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# Synthesis and biological activity of some more heterocyclic compounds containing benzothiophene moiety

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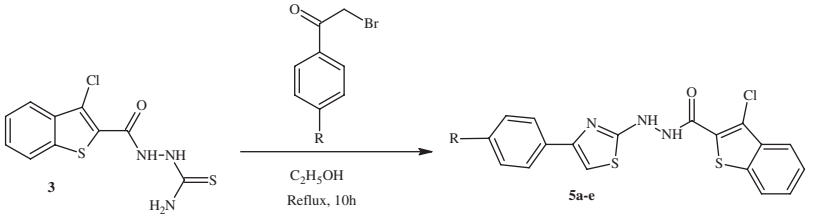
3-Chloro-1-benzothiophene-2-carbonylchloride **1** was allowed to react with hydrazine hydrate to give carbohydrazide **2**. The reaction of 3-chloro-1-benzothiophene-2-carbohydrazide **2** with potassium thiocyanate gave compound **3**, which was cyclized to form thioxotetrahydropyrimidine **4**, thiazoles **5a**–**e**, triazoles **7a**–**e** and oxadiazoles **10a**–**h**. The structures of all the synthesized compounds were confirmed by spectral data and have been screened for antimicrobial, analgesic and anthelmintic activities.




| Compound | R |
|---|---|
| **5a** | -H |
| **5b** | -F |
| **5c** | $-NO_2$ |
| **5d** | -Br |
| **5e** | -Cl |

**Keywords:** benzothiophene; thiazole; triazole; oxadiazole; biological activity

## 1. Introduction

Benzothiophene, second in importance to thiophene among sulfur heterocycles and discovered soon after the latter's discovery, attracted scant attention at that time, apart from some interest shown toward thioindigo dyes. The scenario, however, changed with the advent of bioisosterism,

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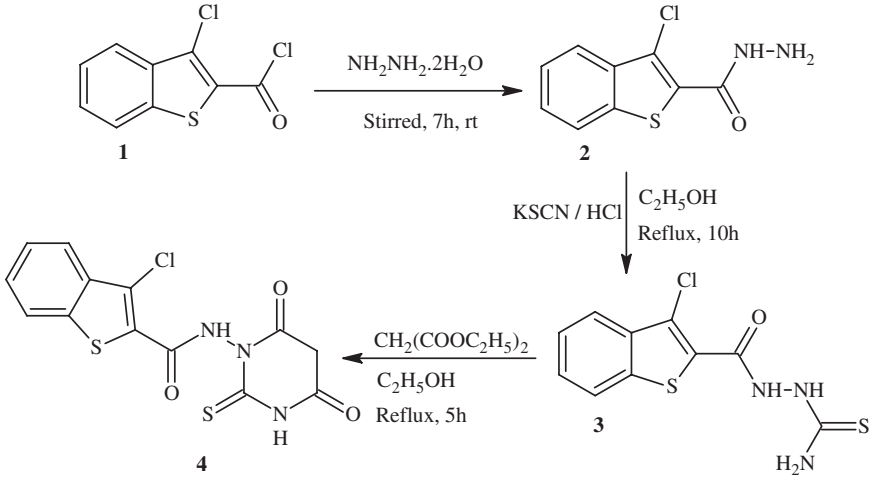
when organic chemists started showing interest in benzothiophene since it is a bioisoster of indole. The synthesis of several sulfur analogs of bioactive furanochromones and furanocoumarins are also reported in the literature (*1*, *2*). These analogs consisting of a benzothiophene core are usually obtained from the latter through suitable annulation reactions. The benzothiophene nucleus is associated with diverse pharmacological activities such as nervous system depression (*3*), analgesic (*4*), herbicidal (*5*), muscle relaxant (*6*) and tranquilizing (*7*) activities. The generation of compounds incorporating thiazole, triazole and oxadiazole moieties have attracted widespread attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory, analgesic and anti-tumor activities (*8–12*). We report here the synthesis of compounds derived from benzothiophene containing thioxotetrahydropyrimidine, thiazoles, triazoles and oxadiazoles moieties via carbothioamide intermediate. We also report the results of biological screening for possible antibacterial, antifungal, analgesic and anthelmintic activity of the resulting derivatives.




Scheme 1. Synthesis of thioxotetrahydropyrimidine **4**.

## 2. Results and discussion

3-Chloro-1-benzothiophene-2-carbonylchloride **1** was prepared by the reaction of cinnamic acid with thionyl chloride in dimethyl formamide (DMF) and dry pyridine according to the reported method (*13*). Compound **1** was then treated with hydrazine hydrate to obtain benzothiophene-2-carbohydrazide **2**. As anticipated, the IR spectrum of compound **2** exhibited peaks at 3020 and 1605 $cm^{-1}$ corresponding to NH and C=O stretching absorption frequencies, respectively. The $^1$H-nuclear magnetic resonance (NMR) spectrum of compound **2** exhibited a multiplet in the region between 7.92 and 7.41 ppm (parts per million) due to four aromatic protons and a singlet at 8.22 ppm which corresponds to the one proton of the CONH group and a broad peak at 4.22 ppm ($D_2O$ exchangeable) corresponding to the two protons of the $NH_2$ group. Finally, compound **2** produced a molecular ion peak at $m/z$ 226.68 which is in accordance with the structure. Condensation of compound **2** with potassium thiocyanate gave carbothioamide **3**. Compound **3** was reacted with diethyl malonate, resulting in compound **4** which showed a characteristic singlet at 3.25 ppm due to the $CH_2$ proton. Compound **3** also reacts with phenacyl bromide which underwent cyclization to give **5a–e**. The IR spectrum of compound **5a** exhibited peaks at 3212 and 1695 $cm^{-1}$ corresponding to NH and C=O stretching absorption frequencies, respectively.

