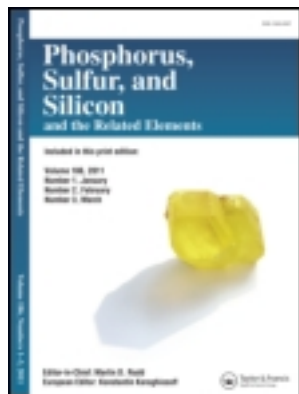


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### Utility of 3-Chlorobenzothiophene-2-Carbonylisoithiocyanate for the Synthesis of Some Novel Biheterocycles of Expected Biological Activity

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## UTILITY OF 3-CHLOROBENZOTHIOPHENE-2-CARBONYLSISOTHIOCYANATE FOR THE SYNTHESIS OF SOME NOVEL BIHETEROCYCLES OF EXPECTED BIOLOGICAL ACTIVITY

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*The behavior of 3-chlorobenzothiophene-2-carbonyl isothiocyanate 2 towards nitrogen nucleophiles such as primary amines, substituted hydrazines, aryl hydrazines, glycine, anthranilic acid; sulfur nucleophiles such as thioglycolic acid; and oxygen nucleophiles such as substituted phenols has been investigated and found that it proceeds via isothiocyanate heterocyclization to furnish noncondensed heterocyclic compounds containing thiourea, triazole, oxazole, thiazole, and benzoxazole nuclei besides the benzo[b]thiophene nucleus. The structures of the newly synthesized compounds were elucidated on the basis of IR, <sup>1</sup>H NMR, and mass spectral data of the compounds, and they have been screened for antimicrobial, analgesic, and anti-inflammatory activities.*

*Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements to view the free supplemental file.*

**Keywords** Analgesic activity; anti-inflammatory activity; antimicrobial activity; 3-chlorobenzothiophene-2-carbonyl isothiocyanate

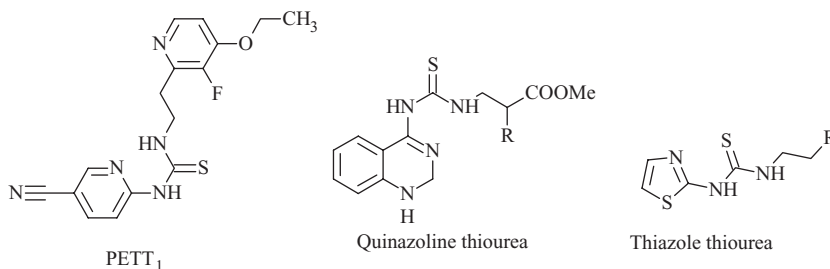
## INTRODUCTION

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 towards thioindigo dyes. The scenario, however, changed with the advent of bioisosterism, when organic chemists started showing interest in benzothiophene since it is a bioisoster of indole. The synthesis of several sulfur analogues of bioactive furanochromones and furanocoumarins are also reported in the literature. These analogues, consisting of a benzothiophene core, are usually obtained from the latter through suitable annulation reactions.<sup>1–2</sup>

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**Figure 1** Potent NNRTIs.

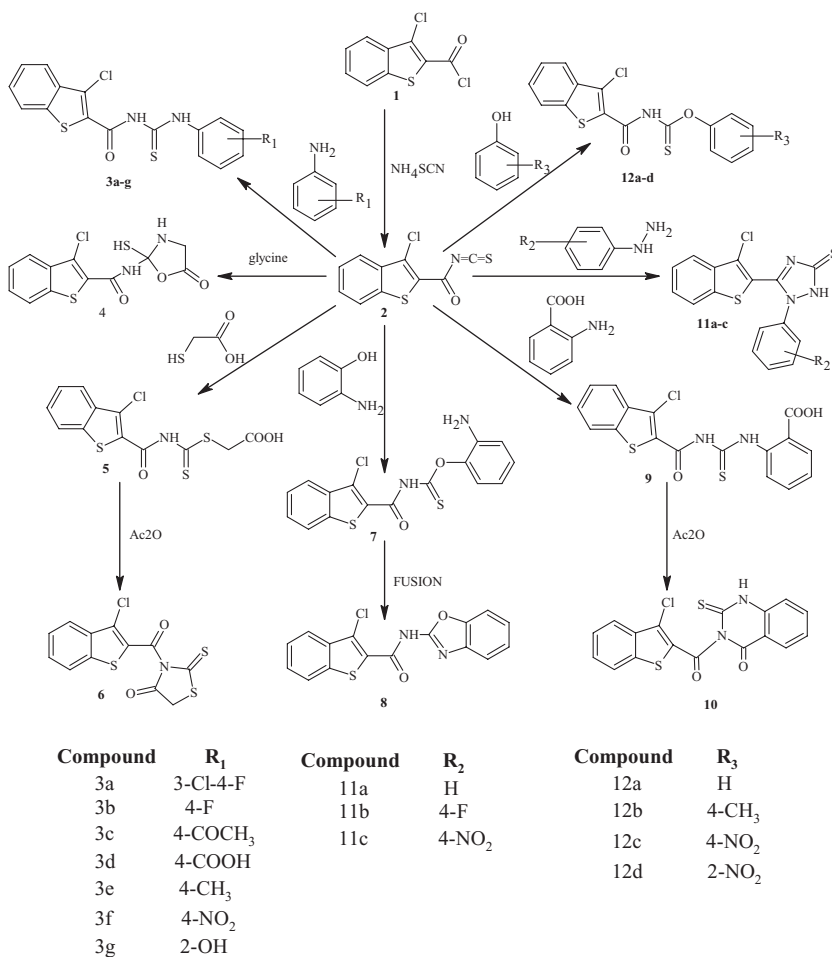
Multiple antiretroviral agents have been produced to block replication of the HIV-1 virus by blocking HIV reverse transcriptase<sup>3-4</sup> or by blocking HIV protease.<sup>5</sup> Among the most important antiretroviral agents recently introduced are the non-nucleoside reverse transcriptase inhibitors (NNRTI), such as nevirapine<sup>6</sup> and delavirdine,<sup>7</sup> which are able to reduce reverse transcriptase inhibition to subnanomolar concentrations. Several heterocyclic thioureas<sup>8-11</sup> have been reported as a new class of potent NNRTIs such as phenethylthiazolyl-thiourea (PETT<sub>1</sub>) derivatives (Figure 1).

