Supporting Information

Molecular Editing of NSC-666719 Enabling Discovery of Benzodithiazinedioxide-guanidines as Anticancer Agents

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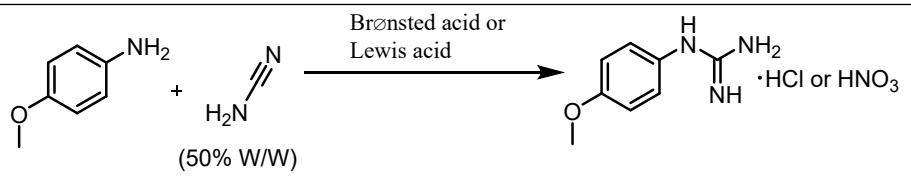
Table of Contents

1 Supporting Figures, Tables, Schemes:

Synthesis of *N*-arylguanidines from aromatic amines

For the synthesis of *N*-arylguanidines from aromatic amines, we screened various methods[1-4] known for the reaction of arylamines and cyanamide (Table S1). All these reactions continued up to 24 hours provided *N*-*p*-Methoxyphenyluanidine hydrochloride in low to moderate yield. In the $Sc(OTf)_3$-catalyzed reaction, product formed in moderate yield. Then, reactions using microwave irradiation conditions were performed. Various catalysts, such as copper (I) and copper (II), $ZnCl_2$, $FeCl_3$, and $AlCl_3$ were evaluated. $AlCl_3$ was found to be most effective and provided very good yield of the product (80%). The reaction with $AlCl_3$-catalysis and performed at higher temperature (130 °C) produced the desired phenylguanidine hydrochloride in excellent yield (94%).

Table S1: Evaluation of catalysts for the synthesis of *N*-4-Methoxyphenylguanidine hydrochloride under microwave irradiation***[1-5]***

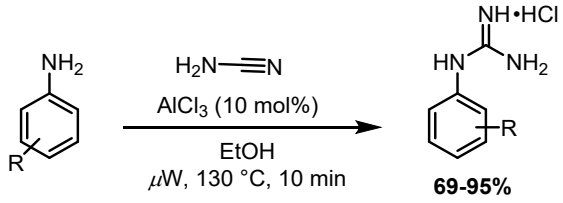


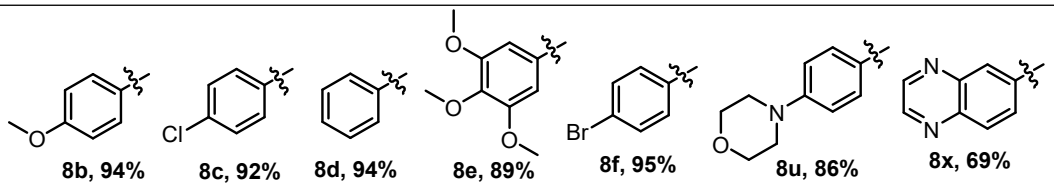
S. No.[a]	Acid or Lewis acid	Solvent	Conditions	% yield
1.	Excess HCl	H_2O	100 °C, 24 h	48
2.	Excess HNO_3	1, 4 Dioxane	100 °C, 24 h	53
3.	$Sc(OTf)_3$ (10 mol%)	H_2O:1, 4 Dioxane (1:1)	100 °C, 24 h	48
4.	CuCl	EtOH	μW, 100 °C, 10 min	26
5.	CuBr	EtOH	μW, 100 °C, 10 min	35
6.	$CuCl_2$	EtOH	μW, 100 °C, 10 min	40
7.	$CuBr_2$	EtOH	μW, 100 °C, 10 min	42
8.	$Cu(OAc)_2$	EtOH	μW, 100 °C, 10 min	32
9.	$Cu(OTf)_2$	EtOH	μW, 100 °C, 10 min	45
10.	ZnI_2	EtOH	μW, 100 °C, 10 min	42
11.	$ZnCl_2$	EtOH	μW, 100 °C, 10 min	65

12.	$SnCl_2$	EtOH	μW, 100 °C, 10 min	41
13.	$NiCl_2$	EtOH	μW, 100 °C, 10 min	40
14.	$FeCl_3$	EtOH	μW, 100 °C, 10 min	72
15.	**$AlCl_3$**	EtOH	μW, 100 °C, 10 min	**80**
16.	**$AlCl_3$**	EtOH	μW, 130 °C, 10 min	**94**

[a] All reactions were performed at 1 mmol scale

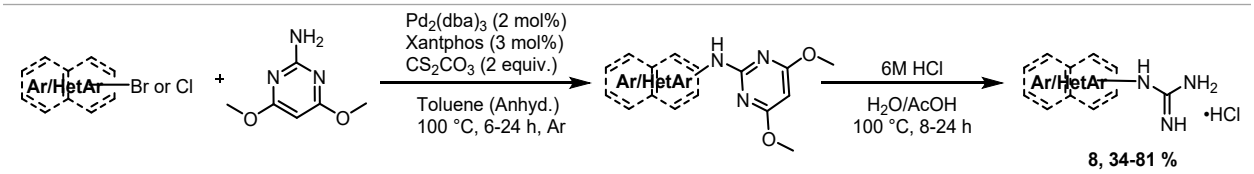
Table S2. Synthesis of *N*--(hetero)arylguanidine hydrochlorides from Ar/HetAr-amines[1-4]

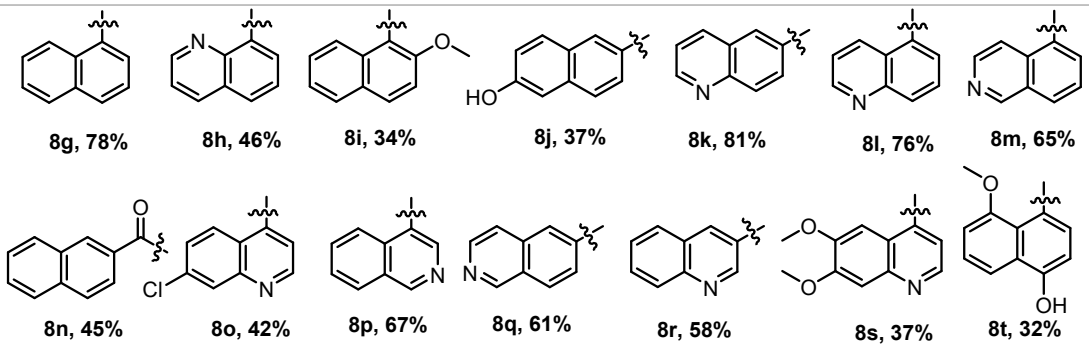


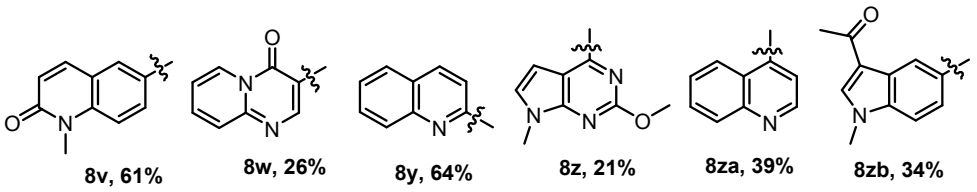


[a] All reactions were performed at 2 mmol scale.

Table S3. Synthesis of *N*--(hetero)arylguanidine hydrochlorides from Ar/HetAr-chlorides[6, 7]







[a]All reactions were performed at 2 mmol scale.

In vitro Polβ nucleotide insertion assays

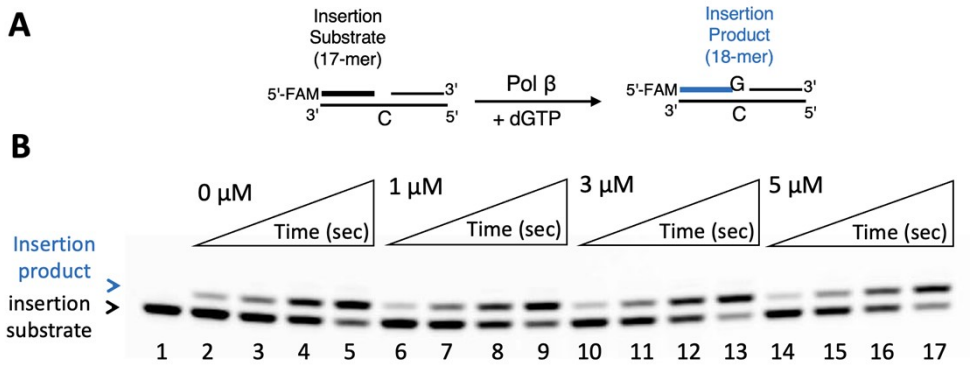


Figure S1: Impact of the best active compounds on Polβ activity. (A) Schematic of the insertion assay used to monitor the gap filling activity of Polβ. (B) Lane 1 is the negative enzyme control containing the reaction mixture and the gap DNA substrate but no Polβ. Lanes 2-5 are the positive control of Polβ dGTP:C insertion products in the absence of the compound. Lanes 6-9, 10-13, and 14-17 are Polβ dGTP:C insertion products in the presence 11a at concentrations of 1, 3, and 5 μM, respectively, and correspond to time points of 15, 30, 45, and 60 sec.

Table S4: Gap-DNA substrate used in pol β dGTP:C insertion assays. One nucleotide gap-DNA substrate with template base C was used in the nucleotide insertion assays. FAM denotes a fluorescent tag and is located at 5'-end of DNA substrates. The base at the template position is underlined.

Gap-DNA Substrate	Sequence
Template C	5'-FAM-CATGGGCGGCATGAACC GAGGCCCATCCTCACC-3' 3'-GTACCCGCCGTACTTGGCCTCCGGGTAGGAGTGG-5'

2 Characterization data for *N*-hetiroarylguanidine hydrochlorides (8g-8z, 8aa and 8bb):

1-(Naphthalen-1-yl)guanidine hydrochloride (Table S3, 8g): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8g**; Purple semisolid (yield 78%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.99-7.90 (m, 3H), 7.76 (broad singlet, 1H [NH]), 7.60-7.51 (m, 3H), 7.43 (d, J = 8 Hz, 1H). ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 157.8, 134.6, 131.3, 130.0, 128.8, 128.3, 127.4, 127.2, 126.5, 125.2, 122.7; LCMS-LTQ (ESI+) calcd for $C_{11}H_{11}N_3^+$ $[M+H]^+$ 186.10, found 185.93.

1-(Quinolin-8-yl)guanidine hydrochloride (Table S3, 8h): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8h**; Yellow semisolid (yield 46%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.94 (d, J = 3 Hz, 1H), 8.44 (d, J =8 Hz, 1H), 7.90 (d, J = 3.5, 1H), 7.74 (broad singlet, 2H [NH]), 7.69 (d, J = 7.5 Hz, 1H), 7.63-7.60 (m, 2H), 7.28 (broad singlet, 2H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 157.1, 150.4, 142.4, 137.0, 134.5, 129.3, 127.3, 125.7, 124.0, 122.6; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.92.

1-(2-Methoxynaphthalen-1-yl)guanidine hydrochloride (Table S3, 8i): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8i**; Pale pink semisolid (yield 34%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87 (d, J = 7.8 Hz, 1H), 7.78-7.75 (m, 2H), 7.38 (d, J = 7.8 Hz, 1H), 7.33-7.30 (m, 2H), 5.99 (broad singlet, 3H [NH]), 3.90 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 157.8, 153.6, 131.9, 130.0, 129.2, 128.6, 127.8, 127.2, 124.5, 121.8, 115.0, 56.8; LCMS-LTQ (ESI+) calcd for $C_{12}H_{14}N_3O^+$ $[M+H]^+$ 216.26, found 215.93.

1-(6-Hydroxynaphthalen-2-yl)guanidine hydrochloride (Table S3, 8j): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8j**; Pale pink semisolid (yield 37%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.74 (s, 1H), 7.56 (dd, J = 16.8, 8.8 Hz, 2H), 7.29 (s, 1H), 7.07 – 6.97 (m, 3H), 4.54 (broad singlet, 3H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 155.4, 155.2, 132.02, 128.9, 128.7, 127.3, 124.9, 120.5, 119.4, 109.1; LCMS-LTQ (ESI+) calcd for $C_{11}H_{12}N_3O^+$ $[M+H]^+$ 202.23, found 201.91.

1-(Quinolin-6-yl)guanidine hydrochloride (Table S3, 8k): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8k**; Yellow semisolid (yield 81%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.88 – 8.80 (m, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H),

7.90 (broad singlet, 2H [NH]), 7.79 (d, J = 2.2 Hz, 1H), 7.54 (ddd, J = 12.5, 8.5, 3.1 Hz, 2H), 7.23 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 156.9, 150.9, 146.3, 136.4, 134.1, 130.9, 128.8, 127.1, 122.5, 122.1; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.88.

1-(Quinolin-5-yl)guanidine hydrochloride (Table 3, 8l): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8l**; Yellow semisolid (yield 76%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82 – 8.70 (m, 1H), 8.37 (d, J = 8.5 Hz, 1H), 7.60 – 7.48 (m, 2H), 7.37 (dd, J = 8.5, 3.9 Hz, 1H), 6.99 (d, J = 6.8 Hz, 1H), 6.00 (broad singlet, 4H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 167.6, 154.7, 150.4, 149.5, 132.9, 130.3, 125.1, 122.3, 120.4, 119.0; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.91.

1-(Isoquinolin-5-yl)guanidine hydrochloride (Table 3, 8m): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8m**; Yellow semisolid (yield 65%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.35 (s, 1H), 8.55 (d, J = 7.3 Hz, 1H), 8.08 (d, J = 7.3 Hz, 1H), 7.76 (s, 1H), 7.69-7.67 (m, 2H), 7.31 (broad singlet, 4H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 13C NMR (125 MHz, DMSO- d_6) δ 157.3, 153.1, 144.1, 132.6, 131.9, 129.6, 129.0, 128.2, 127.3, 115.8; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.97.

***N*-Carbamimidoyl-2-naphthamide hydrochloride (Table S3, 8n):** Purification by column chromatography (MeOH-DCM, 1:10 V/V) afforded **8n**; White solid (yield 45%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.29 – 7.91 (m, 3H), 7.87 (dd, J = 16.6, 8.2 Hz, 2H), 7.50 (dq, J = 13.0, 6.5 Hz, 2H), 6.77 (broad singlet, 2H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 176.2, 163.5, 137.1, 134.6, 132.8, 129.4, 129.1, 128.0, 127.5, 126.6, 126.3; LCMS-LTQ (ESI+) calcd for $C_{12}H_{12}N_3O^+$ $[M+H]^+$ 214.24, found 213.92.

1-(7-Chloroquinolin-4-yl)guanidine hydrochloride (Table S3, 8o): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8o**; Yellow semisolid (yield 42%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.39 (d, J = 8.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.80 (s, 1H), 7.37 (d, J = 8.5, 1H), 6.59 (d, J = 6.8 Hz, 1H), 7.03 (broad singlet, 4H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 158.2, 153.2, 144.1, 137.4, 136.7, 132.3, 131.0, 130.5, 129.5, 128.1, 127.6, 126.7, 115.9; LCMS-LTQ (ESI+) calcd for $C_{10}H_{10}ClN_4^+$ $[M+H]^+$ 221.66, found 220.89.

1-(Isoquinolin-4-yl)guanidine hydrochloride (Table S3, 8p): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8p**; Yellow semisolid (yield 67%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.67 (d, J = 2.2 Hz, 1H), 8.40 (s, 3H), 8.03 (d, J = 2.3 Hz, 1H), 7.96 (d,

J = 8.3 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 5.44 (s, 1H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 13C NMR (126 MHz, DMSO-D6) δ 160.2, 148.4, 145.4, 132.6, 129.1, 129.0, 128.5, 128.3, 128.3, 127.5; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.88.

1-(Isoquinolin-6-yl)guanidine hydrochloride (Table S3, 8q): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8q**; Yellow semisolid (yield 61%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.46 (s, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.01 – 7.70 (m, 5H), 7.49 (d, *J* = 8.0 Hz, 1H), 5.43 (s, 1H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 13C NMR (126 MHz, DMSO- d_6) δ 156.5, 152.4, 143.9, 137.9, 136.5, 130.0, 126.5, 124.4, 120.7, 119.2; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.90.

1-(Quinolin-3-yl)guanidine hydrochloride (Table S3, 8r): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8r**; Yellow semisolid (yield 58%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.24 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 4H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 5.43 (s, 1H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 157.7, 150.0, 140.3, 132.8, 131.3, 131.0, 129.3, 128.1, 122.6; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.22, found 186.88.

1-(6,7-Dimethoxyquinolin-4-yl)guanidine hydrochloride (Table S3, 8s): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8s**; Yellow semisolid (yield 37%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 3H), 8.39 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.37 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 132.4, 131.8, 125.9, 125.6, 124.6, 123.8, 123.3, 56.4, 56.2; LCMS-LTQ (ESI+) calcd for $C_{12}H_{15}N_4O_2^+$ $[M+H]^+$ 247.27, found 247.95.

1-(4-Hydroxy-8-methoxynaphthalen-1-yl)guanidine hydrochloride (Table S3, 8t): Purification by column chromatography (MeOH-DCM, 1:10 V/V) afforded **8t**; Yellow semisolid (yield 32%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.25 (s, 1H), 8.25 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 4.90 (broad singlet, 3H [NH]), 3.96 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 159.6, 155.7, 144.8, 129.7, 129.1, 127.1, 122.7, 122.3, 117.6, 113.7, 56.0; LCMS-LTQ (ESI+) calcd for $C_{12}H_{14}N_3O_2^+$ $[M+H]^+$ 232.26, found 231.96.

1-(4-Morpholinophenyl)guanidine hydrochloride (Table S2, 8u): Purification by column chromatography (MeOH-DCM, 1:10 V/V) afforded **8u**; Pale yellow semisolid (yield 86%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.96 (broad singlet, 4H [NH]), 7.00 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.69 (t, J = 4.5 Hz, 4H), 3.05 (t, J = 4.5 Hz, 4H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 160.2, 157.3, 149.7, 126.1, 116.3, 66.5, 49.0; LCMS-LTQ (ESI+) calcd for $C_{11}H_{16}N_4O^+$ $[M+H]^+$ 221.28, found: 220.94.

1-(1-Methyl-2-oxo-1,2-dihydroquinolin-6-yl)guanidine hydrochloride (Table S3, 8v): Purification by column chromatography (MeOH-DCM, 3:10 V/V) afforded **8v**; Yellow semisolid (yield 61%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.90 (s, 1H), 7.85 (d, J = 9.4 Hz, 1H), 7.54 (dd, J = 21.0, 8.4 Hz, 2H), 6.90 (broad singlet, 3H [NH]), 6.60 (d, J = 9.5 Hz, 1H), 3.57 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 167.8, 161.4, 136.7, 131.1, 127.0, 126.7, 122.2, 29.6; LCMS-LTQ (ESI+) calcd for $C_{11}H_{13}N_4O^+$ $[M+H]^+$ 217.25, found 216.93.

1-(4-Oxo-4H-pyrido[1,2-*a*]pyrimidin-3-yl)guanidine hydrochloride (Table S3, 8w): Purification by column chromatography (MeOH-DCM, 3:10 V/V) afforded **8w**; Yellow semisolid (yield 26%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.54 (s, 1H), 7.96 (d, J = 14.4 Hz, 1H), 7.91 (d, J = 10.9 Hz, 2H), 7.04 (s, 2H), 6.79 (broad singlet, 3H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 164.5, 145.4, 137.5, 131.6, 127.5, 126.7, 120.2, 114.8; LCMS-LTQ (ESI+) calcd for $C_9H_9N_5O^+$ $[M+H]^+$ 204.21, found 203.88.

1-(Quinoxalin-6-yl)guanidine hydrochloride (Table S2, 8x): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8x**; Red semisolid (yield 69%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.90 (d, J = 1.5 Hz, 1H), 8.85 (d, J = 1.6 Hz, 1H), 8.26 (s, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.76 (dd, J = 9.0, 2.3 Hz, 1H), 6.90 (broad singlet, 3H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 168.9, 157.8, 134.6, 128.3, 127.4, 127.2, 126.5, 122.7; LCMS-LTQ (ESI+) calcd for $C_9H_{10}N_5^+$ $[M+H]^+$ 188.21, found 187.93.

1-(Quinolin-2-yl)guanidine hydrochloride (Table S3, 8y): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8y**; White semisolid (yield 64%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.35 (d, J = 8.9 Hz, 1H), 7.97 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.3 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 5.63 (broad singlet, 3H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 169.1, 156.4, 152.5,

131.1, 130.7, 127.7, 126.2, 125.3; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.21, found 186.93.

1-(2-Methoxy-7-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)guanidine hydrochloride (Table S3, 8z): Purification by column chromatography (MeOH-DCM, 1:10 V/V) afforded **8z**; Yellow semisolid (yield 21%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47 (d, J = 3.4 Hz, 1H), 6.71 (d, J = 3.5 Hz, 1H),) 5.87 (broad singlet, 3H [NH]), 3.81 (s, 3H), 2.44 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 161.2, 145.3, 138.3, 124.4, 106.6, 102.5, 43.9, 32.1; LCMS-LTQ (ESI+) calcd for $C_{12}H_{15}N_4O^+$ $[M+H]^+$ 221.24, found 220.91.

1-(Quinolin-4-yl)guanidine hydrochloride (Table S3, 8za): Purification by column chromatography (MeOH-DCM, 2:10 V/V) afforded **8aa**; Yellow semisolid (yield 39%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.73 (d, J = 5.1 Hz, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 5.0 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 6.79 (broad singlet, 3H [NH]); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 159.3, 151.0, 149.2, 143.5, 129.7, 129.6, 125.8, 123.3, 121.6; LCMS-LTQ (ESI+) calcd for $C_{10}H_{11}N_4^+$ $[M+H]^+$ 187.21, found 186.97.

1-(3-Acetyl-1-methyl-1*H*-indol-5-yl)guanidine hydrochloride (Table S3, 8zb): Purification by column chromatography (MeOH-DCM, 3:10 V/V) afforded **8bb**; Red semisolid (yield 34%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.40 (s, 1H), 8.04 (s, 1H), 7.91 (s, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 5.8 Hz, 1H), 6.90 (broad singlet, 3H [NH]), 3.84 (s, 3H), 2.37 (s, 3H); ^{13}C NMR {1H} (125 MHz, DMSO-d_6): δ 192.6, 139.5, 137.4, 136.1, 131.1, 127.0, 126.4, 116.1, 111.9, 33.8, 27.7; LCMS-LTQ (ESI+) calcd for $C_{12}H_{15}N_4O^+$ $[M+H]^+$ 231.26, found 230.93.

3 ^{1}H-NMR and ^{13}C-NMR spectra of final compounds (10a-z):

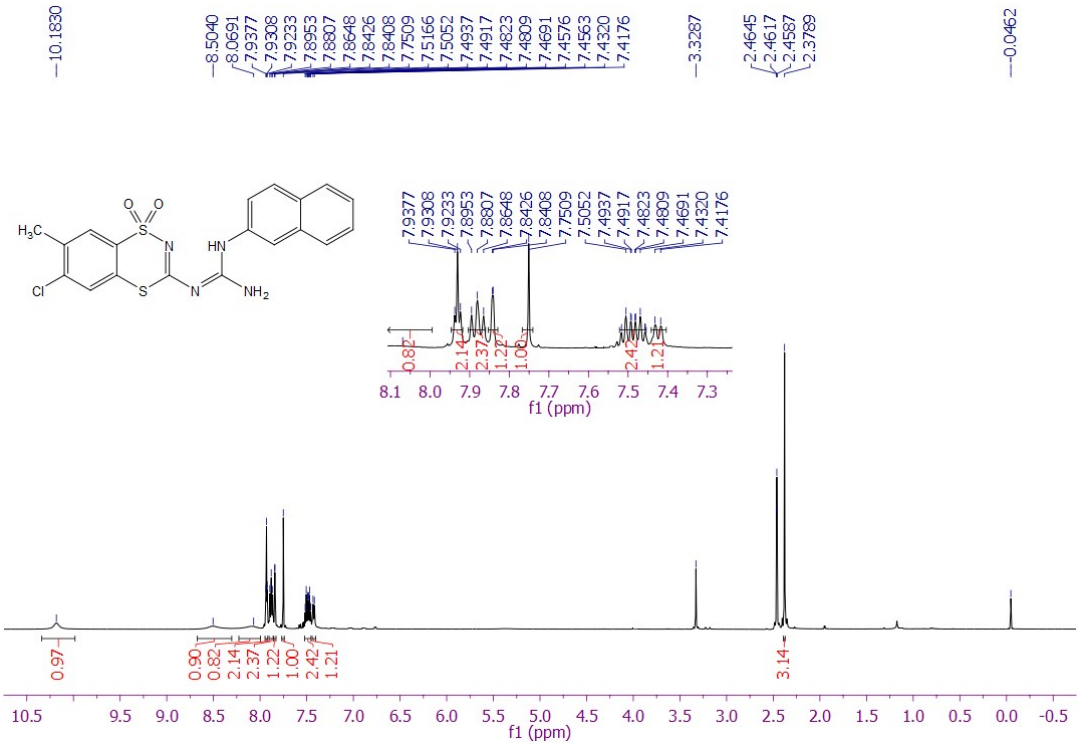


Figure S2. ^{1}H NMR spectrum of **10a** (600 MHz, DMSO-d_6)

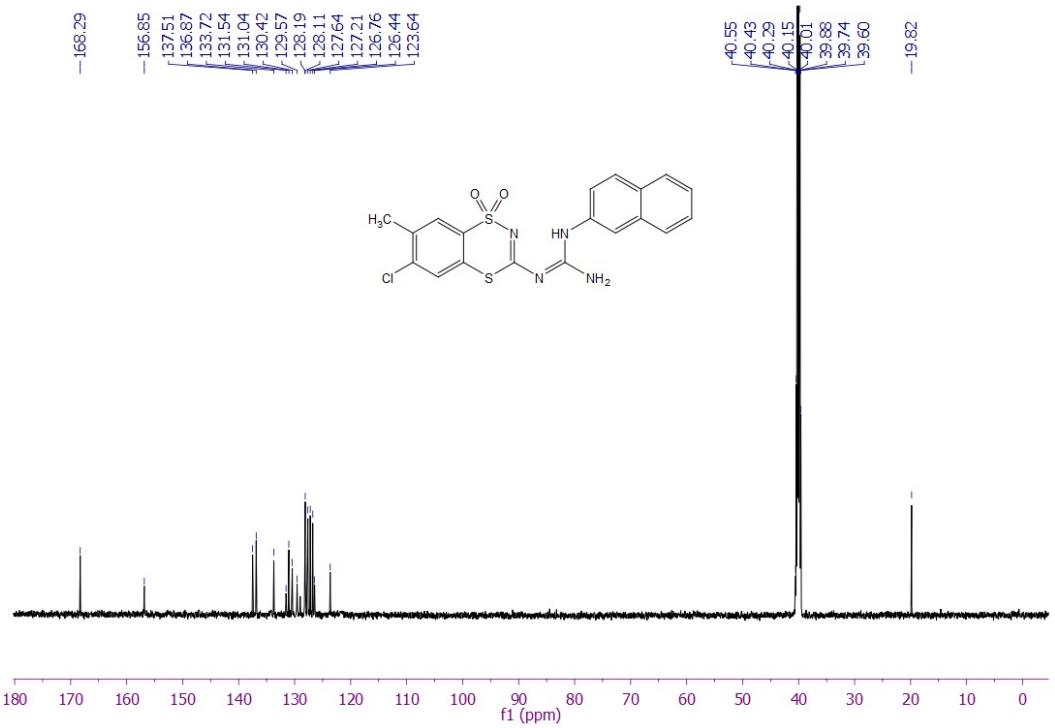


Figure S3. ^{13}C NMR spectrum of **10a** (151 MHz, DMSO-d_6)

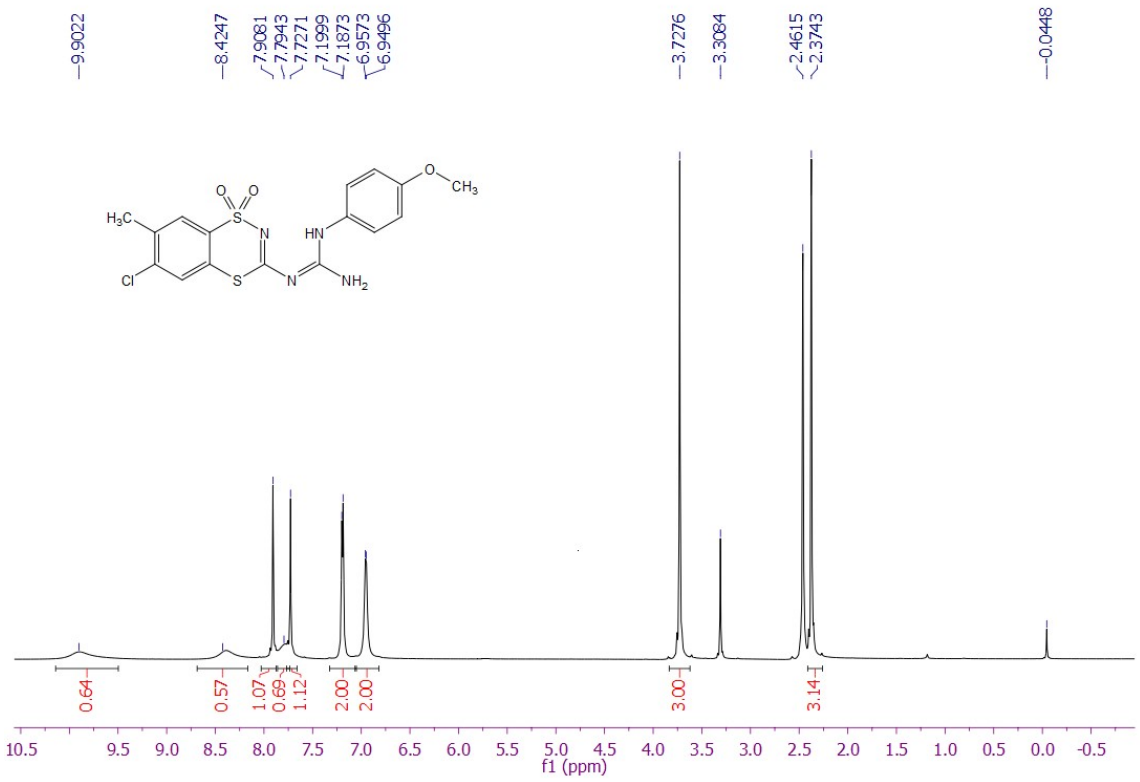


Figure S4. ^{1}H NMR spectrum of **10b** (600 MHz, DMSO-d_6)

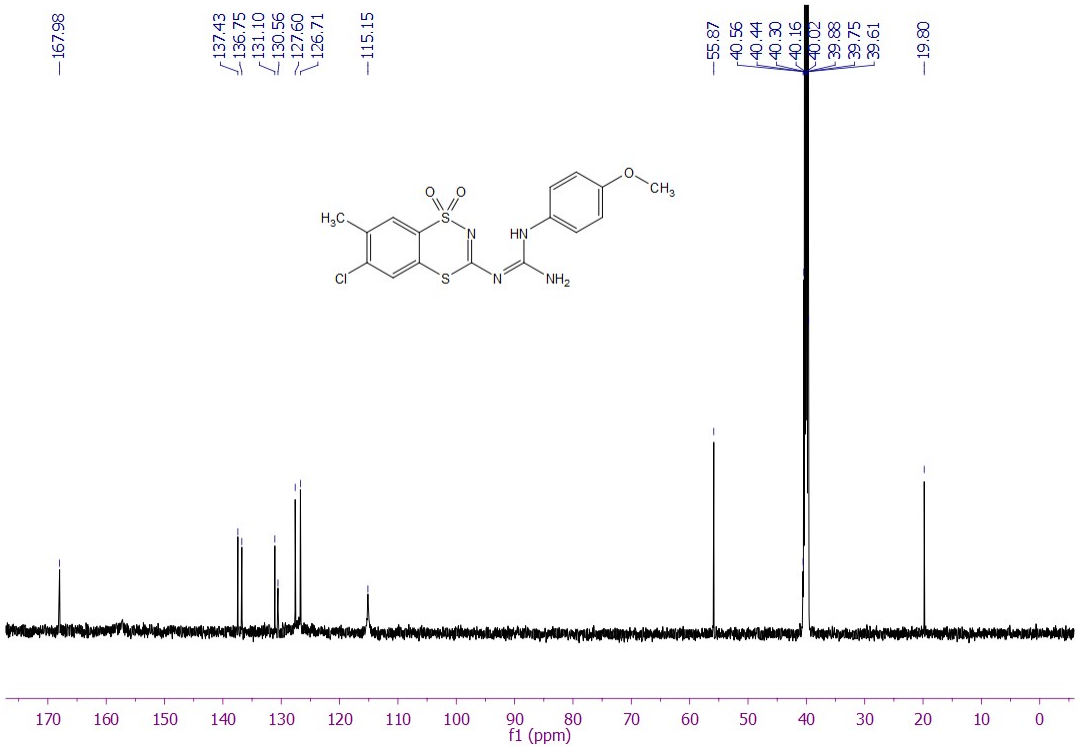


Figure S5. ^{13}C NMR spectrum of **10b** (151 MHz, DMSO-d_6)

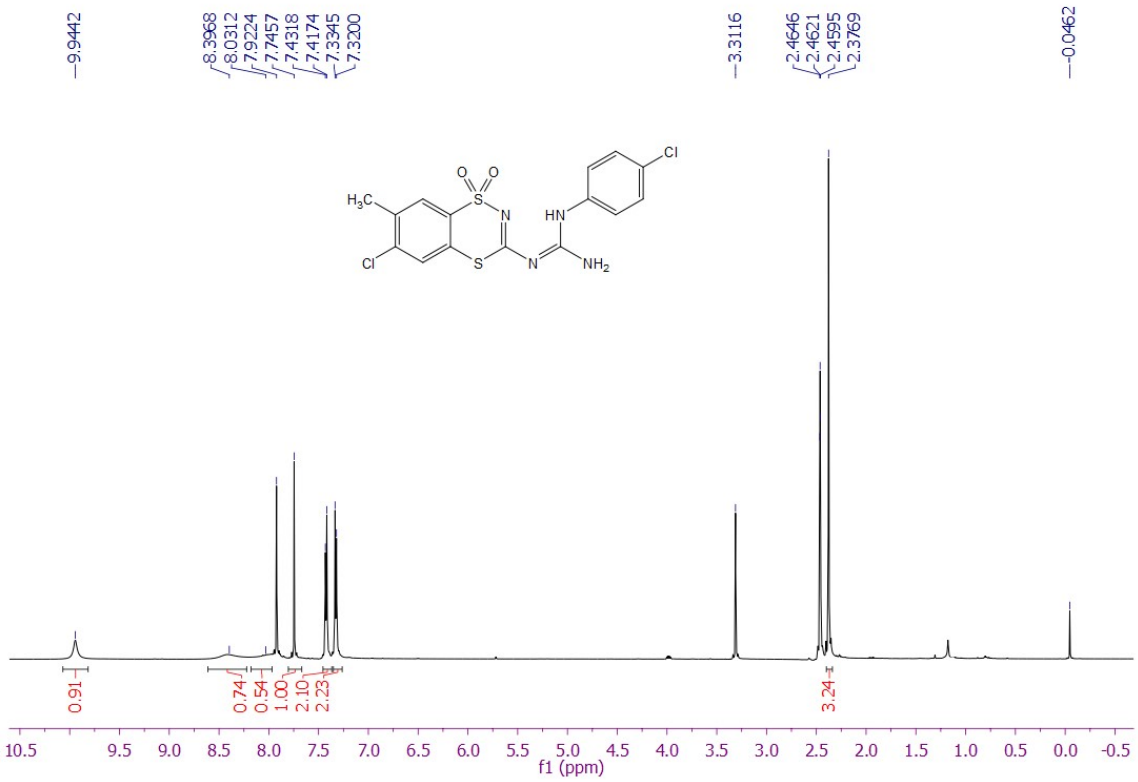


Figure S6. ^{1}H NMR spectrum of **10c** (600 MHz, DMSO-d_6)

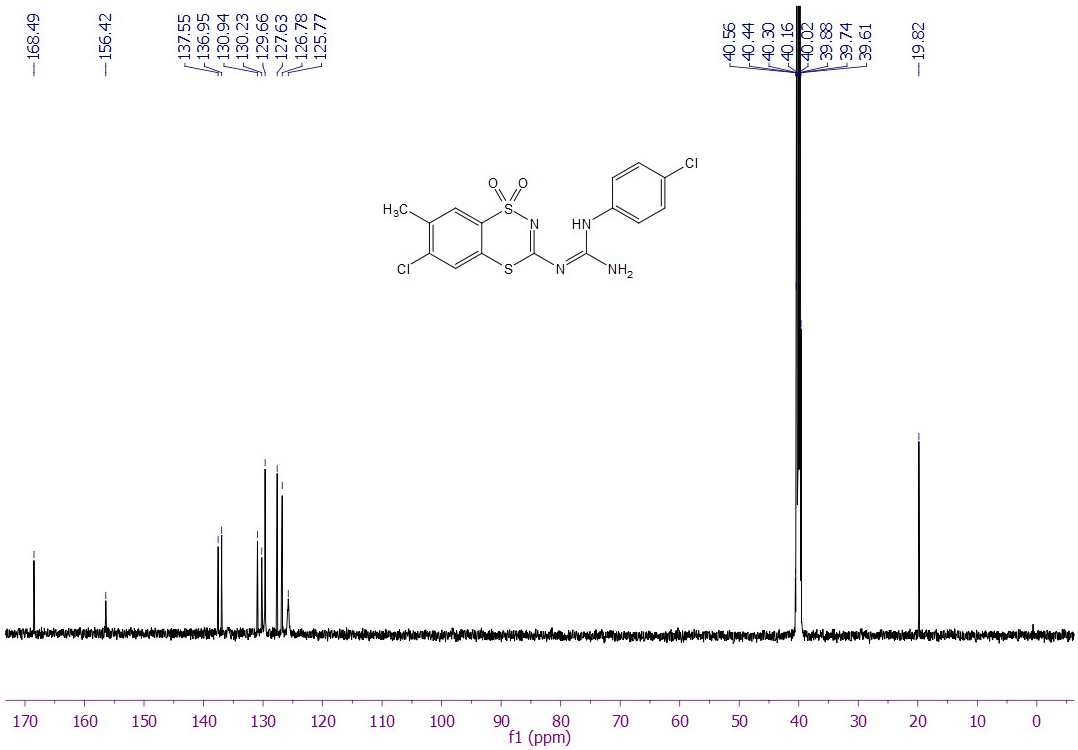


Figure S7. ^{13}C NMR spectrum of **10c** (151 MHz, DMSO-d_6)

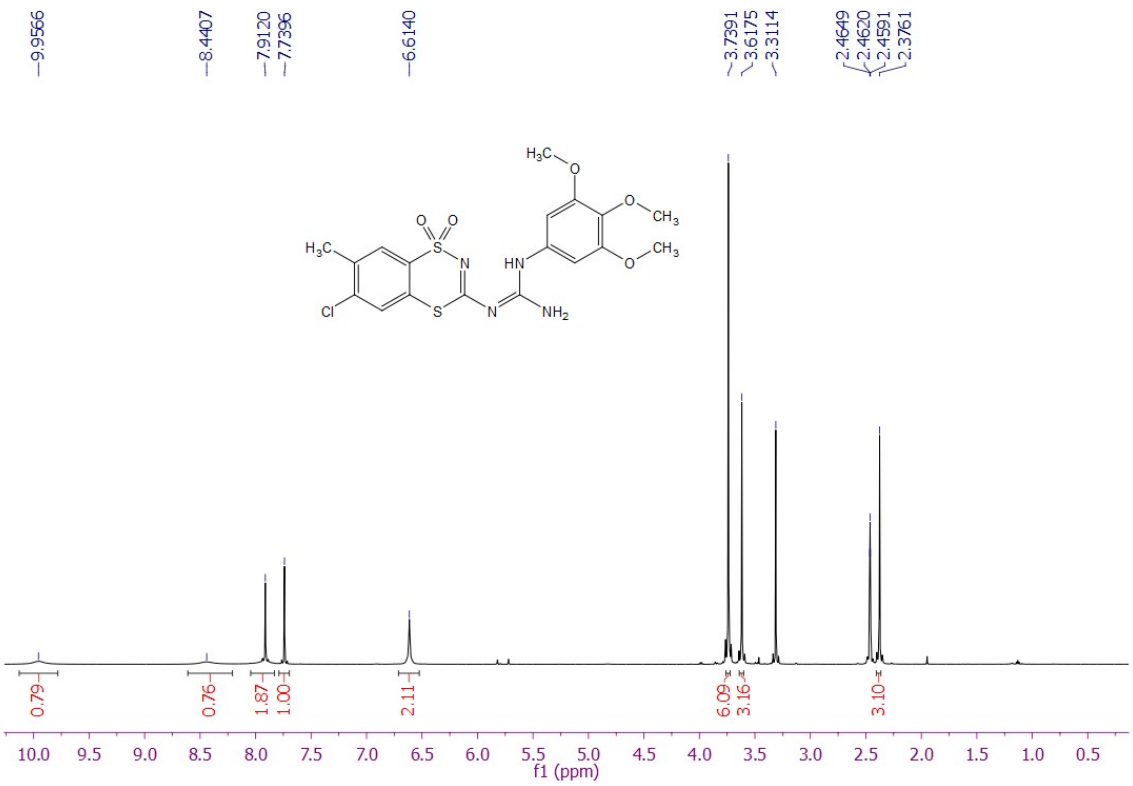


Figure S8. ^{1}H NMR spectrum of **10d** (600 MHz, DMSO-d_6)

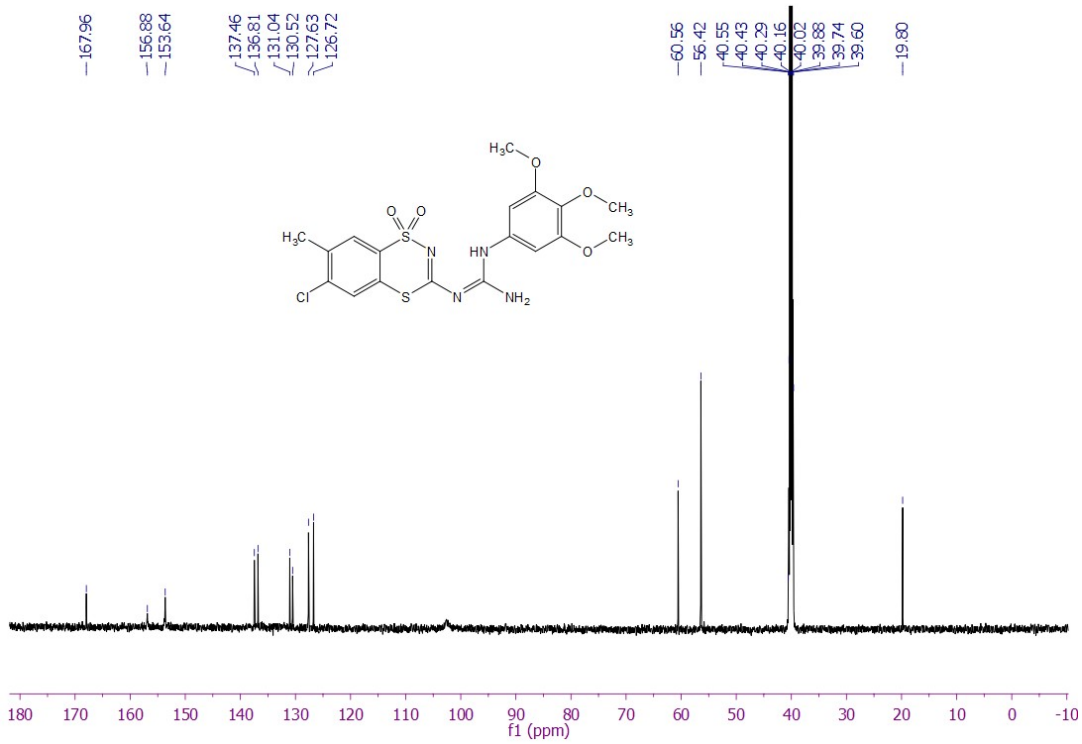


Figure S9. ^{13}C NMR spectrum of **10d** (151 MHz, DMSO-d_6)

