SUPPORTING INFORMATION

Discovery of Novel Tricyclic Thiazepine Derivatives as Anti-Drug-Resistant Cancer Agents by Combining Diversity-Oriented Synthesis and Converging Screening Approach

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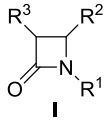
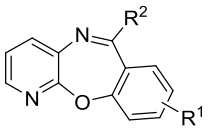
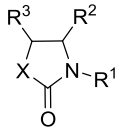
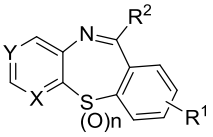
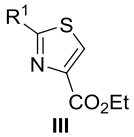
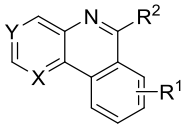
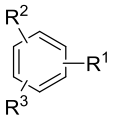
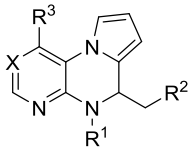
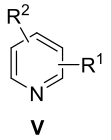
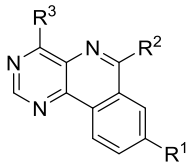
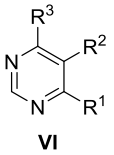
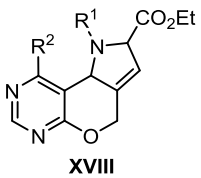
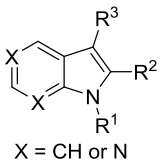
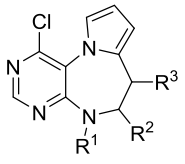
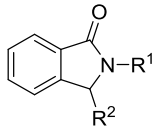
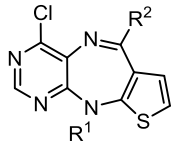
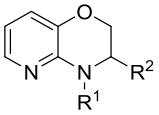
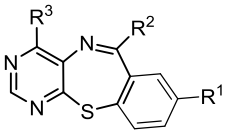
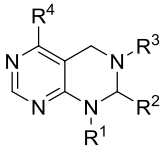
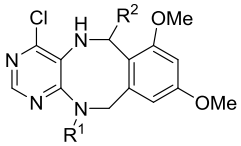
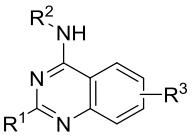
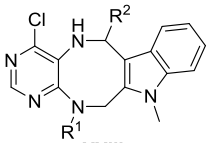
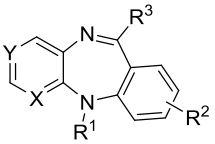
Table S1. The scaffolds and the number of compounds containing each scaffold[a]

Scaffold	Number of compounds	Scaffold	Number of compounds
 **I**	12	 **XIII**	14
 **II**	5	 X = N, Y = CH or X= CH, Y = N n = 0, 1, 2 **XIV** (ref. 1)	23
 **III**	2	 X = N, Y = CH or X= CH, Y = N **XV** (ref. 1)	13
 **IV**	29	 X = N or CH **XVI** (ref. 6-8)	16
 **V** (ref. 1)	43	 **XVII** (ref. 9)	9
 **VI**	16	 **XVIII**	1
 X = CH or N **VII**	2	 **XIX** (ref. 8)	6

 **VIII** (ref. 2)	6	 **XX**	4
 **IX**	2	 **XXI** (ref. 10)	2
 **X** (ref. 3)	8	 **XXII** (ref. 11)	1
 **XI** (ref. 4)	5	 **XXIII** (ref. 11)	6
 X = N, Y = CH or X= CH, Y = N **XII** (ref. 5)	20		

[a]Most of the compounds were >95% purity as assessed by HPLC or ^{1}H NMR.

Cell Type		DMSO	1i	1w	1q	XIII-147	III-17
	HEK293	100	64.8	74.2	71.9	67.5	72.7
	FTCP	100	48.6	61.1	137	111	95.8
T-ALL	Molo4	100	18	21.6	34	16.1	36.1
	Dnd41	100	43.2	64.1	50.8	53.8	101
	Hpa-ALL	100	43	58	46	54.9	39.1
	Sil-ALL	100	20.1	21.9	21.1	20.2	70.7
	T-ALL	100	48.7	58.2	48.5	43.8	1.6
	Kopt	100	33.3	12.1	30.9	12.4	31.9
	Rpm8402	100	14.8	36.9	15.8	19.5	75.7
	CUTLL1	100	60.9	47.7	53.6	50	95.1
B-ALL	SP-15	100	58.9	75.6	86.2	80.7	88
	TOMO-1	100	32.9	38.7	41.4	38.8	90
	OP-1	100	46.3	44.8	45.4	55.2	3.1
	380	100	87.1	87.8	85.2	87.2	86
	697	100	6.7	35.1	5.9	11	64.1
	UOCB-1	100	17.9	26.7	22.5	38.6	4.4
	Reh	100	20.4	5.6	6.2	7.7	77.3
	RS(4;11)	100	34.1	32.1	35.8	33.6	20.5
	NALM6	100	30.6	39.5	39.9	58.4	2.6
	KASUMI-2	100	26.8	46.9	49.5	54.8	6.2
AML	Nomo-1	100	31.1	14.1	17.6	37.7	40.6
	Mono Mac 6	100	19.1	44.9	25.5	71.7	112
	Kasumi-1	100	13.1	55.3	16.2	25.4	68.3
	KG-1	100	20.1	21.9	21.1	20.2	81.9
	NB-4	100	3.6	4.6	4.1	3.9	93.7
	ML-2	100	12.8	42.6	12.8	11.8	101
	MV4-11	100	6.5	30.1	6.1	6	95.3
	U937	100	7.1	23.7	8.2	10.1	66.7
	CMK	100	60.1	76.5	60.1	59.5	91.6
	Mo7e	100	64.2	71.4	55.1	60.3	85.4

Viability (%):	< 20	20-50	>50

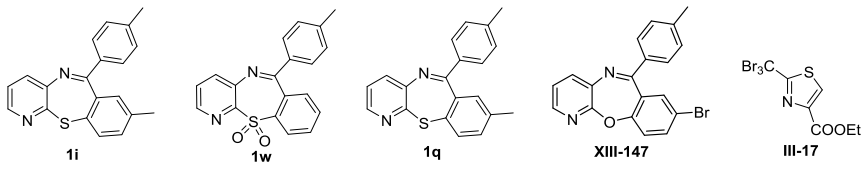


Figure S1. Cytotoxic activity of 5 representative active compounds against 28 selected acute leukemia cell lines (10 μM).

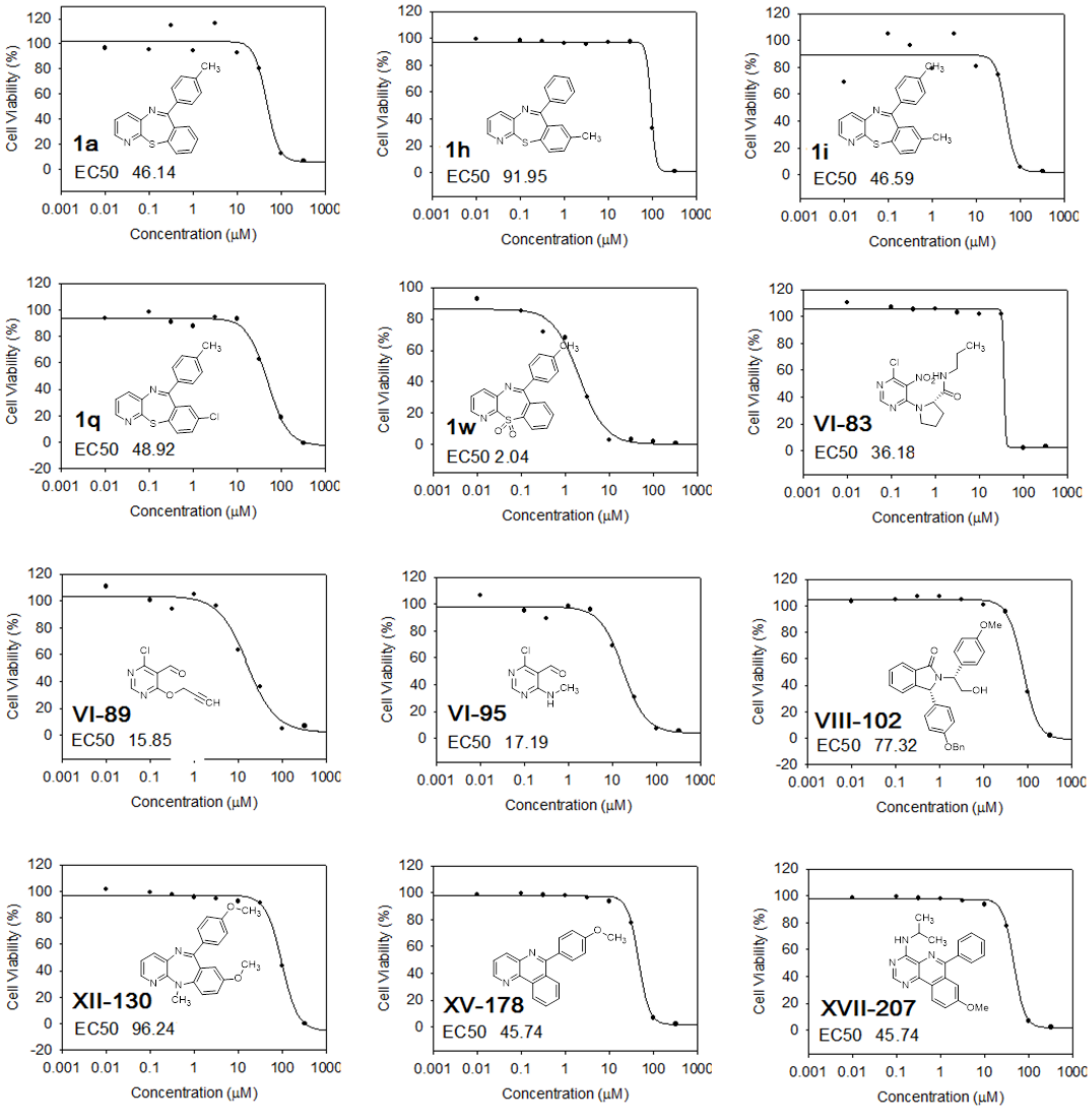


Figure S2. The dose-dependent cytotoxicity of 12 representative active compounds against OP-1.

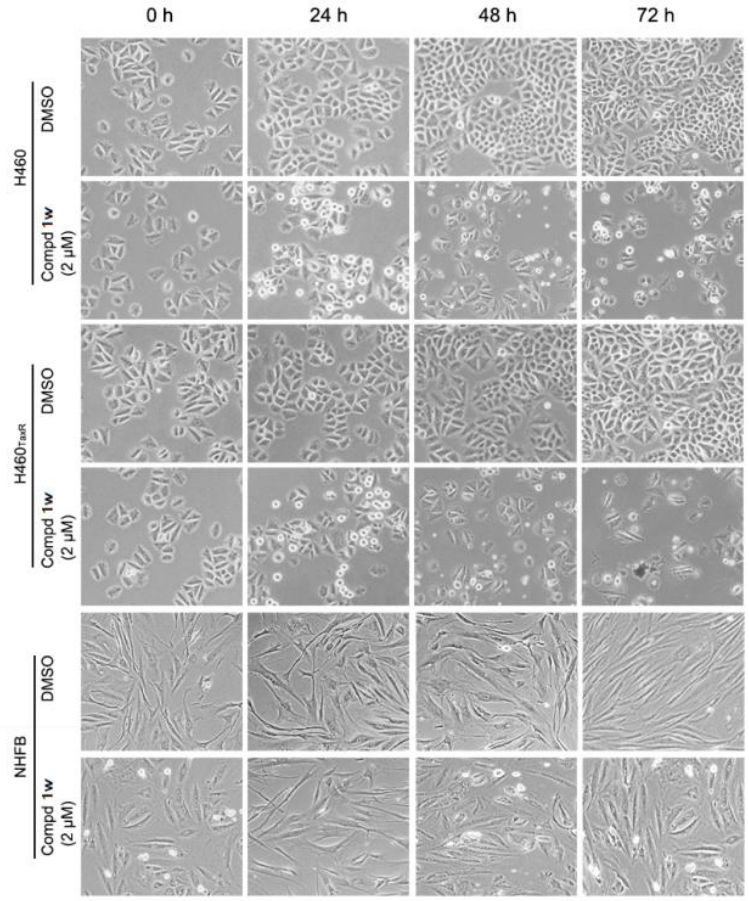
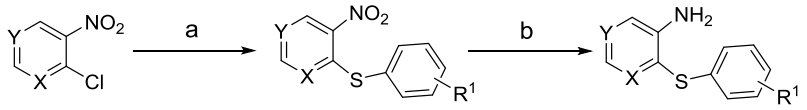


Figure S3. Cell photos of H460, $H460_{TaxR}$ and NHFB cell lines. The cells were treated with compound **1w** (2 μM) or DMSO for indicated time.

Chemistry. All commercial chemistry reagents except for $POCl_3$ and CH_2Cl_2 were used as received without additional purification. $POCl_3$ was used after being freshly distilled. CH_2Cl_2 was used after being dried over anhydrous $CaCl_2$. Melting point was uncorrected. The ^1H and ^{13}C NMR data were obtained using a 300 MHz NMR spectrometer with TMS as the internal standard. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) where noted are quoted in Hz. Compounds **1w** and **2** are known compounds, and have been reported in our previous literature.[1] Purity of all the final products tested in biological assays were determined to be >95% by HPLC. HPLC analysis was performed on a HPLC system equipped with a C_{18} column (2.0 μm, 2.0×50 mm). The eluent was a mixture containing 0.05%

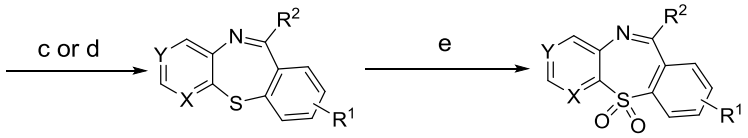
trifluoroacetic acid with a linear gradient from 50:50 v/v methanol/H_2O to 100% methanol over 6.5 min at a 1.0 mL/min flow rate. UV detection wavelength was at 214 nm.

Scheme S1. Synthetic routes for tricyclic thiazepine derivatives (Compounds **1w** and **2-15**).



29a X = N; Y = CH, R^1 = H, 98%
29b X = N; Y = CH, R^1 = 4-F
29c X = N; Y = CH, R^1 = 4-Cl, 82%
29d X = N; Y = CH, R^1 = 4-Me, 96%
29e X = N; Y = CH, R^1 = 4-MeO, 98%
29f X = N; Y = CH, R^1 = 3-MeO, 94%
29g X = N; Y = CH, R^1 = 2-MeO, 94%
29h X = CH; Y = N, R^1 = H

30a X = N; Y = CH, R^1 = H, 92%
30b X = N; Y = CH, R^1 = 4-F
30c X = N; Y = CH, R^1 = 4-Cl, 74%
30d X = N; Y = CH, R^1 = 4-Me, 96%
30e X = N; Y = CH, R^1 = 4-MeO, 84%
30f X = N; Y = CH, R^1 = 3-MeO, 92%
30g X = N; Y = CH, R^1 = 2-MeO, 91%
30h X = CH; Y = N, R^1 = H

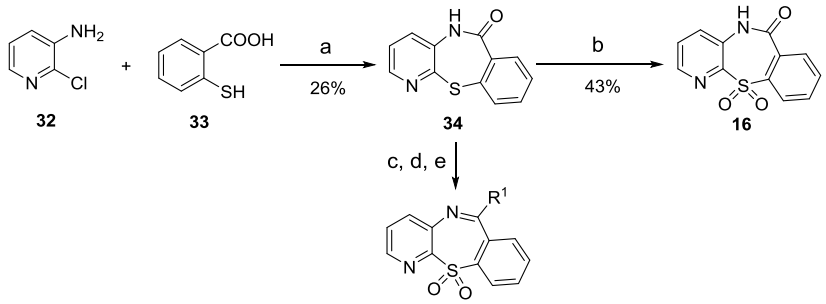


31a X = N; Y = CH, R^1 = H, R^2 = 4-MePh, 77%
31b X = N; Y = CH, R^1 = H, R^2 = Ph, 78%
31c X = N; Y = CH, R^1 = H, R^2 = 2-MePh
31d X = N; Y = CH, R^1 = H, R^2 = 3-MePh, 76%
31e X = N; Y = CH, R^1 = H, R^2 = 4-MeOPh, 75%
31f X = N; Y = CH, R^1 = H, R^2 = 4-FPh, 80%
31g X = N; Y = CH, R^1 = H, R^2 = 4-CF_3Ph, 57%
31h X = N; Y = CH, R^1 = H, R^2 = furan-2-yl, 45%
31i X = N; Y = CH, R^1 = 8-F, R^2 = 4-MePh
31j X = N; Y = CH, R^1 = 8-Cl, R^2 = 4-MePh, 41%
31k X = N; Y = CH, R^1 = 8-Me, R^2 = 4-MePh, 87%
31l X = N; Y = CH, R^1 = 8-MeO, R^2 = 4-MePh, 23%
31m X = N; Y = CH, R^1 = 9-MeO, R^2 = 4-MePh, 70%
31n X = N; Y = CH, R^1 = 10-MeO, R^2 = 4-MePh, 60%
31o X = CH; Y = N, R^1 = H, R^2 = 4-MePh

