Supporting Information

Microwave-Assisted Single-step Synthesis of Cyclic and Acyclic β-Aminosulfones and Evaluation of Their Antifungal Activity Targeting CYP51

Abigail Bibiana Pinheiro,[a] Soumik Saha,[a] Madhuri Madduri,[b] Utpal Roy,[b] Lakshmi Sudhir Menon,[b] Sumit Biswas,[b] Amrita Chatterjee*[a] and Mainak Banerjee*[a]

[a]Department of Chemistry, Birla Institute of Technology and Science, Pilani, KK Birla Goa Campus, Zuarinagar, Sancoale, Goa 403726, India

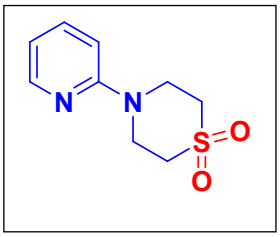
[b]Department of Biological Sciences, Birla Institute of Technology and Science, Pilani, KK Birla Goa Campus, Zuarinagar, Sancoale, Goa 403726, India

E-mail addresses: amrita@goa.bits-pilani.ac.in (A.C.); mainak@goa.bits-pilani.ac.in (M.B.)

Table of contents: Docking scores, Representation of the Binding sites, and copies of spectra

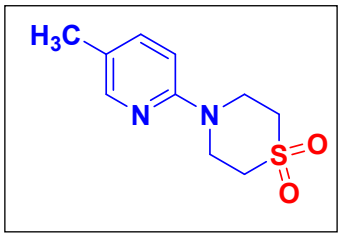
Spectral data of heteroaromatic and functionalized carbocycle-derived aza-sulfones (5)

4-(Pyridin-2-yl)thiomorpholine-1,1-dioxide (**5h**): [1] Yellow solid, 97 mg (92%); mp. 161-162



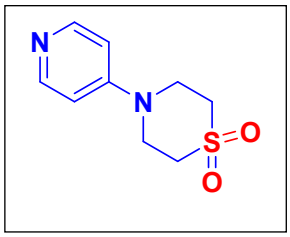
°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.19 (d, J = 5.3 Hz, 1H), 7.55-7.51 (m, 1H), 6.73-6.70 (m, 2H), 4.14 (t, J = 5.3 Hz, 4H), 3.02 (t, J = 5.3 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 156.5, 148.4, 138.2, 114.7, 107.3, 50.8, 44.1.

4-(5-Methylpyridin-2-yl)thiomorpholine-1,1-dioxide (**5i**):[1] White solid, 105 mg (93%); mp.



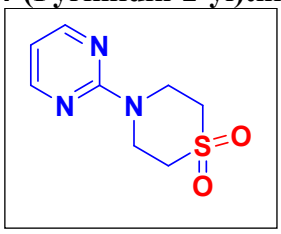
133-135 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.01 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.7 Hz, 1H), 4.01 (s, 4H), 3.06 (s, 4H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 155.4, 147.8, 139.4, 122.9, 108.0, 50.5, 44.1, 17.3.

4-(Pyridin-4-yl)thiomorpholine-1,1-dioxide (**5j**):[1] White solid, 76 mg (72%); mp. 208-209



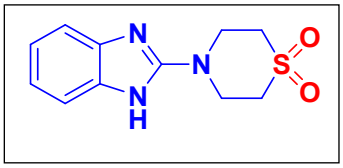
°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.22 (d, J = 6.0 Hz, 2H), 6.94 (d, J = 6.1 Hz, 2H), 3.92 (bs, 4H), 3.12 (bs, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 152.4, 150.6, 109.3, 50.4, 44.8.

4-(Pyrimidin-2-yl)thiomorpholine-1,1-dioxide (**5k**):[1] Yellow solid, 82 mg (77%); mp. 194-



195 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.29 (d, J = 6.4 Hz, 2H), 6.62 (t, J = 6.1 Hz, 1H), 3.39 (bs, 4H), 3.36 (bs, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 162.3, 158.5, 111.1, 52.2, 34.9.

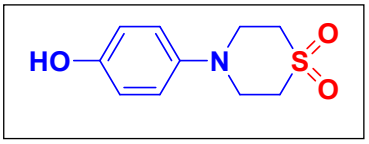
4-(1*H*-Benzo[*d*]imidazol-2-yl)thiomorpholine 1,1-dioxide (**5l**): White solid, 109 mg (87%),



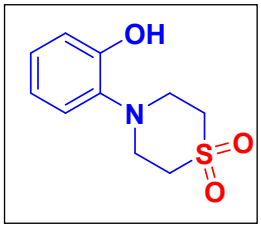
mp. 174–175 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.37-

7.34 (m, 2H), 7.09-7.08 (m, 2H), 4.28 (bs, 4H), 4.27 (bs, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 154.9, 120.6, 117.2, 109.4, 55.5, 55.0.

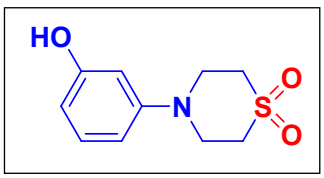
4-(4-Hydroxyphenyl)thiomorpholine-1,1-dioxide (**5m**):[1] Blue solid, 111 mg (98%); mp. 152-154 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 8.98 (s, 1H), 6.87 (d, J = 8.6 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 3.53 (bs, 4H), 3.13 (bs, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 152.0, 141.9, 119.3, 116.2, 50.7, 49.3.



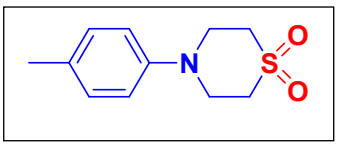
4-(2-Hydroxyphenyl)thiomorpholine-1,1-dioxide (**5n**):[1] Green solid, 103 mg (91%); mp. 195-196 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15 (d, J = 7.9 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 3.40 (t, J = 5.5 Hz, 4H), 3.24 (t, J = 5.6 Hz, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 150.5, 137.5, 127.6, 121.7, 120.6, 115.1, 52.4, 51.4.



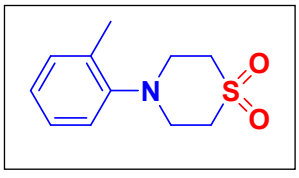
4-(3-Hydroxyphenyl)thiomorpholine-1,1-dioxide (**5o**):[1] White solid, 102 mg (90%); mp. 142-143 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.26 (s, 1H), 7.03 (t, J = 8.1 Hz, 1H), 6.44 (d, J = 8.3 Hz, 1H), 6.38 (s, 1H), 6.30-6.24 (m, 1H), 3.70 (bs, 4H), 3.09 (bs, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 158.9, 149.4, 130.6, 130.1, 107.2, 103.3, 50.3, 47.2.



4-(4-Tolyl)thiomorpholine-1,1-dioxide (**5p**):[1] White solid, 106 mg (94%); mp. 146-147 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.09 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 3.77 (t, J = 5.4 Hz, 4H), 3.08 (t, J = 5.4 Hz, 4H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 145.6, 130.5, 130.2, 116.8, 50.5, 48.1, 20.4.

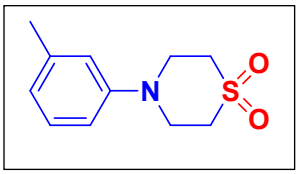


4-(2-Tolyl)thiomorpholine-1,1-dioxide (**5q**):[1] White solid, 104 mg (92%); mp. 143-144 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.15-7.09 (m, 2H), 6.99 (d,

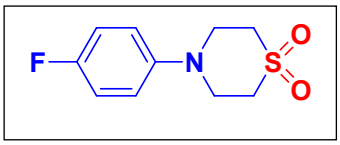


J = 8.4 Hz, 2H), 3.33 (t, J = 5.1 Hz, 4H), 3.13 (t, J = 5.4 Hz, 4H), 2.25 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 150.0, 136.7, 131.1, 129.7, 124.6, 120.1, 52.4, 50.4, 17.6.

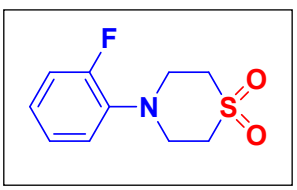
4-(3-Tolyl)thiomorpholine-1,1-dioxide (**5r**):[1] White solid, 100 mg (89%); mp. 78-80 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.16 (t, J = 7.6 Hz, 1H), 6.60-6.55 (m, 1H), 6.44-6.41 (m, 1H), 6.11 (d, J = 9.2 Hz, 1H), 3.81 (t, J = 5.1 Hz, 4H), 3.09 (t, J = 5.4 Hz, 4H), 2.30 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 139.7, 136.9, 129.9, 122.0, 117.3, 113.6, 50.5, 47.9, 21.7.



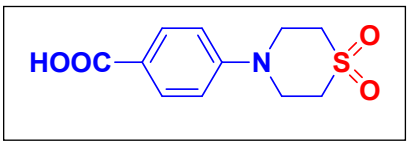
4-(4-Fluorophenyl)thiomorpholine-1,1-dioxide (**5s**):[1] White solid, 98 mg (86%); mp. 107-110 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.97 (t, J = 8.9 Hz, 2H), 6.87 (dd, J_1 = 9.2 Hz, J_2 = 4.5 Hz, 2H), 3.69 (bs, 4H), 3.09 (bs, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 158.8, 145.1, 119.1 (d, J = 7.5 Hz), 116.2 (d, J = 22.5 Hz), 50.8, 49.0.



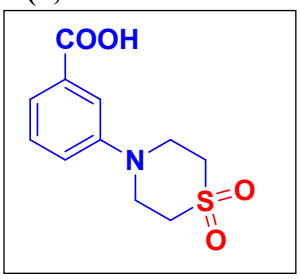
4-(2-Fluorophenyl)thiomorpholine-1,1-dioxide (**5t**):[1] White solid, 93 mg (82%); mp. 117-118 °C; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.08-6.96 (m, 4H), 3.59 (bs, 4H), 3.19 (bs, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 155.7 (d, J = 243.8 Hz), 138.4 (d, J = 10.0 Hz), 124.7 (d, J = 3.8 Hz), 124.3 (d, J = 7.5 Hz), 120.7, 116.6 (d, J = 20.0 Hz), 52.1, 49.5.



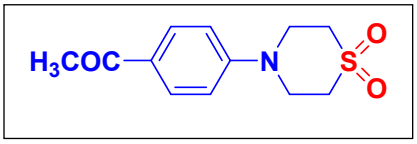
4-(1,1-Dioxidothiomorpholino)benzoic acid (**5u**):[1] White solid, 104 mg (82%); mp. 230-231 °C; ^1H NMR (500 MHz, DMSO-d_6): δ (ppm) 12.39 (s, 1H), 7.80 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 3.92 (s, 4H), 3.12 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6): δ (ppm) 167.6, 151.0, 131.6, 120.7, 114.3, 50.5, 46.1.



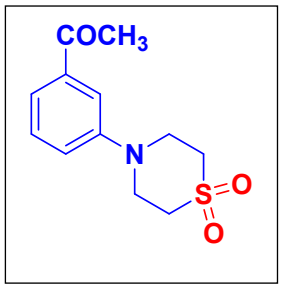
3-(1,1-Dioxidothiomorpholino)benzoic acid (**5v**):[1] White solid, 112 mg (87%); mp. 210-212 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 12.92 (s, 1H), 7.52 (s, 1H), 7.42-7.35 (m, 2H), 7.28 (d, J = 8.3 Hz, 1H), 3.81 (bs, 4H), 3.15 (bs, 4H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 168.0, 148.4, 132.4, 130.1, 120.7, 120.6, 116.5, 50.4, 47.2.



1-(4-(1,1-Dioxidothiomorpholino)phenyl)ethan-1-one (**5w**):[1] Brown solid, 103 mg (83%); mp. 119-120 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.84 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H), 3.94 (t, J = 5.4 Hz, 4H), 3.13 (t, J = 5.5 Hz, 4H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 196.7, 151.2, 130.9, 114.1, 113.0, 50.5, 46.0, 26.6.



1-(3-(1,1-Dioxidothiomorpholino)phenyl)ethan-1-one (**5x**):[1] Brown solid, 102 mg (81%); mp. 108-110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.49-7.45 (m, 2H), 7.37 (t, J = 8.0 Hz, 1H), 7.10 (dd, J_1 = 8.1 Hz, J_2 = 2.9 Hz, 1H), 3.88 (t, J = 5.4 Hz, 4H), 3.09 (t, J = 5.4 Hz, 4H), 2.57 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 198.0, 147.9, 138.5, 130.0, 121.2, 120.7, 114.9, 50.5, 47.4, 26.7.



***N*-(4-(1,1-Dioxidothiomorpholino)phenyl)acetamide** (**5y**):[1] White solid, 111 mg (83%); mp. 198-200 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 9.75 (s, 1H), 7.45 (d, J = 8.9 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.68 (bs, 4H), 3.11 (bs, 4H), 2.0 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6): δ (ppm) 168.2, 144.1, 132.5, 120.8, 116.9, 50.3, 47.9, 24.3.

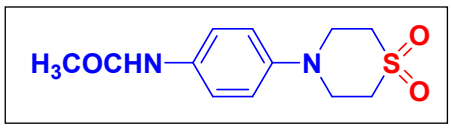
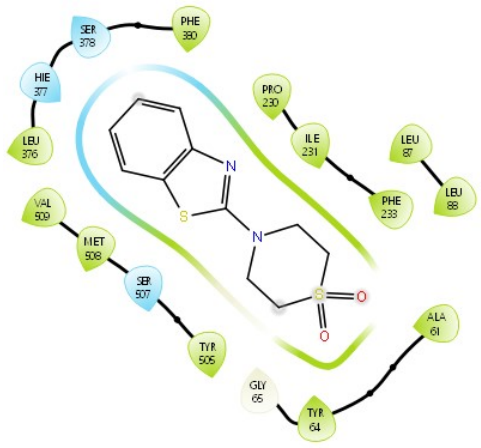
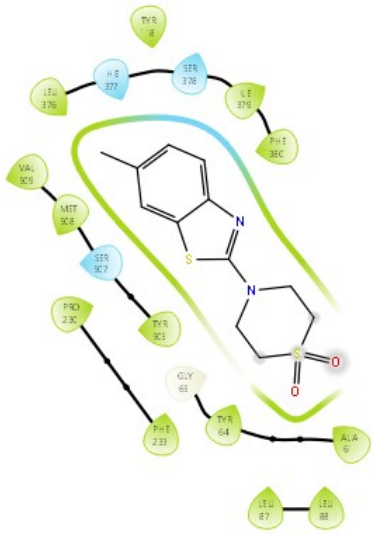
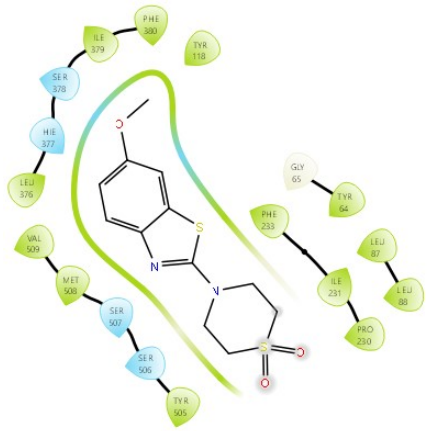
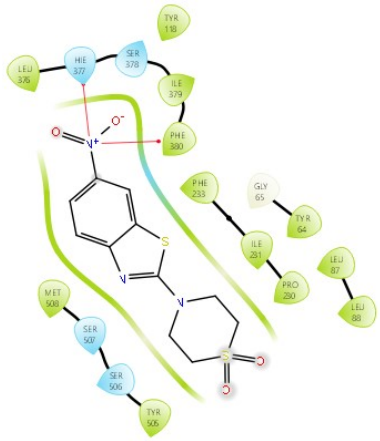
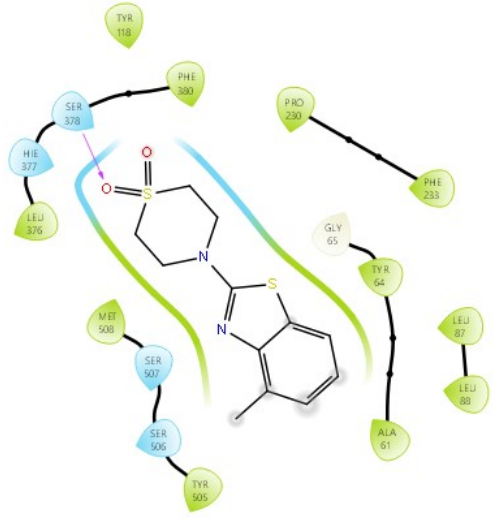
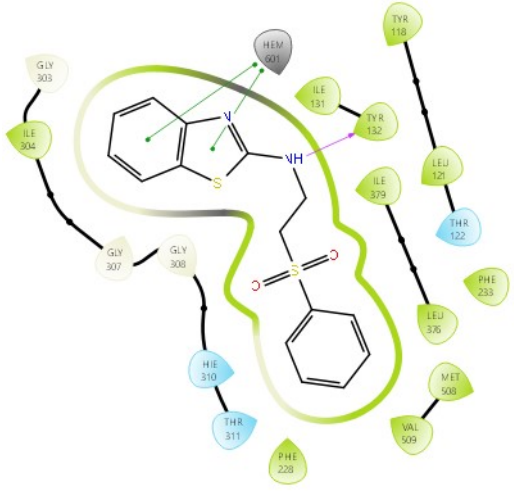
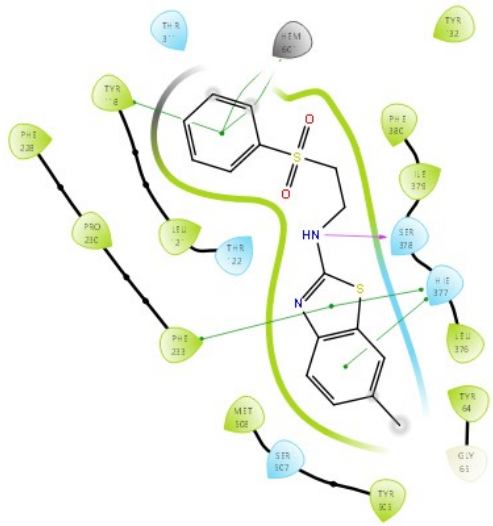


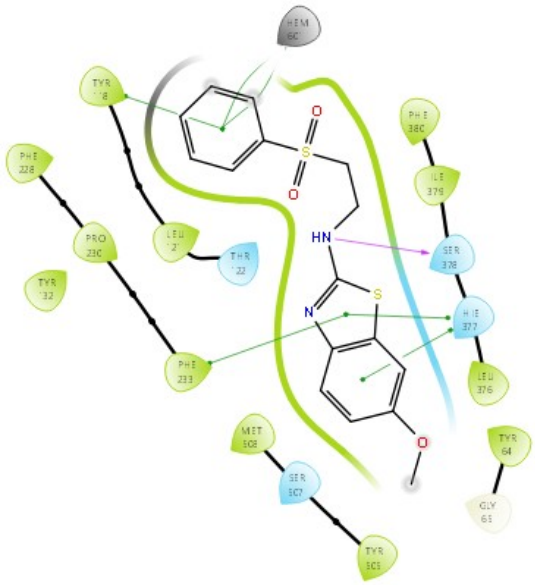
Table S1. Comparing the binding profile showing haem binding for compounds **3a-3m**, **5a-5g**, targeting CYP51, PDB ID: 5V5Z.

3a 	***3b*** 
3c 	***3d*** 
3e 	***3f*** 

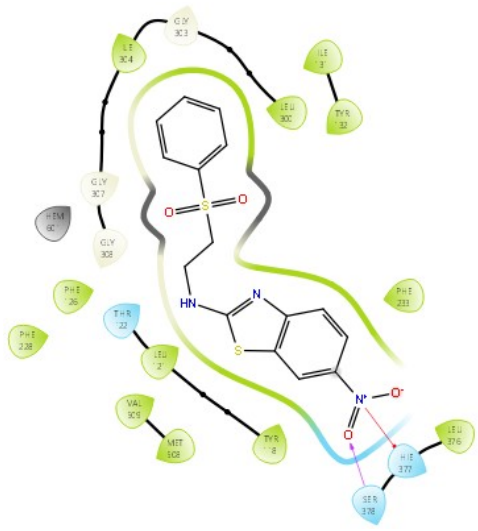
3g



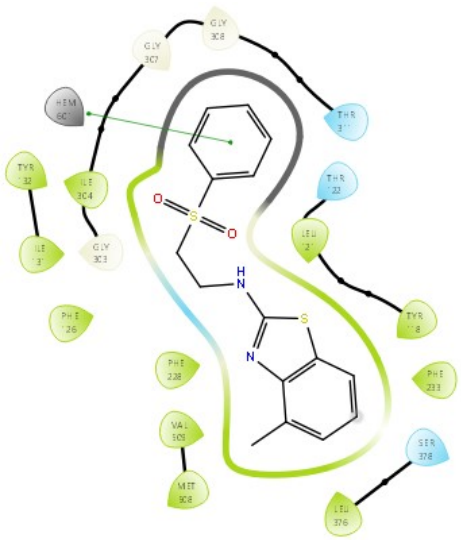
3h



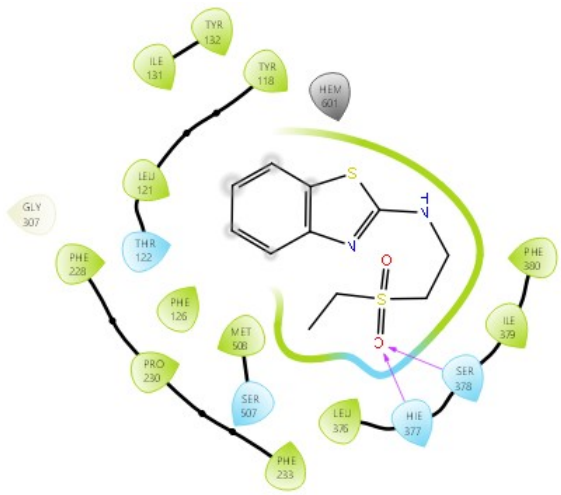
3i



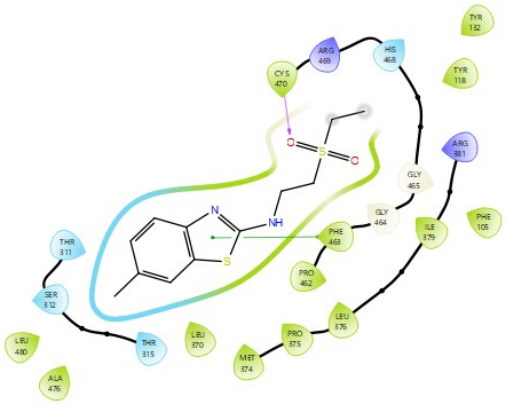
3j

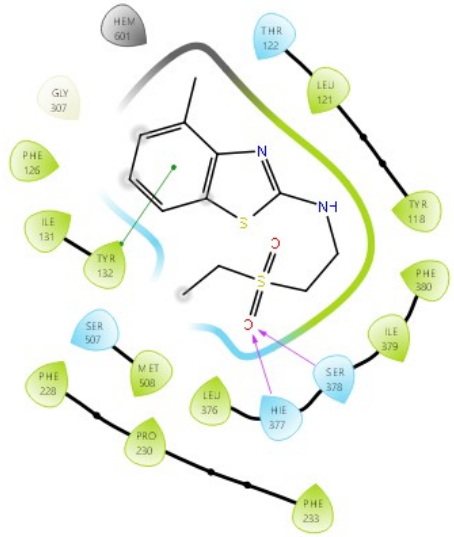
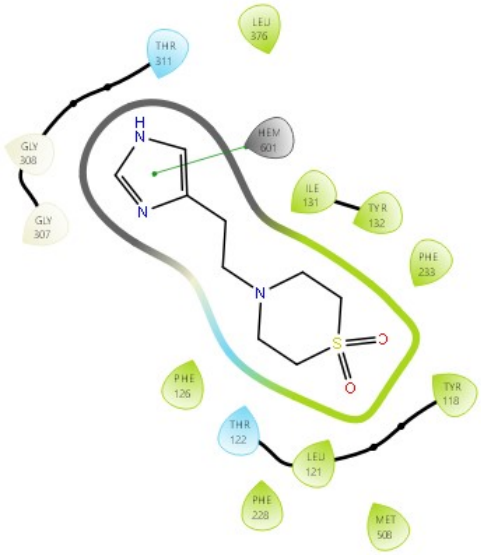
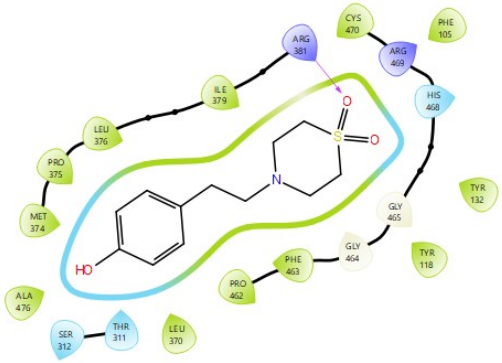
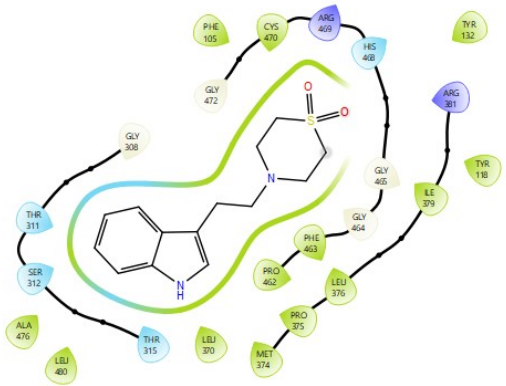
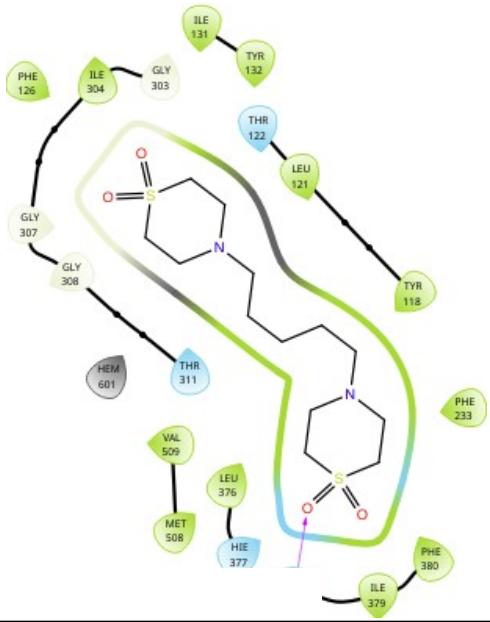
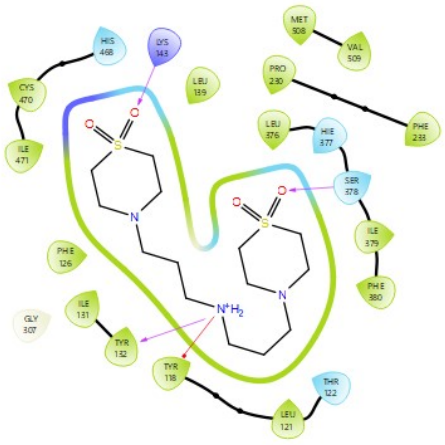


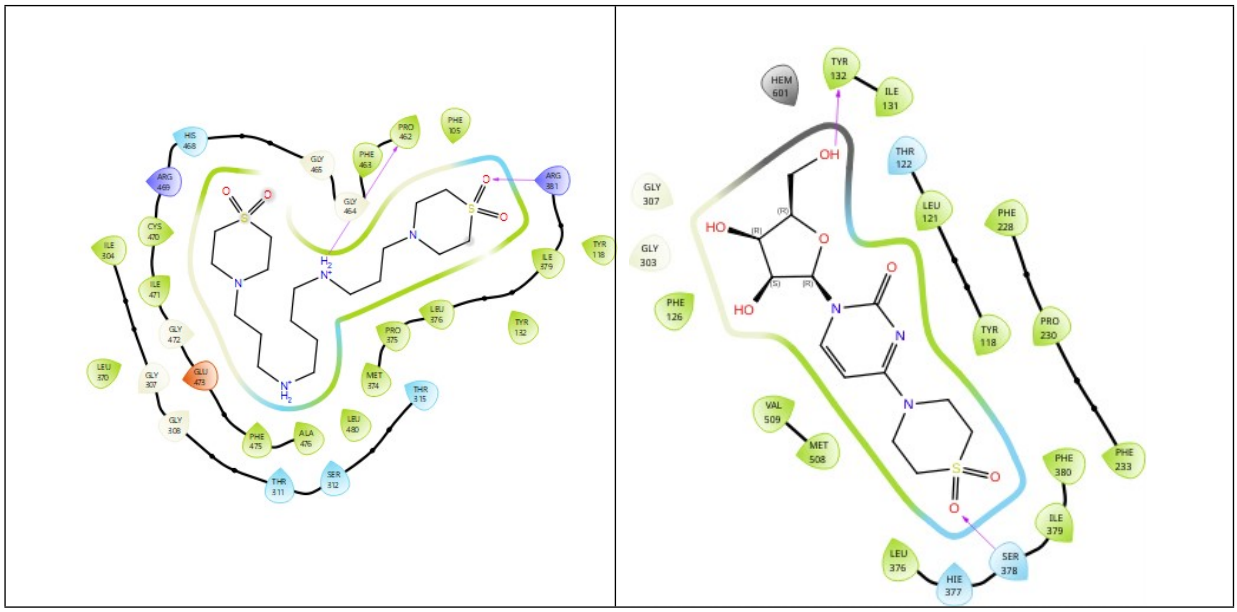
3k



3l

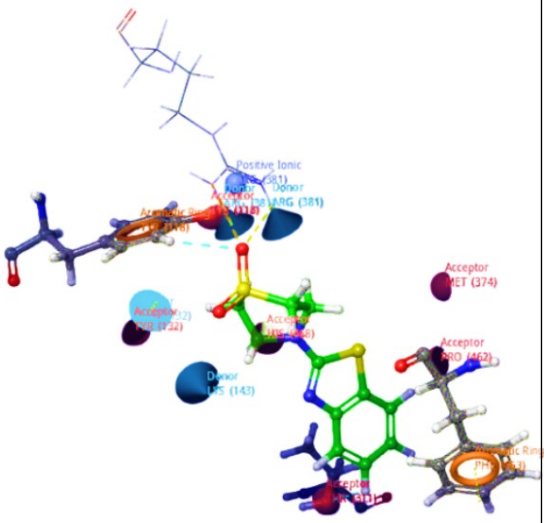


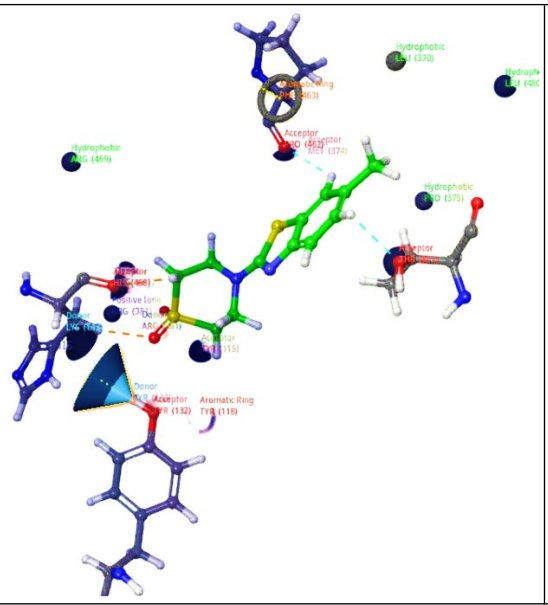
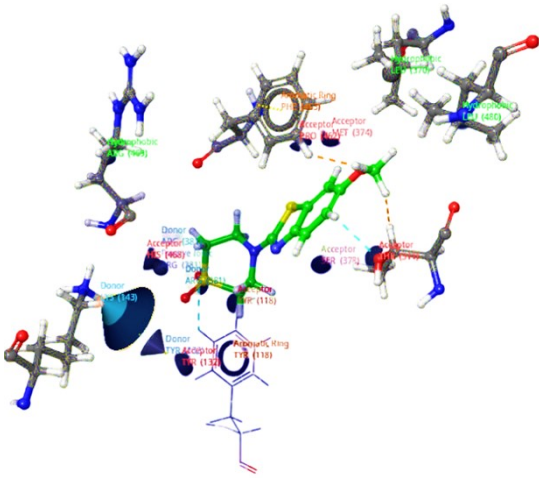
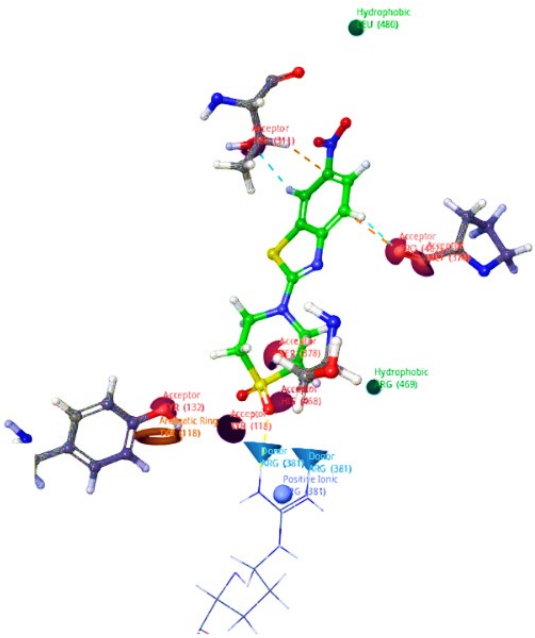
3m 	***5a*** 
5b 	***5c*** 
5d 	***5e*** 
5f	***5g***

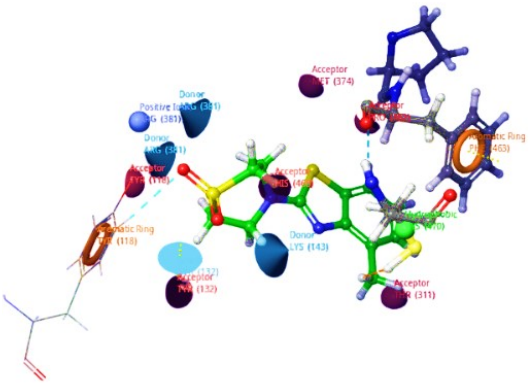
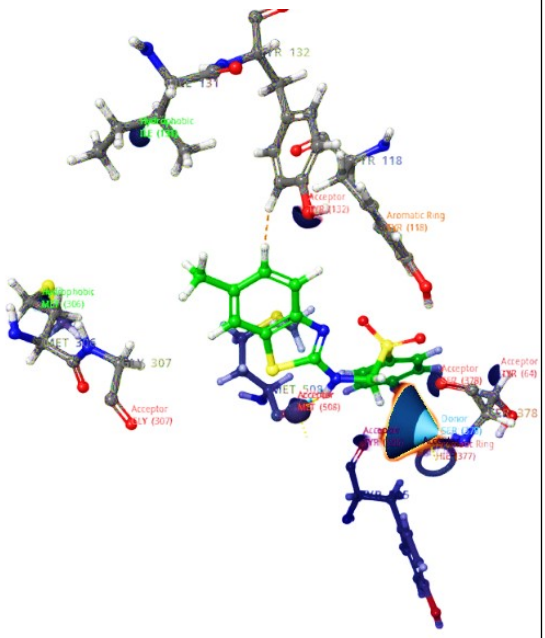


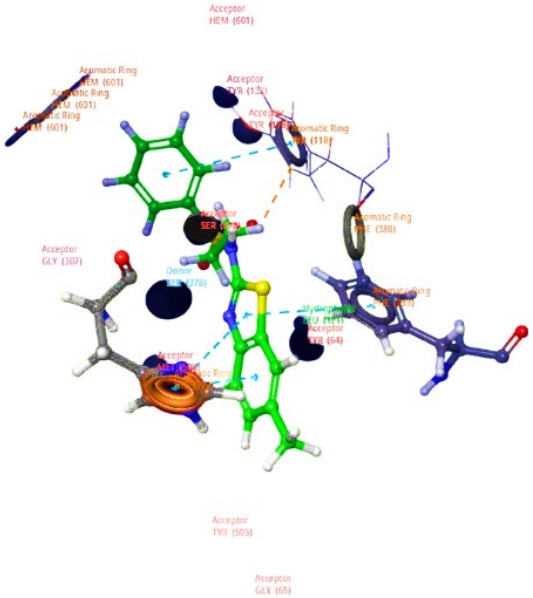
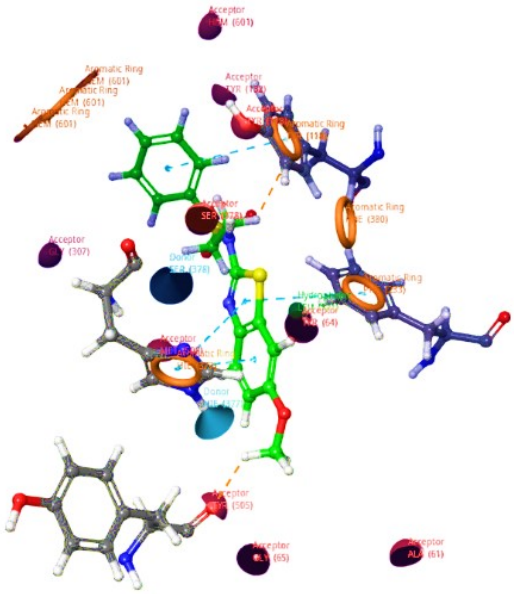
2D LigPlot figures of benzothiazoles and biogenic amine-derived β-amino sulfones within the CYP51 active site, illustrating all amino acids within the CYP51 active site surrounding the ligands.

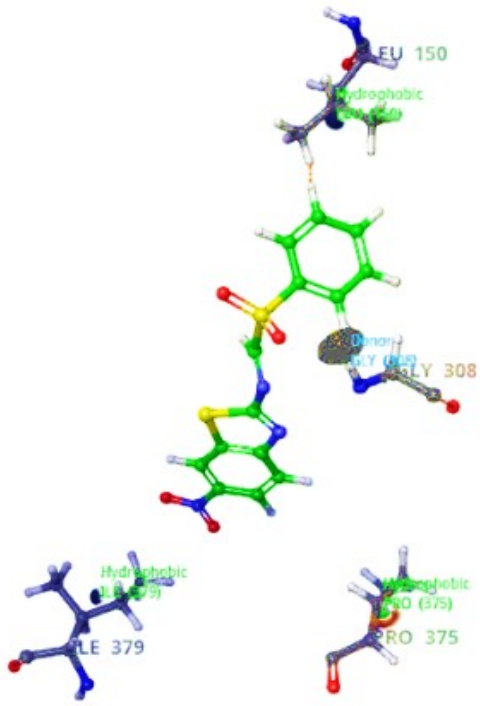
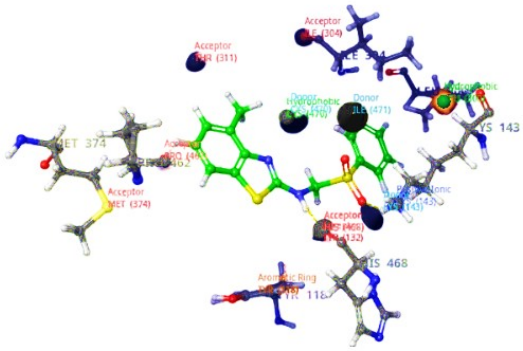
Table S2. Images illustrating binding position and key binding interactions between protein-ligand for **3a-3m**, **5a-5g**, targeting CYP51, PDB ID: 5V5Z.

