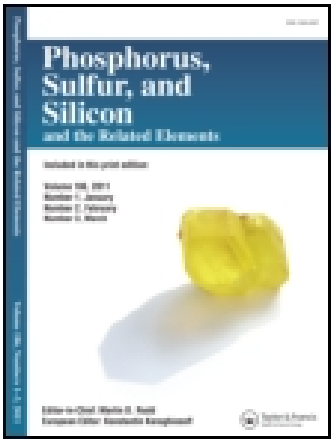

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Synthesis and Antimicrobial Activity of Some New 5-(3-Chloro-1-Benzothiophen-2-YL)-1,3,4-Oxadiazole-2-Thiol and Their Derivatives

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 5-(3-CHLORO-1-BENZOTHIOPHEN-2-YL)-1,3,4-OXADIAZOLE-2-THIOL AND THEIR DERIVATIVES

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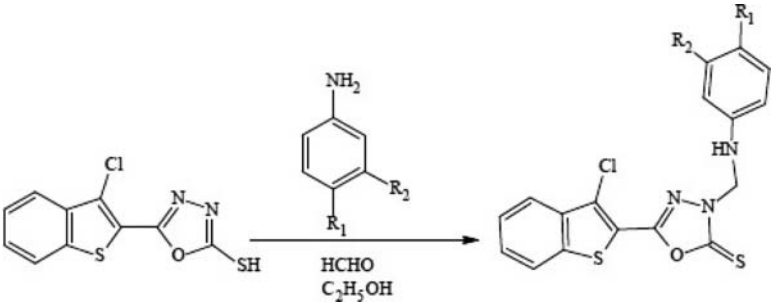
GRAPHICAL ABSTRACT



Abstract *3-Chloro-1-benzothiophene-2-carbonylchloride* ***1*** *was made to reacts with hydrazine hydrate afforded 3-chloro-1-benothiophene-2-carbohydrazide* ***2*** *in good yield. 5-(3-chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazole-2-thiol* ***4*** *was synthesized from 3-chloro-1-benzothiophene-2-carbohydrazide* ***2****. Mannich bases, alkyl halide, and acid chlorides derivatives were then prepared. Compound* ***4*** *on condensation with chloroacetone in the presence of NaOH as base and ethanol as solvent gave 1-{[5-(3-chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}propan-2-on* ***6****. Condensation of compound* ***6*** *with various aromatic aldehydes afforded a series of chalcones* ***7a–h****. The structures of all the synthesized compounds were confirmed by spectral data and have been screened for antibacterial activity.*

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 Benzothiophene; oxadiazole-2-thiol; Mannich bases; antibacterial activity

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INTRODUCTION

The study of nitrogen- and sulfur-containing heterocycles is currently an interesting topic in pesticide chemistry.[1–7] Benzothiophene compounds are of current interest due to their wide spectrum of pharmacological properties as antiallergic,[8] anti-inflammatory,[9] analgesic,[10] and ocular hypotensive activities.[11] The substituted oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores, and many of them are key elements with potential biological activities[12–14] such as pesticidal,[15] hypotensive,[16] insecticidal,[17] bactericidal,[18] diuretic,[19] herbicidal,[20,21] and fungicidal activities.[22,23] This study focuses mainly on benzothiophene as our basic structure and investigation of its combination with oxadiazole heterocyclic, prompted by the biological interest and continuation of our search for bioactive molecules. We report on the synthesis of compounds derived from benzothiophene containing oxadiazole moiety; with the purpose of investigation in the future, all derivatives of their possible antibacterial and antifungal activities of the resulting derivatives were screened and the relationship of molecular structure and the bioactivity are discussed.