The $^1$H-NMR spectrum of compound **5a** exhibited a multiplet in the region between 8.23 and 8.11 ppm due to ten aromatic protons and two singlets at 9.94 and 4.12 ppm which corresponds to the two protons of the CONH and NH groups. Finally, **5a** produced a molecular ion peak at $m/z$ 385.89 which is in accordance with the structure. Compound **3** upon heating with 4% NaOH in ethanol underwent cyclization with loss of water to form 1,2,4-triazole-3-thiol **6**. Condensation of phenacyl bromide with compound **6** gave compound **7a**. This was confirmed by its mass spectrum (MS) that showed a molecular ion peak at $m/z$ 385.89, which agrees with the molecular weight of the compound. Compound **2** was also treated with chloroacetyl chloride, resulting in compound **8** which showed a characteristic singlet at 3.48 ppm due to the $CH_2$ proton. Compound **8** when treated with $POCl_3$ gave 2-(3-chloro-1-benzothiophen-2-yl)-5-(chloromethyl)-1,3,4-oxadiazole **9**. Compound **9** served as the precursor of compounds **10a**–**h** by nucleophilic displacement of the chloride with a series of aromatic amines. Two singlets in the $^1$H-NMR spectrum at 10.02 and 3.38 ppm corresponding to the NH and $CH_2$ groups in **10a**, provided confirmation of its structure. The $^1$H and $^{13}$C, IR, MS and combustion analyses of **10a**–**h**, which are given in the experimental section, provide compelling evidence for the structures of these new benzothiophene derivatives.

## 3. Biological evaluation

### 3.1. *Antibacterial activity*

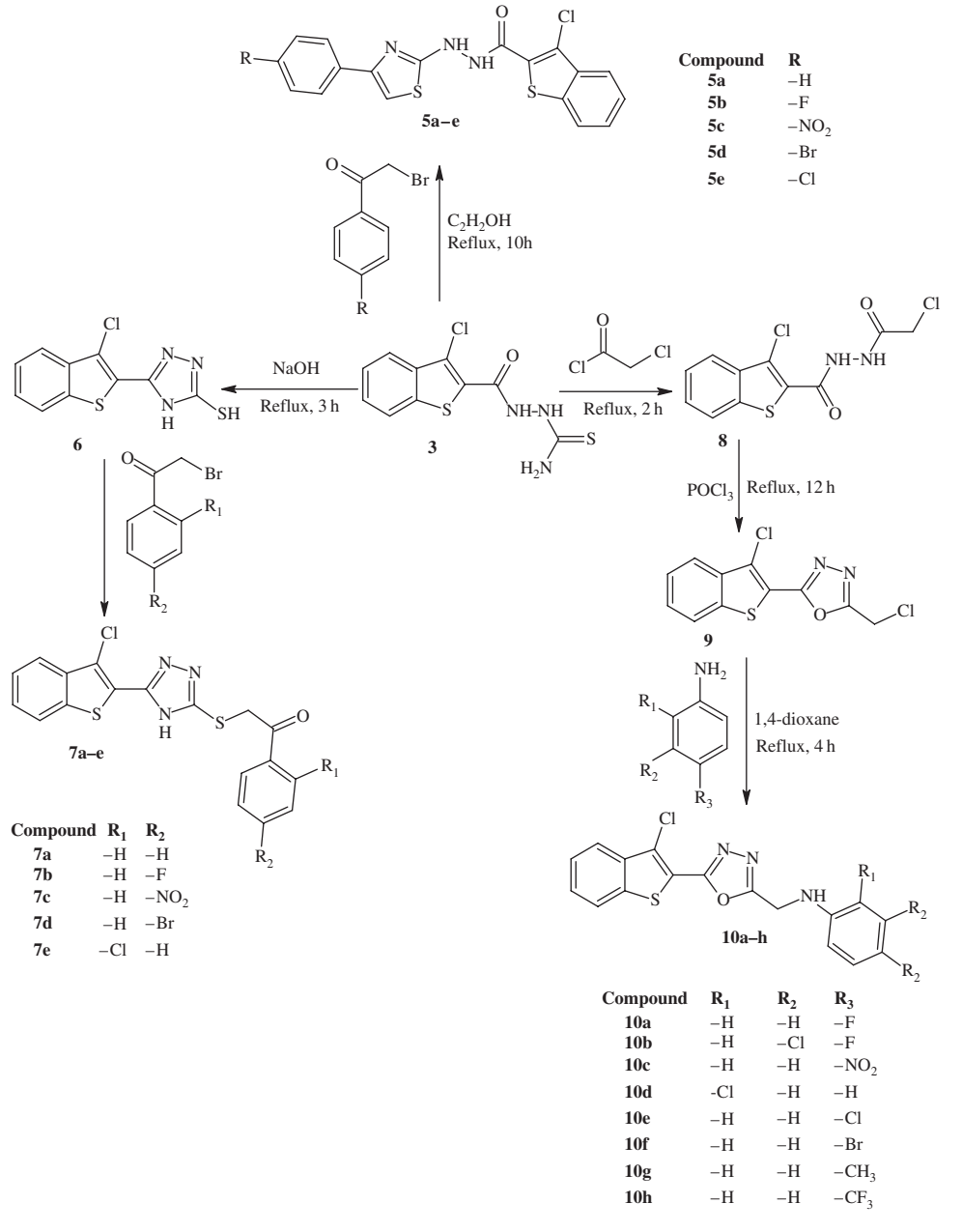
The cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of the synthesized compounds against two Gram-positive bacteria, *Staphylococcus aureus*-ATCC 25923, *Bacillus subtilis*-ATCC 6633 and Gram-negative bacteria, *Pseudomonas aeruginosa*-ATCC 10145, *Escherichia coli*-ATCC 35218. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water was carried out according to a standard procedure (*14*). Each test compound (50 mg) was dissolved in DMF (50 ml, 1000 $\mu$g/ml) to obtain a sample solution. The sample volume for all the compounds was fixed at 0.1 ml. The cups were made by scooping out agar medium with sterilized cork borer in a Petri dish, which was previously inoculated with the microorganisms. The solution of each test compound (0.1 ml) was added in the cups and Petri dishes were subsequently incubated at 37 °C for 48 h. Ampicillin and streptomycin were used as reference drugs and DMF as a control. The zone of inhibition produced by each compound was measured in millimeters. As shown in Table 1, the tested compounds showed moderate antibacterial activity compared with standard drugs against each microorganism.