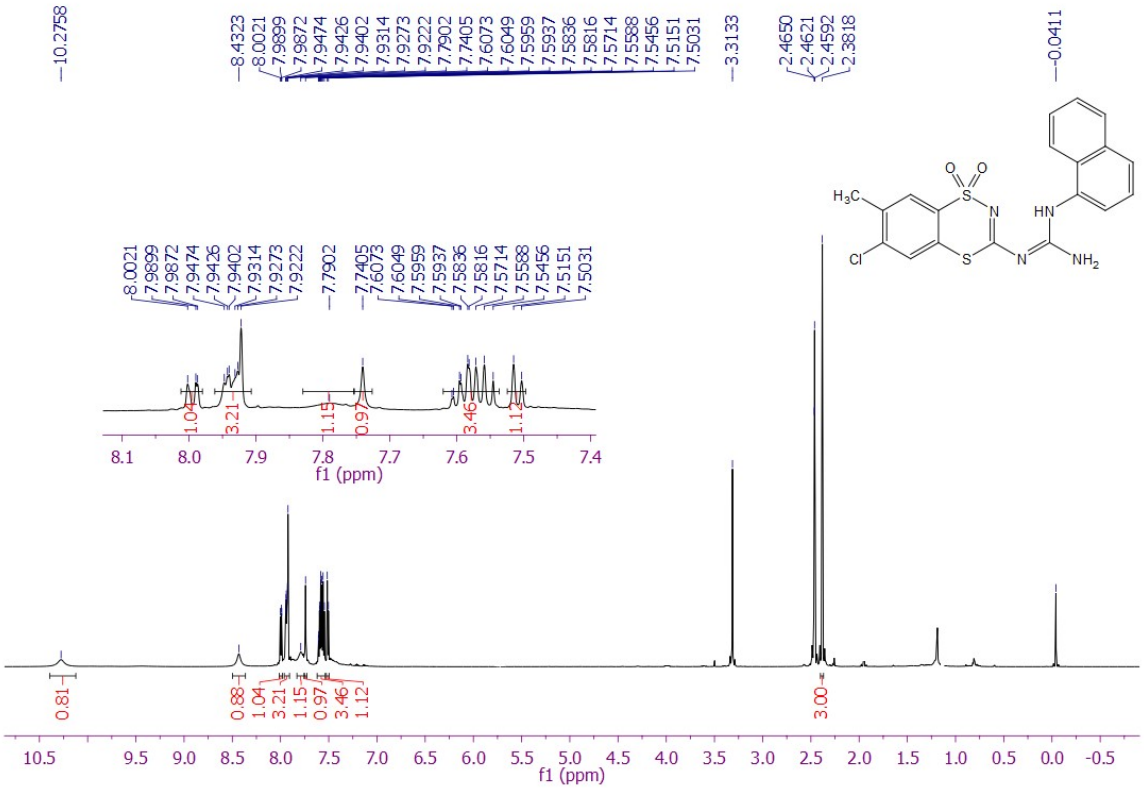


Figure S10. ^{1}H NMR spectrum of **10e** (600 MHz, DMSO-d_6)

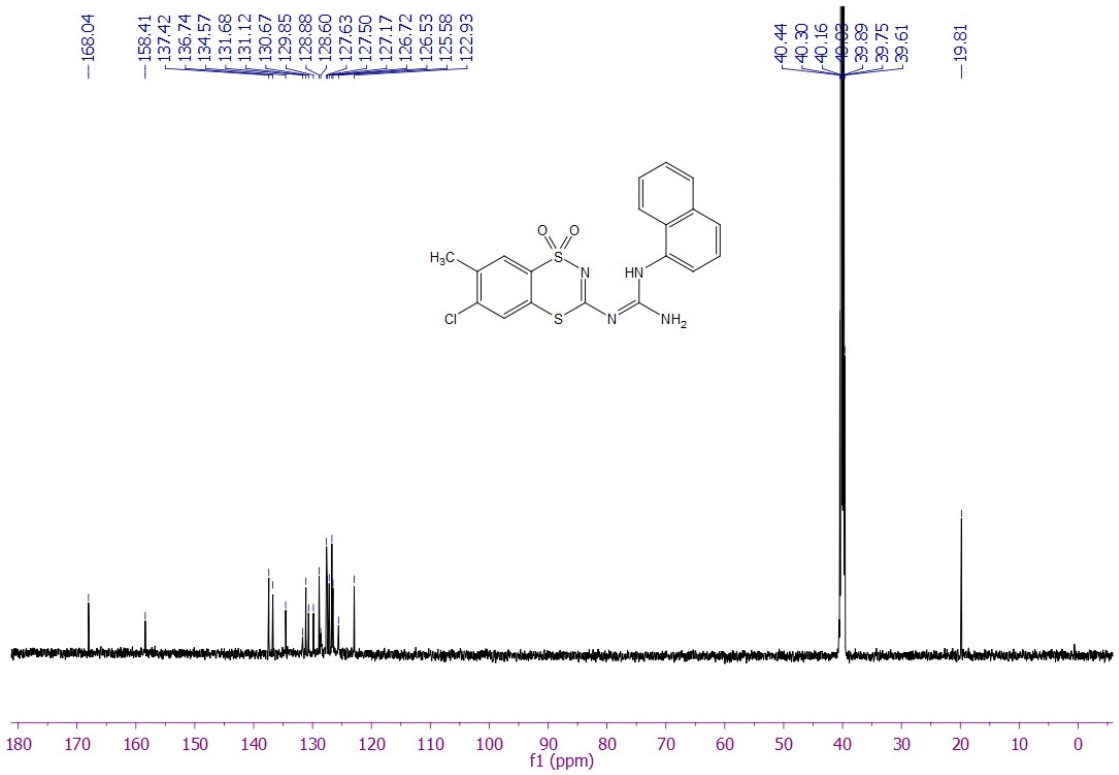


Figure S11. ^{13}C NMR spectrum of **10e** (151 MHz, DMSO-d_6)

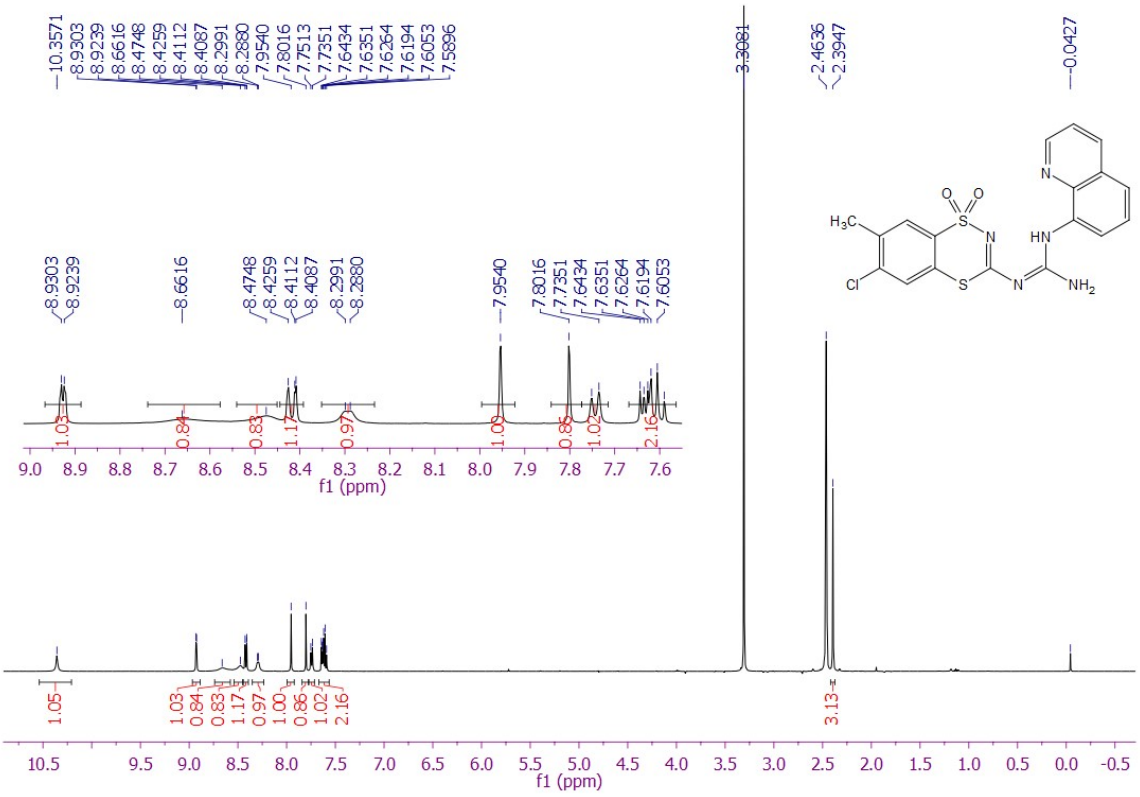


Figure S12. ^{1}H NMR spectrum of **10f** (600 MHz, DMSO-d_6)

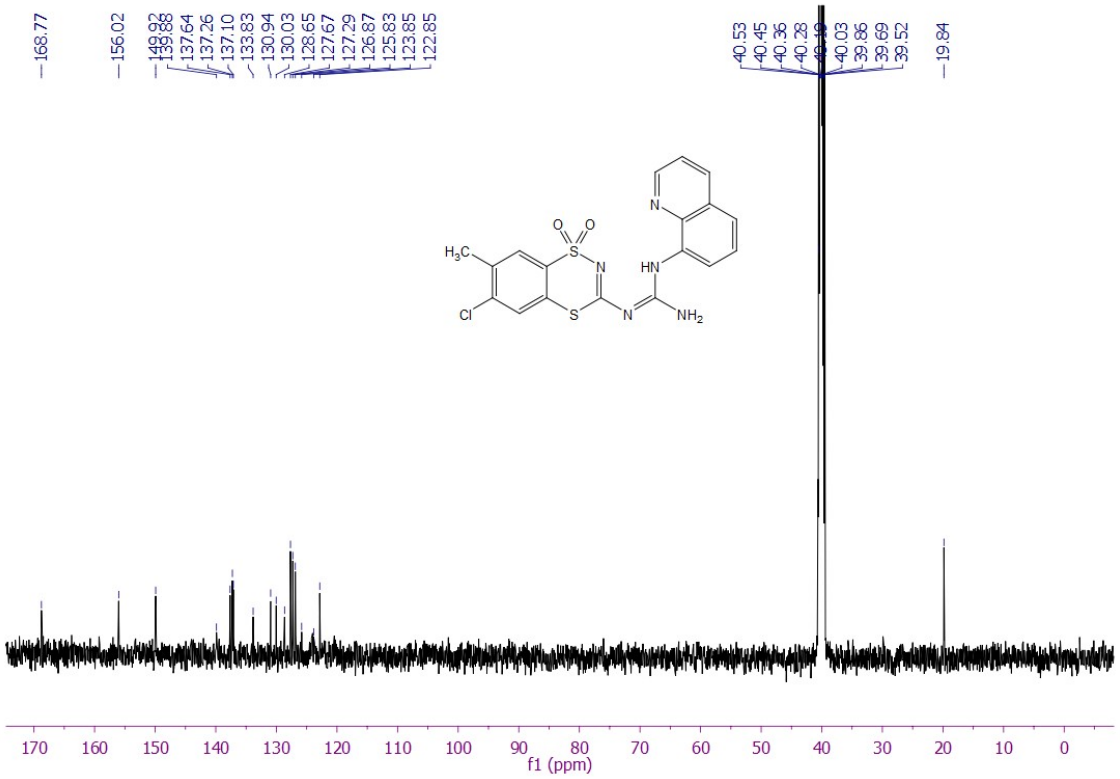


Figure S13. ^{13}C NMR spectrum of **10f** (151 MHz, DMSO-d_6)

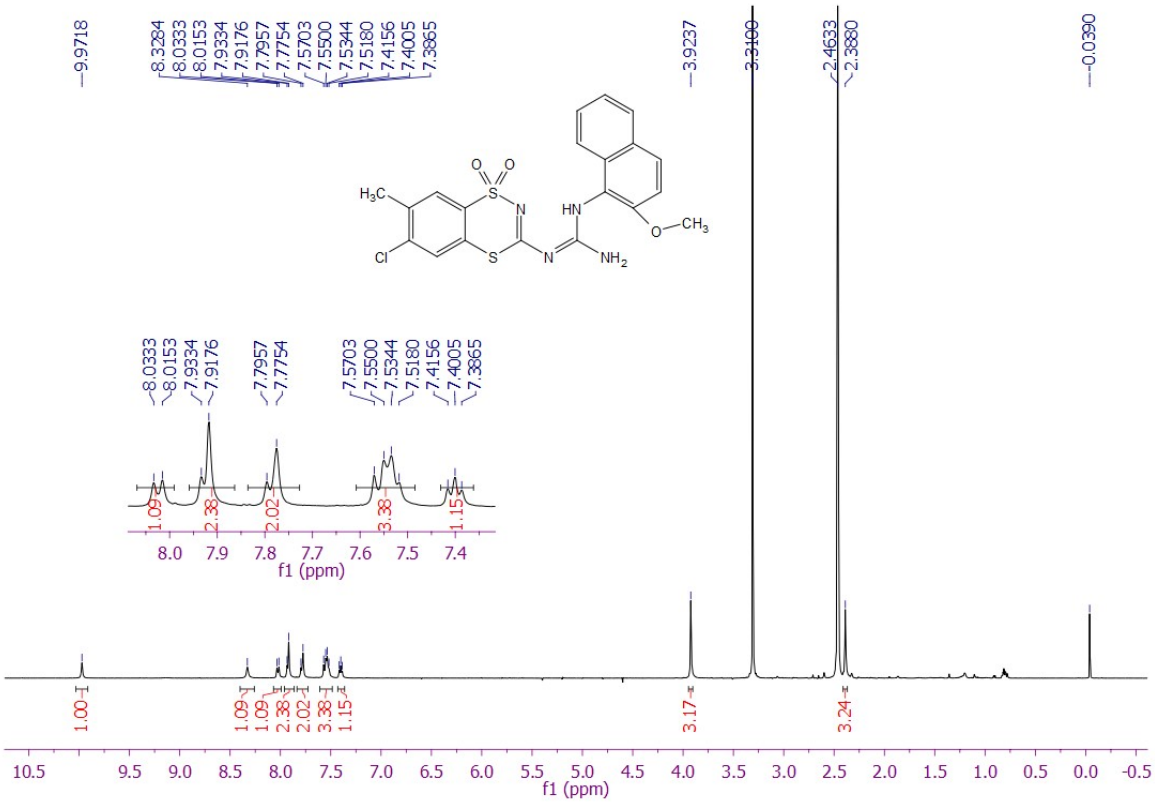


Figure S14. [1]H NMR spectrum of **10g** (600 MHz, DMSO-d_6)

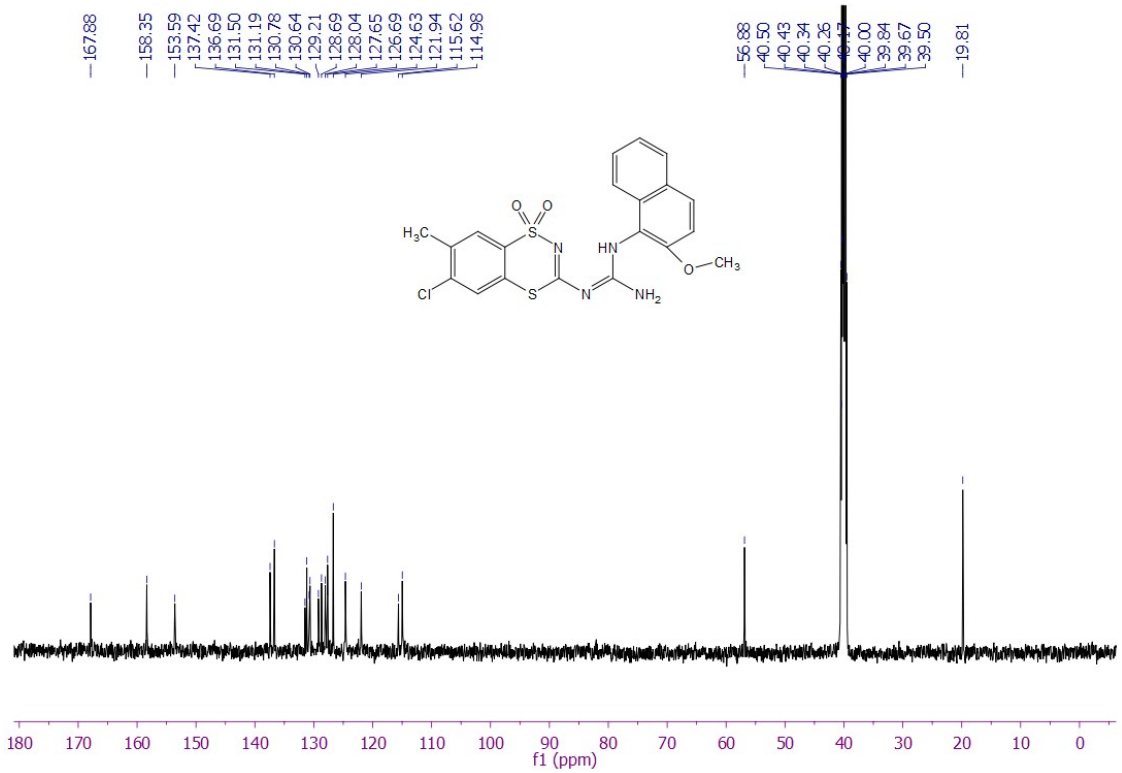


Figure S15. [13]C NMR spectrum of **10g** (151 MHz, DMSO-d_6)

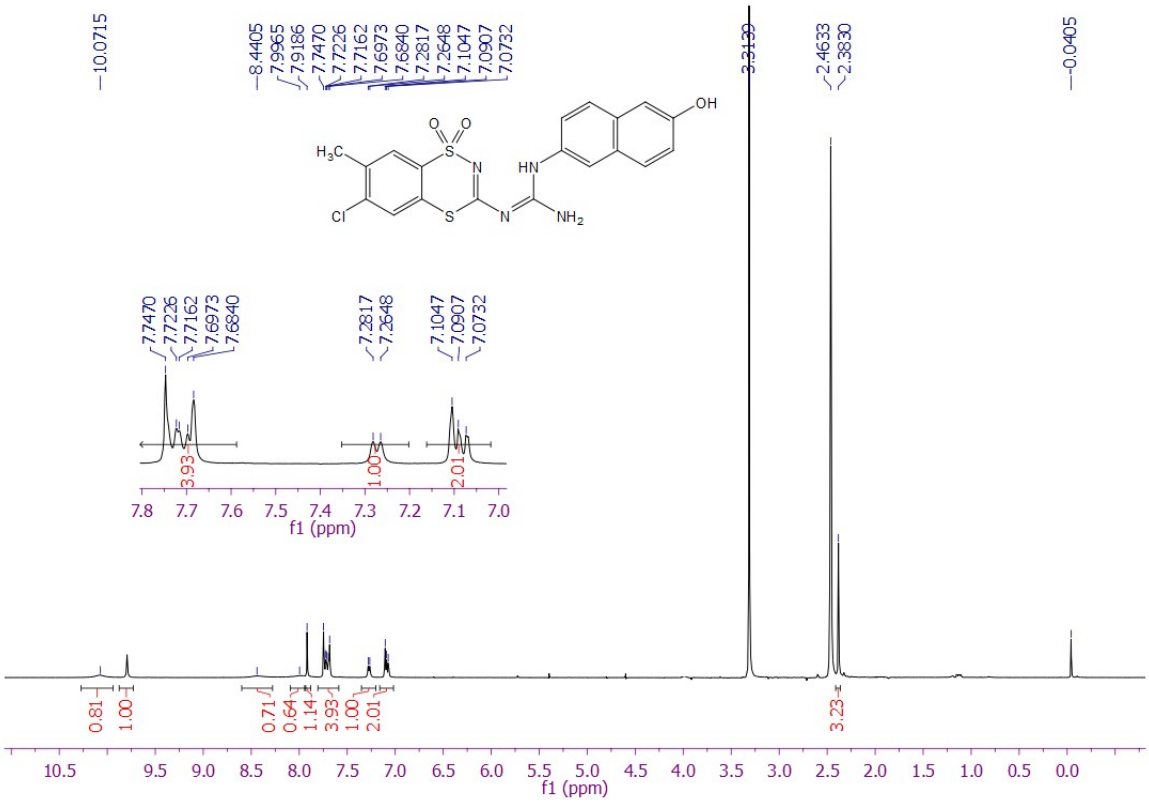


Figure S16. ^{1}H NMR spectrum of **10h** (600 MHz, DMSO-d_6)

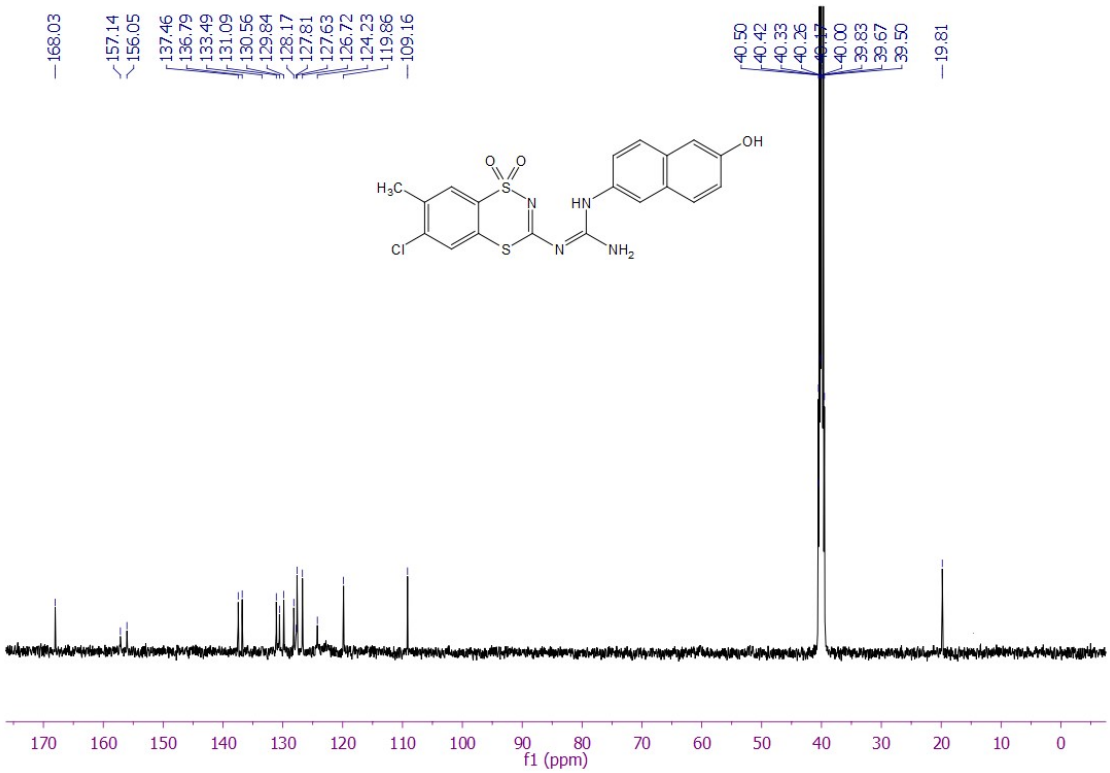


Figure S17. ^{13}C NMR spectrum of **10h** (151 MHz, DMSO-d_6)

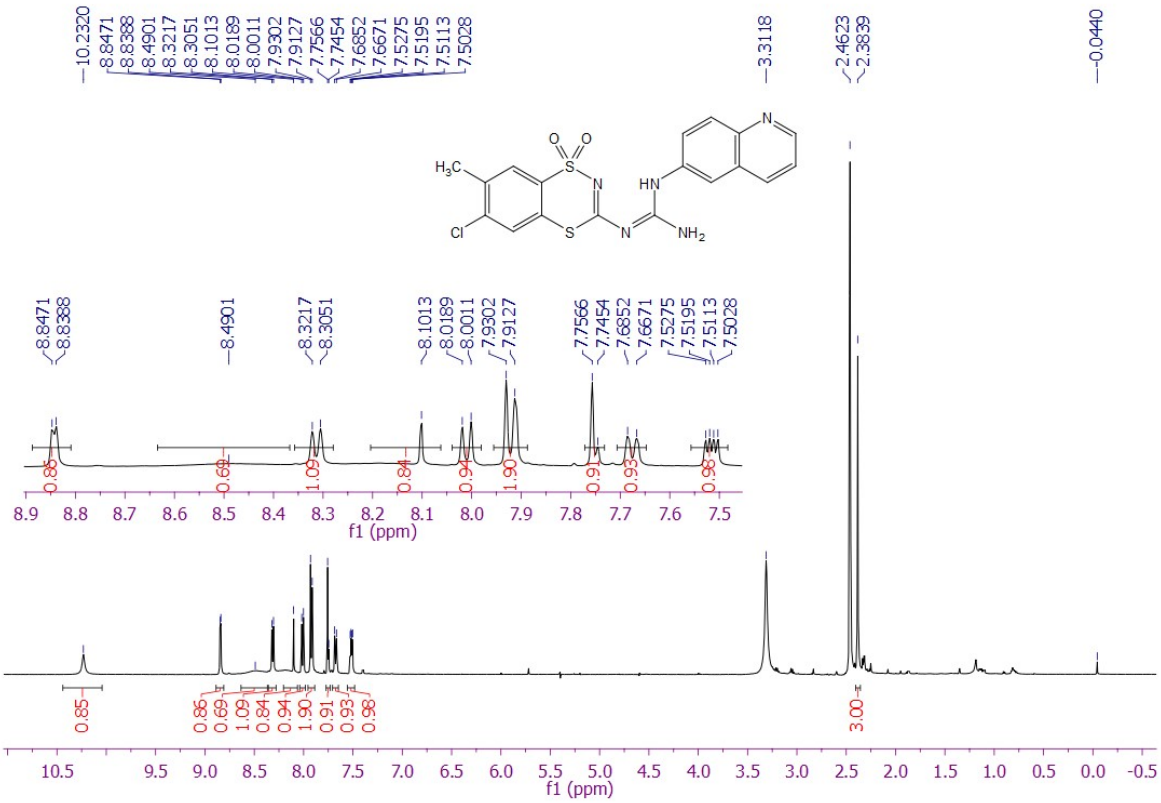


Figure S18. [1]H NMR spectrum of **10i** (600 MHz, DMSO-d_6)

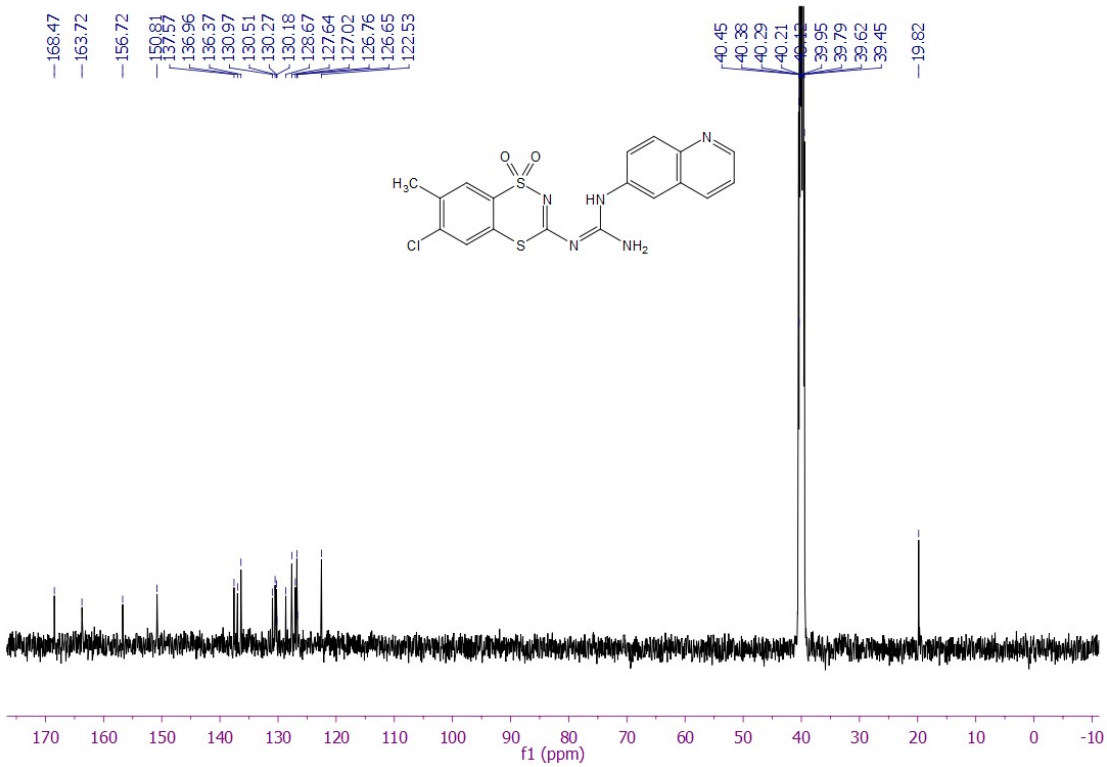


Figure S19. [13]C NMR spectrum of **10i** (151 MHz, DMSO-d_6)

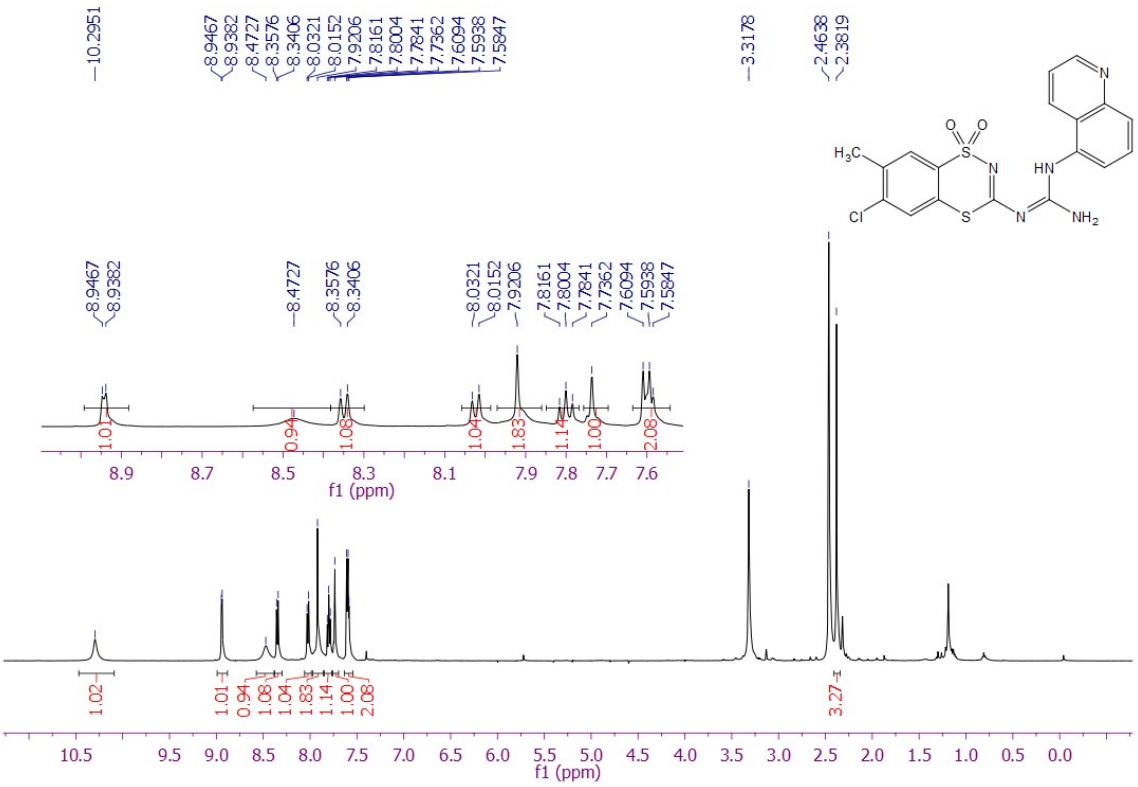


Figure S20. ^{1}H NMR spectrum of **10j** (600 MHz, DMSO-d_6)

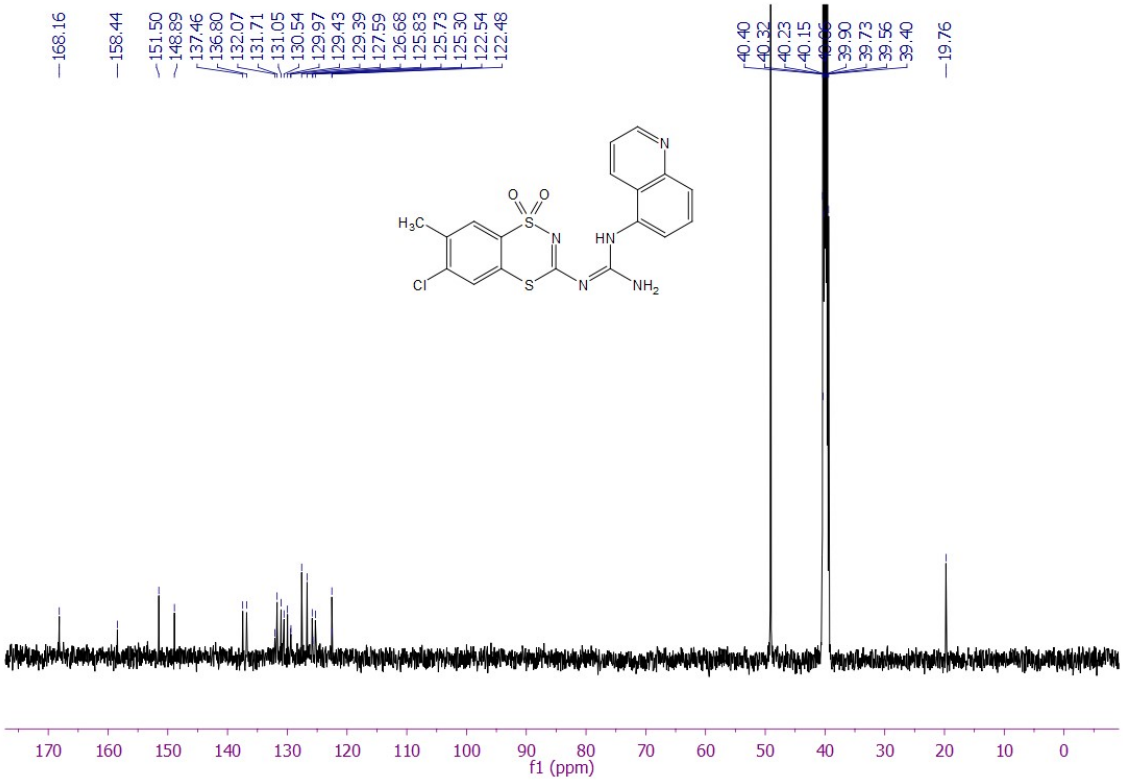


Figure S21. ^{13}C NMR spectrum of **10j** (151 MHz, DMSO-d_6)

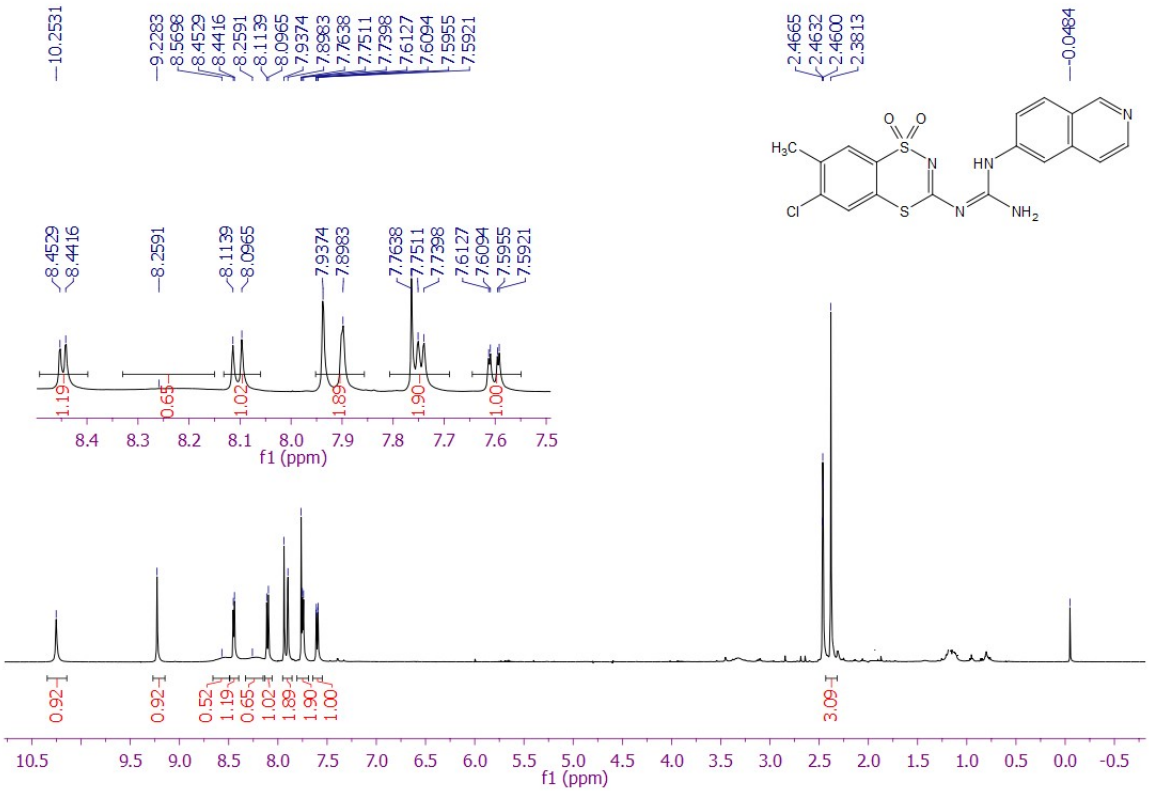


Figure S22. ^{1}H NMR spectrum of **10k** (600 MHz, DMSO-d_6)

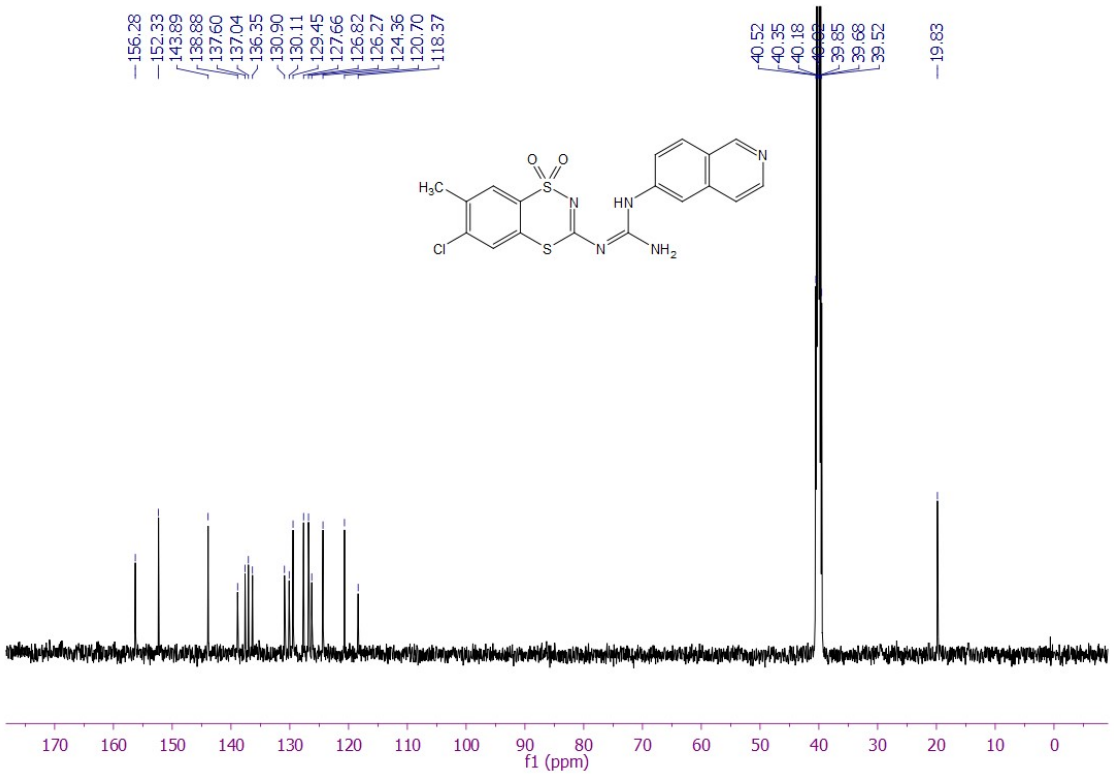


Figure S23. ^{13}C NMR spectrum of **10k** (151 MHz, DMSO-d_6)

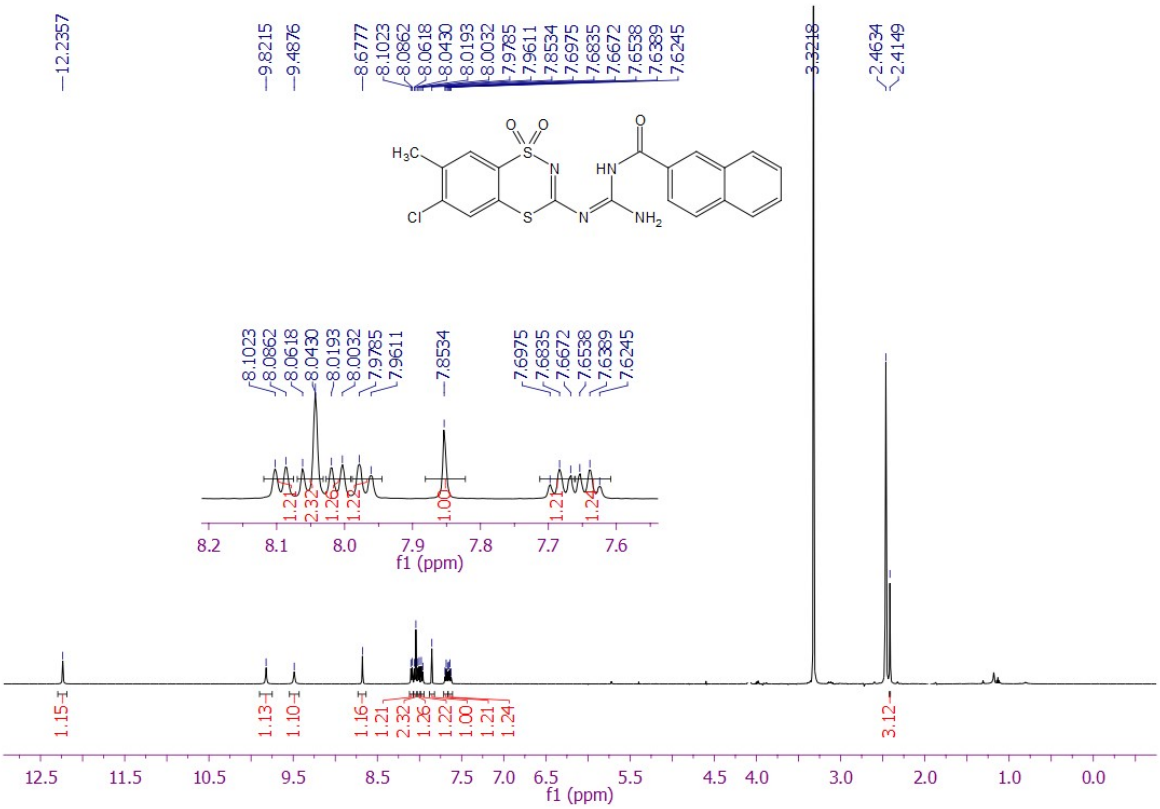


Figure S24. ^{1}H NMR spectrum of **10l** (600 MHz, DMSO-d_6)

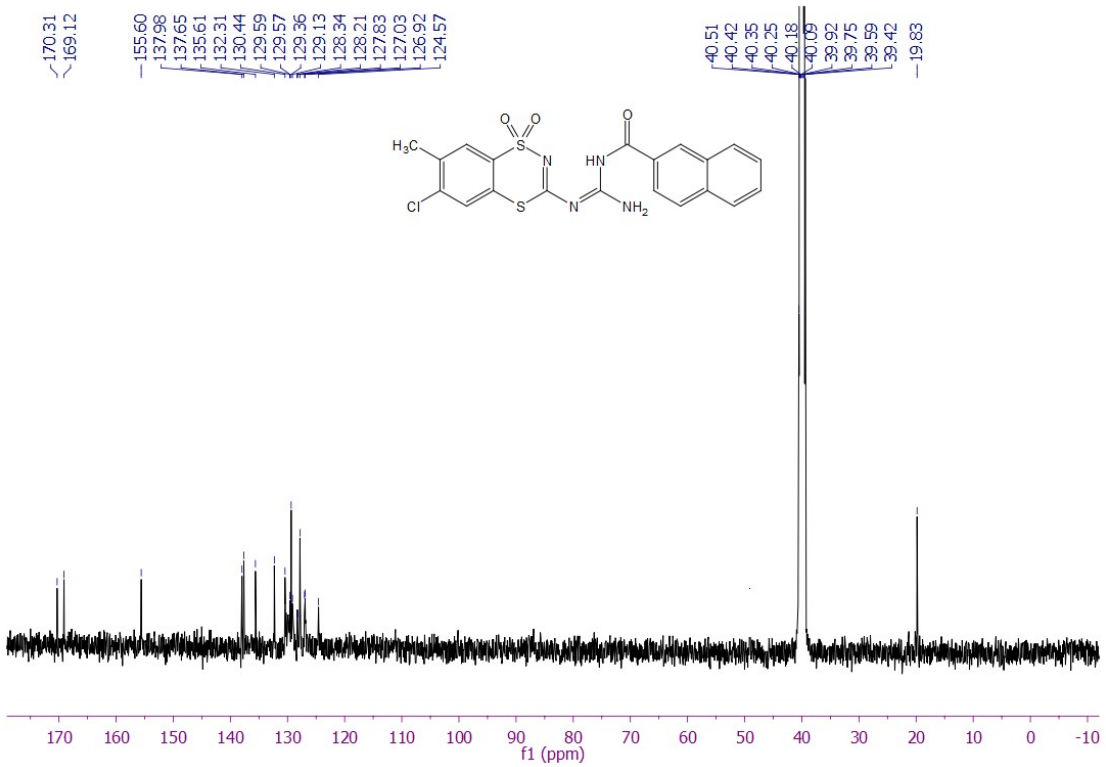


Figure S25. ^{13}C NMR spectrum of **10l** (151 MHz, DMSO-d_6)

