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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(4):38-51

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Synthesis, Antimicrobial activity of 3,5-bistrifluromethylphenyl-1,3,4 oxadiazoles substituted heterocyclic compounds

Sachin S Patil,* Rahul P Jadhav, Amar A Patil, Sachin V Patil and Vivek D Bobade*

Department of Chemistry, HPT Arts and RYK Science College, Nasik-422005, India.

ABSTRACT

3,5-bistrifluoromethylphenyl-1,3,4-oxadiazolethiol was abtained from the reaction of hydrazide derivative with carbondisulphide in basic media, which was alkylated in to nitrile derivative. Nitrile compound 3 undergoes pinner reaction using dry methanolic HCl to abtained imidoether hydrochloride salt 4. Which was further react with 2-aminoethanol, cysteamine, ethylenediamine, semicarbazide, thiosemicarbazide, 2-aminophenol, 2-aminothiphenol, orthophenylenediamine, to give substituted oxazoline, thiazoline, imidazoline, triazolone, triazolethiol, benzoxazoles, benzothiazoles and benzimidazoles derivative respectively. Conversion of sulphide to sulphoxide was achieved by oxidation with m-CPBA (Compounds 8a-8l). All newly synthesized compounds screened for their antimicrobial activity. The antibacterial activity revealed that all compounds screened to showed good or moderate activity.

Key word: 1,3,4-oxadiazole, imidoether and antimycobacterial.

INTRODUCTION

Among different five-membered heterocyclic system pyrrole, oxadiazole, thiadiazole, triazole and their derivatives have gained importance as they constitute the structural feature of many bioactive compounds. Among 1,3,4-oxadiazole are of significant importance in medicinal chemistry in number of biological targets including benzodiazepine receptor agonists [1], 5-HT receptor agonist [2], muscarine agonists [3], antiviral [4], anti-inflammatory activity [5-9], anticonvulsant [10], antiproliferative agent [11], insecticidal properties [12-13], antimalerial [14], hyperglycaemic [15], cytotoxic activity [16], antifungal [17] and antitumor agent [18]. Synthesis of heterocyclic compounds containing multi structure in molecule received much attention in recent years. The linked of diheterocyclic compound may enhanced biological activity and enlarge bioactive spectrum. In literature integrating 1,3,4-oxadiazole moiety in to

scaffold of 1,2,4 triazolo[1,5]pyrimidine. It has been found that these diheterocyclic compounds displayed good antifungal activity [19] and antibacterial activity [20]. Furthermore introduction of fluorine atom or CF_3 group in to organic molecule largely enhanced the pharmalogical properties as compared to non fluorinated analogous. Incorporation of CF_3 group be lead to increased lipid solubility they by enhanced rate of absorption and transport of in drug in vivo.

EXPERIMENTAL SECTION

Chemicals were procured from Aldrich Chemical Co. Reactions were monitored and purity of the products was checked by thin layer chromatography (TLC). TLC was performed on Merck60 F-254 silica gel plates with visualization by UV-light. Melting points were determined on a Bu¨ chi Melting Point B-545 apparatus. The IR spectra (in KBr pellets) were recorded on a Nicolet 6700 FT-IR spectrometry. ^{1}H NMR were recorded (200 and 400 MHz) spectrometer instruments while ^{13}CMR spectra in recorded on Bruker (50 and 100 MHz) $CDCl_3$ and DMSO d_6. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded on LC–MS QP trap spectrophotometer. Elemental analysis was performed on a Carlo Erba Perkin-Elmer model 240 analyzer. Analysis results were within 0.4% of the calculated value. Column chromatography was performed on silica gel (230–400 mesh) supplied by Acme Chemical Co the chemicals and solvents were used for laboratory grade.

General procedure for the synthesis of 3,5-bistrifluoromethyl- phenyl-oxadiazole 2-thiol(2).
To a mixture of 3,5-bistrifluoromethylphenylhydrazide (4.0 g 0.014mol) in ethanol (40 ml), carbondisulphide (6.3 g, 0.082 mol) and potassium hydroxide (2.55 g in 10 ml water) was added. The reaction mixture reflux gently on water bath till evolution H_2S ceased. Progress of reaction monitored by TLC using solvent system (EtOAc: Hexane, 20:80) distilled solvent completely residue abtained was quenched in to water and acidified with Conc. HCl. Solid abtained was filtered and purified by flash chromatography on silica gel column eluting with EtOAc/hexane (20:80); yield: 2.2 g (48 %) M.p.: 214-216^{0}C; IR (KBr, cm^{-1}) 3199 (S-H), 1596 1180; ^{1}HNMR (200 MHz, $CDCl_3$) δ: 8.30 (s, 1H, Ar-H), 8.40 (s, 2H, Ar-H), 10.22 (s, 1H, S-H); EIMS (m/z): 313 (M^-).

General procedure for the synthesis of 5-[{(3, 5-bistrifluoromethyl- phenyl)-oxadiazole-2yl}sulfanyl]acetonitrile (3):
3,5-bistrifluoromethyl-phenyl-oxadiazole-2-thiol (5 g, 0.0159 mol), chloroacetonitrile (1.44 g, 0.0159 mol) and K_2CO_3 (1.5 g, 0.0159) were added to solution DMF (30 ml). The reaction was stirred at ambient temperature for 4h Progress of reaction monitored by TLC using solvent system (EtOAc: Hexane, 40:60) after completion of reaction mixture was quenched in to water the product was extracted with ethylacetate and crystallized from methanol. Yield: 3.2 g (57%) M.p.: 141-145 ^{0}C. IR (KBr, cm^{-1}) 2997, 2254 (CN), 1624, 1479, 1182, 1136. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.57(s, 2H, S-CH_2), 8.38(s, 1H, Ar-H), 8.45(s, 2H, Ar-H).

