



**Universidad de Valladolid**

Facultad de Ciencias



**TRABAJO FIN DE GRADO**

**GRADO EN QUÍMICA**

**ESTUDIO DE LA REACCIÓN DE MANNICH  
ORGANOCATALIZADA DE BOC-CETOIMINAS  
DERIVADAS DE 1H-PIRAZOL-4,5-DIONA CON 1,3-  
DICETONAS**

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## *RESUMEN*

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En este trabajo hemos utilizado una serie de N-Boc cetoiminas derivadas de pirazolin-5-onas como electrófilos en reacciones de Mannich enantioselectivas con diferentes compuestos 1,3-dicarbonílicos. Este método proporciona una vía directa de acceso a derivados de 4-amino-5-pirazolona con un estereocentro tetrasustituido, que contienen dos motivos estructurales privilegiados, las subestructuras de  $\beta$ -dicetona y de pirazolinona. Los aductos se obtienen con excelentes rendimientos químicos (hasta 90 %) y enantioselectividades (hasta 94:6 er) empleando sólo un 2 mol % de una escuaramida bifuncional derivada de la quinina como organocatalizador para una amplia variedad de sustratos. Además, se ha demostrado la utilidad de los productos obtenidos mediante su transformación en un solo paso en sistemas diheterocíclicos (4-pirazolil-pirazolona y 4-isoxazolil-pirazolona) enantioenriquecidos de interés biológico.

## *ABSTRACT*

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A series of N-Boc ketimines derived from pyrazolin-5-ones have been used as electrophiles in enantioselective Mannich reactions with different 1,3-dicarbonyl compounds. This method provides a direct pathway to access to the 4-amino-5-pyrazolone derivatives bearing a tetra-substituted stereocenter and containing two privileged structure motifs, the  $\beta$ -diketone and pyrazolinone substructures. The aducts are obtained in excellent yields (up to 90%) and enantioselectivities (up to 94:6 er) by employing a very low loading of 2 mol % of a quinine-derived bifunctional squaramide as a organocatalyst for a wide range of substrates. In addition, the utility of the obtained products was demonstrated through one step transformations to enantioenriched diheterocyclic systems (4-pyrazolyl-pyrazolone and 4-isoxazolyl-pyrazolone) of biological interest.



## **ABREVIATURAS Y ACRÓNIMOS**

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<b>A<sub>N</sub></b>	Adición nucleófila
<b>Ar</b>	Arilo
<b>ATR</b>	Reflectancia total atenuada (Attenuated Total Reflection)
<b>Boc</b>	terc-Butoxicarbonilo (tert-butoxycarbonyl)
<b>°C</b>	Grado(s) centígrado(s)
<b>Cat.</b>	Catalizador
<b>d</b>	Día(s)
<b>DMSO</b>	Dimetil sulfoxido (dimethyl sulfoxide)
<b>dr</b>	Diastereomeric ratio (Relación de diastereoisómeros)
<b>E</b>	Eliminación
<b>ee</b>	Exceso enantiomérico
<b>ent</b>	Enantiómero
<b>equiv</b>	Equivalente(s)
<b>er</b>	Enantiomeric ratio (Relación de enantiómeros)
<b>Et</b>	Etilo
<b>g</b>	Gramo(s)
<b>GC/MS</b>	Cromatografía de gases acoplada a espectrometría de masas
<b>h</b>	Hora(s)
<b>HPLC</b>	High Performance Liquid Chromatography (Cromatografía líquida de alta resolución)
<b>HRMS</b>	High Resolution Mass Spectrometry (Espectrometría de masas de alta resolución)
<b>Hz</b>	Hertzio(s)
<b><sup>i</sup>Bu</b>	Isobutilo
<b><sup>i</sup>Pr</b>	Isopropilo
<b>IR</b>	Infrarrojo (Infrared)

<b>J</b>	Constante de acoplamiento
<b>Lit.</b>	Literatura
$\lambda$	Longitud de onda
<b>M</b>	Molaridad
<b>Me</b>	Metilo
<b>mg</b>	Miligramo(s)
<b>MHz</b>	Megahertzio(s)
<b>mL</b>	Mililitros(s)
<b>mm</b>	Milímetros(s)
<b>mmol</b>	Milimol(es)
<b>mol%</b>	Tanto por cien molar
<b>M.p.</b>	Melting point (Punto de fusión)
<b>MS 4Å</b>	Tamiz molecular 4Å (Molecular Sieves)
<b>m/z</b>	Relación masa/carga
<b>nm</b>	Nanómetro(s)
<b>NMR/RMN</b>	Nuclear Magnetic Resonance (Resonancia magnética nuclear)
<b>Ph</b>	Fenilo
<b>ppm</b>	Parte(s) por millón
<b>QTOF</b>	Cuadruple Time Of Flight (Cuadrupolo de tiempo de vuelo)
<b>R</b>	Sustituyente
<b>Rdto.</b>	Rendimiento
<b>t</b>	Tiempo
<b>ta/rt</b>	Temperatura ambiente (room temperatura)
<b><sup>t</sup>Bu</b>	<i>tert</i> -Butilo
<b>THF</b>	Tetrahidrofurano (tetrahydrofuran)
<b>TLC</b>	Cromatografía en capa fina (Thin Layer Chromatography)
<b>TMS</b>	Tetrametilsililo, tetrametilsilano



**t<sub>R</sub>** Tiempo de retención (Retention time)  
**UV** Ultravioleta



## 1. INTRODUCCIÓN

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Uno de los principales retos de la sociedad moderna actual es la reducción del empleo de recursos y de la generación de residuos junto con el mantenimiento del ritmo actual de producción de sustancias de valor añadido. En este contexto, la **economía circular**, que es un modelo de producción y consumo que implica reciclar y reutilizar los materiales y productos existentes durante el mayor tiempo posible, es uno de los pilares en los que se apoya la **transición ecológica**. Un avance muy destacable en este sentido es la utilización de una pequeña cantidad de una sustancia, conocida como **catalizador**, para promover una determinada transformación química en condiciones más suaves, de forma más selectiva o directamente inaccesible de otro modo. La implementación de procesos catalíticos está perfectamente alineada con muchos de los 12 principios de la Química Verde,<sup>1</sup> un conjunto de pautas básicas propuestas por Anastas y Warner para iluminar el camino hacia una evolución sostenible de la práctica química.

La demanda de compuestos enantiopuros está creciendo como consecuencia de su uso en materiales avanzados y las regulaciones farmacéuticas cada vez más restrictivas.<sup>2</sup> En este escenario, las ventajas de desarrollar nuevas transformaciones enantioselectivas catalíticas<sup>3</sup> se vuelven más evidentes, ya que las alternativas se ven obstaculizadas por la disponibilidad del sustrato (enfoque de *chiral pool*) o la especificidad excesiva del sustrato (biocatálisis). En la búsqueda de métodos de síntesis enantioselectiva de moléculas para diferentes aplicaciones, la **organocatálisis** se ha mostrado como una alternativa complementaria a la catálisis promovida por complejos de metales de transición y enzimas.<sup>4</sup> Recientemente, ha recibido mucha atención la

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<sup>1</sup> (a) P. T. Anastas, J. C. Warner. *Green Chemistry: Theory and Practice*, Oxford University Press, **2000**.

(b) P. Anastas, N. Eghbali. *Chem. Soc. Rev.* **2010**, *39*, 301.

<sup>2</sup> M. C. Nunez, M. E. Garcia-Rubino, A. Conejo-Garcia, O. Cruz-López, M. Kimatrai, M. A. Gallo, A. Espinosa, J. M. Campos. *Curr. Med. Chem.* **2009**, *16*, 2064.

<sup>3</sup> E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis. Supplement*, Springer, Berlin; New York, **2004**.

<sup>4</sup> *Reviews recientes*: (a) B. List, K. Maruoka, (Eds.), *Science of Synthesis: Asymmetric Organocatalysis*, Vols. 1 and 2, Georg Thieme Verlag, Stuttgart, **2012**. (b) M. Rueping, D. Parmar, E. Sugiono, *Asymmetric Brønsted Acid Catalysis*, Wiley-VCH, Weinheim, **2016**. (c) J. Alemán, S. Cabrera. *Chem. Soc. Rev.* **2013**, *42*, 774. (d) M. R. Volla, I. Atodiresei, M. Rueping. *Chem. Rev.* **2014**, *114*, 2390. (e) P. Chauhan, U. Kaya, D. Enders. *Adv. Synth. Catal.* **2017**, *359*, 888. (f) J. Liu, L. Wang. *Synthesis* **2017**, *49*, 960.

preparación de organocatalizadores capaces de activar la reacción mediante la formación de enlaces de hidrógeno,<sup>5</sup> habiéndose desarrollado derivados de ácido fosfórico,<sup>6</sup> escuaramidas<sup>7</sup> y ureas y tioureas,<sup>8</sup> capaces de promover diferentes transformaciones enantioselectivas con excelente discriminación estérica. Una prueba del interés que ha suscitado la organocatálisis ha sido la reciente concesión del premio Nobel de Química de 2021 a los profesores List y MacMillan por sus contribuciones a este campo.

Los pirazoles y las pirazolonas son una clase privilegiada de aza-heterociclos de cinco eslabones con amplias aplicaciones como productos farmacéuticos y agroquímicos. Aunque las pirazolonas no son un elemento estructural habitual de productos naturales biológicamente activos, una amplia gama de derivados sintéticos de ellas exhibe propiedades farmacológicas variadas (antipiréticos, analgésicos, neuroprotectores, antibacteriales, antitumorales, inhibidores de HIV-1, etc) (Figura 1). Por ese motivo, la síntesis asimétrica de derivados de pirazolin-5-ona estructuralmente diversos es objeto actualmente de gran interés.<sup>9</sup>

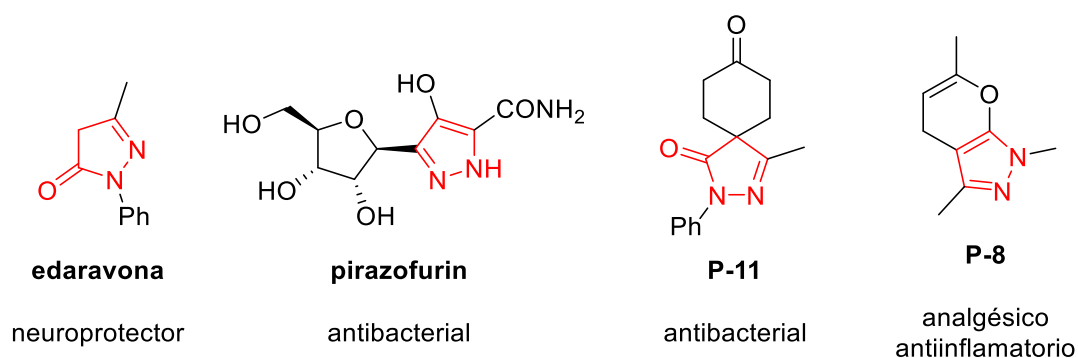


Figura 1

<sup>5</sup> (a) L.-Q. Lu, X.-L. An, J.-R. Chen, W.-J. Xiao. *Synlett* **2012**, 490. (b) M. J. Ajitha, K.-W. Huang. *Synthesis* **2016**, 48, 3449.

<sup>6</sup> (a) F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto. *Chem. Soc. Rev.* **2012**, 41, 2406. (b) D. Parmar, E. Sugiono, S. Raja and M. Rueping. *Chem. Rev.* **2014**, 114, 9047.

<sup>7</sup> (a) R. I. Storer, C. Aciroa, L. H. Jones. *Chem. Soc. Rev.* **2011**, 40, 2330 (b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen. *Chem. Eur. J.* **2011**, 17, 6890. (c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders. *Adv. Synth. Catal.* **2015**, 357, 253. (d) B.-L. Zhao, J.-H. Li, D.-M. Du. *Chem. Rec.* **2017**, 17, 1.

<sup>8</sup> (a) W.-Y. Siau, J. Wang. *Catal. Sci. Technol.* **2011**, 1, 1298. (b) O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva. *Org. Biomol. Chem.* **2013**, 11, 7051. (c) X. Fanga, C.-J. Wang. *Chem. Commun.* **2015**, 51, 1185.

<sup>9</sup> *Reviews*: (a) X. Xie, L. Xiang, C. Peng, B. Han. *Chem. Rec.* **2019**, 19, 2209. (b) P. Chauhan, S. Mahajan D. Enders. *Chem. Commun.* **2015**, 51, 12890. (c) S. Liu, X. Bao, B. Wang. *Chem. Commun.* **2018**, 54, 11515.

Las pirazolin-5-onas presentan, entre otros, un centro nucleofílico en la posición C-4, dado su carácter de amidas enolizables. Por otra parte, a partir de ellas se pueden sintetizar pirazolin-4,5-dionas e iminas en las que la posición C-4 es electrófila (Figura 2).

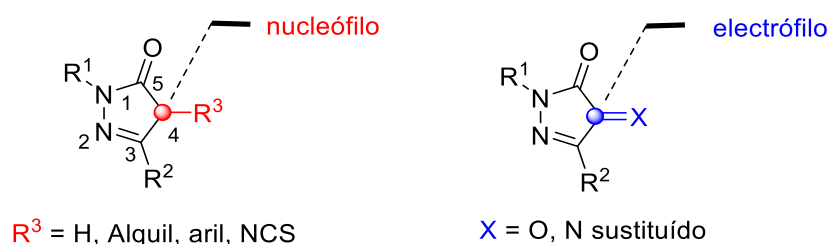
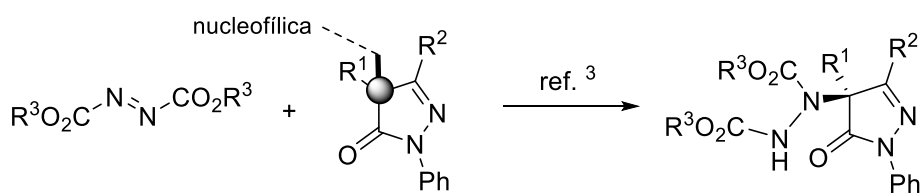


Figura 2

El grupo de Enders<sup>10</sup> sintetizó por primera vez en 2017 N-Boc cetoiminas, a partir de pirazolin-5-onas, sustratos de gran interés, ya que pueden utilizarse como productos de partida en nuevas transformaciones organocatalizadas enantioselectivas en las que se generan estereocentros cuaternarios 4-amino sustituidos. Con anterioridad a la publicación de su trabajo, la preparación de pirazolonas con un estereocentro nitrogenado tetrasustituido, se había realizado mediante la  $\alpha$ -aminación electrofílica de pirazolonas 4-sustituídas con azodicarboxilatos (Esquema 1).<sup>11</sup>

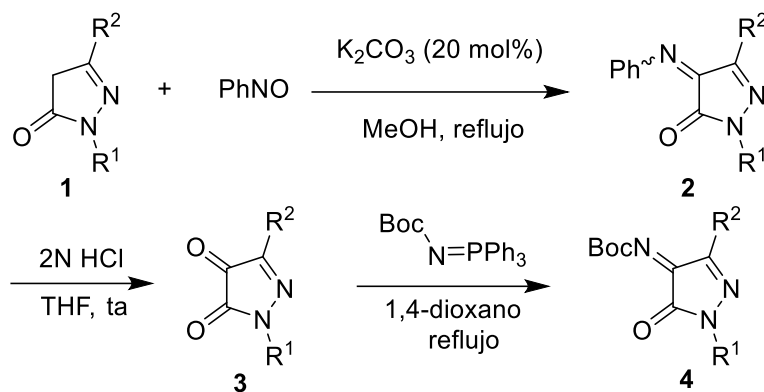


Esquema 1

La síntesis de las N-Boc cetoiminas la realizan mediante la condensación promovida por  $\text{K}_2\text{CO}_3$  de las pirazolonas **1** con nitrosobenceno, seguida de hidrólisis ácida de las feniliminas intermediarias **2** a las correspondientes dionas **3** (Esquema 2). Éstas las convierten posteriormente en N-Boc cetoiminas **4** mediante una reacción aza-Wittig con N-Boc-imino-(trifenil)fosforano.

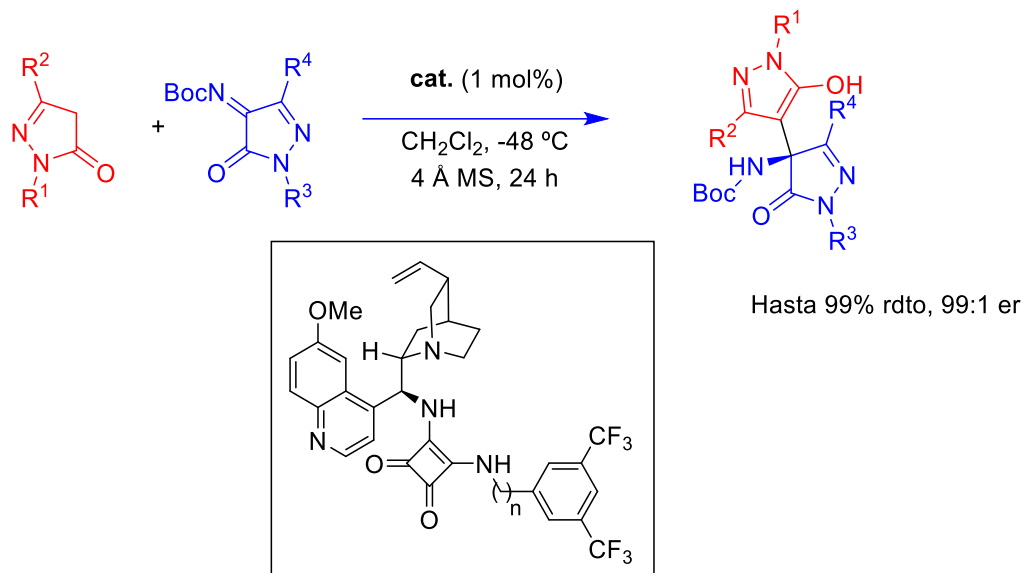
<sup>10</sup> P. Chauhan, S. Mahajan, U. Kaya, A. Peuronen, K. Rissanen, D. Enders. *J. Org. Chem.* **2017**, *82*, 7050.

<sup>11</sup> (a) Z. Yang, Z. Wang, S. Bai, X. Liu, L. Lin, X. Feng. *Org. Lett.* **2011**, *13*, 596. (b) M. Šimek, M. Remeš, J. Veselý, R. Rios. *Asian J. Org. Chem.* **2013**, *2*, 64. (c) B. Formánek, V. Šeferna, M. Meazza, R. Rios, M. Patil, J. Veselý. *Eur. J. Org. Chem.* **2021**, 2362.



Esquema 2

En ese mismo trabajo, Enders utiliza las N-Boc cetoinimas sintetizadas como electrófilos en la preparación de aductos de amino-bis-pirazolona a través de una reacción de Mannich organocatalizada que emplea pirazolonas como nucleófilos. La reacción transcurre con excelentes rendimientos químicos y enantioselectividad en presencia de sólo un 1 mol% de una escuaramida bifuncional derivada de la quinina (Esquema 3).

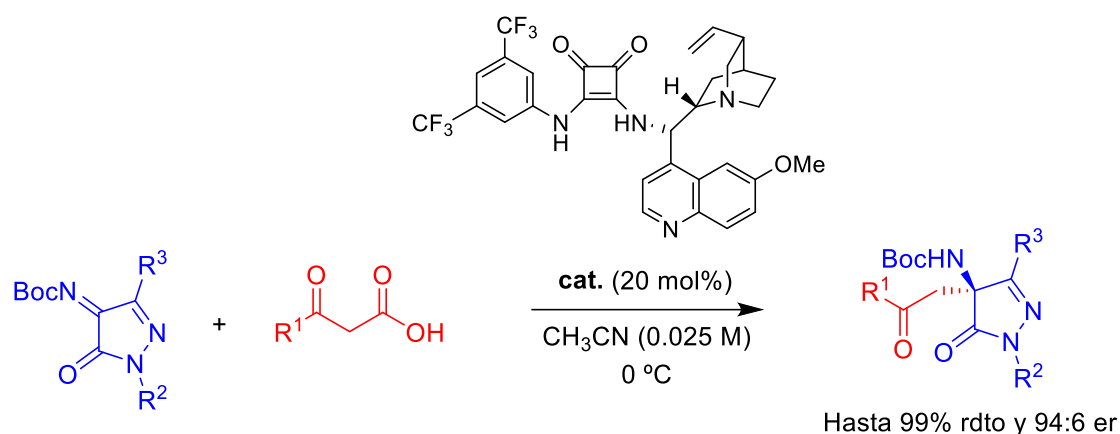


Esquema 3

Yuan<sup>12</sup> ha estudiado la reacción de Mannich descarboxilativa de  $\beta$ -cetoácidos con Boc-iminas derivadas de pirazolin-5-onas promovida de nuevo por una escuaramida bifuncional quiral derivada de la quinina (Esquema 4). A través de este protocolo,

<sup>12</sup> Y. Zhou, Y. You, Z.-H. Wang, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan. *Eur. J. Org. Chem.* **2019**, 3112.

obtiene una serie de derivados de  $\beta$ -amino cetona-pirazolinona quirales con excelentes rendimientos (hasta 99%) y enantioselectividades (hasta er 94:6).



Esquema 4

La estereoquímica observada se explica a través de la activación mediante enlace de hidrógeno de la N-Boc cetoinmina por los grupos NH de la escuaramida, que orienta el ataque nucleofílico del enolato de la metilcetona a la imina por la cara-*Re*, conduciendo a la obtención del aducto de configuración (*S*) (Figura 3).

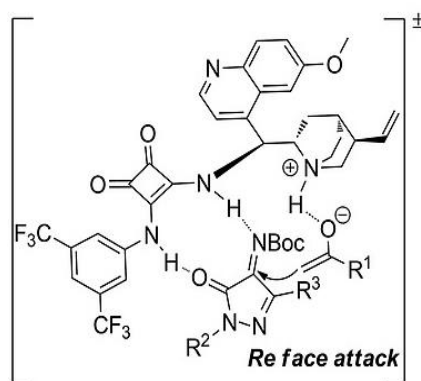
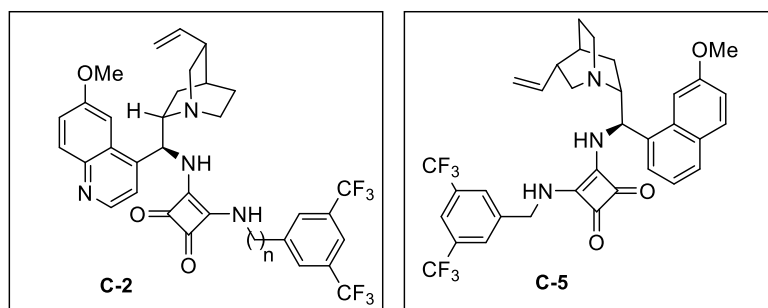
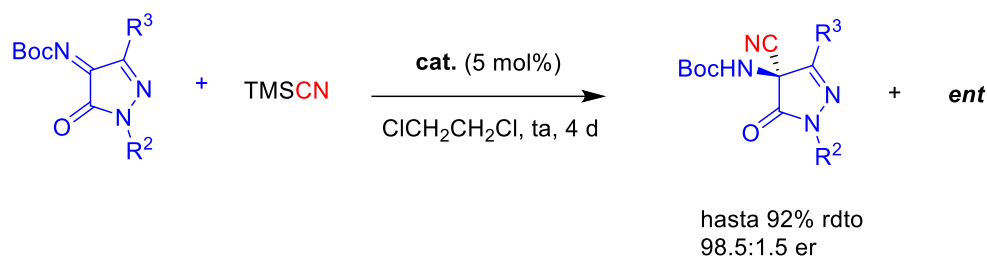


Figura 3

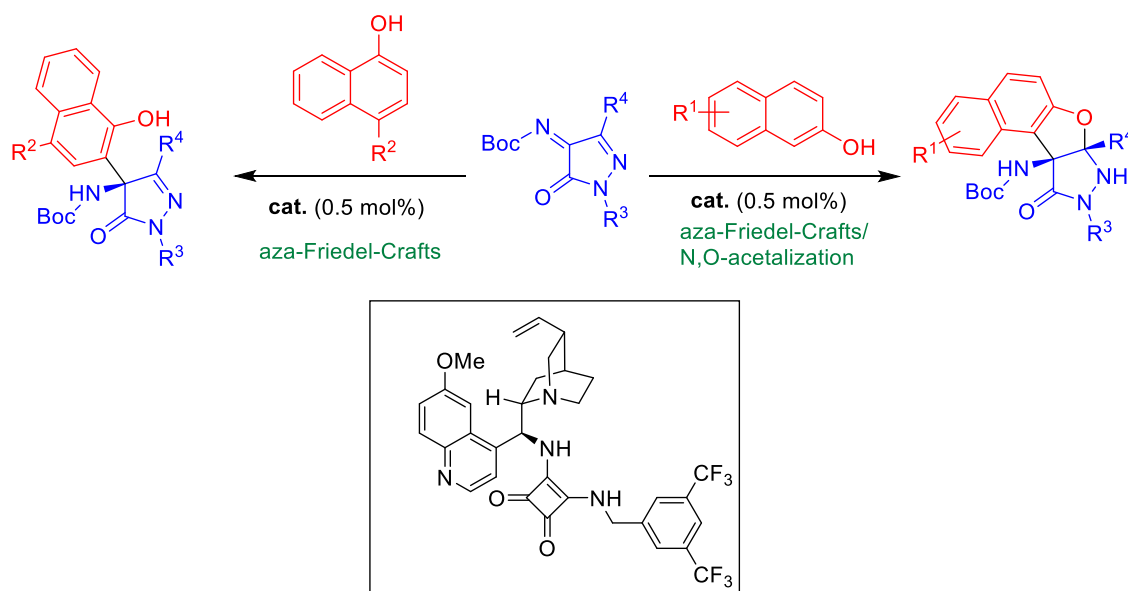
En 2017, el grupo de Enders describió el primer ejemplo de reacción de Strecker enantioselectiva organocatalizada con Boc-cetoinminas derivadas de pirazolona (Esquema 5).<sup>13</sup> En presencia de las escuaramidas pseudoenantiómeras derivadas de la quinina (**C-2**) y de la quinidina (**C-5**), la adición nucleofílica de cianuro de trimetilsililo a las cetoinminas proporciona uno u otro enantiómero de los derivados de pirazolona  $\alpha$ -aminonitrilo con buenos rendimientos químicos y elevada enantioselectividad con una amplia variedad de sustratos.

<sup>13</sup> S. Mahajan, P. Chauhan, U. Kaya, K. Deckers, K. Rissanen, D. Enders. *Chem. Commun.* **2017**, 53, 6633.



Esquema 5

El grupo de Enders ha estudiado a su vez la reacción dominó asimétrica aza-Friedel-Crafts/N,O-acetalización de 2-naftoles con Boc-cetoiminas derivadas de pirazolinona catalizada por sólo un 0.5 mol% de una escuaramida bifuncional quiral derivada de la quinina (Esquema 6).<sup>14</sup>



Esquema 6

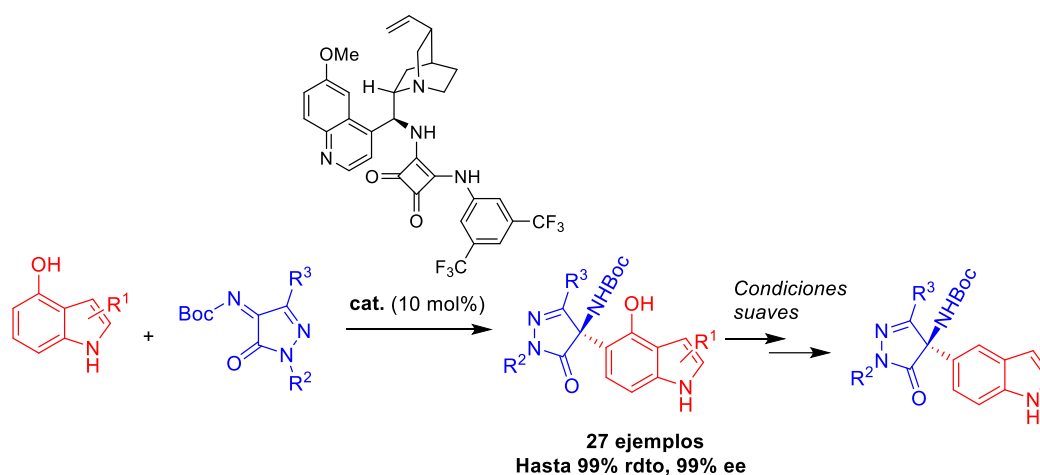
La reacción proporciona derivados de furanonaftopirazolidinona con dos estereocentros vecinales tetra-sustituidos con excelentes rendimientos (95-98%) y

<sup>14</sup> U. Kaya, P. Chauhan, S. Mahajan, K. Deckers, A. Valkonen, K. Rissanen, D. Enders. *Angew. Chem. Int. Ed.* **2017**, *56*, 15358.



estereoselectividades (>99:1 dr y 97–98% ee). Una reactividad diferente se observa en el caso de 1-naftoles y otros fenoles ricos en electrones, que conducen a los aductos aza-Friedel-Crafts con un rendimiento del 70-98% y 47-98% ee.

Posteriormente, Deng ha descrito la reacción asimétrica aza-Friedel-Crafts de Boc-cetoiminas derivadas de pirazolonas con hidroxindoles catalizada por una escuaramida bifuncional derivada de la quinina (Esquema 7).<sup>15</sup> Esta reacción funciona también con fenoles ricos en electrones, proporcionando los productos deseados con elevados rendimientos (hasta 99%) y enantioselectividades (91-99% ee).

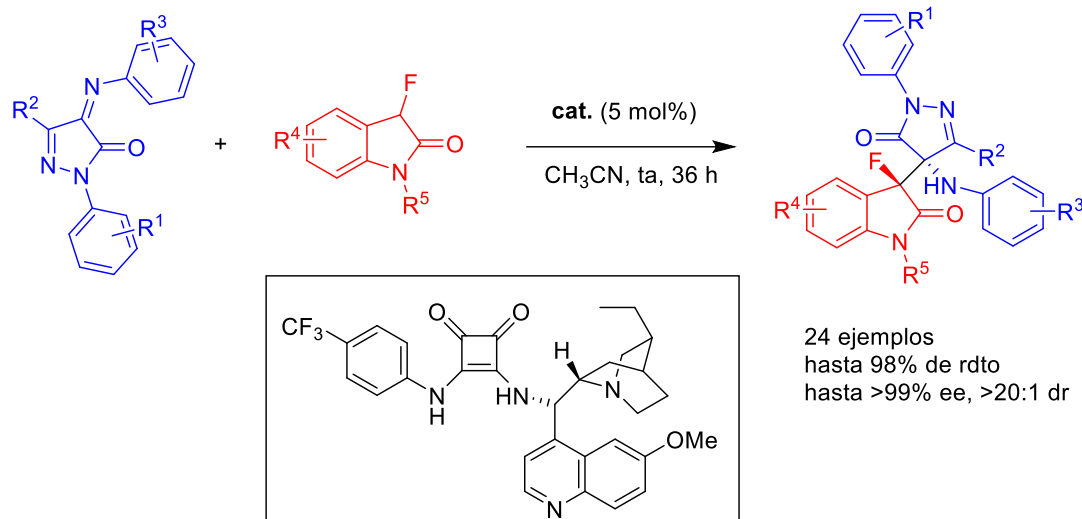


Esquema 7

Du ha estudiado la reacción de Mannich enantioselectiva de N-aril cetoiminas derivadas de pirazolin-4,5-dionas con 3-fluorooxindoles que permite la preparación de derivados de amino-pirazolona-oxindol fluorados con dos estereocentros adyacentes tetrasustituídos (Esquema 8).<sup>16</sup> De todos los organocatalizadores utilizados, la escuaramida derivada de la hidroquinina fue la que proporcionó mayores rendimientos químicos (hasta 98%) y diastereo- y enantioselectividad (>20:1 dr y >99% ee).

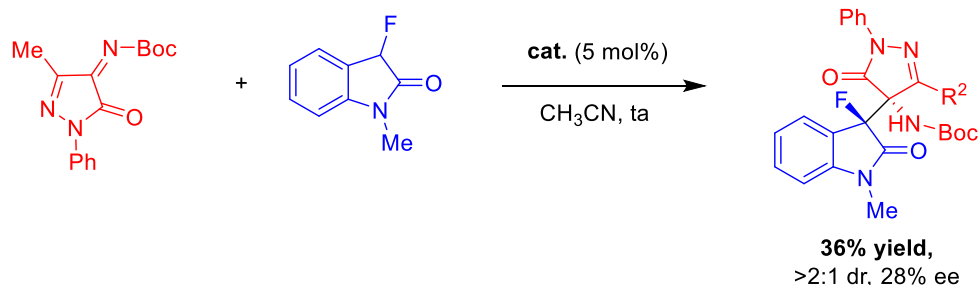
<sup>15</sup> Z.-T. Yang, W.-L. Yang, L. Chen, H. Sun, W. i-P. Deng. *Adv. Synth. Catal.* **2018**, *360*, 2049.

<sup>16</sup> Q.-D. Zhang, B.-L. Zhao, B.-Y. Li, D.-M. Du. *Org. Biomol. Chem.* **2019**, *17*, 7182.



Esquema 8

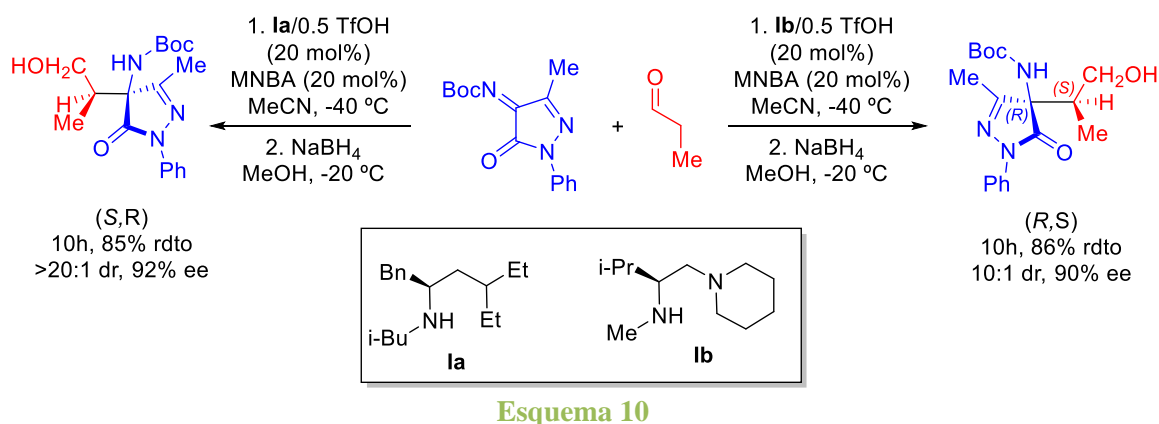
No obstante, la reacción no es extrapolable a las N-Boc cetoiminas derivadas de pirazolona. En las condiciones optimizadas de reacción, el rendimiento químico y la estereoselectividad conseguidas con estos sustratos no fueron satisfactorios (Esquema 9).



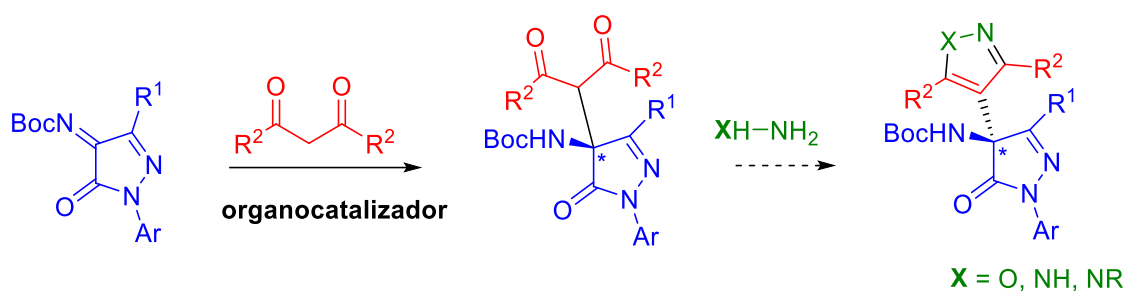
Esquema 9

Shao<sup>17</sup> ha descrito una reacción de Mannich de Boc-iminas derivadas de pirazolonas con propionaldehído, catalizada por aminas secundarias acíclicas quirales, que proporciona los correspondientes aductos de manera enantiodivergente con excelentes diastereoselectividades y buenas relaciones enantioméricas (Esquema 11). La simple pero estratégica modificación del sustituyente nitrogenado de la amina secundaria del catalizador (de N-*i*-Bu en **Ia** al grupo N-Me en **Ib**), manteniendo la misma configuración del estereocentro, condujo a la inversión de la enantioselectividad a través de la modulación de la conformación del catalizador.

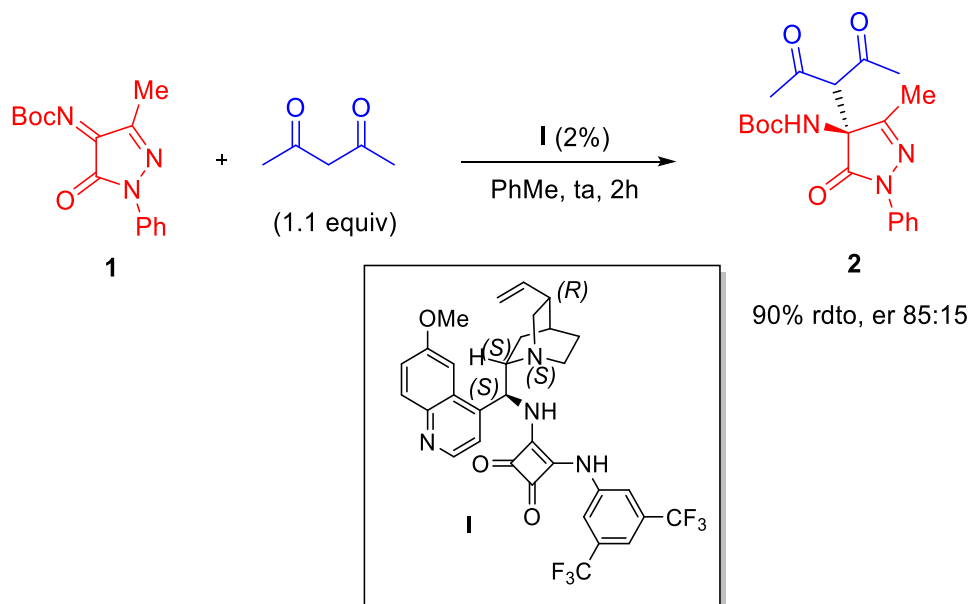
<sup>17</sup> J. Dai, Z. Wang, Y. Deng, L. Zhu, F. Peng, Y. Lan, Z. Shao. *Nat. Commun.* **2019**, *10*, 5182.



En la literatura no existe ningún antecedente de adición enantioselectiva organocatalizada de compuestos 1,3-dicarbonílicos a Boc-cetoiminas derivadas de pirazolonas. Esta reacción es de gran interés por la posibilidad de transformar los aductos obtenidos en nuevos diheterociclos (pirazolil-pirazolonas, isoxazolil-pirazolonas), con propiedades biológicas potencialmente interesantes, mediante su reacción con diferentes 1,2-dinucleófilos (hidracinas diferentemente sustituidas, hidrocloreuro de hidroxilamina) (Esquema 11).



En un trabajo previo realizado en el grupo de investigación en el que he realizado este TFG, han estudiado la adición enantioselectiva de acetilacetona a la N-Boc cetoimina **1** promovida por organocatalizadores bifuncionales quirales en diferentes condiciones experimentales (disolvente, temperatura, estequiometría, % de catalizador). Las condiciones optimizadas de reacción se corresponden con la utilización de tolueno como disolvente, temperatura ambiente, 1.1 equiv de dicetona y un 2% de la escuaramida bifuncional **I**, derivada de la quinina (Esquema 12).



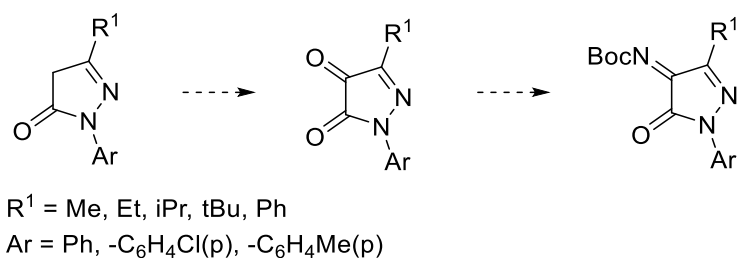
### Esquema 12

Como continuación de este trabajo, en este TFG nos planteamos el estudio del alcance de esta reacción, utilizando para ello pirazolonas y  $\beta$ -dicetonas diferentemente sustituidas, y la transformación de los aductos obtenidos en nuevos derivados de pirazolil-pirazolona e isoxazolil-pirazolona enantioenriquecidos.

## 2.OBJETIVOS Y PLAN DE TRABAJO

### 2.1. Síntesis de N-Boc-cetoiminas derivadas de pirazolonas.

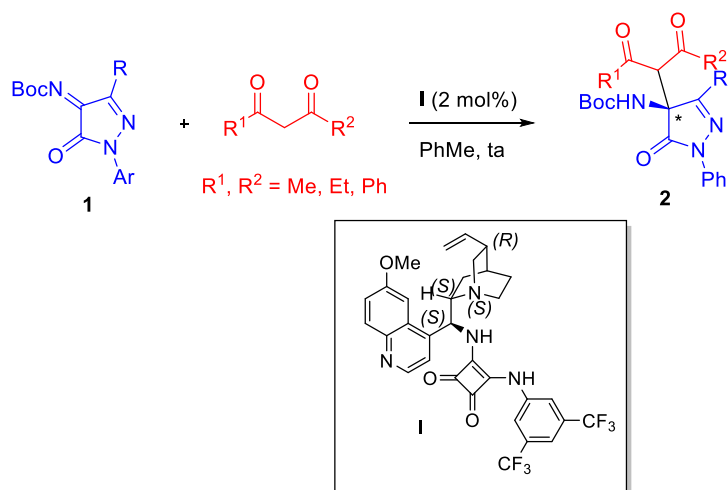
En primer lugar, prepararemos las N-Boc cetoiminas derivadas de pirazolonas, diferentemente sustituidas, mediante un procedimiento en dos etapas: transformación de las pirazolin-5-onas en las correspondientes pirazolin-4,5-dionas, seguida de reacción aza-Wittig con N-Boc-trifeniliminofosforano (Esquema 1).



Esquema 1

### 2.2. Estudio del alcance y limitaciones sintéticas de la reacción de Mannich organocatalizada de N-Boc cetoiminas derivadas de pirazolonas con β-dicetonas.

Inicialmente, estudiaremos la reacción de N-Boc cetoiminas derivadas de pirazolona (**1**) diferentemente sustituidas con acetilacetona promovida por la escuaramida bifuncional I derivada de la quinina, para extender posteriormente el estudio a otras β-dicetonas (Esquema 2).

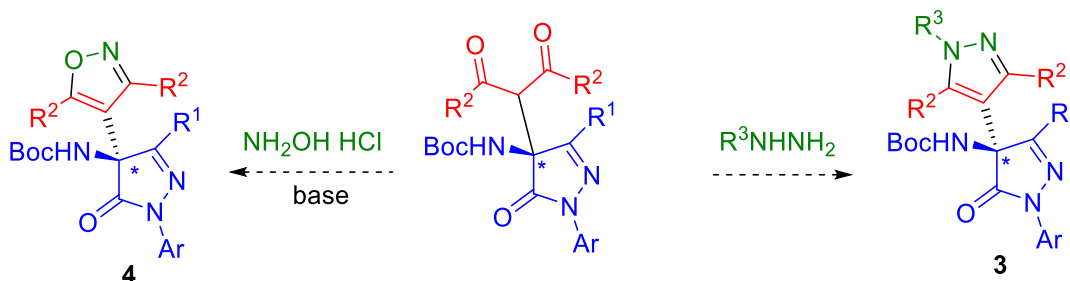


Esquema 2

Estudiaremos la influencia de la naturaleza de los sustituyentes R y Ar de la pirazolona y R<sup>1</sup> y R<sup>2</sup> de la dicetona en la velocidad de reacción, en el rendimiento químico y en la enantioselectividad de los aductos obtenidos.

### 2.3. Estudio de la transformación de los aductos obtenidos en nuevos diheterociclos enantioenriquecidos mediante reacción con 1,2-dinucleófilos.

Finalmente, en este tercer apartado estudiaremos la transformación de los aductos **2**, obtenidos en el apartado anterior, en nuevos derivados de 4-pirazolil-4-aminopirazolona (**3**) y 4-isoxazolil-4-aminopirazolona (**4**) enantioenriquecidos mediante su reacción respectiva con hidrato de hidracina o hidrocloreto de 4-clorfenilhidracina e hidrocloreto de hidroxilamina (Esquema 3). Comprobaremos en todos los casos que dichas transformaciones transcurren sin erosión alguna de la enantioselectividad.



