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Synthesis and Antitubercular Screening of 2-Chloro-N-(3-Cyano-4,5,6,7-Tetrahydro-1-Benzothiophen-2-Yl)Acetamide Clubbed Substituted 5-Phenyl-1,3,4-Oxadiazole-2-Thiol

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ABSTRACT

Reactions of 2-chloro-N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)acetamide with substituted 5-phenyl-1,3,4-oxadiazole-2 thiol gave N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-aryl-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide were synthesized and assessed for their efficacy as antitubercular agents against tuberculosis H37Rv. The structural assignments of the new products were done on the basis of Infrared radiation (IR), Proton nuclear magnetic resonance ([1]H-NMR) and elemental analysis.

Keywords: 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, Acetamide, 1,3,4-Oxadiazole, Antitubercular activity

INTRODUCTION

At the present time, the frightening threat of pathogens with multidrug resistance acquirement to the well-established antimicrobial arsenal constitutes a serious public health threat. These organisms possessed the ability to withstand attack by antimicrobial drugs currently available, and the uncontrolled rise in resistant pathogens threatens lives. Such infections most commonly affect patients with decreased immunity, neoplastic disorders and undergoing organ transplantation [1]. On the other hand; Mycobacteria are ubiquitous organisms that are responsible to cause mycobacterium tuberculosis, the most common infectious diseases known by the mankind admitting high mortality rate worldwide. Due to the quiescent form of mycobacterium tuberculosis strains, many of the current frontline therapeutics have become ineffective by the imminent exigency of multi drug resistant [2-4]. The 2010 statistics from World Health Organization (WHO) indicated that, 1.3 million MDReTB cases will need to be treated in the 27 high MDReTB burden countries between 2010 and 2015 [5]. Thus the above mentioned factors reveal the necessity for newer, potent unique antibacterial agents to be implemented as a best way to develop effective therapy.

The exploration of new heterocycles that can accommodate potency to multiple biological (anti tuberculosis) targets remains an intriguing scientific endeavor. In continuation to extend our research [6] it was sought of interest to design and synthesize 1,3,4-oxadiazole derivatives hoping to go a step forward in the field of antimicrobial agents and thus, we undertook design, synthesis and examination of antitubercular activities of novel 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile clubbed 1,3,4-oxadiazoles as antitubercular precursors. 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile nucleus is a fertile source of bioactivity in the area of drug discovery because of its varied biological activities viz. antimicrobial [7,8], antiinflammatory [9-11], antituberculosis [12,13] and anticonvullsant [14] anticancer [15,16]. Moreover, It has long been known that compounds bearing 1,3,4-oxadiazole ring occupy a prominent place in medicinal chemistry due to its significant biological properties such as antimicrobial [17-22], antituberculosis [23-25] and anticancer [26].

Taking the above points in consideration, we studied the antituberculosis action of the resultant molecules against wide range of different human pathogenic microorganisms in order to obtain comprehensive SAR indications. Furthermore, according to the thumb rule for physicochemical parameter logP as calculated hydrophobicity, to a drug like molecule it must be lower than 5 to by-pass the cell barrier. To describe the uptake, distribution, biotransformation, and excretion of organic chemicals in biological systems, partition or distribution coefficient is critical elements [27] and hence, in this context, the newer molecules with appreciable lipophilic character are presented here in order to produce remarkable bioactivities.

RESULTS AND DISCUSSIONS

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-aryl-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide 5(a-j) were obtained in 62-80% yield by converting Aryl phenyl benzoic acids to the aryl phenyl benzoate (1) and An ester intermediate was hydrazinolyzed with 99% hydrazine hydrate to afford Aryl phenyl benzohydrazide (2), which reacted with carbon disulfide and potassium hydroxide in ethanol followed by

acidification furnished the corresponding 5-(Aryl phenyl)-1,3,4-oxadiazole-2-thiol (3). Compound (4) 2-chloro-N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)acetamide was prepared by the condensation of 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile and Chloroacetyl chloride in Benzene at 800, which reacts with corresponding 5-(Aryl phenyl)-1,3,4-oxadiazole-2-thiol (3) in dry. Acetone at R.T. gave compound N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-aryl-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide 5(a-j).
Mass spectral data support the proposed structures. The mass spectrum showed various characteristic peaks. A peak at m/z 414 was assigned to the molecular ion.