### 3.2. *Antifungal activity*

The antifungal activity of the synthesized compounds was tested against four different fungi, *i.e. Candida albicans*, *Crysosporium pannical*, *Aspergillus niger* and *Rhizopus oryzae* by the filter paper disc technique (*15*). The concentration of test compounds was 1000 $\mu$g/ml. After 48 h treatment, the zone of inhibition produced by each compound was measured in millimeters. Griseofulvin was used as the standard antifungal agent and DMF as a control. The results of the antifungal activity are depicted in Table 2. Tested compounds showed slight to moderate antifungal activity.

### 3.3. *Analgesic activity*

Albino mice of either sex (20–30 g) were used to evaluate acetic acid induced writhing analgesic activity (*16*). Acetic acid (0.6%, 10 ml/kg) was used to induce writhing in mice. The




Scheme 2. Synthesis of thiazoles **5a**–**e**, triazoles **7a**–**e** and oxadiazoles **10a**–**h**.

mice were divided into five groups, each consisting of six animals. The analgesic response was assessed by counting the number of abdominal constrictions for 20 min starting 3 min after the injection of acetic acid solution. Groups 1–4 received the suspension of test compounds at the dose of 100 mg/kg, respectively, and Group 5 received the standard drug suspension (Ibuprofen) at the dose of 100 mg/kg. After 1 h, an acetic acid solution was administered intraperitoneally and the number of abdominal constrictions was recorded for 20 min starting from 3 min, after the injection of acetic acid solution. All tested compounds showed varying degree of

Table 1. Antibacterial activity of the tested compounds.

| | Zone of inhibition (mm) | | | |
|---|---|---|---|---|
| | Gram-positive bacteria | | Gram-negative bacteria | |
| Compound | *S. aureus* | *B. subtilis* | *P. aeruginosa* | *E. coli* |
| **4** | 14 | 14 | 13 | 15 |
| **5a** | 15 | 14 | 12 | 13 |
| **5b** | 13 | 13 | 10 | 13 |
| **6** | 15 | 14 | 13 | 12 |
| **7a** | 14 | 14 | 14 | 12 |
| **7b** | 16 | 15 | 15 | 12 |
| **9** | 14 | 14 | 12 | 14 |
| **10a** | 14 | 15 | 13 | 12 |
| **10b** | 13 | 14 | 10 | 13 |
| **10c** | 14 | 15 | 12 | 10 |
| Control (DMF) | 00 | 00 | 00 | 00 |
| Ampicillin | 22 | 25 | 20 | 22 |
| Streptomycin | 23 | 20 | 18 | 20 |

Table 2. Antifungal activity of the tested compounds.

| | Zone of inhibition (mm) | | | |
|---|---|---|---|---|
| Compound | *C. albicans* | *C. pannical* | *A. niger* | *R. oryzae* |
| **4** | 12 | 17 | 15 | 15 |
| **5a** | 15 | 15 | 11 | 12 |
| **5b** | 14 | 11 | 11 | 11 |
| **6** | 14 | 13 | 14 | 14 |
| **7a** | 16 | 12 | 11 | 13 |
| **7b** | 12 | 11 | 12 | 14 |
| **9** | 12 | 15 | 14 | 11 |
| **10a** | 13 | 10 | 13 | 13 |
| **10b** | 12 | 17 | 15 | 15 |
| **10c** | 15 | 12 | 12 | 15 |
| Control (DMF) | 00 | 00 | 00 | 00 |
| Griseofulvin | 24 | 25 | 23 | 22 |



analgesic activity with respect to ibuprofen taken as the standard drug. The analgesic activity was calculated as the percentage maximum possible effect (% MPE) and the results are given in Table 3.

### 3.4. *Anthelmintic activity*

The anthelmintic activity studies were carried out against earthworms (*pontoscolex corethrusus*) according to a reported method (*17*). Six earthworms of approximately the same size were placed in each Petri dish containing a 50 ml suspension of the specific concentration at 28 ± 1 °C. Simultaneously, a control study comprising six worms in distilled water and Tween-80 (0.5%) was run. The drug concentrations were 0.1% (wt/vol.) for the standard and the test sample. The times required for paralysis (movement stopped) and deaths of the worms were noted using a stopwatch and the results are given in Table 4.

Table 3. Analgesic activity of the tested compounds.

| Compound | Dose (mg/kg) | Mean number of abdominal constrictions that occurred between 3 and 20 min | | % MPE |
|---|---|---|---|---|
| | | Before drug | After drug | |
| **4** | 100 | 40.1 ± 2.00 | 15.2 ± 1.40 | 60.1* |
| **5a** | 100 | 24.8 ± 1.21 | 08.4 ± 0.92 | 66.1* |
| **5b** | 100 | 40.1 ± 2.00 | 15.2 ± 1.40 | 60.1* |
| **6** | 100 | 28.6 ± 1.73 | 12.2 ± 1.21 | 64.1* |
| **7a** | 100 | 40.6 ± 2.12 | 13.8 ± 0.43 | 61.3* |
| **7b** | 100 | 52.4 ± 2.51 | 17.2 ± 2.61 | 60.3* |
| **9** | 100 | 23.1 ± 1.51 | 08.9 ± 0.82 | 66.4* |
| **10a** | 100 | 26.4 ± 1.63 | 10.4 ± 1.33 | 62.2* |
| **10b** | 100 | 23.8 ± 1.02 | 08.3 ± 1.22 | 61.7* |
| **10c** | 100 | 40.1 ± 2.00 | 15.2 ± 1.40 | 60.1* |
| Ibuprofen | 100 | 47.1 ± 2.50 | 11.8 ± 1.27 | 75.1* |

Notes: Analgesic activity, Student's *t*-test, $n = 6$.
* $P < 0.001$ *vs.* control.

