BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

# Supporting Information

for

# Challenge *N*- versus *O*-six-membered annulation: $FeCl_3$-catalyzed synthesis of heterocyclic *N*,*O*-aminals

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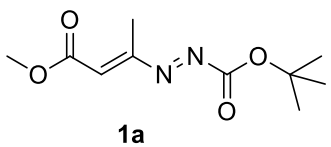
## General experimental information, synthetic procedures, analytical data and NMR spectra for the reported compounds

**Table of contents**

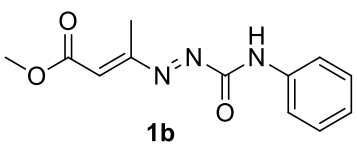
## 1. General information

All commercially available reagents and solvents were used without further purification. The control experiment to increase hemiaminal formation was conducted using ACN from Merck, ACS reagent purity grade (≥ 99.5%).The control experiment with benzyl alcohol was conducted using DCM distilled over $CaH_2$ and preserved on activated MS 4Å. 1,2-Diaza-1,3-dienes **1a**–**f** were synthesized as a mixture of *E*/*Z* isomers as previously reported.[1,2] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)•4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}•4H_2O$ in 10% sulphuric acid followed by heating on a hot plate. Melting points were determined in open capillary tubes with a Gallenkamp apparatus and are uncorrected. All $^1H$ NMR, $^{13}C$ NMR spectra and 2D experiments were recorded on a Bruker Avance at 400 and 100 MHz, respectively, using [$D_6$]DMSO as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet and br = broad signal, Ar, aromatic hydrogen. All coupling constants (*J* value) are given in hertz [Hz]. All the OH, NH and $NH_2$ exchanged with $D_2O$. The multiplicities in $^{13}C$ NMR spectra were obtained using HMQC experiments to aid in assignment (q = methyl, t = methylene, d = methine, s = quaternary). In some spectra double peaks are due to *E*/*Z* isomerism or to a mixture of diastereomers. High- and low-resolution mass spectrometry was performed on a Micromass Q-ToF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source.

## 2 Table S1: Substituted 1,2-diaza-1,3-dienes (DDs) 1a–f employed.[1]



**1a**



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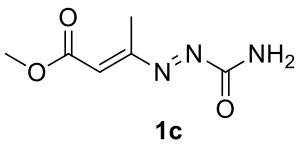
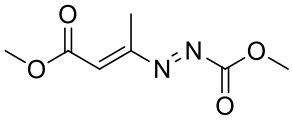


**1c**



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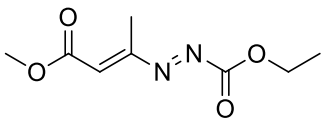
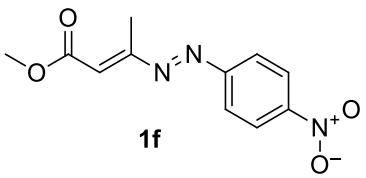
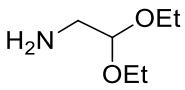


**1e**

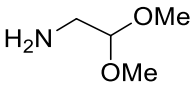


**1f**

## 3 Table S2: Nucleophiles 2a,b.

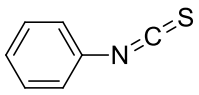


**2a**

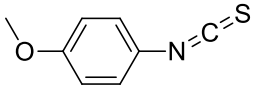


**2b**

## 4 Table S3: Substituted isothiocyanates 3a–f and isocyanates 3g,h employed.



**3a**



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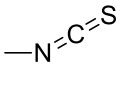

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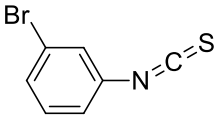

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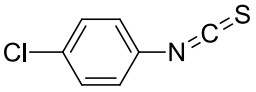
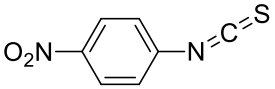
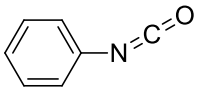


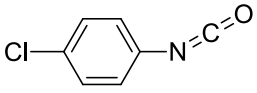
**3e**



**3f**



**3g**



**3h**

## 5 General procedures

*Sequential MCR procedure for the synthesis of substituted 2-thiohydantoins **4a–n**.*

In a similar manner,[3] to a solution of DD **1a–f** (1.0 mmol) in DCM (10.0 mL) at room temperature, α-aminoacetal **2a**,**b** (1.0 mmol) was added and the reaction mixture was stirred at room temperature until the disappearance of the corresponding DD and the formation of the *N*-adduct (TLC control, 0.50–2.0 h). Directly, to the reaction medium, 1.0 equiv of isothiocyanate **3a**–**f** was then added, and the reaction was left at room temperature under magnetic stirring (2–18 h). After the removal of the reaction solvent under reduced pressure, derivatives **4a**,**d**,**f**,**h–j**,**l–n** were obtained by column chromatography (eluting with a mixture of cyclohexane/ethyl acetate, from 60:40 to pure ethyl acetate) and crystallized from appropriate solvents. In the cases of derivatives **4b**,**c**,**e**,**g**,**k**, the products precipitated directly from the reaction mixture and were collected by filtration in vacuo. Then, their mother liquors were dried over anhydrous $Na_2SO_4$, the solvent removed under reduced pressure and the crudes chromatographed on silica gel column (eluting with a mixture of cyclohexane/ethyl acetate, from 60:40 to pure ethyl acetate). The pure products **4a–n**, were then crystallized from appropriate solvents.

*Sequential MCR procedure for the synthesis of substituted hydantoins **4o**–**r***

In a similar manner,[3] to a solution of DD **1a**,**e** (1.0 mmol) in EtOH (10.0 mL) at room temperature, α-aminoacetal **2a**,**b** (1.0 mmol) was added and the reaction mixture was stirred at room temperature until the disappearance of the corresponding DD and the formation of the *N*-adduct (TLC control, 0.50–2.0 h). Directly to the reaction medium, 1.0 equiv of isocyanate **3g,h** was then added, and the reaction was left at room temperature under magnetic stirring (18–30 h). Then, the solvent was removed under reduced pressure and the crude reaction mixture was chromatographed on silica gel column (eluting with a mixture of cyclohexane/ethyl acetate, from 60:40 to pure ethyl acetate). The obtained products **4o**–**r** were precipitated from ethyl acetate/light petroleum ether and recrystallized from appropriate solvents.

*Procedure for the synthesis of substituted heterocyclic N,O-aminals 5a–r and hemiaminals 6a–p.*

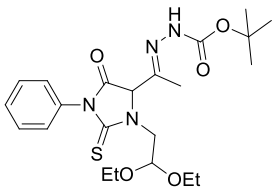
Derivative **4a–r** (1.0 mmol) was dissolved in DCM (10 mL) under magnetic stirring at room temperature. Then, $FeCl_3$ (0.3 mmol) was added and the reaction mixture was stirred until the disappearance of **4a**–**r** (0.5–4.0 h; TLC monitoring). After the removal of DCM under reduced pressure, the crude reaction mixture was chromatographed on silica gel column

(eluting with a mixture of cyclohexane/ethyl acetate, from 70:30 to 30:70) to separate **5a**–**r** from **6a**–**p** that were subjected to crystallization from appropriate solvents.

*Procedure for the conversion of 2-thiohydantoin **4j** into hemiaminal **6a** and N,O-aminal **5j**.*
Derivative **4j** (0.5 mmol, 218 mg) was dissolved in ACN (5 mL) under magnetic stirring at room temperature. Then, $FeCl_3$ (0.15 mmol, 24 mg) was added, and the reaction mixture was stirred for 96 h. After the removal of the solvent under reduced pressure, the crude reaction mixture was chromatographed on silica gel column (eluting with a mixture of cyclohexane/ethyl acetate, from 70:30 to 30:70) to separate the prevalent **6a** from **5j** that were subjected to crystallization from appropriate solvents.

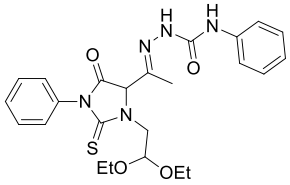
*Conversion of **4j** into **7** under nitrogen atmosphere.*
In a flame-dried Schlenk flask under nitrogen, containing a magnetic stirring bar and activated MS 4Å (330 mg), derivative **4j** (0.15 mmol, 66 mg), $FeCl_3$ (0.045 mmol, 7.3 mg), benzyl alcohol (0.225 mmol, 24 μL) and DCM (1.5 mL) were added and the reaction mixture was stirred under nitrogen for 24 h. The crude reaction mixture was filtered through a plug of silica gel, washing with ethyl acetate/cyclohexane (v:v; 60:40) and the resulting filtrate was evaporated under reduced pressure. The mixture was chromatographed on silica gel column, eluting with dichloromethane until all the remaining benzyl alcohol had been removed (TLC check). Then, DCM/$Et_2O$ (v:v; 90:10) was utilized, to obtain the pure product **7** as a yellow solid in 70% isolated yield.

## 6 Characterization of compounds 4a–r, 5a–r, 6a–p, and 7

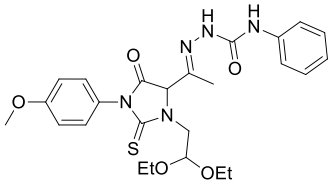


***tert*-Butyl 2-(1-(3-(2,2-diethoxyethyl)-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4a)**[3]:

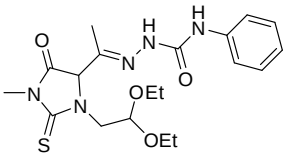
The characterization data of **4a** are available at: https://chemistry-europe.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejoc.202201053&file=ejoc202201053-sup-0001-misc_information.pdf.



**2-(1-(3-(2,2-Diethoxyethyl)-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)ethylidene)-*N*-phenylhydrazinecarboxamide (4b)**: reaction time: 8 h; yield 42%, (203.1 mg); white powder from DCM; m.p. 194-195 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.10-1.17 (m, 6H, 2 x $OCH_2CH_3$ ), 1.85 (s, 3H, $CH_3$ ), 3.48-3.69 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.11 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.88 (t, $J$ = 5.2 Hz, 1H, CH), 5.24 (s, 1H, CH), 7.02 (t, $J$ = 7.6 Hz, 1H, Ar), 7.29-7.37 (m, 4H, Ar), 7.47- 7.58 (m, 5H, Ar), 8.87 (s, 1H, NH, $D_2O$ exch.), 10.12 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.3, 15.1, 15.2, 48.1, 61.7, 62.1, 69.9, 98.8, 119.2, 122.5, 128.6, 128.7, 128.9, 133.5, 138.8, 140.1, 152.8, 170.0, 182.8; HRMS (ESI) calcd. for $C_{24}H_{30}N_5O_4S$ [M + $H^+$] 484.2013; found 484.2005.

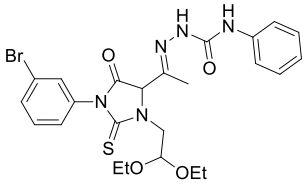


**2-(1-(3-(2,2-Diethoxyethyl)-1-(4-methoxyphenyl)-5-oxo-2 thioxo-imidazolidin-4-yl)ethylidene)-*N*-phenylhydrazinecarboxamide (4c)**: reaction time: 15 h; yield 77%, (395.5 mg); white powder from DCM; m.p. 188-189 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.10-1.16 (m, 6H, 2 x $OCH_2CH_3$ ), 1.83 (s, 3H, $CH_3$ ), 3.47-3.68 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 3.81 (s, 3H, $OCH_3$ ), 4.09 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.87 (t, $J$ = 5.2 Hz, 1H, CH), 5.20 (s, 1H, CH), 7.00-7.06 (m, 3H, Ar), 7.24-7.33 (m, 4H, Ar), 7.57 (d, $J$ = 8.8 Hz, 2H, Ar), 8.88 (s, 1H, NH, $D_2O$ exch.), 10.13 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.3, 15.1, 15.2, 48.1, 55.4, 61.7, 62.0, 69.8, 98.8, 114.1, 119.2, 122.5, 126.0, 128.6, 129.8, 138.8, 140.2, 152.9, 159.4, 170.2, 183.3; HRMS (ESI) calcd. for $C_{25}H_{32}N_5O_5S$ [M + $H^+$] 514.2119 found 514.2125.



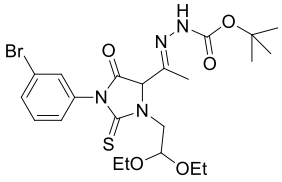
**2-(1-(3-(2,2-Diethoxyethyl)-1-methyl-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)-*N*-phenylhydrazinecarboxamide (4d)**:

reaction time: 18 h; yield 81%, (341.4 mg); white powder from cyclohexane/EtOAc; m.p. 140-141 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 1.07-1.13 (m, 6H, 2 x $OCH_2CH_3$ ), 1.70 (s, 3H, $CH_3$ ), 3.18 (s, 3H, $CH_3$ ), 3.41-3.64 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.06 (dd, $^{2}J$ = 14.4 Hz, $^{3}J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.80 (t, $J$ = 5.2 Hz, 1H, CH), 5.04 (s, 1H, CH), 7.01 (t, $J$ = 7.2 Hz, 1H, Ar), 7.30 (t, $J$ = 7.2 Hz, 2H, Ar), 7.56 (d, $J$ = 6.4 Hz, 2H, Ar), 8.85 (s, 1H, NH, $D_2O$ exch.), 10.08 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.1, 15.0, 15.1, 28.2, 61.6, 62.0, 69.2, 98.7, 119.1, 122.4, 128.5, 138.6, 140.1, 152.7, 170.4, 183.3; HRMS (ESI) calcd. for $C_{19}H_{27}N_5O_4SNa$ [M + $Na^+$]: 444.1676; found: 444.1686.



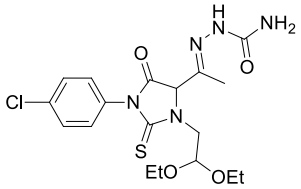
**2-(1-(1-(3-Bromophenyl)-3-(2,2-diethoxyethyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)-*N*-phenylhydrazinecarboxamide (4e)**:

reaction time: 16.5 h; yield 59%, (331.8 mg); white powder from DCM; m.p. 180-182 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 1.11-1.18 (m, 6H, 2 x $OCH_2CH_3$ ), 1.86 (s, 3H, $CH_3$ ), 3.48-3.69 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.10 (dd, $^{2}J$ = 14.4 Hz, $^{3}J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.86 (t, $J$ = 5.2 Hz, 1H, CH), 5.23 (s, 1H, CH), 7.02 (t, $J$ = 7.6 Hz, 1H, Ar), 7.31 (t, $J$ = 7.6 Hz, 2H, Ar), 7.41-7.44 (m, 1H, Ar), 7.50 (t, $J$ = 8.4 Hz, 1H, Ar), 7.58 (d, $J$ = 7.6 Hz, 2H, Ar), 7.68-7.70 (m, 2H, Ar), 8.87 (s, 1H, NH, $D_2O$ exch.), 10.12 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.4, 15.1, 15.2, 48.2, 61.7, 62.0, 70.0, 98.8, 119.2, 121.1, 122.5, 128.1, 128.6, 130.7, 131.5, 132.0, 134.9, 138.8, 140.0, 152.8, 169.8, 182.4; HRMS (ESI) calcd. for $C_{24}H_{29}BrN_5O_4S$ [M + $H^+$]: 562.1118; found: 562.1126.

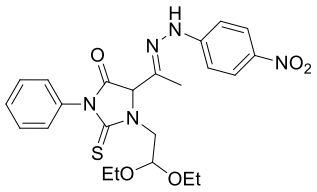


***tert*-Butyl 2-(1-(1-(3-bromophenyl)-3-(2,2-diethoxyethyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4f)**[3]:

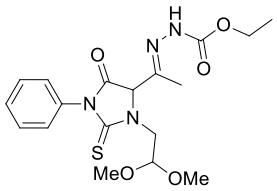
The characterization data of **4f** are available at: https://chemistry-europe.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejoc.202201053&file=ejoc202201053-sup-0001-misc_information.pdf.



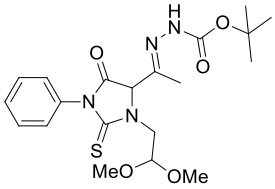
**2-{1-[1-(4-Chlorophenyl)-3-(2,2-diethoxyethyl)-5-oxo-2-thioxoimidazolidin-4-yl]ethylidene}hydrazine carboxamide (4g)**: reaction time: 12.5 h; yield 72%, (318.2 mg); white powder from EtOAc/MeOH/$Et_2O$; m.p. 126-128 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.02-1.16 (m, 6H, 2 x $OCH_2CH_3$), 1.77 (s, 3H, $CH_3$), 3.44-3.67 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.08 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.82 (t, $J$ = 5.2 Hz, 1H, CH), 5.07 (s, 1H, CH), 6.45 (brs, 2H, $NH_2$, $D_2O$ exch.), 7.40 (d, $J$ = 8.4 Hz, 2H, Ar), 7.59 (d, $J$ = 8.4 Hz, 2H, Ar), 9.69 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.3, 15.1, 15.2, 48.0, 61.7, 62.1, 64.9, 70.0, 98.8, 129.0, 130.6, 132.3, 133.6, 138.4, 156.6, 169.9, 183.4; HRMS (ESI) calcd. for $C_{18}H_{25}ClN_5O_4S$ [M + $H^+$]: 442.1310; found: 442.1329.



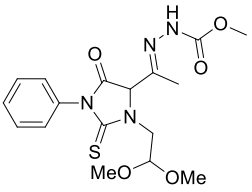
**1-(2,2-Diethoxyethyl)-5-(1-(2-(4-nitrophenyl)hydrazono)ethyl)-3-phenyl-2-thioxoimidazolidin-4-one (4h)**: reaction time: 10 h; yield 48%, (233.0 mg); light orange powder from EtOAc/$Et_2O$; m.p. 129-130 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.11 (t, $J$ = 7.2 Hz, $OCH_2CH_3$), 1.18 (t, $J$ = 7.2 Hz, $OCH_2CH_3$), 1.96 (s, 3H, $CH_3$), 3.46-3.70 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.21 (dd, $^2J$ = 14.0 Hz, $^3J$ = 4.0 Hz, 1H, $NCH_aH_b$), 4.82-4.85 (m, 1H, CH), 5.23 (s, 1H, CH), 7.28 (d, $J$ = 9.2 Hz, 2H, Ar), 7.35 (d, $J$ = 7.2 Hz, 2H, Ar), 7.45-7.54 (m, 3H, Ar), 8.17 (d, $J$ = 9.2 Hz, 2H, Ar), 10.35 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.8, 15.1, 15.2, 47.8, 61.8, 62.1, 69.8, 99.1, 111.9, 125.8, 128.6, 128.9, 129.0, 133.5, 139.1, 140.6, 150.7, 170.1, 182.6; HRMS (ESI) calcd for $C_{23}H_{28}N_5O_5S$ : [M + $H^+$]: 486.1806; found: 486.1815.



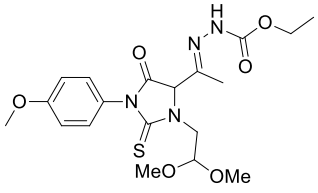
**Ethyl 2-(1-(3-(2,2-dimethoxyethyl)-1-(4-methoxyphenyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4i)**: reaction time: 6 h; yield 78%, (318.6 mg); white solid from DCM; m.p 150 °C; $^1$H NMR (400 MHz, , DMSO-$d_6$): δ 1.25 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$ ), 1.82 (s, 3H, $CH_3$ ), 3.29 (s, 3H, $OCH_3$ ), 3.33 (s, 3H, $OCH_3$ ), 3.60 (dd, $^2J$ = 14.0 Hz, $^3J$ = 5.6 Hz, 1H, $NCH_aH_b$), 4.03 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.17 (q, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 4.69 (t, $J$ = 5.2 Hz, 1H, CH), 5.12 (s, 1H, CH), 7.34 (d, $J$ = 8.4 Hz, 2H, Ar), 7.46-7.53 (m, 3H, Ar), 10.37 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.7, 14.5, 47.3, 53.7, 53.8, 60.7, 69.8, 100.8, 128.6, 129.8, 129.0, 133.4, 143.9, 153.9, 169.9, 182.6; HRMS (ESI) calcd. for $C_{18}H_{25}N_4O_5S$ : [M + $H^+$]: 409.1540; found: 409.1527.



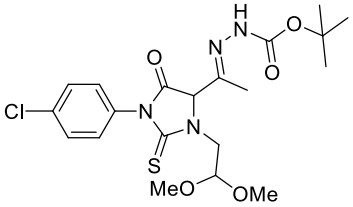
***tert*-Butyl 2-(1-(3-(2,2-dimethoxyethyl)-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4j)**: reaction time: 13.5 h; yield 58%, (253.2 mg); white powder from DCM; m.p. 163-164 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 1.47 (s, 9H, Bu$^t$), 1.81 (s, 3H, $CH_3$ ), 3.30 (s, 3H, $OCH_3$), 3.33 (s, 3H, $OCH_3$), 3.55 (dd, $^2J$ = 14.4 Hz, $^3J$ = 6.0 Hz, 1H, NC*H*$_a$H$_b$), 4.07 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.4 Hz, 1H, NCH$_a$*H*$_b$,), 4.69 (t, 1H, *J*= 5.2 Hz, CH), 5.10 (s, 1H, CH), 7.33 (d, *J* = 7.2 Hz, 2H, Ar), 7.44-7.53 (m, 3H, Ar), 10.08 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.7, 28.0, 47.1, 53.7, 53.8, 69.8, 79.8, 100.8, 128.6, 128.8, 128.9, 133.5, 143.1, 152.7, 169.9, 182.7; HRMS (ESI) calcd. for $C_{20}H_{29}N_4O_5S$ [M + H$^+$]: 437.1853; found: 437.1865.



**Methyl 2-(1-(3-(2,2-dimethoxyethyl)-5-oxo-1-phenyl-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4k)**: reaction time: 2 h; yield 73%, (287.9 mg); white solid from DCM; m.p 125-126 °C; $^1$H NMR (400 MHz, , DMSO-*d*$_6$): δ 1.81 (s, 3H, $CH_3$ ), 3.29 (s, 3H, $OCH_3$ ), 3.33 (s, 3H, $OCH_3$ ), 3.60 (dd, $^2J$ = 14.4 Hz, $^3J$ = 5.6 Hz, 1H, NC*H*$_a$H$_b$), 3.70 (s, 3H, $OCH_3$), 4.00 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, NCH$_a$*H*$_b$), 4.69 (t, *J* = 5.2 Hz, 1H, CH), 5.10 (s, 1H, CH), 7.33 (d, *J* = 6.8 Hz, 2H, Ar), 7.45-7.54 (m, 3H, Ar), 10.41 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.6, 47.3, 52.1, 53.7, 53.9, 69.9, 100.8, 128.6, 129.9, 129.0, 133.5, 144.0, 154.4, 169.9, 182.9; HRMS (ESI) calcd. for $C_{17}H_{23}N_4O_5S$ [M + H$^+$]: 395.1384; found: 395.1391.

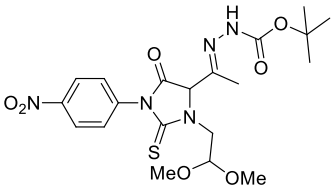


**Ethyl 2-(1-(3-(2,2-dimethoxyethyl)-1-(4-methoxyphenyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4l)**: reaction time: 8 h; yield 58%, (254.3 mg); white solid from DCM; m.p 155 °C; $^1$H NMR (400 MHz, , DMSO-*d*$_6$): δ 1.24 (t, *J* = 7.2 Hz, 3H, $OCH_2CH_3$ ), 1.80 (s, 3H, $CH_3$ ), 3.28 (s, 3H, $OCH_3$ ), 3.32 (s, 3H, $OCH_3$ ), 3.57 (dd, $^2J$ = 14.0 Hz, $^3J$ = 5.6 Hz, 1H, NC*H*$_a$H$_b$), 3.80 (s, 3H, $OCH_3$) 4.01 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, NCH$_a$*H*$_b$), 4.16 (q, *J* = 7.2 Hz, 3H, $OCH_2CH_3$), 4.68 (t, *J* = 5.2 Hz, 1H, CH), 5.07 (s, 1H, CH), 7.03 (d, *J* = 9.2 Hz, 2H, Ar), 7.23 (d, *J* = 8.8 Hz, 2H, Ar), 10.35 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.6, 14.5, 47.3, 53.7, 53.8, 55.4, 60.7, 69.7, 100.8, 114.1, 126.0, 129.8, 143.9, 153.6, 159.4, 170.1, 183.3; HRMS (ESI) calcd. for $C_{19}H_{27}N_4O_6S$ [M + H$^+$]: 439.1646; found: 439.1631.



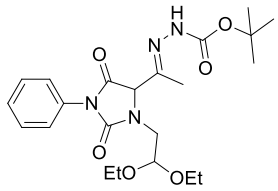
***tert*-Butyl 2-(1-(1-(4-chlorophenyl)-3-(2,2-dimethoxyethyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)hydrazine-carboxylate (4m)**[3]:

The characterization data of **4m** are available at: https://chemistry-europe.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejoc.202201053&file=ejoc202201053-sup-0001-misc_information.pdf.



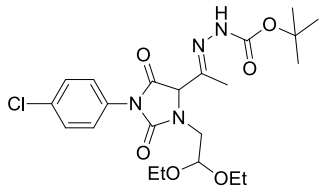
***tert*-Butyl 2-(1-(3-(2,2-dimethoxyethyl)-1-(4-nitrophenyl)-5-oxo-2-thioxoimidazolidin-4-yl)ethylidene)hydrazine-carboxylate (4n)**:

reaction time: 14.5 h; yield 63% (303.3 mg); beige powder from DCM/light petroleum ether; m.p. 150-154 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.45 and 1.47 (2s, 9H, Bu$^t$), 1.83 (s, 3H, $CH_3$), 3.31 (s, 3H, $OCH_3$), 3.34 (s, 3H, $OCH_3$), 3.56 (dd, $^2J$ = 14.4 Hz, $^3J$ = 6.4 Hz, 1H, NC$H_a$H$_b$), 4.10 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.4 Hz, 1H, NCH$_a$$H_b$,), 4.68 (t, $J$ = 5.6 Hz, 1H, CH), 5.12 (s, 1H, CH), 7.71 (d, $J$ = 9.2 Hz, 2H, Ar), 8.37 (d, $J$ = 8.8 Hz, 2H, Ar), 10.09 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.9, 27.9, 28.0, 47.1, 53.8, 69.9, 79.8, 100.8, 124.0, 130.1, 138.9, 147.2, 152.7, 169.5 181.6; HRMS (ESI) calcd. for $C_{20}H_{28}N_5O_7S$ [M + H$^+$]: 482.1704; found: 482.1716.

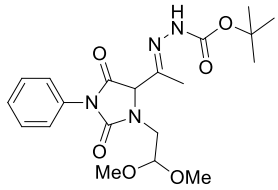


***tert*-Butyl 2-(1-(3-(2,2-diethoxyethyl)-2,5-dioxo-1-phenylimidazolidin-4-yl)ethylidene)hydrazine-carboxylate (4o)**:

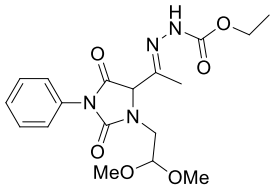
reaction time: 25 h; yield 30%, (134.5 mg); white powder from $Et_2O$/light petroleum ether; m.p. 124-125 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.09-1.14 (m, 6H, 2 x $OCH_2CH_3$ ), 1.46 (s, 9H, Bu$^t$), 1.80 (s, 3H, $CH_3$ ), 3.23 (dd, $^2J$ = 14.4 Hz, $^3J$ = 5.6 Hz, 1H, NC$H_a$H$_b$), 3.45-3.64 (m, 5H, 2 x $OCH_2CH_3$ and NCH$_a$$H_b$), 4.64 (t, 1H, $J$ = 5.6 Hz, CH), 4.88 (s, 1H, CH), ), 7.36-7.44 (m, 3H, Ar), 7.50 (t, $J$ = 7.2 Hz, 2H, Ar), 9.99 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 12.4, 15.1, 15.2, 28.0, 44.0, 61.6, 61.7, 67.2, 79.6, 99.4, 126.4, 128.2, 128.8, 131.6, 144.0, 152.7, 155.0, 168.7; HRMS (ESI) calcd. for $C_{22}H_{32}N_4O_6Na$ [M + Na$^+$]; 471.2214; found: 471.2216.



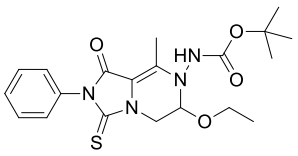
***tert*-Butyl 2-(1-(1-(4-chlorophenyl)-3-(2,2-diethoxyethyl)-2,5-dioxoimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4p)**: reaction time: 18 h; yield 56%, (270.5 mg); white powder from $Et_2O$ /Petroleum ether; m.p. 147-148 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 1.09-1.14 (m, 6H, 2 x $OCH_2CH_3$ ), 1.46 (s, 9H, Bu$^t$), 1.80 (s, 3H, $CH_3$ ), 3.23 (dd, $^2J$ = 14.8 Hz, $^3J$ = 5.6 Hz, 1H, $NCH_aH_b$,), 3.45-3.64 (m, 5H, 2 x $OCH_2CH_3$ and $NCH_aH_b$), 4.63 (t, 1H, *J* = 5.2 Hz, CH), 4.88 (s, 1H, CH), ), 7.43 (d, *J* = 8.8 Hz, 2H, Ar), 7.58 (d, *J* = 8.8 Hz, 2H, Ar), 10.00 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.4, 15.1, 15.2, 28.0, 44.1, 61.5, 61.7, 67.1, 79.6, 99.4, 128.2, 128.9, 130.5, 132.5, 143.9, 152.7, 154.9, 168.6; HRMS (ESI) calcd. for $C_{22}H_{32}ClN_4O_6$ [M + H$^+$]: 483.2005; found: 483.2009.



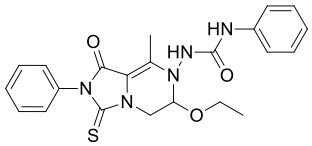
***tert*-Butyl 2-(1-(3-(2,2-dimethoxyethyl)-2,5-dioxo-1-phenylimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4q)**: reaction time: 22 h; yield 48%, (201.8 mg); white powder from $Et_2O$/Petroleum ether; m.p. 151-152 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 1.48 (s, 9H, Bu$^t$), 1.82 (s, 3H, $CH_3$ ), 3.28 (s, 3H, $OCH_3$), 3.31 (s, 3H, $OCH_3$), 3.34 (d, *J* = 3.6 Hz, 1H, $NCH_aH_b$), 3.53 (dd, $^2J$ = 14.4 Hz, $^3J$ = 4.8 Hz, 1H, $NCH_aH_b$), 4.52 (t, 1H, *J* = 5.2 Hz, CH), 4.90 (s, 1H, CH), 7.38-7.45 (m, 3H, Ar), 7.51 (t, *J* = 7.2 Hz, 2H, Ar), 10.02 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.4, 28.0, 43.2, 53.3, 53.4, 67.2, 79.7, 100.2, 126.6, 128.2, 128.9, 131.8, 144.4, 152.8, 155.2, 168.7; HRMS (ESI) calcd. for $C_{20}H_{29}N_4O_6$ [M + H$^+$]: 421.2082; found: 421.2075.



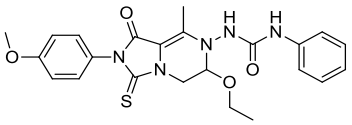
**Ethyl 2-(1-(3-(2,2-dimethoxyethyl)-2,5-dioxo-1-phenylimidazolidin-4-yl)ethylidene)hydrazinecarboxylate (4r)**: reaction time: 30 h; yield 45% (176.6 mg); white powder from $Et_2O$/light petroleum ether; m.p 125-126 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 1.24 (t, *J* = 7.2 Hz, 3H, $OCH_2CH_3$), 1.82 (s, 3H, $CH_3$ ), 3.26 (s, 3H, $OCH_3$ ), 3.29 (s, 3H, $OCH_3$ ), 3.33 (d, *J* = 6.0 Hz, 1H, $NCH_aH_b$), 3.48 (dd, $^2J$ = 14.8 Hz, $^3J$ = 5.2 Hz, 1H, $NCH_aH_b$), 4.16 (q, *J* = 7.2 Hz, 2H, $OCH_2CH_3$), 4.50 (t, *J* = 5.2 Hz, 1H, CH), 4.90 (s, 1H, CH), 7.37-7.44 (m, 3H, Ar), 7.50 (t, *J* = 7.2 Hz, 2H, Ar), 10.29 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 12.3, 14.5, 43.3, 53.3, 53.4, 60.7, 67.3, 101.1, 128.6, 128.2, 128.9, 131.7, 145.1, 153.9, 155.3, 168.7; HRMS (ESI) calcd. for $C_{18}H_{25}N_4O_6$ [M +H$^+$]: 393.1769; found: 393.1781.



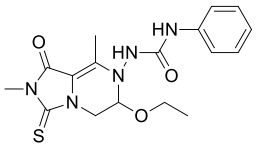
***tert*-Butyl (6-ethoxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5a)**: reaction time: 0.5 h; yield 73%, (305.5 mg); light yellow powder from EtOAc/cyclohexane; m.p 174-175 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.14 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 1.43 and 1.45 (2 s, 9H, Bu$^t$), 2.25 (s, 3H, $CH_3$), 3.57-3.67 (m, 2H, $OCH_aH_bCH_3$ and $NCH_aH_b$), 3.72-3.80 (m, 1H, $OCH_aH_bCH_3$), 4.50 (d, $J$ = 13.2 Hz, 1H, $NCH_aH_b$), 5.04 (brs, 1H, CH), 7.33 (d, $J$ = 6.8 Hz, 2H, Ar), 7.41-7.51 (m, 3H, Ar), 9.83 and 10.17 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 14.9, 27.9, 45.8, 63.7, 80.8, 86.9, 105.6, 128.3, 128.6, 128.7, 139.3, 154.9, 160.4, 168.8; HRMS (ESI) calcd. for $C_{20}H_{27}N_4O_4S$ [M + H$^+$]: 419.1748; found: 419.1747.



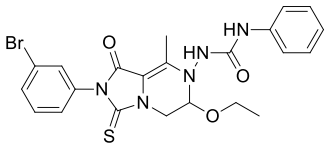
**1-(6-Ethoxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimi-dazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (5b)**: reaction time: 1.5 h; yield 61%, (266.9 mg); light yellow powder from EtOAc/cyclohexane; m.p. 152-153 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.18 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 2.34 (s, 3H, $CH_3$), 3.67-3.90 (m, 3H, $OCH_2CH_3$ and $NCH_aH_b$), 4.50 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 5.11 (t, $J$ = 2.4 Hz, 1H, CH), 7.01 (t, $J$ = 7.2 Hz, 1H, Ar), 7.27-7.34 (m, 4H, Ar), 7.42-7.52 (m, 5H, Ar), 8.90 (s, 1H, NH, $D_2O$ exch.), 9.26 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 15.1, 45.7, 64.3, 86.9, 105.9, 119.2, 122.5, 128.4, 128.6, 128.7, 133.9, 139.0, 140.8, 154.5, 160.4, 168.6; HRMS (ESI) calcd. for $C_{22}H_{24}N_5O_3S$ [M +H$^+$]:438.1594; found: 438.1607.



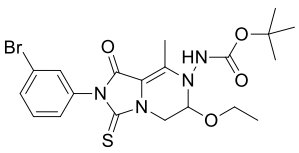
**1-(6-Ethoxy-2-(4-methoxyphenyl)-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (5c)**: reaction time: 2.5 h; yield 57%, (266.5 mg); dark yellow powder from EtOAc/cyclohexane; m.p. 158-159 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.17 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$), 2.33 (s, 3H, $CH_3$), 3.64-3.71 (m, 1H, $OCH_aH_bCH_3$), 3.78-3.88 (m, 5H, $OCH_3$, $OCH_aH_bCH_3$ and $NCH_aH_b$), 4.48 (d, $J$ = 13.2 Hz, 1H, $NCH_aH_b$), 5.10 (brs, 1H, CH), 6.99-7.04 (m, 3H, Ar), 7.22 (d, $J$ = 8.8 Hz, 2H, Ar), 7.28 (t, $J$ = 8.4 Hz, 2H, Ar), 7.48 (d, $J$ = 8.0 Hz, 2H, Ar), 8.91 (s, 1H, NH, $D_2O$ exch.), 9.27 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 15.1, 45.7, 52.3, 64.3, 86.9, 105.9, 113.9, 119.2, 122.5, 126.5, 128.6, 129.8 139.0, 140.5, 154.5, 159.0, 160.7, 169.0; HRMS (ESI) calcd. for $C_{23}H_{26}N_5O_4S$ [M +H$^+$]: 468.1700; found:468.1716.



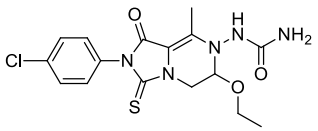
**1-(6-Ethoxy-2,8-dimethyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (5d)**: reaction time: 4 h; yield 54%, (202.7 mg); yellow powder from EtOAc/cyclohexane; m.p. 194-195 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.14 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 2.31 (s, 3H, $CH_3$), 3.16 (s, 3H, $CH_3$), 3.59-3.67 (m, 1H, $OCH_aH_bCH_3$), 3.72-3.80 (m, 2H, $OCH_aH_bCH_3$ and $NCH_aH_b$), 4.41 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 5.04 (t, $J$ = 2.4 Hz, 1H, CH), 6.99 (t, $J$ = 7.6 Hz, 1H, Ar), 7.27 (t, $J$ = 7.6 Hz, 2H, Ar), 7.46 (d, $J$ = 7.6 Hz, 2H, Ar), 8.86 (s, 1H, NH, $D_2O$ exch.), 9.19 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 15.0, 27.3, 45.4, 64.1, 86.8, 106.0, 119.1, 122.5, 128.6, 139.0, 140.2, 154.5, 160.8, 168.9; HRMS (ESI) calcd. for $C_{17}H_{22}N_5O_3S$ [M + $H^+$]: 376.1438; found: 376.1447.



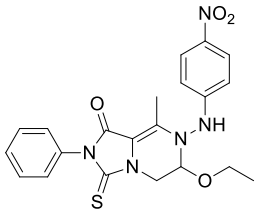
**2-(2-(3-Bromophenyl)-6-ethoxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-*N*-phenylacetamide (5e)**: reaction time: 4 h; yield 58%, (299.5 mg); white powder from EtOAc/cyclohexane; m.p. 119-120 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.18 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$), 2.34 (s, 3H, $CH_3$), 3.65-3.72 (m, 1H, $OCH_aH_bCH_3$), 3.78-3.88 (m, 2H, $OCH_aH_bCH_3$ and $NCH_aH_b$), 4.49 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 5.11 (brs, 1H, CH), 7.01 (t, $J$ = 7.2 Hz, 1H, Ar), 7.29 (t, $J$ = 7.6 Hz, 2H, Ar), 7.39 (d, $J$ = 8.0 Hz, 1H, Ar), 7.47 (t, $J$ = 8.0 Hz, 3H, Ar), 7.62 (s, 1H, Ar), 7.65 (d, $J$ = 8.0 Hz, 1H, Ar), 8.91 (s, 1H, NH, $D_2O$ exch.), 9.27 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7, 15.1, 45.7, 64.3, 86.9, 105.6, 119.1, 120.9, 122.5, 128.0, 128.6, 130.5, 131.3, 131.4, 135.3, 139.0, 141.2, 154.4, 160.1, 168.1; HRMS (ESI) calcd. for $C_{22}H_{23}BrN_5O_3S$ [M + $H^+$]: 516.0699; found: 516.0712.



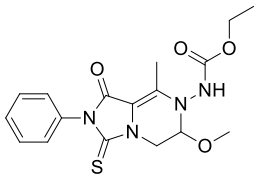
***tert*-Butyl (2-(3-bromophenyl)-6-ethoxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5f)**[4]: reaction time: 2.5 h; yield 82%, (407.9 mg); white powder from EtOAc/cyclohexane; m.p. 180-181 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.14 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 1.45 (s, 9H, $Bu^t$), 2.25 (s, 3H, $CH_3$), 3.59-3.67 (m, 2H, $OCH_aH_bCH_3$ and $NCH_aH_b$), 3.72-3.79 (m, 1H, $OCH_aH_bCH_3$), 4.49 (d, $J$ = 13.2 Hz, 1H, $NCH_aH_b$), 5.04 (brs, 1H, CH), 7.39 (d, $J$ = 8.0 Hz, 1H, Ar), 7.46 (t, $J$ = 8.0 Hz, 1H, Ar), 7.62-7.65 (m, 2H, Ar), 9.82 and 10.15 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.5, 14.9, 27.9, 45.9, 63.8, 81.9, 86.9, 105.5, 120.9, 128.0, 130.5, 131.3, 131.5, 135.3, 139.8, 155.0, 160.1, 168.4; HRMS (ESI) calcd. for $C_{20}H_{26}BrN_4O_4S$ [M + $H^+$]: 497.0853; C; found: 497.0841.



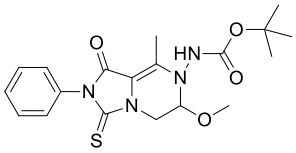
**1-(6-Ethoxy-2-(4-chlorophenyl)-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)urea (5g)**: reaction time: 3.5 h; yield 51.0%, (201.9 mg); light yellow powder from EtOAc/cyclohexane; m.p. 188-189 °C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 1.15 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$ ), 2.28 (s, 3H, $CH_3$ ), 3.60-3.68 (m, 1H, $OCH_aH_bCH_3$), 3.74-3.82 (m, 1H, $OCH_aH_bCH_3$), 3.86 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 4.44 (d, $J$ = 13.2 Hz, 1H, $NCH_aH_b$), 5.00 (brs, 1H, CH), 6.33 (brs, 2H, $NH_2$, $D_2O$ exch.), 7.37 (d, $J$ = 8.8 Hz, 2H, Ar), 7.56 (d, $J$ = 8.8 Hz, 2H, Ar), 9.00 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 15.1, 45.9, 64.4, 86.8, 105.4, 128.8, 130.5, 132.7, 132.9, 141.4, 157.7, 160.1, 167.9; HRMS (ESI) calcd. for $C_{16}H_{19}ClN_5O_3S$ [M + $H^+$]: 396.0892; found: 396.0905.



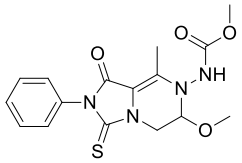
**6-Ethoxy-8-methyl-7-((4-nitrophenyl)amino)-2-phenyl-3-thioxo-2,3,6,7-tetrahydroimidazo[1,5-*a*]pyrazin-1(5*H*)-one (5h)**: reaction time: 3.0 h; 62 %, (272.5 mg); dark orange powder from EtOAc/light petroleum ether; m.p 184-187 °C dec.; $^{1}$H NMR (400 MHz, , DMSO-$d_6$): δ 1.19 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$ ), 2.27 (s, 3H, $CH_3$ ), 3.65-3.73 (m, 1H, $OCH_aH_bCH_3$), 3.77-3.85 (m, 1H, $OCH_aH_bCH_3$), 4.05 (d, $J$ = 14.4 Hz, 1H, $NCH_aH_b$), 4.61 (d, $J$ = 13.6 Hz, 1H, $NCH_aH_b$), 5.10 (s, 1H, CH), 6.97 (d, $J$ = 9.2 Hz, 2H, Ar), 7.33 (d, $J$ = 7.2 Hz, 2H, Ar), 7.44 (t, $J$ = 7.2 Hz, 1H, Ar), 7.51 (t, $J$ = 7.6 Hz, 2H, Ar), 8.13 (d, $J$ = 8.8 Hz, 2H, Ar), 9.82 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.3, 15.1, 45.8, 64.4, 85.1, 106.2, 110.9, 126.2, 128.4, 128.6, 128.7, 133.8, 139.3, 140.1, 152.7, 160.3, 168.8; HRMS (ESI) calcd. for $C_{21}H_{22}N_5O_4S$ [M + $H^+$]: 440.1387; found: 440.1398.



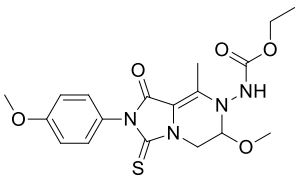
**Ethyl (6-methoxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5i)**: reaction time: 0.5 h; yield 62%, (233.4 mg); orange powder from EtOAc/cyclohexane; m.p 144-145 °C; $^{1}$H NMR (400 MHz, , DMSO-$d_6$): δ 1.24 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$ ), 2.27 (s, 3H, $CH_3$ ), 3.41 (s, 3H, $OCH_3$ ), 3.61 (d, $J$ = 12.4 Hz, 1H, $NCH_aH_b$), 4.15 (q, $J$ = 7.2 Hz, 2H, $OCH_2CH_3$), 4.58 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 5.00 (brs, 1H, CH), 7.33 (d, $J$ = 8.4 Hz, 2H, Ar), 7.41-7.51 (m, 3H, Ar), 10.42 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 14.3, 45.4, 55.7, 61.5, 88.4, 105.8, 128.3, 128.6, 128.7, 133.8, 138.8, 155.9, 160.4, 169.1; HRMS (ESI) calcd. for $C_{17}H_{21}N_4O_4S$ [M + $H^+$]: 377.1278; found: 377.1294.



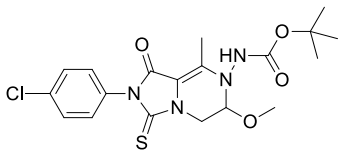
***tert*-Butyl (6-methoxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5j)**[4]: reaction time: 0.5 h; yield 67%, (271.0 mg); yellow powder from EtOAc/$Et_2O$; m.p. 187-188 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.46 (s, 9H, Bu$^t$), 2.26 (s, 3H, $CH_3$ ), 3.40 (s, 3H, $OCH_3$), 3.61 (d, $J$ = 12.0 Hz, 1H, NC$H_a$H$_b$), 4.56 (d, $J$ = 13.2 Hz, 1H, NCH$_a$$H_b$), 4.96 (brs, 1H, CH), 7.32 (d, $J$ = 8.4 Hz, 2H, Ar), 7.40-7.51 (m, 3H, Ar), 9.85 and 10.20 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 27.9, 45.5, 55.7, 80.9, 88.6, 105.8, 128.3, 128.6, 128.7, 133.8, 138.9, 155.0, 160.4, 169.0; HRMS (ESI) calcd. for $C_{19}H_{25}N_4O_4S$ [M + H$^+$]: 405.1591; found: 405.1607.



**Methyl (6-methoxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5k)**[4]: reaction time: 1.5 h; yield 79%, (286.3 mg); yellow powder from EtOAc/cyclohexane; m.p 165-166 °C; $^1$H NMR (400 MHz, , DMSO-$d_6$): δ 2.27 (s, 3H, $CH_3$ ), 3.41 (s, 3H, $OCH_3$ ), 3.62 (d, $J$ = 13.2 Hz, 1H, NC$H_a$H$_b$), 3.70 (s, 3H, $OCH_3$), 4.58 (d, $J$ = 13.2 Hz, 1H, NCH$_a$$H_b$), 5.01 (brs, 1H, CH), 7.32 (d, $J$ = 7.2 Hz, 2H, Ar), 7.41-7.51 (m, 3H, Ar), 10.15 and 10.45 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 45.4, 52.8, 55.8, 88.6 105.8, 128.4, 128.7, 128.8, 133.8, 139.1, 156.6, 160.4, 169.1; HRMS (ESI) calcd. for $C_{16}H_{19}N_4O_4S$ [M + H$^+$]: 363.1122; found: 363.1106.

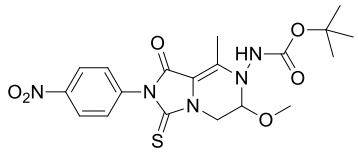


**Ethyl (6-methoxy-2-(4-methoxyphenyl)-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5l)**[4]: reaction time: 2.5 h; yield 81.0%, (329.2 mg); pale yellow powder from EtOAc/cyclohexane; m.p 154-155 °C; $^1$H NMR (400 MHz, , DMSO-$d_6$): δ 1.23 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$ ), 2.26 (s, 3H, $CH_3$ ), 3.40 (s, 3H, $OCH_3$ ), 3.60 (d, $J$ = 12.0 Hz, 1H, NC$H_a$H$_b$), 3.80 (s, 3H, $OCH_3$) 4.14 (q, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 4.57 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 4.99 (brs, 1H, CH), 7.01 (d, $J$ = 9.2 Hz, 2H, Ar), 7.22 (d, $J$ = 8.8 Hz, 2H, Ar), 10.40 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 14.4, 45.4, 55.3, 55.7, 61.6, 88.4, 105.9, 113.9, 126.4, 129.8, 138.6, 155.9, 159.0, 160.6, 169.5; HRMS (ESI) calcd. for $C_{18}H_{23}N_4O_5S$ [M + H$^+$]: 407.1384; found: 407.1397.



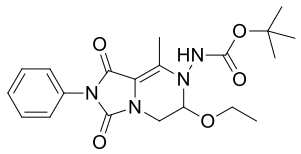
***tert*-Butyl (2-(4-chlorophenyl)-6-methoxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5m)**[4]:

reaction time: 1 h; yield 70%, (307.2 mg); yellow powder from EtOAc/$Et_2O$ m.p. 184-188 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.39 and 1.45 (2 s, 9H, Bu$^t$), 2.26 (s, 3H, $CH_3$ ), 3.40 (s, 3H, $OCH_3$), 3.62 (d, $J$ = 12.8 Hz, 1H, NC$H_a$H$_b$), 4.57 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 4.96 (s, 1H, CH), 7.39 (d, $J$ = 8.8 Hz, 2H, Ar), 7.55 (d, $J$ = 8.8 Hz, 2H, Ar), 9.87 and 10.20 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.5, 27.9, 45.5, 55.7, 80.9, 88.6, 105.7, 128.7, 130.5, 132.7, 132.9, 139.3, 155.0, 160.2, 168.6; HRMS (ESI) calcd. for $C_{19}H_{24}ClN_4O_4S$ [M + H$^+$]: 439.1201; found: 439.1211.



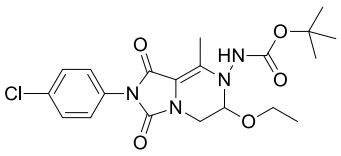
***tert*-Butyl (6-methoxy-8-methyl-2-(4-nitrophenyl)-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5n)**[4]:

reaction time: 3 h; yield 75%, (337.1 mg); orange powder from DCM/light petroleum ether; m.p. 190-193 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.40 and 1.46 (s, 9H, Bu$^t$), 2.27 (s, 3H, $CH_3$ ), 3.41 (s, 3H, $OCH_3$), 3.64 (d, $J$ = 14.4 Hz, 1H, NC$H_a$H$_b$), 4.58 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 4.98 (s, 1H, CH), 7.72 (d, $J$ = 9.2 Hz, 2H, Ar), 8.34 (d, $J$ = 9.2 Hz, 2H, Ar), 9.90 and 10.24 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.5, 26.3, 27.9, 45.5, 55.8, 81.0, 88.5, 105.5, 123.8, 129.9, 139.4, 139.9, 146.7, 154.9, 159.8, 167.8; HRMS (ESI) calcd. for $C_{19}H_{25}N_5O_6S$ [M + H$^+$]: 450.1442; found: 450.1445.



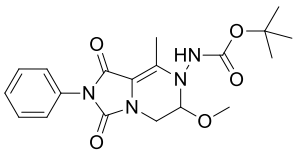
***tert*-Butyl (6-ethoxy-8-methyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5o)**[4]:

reaction time: 3.5 h; yield 59%, (237.4 mg); orange powder from EtOAc/DCM/$Et_2O$; m.p. 114-115 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.14 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$ ), 1.44 (s, 9H, Bu$^t$), 2.21 (s, 3H, $CH_3$ ), 3.47 (d, $J$ = 11.2 Hz, 1H, NC$H_a$H$_b$), 3.54-3.61 (m, 1H, OC$H_a$H$_b$CH$_3$), 3.71-3.78 (m, 1H, OCH$_a$$H_b$CH$_3$), 4.02 (d, $J$ = 12.0 Hz, 1H, NCH$_a$$H_b$), 4.89 (brs, 1H, CH), 7.35-7.39 (m, 3H, Ar), 7.47 (t, $J$ = 8.4 Hz, 2H, Ar) 9.59 and 9.94 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7 14.9, 27.9, 42.3, 63.2, 80.4, 87.2, 104.3, 126.7, 127.4, 128.6, 132.4, 135.4, 149.9, 155.2, 159.9; HRMS (ESI) calcd. for $C_{20}H_{27}N_4O_5$ [M + H$^+$]: 403.1976; found: 403.1990 .



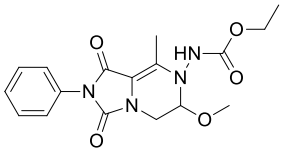
***tert*-Butyl (2-(4-chlorophenyl)-6-ethoxy-8-methyl-1,3-dioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5p)**[4]:

reaction time: 2.5 h; yield 67%, (292.7 mg); yellow powder from EtOAc/cyclohexane; m.p. 139-140 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.14 (t, $J$ = 6.8 Hz, 3H, $OCH_2CH_3$), 1.45 (s, 9H, Bu$^t$), 2.21 (s, 3H, $CH_3$), 3.47 (d, $J$ = 11.2 Hz, 1H, $NCH_aH_b$), 3.54-3.61 (m, 1H, $OCH_aH_bCH_3$), 3.70-3.78 (m, 1H, $OCH_aH_bCH_3$), 4.01 (d, $J$ = 11.6 Hz, 1H, $NCH_aH_b$), 4.89 (brs, 1H, CH), 7.45 (d, $J$ = 8.8 Hz, 2H, Ar), 7.54 (d, $J$ = 8.4 Hz, 2H, Ar), 9.61 and 9.96 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7 14.9, 27.9, 42.3, 63.2, 80.5, 87.2, 104.1, 128.3, 128.7, 131.3, 131.8, 135.7, 149.7, 155.2, 159.7; HRMS (ESI) calcd. for $C_{20}H_{26}ClN_4O_5$ [M + H $^+$]: 437.1586; found: 437.1591.



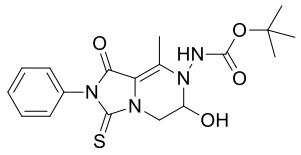
***tert*-Butyl (6-methoxy-8-methyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5q)**[4]:

reaction time: 1.5 h; yield 62%, (240.8 mg); yellow powder from DCM/light petroleum ether; m.p. 139-140 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.44 (s, 9H, Bu$^t$), 2.21 (s, 3H, $CH_3$), 3.37 (s, 3H, $OCH_3$), 3.43 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 4.05 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 4.80 (s, 1H, CH), 7.36-7.39 (m, 3H, Ar), 7.47 (t, $J$ = 7.6 Hz, 2H, Ar) 9.63 and 9.98 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7, 28.0, 42.0, 55.3, 80.6, 88.7, 104.4, 126.8, 127.6, 128.7, 132.3, 135.1, 149.9, 155.3, 160.0; HRMS (ESI) calcd. for $C_{19}H_{25}N_4O_5$ [M + H$^+$]: 389.1819; found: 389.1822.

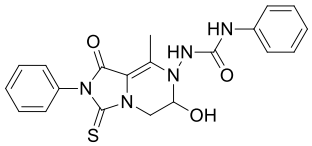


**Ethyl (6-methoxy-8-methyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (5r)**[4]:

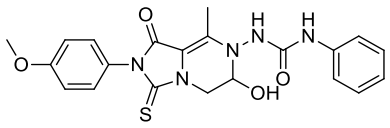
reaction time: 2 h; yield 42%, (151.3 mg); white powder from EtOAc/$Et_2O$; m.p. 158-160 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.23 (t, $J$ = 8.0 Hz, 3H, $OCH_2CH_3$), 2.23 (s, 3H, $CH_3$), 3.38 (s, 3H, $OCH_3$), 3.44 (d, $J$ = 11.6 Hz, 1H, $NCH_aH_b$), 4.11-4.13 (m, 3H, $NCH_aH_b$ and $OCH_2CH_3$), 4.85 (brs, 1H, CH), 7.36-7.39 (m, 3H, Ar), 7.47 (t, $J$ = 7.6 Hz, 3H, 2H, Ar) 9.88 and 10.20 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7, 14.4, 41.9, 55.3, 61.3, 88.6, 104.5, 126.8, 127.5, 128.7, 132.3, 134.8, 149.9, 156.2, 160.0; HRMS (ESI) calcd. for $C_{17}H_{21}N_4O_5$ [M + H$^+$]: 361.1506; found: 361.1491.



