Synthesis of a Library of "Lead-Like" γ-Lactams by a One Pot, Four-Component Reaction

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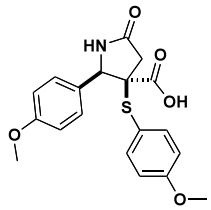
Supporting Information

Materials: Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina.

Instrumentation: 1H NMR spectra and proton-decoupled 13C NMR spectra were obtained on a 300, 400 or 600 MHz Varian NMR spectrometer. Chemical shifts (") are reported in parts per million (ppm) relative to TMS (s, " 0). Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br m (broad multiplet), brs (broad singlet). 13C NMR chemical shifts are reported relative to CDCl3 (t," 77.4) unless otherwise noted. High resonance mass spectra were recorded on positive ESI mode in methanol or acetonitrile. Melting points were taken on an EZmelting apparatus and were uncorrected. Infrared spectra were taken on a Bruker Tensor 27 spectrometer. Chromatographic purifications were performed by flash chromatography with silica gel (Silicycle, 40–63 μm) packed in glass columns. The eluting solvent for the purification of each compound was determined by thin layer chromatography (TLC) on glass plates coated with EMD silica gel 50 F254 and visualized by ultraviolet light. Purification of library members using basic conditions via

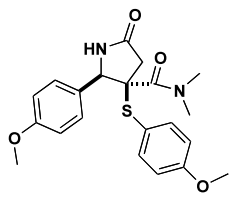
preparative chromatography was achieved utilizing a Waters X-Bridge C18 column (19 x 150mm, 5!m, w/ 19 x 10mm guard column) at a flow rate of 20 mL/min. Samples were diluted in DMSO and purified using an elution mixture of water (pH 9.8 with NH4OH) and CH3CN, running a concentration gradient which increased by 20% CH3CN over a 4 minute period. The corresponding preparative gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis after preparative chromatography utilized a Waters Acquity system with UV-detection and mass-detection (Waters LCT Premier). The analytical methodconditions included a Waters Aquity BEH C18 column (2.1 x 50mm, 1.7um) and elutionwith a linear gradient of 5% water (pH 9.8 with NH4OH) to 100% CH3CN at 0.6 mL/minflow rate. Purity of each sample was determined using UV peak area detected at 214nm wavelength. Purification of library members using acidic conditions via preparativechromatography was achieved utilizing a Waters Atlantis Prep T3 (19 x 150mm, 5**!**m, w/ 19 x 10mm guard column) at a flow rate of 20 mL/min. Samples were diluted in50:50 CH3CN:water and purified using a elution mixture of water (0.05% formic acid)and CH3CN, running a concentration gradient which increased by 20% CH3CN over a 4minute period. The corresponding preparative gradient, triggering thresholds, and UV wavelength were selected based on the HPLC analysis of each crude sample. Analytical analysis after preparative chromatography utilized a Waters Acquity system with UV-detection and mass-detection (Waters LCT Premier). The analytical method conditions included a Waters Aquity HSS T3 C18 column (2.1 x 50mm, 1.8um) and elution with a linear gradient of 1% water (0.01% formic acid) to 100% CH3CN at 0.6 mL/min flow rate. Purity of each sample was determined using UV peak area detected at 214 nm wavelength. The following abbreviations are used throughout: acetonitrile (ACN), room temperature (rt), ethyl acetate (EtOAc), methanol (MeOH), ethanol (EtOH),isopropanol (i-PrOH), tert-butanol (t-BuOH), diisopropylethylamine (DIPEA), N,Ndimethylformamide (DMF), tetrahydrofuran (THF), and dichloromethane (DCM).

Experimental Procedures



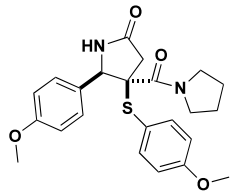
(15). Ammonium acetate (2.31 g, 30.0 mmol), maleic anhydride (2.94 g, 30.0 mmol), *p*-anisaldehyde (3.66 mL, 30.0 mmol), *p*-methoxybenzenethiol (3.7 mL, 30.0 mmol), and toluene (40 ml) were combined in a round bottom flask and the mixture was refluxed under argon with a dean stark trap for 24 hr. The reaction was allowed to cool to room temperature and white and orange precipitate was collected by gravity filtration. Rinsing of the solid with cold methanol yielded a clean white powder of the major diastereomer (5.04 g, 45%): mp 260-263 °C; ^{1}H NMR (400 MHz, *d*-DMSO) δ 13.20 (s, 1H), 8.33 (s, 1H) 7.29 (d, J=7.4 Hz, 2 H), 7.17 (d, J=7.5 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 6.84 (d, J= 8.8 Hz, 2H), 5.11 (s, 1H), 3.73 (s, 3H) 3.70 (s, 3H), 2.77 (d, J=16.9 Hz, 1H), 2.44 (d, J=17.1 Hz, 1H); ^{13}C NMR (151 MHz, DMSO-d6) δ 174.0, 173.5, 161.1, 160.0, 138.5, 130.2, 129.5, 121.4, 115.2, 113.9, 62.9, 61.3, 55.9, 55.8, 40.9; IR (neat) 3197, 1722, 1672, 1668, 1248 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_5S$ $(M+H)^+$374.1057, found 374.1060.

General Experimental A: Formation of amides 18*{1-3}*. Acid **15** was added to a round bottom flask and dissolved in benzene. Thionyl chloride was added dropwise at 0 °C. The reaction was then heated to reflux for 2-8 hours until all starting material was consumed. Benzene was then removed *in vacuo* to yield the acid chloride as a brown foam. The acid chloride was immediately dissolved in DCM (0.1M) and cooled to 0 °C in an ice bath. A primary or secondary amines **26***{1-14}* (2 equiv) was then added dropwise at 0 °C and reaction was allowed to warm to room temperature overnight. After 24 h, DCM was removed *in vacuo* and the residue was taken up in EtOAc and water and the layers were separated. The aqueous layer was extracted twice more with EtOAc. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography afforded the desired NH γ-Lactam products **18** in 29-86% yield.

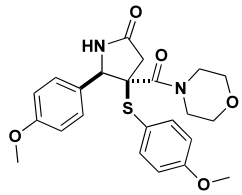


18*{1}*. The title compound was prepared from **15** (2.0 g, 5.36 mmol) according to general experimental A. Flash column chromatography with 50%-100% EtOAc:hexanes afforded **18***{1}* as a brown to white solid (1.23 g, 57%). mp 191-194°C; ^{1}H NMR (600

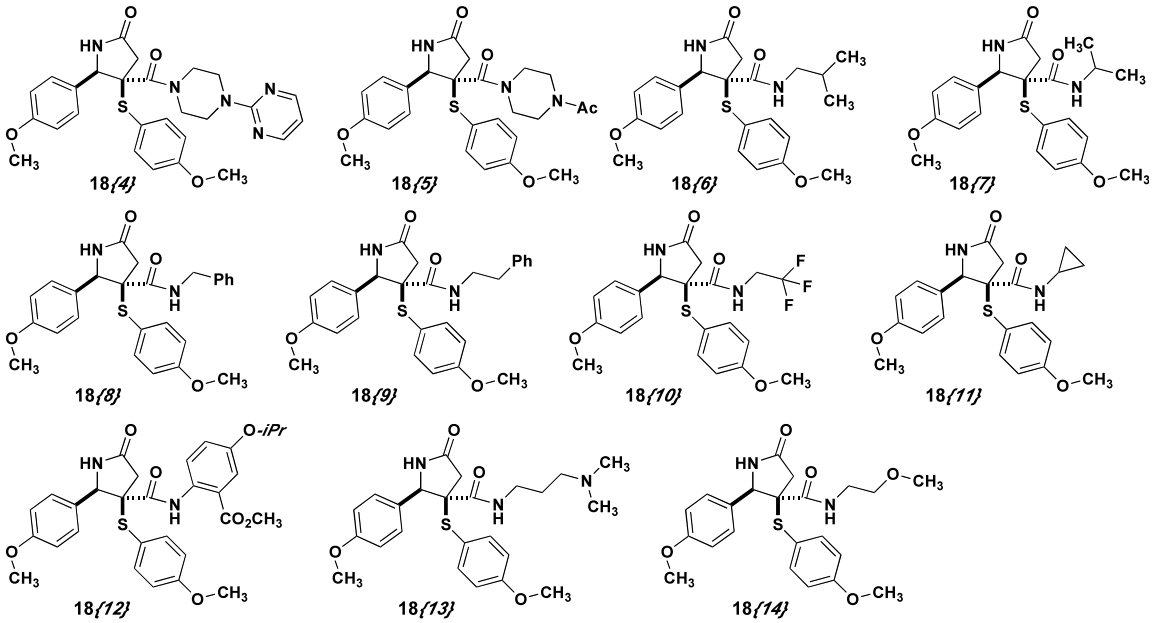
MHz, $CDCl_3$) δ 7.42 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.9 Hz, 2H), 6.85 (s, 1H) 6.72 (d, J=9.0 Hz, 2H) 6.60 (d, J=9.0 Hz, 2H) 5.37 (s, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.36 (bs, 3H), 3.27 (d, J=17.1, 1H), 2.86 (bs, 3H) 2.78 (d, J=17.0, 1H); ^{13}C NMR (151 MHz,) δ 174.2, 169.4, 160.3, 159.8, 136.4, 130.3, 129.1, 121.0, 114.2, 113.5, 63.4, 61.6, 55.3, 55.2, 43.1, 39.2, 37.8; IR (neat) 3255, 2957, 1709, 1666, 1625 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2O_4S$ $(M+H)^+$ 401.1530, found 401.1527.



18*{2}*. The title compound was prepared from **15** (1.167 g, 3.13 mmol) according to general experimental A. Flash column chromatography with 50%-100% EtOAc:hexanes afforded **18***{2}* as a brown foam (1.146 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J=8.6 Hz, 2H) 6.88 (d, J= 8.6 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H) 6.60 (d, J=9.0 Hz, 2H) 6.36 (s, 1H), 5.48 (s, 1H), 4.06-3.91 (m, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.48-3.44 (m, 1H), 3.28 (d, J=, 1H), 3.28-3.23 (m, 1H), 2.8 (d, J=, 1H), 2.02-1.97 (m, 1H), 1.90-1.78 (m, 4H); ^{13}C NMR (151 MHz,) δ 174.0, 168.0, 160.5, 160.0, 136.4, 130.7, 129.3, 121.4, 114.3, 113.7, 63.3, 62.8, 55.6, 55.4, 48.3, 48.0, 42.7, 27.3, 23.5; IR (neat) 3230, 2915, 1696, 1612, 1284 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{26}N_2O_4S$ $(M+H)^+$ 427.1686, found 427.1685.

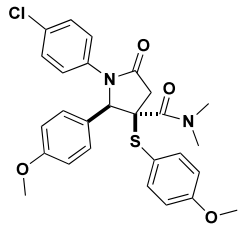


18*{3}*. The title compound was prepared from **15** (2.0 g, 5.36 mmol) according to general experimental A. Flash column chromatography with 50%-100% EtOAc:hexanes afforded **18***{3}* as a brown foam (1.66 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J=8.7 Hz, 2H) 6.92-6.87 (m, 4H), 6.68 (d, J= 8.9 Hz, 2H), 6.49 (s, 1H), 5.29 (s, 1H), 3.84-3.70 (bm, 8H), 3.82 (s, 3H), 3.74 (s, 3H), 3.27 (d, J=16.9 Hz, 1H) 2.74 (d, J=16.9 Hz, 1H); ^{13}C NMR (151 MHz,) δ 174.2, 169.2, 160.6,160.3, 136.1, 130.1, 129.0, 121.2, 114.7, 114.0, 66.7, 63.7, 61.1, 55.6, 55.5, 42.8; IR (neat) 3247, 2852, 1701, 1633, 1503 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{26}N_2O_5S$ $(M+H)^+$ 443.1635, found 443.1635.

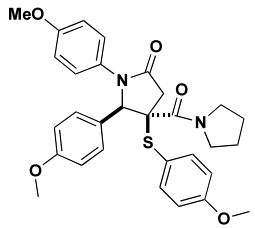


Cmpd #	Formula	M +	Calc'd Mass	Found Mass	%Purity HPLC
18*{4}*	$C_{27}H_{29}N_5O_4S$	H	520.2013	520.2041	94.4
18*{5}*	$C_{25}H_{29}N_3O_5S$	H	484.1901	484.1877	96.2
18*{6}*	$C_{23}H_{28}N_2O_4S$	H	429.1843	429.1832	100
18*{7}*	$C_{22}H_{26}N_2O_4S$	H	415.1687	415.1664	99.5
18*{8}*	$C_{26}H_{26}N_2O_4S$	H	463.1683	463.1661	98.6
18*{9}*	$C_{27}H_{28}N_2O_4S$	H	477.1843	477.1876	96.9
18*{10}*	$C_{21}H_{21}F_3N_2O_4S$	H	455.1247	455.1244	98.0
18*{11}*	$C_{22}H_{24}N_2O_4S$	H	413.1530	413.1505	98.3
18*{12}*	$C_{30}H_{32}N_2O_7S$	H	565.2003	565.1969	100.0
18*{13}*	$C_{24}H_{31}N_3O_4S$	H	458.2108	458.2139	93.4
18*{14}*	$C_{22}H_{26}N_2O_5S$	H	431.1635	431.1643	98.5

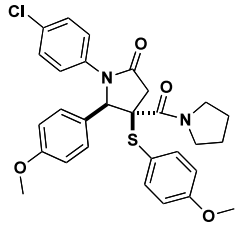
General Experimental B: Arylation of lactams 18*{1-4}*. Reaction vials for the Heidolph Carousel 12 reaction block were charged with a stir bar and 3 angstrom molecular sieves. Lactams **18***{1-4}* were added to reaction vials followed by copper (II) acetate (2 equiv.) and arylboronic acids **27***{1-8}* (4 equiv.). Reagents were then dissolved in CH_3CN (0.05 M) and triethylamine (4 equiv.) and reaction was stirred at room temperature for 48 hours. CH_3CN was removed *in vacuo* and the residue was taken up in DCM and water and the layers were separated. The aqueous layer was extracted twice more with DCM. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography afforded the title compounds **19** in 4.5-69% yield.



19*{1,7}* he title compound was prepared from **18***{1}* (0.040 g, 0.100 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **19***{1,7}* as an oil (0.021 g, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J=9.0 Hz, 2H), 7.27-7.25 (m, 2H), 7.17 (d, J=8.9 Hz, 2H), 6.93 (d, J=8.7 Hz, 2H), 6.91 (d, J=8.8 Hz, 2H), 6.72 (d, J=8.8 Hz, 2H), 5.71 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.62-3.48 (bs, 3H), 3.51 (d, J=16.9, 1H), 3.03 (d, J=16.9, 1H), 3.02-2.85 (bs, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.0, 169.0, 160.6, 160.0, 136.5, 136.4, 130.5, 129.6, 128.8, 127.5, 123.6, 120.4, 114.5, 114.1, 69.5, 58.4, 55.3, 55.2, 43.3, 39.4, 37.9; IR (neat) 2931, 2840, 1704, 1631, 1591, cm^{-1} HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_5S$ $(M+H)^+$ 511.1453, found 511.1452.

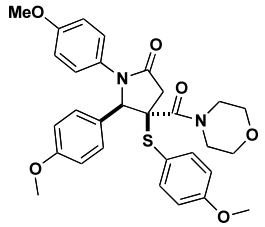


19*{2,3}*. The title compound was prepared from **18***{2}* (0.050 g, 0.117 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **19***{2,3}* as a clear oil (0.043 g, 69%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J=8.6 Hz, 2H), 7.21 (d, J=9.0 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7, 2H), 6.74 (d, J=8.9, 2H), 6.70 (d, J=8.7, 2H), 5.78 (s, 1H), 4.12 (bs, 1H), 4.02 (bs, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.70 (s, 3H), 3.52 (d, J=16.9, 1H), 3.47 (bs, 1H), 3.40 (bs, 1H), 3.05 (d, J=16.9, 1H), 2.08-1.92 (m, 2H), 1.85-1.77 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.8, 167.5, 160.4, 159.7, 157.2, 136.1, 130.7, 130.1, 128.1, 124.7, 120.9, 114.3, 114.0, 113.8, 69.5, 59.4, 55.3, 55.2, 48.5, 42.5, 27.3, 23.3; IR (neat) 2960, 2832, 1688, 1592, 1507 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_5S$ $(M+H)^+$ 533.2105, found 533.2105.

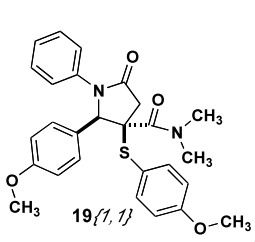


19*{2,7}*. The title compound was prepared from **18***{2}* (0.050 g, 0.117 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **19***{2,7}* as a faint yellow oil (0.036 g, 57%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J=8.8 Hz, 2H), 7.26-7.24 (m, 2H), 7.15 (d, J=8.8 Hz, 2H), 6.90-6.86 (m, 4H), 6.69 (d, J=8.7, 2H), 5.81 (s, 1H), 4.14 (bs, 1H), 4.00 (bs, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.50 (d, J=16.9 Hz, 1H), 3.44 (bs, 1H), 3.38 (bs, 1H), 3.03 (d, J=16.9, 1H), 2.05-1.94 (bm, 2H), 1.88-1.78 (bm, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 167.6, 160.7, 160.1, 136.6, 136.4, 130.7, 130.1, 129.0, 127.8, 123.9, 120.8, 117.0, 114.6, 114.2, 69.1, 59.5, 55.5, 48.7, 42.8, 27.5, 23.5; IR (neat) 2975, 1708, 1639, 1366, 1249 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{29}H_{29}ClN_2O_4S$ $(M+H)^+$ 537.1610, found 537.1608.



19*{3,3}*. The title compound was prepared from **18***{3}* (0.040 g, 0.090 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **19***{3,3}* as a light brown solid (0.022 g, 45%). mp 180-185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19-7.15 (m, 4H), 6.98 (d, J=8.4 Hz, 2H), 6.89 (d, J=8.2, 2H), 6.74-6.72 (m, 4H), 5.52 (s, 1H), 3.95-3.72 (bm, 8H), 3.80 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.40 (d, J=16.7 Hz, 1H), 2.98 (d, J=16.6, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.6, 168.8, 160.5, 160.0, 157.4, 136.0, 130.6, 129.6, 127.8, 124.7, 120.6, 116.0, 114.5, 114.1, 70.6, 66.6, 58.0, 55.33, 55.30, 55.28, 42.8; IR (neat) 3060, 2966, 1706, 1635, 1233 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_6S$ $(M+H)^+$ 549.2054, found 549.2051.