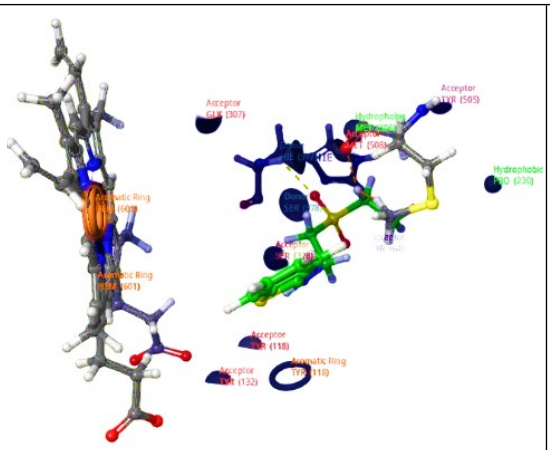
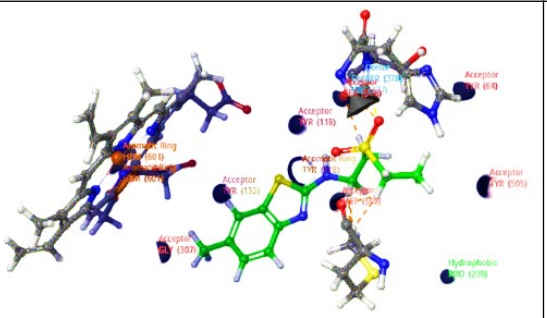
Compound no.	Simulation	Key interactions
3a		**Hydrogen bonds/polar:** SER 378, SER 507 with nitrogen/ oxygen, HIS 377: hydrophilic interaction or H-bond contributor. **Van der Waals or hydrophobic stabilization**: LEU 376, VAL 509, MET 508, PHE 380, PRO 230, ILE 231, LEU 87, LEU 88 (right side), PHE 233, ALA 61, TYR 64, TYR 505 by surrounding the ligands. **Aromatic/π-stacking interactions:** PHE 233: π-π stacking with the aromatic ring of the ligand. TYR 64 and TYR 505: π-sulfur or edge-on aromatic interactions. **Sulfonyl group interactions:** TYR 64 and GLY 65: hydrogen bonding/dipole-dipole interactions with the oxygens of the sulfonyl group.

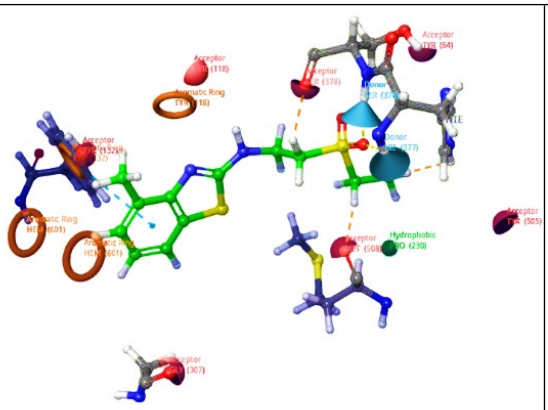
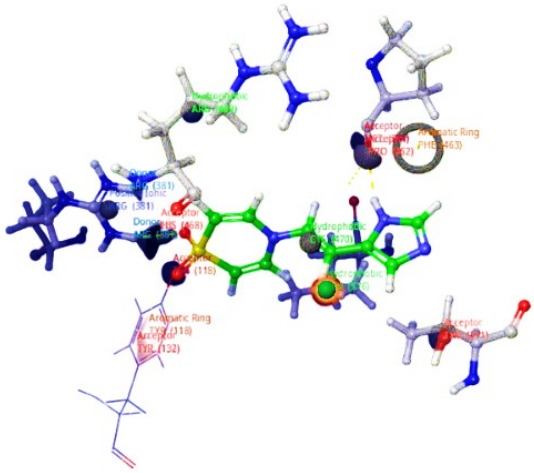
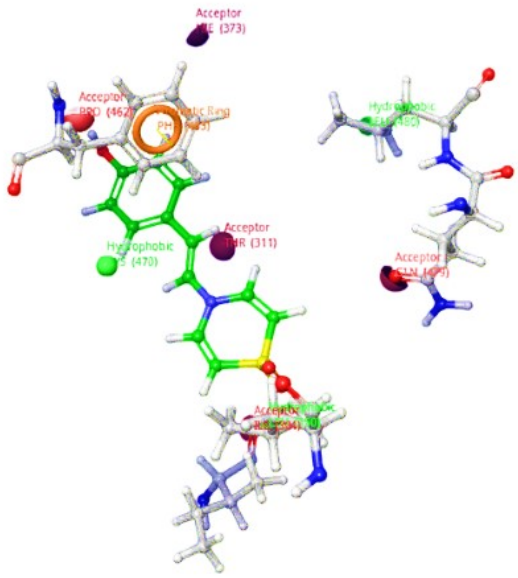
3b		**Hydrogen bonds / polar:** SER 367, SER 378, HIS 377, TYR 8. **Hydrophobic contacts:** ILE 379, PHE 380, LEU 376, MET 508, LEU 88, ALA 6. **Aromatic/π-π stacking:** PHE 233. **Dipole/sulfonyl interactions:** SER 367, TYR 64 with SO_2 group.
3c		**Hydrogen bonds:** SER 505 and SER 507 with oxygen or nitrogen on the ligand. **Van der Waals/hydrophobic interactions:** ILE 378, ILE 379, PHE 380, LEU 376, VAL 509, MET 508. **Pi-stacking/pi-sulfur interactions:** PHE 233: positioned near the aromatic ring of the ligand, involved in π-π stacking or aromatic interactions. **Polar interactions:** TYR 118 and TYR 64 **Ionic or dipole interactions:** The (SO_2) group on the ligand can form dipole-dipole interactions/hydrogen bonds with nearby residues such as SER 507.
3d		**Hydrogen bonds/polar interactions:** HIS 377, SER 378: to the negatively charged oxygen (O^-) on the ligand's phenolate group. SER 507 and SER 506: weak polar interactions with sulfur/nitrogen. TYR 505: polar interaction with ligand due to proximity and orientation. **Hydrophobic interactions:** LE 379, PHE 380, MET 508, LEU 376, ILE 231, PRO 230, LEU 87, LEU 88, PHE 233, and TYR 64 contribute both hydrophobic and π interactions. **π–π stacking/aromatic interactions:** PHE 233: located next to the ligand's aromatic system, promoting π–π stacking. TYR 64: participates in edge-to-face π interactions or weak hydrogen bonding. **Sulfonyl group interactions:** The SO_2 group:

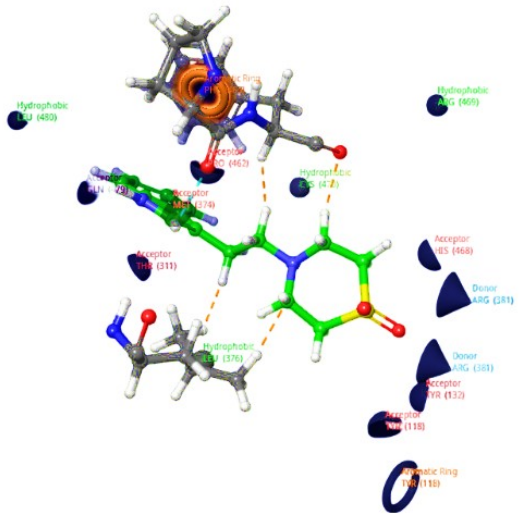
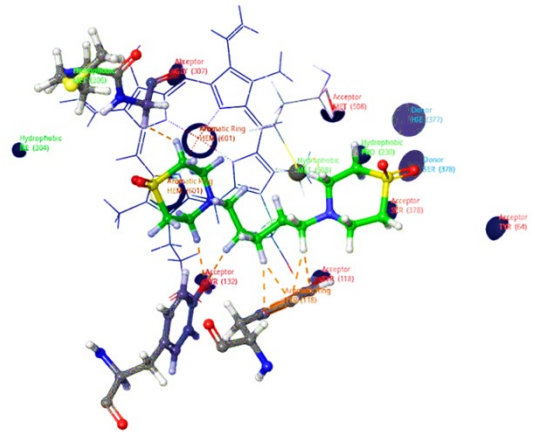
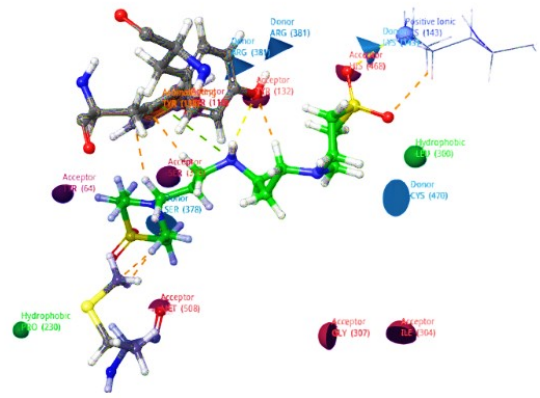
		hydrogen bonding/dipole interactions with polar residues nearby, SER 506, SER 507, or TYR 505.
3e		**Hydrogen bonds/polar interactions:** SER 378: with a sulfonyl oxygen on the ligand. SER 507 and SER 506: polar interactions with nearby heteroatoms, nitrogen/sulfur in the ligand. HIS 377: hydrogen bonding with the ligand's carbonyl or sulfonyl group. TYR 505: polar or weak hydrogen bonding. **Hydrophobic interactions:** LEU 376, MET 508, PHE 380 (left side), ILE 87, LEU 88, ALA 61, ILE 231, PRO 230, PHE 233, TYR 64, classic hydrophobic pocket. **Aromatic/π-stacking:** PHE 233, TYR 64 **Sulfonyl and carbonyl group interactions:** The sulfonyl group forms a hydrogen bond with SER 378. The carbonyl oxygen (adjacent to the phenyl ring) participates in polar interactions with HIS 377/ SER 507.
3f		**Coordination bond to heme iron:** Ligand atom: nitrogen, Protein group: heme iron (Fe) of the heme prosthetic group (HEM 601). **Hydrogen bonds:** Ligand NH forms hydrogen bonds with: TYR 131 – oxygen likely acting as an H-bond acceptor, HIE 310 – nitrogen of imidazole ring acting as H-bond acceptor/donor. ***π–π* stacking/aromatic interactions:** The central aromatic system of the ligand is involved in hydrophobic/aromatic stacking interactions with PHE 228 and PHE 233. **Hydrophobic interactions:** These residues interact hydrophobically with the ligand: ILE 131, TYR 118, LEU 121, ILE 379, LEU 236, MET 508, VAL 509, PHE 228, PHE 233, GLY 303–308 (nonpolar backbone interactions). **Polar contacts/solvent exposure:** THR 122 and THR 311 are polar residues nearby.

3g		**<u>Hydrogen bonds/polar interactions:</u>** THR 82: hydrogen bond with the NH group of the ligand. SER 378: interacts with a heteroatom on the ligand, the thiazole ring nitrogen/sulfur. HIS 377: participates in a hydrogen bond/ electrostatic interaction with the ligand. SER 507: positioned close to a ligand heteroatom (e.g., sulfur), contributing to polar interactions. **<u>Hydrophobic contacts:</u>** ILE 376, MET 508, LEU 379, ILE 231, PRO 230, PHE 380, PHE 233, PHE 228, TYR 64, TYR 161 provide a nonpolar environment that stabilizes the ligand via van der Waals and hydrophobic forces. **<u>Aromatic/π–stacking interactions:</u>** PHE 233 and PHE 228: π–π stacking with the ligand's aromatic rings. TYR 122: edge-on π-interactions with the phenyl ring of the ligand. **<u>Sulfonyl group interactions:</u>** The SO_2 of the ligand forms a hydrogen bond (or strong dipole interaction) with THR 82. Stabilized by electrostatic interactions from nearby polar residues.
3h		**<u>Hydrogen bonds/polar interactions</u>:** THR 82: hydrogen bond with the sulfonamide group of the ligand. SER 378: hydrogen bonding (to the NH of the thiazole-linked moiety). HIS 377: likely forms polar interactions with the ligand's nitrogen/sulfur. SER 507: potential hydrogen bond (to ligand sulfur/nitrogen). TYR 161: polar contact from the ligand's end carbonyl. **<u>Hydrophobic and van der Waals contacts</u>:** ILE 376, MET 508, LEU 379, PHE 380, PHE 233, PHE 228, TYR 64, TYR 118, TYR 161, TYR 122 involved in π–alkyl/hydrophobic stacking. PRO 230 and ILE 231 contribute to a non-polar pocket. **<u>Aromatic/ π–π stacking interactions</u>**: PHE 233 and PHE 228 are positioned near the aromatic ring of the ligand, enabling π–π stacking. TYR 122: potential edge-on π interaction with the ligand's phenyl ring. **<u>Sulfonyl group interactions:</u>** SO_2 group of the ligand interacting with THR 82 via hydrogen bonding. Additional stabilization is likely from

		hydrophobic surroundings.
3i		**<u>Hydrogen bonding interactions:</u>** Hydrogen bond acceptors (from the ligand): N-O^- (nitro group) oxygen interacts with SER 378 (OH group), HIE 377 (imidazole nitrogen). Hydrogen bond donor (from the ligand): amide NH forms an H-bond with THR 122 (backbone oxygen). **<u>Sulfonyl group (SO_2) interactions:</u>** The SO_2 group (top of the ligand) is involved in polar interactions, oriented toward GLY 362–364. **<u>Hydrophobic and aromatic interactions</u>:** Residues surrounding the ligand via hydrophobic contacts: PHE 233, PHE 238: aromatic side chains, involved in π–π stacking/ van der Waals interactions. ILE 300, ILE 376 aliphatic side chains. VAL 367, MET 508: contribute to hydrophobic stabilization. TYR 118, TYR 308: participate in both π/polar interactions.
3j		**<u>Metal coordination:</u>** A coordination bond from the ligand's nitrogen atom to the heme iron (Fe) in HEM 601. Critical for positioning the ligand in the active site and often involved in enzyme inhibition (common in cytochrome P450s). **<u>Hydrogen bonding:</u>** Ligand's NH group (part of the sulfonamide or thiazole-amide linkage) forms a hydrogen bond with THR 122. **<u>Hydrophobic interactions:</u>** Van der Waals/hydrophobic packing with the ligand: PHE 233, PHE 238: π–π/edge-to-face aromatic interactions with ligand rings. VAL 367, MET 508: aliphatic hydrophobic interactions. ILE 376: hydrophobic environment around the thiazole ring. LEU 121, ILE 324: stabilize ligand near sulfonyl and benzene. TYR 118: aromatic stacking or polar contacts. **<u>Sulfonyl group (SO_2) interactions:</u>** Two oxygen atoms on the SO_2 group act as potential hydrogen bond acceptors.

3k		**Hydrogen bonding:** HIE 377: sulfonyl oxygen H-bond acceptor forms H-bond with the imidazole side chain of His. SER 378: forms an H-bond with SER side chain OH. **Hydrophobic and aromatic contacts**: PHE 228, PHE 233, PHE 380: π–π interactions with the ligand's aromatic ring, LEU 121, LEU 336, LEU 373: aliphatic hydrophobic interactions stabilizing the backbone, MET 508: hydrophobic contact near the sulfonyl side, ILE 131, ILE 378: contribute to hydrophobic cavity structure, TYR 118, TYR 132: potential π or polar–π contacts. **Polar interactions**: THR 122, SER 507: polar residues near the ligand; form water-mediated interactions.
3l		**Hydrogen bonds:** CYS 470, ARG 463: H-bond acceptor. Forms a hydrogen bond with the thiol/guanidinium group or backbone NH group of CYS 470 and ARG 463, respectively. These hydrogen bonds stabilize the sulfonyl group and anchor the ligand at one end. **Hydrophobic and aromatic interactions:** These residues interact with the ligand primarily through van der Waals forces and hydrophobic packing: PHE 105, PHE 379: π–π/edge-to-face interactions with the ligand's heterocycle. LEU 376, LEU 370, MET 374: hydrophobic stabilization around the ligand's central and tail region. PRO 452, PRO 275: provide structural rigidity/hydrophobic contacts. **Polar residues:** THR 311, THR 315, SER 312, ARG 481, HIS 486: electrostatic or polar interactions to the sulfonyl group. **Ligand features:** SO_2 is the main polar center, forming two strong H-bonds. The aromatic system is stabilized by surrounding hydrophobic and aromatic residues. NH linker may contribute to intramolecular stability or indirect protein interactions.

3m		**Aromatic π–π interaction:** Ligand's aromatic ring to TYR 132. π–π stacking/aromatic–aromatic interaction helps anchor the ligand via face-to-face or edge-to-face stacking with tyrosine's phenol ring. **Hydrogen bonding interactions:** HIE 377: H-bond with histidine side chain, SER 378: H-bond with serine OH group. **Hydrophobic and π-stacking interactions:** PHE 228, PHE 233, PHE 380: π–π or edge-to-face interactions with ligand rings, ILE 121, ILE 131, ILE 379: hydrophobic pocket stabilization, LEU 376, MET 508: hydrophobic support near ligand core, PRO 230: adds conformational rigidity and hydrophobic contact, TYR 118, TYR 132: π–π or polar-π–π interactions.
5a		**π–π interaction with heme group:** Interaction: π–π stacking, close π-stacking with the heme group, suggests that the ligand may modulate or inhibit heme-dependent enzymatic activity (e.g., cytochrome P450 or oxidoreductase). **Hydrophobic and aromatic contacts:** TYR 118, TYR 132: π–π interactions or hydrophobic stacking, PHE 126, PHE 228, PHE 233: potential for π–π or edge-to-face interactions with ligand rings, ILE 131, LEU 121, LEU 376: form a hydrophobic pocket for the ligand, MET 508: stabilizes the sulfonyl end of the ligand.
5b		**Hydrogen bond interactions:** ARG 469: sulfonyl oxygen (O=), Strong H-bond from sulfonyl O to guanidinium NH; SER 312: hydroxy group (OH), forms H-bond with serine OH group. **Hydrophobic and π-stacking contacts:** TYR 118, TYR 132: π–π interactions with the aromatic rings. PHE 105, PHE 463: π–π or edge-to-face stacking, LEU 370, LEU 376, ILE 379: provide van der Waals stabilization, MET 374, PRO 375: adds to hydrophobic surface for ligand binding. **Polar residues nearby (potential for water bridging):** HIS 468: close to sulfonyl ring; may participate in water-mediated bonding. THR 311, THR 312: positioned near the hydroxy

		end; support polar interactions.
5c		**Hydrogen bond interaction:** ARG 469: sulfonyl oxygen: strong hydrogen bond between the guanidinium group of arginine and the sulfonyl oxygen of the ligand. Anchors the ligand's polar tail in the active site. **Hydrophobic and aromatic contacts:** PHE 105, PHE 463: likely π–π or edge-to-face stacking with aromatic rings, TYR 118, TYR 132: provide aromatic and hydrophobic environment, LEU 379, LEU 376, LEU 370: stabilize the central linker of the ligand, PRO 462, PRO 375, PRO 373: contribute to the hydrophobic pocket shaping, MET 374: supports interaction near the sulfonamide ring. **Polar/charged residues nearby:** HIS 468, ARG 381: near sulfonyl end; may participate via water bridges, SER 312, THR 311: located near the benzene ring's hydroxyl side, CYS 470, GLY 472, GLY 465: forms the polar boundary near the sulfonyl pocket.
5d		**Hydrogen bonds:** THR 122 and THR 311, SER 380. **Hydrophobic interactions:** TYR 118, LEU 121, TYR 132, ILE 131, ILE 126, ILE 304, GLY 303, GLY 307, GLY 308, PHE 126, PHE 233, ILE 379, LEU 376, MET 508, VAL 509. **π-π stacking or aromatic interactions:** PHE 126 and PHE 233.
5e		**Hydrogen bond:** ARG 381: sulfonyl oxygen, strong hydrogen bond between the positively charged guanidinium group of ARG 381 and the negatively charged sulfonyl oxygen. **Hydrophobic and aromatic interactions:** PHE 105, PHE 463: π–π interactions or hydrophobic stabilization. TYR 118, TYR 132: hydrophobic enclosure near binding cavity, LEU 376, LEU 370: shape complementarity and hydrophobic packing, MET 374, PRO 373, PRO 462, ILE 379: hydrophobic environment for the linker and tail.

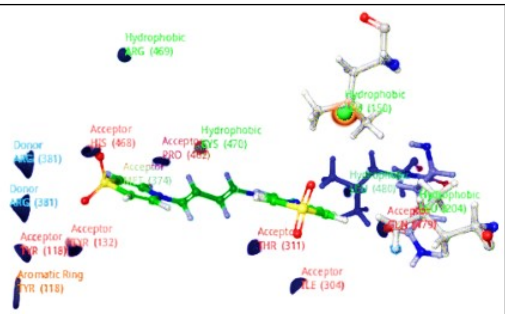
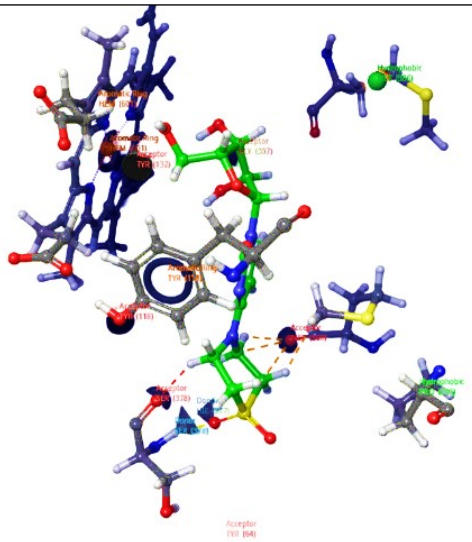
5f		**Hydrogen bonds:** HIE 377 → sulfonyl oxygen, classic hydrogen bonding interaction. stabilizes the sulfonamide moiety. SER 378 → sulfonyl oxygen hydrogen bond reinforcing the sulfonyl group anchoring. THR 122 → terminal Amine group (–NH_2) TYR 118 → terminal Amine group. **Hydrophobic and van der Waals interactions:** PHE 233, PHE 228, PHE 187: π-π stacking or hydrophobic interaction with aromatic rings, LEU 121, LEU 189, LEU 379: general hydrophobic pocket stabilization, ILE 131, ILE 379, ILE 471: contributes to a snug fit and hydrophobic enclosure, VAL 509, MET 508: terminal region of the ligand.
5g		**Hydrogen Bonds:** THR 122, SER 378, TYR 132. **Hydrophobic interactions:** TYR 118, LEU 121, ILE 131, ILE 379, PHE 233, PHE 380, PRO 230, PHE 228, LEU 376, HIE 377, VAL 509, MET 508. **Aromatic & π-interactions:** PHE 380 and PHE 233

Table S3. Antimicrobial activity prediction for previously synthesized heteroaromatic-derived-β-amino sulfones compounds against 5V5Z.

Compounds	Binding affinities PDB ID: 5V5Z (kcal/mol)	Binding affinities PDB ID: 1KZN (kcal/mol)
5h	-5.15	-4.34
5i	-5.23	-5.06
5j	-6.01	-5.33
5k	-6.34	-5.60
5l	-5.46	-4.79
5m	-6.02	-5.01
5n	-5.74	-4.14
5o	-5.36	-5.30
5p	-5.81	-5.06
5q	-5.62	-4.68
5r	-5.81	-4.66
5s	-6.34	-5.76
5t	-6.23	-4.90
5u	-6.77	-5.10
5v	-6.45	-5.34
5w	-6.73	-5.89
5x	-6.10	-5.39
5y	-5.16	-4.22

Table S4. Antimicrobial activity prediction for synthesized benzothiazole-derived/biogenic amines-derived-β-amino sulfones against 1KZN.

Compound no.	Binding affinities PDB ID: 1KZN (kcal/mol)	Compound no.	Binding affinities PDB ID: 1KZN (kcal/mol)
3a	-5.19	**5a**	-5.45
3b	-5.37	**5b**	-4.97
3c	-5.38	**5c**	-5.47
3d	-5.59	**5d**	-4.04
3e	-4.80	**5e**	-5.17
3f	-4.67	**5f**	-4.52
3g	-4.79	**5g**	-5.47
3h	-5.63		
3i	-5.01		
3j	-4.52		
3k	-4.61		
3l	-4.76		
3m	-3.96		

Figure S1. A typical image of the spot-test inhibition assay of selected compounds against *Candida glabrata* (Cg 2001/-). The concentration of compounds is 2 mg/mL.

Table S5. In vitro antifungal activities of compounds **5h-5y** (MIC, μM).

Compound	*C. alb.*	*C. gla.*	*C.tro.*
5h	0.301	0.150	0.301
5i	0.282	0.141	0.282
5j	0.301	0.150	0.301
5k	0.30	0.30	0.30
5l	0.254	0.127	0.254
5m	0.281	0.281	0.281
5n	0.281	0.281	0.281
5o	0.281	0.281	0.281
5p	0.284	0.142	0.284
5q	0.284	0.142	0.284
5r	0.284	0.142	0.284
5s	0.139	0.139	0.139
5t	0.139	0.139	0.139
5u	0.250	0.250	0.250
5v	0.250	0.250	0.250
5w	0.252	0.252	0.252
5x	0.252	0.252	0.252
5y	0.238	0.119	0.238

Abbreviations: *C. alb*., *Candida albicans* (SC 5314); *C. gla*., *Candida glabrata* (Cg 2001/-); *C. tro.*, *Candida tropicalis* (Ct 750/-), Standards: Fluconazole = 8 μg/mL (0.0261 μM) for *C. alb*., 16 μg/mL (0.052 μM) for *C. gla.,* and 4 μg/mL (0.013 μM) for *C. tro.* Amphoterin B = 0.5 μg/mL (0.0001 μM) for *C. alb*., and 1 μg/mL (0.001 μM) for *C. gla., C. tro.*

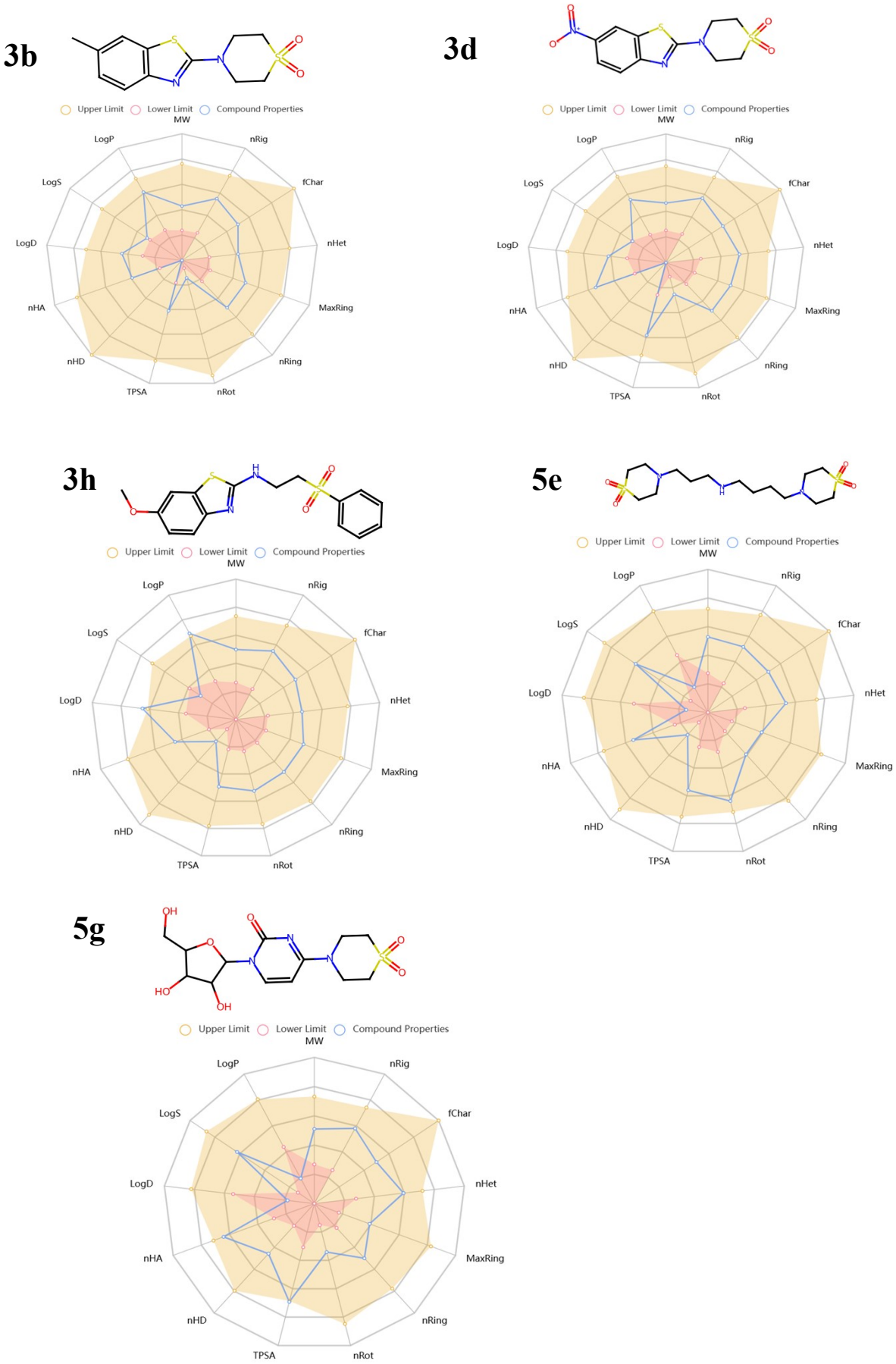


Figure S2: ADMET pharmacokinetics features for **3b, 3d, 3h, 5g, 5e** in radar plot.

SEM analysis

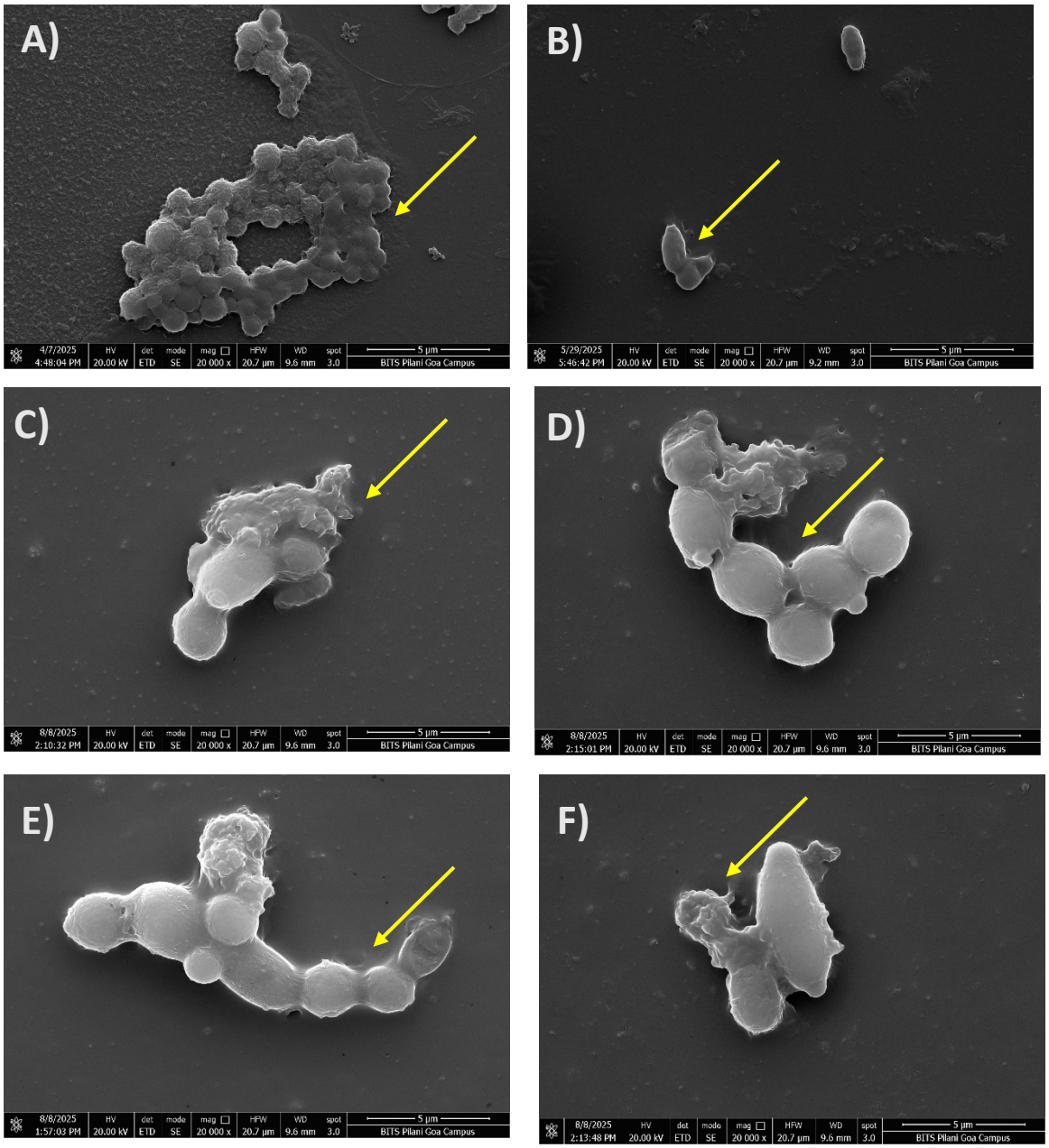


Figure S3. SEM images illustrate pronounced morphological alterations in *Candida* species following treatment with fluconazole (positive control) and compounds. (A) treated with fluconazole (positive control) at 16 µg/mL (0.052 µM), for *C. gla.,* (B) treated with fluconazole (positive control) at 4 µg/ml (0.013 µM) for *C. tro.,* (C) treated with **3h** at 32 µg/mL (0.096 µM), for *C. gla.,* (D) treated with **5g** at 32 µg/mL (0.088 µM), for *C. gla.,* (E) treated with **3h** at 32 µg/mL (0.091 µM), for *C. tro.,* (F) treated with **5g** at 32 µg/mL (0.088 µM), for *C. tro.*

Analysis of the components of *Candida* cells

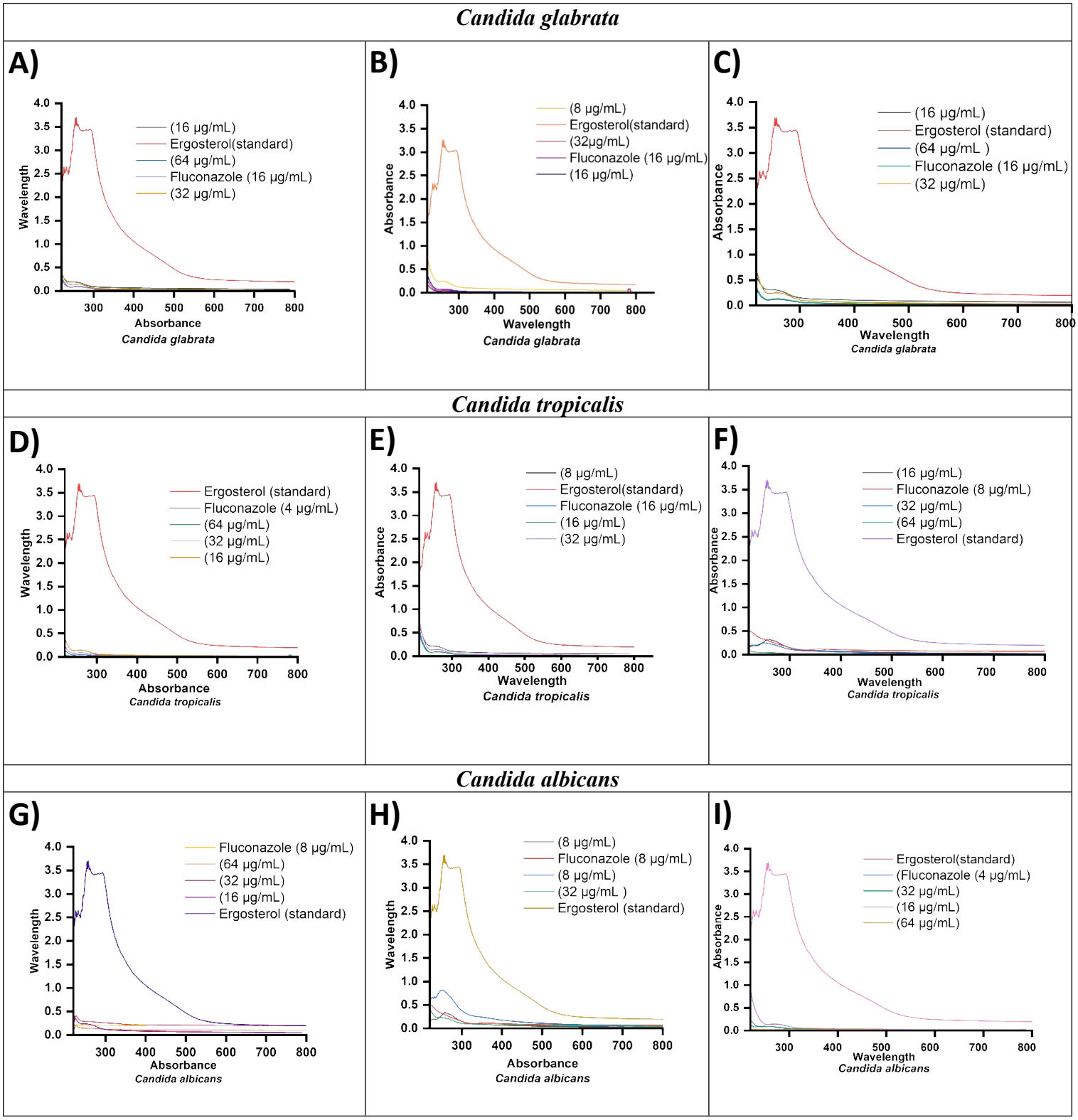


Figure S4. UV spectrophotometric sterol profiles of representative compound **5e, 3d, 3c:** A, B, C**;** *Candida glabrata,* D, E, F**;** *Candida tropicalis* G, H, I; *Candida albicans;* Isolates were grown for 16 h in Sabouraud dextrose broth containing ergosterol, fluconazole, 8, 16, and 32 µg/mL for **3d** and 16, 32 and 64 µg/mL for **3c** and **5e** and spectral profiles between 200 and 800 nm were determined.