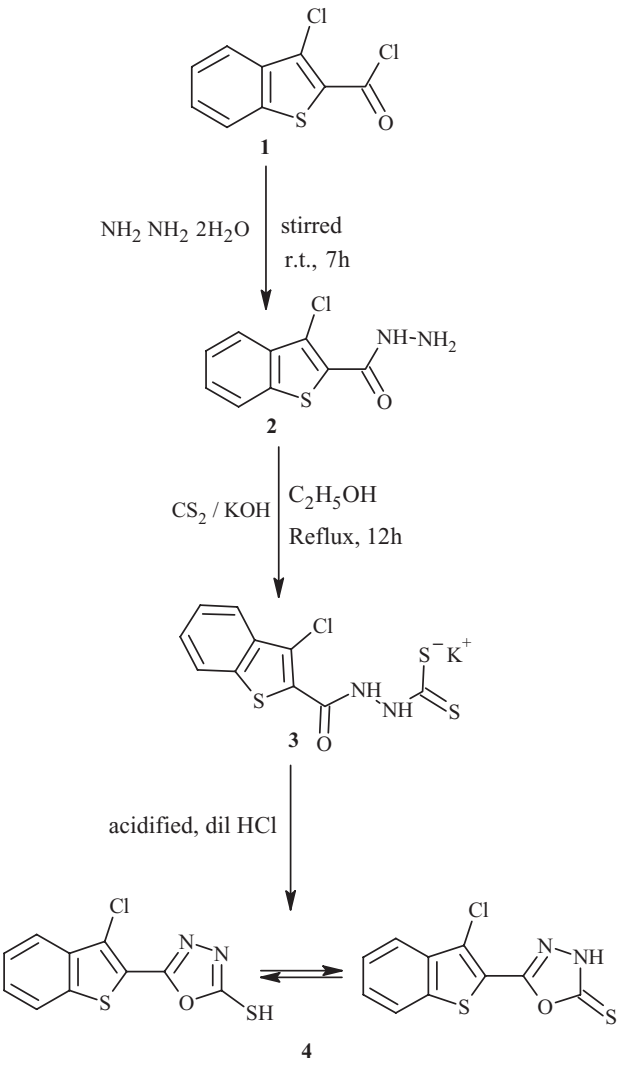
RESULTS AND DISCUSSION

The starting material for the synthesis of the target compound is 3-chlorobenzo thiophene-2-carbonylchloride **1** which was prepared by the reaction of cinnamic acid with thionyl chloride in dimethylformamide and dry pyridine according to the reported method.[24] Reaction between compound **1** and hydrazine hydrate afforded the 3-chlorobenzothiophene-2-carbohydrazide **2** in good yield. In confirmation, the IR spectrum of the compound **2** showed the peaks near 3020 and 1605 cm^{-1} due to N—H and C=O stretching absorption frequencies. Compound **2** was refluxed with carbon disulfide and potassium hydroxide in distilled ethanol to get compound **3**, which on subsequent treatment with dilute hydrochloric acid to gave 5-(3-chloro-1-benzo[*b*]thiophen-2-yl)-1,3,4-oxadiazole-2-thiol **4**, which exists in tautomeric thiol-thione equilibrium, as indicated by the C=S stretching band at 1255 cm^{-1} in its IR spectrum (Scheme 1). Compound **4** by using alkyl halide and various acid chlorides afford the compounds **5a–d**. The formation of compound **5a** was indicated by the absence of C—S stretching band at 760 cm^{-1} and C=N at 1630 cm^{-1}. The compound **4** was also treated with chloroacetone in the presence of a base to obtain compound **6** that on condensation with various aldehydes in the presence of potassium hydroxide afforded various chalcones **7a–h**. The peaks at 1625 cm^{-1} indicated at C=N the formation of the compound **7a**. Similarly, compound **4** was also subjected to Mannich reaction in the presence of formaldehyde and various amines to get **8a–c**. Compound **8a** that exhibited a stretching absorption peaks at 3320 cm^{-1} and 1265 cm^{-1} corresponds to N—H and C=S groups indicated its formation (Scheme 2).

BIOLOGICAL EVALUATION

Antibacterial Activity

A cup–plate method using HiMedia agar medium was employed to study the antibacterial activity of the synthesized compounds against two Gram-positive bacteria, *Staphylococcus aureus*-ATCC 25923 and *Bacillus subtilis*-ATCC 6633, and Gram-negative bacteria, *Pseudomonas aeruginosa*-ATCC 10145 and *Escherichia coli*-ATCC 35218. Preparation of nutrient broth, subculture, base layer medium, agar medium, and peptone water was carried