Uckun and Venkatachalam<sup>12</sup> have described the synthesis of a series of thiazolthioureas with alkyl, aryl, and heteroaryl substituents as newly identified NNRTIs of HIV, including mutant strains of HIV, that are effective in the treatment of multidrug-resistant HIV infection. Fathala and Pazdera have recently reported a new and efficient synthesis of novel quinazoline thioureas based on the Domino reaction.<sup>13</sup> On the other hand, benzothiophenes are of current interest due to their wide spectrum of pharmacological properties such as antiallergic, anti-inflammatory, analgesic, antitubercular, antimicrobial, ocular hypotensive, and serotonin N-acetyltransferase inhibitors activities.<sup>14-19</sup> A drug based on the benzothiophene ring is raloxifene, approved by the U.S. Food and Drug Administration for the prevention and treatment of osteoporosis associated with postmenopausal women.<sup>20</sup> In view of these factors, it was thought important to synthesize a benzothiophene-incorporated biheterocyclic to explore its biological efficacy.

## RESULTS AND DISCUSSION

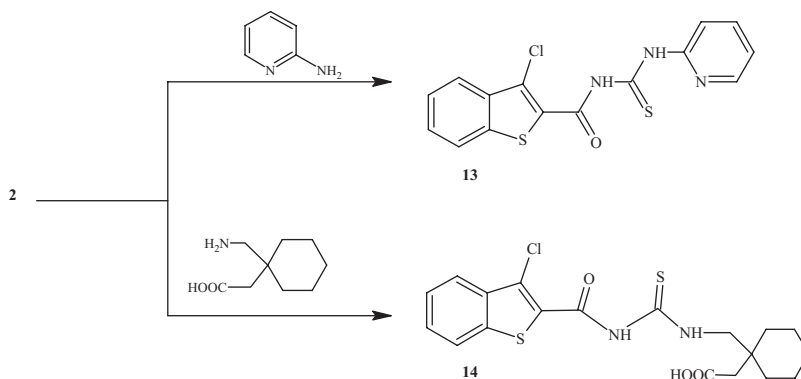
The starting material for the synthesis of the target compounds was 3-chloro benzothiophene-2-carbonyl chloride **1**, which was prepared by the reaction of cinnamic acid and thionyl chloride in the presence of pyridine in DMF.<sup>21</sup> Compound **1**, upon treatment with ammonium thiocyanate in dry acetone, produced 3-chlorobenzothiophene-2-carbonyl isothiocyanate **2**, which was used for further reactions in situ to prevent its decomposition. Isothiocyanate **2** was reacted with substituted anilines in dry acetone to obtain the corresponding thioureas **3a-g**. Compound **3a** has peaks in its IR spectrum at 3280, 1650, 1570, 1220, 1070, and 681 cm<sup>-1</sup> corresponding to N-H, C=O, C=C, C=S, C-Cl, and C-S-C groups, respectively; the <sup>1</sup>H NMR spectrum of **3a** exhibited singlets integrating for one proton each at 11.08 and 12.19  $\delta$  ppm due to -CONH and -CSNH protons, respectively, and a multiplet in between 7.29 and 8.03  $\delta$  ppm due to seven aromatic protons. Furthermore, the structure of **3a** was confirmed from its mass spectrum, which exhibited a molecular ion peak at *m/z* 399 corresponding to its molecular weight. When glycine was reacted with 3-chlorobenzothiophene-2-carbonylisothiocyanate **2** in the presence of

