Research Article

Synthesis, Characterization and biological evaluation of novel Pyrimidine linked 1,3,4-oxadiazoles possessing Piperdine, Morpholine, Thiomorpholine, N-Methyl Piperazine with Tri fluoro methyl moieties

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ABSTRACT

Objectives: To synthesize a variety of Pyrimidine derivatives and their biological activity was determined. **Methods:** Using methyl 4-(3-oxoprop-1-ynyl) benzoate and acetamidine hydro chloride, new compounds were synthesized. The structures of all the new compounds are established on the basis of FT-IR,^{1}H NMR,^{13}C NMR and Mass Spectral Data. The antibacterial activity and antifungal activity of synthesised compounds was studied by the disc diffusion method. **Results:** All the novel compounds were synthesized in good yield. Among the new compounds 7b, 7c,9b, 9c are found to be most biological activity. **Conclusion:** The results obtained justify the usage of these compounds from their promising antibacterial activity and antifungal activity. Therefore The nature of groups is very important for antibacterial activity and antifungal activity in disc diffusion method.

Keywords: Antibacterial and antifungal, morpholines, oxa diazoles, thiomorpholine,trifluoromethyl, N-methyl piperazine

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INTRODUCTION

Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics [1,2]. Hence, they have attracted considerable attention in the design of biologically active molecules [3,4] and advanced organic chemistry [5,6]. Also in the family of heterocyclic compounds nitrogen containing Heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes [7]. A totally unsaturated six membered -ring containing nitrogen is known as azine [8]or pyridine (**1**); with two nitrogen atoms it is known as diazine [9]. and with a nitrogen at 1,2-position, it isknown as pyridazine, at 1,3-position as Pyrimidine and at 1,4-position as pyrazine (Figure1). However, the current review intends to focus on the significance of Pyrimidines class of antimicrobial agents along with clinical andin vitro applications of pyrimidine derivatives to facilitate the development of more potent as well as effective antimicrobial agents.

Pyrimidine: General Introduction

Pyrimidines [10] are the heterocyclic aromatic compounds similar to benzene and pyridine containing two nitrogen atoms at positions 1 and 3 of the six membered rings. Heterocycles containing pyrimidine moiety are of great interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities and clinical applications [11, 12]]. Substituted purines and pyrimidines occur very widely in living organisms and were some of the first compounds studied by the organic chemists [13].

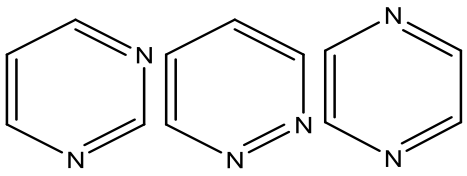

Figure 1

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Pyrimidines are biologically very important Heterocycles and represent by far the most important of the di azine family with uracil [14] and thymine [15] being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine [16].

In addition to this, pyrimidines skeleton is also present in many natural products such as vitamin B_1 (thiamine) and many synthetic compounds, such as barbituric acid [17] and Veranal [18] which are used as hypnotics [19].

Medicinal Properties of Pyrimidines

The presence of Pyrimidine base in thymine, cytosine, and uracil, which are the essential building blocks of nucleic acids DNA and RNA, is one possible reason for their widespread therapeutic applications. The Pyrimidines represent one of the most active classes of compounds possessing wide spectrum of biological activities like significantin vitroactivity against unrelated DNA and RNA, viruses including polioherpes viruses, diuretic, antitumour, anti-HIV, and cardiovascular [20]. The literature survey indicated that a wide range of pharmacological activities are exhibited by the compounds encompassing pyrimidines nucleus. In addition to this, various analogs of pyrimidines have been found to possesantibacterial [21–27], antifungal [28–31], antileishmanial [32], anti-inflammatory [33,34], analgesic [35], antihypertensive [36,37], antipyretic [38], antiviral [39-41], antidiabetic [42], antiallerggic [43], anticonvulsant [44], antioxidant [45,46], antihistaminic [47], herbicidal (48), and anticancer activities [49–52] and many of Pyrimidines derivatives are reported to possess potential central nervous system (CNS) depressant properties [53,54] and also act as calcium channel blockers [55].

Clinical and Pharmacological Applications of Pyrimidine in Microbial World: Marketed Drugs

During the last two decades several Pyrimidine derivatives have been developed which are found to have wide clinical and pharmacological applications [56].