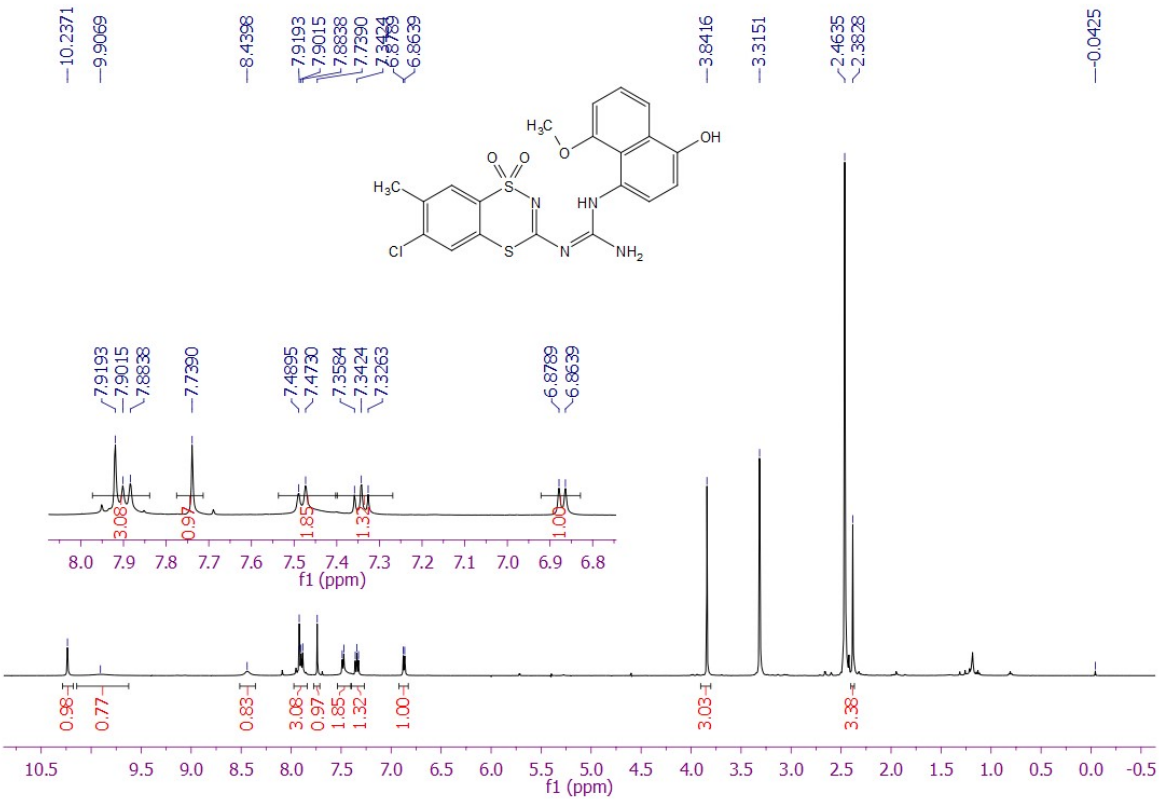


Figure S26. ^{1}H NMR spectrum of **10m** (600 MHz, DMSO-d_6)

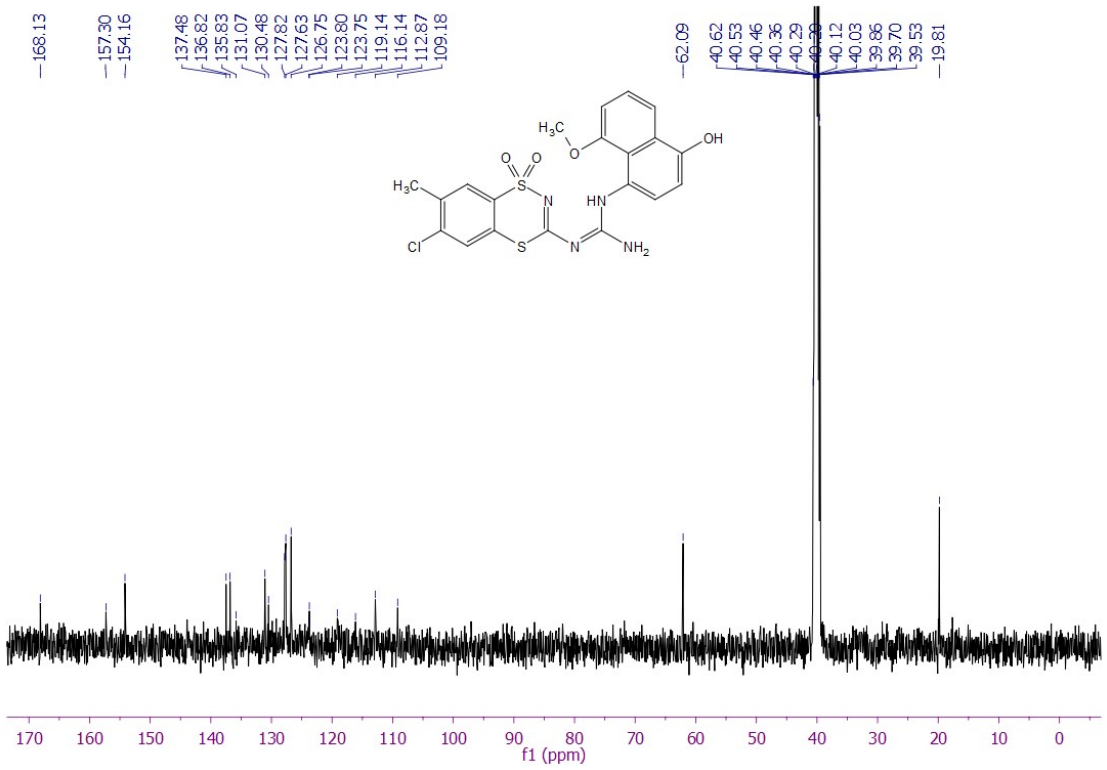


Figure S27. ^{13}C NMR spectrum of **10m** (151 MHz, DMSO-d_6)

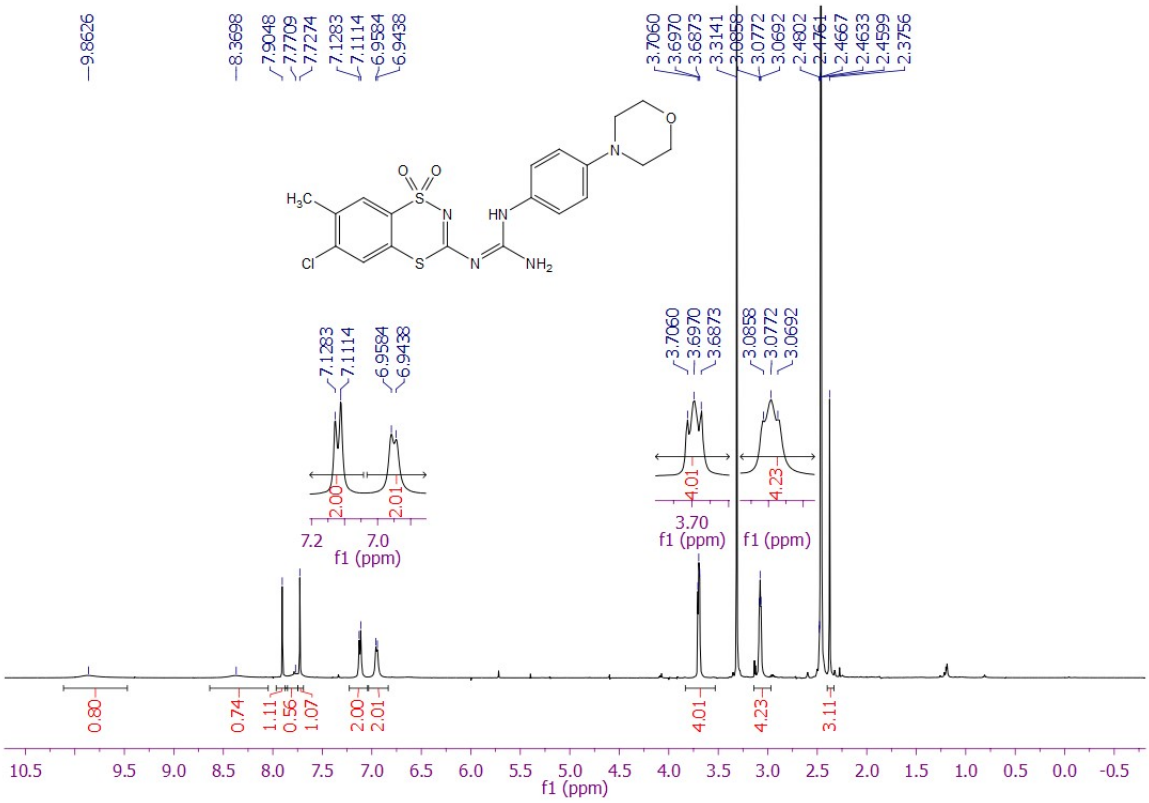


Figure S28. ^{1}H NMR spectrum of **10n** (600 MHz, DMSO-d_6)

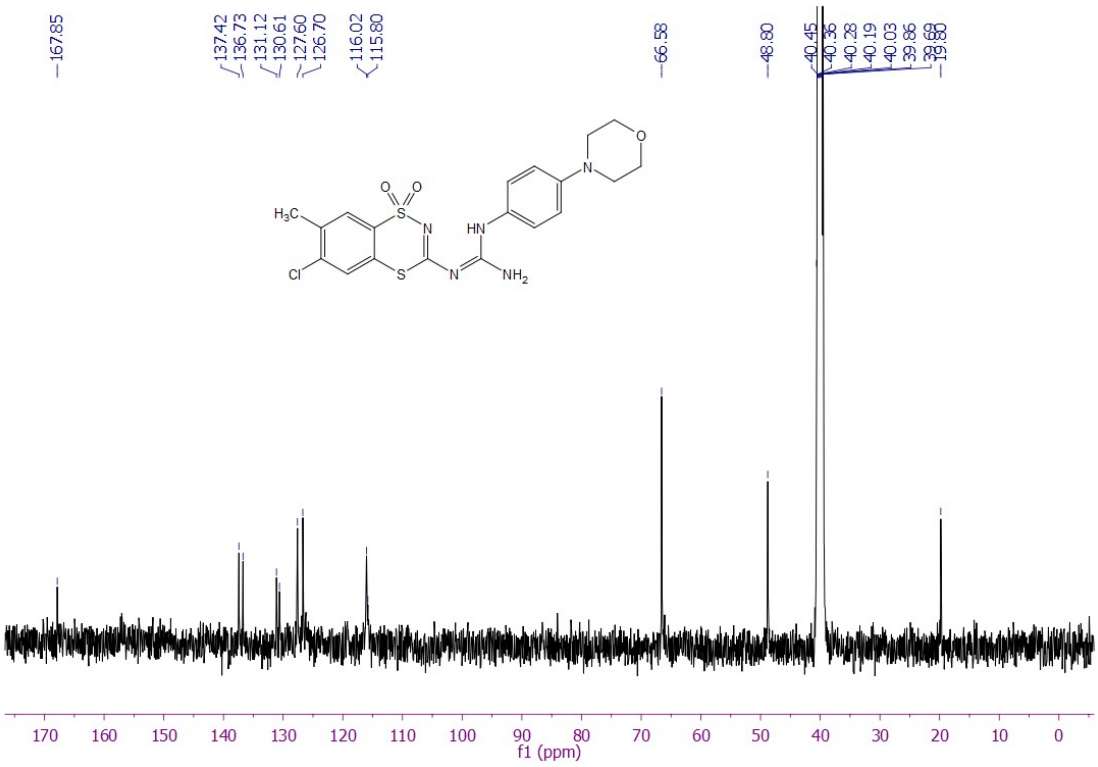


Figure S29. ^{13}C NMR spectrum of **10n** (151 MHz, DMSO-d_6)

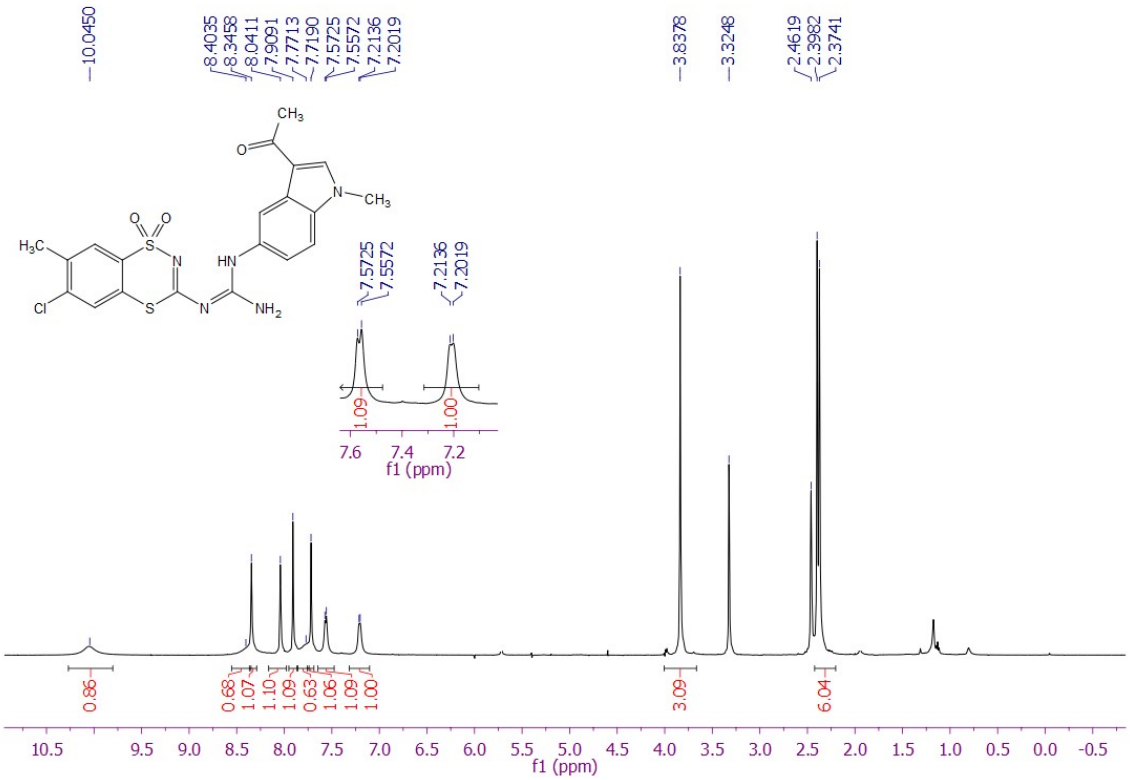


Figure S30. ^{1}H NMR spectrum of **10o** (600 MHz, DMSO-d_6)

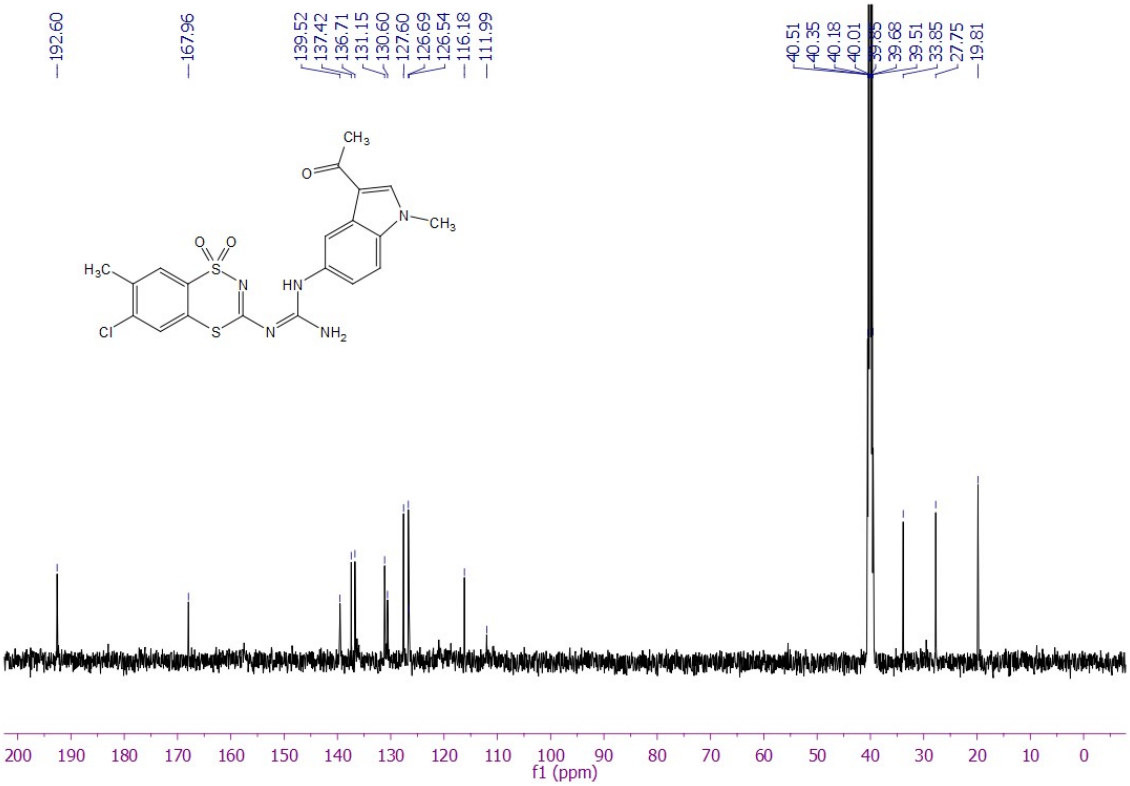


Figure S31. ^{13}C NMR spectrum of **10o** (151 MHz, DMSO-d_6)

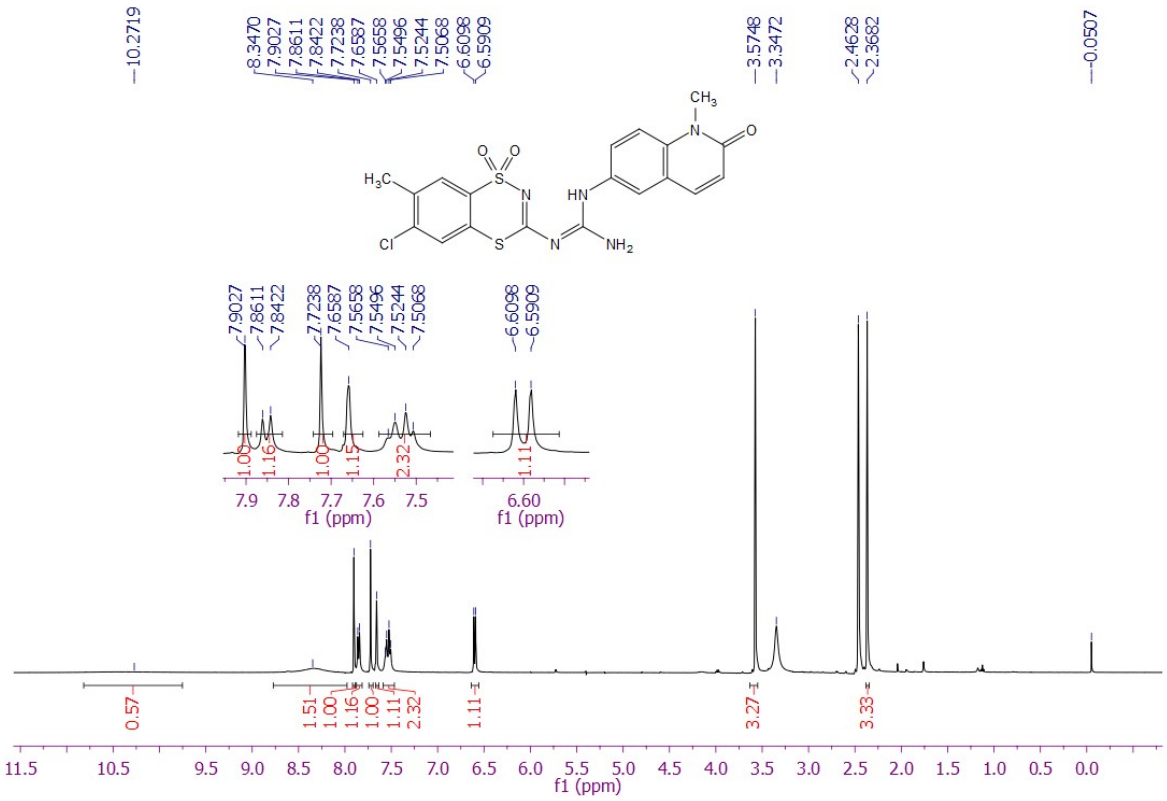


Figure S32. ^{1}H NMR spectrum of **10p** (600 MHz, DMSO-d_6)

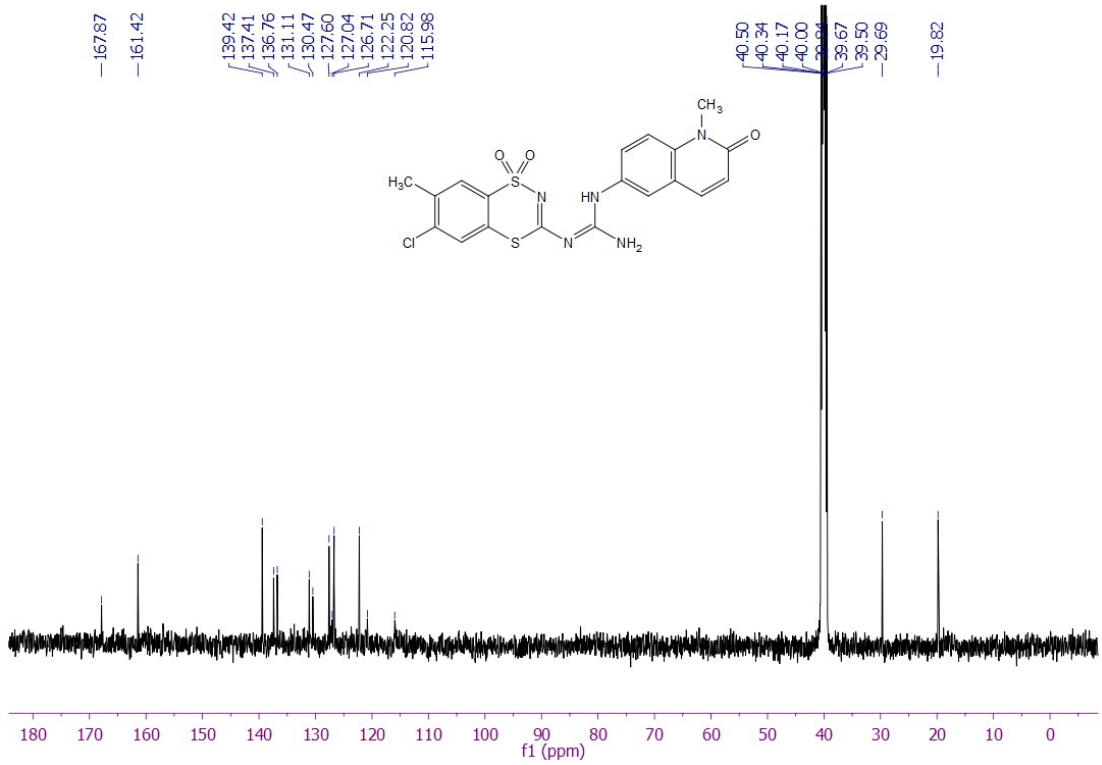


Figure S33. ^{13}C NMR spectrum of **10p** (151 MHz, DMSO-d_6)

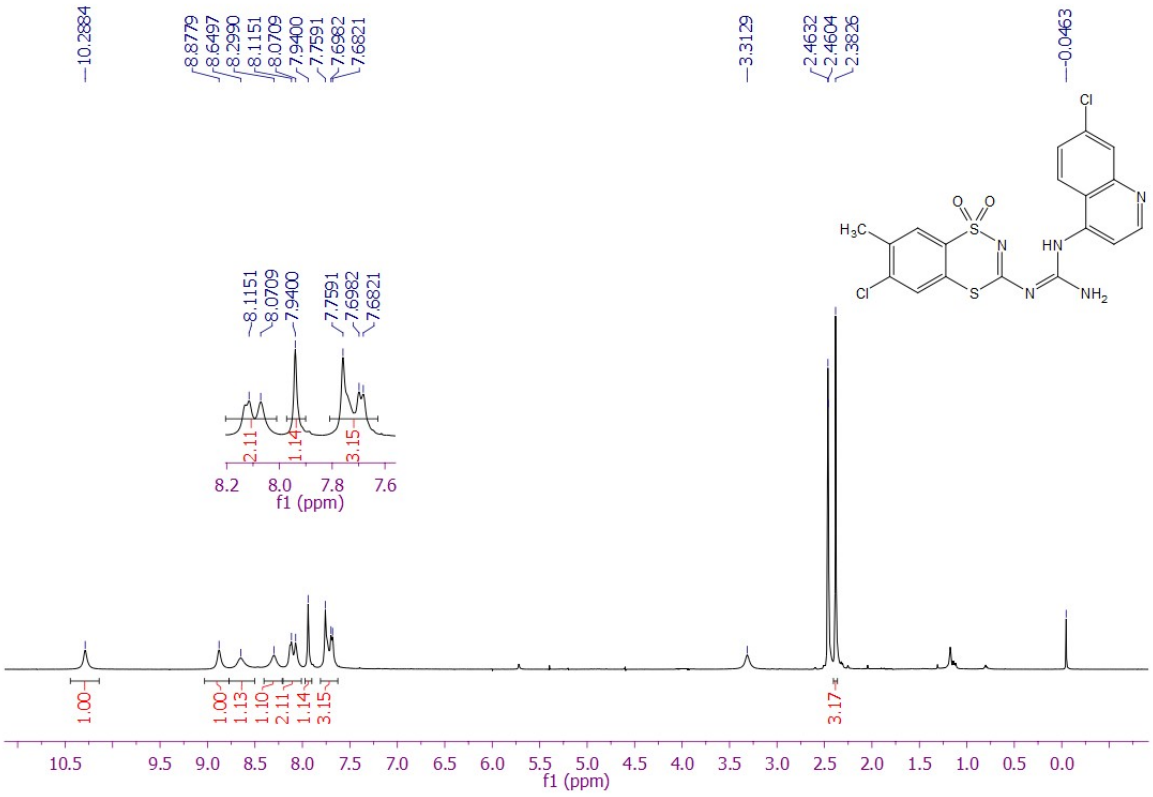


Figure S34. ^{1}H NMR spectrum of **10q** (600 MHz, DMSO-d_6)

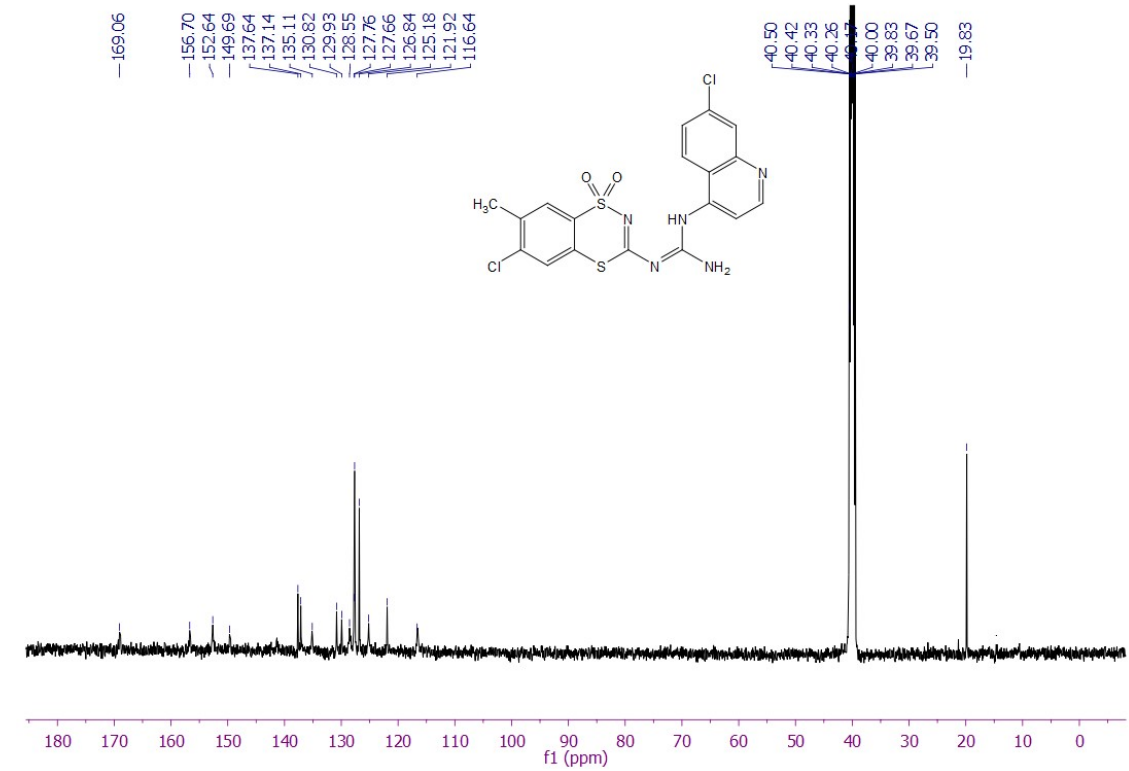


Figure S35. ^{13}C NMR spectrum of **10q** (151 MHz, DMSO-d_6)

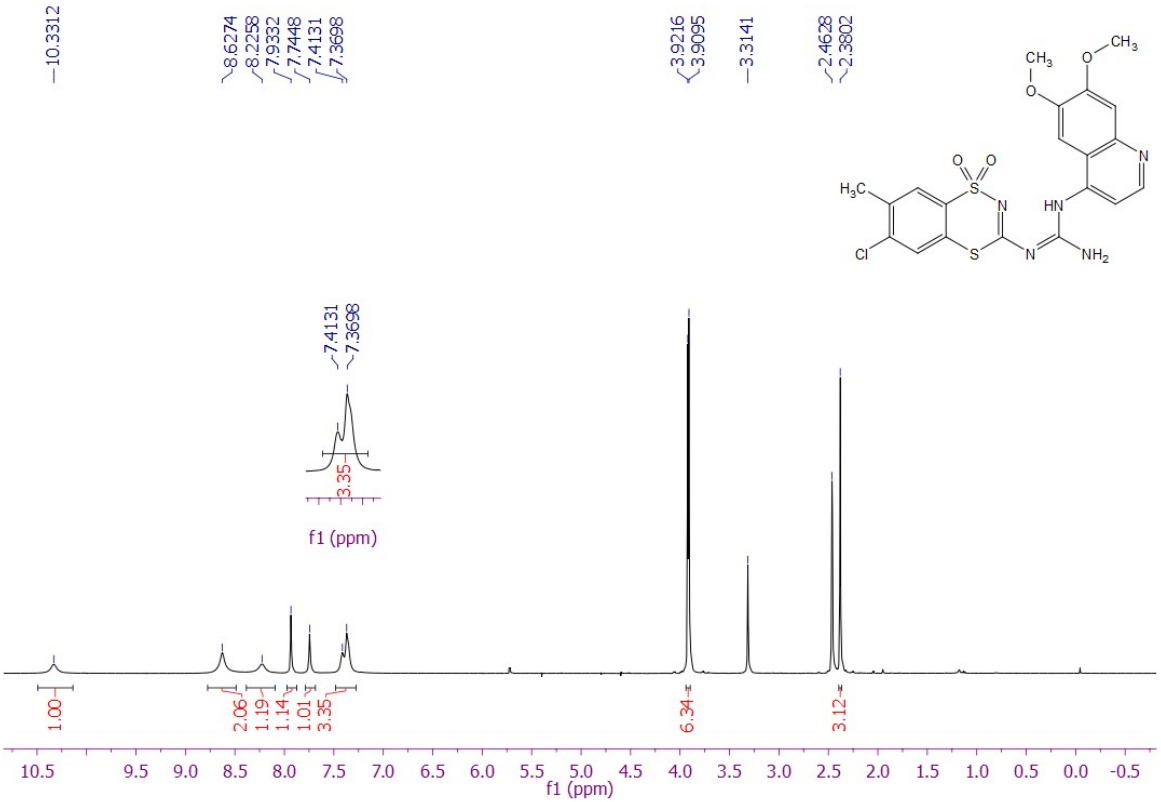


Figure S36. ^{1}H NMR spectrum of **10r** (600 MHz, DMSO-d_6)

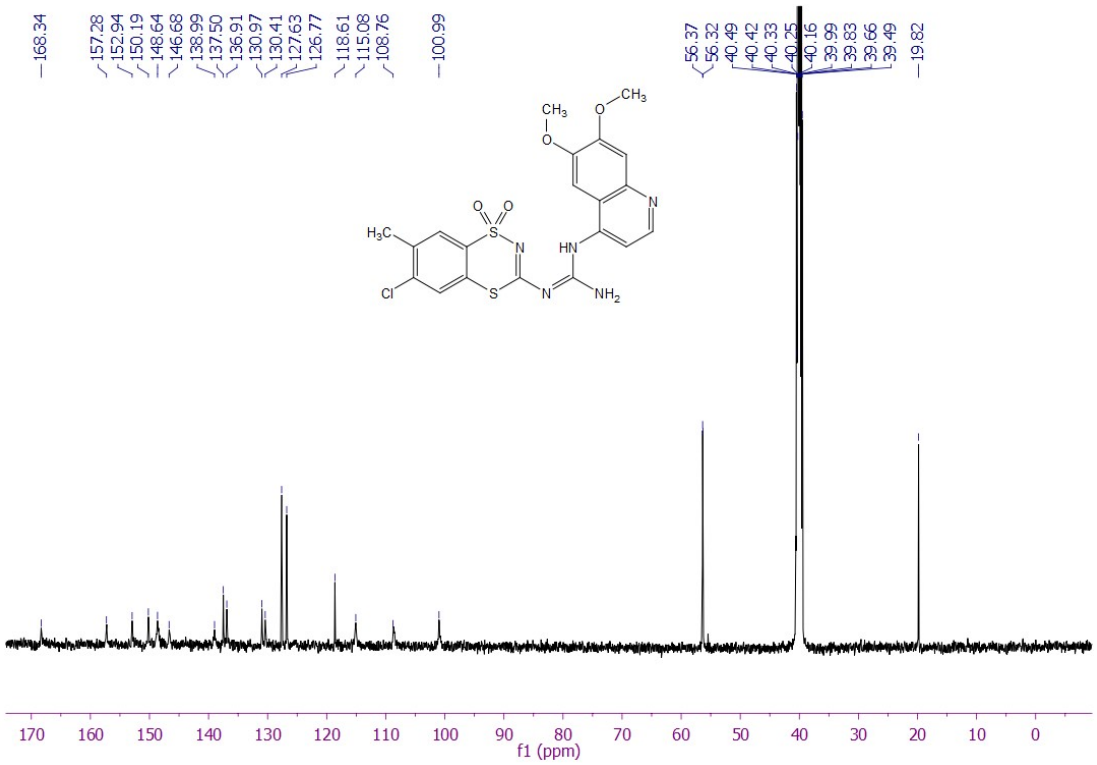


Figure S37. ^{13}C NMR spectrum of **10r** (151 MHz, DMSO-d_6)

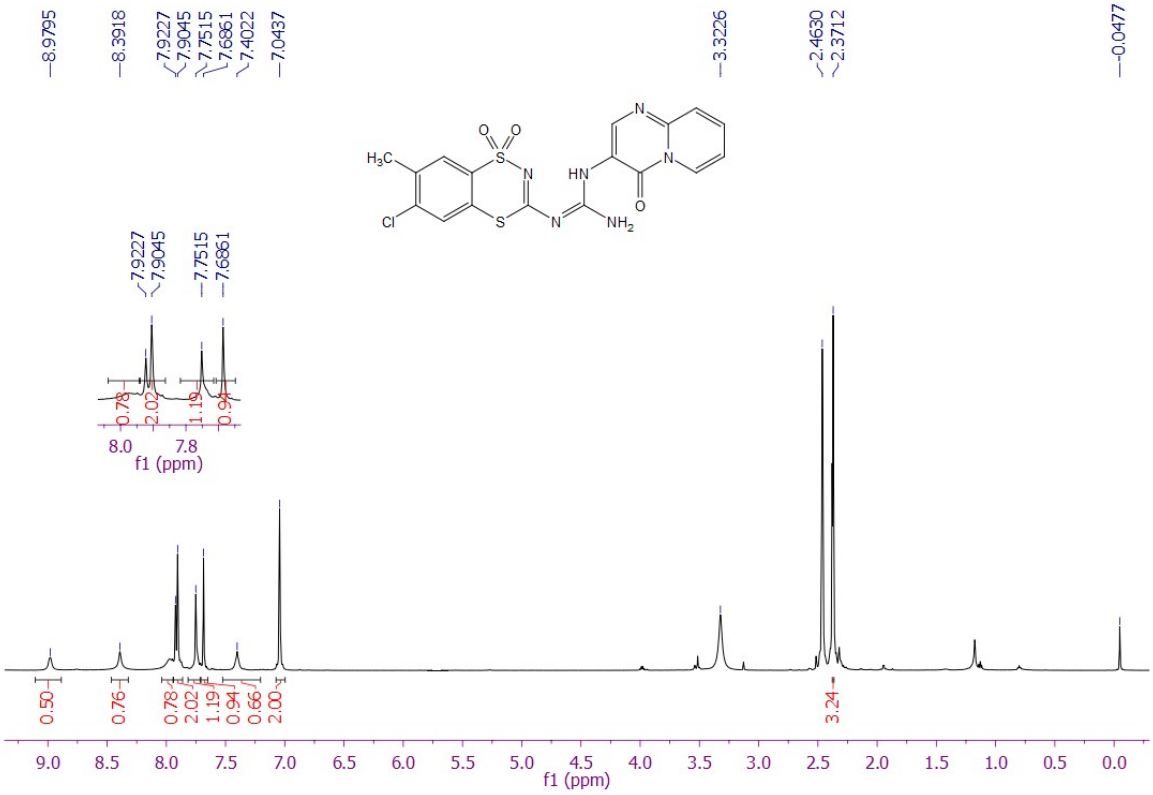


Figure S38. [1]H NMR spectrum of **10s** (600 MHz, DMSO-d_6)

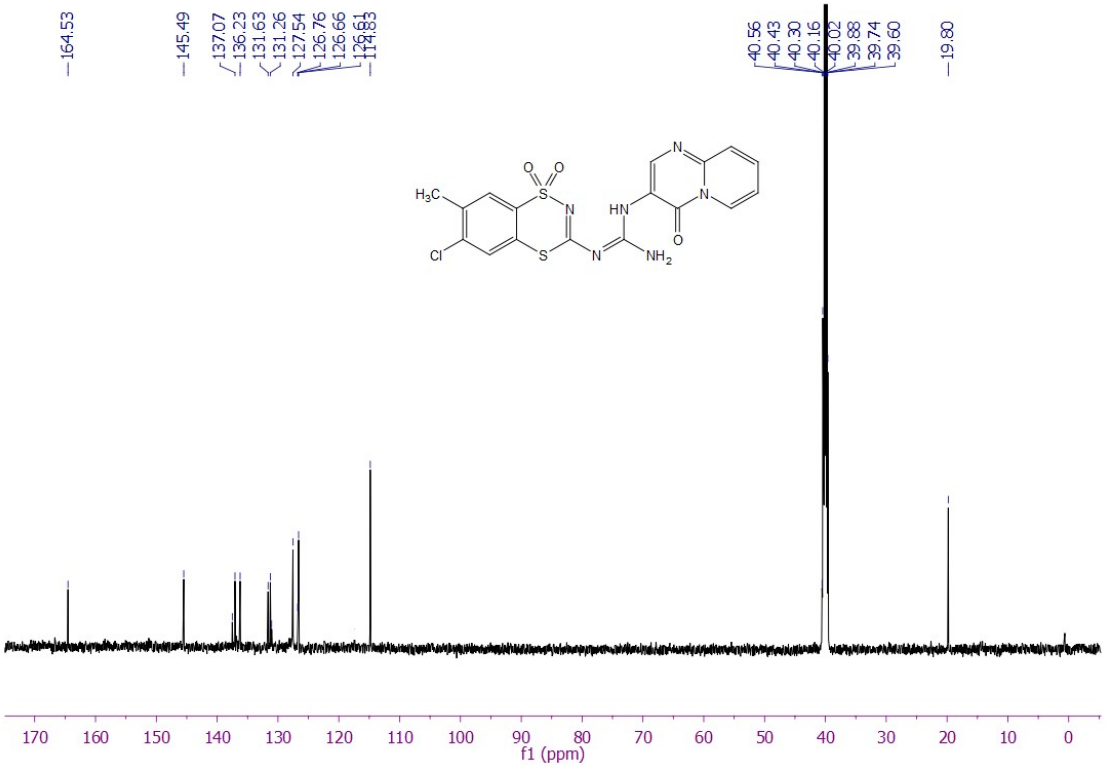


Figure S39. [13]C NMR spectrum of **10s** (151 MHz, DMSO-d_6)

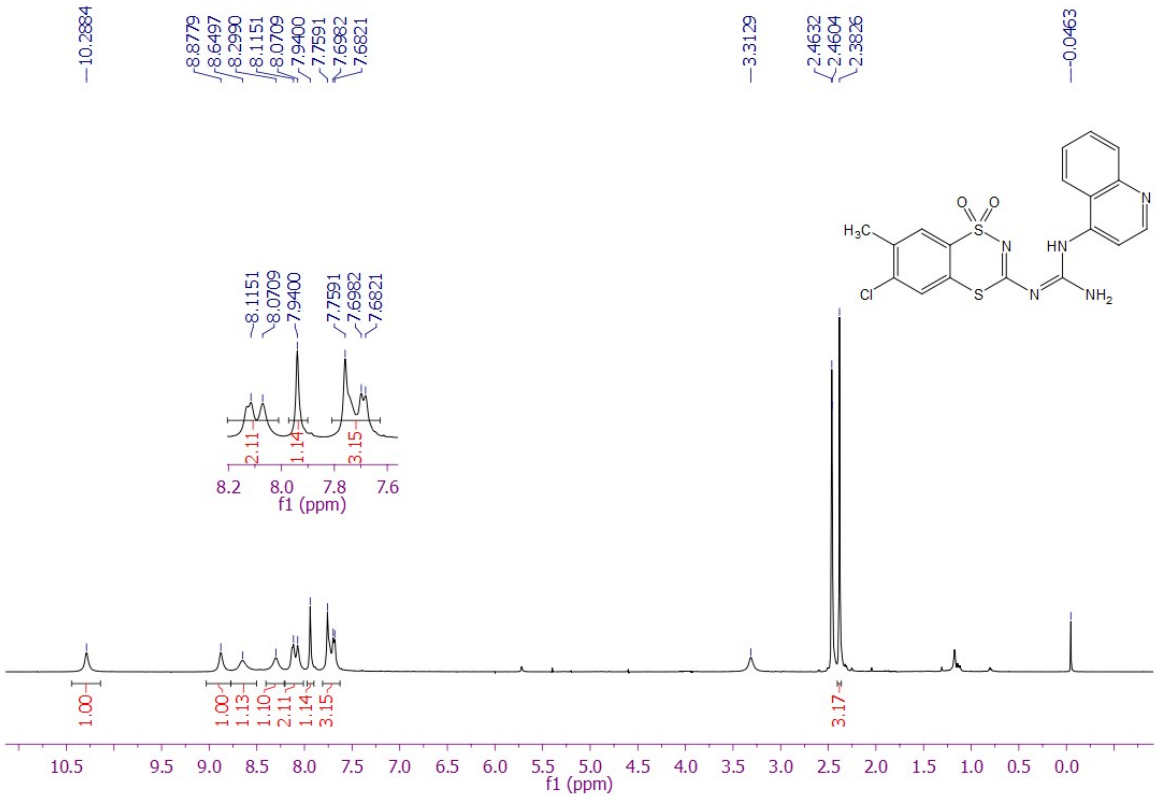


Figure S40. ^{1}H NMR spectrum of **10t** (600 MHz, DMSO-d_6)