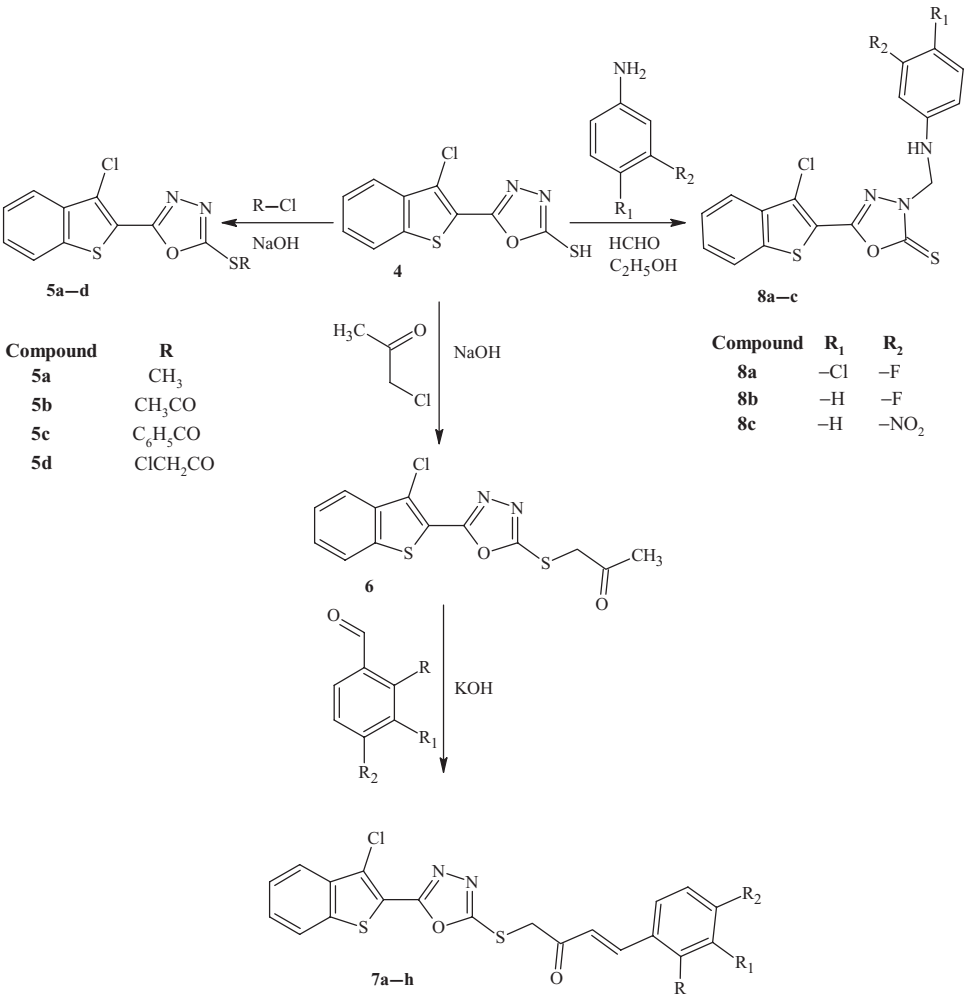


Scheme 1 Synthesis of 5-(3-chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazole-2-thiol **4**.

out as per the standard procedure.[25] The activities are shown in the supplemental materials (Table S 1).

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 a filter paper disc technique.[26] The activities are shown in the supplemental materials (Table S 2).



Compound	R
5a	CH_3
5b	CH_3CO
5c	C_6H_5CO
5d	$ClCH_2CO$

Compound	R_1	R_2
8a	–Cl	–F
8b	–H	–F
8c	–H	$–NO_2$

Compound	R	R_1	R_2
7a	–H	–H	–H
7b	–H	–H	–OH
7c	–Cl	–H	–H
7d	–H	–H	–Cl
7e	–H	–H	$–OCH_3$
7f	–H	$–NO_2$	–H
7g	–H	–H	$–NO_2$
7h	–H	–Br	–H

Scheme 2 Synthesis of 5-(3-chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazole-2-thiol derivatives.

CONCLUSION

In conclusion, a new series of benzothiophene-oxadiazole-2(3H)-thione derivatives were synthesized and evaluated for their antibacterial and antifungal 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.* It can be concluded that these classes of compounds certainly hold great promise toward good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

EXPERIMENTAL

All chemicals were 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 (FT-IR) spectra (KBr disks) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR were obtained in DMSO-d_6 at 500 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei (Bruker and Varian Company, USA). All chemical shifts were reported in parts per million (ppm) using residual proton or carbon signal in deuterated solvents as internal references. Mass spectra (MS) are recorded on Schimadzu GC-MS. Elemental analysis (C, H, N and S) was performed on Perkin Elmer 2400 analyzer and all products were purified by recrystallization. The purity of the compounds was checked by TLC on silica gel and further purification was performed through column chromatography (silica gel, 60–120 mesh).

Preparation of 3-Chloro-1-benzo[b]thiophene-2-carbonylchloride (1)

Compound **1** was prepared according to the literature procedure,[24] melting point (mp) 112–114 °C [Literature melting point (Lit. mp) 110–112 °C).

Preparation of 3-Chloro-1-benzo[b]thiophene-2-carboxylic Acid Hydrazide (2)

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

Yield 89%; mp 183–186 °C; IR ν (cm^{-1}): 3020 (N—H), 1605 (C=O), 1570 (C=C), 1070 (=C—Cl), 680 (C—S—C); ^{1}H NMR δ (ppm): 8.22 (s, 1H, CONH), 7.92–7.41 (m, 4H, Ar—CH), 4.22 (2H, NH_2); ^{13}C NMR δ (ppm): 185, 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%.

Preparation of 5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazole-2-thiol (4)

A mixture of compound **2** (2.26 g, 0.01 mol), potassium hydroxide (0.4 g, 0.01 mol), carbon disulfide (1.52 g, 1.45 mL, 0.02 mol), and absolute ethanol (100 mL) was refluxed for 12 h. The excess of solvent was removed by vacuum, and the residue was dissolved in water and filtered; the filtrate was acidified with dilute hydrochloric acid (50%); the precipitate was filtered and washed thoroughly with ice-cold water. The product was recrystallized from ethanol to give compound **4** as light yellowish solid.

