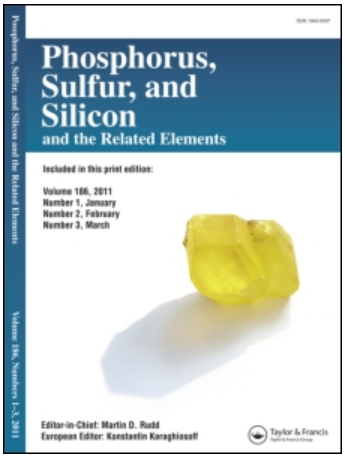

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Synthesis, Antimicrobial, and Anthelmintic Activities of Some New 3-Chlorobenzothiophene-2-Carbonylchloride Derivatives

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SYNTHESIS, ANTIMICROBIAL, AND ANTHELMINTIC ACTIVITIES OF SOME NEW 3-CHLOROBENZOTHIOPHENE-2-CARBONYLCHLORIDE DERIVATIVES

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3-Chlorobenzothiophene-2-carbonylchloride 1 was prepared from cinnamic acid and then converted into the acid hydrazide 2. Reaction of 3-chloro-1-benzothiophene-2-carbohydrazide 2 with the appropriate isothiocyanate yielded the substituted thiosemicarbazides 3a–b, which are cyclized into thioxotetrahydropyrimidine 4a–b, 1,3,4-thiadiazoles 5a–b, thiazolidine 6a–b, 1,3,4-oxadiazole 7a–b, triazoles 8a–b, 1,2,4-triazole substitutedthioate 9a–f, and 1,3-thiazolylidenes 10a–b, respectively. The structures of the newly synthesized compounds were elucidated on the basis of elemental analyses, IR, ^{1}H NMR, and mass spectral data and have been screened for antimicrobial and anthelmintic activities.

Keywords Benzothiophene; biological activity; 1,3,4-oxadiazoles; 1,3,4-thiadiazoles; 1,3-thiazolylidenes; triazoles

INTRODUCTION

The synthesis of biheterocycles has recently been of great interest because they possess a high biological profile. They are grabbing the attention of medicinal chemists for molecular manipulation and of biologists for further pharmacological evaluation. It has been reported that the presence of two or more pharmacophores in a drug molecule would enhance the biological profile many times over. In view of this observation, in this article we report the synthesis of benzothiophene linked to pyrimidine, thiadiazole, oxadiazole, triazole, and thiazole moieties.

Benzothiophene, second in importance to thiophene among sulfur heterocycles, has attracted scant attention of organic chemists since it is a bioisoster of indole. The chemistry of benzothiophene, in the 1960s and 1970s, was centered around the synthesis of its derivatives, which are analogues of bioactive indole derivatives, and the literature on benzothiophene up to 1980 has been reviewed.[1–3] The interest in this class of compounds

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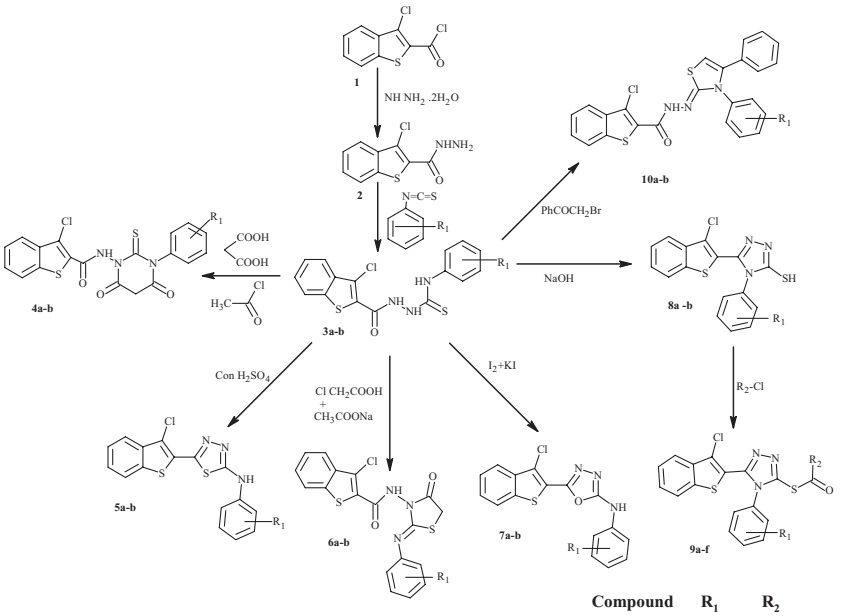
is principally due to their usefulness in the synthesis of sulfur analogues of several important bioactive indole derivatives, viz. serotonin, and annulation of oxygenated rings onto the benzothiophene core. The benzothiophene nucleus is associated with diverse pharmacological activities such as nervous system depressing,[4] analgesic,[5] herbicidal,[6] muscle relaxant,[7] and tranquilizing[8] activities. The synthesis of compounds incorporating pyrimidine, thiadiazole, oxadiazole, triazole, and thiazole moieties has been attracting widespread attention due to their diverse pharmacological properties such as antimicrobial, antiinflammatory, analgesic, and antitumor activities.[9–13] Because the substituted thiosemicarbazides are valuable building blocks for the synthesis of five-memberd heterocyclics,[14] we thought to synthesize benzothiophene linked to pyrimidine, thiadiazole, oxadiazole, triazole, and thiazole moieties via semicarbazides intermediate, with the purpose of investigating in the future their possible antibacterial, antifungal, and anthelmintic activities.

