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Synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents

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Abstract—Based on 2-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid[2-(cyclohexanecarbonylamino)benzothiazol-6-yl]amide (**1**), which shows selective cytotoxicity against tumorigenic cell lines, 2,6-dichloro-*N*-[2-(cyclopropanecarbonylamino)benzothiazol-6-yl]benzamide (**13b**) was designed and synthesized as a biologically stable derivative containing no nitro group. The highly potent derivative **13b** exhibited excellent in vivo inhibitory effect on tumor growth.

Cancer is a disease of striking significance in the world today. It is the second leading cause of death in the United States after cardiovascular disease and it is projected to becoming the primary cause of death there within the coming years.[1] In our project to develop new anticancer drugs as small molecules,[2] 2-methyl-4-nitro-2*H*-pyrazole-3-carboxylic acid[2-(cyclohexanecarbonylamino)benzothiazol-6-yl]amide (**1**) was selected as one of the most promising screening hit compounds. Compound **1** with a benzothiazole core[3] exhibited potent and selective cytotoxicity against a tumorigenic cell line, WI-38 VA-13 subline 2RA (VA-13) (EC_{50} = 26 ng/mL), despite the fact that no cytotoxicity was observed against the normal parental cell line, WI-38 (EC_{50} > 4000 ng/mL).[2] Screening hit **1** showed remarkable biological activity in the cell-based screening. Nevertheless, the results of an in vivo antitumor test of compound **1** were disappointing. It was predicted that metabolic instability of compound **1** could make a difference in the results between the in vitro and in vivo tests. This article describes our procedure to discover derivatives that possess remarkable in vivo inhibitory effect on tumor growth by stabilizing metabolic degradation, along with improving in vitro activity, employing a structure–activity relationship (SAR) study.

Figure 1 illustrates the two regions of interest for SAR evaluation of screening hit **1**. In general, the nitro group in the structure of **1** is not preferred for drug design in medicinal chemistry on account of its metabolic instability.[4] To evaluate the structural requirements of the left-hand acyl group region, Region 1, solid-phase chemistry, which is a powerful tool for large-size library construction, was employed for examining the diverse

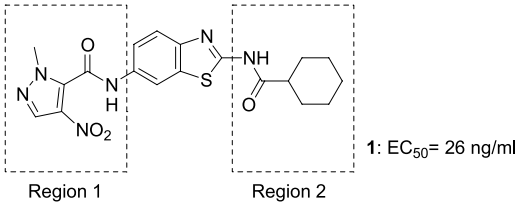

Figure 1. Selected regions of interest for SAR evaluation of screening hit compound **1**.

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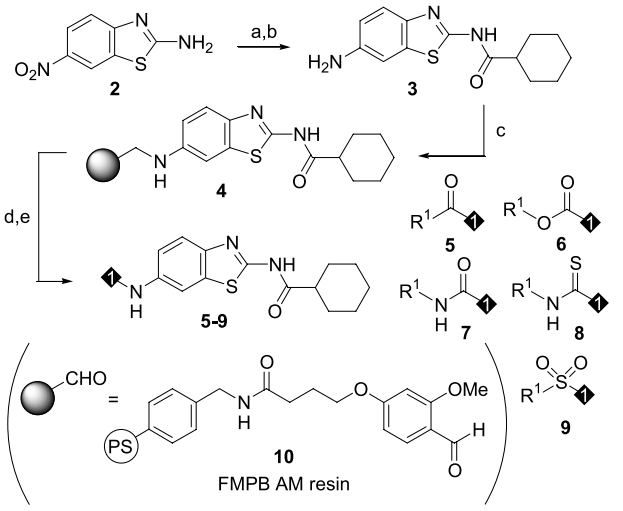


