**SUPPORTING INFORMATION**

# Novel N-(4,5,6,7-tetrahydrobenzisoxazol-4-yl)amides as HSP90 inhibitors: design, synthesis and biological evaluation

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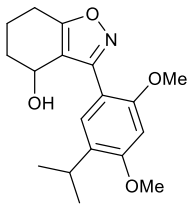
# Chemistry

**General methods and materials**. $^{1}H$, $^{13}C$, and $^{19}F$ NMR spectra were recorded on a Bruker AVANCE 500 spectrometer (500 Hz for $^{1}H$, 126 MHz for $^{13}C$ and 470 MHz for $^{19}F$). Chemical shift values are given in δ (ppm) relative to the residual solvent signals for $\delta_H$ 7.26 ppm ($CDCl_3$), 2.50 ppm (DMSO-$d_6$) and $\delta_C$ 77.16 ppm ($CDCl_3$), 39.52 ppm (DMSO-$d_6$). Constants (J) are given in Hertz (Hz). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet), br.s (broad singlet), or combinations thereof. High resolution MS were obtained on Agilent technologies 6550 iFunnel Q-TOF LC/MS system using electrospray ionization (ESI) method. High-performance liquid chromatography (HPLC) was performed on an Agilent 1200 RRPL HPLC instrument. Optical rotations were measured using an Autopol III automatic polarimeter (2-mL cell, 1 dm path length; concentration (c) is in g/100mL and $[\alpha]_D$ values are in degrees). Melting points were measured on Boetius apparatus and are uncorrected. Flash column chromatography was performed through silica gel (200−300 mesh). The progress of the reactions was followed by TLC on pre-coated silica gel or alumina F254 plates. The progress of the reactions was followed by TLC on pre-coated silica gel or alumina F254 plates. All solvents were purchased from commercial sources and, unless otherwise noted, used without further purification. If necessary, solvents were distilled and dried before use by standard methods.

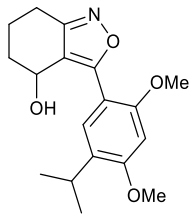
**General procedure for the synthesis of compounds 2a–b**. 3-(5-Isopropyl-2,4-dimethoxyphenyl)-6,7-dihydrobenzisoxazol-4(5*H*)-ones **1a-b** (2.26 g, 7.17 mmol, 1 eq.) were dissolved in EtOH (48 ml) and treated with $NaBH_4$ (543 mg, 14.3 mmol, 2 eq.). The reaction mixture was stirred overnight at room temperature. After the completion of the reaction, EtOH was removed by rotary evaporation. The residue was partitioned between saturated aqueous $NH_4Cl$ (100 mL) and EtOAc (100 mL), the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30% EtOAc/PE) to give alcohols **2a-b**.




**2a**

*3-(5-Isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-ol* **2a**. Yield 88%. White solid, mp 45–50 °C. $^{1}H$ NMR (500 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.55 (s, 1H), 4.68 (t, *J* = 3.4 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.25 (hept, *J* = 6.9 Hz, 1H), 3.10 (br. s, 1H), 2.87 (ddd, *J* = 17.1, 5.6, 3.2 Hz, 1H), 2.70 – 2.56 (m, 1H), 2.22 – 2.09 (m, 1H), 2.01 – 1.87 (m, 2H), 1.75 –

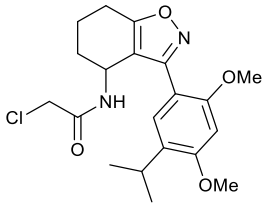
1.65 (m, 1H), 1.20 (d, *J* = 3.4 Hz, 3H), 1.19 (d, *J* = 3.4 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.74 (C), 159.38 (C), 159.28 (C), 155.74 (C), 130.60 (C), 129.16 (CH), 116.21 (C), 110.24 (C), 96.22 (CH), 61.45 (CH), 56.72 ($CH_3$), 55.71 ($CH_3$), 31.01 ($CH_2$), 26.52 (CH), 23.04 ($CH_2$), 22.76 ($2CH_3$), 17.61 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$: 340.1525, found 340.1518.




**2b**

*3-(5-Isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-ol* **2b**. Yield 80%. Pale yellow solid, mp 77–79 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.53 (s, 1H), 4.88 (t, *J* = 4.3 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.25 (hept, *J* = 6.9 Hz, 1H), 2.94 – 2.86 (m, 2H), 2.67 (ddd, *J* = 16.9, 9.8, 5.9 Hz, 1H), 2.15 – 2.04 (m, 1H), 1.98 – 1.88 (m, 1H), 1.87 – 1.73 (m, 2H), 1.21 (d, *J* = 2.6 Hz, 3H), 1.20 (d, *J* = 2.6 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.73 (C), 161.07 (C), 159.68 (C), 155.22 (C), 130.60 (C), 128.34 (CH), 115.04 (C), 109.36 (C), 95.62 (CH), 61.57 (CH), 56.42 ($CH_3$), 55.67 ($CH_3$), 31.34 ($CH_2$), 26.46 (CH), 22.77 ($CH_3$), 22.75 ($CH_3$), 21.81 ($CH_2$), 17.69 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$: 340.1525, found 340.1518.

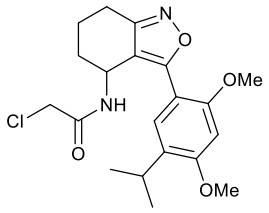
**General procedure for the synthesis of compounds 3a–b**. Chloroacetonitrile (2.0 mL, 32.0 mmol, 4 eq.) was added to a solution of alcohols **2a-b** (2.54 g, 8.0 mmol, 1 eq.) in glacial acetic acid (8 mL), followed by sulfuric acid (4.3 mL, 80.0 mmol, 10 eq.). The resulting reaction mixture was stirred at 60 °C for 25 h. The reaction mixture was cooled to 0 °C, poured into a vigorously stirred 10% aqueous solution of NaOH (100 mL) at 0 °C and extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried over $Na_2SO_4$. After removal of the solvent in vacuum, the residue was purified by column chromatography on silica gel (35→45% EtOAc/PE) to give products **3a-b**.




**3a**

*2-Chloro-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide* **3a**. Yield 79%. Light brown solid, mp 133–137 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.43 (s, 1H), 6.27 (br. d, *J* = 7.9 Hz, 1H), 5.13 (dd, *J* = 13.3, 7.5 Hz, 1H), 3.87 (s,

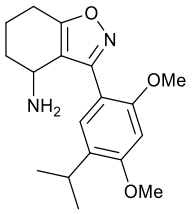
3H), 3.80 (s, 3H), 3.78 (d, *J* = 15.1 Hz, 1H), 3.51 (d, *J* = 15.1 Hz, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.80 – 2.74 (m, 2H), 2.22 – 2.12 (m, 1H), 2.05 – 1.88 (m, 2H), 1.65 – 1.54 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.60 (C), 165.06 (C), 159.48 (C), 159.26 (C), 156.50 (C), 129.40 (C), 128.12 (CH), 113.34 (C), 109.23 (C), 94.74 (CH), 55.79 ($2CH_3$), 44.03 (CH), 42.36 ($CH_2$), 30.43 ($CH_2$), 26.37 (CH), 22.95 ($CH_3$), 22.82 ($CH_2$), 22.75 ($CH_3$), 20.15 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{25}ClN_2O_4Na$ $[M+Na]^+$: 415.1400, found 415.1396.




**3b**

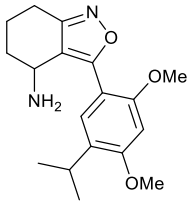
*2-Chloro-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-yl)acetamide* **3b** Yield 76%. Light brown solid, mp 160–163 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.42 (s, 1H), 6.31 (br. d, *J* = 7.5 Hz, 1H), 5.20 (td, *J* = 8.0, 5.7 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.80 (m, 3H), 3.62 (d, *J* = 15.0 Hz, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.85 (dt, *J* = 16.8, 5.5 Hz, 1H), 2.75 (ddd, *J* = 16.9, 9.1, 5.6 Hz, 1H), 2.26 – 2.17 (m, 1H), 2.00 – 1.90 (m, 1H), 1.90 – 1.78 (m, 1H), 1.64 – 1.52 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.03 (C), 164.25 (C), 161.35 (C), 160.04 (C), 156.26 (C), 129.59 (C), 127.60 (CH), 111.88 (C), 108.41 (C), 94.59 (CH), 55.92 ($CH_3$), 55.72 ($CH_3$), 43.94 (CH), 42.37 ($CH_2$), 30.56 ($CH_2$), 26.36 (CH), 22.86 ($CH_3$), 22.74 ($CH_3$), 21.80 ($CH_2$), 20.12 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{25}ClN_2O_4Na$ $[M+Na]^+$: 415.1400, found 415.1399.

**General procedure for the synthesis of compounds 4a–b**. Thiourea (690 mg, 9.08 mmol, 2 eq.) was added to a solution of compounds **3a-b** (1.78 g, 4.54 mmol, 1 eq.) in EtOH (35 mL). The resulting reaction mixture was heated under reflux for 24 h and then EtOH was removed by rotary evaporation. The residue was dissolved in $CHCl_3$ (100 mL) and washed with 10% aqueous solution of NaOH (30 mL). The organic phase was dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified on silica gel (5→10% MeOH/$CHCl_3$) to provide amines **4a-b**.




**4a**

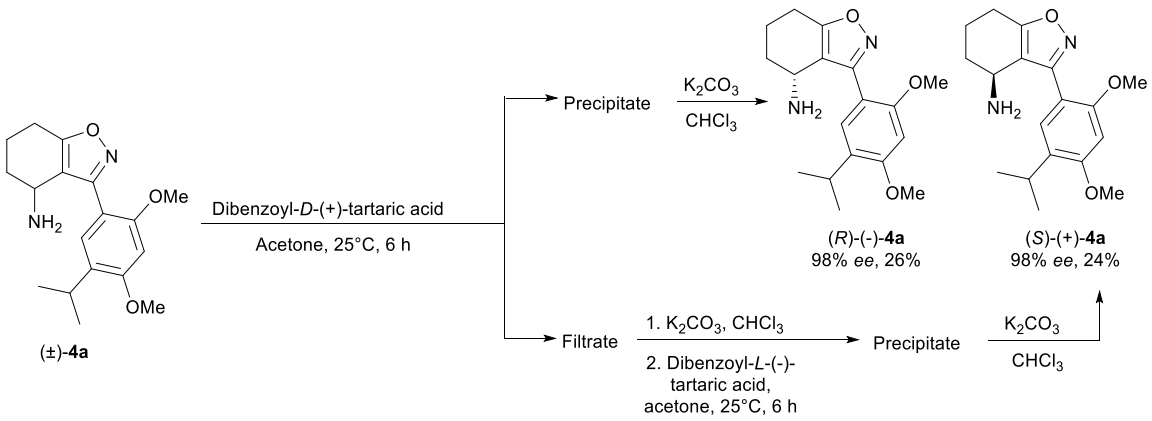
*3-(5-Isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-amine* **4a**. Yield 72%. Light brown oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 6.51 (s, 1H), 4.05 – 4.01 (m, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 2.75 – 2.69 (m, 2H), 2.10 – 2.01 (m, 2H), 1.91 – 1.81 (m, 1H), 1.50 – 1.41 (m, 1H), 1.32 (br. s., 2H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.83 (C), 159.31 (C), 159.27 (C), 156.14 (C), 129.73 (C), 128.58 (CH), 118.23 (C), 110.49 (C), 95.27 (CH), 55.95 ($CH_3$), 55.64 ($CH_3$), 44.99 (CH), 33.07 ($CH_2$), 26.46 (CH), 23.00 ($CH_2$), 22.91 ($CH_3$), 22.69 ($CH_3$), 20.12 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{24}N_2O_3Na$ $[M+Na]^+$: 339.1685, found 339.1681.




**4b**

*3-(5-Isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-amine* **4b**. Yield 58%. Light brown oil. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.50 (s, 1H), 4.13 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.25 (hept, *J* = 6.9 Hz,1H), 2.82 (dt, *J* = 16.7, 5.2 Hz, 1H), 2.76 – 2.66 (m, 1H), 2.13 – 1.98 (m, 2H), 1.90 (br. s, 2H), 1.82 – 1.70 (m, 1H), 1.47 (ddd, *J* = 21.1, 10.5, 1.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.39 (C), 161.06 (C), 159.67 (C), 155.62 (C), 130.05 (C), 127.96 (CH), 116.97 (C), 109.71 (C), 95.26 (CH), 56.05 ($CH_3$), 55.64 ($CH_3$), 44.79 (CH), 33.07 ($CH_2$), 26.45 (CH), 22.85 ($CH_3$), 22.75 ($CH_3$), 22.08 ($CH_2$), 20.30 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{24}N_2O_3Na$ $[M+Na]^+$: 339.1685, found 339.1681.

**Resolution of 3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[*d*]isoxazol-4-amine 4a**.




*(R)-3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-amine (R)-(-)-**4a**.* Dibenzoyl-*D*-(+)-tartaric acid (989 mg, 2.76 mmol, 1 eq.) was added to a solution of racemic amine **4a** (872 mg, 2.76 mmol, 1 eq.) in acetone (28 mL). The resulting mixture was

stirred at room temperature for 6 h and then filtered. The filtrate was further used to obtain (*S*)-(+)-**4a**. The precipitate, contained (*R*)-(-)-**4a**·Dibenzoyl-*D*-(+)-tartaric acid, was suspended in a mixture of $CHCl_3$ (6 mL) and 10% aqueous solution of $K_2CO_3$ (10 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated completely to obtain the (*R*)-(-)-**4a** (227 mg, 0.72 mmol, 26% yield) (this procedure was carried out three times). White solid, mp 110–115 °C. $[\alpha]_D^{20}$ = -93.7 (c=0.4 in $CHCl_3$). Spectroscopic data are consistent with those of racemic amine **4a**.

The absolute configuration and *ee* was determined by the Mosher method. *Ee* determined by the Mosher method was 98%. Selected $^1$H NMR chemical shift for *(R)*-Mosher acid·*(R)*-amine **S1**: δ 6.48 (s, 1H, $CH_{Ar}$). Selected $^1$H NMR chemical shift for *(R)*-Mosher acid·*(S)*-amine **S2**: δ 6.36 (s, 1H, $CH_{Ar}$).

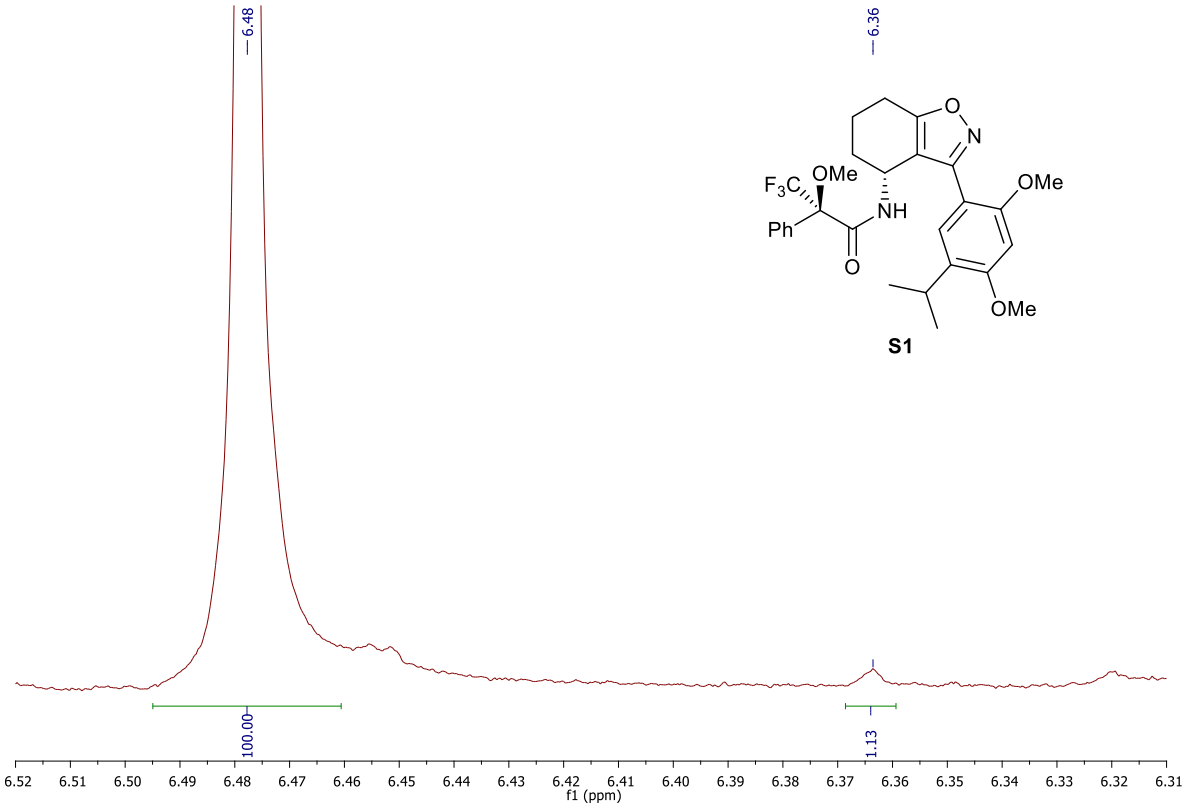



**Fig. S1** Fragment of $^1$H NMR spectra of amide **S1** obtained from (*R*)-Mosher acid and (*R*)-(-)-**4a**

*(S)-3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-amine* *(S)-(+)-***4a**. The filtrate from the above was concentrated, suspended in a mixture of $CHCl_3$ (9 mL) and 10% aqueous solution of $K_2CO_3$ (15 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was

evaporated to obtain a mixture of (*R)*-(-)- and (*S)*-(+)-**4a** (248 mg, 0.78 mmol), enriched with the (*S)*-(+)-isomer.

Dibenzoyl-*L*-(-)-tartaric acid (280 mg, 0.78 mmol, 1 eq.) was added to a solution of obtained mixture (248 mg, 0.78 mmol, 1 eq.) in acetone (8 mL). The resulting mixture was stirred at room temperature for 6 h and then filtered. The precipitate, contained (*S)*-(+)-**4a**·Dibenzoyl-*L*-(-)-tartaric acid, was suspended in a mixture of $CHCl_3$ (8 mL) and 10% aqueous solution of $K_2CO_3$ (14 mL) and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and the solvent was evaporated completely to obtain the (*S)*-(+)-**4a** (209 mg, 0.66 mmol, 24% yield) (this procedure was carried out two times). White solid, 110–115 °C. $[\alpha]_D^{20}$ = +100.9 (c=0.4 in $CHCl_3$). Spectroscopic data are consistent with those of racemic amine.

The absolute configuration and *ee* was determined by the Mosher method. *Ee* determined by the Mosher method was 98%. Selected $^1$H NMR chemical shift for (*R*)-Mosher acid·(*S*)-amine **s2**: δ 6.36 (s, 1H, $CH_{Ar}$). Selected $^1$H NMR chemical shift for (*R*)-Mosher acid·(*R*)-amine **S1**: δ 6.48 (s, 1H, $CH_{Ar}$).

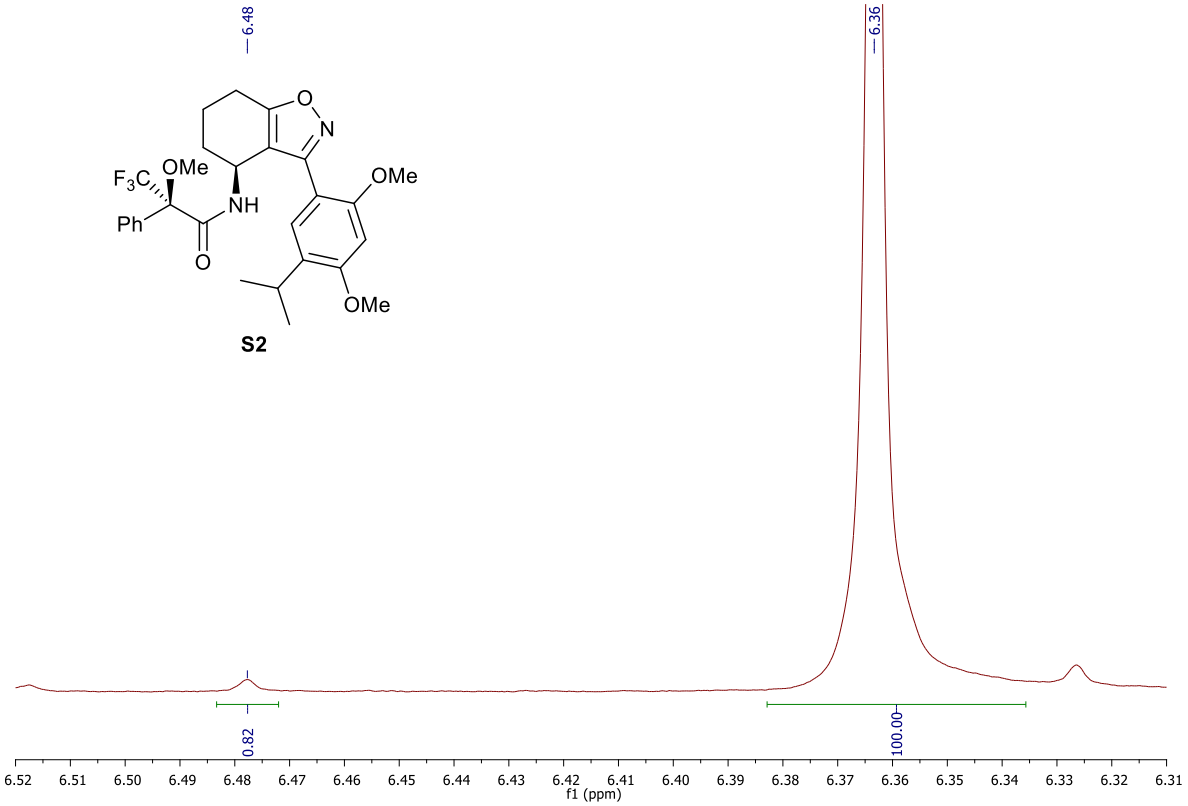



**Fig. S2** Fragment of $^1$H NMR spectra of amide **S2** obtained from (*R*)-Mosher acid and (*S*)-(+)-**4a**

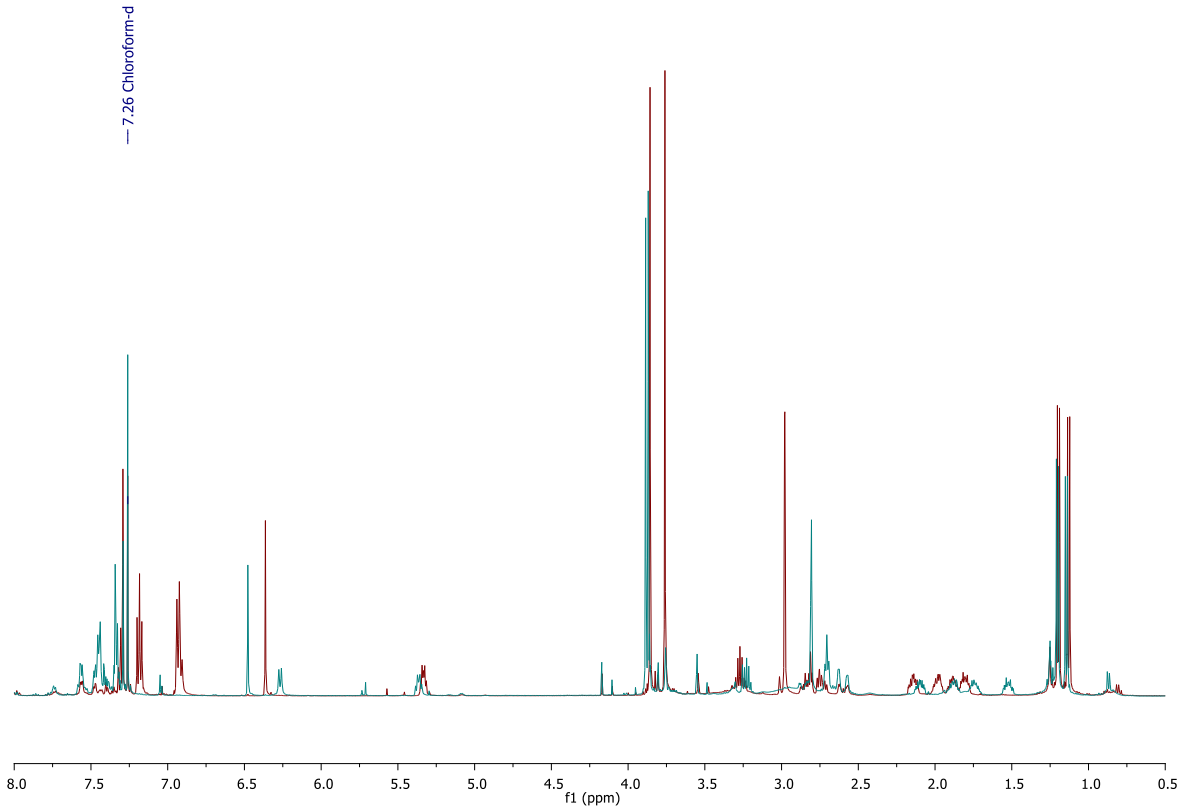
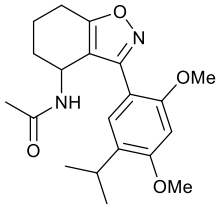



**Fig. S3.** $^{1}$H NMR spectra of (*R*)-Mosher acid·(*R*)-amine **S1** (green curve) and (*R*)-Mosher acid·(*S*)-amine **S2** (red curve)

**General procedure for the synthesis of compounds 5 and 6**. **Procedure A**. A round-bottomed flask was charged with dry DCM (1 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) (55 mg, 0.29 mmol, 1.3 eq.), and DMAP (38 mg, 0.31 mmol, 1.4 eq.) or hydroxybenzotriazole (HOBt) (3 mg, 0.02 mmol, 0.1 eq.) under argon atmosphere. The reaction flask was cooled to zero degree in an ice bath, and the carboxylic acid (0.24 mmol, 1.1 eq.) was then added. After five minutes of stirring, a solution of the amine (70 mg, 0.22 mmol, 1 eq.) in dry DCM (1 mL) was added into the flask. The ice bath was removed, and the reaction mixture was allowed to stir at room temperature until the starting material was consumed completely as indicated by TLC (1 – 2 h). The reaction was quenched with HCl (1.0 M, 2 mL), and the organic layer was separated from the aqueous layer. The aqueous layer was then extracted with DCM (2 × 2 mL). The organic layers were combined and dried over $Na_2SO_4$. After removing the solvent with a rotary evaporator, the crude product was purified by silica gel column chromatography using either PE/EtOAc or $CHCl_3$/MeOH as eluent.

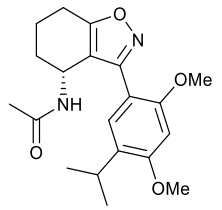
**General procedure for the synthesis of compounds 5 and 6. Procedure B.** Triethylamine (TEA) (46 μL, 0.33 mmol, 1.5 eq.) was added to a solution of the amine (70 mg, 0.22 mmol, 1 eq.) in dry DCM (2 mL) under argon atmosphere. Then the acid chloride (0.33 mmol, 1.5 eq.) or anhydride (0.24 – 0.33 mmol, 1.1 – 1.5 eq.) was added at 0 °C. The reaction mixture

was stirred at room temperature until the starting material was consumed completely as indicated by TLC (0.5 – 12 h). The reaction was quenched with HCl (1.0 M, 2 mL), and the organic layer was separated from the aqueous layer. The aqueous layer was then extracted with DCM (2 × 2 mL). The organic layers were combined and dried over $Na_2SO_4$. After removing the solvent with a rotary evaporator, the crude product was purified by silica gel column chromatography using either PE/EtOAc or $CHCl_3$/MeOH as eluent.



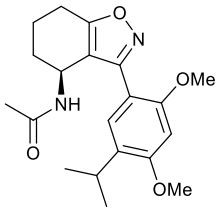

**5a**

*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide* **5a**. Synthesized according to the general procedure B from amine **4a** and acetic anhydride (1.5 eq.). The crude product was purified by column chromatography on silica gel (2→4% MeOH/$CHCl_3$). Yield 93%. White solid, mp 171–173 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.46 (s, 1H), 5.33 (br. d, *J* = 7.6 Hz, 1H), 5.08 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.87 (s, 1H), 3.83 (s, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.74 (t, *J* = 6.2 Hz, 2H), 2.16 – 2.08 (m, 1H), 1.99 – 1.86 (m, 2H), 1.64 – 1.61 (m, 1H), 1.59 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.58 (C), 169.19 (C), 159.36 (C), 159.27 (C), 156.49 (C), 129.29 (C), 128.01 (CH), 113.73 (C), 109.49 (C), 94.94 (CH), 55.94 ($CH_3$), 55.71 ($CH_3$), 43.44 (CH), 30.66 ($CH_2$), 26.41 (CH), 23.08 ($CH_2$), 22.87 ($2CH_3$), 22.82 ($CH_3$), 19.94 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{27}N_2O_4$ $[M+H]^+$: 359.1971, found 359.1978.



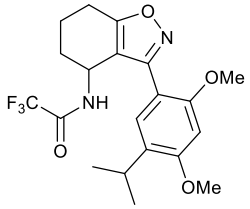

(*R*)-**5a**

*(R)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide (R)*-**5a**. Synthesized according to the general procedure B from amine *(R)*-**4a** and acetic anhydride (1.5 eq.). The crude product was purified by column chromatography on silica gel (2→4% MeOH/$CHCl_3$). Yield 91%. White solid, mp 161–165 °C. $[\alpha]_D^{20}$ = -40.8 (c=0.4 in $CHCl_3$). HRMS (ESI+): m/z calc'd for $C_{20}H_{26}N_2O_4Na$ $[M+Na]^+$: 381.1790, found 381.1785. Spectroscopic data are consistent with those of racemic acetamide **5a**.



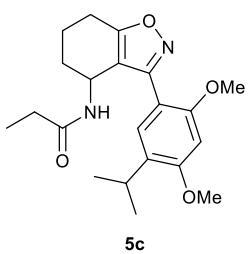
(*S*)-**5a**

*(S)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide (S)*-**5a**. Synthesized according to the general procedure B from amine *(S)*-**4a** and acetic anhydride (1.5 eq.). The crude product was purified by column chromatography on silica gel (2→4% MeOH/$CHCl_3$). Yield 93%. White solid, mp 157–161 °C. $[\alpha]_D^{20}$ = +44.9 (c=0.4 in $CHCl_3$). HRMS (ESI+): m/z calc'd for $C_{20}H_{26}N_2O_4Na$ $[M+Na]^+$: 381.1790, found 381.1786. Spectroscopic data are consistent with those of racemic acetamide **5a**.



**5b**

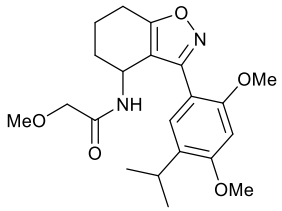
*2,2,2-Trifluoro-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide* **5b**. Synthesized according to the general procedure B from amine **4a** and trifluoroacetic anhydride (1.5 eq.). The crude product was purified by column chromatography on silica gel (20→30% EtOAc/PE). Yield 77%. White solid, mp 104–109 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.44 (s, 1H), 6.31 (br. d, *J* = 7.3 Hz, 1H), 5.11 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.80 – 2.75 (m, 2H), 2.25 – 2.16 (m, 1H), 2.05 – 1.90 (m, 2H), 1.73 – 1.63 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.96 (C), 159.71 (C), 159.10 (C), 156.41 (q, *J* = 36.9 Hz, C), 156.17 (C), 129.76 (C), 128.01 (CH), 115.61 (q, *J* = 288.6 Hz, C), 112.38 (C), 108.69 (C), 95.08 (CH), 55.87 ($CH_3$), 55.73 ($CH_3$), 44.45 (CH), 29.87 ($CH_2$), 26.38 (CH), 22.83 ($CH_3$), 22.75 ($CH_2$), 22.68 ($CH_3$), 19.96 ($CH_2$). $^{19}$F NMR (470 MHz, $CDCl_3$) δ -76.30 (s). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{23}F_3N_2O_4Na$ $[M+Na]^+$: 435.1508, found 435.1497.



**5c**

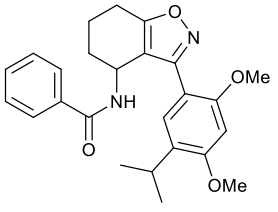
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)propionamide* **5c**. Synthesized according to the general procedure B from amine **4a** and

propionyl chloride. The crude product was purified by column chromatography on silica gel (65→75% EtOAc/PE). Yield 65%. White solid, mp 157–160 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.43 (s, 1H), 5.26 (br. d, *J* = 7.8 Hz, 1H), 5.12 (dd, *J* = 13.2, 7.1 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.76 – 2.69 (m, 2H), 2.20 – 2.10 (m, 1H), 1.97 – 1.89 (m, 2H), 1.88 – 1.81 (m, 1H), 1.80 – 1.70 (m, 1H), 1.61 – 1.49 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.76 (t, *J* = 7.6 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.77 (C), 169.49 (C), 159.36 (C), 159.26 (C), 156.56 (C), 129.20 (C), 127.94 (CH), 113.94 (C), 109.54 (C), 94.88 (CH), 55.84 ($CH_3$), 55.71 ($CH_3$), 43.24 (CH), 30.83 ($CH_2$), 29.66 ($CH_2$), 26.37 (CH), 22.94 ($CH_3$), 22.88 ($CH_2$), 22.74 ($CH_3$), 20.07 ($CH_2$), 9.60 ($CH_3$). HRMS (ESI+): *m/z* calc'd for $C_{21}H_{28}N_2O_4Na$ $[M+Na]^+$: 395.1947, found 395.1945.



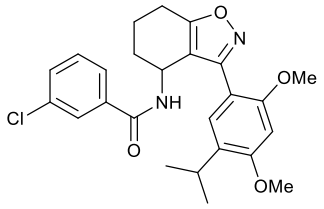

**5d**

*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-methoxyacetamide* **5d.** A solution of KOH (86 mg, 1.53 mmol, 5 eq.) in water (1.5 mL) was added to a solution of chloroacetamide **3a** (120 mg, 0.31 mmol, 1 eq.) in MeOH (3 mL). The reaction mixture was stirred at reflux overnight. It was then diluted with 20% HCl (1 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified on silica gel (50→60% EtOAc/PE) to provide amide **5d**. Yield 73%. White solid, mp 100–103 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.43 (s, 1H), 6.28 (br. d, *J* = 8.2 Hz, 1H), 5.19 (dd, *J* = 13.7, 7.0 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.75 (d, *J* = 15.2 Hz, 1H), 3.34 (d, *J* = 15.2 Hz, 1H), 3.21 (hept, *J* = 6.9 Hz, 1H), 2.97 (s, 3H), 2.79 – 2.73 (m, 2H), 2.18 – 2.08 (m, 1H), 2.01 – 1.88 (m, 2H), 1.67 – 1.57 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.59 (C), 168.83 (C), 159.34 (C), 159.33 (C), 156.61 (C), 129.02 (C), 128.14 (CH), 113.61 (C), 109.42 (C), 94.58 (CH), 71.83 ($CH_2$), 58.99 ($CH_3$), 55.71 ($2CH_3$), 42.73 (CH), 30.71 ($CH_2$), 26.35 (CH), 22.87 ($CH_2$ +$CH_3$), 22.80 ($CH_3$), 19.98 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{21}H_{29}N_2O_5$ $[M+H]^+$: 389.2076, found 389.2074.



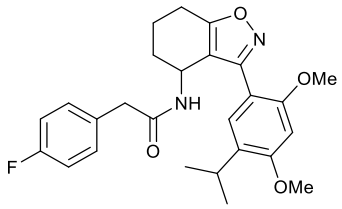

**5e**

*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)benzamide* **5e**. Synthesized according to the general procedure A from amine **4a** and benzoic acid using DMAP. The crude product was purified by column chromatography on silica gel (40→45% EtOAc/PE). Yield 75%. White solid, mp 195–198 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.37 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.32 (s, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.09 (dd, *J* = 8.2, 1.2 Hz, 2H), 6.24 (s, 1H), 5.84 (br. d, *J* = 7.7 Hz, 1H), 5.28 (dd, *J* = 13.4, 7.8 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 2.86 – 2.69 (m, 2H), 2.41 – 2.31 (m, 1H), 2.10 – 1.92 (m, 2H), 1.57 (tdd, *J* = 13.6, 8.2, 3.1 Hz, 1H), 1.21 (d, *J* = 4.9 Hz, 3H), 1.20 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.57 (C), 167.10 (C), 159.55 (C), 159.13 (C), 156.71 (C), 134.72 (C), 131.34 (CH), 129.28 (C), 128.33 (2CH), 128.01 (CH), 126.75 (2CH), 113.93 (C), 109.48 (C), 95.04 (CH), 55.81 ($CH_3$), 55.57 ($CH_3$), 44.71 (CH), 30.93 ($CH_2$), 26.47 (CH), 23.21 ($CH_3$), 22.89 ($CH_2$), 22.68 ($CH_3$), 20.46 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{25}H_{28}N_2O_4Na$ $[M+Na]^+$: 443.1947, found 443.1944.



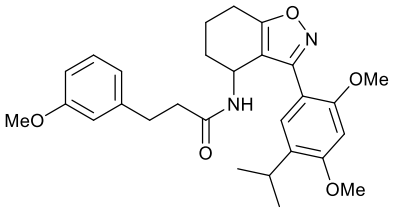

**5f**

*3-Chloro-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)benzamide* **5f**. Synthesized according to the general procedure A from amine **4a** and 3-chlorobenzoic acid using DMAP. The crude product was purified by column chromatography on silica gel (30% EtOAc/PE). Yield 77%. White solid, mp 202–205 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.35 (ddd, *J* = 7.9, 1.8, 1.0 Hz, 1H), 7.32 (s, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 1.8 Hz, 1H), 6.94 – 6.90 (m, 1H), 6.28 (s, 1H), 5.86 (br. d, *J* = 7.8 Hz, 1H), 5.27 (dd, *J* = 13.8, 8.1 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.87 – 2.69 (m, 2H), 2.41 – 2.33 (m, 1H), 2.10 – 1.92 (m, 2H), 1.60 – 1.49 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.63 (C), 165.85 (C), 159.60 (C), 159.00 (C), 156.57 (C), 136.51 (C), 134.60 (C), 131.39 (CH), 129.66 (CH), 129.46 (C), 127.99 (CH), 127.17 (CH), 124.82 (CH), 113.66 (C), 109.26 (C), 94.91 (CH), 55.89 ($CH_3$), 55.59 ($CH_3$), 44.93 (CH), 30.84 ($CH_2$), 26.38 (CH), 22.90 ($CH_2$), 22.85 ($2CH_3$), 20.51 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{25}H_{27}ClN_2O_4Na$ $[M+Na]^+$: 377.1557, found 377.1549.



**5g**

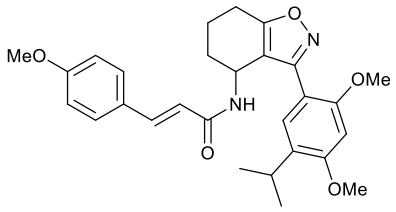
*2-(4-Fluorophenyl)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide* **5g**. Synthesized according to the general procedure A from amine **4a** and 2-(4-fluorophenyl)acetic acid using DMAP. The crude product was purified by column chromatography on silica gel (40→45% EtOAc/PE). Yield 81%. White solid, mp 176–178 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.87 – 6.80 (m, 2H), 6.73 – 6.67 (m, 2H), 6.42 (s, 1H), 5.20 (dd, *J* = 13.3, 7.3 Hz, 1H), 5.15 (br. d, *J* = 8.1 Hz, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.29 (hept, *J* = 6.9, 1H), 3.24 – 3.09 (m, 2H), 2.77 – 2.62 (m, 2H), 2.21 – 2.12 (m, 1H), 1.93 – 1.83 (m, 2H), 1.49 – 1.40 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.22 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.66 (C), 169.63 (C), 161.94 (d, *J* = 246.0 Hz, C), 159.56 (C), 158.96 (C), 156.66 (C), 130.81 (d, *J* = 8.0 Hz, 2CH), 130.21 (d, *J* = 2.4 Hz, C), 129.09 (C), 128.03 (CH), 115.78 (d, *J* = 21.3 Hz, 2CH), 113.35 (C), 109.44 (C), 94.67 (CH), 55.85 ($CH_3$), 55.66 ($CH_3$), 43.84 (CH), 42.87 ($CH_2$), 30.84 ($CH_2$), 26.55 (CH), 23.10 ($CH_3$), 22.87 ($CH_2$), 22.62 ($CH_3$), 20.15 ($CH_2$). $^{19}$F NMR (470 MHz, $CDCl_3$) δ -115.12 – -115.20 (m). HRMS (ESI+): m/z calc'd for $C_{26}H_{30}FN_2O_4$ $[M+H]^+$: 453.2190, found 453.2186.



**5h**

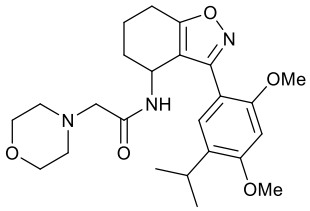
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(3-methoxyphenyl)propanamide* **5h**. Synthesized according to the general procedure A from amine **4a** and 3-(3-methoxyphenyl)propanoic acid using DMAP. The crude product was purified by column chromatography on silica gel (40→45% EtOAc/PE). Yield 47%. Light brown solid, mp 142–147 °C. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.71 (dd, J = 8.2, 2.3 Hz, 1H), 6.63 – 6.57 (m, 2H), 6.44 (s, 1H), 5.28 (br. d, J = 7.9 Hz, 1H), 5.12 (dd, *J* = 13.0, 7.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.23 (hept, J = 6.9 Hz, 1H), 2.75 – 2.60 (m, 3H), 2.51 – 2.42 (m, 1H), 2.14 – 2.00 (m, 3H), 1.93 – 1.78 (m, 2H), 1.56 – 1.47 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.16 (C), 169.55 (C), 159.86 (C), 159.39 (C), 159.21 (C), 156.55 (C), 142.40 (C), 129.57 (CH), 129.30 (C), 128.06 (CH), 120.59 (CH), 114.08 (CH), 113.71 (C), 111.67 (CH), 109.56 (C), 94.98 (CH), 55.90 ($CH_3$), 55.66

($CH_3$), 55.24 ($CH_3$), 43.32 (CH), 38.34 ($CH_2$), 31.79 ($CH_2$), 30.66 ($CH_2$), 26.41 (CH), 22.88 ($CH_2$), 22.85 ($2CH_3$), 19.89 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{28}H_{34}N_2O_5Na$ $[M+Na]^+$: 501.2365, found 501.2359.




**5i**

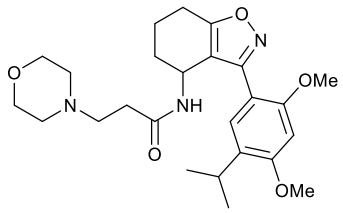
*(E)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(4-methoxyphenyl)acrylamide* **5i**. Synthesized according to the general procedure A from amine **4a** and (*E*)-3-(4-methoxyphenyl)acrylic acid using DMAP. The crude product was purified by column chromatography on silica gel (40% EtOAc/PE). Yield 47%. White solid, mp 205–207 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 3H), 7.13 (d, *J* = 15.7 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.36 (s, 1H), 5.86 (d, *J* = 15.7 Hz, 1H), 5.54 (br. d, *J* = 7.4 Hz, 1H), 5.17 (dd, *J* = 12.5, 7.0 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.21 (hept, *J* = 6.9, 1H), 2.76 (t, *J* = 6.2 Hz, 2H), 2.24 – 2.14 (m, 1H), 2.03 – 1.89 (m, 2H), 1.72 – 1.62 (m, 1H), 1.19 (d, *J* = 1.1 Hz, 3H), 1.17 (d, *J* = 1.1 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.70 (C), 165.77 (C), 160.96 (C), 159.38 (C), 159.19 (C), 156.55 (C), 139.84 (CH), 129.21 (2CH), 129.12 (C), 128.03 (CH), 127.48 (C), 118.57 (CH), 114.31 (2CH), 113.71 (C), 109.26 (C), 94.96 (CH), 55.93 ($CH_3$), 55.47 ($2CH_3$), 43.97 (CH), 30.62 ($CH_2$), 26.46 (CH), 22.86 ($CH_2$), 22.79 ($2CH_3$), 19.86 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{28}H_{32}N_2O_5Na$ $[M+Na]^+$: 499.2209, found 499.2207.




**5j**

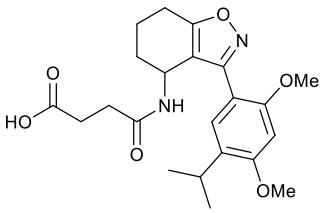
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-morpholinoacetamide* **5j**. Morpholine (86 μL, 1 mmol, 4 eq.) was added to a solution of chloroacetamide **3a** (100 mg, 0.25 mmol, 1 eq.) in toluene (10 mL). The reaction mixture was heated under reflux for 6 h. The precipitate formed was filtered off and washed with toluene. The filtrate was evaporated on a rotary evaporator and the residue was purified by column chromatography on silica gel (80→90% EtOAc/PE) to give product **5j**. Yield 78%. White solid, mp 143–147 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.42 (s, 1H), 5.28 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.59 – 3.29 (m, 4H), 3.17 (hept, *J* = 6.9 Hz, 1H), 2.76 (d, *J* = 5.6 Hz, 3H), 2.33 – 2.07 (m, 3H), 2.04 – 1.68 (m, 5H), 1.66 – 1.48 (m, 1H), 1.18 (d, *J* = 6.9 Hz,

3H), 1.16 (d, *J* = 6.9 Hz, 3H). The exchange proton NH did not appear in the spectrum. $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.78 (C), 159.45 (2C), 158.97 (C), 156.67 (C), 128.95 (C), 128.05 (CH), 113.30 (C), 109.64 (C), 94.57 (CH), 66.50 ($3CH_2$), 55.84 ($CH_3$), 55.67 ($CH_3$), 53.30 ($2CH_2$), 43.13 (CH), 30.98 ($CH_2$), 26.53 (CH), 23.22 ($CH_3$), 22.96 ($CH_2$), 22.23 ($CH_3$), 20.12 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{24}H_{34}N_3O_5$ $[M+H]^+$: 444.2498, found 444.2494.




**5k**

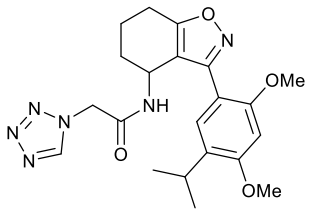
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-morpholinopropanamide* **5k**. Synthesized according to the general procedure A from amine **4a** and 3-morpholinopropanoic acid hydrochloride using DMAP and TEA (77μL, 0.55 mmol, 2.5 eq.). The crude product was purified by column chromatography on silica gel (2→4% MeOH/$CHCl_3$). Yield 53%. White solid, mp 159–162 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 6.51 (s, 1H), 5.16 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.60 (br. s, 4H), 3.20 (hept, *J* = 6.9 Hz, 1H), 2.79 – 2.72 (m, 2H), 2.55 – 2.38 (m, 3H), 2.35 – 2.19 (m, 4H), 2.18 – 2.07 (m, 2H), 1.97 – 1.87 (m, 2H), 1.62 – 1.52 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H). The exchange proton NH did not appear in the spectrum. $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.40 (C), 159.40 (C), 159.06 (C), 156.59 (C), 128.93 (2C), 127.94 (CH), 113.74 (C), 109.69 (C), 95.13 (CH), 66.04 ($2CH_2$), 56.06 ($CH_3$), 55.77 ($CH_3$), 53.63 ($CH_2$), 52.42 ($2CH_2$), 42.86 (CH), 31.24 ($CH_2$), 30.91 ($CH_2$), 26.55 (CH), 22.88 ($2CH_3$), 22.71 ($CH_2$), 20.09 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{25}H_{36}N_3O_5$ $[M+H]^+$: 458.2655, found 458.2651.