Table S6. %Ergosterol biosynthesis in *Candida glabrata* isolates by fluconazole and representative

Compd →	3c		3d		5e		Fluconazole	
µg/mL ↓	mean ± SD	% ergosterol	mean ± SD	% ergosterol	mean ± SD	% ergosterol	mean ± SD	% ergosterol
8	-	-	0.0155 ± 0.0009	11.3	-	-	0.0029 ± 0.0001	2.11
16	0.0062 ± 0.0006	4.52	0.0065 ± 0.0005	4.74	0.0065 ± 0.0030	4.74	0.0027 ± 0.00006	1.99
32	0.0036 ± 0.0011	2.62	0.0040 ± 0.0010	2.91	0.0040 ± 0.0025	2.92	0.0019 ± 0.0009	1.38
64	0.0022 ± 0.0012	1.62	-	-	0.0022 ± 0.00122	1.78	-	-

compounds **3c, 3d, 5e,** fluconazole at 290 nm

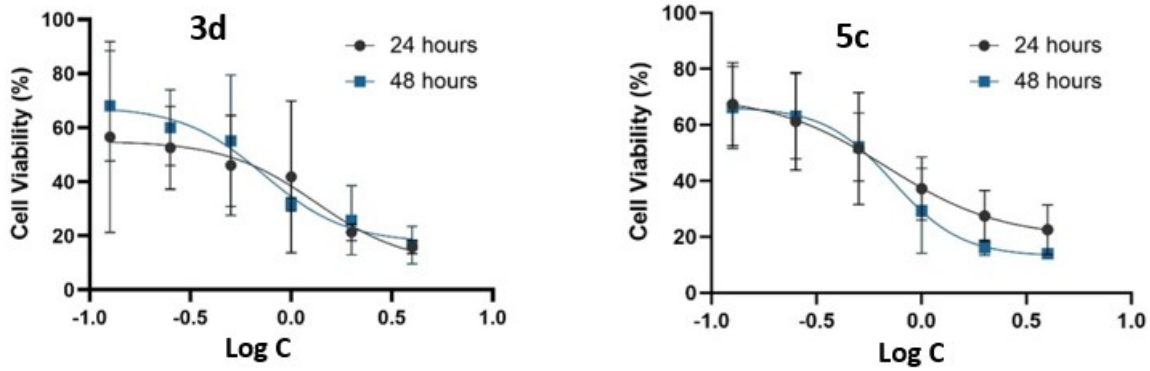
[a]The absorbance data represent the mean value of three independent replicas. [b]The absorbance of our standard ergosterol was 0.137 at 290 nm, which corresponds to 100 % of ergosterol.

Table S7. %Ergosterol biosynthesis in *Candida albicans* isolates by fluconazole and representative

Compd →	3c		3d		5e		Fluconazole	
µg/mL ↓	mean ± SD	% ergosterol	mean ± SD	% ergostero	mean ± SD	% ergosterol	mean ± SD	% ergosterol
8	-	-	0.1320 ± 0.008	96.28	-		0.0029 ± 0.0001	2.11
16	0.0880 ± 0.0125	64.18	0.0801 ± 0.010	58.35	0.0863 ± 0.010	62.94	0.0027 ± 0.0001	1.99
32	0.0261 ± 0.0078	19.03	0.0189 ± 0.005	13.78	0.0270 ± 0.021	19.69	0.0019 ± 0.0009	1.38
64	0.0133 ± 0.0057	9.72	-	-	0.0066 ± 0.002	4.81	-	-

compounds **3c, 3d, 5e,** fluconazole at 290 nm

[a]The absorbance data represent the mean value of three independent replicas. [b]The absorbance of our standard ergosterol was 0.137 at 290 nm, which corresponds to 100 % of ergosterol.



Compound no.	IC_{50} (μM)	MIC (μM)	Selectivity Index (SI)
3d	1.088	0.051	21.2
5e	0.457	0.083	5.5

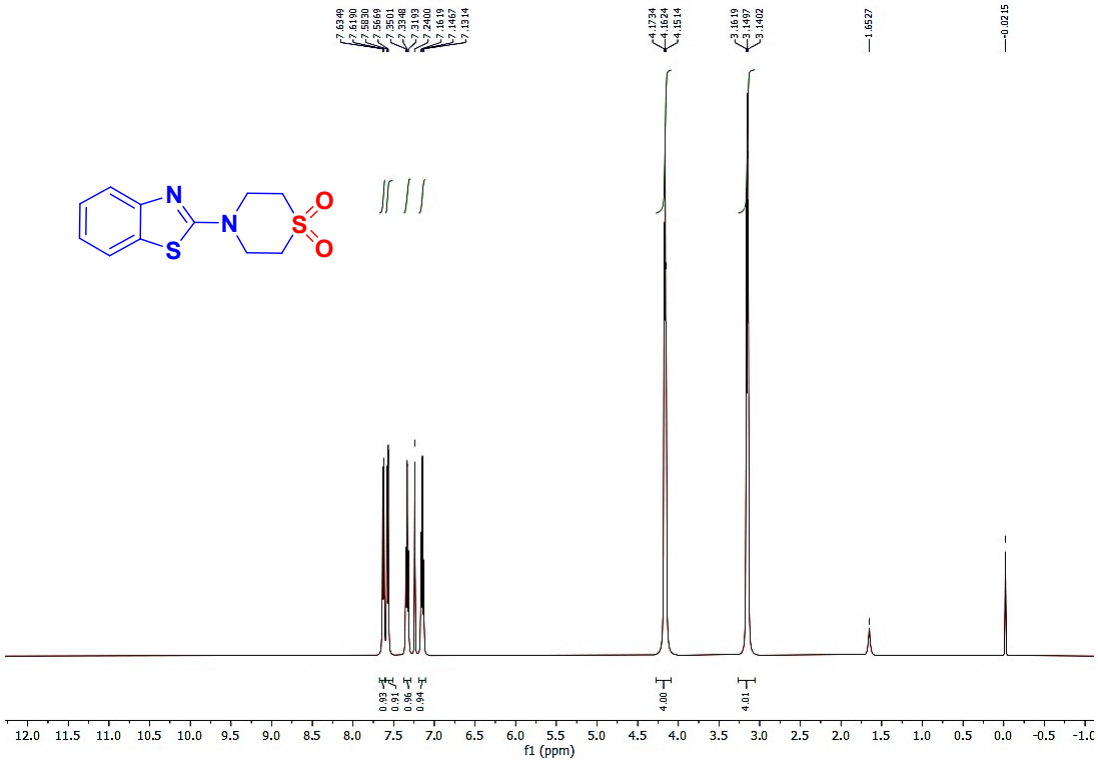
Figure S5. The cell viability against concentration plots (LogC in μM) to determine the IC_{50} values of compounds **3d** and **5e**. SI is calculated by dividing the IC_{50} value at 24 h by the MIC of the corresponding compound against *C albicans*.

References

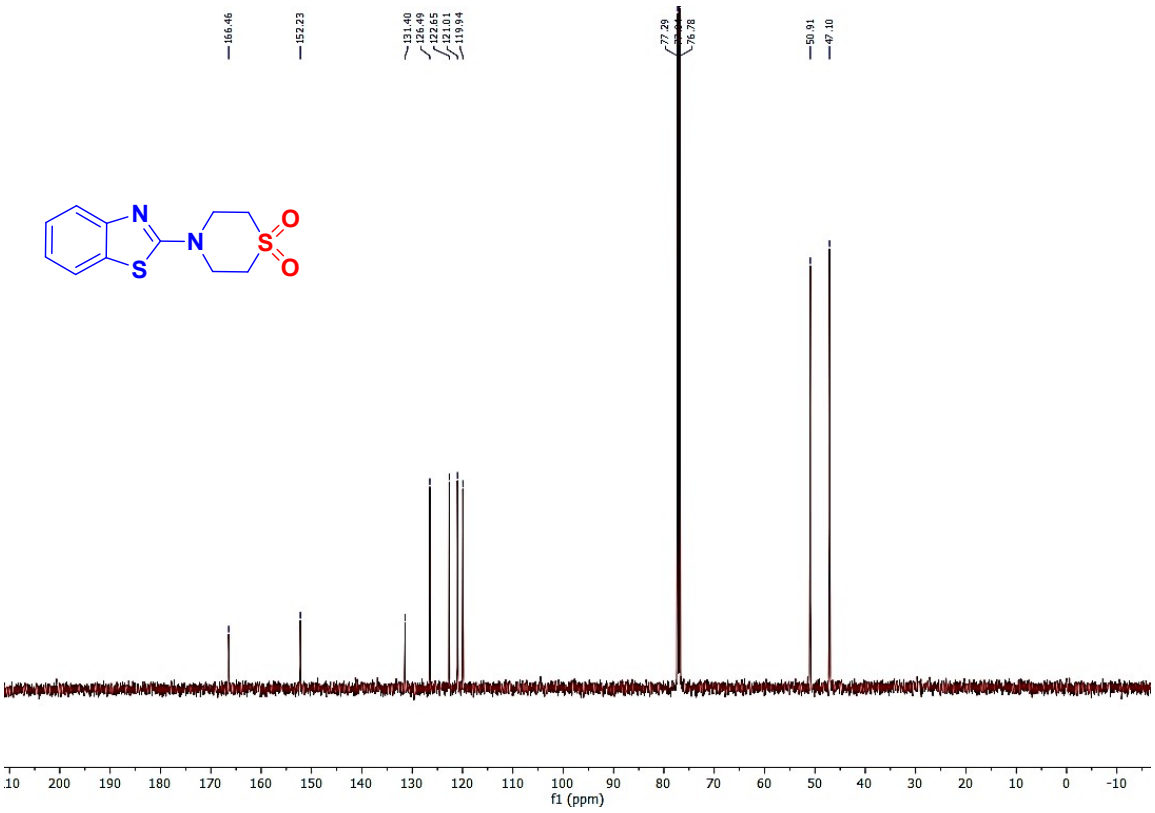
1. S. Saha, A. Chatterjee, and M. Banerjee, Reagentless Chemistry "On-Water: An Atom-Efficient and "Green" Route to Cyclic and Acyclic β-Amino Sulfones via Aza-Michael Addition Using Microwave Irradiation. *J. Org. Chem.*, 2023, **88**, 15358–15366.

Copies of NMR spectra

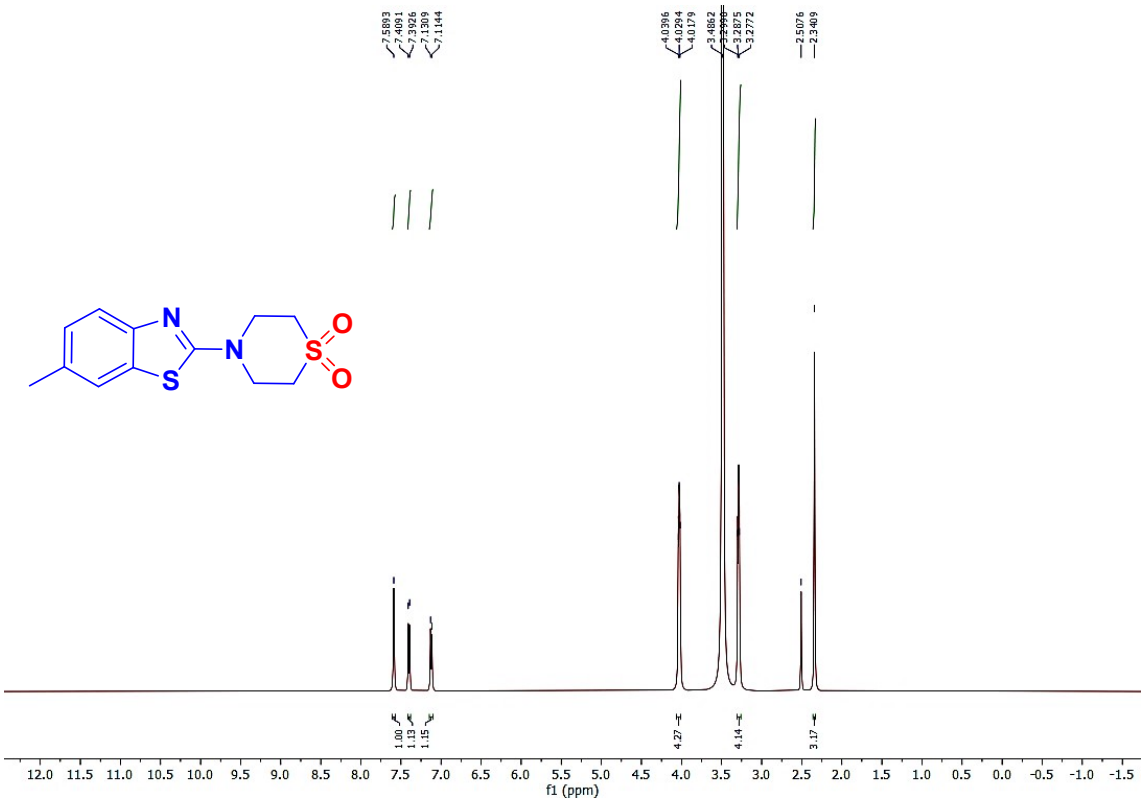
^{1}H NMR spectrum of compound **3a**, ($CDCl_3$, 500 MHz).



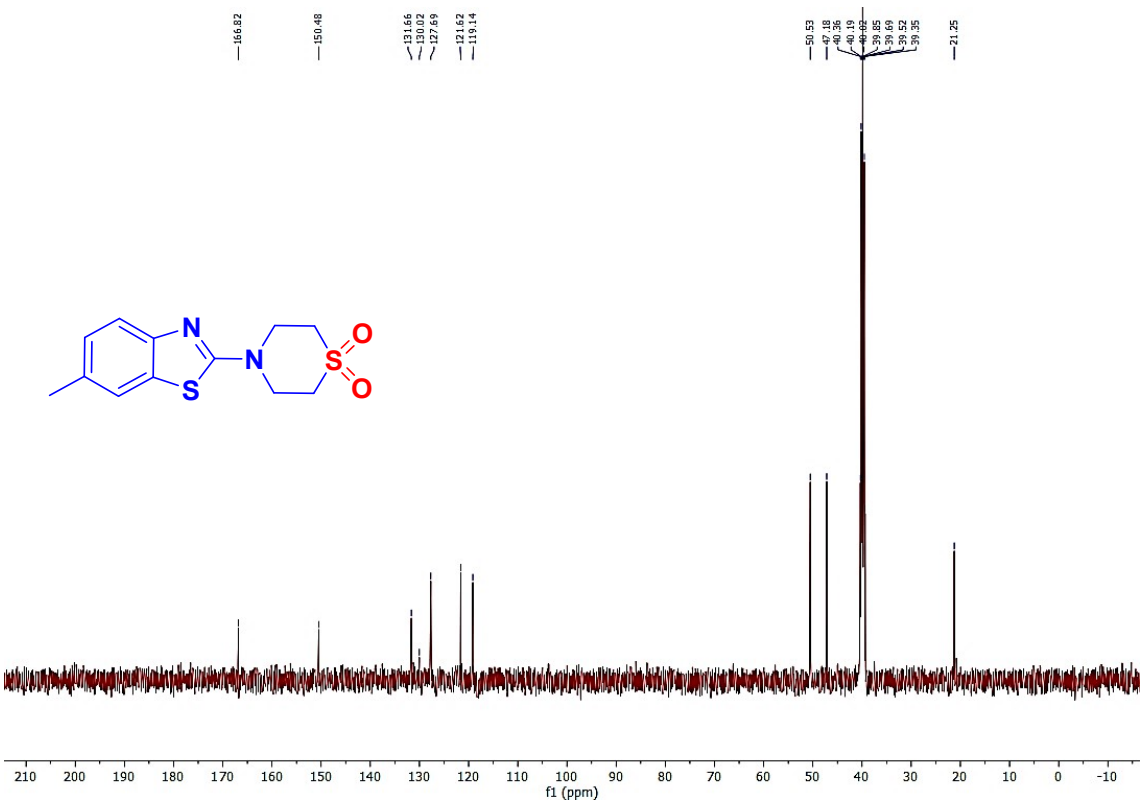
^{13}C NMR spectrum of compound **3a**, ($CDCl_3$, 125 MHz).



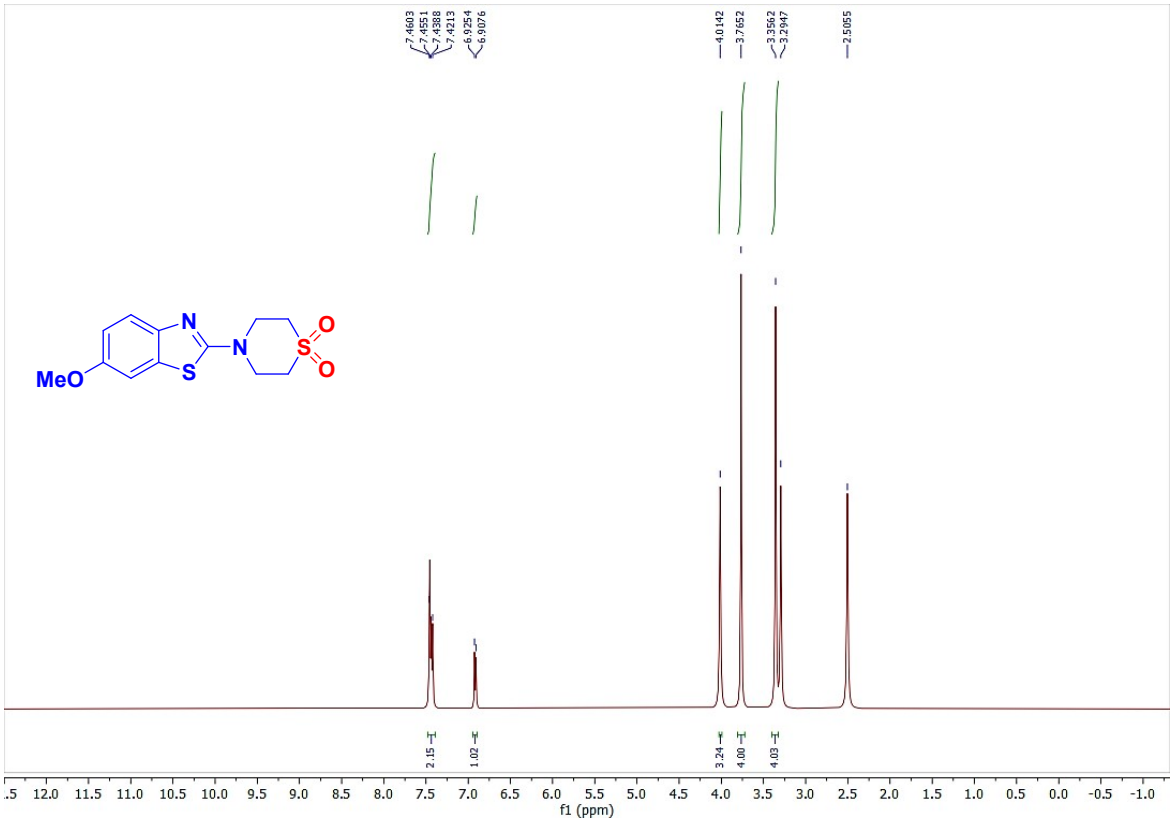
^{1}H NMR spectrum of compound **3b**, (DMSO-d_6, 500 MHz).



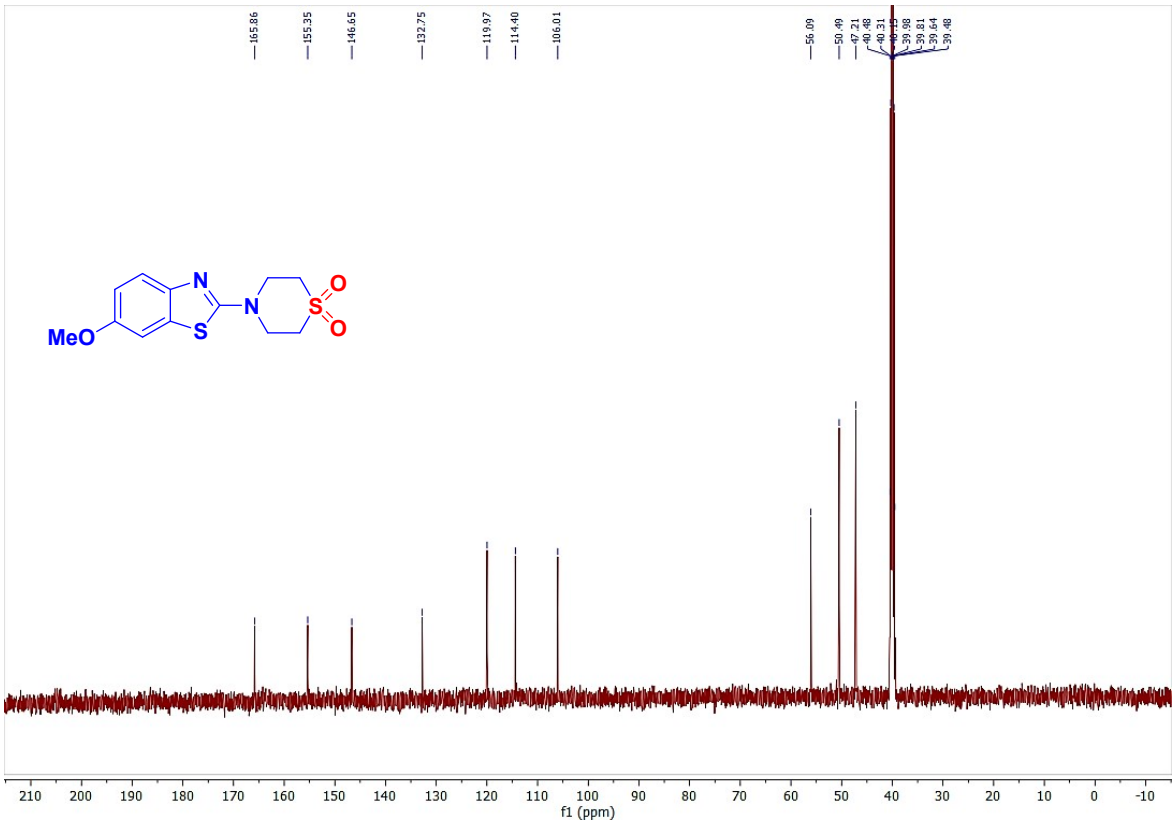
^{13}C NMR spectrum of compound **3b**, (DMSO-d_6, 125 MHz).



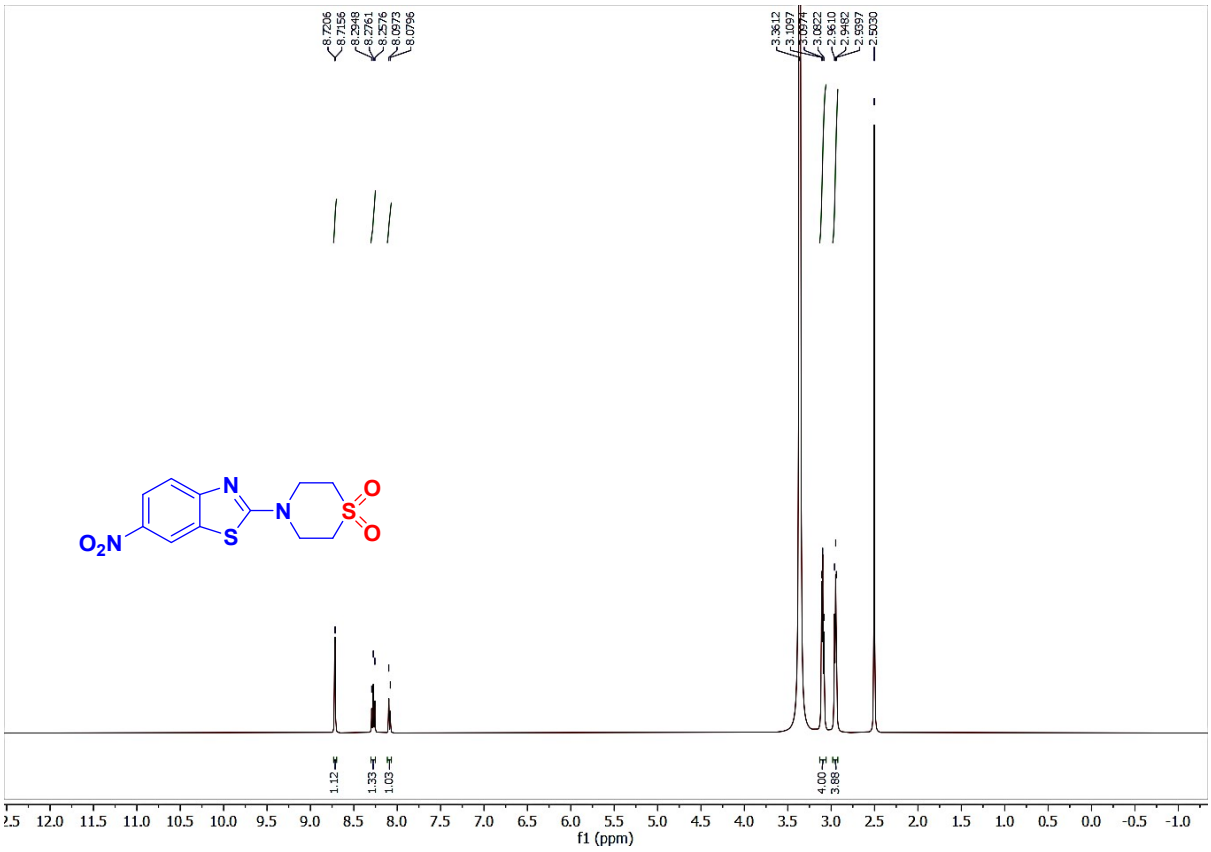
^{1}H NMR spectrum of compound **3c**, (DMSO-d_6, 500 MHz).



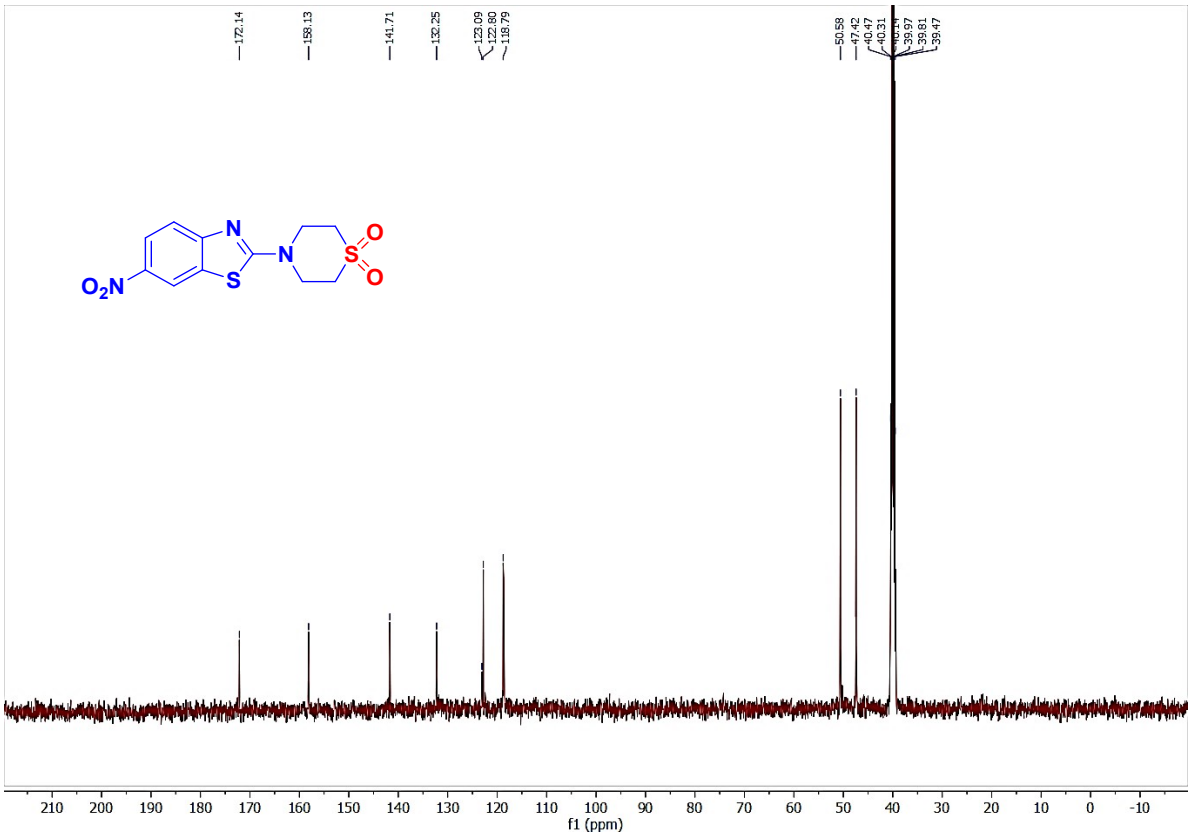
^{13}C NMR spectrum of compound **3c**, (DMSO-d_6, 125 MHz).



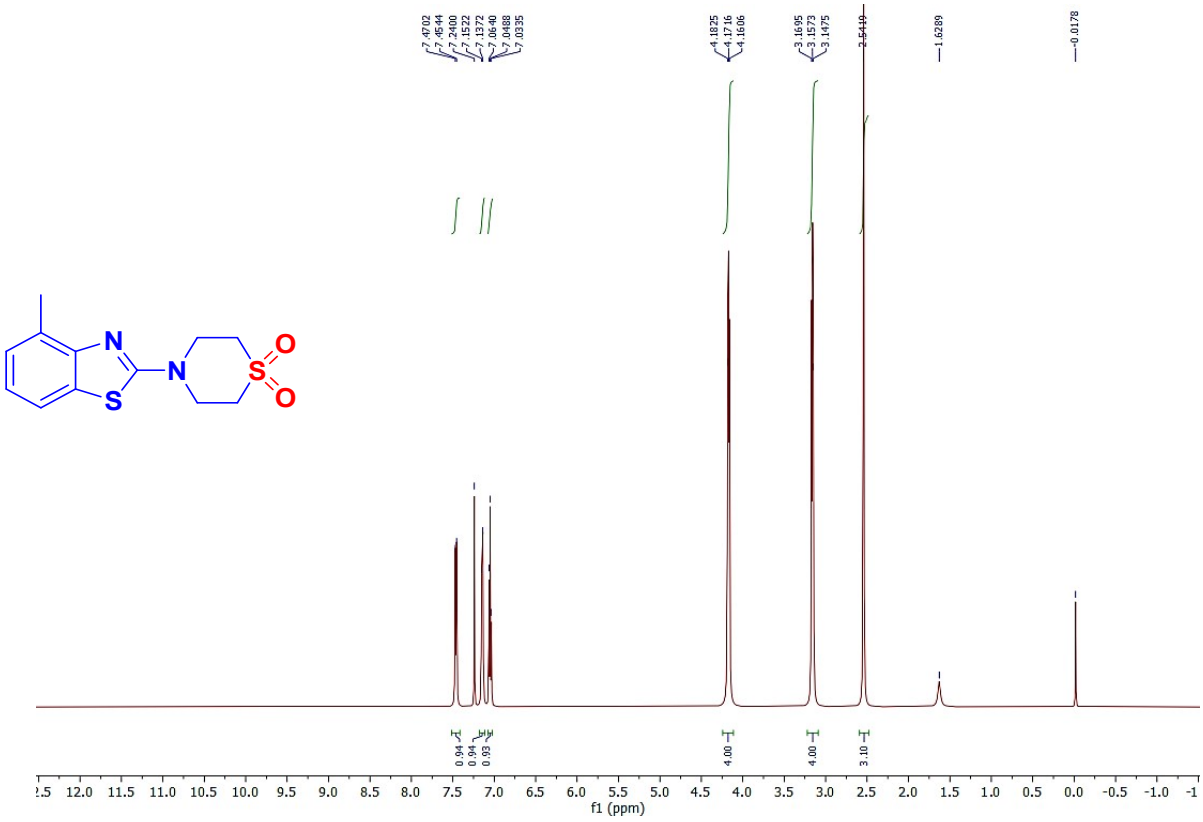
^{1}H NMR spectrum of compound **3d**, (DMSO-d_6, 500 MHz).



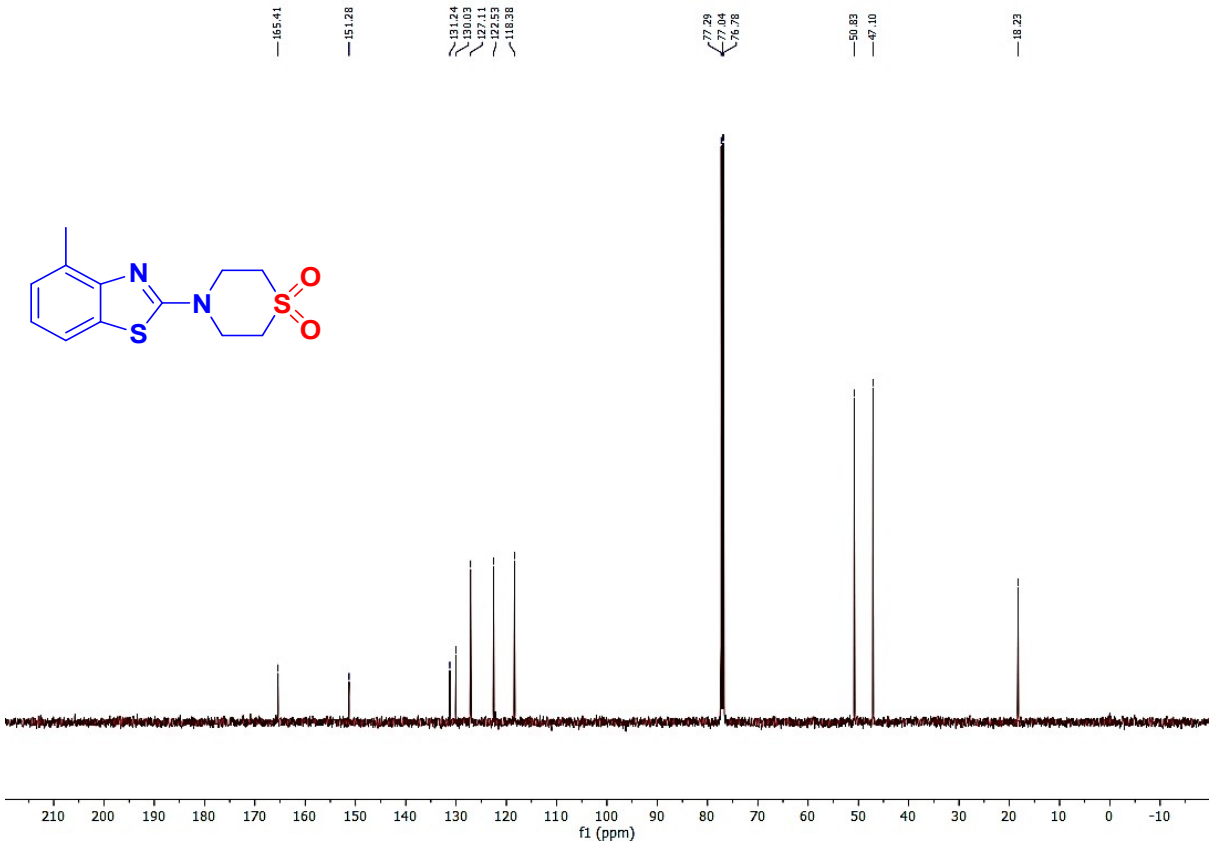
^{13}C NMR spectrum of compound **3d**, (DMSO-d_6, 125 MHz).



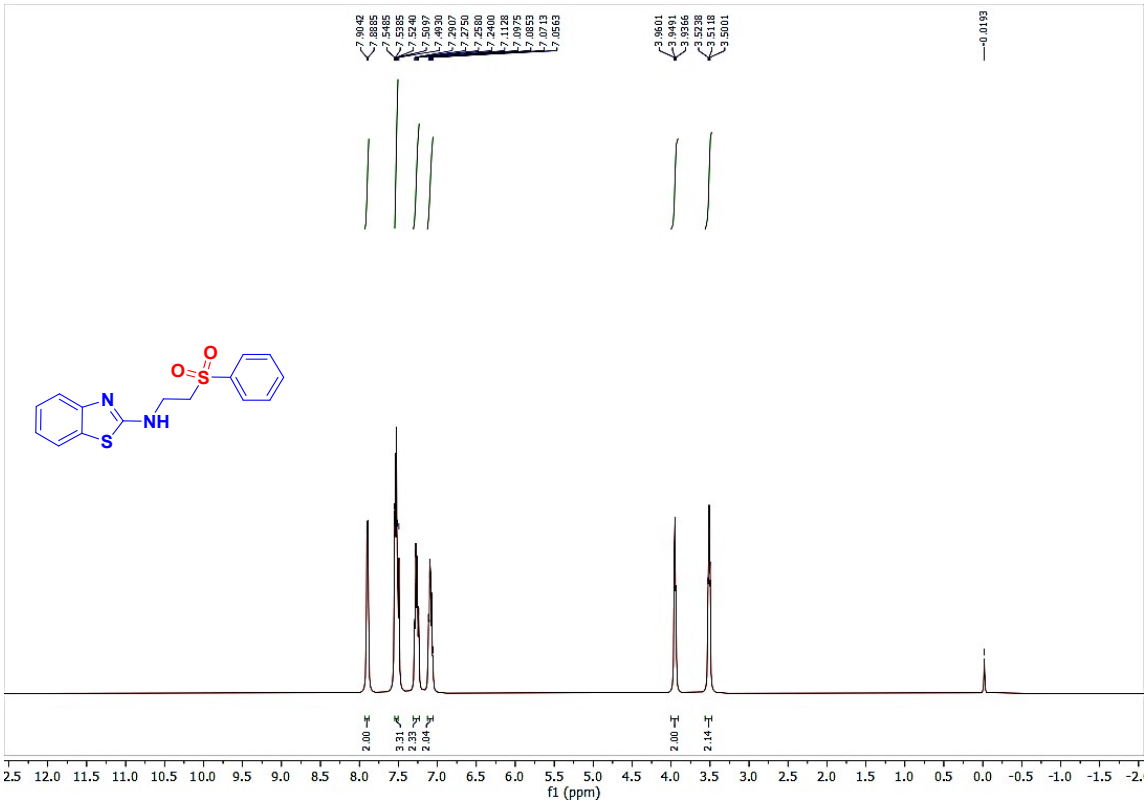
^{1}H NMR spectrum of compound **3e**, ($CDCl_3$, 500 MHz).



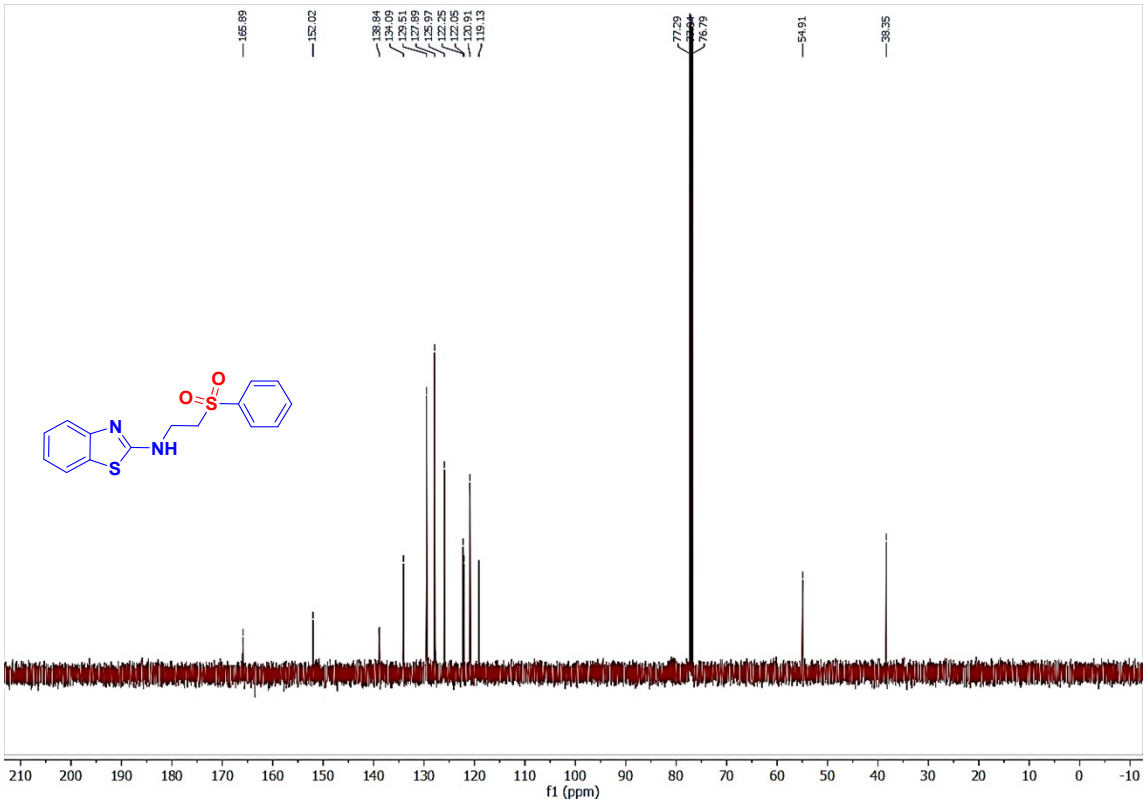
^{13}C NMR spectrum of compound **3e**, ($CDCl_3$, 125 MHz).



