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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY EVALUATION OF 2-MERCAPTO-4(*3H*)-QUINAZOLINONE DERIVATIVES AS NOVEL INHIBITORS OF PROTEIN TYROSINE PHOSPHATASE 1B

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Abstract – A series of novel 2-mercapto-4(*3H*)-quinazolinone derivatives have been synthesized and their inhibitory effects on PTP1B and TCPTP are evaluated for the first time. Most of these derivatives showed good inhibitory activity on PTP1B and reasonable selectivity for PTP1B over TCPTP, among them **32** was the most potent PTP1B inhibitor (IC_{50} = 1.50 μg/mL), and **27** possessed the best selectivity of 3.0-fold.

INTRODUCTION

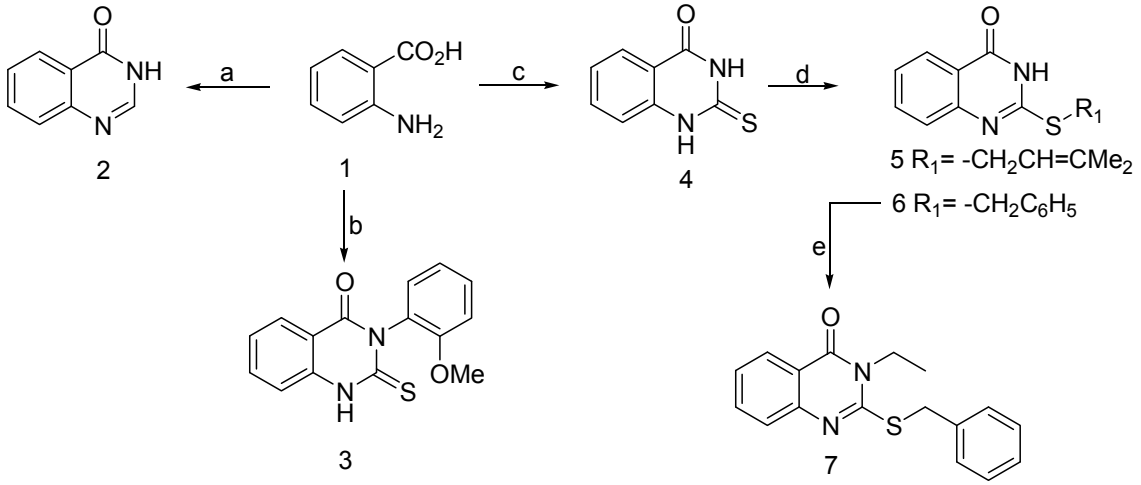
Protein tyrosine phosphatases (PTPs) form a superfamily containing more than 100 members,[1] which are expressed in insulin sensitive tissues and play a regulatory role in insulin signaling pathway.[2,3] Malfunctions in PTP activity lead to aberrant tyrosine phosphorylation which causes various diseases, such as diabetes, obesity, cancer, inflammation and neurodegenerative diseases.[4-7] Protein tyrosine phosphatase 1B (PTP1B), one of the PTPs, has been implicated as a key negative regulator of the insulin and the leptin signaling pathway respectively by dephosphorylating the phosphotyrosine (*p*Tyr) residues on the insulin receptor (IR), [8] insulin receptor substrates (IRS)[9] and Janus kinase 2 (JAK2),[10,11] which is

downstream of leptin receptor. PTP1B deficient mice display more sensitive to insulin and resistant to diet induced obesity.[12,13] Thereby, inhibition of PTP1B enhances sensitivity to insulin and resistance to obesity.[14] PTP1B inhibitors represent potential and attractive therapeutic agents for treating type II diabetes and obesity.[15-17] Numerous PTP1B inhibitors have been developed recently as candidates for anti-diabetes and anti-obesity.[17-21] However, most of them have not been successfully applied in clinical trials due to the poor bioavailability and low selectivity for PTP1B over the most homogeneous T-Cell protein tyrosine phosphatase (TCPTP).[22-24] Therefore it is quite worthwhile to find novel PTP1B inhibitors for the development of antidiabetic drugs.

Quinazolinone derivatives have showed various pharmacological and biological properties, such as antimicrobial,[25,26] anticonvulsant,[27] sedative,[28] antidepressant,[29] anti-inflammatory,[29,30] antimalarial[31] and diuretic,[32] Histamine H_3 Receptor Inverse Agonists[33] as well as cholecystokinin inhibitor.[34,35] Herein, we disclosed for the first time the inhibitory activities on PTP1B of a series of 2-mercapto-4(*3H*)-quinazolinone derivatives.