1w X = N; Y = CH, R^1 = H, R^2 = 4-MePh, 98%
2 X = N; Y = CH, R^1 = H, R^2 = Ph, 95%
3 X = N; Y = CH, R^1 = H, R^2 = 2-MePh, 41% (2 steps)
4 X = N; Y = CH, R^1 = H, R^2 = 3-MePh, 75%
5 X = N; Y = CH, R^1 = H, R^2 = 4-MeOPh, 90%
6 X = N; Y = CH, R^1 = H, R^2 = 4-FPh, 98%
7 X = N; Y = CH, R^1 = H, R^2 = 4-CF_3Ph, 63%
8 X = N; Y = CH, R^1 = H, R^2 = furan-2-yl, 96%
9 X = N; Y = CH, R^1 = 8-F, R^2 = 4-MePh, 14% (4 steps)
10 X = N; Y = CH, R^1 = 8-Cl, R^2 = 4-MePh, 91%
11 X = N; Y = CH, R^1 = 8-Me, R^2 = 4-MePh, 97%
12 X = N; Y = CH, R^1 = 8-MeO, R^2 = 4-MePh, 43%
13 X = N; Y = CH, R^1 = 9-MeO, R^2 = 4-MePh, 50%
14 X = N; Y = CH, R^1 = 10-MeO, R^2 = 4-MePh, 50%
15 X = CH; Y = N, R^1 = H, R^2 = 4-MePh, 38% (4 steps)

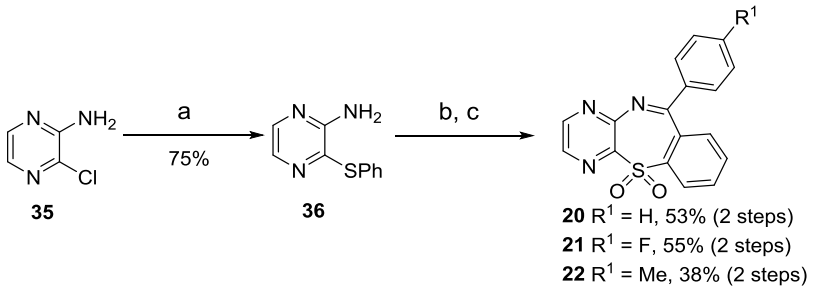
Reagents and conditions: (a) R^1PhSH, EtONa/EtOH, 0 °C, 1 h; (b) Fe/NH_4Cl, reflux, 1 h; (c) R^2CO_2H, $SnCl_4$ or PPA, $POCl_3$, reflux, 0.8–7 d; (d) (i) R_2COCl, Et_3N, CH_2Cl_2, 0 °C, rt, 5 h; (ii) $POCl_3$, reflux, 3 d; (e) *m*-CPBA/CH_2Cl_2, rt, 0.5–6 h.

Scheme S2. Synthetic routes for tricyclic thiazepine derivatives (Compounds **16-19**).



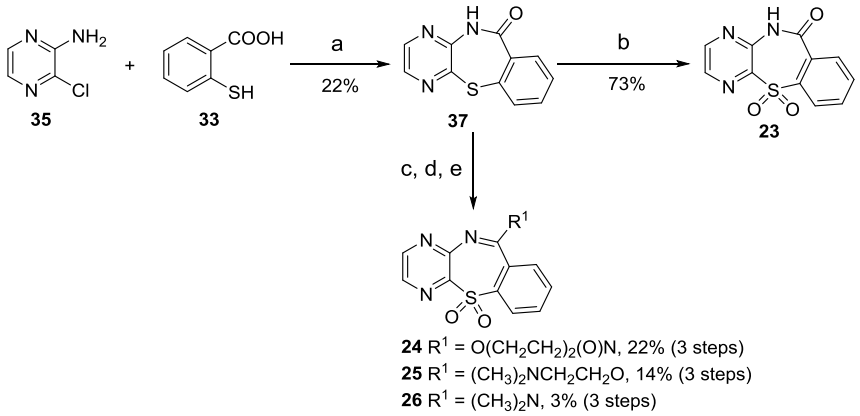
Reagents and conditions: (a) 1,2-dichlorobenzene, reflux, 0.8 h; (b) *m*-CPBA/CH_2Cl_2, rt, 6 h; (c) *N*,*N*-diethylaniline, $POCl_3$, 20 h; (d) Nucleophile (R^1H), toluene, reflux, 1–24 h; (e) *m*-CPBA/ CH_2Cl_2, rt, 1–8 h.

Scheme S3. Synthetic routes for tricyclic thiazepine derivatives (Compounds **20-22**).



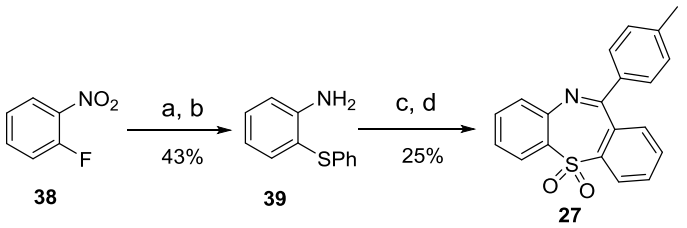
Reagents and conditions: (a) PhSH, Et_3N, *n*-BuOH, reflux, 11 h; (b) 4-R^1PhCO_2H, $SnCl_4/POCl_3$, reflux, 4–7 d; (c) *m*-CPBA/CH_2Cl_2, rt, 2–48 h.

Scheme S4. Synthetic routes for tricyclic thiazepine derivatives (Compounds **23-26**).



Reagents and conditions: (a) 1,2-dichlorobenzene, reflux, 7 h; (b) *m*-CPBA/CH_2Cl_2, rt, 8 h; (c) *N*,*N*-diethylaniline, $POCl_3$, 13 h; (d) Nucleophile (R^1H), toluene, reflux, 0.4–24 h; (e) *m*-CPBA/CH_2Cl_2, rt, 2–48 h.

Scheme S5. Synthetic routes for tricyclic thiazepine derivative (Compound **27**).



Reagents and conditions: (a) PhSH, $NaOH/H_2O$, reflux, 1 h; (b) Fe/NH_4Cl, reflux, 2 h; (c) 4-$MePhCO_2H$, $PPA/POCl_3$, reflux, 14 h; (d) *m*-$CPBA/CH_2Cl_2$, rt, 6 h.

General Procedure for Nucleophilic Displacement from Chloropyridine. Corresponding thiophenol (1.0 mmol) was added to a solution of EtONa in EtOH (1 N, 1.0 mL) at 0 °C. 2-Chloro-3-nitropyridine or 4-chloro-3-nitropyridine (**28**; 1.0 mmol) was added to the mixture. The resulting solution was stirred for an additional 20 min. The volatiles were removed *in vacuo*, and water (2.5 mL) was added. The precipitate was filtered, washed with water (0.5 mL), and then dried to yield the desired product.

General Procedure for Nitro Reduction. Nitro compound (1.0 mmol), iron powder (3.0 mmol), and NH_4Cl (1.0 mmol) were added in sequence to a solution of water (1 mL) in EtOH (4 mL). The mixture was stirred and heated to reflux for 1 h and filtered through Celite. The filtrate was concentrated *in vacuo*, water (4 mL) was added, and the filtrate was extracted with EtOAc (3 × 2 mL). The combined EtOAc layer was washed with brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to yield the desired product**.**

General Procedure for Friedel–Crafts Cyclization. Method A: Amino compound (1.0 mmol), aromatic acid (1.5 mmol), and $SnCl_4$ (2 mmol) were dissolved in $POCl_3$ (5 mL), and the mixture was stirred under reflux for the appropriate time. The mixture was poured into ice water (20 mL) and treated with 5 N aqueous NaOH to pH 9–10. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined EtOAc layer was washed with saturated Na_2CO_3 (20 mL) and brine (20 mL), dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 10:1, v/v) to produce the desired product. **Method B:** Amino compound (1.0 mmol), aromatic acid (1.5 mmol), and PPA (2.0 mmol) were

dissolved in $POCl_3$ (5 mL), and the mixture was stirred under reflux for 14 h. The mixture was poured into ice water (20 mL) and treated with 5 N aqueous NaOH to pH 9–10. The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined EtOAc layer was washed with saturated Na_2CO_3 (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 15:1, v/v) to produce the desired product.

Method C: Amino compound (1.0 mmol), 4-methylbenzoyl chloride (1.2 mmol), and Et_3N (1.5 mmol) were dissolved in CH_2Cl_2 (10 mL) at 0 °C。 The resulting solution was stirred at rt for 5 h. The reaction mixture was diluted in CH_2Cl_2 (40 mL), washed in 1N HCl (10 mL), water (10 mL), and brine (10 mL) in sequence, dried over Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 5:1 to 3:1, v/v) to produce the corresponding amide**.** Then, the amide was dissolved in $POCl_3$ (10 mL). The resulting solution was stirred at reflux for 3 d. The reaction mixture was concentrated *in vacuo* to remove approximately 8 mL of $POCl_3$. The residue was poured into ice water (10 mL), and was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layer was washed in 1N NaOH (10 mL), water (10 mL), and brine (10 mL) in sequence, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 15:1, v/v) to produce the desired product.

General Procedure for Cyclization with 2-Mercaptobenzoic Acid. To a stirred solution of 2-chloropyridin-3-amine or 3-chloropyrazin-2-amine (1.0 mmol) in 1,2-dichlorobenzene (2 mL) was added 2-mercaptobenzoic acid (1.0 mmol). The resulting solution was heated at reflux for the appropriate time. The volatiles were removed *in vacuo*, water (5 mL) was added, and extraction was performed with CH_2Cl_2 (4 × 5 mL). The combined CH_2Cl_2 layer was dried over $MgSO_4$, concentrated *in vacuo*, and purified via flash chromatography (CH_2Cl_2/EtOAc = 20:1, v/v) to produce the desired product.

General Procedure for Chlorination and Nucleophilic Displacement. To a stirred solution of compound **34** or **37** (1.0 mmol) in $POCl_3$ (14 mL) was added *N*, *N*-diethylaniline (0.44 mL). The resulting solution was heated at reflux for the

appropriate time. The volatiles were removed *in vacuo* to produce the chlorinated compound. Then, the chlorinated compound was dissolved in toluene (10 mL), and the corresponding amine or alcohol (10 mol) was added. The resulting solution was heated at reflux for the appropriate time. The volatiles were removed *in vacuo*, water (20 mL) was added, and extraction was performed with CH_2Cl_2 (3 × 20 mL). The combined CH_2Cl_2 layer was washed with brine (20 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 1:2) to produce the desired product.

General Procedure for Oxidation with *m*-CPBA. To a stirred solution of sulfur compound (1.0 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (3.0 mmol). The resulting solution was stirred at room temperature for the appropriate time. The reaction mixture was washed with saturated $NaHSO_3$ (40 mL), saturated Na_2CO_3 (40 mL), and brine (40 mL) in sequence, dried over Na_2SO_4, concentrated *in vacuo*, and purified via flash chromatography (petroleum ether/EtOAc = 5:1 to 1:2, v/v) to produce the desired product**.**

3-Nitro-2-(phenylthio)pyridine (29a). 29a was synthesized from 2-chloro-3-nitropyridine (6.34 g, 40 mmol) and benzenethiol (4.1 mL, 40 mmol) following the general procedure for nucleophilic displacement from chloropyridine. Yield: 9.105 g (98%); mp: 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 8.50–8.48 (m, 2H), 7.57–7.54 (m, 2H), 7.47–7.45 (m, 3H), 7.20–7.15 (m, 1H); ES-MS *m/z* 232.9 [M + H^+].

3-Nitro-2-((4-chlorophenyl)thio)pyridine (29c). 29c was synthesized from 2-chloro-3-nitropyridine (1.0 g, 6.31 mmol) and 4-chlorobenzenethiol (912 mg, 6.31 mmol) following the general procedure for nucleophilic displacement from chloropyridine. Yield: 1.38 g (82%); mp: 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 8.53–8.50 (m, 2H), 7.49 (d, *J* = 8.7, 2H), 7.43 (d, *J* = 8.7, 2H), 7.21 (dd, *J* = 8.1, 4.8, 1H); ES-MS *m/z* 267.0 [M + H^+].

3-Nitro-2-(*p*-tolylthio)pyridine (29d). 29d was synthesized from 2-chloro-3-nitropyridine (1.0 g, 6.31 mmol) and 4-methylbenzenethiol (784 mg, 6.31 mmol) following the general procedure for nucleophilic displacement from

chloropyridine. Yield: 1.49 g (96%); mp: 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 8.51–8.47 (m, 2H), 7.43 (d, *J* = 7.8, 2H), 7.26 (d, *J* = 7.8, 2H), 7.18–7.14 (m, 1H), 2.42 (s, 3H); ES-MS *m/z* 247.0 [M + H^+].

3-Nitro-2-((4-methoxyphenyl)thio)pyridine (29e). 29e was synthesized from 2-chloro-3-nitropyridine (1.0 g, 6.31 mmol) and 4-methoxybenzenethiol (885 mg, 6.31 mmol) following the general procedure for nucleophilic displacement from chloropyridine. Yield: 1.62 g (98%); mp: 140–142 °C; ^{1}H NMR ($CDCl_3$) δ 8.52–8.47 (m, 2H), 7.47 (d, *J* = 9.0, 2H), 7.19–7.14 (m, 1H), 6.98 (d, *J* = 9.0, 2H), 3.86 (s, 3H); ES-MS *m/z* 263.0 [M + H^+].

3-Nitro-2-((3-methoxyphenyl)thio)pyridine (29f). 29f was synthesized from 2-chloro-3-nitropyridine (1.0 g, 6.31 mmol) and 3-methoxybenzenethiol (885 mg, 6.31 mmol) following the general procedure for nucleophilic displacement from chloropyridine. Yield: 1.554 g (94%); mp: 112–113 °C; ^{1}H NMR ($CDCl_3$) δ 8.50–8.45 (m, 2H), 7.56–7.45 (m, 2H), 7.16–7.12 (m, 1H), 7.06–6.97 (m, 2H), 3.74 (s, 3H); ES-MS *m/z* 263.0 [M + H^+].

3-Nitro-2-((2-methoxyphenyl)thio)pyridine (29g). 29g was synthesized from 2-chloro-3-nitropyridine (1.0 g, 6.31 mmol) and 2-methoxybenzenethiol (885 mg, 6.31 mmol) following the general procedure for nucleophilic displacement from chloropyridine. Yield: 1.552 g (94%); mp: 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 8.53–8.47 (m, 2H), 7.37 (t, *J* = 7.8, 1H), 7.20–7.10 (m, 3H), 7.03–6.99 (m, 1H), 3.82 (s, 3H); ES-MS *m/z* 263.0 [M + H^+].

3-Amino-2-(phenylthio)pyridine (30a). 30a was synthesized from **29a** (8.13 g, 35 mmol) following the general procedure for reduction of nitro. Yield: 6.51 g (92%); mp: 68–69 °C; ^{1}H NMR ($CDCl_3$) δ 8.04–8.02 (m, 1 H), 7.30–7.18 (m, 5H), 7.10–7.06 (m, 1 H), 7.03–7.00 (m, 1H); ES-MS *m/z* 203.0 [M + H^+].

3-Amino-2-((4-chlorophenyl)thio)pyridine (30c). 30c was synthesized from **29c** (1.333 g, 5 mmol) following the general procedure for reduction of nitro. Yield: 876 mg (74%); mp: 88–100 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, *J* = 4.5, 1H), 7.26 (d, *J* = 8.4, 2H), 7.23 (d, *J* = 8.4, 2H), 7.11 (dd, *J* = 8.1, 4.5, 1H), 7.04 (d, *J* = 8.1, 1H), 4.23 (br, 2H); ES-MS *m/z* 237.0 [M + H^+].

3-Amino-2-(*p*-tolylthio)pyridine (30d). 30d was synthesized from **29d** (1.232 g, 5 mmol) following the general procedure for reduction of nitro. Yield: 1.037 g (96%); mp: 94–96 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (dd, *J* = 4.2, 1.5, 1H), 7.22 (d, *J* = 8.1, 2H), 7.08 (d, *J* = 8.1, 2H), 7.05–6.95 (m, 2H), 4.18 (br, 2H), 2.30 (s, 3H); ES-MS *m/z* 217.0 [M + H^+].

3-Amino-2-((4-methoxyphenyl)thio)pyridine (30e). 30e was synthesized from **29e** (1.312 g, 5 mmol) following the general procedure for reduction of nitro. Yield: 974 mg (84%); mp: 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (dd, *J* = 4.2, 1.5, 1H), 7.35 (d, *J* = 6.9, 2H), 6.99–6.93 (m, 2H), 6.85 (d, *J* = 6.9, 2H), 4.15 (br, 2H), 3.78 (s, 3H); ES-MS *m/z* 233.0 [M + H^+].