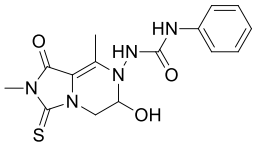
***tert*-Butyl (6-hydroxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6a)**: reaction time: 0.5 h; yield 8%, (31.2 mg) from **4a**; reaction time: 0.5 h; yield 6%, (23.4 mg) from **5j**; ocher powder from EtOAc/$Et_2O$; m.p. 168-169 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.45 (s, 9H, Bu$^t$), 2.25 (s, 3H, $CH_3$), 3.86 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 4.25 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 5.09 (t, $J$ = 3.2 Hz,, 1H, CH), 7.02 (brs, 1H, OH, $D_2O$ exch.) 7.31 (d, $J$ = 7.6 Hz, 2H, Ar), 7.42 (t, $J$ = 7.2 Hz, 1H, Ar), 7.49 (t, $J$ = 7.2 Hz, 2H, Ar), 9.80 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 27.9, 47.5, 80.5, 104.9, 128.2, 128.6, 128.7,134.1 140.8, 154.7, 160.3, 168.2; HRMS (ESI) calcd. for $C_{18}H_{23}N_4O_4S$ [M + H$^+$]: 391.1435; found: 391.1422.



**1-(6-Hydroxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydro-imidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (6b)**: reaction time: 1.5 h; yield 25%, (102.3 mg); orange powder from EtOAc/light petroleun ether; m.p. 149-150 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.34 (s, 3H, $CH_3$ ), 4.07 (d, $J$ = 14.4 Hz, 1H, $NCH_aH_b$), 4.27 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 5.17 (t, $J$ = 2.8 0 Hz, 1H, CH), 7.01 (t, $J$ = 7.2 Hz, 1H, Ar), 7.07 (brs, 1H, OH, $D_2O$ exch.), 7.27-7.33 (m, 4H, Ar), 7.43 (t, $J$ = 7.2 Hz, 1H, Ar), 7.49-7.52 (m, 4H, Ar), 8.88 (brs, 1H, NH, $D_2O$ exch.), 8.94 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7, 47.5, 79.5, 105.6, 119.2, 122.5, 128.3, 128.6, 128.7, 134.0, 139.0, 141.6, 154.5, 160.4, 168.1; HRMS (ESI) calcd. for $C_{20}H_{20}N_5O_3S$ [M + H$^+$]: 410.1281; found: 410.1271.

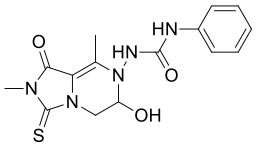


**1-(6-Hydroxy-2-(4-methoxyphenyl)-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (6c)**: reaction time: 2.5 h; yield 11%, (48.3 mg); light yellow powder from EtOAc/$Et_2O$; m.p. 159-160°C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.32 (s, 3H, $CH_3$ ), 3.80 (s, 3H, $OCH_3$), 4.05 (d, $J$ = 12.0 Hz, 1H, $NCH_aH_b$), 4.24 (d, $J$ = 12.8 Hz, 1H, $NCH_aH_b$), 5.15 (t, $J$ = 2.8 Hz, 1H, CH), 6.98-7.05 (m, 3H, Ar and OH), 7.21 (d, $J$ = 9.2 Hz, 2H, Ar), 7.28 (t, $J$ = 7.2 Hz, 2H, Ar), 7.50 (d, $J$ = 7.6 Hz, 2H, Ar), 8.87 (brs, 1H, NH, $D_2O$ exch.), 8.93 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.7, 47.5, 55.4, 79.5, 105.6, 113.9, 119.2, 122.5, 126.6, 128.6, 129.8 139.1, 141.4, 154.3, 158.9, 160.7, 168.5; HRMS (ESI) calcd. for $C_{21}H_{22}N_5O_4S$ [M + H$^+$]: 440.1387; found: 440.1379.



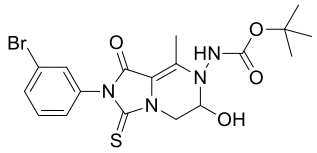
**1-(6-Hydroxy-2,8-dimethyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (6d)**:

reaction time: 4 h; yield 22%, (76.4 mg); beige powder from EtOAc/cyclohexane; m.p. 188-192 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.30 (s, 3H, $CH_3$ ), 3.17 (s, 3H, $CH_3$), 3.97 (d, $J$ = 11.2 Hz, 1H, NC$H_a$H$_b$), 4.17 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 5.08-5.11 (m, 1H, CH), 6.94 (brs, 1H, OH, $D_2O$ exch.), 6.99 (t, $J$ = 7.2 Hz, 1H, Ar), 7.27 (t, $J$ = 7.6 Hz, 2H, Ar), 7.48 (d, $J$ = 7.6 Hz, 2H, Ar), 8.78 (s, 1H, NH, $D_2O$ exch.), 8.89 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 27.3, 47.3, 79.5, 105.8, 119.1, 122.4, 128.6, 139.0, 141.0, 154.6, 160.8, 168.5; HRMS (ESI) calcd. for $C_{15}H_{18}N_5O_3S$ [M + H$^+$]: 348.1125; found: 348.1134.



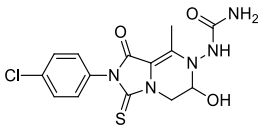
**1-(2-(3-Bromophenyl)-6-hydroxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)-3-phenylurea (6e)**:

reaction time: 4 h; yield 16%, (78.1 mg); white powder from EtOAc/light petroleun ether; m.p. 217-218 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 2.33 (s, 3H, $CH_3$ ), 4.05 (d, $J$ = 14.0 Hz, 1H, NC$H_a$H$_b$), 4.24 (d, $J$ = 12.0 Hz, 1H, NCH$_a$$H_b$), 5.17 (t, $J$ = 2.8 Hz 1H, CH), 7.00 (t, $J$ = 7.2 Hz, 1H, Ar), 7.06 (brs, 1H, OH, $D_2O$ exch.), 7.28 (t, $J$ = 7.6 Hz, 2H, Ar), 7.37 (d, $J$ = 8.0 Hz, 1H, Ar), 7.46-7.50 (m, 3H, Ar), 7.58 (s, 1H, Ar), 7.65 (d, $J$ = 8.4 Hz, 1H, Ar), 8.88 (brs, 1H, NH, $D_2O$ exch.), 8.95 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 47.4, 79.5, 105.4, 119.1, 120.9, 122.5, 128.0, 128.6, 130.6, 131.3, 131.4, 135.4, 138.9, 142.0, 154.4, 160.1, 167.6; HRMS (ESI) calcd. for $C_{20}H_{19}BrN_5O_3S$ [M + H$^+$]: 488.0386; found: 488.0398.



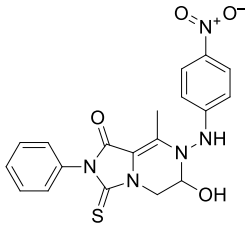
***tert*-Butyl (2-(3-bromophenyl)-6-hydroxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6f)**:

reaction time: 2.5 h; yield 12%, (56.3 mg); yellow powder from DCM/light petroleum ether; m.p. 128-129 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.45 (s, 9H, Bu$^t$), 2.26 (s, 3H, $CH_3$ ), 3.87 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 4.25 (d, $J$ = 12.4 Hz, 1H, NCH$_a$$H_b$), 5.10 (t, $J$ = 3.2 Hz, 1H, CH), 7.02 (brs, 1H, OH, $D_2O$ exch.) 7.38 (d, $J$ = 8.0 Hz, 1H, Ar), 7.47 (t, $J$ = 8.0 Hz, 1H, Ar), 7.59 (s, 1H, Ar), 7.65 (d, $J$ = 8.0 Hz, 1H, Ar), 9.83 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 27.9, 47.4, 79.2, 80.5, 104.8, 120.8, 128.0, 130.5, 131.2, 131.5, 135.5, 141.1, 154.5, 160.1, 167.7; HRMS (ESI) calcd. for $C_{18}H_{22}BrN_4O_4S$ [M + H$^+$]: 469.0540; found: 469.0527.



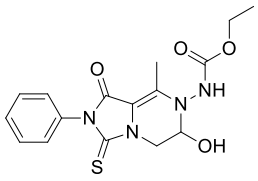
**1-(2-(4-Chlorophenyl)-6-hydroxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)urea (6g)**:

reaction time: 3.5 h; yield 28%, (103.0 mg); light yellow powder from EtOAc/$Et_2O$; m.p. 187-188 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 2.28 (s, 3H, $CH_3$ ), 3.97 (d, *J* = 12.8 Hz, 1H, NC*H*$_a$H$_b$), 4.27 (d, *J* = 12.4 Hz, 1H, NCH$_a$*H*$_b$), 5.07 (t, *J* = 2.4 Hz, 1H, CH), 6.39 (brs, 2H, $NH_2$, $D_2O$ exch.), 6.96 (brs, 1H, OH, $D_2O$ exch), 7.36 (d, *J* = 8.4 Hz, 2H, Ar), 7.56 (d, *J* = 8.4 Hz, 2H, Ar), 8.65 (s, 1H, NH, $D_2O$ exch); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 11.6, 47.5, 79.7, 105.2, 128.7, 130.5, 132.8, 132.9, 142.1, 157.9, 160.1, 167.5; HRMS (ESI) calcd. for $C_{14}H_{15}ClN_5O_3S$ [M + H$^+$]: 368.0579; found: 368.0565.



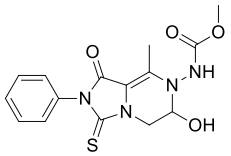
**6-Hydroxy-8-methyl-7-((4-nitrophenyl)amino)-2-phenyl-3-thioxo-2,3,6,7-tetrahydroimidazo[1,5-*a*]pyrazin-1(5*H*)-one (6h)**:

reaction time: 3 h; 9%, (39.5 mg); red powder from EtOAc/$Et_2O$; m.p 184-188 °C dec.; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 2.27 (s, 3H, $CH_3$ ), 4.09 (d, *J* = 11.2 Hz, 1H, NC*H*$_a$H$_b$), 4.47 (d, *J* = 13.2 Hz, 1H, NCH$_a$*H*$_b$), 5.11 (d, *J* = 6.0 Hz, 1H, CH), 6.96 (d, *J* = 8.8 Hz, 2H, Ar), 7.16 (d, *J* = 6.4 Hz, 1H, OH, $D_2O$ exch.), 7.32 (d, *J* = 8.0 Hz, 2H, Ar), 7.44 (t, *J* = 7.6 Hz, 1H, Ar), 7.51 (t, *J* = 7.2 Hz, 2H, Ar), 8.12 (d, *J* = 9.2 Hz, 2H, Ar), 9.71 (s, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 11.4, 14.3, 45.4, 55.7, 61.5, 88.4, 105.8, 128.3, 128.6, 128.7, 133.8, 138.8, 155.9, 160.4, 169.1; HRMS (ESI) calcd. for $C_{19}H_{18}N_5O_4S$ [M + H$^+$]: 412.1074; found: 412.1066.



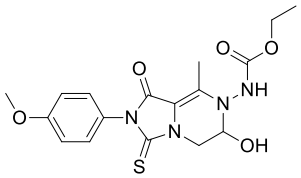
**Ethyl (6-hydroxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6i)**:

reaction time: 0.5 h; yield 22.0%, (79.7 mg); orange powder from EtOAc/$Et_2O$; m.p 140-141 °C; $^1$H NMR (400 MHz, DMSO-*d*$_6$): δ 1.22 (t, *J* = 7.2 Hz, 3H, OCH$_2$C*H*$_3$), 2.26 (s, 3H, $CH_3$ ), 3.89 (d, *J* = 12.8 Hz, 1H, NC*H*$_a$H$_b$), 4.13 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$CH$_3$), 4.24 (d, *J* = 13.6 Hz, 1H, NCH$_a$*H*$_b$), 5.12 (t, *J* = 3.2 Hz,, 1H, CH), 7.06 (brs, 1H, OH, $D_2O$ exch.), 7.31 (d, *J* = 8.0 Hz, 2H, Ar), 7.40-7.51 (m, 3H, Ar), 10.04 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-*d*$_6$): δ 11.4, 14.4, 47.11, 61.4, 79.01, 105.0, 128.3, 128.6, 128.7, 133.9, 140.5, 155.7, 160.4, 168.4; HRMS (ESI) calcd. for $C_{16}H_{19}N_4O_4S$ [M + H$^+$]: 363.1122; found: 363.1105.



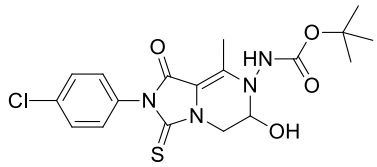
**Methyl (6-hydroxy-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6j)**:

reaction time: 1.5 h; yield 8%, (27.8 mg); yellow powder from EtOAc/$Et_2O$; m.p. 173-174 °C; $^1$H NMR (400 MHz, , DMSO-$d_6$): δ 2.26 (s, 3H, $CH_3$), 3.68 (s, 3H, $OCH_3$ ), 3.91 (d, $J$ = 12.0 Hz, 1H, NC$H_a$H$_b$), 4.24 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 5.11-5.14 (m, 1H, CH), 7.07 (d, $J$ = 5.6 Hz, 1H, OH, $D_2O$ exch.), 7.31 (d, $J$ = 7.2 Hz, 2H, Ar), 7.40-7.51 (m, 3H, Ar), 10.08 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 47.4, 52.5, 79.0, 105.0, 128.2, 128.6, 128.7, 134.0, 140.5, 156.1, 160.4, 168.4; IR (Nujol, ν, cm$^{-1}$): 3719, 3293, 1749, 1699, 1627; HRMS (ESI) calcd. for $C_{15}H_{17}N_4O_4S$ [M + H$^+$]: 349.0965; found: 349.0978.



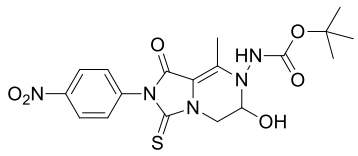
**Ethyl (6-hydroxy-2-(4-methoxyphenyl)-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6k)**:

reaction time: 2.5 h; yield 4.0%, (15.7 mg); orange oil; $^1$H NMR (400 MHz, , DMSO-$d_6$): δ 1.22 (t, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$ ), 2.26 (s, 3H, $CH_3$ ), 3.80 (s, 3H, $OCH_3$), 3.88 (d, $J$ = 12.0 Hz, 1H, NC$H_a$H$_b$), 4.13 (q, $J$ = 7.2 Hz, 3H, $OCH_2CH_3$), 4.23 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 5.10-5.13 (m, 1H, CH), 7.01-7.04 (m, 3H, Ar and OH, $D_2O$ exch.), 7.21 (d, $J$ = 8.8 Hz, 2H, Ar), 10.02 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 14.4, 47.5, 55.3, 61.3, 79.0, 105.0, 113.9, 126.6, 129.7, 140.3, 155.6, 158.9, 160.6, 168.8; HRMS (ESI) calcd. for $C_{17}H_{21}N_4O_5S$ [M + H$^+$]: 393.1227; found: 393.1218.



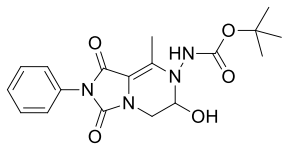
***tert*-Butyl (2-(4-chlorophenyl)-6-hydroxy-8-methyl-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6l)**:

reaction time: 1 h; yield 8%, (34.0 mg); light orange powder from EtOAc/$Et_2O$; m.p. 138-141 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.40 and 1.44 (2 s, 9H, Bu$^t$), 2.25 (s, 3H, $CH_3$ ), 3.86 (d, $J$ = 12.4 Hz, 1H, NC$H_a$H$_b$), 4.25 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 5.09 (t, $J$ = 2.8 Hz, 1H, CH), 7.00 (brs, 1H, OH, $D_2O$ exch), 7.37 (d, $J$ = 8.8 Hz, 2H, Ar), 7.56 (d, $J$ = 8.8 Hz, 2H, Ar), 9.51 and 9.80 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 27.9, 47.7, 79.5, 80.7, 104.9, 128.7, 130.5, 132.8, 132.9, 141.2, 154.7, 160.1, 167.8; HRMS (ESI) calcd. for $C_{18}H_{22}ClN_4O_4S$ [M + H$^+$]: 425.1045; found: 425.1058.



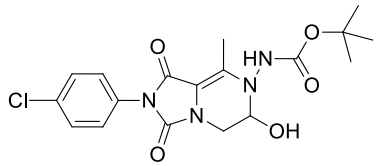
***tert*-Butyl (6-hydroxy-8-methyl-2-(4-nitrophenyl)-1-oxo-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6m)**:

reaction time: 3 h; yield 5%, (21.7 mg); orange powder from DCM/$Et_2O$; m.p. 179-182 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.45 (s, 9H, Bu$^t$), 2.27 (s, 3H, $CH_3$ ), 3.88 (d, $J$ = 12.4 Hz, 1H, NC$H_a$H$_b$), 4.28 (d, $J$ = 12.0 Hz, 1H, NCH$_a$$H_b$), 5.09-5.12 (m, 1H, CH), 7.04 (brs, 1H, OH, $D_2O$ exch.), 7.70 (d, $J$ = 9.2 Hz, 2H, Ar), 8.35 (d, $J$ = 8.8 Hz, 2H, Ar), 9.84 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.5, 27.9, 47.5, 79.2, 80.6, 104.6, 123.8, 129.8, 139.7, 141.7, 146.7, 154.5, 159.7, 167.1; HRMS (ESI) calcd. for $C_{18}H_{22}N_5O_6S$ [M + H$^+$]: 436.1285; found: 436.1273.



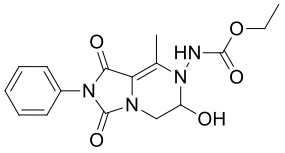
***tert*-Butyl (6-hydroxy-8-methyl-1,3-dioxo-2-phenyl-3-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6n)**:

reaction time: 3.5 h; yield 21%, (78.6 mg) from **5o**; reaction time: 1.5 h yield 29%, (108.5 mg) from **5q**; light yellow powder from DCM/EtOAc//$Et_2O$; m.p. 140-141 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.44 (s, 9H, Bu$^t$), 2.21 (s, 3H, $CH_3$), 3.64 (d, $J$ = 11.2 Hz, 1H, NC$H_a$H$_b$), 3.80 (d, $J$ = 11.6 Hz, 1H, NCH$_a$$H_b$), 4.94-4.97 (m, 1H, CH), 6.71 (brs, 1H, OH, $D_2O$ exch.) 7.36-7.39 (m, 3H, Ar), 7.47 (t, $J$ = 8.0 Hz, 2H, Ar), 9.55 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 28.0, 44.2, 78.9, 80.1, 103.4, 126.7, 127.4, 128.6, 132.6, 137.0, 150.0, 159.9; HRMS (ESI) calcd. for $C_{18}H_{23}N_4O_5$ [M + H$^+$]: 375.1663; found: 375.1662.

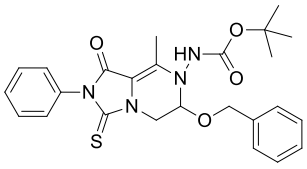


***tert*-Butyl (2-(4-chlorophenyl)-6-hydroxy-8-methyl-1,3-dioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6o)**:

reaction time: 2.5 h; yield 24%, (98.1 mg); light yellow powder from EtOAc/$Et_2O$; m.p. 144-145 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.43 (s, 9H, Bu$^t$), 2.21 (s, 3H, $CH_3$ ), 3.64 (d, $J$ = 11.6 Hz, 1H, NC$H_a$H$_b$), 3.79 (d, $J$ = 12.8 Hz, 1H, NCH$_a$$H_b$), 4.94-4.97 (m, 1H, CH), 6.71 (brs, 1H, OH, $D_2O$ exch.), 7.43 (d, $J$ = 8.8 Hz, 2H, Ar), 7.53 (d, $J$ = 8.8 Hz, 2H, Ar), 9.55 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.6, 27.9, 44.2, 78.8, 80.2, 103.2, 128.2, 128.6, 131.5, 131.6, 137.4, 149.6, 154.9, 159.6; HRMS (ESI) calcd. for $C_{18}H_{22}ClN_4O_5$ [M + H$^+$]: 409.1273; found: 409.1257.



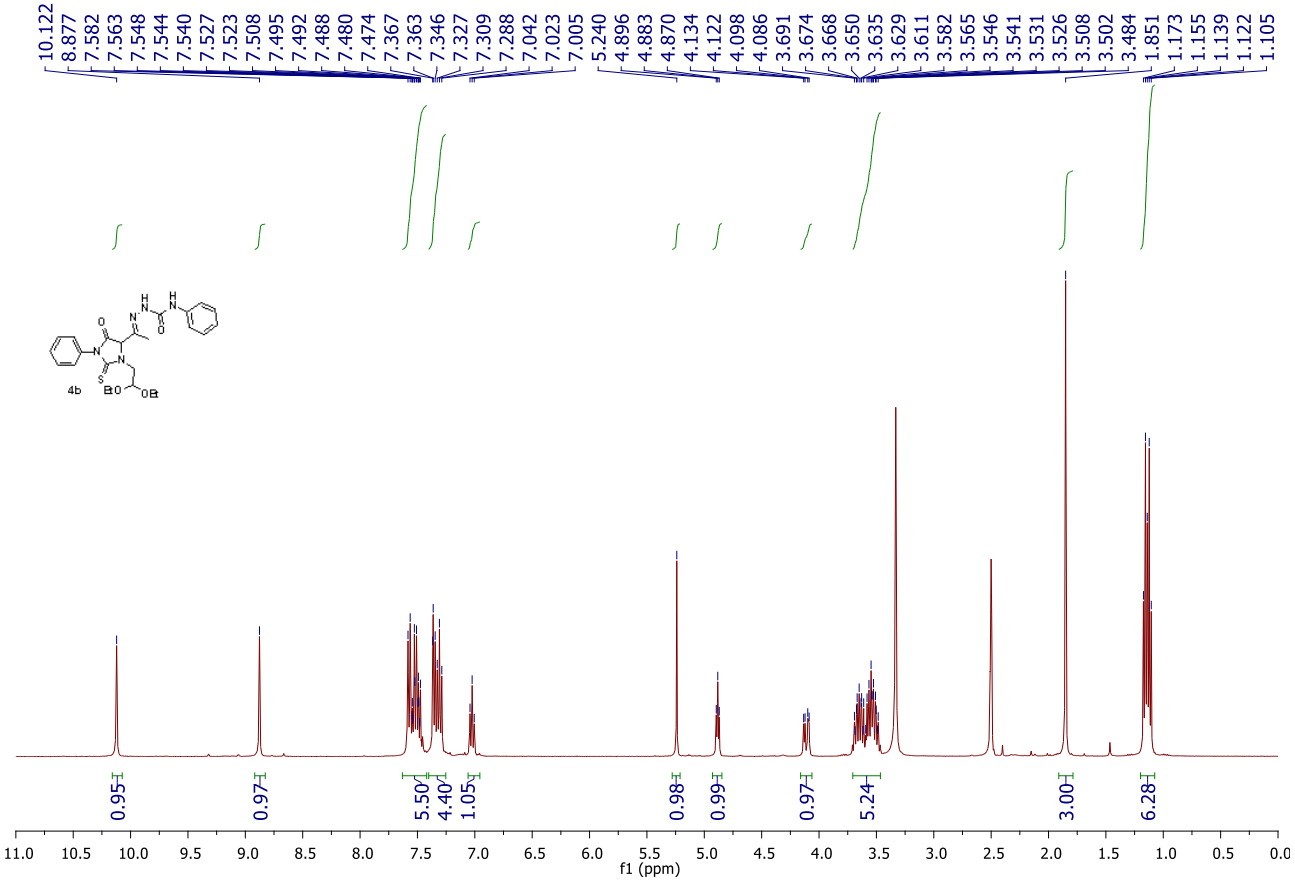
**Ethyl (6-hydroxy-8-methyl-1,3-dioxo-2-phenyl-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (6p)**: reaction time: 2 h; yield 35%, (121.2 mg); white powder from EtOAc/$Et_2O$; m.p. 170-171°C; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.21 (t, $J$ = 6.8Hz, 3H, $OCH_2CH_3$), 2.21 (s, 3H, $CH_3$ ), 3.67 (d, $J$ = 11.6 Hz, 1H, $NCH_aH_b$), 3.80 (d, $J$ = 11.2 Hz, 1H, $NCH_aH_b$), 4.11 (q, $J$ = 7.2 Hz, 2H, $OCH_2CH_3$), 4.96-4.99 (m, 1H, CH), 6.76 (m, 1H, CH), 7.35-7.39 (m, 3H, Ar), 7.47 (t, $J$ = 7.6 Hz, 2H, Ar) 9.78 (brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.5, 14.4, 41.2, 55.3, 61.0, 78.6, 103.5, 126.7, 127.4, 128.6, 132.6, 136.7, 149.9, 156.0, 159.9; HRMS (ESI) calcd. for $C_{16}H_{19}N_4O_5$ [M + H$^+$]: 347.1350; found: 347.1358.

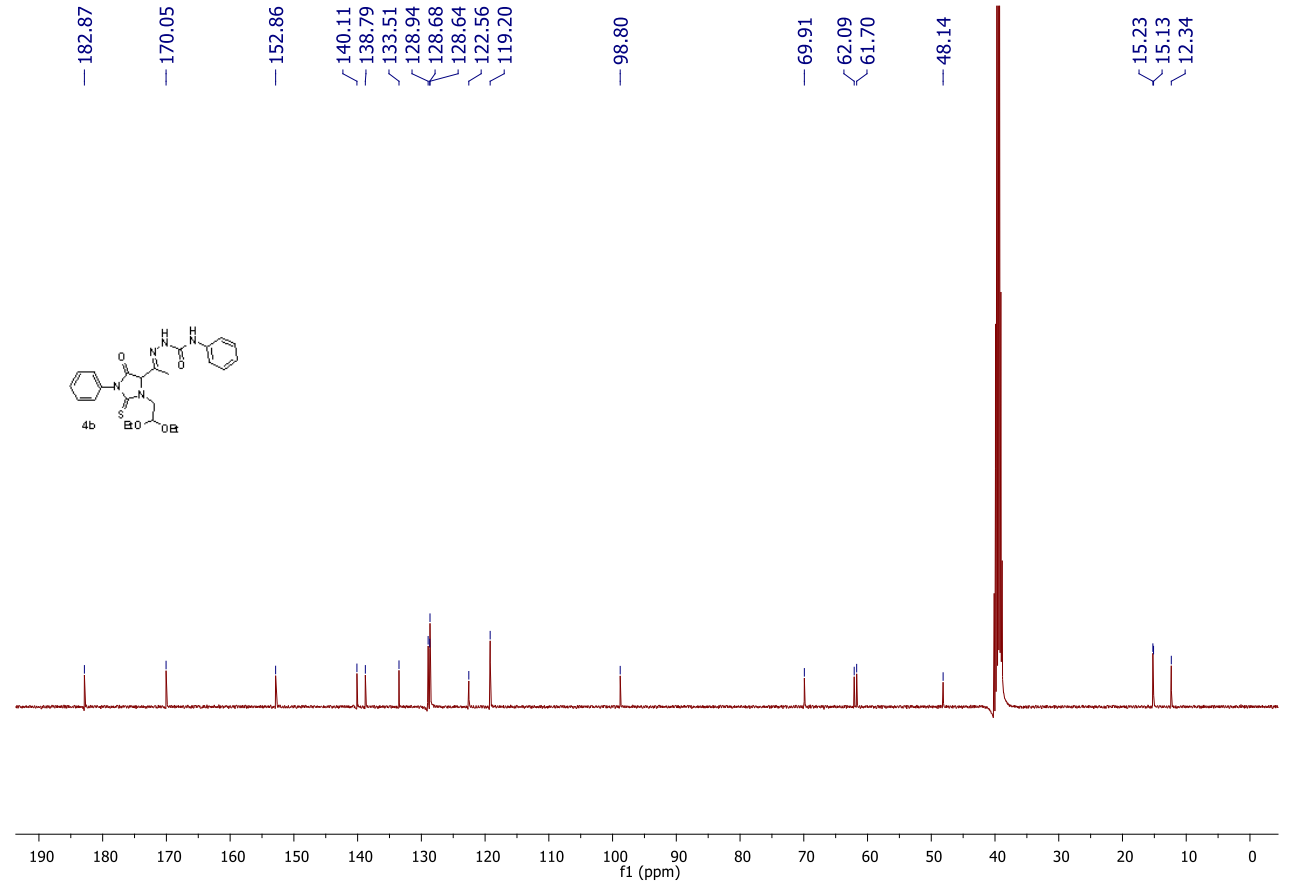


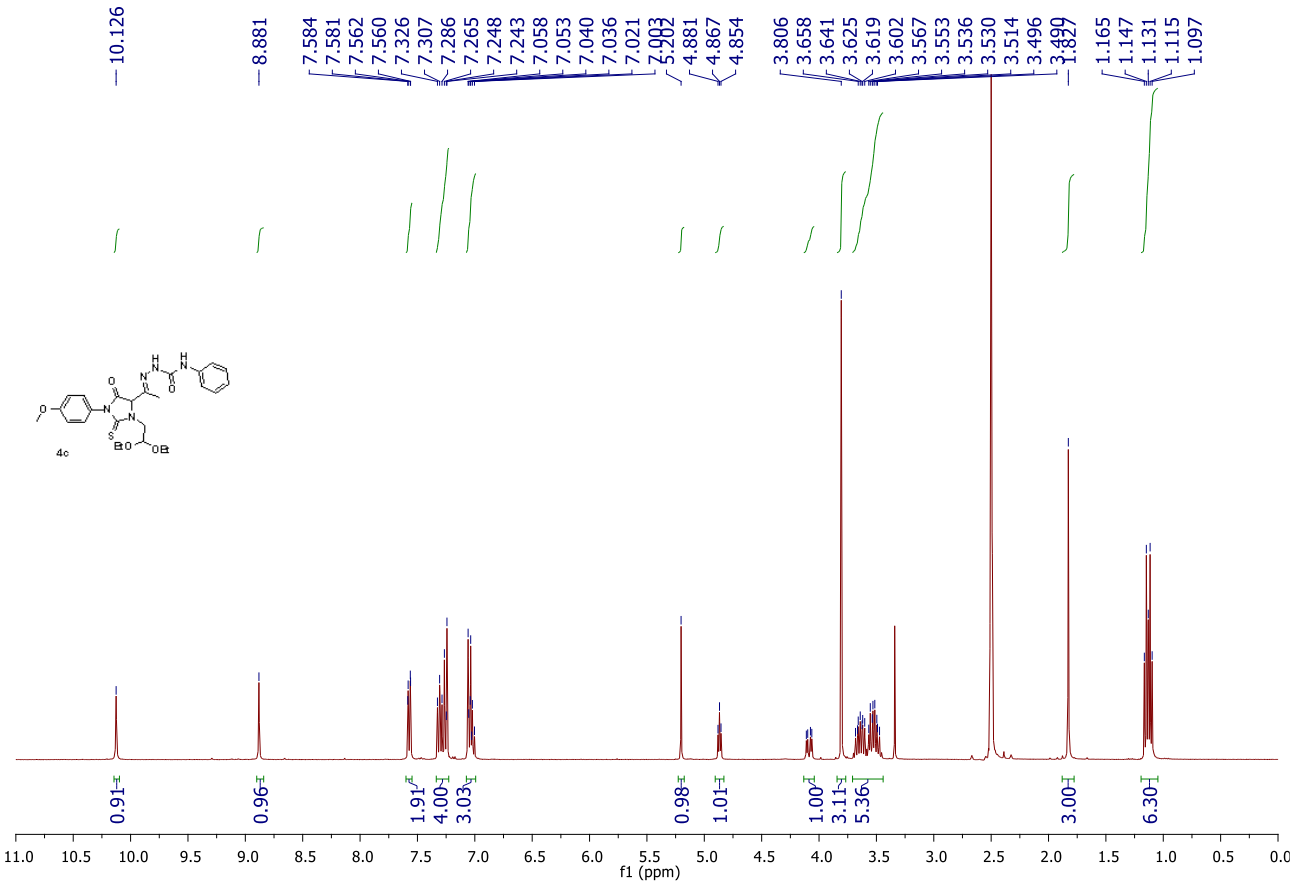
7

***tert*-Butyl (6-(benzyoxy)-8-methyl-1-oxo-2-phenyl-3-thioxo-2,3,5,6-tetrahydroimidazo[1,5-*a*]pyrazin-7(1*H*)-yl)carbamate (7)**: reaction time: 16 h; yield 70%, (50.5 mg); pale orange powder from DCM/$Et_2O$; m.p. 138-141 °C dec.; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 1.45 (s, 9H, $Bu^t$), 2.28 (s, 3H, $CH_3$ ), 3.68 (d, $J$ = 12.4 Hz, 1H, $NCH_aH_b$), 4.60 (d, $J$ = 13.2 Hz, 1H, $NCH_aH_b$), 4.67 (d, $J$ = 12.0 Hz, 1H, $OCH_aH_b$), 4.77 (d, $J$ = 11.6 Hz, 1H, $OCH_aH_b$), 5.12 (brs, 1H, CH), 7.30-7.50 (m, 10H, Ar), 9.90 and 10.21 (2 brs, 1H, NH, $D_2O$ exch.); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 11.4, 27.9, 45.6, 69.5, 80.9, 86.5, 105.9, 127.8, 127.9, 128.3, 128.6, 128.7, 133.8, 137.2, 139.1, 154.9, 160.4, 169.1; HRMS (ESI) calcd. for $C_{25}H_{29}N_4O_4S$ [M + H$^+$]: 481.1904; found: 481.1915.

**7 Copies of NMR spectra for compounds 4b–e, 4g–l, 4n–r, 5a–r, 6a–p, and 7**

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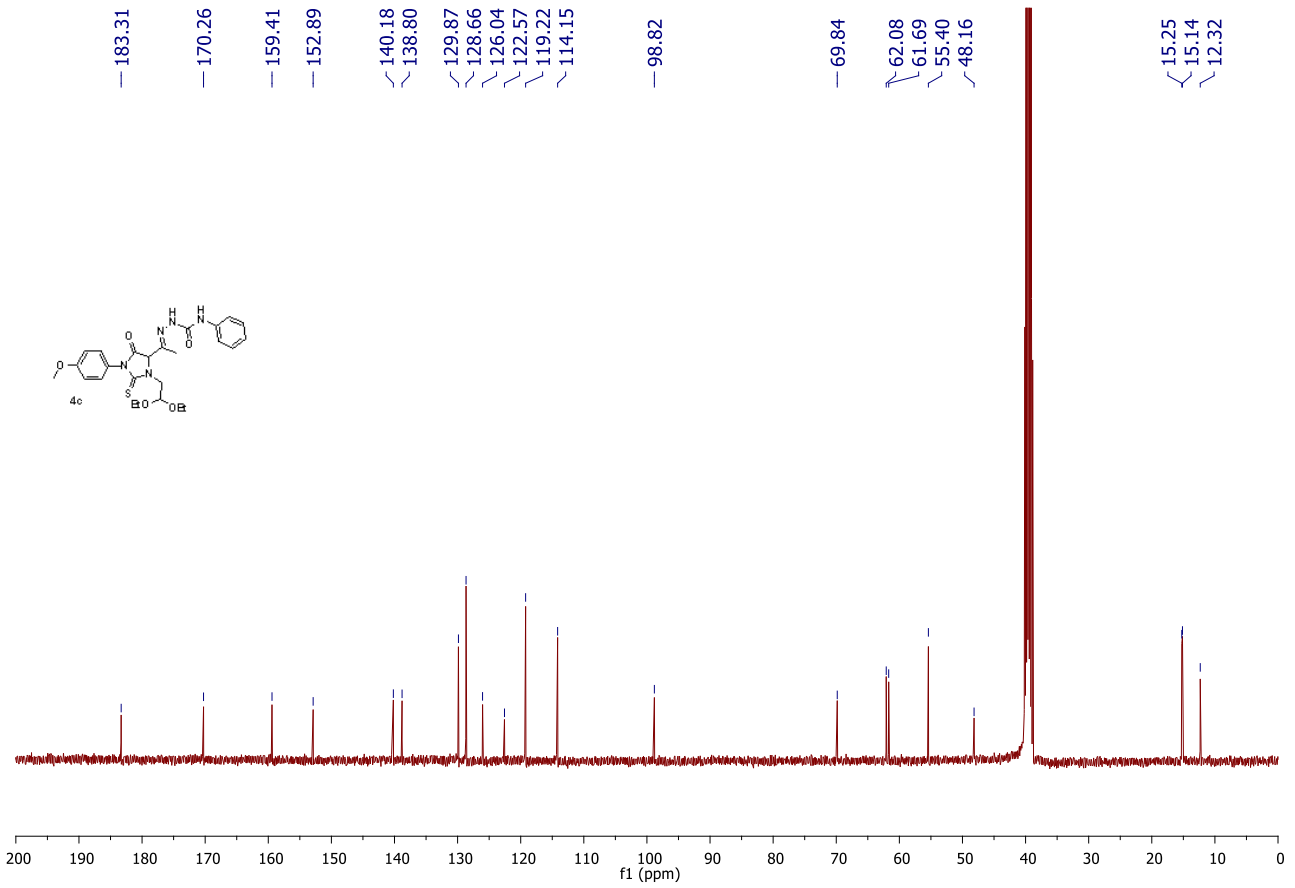
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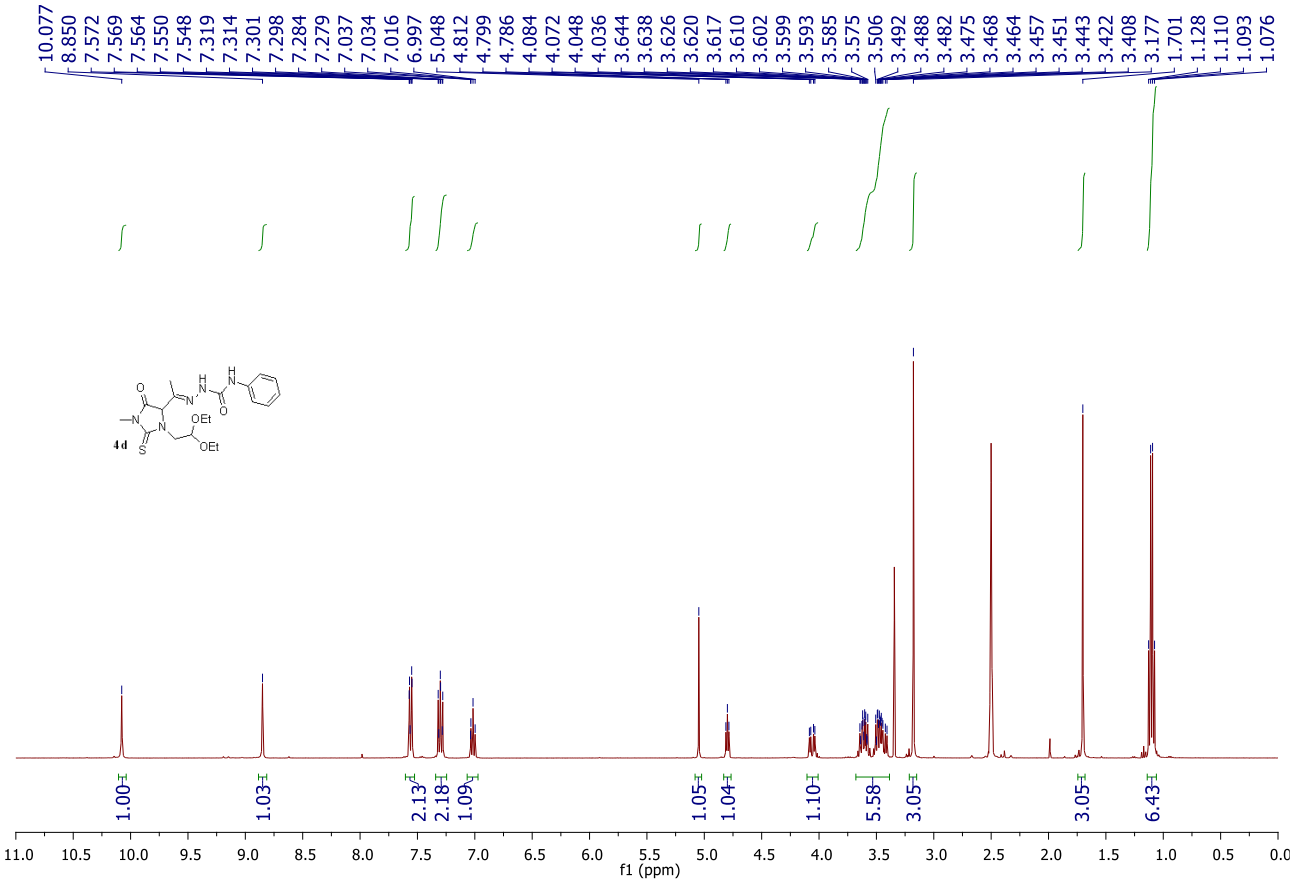
12.32
f1 (ppm)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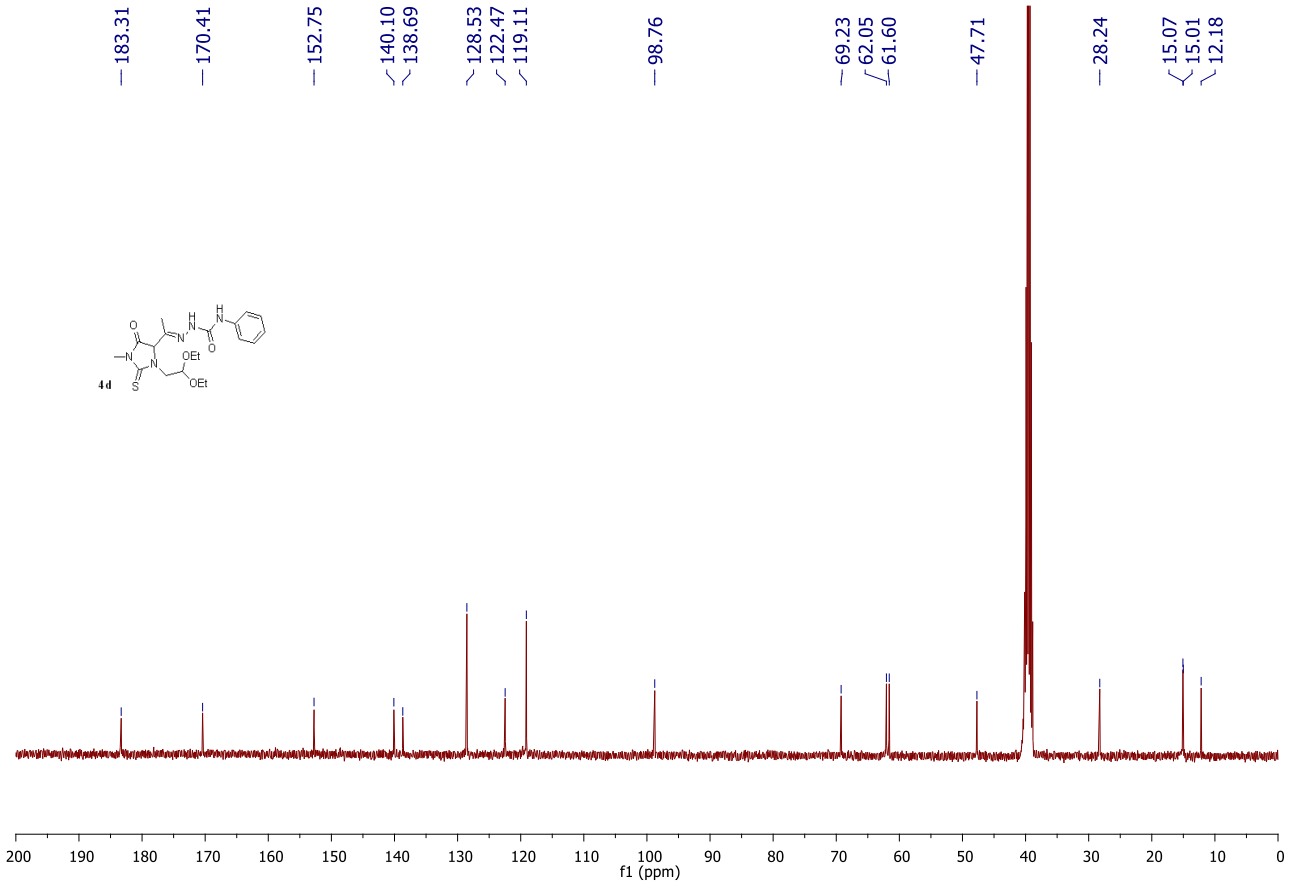
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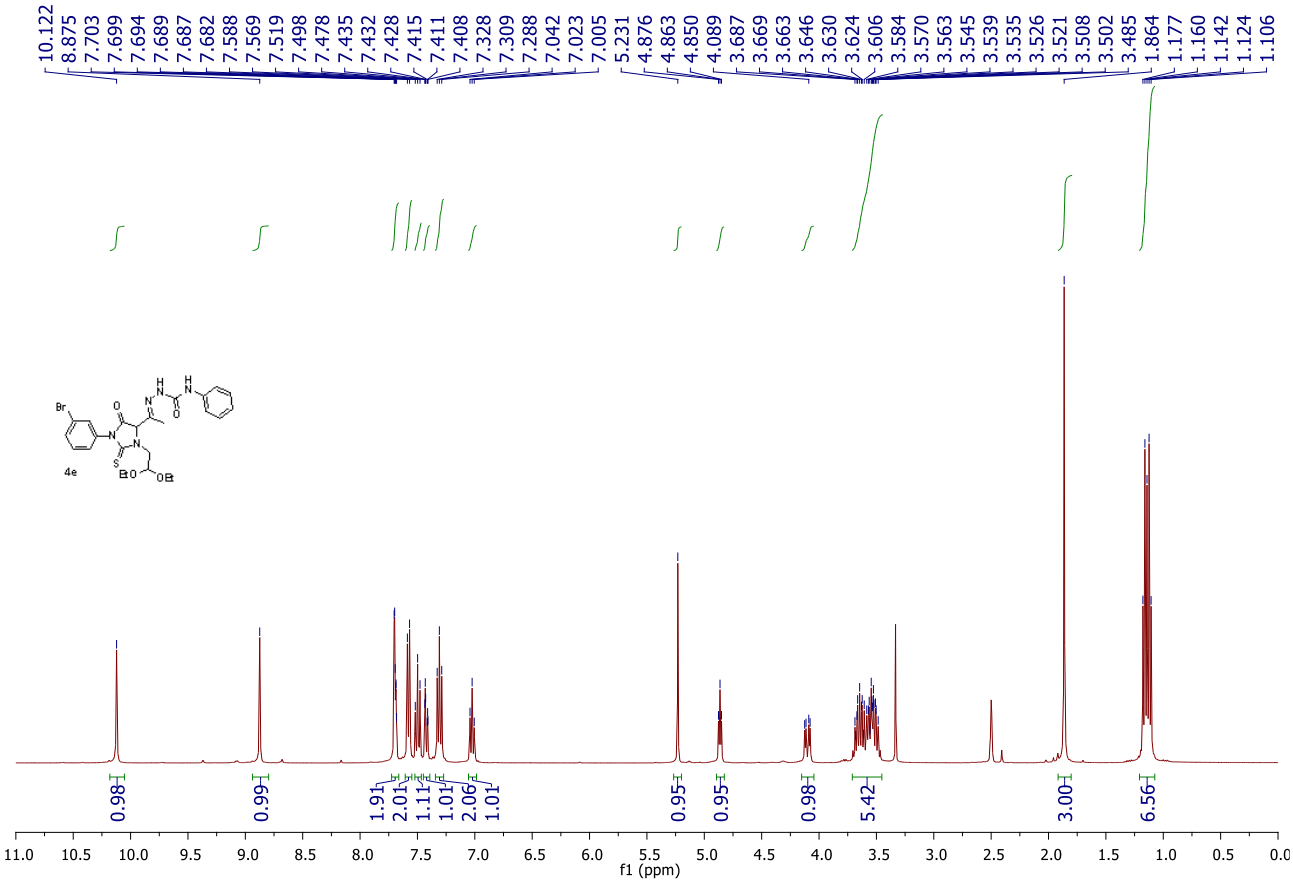
f1 (ppm)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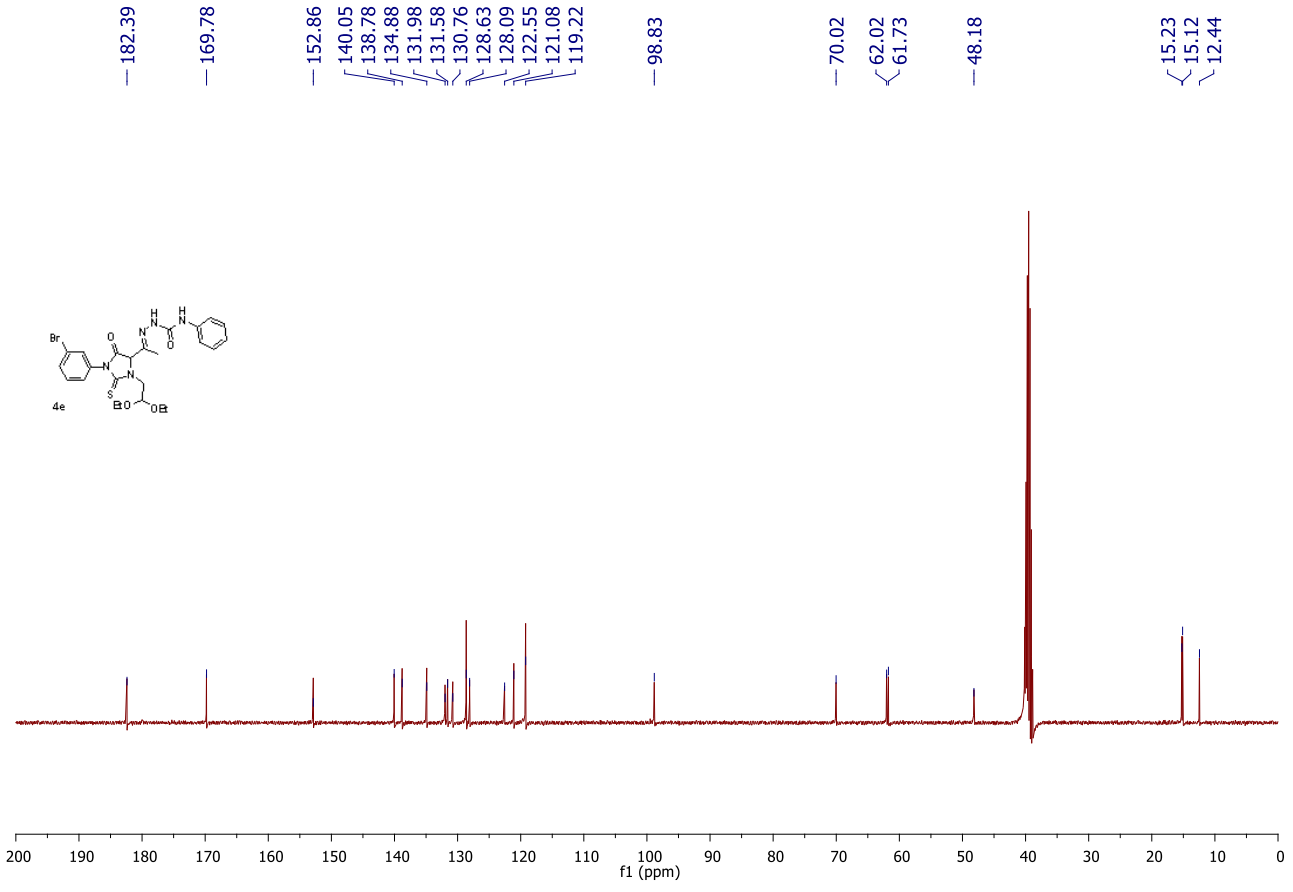
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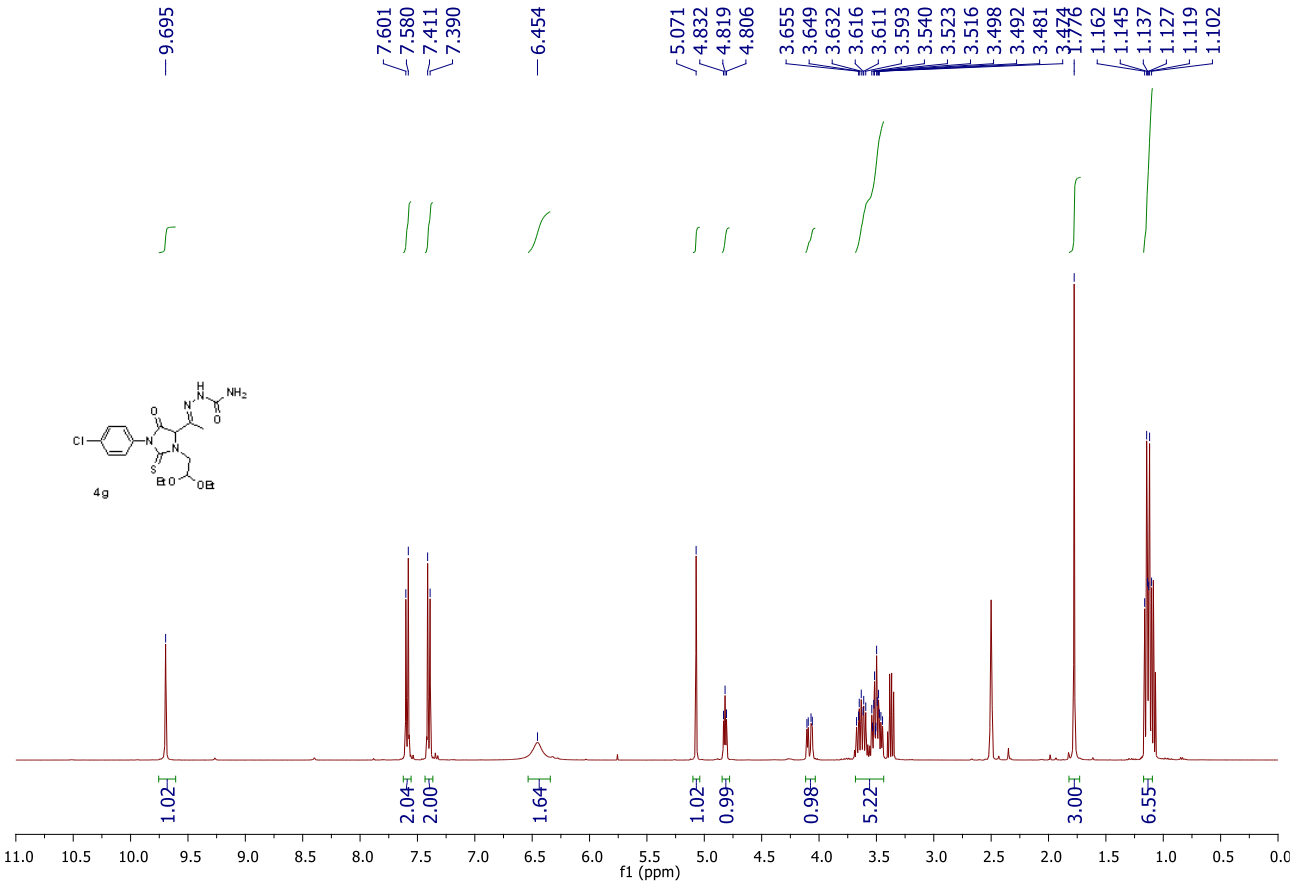
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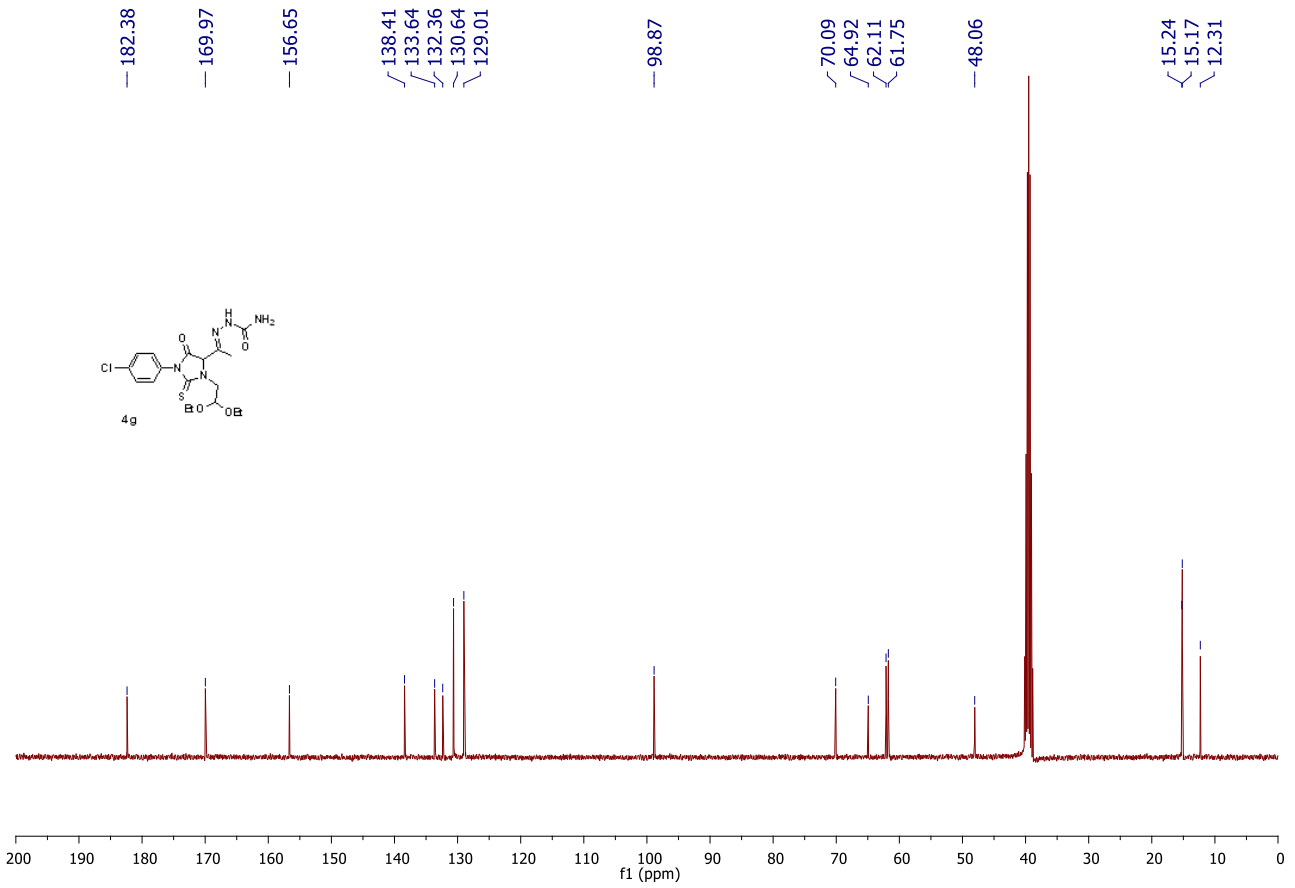
4g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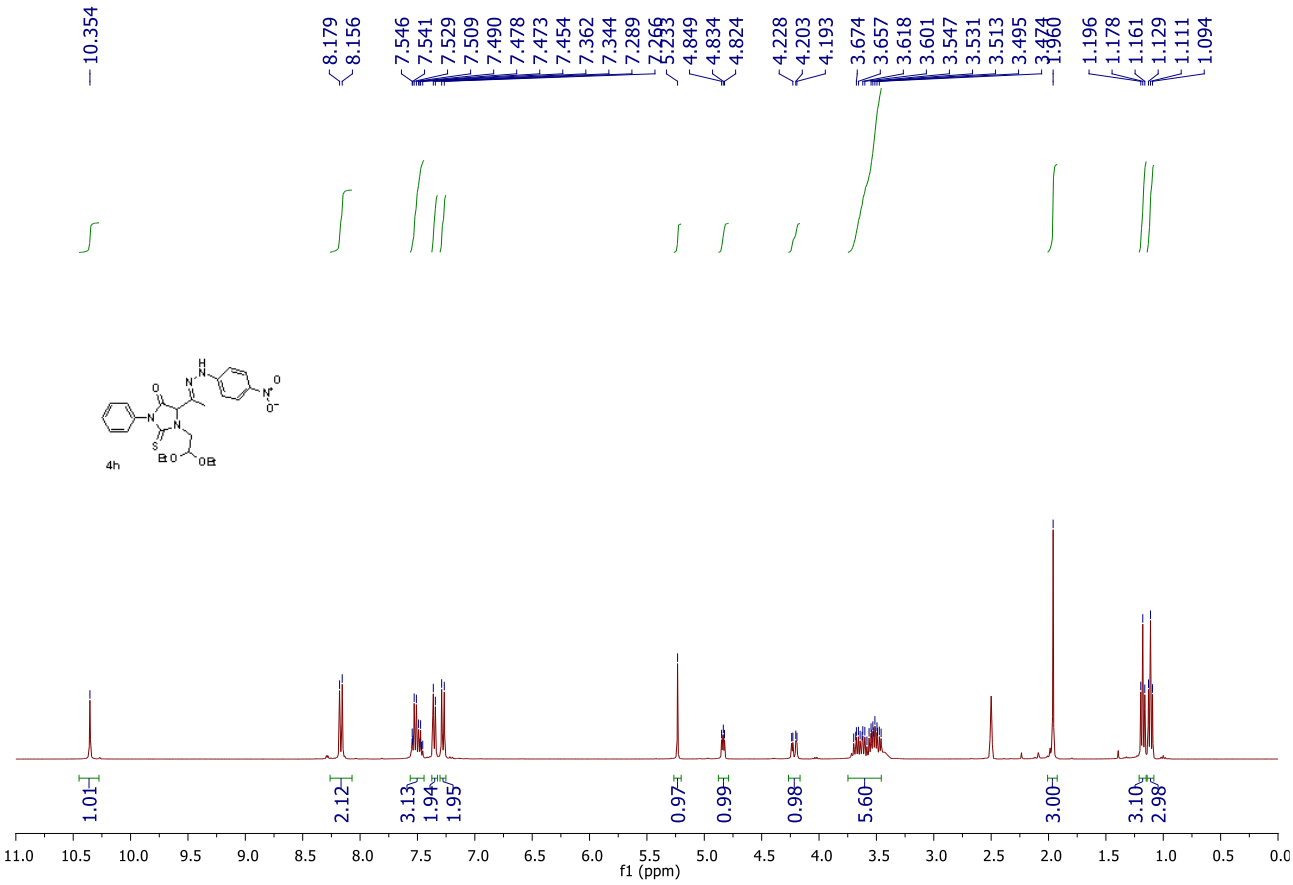
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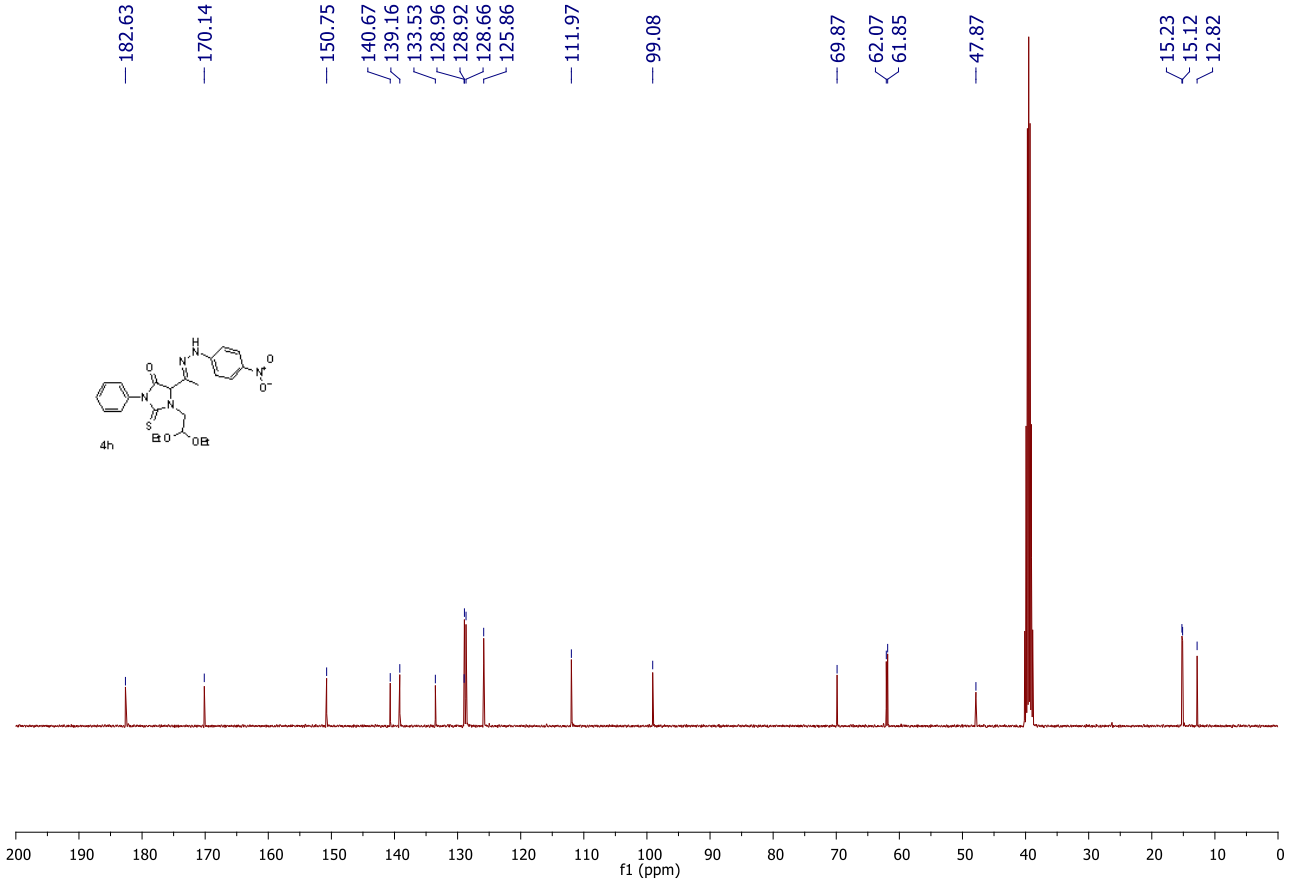
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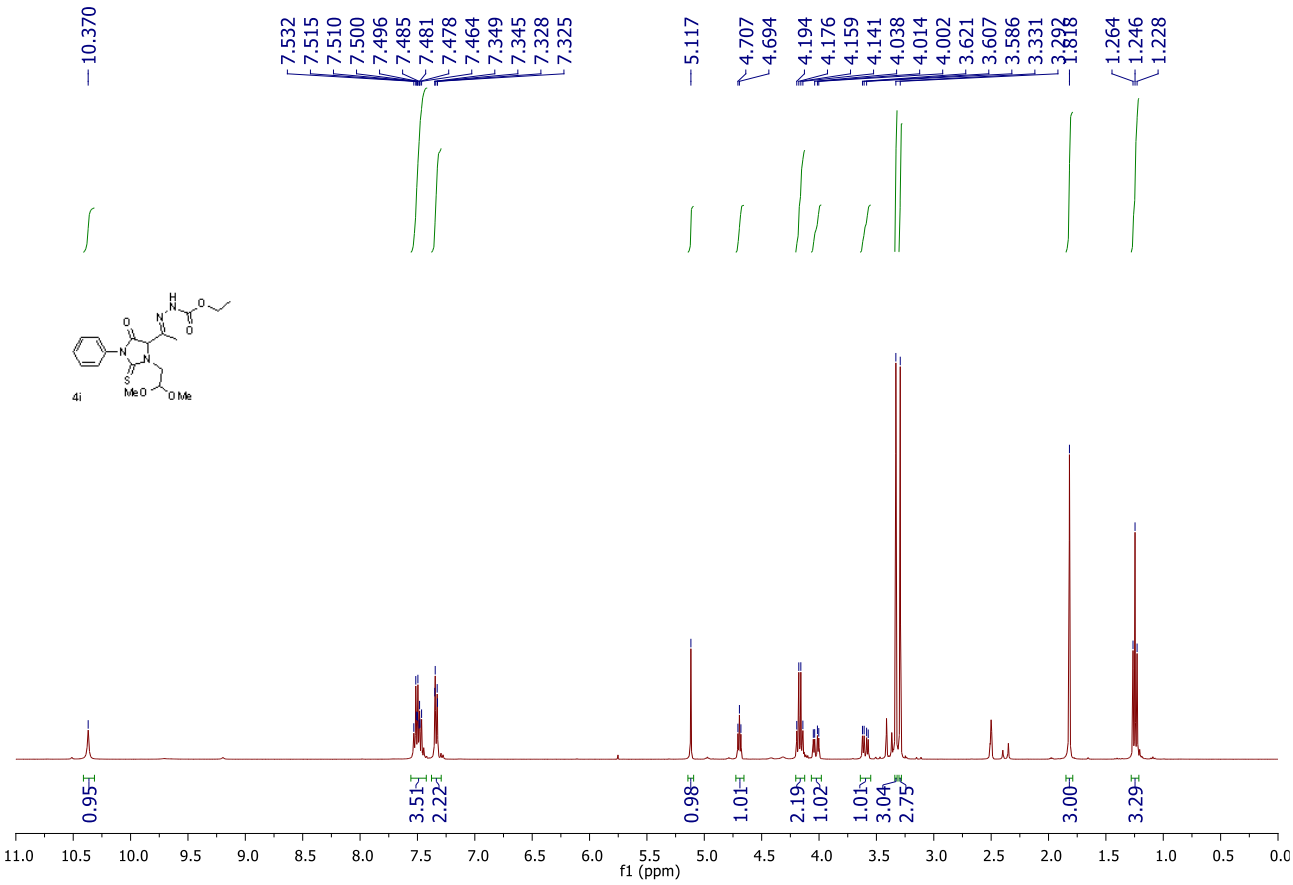
62.07
61.85
47.87
15.23
15.12
12.82
4h
f1 (ppm)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7.485
7.481
7.478
7.464
7.349
7.345
7.328
7.325
5.117
4.707
4.694
4.194
4.176
4.159
4.141
4.038
4.014
4.002
3.621
3.607
3.586
3.331
3.292
1.818
1.264
1.246
1.228
4i
0.95
3.51
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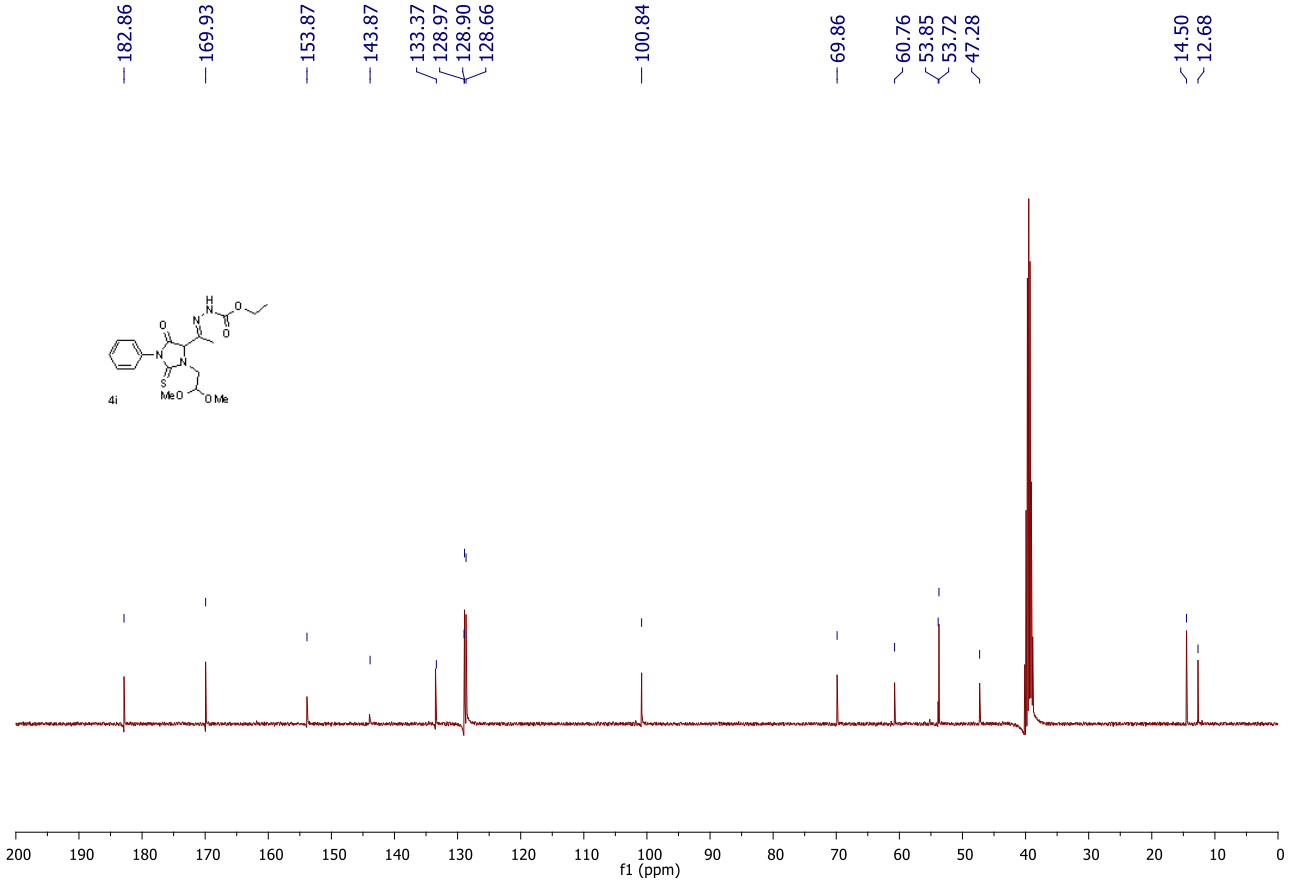
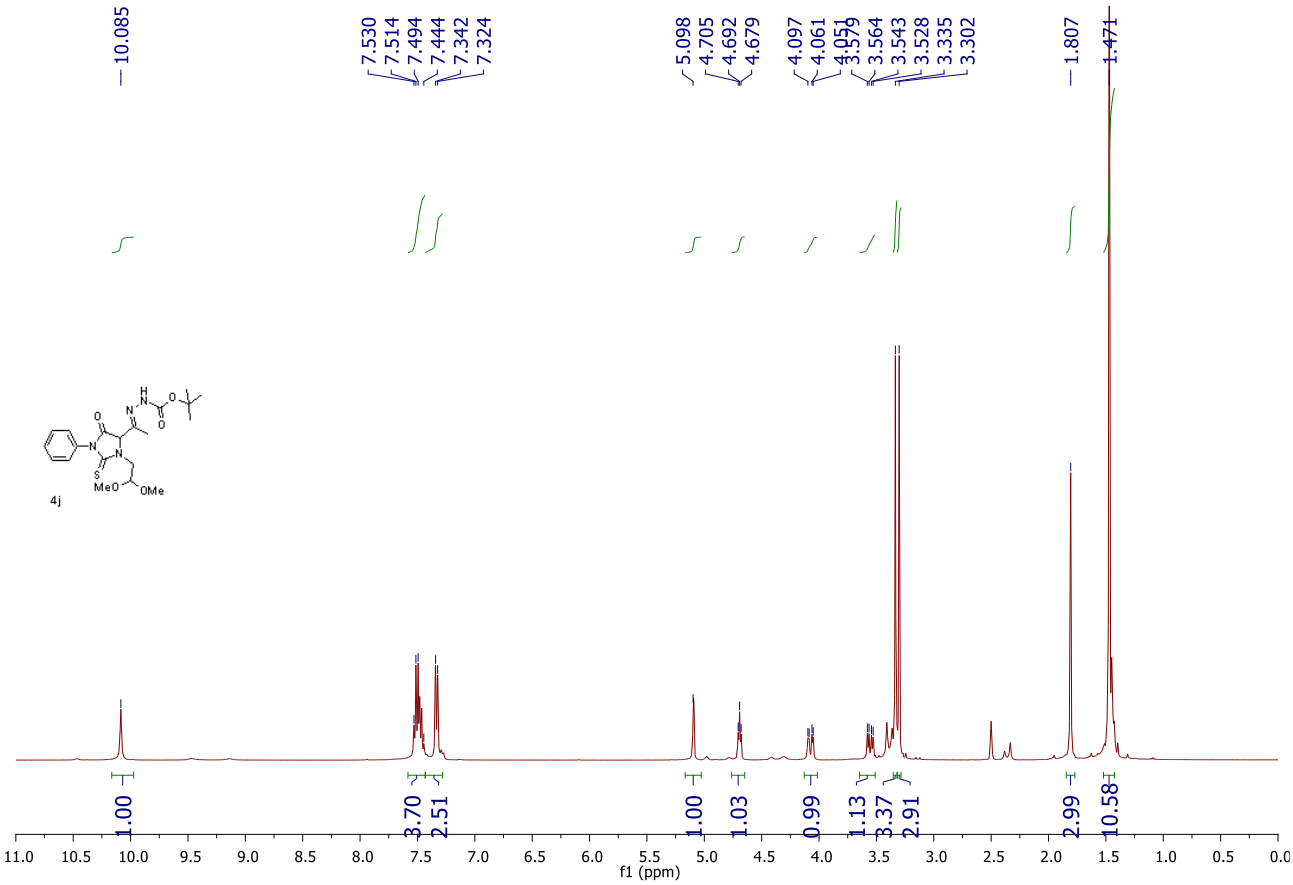
1.01
2.19
1.02
1.01
3.04
2.75
3.00
3.29
f1 (ppm)