RESULTS AND DISCUSSION

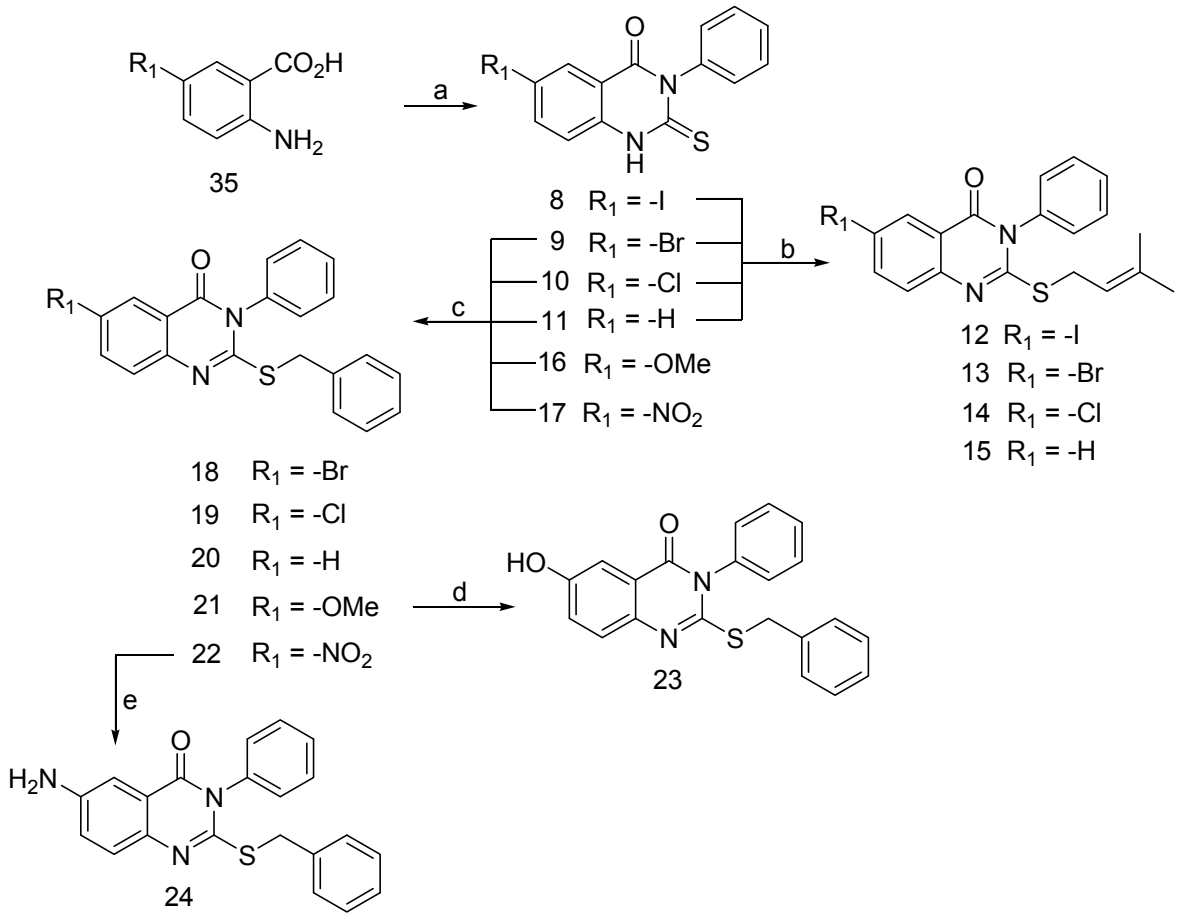
1. Chemistry. The synthetic method of compound **2** is based on classical procedure, which involves the fusion of 2-aminobenzoic acid with formamide.[36] 2-Methoxyphenyl isothiocyanate reacted with 2-aminobenzoic acid in EtOH to give **3**.[37,38] 2-Aminobenzoic acid was refluxed in the presence of $SOCl_2$, then reacted with NH_4SCN to afford the intermediate **4**. Compounds **5** and **6** were produced by reaction of **4** with prenyl bromide or benzyl bromide respectively in EtOH. Compound **6** reacted with EtI to afford 2, 3-disubstituted-2-mercapto-4(*3H*)-quinazolinone derivative **7**[39] as shown in Scheme 1.



Scheme 1

a) $HCONH_2$, reflux, 3 h, 65%. b) 2-methoxyphenyl isothiocyanate, EtOH, reflux, 5 h, 66%. c) $SOCl_2$, reflux, 2 h, then NH_4SCN, rt, 0.5 h. d) KOH, EtOH, prenyl bromide or benzyl bromide, rt, 2 h, 72% for **5**, 78% for **6.** e) KOH, DMF, EtI, rt, 2 h, 90% for **7**.

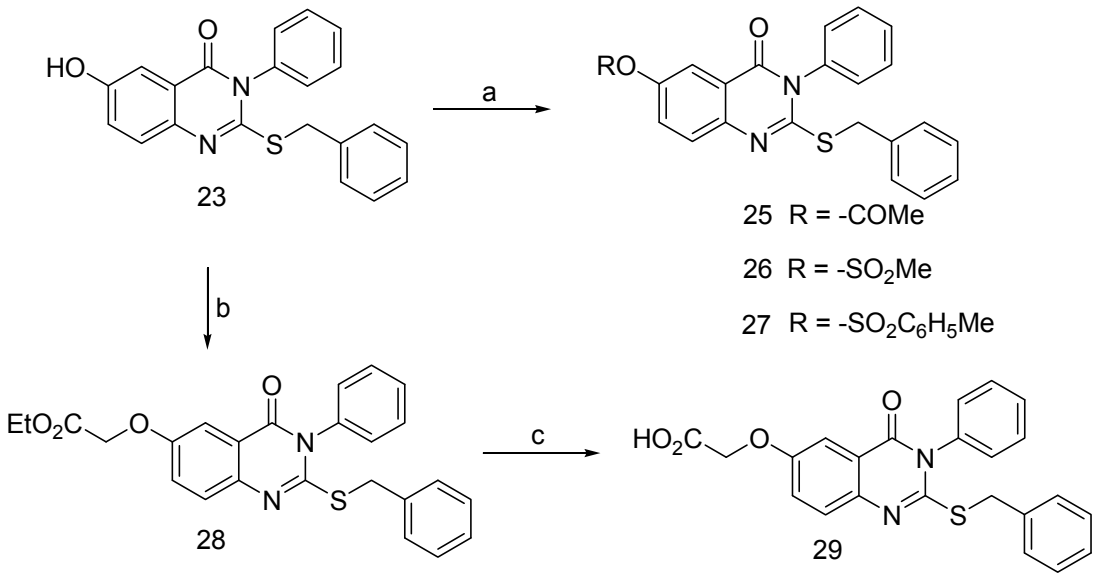
Compounds **8**, **9**, **10**, **11, 16** and **17** were obtained by the reaction of phenyl isothiocyanate with 2-aminobenzoic acid or 4-substituted 2-aminobenzoic acid derivatives, respectively, in refluxing EtOH. Prenyl bromide reacted with **8**, **9**, **10** and **11** respectively in the presence of KOH to produce **12**, **13**, **14** and **15**. Compounds **18**, **19**, **20**, **21** and **22** were generated by the reaction of benzyl bromide with 2,3-dihydro-3-phenyl-2-thioxoquinazolin-4(*1H*)-one derivatives respectively.[39] Compound **23** was afforded by demethylation of C-6 methyl ether of **21** with boron tribromide in DCM. Compound **24** was prepared by reduction of C-6 nitro group of **22** with zinc powder, as shown in Scheme 2.