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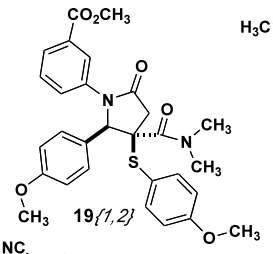

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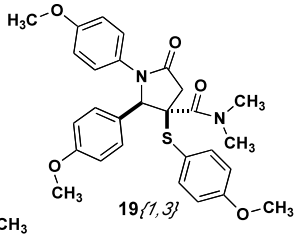

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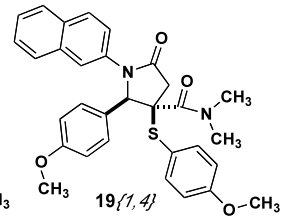

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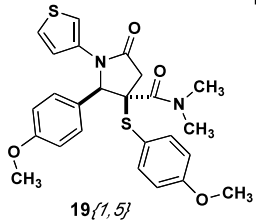

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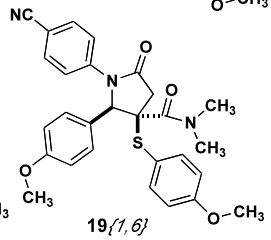

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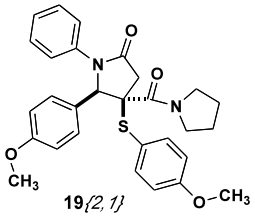

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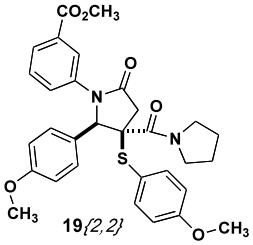

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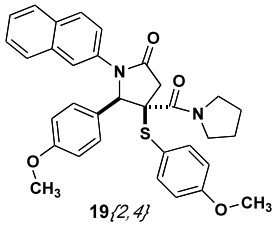

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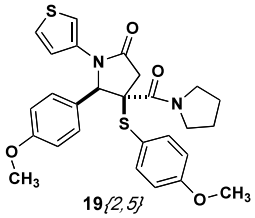

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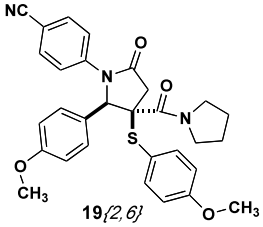

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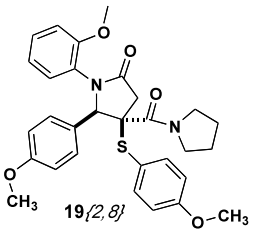
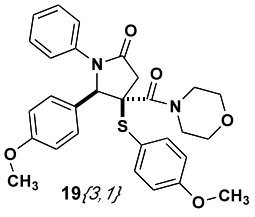
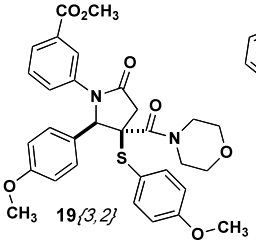


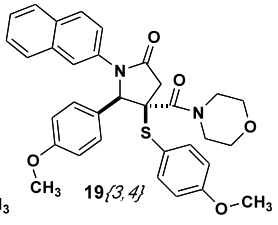
19{2, 8}



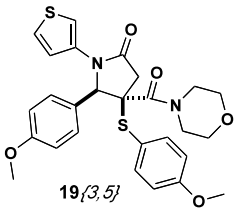
19{3, 1}



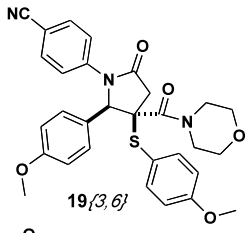
19{3, 2}



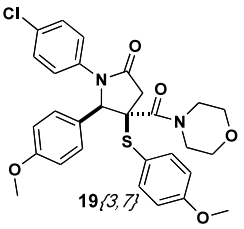
19{3, 4}



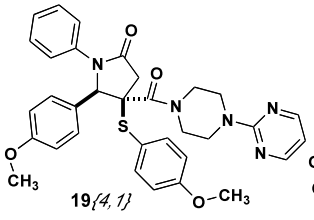
19{3, 5}



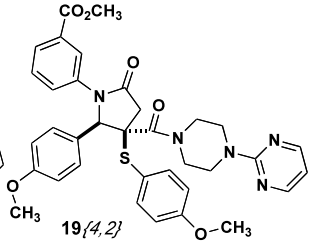
19{3, 6}



19{3, 7}



19{4, 1}



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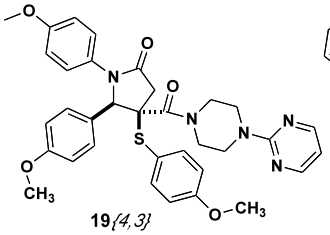
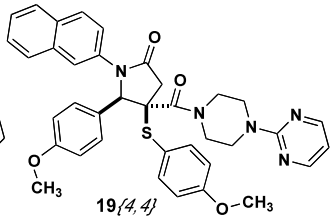
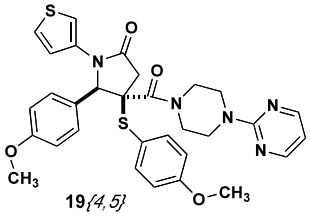


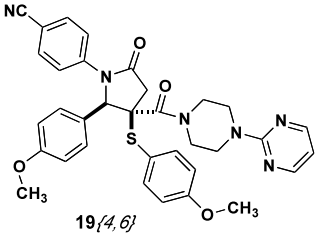
19{4, 3}



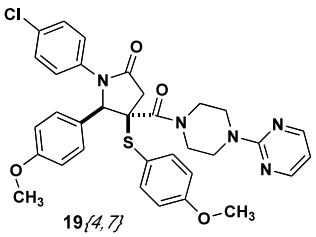
19{4, 4}



19{4, 5}



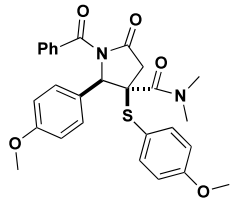
19{4, 6}



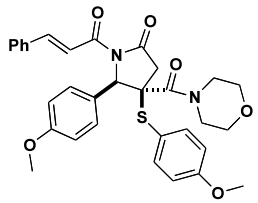
19{4, 7}

Cmpd #	Formula	M +	Calc'd Mass	Found Mass	Purity HPLC
19*{1,1}*	$C_{27}H_{28}N_2O_4S$	H	477.1843	477.1841	97.0
19*{1,2}*	$C_{29}H_{30}N_2O_6S$	H	535.1897	535.1909	97.0
19*{1,3}*	$C_{28}H_{30}N_2O_5S$	H	507.1948	507.1950	100.0
19*{1,4}*	$C_{31}H_{30}N_2O_4S$	H	527.1999	527.2003	90.0
19*{1,5}*	$C_{25}H_{26}N_2O_4S_2$	H	483.1407	483.1402	91.3
19*{1,6}*	$C_{28}H_{27}N_3O_4S$	H	502.1798	502.1791	98.1
19*{2,1}*	$C_{29}H_{30}N_2O_4S$	H	503.1999	503.2021	97.6
19*{2,2}*	$C_{31}H_{32}N_2O_6S$	H	561.2054	561.2072	96.0
19*{2,4}*	$C_{33}H_{32}N_2O_4S$	H	553.2156	553.2164	98.9
19*{2,5}*	$C_{27}H_{28}N_2O_4S_2$	H	509.1563	509.1565	95.1
19*{2,6}*	$C_{30}H_{29}N_3O_4S$	H	528.1952	528.1947	98.2
19*{2,8}*	$C_{30}H_{32}N_2O_5S$	H	533.2105	533.2095	93.1
19*{3,1}*	$C_{29}H_{30}N_2O_5S$	H	519.1948	519.1939	99.2
19*{3,2}*	$C_{31}H_{32}N_2O_7S$	H	577.2003	577.1992	100.0
19*{3,4}*	$C_{33}H_{32}N_2O_5S$	H	569.2105	569.2106	100.0
19*{3,5}*	$C_{27}H_{28}N_2O_5S_2$	H	525.1512	525.1501	100.0
19*{3,6}*	$C_{30}H_{29}N_3O_5S$	H	544.1901	544.1909	100.0
19*{3,7}*	$C_{29}H_{29}ClN_2O_5S$	H	553.1558	553.1592	96.3
19*{4,1}*	$C_{33}H_{33}N_5O_4S$	H	596.2326	596.2321	94.6
19*{4,2}*	$C_{35}H_{35}N_5O_6S$	H	654.2381	654.2383	100.0
19*{4,3}*	$C_{35}H_{35}N_5O_5S$	H	626.2432	626.2418	97.4
19*{4,4}*	$C_{37}H_{35}N_5O_4S$	H	646.2483	646.2473	95.9
19*{4,5}*	$C_{31}H_{31}N_5O_4S_2$	H	602.1890	602.1886	100.0
19*{4,6}*	$C_{34}H_{32}N_6O_4S$	H	621.2279	621.2263	94.2
19*{4,7}*	$C_{33}H_{32}ClN_5O_4S$	H	630.1936	630.1924	100.0

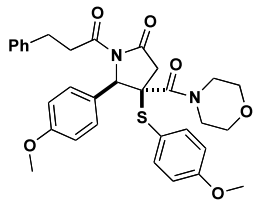
General Experimental C: Acylation of Amides 18*{1-5}*. Reaction vials for the Heidolph Carousel 12 reaction block were charged with a stir bar. Lactams **18***{1-5}* were added to reaction vial and dissolved in THF (0.05 M) and cool to -78 °C in a dry ice:acetone bath. *n*-BuLi (2.5 M in hexanes, 1.2 equiv.) was then added and reaction was allowed to stir at -78 °C for two hours. Acylating agent **28***{1-8}* were then added and reaction was allowed to warm to room temperature and run overnight. After 12-16 hours THF was removed *in vacuo* and the residue was taken up in DCM and water and the layers were separated. The aqueous layer was extracted twice more with DCM. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography afforded the title compounds **20** in 12-90% yield.



20*{1,1}* The title compound was prepared from **18***{1}* (0.066 g, 0.165 mmol) according to general experimental C. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **20***{1,1}* as an oil (0.058 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.49-7.45 (m, 1H), 7.38-7.34 (m, 4H), 7.03 (d, J=8.8 Hz, 2H), 6.98 (d, J=8.7 Hz, 2H), 6.75 (d, J=8.7 Hz, 2H), 5.79 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.70-3.56 (bs, 3H), 3.60 (d, J=17.2 Hz, 1H), 3.08-2.92 (bs, 3H), 3.03 (d, J=17.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.0, 169.6, 161.1, 160.2, 137.3, 134.2, 133.7, 132.3, 130.3, 129.1, 128.8, 128.1, 120.2, 114.9. 114.4, 66.1, 57.8, 55.6, 55.6, 45.2, 40.1, 38.3; IR (neat) 2939, 2841, 1761, 1674, 1616 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{30}H_{32}N_2O_5S$ $(M+H)^+$ 505.1792, found 505.1782.

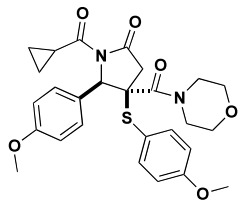


20*{3,2}* The title compound was prepared from **18***{3}* (0.098 g, 0.221 mmol) according to general experimental C. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **20***{3,2}* as an oil (0.114g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J=15.7 Hz, 1H), 7.71 (d, J=15.8 Hz, 1H), 7.58-7.52 (m, 2H), 7.37-7.32 (m, 3H), 7.24 (d, J=8.6 Hz, 2H), 7.09 (d, J=8.9, 2H), 6.96 (d, J=8.0 Hz, 2H), 6.77 (d, J=8.2 Hz, 2H), 5.76 (s, 1H), 4.12-3.70 (bm, 8H), 3.82 (s, 3H), 3.77 (s, 3H), 3.55 (d, J=17.0, 1H), 3.05 (d, J=17.0, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 168.7, 165.1, 160.9, 160.0, 146.5, 137.1, 134.6, 130.6, 128.8, 128.6, 128.5, 127.5, 119.7, 118.9, 114.7, 114.3, 66.5, 65.4, 56.5, 55.3, 55.2, 45.2; IR (neat) 2927, 2843, 1750, 1685, 1642 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{32}H_{32}N_2O_6S$ $(M+H)^+$ 573.2054, found 573.2035.

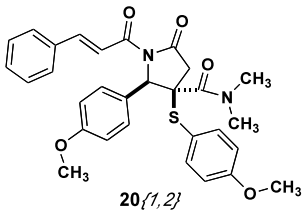


20*{3,5}* The title compound was prepared from **18***{3}* (0.104 g, 0.235 mmol) according to general experimental C. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **20***{3,5}* as an oil (0.106 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25-8.21 (m, 2H), 8.18-8.12 (m, 5H), 8.06 (d, J=8.5 Hz, 2H), 7.95 (d, J=8.6 Hz, 2H), 7.75 (d, J=8.9 Hz, 2H), 6.63 (s, 1H), 5.02-4.70 (bm, 8H), 4.84 (s, 3H), 4.76 (s, 3H), 4.49 (d, J=17.0 Hz, 1H), 4.29-4.13 (m, 2H), 3.98 (d, J=17.1 Hz, 1H), 3.91-3.80 (m, 2H); ^{13}C NMR (101 MHz,

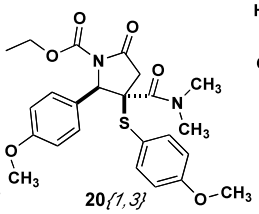
$CDCl_3$) δ 172.5, 172.2, 169.0. 161.2, 160.3, 140.7, 137.2, 128.7, 128.6, 128.0, 127.7, 126.3, 120.0, 115.0, 114.5, 66.7, 65.3, 56.8, 55.6, 55.5, 45,1, 39.1, 30.2, ; IR (neat) 2918, 2859, 1752, 1684, 1515 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{32}H_{34}N_2O_6S$ ($M+H_2O$) 592.2243, found 592.2484.



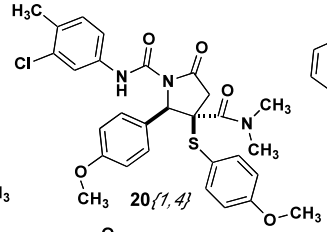
20*{3,6}* The title compound was prepared from **18***{3}* (0.100 g, 0.226 mmol) according to general experimental C. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **20***{3,6}* as a yellow oil (0.104 g, 90%) that solidified after freezing. mp 229-232 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J=8.7 Hz, 2H), 7.08 (d, J=8.8 Hz, 2H), 6.95 (d, J= 8.7 Hz, 2H), 6.76 (d, J=8.8 Hz, 2H), 5.63 (s, 1H), 4.14-3.70 (bm, 8H), 3.83 (s, 3H), 3.77 (s, 3H), 3.53 (d, J=17.0 Hz, 1H), 3.22-3.16 (m, 1H), 3.03 (d, J=17 Hz, 1H), 1.09-1.04 (m, 1H), 1.00-0.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 172.6, 168.9, 161.2, 160.2, 137.2, 128.6, 127.9, 120.0, 114.9, 114.5, 66.7, 65.7, 56.5, 55.5, 45.4, 14.2, 11.5, 10.9; IR (neat) 2969, 1760, 1740, 1690, 1638 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}N_2O_6S$ $(M+H)^+$ 511.1897, found 511.1859.



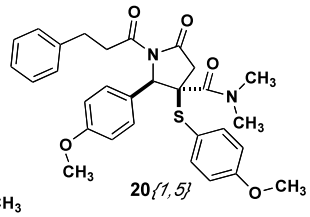
20{1,2}



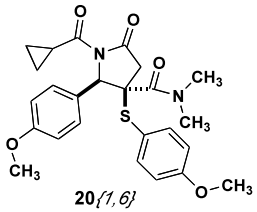
20{1,3}



20{1,4}



20{1,5}



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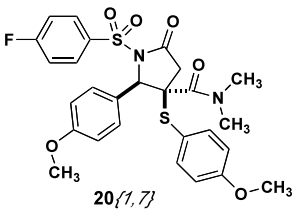
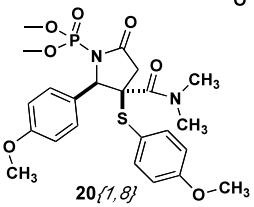
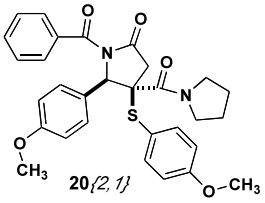


20{1,7}



20{1,8}



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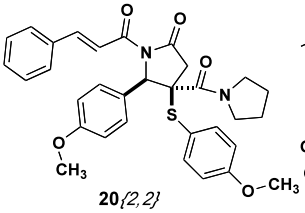

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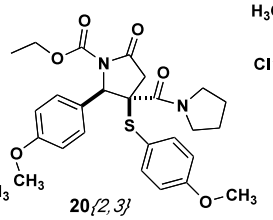
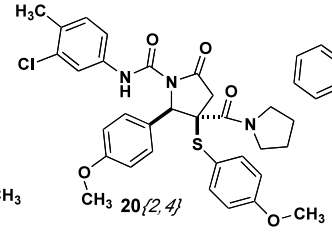


20{2,3}



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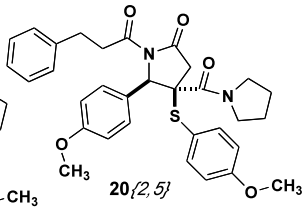
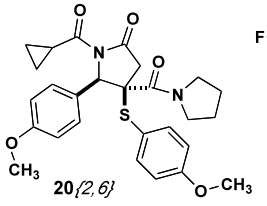


20{2,5}



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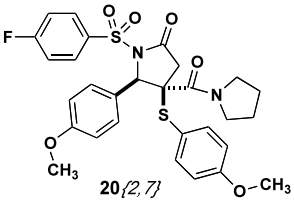
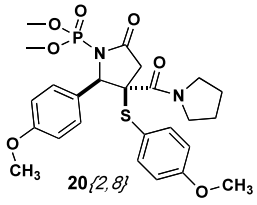


20{2,7}



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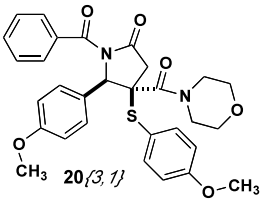

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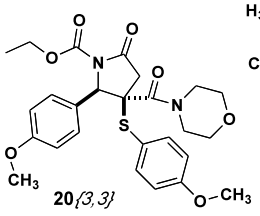

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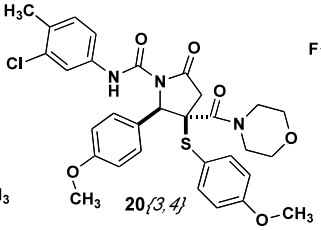
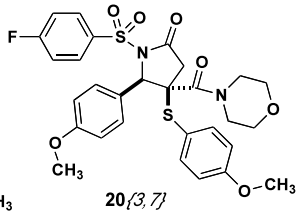