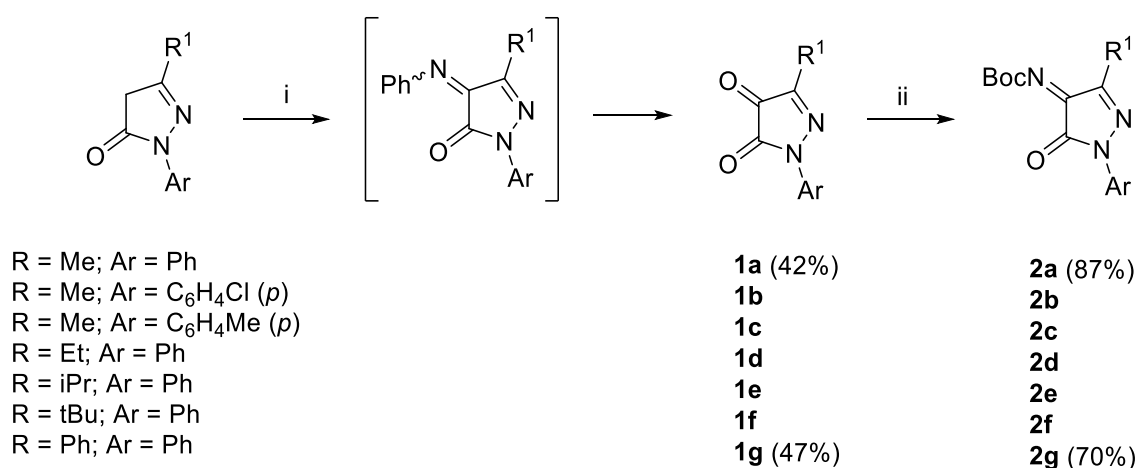
Esquema 3

Paralelamente, habrá que realizar la síntesis de los racematos de todos los compuestos preparados para su resolución posterior mediante HPLC quiral.

### 3. RESULTADOS Y DISCUSIÓN

#### 3.1. Síntesis de *N*-Boc cetoiminas derivadas de pirazolonas.

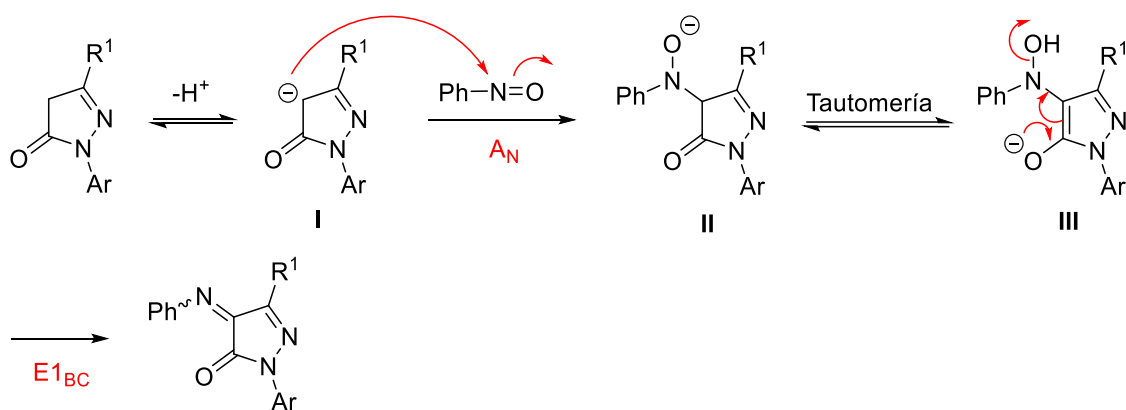
La síntesis de las 1*H*-pirazol-4,5-dionas (**1a-g**) se realiza mediante la condensación de las pirazolonas de partida con nitrosobenceno en metanol a reflujo catalizada por K<sub>2</sub>CO<sub>3</sub>, seguida de la hidrólisis ácida de las feniliminas intermediarias (Esquema 1). Éstas se convierten posteriormente en las *N*-Boc cetoiminas **2a-g** mediante la reacción aza-Wittig con *N*-Boc-trifeniliminofosforano en 1,4-dioxano a reflujo, según el procedimiento descrito por Enders.<sup>10</sup>



**Esquema 1. Reactivos y condiciones:** (i) 1. PhNO, K<sub>2</sub>CO<sub>3</sub> (20 mol%), MeOH, reflujo. 2. 2N HCl, THF, ta. (ii) BocN=PPh<sub>3</sub>, 1,4-dioxano, reflujo.

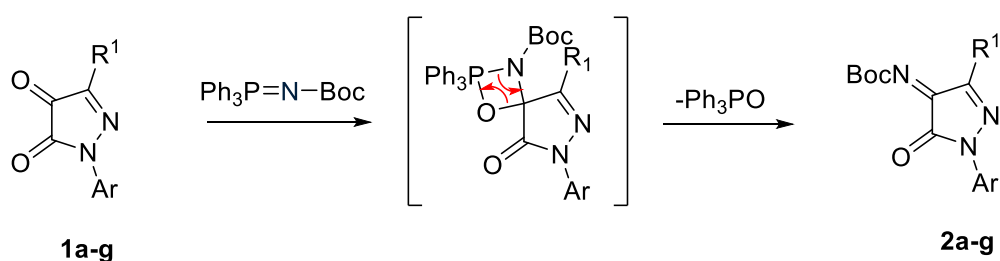
La mayoría de las Boc-iminas de partida habían sido sintetizadas previamente en el grupo. Por ese motivo sólo tuve que realizar la síntesis de las iminas **2a** (R = Me) y **2g** (R = Ph), las más utilizadas en las transformaciones estudiadas, y cuyos rendimientos son los únicos que figuran en el Esquema 1.

El mecanismo de la reacción de condensación de la pirazolona con nitrosobenceno es referible al de la condensación aldólica (Esquema 2). En la primera etapa, el carbonato potásico sustrae el hidrógeno en  $\alpha$  de la pirazolona para generar un enolato (**I**) que se adiciona al nitrosobenceno para formar el intermedio **II**. Éste se transforma en el nitrosoenolato **III**, mediante un equilibrio tautomérico catalizado por base, que conduce a la fenilimina final mediante una eliminación E1<sub>CB</sub>.



Esquema 2

En el Esquema 3 se muestra el mecanismo de la reacción de la reacción aza-Wittig de las pirazolin-4,5-dionas con N-Boc-trifeniliminofosforano. Las reacciones de Aza-Wittig son similares a las reacciones de Wittig y consisten en la reacción de un iluro de fosonio, en este caso un iminofosforano, con el grupo carbonilo de la pirazolin-4,5-diona para formar el doble enlace carbono-nitrógeno de la Boc-imina junto con el óxido de trifenilfosfina como subproducto.



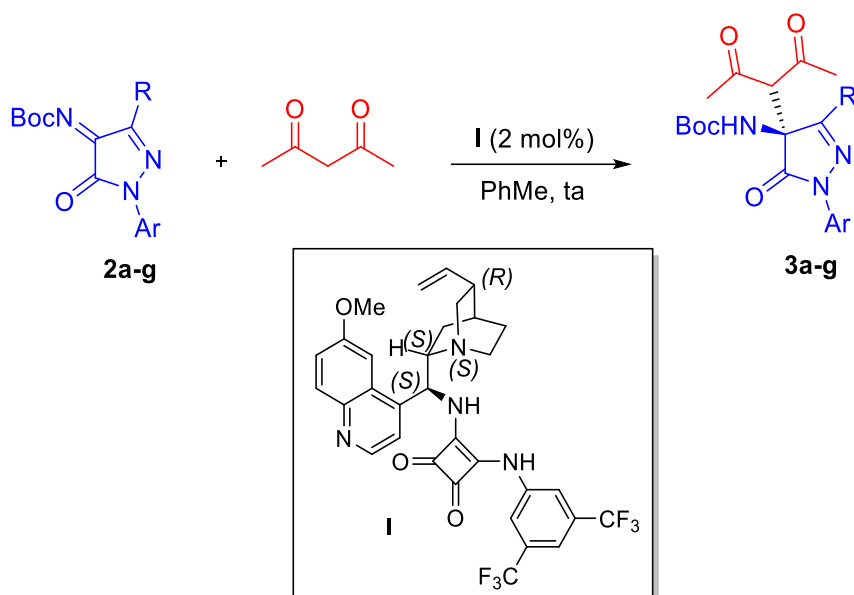
Esquema 3

### 3.2. Reacción de Mannich enantioselectiva de N-Boc cetoiminas derivadas de pirazolonas con $\beta$ -dicetonas.

En este apartado estudiamos inicialmente el alcance de la reacción haciendo reaccionar Boc-cetoiminas **2a-g** diferentemente sustituidas con acetilacetona en presencia de la escuaramida **I** (Tabla 1). Para ello realizamos diferentes ensayos en las condiciones de reacción optimizadas: 2% de catalizador, 1.1 equivalentes de dicetona, tolueno como disolvente y temperatura ambiente.



**Tabla 1.** Alcance de la reacción con diferentes Boc-iminas.<sup>a</sup>



Entrada	R	Ar	t (h)	Producto (%) <sup>b</sup>	er <sup>c</sup>
1	Me	Ph	2.5	<b>3a</b> (90)	<b>85:15</b> (95:5) <sup>e</sup>
2	Me	C <sub>6</sub> H <sub>4</sub> Cl ( <i>p</i> )	1	<b>3b</b> (81)	<b>87:13</b> (96:4) <sup>e</sup>
3	Me	C <sub>6</sub> H <sub>4</sub> Me ( <i>p</i> )	2	<b>3c</b> (68)	<b>89:11</b>
4	Et	Ph	3	<b>3d</b> (67)	<b>84:16</b>
5	iPr	Ph	24	<b>3e</b> (71)	88:12
6	tBu	Ph	>7d	<b>3f</b> (0)	-
7 <sup>d</sup>	Ph	Ph	48	<b>3g</b> (68)	<b>94:6</b>

<sup>a</sup>Reacción llevada a cabo con 0.1 mmol de imina, acetilacetona (0.11 mmol, 1.1 equiv) y catalizador **I** (0.002 mmol, 0.02 equiv) en 1 mL de PhMe a temperatura ambiente. <sup>b</sup>Rendimiento aislado. <sup>c</sup>Determinado mediante HPLC quiral. <sup>d</sup>Reacción realizada en presencia de un 5% del catalizador. <sup>e</sup>Aguas madres.

La reacción de la imina **2a** con acetilacetona condujo al aducto **3a** con excelente rendimiento químico y una relación enantiomérica de 85:15 (entrada 1). Las iminas **2b-c** con grupos electroaceptores (-Cl) o electrodonadores (-Me) en la posición *para* del fenilo en N-1 reaccionaron en las mismas condiciones con la acetilacetona, proporcionando los productos deseados **3b-c** con buenos rendimientos y una mayor enantioselectividad, siendo este aumento más acusado para el caso del grupo *p*-tolilo (comparar entradas 1 y 2-3).

A continuación, estudiamos el efecto del sustituyente R situado en la posición C-3 de la imina. La cetoimina **2d**, sustituida por un grupo etilo, condujo al aducto **3d** con una relación enantiomérica análoga a la conseguida con **3a**, en un tiempo de reacción comparable (comparar entradas 1 y 4). En cambio, se consiguió un aumento de la enantioselectividad (er 88:12, entrada 5) con la imina **2e** sustituida por un grupo isopropilo, de mayor impedimento estérico, aunque a costa de un aumento considerable del tiempo de reacción (24 h). No obstante, un incremento mayor del volumen estérico (R = tBu) condujo a una brusca disminución de la reactividad incluso a temperatura ambiente, no detectando cantidad alguna del aducto **3f** en el análisis de  $^1\text{H-RMN}$  de la masa de reacción después de 7 días (entrada 6).

Finalmente, un último ensayo realizado con la imina **3g**, 3-fenil sustituida, proporcionó el aducto **3g** con buen rendimiento y la mejor relación enantiomérica conseguida hasta el momento (er 94:6, entrada 7). En este caso se tuvo que utilizar un 5% de catalizador para que la reacción se completara a las 48h.

La configuración de los aductos **3a-g**, obtenidos con la escuaramida **I**, derivada de la hidroquinina, se ha propuesto de manera tentativa como (*S*) de acuerdo con un modelo de activación análogo al propuesto por Yuan<sup>12</sup> (Figura 1). La activación mediante enlace de hidrógeno de la N-Boc cetoimina **2** por el grupo escuaramida del catalizador **I** facilita el ataque nucleofílico del enolato de la acetilacetona por la cara-*Re* del grupo imina, conduciendo al aducto deseado **3** con una configuración específica. Esta configuración deberá de ser confirmada más adelante mediante análisis de difracción de rayos X.

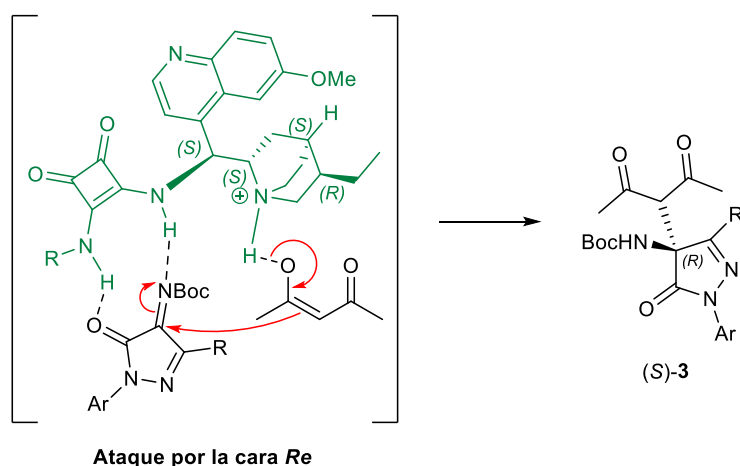
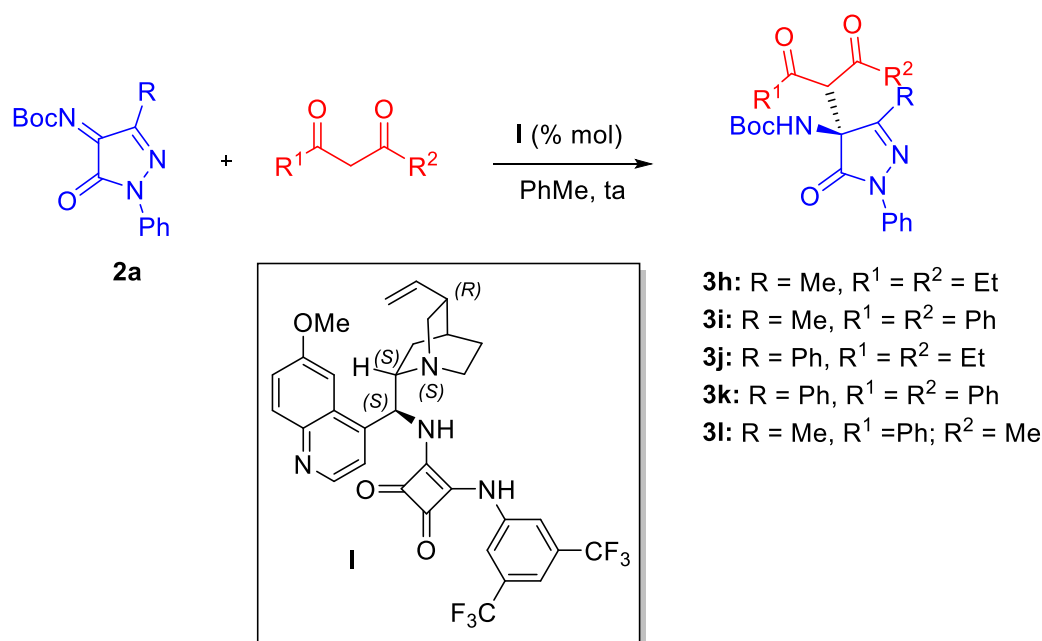


Figura 1

Intentos de aumentar la pureza enantiomérica de los aductos **3a** y **3b** mediante su recristalización en una mezcla de hexano-acetato resultaron fallidos, obteniendo en ambos casos pequeñas cantidades de producto cuasi-racémico. No obstante, sí se observó un incremento de la enantioselectividad en las aguas madres, obteniendo de esta manera los productos **3a** y **3b** enantioenriquecidos con una er de 95:5 y 96:4, respectivamente (ver entradas 1-2 en Tabla 1).

Paralelamente al estudio de sustituyentes de la Boc-imina de partida, estudiamos la reactividad de las cetoiminas **3a** y **3b**, 3-metil y 3-fenil-sustituidas, con otras dicetonas. Los resultados del estudio realizado se recogen en la Tabla 2.

**Tabla 2.** Alcance de la reacción con diferentes compuestos  $\beta$ -dicarbonílicos.<sup>a</sup>



Entrada	R	R <sup>1</sup>	R <sup>2</sup>	% Cat.	t (h)	Producto (%) <sup>b</sup>	dr <sup>c</sup>	er <sup>d</sup>
1	Me	Et	Et	(2%)	4.5	<b>3h</b> (66)	-	<b>85:15</b>
2	Me	Ph	Ph	(2%)	5	<b>3i</b> (75)	-	<b>88:12</b>
3	Ph	Et	Et	(10%)	24	<b>3j</b> (60)	-	<b>93:7</b>
4	Ph	Ph	Ph	(10%)	72	<b>3k</b> (46)	-	<b>93:7</b>
5	Me	Ph	Me	(2%)	2.5	<b>3l</b> (66)	72:28	56:44 major 57:43 minor

<sup>a</sup>Reacción llevada a cabo con 0.1 mmol de imina, dicetona (0.11 mmol, 1.1 equiv) en 1 mL de tolueno a temperatura ambiente. <sup>b</sup>Rendimiento aislado. <sup>c</sup>Determinado mediante <sup>1</sup>H-RMN. <sup>d</sup>Determinado mediante HPLC quiral.

La adición de la 3,5-heptanodiona a la cetoimina **2a** en presencia de un 2% de la escuaramida **I** transcurre más lentamente que la reacción con la acetilacetona y condujo al aducto **3h** con buen rendimiento y análoga relación enantiomérica (ver entrada 1, Tabla 2). En cambio, un aumento significativo de la enantioselectividad (er 88:12 entrada 2) se observó en la reacción de la misma cetoimina con la 1,3-difenilpropano-1,3-diona.

Como era de esperar, la reacción de la cetoimina **2g**, 3-fenil sustituida, con ambas dicetonas, condujo a los aductos **3j** y **3k** con una excelente relación enantiomérica (er 93:7) y bueno o moderado rendimiento, después de 24h y 72h de reacción (entradas 3 y 4). Dada la menor reactividad de esta cetoimina, hubo que utilizar un 10% de catalizador para que la reacción se completara en un tiempo razonable.

Finalmente, la reacción la cetoimina **2a** con la benzoilacetona, una 1,3-dicetona asimétricamente sustituida, en presencia de sólo un 2% de la escuaramida **I** (entrada 5) proporcionó el aducto **3l** como una mezcla 72:28 de diastereoisómeros con buen rendimiento químico pero con baja enantioselectividad en ambos diastereoisómeros. Esta experiencia se repitió, obteniendo resultados comparables. Asimismo, se analizó mediante HPLC quiral la mezcla de diastereoisómeros antes y después de su purificación mediante cromatografía en columna, no observando diferencias significativas.

### *3.3. Síntesis de derivados de 4-pirazolil-4-aminopirazolona y de 4-isoxazolil-4-aminopirazolona enantioenriquecidos.*

Para ilustrar la versatilidad de los aductos **3** obtenidos en estas reacciones de Mannich organocatalizadas, y dada la importancia biológica del núcleo de pirazol,<sup>18</sup> decidimos preparar inicialmente compuestos híbridos con los componentes pirazol y pirazolona, con potencial actividad biológica (Tabla 3).

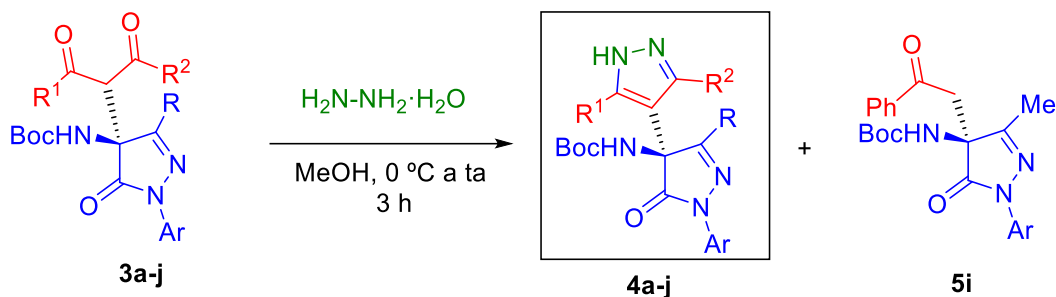
La condensación de los aductos **3a-e,g** (todos ellos obtenidos en la reacción con acetilacetona) con monohidrato de hidracina (2 equiv) en metanol proporcionó, después de 3h de reacción a temperatura ambiente, los aductos 4-pirazolil-4-aminopirazolona **4a-e,g** con buenos rendimientos químicos (60-82%, entradas 1-6). En cambio, el aducto **3j**, obtenido en la reacción con heptano-3,5-diona, condujo al correspondiente derivado

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<sup>18</sup> V. Kumar, K. Kaur, G.K. Gupta, A.K. Sharma. *Eur. J. Med. Chem.* **2013**, 69, 735.

de pirazol **4j** con rendimiento moderado (40%, entrada 7). Como era de esperar, el análisis realizado mediante HPLC quiral de los productos obtenidos muestra que la relación enantiomérica se mantiene en valores comparables a los aductos de Mannich de partida, no observando erosión de la pureza enantiomérica durante la transformación.

**Tabla 3.** Preparación de derivados de pirazol.<sup>a</sup>



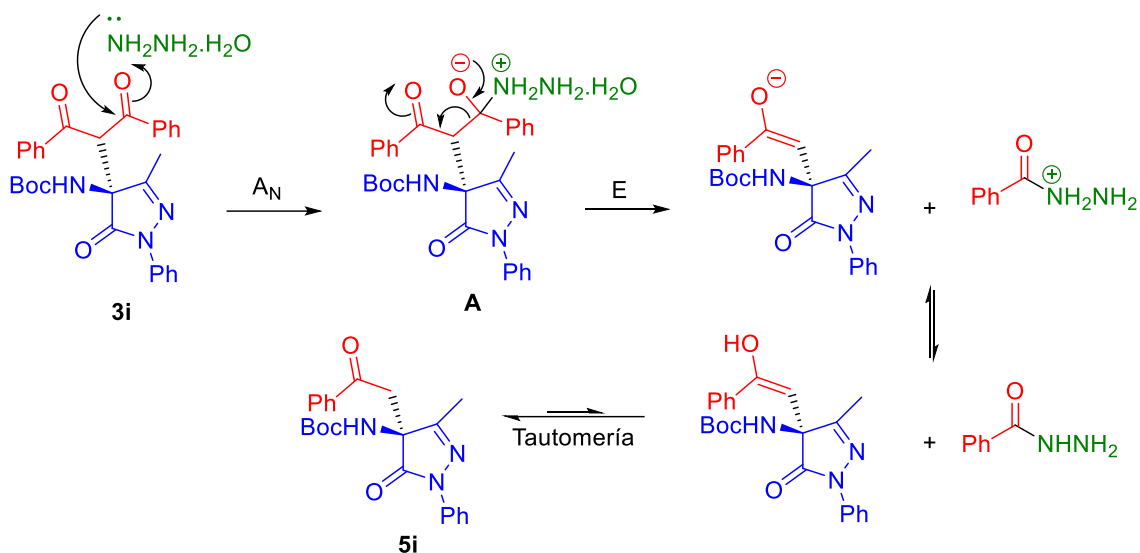
Entrada	R	Ar	R <sup>1</sup>	R <sup>2</sup>	er 3a-j	Producto (%) <sup>b</sup>	er <sup>c</sup>
1	Me	Ph	Me	Me	95:5	<b>4a</b> (81)	94:6
2	Me	C <sub>6</sub> H <sub>4</sub> Cl ( <i>p</i> )	Me	Me	87:13	<b>4b</b> (60)	82:18
3	Me	C <sub>6</sub> H <sub>4</sub> Me ( <i>p</i> )	Me	Me	89:11	<b>4c</b> (63)	88:12
4	Et	Ph	Me	Me	84:16	<b>4d</b> (68)	85:15
5	iPr	Ph	Me	Me	88:12	<b>4e</b> (78)	90:10
6	Ph	Ph	Me	Me	94:6	<b>4g</b> (82)	94:6
7	Ph	Ph	Et	Et	93:7	<b>4j</b> (40)	95:5
8	Me	Ph	Ph	Ph	88:12	<b>5i</b> (52)	77:23

<sup>a</sup>Reacción llevada a cabo con 2 equiv de H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O en MeOH, de 0 °C a temperatura ambiente.

<sup>b</sup>Rendimiento aislado. <sup>c</sup>Determinado mediante HPLC quiral.

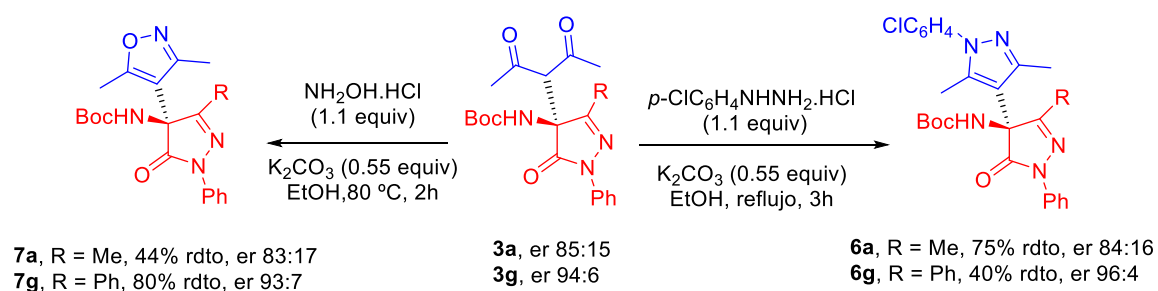
Sorprendentemente, la reacción del aducto **3i**, obtenido en la reacción de **2a** con con dibenzoilmetano, con hidrato de hidracina en las mismas condiciones experimentales, proporcionó como único producto el compuesto **5i**, resultado de una desbenzoilacilación del compuesto 1,3-dicarbonílico (entrada 8). En este caso, sí se observó una erosión de la relación enantiomérica con respecto a la del producto de partida (er 77:23 frente a 88:12). Afortunadamente, el compuesto **5i** está descrito en la literatura,<sup>12</sup> y la comparación de su rotación específica y de los tiempos de retención de los enantiómeros en HPLC quiral con los descritos en la literatura permitió confirmar la estereoquímica absoluta (*S*) propuesta anteriormente para los aductos **3a-l**.

En el Esquema 4 se propone un mecanismo para esta deacilación promovida por el monohidrato de hidracina, que ya había sido observada anteriormente por Wu<sup>19</sup> en la síntesis de 3,6-diarilpiridazinas y 6-arilpiridazin-3-onas a partir de compuestos 1,3-dicarbonílicos. El hidrato de hidracina puede actuar como nucleófilo adicionándose a uno de los grupos carbonilo del aducto **3i** para conducir el intermedio **A**, que experimenta un proceso de eliminación con fragmentación de un enlace C-C para proporcionar el producto **5i**.



Esquema 4

La reacción de los aductos **3a,g** con hidroclicloro de 4-clorofenilhidracina en etanol a reflujo y en presencia de  $K_2CO_3$  como base condujo de modo análogo a los pirazoles **6a,g**, N-4-clorofenilsustituidos, con rendimientos entre moderados y buenos y con relaciones enantioméricas análogas a las de los aductos de partida (Esquema 5).



Esquema 5

<sup>19</sup> Q. Gao, Y. Zhu, M. Lian, M. Liu, J. Yuan, G. Yin, A. Wu. *J. Org. Chem.* **2012**, 77, 9865.

Finalmente, la transformación de los aductos **3a,g** en los derivados de isoxazol **7a,g** se realizó mediante reacción con hidrocloreuro de hidroxilamina (1.1 equiv) en las mismas condiciones experimentales que las utilizadas en la preparación de los pirazoles **6a,g** (Esquema 5). De nuevo, no se observó erosión alguna en la relación enantiomérica de los productos obtenidos.

En resumen, partiendo de N-Boc cetoiminas derivadas de pirazolonas y  $\beta$ -dicetonas hemos desarrollado una reacción de Mannich enantioselectiva que proporciona derivados de 4-amino-5-pirazolona, con un estereocentro cuaternario y funcionalizados con grupos 1,3-dicarbonilo, con buenos rendimientos químicos y relaciones enantioméricas. La utilidad de los productos obtenidos se ha demostrado a través de su transformación en una etapa en nuevos derivados heterocíclicos enantioenriquecidos de posible interés biológico.





## CONCLUSIONES

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1. La reacción de N-Boc cetoiminas derivadas de pirazolona con acetilacetona en presencia de un 2 mol% de la escuaramida bifuncional **I**, derivada de la quinina, proporciona los correspondientes derivados de 4-aminopirazolona con un estereocentro cuaternario con buenos rendimientos químicos y enantioselectividades que dependen de los sustituyentes en el nitrógeno y en la posición C-3 de la imina de partida. Las mejores relaciones enantioméricas se han conseguido con las Boc-cetoiminas **2c**, N-*p*-tolilsustituída, (er 89:11) y **2g**, sustituida en C-3 por un grupo fenilo (er 94:6).
2. La reacción se puede extender a otras dicetonas dialquílicas o diarílicas, obteniendo los aductos correspondientes con buenos rendimientos y análogas enantioselectividades en tiempos de reacción mayores. Por ese motivo con las iminas menos reactivas (R = Ph) es necesario utilizar un 10% de catalizador.
3. La reacción de los aductos **3a-g,j** con hidrato de hidracina en metanol a temperatura ambiente conduce a los pirazoles **4a-j** con buenos rendimientos químicos y enantioselectividades análogas a las de los aductos de partida. La reacción no funciona con el aducto **3i**, sustituido por un grupo dibenzoilmetilo, que conduce al producto de deacilación **5i**. La correlación de su rotación específica con la descrita en la literatura nos ha permitido confirmar la estereoquímica absoluta (*S*) propuesta inicialmente para los aductos **3a-l**.
4. La utilidad sintética de los productos obtenidos se ha demostrado además a través de su transformación en una etapa en otros derivados heterocíclicos, (pirazoles N-4-clorofenilsustituídos e isoxazoles) de previsible interés biológico, mediante su reacción con los hidroclouros de 4-clorofenilhidracina e hidroxilamina, sin erosión alguna de su pureza enantiomérica.



## EXPERIMENTAL

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<sup>1</sup>H NMR (500 MHz, 400 MHz) and <sup>13</sup>C NMR (126 MHz, 101 MHz) spectra were recorded in CDCl<sub>3</sub> or DMSO-d<sub>6</sub> as solvent (Laboratory of Instrumental Techniques, University of Valladolid). Chemical shifts for protons are reported in ppm from TMS with the residual CHCl<sub>3</sub> resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, br s = broad signal), coupling constants in Hertz, and integration. Specific rotations were measured on a Perkin-Elmer 341 digital polarimeter using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer and are reported in frequency of absorption (only the structurally most important peaks are given). Melting points were obtained with a micro melting point Leica Gallen III apparatus and are uncorrected.

Flash chromatography was carried out using silica gel (230-240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F<sub>254</sub> indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a JASPO HPLC system (JASCO PU-2089 pump and UV-2075 UV/Vis detector) equipped with a quaternary pump, using a Chiralpak AD-H, Chiralpak IA, Lux-Amylose-2 and Lux-i-Amylose-3 analytical columns (250 x 4.6 mm). UV detection was monitored at 254 nm. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system.

Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave-activated 4 Å molecular sieves. N-Boc-triphenyliminophosphorane,<sup>20</sup> pyrazolones,<sup>21</sup> and squaramide **1**<sup>22</sup> were prepared according to literature procedures. Racemic mixtures were synthesized

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<sup>20</sup> P. Calí, M. Begtrup. *Synthesis*. **2002**, 63.

<sup>21</sup> (a) X. Li, F.-Y. Chen, J.-W. Kang, J. Zhou, C. Peng, W. Huang, M.-K. Zhou, G. He, B. H. *J. Org. Chem.* **2019**, *84*, 9138. (b) P. Yadav, A. Awasthi, S. Gokulnath, D. K. Tiwari. *J. Org. Chem.* **2021**, *86*, 2658.

<sup>22</sup>S. Del Pozo, S. Vera, M. Oiarbide, C. Palomo. *J. Am. Chem. Soc.* **2017**, *139*, 15308.

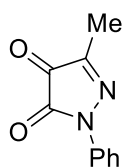
according to general procedure using an aquiral bifunctional thiourea derived from *N*<sup>1</sup>,*N*<sup>1</sup>-dimethylethane-1,2-diamine<sup>23</sup> (0.01 mmol) as catalyst.

### General Procedure for the Synthesis of Pyrazolone-Derived Ketones 1a-g.

Nitrosobenzene (25.0 mmol, 1.0 equiv) and K<sub>2</sub>CO<sub>3</sub> (0.2 equiv) were added to a solution of pyrazolone derivative (25.0 mmol, 1.0 equiv) in MeOH (0.6 M) at room temperature. The reaction mixture was then refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic layer was washed three times with water and once with brine and then dried over anhydrous MgSO<sub>4</sub>. After evaporation of ethyl acetate under reduced pressure, the crude product was purified by flash column chromatography (hexane/ethyl acetate, 20:1) to afford pyrazolone-derived phenyl ketimine.

Phenyl-ketimine (10 mmol) was dissolved in THF (0.13 M), and an aqueous HCl (2 M) solution (25 mL) was added to it at room temperature. The progress of the reaction was monitored via TLC. After completion of the reaction, the mixture was diluted with water. The organic layer was extracted three times with dichloromethane, and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>. The solvent was removed under reduced pressure.

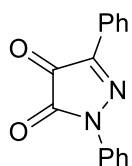
#### ▪ **3-Methyl-1-phenyl-1*H*-pyrazole-4,5-dione (1a).**<sup>10</sup>



**1a**

Compound **1a** was prepared from 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (2.0 g, 11.5 mmol) as described in general procedure. The crude product was directly purified by flash column chromatography (Hexane/EtOAc = 4:1) to afford the desired product **1a** as a red solid: 0.90 g (4.8 mmol, 42% yield). The <sup>1</sup>H-NMR spectrum of the product was matched with reported.<sup>10</sup>

#### ▪ **1,3-Diphenyl-1*H*-pyrazole-4,5-dione (1g).**<sup>10</sup>



**1g**

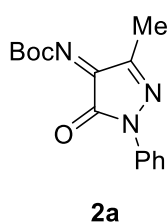
Compound **1g** was prepared from 2,5-diphenyl-2,4-dihydro-3*H*-pyrazol-3-one (2.07 g, 8.76 mmol) as described in general procedure. The crude product was directly purified by flash column chromatography (Hexane/EtOAc = 3:1) to afford the desired product **1g** as a red solid: 1.03 g (4.12 mmol, 47% yield). The <sup>1</sup>H-NMR spectrum of the product was matched with reported.<sup>10</sup>

<sup>23</sup> S. M. Opalka, J. L. Steinbacher, B. A. Lambiris, D. Tyler, McQuade. *J. Org. Chem.*, **2011**, *76*, 6503.

### General Procedure for the Synthesis of Pyrazolone-Derived N-Boc Ketimines 2a-g.

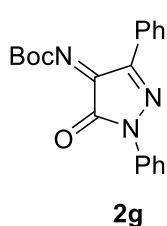
*tert*-Butyl(triphenylphosphoranylidene)acetate (2.2 mmol, 1.1 equiv) was added to a solution of the pyrazolone-derived ketone **1** (2 mmol) in 1,4-dioxane (0.2 M) at room temperature, and the mixture was refluxed. After the completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was purified by flash chromatography.

- ***tert*-Butyl (Z)-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol-4-ylidene) carbamate (2a).**<sup>10</sup>



Compound **2a** was prepared from **1a** (1.13 g, 6.0 mmol) as described in general procedure and the crude product was purified by flash column chromatography (n-Hexane/EtOAc = 15:1) to afford the desired N-Boc ketimine **2a** as a red solid: 1.50 g (5.22 mmol, 87% yield). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 7.83 (d, J = 7.6 Hz, 2H, H<sub>ar</sub>), 7.42 (m, 2H, H<sub>ar</sub>), 7.23 (m, 1H, H<sub>ar</sub>), 2.30 (s, 3H, CH<sub>3</sub>), 1.64 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.

- ***tert*-Butyl (Z)-(5-oxo-1,3-diphenyl-1,5-dihydro-4H-pyrazol-4-ylidene)carbamate (2g).**<sup>10</sup>



Compound **2g** was prepared from **1g** (0.50 g, 2.0 mmol) as described in general procedure and the crude product was purified by flash column chromatography (n-Hexane/EtOAc = 8:1) to afford the desired N-Boc ketimine **2g** as a red solid: 0.49 g (1.4 mmol, 70% yield). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.23 (m, 2H, H<sub>ar</sub>), 7.95 (dd, J = 8.8, 1.1 Hz, 2H, H<sub>ar</sub>), 7.48 (m, 5H, H<sub>ar</sub>), 7.28 (m, 1H, H<sub>ar</sub>), 1.67 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.

### General procedure for the synthesis of Mannich products 3a-l by enantioselective Mannich reaction of N-Boc ketimines with β-diketones.

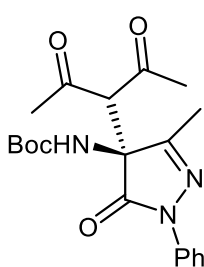
To a mixture of N-Boc ketimine **2** (0.1 mmol), catalyst **I** (0.002 mmol, 0.02 equiv) in 1.0 mL of toluene, β-diketone (0.11 mmol, 1.1 equiv) was added at room temperature and the reaction mixture was stirred in a Wheaton vial. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography to afford the corresponding product **3a-l**. The diastereomeric

excess was determined by  $^1\text{H-NMR}$ . The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

### Synthesis of ( $\pm$ )-Mannich products.

Racemic mixture of the enantiomers was synthesized according to general procedure, using an aquiral bifunctional thiourea derived from  $N^l,N^l$ -dimethylethane-1,2-diamine (0.01 mmol, 0.1 equiv) as catalyst.

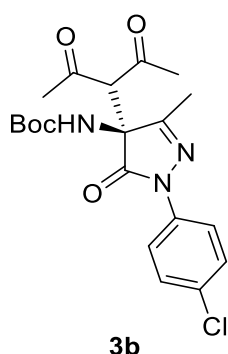
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3a**).**



**3a**

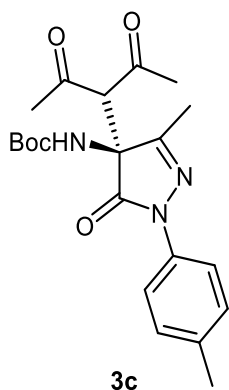
Product **3a** was obtained according to general procedure using pentane-2,4-dione (11  $\mu\text{L}$ , 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **3a** as a colorless solid (35 mg, 0.09 mmol, 90% yield). M.p. 140-141  $^\circ\text{C}$  (hexane-ethyl acetate).  $[\alpha]_{\text{D}}^{25} = +18.9$  ( $c = 0.9$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.87 (dd,  $J = 8.6, 1.2$  Hz, 2H, Har), 7.39 (dd,  $J = 8.6, 7.4$  Hz, 2H, Har), 7.19 (tt,  $J = 7.4, 1.3$  Hz, 1H, Har), 6.38 (br s, 1H, NH), 4.08 (s, 1H, CH), 2.31 (s, 3H, CH<sub>3</sub>CO), 2.30 (s, 3H, CH<sub>3</sub>CO), 2.08 (s, 3H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.4 (CO), 169.9 (CON), 137.7 (Car), 128.9 (CHar), 125.4 (CHar), 118.9 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 66.9 (CH), 66.7 (CNHBoc), 32.1 (CH<sub>3</sub>CO), 31.9 (CH<sub>3</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3403, 3356, 2974, 2931, 1707, 1596, 1496, 1375, 1254, 1154, 758, 688  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_5$  388.1867; Found 388.1868. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 11.5$  min, minor enantiomer (*R*)  $t_r = 26.1$  min. (er: **85:15**). A sample of **3a** (er: 85:15) was recrystallized from MeOH to afford **3a** as white crystals (quasi-racemic mixture, er 58:42) and almost enantiomerically pure **3a** from the mother liquors (er 95:5). This last fraction was then used to prepare compound **4a**.

- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3b**).**



Product **3b** was obtained according to general procedure using pentane-2,4-dione (11  $\mu$ L, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **3b** as a colorless solid (34 mg, 0.081 mmol, 81% yield). M.p. 166-167  $^{\circ}$ C (hexane-ethyl acetate).  $[\alpha]_D^{25} = +17.9$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.84 (d,  $J = 8.9$  Hz, 2H,  $\underline{\text{H}}_{\text{ar}}$ ), 7.34 (d,  $J = 8.9$  Hz, 2H,  $\underline{\text{H}}_{\text{ar}}$ ), 6.36 (br s, 1H,  $\underline{\text{N}}_{\text{H}}$ ), 4.05 (s, 1H,  $\underline{\text{C}}_{\text{H}}$ ), 2.30 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 2.29 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 2.07 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}$ ), 1.35 (s, 9H,  $\text{C}(\underline{\text{C}}_{\text{H}_3})_3$ ) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  200.4 ( $\underline{\text{C}}_{\text{O}}$ ), 169.9 ( $\underline{\text{C}}_{\text{ON}}$ ), 136.3 ( $\underline{\text{C}}_{\text{ar}}$ ), 130.5 ( $\underline{\text{C}}_{\text{ar}}$ ), 128.9 ( $\underline{\text{C}}_{\text{Har}}$ ), 120.0 ( $\underline{\text{C}}_{\text{Har}}$ ), 77.3 ( $\underline{\text{C}}(\underline{\text{C}}_{\text{H}_3})_3$ ), 66.9 ( $\underline{\text{C}}_{\text{H}}$ ), 66.6 ( $\underline{\text{C}}_{\text{NHBoc}}$ ), 32.1 ( $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 31.9 ( $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 28.1 ( $\text{C}(\underline{\text{C}}_{\text{H}_3})_3$ ), 14.7 ( $\underline{\text{C}}_{\text{H}_3}$ ) ppm. **IR (ATR)**: 3419, 2975, 2905, 1714, 1494, 1461, 1365, 1251, 1152, 836, 810  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{20}\text{H}_{25}\text{ClN}_3\text{O}_5$  422.1477; Found 422.1487. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 10.2$  min, minor enantiomer (*R*)  $t_r = 33.6$  min. (er: **87:13**). A sample of **3b** (er: 85:15) was recrystallized from hexane-ethyl acetate to afford **3b** as white crystals (quasi-racemic mixture, er 59:41) and almost enantiomerically pure **3a** from the mother liquors (er 96:4).

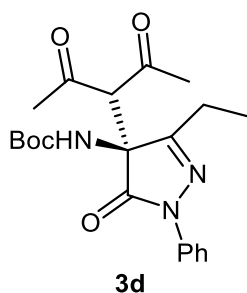
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3c**).**



Product **3c** was obtained according to general procedure using pentane-2,4-dione (11  $\mu$ L, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **3c** as a colorless solid (27 mg, 0.068 mmol, 68% yield). M.p. 150-151  $^{\circ}$ C (hexane-ethyl acetate).  $[\alpha]_D^{25} = +19.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.73 (d,  $J = 8.4$  Hz, 2H,  $\underline{\text{H}}_{\text{ar}}$ ), 7.18 (d,  $J = 8.4$  Hz, 2H,  $\underline{\text{H}}_{\text{ar}}$ ), 6.35 (br s, 1H,  $\underline{\text{N}}_{\text{H}}$ ), 4.07 (s, 1H,  $\underline{\text{C}}_{\text{H}}$ ), 2.33 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}\text{C}_6\text{H}_4$ ), 2.30 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 2.29 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}\text{CO}$ ), 2.07 (s, 3H,  $\underline{\text{C}}_{\text{H}_3}$ ), 1.35 (s,

9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 200.4 (C=O), 169.7 (CON), 135.3 (Car), 135.1 (Car), 129.4 (CHar), 119.0 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 67.0 (CH), 66.7 (CNHBoc), 32.1 (CH<sub>3</sub>CO), 31.9 (CH<sub>3</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 21.0 (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), 14.8 (CH<sub>3</sub>) ppm. IR (ATR): 3423, 2978, 2923, 1714, 1703, 1512, 1472, 1369, 1255, 1156, 1056, 814 cm<sup>-1</sup>. HRMS (ESI-QTOF) m/z: [M+H]<sup>+</sup> Calcd. For C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>5</sub> 402.2023; Found 402.2043. HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min, λ = 254 nm, mayor enantiomer (*S*) *tr* = 11.5 min, minor enantiomer (*R*) *tr* = 44.7 min. (er: **89:11**).