Scheme 2

a) phenyl isothiocyanate, EtOH, reflux, 5 h. b) KOH, EtOH, prenyl bromide, rt, 2 h, 76% for **12**, 80% for **13**, 68% for **14**, 83% for **15**. c) KOH, EtOH, benzyl bromide, rt, 2 h, 67% for **18**, 62% for **19**, 67% for **20**, 65% for **21**, 60% for **22**. d) BBr_3, DCM, -50 ℃-rt, 10 h, 96%. e) Zn, NH_4Cl, MeOH/THF/H_2O, reflux, 2 h, 80%.

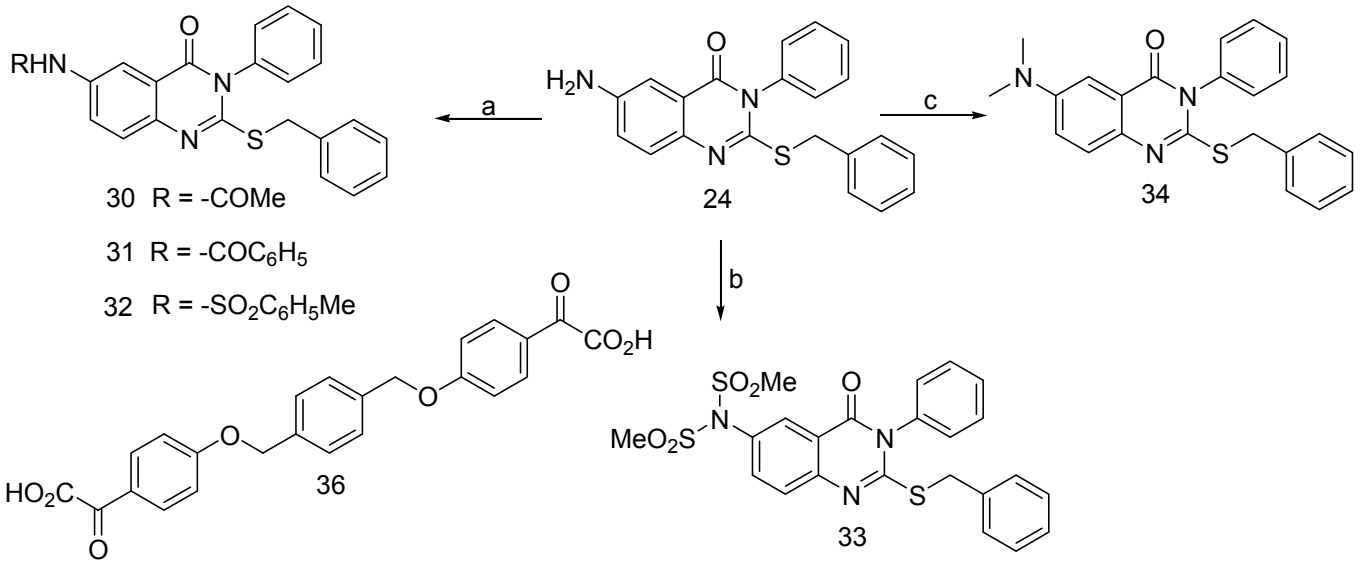
Compound **23** reacted with Ac_2O, MsCl or TsCl respectively in the presence of TEA to give **25**, **26** and **27**. Compound **28** was synthesized by the reaction of ethyl bromoacetate with **23** in the presence of K_2CO_3 in DMF. Compound **29** was generated by hydrolysis of **28** with LiOH in MeOH as shown in Scheme 3.



Scheme 3

a) Ac_2O, MsCl or TsCl, DCM, Et_3N, rt, 10 h, 68% for **25,** 57% for **26** and 56% for **27**. b) K_2CO_3, $BrCH_2CO_2CH_2CH_3$, DMF, rt, 1 h, 62% for **28**. c) LiOH, MeOH, rt, 5 h, 73% for **29.**

Acylation and sulfonylation of **24** with AcCl, BzCl or TsCl, respectively, afforded **30**, **31** and **32**. Compound **33** was obtained by reaction of **24** with MsCl. Compound **34** was prepared by deprotonation of **24** with NaH, then reacted with MeI in DMF, as shown in Scheme 4.



Scheme 4

a) AcCl, BzCl or TsCl, pyridine, rt, 10 h, 76% for **30**, 96% for **31,** 72% for **32**. b) MsCl, DCM, Et_3N, rt, 10 h, 64% for **33**. c) NaH, DMF, MeI, rt, 14 h, 78% for **34**.

2. In vitro biological evaluation. In this paper, we designed and synthesized a series of 2-mercapto-4(*3H*)-quinazolinone derivatives. All these compounds were evaluated in the enzyme

inhibition assay against PTP1B by the method of *p*-nitrophenyl phosphate using compound **36** as a reference compound (Table 1).[40] Homogeneous TCPTP inhibitory activities were investigated simultaneously by the same method for further selectivity study (Table 2).

Table 1. Inhibitory activity of 2-mercapto-4(*3H*)-quinazolinone derivatives on PTP1B

Compounds	IC_{50} (μM)	Compounds	IC_{50} (μM)
2	>60	23	21.28 ± 1.55
3	>60	24	22.73 ± 1.00
5	>60	25	29.34 ±1.74
6	>60	26	23.53 ± 1.74
7	51.86 ± 21.49	27	9.64 ± 1.05
12	24.45 ± 5.22	28	26.65 ± 3.16
13	>60	29	>60
14	>60	30	33.20 ± 5.73
15	42.27 ± 8.13	31	8.89 ± 0.54
18	22.30 ± 1.82	**32**	**2.92 ± 0.35**
19	29.48 ± 6.94	33	9.97 ± 0.78
20	35.86 ± 3.05	34	18.92 ± 1.29
21	23.60 ± 4.19	36[a]	3.89 ± 0.10
22	39.47 ± 16.36		

a) Positive control.