*Methyl2-({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)ethanimidotate. (**4**)*
5-[{(3,5-bistrifluoromethyl-phenyl)-oxadiazole-2yl}sulfanyl]acetonitrile **3**; (3.2 g, 0.007 mol) was dissolved in 1:1 mixture methyl *tert*-butyl ether and methanol (30 ml) under nitrogen atmosphere. The mixture was cooled to ^{0}0C, dry hydrogen chloride gas was purged until the pH was 3 the resulting solution was allowed to stand at 0^{0}C for 2h solid was separated out was filtered washed with methyl *tert*-butyl ether to remove the excess of HCl. Solid obtained was kept in desiccator. Yield 3.1g (78.7%) M.p=201-203^{0}C.
*2-[3,5-bis(trifluromethyl)phenyl]-5-[4,5dihydro-oxazoline-2-methyl)sulfanyl]-1,3,4-oxadiazole (**5a**).*

Methyl-2-({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)ethanimidotate **4**, (3.0 g, 0.0071mol) dissolved in methanol (25 ml) in flask of suitable size fitted with reflux condenser, reaction mixture protected against moisture and stirred reaction mixture at reflux temperature untilled salt went in to solution. To same solution 2-aminoethanol (0.52 g, 0.0081mol) was added, continued reflux until consumption of starting material monitored on TLC. Similar experimental procedures were applied for synthesis entry (5a-7l).

IR (KBr, cm^{-1}) 2925.6, 1546 (C=N), 1482 (C=C), 1382, 1280, 1180, 1137, ^{1}HNMR (200 MHz, $CDCl_3$) δ: 3.59(t, 2H, N-CH_2), 4.01(t, 2H, O-CH_2)), 5.55(s, 2H, S-CH_2), 8.01(s, 1H), 8.35(s, 2H). ^{13}CNMR (50 MHz, CDCl3) δ: 29.16, 50.47, 51.57, 119.78, 124.40, 126.45, 128.16, 132.19, 146.56, 158.82, 178.15.

*2-[3,5-bis(trifluromethyl)phenyl]-5-[4,5-dihydro-thiazoline-2-methyl)sulfanyl]-1,3,4-oxadiazole (**5b**)*.

Similar procedure as in 4.4, ^{1}HNMR (200 MHz, $CDCl_3$) δ: 3.25(t, 2H, S-CH_2), 3.79(t, 2H, O-CH_2)), 4.57(s, 2H, S-CH_2), 8.18(s, 1H), 8.33(s, 2H), ^{13}C NMR (50 MHz, CDCl3) δ: 33.5 (O-CH_2), 39.4 (S-CH_2), 63.7 (N-CH2), 121.11(CH), 124.72 (2C, CF_3), 126.75 (C), 129.82 (2CH), 131.83 (2C), 163.72 (C), 164.53 (C), 166.55(C).

*2-[3,5-bis(trifluromethyl)phenyl]-5-[4,5dihydro-1H-imidazoline-2-methyl)sulfanyl]-1,3,4-oxadiazole.(**5c**).*

^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.74 (m, 4H), 4.45 (s, 2H, CH_2), 8.18(s, 1H), 8.33(s, 2H), 9.10 (brs, 1H,) ^{13}C NMR (50 MHz, CDCl3) δ: 39.3 (S-CH_2), 50.5 (N-CH_2), 123.22 (CH), 124.71 (CF_3), 126.72 (C), 129.86 (C), 131.82 (C), 164.52 (C), 166.00 (C), 168.22 (C). Mass m/z=397.05 (M^+),

2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-1H-1,2,4-triazol-5(4H)-one. (***6a*).**

IR (KBr, cm^{-1}) 3403.8 (N-H), 3208.9 (N-H), 1679 (C=O), 1566 (C=N), 1518 (C=C, Ar), ^{1}HNMR (200 MHz, DMSO d_6) δ: 4.47(s, 2H, S-CH_2), 8.45(s, 1H, Ar-H), 8.57(s, 2H, Ar-H), 11.44 (s, 1H-amide N-H), 11.56 (s, 1H-amide N-H), ^{13}CNMR(50 MHz, DMSOd_6) δ: 27.56, 118.64, 121.35, 124.07, 125.30, 125.65, 126.94, 131.62, 142.88, 155.94, 163.47, 163.64.

2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-1H-1,2,4-triazol-5(4H)-thione (***6b*)**.

^{1}HMR (200 MHz, DMSOd^6) δ: 3.88 (s, 1H), 4.20 (s, 2H), 6.65 (s, 1H), 8.16 (s, 1H), 8.33 (s, 2H).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-1,3-benzoxazole (**7a**)*.

IR (KBr, cm^{-1}) 2985 (Ar-H), 1624 (C=N), 1498.6 (C=C, Ar), 1278; ^{1}HNMR (200 MHz, $CDCl_3$) δ:4.52 (s, 2H), 7.74 (m, 2H), 7.52 (m, 1H), 7.70 (m, 1H), 8.08 (s, 1H), 8.47(s, 2H), ^{13}C NMR (50 MHz, $CDCl_3$) 29.37(CH_2), 110.91, 120.44 (CH), 121.46 (CH), 124.17(CH), 124.98 (CF_3), 125.91(C), 126.84(CH),130.47, 132.93 (C), 141.07 (C), 151.31, 160.60 (C), 164.13(C). Mass m/z=445.9 (M^{+1}).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-chloro-1,3-benzoxazole (**7b**)*.