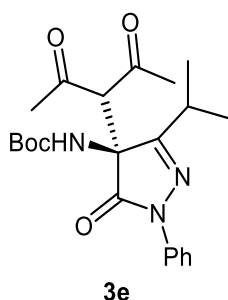
▪ ***tert*-Butyl (*S*)-(4-(2,4-dioxopentán-3-yl)-3-ethyl-5-oxo-1-fenil-4,5-dihidro-1H-pirazol-4-yl)carbamate (3d).**



Product **3d** was obtained according to general procedure using pentane-2,4-dione (11 μL, 0.11 mmol, 1.1 equiv) as β-diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **3d** as a colorless solid (27 mg, 0.067 mmol, 67% yield). [α]<sub>D</sub><sup>25</sup> = +10.7 (*c* = 0.5, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.89 (dd, *J* = 8.7, 1.2 Hz, 2H, Har), 7.38 (dd, *J* = 8.7, 7.4 Hz, 2H, Har), 7.18 (tt, *J* = 7.4, 1.2 Hz, 1H, Har), 6.40 (br s, 1H, NH), 4.05 (s, 1H, CH), 2.41 (m, 1H, CHHCH<sub>3</sub>), 2.34 (m, 1H, CHHCH<sub>3</sub>), 2.30 (s, 3H, CH<sub>3</sub>CO), 2.29 (s, 3H, CH<sub>3</sub>CO), 1.34 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (t, *J* = 7.3 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 200.7 (C=O), 170.1 (CON), 137.9 (Car), 128.8 (CHar), 125.3 (CHar), 118.9 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 67.1 (CH), 66.9 (CNHBoc), 32.1 (CH<sub>3</sub>CO), 31.9 (CH<sub>3</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 22.2 (CH<sub>2</sub>CH<sub>3</sub>), 9.6 (CH<sub>3</sub>CH<sub>2</sub>) ppm. IR (ATR): 3388, 2985, 2942, 1707, 1596, 1493, 1453, 1351, 1279, 1152, 1054, 761, 692 cm<sup>-1</sup>. HRMS (ESI-QTOF) m/z: [M+H]<sup>+</sup> Calcd. For C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>5</sub> 402.2023; Found 402.2029. HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min, λ = 254 nm, mayor enantiomer (*S*) *tr* = 10.0 min, minor enantiomer (*R*) *tr* = 20.0 min. (er: **84:16**).

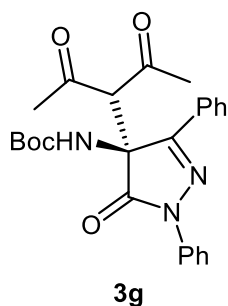


- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-isopropyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3e**).**



Product **3e** was obtained according to general procedure using pentane-2,4-dione (11  $\mu$ L, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 4:1 as eluent afforded compound **3e** as a colorless solid (30 mg, 0.071 mmol, 71% yield).  $[\alpha]_D^{25} = +42.5$  ( $c = 0.8$ , MeOH).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.89 (d,  $J = 8.1$  Hz, 2H, Har), 7.38 (dd,  $J = 8.7, 7.4$  Hz, 2H, Har), 7.17 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 6.49 (br s, 1H, NH), 4.04 (s, 1H, CH), 2.65 (sept,  $J = 6.9$  Hz, 1H, CH( $\text{CH}_3$ )<sub>2</sub>), 2.29 (s, 3H, CH<sub>3</sub>CO), 2.28 (s, 3H, CH<sub>3</sub>CO), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (d,  $J = 6.8$  Hz, 6H, (CH<sub>3</sub>)<sub>2</sub>CH) 1.24 (d,  $J = 7.0$  Hz, 6H, (CH<sub>3</sub>)<sub>2</sub>CH) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  201.1 (CO), 169.8 (CON), 138.0 (Car), 128.8 (CHar), 125.2 (CHar), 119.1 (CHar), 77.3 (C( $\text{CH}_3$ )<sub>3</sub>), 67.4 (CH( $\text{COCH}_3$ )<sub>2</sub>), 67.0 (CNHBoc), 32.1 (CH<sub>3</sub>CO), 31.7 (CH<sub>3</sub>CO), 28.8 (CH( $\text{CH}_3$ )<sub>2</sub>), 28.1 (C( $\text{CH}_3$ )<sub>3</sub>), 20.3 ((CH<sub>3</sub>)<sub>2</sub>CH) ppm. **IR (ATR)**: 3413, 2975, 2935, 1710, 1598, 1493, 1457, 1359, 1283, 1156, 1083, 1054, 754, 688  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. For  $\text{C}_{22}\text{H}_{29}\text{N}_3\text{NaO}_5$  438.1999; Found 438.1999. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 95:5, 0.7 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 18.6$  min, minor enantiomer (*R*)  $t_r = 27.0$  min. (er: **88:12**).

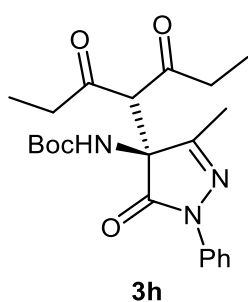
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3g**).**



Product **3g** was obtained according to general procedure using pentane-2,4-dione (11  $\mu$ L, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (3.2 mg, 0.005 mmol, 0.05 equiv). Chromatography on a silica gel using hexane/EtOAc = 4:1 as eluent afforded compound **3g** as a colorless solid (31 mg, 0.068 mmol, 68% yield).  $[\alpha]_D^{25} = +56.3$  ( $c = 0.6$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.98 (dd,  $J = 8.4, 1.2$  Hz, 2H, Har), 7.90 (dd,  $J = 7.8, 2.0$  Hz, 2H, Har), 7.43 (m, 5H, Har), 7.23 (tt,  $J = 7.4, 1.0$  Hz, 1H, Har), 6.82 (br s, 1H, NH), 3.97 (s, 1H, CH), 2.11 (s, 3H, CH<sub>3</sub>CO), 2.03 (s, 3H, CH<sub>3</sub>CO), 1.31 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.2 (CO), 200.5 (CO), 170.0 (CON), 137.9 (Car), 130.8 (CHar), 129.0 (CHar), 128.9

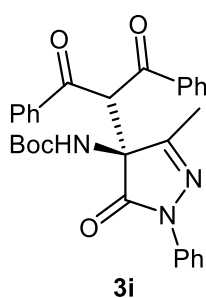
(CHar), 126.7 (CHar), 125.6 (CHar), 119.2 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 66.3 (CH), 66.2 (CNHBoc), 32.3 (CH<sub>3</sub>CO), 32.2 (CH<sub>3</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>) ppm. **IR (ATR):** 3379, 2982, 1714, 1597, 1490, 1358, 1255, 1156, 751, 689 cm<sup>-1</sup>. **HRMS (ESI-QTOF) m/z:** [M+Na]<sup>+</sup> Calcd. For C<sub>25</sub>H<sub>27</sub>N<sub>3</sub>NaO<sub>5</sub> 472.1843; Found 472.1842. **HPLC:** Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min, λ = 254 nm, mayor enantiomer (*S*) *tr* = 12.7 min, minor enantiomer (*R*) *tr* = 29.1 min. (er **94:6**).

- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3h**).**



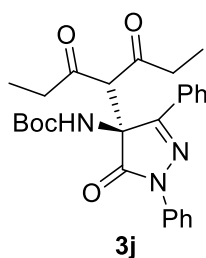
Product **3h** was obtained according to general procedure using heptane-3,5-dione (15 μL, 0.11 mmol, 1.1 equiv) as β-diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 4:1 as eluent afforded compound **3h** as a colorless solid (27 mg, 0.066 mmol, 66% yield). M.p. 119-120 °C (hexane-ethyl acetate). [α]<sub>D</sub><sup>25</sup> = +12.9 (*c* = 0.6, CHCl<sub>3</sub>). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>): δ 7.85 (dd, *J* = 8.7, 1.2 Hz, 2H, H<sub>ar</sub>), 7.37 (dd, *J* = 8.6, 7.4 Hz, 2H, H<sub>ar</sub>), 7.17 (tt, *J* = 7.4, 1.2 Hz, 1H, H<sub>ar</sub>), 6.55 (br s, 1H, NH), 4.03 (s, 1H, CH), 2.60 (m, 2H, CHHCH<sub>3</sub>), 2.54 (m, 2H, CHHCH<sub>3</sub>), 2.05 (s, 3H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.08 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>), 0.99 (t, *J* = 7.1 Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>): δ 202.7 (CO), 170.1 (CON), 137.8 (Car), 128.8 (CHar), 125.3 (CHar), 118.9 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 67.0 (CH), 65.1 (CNHBoc), 38.6 (CH<sub>2</sub>CO), 38.4 (CH<sub>2</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.8 (CH<sub>3</sub>), 7.4 (CH<sub>3</sub>CH<sub>2</sub>), 7.3 (CH<sub>3</sub>CH<sub>2</sub>) ppm. **IR (ATR):** 3339, 2978, 2942, 1714, 1597, 1497, 1369, 1270, 1152, 1104, 759, 689 cm<sup>-1</sup>. **HRMS (ESI-QTOF) m/z:** [M+H]<sup>+</sup> Calcd. For C<sub>22</sub>H<sub>30</sub>N<sub>3</sub>O<sub>5</sub> 416.2180; Found 416.2189. **HPLC:** Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min, λ = 254 nm, mayor enantiomer (*S*) *tr* = 9.2 min, minor enantiomer (*R*) *tr* = 23.8 min. (er **85:15**).

- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3i**).**



Product **3i** was obtained according to general procedure using 1,3-diphenylpropane-1,3-dione (25 mg, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 4:1 as eluent afforded compound **3i** as a colorless solid (38 mg, 0.075 mmol, 75% yield). M.p. 201-202 °C (hexane-ethyl acetate).  $[\alpha]_D^{25} = -68.6$  ( $c = 0.7$ , CHCl<sub>3</sub>). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.89 (dd,  $J = 11.9, 8.6$  Hz, 4H, Har), 7.51 (m, 4H, Har), 7.39 (m, 4H, Har), 7.22 (dd,  $J = 8.6, 7.2$  Hz, 2H, Har), 7.07 (td,  $J = 7.4, 1.3$  Hz, 1H, Har), 6.61 (br s, 1H, NH), 5.91 (s, 1H, CH), 2.22 (s, 3H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  191.1 (CO), 170.1 (CON), 137.5 (Car), 136.1 (Car), 135.2 (Car), 134.5 (CHar), 134.2 (CHar), 129.1 (CHar), 129.1 (CHar), 128.7 (CHar), 128.5 (CHar), 128.5 (CHar), 125.0 (CHar), 118.6 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 67.8 (CNHBoc), 56.6 (CH), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 15.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3276, 3147, 2986, 1729, 1700, 1593, 1490, 1446, 1365, 1270, 1214, 1152, 770, 751, 696, 682 cm<sup>-1</sup>. **HRMS** (ESI-QTOF)  $m/z$ : [M+H]<sup>+</sup> Calcd. For C<sub>30</sub>H<sub>30</sub>N<sub>3</sub>O<sub>5</sub> 512.2180; Found 512.2214. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 14.2$  min, minor enantiomer (*R*)  $t_r = 35.8$  min. (er: **88:12**).

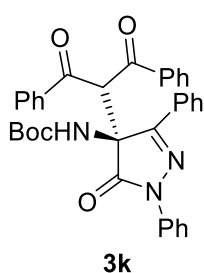
- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3j**).**



Product **3j** was obtained according to general procedure using heptane-3,5-dione (15  $\mu$ L, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (6.3 mg, 0.01 mmol, 0.1 equiv). Chromatography on a silica gel using hexane/EtOAc = 8:1 as eluent afforded compound **3j** as a colorless solid (29 mg, 0.06 mmol, 60% yield).  $[\alpha]_D^{25} = +48.4$  ( $c = 0.5$ , CHCl<sub>3</sub>). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.98 (dd,  $J = 8.6, 1.3$  Hz, 2H, Har), 7.88 (dd,  $J = 7.3, 2.5$  Hz, 2H, Har), 7.43 (m, 5H, Har), 7.23 (m, 1H, Har), 7.12 (br s, 1H, NH), 3.94 (s, 1H, CH), 2.59 (dq,  $J = 20.6, 7.1$  Hz, 1H, CHHCH<sub>3</sub>), 2.38 (dq,  $J = 19.0, 7.0$  Hz, 1H, CHHCH<sub>3</sub>), 2.19 (dq,  $J = 19.2, 7.1$  Hz, 1H, CHHCH<sub>3</sub>), 2.03 (dq,  $J = 19.4, 7.0$  Hz, 1H, CHHCH<sub>3</sub>), 1.33 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 0.90 (t,  $J = 7.1$  Hz, 3H, CH<sub>3</sub>), 0.79 (t,  $J = 7.0$  Hz, 3H,

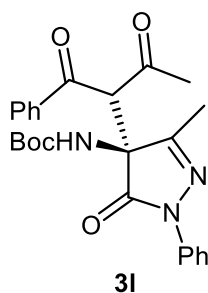
$\underline{\text{CH}_3}$ ) ppm.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  204.0 ( $\underline{\text{CO}}$ ), 202.7 ( $\underline{\text{CO}}$ ), 170.2 ( $\underline{\text{CON}}$ ), 137.9 ( $\underline{\text{Car}}$ ), 130.7 ( $\underline{\text{CHar}}$ ), 128.9 ( $\underline{\text{CHar}}$ ), 126.8 ( $\underline{\text{CHar}}$ ), 125.5 ( $\underline{\text{CHar}}$ ), 119.2 ( $\underline{\text{CHar}}$ ), 77.3 ( $\underline{\text{C(CH}_3)_3}$ ), 66.7 ( $\underline{\text{CNHBoc}}$ ), 39.0 (2  $\underline{\text{CH}_2}$ ), 28.1 ( $\underline{\text{C(CH}_3)_3}$ ), 7.2 ( $\underline{\text{CH}_3}$ ), 6.9 ( $\underline{\text{CH}_3}$ ) ppm. IR (ATR): 3369, 2979, 2939, 1731, 1698, 1599, 1489, 1397, 1283, 1158, 1114, 1015, 758, 736, 689  $\text{cm}^{-1}$ . HRMS (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{27}\text{H}_{32}\text{N}_3\text{O}_5$  478.2336; Found 478.2345. HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 8.9$  min, minor enantiomer (*R*)  $t_r = 22.3$  min. (er **93:7**).

- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3k**).**



Product **3k** was obtained according to general procedure using 1,3-diphenylpropane-1,3-dione (25 mg, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone and catalyst **I** (6.3 mg, 0.01mmol, 0.1equiv). Chromatography on a silica gel using hexane/EtOAc = 4:1 as an eluent afforded compound **3k** as a colorless solid (26 mg, 0.046 mmol, 46% yield).  $[\alpha]_{\text{D}}^{25} = +41.7$  ( $c = 0.34$ ,  $\text{CHCl}_3$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.88 (ddd,  $J = 8.6, 7.6, 1.3$  Hz, 4H,  $\underline{\text{Har}}$ ), 7.75 (d,  $J = 7.2$  Hz, 2H,  $\underline{\text{Har}}$ ), 7.58 (m, 1H,  $\underline{\text{Har}}$ ), 7.49 (dd,  $J = 8.5, 1.3$  Hz, 2H,  $\underline{\text{Har}}$ ), 7.40 (m, 5H,  $\underline{\text{Har}}$ ), 7.21 (m, 6H,  $\underline{\text{Har}}$ ), 5.80 (s, 1H,  $\underline{\text{CH}}$ ), 1.39 (s, 9H,  $\underline{\text{C(CH}_3)_3}$ ) ppm.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  190.4 ( $\underline{\text{CO}}$ ), 170.3 ( $\underline{\text{CON}}$ ), 137.9 ( $\underline{\text{Car}}$ ), 137.0 ( $\underline{\text{Car}}$ ), 136.6 ( $\underline{\text{Car}}$ ), 134.1 ( $\underline{\text{CHar}}$ ), 133.8 ( $\underline{\text{CHar}}$ ), 130.4 ( $\underline{\text{CHar}}$ ), 129.1 ( $\underline{\text{CHar}}$ ), 128.9 ( $\underline{\text{CHar}}$ ), 128.6 ( $\underline{\text{CHar}}$ ), 128.4 ( $\underline{\text{CHar}}$ ), 128.2 ( $\underline{\text{CHar}}$ ), 128.1 ( $\underline{\text{CHar}}$ ), 127.5 ( $\underline{\text{CHar}}$ ), 125.4 ( $\underline{\text{CHar}}$ ), 118.9 ( $\underline{\text{CHar}}$ ), 77.3 ( $\underline{\text{C(CH}_3)_3}$ ), 68.6 ( $\underline{\text{CNHBoc}}$ ), 51.9 ( $\underline{\text{CH}}$ ), 28.2 ( $\underline{\text{C(CH}_3)_3}$ ) ppm. IR (ATR): 3420, 3068, 2979, 2928, 1709, 1695, 1595, 1482, 1280, 1258, 1159, 971, 758, 685  $\text{cm}^{-1}$ . HRMS (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{35}\text{H}_{32}\text{N}_3\text{O}_5$  574.2336; Found 574.2342. HPLC: Chiralpak AD-H column, hexane/*i*-PrOH 80:20, 1 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 10.9$  min, minor enantiomer (*R*)  $t_r = 23.8$  min. (er **93:7**).

- ***tert*-Butyl ((*S*)-4-((*R*)-1,3-dioxo-1-phenylbutan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3l**).**



**3l**

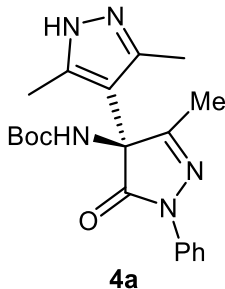
Product **3l** was obtained according to general procedure, using 1-phenylbutane-1,3-dione (18 mg, 0.11 mmol, 1.1 equiv) as  $\beta$ -diketone, and catalyst **I** (1.3 mg, 0.002 mmol, 0.02 equiv). Chromatography on a silica gel using hexane/EtOAc = 3:1 as an eluent afforded compound **3l** as an inseparable mixture (72:28) of diastereoisomers. Colorless solid (30 mg, 0.066 mmol, 66% yield). **<sup>1</sup>H NMR** (500

MHz, CDCl<sub>3</sub>):  $\delta$  7.90 (m, 3H, Har), 7.60 (m, 2H, Har), 7.45 (m, 3H, Har), 7.26 (m, 1H, Har), 7.19 (tt, J = 7.4, 1.2 Hz, 0.3H, Har), 7.10 (tt, J = 7.4, 1.2 Hz, 0.7H, Har), 6.72 (br s, 0.7H, NH), 6.29 (br s, 0.3H, NH), 4.99 (s, 0.7H, CH), 4.85 (s, 0.3H, CH), 2.28 (s, 2.1H, CH<sub>3</sub>CO), 2.25 (s, 0.9H, CH<sub>3</sub>CO), 2.09 (s, 2.1H, CH<sub>3</sub>), 2.05 (s, 0.9H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  201.0, 200.0 (COMe), 192.5 (COPh), 170.2, 169.7 (CON), 157.1 (CMe), 137.9, 137.5 (Car), 136.1, 135.6 (Car), 134.9, 134.7 (CHar), 129.3, 129.2 (CHar), 128.9, 128.8 (CHar), 128.6, 128.4 (CHar), 125.2, 125.1 (CHar), 118.9 (CHar), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 67.4, 66.6 (CNHBoc), 61.7 (CH), 31.4, 31.1 (CH<sub>3</sub>CO), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 15.2, 14.4 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3401, 2978, 2942, 1729, 1711, 1648, 1505, 1361, 1284, 1255, 1156, 755, 689 cm<sup>-1</sup>. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 85:15, 0.7 mL/min,  $\lambda$  = 254 nm, mayor diastereomer: mayor enantiomer (*S*)  $t_r$  = 13.6 min, minor enantiomer (*R*)  $t_r$  = 21.9 min. (er: **55:45**); minor diastereomer: mayor enantiomer (*S*)  $t_r$  = 11.4 min, minor enantiomer (*R*)  $t_r$  = 16.7 min (er: **57:43**).

#### General procedure for the synthesis of pyrazole derivatives 4a-j by reaction of adducts 3a-j with hydrazine hydrate.

To a solution of adduct **3** (0.1 mmol) in 1.0 mL of methanol, hydrated hydrazine (12  $\mu$ l, 0.2 mmol, 2 equiv) was added at 0 °C and the reaction mixture was then stirred at rt. The progress of the reaction was monitored by TLC analysis. After the completion of the reaction, the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography to afford the corresponding product **4**. The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

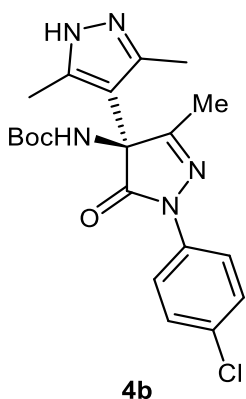
- ***tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4a**).**



**4a**

Product **4a** was obtained according to general procedure. Chromatography on a silica gel using EtOAc as eluent afforded compound **4a** as a colorless solid (31 mg, 0.081 mmol, 81% yield).  $[\alpha]_{\text{D}}^{25} = +96.5$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.93 (dd,  $J = 8.0, 0.8$  Hz, 2H, Har), 7.39 (t,  $J = 7.8$  Hz, 2H, Har), 7.18 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 5.92 (br s, 1H, NH), 2.28 (s, 6H, CH<sub>3</sub>), 2.11 (s, 3H, CH<sub>3</sub>), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.0 (CON), 160.5 (CO<sub>2</sub>tBu), 154.1 (CCH<sub>3</sub>), 142.3 (CMe), 138.0 (Car), 128.9 (CHar), 125.0 (CHar), 118.6 (CHar), 107.5 (C<sub>4</sub>pyrazole), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 65.6 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.2 (CH<sub>3</sub>), 12.9 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3247, 2978, 2934, 1711, 1692, 1593, 1501, 1365, 1251, 1156, 759, 693  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. For  $\text{C}_{20}\text{H}_{25}\text{N}_5\text{NaO}_3$  406.1850; Found 406.1860. **HPLC**: Lux Amylose-2 column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, minor enantiomer (*R*)  $t_r = 19.9$  min, mayor enantiomer (*S*)  $t_r = 29.1$  min. (er **94:6**).

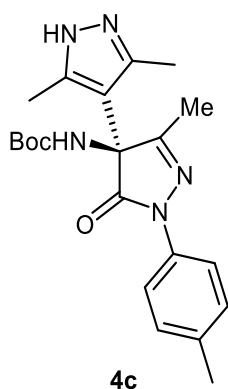
- ***tert*-Butyl (*S*)-(1'-(4-chlorophenyl)-3,3',5-trimethyl-5'-oxo-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4b**).**



**4b**

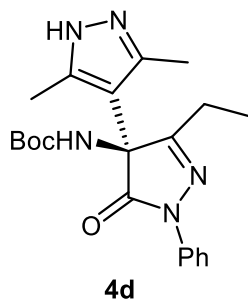
Product **4b** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 1:3 as eluent afforded compound **4b** as a colorless solid (25 mg, 0.060 mmol, 60% yield).  $[\alpha]_{\text{D}}^{25} = +42.7$  ( $c = 0.22$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (d,  $J = 8.9$  Hz, 2H, Har), 7.35 (d,  $J = 8.9$  Hz, 2H, Har), 5.84 (br s, 1H, NH), 2.27 (s, 6H, CH<sub>3</sub>), 2.10 (s, 3H, CH<sub>3</sub>), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.9 (CON), 160.7 (CO<sub>2</sub>tBu), 154.0 (CMe), 142.3 (CCH<sub>3</sub>pyrazole), 136.6 (Car), 130.1 (Car), 128.9 (CHar), 119.6 (CHar), 107.4 (C<sub>4</sub>pyrazole), 77.2 (C(CH<sub>3</sub>)<sub>3</sub>), 65.5 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.2 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3268, 2978, 2931, 1708, 1490, 1361, 1254, 1159, 1093, 1011, 910, 828, 727  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{20}\text{H}_{25}\text{ClN}_5\text{O}_3$  418.1640; Found 418.1633. **HPLC**: Lux *i*-Amylose-3 column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 23.7$  min, minor enantiomer (*R*)  $t_r = 45.6$  min. (er: **82:18**).

- ***tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-(*p*-tolyl)-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4c).**



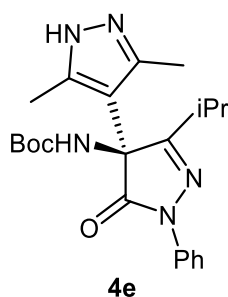
Product **4c** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 1:3 as an eluent afforded compound **4c** as a colorless solid (25 mg, 0.063 mmol, 63% yield).  $[\alpha]_D^{25} = +61.2$  ( $c = 0.3$ ,  $\text{CHCl}_3$ ).  **$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (d,  $J = 8.6$  Hz, 2H, Har), 7.19 (d,  $J = 8.6$  Hz, 2H, Har), 6.00 (br s, 1H, NH), 2.34 (s, 3H, CH<sub>3</sub>C<sub>6</sub>H<sub>6</sub>), 2.26 (s, 6H, CH<sub>3</sub>), 2.09 (s, 3H, CH<sub>3</sub>), 1.37 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  **$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.8 (CON), 160.5 (CO<sub>2</sub>tBu), 154.1 (CCH<sub>3</sub>), 142.3 (CCH<sub>3</sub>pyrazole), 135.6 (Car), 134.7 (Car), 129.4 (CHar), 118.6 (CHar), 107.6 (C<sub>4</sub>pyrazole), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 65.5 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 20.9 (CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>), 14.1 (CH<sub>3</sub>), 12.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3268, 2982, 2928, 1705, 1509, 1361, 1250, 1159, 815, 730  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{21}\text{H}_{28}\text{N}_5\text{O}_3$  398.2187; Found 398.2183. **HPLC**: Chiralpak IA, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, major enantiomer (*S*)  $t_r = 23.5$  min, minor enantiomer (*S*)  $t_r = 47.2$  min. (er: **88:12**).

- ***tert*-Butyl (*S*)-(3'-ethyl-3,5-dimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4d).**



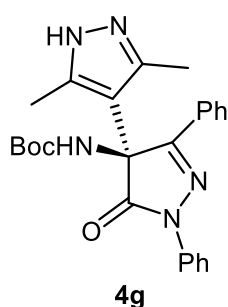
Product **4d** was obtained according to general procedure. Chromatography on a silica gel using EtOAc as eluent afforded compound **4d** as a colorless solid (27 mg, 0.068 mmol, 68% yield).  $[\alpha]_D^{25} = +62.8$  ( $c = 0.14$ ,  $\text{CHCl}_3$ ).  **$^1\text{H NMR}$**  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.97 (dd,  $J = 8.7, 1.2$  Hz, 2H, Har), 7.40 (dd,  $J = 8.7, 7.4$  Hz, 2H, Har), 7.18 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 5.71 (br s, 1H, NH), 2.50 (dq,  $J = 17.6, 7.4$  Hz, 1H, CHHCH<sub>3</sub>), 2.37 (m, 1H, CHHCH<sub>3</sub>), 2.28 (s, 6H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.30 (t,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>) ppm.  **$^{13}\text{C NMR}$**  (126 MHz,  $\text{CDCl}_3$ ): 172.1 (CON), 164.0 (CO<sub>2</sub>tBu), 154.0 (CEt), 142.3 (CCH<sub>3</sub>), 138.2 (Car), 128.8 (CHar), 124.9 (CHar), 118.5 (CHar), 108.0 (C<sub>4</sub> pyrazole), 77.2 (C(CH<sub>3</sub>)<sub>3</sub>), 65.6 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 21.5 (CH<sub>2</sub>CH<sub>3</sub>), 12.9 (CH<sub>3</sub>), 9.1 (CH<sub>3</sub>CH<sub>2</sub>) ppm. **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{21}\text{H}_{28}\text{N}_5\text{O}_3$  398.2187; Found 398.216. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, major enantiomer (*S*)  $t_r = 25.8$  min, minor enantiomer (*R*)  $t_r = 31.8$  min. (er: **85:15**).

▪ ***tert*-Butyl (*S*)-(3'-isopropyl-3,5-dimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4e**).**



Product **4e** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 2:1 as an eluent afforded compound **4e** as a colorless solid (32 mg, 0.078 mmol, 78% yield).  $[\alpha]_D^{25} = +139.8$  ( $c = 0.46$ ,  $\text{CHCl}_3$ ). **<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.99 (d,  $J = 7.1$  Hz, 2H, Har), 7.40 (dd,  $J = 8.5, 7.4$  Hz, 2H, Har), 7.18 (t,  $J = 7.4$  Hz, 1H, Har), 6.22 (br s, 1H, NH), 2.66 (sept,  $J = 6.8$  Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.23 (s, 6H, CH<sub>3</sub>), 1.36 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.32 (d,  $J = 7.0$  Hz, 3H, CH<sub>3</sub>CH), 1.07 (d,  $J = 6.8$  Hz, 3H, CH<sub>3</sub>CH) ppm. **<sup>13</sup>C NMR** (126 MHz,  $\text{CDCl}_3$ ): 172.3 (CON), 167.0 (CO<sub>2</sub>tBu), 154.4 (CIPr), 141.9 (CCH<sub>3</sub>), 138.1 (Car), 128.8 (CHar), 125.0 (CHar), 118.6 (CHar), 107.8 (C<sub>4</sub>pyrazole), 77.2 (C(CH<sub>3</sub>)<sub>3</sub>), 66.2 (CNHBoc), 28.2 (CH(CH<sub>3</sub>)<sub>2</sub>), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 21.1 (CH<sub>3</sub>CH), 20.8 (CH<sub>3</sub>CH), 12.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3290, 2975, 2931, 1708, 1597, 1494, 1367, 1159, 759, 737, 693  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. For  $\text{C}_{22}\text{H}_{29}\text{N}_5\text{NaO}_3$  434.2163; Found 434.2162. **HPLC**: Lux Amylose-2 column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, minor enantiomer (*R*)  $t_r = 17.5$  min, mayor enantiomer (*S*)  $t_r = 23.5$  min. (er: **90:10**).

▪ ***tert*-Butyl (*S*)-(3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4g**).**

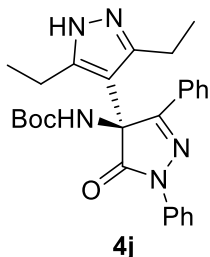


Product **4g** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 1:1 as eluent afforded compound **4g** as a colorless solid (36 mg, 0.082 mmol, 82% yield).  $[\alpha]_D^{25} = -190.0$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ). **<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.13 (br s, 1H, NH), 7.99 (dd,  $J = 8.7, 1.2$  Hz, 2H, Har), 7.85 (d,  $J = 7.1$  Hz, 2H, Har), 7.39 (m, 5H, Har), 7.19 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 2.30 (s, 6H, CH<sub>3</sub>), 1.19 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.5 (CON), 167.0 (CO<sub>2</sub>tBu), 153.7 (CPh), 143.1 (CCH<sub>3</sub>), 138.3 (Car), 138.2 (Car), 128.9 (CHar), 128.8 (CHar), 126.4 (CHar), 125.1 (CHar), 118.7 (CHar), 108.7 (C<sub>4</sub>pyrazole), 77.2 (C(CH<sub>3</sub>)<sub>3</sub>), 64.1 (CNHBoc), 27.9 (C(CH<sub>3</sub>)<sub>3</sub>), 12.8 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3237, 3123, 3060, 2978, 2931, 1730, 1708, 1594, 1500, 1367, 1159, 759, 737, 689  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{25}\text{H}_{28}\text{N}_5\text{O}_3$  446.2187; Found



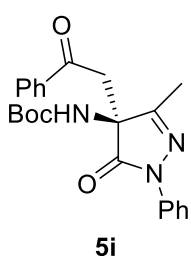
446.2205. **HPLC**: Lux *i*-Amylose-3 column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*) *tr* = 12.8 min, minor enantiomer (*R*) *tr* = 32.5 min. (er: **94:6**).

- ***tert*-Butyl (S)-(3,5-diethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4j).**



Product **4j** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 2:1 as eluent afforded compound **4j** as a colorless solid (19 mg, 0.040 mmol, 40% yield).  $[\alpha]_D^{25} = -134.3$  ( $c = 0.2$ , CHCl<sub>3</sub>). **<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.97 (dd,  $J = 8.6, 1.2$  Hz, 2H, Har), 7.82 (d,  $J = 7.6$  Hz, 2H, Har), 7.42 (m, 5H, Har), 7.21 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 2.98 (m, 2H, CHHCH<sub>3</sub>), 2.86 (dq,  $J = 15.5, 7.6$  Hz, CHHCH<sub>3</sub>), 1.24 (t,  $J = 7.5$ , 6H), 1.20 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  166.1 (CON), 148.5 (CPh), 144.0 (CEt), 133.4 (Car), 124.3 (CHar), 124.2 (CHar), 121.7 (CHar), 120.6 (CHar), 114.1 (CHar), 104.4 (C<sub>4pyrazole</sub>), 72.3 (C(CH<sub>3</sub>)<sub>3</sub>), 23.2 (C(CH<sub>3</sub>)<sub>3</sub>), 15.1 (CH<sub>3</sub>CH<sub>2</sub>), 8.7 (CH<sub>3</sub>CH<sub>2</sub>), 7.3 (CH<sub>3</sub>CH<sub>2</sub>) ppm. **IR (ATR)**: 3250, 2975, 2928, 1701, 1594, 1490, 1368, 1159, 756, 693 cm<sup>-1</sup>. **HRMS** (ESI-QTOF) *m/z*: [M+H]<sup>+</sup> Calcd. For C<sub>27</sub>H<sub>32</sub>N<sub>5</sub>O<sub>3</sub> 474.2500; Found 474.2486. **HPLC**: Chiralpak IA, hexane/*i*-PrOH 95:5, 1 mL/min,  $\lambda = 254$  nm, minor enantiomer (*R*) *tr* = 20.158 min, major enantiomer (*S*) *tr* = 25.042 min. (er: **95:5**).

- ***tert*-Butyl (S)-(3-methyl-5-oxo-4-(2-oxo-2-phenylethyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (5i).**<sup>12</sup>



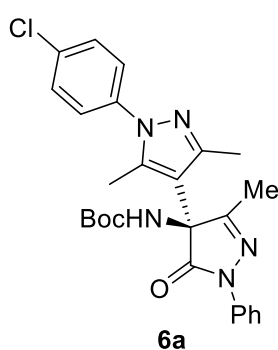
Product **5i** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **5i** as a colorless solid (21 mg, 0.052 mmol, 52% yield).  $[\alpha]_D^{25} = -17.5$  ( $c = 0.3$ , CH<sub>2</sub>Cl<sub>2</sub>). [Lit.<sup>12</sup>  $[\alpha]_D^{20} = -20.2$  ( $c = 1$ , CH<sub>2</sub>Cl<sub>2</sub>, er 94:6 for (*S*) enantiomer)]. **<sup>1</sup>H NMR** (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  7.90 (br s, 1H, Har), 7.83 (m, 2H, Har), 7.74 (d,  $J = 7.8$  Hz, 2H, Har), 7.62 (tt,  $J = 7.4, 1.3$  Hz, 1H, Har), 7.49 (t,  $J = 7.8$  Hz, 2H, Har), 7.38 (dd,  $J = 8.7, 7.4$  Hz, 2H, Har), 7.14 (tt,  $J = 7.4, 1.3$  Hz, 1H, Har), 3.74 (d,  $J = 17.2$  Hz, 1H, CHHCOPh), 3.62 (d,  $J = 17.2$  Hz, 1H, CHHCOPh), 1.99 (s, 3H, CH<sub>3</sub>), 1.31 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (100 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  195 (CO), 172.3 (CON), 158.8 (CO<sub>2</sub>tBu), 153.8 (CCH<sub>3</sub>), 138.7 (Car), 136.2 (Car), 134.2 (CHar), 129.3 (CHar), 129.2 (CHar), 128.4 (CHar), 124.7 (CHar), 118.1 (CHar), 80.0 (C(CH<sub>3</sub>)<sub>3</sub>), 63.6 (CNHBoc), 42.6 (CH<sub>2</sub>), 28.4 (C(CH<sub>3</sub>)<sub>3</sub>),

13.5 ( $\underline{\text{C}}\text{H}_3$ ) ppm. **IR (ATR):** 2856, 1714, 1594, 1500, 1364, 1251, 1159, 753, 693  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. For  $\text{C}_{35}\text{H}_{25}\text{N}_3\text{NaO}_4$  430.1737; Found 430.1759. **HPLC:** Chiralpak IA column, hexane/*i*-PrOH 80:20, 1 mL/min,  $\lambda = 254$  nm, minor enantiomer (*R*)  $t_r = 6.9$  min, major enantiomer (*S*)  $t_r = 32.4$  min. (er **77:23**).

### General procedure for the synthesis of pyrazole derivatives 6.

A solution of **3** (0.1 mmol), 4-chlorophenylhydrazine hydrochloride (19 mg, 0.11 mmol, 1.1 equiv) and  $\text{K}_2\text{CO}_3$  (8 mg, 0.055 mmol, 0.55 equiv) in ethanol (1 mL) was heated to 80 °C for 2-3 h. After that, the solvent of reaction mixture was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford product **6**.

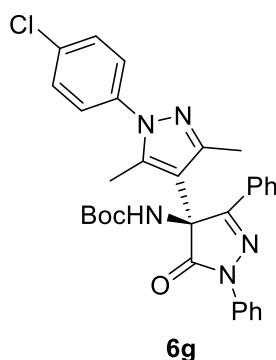
- ***tert*-Butyl (S)-(1-(4-chlorophenyl)-3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (6a).**



Product **6a** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 4:1 as an eluent afforded compound **6a** as a colorless solid (37 mg, 0.075 mmol, 75% yield). M.p. 166-167 °C (hexane-ethyl acetate). M.p. 196-197 °C.  $[\alpha]_{\text{D}}^{25} = +59.9$  ( $c = 0.7$ ,  $\text{CHCl}_3$ ).  **$^1\text{H}$  NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.94 (dd,  $J = 8.7, 1.2$  Hz, 2H, Har), 7.40 (m, 4H, Har), 7.28 (d,  $J = 8.5$  Hz, 2H, Har), 7.18 (tt,  $J = 7.4, 1.2$

Hz, 1H, Har), 5.41 (br s, 1H, NH), 2.40 (s, 3H, CH<sub>3</sub>), 2.33 (s, 3H, CH<sub>3</sub>), 2.19 (s, 3H, CH<sub>3</sub>), 1.39 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm.  **$^{13}\text{C}$  NMR** (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.5 (CON), 159.8 (CO<sub>2</sub>tBu), 153.7 (CCH<sub>3</sub>), 146.6 (CCH<sub>3</sub>), 138.0 (Car), 137.1 (Car), 134.4 (Car), 129.4 (CHar), 128.9 (CHar), 127.1 (CHar), 125.1 (CHar), 118.6 (CHar), 110.0 (C<sub>4</sub>pyrazole), 79.7 (C(CH<sub>3</sub>)<sub>3</sub>), 65.4 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>), 12.3 (CH<sub>3</sub>) ppm. **IR (ATR):** 3269, 2982, 2928, 1711, 1598, 1500, 1393, 1364, 1295, 1254, 1163, 1093, 1014, 838, 759, 690, 645  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{H}]^+$  Calcd. For  $\text{C}_{26}\text{H}_{29}\text{ClN}_5\text{O}_3$  494.1953; Found 494.1931. **HPLC:** Chiralpak AD-H column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, major enantiomer (*S*)  $t_r = 45.0$  min, minor enantiomer (*R*)  $t_r = 74.2$  min. (er **84:16**).

- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**6g**).**

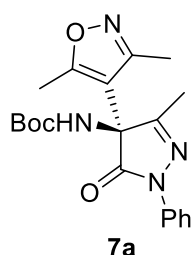


Product **6g** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 4:1 as eluent afforded compound **6g** as a colorless solid (22 mg, 0.040 mmol, 40% yield).  $[\alpha]_D^{25} = -155.0$  ( $c = 0.4$ ,  $\text{CHCl}_3$ ). **<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (dd,  $J = 8.8, 1.1$  Hz, 2H, Har), 7.91 (d,  $J = 6.5$  Hz, 2H, Har), 7.44 (m, 5H, Har), 7.42 (d,  $J = 8.7$  Hz, 2H, Har), 7.29 (d,  $J = 8.7$  Hz, 2H, Har), 7.20 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 5.54 (br s, 1H, NH), 2.41 (s, 3H, CH<sub>3</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 1.22 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. **<sup>13</sup>C NMR** (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7 (CON), 153.6 (CCH<sub>3</sub>), 146.9 (CPh), 138.4 (Car), 137.5 (Car), 134.1 (Car), 130.7 (CCH<sub>3</sub>), 130.3 (Car), 129.3 (CHar), 128.9 (CHar), 126.9 (CHar), 126.5 (CHar), 125.1 (CHar), 118.9 (CHar), 110.5 (C<sub>4</sub>pyrazole), 79.7 (C(CH<sub>3</sub>)<sub>3</sub>), 64.4 (CNH<sub>3</sub>Boc), 27.9 (C(CH<sub>3</sub>)<sub>3</sub>), 14.2 (CH<sub>3</sub>), 12.6 (CH<sub>3</sub>) ppm. **IR (ATR)**: 3245, 2975, 2854, 1727, 1701, 1596, 1500, 1362, 1260, 1158, 1092, 1016, 829, 756, 735, 691  $\text{cm}^{-1}$ . **HRMS** (ESI-QTOF)  $m/z$ :  $[\text{M}+\text{Na}]^+$  Calcd. For  $\text{C}_{31}\text{H}_{30}\text{N}_5\text{ClNaO}_3$  578.1929; Found 578.1943. **HPLC**: Chiralpak AD-H column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, mayor enantiomer (*S*)  $t_r = 10.1$  min, minor enantiomer (*R*)  $t_r = 63.7$  min. (er **96:4**).

#### General Procedure for the synthesis of isoxazole derivatives 7.

A solution of **3a** (0.1 mmol), hydroxylamine hydrochloride (8 mg, 0.11 mmol, 1.1 equiv) and  $\text{K}_2\text{CO}_3$  (8 mg, 0.055 mmol, 0.55 equiv) in ethanol (1 mL) was heated to 80 °C for 2-3 h. After that, the solvent of reaction mixture was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford product **7**.

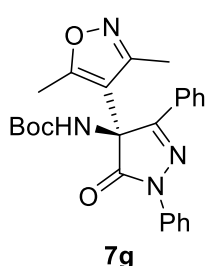
- ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**7a**).**



Product **7a** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 3:1 as an eluent afforded compound **7a** as a colorless solid (17 mg, 0.044 mmol, 44% yield).  $[\alpha]_D^{25} = +45.2$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ). **<sup>1</sup>H NMR** (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.91 (dd,  $J = 8.8, 1.1$  Hz, 2H, Har), 7.41 (dd,  $J = 8.7, 7.4$  Hz, 2H, Har),

7.20 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 5.35 (br s, 1H, NH), 2.47 (s, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 2.15 (s, 3H, CH<sub>3</sub>), 1.38 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  170.6 (CON), 167.3 (CCH<sub>3</sub>), 157.8 (CO<sub>2</sub>tBu), 153.8 (CCH<sub>3</sub>), 137.8 (Car), 129.0 (CHar), 125.33 (CHar), 118.5 (CHar), 107.2 (C<sub>4</sub>isoxazole), 77.3 (C(CH<sub>3</sub>)<sub>3</sub>), 63.9 (CNHBoc), 28.1 (C(CH<sub>3</sub>)<sub>3</sub>), 14.3 (CH<sub>3</sub>), 12.9 (CH<sub>3</sub>), 11.8 (CH<sub>3</sub>) ppm. **IR (ATR):** 3270, 2982, 2931, 2249, 1705, 1596, 1497, 1362, 1253, 1158, 1063, 1023, 906, 756, 727, 691, 643 cm<sup>-1</sup>. **HRMS** (ESI-QTOF)  $m/z$ : [M+Na]<sup>+</sup> Calcd. For C<sub>20</sub>H<sub>24</sub>N<sub>4</sub>NaO<sub>4</sub> 407.1690; Found 407.1693. **HPLC:** Chiralpak AD-H column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, major enantiomer (*S*)  $t_r = 10.6$  min, minor enantiomer (*R*)  $t_r = 19.5$  min. (er **83:17**).

- ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (7g).**



Product **7g** was obtained according to general procedure. Chromatography on a silica gel using hexane/EtOAc = 3:1 as eluent afforded compound **7g** as a colorless solid (36 mg, 0.080 mmol, 80% yield).  $[\alpha]_D^{25} = -151.4$  ( $c = 0.5$ , CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.98 (dd,  $J = 8.7, 1.3$  Hz, 2H, Har), 7.83 (m, 2H, Har), 7.43 (m, 4H, Har), 7.34 (br s, 2H, Har and NH), 7.22 (tt,  $J = 7.4, 1.2$  Hz, 1H, Har), 2.38 (s, 6H, CH<sub>3</sub>), 1.20 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>) ppm. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  170.7 (CON), 167.8 (CCH<sub>3</sub>), 158.2 (CO<sub>2</sub>tBu), 153.8 (CPh), 138.1 (Car), 131.0 (CHar), 129.0 (CHar), 128.9 (CHar), 126.2 (CHar), 125.4 (CHar), 118.7 (CHar), 107.7 (C<sub>4</sub>isoxazole), 77.2 (C(CH<sub>3</sub>)<sub>3</sub>), 62.7 (CNHBoc), 27.9 (C(CH<sub>3</sub>)<sub>3</sub>), 13.0 (CH<sub>3</sub>), 11.9 (CH<sub>3</sub>) ppm. **IR (ATR):** 3245, 3128, 2978, 2927, 1731, 1705, 1599, 1490, 1380, 1366, 1256, 1150, 1052, 1026, 906, 756, 735, 687 cm<sup>-1</sup>. **HRMS** (ESI-QTOF)  $m/z$ : [M+Na]<sup>+</sup> Calcd. For C<sub>25</sub>H<sub>26</sub>N<sub>4</sub>NaO<sub>4</sub> 469.1846; Found 469.1858. **HPLC:** Chiralpak AD-H column, hexane/*i*-PrOH 90:10, 1 mL/min,  $\lambda = 254$  nm, minor enantiomer (*R*)  $t_r = 10.1$  min, major enantiomer (*S*)  $t_r = 14.6$  min. (er **93:7**).

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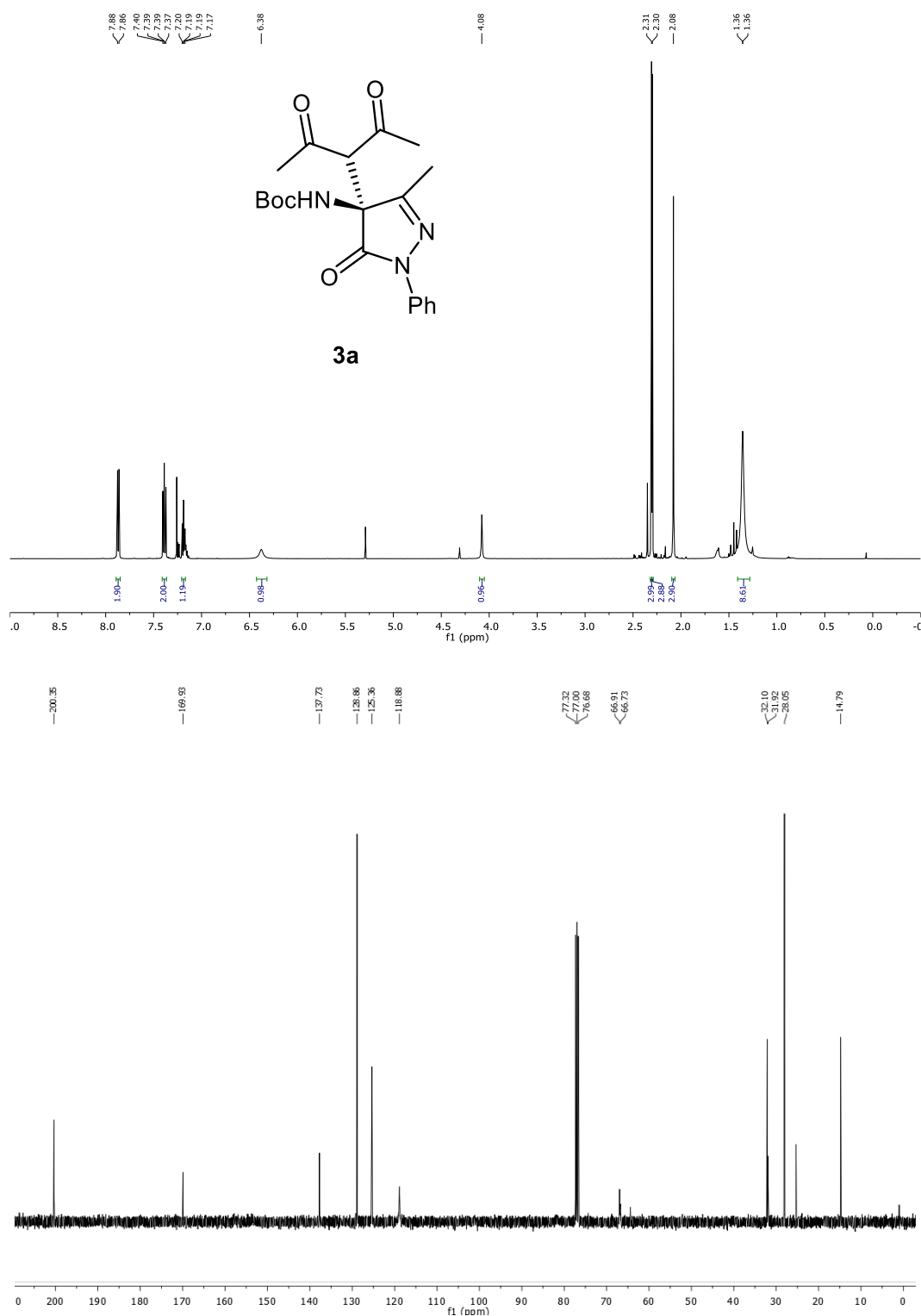
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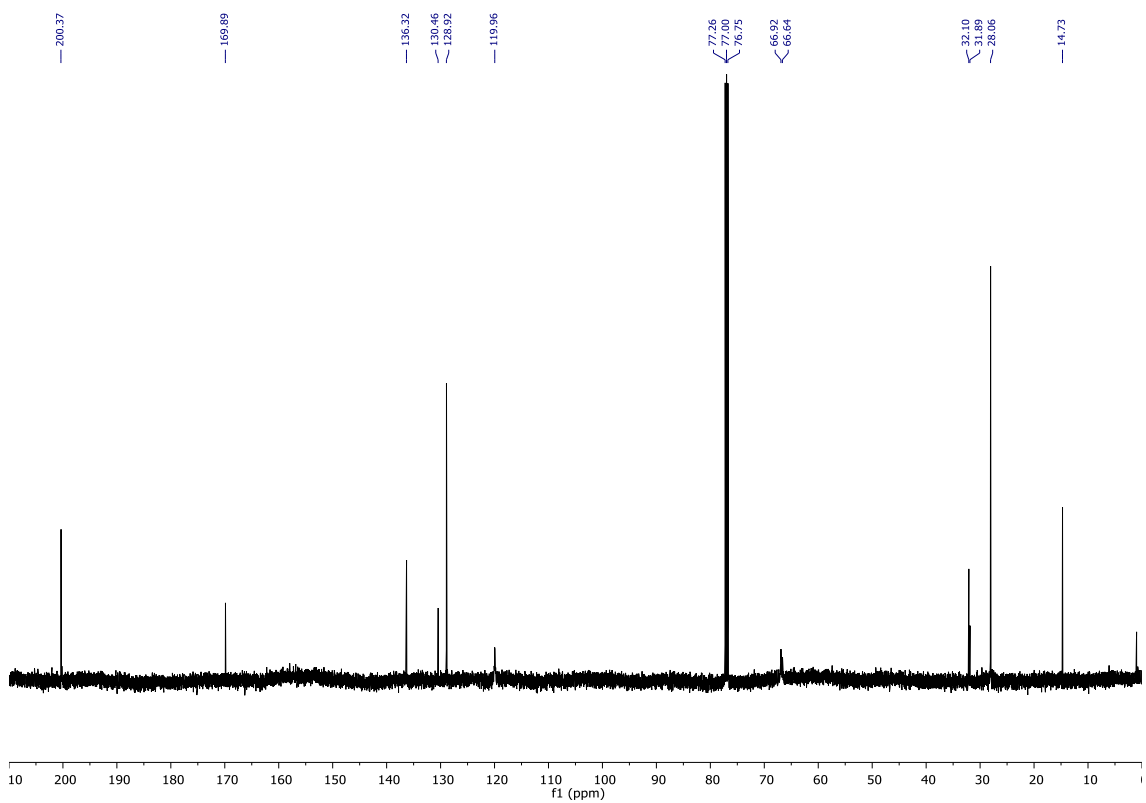
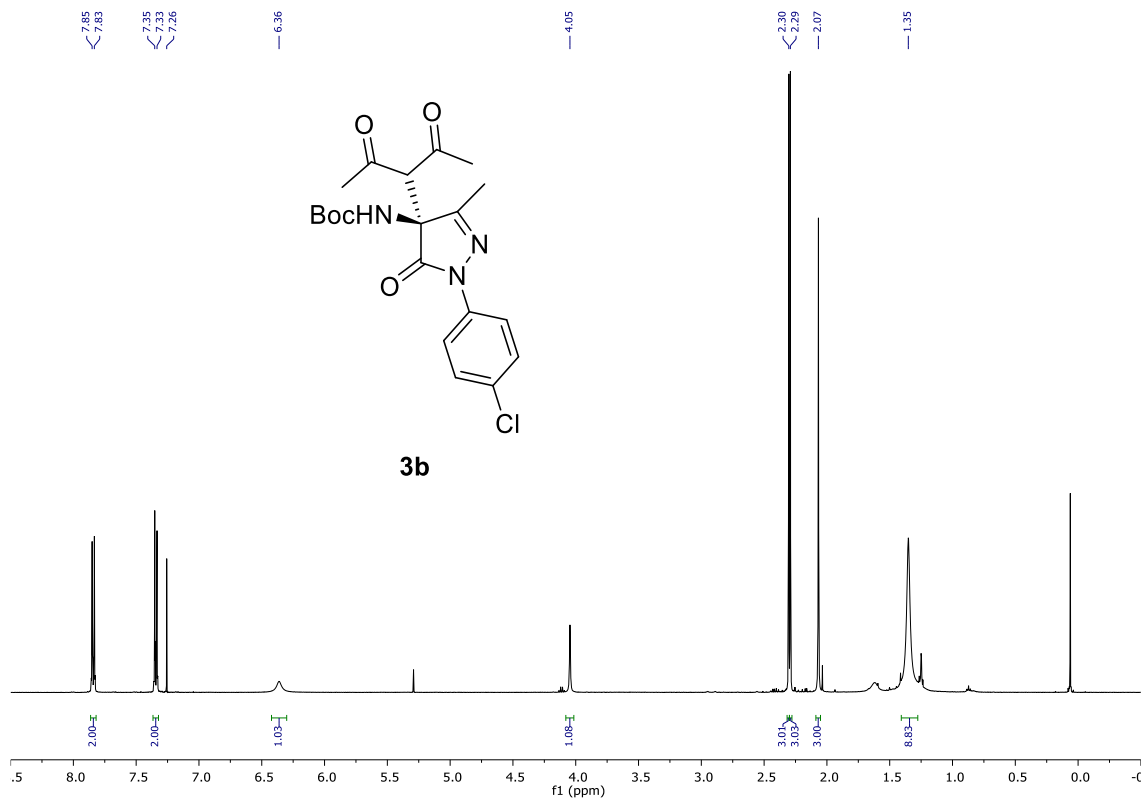
## SUPPORTING INFORMATION

### 7.1. NMR Spectra for New Compounds

- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3a).**

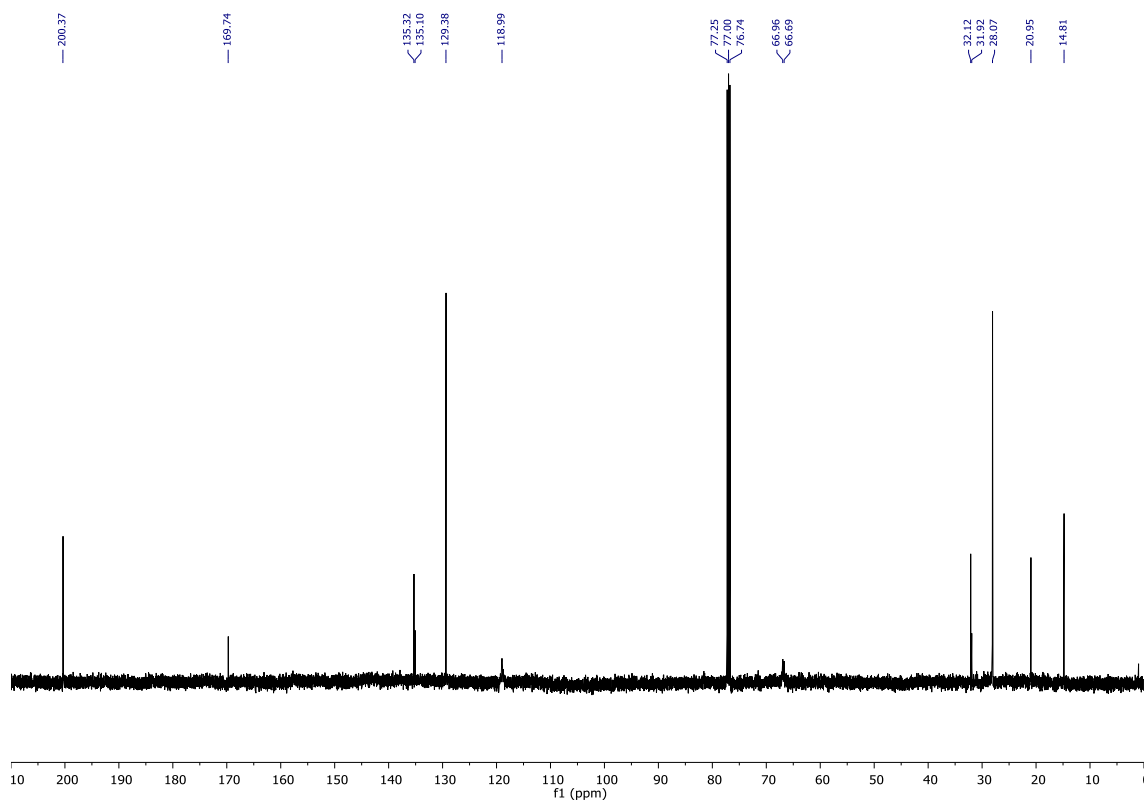
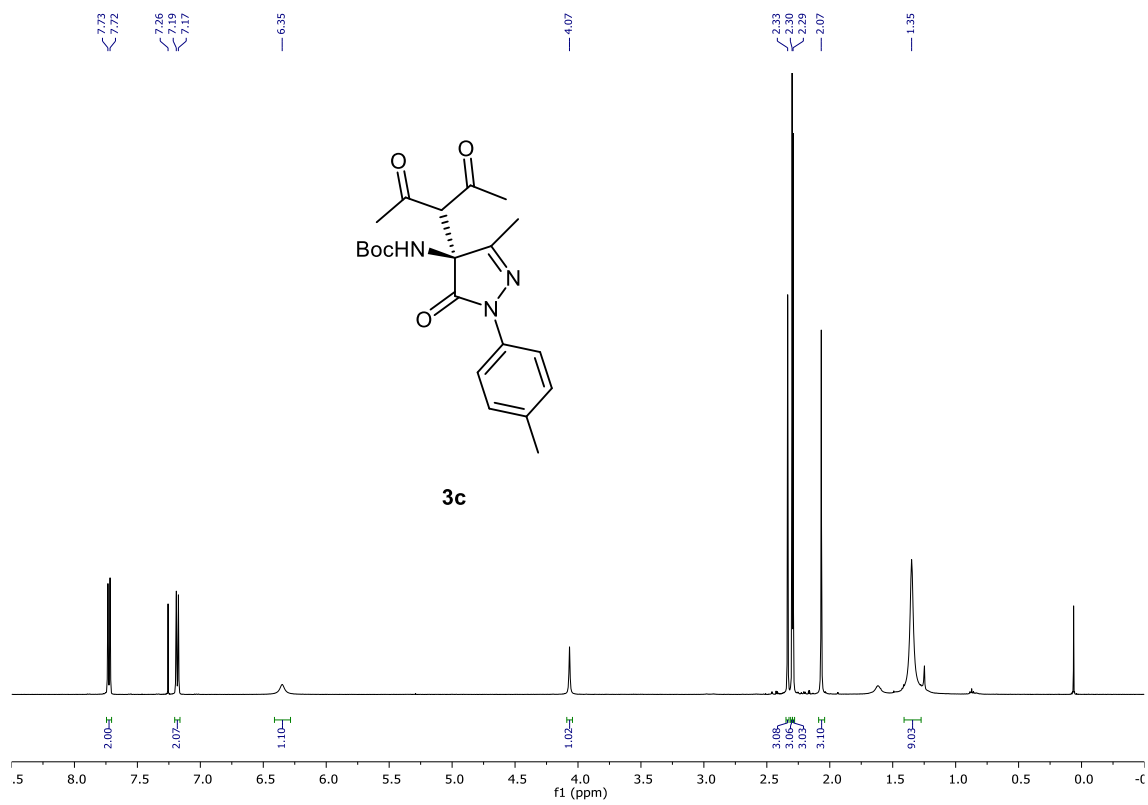


- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3b).**

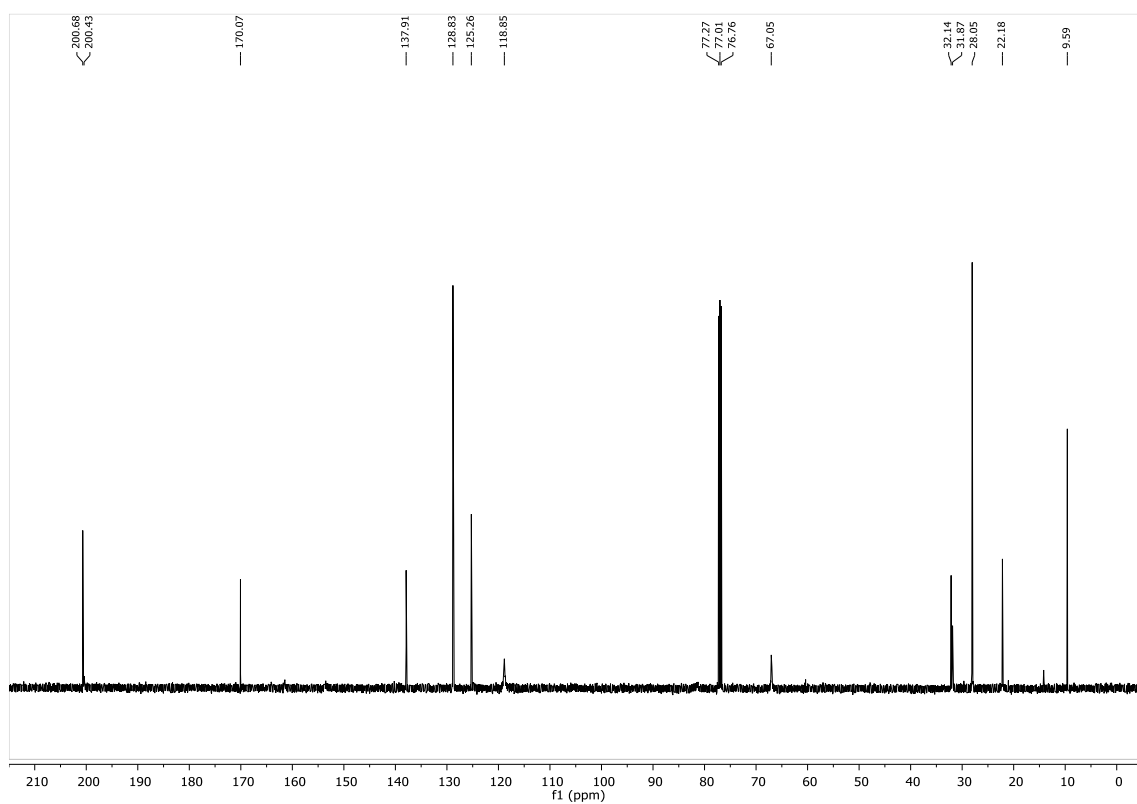
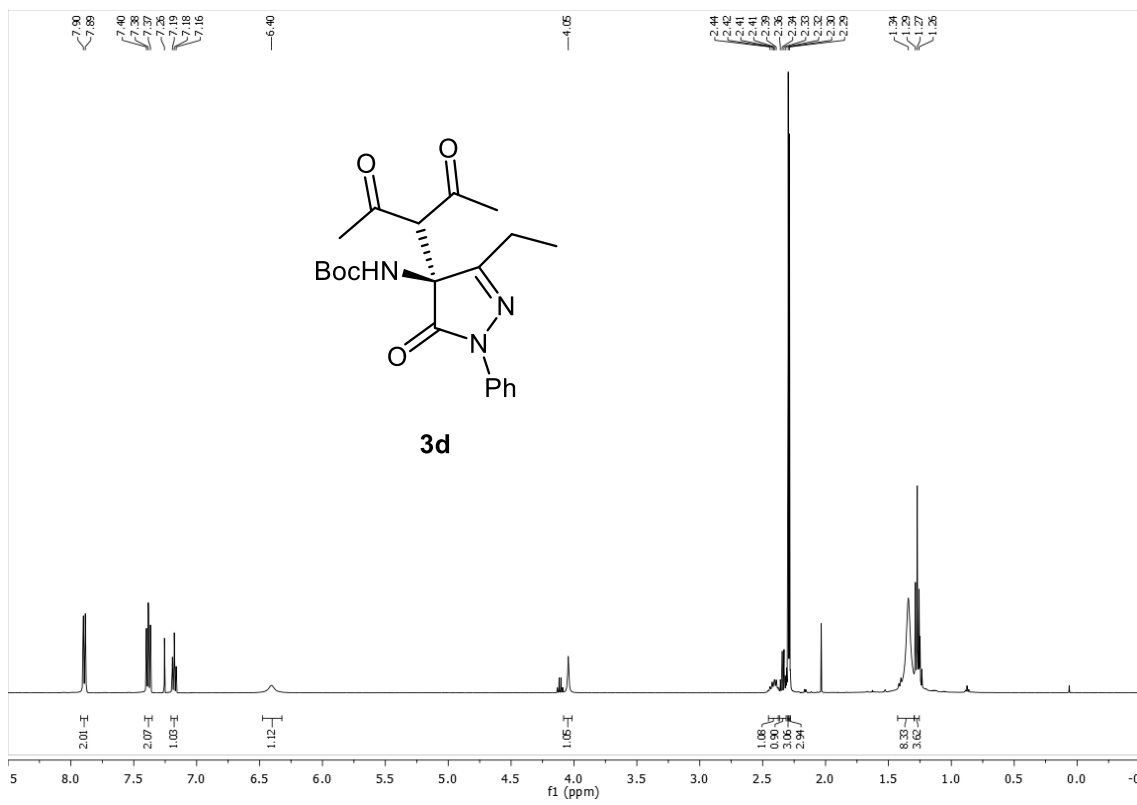




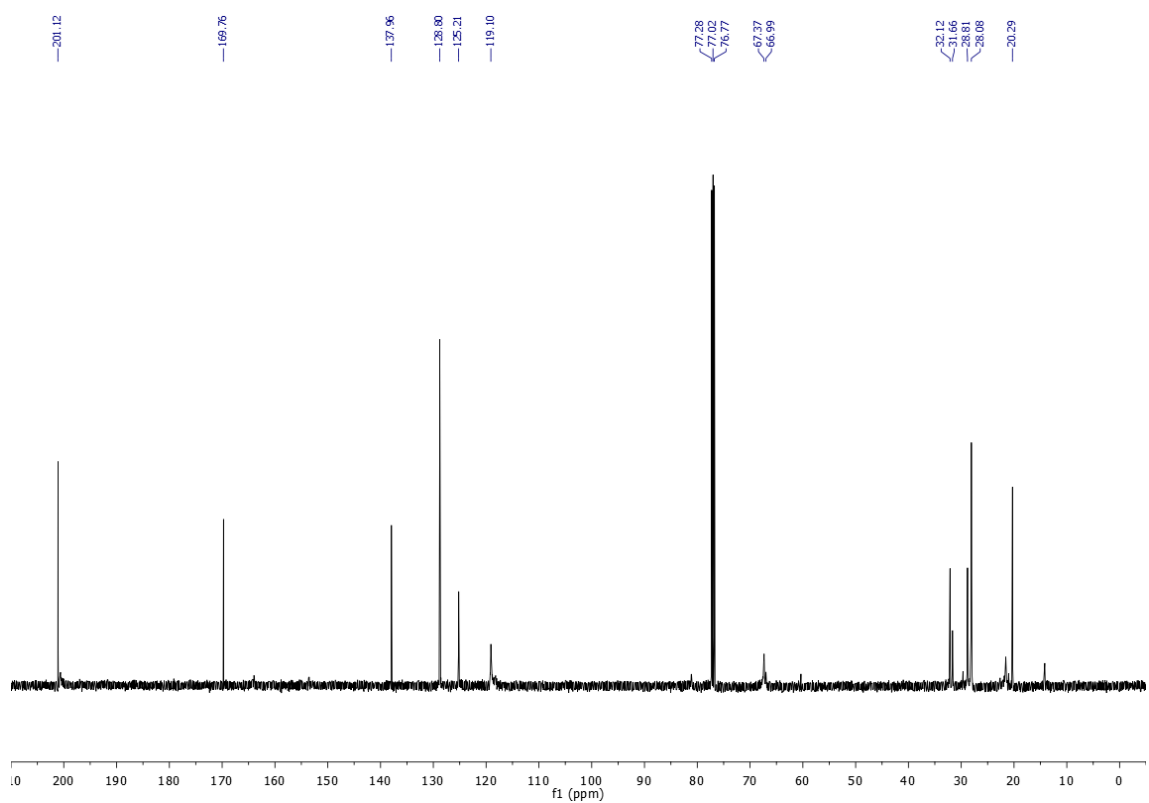
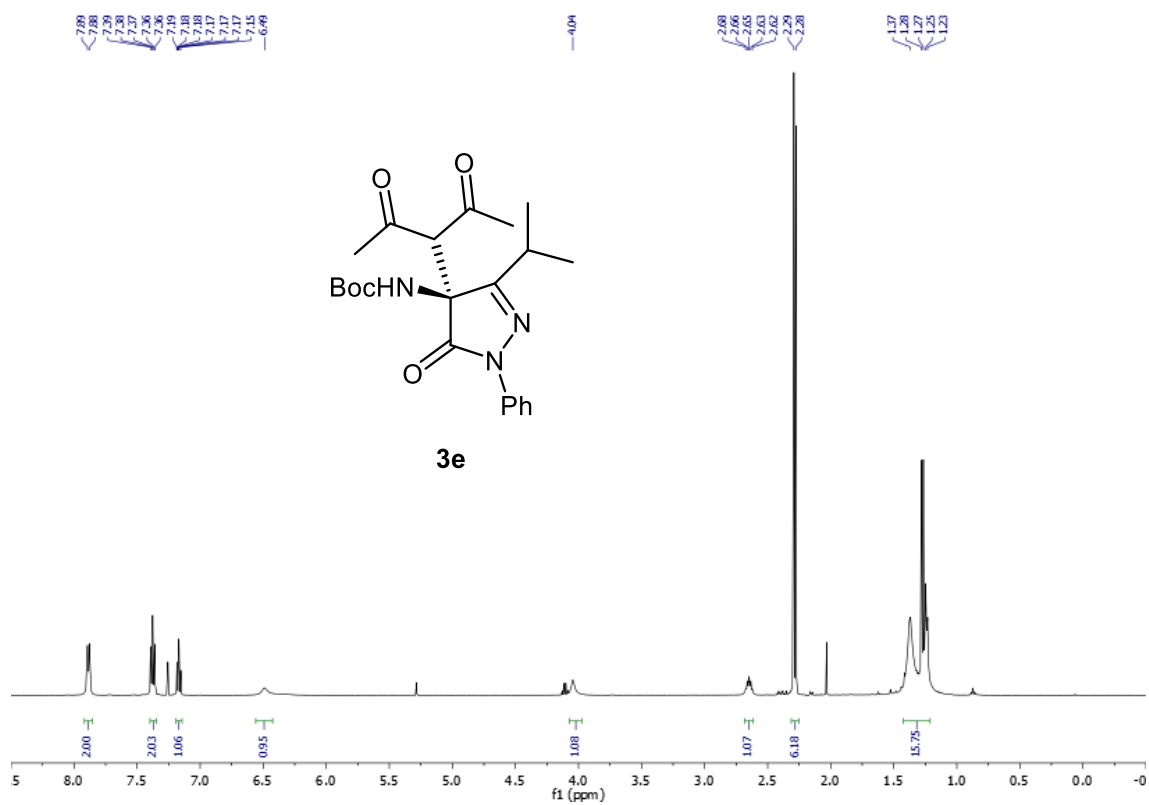
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3c**).**



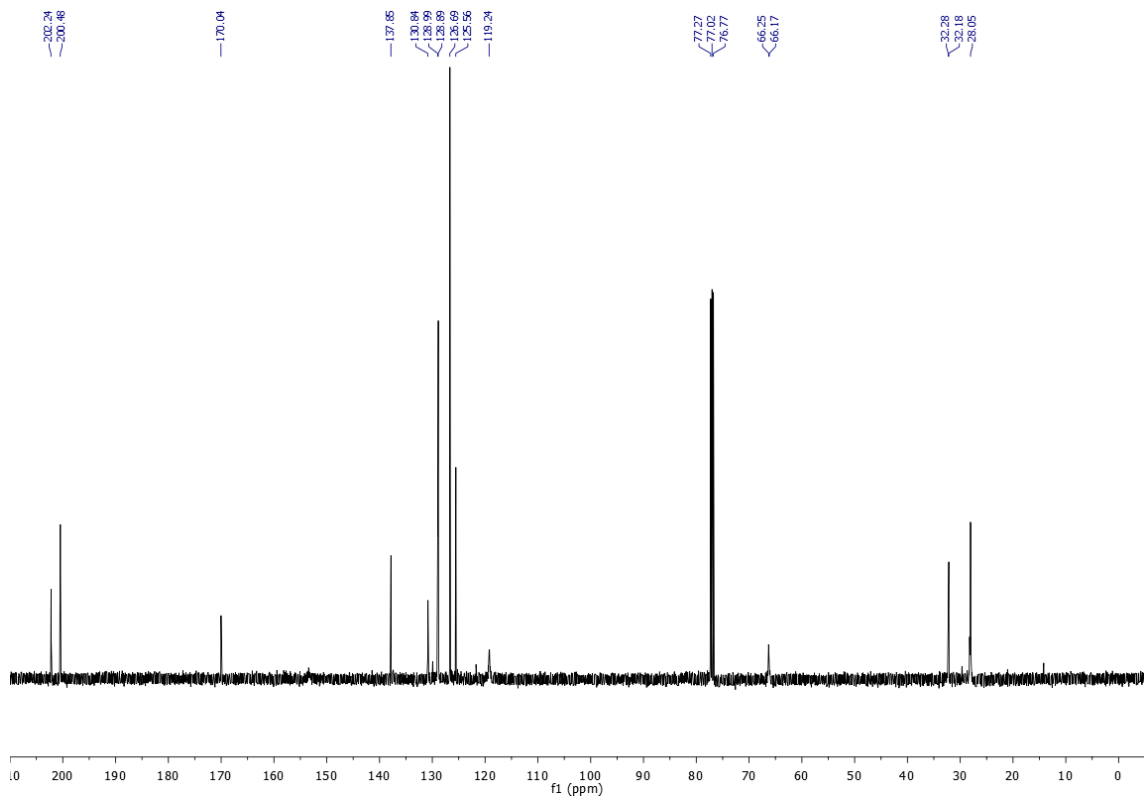
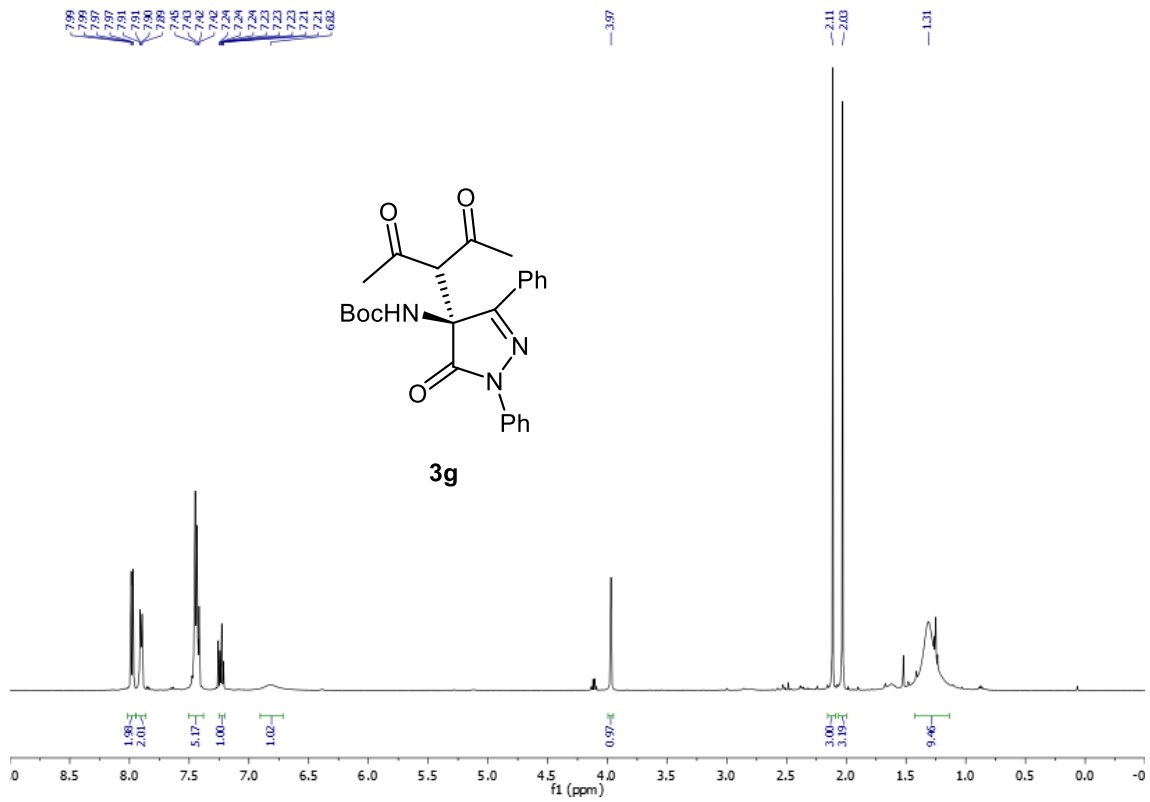
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-ethyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3d).**



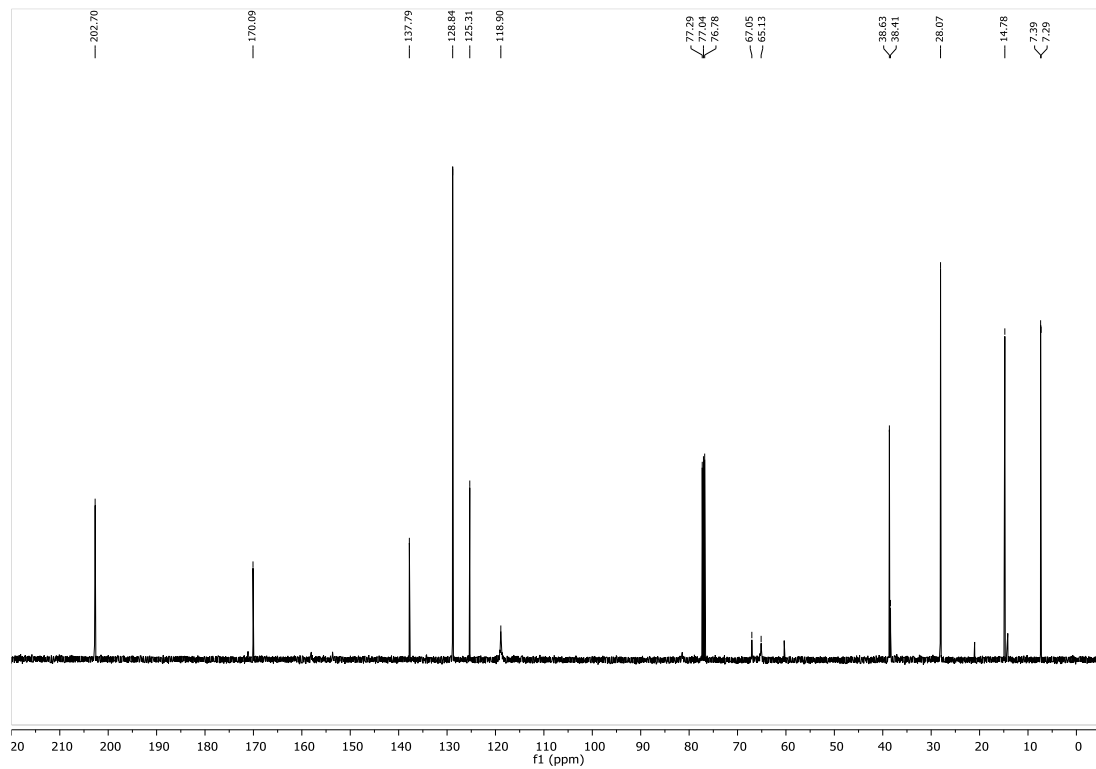
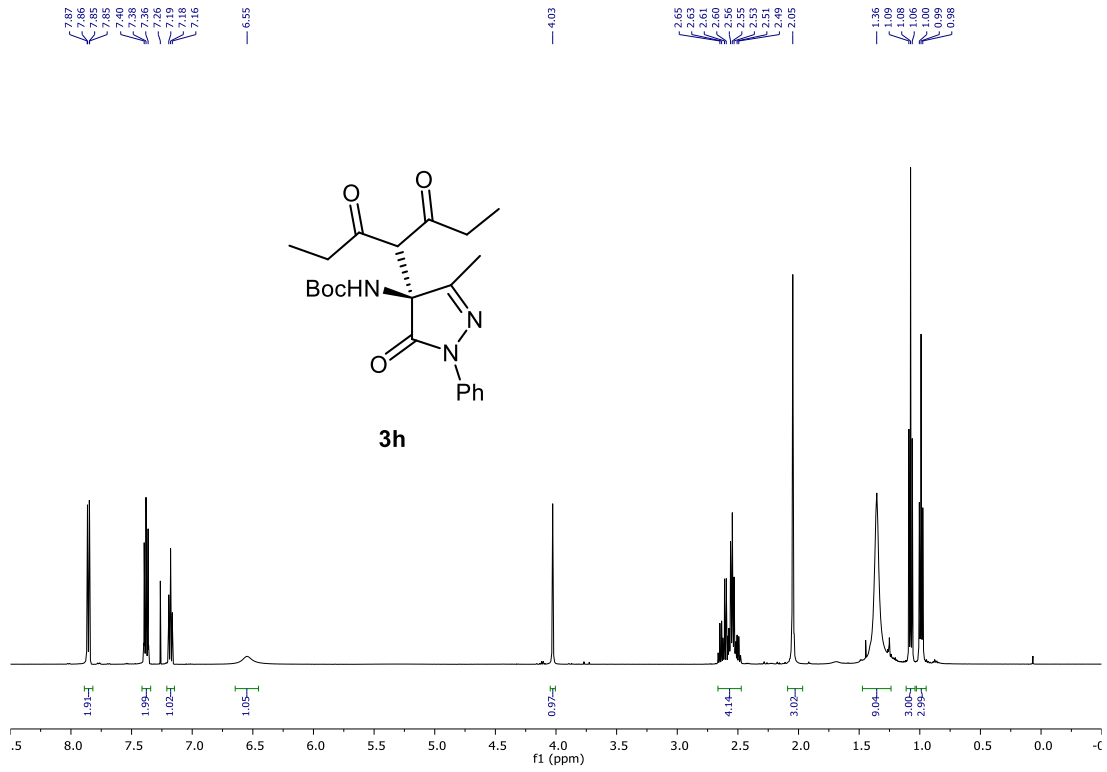
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-isopropyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3e**).**



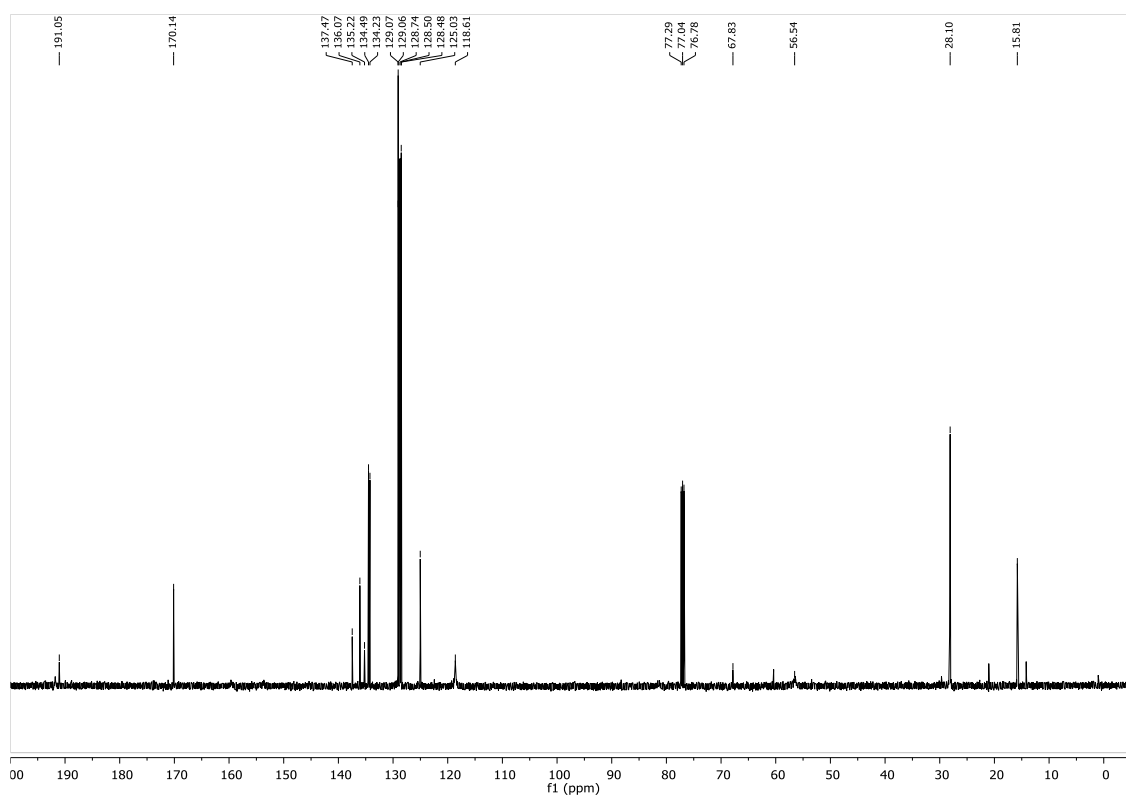
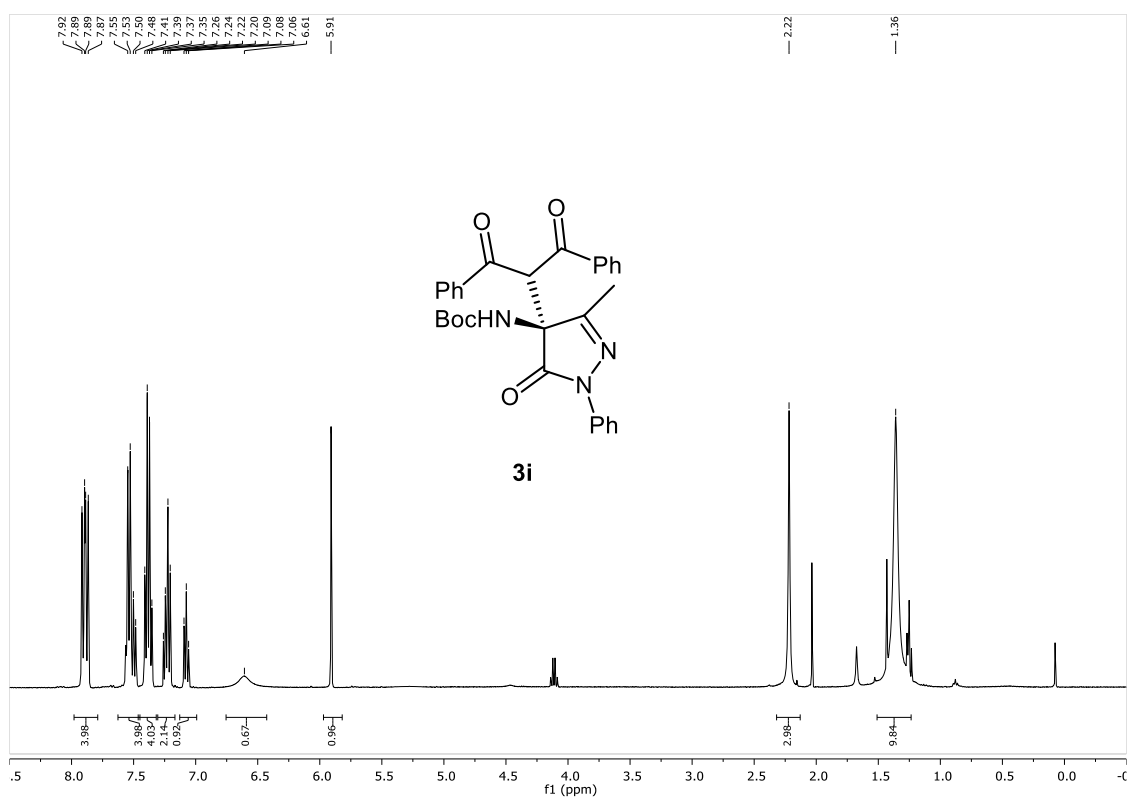
- ***tert*-Butyl (S)-4-(2,4-dioxopentan-3-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)carbamate (3g).**