The IC_{50} of these 2-mercapto-4(*3H*)-quinazolinone derivatives (**2**-**34**) were tested on PTP1B. The results (Table 1) indicated that the quinazolinone (**2**) and the 2- or 3-substituted- 2-mercapto-4(*3H*)-quinazolinone derivatives (**3**, **5** and **6**) showing no inhibition on PTP1B. Whereas, to our delight, the inhibition on PTP1B of all the 2,3-disubstituted-2-mercapto-4(*3H*)-quinazolinone derivatives (**7**, **15** and **20**) and most of 2,3,6-trisubstituted-2-mercapto-4(*3H*)-quinazolinone derivatives (**18**, **19**, **20**, **21**, **22**, **23**, **24**, **25**, **26**, **27**, **28**, **30**, **31**, **32**, **33** and **34**) were increased significantly, and the IC_{50} value of the most potent compound **32** was improved to 2.92 μM. The benzyl substituent is a better group than prenyl group at 2-position on PTP1B inhibition (**15** vs. **20**, **13** vs. **18** and **14** vs. **19**). The inhibitory activity was increased in some extent when the nitro group of **22** was reduced to amino group (**22** vs. **24**). The inhibition of the derivatives (**25**, **26**, **28** and **29**) was decreased slightly by introducing small substituted groups at 6-hydroxy group of **23**, whereas the inhibition was improved significantly (**27**) when *p*-tolysulfonyl group was introduced at the same position. To our delight, the inhibition of the

derivatives (**31**, **32**, **33** and **34**), except compound **30**, was increased while small substituents were linked with 6-amino group of **24**, especially for the *p*-tolysulfonyl substituted derivative **32**, which inhibition was 7-fold more potent than **24**. Hence, the results indicated that *p*-tolysulfonyl group connecting with 6-hydroxy of **23** or 6-amino of **24** could ameliorate the PTP1B inhibitory potency dramatically.

Table 2. Inhibitory activity of selected 2-mercapto-4(*3H*)-quinazolinone derivatives on TCPTP and their selectivity for PTP1B over TCPTP

Compounds	IC_{50} (μM)	TCPTP/PTP1B[a]
	TCPTP	
21	>60	>2.5
23	29.33 ± 5.60	1.4
24	>60	>2.6
25	>60	>2.0
26	>60	>2.5
27	28.91 ± 5.36	3.0
30	42.87 ± 4.61	1.3
31	5.52 ± 0.71	0.6
32	4.38 ± 0.84	1.5
33	27.99 ± 4.71	2.8
34	40.62 ± 6.32	2.1
35[b]	5.92 ± 0.18	1.6

a) TCPTP/PTP1B, the ratio of IC_{50} of TCPTP and PTP1B. b) Positive control

Moreover, some derivatives which had good inhibition on PTP1B were also evaluated on the homogenous enzymes TCPTP (Table 2). The results showed that these compounds, except compound **31**, had some selectivity, and the compound **27** had the best selectivity of 3-fold for PTP1B over TCPTP.

CONCLUSION

In summary, a series of 2-mercapto-4(*3H*)-quinazolinone derivatives were synthesized and evaluated on PTP1B and TCPTP for the first time. Some potent PTP1B inhibitors with *p*-tolysulfonyl or benzoyl substituted group at 6-position were discovered. Most of these derivatives had good inhibitory activity on PTP1B and reasonable selectivity between PTP1B and TCPTP. These novel 2-mercapto-4(*3H*)-quinazolinone derivatives could be promising lead compounds for the development of a new class of PTP1B inhibitors.

EXPERIMENTAL

General. ^{1}H (400 and 500 MHz) and ^{13}C (100 and 125 MHz) NMR spectra were recorded on a JEOL-400 or Bruker AM-500 Fourier transform spectrometer. The chemical shifts were reported (δ in ppm) using the δ = 7.26, 2.5 signals of $CDCl_3$, DMSO-d_6 (^{1}H NMR), and using the δ = 77.23, 39.51 signals of $CDCl_3$, DMSO-d_6 (^{13}C NMR) as internal standards. High-resolution mass data were obtained on a Micromass Tof II spectrometer.

General procedure for synthesis of compounds 5-6, 12-15, and 18-22. Compound **4** or its derivatives (1.0 mmol) was dissolved in EtOH (10.0 mL). To this solution, KOH (56 mg, 1.0 mmol) and RBr (1.0 mmol) were added. After stirring for 0.5 h at rt, the reaction mixture was poured into 1 M HCl (40 mL) and extracted with AcOEt (3×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (CC).

General procedure for synthesis of compounds 3, 8-11, and 16-17. Compound **35** (2.75 mmoL) and 2-methoxyphenyl isothiocyanate or phenyl isothiocyanate (3.30 mmol) were dissolved in EtOH (5.0 mL). The reaction mixture was heated under reflux for 5 h. After cooling, the mixture was concentrated. The residue was purified by CC.

General procedure for synthesis of compounds 25-27. Compound **23** (0.12 g, 0.33 mmol) was dissolved in pyridine (5.0 mL). To this solution, Ac_2O, MsCl or TsCl (0.66 mmoL) was added. The reaction mixture was stirred for 12 h at rt, then poured into 1 M HCl (40 mL) and extracted with AcOEt (3×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC.

General procedure for synthesis of compounds 30-33. Compound **24** (0.36 g, 1.0 mmol) was dissolved in pyridine (5.0 mL). To this solution, AcCl, PhCOCl, MsCl or TsCl (0.66 mmol) was added. The reaction mixture was stirred for 12 h at rt, then poured into 1 M HCl (40 mL) and extracted with AcOEt (3×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC.