RESULTS AND DISCUSSION

In this article, we report the synthesis and biological properties of some new thioxotetrahydropyrimidines, 1,3,4-thiadiazoles, thiazolidines, 1,3,4-oxadiazoles, thiotriazoles, and 1,3-thiazolylidenes derivative incorporated with the benzothiophene ring, following the sequence of reactions as depicted in Scheme 1. The starting material for the synthesis of the



Scheme 1 General synthetic procedure for 3-chlorobenzothiophene-2-carbonyl chloride substituted thiosemicarbazides **3a–b,** thioxotetrahydropyrimidines **4a–b,** 1,3,4-thiadiazoles **5a–b,** thiazolidines **6a–b,** 1,3,4-oxadiazoles **7a–b,** triazoles **8a–b,** 1,2,4-triazole substitutedthioates **9a–f,** and 1,3-thiazolylidenes **10a–b.**

target compounds is 3-chlorobenzothiophene-2-carbonylchloride **1**, which was prepared by the reaction of cinnamic acid, thionyl chloride in the presence of pyridine in DMF.[15] The compound **1** was treated with hydrazine hydrate to obtain 3-chloro-1-benzothiophene-2-carbohydrazide **2** in good yield. The IR spectrum of compound **2** was found to exhibit peaks at 3020 and 1605 cm^{-1} due to N—H and C=O groups stretching absorption frequencies, respectively. The ^1H NMR spectrum of the same compound was found to show a singlet corresponding to one proton at 8.20 δ ppm due to CONH proton, a multiplet in the region 7.92–7.41 δ ppm corresponding to four aromatic protons and a broad peak at 4.21 δ ppm (D_2O exchangeable) corresponding to two NH_2 protons. The ^{13}C NMR spectrum of the compound **2** exhibited a peak at 185 δ ppm due to **C**ONH carbon, the peaks at 138, 131, 129, 128, 125, 123, and 122.98 correspond to eight aromatic carbons. The formation of the compound **2** was also confirmed by its mass spectrum, which exhibited a molecular ion peak at m/z 226.68.

Condensation of carbohydrazide **2** with aryl isothiocyanates separately afforded thiosemicarbazides **3a–b** in good yields. In confirmation, compound **3a** exhibited peaks at 3170, 1660, and 1220 cm^{-1} stretching absorption frequencies in its IR spectrum corresponding to N—H, C=O, and C=S groups. ^1H NMR spectrum of compound **3a** showed three singlets in the region 10.41–9.72 δ ppm due to three NH protons separately and a multiplet in between 8.15 and 7.15 δ ppm due to eight aromatic protons. This was further confirmed by its mass spectrum that showed a molecular ion peak at m/z 360.10, which agrees with the molecular weight of the compound.