pyridine, the thiourea derivative produced was cyclized to 3-chloro-*N*-(5-oxo-2-sulfanyll-1,3-oxazolidin-2-yl)-1-benzothiophene-2-carboxamide **4**. The IR spectrum of compound **4** exhibited peaks at 3280, 2320, and 1670  $\text{cm}^{-1}$  due to N—H, S—H, and C=O stretching absorptions. The singlets integrating for one proton at 12.11, 10.23, and 3.50  $\delta$  ppm in the  $^1\text{H}$  NMR spectra correspond to —NH, —CONH, and —SH protons. A singlet at 2.40  $\delta$  is due to —CH<sub>2</sub> protons, and a multiplet in between 6.80 and 7.70  $\delta$  ppm is due to four aromatic protons. A molecular ion peak at  $m/z$  328 in its mass spectrum is additional proof for its formation. Isothiocyanate **2** reacted with thioglycolic acid in which the adduct **5** was produced, which underwent cyclization in the presence of acetic anhydride to 3-[(3-chloro-1-benzothiophen-2-yl)carbonyl]-2-thioxo-1,3-thiazolidin-4-one **6**. The IR spectrum of compound **6** exhibited peaks at 3280, 1670, and 1230  $\text{cm}^{-1}$  corresponding to N—H, C=O, and C=S stretching absorption frequencies, respectively. The  $^1\text{H}$  NMR spectrum of compound **6** exhibited a multiplet in the region 7.70–8.35  $\delta$  ppm due to four aromatic protons and a singlet at 2.40  $\delta$  ppm, which corresponds to two protons of —CH<sub>2</sub> groups. The mass spectrum of compound **6** exhibited a molecular ion peak at  $m/z$  327, which is in accordance with the structure. 2-Aminophenol was treated with **2** to yield thiocarbamate **7**, the IR spectrum of which exhibited peaks at 3285, 1665, and 1225  $\text{cm}^{-1}$  due to N—H, C=O, and C=S stretching absorption frequencies, respectively. The  $^1\text{H}$  NMR spectrum of **7** showed two singlets, one at 10.29  $\delta$  ppm and at other 9.86  $\delta$  ppm, due to —NH<sub>2</sub> and —CONH protons, respectively. Compound **7** exhibited a molecular ion peak at  $m/z$  362 in its mass spectrum, which confirmed its formation. Fusion of compound **7** also was associated with the evolution of H<sub>2</sub>S gas and led to the formation of *N*-(1,3-benzoxazol-2-yl)-3-chloro-1-benzothiophene-2-carboxamide **8**. Compound **8** showed a peak at 1230  $\text{cm}^{-1}$  due to C—S stretching absorption in its IR spectrum and the absence of a peak at 10.23  $\delta$  ppm in its  $^1\text{H}$  NMR spectrum due to a CONH proton, which indicated the formation of compound **8**. Addition of anthranilic acid to isothiocyanate leads to the formation of thiourea **9**, which showed a peaks at 3295  $\text{cm}^{-1}$  in its IR spectrum due to —NH stretching; singlets at 13.16 and 10.70  $\delta$  ppm in its  $^1\text{H}$  NMR spectrum correspond to —CSNH and —CONH protons, respectively. As an additional proof, the mass spectrum of **9** exhibited a molecular ion peak at  $m/z$  390, which confirmed its formation. Compound **10** was prepared by reacting **9** with acetic anhydride. Compound **10** showed a singlet at 14.26  $\delta$  ppm due to —NH proton in its  $^1\text{H}$  NMR spectrum. The mass spectrum of **10** showed a molecular ion peak at  $m/z$  372 corresponding to its molecular weight. The reaction of isothiocyanate **2** with substituted hydrazines afforded 5-(3-chloro-1-benzothiophen-2-yl)-1-substitued-1,2-dihydro-3*H*-1,2,4-triazole-3-thiones **11a–c**. Compound **11a** exhibited peaks at 3281, 1655, and 1230  $\text{cm}^{-1}$  due to N—H, C—O, and C—S stretching absorption frequencies, respectively, in its IR spectrum. The  $^1\text{H}$  NMR spectrum of **11a** showed a singlet at 10.50  $\delta$  ppm due to —NH proton and a multiplet in the region 7.27 to 8.05  $\delta$  ppm due to nine aromatic protons, and its mass spectrum showed a molecular ion peak at  $m/z$  343. Compound **2** was treated with various phenols to obtain the series of substituted [(3-chloro-1-benzothiophen-2-yl)carbonyl]carbamothioates **12a–d** (Scheme 1). Compound **12a** exhibited peaks at 3285, 1665, and 1230  $\text{cm}^{-1}$  stretching absorption frequencies in its IR spectrum corresponds to N—H, C=O, and C=S groups, respectively. The  $^1\text{H}$  NMR spectrum of **12a** showed a singlet at 11.22  $\delta$  ppm due to a CONH proton and a multiplet in between 7.52 and 7.90  $\delta$  ppm due to nine aromatic protons. Furthermore, **12a** was confirmed from its mass spectrum, which exhibited a molecular ion peak at  $m/z$  347 corresponding to its molecular weight. Finally, 3-chlorobenzothiophene-2-carbonylisothiocyanate **2** reacted with 2-aminopyridine and [1-(aminomethyl)cyclohexyl]acetic acid in the presence of acetone to produce separately



**Scheme 1** General synthetic procedure for 3-chlorobenzothiophene substituted thioureas **3a-g**, oxazole **4**, thiazolidinone **6**, benzoxazole **8**, quinoxaline **10**, triazoles **11a-d**, and carbamothioates **12a-d**.