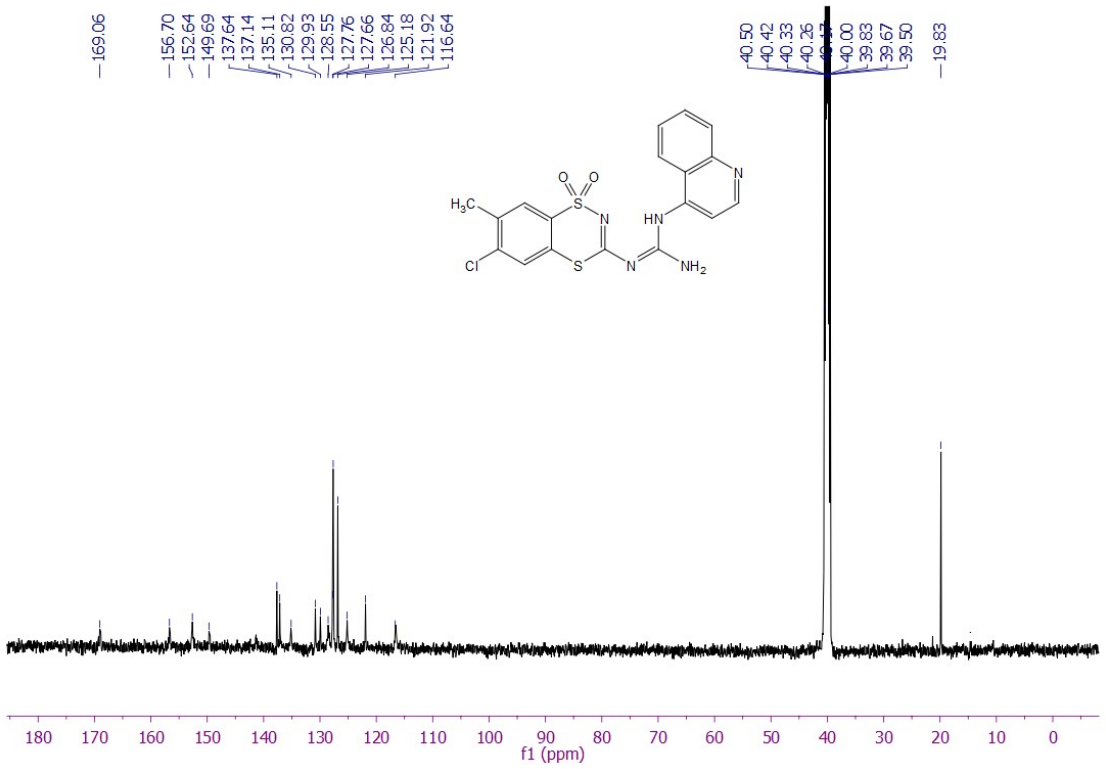


Figure S41. ^{13}C NMR spectrum of **10t** (151 MHz, DMSO-d_6)

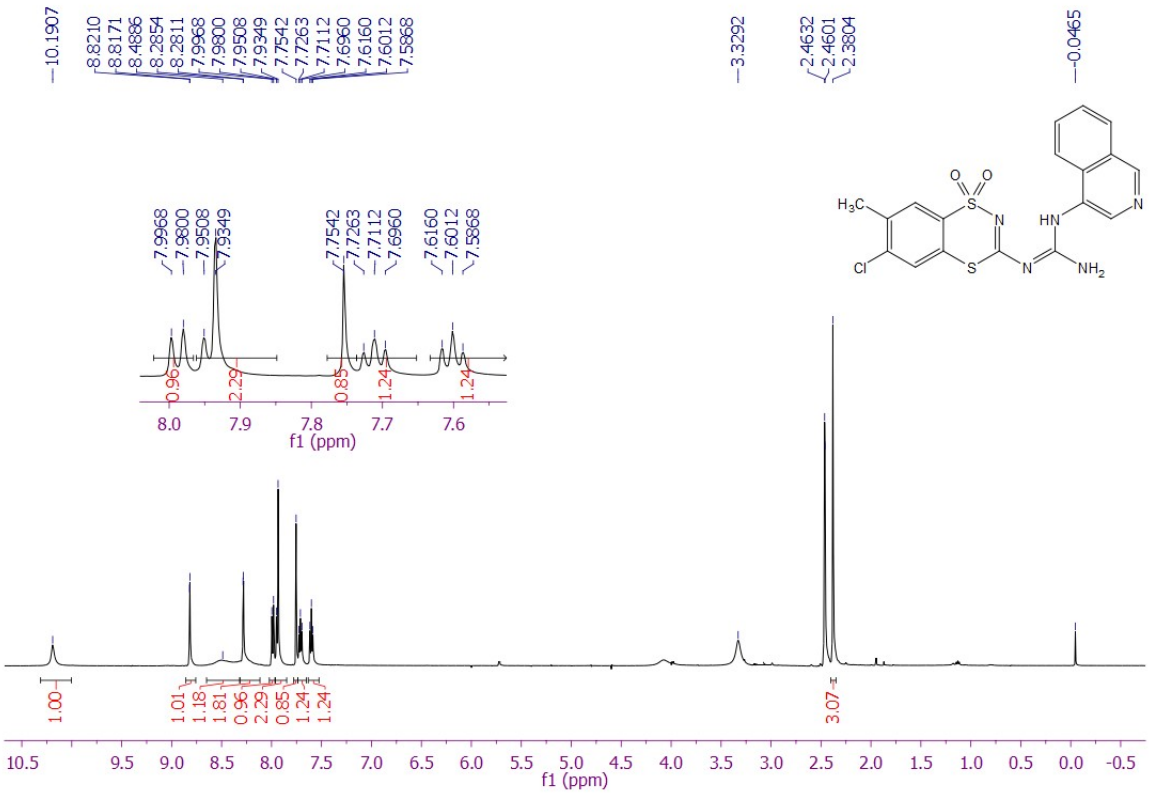


Figure S42. [1]H NMR spectrum of **10u** (600 MHz, DMSO-d_6)

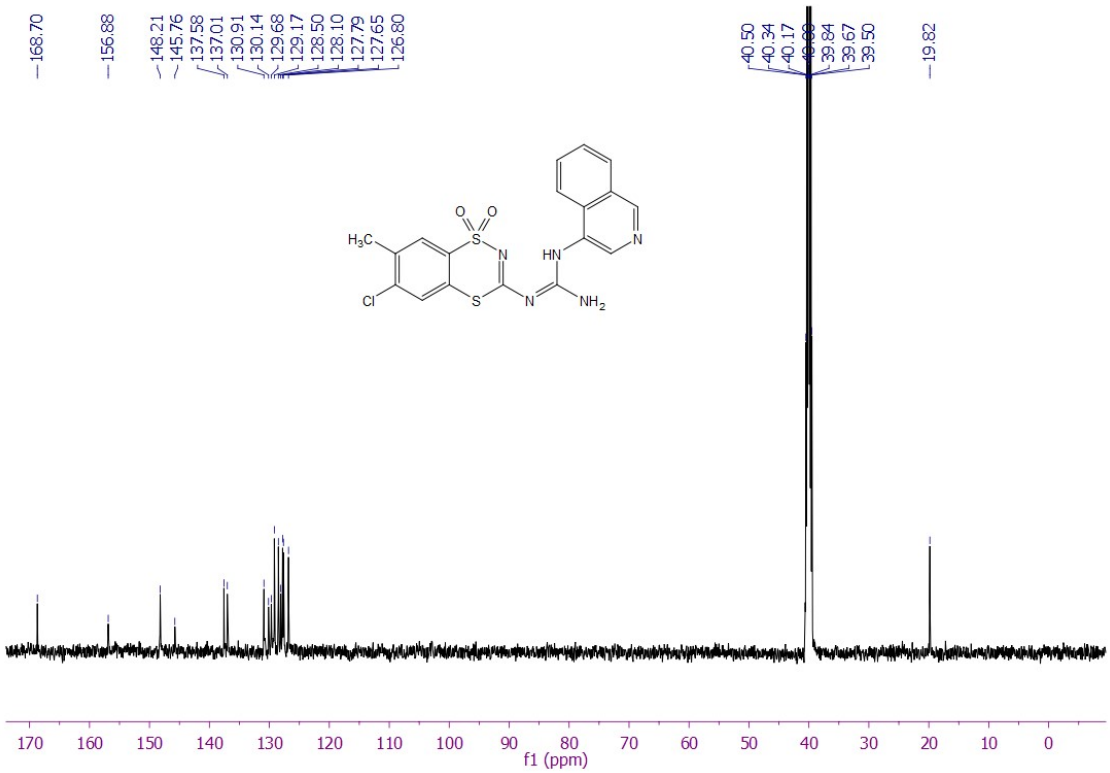


Figure S43. [13]C NMR spectrum of **10u** (151 MHz, DMSO-d_6)

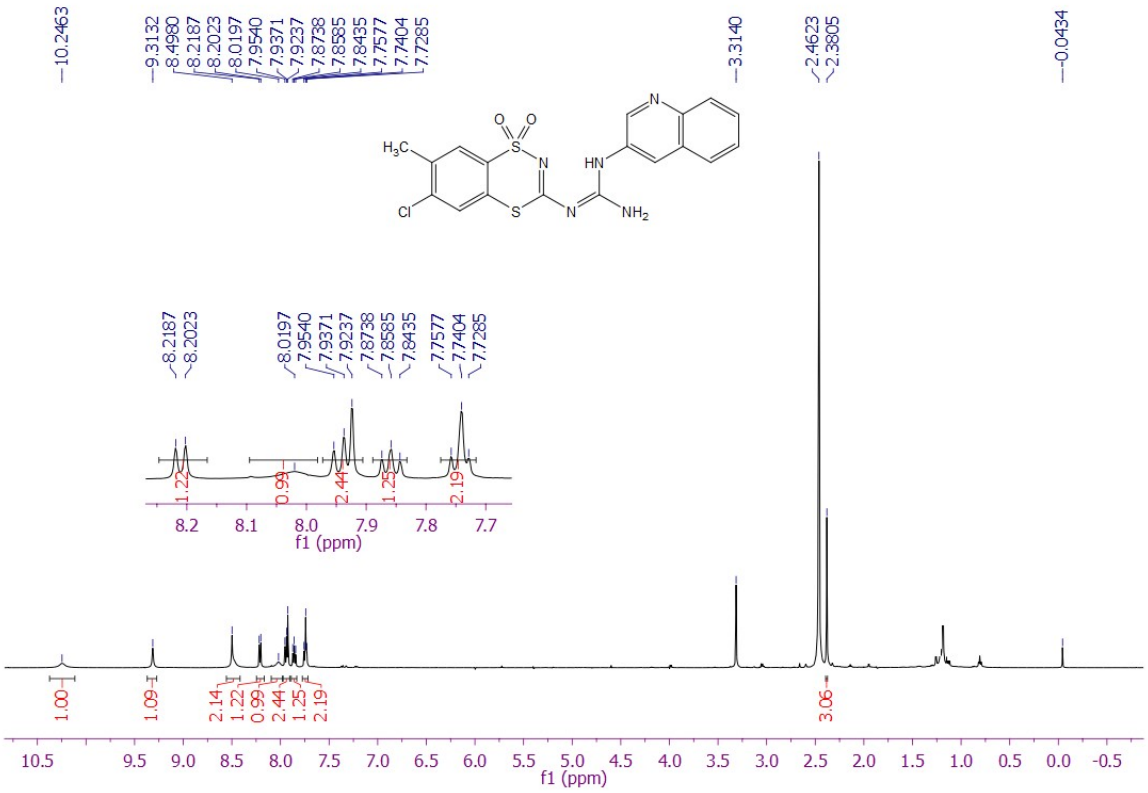


Figure S44. ^{1}H NMR spectrum of **10v** (600 MHz, DMSO-d_6)

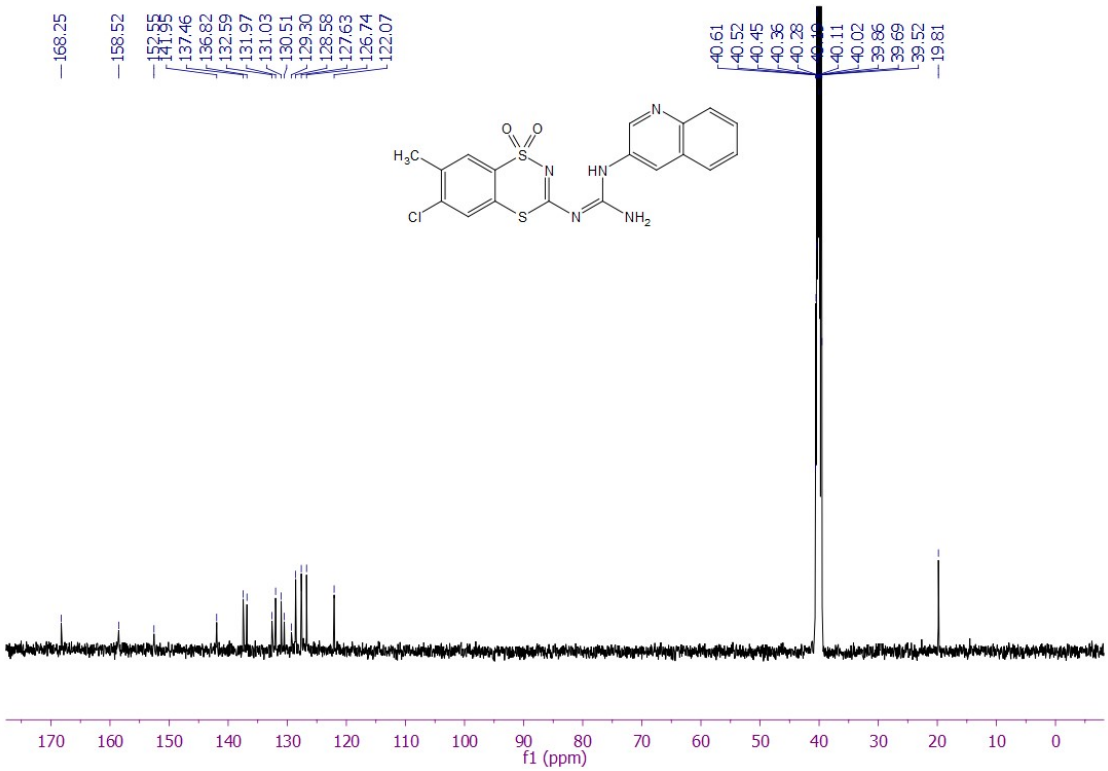


Figure S45. ^{13}C NMR spectrum of **10v** (151 MHz, DMSO-d_6)

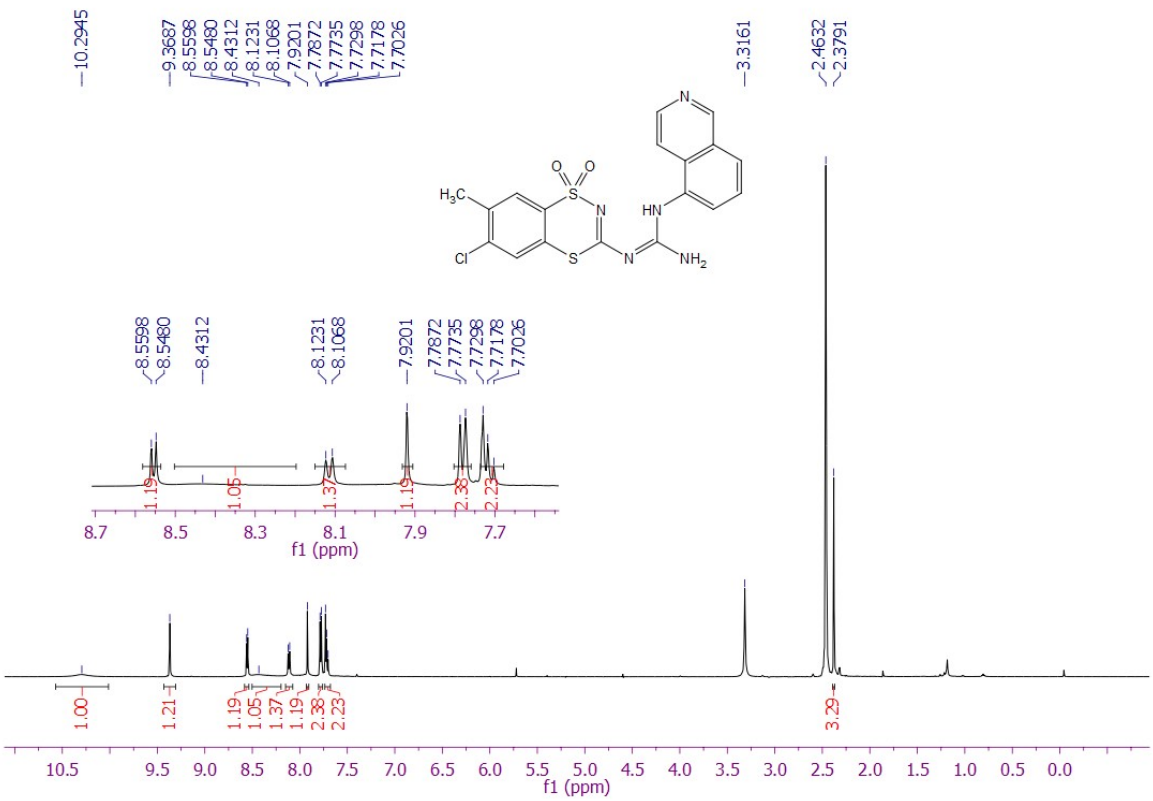


Figure S46. ^{1}H NMR spectrum of **10w** (600 MHz, DMSO-d_6)

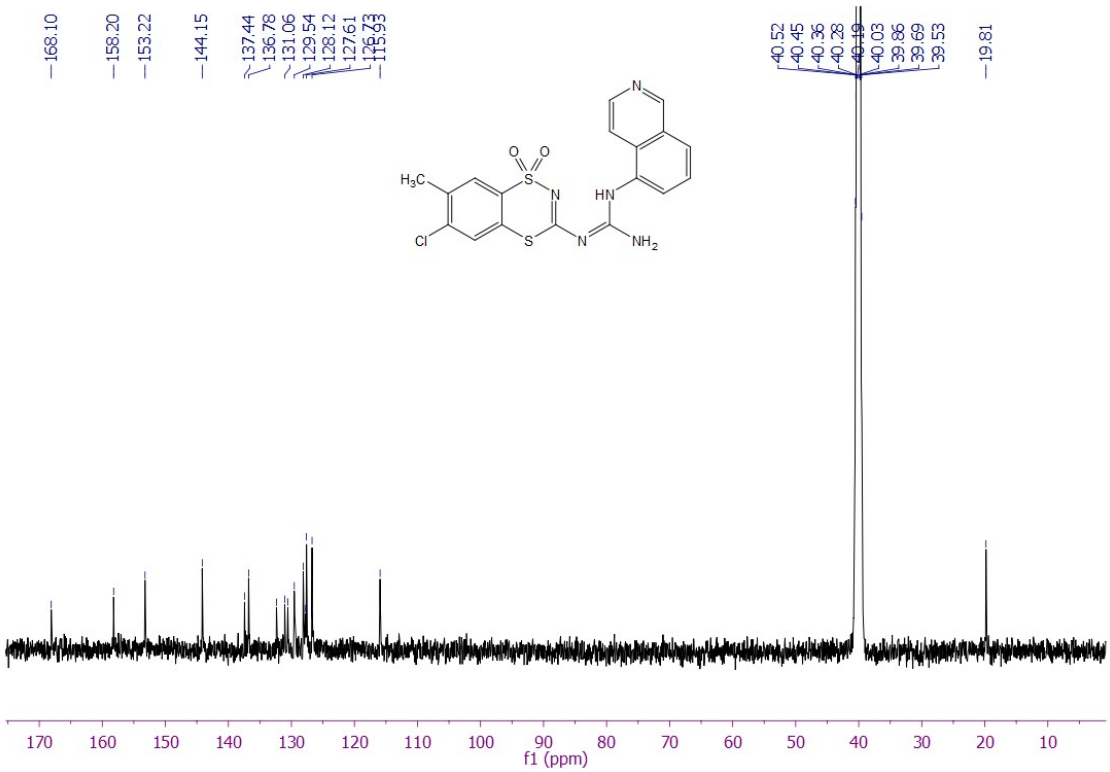


Figure S47. ^{13}C NMR spectrum of **10w** (151 MHz, DMSO-d_6)

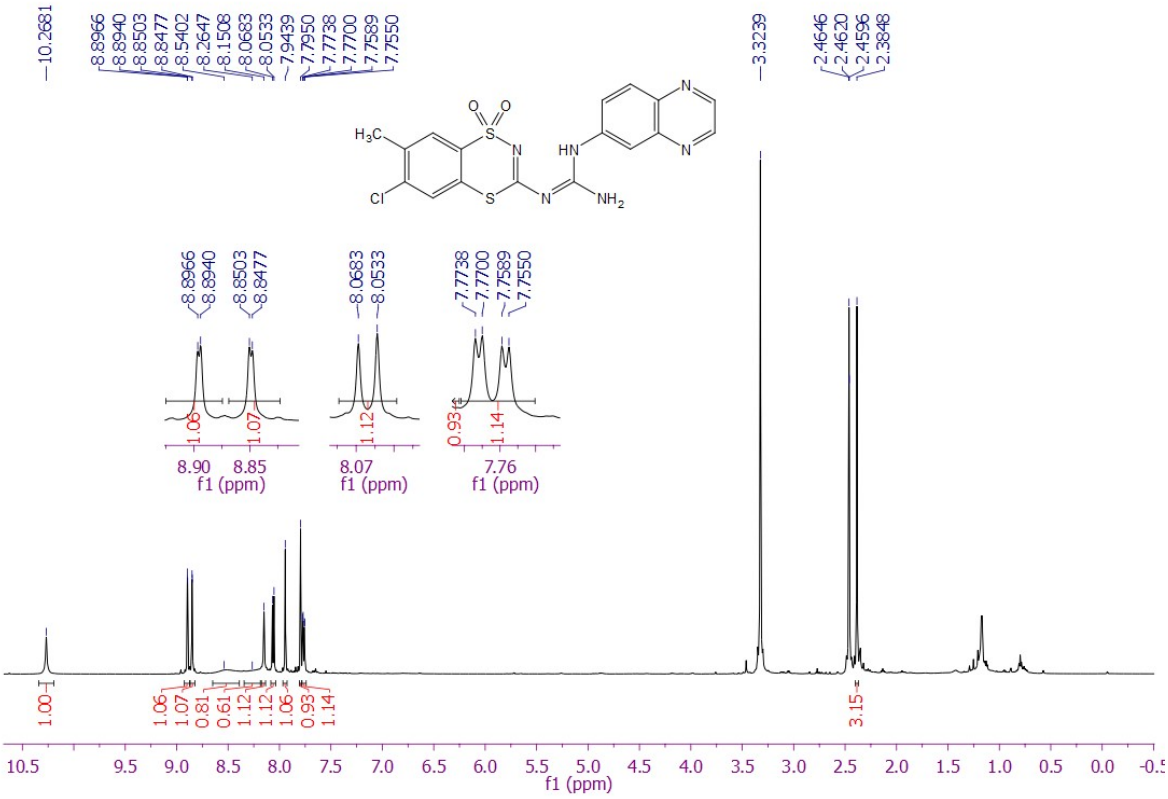


Figure S48. ^{1}H NMR spectrum of **10x** (600 MHz, DMSO-d_6)

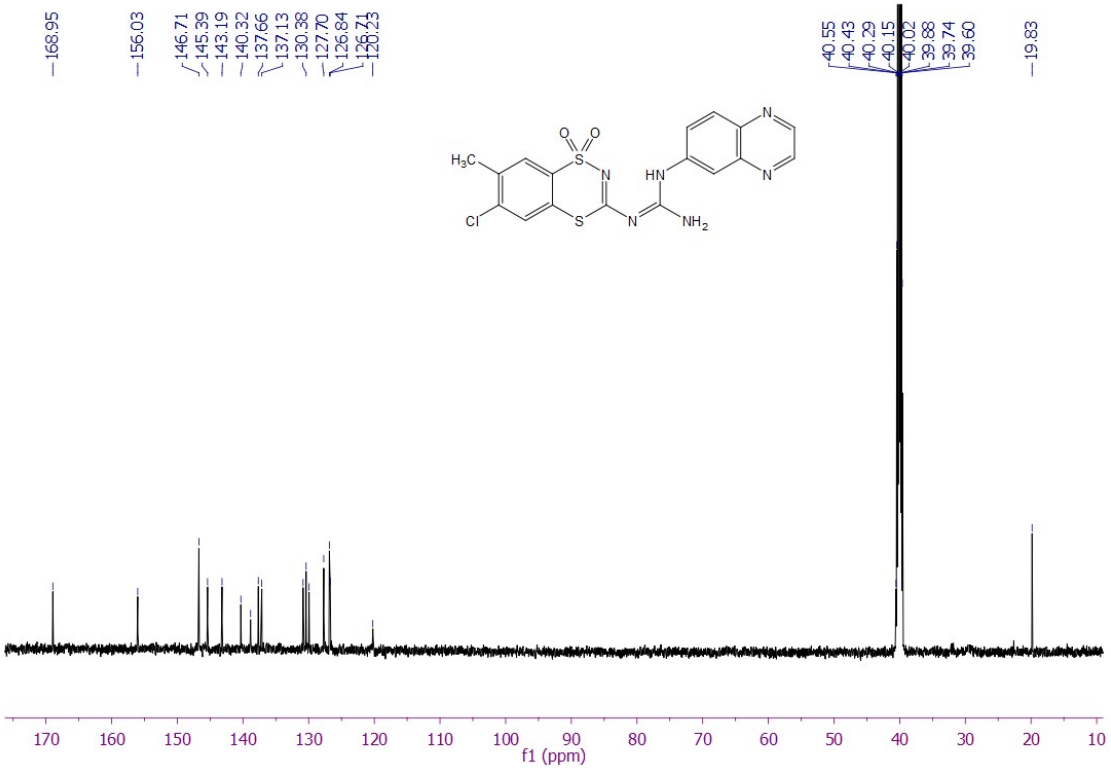


Figure S49. ^{13}C NMR spectrum of **10x** (151 MHz, DMSO-d_6)

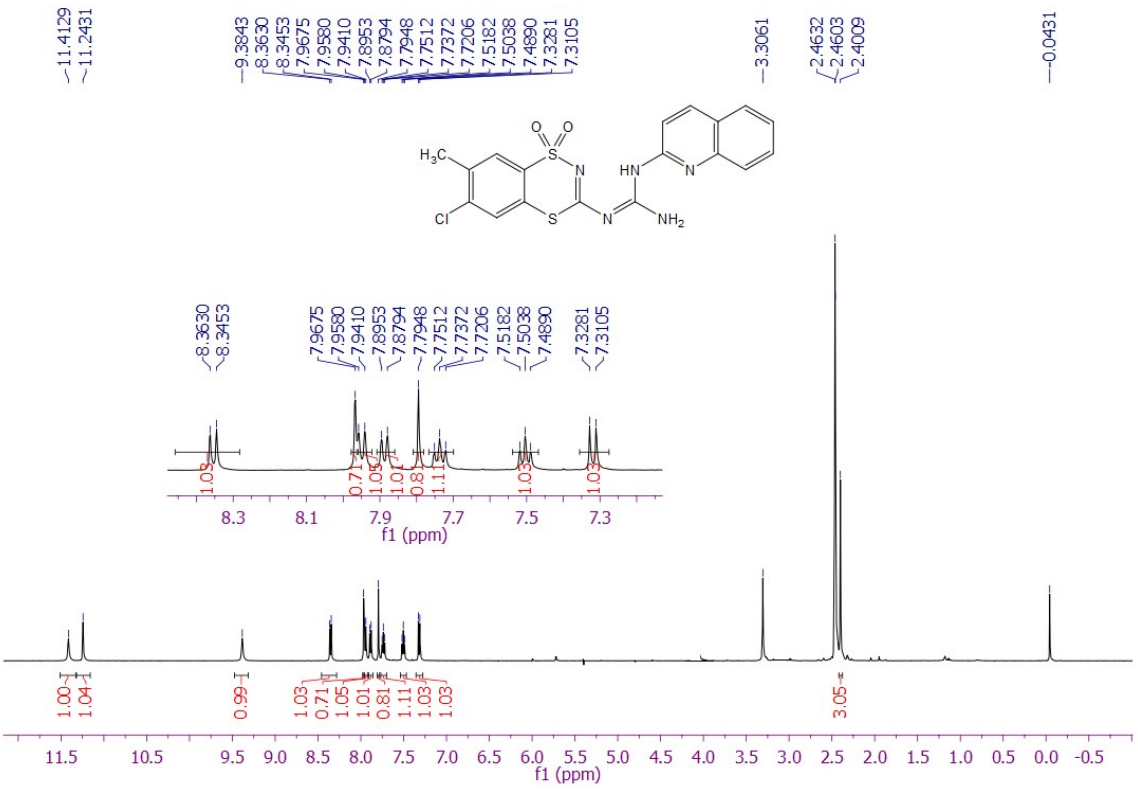


Figure S50. ^{1}H NMR spectrum of **10y** (600 MHz, DMSO-d_6)

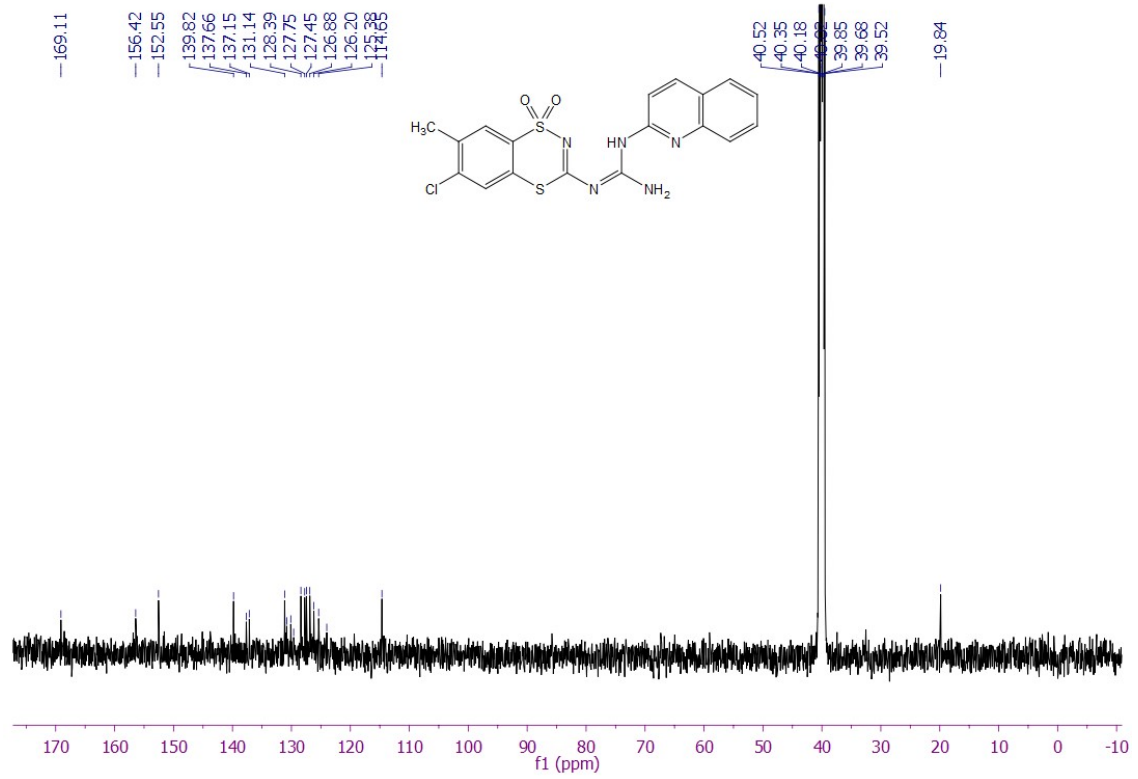


Figure S51. ^{13}C NMR spectrum of **10y** (151 MHz, DMSO-d_6)

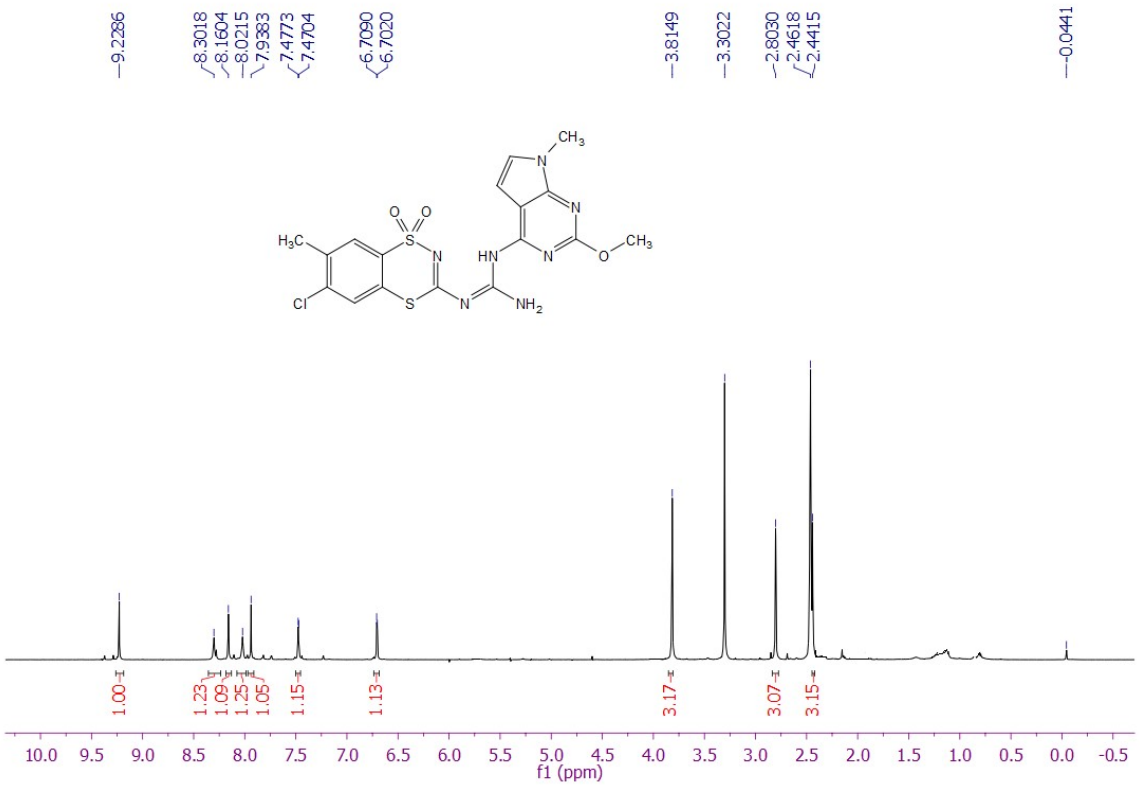


Figure S52. [1]H NMR spectrum of **10z** (600 MHz, DMSO-d_6)

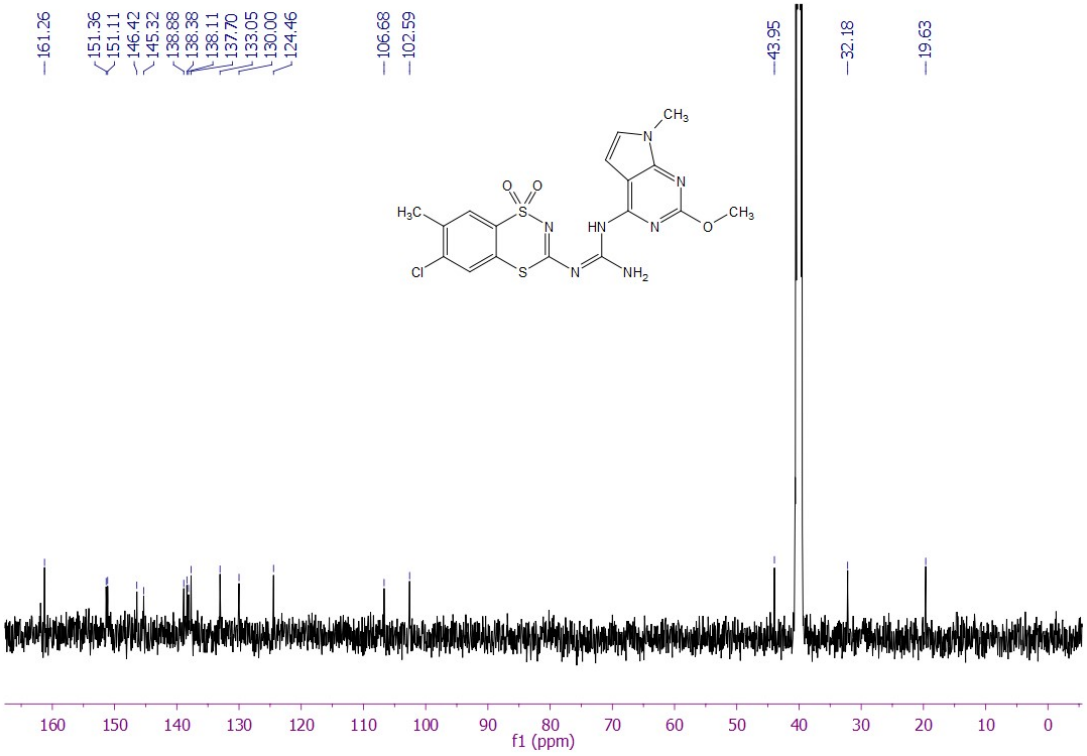


Figure S53. [13]C NMR spectrum of **10z** (151 MHz, DMSO-d_6)

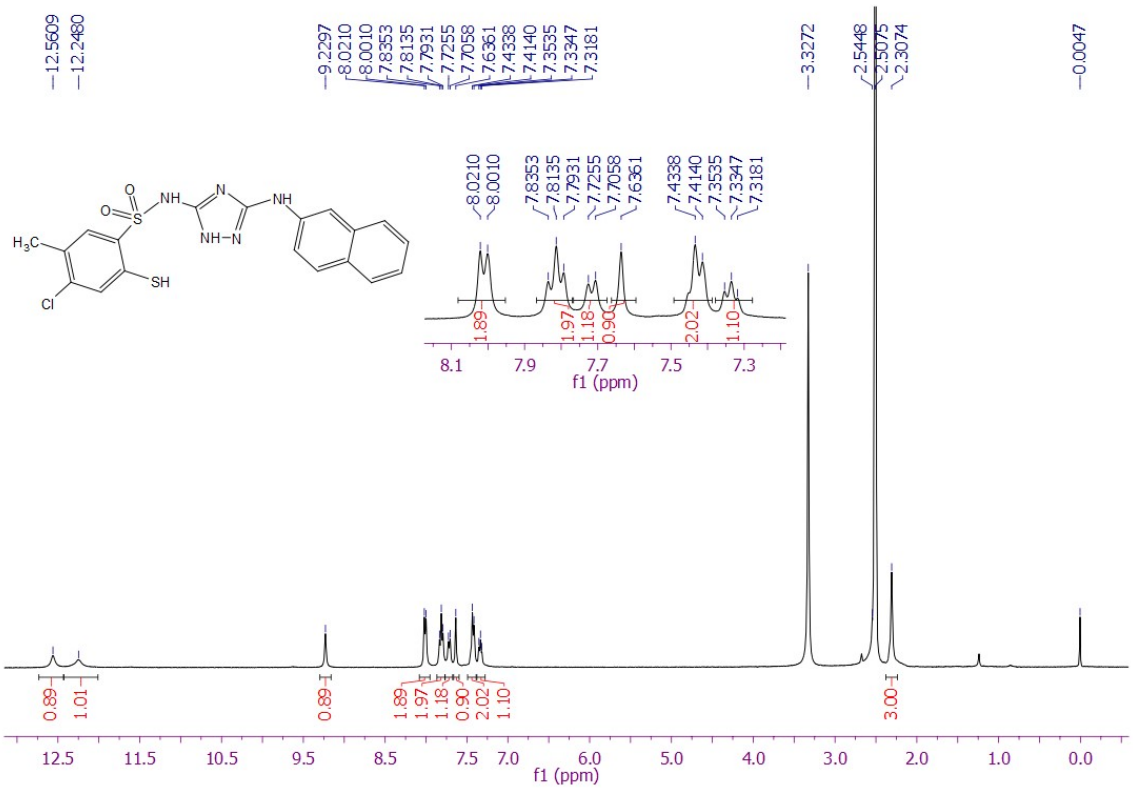


Figure S54. [1]H NMR spectrum of **NSC-666719 (11a)** (400 MHz, DMSO-d_6)

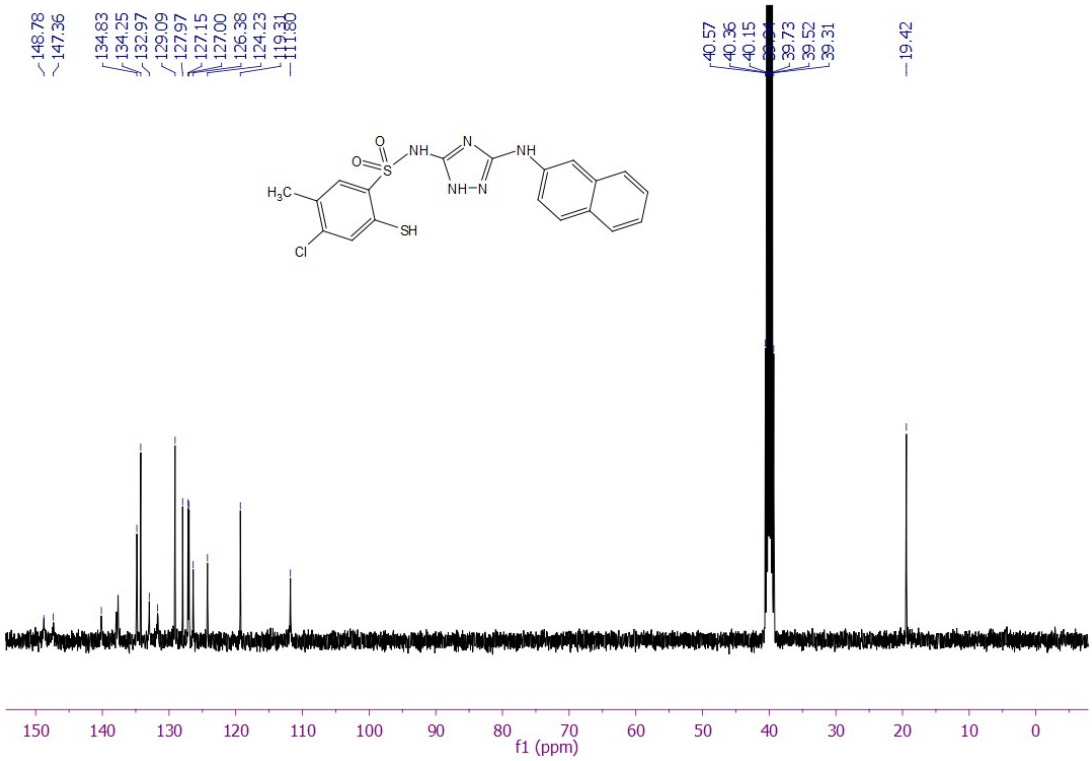


Figure S55. [13]C NMR spectrum of **NSC-666719 (11a)** (101 MHz, DMSO-d_6)

