

SUPPORTING INFORMATION

Development of Potent and Selective Indomethacin Analogues for the Inhibition of AKR1C3 (Type 5 17 β - Hydroxysteroid Dehydrogenase/Prostaglandin F Synthase) in Castrate Resistant Prostate Cancer

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Experimental Section

General:

The purity of all target compounds was determined using HPLC with UV detection at 215 and/or 254 nm along with ELSD detection and was $\geq 95\%$, if not denoted otherwise. NMR spectra were processed and visualized using ACDLABS 12.0 software. Given systematic compound names were generated with ChemDraw Ultra Vers. 12.0.

Materials and methods:

i) *Solvents and Reagents:*

All reagents and solvents were of commercial quality and were used as such without further purification. HPLC grade solvents obtained from Fischer (Pittsburg, PA) were used for chromatographic separations. Column chromatography was performed using standard grade silica gel from Sorbent Technologies, Twinsburg, OH (Catalog #: 10930-5, Porosity: 60 A, Particle Size: 32-63 μm , 230x450 mesh, pH range 6.5-7.5). Flash chromatography was conducted on a Biotage SP1 automated flash chromatography system equipped with a fixed wavelength UV detector ($\lambda = 254 \text{ nm}$) using prefabricated 'Flash KP-SIL' columns (size according to requirements). Analytical thin-layer chromatography (TLC) analyses were performed on fluorescent silica gel 60 F₂₅₄ plates (250 μm) from Whatman (Partisil[®] LK6D, Cat. No. 4865-821). Spots were visualized under natural light, and UV illumination at $\lambda = 254$ and 365 nm.

ii) *Instrumental Analysis:*

¹H and ¹³C NMR experiments were run on a Bruker AV-400 with sample changer (BACS 60) at 400 and 100 MHz, respectively. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 2.52 and δ 40.45 (DMSO-*d*₆). ¹⁹F NMR spectra were collected on a Bruker AV-300 at 282 MHz. Data is formatted as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, br = broad, dd = doublet of doublets, dq =

douplet of quartets, td = triplet of douplets, pd = pentet of douplets, m = multiplet), coupling constant (Hz), and integration.

Low-resolution mass analyses (LCMS) were carried out on an Agilent 1200 LCMS system with electrospray ionization, (Agilent 6130 quadrupole analyzer, positive ion mode). ESI-MS results are given as m/z ratio ($[M+H]^+$). Purity of compounds was determined by analytical high performance liquid chromatography (HPLC) on a Supelco Supelcosil LC-18 column (15 cm x 3 mm, 5 μ m) 'method 1' or a YMC J'sphere H-80 S-4 column (3.0 x 50 mm) 'method 2', which were eluted with a gradient (see time tables below) with a MeOH-0.01 M KH_2PO_4 system at a flow rate of 1.0 mL/min or an ACN- H_2O (plus 0.1 % TFA) system at a flow rate of 1.4 mL/min, respectively. (HP)LC was performed either on a Waters HPLC system^a with PDA detector (UV detection essentially at 254 nm) or an Agilent 1200 analytical LCMS with UV detection at 215 and 254 nm along with ELCD detection. LC results are presented as t_R (min) and relative purity (%). The purity of all tested compounds is $\geq 95\%$, if not denoted otherwise.

^aequipped with a Waters 1525 Binary HPLC Pump, a Waters 2996 Photodiode Detector and a Waters 717plus Autosampler as well as a Shimadzu CTO-6A Column Oven.

HPLC samples were diluted to a final concentration of about 0.1 – 0.2 mg/ml using MeOH. ESI samples (for direct detector injection) were diluted to similar concentrations using 0.5 % TFA in MeOH for measuring in the positive ionization mode and 0.5 % NH_4^+ -acetate in MeOH for measuring in the negative ionization mode. If required, samples were filtered through a Spartan-Filter 13/0,45 RC into the 1 ml HPLC glass vials in order to separate from particulate material.

Method 1:

Waters 1525 binary pump and Shimadzu CTO-6A thermostat settings:

Solvent A: 60.0 % (0.01 M KH_2PO_4)^b

Solvent B: 40.0 % (methanol)

Gradient

<i>Time</i>	<i>Solv. B</i>	<i>Flow</i>
0.01	40.0	1.400
0.25	40.0	
8.00	85.0	
13.00	85.0	
14.00	40.0	

Stop time: 18.0 min

Pressure Limits (psi)

Minimum pressure: 0

Maximum pressure: 4000

Column temperature: 35 °C

^bMonobasic potassium phosphate solution 0.01 M (pH 2.3) was prepared by dissolving 1.361 g of monobasic potassium phosphate in 800 mL of water (bidest.), adjusting to pH 2.3 with 10% H₃PO₄ (v/v) and diluting to 1000 mL with water.

HPLC mobile phases (Fisher, HPLC grade, submicron filtered) were degassed by vacuum filtration through a Nylon Membrane Filter (Nyaflo®, 0.45 mm, 47 mm, P/N 66608) from Pall Life Sciences Inc. before usage. HPLC results are presented as retention times (min) and relative chemical purity (%). The Empower Pro software (Copyright® 2002, Waters Corporation) was used for the instrument control and data analysis.

Method 2:

Agilent 1200 binary pump and thermostat settings:

Solvent A: 95 % (water (0.1% TFA))

Solvent B: 5.0 % (Acetonitrile)

Gradient

<u>Time</u>	<u>Solv. B</u>	<u>Flow</u>
0.00	5.0	1.400
3.60	100.0	
4.00	100.0	
4.05	5.0	

Stop time: 4.20 min

Pressure Limits (bar)

Minimum pressure: 0

Maximum pressure: 400

Column temperature: 45 °C

Synthetic procedures:

The detailed synthetic procedures and analytical data of target compounds **2-13**, **17**, **19**, **20-25**, **42-44** and **62** have been published elsewhere.¹

General Methods:

General Procedure A: Fischer Indolization of (substituted) N-Phenyl Benzohydrazide HCl with different ketoacids.²

4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride and 1.2 equivalents of the appropriate acyclic or cyclic keto acid reagent were dissolved in acetic acid (3 mL/mmol). The mixture was heated at 80 °C with stirring under argon for 3 h, cooled, diluted with water (6 mL/mmol) and the resulting fine precipitate was collected by filtration, gently washed with water and dried *in vacuo* to yield the desired compound quantitatively and in acceptable analytical quality as an amorphous solid. Alternatively (when product precipitates as oil or coagulates to a viscous mass), the desired Fischer indole artifact was isolated from the acidic watery reaction mixture by repeated extraction with DCM. The organic extracts

were combined, dried over Na_2SO_4 , and filtered. Evaporation of the solvent under reduced pressure and recrystallization of the residue in alcohol or purification by column chromatography yielded again the desired target compound.

General Procedure B: Synthesis of sulfonimides via CDI carbodiimide coupling.³

To an ice-cold mixture (0-5 °C) of the free acid derivative of the respective indomethacin analog in dry CH_2Cl_2 (2 mL/0.5 mmol) under argon, one equiv. of 1,1'-carbonyldiimidazole (CDI) was added. After the reaction mixtures were stirred for two hours at 0-5 °C, the appropriate (substituted) aryl or alkyl sulfonamide (1 equiv.) and diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv.) were added. The mixtures were left stirring for another 4 to 6 hours at ambient temperature before they were quenched by the addition of glacial acetic acid (60 μL /0.5 mmol) and diluted with CH_2Cl_2 (1 mL/0.5 mmol). The organic layer was separated and washed with 10% NaH_2PO_4 buffer (pH 4) (2 x 2 mL) and water (3 x 2 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give crude residues. Chromatographic purification was carried out on SiO_2 as stationary phase using hexane/ethyl acetate as eluent mixture to afford the appropriate acyl sulfonimides.

General Procedure C: Carboxylic acid activation with oxalylchloride.^{4,5}

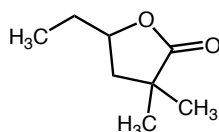
Oxalyl chloride (1.2 equiv.) was added dropwise to a solution of the respective free acid derivative of (2'-*des*-methyl) indomethacin in dry CH_2Cl_2 (20-25 mL/mmol) under argon at ambient temperature and the reaction mixture was stirred overnight. The completion of the reaction was monitored by TLC (SiO_2 , EtOAc+hexane: 1+1 (0.5% AcOH)). The solvent was evaporated under reduced pressure and, if required, the crude product repeatedly washed with a little ice-cold hexane. Typically the crude material was applied to the following reaction step without further purification.

General Procedure D: Preparation of alkyl-/arylsulfonimides from the indole acetic acid chlorides.⁶

The reactive ‘acid chloride derivative’ and 1.5 equivalents of the respective (substituted) sulfonamide were dissolved in 1,2-DCE or CH₂Cl₂ (20 mL/mmol) under argon and constant stirring. Then, pyridine (1 equiv.) was added and the reaction aged overnight at 25 °C. The reaction mixture was washed with diluted NaHCO₃ and water and the organic layer was dried over Na₂SO₄, filtered, concentrated and chromatographed over silica gel using an EtOAc/hexane (0.5% AcOH)-gradient to afford the pure ‘sulfonimide’ compounds.

Synthesis of intermediates and final compounds:

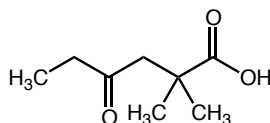
Synthesis of non-commercial aliphatic keto acids:



5-ethyl-3,3-dimethyldihydrofuran-2(3H)-one.⁷

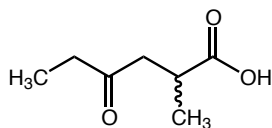
A ready solution of lithium diisopropylamide (LDA, 2M in tetrahydrofuran/heptane/ethylbenzene) in 30.0 mL (60.00 mmol) THF at -60°C was combined with ethyl isobutyrate (6.0 g, 51.65 mmol; temperature held below -50°C) and the reaction mixture was then stirred for 45 min at continued cooling (-60 to -50 °C). 2-ethyloxirane (3.72 g, 51.65 mmol) was added in one portion and the reaction allowed to warm to ambient temperature and then aged overnight. The reaction was quenched with 98 mL cold 1N HCl, the layers were separated and the aqueous phase was washed with 25 mL ethyl acetate. The combined organic extract was treated with 15 mL 1.5 N HCl and 15 mL of brine. The organic layer was dried over Na₂SO₄, filtered and finally concentrated *in vacuo* keeping the temperature close to ambient. The residue was distilled at 115-120°C (~0.5 psi) using a Vigreux column to yield 4.8 g (65%) of a colorless liquid that impermanently congealed to a white solid upon storage at 4°C. The product was used in the next reaction step without further purification. C₈H₁₄O₂, M_r = 142.20; ¹H NMR (400 MHz,

DMSO- d_6) δ : 0.90 (t, $J=7.4$ Hz, 3H), 1.14 (s, 3H), 1.15 (s, 3H), 1.53-1.71 (m, 3H), 2.14 (dd, $J=5.8/12.6$ Hz, 1H), 4.36-4.43 (m, 1H, methin-H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 9.75 (s, ethyl- CH_3), 24.29 (s), 25.03 (s), 28.26 (s), 40.28 (s; overlaid by solvent signal), 42.29 (s), 78.18 (s), 181.70 (s, $>\text{C}=\text{O}$); LCMS (ESI) (method 2) $t\text{R}$: 1.90 min ($>95\%$, UV220), m/z : 143.2 $[\text{M}+\text{H}]^+$.



2,2-dimethyl-4-oxohexanoic acid.⁷

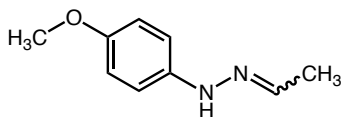
The crude lactone from the preceding reaction step (0.53 g, 3.73 mmol) was suspended in 1.9 mL water and saponified with 5N NaOH (0.85 mL) for 1h. The mixture was chilled to 0-5°C, at which point ruthenium dioxide hydrate ($\text{RuO}_2 \cdot x\text{H}_2\text{O}$) was added. A total of 3.5 mL sodium hypochlorite solution (10-15% active chlorine) was added dropwise, while the temperature was maintained below 10°C (color no longer turned black (RuO_2) but remained a greenish yellow. Then, the reaction was quenched with isopropanol (0.5 mL) and filtered using a Steriflip® (0.45 μm Durapore PVDF Membrane) disposable vacuum filtration system to remove the catalyst. The colorless filtrate was acidified with 5N HCl (2.5 mL) and extracted with methylene chloride (3x8 mL). The organic layer was dried over Na_2SO_4 (Biotage Phase separator with drying cartridge) and the solvent evaporated at reduced pressure. The oily residue was frozen in dry ice and scratched with a fine needle to initiate crystallization. Yield: (0.57 g (97%) white solid. $\text{C}_8\text{H}_{14}\text{O}_3$, $M_r = 158.19$; ^1H NMR (400 MHz, DMSO- d_6) δ : 0.88 (t, $J=7.4$ Hz, 3H), 1.10 (s, 6H), 2.36 (q, $J=7.2$ Hz, 2H), 2.67 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6) δ : 7.94 (s, C6), 25.75 (s, $\alpha\text{-(CH}_3)_2$), 35.81 (s, C5), ~40 (s, C2, peak overlaid by DMSO signal), 51, 25 (s, C3), 178.62 (s, C1), 209.39 (s, C4); LCMS (ESI) (method 2) $t\text{R}$: 1.48 min ($>99\%$, UV220), m/z : 159.2 $[\text{M}+\text{H}]^+$.



2-methyl-4-oxohexanoic acid.⁸

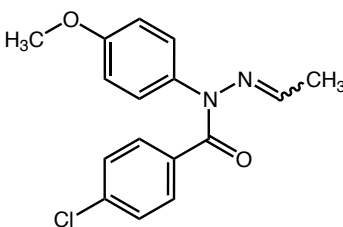
Methyl 3-oxopentanoate (3.0 g, 23.1 mmol) in acetone (90 mL) was combined with methyl 2-bromopropionate (3.85 g, 23.1 mmol), K_2CO_3 (16.2 g), and tetrabutylammonium iodide (1.70 g, 4.61 mmol). The resulting mixture was stirred at room temperature for 3h whereupon inorganic constituents were filtered off. The solvent of the reaction solution was evaporated *in vacuo* and the residue combined with ethyl acetate. The organic layer was treated with water and brine, dried over Na_2SO_4 and finally concentrated. The residue was purified by flash chromatography (SiO_2 , ethyl acetate/hexane: 3+7) to afford the intermediate alkylation product (1.35 g). This compound was dissolved in a mixture of AcOH (23 mL), concentrated HCl (23 mL), and water (11.5 mL), and the reaction heated up over an oil bath and held at reflux temperature for 4h. After removal of AcOH by evaporation, a little water was added and the mixture repeatedly extracted with diethyl ether. Evaporation of the ether of the combined extracts afforded the desired pure carboxylic acid. Yield: 0.46 g (14%, over two steps). $C_7H_{12}O_3$, $M_r = 144.17$; 1H NMR (400 MHz, $DMSO-d_6$) δ : 0.90 (t, $J=7.2$ Hz, 3H), 1.05 (d, $J=7.2$ Hz, 3H), 2.37-2.50 (m, 3H), 2.65-2.75 (m, 2H); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 7.97 (s, C6), 17.31 (s, alpha-methyl-C), 34.59 (s, C2), 35.44 (s, C5), 45.19 (s, C3), 177.12 (s, C1), 209.69 (s, C4); LCMS (ESI) (method 2) *t*R: 1.24 min (>95%, MSD), *m/z*: 145.2 $[M+H]^+$.

Synthesis of the substituted *N*-phenyl benzohydrazide HCl precursor:



1-ethylidene-2-(4-methoxyphenyl)hydrazine (**B**, mixture of *cis/trans* isomers).²

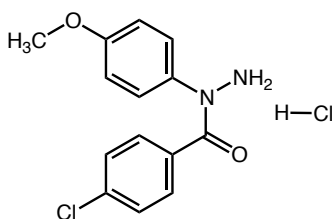
A stirred suspension of (4-methoxyphenyl)hydrazine hydrochloride **A** (8.0 g, 45.8 mmol) in toluene (50 mL) was combined dropwise with triethylamine (6 mL, 4.4 g, 43.5 mmol). The mixture was stirred at room temperature for 30 min, and then it was filtered and dried over MgSO₄. The clear filtrate (4-methoxyphenyl)hydrazine solution) was cooled to 0°C and acetaldehyde (3.9 mL, 3.0 g, 68.1 mol) was added dropwise. The reaction mixture was allowed to warm to ambient temperature, then it was aged under argon for 3 h, filtered through Celite®, and the solvent was removed *in vacuo*. The resulting black oily residue **B** (4.26 g) was directly used in the following reacton step without purification. C₉H₁₂N₂O, M_r = 164.20; LCMS (ESI) (method 2) *t*R: 1.95 min (UV254), *m/z*: 165.2 [M+H]⁺.



4-chloro-*N'*-ethylidene-*N*-(4-methoxyphenyl)benzohydrazide (**C**).²

4-chlorobenzoyl chloride (8.74 g, 49.9 mmol) was added dropwise at 10°C under argon to a stirred solution of 1-ethylidene-2-(4-methoxyphenyl)hydrazine **B** (4.1 g, 25.0 mol) in pyridine (13 mL). The mixture was stirred at room temperature for 2 h, and then it was quenched with water (37 mL). The acylated hydrazon product was extracted into dichloromethane (2 x 40 mL), the combined organic extracts were washed with water (2 x 20 mL), dried (MgSO₄), and the solvent was evaporated under reduce pressure. The residual black oil (11.76 g, residual pyridine) was chromatographed on silica using a 3+7 mixture of ethyl acetate and hexane as eluant. Appropriate fractions were collected and

concentrated to yield the title compound **C** (3.27 g, 43%) as a yellow-orange solid. $C_{16}H_{15}ClN_2O_2$, $M_r = 302.76$; 1H NMR (400 MHz, $DMSO-d_6$) δ : 1.76 (d, $J=5.2$ Hz, 3H, =CH-CH₃), 3.80 (s, 3H, -OCH₃), 6.71 (q, $J=5.2$ Hz, 1H, =CH-), 7.07-7.10 (m, 2H, Ar-H, Phe), 7.17-7.21 (m, 2H, Ar-H), 7.48-7.50 (m, 2H, Ar-H), 7.66 (d, $J=8.4$ Hz, 2H, Ar-H, benzoyl); ^{13}C NMR (100 MHz, $DMSO-d_6$) δ : 18.58 (s), 55.79 (s), 115.58 (s, 2C), 127.97 (s, 2C), 131.00 (s, 2C), 131.35 (s, 2C), 134.97 (s), 135.20 (s), 159.74 (s), (4 carbons invisible); LCMS (ESI) (method 2) tR : 2.67 min (94%, ELSD), m/z : 303.1 [M+H]⁺.

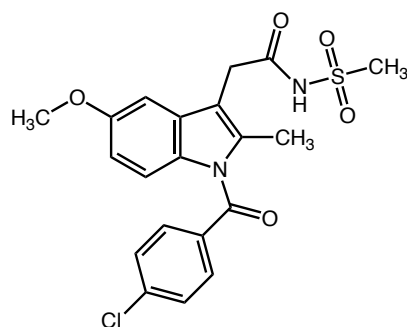


4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (D**).**²

Dry hydrogen chloride gas was bubbled through a chilled (5-0°C) solution of 4-chloro-*N*-ethylidene-*N*-(4-methoxyphenyl)benzohydrazide **C** (3.25 g, 10.73 mmol) in methylene chloride (80 mL) for 90 min. The solvent was evaporated *in vacuo* and the residual solid was repeatedly triturated with diethyl ether (3 x 30 mL). The resulting white to bright beige solid was collected by filtration and dried *in vacuo* to give 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride **D** in 99% yield (3.34 g). $C_{14}H_{14}Cl_2N_2O_2$, 313.18; 1H NMR (400 MHz, $DMSO-d_6$) δ : 3.72 (s, 3H, -OCH₃), 6.89-6.93 (m, 2H), 7.30-7.39 (m, 6H); LCMS (ESI) (method 2) tR : 2.03 min (95%, UV220, UV254), m/z (base): 277.1 [M+H]⁺.

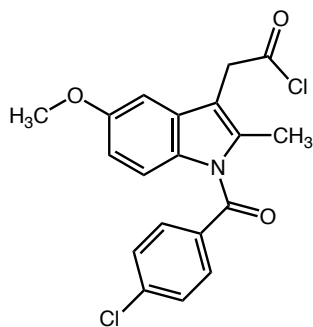
Fischer Indolization Products (free acid analogs) and (substituted) Aryl-/Alkyl-Sulfonimide

Derivatives as COOH Bioisosters:



2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-(methylsulfonyl)acetamide (14).

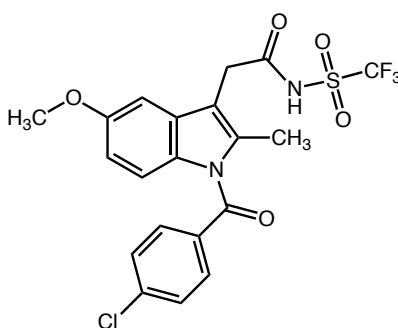
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (INDO) (60 mg, 0.17 mmol) and methansulfonamide (16 mg, 0.17 mmol) after 20 h at room temperature. The crude product was purified by flash chromatography (SiO₂, ethyl acetate/hexane gradient). Yield: 55 mg (75%), a white solid: C₂₀H₁₉ClN₂O₅S, M_r = 434.89; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.23 (s, 3H), 3.24 (s, 3H), 3.72 (s, 2H), 3.76 (s, 3H), 6.71 (dd, *J*=2.4/8.8 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 1H), 7.08 (d, *J*=2.8 Hz, 1H), 7.63-7.69 (m, 4H); LCMS (ESI) (method 2) *t*R: 2.55 min (>99%, UV220, UV254), *m/z*: 435.0 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl chloride.

In accordance with general procedure C: Oxalyl chloride (144 μL, 1.68 mmol) was added dropwise to a solution of 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (500 mg, 1.40 mmol) in 5 mL of dry CH₂Cl₂ under argon. The reaction mixture was stirred for 8 h at room temperature. The

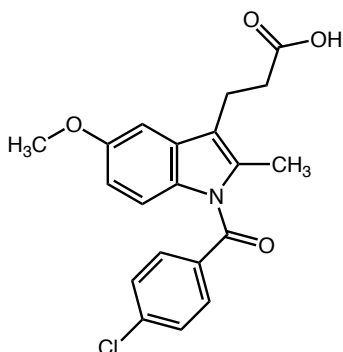
solvent was evaporated and the crude material first washed with hexane (3x2 mL) and then elutriated with a little methanol to remove residual starting material. The so purified product (yellowish-beige solid) was dried *in vacuo*. Yield: 503 mg (96%). C₁₉H₁₅Cl₂NO₃, M_r = 376.23; ¹H NMR (400 MHz, CDCl₃) δ: 2.43 (s, 3H, C2'-CH₃), 3.85 (s, 3H, -OCH₃), 4.19 (s, 2H, -CH₂-), 6.71 (dd, J=2.4/8.5 Hz, 1H, C6'-H), 6.87 (d, J=8.8 Hz, 1H, C7'-H), 6.89 (d, J=2.4 Hz, 1H, C4'-H), 7.48-7.53 (m, 2H, ar-H acyl moiety), 7.66-7.72 (m, 2H, ar-H acyl moiety); LCMS (ESI) (method 2) *t*R: 2.80 min (99%, ELSD), *m/z*: 372.2 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)-N-((trifluoromethyl)sulfonyl)acetamide (15).

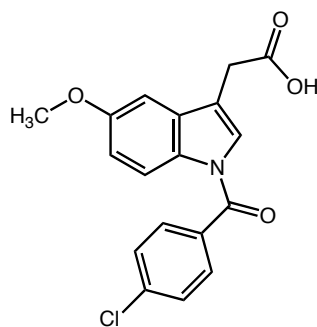
In accordance with general procedure D: 95 mg (0.27 mmol) 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetyl chloride and 59.4 mg (0.40 mmol) trifluoromethanesulfonamide were dissolved in 2 mL 1,2-dichloro ethane (DCE) under stirring. Then 21 mg (0.27 mmol) pyridine were added and the reaction was allowed to run at ambient temperature until the starting material was consumed (overnight). After the addition of 16 μL of AcOH to the organic solution was washed with H₂O (3x2 mL), dried over Na₂SO₄, filtered and the concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO₂, ethyl acetate/hexane, 0.5% AcOH gradient) and the fractionated product treated with a little aqueous NaHCO₃ to afford the title compound in 76% yield (94 mg). C₂₀H₁₆ClF₃N₂O₅S, M_r = 488.86; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.16 (s, 3H, C2'-CH₃), 3.43 (s, 2H, -CH₂-), 3.74 (s, 3H, -OCH₃), 6.69 (dd, J=2.4/9.0 Hz, 1H, C6'-H), 6.94 (d, J=8.8 Hz, 1H, C7'-H), 7.03 (d,

$J=2.4$ Hz, 1H, C4'-H), 7.61-7.67 (m, 4H, ar-H acyl moiety); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ : -75.52 (s, $-\text{CF}_3$); LCMS (ESI) (method 2) t_R : 2.45 min (91%, UV254, ELSD), m/z : 489.0 $[\text{M}+\text{H}]^+$.



3-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)propanoic acid (16).

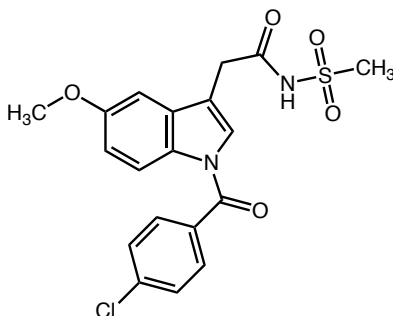
According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (50 mg, 0.16 mmol), 5-oxohexanoic acid (25 mg, 0.19 mmol) in AcOH (0.5 mL) after 3 h at 80 °C in 69% yield (41 mg) as an off-white solid. $\text{C}_{20}\text{H}_{18}\text{ClNO}_4$, $M_r = 371.81$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 2.19 (s, 3H, C2'- CH_3), 2.49 (t, $J=7.4$ Hz, 2H, overlaid by DMSO-signal), 2.88 (t, $J=7.4$ Hz, 2H), 3.77 (s, 3H, $-\text{OCH}_3$), 6.69 (dd, $J=2.6$ Hz, 1H), 6.93 (d, $J=8.8$ Hz, 1H), 7.06 (d, $J=2.4$ Hz, 1H), 7.61-7.64 (m, 4H); LCMS (ESI) (method 2) t_R : 2.69 min (>99%, UV220, UV254), m/z : 372.0 $[\text{M}+\text{H}]^+$.



2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid (20)

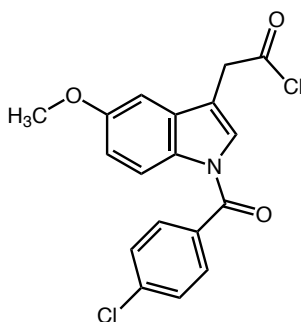
According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (200 mg, 0.64 mmol), 4-oxobutanoic acid (succinic

semialdehyde, 15% solution in H₂O; 565 mg, 0.83 mmol) in AcOH (1.5 mL) after 3 h at 80 °C in 45% yield (99 mg) as an off-white solid. C₁₈H₁₄ClNO₄, Mr = 343.76; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.67 (s, 2H), 3.81 (s, 3H), 6.99 (dd, *J*=2.4/9.2 Hz, 1H), 7.12 (d, *J*=2.4 Hz, 1H), 7.32 (s, 1H), 7.65-7.77 (m, 4H), 8.17 (d, *J*=9.2 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.60 min (>99%, ELSD), *m/z*: 344.0 [M+H]⁺.



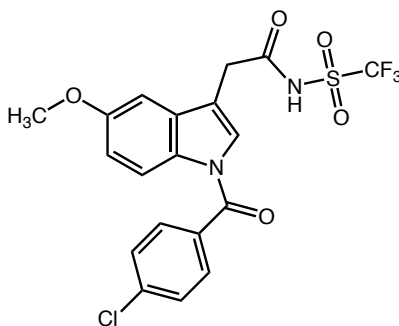
2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-(methylsulfonyl)acetamide (26).

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (100 mg, 0.29 mmol) and methanesulfonamide (28 mg, 0.29 mmol) after 20 h at room temperature. The crude product was purified by recrystallization from methanol. Yield: 44 mg (36%), a white solid: C₁₉H₁₇ClN₂O₅S, M_r = 420.87; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.20 (s, 3H), 3.69 (s, 2H), 3.81 (s, 3H), 7.00 (dd, *J*=2.4/9.0 Hz, 1H), 7.12 (d, *J*=2.4 Hz, 1H), 7.33 (s, 1H), 7.66-7.69 (m, 2H), 7.75-7.77 (m, 2H), 8.18 (d, *J*=8.8 Hz, 1H); HPLC (method 1), *t*R: 7.64 min (98%, UV254), ESI/MS (detector injection, positive ion mode): calcd mass for C₁₉H₁₇ClN₂O₅S [M+H]⁺: 421.06, found: 421.0.



2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetyl chloride.

In accordance with general procedure C: Oxalyl chloride (30 μ L, 0.35 mmol) was added dropwise to a solution of 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (100 mg, 0.29 mmol) in 2 mL of dry CH₂Cl₂ under argon. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the crude product was washed with dry hexane (3x1 mL) and dried *in vacuo* to give the title compound (pale white solid) in 95% yield (100 mg). C₁₈H₁₃Cl₂NO₃, M_r = 362.21; ¹H NMR (400 MHz, CDCl₃) δ : 3.90 (s, 3H), 4.21 (s, 2H), 6.95 (d, *J*=2.4 Hz, 1H), 7.04 (dd, *J*=2.4/9.0 Hz, 1H), 7.29 (s, 1H), 7.52-7.55 (m, 2H), 7.67-7.71 (m, 2H), 8.29 (d, *J*=9.2 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.72 min (>99%, UV254), *m/z*: 358.2 [M+H]⁺.



