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Synthesis and characterization of novel benzothiophene substituted oxadiazole derivatives and their antimicrobial activity.

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ABSTRACT

*The compound **2** was refluxed with various acetophenones and benzaldehydes to produce Schiff's bases **4a-e** and **6a-e**. The reaction of these Schiff's bases with acetic anhydride and phosphorous oxychloride to give benzothiophene linked 2, 5-disubstituted-1,3,4-oxadiazoles **5a-e** and **7a-e**. The compound **2** was directly cyclized by refluxing with phosphorus oxychloride to give benzothiophene substituted oxadiazoles **3a-e**. All the newly synthesized compounds were screened for their antimicrobial activity and were characterized by elemental analyses, IR, 1H NMR and mass spectral data.*

Keywords: Benzothiophene. Oxadiazole. Schiff base. Antimicrobial studies.

INTRODUCTION

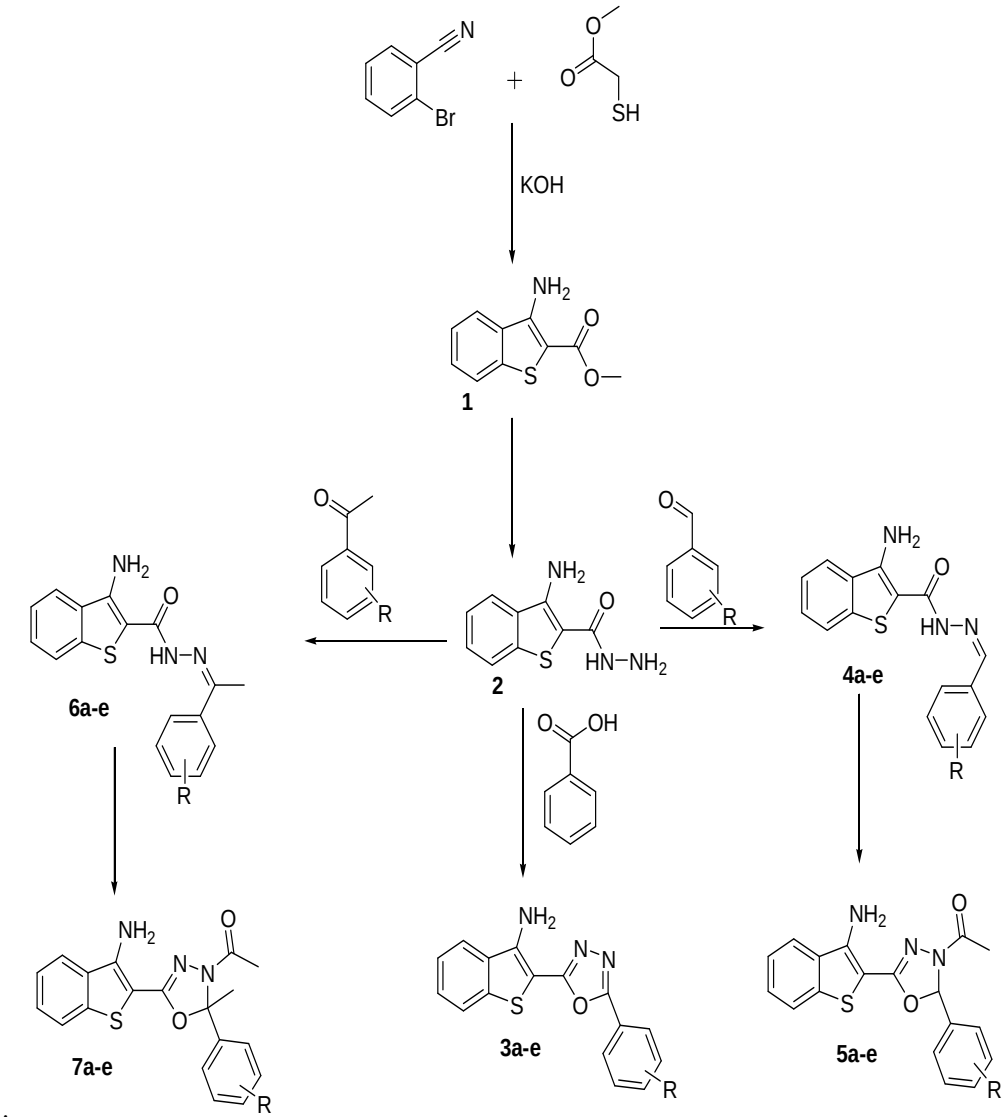
The constant and growing interest in the development of new efficient and general synthetic methods for the preparation of fused heterocyclic systems involving benzothiophene and oxadiazole subunits is justified by their well-established valuable physiological and pharmacological properties [1-5]. The oxadiazole drugs were the first effective chemotherapeutic agents to be employed systematically for the prevention and cure of bacterial infection in human beings. The capacity of 1,3,4-oxadiazole nucleus to undergo variety of chemical reactions have made it medicinal backbone on which number of potential molecules can be constructed [6-8].

