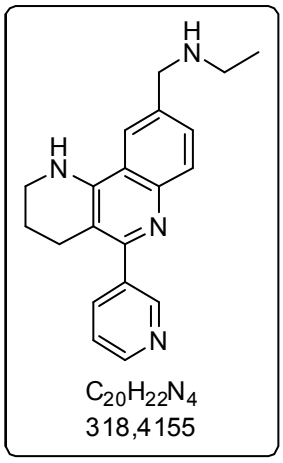
Ethyl 5-(4-chlorophenyl)-1-(4-methoxybenzyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (18)



$C_{29}H_{27}ClN_2O_3$
486,9893

Following the general procedure H, the reaction of **17a** afforded compound **18** (40% of the alquilation - 21% from the MCR) after flash chromatography as a white powder.
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.81 (s, 1H), 8.17 (d, *J*= 8.3 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.51-7.39 (m, 5H), 7.00 (dd, *J* = 9.1, 2.5 Hz, 2H), 4.64 (bs, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 3.32-3.25 (m, 2H), 2.74 (t, *J* = 6.2 Hz, 2H), 1.92-1.80 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, $CDCl_3$) δ: 166.6, 160.6, 159.3, 153.9, 149.9, 139.4, 134.5, 130.3, 130.1, 126.8, 128.7, 128.4, 126.7, 126.2, 120.7, 117.3, 114.4, 61.0, 60.5, 55.5, 48.8, 27.2, 19.3, 14.2 ppm. **IR** (film) ν_{max}: 2937, 2828, 1720, 1610, 1559, 1502, 1451, 1322, 1252, 1085, 1021, 848, 720. **HRMS**: calcd for $C_{29}H_{28}ClN_2O_3$ 487.1783 ($M+H^+$); found, 457.1795.

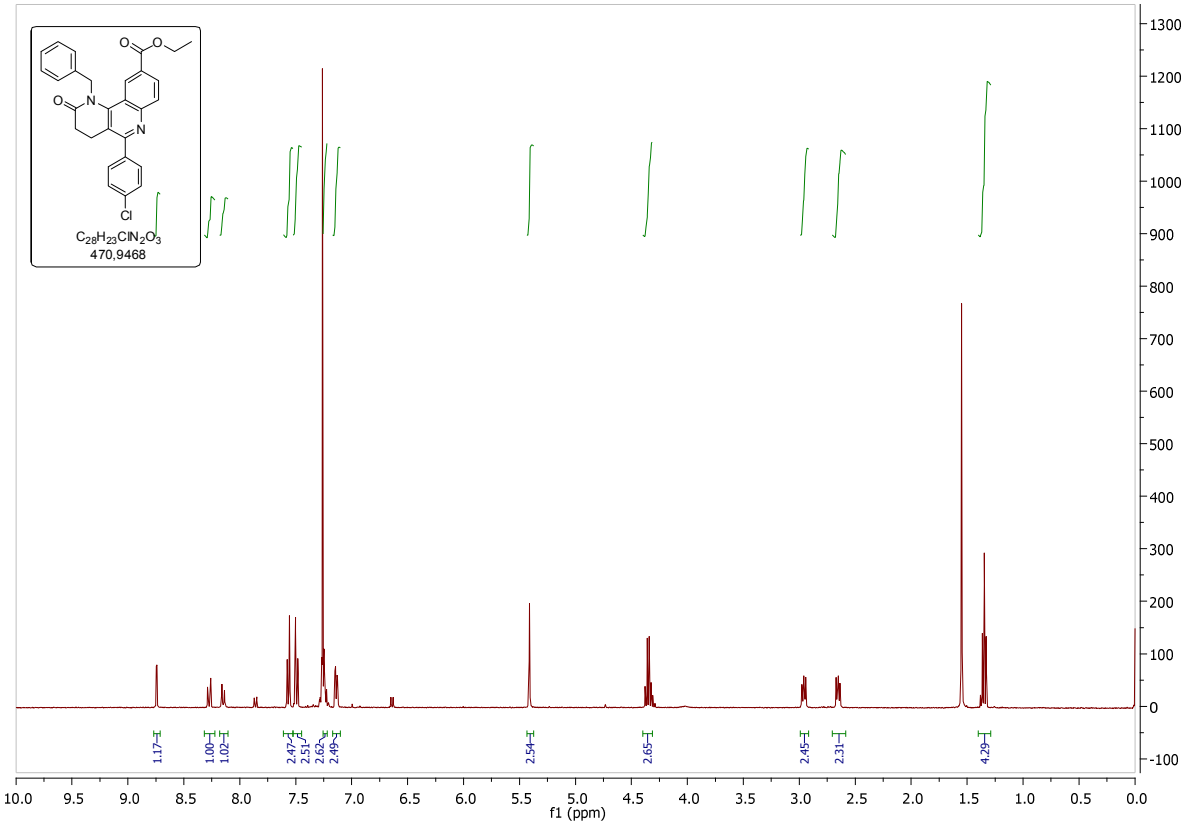
***N*-((5-(pyridin-3-yl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridin-9-yl)methyl)ethanamine (21b)**

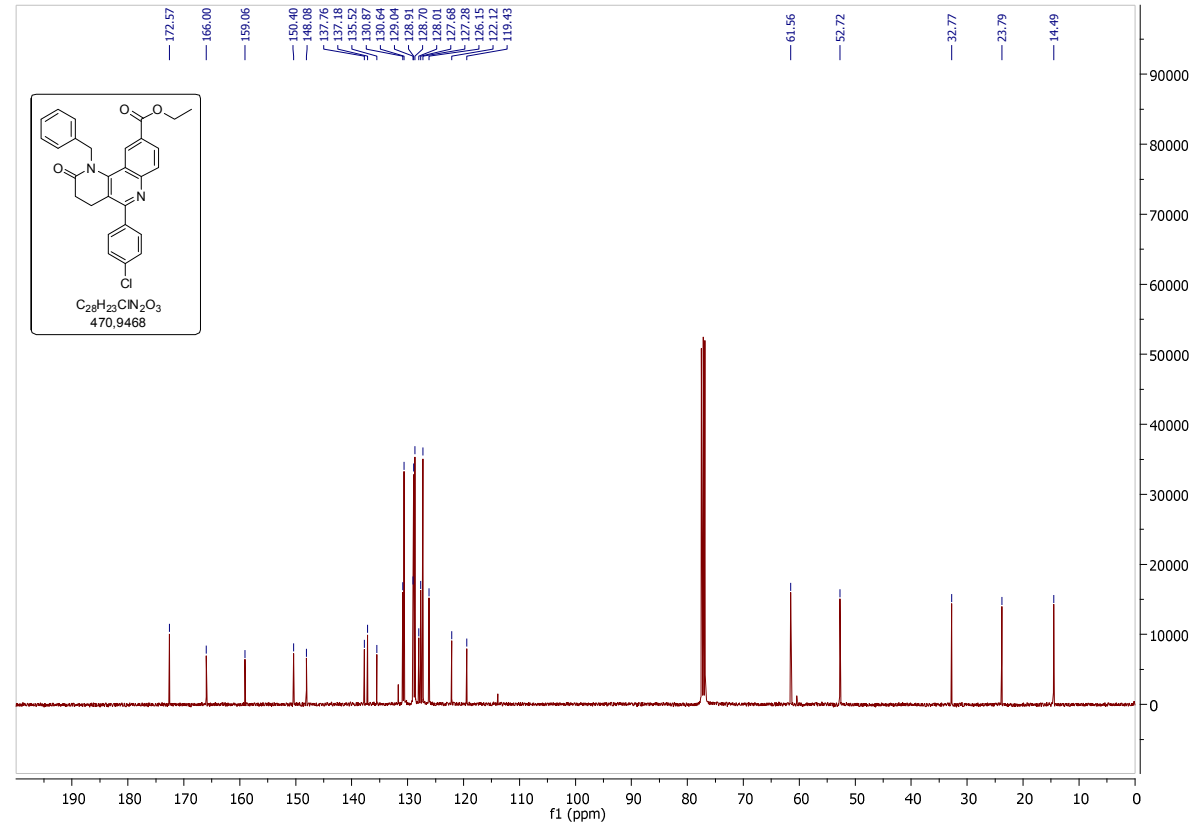


$C_{20}H_{22}N_4$
318,4155

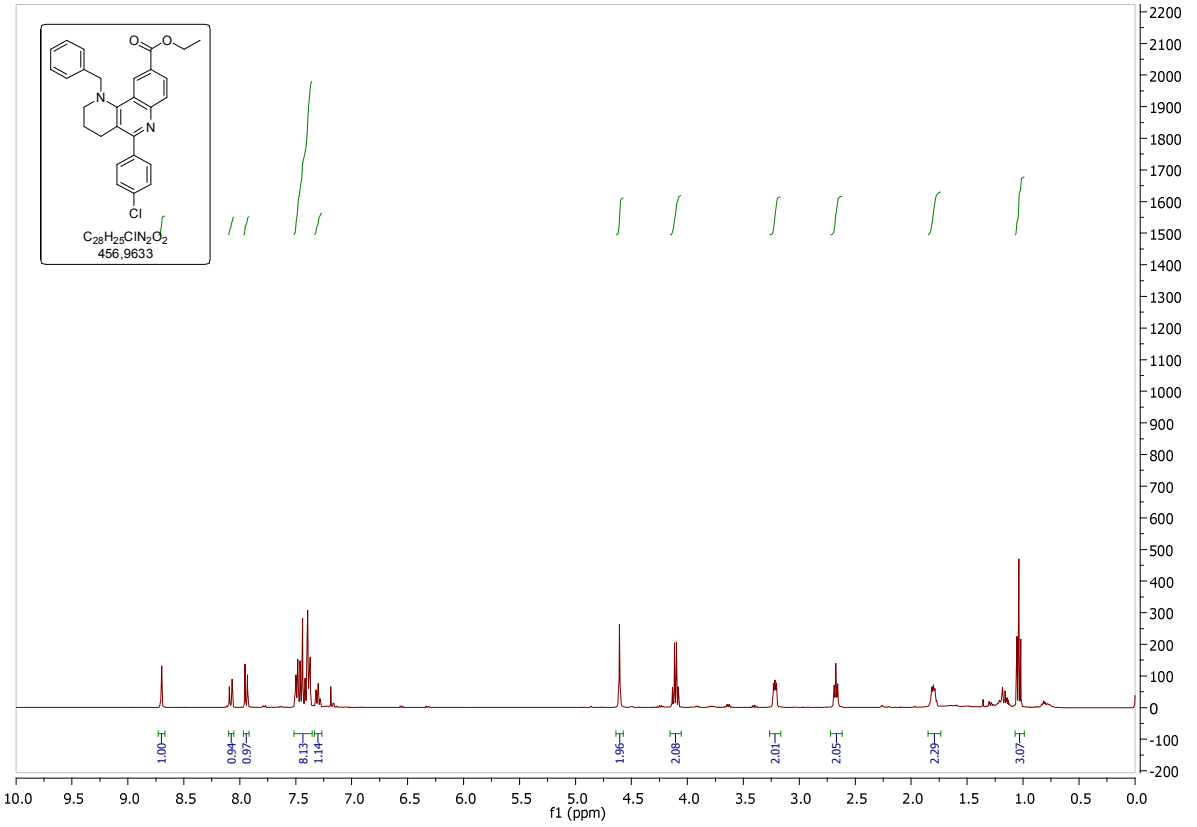
Following the general procedure F, the reduction of the corresponding amide **20** afforded compound **21b** (50% of the reduction - 7% from the MCR) after flash chromatography as a white powder.
^{1}H-NMR (400 MHz, MeOD) δ: 8.88-8.84 (m, 1H), 8.83-8.79 (m, 1H), 8.46-8.42 (m, 1H), 8.18 (dt, *J* = 7.9, 1.8 Hz, 1H), 8.04-7.99 (m, 1H), 7.90 (d, *J* = 8.7 Hz, 1H), 7.71 (dd, *J* = 7.9, 5.0 Hz, 1H), 4.44 (s, 2H), 3.76-3.71 (m, 2H), 3.27-3.19 (m, 2H), 2.78-2.72 (m, 2H), 2.11-1.95 (m, 2H), 1.39 (t, *J*= 7.3 Hz, 3H) ppm. **^{13}C-NMR** (100MHz, MeOD) δ: 155.5, 148.4, 146.7, 144.1, 139.2, 135.8, 131.7, 131.4, 127.4, 125.9, 121.9, 116.8, 111.4, 110.7, 51.5, 44.2, 43.1, 24.7, 19.9, 11.6 ppm. **HRMS**: calcd for $C_{20}H_{23}N_4$ 319.1917 ($M+H^+$); found, 319.1922.