6-(*p*-Tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31a). 31a was synthesized from **30a** (202 mg, 1.0 mmol) and 4-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 234 mg (77%); mp: 159–161 °C; ^{1}H NMR ($CDCl_3$) δ 8.27 (dd, *J* = 4.5, 1.8, 1H), 7.69 (d, *J* = 8.4, 2H), 7.66–7.61 (m, 2H), 7.45 (td, *J* = 7.5, 1.8, 1H), 7.34–7.31 (m, 1H), 7.29–7.25 (m, 2H), 7.24 (d, *J* = 8.4, 2H), 2.43 (s, 3H); ES-MS *m/z* 303.0 [M + H^+].

6-Phenylbenzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31b). 31b was synthesized from **30a** (202 mg, 1.0 mmol) and benzoic acid (183 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 225 mg (78%); mp: 131–133 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 4.8, 1.5, 1H), 7.81–7.78 (m, 2H), 7.68–7.62 (m, 2H), 7.51–7.41 (m, 4H), 7.33–7.22 (m, 3H); ES-MS *m/z* 289.0 [M + H^+].

6-(*m*-Tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31d). **31d** was synthesized from **30a** (202 mg, 1.0 mmol) and 3-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 230 mg (76%); mp: 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, *J* = 4.8, 1H), 7.68–7.63 (m, 3H), 7.52–7.44 (m, 2H), 7.34–7.23 (m, 5H), 2.41 (s, 3H); ES-MS *m/z* 303.0 [M + H^+].

6-(4-Methoxyphenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31e). **31e** was synthesized from **30a** (202 mg, 1.0 mmol) and 4-methoxybenzoic acid (228 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A).

Yield: 238 mg (75%); mp: 148–150 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, *J* = 4.8, 1.8, 1H), 7.77 (d, *J* = 8.7, 2H), 7.67 (dd, *J* = 8.7, 0.6, 1H), 7.61 (dd, *J* = 8.4, 1.5, 1H), 7.46 (td, *J* = 7.5, 1.8, 1H), 7.32 (td, *J* = 7.8, 1.2, 1H), 7.28–7.23 (m, 2H), 6.95 (d, *J* = 8.7, 2H), 3.88 (s, 3H); ES-MS *m/z* 319.0 [M + H^+].

6-(4-Fluorophenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31f). 31f was synthesized from **30a** (202 mg, 1.0 mmol) and 4-fluorobenzoic acid (210 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 245 mg (80%); mp: 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (dd, *J* = 4.8, 1.5, 1H), 7.84–7.79 (m, 2H), 7.68 (dd, *J* = 7.2, 0.9, 1H), 7.62 (dd, *J* = 8.1, 1.8, 1H), 7.48 (td, *J* = 7.2, 1.8, 1H), 7.33 (td, *J* = 7.2, 0.9, 1H), 7.29–7.22 (m, 2H), 7.16–7.10 (m, 2H); ES-MS *m/z* 307.1 [M + H^+].

6-(4-(Trifluoromethyl)phenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31g). **31g** was synthesized from **30a** (202 mg, 1.0 mmol) and 4-(trifluoromethyl)benzoic acid (285 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 203 mg (57%); mp: 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 8.36–8.34 (m, 1H), 7.95–7.91 (m, 2H), 7.72–7.67 (m, 4H), 7.53–7.48 (m, 1H), 7.37–7.30 (m, 2H), 7.22–7.19 (m, 1H); ES-MS *m/z* 357.1 [M + H^+].

6-(Furan-2-yl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31h). **31h** was synthesized from **30a** (202 mg, 1.0 mmol) and furan-2-carboxylic acid (168 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 125 mg (45%); mp: 159–161 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 4.5, 1.5, 1H), 7.72–7.65 (m, 3H), 7.55 (dd, *J* = 7.8, 1.5, 1H), 7.49 (td, *J* = 7.5, 1.5, 1H), 7.41–7.36 (m, 1H), 7.29–7.25 (m, 1H), 6.76 (d, *J* = 3.3, 1H), 6.57 (dd, *J* = 3.6, 1.8, 1H); ES-MS *m/z* 279.0 [M + H^+].

8-Chloro-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31j). **31j** was synthesized from **30c** (237 mg, 1.0 mmol) and 4-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 138 mg (41%); mp: 175–176 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (dd, *J* = 4.2, 1.5, 1H), 7.69 (d, *J* = 7.8, 2H), 7.64–7.58 (m, 2H), 7.42 (dd, *J* = 8.4, 2.1, 1H), 7.30–7.27 (m, 3H), 7.23 (d, *J* = 2.7, 1H), 2.44 (s, 3H); ES-MS *m/z* 336.9 [M + H^+].

8-Methyl-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31k). 31k was synthesized from **30d** (216 mg, 1.0 mmol) and 4-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 275 mg (87%); mp: 184–186 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, *J* = 4.5, 1.5, 1H), 7.70 (d, *J* = 8.4, 2H), 7.63 (dd, *J* = 8.1, 1.5, 2H), 7.27–7.22 (m, 4H), 7.05 (s, 1H), 2.43 (s, 3H), 2.27 (s, 3H); ES-MS *m/z* 317.0 [M + H^+].

8-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31l). **31l** was synthesized from **30e** (232 mg, 1.0 mmol) and 4-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A). Yield: 76 mg (23%); mp: 173–175 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (dd, *J* = 4.5, 0.9, 1H), 7.73 (d, *J* = 8.1, 2H), 7.60 (dd, *J* = 7.5, 0.9, 1H), 7.56 (d, *J* = 9.0, 1H), 7.26–7.23 (m, 3H), 6.99 (dd, *J* = 7.5, 2.4, 1H), 6.75 (d, *J* = 2.4, 1H), 3.70 (s, 3H), 2.43 (s, 3H); ES-MS *m/z* 333.0 [M + H^+].

9-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31m). 31m was synthesized from **29f** (262 mg, 1.0 mmol) and 4-methylbenzoyl chloride (0.147 mL, 1.104 mmol) following the general procedure for reduction of nitro and Friedel–Crafts cyclization (Method C). Yield: 213 mg (64%); mp: 135–136 °C; ^{1}H NMR ($CDCl_3$) δ 8.29–8.27 (m, 1H), 7.70–7.67 (m, 2H), 7.64–7.61 (m, 1H), 7.28–7.13 (m, 5H), 6.85–6.81 (m, 1H), 3.83 (s, 3H), 2.42 (s, 3H); MS (ESI): m/z 333.0 [M + H^+].

10-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine (31n). **31n** was synthesized from **29g** (262 mg, 1.0 mmol) and 4-methylbenzoyl chloride (0.145 mL, 1.092 mmol) following the general procedure for reduction of nitro and Friedel–Crafts cyclization (Method C). Yield: 183 mg (55%); mp: 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 8.28–8.26 (m, 1H), 7.70–7.67 (m, 2H), 7.63–7.60 (m, 1H), 7.27–7.21 (m, 4H), 7.02–6.99 (m, 1H), 6.82–6.79 (m, 1H), 3.93 (s, 3H), 2.42 (s, 3H); ES-MS *m/z* 333.0 [M + H^+].

6-(*p*-Tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (1w). 1w was synthesized from **31a** (60 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 65 mg (98%); mp: 236–238 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.54 (dd, *J* = 4.5, 1.5, 1H), 8.27 (dd, *J* = 7.5, 1.5, 1H), 7.91 (dd, *J* =

8.1, 1.2, 1H), 7.78–7.66 (m, 4H), 7.57 (dd, *J* = 8.1, 4.5, 1H), 7.52 (dd, *J* = 7.5, 1.5, 1H), 7.30–7.27 (m, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.5, 147.7, 146.1, 143.4, 142.5, 141.3, 136.6, 135.7, 133.1, 131.6, 131.0, 130.2, 129.3, 129.2, 127.9, 125.6, 21.5; HRMS (ESI) m/z calcd for $[C_{19}H_{14}N_2O_2S + H]^+$, 335.0849; found, 335.0847.

6-Phenylbenzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (2). 2 was synthesized from **31b** (58 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 61 mg (95%); mp: 214–216 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.56 (dd, *J* = 4.5, 1.5, 1H), 8.29 (dd, *J* = 7.5, 1.5, 1H), 7.94 (dd, *J* = 8.4, 1.8, 1H), 7.88–7.56 (m, 5H), 7.54–7.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 168.6, 146.4, 143.5, 141.2, 139.3, 135.7, 134.4, 133.2, 131.8, 131.0, 130.1, 129.2, 128.4, 128.0, 125.6; HRMS (ESI) m/z calcd for $[C_{18}H_{12}N_2O_2S + H]^+$, 321.0692; found, 321.0691.

6-(*o*-Tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (3). **3** was synthesized from **30a** (202 mg, 1.0 mmol) and 2-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method B) and oxidation with *m*-CPBA. Yield: 137 mg (41%); mp: 248–250 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.62–8.60 (m, 1H), 8.32–8.29 (m, 1H), 8.00–7.97 (m, 1H), 7.78–7.73 (m, 1H), 7.67–7.59 (m, 3H), 7.44–7.29 (m, 4H), 2.29 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{14}N_2O_2S + H]^+$, 335.0849; found, 335.0850.

6-(*m*-Tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (4). **4** was synthesized from **31d** (60 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 50 mg (75%); mp: 221–222 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.57–8.55 (m, 1H), 8.30–8.27 (m, 1H), 7.95–7.92 (m, 1H), 7.79–7.67 (m, 3H), 7.63–7.56 (m, 2H), 7.53–7.50 (m, 1H), 7.38–7.36 (m, 2H), 2.43 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{14}N_2O_2S + H]^+$, 335.0849; found, 335.0844.

6-(4-Methoxyphenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (5). **5** was synthesized from **31e** (64 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 63 mg (90%); mp: 249–251 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.54–8.52 (m, 1H), 8.29–8.26 (m, 1H), 7.91–7.83 (m, 3H), 7.78–7.67 (m, 2H), 7.58–7.52 (m, 2H), 7.00–6.97 (m, 2H), 3.89 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{14}N_2O_3S + H]^+$, 351.0793; found, 351.0794.

6-(4-Fluorophenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (6). 6 was synthesized from **31f** (61 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 66 mg (98%); mp: 263–265 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.58–8.56 (m, 1H), 8.31–8.28 (m, 1H), 7.90–7.86 (m, 3H), 7.81–7.69 (m, 2H), 7.62–7.57 (m, 1H), 7.53–7.50 (m, 1H), 7.20–7.14 (m, 2H); HRMS (ESI) m/z calcd for $[C_{18}H_{11}FN_2O_2S + H]^+$, 339.0598; found, 339.0595.

6-(4-(Trifluoromethyl)phenyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (7). **7** was synthesized from **31g** (71 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 49 mg (63%); mp: 232–233 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.61–8.59 (m, 1H), 8.33–8.30 (m, 1H), 8.00–7.95 (m, 3H), 7.83–7.70 (m, 4H), 7.64–7.60 (m, 1H), 7.50–7.47 (m, 1H); HRMS (ESI) m/z calcd for $[C_{19}H_{11}F_3N_2O_2S + H]^+$, 389.0566; found, 389.0563.

6-(Furan-2-yl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (8). **8** was synthesized from **31g** (56 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 60 mg (96%); mp: 257–259 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.55–8.53 (m, 1H), 8.29–8.26 (m, 1H), 7.96–7.92 (m, 1H), 7.85–7.75 (m, 4H), 7.60–7.56 (m, 1H), 6.98–6.96 (m, 1H), 6.64–6.62 (m, 1H); HRMS (ESI) m/z calcd for $[C_{16}H_{10}N_2O_3S + H]^+$, 311.0485; found, 311.0484

8-Fluoro-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (9). **9** was synthesized from 2-chloro-3-nitropyridine (158 mg, 1.0 mmol), 4-fluorobenzenethiol (0.106 mL, 1.0 mmol) and 4-methylbenzoic acid (112 mg, 0.828 mmol) following the general procedure for nucleophilic displacement from chloropyridine, reduction of nitro, Friedel–Crafts cyclization (Method A) and oxidation with *m*-CPBA. Yield: 49 mg (14%); mp: 225–226 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.56–8.54 (m, 1H), 8.31–8.26 (m, 1H), 7.93–7.89 (m, 1H), 7.76 (d, J = 8.1, 2H), 7.61–7.57 (m, 1H), 7.46–7.39 (m, 1H), 7.31 (d, J = 7.8, 2H), 7.22–7.18 (m, 1H), 2.45 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{13}FN_2O_2S + H]^+$, 353.0755; found, 353.0755.

8-Chloro-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (10). **10** was synthesized from **31j** (67 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 67 mg (91%); mp: 232–233 °C; Purity: 99%; ^{1}H

NMR ($CDCl_3$) δ 8.56–8.55 (m, 1H), 8.20 (d, *J* = 8.7, 1H), 7.92–7.89 (m, 1H), 7.76 (d, *J* = 8.4, 2H), 7.72–7.69 (m, 1H), 7.62–7.58 (m, 1H), 7.49 (d, *J* = 2.1, 1H), 7.32 (d, *J* = 8.7, 2H), 2.46 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{13}ClN_2O_2S + H]^+$, 369.0459; found, 369.0459.

8-Methyl-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (11). 11 was synthesized from **31k** (63 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 67 mg (97%); mp: 230–231 °C; Purity: 97%; ^1H NMR ($CDCl_3$) δ 8.52 (d, *J* = 3.3, 1H), 8.14 (d, *J* = 8.1, 1H), 7.89 (d, *J* = 8.1, 1H), 7.76 (d, *J* = 8.1, 2H), 7.57–7.52 (m, 2H), 7.30–7.26 (m, 3H), 2.45 (s, 3H), 2.40 (s, 3H); HRMS (ESI) m/z calcd for $[C_{20}H_{16}N_2O_2S + H]^+$, 349.1005; found, 349.1005.

8-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (12). **12** was synthesized from **31l** (66 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 31 mg (43%); mp: 242–244 °C; Purity: 99%; ^1H NMR ($CDCl_3$) δ 8.51 (dd, *J* = 4.5, 1.5, 1H), 8.18 (d, *J* = 8.7, 1H), 7.88 (dd, *J* = 8.1, 1.5, 1H), 7.83–7.75 (m, 2H), 7.55 (dd, *J* = 8.1, 4.5, 1H), 7.34–7.24 (m, 2H), 7.19 (dd, *J* = 8.7, 2.4, 1H), 6.95 (d, *J* = 2.4, 1H), 3.80 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 163.3, 148.5, 146.0, 142.6, 141.3, 136.6, 136.5, 135.6, 131.4, 130.3, 129.3, 128.2, 127.8, 116.8, 116.4, 56.0, 21.6; HRMS (ESI) m/z calcd for $[C_{20}H_{16}N_2O_3S + H]^+$, 365.0954; found, 365.0952.

9-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (13). 13 was synthesized from **31m** (66 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 36 mg (50%); mp: 231–232 °C; Purity: 98%; ^1H NMR ($CDCl_3$) δ 8.55 (d, *J* = 3.3, 1H), 7.92 (d, *J* = 7.2, 1H), 7.77–7.73 (m, 3H), 7.59–7.55 (m, 1H), 7.41 (d, *J* = 8.7, 1H), 7.28 (d, *J* = 8.7, 2H), 7.17–7.13 (m, 1H), 3.93 (s, 3H), 2.44 (s, 3H); HRMS (ESI) m/z calcd for $[C_{20}H_{16}N_2O_3S + H]^+$, 365.0954; found, 365.0954.

10-Methoxy-6-(*p*-tolyl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (14). **14** was synthesized from **31n** (66 mg, 0.2 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 36 mg (50%); mp: 282–283 °C; Purity: 98%; ^1H NMR ($CDCl_3$) δ 8.54–8.52 (m, 1H), 7.88–7.85 (m, 1H), 7.75–7.72 (m, 2H), 7.57–7.47

(m, 2H), 7.27–7.24 (m, 2H), 7.19–7.16 (m, 1H), 6.98–6.95 (m, 1H), 3.99 (s, 3H), 2.42 (s, 3H); HRMS (ESI) m/z calcd for $[C_{20}H_{16}N_2O_3S + H]^+$, 365.0954; found, 365.0953.

10-(*p*-Tolyl)benzo[*f*]pyrido[4,3-*b*][1,4]thiazepine 5,5-dioxide (15). **15** was synthesized from 4-chloro-3-nitropyridine (158 mg, 1.0 mmol), benzenethiol (0.103 mL, 1.0 mmol) and 4-methylbenzoic acid (161 mg, 1.186 mmol) following the general procedure for nucleophilic displacement from chloropyridine, reduction of nitro, Friedel–Crafts cyclization (Method A) and oxidation with *m*-CPBA. Yield: 127 mg (38%); mp: 214–216 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 8.18–8.15 (m, 1H), 7.94–7.91 (m, 1H), 7.83–7.78 (m, 1H), 7.73–7.70 (m, 2H), 7.62–7.53 (m, 2H), 7.38–7.36 (m, 1H), 7.32–7.29 (m, 2H), 2.46 (s, 3H); HRMS (ESI) m/z calcd for $[C_{19}H_{14}N_2O_2S + H]^+$, 335.0849; found, 335.0845.