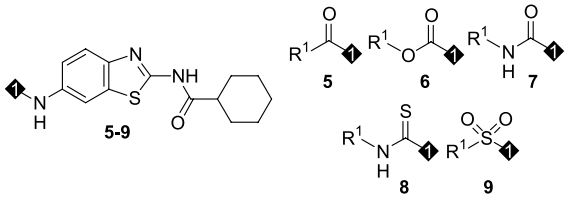
Scheme 1. Solid-phase synthesis of amide, urethane, urea, thiourea, and sulfonamide derivatives. Reagents and conditions: (a) cyclohexanecarbonyl chloride, 4-pyrrolidinopyridine, DMA, 25 °C, 15 h; (b) H_2/Pd-C, THF, 25 °C, 5 h (93%, two steps); (c) FMPB AM resin (**10**, 0.94 mmol/g), $MgSO_4$, DMA–AcOH (9:1), 80 °C, 1 h, then $NaBH(OAc)_3$, 80 °C, 4 h; (d) **5**: R^1CO_2H, PPh_3, *N*-chlorosuccinimide, pyridine, DCM, 25 °C, 2 h, **6**: $R^1OC(O)Cl$, $NaHCO_3$, THF, 80 °C, 4 h; **7**: R^1NCO, DCM, 25 °C, 20 h; **8**: R^1NCS, DCM, 25 °C, 20 h; **9**: R^1SO_2Cl, pyridine, 60 °C, 16 h; (e) **5–9**: 20% TFA in DCM, 25 °C, 20 h.

substructures for potent anticancer agents. The structural optimization of the right-hand region, Region 2, was carried out by parallel solution-phase chemistry.[5]

Scheme 1 summarizes our synthesis of Region 1 derivatives of hit compound **1**. Acylation of commercially available 2-amino-6-nitrobenzothiazole (**2**) with cyclohexanecarbonyl chloride was executed, and the product was reduced to furnish key intermediate **3**. Compound **3** was then loaded onto a polystyrene solid support with a BAL-type linker,[6] 4-(4-formyl-3-methoxyphenoxy)butyrylamide resin (FMPB AM resin, **10**), purchased from Novabiochem Corp. by reductive amination. The resulting secondary amine **4** was acylated with one of the various reagents to give amide,[7] urethane, urea, thiourea, or sulfonamide resins, and the ensuing cleavage from the polymer support under acidic conditions yielded the desired derivatives **5–9**. In this process, a ca. 200-member library was constructed employing a solid-phase strategy. Individual library members were identified via radiofrequency encoding using IRORI™ tags and MiniKan™ technologies.[8,9]

The cytotoxicity of the synthesized derivatives is given in Table 1. Most of the compounds that had a substitute at the *ortho*-position (**5a–e**) of the benzene ring showed almost the same or a slightly weaker cytotoxicity than hit compound **1**. While derivatives with a *meta* substituent (**5f–h**) weakened the biological activity, those that had a substituent at the *para*-position (**5i–m**) completely lost their biological activity. The *ortho*-di-substituted compounds (**5n** and **o**) displayed a stronger biological activity, and 2,6-dichlorophenyl amide **5n** (EC_{50} = 15 ng/ml) was, in particular, more potent than

Table 1. Cytotoxicity of amide, urethane, urea, thiourea and sulfonamide derivatives (Region 1)



Compound	R^1	Cytotoxicity EC_{50} (ng/mL)[a]
1	2-Methyl-4-nitro-2*H*-pyrazol-3-yl	26
5a	2-Methylphenyl	85
5b[b]	2-Fluorophenyl	140
5c[b]	2-Chlorophenyl	25
5d[b]	2-Trifluoromethylphenyl	24
5e	2-Phenoxyphenyl	100
5f	3-Fluorophenyl	640
5g	3-Cyanophenyl	520
5h	3-Phenoxyphenyl	>4000
5i	4-Methoxyphenyl	4900
5j	4-Methylphenyl	5100
5k	4-Cyanophenyl	3300
5l	4-Bromophenyl	>4000
5m	2,4-Dichlorophenyl	>4000
5n[b]	2,6-Dichlorophenyl	15
5o[b]	2-Fluoro-6-trifluoromethylphenyl	32
5p	Methyl	2700
5q	2-Pentyl	140
5r	2-Methylbut-2-yl	1000
5s	2-Tetrahydrofuranyl	1300
5t[b]	2-Chloropyridin-3-yl	75
5u[c]	2-Methyl-2*H*-pyrazol-3-yl	580
5v[c]	2,5-Dimethyl-2*H*-pyrazol-3-yl	120
5w[c]	1,3,5-Trimethyl-1*H*-pyrazol-4-yl	12
5x	2,4-Dimethylthiazol-5-yl	390
5y[c]	2,4-Dimethylfuran-3-yl	2700
5z[c]	1,2,5-Trimethyl-1*H*-pyrrol-3-yl	>6200
6a	Allyl	580
6b	Isobutyl	720
7a	2,6-Dimethylphenyl	560
7b	Phenethyl	700
8a	1,4-Benzodioxan-6-yl	1600
8b	2-Trifluoromethoxyphenyl	2300
9a	4-Butoxyphenyl	750
9b	5-Fluoro-2-methylphenyl	700

[a] Selective cytotoxicity against a tumorigenic cell line, WI-38 VA-13 subline 2RA (VA-13), and no cytotoxicity was observed against the normal parental cell line, WI-38.