Yield 65%; mp 210–212 °C; IR ν (cm^{-1}): 3356 (N—H), 1642 (C=N), 1255 (C=S), 1070 (=C—Cl), 683 (C—S—C); ^{1}H NMR δ (ppm): 8.23–7.65 (m, 4H, Ar—CH), 3.40 (s, 1H, SH); ^{13}C NMR δ (ppm): 161.4, 141.3, 138.2, 136.1, 124.4, 124.3, 123.2, 122.4, 118.3; MS, m/z: 268.70 (M^+). Anal. calcd. for $C_{10}H_5ClN_2OS_2$: C, 44.69; H, 1.88; N, 10.42; S, 23.86; found: C, 44.65; H, 1.81; N, 10.35; S, 23.80%.

General Procedure for Synthesis of Compounds 5a–d. Exemplary Detail for 2-(3-Chloro-1-benzo[b]thiophen-2-yl)-5-(methylsulfanyl)-1,3,4-oxadiazole (5a)

A mixture of compound **4** (2.68 g, 0.01 mol), 4-fluoroaniline (1.11 g, 0.98 mL, 0.01 mol) in the presence of 36% formaldehyde (0.02 mol) in absolute ethanol (30 mL) was refluxed for 10 h. The completion of the reaction was monitored by TLC. The reaction mixture was allowed to cool down to room temperature, and then poured into crushed ice. The precipitate was filtered, dried and recrystallized from methanol. The resulting solid was further purified by column chromatography [silica, petroleum ether/ethyl acetate (70:30)], leading to pure compound **8a**. Similarly, compounds **8b–c** were prepared.

Yield 56%; mp 231–232 °C; IR ν (cm^{-1}): 1630 (C=N), 1070 (=C—Cl), 760 (C—S), 681 (C—S—C); ^{1}H NMR δ (ppm): 8.23–7.44 (m, 4H, Ar—CH), 2.11 (s, 3H, SCH_3); ^{13}C NMR δ (ppm): 161.3, 141.2, 138.4, 136.3, 124.4, 124.3, 123.2, 122.4, 118.1, 14.2; MS, m/z: 282.76 (M^+). Anal. calcd. for $C_{11}H_7ClN_2OS_2$: C, 46.72; H, 2.50; N, 9.91; S, 22.68; found: C, 46.54; H, 2.45; N, 9.76; S, 21.22%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]ethanethioate (5b). Yield 55%; mp 240–242 °C; IR ν (cm^{-1}): 1650 (C=O), 1625 (C=N); ^{1}H NMR δ (ppm): 8.15–7.14 (m, 4H, Ar—CH), 2.30 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 193.1, 161.8, 141.4, 138.3, 124.4, 124.3, 123.2, 122.4, 118.2, 36.5, 30.4; MS, m/z: 310.77 (M^+). Anal. calcd. for $C_{12}H_7ClN_2O_2S_2$: C, 46.38; H, 2.27; N, 9.01; S, 20.64; found: C, 45.30; H, 2.20; N, 8.98; S, 20.60%.

5-(3-Chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazol-2-yl]benzenecarbothioate (5c). Yield 54%; mp 240–241 °C; IR ν (cm^{-1}): 1652 (C=O), 1630 (C=N); ^{1}H NMR δ (ppm): 8.46–7.31 (m, 9H, Ar—CH); ^{13}C NMR δ (ppm): 187.3, 161.7, 141.4, 138.5, 136.4, 134.7, 134.1, 128.9, 128.9, 128.1, 128.1, 124.4, 124.3, 123.2, 122.8, 118.4; MS, m/z: 372.84 (M^+). Anal. 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, 2.33; N, 7.47; S, 17.13%.

5-(3-Chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazol-2-yl]chloroethanethioate (5d). Yield 58%; mp 212–214 °C; IR ν (cm^{-1}): 1645 (C=O), 1620 (C=N); ^{1}H NMR δ (ppm): 8.25–7.74 (m, 4H, Ar—CH), 4.40 (s, 2H, CH_2); ^{13}C NMR δ (ppm): 188.3, 161.6, 141.4, 138.5, 136.5, 124.4, 124.3, 123.2, 122.4, 118.1, 47.4; MS, m/z: 342.22 (M^+). Anal. calcd. for $C_{12}H_6Cl_2N_2O_2S_2$: C, 41.75; H, 1.75; N, 8.11; S, 18.58; found: C, 41.65; H, 1.71; N, 8.09; S, 18.54%.