Benzo[*f*]pyrido[2,3-*b*][1,4]thiazepin-6(5*H*)-one (34).[12] **34** was synthesized from 2-chloropyridin-3-amine (1.29 g, 10 mmol) and 2-mercaptobenzoic acid (1.54 g, 10 mmol) following the general procedure for cyclization with 2-mercaptobenzoic acid. Yield: 594 mg (26%); MS (ESI): m/z 229.1 $[M + H^+]$.

Benzo[*f*]pyrido[2,3-*b*][1,4]thiazepin-6(5*H*)-one 11,11-dioxide (16). **16** was synthesized from **34** (50 mg, 0.219 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 25 mg (43%); mp > 300 °C; Purity: 98%; ^{1}H NMR (DMSO-*d6*) δ 11.53 (s, 1H), 8.54–8.52 (m, 1H), 8.04–7.95 (m, 2H), 7.93–7.85 (m, 3H), 7.81–7.77 (m, 1H); HRMS (ESI) m/z calcd for $[C_{12}H_8N_2O_3S + H]^+$, 261.0328; found, 261.0326.

6-Morpholinobenzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (17). 17 was synthesized from **34** (100 mg, 0.439 mmol) and morpholine (0.382 mL, 4.39 mmol) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 66 mg (46%); mp: 99–101 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J = 3.9, 1H), 8.19–8.16 (m, 1H), 7.73–7.63 (m, 3H), 7.54 (d, J = 6.3, 1H), 7.43–7.39 (m, 1H), 3.79–3.37 (m, 8H); HRMS (ESI) m/z calcd for $[C_{16}H_{15}N_3O_3S + H]^+$, 330.0907; found, 330.0905.

6-(4-Methylpiperazin-1-yl)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (18). 18 was synthesized from **34** (100 mg, 0.439 mmol) and 1-methylpiperazine

(0.486 mL, 4.39 mmol) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 32 mg (21%); mp: 188–190 °C; Purity: 96%; ^{1}H NMR (DMSO-*d6*) δ 8.34–8.32 (m, 1H), 8.06–8.04 (m, 1H), 7.97–7.83 (m, 3H), 7.71–7.61 (m, 2H), 3.71–3.10 (m, 8H), 2.86 (s, 3H); HRMS (ESI) m/z calcd for $[C_{17}H_{18}N_4O_2S + H]^+$, 343.1223; found, 343.1229.

6-(Dimethylamino)benzo[*f*]pyrido[2,3-*b*][1,4]thiazepine 11,11-dioxide (19). **19** was synthesized from **34** (100 mg, 0.439 mmol) and dimethylamine (0.555 mL, 4.39 mmol, 40% in H_2O) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 42 mg (33%); mp: 163–165 °C; Purity: 98%; ^{1}H NMR ($CDCl_3$) δ 8.29–8.27 (m, 1H), 8.18–8.14 (m, 1H), 7.74–7.63 (m, 2H), 7.59–7.56 (m, 1H), 7.52–7.49 (m, 1H), 7.39–7.35 (m, 1H), 3.30 (s, 3H), 3.08 (s, 3H); HRMS (ESI) m/z calcd for $[C_{14}H_{13}N_3O_2S + H]^+$, 288.0801; found, 288.0803.

3-(Phenylthio)pyrazin-2-amine (36): To a stirred solution of 3-chloropyrazin-2-amine (3.0 g, 23.16 mmol) and Et_3N (6.42 mL, 46.32 mmol) in *n*-BuOH (12 mL) was added benzenethiol (3.57 mL, 34.74 mmol). The resulting solution was stirred at reflux for 11 h. The volatiles were removed *in vacuo* and water (100 mL) was added, extracted with EtOAc (3 x 100 mL). The combined EtOAc layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (Petroleum ether/EtOAc = 20:1, v/v) afforded the desired product **36**. Yield: 3.531 g (75%); mp: 83–85 °C; MS (ESI): m/z 204.1 [M + H^+].

10-Phenylbenzo[*f*]pyrazino[2,3-*b*][1,4]thiazepine 5,5-dioxide (20). **20** was synthesized from **36** (203 mg, 1.0 mmol) and benzoic acid (183 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A) and oxidation with *m*-CPBA. Yield: 170 mg (53%); mp: 251–253 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.79 (d, *J* = 2.1, 1H), 8.54 (d, *J* = 2.1, 1H), 8.29–8.26 (m, 1H), 7.97–7.93 (m, 2H), 7.84–7.74 (m, 2H), 7.61–7.48 (m, 4H); HRMS (ESI) m/z calcd for $[C_{17}H_{11}N_3O_2S + H]^+$, 322.0645; found, 322.0642.

10-(4-Fluorophenyl)benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepine 5,5-dioxide (21). **21** was synthesized from **36** (203 mg, 1.0 mmol) and 4-fluorobenzoic acid (210 mg, 1.5

mmol) following the general procedure for Friedel–Crafts cyclization (Method A) and oxidation with *m*-CPBA. Yield: 186 mg (55%); mp: 290–291 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.79 (d, *J* = 2.4, 1H), 8.54 (d, *J* = 1.8, 1H), 8.29–8.26 (m, 1H), 8.00–7.96 (m, 2H), 7.82–7.78 (m, 2H), 7.58–7.56 (m, 1H), 7.23–7.17 (m, 2H); HRMS (ESI) m/z calcd for $[C_{17}H_{10}FN_3O_2S + H]^+$, 340.0551; found, 340.0553.

10-(*p*-Tolyl)benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepine 5,5-dioxide (22). **22** was synthesized from **36** (203 mg, 1.0 mmol) and 4-methylbenzoic acid (204 mg, 1.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method A) and oxidation with *m*-CPBA. Yield: 127 mg (38%); mp: 293–295 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.78 (d, *J* = 3.9, 1H), 8.52 (d, *J* = 2.4, 1H), 8.27–8.24 (m, 1H), 7.85 (d, *J* = 8.1, 2H), 7.80–7.75 (m, 2H), 7.59–7.56 (m, 1H), 7.31 (d, *J* = 8.1, 2H), 2.46 (s, 3H); HRMS (ESI) m/z calcd for $[C_{18}H_{13}N_3O_2S + H]^+$, 336.0801; found, 336.0802.

Benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepin-10(11*H*)-one (37).[13] **37** was synthesized from 3-chloropyrazin-2-amine (3.885 g, 30 mmol) and 2-mercaptobenzoic acid (4.626 g, 30 mmol) following the general procedure for cyclization with 2-mercaptobenzoic acid. Yield: 1.512 g (22%); mp: 234–235 °C; MS (ESI): m/z 230.0 $[M + H^+]$.

Benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepin-10(11*H*)-one 5,5-dioxide (23). **23** was synthesized from **37** (100 mg, 0.436 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 83 mg (73%); mp: 299–300 °C; Purity: 99%; ^{1}H NMR (DMSO-*d6*) δ 12.29 (s, 1H), 8.87 (d, *J* = 2.4, 1H), 8.63 (d, *J* = 2.1, 1H), 8.07–7.91 (m, 4H); HRMS (ESI) m/z calcd for $[C_{11}H_7N_3O_3S + H]^+$, 262.0281; found, 262.0283.

4-(5,5-Dioxidobenzo[*f*]pyrazino[2,3-*b*][1,4]thiazepin-10-yl)morpholine 4-oxide (24). **24** was synthesized from **37** (747 mg, 3.262 mmol) and morpholine (2.84 mL, 32.62 mmol) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 248 mg (22%); mp: 293–295 °C; Purity: 96%; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, *J* = 3.6, 1H), 8.16 (d, *J* = 8.1, 1H), 8.07 (d, *J* = 3.6, 1H), 7.84–7.73 (m, 2H), 7.52 (d, *J* = 6.9, 1H), 4.83 (d, *J* = 12.6, 1H), 3.97–3.79 (m, 1H), 3.76–3.59 (m, 5H), 3.56–3.49 (m, 1H); HRMS (ESI) m/z calcd for $[C_{15}H_{14}N_4O_4S + H]^+$, 347.0808; found, 347.0825.

10-(2-(Dimethylamino)ethoxy)benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepine 5,5-dioxide (25). **25** was synthesized from **37** (747 mg, 3.262 mmol) and 2-(dimethylamino)ethan-1-ol (3.26 mL, 32.62 mmol) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 152 mg (14%); mp: 134–136 °C; Purity: 97%; ^{1}H NMR (DMSO-*d6*) δ 8.92 (d, *J* = 2.4, 1H), 8.68 (d, *J* = 2.1, 1H), 8.21–7.94 (m, 4H), 4.85–4.81 (m, 2H), 3.68 (s, 2H), 2.93 (s, 6H); HRMS (ESI) m/z calcd for $[C_{15}H_{16}N_4O_3S + H]^+$, 333.1016; found, 333.1013.

10-(Dimethylamino)benzo[*f*]pyrazino[2,3-*b*][1,4]thiazepine 5,5-dioxide (26). **26** was synthesized from **37** (747 mg, 3.262 mmol) and dimethylamine (4.12 mL, 32.62 mmol, 40% in H_2O) following the general procedure for chlorination and nucleophilic displacement and oxidation with *m*-CPBA. Yield: 25 mg (3%); mp: 261–263 °C; Purity: 97%; ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 8.1, 1H), 7.77–7.67 (m, 2H), 7.51 (d, *J* = 7.5, 1H), 3.43 (s, 3H), 3.12 (s, 3H); HRMS (ESI) m/z calcd for $[C_{13}H_{12}N_4O_2S + H]^+$, 289.0754; found, 289.0754.

11-(*p*-Tolyl)dibenzo[*b*,*f*][1,4]thiazepine 5,5-dioxide (27). The solution of 1-fluoro-2-nitrobenzene **38** (3.1 g, 22 mmol) in EtOH (100 mL) was added dropwise to a stirred solution of NaOH (1.32 g, 33 mmol) and benzenethiol (2.24 mL, 22 mmol) in H_2O (15 mL) at 15 ^oC. The resulting solution was stirred at reflux for 1 h. The reaction mixture was poured into ice water and acidified with 1 N HCl to pH 2. The precipitate was filtered and purified via recrystallization in toluene/Et_2O to yield (2-nitrophenyl)(phenyl)sulfane. Yield: 2.54 g (50%); mp: 80–81 °C; MS (ESI): m/z 232.2 [M + H^+]. 2-(Phenylthio)aniline **39** was synthesized from (2-nitrophenyl)(phenyl)sulfane (1.113 g, 4.82 mmol) following the general procedure for reduction of nitro. Yield: 840 mg (86%); mp: 43–45 °C; ^{1}H NMR ($CDCl_3$) δ 7.47–7.44 (m, 1H), 7.24–7.19 (m, 3H), 7.14–7.07 (m, 3H), 6.80–6.73 (m, 2H), 4.03 (br, 2H); MS (ESI): m/z 202.1 [M + H^+]. The desired product **27** was synthesized from **39** (602 mg, 3.0 mmol) and 4-methylbenzoic acid (612 mg, 4.5 mmol) following the general procedure for Friedel–Crafts cyclization (Method B) and oxidation with *m*-CPBA. Yield: 250 mg (25%); mp: 222–224 °C; Purity: 99%; ^{1}H NMR ($CDCl_3$) δ 8.15–8.12 (m, 1H), 8.05–8.02 (m, 1H), 7.76–7.73 (m, 2H), 7.68–7.56 (m, 3H),

7.52–7.45 (m, 2H), 7.34–7.27 (m, 3H), 2.44 (s, 3H); HRMS (ESI) m/z calcd for $[C_{20}H_{15}NO_2S + H]^+$, 334.0896; found, 334.0896.

Biological Reagents and Cell Culture. All biological reagents and solvents were obtained from commercial suppliers and used as recommended. Both human NSCLC cell lines H460 and $H460_{TaxR}$ were cultured in RPMI-1640 medium supplemented with fetal bovine serum (10%), penicillin (100 units/mL), and streptomycin (100 mg/mL). The normal human fibroblast cell line NHFB was cultured in DMEM with the same supplements. All cells were maintained in a cell incubator (37 °C, 95% humidity, 5% CO_2).

Cell Viability Assay. Sulforhodamine B assay was performed to determine the cell viability.[14] In brief, 4000 cells were seeded in 100 μL medium each well in 96-well culture plates. After the cells were adherent, they were treated with the compounds or with an equal volume (0.1%) of DMSO for 72 h. The cells were stained using sulforhodamine B and dissolve in Tris solution. The cell viability was calculated using the ratio of its absorbance to control's absorbance. The EC_{50} values were determined using the Sigma Plot 10.0 software package (Systat Software Inc.).

***In Vitro* ADME Assays.** The PAMPA and Caco-2 cell bi-directional transport assay of the derivatives were conducted as described in our previous report.[15,16] The human liver microsome, plasma stability and plasma protein binding assays were conducted following modified protocols reported by Cyprotex[17-20] (Macclesfield, UK).

References

1. Xu, X.; Guo, S.; Dang, Q.; Chen, J.; Bai, X. *ACS Comb. Sci.* **2007,** *9*, 773.

2. Hu, C.; Zheng, L.; Pei, Y.; Bai, X. *Chem. Res. Chin. Univ.* **2013**, *29*, 487.

3. Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889.

4. Wei, Z.; Zheng, L.; Dang, Q.; Bai, X. *J. Heterocyclic Chem.* **2009**, *46*, 1425.

5. Shi, F.; Xu, X.; Zheng, L.; Dang, Q.; Bai, X. *ACS Comb. Sci.* **2008**, *10*, 158.

6. Xiang, J.; Xie, H.; Wen, D.; Dang, Q.; Bai, X. *J. Org. Chem.* **2008**, *73*, 3281.

7. Xiang, J.; Zheng, L.; Xie, H.; Hu, X.; Dang, Q.; Bai, X. *Tetrahedron* **2008**, *64*, 9101.

8. Xiang, J.; Zheng, L.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765.

9. Fu, R.; Xu, X.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 571.

10. Fu, R.; Xu, X.; Dang, Q.; Bai, X. *J. Org. Chem.* **2005**, *70*, 10810.

11. Che, X.; Zheng, L.; Dang, Q.; Bai, X. *J. Org. Chem.* **2008**, *73*, 1147.

12. Liégeois, J.-F. F.; Rogister, F. A.; Bruhwyler, J.; Damas, J.; Nguyen, T. P.; Inarejos, M.-O.; Chleide, E. M. G.; Mercier, M. G. A.; Delarge, J. E. *J. Med. Chem.* **1994**, *37*, 519.

13. Kamigata, N.; Iizuka, H.; Kobayashi, M. *Bull. Chem. Soc. Jap.* **1986**, *59*, 1601.

14. Vichai, V.; Kirtikara, K. *Nat. Protoc.* **2006,** 1, 1112.

15. Liu, Y.; Li, F.; Wu, L.; Wang, W.; Zhu, H.; Zhang, Q.; Zhou, H.; Yan, B. *Bioorg. Med. Chem. Lett.* **2015,** *25*, 1971.