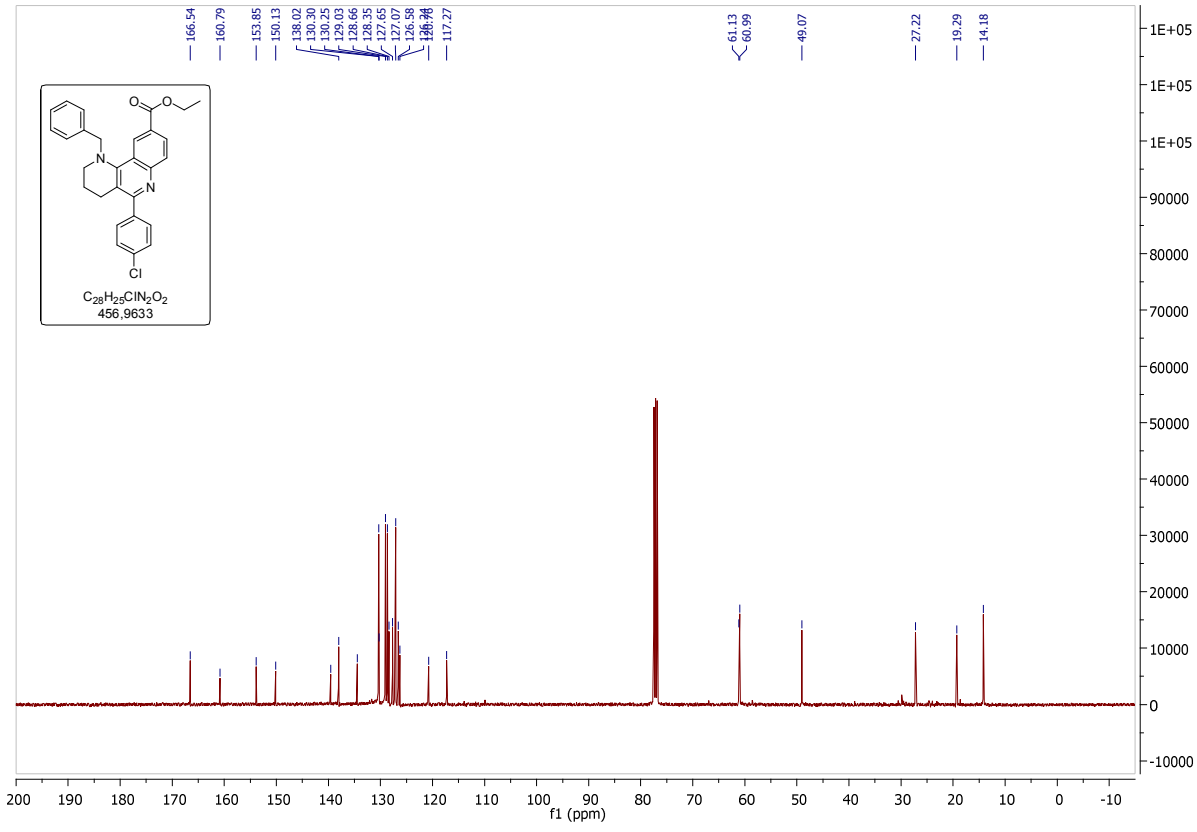
Ethyl 1-benzyl-5-(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (9a)



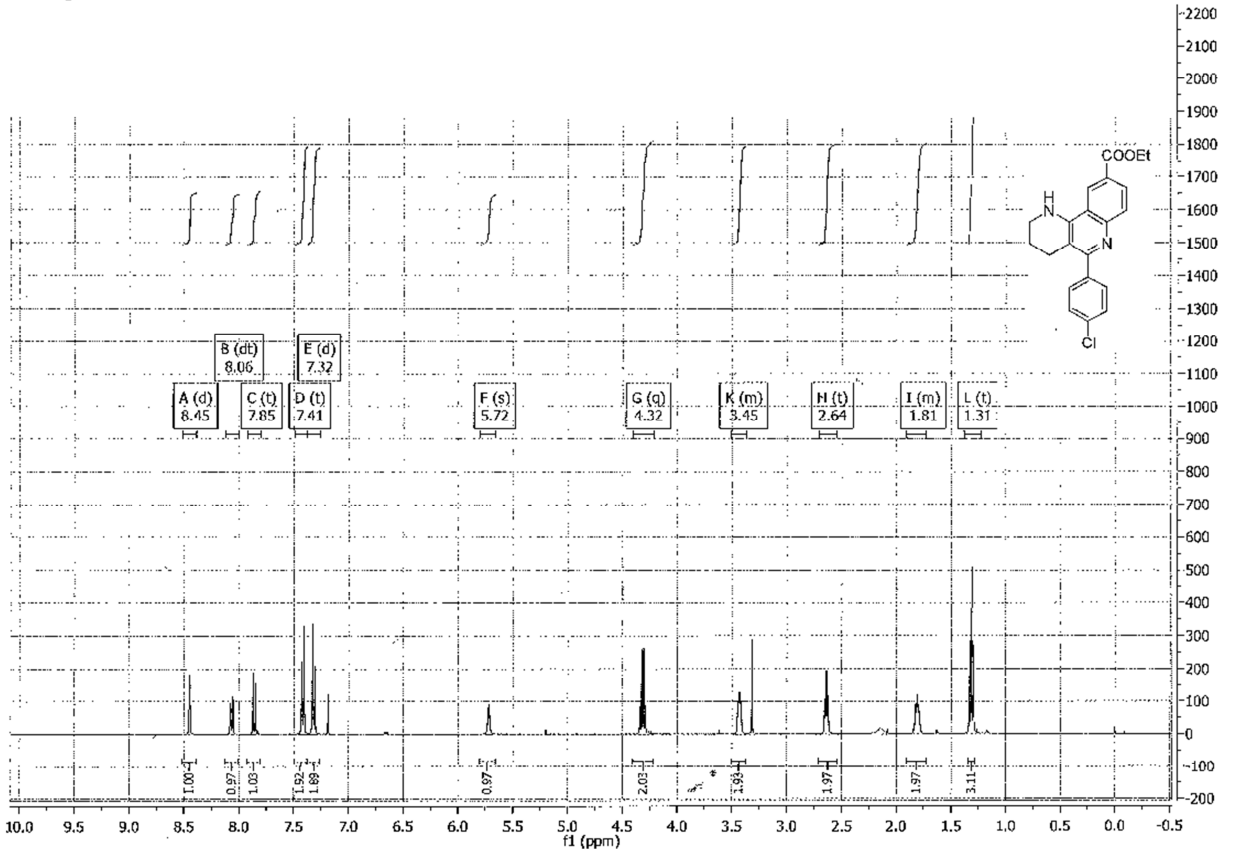


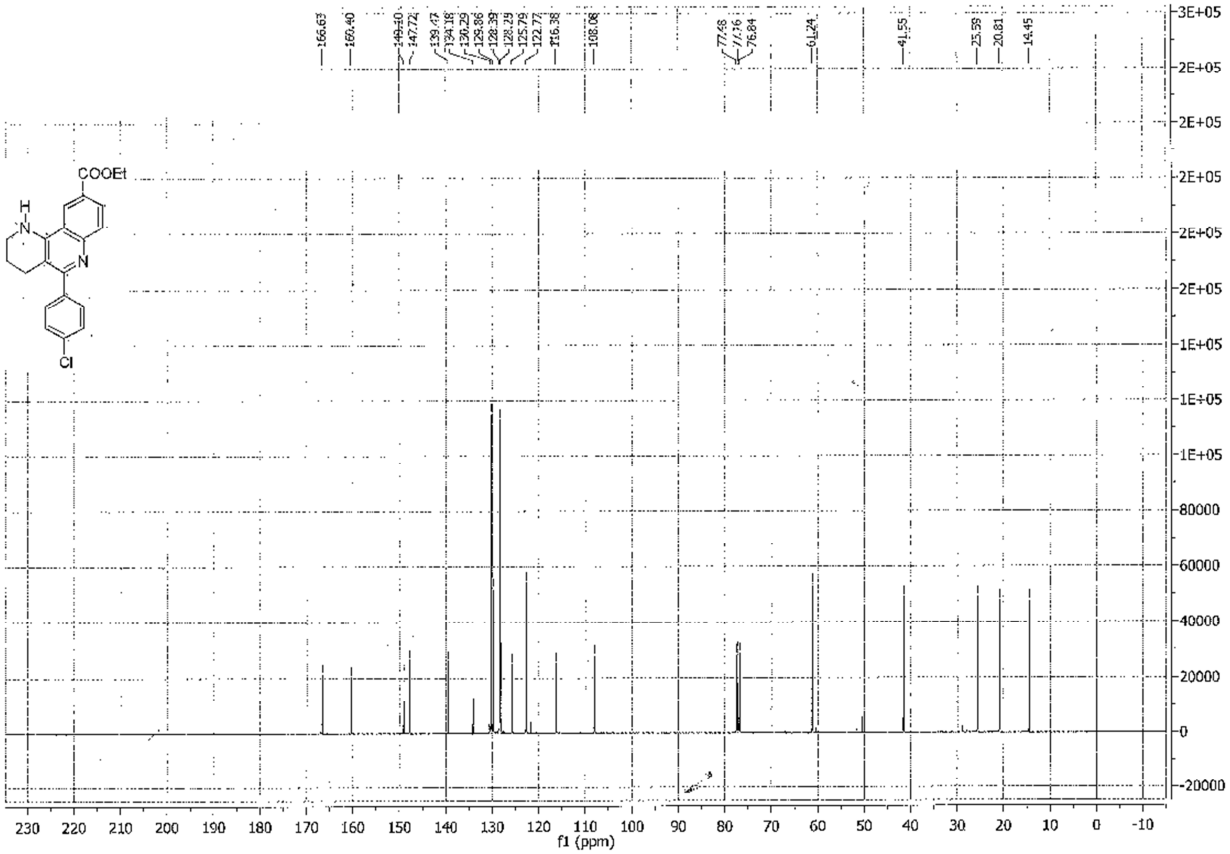
Ethyl 1-benzyl-5-(4-chlorophenyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (10a)