^{1}HNMR (200 MHz, $CDCl_3$) δ: 4.80 (s, 2H), 7.33 (dd, 1H, J=2Hz, J=10Hz), 7.44 (d, 1H, J=10Hz), 7.69 (d, 1H, J=2Hz), 8.04 (s, 1H), 8.46 (s, 2H). ^{13}CNMR (50 MHz, $CDCl_3$) δ: 29.17, 111.62, 120.33, 121.40, 124.11, 125.26, 125.51, 126.19, 126.76, 130.47, 132.52, 142.06, 149.77, 162.14, 163.93, 164.10. Mass m/z=480.4, (M^+), 483.3(M^{+2}), 502.3 (M^{+Na}).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-methyl-1,3-benzoxazole (**7c**).*

^{1}HNMR (200 MHz, $CDCl_3$) δ: 2.48 (s, 3H, CH_3), 4.80 (s, 2H), 7.17 (d, 1H, J=8Hz), 7.39(d, 1H, J=8Hz), 7.51 (s, 1H), 8.05(s, 1H), 8.47(s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.24, 29.16,

109.97, 119.82, 119.99, 124.89, 125.04, 125.37, 126.60, 131.77, 134.63, 140.97, 140.97, 149.26, 160.31, 163.82. Mass m/z= 460 (M^+), 482 (M^{+Na}).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-nitro-1,3-benzoxazole (**7d**)*

^{1}HNMR (200MHz, $DMSOd_6$) δ: 4.96 (s, 2H), 7.70 (m, 1H), 8.09 (m, 1H), 8.43 (m, 4H).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-fluoro-1,3-benzoxazole (**7e**)*.

^{1}HNMR (400 MHz, $CDCl_3$) δ: 4.76 (s, 2H), 7.27 (dt, 1H, J=8.0Hz, J=2.4Hz), 7.78 (d, 1H, J=8.0Hz), 7.98 (d, 1H, J=2.4), 8.23 (s, 1H), 8.40 (s, 2H),), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.11 (CH_2), 107.30(CH), 112.73 (CH),115.15(C), 120.93 (CH), 124.38 (C), 124.46 (CH), 124.63 (CH), 125.46 (CH), 134.45 (C), 136.52 (C), 152.43 (C), 158.16 (C), 160.37(C), 162.14, 168.13 (C).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-methyl-1,3-benzothiazole (**7**).*

^{1}HNMR (400 MHz, $CDCl_3$) δ: 2.50 (s, 3H), 4.56 (s, 2H) 7.33 (dd, 1H, J =1.5, 8.3Hz), 7.69 (s, 1H), 7.94 (s, 1H), 7.96 (d, 1H, J=8.8 Hz), 8.47 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.3, 37.5, 121.6, 121.7, 123.3, 124.7, 125.8, 126.7, 129.8, 131.8, 132.2, 135.1, 152.7, 164.5 168.7.

2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-fluoro-1,3-benzothiazole (***7g***).

^{1}HNMR (400 MHz, CDCl3) δ 4.51(s, 2H, CH_2), 7.27 (dt, 1H, J = 2.8, 8.2 Hz,), 7.60 (dd, 1H, J = 2.4, 7.8 Hz,), 7.97 (s, 1H), 8.04 (dd, J = 4.8, 8.8Hz, 1H), 8.46 (s, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ: 34.57, 108.0 (d, J = 26.7 Hz), 115.8 (d, J = 24.4Hz), 122.9 (q, J = 270.9Hz), 123.91, 124.0, 124.64, 124.9 (d, J=9.1Hz), 127.1, 132.6 (q, J= 33.6Hz), 135.2, 136.1 (d, J = 11.4 Hz), 150.4, 161.0 (d, J = 246.5 Hz), 163.7, 167.9.

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-bistrifluromethyl)-1,3-benzothiazole (**7h**).*

^{1}HNMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2H) 7.78 (d, J = 8.3 Hz, 1H), 8.01 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.24 (s, 1H), 8.52 (s, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 33.5, 107.9, 108.1, 115.7, 115.9, 124.0, 124.1, 124.8, 124.9, 127.1, 132.4, 132.8, 135.2, 155.4, 159.60, 162.2, 163.7.

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-1,3-benzothiazole (**7i**).*

^{1}HNMR (400 MHz, $CDCl_3$) δ: 4.99 (s, 2H, CH_2), 7.37 (t, 1H, J=8.0), 7.46 (m, 1H), 7.50 (t, 1H, J=8.0), 7.54 (m, 1H), 7.84 (m, 1H), 8.04 (s, 1H), 8.46 (s, 2H). ^{13}CNMR (100 MHz, $CDCl_3$): δ 34.31, 118.68, 121.40, 121.76, 123.29, 124.11, 125.13, 125.56, 125.83, 126.55, 126.71, 132.46, 135.76, 152.78, 164.00, 164.60, 164.94, Mass m/z= 461(M^+), 464.7, 483.9 (M^{+Na}).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-1H-benzimidazole. (**7j**).*

IR(KBr, cm^{-1}): 3192 (N-H), 2976 (Ar-H), 1668 (C=N), 1554 (C=C), 1278 (C-O), ^{1}HNMR (200 MHz, DMSO, d_6) δ: 4.79 (s, 2H, SCH_2), 7.42 (t, 2H, J=2Hz, 8Hz), 7.75 (d, 1H, J=6Hz), 8.10 (d, 1H, J=6 Hz), 8.40 (s, 1H), 8.54 (s, 2H), ^{13}CNMR (100 MHz, $CDCl_3$), 52.26, 113.04, 119.74, 121.66, 123.94, 124.38, 127.09, 128.40, 129.49, 130.00, 135.42, 148.54, 153.45, 156.73, 160.52, Mass m/z= 445.2 (M+), 467 (M^{+Na}).

*2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazole-2-yl}sulfanyl)methyl)-5-Nitro-1H-benzimidazole (**7k**).*

IR (KBr, cm^{-1}): 3203(N-H), 1627 (C=N), 1521, 1384, 1340, 1280, 1134, ^{1}H NMR(200 MHz, DMSO,d_6) 4.26 (s, 2H), 7.89 (d, 1H, J=8.4Hz), 8.11 (s, 1H), 8.23 (dd, 1H, J=1.6, 8.4Hz), 8.40 (s, 2H), 8.55(d, 1H, J=1.6Hz), Mass m/z=489.9(M+),510.7 (M^{+Na}).

General experimental procedure for 2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4- oxadiazol-2-yl}sulfinyl)methyl)-1,3-benzoxazole (8a).