**5l**

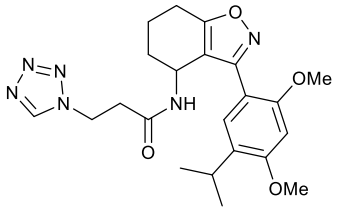
*4-((3-(5-Isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)amino)-4-oxobutanoic acid* **5l**. Synthesized according to the general procedure B from amine **4a** and succinic anhydride (1.1 eq.). The crude product was purified by column chromatography on silica gel (6% MeOH/$CHCl_3$). Yield 85%. White solid, mp 188–190 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.45 (s, 1H), 5.70 (br. d, *J* = 7.9 Hz, 1H), 5.13 (dd, *J* = 13.4, 7.0 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.76 – 2.69 (m, 2H), 2.38 – 2.31 (m, 2H), 2.23 – 2.08 (m, 2H), 2.00 – 1.84 (m, 3H), 1.62 – 1.52 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.15 (d, *J*

= 6.9 Hz, 3H). The exchange proton COOH did not appear in the spectrum. $^{13}$C NMR (126 MHz, $CDCl_3$) δ 175.70 (C), 171.59 (C), 169.58 (C), 159.47 (C), 159.18 (C), 156.45 (C), 129.27 (C), 127.96 (CH), 113.47 (C), 109.22 (C), 94.95 (CH), 55.88 ($CH_3$), 55.68 ($CH_3$), 43.70 (CH), 30.52 ($CH_2$), 30.43 ($CH_2$), 29.87 ($CH_2$), 26.39 (CH), 22.83 ($CH_3$), 22.80 ($CH_2$), 22.77 ($CH_3$), 20.05 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{28}N_2O_6Na$ $[M+Na]^+$: 439.1845, found 439.1836.




**5m**

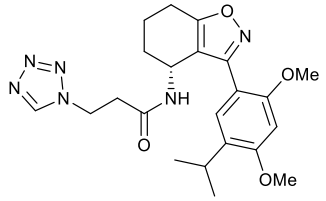
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-(1H-tetrazol-1-yl)acetamide* **5m**. Synthesized according to the general procedure A from amine **4a** and 2-(1*H*-tetrazol-1-yl)acetic acid using DMAP. The crude product was purified by column chromatography on silica gel (3% MeOH/$CHCl_3$). Yield 80%. White solid, mp 185–190 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.19 (s, 1H), 6.44 (s, 1H), 6.06 (br. d, *J* = 8.0 Hz, 1H), 5.16 (dd, *J* = 13.0, 6.9 Hz, 1H), 4.72 (d, *J* = 16.2 Hz, 1H), 4.56 (d, *J* = 16.2 Hz, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.24 (hept, *J* = 6.9 Hz, 1H), 2.81 – 2.63 (m, 2H), 2.18 – 2.08 (m, 1H), 2.00 – 1.86 (m, 2H), 1.63 – 1.50 (m, 1H), 1.18 (d, *J* = 2.5 Hz, 3H), 1.17 (d, *J* = 2.5 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.71 (C), 169.71 (C), 162.61 (C), 159.59 (C), 158.95 (C), 156.40 (C), 143.47 (CH), 129.54 (C), 128.07 (CH), 113.01 (C), 109.13 (C), 95.16 (CH), 56.16 ($CH_3$), 55.77 ($CH_3$), 49.89 ($CH_2$), 44.22 (CH), 30.40 ($CH_2$), 26.45 (CH), 22.83 ($CH_3$), 22.74 ($CH_3$), 22.71 ($CH_2$), 20.14 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{21}H_{26}N_6O_4Na$ $[M+Na]^+$: 449.1913, found 449.1905.




**5n**

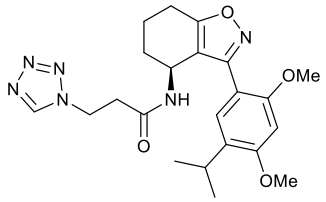
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide* **5n**. Synthesized according to the general procedure A from amine **4a** and 3-(1*H*-tetrazol-1-yl)propanoic acid using DMAP. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 90%. Light yellow solid, mp 70–75 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.16 (s, 1H), 6.34 (s, 1H), 5.63 (br. d, *J* = 7.4 Hz, 1H), 5.02 (dd, *J* = 12.6, 6.9 Hz, 1H), 4.59 – 4.49 (m, 2H), 3.91 (s, 3H), 3.64 (s, 3H), 3.21 (hept, *J* = 6.9 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.55 – 2.45 (m, 1H), 2.29 – 2.19 (m, 1H), 2.12 – 2.03 (m, 1H), 1.94 – 1.82 (m, 2H), 1.55 – 1.43 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR

(126 MHz, $CDCl_3$) δ 169.67 (C), 167.80 (C), 159.52 (C), 158.95 (C), 156.33 (C), 143.80 (CH), 129.46(C), 127.94 (CH), 113.12 (C), 109.12 (C), 95.09 (CH), 56.00 ($CH_3$), 55.76 ($CH_3$), 43.94 (CH), 43.70 ($CH_2$), 34.98 ($CH_2$), 30.44 ($CH_2$), 26.37 (CH), 22.81 ($CH_3$), 22.76 ($CH_3$), 22.74 ($CH_2$), 19.88 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{28}N_6O_4Na$ $[M+Na]^+$: 463.2070, found 463.2063.



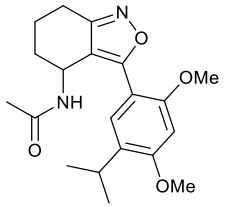

*(R)*-**5n**

*(R)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide (R)*-**5n**. Synthesized according to the general procedure A from amine *(R)*-**4a** and 3-(1*H*-tetrazol-1-yl)propanoic acid using HOBt. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 88%. White solid, mp 197–201 °C. $[\alpha]_D^{20}$ = -38.4 (c=0.5 in $CHCl_3$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{28}N_6O_4Na$ $[M+Na]^+$: 463.2070, found 463.2063. Spectroscopic data are consistent with those of racemic amide **5n**.




(*S*)-**5n**

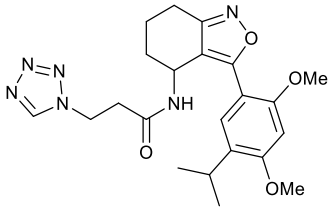
*(S)-N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide (S)*-**5n**. Synthesized according to the general procedure A from amine *(S)*-**4a** and 3-(1*H*-tetrazol-1-yl)propanoic acid using HOBt. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 94%. White solid, mp 193–197 °C. $[\alpha]_D^{20}$ = +38.7 (c=0.5 in $CHCl_3$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{28}N_6O_4Na$ $[M+Na]^+$: 463.2070, found 463.2061. Spectroscopic data are consistent with those of racemic amide **5n**.




**6a**

*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-yl)acetamide* **6a**. Yield 90%. Synthesized according to the general procedure B from amine **4b** and acetic anhydride (1.5 eq.). The crude product was purified by column chromatography on silica gel (2→4% MeOH/$CHCl_3$). White solid, mp 165–168 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.44 (s, 1H), 5.40 (br. d, *J* = 7.4 Hz, 1H), 5.19 (td, *J* = 7.6, 5.7 Hz, 1H), 3.88 (s, 3H), 3.84 (s,

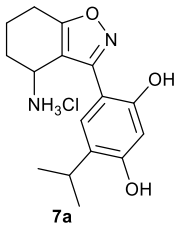
3H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.84 – 2.68 (m, 2H), 2.21 – 2.13 (m, 1H), 1.95 – 1.76 (m, 2H), 1.67 (s, 3H), 1.63 – 1.52 (m, 1H), 1.19 (pseudo-t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 169.07 (C), 163.90 (C), 161.51 (C), 159.89 (C), 156.23 (C), 129.39 (C), 127.57 (CH), 112.27 (C), 108.62 (C), 94.61 (CH), 56.00 ($CH_3$), 55.65 ($CH_3$), 43.40 (CH), 30.86 ($CH_2$), 26.41 (CH), 23.14 ($CH_3$), 22.88 ($CH_3$), 22.68 ($CH_3$), 21.90 ($CH_2$), 19.95 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{26}N_2O_4Na$ $[M+Na]^+$: 381.1790, found 381.1788.




**6b**

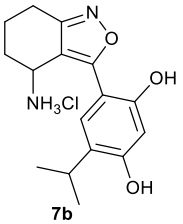
*N-(3-(5-isopropyl-2,4-dimethoxyphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide* **6b**. Synthesized according to the general procedure A from amine **4b** and 3-(1*H*-tetrazol-1-yl)propanoic acid using HOBt. The crude product was purified by column chromatography on silica gel (2% MeOH/$CHCl_3$). Yield 51%. White solid, mp 72–77 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.29 (s, 1H), 6.31 (s, 1H), 5.62 (br. d, *J* = 5.7 Hz, 1H), 5.14 (dd, *J* = 12.5, 6.5 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.59 – 4.50 (m, 1H), 3.94 (s, 3H), 3.59 (s, 3H), 3.22 (hept, *J* = 6.9 Hz, 1H), 2.77 (dt, *J* = 16.5, 5.2 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.60 – 2.51 (m, 1H), 2.44 – 2.35 (m, 1H), 2.14 (td, *J* = 10.6, 5.1 Hz, 1H), 1.92 – 1.73 (m, 2H), 1.54 – 1.42 (m, 1H), 1.18 (d, *J* = 2.9 Hz, 3H), 1.16 (d, *J* = 2.9 Hz, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.69 (C), 163.97 (C), 161.36 (C), 160.14 (C), 156.03 (C), 143.97 (CH), 129.64 (C), 127.34 (CH), 111.63 (C), 108.18 (C), 94.96 (CH), 56.05 ($CH_3$), 55.75 ($CH_3$), 43.88 (CH), 43.70 ($CH_2$), 34.87 ($CH_2$), 30.70 ($CH_2$), 26.37 (CH), 22.90 ($CH_3$), 22.61 ($CH_3$), 21.80 ($CH_2$), 19.92 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{29}N_6O_4$ $[M+H]^+$: 441.2250, found 441.2243.

**General procedure for the synthesis of compounds 7a–b**. To a dry round-bottomed flask equipped with a stir bar, amine **4** (1 eq.) was added followed by the addition of dry DCM (0.1 M). The flask was filled with argon, after which $BBr_3$ (3 eq. per OMe-group) was added slowly at 0°C. The reaction mixture was stirred at room temperature until the starting material was consumed completely as indicated by TLC (72 – 96 h). The reaction was quenched with saturated solution of $NaHCO_3$, and the organic layer was separated from the aqueous layer. The aqueous layer was then extracted with EtOAc. The organic layers were combined and dried over $Na_2SO_4$. After removing the solvent with a rotary evaporator, the crude product was purified by preparative TLC using $CHCl_3$/MeOH as eluent. The product was dissolved in a solution of HCl (70 eq.) in MeOH (1.8 M) and was stirred for 12 h at room temperature. The solvent was removed under reduced pressure to provide compounds **7a-b**.




7a

*3-(2,4-Dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-aminium chloride* **7a**. The crude product was purified by preparative TLC on silica gel (9% MeOH/$CHCl_3$). Yield 45%. Pale yellow solid, mp 186–188 °C. $^1$H NMR (500 MHz, DMSO) δ 10.32 (br. s, 1H), 9.84 (br. s, 1H), 8.09 (br. s, 3H), 7.10 (s, 1H), 6.66 (s, 1H), 4.48 (dd, *J* = 8.2, 4.0 Hz, 1H), 3.10 (hept, *J* = 6.9 Hz, 1H), 2.86 – 2.65 (m, 2H), 2.16 – 1.98 (m, 2H), 1.96 – 1.82 (m, 2H), 1.14 (d, *J* = 1.9 Hz, 3H), 1.13 (d, *J* = 1.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 170.62 (C), 159.05 (C), 157.46 (C), 153.48 (C), 127.70 (CH), 126.15 (C), 110.14 (C), 105.57 (C), 103.14 (CH), 42.94 (CH), 26.82 ($CH_2$), 25.89 (CH), 22.71 ($CH_3$), 22.54 ($CH_3$), 21.75 ($CH_2$), 16.69 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{16}H_{21}N_2O_3$ [M-Cl]$^+$: 289.1547, found 289.1547.

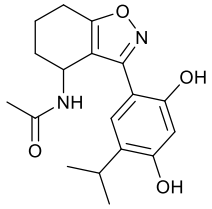



7b

*3-(2,4-Dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-aminium chloride* **7b**. The crude product was purified by preparative TLC on silica gel (30% MeOH/$CHCl_3$). Yield 54%. Pale yellow solid, mp 163–165 °C. $^1$H NMR (500 MHz, DMSO) δ 10.65 (br. s, 1H), 10.09 (br. s, 1H), 8.04 (br. s, 3H), 7.26 (s, 1H), 6.70 (s, 1H), 4.74 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.11 (hept, *J* = 6.9 Hz, 1H), 2.80 – 2.69 (m, 1H), 2.67 – 2.57 (m, 1H), 2.07 – 1.91 (m, 3H), 1.86 – 1.70 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.13 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 164.87 (C), 160.66 (C), 158.26 (C), 153.76 (C), 126.68 (C), 126.28 (CH), 107.08 (C), 105.12 (C), 103.18 (CH), 42.79 (CH), 27.21 ($CH_2$), 25.95 (CH), 22.66 ($CH_3$), 22.58 ($CH_3$), 20.75 ($CH_2$), 17.09 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{16}H_{21}N_2O_3$ [M-Cl]$^+$: 289.1547, found 289.1545.

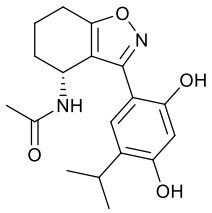
**General procedure for the synthesis of compounds 8 and 9**. To a dry round-bottomed flask equipped with a stir bar, amide **5** or **6** (1 eq.) was added, followed by the addition of dry DCM (0.1 M). The flask was filled with argon, after which $BBr_3$ (3 eq. per OMe group) was added slowly at 0 °C. The reaction mixture was stirred at room temperature until the starting material was consumed completely as indicated by TLC (72 – 96 h). The reaction was quenched with saturated solution of $NaHCO_3$, and the organic layer was separated from the aqueous layer. The

aqueous layer was then extracted with EtOAc. The organic layers were combined and dried over $Na_2SO_4$. After removing the solvent with a rotary evaporator, the crude product was purified by silica gel column chromatography or preparative TLC using either PE/EtOAc or $CHCl_3$/MeOH as eluent.



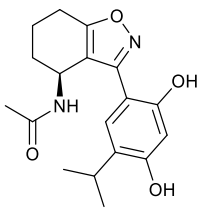

**8a**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide* **8a**. The crude product was purified by column chromatography on silica gel (60% EtOAc/PE). Yield 65%. White solid, mp 245–250 °C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.69 (br. s, 1H), 9.57 (br. s, 1H), 8.16 (br. d, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 6.43 (s, 1H), 4.99 (dt, *J* = 7.5, 3.4 Hz, 1H), 3.09 (hept, *J* = 6.9 Hz, 1H), 2.84 – 2.75 (m, 1H), 2.72 – 2.61 (m, 1H), 1.91 – 1.74 (m, 3H), 1.69 (s, 3H), 1.67 – 1.61 (m, 1H), 1.09 (pseudo-t, *J* = 6.4 Hz, 6H). $^{13}$C NMR (126 MHz, DMSO) δ 169.50 (C), 168.14 (C), 159.50 (C), 156.81 (C), 154.84 (C), 126.46 (CH), 126.02 (C), 111.90 (C), 105.52 (C), 102.65 (CH), 40.99 ($CH_3$), 29.30 ($CH_2$), 25.66 (CH), 22.65 (CH), 22.52 ($CH_3$), 22.49 ($CH_3$), 22.00 ($CH_2$), 17.13 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_4Na$ $[M+Na]^+$: 353.1477, found 353.1473.



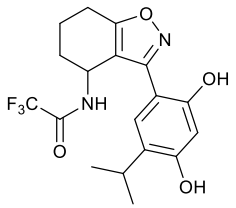

(*R*)-**8a**

*(R)-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide (R)*-**8a**. The crude product was purified by column chromatography on silica gel (60% EtOAc/PE). Yield 74%. White solid, mp > 205 °C (dec.). $[\alpha]_D^{20}$ = -9.3 (c=0.4 in MeOH). HRMS (ESI+): m/z calc'd for $C_{18}H_{22}N_2O_4Na$ $[M+Na]^+$: 353.1477, found 353.1478. Spectroscopic data are consistent with those of racemic acetamide **8a**.



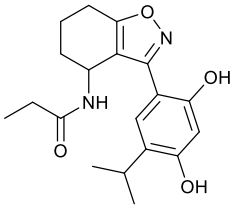

(*S*)-**8a**

*(S)-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)acetamide (S)*-**8a**. The crude product was purified by column chromatography on silica gel (60% EtOAc/PE). Yield 74%. White solid, mp > 205 °C (dec.). $[\alpha]_D^{20}$ = +10.4 (c=0.4 in MeOH). HRMS (ESI+): m/z calc'd for $C_{18}H_{22}N_2O_4Na$ $[M+Na]^+$: 353.1477, found 353.1476. Spectroscopic data are consistent with those of racemic acetamide **8a**.




**8b**

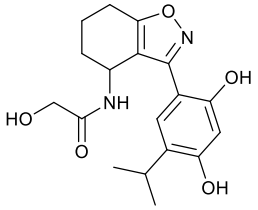
*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2,2,2-trifluoroacetamide* **8b**. The crude product was purified by column chromatography on silica gel (30→40% EtOAc/PE). Yield 83%. White solid, mp > 214 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.54 (br. s, 1H), 9.52 (br. s, 1H), 9.45 (br. d, *J* = 7.8 Hz, 1H), 6.98 (s, 1H), 6.42 (s, 1H), 5.16 (dt, *J* = 7.8, 3.9 Hz, 1H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.80 – 2.64 (m, 2H), 1.96 – 1.79 (m, 3H), 1.78 – 1.67 (m, 1H), 1.09 (d, *J* = 5.1 Hz, 3H), 1.08 (d, *J* = 5.1 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.50 (C), 159.50 (C), 156.73 (C), 155.20 (q, *J* = 36.7 Hz, C), 154.40 (C), 126.49 (CH), 125.54 (s), 115.66 (q, *J* = 288.4 Hz, C), 111.42 (C), 105.68 (C), 102.47 (CH), 42.48 (CH), 28.91 ($CH_2$), 25.77 (CH), 22.53 ($CH_3$), 22.44 ($CH_3$), 21.94 ($CH_2$), 17.98 ($CH_2$). $^{19}$F NMR (470 MHz, $CDCl_3$) δ -69.51 (s). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{19}F_3N_2O_4Na$ $[M+Na]^+$: 407.1195, found 407.1193.




**8c**

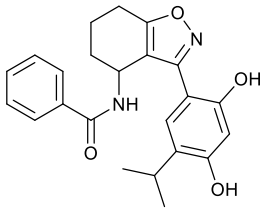
*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)propionamide* **8c.** The crude product was purified by column chromatography on silica gel (70→80% EtOAc/PE). Yield 70%. White solid, mp > 237 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.63 (br. s, 1H), 9.55 (br. s, 1H), 7.97 (br. d, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 6.43 (s, 1H), 5.02 (dt, *J* = 7.7, 3.6 Hz, 1H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.77 (dt, *J* = 17.1, 4.3 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.00 – 1.86 (m, 2H), 1.86 – 1.74 (m, 3H), 1.74 – 1.63 (m, 1H), 1.10 (d, *J* = 4.2 Hz, 3H), 1.08 (d, *J* = 4.2 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 171.86 (C), 169.28 (C), 159.56 (C), 156.79 (C), 154.78 (C), 126.51 (CH), 125.84 (C), 112.20 (C), 105.63 (C), 102.62 (CH), 40.92 (CH), 29.39 ($CH_2$), 28.37 ($CH_2$), 25.81 (CH), 22.60 ($CH_3$), 22.47 ($CH_3$), 22.00 ($CH_2$),

17.29 ($CH_2$), 9.66 ($CH_3$). HRMS (ESI+): *m/z* calc'd for $C_{19}H_{24}N_2O_4Na$ $[M+Na]^+$: 367.1634, found 367.1627.



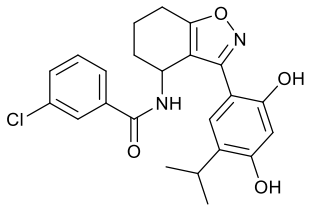

**8d**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-hydroxyacetamide* **8d**. The crude product was purified by preparative TLC on silica gel (70% EtOAc/PE). Yield 56%. White solid, mp > 187 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.61 (br. s, 2H), 7.79 (br. d, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 6.43 (s, 1H), 5.21 (br. s, 1H), 5.09 (dt, *J* = 6.9, 3.3 Hz, 1H), 3.72 (d, *J* = 15.6 Hz, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.71 – 2.60 (m, 1H), 1.94 – 1.79 (m, 3H), 1.78 – 1.66 (m, 1H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 170.88 (C), 169.77 (C), 159.38 (C), 156.83 (C), 154.79 (C), 126.44 (CH), 126.01(C), 111.66 (C), 105.56 (C), 102.67 (CH), 61.29 ($CH_2$), 40.88 (CH), 29.35 ($CH_2$), 25.76 (CH), 22.63 ($CH_3$), 22.42 ($CH_3$), 21.99 ($CH_2$), 17.13 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_5Na$ $[M+Na]^+$: 369.1426, found 369.1420.



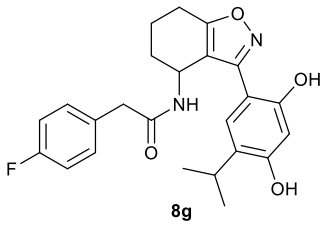

**8e**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)benzamide* **8e**. The crude product was purified by preparative TLC on silica gel (50% EtOAc/PE). Yield 71%. White solid, mp > 240 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.57 (br. s, 1H), 9.52 (br. s, 1H), 8.50 (br. d, *J* = 7.6 Hz, 1H), 7.57 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.44 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.14 (s, 1H), 6.36 (s, 1H), 5.26 (dt, *J* = 7.8, 3.8 Hz, 1H), 3.01 (hept, *J* = 6.9 Hz, 1H), 2.85 – 2.65 (m, 2H), 1.98 – 1.77 (m, 4H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.31 (C), 165.75 (C), 159.68 (C), 156.71 (C), 154.79 (C), 134.58 (C), 130.96 (CH), 127.87 (2CH), 127.38 (2CH), 126.55 (CH), 125.76 (C), 112.27 (C), 105.87 (C), 102.53 (CH), 42.21 (CH), 29.58 ($CH_2$), 25.70 (CH), 22.50 ($2CH_3$), 22.13 ($CH_2$), 17.86 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{23}H_{24}N_2O_4Na$ $[M+Na]^+$: 415.1634, found 415.1632.



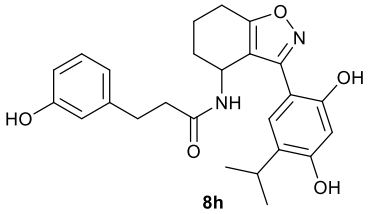

**8f**

*3-Chloro-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)benzamide* **8f**. The crude product was purified by preparative TLC on silica gel (10% MeOH/$CHCl_3$). Yield 93%. Yellow solid, mp > 270 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.61 (br. s, 1H), 9.56 (br. s, 1H), 8.64 (br. d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.09 (s, 1H), 6.34 (s, 1H), 5.22 (dt, *J* = 7.7, 3.8 Hz, 1H), 2.99 (hept, *J* = 6.9 Hz, 1H), 2.83 – 2.65 (m, 2H), 1.97 – 1.75 (m, 4H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.26 (C), 164.19 (C), 159.67 (C), 156.71 (C), 154.72 (C), 136.46 (C), 132.85 (C), 130.82 (CH), 129.91 (CH), 127.11 (CH), 126.52 (CH), 126.14 (CH), 125.66 (C), 112.24 (C), 105.82 (C), 102.47 (CH), 42.36 (CH), 29.50 ($CH_2$), 25.66 (CH), 22.57 ($CH_3$), 22.36 ($CH_3$), 22.10 ($CH_2$), 17.98 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{23}H_{23}ClN_2O_4Na$ $[M+Na]^+$: 449.1244, found 449.1240.



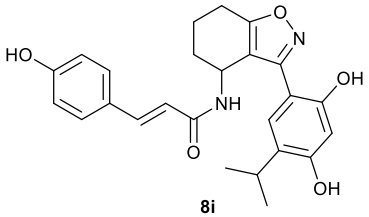

**8g**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-(4-fluorophenyl)acetamide* **8g.** The crude product was purified by flash column chromatography on silica gel (EtOAc). Yield 72%. Pale yellow solid, mp > 280 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.66 (br. s, 1H), 9.55 (br. s, 1H), 8.27 (br. d, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 7.02 – 6.90 (m, 4H), 6.44 (s, 1H), 5.10 (dt, *J* = 7.1, 3.4 Hz, 1H), 3.21 (q, *J* = 14.1 Hz, 2H), 3.08 (hept, *J* = 6.9 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.71 – 2.61 (m, 1H), 1.89 – 1.65 (m, 4H), 1.08 (d, *J* = 3.3 Hz, 3H), 1.07 (d, *J* = 3.3 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.28 (C), 168.81 (C), 160.78 (d, *J* = 241.7 Hz, C), 159.72 (C), 156.77 (C), 154.56 (C), 132.48 (d, *J* = 2.3 Hz, C), 130.45 (d, *J* = 7.8 Hz, 2CH), 126.83 (CH), 125.59 (C), 114.67 (d, *J* = 21.1 Hz, 2CH), 112.41 (C), 105.94 (C), 102.60 (CH), 41.19 ($CH_2$), 41.12 (CH), 29.32 ($CH_2$), 25.79 (CH), 22.69 ($CH_3$), 22.46 ($CH_3$), 22.05 ($CH_2$), 17.45 ($CH_2$). $^{19}$F NMR (470 MHz, DMSO) δ -117.04 – -117.17 (m). HRMS (ESI+): *m/z* calc'd for $C_{24}H_{25}FN_2O_4Na$ $[M+Na]^+$: 447.1696, found 447.1694.



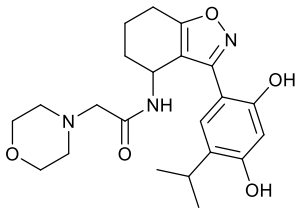

8h

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(3-hydroxyphenyl)propanamide* **8h**.The crude product was purified by preparative TLC on silica gel (9% MeOH/$CHCl_3$). Yield 65%. White solid, mp 215–220 °C. $^1$H NMR (500 MHz, DMSO) δ 9.58 (br. s, 2H), 9.28 (br. s, 1H), 8.07 (br. d, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 6.56 – 6.48 (m, 3H), 6.44 (s, 1H), 5.02 (dt, *J* = 6.9, 3.3 Hz, 1H), 3.08 (hept, *J* = 6.9, 1H), 2.80 – 2.71 (m, 1H), 2.69 – 2.54 (m, 2H), 2.49 – 2.43 (m, 1H), 2.15 (dddd, *J* = 15.3, 14.2, 9.9, 6.3 Hz, 2H), 1.85 – 1.58 (m, 4H), 1.09 (d, *J* = 3.0 Hz, 3H), 1.08 (d, *J* = 3.0 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 170.41 (C), 169.30 (C), 159.62 (C), 157.29 (C), 156.90 (C), 154.80 (C), 142.59 (C), 129.13 (CH), 126.59 (CH), 125.83 (CH), 118.68 (CH), 115.08 (CH), 112.80 (CH), 112.25 (C), 105.64 (C), 102.62 (C), 41.04 (CH), 37.18 ($CH_2$), 31.33 ($CH_2$), 29.36 ($CH_2$), 25.77 (CH), 22.73 ($CH_3$), 22.53 ($CH_3$), 22.01 ($CH_2$), 17.33 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{25}H_{28}N_2O_5Na$ $[M+Na]^+$: 459.1896, found 459.1891.



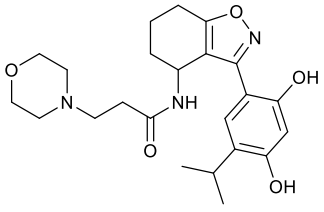

8i

*(E)-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(4-hydroxyphenyl)acrylamide* **8i**. The crude product was purified by preparative TLC on silica gel (10% MeOH/$CHCl_3$). Yield 87%. Pale yellow solid, mp > 250 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 10.01 (br. s, 1H), 9.82 (br. s, 1H), 9.62 (br. s, 1H), 8.38 (br. d, *J* = 7.6 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.15 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 2H), 6.51 (s, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 5.12 (dt, *J* = 7.1, 3.4 Hz, 1H), 3.01 (hept, *J* = 6.9 Hz 1H), 2.88 – 2.76 (m, 1H), 2.74 – 2.62 (m, 1H), 1.95 – 1.81 (m, 3H), 1.78 – 1.65 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.62 (C), 164.59 (C), 159.54 (C), 158.98 (C), 156.98 (C), 154.83 (C), 138.89 (CH), 129.03 (2CH), 126.46 (CH), 126.13 (C), 125.78 (C), 118.47 (CH), 115.76 (2CH), 111.73 (C), 105.29 (C), 102.79 (CH), 41.09 (CH), 29.42 ($CH_2$), 25.68 (CH), 22.56 ($CH_3$), 22.35 ($CH_3$), 22.03 ($CH_2$), 17.04 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{25}H_{26}N_2O_5Na$ $[M+Na]^+$: 457.1739, found 457.1738.



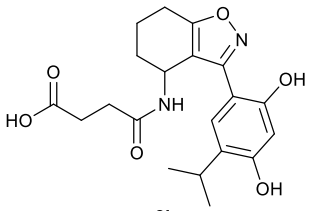
**8j**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-morpholinoacetamide* **8j**. The crude product was purified by preparative TLC on aluminia (6% MeOH/$CHCl_3$). Yield 37%. White solid, mp 210–215 °C. $^1$H NMR (500 MHz, DMSO) δ 9.54 (br. s, 1H), 9.51 (br. s, 1H), 7.61 (br. d, *J* = 7.9 Hz, 1H), 7.03 (s, 1H), 6.40 (s, 1H), 5.16(dt, *J* = 7.9, 4.0 Hz, 1H), 3.38 – 3.35 (m, 4H), 3.05 (hept, *J* = 6.9 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.70 – 2.60 (m, 2H), 2.17 – 2.06 (m, 2H), 2.05 – 1.96 (m, 2H), 1.88 – 1.77 (m, 3H), 1.75 – 1.63 (m, 1H), 1.11 (d, *J* = 5.9 Hz, 3H), 1.10 (d, *J* = 5.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.25 (C), 167.86 (C), 159.30 (C), 156.77 (C), 154.46 (C), 126.79 (CH), 125.39 (C), 112.47 (C), 106.05 (C), 102.42 (CH), 65.95 ($2CH_2$), 61.53 ($CH_2$), 52.88 ($2CH_2$), 41.50 (CH), 29.67 ($CH_2$), 25.86 (CH), 22.87 ($CH_3$), 22.21 ($CH_3$), 22.15 ($CH_2$), 18.24 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{22}H_{29}N_3O_5Na$ $[M+Na]^+$: 438.2005, found 438.1998.



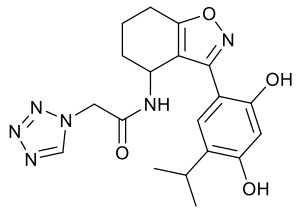
**8k**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-morpholinopropanamide* **8k**. The crude product was purified by preparative TLC on silica gel (9% MeOH/$CHCl_3$). Yield 24%. White solid, mp > 215 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.64 (br. s, 1H), 9.55 (br. s, 1H), 8.15 (br. d, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 6.42 (s, 1H), 5.05 (dt, *J* = 7.5, 3.7 Hz, 1H), 3.50 – 3.41 (m, 4H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.78 (dt, *J* = 17.1, 4.4 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.44 – 2.35 (m, 1H), 2.28 – 2.17 (m, 5H), 2.15 – 1.98 (m, 2H), 1.89 – 1.75 (m, 3H), 1.74 – 1.65 (m, 1H), 1.11 (d, *J* = 6.1 Hz, 3H), 1.09 (d, *J* = 5.8 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 170.01 (C), 169.29 (C), 159.51 (C), 156.84 (C), 154.72 (C), 126.57 (CH), 125.73 (C), 112.24 (C), 105.68 (C), 102.59 (CH), 66.15 ($2CH_2$), 54.37 ($CH_2$), 52.83 ($2CH_2$), 41.00 (CH), 32.86 ($CH_2$), 29.34 ($CH_2$), 25.82 (CH), 22.72 ($CH_3$), 22.44 ($CH_3$), 22.01 ($CH_2$), 17.46 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{23}H_{32}N_3O_5$ $[M+H]^+$: 430.2342, found 430.2340.



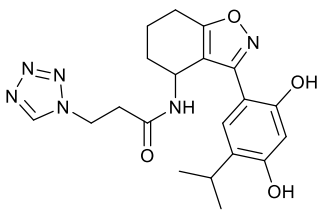
**8l**

*4-((3-(2,4-Dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)amino)-4-oxobutanoic acid* **8l**. The crude product was purified by column chromatography on silica gel (15→30% MeOH/$CHCl_3$). Yield 63%. White solid, mp > 210 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 12.00 (br. s, 1H), 9.65 (br. s, 1H), 9.55 (br. s, 1H), 8.10 (br. d, *J* = 7.7 Hz, 1H), 7.09 (s, 1H), 6.43 (s, 1H), 5.01 (dt, *J* = 7.7, 3.6 Hz, 1H), 3.07 (hept, *J* = 6.7 Hz, 1H), 2.78 (dt, *J* = 17.1, 4.3 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.42 – 2.32 (m, 1H), 2.29 – 2.18 (m, 2H), 2.12 – 2.03 (m, 1H), 1.88 – 1.75 (m, 3H), 1.72 – 1.61 (m, 1H), 1.08 (pseudo-t, *J* = 6.7 Hz, 6H). $^{13}$C NMR (126 MHz, DMSO) δ 173.79 (C), 170.02 (C), 169.37 (C), 159.54 (C), 156.82 (C), 154.78 (C), 126.50 (CH), 125.91 (C), 112.09 (C), 105.60 (C), 102.63 (CH), 41.09 (CH), 30.16 ($CH_2$), 29.28 ($2CH_2$), 25.78 (CH), 22.62 ($CH_3$), 22.48 ($CH_3$), 21.99 ($CH_2$), 17.28 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{24}N_2O_6Na$ $[M+Na]^+$: 411.1532, found 411.1526.



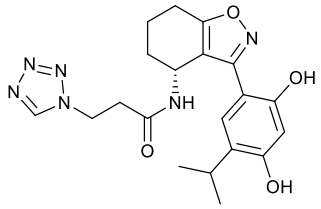
**8m**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-2-(1H-tetrazol-1-yl)acetamide* **8m**. The crude product was purified by preparative TLC on aluminia (6% MeOH/$CHCl_3$). Yield 54%. White solid, mp > 215 °C (dec.). $^1$H NMR (500 MHz, DMSO) δ 9.67 (br. s, 1H), 9.57 (br. s, 1H), 9.15 (s, 1H), 8.67 (br. d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.45 (s, 1H), 5.11 – 5.04 (m, 2H), 4.89 (d, *J* = 16.6 Hz, 1H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.82 (dt, *J* = 17.4, 4.7 Hz, 1H), 2.75 – 2.65 (m, 1H), 1.93 – 1.79 (m, 3H), 1.78 – 1.68 (m, 1H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 169.56 (C), 163.32 (C), 159.52 (C), 156.90 (C), 154.63 (C), 144.82 (CH), 126.64 (CH), 125.83 (C), 111.85 (C), 105.65 (C), 102.60 (CH), 49.17 ($CH_2$), 41.81 (CH), 29.11 ($CH_2$), 25.80 (CH), 22.68 ($CH_3$), 22.52 ($CH_3$), 21.94 ($CH_2$), 17.44 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{19}H_{22}N_6O_4Na$ $[M+Na]^+$: 421.1600, found 421.1593.



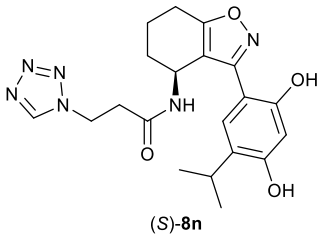
**8n**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide* **8n**. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 62%. White solid, mp 144–147 °C. $^1$H NMR (500 MHz, DMSO) δ 9.65 (br. s, 1H), 9.54 (br. s, 1H), 9.22 (s, 1H), 8.27 (br. d, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 6.43 (s, 1H), 4.99 (dt, *J* = 6.8, 3.0 Hz, 1H), 4.63 – 4.44 (m, 2H), 3.06 (hept, *J* = 6.9 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.70 – 2.59 (m, 2H), 2.49 – 2.42 (m, 1H), 1.84 – 1.74 (m, 1H), 1.73 – 1.58 (m, 3H), 1.06 (d, *J* = 6.9 Hz, 6H). $^{13}$C NMR (126 MHz, DMSO) δ 169.45 (C), 167.65 (C), 159.49 (C), 156.81 (C), 154.71 (C), 143.97 (CH), 126.53 (CH), 125.85 (C), 111.90 (C), 105.63 (C), 102.60 (CH), 44.06 ($CH_2$), 41.22 (CH), 34.86 ($CH_2$), 29.09 ($CH_2$), 25.67 (CH), 22.62 ($CH_3$), 22.51 ($CH_3$), 21.92 ($CH_2$), 17.22 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{24}N_6O_4Na$ $[M+Na]^+$: 435.1757, found 435.1749.



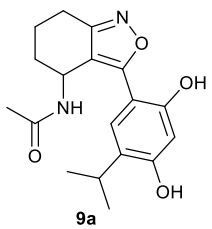
(*R*)-**8n**

*(R)-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide (R)*-**8n**. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 69%. White solid, mp 112–117 °C. $[\alpha]_D^{20}$ = -24.7 (c=0.4 in MeOH). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{24}N_6O_4Na$ $[M+Na]^+$: 435.1757, found 435.1751. Spectroscopic data are consistent with those of racemic amide **8n**.



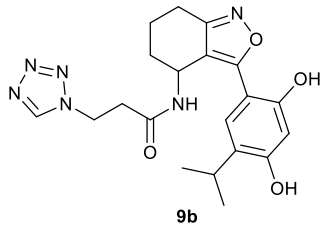
(*S*)-**8n**

*(S)-N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[d]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide (S)*-**8n**. The crude product was purified by column chromatography on silica gel (5% MeOH/$CHCl_3$). Yield 57%. White solid, mp 115–120 °C. $[\alpha]_D^{20}$ = -24.7 (c=0.4 in MeOH). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{24}N_6O_4Na$ $[M+Na]^+$: 435.1757, found 435.1747. Spectroscopic data are consistent with those of racemic amide **8n**.



**9a**

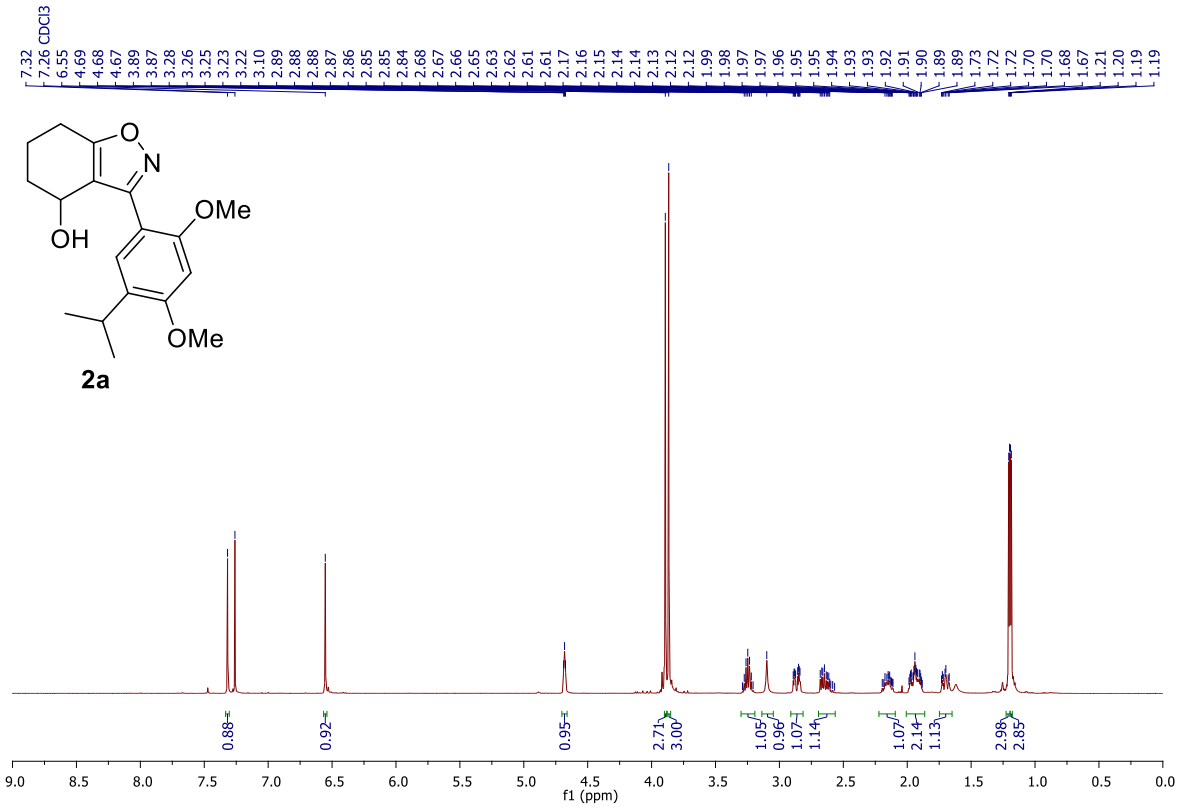
*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-yl)acetamide* **9a**. The crude product was purified by preparative TLC on silica gel (9% MeOH/$CHCl_3$). Yield 98%. White solid, mp 140–145 °C. $^1$H NMR (500 MHz, DMSO) δ 9.69 (br. s, 1H), 9.68 (br. s, 1H), 8.06 (br. d, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.47 (s, 1H), 5.02 (dt, *J* = 8.6, 4.4 Hz, 1H), 3.07 (hept, *J* = 6.9 Hz, 1H), 2.74 (dt, *J* = 16.6, 4.8 Hz, 1H), 2.64 – 2.53 (m, 1H), 1.85 – 1.67 (m, 4H), 1.65 (s, 3H), 1.11 (d, *J* = 4.9 Hz, 3H), 1.10 (d, *J* = 4.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 167.75 (C), 164.80 (C), 160.47 (C), 157.10 (C), 154.34 (C), 126.74 (CH), 125.40 (C), 110.93 (C), 105.75 (C), 102.60 (CH), 40.68 (CH), 29.82 ($CH_2$), 25.69 (CH), 22.64 ($CH_3$), 22.52 ($CH_3$), 22.42 ($CH_3$), 21.06 ($CH_2$), 17.82 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{18}H_{22}N_2O_4Na$ $[M+Na]^+$: 353.1477, found 353.1475.



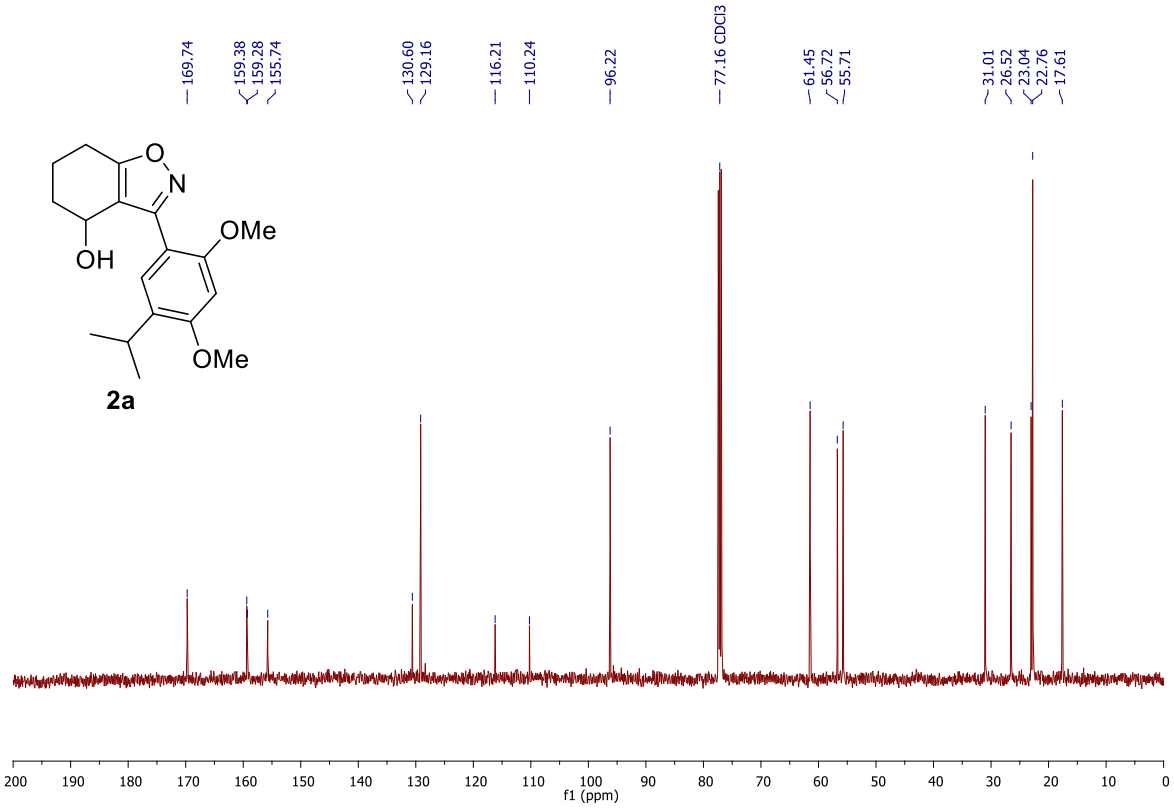

**9b**

*N-(3-(2,4-dihydroxy-5-isopropylphenyl)-4,5,6,7-tetrahydrobenzo[c]isoxazol-4-yl)-3-(1H-tetrazol-1-yl)propanamide* **9b**. The crude product was purified by column chromatography on silica gel (1→2% MeOH/$CHCl_3$). Yield 54%. Pale yellow solid, mp 128–132 °C. $^1$H NMR (500 MHz, DMSO) δ 9.71 (br. s, 1H), 9.68 (br. s, 1H), 9.21 (s, 1H), 8.20 (br. d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 6.46 (s, 1H), 5.05 (dt, *J* = 8.2, 4.0 Hz, 1H), 4.56 (ddd, *J* = 14.8, 8.3, 6.6 Hz, 1H), 4.51 – 4.42 (m, 1H), 3.05 (hept, *J* = 6.9 Hz, 1H), 2.71 (dt, *J* = 9.1, 3.8 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.44 (dt, *J* = 15.3, 6.2 Hz, 1H), 1.73 – 1.53 (m, 4H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (126 MHz, DMSO) δ 167.29 (C), 164.79 (C), 160.51 (C), 157.21 (C), 154.29 (C), 143.92 (CH), 126.66 (CH), 125.48 (C), 110.67 (C), 105.68 (C), 102.53 (CH), 44.12 ($CH_2$), 40.94 (CH), 34.85 ($CH_2$), 29.58 ($CH_2$), 25.70, 22.65 ($CH_3$), 22.45 ($CH_3$), 21.01 ($CH_2$), 17.83 ($CH_2$). HRMS (ESI+): *m/z* calc'd for $C_{20}H_{24}N_6O_4Na$ $[M+Na]^+$: 435.1757, found 435.1748.