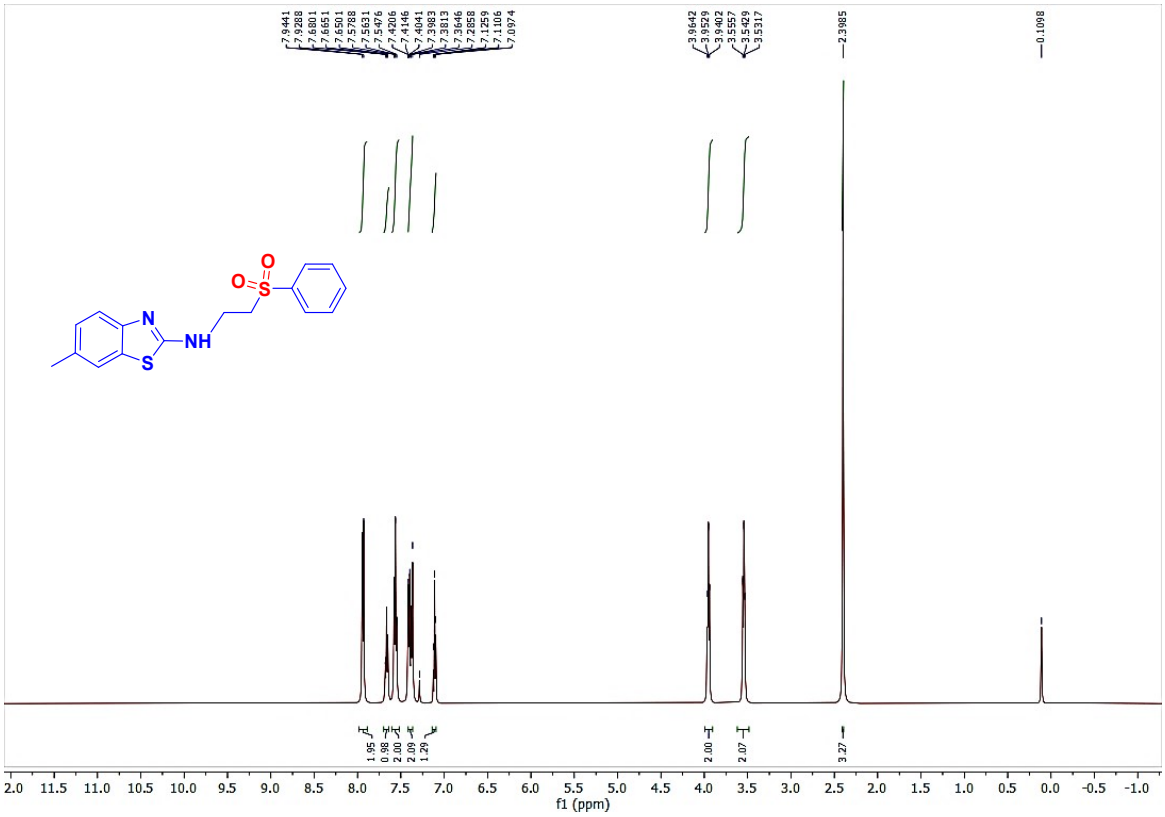
^{1}H NMR spectrum of compound **3f**, ($CDCl_3$, 500 MHz).



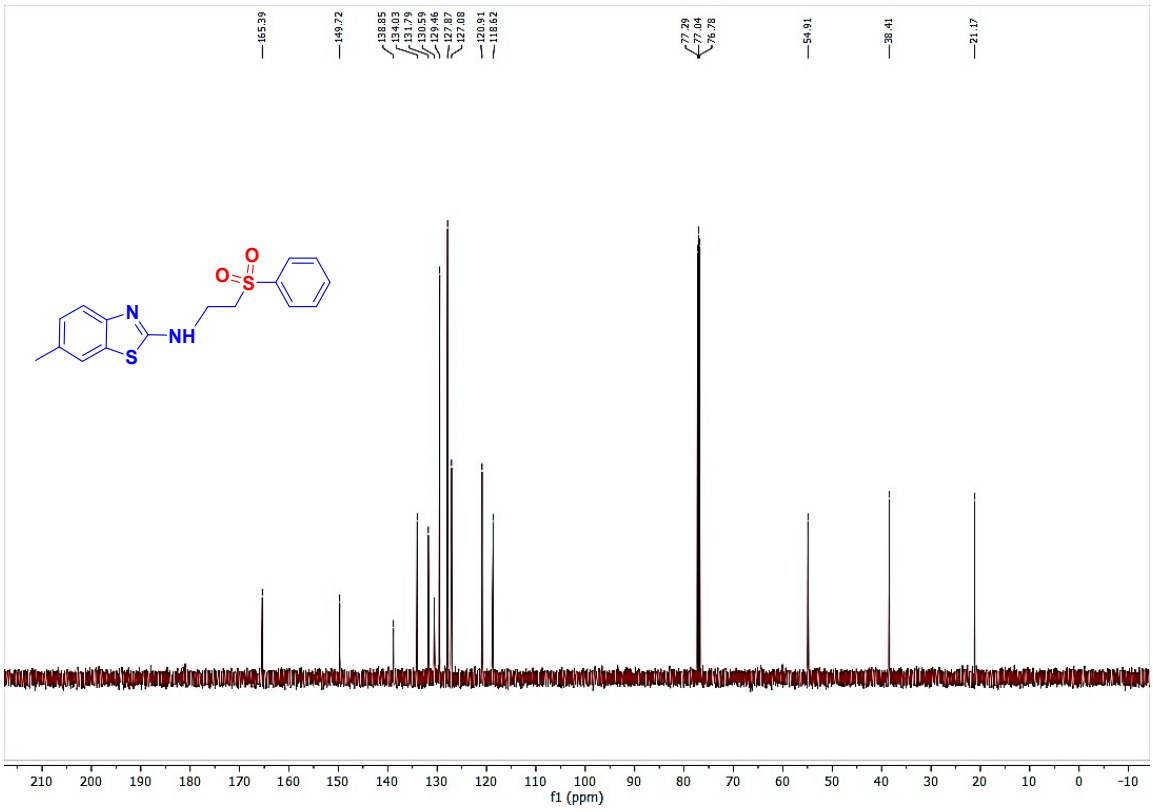
^{13}C NMR spectrum of compound **3f**, ($CDCl_3$, 125 MHz).



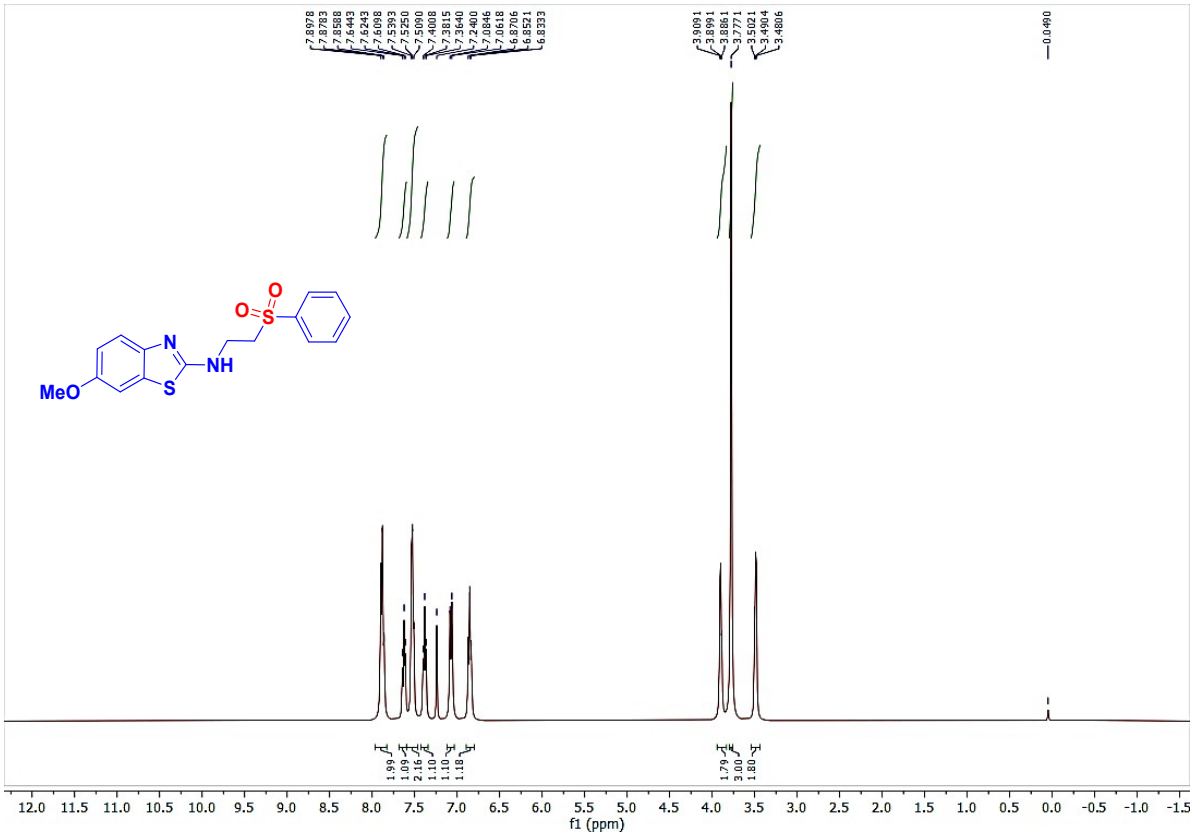
^{1}H NMR spectrum of compound **3g**, ($CDCl_3$, 500 MHz).



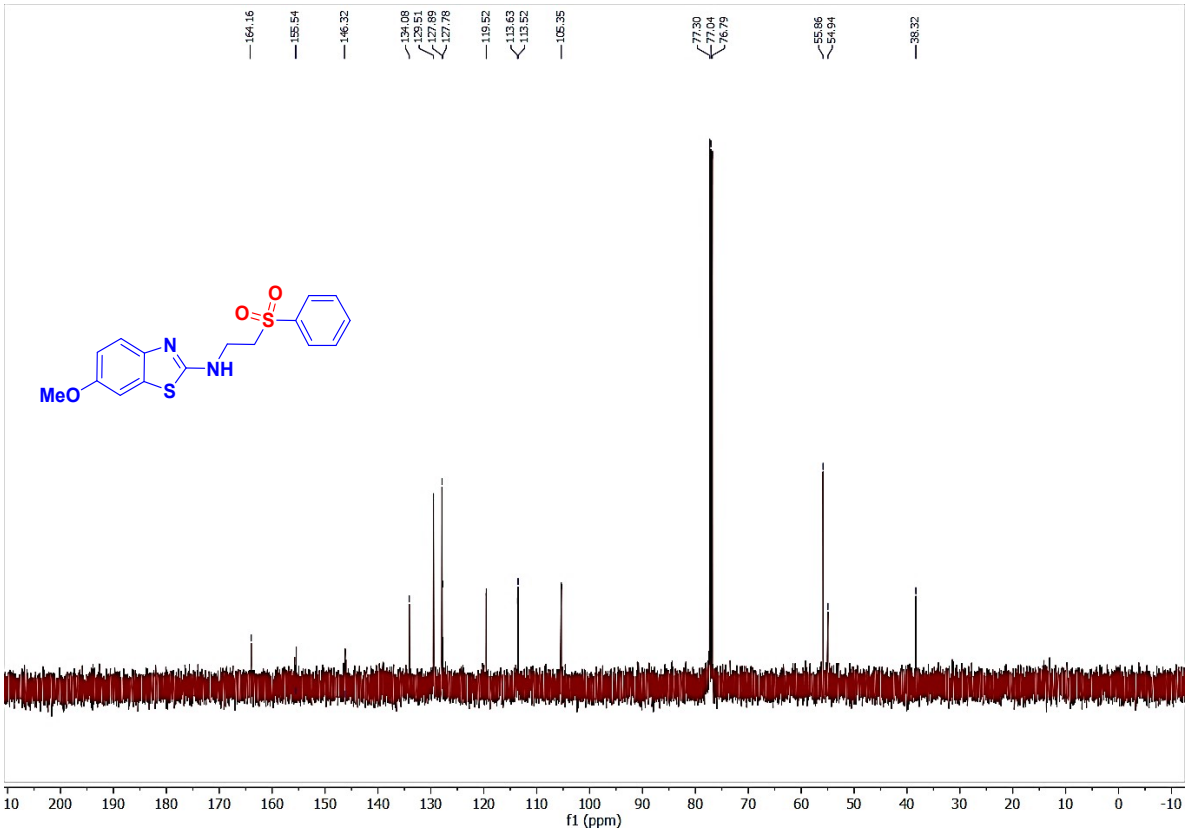
^{13}C NMR spectrum of compound **3g**, ($CDCl_3$, 125 MHz).



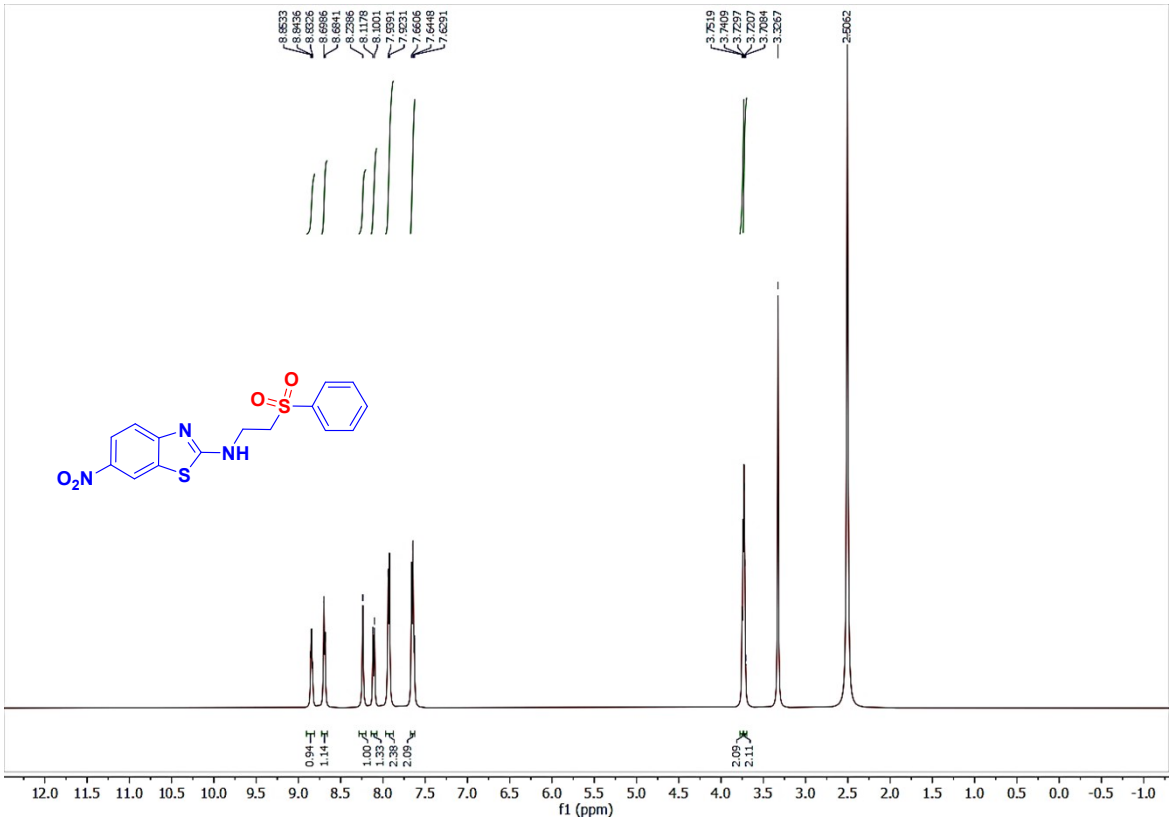
^{1}H NMR spectrum of compound **3h**, ($CDCl_3$, 500 MHz).



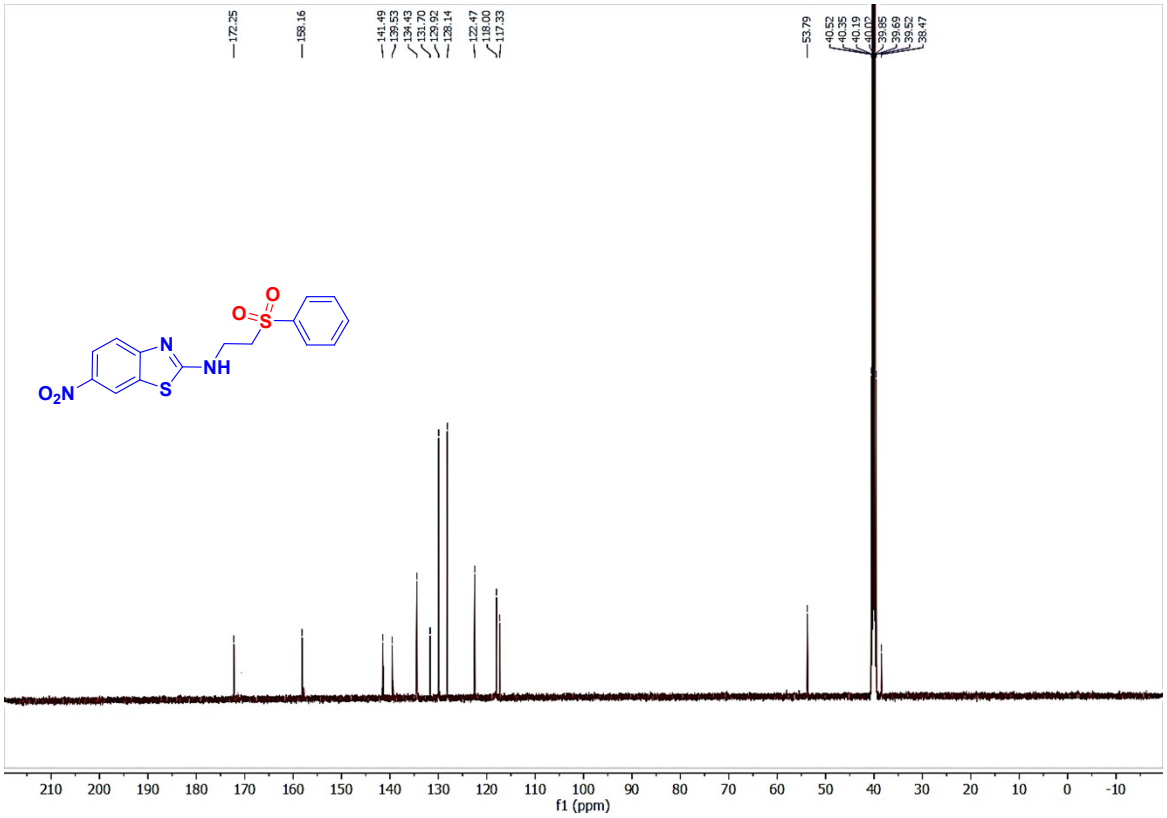
^{13}C NMR spectrum of compound **3h**, ($CDCl_3$, 125 MHz).



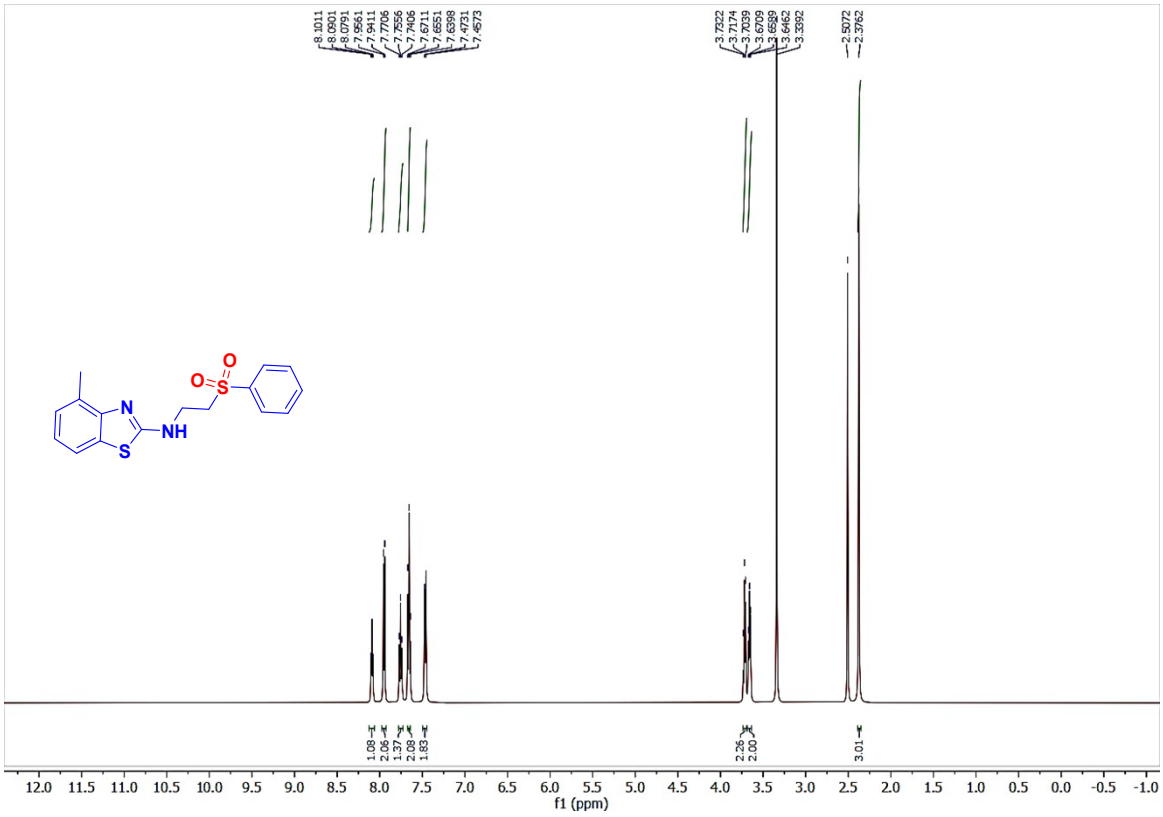
^{1}H NMR spectrum of compound **3i**, (DMSO-d_6, 500 MHz).



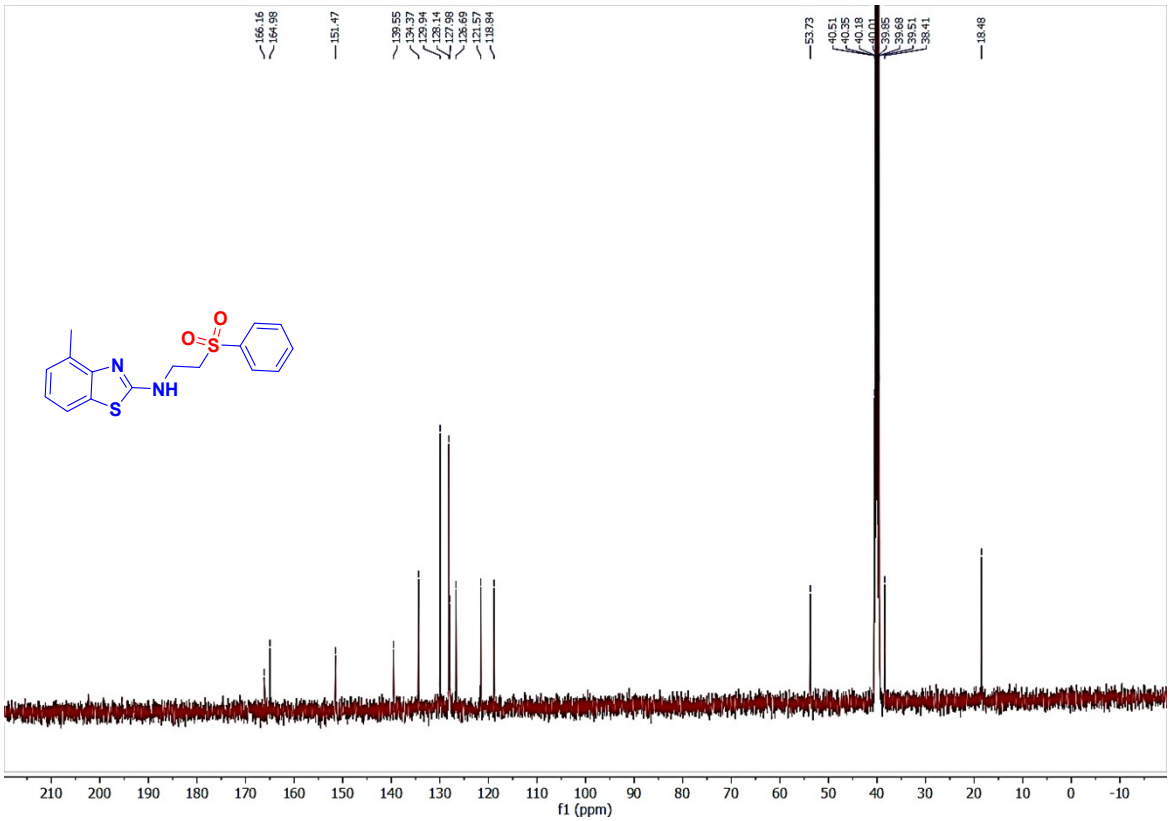
^{13}C NMR spectrum of compound **3i**, (DMSO-d_6, 125 MHz).



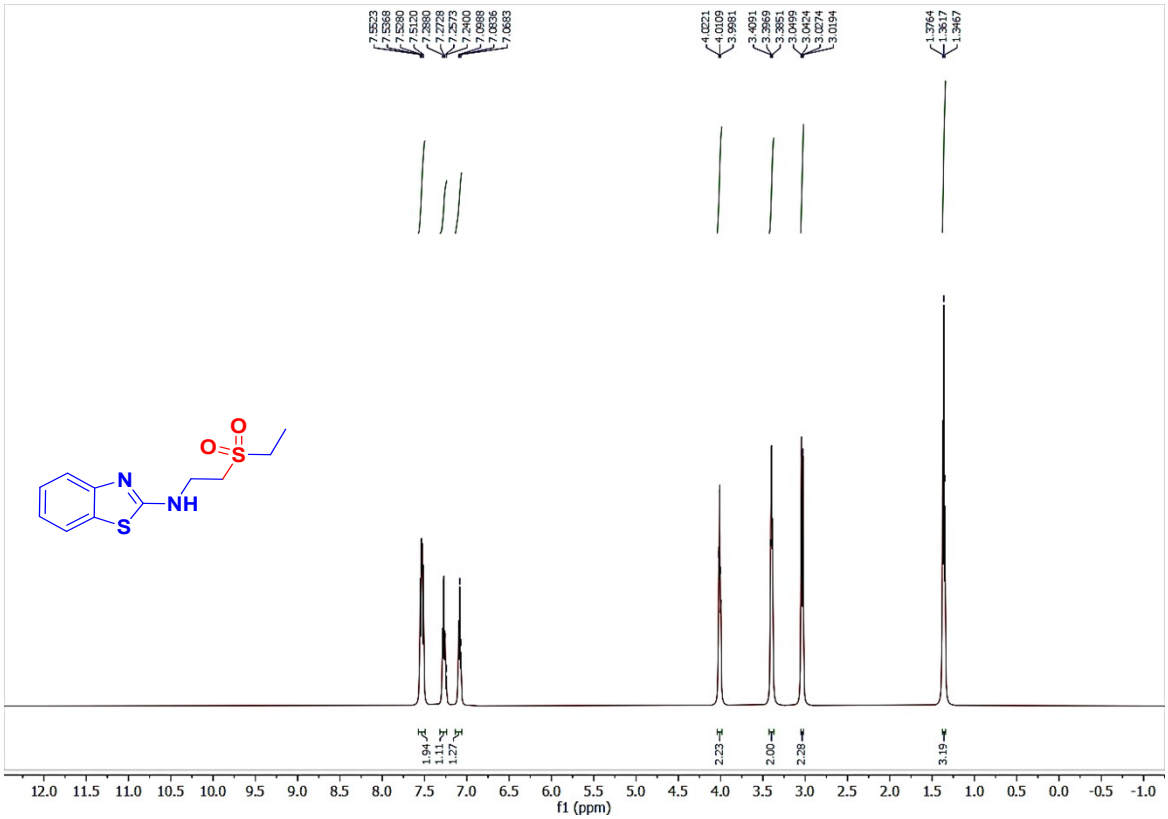
^{1}H NMR spectrum of compound **3j**, (DMSO-d_6, 500 MHz).



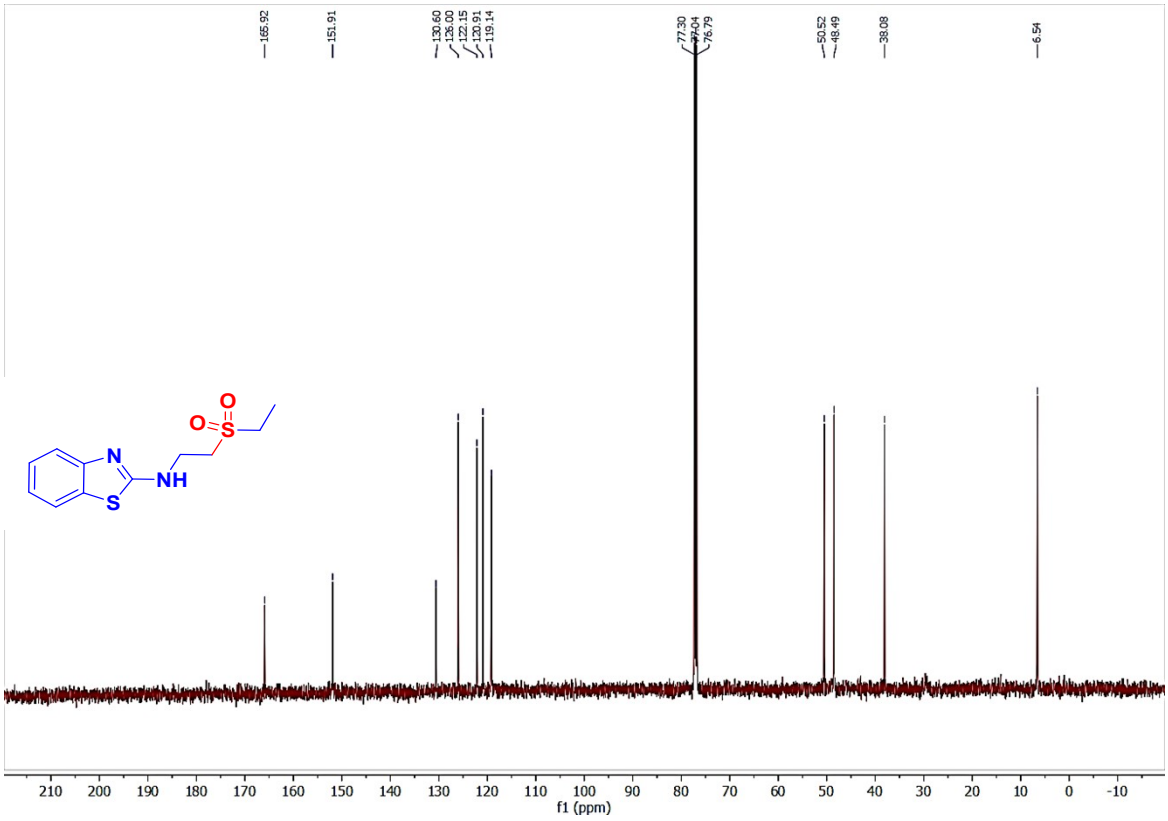
^{13}C NMR spectrum of compound **3j**, (DMSO-d_6, 125 MHz).



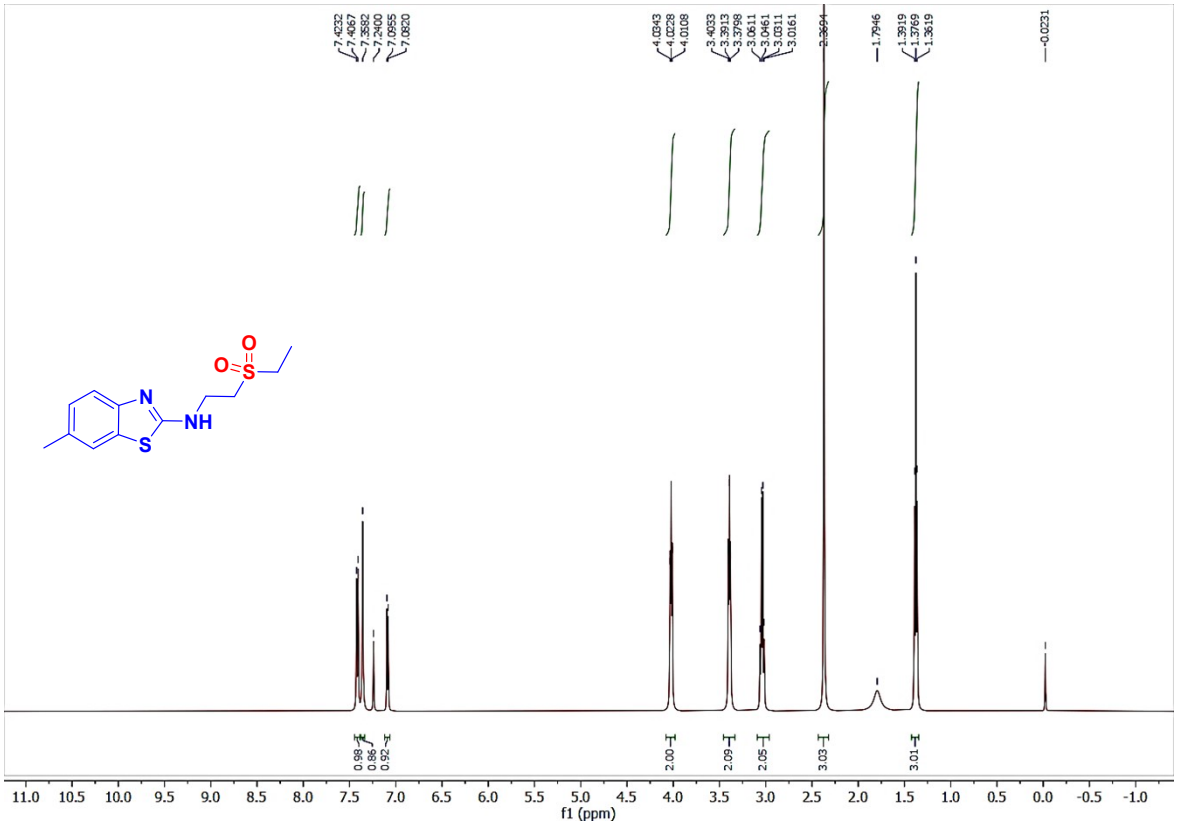
^{1}H NMR spectrum of compound **3k**, ($CDCl_3$, 500 MHz).



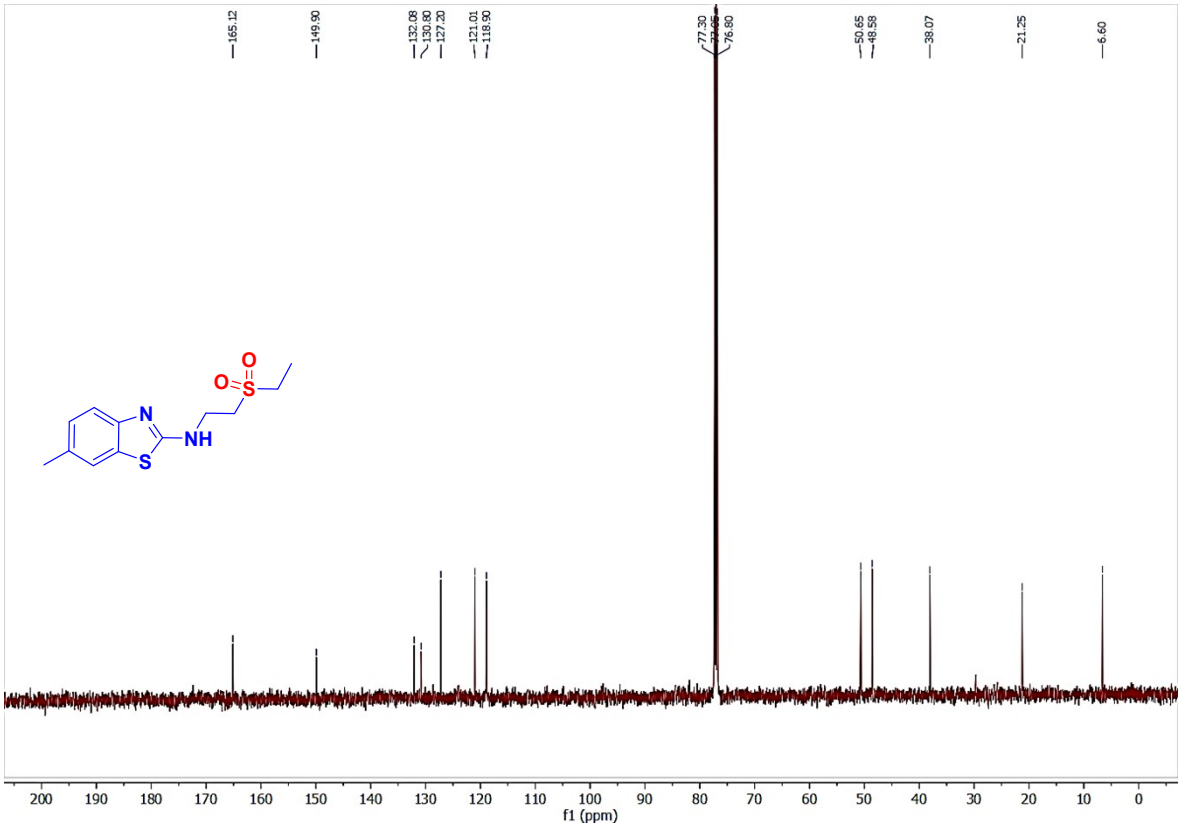
^{13}C NMR spectrum of compound **3k**, ($CDCl_3$, 125 MHz).