compounds **13** and **14** (Scheme 2). Compound **13** exhibited peaks at 3285, 1650, and 1227  $\text{cm}^{-1}$  due to N-H, C=O, and C=S groups stretching absorption frequencies. The  $^1\text{H}$  NMR spectrum of **13** showed two singlets integrating for one proton each, one at 10.15  $\delta$  ppm and another at 12.85  $\delta$  ppm, due to -CONH and -CSNH protons, respectively. Compound **13** exhibited a molecular ion peak at  $m/z$  347 in its mass spectrum, which confirmed its formation. Compound **14** exhibited peaks at 3285, 1650, and 1227  $\text{cm}^{-1}$  due to N-H, C=O, and C=S stretching absorption frequencies in its IR spectrum. The  $^1\text{H}$  NMR spectrum of **14** showed a singlet at 10.90  $\delta$  ppm due to -CSNH proton and a multiplet in the region 7.26 to 7.86  $\delta$  ppm due to four aromatic protons and in its mass spectrum, which showed a molecular ion peak at  $m/z$  424. All the synthesized compounds were characterized by elemental analysis and spectral data, and have been screened for their antimicrobial, analgesic, and anti-inflammatory activities. The characterization of the synthesized compounds is presented in Table I.



**Scheme 2** General synthetic procedure for 3-chlorobenzothiophene substituted thioureas **13** and **14**.

## ANTIBACTERIAL ACTIVITY

Cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of the selected synthesized compounds against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli*. Preparation of nutrient broth, subculture, base layer medium, agar medium, and peptone water is done as per the standard procedure.<sup>22</sup> (See the Supplemental Materials available online, Table S1.)

**Table I** Characterization data of the compounds

Sl. No.	Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)	Mp (°C)
1	<b>3a</b>	3-Cl-4-F	—	—	90	209–211
2	<b>3b</b>	4-F	—	—	89	202–204
3	<b>3c</b>	4-COCH <sub>3</sub>	—	—	90	231–233
4	<b>3d</b>	4-COOH	—	—	77	203–205
5	<b>3e</b>	4-CH <sub>3</sub>	—	—	87	213–215
6	<b>3f</b>	4-NO <sub>2</sub>	—	—	78	210–212
7	<b>3g</b>	2-OH	—	—	88	216–218
8	<b>4</b>	—	—	—	45	230–232
9	<b>5</b>	—	—	—	88	221–223
10	<b>6</b>	—	—	—	67	210–212
11	<b>7</b>	—	—	—	76	240–242
12	<b>8</b>	—	—	—	66	231–233
13	<b>9</b>	—	—	—	88	240–242
14	<b>10</b>	—	—	—	77	231–233
15	<b>11a</b>	—	H	—	76	210–212
16	<b>11b</b>	—	4-F	—	78	241–243
17	<b>11c</b>	—	4-NO <sub>2</sub>	—	66	231–233
18	<b>12a</b>	—	—	H	65	218–220
19	<b>12b</b>	—	—	4-CH <sub>3</sub>	67	231–233
20	<b>12c</b>	—	—	4-NO <sub>2</sub>	65	260–262
21	<b>12d</b>	—	—	2-NO <sub>2</sub>	61	238–240
22	<b>13</b>	—	—	—	66	241–243
23	<b>14</b>	—	—	—	81	221–223

## ANTIFUNGAL ACTIVITY

The antifungal activity of the synthesized compounds was tested against four different fungi, *C. albicans*, *C. pannical*, *A. niger*, and *R. oryzae*, by the filter paper disc technique.<sup>23</sup> (See the Supplemental Materials, Table S2.)

## ANALGESIC ACTIVITY

Albino mice of either sex (20–30 g) were used to evaluate the acetic acid-induced writhing analgesic activity.<sup>24</sup> (See the Supplemental Materials, Table S3.)

## ANTI-INFLAMMATORY ACTIVITY

The anti-inflammatory activity of all the newly synthesized compounds was evaluated using the carrageenan-induced rat hind paw edema method.<sup>25</sup> (See the Supplemental Materials, Table S4.)

## EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. IR spectra (KBr disks) were recorded using a Perkin-Elmer 237 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on a Bruker Aveance II spectrometer (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO as a solvent. Chemical shifts were given in parts per million (ppm). Splitting patterns were designated as follows: s–singlet, d–doublet, t–triplet, q–quartet, and m–multiplet. Mass spectra (MS) were recorded on a Shimadzu 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 silica gel and the compounds were further purified through column chromatography.

### Preparation of 3-Chlorobenzothiophene-2-carbonyl chloride (1)

Compound **1** was prepared according to the procedure in the literature,<sup>21</sup> mp 112–114°C (Literature mp 110–112°C).

### Preparation of 3-Chlorobenzothiophene-2-carbonyl isothiocyanate (2)

Ammonium thiocyanate (0.076 g, 1.0 mmol) was added dropwise to a stirred solution of 3-chlorobenzothiophene-2-carbonylchloride **1** (0.231 g, 1.0 mmol) in dry acetone (50 mL) at 0°C. Stirring was continued for 1 h at room temperature. Ammonium chloride was precipitated during the progress of the reaction; it was filtered, and a pale yellow solution of 3-chlorobenzothiophene-2-carbonylisothiocyanate **2** was obtained.