182.86
169.93
153.87
143.87
133.37
128.97
128.90
128.66
100.84
69.86
60.76
53.85
53.72
47.28
14.50
12.68
4i
f1 (ppm)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7.324
5.098
4.705
4.692
4.679
4.097
4.061
4.051
3.579
3.564
3.543
3.528
3.335
3.302
1.807
1.471
1.00
3.70
2.51
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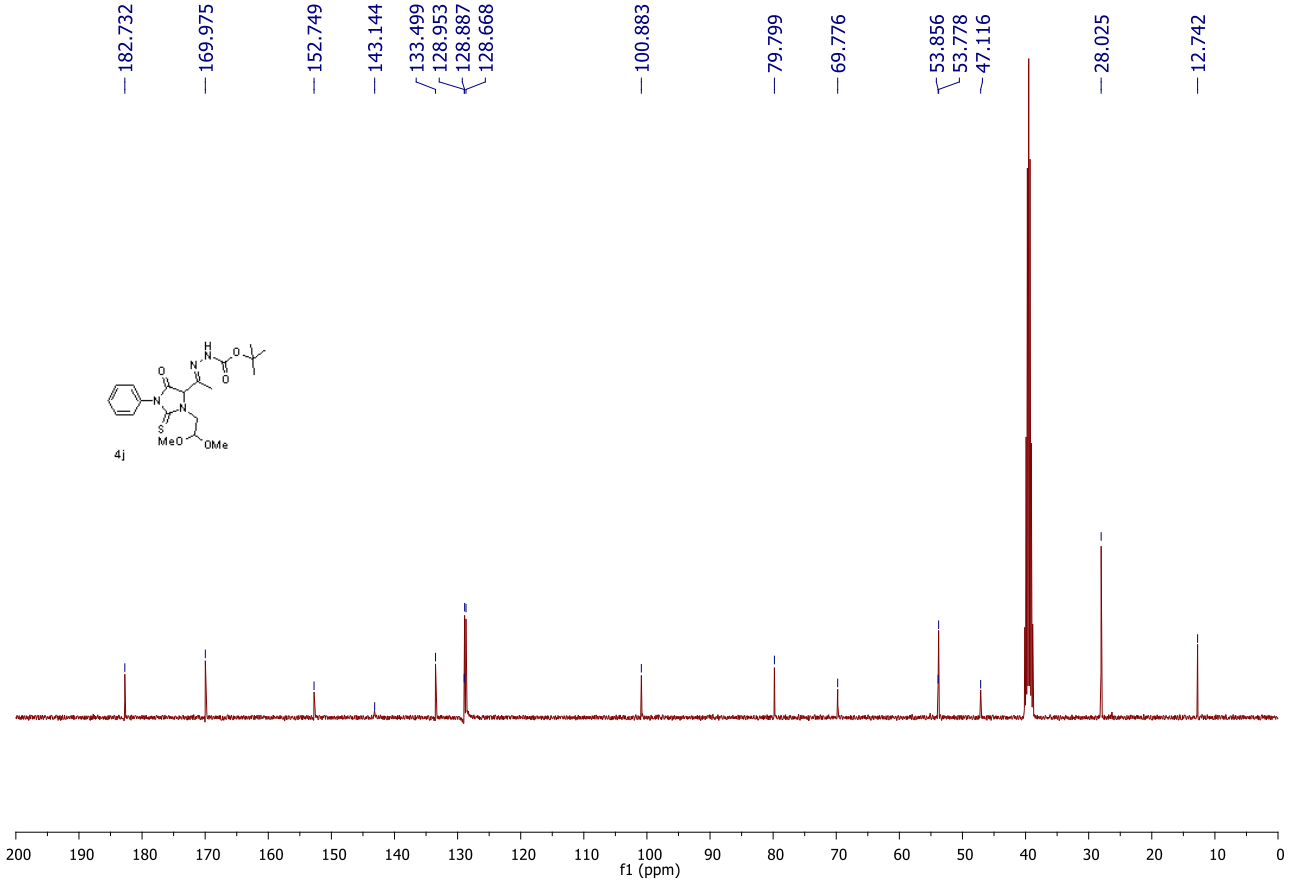
1.03
0.99
1.13
3.37
2.91
2.99
10.58
f1 (ppm)
4j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128.953
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128.668
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79.799
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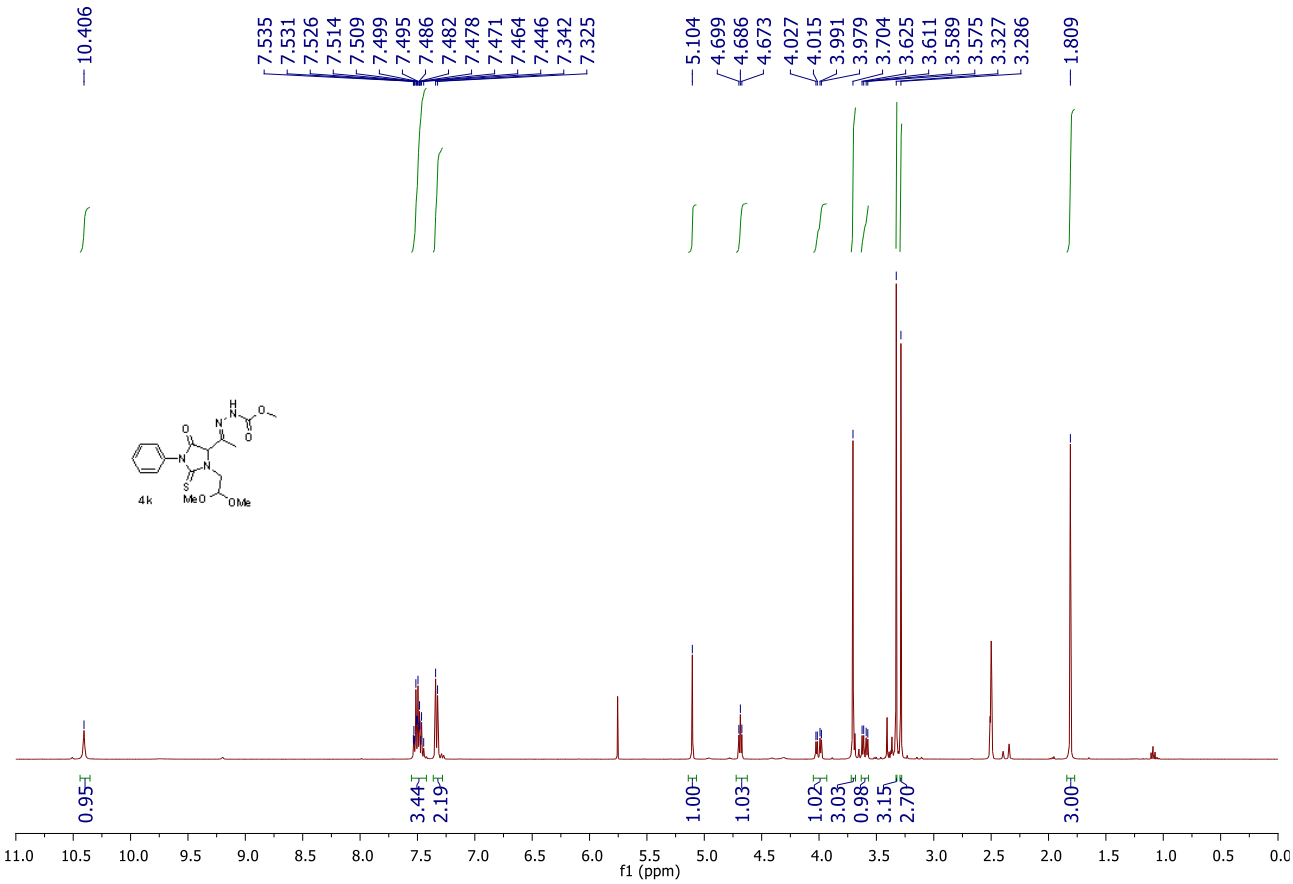
53.856
53.778
47.116
28.025
12.742
f1 (ppm)
4j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7.509
7.499
7.495
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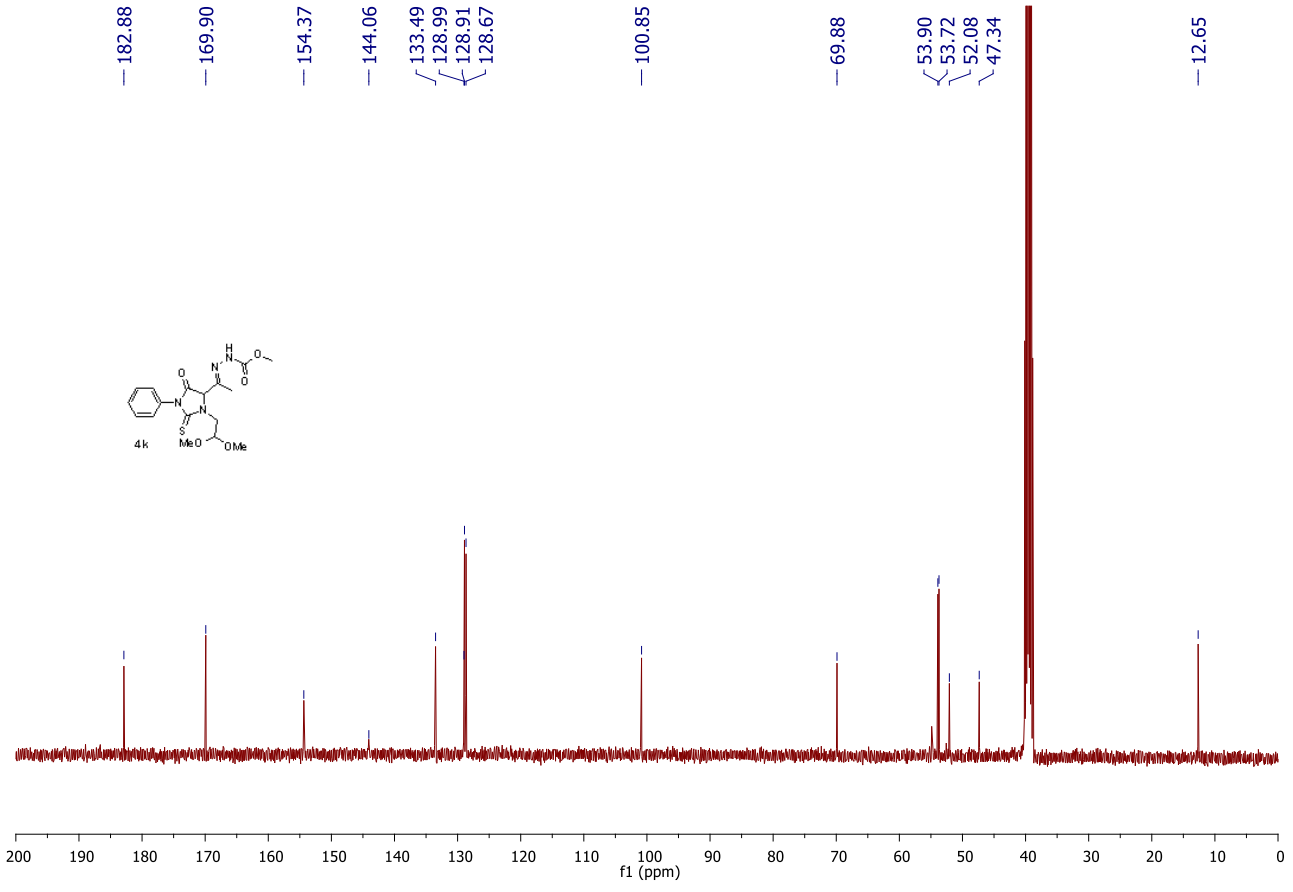
7.482
7.478
7.471
7.464
7.446
7.342
7.325
5.104
4.699
4.686
4.673
4.027
4.015
3.991
3.979
3.704
3.625
3.611
3.589
3.575
3.327
3.286
1.809
0.95
3.44
2.19
1.00
1.03
1.02
3.03
0.98
3.15
2.70
3.00
4k
f1 (ppm)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128.67
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69.88
53.90
53.72
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47.34
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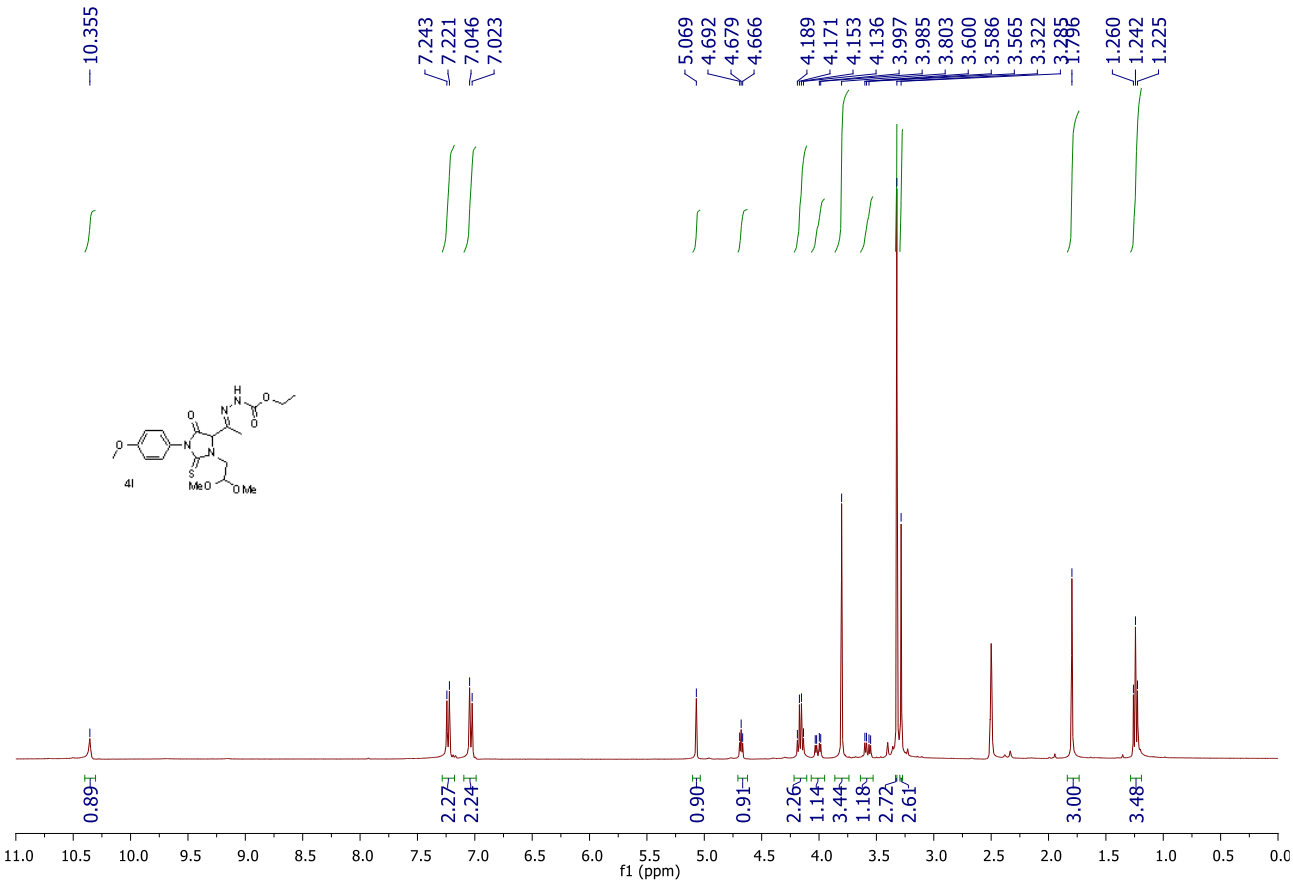
4k
f1 (ppm)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7.221
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5.069
4.692
4.679
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4.189
4.171
4.153
4.136
3.997
3.985
3.803
3.600
3.586
3.565
3.322
3.285
1.796
1.260
1.242
1.225
0.89
2.27
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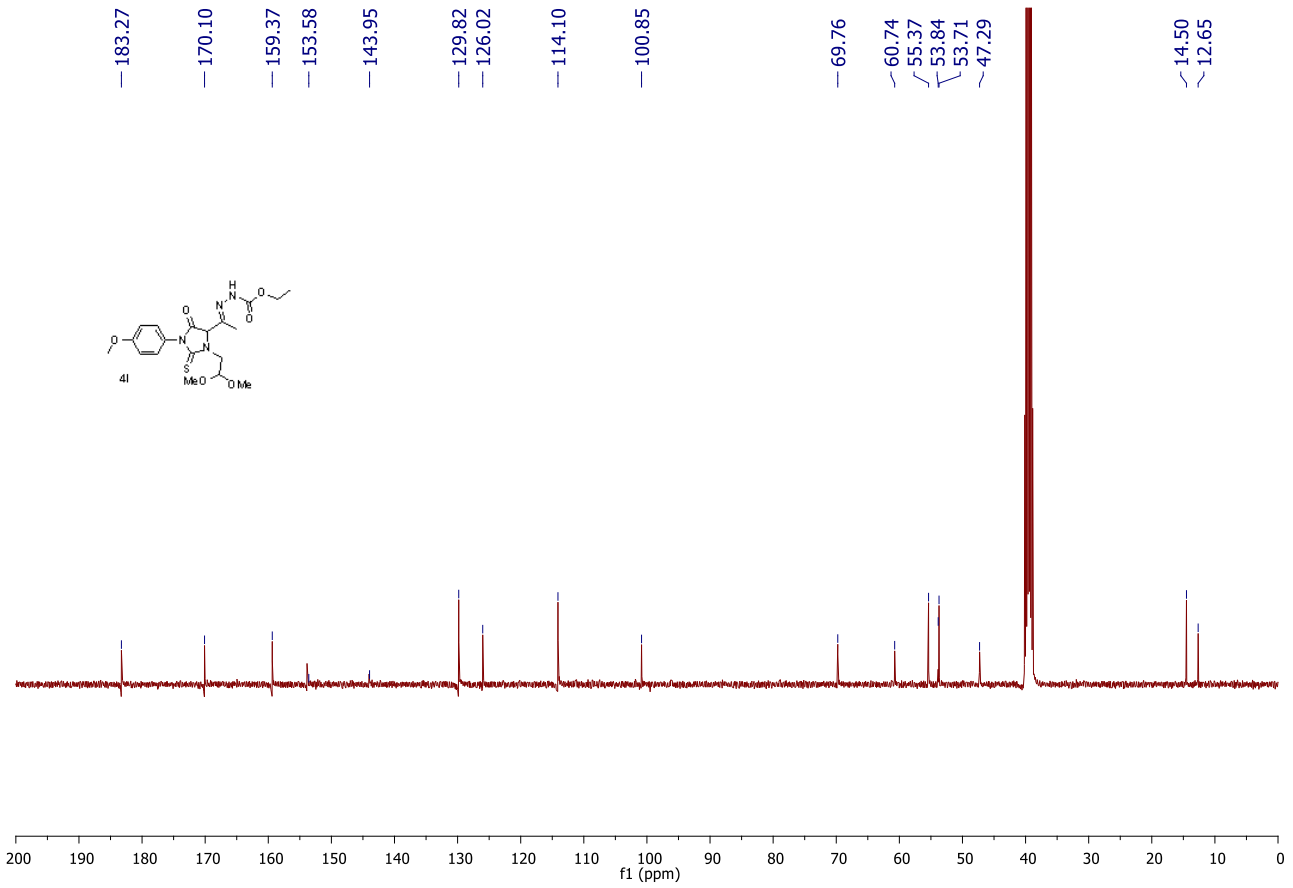
0.91
2.26
1.14
3.44
1.18
2.72
2.61
3.00
3.48
f1 (ppm)


183.27
170.10
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153.58
143.95
129.82
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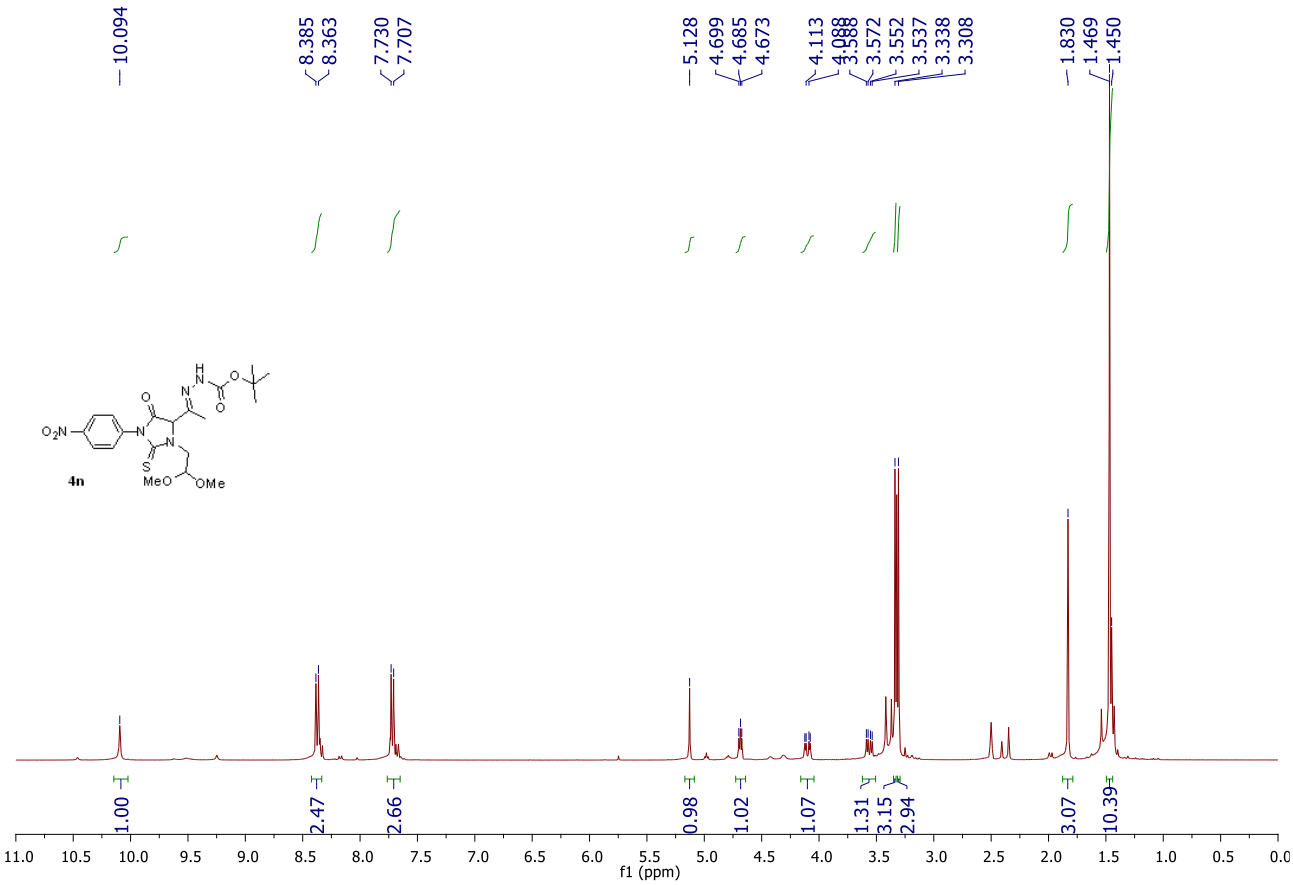
114.10
100.85
69.76
60.74
55.37
53.84
53.71
47.29
14.50
12.65
f1 (ppm)