There are large number of synthetic compounds with oxadiazole nucleus used for antitumor [9] antiparkinsonian [10] anti-TB [11] antiproliferative, anticancer, HIV-1 integrase inhibitory [12-14] tyrosinase inhibitory activities and fluorescent whiteners [14-17]. When substituted at 2 and 5 positions, benzothiophene derivatives reported in the literature were known to possess varied biological activities *viz*. antimicrobial, antituberculosis [18-19] analgesic nervous system depressing [20] muscle relaxant and tranquilizing activities [21].

In view of these above findings and in continuation of research work on benzothiophene containing heterocycles, an attempt have been made to develop synthetic route for a novel series of 2,5-disubstituted-1,3,4-oxadiazole substituted benzothiophene derivatives as better and potent antimicrobial.

MATERIALS AND METHODS

Melting points (in ^{0}C) were determined in open capillary tubes and are uncorrected.IR spectra were recorded on Perkin-Elmer FTIR 1000 and Shimadzu Spectrophotometer using KBr pellets. Wave numbers are expressed in cm^{-1}. ^{1}H NMR Spectra were recorded on Bruker AV Spectrometer, and JEOL MODEL GSX 270 FT NMR Spectrophotometer, Supercon Spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and TMS as an internal standard reference. The mass spectra were recorded on a JEOL JMS-D 300 spectrometer operating at 70 eV. Elemental analyses were performed on a Flash EA 1112 series CHNS Analyzer



Comp	R	Comp	R	Comp	R
3a	4-Cl	5a	3-NO_2	7a	4-Cl
3b	2,4-NO_2	5b	4-Cl	7b	4-OCH_3
3c	4-NH_2	5c	3-OH	7c	4-OH
3d	2-Cl	5d	4-NH_2	7d	3-NH_2
3e	4-F	5e	4-OCH_3	7e	3-NO_2

Synthesis of 2-[5-(4-chlorophenyl)-1, 3, 4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3a-e):
3-Amino-1-benzothiophene-2-corbohydrazide **2** (2.07g, 0.01mol) and 4-chloro benzoic acid (1.56g, 0.01mol) were taken in a round bottom flask to this phosphorous oxychloride (5ml) was added. The reaction mixture was refluxed on oil bath until completion of the reaction. The completion of reaction was monitored by TLC. Then reaction mass was allowed to room temperature and poured in to crushed ice and neutralized with 20% sodium bicarbonate solution. The solid separated was filtered, washed with water, dried and recrystallized from ethyl acetate solvent to give oxadiazole 3a. Similarly, the compounds 3b-e were prepared by using substituted aromatic carboxylic acids.

2-[5-(4-Chlorophenyl)-1, 3, 4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3a):
Solid (Crystalline); Yield (78%); IR (KBr) (ν_{max} cm^{-1}): 3436, 3355 (NH_2), 1590 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.27–7.42 (8H, m, Ar-H), 5.43 (1H, bs, OH), 4.85 (2H, bs, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{11}N_3O_2S$: C, 62.12. H, 3.58. N, 13.58. S, 10.36; Found: C, 62.08. H, 3.54. N, 13.55. S, 10.32; LC-MS m/z: 309 ; M.P: 290-293 ^{0}C.

2-[5-(2,4-Dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3b):
Solid (Crystalline); Yield (65%); IR (KBr) (ν_{max} cm^{-1}): 3429, 3365 (NH_2), 1585 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.59–7.90 (7H, m, Ar-H), 4.91 (2H, bs, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_9N_5O_5S$: C, 50.13; H, 2.36; N, 18.26. S, 8.36; Found: C, 50.10; H, 2.31; N, 18.23. S, 8.33; LC-MS m/z: 383.33 ; M.P: 311-314^{0}C.