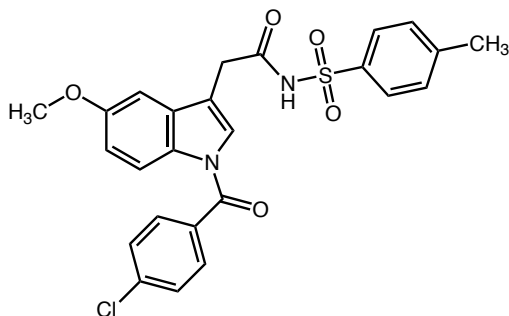
2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((trifluoromethyl)sulfonyl) acetamide (27**).**

In accordance with general procedure D:*) 80 mg (0.22 mmol) 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetyl chloride and 49.4 mg (0.33 mmol) trifluoromethanesulfonamide were dissolved in 1.8 mL 1,2-dichloro ethane (DCE) under stirring. Then 17.5 mg (0.22 mmol) pyridine were added and the reaction was allowed to run at ambient temperature until the starting material was consumed (~ 4 h). After the addition of 13 μ L of AcOH to the organic solution was washed with H₂O (3x2 mL), dried over Na₂SO₄, filtered and the concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO₂, ethyl acetate/hexane, 0.5% AcOH gradient) to afford the title compound in 70% yield (73 mg). C₁₉H₁₄ClF₃N₂O₅S, M_r = 474.84; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 3.44 (s, 2H), 3.79 (s, 3H), 6.95 (dd, *J*=2.6/9.0 Hz, 1H), 7.14 (d, *J*=2.4 Hz, 1H), 7.23 (s, 1H), 7.64-7.66 (m, 2H), 7.72-7.74 (m,

2H), 8.15 (d, $J=8.8$ Hz, 1H, C7'-H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ : -75.58 (s, $-\text{CF}_3$); LCMS (ESI)

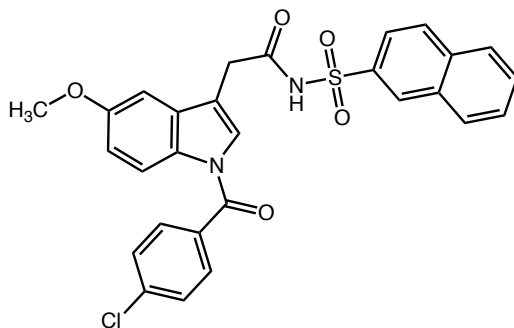
(method 2) $t\text{R}$: 2.37 min (>99%, UV254, ELSD), m/z : 475.0 $[\text{M}+\text{H}]^+$.

*) Alternatively, 2.8 mg (7%) of the title compound were obtained *via* general procedure B (starting from 30 mg of compound **20**) and subsequent automated mass-directed HPLC purification.



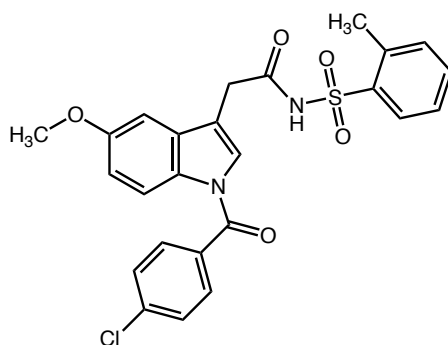
2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)-N-tosylacetamide (**28**).

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-methylbenzenesulfonamide (14.9 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/ H_2O gradient). Yield: 14.7 mg (34%). $\text{C}_{25}\text{H}_{21}\text{ClN}_2\text{O}_5\text{S}$, $M_r = 496.96$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 2.36 (s, 3H), 3.62 (s, 2H), 3.74 (s, 3H), 6.90 (d, $J=2.4$ Hz, 1H), 6.97 (dd, $J=2.6/9.0$ Hz, 1H), 7.23 (s, 1H), 7.34 (d, $J=8.0$ Hz, 1H), 7.65-7.68 (m, 2H), 7.71-7.75 (m, 4H), 8.14 (d, $J=8.8$ Hz, 1H); LCMS (ESI) (method 2) $t\text{R}$: 2.90 min (98%, UV254, ELSD), m/z : 497.0 $[\text{M}+\text{H}]^+$.



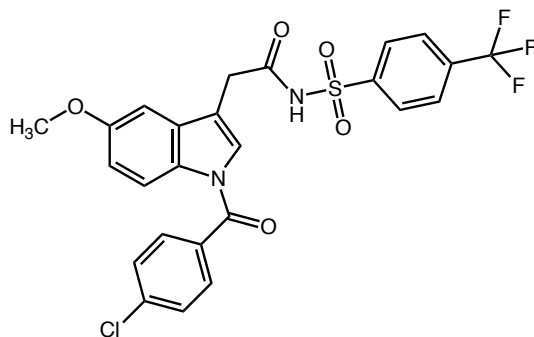
2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)-N-(naphthalen-2-ylsulfonyl)acetamide (**29**).

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and naphthalene-2-sulfonamide (18.1 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 21 mg (45%). C₂₈H₂₁ClN₂O₅S, M_r = 532.99; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.64 (s, 3H), 3.65 (s, 2H), 6.87 (d, *J*=2.4 Hz, 1H), 6.92 (dd, *J*=2.6/9.0 Hz, 1H), 7.21 (s, 1H), 7.61-7.75 (m, 6H), 7.82 (dd, *J*=2.0/8.8 Hz, 1H), 8.02-8.16 (m, 4H), 8.55 (d, *J*=1.6 Hz, 1H); LCMS (ESI) (method 2) *t*R: 3.01 min (98%, UV254, ELSD), *m/z*: 533.1 [M+H]⁺.



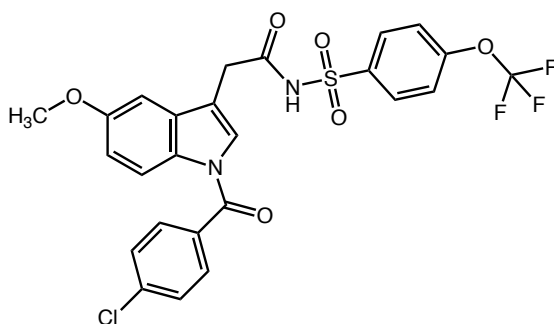
2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-(*o*-tolylsulfonyl)acetamide (30**).**

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 2-methylbenzenesulfonamide (14.9 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 17 mg (39%). C₂₅H₂₁ClN₂O₅S, M_r = 496.96; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.47 (s, 3H), 3.65 (s, 2H), 3.74 (s, 3H), 6.90 (d, *J*=2.8 Hz, 1H), 6.97 (dd, *J*=2.6/9.0 Hz, 1H), 7.21 (s, 1H), 7.29 (d, *J*=7.6 Hz, 1H), 7.35 (t, *J*=7.8 Hz, 1H), 7.51 (td, *J*=7.6 Hz, 1H), 7.65-7.74 (m, 4H), 7.89 (dd, *J*=1.4/7.8 Hz, 1H), 8.14 (d, *J*=9.2 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.89 min (99%, UV254, ELSD), *m/z*: 497.0 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((4-(trifluoromethyl)phenyl)sulfonyl)-acetamide (31).

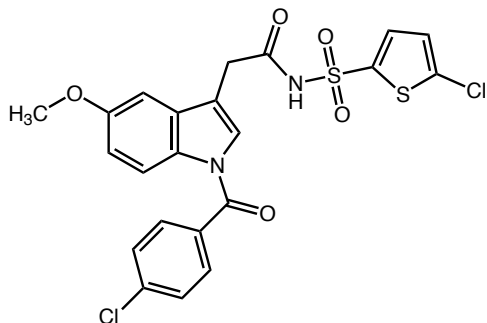
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-(trifluoromethyl)benzenesulfonamide (19.7 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 20.5 mg (43%). C₂₅H₁₈ClF₃N₂O₅S, M_r = 550.93; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.67 (s, 2H), 3.72 (s, 3H), 6.86 (d, *J*=2.4 Hz, 1H), 6.96 (dd, *J*=2.8/9.0 Hz, 1H), 7.25 (s, 1H), 7.64-7.75 (m, 4H), 7.95 (d, *J*=8.4 Hz, 1H), 8.08 (d, *J*=8.4 Hz, 1H), 8.14 (d, *J*=8.8 Hz, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ: -59.94 (s, CF₃); LCMS (ESI) (method 2) *t*R: 3.05 min (98%, UV254, ELSD), *m/z*: 551.0 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((4-(trifluoromethoxy)phenyl)sulfonyl)-acetamide (32).

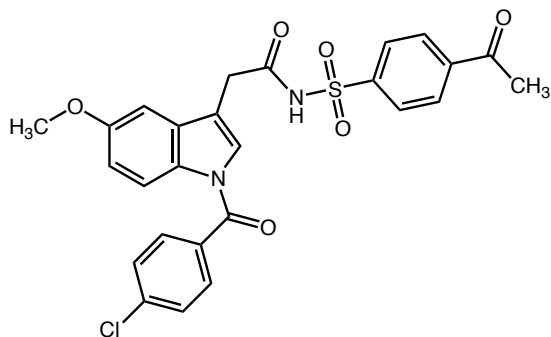
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-(trifluoromethoxy)benzenesulfonamide (21 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by

automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 25.4 mg (51%). C₂₅H₁₈ClF₃N₂O₆S, M_r = 566.93; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.66 (s, 2H), 3.74 (s, 3H), 6.89 (d, *J*=2.4 Hz, 1H), 6.97 (dd, *J*=2.6/9.0 Hz, 1H), 7.24 (s, 1H), 7.55 (dd, *J*=0.8/8.8 Hz, 1H), 7.64-7.75 (m, 4H), 7.99-8.02 (m, 2H), 8.14 (d, *J*=9.2 Hz, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ: -54.88 (s, OCF₃); LCMS (ESI) (method 2) *t*R: 3.08 min (98%, UV254, ELSD), *m/z*: 567.0 [M+H]⁺.



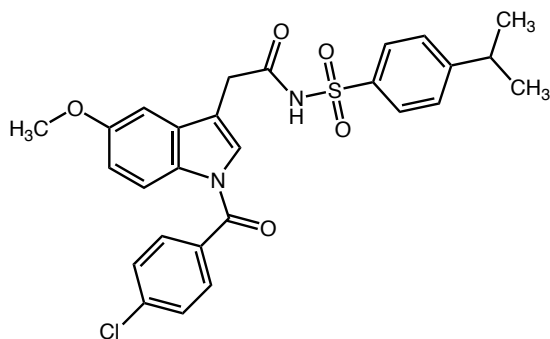
2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((5-chlorothiophen-2-yl)sulfonyl)acetamide (33).

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 5-chlorothiophene-2-sulfonamide (17.2 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 17.7 mg (39%). C₂₂H₁₆Cl₂N₂O₅S₂, M_r = 523.41; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.68 (s, 2H), 3.77 (s, 3H), 6.96 (d, *J*=2.4 Hz, 1H), 6.99 (dd, *J*=2.6/9.0 Hz, 1H), 7.22 (d, *J*=4.0 Hz, 1H), 7.27 (s, 1H), 7.62 (d, *J*=4.0 Hz, 1H), 7.66-7.76 (m, 4H), 8.16 (d, *J*=8.8 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.99 min (99%, UV254, ELSD), *m/z*: 522.9 [M+H]⁺.



***N*-((4-acetylphenyl)sulfonyl)-2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetamide (34).**

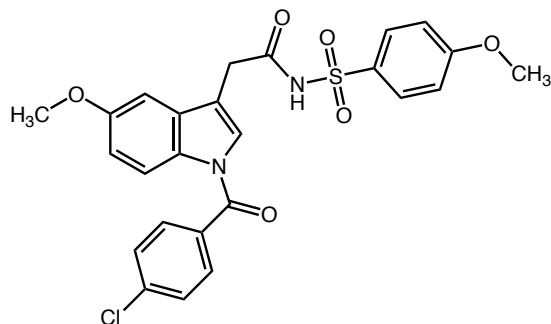
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-acetylbenzenesulfonamide (17.3 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 21.5 mg (47%). C₂₆H₂₁ClN₂O₆S, M_r = 524.97; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.61 (s, 3H), 3.65 (s, 2H), 3.72 (s, 3H), 6.87 (d, *J*=2.4 Hz, 1H), 6.96 (dd, *J*=2.6/9.0 Hz, 1H), 7.24 (s, 1H), 7.64-7.75 (m, 4H), 7.96-7.98 (m, 2H), 8.05-8.08 (m, 2H), 8.13 (d, *J*=8.8 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.78 min (>99%, UV254, ELSD), *m/z*: 525.1 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((4-isopropylphenyl)sulfonyl)acetamide (35).

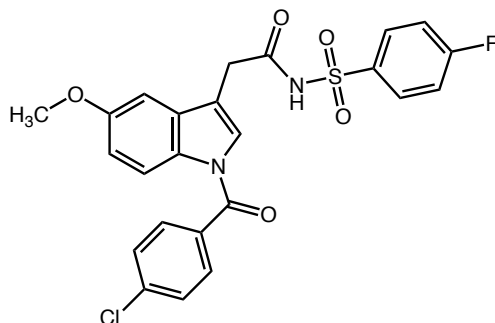
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-isopropylbenzenesulfonamide (17.3 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 19.8 mg (43%). C₂₇H₂₅ClN₂O₅S, M_r = 525.02; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.18 (d, *J*=6.8 Hz, 6H), 2.95 (sept, *J*=6.8 Hz, 1H), 3.64 (s, 2H), 3.74 (s,

3H), 6.92 (d, $J=2.8$ Hz, 1H), 6.97 (dd, $J=2.6/9.0$ Hz, 1H), 7.25 (s, 1H), 7.42 (d, $J=8.4$ Hz, 2H), 7.65-7.75 (m, 4H), 7.76-7.80 (m, 2H), 8.14 (d, $J=8.8$ Hz, 1H); LCMS (ESI) (method 2) t_R : 3.11 min (98%, UV254, ELSD), m/z : 525.1 $[M+H]^+$.



2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)-N-((4-methoxyphenyl)sulfonyl)acetamide (36).

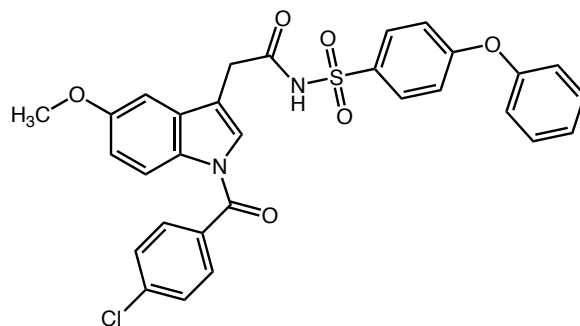
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-methoxybenzenesulfonamide (16.3 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 18.3 mg (41%). C₂₅H₂₁ClN₂O₆S, $M_r = 512.96$; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 3.61 (s, 2H), 3.74 (s, 3H), 3.82 (s, 3H), 6.90 (d, $J=2.4$ Hz, 1H), 6.97 (dd, $J=2.6/9.0$ Hz, 1H), 7.03-7.07 (m, 2H), 7.23 (s, 1H), 7.65-7.74 (m, 4H), 7.77-7.81 (m, 2H), 8.14 (d, $J=8.8$ Hz, 1H); LCMS (ESI) (method 2) t_R : 2.84 min (99%, UV254, ELSD), m/z : 513.1 $[M+H]^+$.



2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)-N-((4-fluorophenyl)sulfonyl)acetamide (37).

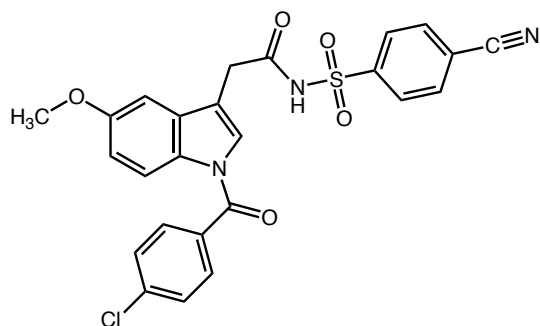
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-fluorobenzenesulfonamide (15.2 mg,

0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 15.1 mg (35%). C₂₄H₁₈ClFN₂O₅S, M_r = 500.93; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.64 (s, 2H), 3.74 (s, 3H), 6.88 (d, *J*=2.8 Hz, 1H), 6.97 (dd, *J*=2.6/9.0 Hz, 1H), 7.22 (s, 1H), 7.37-7.43 (m, 2H), 7.65-7.75 (m, 4H), 7.91-7.96 (m, 2H), 8.14 (d, *J*=8.8 Hz, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ: -102.85 (s, 4-F-Phe sulfonyl); LCMS (ESI) (method 2) *t*R: 2.87 min (>99%, UV254, ELSD), *m/z*: 501.0 [M+H]⁺.



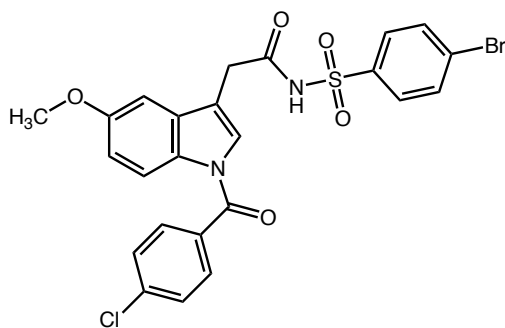
2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)-*N*-((4-phenoxyphenyl)sulfonyl)acetamide (38).

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-phenoxybenzenesulfonamide (21.7 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 20.5 mg (41%). C₃₀H₂₃ClN₂O₆S, M_r = 575.03; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.64 (s, 2H), 3.75 (s, 3H), 6.92 (d, *J*=2.4 Hz, 1H), 6.98 (dd, *J*=2.4/9.2 Hz, 1H), 7.03-7.07 (m, 2H), 7.09-7.12 (m, 2H), 7.25-7.29 (m, 2H), 7.44-7.49 (m, 2H), 7.64-7.75 (m, 4H), 7.84-7.87 (m, 2H), 8.15 (d, *J*=9.2 Hz, 1H); LCMS (ESI) (method 2) *t*R: 3.14 min (>99%, UV254, ELSD), *m/z*: 575.1 [M+H]⁺.



2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)-N-((4-cyanophenyl)sulfonyl)acetamide (39).

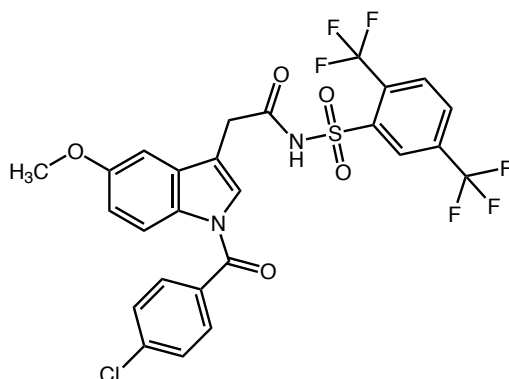
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-cyanobenzenesulfonamide (15.9 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 16.7 mg (38%). C₂₅H₁₈ClN₃O₅S, M_r = 507.95; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.66 (s, 2H), 3.75 (s, 3H), 6.85 (d, *J*=2.4 Hz, 1H), 6.97 (dd, *J*=2.6/9.0 Hz, 1H), 7.24 (s, 1H), 7.65-7.75 (m, 4H), 7.99-8.05 (m, 4H), 8.14 (d, *J*=9.2 Hz, 1H); LCMS (ESI) (method 2) *t*R: 2.80 min (99%, UV254, ELSD), *m/z*: 508.0 [M+H]⁺.



N-((4-bromophenyl)sulfonyl)-2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetamide (40).

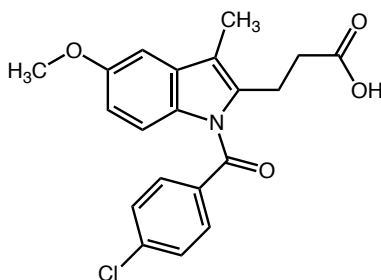
According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 4-bromobenzenesulfonamide (20.5 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 22.3 mg (45%). C₂₄H₁₈BrClN₂O₅S, M_r = 561.83; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 3.65 (s, 2H), 3.75 (s, 3H), 6.88 (d, *J*=2.8 Hz, 1H), 6.97 (dd, *J*=2.6/9.0

Hz, 1H), 7.24 (s, 1H), 7.65-7.75 (m, 4H), 7.78 (pseudo-s, 4H), 8.14 (d, $J=8.8$ Hz, 1H); LCMS (ESI) (method 2) t_R : 3.02 min (>99%, UV254, ELSD), m/z : 562.9 [M+H]⁺.



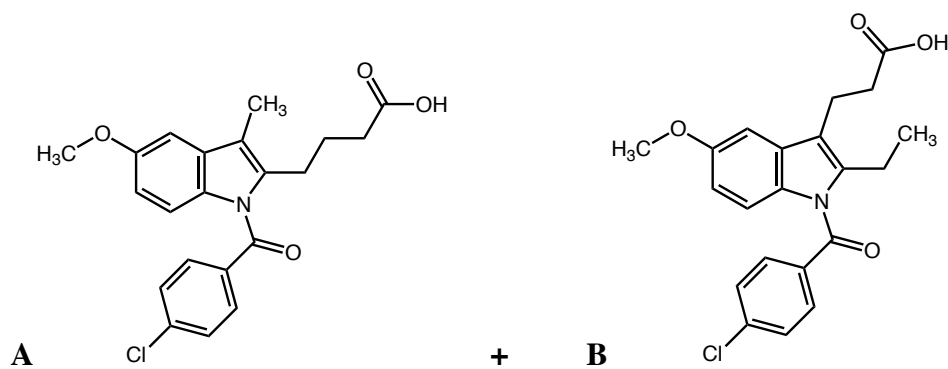
***N*-((2,5-bis(trifluoromethyl)phenyl)sulfonyl)-2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetamide (41).**

According to general procedure B, the title compound was obtained from 2-(1-(4-chlorobenzoyl)-5-methoxy-1*H*-indol-3-yl)acetic acid **20** (30 mg, 0.087 mmol) and 2,5-bis(trifluoromethyl)benzenesulfonamide (25.5 mg, 0.087 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 20.1 mg (37%). C₂₆H₁₇ClF₆N₂O₅S, $M_r = 618.93$; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 3.67 (s, 2H), 3.73 (s, 3H), 6.85 (d, $J=2.4$ Hz, 1H), 6.96 (dd, $J=2.6/9.0$ Hz, 1H), 7.23 (s, 1H), 7.64-7.74 (m, 4H), 8.14 (pseudo-d, $J=8.8$ Hz, 2H), 8.27 (d, $J=8.4$ Hz, 1H), 8.43 (s, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ : -60.41 (s, *o*-CF₃), -55.09 (s, *m*-CF₃); LCMS (ESI) (method 2) t_R : 3.15 min (99%, UV254, ELSD), m/z : 619.0 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid (44).

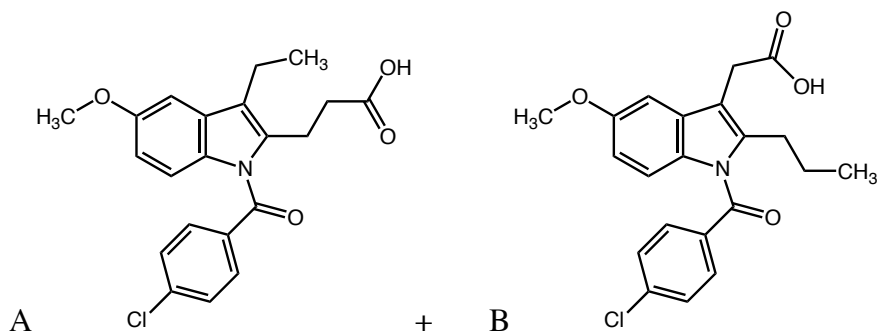
According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (400 mg, 1.28 mmol), 4-oxohexanoic acid (200 mg, 1.54 mmol) in AcOH (4 mL) after 3 h at 80 °C in 75% yield (368 mg) as an off-white solid. C₂₀H₁₈ClNO₄, M_r = 371.81; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.20 (s, 3H), 2.46 (t, *J*=7.2 Hz, 2H), 3.08 (t, *J*=7.6 Hz, 2H), 3.75 (s, 3H), 6.44 (d, *J*=8.8 Hz), 6.63 (dd, *J*=2.4/9.0 Hz, 1H), 7.01 (d, *J*=2.4 Hz, 1H), 7.63-7.68 (m, 4H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ: 8.78 (s, -CH₃), 21.61 (s, -CH₂-), 34.12 (s, -CH₂CO), 55.81 (s, -OCH₃), 101.93 (s, C4' indole), 111.97 (s, C6' indole), 114.76 (s, C7' indole), 116.11 (s, C3' indole), 129.53 (s, C3'/C5' 4-Cl-benzoyl-), 130.63 (s), 131.58 (s), 131.62 (s, C2'/C6' 4-Cl-benzoyl-), 134.42 (s), 137.09 (s), 138.14 (s), 155.83 (s, C5' indole), 168.14 (s, >C=O), 173.77 (s, -C=O(OH)); LCMS (ESI) (method 2) *t*R: 2.68 min (99%, UV254, ELSD), *m/z*: 372.1 [M+H]⁺.



Isomer mixture (3:1): 4-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)butanoic acid (isomer A) & 3-(1-(4-chlorobenzoyl)-2-ethyl-5-methoxy-1*H*-indol-3-yl)propanoic acid (isomer B) (45).

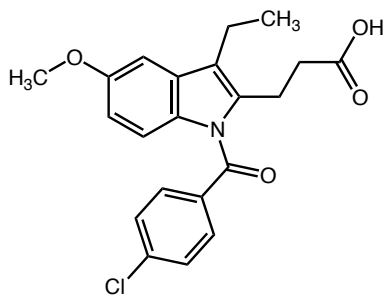
According to general procedure A, 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (100 mg, 0.32 mmol) was subjected to reaction with 5-oxoheptanoic acid (55.2 mg, 0.38 mmol) in AcOH (1 mL) for 3 h at 80 °C. The crude material was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient) to afford a 3:1-mixture of isomers A & B in 15% yield (18.5 mg) as a bright yellowish solid. C₂₁H₂₀ClNO₄, M_r = 385.84; ¹H NMR (400 MHz, DMSO-*d*₆) Isomer A: δ: 1.70 (quint, *J*=7.2 Hz, 2H), 2.14 (t, *J*=7.2 Hz, 2H), 2.19 (s, 3H), 2.86 (t, *J*=7.4 Hz, 2H), 3.76 (s, 3H), 6.49 (d, *J*=8.8

Hz, 1H), 6.64 (dd, $J=2.6/9.0$ Hz, 1H), 7.01 (d, $J=2.4$ Hz, 1H), 7.62-7.70 (m, 4H), Isomer B: δ : 1.05 (t, $J=7.4$ Hz, 3H), ~2.5 (t, $J=7.4$ Hz, 2H, peaks overlaid by DMSO signal), 2.76-2.96 (m, 4H), 3.76 (s, 3H), 6.55 (d, $J=8.8$ Hz, 1H), 6.65 (dd, $J=2.6/8.8$ Hz, 1H), 7.06 (d, $J=2.4$ Hz, 1H), 7.61-7.70 (m, 4H); LCMS (ESI) (method 2) t_R : 2.97 min (>99%, ELSD), m/z : 386.1 $[M+H]^+$.



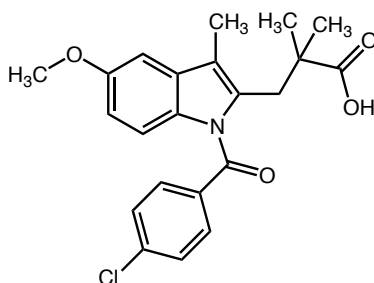
Isomer mixture: 3-(1-(4-chlorobenzoyl)-3-ethyl-5-methoxy-1H-indol-2-yl)propanoic acid (isomer A) & 2-(1-(4-chlorobenzoyl)-5-methoxy-2-propyl-1H-indol-3-yl)acetic acid (isomer B) (46).

According to general procedure A, 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (100 mg, 0.32 mmol) was subjected to reaction with 4-oxoheptanoic acid (55.2 mg, 0.38 mmol) in AcOH (1 mL) for 3 h at 80 °C. The crude material was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient) to afford a 3:1-mixture of isomers A & B in 43% yield (52.5 mg) as an off-white solid. C₂₁H₂₀ClNO₄, $M_r = 385.84$; ¹H NMR (400 MHz, DMSO-*d*₆) Isomer A: δ : 1.18 (t, $J=7.4$ Hz, 3H), 2.46 (t, $J=7.2$ Hz, 2H), 2.69 (q, $J=7.4$ Hz, 2H), 3.09 (t, $J=7.6$ Hz, 2H), 3.75 (s, 3H), 6.42 (d, $J=8.8$ Hz, 1H), 6.63 (dd, $J=2.4/9.2$ Hz, 1H), 7.03 (d, $J=2.4$ Hz, 1H), 7.63-7.69 (m, 4H), Isomer B: δ : 0.79 (t, $J=7.4$ Hz, 3H), 1.46 (quint, $J=7.6$ Hz, 2H), 2.77 (t, $J=7.6$ Hz, 2H), 3.67 (s, 2H), 3.73 (s, 3H), 6.59 (d, $J=8.8$ Hz, 1H), 6.66 (dd, $J=2.6/9.0$ Hz, 1H), 7.03 (d, $J=2.4$ Hz, 1H), 7.63-7.69 (m, 4H); LCMS (ESI) (method 2) t_R : 2.98 min (>99%, ELSD), m/z : 386.1 $[M+H]^+$.



3-(1-(4-chlorobenzoyl)-3-ethyl-5-methoxy-1H-indol-2-yl)propanoic acid (47).

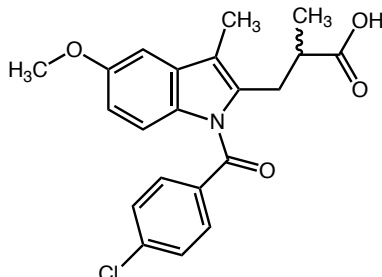
The title compound was synthesized as described for isomer mixture **46**. H₂O was added. The watery reaction mixture was extracted with methylene chloride (2x) and the combined organic phases dried over Na₂SO₄. The solvent was removed under reduced pressure and the residual beige solid repeatedly triturated with diethyl ether. The resulting white precipitation was collected by filtration (ether wash phases abolished) and dried *in vacuo* to afford **47** as a single product! Yield: 36 mg, 29%. C₂₁H₂₀ClNO₄, M_r = 385.84; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.18 (t, *J*=7.6 Hz, 3H), 2.46 (t, *J*=7.6 Hz, 2H), 2.69 (q, *J*=7.6 Hz, 2H), 3.09 (t, *J*=7.6 Hz, 2H), 3.75 (s, 3H), 6.42 (d, *J*=9.2 Hz, 1H), 6.63 (dd, *J*=2.4/9.0 Hz, 1H), 7.03 (d, *J*=2.4 Hz, 1H), 7.63 (m, 4H); LCMS (ESI) (method 2) *t*R: 2.82 min (95%, UV220, UV254), *m/z*: 386.2 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-2,2-dimethylpropanoic acid (48).