### Preparation of 3-Chloro-*N*-[(3-chloro-4-fluorophenyl)carbamothioyl]-1-benzothiophene-2-carboxamide (3a)

To a solution isothiocyanate **2** (0.253 g, 1.0 mmol) in dry acetone (10 mL), 3-chloro-4-fluoroaniline (0.146 g, 1.0 mmol) in dry acetone (10 mL) was added with continuous stirring; thereafter two-thirds of the solvent was distilled under vacuum. The concentrate was left overnight in refrigerator. The solid product obtained was filtered, washed with water, and recrystallized from ethanol. Similarly, the compounds **3b–g** were prepared.

**3-Chloro-*N*-[(3-chloro-4-fluorophenyl)carbamothioyl]benzothiophene-2-carboxamide (3a).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N–H), 1650 (C=O), 1570 (C=C), 1220 (C=S), 1070 (C–Cl), 681 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.29–8.03 (7H, m, Ar H), 11.08 (1H, s, CONH), 12.19 (1H, s, CSNH); MS ( $\text{M}^+$ ): 399 (12%), 302 (22%). Calcd. (%) for  $\text{C}_{16}\text{H}_9\text{Cl}_2\text{FN}_2\text{OS}_2$ : C, 68.13; H, 2.27; N, 7.02; S, 16.06. Found: C, 48.08; H, 2.20; N, 7.00; S, 16.00.

**3-Chloro-*N*-[(4-fluorophenyl)carbamothioyl]benzothiophene-2-carboxamide (3b).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3275 (N–H), 1654 (C=O), 1565 (C=C), 1343 (C–F), 1215 (C=S), 1077 (C–Cl), 685 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.10–7.99 (8H, m, ArH), 10.62 (1H, s, CONH), 12.21 (1H, s, CSNH); MS ( $\text{M}^+$ ): 364 (18%), 312 (34%). Calcd. (%) for  $\text{C}_{16}\text{H}_{10}\text{ClFN}_2\text{OS}_2$ : C, 57.67; H, 2.76; N, 7.68; S, 17.58. Found: C, 57.63; H, 2.70; N, 7.66; S, 17.55.

**4-(Acetylphenyl)carbamothioyl]-3-chlorobenzothiophene-2g-carboxamide (3c).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3285 (N–H), 1639 (C=O), 1565 (C=C), 1220 (C=S), 1072 (C–Cl), 688 (C–S–C),  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 2.61 (3H, s,  $\text{CH}_3$ ), 7.57–8.02 (8H, m, ArH), 10.57 (1H, s, CONH), 12.59 (1H, s, CSNH); MS ( $\text{M}^+$ ): 388 (10%), 322 (28%). Calcd. (%) for  $\text{C}_{18}\text{H}_{13}\text{ClN}_2\text{O}_2\text{S}_2$ : C, 55.59; H, 3.37; N, 7.20; S, 16.49. Found: C, 55.50; H, 3.35; N, 7.16; S, 16.45.

**3-(Chlorobenzothiophen-2-yl)carbonylcarbamothioylaminobenzoic acid (3d).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N–H), 1650 (C=O), 1570 (C=C), 1224 (C=S), 1077 (C–Cl), 682 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 1.25 (1H, s, COOH), 7.49–8.10 (8H, m, ArH), 10.38 (1H, s, CONH), 12.57 (1H, s, CSNH); MS ( $\text{M}^+$ ): 390 (24%), 352 (44%). Calcd. (%) for  $\text{C}_{17}\text{H}_{11}\text{ClN}_2\text{O}_3\text{S}_2$ : C, 52.24; H, 2.84; N, 7.17; S, 16.41. Found: C, 52.18; H, 2.80; N, 7.15; S, 16.37.

**3-Chloro-*N*-[(4-methylphenyl)carbamothioyl]benzothiophene-2-carboxamide (3e).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3288 (N–H), 1663 (C=O), 1565 (C=C), 1222 (C=S), 1073 (C–Cl), 690 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 2.37 (3H, s,  $\text{CH}_3$ ), 7.22–8.00 (8H, m, ArH), 10.45 (1H, s, CONH), 12.22 (1H, s, CSNH); MS ( $\text{M}^+$ ): 360 (16%), 325 (36%). Calcd. (%) for  $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{OS}_2$ : C, 56.58; H, 3.63; N, 7.76; S, 17.77. Found: C, 56.55; H, 3.60; N, 7.70; S, 17.75.

**3-Chloro-*N*-[(4-nitrophenyl)carbamothioyl]benzothiophene-2-carboxamide (3f).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3281 (N–H), 1664 (C=O), 1565 (C=C), 1490 ( $\text{NO}_2$ ), 1230 (C=S), 1065 (C–Cl), 688 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.61–8.29 (8H, m, Ar H), 11.27 (1H, s, CONH), 12.59 (1H, s, CSNH); MS ( $\text{M}^+$ ): 391 (12%), 351 (23%). Calcd. (%) for  $\text{C}_{16}\text{H}_{10}\text{ClN}_3\text{O}_3\text{S}_2$ : C, 49.04; H, 2.57; N, 10.72; S, 16.37. Found: C, 49.00; H, 2.55; N, 10.69; S, 16.30.