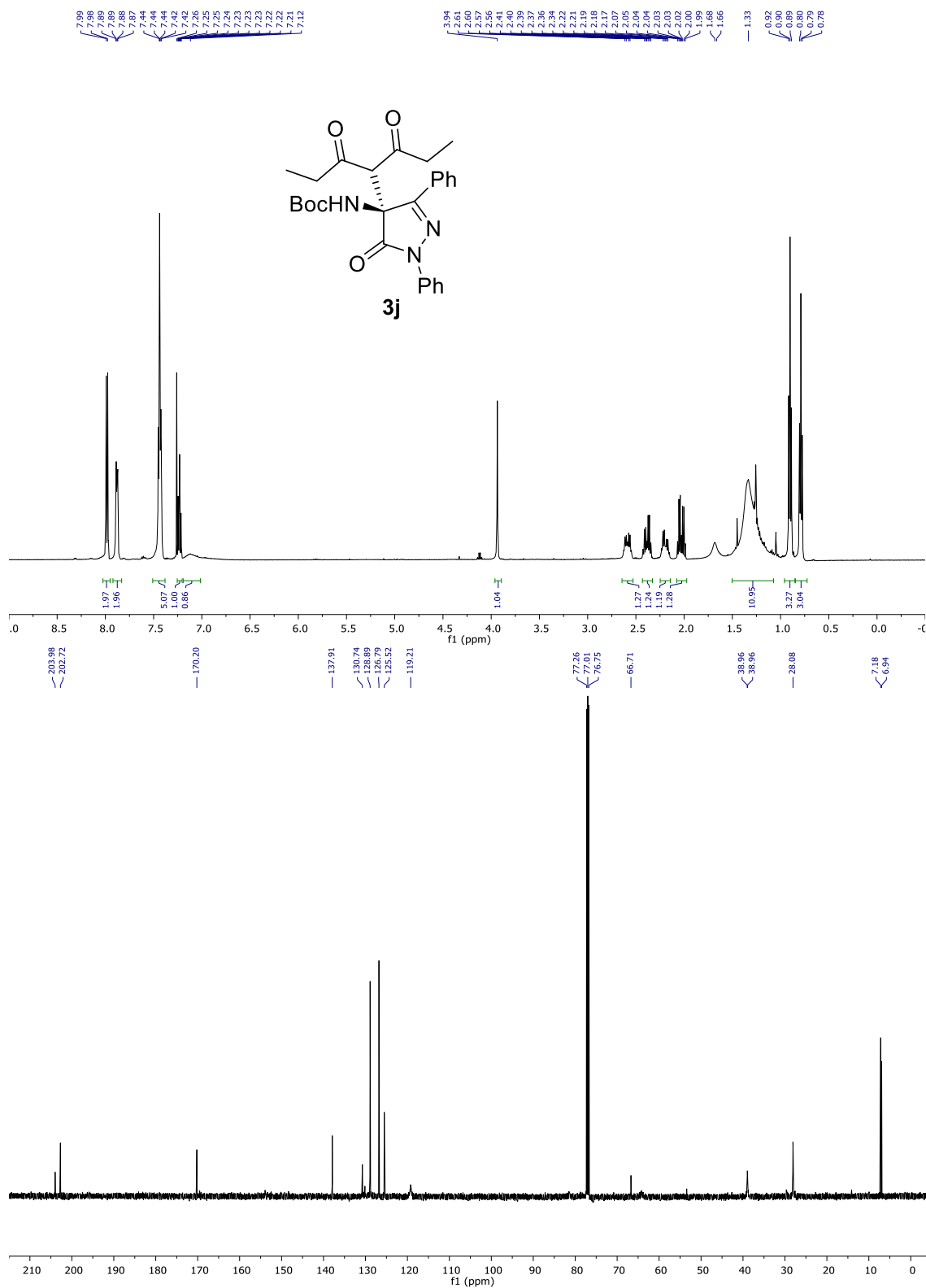
- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3h**).**



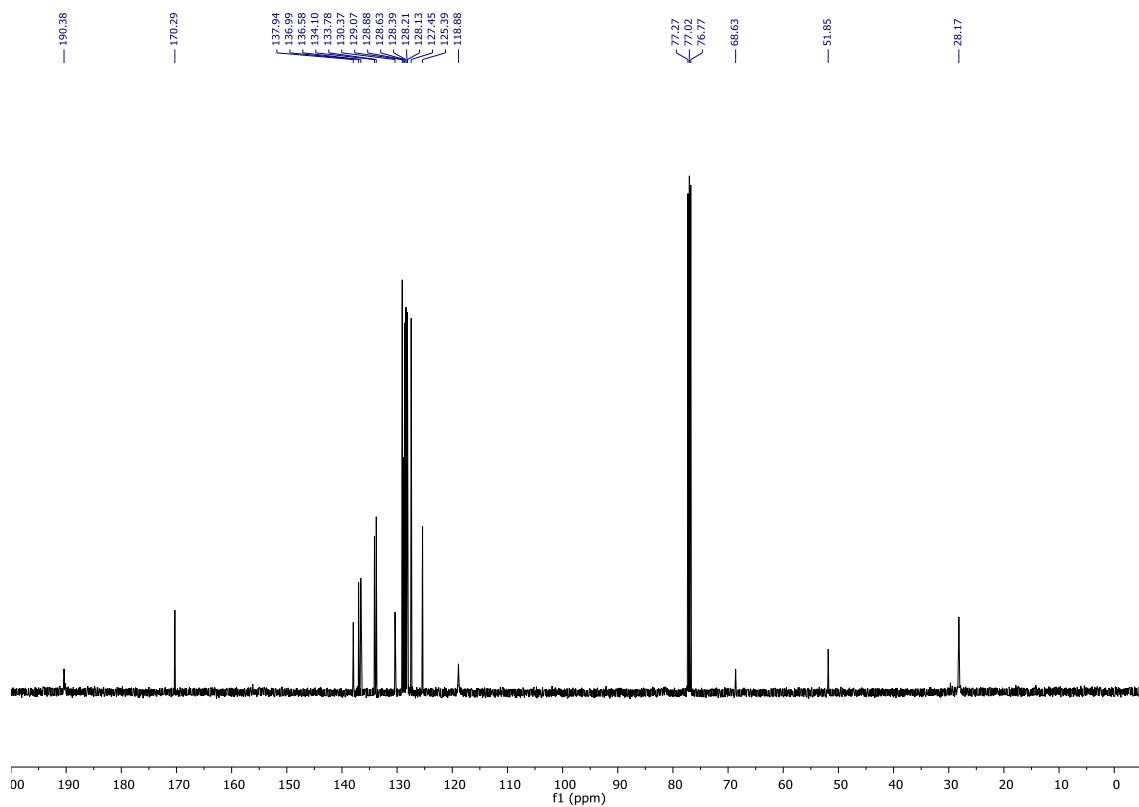
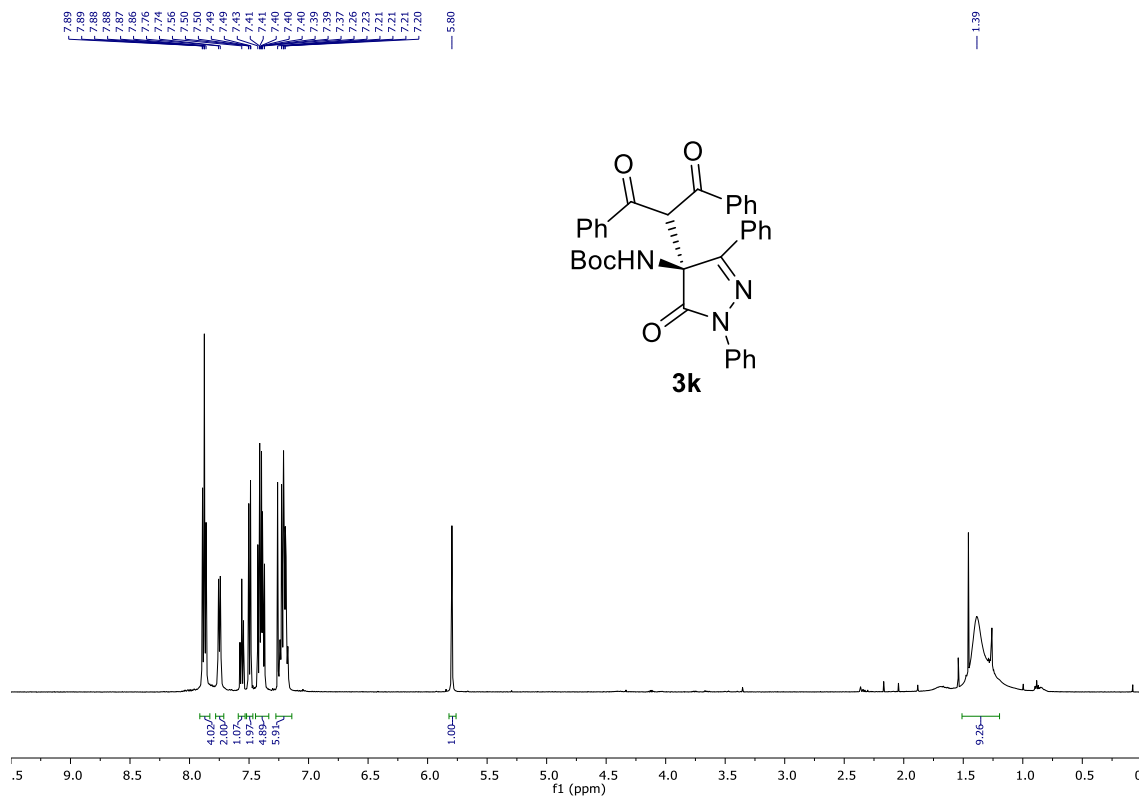
- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3i**).**



- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3j**).**

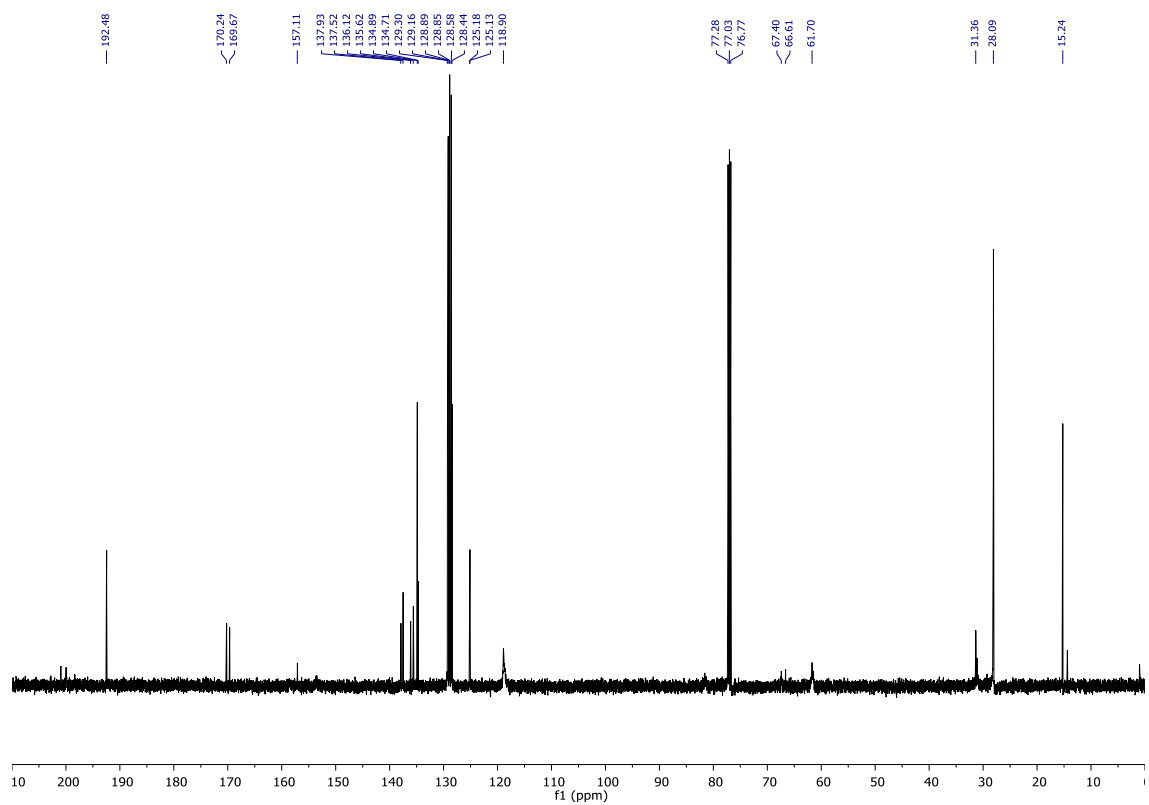
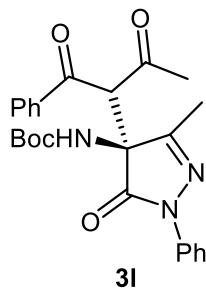
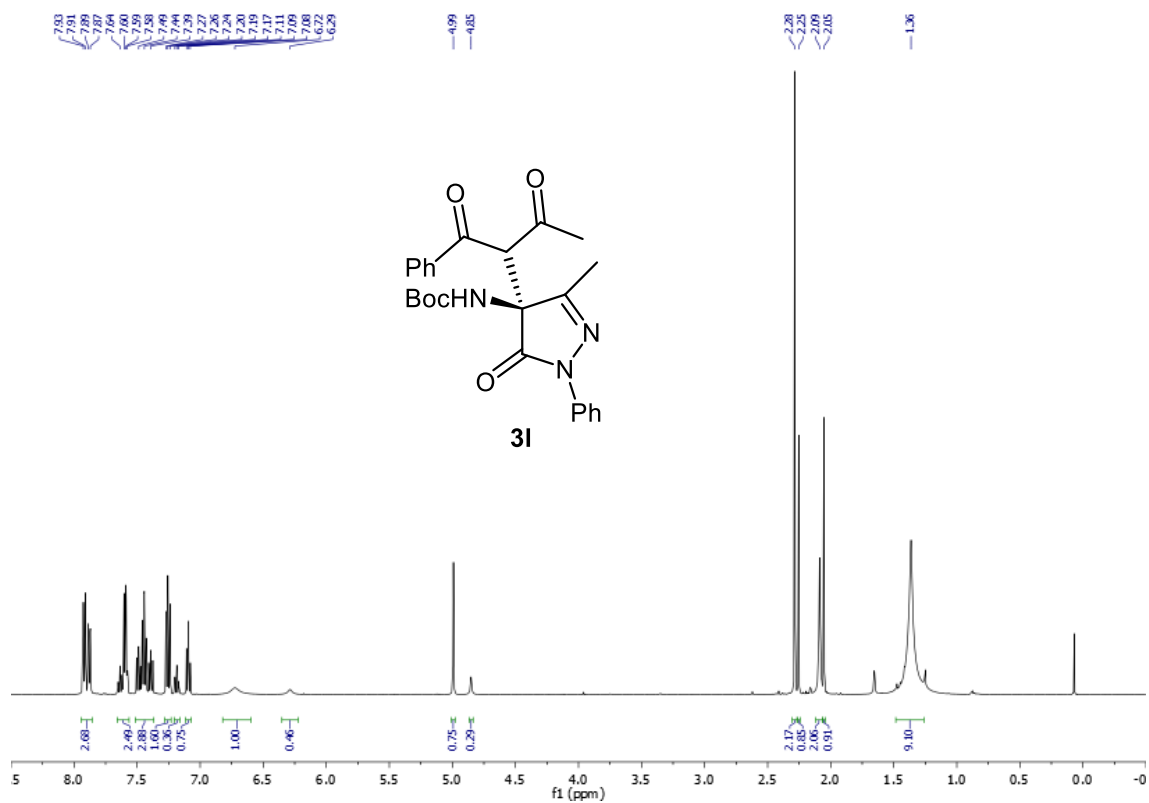


- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3k).**

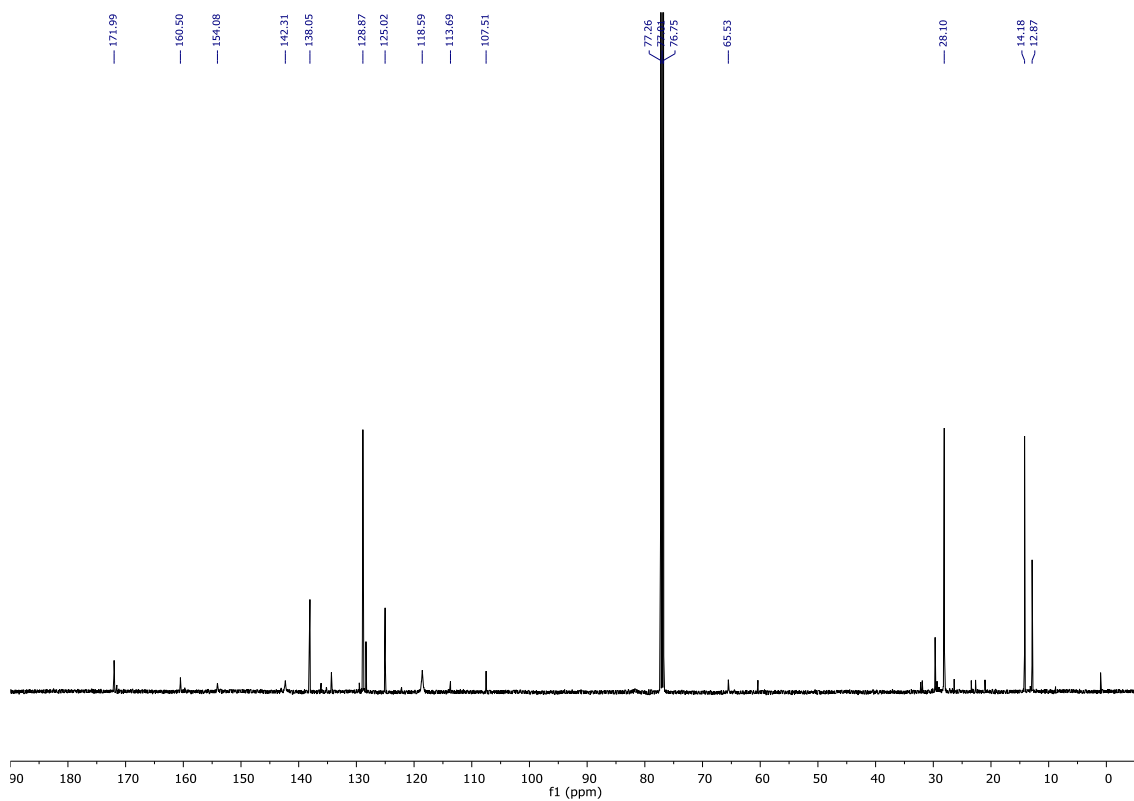
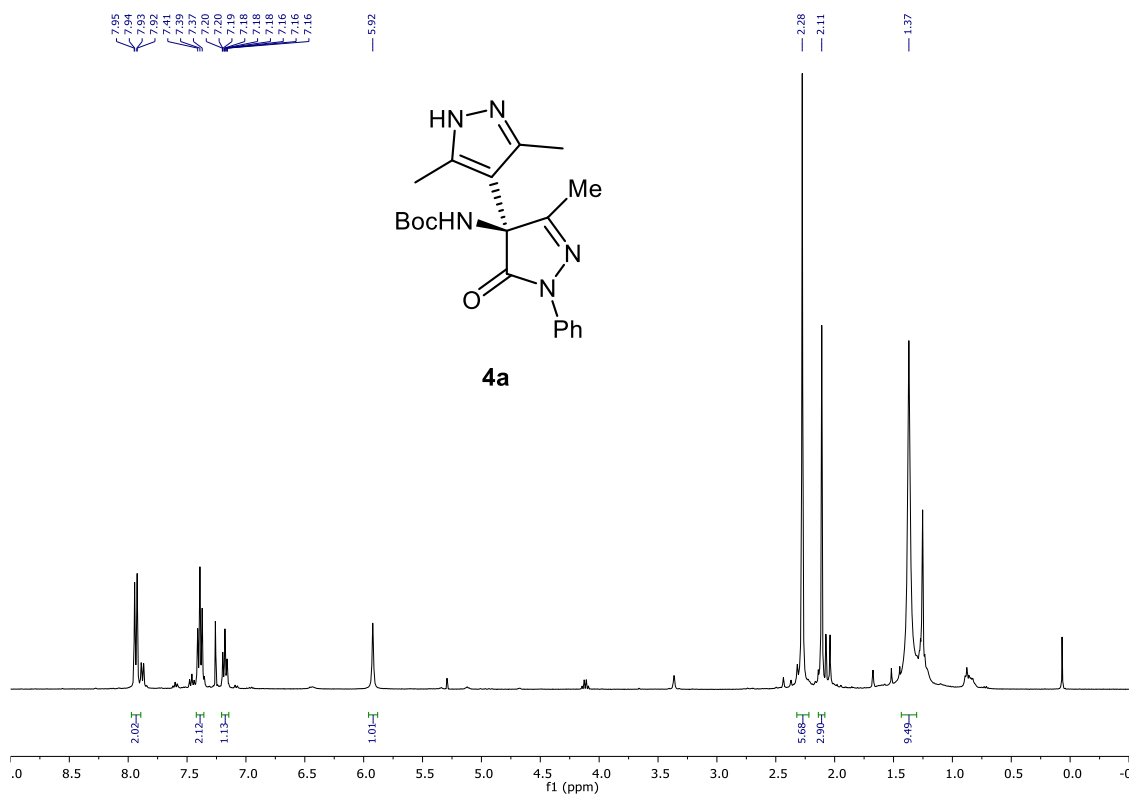




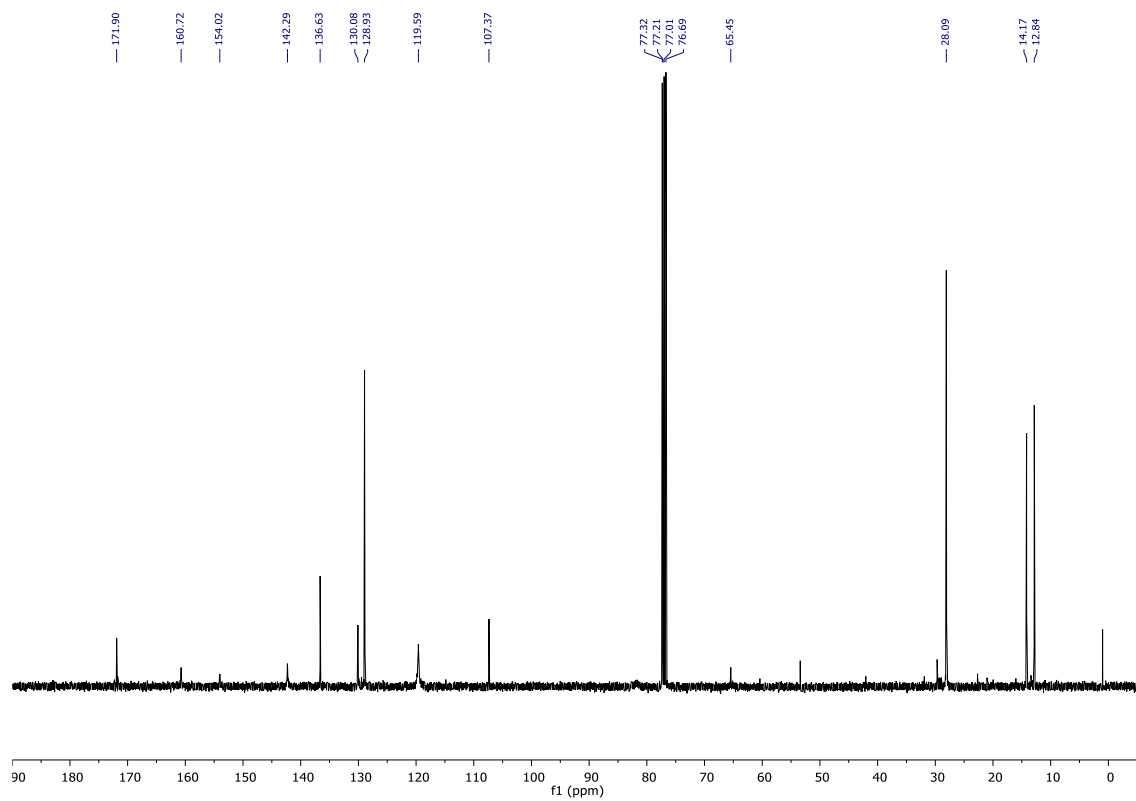
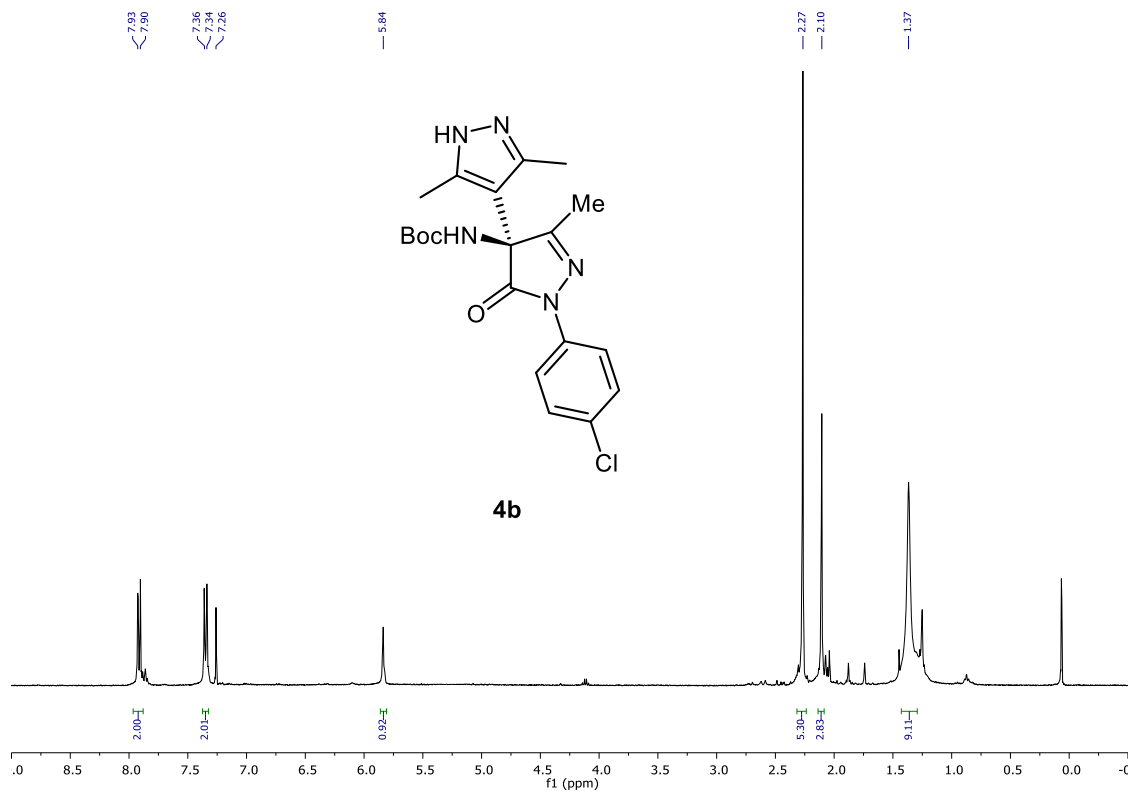
- ***tert*-Butyl ((*S*)-4-((*R*)-1,3-dioxo-1-phenylbutan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3l**).**



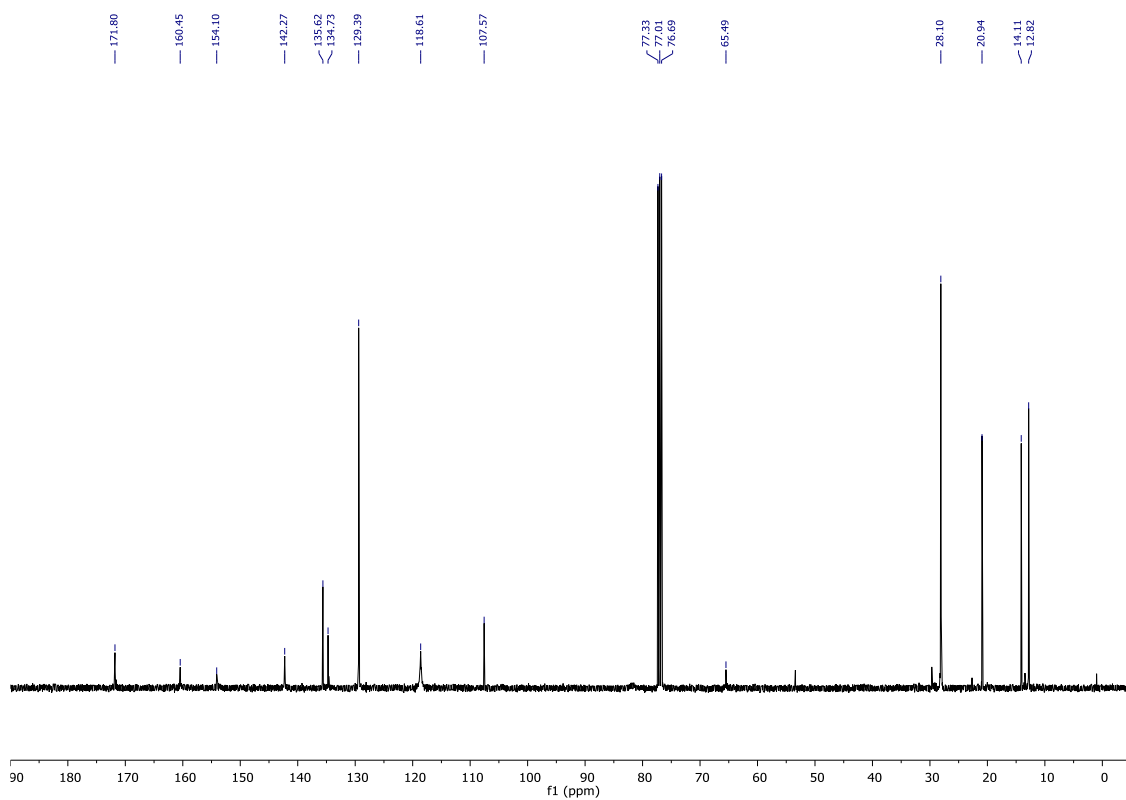
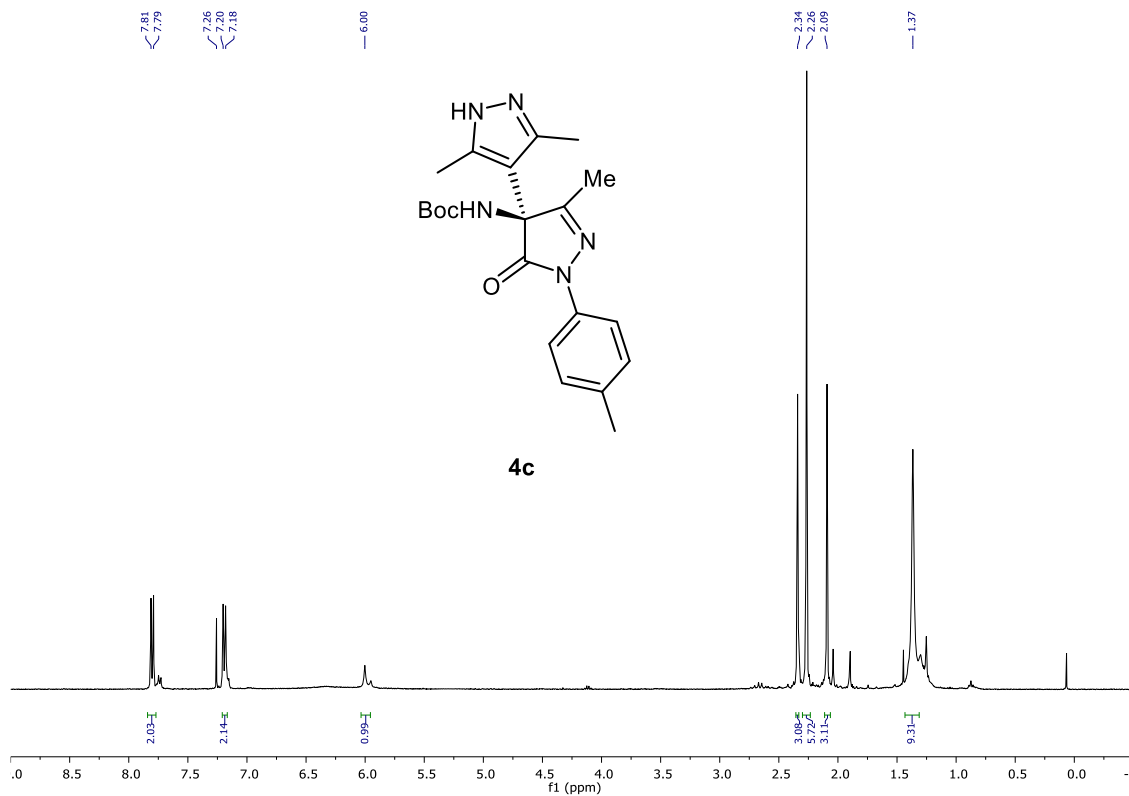
- ***tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4a**).**



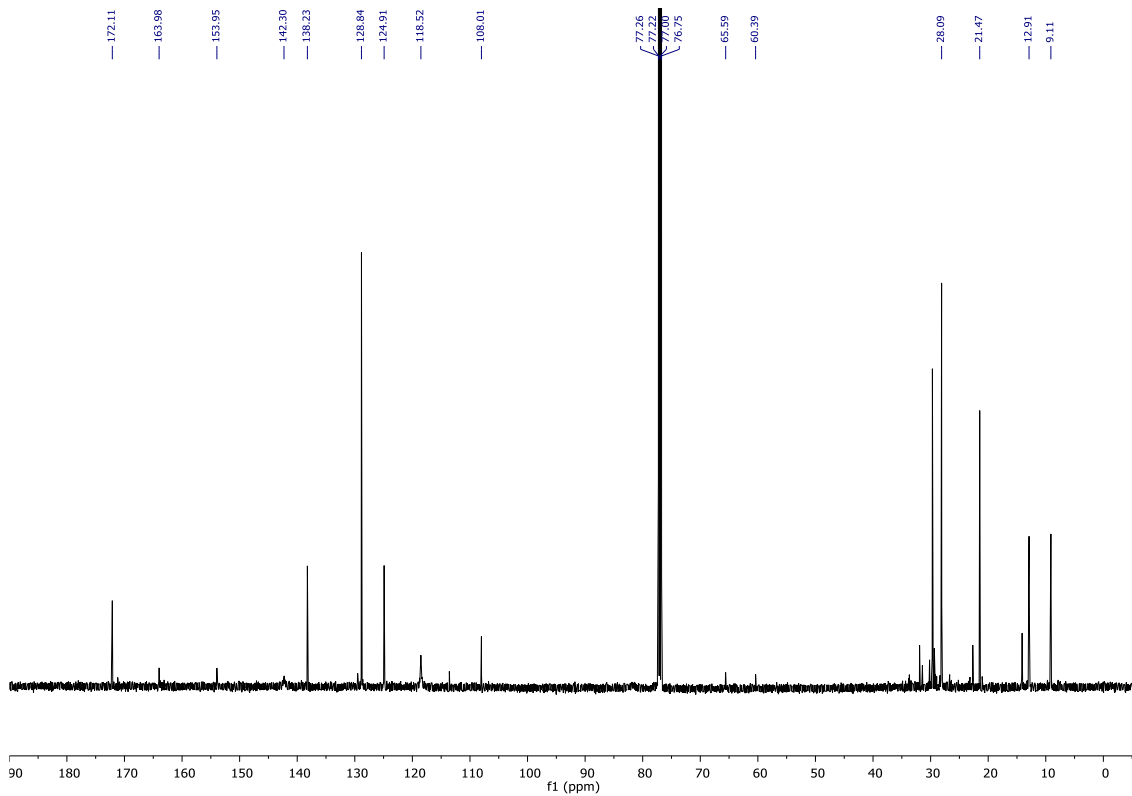
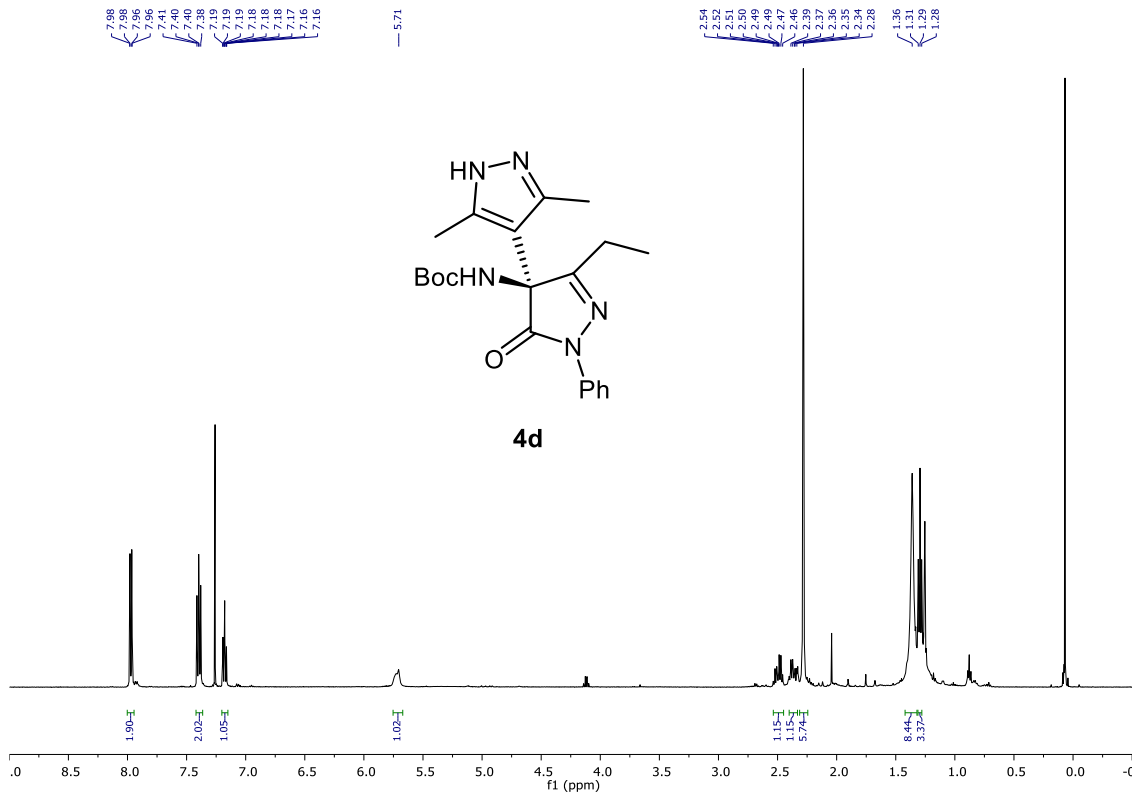
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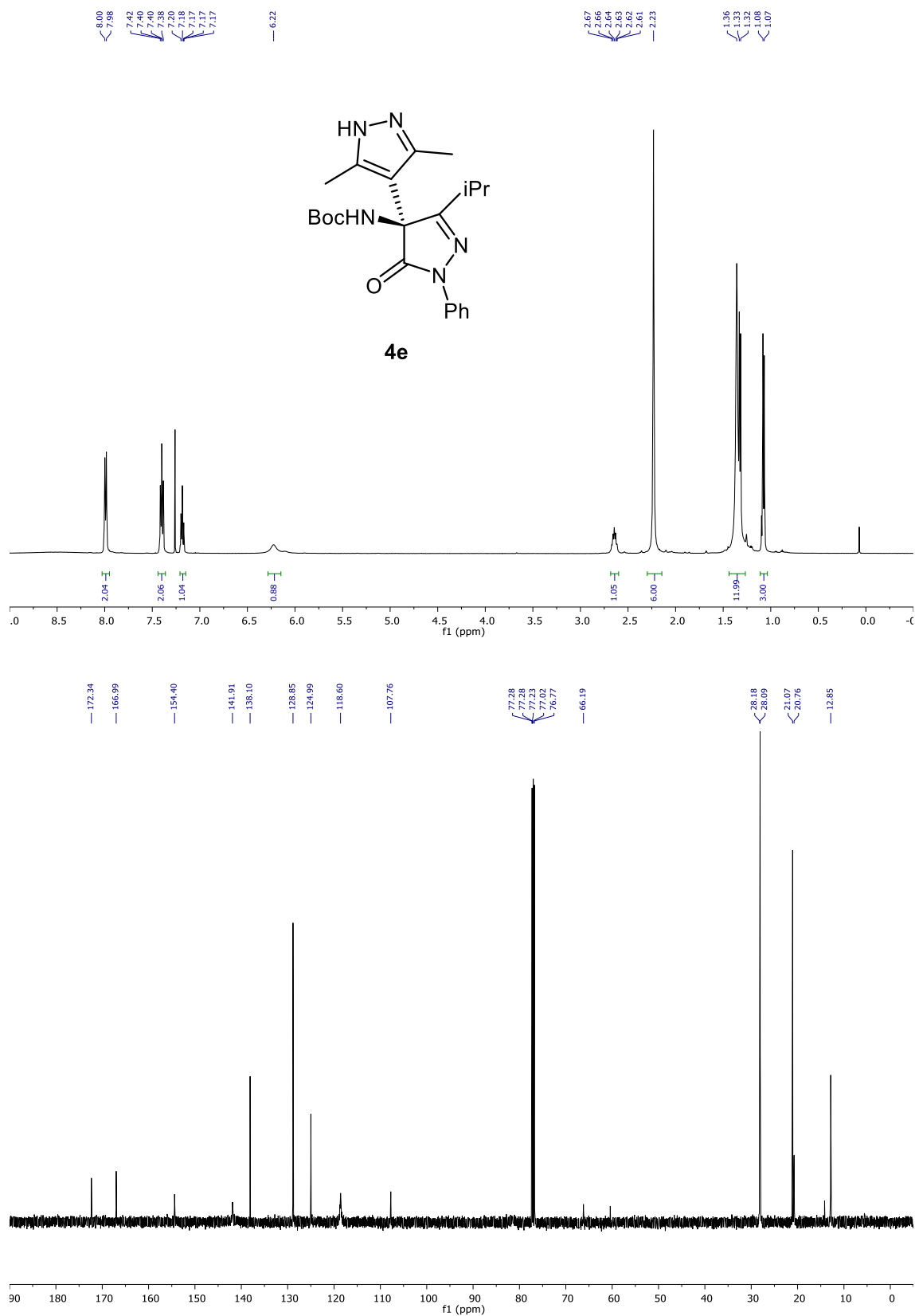
- ***tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-(*p*-tolyl)-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4c).**