Antivirals and Anti-HIV (AIDS) Agents

Pyrimidine derivatives also possess good antiviral properties; for example, 5-iododeoxyuridine and IDU (5-iodo-2′-deoxyuridine) have been extensively utilized for viral infections. 5-Trifluoromethyl-2′-deoxyuridine has been found useful against infections resistant to IDU therapy [57]. 1-(3-Azido-2,3-dideoxypentofuranosyl)-5-methyl-2,4(1*H*,3*H*)-pyrimidinedione[58]is a potent inhibitor of thein vivo replication and cytopathic effects of HIV and has been approved for use against AIDS and severe AIDS-Related Complex (ARC) [59].

General information of 1, 3, 4 OXA DIAZOLES:

Five-membered Heterocycles are privileged structures with utility in synthetic and medicinal chemistries [60]. In general, Oxazoline and Oxadiazole building blocks have found widespread applications as synthetic intermediates, protecting groups, pharmacophore, and ester and amide surrogates[61–63]. They also possess a wide spectrum of biological activities with anti-inflammatory, anti- hypertensive,

anticonvulsant, and analgesic properties[64-66].

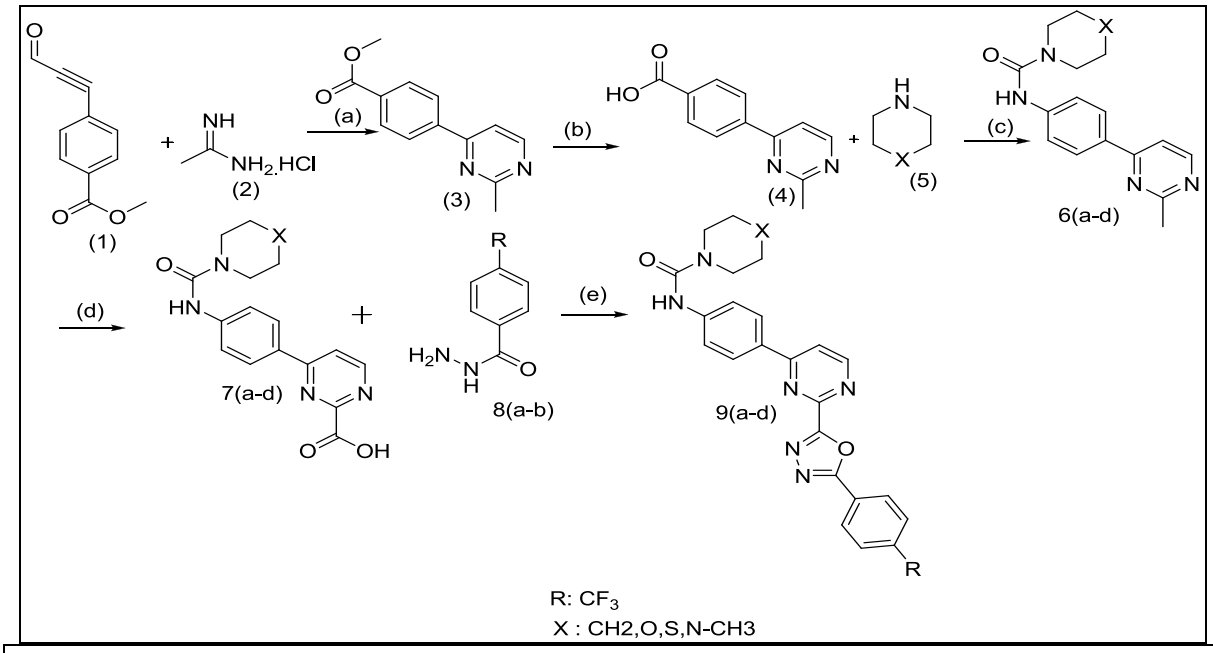
MATERIALS AND METHODS

Experimental

Chemistry:

Melting points (mp) were determined using a Thomas Hoover capillary apparatus (Philadelphia,). Infrared spectra were acquired on a Perkin-Elmer 1420 ratio recording spectrometer. A Bruker FT-500 MHz instrument (Bruker Biosciences) was used to acquire ^{1}H-NMR spectra; chloroform-d, DMSO-d6 were used as solvents. Mass spectra were acquired with a Finnigan TSQ-70 mass spectrometer. Electron-impact ionization was performed at an ionizing energy of 70 eV; the source temperature was 250^{0}c. Elemental analyses were carried out with a Perkin Elmer Model 240-C apparatus (Perkin Elmer, Norwalk). The results of the elemental analyses (C,H,N) were within ± 0.4% of the calculated amounts. All chemicals and reagents were obtained from Aldrich (INDIA) were used without further purification.