20{3,4}



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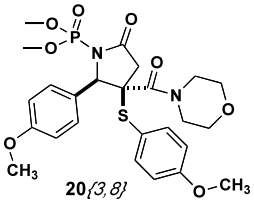

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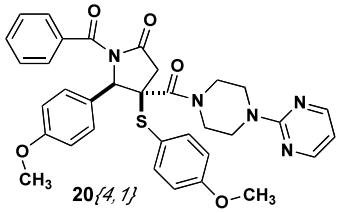

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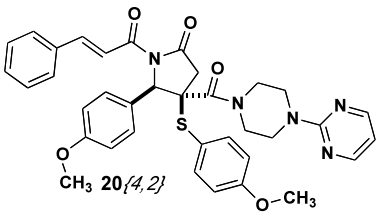

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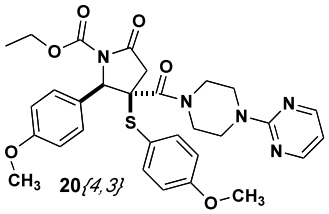

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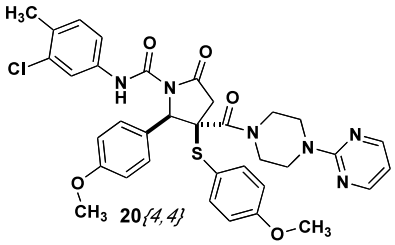

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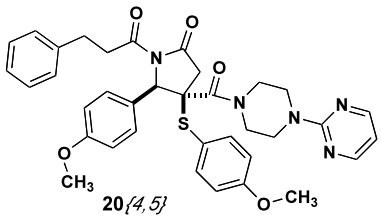

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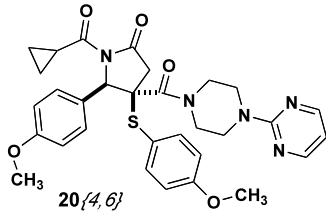
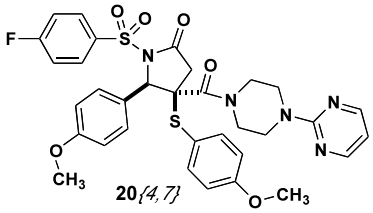


20{4, 6}



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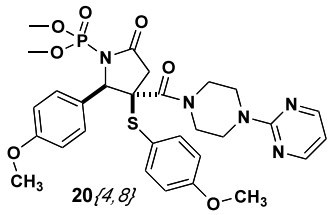

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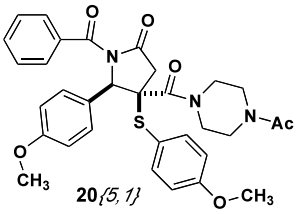

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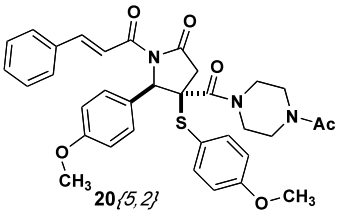

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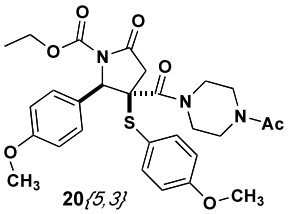

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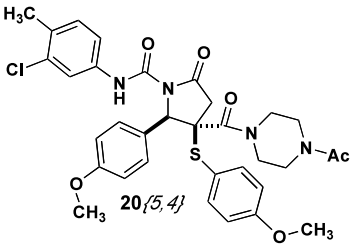

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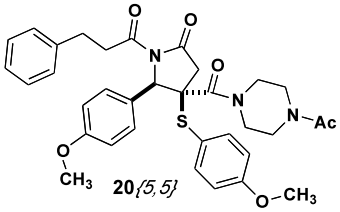

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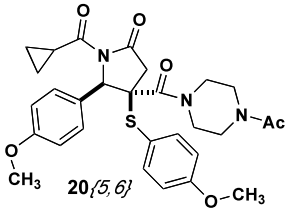

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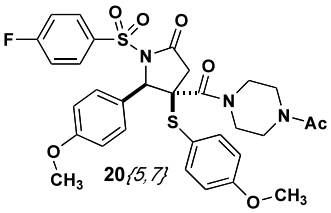

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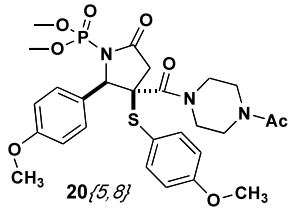
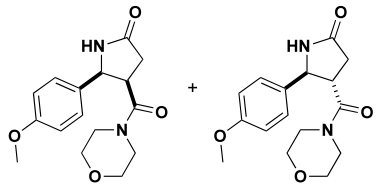


20{5, 8}

Cmpd #	Formula	M +	Calc'd Mass	Found Mass	%Purity HPLC
20*{1,2}*	$C_{30}H_{30}N_2O_5S$	H	531.1948	531.1944	97.0
20*{1,3}*	$C_{24}H_{28}N_2O_6S$	H	473.1741	473.1755	100.0
20*{1,4}*	$C_{29}H_{30}ClN_3O_5S$	H	568.1667	568.1619	94.6
20*{1,5}*	$C_{30}H_{32}N_2O_5S$	H	533.2105	533.2104	98.3
20*{1,6}*	$C_{25}H_{30}N_2O_5S$	H	469.1792	469.1782	100.0
20*{1,7}*	$C_{27}H_{27}FN_2O_6S_2$	H	559.1367	559.1381	99.6
20*{1,8}*	$C_{23}H_{29}N_2O_7PS$	H	509.1506	509.1500	98.5
20*{2,1}*	$C_{30}H_{30}N_2O_5S$	H	531.1948	531.1935	100.0
20*{2,2}*	$C_{32}H_{32}N_2O_5S$	H	557.2105	557.2109	96.7
20*{2,3}*	$C_{26}H_{30}N_2O_6S$	NH_4	516.2168	516.2154	95.4
20*{2,4}*	$C_{31}H_{32}ClN_3O_5S$	H	594.1824	594.1813	99.8
20*{2,5}*	$C_{32}H_{34}N_2O_5S$	NH_4	576.2532	576.2523	98.4
20*{2,6}*	$C_{27}H_{30}N_2O_5S$	H	495.1948	495.1949	98.2
20*{2,7}*	$C_{29}H_{29}FN_2O_6S_2$	H	585.1524	585.1548	92.8
20*{2,8}*	$C_{25}H_{31}N_2O_7PS$	NH_4	552.1933	552.1912	92.5
20*{3,1}*	$C_{30}H_{30}N_2O_6S$	H	547.1897	547.1895	100.0
20*{3,3}*	$C_{26}H_{30}N_2O_7S$	H	515.1846	515.1840	100.0
20*{3,4}*	$C_{31}H_{32}ClN_3O_6S$	H	610.1773	610.1766	97.1
20*{3,7}*	$C_{29}H_{29}FN_2O_7S_2$	H	601.1473	601.1369	100.0
20*{3,8}*	$C_{25}H_{31}N_2O_8PS$	H	551.1611	551.1632	98.9
20*{4,1}*	$C_{34}H_{33}N_5O_5S$	H	624.2275	624.2255	99.3
20*{4,2}*	$C_{36}H_{35}N_5O_5S$	H	650.2432	650.2452	90.7
20*{4,3}*	$C_{30}H_{33}N_5O_6S$	H	592.2224	592.2276	95.9
20*{4,4}*	$C_{35}H_{35}ClN_6O_5S$	H	687.2151	687.2177	99.4
20*{4,5}*	$C_{36}H_{37}N_5O_5S$	H	652.2588	652.2590	92.4
20*{4,6}*	$C_{31}H_{33}N_5O_5S$	H	588.2275	588.2281	100.0
20*{4,7}*	$C_{33}H_{32}FN_5O_6S_2$	H	678.1851	678.1839	100.0
20*{4,8}*	$C_{29}H_{34}N_5O_7PS$	H	628.1989	628.2016	99.9
20*{5,1}*	$C_{32}H_{33}N_3O_6S$	H	588.2163	588.2127	100.0
20*{5,2}*	$C_{34}H_{35}N_3O_6S$	H	614.2319	614.2289	99.4
20*{5,3}*	$C_{28}H_{33}N_3O_7S$	H	556.2112	556.2090	99.9
20*{5,4}*	$C_{33}H_{35}ClN_4O_6S$	H	651.2039	651.2021	99.7
20*{5,5}*	$C_{34}H_{37}N_3O_6S$	H	616.2476	616.2476	99.5
20*{5,6}*	$C_{29}H_{33}N_3O_6S$	H	552.2163	552.2157	99.6
20*{5,7}*	$C_{31}H_{32}FN_3O_7S_2$	H	642.1738	642.1762	100.0
20*{5,8}*	$C_{27}H_{34}N_3O_8PS$	H	592.1877	592.1893	97.6

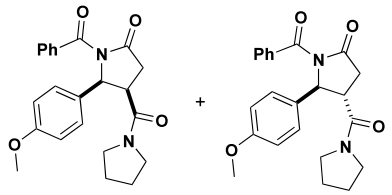
Preparation of desulfurized amides 31*{3}*.



31*{3}*. NH amide **18*{3}*** (1.5 g, 3.39 mmol) was added to a round bottom flask and dissolved in 136 ml (0.025 M) of a 1:2 mixture of THF and EtOH at room temperature. 10 ml of Raney Nickel 2800 (Sigma Aldrich) in water was then added as a slurry and the reaction was stirred at room temperature. After 24 hours the reaction was filtered through celite and solvent was removed *in vacuo* and the residue was taken up in EtOAc and water and the layers were separated. The aqueous layer was extracted twice more with EtOAc. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography with 50%-100% EtOAc:hexanes afforded a 10:90 mixture of diastereomers as a brown foam (0.618 g, 60%). Treatment of the mixture with 40% EtOAc:hexanes led to crystallization of some of the minor diastereomer and x-ray crystallography revealed it to be the *syn* diastereomer of **31*{3}***.

Syn diastereomer: mp 193-197 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 6.03 (s, 1H), 4.93 (d, J=8.4 Hz, 1H), 3.86-3.80 (m, 1H), 3.80 (s, 3H), 3.56-3.48 (m, 2H), 3.40-3.37 (m, 2H), 3.30-3.26 (m, 1H), 3.19 (dd, J=17.2, 6.0 Hz, 1H), 3.21-3.15 (m, 2H), 3.08-3.05 (m, 1H), 2.48 (dd, 17.1, 8.8 Hz, 1H); ^{13}C NMR (151 MHz,) δ 176.8, 168.3, 160.0, 129.3, 128.5, 114.0, 66.4, 66.0, 59.4, 55.3, 45.7, 42.0, 41.9, 33.3; IR (neat) 3177, 3077, 1686, 1639, 1519 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}N_2O_4$ $(M+H)^+$ 305.1496, found 305.1494.

Anti diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, J=8.6 Hz, 2H), 6.90 (d, J=8.6 Hz, 2H), 6.23 (s, 1H), 4.96 (d, J=7.6 Hz, 1H), 3.81 (s, 3H), 3.72-3.64 (m, 2H), 3.58-3.52 (m, 2H), 3.46-3.42 (m, 1H), 3.32-3.27 (m, 1H), 3.24-3.15 (m, 2H), 3.03-3.00 (m, 1H), 2.86 (dd, J=16.7, 9.8 Hz, 1H), 2.60 (dd, J=16.7, 8.9 Hz, 1H); ^{13}C NMR (151 MHz,) δ 175.2, 170.0, 160.0, 132.3, 127.4, 114.5, 66.7, 66.4, 60.8, 55.4, 46.9, 46.1, 42.6, 35.2; IR (neat) 3253, 2969, 1694, 1633, 1513 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}N_2O_4$ $(M+H)^+$ 305.1496, found 305.1514.

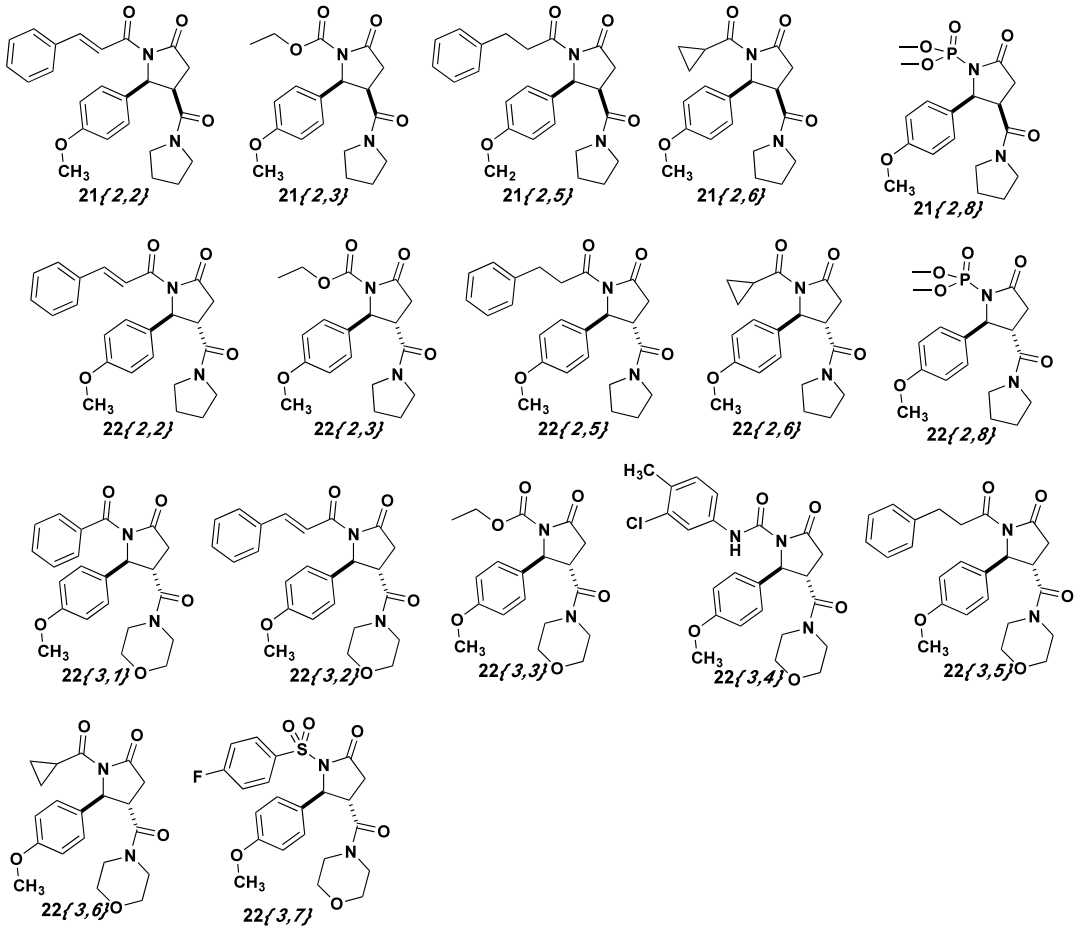


21*{2,1}* **22***{2,1}*

21*{2,1}* and **22***{2,1}*. The title compounds were prepared from acylation **31***{2}* (0.058 g, 0.201 mmol) according to general experimental C. Flash column chromatography with 50%-100% EtOAc:hexanes afforded **21***{2,1}* as a off white foam (0.016 g, 19%) and **22***{2,1}* as a yellow oil (0.014 g, 18%).

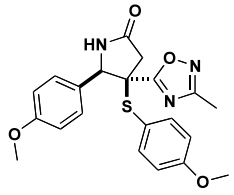
21*{2,1}*: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.54-7.50 (m, 1H), 7.44-7.39 (m, 2H), 7.29 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.8 Hz, 2H), 5.61 (d, J=7.8 Hz, 1H), 3.74 (s, 3H), 3.64-3.61 (m, 1H), 3.36-3.32 (m, 1H), 3.27-3.22 (m, 2H), 3.01-2.96 (m, 1H), 2.93-2.90 (m, 1H), 2.68 (dd, J=17.5, 8.2 Hz, 1H), 1.77-1.71 (m, 1H), 1.69-1.62 (m, 1H), 1.54-1.49 (m, 1H), 1.44-1.38 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 170.6, 168.4, 159.6, 134.2, 133.4, 132.7, 130.1, 129.8, 128.4, 128.0, 127.8, 113.8, 62.9, 55.3, 46.4, 45.7, 41.4, 35.8, 25.8, 24.0; IR (neat) 2955, 2875, 1751, 1673, 1643 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{23}H_{24}N_2O_4$ $(M+H)^+$ 393.1809 found 393.1823.

22*{2,1}*:^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.51-7.50 (m, 1H), 7.42-7.39 (m, 2H), 7.29 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 5.49 (d, J=6.5 Hz, 1H), 3.77 (s, 3H), 3.51-3.49 (m, 2H), 3.30-3.27 (m, 2H), 3.07 (dd, J=17.6, 7.9 Hz, 1H), 2.93-2.89 (m, 1H), 2.84 (dd, J=17.7, 8.4 Hz, 1H), 1.97-1.78 (m, 4H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 170.0, 169.2, 159.4, 134.2, 133.4, 132.4, 130.1, 129.4, 128.4, 127.9, 126.9, 114.5, 64.5, 55.3, 46.6, 46.3, 45.2, 35.6, 26.0, 24.2; IR (neat) 2976, 2881, 1742, 1682, 1638 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{23}H_{24}N_2O_4$ $(M+H)^+$ 393.1809 found 393.1838.

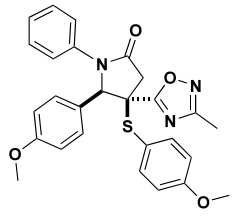


Cmpd #	Formula	M +	Calc'd Mass	Found Mass	Purity HPLC
21{2,2}	$C_{25}H_{26}N_2O_4$	H	419.1965	419.1983	90.6
21{2,3}	$C_{19}H_{24}N_2O_5$	H	361.1758	361.1742	100.0
21{2,5}	$C_{25}H_{28}N_2O_4$	H	421.2122	421.2130	98.8
21{2,6}	$C_{20}H_{24}N_2O_4$	H	357.1809	357.1797	93.0
21{2,8}	$C_{18}H_{25}N_2O_6P$	H	397.1523	357.1526	76.0
22{2,2}	$C_{25}H_{26}N_2O_4$	H	419.1965	419.1954	98.8
22{2,3}	$C_{19}H_{24}N_2O_5$	H	361.1758	362.1752	97.9
22{2,5}	$C_{25}H_{28}N_2O_4$	H	421.2122	421.2143	97.0
22{2,6}	$C_{20}H_{24}N_2O_4$	H	357.1809	357.1855	93.0
22{2,8}	$C_{18}H_{25}N_2O_6P$	H	397.1523	357.1584	94.6
22{3,1}	$C_{23}H_{24}N_2O_5$	NH4	426.2029	426.2039	100.0
22{3,2}	$C_{25}H_{26}N_2O_5$	H	435.1914	435.1913	96.8
22{3,3}	$C_{19}H_{24}N_2O_6$	H	377.1707	377.1716	96.4
22{3,4}	$C_{24}H_{26}ClN_3O_5$	H	472.1634	472.1657	100.0
22{3,5}	$C_{25}H_{28}N_2O_5$	H	437.2071	437.2069	100.0
22{3,6}	$C_{20}H_{24}N_2O_5$	H	373.1758	373.1773	96.5
22{3,7}	$C_{22}H_{23}FN_2O_6S$	H	463.1334	463.1349	100.0

General Experimental D: Prepartion of 1,2,4-oxadiazoles 23*{1-3}*. Acid chloride was prepared according to procedure for the preparation of **15**. The acid chloride was then dissolved in DCM (0.05 M) and oxime **29*{1-3}*** (1 equiv) and DIPEA (5 equiv) were added and reaction allowed to warm to room temperature and stirred overnight. DCM was removed *in vacuo* and residue taken up in water and extracted twice more with DCM. Organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then dissolved in toluene and refluxed with a Dean Stark trap for 2 hours. Toluene was removed *in vacuo* and the residue was taken up in DCM and water and the layers were separated. The aqueous layer was extracted twice more with DCM. The combined organic fractions were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography afforded the title compounds **23*{1-3}*** in 10-40% yield over two steps.