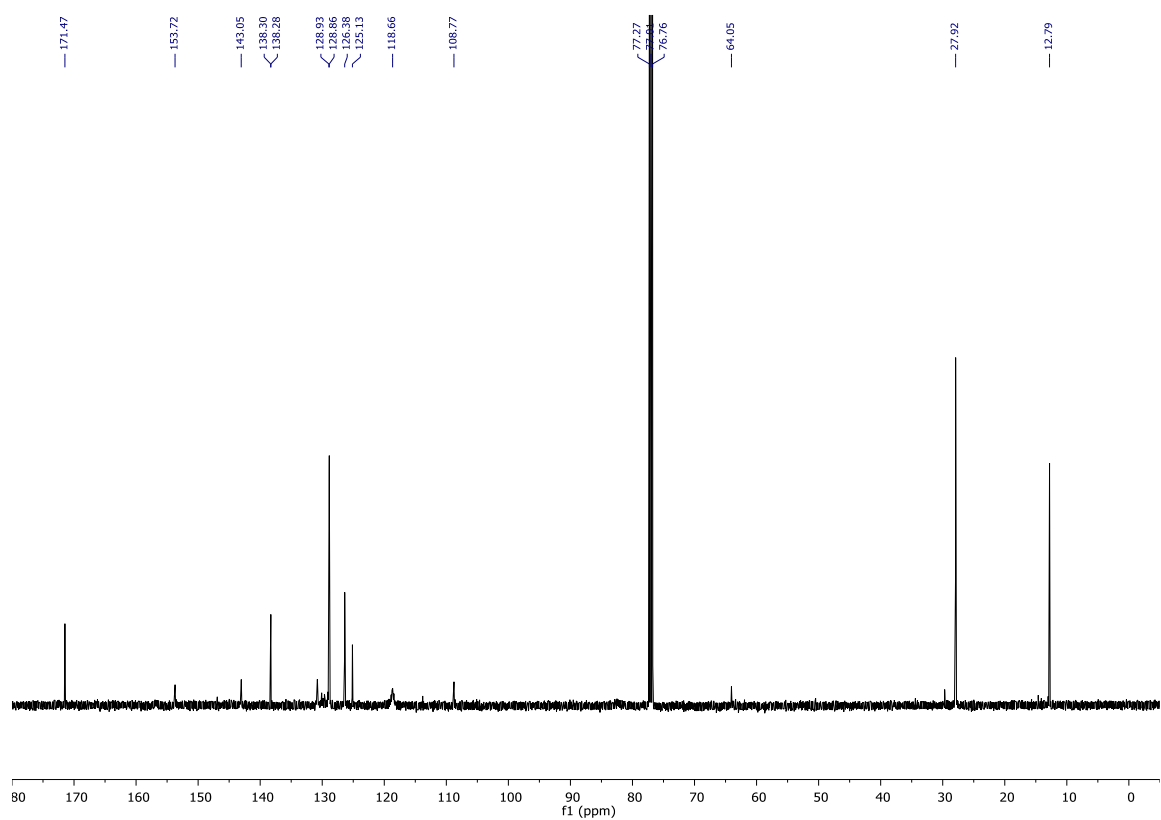
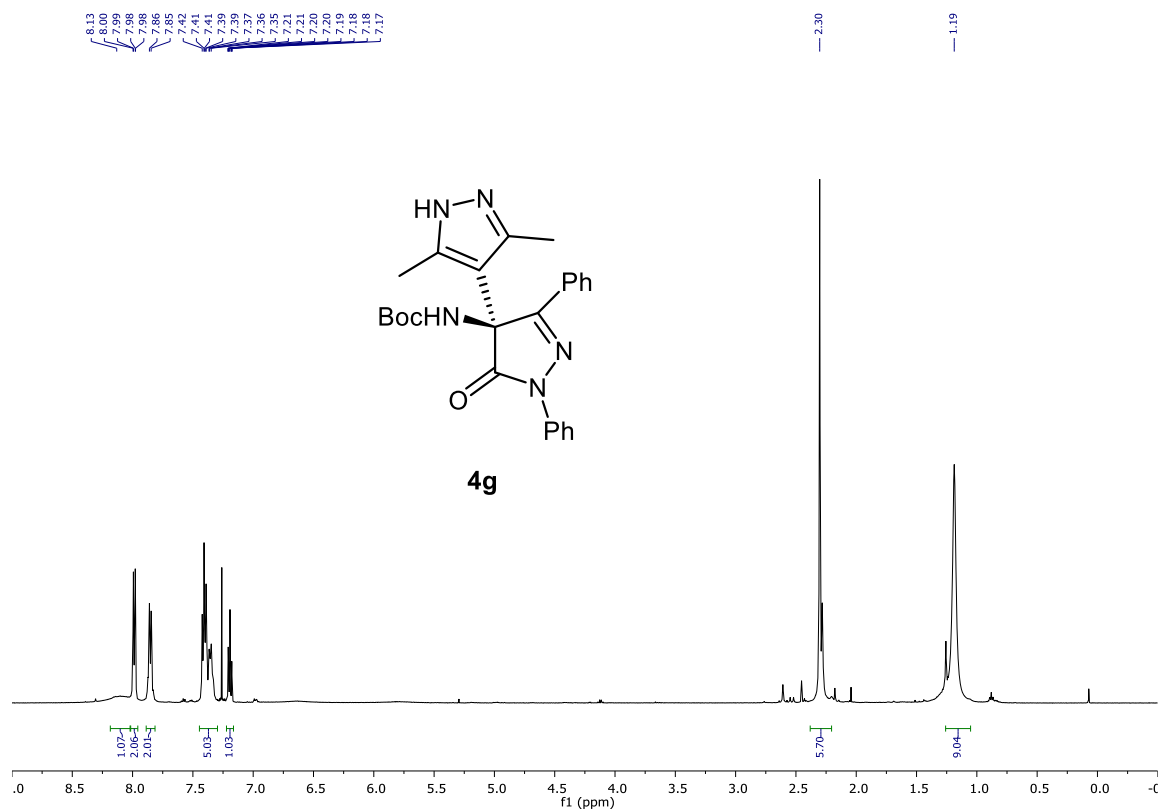
- ***tert*-Butyl (*S*)-(*3'*-ethyl-*3,5*-dimethyl-*5'*-oxo-*1'*-phenyl-*1',5'*-dihydro-*1H,4'H*-[*4,4'*-bipyrazol]-*4'-yl*)carbamate (**4d**).**



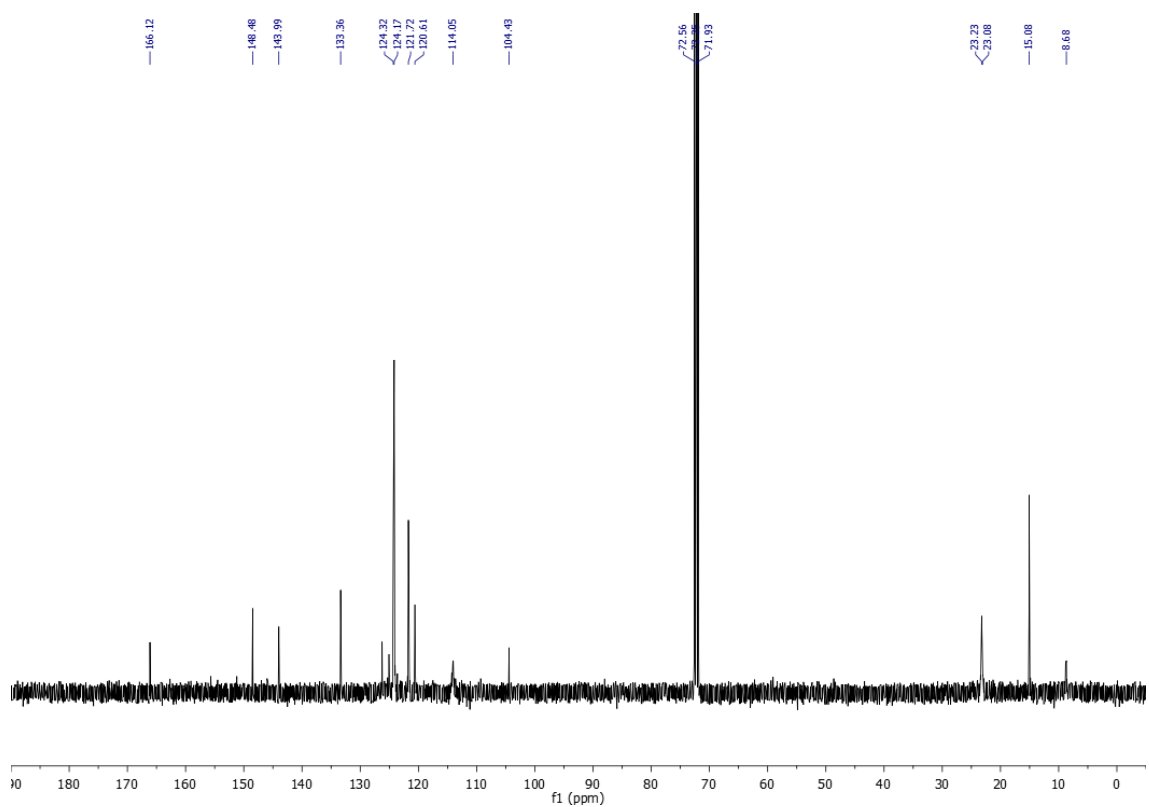
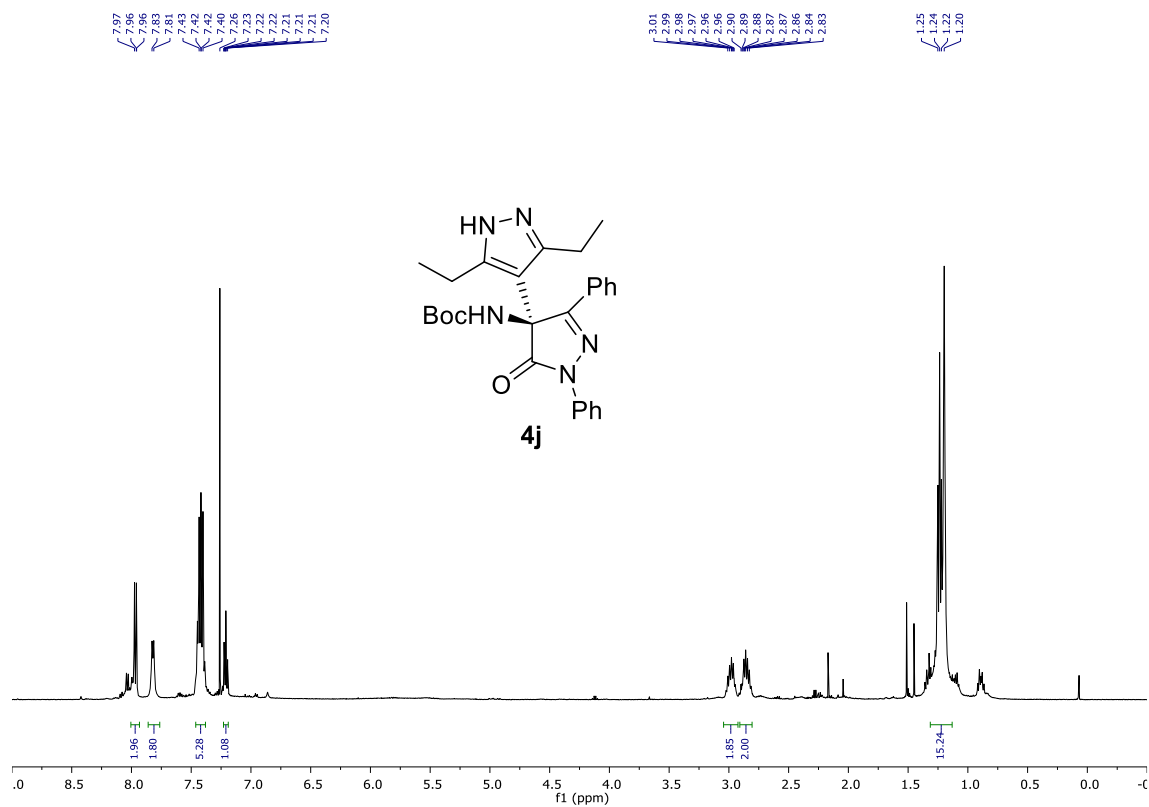
- ***tert*-Butyl (*S*)-(3'-isopropyl-3,5-dimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4e).**



- ***tert*-Butyl (*S*)-(3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4g).**

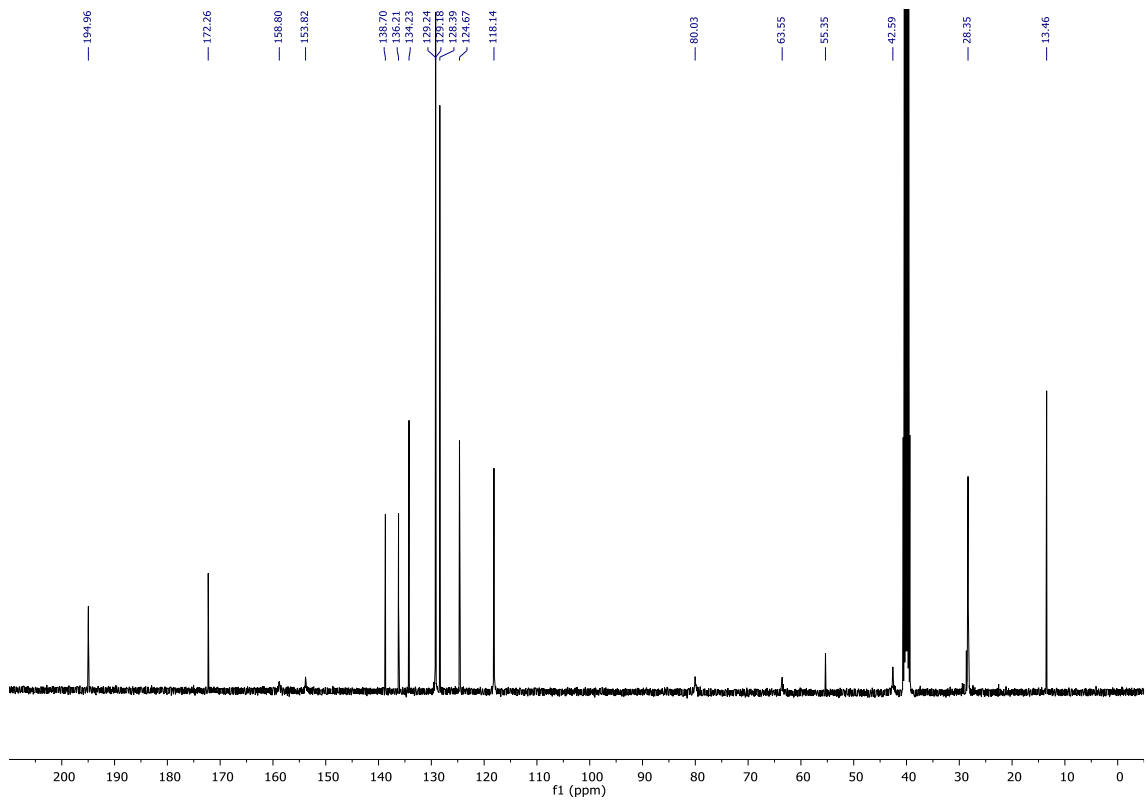
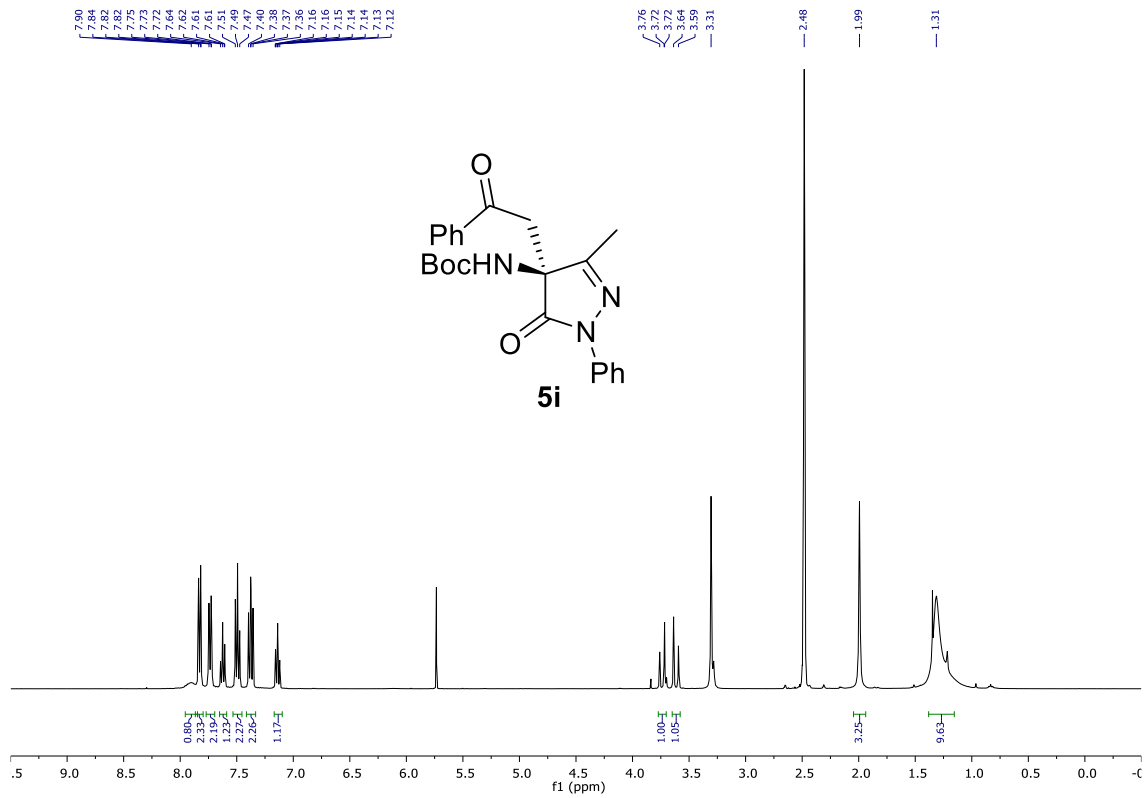


- ***tert*-Butyl (*S*)-(3,5-diethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrrozol]-4'-yl)carbamate (4j).**

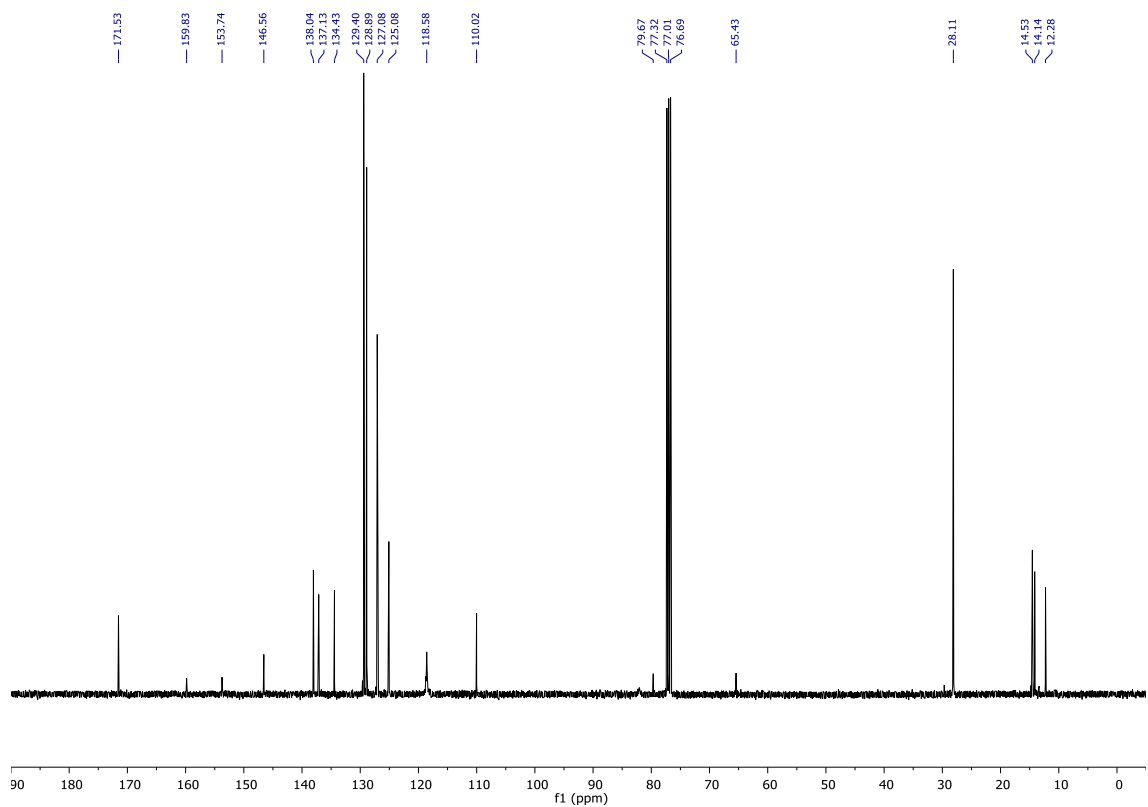
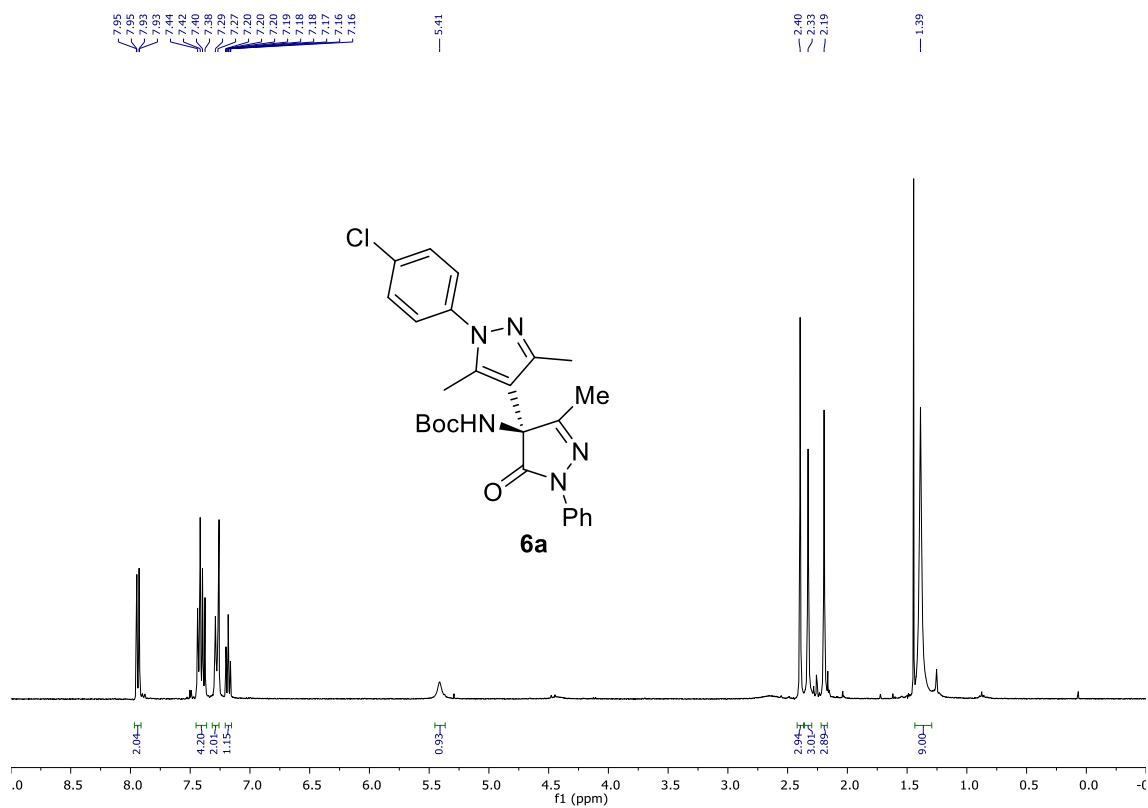




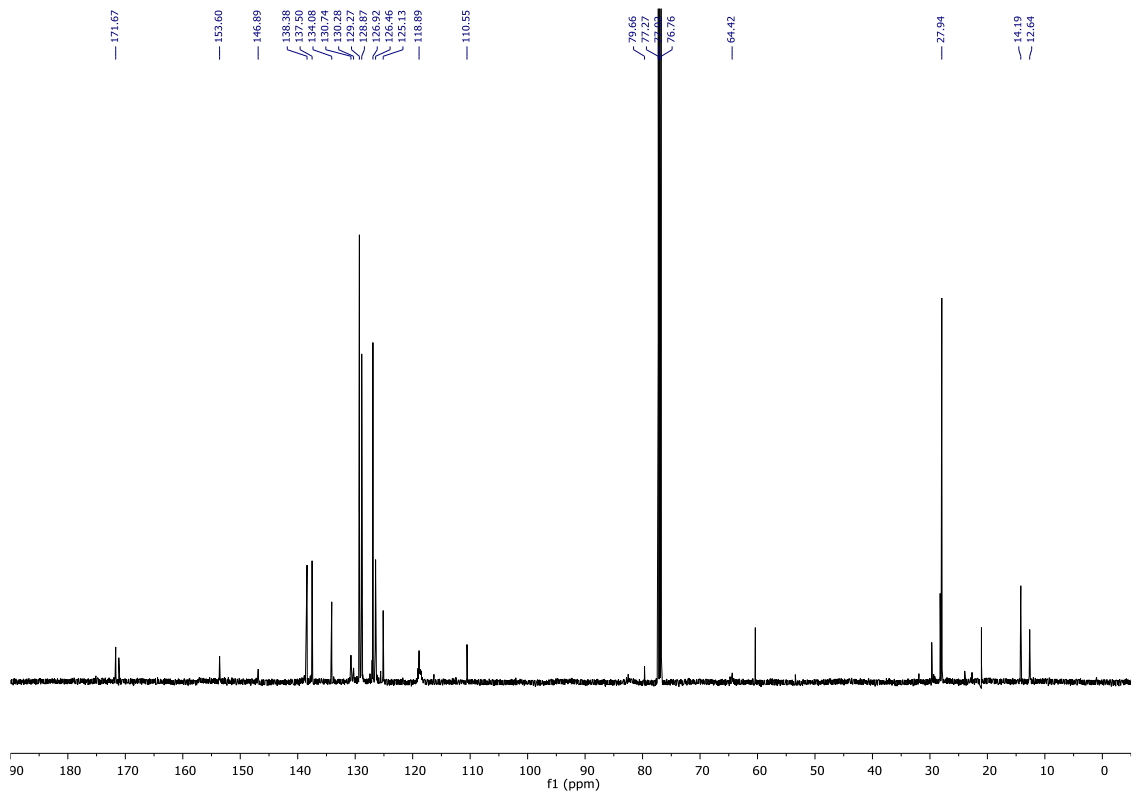
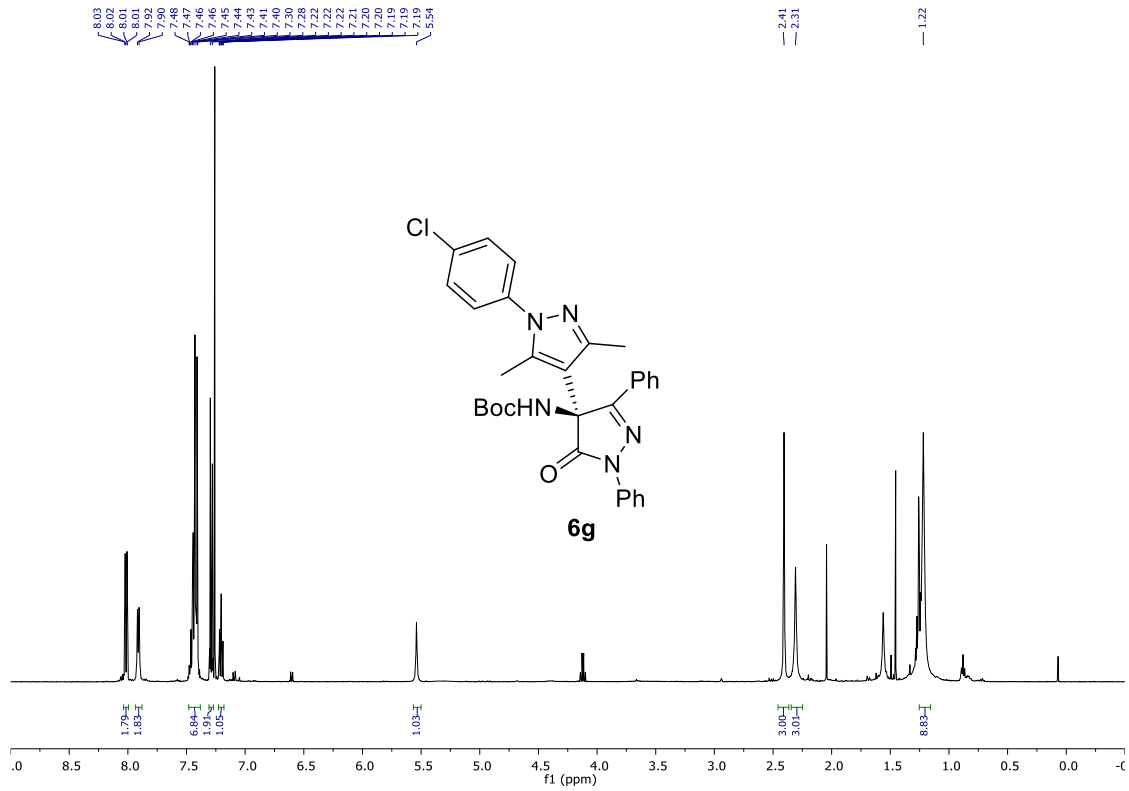
- ***tert*-Butyl (*S*)-(3-methyl-5-oxo-4-(2-oxo-2-phenylethyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**5i**).**



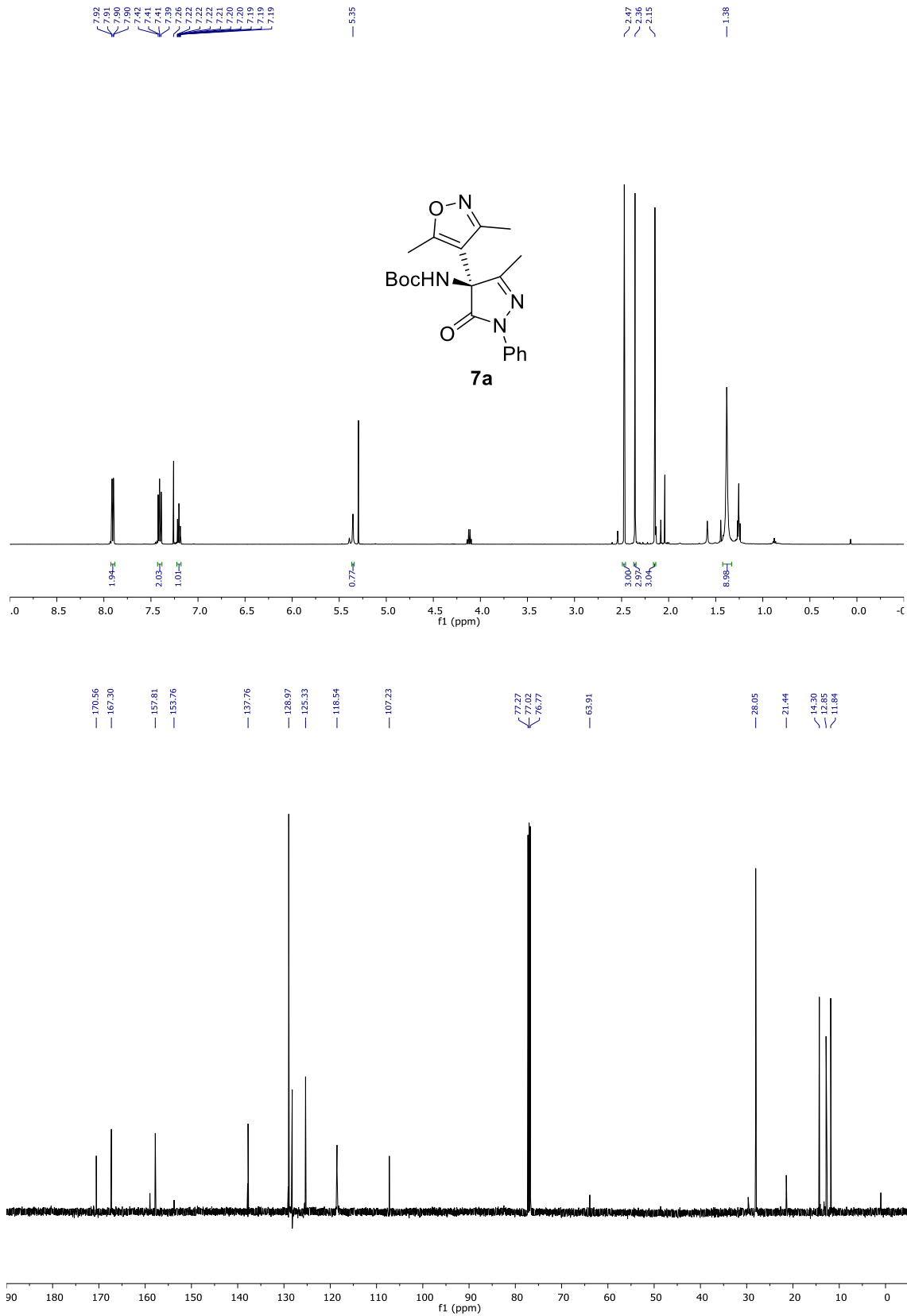
- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (6a).**



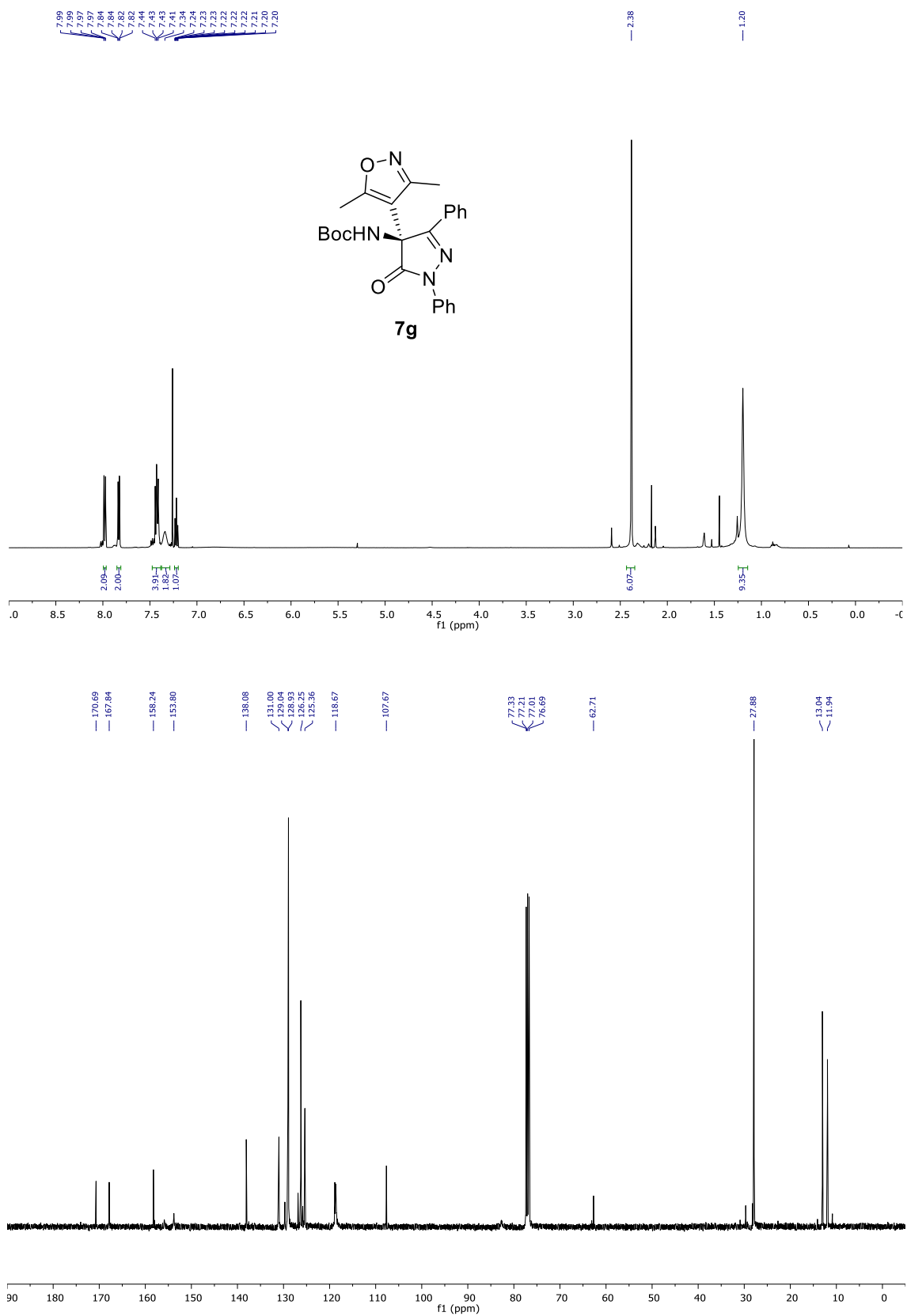
- ***tert*-Butyl (*S*)-1-(4-chlorophenyl)-3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (6g).**



- ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**7a**).**



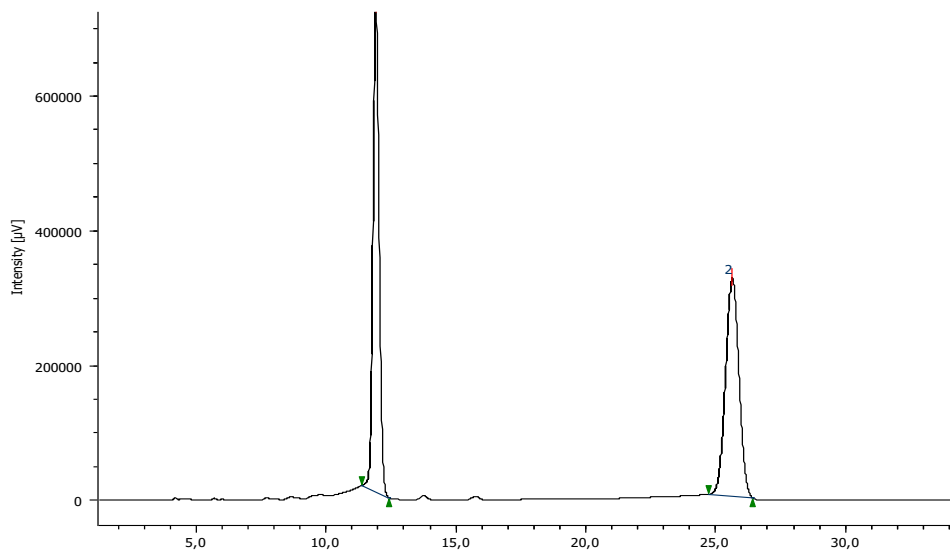
▪ ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**7g**).**



## 7.2.HPLC Profiles for New Compounds

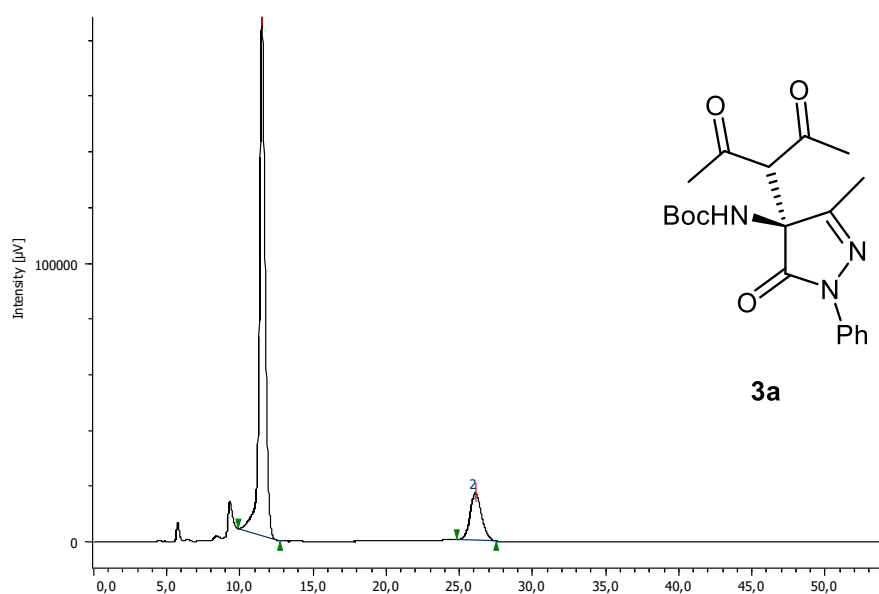
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3a).**

Racemic compound

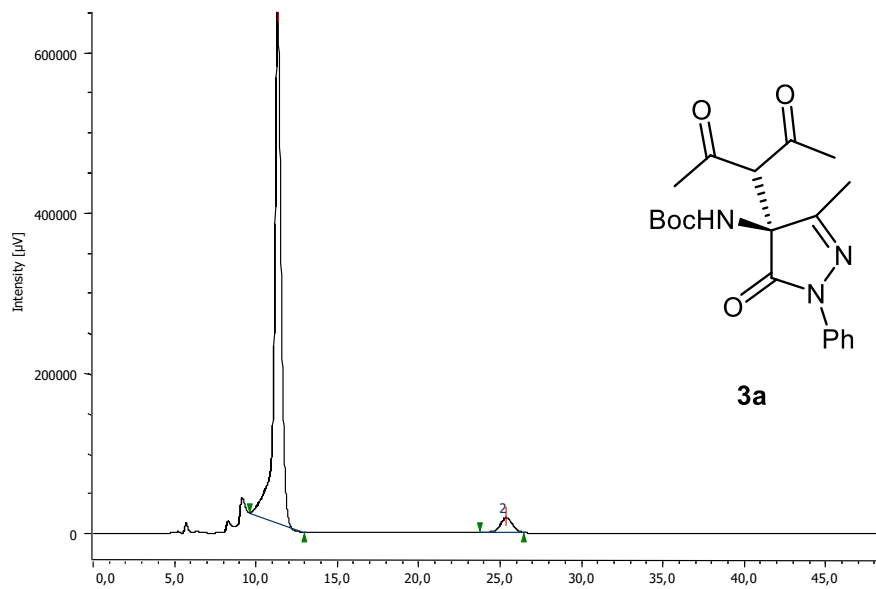


PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.900</b>	11954241	722346	<b>50.613</b>	1.104
2	<b>25.608</b>	11664640	323407	<b>49.387</b>	1.005

**HPLC Profile for 3a compound. Table 1, Entry 1, er: 85:15.**



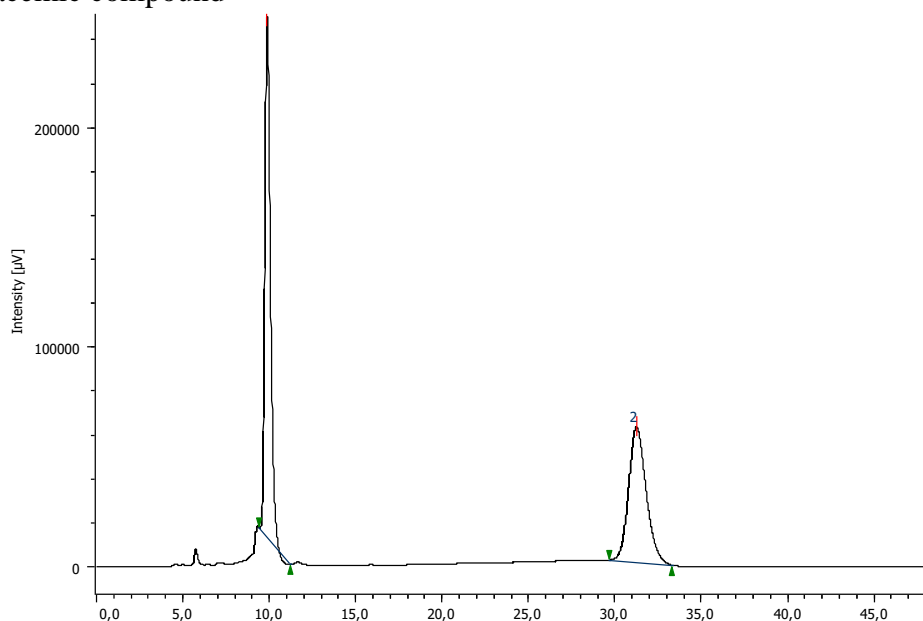
PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.492</b>	5090147	185674	<b>84.771</b>	1.000
2	<b>26.058</b>	914451	16821	<b>15.229</b>	1.136



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.325</b>	18650197	636380	<b>95.160</b>	0.817
2	<b>25.342</b>	948603	18462	<b>4.840</b>	1.000

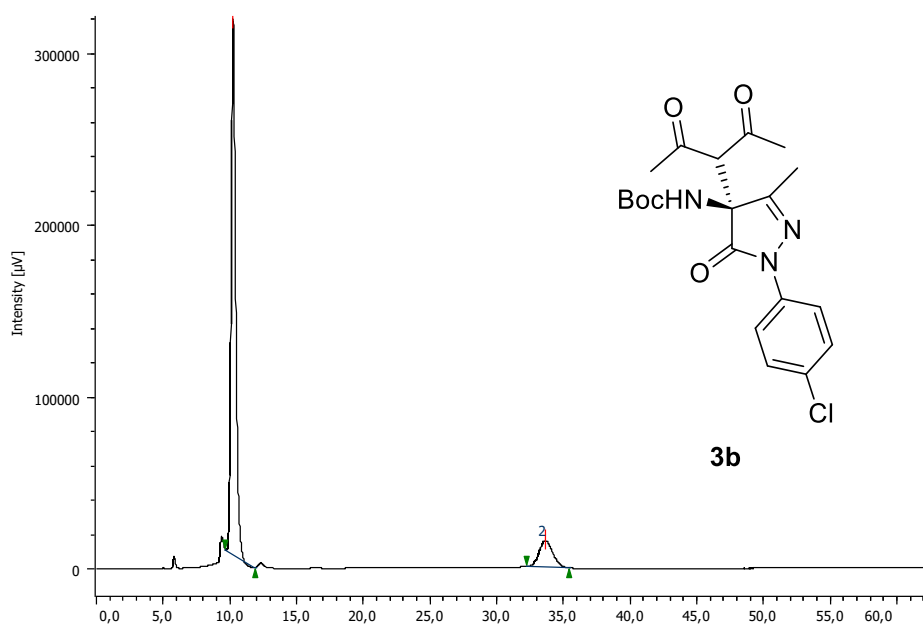
- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3b).**