Thiosemicarbazides **3a–b** upon reaction with malonic acid in the presence of acetyl chloride underwent intermolecular cyclization to afford 3-chloro-N-(4,6-dioxo-3-aryl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)-1-benzothiophene-2-carboxamides **4a–b**. Compound **4a** exhibited peaks at 3140, 1635, and 1220 cm^{-1} due to N—H, C=O, and C=S stretching absorption frequencies in its IR spectrum. ^1H NMR spectrum of compound **4a** showed two singlets at 2.25 and 10.58 δ ppm due to C**H**$_2$ and N**H** protons and a multiplet in the region 8.00–7.20 δ ppm due to nine aromatic protons. This was further confirmed by its mass spectrum, which showed a molecular ion peak at m/z 428.90. Cyclodehydration of the thiosemicarbazides **3a–b** with cold concentrated sulfuric acid produced 1,3,4-thiadiazoles **5a–b**. The IR spectrum of the compound **5a** showed peaks at 3130 and 1643 cm^{-1} due to N—H and C=O stretching absorption frequencies. The ^1H NMR spectrum of compound **5a** exhibited a broad singlet at 10.90 δ ppm corresponding to one proton of NH group and a multiplet in the region 8.16–7.03 δ ppm due to nine aromatic protons. As an additional proof, the mass spectrum of compound **5a** exhibited a molecular ion peak at m/z 343.80.

The compound 3-chloro-*N*-[4-oxo-2-(arylimino)-5-thioxo-1,3-thiazolidin-3-yl]-1-benzothiophene-2-carboxamides **6a–b** were obtained by cyclizing thiosemicarbazides **3a–b** with chloroacetic acid in the presence of sodium acetate in acetic acid. In confirmation, compound **6a** showed peaks at 3155 and 1645 cm^{-1} in its IR spectrum due to N—H and C=N stretching frequencies. Two singlets at 11.05 and 2.85 δ ppm due to CONH and CH_2 protons, and a multiplet in the region 8.00–7.20 δ ppm due to nine aromatic protons in its ^1H NMR spectrum also indicated its formation. As an additional proof, the mass spectrum of compound **6a** exhibited a molecular ion peak at m/z 401.88. Thiosemicarbazides **3a–b** were subjected to oxidative cyclization to 2-arylamino-5-substituted-1,3,4-oxadiazoles **7a–b** by treatment with iodine and potassium iodide in ethanolic sodium hydroxide. The compound **7a** exhibited peaks at 3320, 1635, and 690 cm^{-1} due to N—H, C=N, and C—S—C stretching absorption frequencies in its IR spectrum. ^1H NMR spectrum of compound **7a** showed a singlet at 10.92 δ ppm due to NH proton and a multiplet in the

Table I Characterization data of the compounds

Compound	R_1	R_2	Yield (%)	Mp (°C)
2	—	—	97	183–185
3a	H	—	75	245–247
3b	4-Cl	—	55	231–233
4a	H	—	45	243–245
4b	4-Cl	—	44	254–256
5a	H	—	44	260–262
5b	4-Cl	—	65	241–243
6a	H	—	65	249–251
6b	4-Cl	—	55	254–256
7a	H	—	72	270–272
7b	4-Cl	—	66	278–280
8a	H	—	44	263–265
8b	4-Cl	—	45	245–247
9a	H	$COCH_3$	55	234–236
9b	H	C_6H_5CO	56	225–227
9c	H	CH_3	45	230–232
9d	4-Cl	$COCH_3$	75	234–236
9e	4-Cl	C_6H_5CO	71	243–245
9f	4-Cl	CH_3	72	241–243
10a	H	—	56	270–272
10b	4-Cl	—	54	275–277

region 8.16–7.03 δ ppm due to nine aromatic protons. The mass spectrum molecular ion peak at m/z 326.18 corresponds to its molecular weight.

The compounds **3a–b** upon heating with 4N NaOH in ethanol underwent smooth cyclization through dehydration to form 5-substituted-4-aryl-3-mercapto-4H-1,2,4-triazoles **8a–b**. Condensation of acid chlorides or alkyl halides with compounds **8a–b** afforded the acylated and alkylated derivatives **9a–f**. Compound **9a** exhibited peaks at 1650 and 1615 cm^{-1} due to C=O and C=N stretching absorption frequencies in its IR spectrum. ^{1}H NMR spectrum of compound **9a** showed a multiplet in the region 8.92–8.41 δ ppm due to nine aromatic protons and a singlet at 3.55 δ ppm due to CH_3 proton. Finally, the thiosemicarbazides **3a–b** were refluxed with phenacylbromide to give 1,3-thiazolylidenes derivative **10a–b**. The purity of the newly synthesized compounds was monitored by TLC. The structures of newly synthesized compounds were elucidated on the basis of elemental analyses and spectral data, and have been screened for antimicrobial and anthelmintic activities. The physical constants and yields of the obtained compounds are presented in Table I.