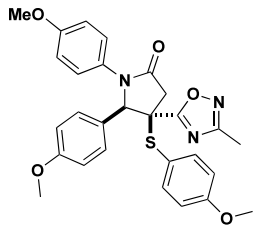


23*{1}* The title compound was prepared from **15** (0.095 g, 0.253 mmol) according to general experimental D. Flash column chromatography with 50%-100% EtOAc:hexanes afforded **23*{1}*** as a blue foam (0.040 g, 40%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, J=8.9 Hz, 2H), 7.01 (d, J=8.9 Hz, 2H), 6.98 (d, J= 8.7 Hz, 2H), 6.76 (s, 1H), 6.73 (d, J=8.9 Hz, 2H), 5.36 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.24 (d, J=17.3, 1H), 2.97 (d, J=17.5, 1H), 2.37 (s, 3H); ^{13}C NMR (151 MHz,) δ 180.0, 174.2, 167.4, 161.5, 160.7, 138.7, 129.8, 126.5, 119.5, 114.9, 114.0, 64.5, 55.7, 55.6, 55.5, 41.8, 11.8; IR (neat) 1724, 1689, 1515, 1497, 1250 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}N_3O_4S$ $(M+H)^+$ 412.1326, found 412.1342.

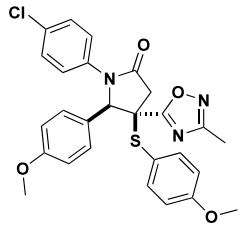


24*{1,1}*. The title compound was prepared from **23*{1}*** (0.038 g, 0.092 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **24*{1,1}*** as an oil (0.009 g, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.36-7.34 (m, 2H), 7.24-7.21 (m, 2H), 7.09-7.06 (m, 1H), 7.03-7.01 (m, 2H), 6.96-6.94 (m, 2H), 6.74-6.72 (m, 2H), 5.86 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.49 (d, J=17.1 Hz, 1H), 3.33 (d, J=17.1 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.9, 170.3, 167.2, 161.2, 160.3, 138.0, 137.4, 129.4, 128.8, 125.9, 125.5, 122.2, 119.2, 114.6, 114.1, 70.4, 55.3, 55.3, 53.6, 42.8, 11.6 IR (neat) 2931, 2848, 1714,

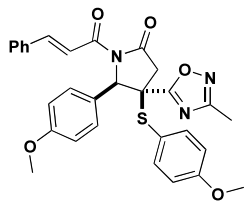
1516, 1256 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{27}H_{25}N_3O_4S$ $(M+H)^+$ 488.1639 found 488.1653



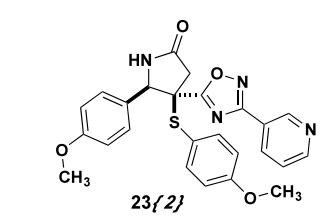
24*{1,3}*. The title compound was prepared from **23***{1}* (0.038 g, 0.092 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **24***{1,3}* as an oil (0.015 g, 31%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, J=8.2 Hz, 2H), 7.21 (d, J=9.5 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 6.75 (d, J=9.2 Hz, 2H), 6.72 (d, J=8.8 Hz, 2H), 5.75 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.47 (d, J=17.1 Hz, 1H), 3.32 (d, J=17.1 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.0, 170.2, 167.2, 161.3, 160.3, 157.3, 138.0, 130.3, 129.6, 126.1, 124.3, 119.3, 114.6, 114.1, 70.9, 55.4, 55.3, 55.3, 53.7, 42.7, 11.6; IR (neat) 2932, 2852, 1698, 1509, 1244 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{28}H_{27}N_3O_5S$ $(M+H)^+$ 518.1744 found 518.1754.

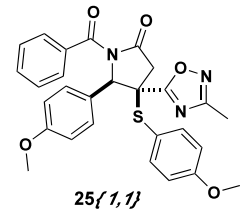


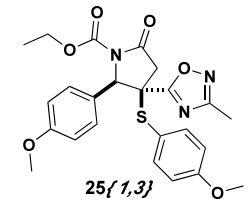
24*{1,7}*. The title compound was prepared from **23***{1}* (0.04 g, 0.097 mmol) according to general experimental B. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **24***{1,7}* as an oil (0.041 g, 41%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, J=8.2 Hz, 2H), 7.32 (d, J=9.0 Hz, 2H), 7.18 (d, J=9.0 Hz, 2H), 7.01 (d, J=8.7 Hz, 2H), 6.95 (d, J=9.0 Hz, 2H), 6.73 (d, J=8.8 Hz, 2H), 5.82 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.48 (d, J=17.1 Hz, 1H), 3.31 (d, J=16.9, 1H), 2.33 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.3, 167.2, 161.3, 160.4, 138.0, 136.0, 130.7, 129.4, 128.9, 125.4, 123.2, 119.0, 114.7, 114.2, 70.2, 55.3, 55.2, 53.5, 42.7, 11.6; IR (neat) 2939, 2840, 1710, 1591, 1256 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{27}H_{24}ClN_3O_4S$ $(M+H)^+$ 522.1249 found 522.1263.

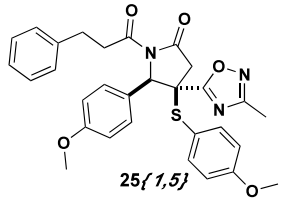


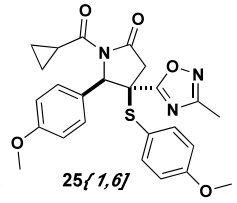
25*{1,2}*. The title compound was prepared from **23***{1}* (0.03 g, 0.073 mmol) according to general experimental C. Flash column chromatography with 20%-100% EtOAc:hexanes afforded **25***{1,2}* as a brown foam (0.040 g, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, J=15.8 Hz, 1H), 7.72 (d, J=15.7 Hz, 1H), 7.55-7.54 (m, 2H), 7.40 (d, J=8.6 Hz, 2H), 7.37-7.35 (m, 3H), 7.01 (d, J=8.7, 2H), 6.98 (d, J=9.0 Hz, 2H), 6.72 (d, J=8.8 Hz, 2H), 6.10 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H), 3.56 (d, J=17.4, 1H), 3.46 (d, J=17.4, 1H), 2.29 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.3, 171.4, 167.2, 164.7, 161.3, 160.2, 146.9, 137.8, 134.5, 130.7, 128.8, 128.7, 128.6, 126.7, 119.0, 118.5, 114.7, 114.1, 67.1, 55.3, 55.2, 52.4, 44.5, 11.5; IR (neat) 2962, 2936, 1741, 1680, 1248 cm^{-1} HRMS (ESI) *m/z* calcd for $C_{30}H_{27}N_3O_5S$ $(M+H)^+$ 542.1744, found 542.1735.

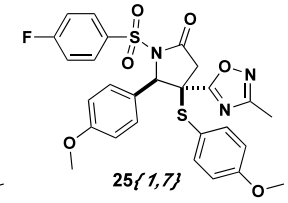


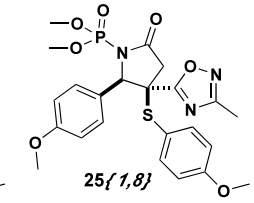




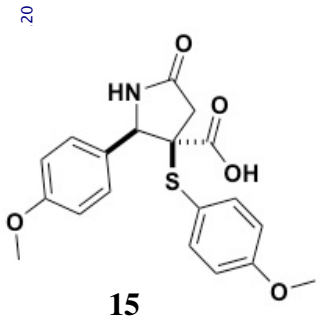






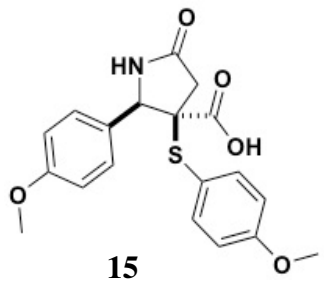


Cmpd #	Formula	M +	Calc'd Mass	Found Mass	Purity HPLC
23*{2}*	$C_{25}H_{22}N_4O_4S$	H	475.1435	475.1454	93.0
25*{1,1}*	$C_{28}H_{25}N_3O_5S$	H	516.1588	516.1607	97.3
25*{1,3}*	$C_{24}H_{25}N_3O_6S$	H	484.1537	484.1554	100.0
25*{1,5}*	$C_{30}H_{29}N_3O_5S$	H	544.1901	544.1899	97.5
25*{1,6}*	$C_{25}H_{25}N_3O_5S$	H	480.1588	480.1594	100.0
25*{1,7}*	$C_{27}H_{24}FN_3O_6S_2$	H	570.1163	570.1147	100.0
25*{1,8}*	$C_{23}H_{26}N_3O_7PS$	H	520.1302	520.1299	100.0


HN
O
O
OH
S
O
O

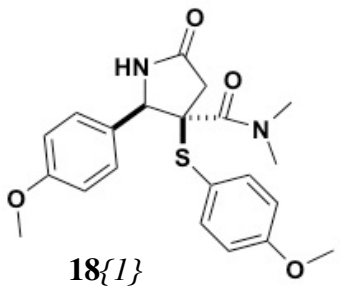
15

8.33
7.30
7.29
7.18
7.16
6.93
6.90
6.85
6.83
5.11
3.73
3.70
2.79
2.75
2.46
2.42
0.85
1.00
1.96
2.02
1.99
2.08
1.00
2.94
3.05
1.01
1.38
f1 (ppm)


HN
O
O
OH
S
O
O

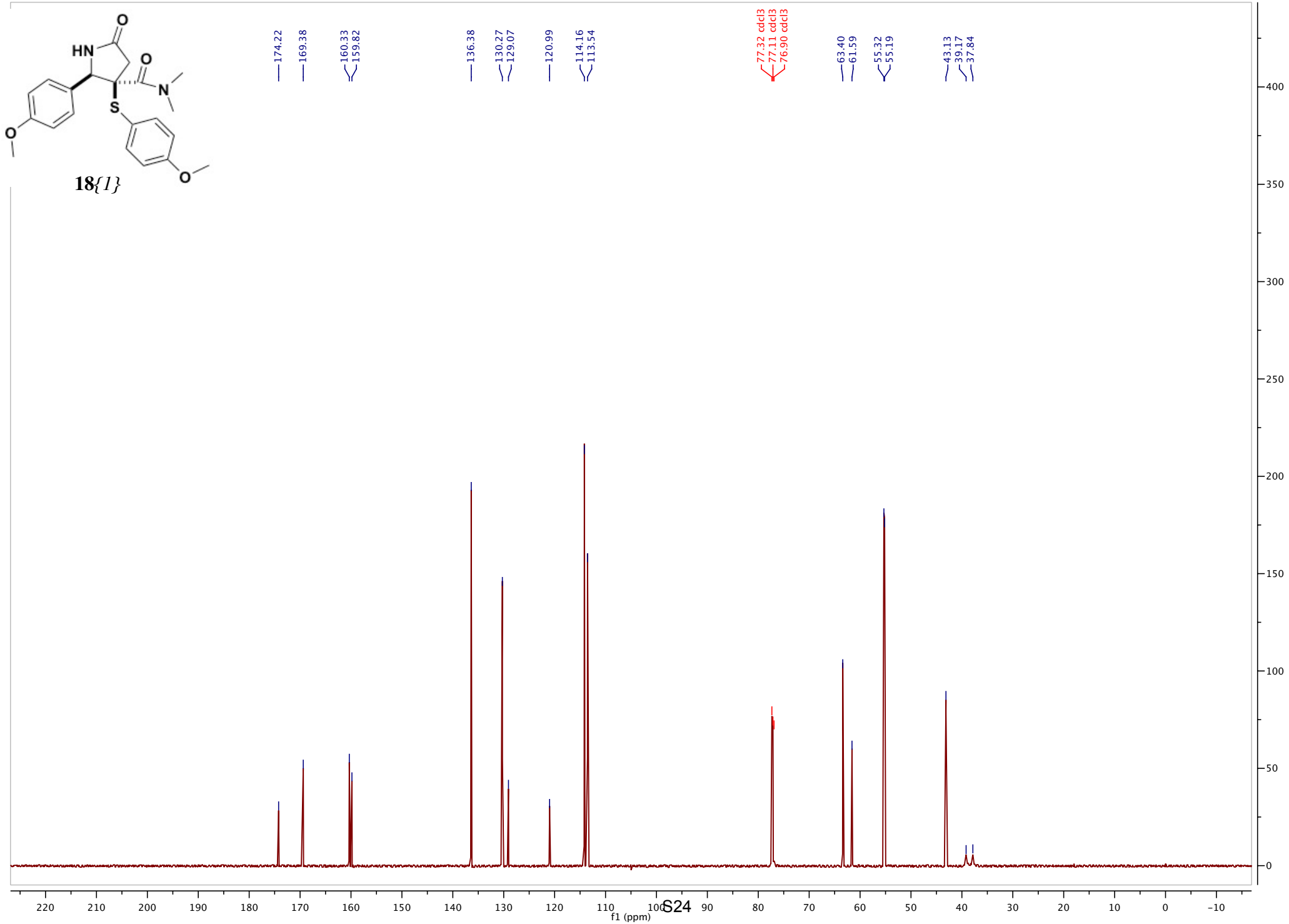
15

173.99
173.45
161.07
159.97
138.46
130.15
129.47
121.44
115.23
113.86
62.85
61.31
55.91
55.81
40.93
40.44 dmso
40.30 dmso
40.16 dmso
40.02 dmso
39.88 dmso
f1 (ppm)

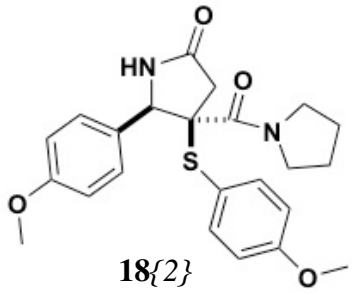

O
HN
O
N
S
O
O

18*{1}*

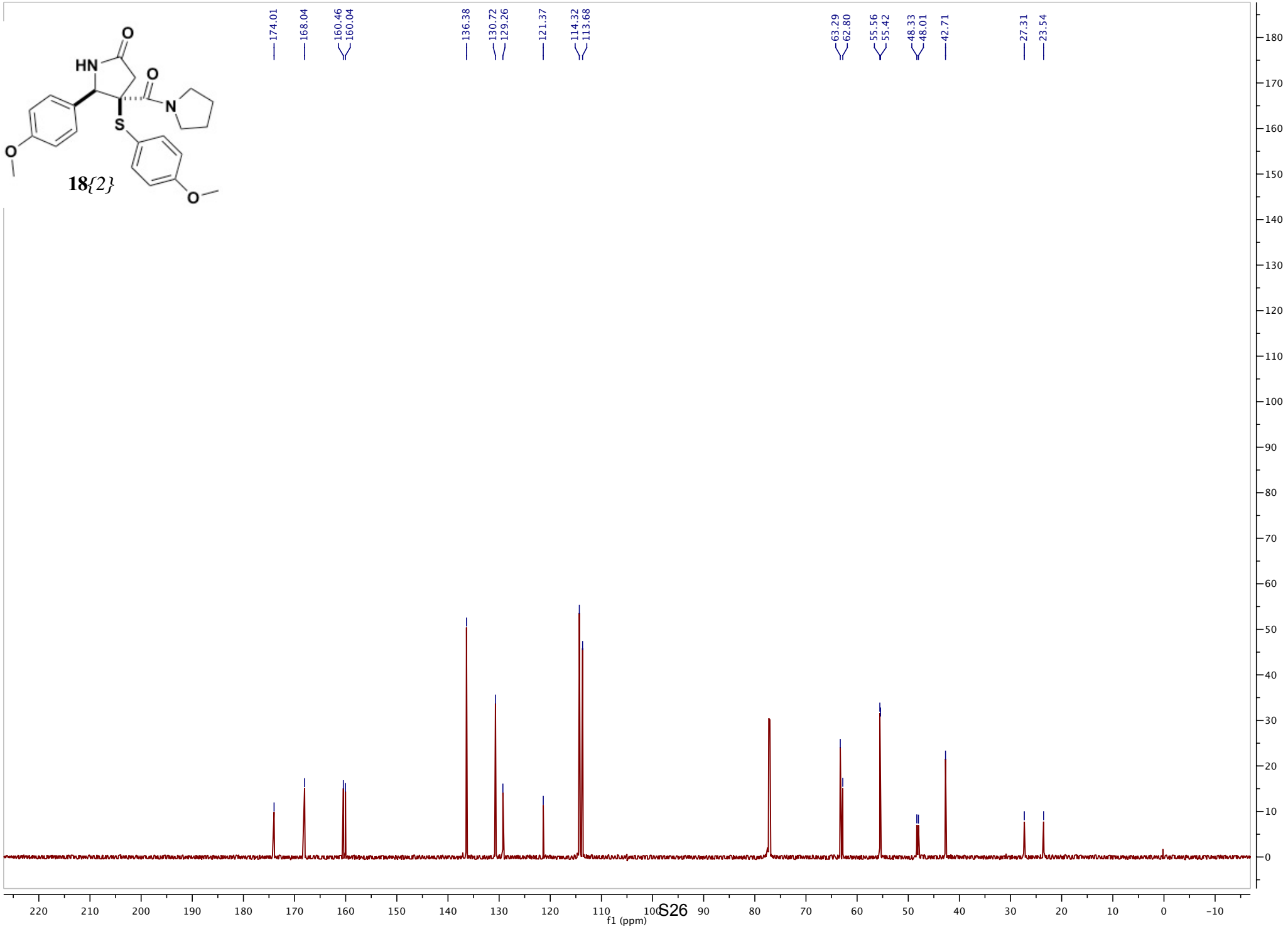
7.43
7.42
6.88
6.88
6.87
6.85
6.73
6.72
6.61
6.60
5.37
3.80
3.69
3.36
3.29
3.26
2.86
2.79
2.76
2.03
2.89
1.88
1.85
1.00
2.94
2.91
3.87
4.01
f1 (ppm)