Scheme:



Reagents and conditions: (a) Aceto Nitrile,Na_2CO_3,Microwave irradiation,0.5 hr**(b)**THF,Methanol,LiOH,RT,8 hrs**(c)**PCl_5,Sodium azide,sodium acetate, water,acetone(1:1),12hrs.**(d)**SeO_2,Pyridine,120^{0}c,2hrs**(e)**$POCl_3$,Reflux

COMPOUND	9(a)	9(b)	9(c)	9(d)
R	-CF_3	-CF_3	-CF_3	-CF_3
X	-CH_2	-O	-S	-N-CH_3

The title compounds 9(a-d) were synthesised in five sequential steps using different reagents and reaction conditions the 9(a-d) were obtained in moderate yields. The structures of 9(a-d) were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.

Experimental section:

General procedure for the preparation of Compound Methyl 4-(2-methylpyrimidin-4-yl)benzoate (Compound 3)

A mixture of methyl 4-(3-oxoprop-1-ynyl)benzoate (0.01 mol) and Acetamidamide hydro chloride (0.01 mol) was stirred in Dry Aceto Nitrile(10 ml) and Dry Na_2CO_3 (0.02mol) was added to it. The stirring was continued for 0.5 hr under Micro Wave conditions at 90^{0}c .Reaction progress was monitored by TLC.After completion of reaction cool to RT. Then concentrated under reduced pressure by using rota evaporator & Purified by column chromatography(100-200 mesh size silica) with elution of 10%

Ethyl acetate to get pure yellow solid **yield:**85% **Melting Point:** 130^{0}c-135^{0}c.
IR(KBr,CM-^{1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1700(C=O), 3040(=C-H aromatic)
^{1}H NMR (DMS0-d$_6$,ppm):
δ3.8(3H,S,-OCH$_3$),7.90(2H,d,j=8HZ,1Ar-H),7.94(2H,d,j=8HZ,Ar-H),7.72(1H,d,j=7 HZ, 1Py-H),8.42(1H,d,j=7 HZ,1Py-H),2.3(3H,S,-CH$_3$)
^{13}C NMR (DMS0-d$_6$,ppm):
δ 51.5(-O-CH$_3$group),165(due to ester carbonyl carbon),130,128,127,140, 161,112,158,167(Ar-C),24(-CH$_3$)

General procedure for the Preparation of 4-(2-methylpyrimidin-4-yl)benzoic acid (Compound 4)

A solution of methyl 4-(2-methylpyrimidin-4-yl) benzoate (0.01 m.mol) in THF-water-ethanol (2 mL/2 mL/1 mL) is treated with lithium hydroxide hydrate (0.05m.mol)) and stirred for 12 h. The solution is evaporated, and the residue is partitioned between 1 M aq. HCl and ethyl acetate. The organic phase is washed with water (20 mL), dried over Sodium sulfate, filtered and evaporated to afford the title compound as a white solid (41percent **yield Melting Point** : 142-145°C
IR(KBr,CM-^{1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3540(-OH), 3040(=C-H aromatic)
^{1}H NMR (DMS0-d$_6$,ppm):
7.90(2H,d,j=8HZ,1Ar-H),7.94(2H,d,j=8HZ,1Ar-H),7.72(1H,d,j=7HZ,1Py-H),8.42(1H,d,j=7 HZ,1Py-H),2.3(3H,S,-CH$_3$),11(1H,S,-COOH)
^{13}C NMR (DMS0-d$_6$,ppm):
δ 165(due to acid carbonyl carbon),130,128,127,140, 161,112,158, 167(Ar-C &Py-C),24(-CH$_3$)

General procedure for the Preparation of N-(4-(2-methylpyrimidin-4-yl)phenyl)piperidine/morpholine/thiomorpholine /N-methyl piperazine-1-carboxamide(Compound 6) (6a-6d)

Schiff base(0.004mol) and PCl_5 (0.004mol) was heated at 100^{0}c for 1h. When the evolution of fumes of HCl ceased, excess of $POCl_3$ was removed under reduced pressure and the residual imidoyl chloride was treated with an ice-cold solution of sodium azide(0.0075 mol) and excess of sodium acetate in water (25ml) and acetone (30ml) with stirring. Stirring was continued for overnight, thereafter acetone was removed under reduced pressure. The remaining aqueous portion wasextracted with chloroform was dried. Then added piperidine/morpholine/Thiomorpholine/N-Methyl piperazine to give Title compounds(6 a-d).