Antibacterial Activity

Cup plate method using Hi-Media agar medium was employed to study the antibacterial activity of the newly 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 was done as per the standard procedure.[16] The compounds were tested at the dose of 1000 μg/mL concentration. Amoxycillin and erythromycin were used as standard drugs and dimethyl formamide was used as a control. The zone of inhibition produced by each compound was measured in mm. The tested compounds showed moderate antibacterial activity compared to the standard drugs against all microorganisms.

Table II Anthelmintic activity of the selected compounds

Compound	Number of earth worms tested	Concentration (wt/vol) (mg)	Mean paralysis time ± SE(min)	Mean death time ± SE(min)
3a	6	100	64.20 ± 2.46	83.42 ± 0.36
3b	6	100	88.40 ± 1.40	126.14 ± 3.16
4a	6	100	28.32 ± 2.14	32.00 ± 2.12
5a	6	100	34.12 ± 2.46	48.16 ± 3.02
5b	6	100	44.20 ± 1.36	68.12 ± 1.46
6a	6	100	28.12 ± 2.42	34.36 ± 1.42
7a	6	100	30.42 ± 3.04	38.26 ± 3.16
7b	6	100	25.10 ± 1.36	30.18 ± 3.10
8a	6	100	40.24 ± 1.22	62.18 ± 2.18
9a	6	100	32.16 ± 2.42	40.10 ± 1.30
9c	6	100	34.12 ± 2.46	48.16 ± 3.02
10b	6	100	71.48 ± 2.16	83.32 ± 3.16
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

Earthworm: Sp. portoscoplex corethrusus; amount of sample: 100 mg; standard drugs: piperazine citrate and mependazole; control: distilled water +0.5% Tween-80; NE: no effect; SE: standard error.

Antifungal Activity

The antifungal activity of the synthesized compounds was tested against four different fungi such as *C. albicans*, *C. pannical*, *A. niger*, and *R. oryzae* by filter paper disc technique.[17] The concentration of test compounds was 1000 μg/mL. After 48 h treatment, the zone of inhibition produced by each compound was measured in mm. Griseofulvin was used as the standard antifungal agent, and dimethyl formamide was used as a control. All the tested compounds showed slight to moderate antifungal activity.

Anthelmintic Activity

The anthelmintic activity studies were carried out against earthworms (pontoscolex corethrusus) according to the method of Grag and Atal.[18] 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 comprising six worms in the distilled water and tween-80 (0.5%) was kept. The drug concentrations were 0.1% (wt/ vol) for the standard and the test sample. The times required for paralysis (movement stopped) and death of the worms were noted using a stopwatch. The compound **4b** and **7a** showed significant anthelmintic activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (KBr disks) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Supercon FT NMR spectrometer (at 400 MHz) using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 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 were further purified through column chromatography (silica gel, 60–120 mesh).

Preparation of 3-Chloro-1-benzothiophene-2-carbonyl chloride (1)

The compound **1** was prepared according to the literature procedure,[29] m.p 112–114°C (literature mp 110–112°C).

Preparation of 3-Chloro-1-benzothiophene-2-carbohydrazide (2)

Compound **1** (2.31 g, 10.0 mmol) was added to hydrazine hydrate (0.54 g, 0.53 mL, 10.0 mmol) directly and slowly with constant stirring, then the reaction mixture was stirred vigorously for 7 h on a magnetic stirrer. The reaction mixture was cooled to room temputure and was decomposed in crushed ice slowly. The solid that separated was filtered, washed with water, and recrystallized from ethanol to furnish a light yellowish solid **2**.

IR (KBr) ν (cm^{-1}): 3020 (N—H), 1605 (C=O), 1570 (C=C), 1070 (=C—Cl), 680 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.20 (1H, s, CONH), 7.92–7.41 (4H, m, Ar-H), 4.21 (2H, NH_2); ^{13}C NMR δ:185 (C=O), 138, 131, 129, 128, 125, 123, 122 (aromatic carbon); MS (M^+): 226.68, 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.