Compound 2. Compound **1** (0.41 g, 3.00 mmol) was dissolved in formamide (5.0 mL). The reaction mixture was heated under reflux for 3 h. After cooling, the mixture was poured into H_2O (20 mL) and extracted with AcOEt (3×15 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (DCM/MeOH 100:1) to give **2** (284 mg, 65%) as a white solid. Mp 215-216 °C (Lit.[41] 216 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13-8.10 (m, 2 H), 7.81-7.79 (m, 1 H), 7.67-7.65 (m, 1 H), 7.53-7.52 (m, 1 H); ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_8H_7N_2O$, 147.0553; found 147.0543.

Compound 3. CC (PE/EA 3:1), afforded **3** (516 mg, 66%) as a white powder solid. Mp 270-271 °C (Lit.[42] 266-268 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1 H), 8.13 (d, 1 H, J = 7.8 Hz), 7.64-7.60 (m,

1 H), 7.48-7.45 (m, 1 H), 7.31-7.28 (m, 1 H), 7.24-7.21 (m, 1 H), 7.17-7.06 (m, 3 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.9, 159.2, 154.3, 139.6, 135.7, 130.1, 129.8, 127.5, 127.4, 124.4, 120.5, 115.7, 115.7, 112.6, 55.7; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{12}N_2NaO_2S$, 307.0512; found 307.0540.

Compound 4. Compound **1** (685 mg, 5.0 mmol) was dissolved in $SOCl_2$ (15.0 mL). The reaction mixture was heated under reflux for 2 h. After cooling, the mixture was concentrated. The residue was dissolved in acetone (10.0 mL) and added to a solution of NH_4SCN (380 mg, 5.00 mmol) in acetone (10.0 mL). The reaction mixture was stirred at rt for 0.5 h, then was filtered, and the filter cake was dissolved in a mixture of DCM and MeOH (10:1). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give **4** (739.2 mg, 83% yield) as a yellow solid, which was used without further purification.

Compound 5. CC (PE/EA 10:1), afforded **5** (171.1 mg, 72%) as a white powder solid. Mp 157-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, 1 H, J = 8.0 Hz), 7.67 (d, 1 H, J = 8.3 Hz), 7.56 (d, 1 H, J = 8.3 Hz), 7.38-7.35 (m, 1 H), 5.36 (t, 1 H, J = 7.8 Hz), 3.92 (d, 2 H, J = 7.8 Hz), 1.77 (s, 3 H), 1.74 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 155.1, 149.4, 137.9, 134.8, 126.8, 126.4, 125.7, 119.9, 118.1, 29.2, 25.7, 18.1; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{13}H_{14}N_2NaOS$, 269.0719; found 269.0712.

Compound 6. CC (PE/EA 10:1), afforded **6** (209.0 mg, 78%) as a white powder solid. Mp 211-212 °C (Lit.[43] 212-213 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1 H), 8.15 (d, 1 H, J = 7.3 Hz), 7.68-7.65 (m, 1 H), 7.56 (d, 1 H, J = 8.0 Hz), 7.38 (d, 2 H, J = 7.1 Hz), 7.35-7.31 (m, 1 H), 7.27-7.21 (m, 3 H), 4.49 (s, 2 H); ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{15}H_{12}N_2NaOS$, 291.0563; found 291.0560.

Compound 7. Compound **6** (268 mg, 1.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol) were dissolved in dry DMF (10.0 mL). MeI (284 mg, 2.0 mmol) was added to the reaction mixture, after stirring for 0.5 h at rt, the reaction mixture was poured into 1 M HCl (40 mL). The mixture was extracted with AcOEt (3×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (PE/EA 10:1) to give **7** (266.4 mg, 90%) as a white powder solid. Mp 88-89 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1 H, J = 8.1 Hz), 7.71-7.67 (m, 1 H), 7.58 (d, 1 H, J = 8.3 Hz), 7.46 (d, 2 H, J = 7.3 Hz), 5.27-7.39 (m, 4 H), 4.55 (s, 2 H), 4.15 (q, 2 H, J = 7.1 Hz), 1.33 (t, 3 H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3, 155.8, 147.3, 136.3, 134.0, 129.2 (×2), 128.5 (×2), 127.5, 126.8, 125.9, 125.5, 119.4, 39.5, 36.3, 13.1; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{17}H_{16}N_2NaOS$, 319.0876; found 319.0825.

Compounds 8, 9, 10, 11, 16 and 17. The products were used without further purification.

Compound 12. CC (PE/EA 10:1), afforded **12** (340.5 mg, 76%) as a white powder solid. Mp 136-137 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, 1 H, J = 2.0 Hz), 7.97 (dd, 1 H, J = 8.6, 2.1 Hz), 7.54 (s, 1 H), 7.53 (d, 2 H, J = 2.2 Hz), 7.34 (d, 1 H, J = 8.6 Hz), 7.30-7.28 (m, 2 H), 5.24 (t, 1 H, J = 8.0 Hz), 3.79 (d,

2 H, *J* = 7.9 Hz), 1.71 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 158.7, 147.2, 143.2, 138.0, 135.9, 135.7, 130.0, 129.7 (×2), 129.0 (×2), 128.1, 121.5, 117.4, 89.4, 31.3, 25.7, 18.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{17}IN_2NaOS$, 470.9998; found 470.9971.

Compound 13. CC (PE/EA 10:1), afforded **13** (320.8 mg, 80%) as a white powder solid. Mp 143-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1 H, *J* = 2.5 Hz), 7.80 (d, 1 H, *J* = 8.8 Hz), 7.54-7.56 (m, 3 H), 7.50 (d, 1 H, *J* = 9.0 Hz), 7.30-7.32 (m, 2 H), 5.28 (t, 1 H, *J* = 8.0 Hz), 3.81 (d, 2 H, *J* = 8.0 Hz), 1.73 (s, 3 H), 1.72 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 158.5, 146.8, 137.9, 137.6, 135.8, 130.0, 129.7, 129.7 (×2), 129.1 (×2), 128.1, 121.3, 118.8, 117.6, 31.3, 25.7, 18.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{17}BrN_2NaOS$, 423.0137; found 423.0188.