HN
O
O
N
S
O
O
174.22
169.38
160.33
159.82
136.38
130.27
129.07
120.99
114.16
113.54
77.32 cdcl3
77.11 cdcl3
76.90 cdcl3
63.40
61.59
55.32
55.19
43.13
39.17
37.84
f1 (ppm)

18{*1*}



18*{2}*


174.01
168.04
160.46
160.04
136.38
130.72
129.26
121.37
114.32
113.68
63.29
62.80
55.56
55.42
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42.71
27.31
23.54
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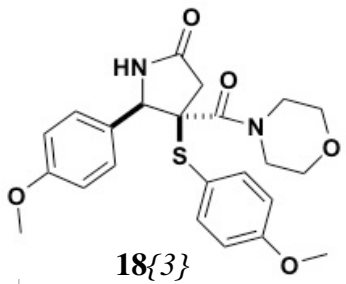
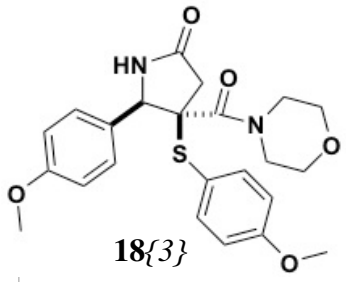
O
O
N
S
O
O
18{2}
f1 (ppm)

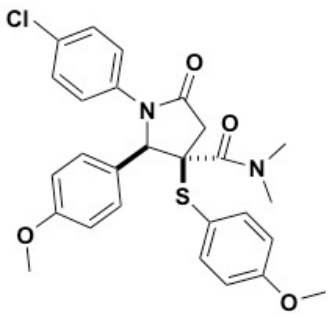


18*{3}*

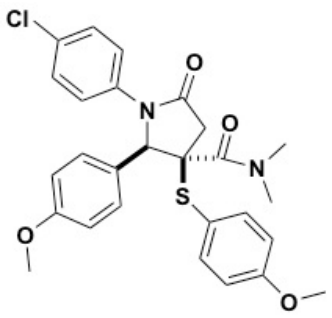

HN
O
O
N
O
S
O
O

18*{3}*

174.18
169.24
160.58
160.27
136.06
130.07
129.01
121.15
114.65
114.01
77.47 cdcl3
77.26 cdcl3
77.04 cdcl3
66.73
63.73
61.05
55.56
55.49
42.76
f1 (ppm)

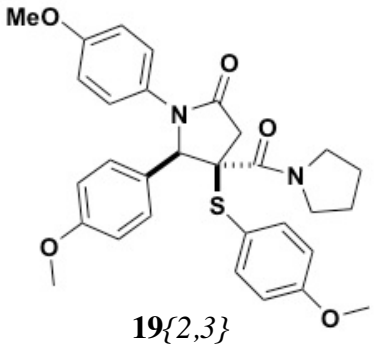


19*{1,7}*

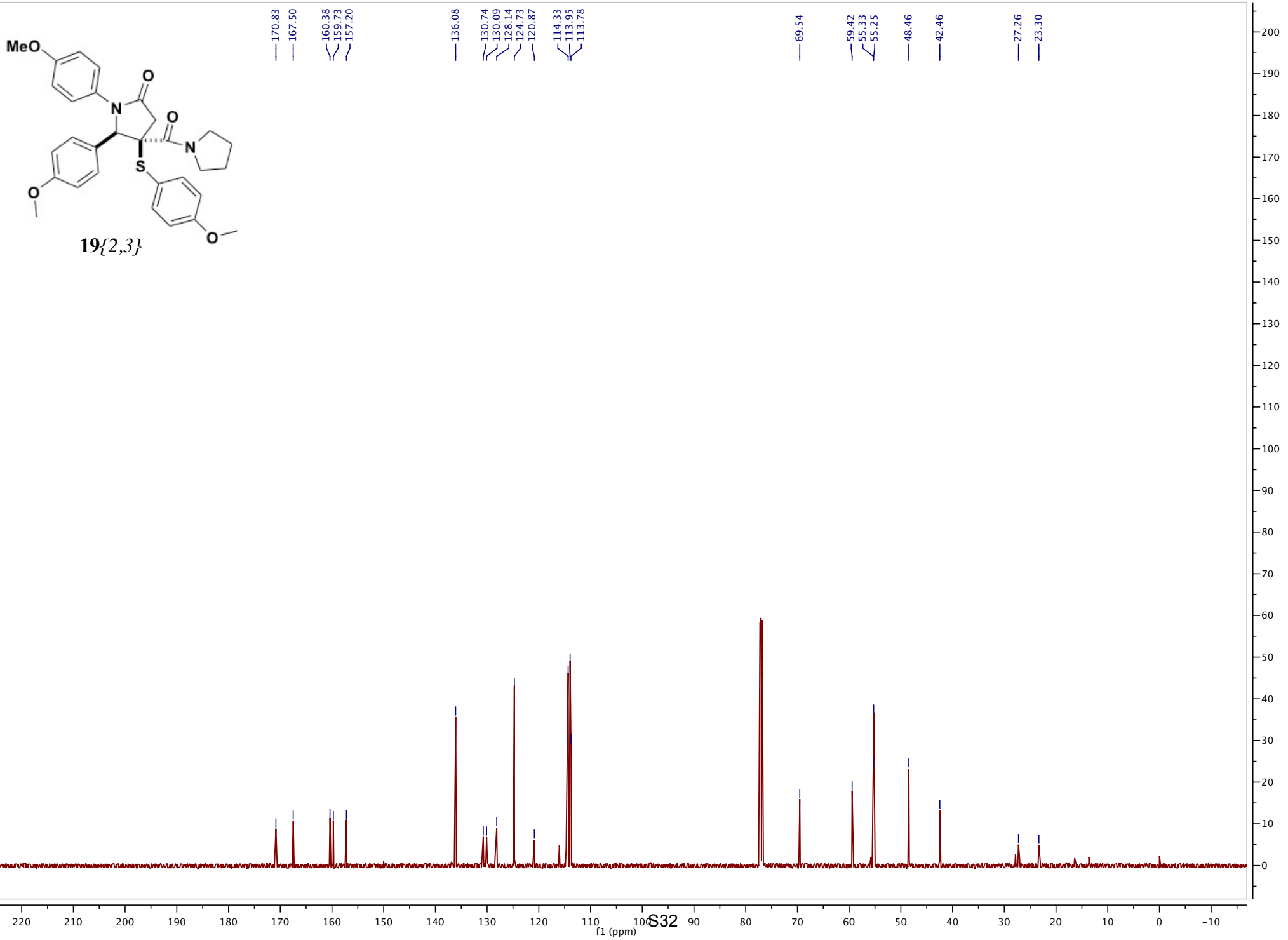

Cl
O
N
O
N
S
O
O

19*{1,7}*

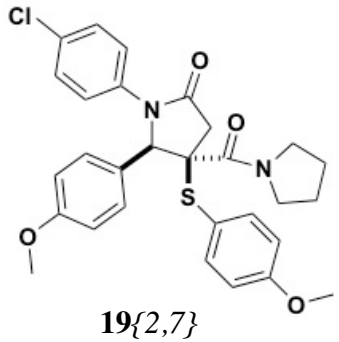
171.01
168.97
160.59
159.97
136.44
136.41
130.52
129.63
128.75
127.52
123.55
120.43
114.45
114.12
69.54
58.44
55.29
55.26
43.27
39.40
37.97
f1 (ppm)



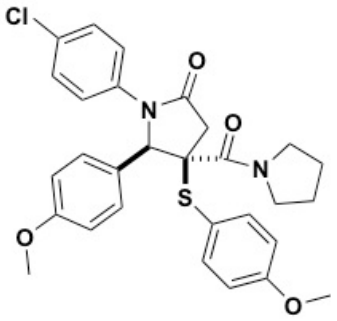
19*{2,3}*


MeO
O
N
O
N
S
O
O
170.83
167.50
160.38
159.73
157.20
136.08
130.74
130.09
128.14
124.73
120.87
114.33
113.95
113.78
69.54
59.42
55.33
55.25
48.46
42.46
27.26
23.30
f1 (ppm)

19*{2,3}*

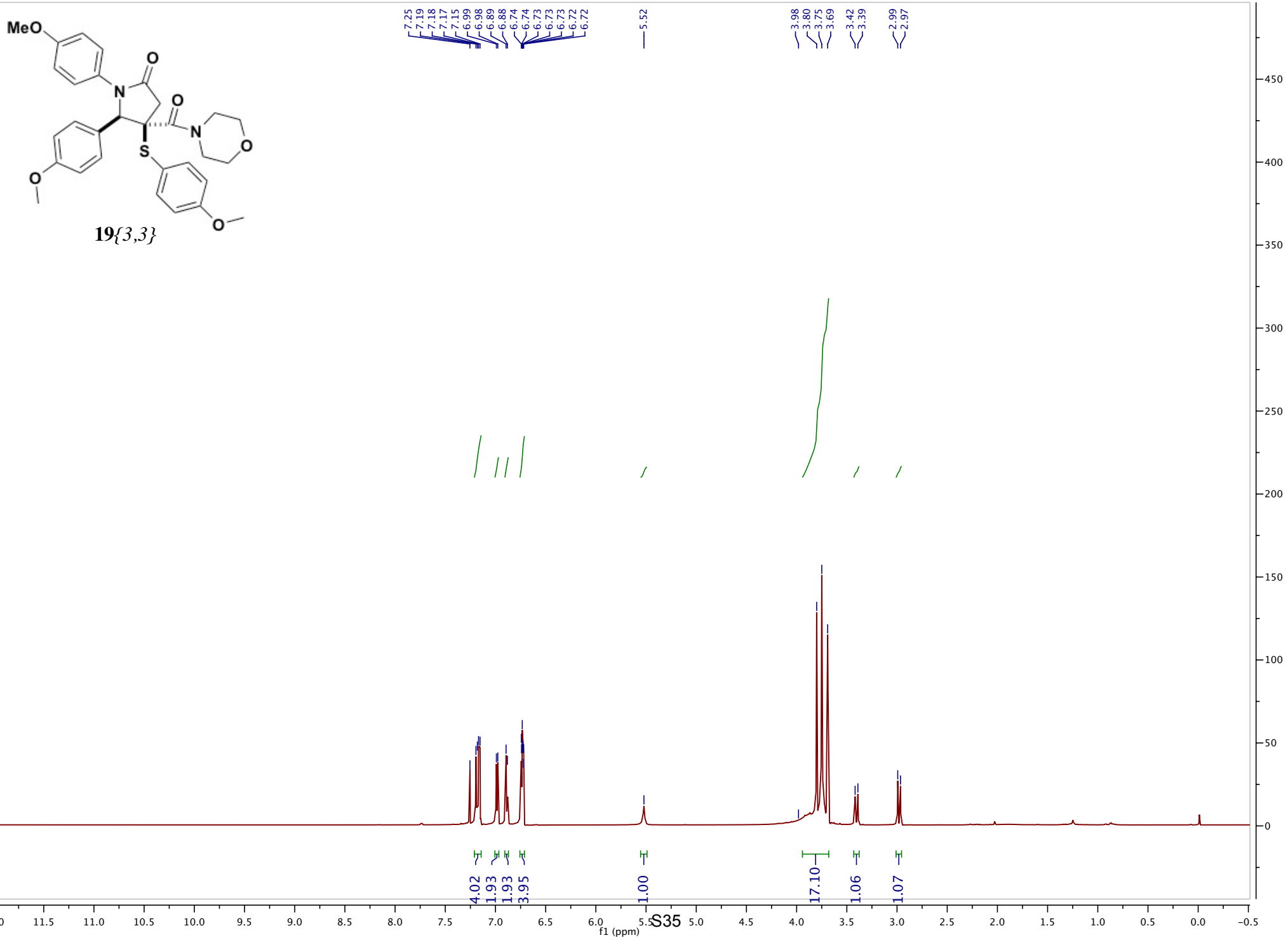


19{*2,7*}


Cl
O
N
O
O
N
S
O
O

19*{2,7}*

171.20
167.56
160.70
160.11
136.62
136.36
130.71
130.06
128.95
127.79
123.88
120.81
114.62
114.21
69.07
59.49
55.48
48.71
42.78
27.47
23.49
f1 (ppm)


MeO
O
N
O
N
O
S
O
O
7.25
7.19
7.18
7.17
7.15
6.99
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6.89
6.88
6.74
6.74
6.73
6.73
6.72
6.72
5.52
3.98
3.80
3.75
3.69
3.42
3.39
2.99
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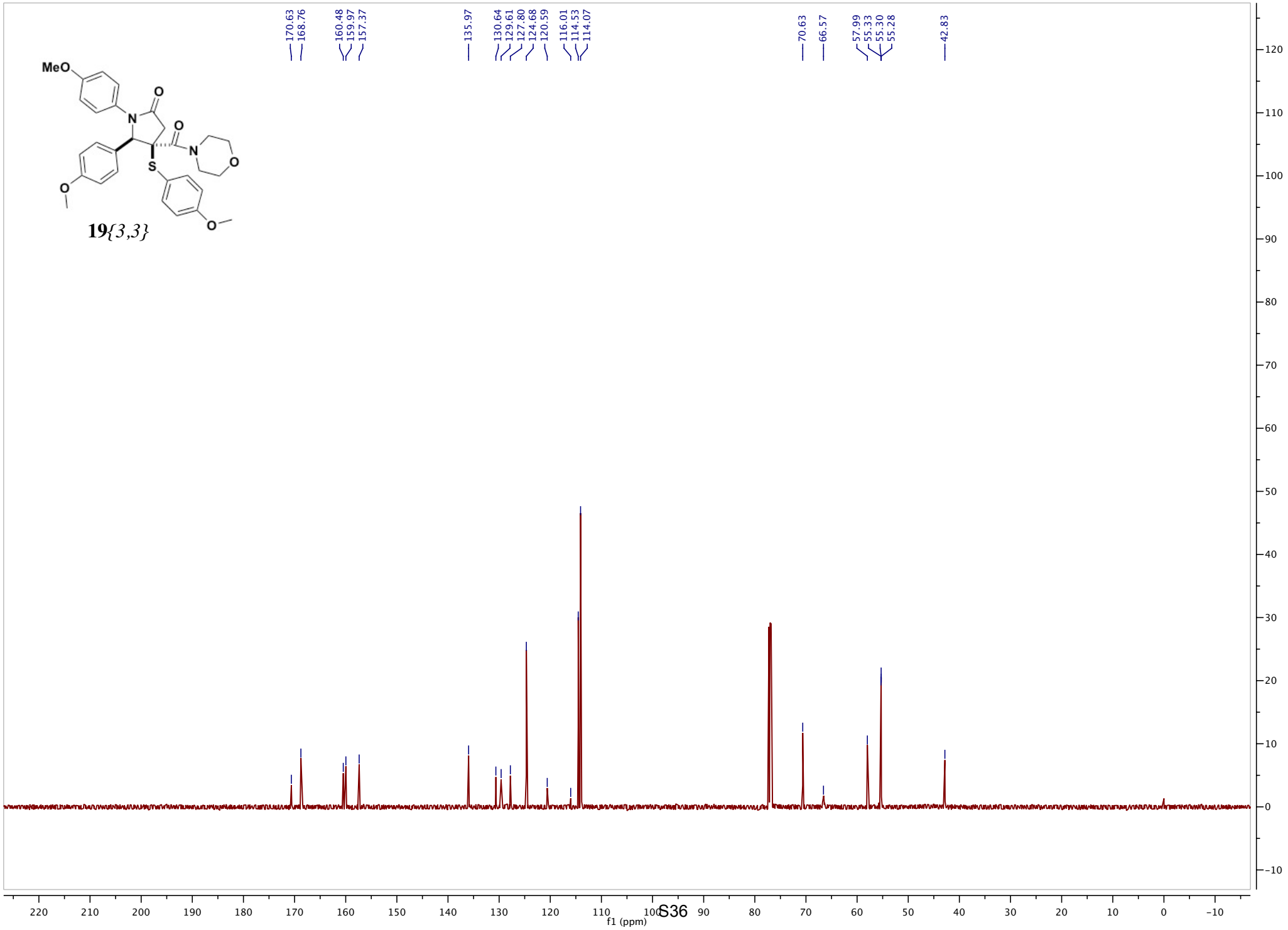
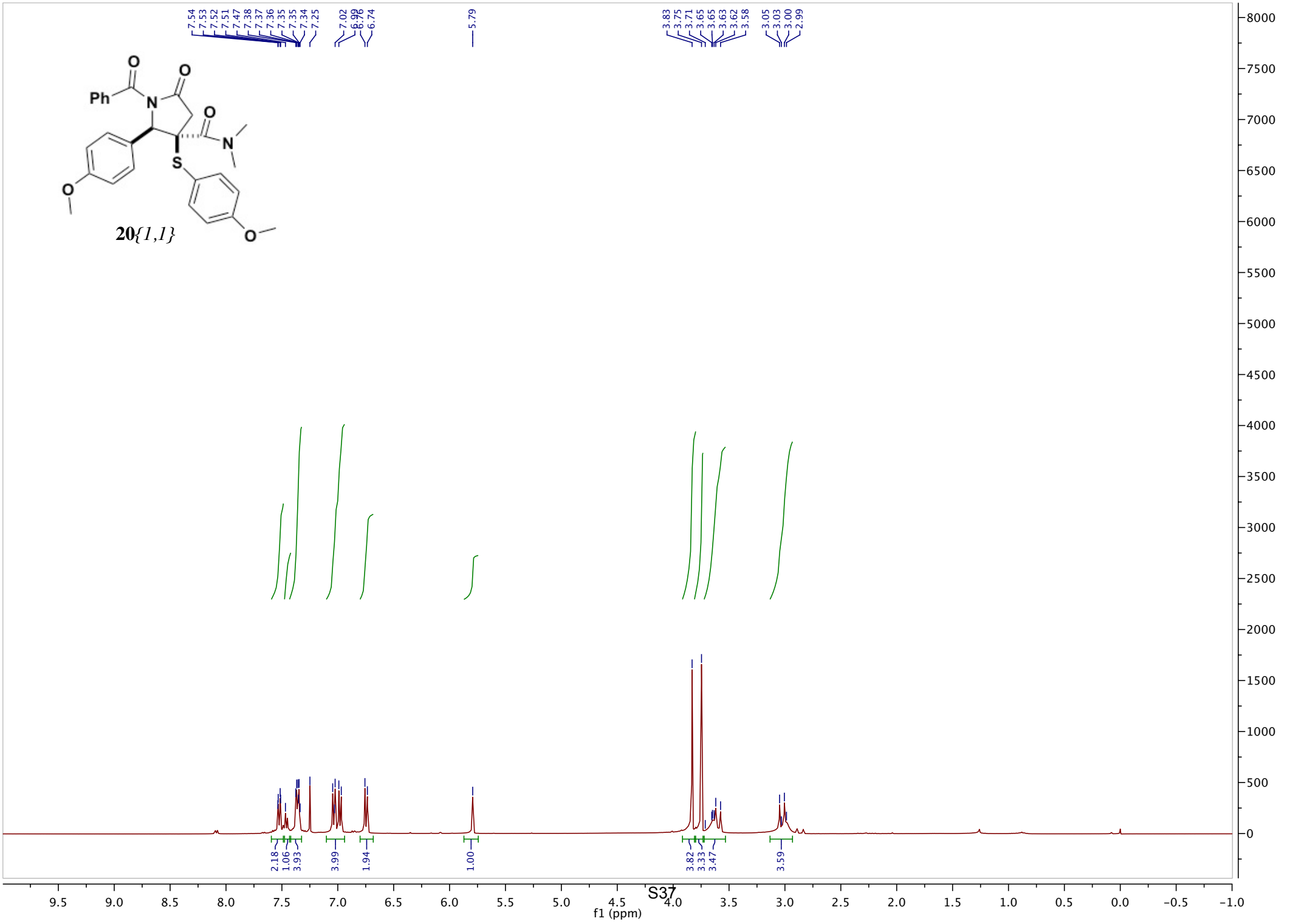
1.06
1.07
f1 (ppm)