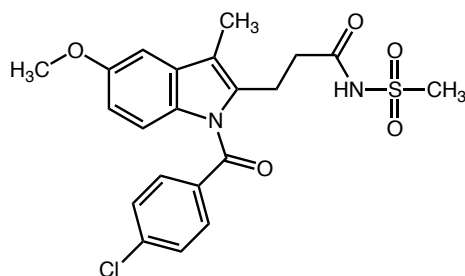
According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (50 mg, 0.16 mmol), 2,2-dimethyl-4-oxohexanoic acid (30 mg, 0.19 mmol) in AcOH (0.5 mL) after 3 h at 80 °C, extraction into hot hexane and subsequent purification by flash chromatography in 36% yield (23 mg) as a yellow oil, which crystallized constantly upon drying at high vacuum. C₂₂H₂₂ClNO₄, M_r = 399.87; ¹H NMR (400 MHz, DMSO-*d*₆) δ:

1.03 (s, 6H), 2.21 (s, 3H), 3.25 (s, 2H), 3.76 (s, 3H), 6.52 (d, $J=9.2$ Hz, 1H), 6.67 (dd, $J=2.6/9.0$ Hz, 1H), 7.03 (d, $J=2.4$ Hz, 1H), 7.64-7.68 (m, 4H); LCMS (ESI) (method 2) t_R : 2.89 min (95%, UV220, UV254), m/z : 400.0 $[M+H]^+$.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-2-methylpropanoic acid (49).

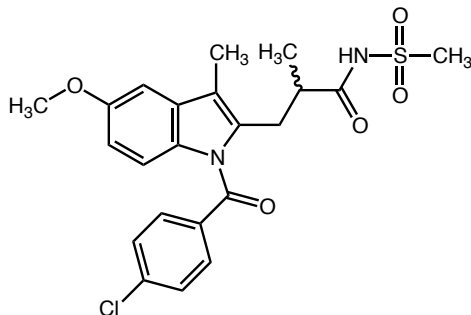
According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (50 mg, 0.16 mmol), 2-methyl-4-oxohexanoic acid (28 mg, 0.19 mmol) in AcOH (0.5 mL) after 3 h at 80 °C in 49% yield (30 mg) as a beige solid. $C_{21}H_{20}ClNO_4$, $M_r = 385.84$; 1H NMR (400 MHz, DMSO- d_6) δ : 1.01 (d, $J=6.8$ Hz, 3H, alpha- CH_3), 2.19 (s, 3H, C^3 - CH_3), 2.54 (sex, $J=7.2$ Hz, 1H, methin-H), 2.91-3.19 (m, 2H, $-CH_2-$), 3.76 (s, 3H, $-OCH_3$), 6.46 (d, $J=9.2$ Hz, 1H, C^7 -H), 6.64 (dd, $J=2.4/9.0$ Hz, 1H, C^6 -H), 7.02 (d, $J=2.4$ Hz, 1H, C^4 -H); LCMS (ESI) (method 2) t_R : 2.75 min (>97%, UV220, UV254, MSD), m/z : 386.1 $[M+H]^+$.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-*N*-(methylsulfonyl)propanamide (50).

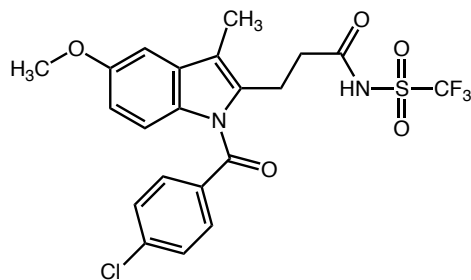
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)propanoic acid **44** (40 mg, 0.11 mmol) and methansulfonamide (10 mg, 0.11 mmol) after 20 h at room temperature. The crude product was purified by flash

chromatography (SiO₂, EtOAc:Hexane gradient = 1+1 (0.5% AcOH). Yield: 32 mg (66%), a bright yellow solid: C₂₁H₂₁ClN₂O₅S, M_r = 448.92; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.21 (s, 3H), 2.55 (t, *J*=7.2 Hz, 2H), 3.11 (t, *J*=7.2 Hz, 2H), 3.16 (s, 3H), 3.75 (s, 3H), 6.43 (d, *J*=9.2 Hz, 1H), 6.64 (dd, *J*=9.0 Hz, 1H), 7.02 (d, *J*=2.4 Hz, 1H), 7.64-7.69 (m, 4H); LCMS (ESI) (method 2) *t*R: 2.74 min (>96%, UV254, ELSD), *m/z*: 249.1 [M+H]⁺.



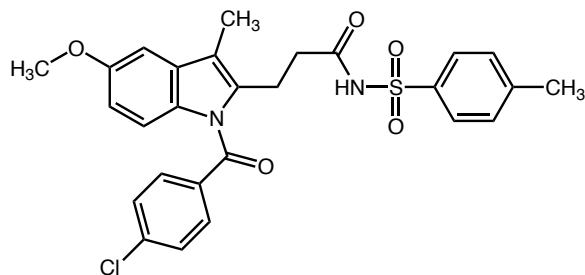
3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-2-methyl-*N*-(methylsulfonyl)propanamide (51).

According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-2-methylpropanoic acid **49** (30 mg, 0.078 mmol) and methansulfonamide (7.5 mg, 0.078 mmol) after 20 h at room temperature. The crude product was purified by flash chromatography (SiO₂, ethyl acetate/hexane gradient). Yield: 29 mg (81%), a white solid: C₂₂H₂₃ClN₂O₅S, M_r = 462.95; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 0.99 (d, *J*=6.8 Hz, 3H, -C(CH₃)CO-), 2.18 (s, 3H, C3'-CH₃), 2.66-2.74 (m, 1H), 2.85-2.93 (m, 1H), 3.09 (s, 3H, -SO₂-CH₃), 3.10-3.16 (m, 1H), 3.76 (s, 3H, -OCH₃), 6.55 (d, *J*=9.2 Hz, 1H, C7'-H), 6.67 (dd, *J*=2.6/9.0 Hz, 1H, C6'-H), 7.02 (d, *J*=2.4 Hz, 1H, C4'-H), 7.64-7.68 (m, 4H, ar-H 4-Cl-benzoyl); LCMS (ESI) (method 2) *t*R: 2.79 min (>99%, UV220, UV254), *m/z*: 463.0 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-((trifluoromethyl)sulfonyl)propanamide (52).

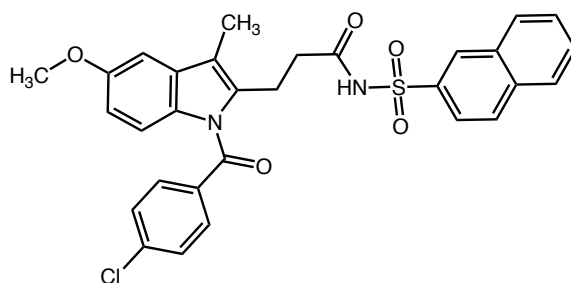
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and trifluoromethanesulfonamide (13.2 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 1 mg (2.5%). C₂₁H₁₈ClF₃N₂O₅S, M_r = 502.89; ¹H NMR (400 MHz, DMSO-*d*₆) δ: n/a; LCMS (ESI) (method 2) *t*R: 2.73 min (>95%, UV254, ELSD), *m/z*: 503.0 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-tosylpropanamide (53).

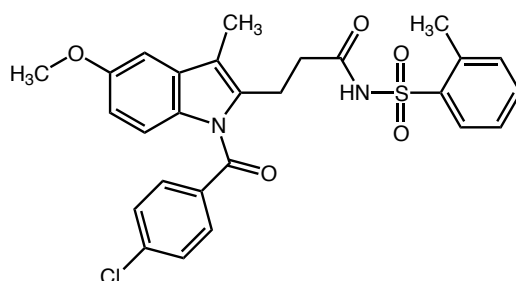
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 4-methylbenzenesulfonamide (15.2 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 23.1 mg (55%). C₂₇H₂₅ClN₂O₅S, M_r = 525.02; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.07 (s, 3H), 2.35 (s, 3H), 2.49 (t, *J*=7.2 Hz, 2H, partially overlaid by solvent signal), 2.99 (t, *J*=7.2 Hz, 2H), 3.76 (s, 3H), 6.37 (d, *J*=9.2 Hz, 1H), 6.63 (dd, *J*=2.6/9.0 Hz, 1H), 6.96 (d, *J*=2.4 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 2H), 7.57-7.64 (m,

4H), 7.69 (d, $J=8.4$ Hz, 2H); LCMS (ESI) (method 2) t_R : 3.09 min (95%, UV254, ELSD), m/z : 525.1 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-N-(naphthalen-2-ylsulfonyl)propanamide (54).

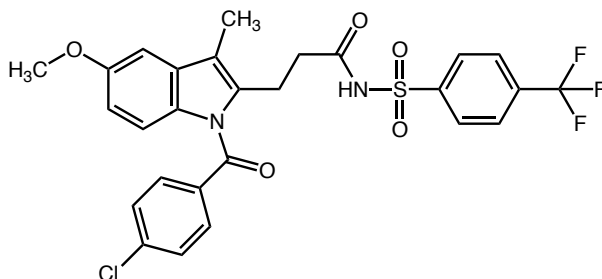
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and naphthalene-2-sulfonamide (18.4 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 3.7 mg (8%). C₃₀H₂₅ClN₂O₅S, M_r = 561.05; ¹H NMR (400 MHz, DMSO-*d*₆) δ : n/a; LCMS (ESI) (method 2) t_R : 3.18 min (>95%, UV254, ELSD), m/z : 561.1 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-N-(o-tolylsulfonyl)propanamide (55).

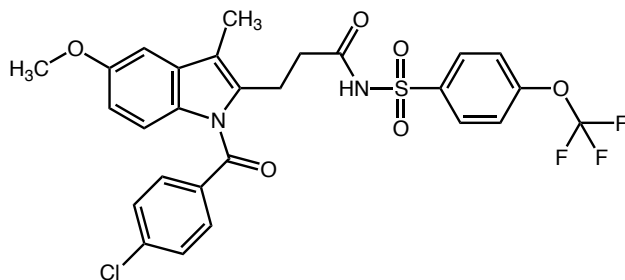
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 2-methylbenzenesulfonamide (15.2 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 9.8 mg (23%). C₂₇H₂₅ClN₂O₅S, M_r

= 525.02; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 1.93 (s, 3H), 2.29 (s, 3H), 2.53 (t, $J=6.8$ Hz, 2H), 2.99 (t, $J=7.2$ Hz, 2H), 3.78 (s, 3H), 6.42 (d, $J=9.2$ Hz, 1H), 6.65 (dd, $J=2.6/9.0$ Hz, 1H), 6.94 (d, $J=2.8$ Hz, 1H), 7.21 (d, $J=7.6$ Hz, 1H), 7.39 (t, $J=7.6$ Hz, 1H), 7.55 (td, $J=1.2/7.6$ Hz, 1H), 7.60-7.65 (m, 4H), 7.89 (dd, $J=1.2/8.0$ Hz, 1H); LCMS (ESI) (method 2) $t\text{R}$: 2.59 min (95%, UV254, ELSD), m/z : 525.1 $[\text{M}+\text{H}]^+$.



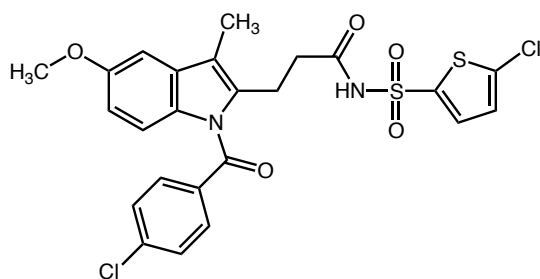
3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)-N-(4-(trifluoromethyl)phenyl)sulfonylpropanamide (56).

According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1H-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 4-(trifluoromethyl)benzenesulfonamide (20 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/ H_2O gradient). Yield: 15.5 mg (33%). $\text{C}_{27}\text{H}_{22}\text{ClF}_3\text{N}_2\text{O}_5\text{S}$, $M_r = 578.99$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ : 2.05 (s, 3H), 2.53 (t, $J=7.2$ Hz, 2H), 3.00 (t, $J=7.2$ Hz, 2H), 3.75 (s, 3H), 6.39 (d, $J=8.8$ Hz, 1H), 6.63 (dd, $J=2.6/9.0$ Hz, 1H), 6.94 (d, $J=2.8$ Hz, 1H), 7.57-7.64 (m, 4H), 7.93 (d, $J=8.4$ Hz, 2H), 8.03 (d, $J=8.0$ Hz, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ : -59.89 (s, CF_3); LCMS (ESI) (method 2) $t\text{R}$: 3.21 min (98%, UV254, ELSD), m/z : 579.1 $[\text{M}+\text{H}]^+$.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-((4-(trifluoromethoxy)phenyl)sulfonyl)propanamide (57).

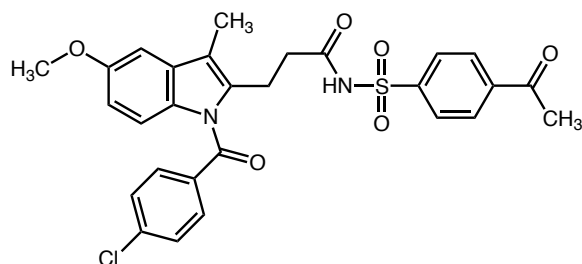
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 4-(trifluoromethoxy)benzenesulfonamide (21.4 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 15.8 mg (33%). C₂₇H₂₂ClF₃N₂O₆S, M_r = 594.99; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 2.04 (s, 3H), 2.53 (t, *J*=7.2 Hz, 2H), 3.01 (t, *J*=7.2 Hz, 2H), 3.75 (s, 3H), 6.38 (d, *J*=9.2 Hz, 1H), 6.62 (dd, *J*=2.4 Hz, 1H), 6.93 (d, *J*=2.4 Hz, 1H), 7.53 (d, *J*=8.0 Hz, 2H), 7.59-7.64 (m, 4H), 7.94-7.98 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ: -54.83 (s, OCF₃); LCMS (ESI) (method 2) *t*R: 3.27 min (97%, UV254, ELSD), *m/z*: 595.1 [M+H]⁺.



3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-((5-chlorothiophen-2-yl)sulfonyl)propanamide (58).

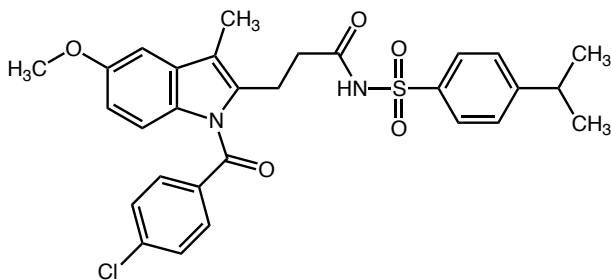
According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 5-chlorothiophene-2-sulfonamide (17.5 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 12.3 mg (28%). C₂₄H₂₀Cl₂N₂O₅S₂,

$M_r = 551.46$; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ : 2.10 (s, 3H), 2.54 (t, $J=7.2$ Hz, 2H), 3.06 (t, $J=7.2$ Hz, 2H), 3.76 (s, 3H), 6.40 (d, $J=9.2$ Hz, 1H), 6.63 (dd, $J=2.6/9.0$ Hz, 1H), 6.96 (d, $J=2.4$ Hz, 1H), 7.21 (d, $J=4.0$ Hz, 1H), 7.60 (d, $J=4.0$ Hz, 1H), 7.64 (pseudo-s, 4H); LCMS (ESI) (method 2) t_R : 3.19 min (99%, UV254, ELSD), m/z : 551.0 $[\text{M}+\text{H}]^+$.



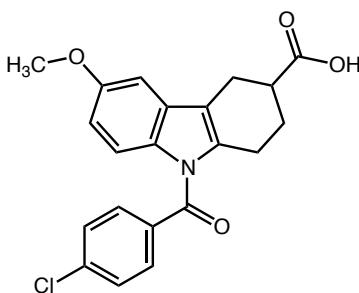
***N*-((4-acetylphenyl)sulfonyl)-3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-propanamide (59).**

According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 4-acetylbenzenesulfonamide (17.7 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/ H_2O gradient). Yield: 2 mg (4.5%). $\text{C}_{28}\text{H}_{25}\text{ClN}_2\text{O}_6\text{S}$, $M_r = 553.03$; $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ : n/a; LCMS (ESI) (method 2) t_R : 2.78 min (>95%, UV254, ELSD), m/z : 553.1 $[\text{M}+\text{H}]^+$.



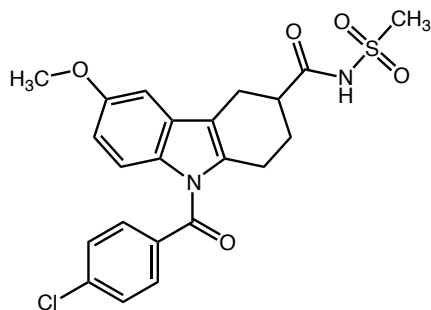
3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)-*N*-((4-isopropylphenyl)sulfonyl)-propanamide (60).

According to general procedure B, the title compound was obtained from 3-(1-(4-chlorobenzoyl)-5-methoxy-3-methyl-1*H*-indol-2-yl)propanoic acid **44** (30 mg, 0.081 mmol) and 4-isopropylbenzenesulfonamide (17.7 mg, 0.089 mmol) after 20 h at room temperature. The crude product was purified by automated mass-directed HPLC (RP-18, ACN/H₂O gradient). Yield: 7.1 mg (16%). C₂₉H₂₉ClN₂O₅S, M_r = 553.07; ¹H NMR (400 MHz, DMSO-*d*₆) δ: n/a; LCMS (ESI) (method 2) *t*R: 3.32 min (>95%, UV254, ELSD), *m/z*: 553.1 [M+H]⁺.



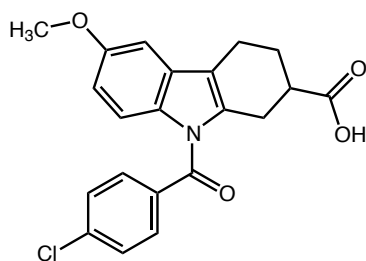
9-(4-chlorobenzoyl)-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid (61).

According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (50 mg, 0.16 mmol), 4-oxocyclohexanecarboxylic acid (27.2 mg, 0.19 mmol) in AcOH (0.5 mL) after 3 h at 80 °C in 83% yield (51 mg) as an off-white solid. C₂₁H₁₈ClNO₄, M_r = 383.82; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.66-1.76 (m, 1H), 2.02-2.08 (m, 1H), 2.52 (m, 2H, partially overlaid by DMSO signal), 2.66-2.75 (m, 2H), 2.87-2.95 (m, 1H, methin-H), 3.77 (s, 3H, -OCH₃), 6.74 (dd, *J*=2.6/9.0 Hz, 1H), 7.02 (d, *J*=2.8 Hz, 1H), 7.10 (d, *J*=8.8 Hz, 1H), 7.61-7.67 (m, 4H, ar-H 4-Cl-benzoyl); LCMS (ESI) (method 2) *t*R: 2.71 min (>99%, ELSD), *m/z*: 384.1 [M+H]⁺.



9-(4-chlorobenzoyl)-6-methoxy-*N*-(methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxamide (63).

According to general procedure B, the title compound was obtained from 9-(4-chlorobenzoyl)-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid **61** (20 mg, 0.052 mmol) and methansulfonamide (5 mg, 0.052 mmol) after 20 h at room temperature. The crude product was purified by flash chromatography (SiO₂, ethyl acetate/hexane gradient). Yield: 19 mg (79%), a white solid: C₂₂H₂₁ClN₂O₅S, M_r = 460.93; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.63-1.73 (m, 1H), 2.03-2.06 (m, 1H), 2.51-2.57 (m, 2H, partially overlaid by DMSO-signal), 2.65-2.76 (m, 2H), 2.88-2.91 (m, 1H), 3.25 (s, 3H, -SO₂-CH₃), 3.77 (s, 3H, -OCH₃), 6.74 (dd, *J*=2.6/9.0 Hz, 1H), 7.03 (d, *J*=2.8 Hz, 1H), 7.09 (d, *J*=8.8 Hz, 1H), 7.61-7.68 (m, 4H); LCMS (ESI) (method 2) *t*R: 2.65 min (>99%, UV220, UV254), *m/z*: 461.0 [M+H]⁺.



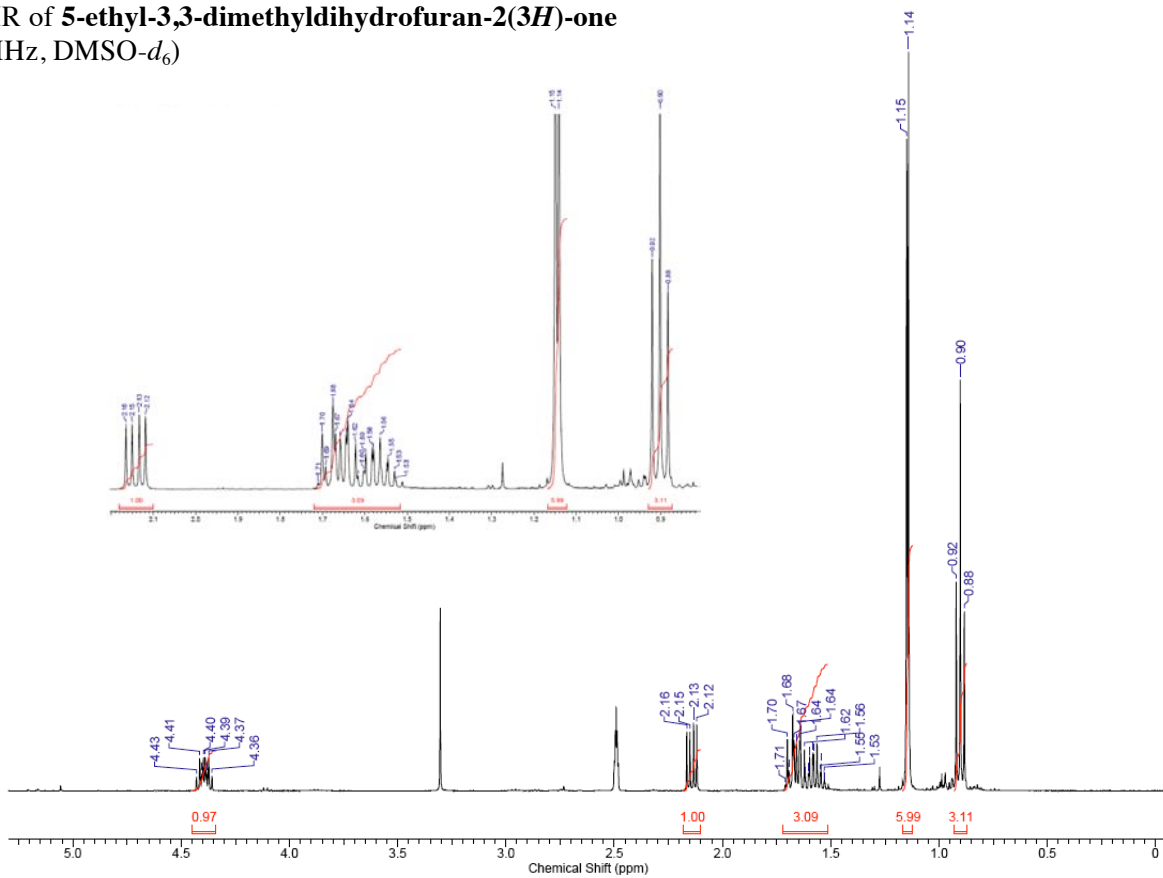
9-(4-chlorobenzoyl)-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazole-2-carboxylic acid (64).

According to general procedure A, the title compound was obtained from 4-chloro-*N*-(4-methoxyphenyl)benzohydrazide hydrochloride (50 mg, 0.16 mmol), 3-oxocyclohexanecarboxylic acid (27.2 mg, 0.19 mmol) in AcOH (0.5 mL) after 3 h at 80 °C in 82% yield (50 mg) as an off-white solid. C₂₁H₁₈ClNO₄, M_r = 383.82; ¹H NMR (400 MHz, DMSO-*d*₆) δ: 1.79-1.87 (m, 1H), 2.11-2.14 (m, 1H),

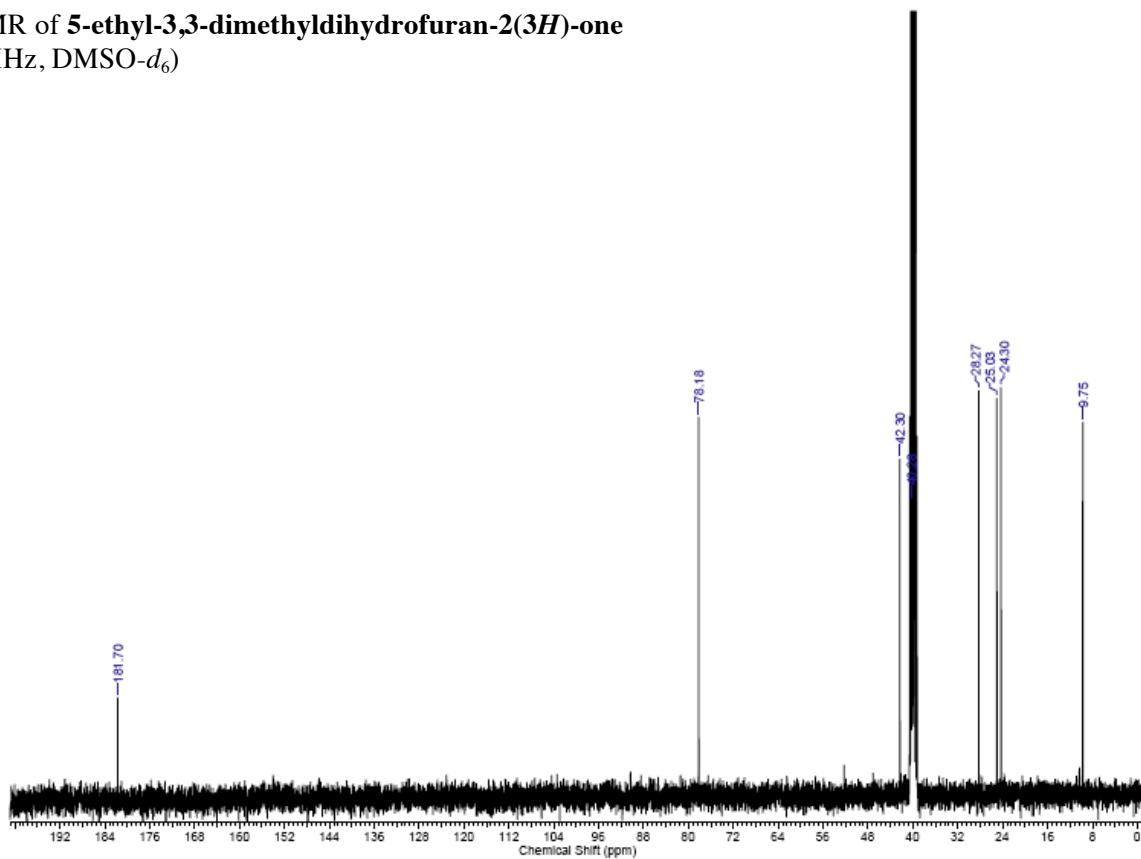
2.57-2.75 (m, 5H), 6.73 (dd, $J=2.8/9.0$ Hz, 1H), 6.97 (d, $J=2.8$ Hz, 1H), 7.06 (d, $J=9.2$ Hz, 1H), 7.62-7.69 (m, 4H); LCMS (ESI) (methid 2) t_R : 2.82 min (>99%, ELSD), m/z : 384.0 $[M+H]^+$.