Preparation of 5-(3-Chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}propan-2-one (6)

A mixture of thione **4** (1.62 g, 0.005 mol), sodium hydroxide (0.2 g, 0.005 mol), and chloroacetone (0.56 g, 0.55 mL, 0.006 mol) was stirred in a mixture of ethyl alcohol (50 mL) and water (5 mL) for about 5 h. The excess of solvent was removed by vacuum

evaporation, and the separated solid was collected by filtration, washed with cold water, dried, recrystallized from methanol, and purified through column chromatography by using *n*-hexane and ethyl acetate (80:20) as an eluent to give pure compound **6**.

Yield 58%; mp 222–224 °C; IR ν (cm^{-1}): 1650 (C=O), 1635 (C=N); ^{1}H NMR δ (ppm): 8.18–7.32 (m, 4H, Ar−CH), 3.65 (s, 2H, SCH_2), 2.13 (s, 3H, CH_3); ^{13}C NMR δ (ppm): 200.1, 161.3, 141.2, 138.6, 136.9, 124.4, 124.1, 123.1, 122.5, 118.3, 47.5, 26.3; MS, m/z: 324.80 (M^+). Anal. calcd. for $C_{13}H_9ClN_2O_2S_2$: C, 48.07; H, 2.79; N, 8.62; S, 19.74; found: C, 48.05; H, 2.75; N, 8.60; S, 19.65%.

General Procedure for Synthesis of Compounds 7a–h. Exemplary Detail for 5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-phenylbut-3-en-2-one (7a)

A mixture of NaOH (2.0 g, 0.05 mol) and alcohol (60 mL) in a 250-mL round-bottomed flask was cooled (crushed ice) with stirring for about 15 min. Compound **6** (3.24 g, 0.01 mol) was added followed by addition of benzaldehyde (1.06 g, 1.02 mL, 0.01 mol); the reaction mixture was kept at 25 °C with stirring until the stirring was no longer possible 2–3 h. The reaction mixture was left overnight in a refrigerator. The separated precipitate product was filtered, washed with cold water until the washing was neutral to litmus, then with chilled alcohol, and recrystallized from 1,4-dioxane to afford pure **7a**. Similarly, the compounds **7b–h** were prepared with little change in stirring time and reaction work-up.

Yield 45%; mp 276–278 °C; IR ν (cm^{-1}): 1645 (C=O), 1625 (C=N); ^{1}H NMR δ (ppm): 8.10–7.26 (m, 9H, Ar−CH), 6.74 (d, 1H, Ar−CH=), 6.53 (d, 1H, −CO−CH=), 3.70 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.3, 161.1, 142.4, 141.3, 138.4, 136.3, 135.2, 128.6, 128.6, 128.5, 128.5, 127.9, 126.2, 124.4, 124.3, 123.1, 122.5, 118.2, 45.3; MS, m/z: 412.91 (M^+). Anal. calcd. for $C_{20}H_{12}ClN_2O_2S_2$: C, 58.18; H, 3.17; N, 6.78; S, 15.53; found: C, 58.13; H, 3.12; N, 6.71; S, 15.44%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(4-hydroxylphenyl)but-3-en-2-one (7b). Yield 48%; mp 266–268 °C; IR ν (cm^{-1}): 3421 (OH), 1640 (C=O), 1625 (C=N); ^{1}H NMR δ (ppm): 10.12 (s, 1H, OH), 7.97–7.26 (m, 8H, Ar−CH), 6.75 (d, 1H, Ar−CH=), 6.50 (d, 1H, −CO−CH=), 3.71 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.6, 161.4, 157.6, 142.5, 141.3, 138.2, 136.1, 130.7, 130.6, 130.6, 126.2, 124.4, 124.3, 123.2, 122.8, 118.4, 115.2, 115.2, 45.8; MS, m/z: 428.91 (M^+). Anal. calcd. for $C_{20}H_{13}ClN_2O_2S_2$: C, 56.01; H, 3.05; N, 6.53; S, 14.95; found: C, 56.05; H, 3.00; N, 6.50; S, 14.88%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(2-chlorophenyl)but-3-en-2-one (7c). Yield 55%; mp 287–289 °C; IR ν (cm^{-1}): 1645 (C=O), 1620 (C=N), 745 (C−Cl), 685 (C−S−C); ^{1}H NMR δ (ppm): 8.12–7.45 (m, 8H, Ar−CH), 6.74 (d, 1H, Ar−CH=), 6.55 (d, 1H, −CO−CH=), 3.72 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.1, 161.1, 142.4, 141.3, 138.2, 136.1, 133.4, 133.3, 129.0, 129.0, 128.7, 128.7, 126.2, 124.4, 124.4, 123.1, 122.3, 118.1, 45.0; MS, m/z: 447.35 (M^+). Anal. calcd. for $C_{20}H_{12}Cl_2N_2O_2S_2$: C, 53.70; H, 2.70; N, 6.26; S, 14.34; found: C, 53.65; H, 2.65; N, 6.22; S, 14.22%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(4-chlorophenyl)but-3-en-2-one (7d). Yield 55%; mp 281−282 °C; IR ν (cm^{-1}): 1642 (C=O), 1625 (C=N); ^{1}H NMR δ (ppm): 8.00–7.22 (m, 8H, Ar−CH), 6.74 (d, 1H, Ar−CH=), 6.50 (d, 1H, −CO−CH=), 3.70 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.9, 161.1, 142.3, 141.2, 138.4, 136.6, 133.3, 133.1, 129.0, 129.0, 128.7, 128.7,