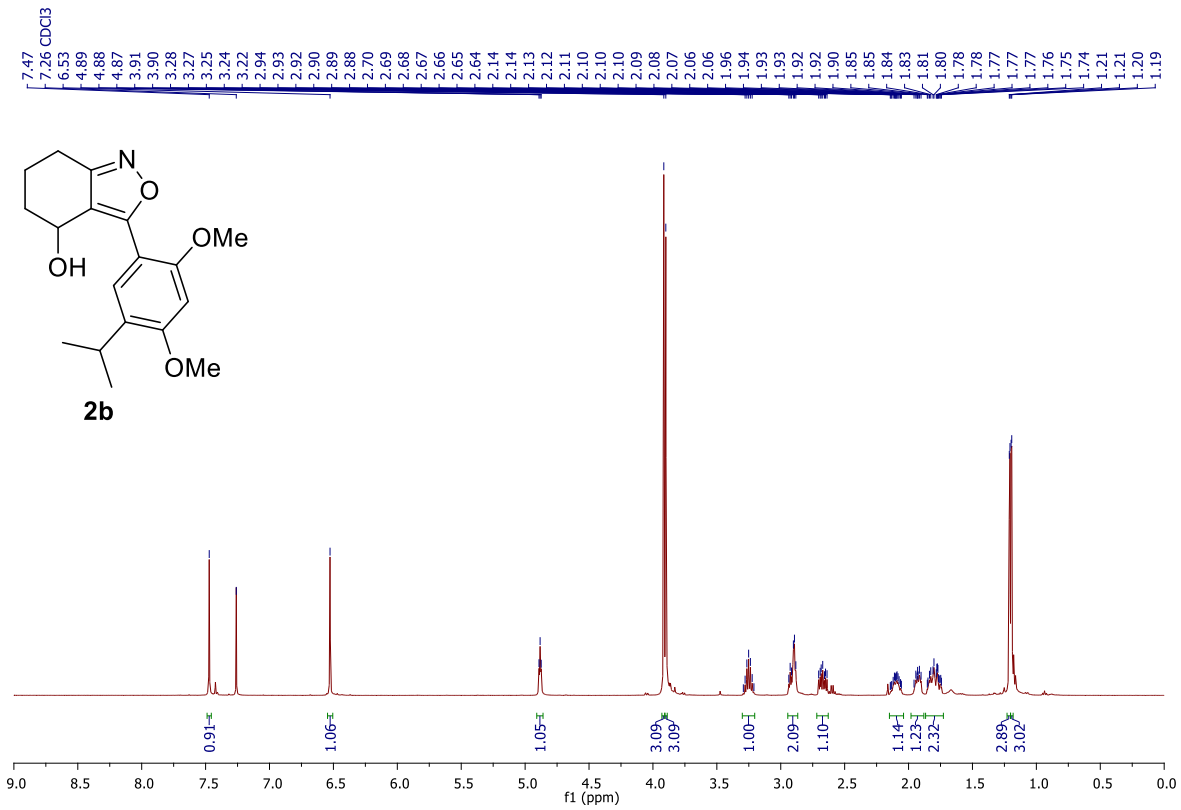
# $^{1}$H NMR, $^{13}$C NMR and $^{19}$F NMR Spectra of compounds 2-9