[b] Synthesized from **3** with acyl chloride under standard conditions (NEt_3, DCM, 25 °C).

[c] Synthesized from **3** with carboxylic acid under standard conditions [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxy-benzotriazole hydrate, DMF, 25 °C].

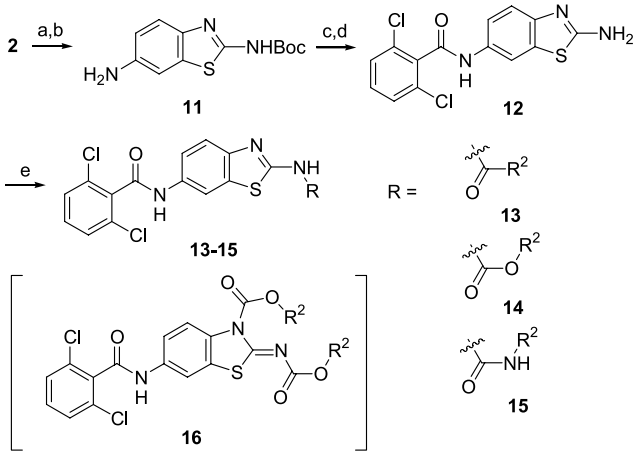
hit compound **1**. The characteristic heterocycle substructure of hit compound **1** was revealed to be replaceable with readily available simple phenyl groups. In addition, derivatives possessing aliphatic substituents (**5p–s**), instead of the benzene ring, showed a relatively weak cytotoxicity. Among the derivatives with heterocycles as the amide substituent (**5t–z**), compound **5w** (EC_{50} = 12 ng/ml) was revealed to possess remarkable potency.

Although various types of urethane, urea, thiourea, and sulfonamide were synthesized, derivatives with different bonding structures were less potent than amide compounds. The biological activities of a few representative examples (**6a**–**9b**) out of the synthesized compounds are also indicated in the table.

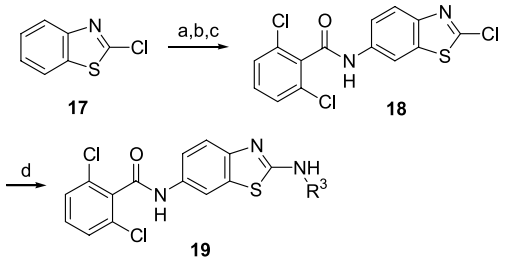
This study of Region 1 derivatization resulted in the discovery of biologically potent derivatives (**5n** for example) possessing a benzene ring instead of a singular hetero-ring with a nitro substituent.

Scheme 2 illustrates the synthesis of Region 2 derivatives of compound **5n**. The *tert*-butoxycarbonyl (Boc) protection of the amino group of **2** was followed by reduction of the nitro group to afford **11**. Acylation of **11** with commercially available 2,6-dichlorobenzoyl chloride was undertaken in *N*,*N*-dimethylacetamide (DMA), and the resulting product was treated with hydrochloric acid to remove the *N*-Boc group, giving **12**. The amino group of **12** was acylated with one of the various acyl groups to yield the desired derivatives **13–15**. Unfortunately, the final step to furnish urethane derivatives was problematic, giving a mixture of **14** and excess acylated **16**. The only fruitful method to afford pure **14** was to treat the resulting mixture with trifluoroacetic acid (TFA) in situ after acylation of **12** was completed with an excess of chloroformate. The derivatives prepared by the optimized procedure employing a solution-phase strategy maintained sufficient purity for evaluation without chromatographic purification.

In addition, our synthetic method of amine derivatives of **5n** is given in Scheme 3. The initial 2-chlorobenzothiazole (**17**) was converted to a 6-nitrated compound,[10] and the product was treated with zinc powder, followed



Scheme 2. Solution-phase synthesis of amide, urethane, and urea derivatives. Reagents and conditions: (a) Boc_2O, DMAP (cat.), DCM, 25 °C, 18 h (92%); (b) H_2/Pd-C, THF, 25 °C, 13 h (91%); (c) 2,6-dichlorobenzoyl chloride, DMA, 25 °C, 20 h (93%); (d) 4 N HCl–l,4-dioxane, 1,4-dioxane–EtOH (5:1), 25 °C, 17 h (92%); (e) **13**: $R^2C(O)Cl$, DMA, 25 °C, 24 h; or R^2CO_2H, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxy-7-azabenzotriazole, NEt_3, DMF, 60 °C, 20 h; **14**: $R^2OC(O)Cl$, DMA, 25 °C, 17 h, then TFA, 40 °C, 5 h; **15**: R^2NCO, pyridine, 60 °C, 16 h.