126.2, 124.4, 124.3, 123.1, 122.3, 118.2, 45.1; MS, m/z: 447.01 (M^+). Anal. calcd. for $C_{20}H_{12}Cl_2N_2O_2S_2$: C, 53.70; H, 2.70; N, 6.26; S, 14.34; found: C, 53.65; H, 2.65; N, 6.22; S, 14.22%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(4-methoxyphenyl)but-3-en-2-one (7e). Yield 57%; mp 290–292 °C; IR ν (cm^{-1}): 1648 (C=O), 1630 (C=N); ^{1}H NMR δ (ppm): 8.05–7.32 (m, 4H, Ar−CH), 6.74 (d, 1H, Ar−CH=), 6.55 (d, 1H, −CO−CH=), 3.80 (s, 3H, OCH_3), 3.79 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.1, 161.7, 159.3, 142.3, 141.3, 138.3, 136.4, 130.2, 130.2, 130.2, 126.2, 124.4, 124.3, 123.2, 122.8, 118.4, 114.2, 114.2, 55.1, 45.3; MS, m/z: 442.93 (M^+). Anal. calcd. for $C_{21}H_{15}ClN_2O_3S_2$: C, 53.94; H, 3.41; N, 6.32; S, 14.48; found: C, 53.80; H, 3.39; N, 6.27; S, 14.41%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(2-nitrophenyl)but-3-en-2-one (7f). Yield 56%; mp 294–296 °C; IR ν (cm^{-1}): 1640 (C=O), 1635 (C=N), 1350 (NO_2); ^{1}H NMR δ (ppm): 7.98–7.32 (m, 8H, Ar−CH), 6.75 (d, 1H, Ar−CH=), 6.50 (d, 1H, −CO−CH=), 3.77 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.0, 161.0, 147.3, 142.3, 141.2, 138.7, 137.3, 136.4, 134.6, 129.5, 126.2, 124.4, 124.3, 123.2, 123.1, 122.8, 122.7, 118.1, 45.0; MS, m/z: 457.80 (M^+). Anal. calcd. for $C_{20}H_{12}ClN_2O_4S_2$: C, 52.46; H, 2.64; N, 9.18; S, 14.00; found: C, 52.41; H, 2.61; N, 9.12; S, 13.78%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}-4-(4-nitrophenyl)but-3-en-2-one (7g). Yield 59%; mp 289–291 °C; IR ν (cm^{-1}): 1647 (C=O), 1631 (C=N), 1353 (NO_2); ^{1}H NMR δ (ppm): 7.95–7.30 (m, 8H, Ar−CH), 6.79 (d, 1H, Ar−CH=), 6.54 (d, 1H, −CO−CH=), 3.69 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.1, 161.0, 147.3, 142.3, 141.2, 138.1, 137.1, 136.1, 134.1, 129.3, 126.2, 124.4, 124.3, 123.2, 123.1, 122.8, 122.5, 118.3, 45.8; MS, m/z: 457.90 (M^+). Anal. calcd. for $C_{20}H_{12}ClN_2O_4S_2$: C, 52.46; H, 2.64; N, 9.18; S, 14.00; found: C, 52.41; H, 2.61; N, 9.12; S, 13.78%.

4-(3-Bromophenyl)-1-{[5-(3-chloro-1-benzothiophen-2-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}but-3-en-2-one (7h). Yield 47%; mp 276–278 °C; IR ν (cm^{-1}): 1635 (C=O), 1625 (C=N), 610 (C−Br); ^{1}H NMR δ (ppm): 7.87–7.04 (m, 8H, Ar−CH), 6.70 (d, 1H, Ar−CH=), 6.55 (d, 1H, −CO−CH=), 3.68 (s, 2H, SCH_2); ^{13}C NMR δ (ppm): 196.0, 161.3, 142.4, 141.2, 138.7, 137.4, 136.9, 133.1, 130.8, 129.6, 127.5, 126.2, 124.4, 124.3, 123.3, 123.1, 122.3, 18.1, 45.9; MS, m/z: 491.80 (M^+). Anal. calcd. for $C_{20}H_{12}ClBrN_2O_2S_2$: C, 48.84; H, 2.46; N, 5.70; S, 13.04; found: C, 48.75; H, 2.41; N, 5.65; S, 13.00%.