16. Zhai, S.; Yang, L.; Cui, Q. C.; Sun, Y.; Dou, Q. P.; Yan, B. *J. Biol. Inorg. Chem.* **2010,** *15*, 259.

17. Obach, R. S. *Drug Metab. Dispos.* **1999,** *27*, 1350.

18. Kariv, I.; Cao, H.; Oldenburg, K. R. *J. Pharm. Sci.* **2001,** *90*, 580.

19. McGinnity, D. F.; Soars, M. G.; Urbanowicz, R. A.; Riley, R. J. *Drug Metab. Dispos.* **2004,** *32*, 1247.

20. Di, L.; Kerns, E. H.; Hong, Y.; Chen, H. *Int. J. Pharm.* **2005,** *297*, 110.

Spectra:

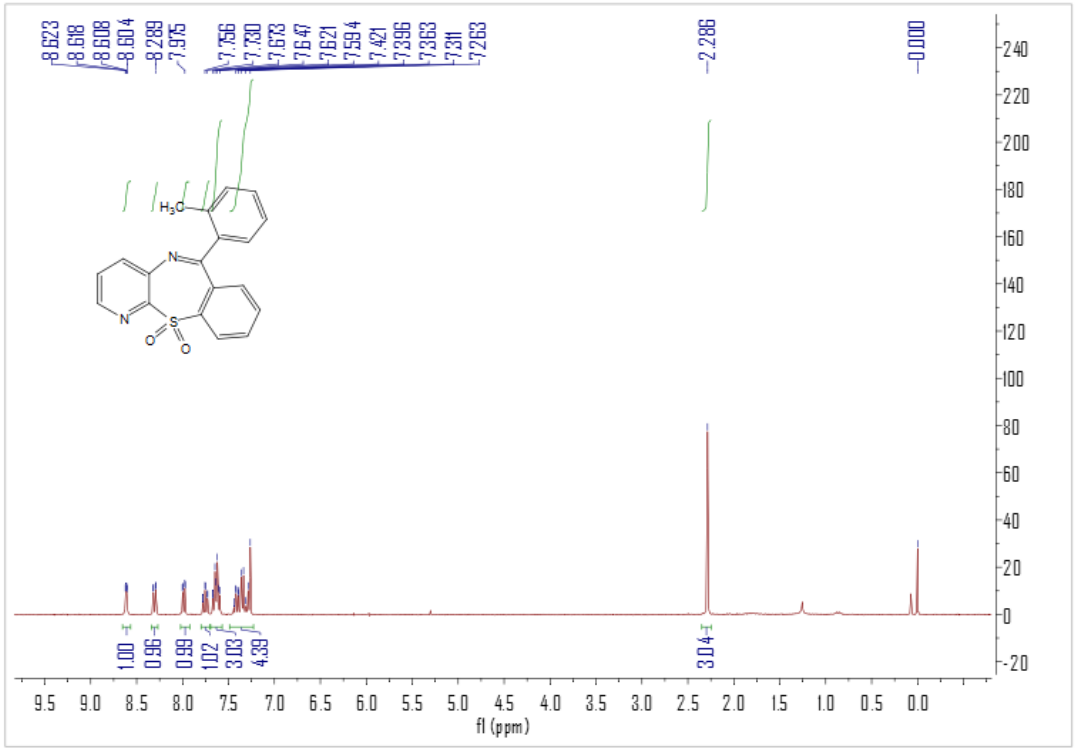


Fig. S-1: ^{1}H Spectra of compound **3**

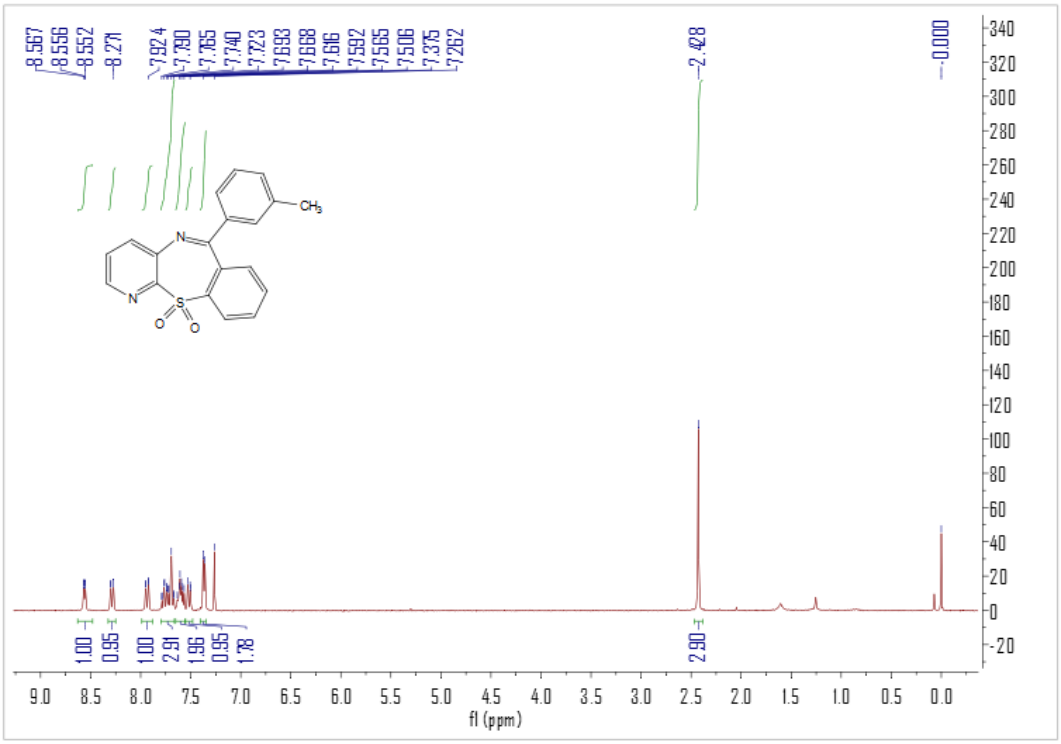


Fig. S-2: ^{1}H Spectra of compound **4**

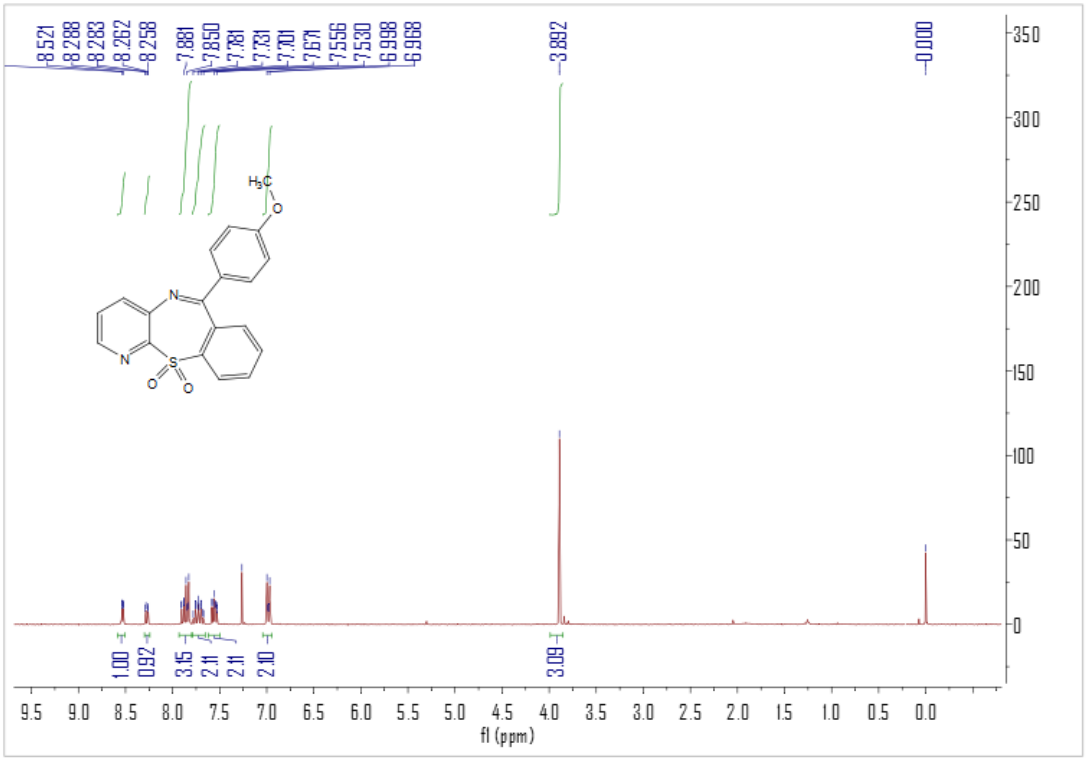