Table 4. Anthelmintic activity of the tested compounds.

| Compound | Number of earth worms tested | Concentration (wt/vol.) (mg) | Mean paralysis time ± SE (min) | Mean death time ± SE (min) |
|---|---|---|---|---|
| **4** | 6 | 100 | 88.40 ± 1.40 | 126.14 ± 3.16 |
| **5a** | 6 | 100 | 28.32 ± 2.14 | 32.00 ± 2.12 |
| **5b** | 6 | 100 | 20.14 ± 0.40 | 25.12 ± 0.68 |
| **6** | 6 | 100 | 72.48 ± 2.16 | 84.32 ± 3.16 |
| **7a** | 6 | 100 | 30.42 ± 3.04 | 38.26 ± 3.16 |
| **7b** | 6 | 100 | 25.10 ± 1.36 | 30.18 ± 3.10 |
| **9** | 6 | 100 | 34.12 ± 2.46 | 48.16 ± 3.02 |
| **10a** | 6 | 100 | 25.44 ± 2.42 | 34.28 ± 2.48 |
| **10b** | 6 | 100 | 71.48 ± 2.16 | 83.32 ± 3.16 |
| **10c** | 6 | 100 | 20.12 ± 0.41 | 25.16 ± 0.65 |
| Piperazine citrate | 6 | 100 | 22.48 ± 2.30 | 46.28 ± 2.42 |
| Mependazole | 6 | 100 | 18.24 ± 2.16 | 55.32 ± 3.42 |
| Control | 6 | 100 | NE | NE |

## 4. Conclusion

In conclusion, a new series of benzothiophene containing thioxotetrahydropyrimidine, thiazoles, triazoles and oxadiazoles derivatives were synthesized and evaluated for their antibacterial, antifungal, analgesic and anthelmintic activities. The newly synthesized heterocyclics exhibited moderate antibacterial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* and significant antifungal activity against *C. albicans*, *C. pannical*, *A. niger* and *R. oryzae* and also moderate analgesic and anthelmintic activities. It can be concluded that these classes of compounds certainly hold great promise toward good active leads in medicinal chemistry.

## 5. Experimental

All chemicals were of analytical grade, purchased from commercial suppliers and used as received without further purification. Melting points were determined in open capillary and were uncorrected. Fourier-transformed infrared spectrum (KBr discs) were recorded using a

Perkin-Elmer 237 spectrophotometer. $^{1}$H-NMR spectra were recorded on a Bruker Supercon FT-NMR spectrometer (at 500 MHz) using DMSO-$d_6$ as a solvent. $^{13}$C-NMR spectrum at 100 MHz was recorded on a Bruker model ACF200 spectrophotometer. All chemical shifts were reported in ppm using residual proton or carbon signals in deuterated solvents as internal references. MS is recorded on Schimadzu GC-MS. Elemental analysis (C, H, N and S) was performed on a Perkin Elmer 240 analyzer and all products were purified by recrystallization. The purity of the compounds was checked by TLC on a silica gel and further purification was performed through column chromatography (silica gel, 60–120 mesh).

### 5.1. *Preparation of 3-chloro-1-benzothiophene-2-carbonyl chloride (1)*

Compound **1** was prepared according to the literature procedure (*13*), mp 112–114 °C (Lit. mp 110–112 °C).

### 5.2. *Preparation of 3-chloro-1-benzo[b]thiophene-2-carboxylicacidhydrazide (2)*

Compound **1** (2.0 g, 0.0086 mol) was added directly to hydrazine hydrate (5.54 g, 5.33 ml and 0.17 mol) slowly with stirring, then the reaction mixture was stirred vigorously for about 7 h on a magnetic stirrer. The reaction mixture was cooled down to room temperature and slowly decomposed in crushed ice. The solid that separated was filtered, washed with water and recrystallized from ethanol to afford **2**.

Yield 85%; mp 183–185 °C; IR $\nu$ (cm$^{-1}$): 3020 (N−H), 1605 (C=O), 1570 (C=C), 1070 (=C−Cl), 680 (C−S−C); $^{1}$H-NMR $\delta$ (ppm): 8.22 (s, 1H, CONH), 7.92–7.41 (m, 4H, Ar−CH), 4.22 (2H, $NH_2$); $^{13}$C-NMR $\delta$ (ppm): 169.2, 138, 131, 129, 128, 125, 123, 122; MS, $m/z$: 226.68 ($M^+$). Anal. calcd. for $C_9H_7ClN_2OS$: C, 47.69; H, 3.11; N, 12.36; S, 14.15; found: C, 47.65; H, 3.09; N, 12.35; S, 14.12%.

### 5.3. *Preparation of 2-[(3-chloro-1-benzo[b]thiophen-2-yl)carbonyl]hydrazinecarbothio amide (3)*

A mixture of carbohydrazide **2** (2.26 g, 0.01 mol) and potassium thiocyanate (0.97 g, 0.01 mol) in the presence of hydrochloric acid (5 ml) in distilled ethanol (50 ml) was refluxed on a steam bath for 10 h. It was then concentrated, cooled and kept overnight in a refrigerator. The precipitate was filtered, washed with ethanol, dried and recrystallized from methanol to get a pure compound **3**.

Yield 66%; mp 194–196 °C; IR $\nu$ (cm$^{-1}$): 3165 (N−H), 1712 (C=O), 1225 (C=S); $^{1}$H-NMR $\delta$ (ppm): 10.75 (s, 1H, CONH), 9.53 (s, $NH_2$), 7.43–7.91 (m, 4H, Ar−CH), 2.13 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 160.6, 182.5, 141.6, 135.9, 133.4, 129.9, 126.7, 124.4, 124.3, 122.8; MS, $m/z$: 285.77 ($M^+$). Anal. calcd. for $C_{10}H_5ClN_2OS_2$: C, 42.03; H, 2.82; N, 14.70; S, 22.44; found: C, 42.01; H, 2.79; N, 14.68; S, 22.40%.