N-(4-(2-methylpyrimidin-4-yl)phenyl)piperidine-1-carboxamide:(6a)
Yield:45%
Melting Point: 130^{0}c-135^{0}c
IR(KBr,CM-^{1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O), 3205(-NH),3040(=C-H aromatic)
^{1}HNMR (DMSO,d$_6$,ppm)
δ 2.4(3H,S,-CH$_3$ in pyrimidine ring),3.77(4H,m,-N-CH$_2$×2-), 1.5(4H,m j=6 HZ), 1.6(2H,m, j=7HZ),6(S,–NH Proton),7.87(2H,d,j=7HZ, Ar-H),7.6(2H,d,j=7HZ,Ar-H),7.7(1H,d,j=7HZ,Py-H),8.42(1H,d,j=7HZ,Py-H)
^{13}C NMR (DMSO,d$_6$,ppm):
δ 49,24,25(aliphatic carbons),155(carbonyl carbon in carboxamide),110 to 165(10 aromatic carbons) ,23(-CH$_3$ in Pyrimidine ring)

N-(4-(2-methylpyrimidin-4-yl)phenyl)morpholine-4-carboxamide:(6b)
yield:65%
Melting Point: 120-122^{0}c
IR(KBr,CM-^{1}):2937(C-H),1630(C=N),1450(C=C),1378(C-,1690(C=O), 1100(C-O),1378(C-N), 3205(-NH), 3040(=C-H aromatic)
^{1}HNMR (DMSO,d$_6$,ppm):
3.3(4H,m,N-CH$_2$×2),3.8(4H,m,O-C**H$_2$**×2),6(1H,S,-NH),7.9(2H,d,j=7 HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),7.8(1H,d,j=8.2HZ,Py-),8.4(1H,d,j=8.2HZ,Py-H),2.5(3H,S,-CH$_3$)
^{13}C NMR (DMSO,d$_6$,ppm): 45,65(Aliphatic carbons),110 to 165(10 aromatic carbons),23(-CH3 in Pyrimidine ring), 155(carbonyl carbon in carboxamide)

N-(4-(2-methylpyrimidin-4-yl)phenyl)thiomorpholine-4-carboxamide(6c):
yield:55%
Melting Point: 180^{0}c-185^{0}c

IR(KBr,CM-1):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic)

1HNMR (DMSO,d_6,ppm)

3.3(4H,m,N-C**H**$_2$×2),2.8(4H,m,S-C**H**$_2$×2),6(1H,S,-NH),7.9(2H,d,j=7 HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),7.8(1H,d,j=8.2HZ,Py-),8.4(1H,d,j=8.2HZ,Py-H),2.5(3H,S,-CH_3 in Pyrimidine ring)

13C NMR (DMSO,d_6,ppm):

45(N-C),65(C-S),110 TO 165(10 Aromatic carbons),23(-CH3 in Pyrimidine ring), 155(carbonyl carbon in carboxamide).

4-methyl-N-(4-(2-methylpyrimidin-4-yl)phenyl)piperazine-1-carboxamide(6d):

yield: 65%

Melting Point: 160^{0}c-165^{0}c

IR(KBr,CM-1):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic)

1HNMR (DMSO,d_6,ppm):

3.3(4H,m,N-C**H**$_2$×2),2.3(4H,m,-C**H**$_2$×2-N-CH_3),6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),7.8(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H),2.5(3H,S,-C**H**$_3$ IN Pyrimidine ring),2.3(3H,S,-N-C**H**$_3$)

13C NMR (DMSO,d_6,ppm):

45(N-**C**H_3),50(N-**C**H_2),52(H_3C-N-**C**H_2)110 to 165(10 aromatic carbons),23(-CH3 in Pyrimidine ring), 165(carbonyl carbon in carboxamide)