^1H and ^{13}C NMR spectra (keto acids)

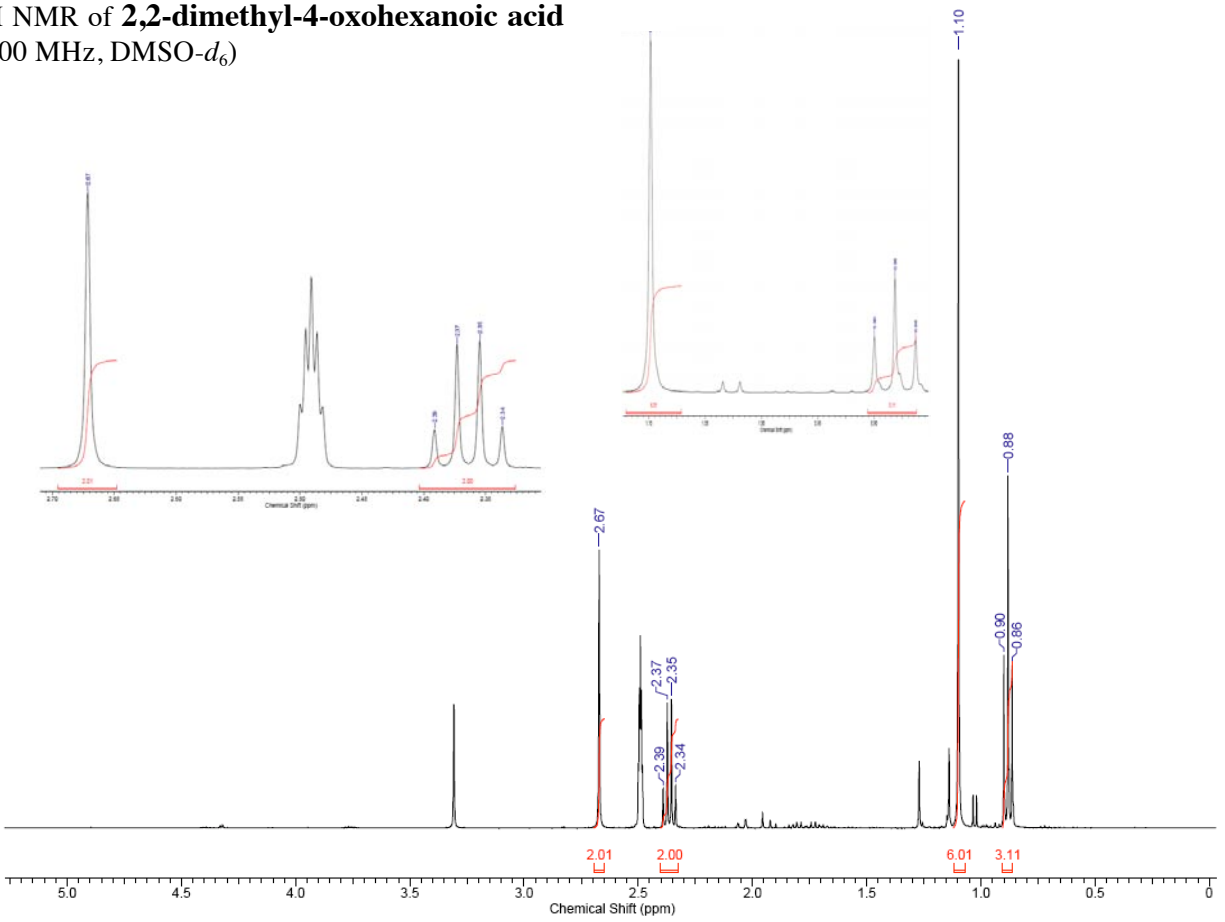
^1H NMR of **5-ethyl-3,3-dimethyldihydrofuran-2(3H)-one**
(400 MHz, $\text{DMSO-}d_6$)



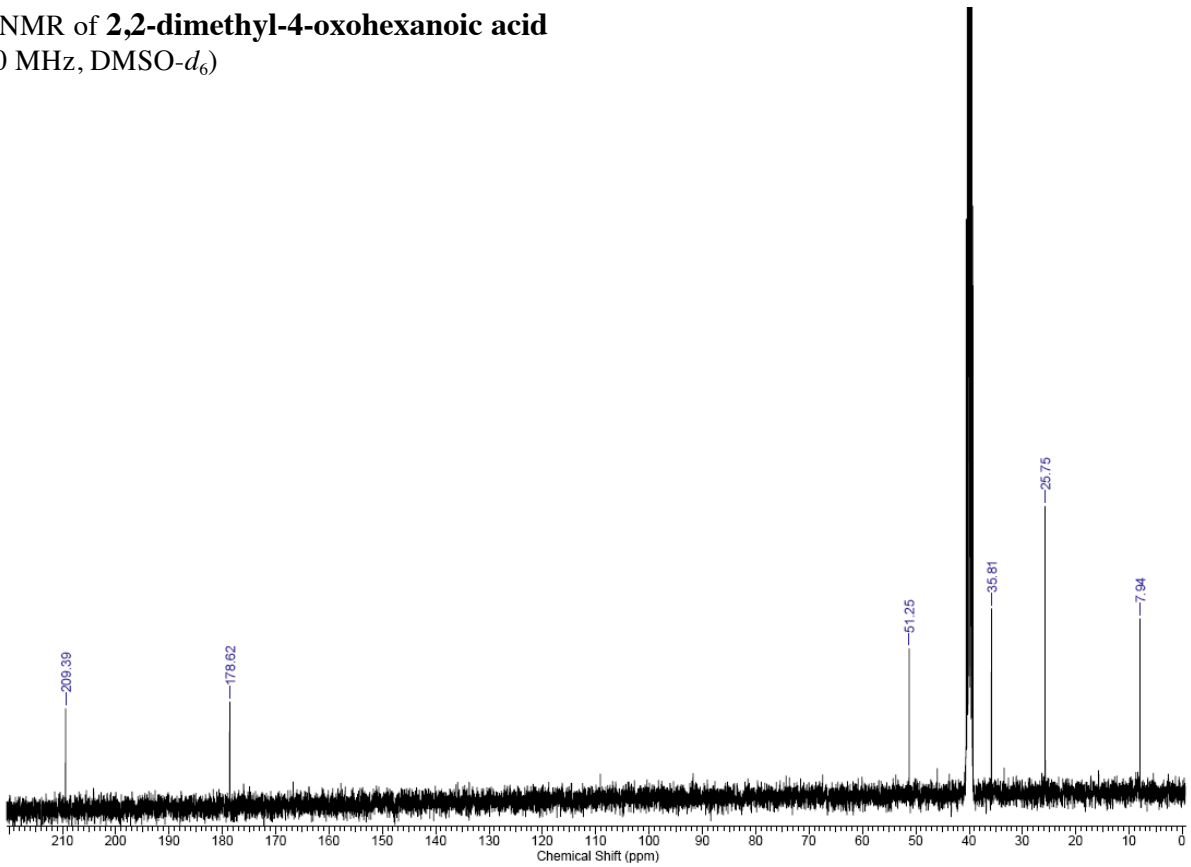
^{13}C NMR of **5-ethyl-3,3-dimethyldihydrofuran-2(3H)-one**
(100 MHz, $\text{DMSO-}d_6$)



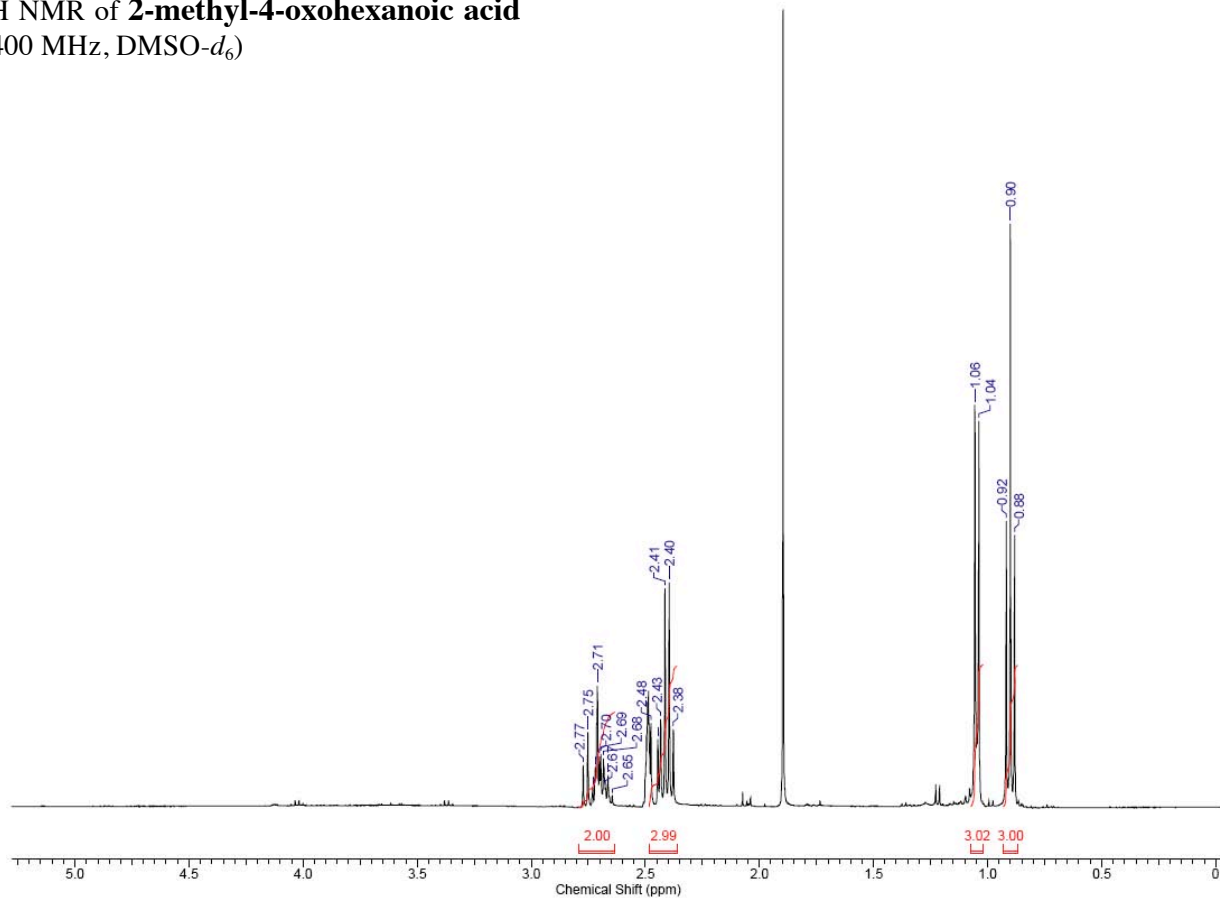
¹H NMR of **2,2-dimethyl-4-oxohexanoic acid**
(400 MHz, DMSO-*d*₆)



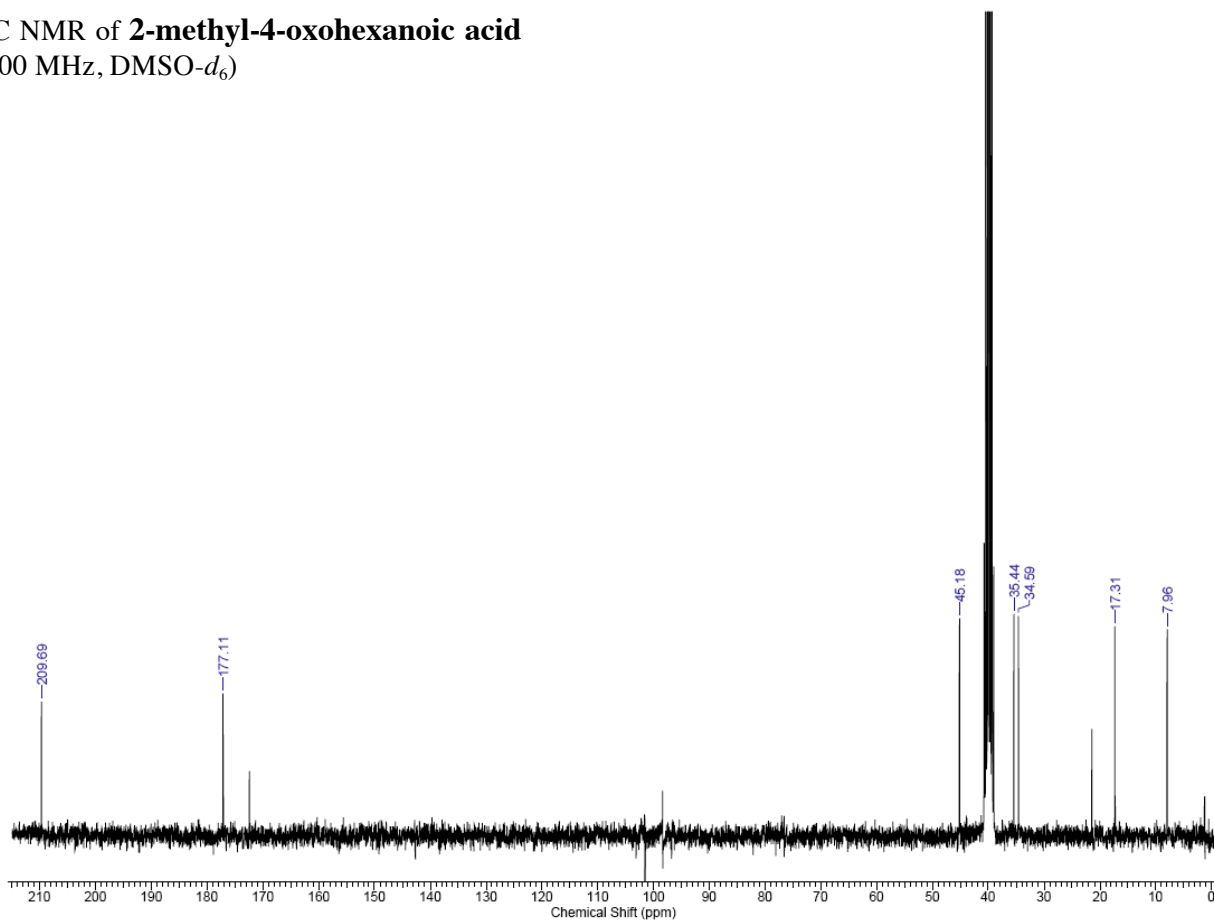
¹³C NMR of **2,2-dimethyl-4-oxohexanoic acid**
(100 MHz, DMSO-*d*₆)



¹H NMR of **2-methyl-4-oxohexanoic acid**
(400 MHz, DMSO-*d*₆)

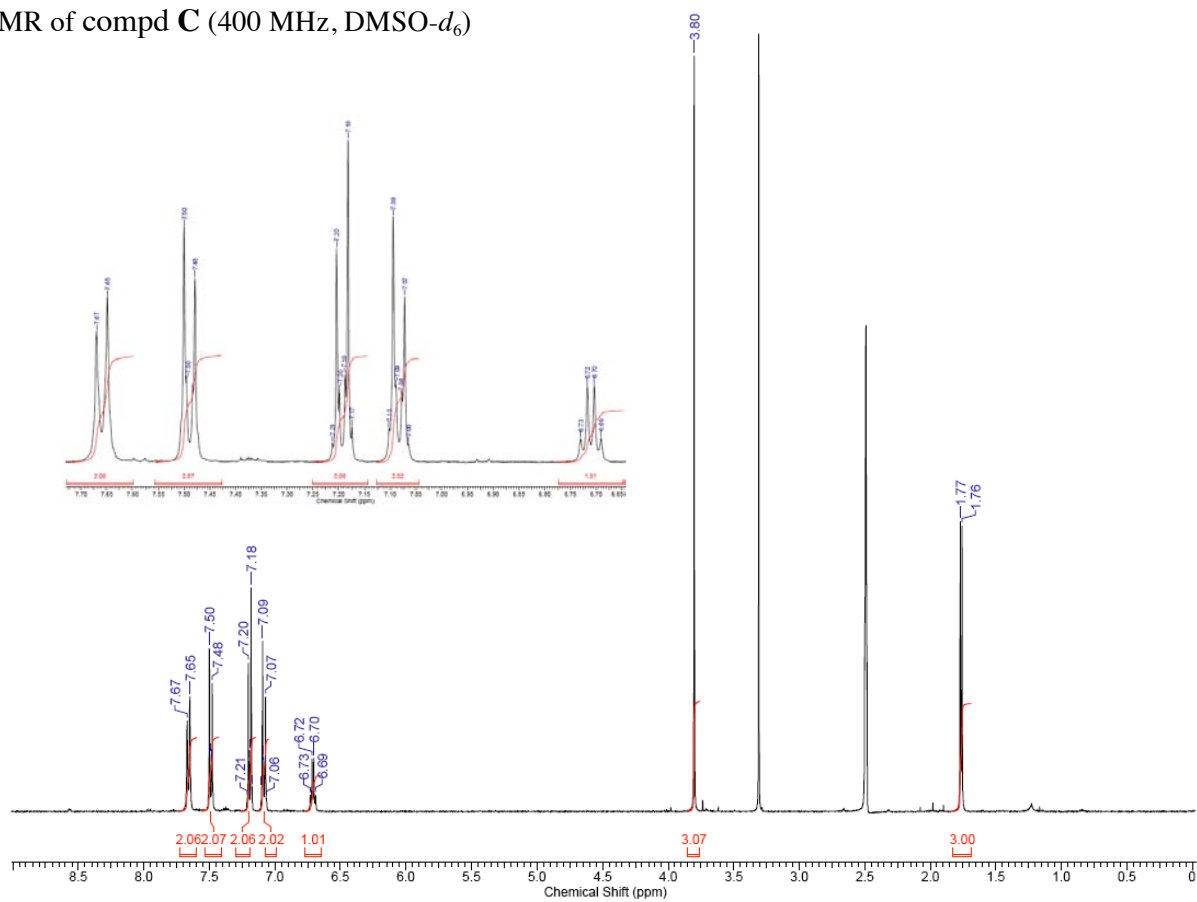


¹³C NMR of **2-methyl-4-oxohexanoic acid**
(100 MHz, DMSO-*d*₆)

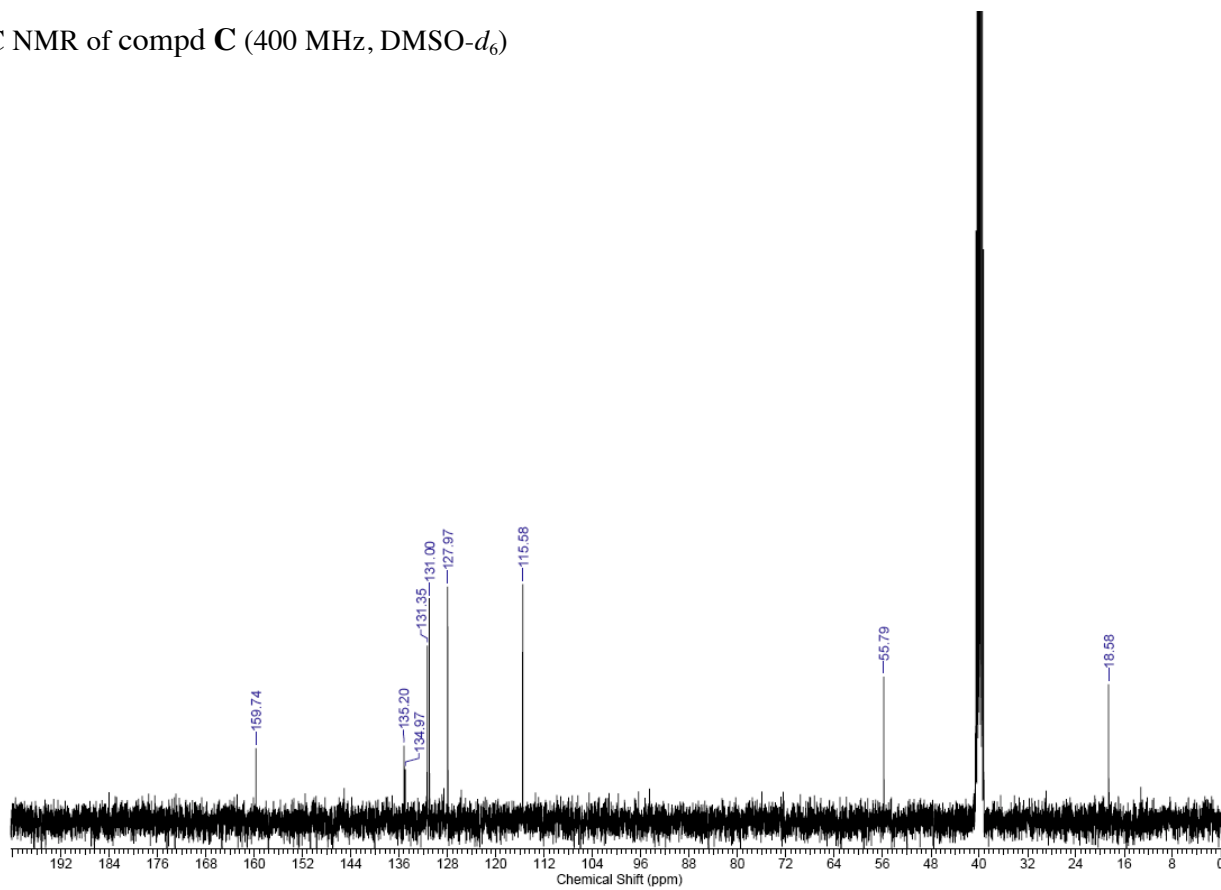


^1H and ^{13}C NMR spectra (indole precursor):

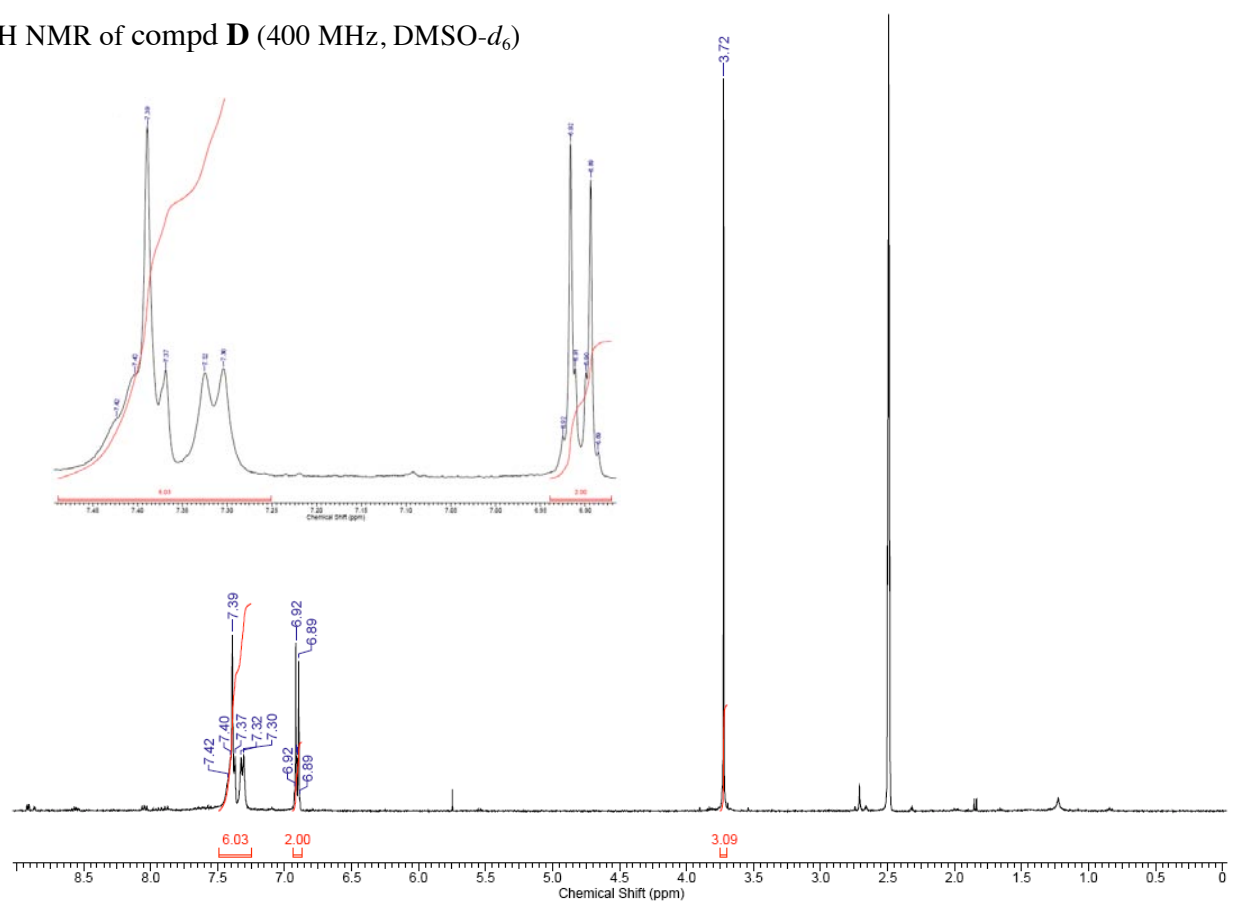
^1H NMR of compd C (400 MHz, $\text{DMSO-}d_6$)



^{13}C NMR of compd C (400 MHz, $\text{DMSO-}d_6$)

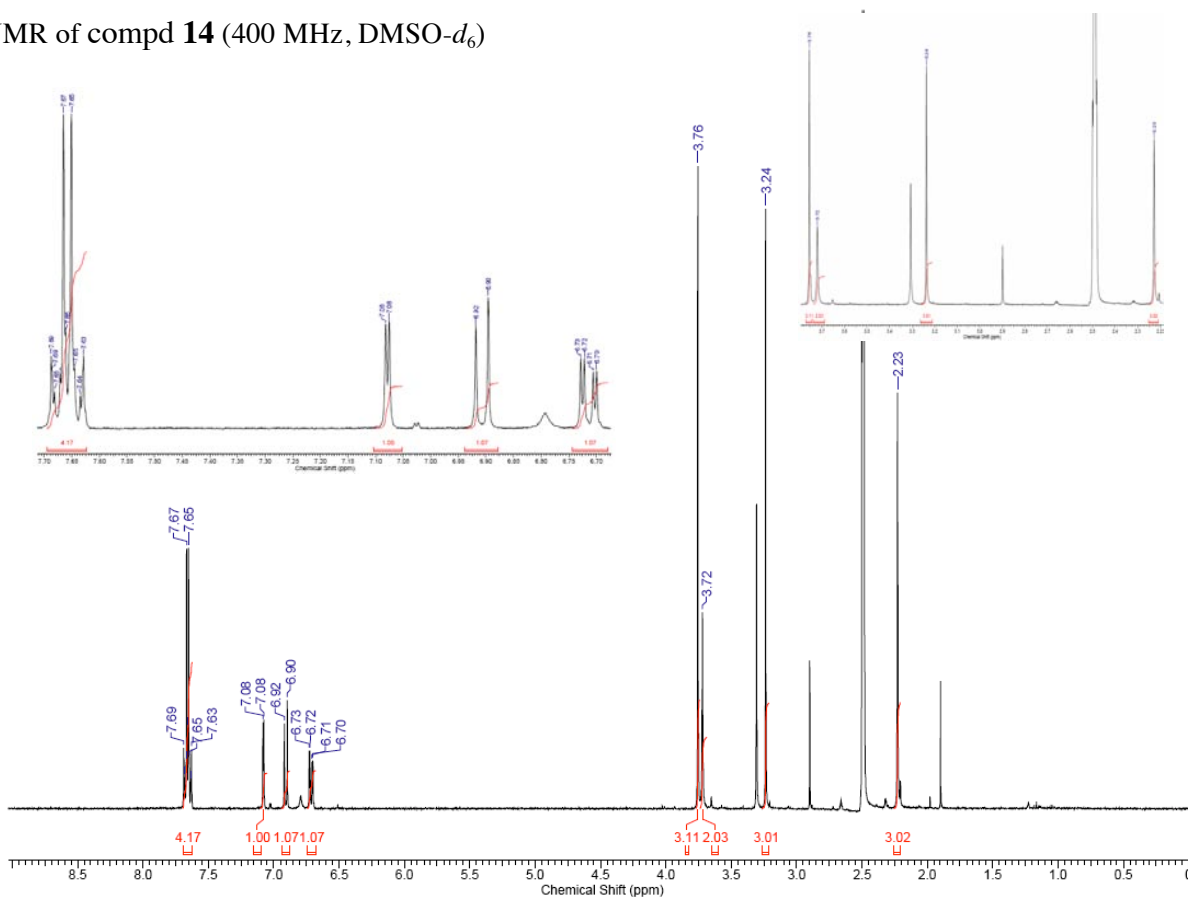


^1H NMR of compd **D** (400 MHz, $\text{DMSO-}d_6$)

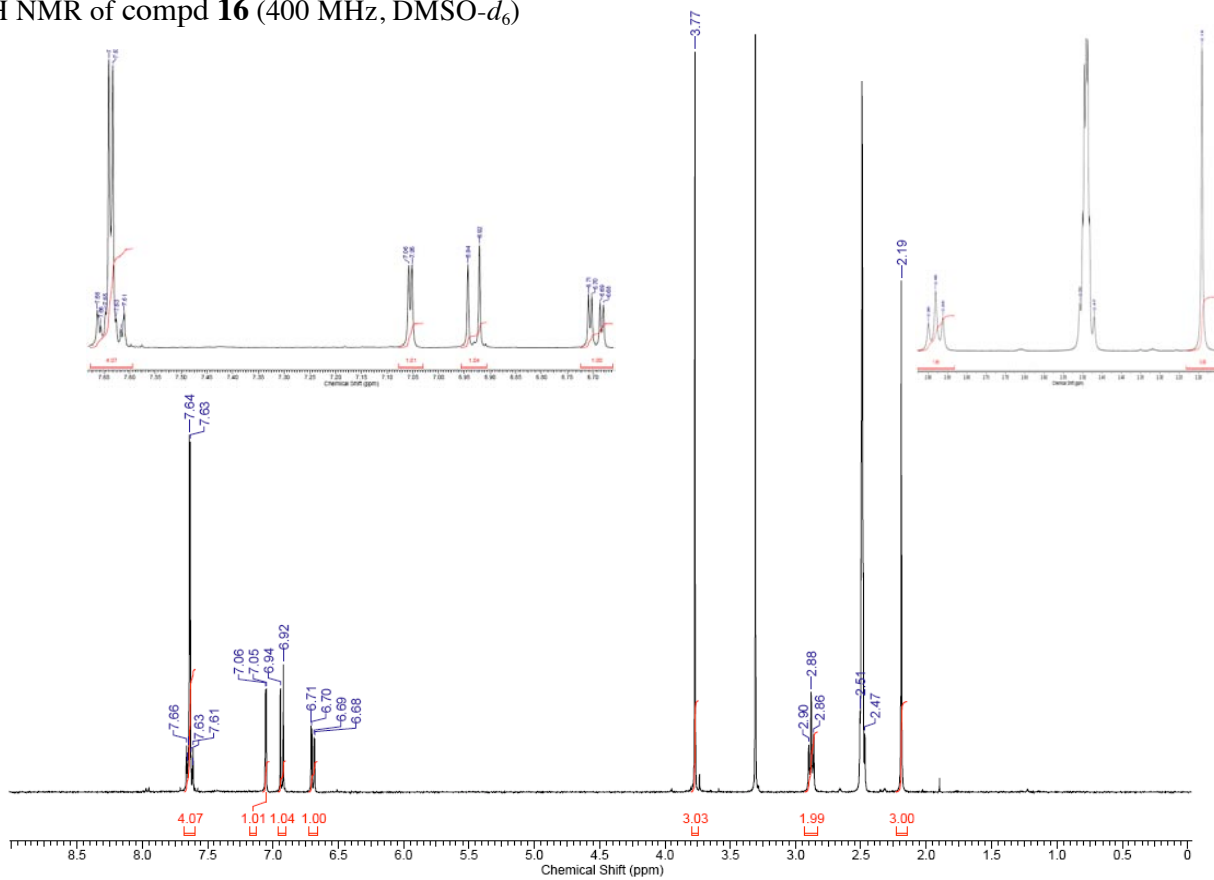


^1H and ^{13}C NMR spectra (Fischer Indolization Products and Sulfonimide Derivatives):