10.094
8.385
8.363
7.730
7.707
5.128
4.699
4.685
4.673
4.113
3.572
3.552
3.537
3.338
3.308
1.830
1.469
1.450
4n
1.00
2.47
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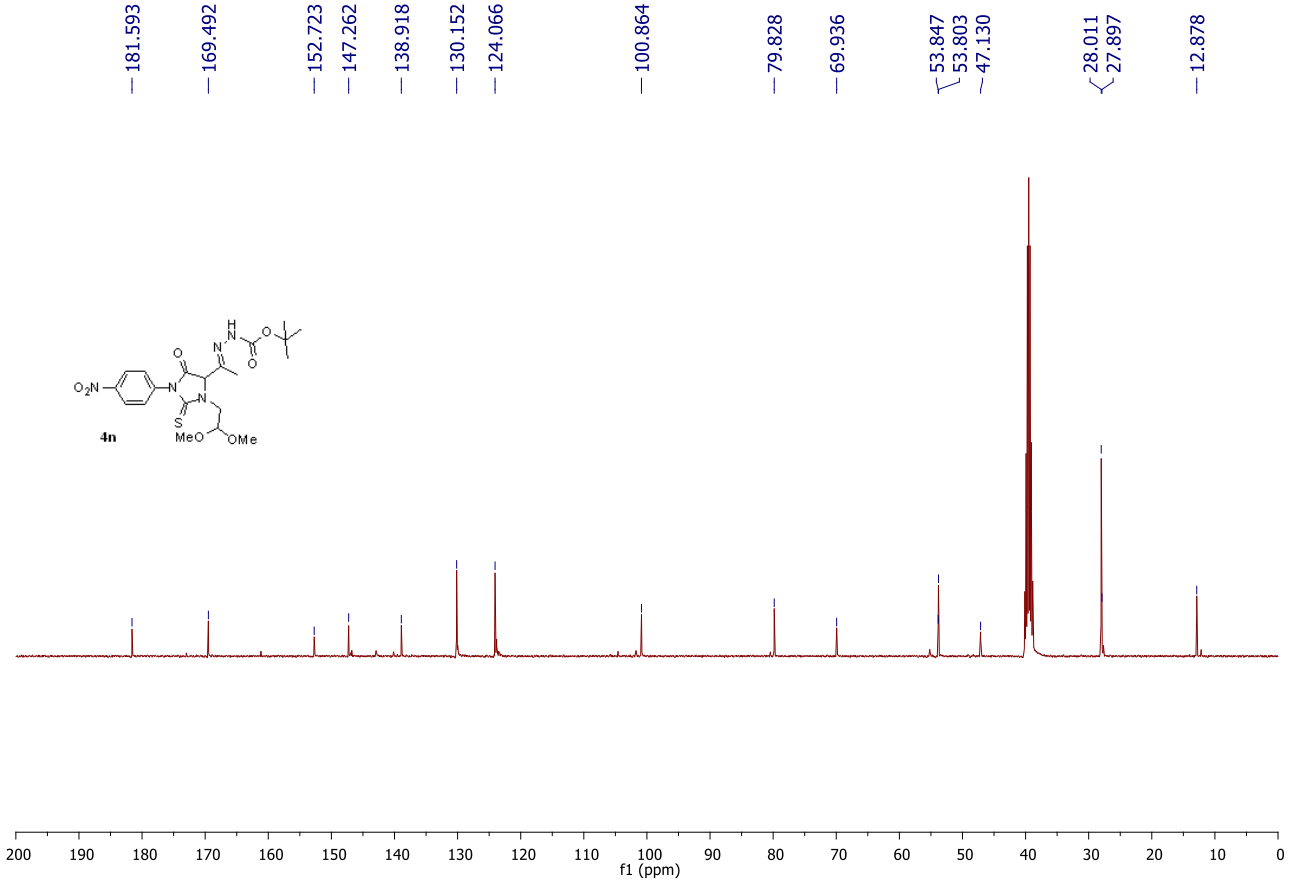
0.98
1.02
1.07
1.31
3.15
2.94
3.07
10.39
f1 (ppm)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138.918
130.152
124.066
100.864
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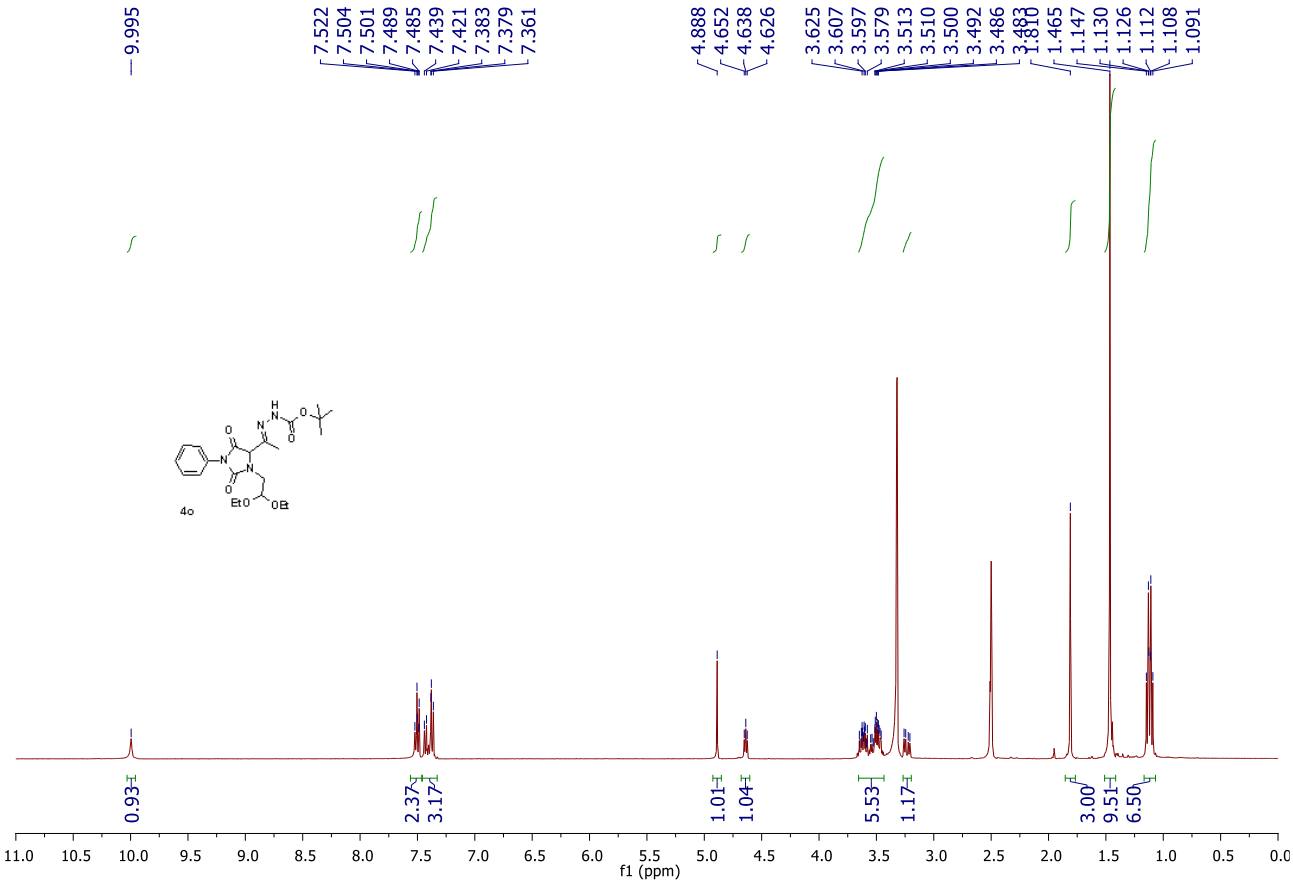
69.936
53.847
53.803
47.130
28.011
27.897
12.878
4n
f1 (ppm)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7.485
7.439
7.421
7.383
7.379
7.361
4.888
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4.638
4.626
3.625
3.607
3.597
3.579
3.513
3.510
3.500
3.492
3.486
3.483
1.810
1.465
1.147
1.130
1.126
1.112
1.108
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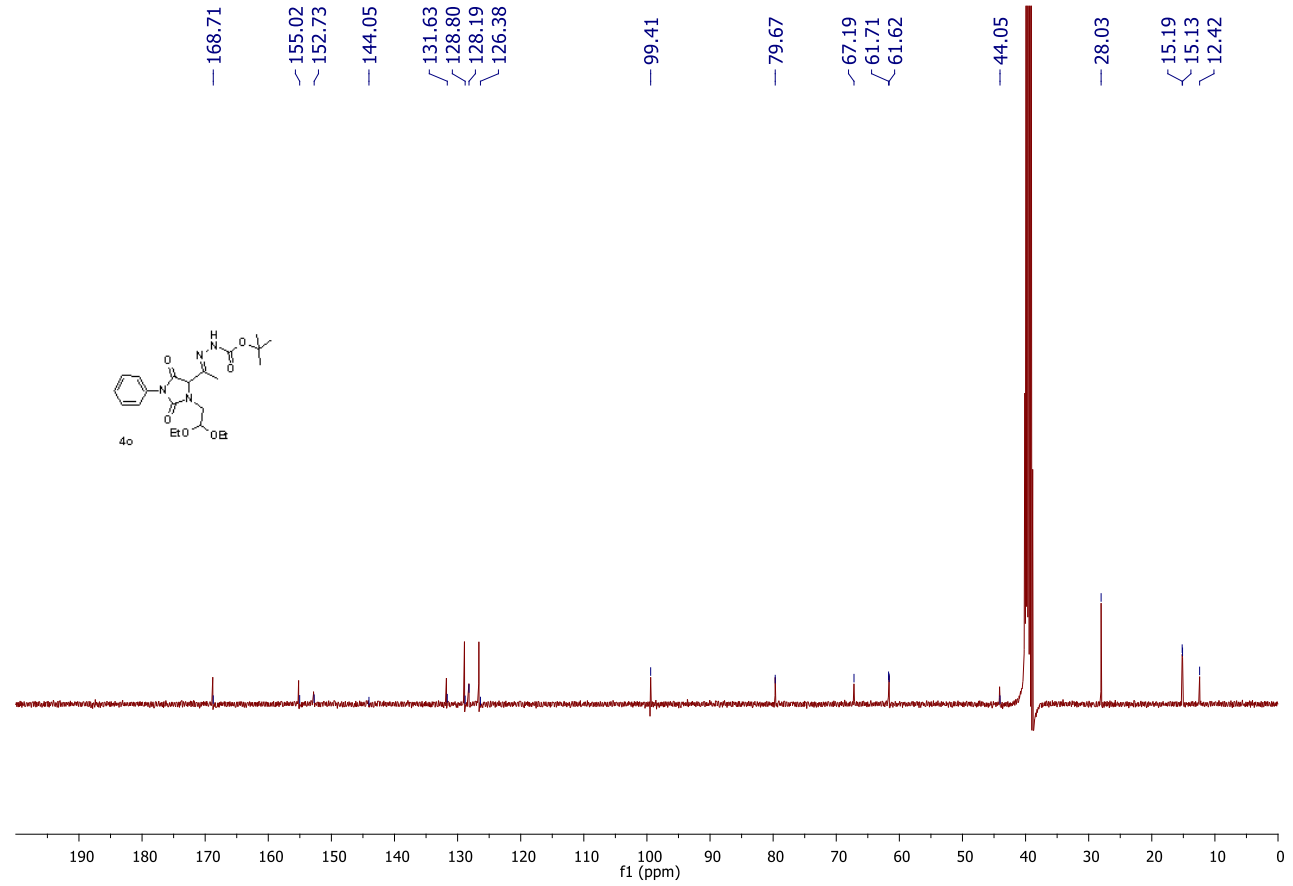
0.93
2.37
3.17
1.01
1.04
5.53
1.17
3.00
9.51
6.50
f1 (ppm)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144.05
131.63
128.80
128.19
126.38
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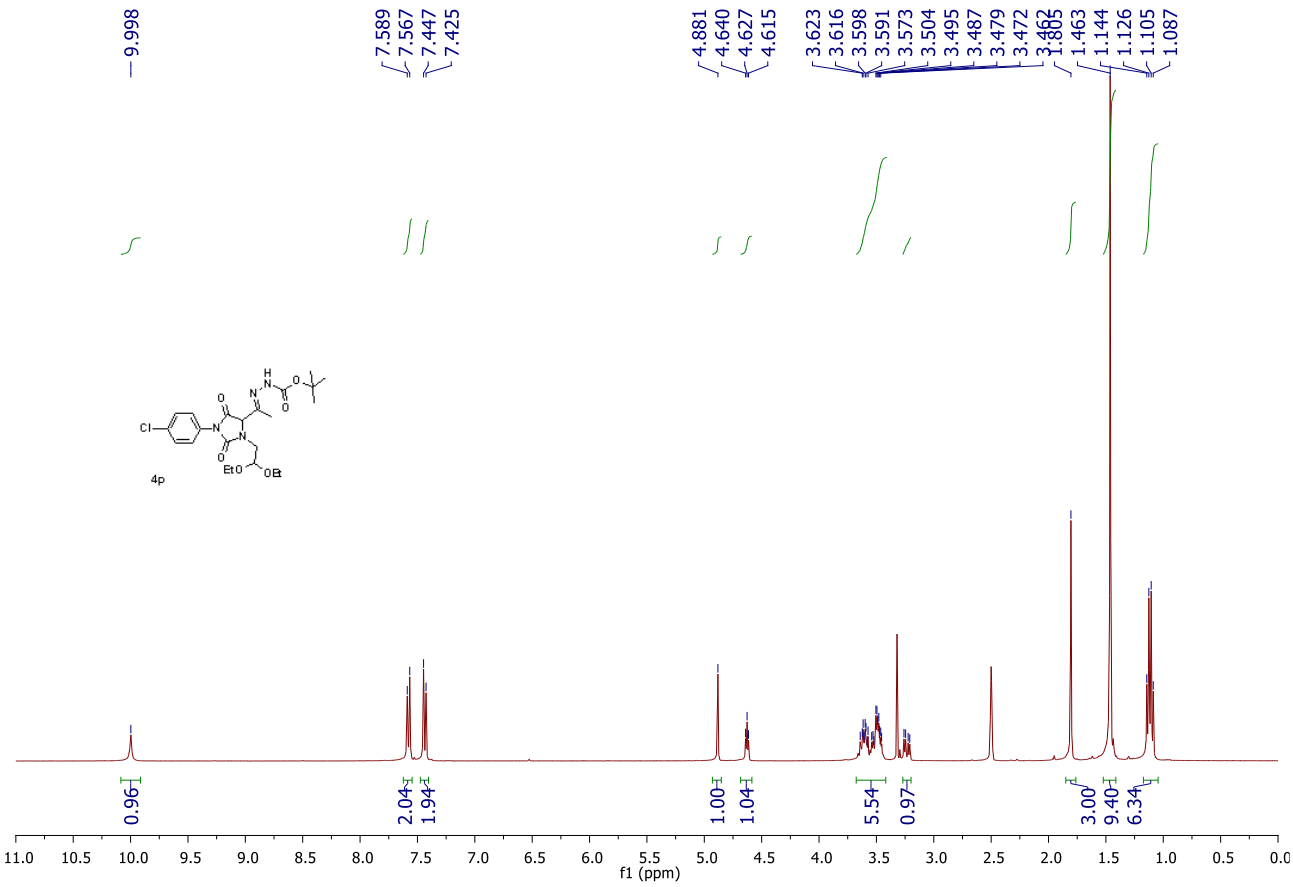
67.19
61.71
61.62
44.05
28.03
15.19
15.13
12.42
f1 (ppm)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7.567
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4.615
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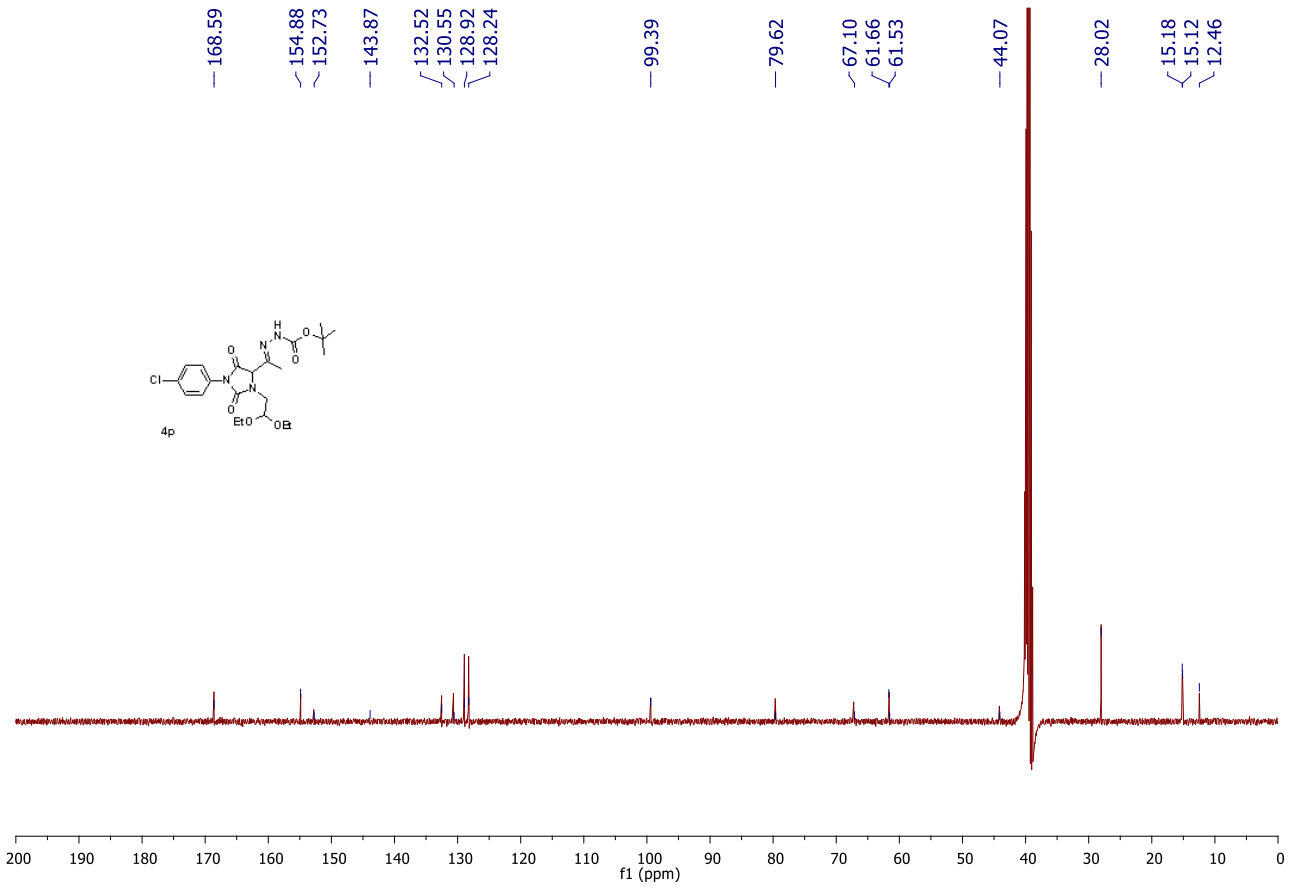
3.616
3.598
3.591
3.573
3.504
3.495
3.487
3.479
3.472
1.463
1.144
1.126
1.105
1.087
0.96
2.04
1.94
1.00
1.04
5.54
0.97
3.00
9.40
6.34
f1 (ppm)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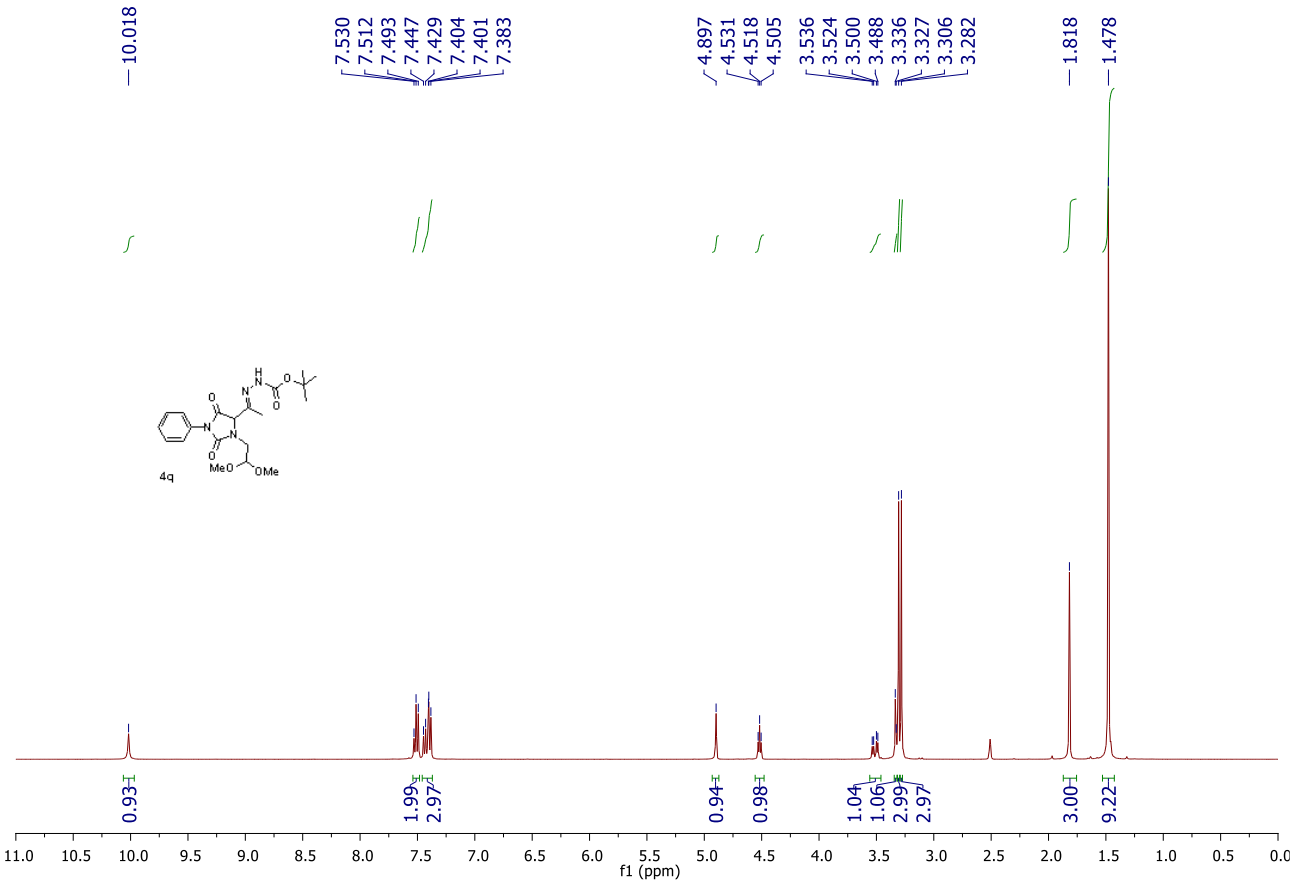
152.73
143.87
132.52
130.55
128.92
128.24
99.39
79.62
67.10
61.66
61.53
44.07
28.02
15.18
15.12
12.46
f1 (ppm)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7.401
7.383
4.897
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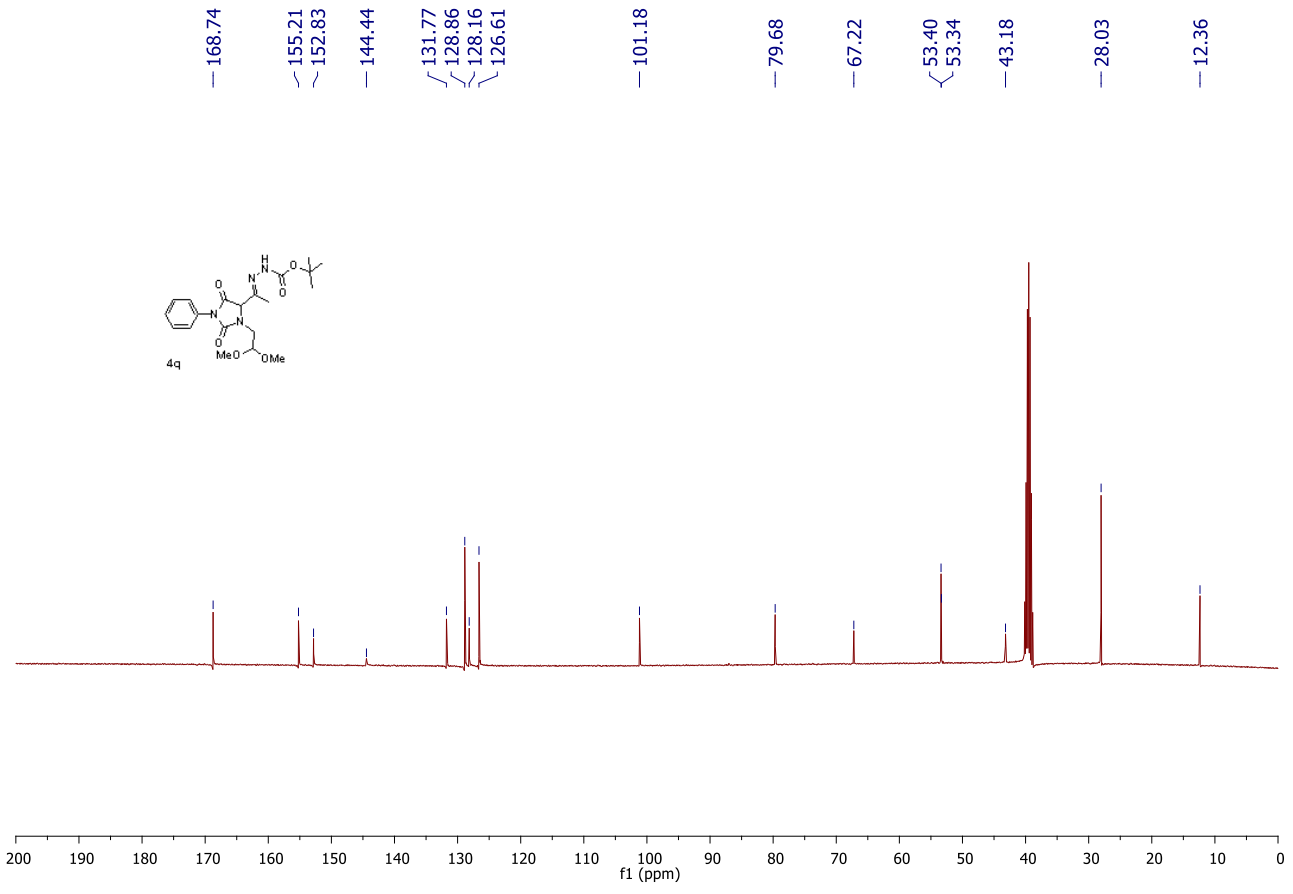
4.505
3.536
3.524
3.500
3.488
3.336
3.327
3.306
3.282
1.818
1.478
4q
0.93
1.99
2.97
0.94
0.98
1.04
1.06
2.99
2.97
3.00
9.22
f1 (ppm)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126.61
101.18
79.68
67.22
53.40
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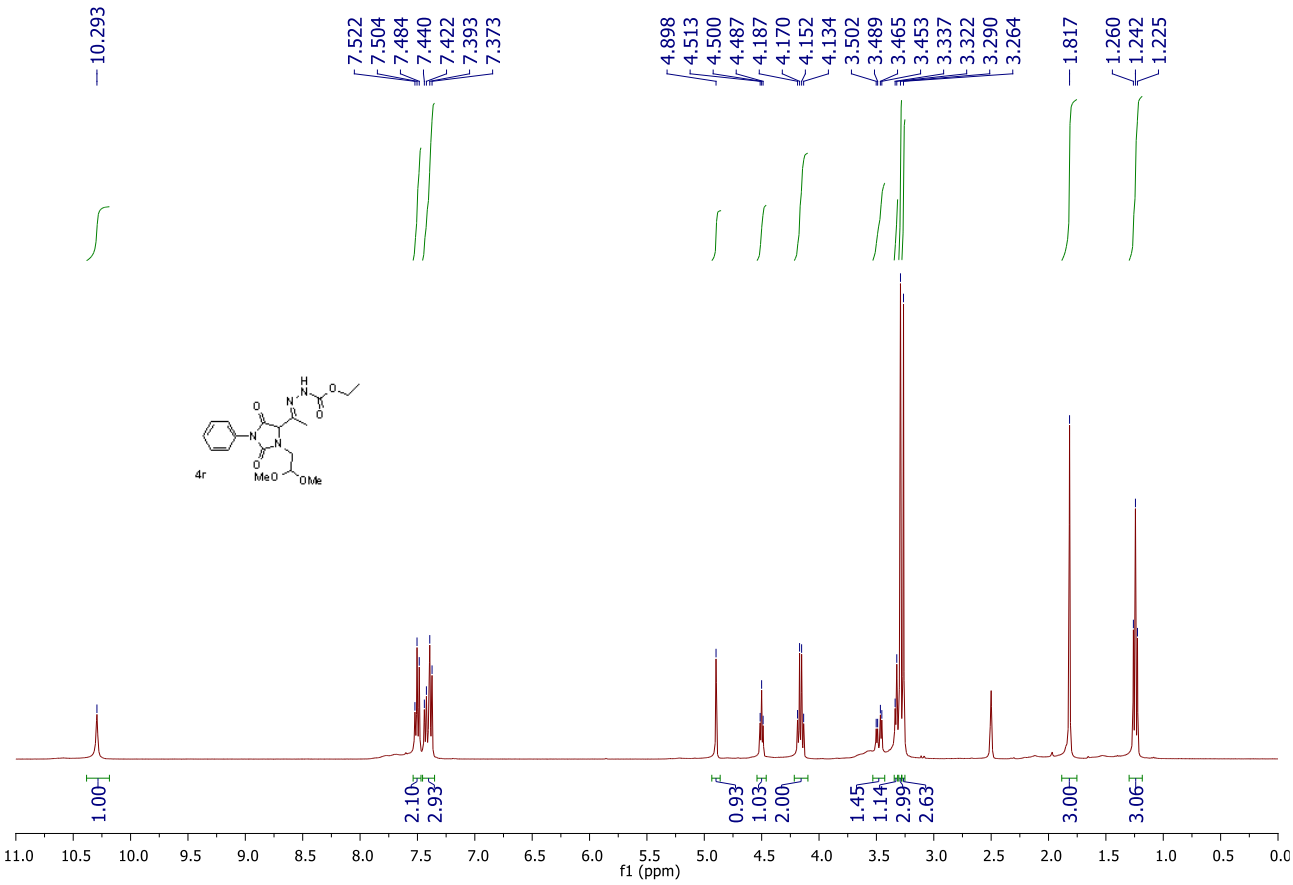
43.18
28.03
12.36
4q
f1 (ppm)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4.487
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4.170
4.152
4.134
3.502
3.489
3.465
3.453
3.337
3.322
3.290
3.264
1.817
1.260
1.242
1.225
4r
MeO
OMe
1.00
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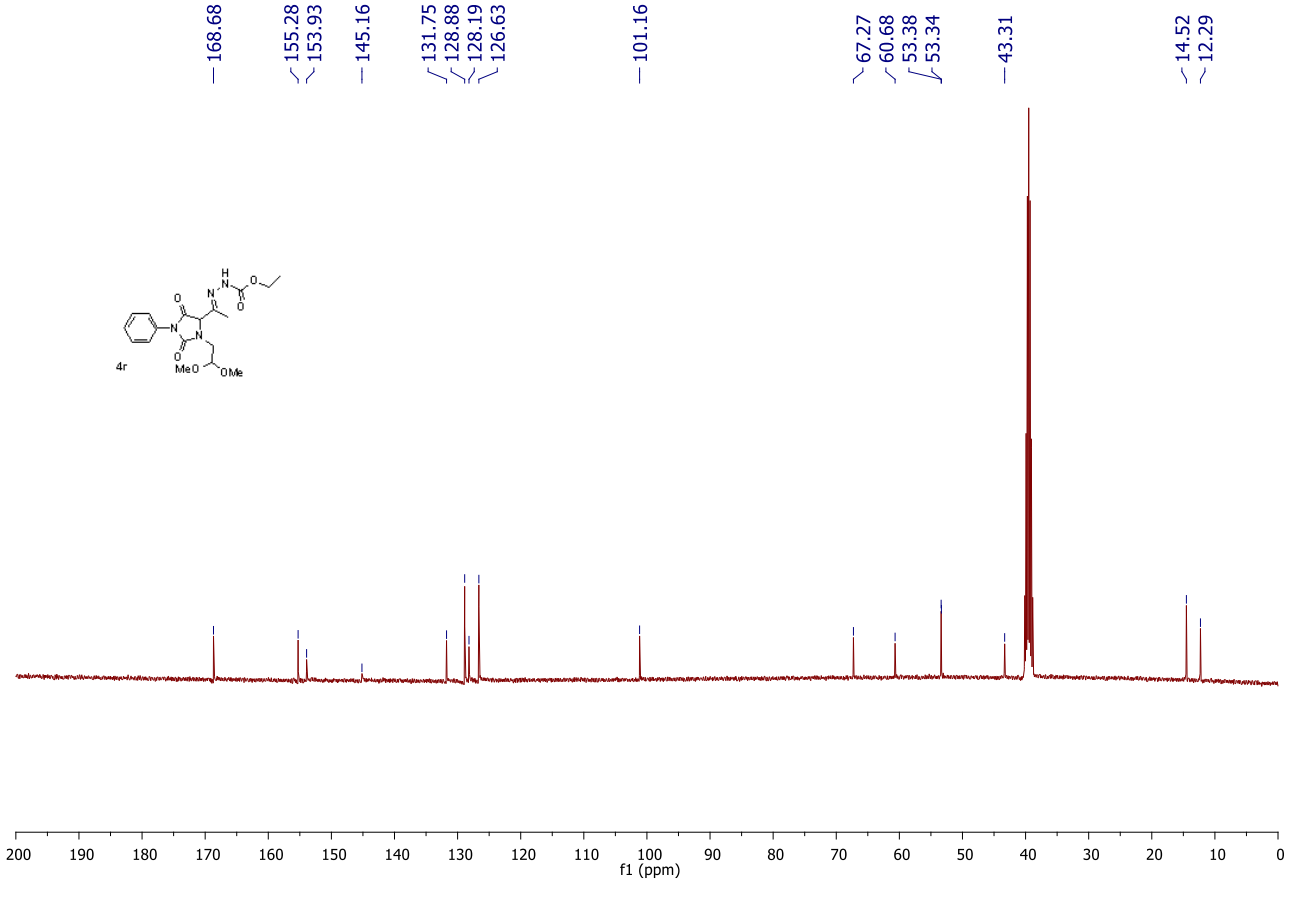
1.14
2.99
2.63
3.00
3.06
f1 (ppm)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128.19
126.63
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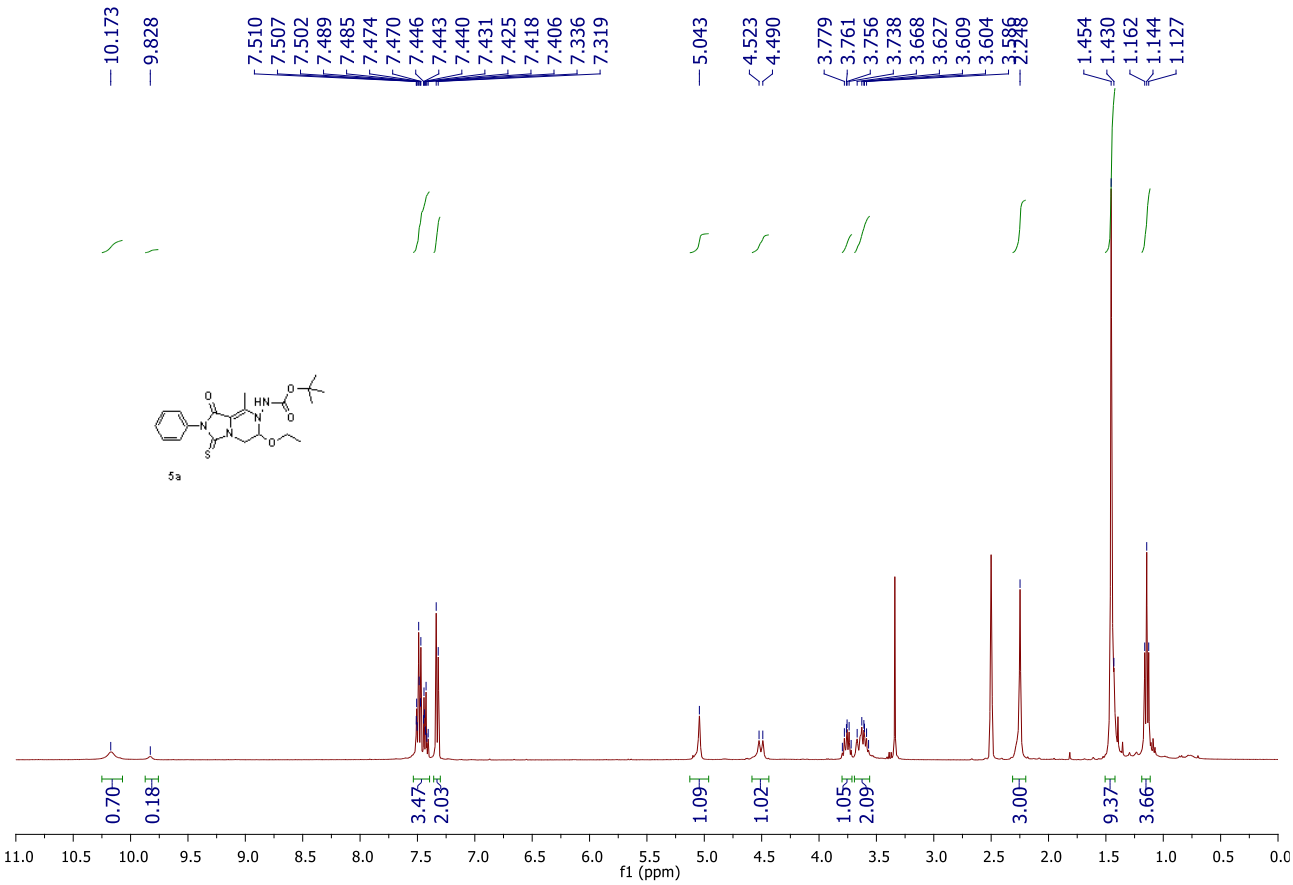
43.31
14.52
12.29
4r
MeO
OMe
f1 (ppm)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7.319
5.043
4.523
4.490
3.779
3.761
3.756
3.738
3.668
3.627
3.609
3.604
1.454
1.430
1.162
1.144
1.127
5a
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1.02
1.05
2.09
3.00
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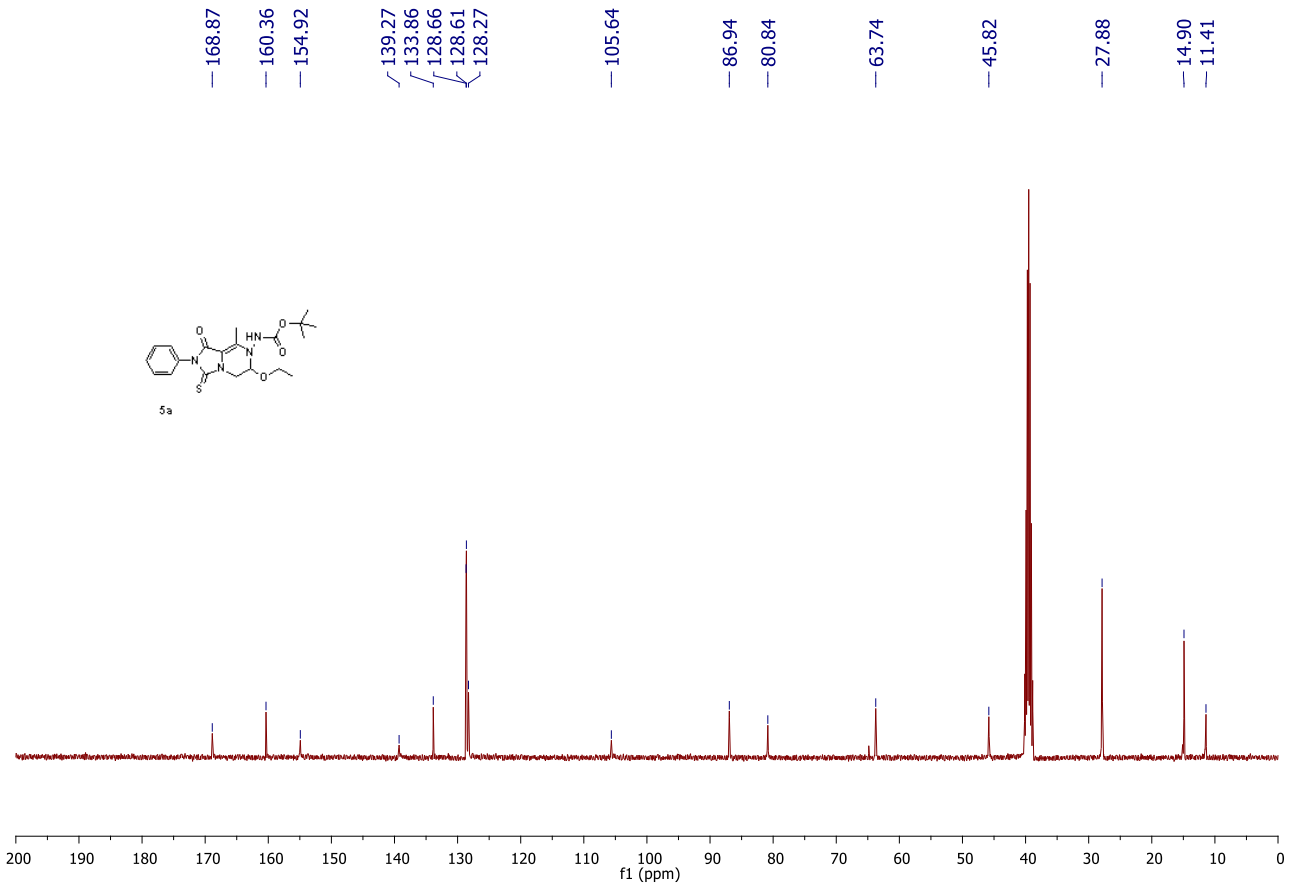
3.66
f1 (ppm)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128.27
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86.94
80.84
63.74
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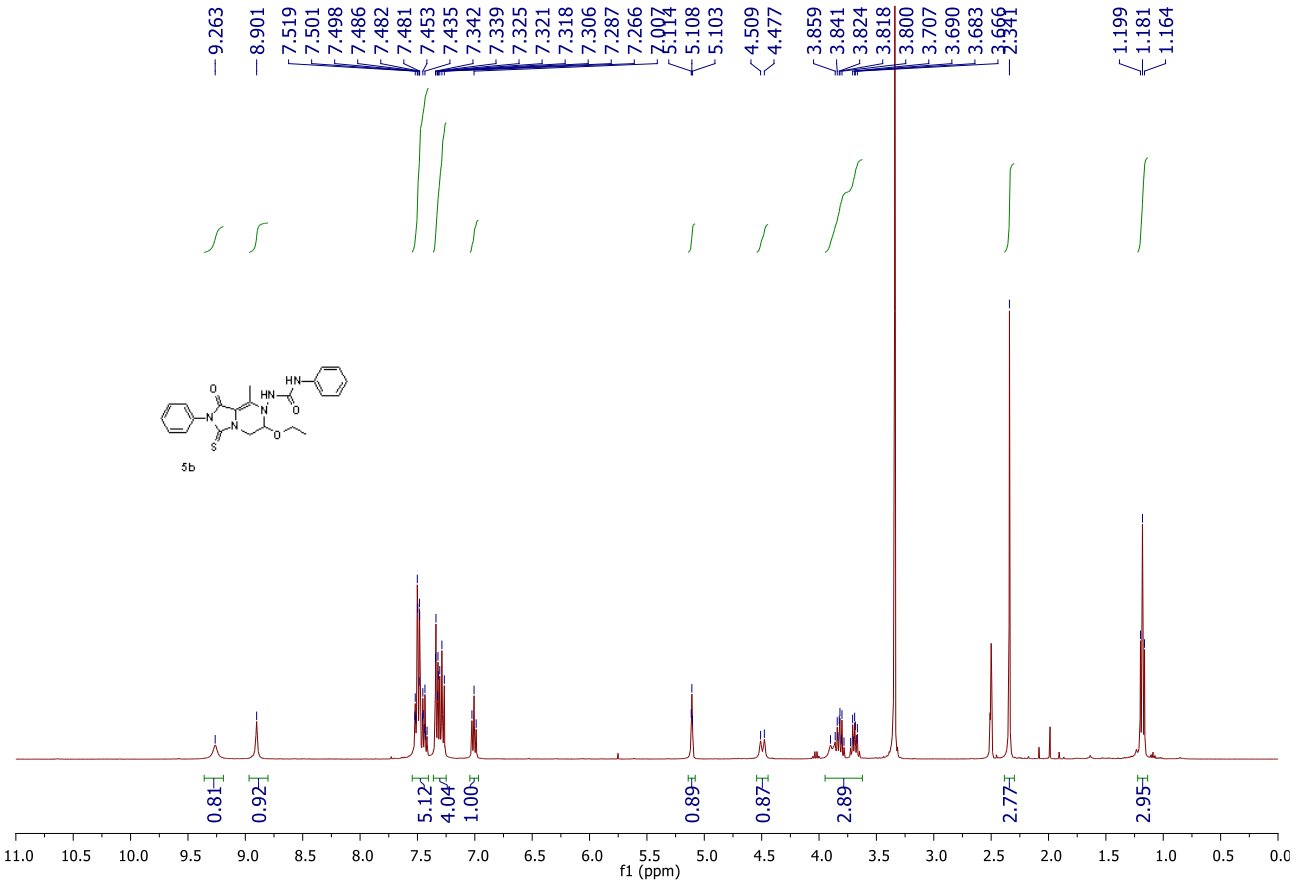
27.88
14.90
11.41
5a
f1 (ppm)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7.306
7.287
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5.114
5.108
5.103
4.509
4.477
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3.841
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3.818
3.800
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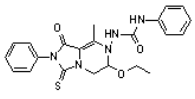
5b