General procedure for the Preparation of 4-(4-(piperidine/morpholine/thiomorpholine /N-methyl piperazine-1-carboxamido)phenyl)pyrimidine-2-carboxylic acid (7a-7d):

A mixture of N-(4-(2-methylpyrimidin-4-yl)phenyl)piperidine/morpholine/Thiomorpholine/N-methyl piperazine-1-carboxamide(0.01mol) and SeO_2(0.02 mol)In Pyridine(10 ml),Then maintain Temparature at 100^{0}c for 2 hrs. Reaction progress was monitored with TLC (60% ETOAC mobile phase) After completion of reaction concentrated under reduced pressure ,then acidified with 6N HCl and extract with ethylacetate(3times) and organic layer wash with brine& dried with Na_2SO_4 Then concentrated under reduced pressure to get white solid.

4-(4-(piperidine-1-carboxamido)phenyl)pyrimidine-2-carboxylic acid(7a):

yield:45%

IR(KBr,CM-1):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic),3340(-OH)

1HNMR (DMSO,d_6,ppm):

3.8(4H,m,N-C**H**$_2$×2),1.5(4H,m),1.6(2H,m,N-CH_2-CH_2-C**H**$_2$)6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H),11(1H,S,COO**H** Proton)

13C NMR (DMSO,d_6,ppm):

45(N-**C**H_2),23,25(aliphatic carbons), 110 to 165(10 aromatic carbons), 165(carbonyl carbon in carboxamide),175(carbonyl carbon in acid)

4-(4-(morpholine-4-carboxamido)phenyl)pyrimidine-2-carboxylic acid(7b):

yield:55%

Melting Point 120^{0}c-125^{0}c

IR(KBr,CM-1):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic), 3340(-OH)

1HNMR (DMSO,d_6,ppm):

3.2(4H,t,j=7HZ,N-C**H**$_2$×2),3.6(4H,t,j=7HZ,O-C**H**$_2$×2),11(1H,S,COO**H**Proton), 6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H),

13C NMR (DMSO,d_6,ppm):

45(N-CH_2),65(O-CH_2), 110 to 165(10 aromatic carbons),165(carbonyl carbon in carboxamide),175(carbonyl carbon in acid)

4-(4-(thiomorpholine-4-carboxamido)phenyl)pyrimidine-2-carboxylic acid(7c):

yield: 56%

Melting Point :130^{0}c-135^{0}c

IR(KBr,CM-1):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic), 3340(-OH)

1HNMR (DMSO,d_6,ppm):

3.5(4H,t,j=7HZ,N-C**H**$_2$×2),2.6(4H,t,j=7HZ,S-C**H**$_2$×2),11(1H,S,COO**H**Proton), 6(1H,S,-

NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H).

^{13}C NMR (DMSO,d_6,ppm):

50 (N-**C**H_2),25(S-**C**H_2), 110 to 165(10 aromatic carbons),165(carbonyl carbon in carboxamide),175(carbonyl carbon in acid)

4-(4-(4-methylpiperazine-1-carboxamido)phenyl)pyrimidine-2-carboxylic acid(7d):

yield: 68%

Melting Point: 110^{0}c-115^{0}c

IR(KBr,CM^{-1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic), 3340(-OH)

^{1}HNMR (DMSO,d_6,ppm):

3.5(4H,m,N-C**H$_2$**×2),2.3(2H,t,j=7HZ,S-C**H$_2$**×2),11(1H,S,COO**H**Proton), 6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H).

^{13}C NMR (DMSO,d_6,ppm):

50 (N-**C**H_2),52 (H_3C-N-**C**H_2), 110 to 165(10 aromatic carbons),165(carbonyl carbon in carboxamide),175(carbonyl carbon in acid),45(N-**C**H_3)

General procedure for the Preparation of N-(4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)phenyl)piperidine/Morpholine/Thio morpholine/N-Methyl Piperazine -1-carboxamide (9 a-d):

Acid hydrazide (0.1 mol), aromatic acid (0.1mol) were refluxed with Phosphorous oxychloride (5ml) for 6 hrs. And the reaction mixture was treated with ice cold water carefully and made basic by adding sodium bi carbonate solution. The resulting solid was filtered, dried and re crystalised by ethanol.