**3-Chloro-*N*-[(4-hydroxyphenyl)carbamothioyl]benzothiophene-2-carboxamide (3g).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3533–3324 (O–H), 3270 (N–H), 1665 (C=O), 1572 (C=C), 1210 (C=S), 1073 (C–Cl), 688 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 6.85–8.64 (8H, m, Ar H), 9.86 (1H, s, CONH), 10.29 (1H, s, CSNH), 12.55 (1H, s, OH); MS ( $\text{M}^+$ ): 362 (18%), 312 (42%). Calcd. (%) for  $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}_2$ : C, 52.96; H, 3.06; N, 7.72; S, 17.67. Found: C, 52.90; H, 3.00; N, 7.7; S, 17.60.

#### Preparation 3-Chloro-*N*-(5-oxo-2-sulfanyl-1,3-oxazolidin-2-yl)benzothiophene-2-carboxamide (4)

To a solution of isothiocyanate **2** (0.253 g, 1.0 mmol) in dry acetone (50 mL), glycine (0.075 g, 1.0 mmol) and a few drops of pyridine were added, and then the reaction mixture



was refluxed for 3 h. After cooling the reaction mixture, a solid product was obtained, filtered, washed with water, and recrystallized from a 1,4-dioxane. It was further purified from column chromatography (silica gel, 60–120 mesh) by using petroleum ether and ethyl acetate (0.5:9.5) as an eluent to yield compound **4**.

IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N–H), 2320 (SH), 1670 (C=O), 1565 (C=C), 1074 (C–Cl), 688 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 2.40 (2H, s,  $\text{CH}_2$ ), 3.50 (1H, s, SH), 6.80–7.70 (4H, m, Ar H), 10.23 (1H, s, CONH), 12.11 (1H, s, NH); MS ( $\text{M}^+$ ): 328 (22%), 302 (36%). Calcd. (%) for  $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_3\text{S}_2$ : C, 43.84; H, 2.76; N, 8.52; S, 19.50. Found: C, 43.79; H, 2.70; N, 8.49; S, 19.46.

### Preparation of Adduct: 3-Chlorobenzothiophen-2-yl-carbonyl-carbamothioyl-sulfanyl Acetic Acid (**5**)

A solution of isothiocyanate **2** (0.253 g, 1.0 mmol) in dry acetone and thioglycolic acid (0.092 g, 0.075 mL, 1.0 mmol) was refluxed for 2 h. The solid that formed after cooling was recrystallized from methanol.

### Preparation of 3-[(3-Chlorobenzothiophen-2-yl)carbonyl]-2-thioxo-1,3-thiazolidin-4-one (**6**)

A solution of adduct **5** (0.345 g, 1.0 mmol) in acetic anhydride (30 mL) was refluxed for 3 h. Solid product was obtained after cooling, and it was recrystallized from methanol to obtain product **6**.

IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N–H), 1670 (C=O), 1575 (C=C), 1230 (C=S), 1072 (C–Cl), 684 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 2.40 (2H, s,  $\text{CH}_2$ ), 7.70–8.35 (4H, m, Ar H); MS ( $\text{M}^+$ ): 327 (10%), 312 (28%). Calcd. (%) for  $\text{C}_{12}\text{H}_6\text{ClNO}_2\text{S}_3$ : C, 43.96; H, 1.84; N, 4.27; S, 29.34. Found: C, 43.90; H, 1.79; N, 4.20; S, 29.30.

### Preparation of *o*-(2-Aminophenyl)-[(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (**7**)

To a solution of isothiocyanate **2** (0.253 g, 1.0 mmol) in dry acetone (15 mL), *o*-aminophenol (0.109 g, 1.0 mmol) in dry acetone (10 mL) was added. The reaction mixture was refluxed for 3 h. The solid product that was obtained after cooling was filtered and recrystallized from methanol to yield solid crystals of the product **7**.

IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3285 (N–H), 1665 (C=O), 1570 (C=C), 1225 (C=S), 1075 (C–Cl), 685 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 6.80–7.70 (8H, m, Ar H), 9.86 (1H, s, CONH), 10.29 (2H, s,  $\text{NH}_2$ ); MS ( $\text{M}^+$ ): 362 (12%), 342 (32%). Calcd. (%) for  $\text{C}_{16}\text{H}_{11}\text{ClN}_2\text{O}_2\text{S}_2$ : C, 52.96; H, 3.06; N, 7.72; S, 17.67. Found: C, 52.90; H, 3.00; N, 7.68; S, 17.65.

### Preparation of *N*-(1,3-Benzoxazol-2-yl)-3-chlorobenzothiophene-2-carboxamide (**8**)

Thiocarbamate derivative **7** was fused for 2 h in an oil bath, which was associated with the evolution of  $\text{H}_2\text{S}$  gas. The reaction mixture was left to cool. The solid product that was obtained was recrystallized from a methanol to get compound **8** in pure form.

IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N–H), 1663 (C=O), 1575 (C=C), 1230 (C=S), 1075 (C–Cl), 682 (C–S–C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.70–8.45 (8H, m, Ar H),

10.23 (1H, s, CONH); MS ( $M^+$ ): 328 (14%), 302 (22%). Calcd. (%) for  $C_{16}H_9ClN_2O_2S$ : C, 58.45; H, 2.76; N, 8.52; S, 9.75. Found: C, 58.41; H, 2.70; N, 8.48; S, 9.70.