^{1}HNMR(200 MHz, DMSO,d_6) δ: 4.42 (d, 1H, J=12Hz), 4.53 (d, 1H, J=12Hz), 6.96 (dd, 1H, J=6, 8, 14Hz), 7.10 (1H, dd, J=6, 8, 14Hz), 7.75(1H, J=6Hz), 7.89 (d,1H, J=6Hz),8.23 (s, 1H), 8.60 (s, 2H).

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-chloro-1,3-benzoxazole (**8b**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 4.47 (d, 1H, J=12Hz), 4.58(d, J=12Hz), 7.42(dd, 1H, J=2, 8.2Hz), 7.46(d, 1H, J=8.2Hz), 8.26 (d, 1H, J=2Hz), 8.32 (s, 1H), 8.60 (s, 2H), ^{13}CNMR (100 MHz, DMSO,d_6) δ: 56.32, 118.59, 120.43, 122.23, 124.38, 125.96, 126.96, 131.74, 132.20, 132.96, 151.91, 153.38, 162.24, 168.40.

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-methyl-1,3-benzoxazole (**8c**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 2.37 (s, 3H, CH3), 4.46 (d, 1H, J=12Hz), 4.57 (d, 1H, J=12Hz), 6.88 (d,1H, J=8Hz), 7.39 (s, 1H), 7.43 (1H, d, J=8Hz), 8.23(s, 1H), 8.60 (s, 2H), ^{13}CNMR (100 MHz, DMSO,d_6) δ: 20.69(CH_3), 52.26 (CH_2), 114.17(CH), 118.59(C), 119.04(CH), 120.93(CH), 124.38(C), 126.97, 131.74, 134.37, 143.99, 148.72, 148.94, 163.55, 166.40.

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-nitro-1,3-benzoxazole (**8d**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 4.54 (d, 1H, J=12Hz), 4.65 (d, 1H, J=12Hz), 8.16 (dd, 1H, J=4,10Hz), 8.23 (s,1H), 8.29 (d, 1H, J=10Hz), 8.73 (s, 2H).

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-fluoro-1,3-benzoxazole (**8e**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 4.38(d, 1H, J=12Hz), 4.49 (d, 1H, J=12Hz), 7.05 (dd, 1H, J=1.6, 8.4Hz), 7.53 (d, J=1.8Hz), 7.79(d, 1H, J=8.4), 8.22 (s, 1H), 8.60(s, 2H), ^{13}CNMR (100 MHz, DMSO,d_6): δ 51.80, 103.10, 111.00, 116.15, 120.93, 124.38, 126.96, 131.74, 138.02, 148.49, 150.09, 160.30, 164.41, 168.82.

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-fluoro-1,3-benzothiazole (**8f**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 4.61(d, 1H, J=12Hz), 4.72(d, 1H, J=12Hz), 7.23(dt, 1H, J=1.8, 4.0, 10Hz), 7.89 (d, 1H, J=4.0Hz), 8.23(s, 1H), 8.33 (d, 1H, J=10Hz).

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-methyl-1,3-benzothiazole (**8g**).*

^{1}HNMR(200 MHz, DMSO,d_6) δ: 2.44(s, 3H), 4.69(d, 1H, J=12Hz), 4.80(d, 1H, J=12Hz), 7.21(d, J=8.8Hz), 7.95 (s, 1H), 8.08 (d, J=8.8Hz), 8.23(s, 1H), 8.58 (s, 2H), ^{13}CNMR (50 MHz, DMSO,d_6):δ 22.59, 55.21, 118.59, 120.93, 122.28, 124.38, 125.50, 126.96, 131.74, 131.85, 132.45, 136.00, 154.44, 152.61, 164.03, 166.29.

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl)-5-(trifluoromethyl)-1,3-benzothiazole (**8h**).*

^{1}HNMR (200 MHz, DMSO,d_6) δ: 4.69(d, 1H, J=12Hz), 4.80(d, 1H, J=12Hz), 7.68 (d, 1H, J=3.2, 10Hz), 8.23 (s, 1H), 8.39(d, J=10Hz), 8.45 (d, 1H, J=3.2Hz), 8.54(s, 2H). ^{13}CNMR (50 MHz, DMSO,d_6):δ 55.15, 116.26(C), 118.59, 120.02, 120.84(q, C),120.93(CH), 124.38(CF_3), 126.96, 127.36 (q, C), 131.74, 132.46, 134.96, 149.61, 154.21,162.34, 168.45.

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl]-1,3-benzothiazole (**8i**).*

^{1}HNMR (200 MHz, DMSO,d_6) δ: 4.69(d, 1H, J=12Hz), 4.80(d, 1H, J=12Hz), 7.37-7.47 (m, 2H), 7.97 (m, 1H), 8.17 (m, 1H), 8.25 (s, 1H), 8.56 (s, 2H).

*2-[({5-[3,5-bis(triflurомethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl]-1H-benzimidazole.(**8j**).*

^{1}HNMR (200 MHz, DMSO,d_6) δ: 4.39(d, 1H, J=12Hz), 4.50(d, 1H, J=12Hz), 7.05 (m, 2H), 7.42(m, 2H), 8.23 (s, 1H), 8.60(s, 1H), 10.19 (s, 1H, N-H), ^{13}CNMR (50 MHz, DMSO,d_6):δ 53.72, 118.71, 118.59, 120.93, 122.53, 124.38, 126.96, 131.74, 138.12, 139.20, 164.12, 170.31.

2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl]-5-nitro-1H-benzimidazole ***(8k)***

^{1}HNMR (200 MHz, DMSO,d_6) δ: 4.51(d, 1H, J=12Hz), 4.62(d, 1H, J=12Hz), 7.89(d, 1H, J=8.4Hz), 8.05(dd, 1H, J=4, 8.4Hz), 8.23 (s, 1H), 8.55 (d, 1H, J=4Hz), 8.60 (s, 1H), 10.19(s, 1H, N-H), ^{13}CNMR (50 MHz, DMSO,d_6):δ 54.28(CH_2), 118.59(CH), 120.93(C), 121.49(CH), 121.91(CH), 124.38(C), 126.14, 126.96(CH), 131.74, 139.64, 142.54, 142.67, 143.49, 166.12, 173.20.