Preparation of 2-[(3-Chloro-1-benzothiophen-2-yl)carbonyl]-*N*-phenyl hydrazinecarbothioamide (3a–b)

A mixture of carbohydrazide **2** (2.26 g, 10.0 mmol) and phenyl isothiocyanate (1.35 g, 1.27 mL, 10.0 mmol) 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 solid that precipitated was filtered, washed with ethanol, dried, and recrystallized from ethanol to get a pure compound **3a**. The compound **3b** was prepared in a similar manner.

2-[(3-Chloro-1-benzothiophen-2-yl)carbonyl]-*N*-phenylhydrazinecarbothioamide (3a). IR (KBr) ν (cm^{-1}): 3170 (N—H), 1660 (C=O), 1570 (C=C), 1220 (C=S), 1070 (=C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.41–9.72 (3H, s, NH), 8.15–7.15 (9H, m, Ar-H); MS (M^+): 360.10, Calcd. (%) for $C_{16}H_{12}ClN_3OS_2$:C, 53.11; H, 3.34; N, 11.61; S, 17.72. Found: C, 53.01; H, 3.30; N, 11.56; S, 17.68.

2-[(3-Chloro-1-benzothiophen-2-yl)carbonyl]-N-(4-chlorophenyl)hydrazinecarbothioamide (3b). IR (KBr) ν (cm^{-1}): 3165 (N—H), 1657 (C=O), 1225 (C=S), 758 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.00–9.52 (3H, s, NH), 8.00–7.20 (8H, m, Ar-H); MS (M^+): 396.10, Calcd. (%) for $C_{16}H_{11}Cl_2N_3OS_2$:C, 48.49; H, 2.80; N, 10.60; S, 16.18. Found: C, 48.41; H, 2.75; N, 10.57; S, 16.12.

Preparation of 3-Chloro-*N*-(4,6-dioxo-3-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)-1-benzothiophene-2-carboxamide (4a–b)

To compound **3a** (1.80 g, 5.0 mmol) in acetyl chloride (10 mL), malonic acid (2.08 g, 10.0 mmol) was added, and the mixture was heated for 6 h at 40°C. It was then cooled and poured into crushed ice, and the resulting solid was recrystallized from ethanol and then purified from column chromatography (silica gel, 60–120 mesh) by using petroleum ether and ethyl acetate (5:95) as an elutent to get pure **4a**. Compound **4b** was similarly prepared.

3-Chloro-*N*-(4,6-dioxo-3-phenyl-2-thioxotetrahydropyrimidin-1(2*H*)-yl)-1-benzothiophene-2-carboxamide (4a). IR (KBr) ν (cm^{-1}): 3140 (N—H), 1635 (C=O), 1570 (C=C), 1220 (C=S), 1065 (=C—Cl), 688 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.58 (1H, s, CONH), 8.00–7.20 (9H, m, Ar-H), 2.25 (2H, s, CH_2); MS (M^+): 428.90, Calcd. (%) for $C_{19}H_{12}ClN_3O_3S_2$:C, 53.08; H, 2.81; N, 9.77; S, 14.92. Found: C, 53.00; H, 2.76; N, 9.71; S, 14.88.

3-Chloro-*N*-[3-(4-chlorophenyl)-4,6-dioxo-2-thioxotetrahydropyrimidin-1(2*H*)-yl]-1-benzothiophene-2-carboxamide (4b). IR (KBr) ν (cm^{-1}): 3135 (N—H), 1620 (C=O), 1570 (C=C), 1225 (C=S), 755 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.05 (1H, s, CONH), 8.07–7.09 (8H, m, Ar-H), 2.30 (2H, s, CH_2); MS (M^+): 464.13, Calcd. (%) for $C_{19}H_{11}Cl_2N_3O_3S_2$:C, 49.15; H, 2.39; N, 9.05; S, 13.81. Found: C, 49.02; H, 2.30; N, 9.00; S, 13.75.