Fig. S-3: ^{1}H Spectra of compound **5**

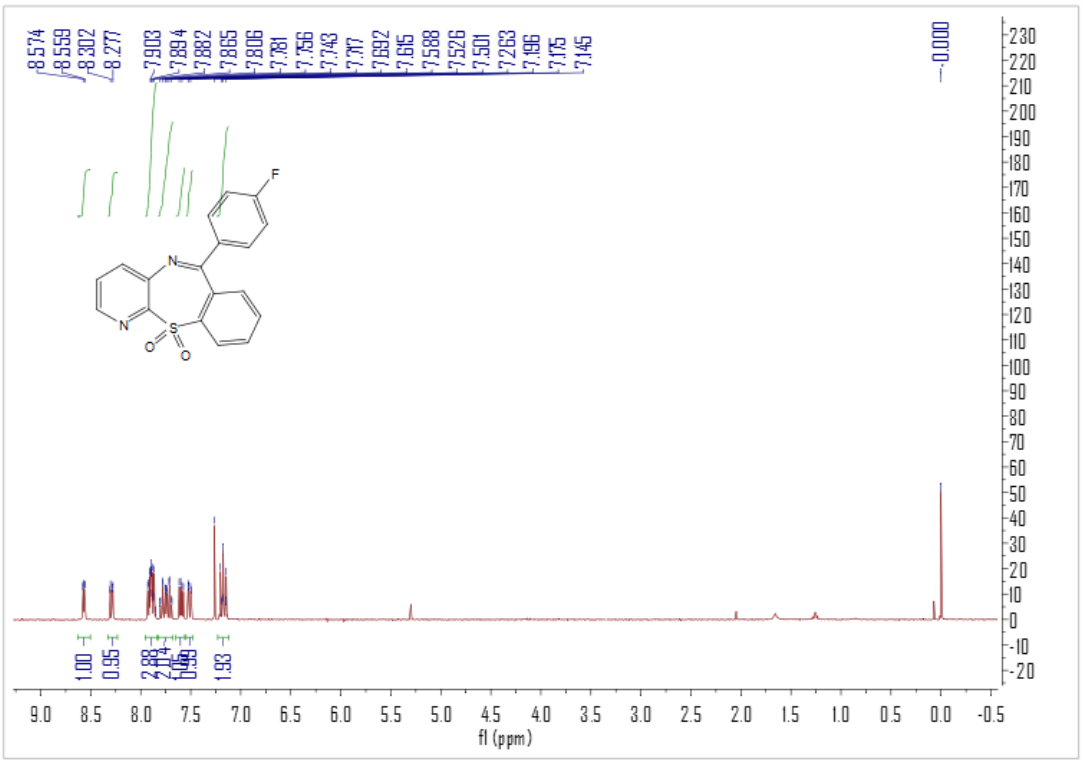


Fig. S-4: ^{1}H Spectra of compound **6**

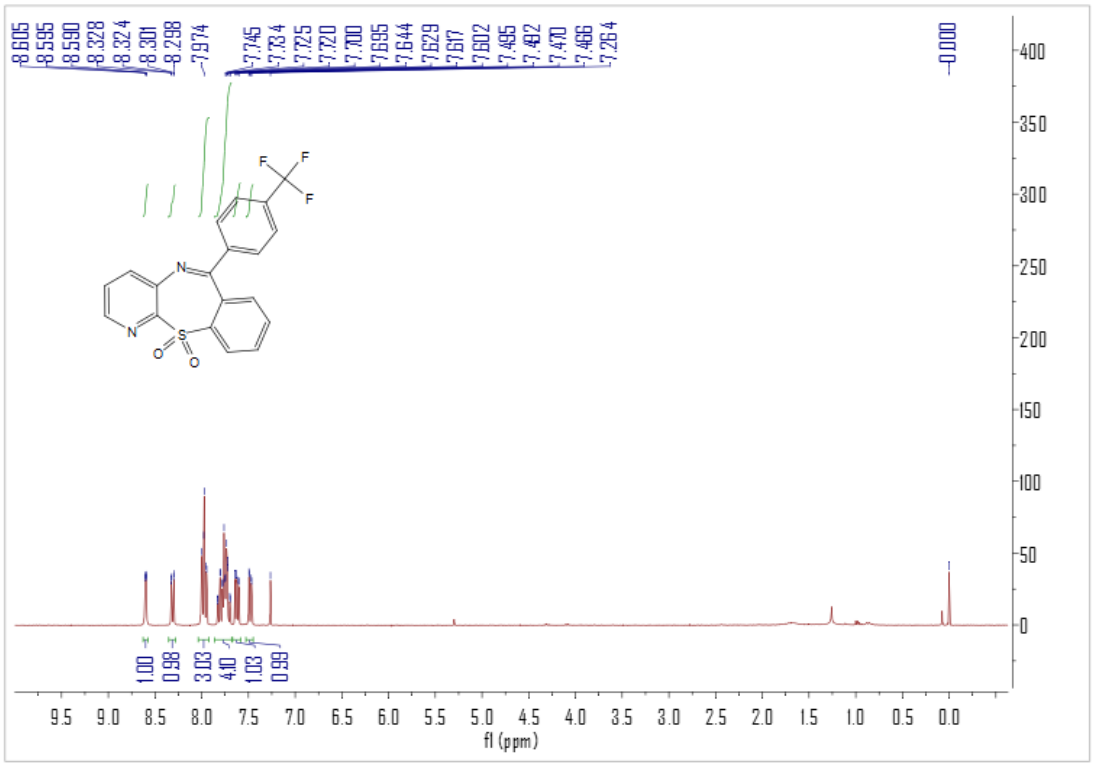


Fig. S-5: ^{1}H Spectra of compound **7**

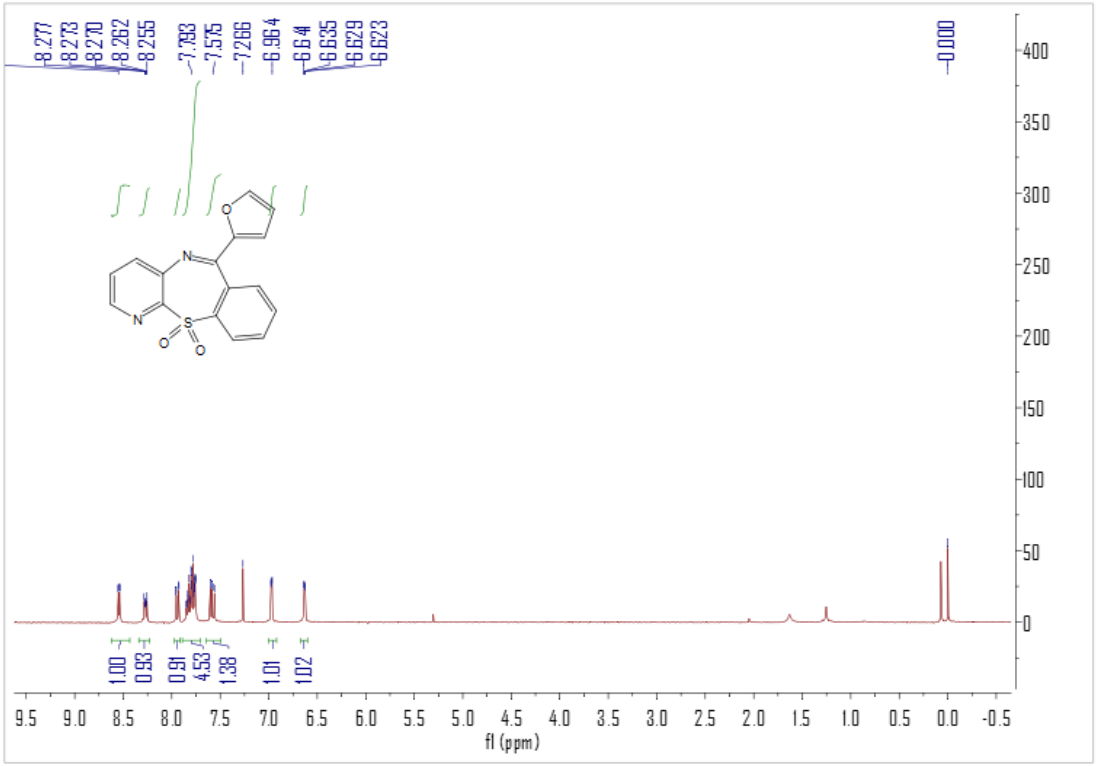


Fig. S-6: ^{1}H Spectra of compound **8**

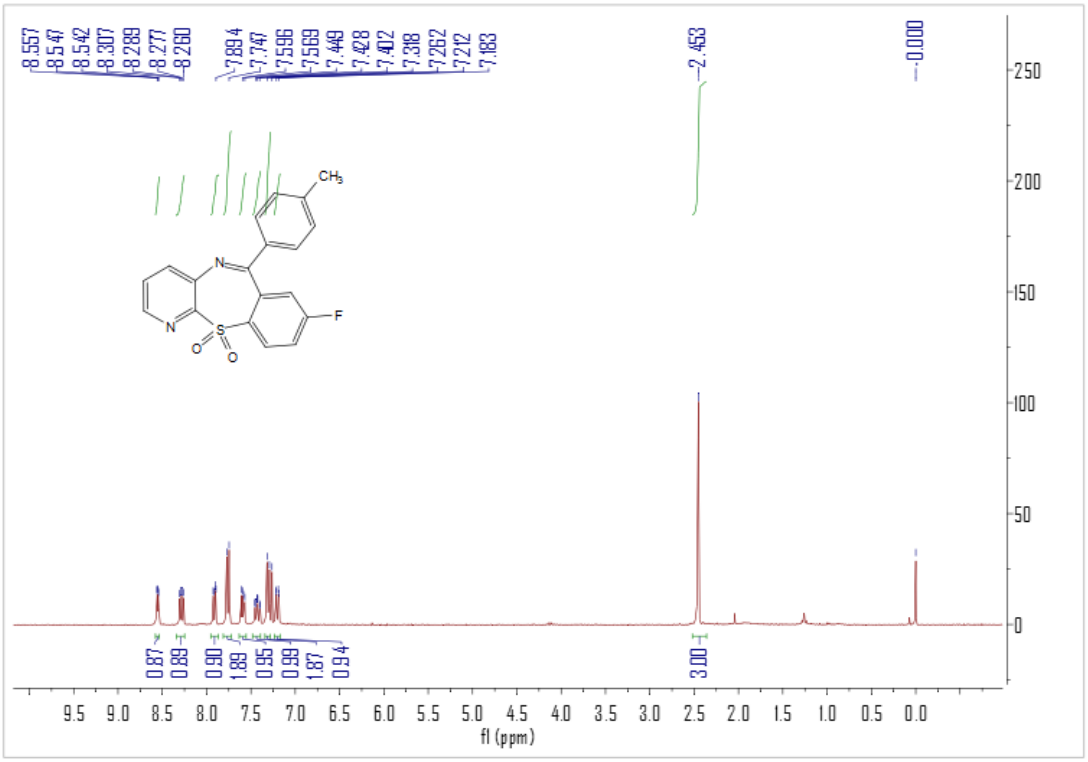


Fig. S-7: ^{1}H Spectra of compound **9**

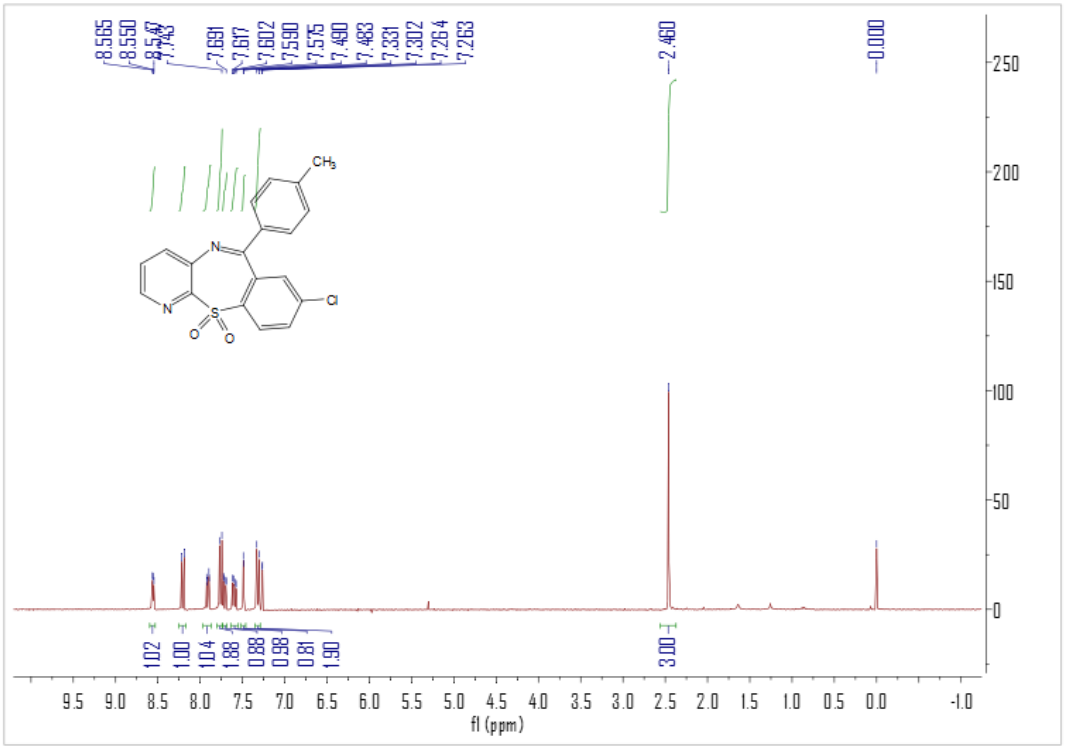


Fig. S-8: ^{1}H Spectra of compound **10**

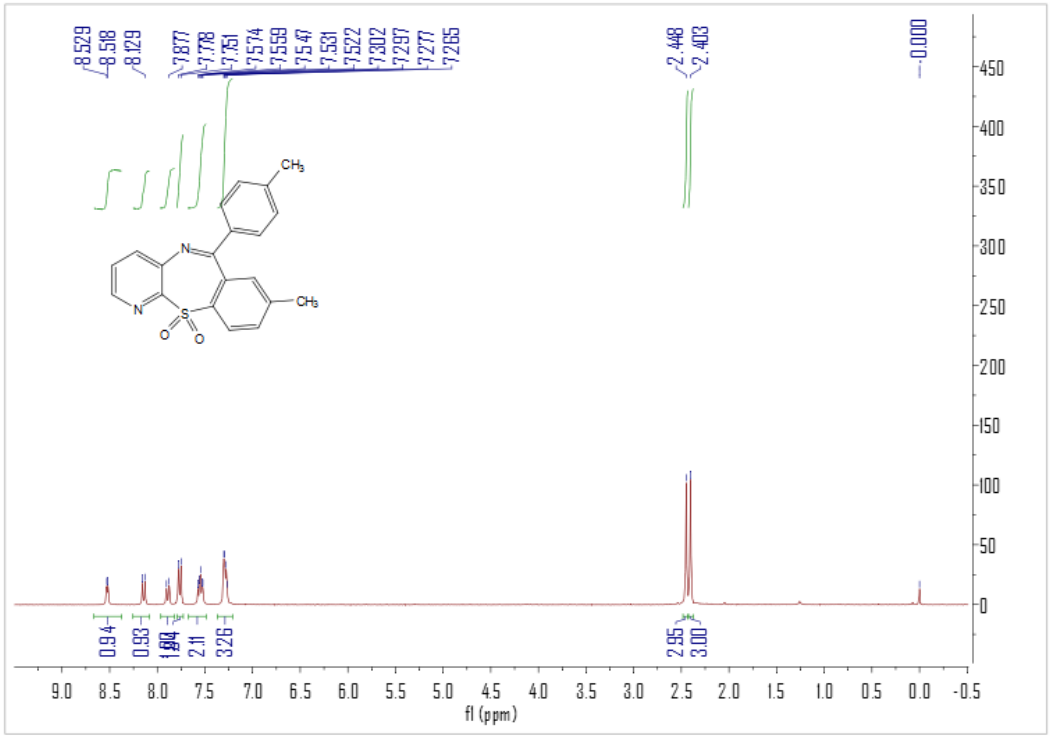


Fig. S-9: ^{1}H Spectra of compound **11**

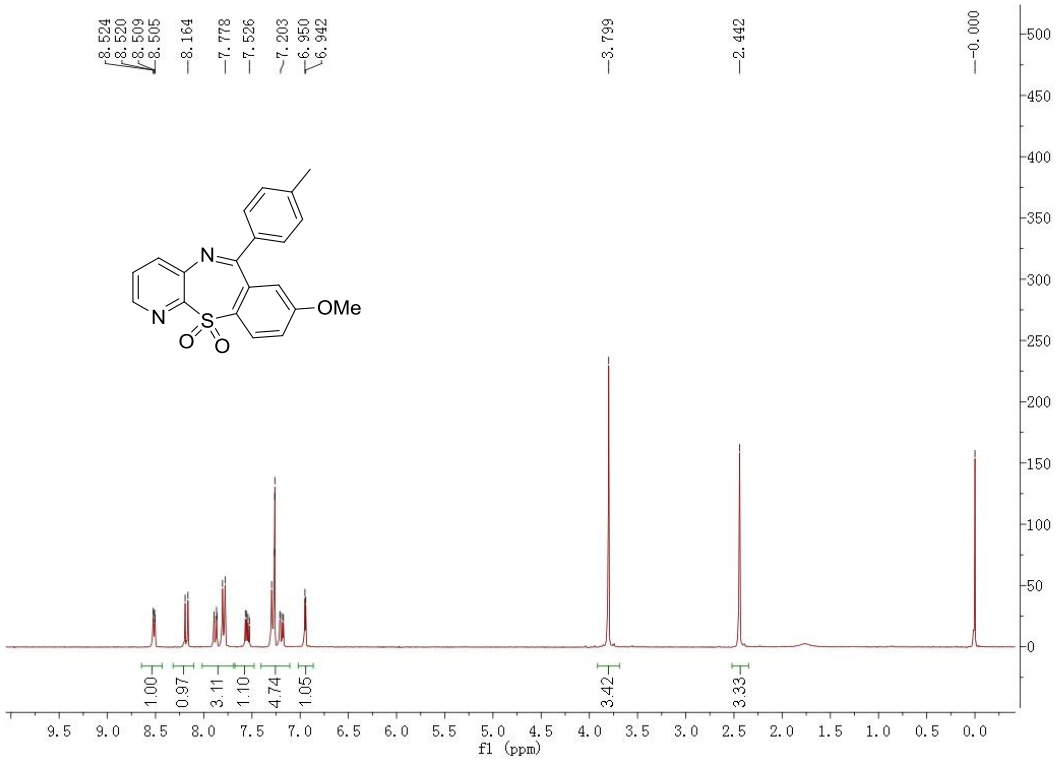


Fig. S-10: ^{1}H Spectra of compound **12**

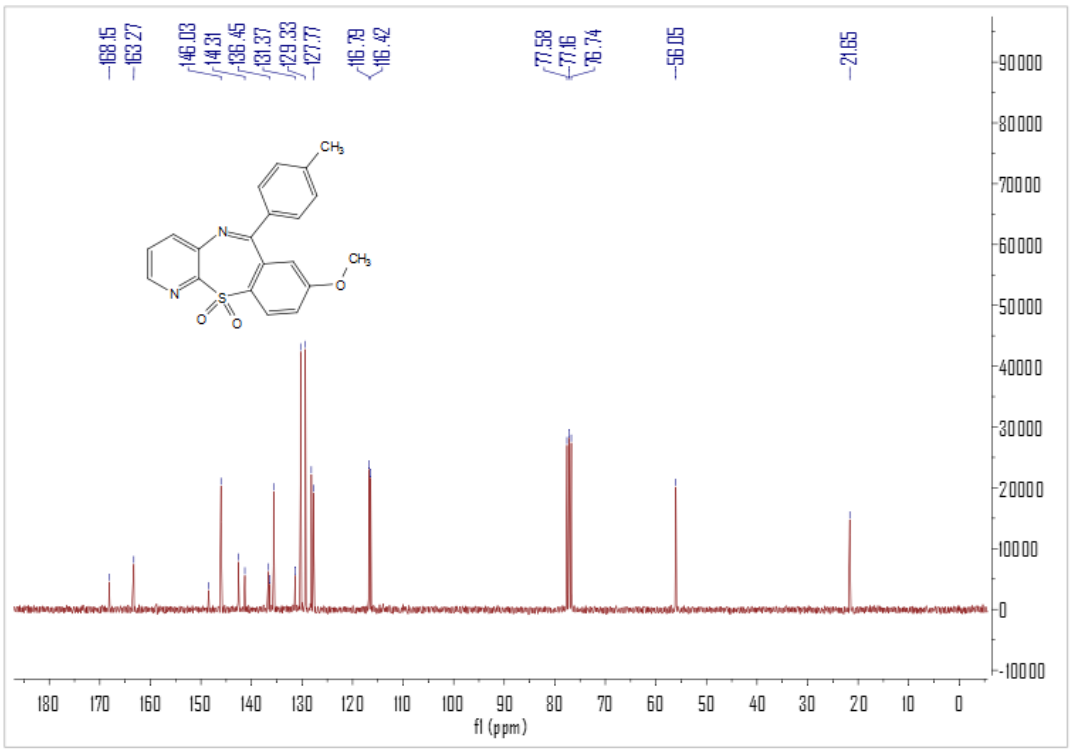