2-[({5-[3,5-bis(trifluromethyl)phenyl]-1,3,4-oxadiazol-2-yl}sulfinyl)methyl]-5-chloro-1H-benzimidazole ***(8l)*** ^{1}HNMR (200 MHz, DMSO,d_6) δ: 4.21(d, 1H, J=12Hz), 4.32(d, 1H, J=12Hz), 7.15 (d, 1H, 8.0Hz), 7.60(dd, 1H, J=3.2, 8.0Hz), 7.73(d, 1H, J=3.2), 8.21(s, 1), 8.54(s, 2H), 10.19 (s, 1H, N-H), ^{13}CNMR (50 MHz, DMSO,d_6):δ 54.94, 118.59, 118.96, 119.22, 120.93, 123.42, 124.38, 126.96, 128.06, 131.74, 136.34, 139.70, 140.05, 168.12, 174.24.

Biology

(A) Antibacterial activity

The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 105 CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of target compounds dilution ranging from 25 to 250 µg/mL separately for each bacterial strain. All the plates were incubated at 370.5 C for 24 h. Zone of inhibition and minimum inhibitory concentrations (MICs) were noted. The results of antibacterial studies are given in Table 3.

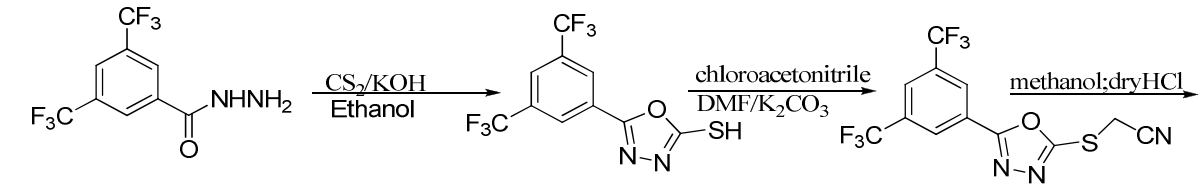
(B) Antifungal activity

For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27-0.2 C for 24–48 h, till sporulation. Spore of strains were transferred in to
5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer (106 CFU/mL). Sterile PDA plate was prepared containing 2% agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27-0.2 C for 12 h. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL compound solution of concentrations 25–250 mg/mL separately to get minimum inhibitory concentration (MIC). The plates were kept in refrigerator for 20 min for diffusion and then incubated at 27-0.2 C for 24–28 h. Zone of inhibition and minimum inhibitory concentrations (MICs) were noted. The results of antifungal studies are given in Table 4.

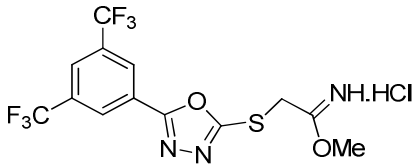
RESULTS AND DISCUSSION

2.1 Chemistry

The synthetic strategies adapted to abtained the target compound are depicted in (scheme 1). The key intermediate in the present study was imidiate **4**, which was prepared hydrazinolysis of ethyl ester of 3,5-bistrifluoromethyl benzoate with hydrazine hydrate. Reacting the starting compound 1 with carbon disulphide under strong basic condition followed by acidification with dilute hydrochloric acid to give 3,5 bistrifluoromethylphenyl-1,3,4-oxadiazole thiol [21] **2** which further alkylated with chloroacetonitrile in DMF using base potassium carbonate to give **3**. Nitrile derivative **3** undergo Pinner reaction using dry methanolic HCl to abtained imidoether hydrochloride salt **4** which was take immediately for next reaction without storage, and react with 2-aminoethanol, cysteamine, ethylenediamine, semicarbazide, thiosemicarbazide, 2-aminophenol, 2-aminothiphenol, orthophenylenediamine, to give substituted oxazoline,