19{*3,3*}


170.63
168.76
160.48
159.97
157.37
135.97
130.64
129.61
127.80
124.68
120.59
116.01
114.53
114.07
70.63
66.57
57.99
55.33
55.30
55.28
42.83
MeO
O
N
O
N
O
S
O
O
f1 (ppm)

19*{3,3}*


7.54
7.53
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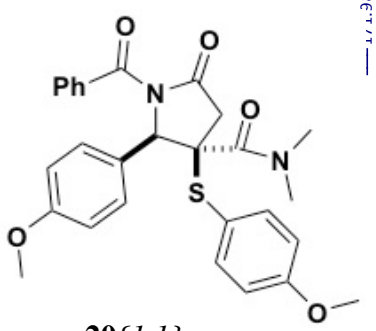
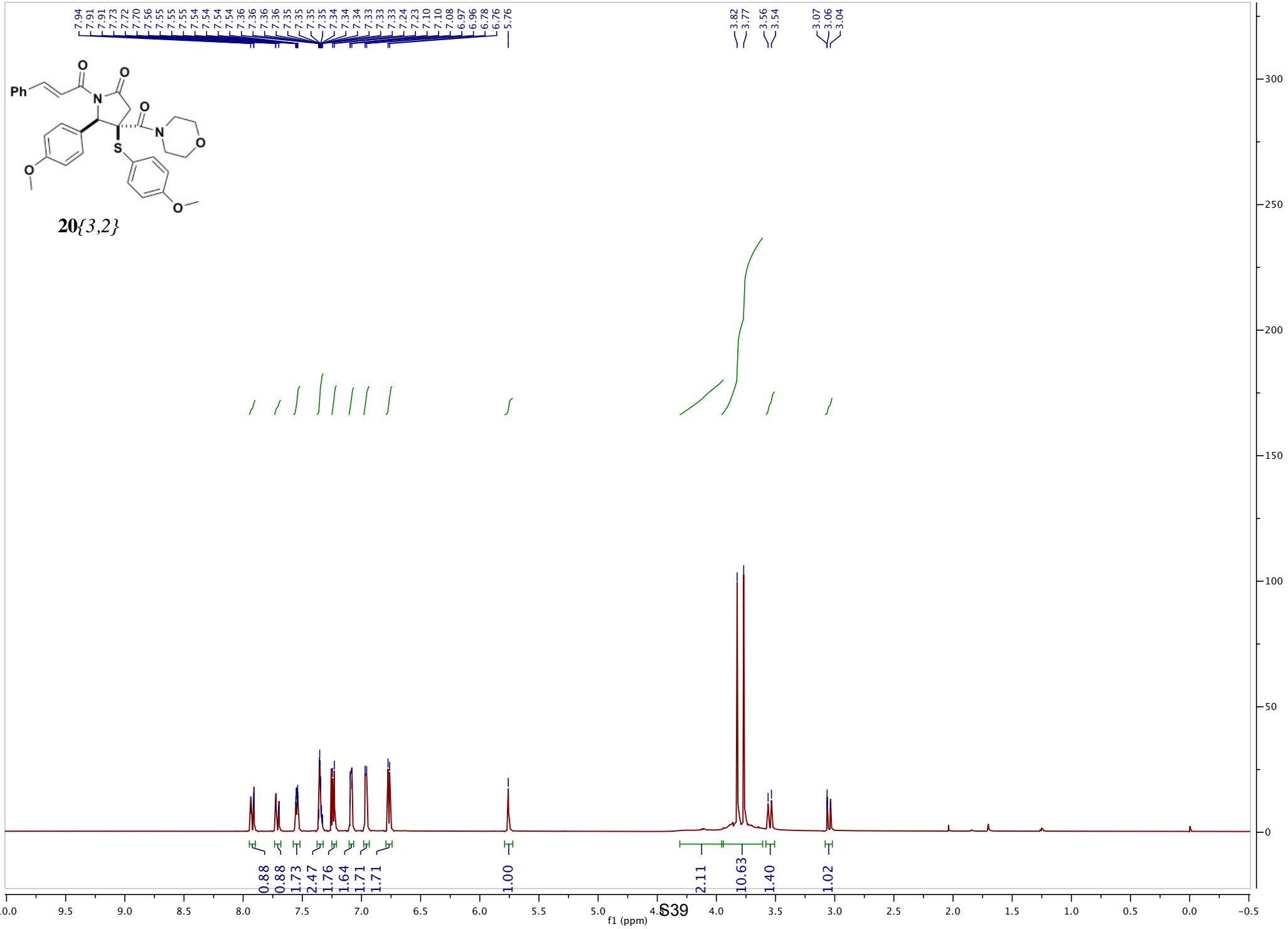
7.51
7.47
7.38
7.37
7.36
7.35
7.35
7.34
7.25
7.02
6.99
6.98
6.74
5.79
3.83
3.75
3.71
3.65
3.65
3.63
3.62
3.58
3.05
3.03
3.00
2.99
Ph
N
O
O
O
N
S
O
O
2.18
1.06
3.93
3.99
1.94
1.00
3.82
3.33
3.47
3.59
f1 (ppm)

20{*1,1*}

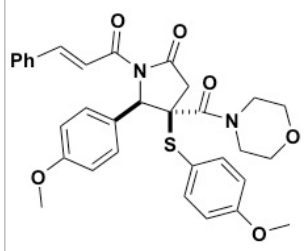

Ph
N
O
O
O
N
S
O
O

20{*1,1*}

171.98
169.55
161.10
160.23
137.28
134.23
133.68
132.33
130.31
129.12
128.79
128.09
120.15
114.91
114.44
77.65 cdcl3
77.33 cdcl3
77.01 cdcl3
66.12
57.84
55.57
55.52
45.16
40.12
38.31
f1 (ppm)

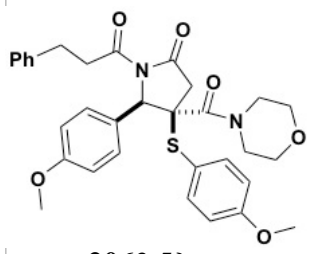

7.94 7.91 7.91 7.73 7.72 7.70 7.56 7.55 7.55 7.55 7.54 7.54 7.54 7.54 7.36 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.34 7.33 7.33 7.33 7.24 7.23 7.10 7.10 7.08 6.97 6.96 6.78 6.76 5.76
3.82 3.77 3.56 3.54 3.07 3.06 3.04
Ph
O
N
O
O
N
O
S
O
O
300
250
200
150
100
50
0
0.88 0.88 1.73 2.47 1.76 1.64 1.71 1.71 1.00 2.11 10.63 1.40 1.02
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 -0.5
f1 (ppm)

20*{3,2}*

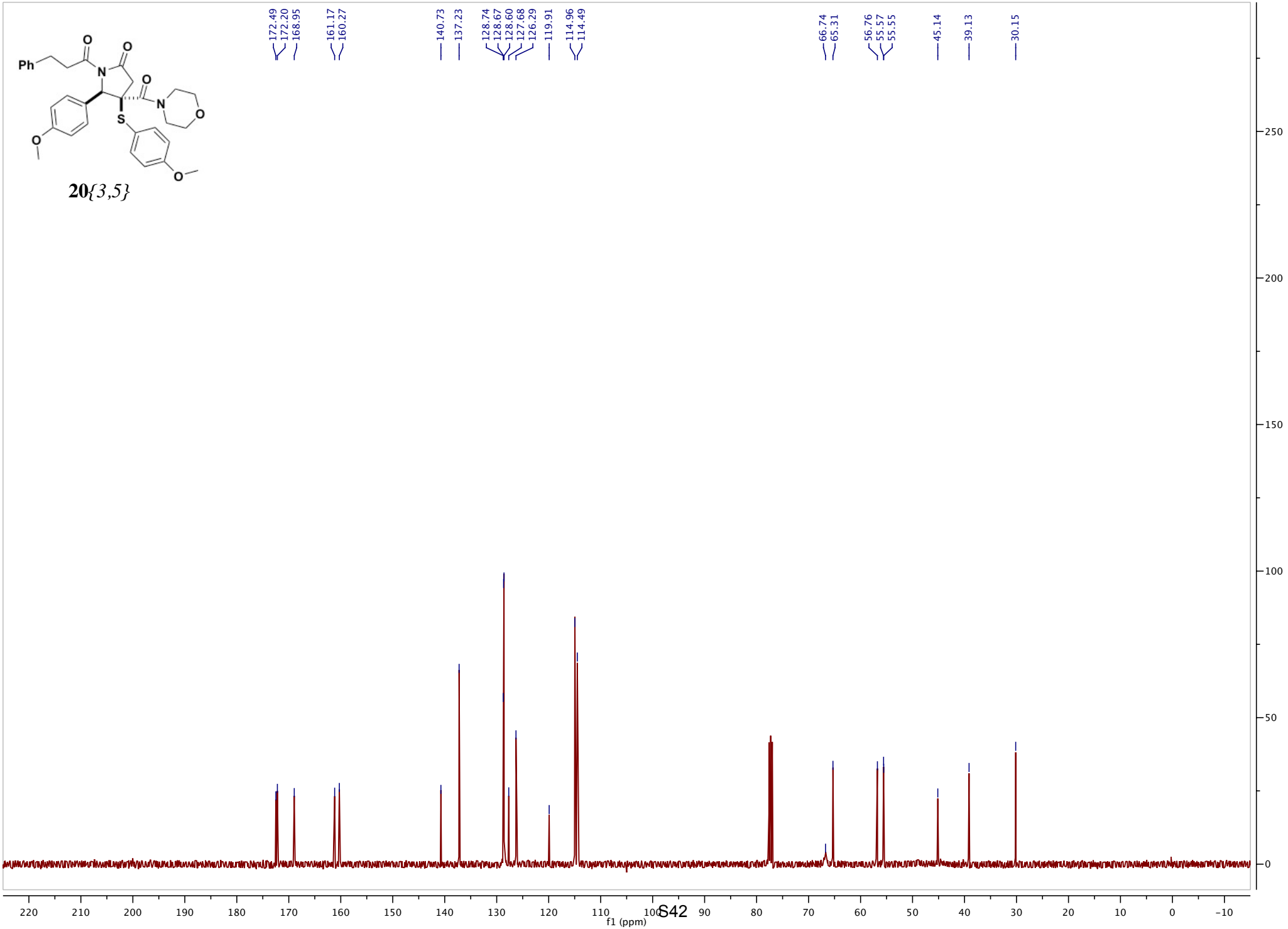

Ph
O
N
O
O
N
O
S
O
O

20{*3,2*}

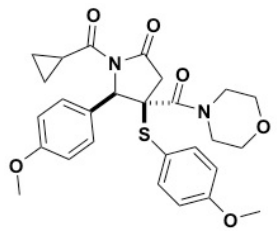
172.23
168.65
165.06
160.94
160.03
146.50
137.06
134.63
130.56
128.80
128.58
128.52
127.54
119.68
118.85
114.74
114.26
66.51
65.44
56.46
55.33
55.32
45.19
600
550
500
450
400
350
300
250
200
150
100
50
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



20{*3,5*}

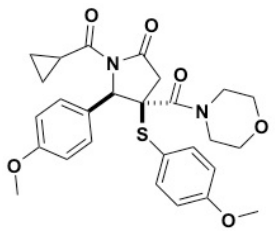

172.49
172.20
168.95
161.17
160.27
140.73
137.23
128.74
128.67
128.60
127.68
126.29
119.91
114.96
114.49
66.74
65.31
56.76
55.57
55.55
45.14
39.13
30.15
Ph
O
N
O
O
N
O
S
O
O
250
200
150
100
50
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

20{*3,5*}



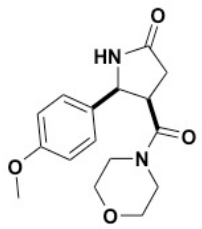
20{*3,6*}

7.19 7.17 7.09 7.07 6.96 6.94 6.77 6.75
5.63
3.83 3.77 3.55 3.51 3.51 3.22 3.21 3.20 3.19 3.19 3.18 3.18 3.17 3.17 3.16 3.05 3.01
1.09 1.09 1.08 1.08 1.07 1.07 1.06 1.06 1.05 1.04 1.04 0.94 0.93 0.92 0.91 0.91 0.90 0.89 0.89 0.88 0.87
1.96 1.95 2.04 1.98 1.00 13.23 1.22 0.98 0.94 1.05 2.78
f1 (ppm)

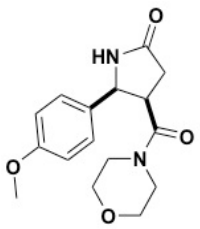


20{*3,6*}

174.43
172.61
168.94
161.15
160.18
137.24
128.61
127.88
119.96
114.94
114.45
77.61 cdcl3
77.29 cdcl3
76.97 cdcl3
66.69
65.69
56.53
55.54
45.43
14.24
11.45
10.90
f1 (ppm)

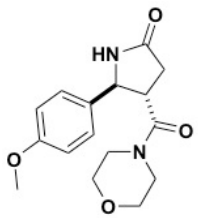


31*{3} syn*

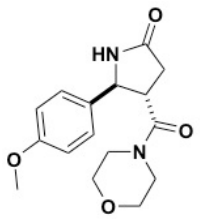

HN
O
O
N
O
O

31{*3*} *syn*

176.77
168.25
160.06
129.27
128.48
113.95
77.22 cdcl3
77.01 cdcl3
76.80 cdcl3
66.43
66.01
59.38
55.31
45.73
41.95
41.86
33.32
f1 (ppm)

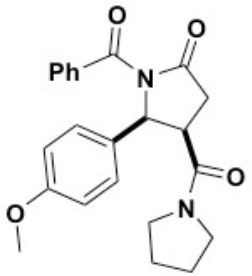


31*{3} anti*

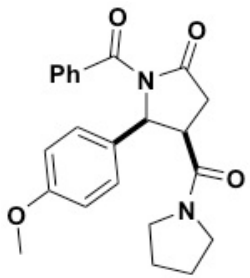

HN
O
O
N
O
O

31*{3} anti*

175.23
169.58
159.83
132.27
127.42
114.47
66.74
66.35
60.75
55.36
46.93
46.06
42.58
35.20
f1 (ppm)

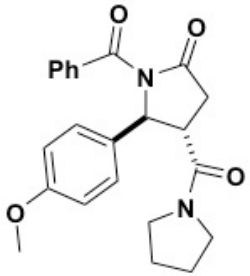


21{*2,1*}

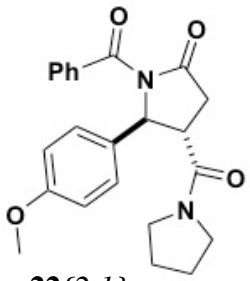

Ph
O
N
O
O
N
O

21{*2,1*}

174.06
170.57
168.44
159.61
134.23
133.39
132.72
130.08
129.80
128.41
128.00
127.83
113.83
62.94
55.27
46.36
45.70
41.36
35.75
25.77
23.95
f1 (ppm)

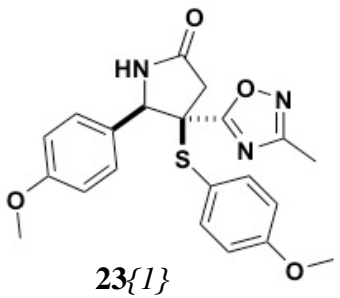


22{*2,1*}


O
Ph
N
O
O
O
N
O

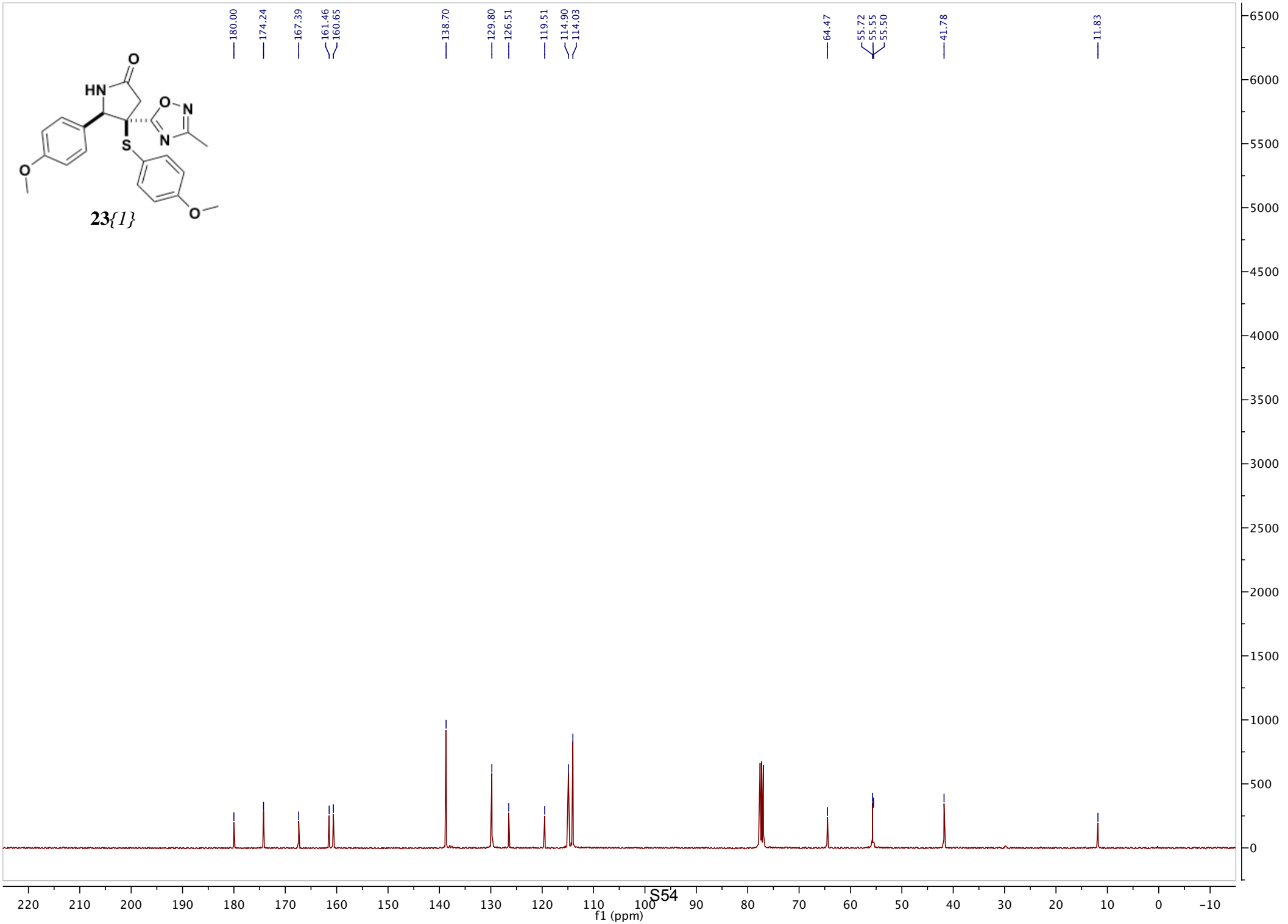
22{*2,1*}

173.26
170.02
169.21
159.40
134.24
133.38
132.39
130.07
129.36
128.38
127.90
126.89
114.45
64.48
55.28
46.56
46.28
45.17
35.58
25.97
24.17
f1 (ppm)