The FTIR spectrum showed absorption bands at 1531 cm^{-1} (C=N stretching in oxadiazole), 3295 cm^{-1} (-NH- stretching in amide), 1232 cm^{-1} (C-O-C) stretching in alkanyl ethe), 1596 cm^{-1} (S-C=O stretching in thioether), 759 cm^{-1} (C-S) stretching) 2220 cm^{-1} (C=N stretching), 2926 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring respectively.

The ^{1}H-NMR spectrum of showed characteristic signals at 4.14 ppm which were assigned to the methylene protons and signals at 9.16 ppm which were assigned to the Amide proton. A multiplet at 1.69-1.72 ppm & A multiplet at 2.51-2.54 ppm were assigned to the 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. And 7.10 ppm & dd 7.43 ppm were assigned to the 4-fluoro phenyl ring.

CONCLUSION

A series of acetamide derivatives has been successfully synthesized and tested for their antitubercular activity. 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile is one of the active constituents present in many standard drugs, and is known to increase in pharmacological activity of the molecules as we have already reported its significant activity. The presence of 1,3,4-Oxadiazole moiety is also an instrumental in contributing the net biological activity. Herein, we have combined all these two potential unit, that is 2-Amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile clubbed substituted 1,3,4-oxadiazole moiety and studied biological behavior of the resultant systems. Overall conclusion placed for synthesized compounds is that most of the compounds shown very good promising activity as compared to standard drug for all representative panel anti tubercular strains.

EXPERIMENTAL

All the melting points were recorded on Cintex melting point apparatus and are uncorrected. IR spectra in KBr were recorded on Schimadzu Fourier-transform infrared (FTIR) spectrophotometer in cm^{-1}. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded in CDCl3 or Dimethyl Sulfoxide (DMSO) on a Bruker DRX-400 MHZ Nuclear Magnetic Resonance (NMR) instrument. Chemical shifts were reported in ppm using TMS as internal standard on δ scale. Completion of the reactions was monitored time to time by Thin-layer chromatography (TLC) using E-Merck 0.25 mm silica gel plates and toluene: acetone (8:2) as solvent system.

General procedure to synthesis of N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-aryl-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide.

Step I

Synthesis of methyl Aryl phenyl benzoate (1): Aryl phenyl benzoic acid (0.1 mol) in 200 ml methanol and 5.0 ml conc. sulfuric acid was refluxed for 12 hrs. Excess solvent distilled off and collect the product. Recrystallized from alcohol. The progress of reaction was monitored by TLC using toluene: acetone (8: 2) as eluent, B.P. =109-110°C.

Synthesis of Aryl phenyl benzohydrazide (2): A mixture of methyl ester of Aryl phenyl benzoate (0.1 mol) and hydrazine hydrate (0.2 mol) in methanol was heated for 14 h and poured into ice. The product was filtered, washed with cold water and crystallized from ethanol. The progress of reaction was monitored by TLC using toluene, acetone (8.2) as eluent, M.P. =161-163°C.

Synthesis of 5-(arylpheneyl)-1,3,4-oxadiazole-2-thiol (3): The mixture of Aryl phenyl benzohydrazide (0.1 mol), CS2 (0.1 mol) and KOH solution (0.05 mol) in methanol (82 ml) was refluxed for 8 to 10 hours. After the completion of reaction the resultant mixture was poured in to crushed ice. Product was filtered, washed with water and recrystallized from alcohol. The progress of reaction was monitored by TLC using toluene: acetone (7: 3) as eluent, M.P. =195-197°C.

Step II

Synthesis of 2-chloro-N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)acetamide (IV): In benzene (30 ml), chloroacetylchloride (0.02 mol) and 4-6 drops of triethyl amine was added, the mixture was stirred in ice bath. The solution of 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile (0.02 mol) in benzene (30.0 ml) was added drop-wise and refluxed for 4 hours and the reaction mixture was cooled to ambient temp. The resulting ppt. were filtered and washed with benzene purifed by re-crystallization from alcohol.