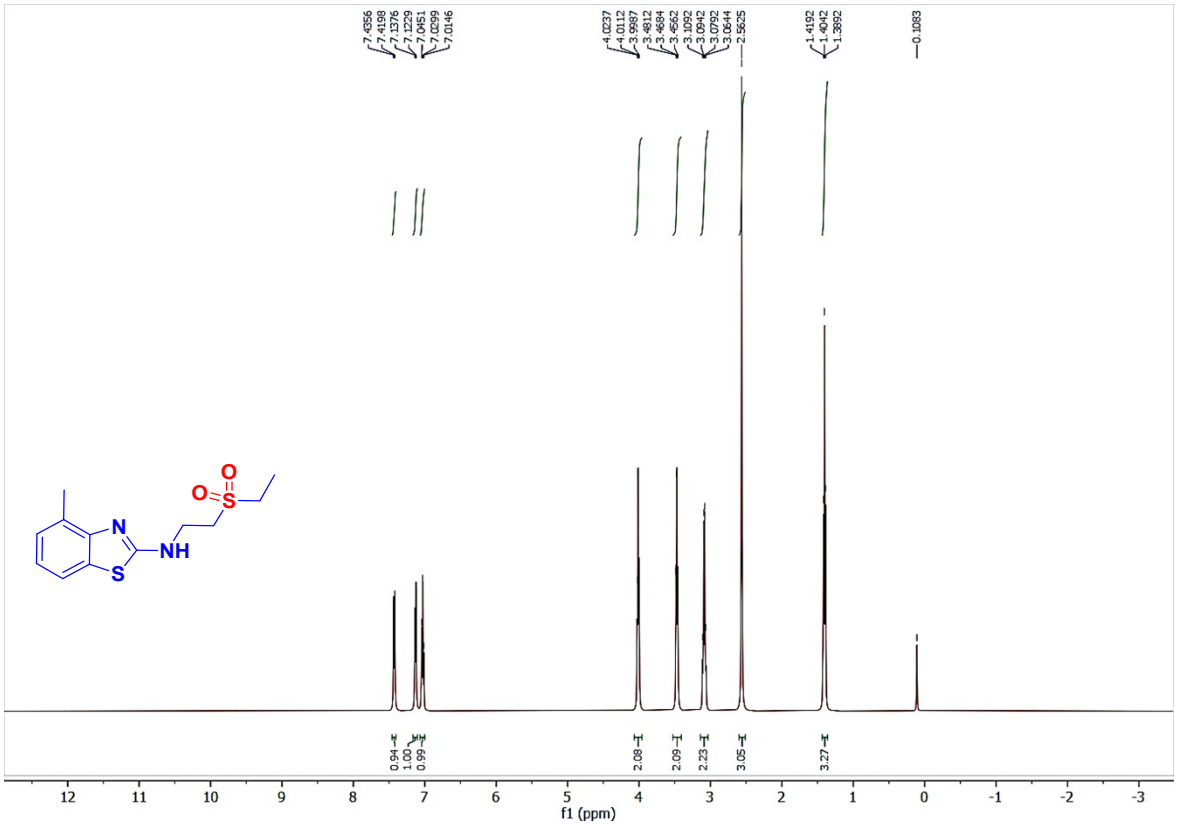
^{1}H NMR spectrum of compound **3l**, ($CDCl_3$, 500 MHz).



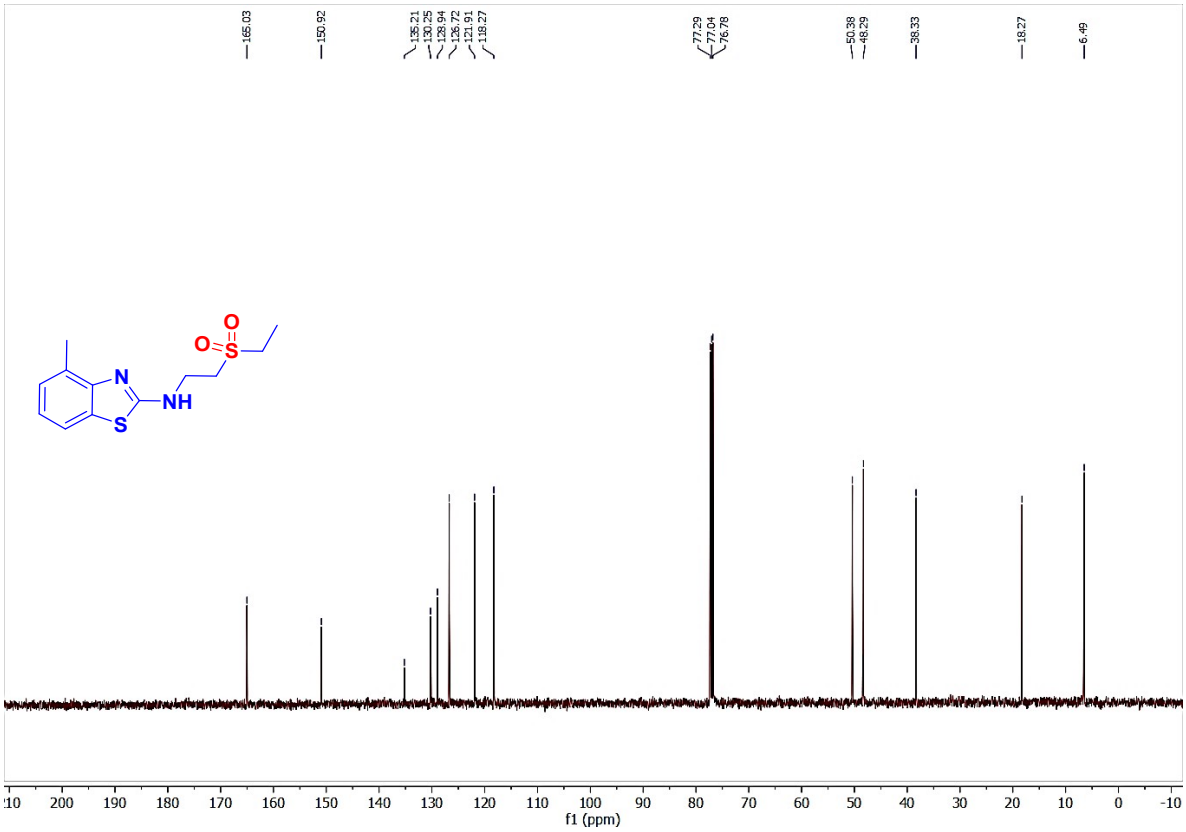
^{13}C NMR spectrum of compound **3l**, ($CDCl_3$, 125 MHz).



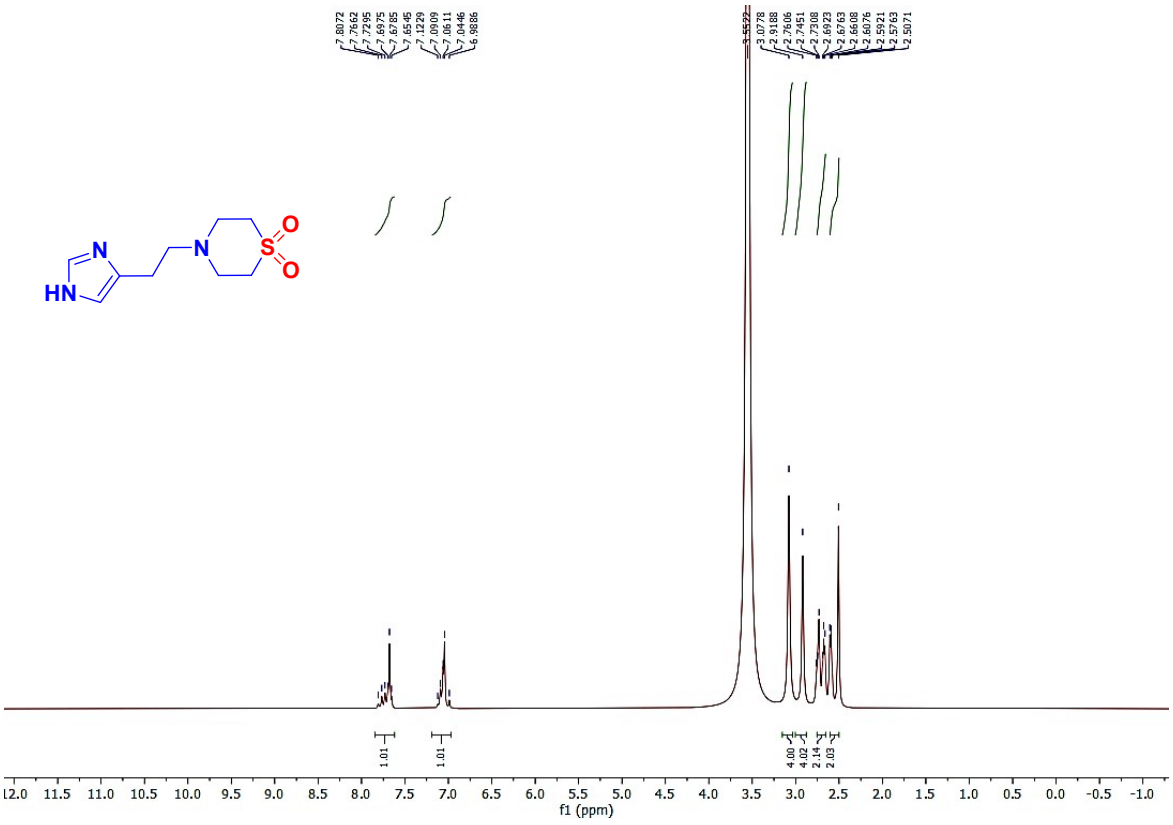
^{1}H NMR spectrum of compound **3m**, ($CDCl_3$, 500 MHz).



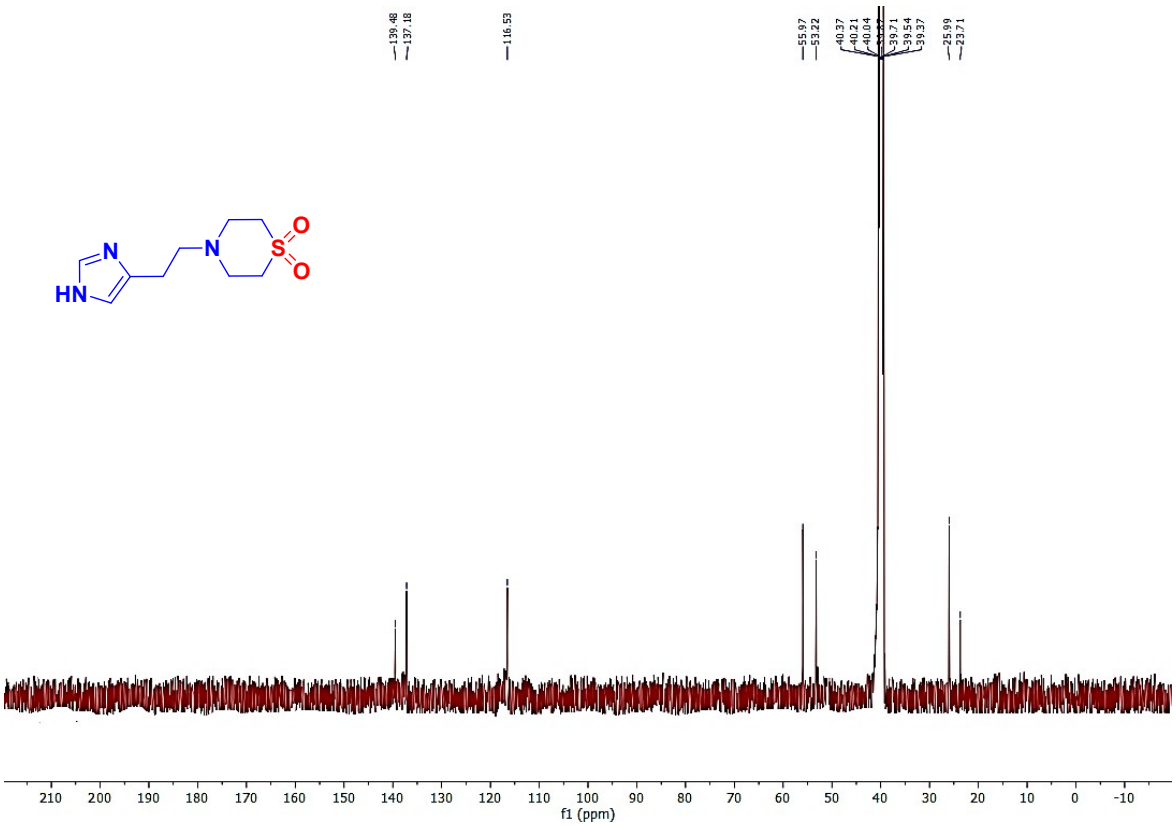
^{13}C NMR spectrum of compound **3m**, ($CDCl_3$, 125 MHz).



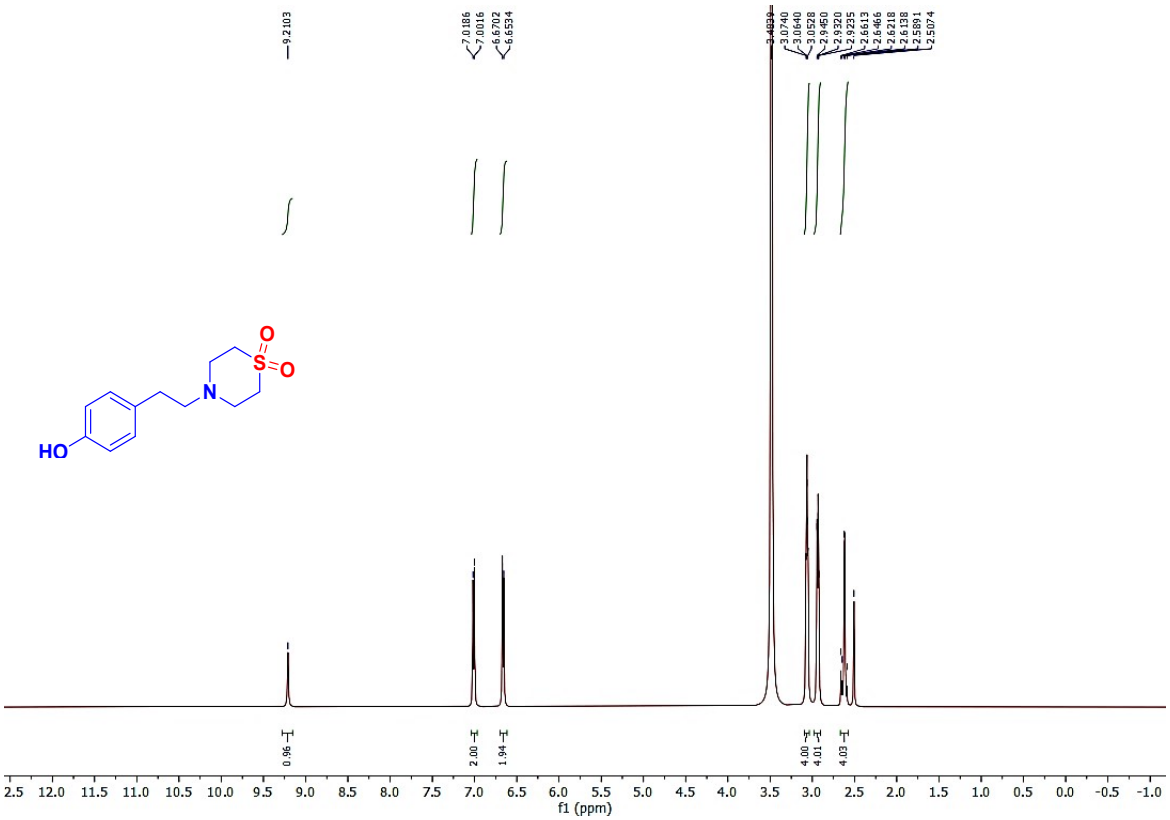
^{1}H NMR spectrum of compound **5a**, (DMSO-d_6, 500 MHz).



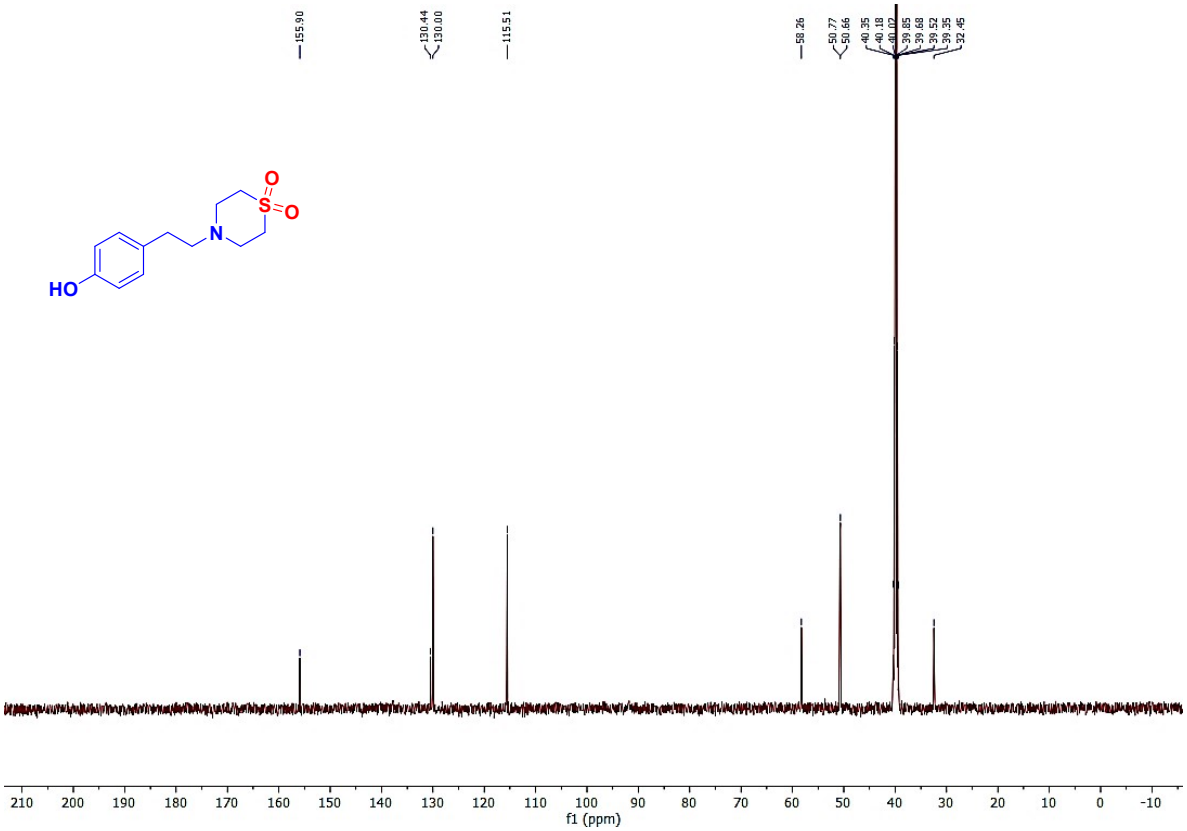
^{13}C NMR spectrum of compound **5a**, (DMSO-d_6, 125 MHz).



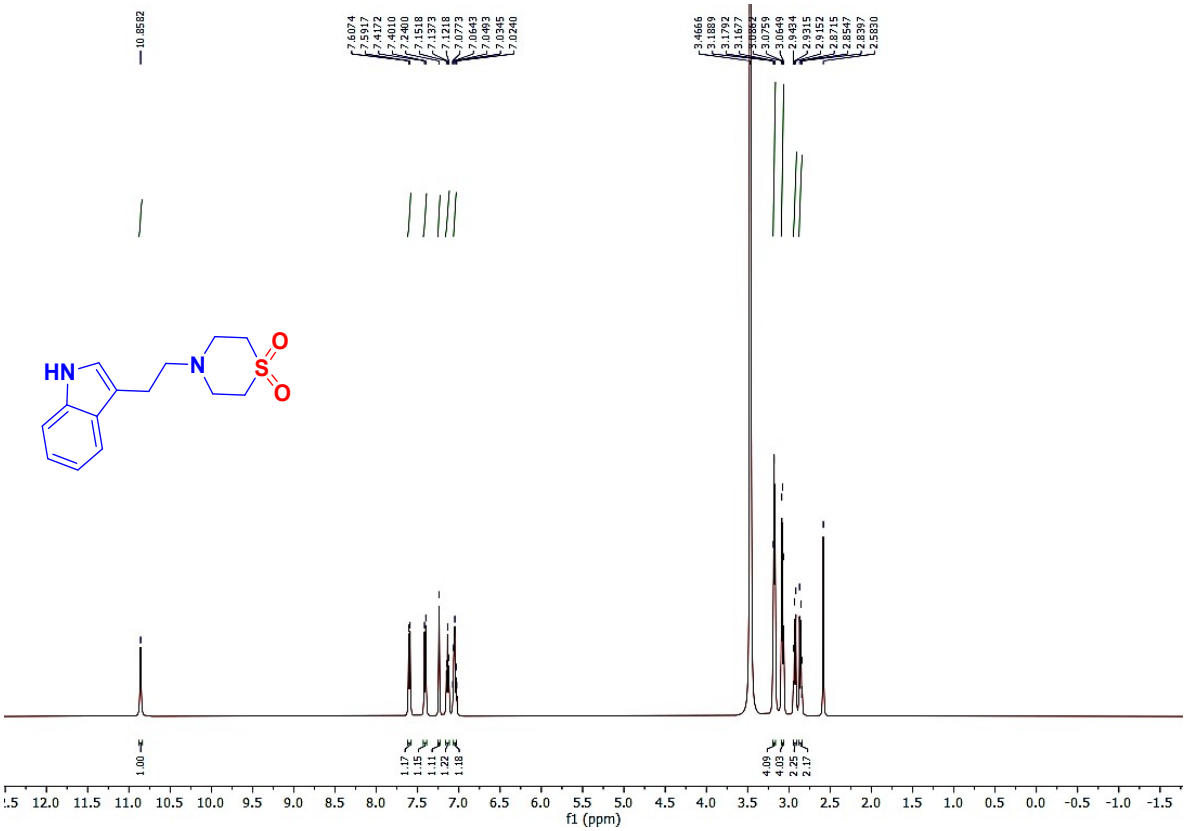
^{1}H NMR spectrum of compound **5b**, (DMSO-d_6, 500 MHz).



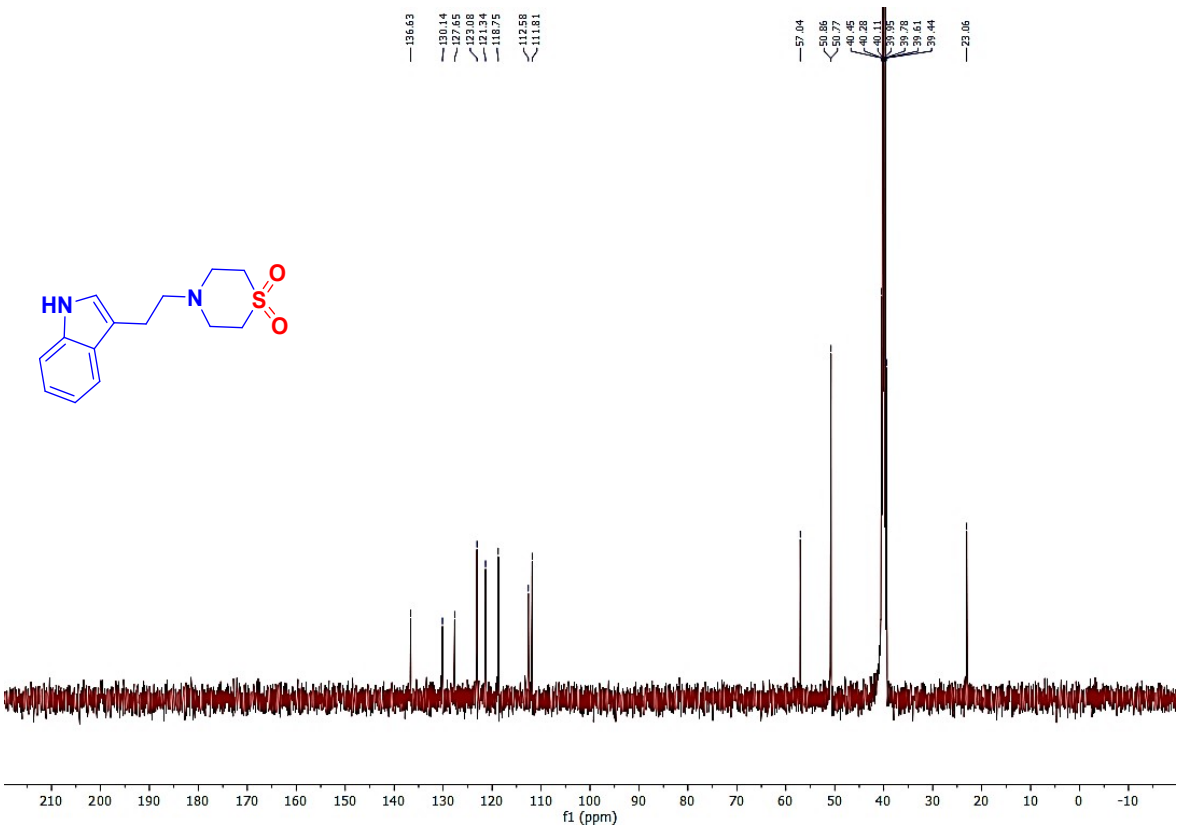
^{13}C NMR spectrum of compound **5b**, (DMSO-d_6, 125 MHz).



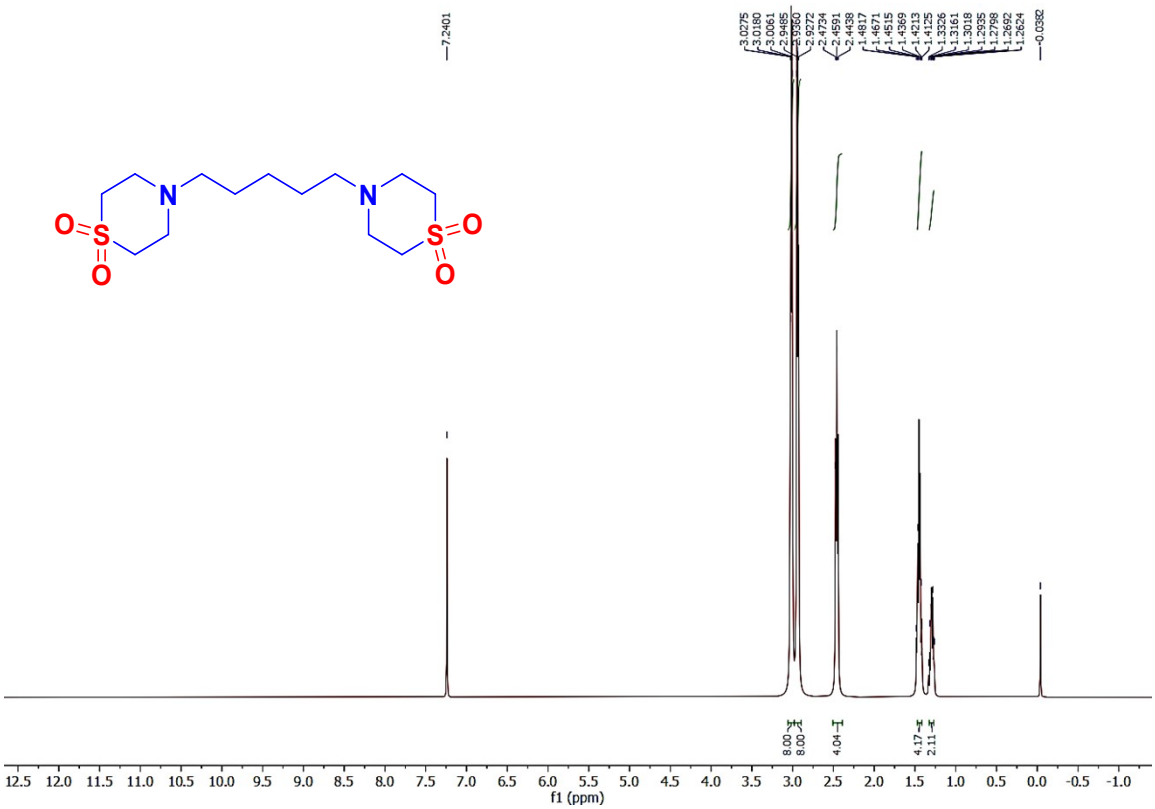
^{1}H NMR spectrum of compound **5c**, (DMSO-d_6, 500 MHz).



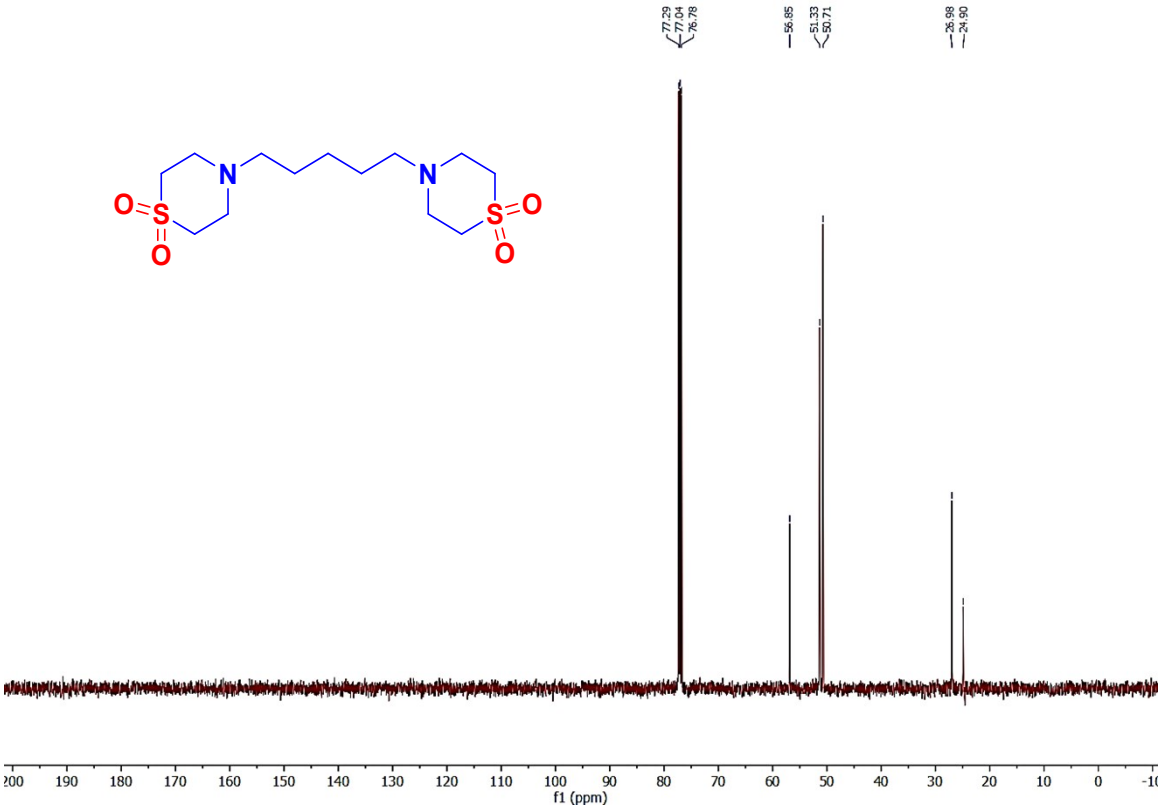
^{13}C NMR spectrum of compound **5c**, (DMSO-d_6, 125 MHz).



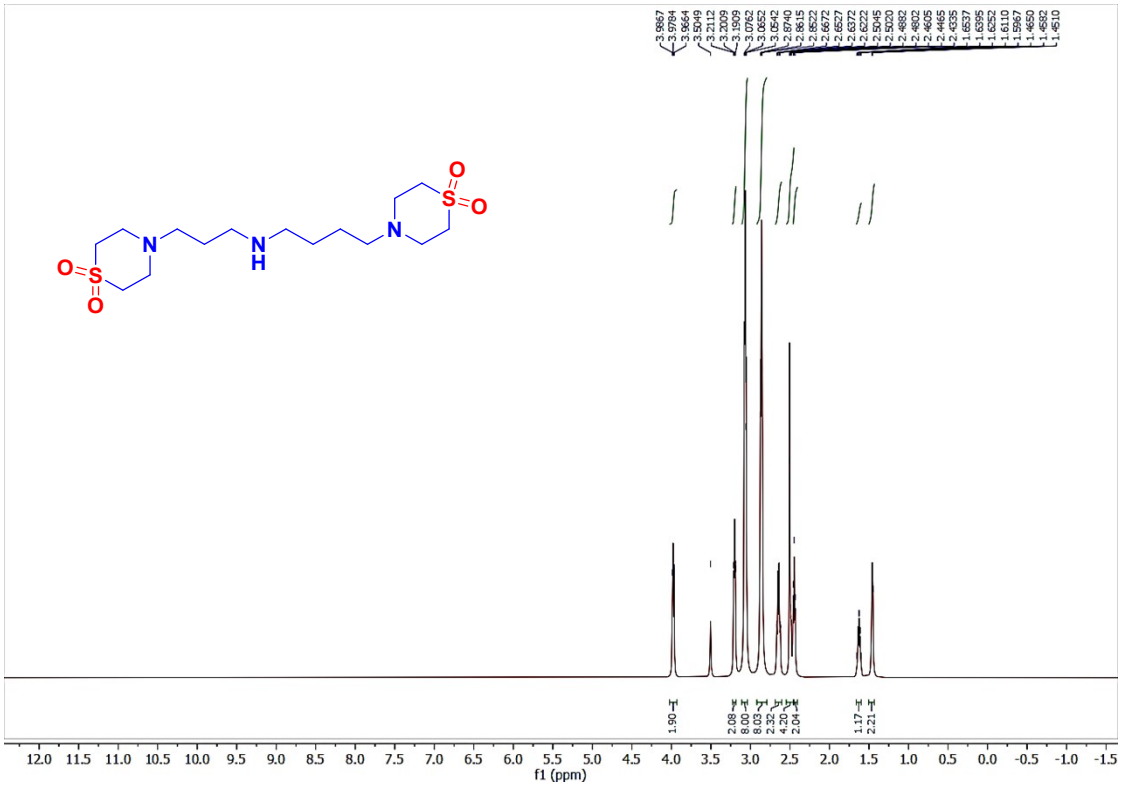
^{1}H NMR spectrum of compound **5d**, ($CDCl_3$, 500 MHz).



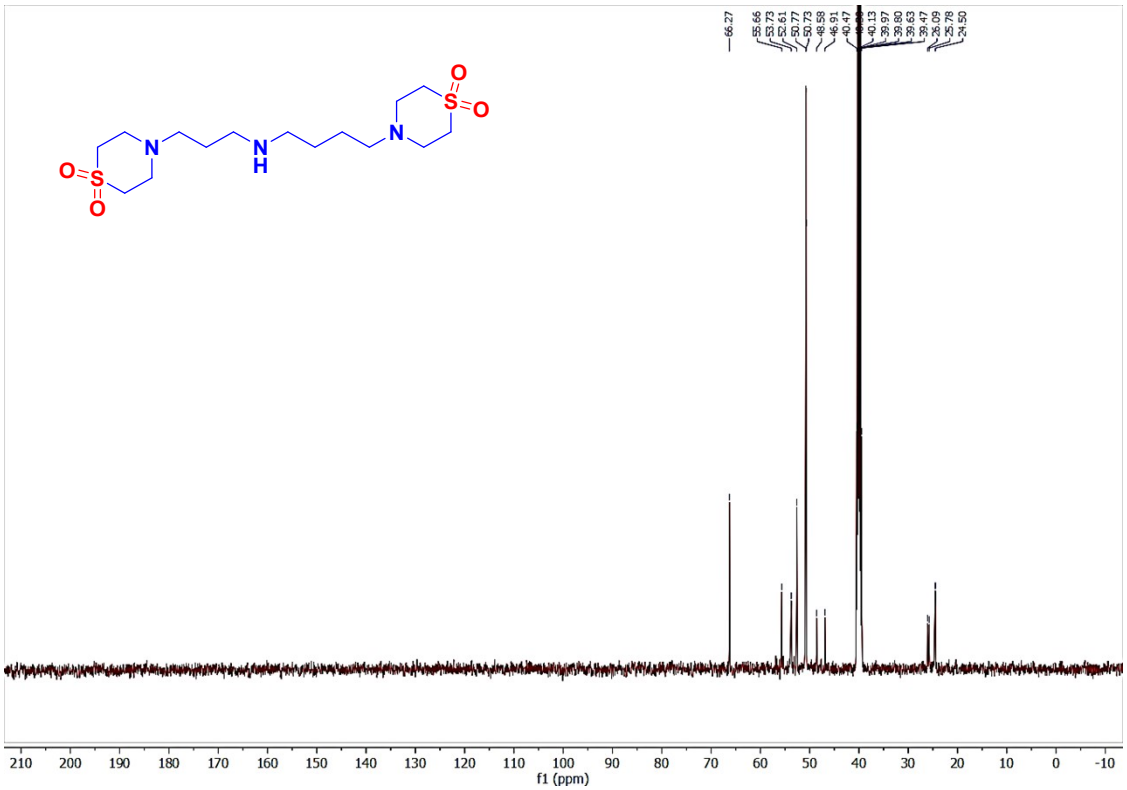
^{13}C NMR spectrum of compound **5d**, ($CDCl_3$, 125 MHz).



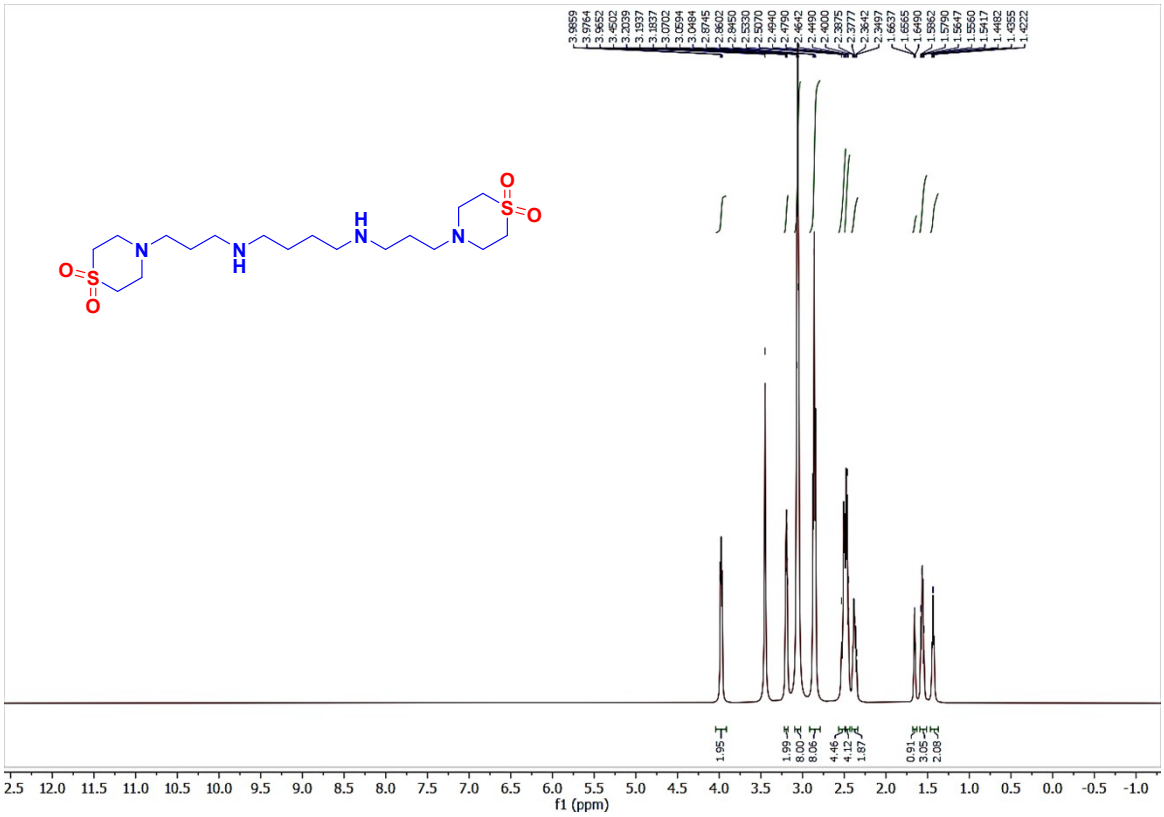
^{1}H NMR spectrum of compound **5e**, (DMSO-d_6, 500 MHz).