### 5.4. *Preparation of 3-chloro-N-(4,6-dioxo-2-thioxotetrahydropyrimidin-1(2H)-yl)-1-benzothiophene-2-carboxamide (4)*

A mixture of **3** (2.85 g, 0.01 mol) and diethyl malonate (1.60 g, 1.45 ml and 0.01 mol) in ethanol (20 ml) and few drops of piperidine in glacial acetic acid was refluxed for 5 h. After the completion of the reaction (TLC monitoring), the reaction mixture was cooled down to room temperature and then poured into cold dilute HCl (10%). The precipitate was filtered, dried and recrystallized from methanol to give pure product **4** as yellow solid.

Yield 58%; mp 203–205 °C; IR $\nu$ ($cm^{-1}$): 3151 (N−H), 1702 (C=O), 1214 (C=S); $^1$H-NMR $\delta$ (ppm): 10.04 (s, 1H, CONH), 8.13 (s, 1H, NH), 7.43–7.91 (m, 4H, Ar−CH), 3.25 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 183.0, 170.2, 166.3, 160.1, 141.4, 135.5, 133.3, 129.2, 126.7, 124.4, 124.1, 122.8, 42.1; MS, $m/z$: 353.80 ($M^+$). Anal. calcd. for $C_{13}H_8ClN_3O_4S_2$: C, 44.13; H, 2.28; N, 11.88; S, 18.13; found: C, 44.10; H, 2.25; N, 11.84; S, 18.10%.

### 5.5. *The general procedure for the synthesis of compounds 5a–e.*

#### 5.5.1. *Exemplary details for 3-chloro-N′-(4-phenyl-1,3-thiazol-2-yl)-1-benzo[b]thiophene-2-carbohydrazide (**5a**)*

A mixture of **3** (2.85 g, 0.01 mol) and phenacyl bromide (1.99 g, 0.01 mol) in absolute ethanol (50 ml) was refluxed for 10 h. The completion of the reaction was monitored through TLC. After completion of the reaction, the reaction mixture was cooled down to room temperature and poured into crushed ice with vigorous stirring. The precipitate was filtered, washed with water, dried and purified through column chromatography by using *n*-hexane and ethyl acetate (70:30) as an elutent to get pure compound **5a**. Compounds **5b**–**e** were prepared in a similar manner.

Yield 65%; mp 210–212 °C; IR $\nu$ ($cm^{-1}$): 3212 (N−H), 1695 (C=O); $^1$H-NMR $\delta$ (ppm): 9.94 (s, 1H, CONH), 8.23–8.11 (m, 10H, Ar−CH and thiazole ring), 4.12 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 173.1, 160.4, 150.5, 141.6, 135.7, 133.4, 133.1, 129.9, 129.2, 129.2, 128.7, 127.5, 127.5, 126.7, 124.4, 124.3, 122.7, 105.0; MS, $m/z$: 385.89 ($M^+$). Anal. calcd. for $C_{18}H_{12}ClN_3OS_2$: C, 56.02; H, 3.13; N, 10.89; S, 16.62; found: C, 56.00; H, 3.09; N, 10.87; S, 16.60%.

#### 5.5.2. *3-Chloro-N′-[4-(4-fluorophenyl)-1,3-thiazol-2-yl]-1-benzo[b]thiophene-2-carbohydrazide (**5b**)*

Yield 66%; mp 234–236 °C; IR $\nu$ ($cm^{-1}$): 3220 (N−H), 1703 (C=O), 1209 (C−F); $^1$H-NMR $\delta$ (ppm): 9.23 (s, 1H, CONH), 8.43–8.01 (m, 9H, Ar−CH and thiazole ring), 4.10 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 173.1, 162.4, 160.3, 150.1, 141.2, 135.4, 133.3, 130.6, 130.6, 129.9, 128.6, 126.7, 124.4, 124.3, 122.8, 116.0, 116.0, 106.1; MS, $m/z$: 403.88 ($M^+$). Anal. calcd. for $C_{18}H_{11}ClFN_3OS_2$: C, 53.53; H, 2.75; N, 10.40; S, 15.88; found: C, 53.50; H, 2.70; N, 10.37; S, 15.85%.

#### 5.5.3. *3-Chloro-N′-[4-(4-nitrophenyl)-1,3-thiazol-2-yl]-1-benzo[b]thiophene-2-carbohydrazide (**5c**)*

Yield 62%; mp 240–242 °C; IR $\nu$ ($cm^{-1}$): 3214 (N−H), 1710 (C=O), 1488 (Ar−$NO_2$); $^1$H-NMR $\delta$ (ppm): 9.22 (s, 1H, CONH), 8.51–8.15 (m, 9H, Ar−CH and thiazole ring), 4.19 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 173.5, 160.3, 150.2, 147.4, 141.3, 139.1, 135.9, 133.4, 129.2, 126.1, 126.2, 126.2, 124.5, 124.5, 124.3, 124.3, 122.5, 106.1; MS, $m/z$: 430.88 ($M^+$); Anal. calcd. for $C_{18}H_{11}ClN_4O_3S_2$: C, 50.17; H, 2.57; N, 13.00; S, 14.88; found: C, 50.15; H, 2.54; N, 12.97; S, 14.84%.

#### 5.5.4. *3-Chloro-N′-[4-(4-bromophenyl)-1,3-thiazol-2-yl]-1-benzo[b]thiophene-2-carbohydrazide (**5d**)*

Yield 63%; mp 250–252 °C; IR $\nu$ ($cm^{-1}$): 3204 (N−H), 1714 (C=O), 576 (C−Br); $^1$H-NMR $\delta$ (ppm): 9.09 (s, 1H, CONH), 8.91–8.05 (m, 9H, Ar−CH and thiazole ring), 4.22 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 173.7, 160.2, 150.2, 141.1, 135.9, 133.4, 132.3, 132.3, 132.0, 129.4, 128.2, 128.3,

126.7, 124.4, 124.3, 122.8, 105.0; MS, $m/z$: 464.78 ($M^+$). Anal. calcd. for $C_{18}H_{11}ClBrN_3OS_2$: C, 46.51; H, 2.39; N, 9.04; S, 13.80; found: C, 46.48; H, 2.35; N, 9.01; S, 13.78%.