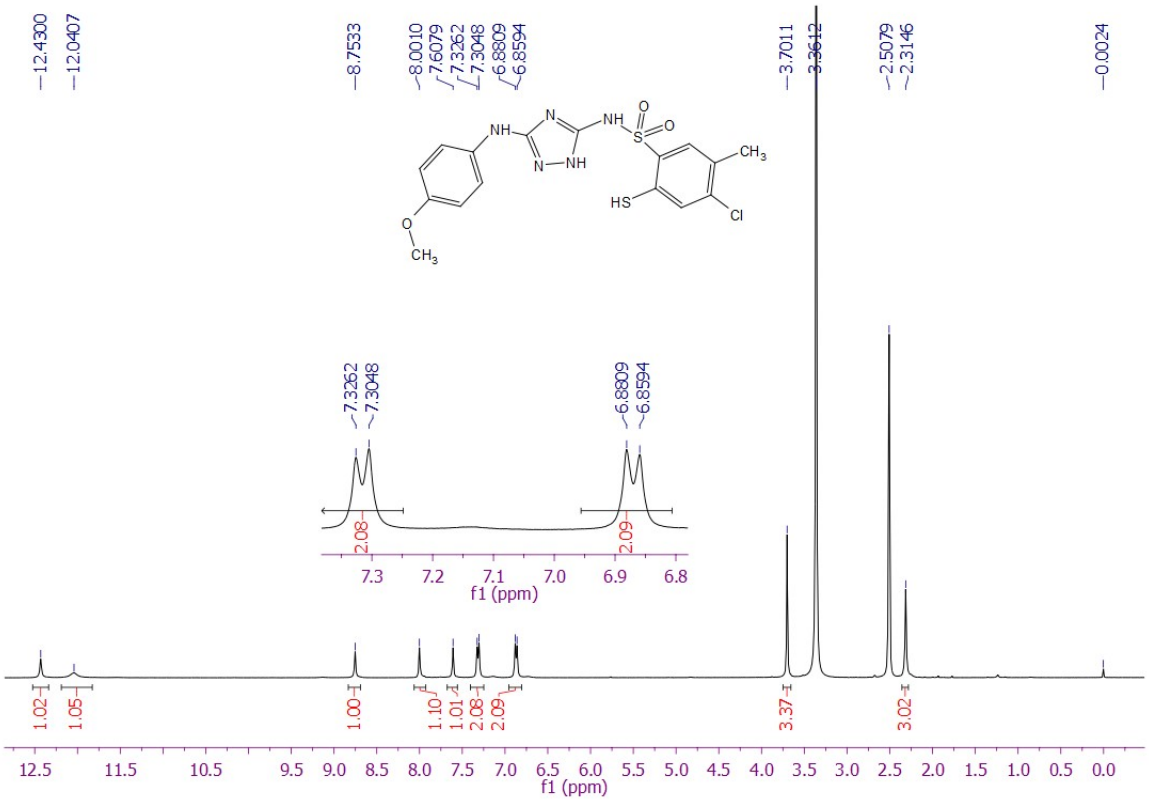


Figure S56. ^{1}H NMR spectrum of **11b** (400 MHz, DMSO-d_6)

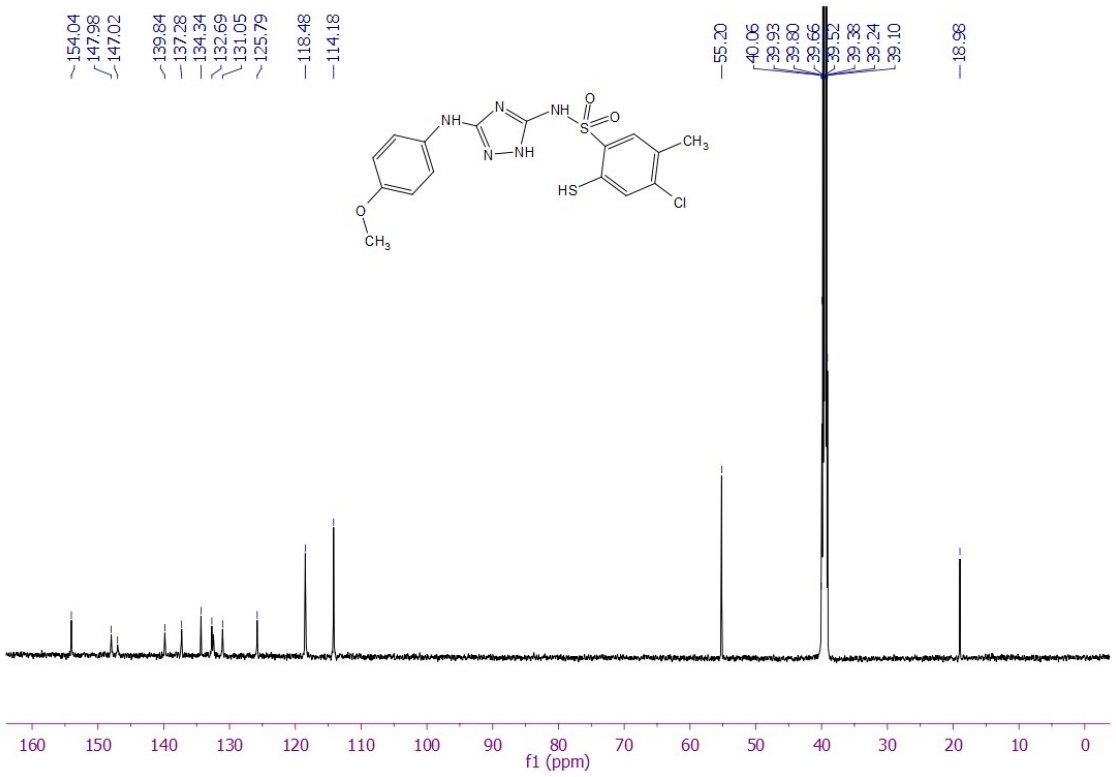


Figure S57. ^{13}C NMR spectrum of **11b** (101 MHz, DMSO-d_6)

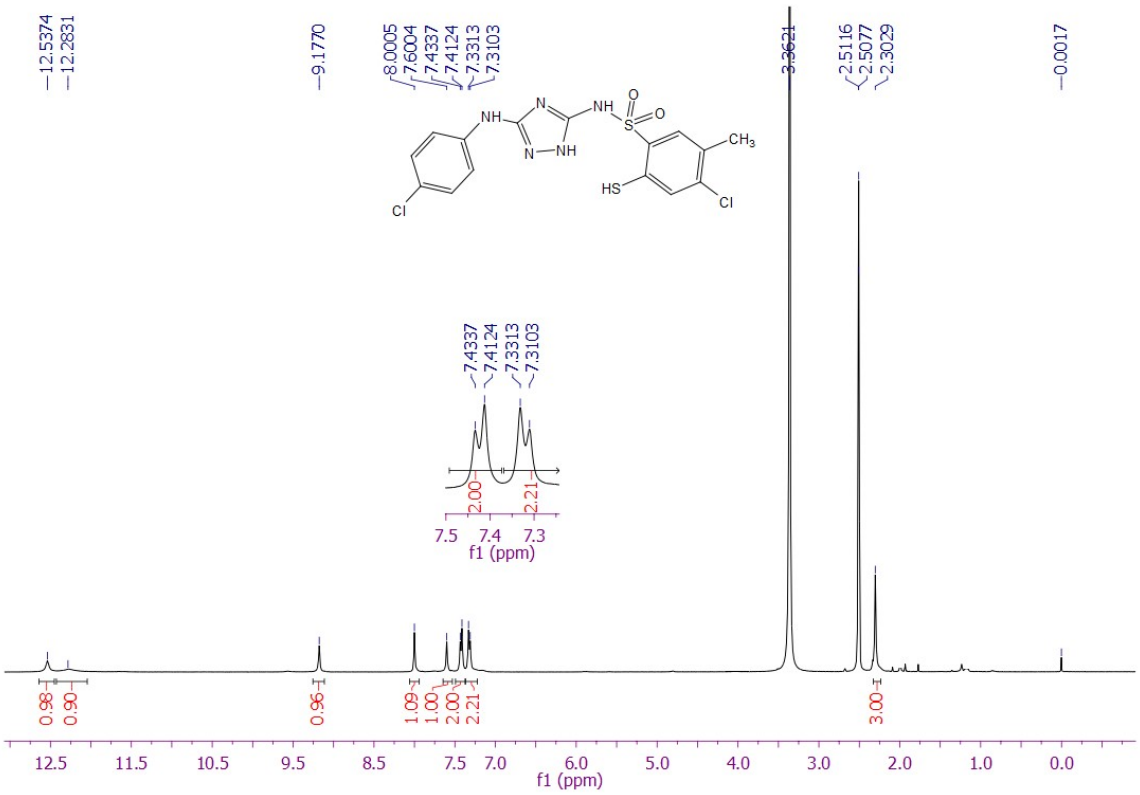


Figure S58. ^{1}H NMR spectrum of **11c** (400 MHz, DMSO-d_6)

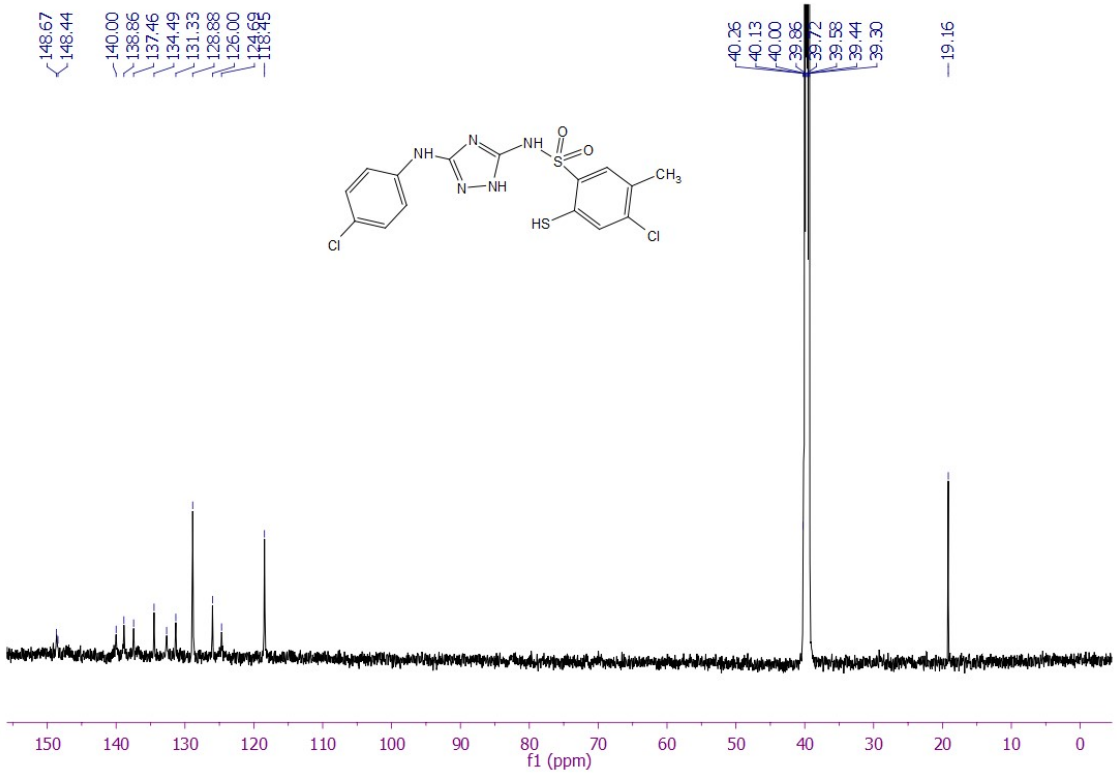


Figure S59. ^{13}C NMR spectrum of **11c** (101 MHz, DMSO-d_6)

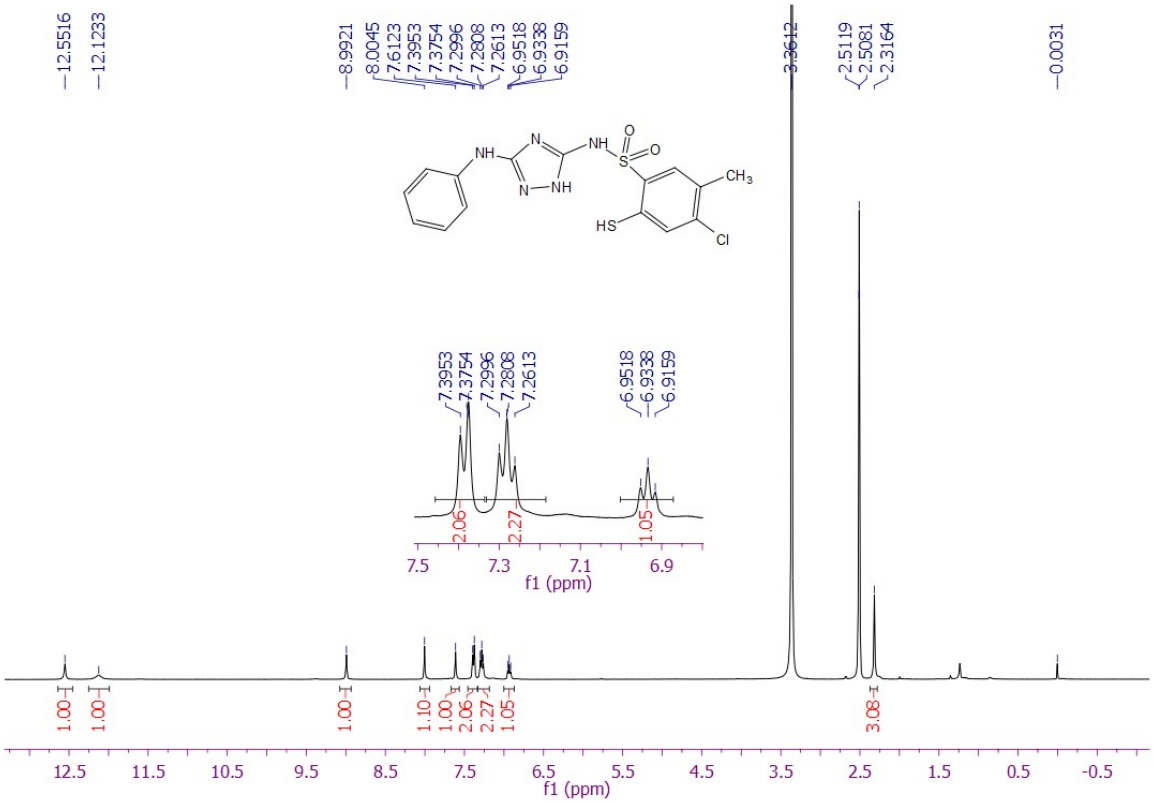


Figure S60. ^{1}H NMR spectrum of **11d** (400 MHz, DMSO-d_6)

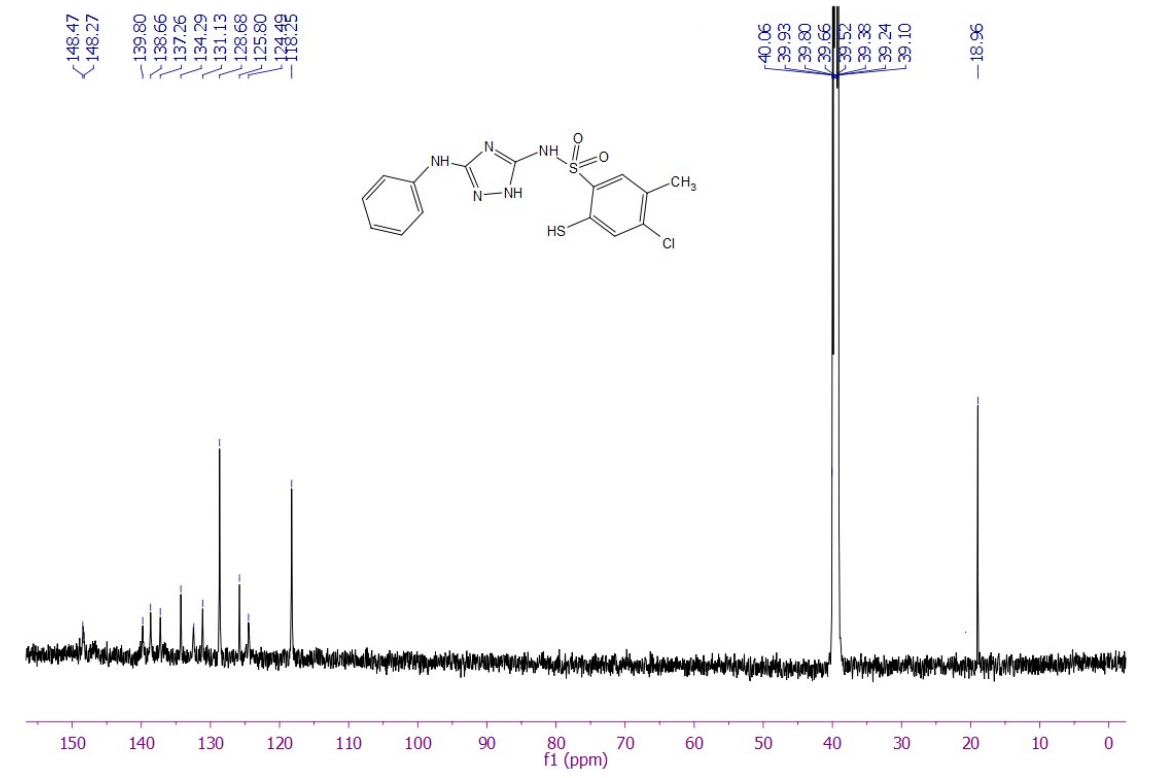


Figure S61. ^{13}C NMR spectrum of **11d** (101 MHz, DMSO-d_6)

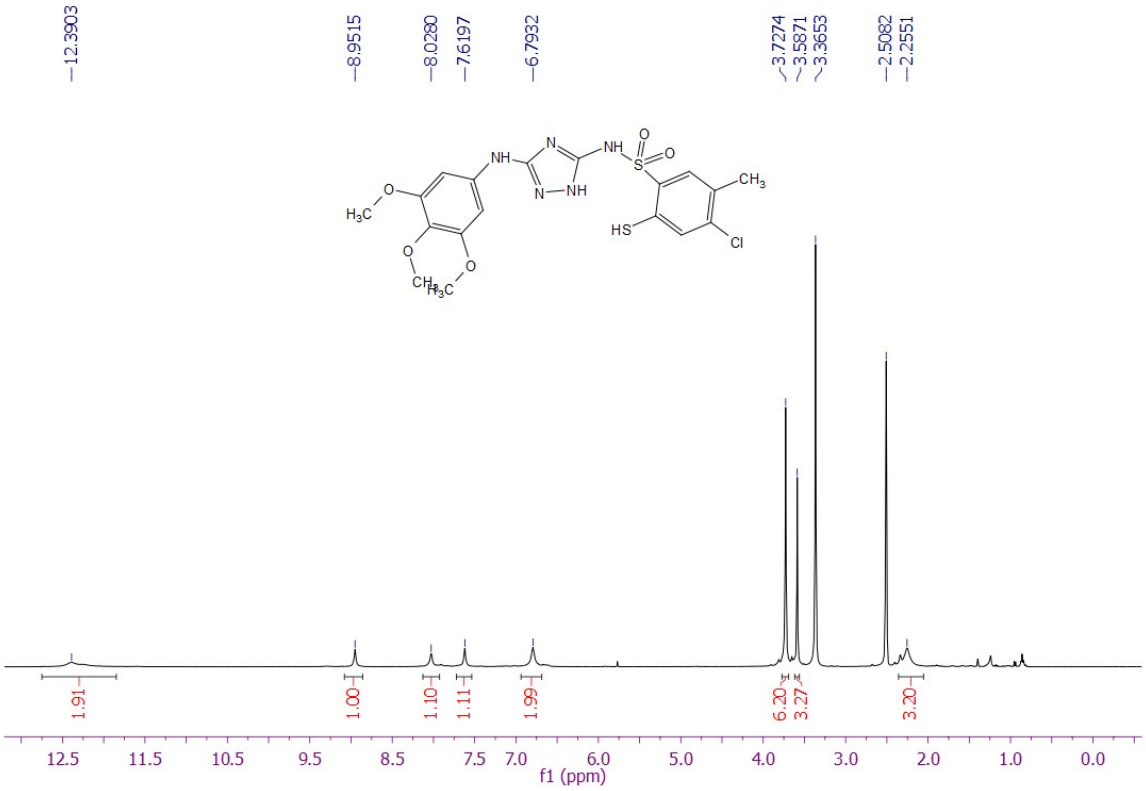


Figure S62. [1]H NMR spectrum of **11e** (400 MHz, DMSO-d_6)

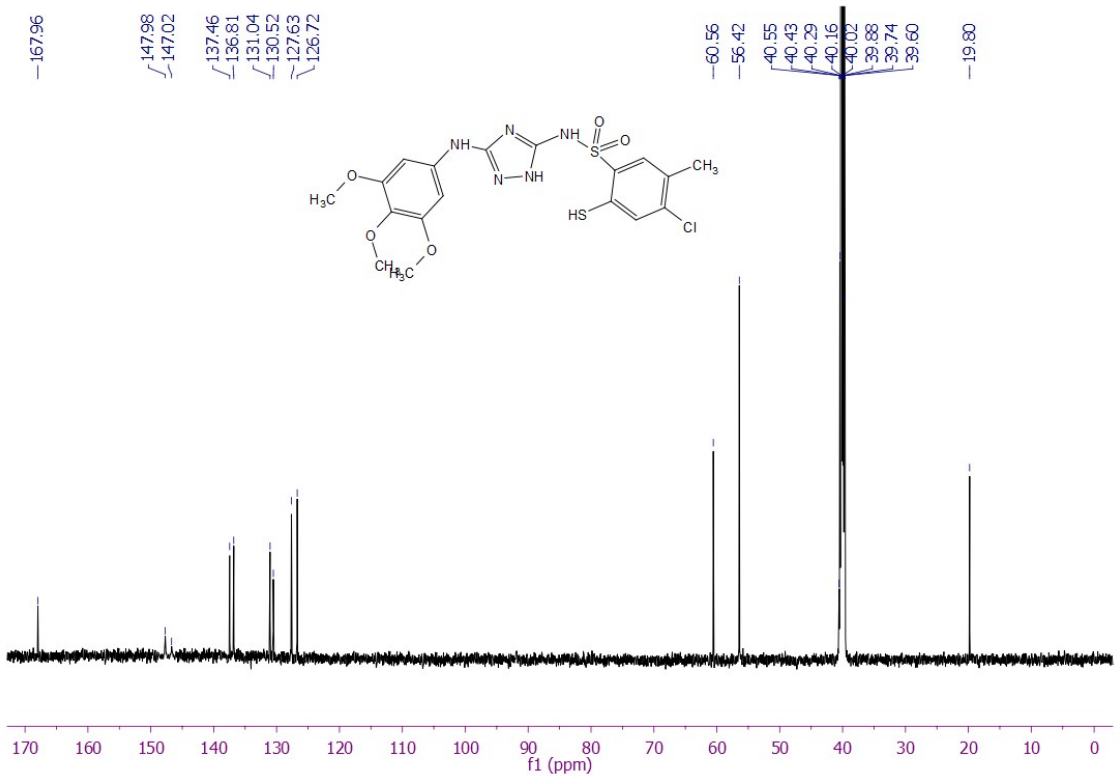


Figure S63. [13]C NMR spectrum of **11e** (101 MHz, DMSO-d_6)

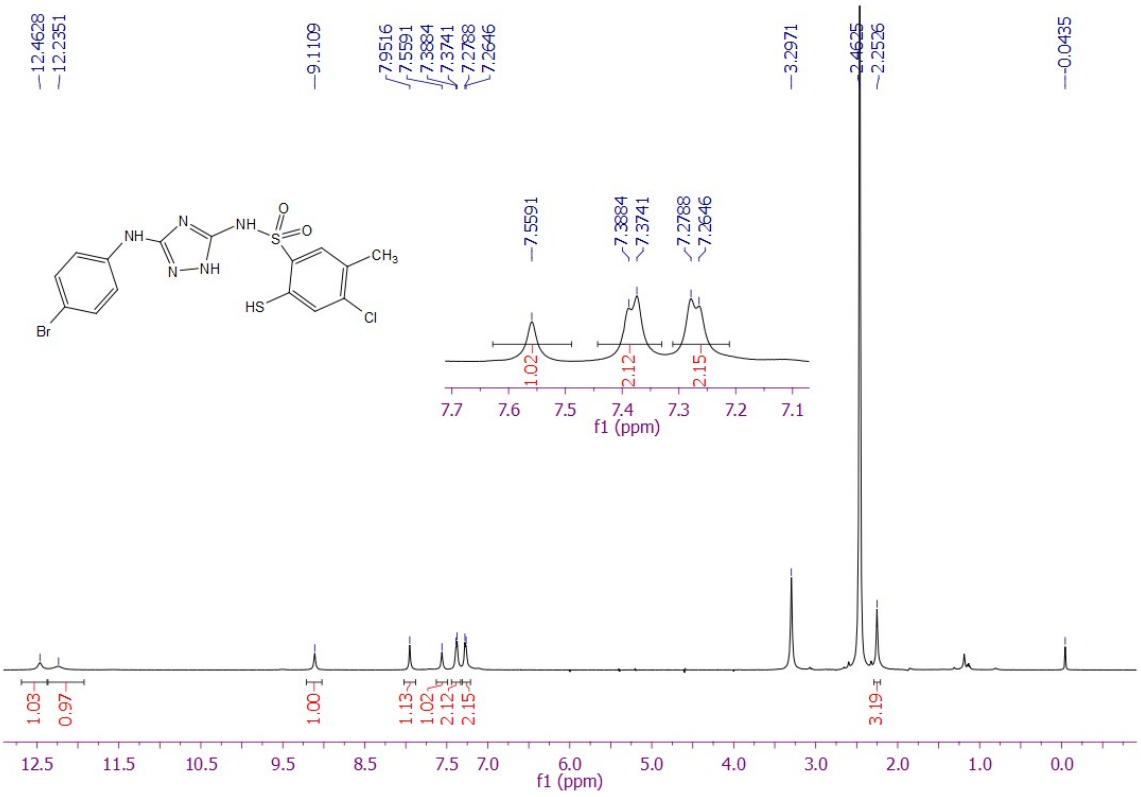


Figure S64. ^{1}H NMR spectrum of **11f** (400 MHz, DMSO-d_6)

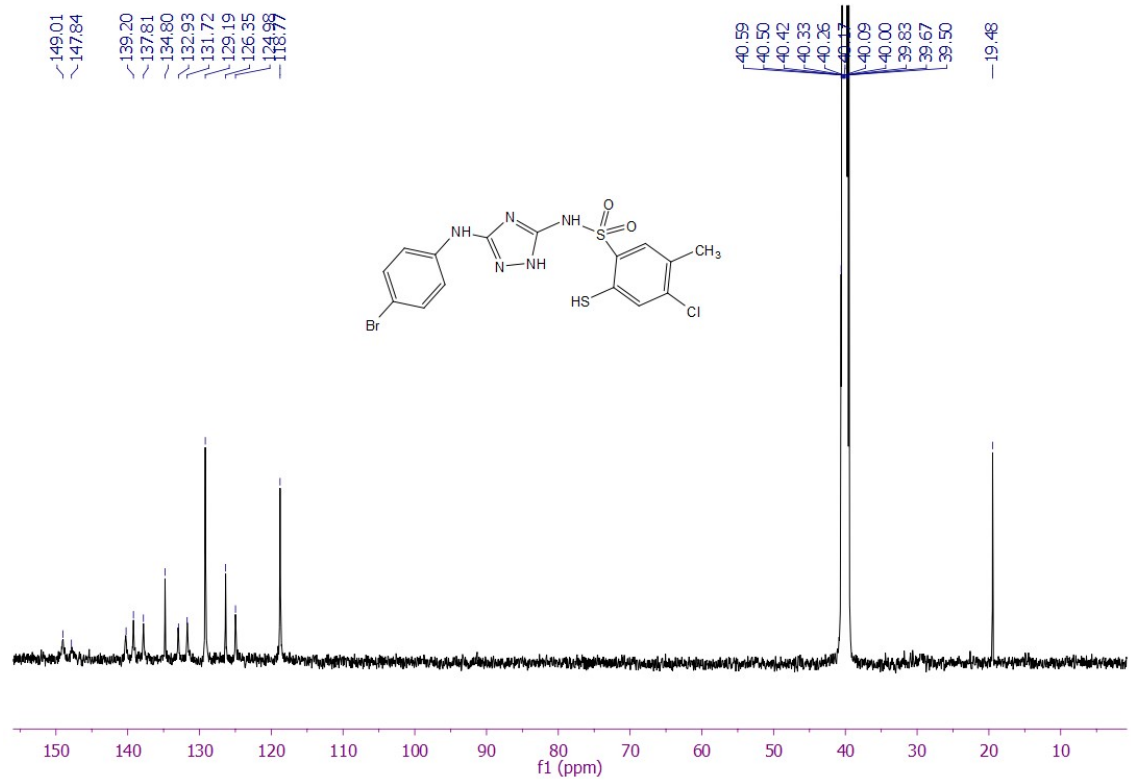


Figure S65. ^{13}C NMR spectrum of **11f** (101 MHz, DMSO-d_6)

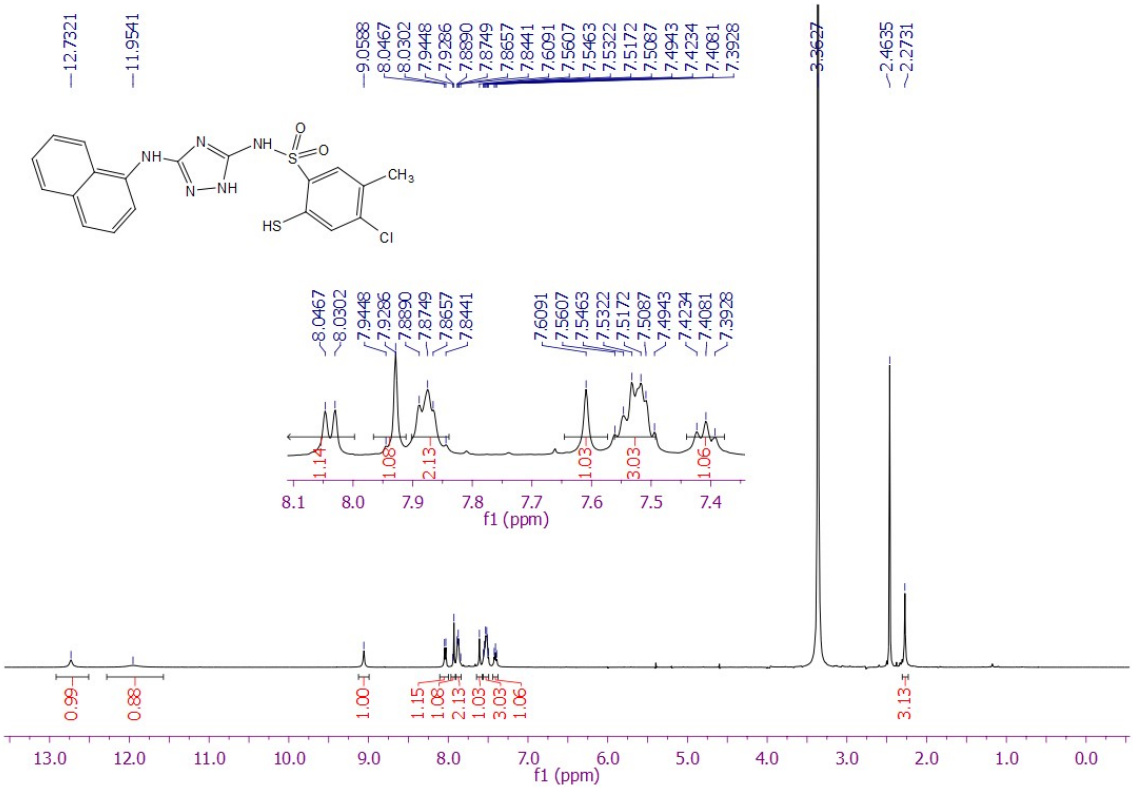


Figure S66. ^{1}H NMR spectrum of **11g** (400 MHz, DMSO-d_6)

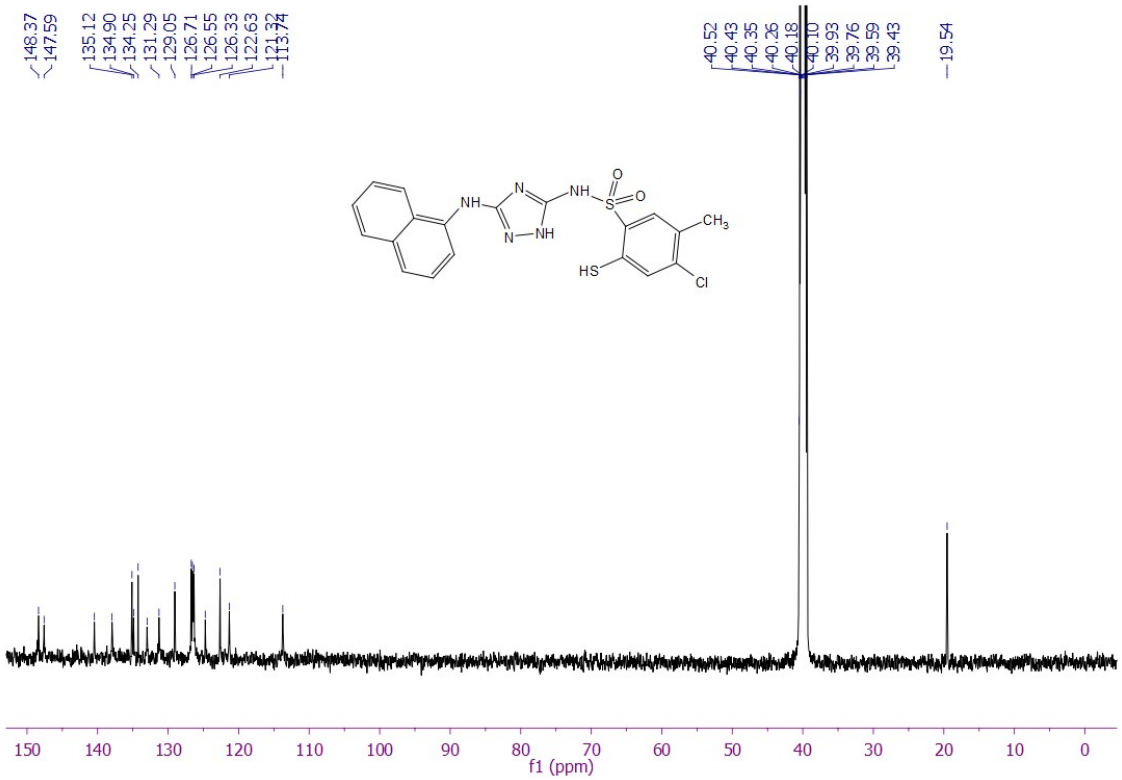


Figure S67. ^{13}C NMR spectrum of **11g** (101 MHz, DMSO-d_6)

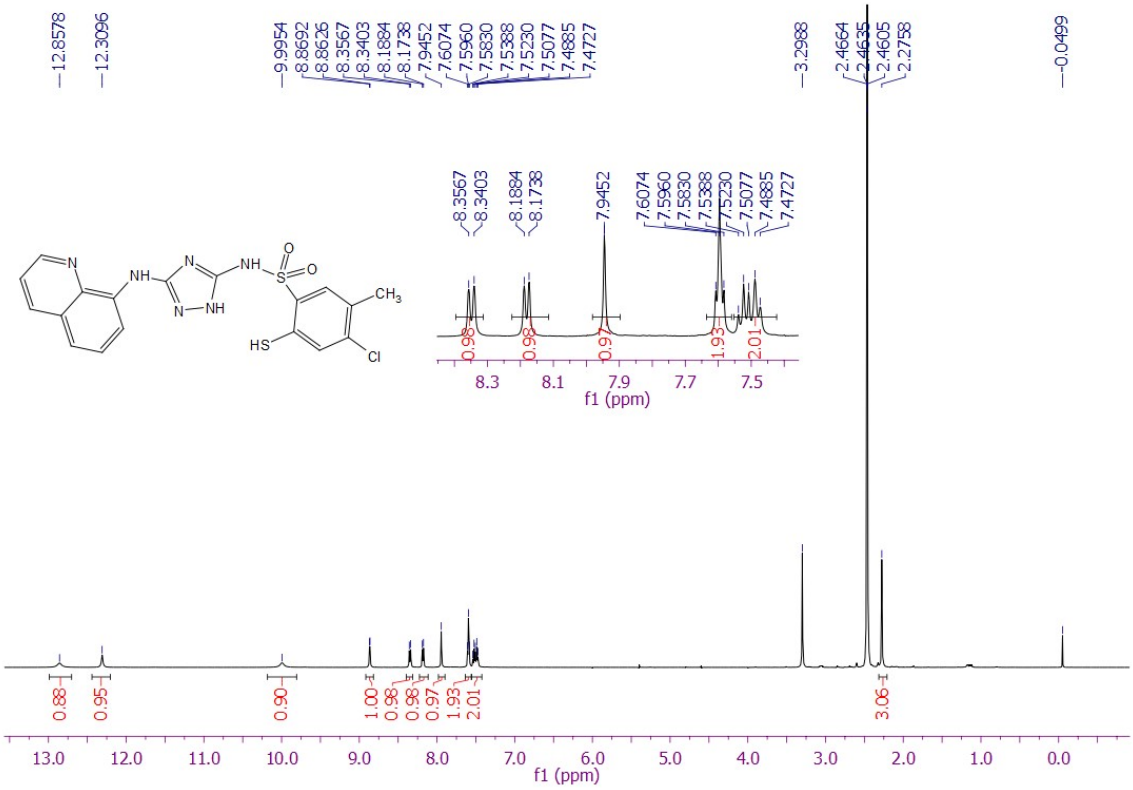


Figure S68. ^{1}H NMR spectrum of **11h** (500 MHz, DMSO-d_6)

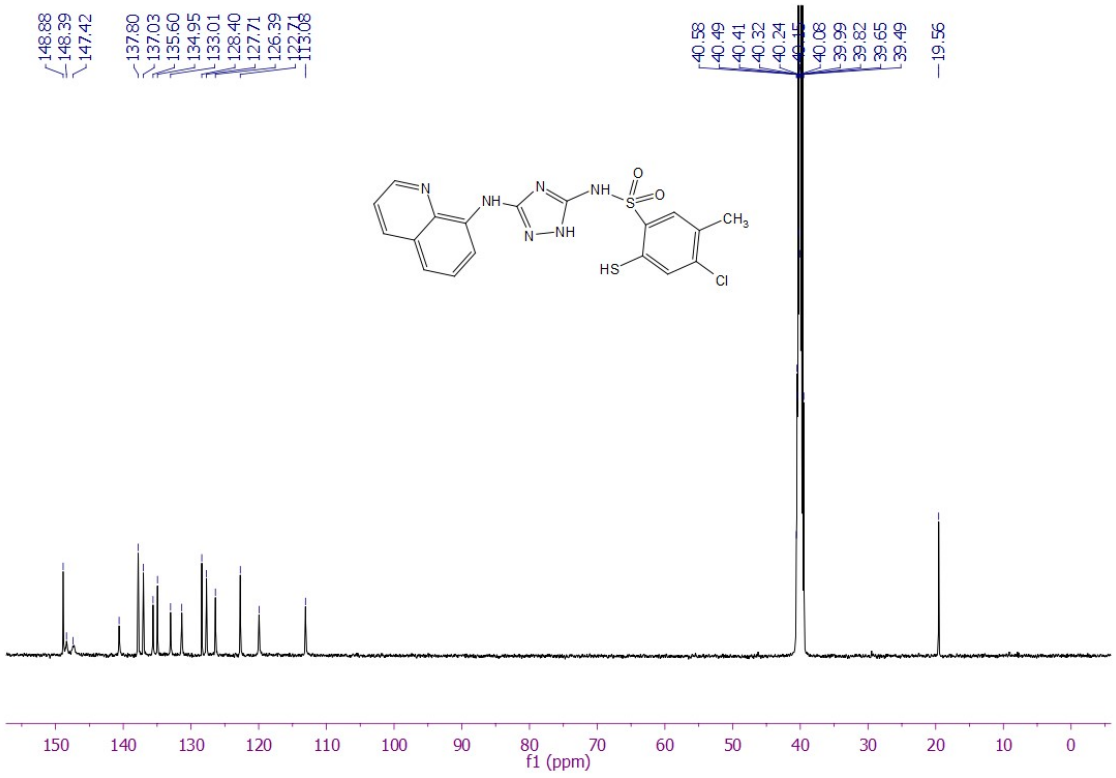


Figure S69. ^{13}C NMR spectrum of **11h** (126 MHz, DMSO-d_6)

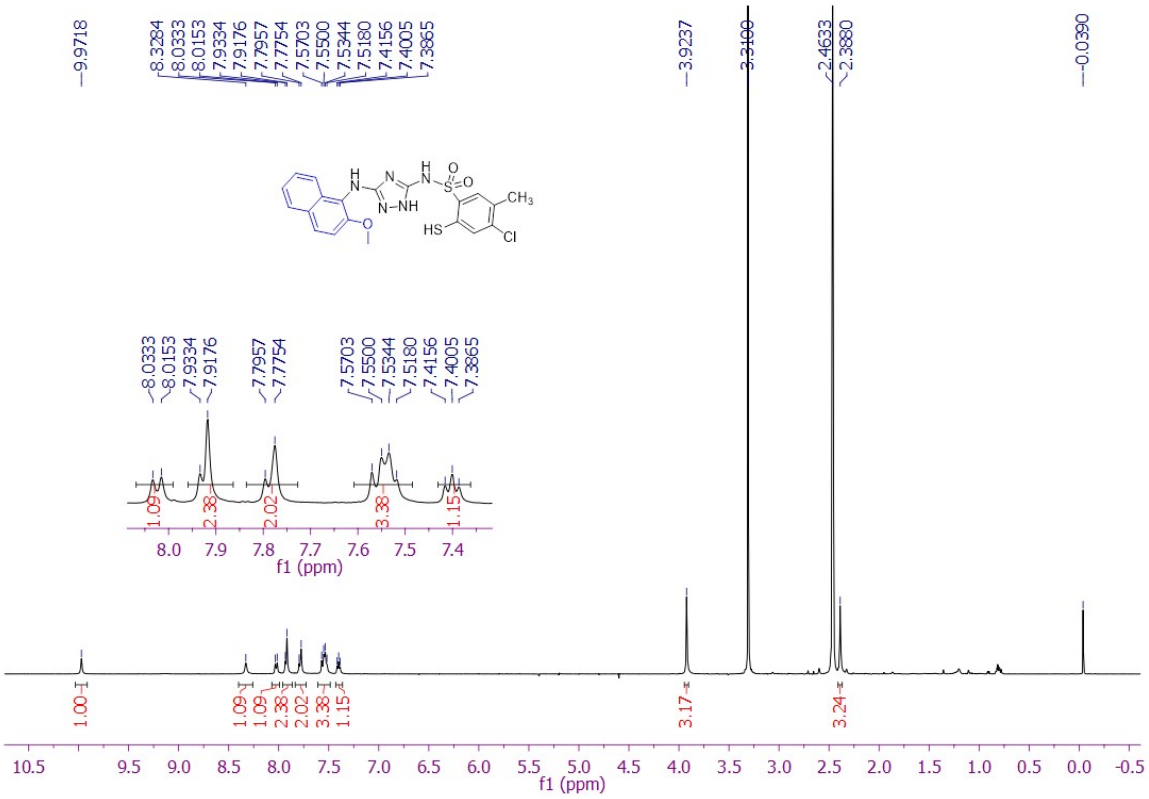


Figure S70. [1]H NMR spectrum of **11i** (500 MHz, DMSO-d_6)

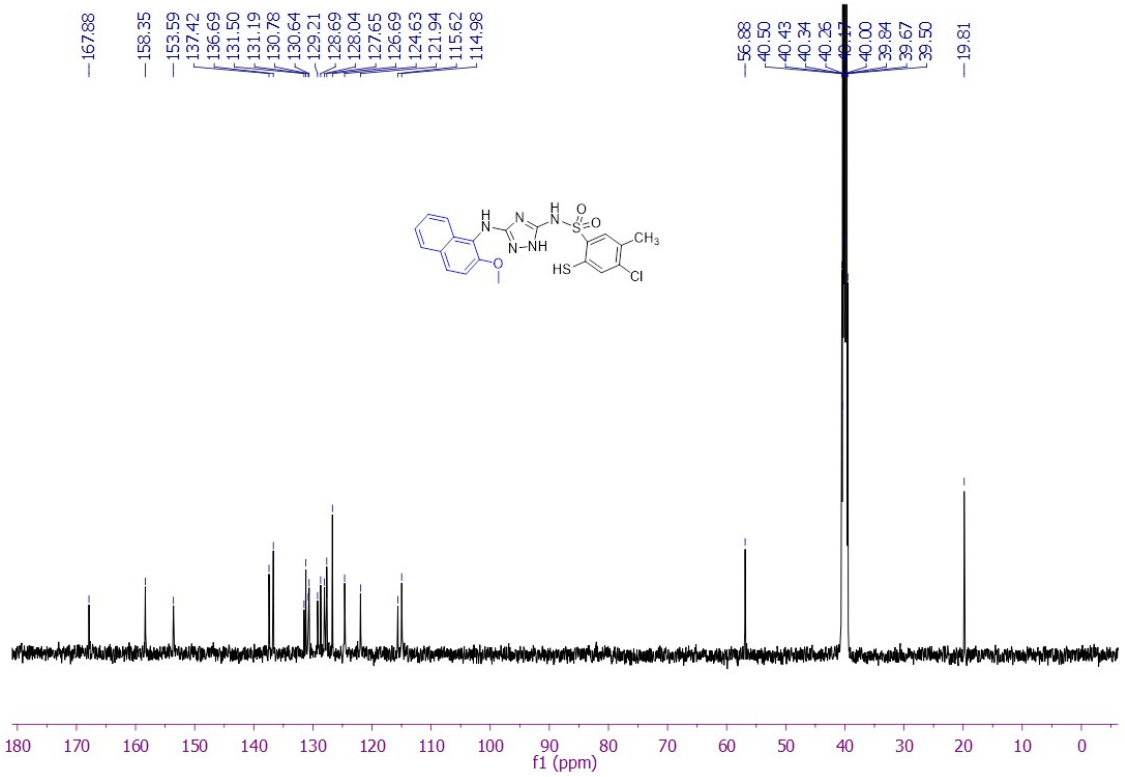


Figure S71. [13]C NMR spectrum of **11i** (126 MHz, DMSO-d_6)