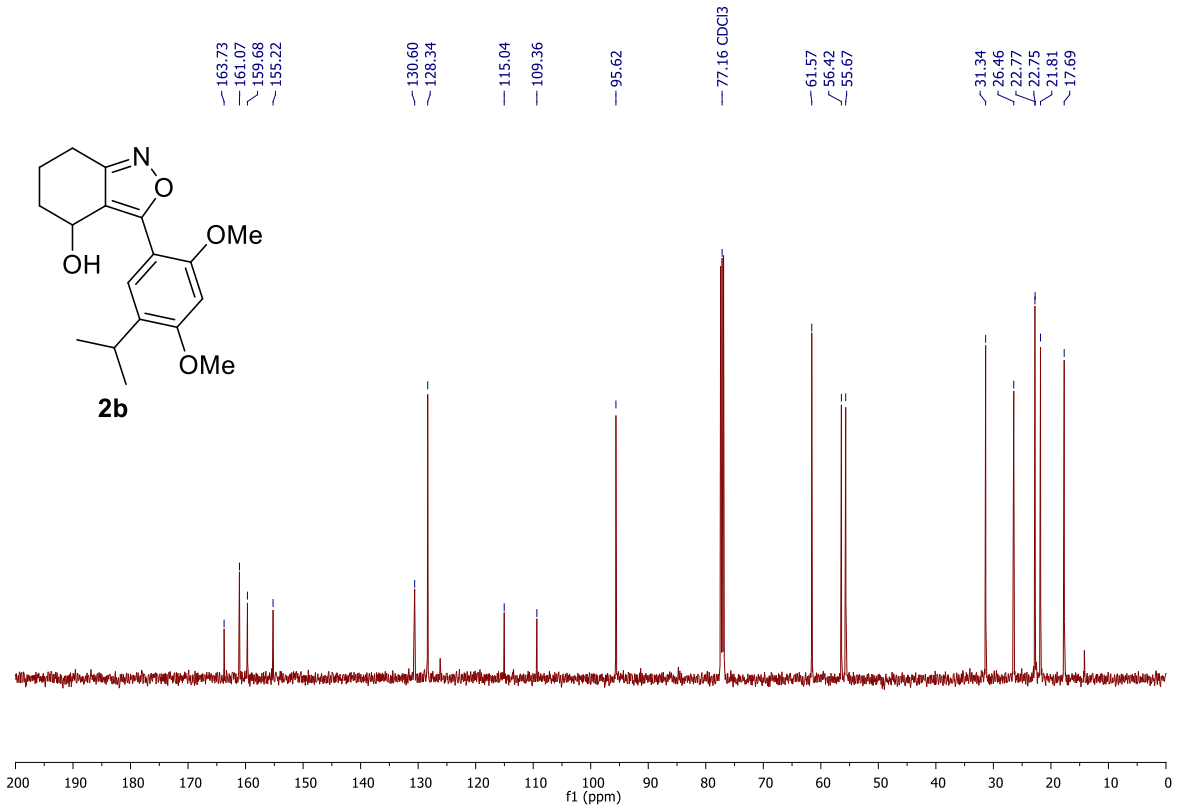

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2a**



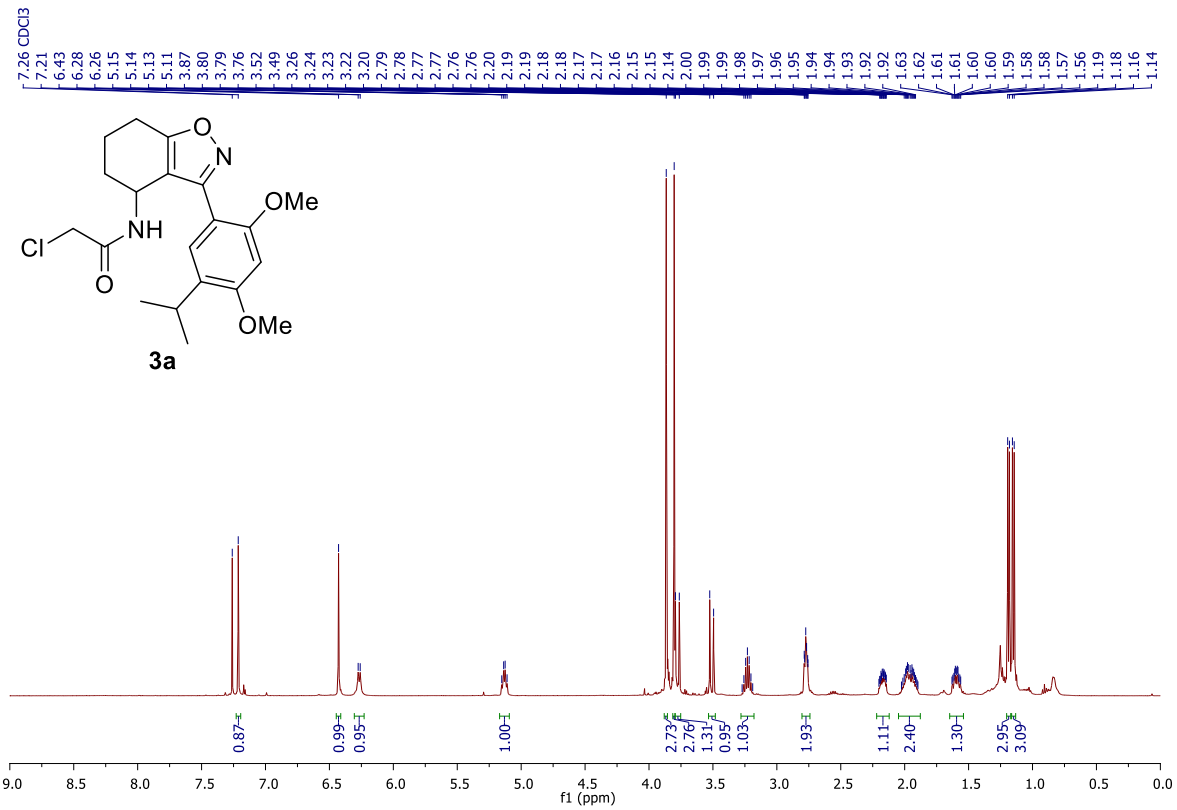

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **2a**



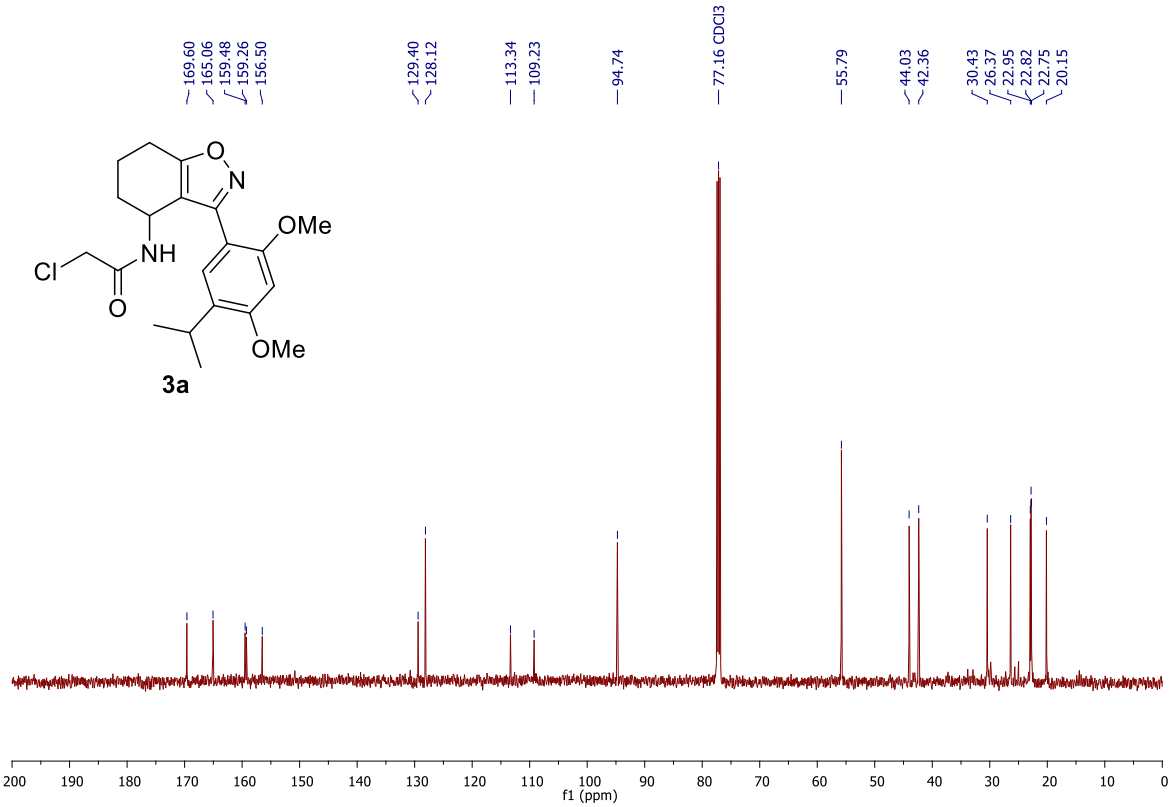

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **2b**



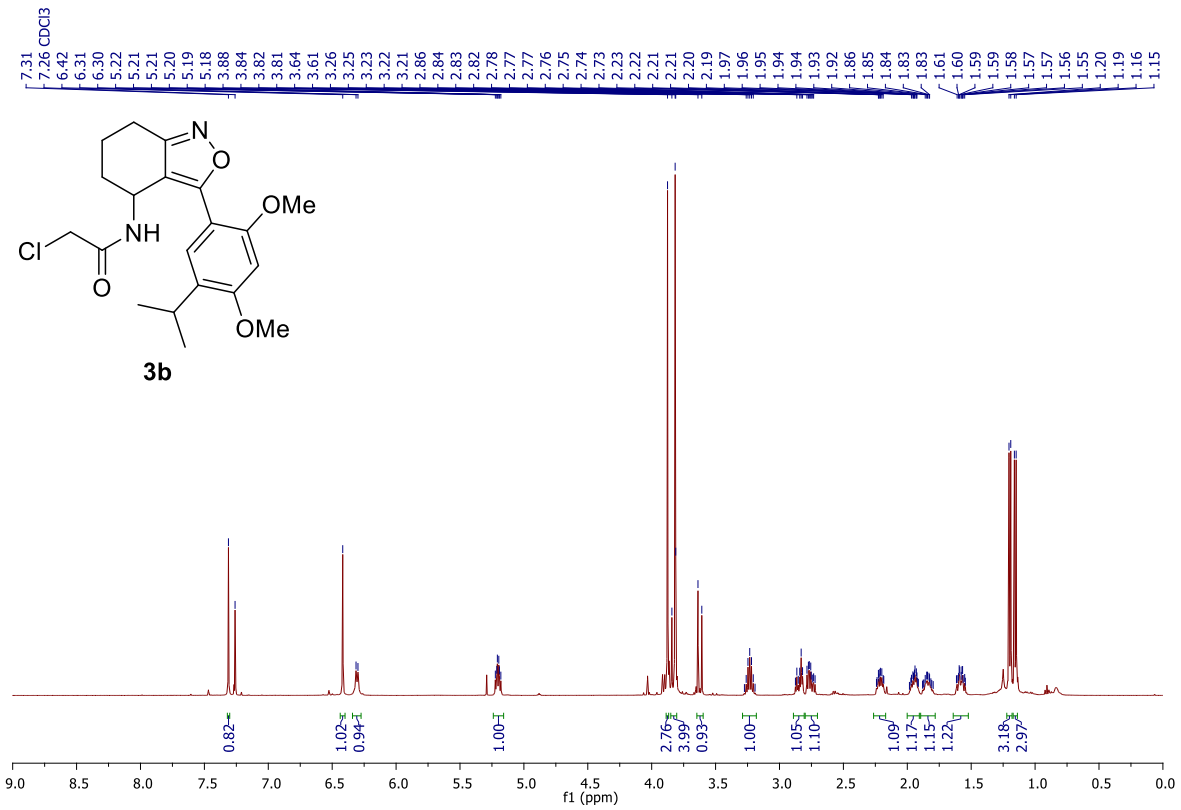

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **2b**



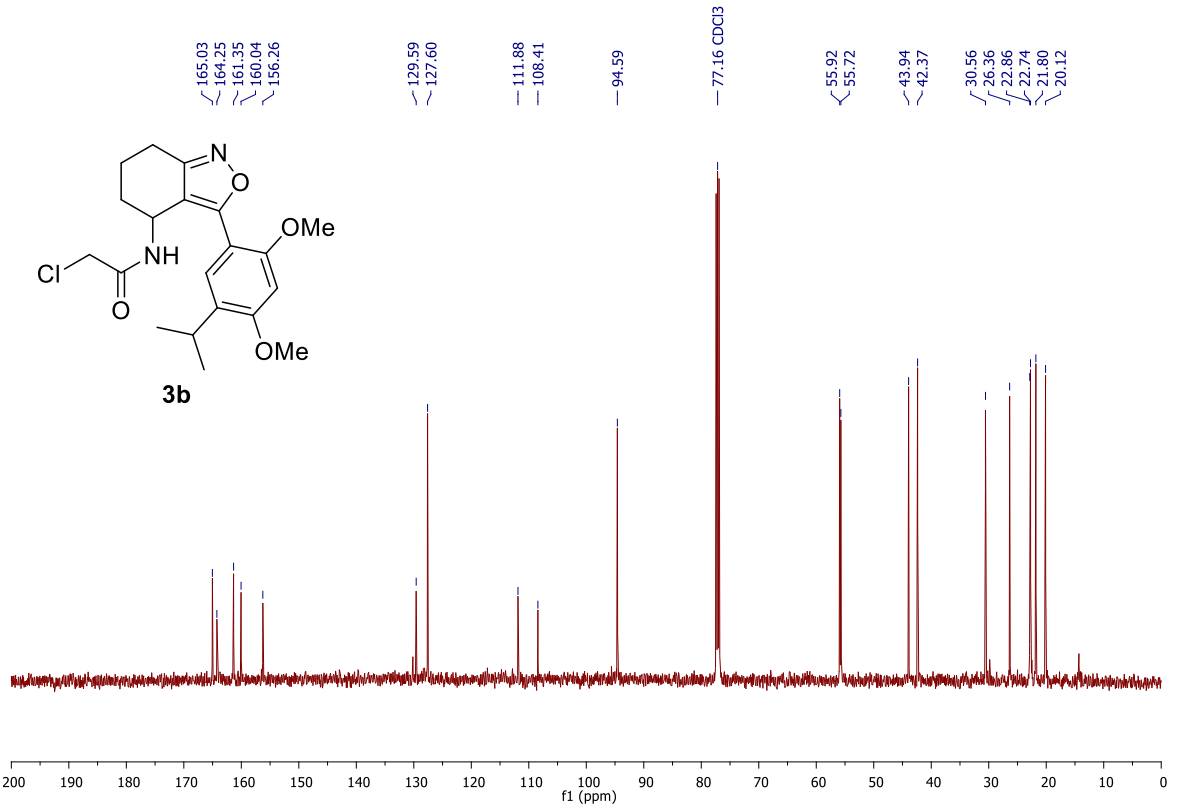

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3a**



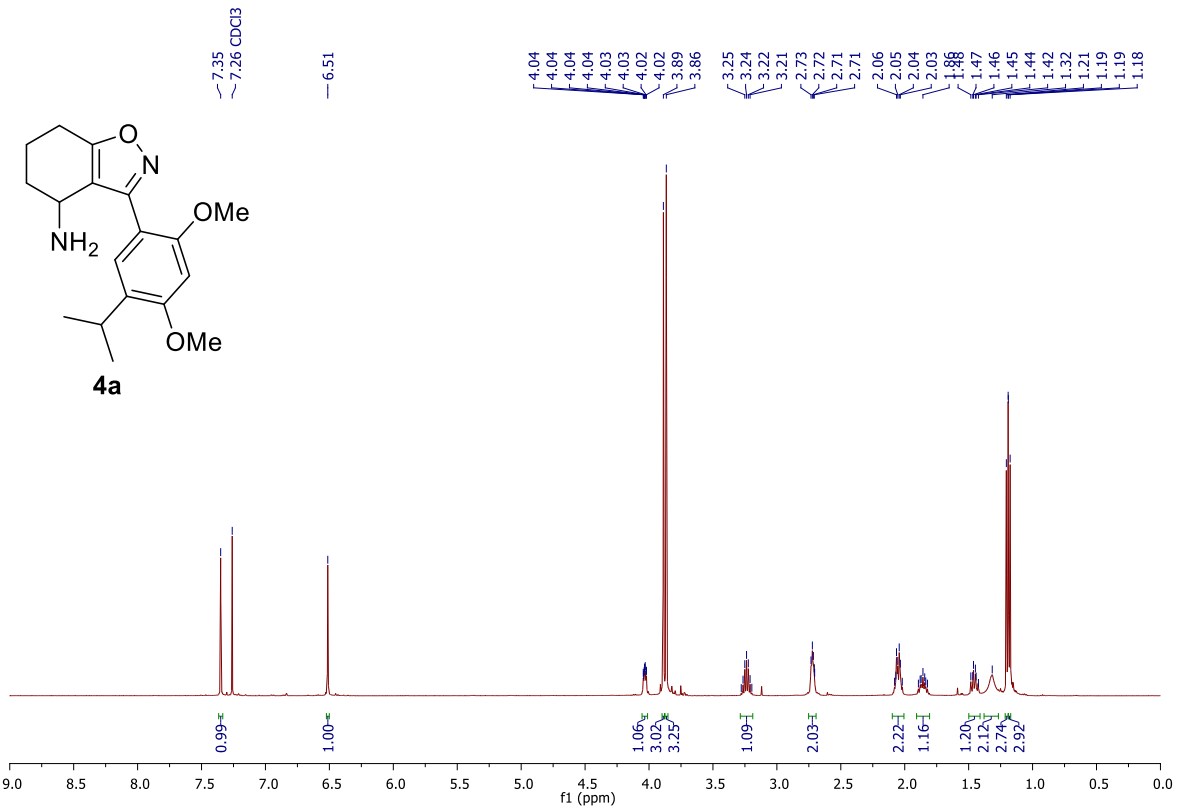

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **3a**



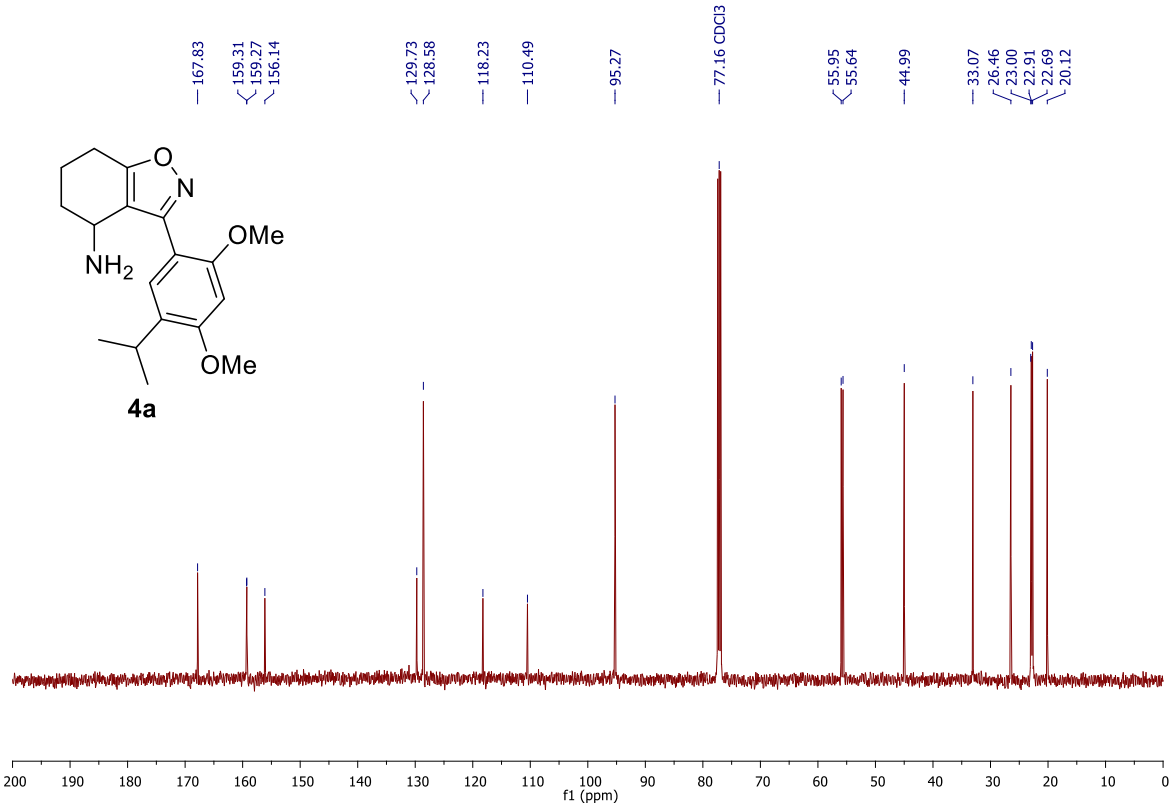

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **3b**



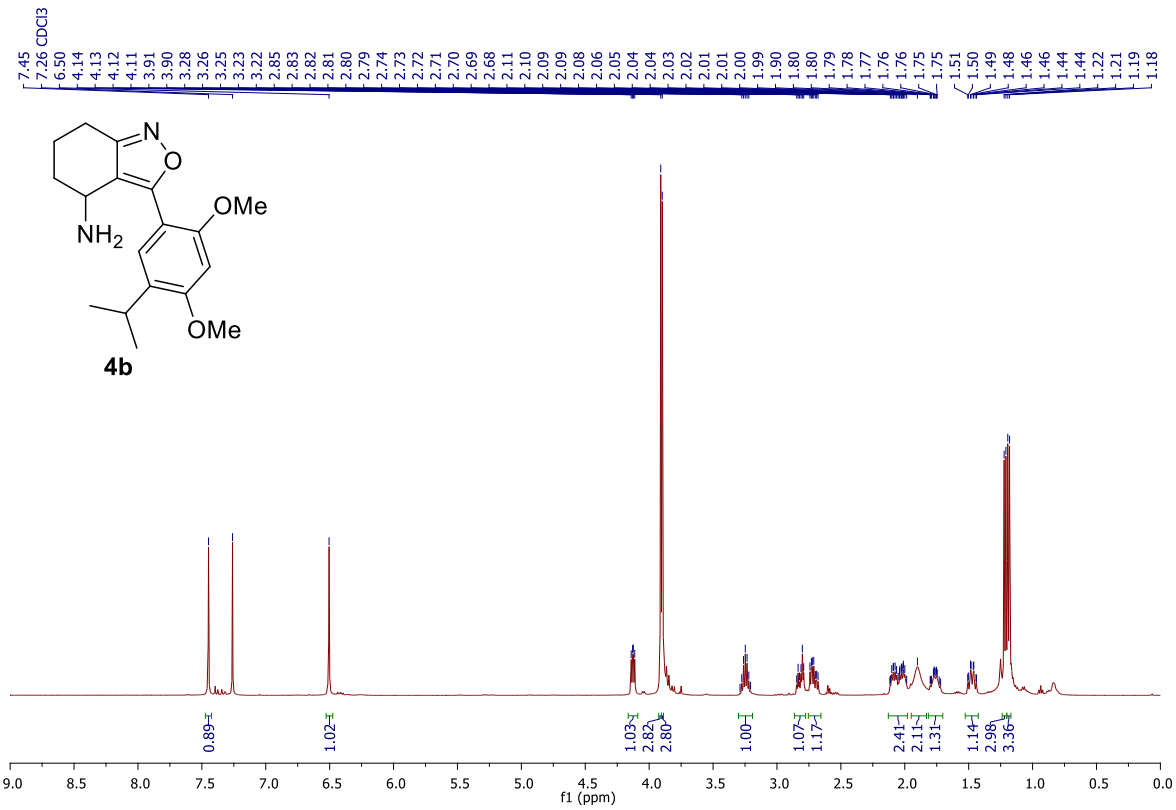

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **3b**



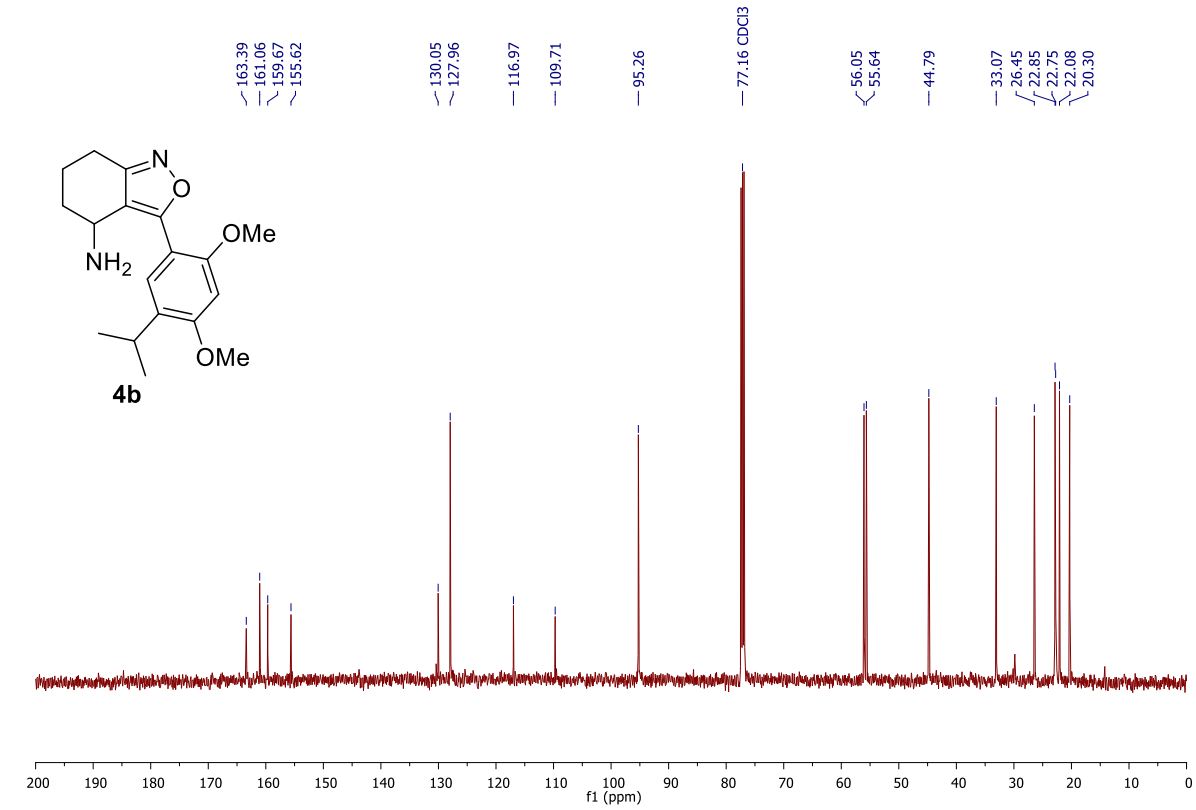

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **4a**



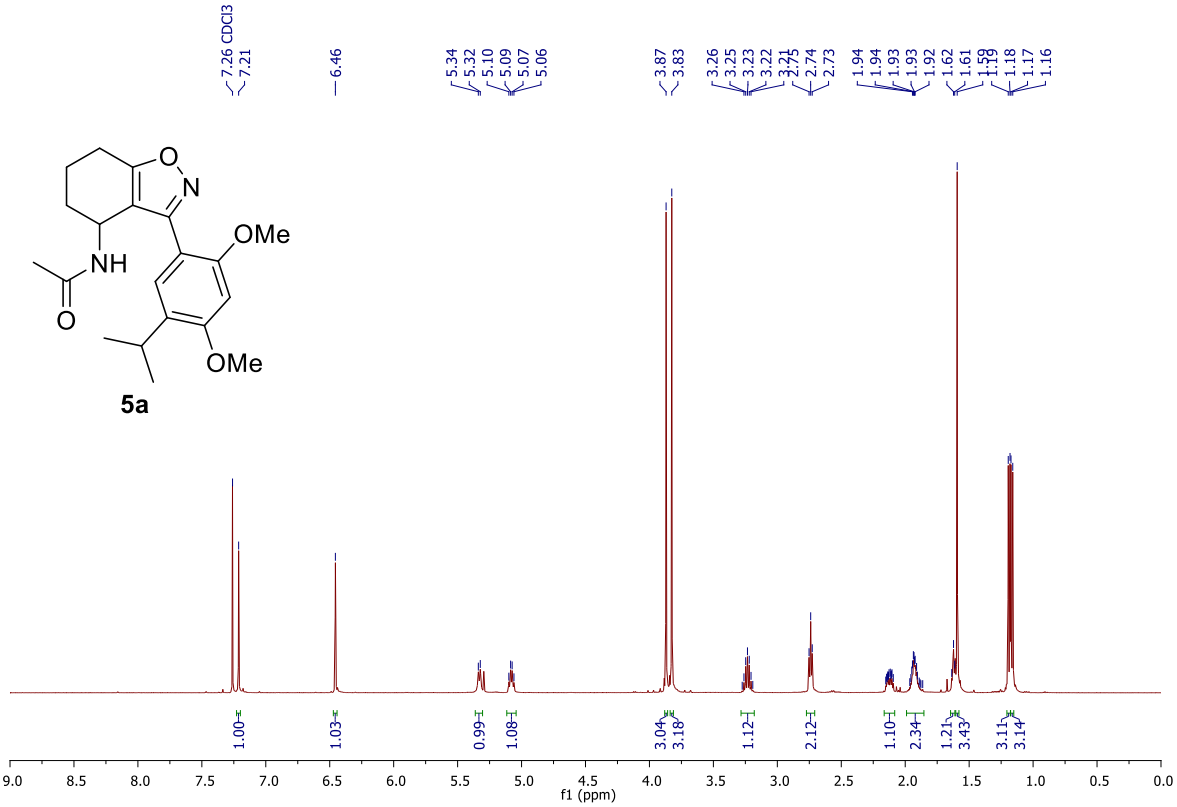

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **4a**



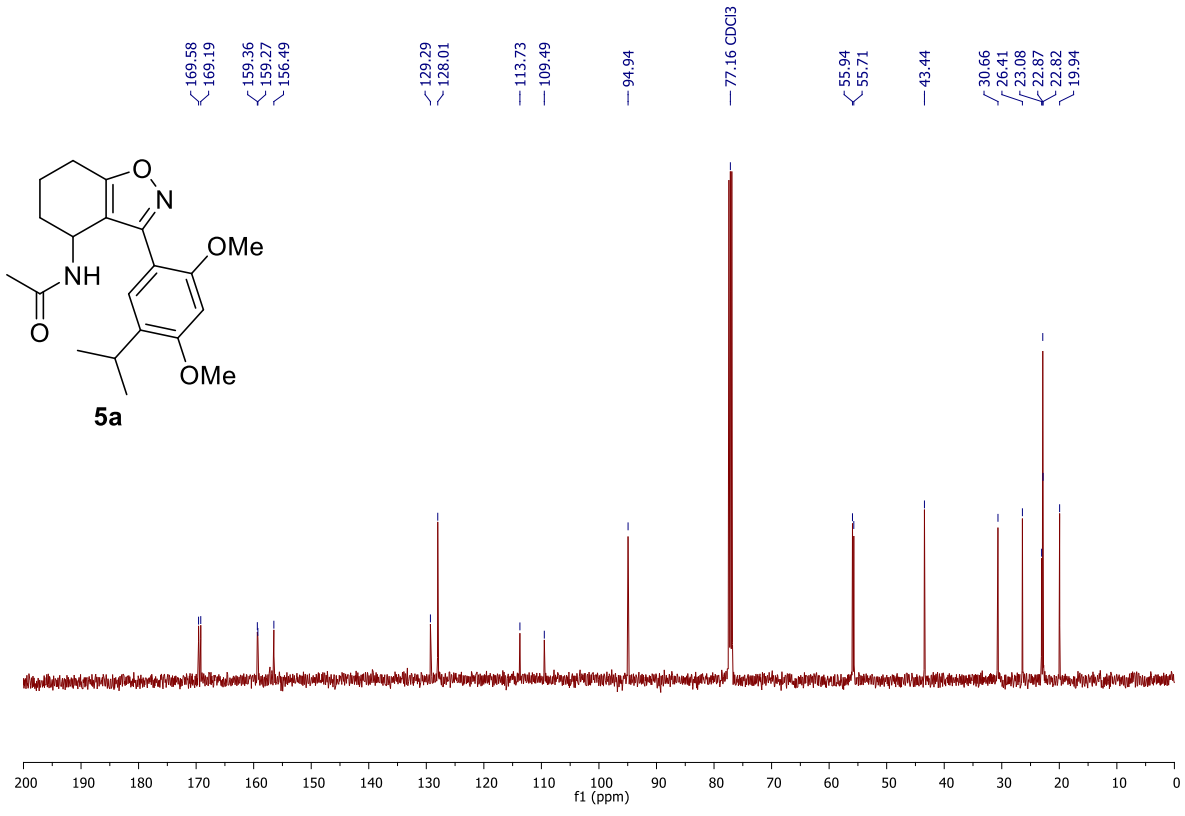

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **4b**



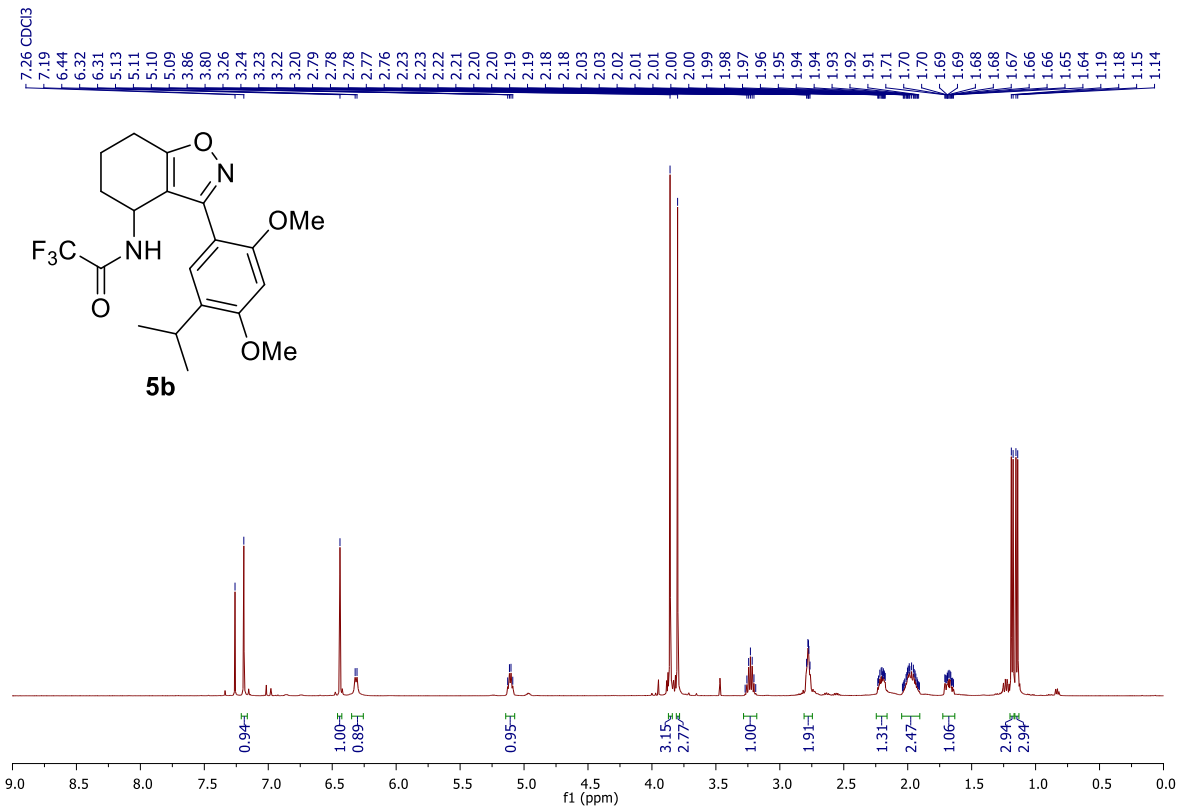

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **4b**



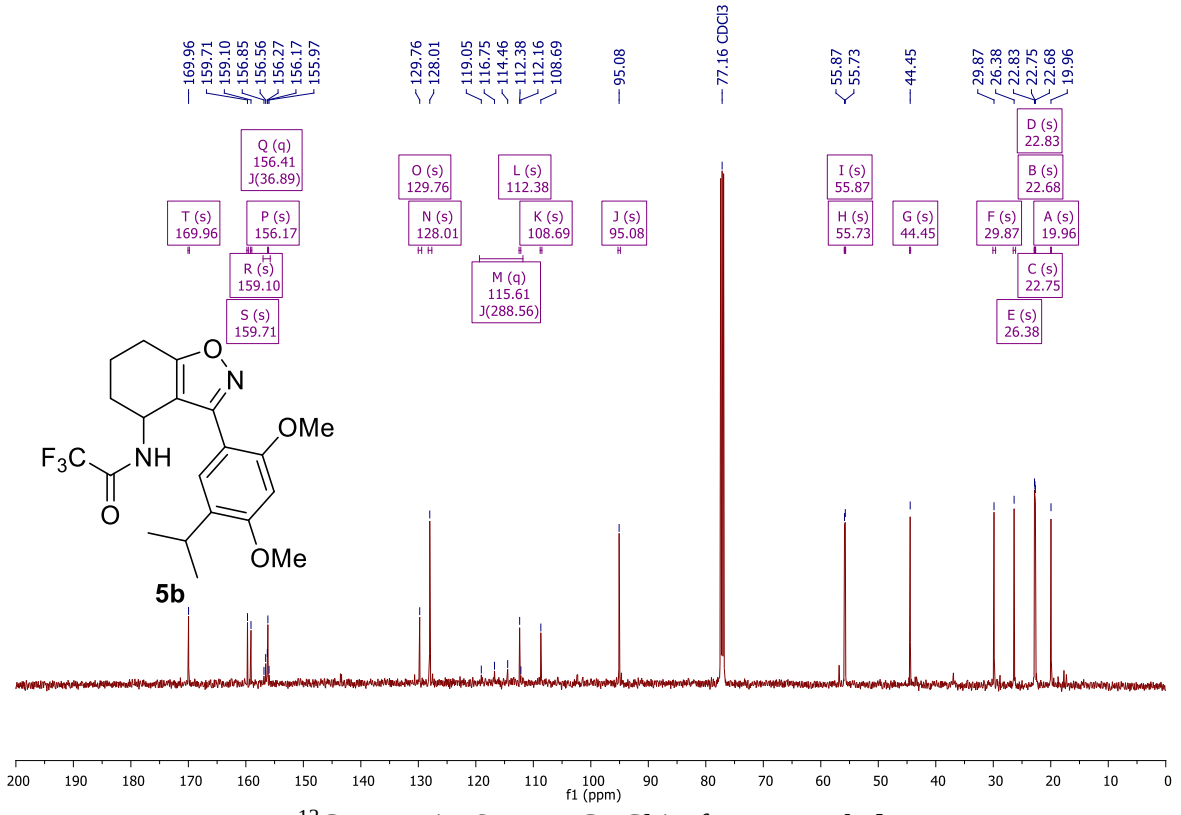

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5a**



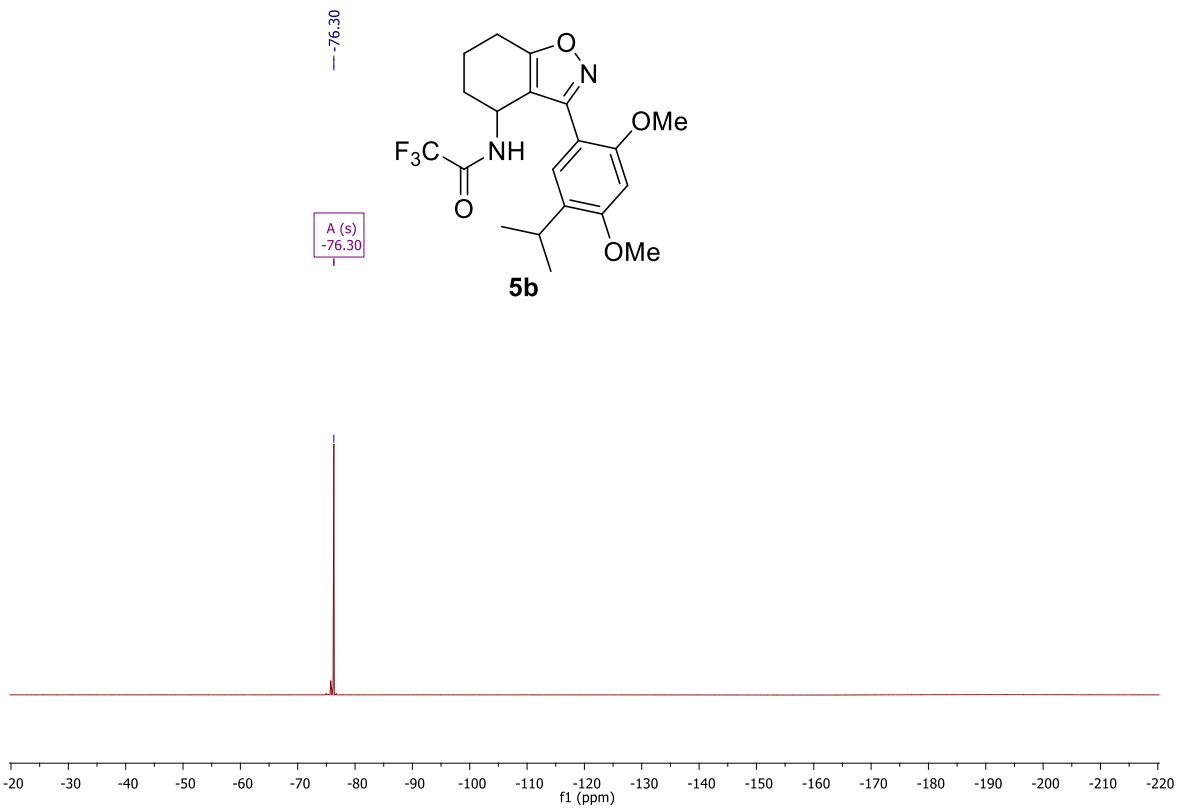

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5a**



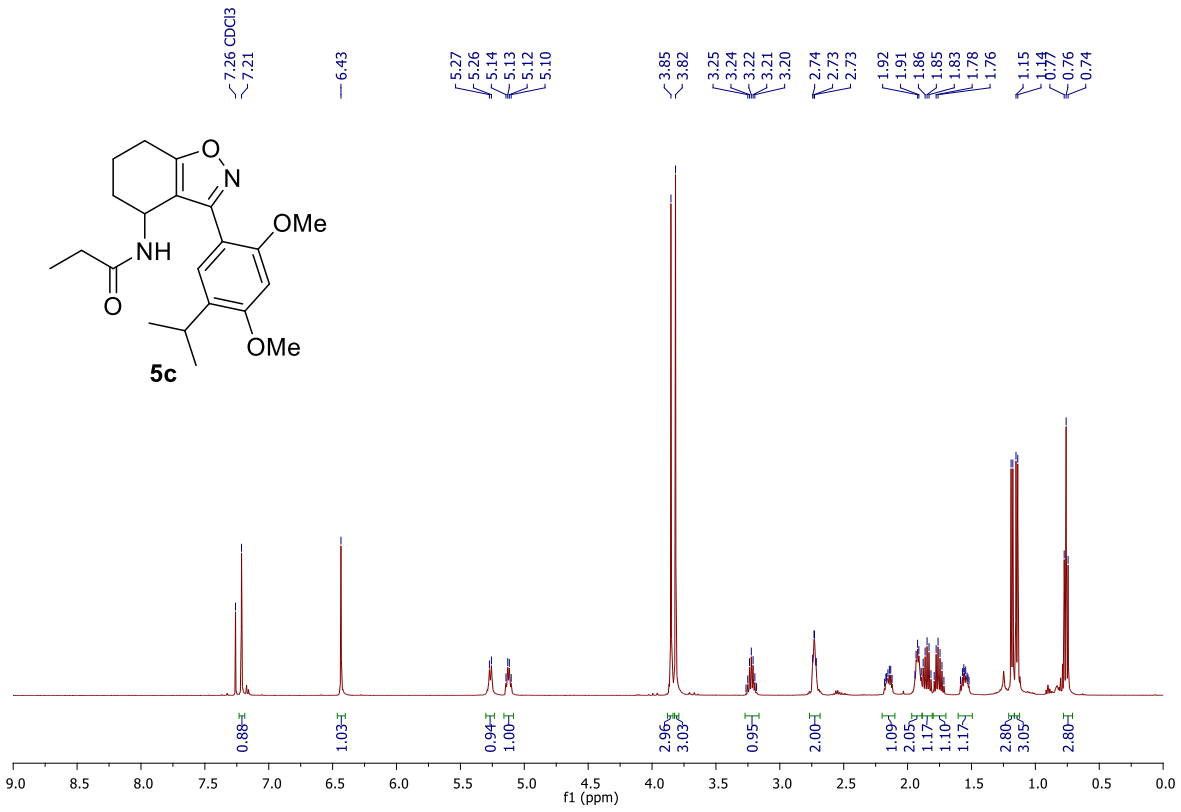

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5b**



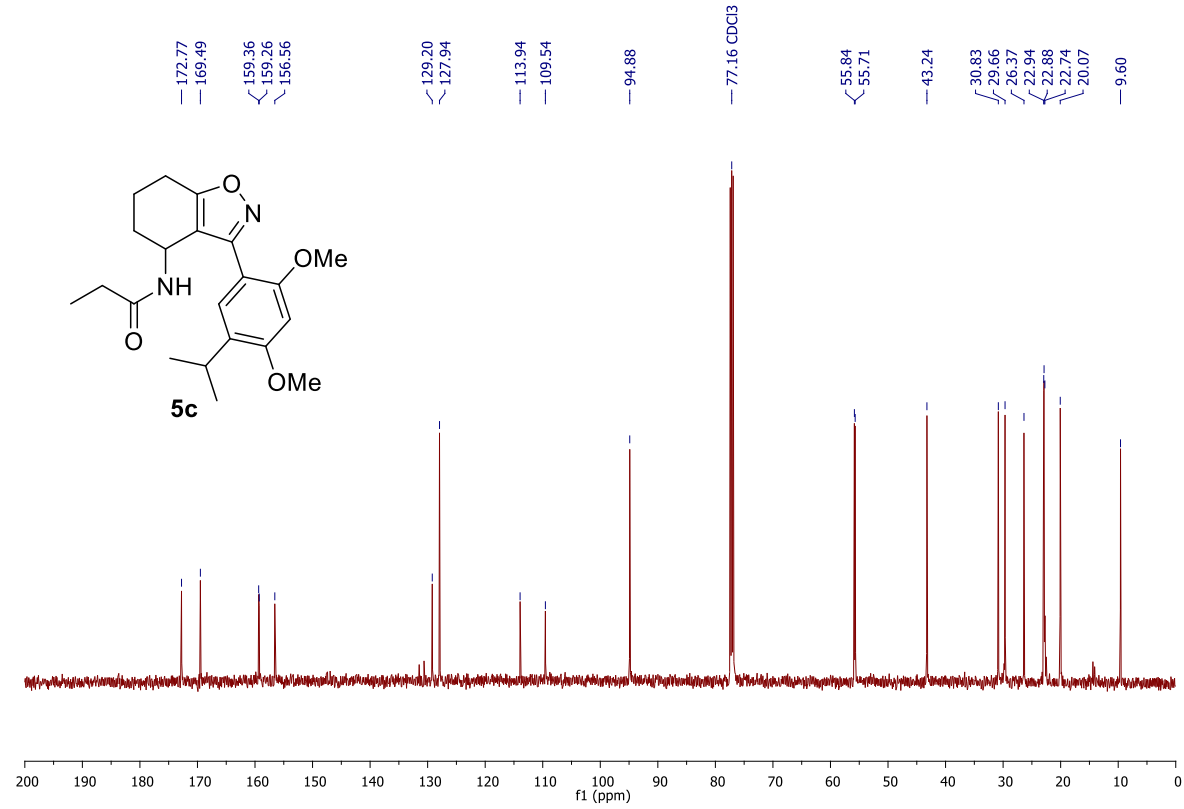

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5b**



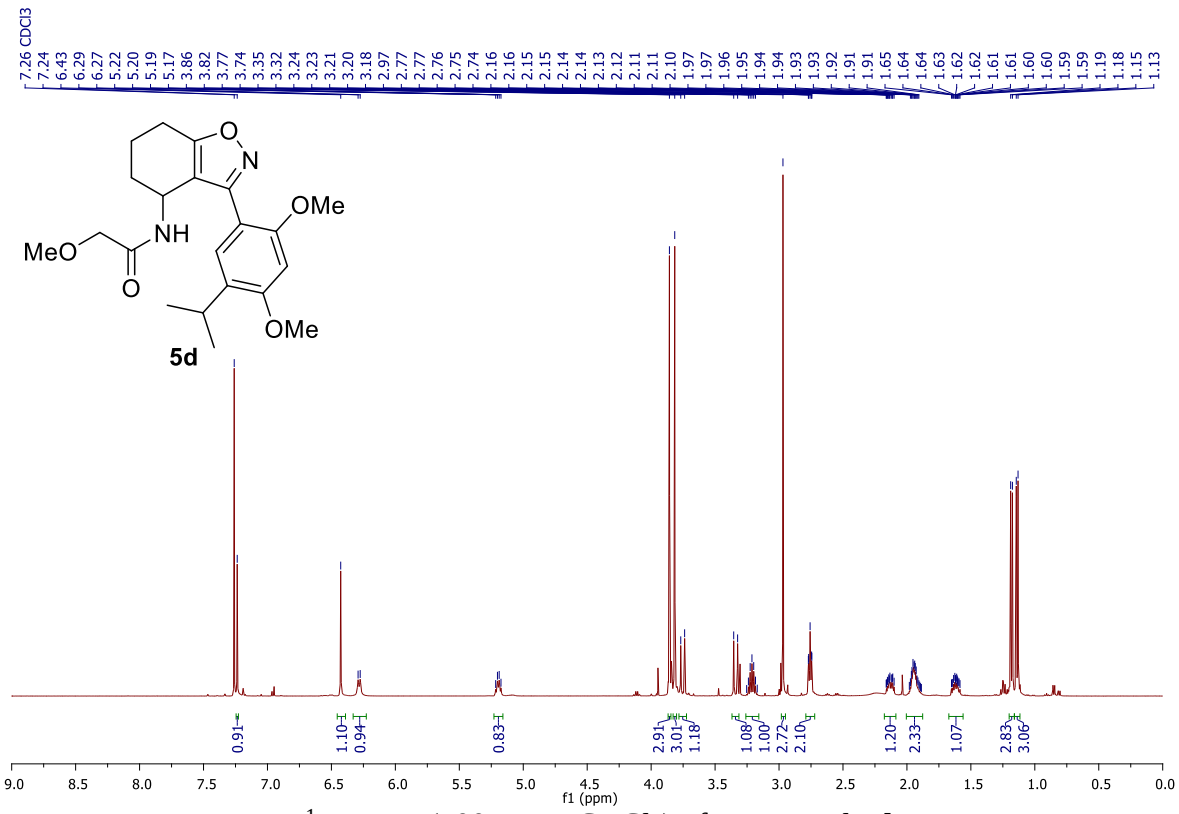

$^{19}$F NMR (470 MHz, $CDCl_3$) of compound **5b**



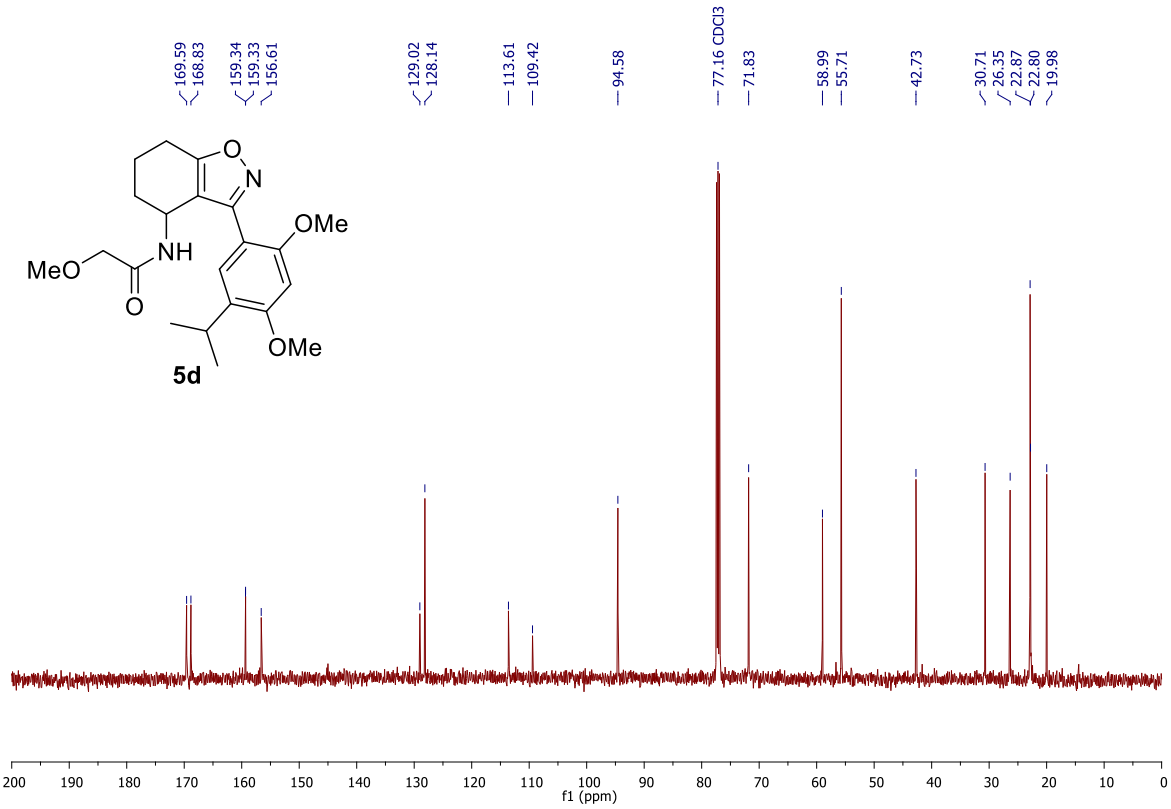

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5c**



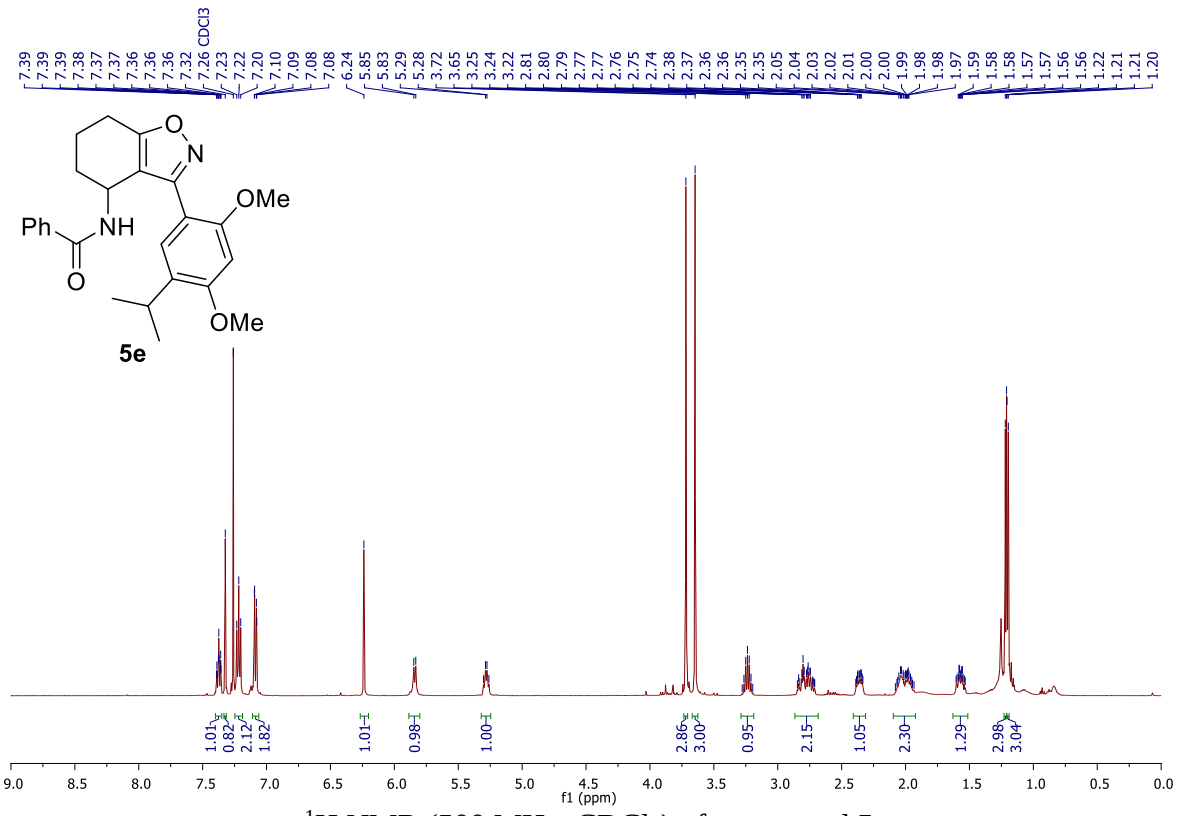