#### 5.5.5. *3-Chloro-N′-[4-(2-chlorophenyl)-1,3-thiazol-2-yl]-1-benzo[b]thiophene-2-carbohydrazide (**5e**)*

Yield 66%; mp 239–241 °C; IR $\nu$ ($cm^{-1}$): 3203 (N−H), 1711 (C=O); $^1$H-NMR $\delta$ (ppm): 9.07 (s, 1H, CONH), 8.66–8.14 (m, 9H, Ar−CH and thiazole ring), 4.16 (s, 1H, NH); $^{13}$C-NMR $\delta$ (ppm): 173.9, 160.1, 150.2, 141.6, 135.9, 134.3, 133.4, 131.2, 129.5, 129.4, 129.4, 128.5, 128.9, 126.7, 124.4, 124.1, 122.5, 105.0; MS, $m/z$: 420.33 ($M^+$). Anal. calcd. for $C_{18}H_{11}Cl_2N_3OS_2$: C, 51.43; H, 2.64; N, 10.00; S, 15.26; found: C, 51.40; H, 2.61; N, 9.97; S, 15.22%.

### 5.6. *Preparation of 5-(3-chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazole-3-thiol (6)*

A mixture of compound **3** (2 g) and sodium hydroxide (4%, 10 ml) was refluxed for 3 h. After completion of reaction, the reaction mixture was acidified with dilute. HCl, the precipitate was collected, dried and recrystallized from ethanol. Purification by column chromatography [silica gel, petroleum ether/ethyl acetate (5:95)] yielded pure **6**.

Yield 70%; mp 200–202 °C; IR $\nu$ ($cm^{-1}$): 3310 (N−H), 1630 (C=N), 1310 (C=S thione); $^1$H-NMR $\delta$ (ppm): 9.17 (s, 1H, NH), 8.32–8.11 (m, 4H, Ar−CH), 3.52 (s, 1H, SH); $^{13}$C-NMR $\delta$ (ppm): 141.5, 138.7, 136.9, 124.4, 124.3, 123.2, 122.8, 118.4; MS, $m/z$: 267.75 ($M^+$). Anal. calcd. for $C_{10}H_6ClN_3S_2$: C, 44.86; H, 2.26; N, 15.69; S, 23.95; found: C, 44.84; H, 2.23; N, 15.65; S, 23.91%.

### 5.7. *General procedure for synthesis of compounds 7a–e*

#### 5.7.1. *Exemplary detail for the preparation of 2-{[5-(3-chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-phenylethanone (**7a**)*

To a stirred solution of compound **6** (2.67 g, 0.01 mol) and sodium acetate (0.02 mol) in ethanol (20 ml), phenacyl bromide (1.99 g, 0.01 mol) was added. The mixture was refluxed for 4 h. After the completion of the reaction mixture (TLC monitoring), the reaction mixture was cooled down to room temperature and then added to crushed ice. The precipitate was filtered, washed with water, dried and purified through column chromatography by using petroleum ether and ethyl acetate (60:40) as an eluent to afford pure **7a**. Compounds **7b**–**e** was prepared in similar methodology.

Yield 62%; mp 231–233 °C; IR $\nu$ ($cm^{-1}$): 3305 (N−H), 1712 (C=O), 1635 (C=N); $^1$H-NMR $\delta$ (ppm): 9.45 (s, 1H, NH), 8.32–7.89 (m, 9H, Ar−CH), 3.40 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 194.6, 158.3, 141.2, 138.1, 136.4, 135.4, 133.2, 128.1, 128.1, 128.4, 128.4, 124.4, 124.3, 123.2, 122.8, 118.4, 38.5; MS, $m/z$: 385.89 ($M^+$). Anal. calcd. for $C_{18}H_{12}ClN_2OS_2$: C, 56.02; H, 3.13; N, 15.60; S, 23.95; found: C, 56.00; H, 3.10; N, 15.63; S, 23.92%.

#### 5.7.2. *2-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-(4-fluorophenyl)ethanone (**7b**)*

Yield 61%; mp 241–243 °C; IR $\nu$ ($cm^{-1}$): 3321 (N−H), 1702 (C=O), 1630 (C=N); $^1$H-NMR $\delta$ (ppm): 9.52 (s, 1H, NH), 8.12–7.99 (m, 8H, Ar−CH), 3.35 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 194.5, 167.3, 158.2, 141.1, 138.4, 136.5, 131.6, 130.4, 124.4, 124.3, 123.2, 122.8, 118.4, 115.4, 115.4, 38.2; MS, $m/z$: 403.88 ($M^+$). Anal. calcd. for $C_{18}H_{11}ClFN_3OS_2$: C, 53.53; H, 2.75; N, 10.40; S, 15.88; found: C, 53.50; H, 2.70; N, 10.38; S, 15.86%.

5.7.3. *2-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-(4-nitrophenyl)ethanone (**7c**)*

Yield 62%; mp 222–224 °C; IR $\nu$ ($cm^{-1}$): 3301 (N−H), 1704 (C=O), 1629 (C=N), 1491 (Ar−$NO_2$); $^1$H-NMR $\delta$ (ppm): 9.11 (s, 1H, NH), 8.76–8.11 (m, 8H, Ar−CH), 3.43 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 194.1, 158.6, 152.1, 141.4, 141.4, 138.5, 136.9, 129.4, 129.4, 124.4, 124.3, 123.8, 123.8, 123.2, 122.8, 118.5, 38.7; MS, $m/z$: 430.88 ($M^+$). Anal. calcd. for $C_{18}H_{11}ClN_4O_3S_2$: C, 50.17; H, 2.57; N, 13.00; S, 14.88; found: C, 50.16; H, 2.56; N, 12.98; S, 14.86%.