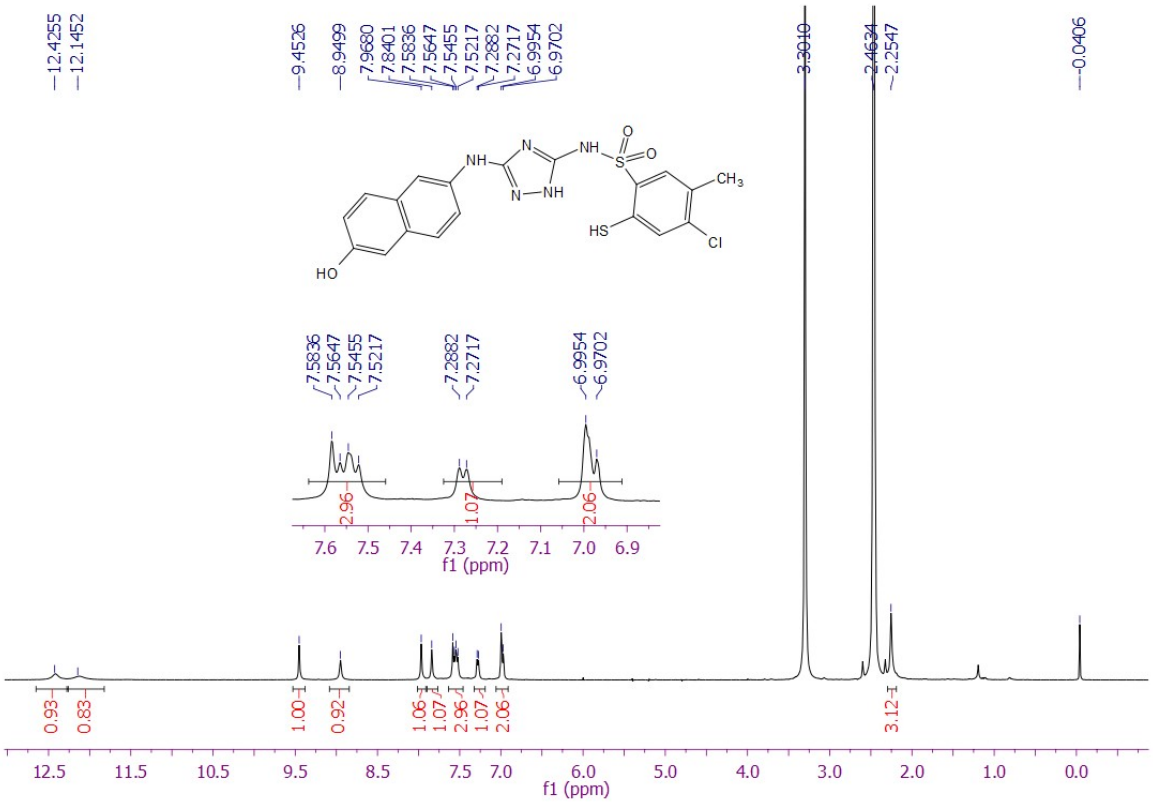


Figure S72. [1]H NMR spectrum of **11j** (500 MHz, DMSO-d_6)

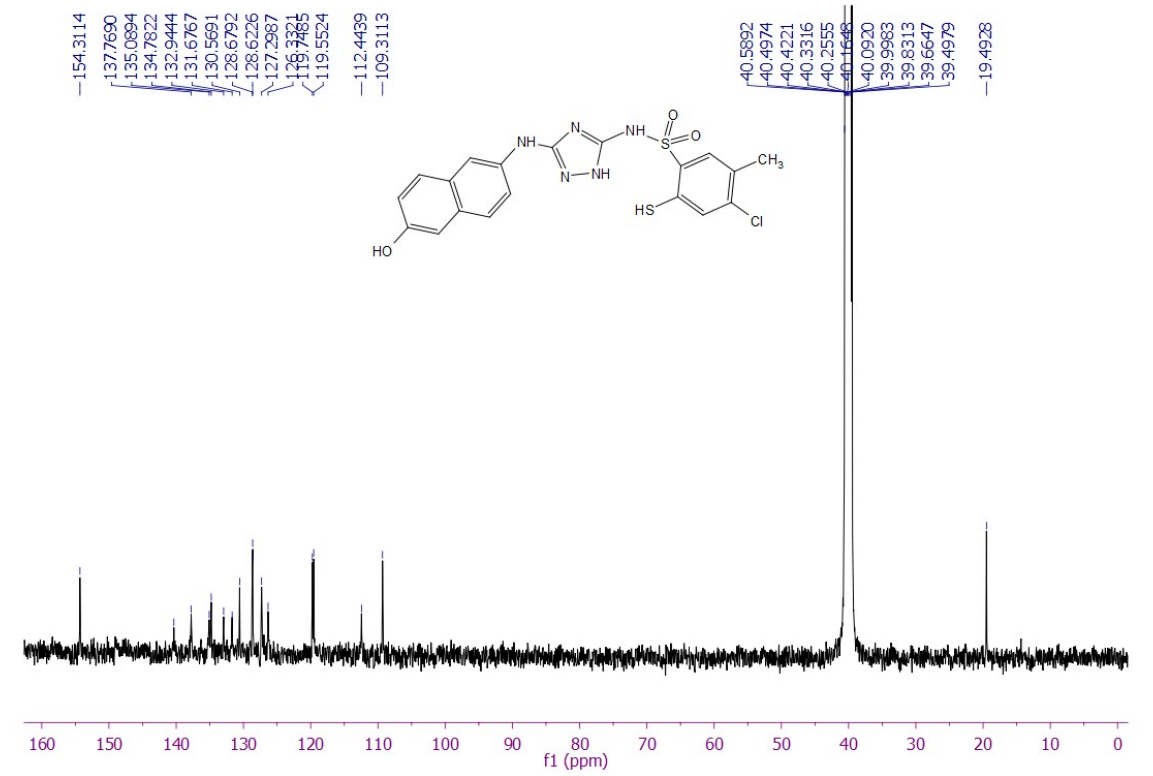


Figure S73. [13]C NMR spectrum of **11j** (126 MHz, DMSO-d_6)

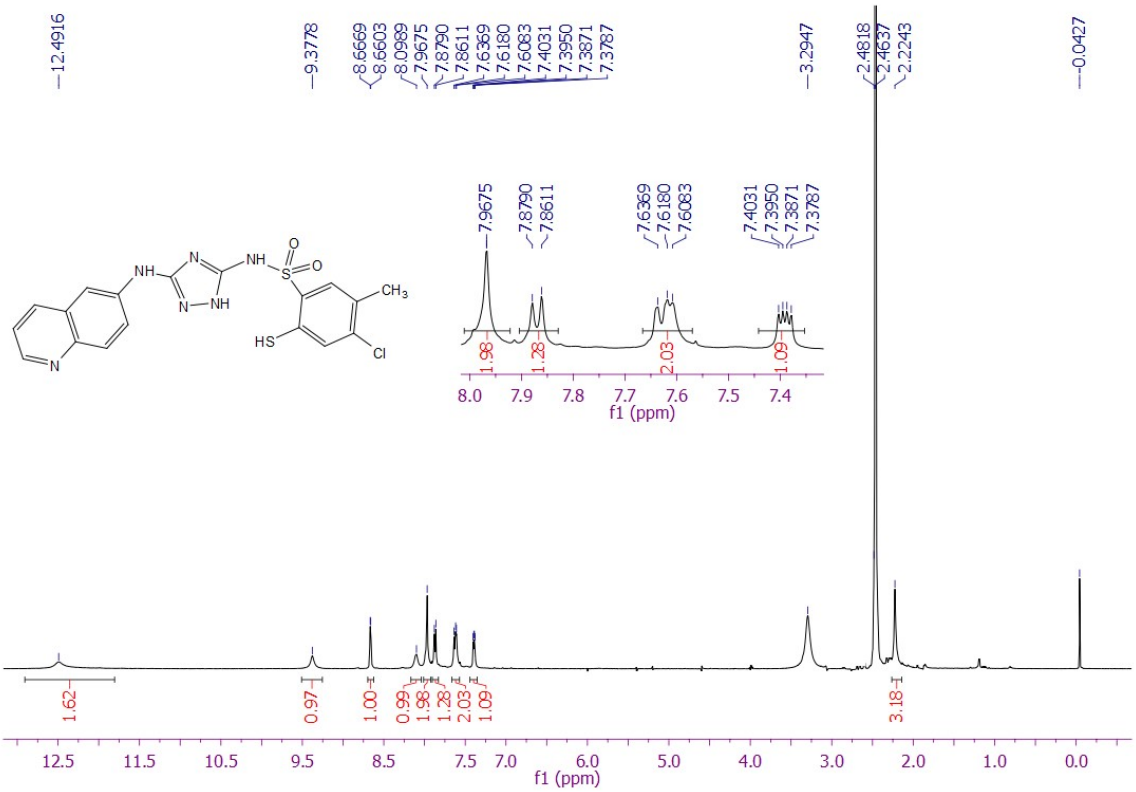


Figure S74. [1]H NMR spectrum of **11k** (500 MHz, DMSO-d_6)

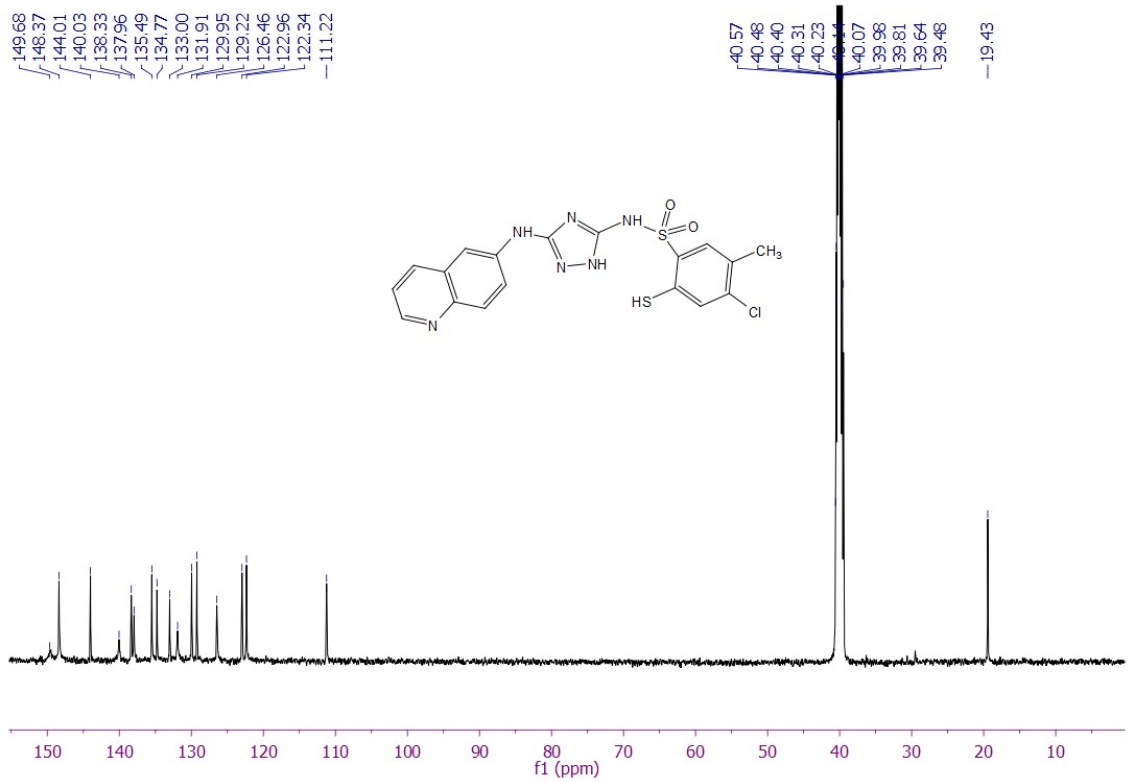


Figure S75. [13]C NMR spectrum of **11k** (126 MHz, DMSO-d_6)

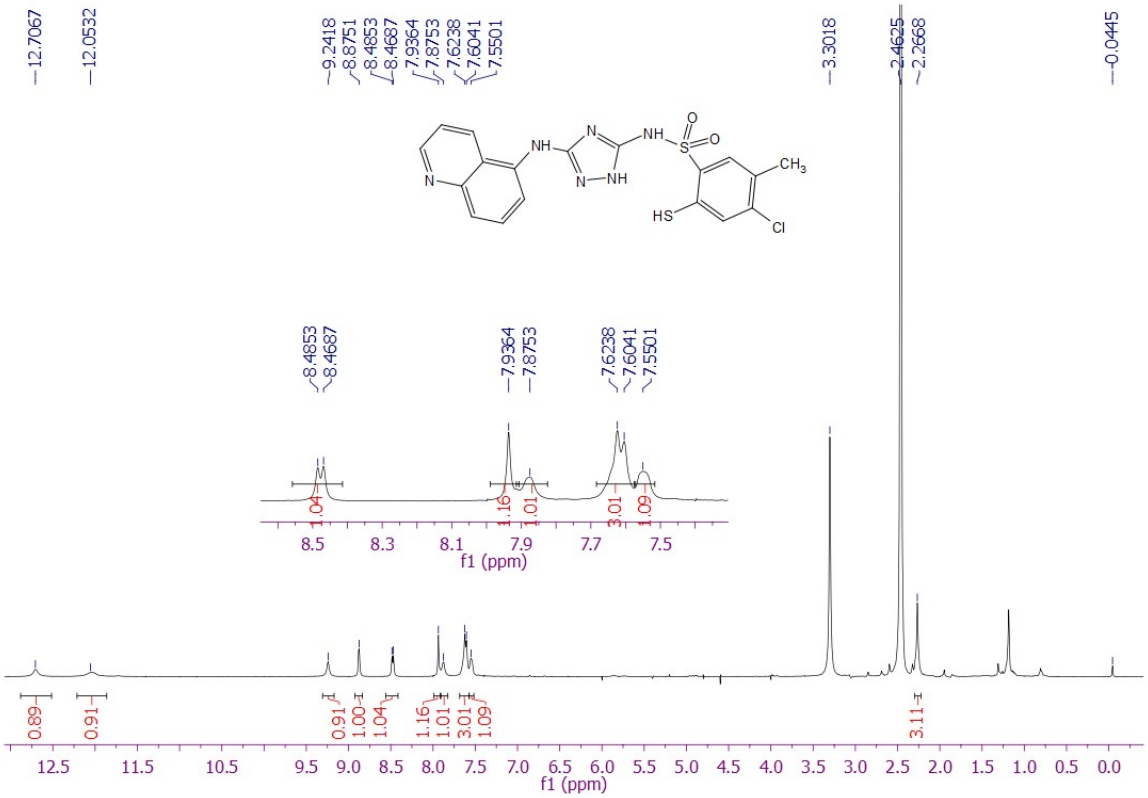


Figure S76. ^{1}H NMR spectrum of **11l** (500 MHz, DMSO-d_6)

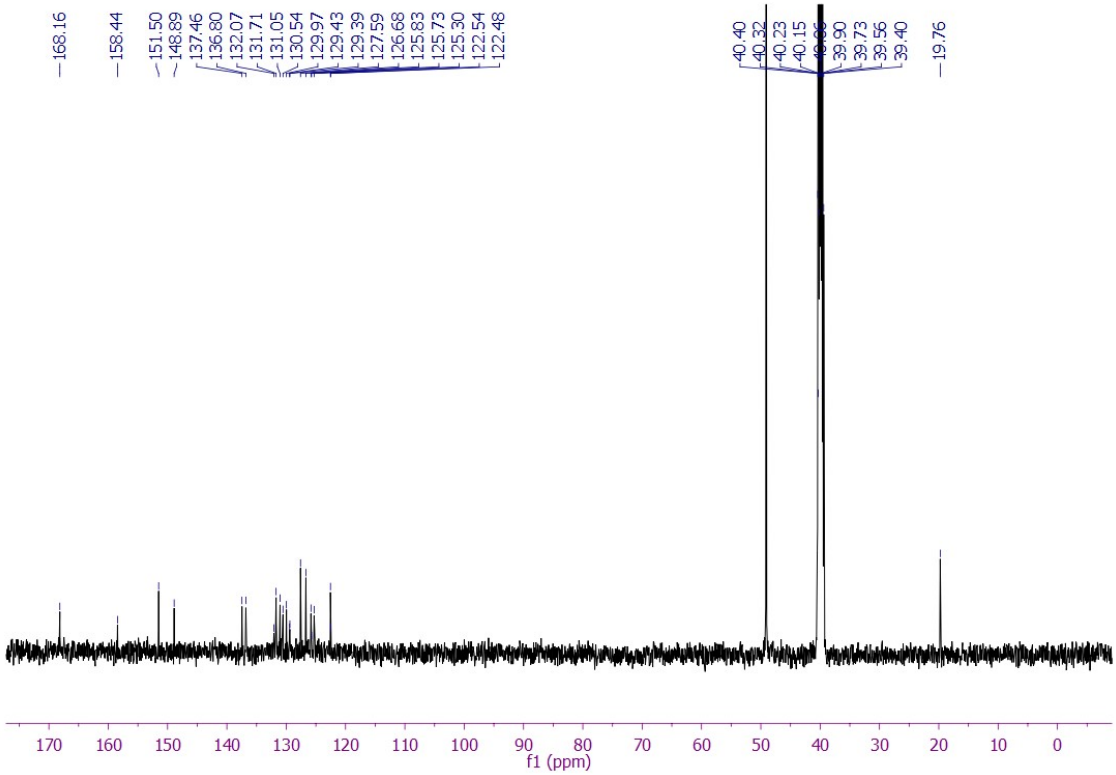


Figure S77. ^{13}C NMR spectrum of **11l** (126 MHz, DMSO-d_6)

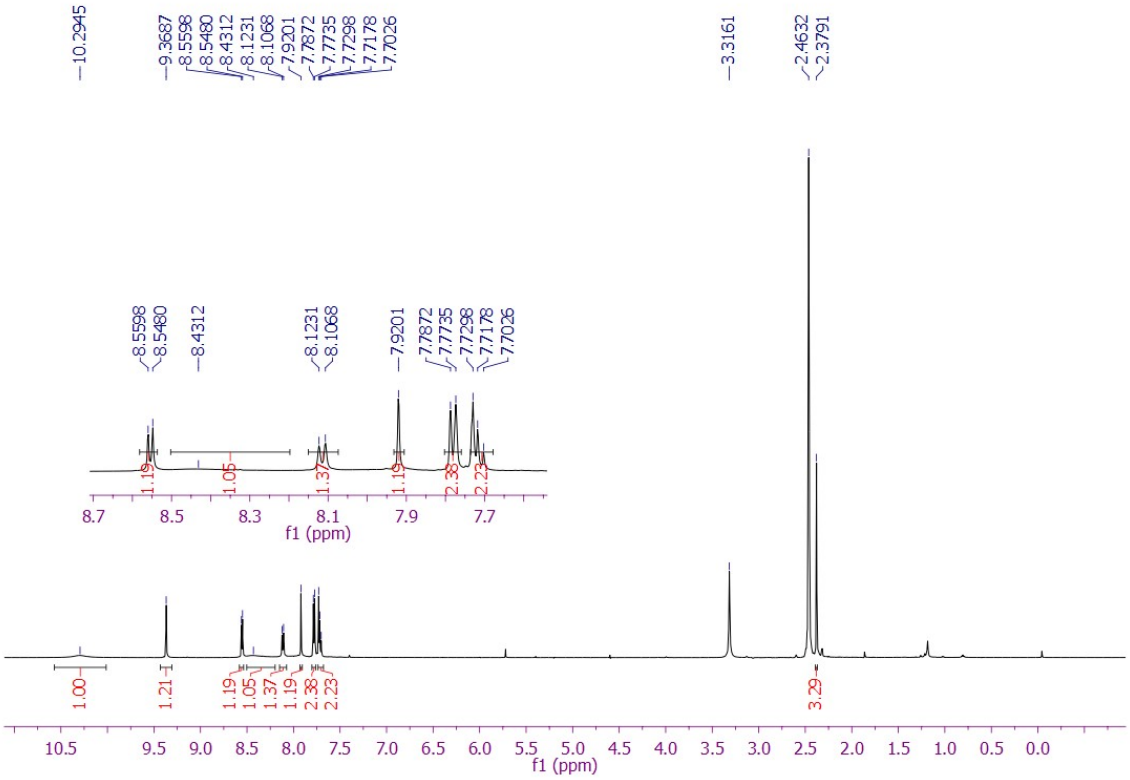


Figure S78. ^{1}H NMR spectrum of **11m** (500 MHz, DMSO-d_6)

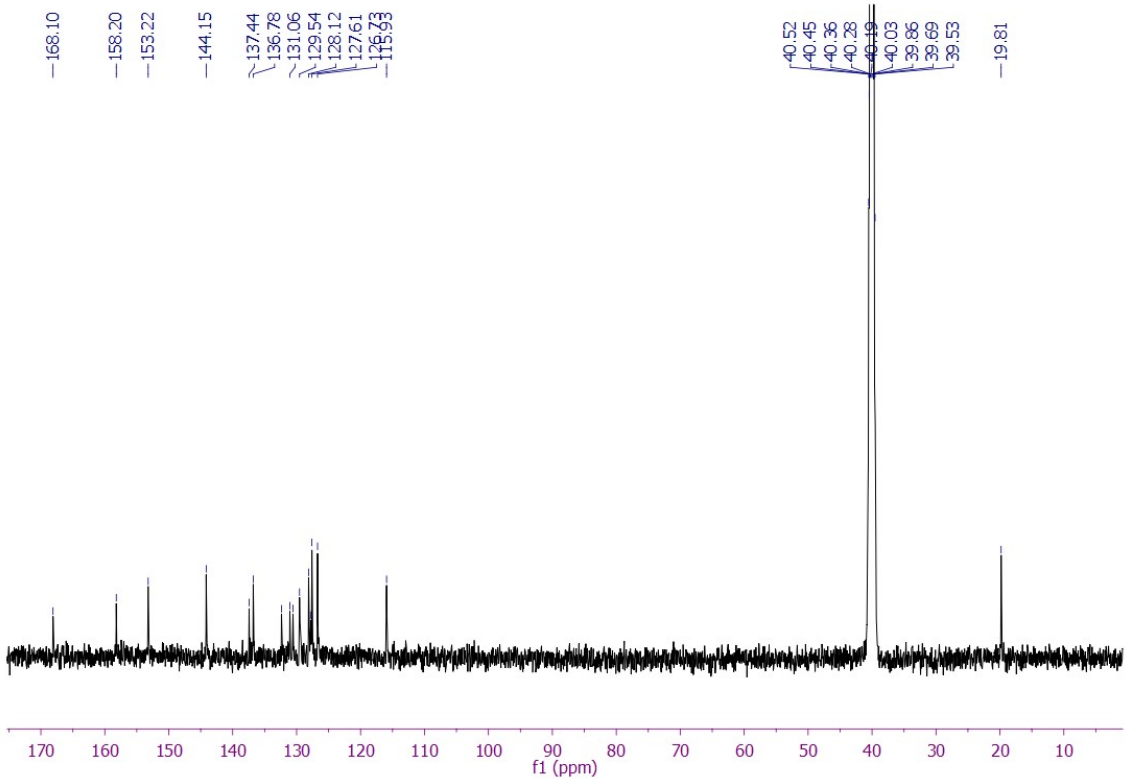


Figure S79. ^{13}C NMR spectrum of **11m** (126 MHz, DMSO-d_6)

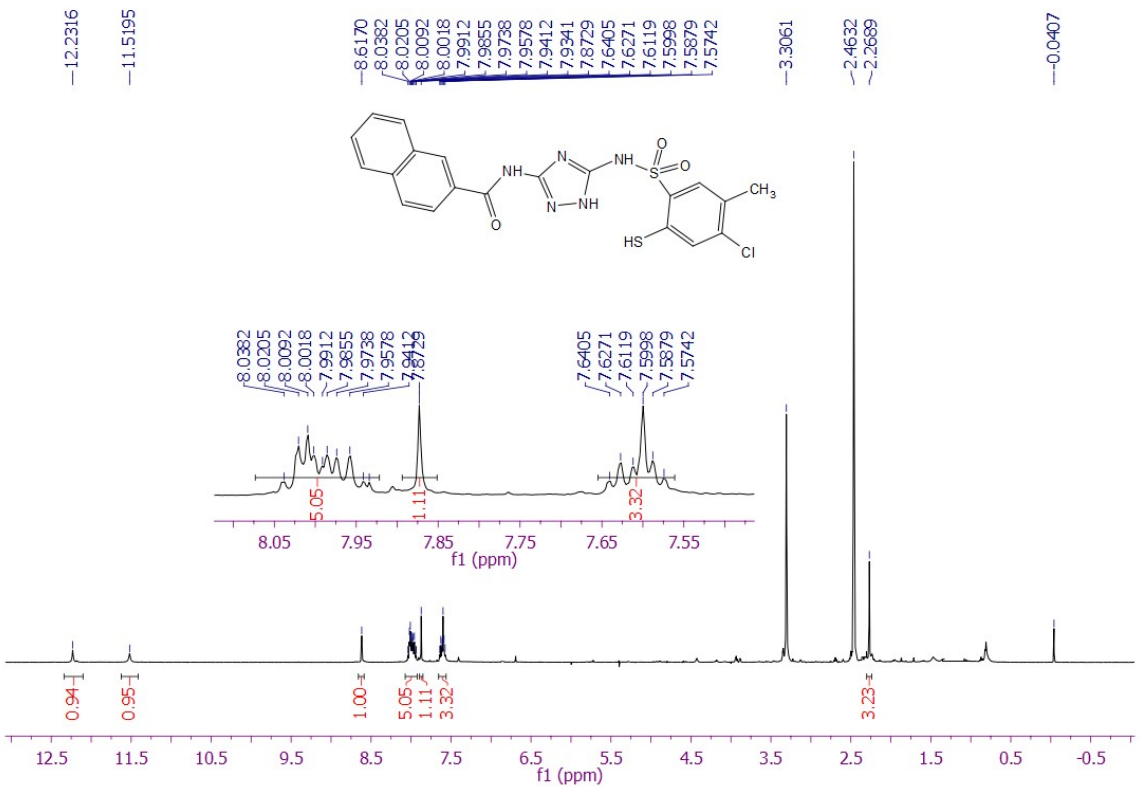


Figure S80. [1]H NMR spectrum of **11n** (500 MHz, DMSO-d_6)

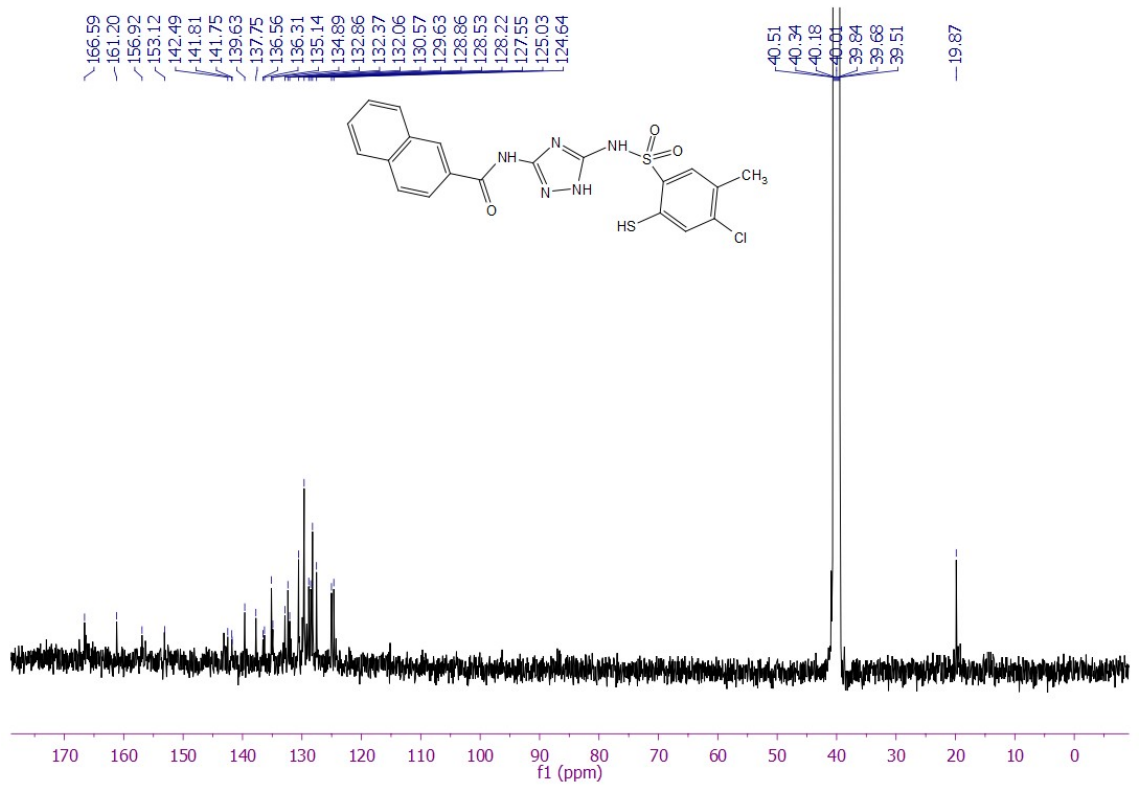


Figure S81. [13]C NMR spectrum of **11n** (126 MHz, DMSO-d_6)

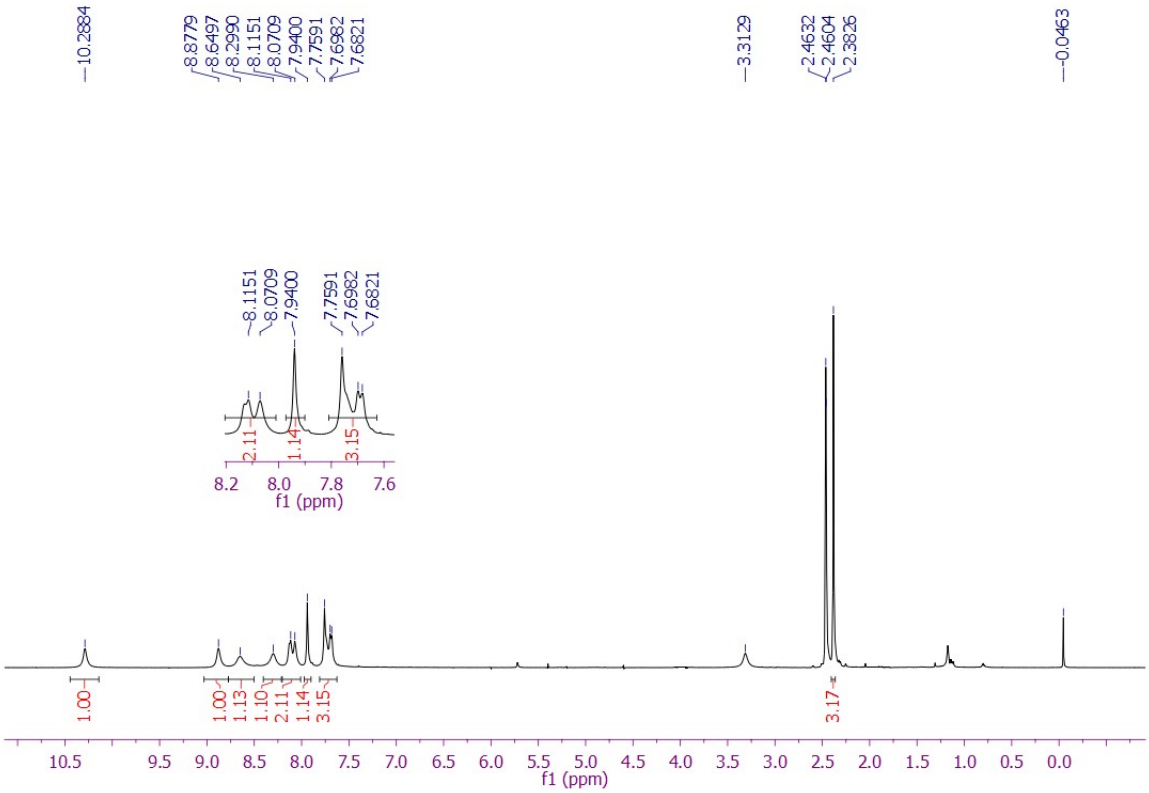


Figure S82. ^{1}H NMR spectrum of **11o** (500 MHz, DMSO-d_6)

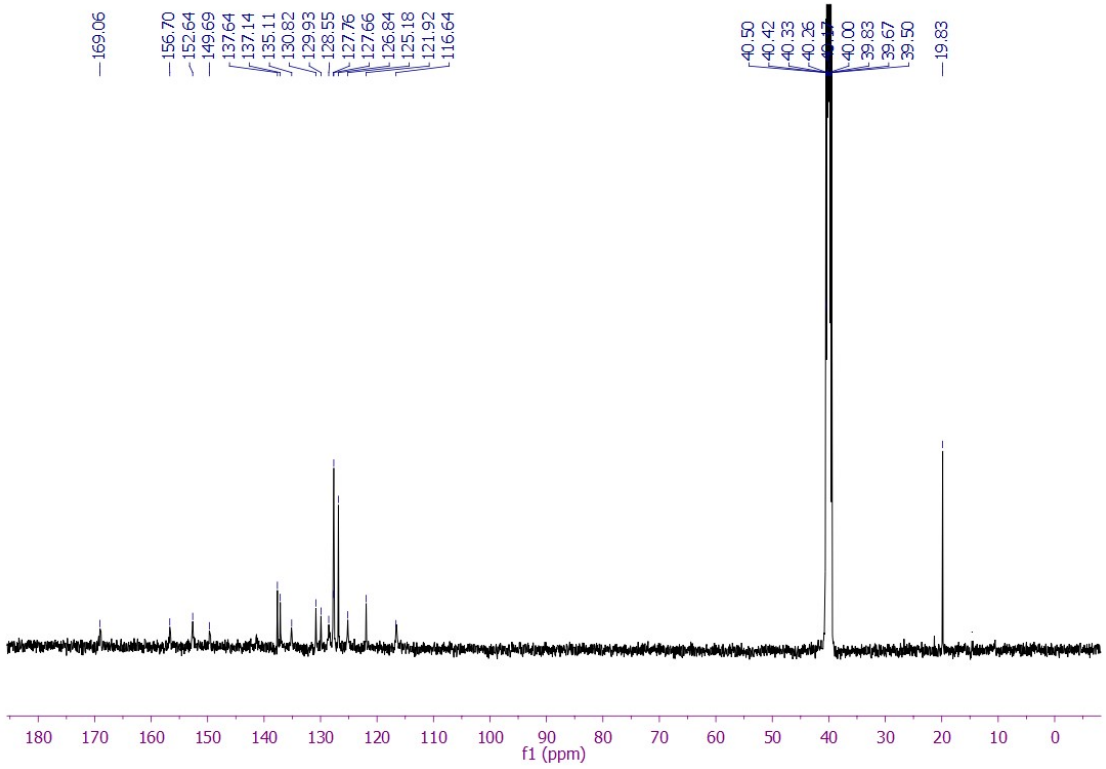


Figure S83. ^{13}C NMR spectrum of **11o** (126 MHz, DMSO-d_6)

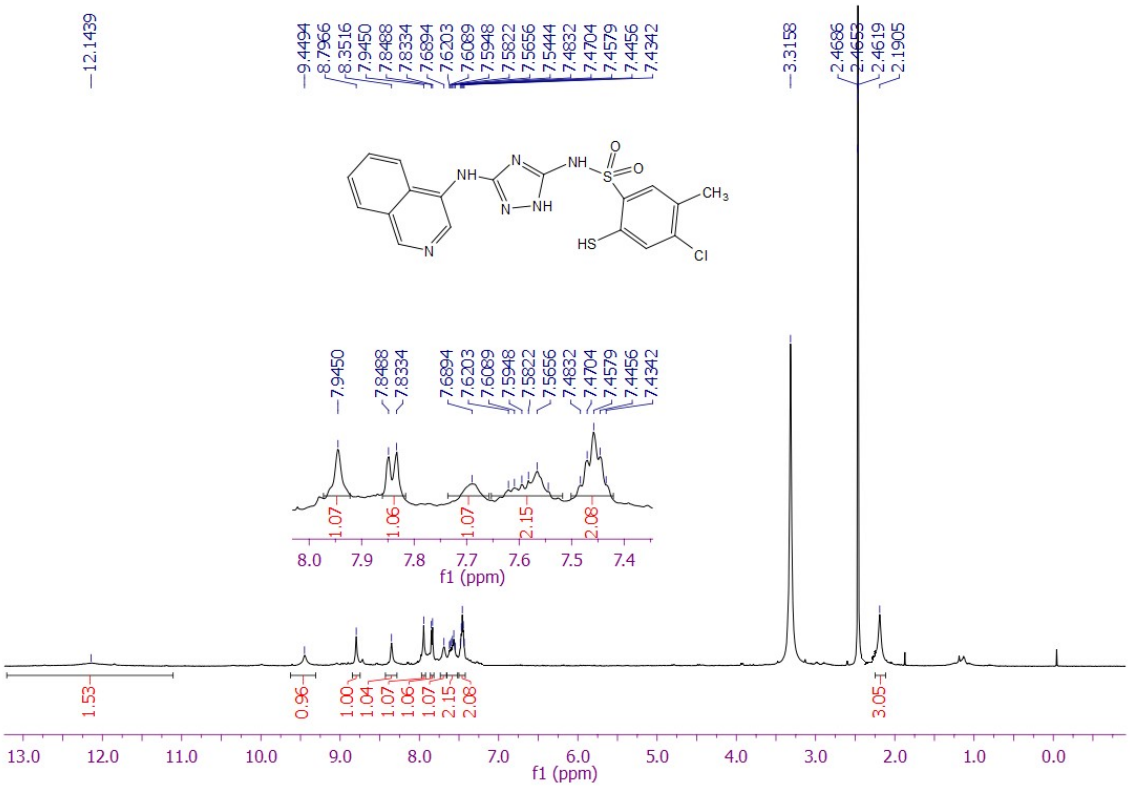


Figure S84. ^{1}H NMR spectrum of **11p** (500 MHz, DMSO-d_6)

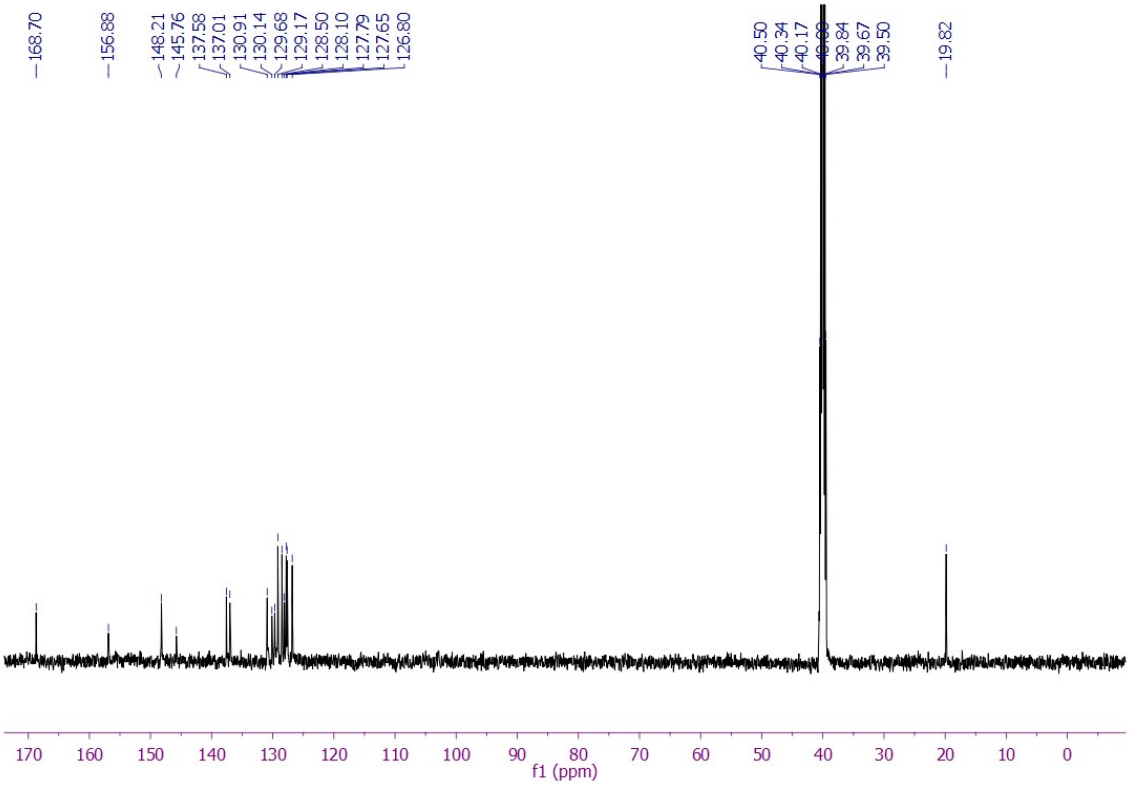


Figure S85. ^{13}C NMR spectrum of **11p** (126 MHz, DMSO-d_6)

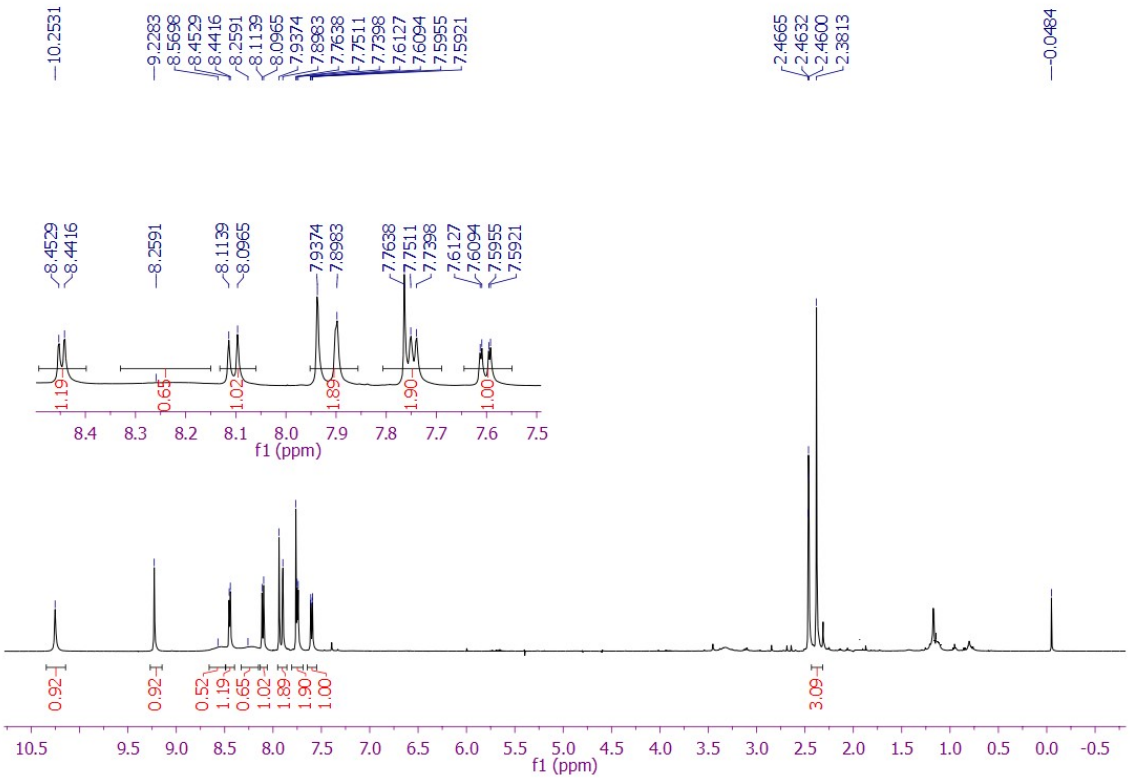


Figure S86. [1]H NMR spectrum of **11q** (500 MHz, DMSO-d_6)