2-[5-(4-Aminophenyl)-1,3,4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3c):
Solid (Amorphous); Yield (72%); IR (KBr) (ν_{max} cm^{-1}): 3420, 3380 (NH_2), 1605 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.45–7.55 (8H, m, Ar-H), 5.57 (2H. s, NH_2), 4.80 (2H, bs, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{12}N_4OS$: C, 62.32. H, 3.92. N, 18.17. S, 10.39; Found: C, 62.29. H, 3.88. N, 18.14. S, 10.36; LC-MS m/z: 308.35 ; M.P: 322-325 ^{0}C.

2-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3d):
Solid (Crystalline); Yield (69%); IR (KBr) (ν_{max} cm^{-1}): 3418, 3379 (NH_2), 1580 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.10–7.33 (8H, m, Ar-H), 4.93 (2H, bs, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{10}ClN_3OS$: C, 58.71. H, 3.07. N, 12.82. S, 9.78; Found: C, 58.67. H, 3.03. N, 12.79. S, 9.4; LC-MS m/z: 327.78 ; M.P: 344-347 ^{0}C.

2-[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]-1-benzothiophen-3-amine (3e):
Solid (Crystalline); Yield (67%); IR (KBr) (ν_{max} cm^{-1}): 3416, 3364 (NH_2), 1570 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.45–7.35 (8H, m, Ar-H), 4.78 (2H, s, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{10}FN_3OS$: C, 61.72; H, 3.23; N, 13.50. S, 10.29; Found: C, 61.68; H, 3.19; N, 13.40. S, 10.26; LC-MS m/z: 311.33 ; M.P: 305-308 ^{0}C.

Preparation of 3-amino-*N*'[(*E*)-(3-nitrophenyl)methylidene]1-benzothiophene-2-carbohydr azide (4a-e):
A mixture of compound 2 (0.176g, 0.001mol) and 3-nitro benzaldehyde (0.120g, 0.121ml 0.001mol) was dissolved in alcohol (20 ml) containing catalytic quantity of acetic acid. The mixture was refluxed on water bath 8 hours. The reaction mixture was cooled to room temperature and poured into crushed ice. The solid thus obtained was filtered, washed with water, dried and recrystallized from alcohol. Similarly, 4b-e were prepared by using appropriately substituted benzaldehydes.

Solid (Amorphous); Yield (71%); IR (KBr) (ν_{max} cm^{-1}): 3452, 3383 (NH_2), 1647 (C=O), 1606 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 10.10 (1H, s, NH), 8.32–7.41 (9H, m, Ar-H), 4.95 (2H, s, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{12}N_4O_3S$: C, 56.46; H, 3.55; N, 16.46; S, 9.42 Found: C, 56.43. H, 3.51. N, 16.43.S, 9.38; LC-MS m/z: 340 ; M.P: 266-269 ^{0}C.

3-Amino-*N*'-[(*Z*)-(4-chlorophenyl)methylidene]-1-benzothiophene-2-carbohydrazide (4b):
Solid (Amorphous); Yield (57%); IR (KBr) (ν_{max} cm^{-1}): 3469, 3375 (NH_2), 1640 (C=O), 1620 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.93 (1H, s, NH), 8.15–7.25 (9H, m, Ar-H), 4.73 (2H, s, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{12}ClN_3OS$: C, 58.26; H, 3.66; N, 12.74; S, 9.72; Found: C, 58.23. H, 3.62. N, 12.70. S, 9.68; LC-MS m/z: 329.80 ; M.P: 274-277 ^{0}C.

3-Amino-*N*'-[(*Z*)-(3-hydroxyphenyl)methylidene]-1-benzothiophene-2-carbohydrazide (4c):
Solid (Crystalline); Yield (57%); IR (KBr) (ν_{max} cm^{-1}): 3473, 3378 (NH_2), 1643 (C=O), 1622 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.98 (1H, s, NH), 8.22–7.58 (9H, m, Ar-H), 6.25 (1H, s, OH), 4.73 (2H, s, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{13}N_3O_2S$: C, 61.72. H, 4.20. N, 13.49. S, 10.30; Found: C, 61.68. H, 4.17. N, 13.45. S, 10.27; LC-MS m/z: 311.35 ; M.P: 258-261 ^{0}C.