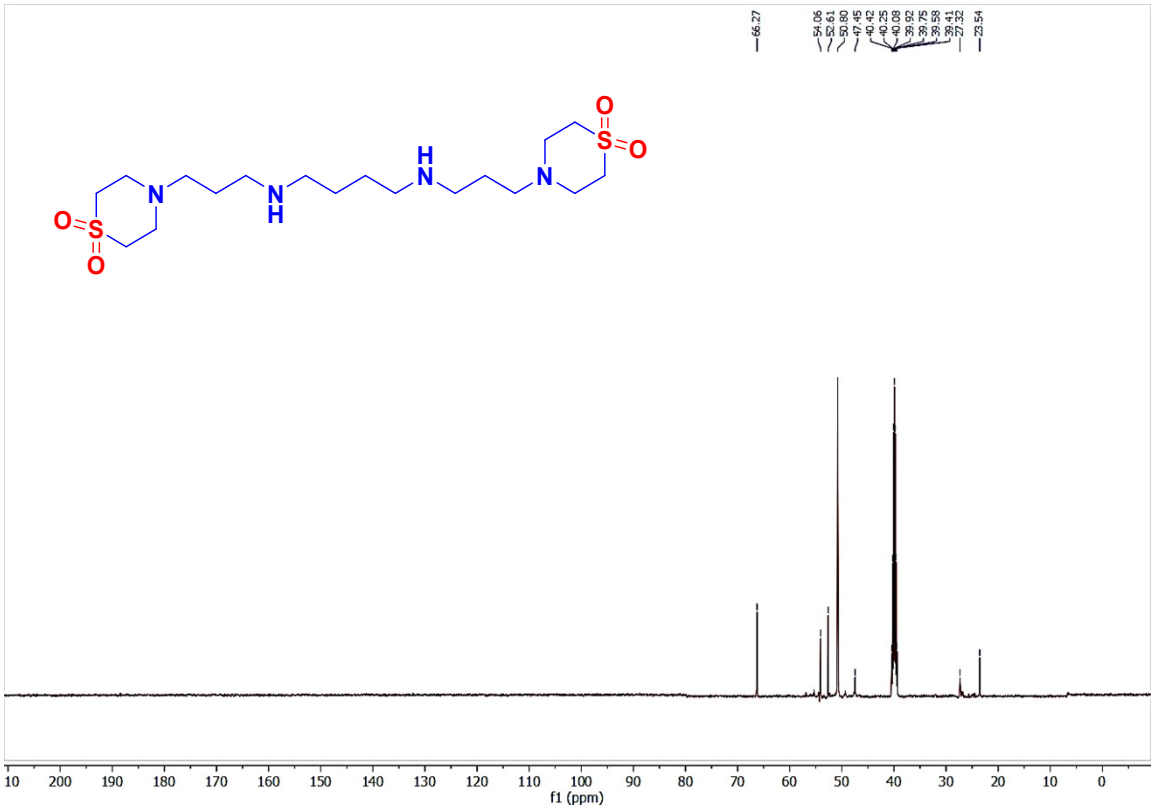
^{13}C NMR spectrum of compound **5e**, (DMSO-d_6, 125 MHz).



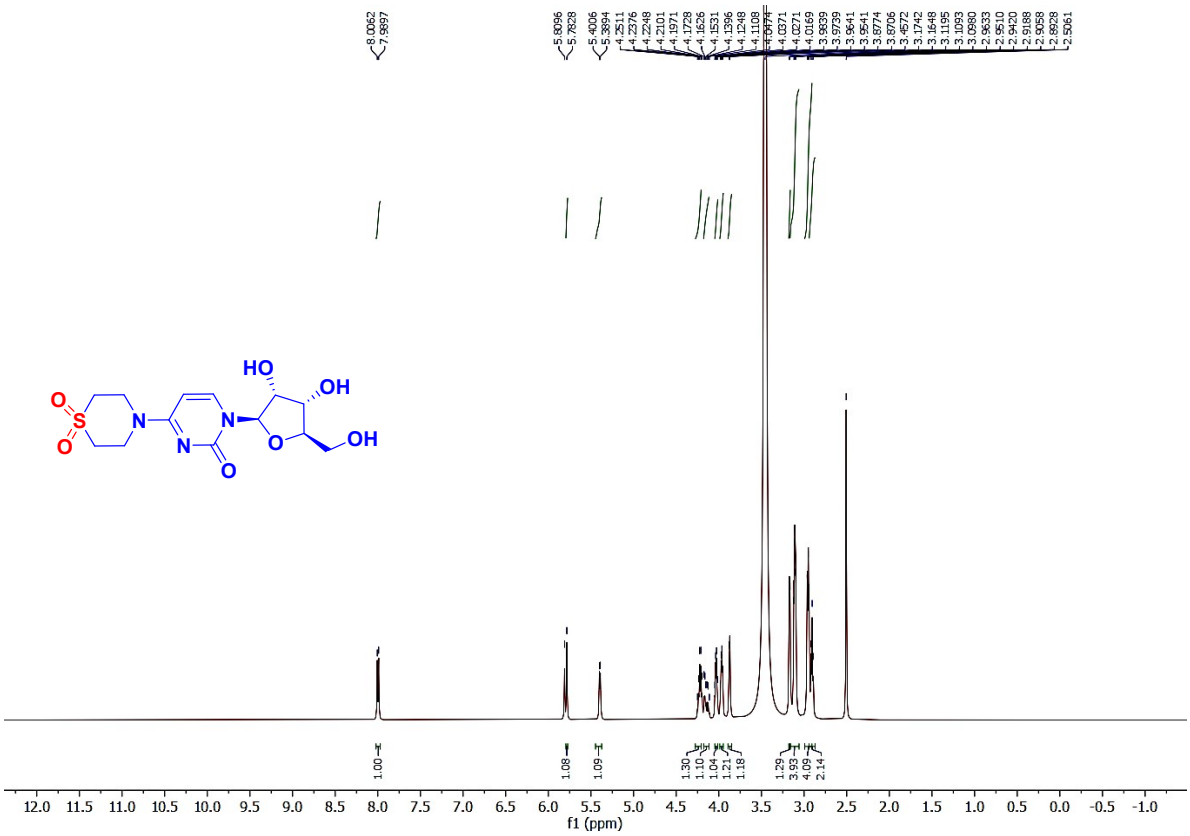
^{1}H NMR spectrum of compound **5f**, (DMSO-d_6, 500 MHz).



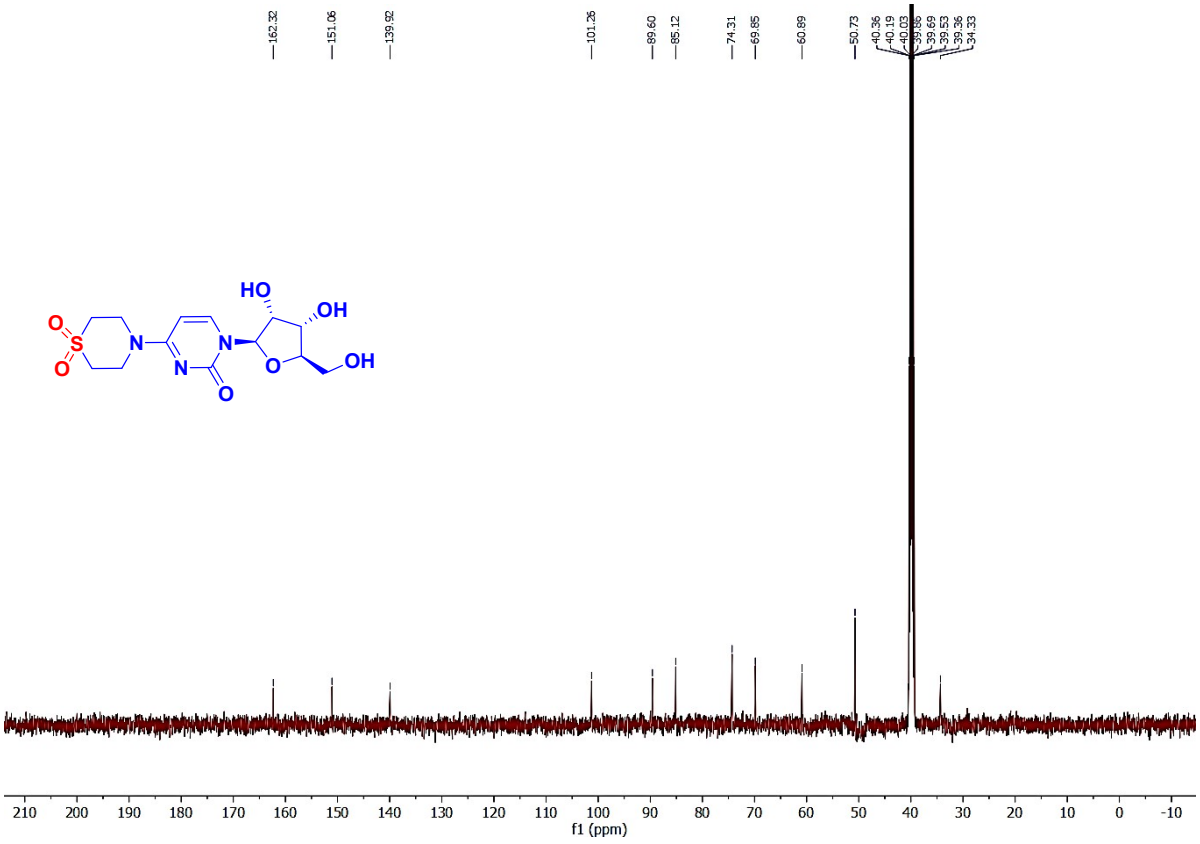
^{13}C NMR spectrum of compound **5f**, (DMSO-d_6, 125 MHz).



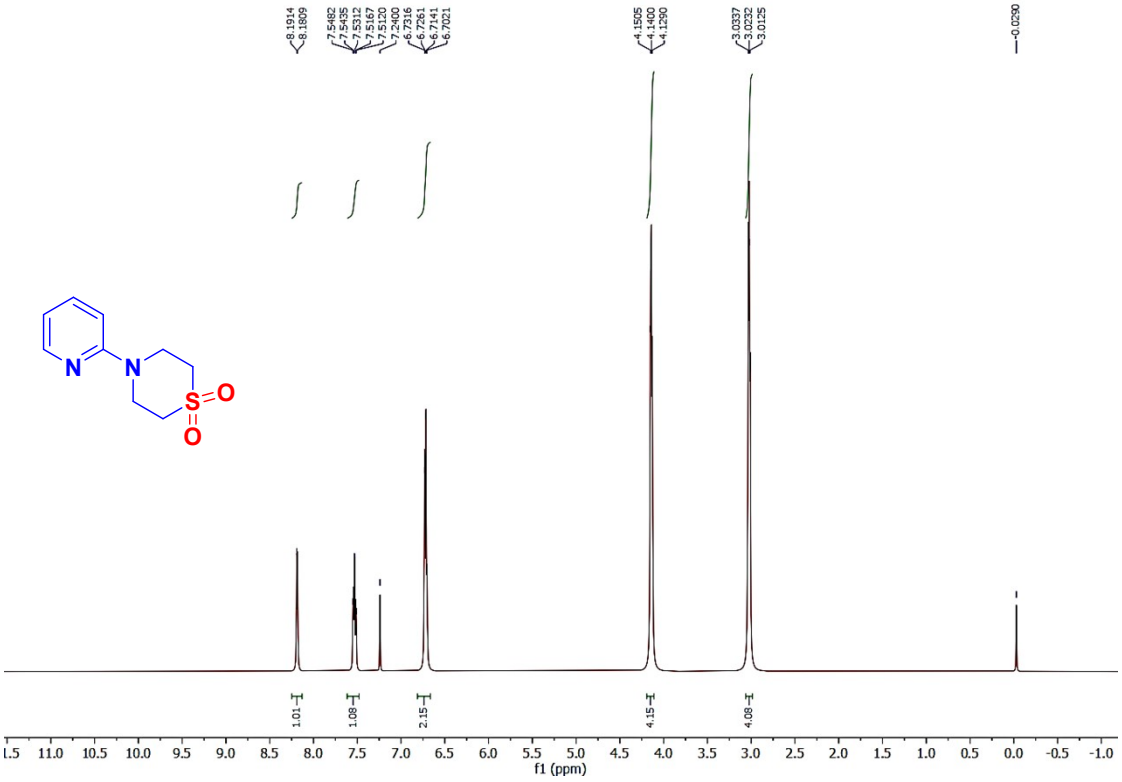
^{1}H NMR spectrum of compound **5g**, (DMSO-d_6, 500 MHz).



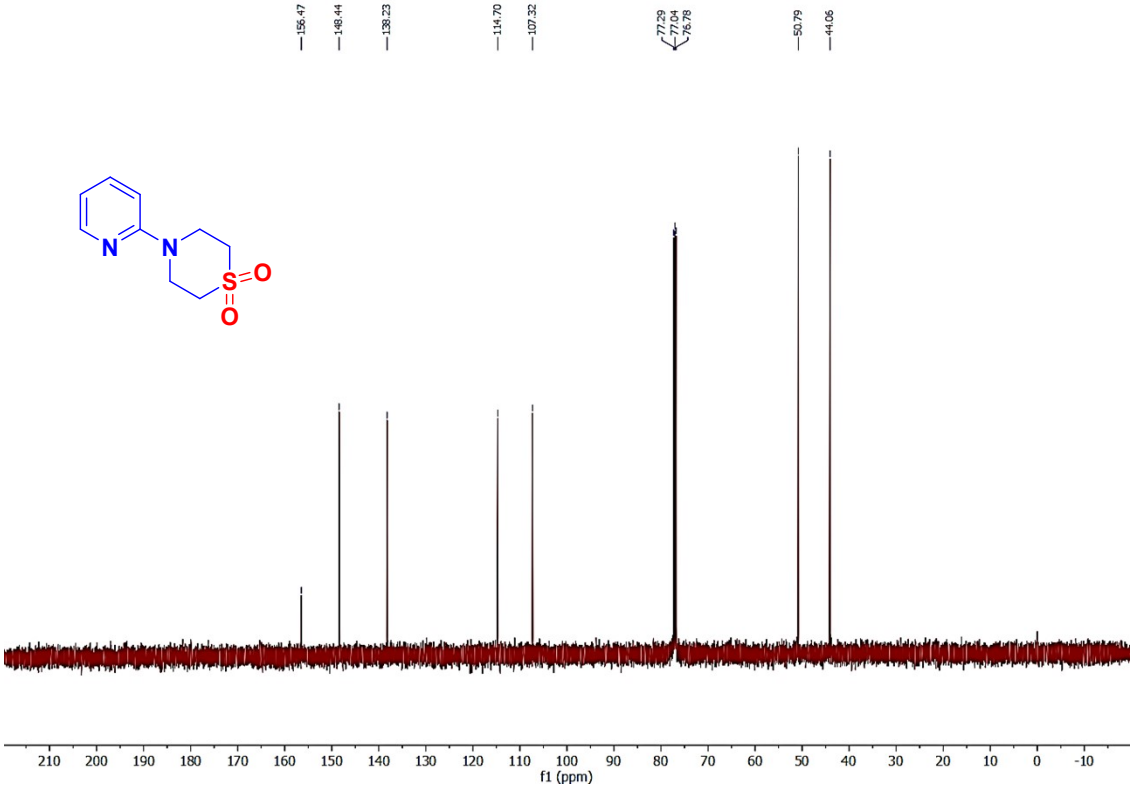
^{13}C NMR spectrum of compound **5g**, (DMSO-d_6, 125 MHz).



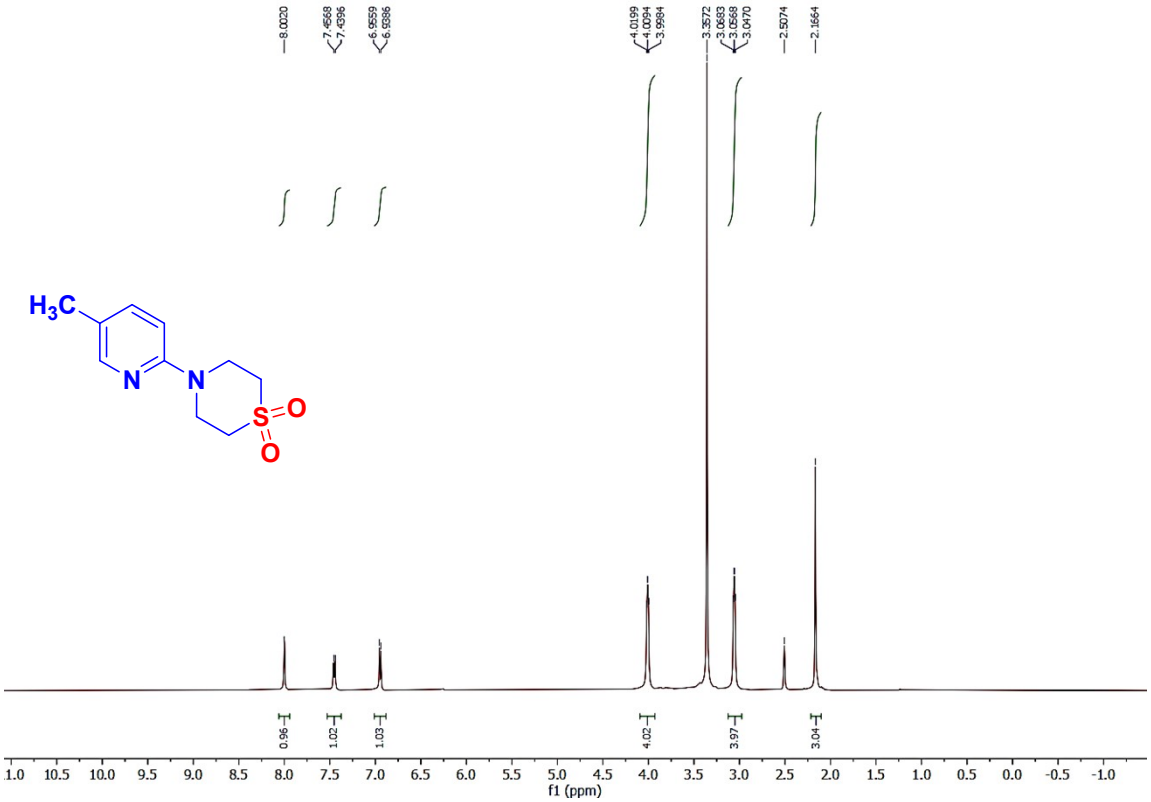
^{1}H NMR spectrum of compound **5h**, ($CDCl_3$, 500 MHz).



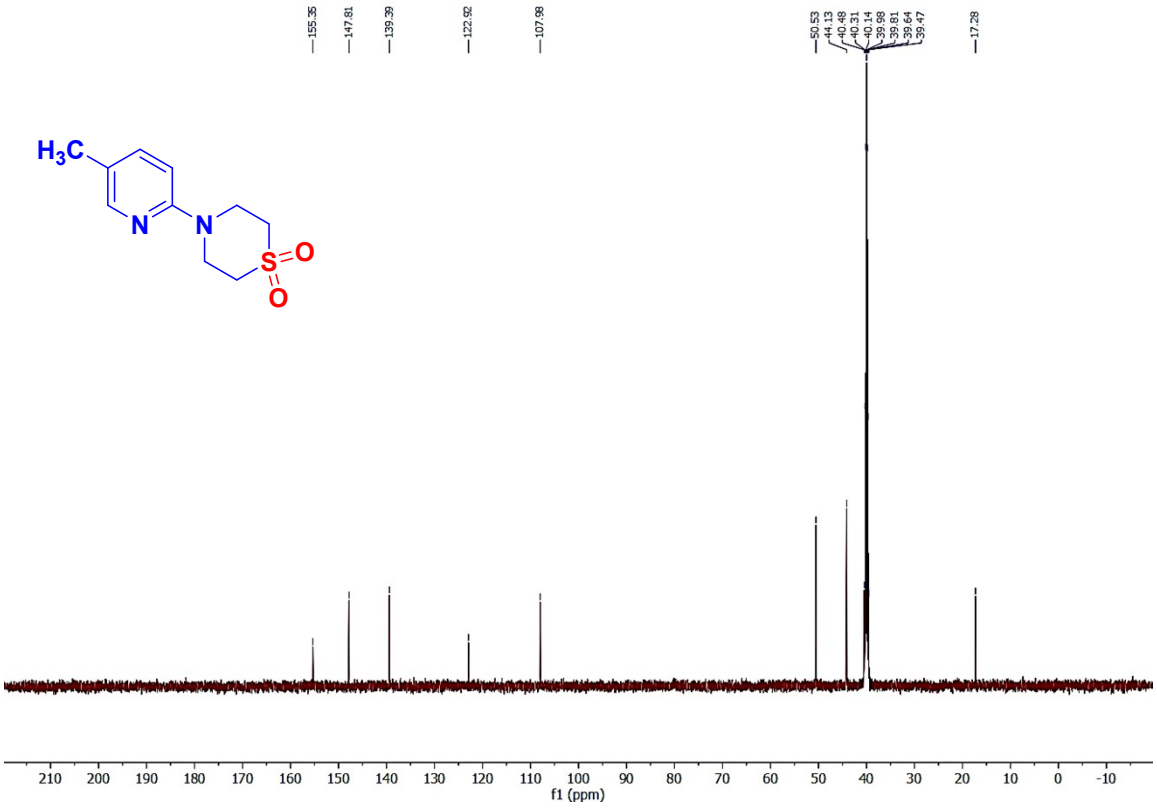
^{13}C NMR spectrum of compound **5h**, ($CDCl_3$, 125 MHz).



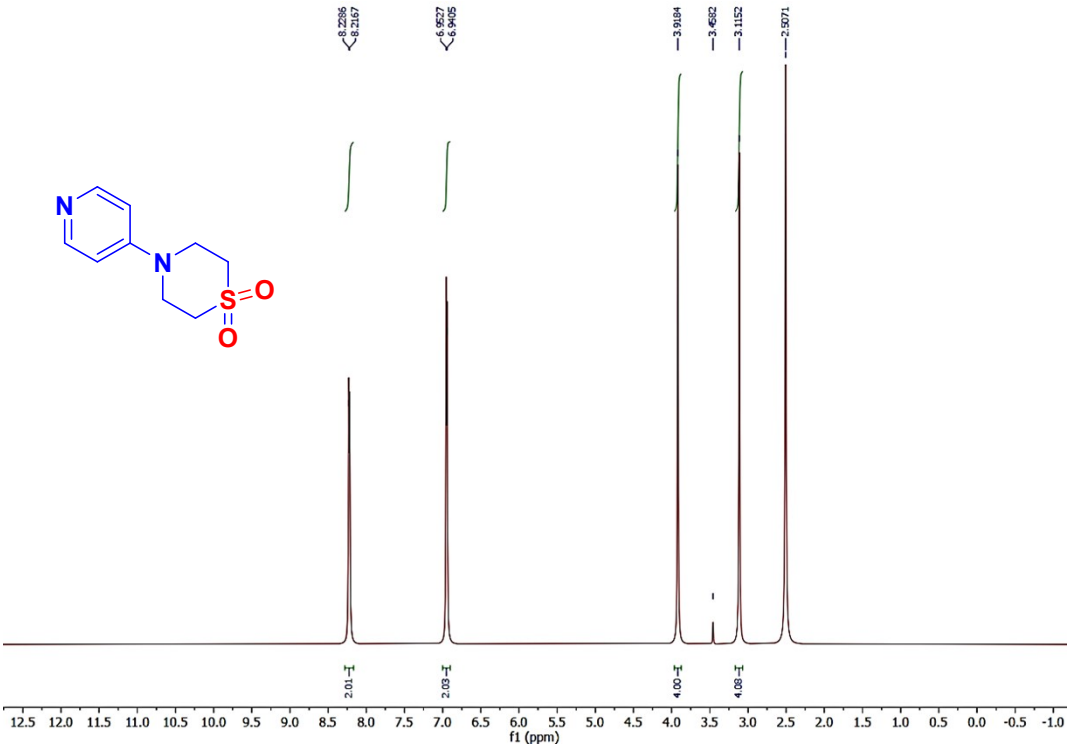
^{1}H NMR spectrum of compound **5i**, (DMSO-d_6, 500 MHz).



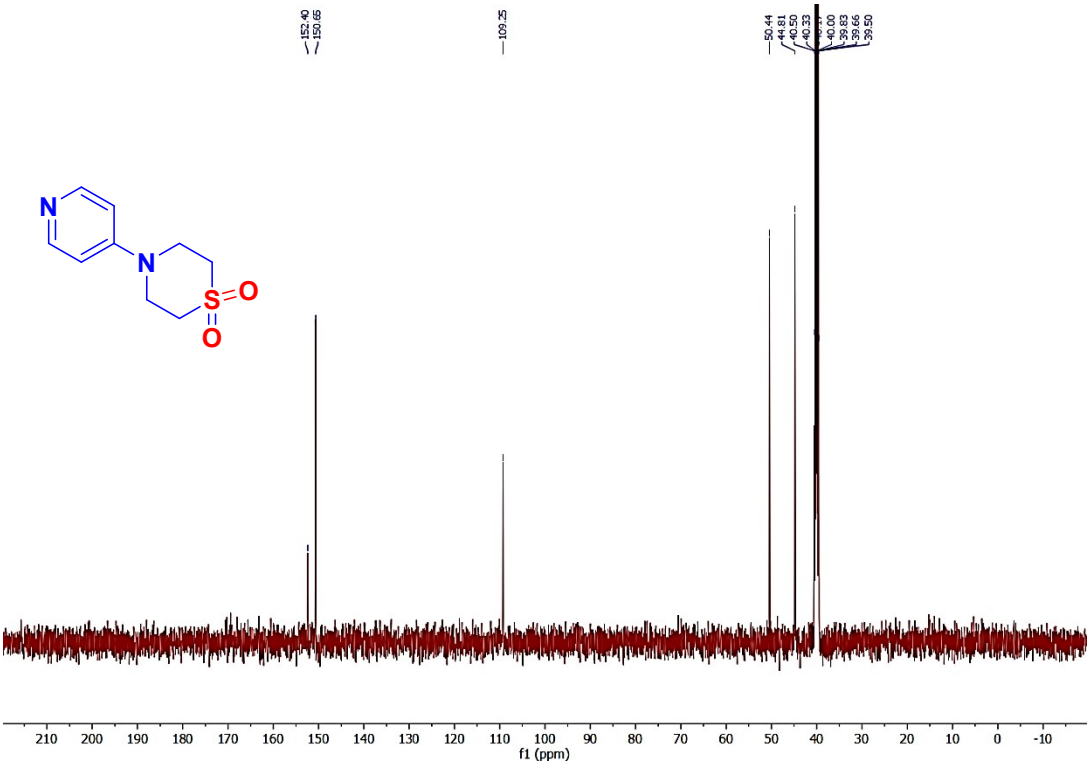
^{13}C NMR spectrum of compound **5i**, (DMSO-d_6, 125 MHz).



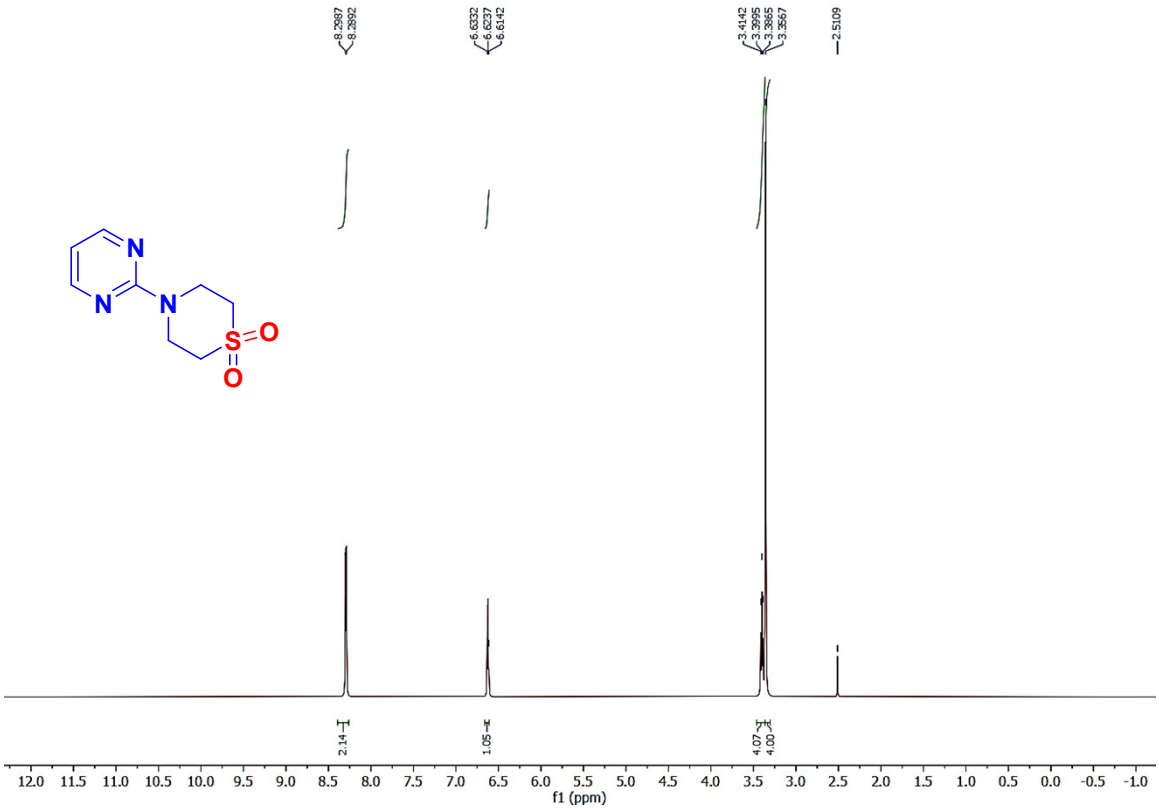
^{1}H NMR spectrum of compound **5j**, (DMSO-d_6, 500 MHz).



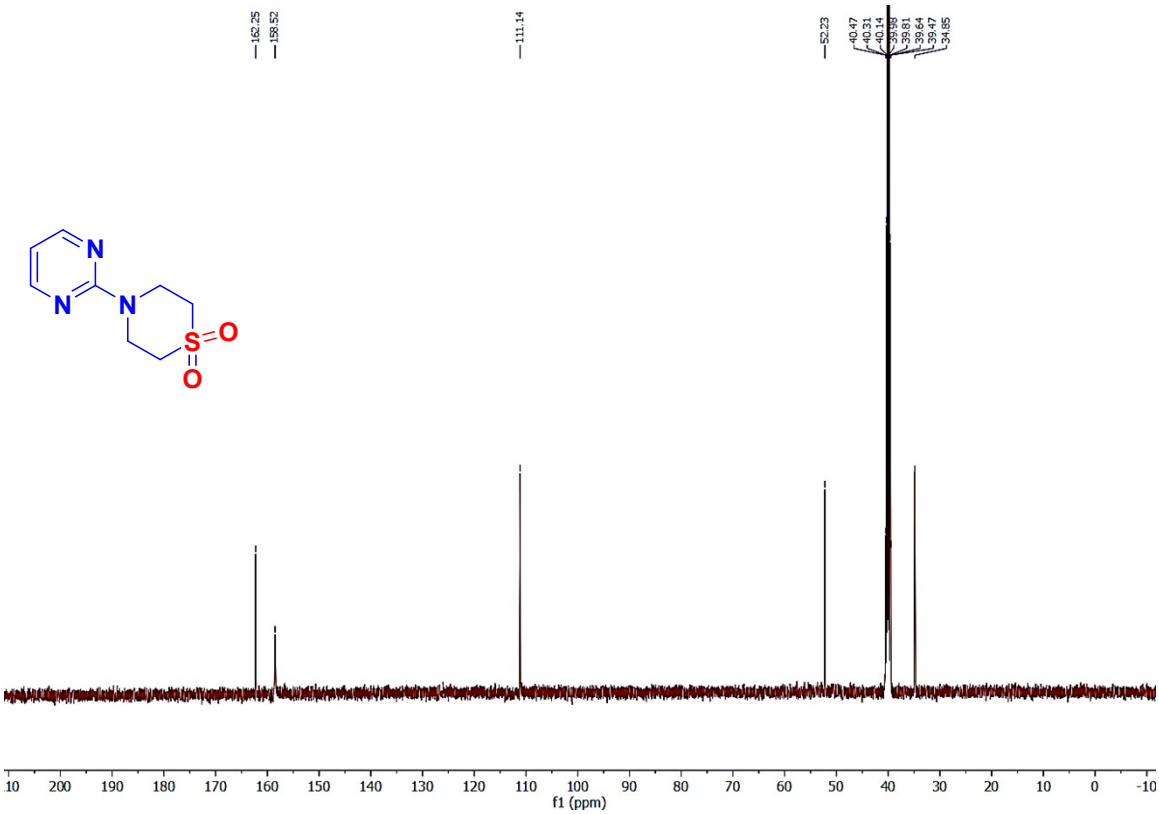
^{13}C NMR spectrum of compound **5j**, (DMSO-d_6, 125 MHz).



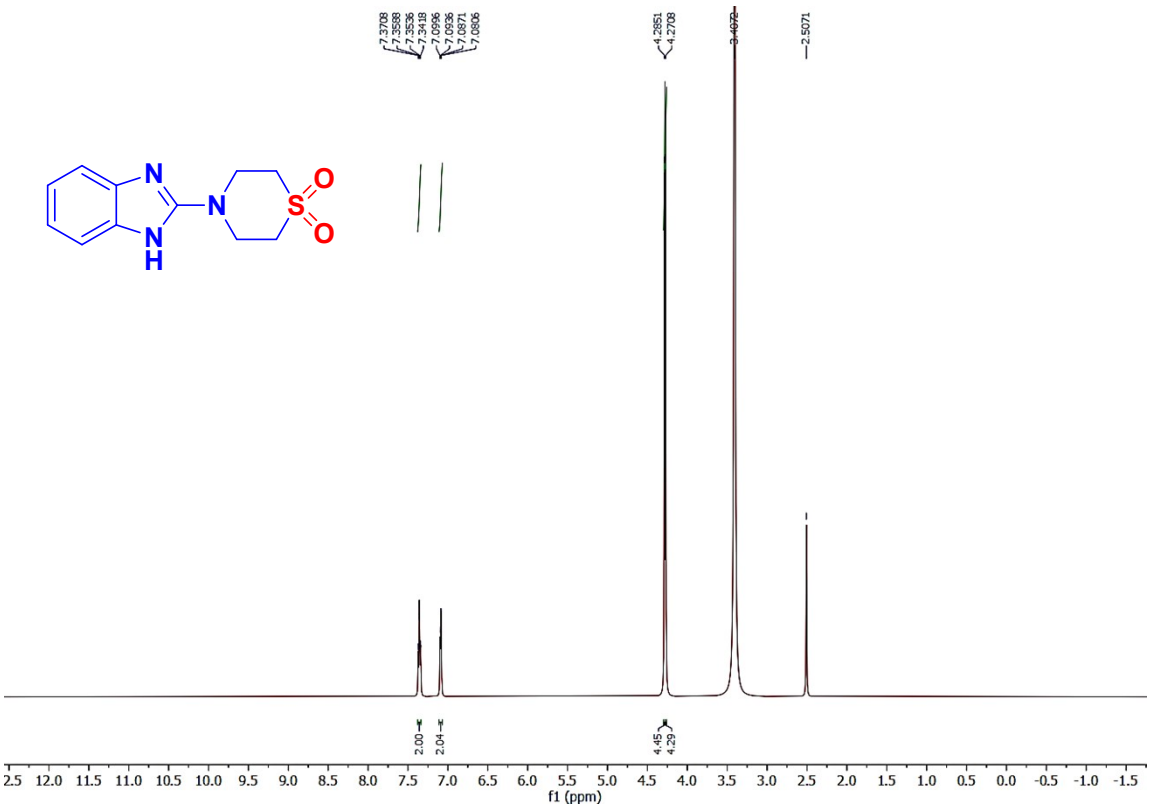
^{1}H NMR spectrum of compound **5k**, (DMSO-d_6, 500 MHz).



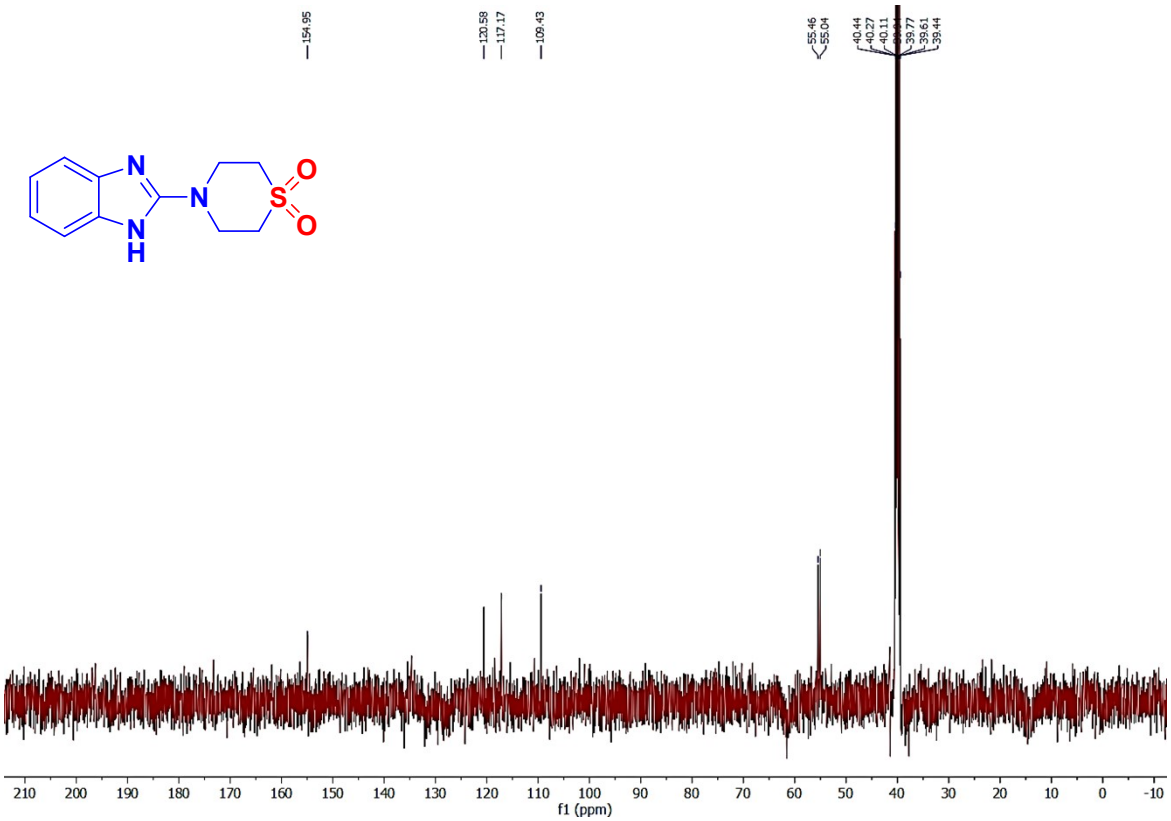
^{13}C NMR spectrum of compound **5k**, (DMSO-d_6, 125 MHz).