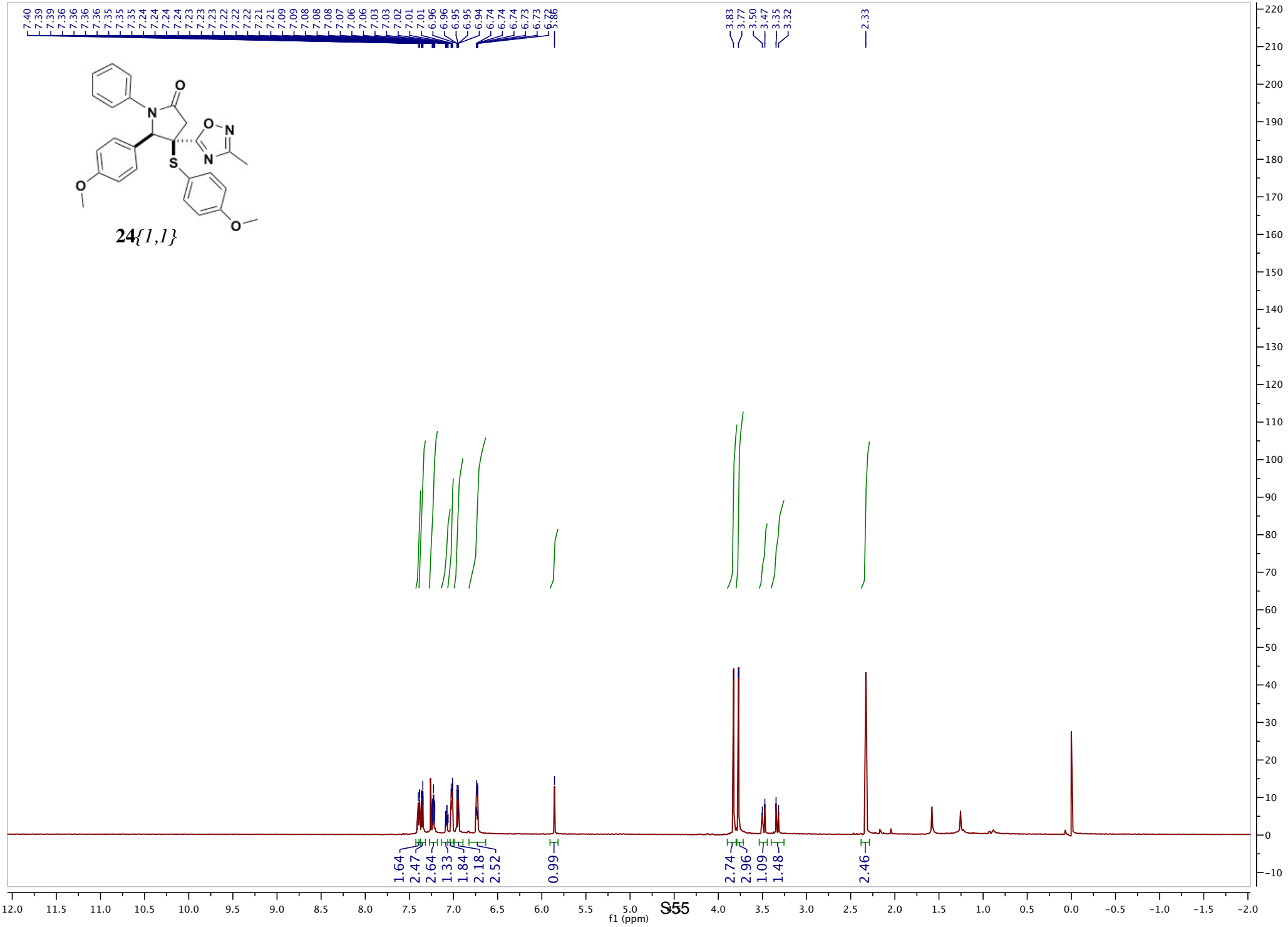

O
HN
O
N
N
S
O
O

23{*1*}

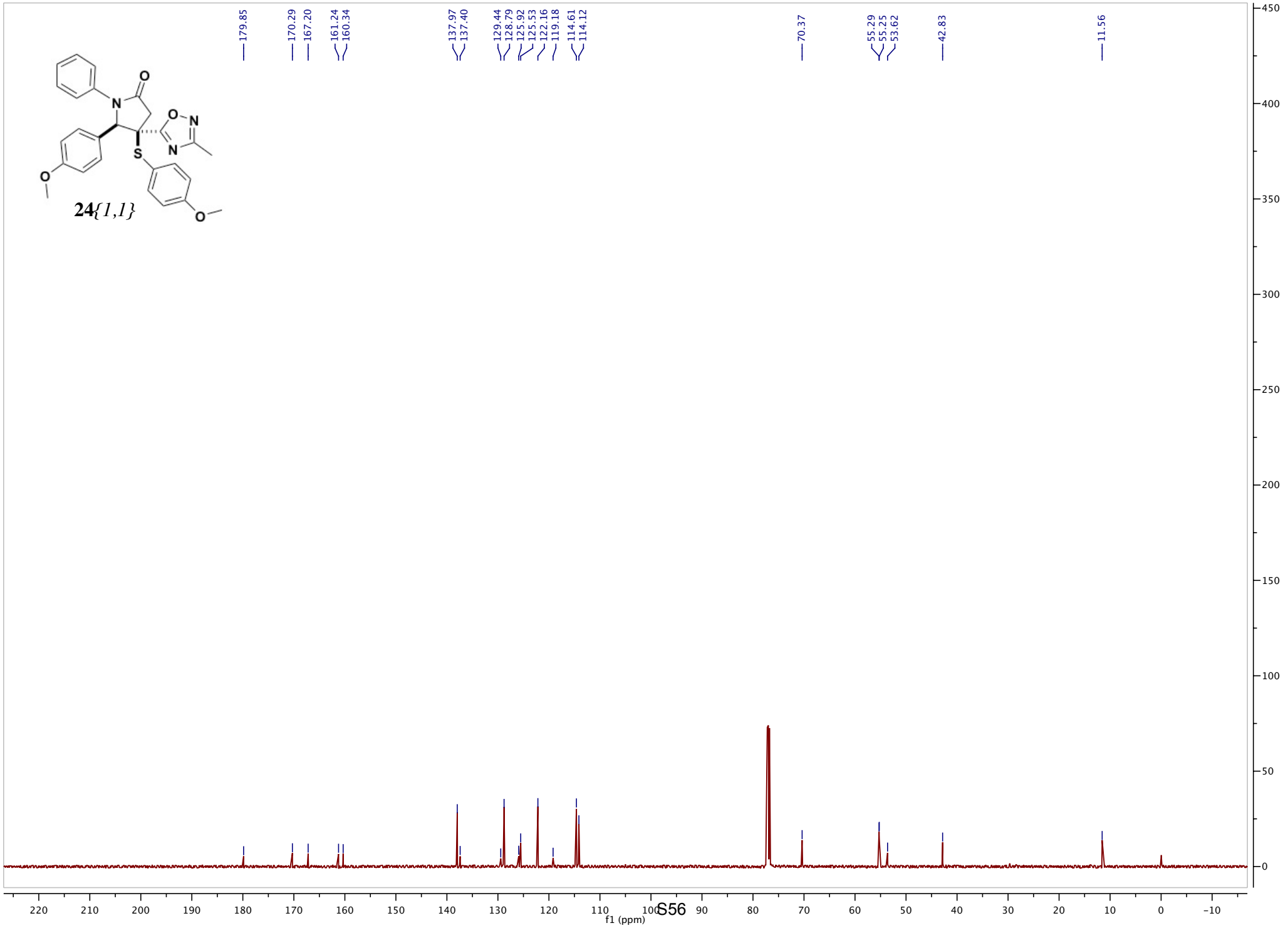
7.51
7.49
7.02
7.01
6.99
6.97
6.76
6.74
6.73
5.36
3.84
3.76
3.25
3.22
2.99
2.99
2.96
2.37
1.83
3.69
2.84
0.97
2.95
3.04
1.01
1.03
2.73
f1 (ppm)

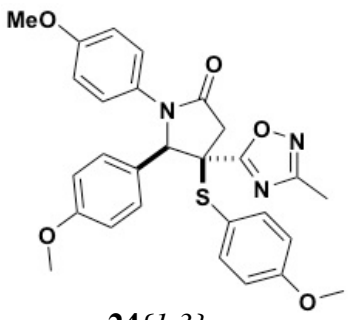

180.00
174.24
167.39
161.46
160.65
138.70
129.80
126.51
119.51
114.90
114.03
64.47
55.72
55.55
55.50
41.78
11.83
HN
O
O
N
N
S
O
O
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)

23{*1*}

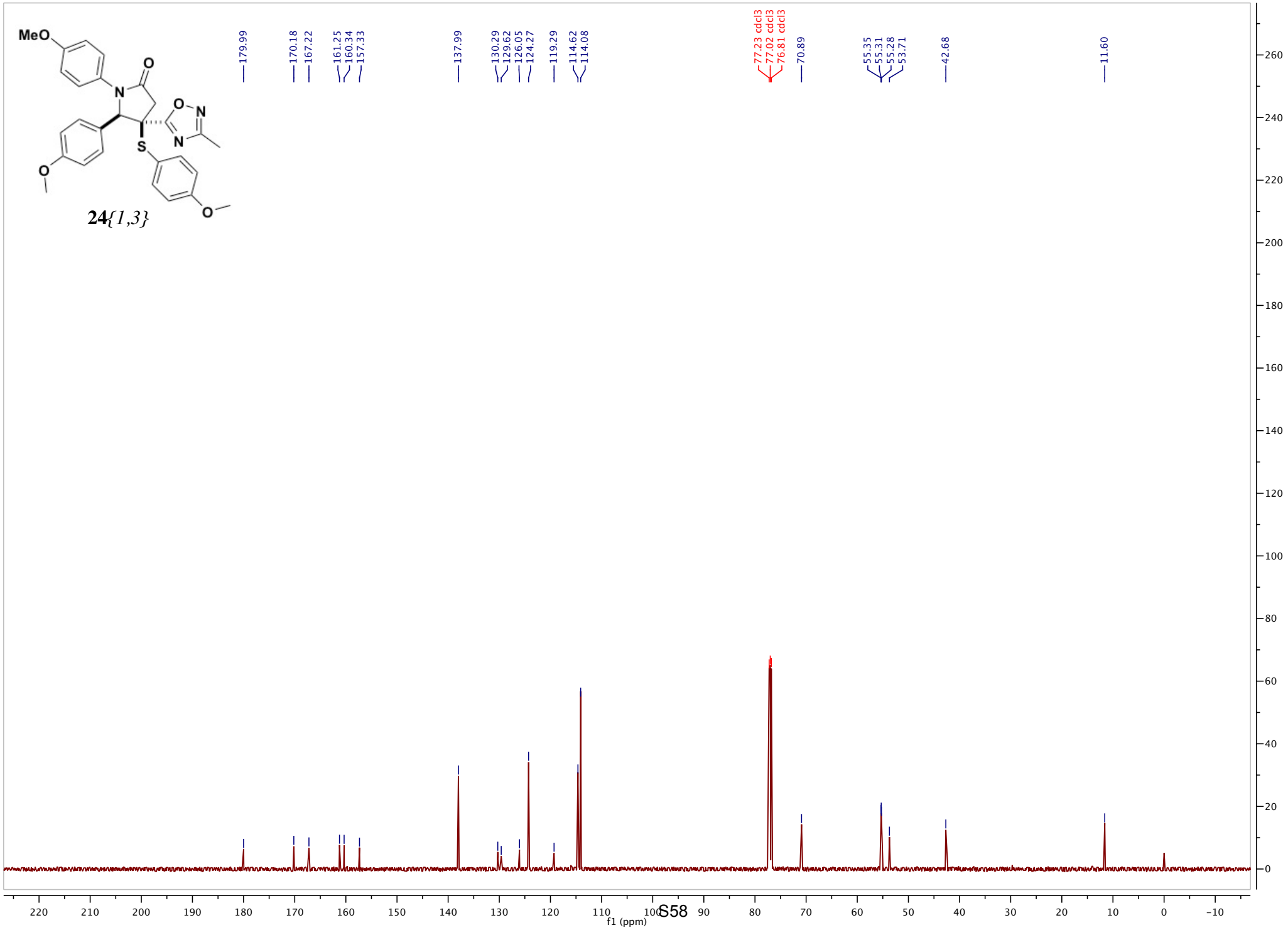

7.40 7.39 7.39 7.36 7.36 7.36 7.35 7.35 7.35 7.24 7.24 7.24 7.23 7.23 7.23 7.22 7.22 7.22 7.21 7.21 7.09 7.09 7.08 7.08 7.08 7.07 7.06 7.06 7.03 7.03 7.02 7.01 7.01 6.96 6.96 6.95 6.95 6.94 6.74 6.74 6.74 6.73 6.73 5.86
3.83 3.77 3.50 3.47 3.35 3.32
2.33
O
N
O
N
N
S
O
O
1.64 2.47 2.64 1.33 1.84 2.18 2.52 0.99 2.74 2.96 1.09 1.48 2.46
f1 (ppm)

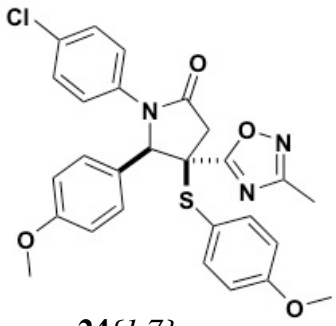
24*{1,1}*


179.85
170.29
167.20
161.24
160.34
137.97
137.40
129.44
128.79
125.92
125.53
122.16
119.18
114.61
114.12
70.37
55.29
55.25
53.62
42.83
11.56
O
N
O
N
S
O
O
24{1,1}
f1 (ppm)

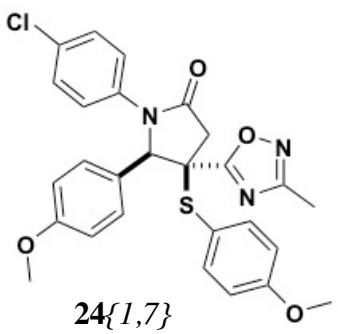


24{*1,3*}


MeO
O
N
O
N
N
S
O
O
24{1,3}
179.99
170.18
167.22
161.25
160.34
157.33
137.99
130.29
129.62
126.05
124.27
119.29
114.62
114.08
77.23 cdcl3
77.02 cdcl3
76.81 cdcl3
70.89
55.35
55.31
55.28
53.71
42.68
11.60
f1 (ppm)



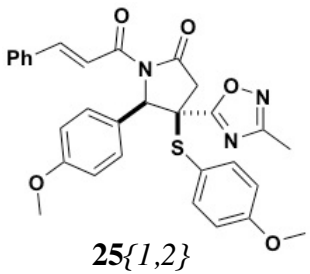
24{*1,7*}



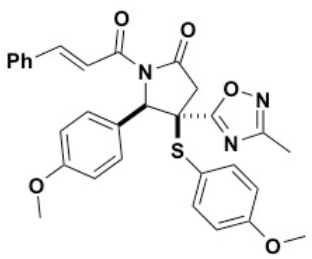
24{*1,7*}

179.70
170.29
167.22
161.29
160.44
138.00
135.95
130.74
129.43
128.86
125.44
123.20
119.02
114.65
114.22
70.20
55.30
55.27
53.45
42.73
11.55

f1 (ppm)



25{*1,2*}


Ph
O
O
N
O
N
N
S
O
O

25*{1,2}*

179.31
171.39
167.16
164.73
161.26
160.24
146.92
137.78
134.52
130.65
128.81
128.65
128.57
126.74
119.01
118.53
114.66
114.11
67.07
55.29
55.28
52.39
44.52
11.50
f1 (ppm)

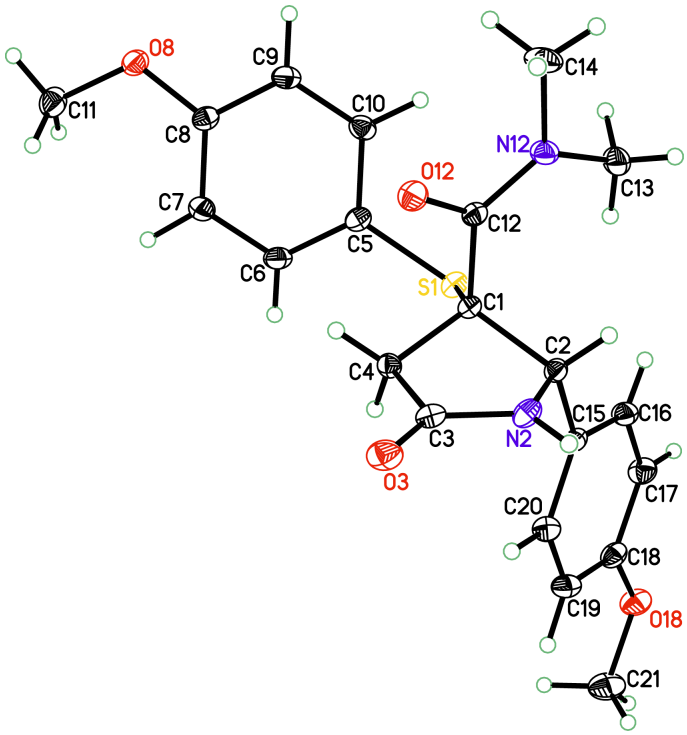
X-Ray Crystallography

18*{1}*

A colorless block with approximate orthogonal dimensions 0.38 x 0.24 x 0.22mm^3 was placed and optically centered on the Bruker Duo APEXII[1] CCD system at 90(2)K. The initial unit cell was indexed using a least-squares analysis of a random set of reflections collected from three series of 0.5° wide ω-scans, 10 seconds per frame, and 30 frames per series that were well distributed in reciprocal space. Five ω-scan data frame series were collected [MoKα] with 0.3° wide scans, 20 seconds per frame and 606 frames were collected, at varying phi angles (phi=0°, 72°, 144°, 216°, 288°), for each series. The crystal to detector distance was 4.96cm, thus providing a complete sphere of data with processing to $2\theta_{max}$=61.02°.