3-Amino-*N*'-[(*Z*)-(4-aminophenyl)methylidene]-1-benzothiophene-2-carbohydrazide (4d):
Solid (Crystalline); Yield (72%); IR (KBr) (ν_{max} cm^{-1}): 3480, 3382 (NH_2), 1649 (C=O), 1626 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.90 (1H, s, NH), 8.19–7.36 (9H, m, Ar-H), 5.95 (2H, s, NH_2), 4.53 (2H, s, NH_2); Elemental analysis: Calculated (%) for $C_{16}H_{14}N_4OS$: C, 61.91. H, 4.54. N, 18.00. S, 10.33; Found: C, 61.87. H, 4.51. N, 17.95. S, 10.28; LC-MS m/z: 310.37 ; M.P: 260-263 ^{0}C.

3-Amino-*N*'-[(*Z*)-(4-methoxyphenyl)methylidene]-1-benzothiophene-2-carbohydrazide (4e):
Solid (Crystalline); Yield (63%); IR (KBr) (ν_{max} cm^{-1}): 3485, 3384 (NH_2), 1651 (C=O), 1629 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 10.02 (1H, s, NH), 8.35–7.59 (9H, m, Ar-H), 4.66 (2H, s, NH_2), 3.76 (3H, s, OCH_3); Elemental analysis: Calculated (%) for $C_{17}H_{15}N_3O_2S$: C, 62.75. H, 4.64. N, 12.79. S, 9.85; Found: C, 63.65. H, 5.01. N, 12.35. S, 9.39; LC-MS m/z: 325.38 ; M.P: 258-261 ^{0}C.

Preparation of 1-[5-(3-amino-1-benzothiophen-2-yl)-2-(3-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (5a-e):
A mixture of 4a (0.264g, 0.001mol) and acetic anhydride (10ml) was refluxed until the completion of reaction. The resulting solution was cooled to room temperature and poured into ice-cold water. The solid thus separated was filter, dried and recrystallized from alcohol to give compound 6a. Similarly, the compounds 5b-f were also prepared.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(3-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (5a):
Solid (Crystalline); Yield (76%); IR (KBr) (ν_{max} cm^{-1}): 3482, 3392 (NH_2), 1693 (C=O), 1625 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.27–7.36 (8H, m, Ar-H), 6.59 (1H, s), 4.85 (2H, s, NH_2), 2.05 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{18}H_{14}N_4O_4S$; C, 56.54. H, 3.69. N, 14.65. S, 8.38; Found: C, 56.51. H, 3.66. N, 14.62. S, 8.35; LC-MS m/z: 382 ; M.P: 352-355 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(4-chlorophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (5b):
Solid (Crystalline); Yield (61%); IR (KBr) (ν_{max} cm^{-1}): 3464, 3386 (NH_2), 1687 (C=N), 1620 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.04–7.18 (8H, m, Ar-H), 6.48 (1H, s), 4.74 (2H, s, NH_2), 2.09 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{18}H_{14}ClN_3O_2S$; C, 58.14. H, 3.79. N, 11.30. S, 8.62; Found: C, 58.09; H, 3.75; N, 11.27. S, 8.59; LC-MS m/z: 371.84 ; M.P: 320-323 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(3-hydroxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (5c):
Solid (Amorphous); Yield (81%); IR (KBr) (ν_{max} cm^{-1}): 3475, 3389 (NH_2), 1695 (C=O), 1621 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.21–7.33 (8H, m, Ar-H), 6.75 (1H, s), 6.48 (1H, s, OH), 4.79 (2H, s, NH_2), 2.09 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{18}H_{15}N_3O_3S$; C, 61.17. H, 4.27. N, 11.89. S, 9.07; Found: C, 61.13. H, 4.23. N, 11.86. S, 9.03; LC-MS m/z: 353.39 ; M.P: 331-334 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(4-aminophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (5d):
Solid (Crystalline); Yield (76%); IR (KBr) (ν_{max} cm^{-1}): 3467, 3392 (NH_2), 1697 (C=O), 1624 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.18–6.69 (8H, m, Ar-H), 6.54 (1H, s), 6.09 (2H, s, NH_2), 4.95 (2H, s, NH_2), 2.06 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{18}H_{16}N_4O_2S$; C, 61.34. H, 4.57. N, 15.89. S, 9.09; Found: C, 61.30; H, 4.53. N, 15.86. S, 9.05; LC-MS m/z: 352.41 ; M.P: 314-317 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(4-methoxyphenyl)-1,3,4-oxadiazol-3(2*H*)-yl] ethanone (5e):
Solid (Crystalline); Yield (59%); IR (KBr) (ν_{max} cm^{-1}): 3495, 3398 (NH_2), 1705 (C=O), 1629 (C=N); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.22–6.85 (8H, m, Ar-H), 6.60 (1H, s), 4.75 (2H, s, NH_2), 3.85 (3H, OMe), 2.05 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{19}H_{17}N_3O_3S$; C, 62.96. H, 4.27. N, 11.43. S, 8.72; Found: C, 62.93. H, 4.24. N, 11.39. S, 8.65; LC-MS m/z: 367.42 ; M.P: 298-301 ^{0}C.