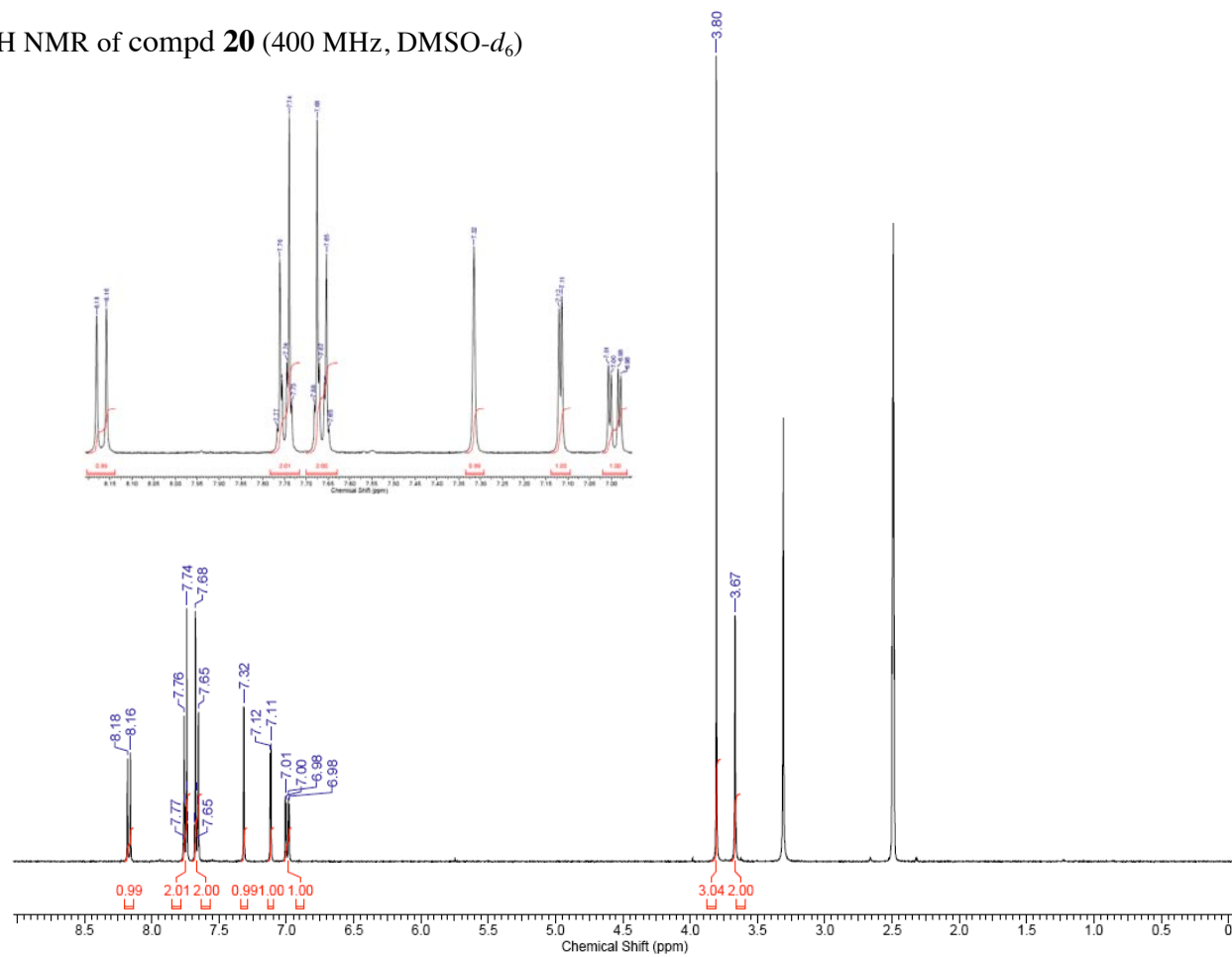
^1H NMR of compd **14** (400 MHz, $\text{DMSO-}d_6$)



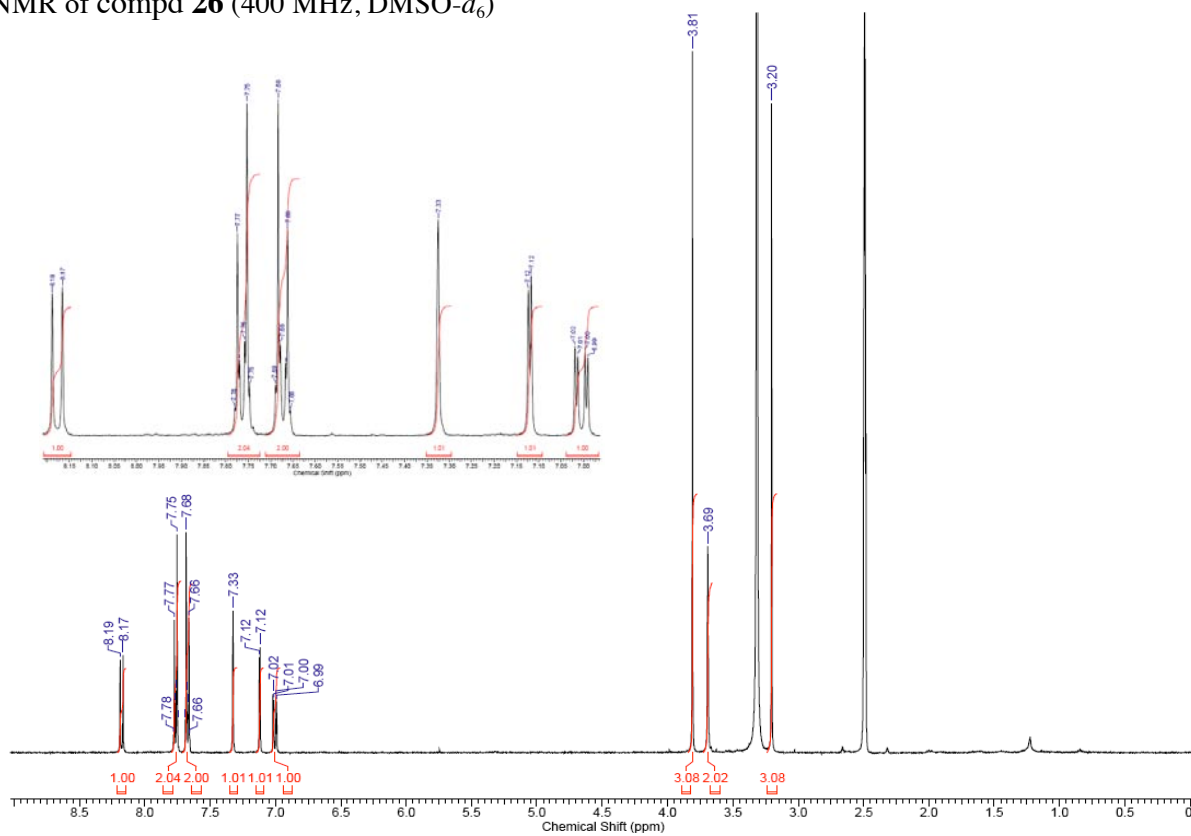
^1H NMR of compd **16** (400 MHz, $\text{DMSO-}d_6$)



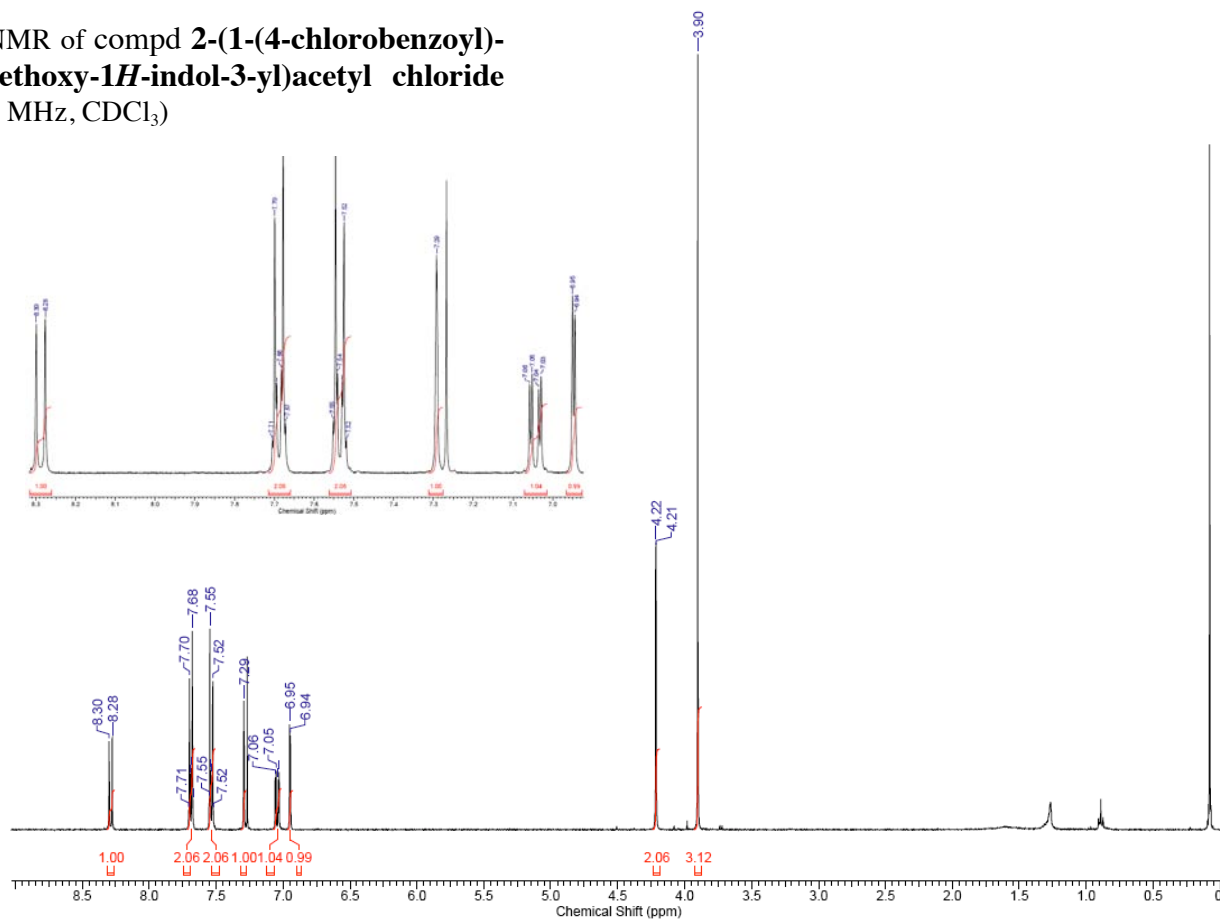
^1H NMR of compd **20** (400 MHz, $\text{DMSO-}d_6$)



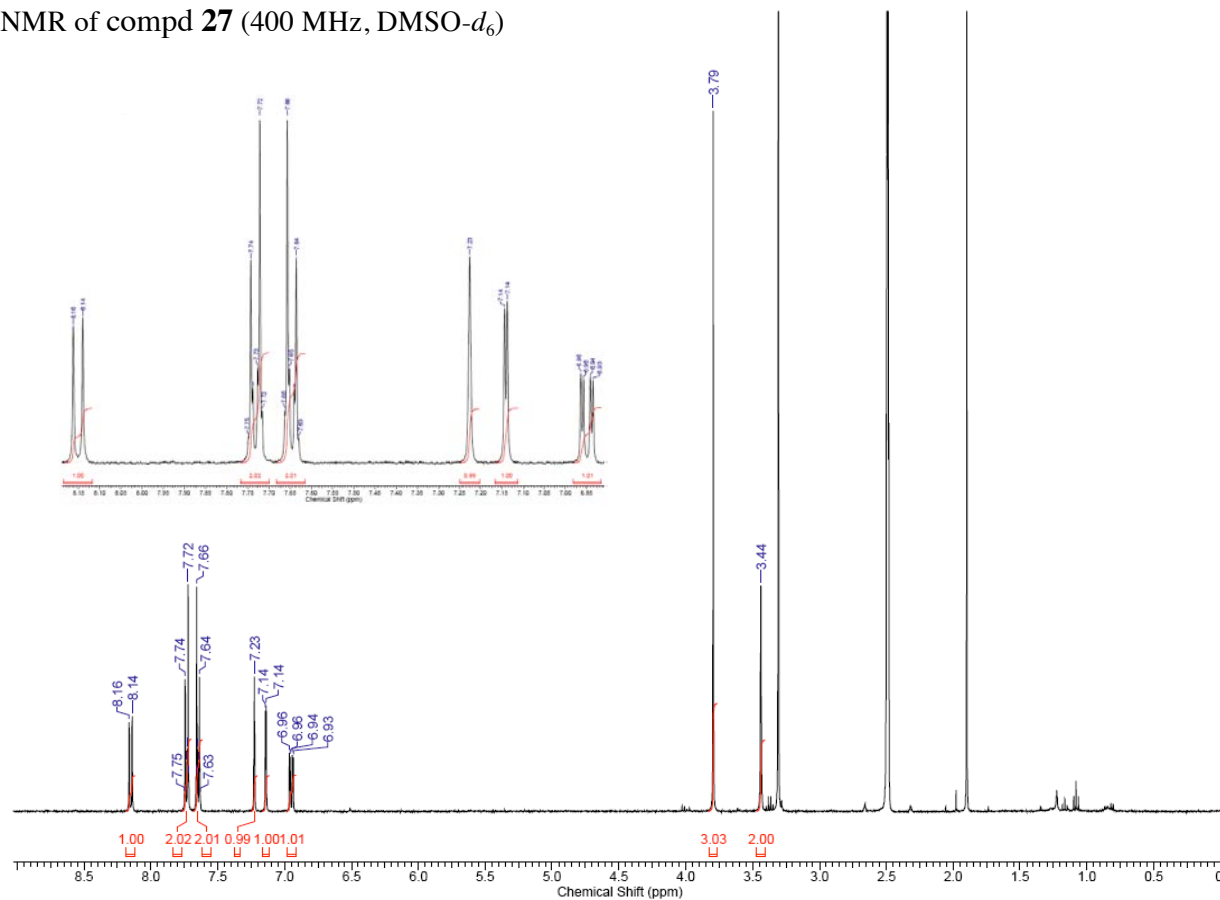
^1H NMR of compd **26** (400 MHz, $\text{DMSO-}d_6$)



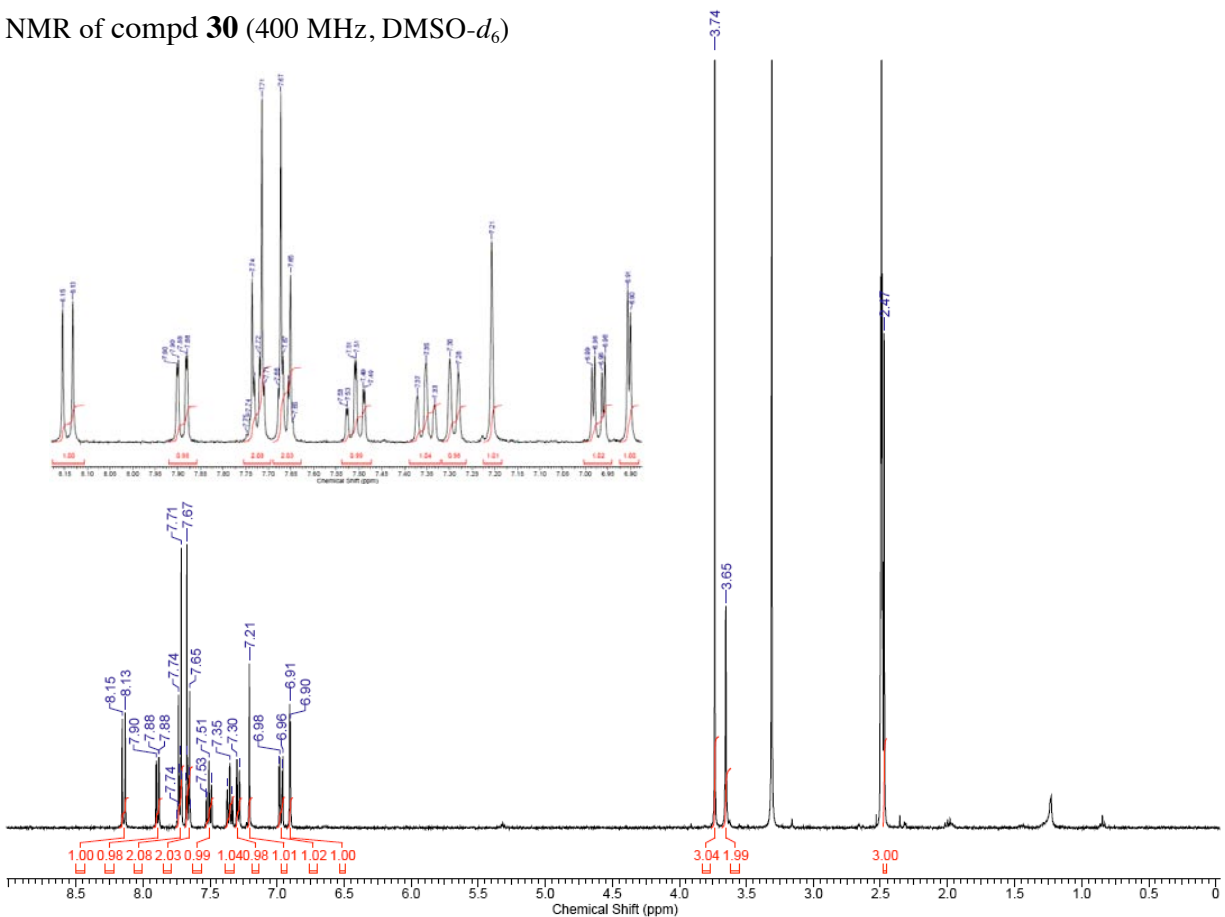
¹H NMR of compd **2**-**(1-(4-chlorobenzoyl)-5-methoxy-1H-indol-3-yl)acetyl chloride**
(400 MHz, CDCl₃)



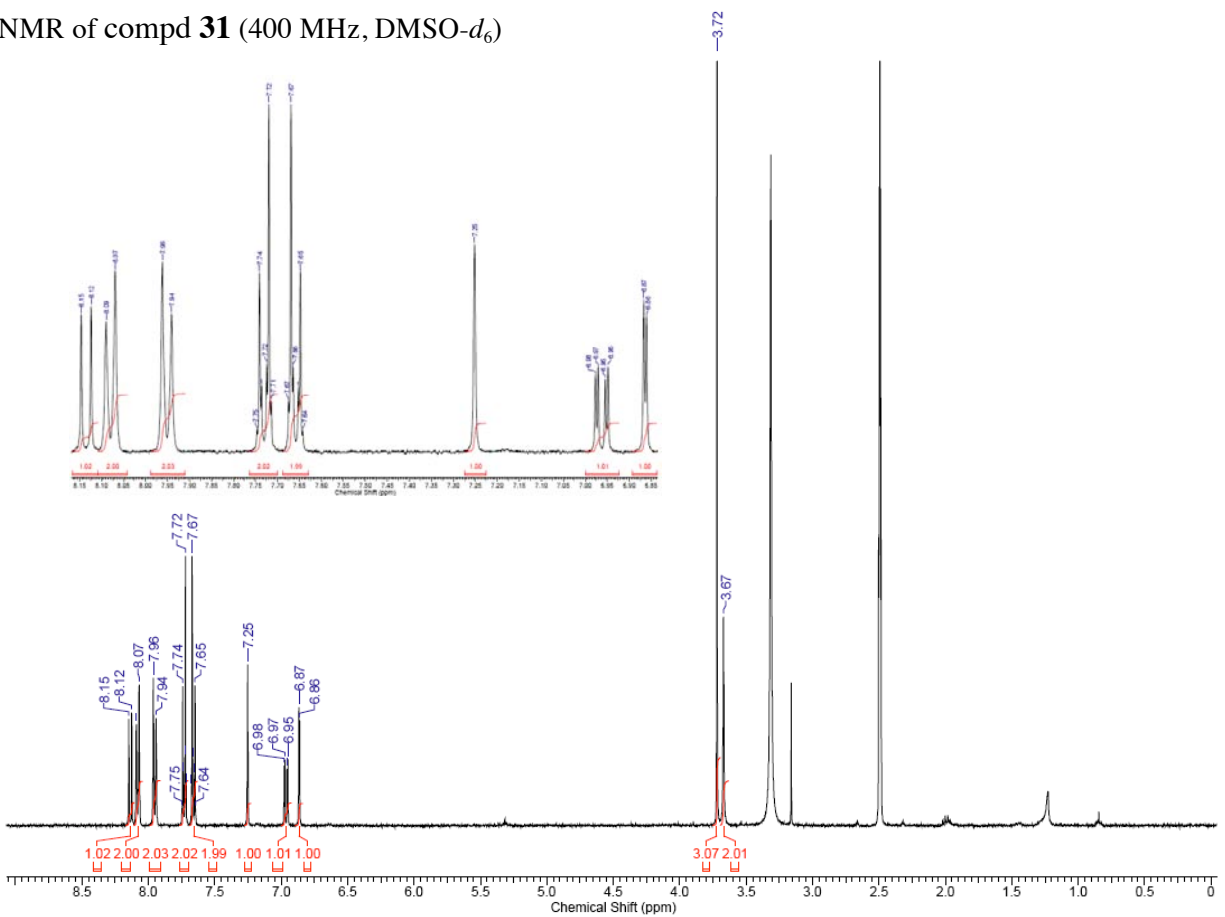
¹H NMR of compd **27** (400 MHz, DMSO-d₆)



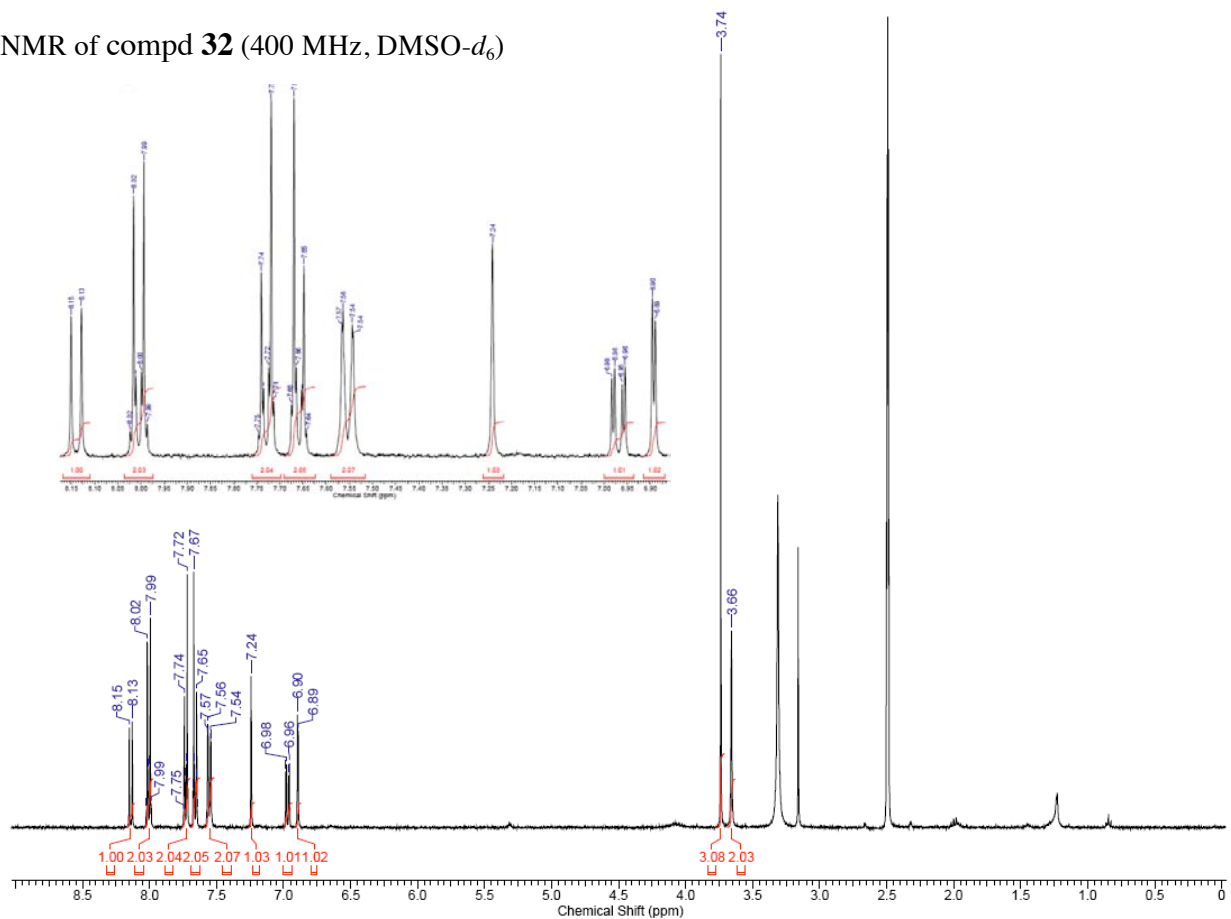
^1H NMR of compd **30** (400 MHz, $\text{DMSO-}d_6$)



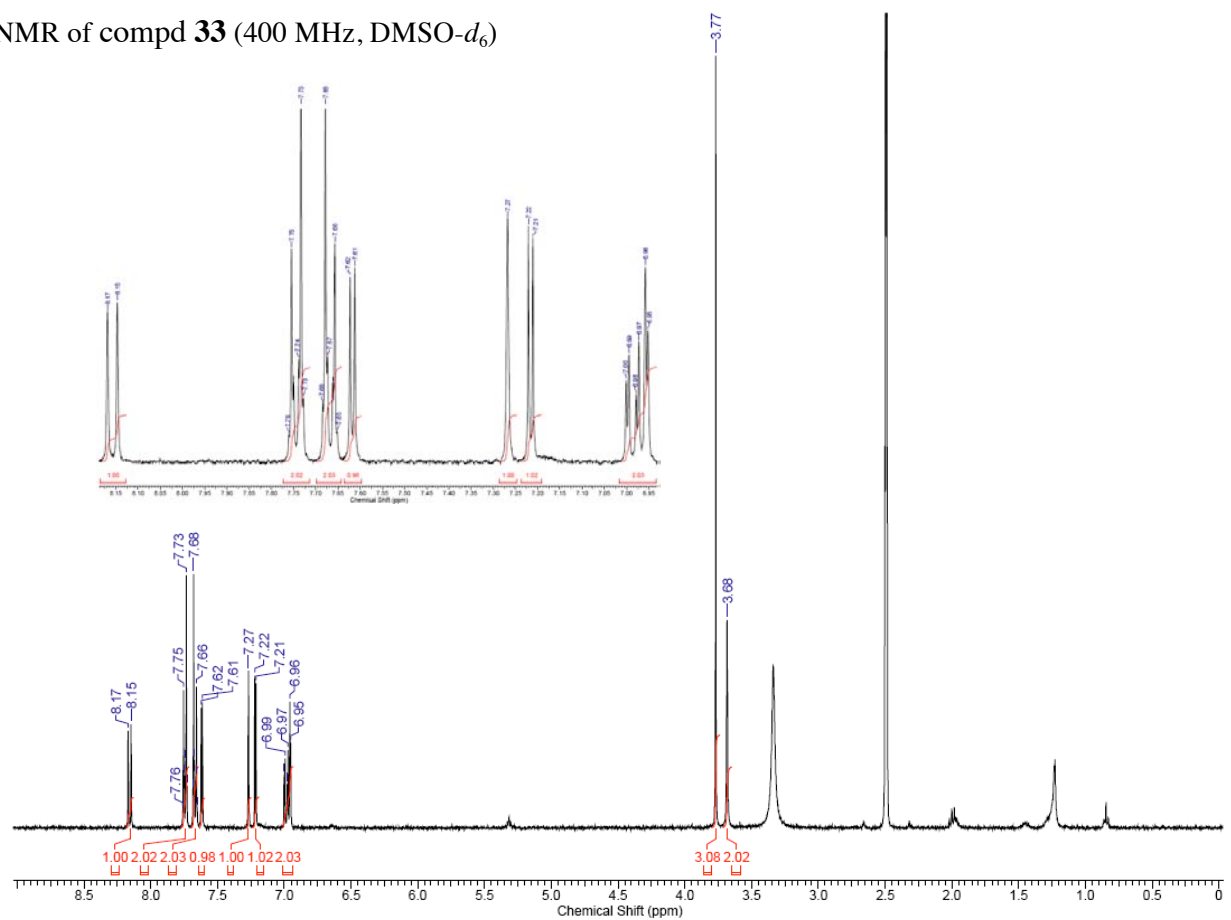
^1H NMR of compd **31** (400 MHz, $\text{DMSO-}d_6$)



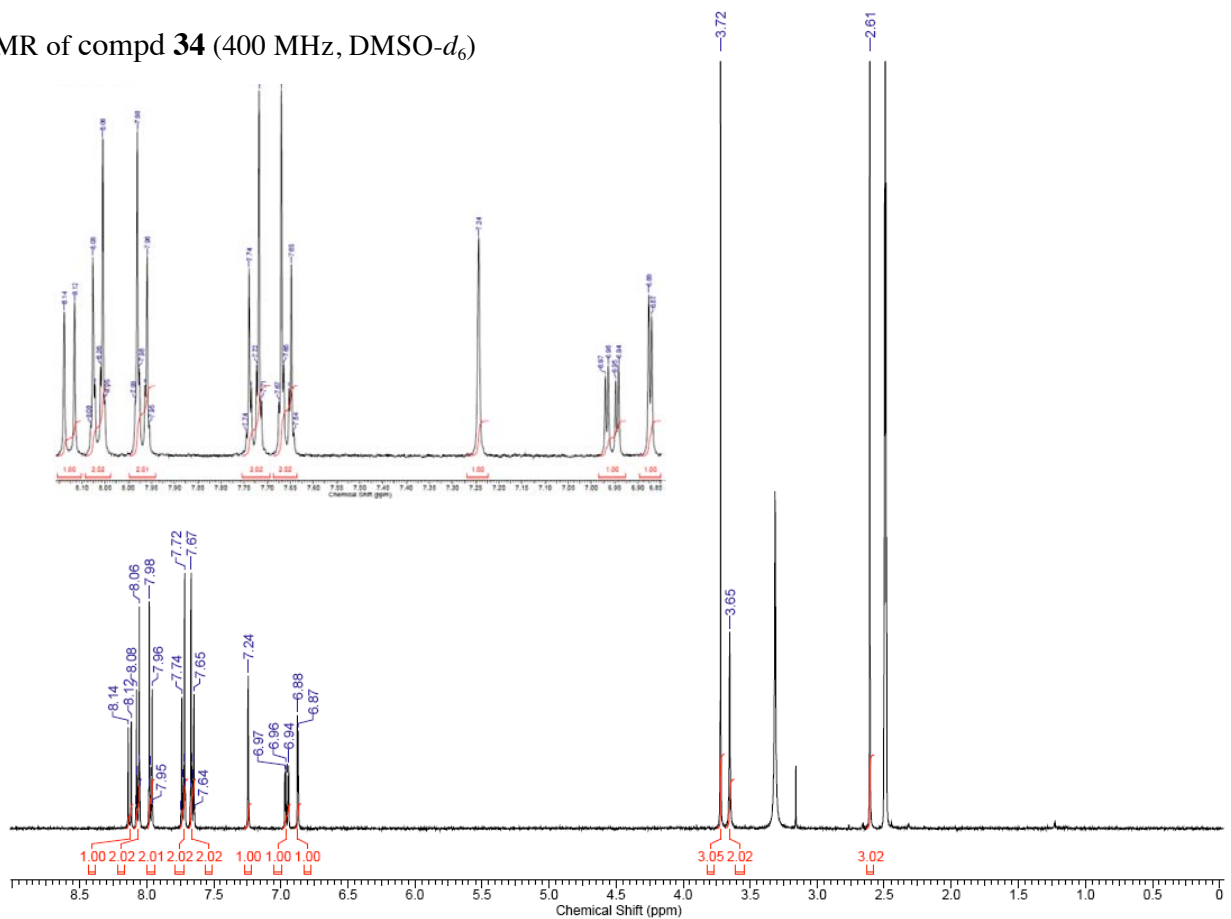
^1H NMR of compd **32** (400 MHz, $\text{DMSO-}d_6$)