General Procedure for Synthesis of Compounds 8a–c. Exemplary Detail for 5-(3-Chloro-1-benzo[b]thiophen-2-yl)-3-{[(3-chloro-4-fluorophenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione (8a)

A mixture of compound **4** (2.68 g, 0.01 mol), 4-fluoroaniline (1.11 g, 0.98 mL, 0.01 mol), and 36% formaldehyde (0.02 mol) in ethyl alcohol was refluxed for 10 h. Mean while a solid that separated was filtered, washed with water, dried, and recrystallized from methanol which was purified by column chromatography using a gradient mixture of petroleum ether/ethyl acetate (70:30) as an eluent to get compound **8a**. Similarly, compounds **8b–c** were prepared.

Yield 56%; mp 245–247 °C; IR ν (cm^{-1}): 3320 (N−H), 2965 (CH), 1629 (C=N), 1265 (C=S), 1054 (C−F); ^{1}H NMR δ (ppm): 8.45–7.12 (m, 7H, Ar−CH), 5.85 (d, 2H, N−$\underline{CH_2}$−NH), 5.45 (br, 1H, N−CH_2−$\underline{NH}$); ^{13}C NMR δ (ppm): 177.3, 155, 147.1, 144.3,

131.2, 126.1, 125.9, 124.4, 124.3, 122.8, 122, 121.5, 119.9, 117.0, 115.5, 114.2, 68.1; MS, m/z: 426.20 (M^+). Anal. calcd. for $C_{17}H_{10}Cl_2FN_3OS_2$: C, 47.89; H, 2.36; N, 9.86; S, 15.04; found: C, 47.81; H, 2.32; N, 9.81; S, 15.00%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-3-{[(4-fluorophenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione (8b). Yield 55%; mp 233–235 °C; IR ν (cm^{-1}): 3315 (N−H), 2970 (CH), 1630 (C=N), 1264 (C=S), 1070 (=C−Cl), 1050 (C−F), 740 (C−Cl), 684 (C−S−C); ^{1}H NMR δ (ppm): 8.22–7.16 (m, 8H, Ar−CH), 5.85 (d, 2H, N−$\underline{CH_2}$−NH), 5.40 (br, 1H, N−CH_2−$\underline{NH}$); ^{13}C NMR δ (ppm): 177.1, 155.7, 155, 143.2, 131.3, 126.2, 125.1, 124.2, 124.1, 122.8, 122, 119.9, 118.9, 118.9, 116.3, 116.1, 68.7; MS, m/z: 391.87 (M^+). Anal. calcd. for $C_{17}H_{11}ClFN_3OS_2$: C, 52.10; H, 2.83; N, 10.72; S, 16.37; found: C, 52.01; H, 2.72; N, 10.65; S, 16.30%.

5-(3-Chloro-1-benzo[b]thiophen-2-yl)-3-{[(4-nitrophenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione (8c). Yield 49%; mp 265–267 °C; IR ν (cm^{-1}): 3322 (N−H), 2972 (CH), 1635 (C=N), 1345 (NO_2), 1260 (C=S); ^{1}H NMR δ (ppm): 8.25–7.23 (m, 8H, Ar−CH), 5.90 (d, 2H, N−$\underline{CH_2}$−NH), 5.42 (br, 1H, N−CH_2−$\underline{NH}$); ^{13}C NMR δ (ppm): 177.7, 155.9, 153.4, 136.2, 131.3, 127.1, 127.5, 126.7, 125.9, 124.4, 124.3, 122.5, 122.1, 119.9, 114.1, 114.2, 68.9; MS, m/z: 418.75 (M^+). Anal. calcd. for $C_{17}H_{11}ClN_4O_3S_2$: C, 48.74; H, 2.65; N, 13.38; S, 15.31; found: C, 48.70; H, 2.59; N, 13.35; S, 15.23%.