Synthesis of 3-amino-*N*'-[(1*Z*)-1-(4-chlorophenyl)ethylidene]-1-benzothiophene-2-carbohy drazide (6a-e):
The compound 2 was refluxed with various acetophenones in alcohol containing catalytic amount of glacial acetic acid on water bath to produce solid 3-amino-*N*'-[(1*E*)-1-(4-chlorophenyl)ethylidene]-1-benzothiophene-2-carbohydrazide 6a.

3-Amino-*N*'-[(1*Z*)-1-(4-chlorophenyl)ethylidene]-1-benzothiophene-2-carbohydrazide (6a):
Solid (Amorphous); Yield (57%); IR (KBr) (ν_{max} cm^{-1}): 3471, 3369 (NH_2), 3187 (NH) 1652 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.21 (1H, NH), 8.22–6.85 (8H, m, Ar-H), 4.59 (2H, s, NH_2), 2.40 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{17}H_{14}ClN_3OS$: C, 59.38. H, 4.10. N, 12.22. S, 9.32; Found: C, 59.35. H, 4.06. N, 12.15. S, 9.28; LC-MS m/z: 343.83 ; M.P: 265-268 ^{0}C.

3-Amino-*N*'[(1*Z*)-1(4-methoxyphenyl)ethylidene]-1-benzothiophene-2-carbohydrazide (6b):
Solid (Crystalline); Yield (73%); IR (KBr) (ν_{max} cm^{-1}): 3483, 3378 (NH_2), 3197 (NH) 1664 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.18 (1H, NH), 8.18–6.88 (8H, m, Ar-H), 4.73 (2H, s, NH_2), 3.86 (3H, OMe) 2.40 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{18}H_{17}N_3O_2S$: C, 63.69. H, 5.04. N, 12.38. S, 9.44; Found: C, 63.65. H, 5.01. N, 12.35. S, 9.39; LC-MS m/z: 339.41 ; M.P: 281-284 ^{0}C.

3-Amino-*N*'[(1*E*)1-(4-hydroxyphenyl)ethylidene]-1-benzothiophene-2-carbohydrazide (6c):
Solid (Crystalline); Yield (66%); IR (KBr) (ν_{max} cm^{-1}): 3480, 3376 (NH_2), 3192 (NH) 1661 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.20 (1H, NH), 8.20–6.80 (8H, m, Ar-H), 5.15 (1H, OH), 4.65 (2H, s, NH_2), 2.48 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{17}H_{15}N_3O_2S$: C, 62.75. H, 4.64. N, 12.91. S, 9.85; Found: C, 62.72. H, 4.61. N, 12.85. S, 9.79; LC-MS m/z: 325.38 ; M.P: 275-278 ^{0}C.

3-Amino-*N*'[(1*Z*)1-(3-aminophenyl)ethylidene]-1-benzothiophene-2-carbohydrazide (6d):
Solid (Crystalline); Yield (68%); IR (KBr) (ν_{max} cm^{-1}): 3478, 3373 (NH_2), 3189 (NH) 1657 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.12 (1H, NH_2), 8.10–6.70 (8H, m, Ar-H), 5.61 (2H, s, NH_2), 4.95 (2H, NH_2) 2.39 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{17}H_{16}N_4OS$: C, 62.94. H, 4.97. N, 17.27. S, 9.88; Found: C, 62.91. H, 4.93. N, 17.22. S, 9.85; LC-MS m/z: 324.40 ; M.P: 281-283 ^{0}C.