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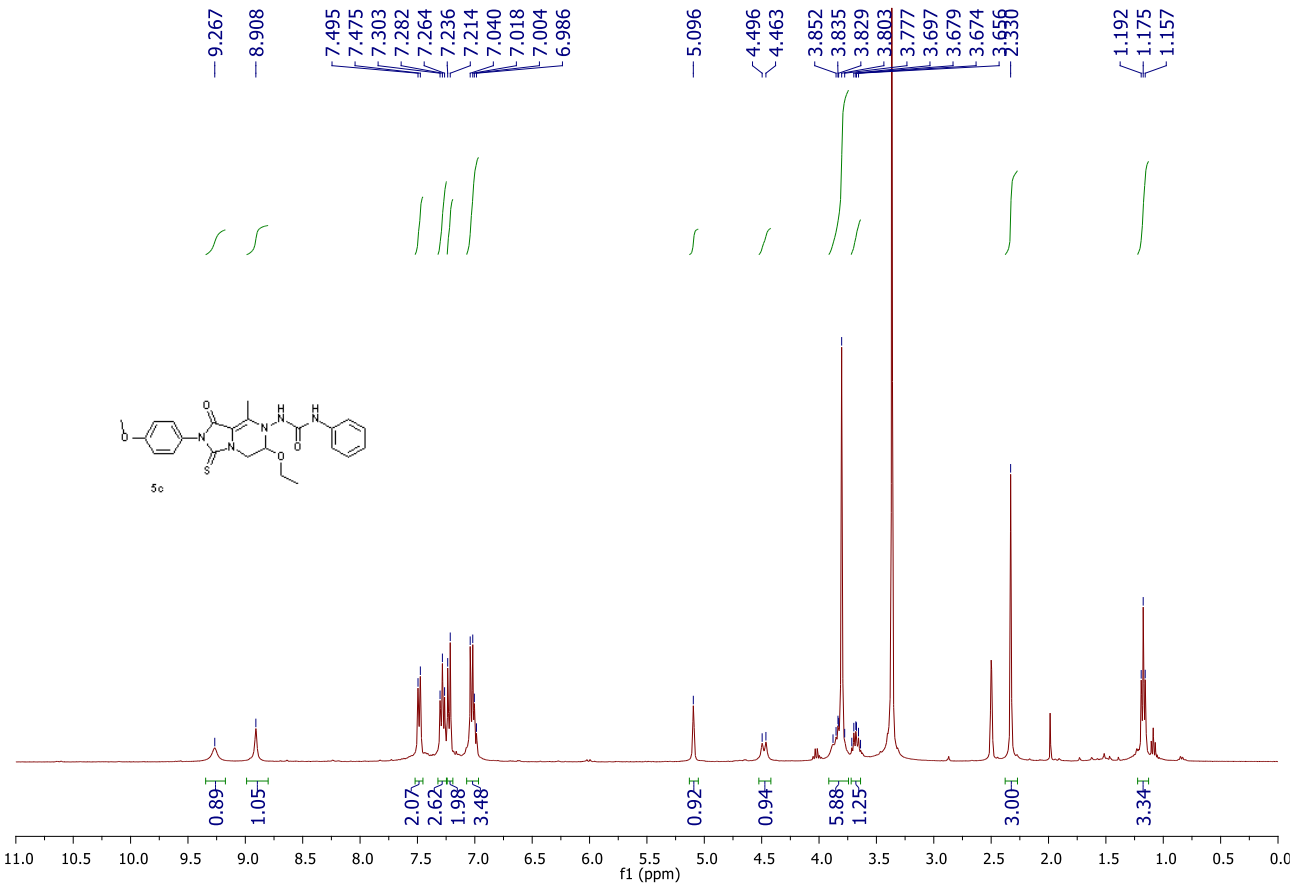
45.77
15.09
11.66
f1 (ppm)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7.236
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7.040
7.018
7.004
6.986
5.096
4.496
4.463
3.852
3.835
3.829
3.803
3.777
3.697
3.679
3.674
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3.330
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1.175
1.157
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1.25
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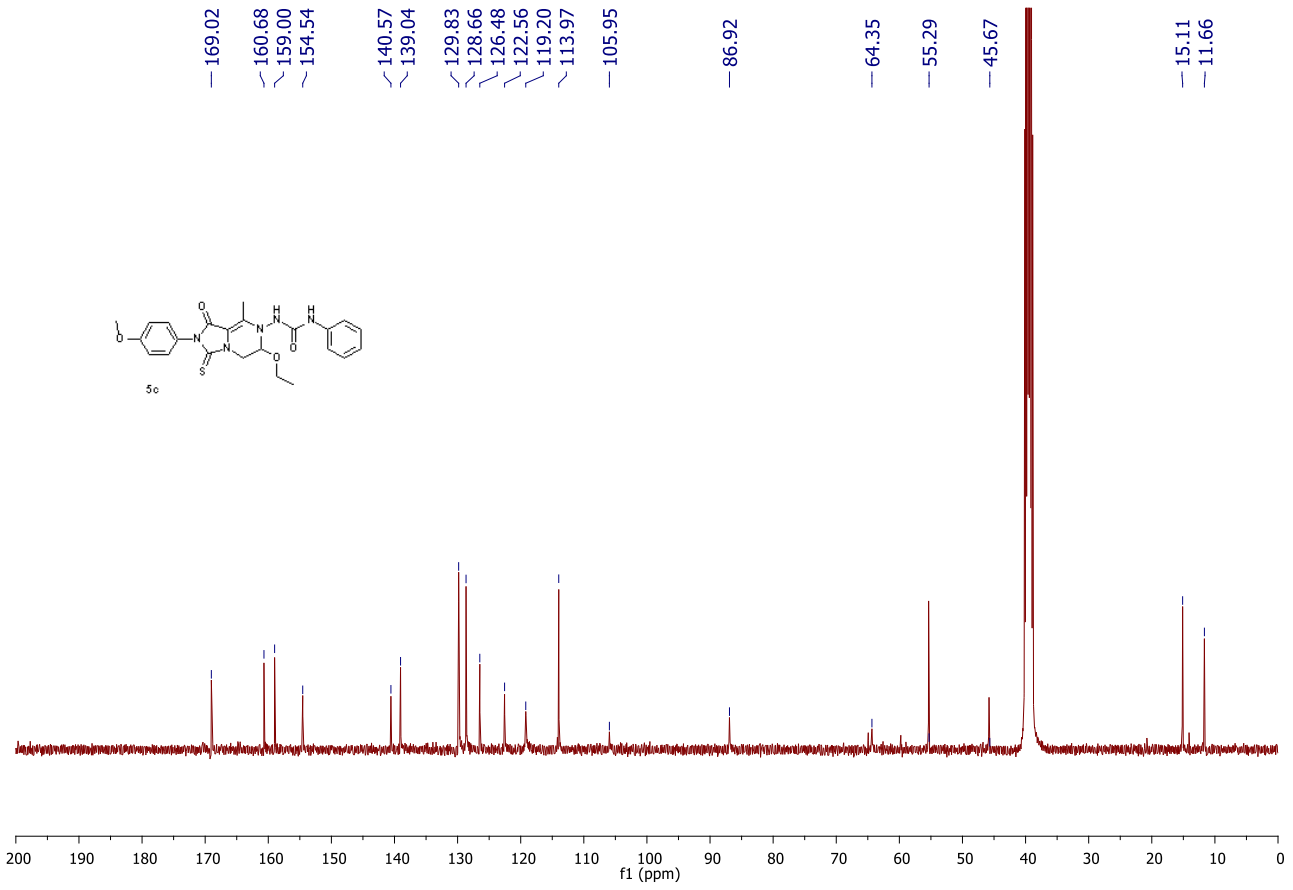
3.34
f1 (ppm)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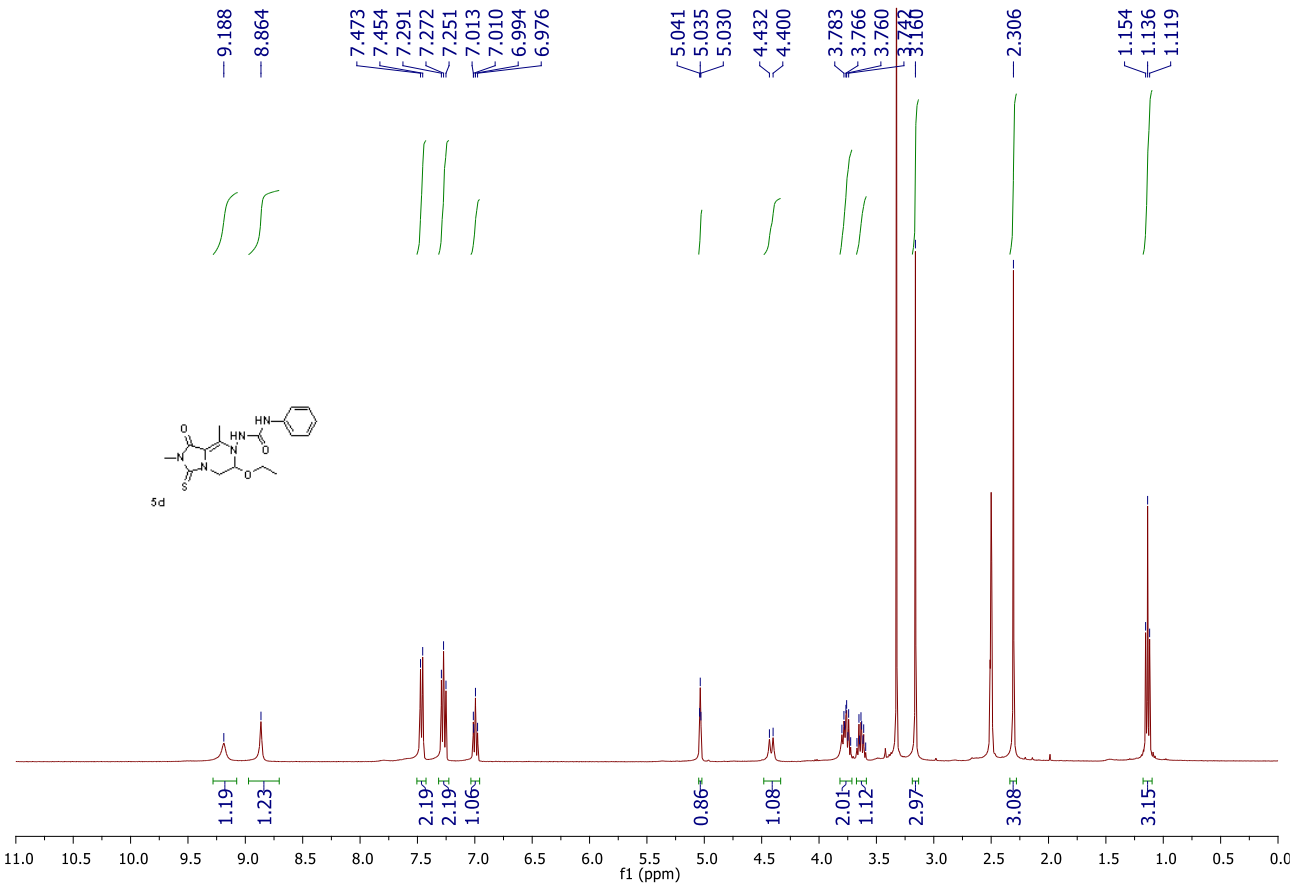
55.29
45.67
15.11
11.66
f1 (ppm)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5.035
5.030
4.432
4.400
3.783
3.766
3.760
3.747
3.160
2.306
1.154
1.136
1.119
1.19
1.23
2.19
2.19
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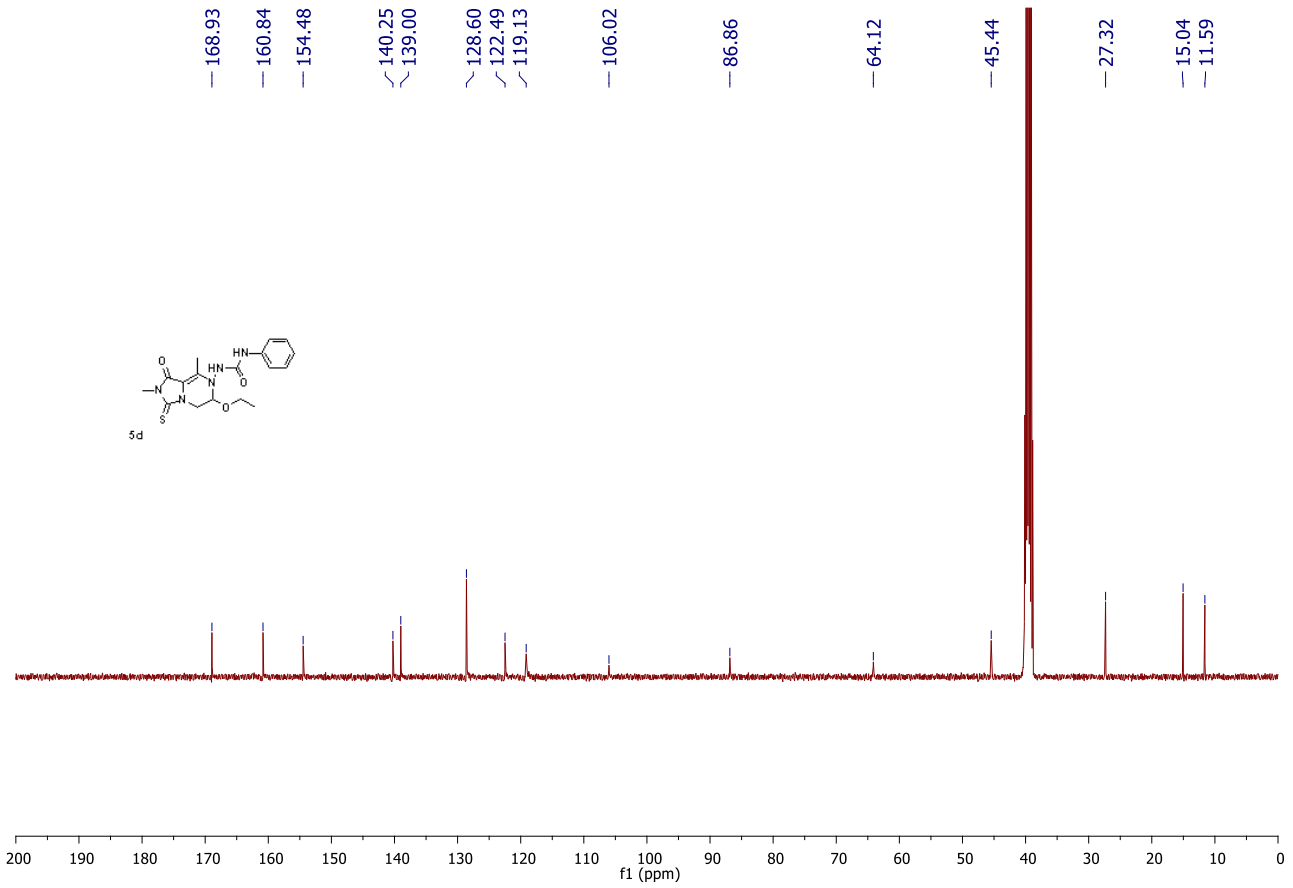
3.08
3.15
f1 (ppm)
5d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106.02
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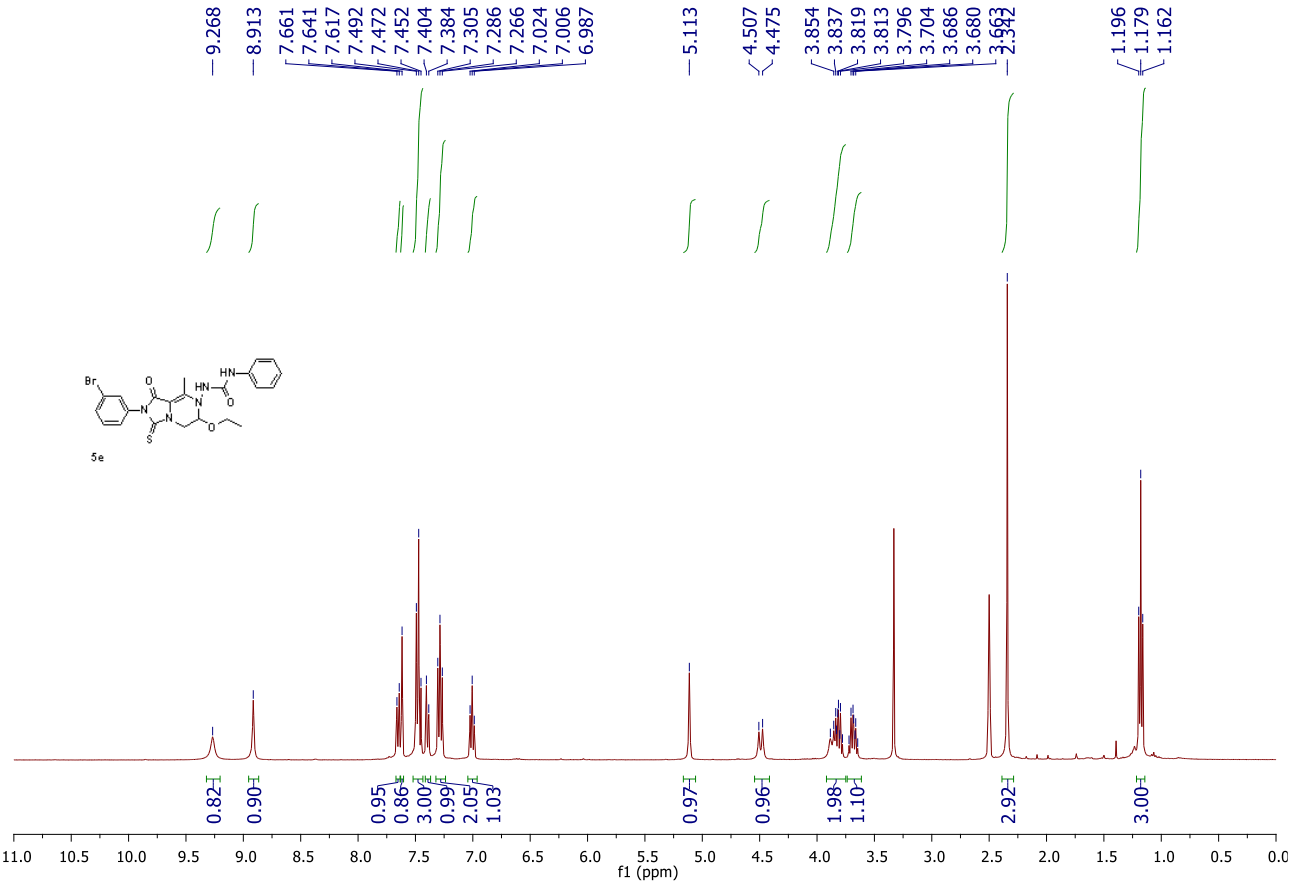
64.12
45.44
27.32
15.04
11.59
f1 (ppm)
5d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6.987
5.113
4.507
4.475
3.854
3.837
3.819
3.813
3.796
3.704
3.686
3.680
2.342
1.196
1.179
1.162
0.82
0.90
0.95
0.86
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1.03
0.97
0.96
1.98
1.10
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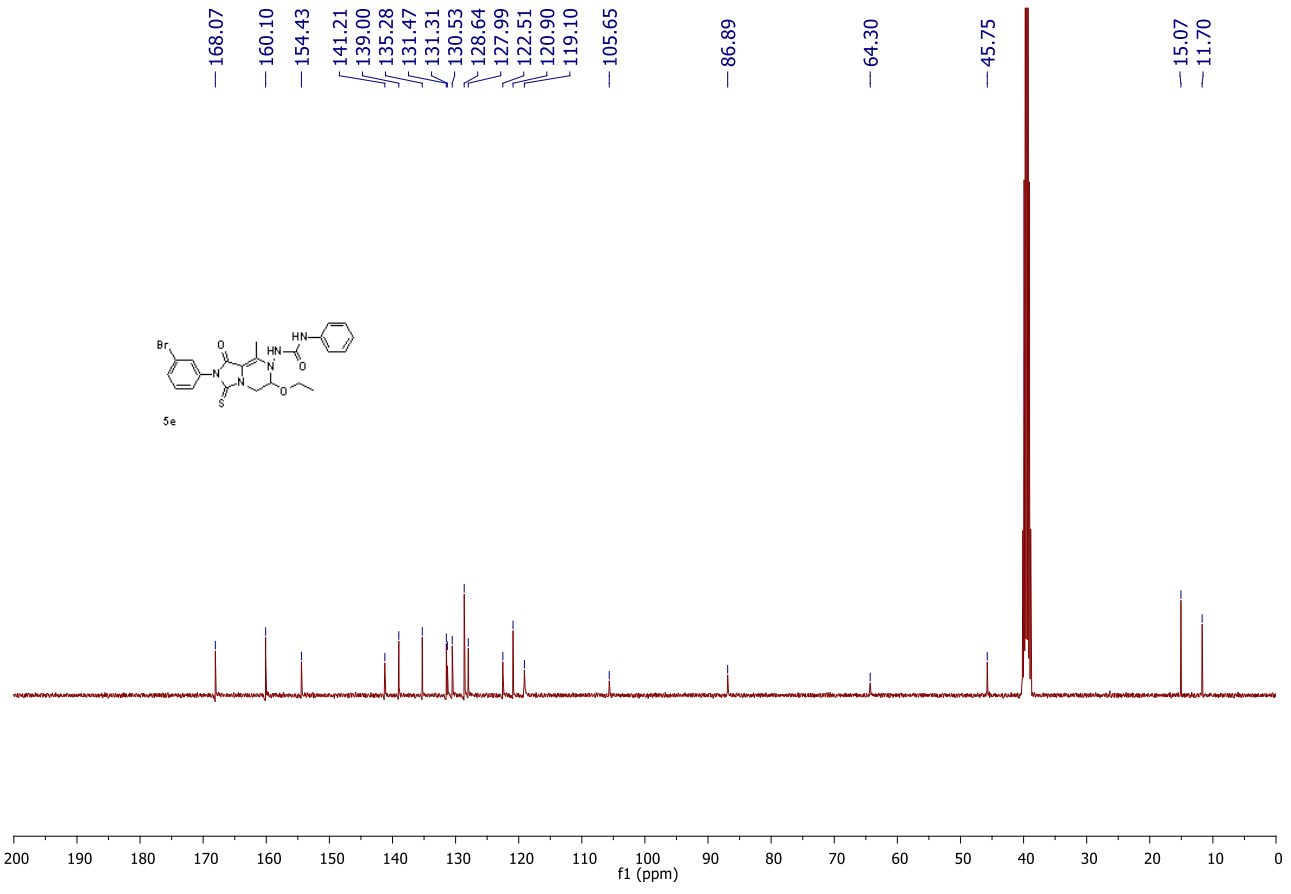
3.00
f1 (ppm)
5e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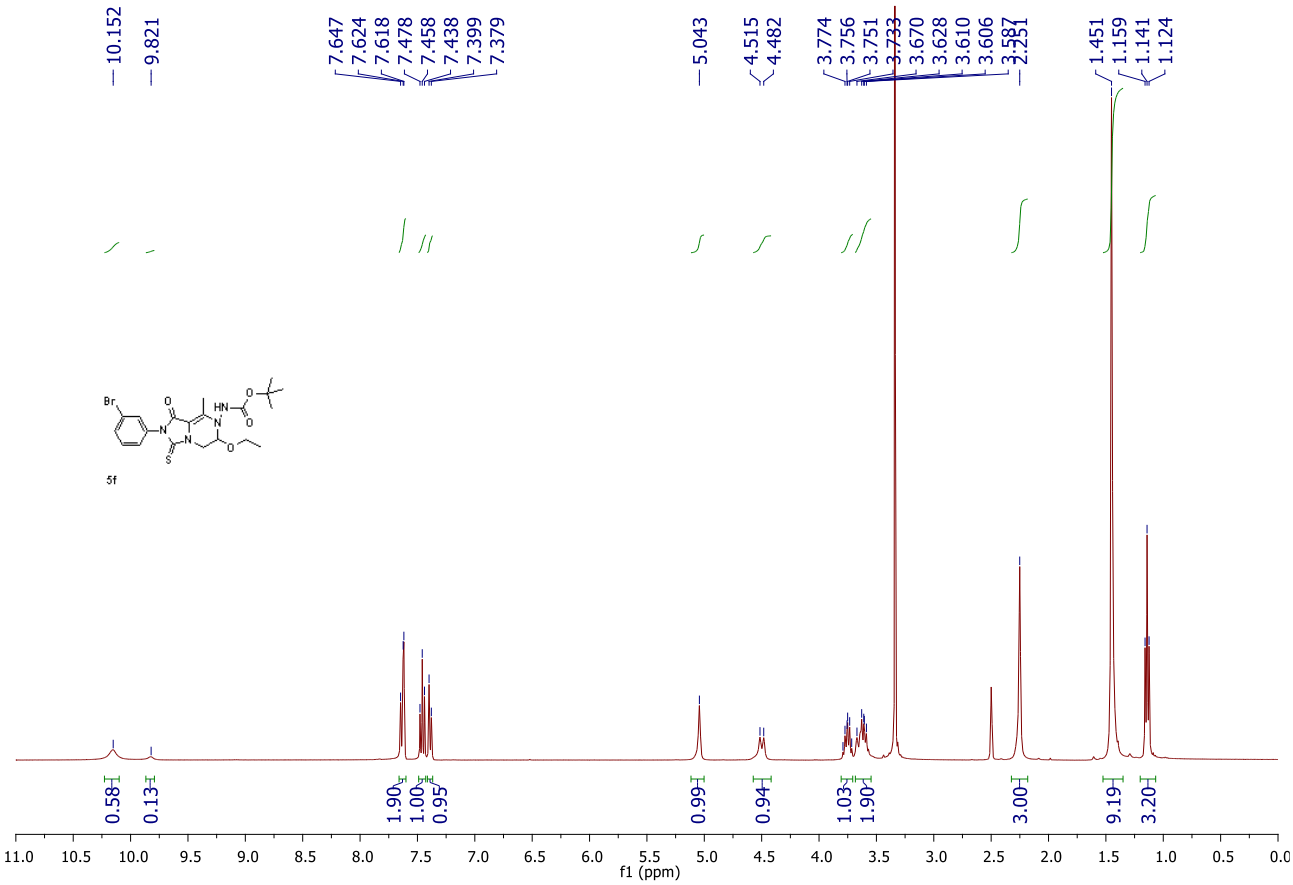
11.70
f1 (ppm)
5e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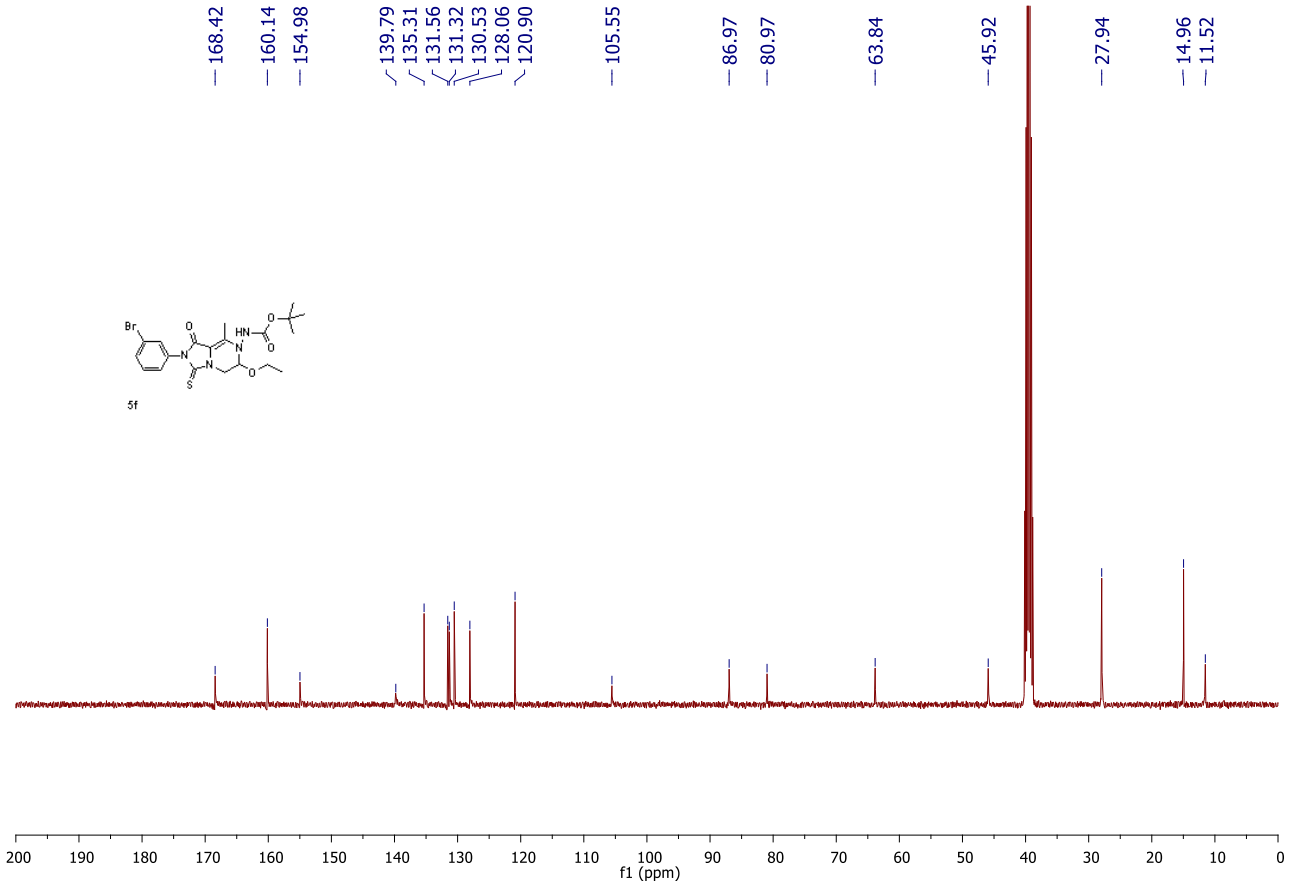
7.379
5.043
4.515
4.482
3.774
3.756
3.751
3.733
3.670
3.628
3.610
3.606
2.251
1.451
1.159
1.141
1.124
0.58
0.13
1.90
1.00
0.95
0.99
0.94
1.03
1.90
3.00
9.19
3.20
f1 (ppm)
5f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154.98
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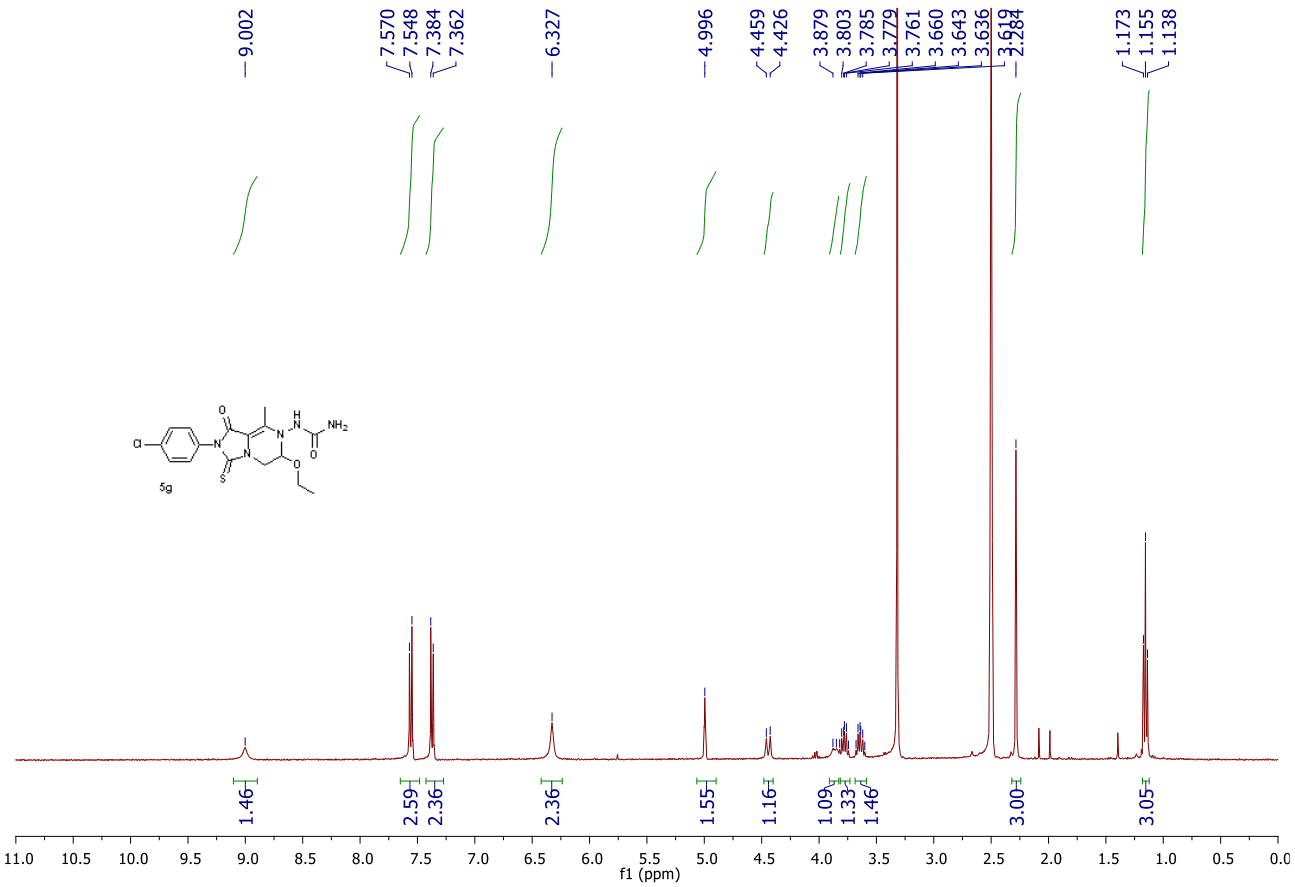
135.31
131.56
131.32
130.53
128.06
120.90
105.55
86.97
80.97
63.84
45.92
27.94
14.96
11.52
f1 (ppm)
5f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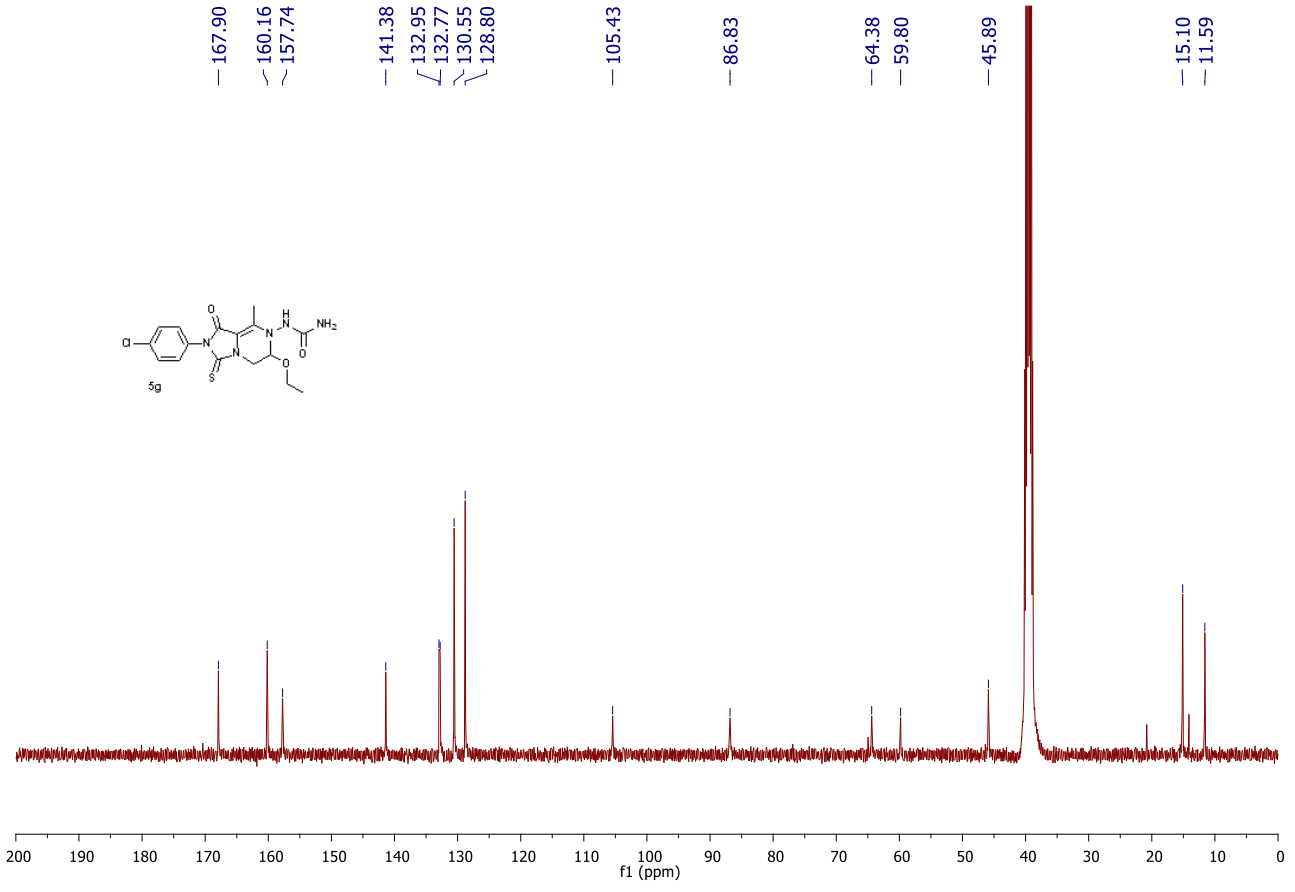
4.459
4.426
3.879
3.803
3.785
3.779
3.761
3.660
3.643
3.636
3.619
2.284
1.173
1.155
1.138
1.46
2.59
2.36
2.36
1.55
1.16
1.09
1.33
1.46
3.00
3.05
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
5g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160.16
157.74
141.38
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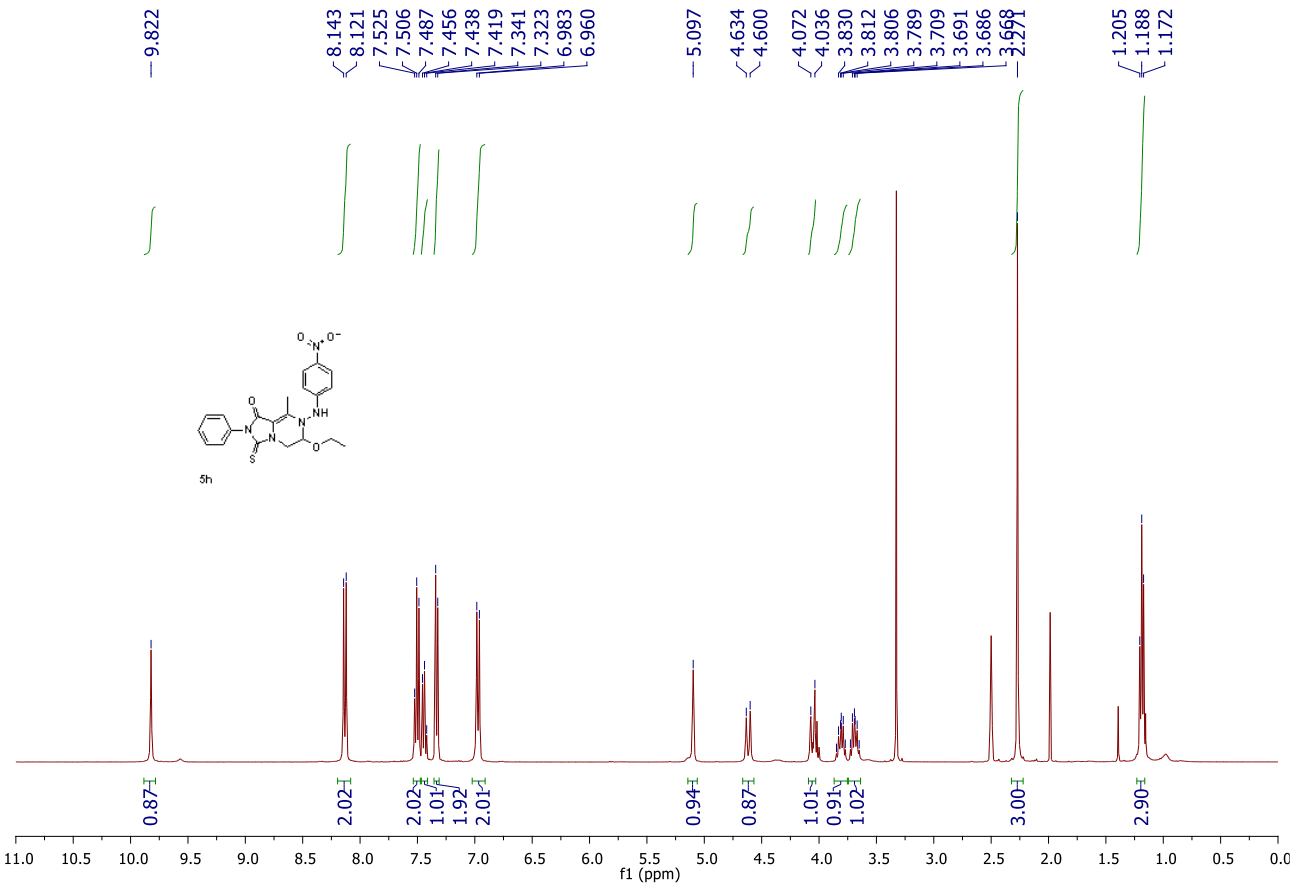
132.77
130.55
128.80
105.43
86.83
64.38
59.80
45.89
15.10
11.59
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
5g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8.121
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7.456
7.438
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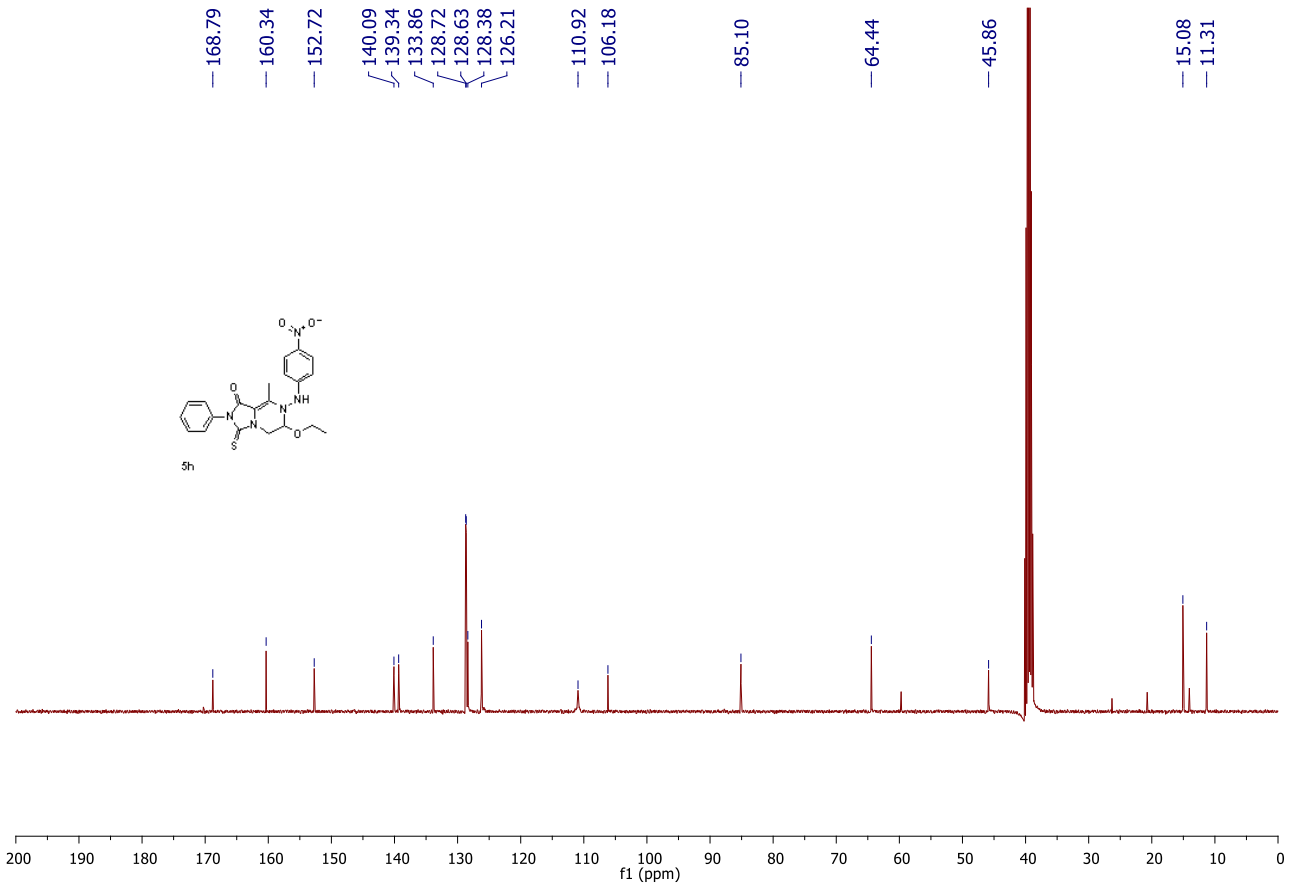
7.341
7.323
6.983
6.960
5.097
4.634
4.600
4.072
4.036
3.830
3.812
3.806
3.789
3.709
3.691
3.686
3.668
2.271
1.205
1.188
1.172
5h
0.87
2.02
2.02
1.01
1.92
2.01
0.94
0.87
1.01
0.91
1.02
3.00
2.90
f1 (ppm)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139.34
133.86
128.72
128.63
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126.21
110.92
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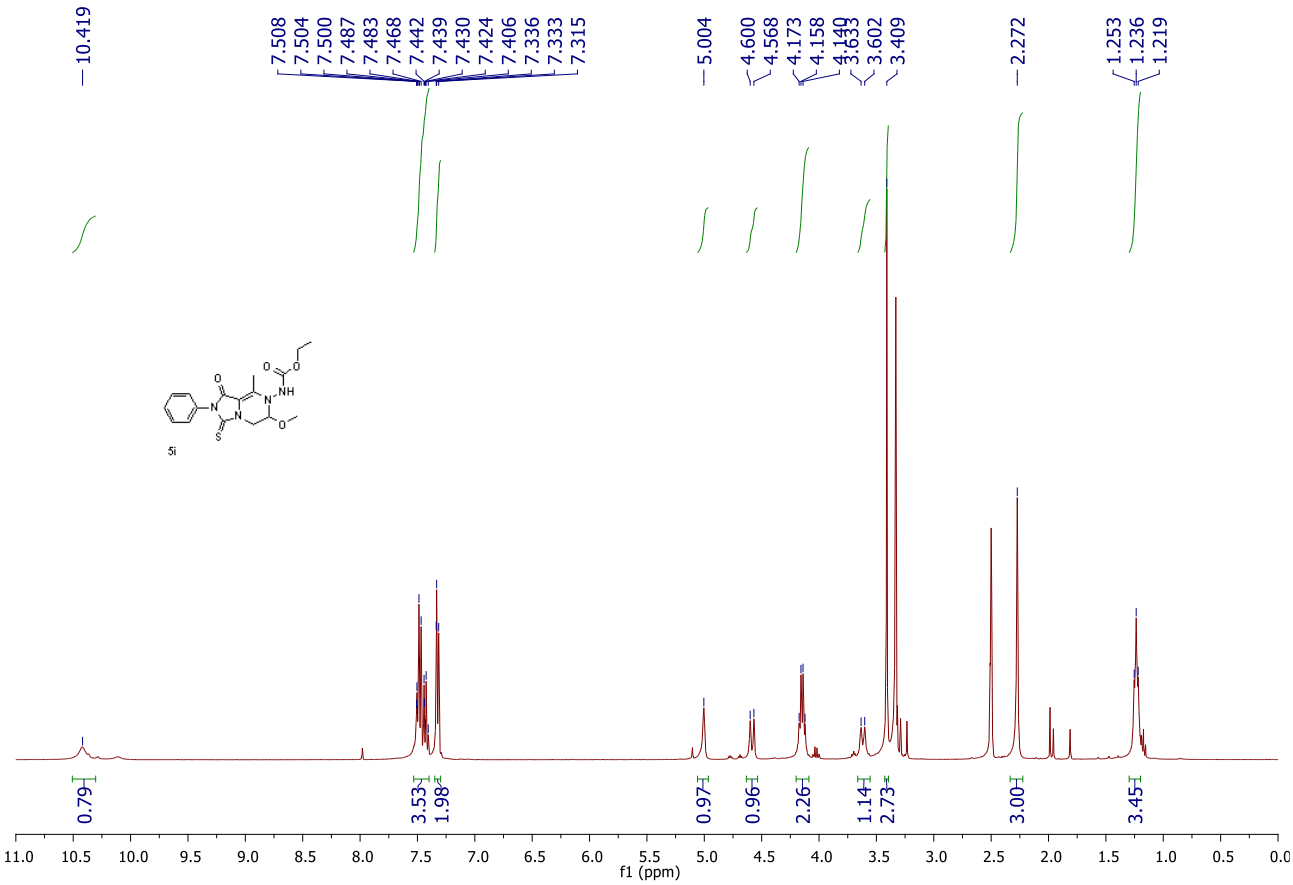
85.10
64.44
45.86
15.08
11.31
5h
f1 (ppm)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7.504
7.500
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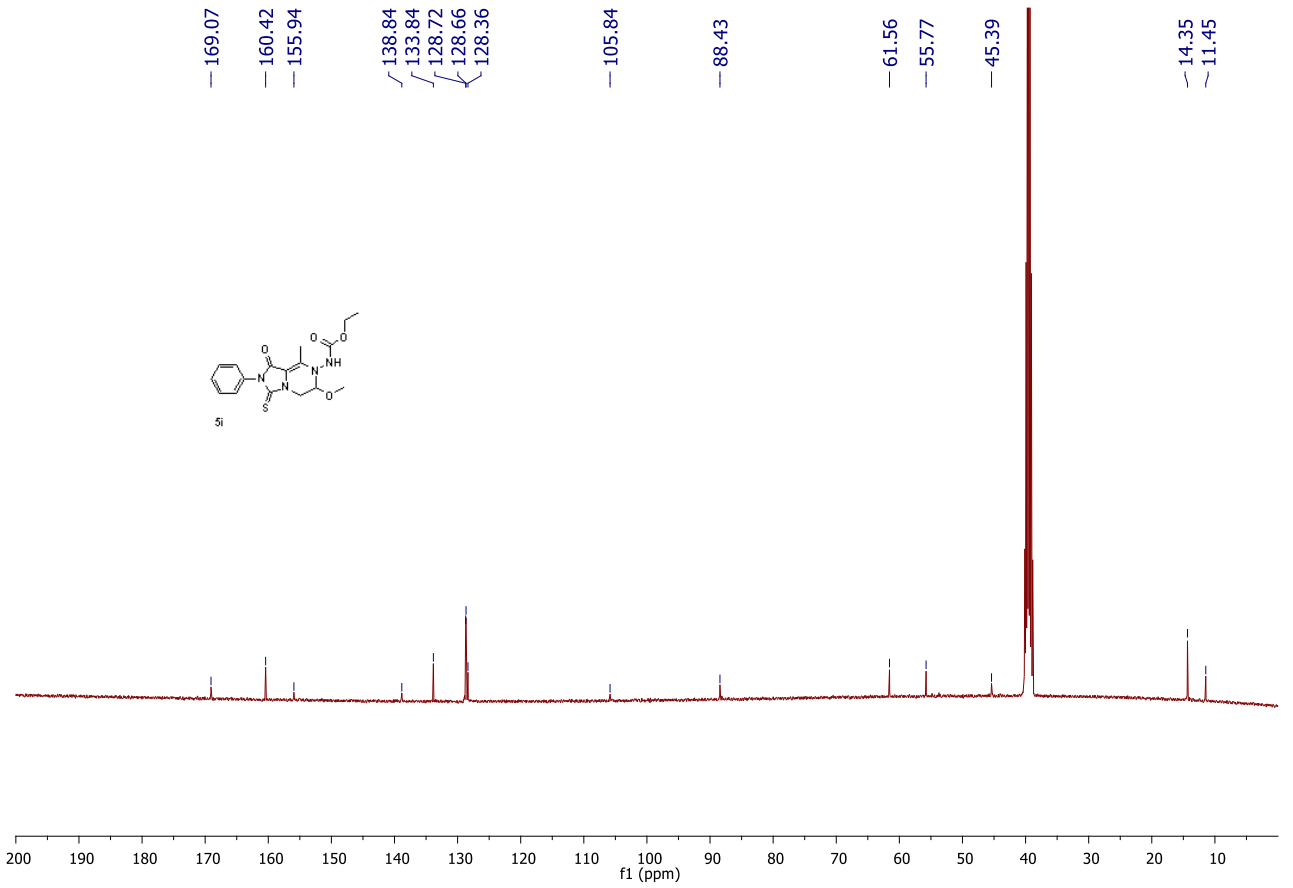
7.442
7.439
7.430
7.424
7.406
7.336
7.333
7.315
5.004
4.600
4.568
4.173
4.158
4.140
3.633
3.602
3.409
2.272
1.253
1.236
1.219
0.79
3.53
1.98
0.97
0.96
2.26
1.14
2.73
3.00
3.45
5i
f1 (ppm)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133.84
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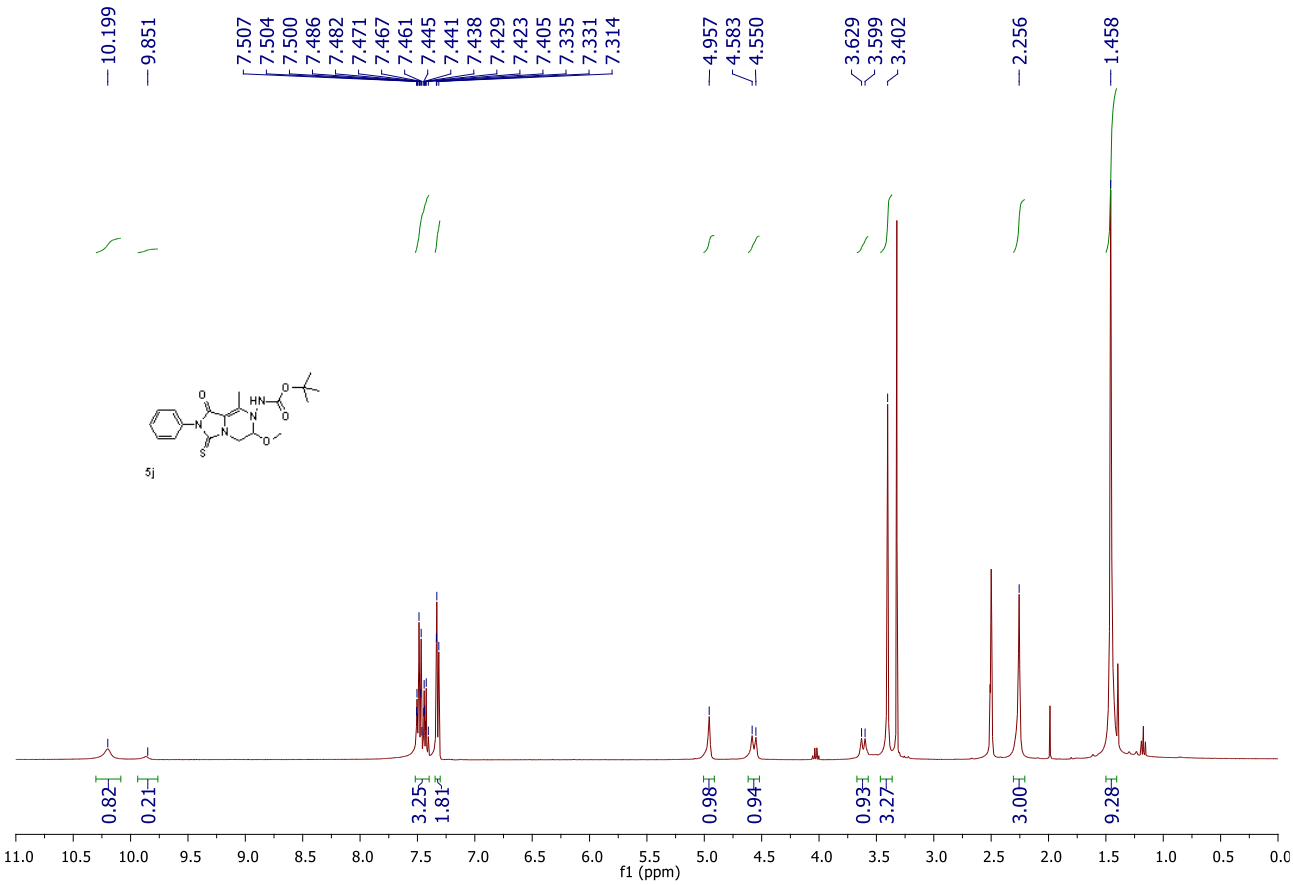
128.66
128.36
105.84
88.43
61.56
55.77
45.39
14.35
11.45
5i
f1 (ppm)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7.467
7.461
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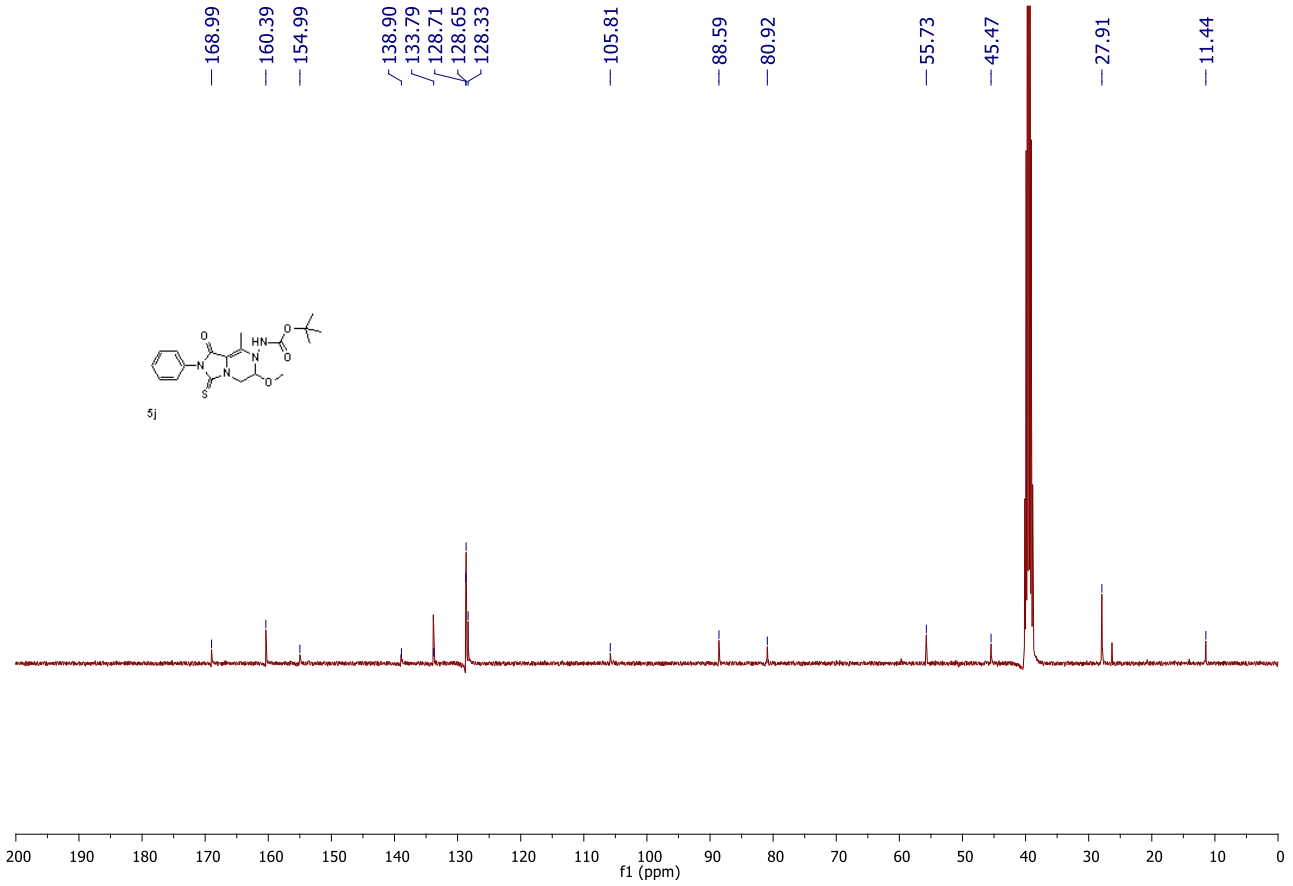
7.441
7.438
7.429
7.423
7.405
7.335
7.331
7.314
4.957
4.583
4.550
3.629
3.599
3.402
2.256
1.458
0.82
0.21
3.25
1.81
0.98
0.94
0.93
3.27
3.00
9.28
5j
f1 (ppm)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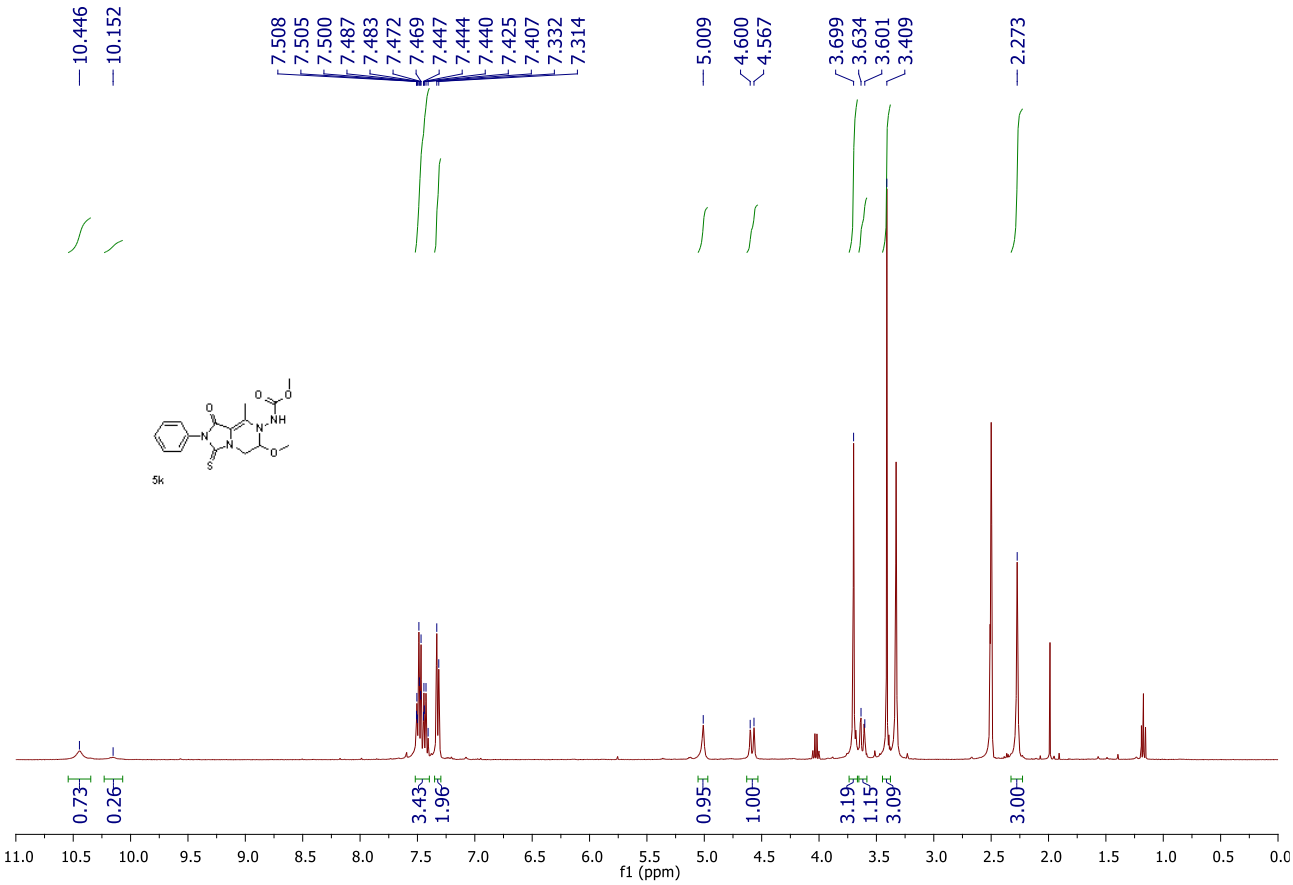
154.99
138.90
133.79
128.71
128.65
128.33
105.81
88.59
80.92
55.73
45.47
27.91
11.44
5j
f1 (ppm)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10.152
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7.505
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7.487
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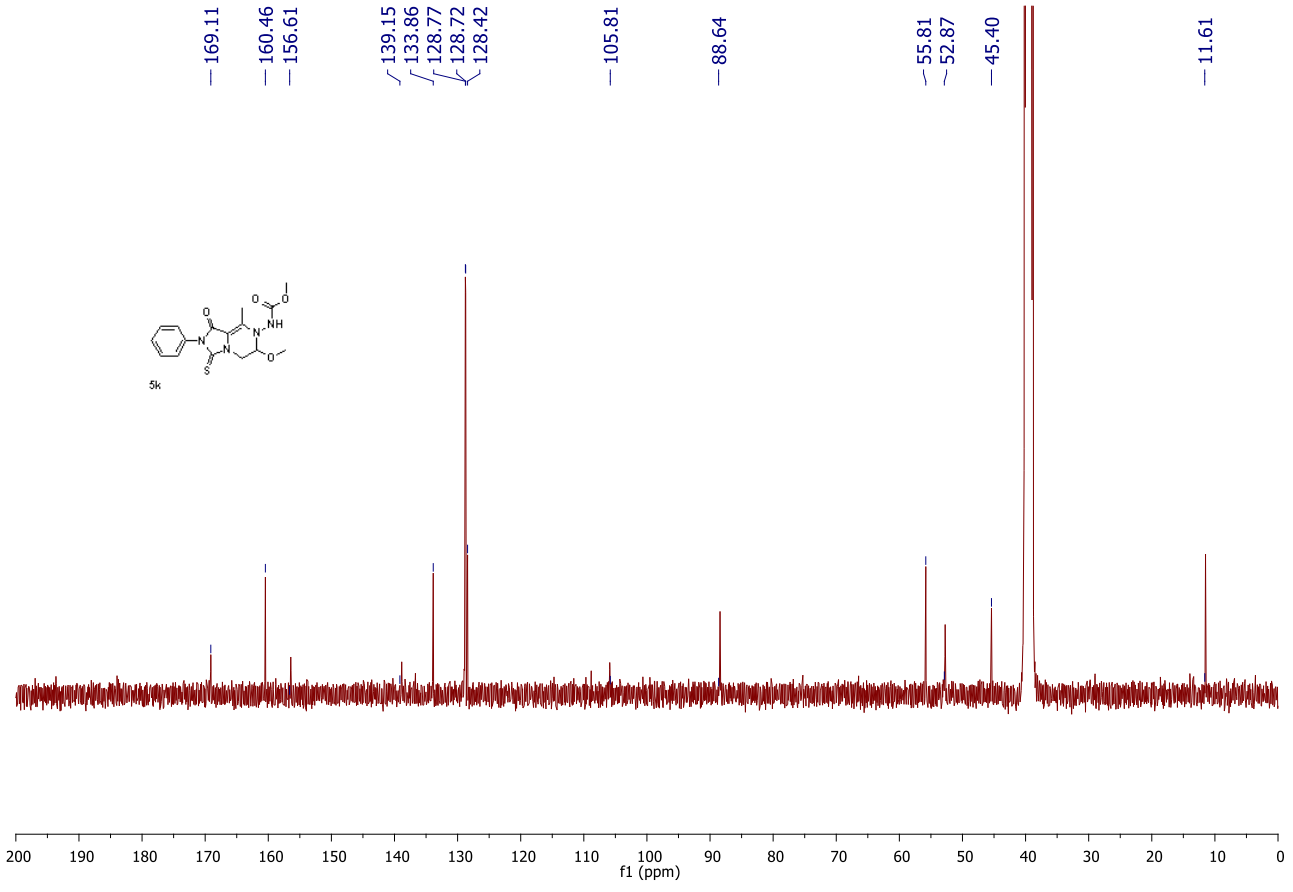
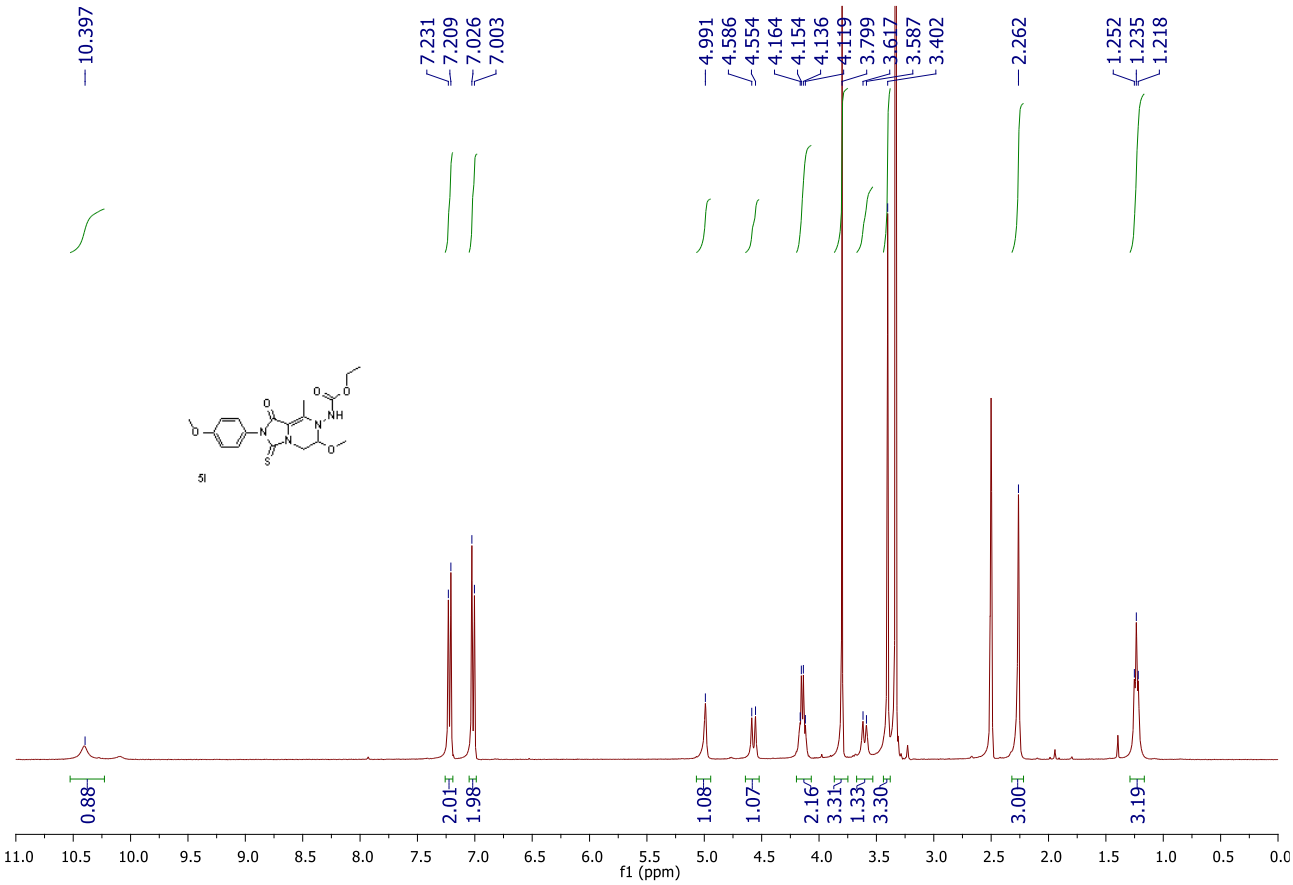
7.472
7.469
7.447
7.444
7.440
7.425
7.407
7.332
7.314
5.009
4.600
4.567
3.699
3.634
3.601
3.409
2.273
0.73
0.26
3.43
1.96
0.95
1.00
3.19
1.15
3.09
3.00
f1 (ppm)