Preparation of 5-(3-Chloro-1-benzothiophen-2-yl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (5a–b)

Thiosemicarbazide **3a** (1.80 g, 5.0 mmol) was added gradually with stirring to cold concentrated sulfuric acid (10 mL) at 70°C during the course of 20 min. The reaction mixture was heated with stirring at 70°C for another 1 h, then it was poured over crushed ice under stirring. The solid precipitated was filtered, washed with water, dried, and recrystallized from methanol to get **5a**. Compound **5b** was similarly prepared.

5-(3-Chloro-1-benzothiophen-2-yl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (5a). IR (KBr) ν (cm^{-1}): 3130 (N—H), 1643 (C=O), 1220 (C=S), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.90 (1H, s, NH), 8.16–7.03 (9H, m, Ar-H); MS (M^+): 343.80, 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, 2.89; N, 12.13; S, 18.61.

5-(3-Chloro-1-benzothiophen-2-yl)-*N*-(4-chlorophenyl)-1,3,4-thiadiazol-2-amine (5b). IR (KBr) ν (cm^{-1}): 3142 (N—H), 1635 (C=O), 1220 (C=S), 760 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.51 (1H, s, NH), 8.20–7.05 (8H, m, Ar-H); MS (M^+): 373.01, Calcd. (%) for $C_{16}H_9Cl_2N_3S_2$:C, 50.80; H, 2.40; N, 11.11; S, 16.95. Found: C, 50.75; H, 2.35; N, 11.05; S, 16.89.

Preparation of 3-Chloro-*N*-[(2*Z*)-4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]-1-benzothiophene-2-carboxamide (6a–b)

Compound **3a** (1.80 g, 5.0 mmol) was treated with chloroacetic acid (0.47 g, 5.0 mmol) in the presence of sodium acetate (0.41 g, 5.0 mmol) in glacial acetic acid (20 mL), and the mixture was refluxed for 10 h at 110°C. The reaction mixture was monitored by TLC. After completion, the reaction mixture was cooled and poured into crushed ice, the

separated solid was filtered, dried, and recrystallized from 1.4-diaxone to obtain pure **6a**. The compound **6b** was prepared in a similar manner.

3-Chloro-*N*-[(2*Z*)-4-oxo-2-(phenylimino)-1,3-thiazolidin-3-yl]-1-benzothiophene-2-carboxamide (6a). IR (KBr) ν (cm^{-1}): 3155 (N—H), 1645 (C=N), 1615 (C=O), 1575 (C=C), 1070 (=C—Cl) 688 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.05 (1H, s, CONH), 8.00–7.20 (9H, m, Ar-H), 2.85 (2H, s, CH_2); MS (M^+): 401.88, Calcd. (%) for $C_{18}H_{12}ClN_3O_2S_2$:C, 53.79; H, 3.01; N, 10.46; S, 15.96. Found: C, 53.75; H, 3.00; N, 10.43; S, 15.94.

3-Chloro-*N*-{(2*Z*)-2-[(4-chlorophenyl)imino]-4-oxo-1,3-thiazolidin-3-yl}-1-benzothiophene-2-carboxamide (6b). IR (KBr) ν (cm^{-1}): 3155 (N—H), 1620 (C=O), 1575 (C=C), 763 (C—Cl), 685 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.06 (1H, s, CONH), 8.04–7.08 (8H, m, Ar-H), 2.92 (2H, s, CH_2); MS (M^+): 436.33, Calcd. (%) for $C_{18}H_{11}Cl_2N_3O_2S_2$:C, 49.55; H, 2.54; N, 9.63; S, 14.70. Found: C, 49.52; H, 2.53; N, 9.61; S, 14.69.

Preparation of 5-(3-Chloro-1-benzothiophen-2-yl)-*N*-phenyl-1,3,4-oxadiazol-2-amine (7a–b)

Compound **3a** (1.90 g, 4.0 mmol) in ethanol (10 mL) was dissolved in aqueous sodium hydroxide (10%, 5 mL) under cooling and stirring, resulting in a clear solution. To this, iodine in potassium iodide solution (5%) was added gradually under stirring until the iodine color persisted at room temperature. The reaction mixture was then refluxed for 6 h in a water bath. It was then cooled and poured over crushed ice. The solid mass that was precipitated was filtered, dried, and recrystallized from ethanol and further purified through column chromatography (silica gel, 60–120 mesh) by using ethyl acetate and petroleum ether (20:80) as an elutent to get pure compound **7a**. Similarly, the compound **7b** was prepared.