Step III

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-[(5-arylphenyl-1,3,4-oxadiazol-2-yl)sulfanyl]acetamide (5): A mixture of 2-chloro-N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)acetamide (0.01 mol), 5-(arylpheneyl)-1,3,4-oxadiazole-2-thiol (0.01 mol) in 30 ml dry acetone and anhydrous K_2CO_3 (0.02 mol) was stirred for 3 h at room temperature and poured into ice. The product was filtered and washed with cold water. Recrystallized from alcohol. The Progress of reaction was monitored by TLC using toluene: acetone (8.2) as Eluent. Purification of all the synthesized compounds was achieved by recrystallization and purity of each compound was monitored by thin layer TLC.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5a): FTIR (KBr, cm^{-1}): 1531 cm^{-1} (C=N in oxadiazole), 3295 cm^{-1} (-NH- in amide), 1232 cm^{-1} (C-O-C) in alkanyl ethe), 1596 cm^{-1} (S-C=O in thioether),759 cm^{-1} (C-S))2220 cm^{-1} (C=N), 2926 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.14 (s, 2H, CH_2), 9.16 (s, 2H, -NH-), 1.69-1.72 (m, 4H, Ar-H) 2.51-2.54 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.10 (dd, J=8, 2H, Ar-H), 7.43 (dd, 2H, J=8, Ar-H) at 4-fluoro phenyl ring; Anal. calcd. for $C_{19}H_{15}FN_4O_2S_2$: C, 55.60; H, 3.65; N, 13.52. Found: C, 55.48; H, 3.56; N, 13.39; Yield: 78%. M.P. 273-275°C, Mass (M+1)-415.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5b): FTIR (KBr,cm^{-1}): 1538 cm^{-1} (C=N in oxadiazole), 3304 cm^{-1} (-NH- in amide), 1240 cm^{-1} (C-O-C) in alkanyl ethe), 1593 cm^{-1} (S-C=O in thioether), 754 cm^{-1} (C-S))2234 cm^{-1} (C=N), 2923 $–CH_2$ in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ

(ppm)=2.27(s, 3H, CH_3), 4.18 (s, 2H, CH_2), 9.07 (s, 2H, -NH-), 1.68-1.71 (m, 4H, Ar-H) 2.52-2.55 (m, 4H, Ar-H) at2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.13 (dd, J=8, 2H, Ar-H), 7.38 (dd, 2H, J=8, Ar-H) at 4-Methyl phenyl ring; Anal. calcd. for $C_{20}H_{18}N_4O_2S_2$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.45; H, 4.28; N, 13.56. Yield: 69%. M.P. 237-241°C, Mass (M+1)-411.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5c): FTIR (KBr,cm^{-1}): 1542 cm-1(C=N in oxadiazole), 3298 cm-1 (-NH- in amide), 1236 cm-1(C-O-C) in alkanyl ethe), 1595 cm^{-1}(S-C=O in thioether),754 cm^{-1}(C-S))2231 cm^{-1} (C=N), 2919 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)= 4.23 (s, 2H, CH2), 9.21 (s, 2H, -NH-) 1.70-1.73 (m, 4H, Ar-H) 2.47-2.52 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.17 (dd, J=8, 2H, Ar-H), 7.44 (dd, 2H, J=8, Ar-H) at 4-chloro phenyl ring; Anal. calcd. for $C_{19}H_{15}ClN_4O_2S_2$: C, 52.96; H, 3.51; N, 13.00. Found: C, 52.90; H, 3.45; N, 12.94. Yield: 65%. M.P. 188-191°C, Mass (M+1)-431.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5d): FTIR (KBr,cm^{-1}): 1524 cm^{-1}(C=N in oxadiazole), 3310 cm^{-1} (-NH- in amide), 1244 cm^{-1}(C-O-C) in alkanyl ethe), 1582 cm^{-1}(S-C=O in thioether),759 cm^{-1}(C-S))2219 cm^{-1} (C=N), 2914 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)= 4.31(s, 2H, CH_2), 9.17(s, 1H, -NH-)1.68-1.72 (m, 4H, Ar-H) 2.43-2.46 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.10 (dd, J=8, 2H, Ar-H), 7.35 (dd, 2H, J=8, Ar-H) at 4-methoxy phenyl ring; Anal. calcd. for $C_{20}H_{18}N_4O_3S_2$: C, 56.32; H, 4.25; N, 13.14. Found: C, 56.23; H, 4.19; N, 13.06. Yield: 63%. M.P. 239-242°C, Mass (M+1)-427.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(3,4,5-methoxyphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5e):
FTIR (KBr,cm^{-1}): 1529 cm^{-1}(C=N in oxadiazole), 3322 cm^{-1} (-NH- in amide), 1237 cm^{-1} (C-O-C) in alkanyl ethe), 1590 cm^{-1} (S-C=O in thioether),753 cm^{-1} (C-S)) 2229 cm^{-1} (C=N), 2926 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.16 (s, 2H, CH_2), 9.33 (s, 1H, -NH-), 1.66-1.70 (m, 4H, Ar-H) 2.45-2.48 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 3.84 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), at 3,4,5-trimethoxy phenyl ring; Anal. calcd. for $C_{22}H_{22}N_4O_5S_2$: C, 54.31; H, 4.56; N, 11.51. Found: C, 54.22; H, 4.49; N, 11.42. Yield: 65%. M.P. 218-221°C, Mass (M+1)-48.