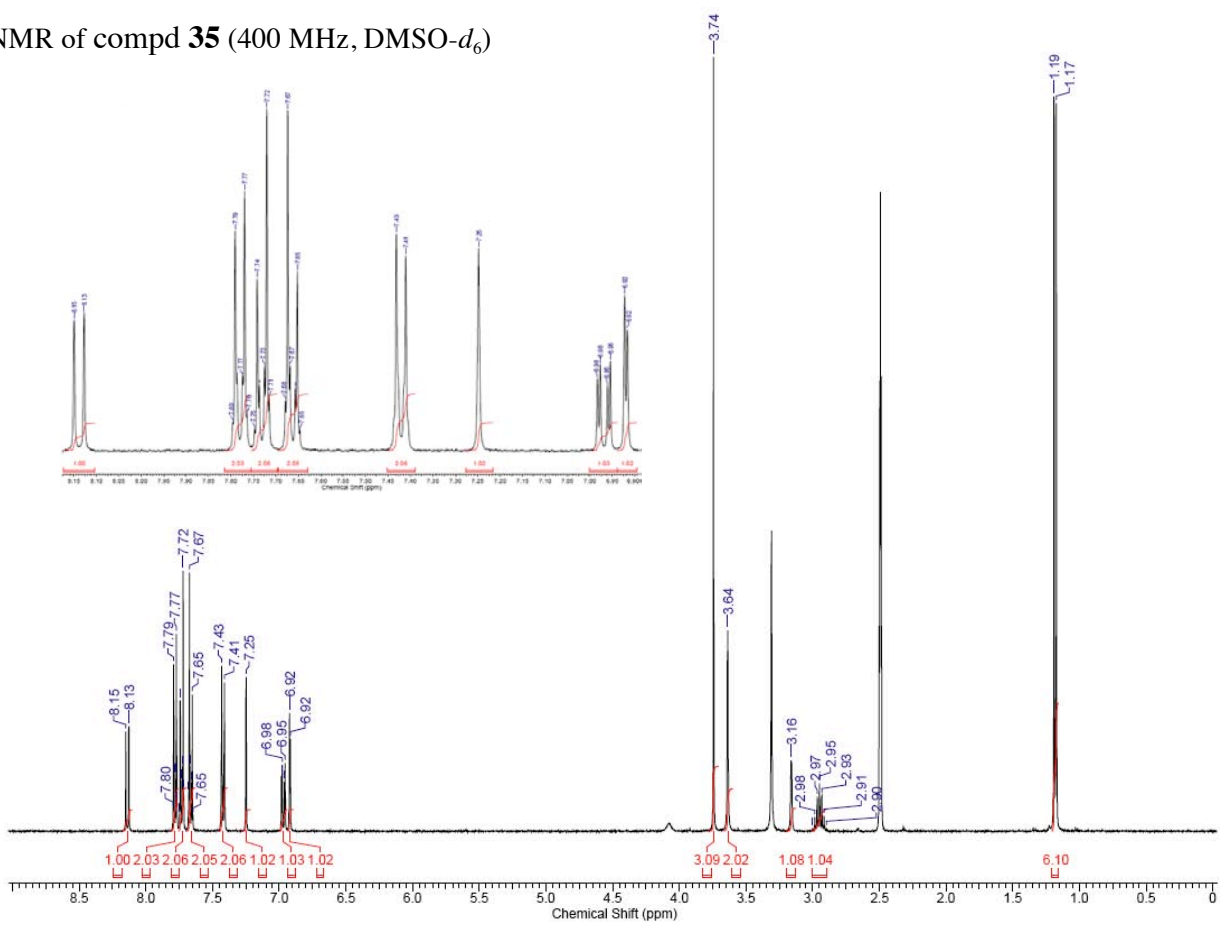
^1H NMR of compd **33** (400 MHz, $\text{DMSO-}d_6$)



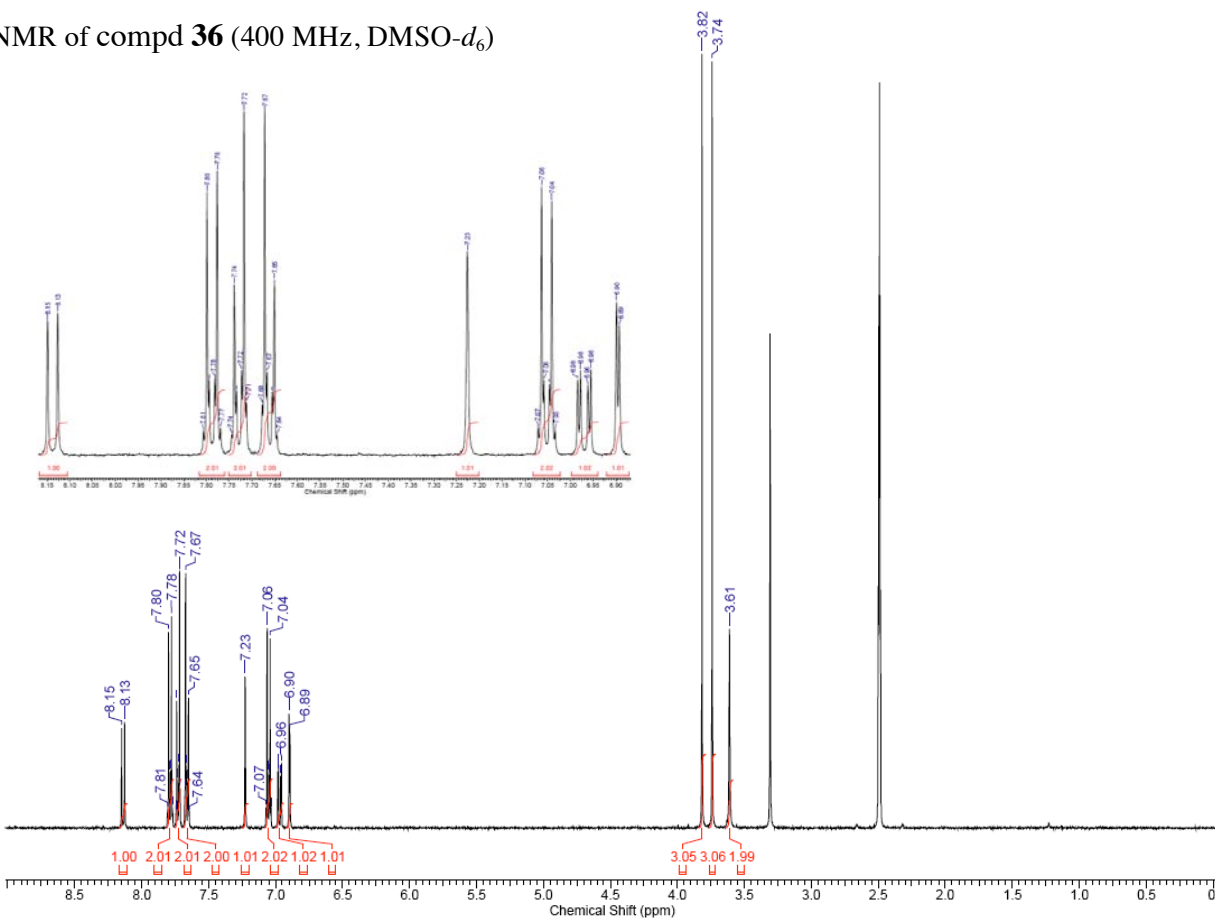
^1H NMR of compd **34** (400 MHz, $\text{DMSO-}d_6$)



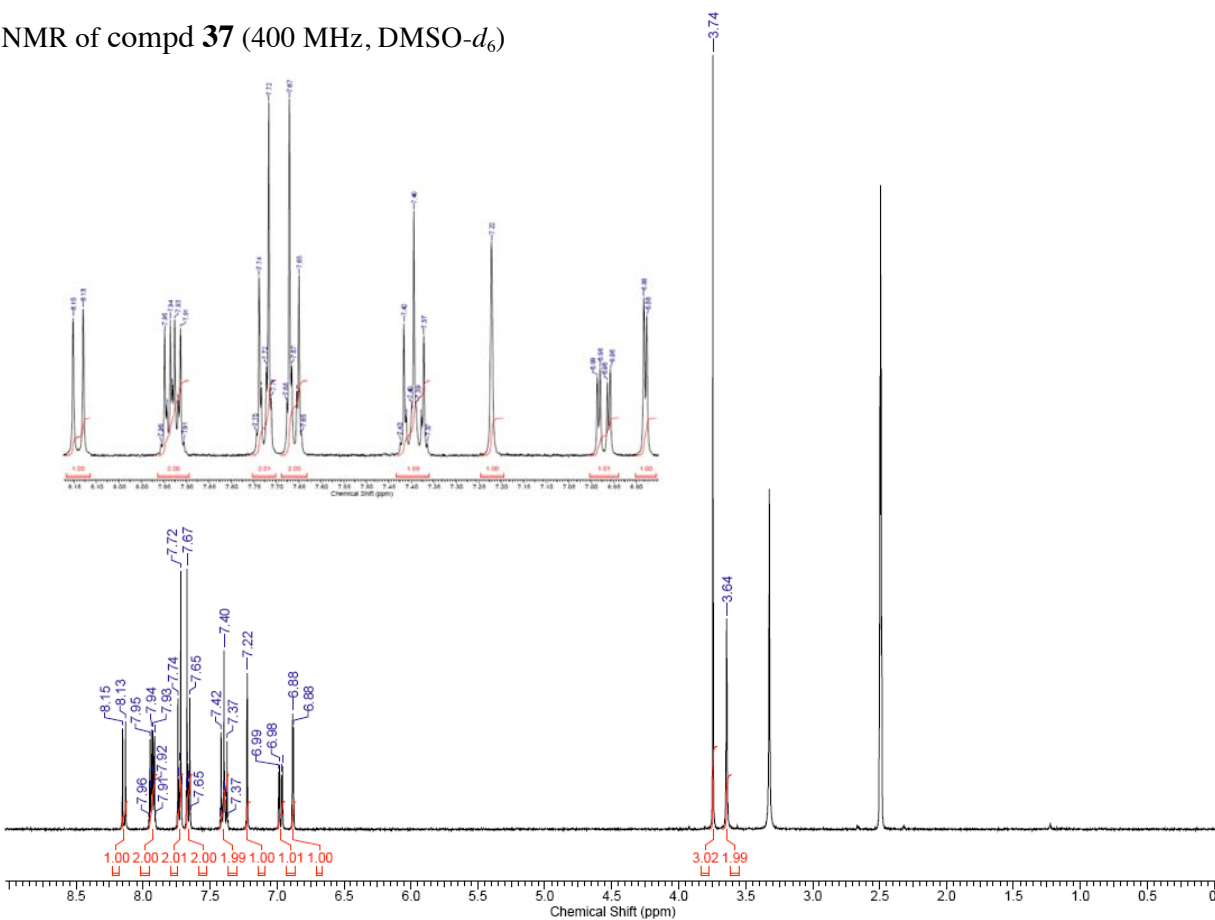
^1H NMR of compd **35** (400 MHz, $\text{DMSO-}d_6$)



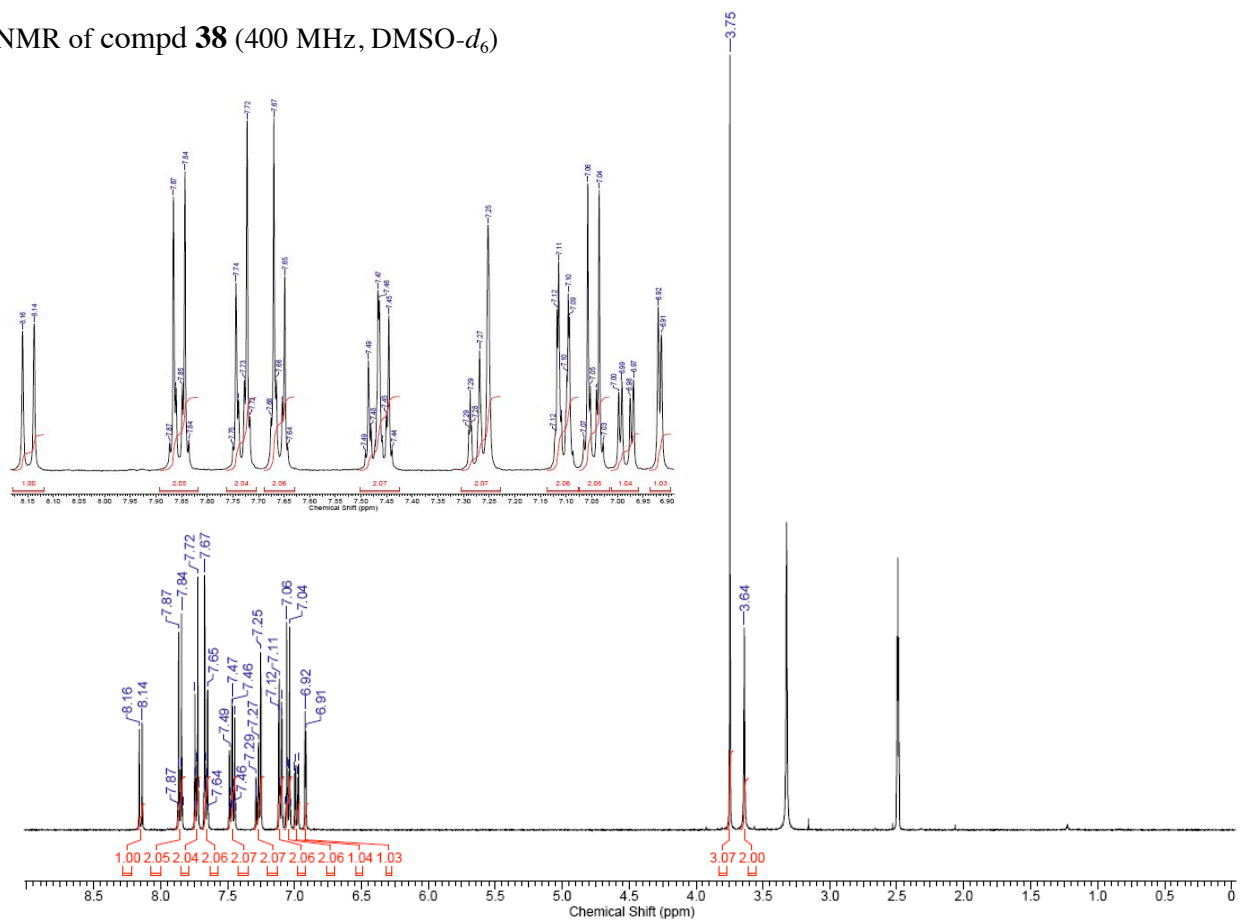
^1H NMR of compd **36** (400 MHz, $\text{DMSO-}d_6$)



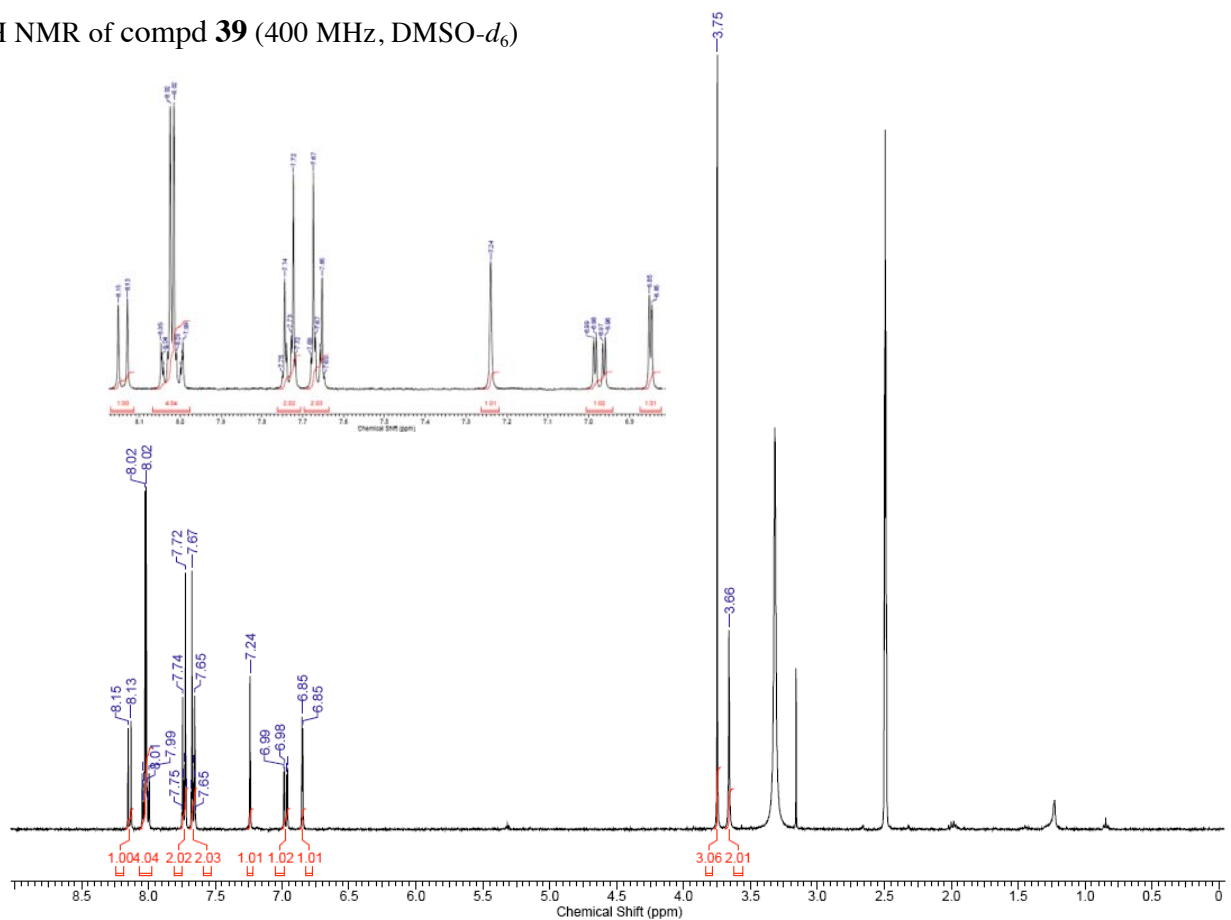
^1H NMR of compd **37** (400 MHz, $\text{DMSO-}d_6$)



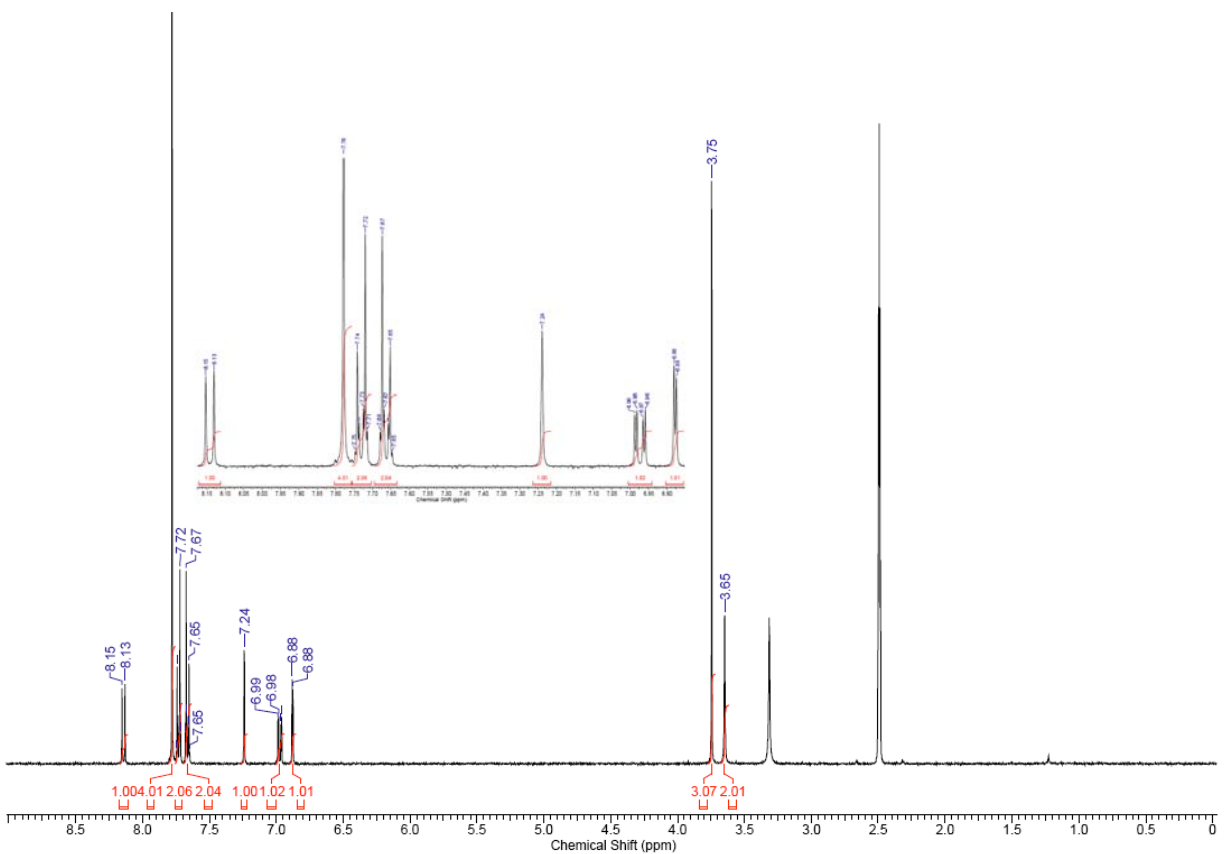
^1H NMR of compd **38** (400 MHz, $\text{DMSO-}d_6$)



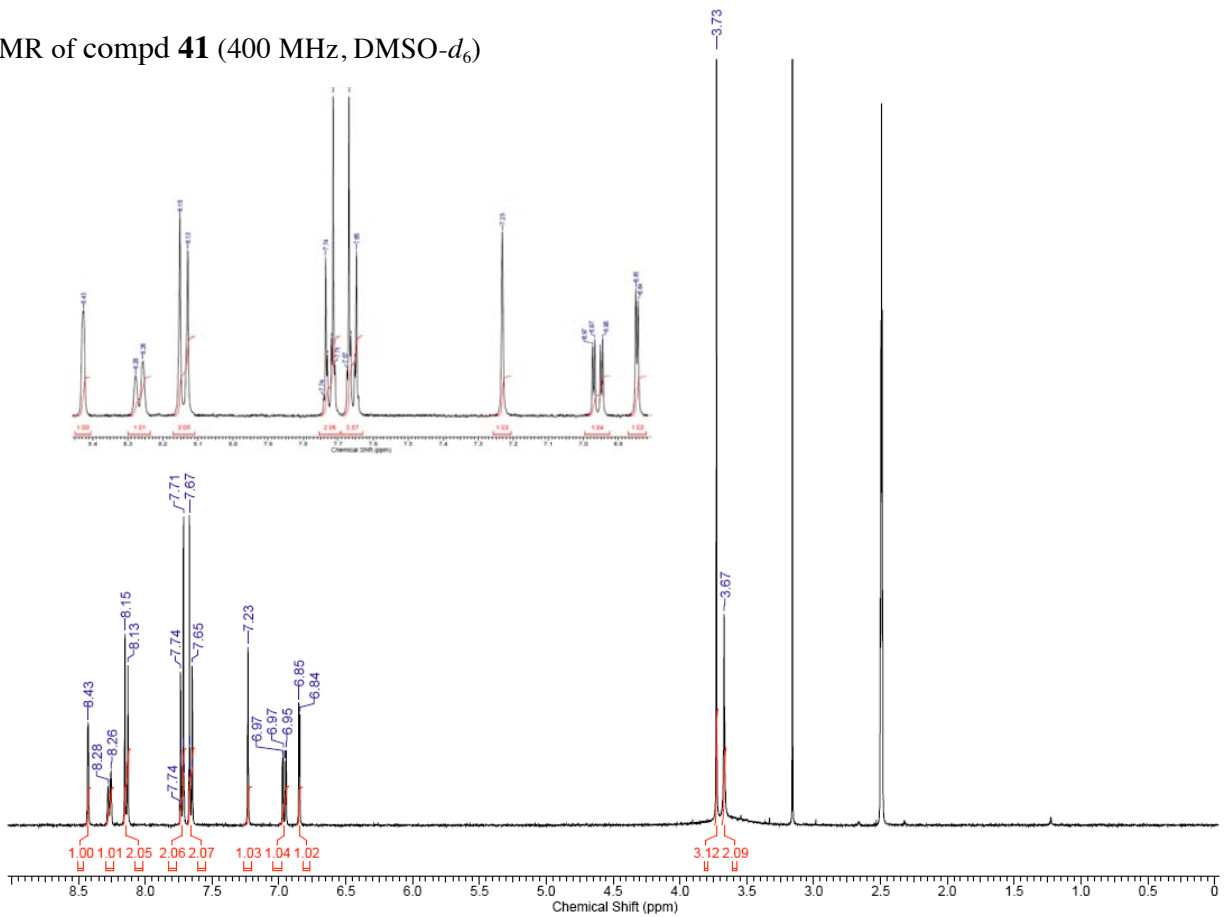
^1H NMR of compd **39** (400 MHz, $\text{DMSO-}d_6$)



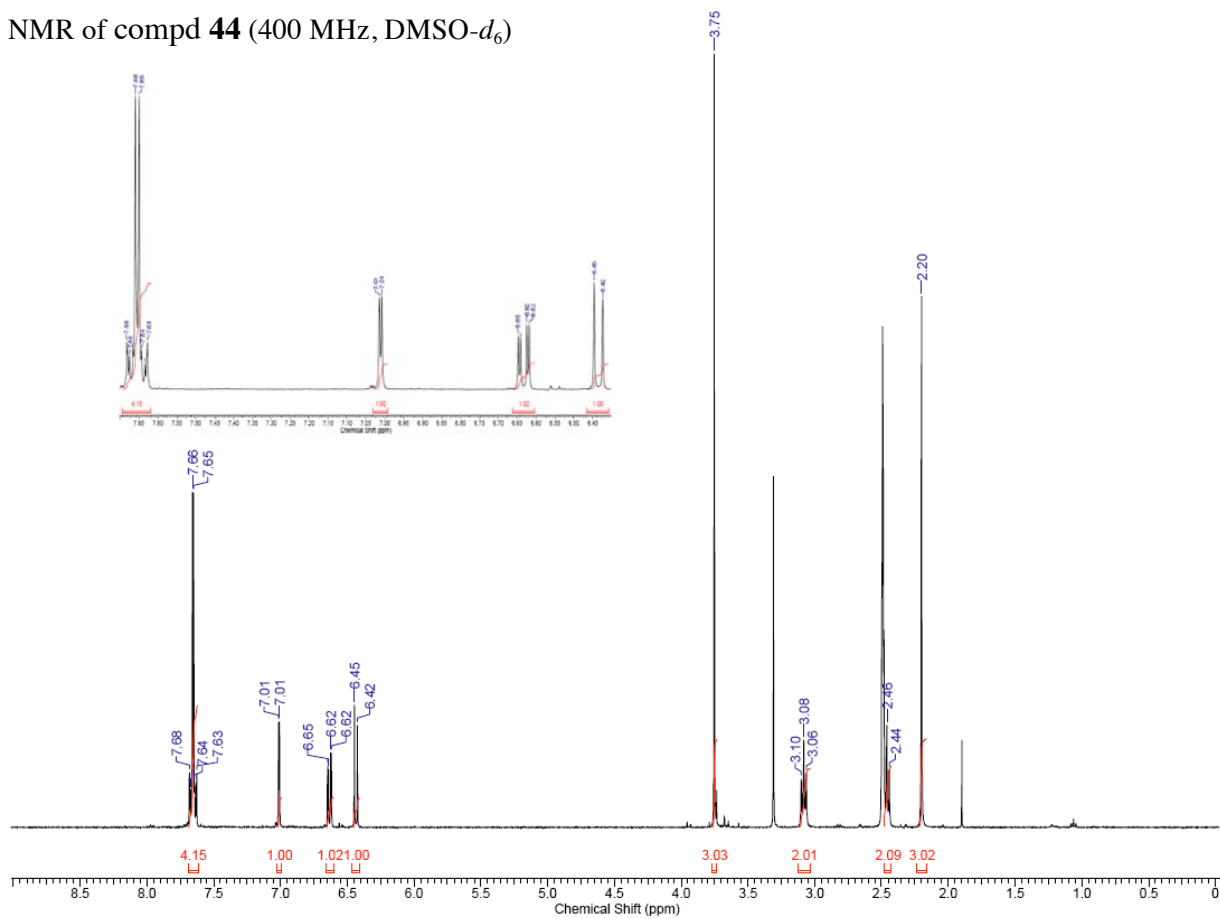
^1H NMR of compd **40** (400 MHz, $\text{DMSO-}d_6$)