3-Amino-*N*'[(1*Z*)-1(3-nitrophenyl)ethylidene]-1-benzothiophene-2-carbohydrazide (6e):
Solid (Crystalline); Yield (74%); IR (KBr) (ν_{max} cm^{-1}): 3474, 3371 (NH_2), 3188 (NH) 1655 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 9.30 (1H, NH_2), 8.32–6.90 (8H, m, Ar-H), 4.95 (2H, s, NH_2), 2.52 (3H, CH_3); Elemental analysis: Calculated (%) for $C_{17}H_{14}N_4O_3S$: C, 57.61. H, 3.98. N, 15.80. S, 9.04; Found: C, 57.58. H, 3.94. N, 15.75. S, 9.01; LC-MS m/z: 354.38 ; M.P: 275-278 ^{0}C.

Synthesis of 1-[5-(3-amino-1-benzothiophen-2-yl)-2-(4-chlorophenyl)-2-methyl-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (7a-e):
A mixture of 6a (0.278g, 0.001mol) and acetic anhydride (10ml) was refluxed until the completion of reaction as monitored by TLC. The resulting solution was cooled to room temperature and poured into ice-cold water. The solid thus separated was filtered, dried and recrystallized from alcohol to give 7a. Similar procedure was adopted for the synthesis of the compounds 7b-e.

Solid (Crystalline); Yield (69%); IR (KBr) (ν_{max} cm^{-1}): 3472, 3388 (NH_2), 1685 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.28–7.36 (8H, m, Ar-H), 4.68 (2H, s, NH_2), 2.21 (3H, CH_3), 1.70 (3H, s, CH_3); Elemental analysis: Calculated (%) for $C_{19}H_{16}ClN_3O_2S$; C, 59.13; H, 4.17; N, 10.89. S, 8.31; Found: C, 59.08; H, 4.13; N, 10.84. S, 8.28; LC-MS m/z: 386 ; M.P: 285-288 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(4-methoxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2*H*)-yl]ethanone.(7b):
Solid (Crystalline); Yield (55%); IR (KBr) (ν_{max} cm^{-1}): 3495, 3394 (NH_2), 1697 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.38–7.41 (8H, m, Ar-H), 4.78 (2H, s, NH_2),3.81 (3H, s), 2.28 (3H, CH_3), 1.73 (3H, s, CH_3); Elemental analysis: Calculated (%) for $C_{20}H_{19}N_3O_3S$; C, 62.97. H, 5.02. N, 11.01. S, 8.40; Found: C, 62.91. H, 4.98. N, 10.98. S, 8.36; LC-MS m/z: 381.44 ; M.P: 316-319 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(4-hydroxyphenyl)-2-methyl-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (7c):
Solid (Crystalline); Yield (74%); IR (KBr) (ν_{max} cm^{-1}): 3487, 3391 (NH_2), 1692 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.05–6.65 (8H, m, Ar-H), 5.55 (1H, OH), 4.86 (2H, s, NH_2), 2.02 (3H, CH_3), 1.89 (3H, s, CH_3);

Elemental analysis: Calculated (%) for $C_{19}H_{17}N_3O_3S$; C, 62.96. H, 4.27. N, 11.43. S, 8.72; Found: C, 62.92. H, 4.25. N, 11.40. S, 8.68; LC-MS m/z: 367.42 ; M.P: 328-331 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-(3-aminophenyl)-2-methyl-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (7d):
Solid (Crystalline); Yield (63%); IR (KBr) (ν_{max} cm^{-1}): 3481, 3386 (NH_2), 1689 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.12–6.70 (8H, m, Ar-H), 6.22 (2H, s, NH_2), 4.80 (2H, NH_2), 2.10 (3H, CH_3), 1.80 (3H, s, CH_3); Elemental analysis: Calculated (%) for $C_{19}H_{18}N_4O_2S$; C, 62.27. H, 4.95. N, 15.28. S, 8.75; Found: C, 62.23; H, 4.91. N, 15.53. S, 8.71; LC-MS m/z: 366.43; M.P : 300-303 ^{0}C.

1-[5-(3-Amino-1-benzothiophen-2-yl)-2-methyl-2-(3-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone (7e):
Solid (Crystalline); Yield (58%); IR (KBr) (ν_{max} cm^{-1}): 3476, 3389 (NH_2), 1687 (C=O); ^{1}H-NMR: (400 MHz: DMSO-d6) δ (ppm): 8.11–6.65 (8H, m, Ar-H), 4.95 (2H, s, NH_2), 2.10 (3H, CH_3), 1.90 (3H, s, CH_3); Elemental analysis: Calculated (%) for $C_{19}H_{16}N_4O_4S$; C, 57.56. H, 4.06. N, 14.13. S, 8.08; Found: C, 57.52. H, 4.02. N, 14.09. S, 8.05 ; LC-MS m/z: 396.41 ; M.P: 319-322 ^{0}C.