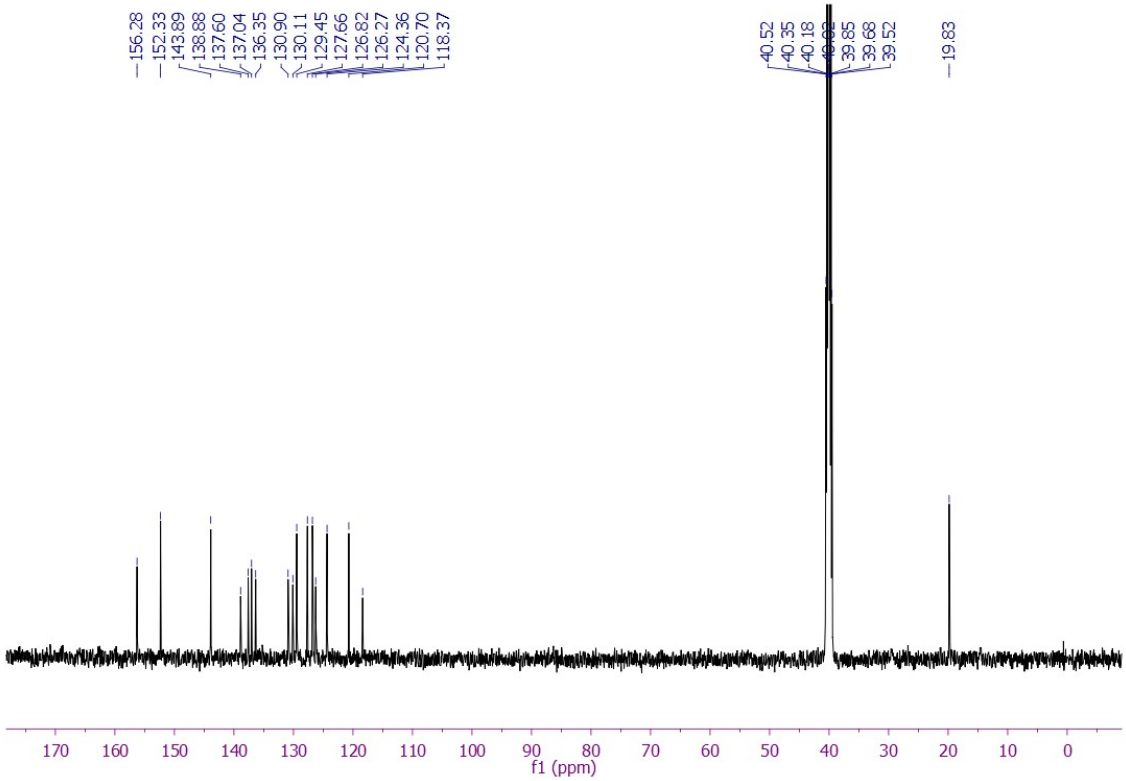


Figure S87. [13]C NMR spectrum of **11q** (126 MHz, DMSO-d_6)

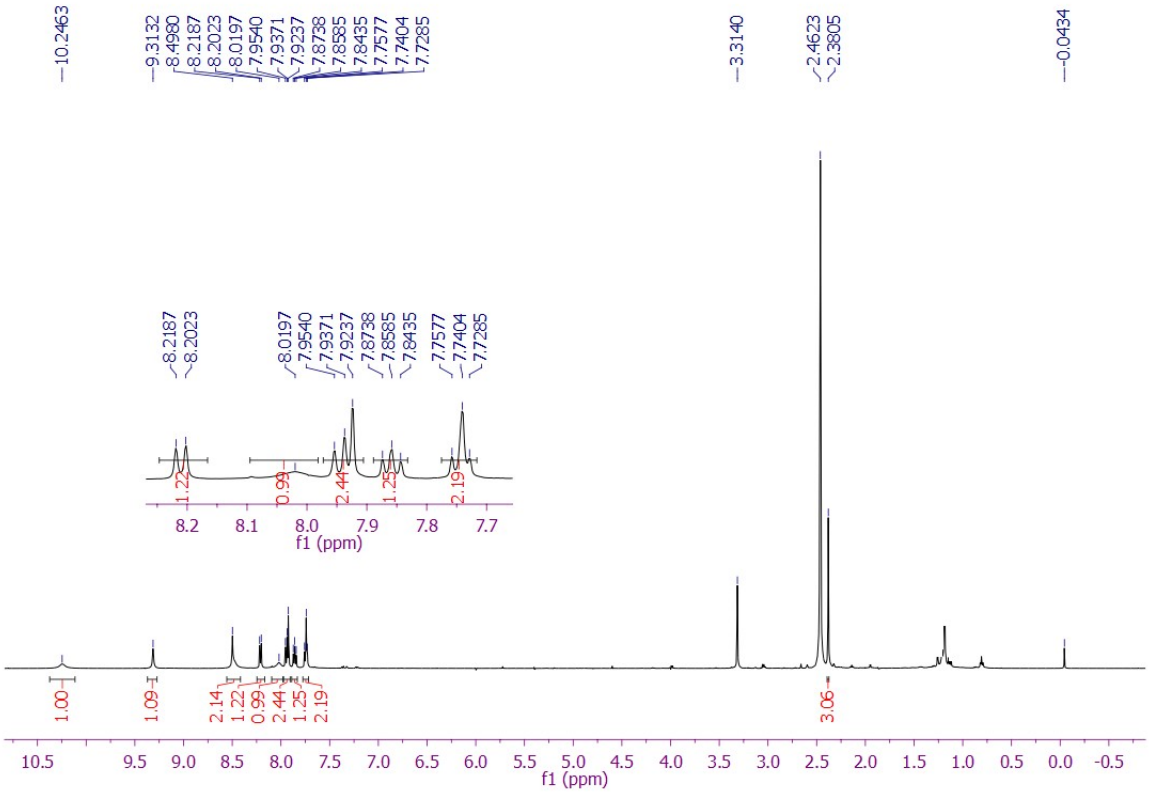


Figure S88. ^{1}H NMR spectrum of **11r** (500 MHz, DMSO-d_6)

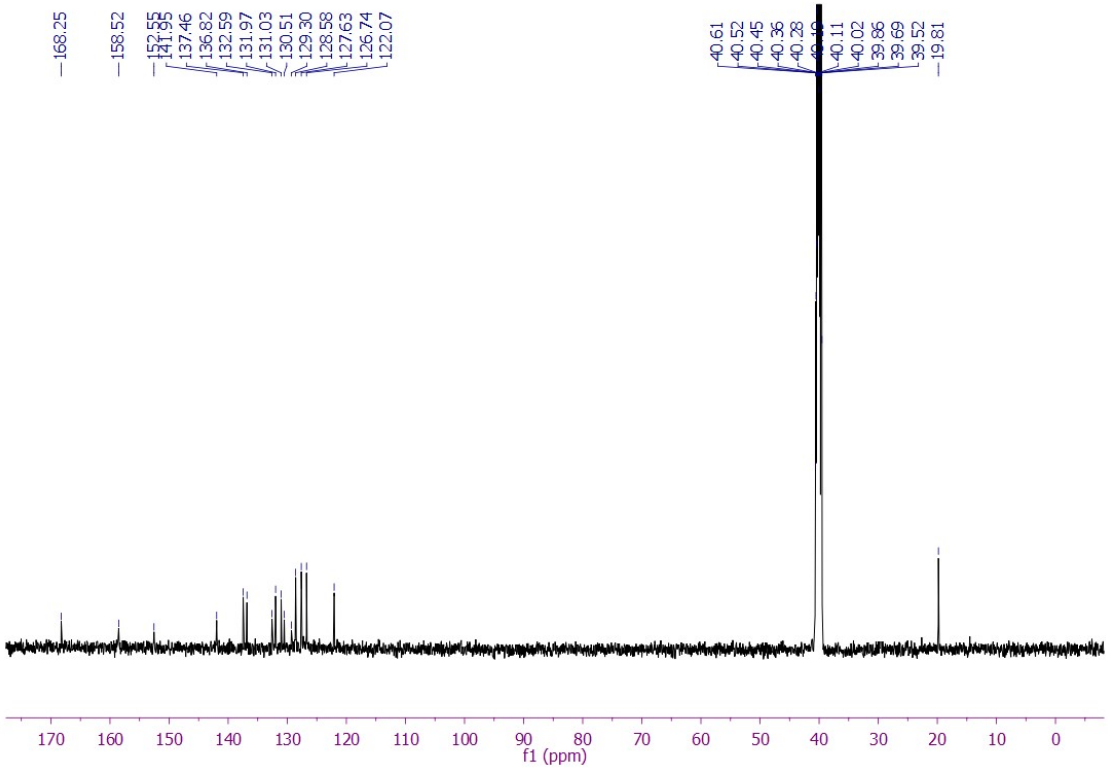


Figure S89. ^{13}C NMR spectrum of **11r** (126 MHz, DMSO-d_6)

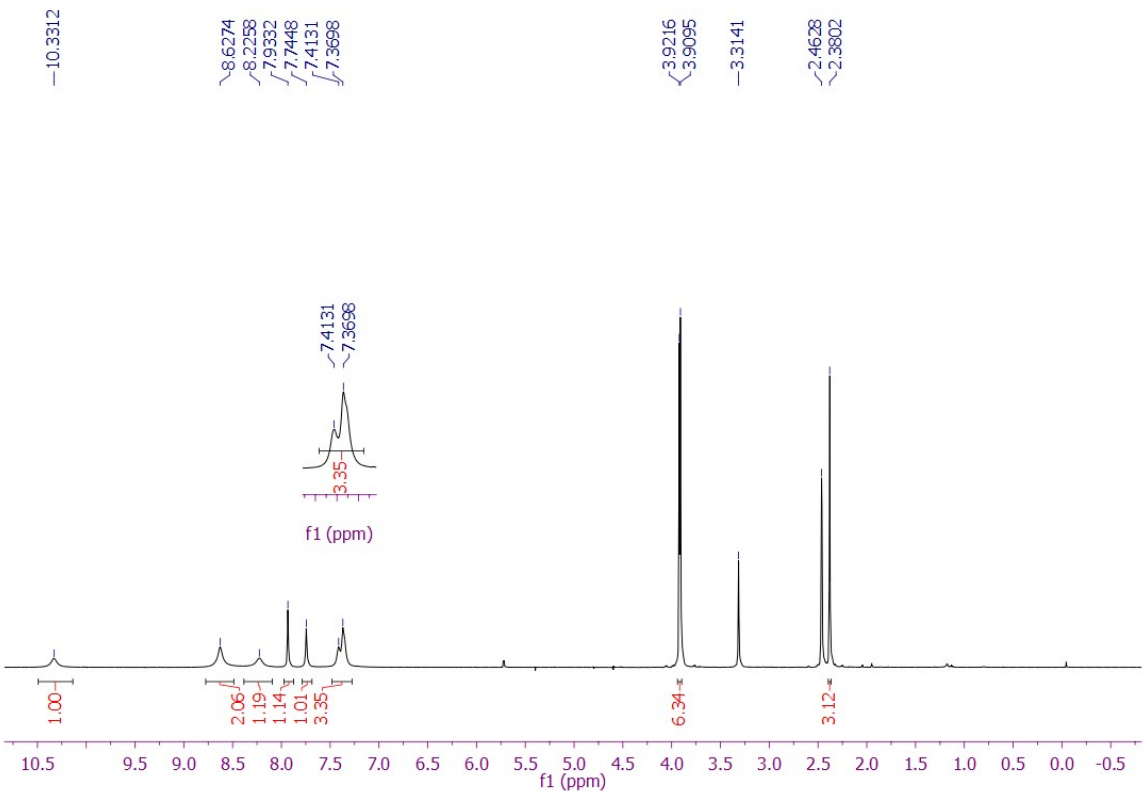


Figure S90. ^{1}H NMR spectrum of **11s** (500 MHz, DMSO-d_6)

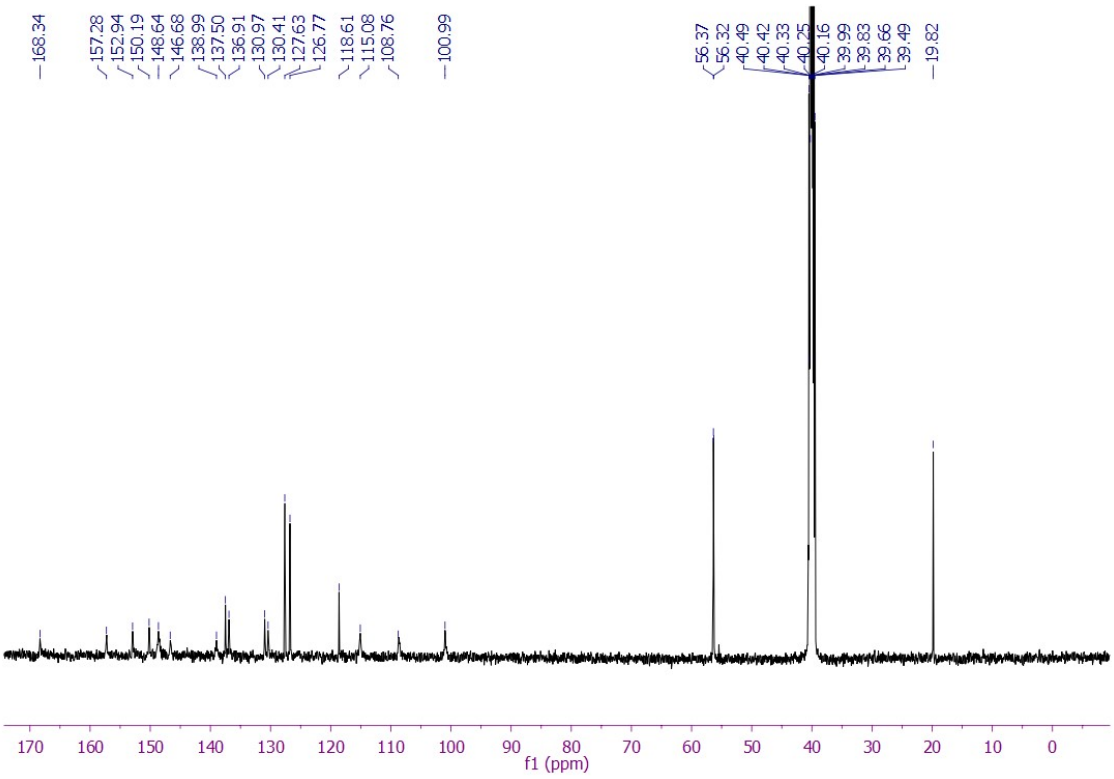


Figure S91. ^{13}C NMR spectrum of **11s** (126 MHz, DMSO-d_6)

4 HRMS (ESI+) Spectra of representative compounds (10a-z and 11a-s):

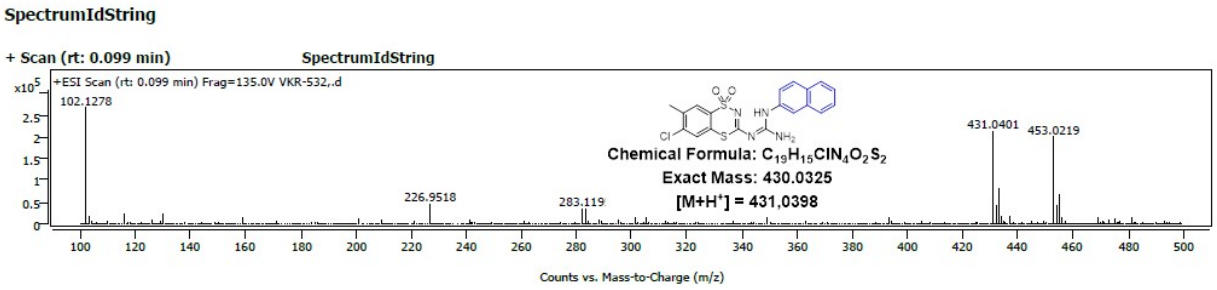


Figure S92. HRMS (ESI+) spectrum of **10a**

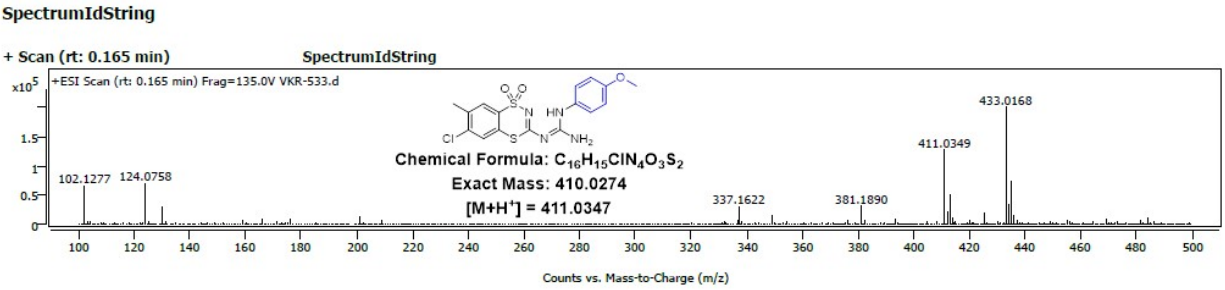


Figure S93. HRMS (ESI+) spectrum of **10b**

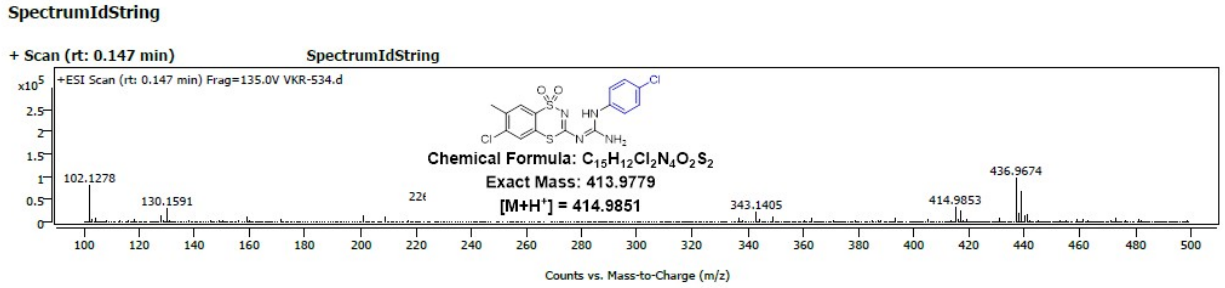


Figure S94. HRMS (ESI+) spectrum of **10c**

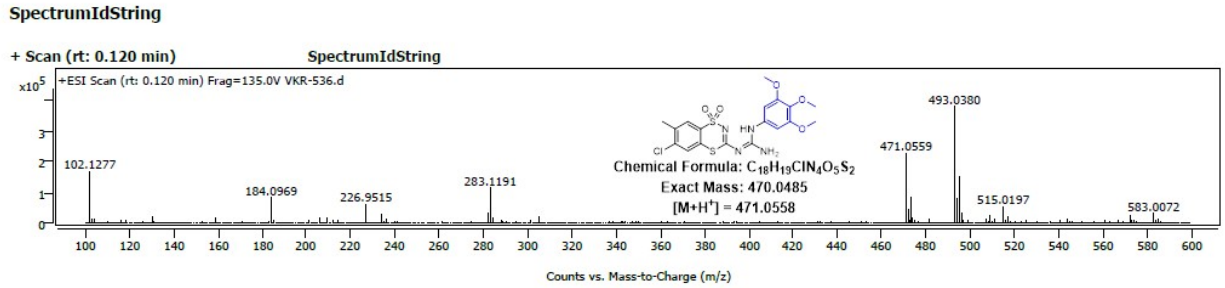


Figure S95. HRMS (ESI+) spectrum of **10d**

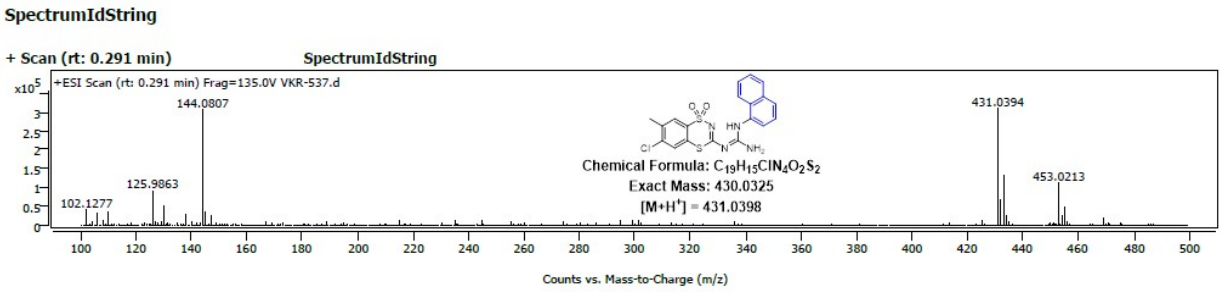


Figure S96. HRMS (ESI+) spectrum of **10e**

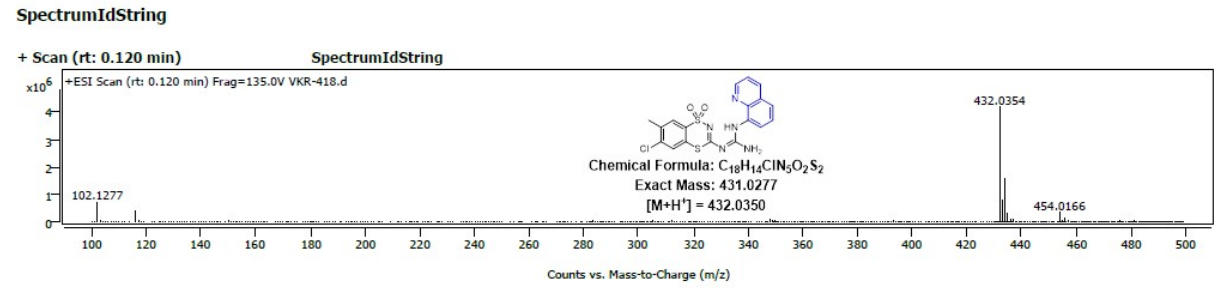


Figure S97. HRMS (ESI+) spectrum of **10f**

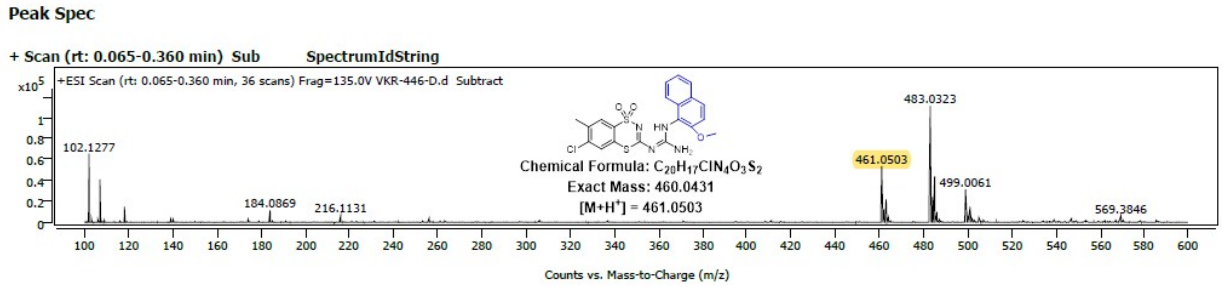


Figure S98. HRMS (ESI+) spectrum of **10g**

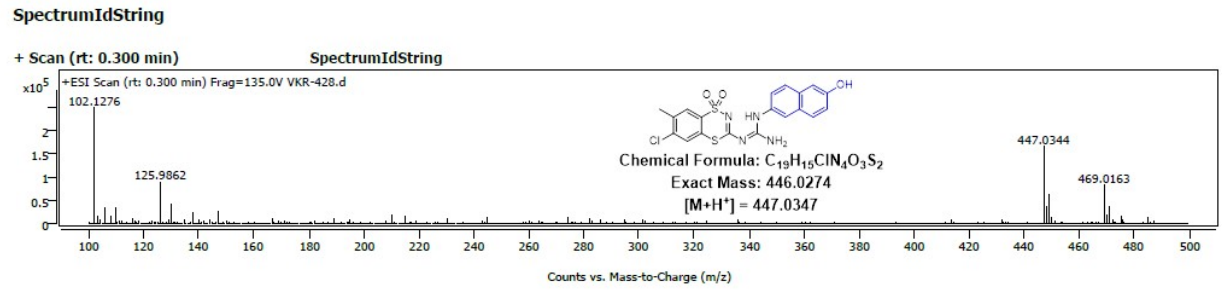


Figure S99. HRMS (ESI+) spectrum of **10h**

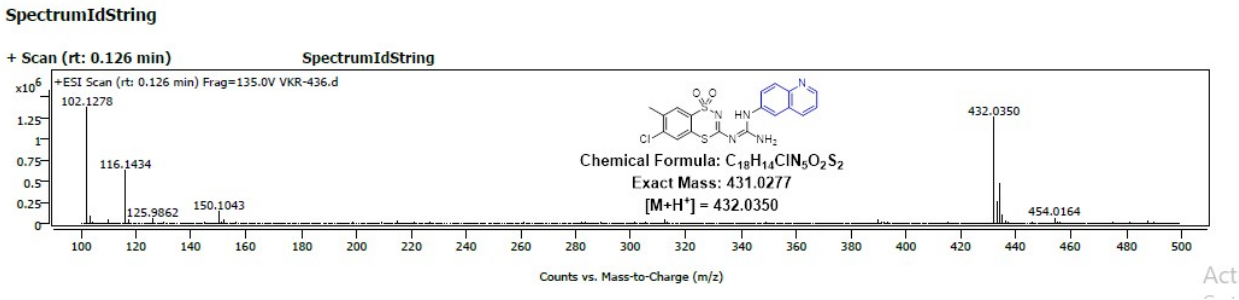


Figure S100. HRMS (ESI+) spectrum of **10i**

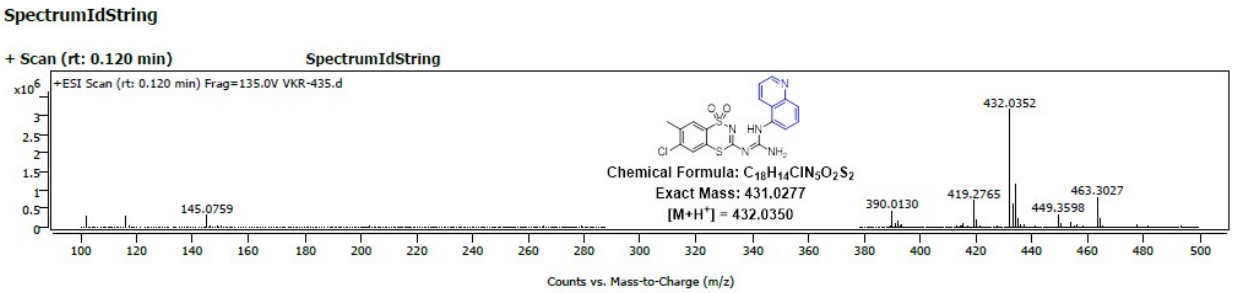


Figure S101. HRMS (ESI+) spectrum of **10j**

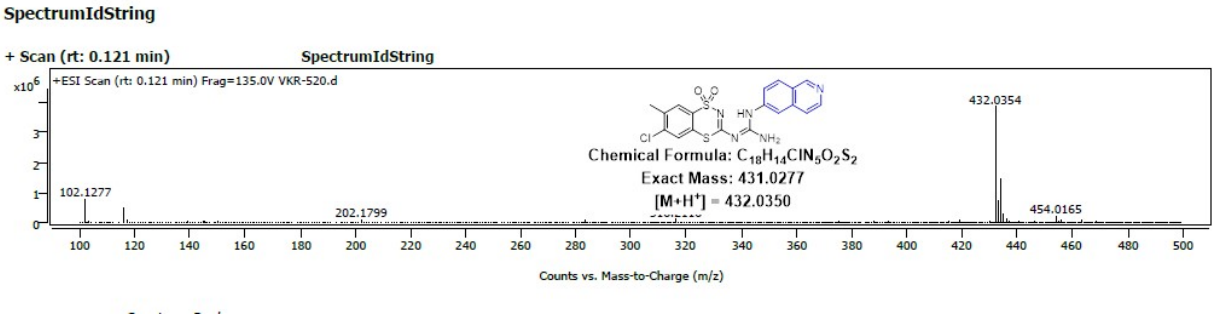


Figure S102. HRMS (ESI+) spectrum of **10k**

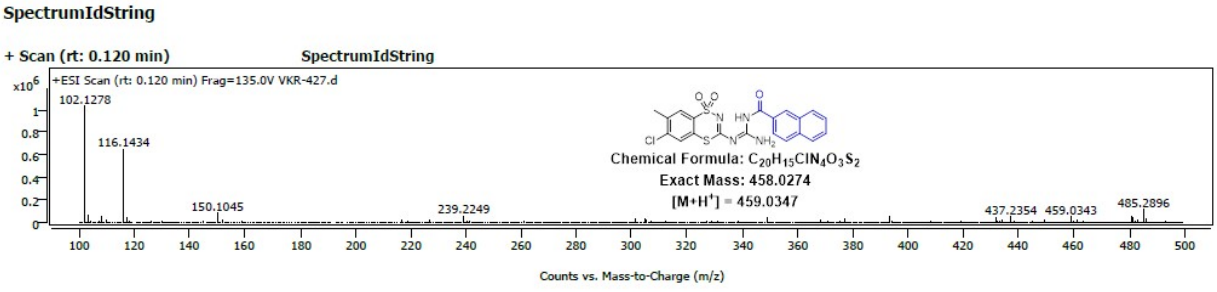
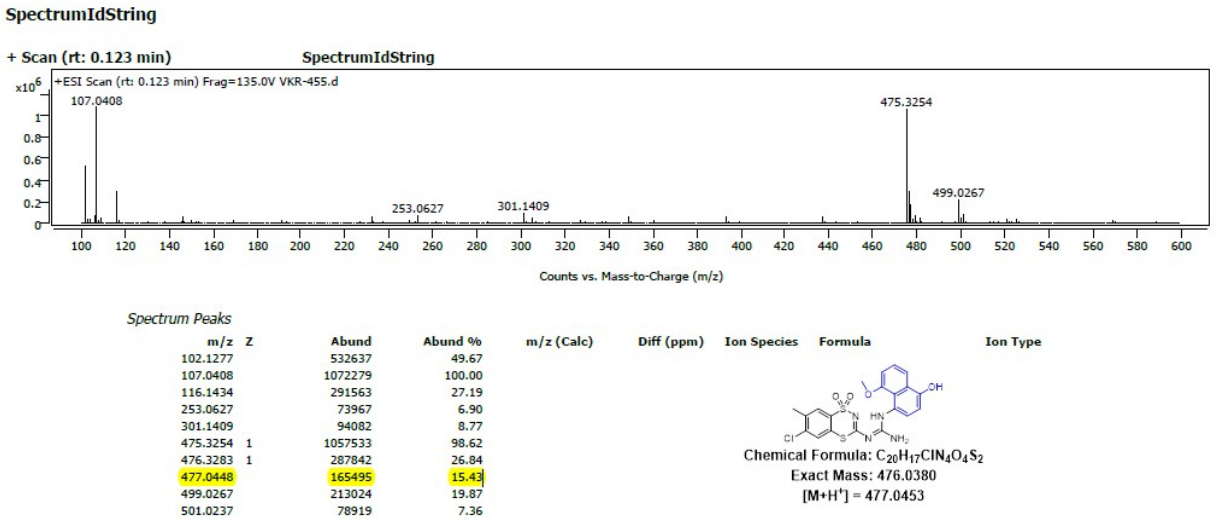


Figure S103. HRMS (ESI+) spectrum of **10l**



Spectrum Peaks

m/z	Z	Abund	Abund %	m/z (Calc)	Diff (ppm)	Ion Species	Formula	Ion Type
102.1277		532637	49.67					
107.0408		1072279	100.00					
116.1434		291563	27.19					
253.0627		73967	6.90					
301.1409		94082	8.77					
475.3254	1	1057533	98.62					
476.3283	1	287842	26.84					
477.0448		165495	15.43					
499.0267		213024	19.87					
501.0237		78919	7.36					