Fig. S-11: ^{13}C Spectra of compound **12**

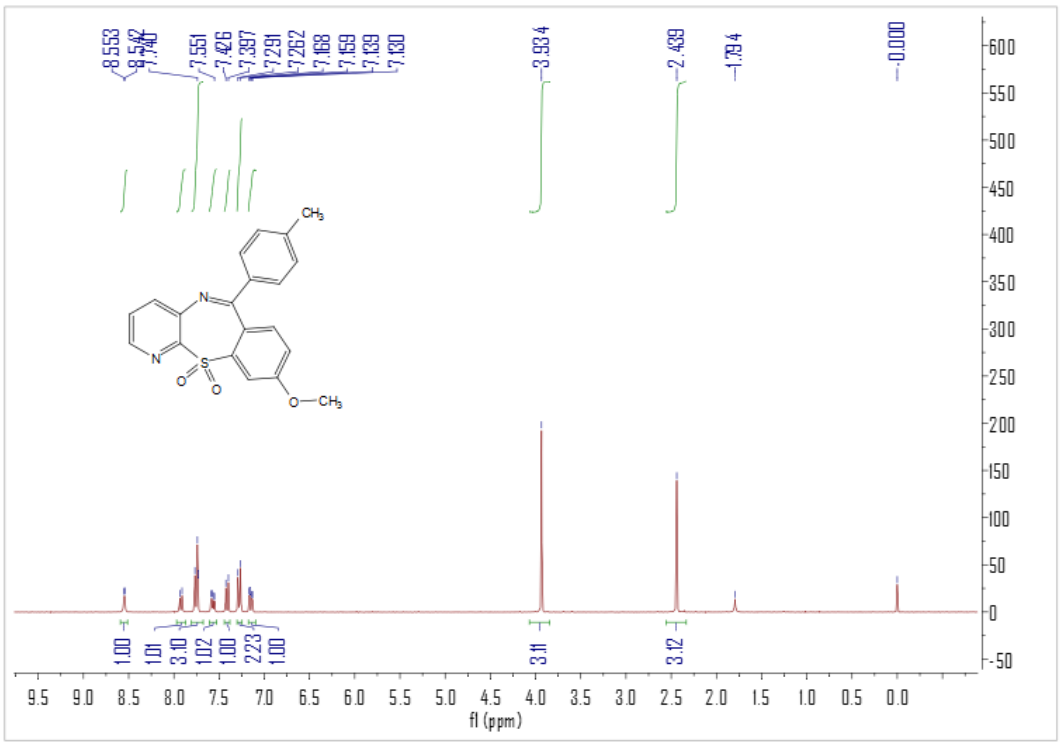


Fig. S-12: ^{1}H Spectra of compound **13**

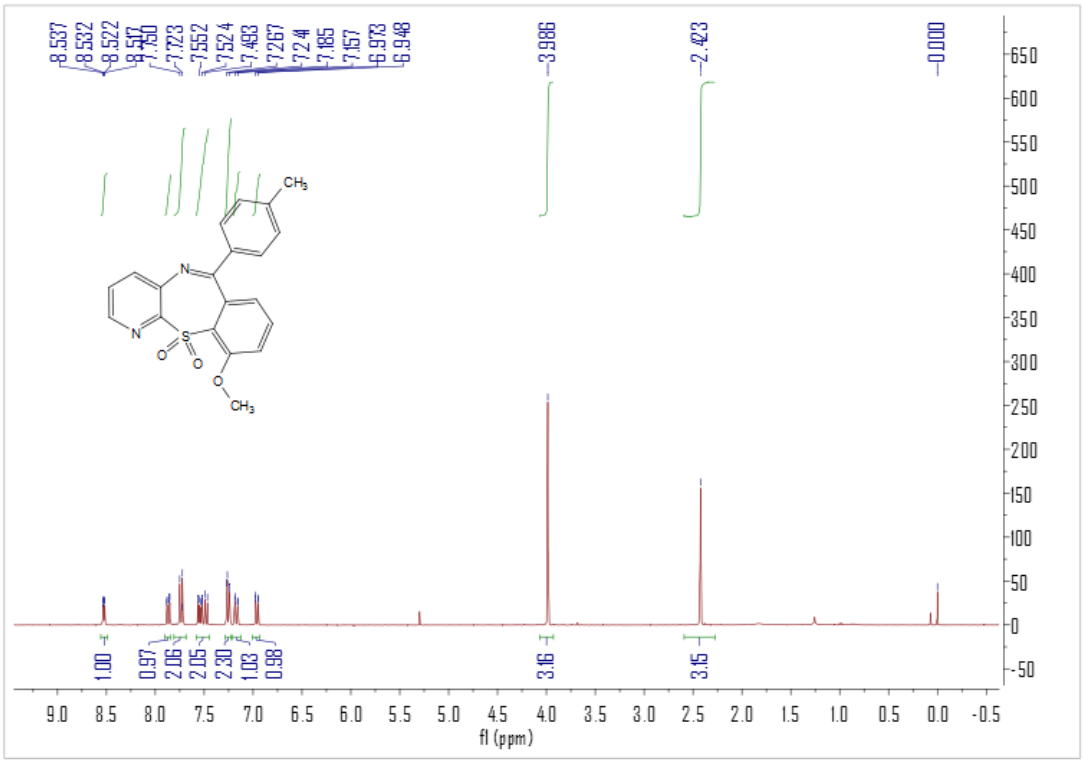


Fig. S-13: ^{1}H Spectra of compound **14**

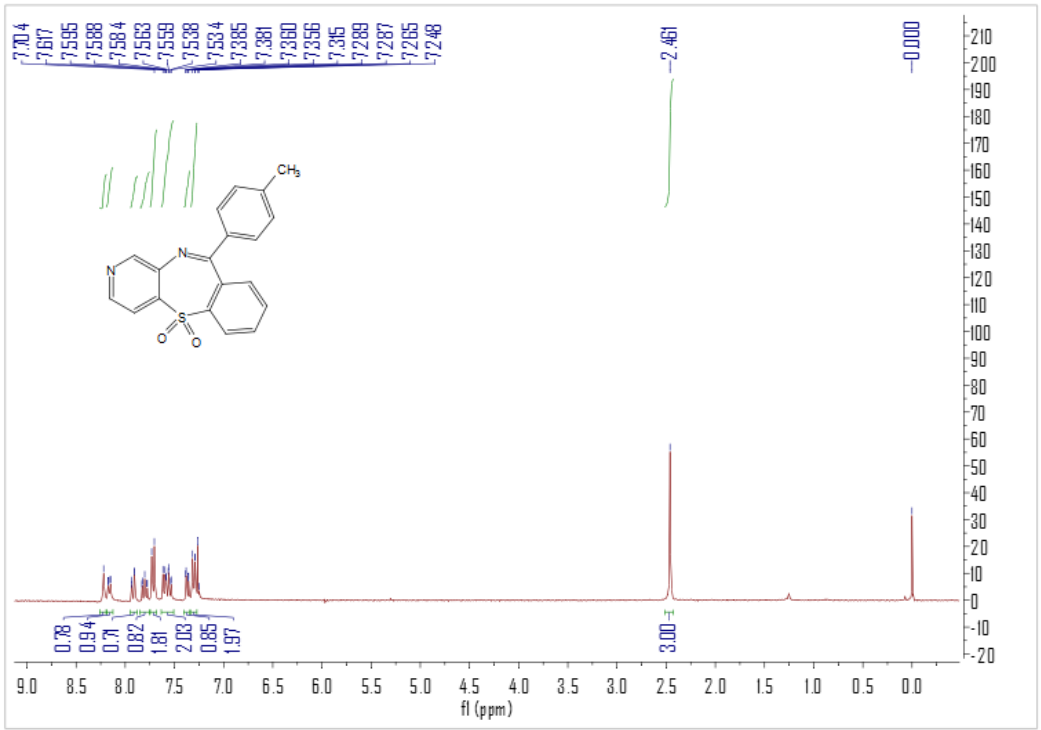


Fig. S-14: ^{1}H Spectra of compound **15**

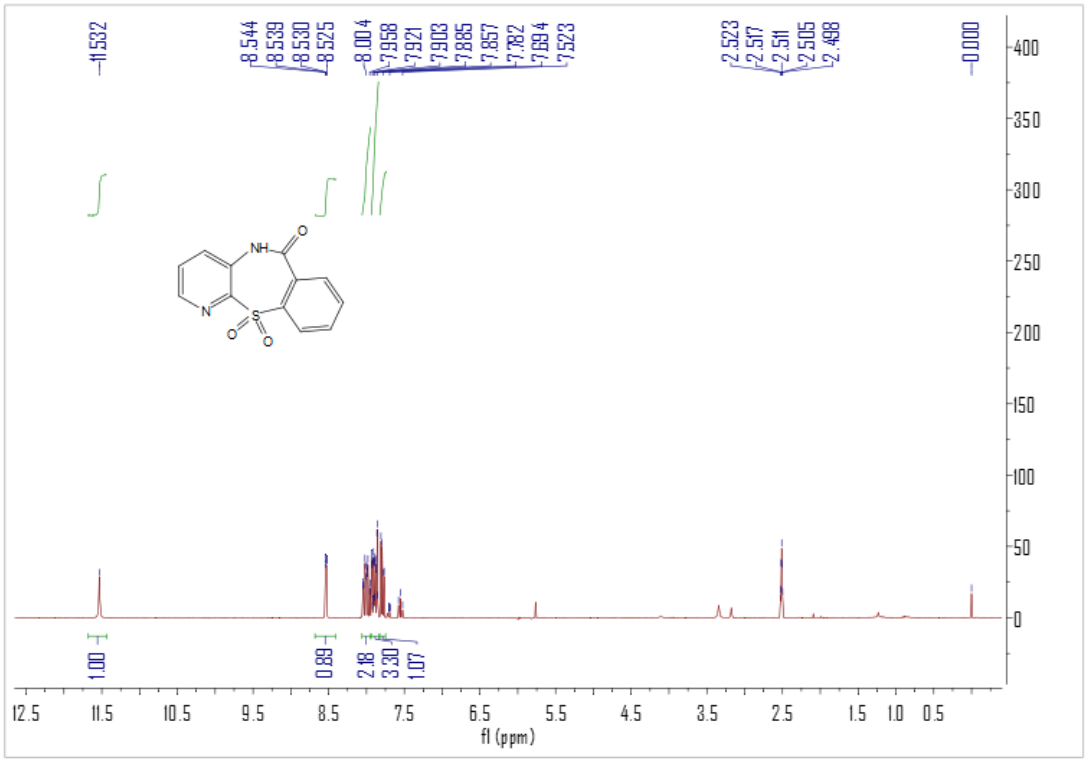


Fig. S-15: ^{1}H Spectra of compound **16**

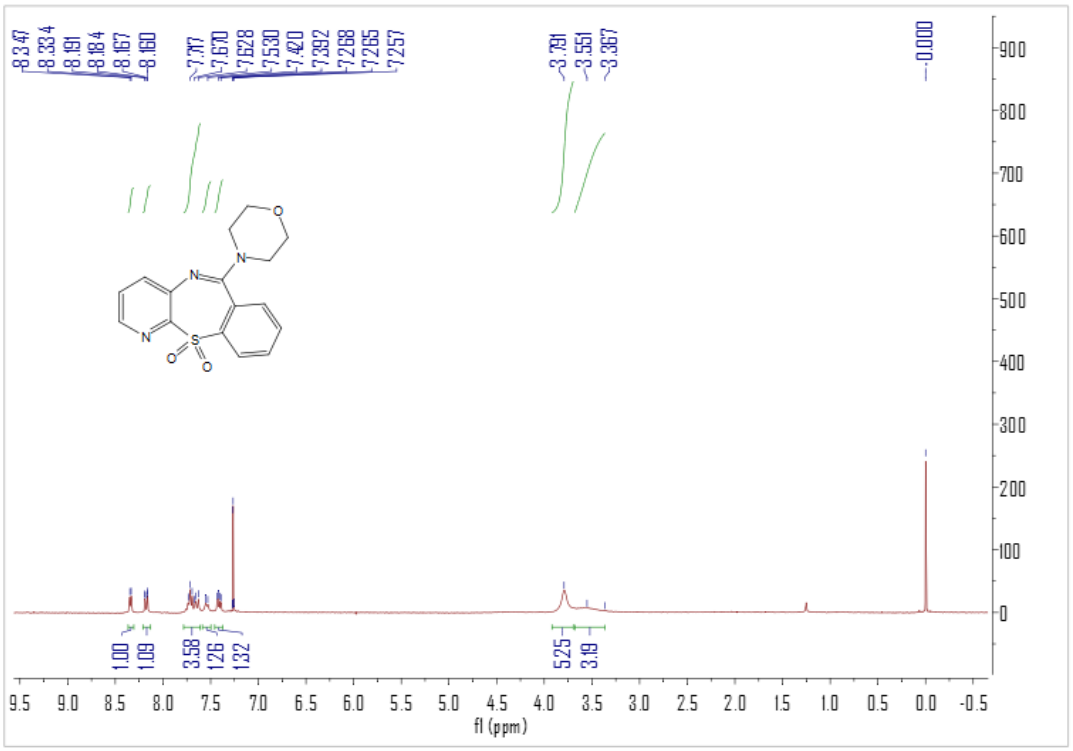


Fig. S-16: ^{1}H Spectra of compound **17**

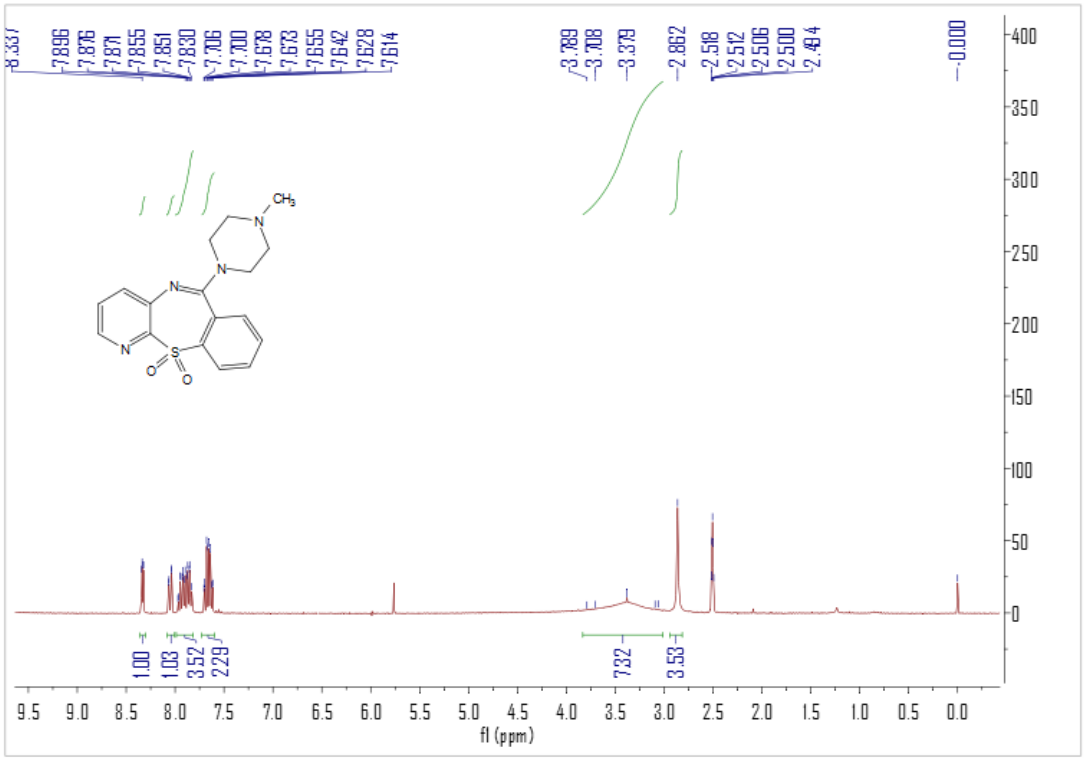


Fig. S-17: ^{1}H Spectra of compound **18**

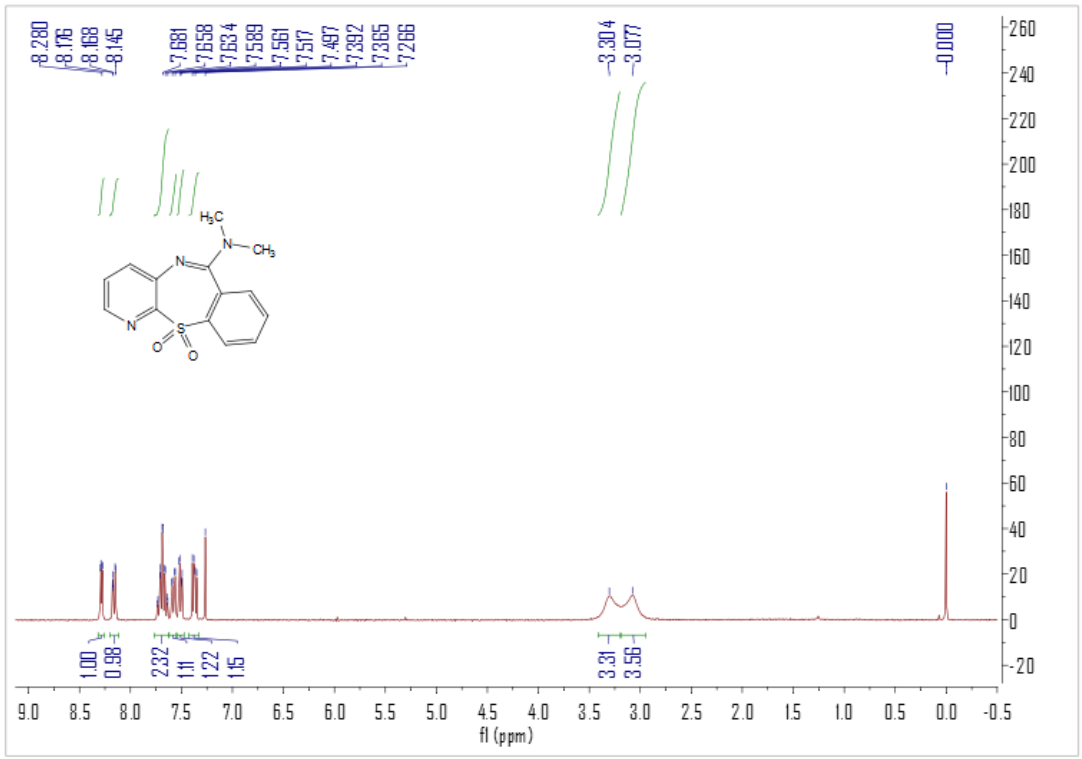


Fig. S-18: ^{1}H Spectra of compound **19**