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5c**



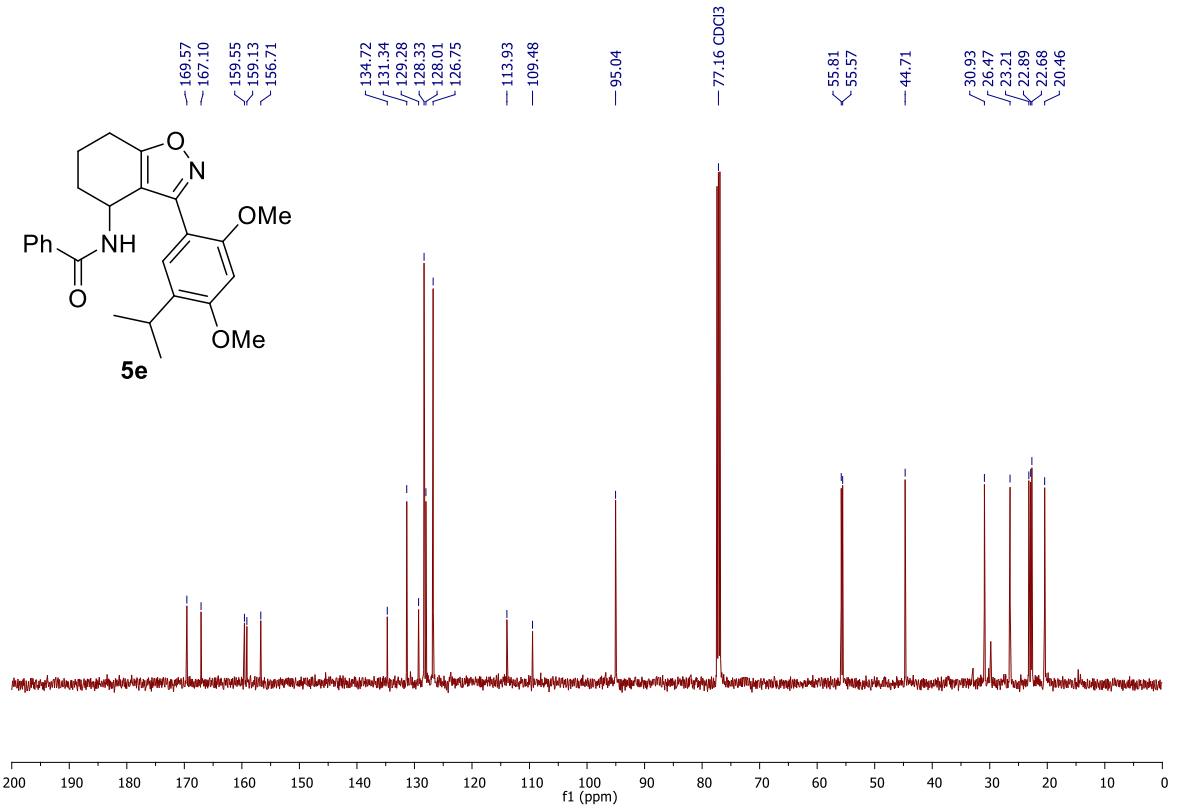

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5d**



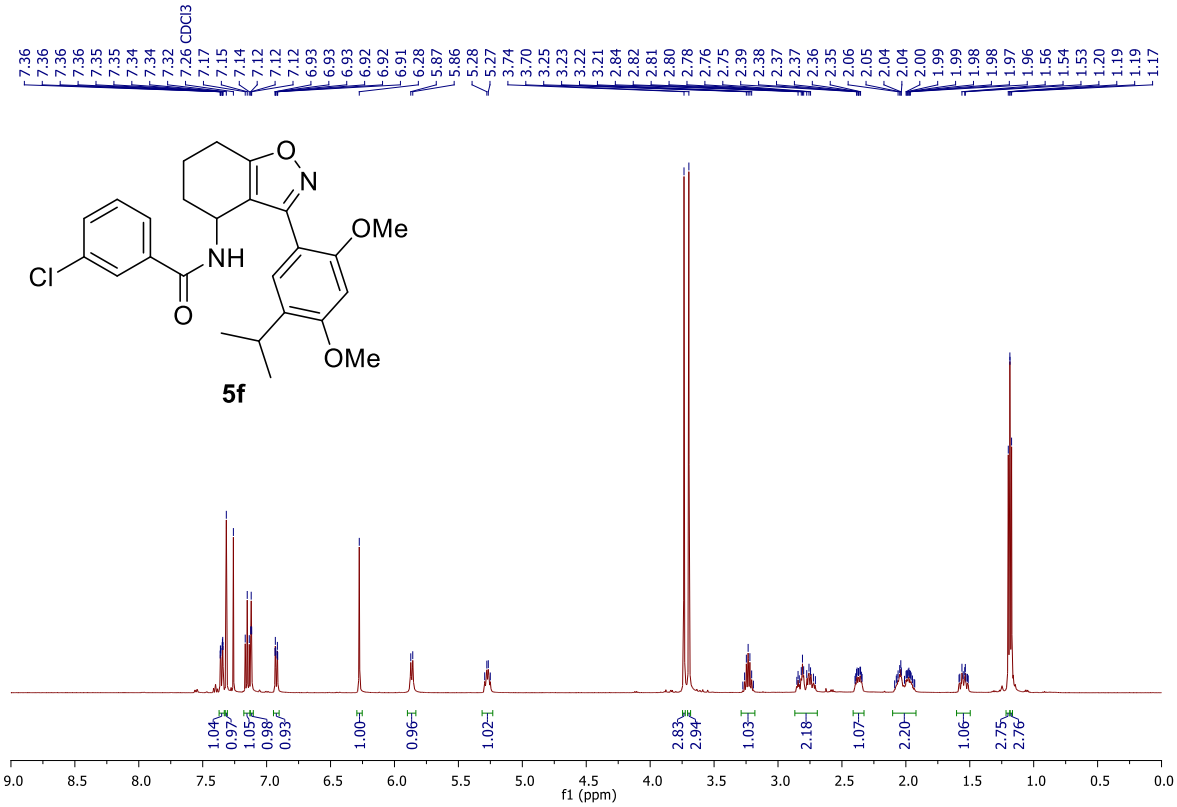

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5d**



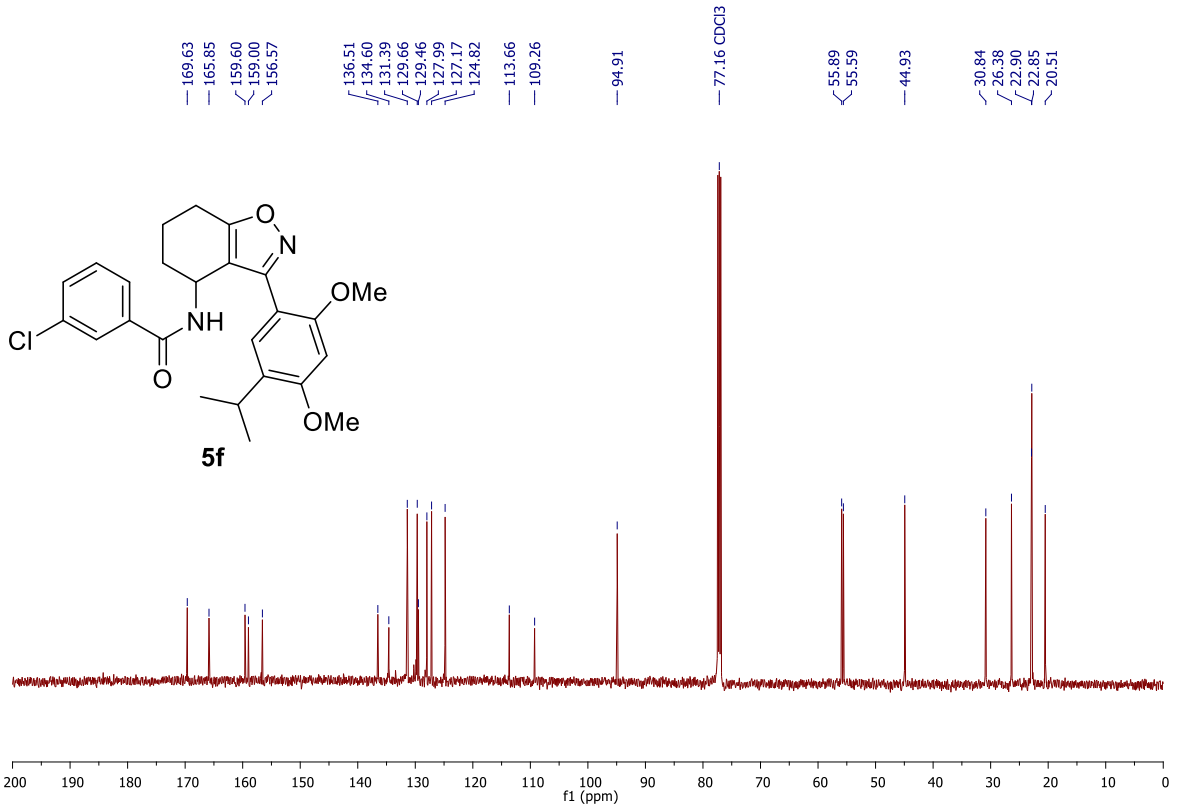

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5e**



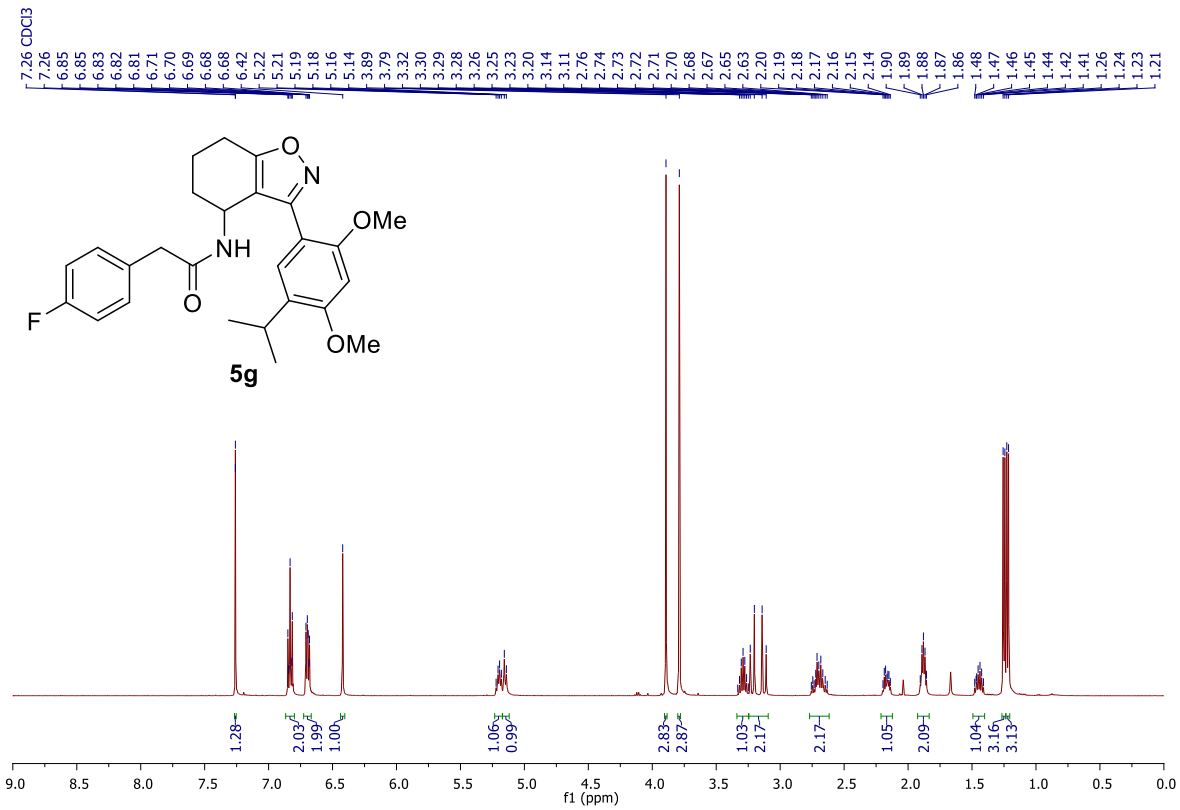

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5e**



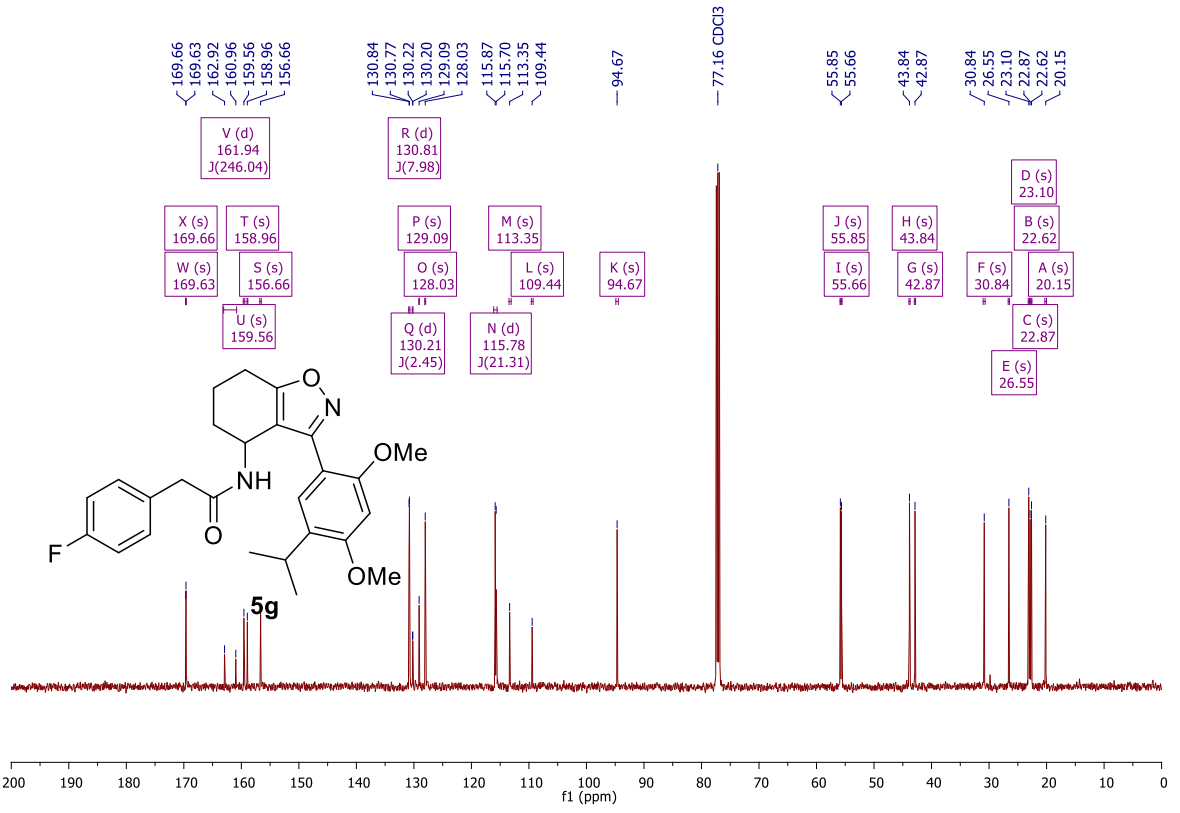

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5f**



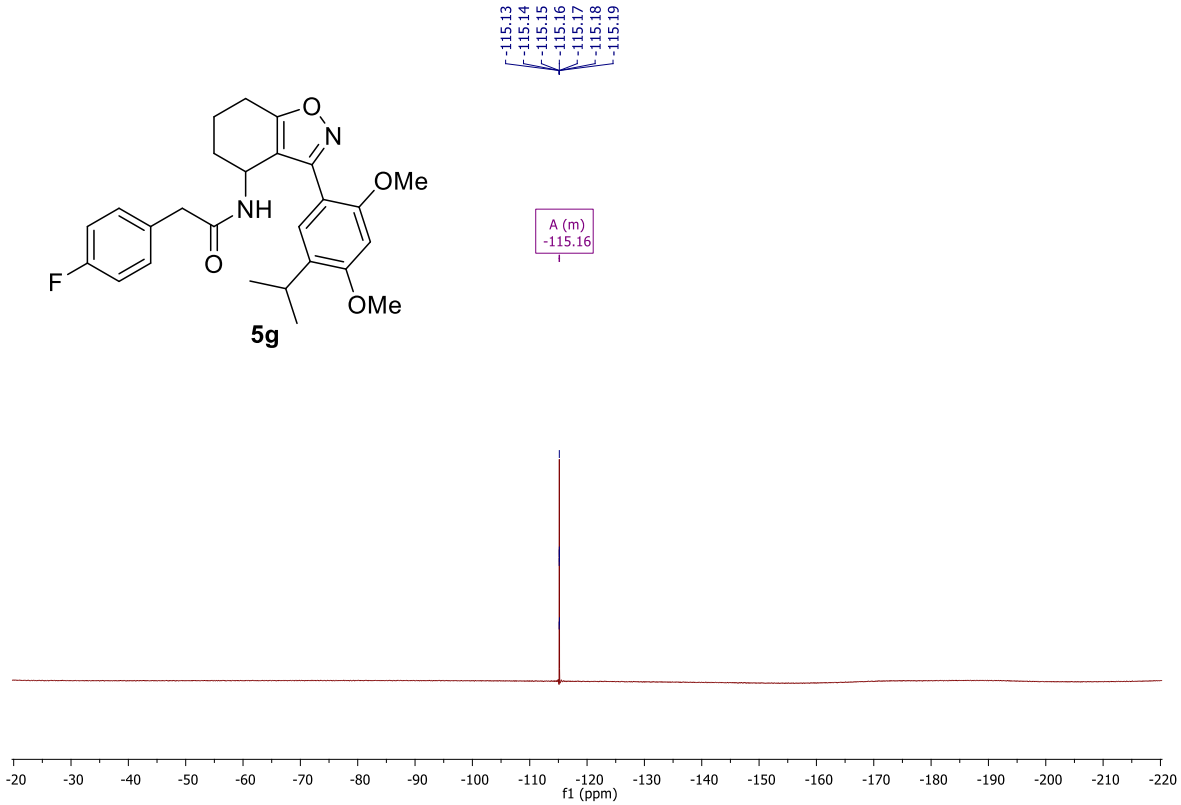

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5f**



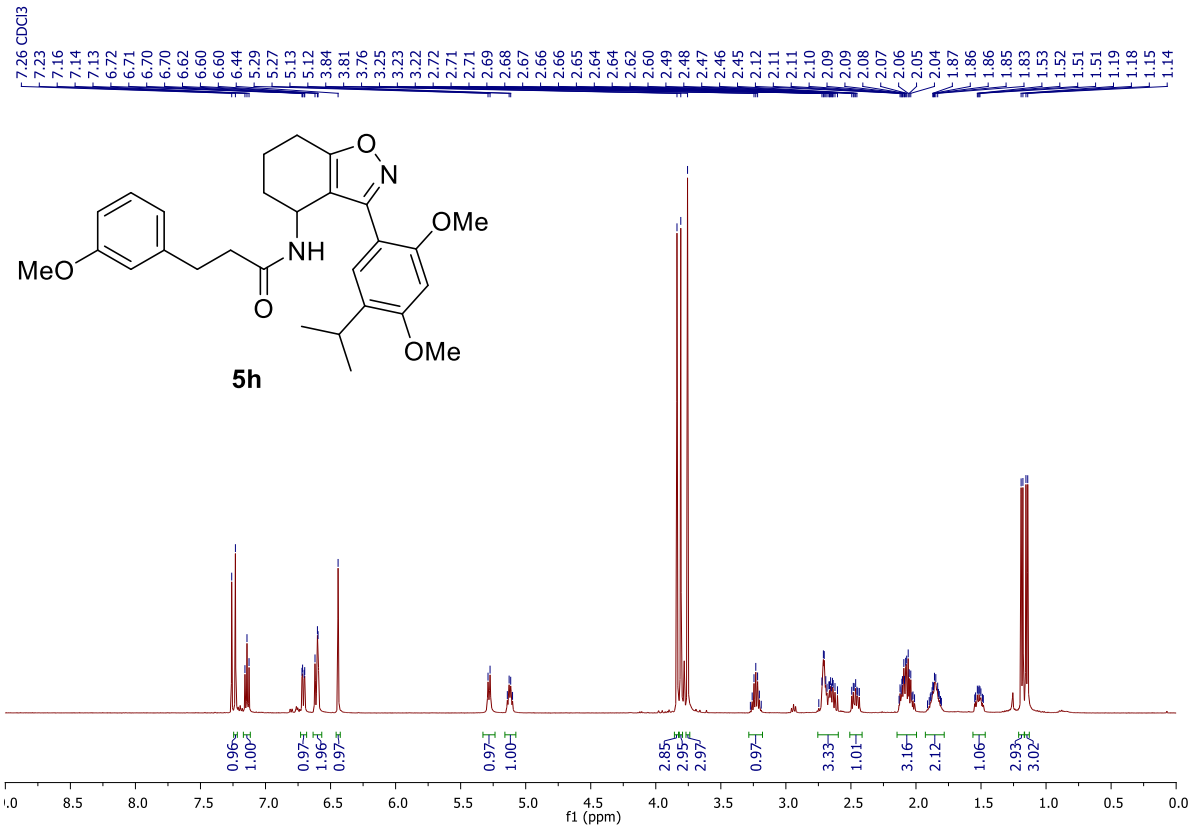

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5g**



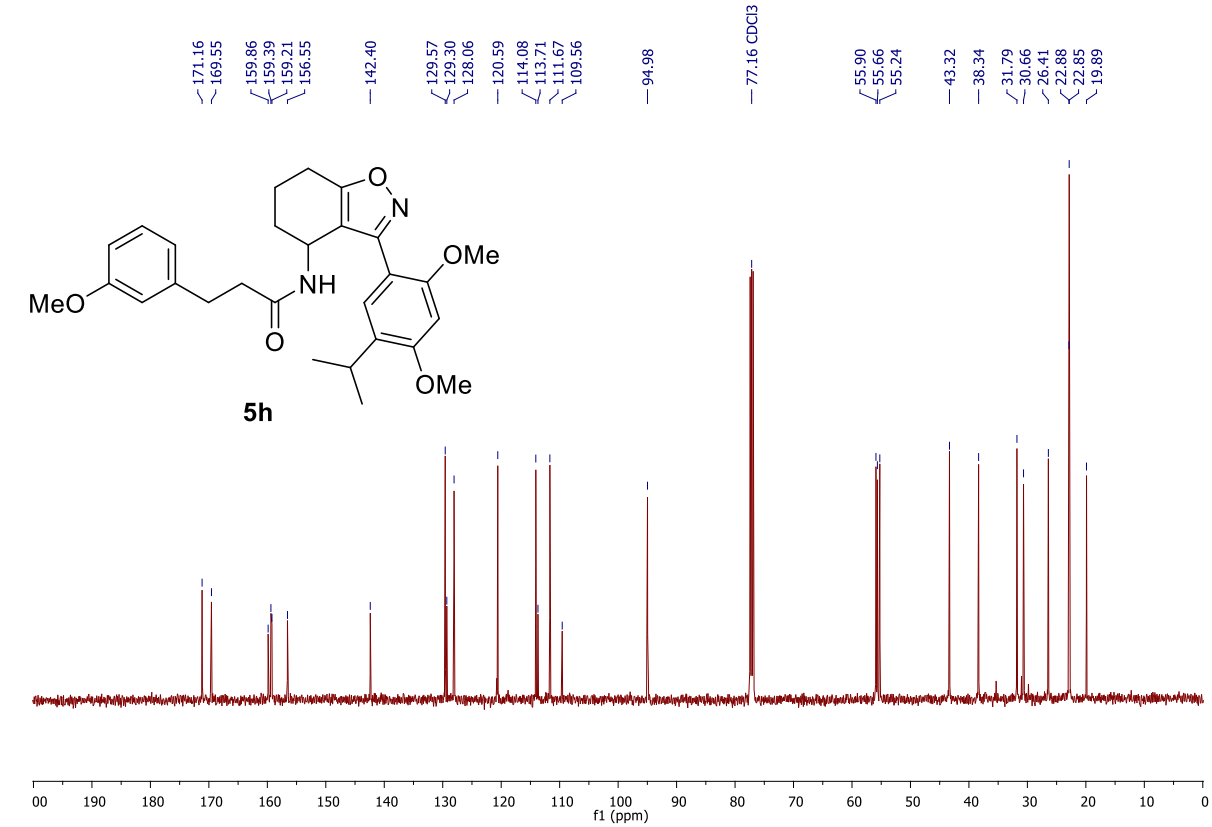

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5g**



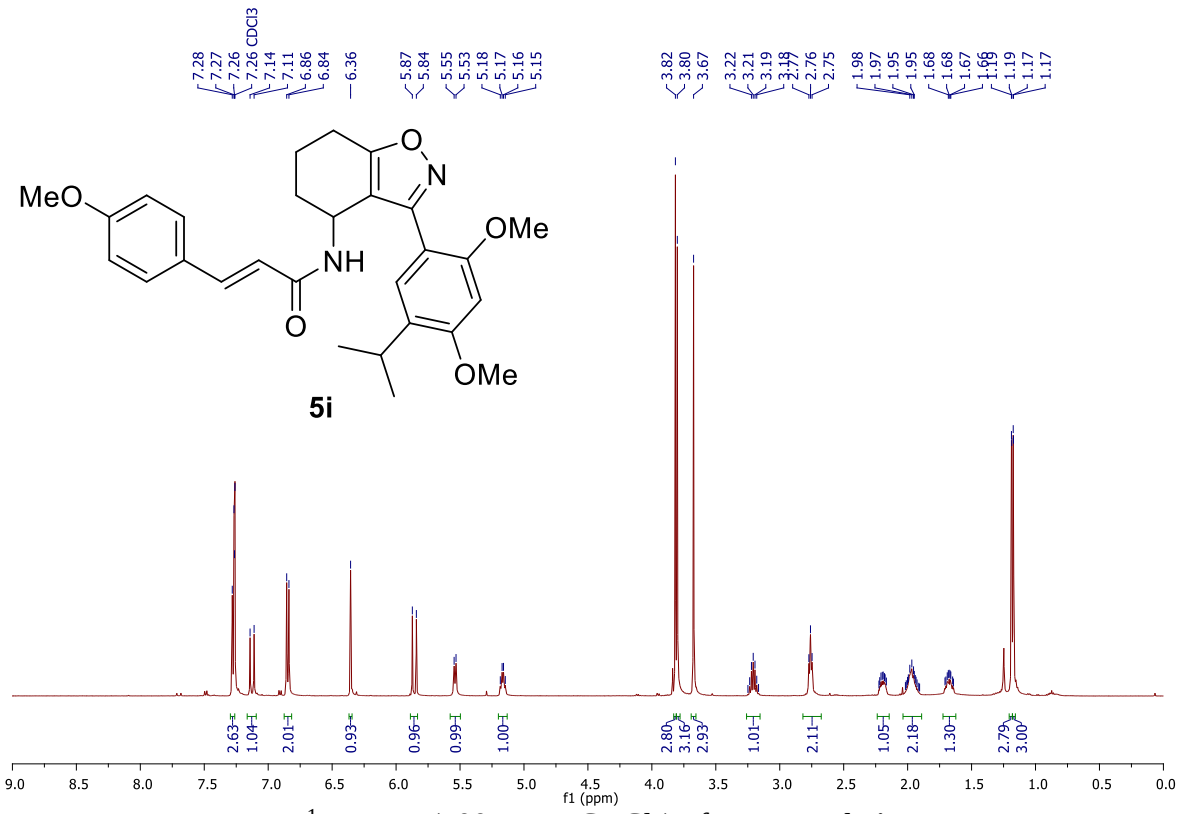

$^{19}$F NMR (470 MHz, $CDCl_3$) of compound **5g**



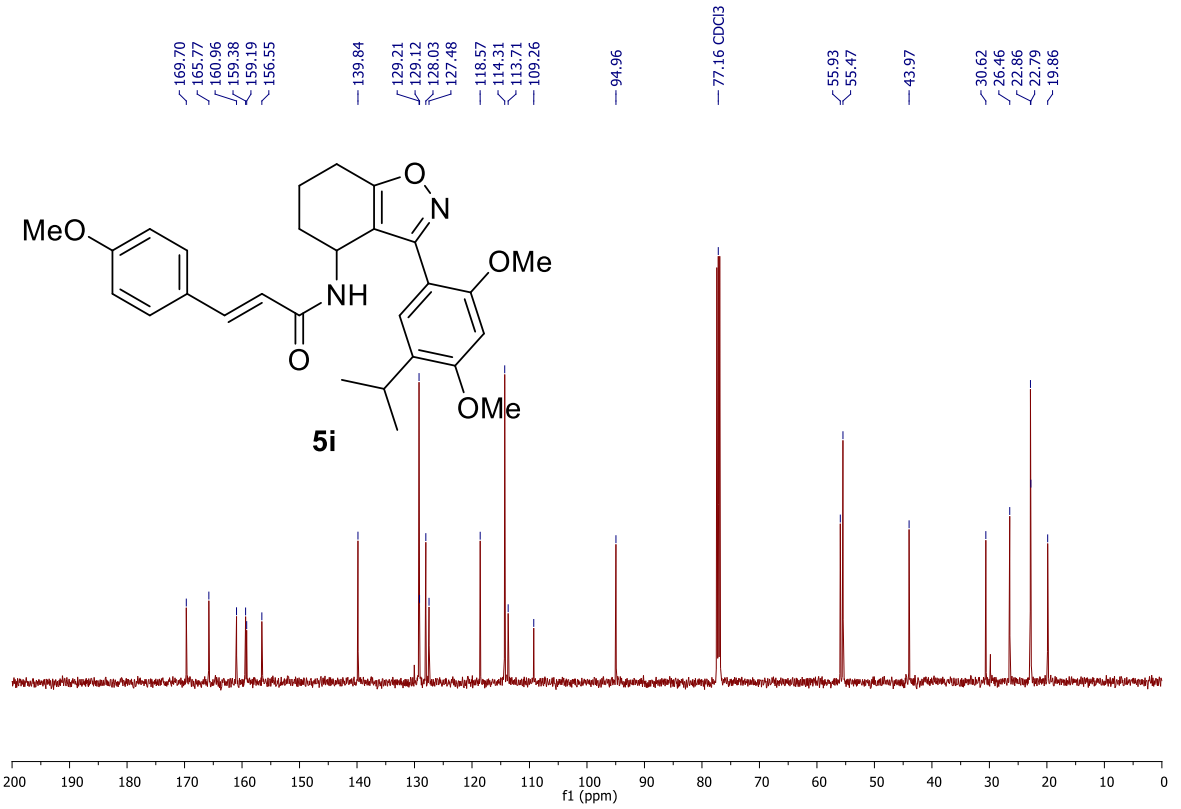

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5h**



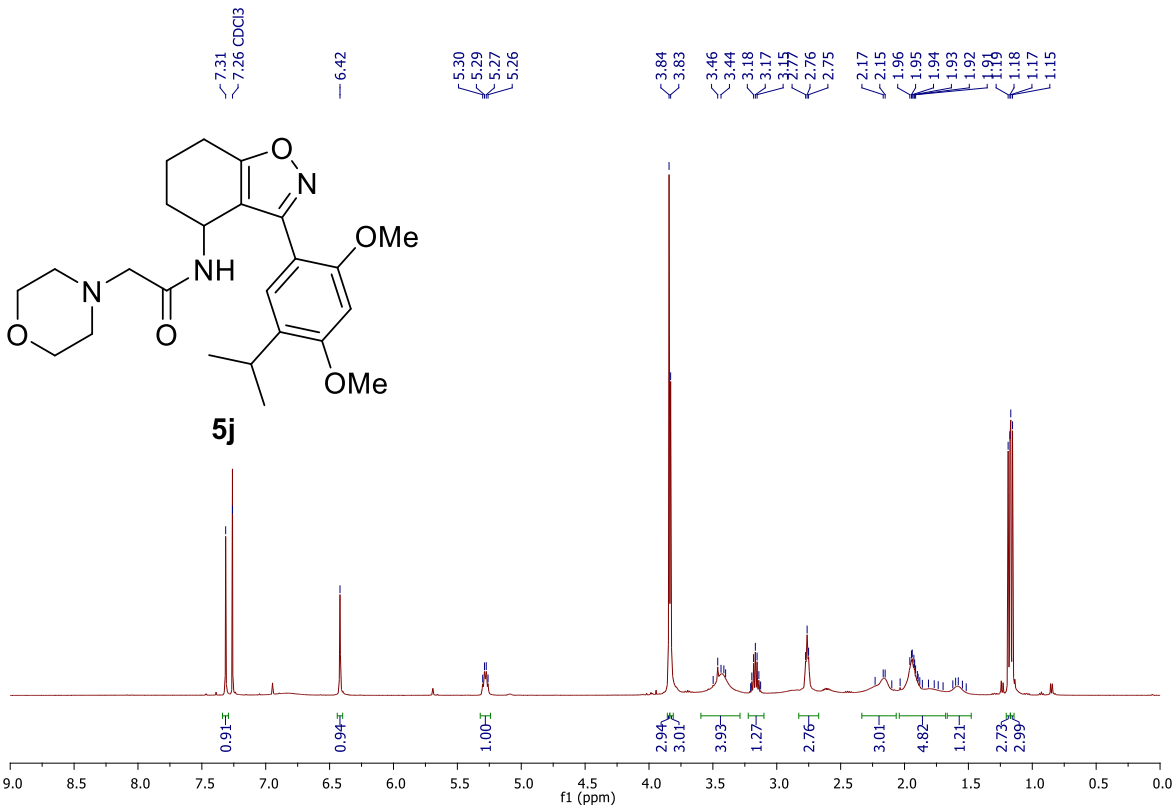

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5h**



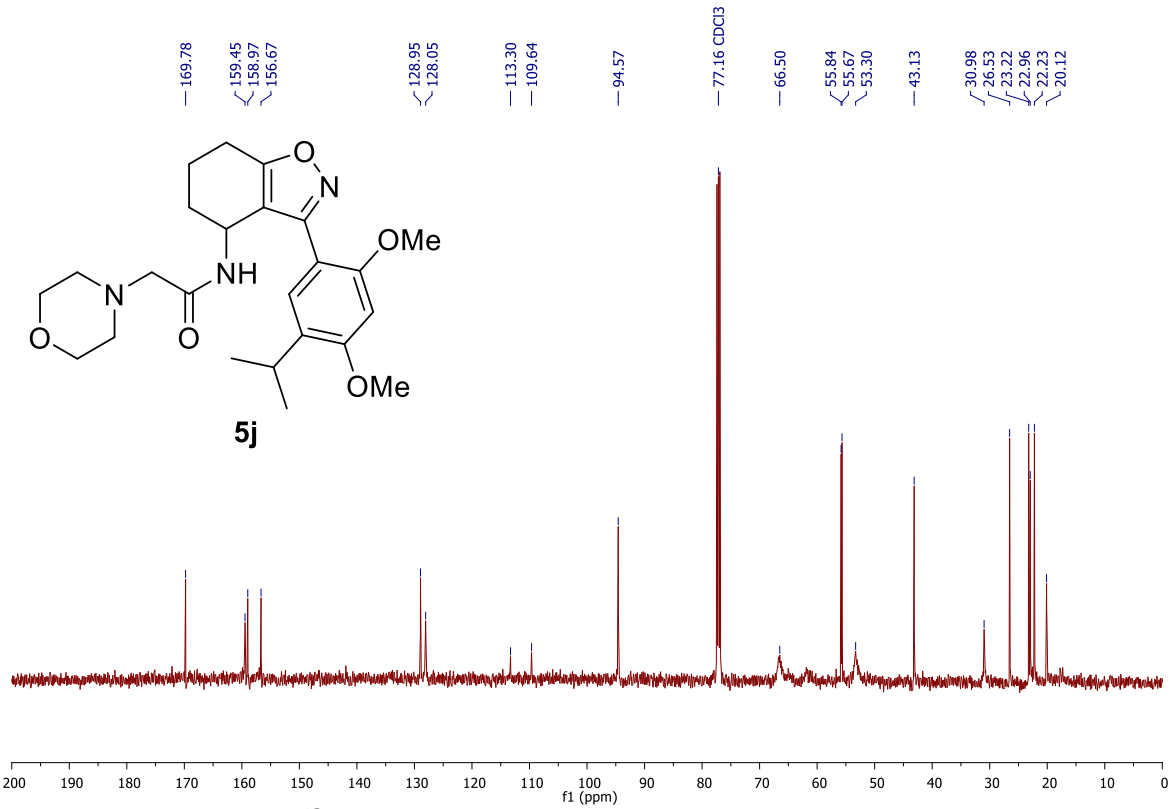

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5i**



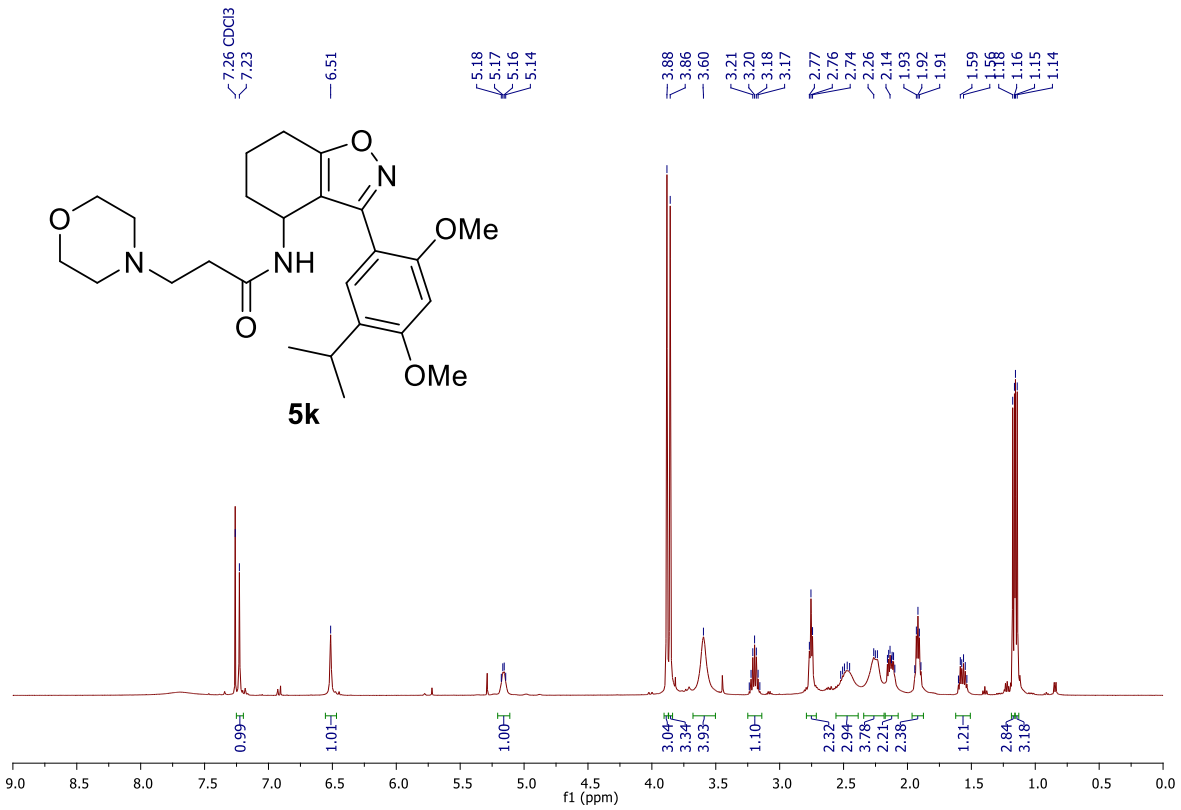

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5i**



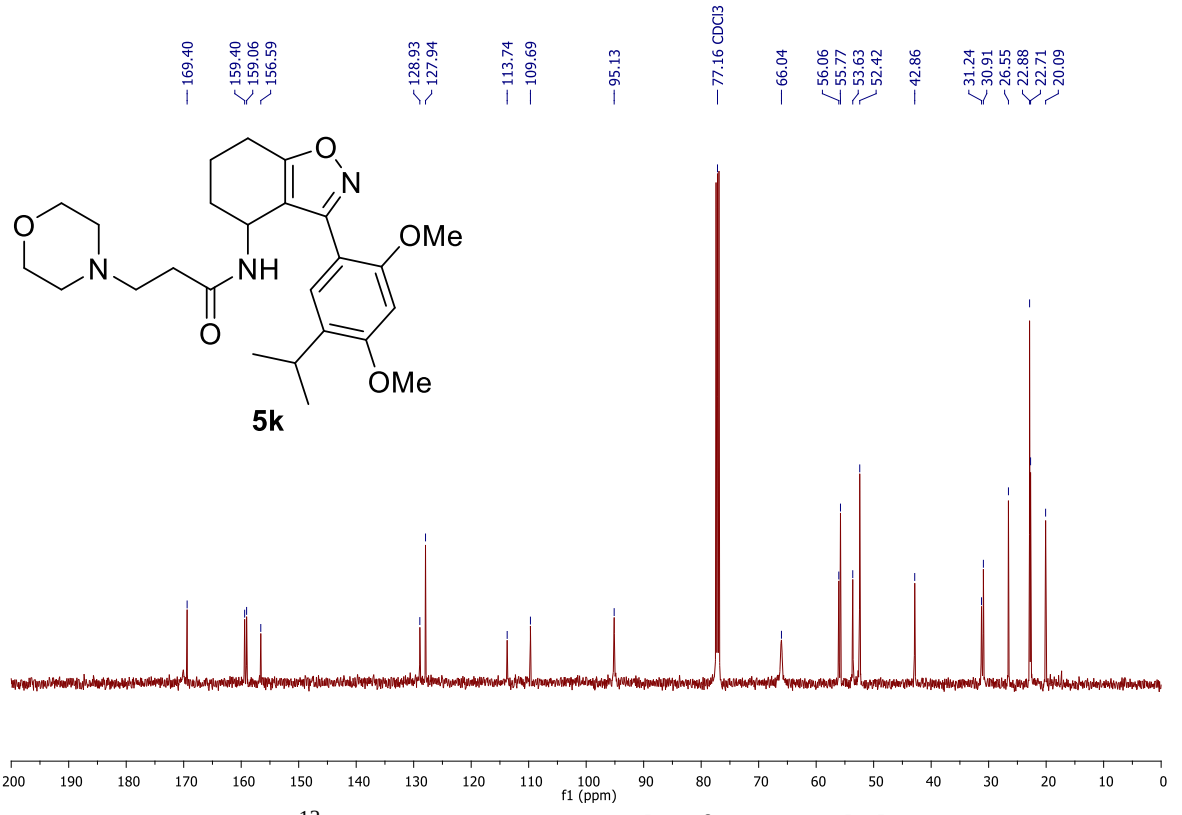

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5j**



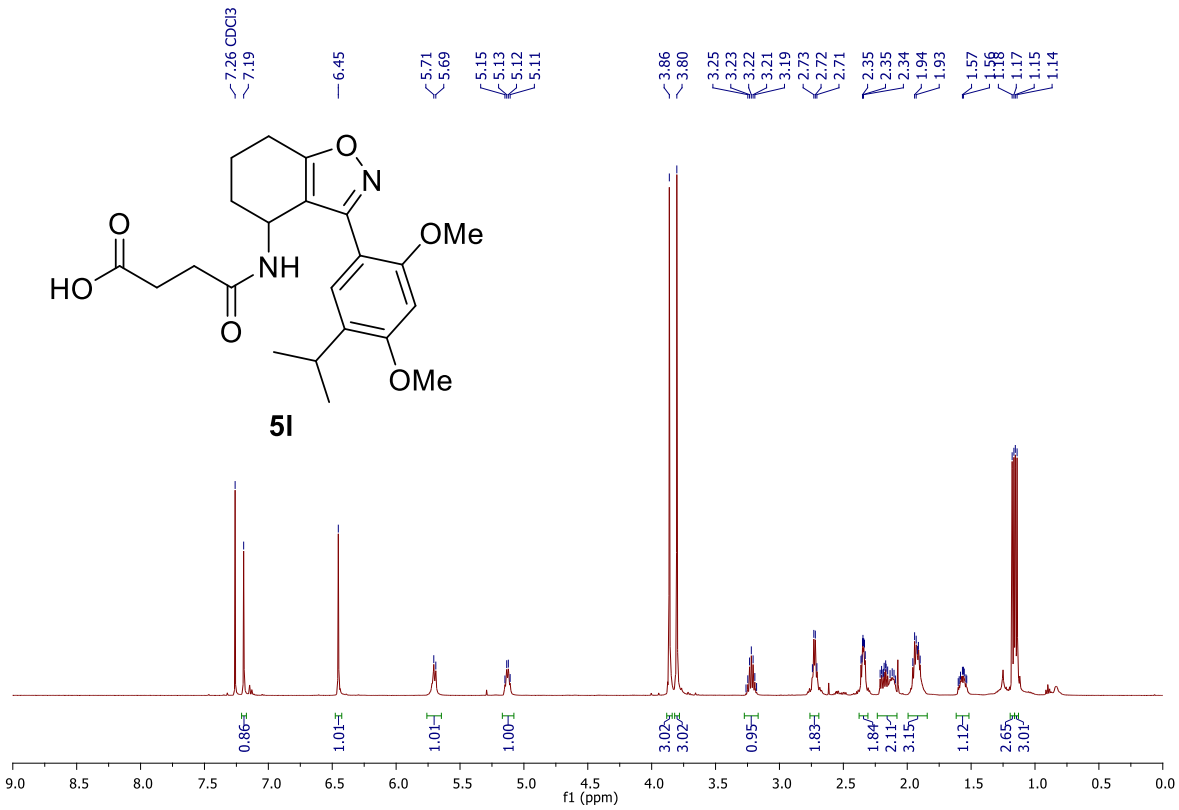

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5j**



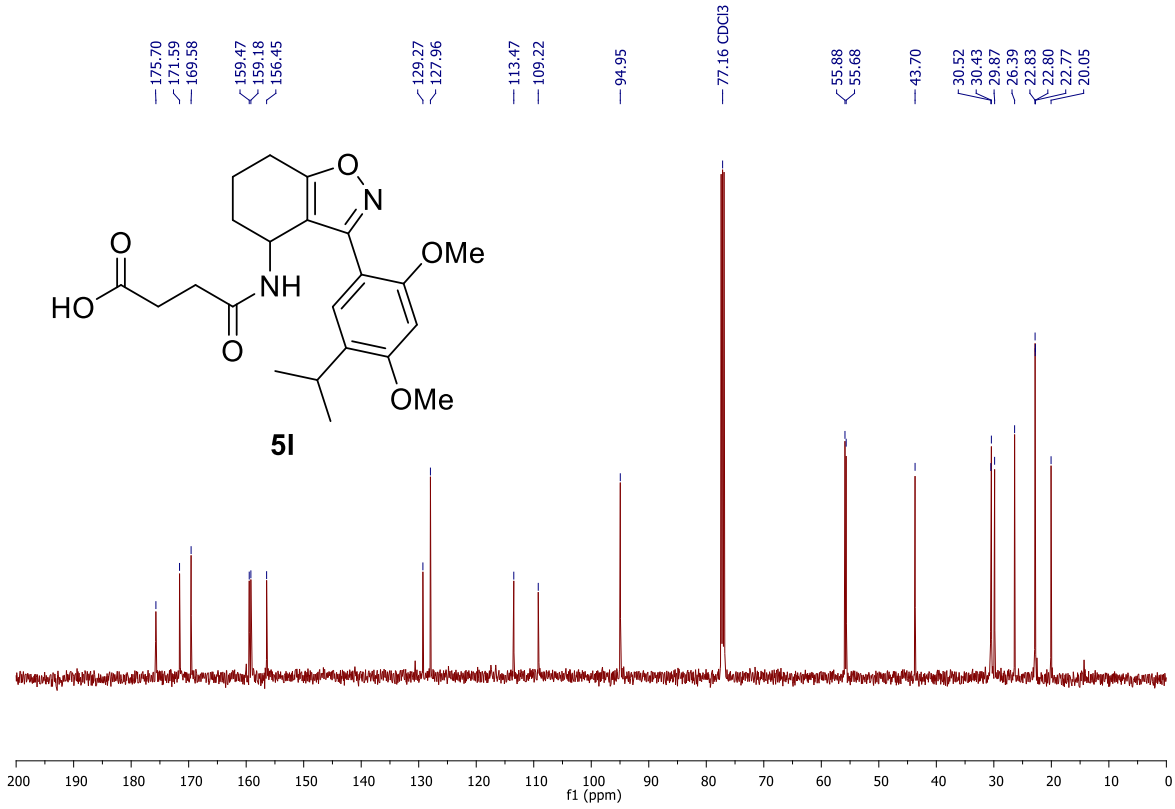

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5k**



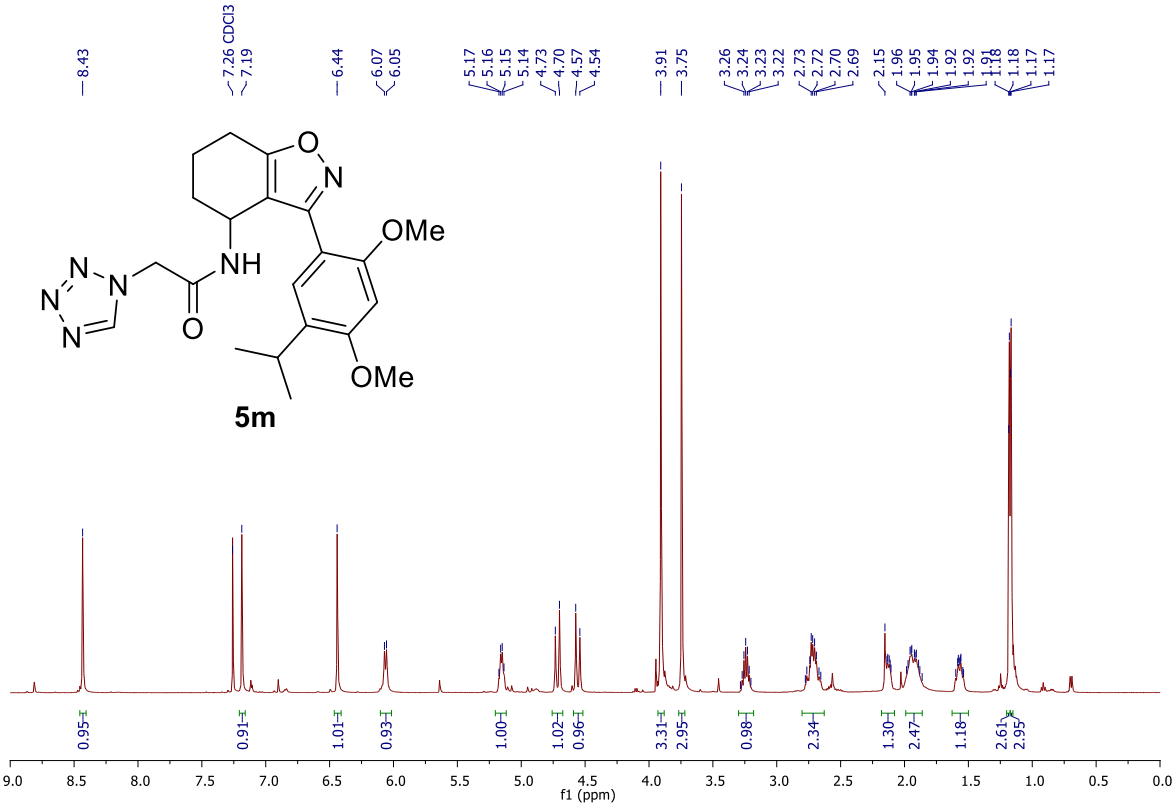

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5k**



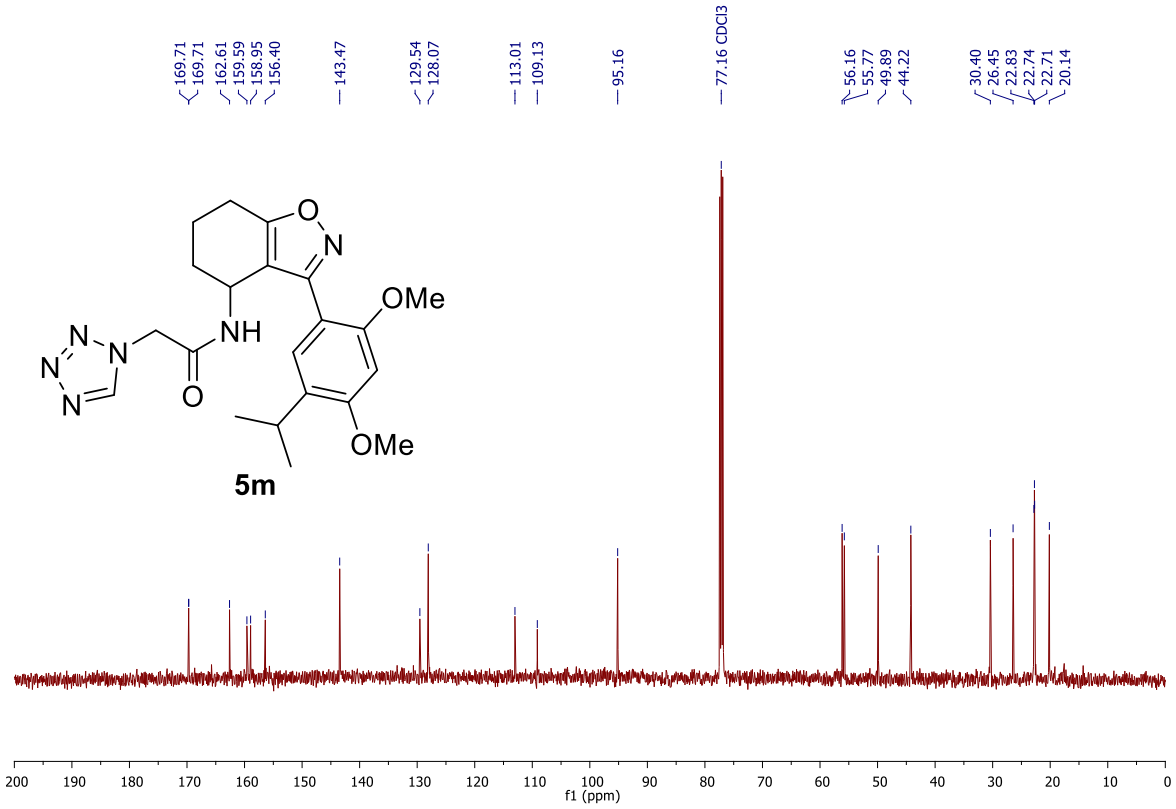

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5l**