Figure S104. HRMS (ESI+) spectrum of **10m**

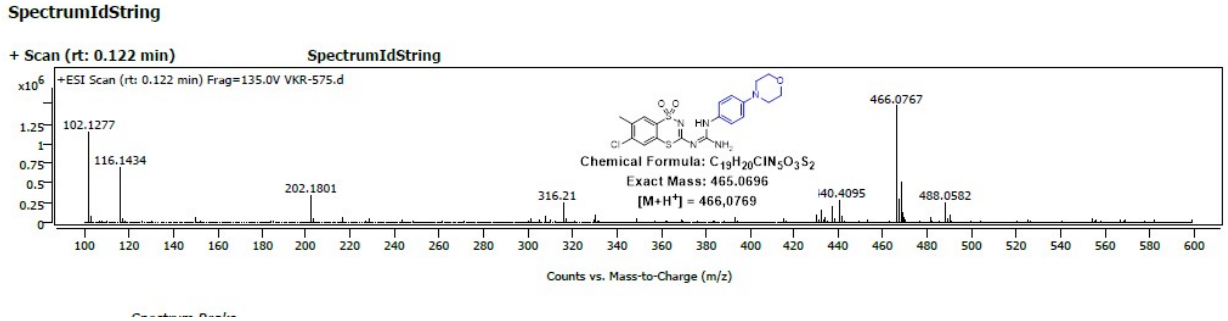


Figure S105. HRMS (ESI+) spectrum of **10n**

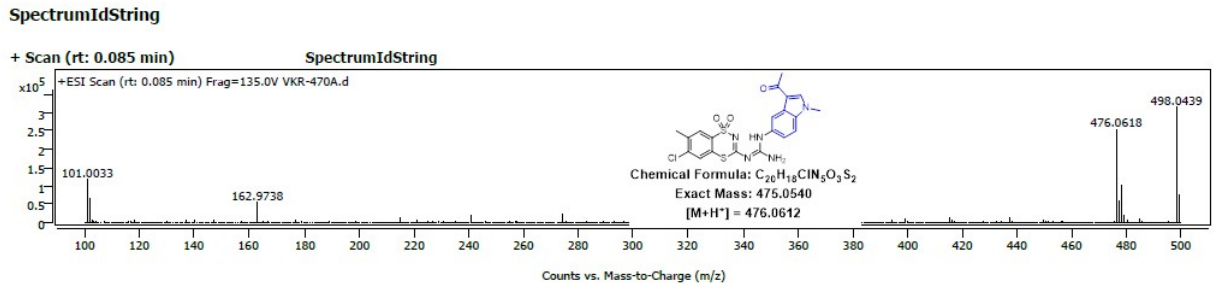


Figure S106. HRMS (ESI+) spectrum of **10o**

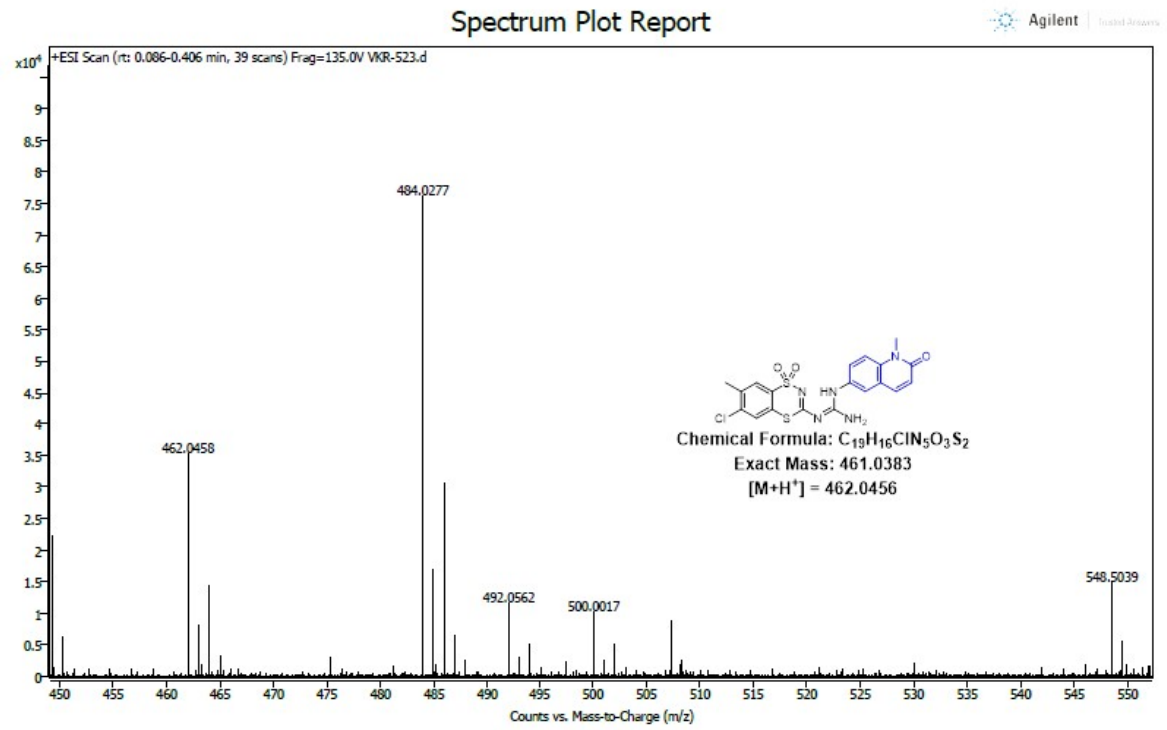


Figure S107. HRMS (ESI+) spectrum of **10p**

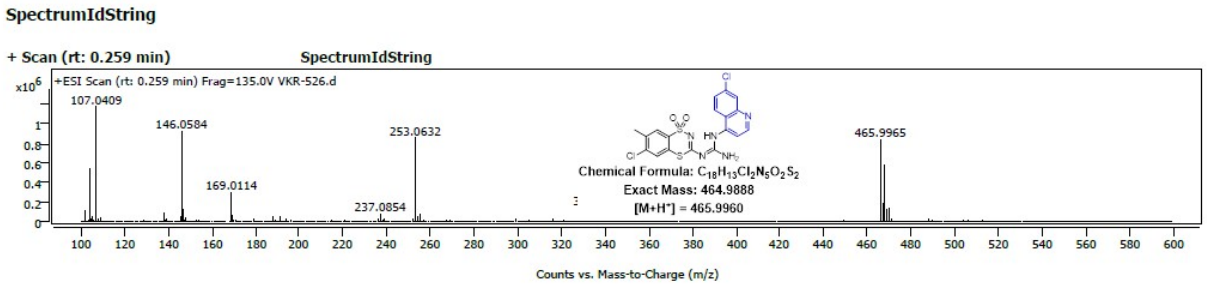


Figure S108. HRMS (ESI+) spectrum of **10q**

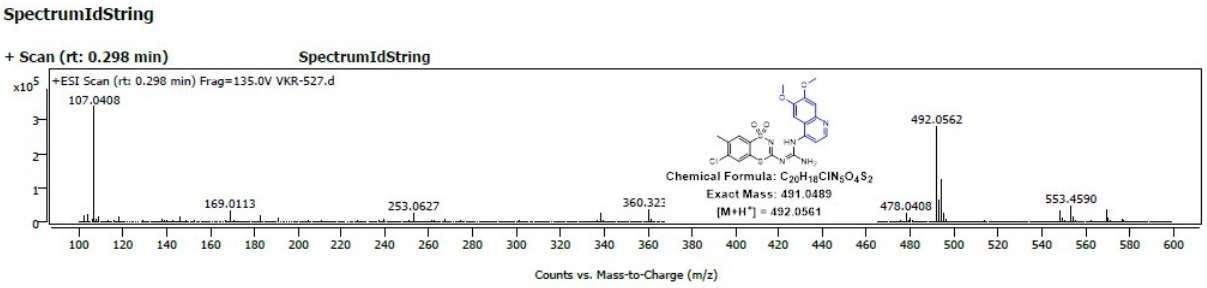


Figure S109. HRMS (ESI+) spectrum of **10r**

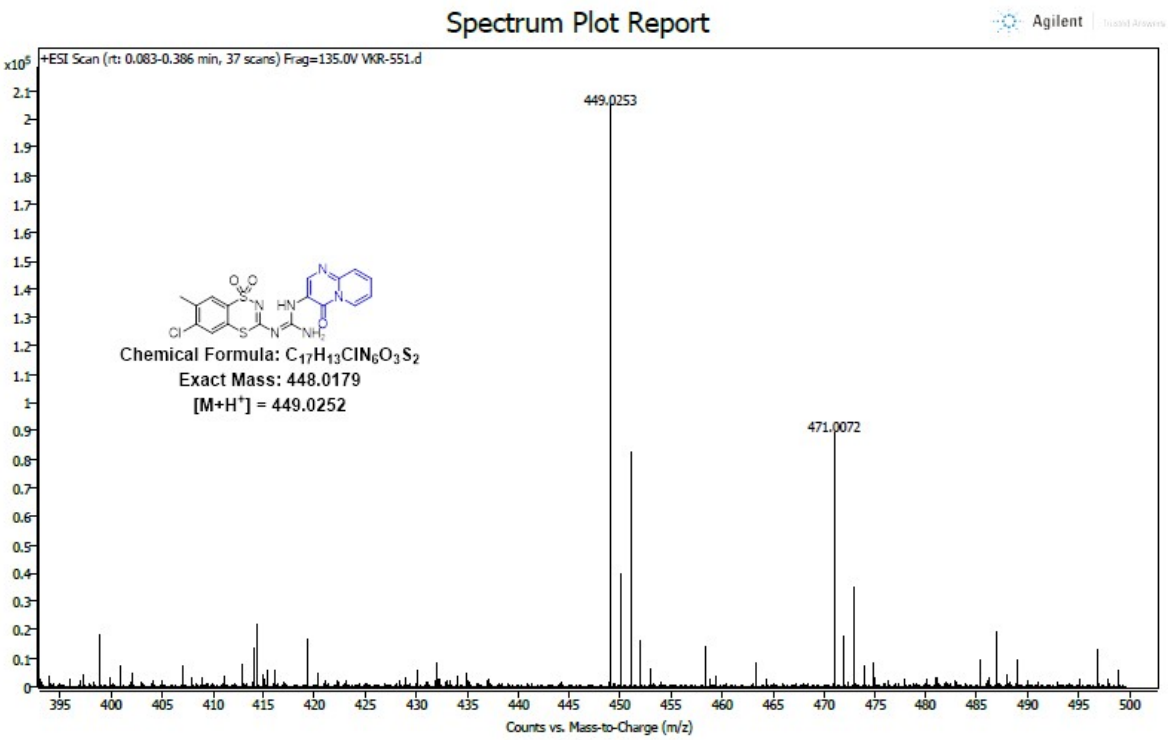


Figure S110. HRMS (ESI+) spectrum of **10s**

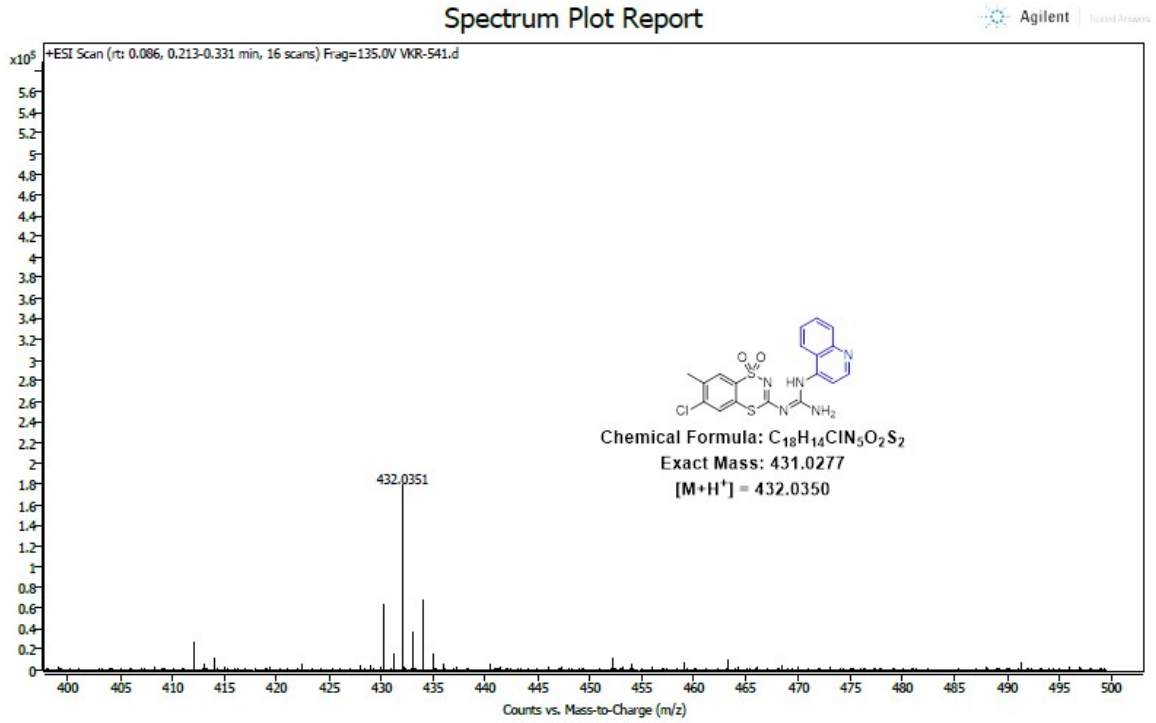


Figure S111. HRMS (ESI+) spectrum of **10t**

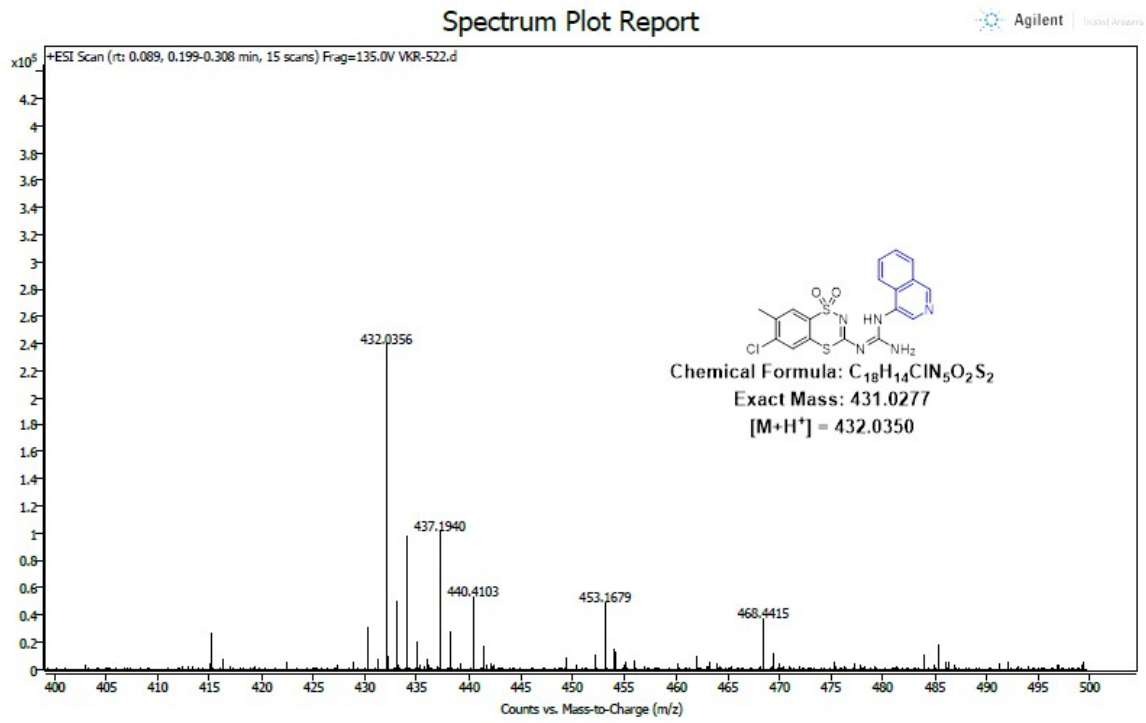


Figure S112. HRMS (ESI+) spectrum of **10u**

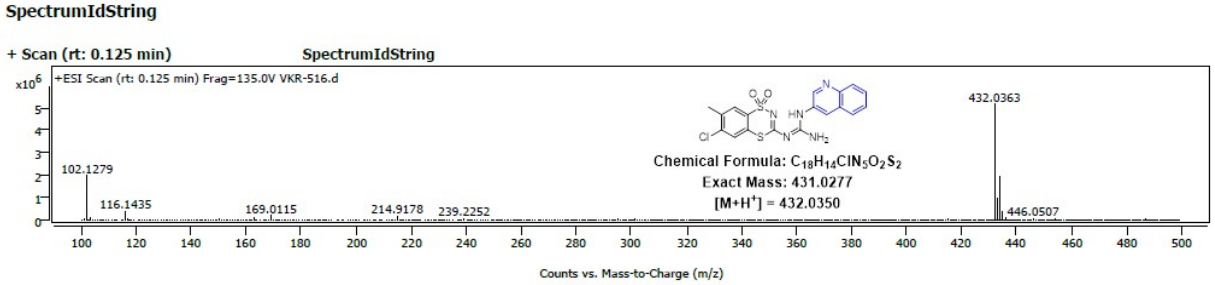


Figure S113. HRMS (ESI+) spectrum of **10v**

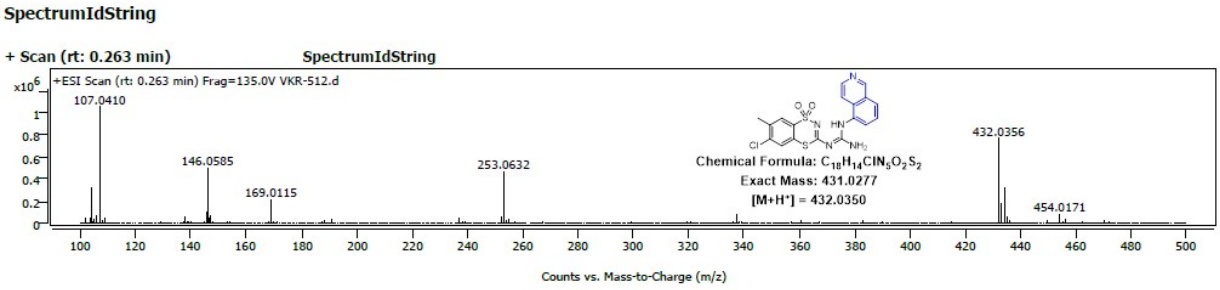


Figure S114. HRMS (ESI+) spectrum of **10w**

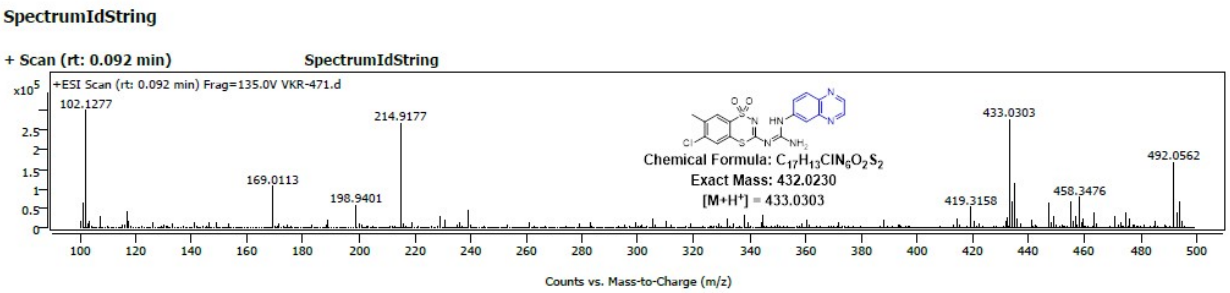


Figure S115. HRMS (ESI+) spectrum of **10x**

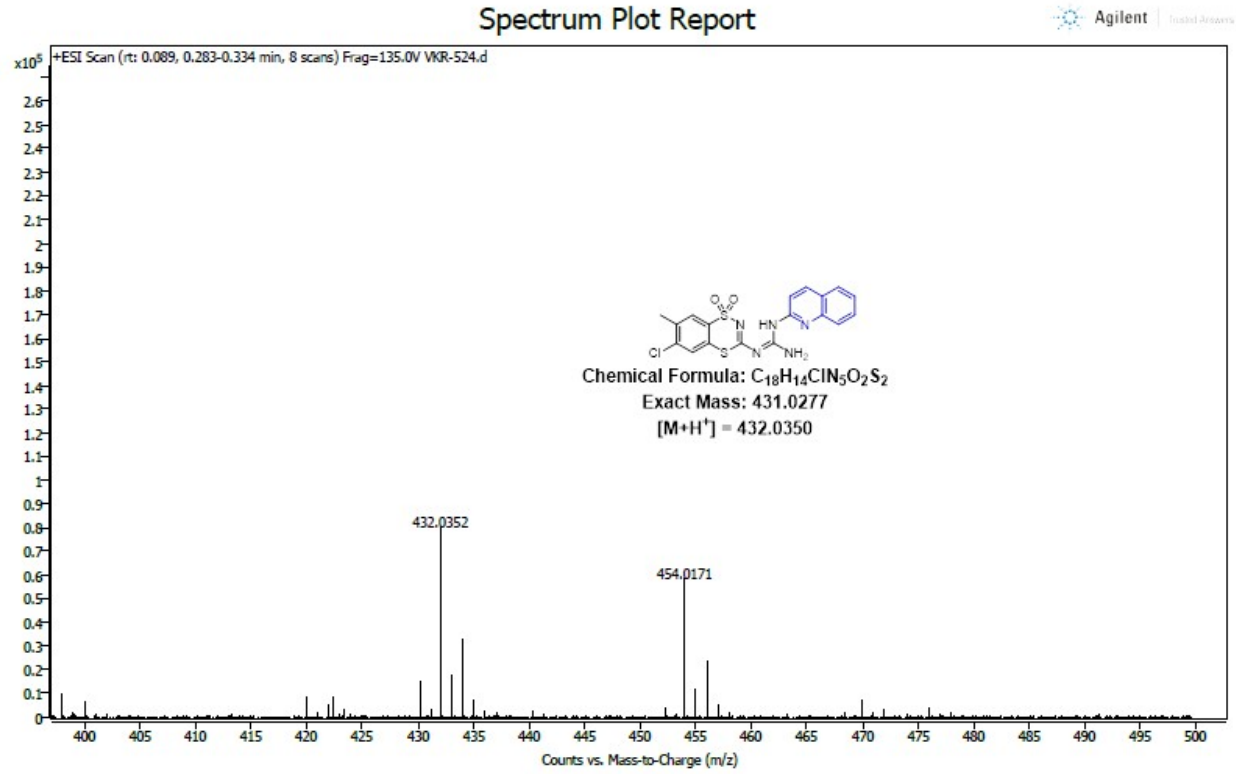


Figure S116. HRMS (ESI+) spectrum of **10y**

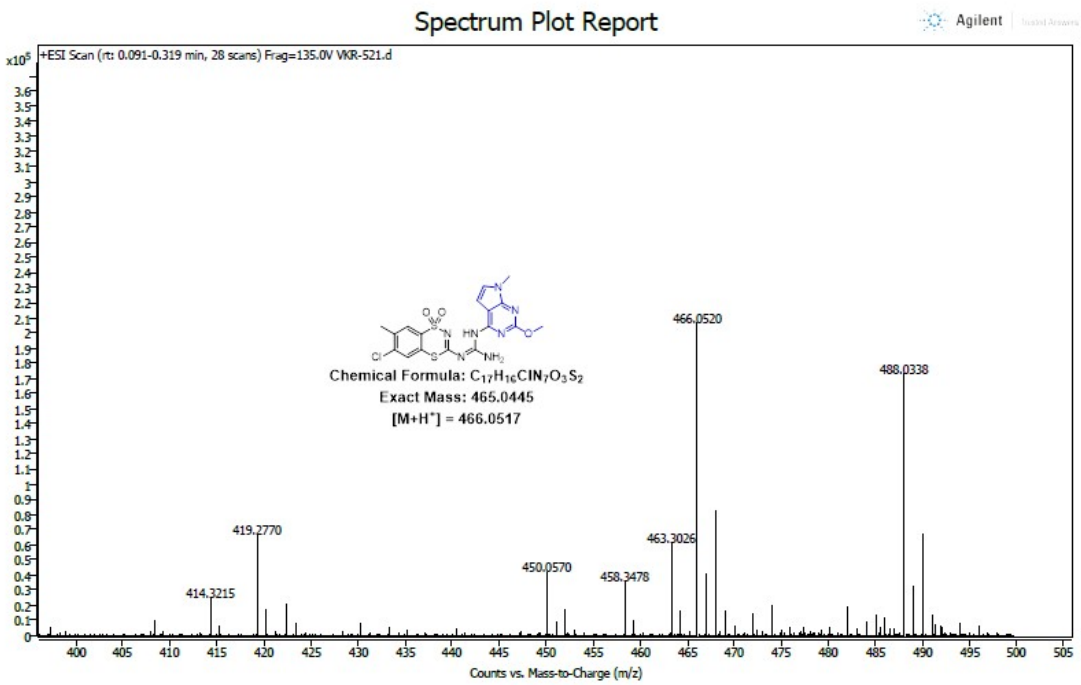


Figure S117. HRMS (ESI+) spectrum of **10z**

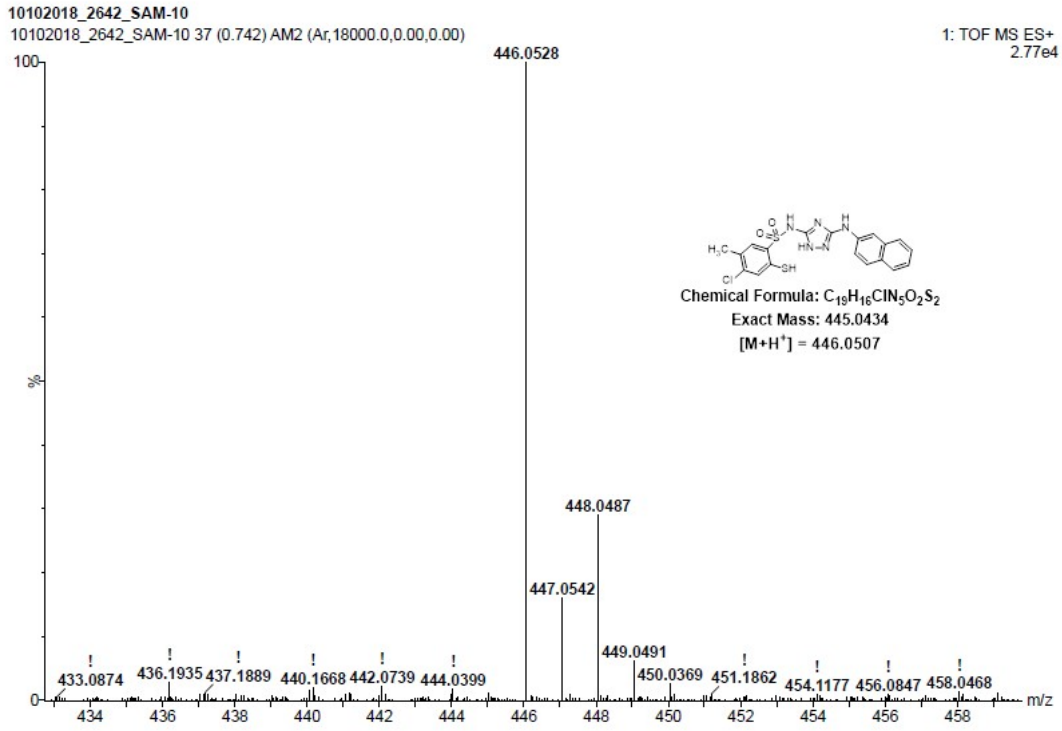


Figure S118. HRMS (ESI+) spectrum of **NSC-666719** (**11a**)

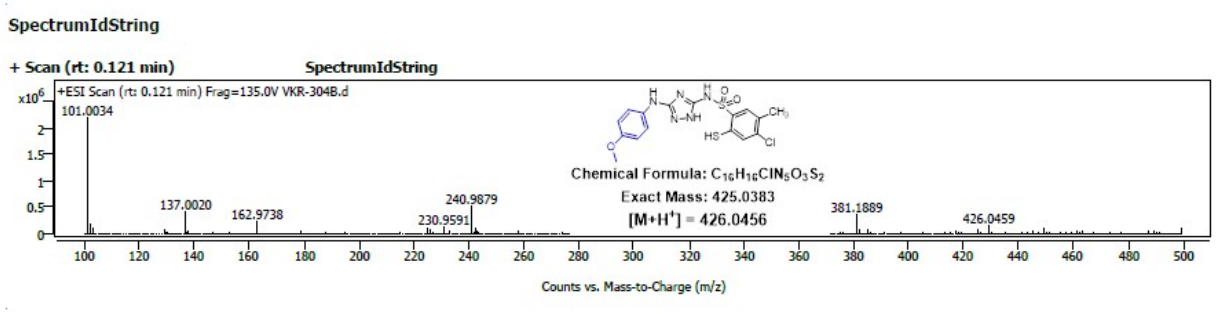


Figure S119. HRMS (ESI+) spectrum of **11b**

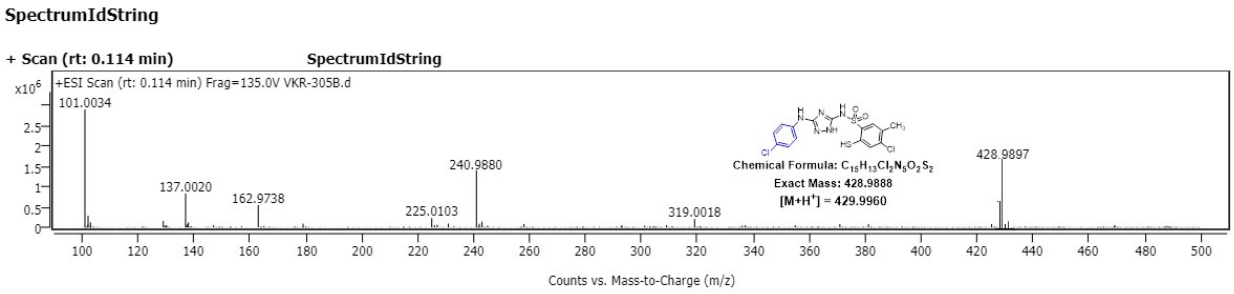


Figure S120. HRMS (ESI+) spectrum of **11c**

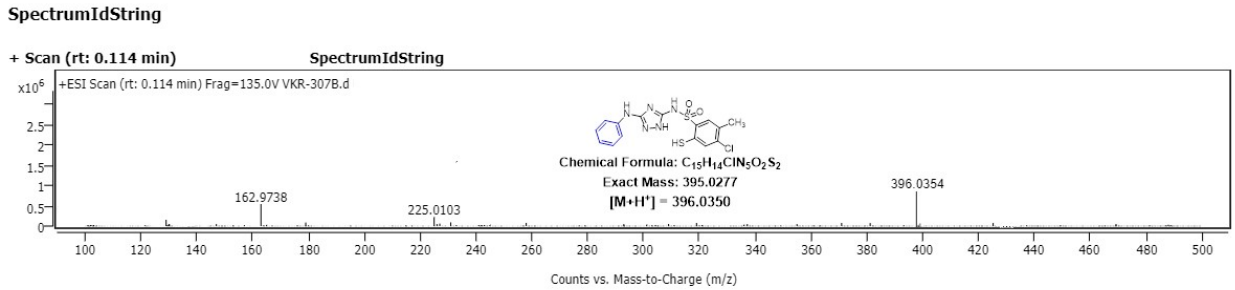


Figure S121. HRMS (ESI+) spectrum of **11d**

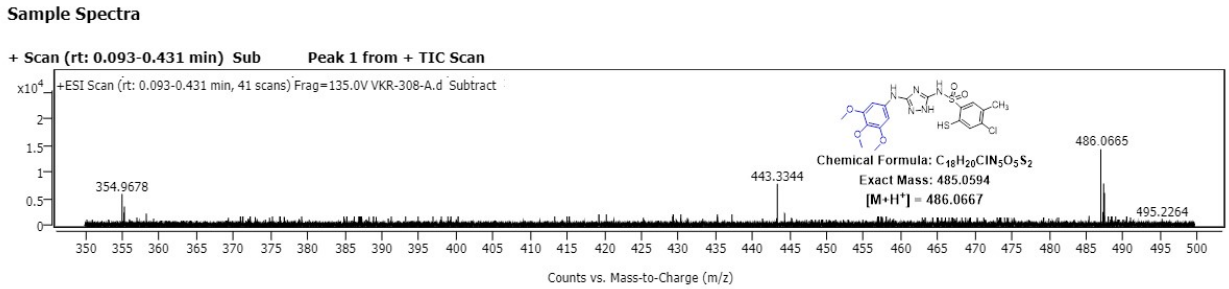


Figure S122. HRMS (ESI+) spectrum of **11e**

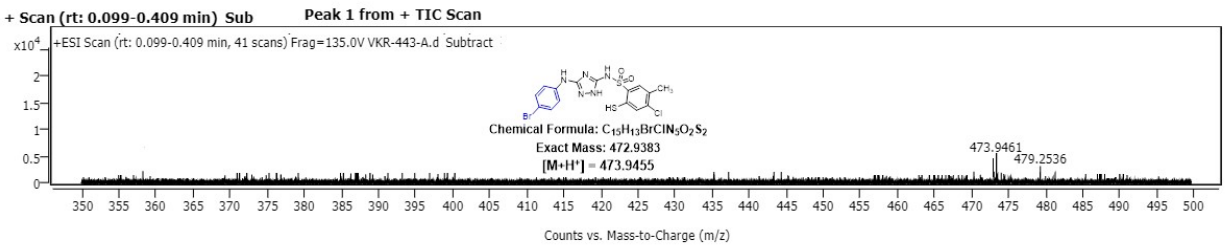


Figure S123. HRMS (ESI+) spectrum of **11f**

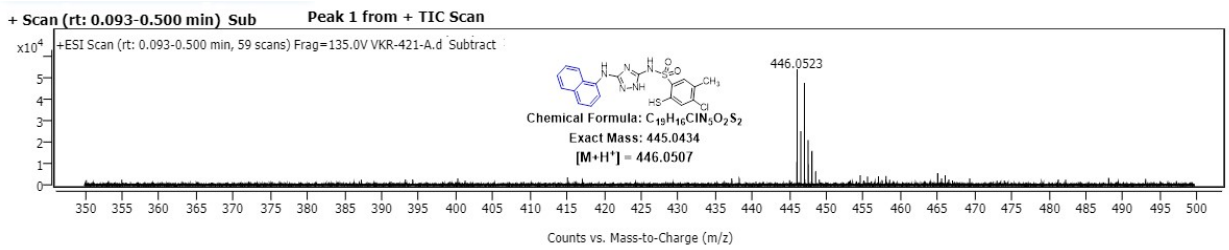


Figure S124. HRMS (ESI+) spectrum of **11g**

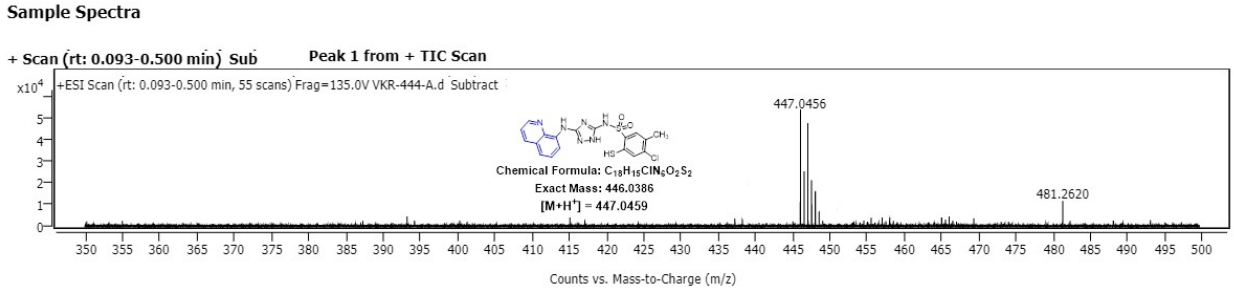


Figure S125. HRMS (ESI+) spectrum of **11h**

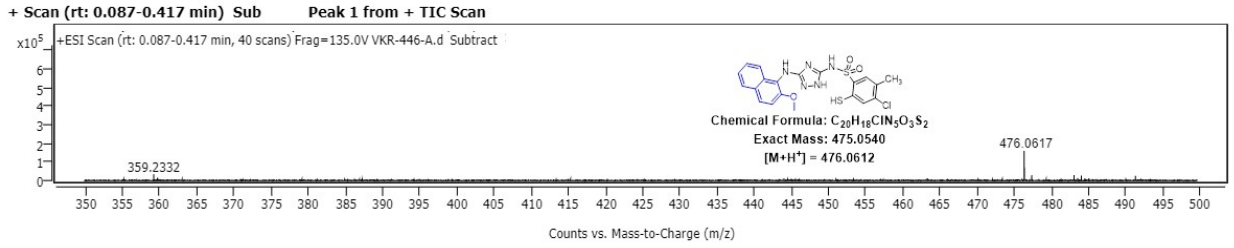


Figure S126. HRMS (ESI+) spectrum of **11i**

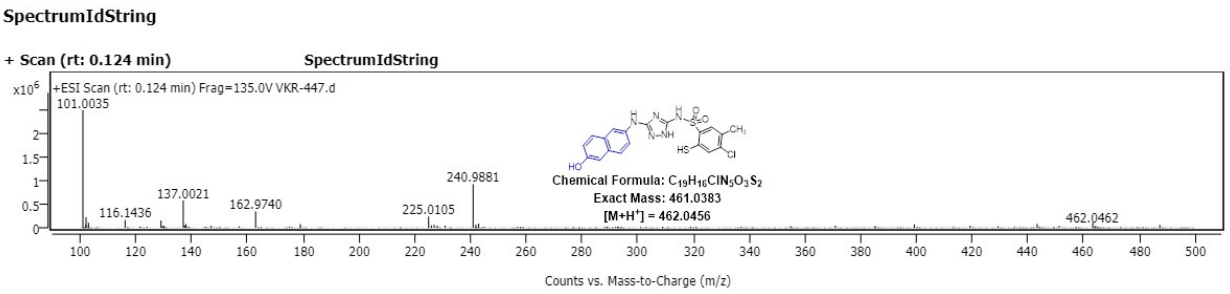


Figure S127. HRMS (ESI+) spectrum of **11j**

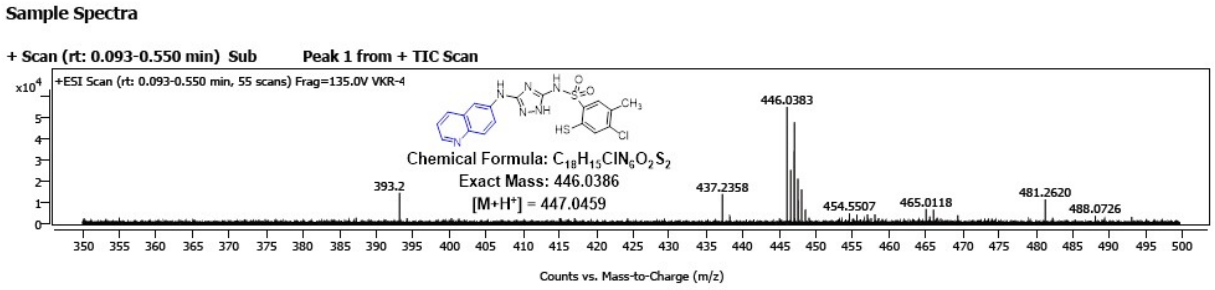


Figure S128. HRMS (ESI+) spectrum of **11k**

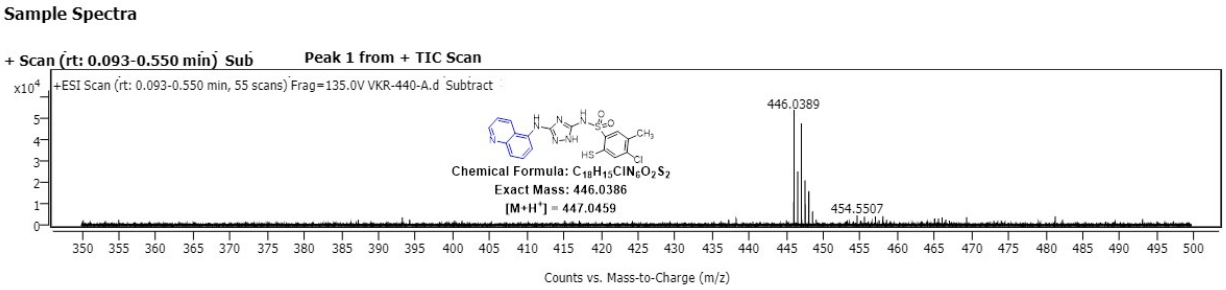


Figure S129. HRMS (ESI+) spectrum of **11l**

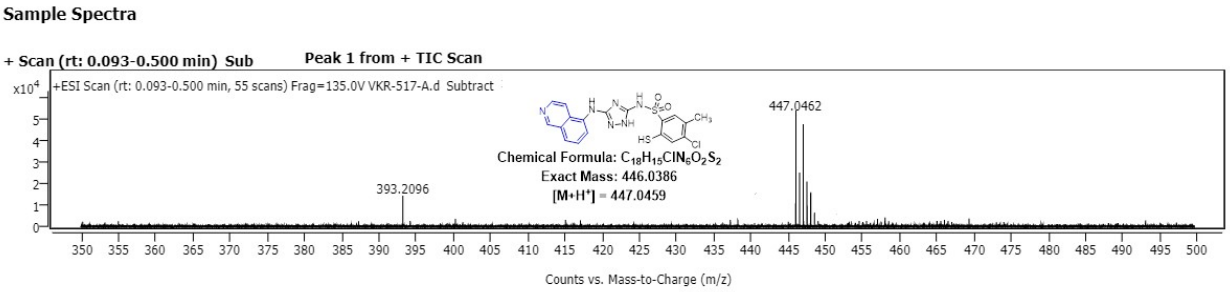


Figure S130. HRMS (ESI+) spectrum of **11m**

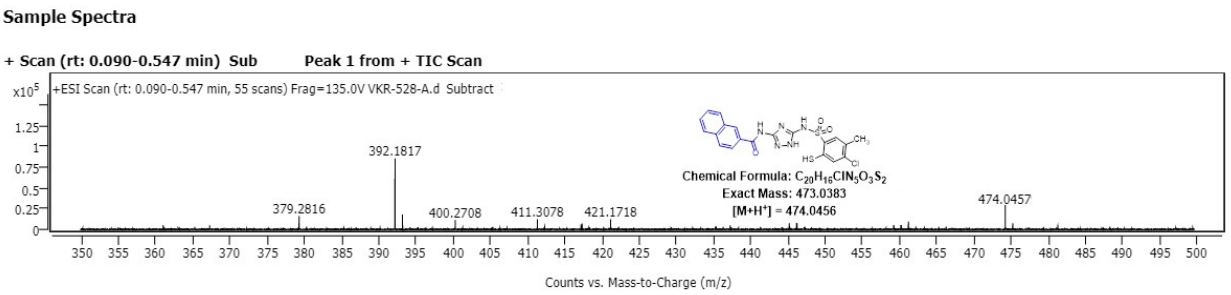


Figure S131. HRMS (ESI+) spectrum of **11n**

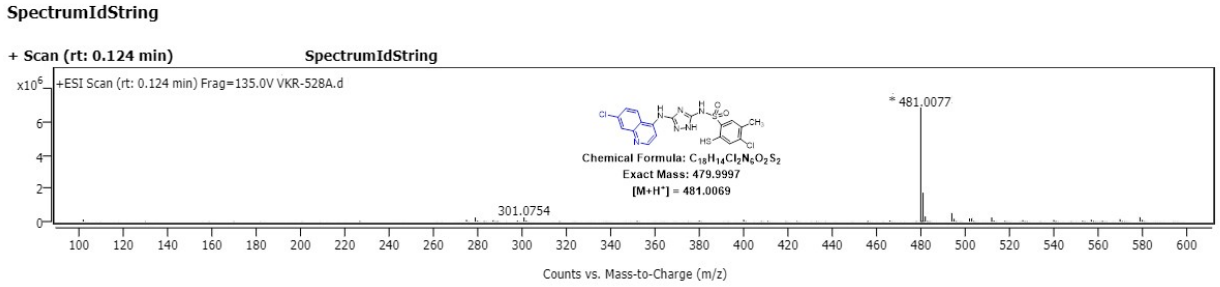


Figure S132. HRMS (ESI+) spectrum of **11o**

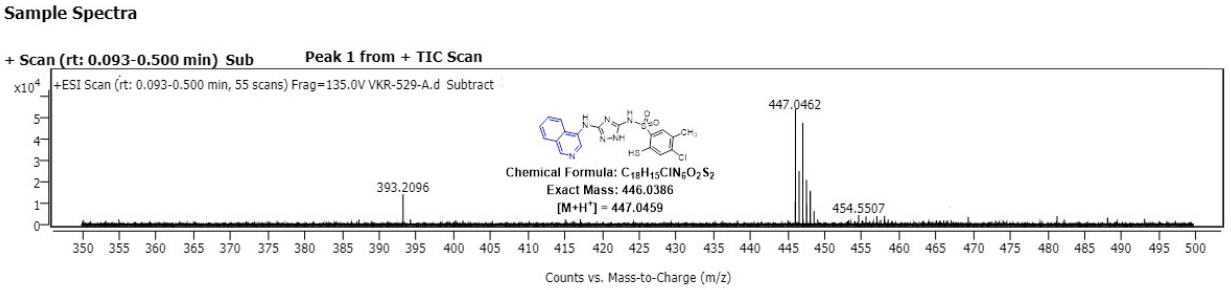


Figure S133. HRMS (ESI+) spectrum of **11p**

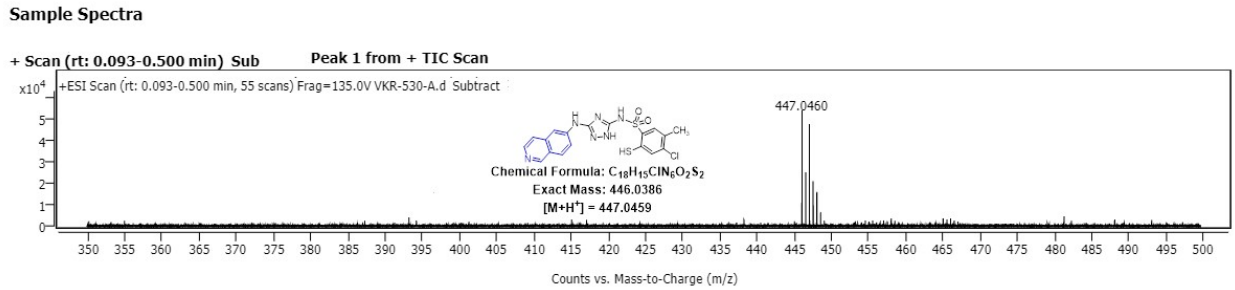


Figure S134. HRMS (ESI+) spectrum of **11q**

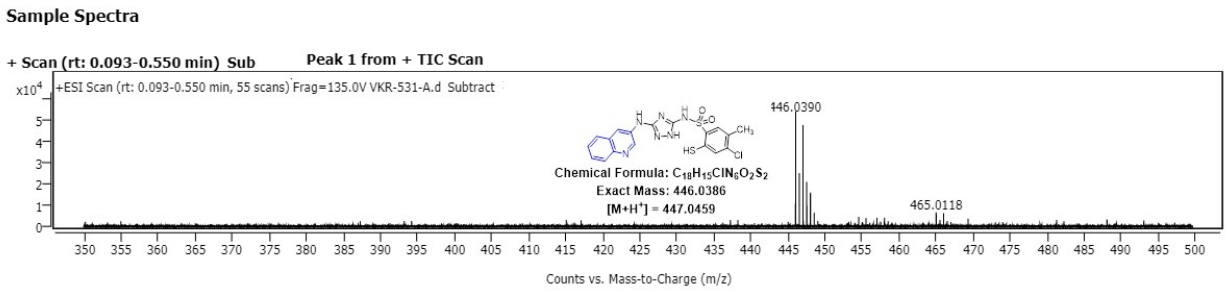


Figure S135. HRMS (ESI+) spectrum of **11r**

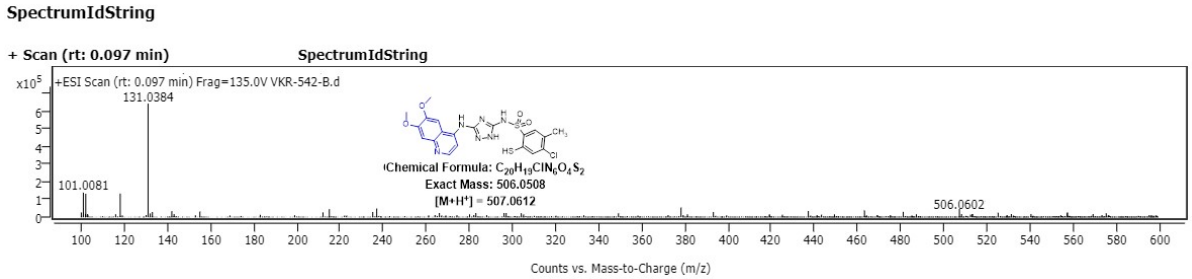
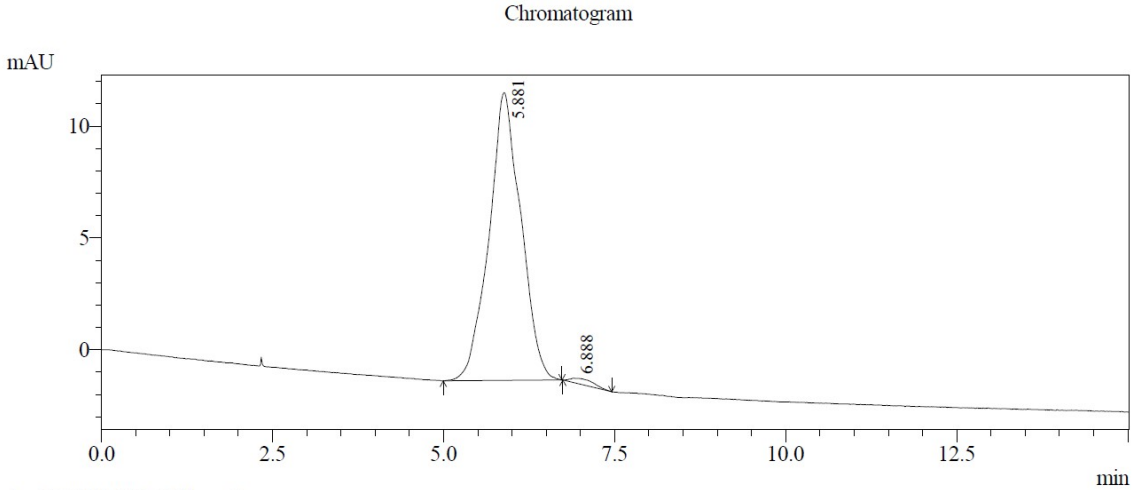


Figure S136. HRMS (ESI+) spectrum of **11s**

5 HPLC traces of 11a, 10e and 10q

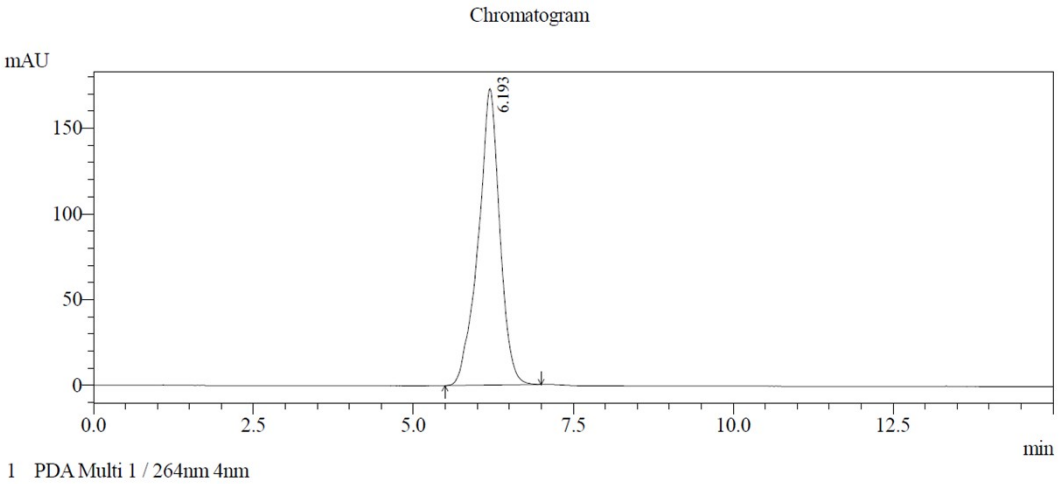


PeakTable

PDA Ch1 261nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.881	418602	12873	98.663	98.592
2	6.888	5673	184	1.337	1.408
Total		424275	13056	100.000	100.000

Figure 137. HPLC chromatogram of compound **11a** (**NSC-666719**)

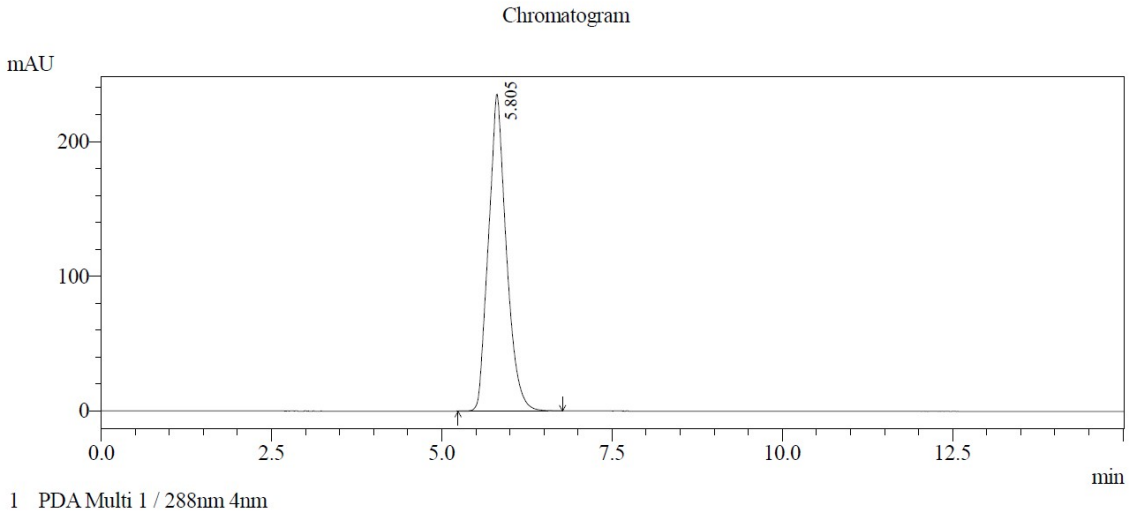


PeakTable

PDA Ch1 264nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.193	4051428	172973	100.000	100.000
Total		4051428	172973	100.000	100.000

Figure 138. HPLC chromatogram of compound **10e**



PeakTable

PDA Ch1 288nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.805	4283344	235138	100.000	100.000
Total		4283344	235138	100.000	100.000

Figure 139. HPLC chromatogram of compound **10q**

6 X-ray crystallography data of 10b

Table S4: Crystallographic table

Parameter	(*Z*)-2-(6-chloro-7-methyl-1,1-dioxidobenzo[*e*][1,4,2]dithiazin-3-yl)-1-(4-methoxyphenyl)guanidine (10b)
Empirical formula	$C_{16}H_{15}ClN_4O_3S_2$
CCDC number	2269969
Formula weight	410.89
Crystal system	monoclinic
Space group	C2/c
Crystal size/mm^3	0.05 × 0.045 × 0.03
Radiation	MoKα (λ = 0.71073)
a (Å)	25.8739(6)
b (Å)	9.36039(17)
c (Å)	14.3273(3)
α (°)	90
β (°)	94.120(2)
γ (°)	90
V (Å^3)	3460.96(13)
Z	8
ρ_{calc} (g/cm^{-3})	1.581
Temperature (K)	293.0(2)
μ/ mm^{-1}	0.488
$2\theta_{min,\ max}$ ()	6.316 to 52.736
F (000)	1704.0
$h_{min,max}$; $k_{min,max}$; $l_{min,max}$	$-32 \le h \le 29$; $-11 \le k \le 11$; $-16 \le l \le 17$

Total no. of reflections	13987
Independent reflections	3343 [R_{int} = 0.0343, R_{sigma} = 0.0334]
No. of unique reflections	3343
R_1 [I>2σ(I)]	R_1 = 0.0378, wR_2 = 0.0946
Final R indexes [all data] wR_2 (all data)	R_1 = 0.0457, wR_2 = 0.1001
GooF on F^2	1.095
$\Delta\rho_{max,min}/eÅ^{-3}$	0.24/-0.63

7 References:

[1] J. Shao, W. Chen, M.A. Giulianotti, R.A. Houghten, Y. Yu, Palladium-catalyzed C–H functionalization using guanidine as a directing group: ortho arylation and olefination of arylguanidines, Org. Lett., 14 (2012) 5452-5455.

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[4] H.-H. Ha, J.S. Kim, B.M. Kim, Novel heterocycle-substituted pyrimidines as inhibitors of NF-κB transcription regulation related to TNF-α cytokine release, Bioorg. Med. Chem. Lett., 18 (2008) 653-656.

[5] K. Tsubokura, T. Iwata, M. Taichi, A. Kurbangalieva, K. Fukase, Y. Nakao, K. Tanaka, Direct guanylation of amino groups by cyanamide in water: catalytic generation and activation of unsubstituted carbodiimide by scandium (III) triflate, Synlett, 25 (2014) 1302-1306.

[6] J.W. Shaw, D.H. Grayson, I. Rozas, Cleavage of 2-(Arylamino)-4, 6-dimethoxypyrimidines To Yield Arylguanidines, Eur. J. Org. Chem., 2014 (2014) 3565-3569.

[7] J.W. Shaw, L. Barbance, D.H. Grayson, I. Rozas, Using N-substituted-2-amino-4, 6-dimethoxypyrimidines in the synthesis of aliphatic guanidines, Tetrahedron Lett., 56 (2015) 4990-4992.