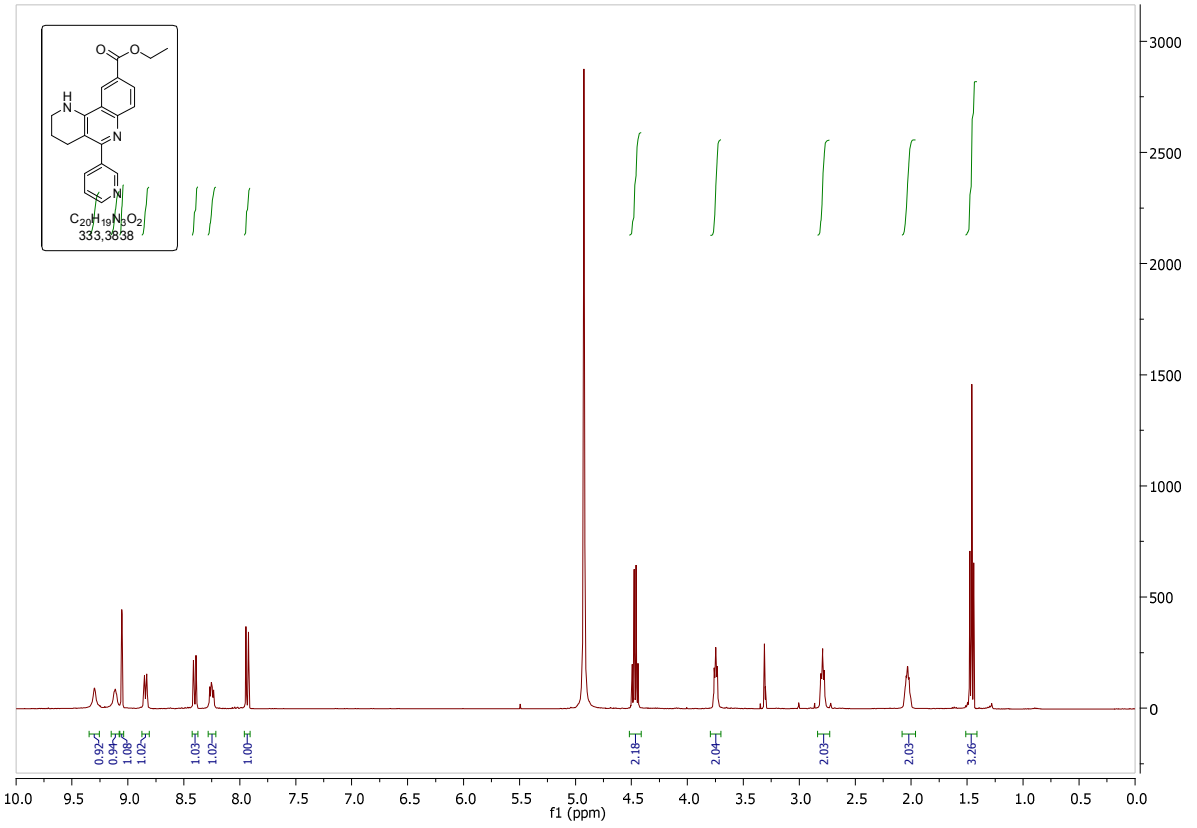


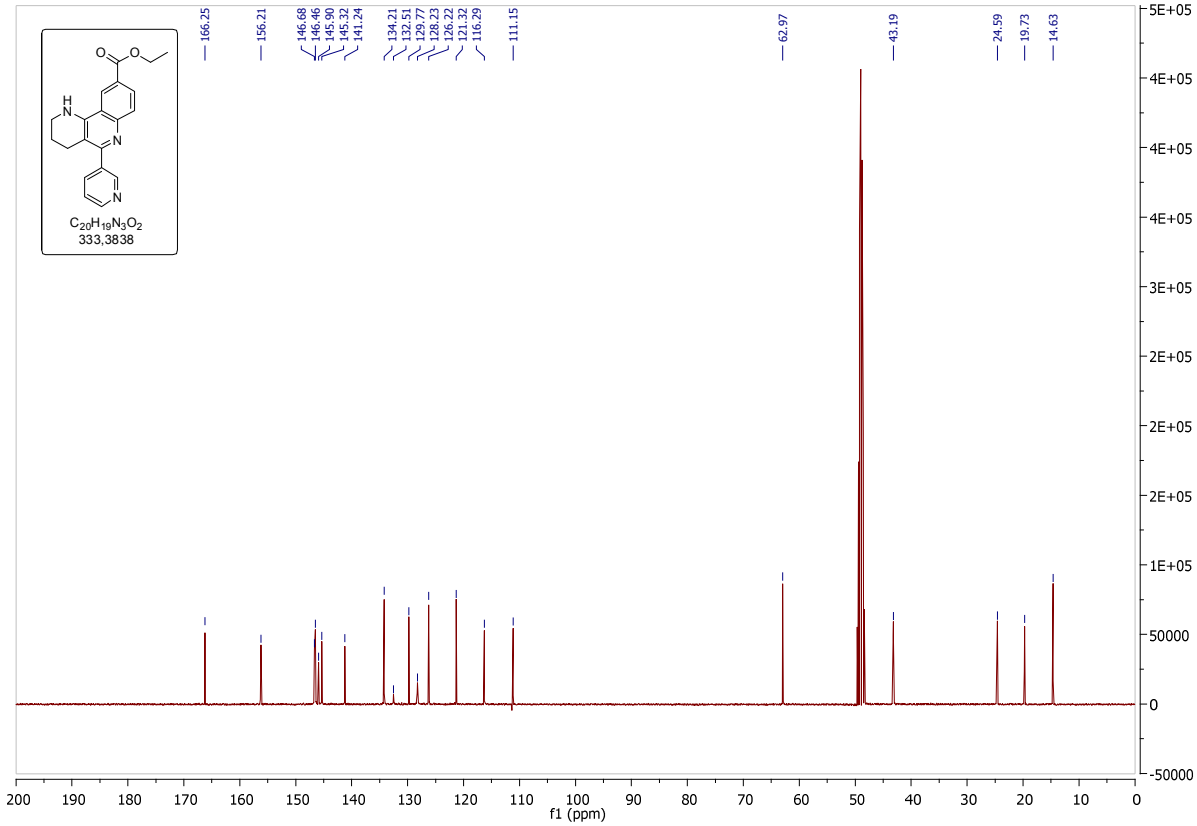
Ethyl 5-(4-chlorophenyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (17a)