Scheme 3. Synthesis of amine derivatives. Reagents and conditions: (a) HNO_3, H_2SO_4, 0–25 °C, 3 h (quant.); (b) Zn, AcOH, THF–MeOH (1:1), 60 °C, 2 h (56%); (c) 2,6-dichlorobenzoyl chloride, DMA, 25 °C, 17 h (77%); (d) R^3NH_2, EtOH, a sealed tube, 120–130 °C, 24 h.

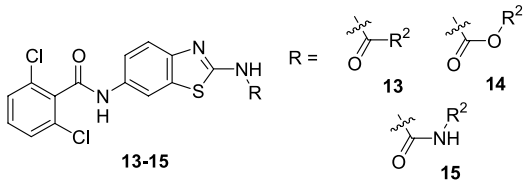
by acylation of the resulting amino group with 2,6-dichlorobenzoyl chloride to furnish **18**. Amination of chloride **18** under thermal conditions [ethanol, sealed tube, 120–130 °C, 24 h] afforded the desired derivatives **19**.

The results of the cytotoxicity test of the synthesized derivatives are shown in Table 2. Most of the compounds possessing aliphatic substituents (**13a**–**f**) had almost the same potency as compound **5n**, except when a smaller substituent, such as the methyl group (**13c**), or a longer substituent, such as the heptyl group (**13f**), was placed at the aliphatic parts. A few derivatives that had an amino group (**13g**) or a carboxylic acid (**13h**) at the terminus of their aliphatic chains had completely lost their biological activity. Interestingly, new-type derivatives (**14a**–**f**) designed by replacing the original amide part with the corresponding urethane were more potent (EC_{50} = 2.5–11 ng/ml). While *tert*-butoxycarbonyl compound **14g** with a bulky substituent showed a slightly lower activity, benzyl (**14h**) or phenyl (**14i**) derivatives possessing an aromatic ring faced considerable loss of cytotoxicity. Additionally, the derivatives of urea linkage types (**15a**–**e**) also had the same potency as the amide or urethane compounds. Lastly, as shown in Table 3, the amine derivatives (**19a**–**e**) that were lacking an original carbonyl group (C=O) showed a relatively weak cytotoxicity.

This study of Region 2 SAR indicated that urethane derivatives (**14b** for instance) were ca. 10 times as biologically potent as the original amide derivatives as a hit compound **1**.

As the most promising substructures were determined by derivatization around Regions 1 and 2, the next challenge was modification of the benzothiazole core structure. We first attempted to synthesize benzothiazole derivatives possessing an amide substituent at the fifth position (Scheme 4). A key intermediate, 2-amino-5-nitrobenzothiazole (**22**), was readily prepared from commercially available **20** by a previously reported procedure.[11] Acylation of **22** with ethyl chloroformate, followed by hydrogenation of the nitro group, furnished compound **23**. An amino group of compound **23** was acylated with 2,6-dichlorobenzoyl chloride to afford the desired compound **24**, which possesses an amide substituent at the fifth position. To our surprise, the

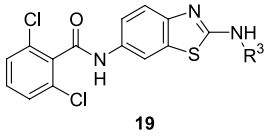
Table 2. Cytotoxicity of amide, urethane, and urea derivatives (Region 2)



Compound	R^2	Yield (%)[a]	Cytotoxicity EC_{50} (ng/mL)[b]
5n	Cyclohexyl	—	15
13a	Cyclobutyl	86	13
13b	Cyclopropyl	35	13
13c	Methyl	52	600
13d	Propyl	62	10
13e	Isobutyl	92	12
13f	Heptyl	56	180
13g	Aminoethyl	34[c]	5300
13h	$HOC(O)CH_2CH_2$	39[d]	>6600
14a	Methyl	20[e]	9.5
14b	Ethyl	93	2.6
14c	Propyl	5.8[e]	2.5
14d	Isopropyl	11[e]	2.6
14e	Isobutyl	17[e]	3.5
14f	Methoxyethyl	91	11
14g[f]	*tert*-butyl	—	27
14h	Benzyl	8.6[e]	180
14i	Phenyl	10[e]	1100
15a	Ethyl	50	32
15b	Isopropyl	41	30
15c	Butyl	60	28
15d	Hexyl	45	290
15e	Benzyl	9.3	150