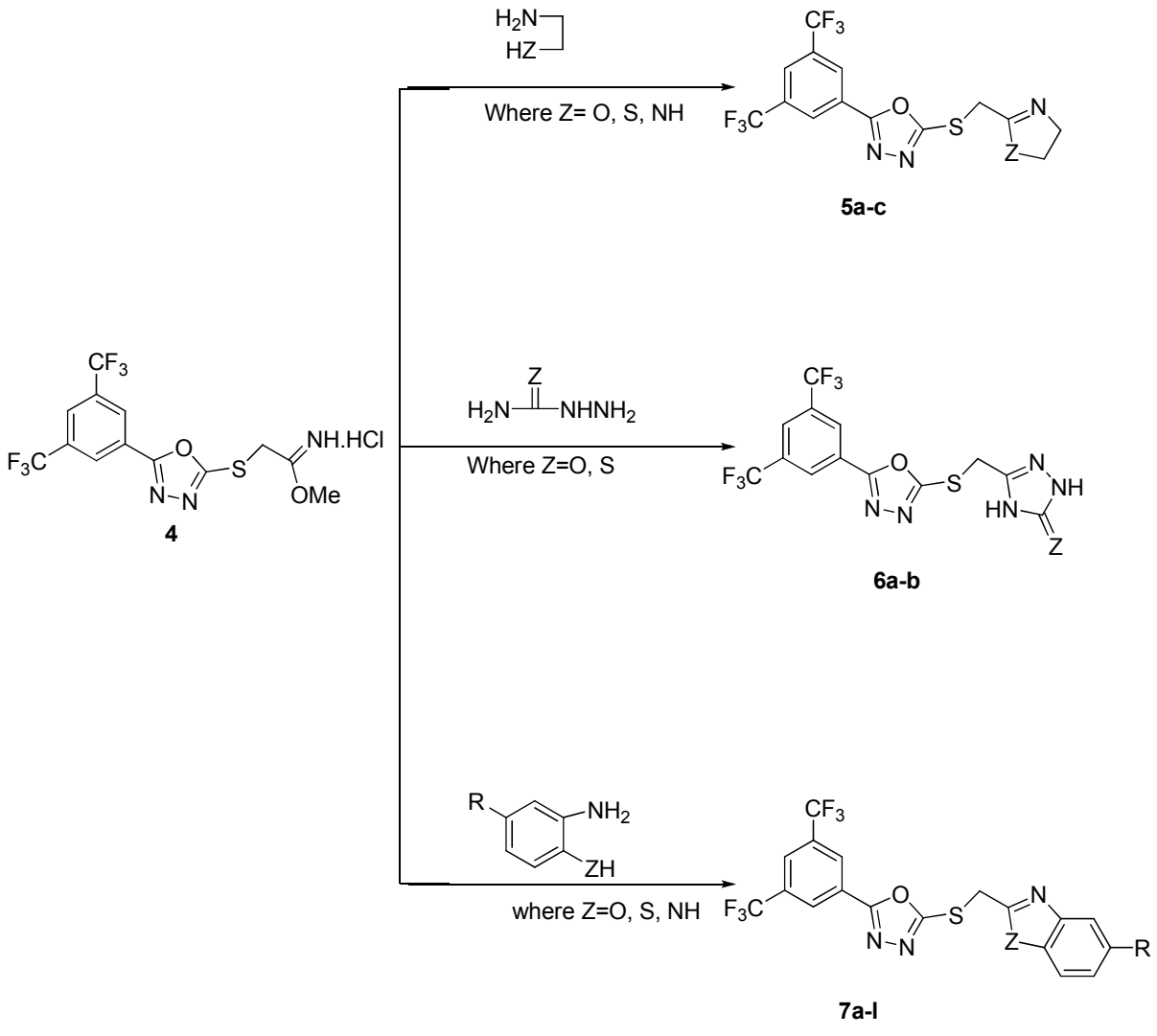


1 **2** **3**



4

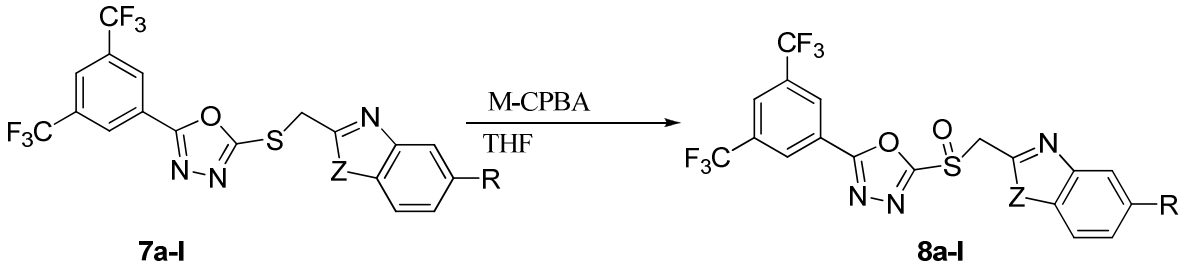
Scheme1



Scheme2

thiazoline, imidazoline, triazolone, triazolethiol, benzoxazoles, benzothiazole and benzimidazole derivatives respectively (scheme 2). Conversion of sulphide to sulphoxide was achieved by oxidation with m-CPBA which afford higher yield than sodium periodate (scheme 3). (entries

8a-8l ,Table 1). For triazolone 6a synthesis condensation of semicarbazide.HCl with imidate. All the synthesized compounds were subjected for antibacterial and antifungal activity.



7a-l **8a-l**

Scheme 3

Table 1. Physical and analytical data of compounds

Compound no	Z	R	M.P ^{0}C	Yield %	Mol. Formula	Analysis% calculated(found)		
						C	H	N
5a	O	-	185-187	60	$C_{14}H_9F_6N_3O_2S$	42.32 (42.12)	2.28 (2.13)	10.58 (10.34)
5b	S	-	200-202	58	$C_{14}H_9F_6N_3OS_2$	40.68 (40.35)	2.19 (2.12)	10.17 (10.15)
5c	NH	-	168-170	45	$C_{14}H_9F_6N_4OS$	42.43 (42.30)	2.54 (2.45)	14.14 (14.10)
6a	O	-	175-178	50	$C_{13}H_7F_6N_5O_2S$	37.96 (37.86)	1.72 (1.72)	17.03 (17.08)
6b	S	-	145-148	53	$C_{13}H_7F_6N_5OS_2$	36.54 (36.51)	1.65 (1.63)	16.39 (16.30)
7a	O	H	199-200	75	$C_{18}H_9F_6N_3O_2S$	48.55 (48.36)	2.04 (1.99)	9.44 (9.40)
7b	O	Cl	219-221	72	$C_{18}H_8ClF_6N_3O_2S$	45.06 (45.03)	1.68 (1.32)	8.76 (8.64)
7c	O	Me	201-202	80	$C_{19}H_{11}F_6N_3O_2S$	49.68 (49.63)	2.41 (2.39)	9.15 (9.01)
7d	O	NO_2	248-250	64	$C_{18}H_8F_6N_4O_4S$	44.09 (44.04)	1.64 (1.63)	11.43 (11.41)
7e	O	F	229-231	68	$C_{18}H_8F_7N_3O_2S$	46.66 (46.42)	1.74 (1.71)	9.07 (9,05)
7f	S	Me	204-206	84	$C_{19}H_{11}F_6N_3OS_2$	48.00 (47.97)	2.33 (2.31)	8.84 (8.82)
7g	S	F	213-215	72	$C_{18}H_8F_7N_3OS_2$	45.10 (45.08)	1.68 (1.62)	8.77 (8.73)
7h	S	CF_3	198-200	67	$C_{19}H_8F_9N_3OS_2$	43.11 (43.07)	1.52 (1.49)	7.94 (7.91)
7i	S	H	188-187	90	$C_{18}H_9F_6N_3OS_2$	46.86 (46.82)	1.97 (1.94)	9.11 (9.09)
7j	NH	H	223-235	73	$C_{18}H_{10}F_6N_4OS$	48.65 (48.61)	2.27 (2.24)	12.61 (12.60)
7k	NH	NO_2	234-236	61	$C_{18}H_9F_6N_5O_3S$	44.18 (44.11)	1.85 (1.82)	14.31 (14.29)