5-(3-Chloro-1-benzothiophen-2-yl)-*N*-phenyl-1,3,4-oxadiazol-2-amine (7a). IR (KBr) ν (cm^{-1}): 3220 (N—H), 1635 (C=N), 1070 (=C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.92 (1H, s, NH), 8.16–7.03 (9H, m, Ar-H); MS (M^+): 326.18, Calcd. (%) for $C_{16}H_{10}ClN_3OS$:C, 58.63; H, 3.07; N, 12.82; S, 9.78. Found: C, 58.55; H, 3.00; N, 12.76; S, 9.72.

5-(3-Chloro-1-benzothiophen-2-yl)- *N*-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (7b). IR (KBr) ν (cm^{-1}): 3215 (N—H), 762 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.82 (1H, s, NH), 8.10–7.06 (8H, m, Ar-H); MS (M^+): 362.01, Calcd. (%) for $C_{16}H_9Cl_2N_3OS$:C, 53.05; H, 2.50; N, 11.60; S, 8.85. Found: C, 53.00; H, 2.45; N, 11.52; S, 8.80.

Preparation of 5-(3-chloro-1-benzothiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8a–b)

The compound **3a** (1.80 g, 5.0 mmol) in ethanol (10 mL) was dissolved in aqueous sodium hydroxide (4%, 8 mL), and the mixture was refluxed gently for 2 h. The resulting solution was treated with decoloring charcoal, cooled, and filtered. The filtrate was adjusted to pH 6 with dilute acetic acid (10%), and the separated solid was filtered, dried, and the residue purified by recrystallization from ethanol to give pure compound of **8a**. Compound **8b** was similarly prepared.

5-(3-Chloro-1-benzothiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazole-3-thiol (8a). IR (KBr) ν (cm^{-1}): 3320 (N—H), 1630 (C=N), 1310 (C=S thione), 1065 (=C—Cl), 686 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92–8.22 (9H, m, Ar-H), 3.82 (1H, s, NH); MS (M^+): 343.80, 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, 12.17; S, 18.60.

5-(3-Chloro-1-benzothiophen-2-yl)-4-(4-chlorophenyl)-4*H*-1,2,4-triazole-3-thiol (8b). IR (KBr) ν (cm^{-1}): 3310 (N—H), 1630 (C=N), 1310 (C=S thione), 756 (C—Cl), 688 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.20–8.51 (8H, m, Ar-H), 3.72 (1H, s, NH); MS (M^+): 378.02, Calcd. (%) for $C_{16}H_9Cl_2N_3S_2$: C, 50.80; H, 2.40; N, 11.11; S, 16.95. Found: C, 50.77; H, 2.37; N, 11.06; S, 16.90.

Preparation of S-[5-(3-Chloro-1-benzothiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]ethanethioate (9a–f)

A mixture of **8a** (1.71 g, 5.0 mmol), acid chlorides/alkyl halides (6.0 mmol) in ethanol (20 mL), and 10% NaOH (5 mL) were created and then refluxed in a water bath for 2 h. The reaction mixture was cooled and filtered, and the filtrate was acidified with dil HCl to get the precipitate, which was collected by filtration and recrystallized from ethanol to get **9a**. Similarly, compounds **9b–f** were prepared with some change in reflux time and reaction workup. Their characteristic spectral and analytical data are given below.

S-[5-(3-Chloro-1-benzothiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]ethanethioate (9a). IR (KBr) ν (cm^{-1}): 1650 (C=O), 1615 (C=N), 1070 (=C—Cl), 685 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.92–8.41 (9H, m, Ar-H), 3.55 (3H, s, CH_3); MS (M^+): 385.80, 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, 10.85; S, 16.58.

S-[5-(3-Chloro-1-benzothiophen-2-yl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]benzenecarbothioate (9b). IR (KBr) ν (cm^{-1}): 1650 (C=O), 1620 (C=N), 1070 (=C—Cl), 689 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.50–8.13 (14H, m, Ar-H); MS (M^+): 443.90, Calcd. (%) for $C_{23}H_{14}ClN_3OS_2$:C, 61.67; H, 3.15; N, 9.38; S, 14.32. Found: C, 61.65; H, 3.09; N, 9.35; S, 14.23.