N-(4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)phenyl)piperidine-1-carboxamide (9 a):

yield: 85%

Melting Point: 140^{0}c-145^{0}c

IR(KBr,CM^{-1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic)

Anal Calcd. for $C_{25}H_{21}F_3N_6O_2$ (%)C, 60.73; H, 4.28; N, 17.00;

Found: C, 60.70; H, 4.25; N, 16.98;

MS m/z: 494.17 ((M+, 100.0%), 495.17 (M+1, 27.4%),

^{1}HNMR (DMSO, d_6,ppm):

3.8(4H,m,N-C**H$_2$**×2),1.5(4H,m),1.6(2H,m,N-CH_2-CH_2-C**H$_2$**)6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H),7.5(2H,d,j=7HZ),7.8(2H,d,j=7HZ)

^{13}C NMR (DMSO,d_6,ppm):

45(N-**C**H_2),23,25(aliphatic carbons), 110 to 165(19 aromatic carbons), 165(carbonyl carbon in carboxamide)

N-(4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)phenyl)morpholine-4-carboxamide (9b):

yield: 85%

Melting Point: 120^{0}c-125^{0}c

IR(KBr,CM^{-1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic)

Anal Calcd. For $C_{24}H_{19}F_3N_6O_3$ C, 58.06; H, 3.86; N, 16.93.Found: C, 58.04; H, 3.8, N, 16.90

MS m/z: 496.15 ((M+, 100.0%), 497.15 (M+1,6.3%)

^{1}HNMR (DMSO,d_6,ppm):

3.2(4H,t,j=7HZ,N-C**H$_2$**×2),3.6(4H,t,j=7HZ,O-C**H$_2$**×2),6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H), 7.5(2H,d,j=7HZ),7.8(2H,d,j=7HZ)

^{13}C NMR (DMSO,d_6,ppm):

45(N-**C**H_2), 65(O-**C**H_2), 110 to 165(19 aromatic carbons), 165(carbonyl carbon in carboxamide)

N-(4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)phenyl)thiomorpholine-4-carboxamide (9c):

yield: 75%

Melting Point: 160^{0}c-165^{0}c

IR(KBr,CM^{-1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH), 3040(=C-H aromatic)

Anal Calcd. for Chemical Formula $C_{24}H_{19}F_3N_6O_2S$ (%) C, 56.24; H, 3.74, N, 16.40 Found: C, 56.22; H, 3.70, N, 16.34
MS m/z: 512.12 (M+,100.0%), 513.13 (M+1, 26.3%)
^{1}HNMR (DMSO,d_6,ppm):
3.5(4H,t,j=7HZ,N-C**H_2**×2),2.6(4H,t,j=7HZ,S-C**H_2**×2),6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H), 7.5(2H,d,j=7HZ),7.8(2H,d,j=7HZ)
^{13}C NMR (DMSO,d_6,ppm):
50 (N-**C**H_2),25(S-**C**H_2), 110 to 165(19 aromatic carbons),165(carbonyl carbon in carboxamide)

4-methyl-N-(4-(2-(5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-yl)phenyl)piperazine-1-carboxamide(9d):
yield: 65%
Melting Point: 150^{0}c-155^{0}c
IR(KBr,CM-^{1}):2937(C-H),1630(C=N),1450(C=C),1378(C-N),1690(C=O),3205(-NH),3040(=C-Haromatic)
Anal Calcd. for Chemical Formula $C_{25}H_{22}F_3N_7O_2$ C, 58.94; H, 4.35; N, 19.24. Found: C, 58.90; H, 4.30; N, 19.20.
MS m/z: 509.18 (M^+,100.0%), 510.18 (M+1, 30.0%).
^{1}HNMR (DMSO,d_6,ppm):
3.5(4H,m,N-C**H_2**×2),2.3(4Hm,H_3C-N--C**H_2**×2),6(1H,S,-NH),7.9(2H,d,j=7HZ,Ar-H),7.6(2H,d,J=7HZ,Ar-H),8.9(1H,d,j=8.2HZ,Py-H),8.4(1H,d,j=8.2HZ,Py-H),),7.5(2H,d,j=7HZ),7.8(2H,d,j=7HZ)
^{13}C NMR (DMSO,d_6,ppm):
50 (N-**C**H_2),52 (H_3C-N-**C**H_2), 110 to 165(19 aromatic carbons),165(carbonyl carbon in carboxamide),175(carbonyl carbon in acid),45(N-**C**H_3)