Structural determination and Refinement:

All crystallographic calculations were performed on an iMac with an Intel Core i7 2.80GHz processor and 8GB of extended memory at 1067MHz DDR3. A total of 41440 reflections were collected and corrected for Lorentz and polarization effects in SAINT[1] and absorption using crystal faces and Blessing's method as incorporated into the program SADABS[2,3,4] with 6715 unique. The SHELXTL[5] program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences and intensity statistics indicated the non-centrosymmetric orthorhombic space group $Pna2_1$ (no. 33). The structure was determined by direct methods with the successful location of the molecule using the program XS[6]. The structure was refined with XL[6]. The data collected were merged, based upon identical indices to 24273 data [R(int)=0.0151], truncated to $2\theta_{max}$=60.00° to 22029 data and then in least-squares refinement to 5830 unique data [R(int)=0.0159]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were initially idealized and then allowed to refine freely throughout the final refinement process. The final structure was refined to convergence with R(F)=2.40%, wR(F^2)=6.19%, GOF=1.053 for all 5830 unique reflections [R(F)=2.34%, wR(F^2)=6.14% for those 5727 data with Fo > 4σ(Fo)]. The final difference-Fourier map was featureless indicating that the structure is both correct



and complete. The absolute structure parameters, Flack(x)[7], was refined and found to be -0.02(3) while the Hooft[8] parameter is -0.02(1) indicating that the structure's absolute configuration has been reliably determined. An empirical correction for extinction was also attempted but found to be negative and therefore not applied.

References:

1. Bruker (2010) APEX (Version 2010-9) and (2009) SAINT (Version 7.68a). Bruker AXS Inc., Madison, Wisconsin, USA.

2. An Empirical Correction for Absorption Anisotropy, Blessing, R. H. (1995). Acta Cryst., A51, 33-38.

3. Sheldrick, G.M., SADABS (2008) Version 2008/1, 'Siemens Area Detector Absorption Correction' Universität Göttingen: Göttingen, Germany.

4. A short history of SHELX, George M. Sheldrick, Acta Cryst. (2008). A64, 112-122

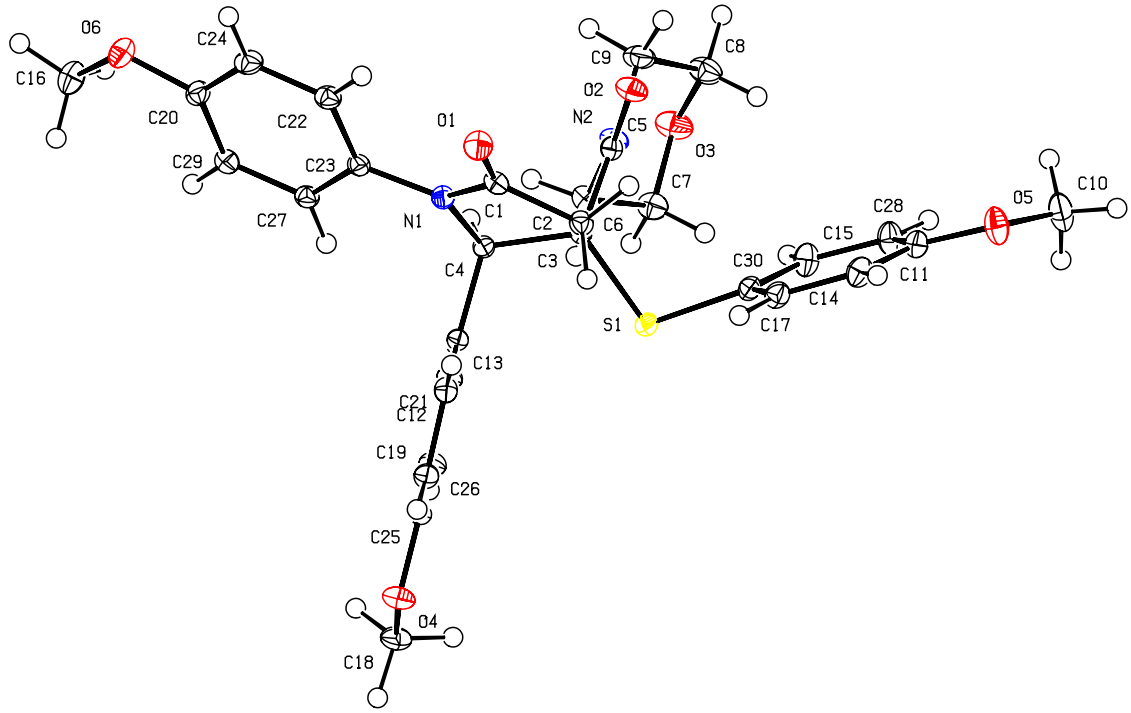
5. Sheldrick, G.M., (2002). SHELXTL. Version 6.1. Bruker AXS Inc., Madison, Wisconsin, USA.

6. Sheldrick, G. M., (1997). SHELXS97 and SHELXL97. Universität Göttingen: Göttingen, Germany.

7. On Enantiomorph-Polarity Estimation, Flack, H.D. (1983). Acta Cryst., A39, 876-881.

8. Hooft, R.W.W, Straver, L.H. & Spek,A.L. (2008). J. Appl, Cryst. 41, 96-103. Thompson,A.L. & Watkin, D.J. (2009). Tetrahedron

X-ray data for 19*{3,3}*



X-ray crystal structure of MD3index **19*{3,3}***. Thermal displacement plot shows 50% probability displacement ellipsoids for non-hydrogrens.

Table 1. Crystal data and structure refinement for MD3index

Identification code	MD3index
Empirical formula	$C_{30}H_{32}N_2O_6S$
Formula weight	548.63
Temperature/K	90 (2) K
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	11.9146(5)
b/Å	13.9399(6)
c/Å	16.1772(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2686.8(2)
Z	4
ϱ_{calc}mg/mm^3	1.356
m/mm^{-1}	0.168
F(000)	1160.0
Crystal size/mm^3	0.559 × 0.519 × 0.512
2Θ range for data collection	5.824 to 55.068°

Index ranges	$-15 \le h \le 15, -18 \le k \le 18, -21 \le l \le 21$
Reflections collected	29672
Independent reflections	6178[R(int) = 0.0512]
Data/restraints/parameters	6178/0/355
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	$R_1 = 0.0254, wR_2 = 0.0673$
Final R indexes [all data]	$R_1 = 0.0265, wR_2 = 0.0680$
Largest diff. peak/hole / e $Å^{-3}$	0.26/-0.17

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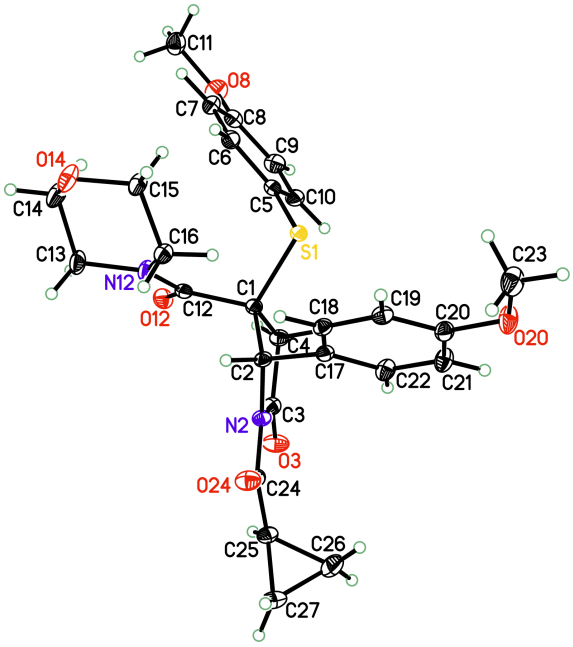
A colorless block with approximate orthogonal dimensions 0.38 x 0.33 x 0.25mm^3 was placed and optically centered on the Bruker APEXII[1] CCD diffractometer at –183°C. The initial unit cell was indexed using a least-squares analysis of a random set of reflections collected from three series of 0.3° wide ω-scans, 10 seconds per frame, and 30 frames per series that were well distributed in reciprocal space. Four ω-scan data frame series were collected [MoKα] with 0.3° wide scans, 25 seconds per frame and 606, 455, 606, 455 frames collected per series at varying φ angles (φ=0°, 90°, 180°, 270°), respectively. The crystal to detector distance was 5.23cm, thus providing a complete sphere of data to $2\theta_{max}$=54.97°.

Structural determination and Refinement:

All crystallographic calculations were performed on an iMac with an Intel Core i7 2.80GHz processor and 8GB of extended memory at 1067MHz DDR3. A total of 28376 reflections were collected and corrected for Lorentz and polarization effects in Saint[1] and absorption using Blessing's method as incorporated into the program SADABS[2,3,5] with 5963 unique. The SHELXTL[4] program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences and intensity statistics indicated the centrosymmetric, non-standard, monoclinic space group $P2_1/n$ (no. 14). The structure was determined by direct methods with the successful location of a majority of the non-hydrogen atoms comprising the molecule using the program XS[5]. The structure was refined with XL[5]. The 28376 data collected were merged, based upon identical indices yielding 21519 data [R(int)=0.0108], and during least-squares refinement to 5668 unique data [R(int)=0.0149]. A single least-squares difference-Fourier cycle was required to locate the remaining non-hydrogen atoms. One larger than normal peak was also located near O(14) and its inclusion necessitated that a partial occupancy group be created. The final ratio was determined to be 0.96:0.04. All non-hydrogen atoms were refined anisotropically. Full occupancy hydrogen atoms were refined freely while the 96:04 disordered pair was idealized throughout. The final structure was refined to convergence with R(F)=3.38%, wR(F^2)=8.18%, GOF=1.026 for all 5668 unique reflections [R(F)=3.09%, wR(F^2)=7.92% for those 5213 data with Fo > 4σ(Fo)]. The final difference-Fourier map was featureless indicating that the structure is both correct



and complete. An empirical correction was found to be negative and therefore not applied.

References:

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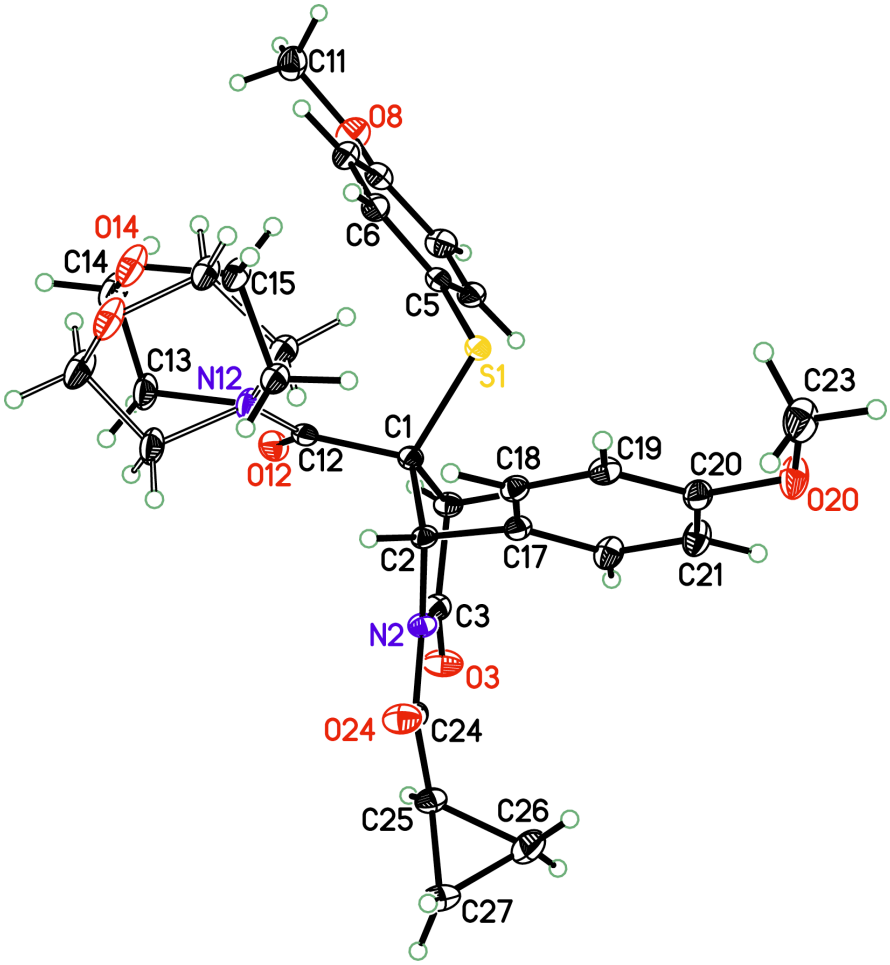
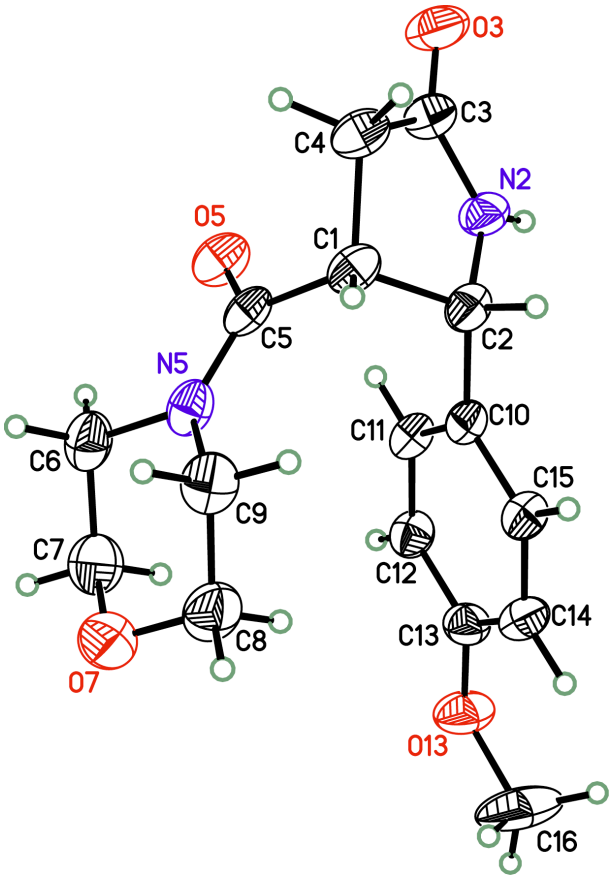

C11
O8
C6
O14
C14
C15
C5
S1
C13
N12
C1
C23
C12
O12
C18
C19
C20
O20
C2
C17
C21
C3
N2
O3
O24
C24
C25
C26
C27

30{3} *syn*

A colorless plate with approximate orthogonal dimensions 0.60 x 0.60 x 0.09mm^3 was placed and optically centered on the Bruker Duo[1] APEXII CCD diffractometer at –183°C. The initial unit cell was indexed using a least-squares analysis of a random set of reflections collected from three series of 0.5° wide ω-scans, 10 seconds per frame, and 30 frames per series that were well distributed in reciprocal space. Twelve ω and phi-scan data frame series were collected [CuKα] with 0.5° wide scans and variable frame times based upon diffraction angle. The crystal to detector distance was 4.96cm, thus providing a nearly complete sphere of data with processing to $2\theta_{max}$=136.48°.

Structural determination and Refinement:

All crystallographic calculations were performed on an iMac with 2.80GHz quad core processor and 8GB of extended memory. A total of 11404 reflections were collected and corrected for Lorentz and polarization effects in SAINT[1] and absorption using Blessing's method as incorporated into the program SADABS[2,3,5] with 3326 unique. The SHELXTL[4] program package was implemented to determine the probable space group and set up the initial files. System symmetry, systematic absences and intensity statistics indicated the centrosymmetric monoclinic space group C2/c (no. 15). The structure was determined by direct methods with the successful location of a majority of the non-hydrogen atoms comprising the molecule using the program XS[5]. The structure was refined with XL[5]. The 11404 data collected were merged, based upon identical indices to 7734 data [R(int)=0.0281] and truncated to 2θ=136.46°, 7381 data, and further merged during least-squares refinement to 3023 unique data [R(int)=0.0230]. A series of least-squares difference-Fourier cycle were required to locate the remaining non-hydrogen atoms comprising the molecule and severely disordered solvent. Due to overall solvent disorder and believed to be a methanol molecule, squeeze[6] was used to remove this solvent density from further consideration. All



non-hydrogen atoms were refined anisotropically. Hydrogen atoms were idealized throughout the final convergence phase. The final structure was refined to convergence with R(F)=5.16%, wR(F^2)=14.21%, GOF=1.037 for all 3023 unique reflections [R(F)=4.99%, wR(F^2)=14.06% for those 2851 data with Fo > 4σ(Fo)]. The final difference-Fourier map was featureless indicating that the structure is both correct and complete. An empirical correction for extinction was also attempted and found to be negative and therefore not applied.

References:

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Computational Analysis

Shape Diversity

Procedure for generation of Ternary Plot:[1,2]
2D Simplified Molecular Input Line Entry Specification (SMILES) strings were generated using CambridgeSoft ® ChemDraw ®.[3] The strings were imported into Windows XP ® Notepad and saved as a .smi files. The .smi files were converted to 3D structures using OpenEye Scientific Software, Inc., OMEGA-V2.4.3;(-ewindow 3.0 kcal/mol).[4] OMEGA was used to directly generate .xyz (Cartesian coordinates). Conformers >3 kcal/mol from the lowest energy conformer and duplicates were discarded. Conformers were estimated using Merks Molecular Force Field 94, MMFF94.[5] The Principal Moments of Inertia (PMI)[3] were calculated using the Perl module Math::MatrixReal.[6] Values at (1,1) correspond to spherical shapes (methane or adamantane), (0.5,0.5) disk shaped (benzene), and (0,1) rod shaped (acetylene).

Graph of Diversity Analysis

Data for molecular weights, XLogP, # of H-bond donors, and # of H-bond acceptors obtained from FILTER.[4]

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