3-(3-Chloro-1-benzothiophen-2-yl)-5-(methylsulfanyl)-4-phenyl-4*H*-1,2,4-triazole (9c). IR (KBr) ν (cm^{-1}): 1620 (C=N), 1570 (C=C), 1070 (=C—Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90–8.04 (9H, m, Ar-H), 3.85 (3H, s, CH_3); MS (M^+): 357.01, Calcd. (%) for $C_{17}H_{12}ClN_2S_2$:C, 57.05; H, 3.38; N, 11.74; S, 17.92. Found: C, 57.00; H, 3.28; N, 11.65; S, 17.87.

S-[5-(3-Chloro-1-benzothiophen-2-yl)-4-(4-chlorophenyl)-4*H*-1,2,4-triazol-3-yl] ethanethioate (9d). IR (KBr) ν (cm^{-1}): 1655 (C=O), 1615 (C=N), 1570 (C=C), 760 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.75–8.00 (8H, m, Ar-H), 3.45 (3H, s, CH_3); MS (M^+): 420.23, 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, 15.20.

S-[5-(3-Chloro-1-benzothiophen-2-yl)-4-(4-chlorophenyl)-4*H*-1,2,4-triazol-3-yl] benzenecarbothioate (9e). IR (KBr) ν (cm^{-1}): 1650 (C=O), 1625 (C=N), 762 (C—Cl), 688 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.00–7.20 (13H, m, Ar-H); MS (M^+): 482.13, Calcd. (%) for $C_{23}H_{13}Cl_2N_3OS_2$:C, 57.26; H, 2.72; N, 8.71; S, 13.29. Found: C, 57.20; H, 2.67; N, 8.68; S, 13.20.

3-(3-Chloro-1-benzothiophen-2-yl)-4-(4-chlorophenyl)-5-(methylsulfanyl)-4*H*-1,2,4-triazole (9f). IR (KBr) ν (cm^{-1}): 1613 (C=N), 1575 (C=C), 760 (C—Cl), 690 (C—S—C); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 8.90–8.02 (8H, m, Ar-H), 3.23 (3H,

s, CH_3); MS (M^+): 391.31, Calcd. (%) for $C_{17}H_{11}Cl_2N_3S_2$:C, 52.04; H, 2.83; N, 10.71; S, 16.35. Found: C, 52.00; H, 2.79; N, 10.65; S, 16.30.

Preparation of 3-Chloro-N′-[(2*Z*)-3,4-diphenyl-1,3-thiazol-2(3*H*)-ylidene]-1-benzothiophene-2-carbohydrazide (10a–b)

A mixture of compound **3a** (1.80 g, 5.0 mmol) and phenacyl bromide (0.98 g, 5.0 mmol) in distilled ethanol (15 mL) was refluxed for 6 h in a water bath and then cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to give **10a** as a white solid. Compound **10b** was similarly prepared.

3-Chloro-N′-[(2*Z*)-3,4-diphenyl-1,3-thiazol-2(3H)-ylidene]-1-benzothiophene-2-carbohydrazide (10a). IR (KBr) ν (cm^{-1}): 3189 (N—H), 1635 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.05 (1H, s, CONH), 8.00–7.20 (14H, m, Ar-H); MS (M^+): 461.98, Calcd. (%) for $C_{24}H_{16}ClN_3OS_2$:C, 62.40; H, 3.49; N, 9.10; S, 13.88. Found: C, 62.38; H, 3.43; N, 9.04; S, 13.85.

3-Chloro-N′-[(2*Z*)-3-(4-chlorophenyl)-4-phenyl-1,3-thiazol-2(3*H*)-ylidene]-1-benzothiophene-2-carbohydrazide (10b). IR (KBr) ν (cm^{-1}): 3189 (N—H), 1635 (C=O), 765 (C—Cl); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): 10.34 (1H, s, CONH), 8.00–7.25 (13H, m, Ar-H); MS (M^+): 496.43, Calcd. (%) for $C_{24}H_{15}Cl_2N_3OS_2$:C, 58.07; H, 3.05; N, 8.46; S, 12.92. Found: C, 58.02; H, 3.00; N, 8.42; S, 12.89.

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