### Preparation of 3-Chloro(benzothiophen-2-yl)carbonyl Carbamothioylaminobenzoic Acid (9)

To a solution of isothiocyanate **2** (0.253 g, 1.0 mmol), anthranilic acid (0.137 g, 1.0 mmol) was added dropwise with constant stirring for about 20 min and then refluxed for 2 h. After cooling, a solid product was obtained. It was filtered and recrystallized from methanol and further purified from column chromatography (silica gel, 60–120 mesh) by using petroleum ether and ethyl acetate (1:9) as an eluent to get compound **9**.

IR (KBr)  $\nu$  ( $cm^{-1}$ ): 3295 (N–H), 1650 (C=O), 1580 (C=C), 1225 (C=S), 1077 (C–Cl), 685 (C–S–C);  $^1H$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 3.80 (1H, s, COOH), 7.31–8.48 (8H, m, Ar H), 10.70 (1H, s, CONH), 13.16 (1H, s, CSNH); MS ( $M^+$ ): 390 (18%), 355 (45%). Calcd. (%) for  $C_{17}H_{11}ClN_2O_3S_2$ : C, 52.24; H, 2.84; N, 7.17; S, 16.41. Found: C, 52.18; H, 2.80; N, 7.15; S, 16.37.

### Preparation of 3-[(3-Chlorobenzothiophen-2-yl)carbonyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (10)

Thiourea **9** (0.390 g, 1.0 mmol) was heated on a water bath with acetic anhydride (50 mL) for 3 h. A solid product was formed during heating. At the end of the reaction period, the solid product was filtered off while hot and crystallized from methanol and further purified from column chromatography (silica gel, 60–120 mesh) by using petroleum ether and ethyl acetate (1.5:8.5) as an eluent to get pure **10**.

IR (KBr)  $\nu$  ( $cm^{-1}$ ): 3285 (N–H), 1666 (C–O), 1570 (C–C), 1220 (C–S), 1078 (C–Cl), 689 (C–S–C);  $^1H$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.41–8.02 (8H, m, Ar H), 14.26 (1H, s, NH); MS ( $M^+$ ): 372 (14%), 341 (31%). Calcd. (%) for  $C_{17}H_9ClN_2O_2S_2$ : C, 54.76; H, 2.43; N, 7.51; S, 17.20. Found: C, 54.70; H, 2.39; N, 7.48; S, 17.16.

### Preparation of 5-(3-Chlorobenzothiophen-2-yl)-1-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (11a)

A solution of isothiocyanate **2** (0.253 g, 1.0 mmol) and phenyl hydrazine (0.108 g, 0.095 mL, 1.0 mmol) in dry acetone (30 mL) was heated under reflux for 1 h, concentrated, and treated with methanol to give a solid. Then it was recrystallized from methanol to obtain pure **11a**. Compounds **11b–c** were prepared using a similar methodology.

**5-(3-Chlorobenzothiophen-2-yl)-1-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-thione (11a).** IR (KBr)  $\nu$  ( $cm^{-1}$ ): 3281 (N–H), 1655 (C=O), 1570 (C=C), 1230 (C=S), 1070 (C–Cl), 692 (C–S–C);  $^1H$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.27–8.05 (9H, m, Ar H), 10.50 (1H, s, NH); MS ( $M^+$ ): 343 (14%). Calcd. (%) for  $C_{16}H_{10}ClN_3S_2$ : C, 55.89; H, 2.93; N, 12.22; S, 18.65. Found: C, 55.80; H, 2.90; N, 12.16; S, 18.60.

**5-(3-Chlorobenzothiophen-2-yl)-1-(4-fluorophenyl)-1,2-dihydro-3H-1,2,4-triazole-3-thione (11b).** IR (KBr)  $\nu$  ( $cm^{-1}$ ): 3285 (N–H), 1650 (C=O), 1575 (C=C), 1342 (C–F), 1220 (C=S), 1070 (C–Cl), 686 (C–S–C);  $^1H$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.54–8.16 (8H, m, Ar H), 10.53 (1H, s, NH); MS ( $M^+$ ): 361 (13%). Calcd. (%) for  $C_{16}H_9ClFN_3S_2$ : C, 53.11; H, 2.51; N, 11.61; S, 17.72. Found: C, 53.00; H, 2.47; N, 11.58; S, 17.70.

**5-(3-Chlorobenzothiophen-2-yl)-1-(4-nitrophenyl)-1,2-dihydro-3H-1,2,4-triazole-3-thione (11c).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3280 (N—H), 1650 (C=O), 1570 (C=C), 1342 ( $\text{NO}_2$ ), 1220 (C=S), 1070 (C—Cl), 681 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.50–7.95 (8H, m, Ar H), 10.53 (1H, s, NH); MS ( $\text{M}^+$ ): 388 (12%). Calcd. (%) for  $\text{C}_{16}\text{H}_9\text{ClN}_4\text{O}_2\text{S}_2$ : C, 49.42; H, 2.33; N, 14.41; S, 16.49. Found: C, 49.37; H, 2.28; N, 14.37; S, 16.45.