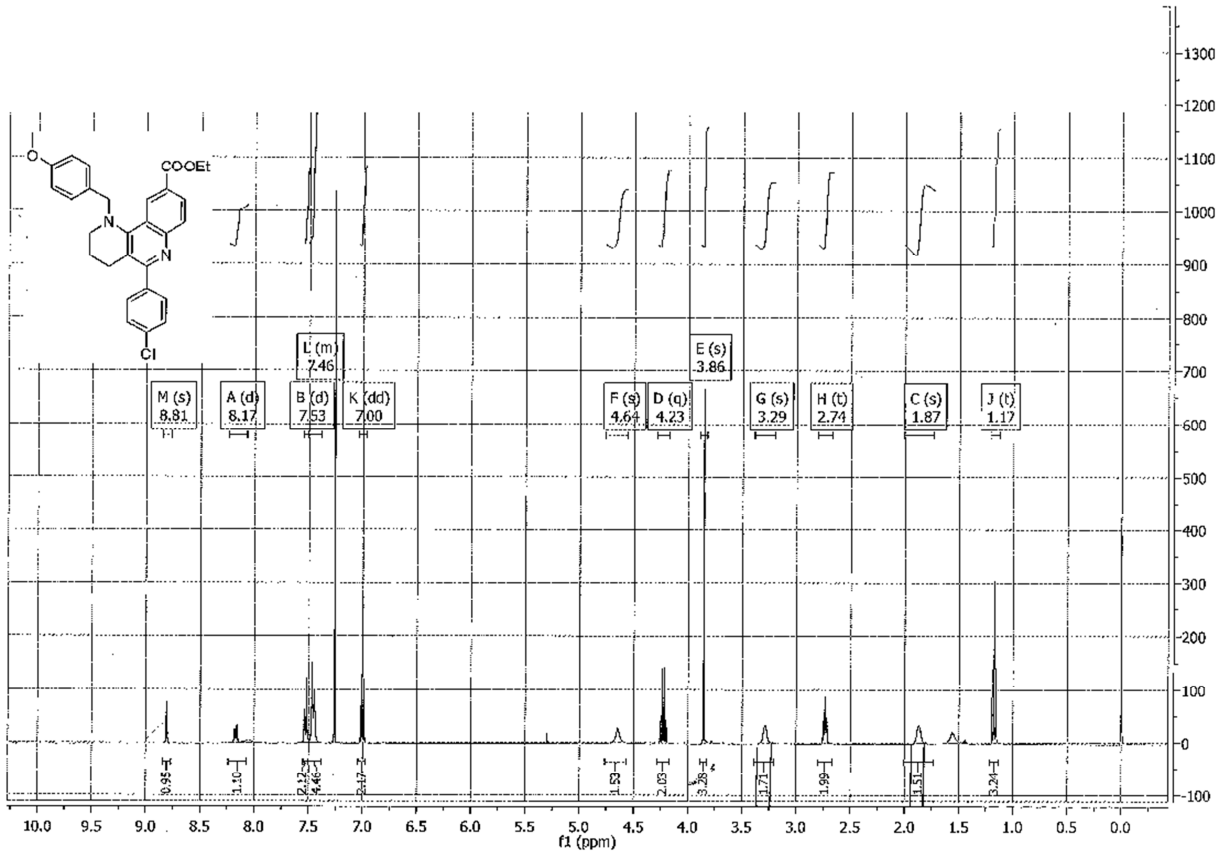


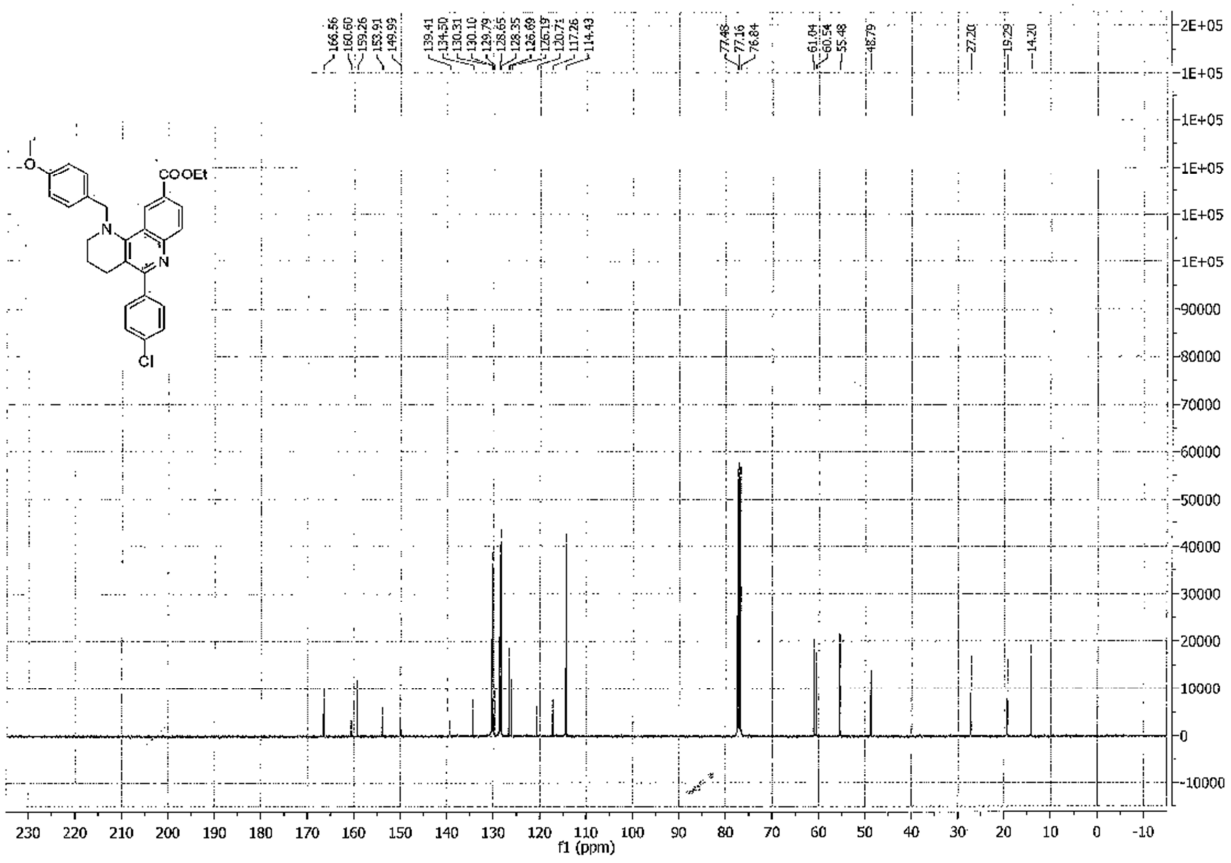
Ethyl 5-(pyridin-3-yl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (17b)



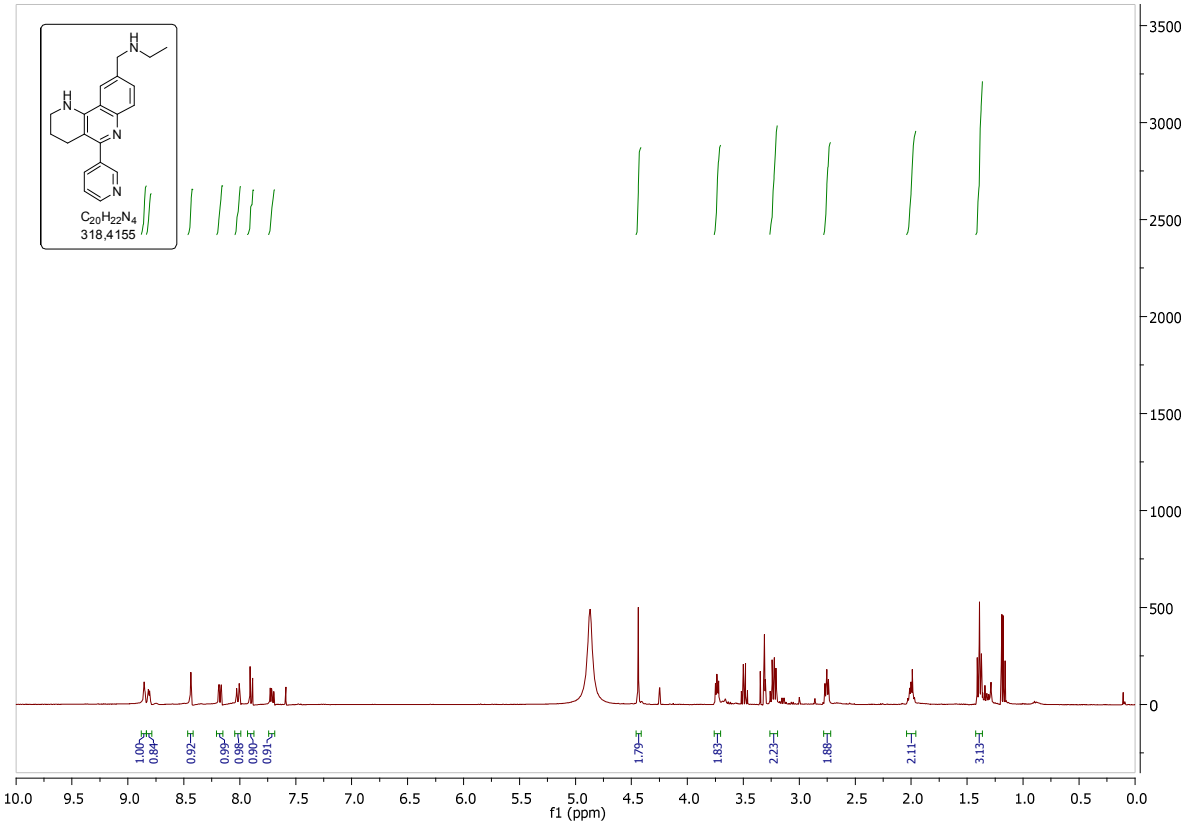


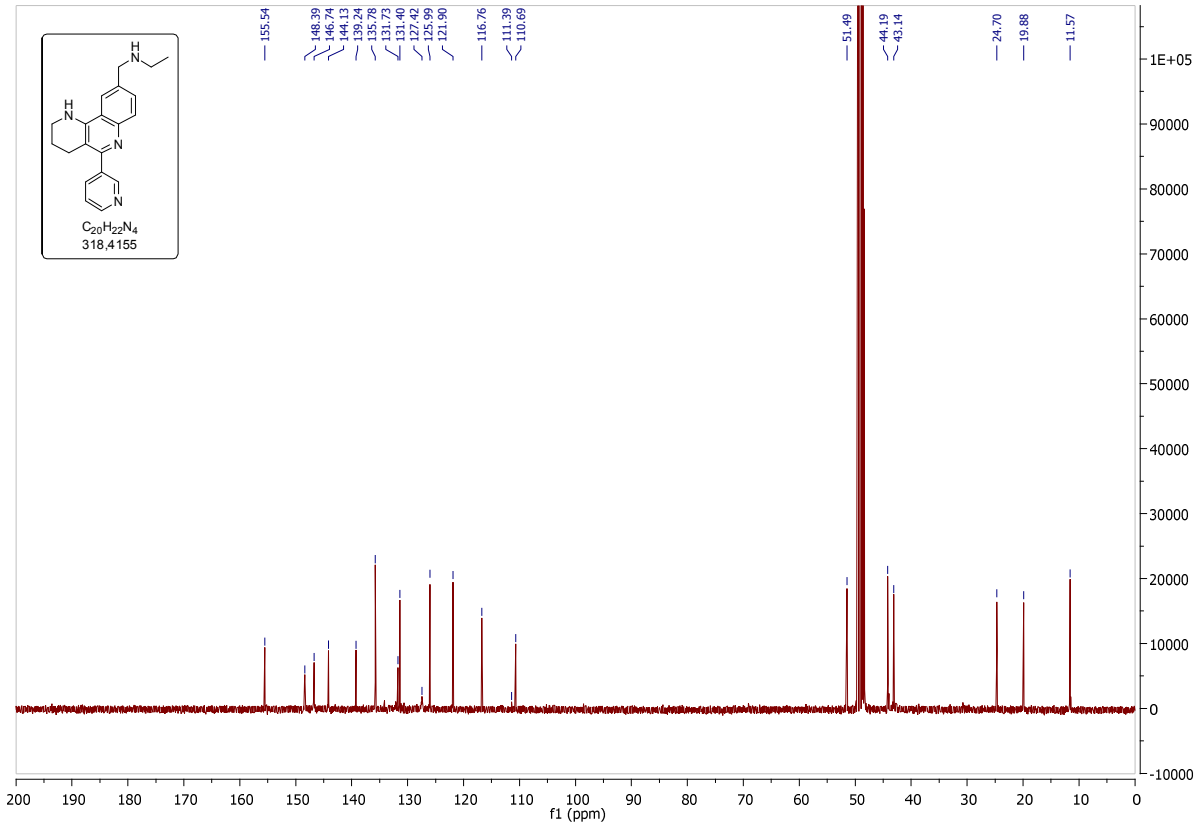
Ethyl 5-(4-chlorophenyl)-1-(4-methoxybenzyl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridine-9-carboxylate (18)





***N*-((5-(pyridin-3-yl)-1,2,3,4-tetrahydrobenzo[*h*][1,6]naphthyridin-9-yl)methyl)ethanamine (21b)**





7. Conclusiones

Conclusiones.

i) Se ha comprobado que las lactamas insaturadas, con diferente sustitución, tamaño de ciclo y posición del doble enlace, en condiciones de reacción de Povarov generan tetrahidroquinolinas con un patrón de sustitución original sin detectar ningún producto alternativo de la reacción. A partir de la oxidación de los aductos obtenidos se han podido obtener quinolinas difíciles de preparar por síntesis lineales alternativas, las cuales son interesantes ya que son estructuras muy comunes en productos naturales y compuestos biactivos.

ii) En el caso de los heterociclos tipo 1,3-tia-, -oxa- y -imidazolona, se ha estudiado su reactividad en condiciones de reacción de Povarov obteniendo resultados satisfactorios. A partir de los aductos obtenidos se ha visto que el proceso es totalmente regioselectivo y es el átomo de nitrógeno del heterociclo el que activa su posición β para que la olefina ataque a la imina. Para demostrar que tanto el oxígeno como el azufre pueden llevar a cabo esta función, se diseñó la versión intramolecular de la reacción. Se ancló el heterociclo, por el nitrógeno, al aldehído a través de un grupo metileno y se sometió a las condiciones de reacción obteniendo el producto deseado con un rendimiento moderado y con alta estereoselectividad. Con todas las tetrahidroquinolinas obtenidas se llevo a cabo la reacción de oxidación para obtener la correspondiente quinolina.

iii) Dado la importancia de las quinolinas se ha desarrollado una nueva metodología para oxidar los aductos obtenidos a partir de la reacción de Povarov, para hacer este proceso de oxidación más rápido, limpio y sencillo. Gran variedad de oxidantes han sido estudiados hasta llegar a una de las condiciones idoneas para esta transformación y así cumplir el objetivo marcado. El catalizador seleccionado ha sido el dióxido de manganeso (MnO_2) de la casa comercial Wako, en un medio básico generado por la presencia de piridina. Este método facilita las tareas de purificación, y genera el producto deseado de manera rápida sin la aparición del subproducto de fragmentación-oxidativa común en procesos de oxidación de este tipo de tetrahidroquinolinas.