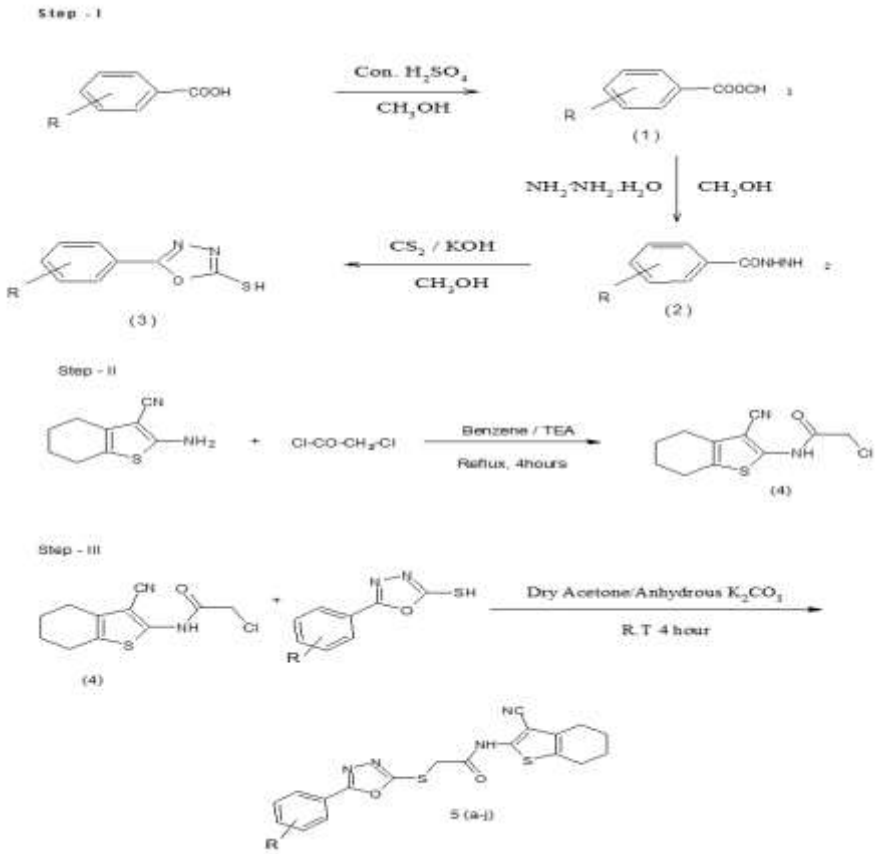
N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide(5f): FTIR (KBr,cm^{-1}): 1522 cm^{-1} (C=N in oxadiazole), 3329 cm^{-1} (-NH- in amide), 1242 cm^{-1} (C-O-C) in alkanyl ethe), 1579 cm^{-1} (S-C=O in thioether), 740 cm^{-1} (C-S))2235 cm^{-1} (C=N), 2937 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.32 (s, 2H, CH_2), 9.30 (s, 1H, -NH-), 1.67-1.70 (m, 4H, Ar-H) 2.48-2.52 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.22-7.70 (m, 4H, Ar-H), at 2-chloro phenyl ring; Anal. calcd. for $C_{19}H_{15}ClN_4O_2S_2$: C, 52.96; H, 3.51; N, 13.00. Found: C, 53.42; H, 4.19; N, 12.37. Yield: 68%. M.P. 195-198°C, Mass (M+1)-431.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(2-bromophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5g): FTIR (KBr, cm^{-1}): 1516 cm^{-1} (C=N in oxadiazole), 3348 cm^{-1} (-NH- in amide), 1250 cm^{-1} (C-O-C) in alkanyl ethe), 1571 cm^{-1} (S-C=O in thioether),727 cm^{-1} (C-S))2226 cm^{-1} (C=N), 2941 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.20 (s, 2H, CH_2), 9.37 (s, 1H, -NH-), 1.69-1.73 (m, 4H, Ar-H) 2.50-2.53 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.25-7.76 (m, 4H, Ar-H), at 2-bromon phenyl ring; Anal. calcd. for $C_{19}H_{15}BrN_4O_2S_2$: C, 48.00; H, 3.18; N, 11.79. Found: C, 47.96; H, 3.13; N, 11.74. Yield: 62%. M.P. 208-211°C, Mass (M+1)-475.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5h): FTIR (KBr, cm^{-1}): 1542 cm^{-1} (C=N in oxadiazole), 3294 cm^{-1} (-NH- in amide), 1235 cm^{-1} (C-O-C) in alkanyl ethe), 1576 cm^{-1} (S-C=O in thioether),735 cm^{-1} (C-S)) 2214 cm^{-1} (C=N), 2929 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.14 (s, 2H, CH_2), 9.16 (s, 1H, -NH-),1.66-1.69 (m, 4H, Ar-H) 2.52-2.55 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.80-7.46 (m, 4H, Ar-H), at 2-methyl phenyl ring; Anal. calcd. for $C_{20}H_{18}N_4O_2S_2$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.45; H, 4.28; N, 13.56. Yield: 69%. M.P. 233-236°C, Mass (M+1)-411.