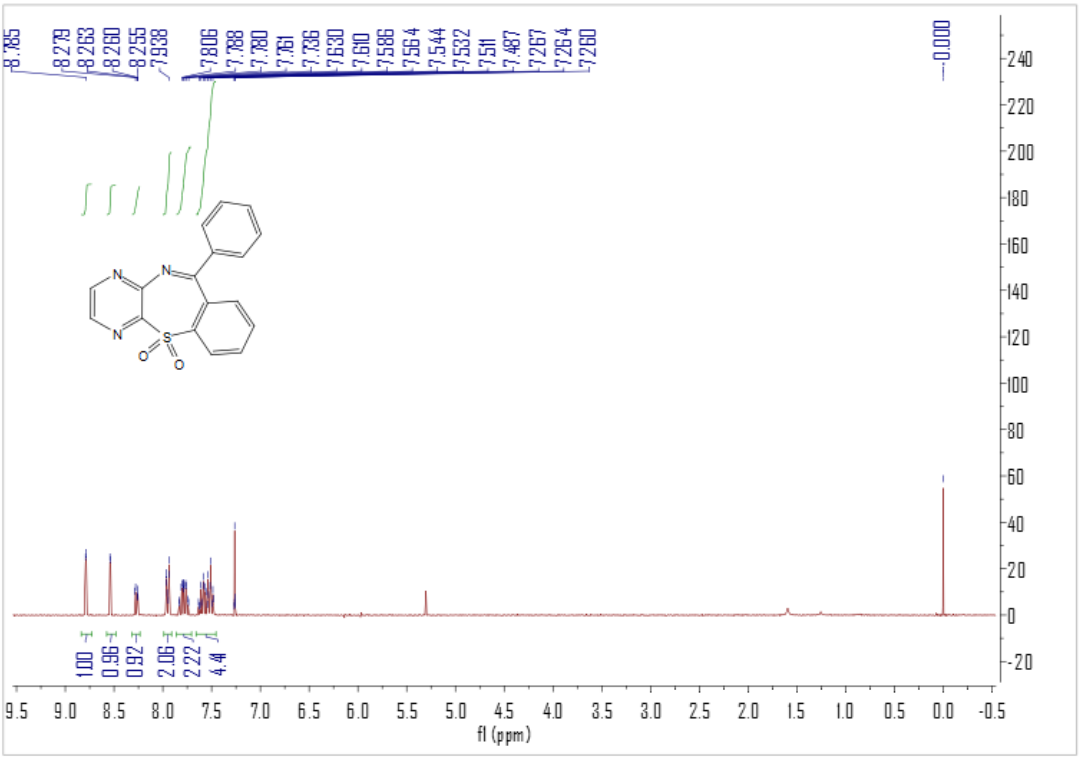


Fig. S-19: ^{1}H Spectra of compound **20**

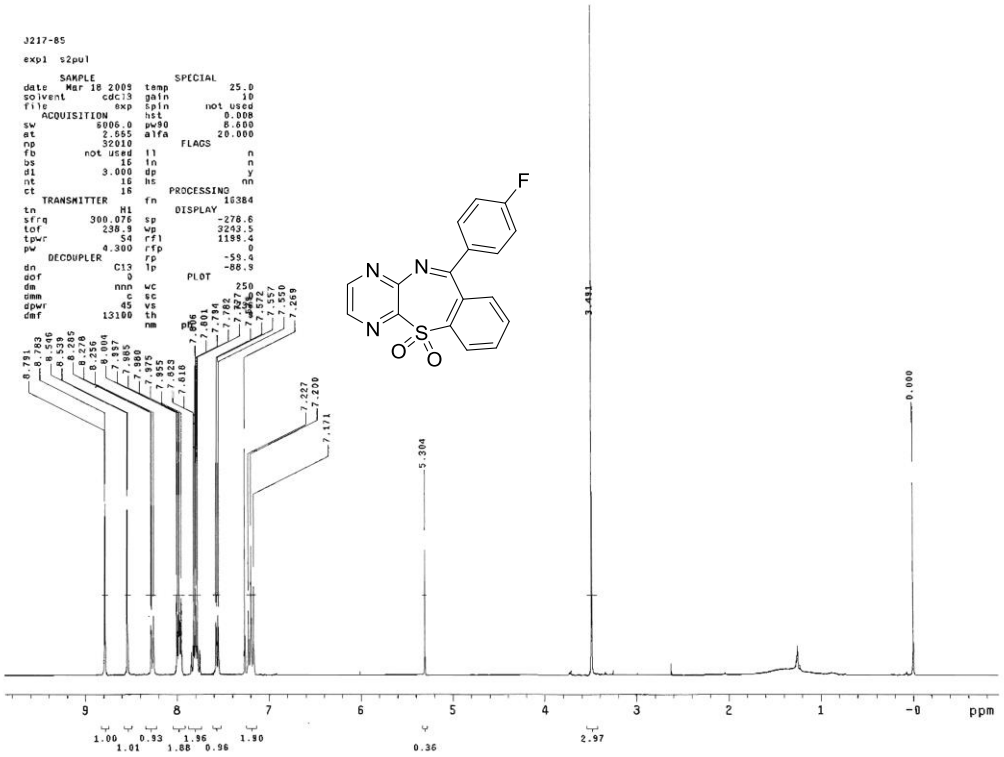


Fig. S-20: ^{1}H Spectra of compound **21**

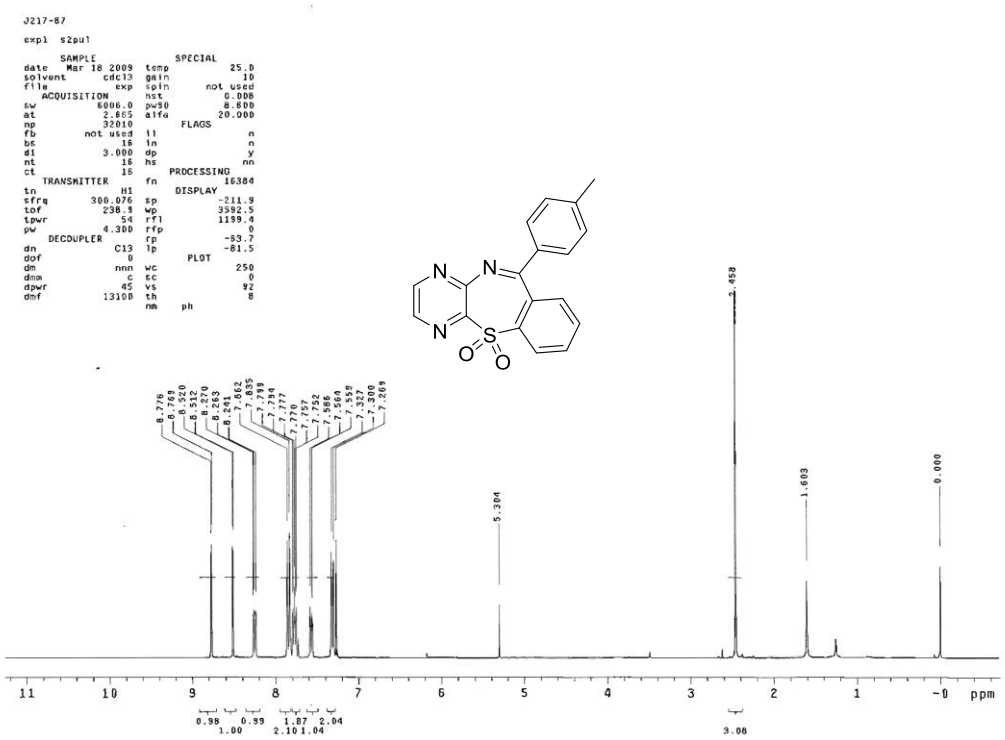


Fig. S-21: ^{1}H Spectra of compound **22**

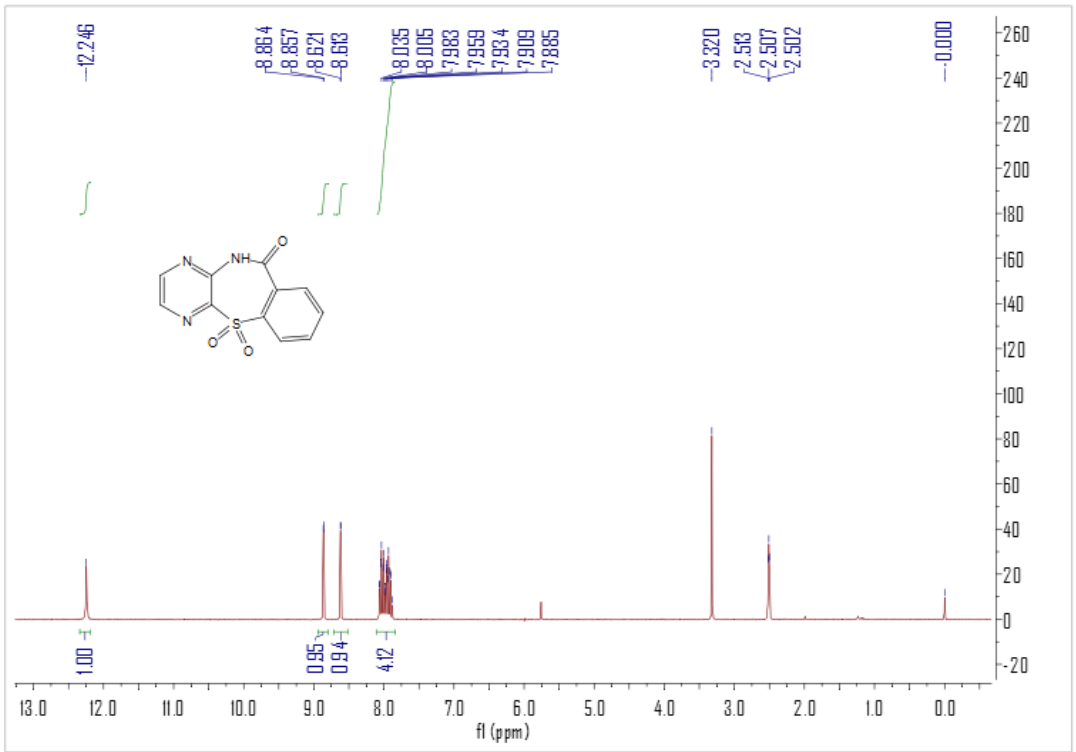


Fig. S-22: ^{1}H Spectra of compound **23**

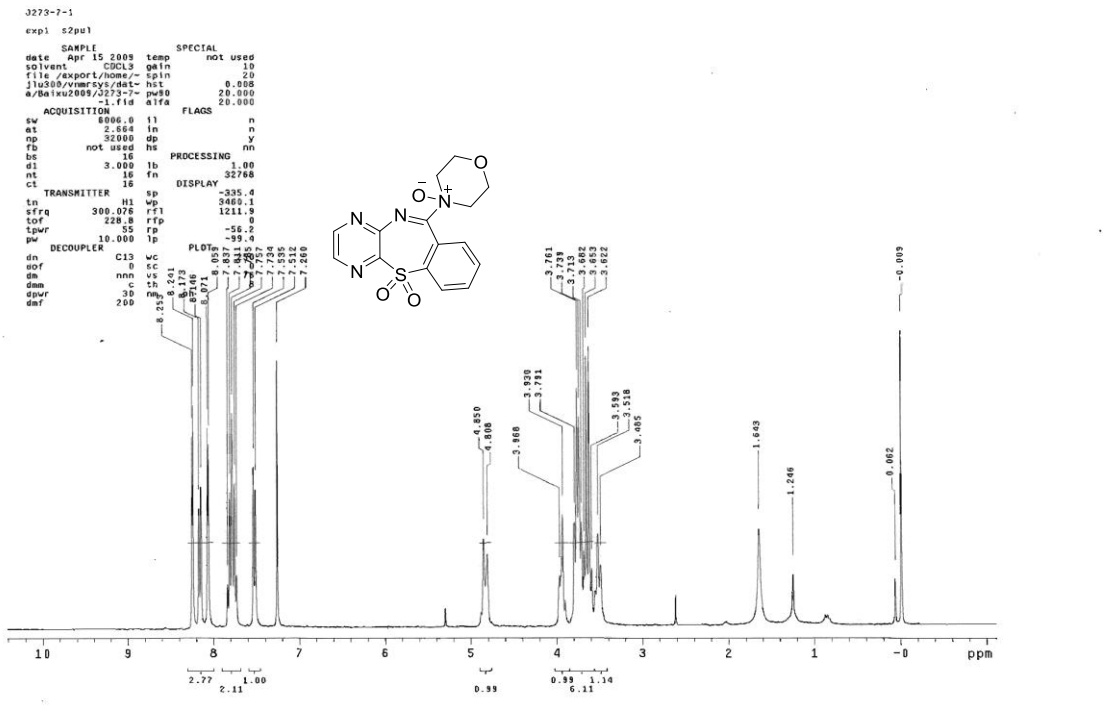


Fig. S-23: ^{1}H Spectra of compound **24**

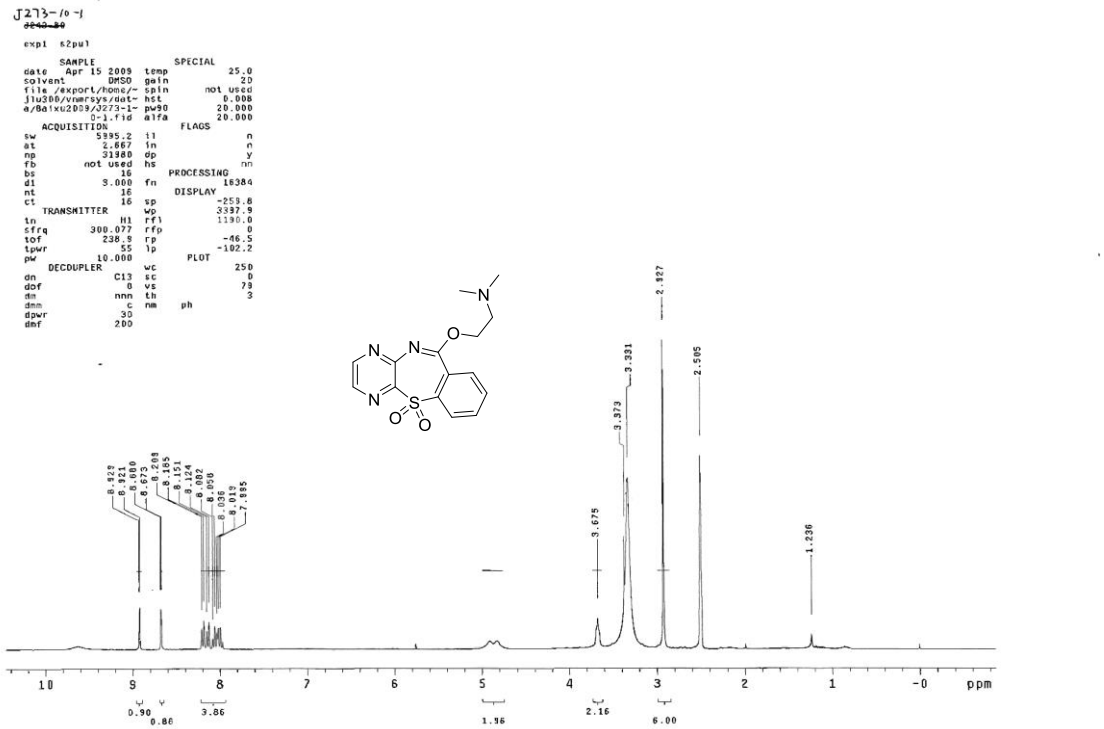


Fig. S-24: ^{1}H Spectra of compound **25**

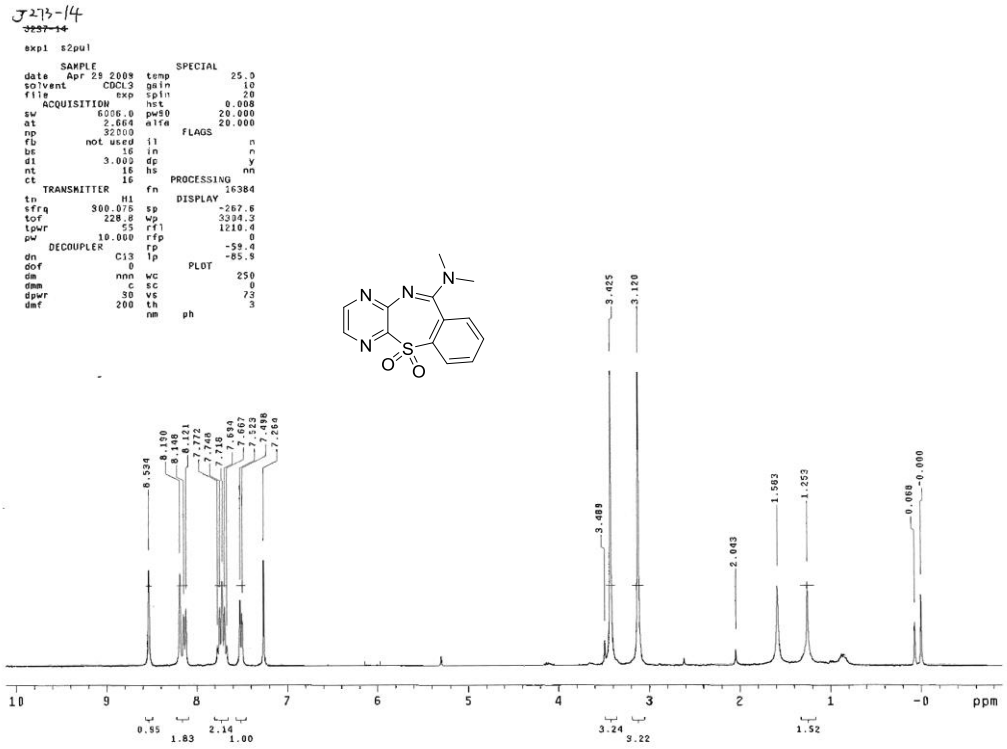


Fig. S-25: ^{1}H Spectra of compound **26**

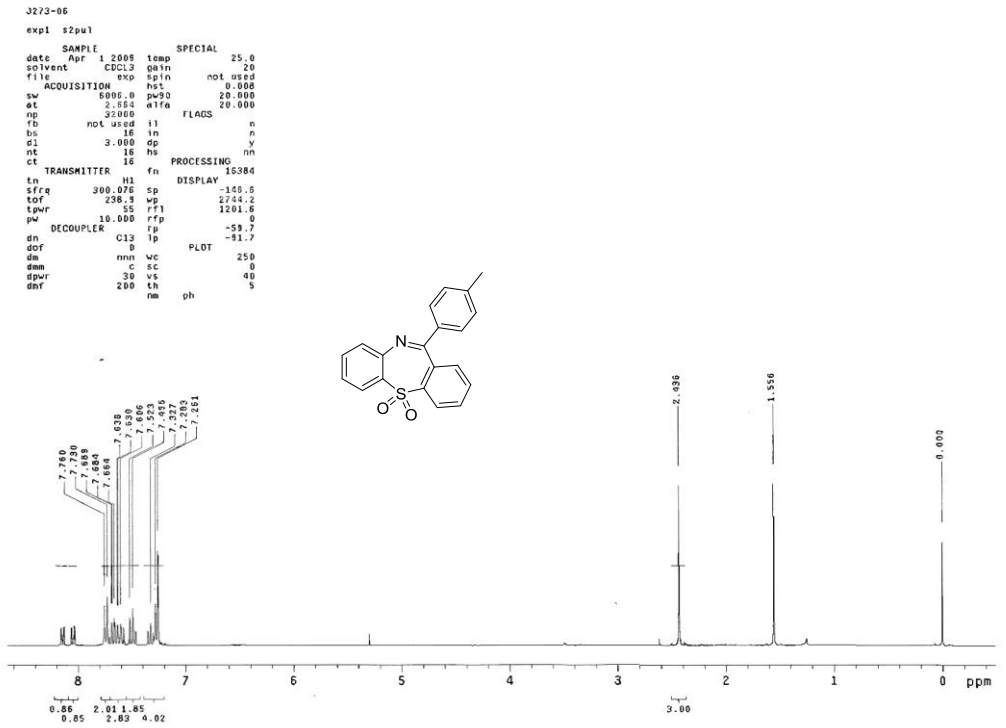


Fig. S-26: ^{1}H Spectra of compound **27**