Compound 14. CC (PE/EA 10:1), afforded **14** (242.4 mg, 68%) as a white powder solid. Mp 139-140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, 1 H, *J* = 2.4 Hz), 7.63 (dd, 1 H, *J* = 8.7, 2.5 Hz), 7.54-7.51 (m, 3 H), 7.29-7.28 (m, 3 H), 5.24 (t, 1 H, *J* = 7.9 Hz), 3.78 (d, 2 H, *J* = 7.9 Hz), 1.70 (s, 3 H), 1.69 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 158.3, 146.4, 137.9, 135.7, 134.9, 131.2, 130.0, 129.7 (×2), 129.0 (×2), 127.8, 126.5, 120.8, 117.4, 31.3, 25.7, 18.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{17}ClN_2NaOS$, 379.0648; found 379.0705.

Compound 15. CC (PE/EA 10:1), afforded **15** (267.3 mg, 83%) as a white powder solid. Mp 130-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1 H, *J* = 8.0 Hz), 7.69 (d, 1 H, *J* = 6.8 Hz), 7.59 (d, 1 H, *J* = 8.0 Hz), 7.71-7.50 (m, 3 H), 7.39-7.37 (m, 1 H), 7.31-7.29 (m, 2 H), 5.27 (t, 1 H, *J* = 7.8 Hz), 3.80 (d, 2 H, *J* = 7.8 Hz), 1.70 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 157.7, 148.0, 137.6, 136.1, 134.6, 129.8, 129.6 (×2), 129.2(×2), 127.3, 126.2, 125.7, 119.9, 117.8, 31.3, 25.7, 18.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{19}H_{18}N_2NaOS$, 345.1032; found 345.1068.

Compound 18. CC (PE/EA 10:1), afforded **18** (283.4 mg, 67%) as a white powder solid. Mp 132-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.81 (d, 1 H, *J* = 8.7 Hz), 7.51-7.55 (m, 4 H), 7.35 (d, 2 H, *J* = 7.3 Hz), 7.23-7.29 (m, 5 H), 4.39 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 157.9, 146.6, 137.8, 136.1, 135.5, 130.1, 129.7 (×2), 129.3 (×2), 129.1 (×2), 128.7 (×2), 128.6, 128.1, 127.6, 121.4, 119.0, 37.2; ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{16}BrN_2OS$, 423.0161; found 423.0227.

Compound 19. CC (PE/EA 10:1), afforded **19** (234.7 mg, 62%) as a white powder solid. Mp 143-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, 1 H, *J* = 2.4 Hz), 7.66 (dd, 1 H, *J* =8.7, 2.5 Hz), 7.59 (d, 1 H, *J* = 8.7 Hz), 7.51-7.50 (m, 3 H), 7.35 (d, 2 H, *J* = 7.0 Hz), 7.29-7.25 (m, 5 H), 4.39 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 157.7, 146.3, 136.2, 135.5, 135.0, 131.4, 130.1, 129.7 (×2), 129.3 (×2), 129.1 (×2), 128.6 (×2), 127.9, 127.6, 126.6, 121.0, 37.2; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{15}ClN_2NaOS$, 401.0491; found 401.0532.

Compound 20. CC (PE/EA 10:1), afforded **20** (220 mg, 67%) as a white powder solid. Mp 172-173 °C (Lit.[44] 176.5-177 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, 1 H, *J* = 7.9 Hz), 7.78-7.75 (m, 1 H), 7.67 (d,

1 H, J = 8.2 Hz), 7.53-7.51 (m, 3 H), 7.43-7.38 (m, 3 H), 7.32-7.22 (m, 5H), 4.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 157.1, 147.8, 136.4, 135.8, 134.6, 129.9, 129.6 (×2), 129.4 (×2), 129.2 (×2), 128.5 (×2), 127.5, 127.3, 126.2, 125.8, 120.0, 37.1; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{16}N_2NaOS$, 367.0876; found 367.0901.

Compound 21. CC (PE/EA 10:1), afforded **21** (243.1 mg, 65%) as a white powder solid. Mp 177-178 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63-7.61 (m, 2 H), 7.53-7.51 (m, 3 H), 7.38-7.35 (m, 3 H), 7.30-7.28 (m, 4 H), 7.25-7.23 (m, 1 H), 4.39 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 157.6, 154.3, 142.6, 136.4, 135.9, 129.8, 129.5 (×2), 129.3 (×2), 129.1 (×2), 128.4 (×2), 127.7, 127.4, 124.6, 120.5, 106.7, 55.7, 36.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{22}H_{18}N_2NaO_2S$, 397.0981; found 397.1011.

Compound 22. CC (PE/EA 10:1), afforded **22** (233.4 mg, 60%) as a yellow powder solid. Mp 184-185 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (d, 1 H, J = 3.0 Hz), 8.52 (dd, 1 H, J = 9.0, 2.5 Hz), 7.74 (d, 1 H, J = 9.0 Hz), 7.55-7.53 (m, 3 H), 7.35 (d, 1 H, J = 7.0 Hz), 7.30-7.25 (m, 5 H), 4.43 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 162.3, 160.4, 151.5, 144.8, 135.6, 135.0, 130.4, 130.0 (×2), 129.3 (×2), 128.9 (×2), 128.7 (×2), 127.7, 127.6, 124.1, 119.9, 37.5; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{15}N_3NaO_3S$, 412.0726; found 412.0755.