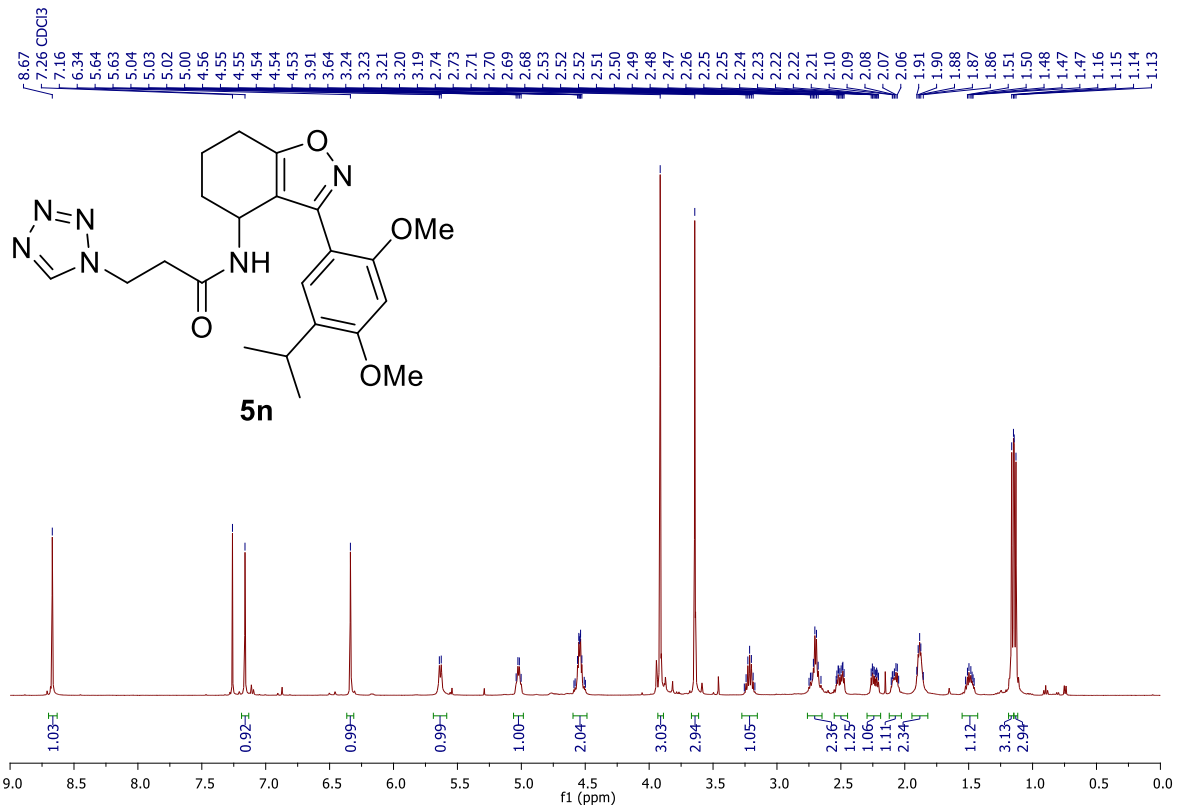

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5l**



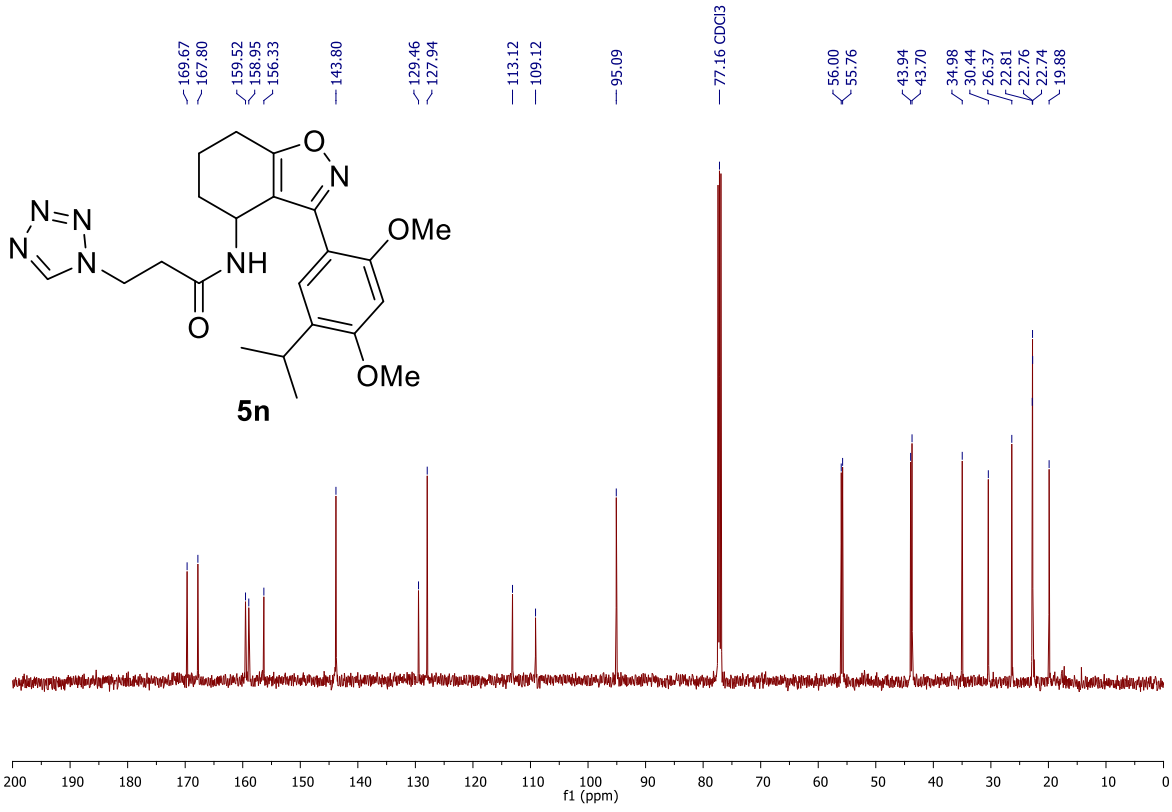

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5m**



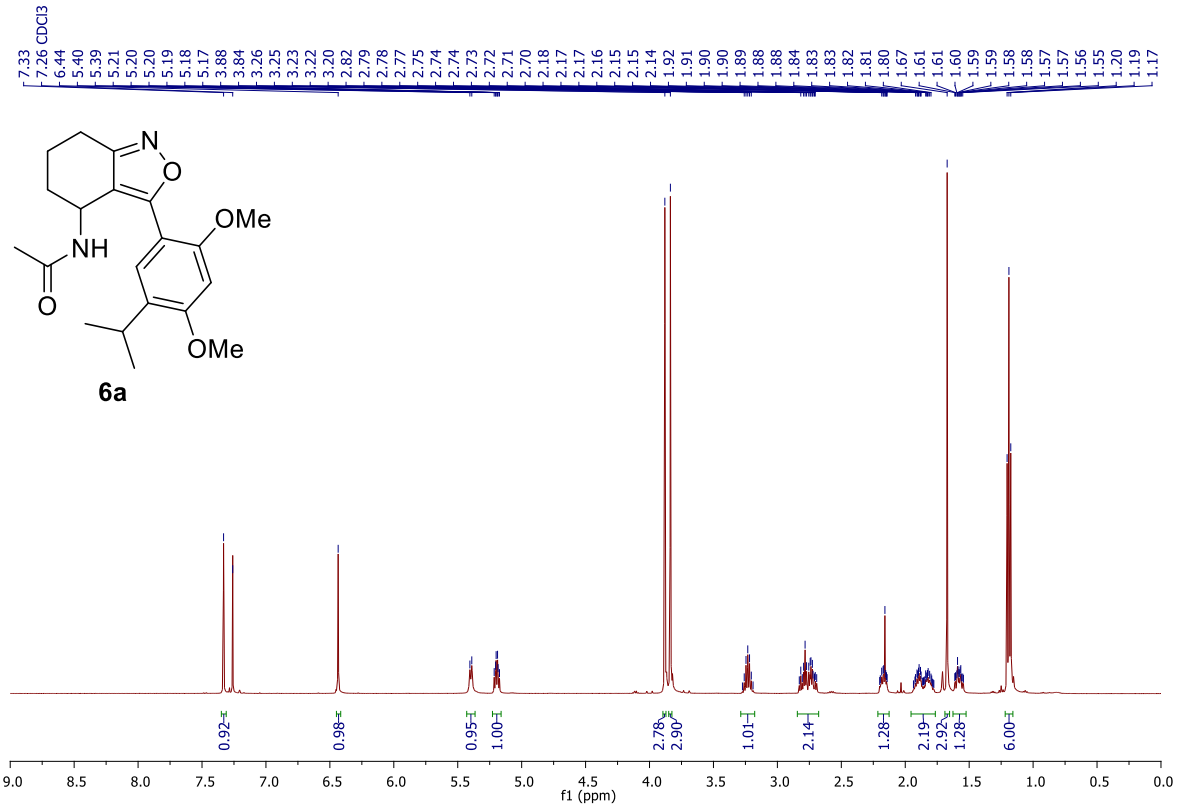

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5m**



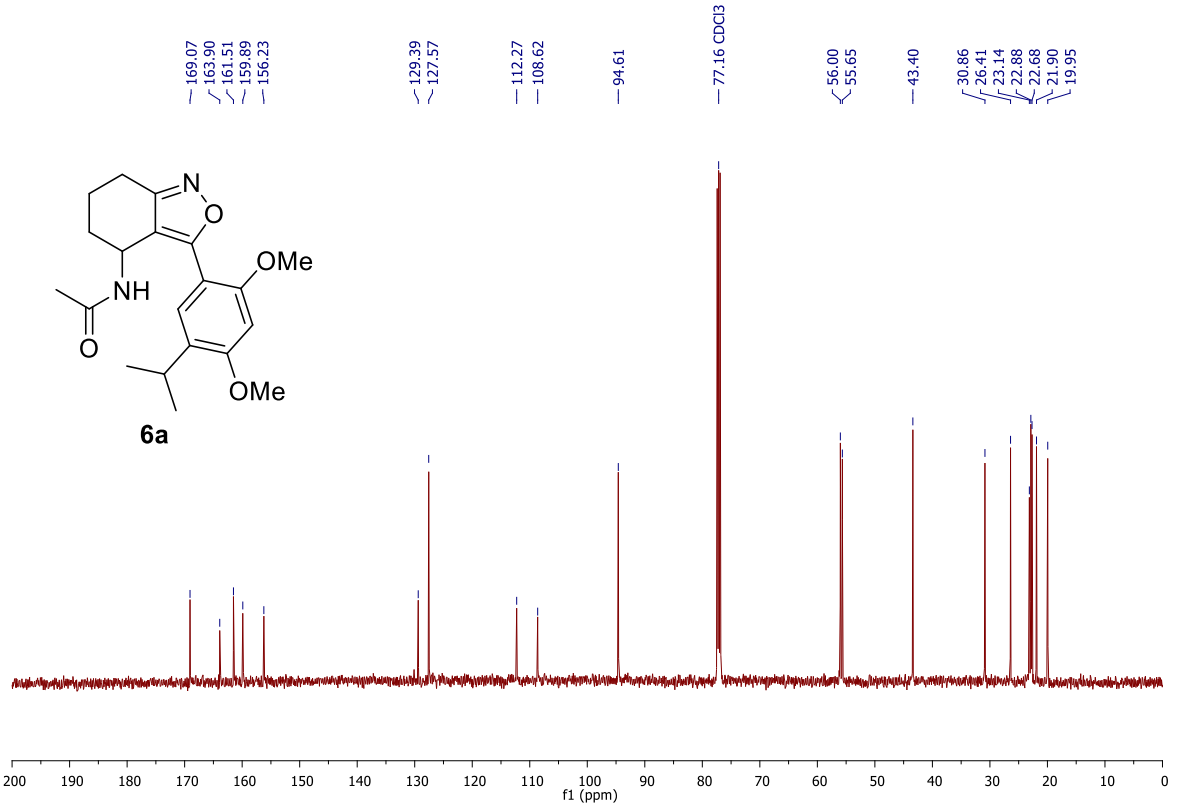

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **5n**



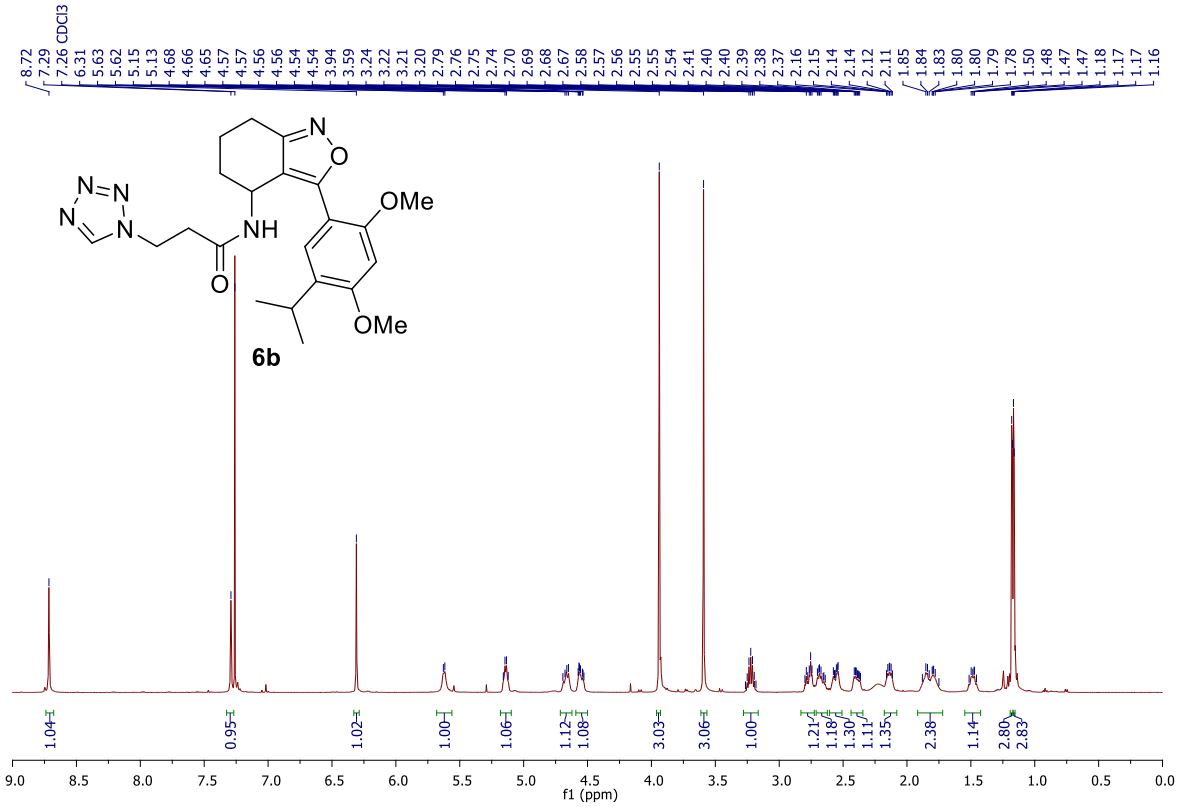

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **5n**



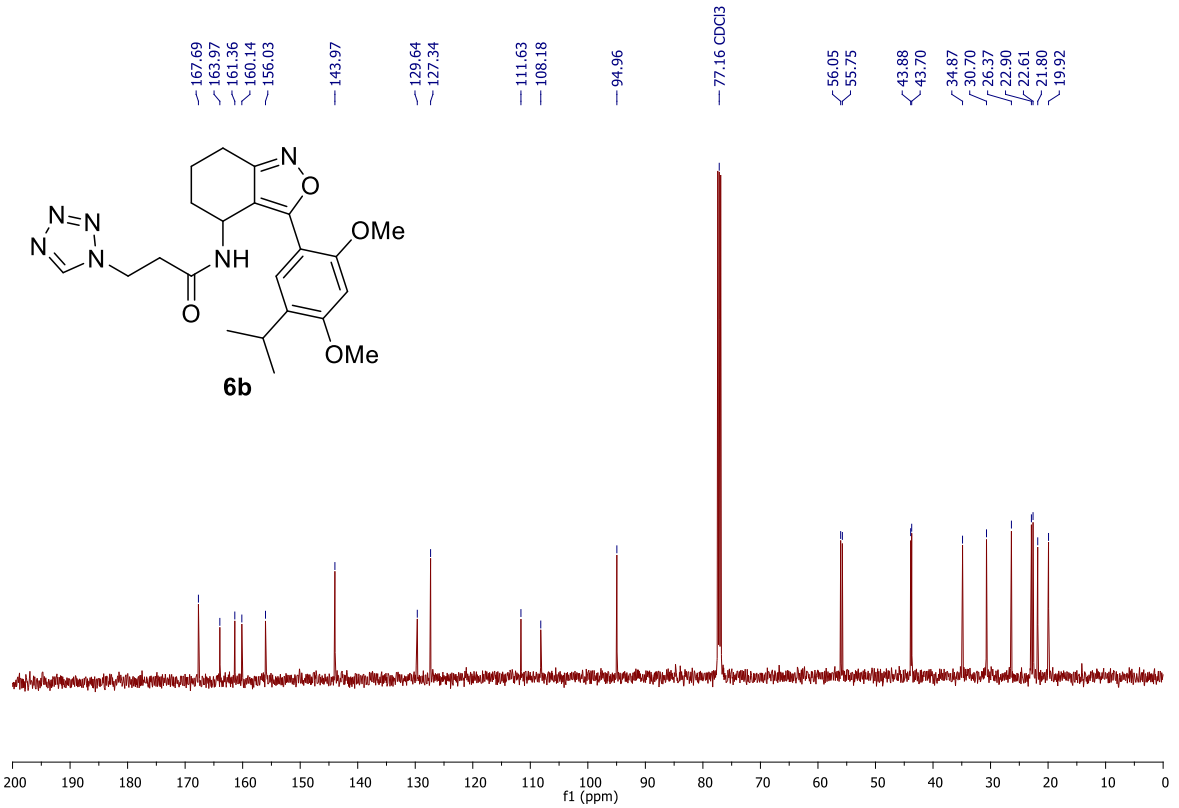

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6a**



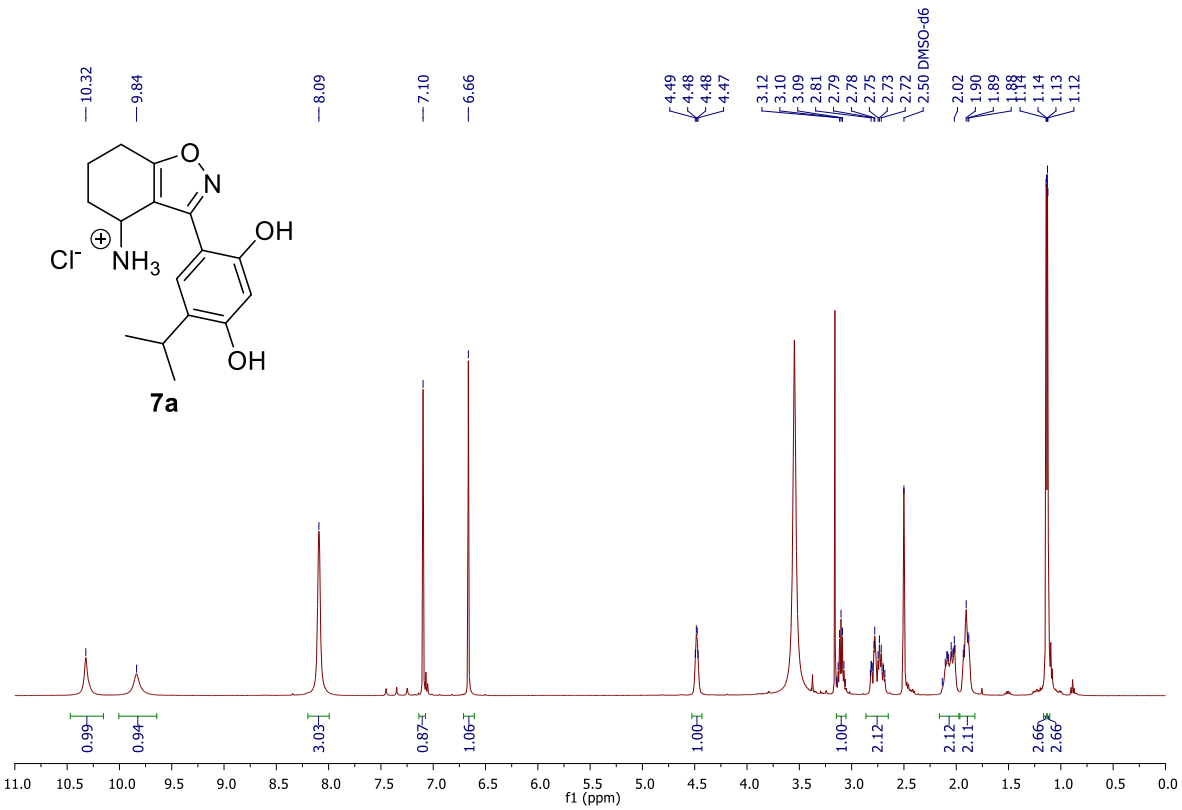

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **6a**



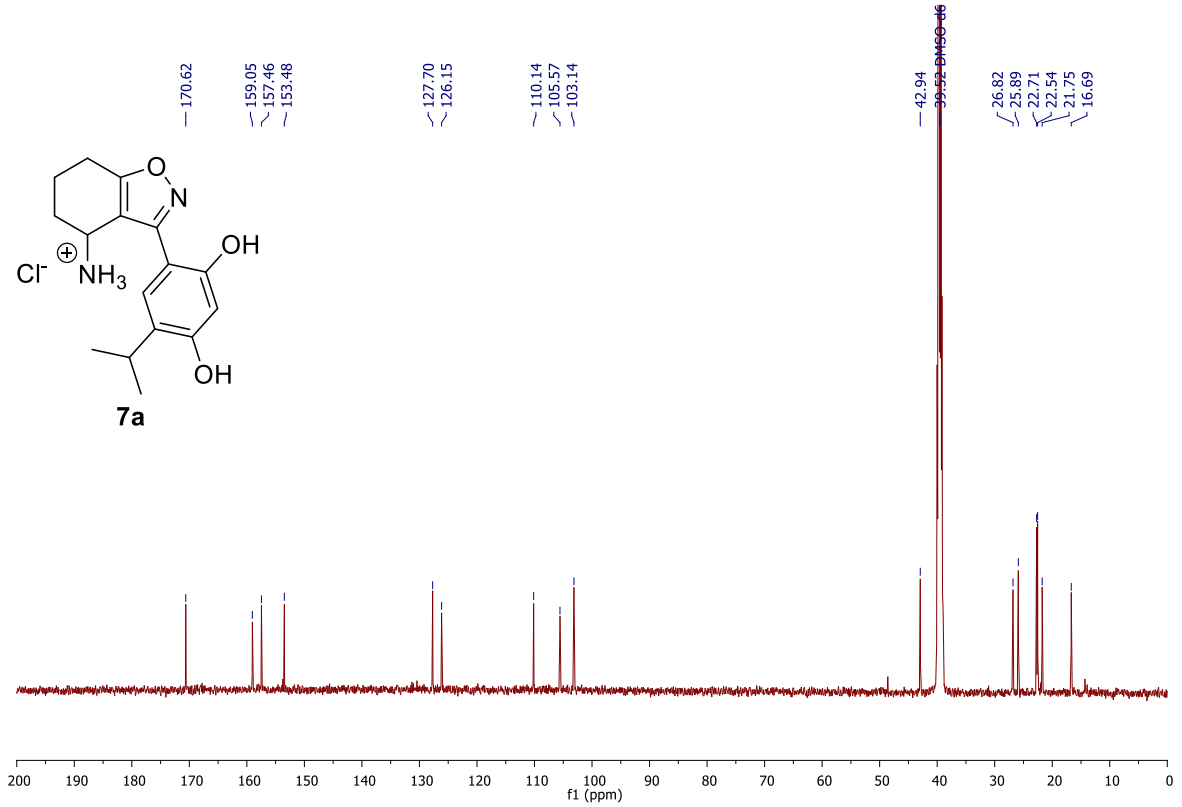

$^{1}$H NMR (500 MHz, $CDCl_3$) of compound **6b**



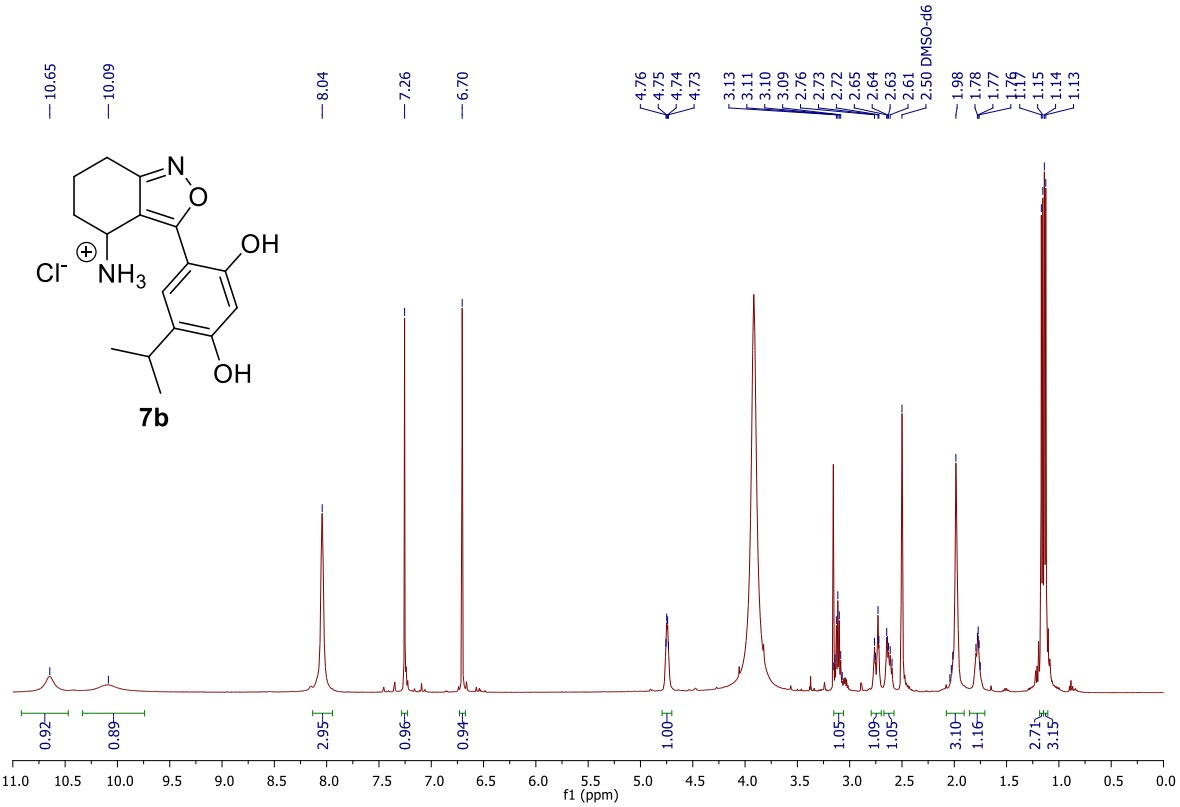

$^{13}$C NMR (126 MHz, $CDCl_3$) of compound **6b**



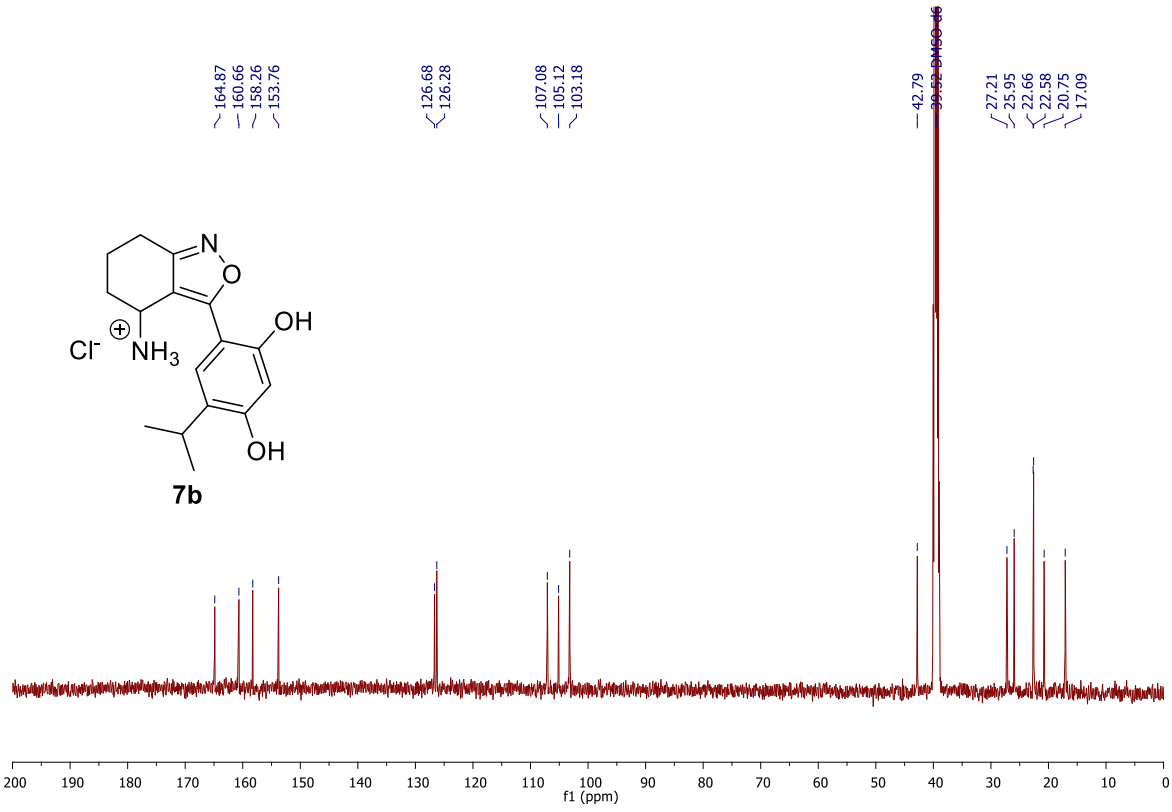

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **7a**



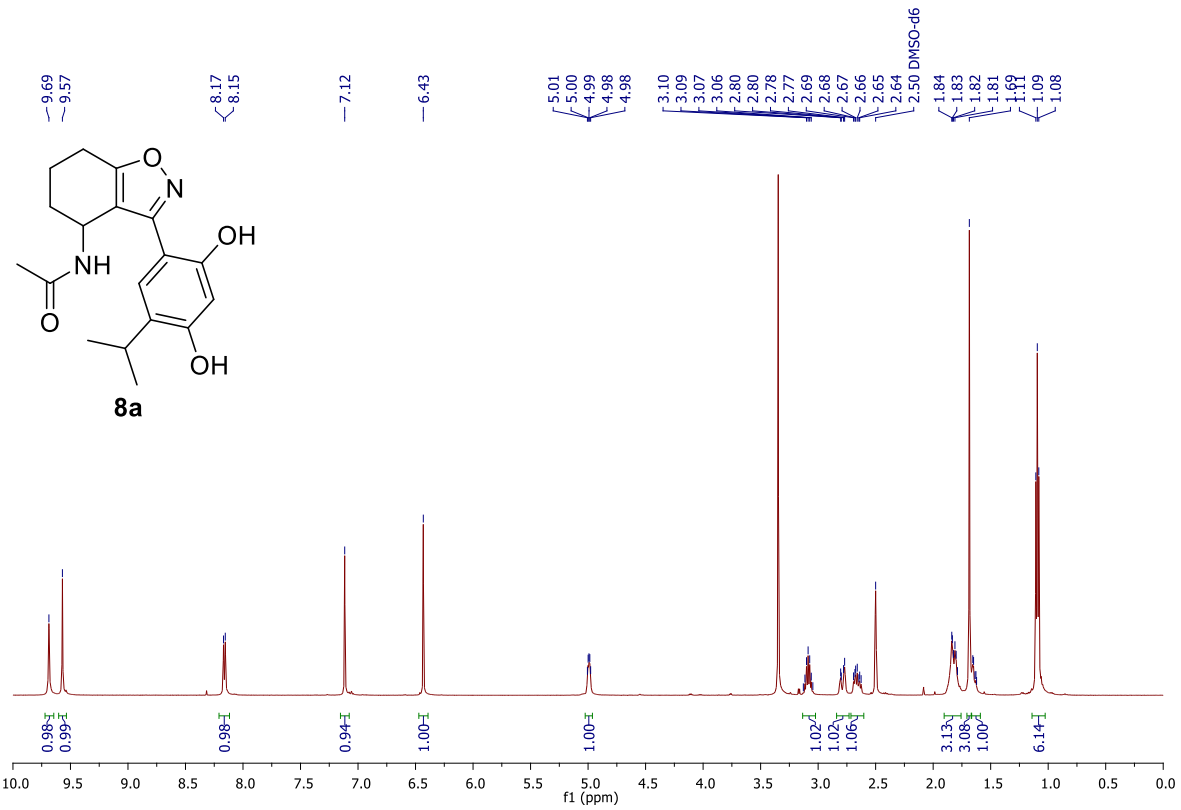

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **7a**



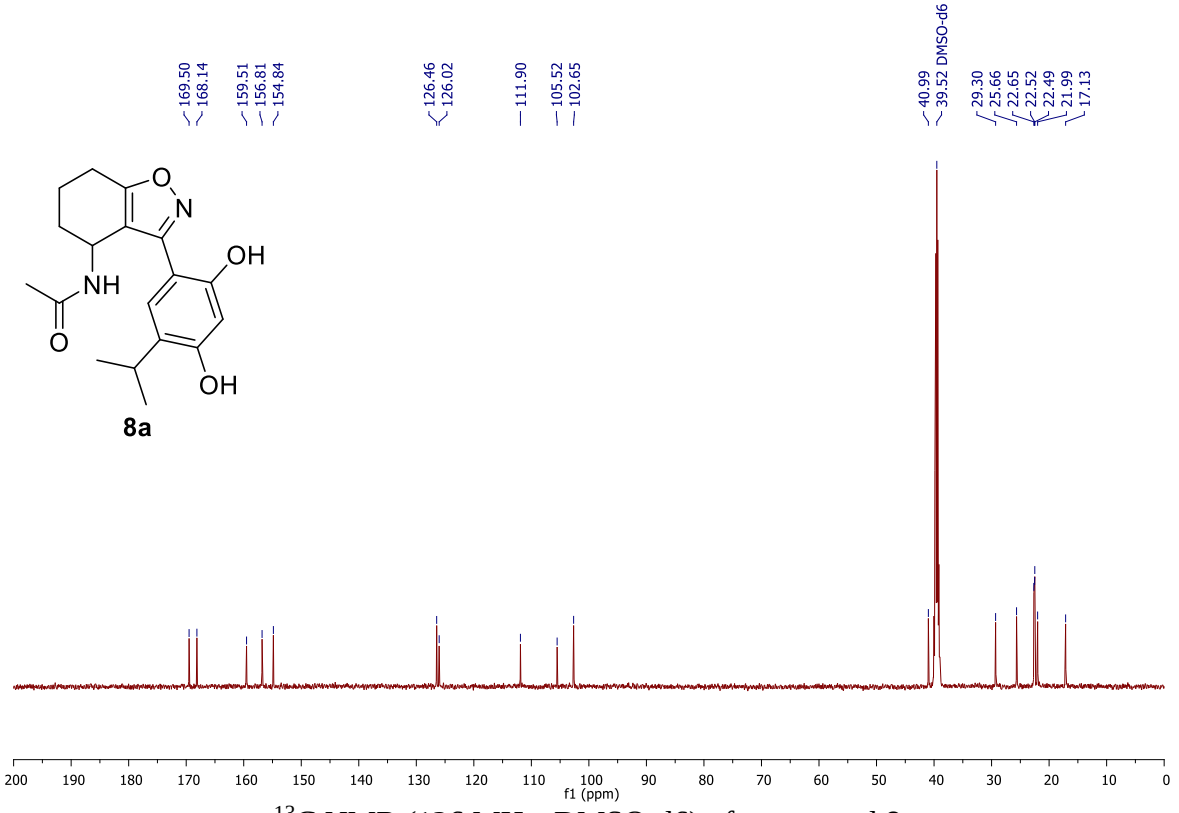

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **7b**



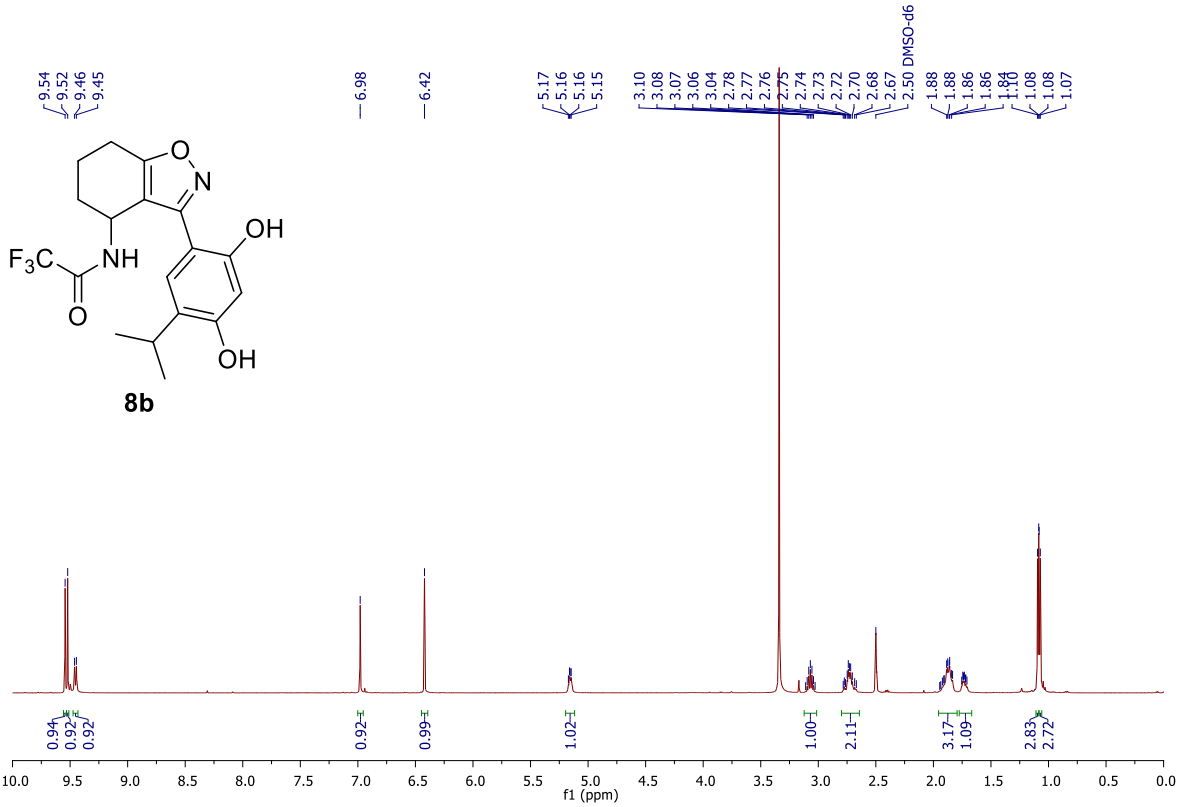

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **7b**



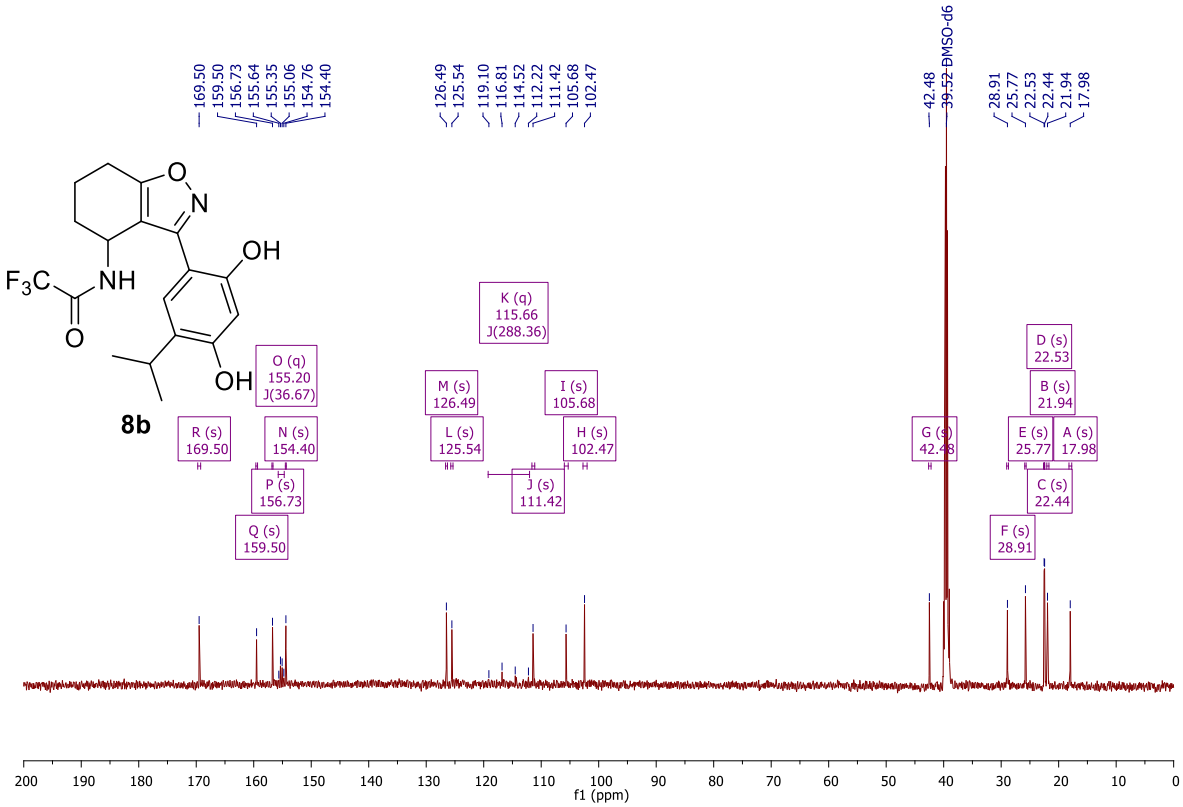

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8a**



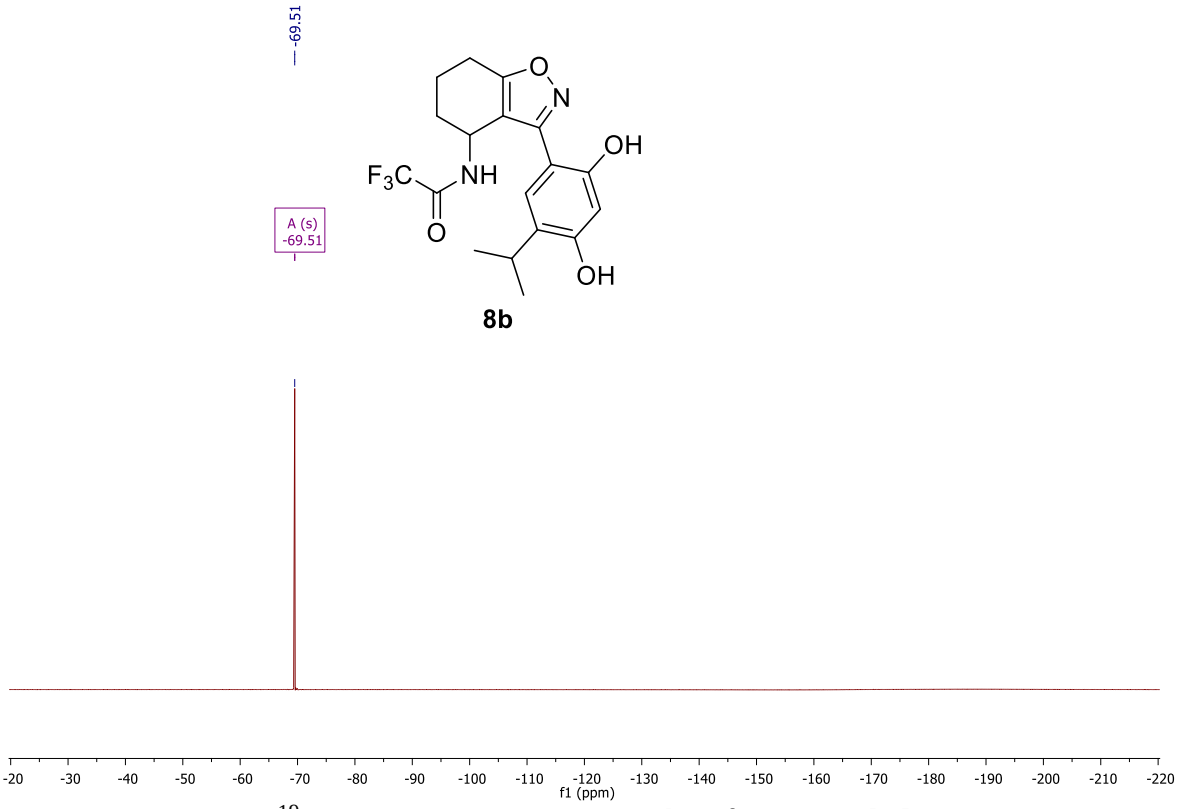

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8a**



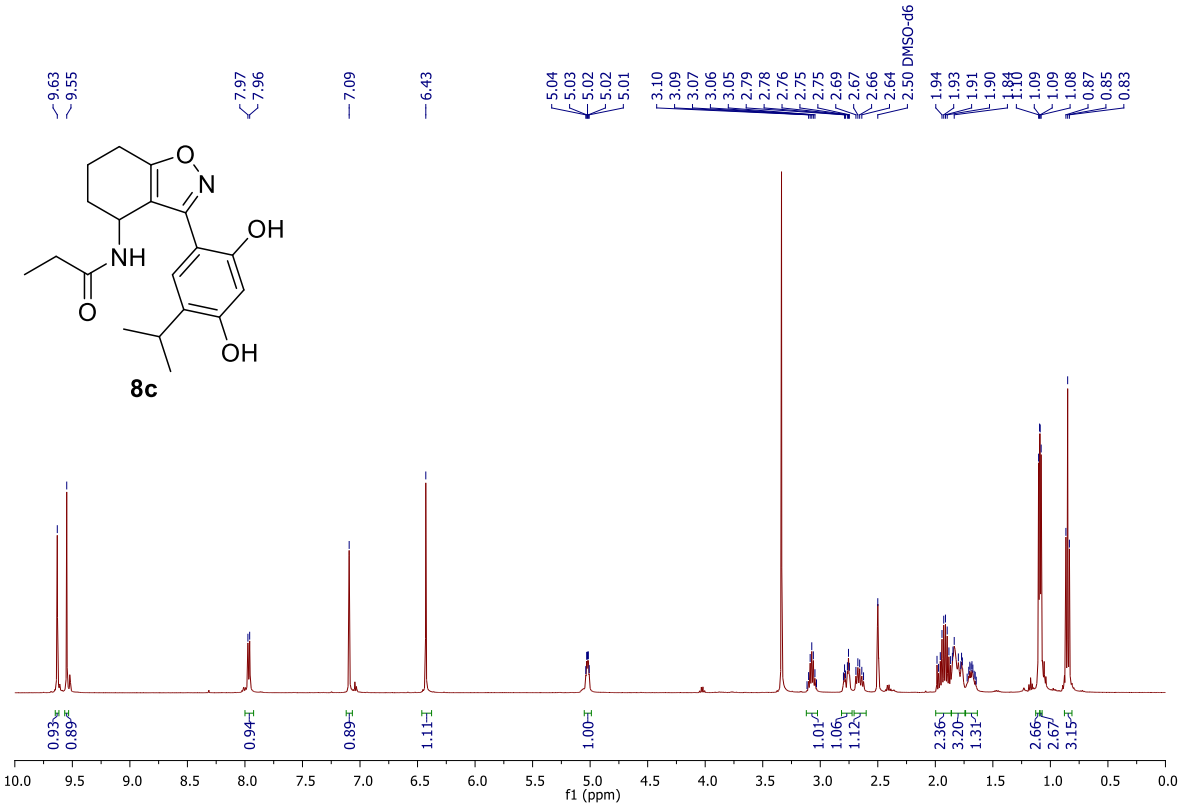

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8b**



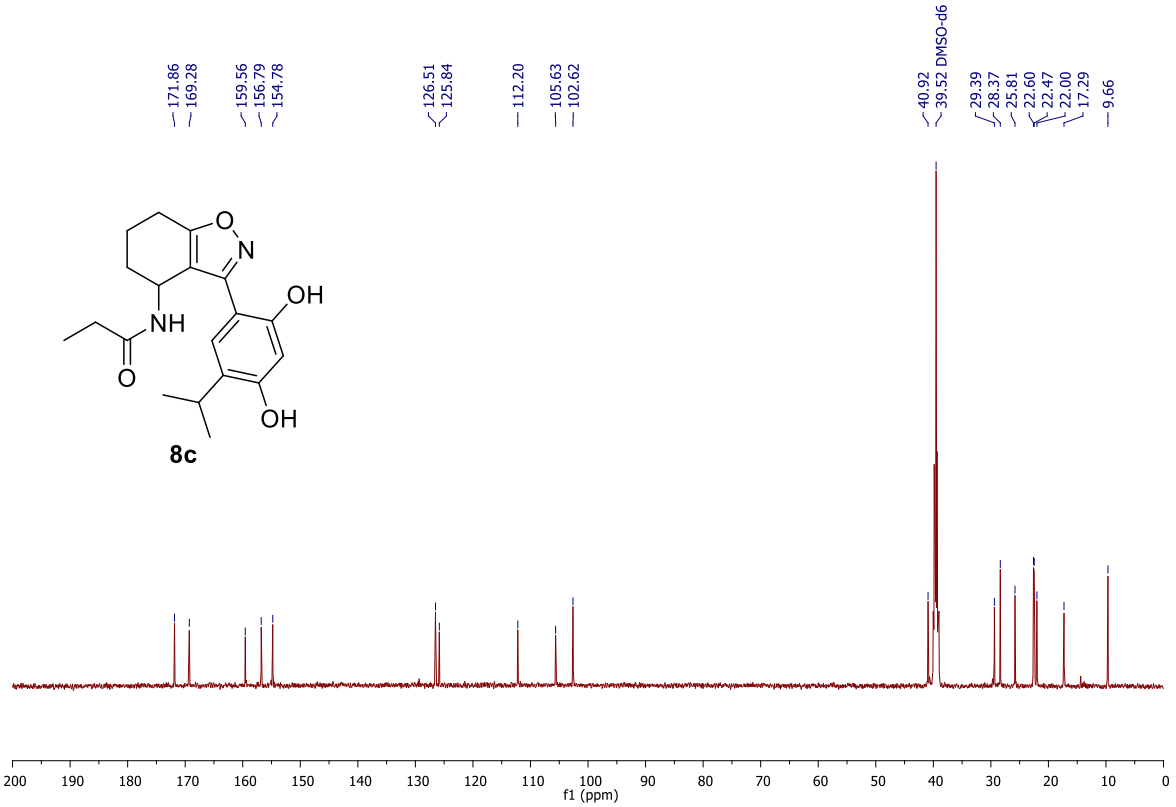

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8b**



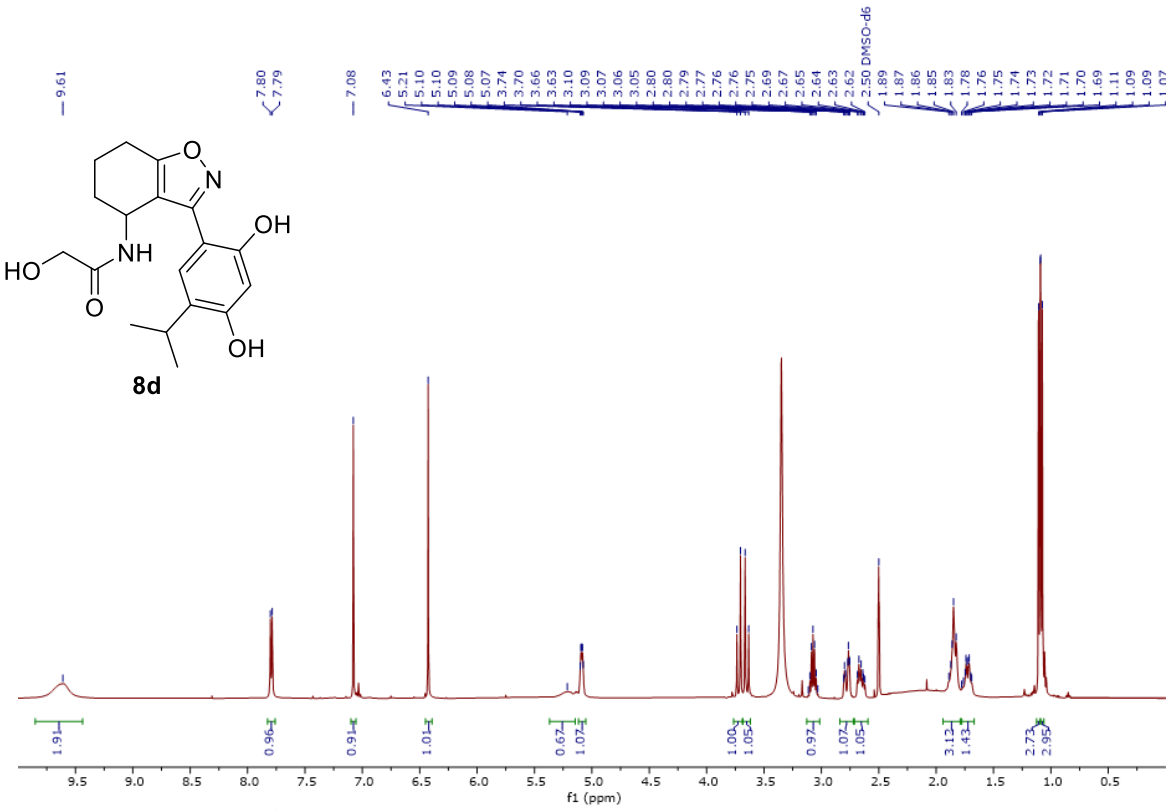

$^{19}$F NMR (470 MHz, DMSO-d6) of compound **8b**



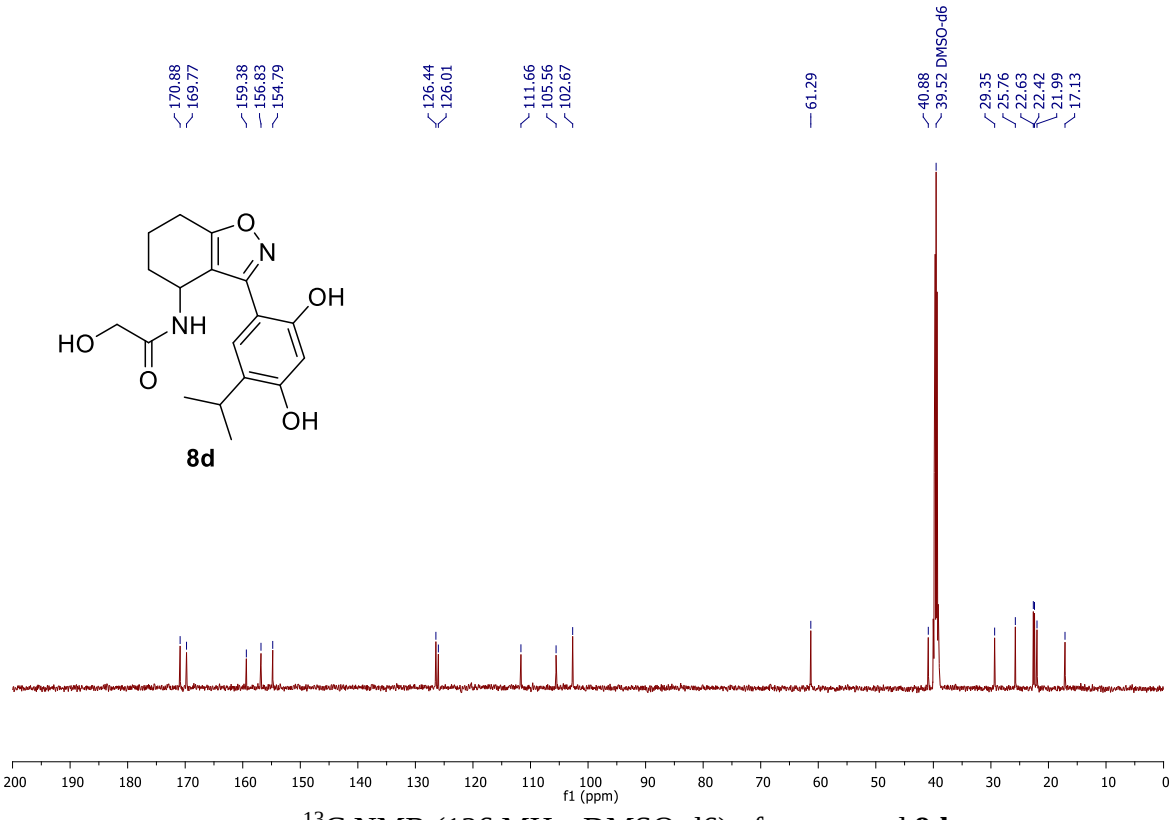