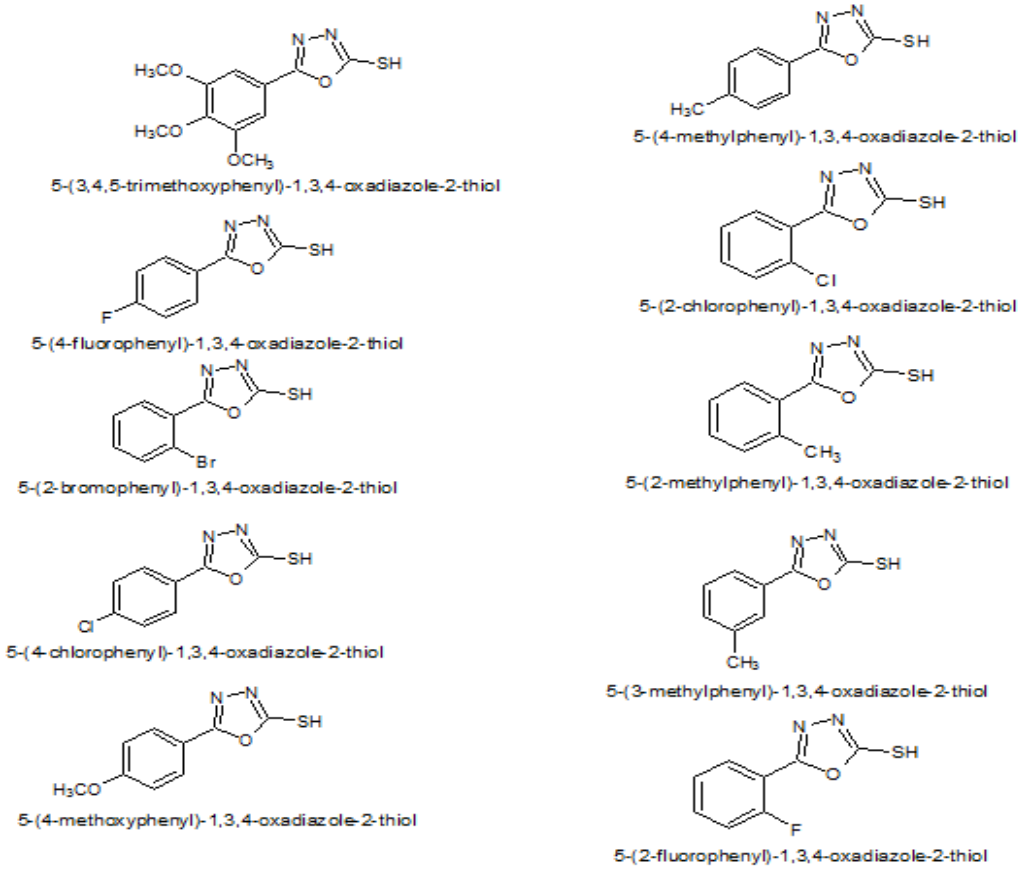
N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5i): FTIR (KBr, cm^{-1}): 1553 cm^{-1} (C=N in oxadiazole), 3307 cm^{-1} (-NH- in amide), 1226 cm^{-1} (C-O-C) in alkanyl ethe), 1557 cm^{-1} (S-C=O in thioether),738 cm^{-1} (C-S)) 2222 cm^{-1} (C=N), 2946 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.27 (s, 2H, CH_2), 9.34 (s, 1H, -NH-),1.71-1.74 (m, 4H, Ar-H) 2.57-2.60 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 6.94-7.52 (m, 4H, Ar-H), at 2-fluoro phenyl ring; Anal. calcd. for $C_{19}H_{15}FN_4O_2S_2$: C, 55.60; H, 3.65; N, 13.52. Found: C, 55.48; H, 3.56; N, 13.39. Yield: 78%. M. P. 259-262°C, Mass (M+1)-415.