REFERENCES

1. Kleschick, W. A.; Gerwick, B. C.; Carson, M. C.; Monte, W. T.; Snider, S. W. *J. Agric. Food Chem.* **1992,** 40, 1083-1085.
2. Yang, G. F.; Jiang, X. H.; Yang, H. Z. *Pest Manag. Sci.* **2002,** 58, 1063-1067.
3. Huang, W.; Zhao, P. L.; Liu, C. L.; Chen, Q.; Liu, Z. M.; Yang, G. F. *J. Agric. Food. Chem.* **2007,** 55, 3004-3004.
4. Luo, Y. P.; Yang, G. F. *Bioorg. Med. Chem.* **2007,** 15, 1716-1724.
5. Yang, G. F.; Liu, Z. M.; Lu, A. H.; Zhuang, N. B. *Acta Chim. Sinica.* **2001,** 59, 594-599.
6. (a) Liu, Z. M.; Yang, G. F.; Qin, X. H. *J. Chem. Technol. Biotechnol.* **2001,** 76, 1154-1156; (b) Ermitas Alcalde, Neus Mesquida, Carmen Alvarez-Rua, Rosa Cuberes, Jordi Frigola and Santiago Garcia-Granda *Molecules.* **2008,** 13, 301-318.
7. Li, Y. X.; Luo, Y. P.; Xi, Z.; Niu, C. W.; He, Y. Z.; Yang, G. F. *J. Agric. Food Chem.* **2006,** 54, 1342-1346.
8. Connor, D. T.; Cetenko, W. A.; Mullican, M. D.; Sorenson, R. J.; Unangst, P. C.; Weikert, R. J.; Adolphson, R. L.; Kennedy, J. A.; Thueson, D. O.; Wright, C. D.; Conroy, M. C. *J. Med. Chem.* **1992,** 35, 958-964.
9. (a) Joachim, G.; Werner, M.; Albrecht, W. *Ger. Offen.* **1973,** 2, 223-228); (b) Colot, M. *Chem. Abstr.* **1974,** 80, 59857q.
10. (a) Descamps, M.; Etienne, V. *Ger. Offen.* **1974,** 2, 328-336; (b) Kropp, K. G.; Goncalves, J. A.; Andersson, J. T.; Fedorak, P. M. *Chem. Abstr.* **1974,** 80, 59856p.
11. Graham, S. L.; Shepard, K. L.; Anderson, P. S.; Baldwin, J. J.; Best, D. B.; Christy, M. E.; Freedman, M. B.; Gautheron, P.; Habecker, C. N.; Hoffman, J. M.; Lyle, P. A.; Michelson, S. R.; Ponticello, G. S.; Robb, C. M.; Schwam, H.; Smith, A. M.; Smith, R. L.; Sondey, J. M.; Strohmaier, K. M.; Sugrue, M. F.; Varga, S. L. *J. Med. Chem.* **1989,** 32, 2548-2558.
12. Joseph, J. P.; Harry, L. Y., U.S. Patent, **1961,** 3, 141–148. [*Chem. Abs.* **1964,** 61, 8317b].
13. (a) Hokfelt, B.; Jonsson, A. *J. Med. Chem.* **1962,** 5, 247; (b) Ansel, P. S., U.S. Patent, **1959,** 2, 883 [*Chem. Abs.* **1959,** 53, 16157g].
14. Ansel, P. S., U.S. Patent, **2**, 883 (1959) [*Chem. Abs.* **1959,** 53, 16157g].

15. (a) Derappe, C.; Rips, R.; Albert, O.; Aurousseau, M. *Chim. Ther.* **1968,** 3, 181 [*Chem. Abs.* 1968, 69, 106626y]; (b) Baiocchi, A.; Chiari, A.; Frigerio, A; Ridolfi, P. *Chem. Abs.* **1970,** 73, 108544b.
16. Deshmukh, A. A.; Sattur, P. B.; Sheth, U. K. *Indian J. Exp. Biol.* **1976,** 4, 166-167.
17. Sen Gupta, A. K.; Garg, M.; Chandra, U. *J. Indian Chem. Soc.* **1979,** 56, 1230-1239.
18. Chiyomaru, I.; Takita, K.; Ito Kumiai, H., (Chem. Ind. Co. Ltd.) Jap. Patent, 7207, 549–533 (1972) [*Chem. Abstr.* **1972,** 77, 549-551].
19. Thomas, J., Ger. Patent, **2**, 403 (1974) [*Chem. Abstr.* **1974,** 81, 136153g].
20. Hodogaya Chemical Co. Ltd., Jap. Patent, **27**, 024 (1980) [*Chem. Abstr.* **1980,** 93, 232719q].
21. Hakko Chem. Ind. Co. Ltd., Brit. Patent, **1**, 266 (1972) [*Chem. Abstr.* **1972,** 77, 5474g].
22. Singh, H.; Yadav, L. D. S. *Agric. Biol. Chem.* **1976,** 40, 759-769.
23. Misato, T.; Honma, K.; Konno, K.; Taniyama, E. *Inst. Phys. Chem. Res.* Jap. Patent, **772**, 508 (1977) [*Chem. Abstr.* **1977,** 87, 147054].
24. Parkey, S.; Castle, N. *J. Heterocycl. Chem.* **1986,** 23, 1571-1577.
25. *British Pharmacopoeia* (**2005**), Vol. IV, Appendix XIV, p. A300.
26. Vincent, J. G.; Vincent, H. W. *Proc. Soc. Exp. Biol. Med.* **1944,** 55, 162-164.