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8c**



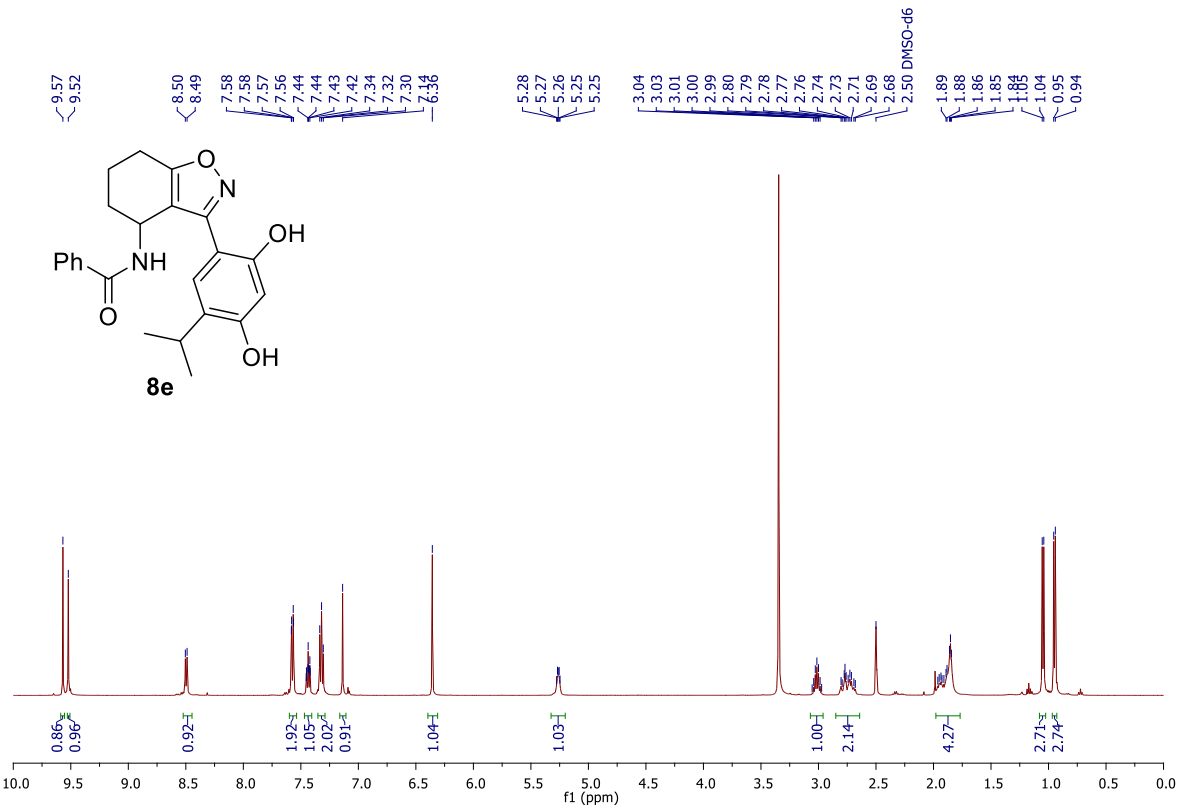

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8c**



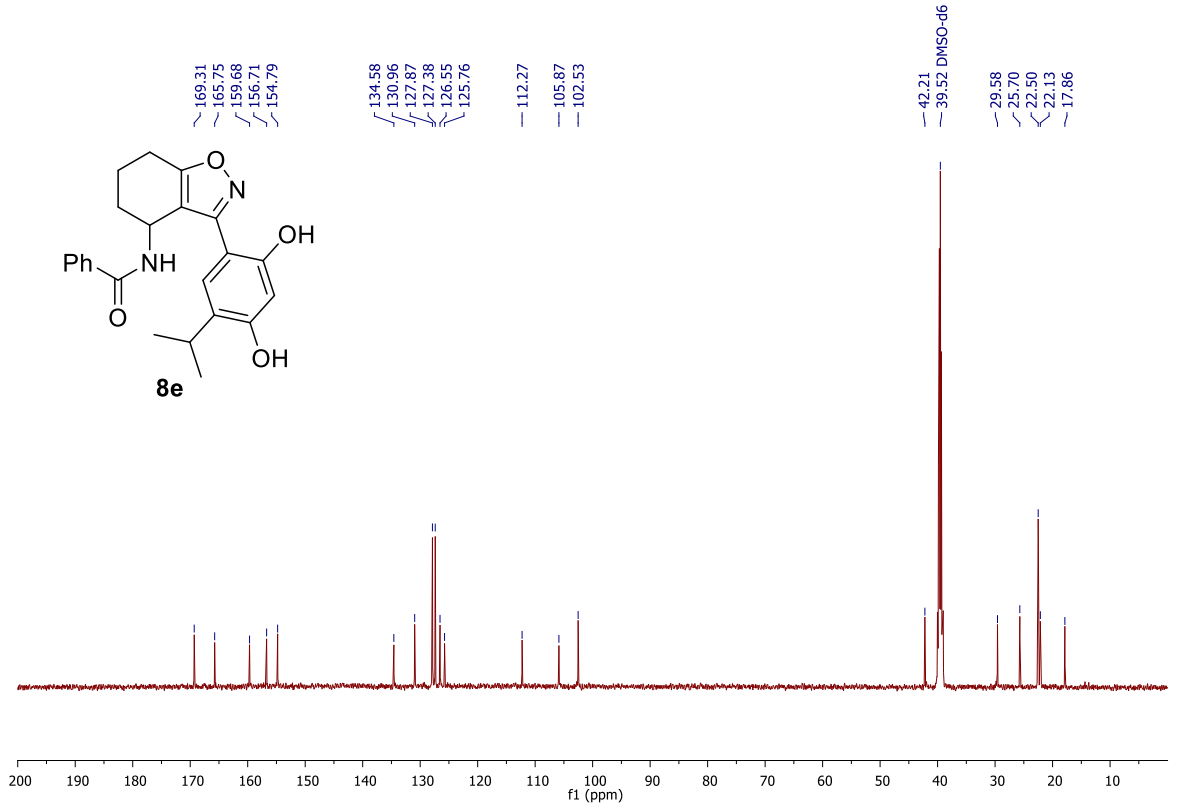

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8d**



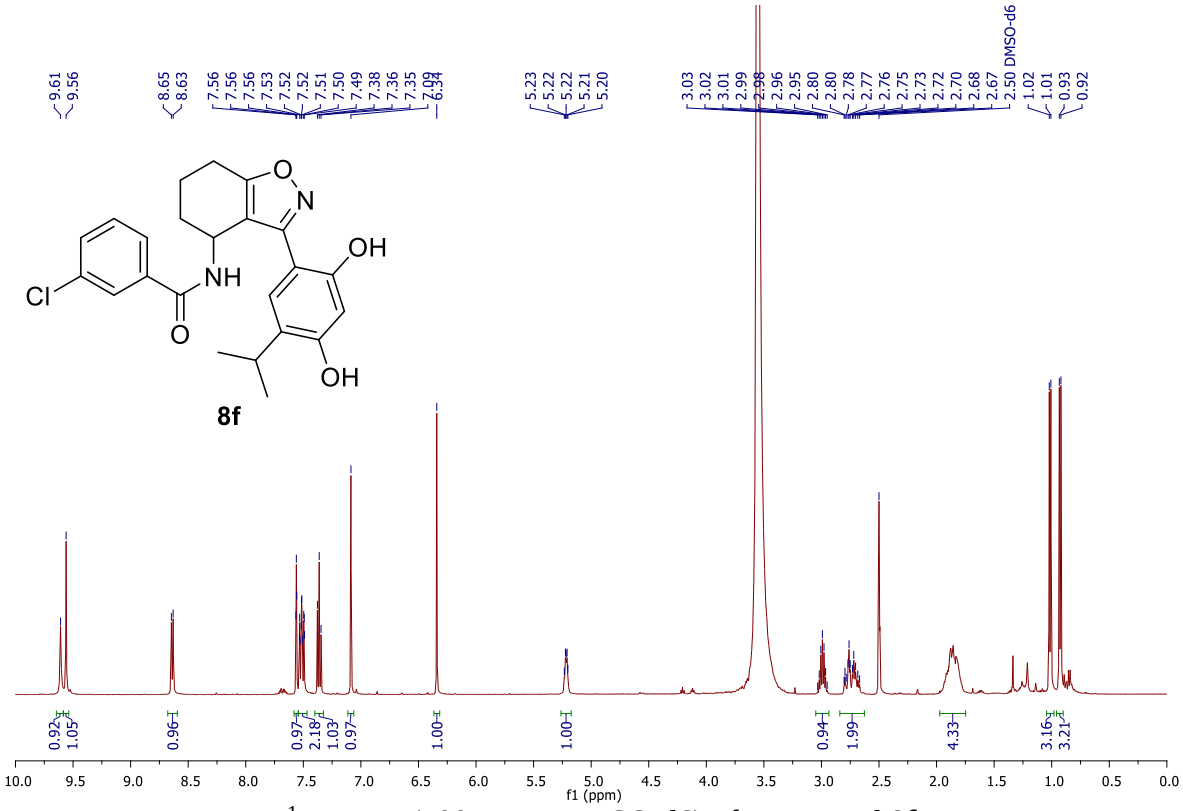

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8d**



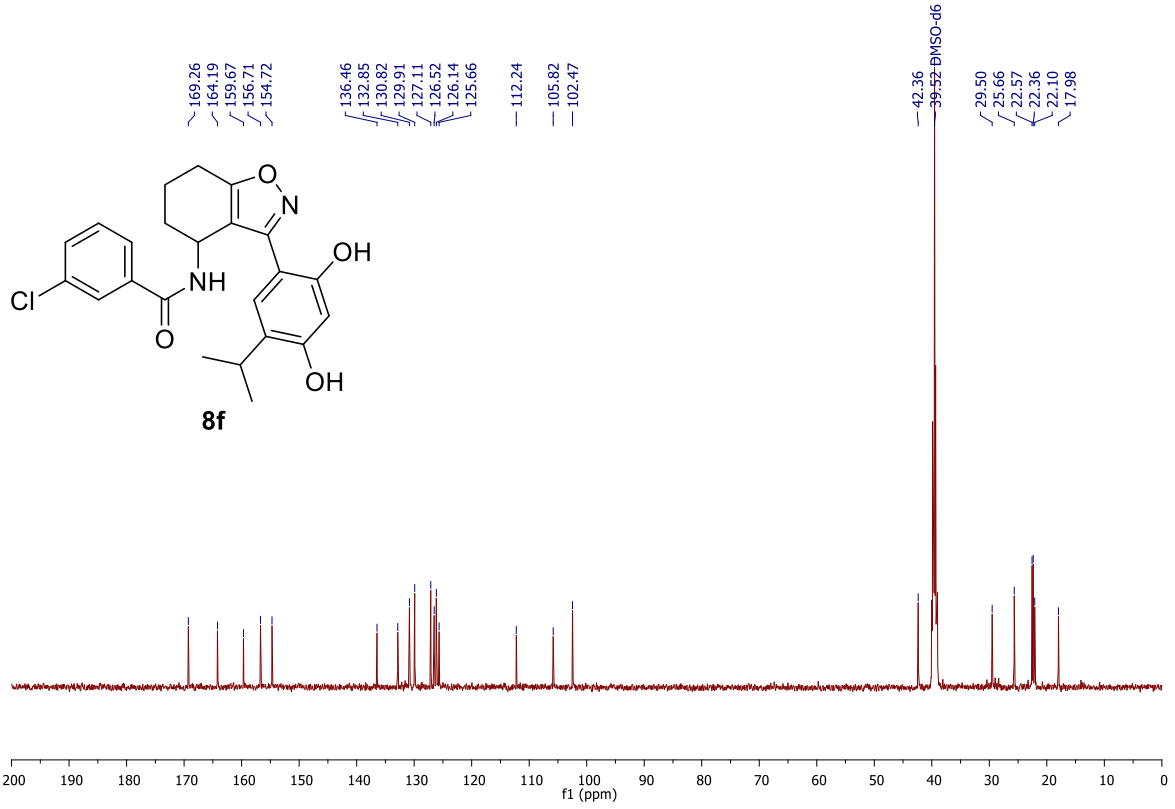

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8e**



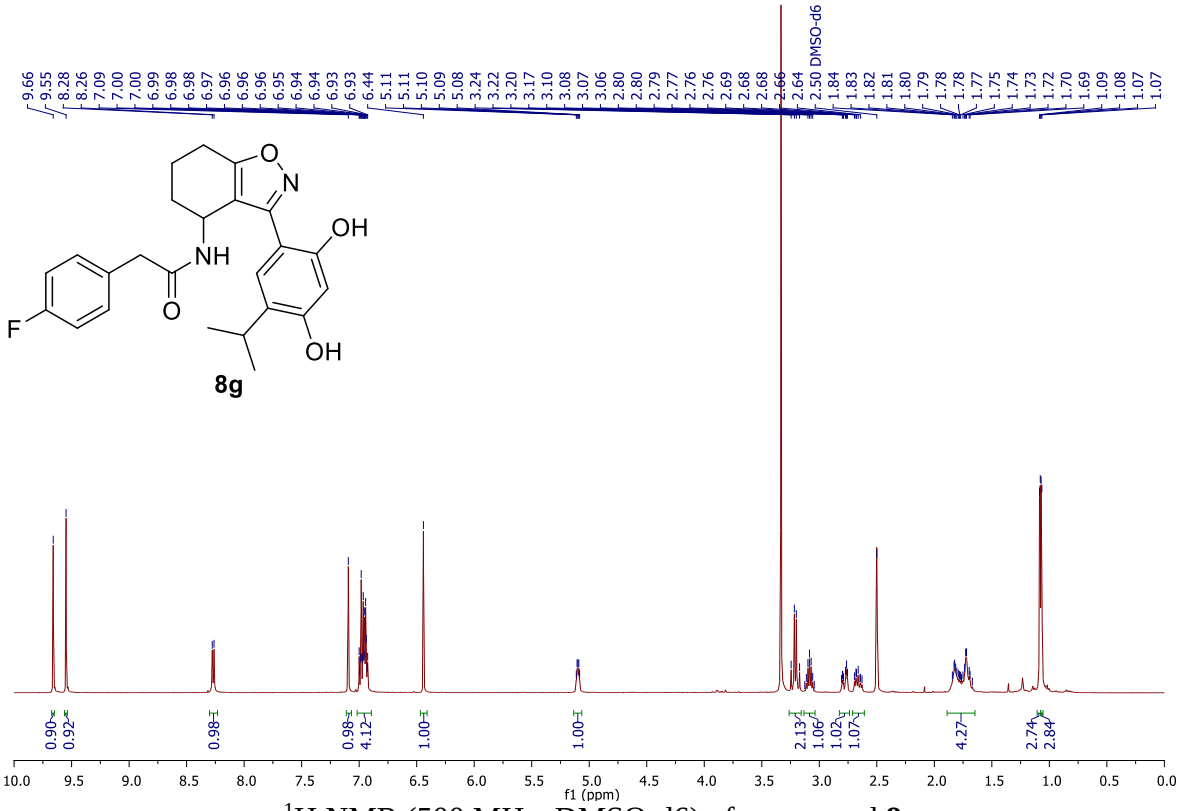

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8e**



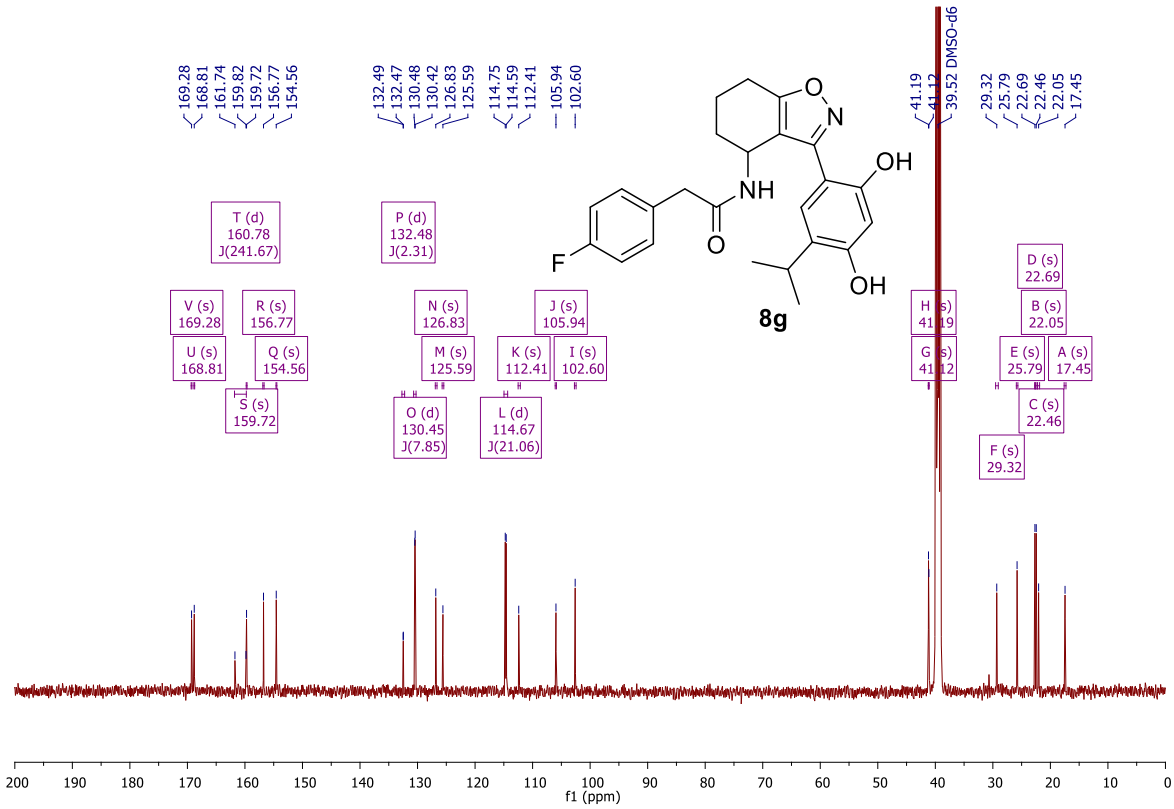

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8f**



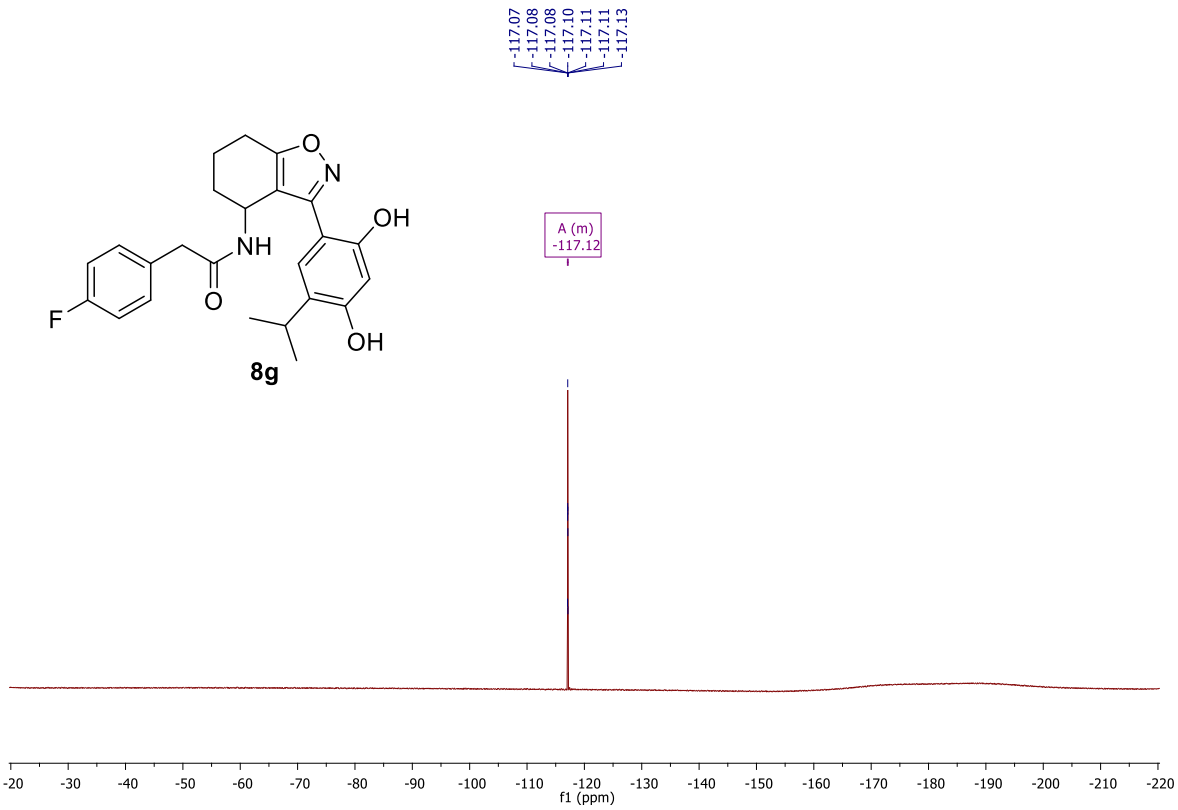

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8f**



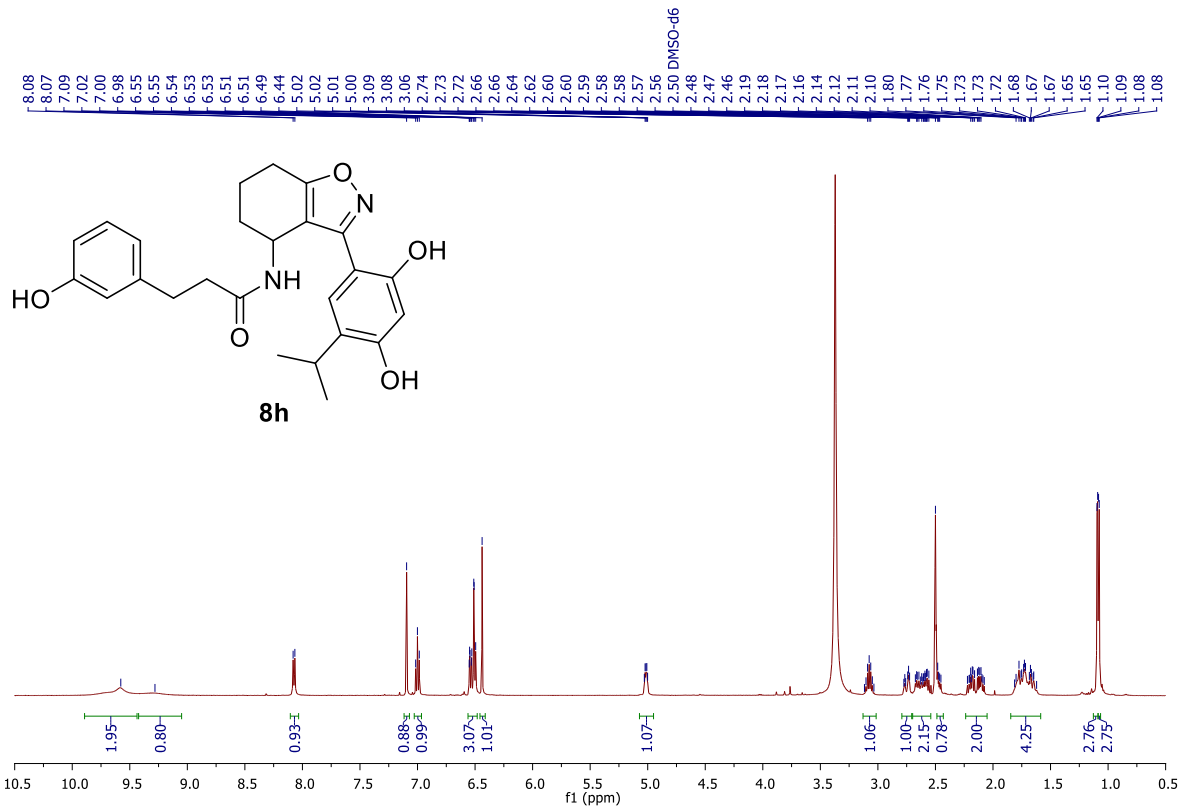

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8g**



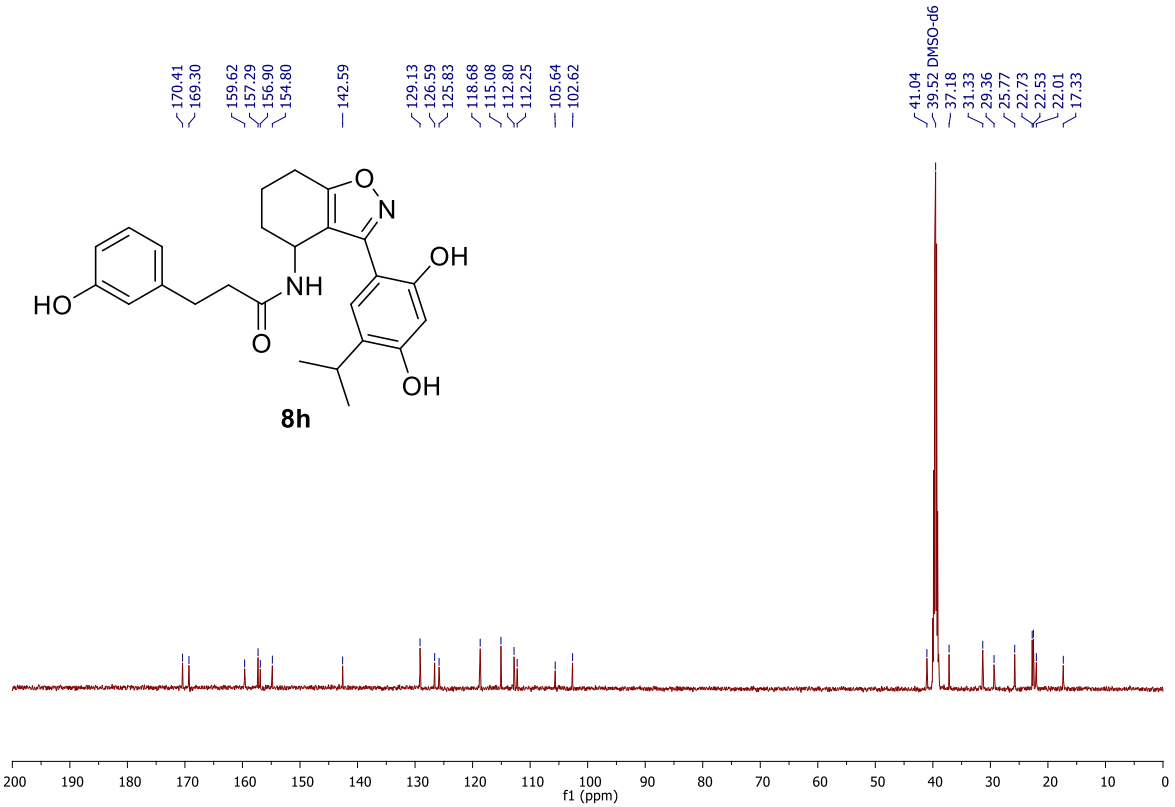

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8g**



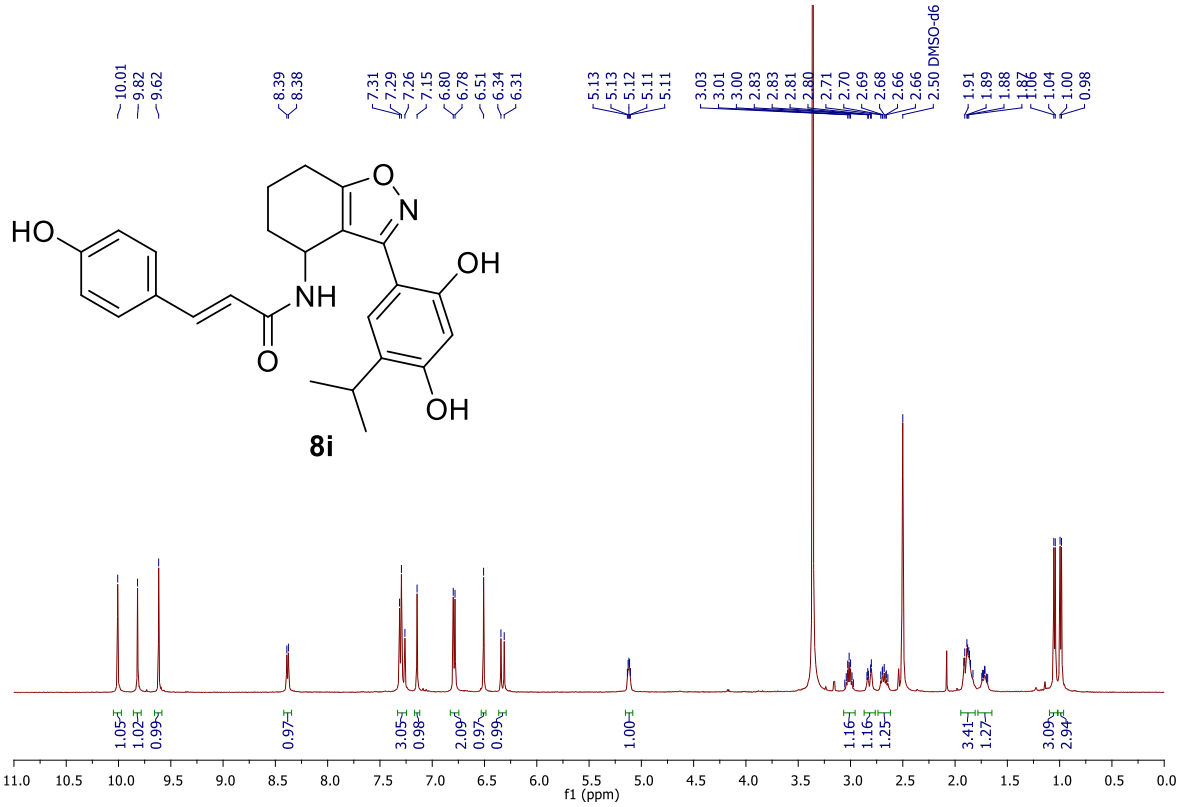

$^{19}$F NMR (470 MHz, $CDCl_3$) of compound **8g**



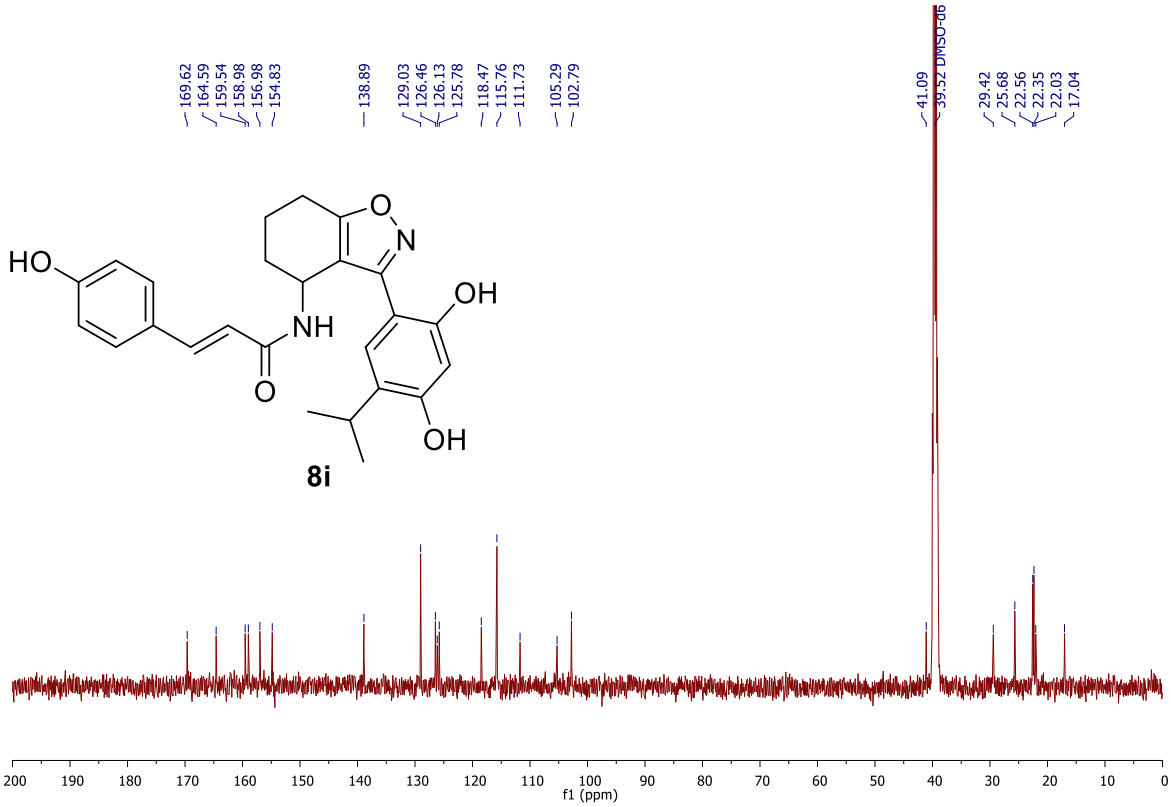

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8h**



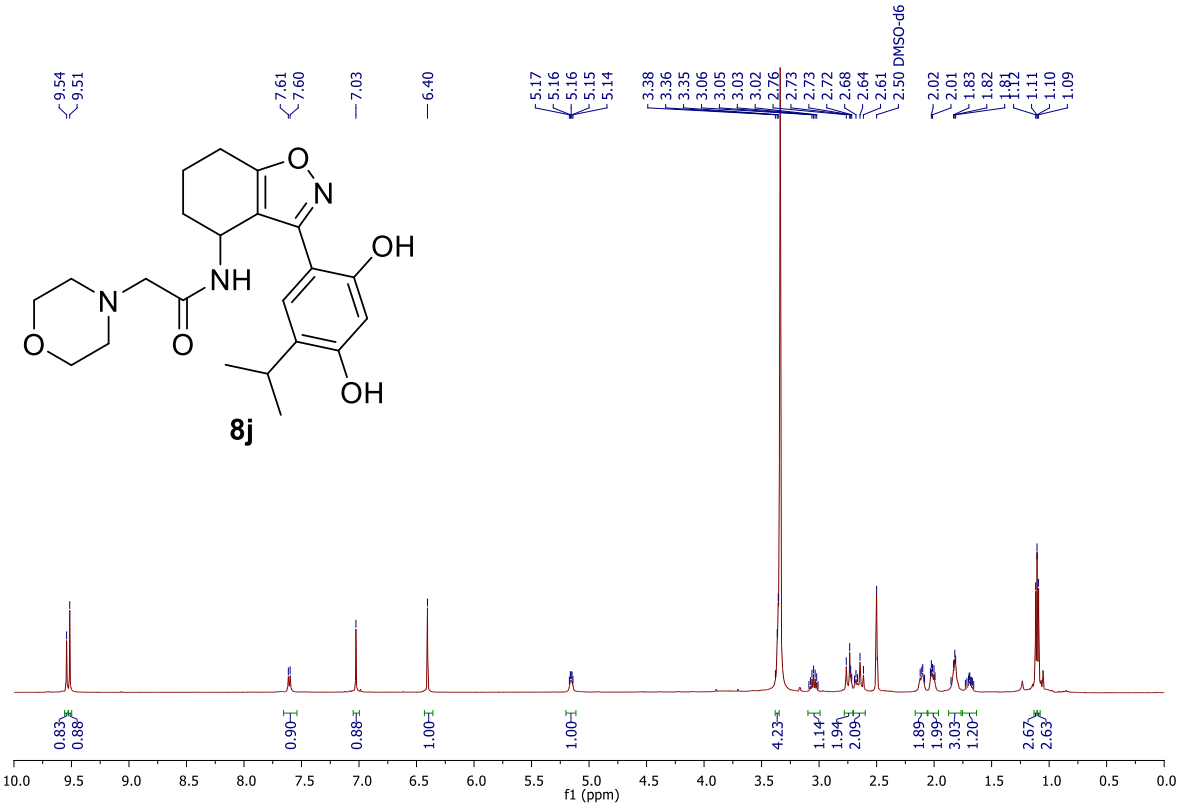

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8h**




$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8i**




$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8i**

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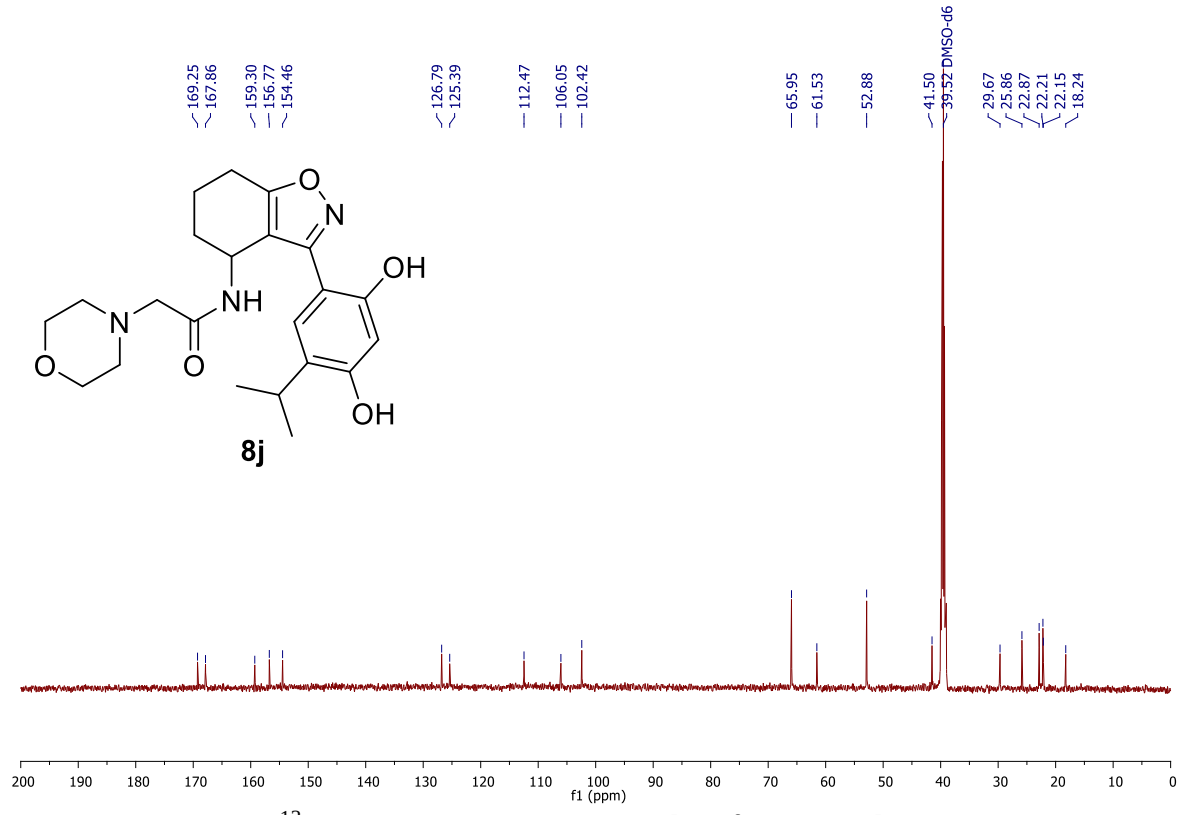


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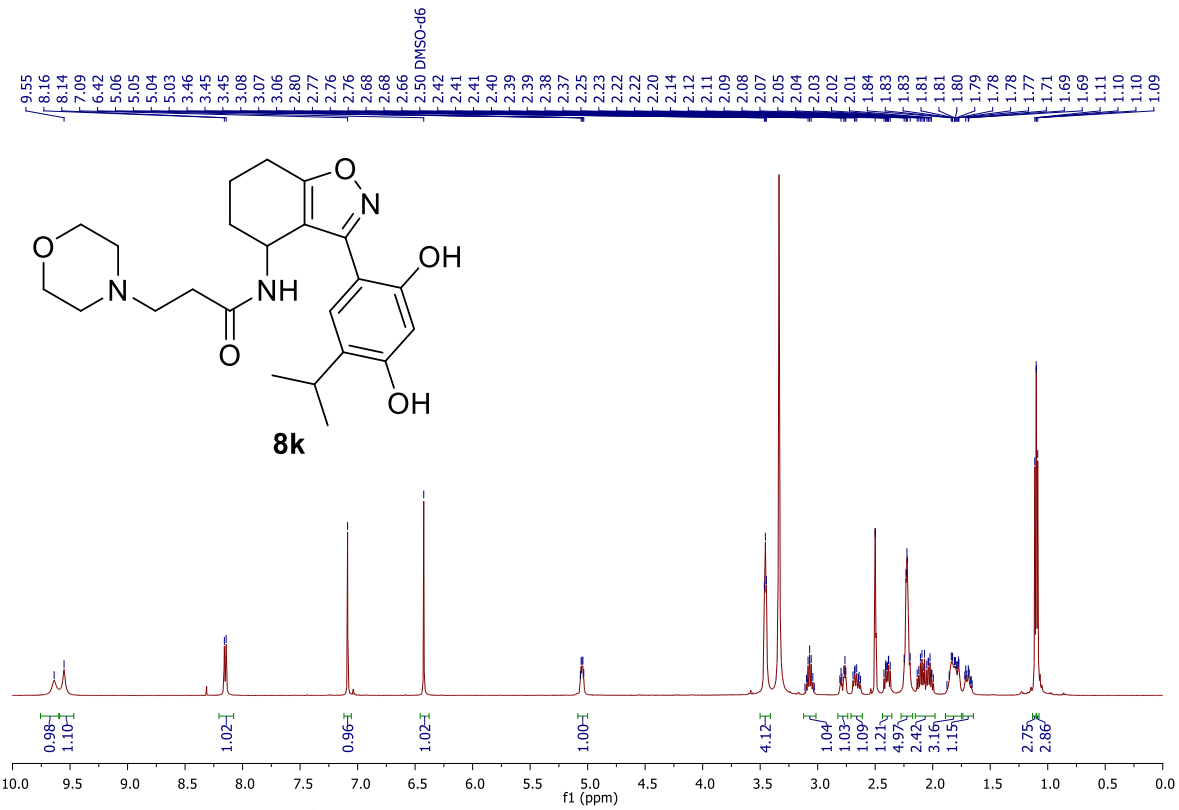
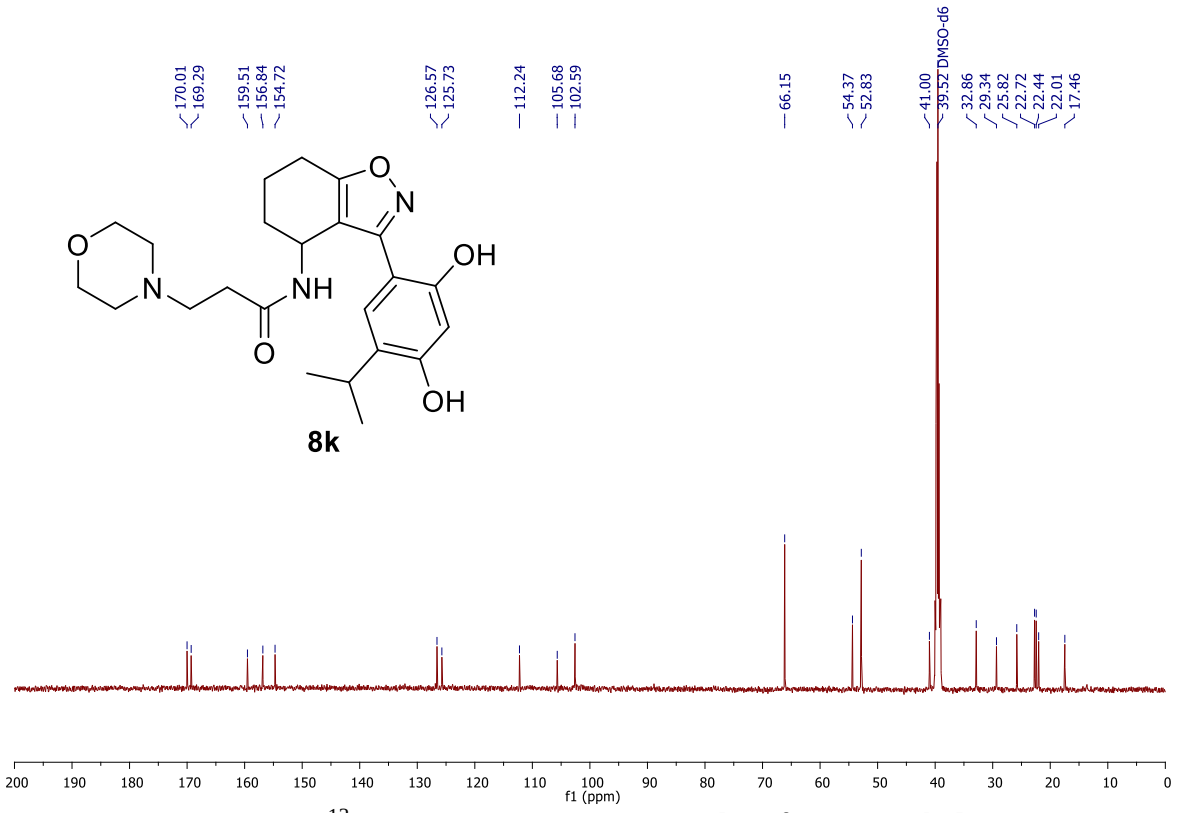



$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8k**

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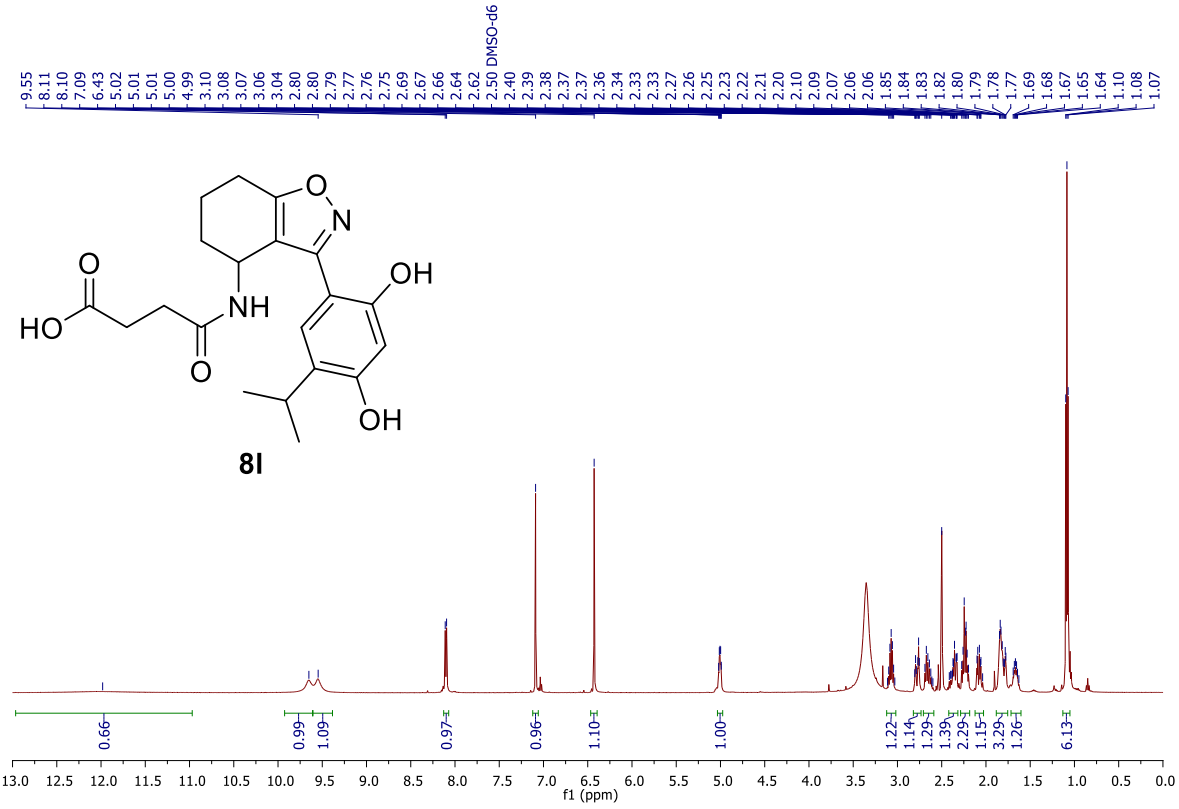
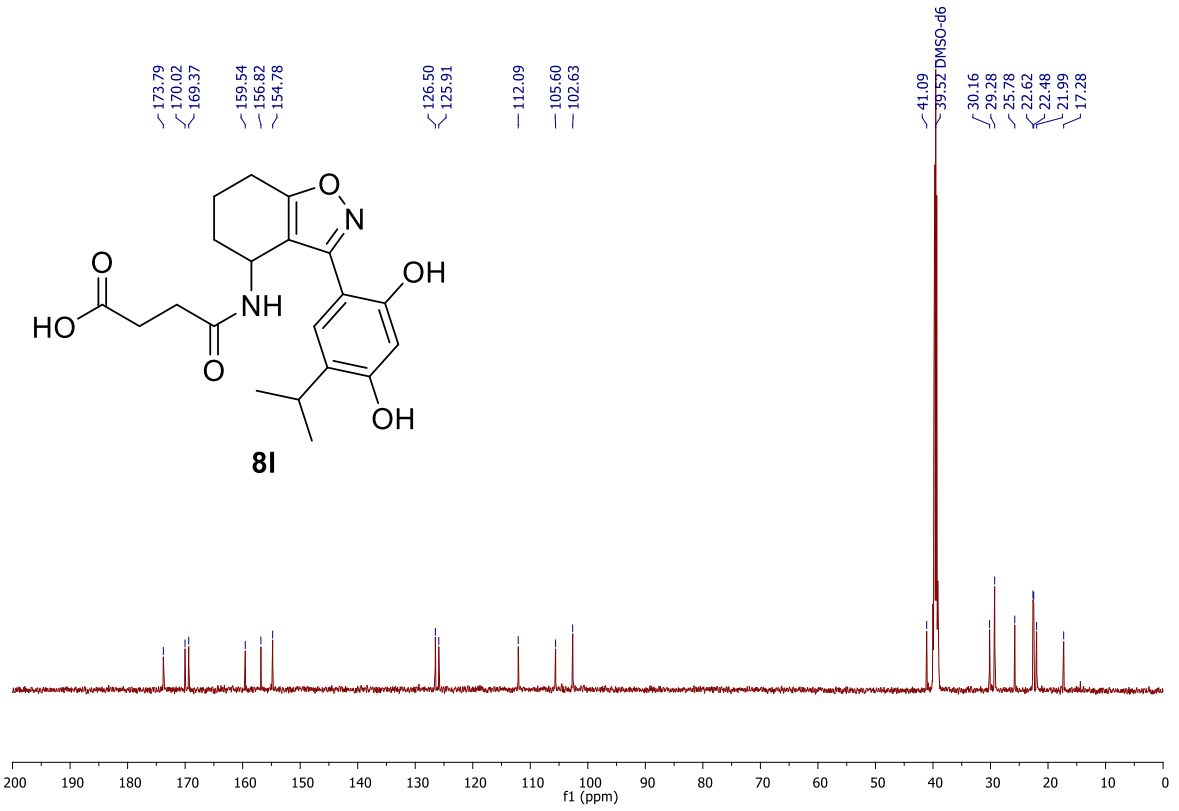
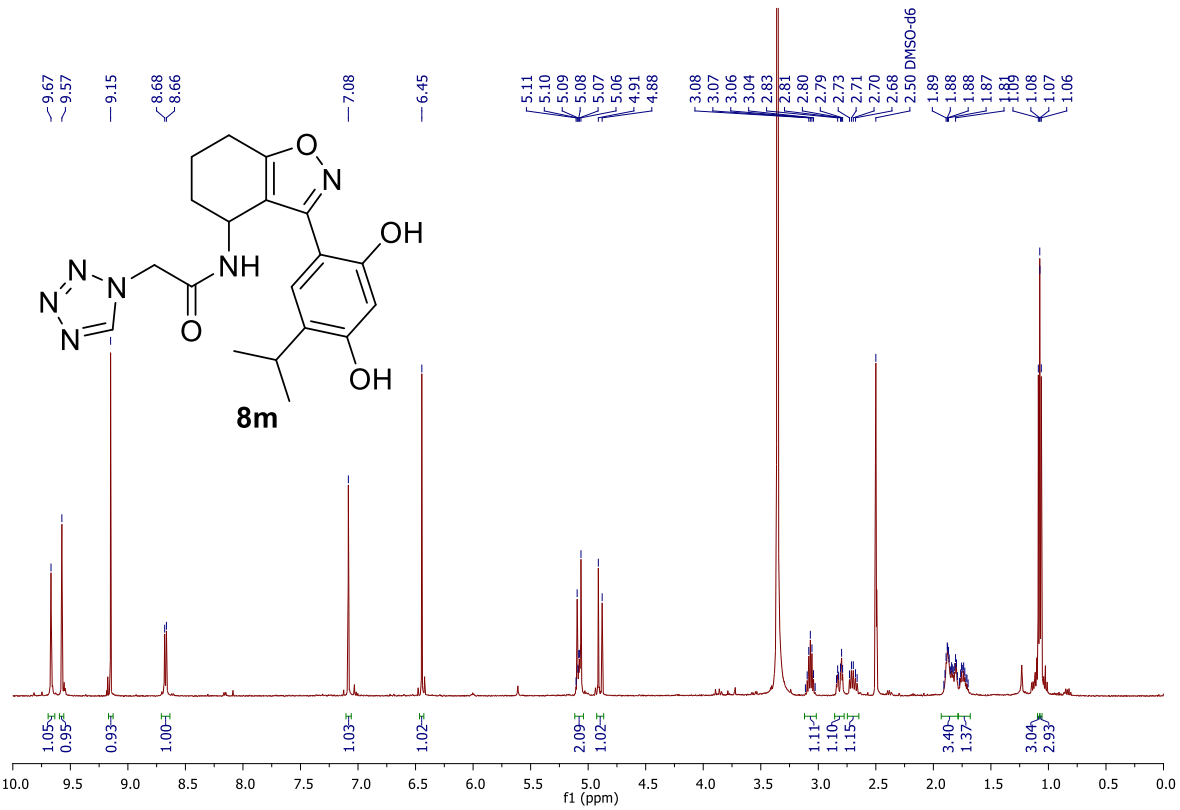