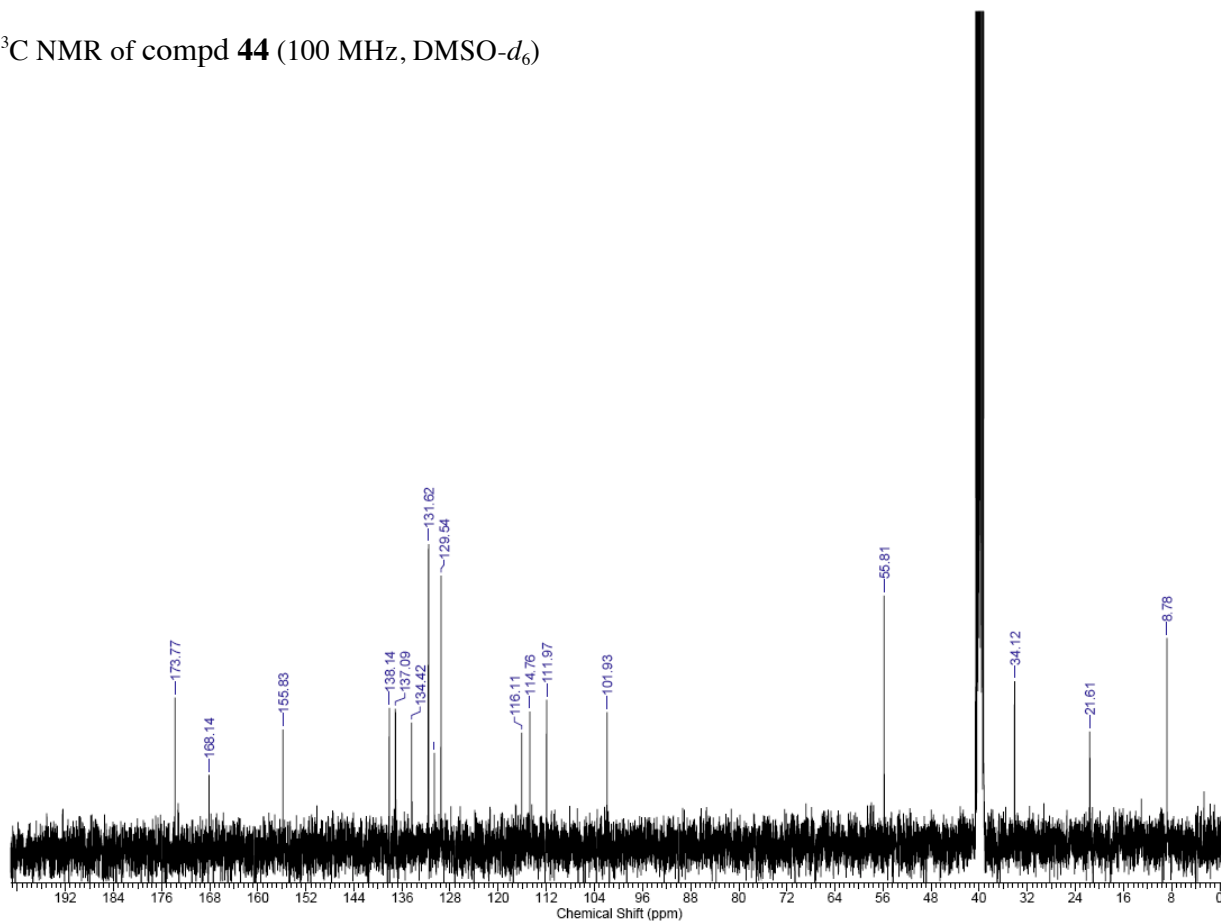
^1H NMR of compd **41** (400 MHz, $\text{DMSO-}d_6$)



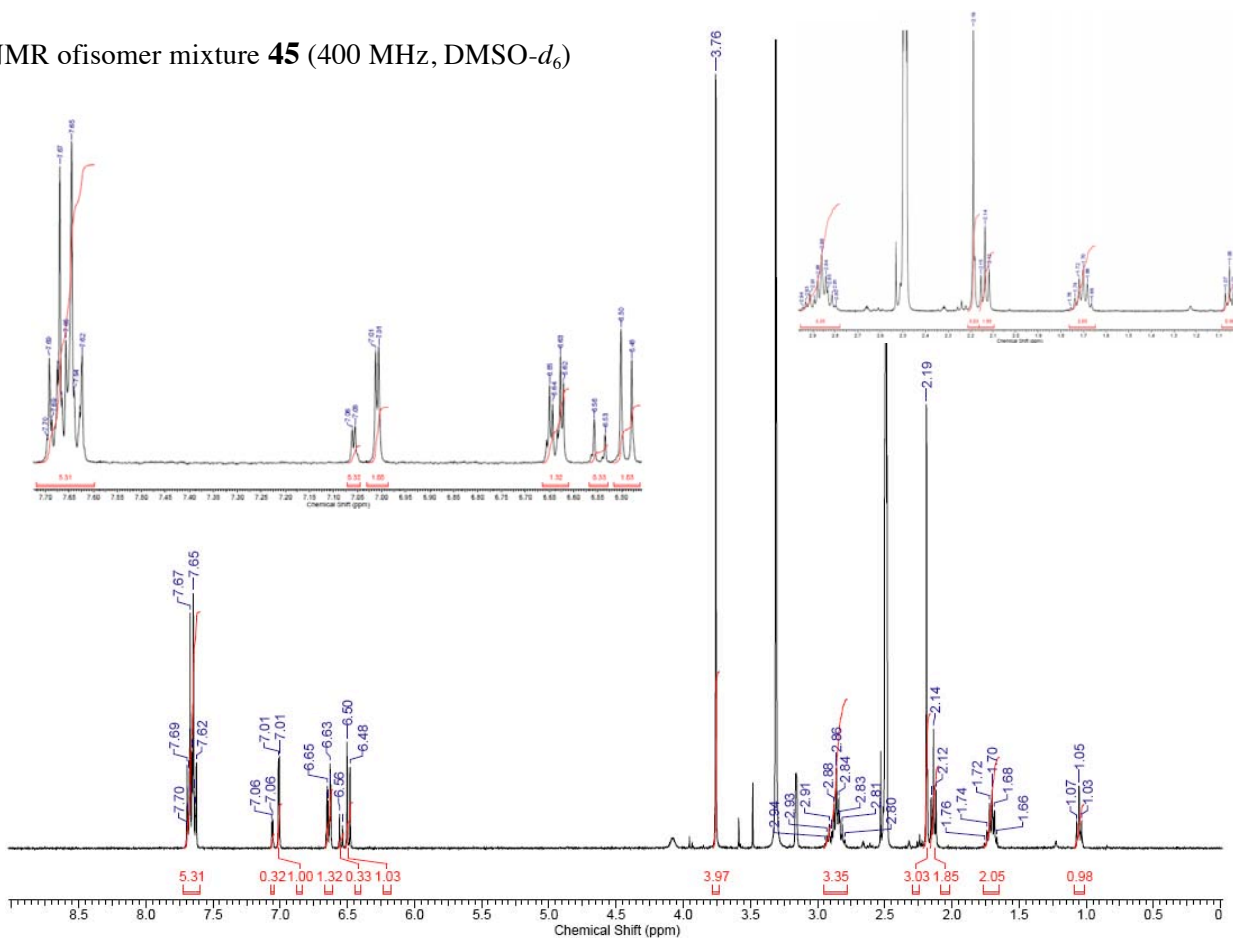
¹H NMR of compd **44** (400 MHz, DMSO-*d*₆)



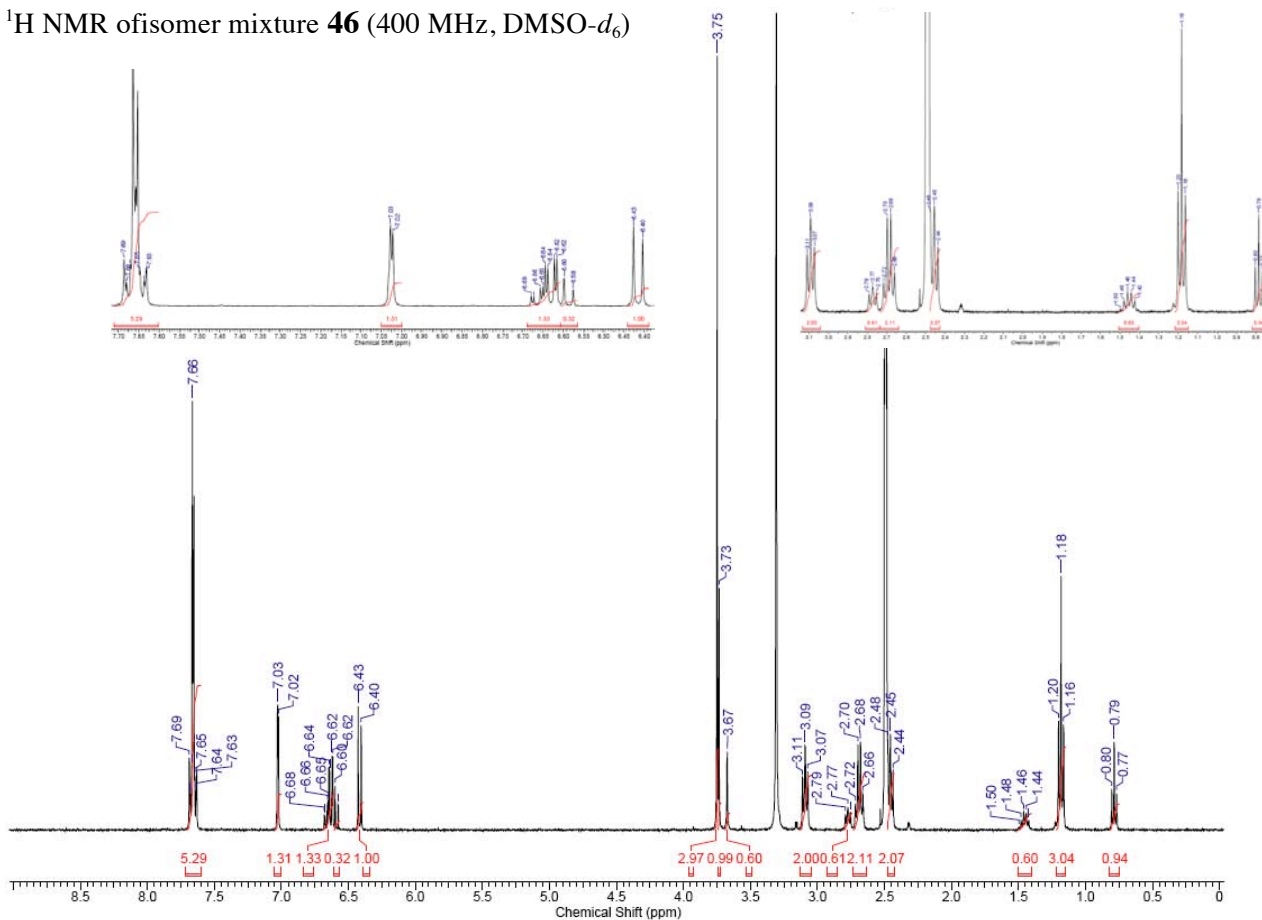
¹³C NMR of compd **44** (100 MHz, DMSO-*d*₆)



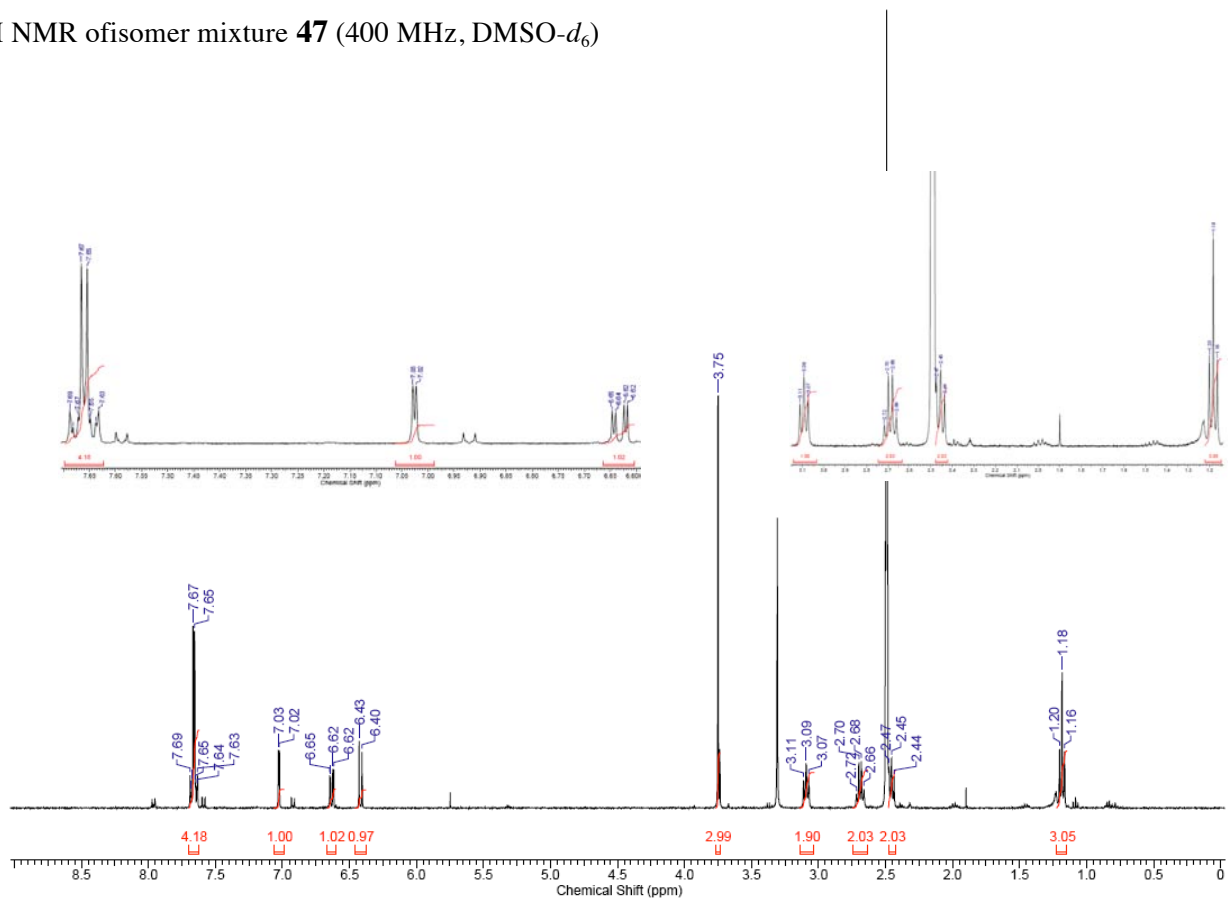
^1H NMR of isomer mixture **45** (400 MHz, $\text{DMSO-}d_6$)



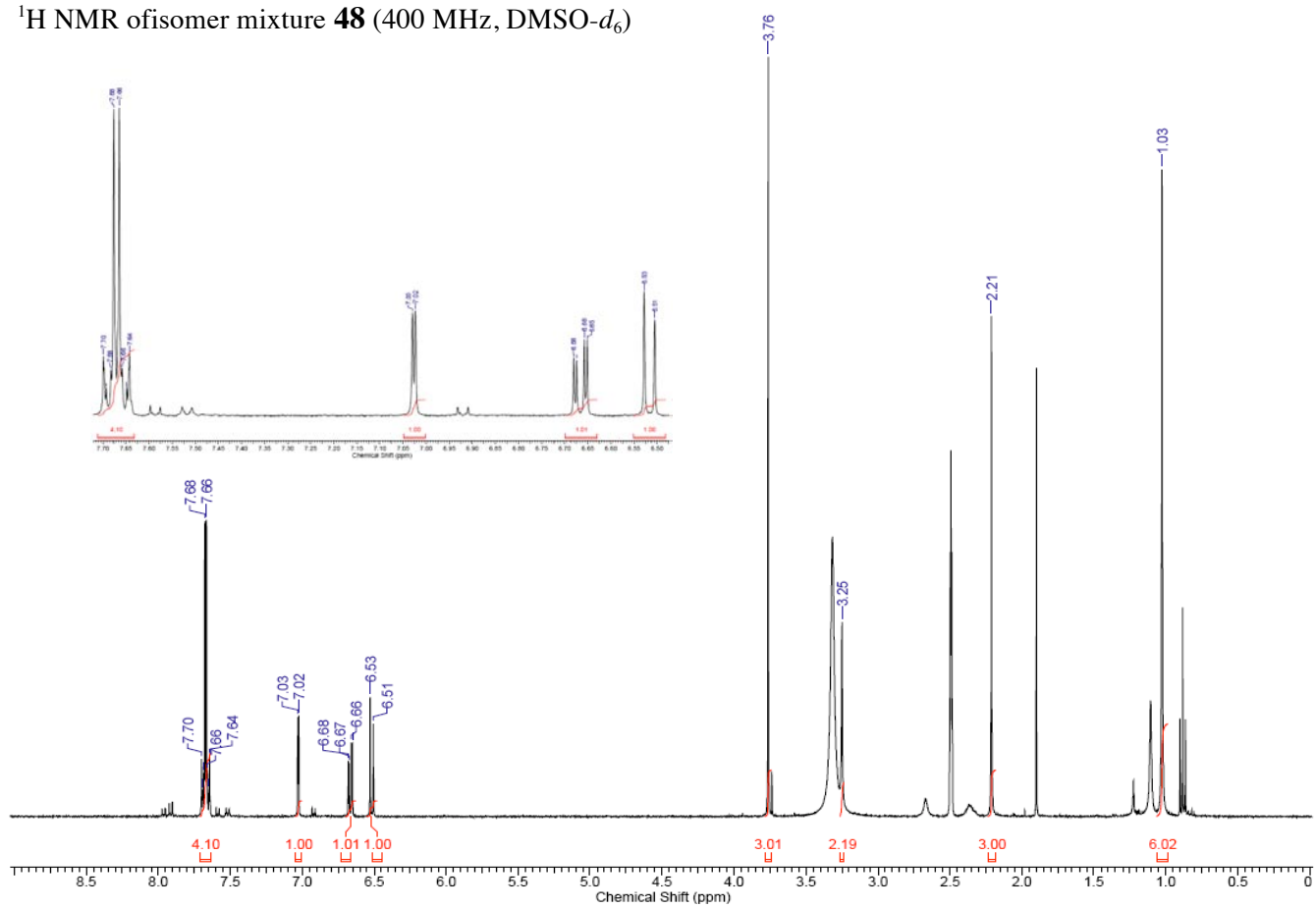
^1H NMR of isomer mixture **46** (400 MHz, $\text{DMSO-}d_6$)



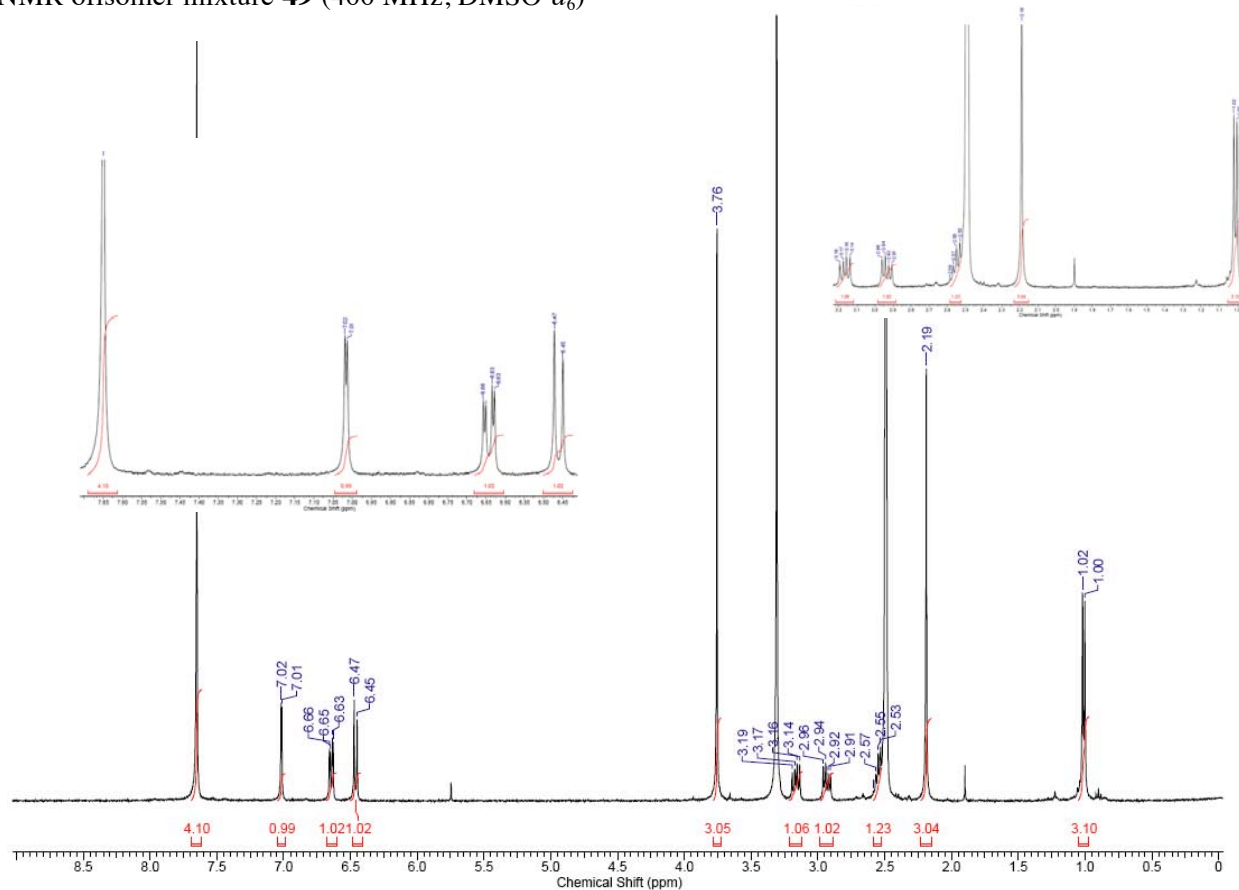
^1H NMR of isomer mixture **47** (400 MHz, $\text{DMSO-}d_6$)



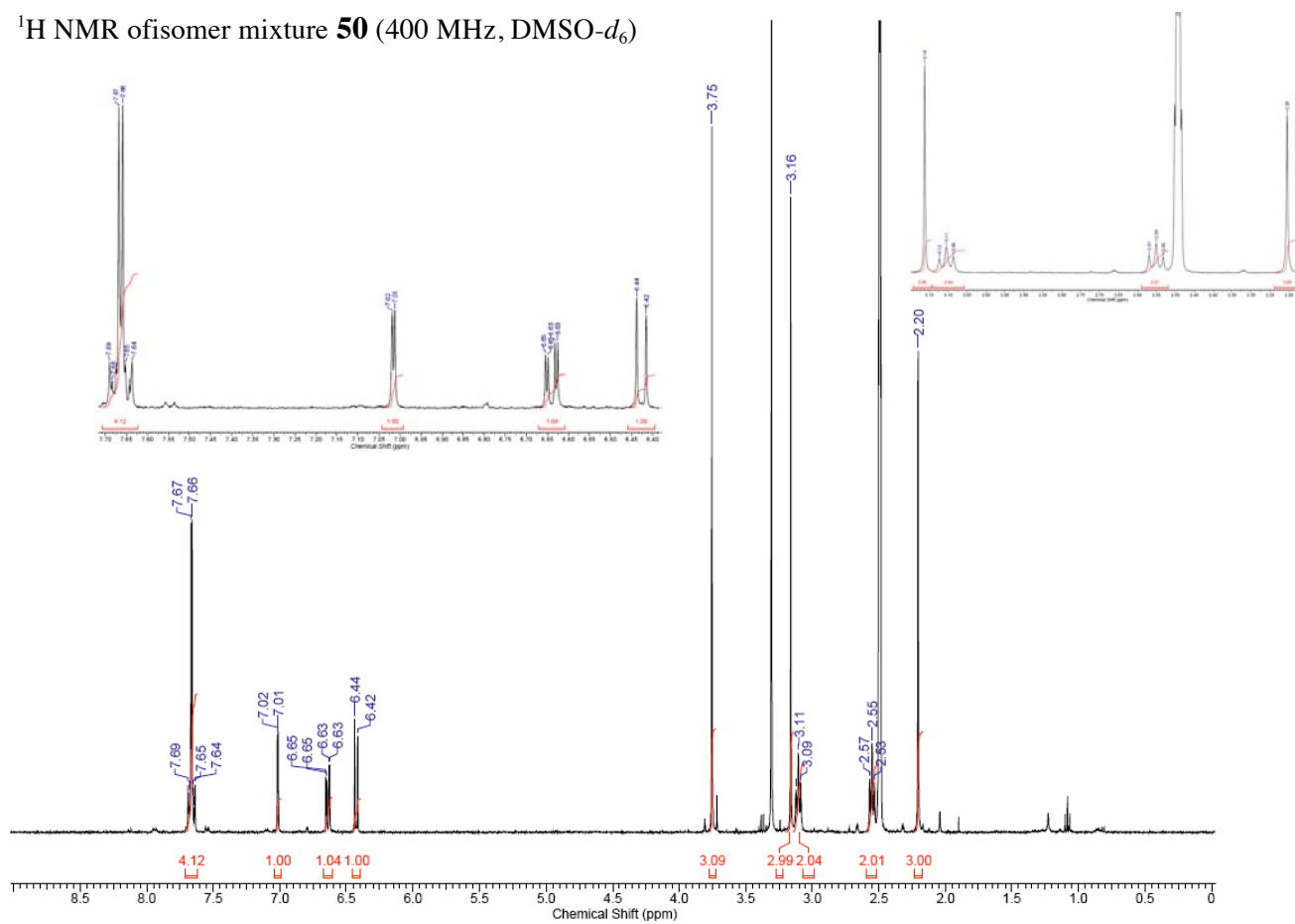
^1H NMR of isomer mixture **48** (400 MHz, $\text{DMSO-}d_6$)



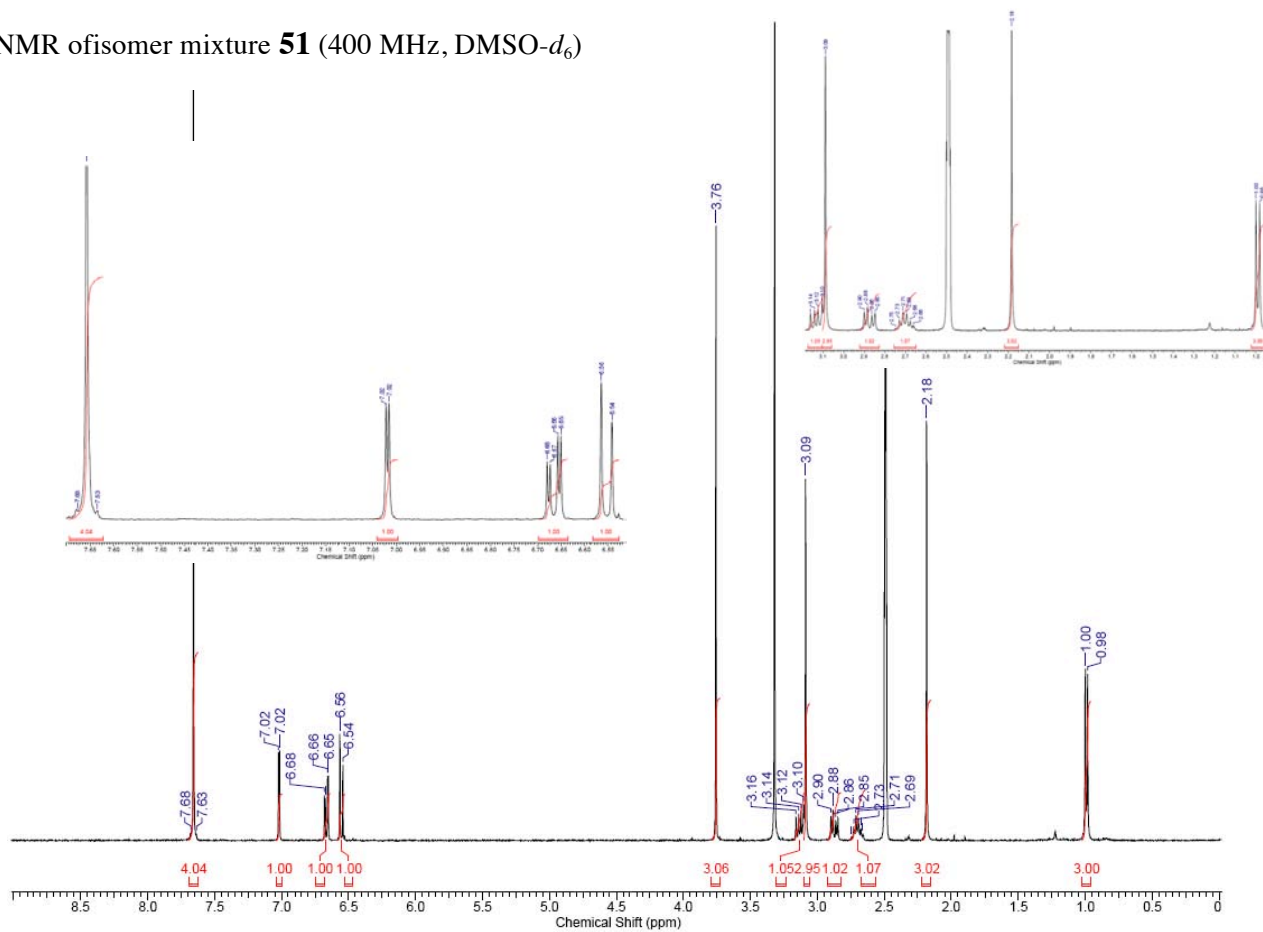
^1H NMR of isomer mixture **49** (400 MHz, $\text{DMSO-}d_6$)