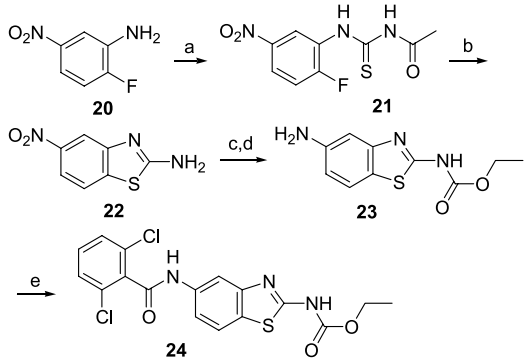
[a] Yields were not optimized.
[b] Selective cytotoxicity against a tumorigenic cell line, WI-38 VA-13 subline 2RA (VA-13), and no cytotoxicity was observed against the normal parental cell line, WI-38.
[c] Yield was calculated after the removal of Boc-protecting group for the amino group.
[d] Synthesized from **12** with succinic anhydride under standard conditions (pyridine, DMAP, 60 °C).
[e] Yields without TFA treatment.
[f] The derivative **14g** is the intermediate in Scheme 2.

Table 3. Cytotoxicity of amine derivatives (Region 2)



Compound	R^3	Yield (%)[a]	Cytotoxicity EC_{50} (ng/mL)[b]
19a	Cyclohexylmethyl	66	4300
19b	Pentyl	15	270
19c	4-Methoxyphenyl	46	870
19d	3-Methoxyphenyl	22	>7200
19e	2-Methoxyphenyl	75	>7200

[a] Yields were not optimized.
[b] Selective cytotoxicity against a tumorigenic cell line, WI-38 VA-13 subline 2RA (VA-13), and no cytotoxicity was observed against the normal parental cell line, WI-38.



Scheme 4. Synthesis of benzothiazole derivatives possessing an amide substituent at the fifth position. Reagents and conditions: (a) MeC(O)NCS, acetone, 25 °C, 3 days (quant.); (b) NaOH, THF–MeOH (2:1), 70 °C, 10 h (76%); (c) ethyl chloroformate, DMA, 50 °C, 18 h (88%); (d) H_2/Pd-C, THF–MeOH–AcOH (8:4:1), 25 °C, 4 h (quant.); (e) 2,6-dichlorobenzoyl chloride, DMA, 25 °C, 15 h (42%).

biological activity of compound **24** (EC_{50} = 2500 ng/ml) was a thousand times weaker than that of the corresponding compound **14b**. This unexpected result suggested that the nitrogen and sulfur atoms of the benzothiazole ring are not interchangeable and that they might play an important role, since the difference between **14b** and **24** lies simply in the positions of these atoms.

The in vivo antitumor activity of synthesized derivatives is shown in Table 4.[12] Although in vivo tests of hit compound **1** (Exp. 1) and derivative **5n**[13] (Exp. 2) did not show any significant therapeutic effect at 40 mg/kg iv administration, compound **13b**[14] (Exp. 3) presented a strong inhibiting effect on tumor growth, even at a much lower dose (5 mg/kg). Figure 2 illustrates the plasma concentration of **1**, **5n**, and **13b** after iv administration to mice. As expected, compound **5n** ($t_{1/2}$ = 1.10 h), which was designed by replacing the nitro pyrazole ring of **1** with a 2,6-dichlorobenzene ring, exhibited improved stability in plasma, rather than screening hit compound **1** ($t_{1/2}$ = 0.53 h). Furthermore, as cyclohexylamide of **5n**

Table 4. Antitumor activity of benzothiazole derivatives against an LLC xenograft model[a]

Exp.	Compound	Dose (mg/kg/shot)[b]	Schedule (day)	TGI (%)[c] at day 11
1	**1**	40	1, 4, 7	15
2	**5n**	40	1, 4, 7	35
3	**13b**	5	1, 4, 7	63*
4	**13b**	20	1	68*

[a] Mouse Lewis lung carcinoma (LLC) was inoculated subcutaneously into BDF1 female mice (n = 6) on Day 0. Each compound was administered iv in a vehicle of 10% DMA/10% HCO60 (poly-oxyethylene hydrogenated castor oil 60)/80% saline.
[b] The applied dose was the maximum tolerated dose.
[c] Percent of inhibition of tumor growth (by volume).
* $p < 0.05$ (t test).