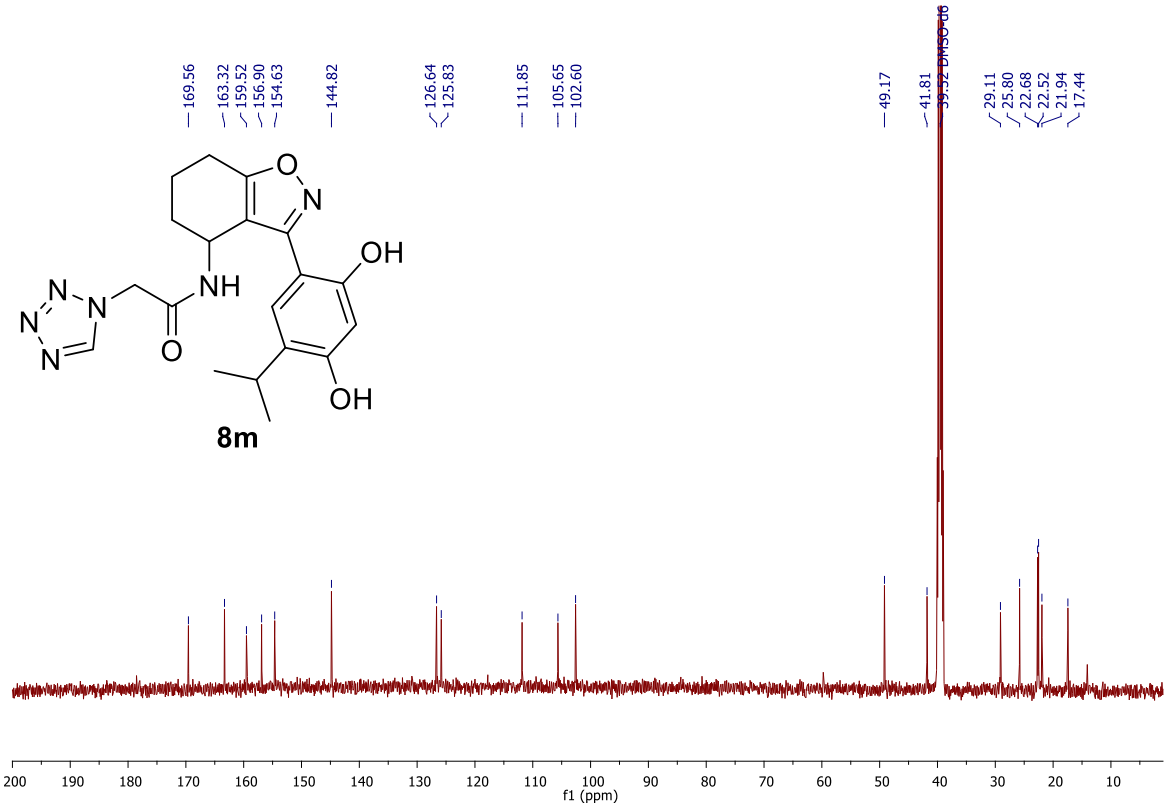

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8l**



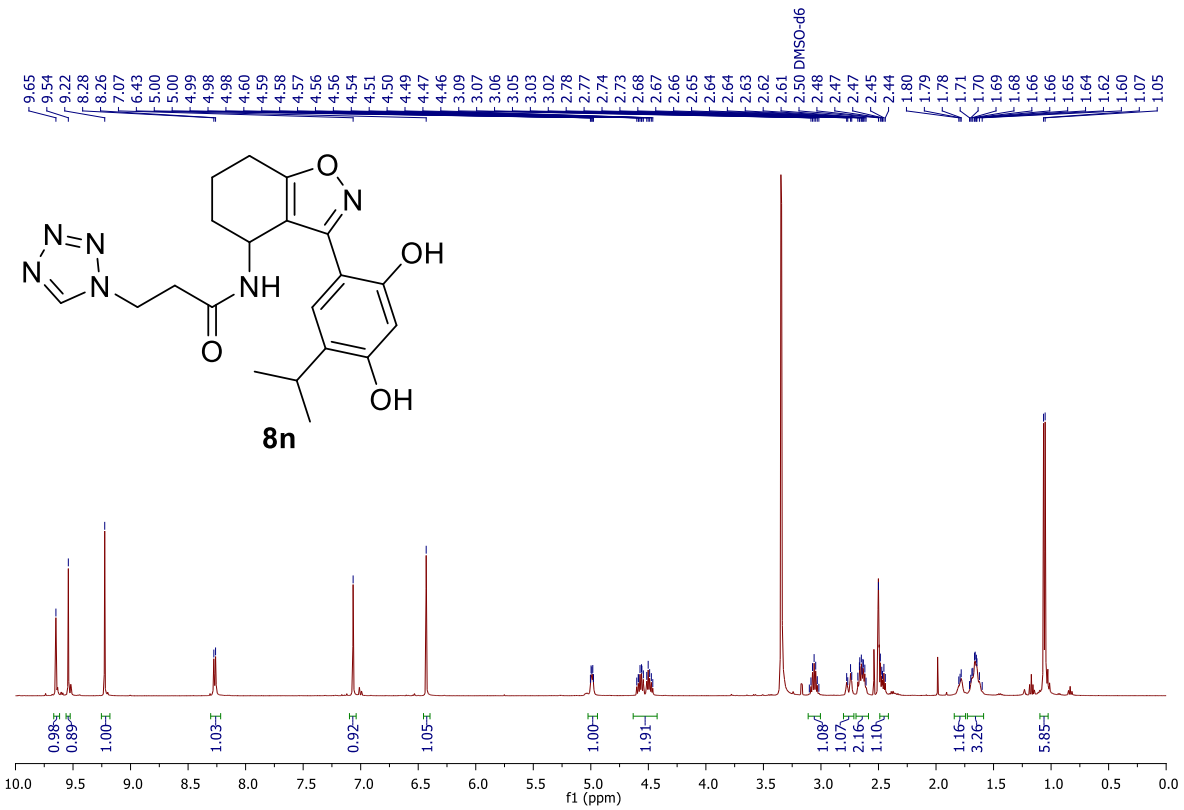

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8l**



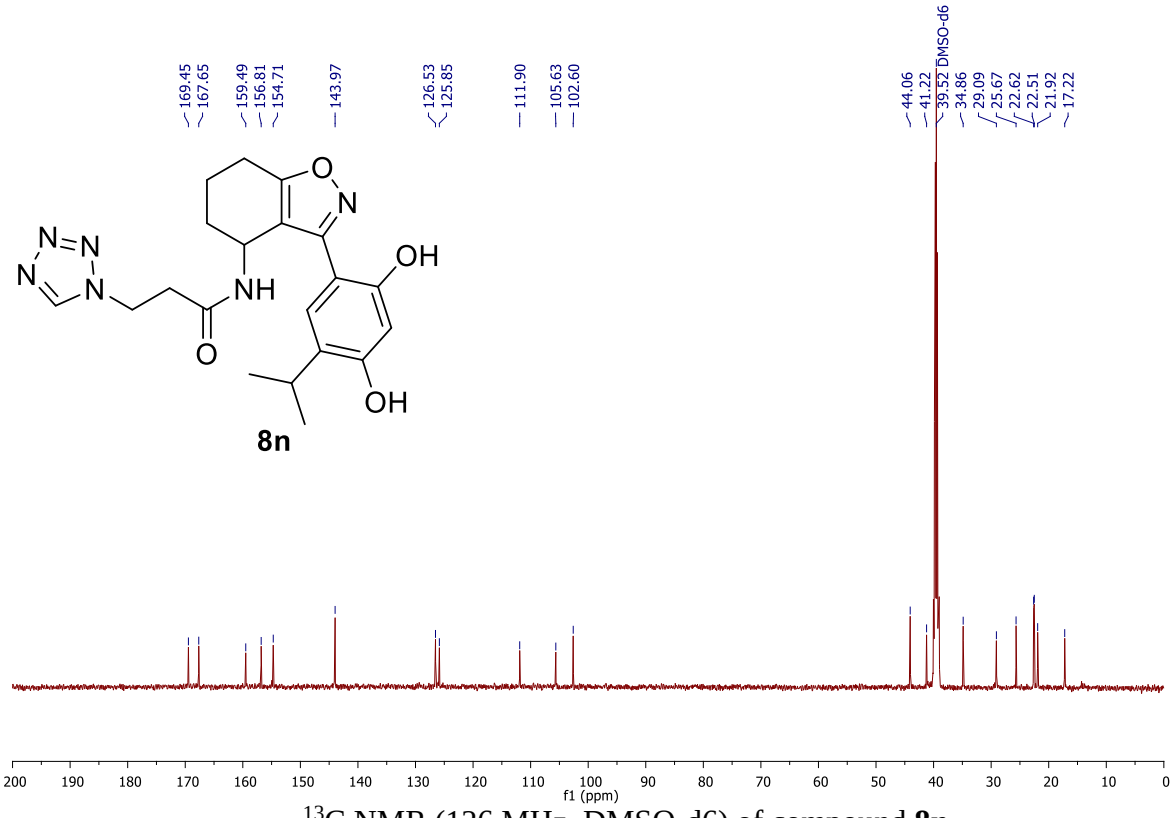

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8m**



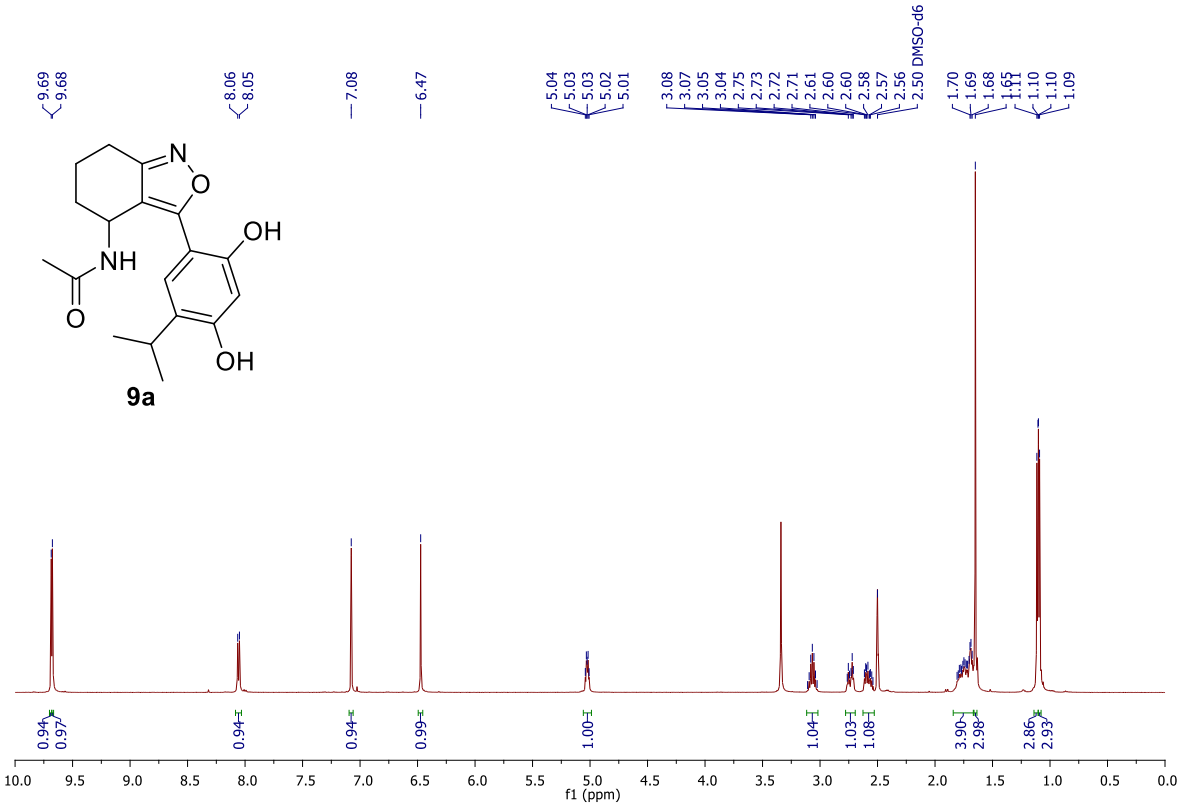

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8m**



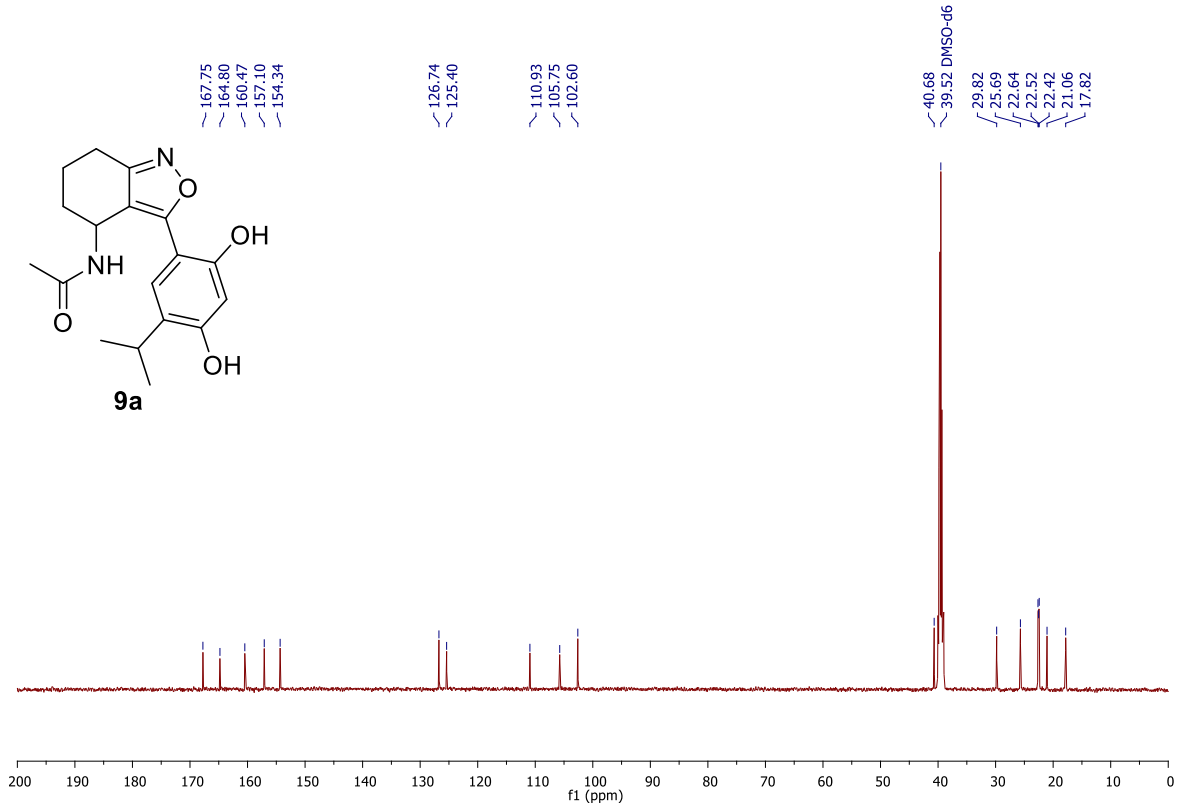

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **8n**



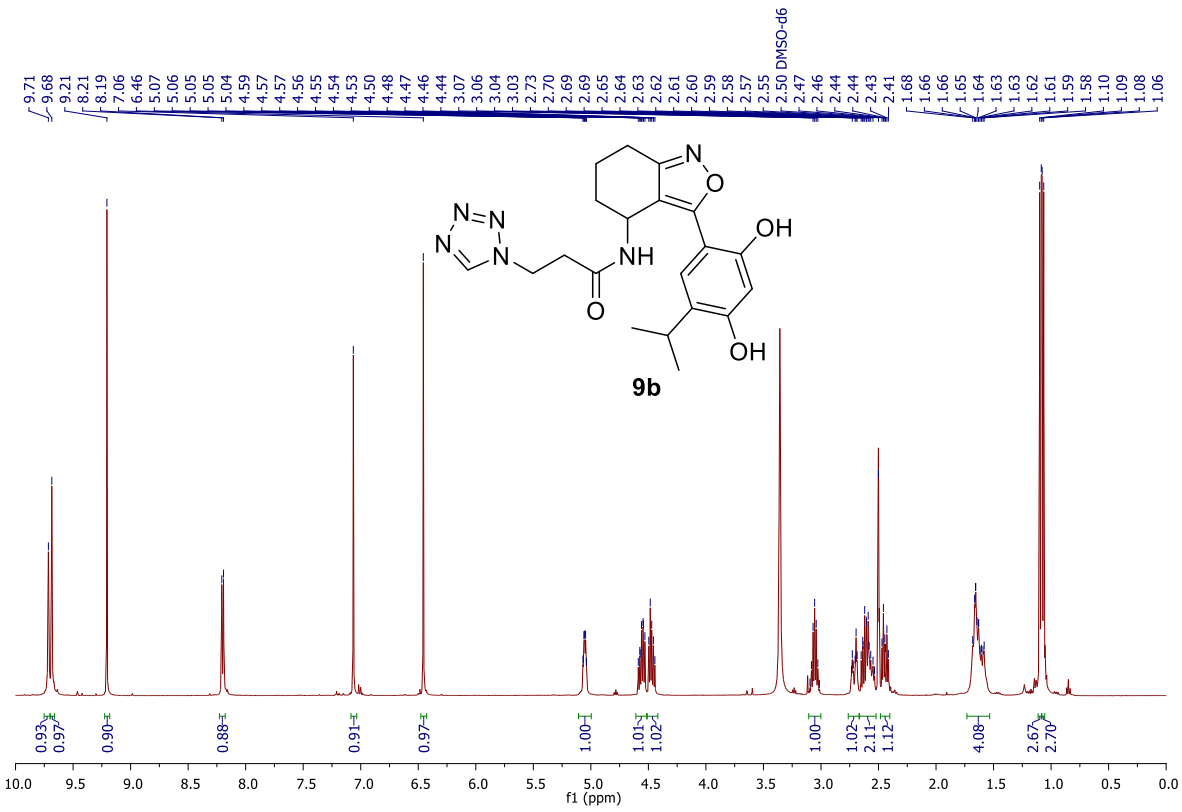

$^{13}$C NMR (126 MHz, DMSO-d6) of compound **8n**



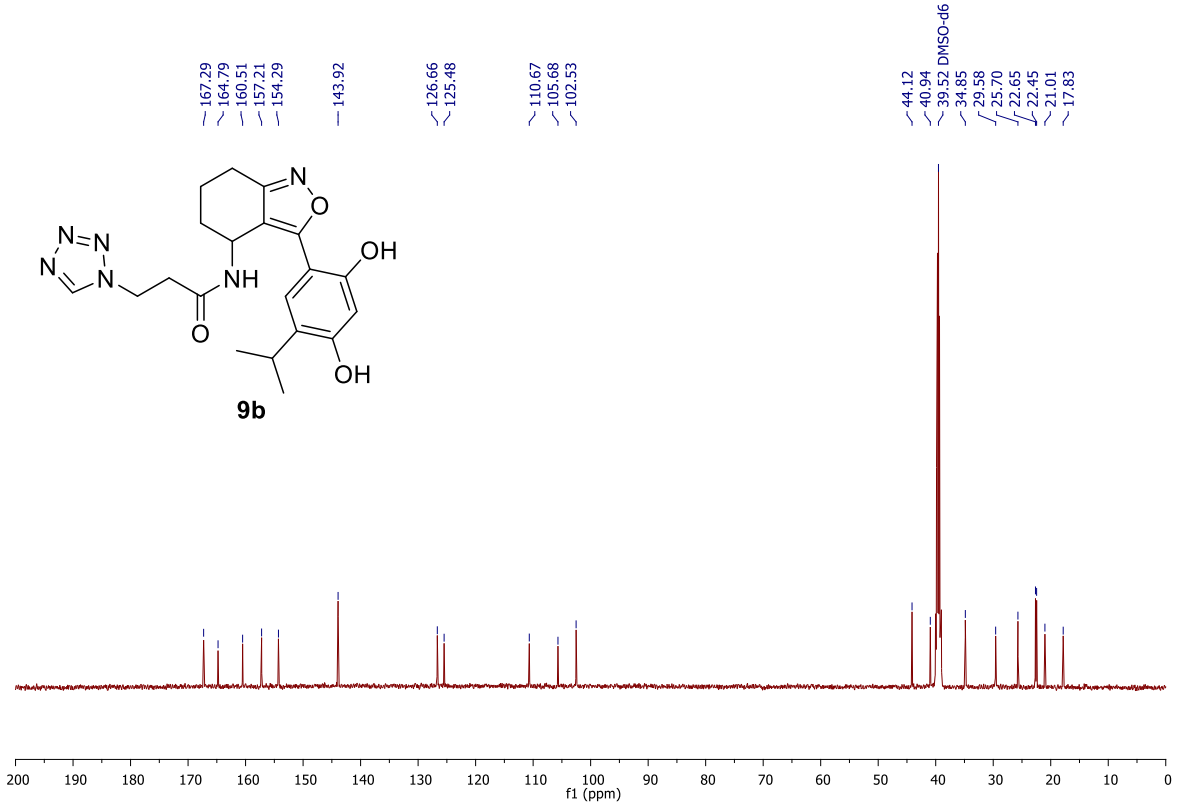

$^{1}$H NMR (500 MHz, DMSO-d6) of compound **9a**




$^{13}$C NMR (126 MHz, DMSO-d6) of compound **9a**

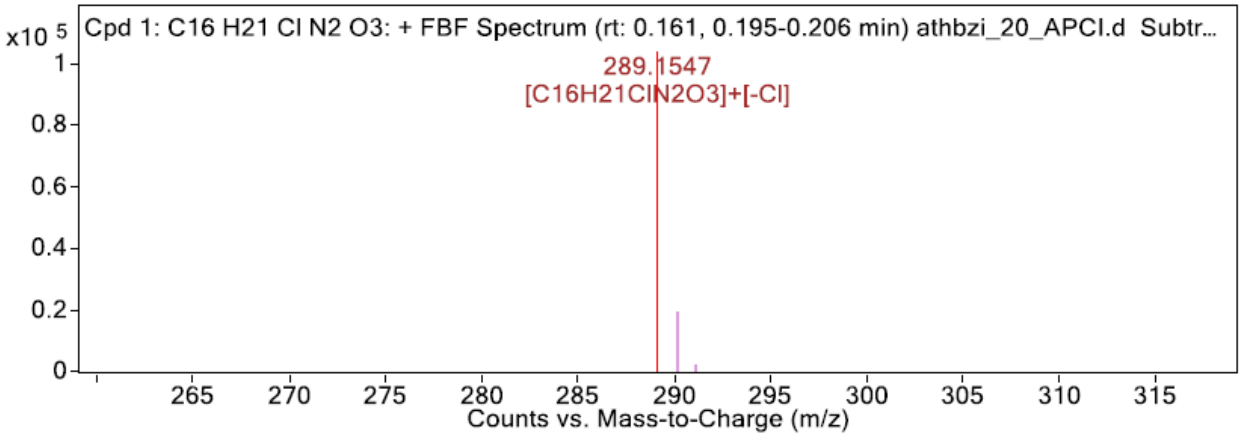



$^{1}$H NMR (500 MHz, DMSO-d6) of compound **9b**

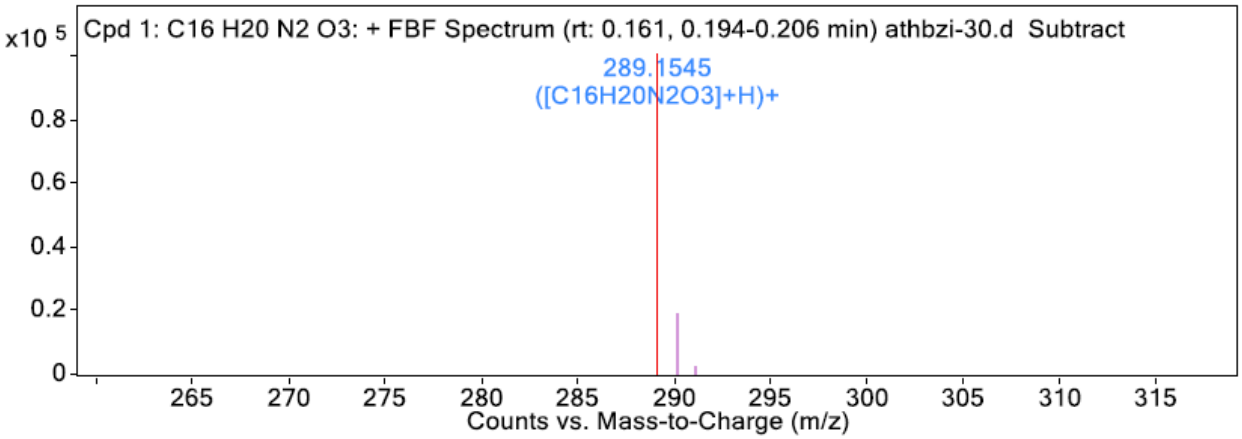



$^{13}$C NMR (126 MHz, DMSO-d6) of compound **9b**

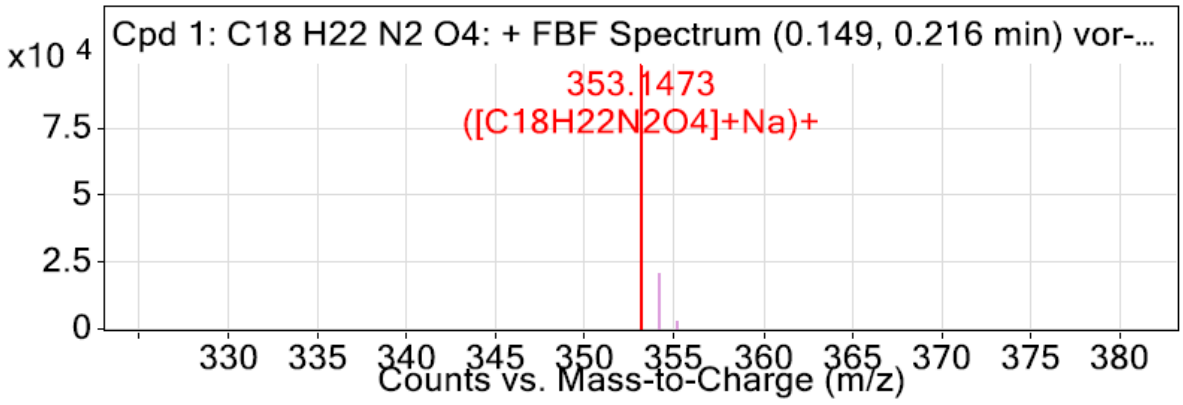
# HRMS of compounds 7-9



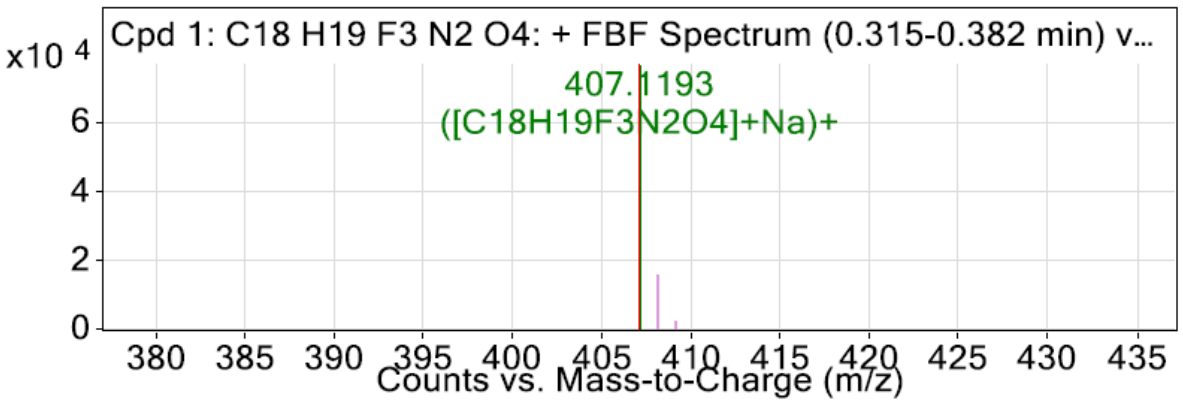

HRMS of **7a**




HRMS of **7b**




HRMS of **8a**

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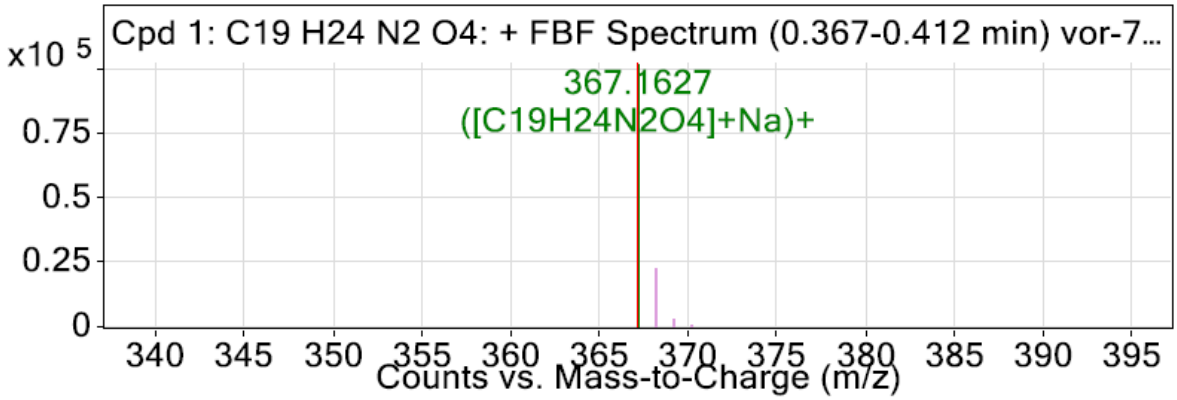


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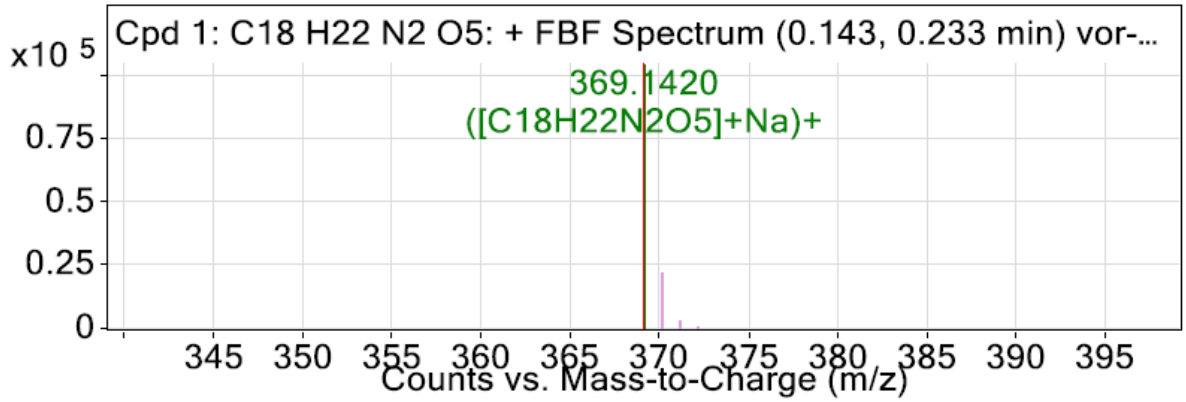
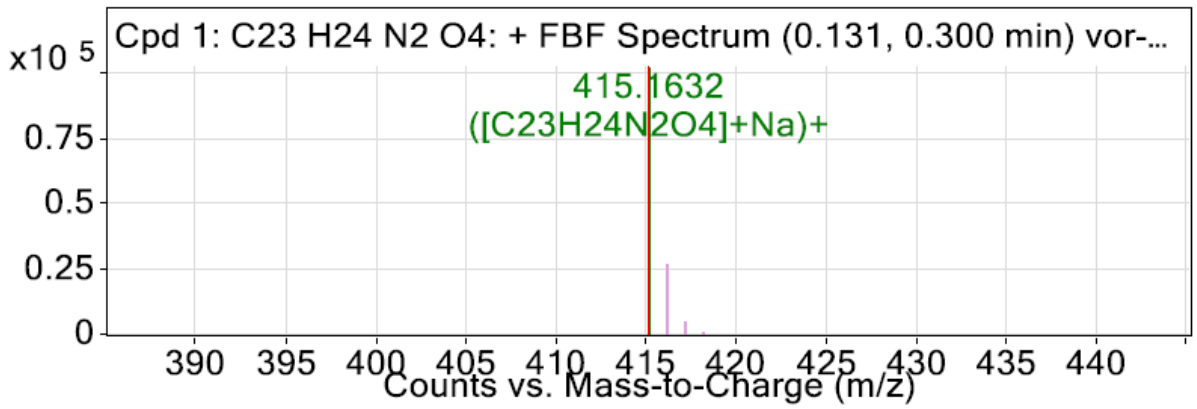



HRMS of **8d**

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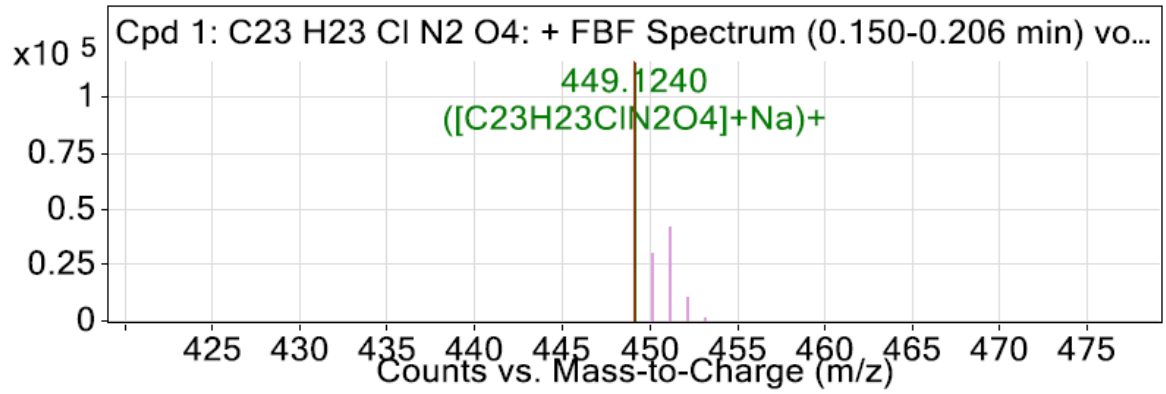


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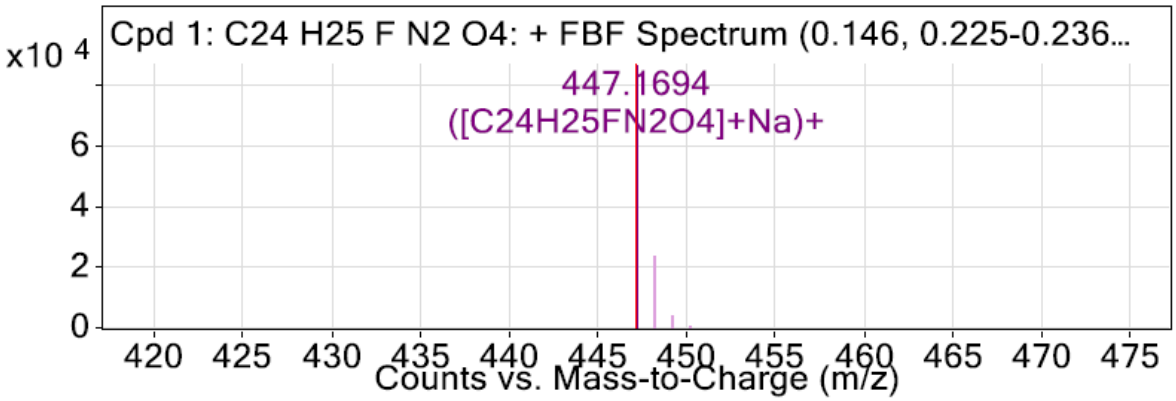


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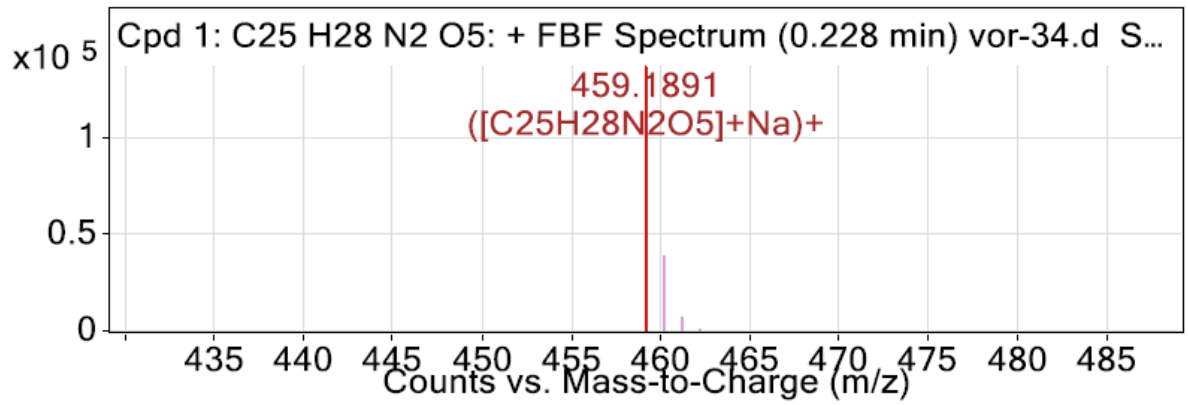


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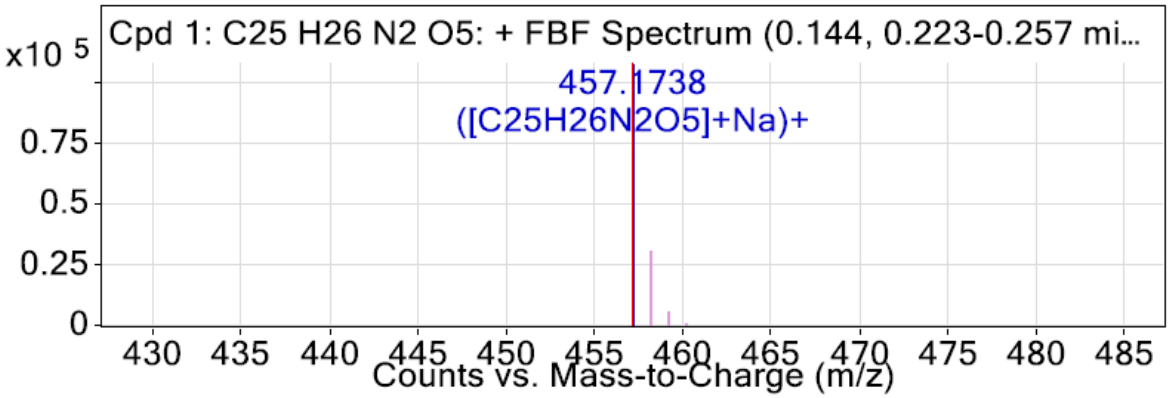


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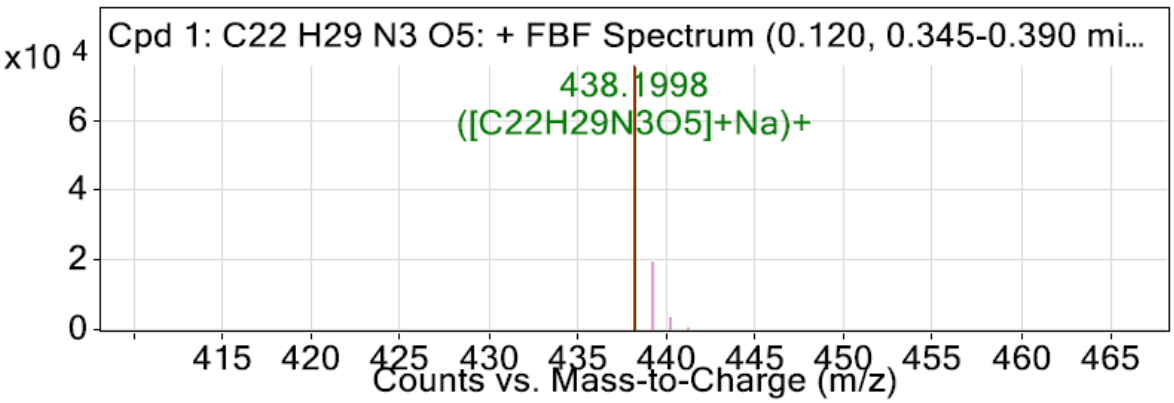
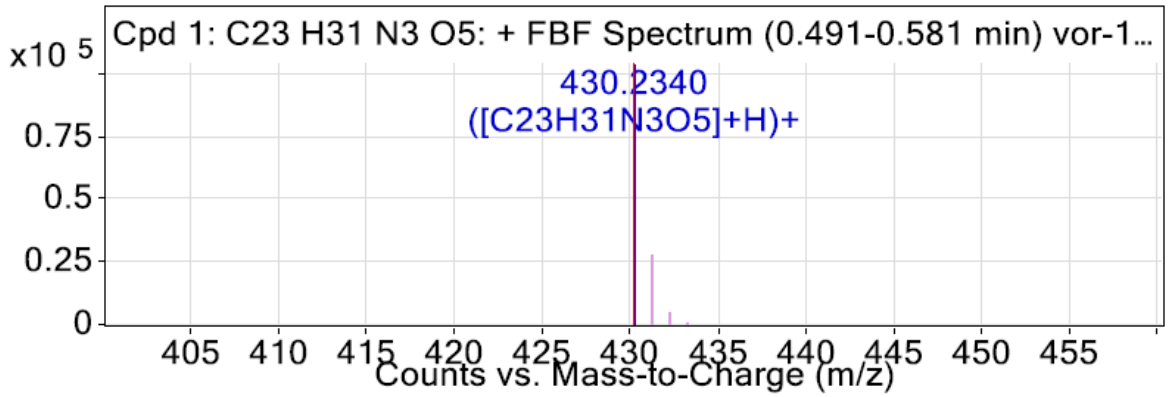



HRMS of **8j**

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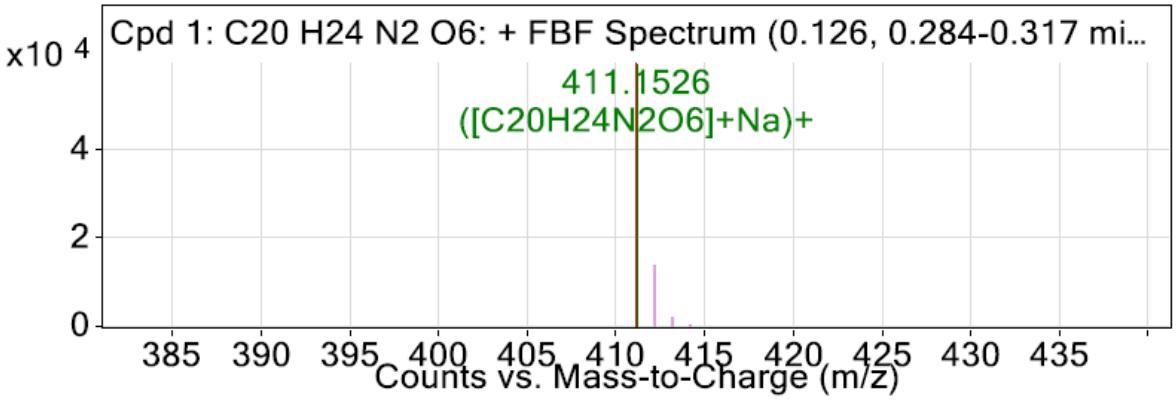
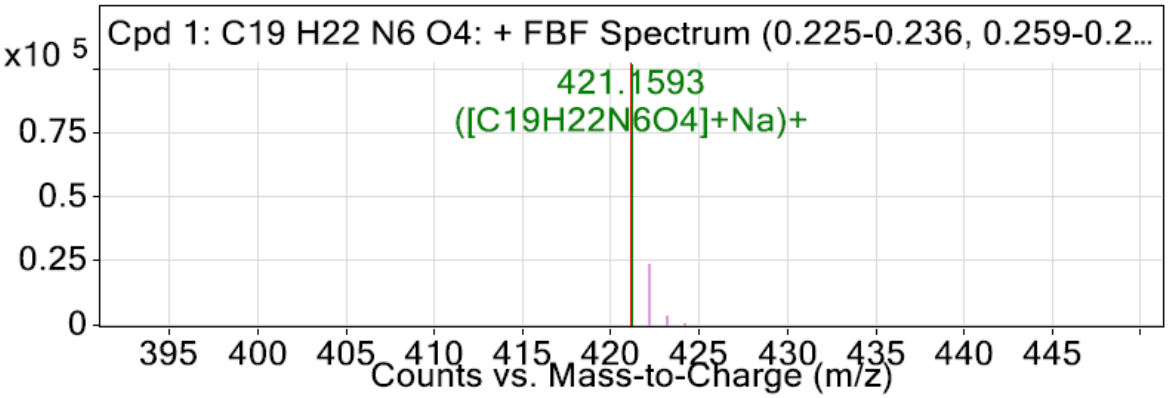
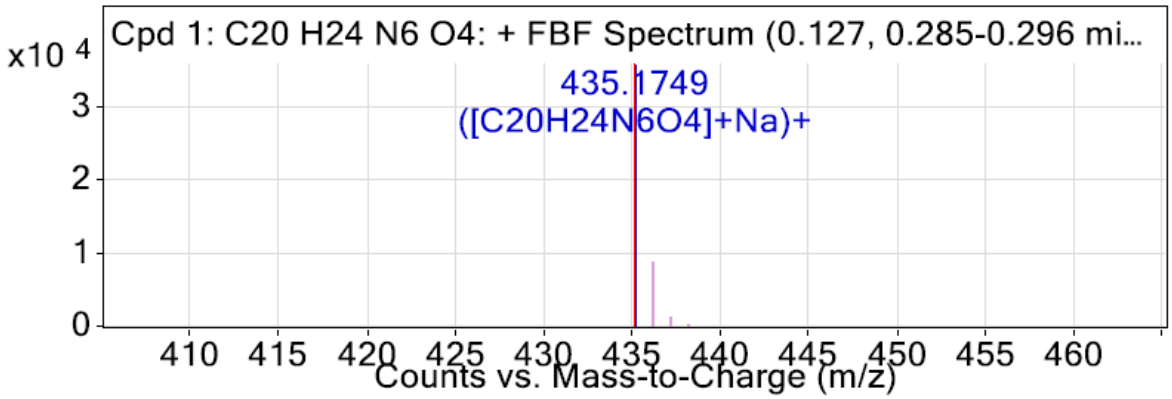


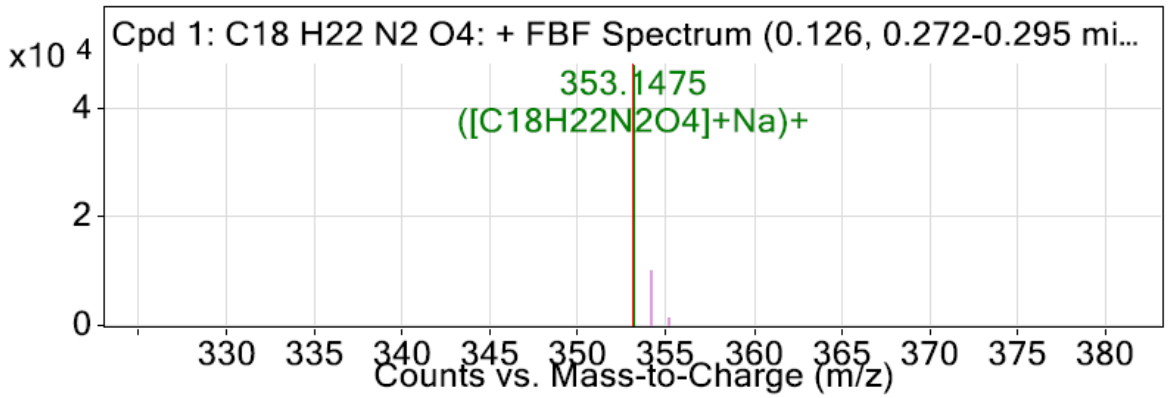

HRMS of **8l**



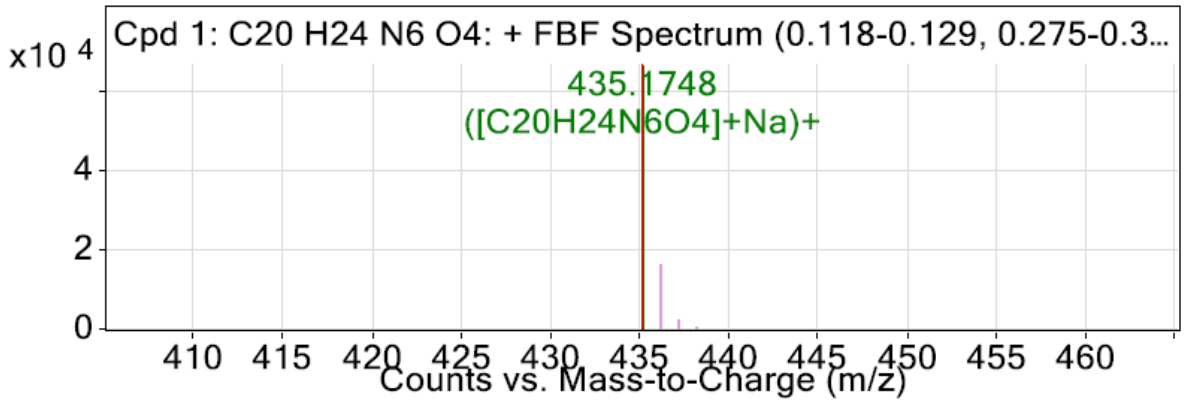

HRMS of **8m**



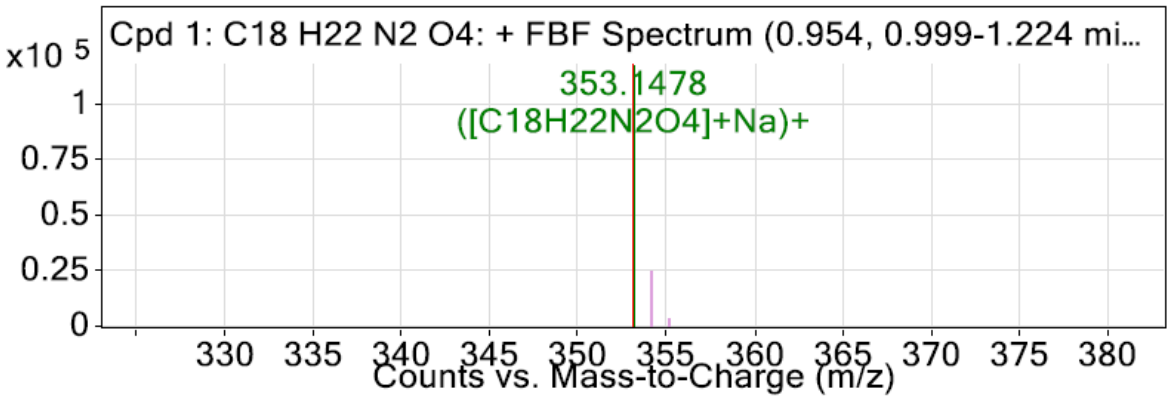

HRMS of **8n**



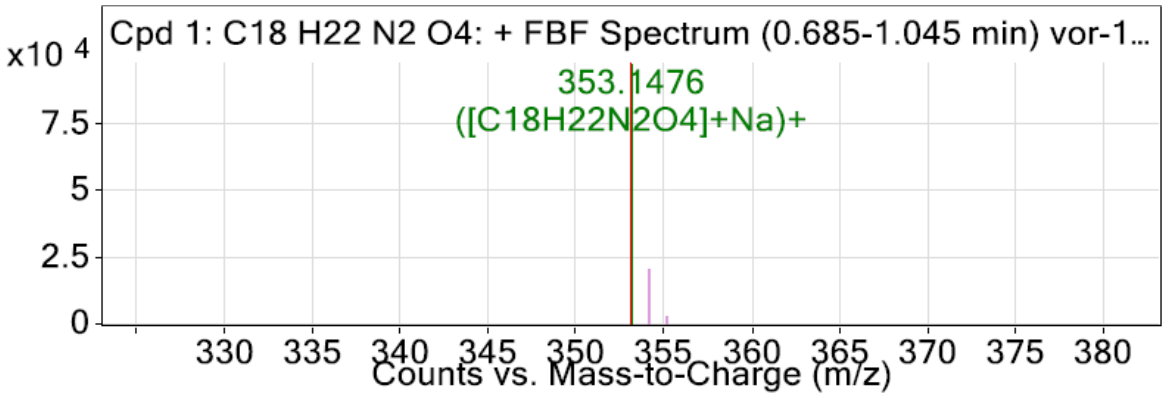

HRMS of **9a**



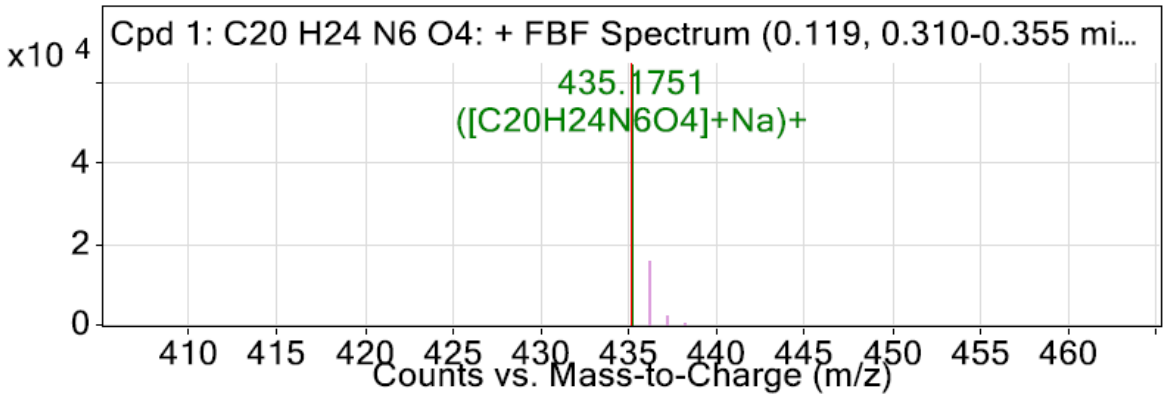

HRMS of **9b**



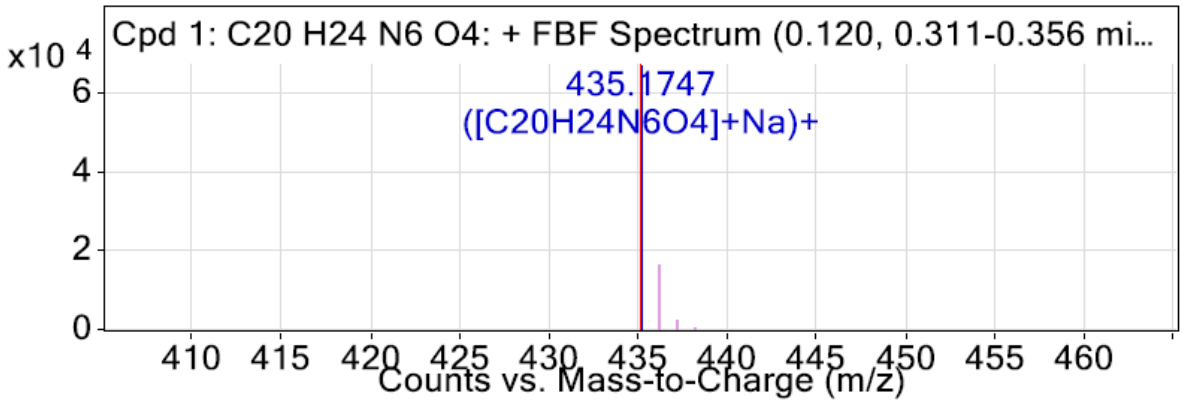

HRMS of *(R)*-**8a**




HRMS of *(S)*-**8a**




HRMS of *(R)*-**8n**


Cpd 1: C20 H24 N6 O4: + FBF Spectrum (0.120, 0.311-0.356 mi...
x10 4
6
4
2
0
435.1747
([C20H24N6O4]+Na)+
410 415 420 425 430 435 440 445 450 455 460
Counts vs. Mass-to-Charge (m/z)

HRMS of *(S)*-**8n**

## Molecular modeling

**Molecular docking.** The compound library were generated with DataWarrior software [1]. Geometry of the compounds was optimized using the MMFF94s+ forcefield. A Sdf file containing multiple compounds was converted into separate mol2 files using Open Babel [2]. Mol2 ligand files were converted into pdbqt files using the prepare_ligand4.py script from the AutoDockTools package [3]. For the protein preparation, the ligand and water were removed from the receptor protein and then it was converted into a pdbqt file using AutoDockTools. The next parameters for the grid box were set up for proteins from following pdbid:

1OSF: ΔX=ΔY=ΔZ=24 Å centered at X = 76 Å, Y = -26 Å, Z = 64 Å;

6LTI: ΔX=ΔY=ΔZ=24 Å centered at X = 34 Å, Y = -9 Å, Z = -25 Å;

5ZR3: ΔX=ΔY=ΔZ=24 Å centered at X = 35 Å, Y = 20 Å, Z = 8 Å;

7UR3: ΔX=ΔY=ΔZ=24 Å centered at X = -2 Å, Y = -13 Å, Z = -2 Å;

Docking was carried out with the use of QVina2 [4]. Discovery Studio Visualizer and PyMol were used for visualization.

**Molecular dynamics simulations and MM/GBSA calculations.** The dynamics simulations obtained from docking complexes were carried out with GROMACS [5] using the AMBER99SB-ILDN forcefield [6]. The ligands were parameterized using ACPYPE [7] (GAFF forcefield and BCC charges). Initially, the complexes were placed in a dodecahedron box and dissolved in water (TIP3P). $Na^+$ ions were added to the systems to make them electrically neutral. Energy minimization was performed using the steepest descent algorithm. The systems were equilibrated in the NVT ensemble (1 ns) followed by equilibration in the NPT ensemble (1 ns) with restraints applied to non-hydrogen atoms. Then all restraints were removed and a 1-ns or 1000-ns simulation in the NPT ensemble was carried out at a temperature of 300 K and a pressure of 1 bar. The ΔH value was calculated on the basis of the trajectories obtained from stimulation with gmx_MMPBSA software [8]. A single trajectory approximation and the GB-HCT model [9] were used for this calculation.

**HSP70 expression in various breast cancer cells treated with compound (R)-8n**

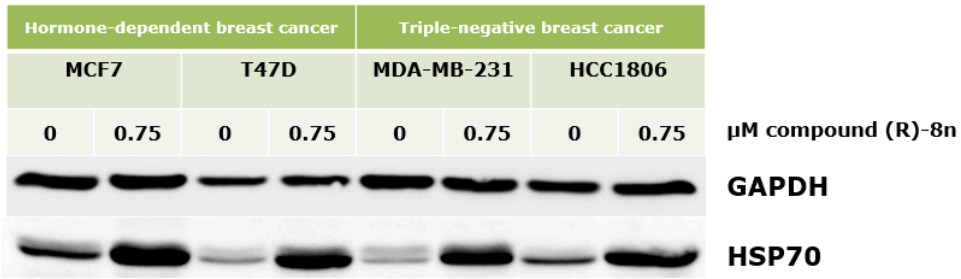



**Fig. S4** HSP70 in hormone-dependent and triple-negative breast cancer cells. The cells were treated with compound **(R)-8n** for 24 hours and then they were used to prepare samples for immunoblotting. In this study, HSP70 was applied as an inhibition marker [10, 11] of the HSP90 axis in cancer cells. GAPDH antibodies were used as loading control.

## Supporting information references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