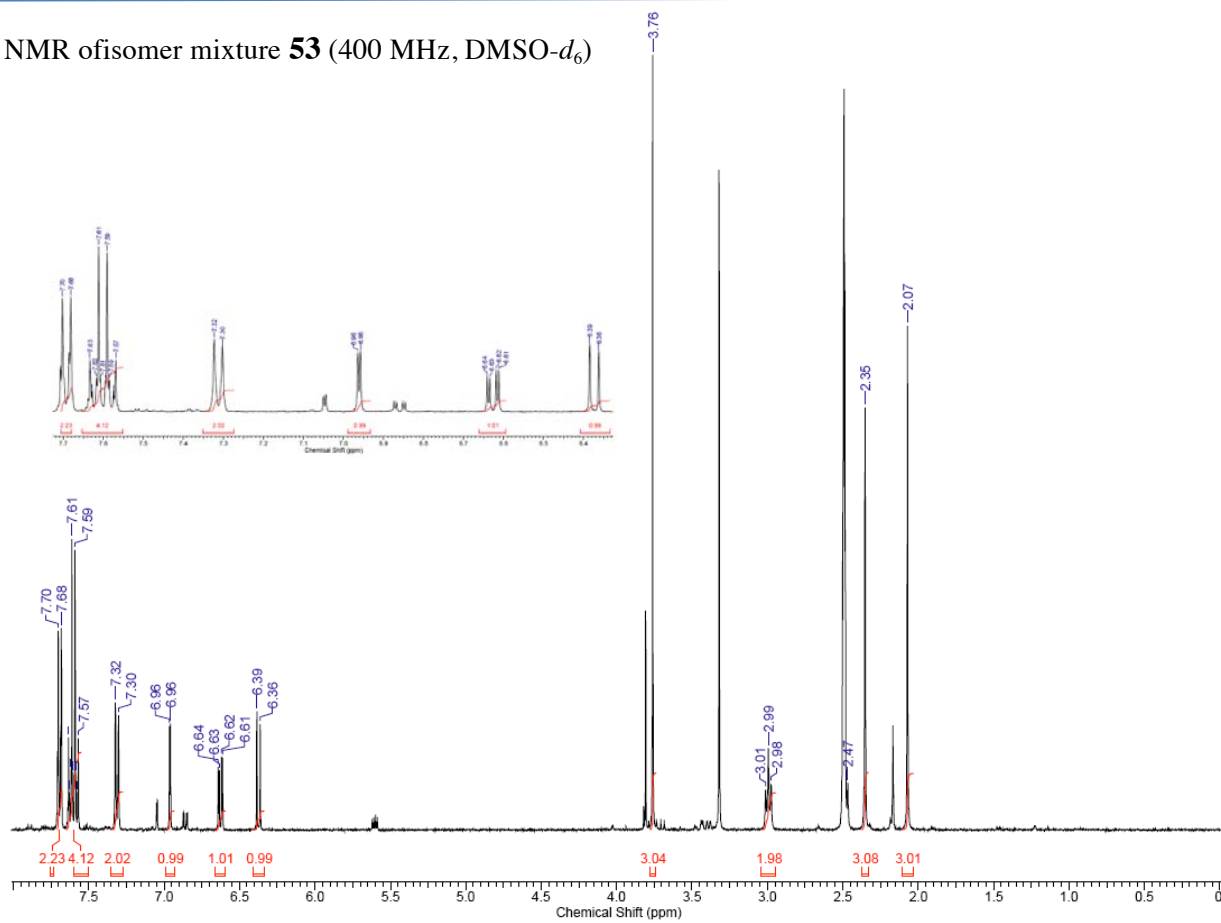
^1H NMR of isomer mixture **50** (400 MHz, $\text{DMSO-}d_6$)



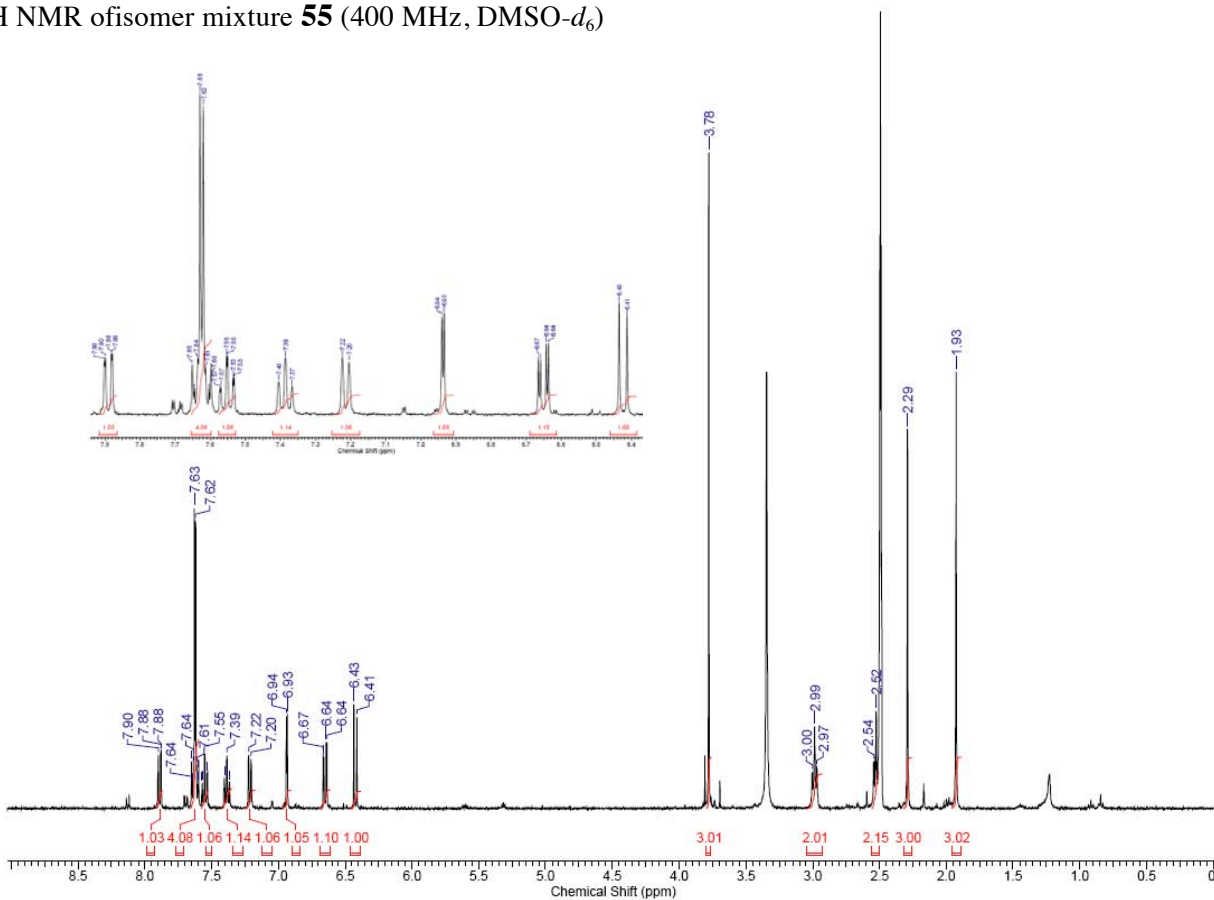
¹H NMR of isomer mixture **51** (400 MHz, DMSO-*d*₆)



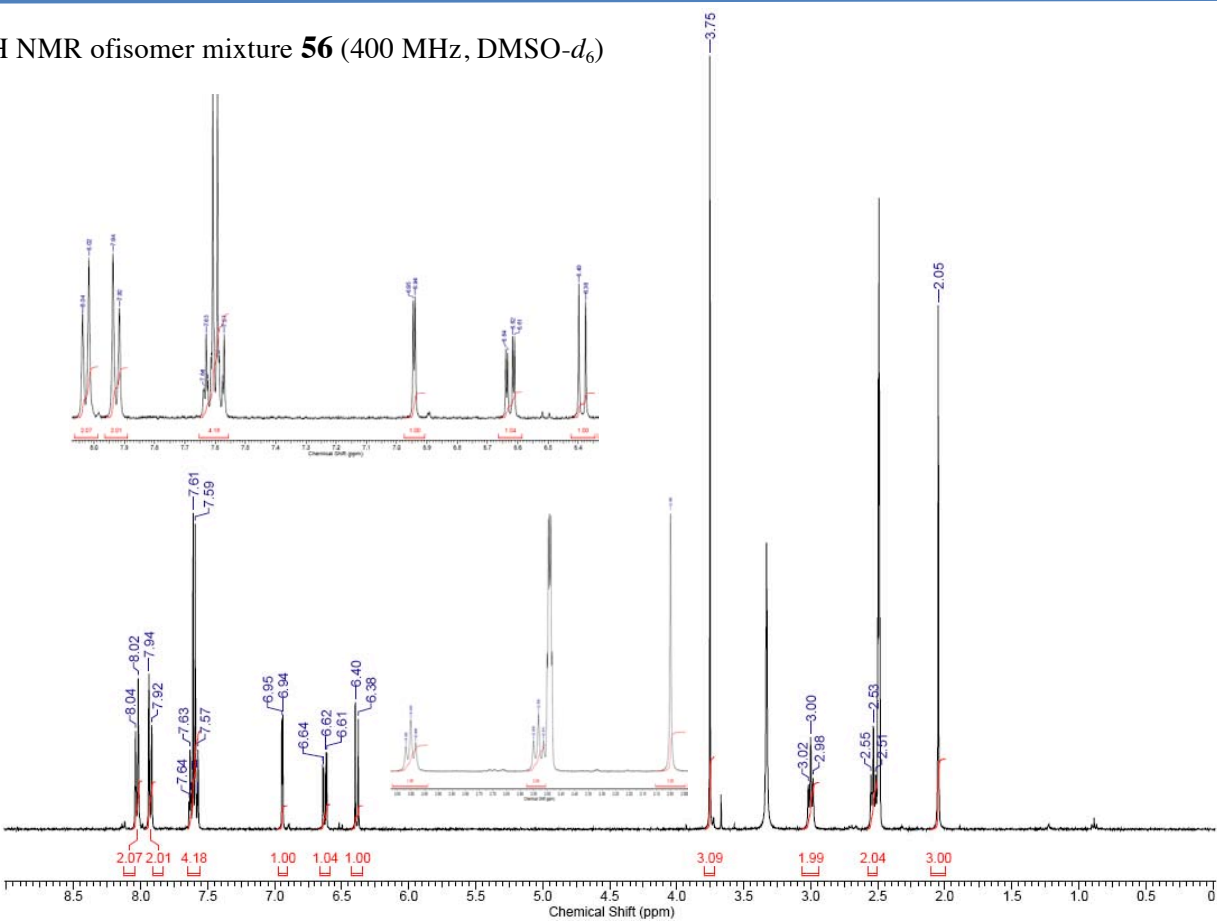
¹H NMR of isomer mixture **53** (400 MHz, DMSO-*d*₆)



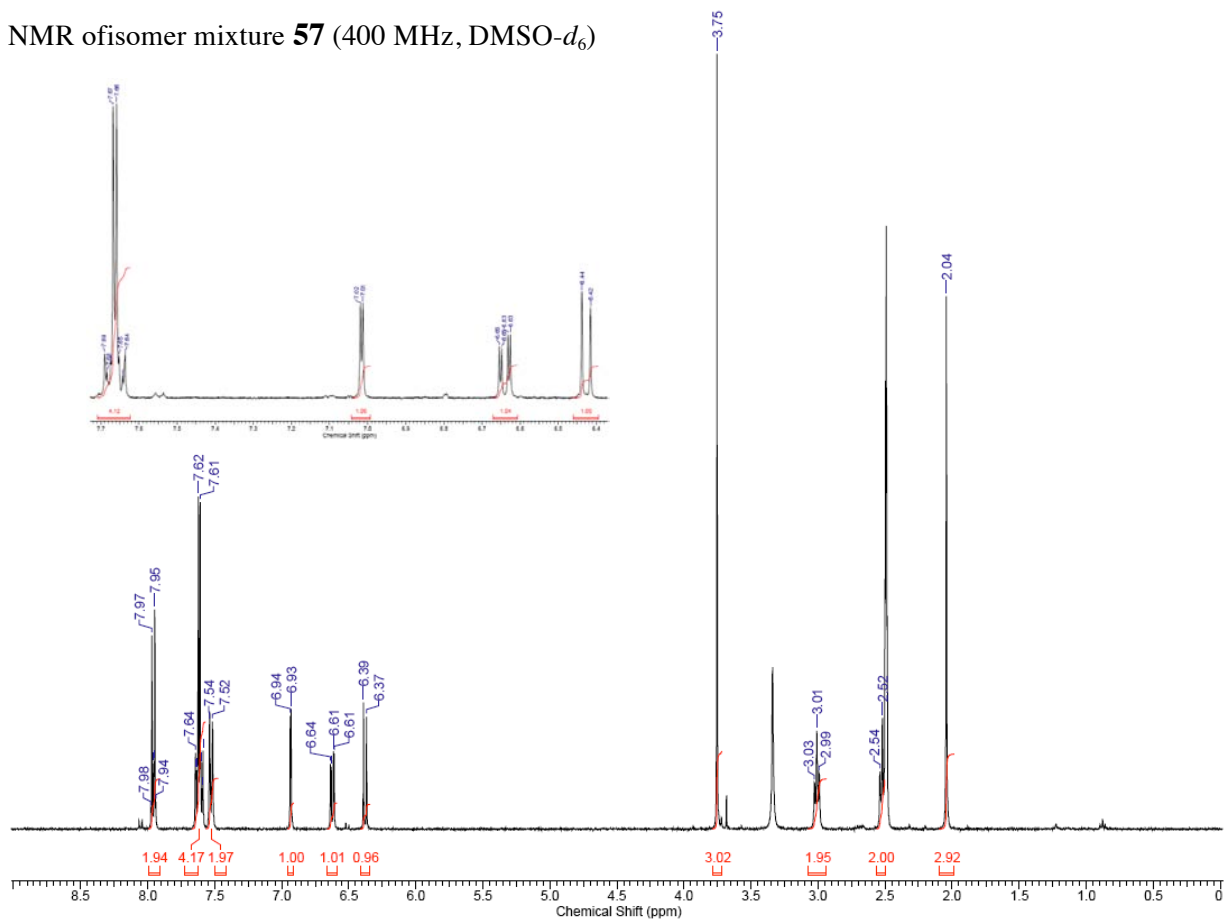
^1H NMR of isomer mixture **55** (400 MHz, $\text{DMSO-}d_6$)



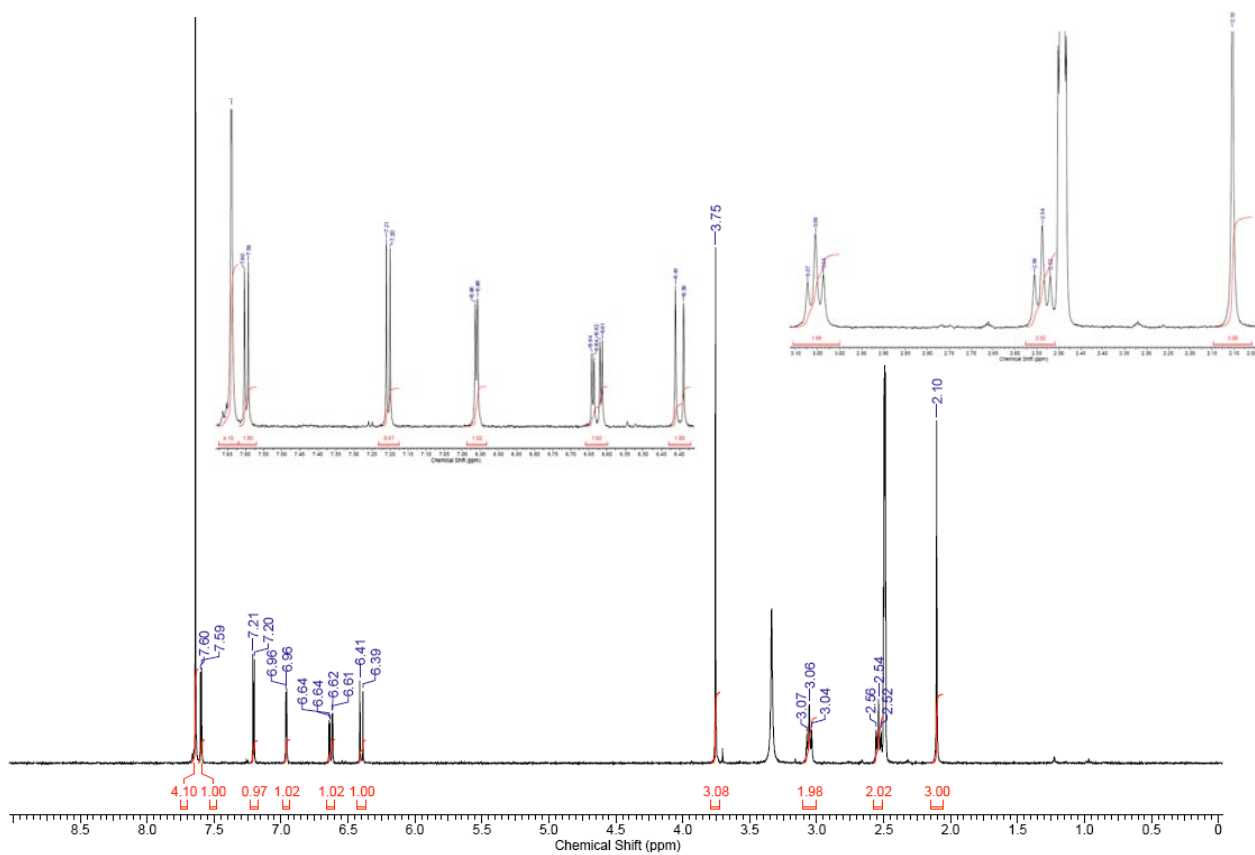
^1H NMR of isomer mixture **56** (400 MHz, $\text{DMSO-}d_6$)



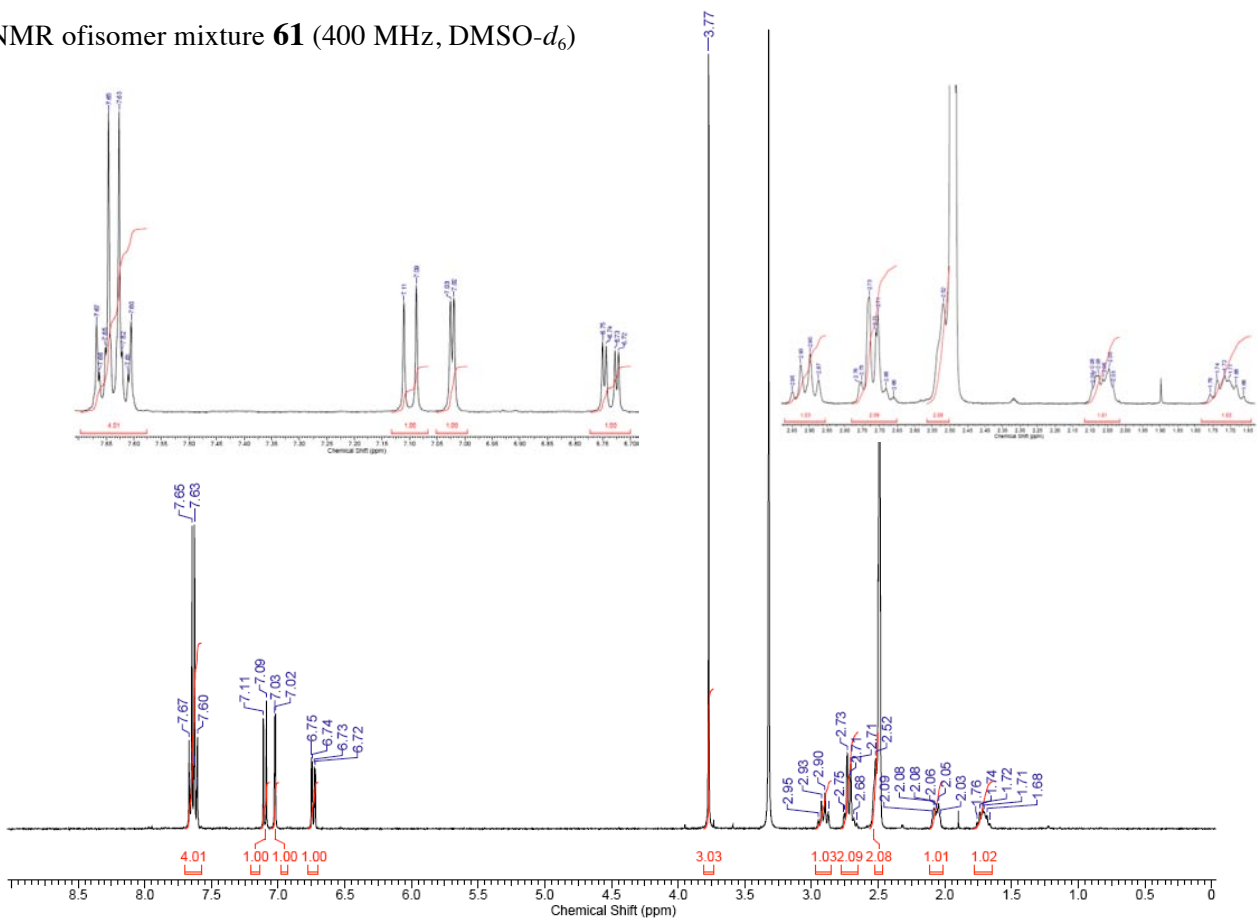
^1H NMR of isomer mixture **57** (400 MHz, $\text{DMSO-}d_6$)



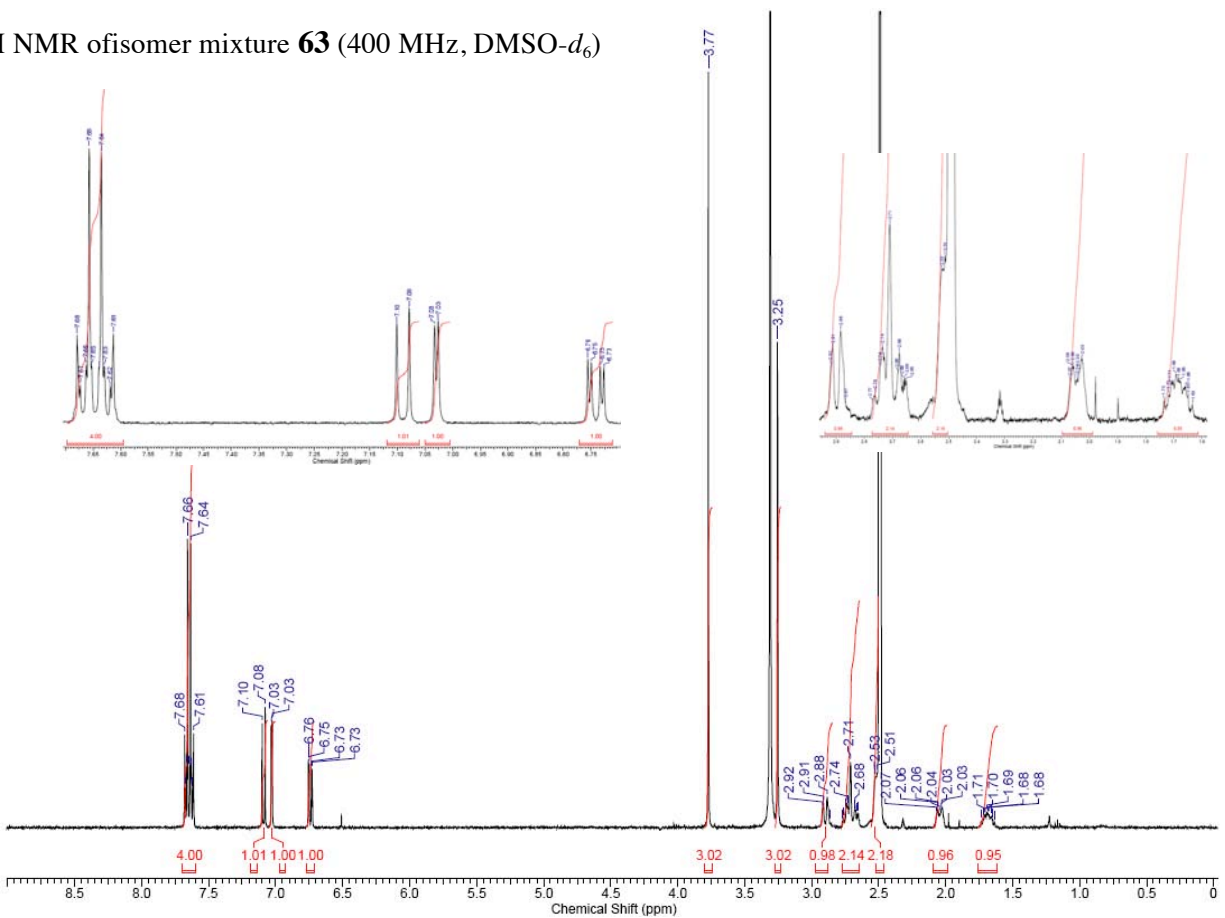
^1H NMR of isomer mixture **58** (400 MHz, $\text{DMSO-}d_6$)



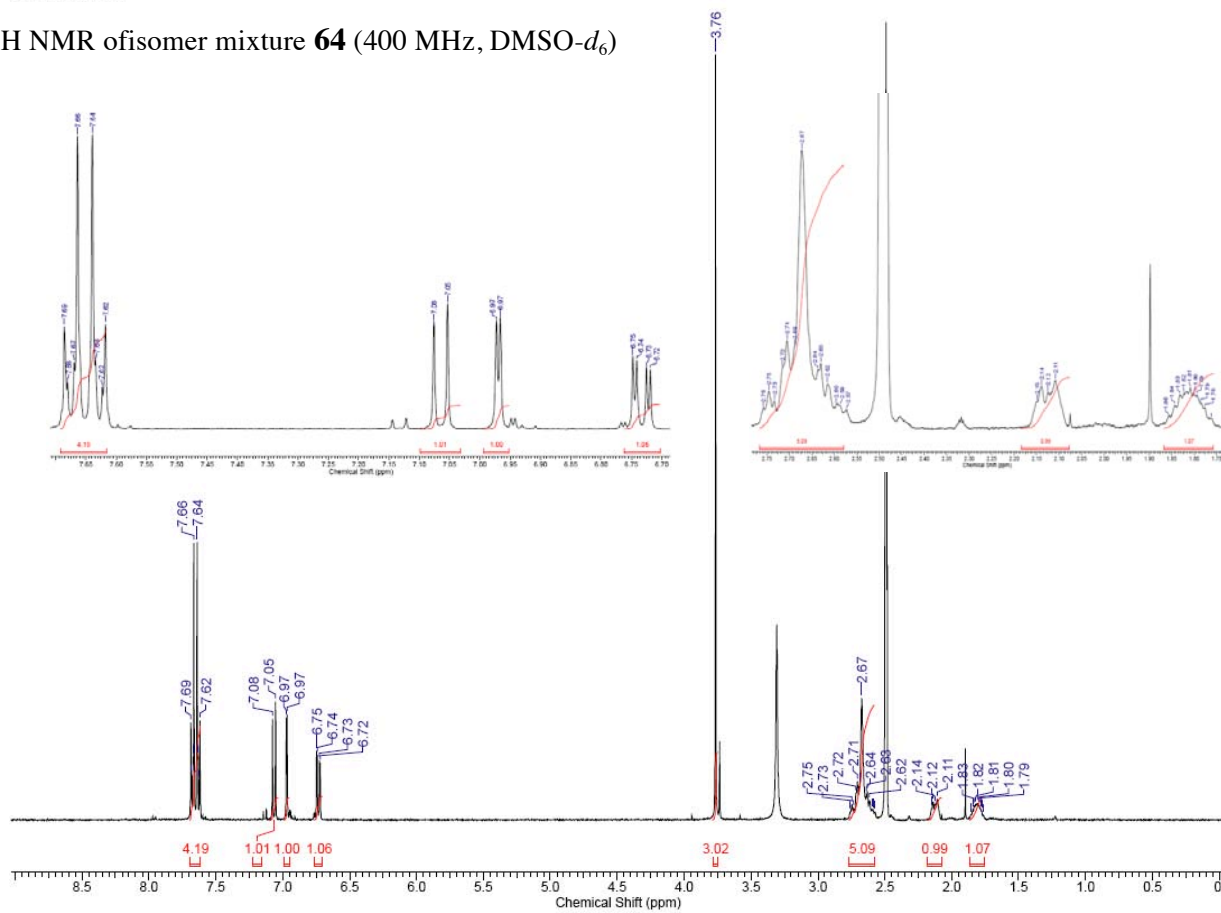
^1H NMR of isomer mixture **61** (400 MHz, $\text{DMSO-}d_6$)



^1H NMR of isomer mixture **63** (400 MHz, $\text{DMSO-}d_6$)



^1H NMR of isomer mixture **64** (400 MHz, $\text{DMSO-}d_6$)



Biochemical screening methods:

¹⁴C-AA TLC COX activity assay

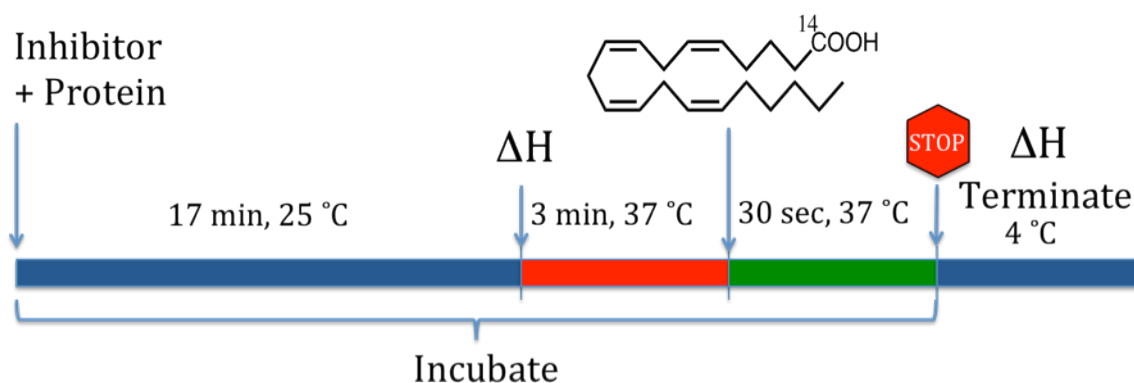


Figure S1. COX inhibition screening assay to evaluate compounds as competitive inhibitors: time- and concentration-dependent inhibition reactions were performed by pre-incubating inhibitor and hematin-reconstituted enzyme in 100 mM Tris-HCl buffer with 500 μ M phenol for 17 min at room temperature followed by a 3 min incubation at 37 °C. Following the addition of 5 μ M [¹⁴C]-AA ($\sim K_m$ of arachidonate), samples were incubated for 30 sec at 37 °C, and the reactions were then terminated by extraction with diethyl ether/methanol/citrate (30:4:1). Some assays were performed at 50 μ M to evaluate the time-depending inhibition of the compounds. The extracts were analyzed for substrate consumption by thin-layer chromatography as previously described.⁹ All inhibitor concentrations for 50% enzyme activity (IC_{50}) were determined by nonlinear regression analysis using Graphpad Prism software and were the average of at least two independent experiments. All inhibitors were prepared as stock solutions in dimethyl sulfoxide (DMSO), and diluted into reaction buffer so that the final DMSO concentration was 2.5% in all samples. Reactions were run with hematin-reconstituted proteins at final enzyme concentrations adjusted to give approximately 30% substrate consumption. AA was prepared as a stock solution in 0.1 N NaOH.

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