ANTIMICROBIAL EVALUATION

Antibacterial activity

A 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 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 done as per the standard procedure[22]. The results of the study are summarized in Table-1. The tested compound showed slight to moderate antibacterial activity compared to the standard drugs against all microorganisms.

Table-1. Antibacterial activity of the tested compounds

Compounds	Diameter of zone of inhibition (in mm)			
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonasaeruginosa*	*Escherichia coli*
3a	14	12	16	15
3b	13	11	15	02
3c	15	13	14	12
3d	19	18	15	20
5a	16	15	15	16
5b	17	18	17	17
5c	16	15	13	14
7b	17	17	17	18
7c	16	15	10	15
7d	18	14	13	17
DMF	00	00	00	00
Chloramphenicol	20	21	18	22

Table-2. Antifungal activity of the tested compounds

Compounds	Diameter of zone of inhibition (in mm)			
	Aspergillus niger	*Pencillium notatum*	*Aspergillus fumigatus*	*Candiada albicans*
3a	14	17	19	14
3b	12	13	15	10
3c	19	17	18	16
3d	20	18	21	17
5a	14	17	10	15
5b	22	19	20	18
5c	17	18	16	14
7b	21	19	19	15
7c	15	18	19	13
7d	17	15	16	14
DMF	00	00	00	00
Fluconazole	25	24	25	19

Antifungal activity

The antifungal activity of the synthesized compounds was tested against four different fungi, *i.e. Aspergillus niger*, *Pencillium notatum*, *Aspergillus fumigatus* and *Candiada albicans* by a filter paper disc technique. The

concentration of test compounds was 100 µg/mL. After 48 h treatment, zone of inhibition produced by each compound was measured in mm. *Fluconazole* was used as the standard antifungal agent and dimethyl formamide as a control. The results are described in Table-2.

RESULTS AND DISCUSSION

The compound 2-[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-benzothiophen-3-amine 3a was prepared by reacting compound 2 with 4-chlorobenzoic acid in the presence of phosphorous oxychloride which underwent cyclization to gave targeted product in good yield. Formation of 3a was confirmed by spectral data. The ^{1}H NMR spectrum shows NH_2 functional group appears as singlet in the region δ 4.85. A multiplet exhibited in the region 8.27–7.42. The mass spectrum of 3a exhibited molecular ion peak at m/z 309 corresponding to its molecular weight.

Schiff base 3-amino-*N*'-[(*E*)-(3-nitrophenyl)methylidene]-1-benzothiophene-2-carbohydrazide 4a thus prepared was refluxed with acetic anhydride to give targeted oxadiazole derivatives 1-[5-(3-amino-1-benzothiophen-2-yl)-2-(3-nitrophenyl)-1,3,4-oxadiazol-3(2*H*)-yl]ethanone 5a was obtained in excellent yields. IR spectrum of 5a exhibited absence of peak corresponding to NH functionality, which indicates the cyclization of 4a to 5a. The IR spectrum of 5a showed NH_2 and C=O bands at 3482, 3392 and 1693 respectively. This was further confirmed by ^{1}H NMR and mass spectral study. Compound 5a exhibited multiplet corresponding to eight aromatic protons at δ 8.27-7.36 and singlet at δ 2.05 for three protons of CH_3 group. The characteristic peak for NH proton was absent in ^{1}H NMR spectrum of 5a, which further supports the formation of target compound. The mass spectral data of 5a complies with structure of compound.

Finally, compound 6a was refluxed with acetic anhydride which underwent cyclization to furnish 7a. Further, ^{1}H NMR spectrum of 7a indicated the absence of peak corresponding to NH protons, presence of multiplet at δ 8.28-7.36 corresponding to eight aromatic protons and singlet at δ 2.2 and 1.7 corresponding to six protons of methyl group. The mass spectrum of confirms the compound.

CONCLUSION

In conclusion, a new series of benzothiophene substituted 1,3,4-oxadiazole derivatives substituted at 2 and 5 positions were synthesized and evaluated for their antibacterial and antifungal activities. The newly synthesized heterocyclics exhibited moderate antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and significant antifungal activity against *Aspergillus niger*, *Pencillium notatum*, *Aspergillus fumigatus* and *Candiada albicans* It can be concluded that these classes of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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