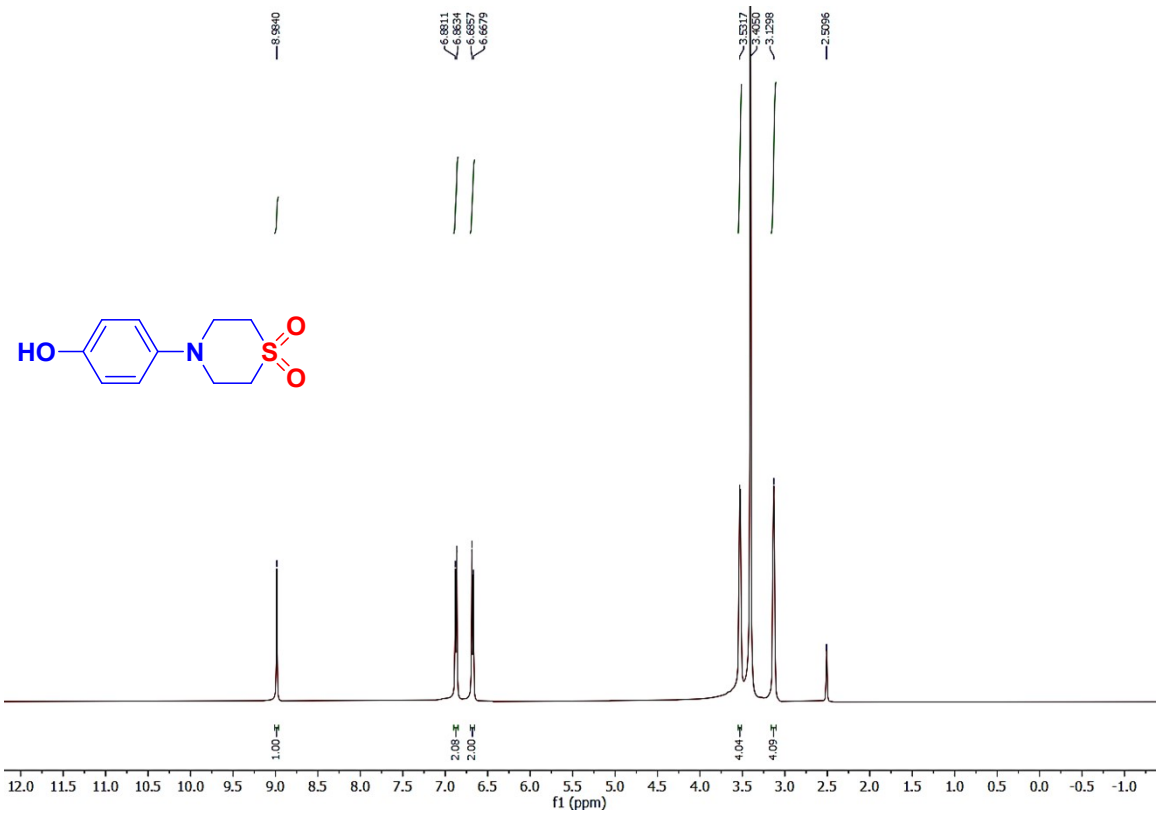
^{1}H NMR spectrum of compound **5l**, (DMSO-d_6, 500 MHz).



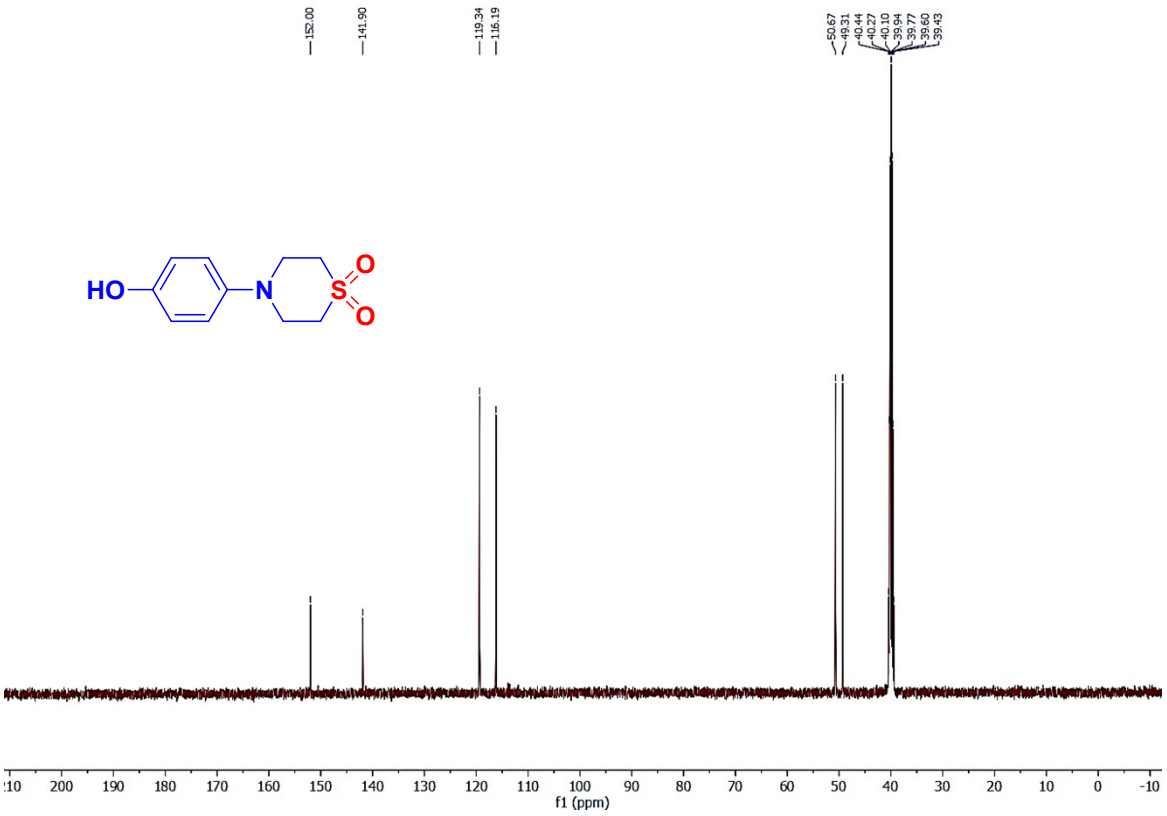
^{13}C NMR spectrum of compound **5l**, (DMSO-d_6, 125 MHz).



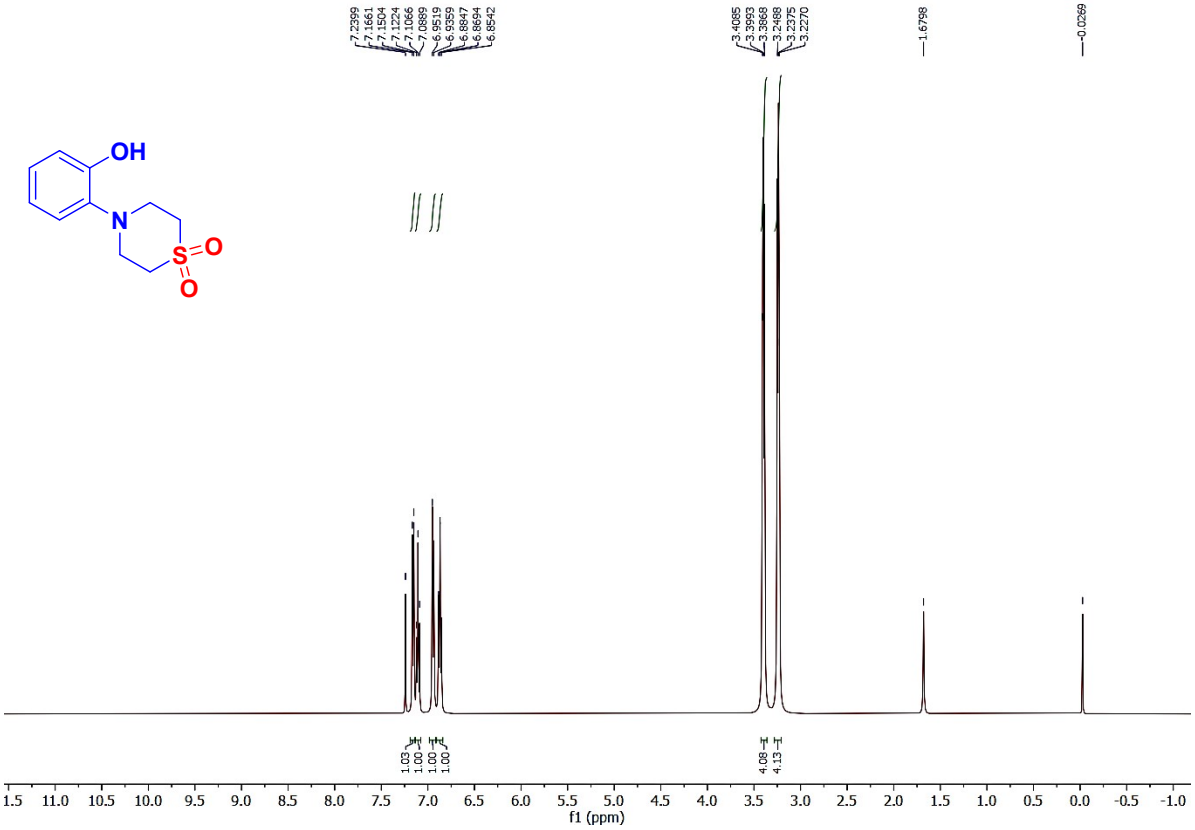
^{1}H NMR spectrum of compound **5m,** (DMSO-d_6, 500 MHz).



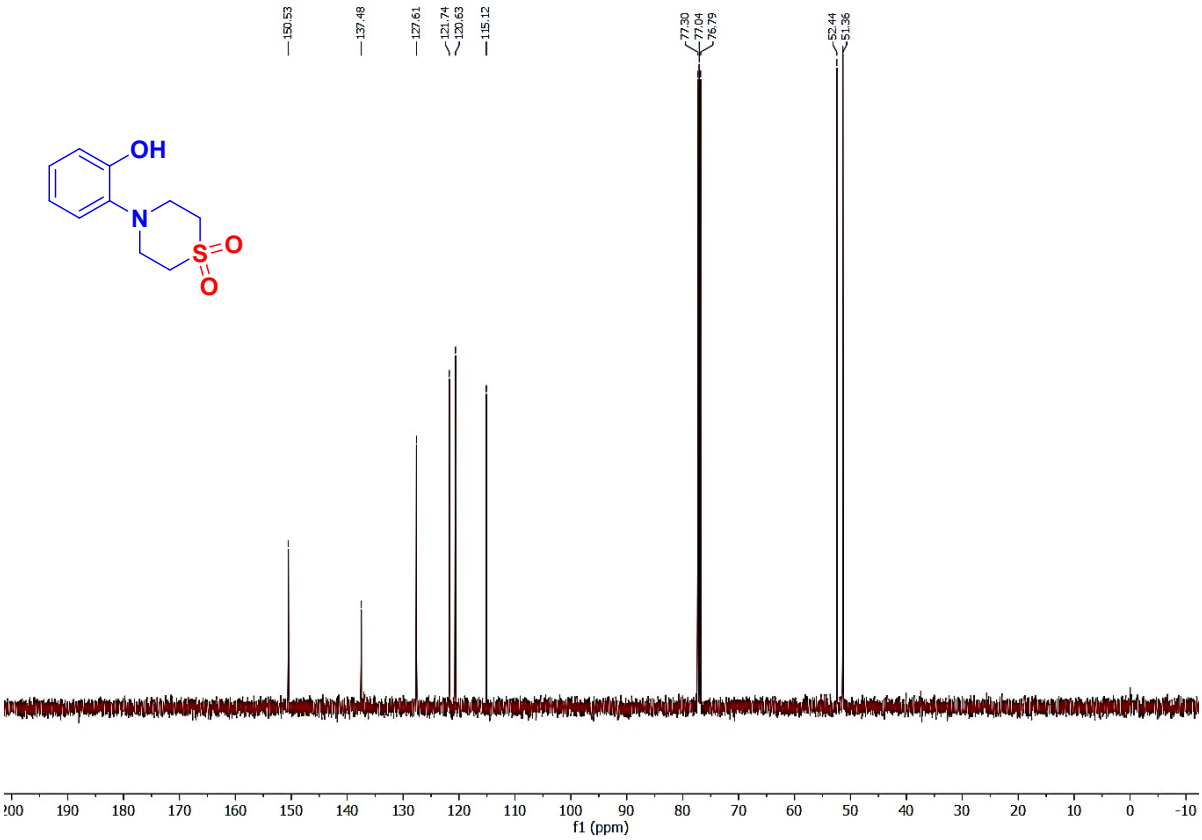
^{13}C NMR spectrum of compound **5m**, (DMSO-d_6, 125 MHz).



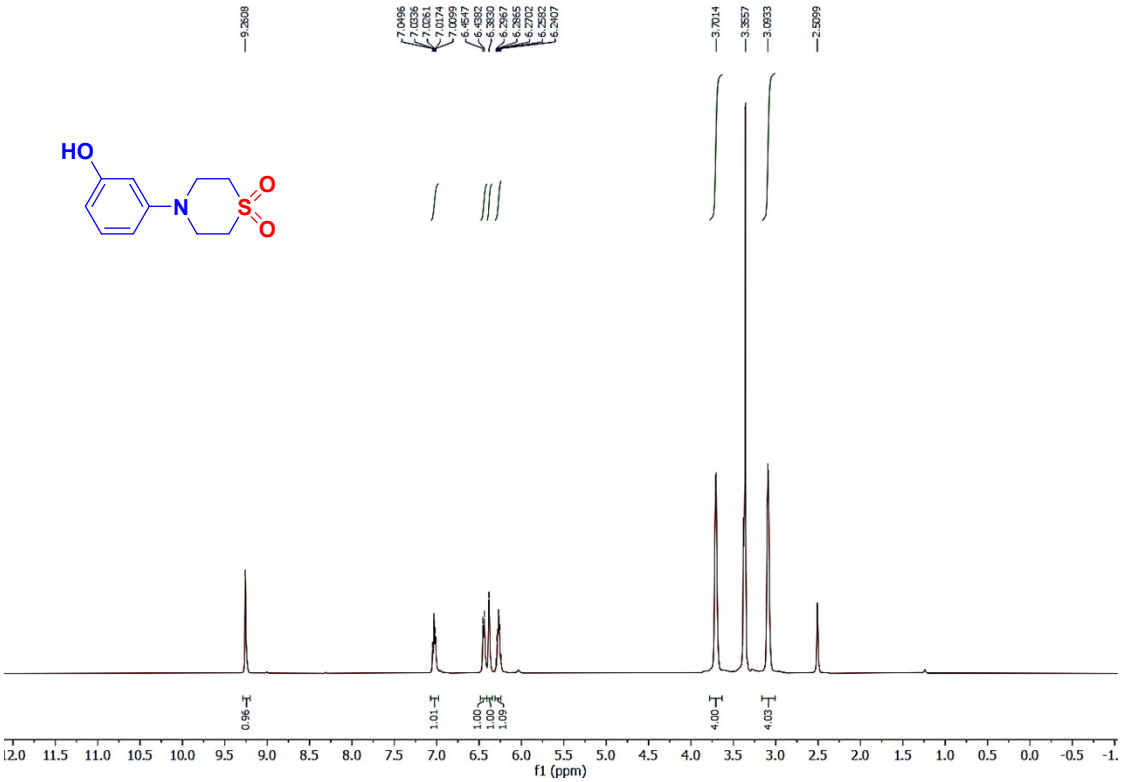
^{1}H NMR spectrum of compound **5n**, ($CDCl_3$, 500 MHz).



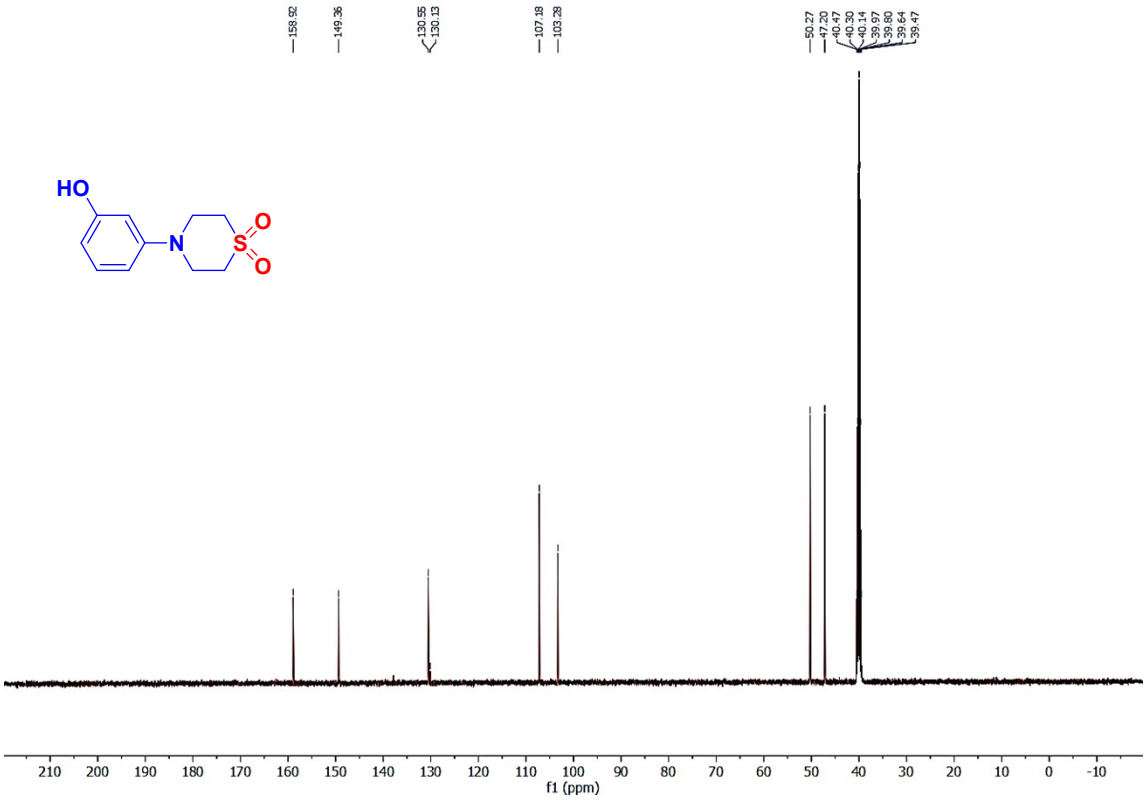
^{13}C NMR spectrum of compound **5n**, ($CDCl_3$, 125 MHz).



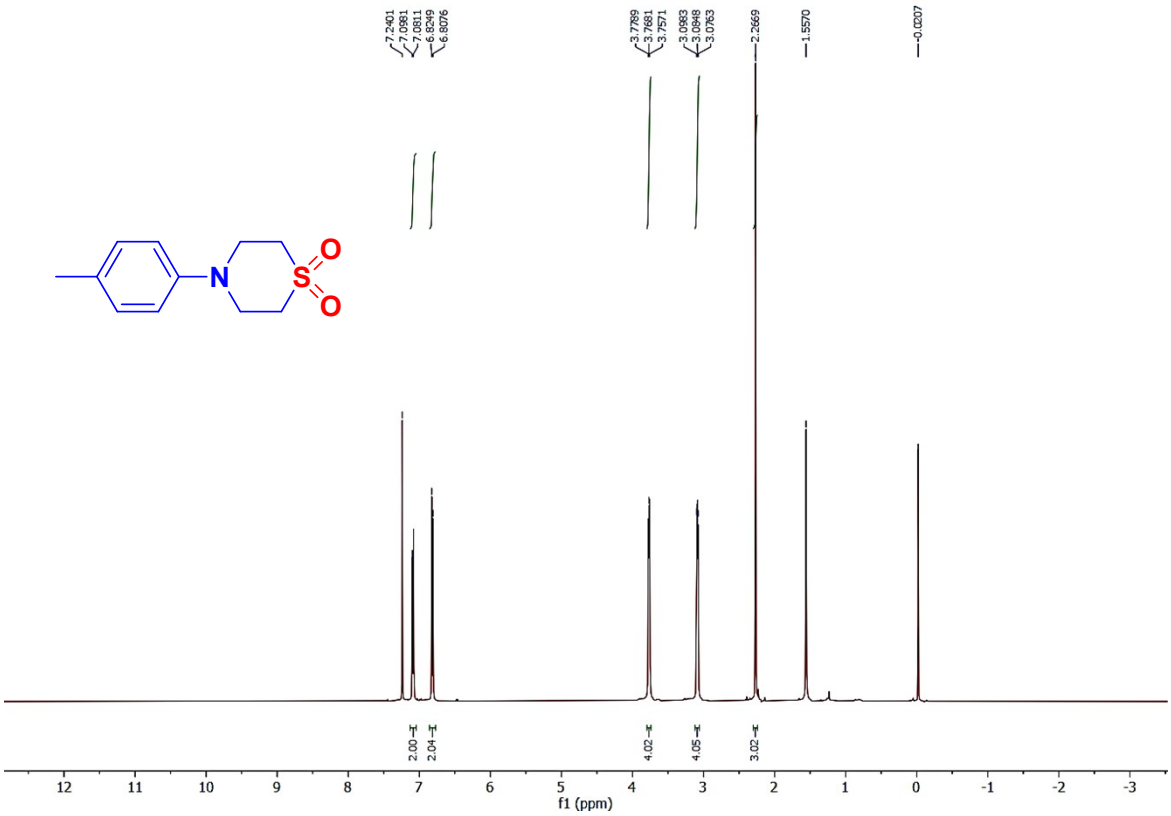
^{1}H NMR spectrum of compound **5o**, (DMSO-d_6, 500 MHz).



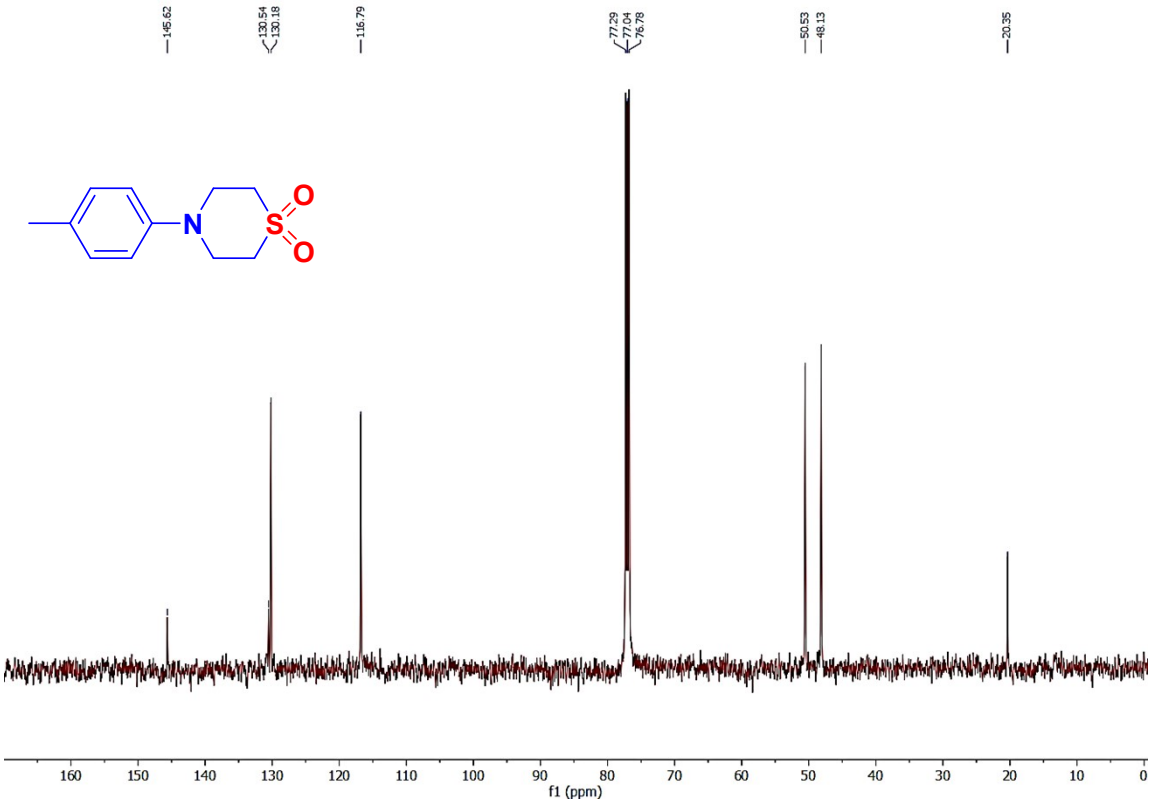
^{13}C NMR spectrum of compound **5o**, (DMSO-d_6, 125 MHz).



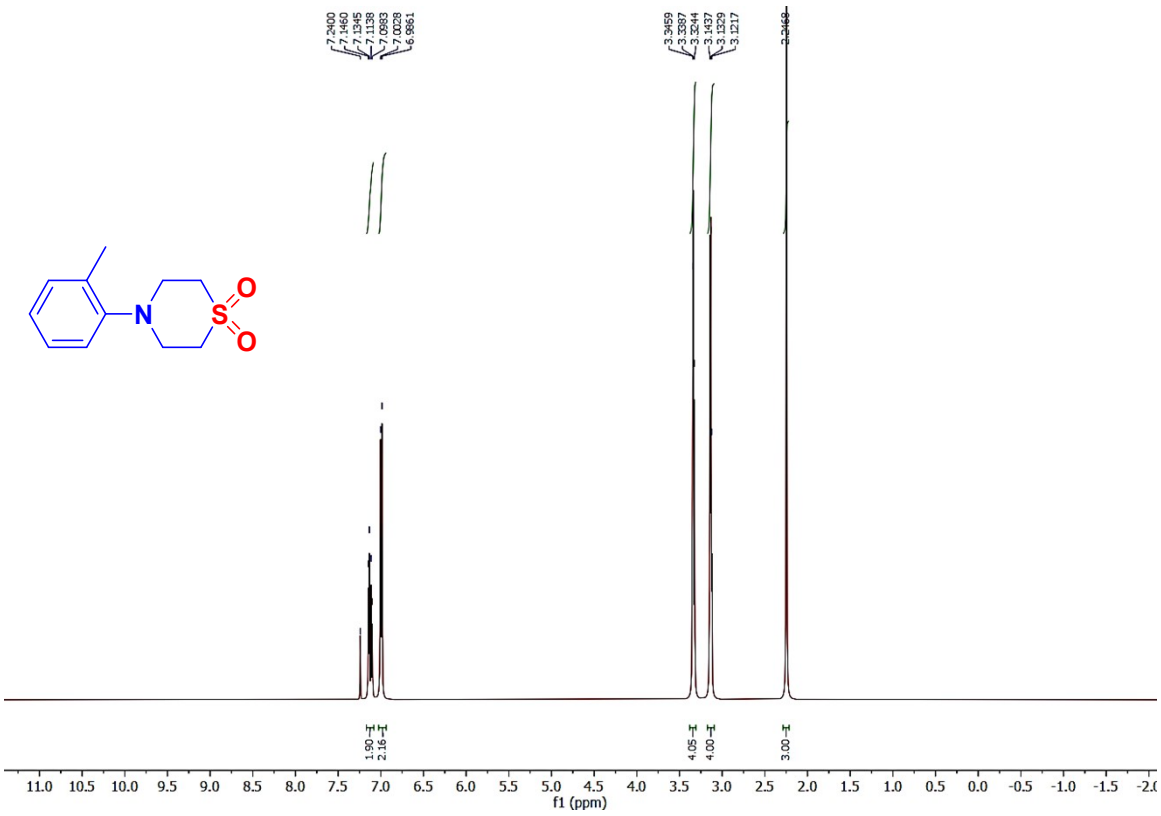
^{1}H NMR spectrum of compound **5p**, ($CDCl_3$, 500 MHz).



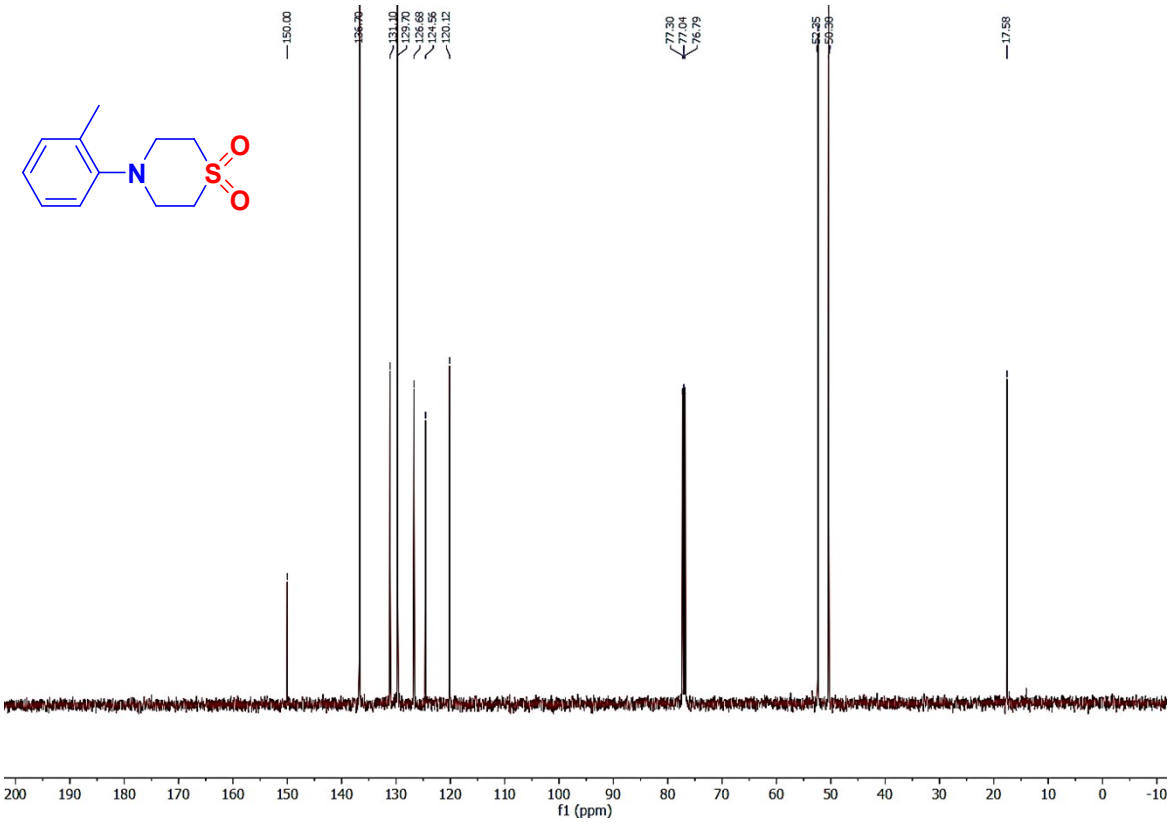
^{13}C NMR spectrum of compound **5p**, ($CDCl_3$, 125 MHz).



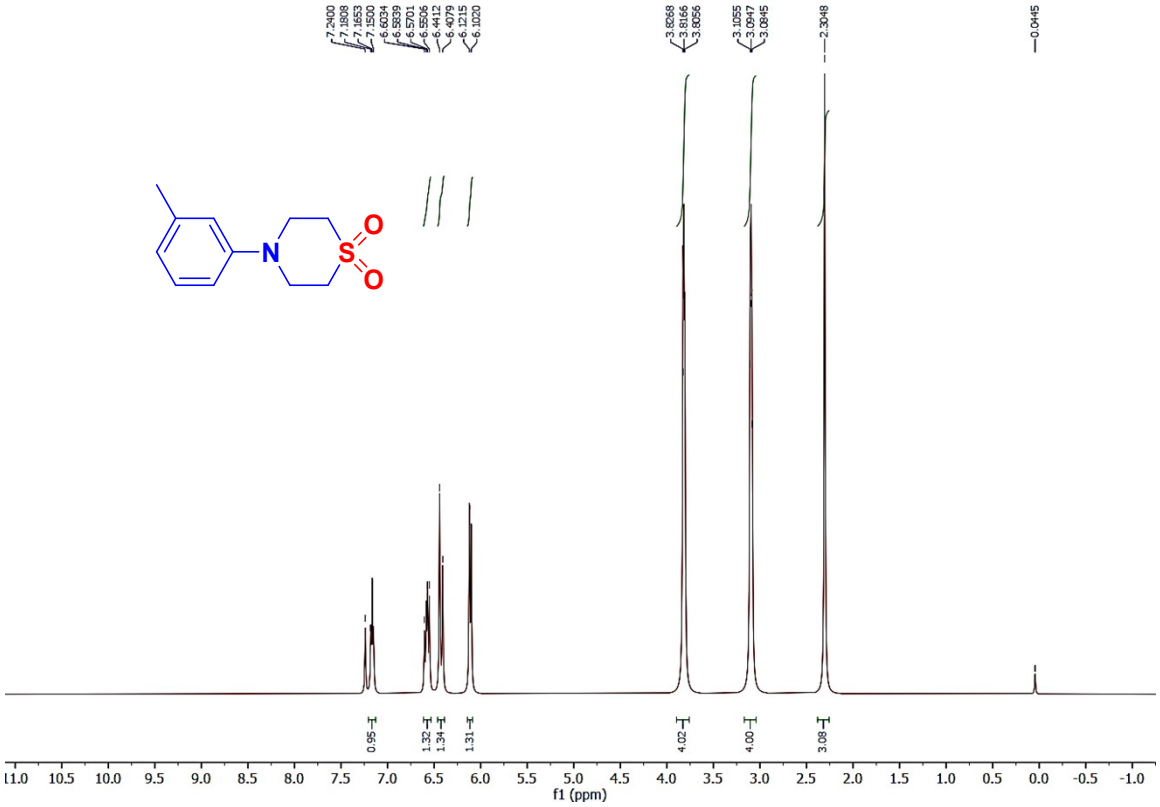
^{1}H NMR spectrum of compound **5q**, ($CDCl_3$, 500 MHz).



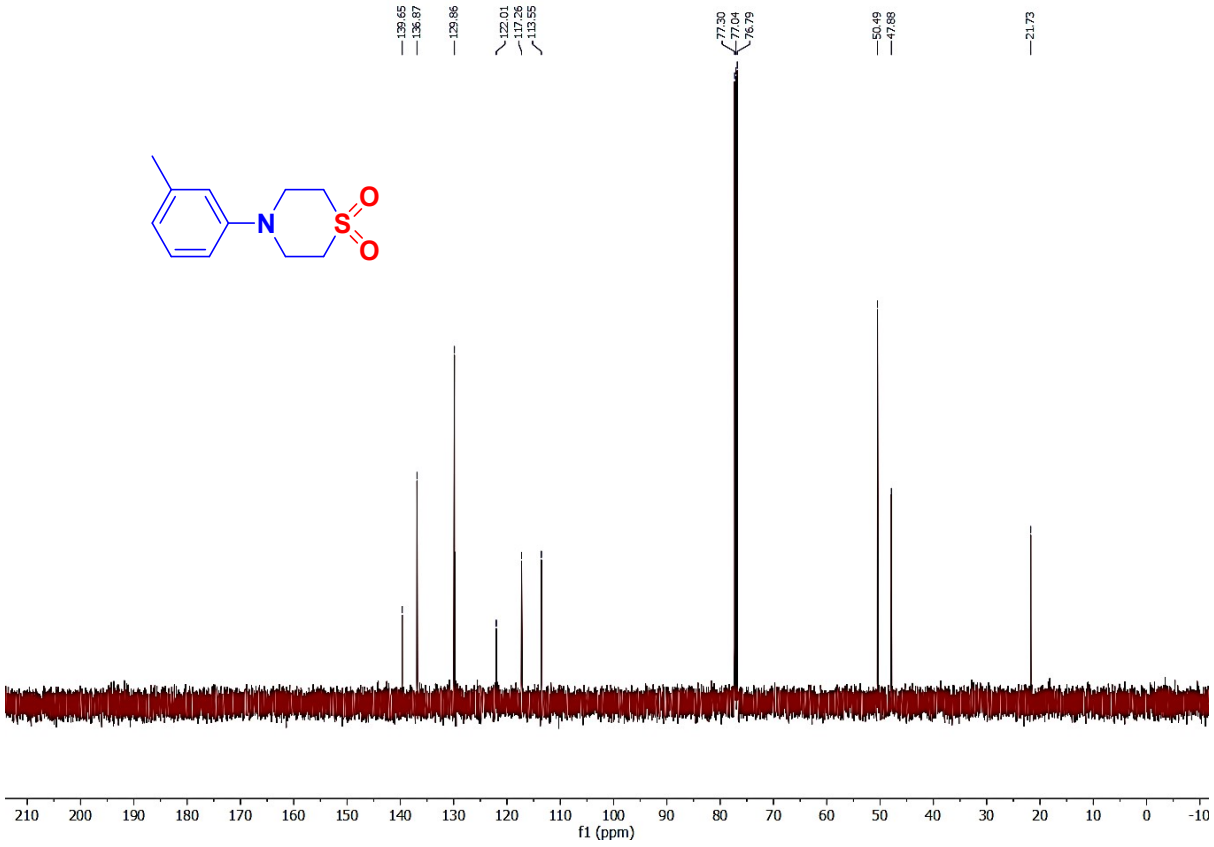
^{13}C NMR spectrum of compound **5q**, ($CDCl_3$, 125 MHz).



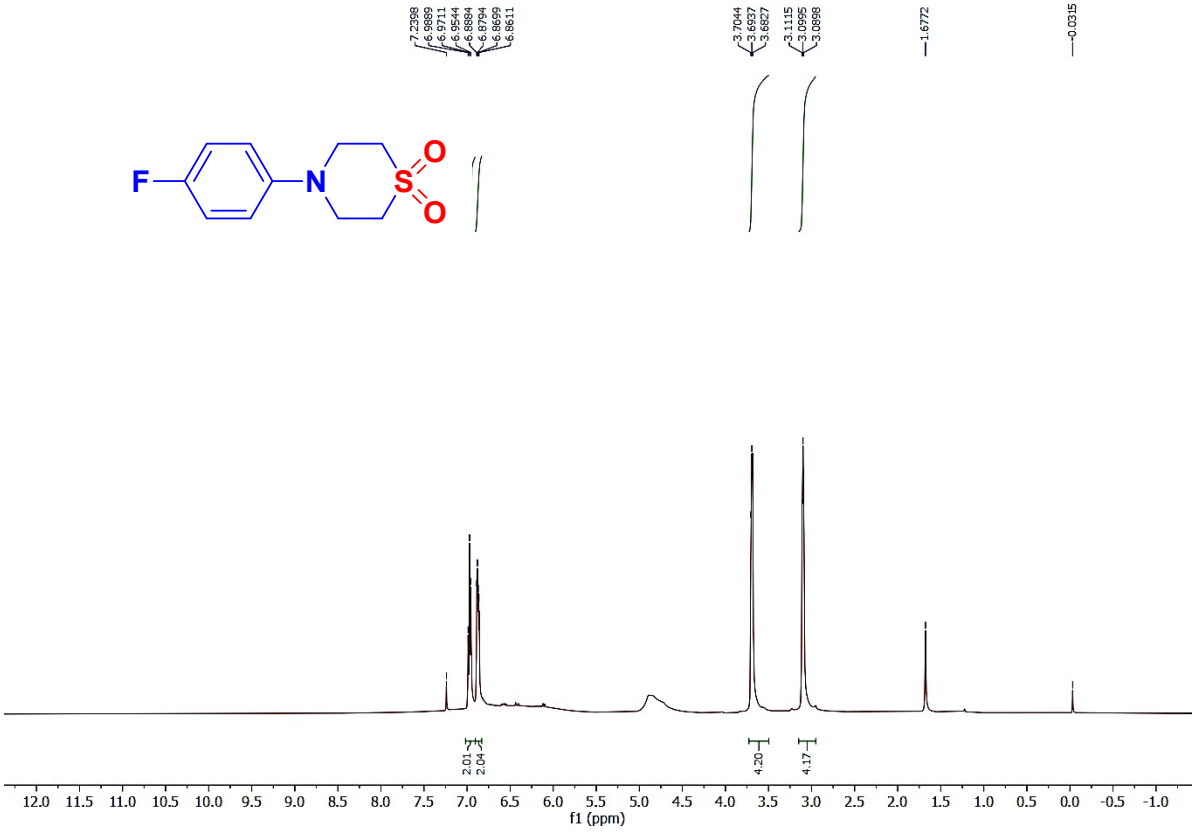
^{1}H NMR spectrum of compound **5r**, ($CDCl_3$, 500 MHz).