5.7.4. *2-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-(4-bromophenyl)ethanone (**7d**)*

Yield 60%; mp 250–252 °C; IR $\nu$ ($cm^{-1}$): 3307 (N−H), 1708 (C=O), 1625 (C=N), 569 (C−Br); $^1$H-NMR $\delta$ (ppm): 9.80 (s, 1H, NH), 8.88–8.14 (m, 8H, Ar−CH), 3.49 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 194.7, 158.4, 141.2, 138.5, 136.9, 134.2, 131.1, 131.5, 129.8, 129.8, 127.5, 124.4, 124.1, 123.1, 122.2, 118.4, 38.2; MS, $m/z$: 464.78 ($M^+$). Anal. calcd. for $C_{18}H_{11}BrClN_3OS_2$: C, 46.51; H, 2.39; N, 9.04; S, 13.80; found: C, 46.49; H, 2.35; N, 9.01; S, 13.76%.

5.7.5. *2-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-4H-1,2,4-triazol-3-yl]sulfanyl}-1-(2-chlorophenyl)ethanone (**7e**)*

Yield 62%; mp 260–262 °C; IR $\nu$ ($cm^{-1}$): 3300 (N−H), 1705 (C=O), 1633 (C=N); $^1$H-NMR $\delta$ (ppm): 10.01 (s, 1H, NH), 8.06–7.77 (m, 8H, Ar−CH), 3.48 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 194.8, 158.4, 141.3, 138.2, 138.7, 136.9, 133.4, 130.1, 130.2, 128.7, 128.7, 124.4, 124.3, 123.2, 122.1, 118.2, 38.4; MS, $m/z$: 420.33 ($M^+$). Anal. calcd. for $C_{18}H_{11}Cl_2N_3OS_2$: C, 51.43; H, 2.64; N, 10.00; S, 15.26; found: C, 51.40; H, 2.60; N, 9.98; S, 15.23%.

### 5.8. *Preparation of 3-chloro-N′-(chloroacetyl)-1-benzo[b]thiophene-2-carbohydrazide (8)*

Carbohydrazide **2** (2.26 g, 0.01 mol) was added to chloroacetyl chloride (1.12 g, 0.81 ml and 0.01 mol) in pyridine (10 ml) and refluxed for 2 h. The reaction mixture was then poured over an ice/HCl mixture. The resulting precipitate was filtered and recrystallized from toluene to afford **8**.

Yield 85%; mp 245–247 °C; IR $\nu$ ($cm^{-1}$): 3291 (N−H), 1691 (C=O); $^1$H-NMR $\delta$ (ppm): 10.71 (s, 1H, NH), 10.07 (s, 1H, CONH), 8.56–8.10 (m, 4H, Ar−CH), 3.41 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 166.3, 160.6, 141.6, 135.5, 133.4, 129.9, 126.7, 124.7, 124.3, 122.8, 41.5; MS, $m/z$: 303.16 ($M^+$). Anal. calcd. for $C_{11}H_8Cl_2N_2O_2S$: C, 43.58; H, 2.66; N, 9.24; S, 10.58; found: C, 43.56; H, 2.62; N, 9.20; S, 10.54%.

### 5.9. *Preparation of 2-(3-chloro-1-benzo[b]thiophen-2-yl)-5-(chloromethyl)-1,3,4-oxadiazole (9)*

3-Chloro-*N′*-(chloroacetyl)-1-benzo[b]thiophene-2-carbohydrazide **8** (3.03 g and 0.01 mol) in $POCl_3$ (50 ml) was refluxed for 12 h. The completion of the reaction was monitored through TLC. Upon completion of the reaction, the reaction mixture was cooled down to room temperature and poured into crushed ice with vigorous stirring and neutralized with saturated sodium bicarbonate solution. The precipitate was filtered, washed with water, dried and purified through column chromatography by using *n*-hexane and ethyl acetate (90:10) as an elutent to afford **9**.

Yield 70%; mp 256–258 °C; IR $\nu$ ($cm^{-1}$): 1635 (C=N); $^1$H-NMR $\delta$ (ppm): 8.76–8.12 (m, 4H, Ar−CH), 3.46 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.1, 141.4, 138.5, 124.3, 124.3, 123.2, 122.5, 118.4, 47.5, 36.5; MS, $m/z$: 285.14 ($M^+$). Anal. calcd. for $C_{11}H_6Cl_2N_2OS$: C, 46.33; H, 2.12; N, 9.82; S, 11.24; found: C, 46.30; H, 2.09; N, 9.79; S, 11.20%.

### 5.10. *General procedure for synthesis of compounds 10a–h*

#### 5.10.1. *Exemplary detail for N-{[5-(3-chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-fluoroaniline (**10a**)*

A mixture of **9** (2.85 g and 0.01 mol) and 4-fluoroaniline (1.11 g, 0.98 ml and 0.01 mol) in 1,4-dioxane (20 ml) was refluxed for 4 h. After completion of the reaction, the reaction mixture was cooled down to room temperature and poured into ice cooled water with stirring, the precipitate was filtered, washed with water, dried and recrystallized from 1,4-dioxane. Purification by column chromatography [silica, petroleum ether/ethyl acetate (50:50)] afforded pure white crystals of **10a**. Similarly, compounds **10b**–**h** were prepared with little change in refluxed time and reaction work-up.

Yield 60%; mp 249–251 °C; IR $\nu$ ($cm^{-1}$): 3303 (N−H), 1623 (C=N); $^1$H-NMR $\delta$ (ppm): 10.02 (s, 1H, NH), 8.74–8.21 (m, 8H, Ar−CH), 3.38 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 163.6, 161.2, 147.3, 141.5, 138.7, 136.9, 131.2, 124.4, 124.3, 123.2, 122.8, 118.4, 110.5, 109.1, 103.4, 51.6; MS, $m/z$: 259.80 ($M^+$). Anal. calcd. for $C_{17}H_{11}ClFN_3OS$: C, 56.75; H, 3.08; N, 11.68; S, 8.91; found: C, 56.74; H, 3.06; N, 11.65; S, 8.89%.