169.11
160.46
156.61
139.15
133.86
128.77
128.72
128.42
105.81
88.64
55.81
52.87
45.40
11.61
f1 (ppm)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4.991
4.586
4.554
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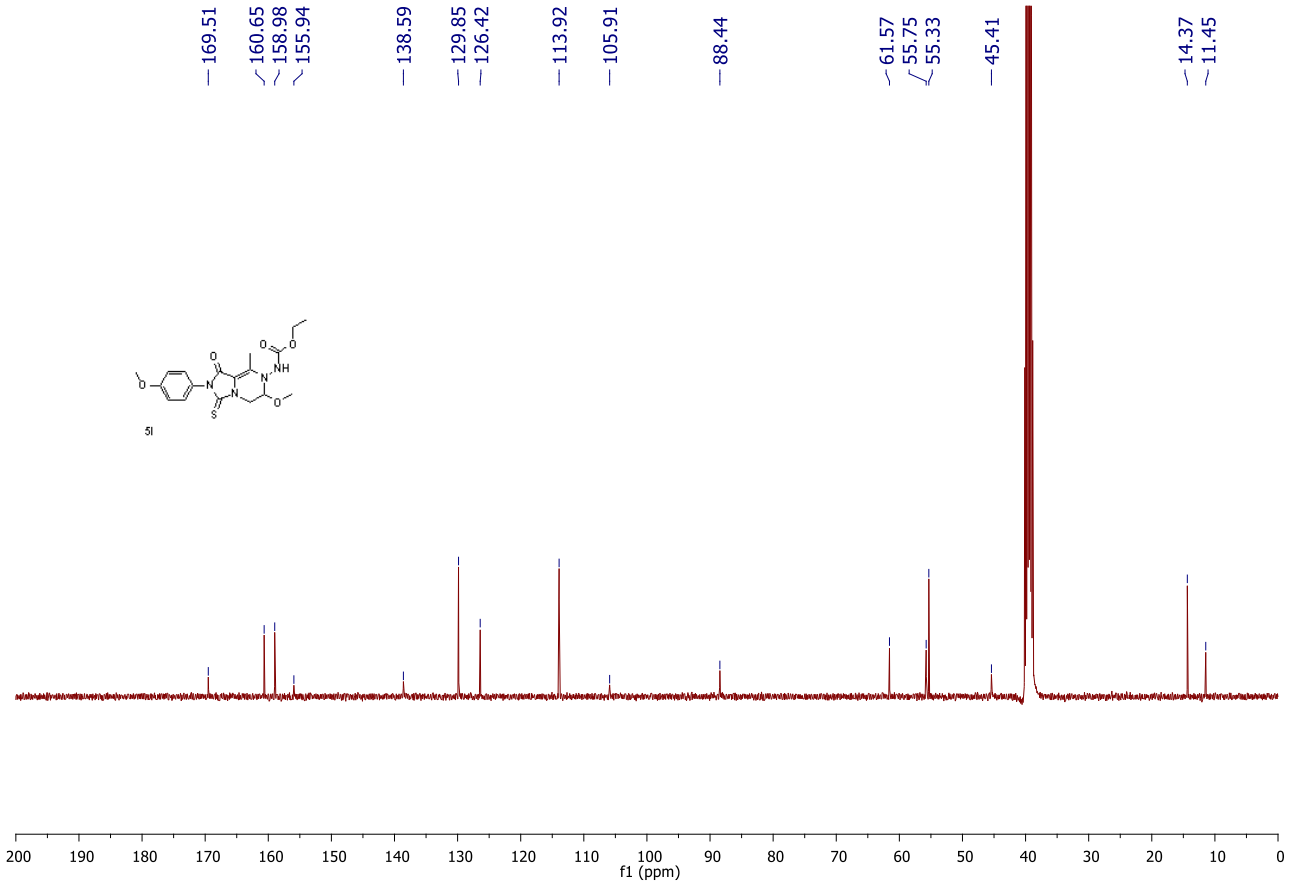
4.154
4.136
4.119
3.799
3.617
3.587
3.402
2.262
1.252
1.235
1.218
0.88
2.01
1.98
1.08
1.07
2.16
3.31
1.33
3.30
3.00
3.19
f1 (ppm)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158.98
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138.59
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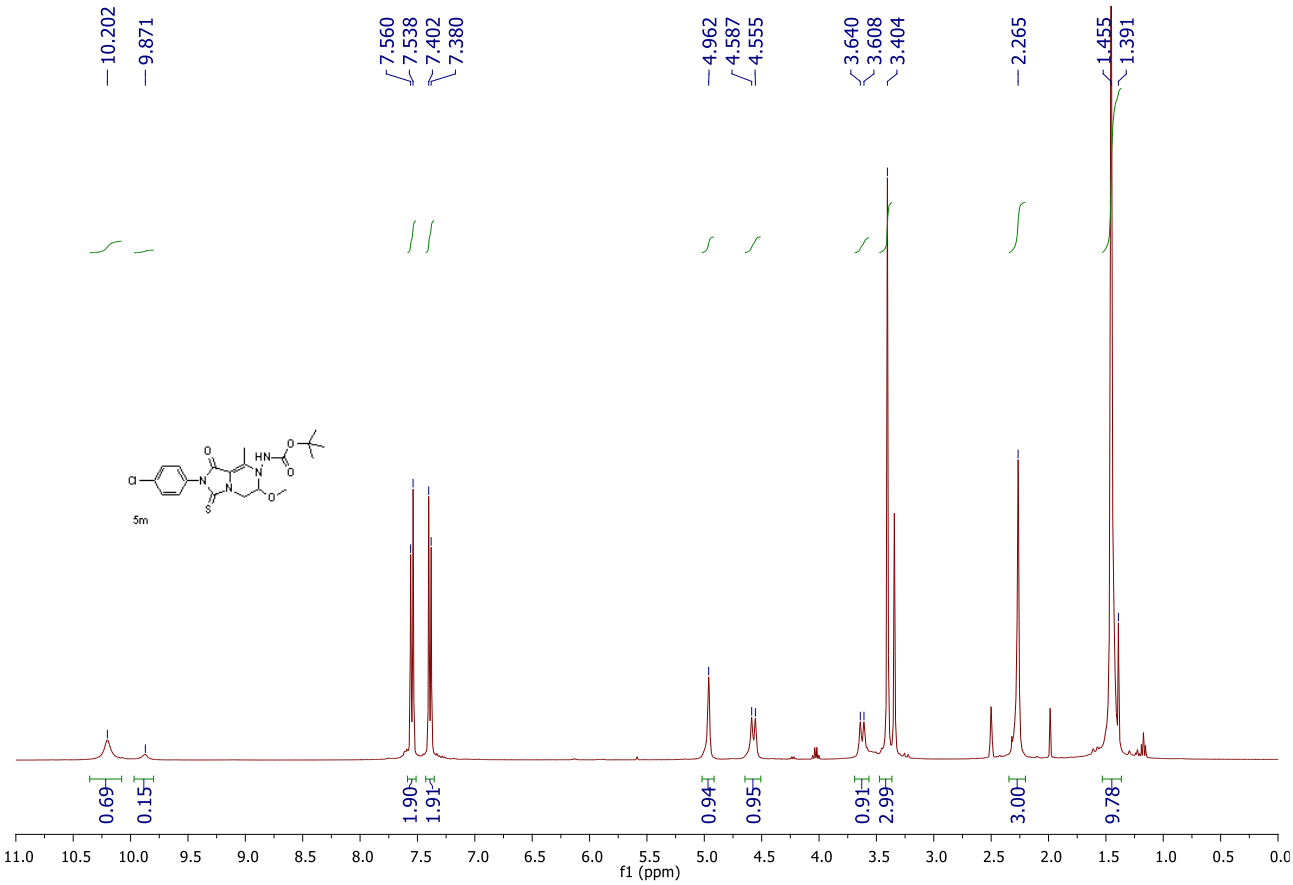
126.42
113.92
105.91
88.44
61.57
55.75
55.33
45.41
14.37
11.45
f1 (ppm)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7.380
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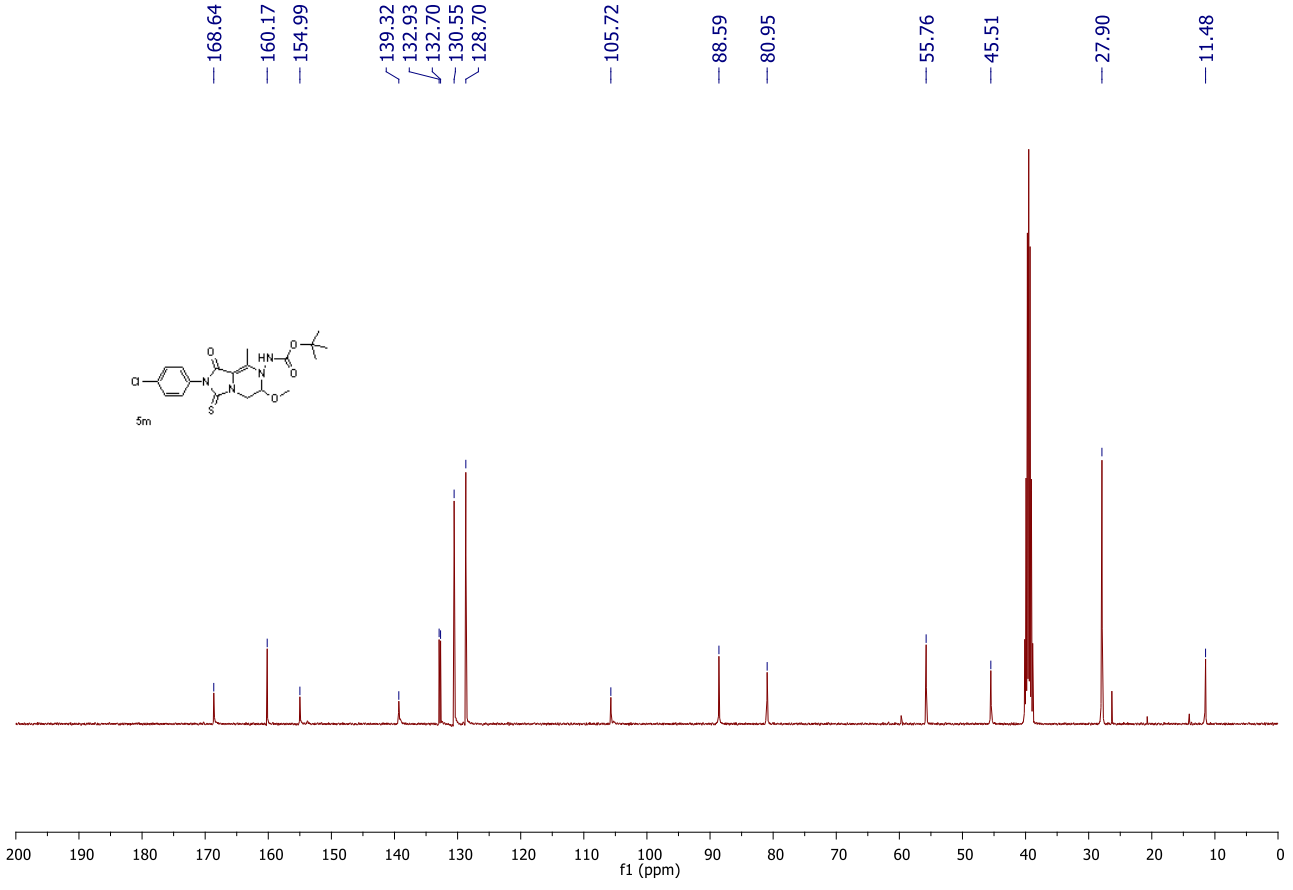
4.587
4.555
3.640
3.608
3.404
2.265
1.455
1.391
0.69
0.15
1.90
1.91
0.94
0.95
0.91
2.99
3.00
9.78
f1 (ppm)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154.99
139.32
132.93
132.70
130.55
128.70
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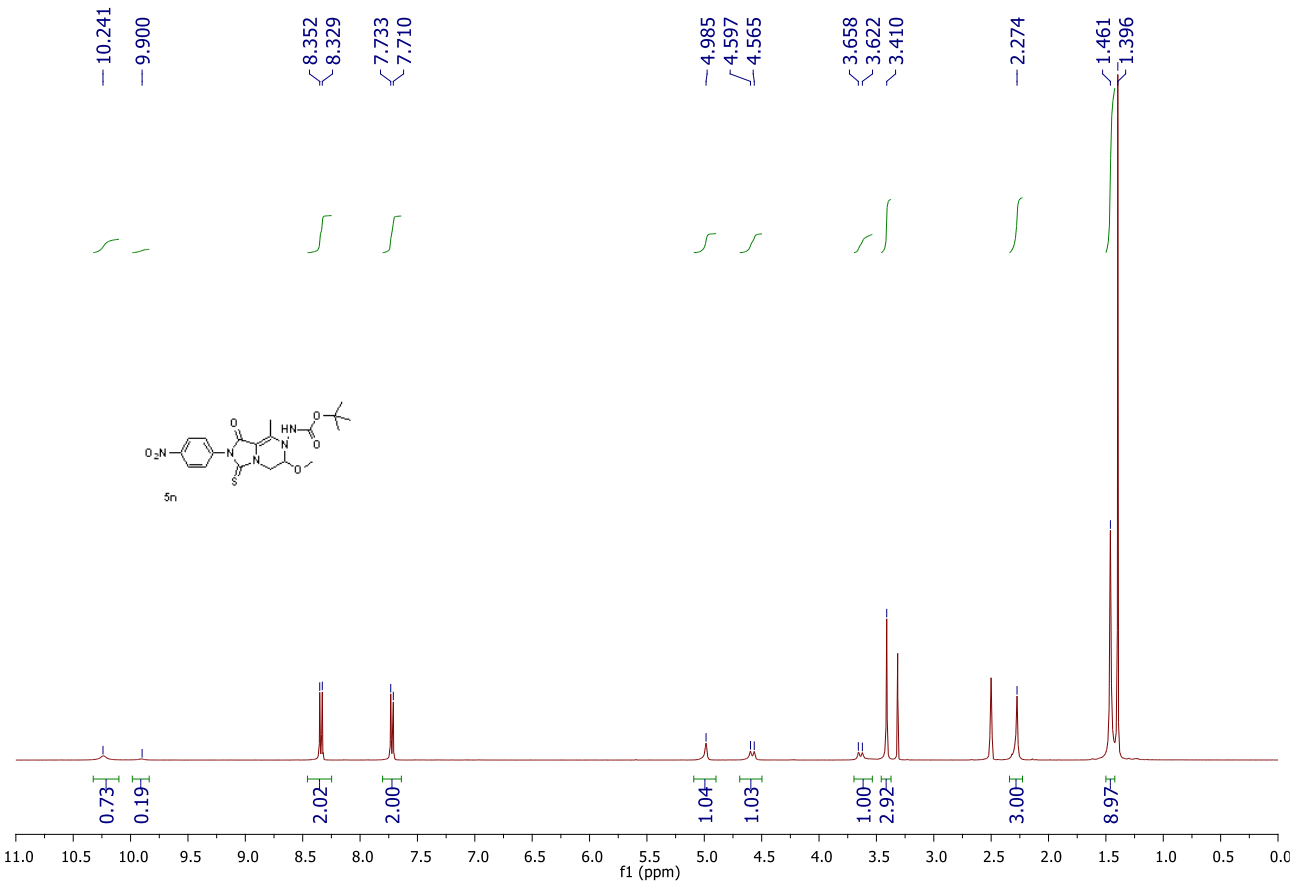
88.59
80.95
55.76
45.51
27.90
11.48
f1 (ppm)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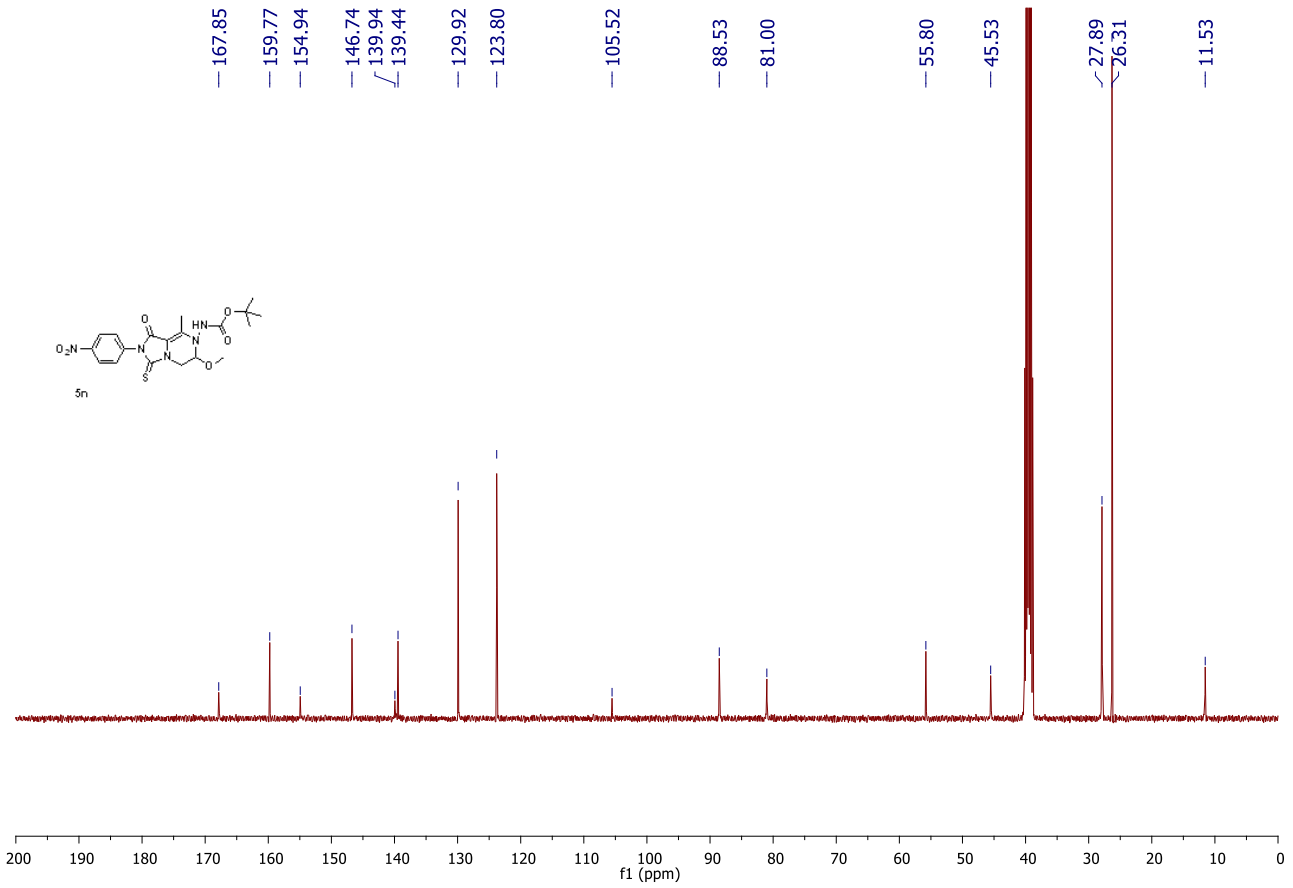
7.710
4.985
4.597
4.565
3.658
3.622
3.410
2.274
1.461
1.396
0.73
0.19
2.02
2.00
1.04
1.03
1.00
2.92
3.00
8.97
f1 (ppm)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139.94
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129.92
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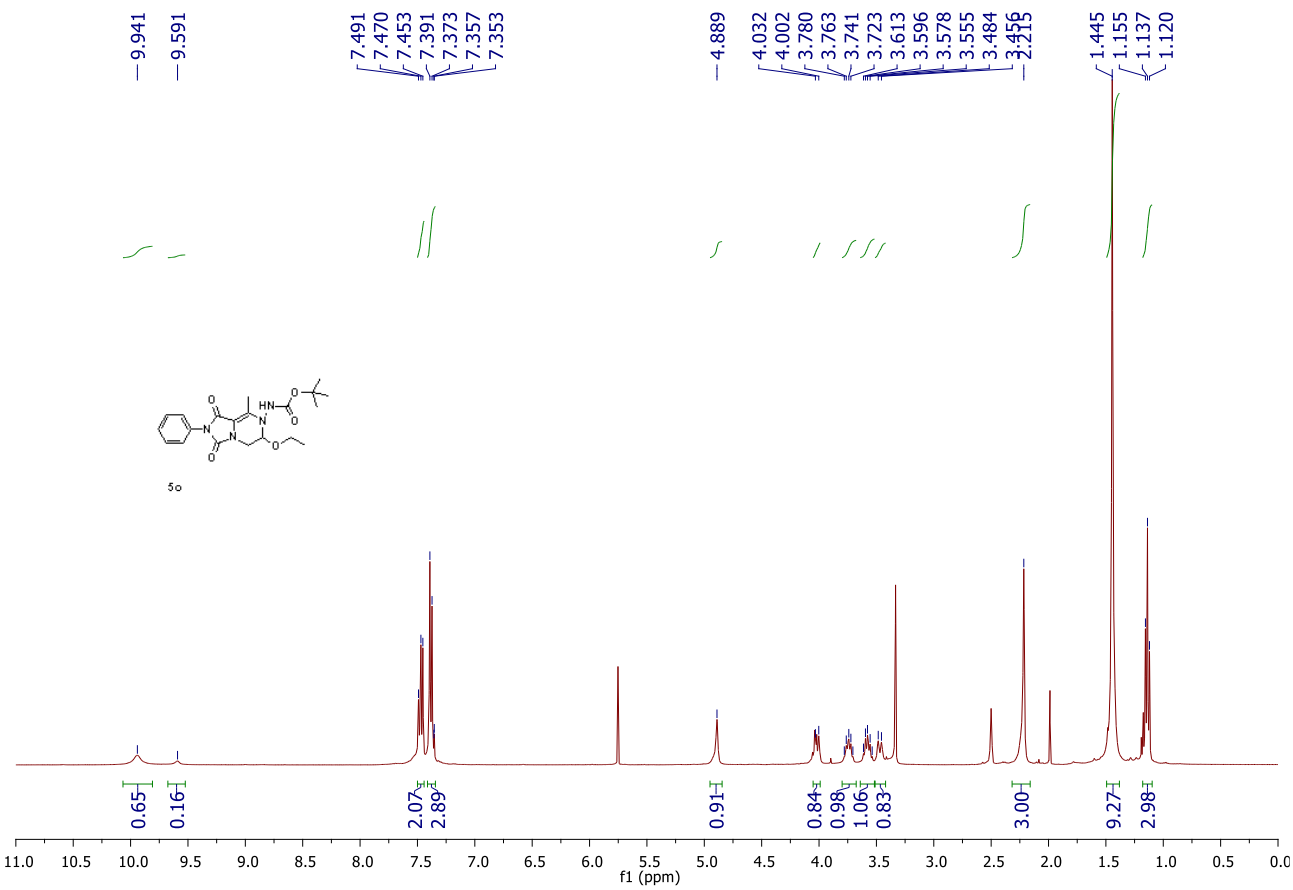
45.53
27.89
26.31
11.53
f1 (ppm)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4.002
3.780
3.763
3.741
3.723
3.613
3.596
3.578
3.555
3.484
3.456
2.215
1.445
1.155
1.137
1.120
0.65
0.16
2.07
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0.84
0.98
1.06
0.83
3.00
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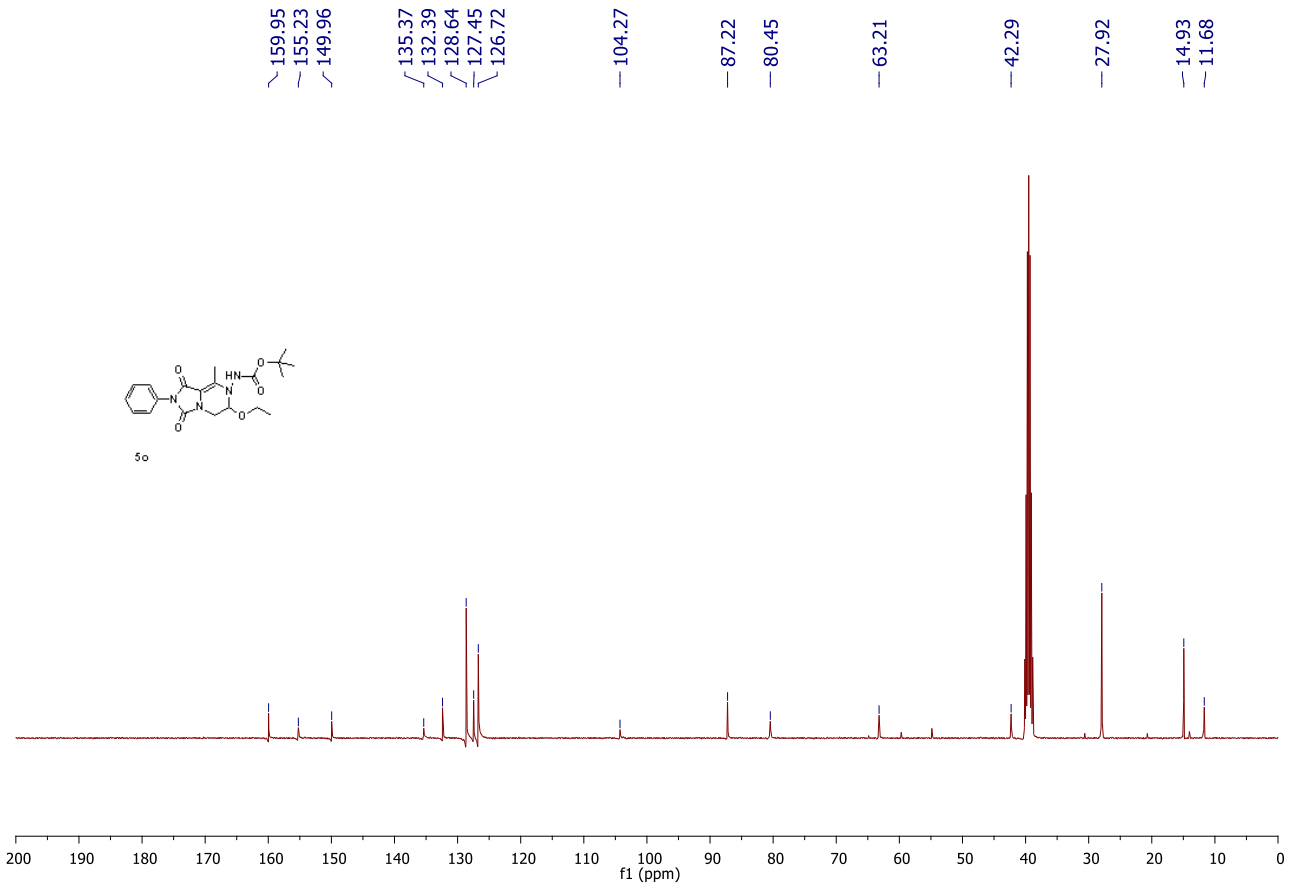
2.98
f1 (ppm)

5o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132.39
128.64
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126.72
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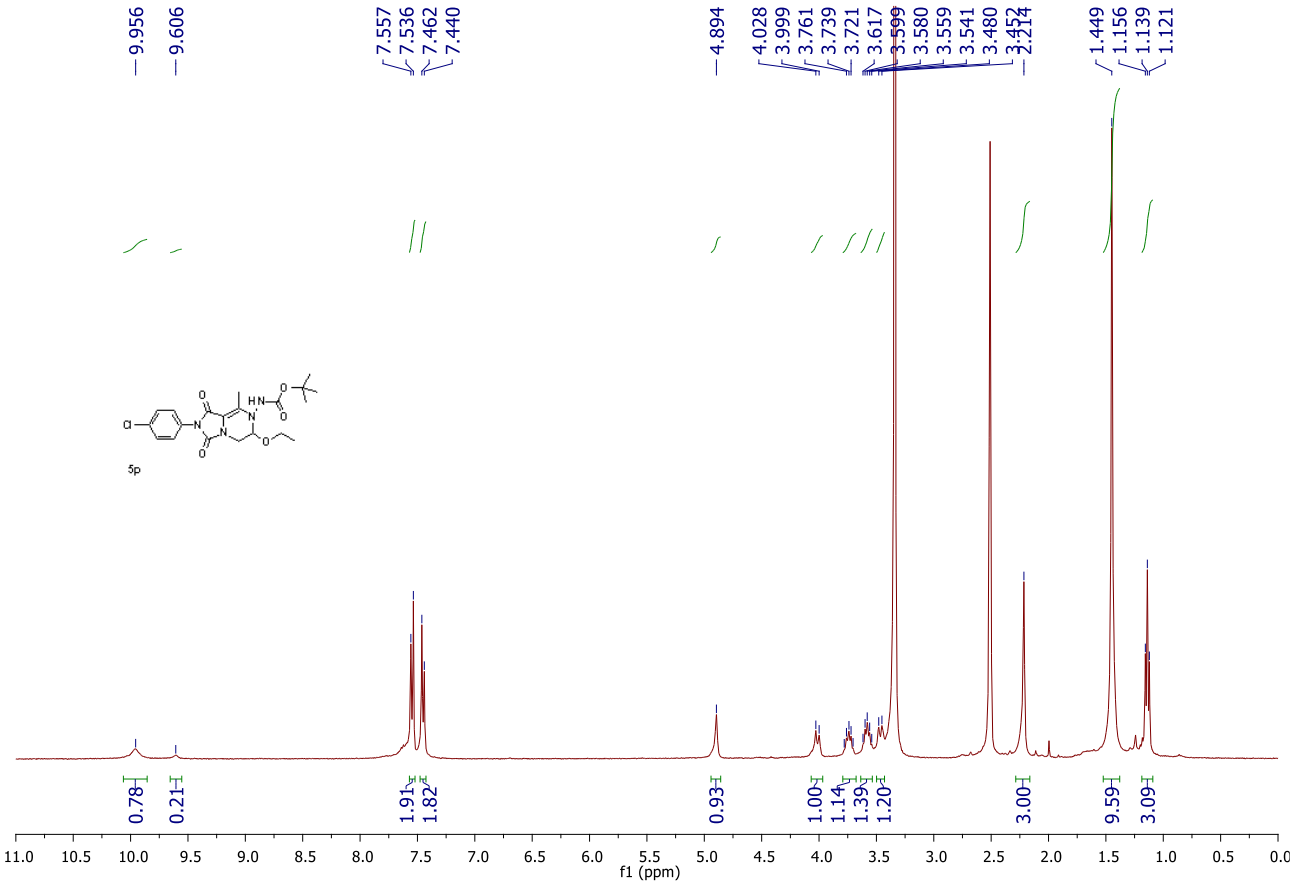
87.22
80.45
63.21
42.29
27.92
14.93
11.68
f1 (ppm)

5o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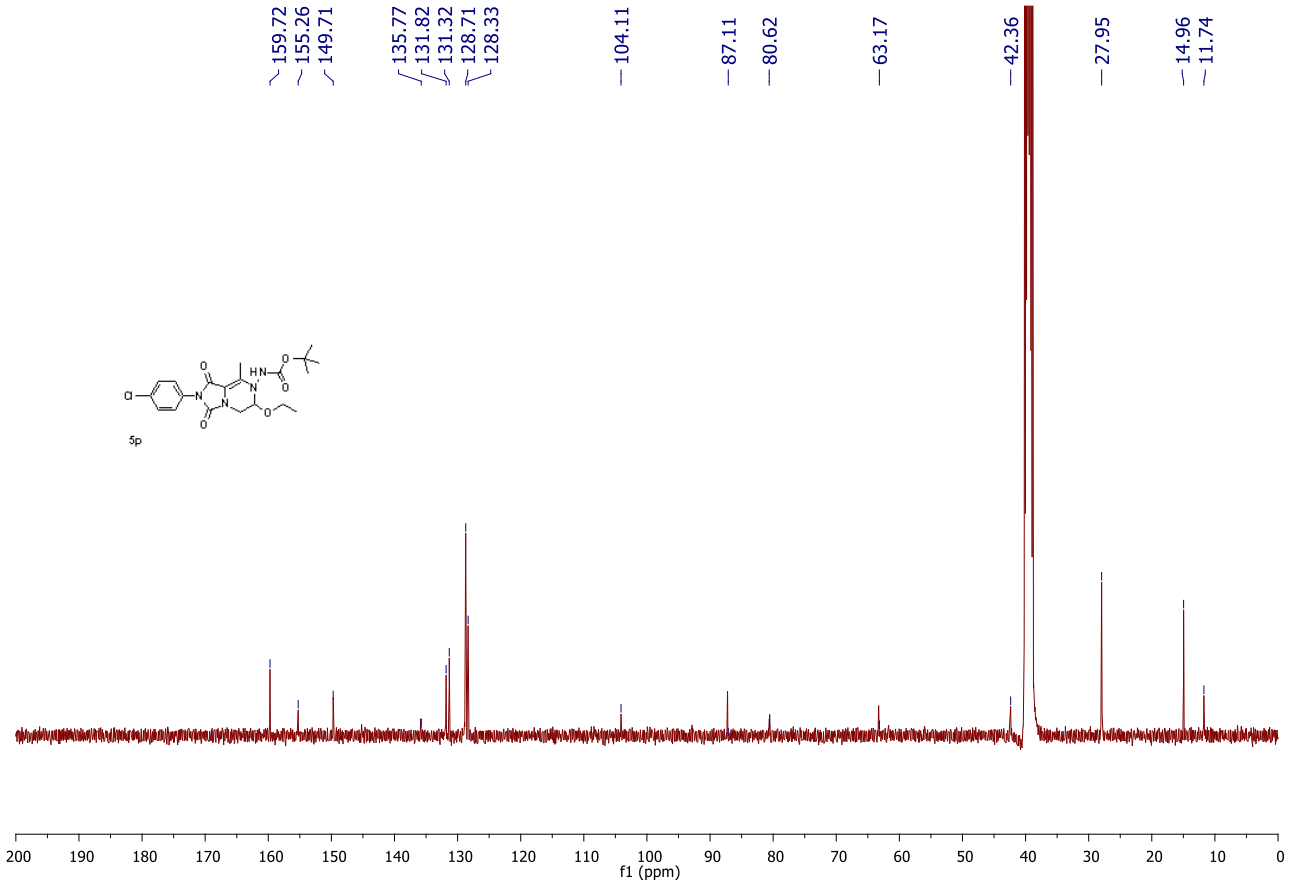
3.739
3.721
3.617
3.599
3.580
3.559
3.541
3.480
3.452
2.214
1.449
1.156
1.139
1.121
0.78
0.21
1.91
1.82
0.93
1.00
1.14
1.39
1.20
3.00
9.59
3.09
5p
f1 (ppm)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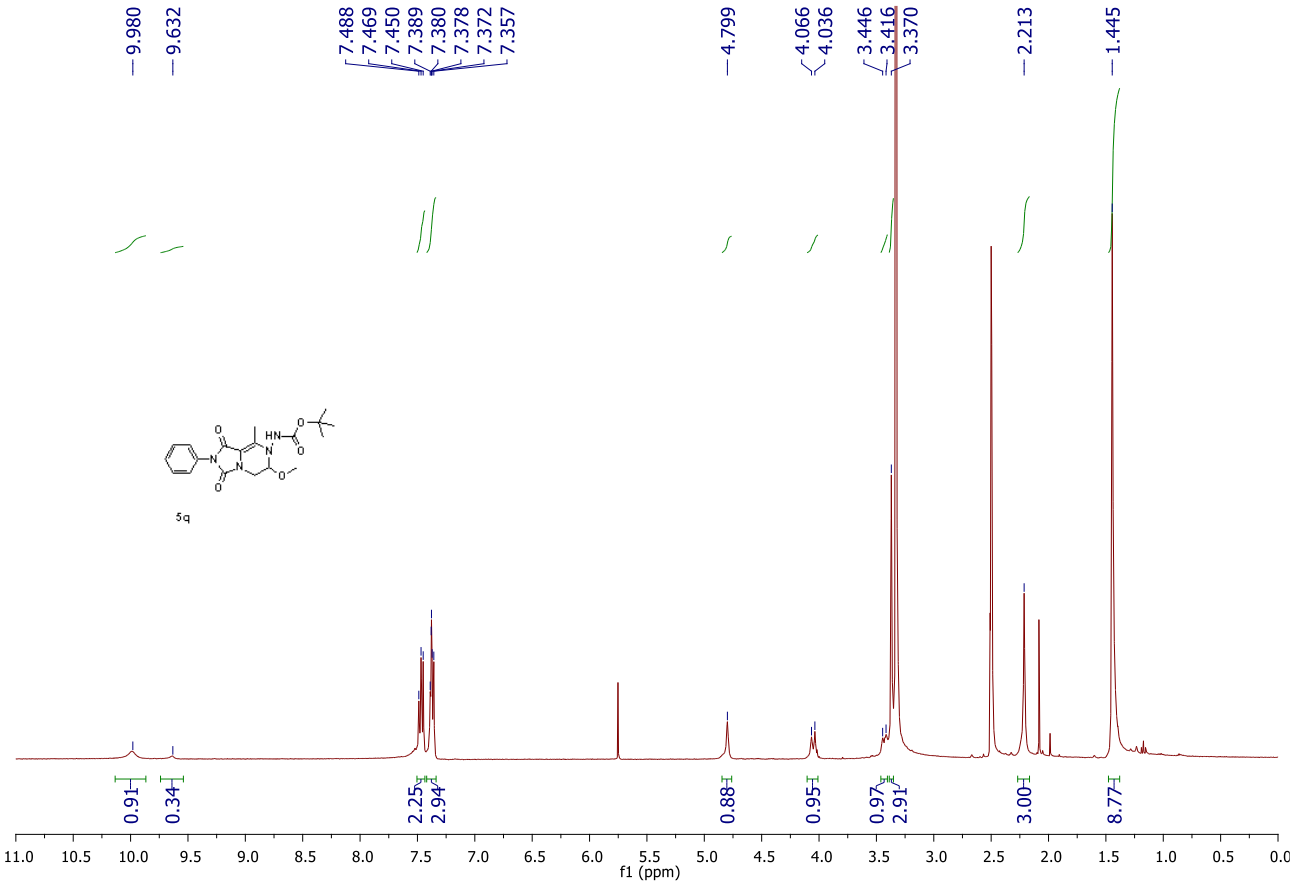
131.82
131.32
128.71
128.33
104.11
87.11
80.62
63.17
42.36
27.95
14.96
11.74
5p
f1 (ppm)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7.378
7.372
7.357
4.799
4.066
4.036
3.446
3.416
3.370
2.213
1.445
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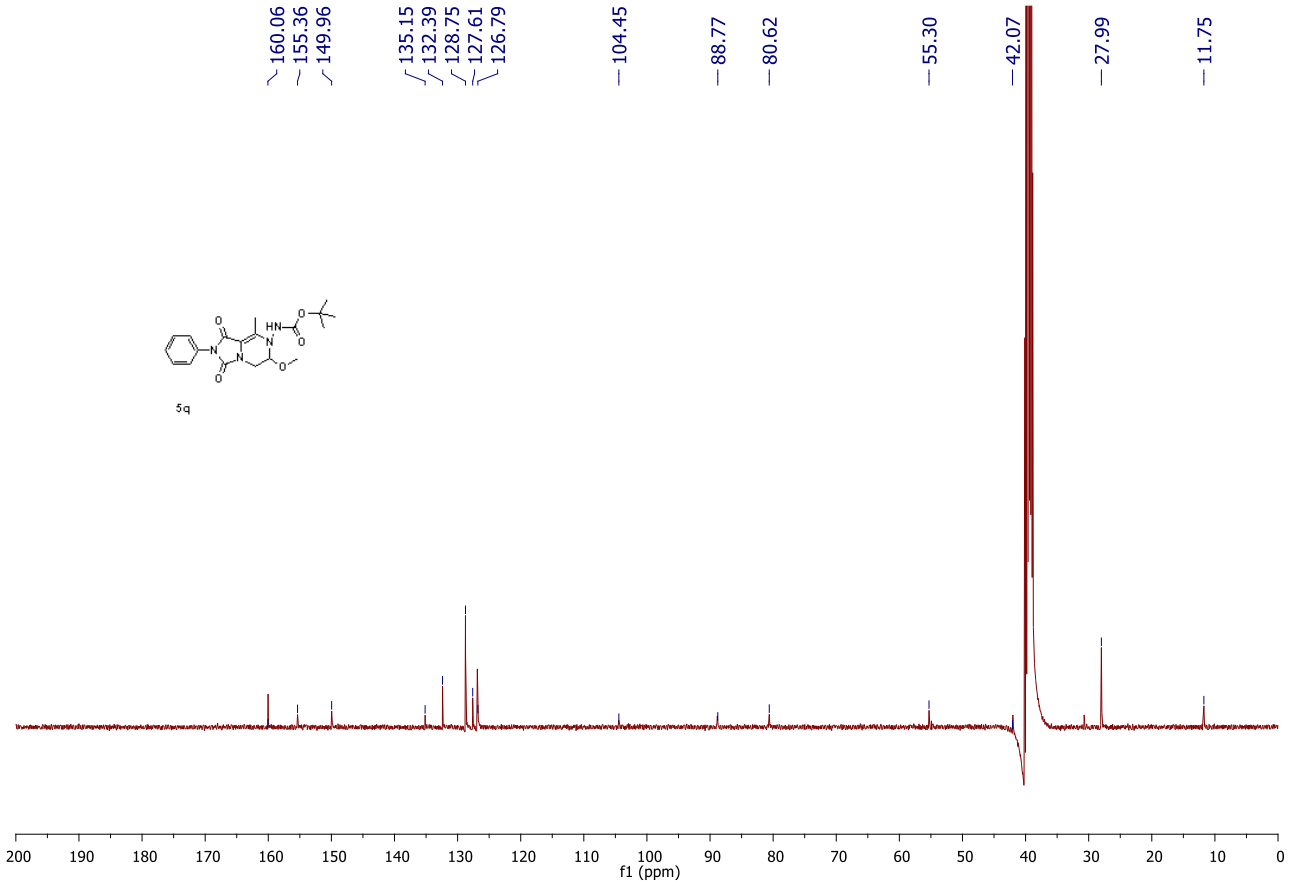
0.34
2.25
2.94
0.88
0.95
0.97
2.91
3.00
8.77
f1 (ppm)
5q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149.96
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132.39
128.75
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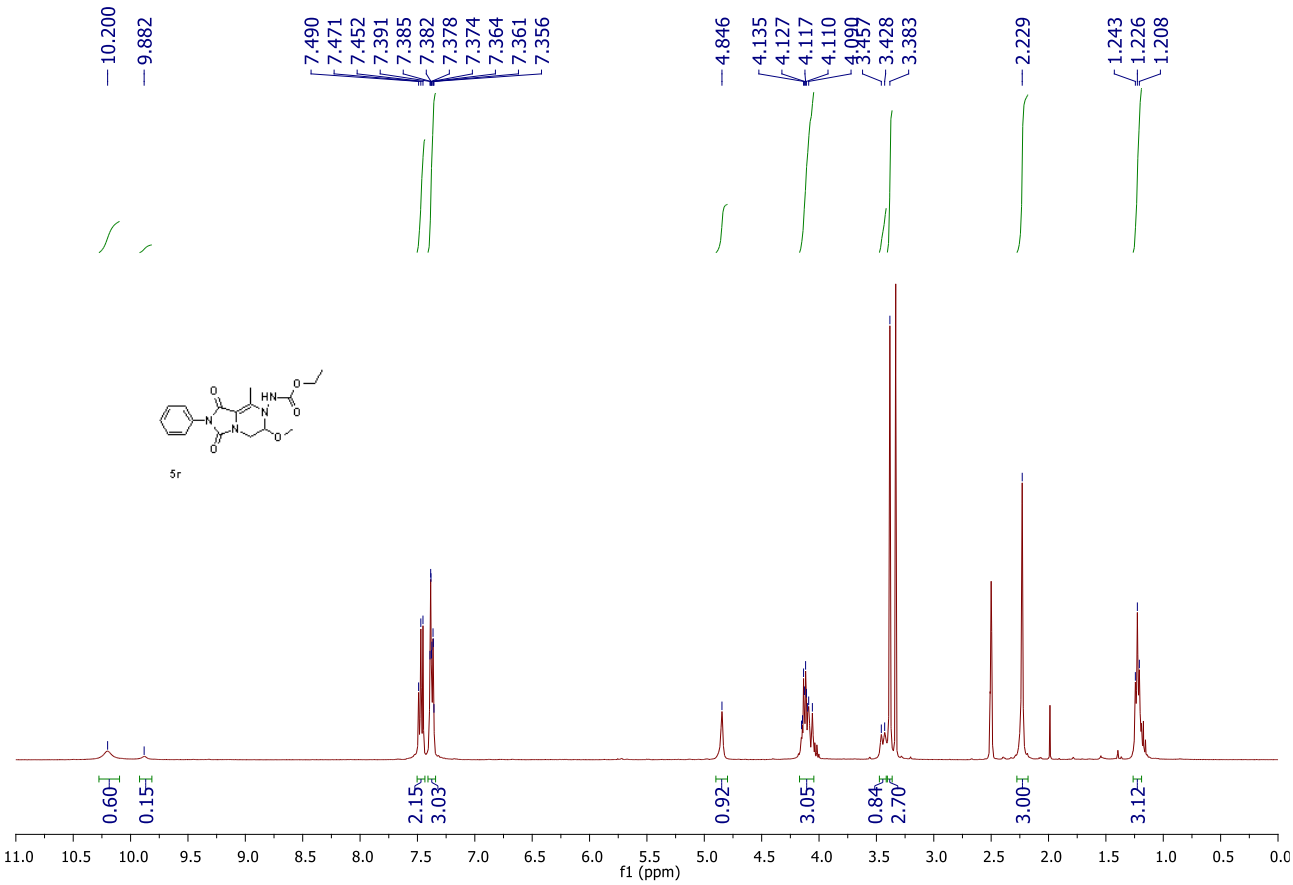
126.79
104.45
88.77
80.62
55.30
42.07
27.99
11.75
f1 (ppm)
5q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4.846
4.135
4.127
4.117
4.110
4.099
3.457
3.428
3.383
2.229
1.243
1.226
1.208
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2.15
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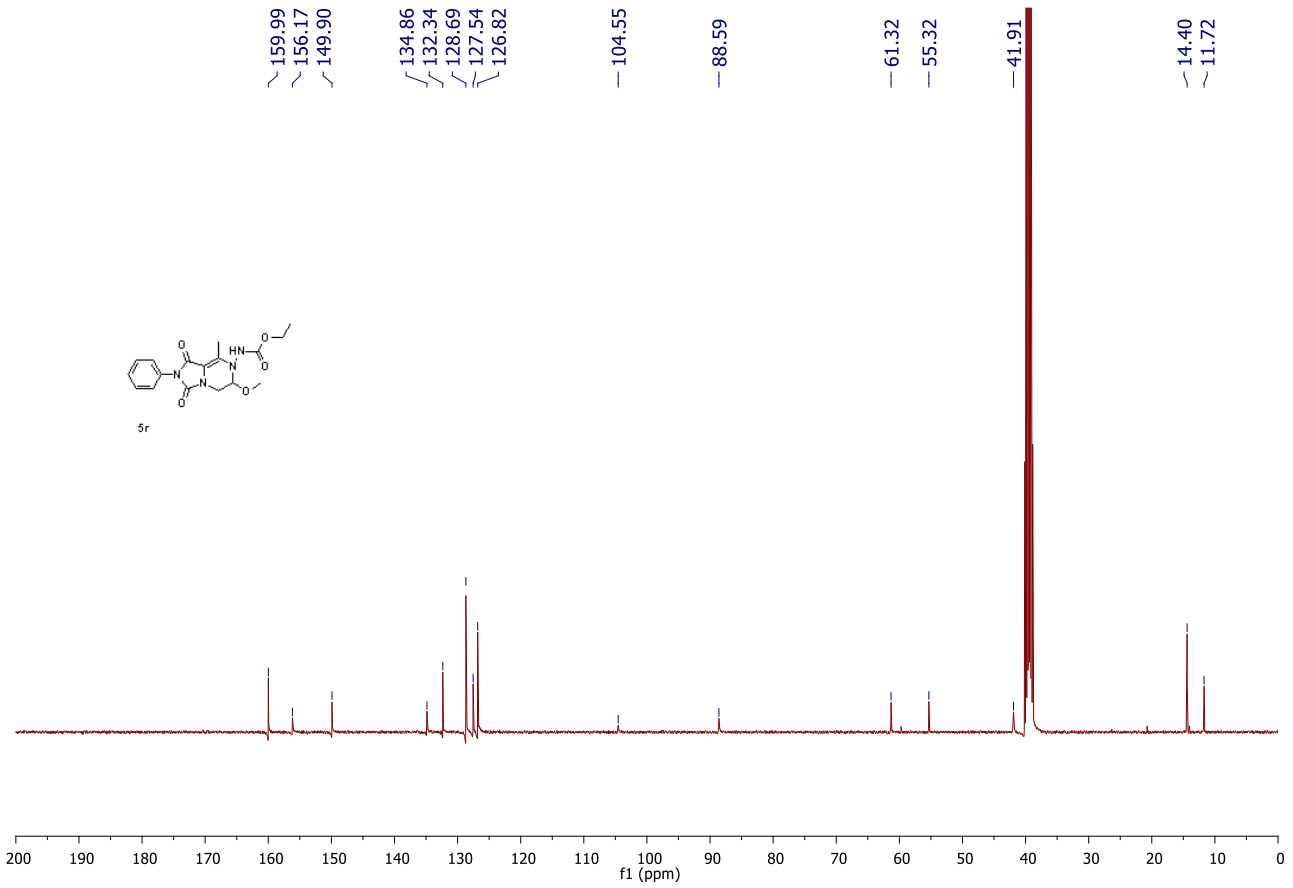
0.92
3.05
0.84
2.70
3.00
3.12
f1 (ppm)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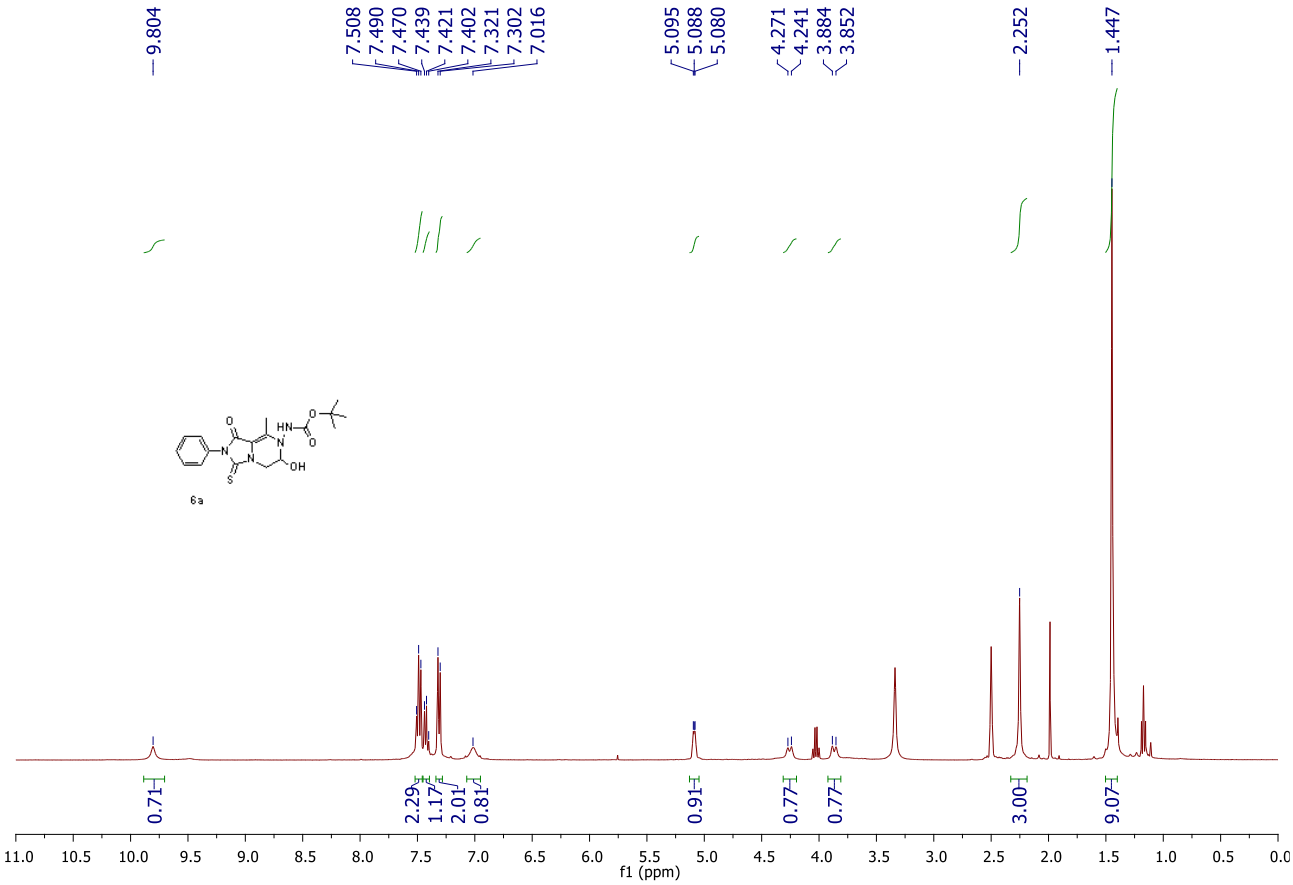
88.59
61.32
55.32
41.91
14.40
11.72
5r
f1 (ppm)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7.016
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5.088
5.080
4.271
4.241
3.884
3.852
2.252
1.447
0.71
2.29
1.17
2.01
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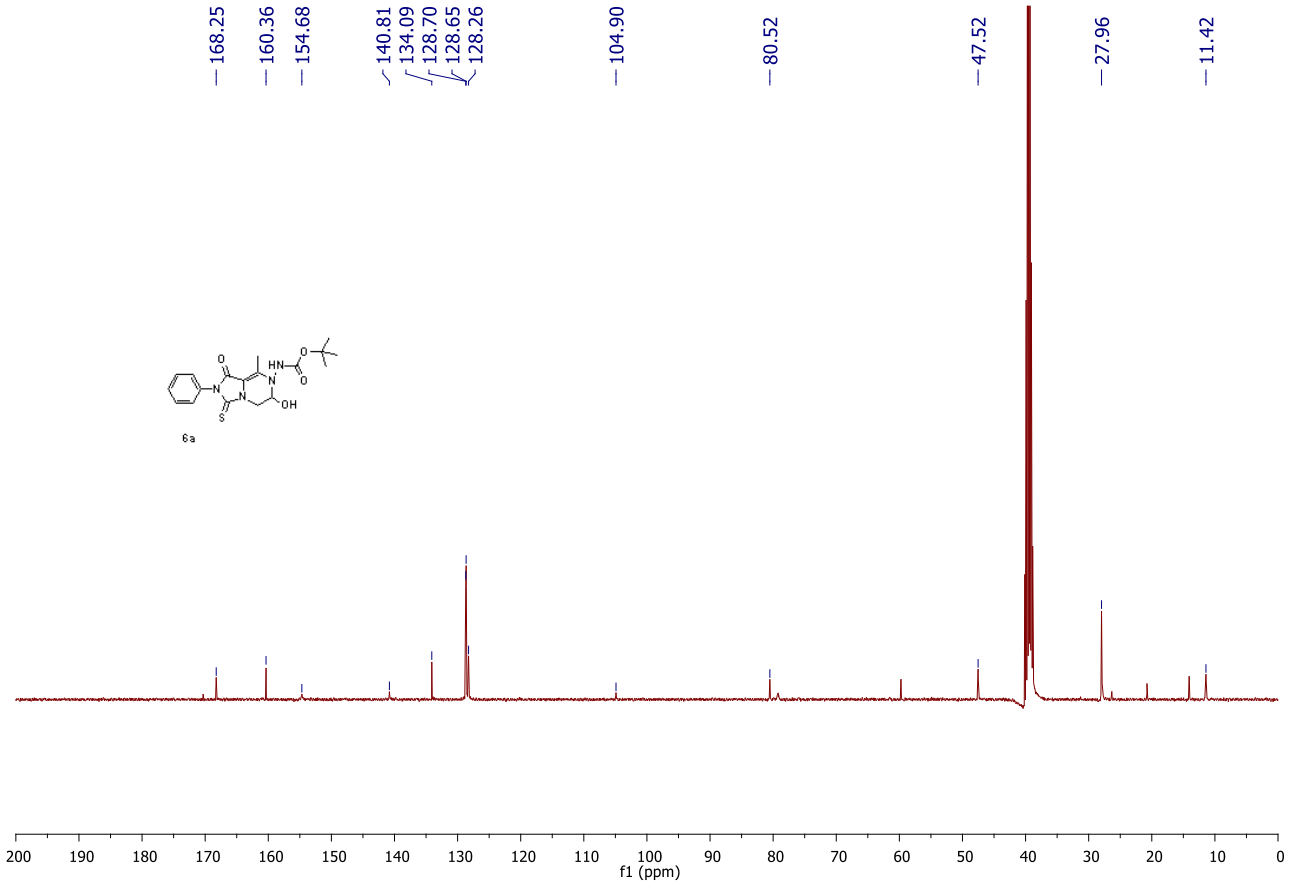
0.91
0.77
0.77
3.00
9.07
f1 (ppm)
6a