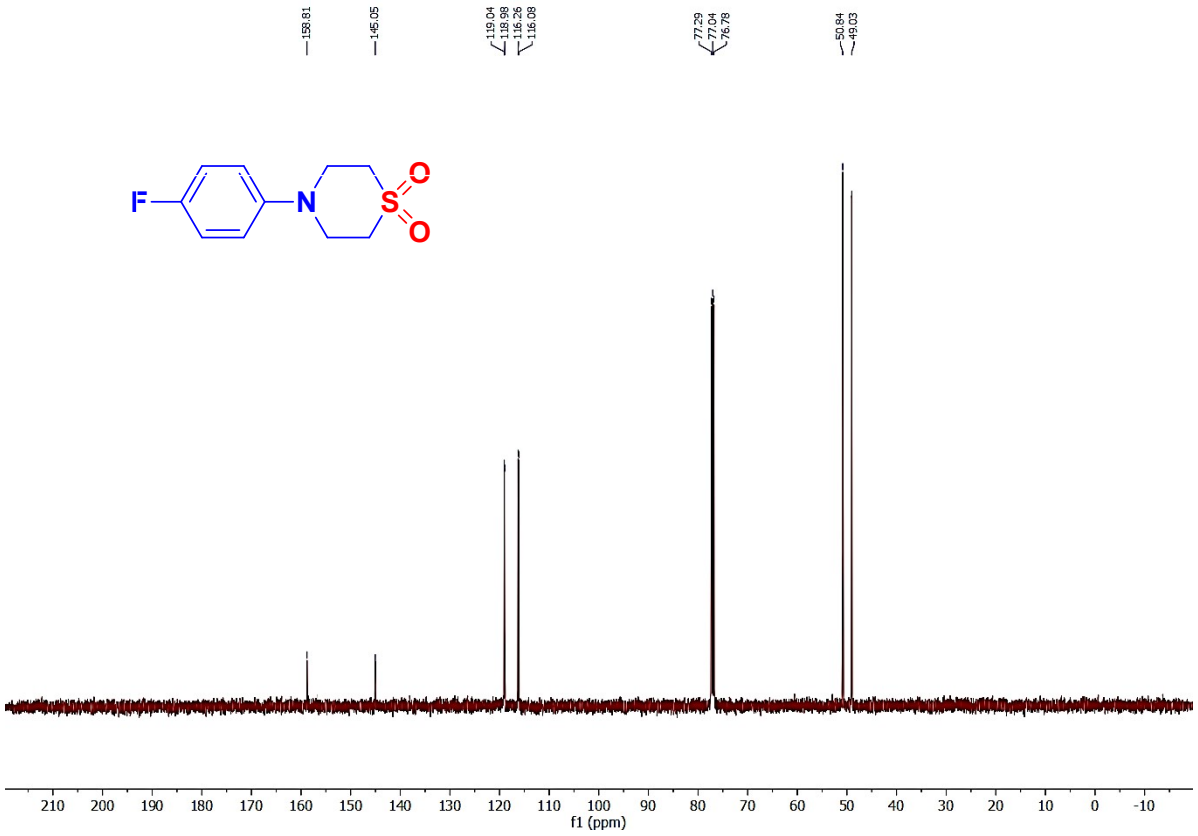
^{13}C NMR spectrum of compound **5r**, ($CDCl_3$, 125 MHz).



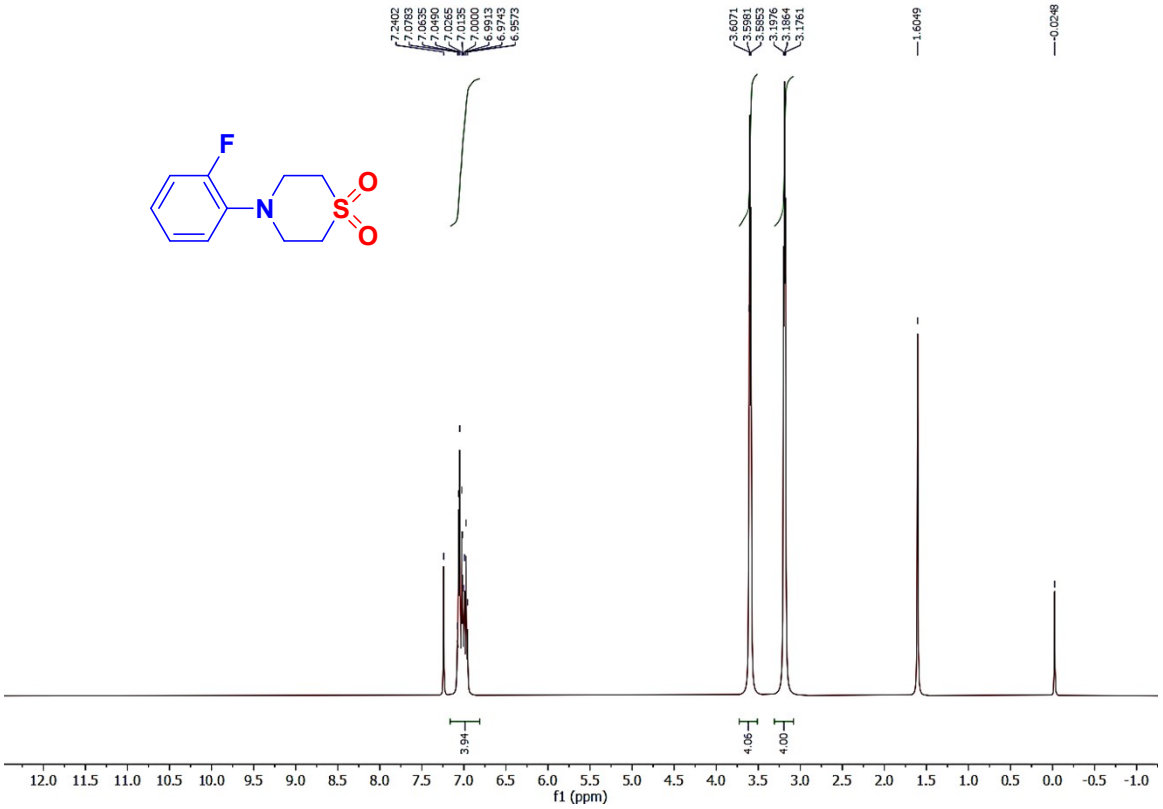
^{1}H NMR spectrum of compound **5s**, ($CDCl_3$, 500 MHz).



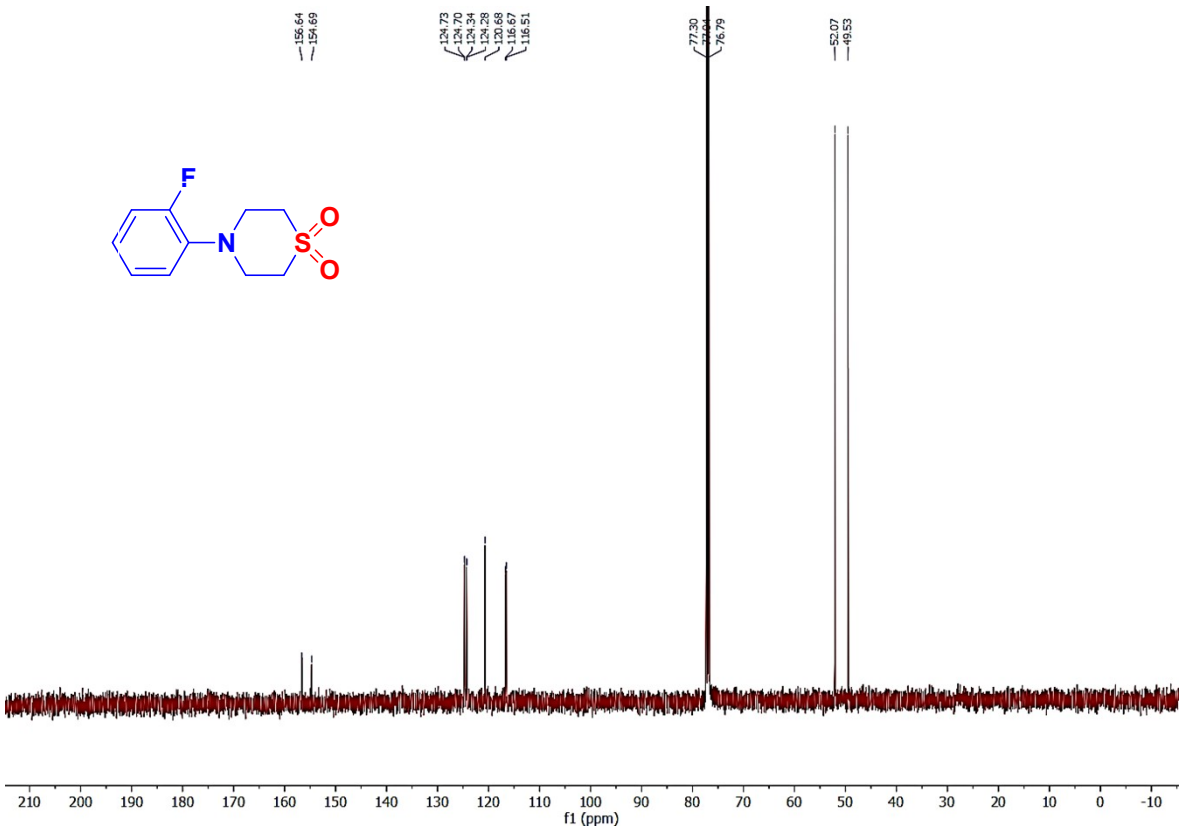
^{13}C NMR spectrum of compound **5s**, ($CDCl_3$, 125 MHz).



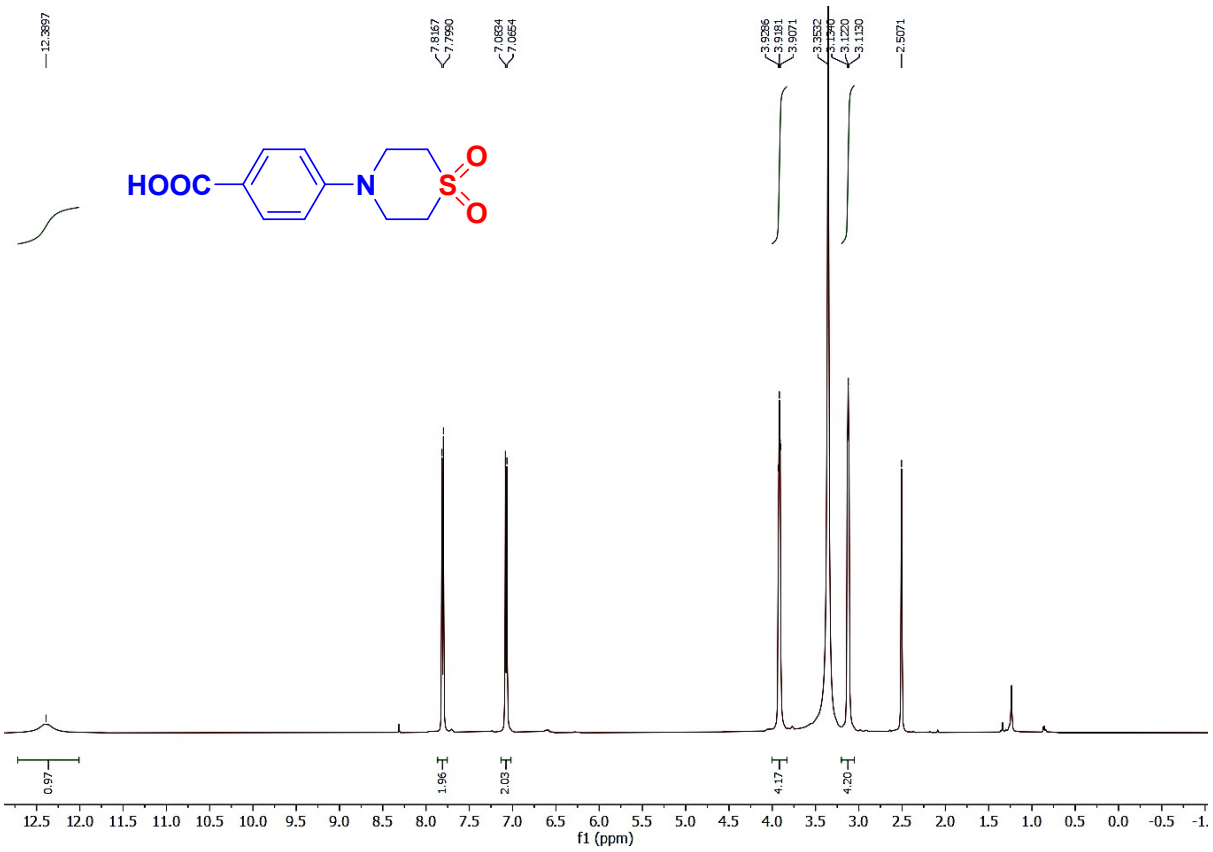
^{1}H NMR spectrum of compound **5t**, ($CDCl_3$, 500 MHz).



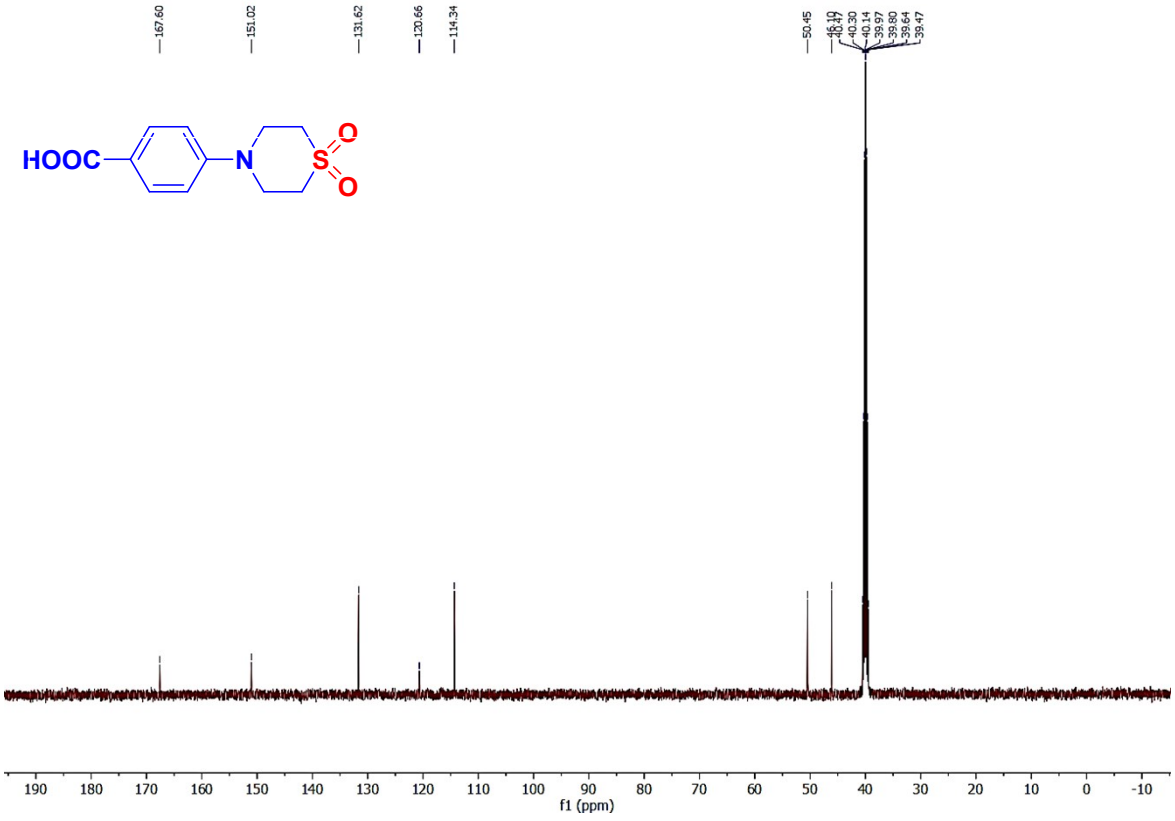
^{13}C NMR spectrum of compound **5t**, ($CDCl_3$, 125 MHz).



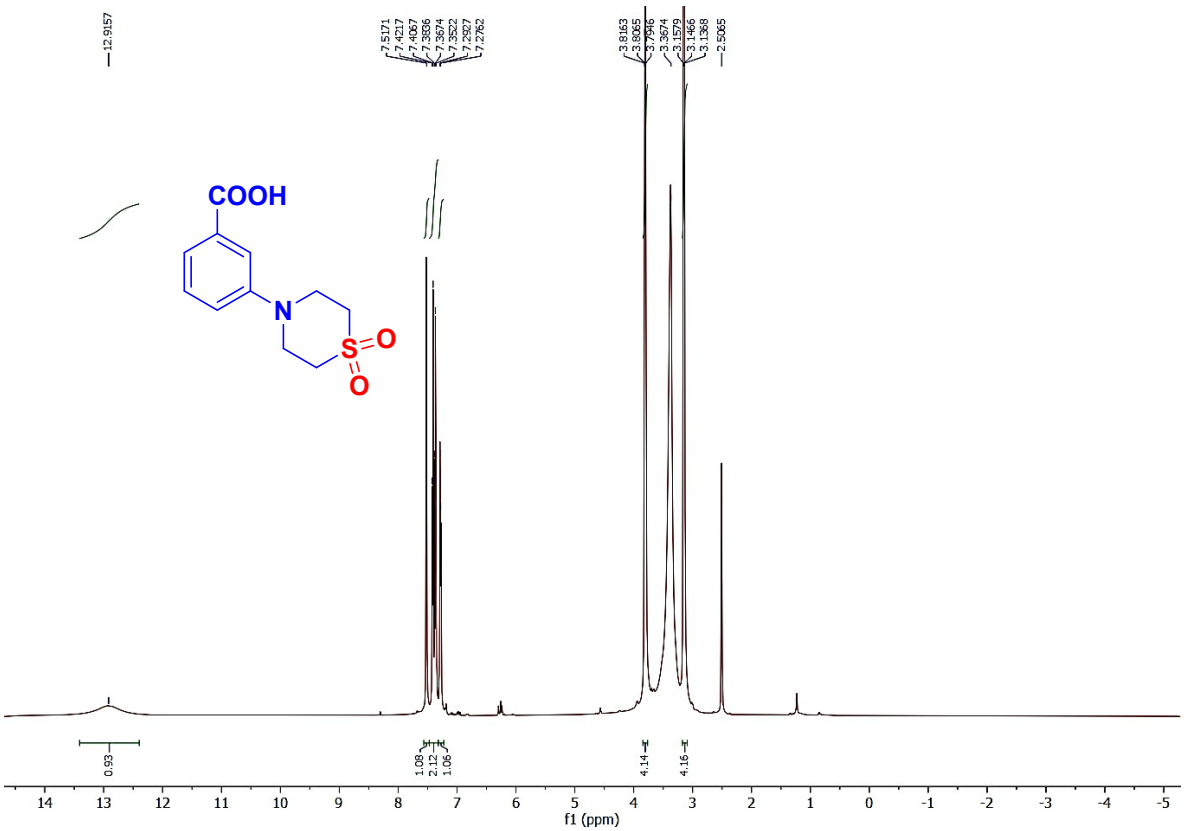
^{1}H NMR spectrum of compound **5u**, (DMSO-d_6, 500 MHz).



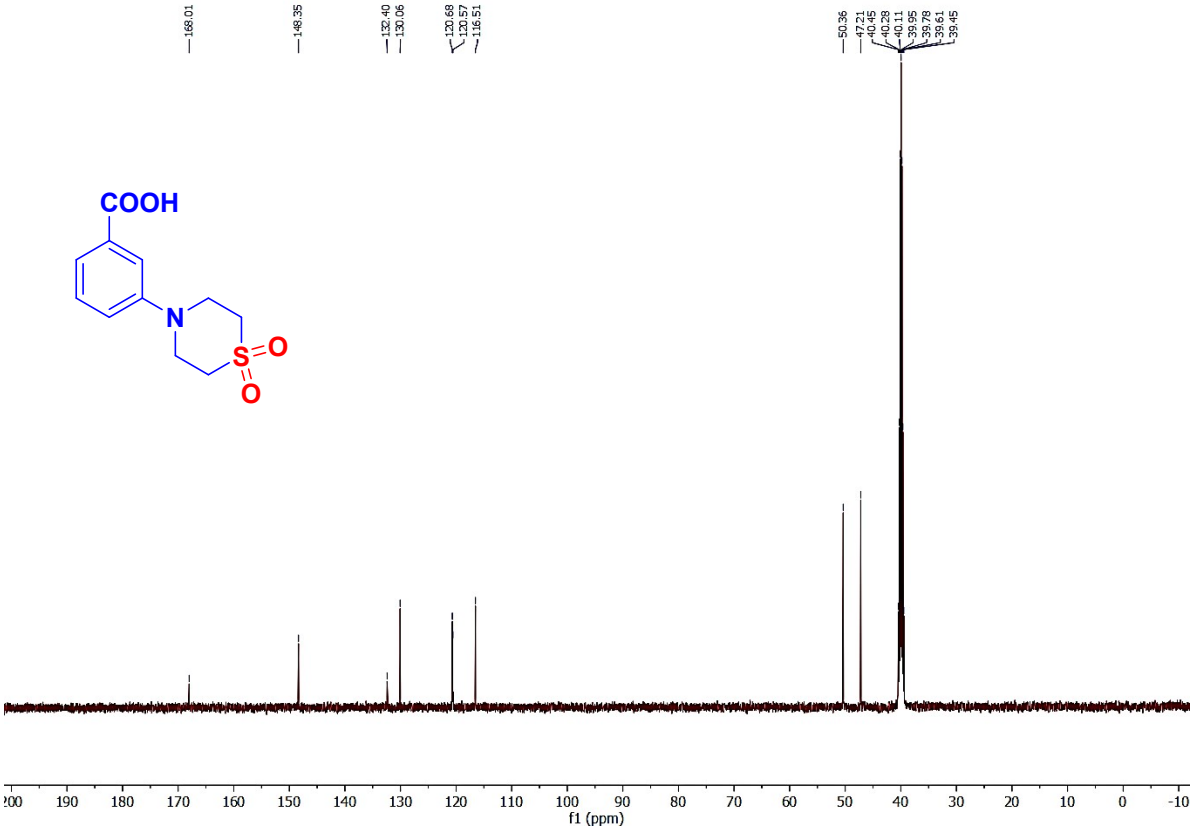
^{13}C NMR spectrum of compound **5u**, (DMSO-d_6, 125 MHz).



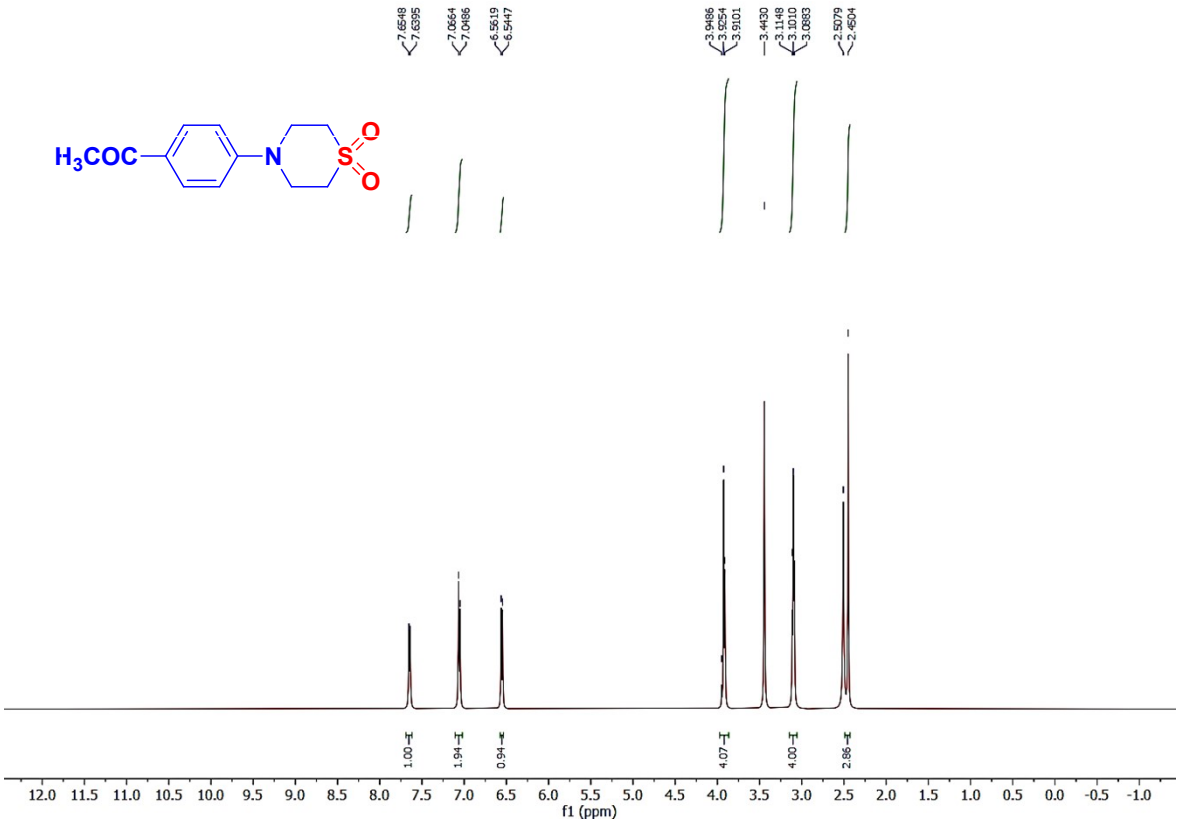
^{1}H NMR spectrum of compound **5v**, (DMSO-d_6, 500 MHz).



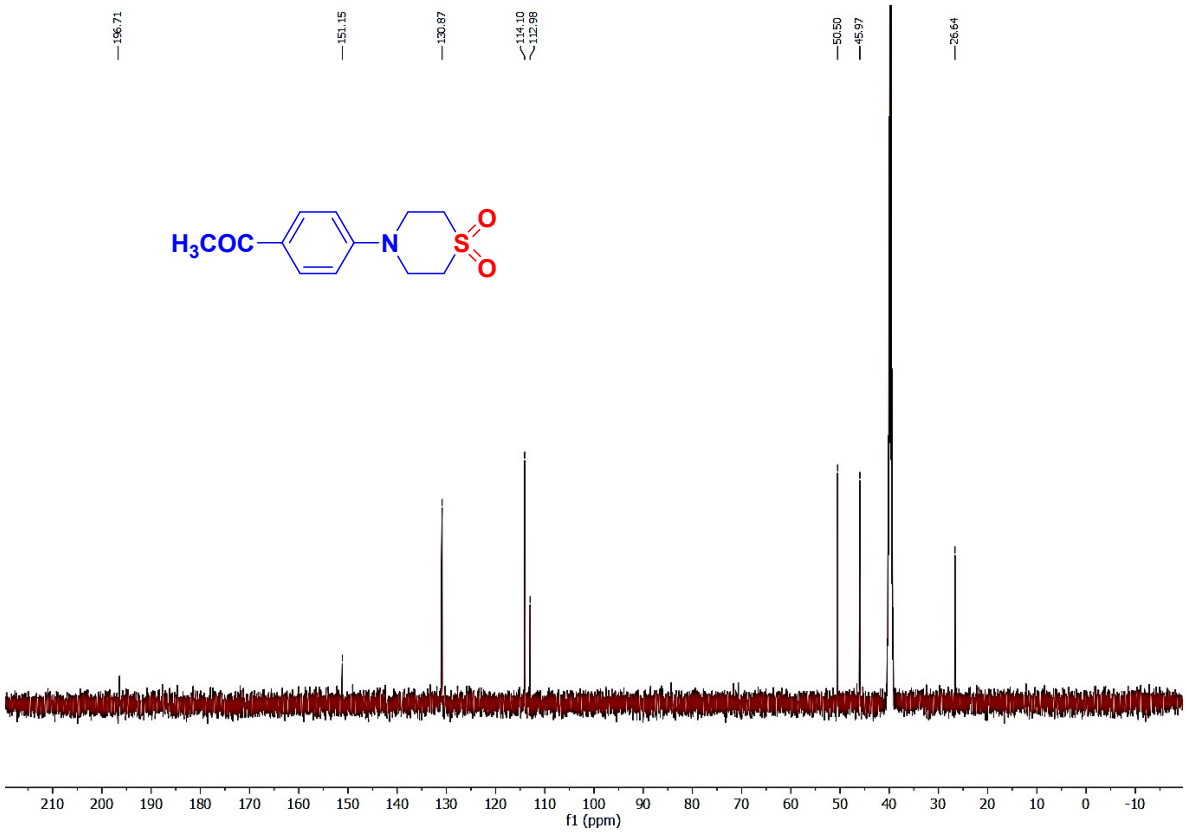
^{13}C NMR spectrum of compound **5v**, (DMSO-d_6, 125 MHz).



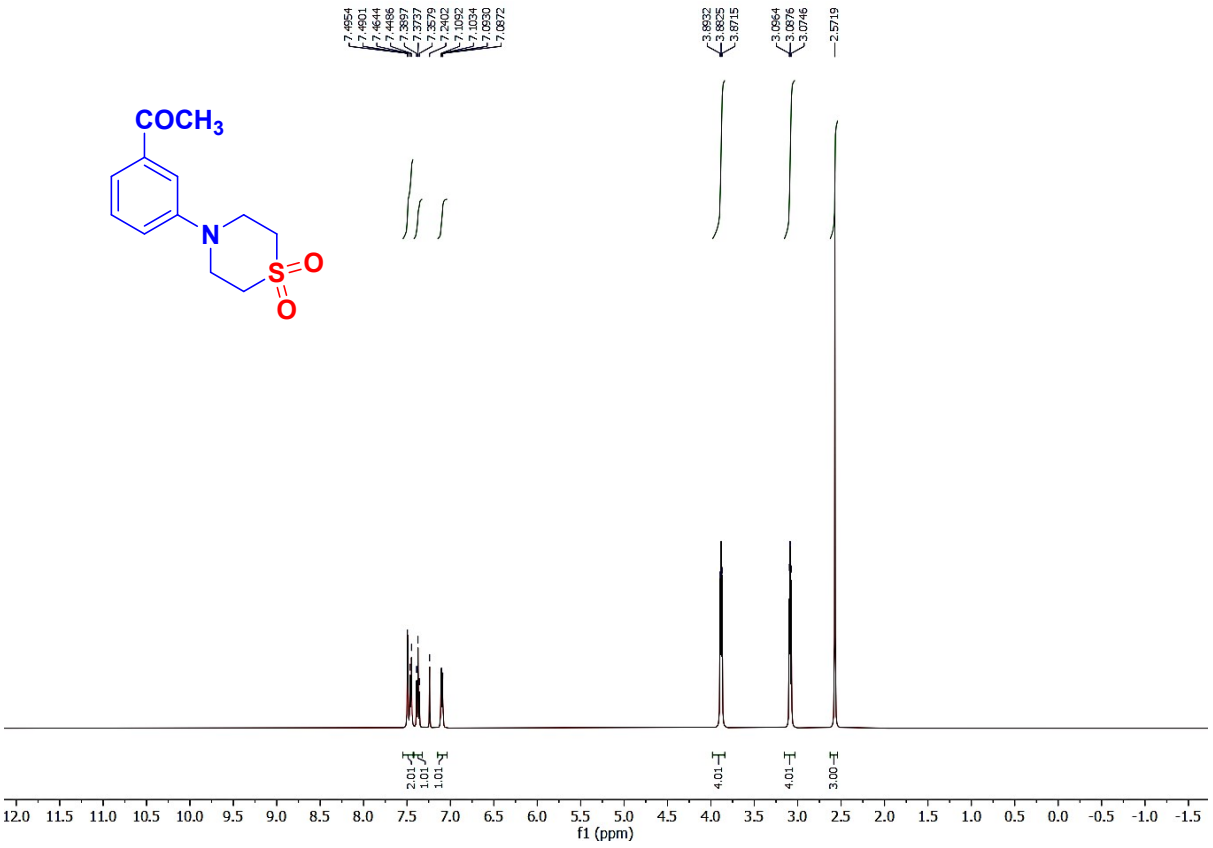
^{1}H NMR spectrum of compound **5w**, (DMSO-d_6, 500 MHz).



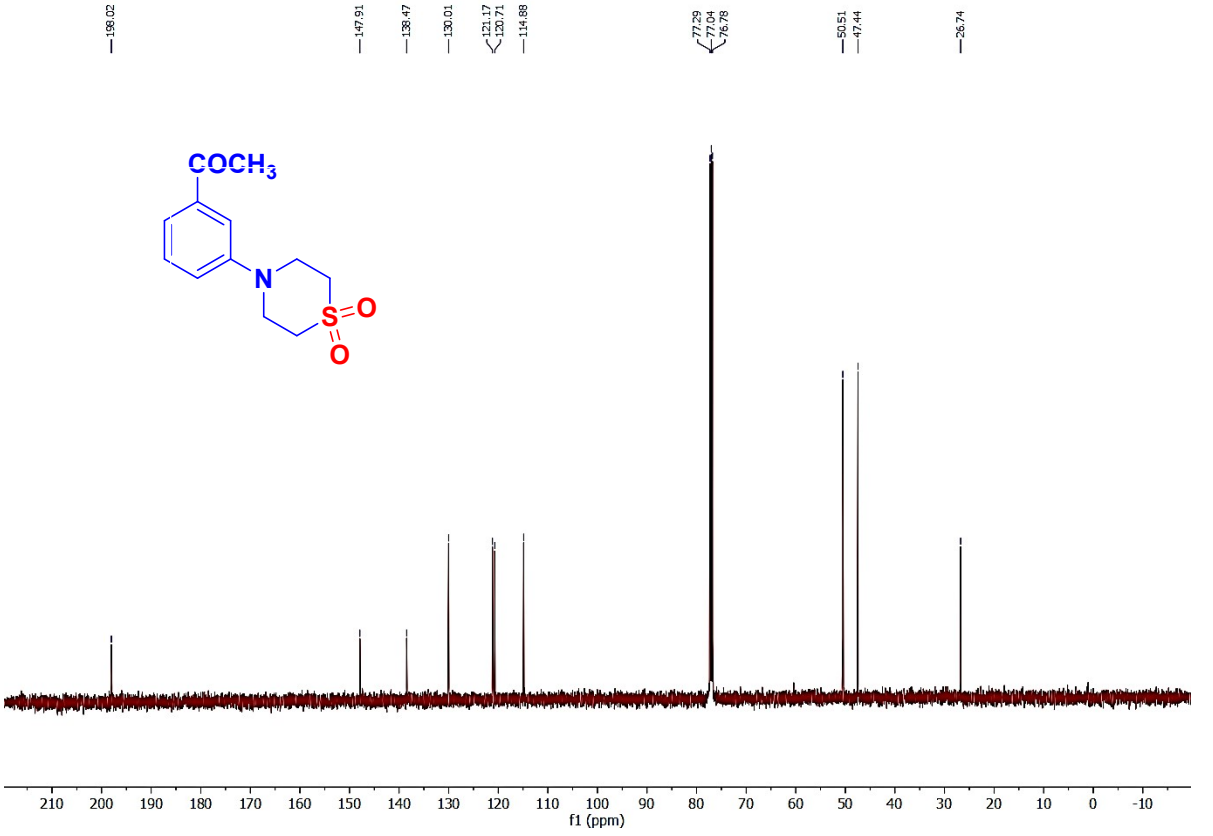
^{13}C NMR spectrum of compound **5w**, (DMSO-d_6, 125 MHz).



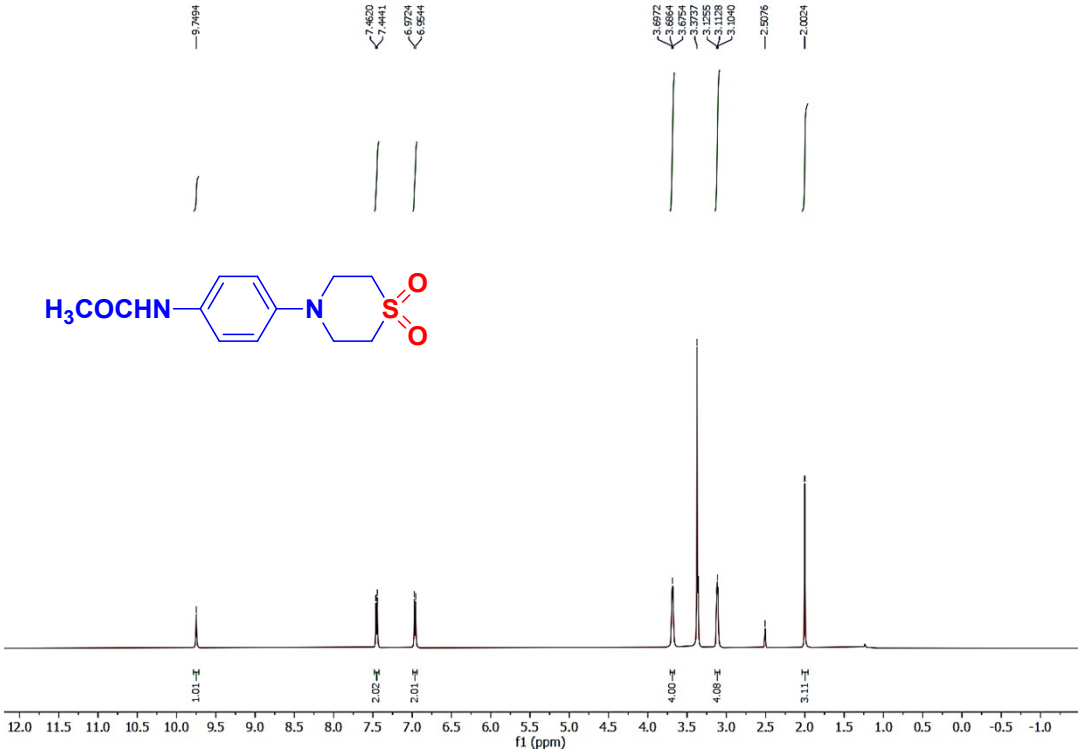
^{1}H NMR spectrum of compound **5x**, ($CDCl_3$, 500 MHz).



^{13}C NMR spectrum of compound **5x**, ($CDCl_3$, 125 MHz).



^{1}H NMR spectrum of compound **5y**, (DMSO-d_6, 500 MHz).



^{13}C NMR spectrum of compound **5y**, (DMSO-d_6, 125 MHz).