#### 5.10.2. *3-Chloro-N-{[5-(3-chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-fluoroaniline (**10b**)*

Yield 61%; mp 260–262 °C; IR $\nu$ ($cm^{-1}$): 3310 (N−H), 1629 (C=N); $^1$H-NMR $\delta$ (ppm): 10.11 (s, 1H, NH), 8.54–8.31 (m, 8H, Ar−CH), 3.32 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 163.7, 161.3, 147.1, 141.5, 138.1, 136.1, 131.2, 124.4, 124.3, 123.2, 122.8, 118.4, 110.5, 109.1, 103.4, 51.3; MS, $m/z$: 394.25 ($M^+$). Anal. calcd. for $C_{17}H_{10}Cl_2N_3OS$: C, 51.79; H, 2.56; N, 10.66; S, 8.13; found: C, 51.74; H, 2.53; N, 10.63; S, 8.09%.

#### 5.10.3. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-nitroaniline (**10c**)*

Yield 66%; mp 278–280 °C; IR $\nu$ ($cm^{-1}$): 3298 (N−H), 1620 (C=N), 1485 (Ar−$NO_2$); $^1$H-NMR $\delta$ (ppm): 9.89 (s, 1H, NH), 8.91–8.09 (m, 8H, Ar−CH), 3.46 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.2, 155.3, 141.1, 138.6, 136.7, 136.1, 127.3, 127.3, 124.2, 124.1, 123.2, 122.8, 118.4, 114.4, 114.4, 51.1; MS, $m/z$: 386.80 ($M^+$). Anal. calcd. for $C_{17}H_{11}ClN_4O_3S$: C, 52.79; H, 2.87; N, 14.48; S, 8.29; found: C, 52.74; H, 2.85; N, 14.44; S, 8.25%.

#### 5.10.4. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-2-chloroaniline (**10d**)*

Yield 60%; mp 245–247 °C; IR $\nu$ ($cm^{-1}$): 3312 (N−H), 1631 (C=N); $^1$H-NMR $\delta$ (ppm): 10.11 (s, 1H, NH), 8.99–8.41 (m, 8H, Ar−CH), 3.44 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.1, 143.4, 141.3, 138.6, 136.5, 130.3, 127.6, 124.4, 124.3, 123.8, 123.2, 122.8, 122.4, 118.4, 114.9, 51.2; MS, $m/z$: 376.25 ($M^+$). Anal. calcd. for $C_{17}H_{11}Cl_2N_3OS$: C, 54.27; H, 2.95; N, 11.17; S, 8.52; found: C, 54.25; H, 2.92; N, 11.15; S, 8.48%.

5.10.5. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-chloroaniline (**10e**)*

Yield 62%; mp 230–232 °C; IR $\nu$ ($cm^{-1}$): 3308 (N−H), 1619 (C=N); $^1$H-NMR $\delta$ (ppm): 9.88 (s, 1H, NH), 8.66–8.21 (m, 8H, Ar−CH), 3.49 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.7, 143.3, 141.2, 138.1, 136.4, 130.5, 124.4, 124.3, 123.8, 123.1, 122.1, 122.4, 118.4, 114.9, 53.1; MS, $m/z$: 376.25 ($M^+$). Anal. calcd. for $C_{17}H_{11}Cl_2N_3OS$: C, 54.27; H, 2.95; N, 11.17; S, 8.52; found: C, 54.25; H, 2.90; N, 11.14; S, 8.50%.

5.10.6. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-bromoaniline (**10f**)*

Yield 57%; mp 278–280 °C; IR $\nu$ ($cm^{-1}$): 3301 (N−H), 1633 (C=N), 581 (C−Br); $^1$H-NMR $\delta$ (ppm): 10.12 (s, 1H, NH), 8.72–8.01 (m, 8H, Ar−CH), 3.43 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.5, 148.1, 141.4, 138.7, 136.9, 132.4, 132.3, 124.3, 124.2, 123.1, 122.1, 118.4, 115.4, 114.4, 114.5, 51.6; MS, $m/z$: 420.71 ($M^+$). Anal. calcd. for $C_{17}H_{11}ClBrN_3OS$: C, 48.53; H, 2.64; N, 9.99; S, 7.62; found: C, 48.50; H, 2.60; N, 9.96; S, 7.59%.

5.10.7. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-methylaniline (**10g**)*

Yield 64%; mp 245–247 °C; IR $\nu$ ($cm^{-1}$): 3293 (N−H), 1631 (C=N); $^1$H-NMR $\delta$ (ppm): 9.85 (s, 1H, NH), 8.76–8.09 (m, 8H, Ar−CH), 3.44 (s, 2H, $CH_2$), 2.89 (s, 3H, $CH_3$); $^{13}$C-NMR $\delta$ (ppm): 161.1, 146.2, 141.4, 138.7, 136.9, 129.8, 129.8, 129.6, 124.4, 124.1, 123.1, 122.4, 118.3, 113.4, 113.4, 51.3, 21.1; MS, $m/z$: 355.84 ($M^+$). Anal. calcd. for $C_{18}H_{14}ClN_3OS$: C, 60.76; H, 3.97; N, 11.81; S, 9.01; found: C, 60.74; H, 3.95; N, 11.78; S, 9.00%.

5.10.8. *N-{[5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]methyl}-4-(trifluoromethyl)aniline (**10h**)*

Yield 66%; mp 250–252 °C; IR $\nu$ ($cm^{-1}$): 3299 (N−H), 1637 (C=N); $^1$H-NMR $\delta$ (ppm): 9.99 (s, 1H, NH), 8.71–8.17 (m, 8H, Ar−CH), 3.46 (s, 2H, $CH_2$); $^{13}$C-NMR $\delta$ (ppm): 161.8, 152.3, 141.2, 138.5, 136.7, 125.7, 125.7, 124.3, 124.4, 124.3, 124.1, 123.2, 122.8, 118.3, 113.4, 113.4, 51.2; MS, $m/z$: 409.81 ($M^+$). Anal. calcd. for $C_{18}H_{11}ClF_3N_3OS$: C, 52.75; H, 2.71; N, 10.25; S, 7.82; found: C, 52.73; H, 2.69; N, 10.23; S, 7.80%.

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