7l	NH	Cl	245-247	77	$C_{18}H_9ClF_6N_4OS$	45.15 (45.13)	1.89 (1.86)	11.70 (11.69)
8a	O	H	222-224	56	$C_{18}H_9F_6N_3O_3S$	46.86 (46.84)	1.97 (1.95)	9.11 (9.10)
8b	O	Cl	238-239	71	$C_{18}H_8ClF_6N_3O_3S$	43.61 (43.59)	1.63 (1.61)	8.48 (8.46)
8c	O	Me	206-208	64	$C_{19}H_{11}F_6N_3O_3S$	48.01 (47.99)	2.33 (2.30)	8.84 (8.81)
8d	O	NO2	252-255	70	$C_{18}H_9F_6N_4O_5S$	42.70 (42.67)	1.59 (1.54)	11.07 (11.04))
8e	O	F	232-234	68	$C_{18}H_8F_7N_3O_3S$	45.10 (45.09)	1.68 (1.67)	8.77 (8.73)
8f	S	Me	188-189	77	$C_{19}H_{11}F_6N_3O_2S_2$	46.44 (46.41)	2.26 (2.23)	8.55 (8.52)
8g	S	F	215-217	71	$C_{18}H_8F_7N_3O_2S_2$	43.64 (43.61)	1.63 (1.60)	8.48 (8.45))
8h	S	CF_3	190-192	69	$C_{19}H_8F_9N_3O_2S_2$	41.84 (81.81)	1.48 (1.43)	7.70 (7.68)
8i	S	H	198-199	79	$C_{18}H_9F_6N_3O_2S_2$	45.29 (45.26)	1.90 (1.88)	8.80 (8.79)
8j	NH	H	210-213	60	$C_{18}H_{10}F_6N_4O_2S$	46.96 (46.93)	2.19 (2.14)	12.17 (12.15)
8k	NH	NO2	256-258	50	$C_{18}H_9F_6N_5O_4S$	42.78 (42.76)	1.88 (1.85)	13.86 (13.83)
8l	NH	Cl	222-224	64	$C_{18}H_9ClF_6N_4O_2S$	43.79 (43.76)	1.83 (1.81)	11.32 (11.29)

2.2. Biology

The compounds were evaluated for antimicrobial activity against bacteria viz. Escherichia coli (MTCC 2939), Salmonella typhi(MTCC 98), Staphylococcus aureus (MTCC 96), Bacillus subtilis (MTCC441) and antifungal activity against various fungi viz. Aspergillus niger (MTCC 281), Trichoderma viridae (MTCC 167), Penicilliumchrysogenum (MTCC 160) and Candida albicans (MTCC 183). The antibiotic Tetracycline (25 µg/mL) and Nystatin (25 µg/mL) are used as reference for antibacterial and antifungal substances, respectively for comparison. Dimethyl sulphoxide (1%, DMSO) was used a control. By comparing antimicrobial activity of synthesized compounds it was found that tested compounds are more effective against the Gram-positive bacteria. It is believed that the strong lipophilic character of the molecule plays an essential role in introducing antimicrobial effect. These properties are seen as an important parameter related to membrane permeation in biological system. Many of the processes of drug disposition depend on capability to cross membrane and hence there is high correlation with measures of lipophilicity. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartment such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum. Hydrophobicity/Lipophilicity play major role in determining where drugs are distributed within the body after adsorption and as a consequence in how rapidly they are metabolized and excreted. In context the presence of the hydrophobic moiety would be important for such activity. Moreover, many of the proteins involved in drugs disposition have hydrophobic binding site further adding to the importance of lipophilicity.

The lipophilicity of the compounds, expressed as log *p* explains the main predictor for the activity. The octanol/water partition coefficient C log *p* being a measure of hydrophobicity and lipophilicity was calculated using ChemDraw Ultra 11.0 software integrated with cambridgesoft Software. The result abtained are given in Table 2.

Table 2 Calculated log *p* and molar refractivity of compounds

Compounds	C log *P*	MR cm^3/mol
5a	3.02	85.36
5b	2.84	90.83
5c	3.24	86.81
6a	2.11	85.47
6b	1.74	92.64
7a	4.18	99.10
7b	4.96	103.70
7c	4.68	105.00
7d	4.06	-
7e	5.87	99.50
7f	5.35	110.47
7g	5.02	104.98
7h	5.81	111.08
7i	4.85	7.08
7j	4.33	100.69
7k	4.24	-
7l	5.12	105.29
8a	2.93	99.24
8b	3.71	103.84
8c	3.43	105.13
8d	2.81	-
8e	3.14	99.64
8f	4.10	110.61
8g	3.77	105.11
8h	4.56	111.21
8i	3.60	104.71
8j	3.088	100.82
8k	3.46	-
8l	3.87	105.43

Table 03: Antibacterial activities of (5a-8l)

Compounds	E. *coli*	S. *typhi*	S. *aureus*	B. *subtilis*
5a	18 (25)	10 (25)	9 (25)	5 (25)
5b	14 (25)	7 (50)	8 (50)	14 (100)
5c	8 (50)	8 (50)	6 (50)	4 (50)
6a	14 (50)	9 (50)	12 (50)	-