iv) De la nueva reacción multicomponente Mannich-Ritter se estudió la reactividad de diferentes olefinas activadas para ver los limites del proceso en lo que respecta a dicho componente. Del estudio se puede deducir que el proceso es muy dependiente de la olefina activada utilizada, ya que olefinas activadas por nitrógeno dan lugar a productos Mannich mientras que las activadas por oxigéno o carbono producen el aducto de la reacción Mannich-Ritter. Este resultado ha motivado el estudio mecanístico del proceso de reacción, esclareciendo los motivos de este comportamiento. A partir del analisis computacional, se puede decir que el motivo por el cual las olefinas activadas por nitrógeno producen un carbocatión mas plano lo que dificulta el ataque por parte del acetonitrilo para formar la amidina cíclica. Por otro lado, en el caso especial del ciclohexadieno el producto mayoritario es el de la interacción tipo Diels-Alder por parte de la imina y la olefina activada, esto hace que el mecanismo de este caso en especial sea

estudiado por cálculos computacionales para esclarecer el origen de ambas especies.

v) Se han sintetizado derivados de la reacción de Povarov con lactamas insaturadas y enaminas cíclicas con el fin de analizar su actividad inhibitoria frente acetilcolinesterasa, butirilcolinesterasa y de auto-agregación del ß amiloide; todos ellos relacionados con la enfermedad de Alzheimer y su causa más conocida: la agregación del ß amiloide para formar las microfibrillas. Los compuestos analizados muestran una buena actividad inhibitoria en el rango nanomolar. A partir de estos resultados, se analizó con simulaciones de *docking* la posible interacción del producto más activo. Los resultados obtenidos indican que los nuevos inhibidores se colocan en la mitad de la garganta catalítica permitiendo su interacción tanto con el sitio periférico como con el sitio catalítico.

8. Resúmenes y Contribución personal a las publicaciones presentadas

1. Resúmenes.

1.1. Publicación 1: Unsaturated Lactams: New Inputs for Povarov-Type Multicomponent Reactions.

Esther Vicente-García, Federica Catti, Rosario Ramón, Rodolfo Lavilla.
Organic Letters, **2010**, *12*, 860-863.

En los últimos años se han realizado una gran variedad de estudios para encontrar nuevos compuestos capaces de actuar como olefinas activadas en la reacción de Povarov. Entre ellos se pueden destacar, los que utilizan éteres de enol cíclicos obteniendo como resultado el aducto de tetrahidroquinolina esperado (Figura 1, **A**). Por otro lado, en uno de los precedentes relevantes, se estudia el uso de enamidas cíclicas (**B**), con las cuales se generan las tetrahidroquinolinas correspondientes, intermedio sintético clave que dará paso al producto natural martinelina y ácido martinélico. Finalmente, en nuestro grupo de investigación se ensayaron los esteres de enol cíclicos, obteniendo sorprendentemente *N*-aril lactamas (**C**) como productos de la reacción. Estos compuestos son consecuencia de la captura nucleófila intramolecular del carbocatión por el nitrógeno de la anilina (Figura 1).

Así, en el presente trabajo se decidió estudiar la reactividad de lactamas insaturadas (**D**) en la reacción de Povarov, con objeto de determinar el tipo de producto que se va a obtener a partir de estos compuestos debido a su similitud con los ésteres de enol y enamidas cíclicas.

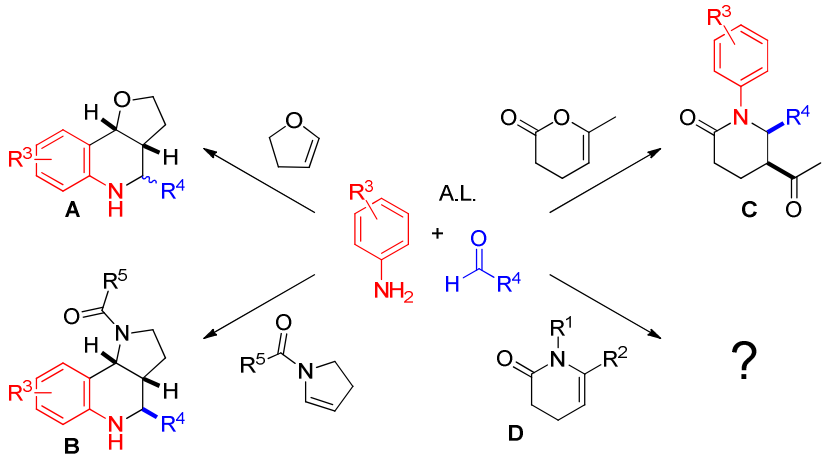


Figura 1. Éteres de enol, enamidas cíclicas y ésteres de enol en la RMC de Povarov.

Se ensayaron un grupo variado de lactamas insaturadas, introduciendo sustituyentes en dos posiciones diferentes: el nitrógeno y su posición α, con el doble enlace endocíclico (**1**) y exocíclico (**2**, Figura 2).

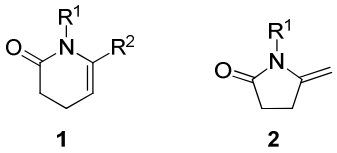
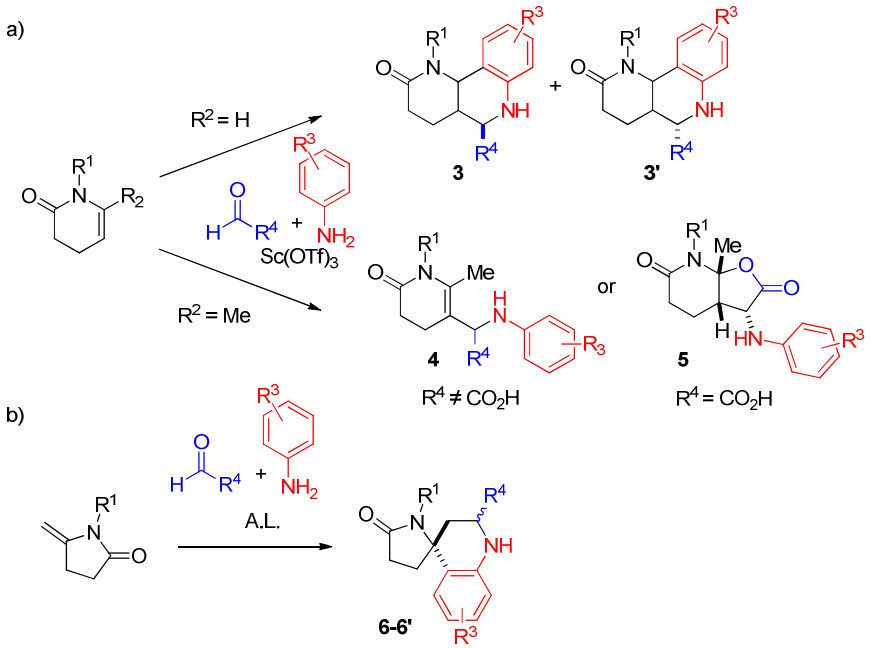


Figura 2. Lactamas insaturadas sometidas al estudio.

Las diferentes lactamas insaturadas *N*-sustituidas (a, Esquema 1) utilizadas en el estudio dieron lugar al producto clásico de la reacción de Povarov. El rendimiento y la relación de los estereoisómeros obtenidos no parecen depender tanto del sustituyente en el nitrógeno, sino más bien del tipo de anilina y aldehído utilizados en la reacción. Estos rendimientos son moderados y pueden variar del 33 al 64 %.

En el caso de las lactamas insaturadas sustituidas en posición α el producto Povarov no se genera, en su lugar, se obtiene el compuesto de adición tipo Mannich (**4**, Esquema 1). Posiblemente esto sea debido al impedimento estérico provocado por el sustituyente en α. Sin embargo, la utilización del ácido glioxílico como componente carbonílico de la reacción, provoca que el carbocatión intermedio sea atrapado por el carboxilato del grupo ácido, obteniéndose el compuesto **5**.

Finalmente, al estudiar las lactamas insaturadas con el doble enlace en *exo*, se obtuvo la espiro-tetrahidroquinolina de tipo Povarov (**6-6'**, Esquema 1). En este caso fue necesaria la activación por microondas para lograr un buen rendimiento (60 %).



Esquema 1. Estudio de la reactividad de las lacatamas insaturadas en la reacción de Povarov.

Finalmente, se realizó la oxidación de las tetrahidroquinolinas obtenidas para producir quinolinas con nuevos patrones de sustitución difíciles de obtener de otro modo. También se estudió el efecto del medio ácido en los productos de Povarov

obtenidos, esto puso de manifiesto la sensibilidad de este tipo de compuestos en condiciones ácidas, generando los productos de la eliminación-oxidativa.

A modo de conclusión, podemos decir que un gran número de lactamas insaturadas han sido estudiadas como olefinas activadas en la reacción de Povarov y se han obtenido tetrahidroquinolinas y quinolinas con novedosos patrones de conectividad y patrones de substitución, como resultado de esta interacción multicomponente.

1.2. Publicación 2: New Heterocyclic Inputs for the Povarov Multicomponent Reaction.

Esther Vicente-García, Rosario Ramón, Rodolfo Lavilla.
Synthesis, **2011**, 2237-2246. Special Topic Issue.

Después de estudiar la reactividad de las lactamas insaturadas como olefinas activadas en la reacción de Povarov, se plantea la idea de ampliar el rango de sustratos heterocíclicos. Para ello se investigan los heterociclos tipo 1,3-oxa-, -tia-, o imida-zol-2-ona.

La novedad estructural en este tipo de compuestos consiste en que el doble enlace puede ser activado por dos tipos de heteroatomos, esto conlleva a que se pueden obtener regioisomerías diferentes en los productos de la RMC.

Así, en este contexto, se ensayaron distintas combinaciones de heteroátomos en estos heterociclos (Figura 1).

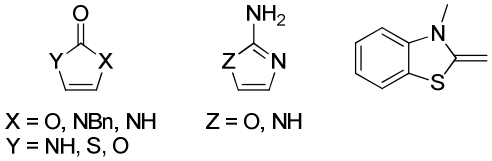
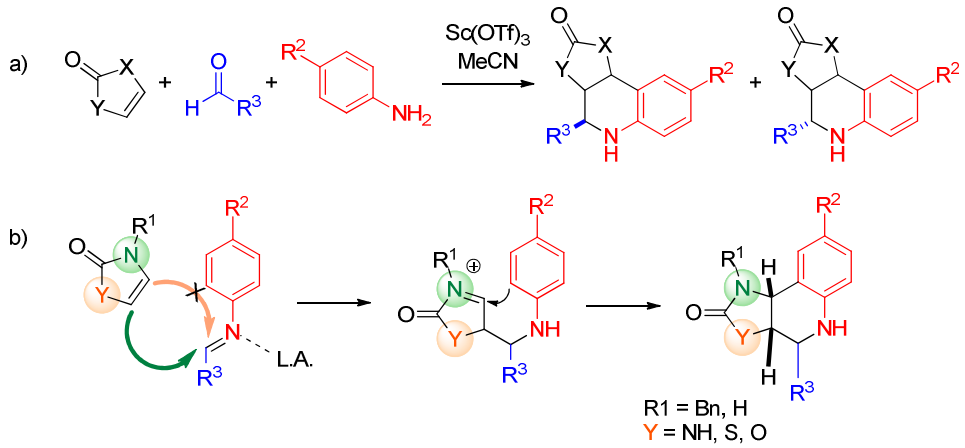


Figura 1. Nuevos heterociclos como olefina activada en la RMC de Povarov.