N-(3-cyano-4,5,6,7-tetrahydro-1-benzothiophen-2-yl)-2-{[5-(3-methylphenyl)-1,3,4-oxadiazol-2-yl]sulfanyl}acetamide (5j): FTIR (KBr, cm^{-1}): 1529 cm^{-1}(C=N in oxadiazole), 3318 cm^{-1} (-NH- in amide), 1245 cm^{-1}(C-O-C) in alkanyl ethe), 1563 cm^{-1} (S-C=O in thioether),721 cm^{-1} (C-S)) 2232 cm^{-1} (C=N), 2941 –CH_2 in 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile, ^{1}H-NMR (DMSO-d_6) δ (ppm)=4.22 (s, 2H, CH_2), 9.26 (s, 1H, -NH-),1.65-1.69 (m, 4H, Ar-H) 2.62-2.65 (m, 4H, Ar-H) at 2-amino-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile ring proton. 7.86-7.46 (m, 4H, Ar-H), at 3-methyl phenyl ring; Anal. calcd. for $C_{20}H_{18}N_4O_2S_2$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.45; H, 4.28; N, 13.56. Yield: 69%. M. P. 248-251°C, Mass (M+1)-411 (Scheme 1).



Scheme 1: Synthesis of 2-(4-flourophenyl-1,3,4-oxadiazolyl)-5-thio-4-(morpholino)-6-(arylamino)-s-triazine

Where 5(a-j) (Scheme 2)



Scheme 2: Compounds (a-j)

In vitro antituberculosis activity

Compound	R	Log p	BACTEC MGIT Method		L. J. MIC Method	
			MIC (mg/mL)	% inhibition	MIC (mg/mL)	% inhibition
5a	4-F	1.4	6.25	-	100	95
5b	4- CH_3	3.69	6.25	-	500	94
5c	4 -Cl	4.25	6.25	-	12.5	99
5d	4-OCH_3	4.52	6.25	-	25	99
5e	3,4,5-OCH_3	2.37	6.25	99	12.5	99
5f	3-Cl	5.05	6.25	-	200	96
5g	2-Br	3.64	6.25	-	12.5	99
5h	2- CH_3	3.72	6.25	-	100	95
5i	4-F	4.18	6.25	-	200	97
5j	3- CH_3	3.56	6.25	-	62.5	95
Isoniazid		0.2	99%			
Refampicin		0.25	99%			
Ethambutol		3.12	99%			
Pyrazinamide		6.25	99%			

In vitro antituberculosis activity of compounds 5(a-j) was assessed against Mycobacterium tuberculosis H37Rv. The results observed from BACTEC MGIT indicated that final derivatives 5e with 3,4,5-tri methoxy group to exhibited highest inhibition (99%) at a constant concentration level (6.25 mg/ml) against M. tuberculosis H37Rv. This compound was considered as a most potent analogue against mycobacteria and was found to indicate similar antituberculosis potency as that of standard drug pyrazinamide. According to BACTEC MGIT method analog 5c & 5g with chloro and bromo group has also shown potential activity s 6.25 mg/ml MIC level. Results of secondary biological screening using LowensteineJensen MIC method revealed that 5c, 5g with chloro and bromo group as well as compound 5e with 3,4,5-tri methoxy group substituted compounds showed 12.5 mg/ml of MIC against mycobacterial strain. All the remaining derivatives were found to exhibit moderate to poor activity at MIC ranging from 25 to 500 mg/ml.

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