Biological activity:
Anti- Bacterial Activity:
The antibacterial activity of synthesised compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were Staphylococcus aureus NCCS 2079 and Bacillus cereus NCCS 2106. The gram negative bacteria screened were Escherichia coli NCCS2065 and Pseudomonas aeruginosa NCCS2200.
The synthesised compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent. The cefaclor 10µg/disc was used as a standard. (Himedia Laboratories Ltd, Mumbai).
The test results presented in the table-1, suggest that 7b, 7c, 9b, 9c exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.
Antifungal Activity:
The antifungal activity of synthesised compounds were studied by disc diffusion method against the organisms of Aspergillus' niger NCCS1196 and Cadidaalbicans NCCS34471.
Compounds were treated at the concentrations of 100µg/ml, 250µg/ml, 500µg/ml and 1000µg/ml using DMSO as solvent. The standard used was Clotrimazole 50µg/ml against both the organisms. The test results were presented in the (**Table 2**).

Table 1:Antibacterial activity by disc diffusion method of Pyrimidine Carboxylic acid(7 a-d) & pyrimidine -1,3,4 –oxadiazole with trifluoromethyl having piperdine,morpholine,thiomorpholine,N-Methyl piperazine moieties(9 a-d):

Compound	Zone of Inhibition(mm)			
	Staphylococcus	Bacillus cerus	Escherichia	Pseudomonas aeruginosa
7a	09	10	07	09
7b	11	10	09	11
7c	13	12	11	13
7d	08	09	10	12
9a	12	13	11	14
9b	14	12	13	15
9c	17	19	16	19
9d	13	11	14	12

Cefaclor	19	22	19	20

Table 2:Antifungal activity by disc diffusion method for Pyrimidine-Carboxylic acid (7a-d) & pyrimidine-1,3,4-oxadiazole with trifluoromethyl having piperdine,morpholine,thiomorpholine,N-Methyl piperazine moieties 9a-d:

Compound	Zone of inhibition(mm)	
	Asperigillusniger	Candida albicans
7a	14	12
7b	17	15
7c	20	18
7d	15	13
9a	13	15
9b	19	19
9c	23	21
9d	15	16
Clotrimazole	25-30	25-30

RESULTS AND DISCUSSION

Methyl 4-(2-methylpyrimidin-4-yl) benzoate (3) was synthesized according to the reported procedure[67]. The reaction of methyl 4-(2-methylpyrimidin-4-yl)benzoate with Lithium hydroxide in THF to affordthe corresponding 4-(2-methylpyrimidin-4-yl)benzoic acid (4) as per the reported procedure[68], which was reacted with PCl_5 and sodium azide according to the reported procedure[69]toaffordN-(4-(2-methylpyrimidin-4-yl)phenyl)piperidine/morpholine/thiomorpholine/N-Methylpiperazine-1-carboxamide

Compound 6 (a-d) which was reacted with SeO_2 in Pyridine as per the reported procedure[70] to afford4-(4-(piperidine-1-carboxamido)phenyl)pyrimidine-2-carboxylicacid 7(a-d) which was reacted with 4-(trifluoromethyl)benzohydrazide as per the reported procedure[71] to get Title compound(9 a-d).

The molecular formulae, structure, of the newly Synthesised compounds 7 a-d and 9 a-d were further conformed and supported by mass, ^1H NMR and IR spectral data, based on occurrence of molecular ion peak of the assigned structures, downfield shifting of protons and different stretching of bands of the compounds. To further support the molecular structure of newly synthesized compounds 7a-d and 9 a-d. antimicrobial evaluation of all the newly synthesized compounds it was seen that each of 4 (a-e) and 5 (a-e) compounds possesses significant antibacterial and antifungal activity.

CONCLUSION

The present investigation discovers a new class of 1,3,4-oxadizoles possessing Pyrimidine core unit bearing piperazine,morpholine,thiomorpholine and N-Methyl piperazine moieties with Trifluoromethyl in a single molecular frame work, which are biologically active. These new class of 1,3,4 oxadiazole have promising antibacterial and antifungal activities. Hence, it can be concluded that, this new class of compounds certainly holds a greater consent in the design of new potent antibacterial and antifungal agents.

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