**Preparation of o-phenyl [(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (12a)**

Ammonium thiocyanate (0.076 g, 1.0 mmol) in dry acetone (10 mL) was slowly added dropwise at  $0^\circ\text{C}$  to an 3-chloro-1-benzothiophene-2-carbonyl chloride **1** (0.231 g, 1.0 mmol) in dry acetone (10 mL) with continuous stirring and then filtered. The filtrate was slowly added at room temperature to a phenol (0.094 g, 0.075 mL, 1.0 mmol) in acetone (10 mL) with continuous stirring. Thereafter, two-thirds of the solvent was distilled under vacuum. The concentrate was left overnight in a refrigerator. The solid product was filtered off, washed with water, and recrystallized from methanol and purified from column chromatography (silica gel, 60–120 mesh) by using petroleum ether and ethyl acetate (0.5:9.5) as an eluent to get pure **12a**. Compounds **12b–d** were prepared in a similar manner.

**Phenyl[(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (12a).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3285 (N—H), 1665 (C=O), 1570 (C=C), 1230 (C=S), 1075 (C—Cl), 683 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.52–7.90 (9H, m, Ar H), 11.22 (1H, s, CONH); MS ( $\text{M}^+$ ): 347 (18%). Calcd. (%) for  $\text{C}_{16}\text{H}_{10}\text{ClNO}_2\text{S}_2$ : C, 55.25; H, 2.90; N, 4.03; S, 18.44. Found: C, 55.19; H, 2.87; N, 4.00; S, 18.38.

**[(4-Methylphenyl)-(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (12b).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3276 (N—H), 1670 (C=O), 1575 (C=C), 1230 (C=S), 1075 (C—Cl), 686 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 2.16 (3H, s,  $\text{CH}_3$ ), 7.42–8.02 (8H, m, Ar H), 10.19 (1H, s, CONH); MS ( $\text{M}^+$ ): 361 (15%). Calcd. (%) for  $\text{C}_{17}\text{H}_{12}\text{ClNO}_2\text{S}_2$ : C, 56.42; H, 3.34; N, 3.87; S, 17.72. Found: C, 56.38; H, 3.30; N, 3.85; S, 17.69.

**[(4-Nitrophenyl)-(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (12c).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3275 (N—H), 1660 (C=O), 1565 (C=C), 1452 ( $\text{NO}_2$ ), 1230 (C=S), 1065 (C—Cl), 684 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.42–8.06 (8H, m, Ar H), 11.19 (1H, s, CONH); MS ( $\text{M}^+$ ): 392.05 (18%). Calcd. (%) for  $\text{C}_{16}\text{H}_9\text{ClN}_2\text{O}_4\text{S}_2$ : C, 48.42; H, 2.31; N, 7.13; S, 16.32. Found: C, 48.38; H, 2.28; N, 7.09; S, 16.21.

**[(2-Nitrophenyl)-(3-chlorobenzothiophen-2-yl)carbonyl]carbamothioate (12d).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3315 (N—H), 1673 (C=O), 1570 (C=C), 1442 ( $\text{NO}_2$ ), 1220 (C=S), 1067 (C—Cl), 684 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 6.80–7.70 (8H, m, ArH), 7.40 (1H, s, CONH); MS ( $\text{M}^+$ ): 392 (14%). Calcd. (%) for  $\text{C}_{16}\text{H}_9\text{ClN}_2\text{O}_4\text{S}_2$ : C, 48.42; H, 2.31; N, 7.13; S, 16.32. Found: C, 48.38; H, 2.28; N, 7.09; S, 16.23.

**Preparation of 3-Chloro-N-(pyridin-3-ylcarbamothioyl)benzothiophene-2-carboxamide **13** and {1-[(2-{[(3-Chlorobenzothiophen-2-yl)carbonyl]carbamothioyl}hydrazinyl)methyl]cyclohexyl}acetic Acid **14****

These compounds were prepared following the same procedure used in preparation of compounds **3a–g**.

**3-Chloro-*N*-(pyridin-3-ylcarbamothioyl)benzothiophene-2-carboxamide (13).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3285 (N—H), 1650 (C=O), 1570 (C=C), 1227 (C=S), 1074 (C—Cl), 688 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 7.16–8.85 (8H, m, Ar H), 10.15 (1H, s, CONH), 12.85 (1H, s, CSNH); MS ( $\text{M}^+$ ): 347 (10%). Calcd. (%) for  $\text{C}_{15}\text{H}_{10}\text{ClN}_3\text{OS}_2$ : C, 51.79; H, 2.90; N, 12.08; S, 18.44. Found: C, 51.73; H, 2.87; N, 12.00; S, 18.39.

**3-Chloro-(benzothiophen-2-carbonyl)carbamothioylaminomethylcyclohexylacetic acid (14).** IR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3285 (N—H), 1650 (C=O), 1570 (C=C), 1227 (C=S), 1075 (C—Cl), 681 (C—S—C);  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  (ppm): 1.48–1.56 (12H, s,  $(\text{CH}_2)_6$ ), 2.58 (1H, s, COOH), 7.26–7.86 (4H, m, Ar H), 9.99 (1H, s, CONH), 10.90 (1H, s, CSNH); MS ( $\text{M}^+$ ): 424 (14%). Calcd. (%) for  $\text{C}_{19}\text{H}_{21}\text{ClN}_2\text{O}_3\text{S}_2$ : C, 57.70; H, 4.98; N, 6.59; S, 15.09. Found: C, 57.68; H, 4.87; N, 6.54; S, 15.04.

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