Compound 23. Compound **21** (0.1 g, 0.27 mmol) was dissolved in DCM (10.0 mL). BBr_3 in DCM (1 M, 0.04 mL) was added to the reaction mixture at -50 °C, and the reaction mixture was stirred at rt for 10 h. The reaction mixture was poured into H_2O (50 mL) and extracted with AcOEt (2×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (PE/EA 3:1) to give **23** (93 mg, 96%) as a white powder solid. It decomposes at 200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1 H), 7.56 (d, 1 H, J = 8.8 Hz), 7.50-7.38 (m, 8 H), 7.32-7.20 (m, 4 H), 4.35 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 155.6, 152.9, 140.7, 136.8, 136.0, 129.7, 129.4 (×2), 129.4 (×2), 129.3 (×2), 128.4 (×2), 127.7, 127.2, 124.2, 120.4, 109.5, 35.8; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{21}H_{16}N_2NaO_2S$, 383.0825; found 383.0843.

Compound 24. Compound **22** (0.1 g, 0.25 mmol) was dissolved in the mixture solution (9.0 mL, MeOH: H_2O: THF = 5:1:3). Zinc dust (0.05 g, 0.75 mmol) and NH_4Cl (0.07 g, 1.25 mmol) were added to the reaction mixture. The reaction mixture was heated under reflux for 2 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with AcOEt (2×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (PE/EA 3:1) to give **24** (72 mg, 80%) as a yellow powder solid. Mp 168-169 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.49 (m, 4 H), 7.43 (d, 1 H, J = 2.1 Hz), 7.36 (d, 2 H, J = 7.5 Hz), 7.30-7.28 (m, 4 H), 7.23-7.22 (m, 1 H), 7.10 (dd, 1 H, J = 8.6, 2.4 Hz), 4.37 (s, 2 H), 3.29 (br, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 152.7, 144.8, 141.0, 136.6, 136.1, 129.7, 129.5 (×2), 129.3 (×2), 129.2 (×2), 128.4 (×2), 127.4, 127.3, 123.3, 120.8, 109.6, 36.9; ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_{21}H_{18}N_3OS$, 360.1165;

found 360.1156.

Compound 25. CC (PE/EA 3:1), afforded **25** (90.2 mg, 68%) as a white powder solid. Mp 180-181 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.67 (d, 1 H, *J* = 8.6 Hz), 7.49-7.47 (m, 6 H), 7.37-7.35 (m, 3 H), 7.28-7.22 (m, 2 H), 4.39 (s, 2 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.30, 161.2, 157.0, 148.1, 145.7, 136.3, 135.6, 130.0, 129.7 (×2), 129.3 (×2), 129.1 (×2), 128.9, 128.5 (×2), 127.6, 127.5, 120.6, 119.2, 37.0, 21.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{23}H_{18}N_2NaO_3S$, 425.0930; found 425.0931.

Compound 26. CC (PE/EA 3:1), afforded **26** (82.4 mg, 57%) as a white powder solid. Mp 179-180 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 1 H, *J* = 2.4 Hz), 8.05-7.66 (m, 2 H), 7.52-7.50 (m, 3 H), 7.35 (d, 2 H, *J* = 7.0 Hz), 7.29-7.22 (m, 5 H), 4.39 (s, 2 H), 3.17 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8, 158.1, 146.6, 146.2, 136.0, 135.3, 130.1, 129.7 (×2), 129.3, 129.2 (×2), 128.9 (×2), 128.5 (×2), 128.4, 127.5, 120.7, 119.6, 37.4, 31.4; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{22}H_{18}N_2NaO_4S_2$, 461.0600; found 461.0616.

Compound 27. CC (PE/EA 3:1), afforded **27** (95.0 mg, 56%) as a white powder solid. Mp 160-161 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, 2 H, *J* = 8.2 Hz), 7.69 (d, 1 H, *J* = 2.6 Hz), 7.62 (d, 1 H, *J* = 8.9 Hz), 7.52-7.50 (m, 4 H), 7.36-7.35 (m, 2 H), 7.31 (d, 2 H, *J* = 8.1 Hz), 7.29-7.24 (m, 5 H), 4.37 (s, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 157.9, 146.8, 146.4, 145.7, 136.1, 135.3, 132.0, 130.0, 129.9 (×2), 129.7, 129.5 (×2), 129.3 (×2), 128.9 (×2), 128.5 (×2), 128.4 (×2), 128.0, 127.5, 120.5, 119.9, 37.1, 21.7; ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_{28}H_{23}N_2O_4S_2$, 515.1094; found 515.1142.

Compound 28. Compound **23** (0.1 g, 0.28 mmol) and K_2CO_3 (0.08 g, 0.56 mmol) were dissolved in DMF (5.0 mL). $BrCH_2CO_2Et$ (0.06 mL, 0.56 mmol) was added to the reaction mixture. After stirring at rt for 1 h, the reaction mixture was poured into 1 M HCl (50 mL) and extracted with AcOEt (2×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (PE/EA 5:1) to give **28** (78 mg, 62%) as a white powder solid. Mp 151-152 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, 1 H, *J* = 9.0 Hz), 7.54-7.50 (m, 4 H), 7.44 (dd, 1 H, *J* = 8.9, 3.0 Hz), 7. 36 (d, 2 H, *J* =7.2 Hz), 7.29-7.28 (m, 4 H), 7.24-7.23 (m, 1 H), 4.72 (s, 2 H), 4.38 (s, 2 H), 4.26 (q, 2 H, *J* = 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 161.5, 155.7, 155.0, 143.2, 136.4, 135.8, 129.9, 129.6 (×2), 129.3 (×2), 129.0 (×2), 128.4 (×2), 128.1, 127.4, 125.1, 120.4, 107.7, 65.5, 61.4, 37.0, 14.1; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{25}H_{22}N_2NaO_4S$, 469.1192; found 469.1199.