168.25
160.36
154.68
140.81
134.09
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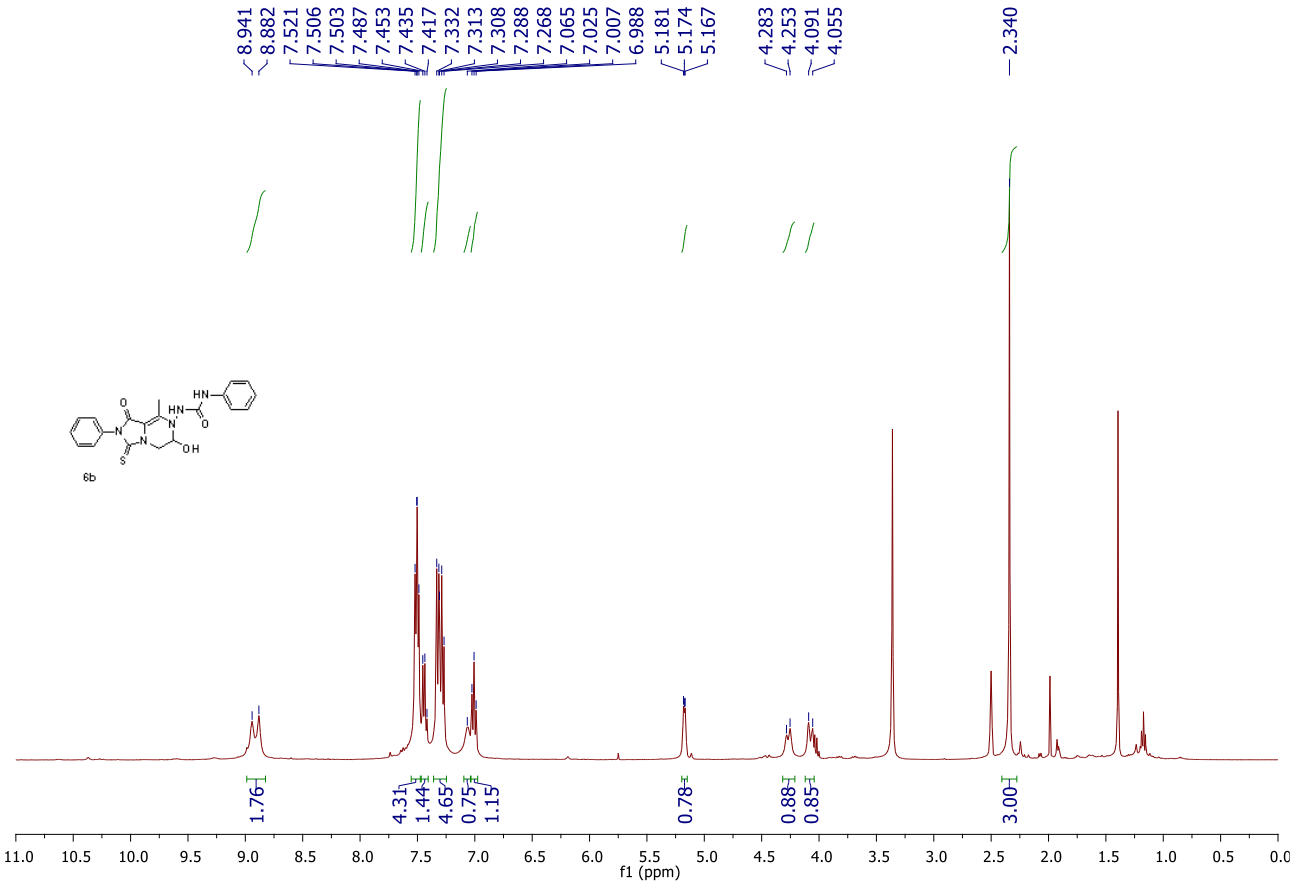
128.65
128.26
104.90
80.52
47.52
27.96
11.42
f1 (ppm)
6a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7.288
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7.065
7.025
7.007
6.988
5.181
5.174
5.167
4.283
4.253
4.091
4.055
2.340
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1.44
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1.15
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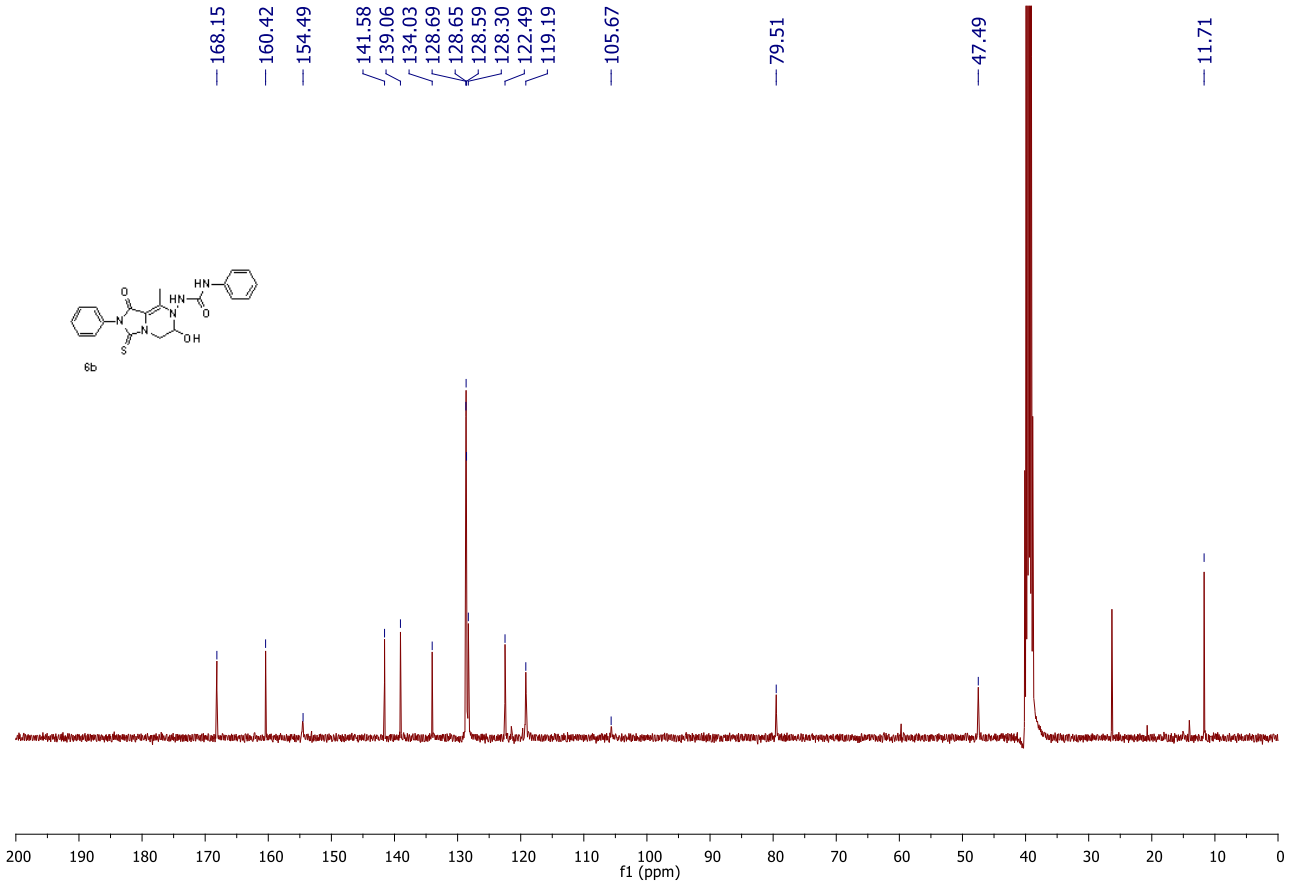
3.00
f1 (ppm)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134.03
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122.49
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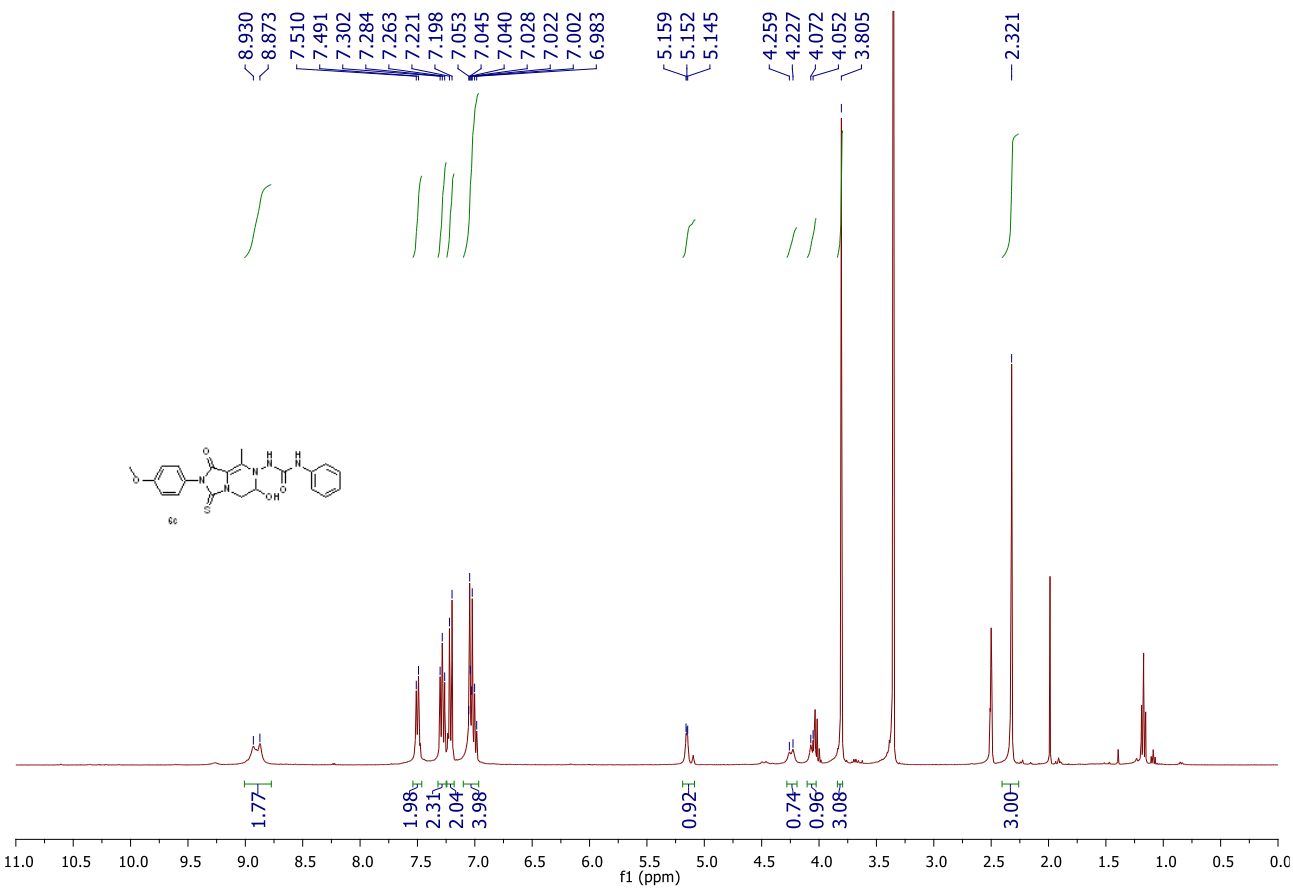
79.51
47.49
11.71
6b
f1 (ppm)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7.284
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7.221
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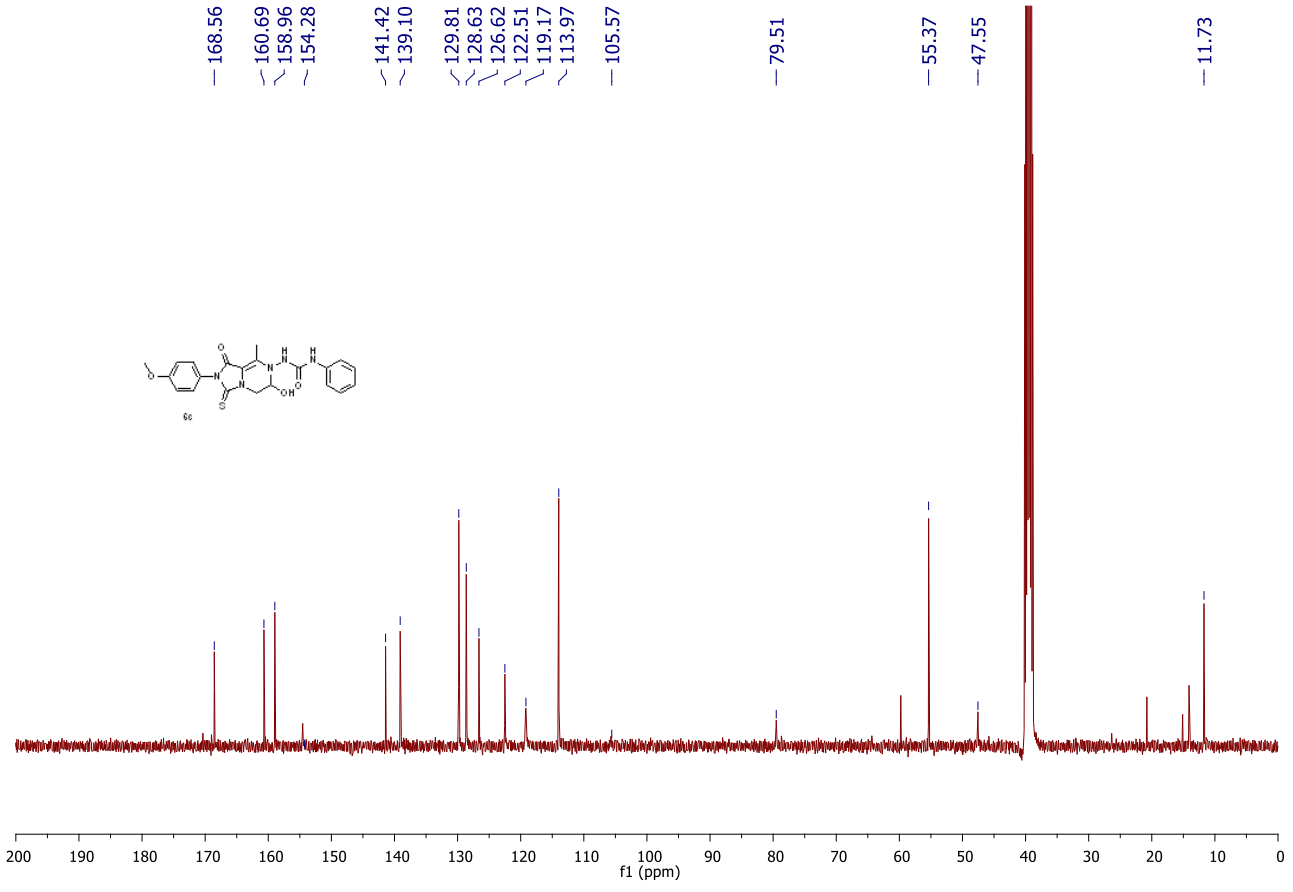
7.022
7.002
6.983
5.159
5.152
5.145
4.259
4.227
4.072
4.052
3.805
2.321
1.77
1.98
2.31
2.04
3.98
0.92
0.74
0.96
3.08
3.00
f1 (ppm)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105.57
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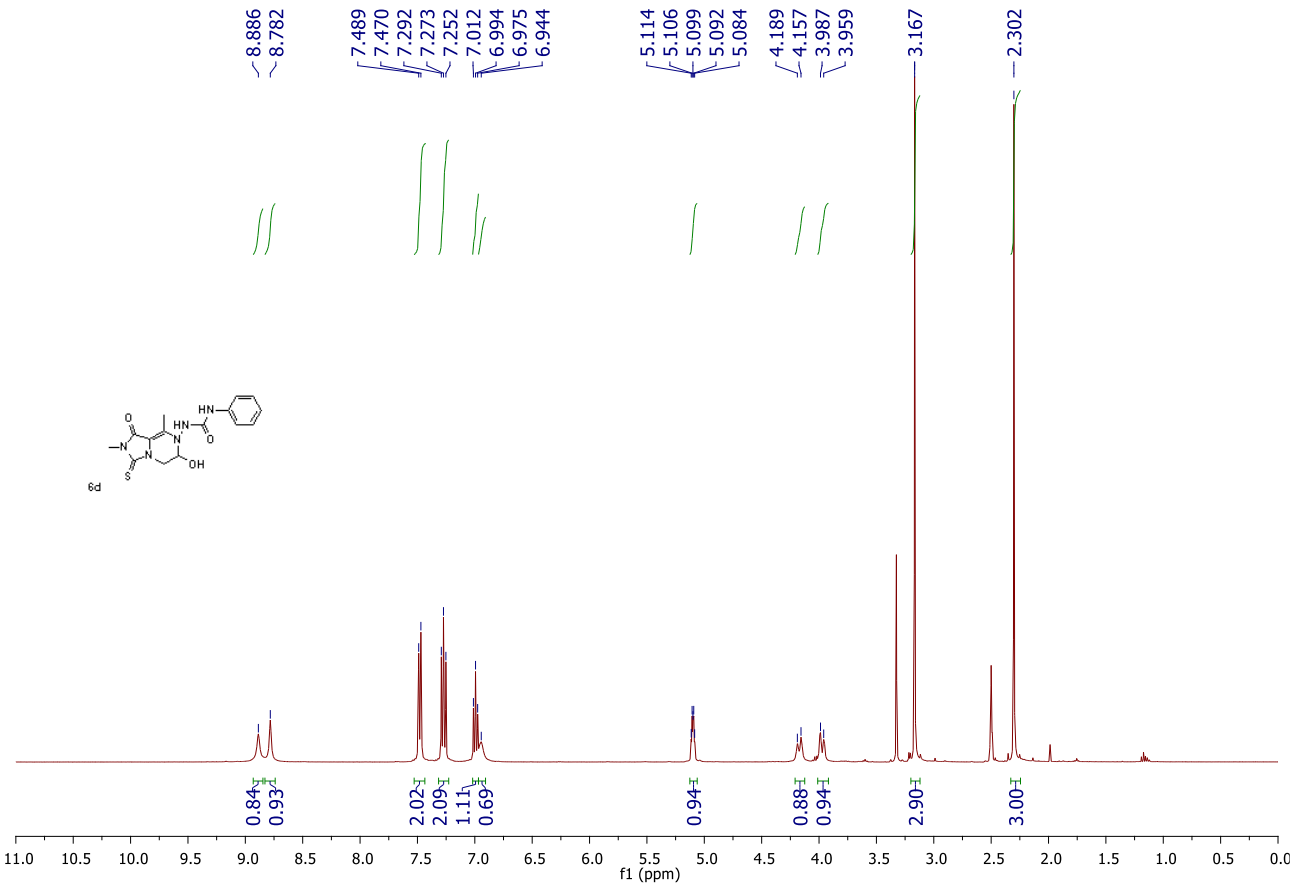
55.37
47.55
11.73
f1 (ppm)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5.106
5.099
5.092
5.084
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4.157
3.987
3.959
3.167
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2.09
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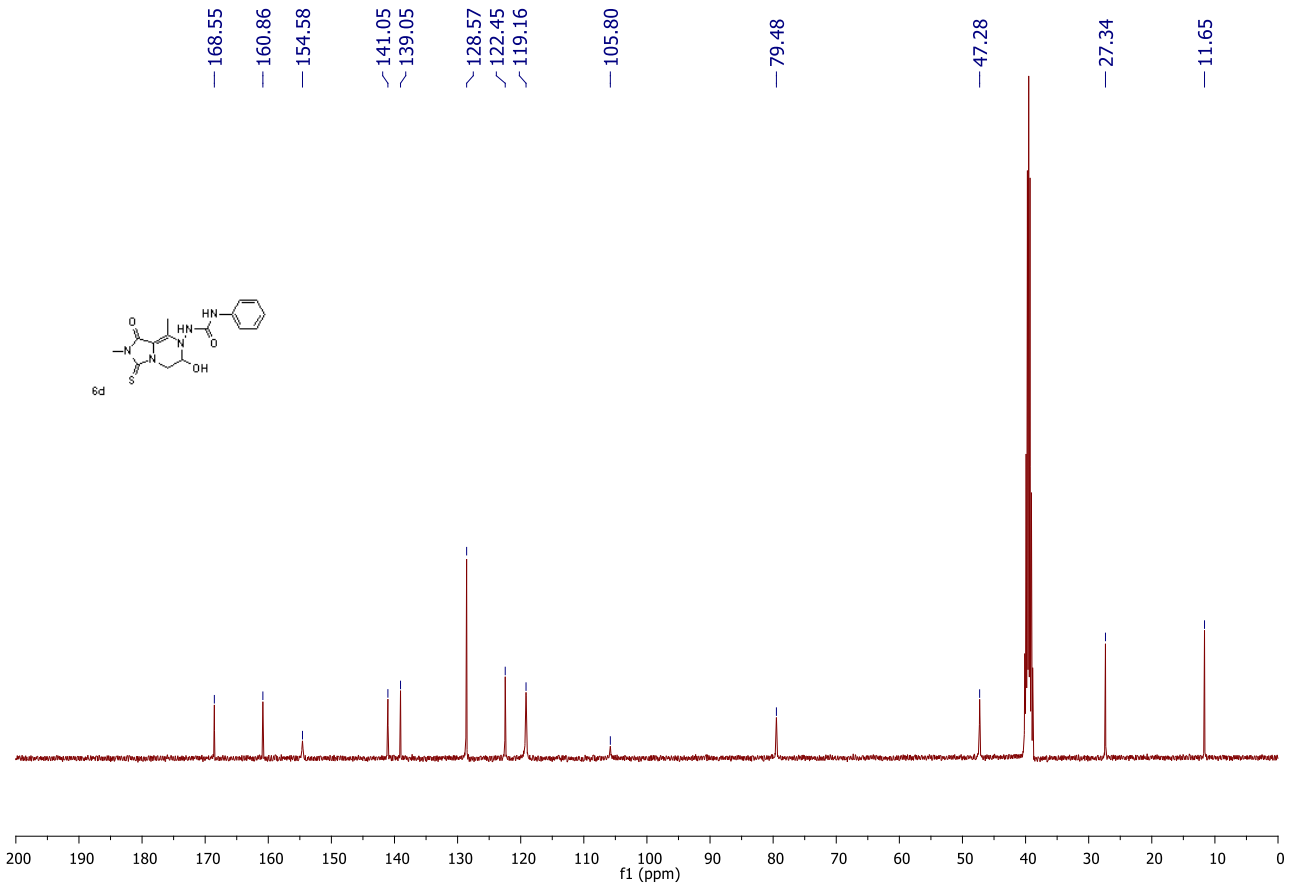
f1 (ppm)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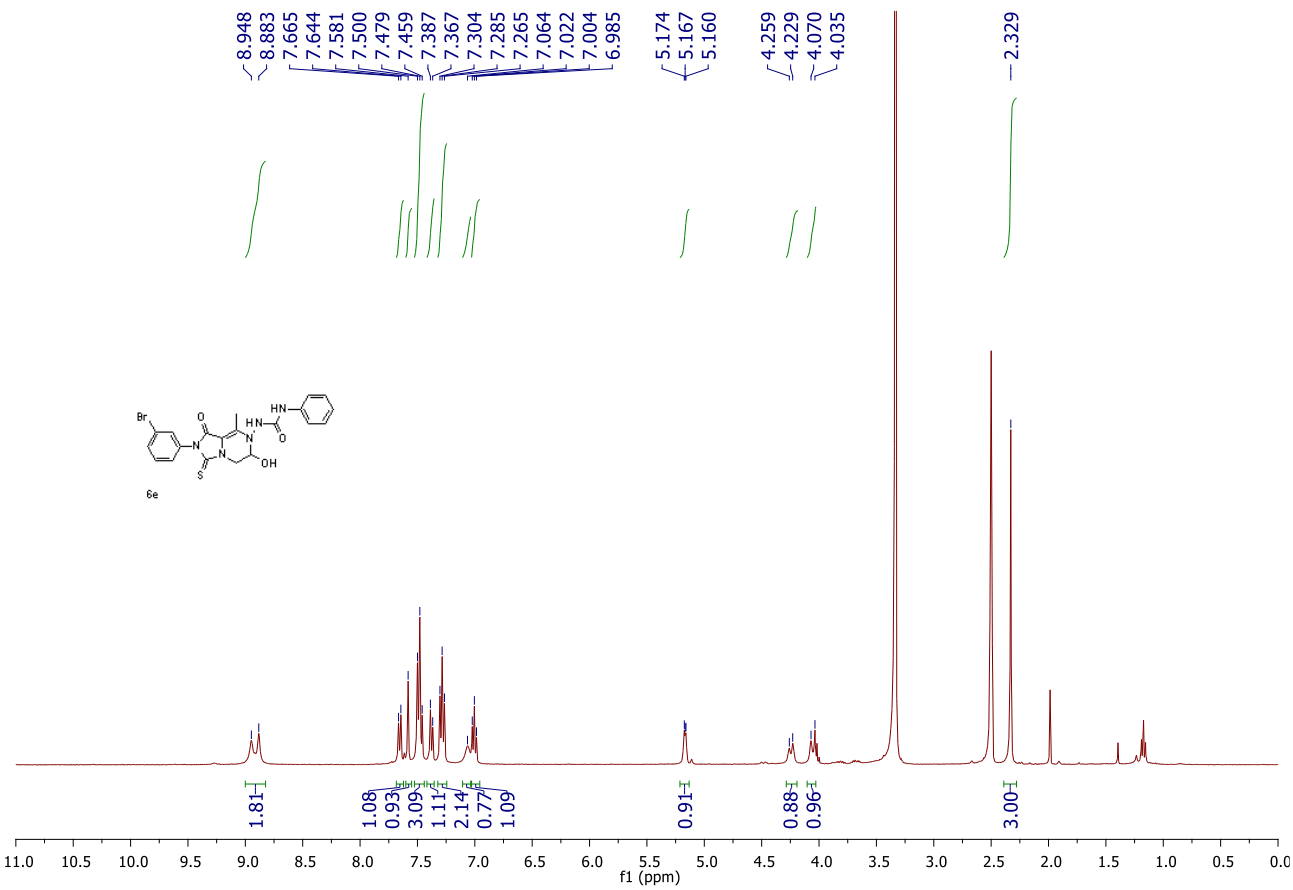
f1 (ppm)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7.064
7.022
7.004
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5.167
5.160
4.259
4.229
4.070
4.035
2.329
1.81
1.08
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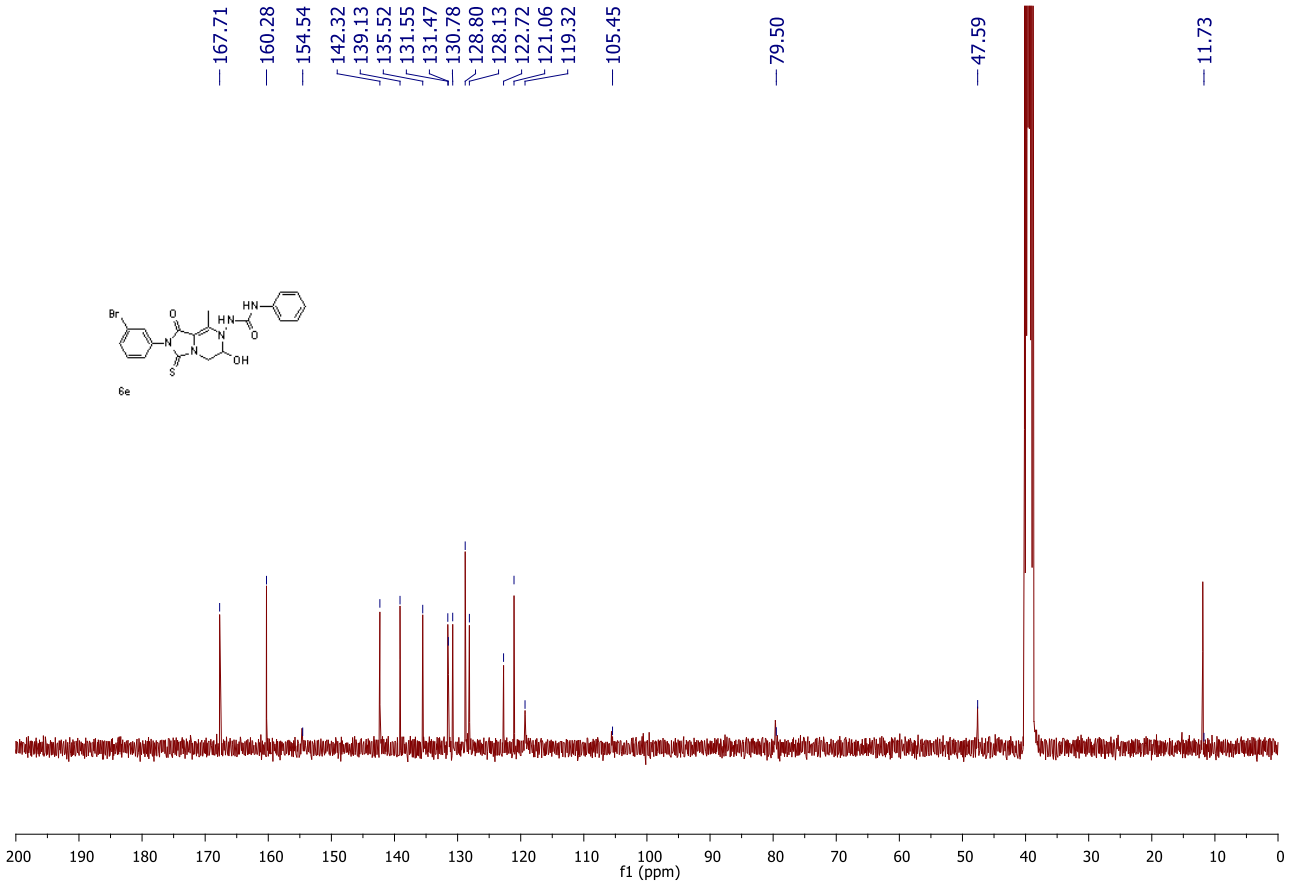
6e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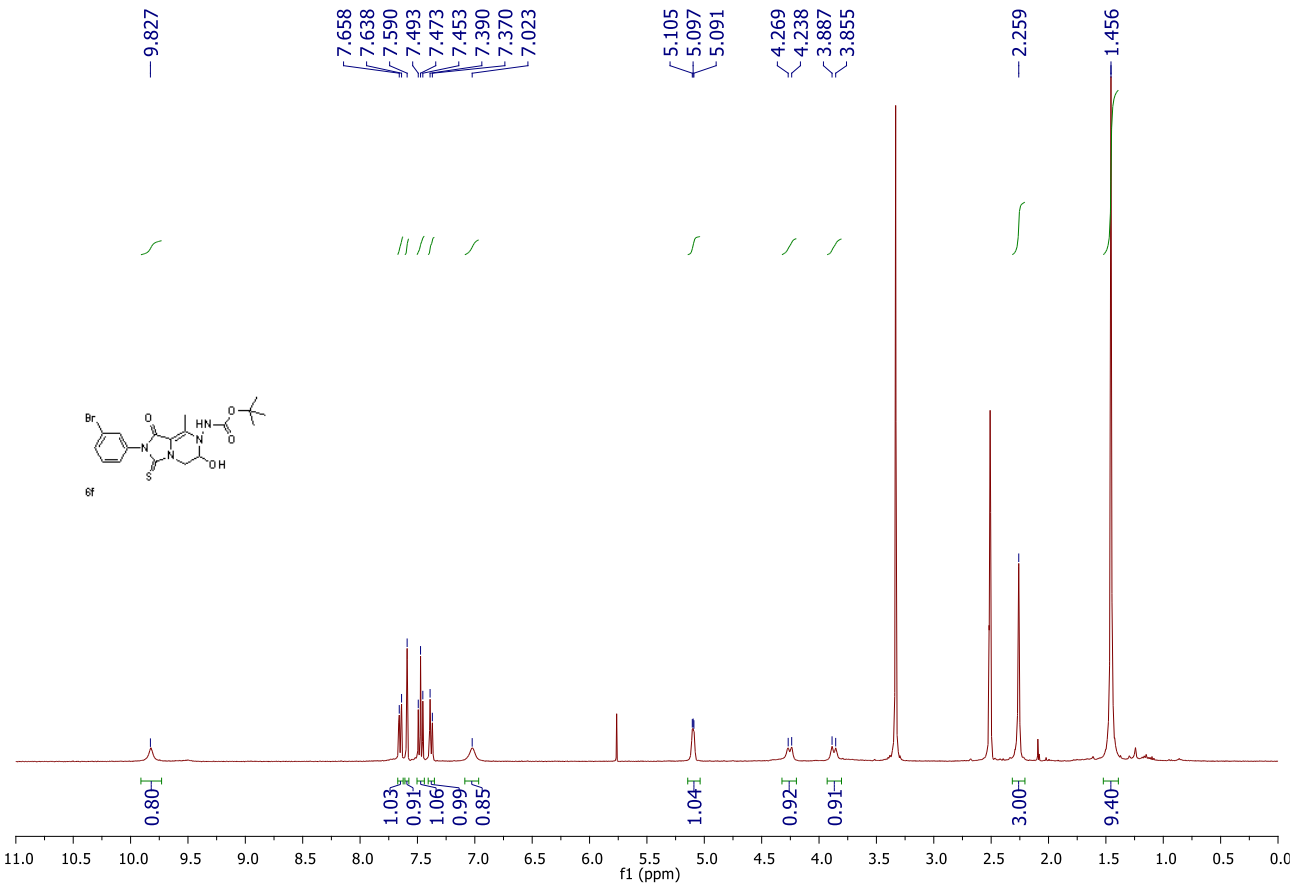
f1 (ppm)
6e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5.091
4.269
4.238
3.887
3.855
2.259
1.456
0.80
1.03
0.91
1.06
0.99
0.85
1.04
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0.91
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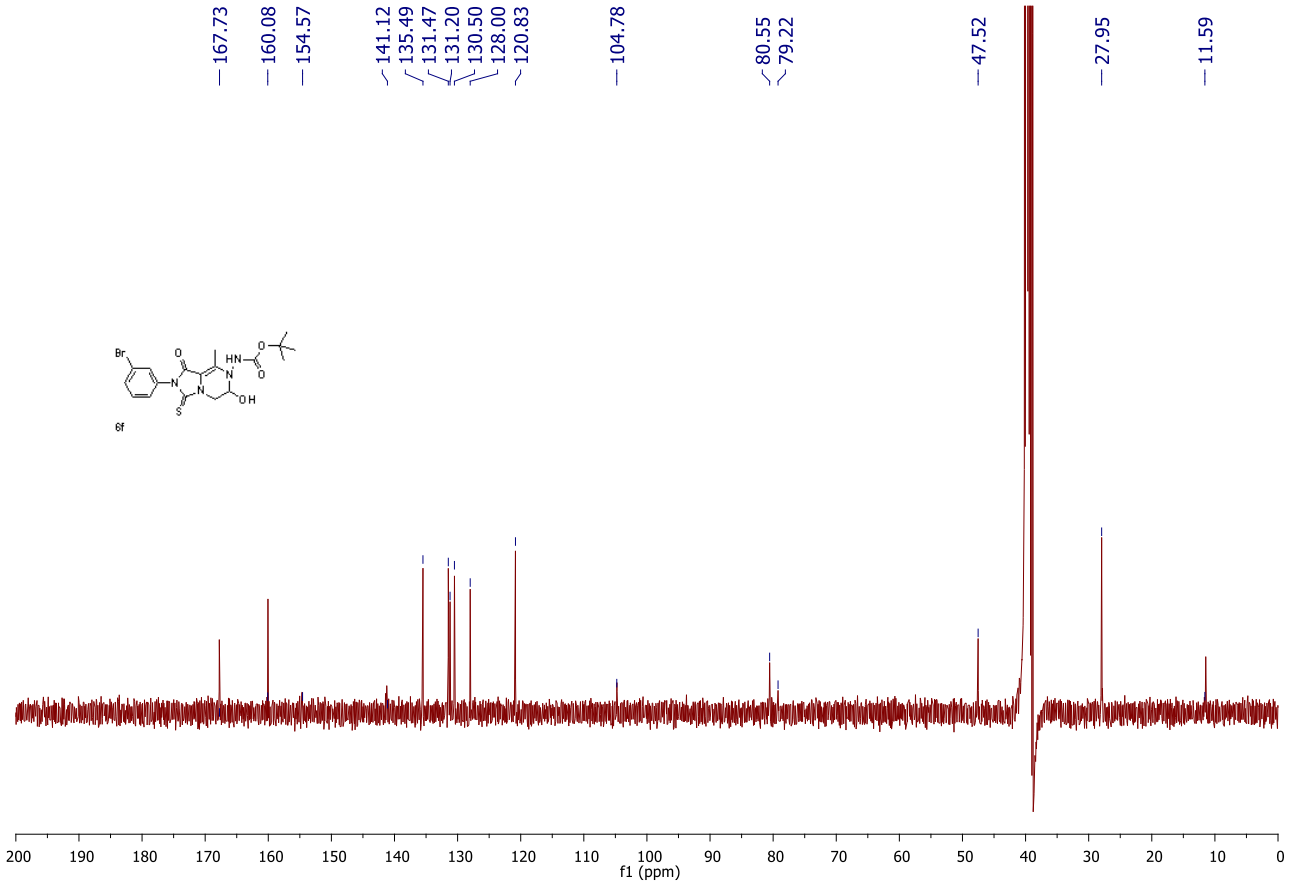
9.40
f1 (ppm)
6f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80.55
79.22
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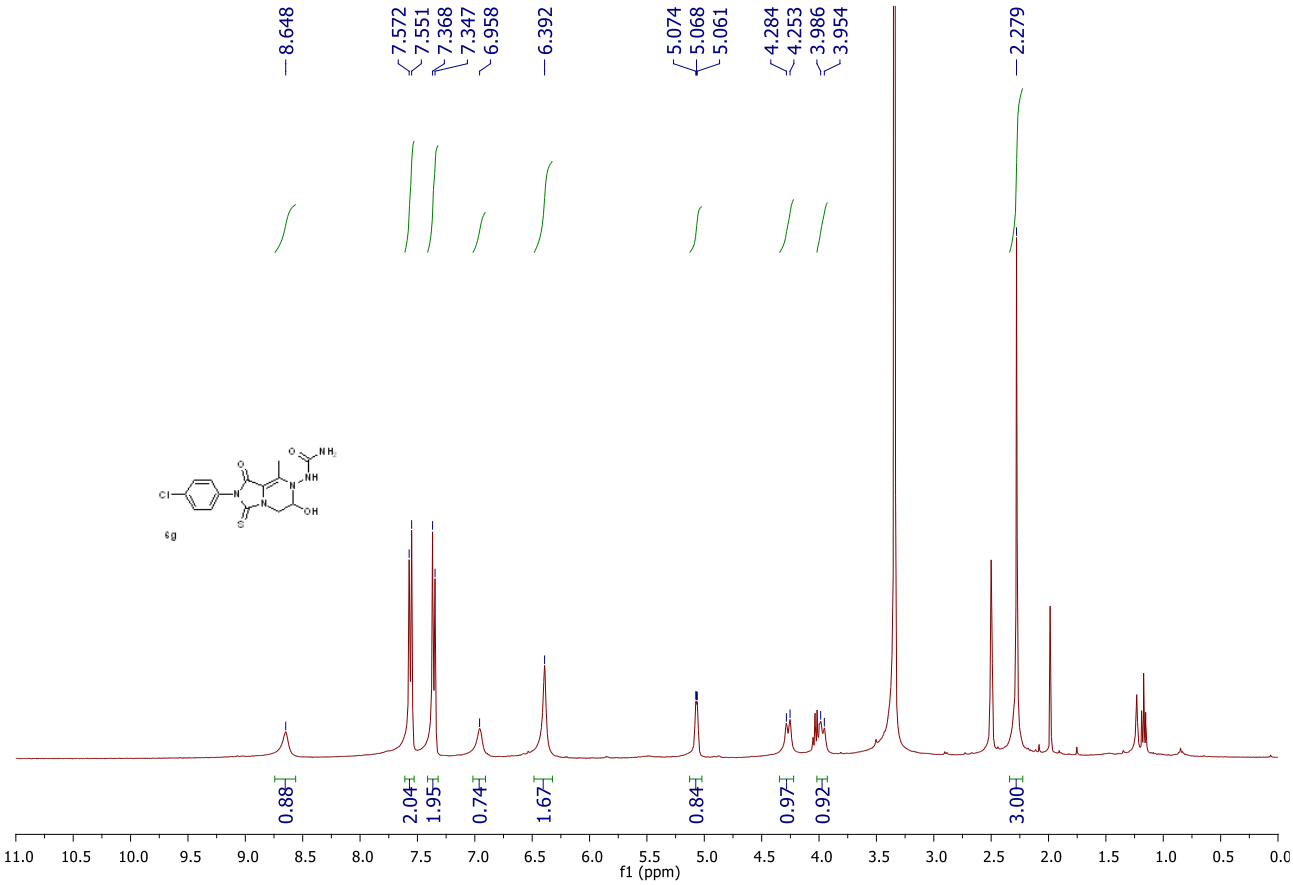
27.95
11.59
f1 (ppm)
6f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6.392
5.074
5.068
5.061
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4.253
3.986
3.954
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2.04
1.95
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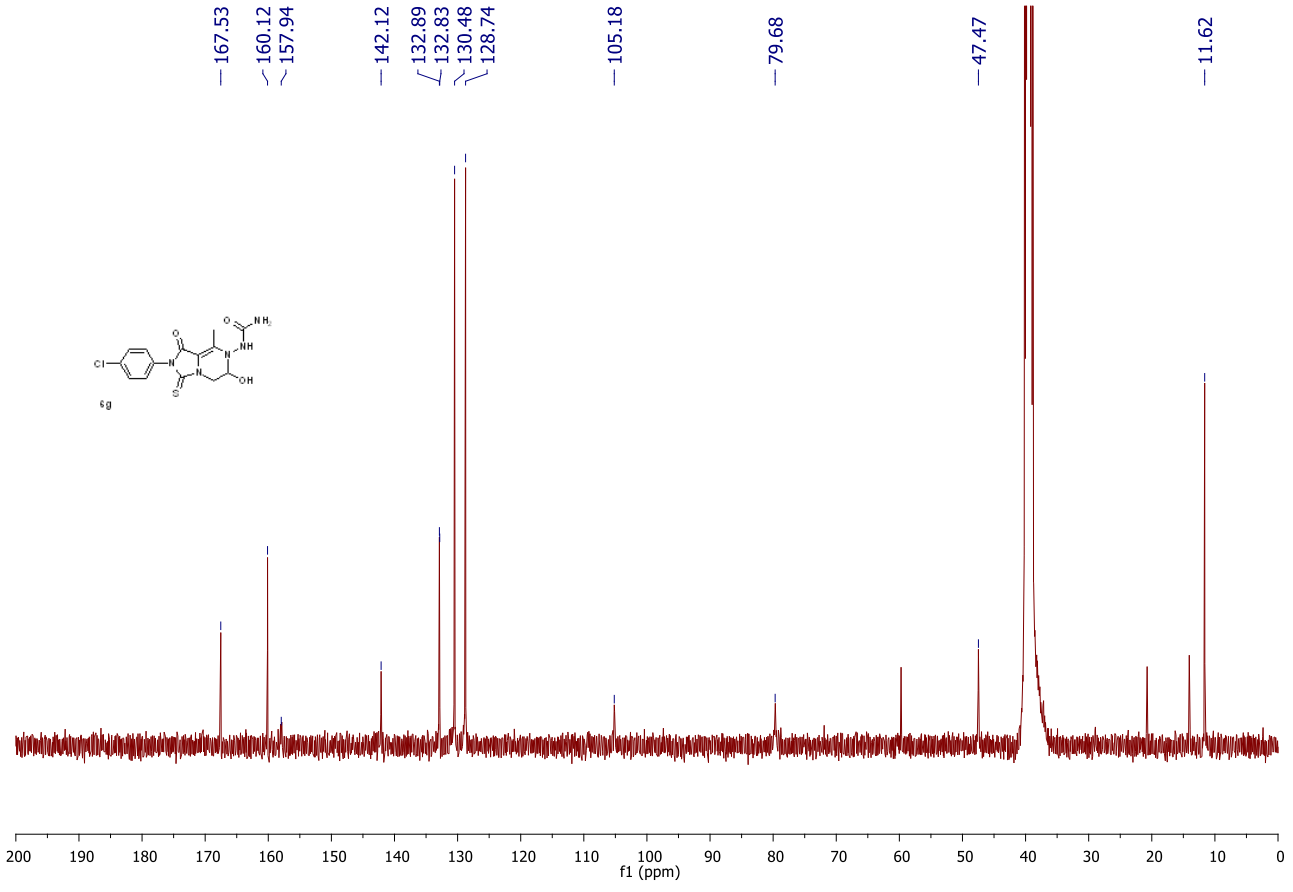
0.84
0.97
0.92
3.00
f1 (ppm)
6g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132.83
130.48
128.74
105.18
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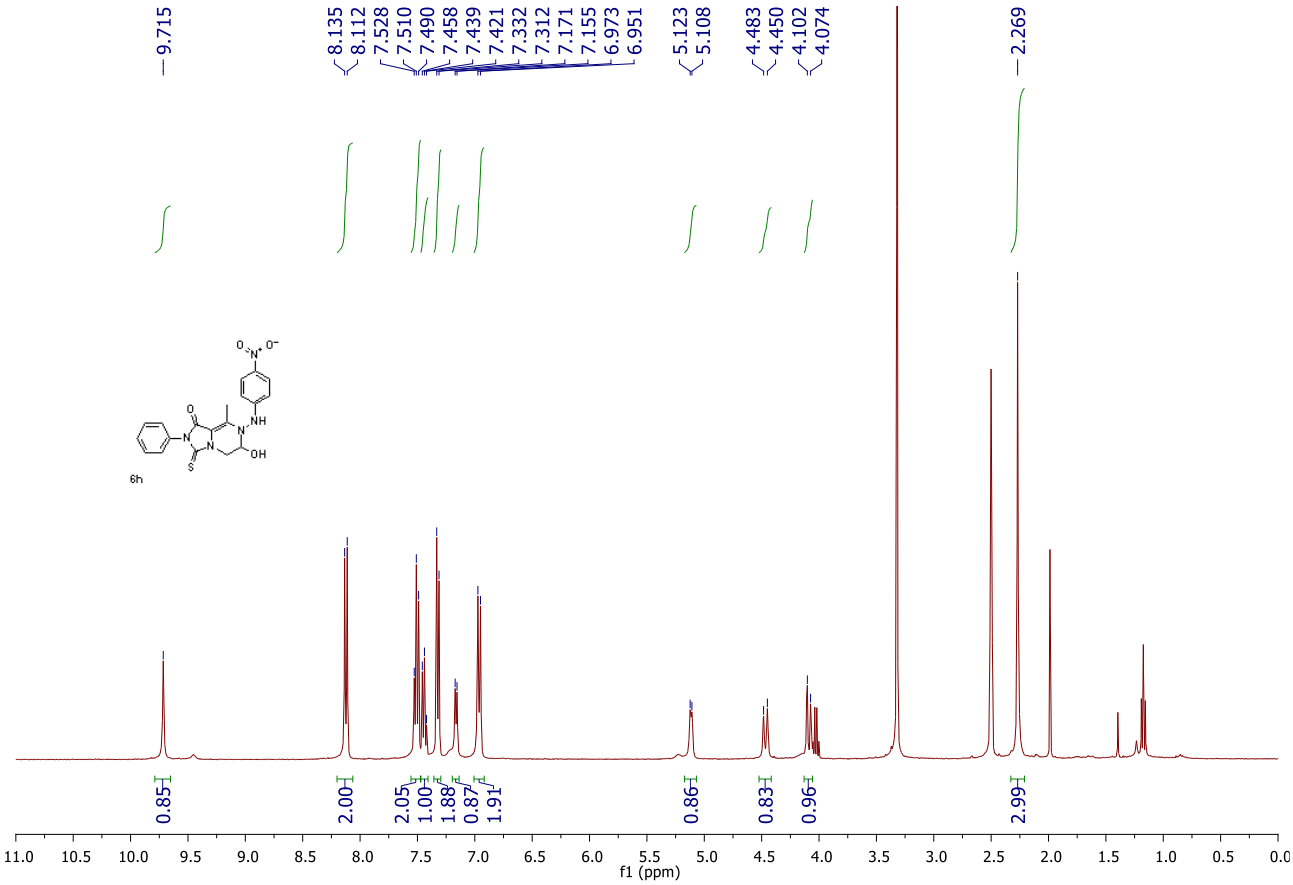
47.47
11.62
f1 (ppm)
6g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7.490
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7.439
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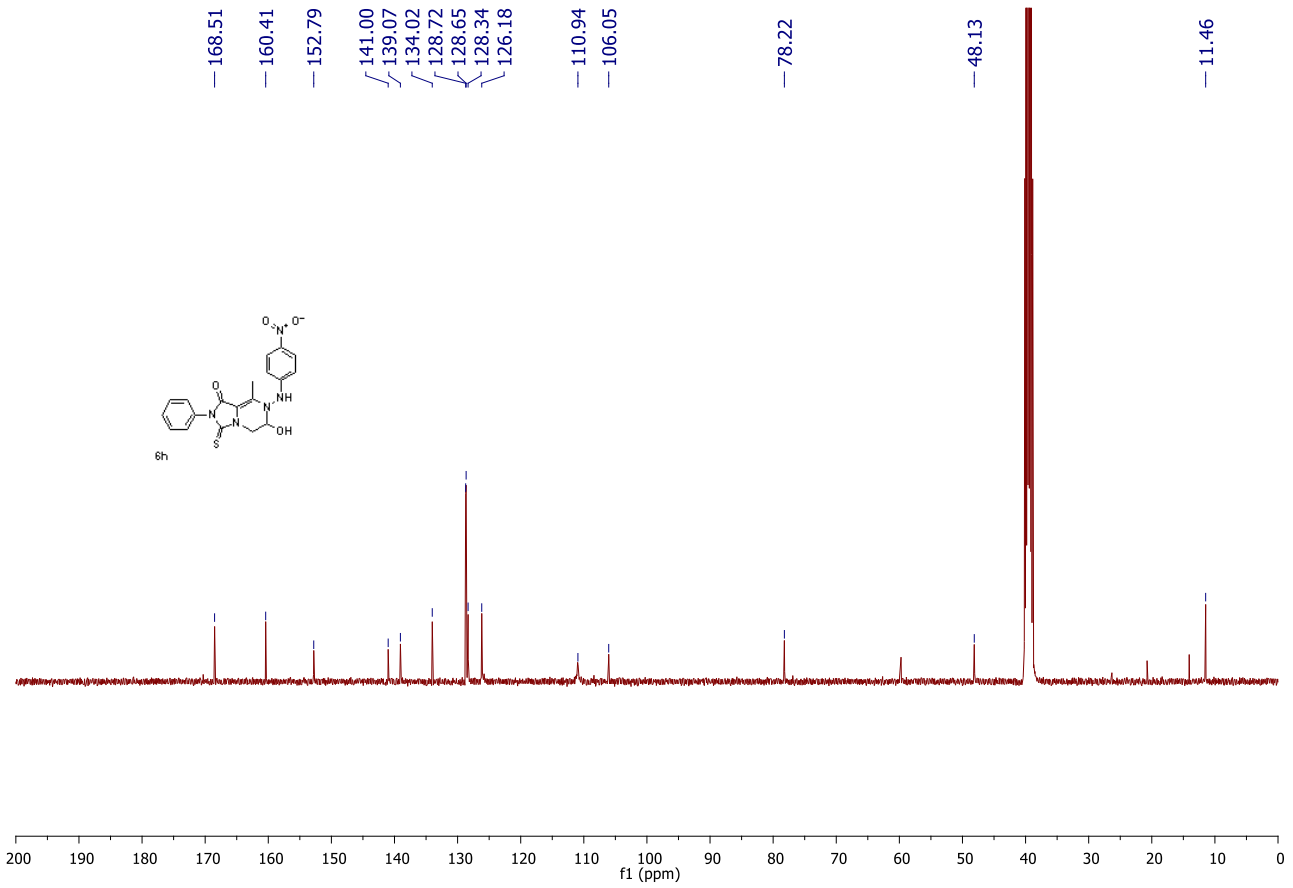
7.332
7.312
7.171
7.155
6.973
6.951
5.123
5.108
4.483
4.450
4.102
4.074
2.269
0.85
2.00
2.05
1.00
1.88
0.87
1.91
0.86
0.83
0.96
2.99
f1 (ppm)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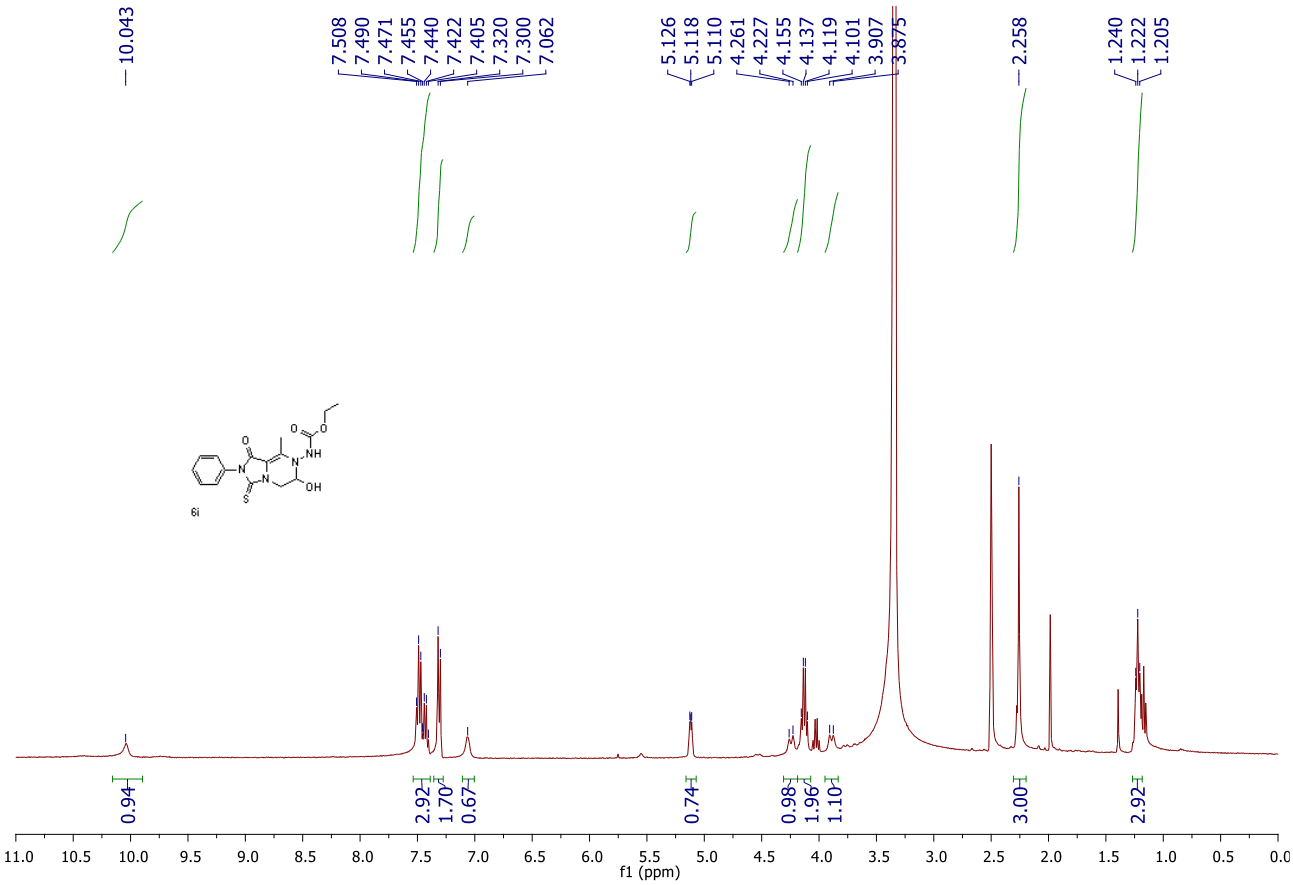
f1 (ppm)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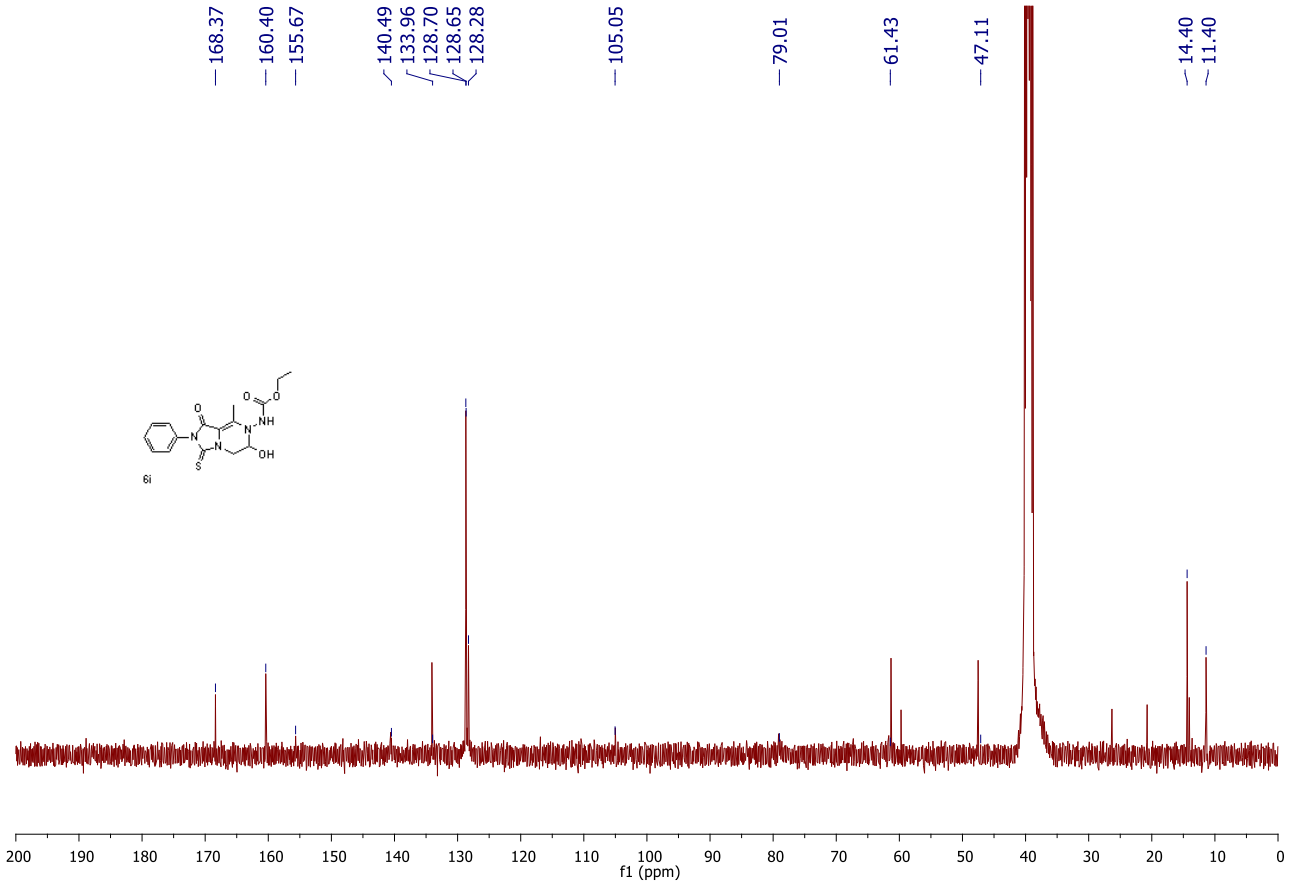
7.405
7.320
7.300
7.062
5.126
5.118
5.110
4.261
4.227
4.155
4.137
4.119
4.101
3.907
3.875
2.258
1.240
1.222
1.205
6i
0.94
2.92
1.70
0.67
0.74
0.98
1.96
1.10
3.00
2.92
f1 (ppm)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128.65
128.28
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79.01
61.43
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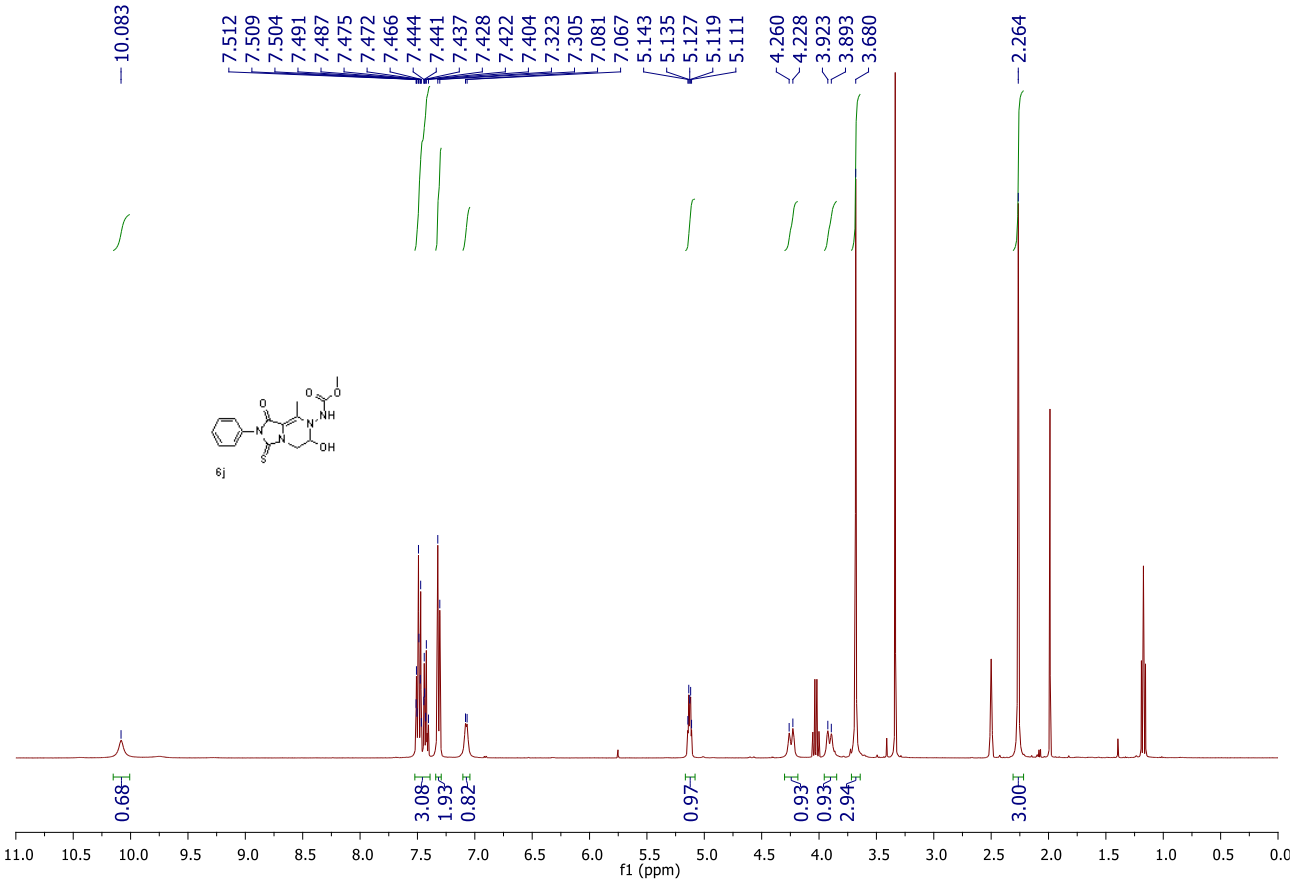
14.40
11.40
6i
f1 (ppm)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7.487
7.475
7.472
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7.444
7.441
7.437
7.428
7.422
7.404
7.323
7.305
7.081
7.067
5.143
5.135
5.127
5.119
5.111
4.260
4.228
3.923
3.893
3.680