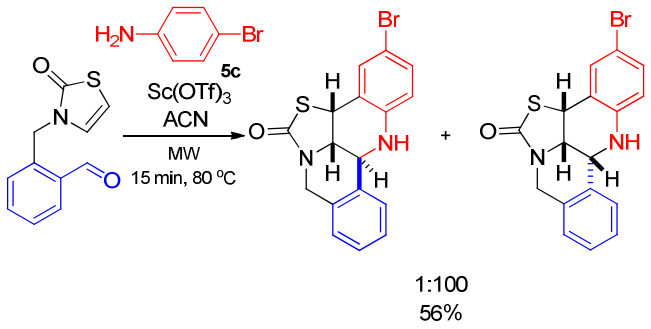
El estudio se inició llevando a cabo la RMC en condiciones estándar. Sin embargo, se pudo observar que en muchos de los casos, la activación por microondas o el aumento de la temperatura durante tiempos prolongados eran requisitos necesarios para obtener rendimientos aceptables (35 – 84 %).

De este modo, se pudo preparar una batería de compuestos, presentando una fusión de ciclos cis, y una disposición definida en cuanto a la regioquímica de la reacción (a, Esquema 1) en el aducto de tetrahidroquinolina. Del análisis estructural, se pudo extraer una tendencia común: el heteroátomo que activa el doble enlace en ß siempre es el nitrógeno, aunque inicialmente se consideró que tanto el azufre como el oxígeno podrían ser capaces de ejercer esa función (b, Esquema 1).



Esquema 1. Resultados del estudio de la reacción de Povarov con nuevos sustratos heterocíclicos como olefinas activadas

Para demostrar que tanto el oxígeno como el azufre pueden activar el doble enlace, promoviendo el ataque sobre la imina, se diseñó un experimento donde se lleva a cabo la reacción de Povarov de manera intramolecular. De ese modo, se enlazó, la olefina por el átomo de nitrógeno a través de un grupo metileno al aldehído en su posición orto. Los resultados mostraron que, en este caso, el azufre puede activar el doble enlace para que tenga lugar la reacción de Povarov intramolecular. También se pudo observar que la reacción tiene lugar con una alta diastereoselectividad de 1:100 y un rendimiento moderado (Esquema 1).



Esquema 1. Versión intramolecular de la reacción de Povarov.

Finalmente, se sintetizaron las correspondientes quinolinas de los productos obtenidos, a través de un proceso de oxidación con la ayuda de DDQ.

Se puede concluir que, en este trabajo, se ha ampliado el rango de heterociclos como olefinas activadas en la reacción de Povarov, determinando también la regioselectividad natural de estos procesos y se ha diseñado una versión intramolecular para probar que otros heteroátomos, no sólo el nitrógeno, pueden activar el doble enlace y dirigir la nucleofilia de la olefina.

1. 3. Publicación 3: Multicomponent Reaction Access to Complex Quinolines Via Oxidation of the Povarov Adducts.

Esther Vicente-García, Rosario Ramón, Sara Preciado, Rodolfo Lavilla.

Beilstein J. Org. Chem. **2011**, *7*, 980-987. Thematic Series.

Una parte de los dos últimos trabajos presentados se basa en la obtención de quinolinas (**2**, Figura 1) con novedosos patrones de substitución, a partir de la oxidación con la diclorodicianoquinona (DDQ) de las tetrahidroquinolinas precursoras (**1-1'**, Figura 1), obtenidas en la reacción multicomponente de Povarov.

A pesar de sus notables ventajas (rendimientos, quimioselectividad o suaves condiciones de reacción), este proceso de oxidación tiene varios inconvenientes, el primero de ellos es la obtención del compuesto de oxidación-eliminación (**3**, Figura 1) como subproducto de la reacción (debido a catálisis ácida) y el segundo es la dificultad a la hora de purificar los crudos de reacción debido a los residuos generados por el oxidante (DDQ).

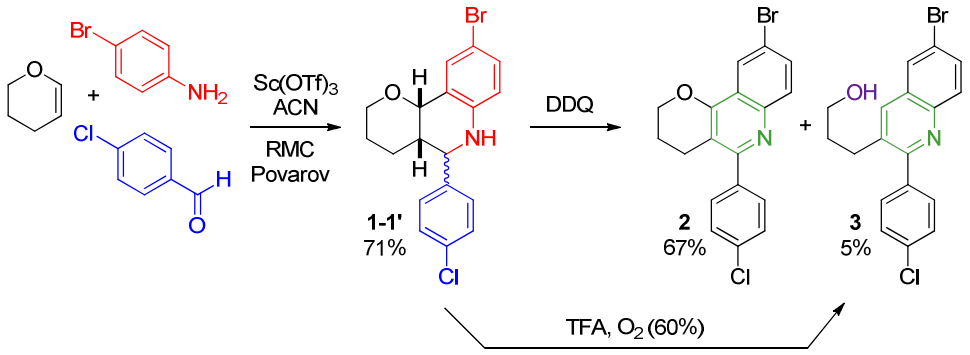


Figura 1. Reacción de Povarov y oxidación de las tetrahidroquinolinas obtenidas.

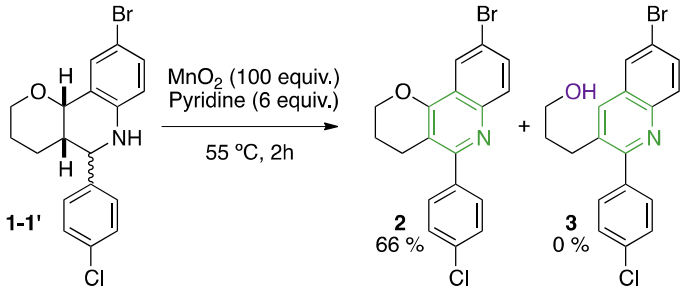
Por este motivo, se realizó una búsqueda bibliográfica para encontrar una metodología que permitiese obtener un solo producto de reacción y que simplificase el proceso de purificación.

Los métodos descritos hasta la fecha también presentan la misma problemática que el DDQ (como es el caso de CAN, nitrobenceno o el MnO_2); o bien como en el caso de azufre elemental o el paladio, se necesitan condiciones de reacción más drásticas para que ésta se lleve a cabo.

Después de ensayar varios oxidantes (paladio sobre carbono, CuCl, Sal de Fremy e IBX) sin obtener resultados satisfactorios; se encontró que este tipo de oxidaciones con dióxido de manganeso dependen mucho del tipo de reactivo utilizado. Así que, se decidió realizar un estudio sobre la reacción de oxidación de tetrahidroquinolinas, aductos de la RMC de Povarov, a quinolinas con ayuda de diferentes tipos de MnO_2.

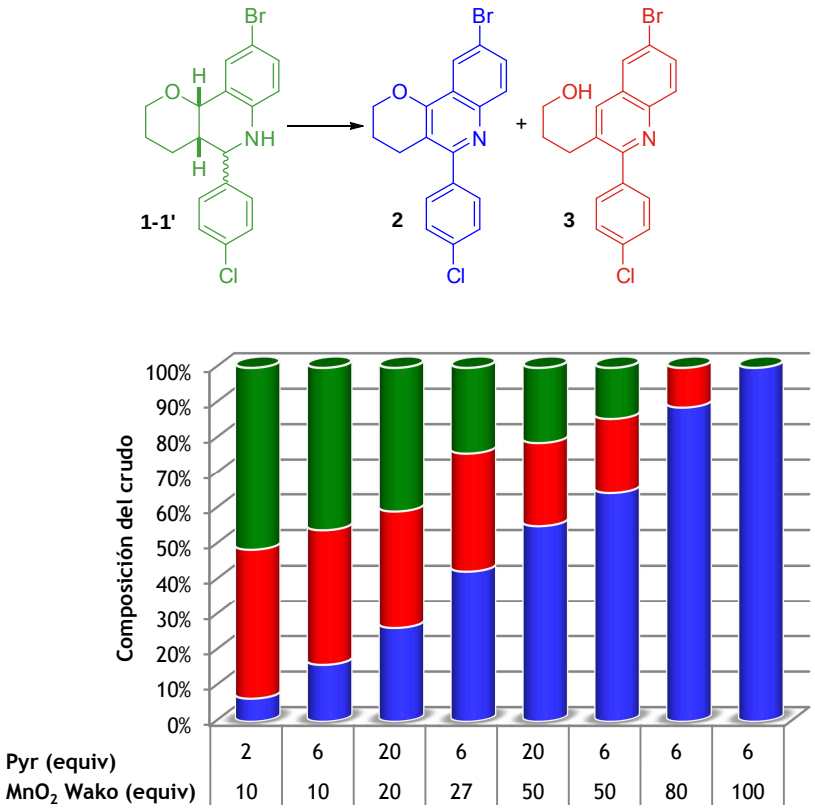
Para realizar dicho estudio se llevaron a cabo pruebas con dióxidos de manganeso de diferentes marcas comerciales, con diferentes características, como porosidad o tamaño de partícula. Para estas pruebas se optimizaron unas condiciones iniciales descritas en las que el dióxido de manganeso es capaz de oxidar tiazolidinas a tiazoles, que se consideraron análogas.

Finalmente, se determinó que el dióxido de manganeso de primer grado de la casa comercial Wako era el adecuado para esta transformación (Esquema 1). Para intentar racionalizar las diferencias de reactividad entre los diferentes tipos de MnO_2, se realizó un estudio sobre el tamaño de partícula, con el se concluye que los dióxidos de manganeso polidisperso con diámetros de partícula medios son los que dan resultados más satisfactorios, entre ellos el obtenido con el MnO_2 de Wako.



Esquema 1. MnO_2 activo para la oxidación de tetrahidroquinolinas.

Una vez identificado el oxidante ideal, con el cual no se detecta el subproducto de oxidación-eliminación, se estudia la optimización de la reacción para intentar disminuir la cantidad de oxidante (Gráfica 1). En el estudio se observa que es necesario un gran exceso (100 equiv.) de MnO_2 para conseguir un resultado óptimo. Esto puede ser debido a que la oxidación tiene lugar en la superficie de la partícula, y que consecuentemente la pasivación de la superficie ralentiza o dificulta el proceso oxidativo, siendo necesario utilizar cantidades supra-estequiométricas.



Gráfica 1. Optimización de la reacción.