Compound 29. Compound **28** (80 mg, 0.18 mmol) and LiOH (0.02 g, 0.36 mmol) were dissolved in MeOH (5.0 mL). After stirring at rt for 5 h, the reaction mixture was poured into 1 M HCl (50 mL) and extracted with AcOEt (2×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (DCM/MeOH 50:1) to give **29** (55

mg, 73%) as a white powder solid. It decomposes at 185 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.64 (d, 1 H, J = 8.9 Hz), 7.52-7.50 (m, 3 H), 7.45 (dd, 1 H, J = 8.9, 2.9 Hz), 7.40-7.38 (m, 4 H), 7.36 (d, 1 H, J = 2.8 Hz), 7.27-7.25 (m, 2 H), 7.22-7.20 (m, 1 H), 4.75 (s, 2 H), 4.36 (s, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.5, 155.6, 154.4, 142.1, 136.7, 135.8, 129.8, 129.4 (×2), 129.3 (×2), 129.2 (×2), 128.3 (×2), 127.8, 127.2, 124.4, 120.1, 107.7, 64.9, 35.8; ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_{23}H_{19}N_2O_4S$, 419.1060; found 419.1065.

Compound 30. CC (PE/EA 3:1), afforded **30** (304.8 mg, 76%) as a white powder solid. It decomposes at 160 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1 H), 8.39 (d, 1 H, J = 2.1 Hz), 8.03 (dd, 1 H, J = 8.8, 2.2 Hz), 7.65 (d, 1 H, J = 8.8 Hz), 7.53-7.52 (m, 3 H), 7.43-7.40 (m, 4 H), 7.28-7.26 (m, 2 H), 7.22-7.20 (m, 1 H), 4.38 (s, 2 H), 2.10 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.6, 160.7, 155.0, 143.1, 137.3, 136.7, 135.9, 129.8, 129.5 (×2), 129.4 (×2), 129.3 (×2), 128.4 (×2), 127.3, 126.7, 126.3, 119.8, 114.9, 36.0, 24.0; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{23}H_{19}N_3NaO_2S$, 424.1090; found 424.1157.

Compound 31. CC (PE/EA 5:1), afforded **31** (444.5 mg, 96%) as a yellow powder solid. Mp 214-215 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, 1 H, J = 2.4, 8.9 Hz), 8.40 (s, 1 H), 8.10 (d, 1 H, J = 2.4 Hz), 7.86 (d, 2 H, J = 7.4 Hz), 7.70 (d, 1 H, J = 8.9 Hz), 7.56-7.53 (m, 1 H), 7.47-7.42 (m, 5 H), 7.37 (d, 2 H, J = 7.3 Hz), 7.30-7.23 (m, 5 H), 4.40 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 161.8, 155.8, 144.5, 136.5, 136.3, 135.6, 134.3, 131.7, 129.9, 129.6 (×2), 129.4 (×2), 129.0 (×2), 128.5 (×2), 128.4 (×2), 127.5, 127.3 (×2), 127.0, 119.8, 117.6, 37.1; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{28}H_{21}N_3NaO_2S$, 486.1247; found 486.1257.

Compound 32. (CC) (PE/EA 5:1), afforded **32** (369.4 mg, 72%) as a white powder solid. Mp 98-99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (dd, 1 H, J = 2.5, 8.7 Hz), 7.68-7.57 (m, 5 H), 7.51-7.49 (m, 4 H), 7.38 (s, 1 H), 7.35 (d, 2 H, J = 8.4 Hz), 7.30-7.20 (m, 8 H), 4.37 (s, 2 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 155.1, 143.7, 142.5, 134.9, 134.6, 134.2, 133.8, 128.7, 128.4 (×2), 128.3 (×2), 128.0 (×2), 127.7 (×2), 127.3, 127.2 (×2), 126.8, 126.1, 125.9 (×2), 118.8, 116.8, 35.8, 20.2; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{28}H_{23}N_3NaO_3S_2$, 536.1073; found 536.1045.

Compound 33. CC (PE/EA 3:1), afforded **33** (329.6 mg, 64%) as a white powder solid. Mp 159-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, 1 H, J = 2.5 Hz), 7.73 (d, 1 H, J = 8.6 Hz), 7.65 (dd, 1 H, J = 8.6, 2.5 Hz), 7.54-7.53 (m, 3 H), 7.36 (d, 2 H, J = 6.9 Hz), 7.30-7.27 (m, 4 H), 7.26-7.24 (m, 1 H), 4.41 (s, 2 H), 3.45 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.7, 159.6, 148.7, 136.4, 136.0, 135.2, 130.4, 130.2, 129.8 (×2), 129.6, 129.2 (×2), 128.9 (×2), 128.5 (×2), 128.0, 127.5, 120.6, 42.8 (×2), 37.1; ESI-HRMS (m/z): $[M+H]^+$ calcd. for $C_{23}H_{22}N_3O_5S_3$, 516.0716; found 516.0760.

Compound 34. Compound **24** (83 mg, 0.23 mmol) and NaH (60% suspended in mineral oil, 0.05 g, 1.15 mmol) were dissolved in DMF (5.0 mL). MeI (0.06 mL, 0.92 mmol) was added to the reaction mixture. After stirring for 14 h at rt, the reaction mixture was poured into 1 M HCl (50 mL) and extracted with

AcOEt (2×15 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by CC (PE/EA 5:1) to give **34** (69.4 mg, 78%) as a yellow powder solid. Mp 175-176 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 1 H, J = 8.0 Hz), 7.50-7.49 (m, 3 H), 7.38-7.36 (m, 3 H), 7.29-7.26 (m, 6 H), 4.39(s, 2 H), 3.05 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 150.2, 147.1, 137.8, 135.1, 134.6, 128.0, 127.9 (×2), 127.8 (×2), 127.6 (×2), 126.8 (×2), 125.7, 125.4, 119.1, 119.0, 105.2, 39.1 (×2), 35.3; ESI-HRMS (m/z): $[M+Na]^+$ calcd. for $C_{23}H_{21}N_3NaOS$, 410.1298; found 410.1298.

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