Racemic compound



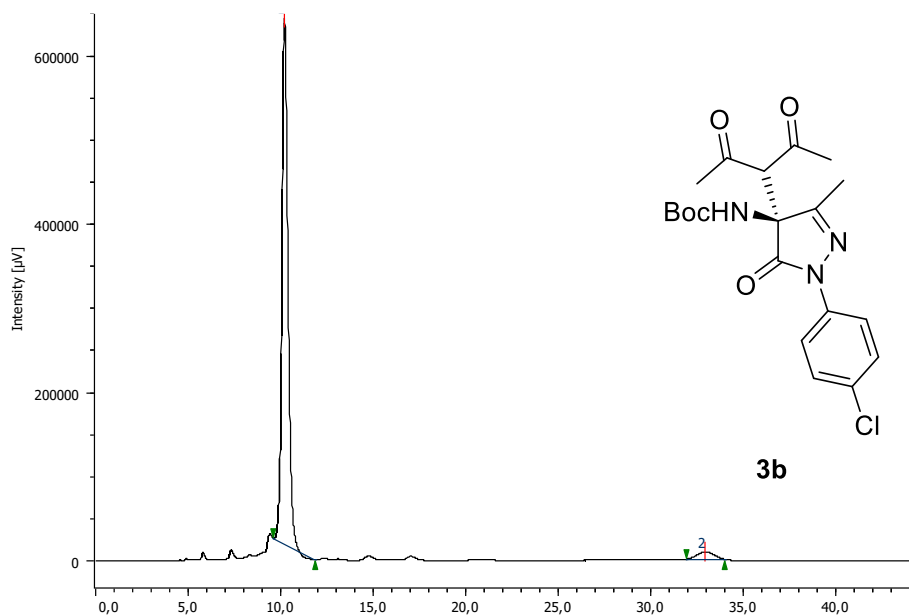
PeakNumber	$t_R$	Area	Height	Area %	SymmetryFactor
1	<b>9.867</b>	5291635	236518	<b>54.969</b>	1.361
2	<b>31.225</b>	4335008	61417	<b>45.031</b>	1.171

**HPLC Profile for 3b compound. Table 1, Entry 2, er: 87:13.**



PeakNumber	$t_R$	Area	Height	Area %	SymmetryFactor
1	<b>10.233</b>	7232983	311064	<b>86.813</b>	1.279
2	<b>33.608</b>	1098698	15363	<b>13.187</b>	1.120

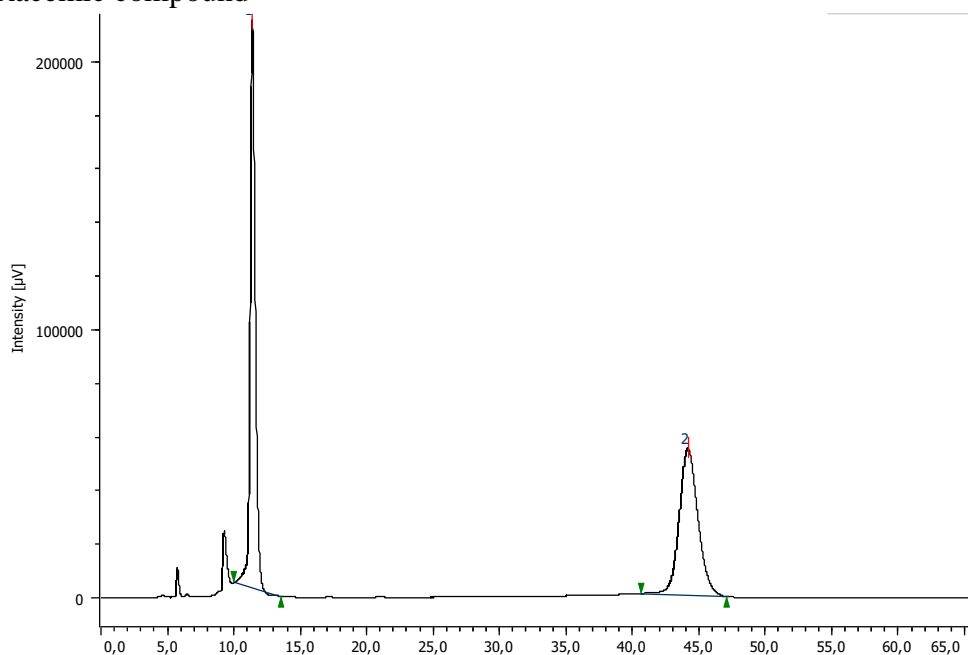




PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>10.200</b>	14221584	623717	<b>96.180</b>	1.191
2	<b>32.892</b>	564856	9087	<b>3.820</b>	1.044

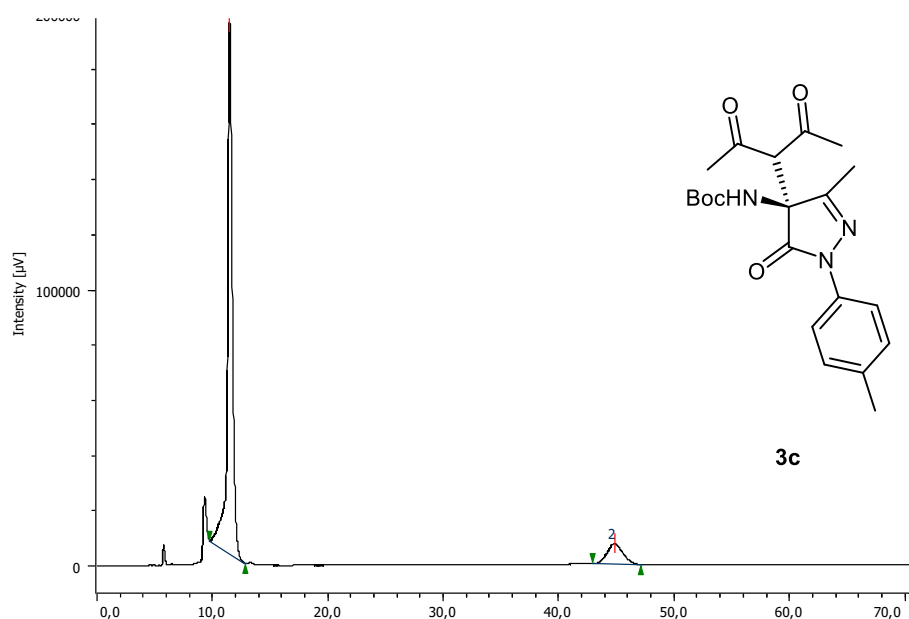
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-methyl-5-oxo-1-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3c**).**

Racemic compound



PeakNumber	<i>t<sub>R</sub></i>	Area	Height	Area %	SymmetryFactor
1	<b>11,383</b>	5657641	211401	<b>51,305</b>	79,505
2	<b>44,117</b>	5369868	54496	<b>48,695</b>	20,495

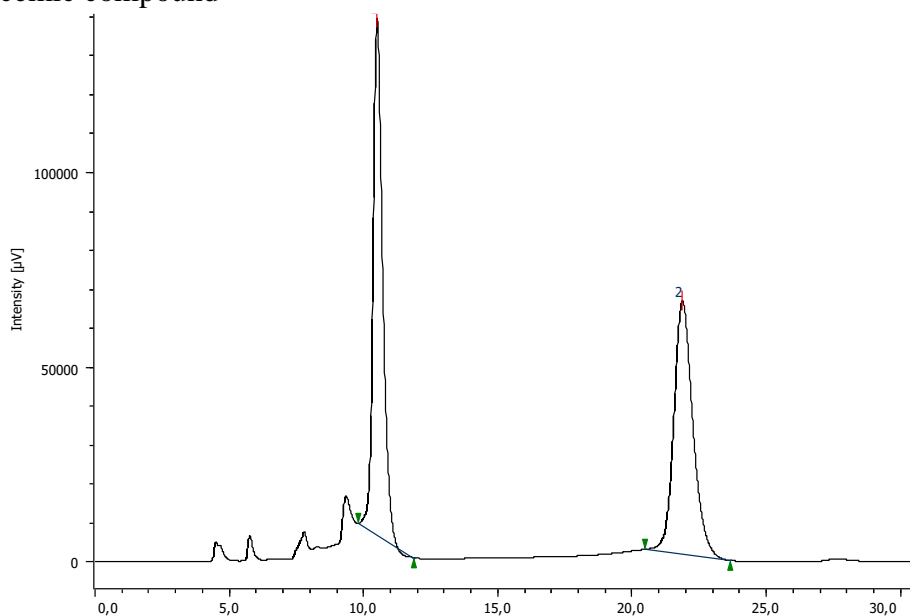
**HPLC Profile for 3c compound. Table 1, Entry 3, er: 89:11.**



PeakNumber	<i>t<sub>R</sub></i>	Area	Height	Area %	SymmetryFactor
1	<b>11.492</b>	5695956	191925	<b>89.075</b>	0.839
2	<b>44.775</b>	698588	7276	<b>10.925</b>	1.120

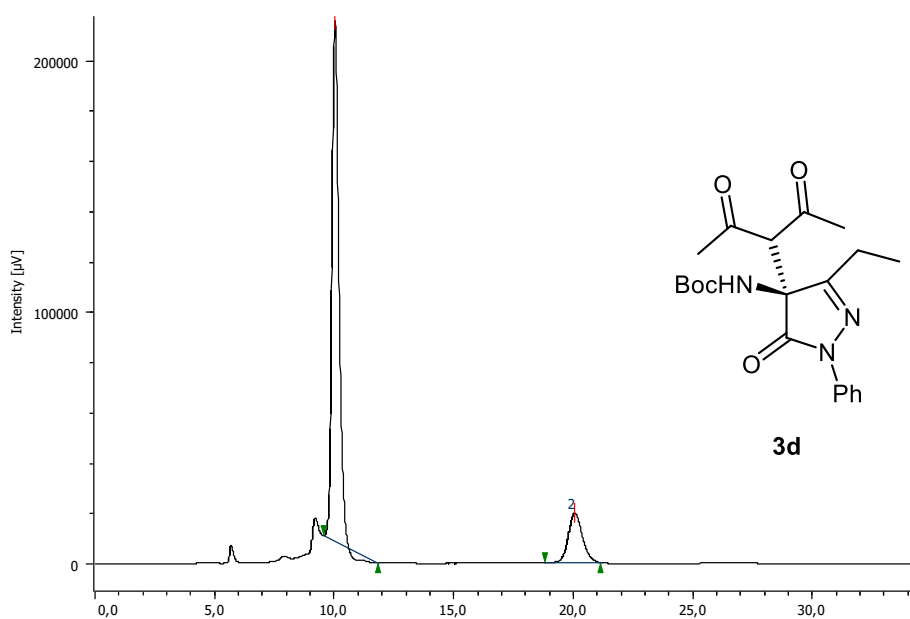
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-ethyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3d).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>10.492</b>	3268688	132530	<b>50.530</b>	1.275
2	<b>21.850</b>	3200091	64980	<b>49.470</b>	1.175

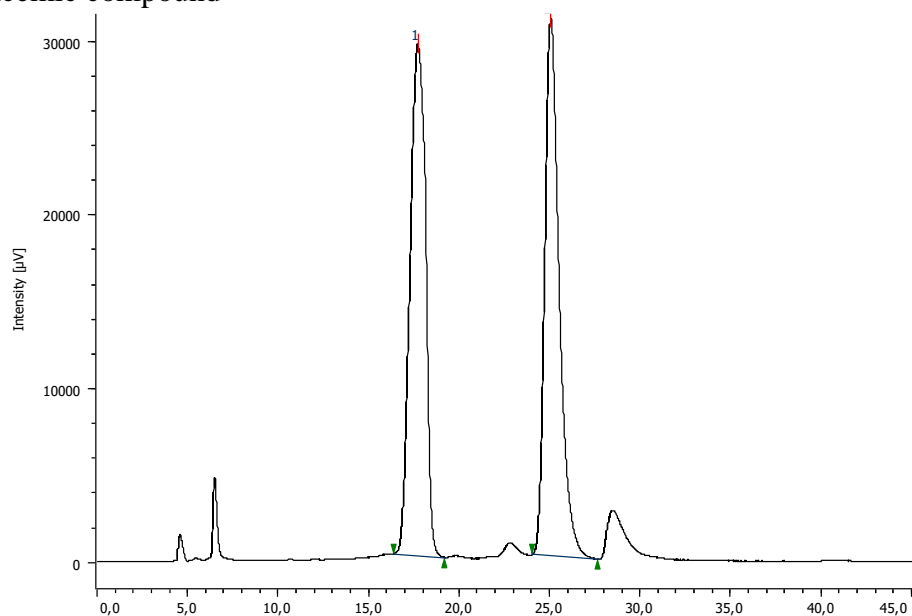
**HPLC Profile for 3d compound. Table 1, Entry 4, er: 84:16.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>10.025</b>	4156356	206525	<b>83.853</b>	1.260
2	<b>20.033</b>	800333	19632	<b>16.147</b>	1.159

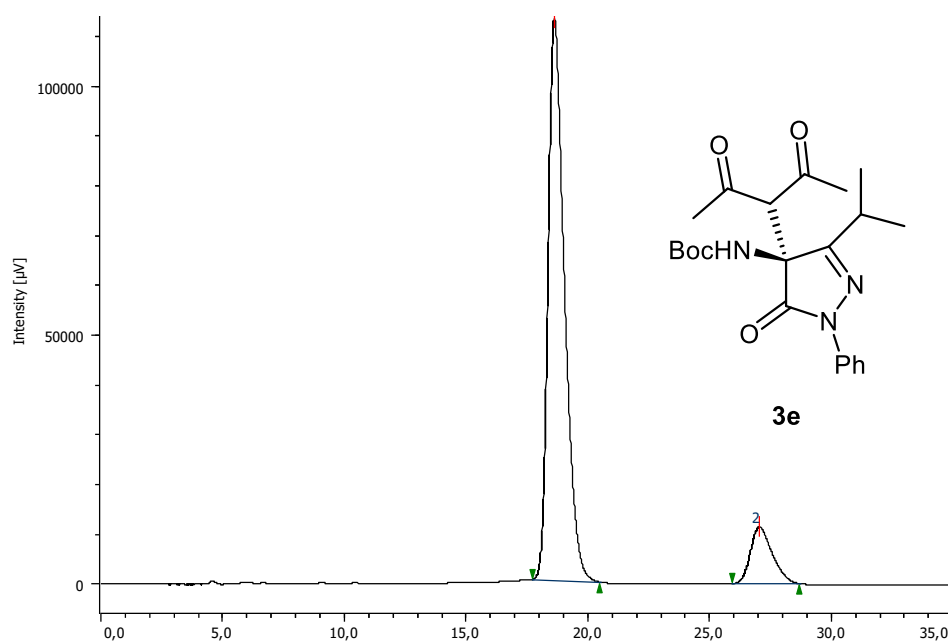
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-3-isopropyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3e**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>17.708</b>	1750023	29389	<b>50.474</b>	0.953
2	<b>25.042</b>	1717121	30883	<b>49.526</b>	1.401

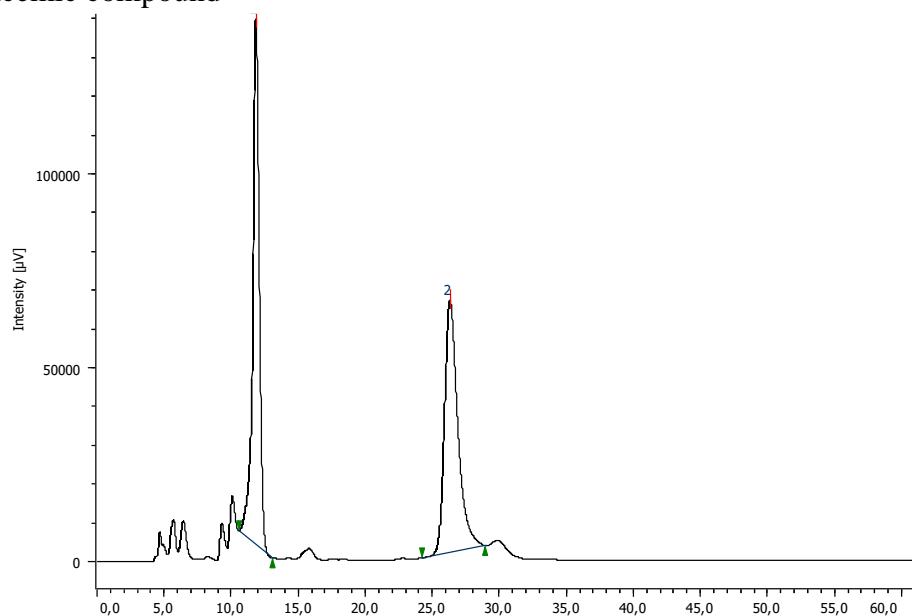
**HPLC Profile for 3e compound. Table 1, Entry 5, er: 88:12.**



Peak Name	t <sub>R</sub>	Area	Height	Area%	Symmetry Factor
1	<b>18,600</b>	5241997	112514	<b>88,074</b>	1,437
2	<b>27,017</b>	709806	11458	<b>11,926</b>	1,290

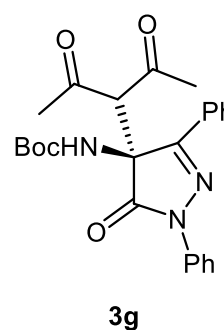
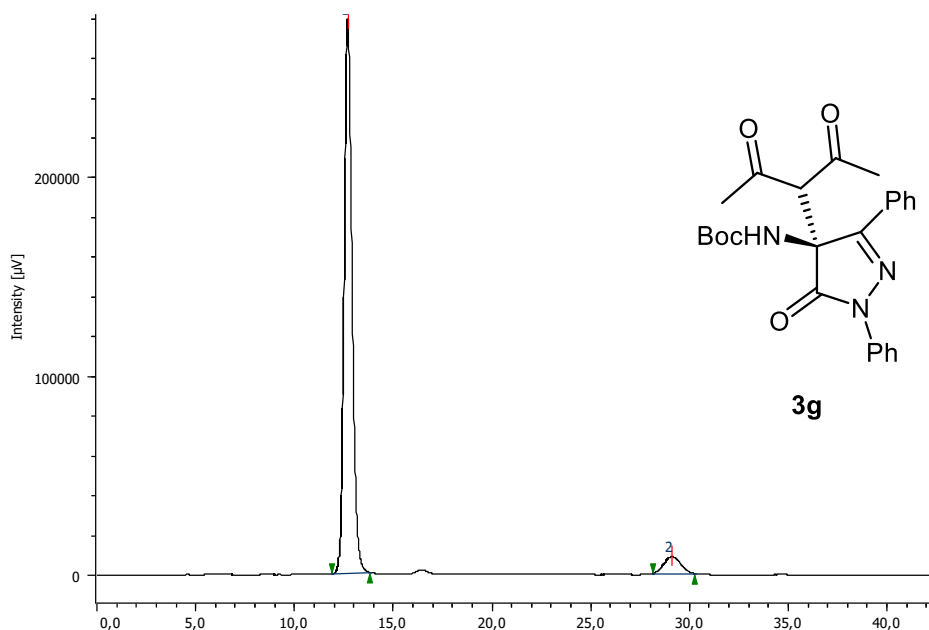
- ***tert*-Butyl (*S*)-(4-(2,4-dioxopentan-3-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3g).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.842</b>	4548326	135340	<b>50.294</b>	0.868
2	<b>26.292</b>	4495142	64882	<b>49.706</b>	1.450

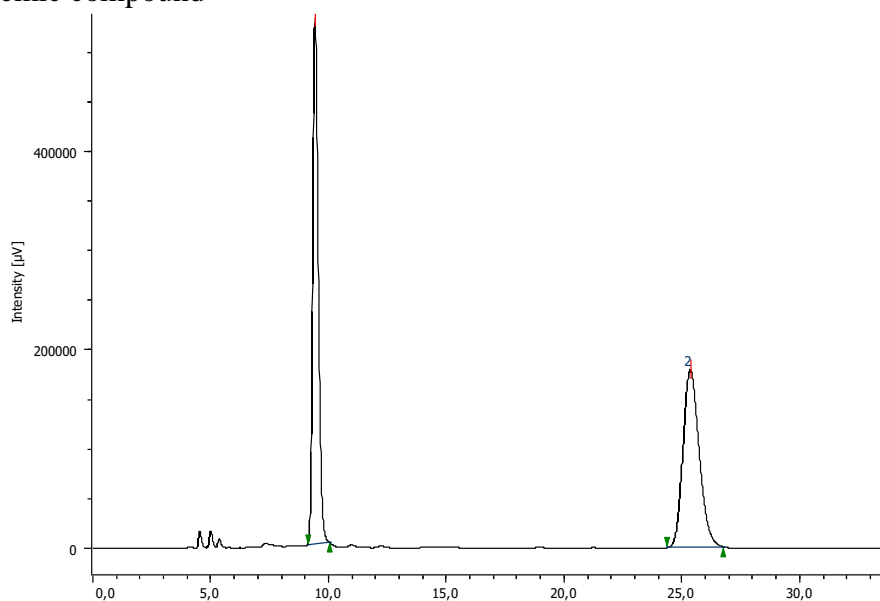
**HPLC Profile for 3g compound. Table 1, Entry 7, er: 94:6.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>12,683</b>	7750572	278161	<b>93,900</b>	97,052
2	<b>29,083</b>	503455	8450	<b>6,100</b>	2,948

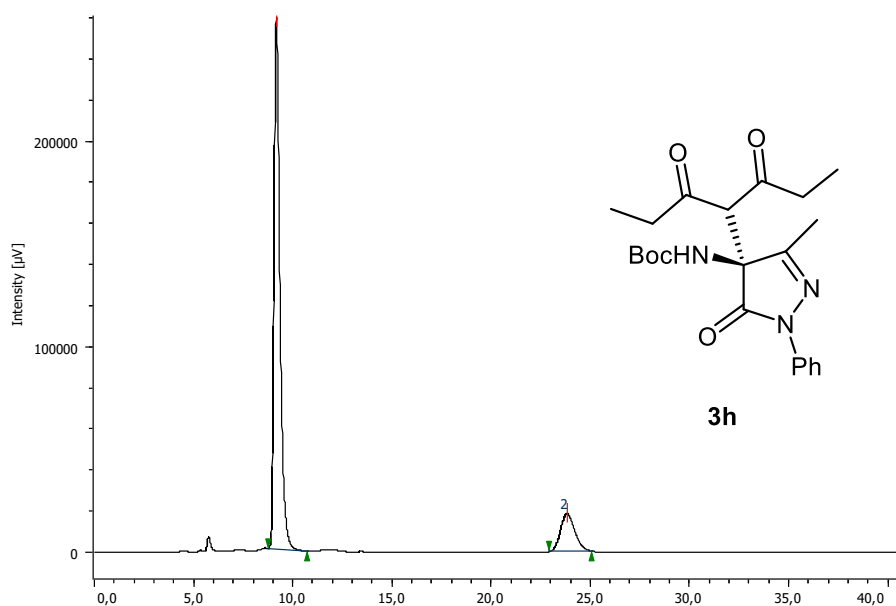
- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3h**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	9.425	8614606	529030	50.208	1.248
2	25.325	8543387	178745	49.792	1.197

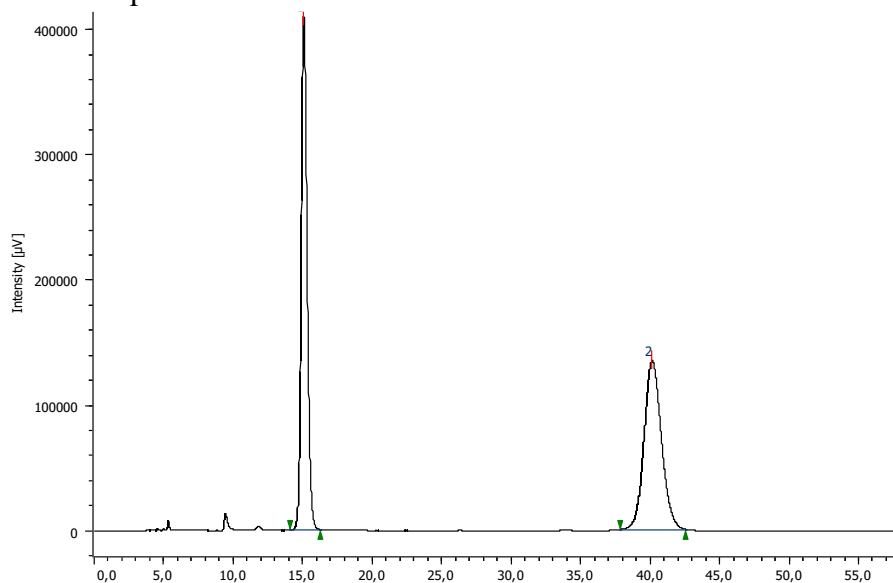
**HPLC Profile for 3h compound. Table 2, Entry 1, er: 85:15.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	9.167	5289670	257882	85.194	1.507
2	23.792	919285	18509	14.806	1.196

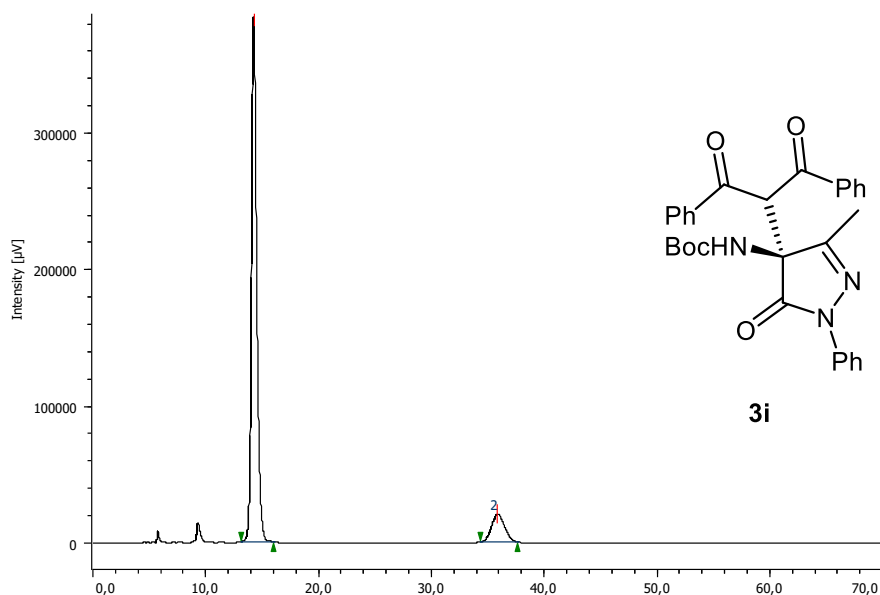
- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3i**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>15.075</b>	11929079	408849	<b>50.462</b>	1.166
2	<b>40.100</b>	11710796	134520	<b>49.538</b>	1.099

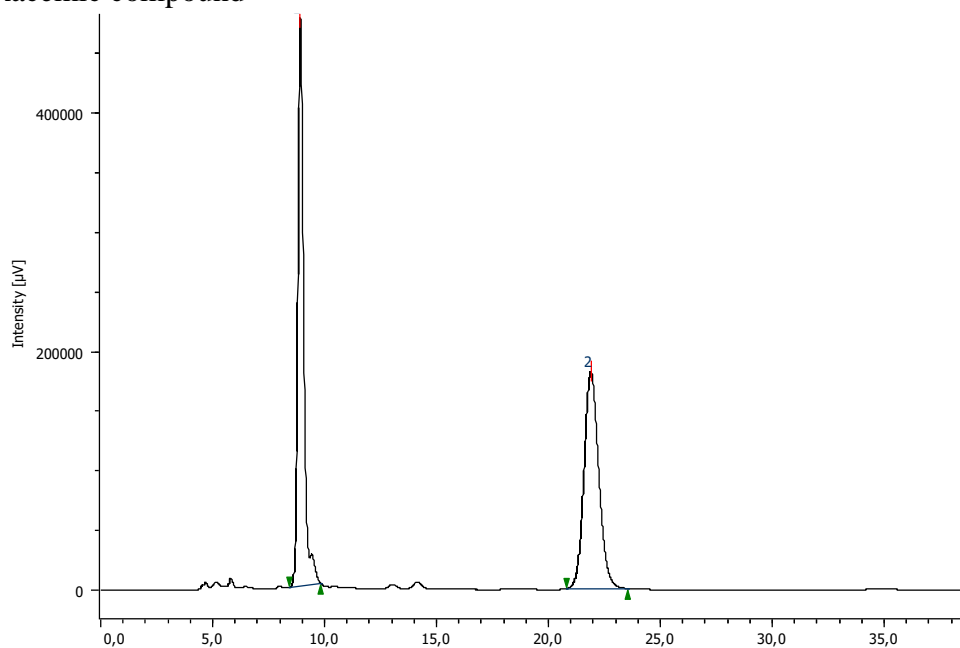
**HPLC Profile for 3i compound. Table 1, Entry 2, er: 88:12.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>14.242</b>	12504213	383289	<b>88.315</b>	1.271
2	<b>35.833</b>	1654430	20551	<b>11.685</b>	1.106

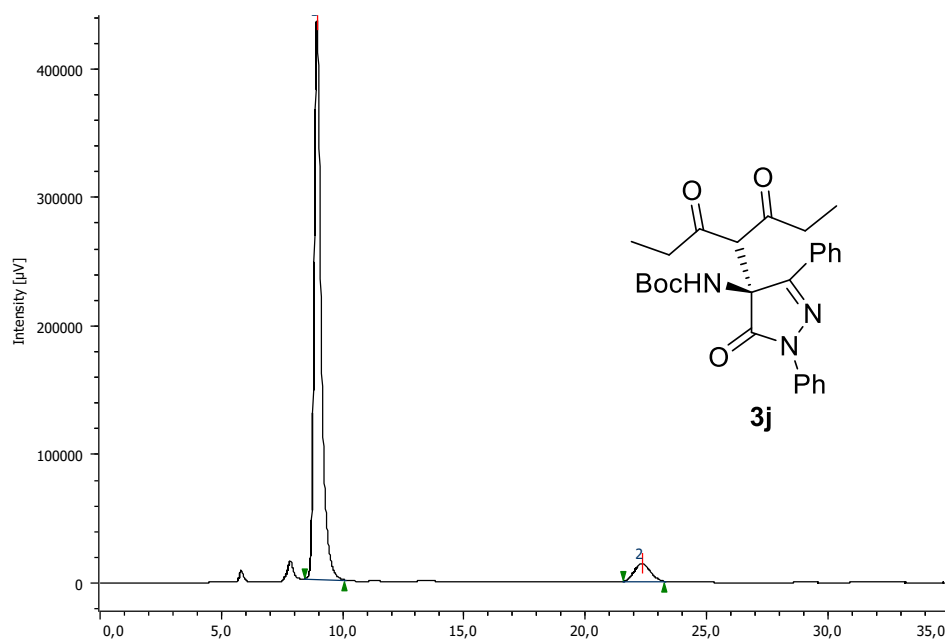
- ***tert*-Butyl (*S*)-(4-(3,5-dioxoheptan-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3j**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>8,908</b>	8625302	476025	<b>50,756</b>	1,599
2	<b>21,867</b>	8368363	182162	<b>49,244</b>	1,118

**HPLC Profile for 3j compound. Table 1, Entry 3, er: 88:12.**

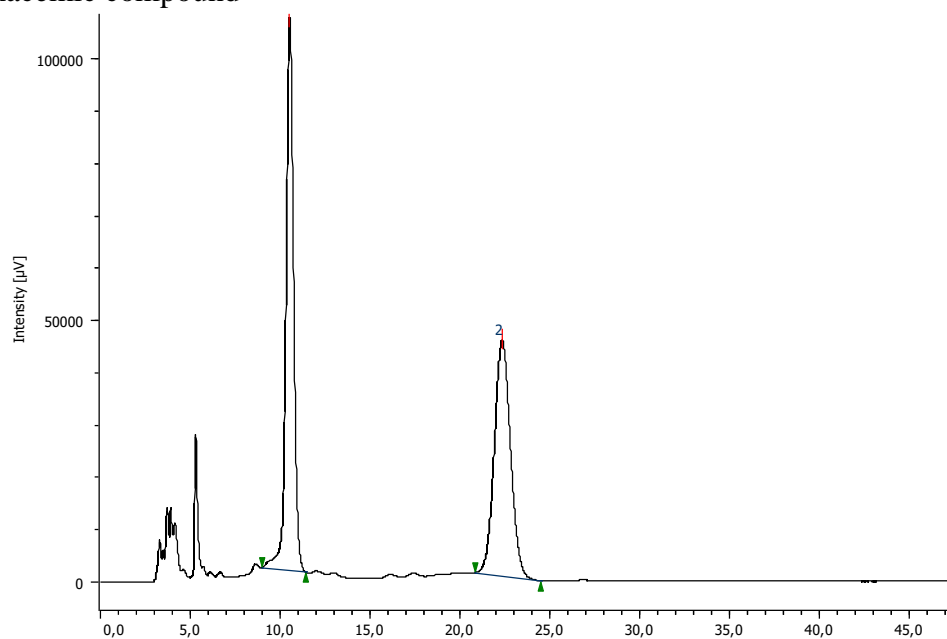


PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>8,933</b>	8714793	433523	<b>93,270</b>	1,473
2	<b>22,308</b>	628810	13809	<b>6,730</b>	1,093



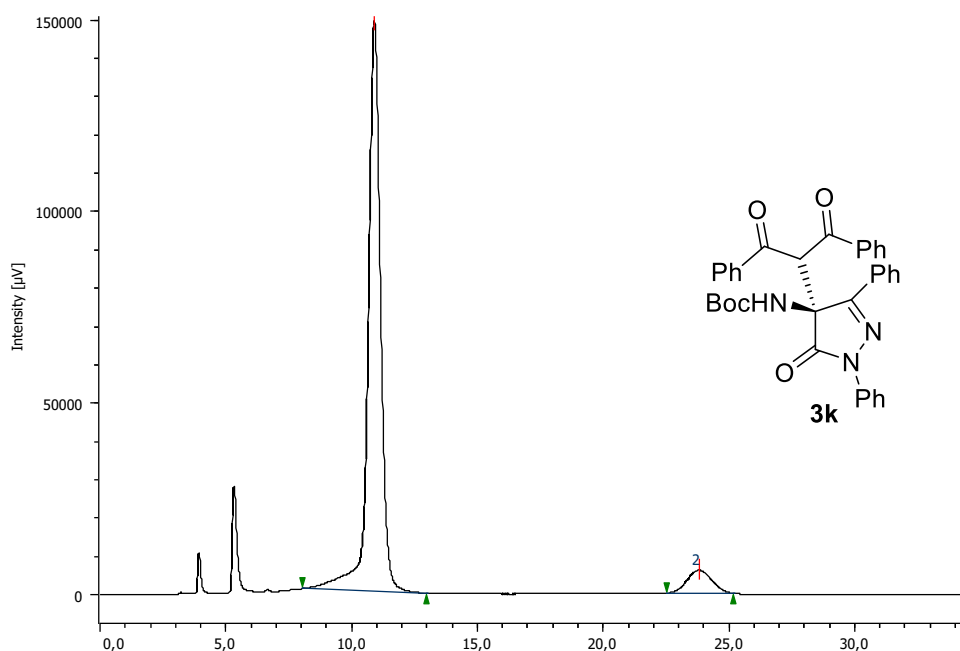
- ***tert*-Butyl (*S*)-(4-(1,3-dioxo-1,3-diphenylpropan-2-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3k).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>10,517</b>	3074291	105439	<b>52,217</b>	1,020
2	<b>22,317</b>	2813199	44943	<b>47,783</b>	1,060

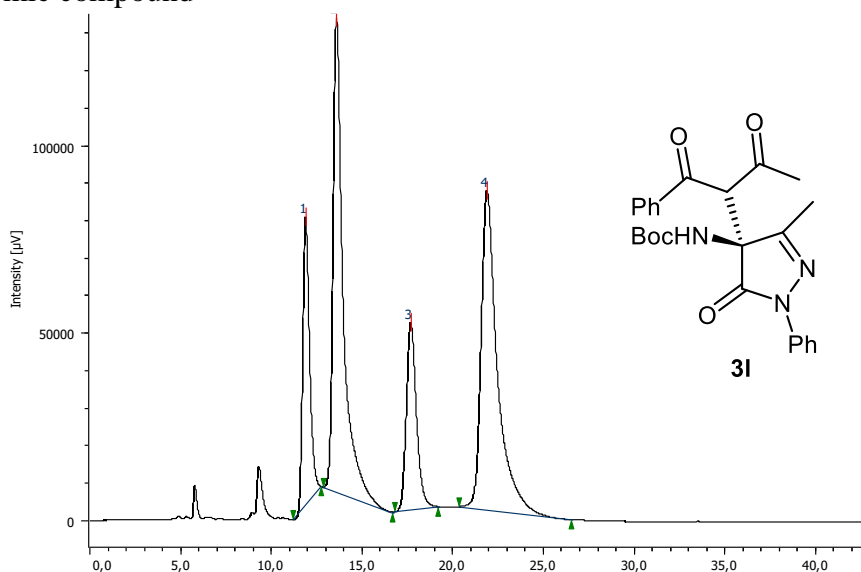
**HPLC Profile for 3k compound. Table 2, Entry 4, er: 88:12.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>10,892</b>	5164528	148763	<b>92,597</b>	1,004
2	<b>23,792</b>	412913	6017	<b>7,403</b>	1,032

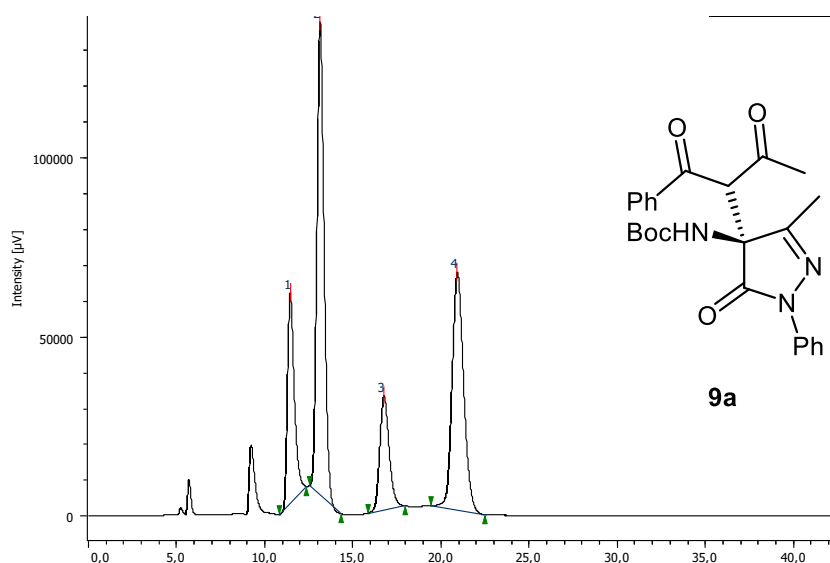
- ***tert*-Butyl ((*S*)-4-((*R*)-1,3-dioxo-1-phenylbutan-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**3l**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.875</b>	2014874	76910	<b>14.346</b>	1.403
2	<b>13.583</b>	4963195	126251	<b>35.338</b>	2.126
3	<b>17.667</b>	1914473	49873	<b>13.631</b>	1.256
4	<b>21.867</b>	5152481	84362	<b>36.685</b>	1.826

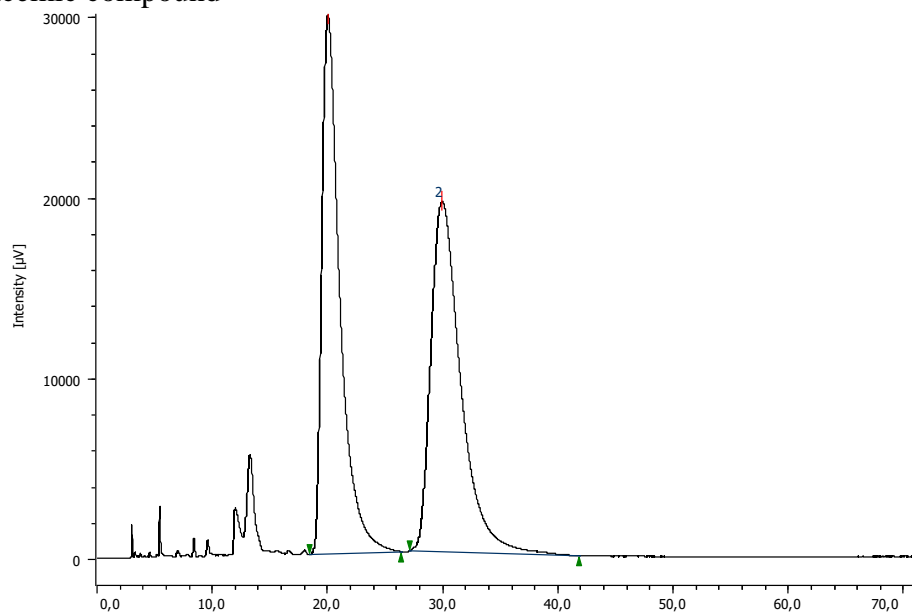
**HPLC Profile for 9a compound.** Table 2, Entry 5, mayor diastereomer er: **56:44**, minor diastereomer er: **57:43**, dr: **72:28**.