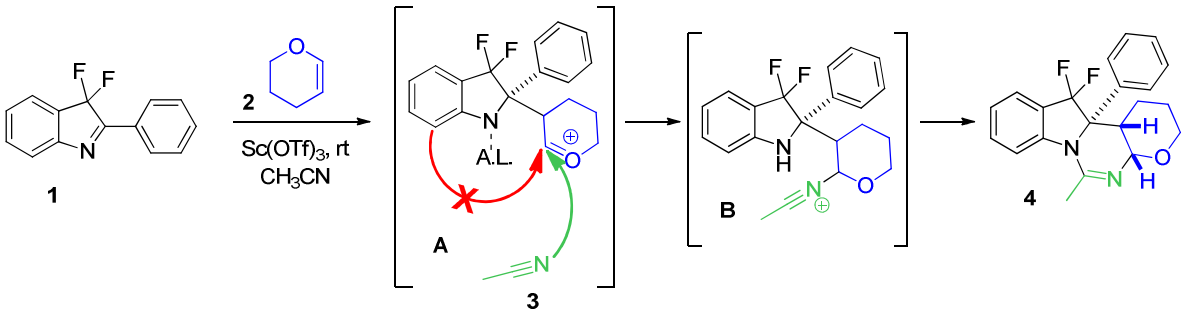
Como conclusión, se puede afirmar que en este trabajo se ha puesto a punto una metodología con la cual es posible oxidar tetrahidroquinolinas a quinolinas de manera selectiva (sin la obtención de subproductos), rápida y de sencilla purificación.

1.4. Publicación 4: Exploration of Forbbiden Povarov Processes as a Source of Unexpected Reactivity: a New Multicomponent Mannich-Ritter Transformation.

Sara Preciado, Esther Vicente-García, Salomé Llabrés, F. Javier Luque, Rodolfo Lavilla.

Angew. Chem. Int. Ed. **2012**, *51*, 6874-6877. Selected as a Hot Paper.

Los avances significativos en RMCs se basan fundamentalmente en encontrar/diseñar nuevos procesos preparativos. Para ello se siguen diferentes estrategias (ver introducción). En este trabajo se estudia la reactividad de iminas, que debido a su geometría no pueden evolucionar por vía Povarov, pero que en cambio, al ensayar su reactividad en condiciones estándar dan lugar a un producto con la participación inesperada de una molécula de disolvente (acetonitrilo) para originar una nueva RMC que da como resultado amidinas cíclicas (Esquema 1).

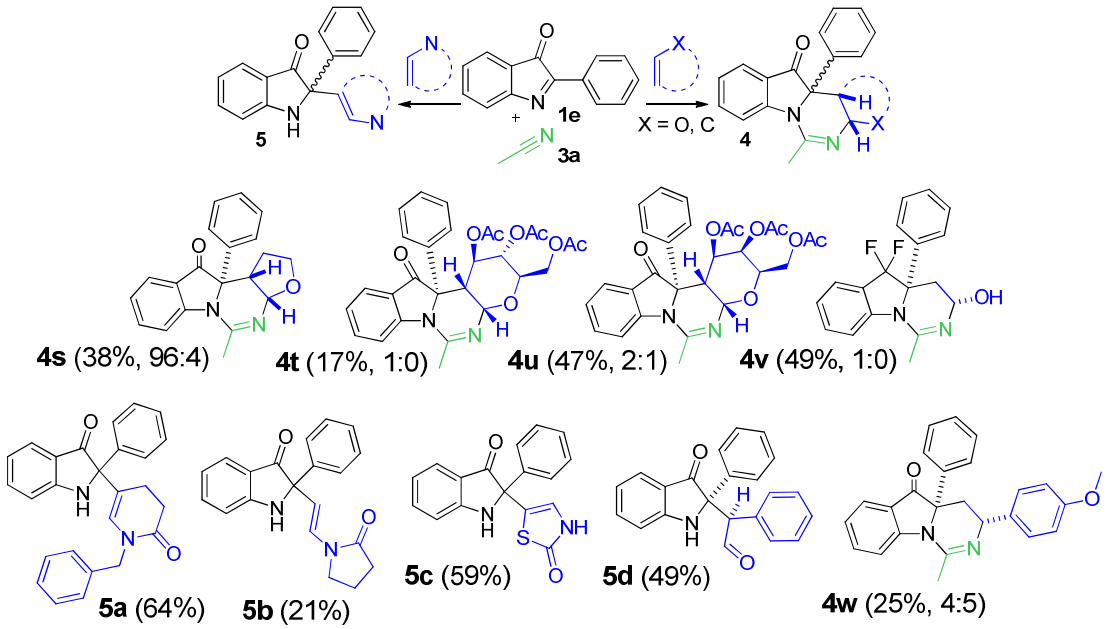


Esquema 1. Descripción de la nueva RMC.

El primer ejemplo de esta nueva reacción, incluyendo el estudio de los diferentes tipos de iminas y nitrilos se llevó a cabo por Sara Preciado dentro de su tesis doctoral. Determinando el rango de reactividad de dichos componentes en la nueva RMC.

Mi trabajo en este proyecto consintió en determinar la reactividad del tercer componente de la reacción: las olefinas activadas. Dentro de este estudio, se evaluó la reactividad de un gran número de componentes olefínicos pertenecientes a distintos tipos estructurales donde la principal variación es el átomo o fragmento que activa el doble enlace de la olefina.

Estos experimentos mostraron que el producto de la reacción obtenido dependía del tipo de olefina utilizada. Así, se observó que las olefinas activadas por oxígeno, como los éteres de enol, dan lugar al producto de la nueva RMC con rendimientos de bajos a moderados (**4s-v**, Esquema 2). Sin embargo en el caso de las olefinas activadas por nitrógeno, como por ejemplo las lactamas insaturadas y enamidas relacionadas, el último paso de la reacción no tiene lugar y generando el producto de tipo Mannich (**5a-d**). Finalmente, el *p*-metoxiestireno si da lugar al producto de la RMC (**4w**) con un rendimiento aceptable.



Esquema 2. Estudio de olefinas activadas en la nueva RMC (17- 64 %).

Para racionalizar este comportamiento, se llevaron a cabo cálculos computacionales con la colaboración del Prof. Luque de la Facultad de Farmacia con el éter de enol cíclico, con el que se obtiene el producto de la RMC en un 60 %, y con la lactama insaturada, con la cual no se detecta el mismo tipo de aducto, generando productos de tipo Mannich (Figura 1). Los perfiles de energía indican que el ataque del acetonitrilo en *cis* al metilo (simula el resto de imina cíclica), es la ruta más favorecida, tal como lo indica la gran accesibilidad del estado de transición de tipo silla. La ausencia de ataque en el caso de la lactama insaturada se puede explicar debido a su alta barrera energética para las adiciones *cis* y *trans* (12.7 y 15.6 Kcal mol^{-1} respectivamente) comparada con el éter de enol (7.5 Kcal mol^{-1}). Esto puede ser debido a la mayor energia del estado de transición de tipo silla, provocada por la planaridad del enlace amida.

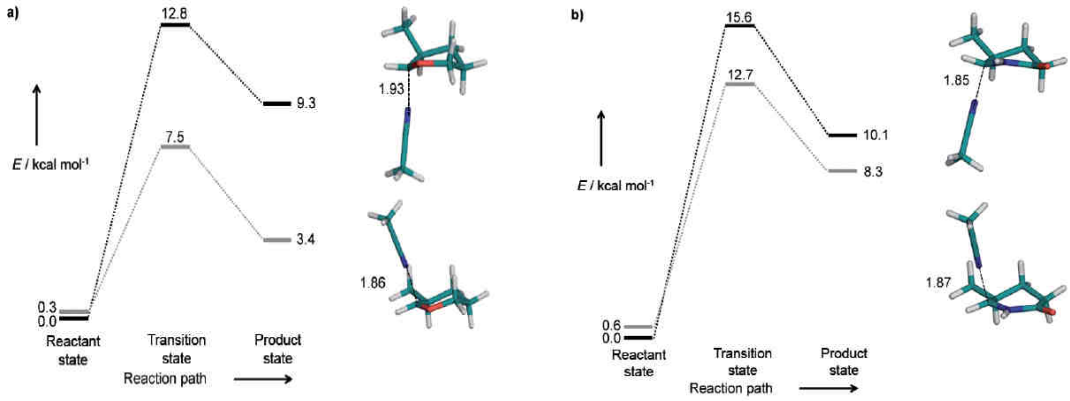


Figura 1. Perfiles de energía (Kcal mol^{-1}) para el ataque en *cis* (gris) y el ataque en *trans* (negro) para la adición del acetonitrilo sobre oxocarbenios y oxoiminios cíclicos.

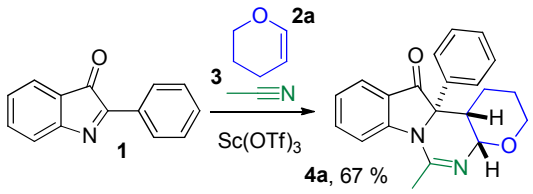
Para concluir se puede afirmar que en este trabajo se ha descubierto una nueva reacción multicomponente, la reactividad de la cual depende de la olefina activada utilizada. Para explicar este hecho se han realizado cálculos computacionales que han justificado este comportamiento.

1.5. Publicación 5: A Divergent Process Leading to Diels-Alder and Mannich-Ritter Adducts. Computational and Mechanistic Evidences of a Cationic Common Intermediate.

Salomé Llabrés, Esther Vicente-García, Sara Preciado, Cristina Guiu, Rodolfo Lavilla, F. Javier Luque.

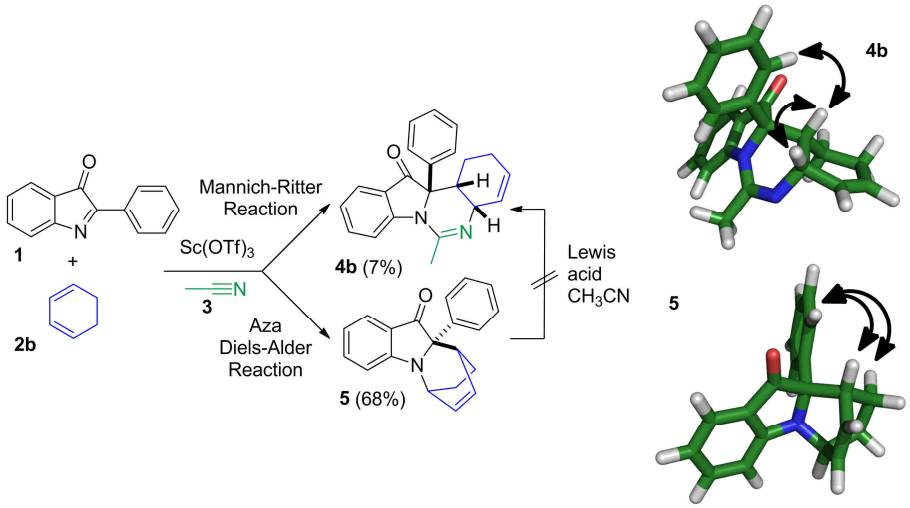
Artículo en preparación.

Teniendo en cuenta el reciente descubrimiento realizado en el grupo de investigación sobre la transformación multicomponente de tipo Mannich-Ritter (Esquema 1) y el estudio de las características del mecanismo del proceso, se decidió estudiar la interacción del ciclohexadieno como componente olefínico en dicho proceso.



Esquema 1. Reacción Mannich-Ritter.