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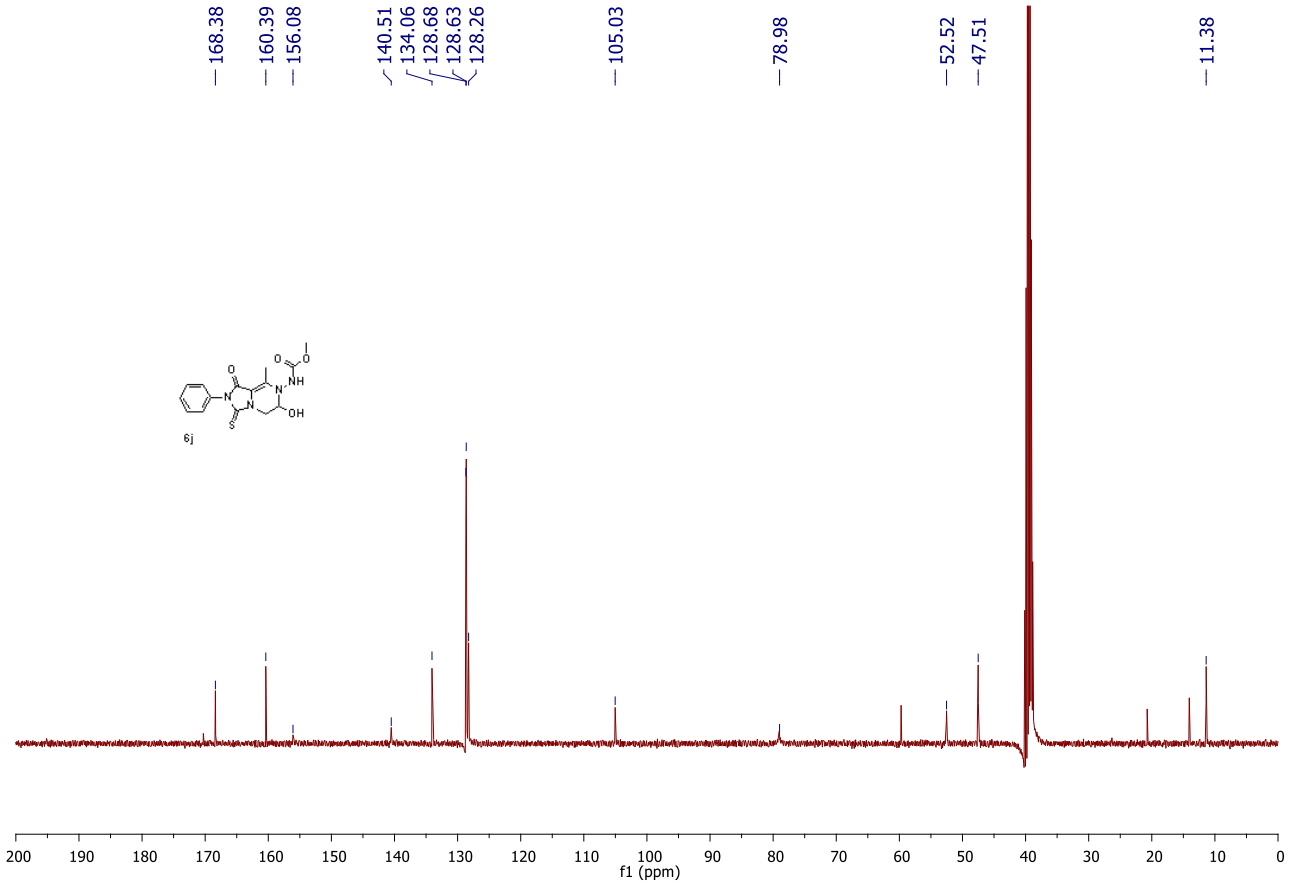
6j
0.68
3.08
1.93
0.82
0.97
0.93
0.93
2.94
3.00
f1 (ppm)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128.68
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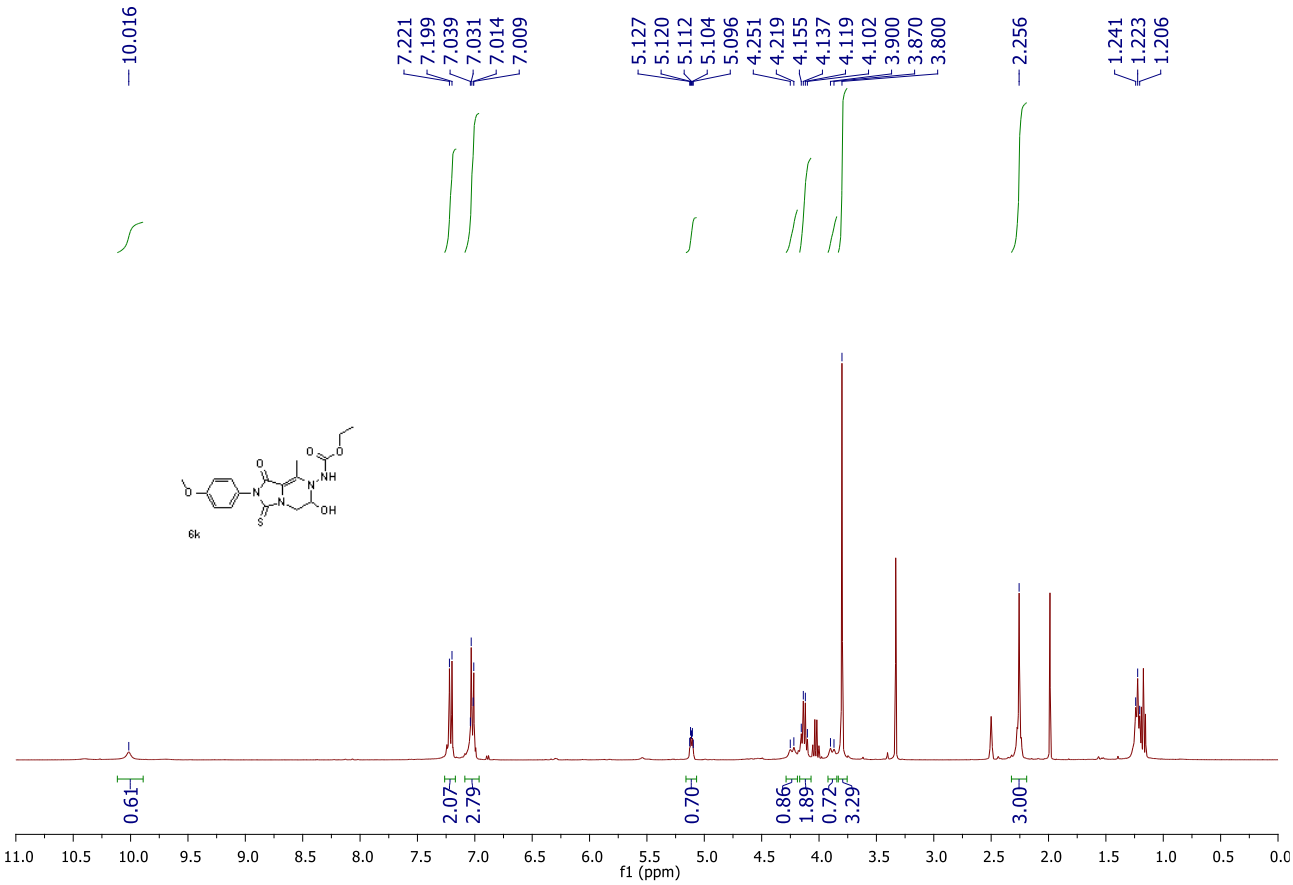
52.52
47.51
11.38
6j
f1 (ppm)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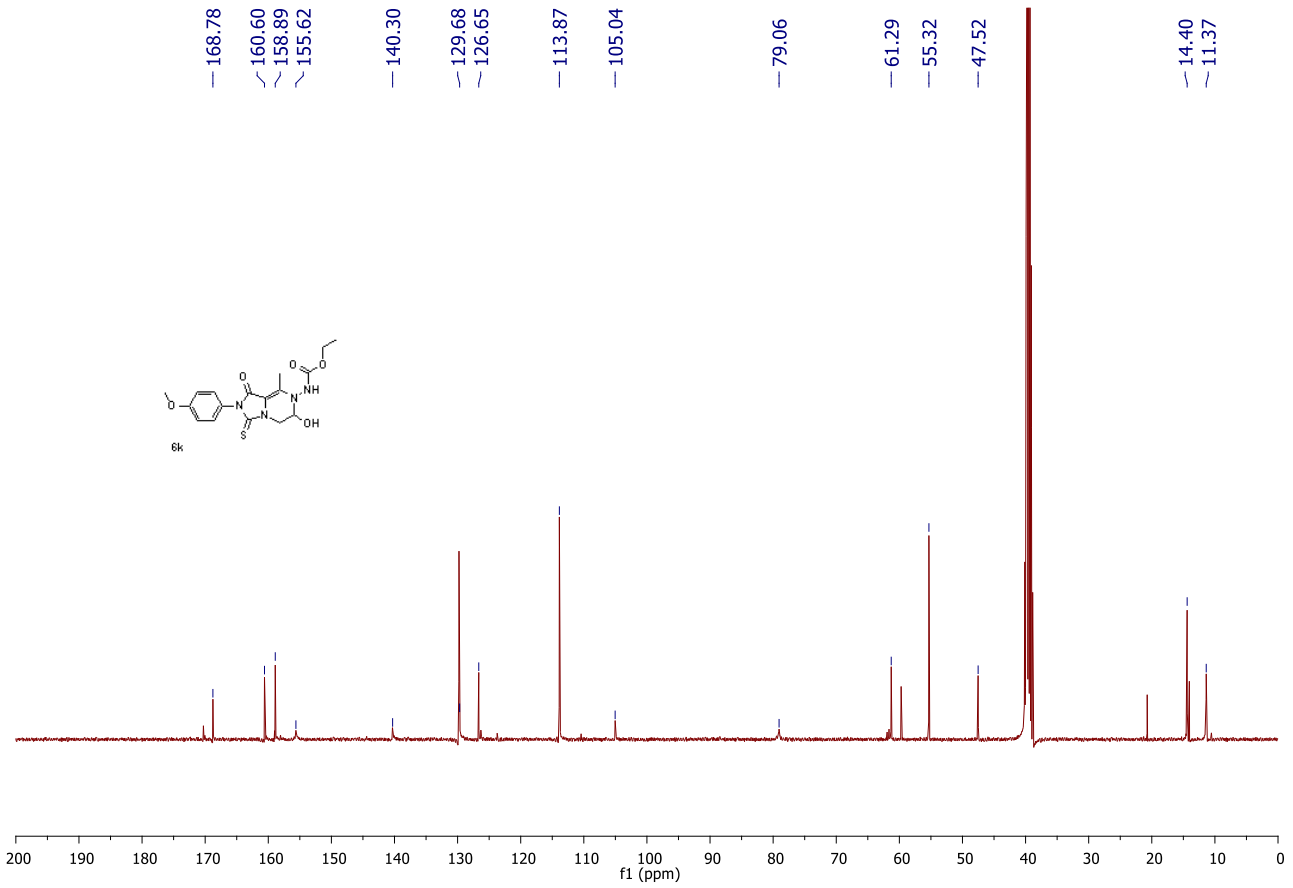
5.120
5.112
5.104
5.096
4.251
4.219
4.155
4.137
4.119
4.102
3.900
3.870
3.800
2.256
1.241
1.223
1.206
6k
0.61
2.07
2.79
0.70
0.86
1.89
0.72
3.29
3.00
f1 (ppm)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140.30
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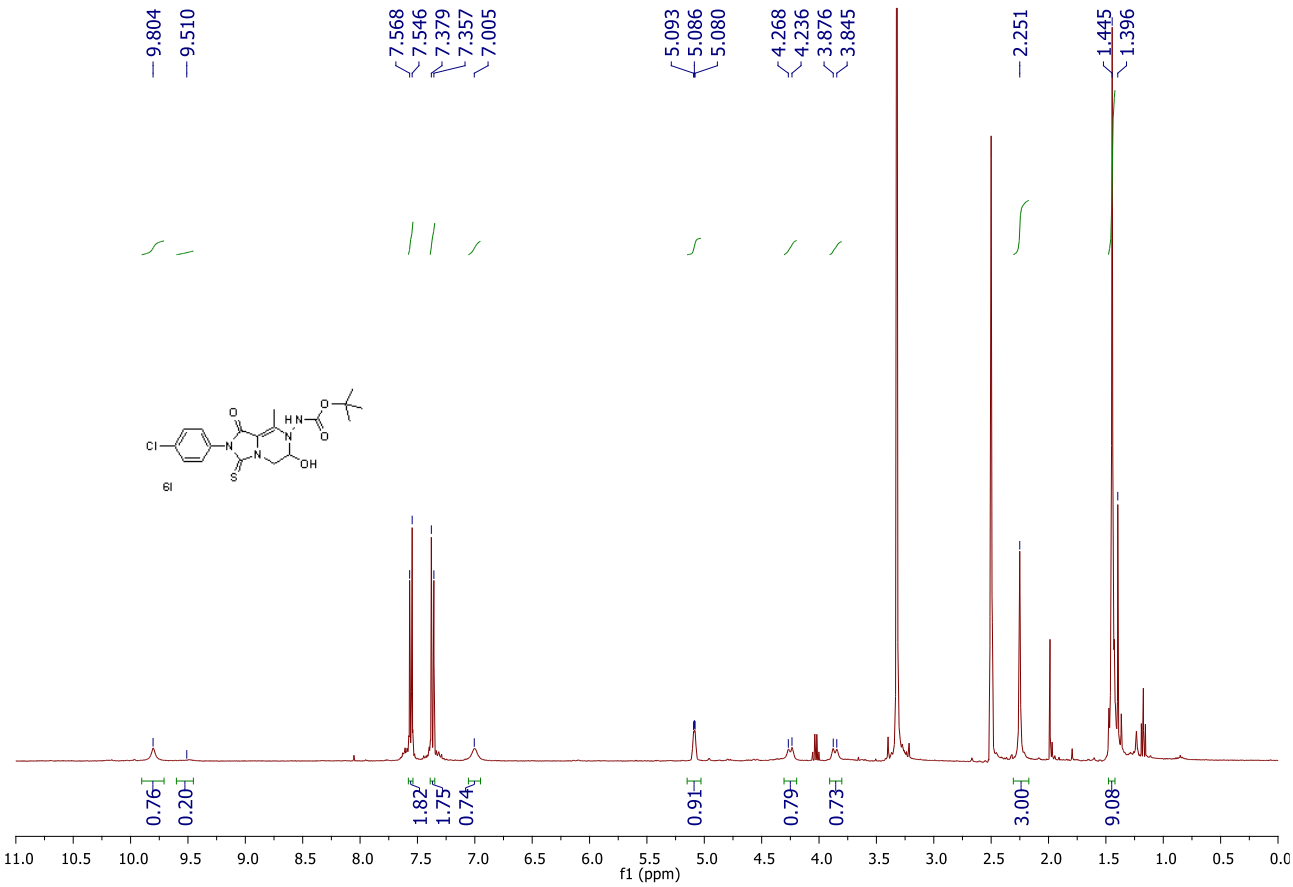
105.04
79.06
61.29
55.32
47.52
14.40
11.37
6k
f1 (ppm)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5.080
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4.236
3.876
3.845
2.251
1.445
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1.82
1.75
0.74
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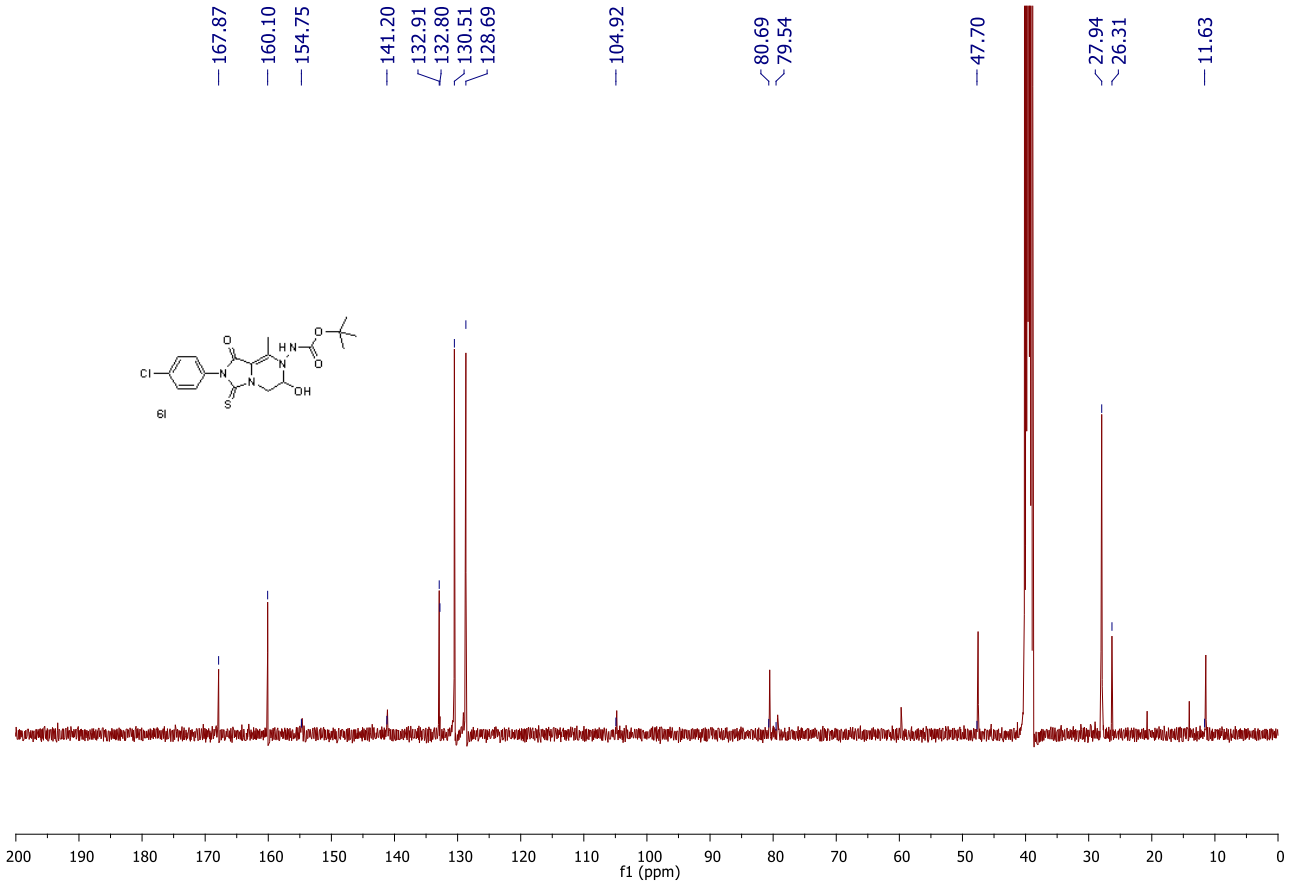
0.79
0.73
3.00
9.08
f1 (ppm)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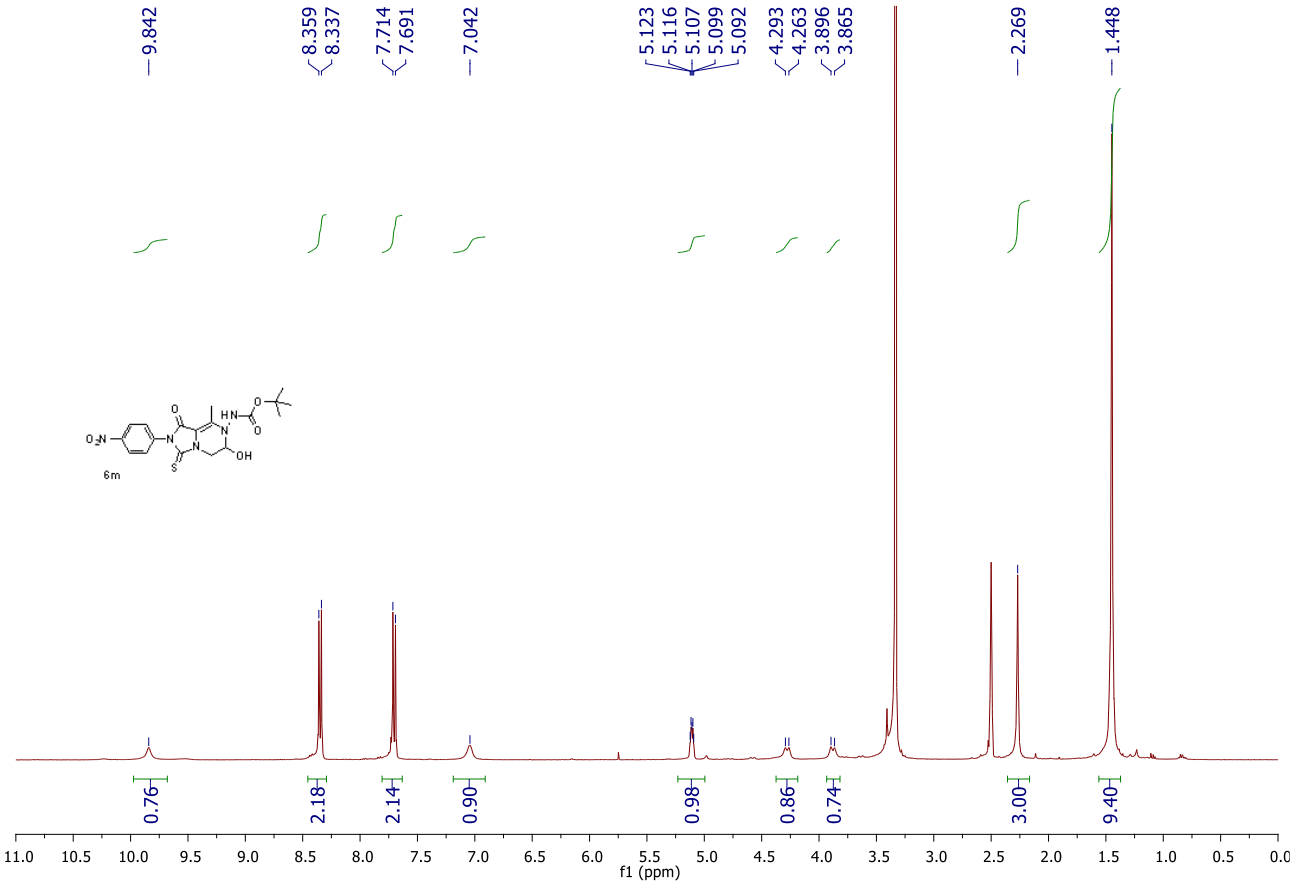
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3.896
3.865
2.269
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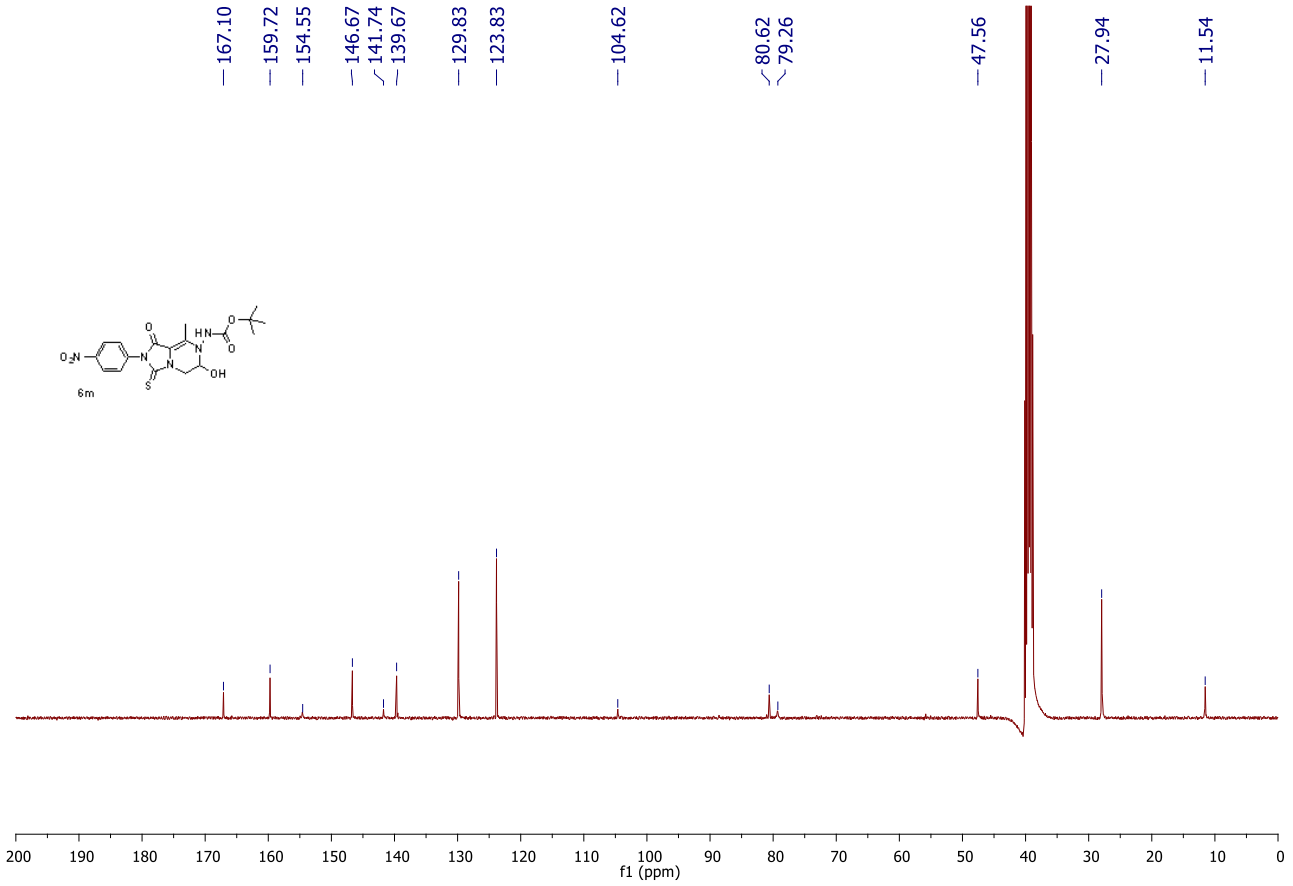
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123.83
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80.62
79.26
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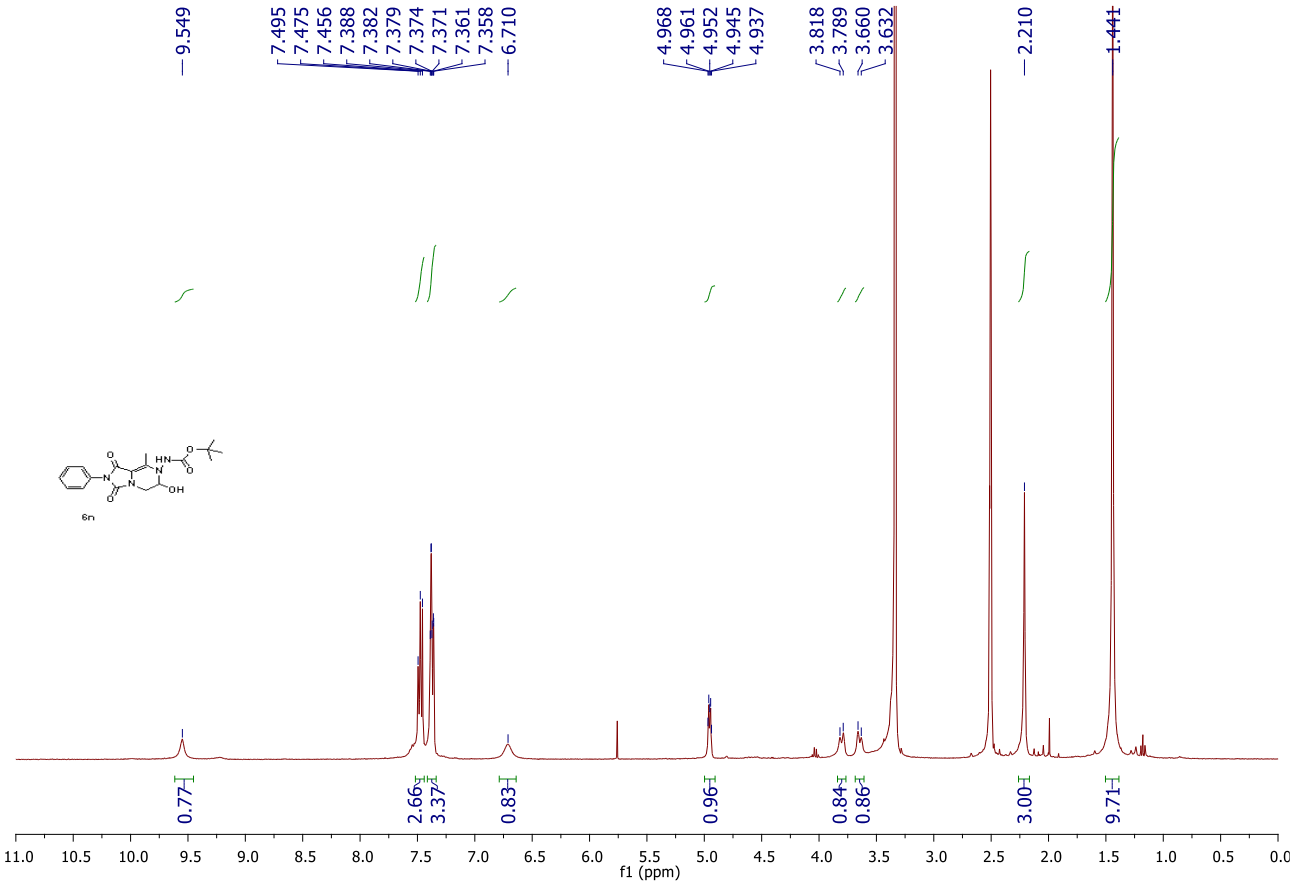
11.54
6m
f1 (ppm)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7.374
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4.968
4.961
4.952
4.945
4.937
3.818
3.789
3.660
3.632
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3.00
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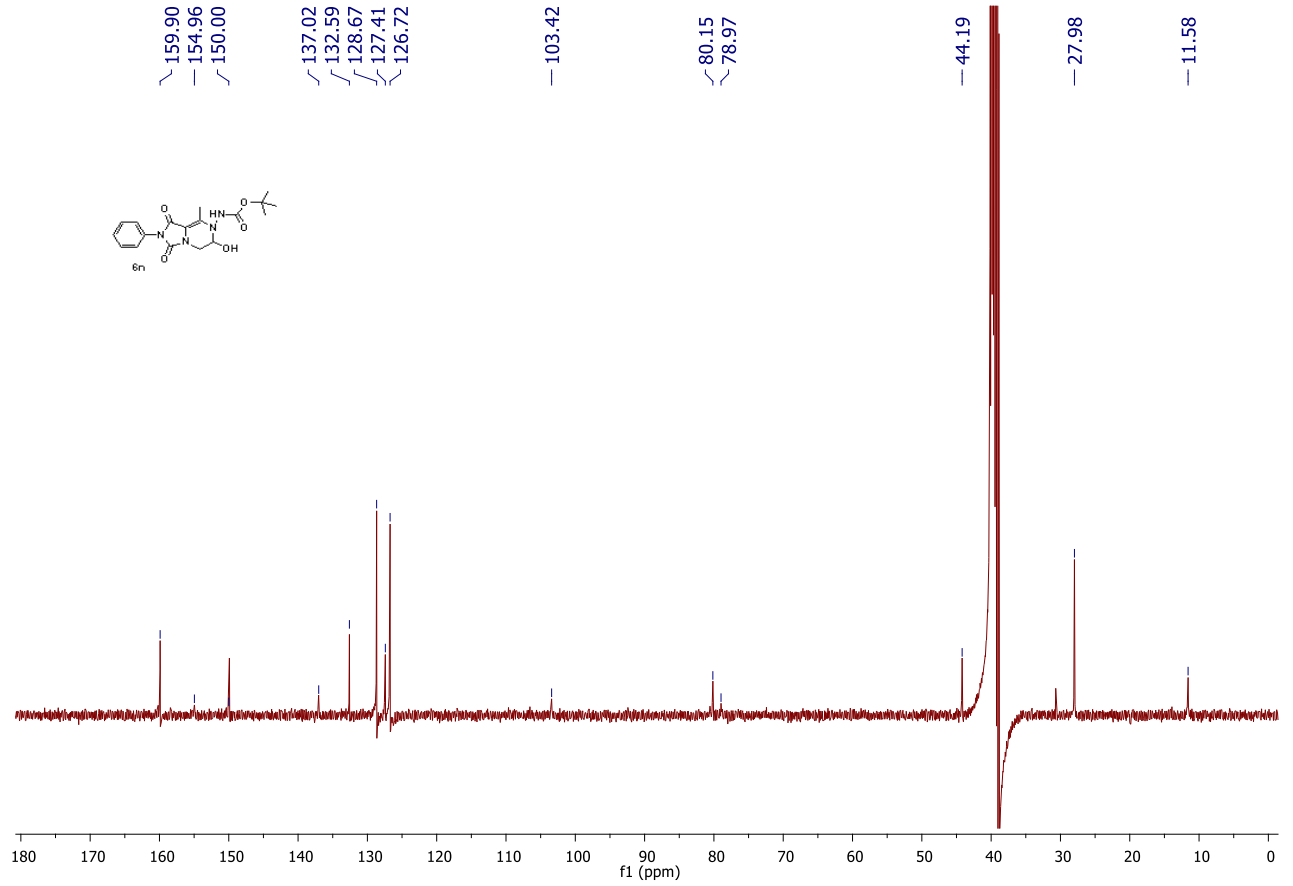
f1 (ppm)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126.72
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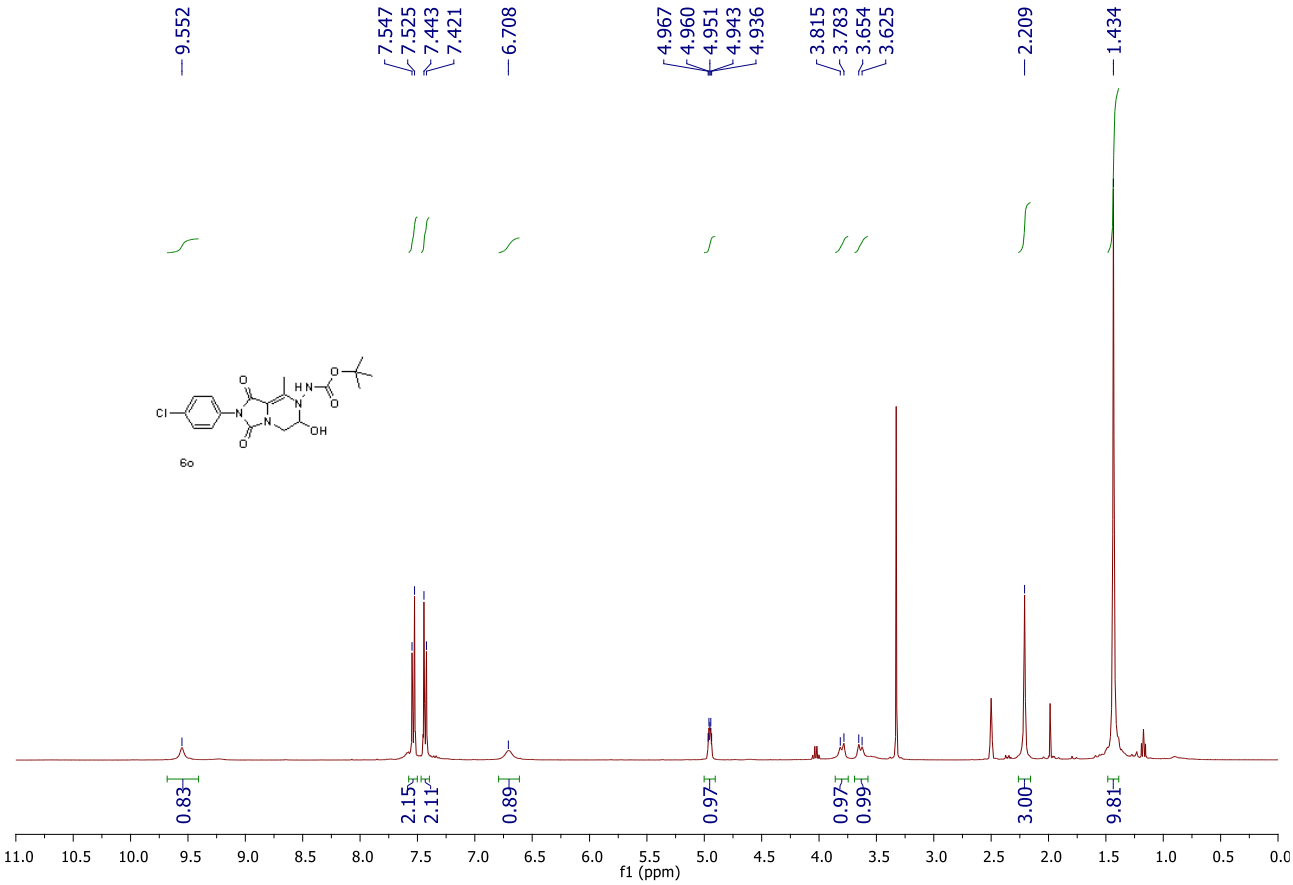
44.19
27.98
11.58
f1 (ppm)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4.960
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4.943
4.936
3.815
3.783
3.654
3.625
2.209
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2.11
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0.97
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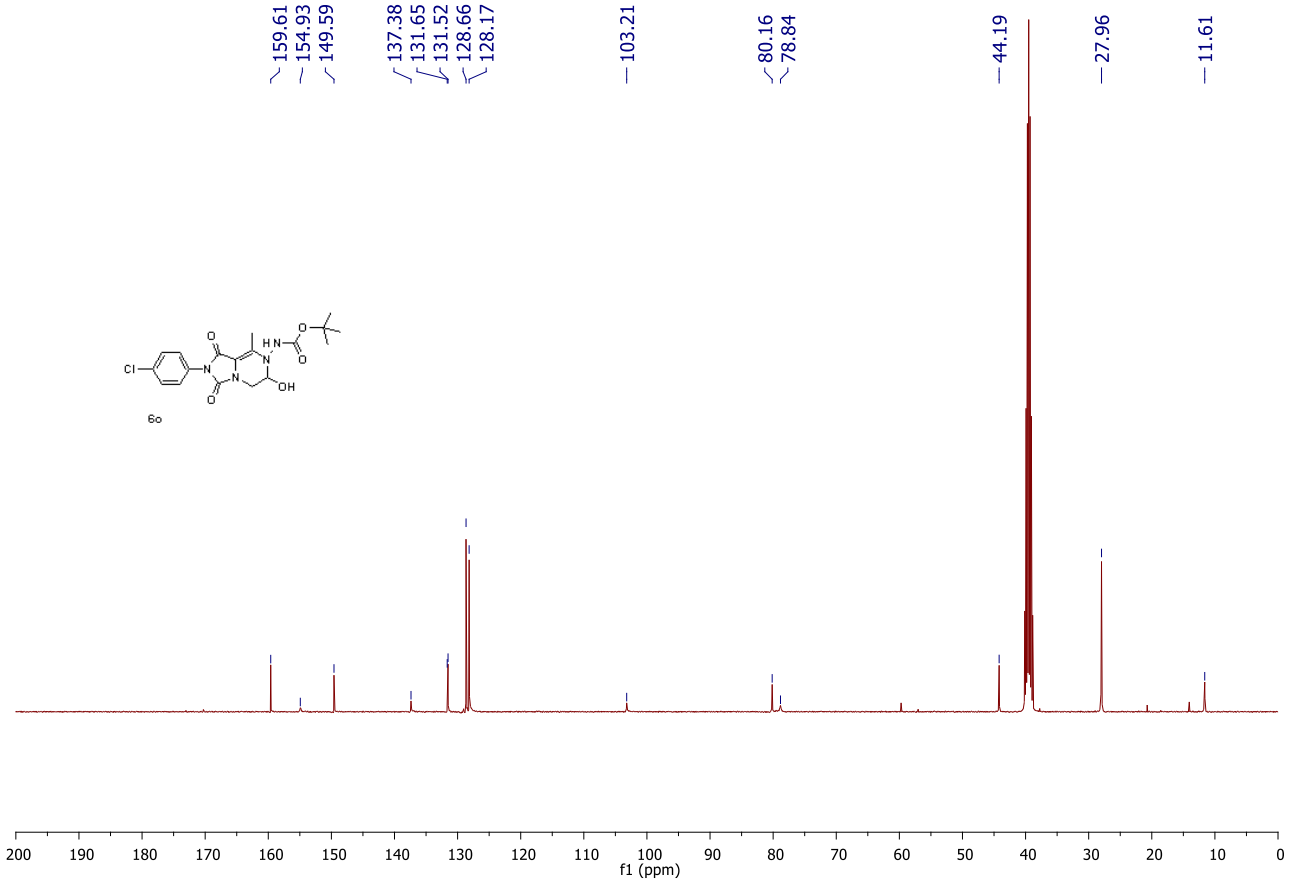
9.81
f1 (ppm)
6o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128.17
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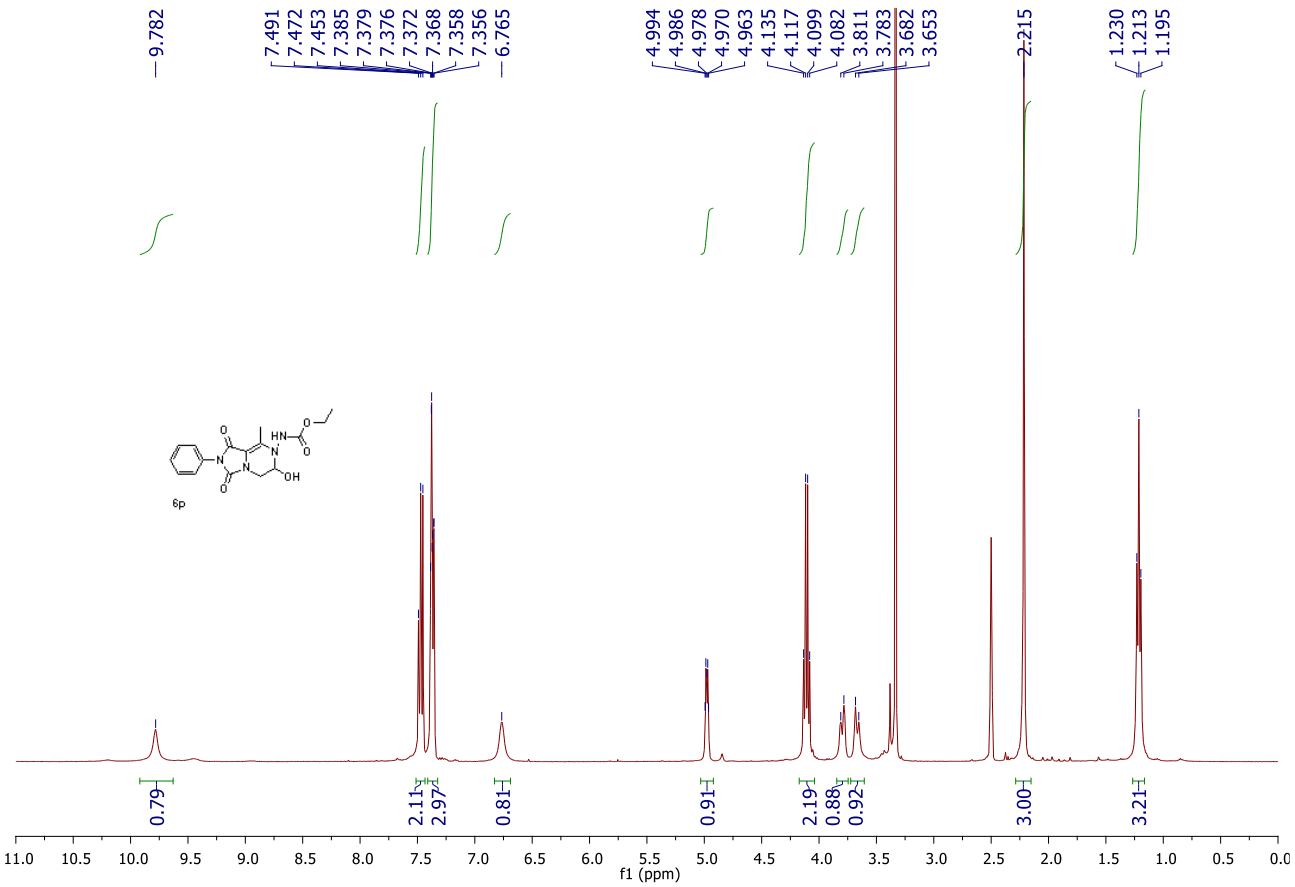
78.84
44.19
27.96
11.61
f1 (ppm)
6o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7.356
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4.994
4.986
4.978
4.970
4.963
4.135
4.117
4.099
4.082
3.811
3.783
3.682
3.653
2.215
1.230
1.213
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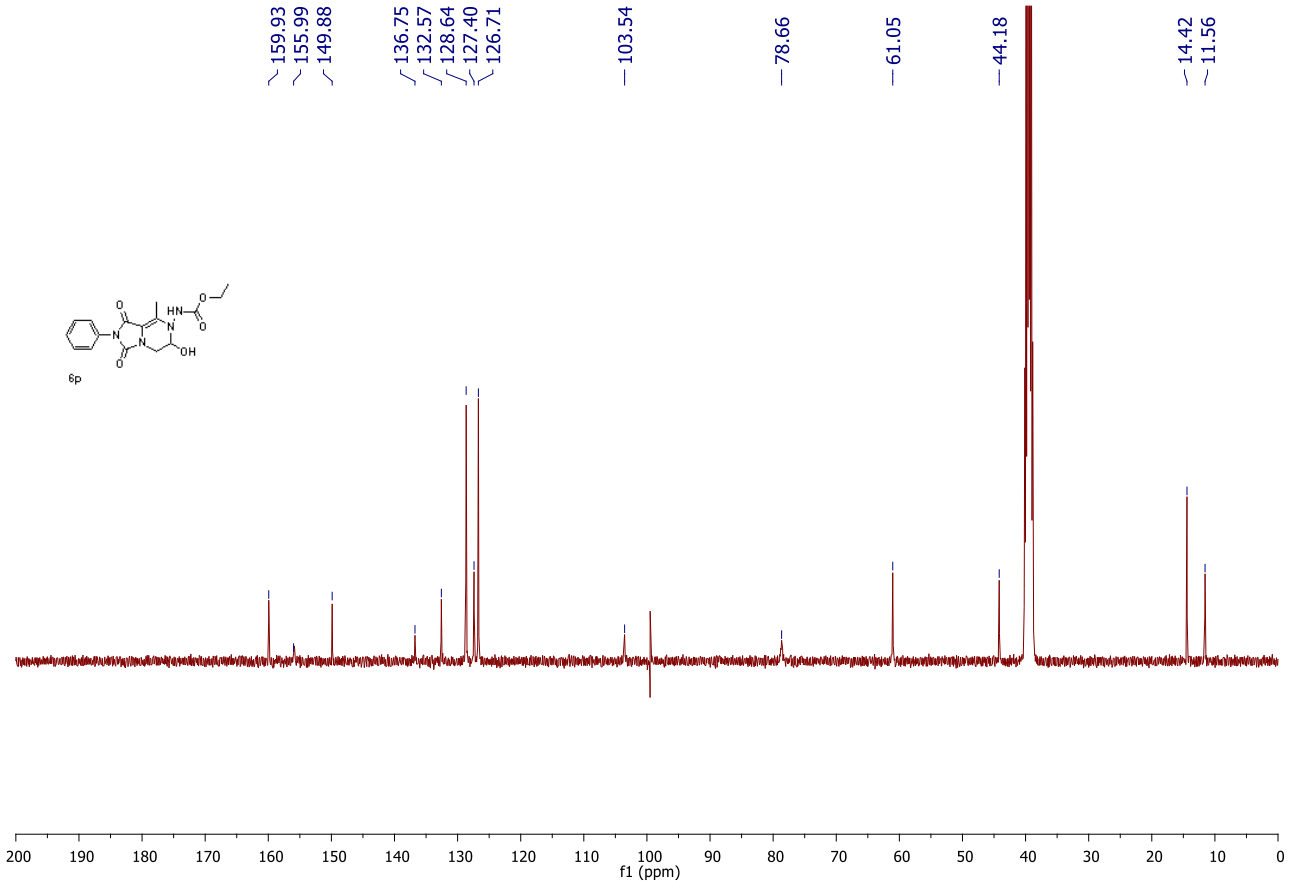
f1 (ppm)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126.71
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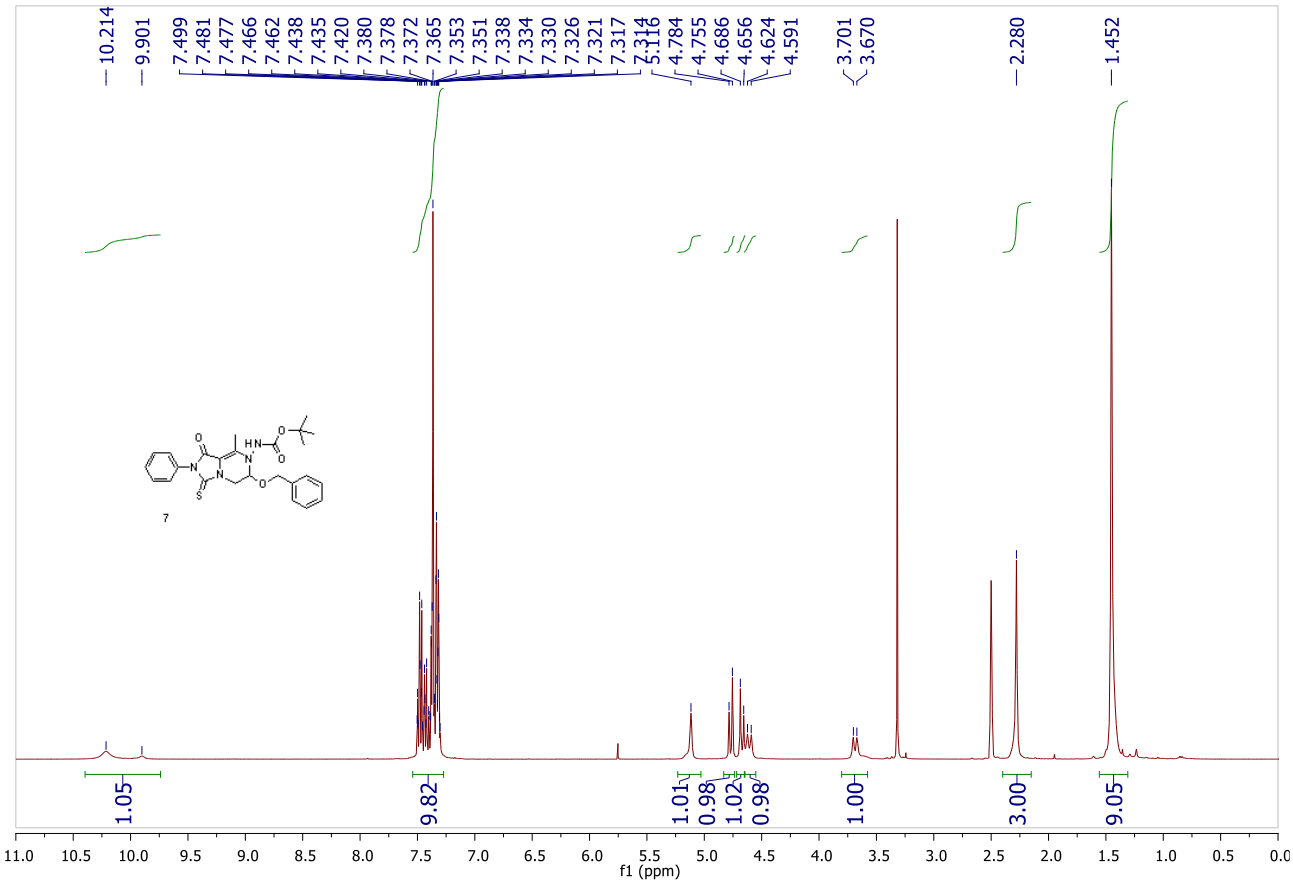
f1 (ppm)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7.365
7.353
7.351
7.338
7.334
7.330
7.326
7.321
7.317
7.314
5.116
4.784
4.755
4.686
4.656
4.624
4.591
3.701
3.670
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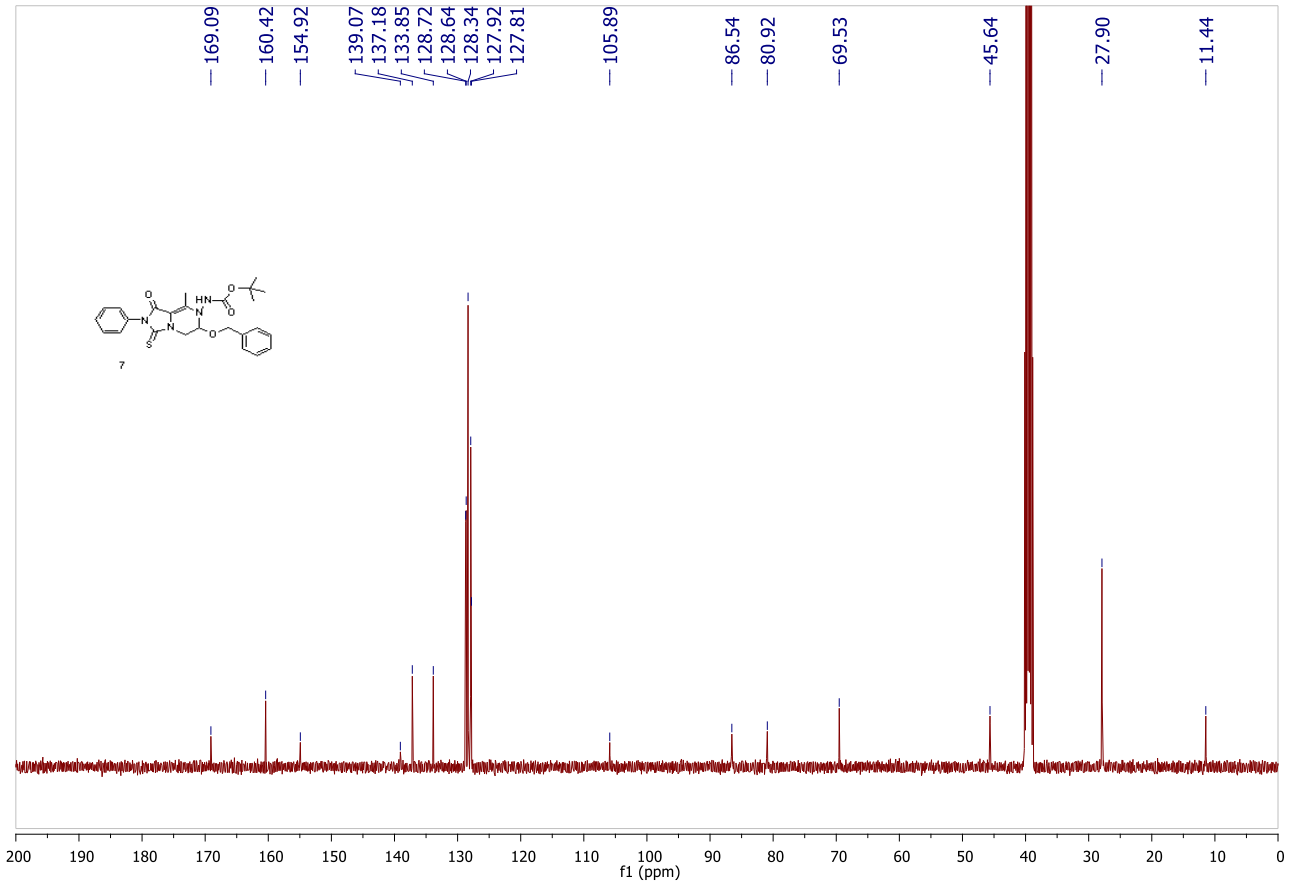
1.02
0.98
1.00
3.00
9.05
f1 (ppm)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128.64
128.34
127.92
127.81
105.89
86.54
80.92
69.53
45.64
27.90
11.44
f1 (ppm)

## 8 References

[1] Preti, L.; Attanasi, O. A.; Caselli, E.; Favi, G.; Ori, C.; Davoli, P.; Felluga, F.; Prati, F. *Eur. J. Org. Chem.*, **2010**, 4312-4320. doi:10.1002/ejoc.201000434

[2] Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, Golobĭc, A.; Lillini, S.; Mantellini, F. *Synlett*, **2006**, 2735-2738. doi:10.1055/s-2006-950275;

[3] Mari, G.; De Crescentini, L.; Favi, G.; Mantellini, F.; Santeusanio, S. *Eur. J. Org. Chem.*, **2022**, *40*, 106-111.

[4] Notably, compounds **5f, 5j–r** at NMR analysis show two sets of peaks for the NH moiety. This observation is probably ascribable to the presence of a second axis along the N–N bond that determines the existence of *syn*/*anti*-rotamers of carbamates.

Barrett, K. T.; Metrano, A. J.; Rablen, P. R.; Miller, S. J. *Nature*, **2014**, *509*, 71–75. doi:10.1038/nature13189