6b	15 (25)	12 (50)	11 (50)	18 (25)
7a	16 (25)	14 (50)	18 (25)	16 (25)
7b	21 (25)	18 (25)	16 (25)	22 (25)
7c	22 (25)	19 (25)	18 (25)	21 (25)
7d	15 (50)	10 (50)	13 (50)	20 (50)
7e	34 (25)	30 (25)	29 (25)	27 (50)
7f	26 (25)	24 (50)	28 (25)	24 (25)
7g	32 (25)	39 (25)	30 (25)	28 (25)
7h	18 (25)	16 (25)	12 (25)	17 (25)
7i	20 (25)	28 (25)	23 (25)	22 (25)
7j	14 (25)	13 (25)	14 (25)	20 (25)
7k	10 (25)	12 (50)	11 (50)	18 (25)
7l	31 (25)	28 (25)	26 (25)	22 (25)
8a	22 (25)	19 (25)	18 (25)	21 (25)
8b	15 (50)	8 (50)	7 (50)	6 (50)
8c	4 (50)	12 (50)	6 (50)	4 (50)
8d	12 (50)	-	10 (50)	8 (50)
8e	7 (50)	4 (50)	7 (50)	12 (50)
8f	15 (50)	6 (50)	16 (50)	20 (50)
8g	4 (50)	5 (50)	18 (50)	14 (50)
8h	21 (25)	18 (25)	17 (25)	23 (25)
8i	14 (25)	11 (25)	22 (25)	18 (25)
8j	18 (25)	16 (25)	14 (25)	19 (25)
8k	15 (25)	16 (25)	14 (25)	12 (25)
8l	18 (25)	19 (25)	16 (25)	14 (25)
Tetracycline	30 (25)	28 (25)	30 (25)	32 (25)

Zone of inhibition measured in mm; MIC values (µg/mL) are given in brackets. Ec- *Escherichia coli*; St-*Salmonella typhi*. Sa-*Staphylococcus aureus*; Bs-*Bacillis subtilis.*
‘‘–’’ Indicates the concentration >100 µg/mL.

Table 4. Antifungal activities

Compounds	A. *niger*	T. *virdea*	P. *chrysogenum*	C. *albicans.*
5a	6 (25)	-	5 (25)	11 (25)
5b	12 (50)	11 (50)	9 (50)	8 (25)
5c	14 (50)	9 (50)	11 (50)	15 (50)
6a	18 (25)	12 (50)	15 (25)	18 (25)
6b	12 (50)	10 (50)	17 (50)	-
7a	12 (100)	11 (100)	7 (100)	-
7b	14 (100)	12 (100)	-	6 (50)
7c	13 (100)	-	-	-
7d	12 (50)	-	-	-
7e	14 (50)	14 (100)	-	8 (50)
7f	12 (50)	11 (25)	09 (50)	08 (50)
7g	12 (25)	12 (25)	15 (25)	13 (25)
7h	22 (25)	22 (25)	21 (25)	23 (25)
7i	10 (50)	11(25)	12 (25)	18 (50)
7j	13 (25)	12 (25)	14 (25)	11 (25)
7k	12 (25)	09 (25)	08 (25)	10 (25)
7l	10 (25)	13 (25)	10 (25)	14 (25)
8a	13 (25)	09 (50)	12 (25)	10 (50)
8b	10 (50)	14 (25)	13 (50)	12 (25)
8c	15 (25)	17 (25)	16 (25)	15 (25)
8d	07 (25)	11 (50)	07 (50)	09(50)
8e	11 (25)	16 (25)	14 (25)	17 (25)
8f	19 (25)	17 (25)	19 (25)	15 (25)
8g	12 (25)	14 (25)	13 (50)	12 (25)
8h	14 (25)	16 (25)	14 (25)	15 (25)
8i	19 (25)	20 (25)	17 (25)	18 (25)
8j	11 (25)	12 (25)	14 (25)	19 (50)
8k	11 (100)	10 (100)	14 (100)	12 (100)
8l	19 (25)	20 (25)	16 (25)	17 (25)
Nystatin	19 (25)	17 (25)	18 (25)	18 (25)

Zone of inhibition measured in mm; MIC values (µg/mL) are given in brackets.
An-*Aspergillus niger*; Tv-*Trichoderma virdea*; Ca-*Candida albicans.*
Pc-*Penicillium chrysogenum*;
‘‘–’’ Indicates the concentration >100 µg/mL.

The results of in vitro antibacterial activities of compounds (5a-8l) against various bacterial strains are summarized in Table 3. It has been observed that some compounds exhibited interesting antibacterial activities. Compounds 7e, 7g, 7i, showed effective against E. *coli* S. *typhi,* S. *aureus* and B. *subtilis*. Compounds 7a, 7b, 7c, 7h, 7i, 8a, 8i, 8j, 8k, 8l.were displayed a good zone of inhibition against all tested bacteria. On other hand it was found that compounds 5a-5c, 6a-6b, and 8b-8e less active against tested bacteria.

The results of antifungal activities of synthesized compounds (5a-8l) are summarized in Table 4. Most of the compounds were showed a significant level of activity at concentration 25 µg/mL in comparison with standard antifungal. For species A. *niger* compounds 6a, 7h, 8f 7i, 8i, 8l exhibited comparative activity with standard nystatin. For species T. *virdea* compounds 7h, 8e, 8f, 8h, 8i, 8l exhibited comparative activity with standard nystatin. For species P. *chrysogenum* compounds 7h, 8f, 8i, and 8l and for C. *albicans* 6a, 7h, 8e, 8i, 8j possess comparative activity standard nystatin. It was observed that compounds 7h, 8i, 8l were exhibited more potent activity against all fungal strain than other compounds. Considering the result abtained from antifungal and antibacterial tests together, it is noteworthy to mention that tested compounds more active towards bacteria than fungi.

CONCLUSION

In conclusion, several substituted 2-[3,5-bis(trifluromethyl)phenyl-2-substituted-1,3,4-oxadiazoles were synthesized. The pharmacological study was undertaken to evaluate effect of substituent on the antibacterial and antifungal activities. All synthesized compounds exhibited good antibacterial activity toward Gram-positive bacteria toward Gram-negative bacteria and some of the synthesized compounds showed good to moderate antifungal activity. In conclusion, antimicrobial activity of the synthesized compounds increases with increasing log *p* and molar refractivity from Table 2

Acknowledgements
The author thanks to Bharti vidyapith college of pharmacy, Mumbai for helping microbial analysis and grateful to IIT Mumbai providing spectral and elemental analysis.

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