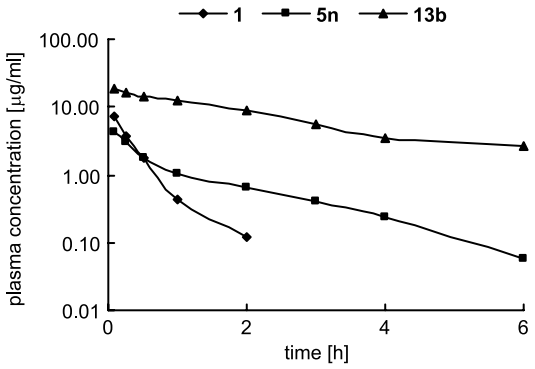


Figure 2. Plasma concentration of screening hit compound **1**, derivatives **5n** and **13b** after iv administration to BDF1 female mice at a dose of 10 mg/kg ($n = 2$, mean). The concentration of remained compounds was determined by HPLC.

was converted to the cyclopropylamide of **13b**, derivative **13b** showed an excellent plasma concentration ($t_{1/2} = 3.29$ h). This result suggested that metabolic hydrolysis of the amide bond of Region 2 was controlled by placing the cyclopropylamide instead of cyclohexylamide. The excellent concentration of **13b** in plasma also brought about a strong inhibitory effect on tumor growth with a single dosing of 20 mg/kg (Exp. 4). Although the urethane derivatives (**14b**[15] for example) showed strong in vitro activity, they were not applied in an in vivo test on account of their low solubility.

In conclusion, derivative **13b**, which had both biological potency and excellent plasma concentration, was designed as a derivative of a screening hit compound **1**. Synthesized compound **13b** exhibited strong in vivo inhibitory effect on tumor growth.

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13. Compound **5n**: yellow powder, mp 157–160 °C; ^{1}H NMR (270 MHz, DMSO-d_6, δ): 12.2 (s, 1H), 10.9 (s, 1H), 8.40 (d, 1H, $J = 1.6$ Hz), 7.71 (d, 1H, $J = 8.9$ Hz), 7.57–7.62 (m, 3H), 7.51 (dd, 1H, $J = 9.5$, 6.2 Hz), 2.41–2.60 (m, 1H), 1.60–1.93 (m, 5H), 1.10–1.52 (m, 5H); MS (APCI, *m*/*z*) 448, 450 $[M+1]^+$; HRMS (ESI) Calcd for $C_{21}H_{19}Cl_2N_3O_2S$: $[M+1]^+$, 448.06533. Found: 448.06831.
14. Compound **13b**: off-white solid, mp 290–292 °C; ^{1}H NMR (270 MHz, DMSO-d_6, δ): 12.6 (s, 1H), 10.9 (s, 1H), 8.39 (d, 1H, $J = 1.6$ Hz), 7.72 (d, 1H, $J = 8.6$ Hz), 7.58–7.62 (m, 3H), 7.51 (dd, 1H, $J = 9.5$, 6.5 Hz), 1.91–2.09 (m, 1H), 0.82–1.01 (m, 4H); MS (APCI, *m*/*z*) 406, 408 $[M+1]^+$; HRMS (EI) Calcd for $C_{18}H_{13}Cl_2N_3O_2S$ $[M+2]^+$, 407.0079. Found: 407.0076.
15. Compound **14b**: off-white solid, mp 335–338 °C (dec.); ^{1}H NMR (270 MHz, DMSO-d_6, δ): 12.0 (br s, 1H), 10.9 (s, 1H), 8.39 (d, 1H, $J = 1.9$ Hz), 7.66 (d, 1H, $J = 8.6$ Hz), 7.54–7.61 (m, 3H), 7.50 (dd, 1H, $J = 9.5$, 6.5 Hz), 4.25 (q, 2H, $J = 7.0$ Hz), 1.29 (t, 3H, $J = 7.0$ Hz); MS (APCI, *m*/*z*) 410, 412 $[M+1]^+$; HRMS (EI) Calcd for $C_{17}H_{13}Cl_2N_3O_3S$ $[M]^+$, 409.0055. Found: 409.0056.