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>11.433</b>	1559264	58796	<b>16.456</b>	1.473
2	<b>13.125</b>	3723136	131734	<b>39.293</b>	1.188
3	<b>16.742</b>	1177777	31925	<b>12.430</b>	1.238
4	<b>20.900</b>	3015031	66299	<b>31.820</b>	1.159

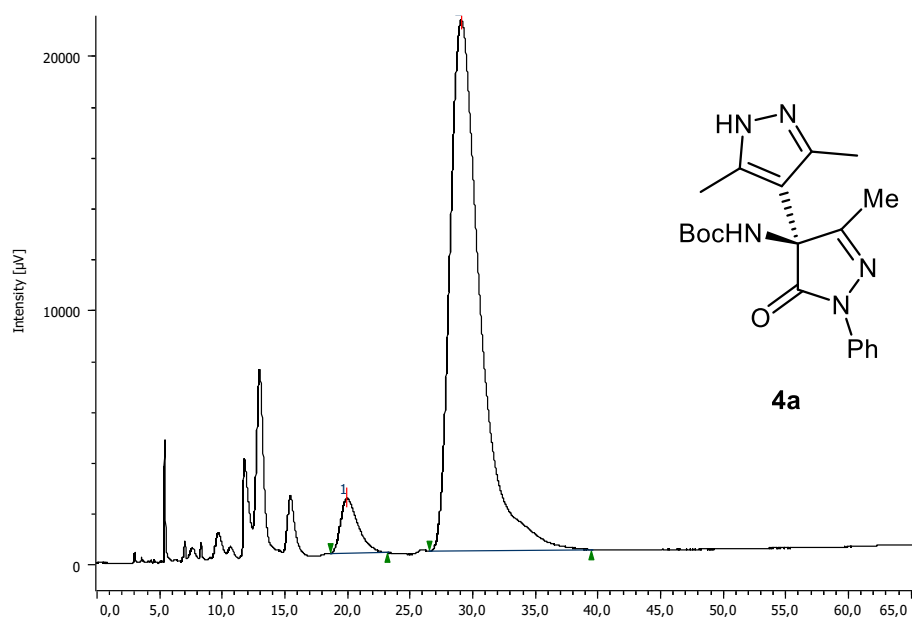
- ***tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4a).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>20.017</b>	3270382	29798	<b>48.354</b>	2.003
2	<b>29.900</b>	3493034	19375	<b>51.646</b>	1.664

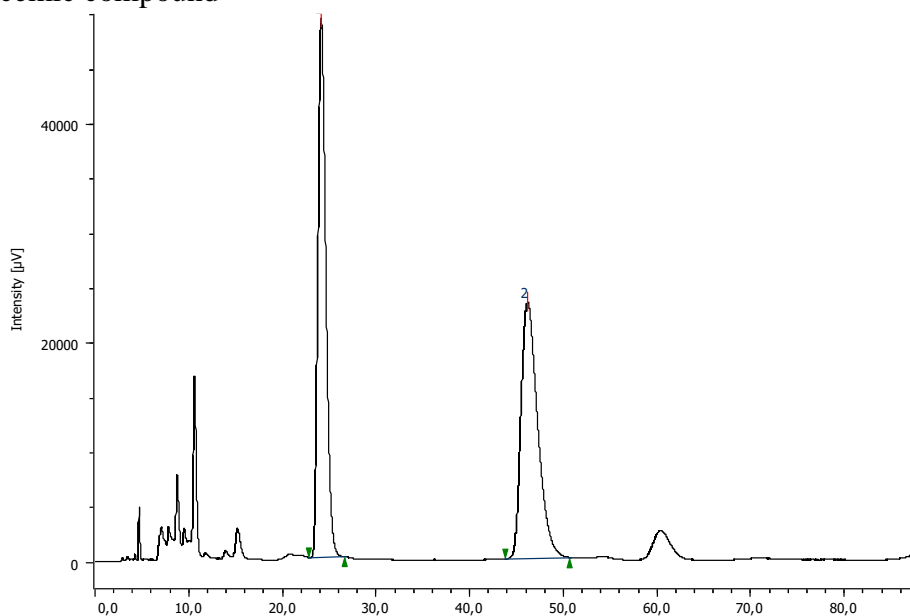
**HPLC Profile for 4a compound. Table 3, Entry 1, er: 6:94.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>19.950</b>	211642	2157	<b>5.740</b>	1.597
2	<b>29.050</b>	3475661	20826	<b>94.260</b>	1.852

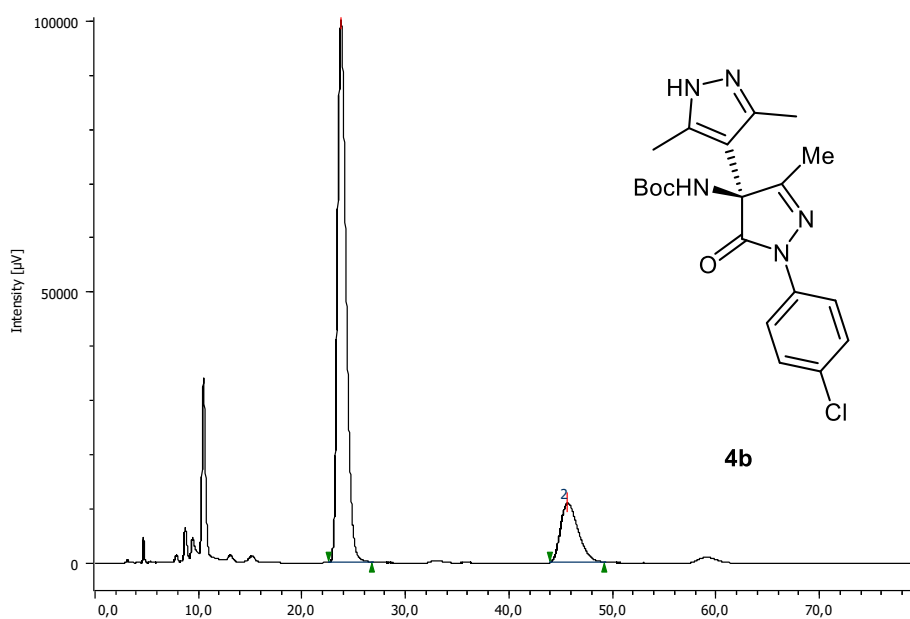
- ***tert*-Butyl (S)-(1'-(4-chlorophenyl)-3,3',5-trimethyl-5'-oxo-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4b).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>24.125</b>	2892464	49109	<b>50.021</b>	1.301
2	<b>46.133</b>	2890085	23356	<b>49.979</b>	1.473

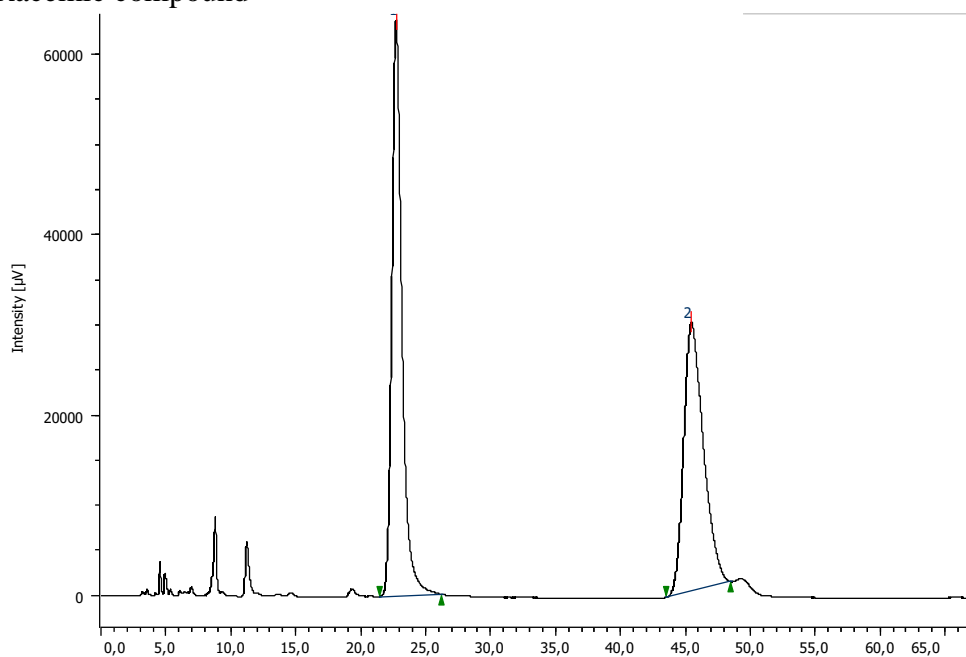
**HPLC Profile for 4b compound. Table 3, Entry 2, er: 82:18.**



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>23.733</b>	5770374	99770	<b>81.626</b>	1.348
2	<b>45.600</b>	1298919	10946	<b>18.374</b>	1.403

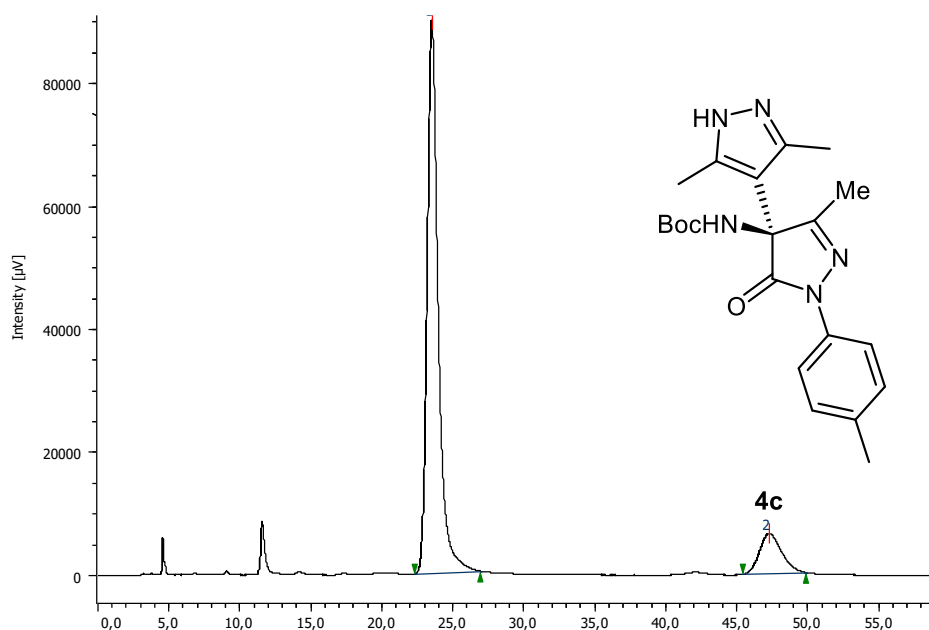
- *tert*-Butyl (*S*)-(3,3',5-trimethyl-5'-oxo-1'-(*p*-tolyl)-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4c**).

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	22,700	3206770	62887	50,486	1,266
2	45,425	3145023	29700	49,514	1,360

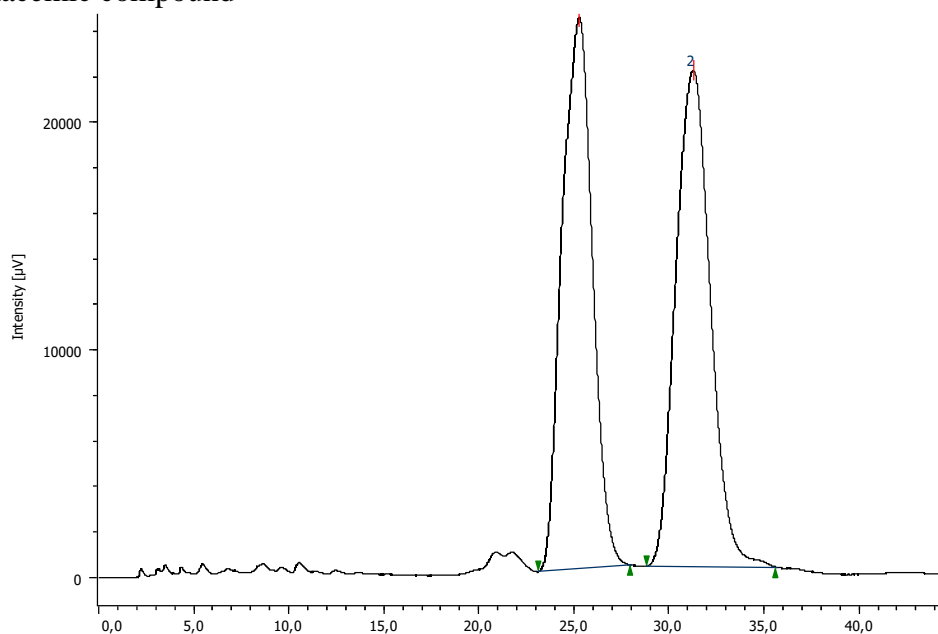
HPLC Profile for **4c** compound. Table 3, Entry 3, er: 88:12.



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	23,492	4908020	89812	88,051	1,382
2	47,217	666014	6319	11,949	1,289

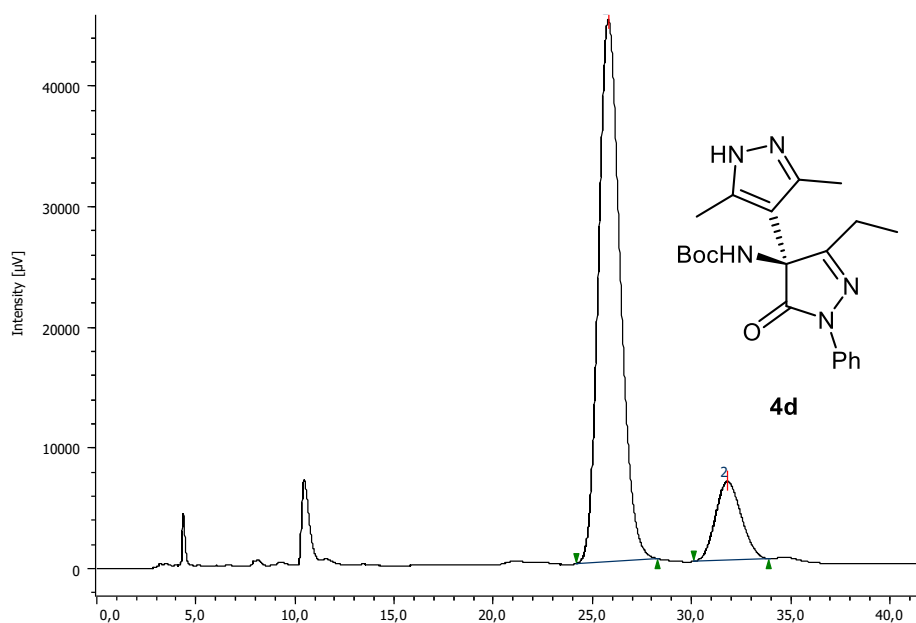
- ***tert*-Butyl (*S*)-(3'-ethyl-3,5-dimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4d).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	25,242	2685984	24175	49,291	1,011
2	31,242	2763309	21758	50,709	1,098

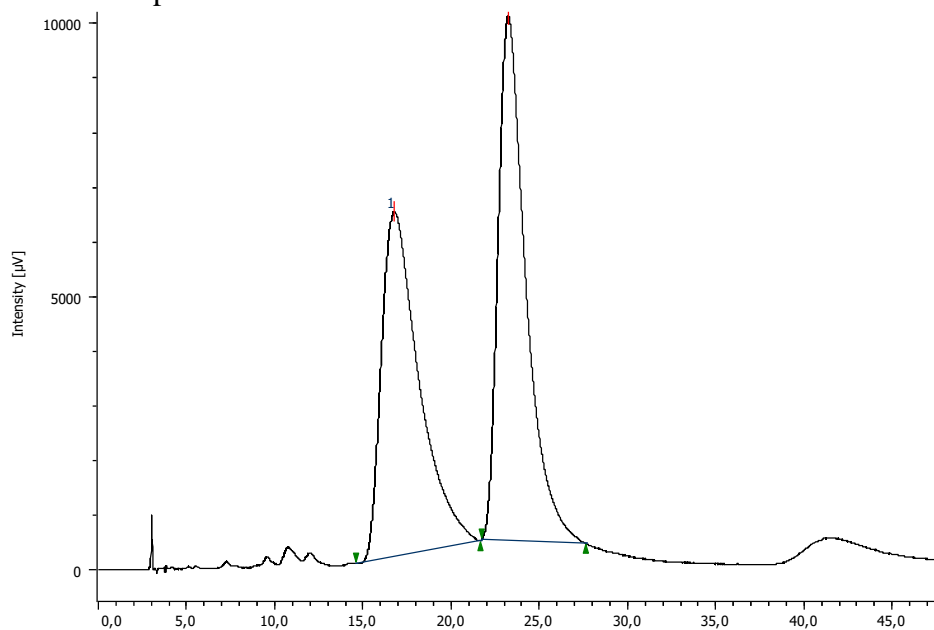
HPLC Profile for 4d compound. Table 3, Entry 4, er: 85:15.



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	25,767	3406140	44845	85,215	1,200
2	31,767	590969	6528	14,785	1,122

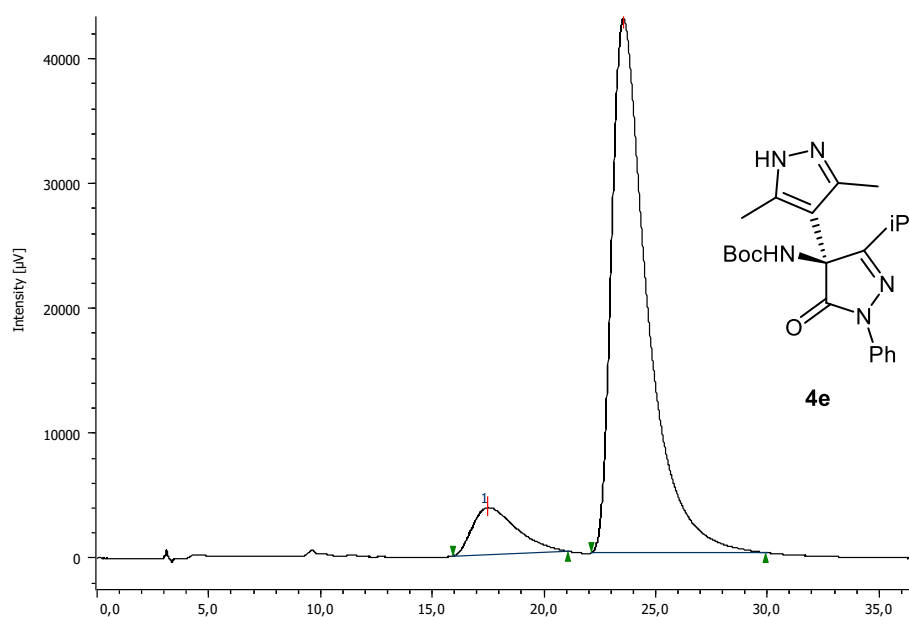
- ***tert*-Butyl (*S*)-(3'-isopropyl-3,5-dimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4e).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>16,775</b>	934391	6310	<b>48,848</b>	1,837
2	<b>23,200</b>	978461	9432	<b>51,152</b>	1,588

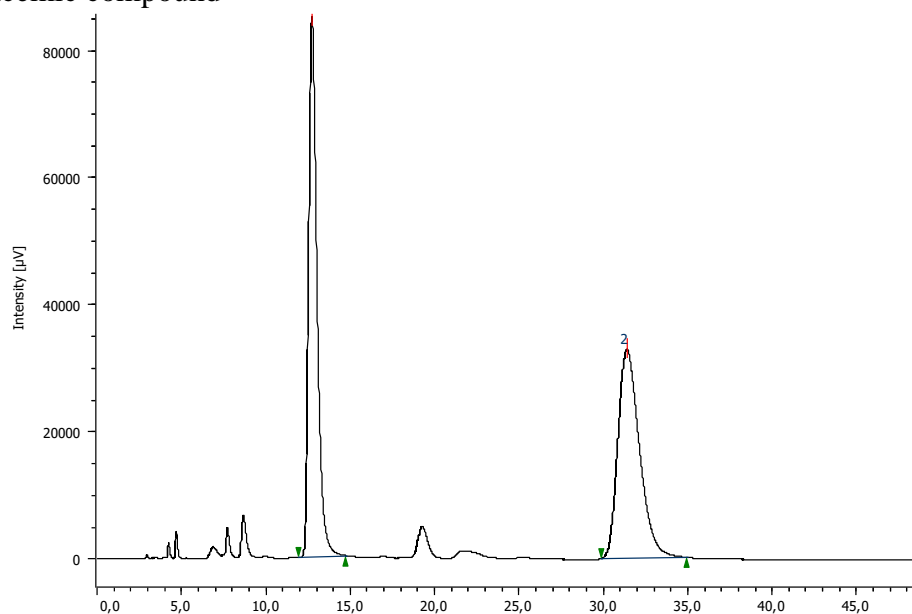
**HPLC Profile for 4e compound. Table 3, Entry 5, er: 10:90.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	Symmetry Factor
1	<b>17,475</b>	515449	3760	<b>9,790</b>	1,660
2	<b>23,533</b>	4749472	42690	<b>90,210</b>	1,998

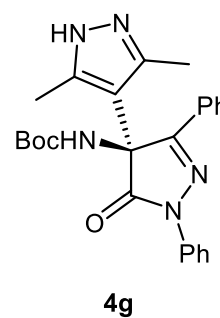
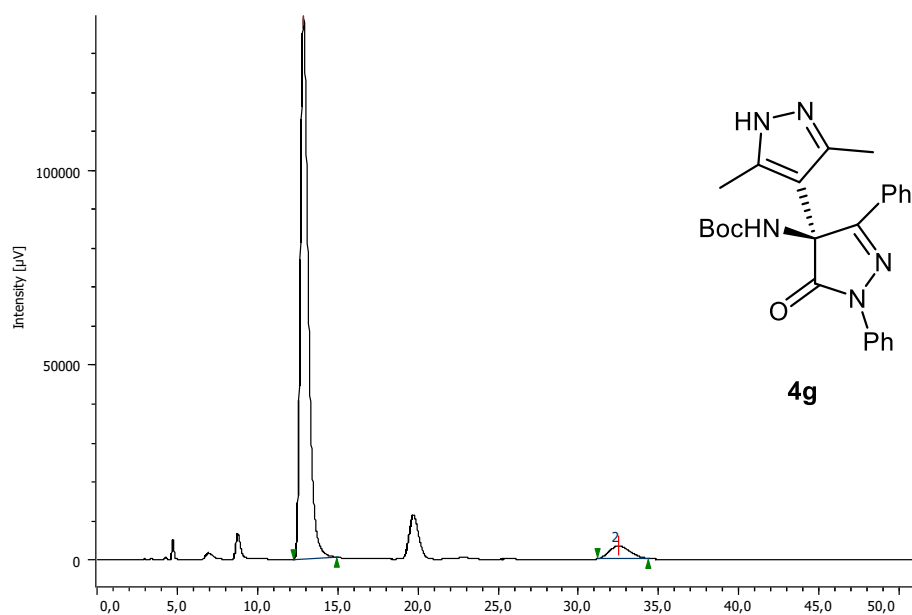
- *tert*-Butyl (*S*)-(3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (**4g**).

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>12.717</b>	2931594	84826	<b>50.086</b>	1.487
2	<b>31.350</b>	2921501	32808	<b>49.914</b>	1.364

HPLC Profile for **4g** compound. Table 3, Entry 6, er: **94:6**.

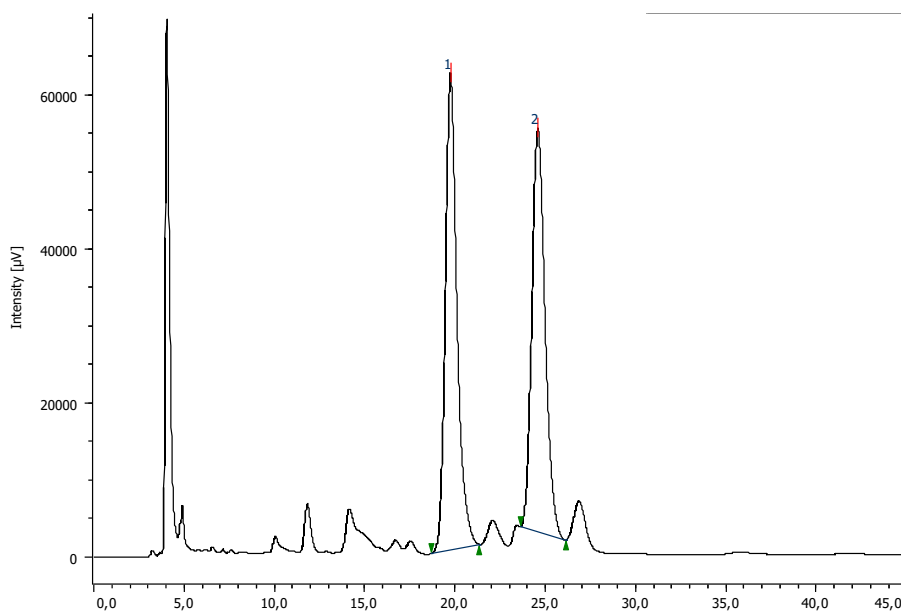


PeakNumber	t <sub>R</sub>	Area	Height	Area %	SymmetryFactor
1	<b>12.850</b>	4772695	138915	<b>94.217</b>	1.496
2	<b>32.458</b>	292947	3283	<b>5.783</b>	1.184



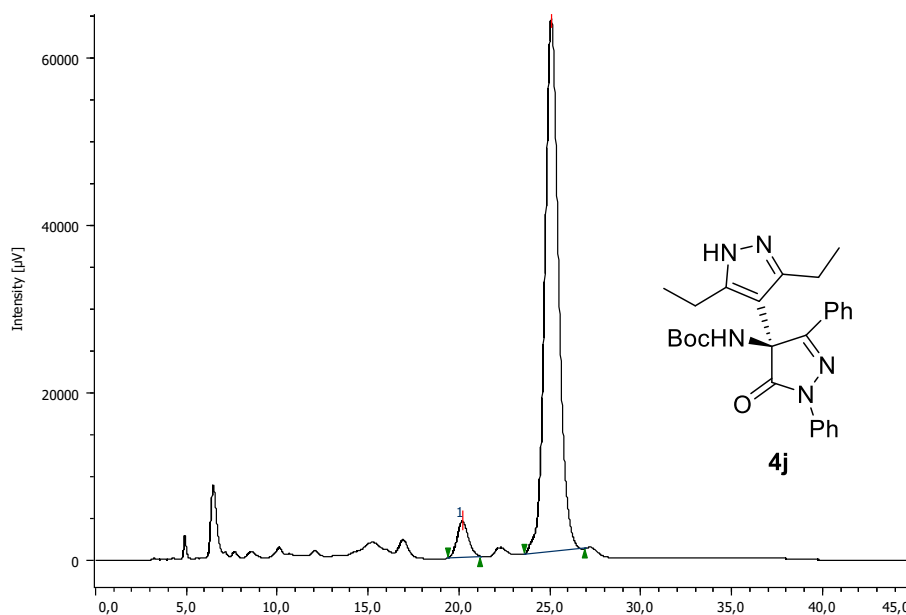
- ***tert*-Butyl (*S*)-(3,5-diethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (4j).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>19,725</b>	276801	61716	<b>51,125</b>	1,299
2	<b>24,550</b>	2646161	52232	<b>48,875</b>	1,205

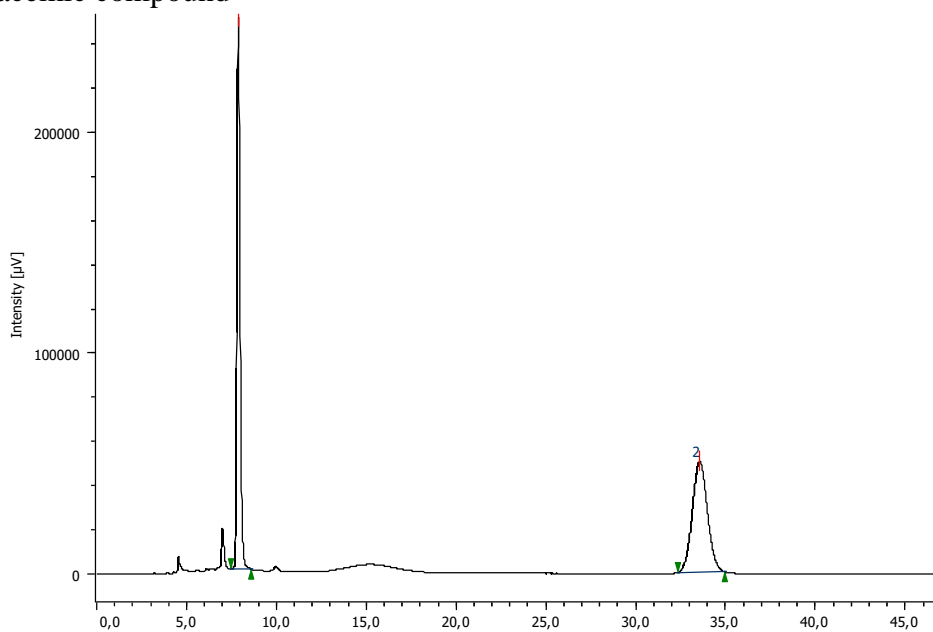
**HPLC Profile for 4j compound.** Table 3, Entry 7, er: **95:5**.



PeakNumbe	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>20,158</b>	185714	4311	<b>5,273</b>	1,125
2	<b>25,042</b>	3336290	63586	<b>94,727</b>	1,118

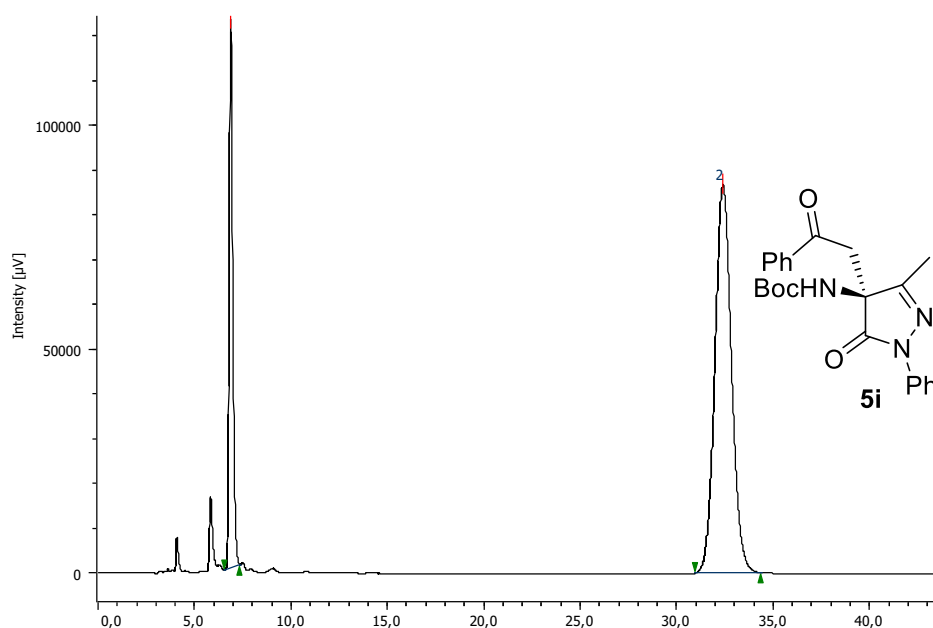
- ***tert*-Butyl (*S*)-(3-methyl-5-oxo-4-(2-oxo-2-phenylethyl)-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**5i**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>7,875</b>	3002905	249516	<b>50,441</b>	1,226
2	<b>33,517</b>	2950438	50333	<b>49,559</b>	1,058

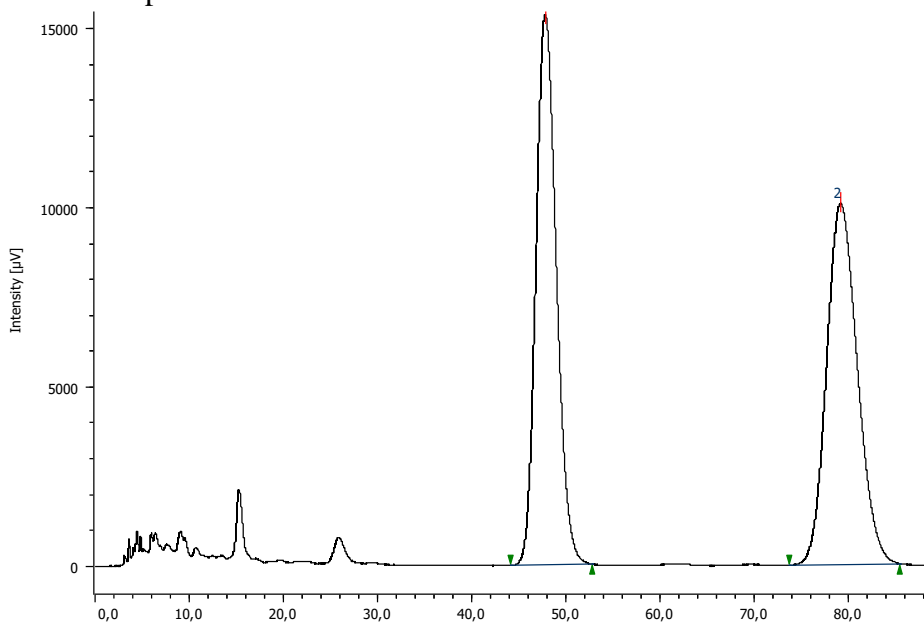
**HPLC Profile for 5i compound.** Table 3, Entry 8, er: **23:77**.



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>6,875</b>	1551170	122385	<b>23,092</b>	1,260
2	<b>32,358</b>	5166215	86600	<b>76,908</b>	1,074

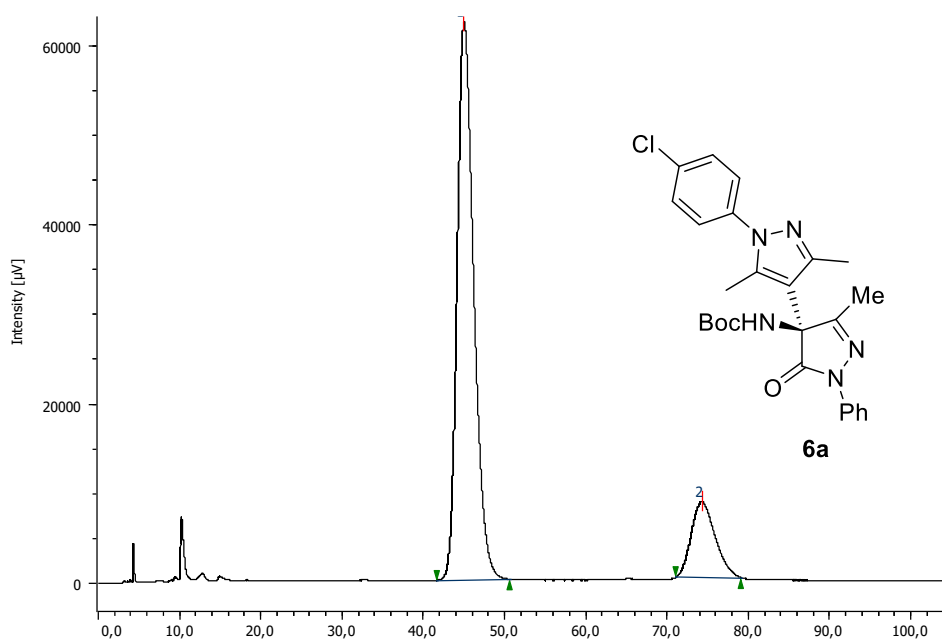
- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-3,3',5-trimethyl-5'-oxo-1'-phenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (6a).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>47,758</b>	2305688	15319	<b>50,132</b>	1,173
2	<b>79,067</b>	2293573	10070	<b>49,868</b>	1,157

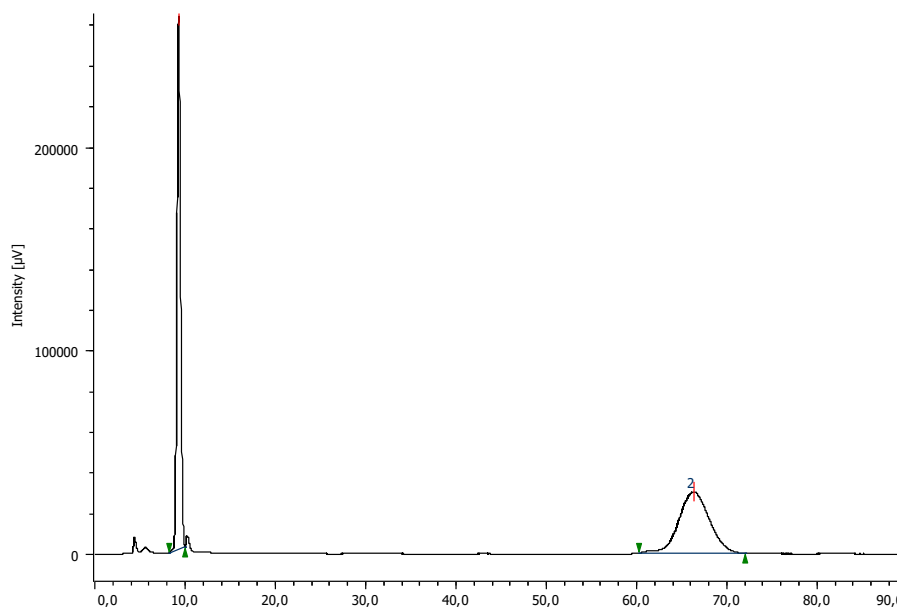
**HPLC Profile for 6a compound. Scheme 5, er: 84:16.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>44,967</b>	8828181	62101	<b>83,614</b>	1,296
2	<b>74,183</b>	1730125	8461	<b>16,386</b>	1,217

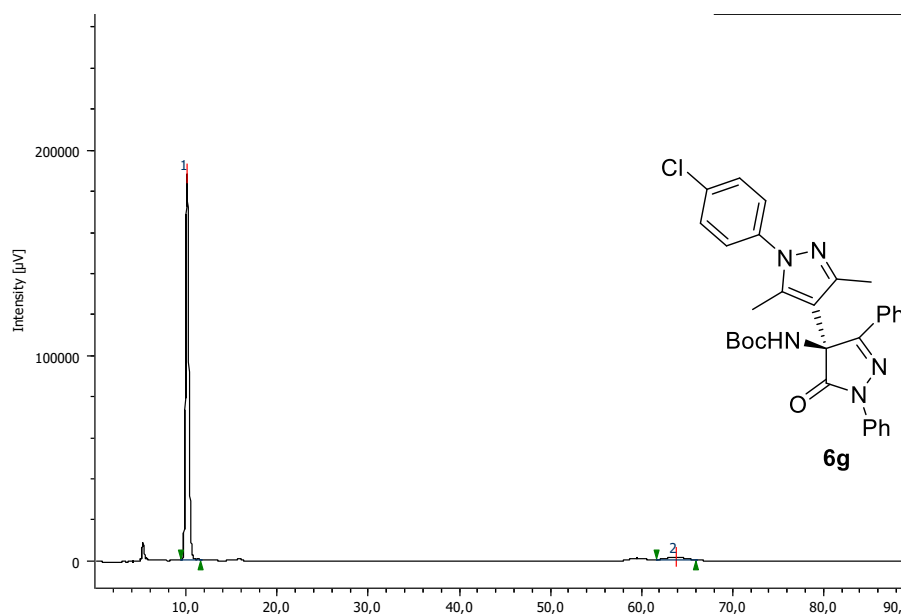
- ***tert*-Butyl (*S*)-(1-(4-chlorophenyl)-3,5-dimethyl-5'-oxo-1',3'-diphenyl-1',5'-dihydro-1*H*,4'*H*-[4,4'-bipyrazol]-4'-yl)carbamate (6g).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>9,275</b>	7170915	261657	<b>50,261</b>	1,120
2	<b>66,267</b>	7096443	30149	<b>49,739</b>	1,008

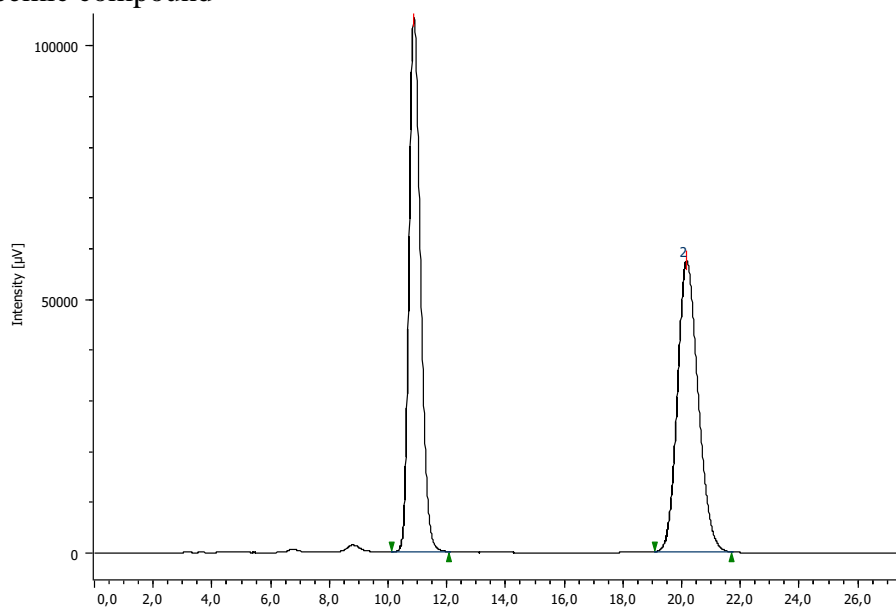
**HPLC Profile for 6g compound. Scheme 5, er: 96:4.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>10,075</b>	4591426	187683	<b>96,419</b>	1,124
2	<b>63,700</b>	170512	1149	<b>3,581</b>	1,007

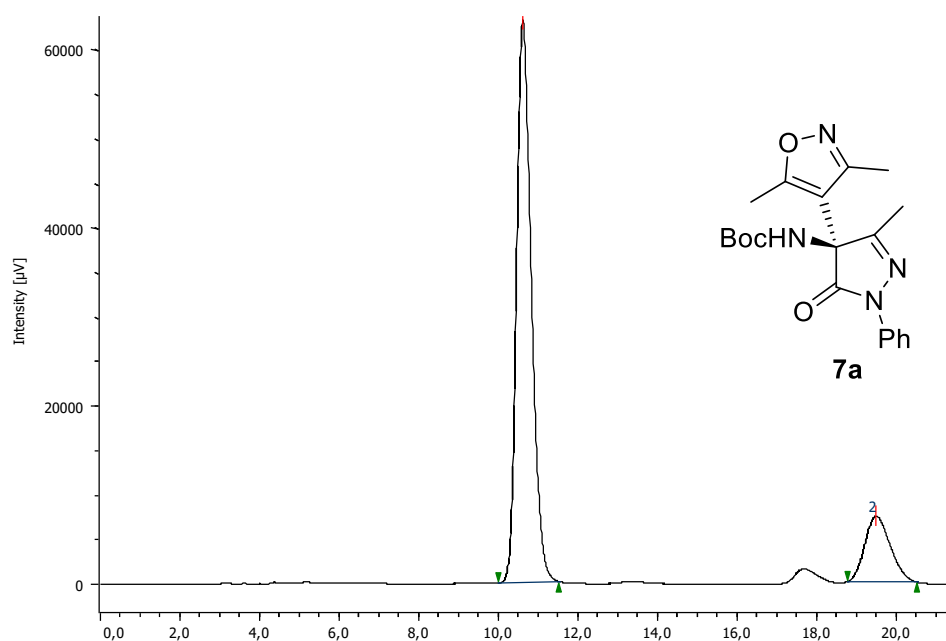
- ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (**7a**).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>10,867</b>	2829567	105132	<b>50,156</b>	1,257
2	<b>20,142</b>	2811934	57245	<b>49,844</b>	1,182

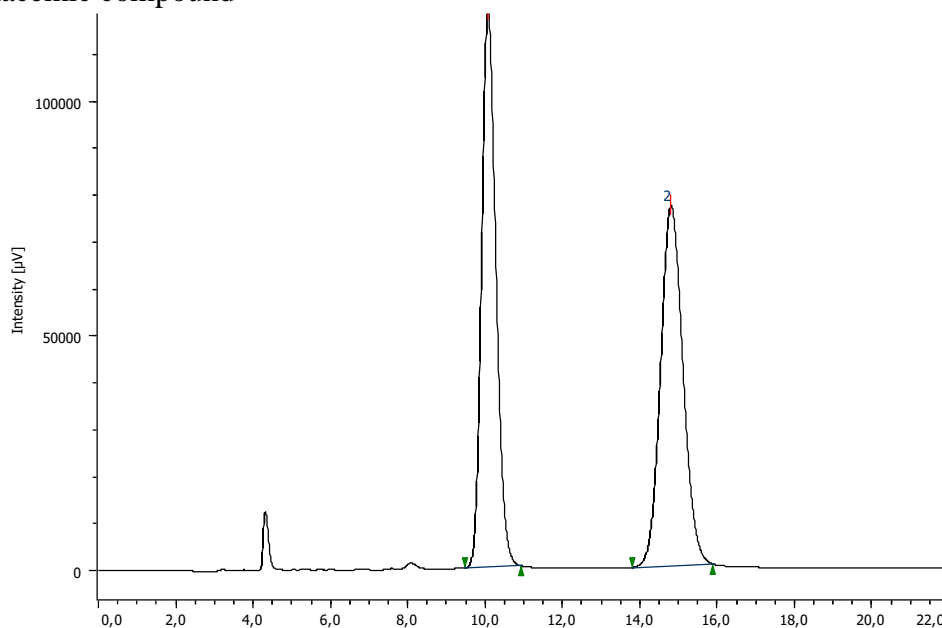
**HPLC Profile for 7a compound. Scheme 5, er: 83:17.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	<b>10,608</b>	1618696	63025	<b>83,159</b>	1,271
2	<b>19,475</b>	327817	7360	<b>16,841</b>	1,195

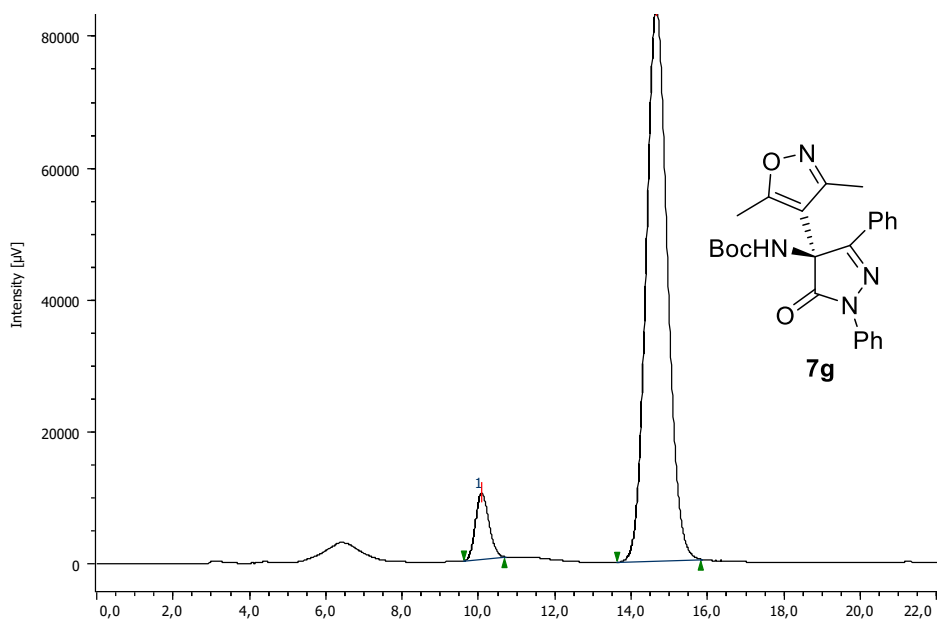
- ***tert*-Butyl (*S*)-(4-(3,5-dimethylisoxazol-4-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (7g).**

Racemic compound



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	10,067	3046066	118497	49,751	1,178
2	14,792	3076553	76594	50,249	1,099

**HPLC Profile for 7g compound. Scheme 5, er: 7:93.**



PeakNumber	t <sub>R</sub>	Area	Height	Area%	SymmetryFactor
1	10,075	246531	10010	7,067	1,139
2	14,633	3242092	83894	92,933	1,109