Sorprendentemente, al utilizar ciclohexadieno (**2b**) como olefina activada el producto Mannich-Ritter (**4b**) se obtiene de forma minoritaria, siendo el producto mayoritario (**5**) el resultante del proceso Diels-Alder entre la imina y el dieno (Esquema 2). Para asegurar que el producto Mannich-Ritter (**4b**) no es el resultado de la evolución de **5** en condiciones de reacción, se somete a este último a las condiciones de reacción, ácido de Lewis y acetonitrilo, sin detectar ningún progreso hacia **4b** (Esquema 2). A partir del resultado obtenido, se plantea la posibilidad de la existencia de un intermedio común entre los dos productos obtenidos y si fuera así, los dos procesos compartirían una parte del camino de reacción. De los compuestos obtenidos se realizó la elucidación estructural (Esquema 2) con el objetivo de clarificar la estereoquímica de éstos y facilitar el estudio del mecanismo de reacción. Por este mismo motivo, se llevo a cabo el estudio de diferentes catalizadores donde se determinó que en ningún caso se conseguía incrementar el porcentaje del producto Mannich-Ritter y que sólo bajo el efecto del $BF_3{\cdot}OEt_2$ se reprodujo el resultado obtenido con $Sc(OTf)_3$.



Esquema 2. Reacción entre la imina **1** y ciclohexadieno.

Adicionalmente, se planearon otros experimentos donde se utilizó como disolvente una mezcla de metanol-acetonitrilo en un porcentaje 20-80 con el objetivo de comprobar si el exceso de metanol presente en el medio facilitaría la actuación de éste como nucleófilo externo y atrapar así el carbocatión que se forma en el proceso. Como resultado se detectaron las especies resultantes de la inserción del metanol y de agua en el producto final, disminuyendo el porcentaje de **4b** y **5**.

A partir de los resultados obtenidos, se pueden llegar a varias hipótesis sobre el mecanismo de la reacción, ya que existe la posibilidad de que **5** provenga de un mecanismo concertado, y que en cambio **4b** sea producto de un mecanismo por pasos. O que en cambio, el estado de transición concertado se polarice y de lugar a los dos productos posibles, **5** y **4b**.

Con el objetivo de esclarecer el mecanismo de la reacción se inició la modelización del mecanismo de la reacción mediante estudios computacionales con tal de clarificar los caminos de reacción de ambos procesos implicados. Para ellos se utiliza la transformación catalizada por $BF_3{\cdot}OEt_2$, ya que este compuesto resulta más sencillo de modelizar.

1.6. Publicación 6: Povarov MCR Derivatives as Novel Peripheric AChE Inhibitors

Elisabet Viayna, Esther Vicente-García, Ornella di Prieto, Rosario Ramón, M. Victoria Clos, Belén Pérez, Albert Badia, Manuela Bartolini, Vicenza Andrisano, F. Javier Luque, Rodolfo Lavilla, Diego Muñoz-Torrero.

Artículo en preparación

En los últimos años en el grupo de investigación se ha estudiado la inhibición de la acetilcolinesterasa (AChE) por parte de inhibidores duales (Figura 1), en colaboración con los grupos de los Profs. Muñoz-Torrero y Luque de la Facultad de Farmacia. Este tipo de compuestos son capaces de actuar en el centro activo y el sitio periférico de la AChE, inhibiendo de este modo la catalización de la agregación del ß amiloide (ßA). En el estudio computacional sobre la interacción de los nuevos inhibidores con la garganta catalítica revela que el fragmento de piranoquinolina, resultado del proceso multicomponente de Povarov-oxidación, interactúa con residuos del sitio periférico.

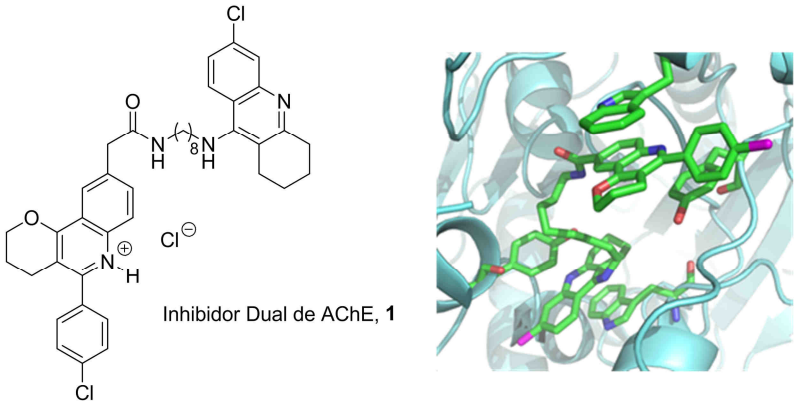


Figura 1. Nuevo inhibidor dual de AChE (1) y su interacción con el encima

A partir de este estudio, se planeó la sustitución del átomo de oxígeno del pirano fusionado en la quinolina por un átomo de nitrógeno para así aumentar la basicidad del compuesto resultante y de este modo mejorar las interacciones de este en sitio periférico.

Para ello se partió de la tetrahidroquinolina producto de la reacción de Povarov con lactamas insaturadas como olefinas activadas para luego oxidar y reducir el carbonilo del fragmento amida. O alternativamente se partió de la Boc-enamina para obtener la tetrahidroquinolina correspondiente y después de un proceso de oxidación y desprotección obtener el producto deseado (Figura 2).

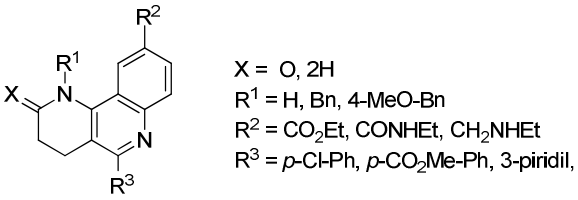


Figura 2. Nuevos inhibidores de AChE

De los productos obtenidos se analizó su actividad frente *electric eel* AChE (eeAChE), butilicolinesterasa (hBChE) y la auto agregación del ß amiloide (ßA). Los nuevos compuestos mostraron actividad relevante frente eeAChE mientras que frente hBChE y ßA fueron prácticamente inactivos.

Del producto más potente frente a eeAChE (**20**) se realizaron los estudios de *docking* para determinar que tipo de interacción establecía con la AChE. Se concluyó que este tipo de compuestos interactúan mayoritariamente en el sitio periférico, pero su colocación en el medio de la garganta también les permite establecer interacciones con residuos del centro catalítico.

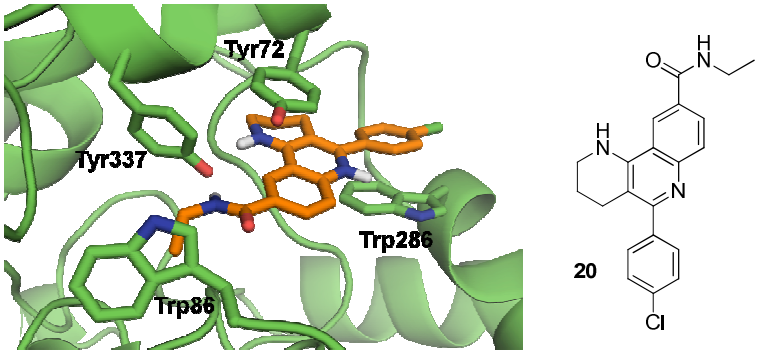


Figura 3. Compuesto más activo (**20**) y modelización de su interacción con AChE

2. Contribución personal a las publicaciones presentadas.

Unsaturated Lactams: New Inputs for Povarov-Type Multicomponent Reactions.
Esther Vicente-García, Federica Catti, Rosario Ramón, Rodolfo Lavilla.
Organic Letters, **2010**, *12*, 860-863.

Mi aportación en este trabajo ha consistido en el estudio de las condiciones de reacción de todos los experimentos realizados con lactamas insaturadas, así como la síntesis de éstas. También he realizado parte de los experimentos de oxidación y tratamiento ácido. He llevado a cabo la caracterización de los productos sintetizados por mi parte así como la elucidación estructural de los mismos por métodos espectroscópicos. He participado en la escritura del manuscrito.

New Heterocyclic Inputs for the Povarov Multicomponent Reaction.
Esther Vicente-García, Rosario Ramón, Rodolfo Lavilla.
Synthesis, **2011**, 2237-2246.

Mi contribución ha consistido en la síntesis de los productos de partida necesarios para el estudio, así como en el diseño de las condiciones de reacción de todos los experimentos con 1,3-tia-, -oxa- y -imidazolonas. Por otra parte he realizado el diseñó de la versión intramolecular de la reacción y todos los experimentos de oxidación. He llevado a cabo la caracterización de los productos sintetizados por mi parte así como la elucidación estructural de los mismos por métodos espectroscópicos. He participado en la escritura del manuscrito.

Multicomponent Reaction Access to Complex Quinolines Via Oxidation of the Povarov Adducts.
Esther Vicente-García, Rosario Ramón, Sara Preciado, Rodolfo Lavilla.
Beilstein J. Org. Chem. **2011**, *7*, 980-987.

Mi participación ha consistido en el estudio de la capacidad oxidativa de los diferentes tipos de dióxido de manganeso hasta encontrar el ideal, del cual se realizó un estudio de condiciones para optimizar el proceso. He colaborado en el análisis granulométrico de las partículas de los diferentes tipos de dióxido de manganeso estudiados. He llevado a cabo la caracterización de los productos sintetizados por mi parte así como la elucidación estructural de los mismos por métodos espectroscópicos. He participado en la escritura del manuscrito.

Exploration of Forbbiden Povarov Processes as a Source of Unexpected Reactivity: a New Multicomponent Mannich-Ritter Transformation.
Sara Preciado, Esther Vicente-García, Salomé Llabrés, F. Javier Luque, Rodolfo Lavilla.
Angew. Chem. Int. Ed. **2012**, *51*, 6874-6877.

Tras el descubrimiento inicial de la reacción por parte de Sara Preciado, mi participación ha consistido en el estudio de la reactividad de las diferentes olefinas activadas en la nueva reacción multicomponente. He analizado los diferentes

resultados obtenidos y he realizado la caracterización y elucidación experimental de los productos sintetizados por mi parte. He participado en la escritura del manuscrito.

A Divergent Process Leading to Diels-Alder and Mannich-Ritter Adducts. Computational and Mechanistic Evidences of a Cationic Common Intermediate.
Salomé Llabrés, Esther Vicente-García, Sara Preciado, Rodolfo Lavilla, F. Javier Luque.
Artículo en preparación.

En relación a la parte experimental, he colaborado en el estudio y diseño de la reacción y sus condiciones. He realizado la caracterización y elucidación estructural de los compuestos obtenidos por métodos espectroscópicos. He participado en la escritura del manuscrito.

Povarov MCR Derivatives as Novel Peripheric AChE Inhibitors
Elisabet Viayna, Esther Vicente-García, Ornella di Prieto, Rosario Ramón, M. Victoria Clos, Belén Pérez, Albert Badia, Manuela Bartolini, Vicenza Andrisano, F. Javier Luque, Rodolfo Lavilla, Diego Muñoz-Torrero.
Artículo en preparación

Mi contribución ha consistido en el diseño de parte de los experimentos y la síntesis de parte de los compuestos que constituyen el trabajo. He llevado a cabo la caracterización de los compuestos correspondientes así como su elucidación estructural por métodos espectroscópicos. He participado en los estudios computacionales preliminares y en la escritura del manuscrito.

Esther Vicente Revisado por el Dr. Rodolfo Lavilla