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Synthesis, Characterization, Biological Evaluation and Docking studies of 2-(benzyl sulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4-oxadiazole Derivatives

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A B S T R A C T

New novel derivatives of 2-((4- substituted benzyl)sulfonyl)-5-(3-(4-(substituted phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4-oxadiazoles (9a-l as per scheme-I)were prepared by condensation of 2-(4-hydrazinylpyrimidin-5-yl)-5-((4-substituted benzyl)sulfonyl)-1,3,4-oxadiazole **(8a-f)** with various 4-substituted benzoic acids. The synthon 8a-f were obtained by the refluxing of 2-(4-chloropyrimidin-5-yl)-5-((4-substituted benzyl) sulfonyl)-1,3,4-oxadiazole**(7a-f)** with hydrazine hydrate in presence of ethanol. The synthon 7a-f were obtained through chlorination of 5-(5-((4-subsitututed benzyl) sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-ol **(6a-f)** in presence of $POCl_3$. The synthon 6a-f were obtained from 5-(5-((4-subsitututed benzyl)thio)-1,3,4-oxadiazol-2-yl)pyrimidin-4-ol **(5a-f)**in presence of H_2O_2/ Glacial acetic acid**.** The synthon 5a-f were obtained from the reaction between 5-(4-hydroxypyrimidin-5-yl)-1,3,4-oxadiazole-2(3H)-thione **(3)**and various aromatic halogenated compounds(4a-f) in presence ofKOH and ethanol. The synthon were obtained from the condensation of 4-hydroxypyrimidine-5-carbohydrazide **(2)** with carbon disulphide in presence of base. The compound 2 were obtained from the condensation of ethyl 4-hydroxy pyrimidine-5-carboxylate **(1)** with hydrazine hydrate in presence of ethanol. All the newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The newly synthesized compounds were subjected to various biological studies both antibacterial and antifungal including docking studies for model compounds.

Keywords: pyrimidine, 1, 2, 4-triazole, 1,3,4-oxadiazole, *$POCl_3$, Biological and Docking studies.*

A R T I C L E I N F O

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1. Introduction

Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms. It isthe biologically important nitrogen-containing molecule called nitrogenous base. Basically pyrimidines are used in our body for the construction of genetic material i.e. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). In addition pyrimidines also possess antibacterial [1-3], antifungal [4,5], antileishmanial [6], anti-inflammatory [7], analgesic [8], antihypertensive [9], antipyretic [10], antiviral [11], antidiabetic [12], antiallergic [13] and antioxidant [14] activities.

Oxadiazole is one of the versatile heterocyclic nucleuses, which has attracted a wide attention of the medicinal chemists for the development of new drugs. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five member ring. Oxadiazoles are exhibits in four isomeric forms(1,2,3-oxadiazole,1,3,4-oxadiazole,1,2,4-oxadiazole and 1,2,5-oxadiazole). Among these isomeric forms 1,3,4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical reactions. 1,3,4-oxadiazole nucleus are known to exhibit Unique anti-inflammatoryactivity [15-18], differently substituted oxadiazole moiety has been found to have other interesting activities such as analgesic [19,20], antitubercular [21],anticonvulsant [22], antimicrobial [23], anti-cancer [24], ulcergenic [25], hypolipidemic [26] and anti-fungalactivities [27].

1,2,4-triazole is one of a pair of Isomeric chemical compounds with molecular formula $C_2H_3N_3$, calledtriazoles which have a five-membered ring of two carbon atoms and three nitrogen atoms. 1,2,4-triazole is a basic aromatic hetero cycle. 1,2,4-Triazole derivatives find use in a wide variety of applications, most notably as antifungals such as Fluconazole and Itraconazole. Triazolic nucleus is now a day's considered an important moiety in the design and synthesis of bioactive compounds that are associated with numerous biological activities [28] such as antibacterial, antifungal [29].Keeping this importance in mind herein we report synthesis of novel pyrimidine moiety containing 1,2,4-triazole and 1,3,4-oxadiazole derivatives **(**9a-l**).** The structure were established by spectral (IR,^{1}H-NMR,^{13}C-NMR and mass) and analytical data. The synthetic route was depicted in scheme-**I**.

2. Experimental

All the chemicals used in the present investigation werepurchased from Sigma-Aldrich Chemicals Company,Inc.USA. And used without further purification. TLC wasperformed on aluminum sheet of silica gel 60F254, E-Merk,Germany using iodine as visualizing agent. Melting pointwas determined in open capillary tubes on Mel-Tempapparatus and is uncorrected. Columnchromatography was performed on silica gel with different solvent systemsaseluents to afford the pure compound. TheIR Spectra were recorded as KBr pellets on Perkin-Elmer 1000 units, instruments.All ^{1}H and ^{13}C-NMR spectra were recorded on a VarianXL-300 spectrometer operating at 400MHzfor ^{1}H-NMRand 75 MHz for ^{13}C-NMR were recorded on a Varian XLspectrometer operating at161.89MHz. The compounds weredissolved in DMSO-d6 and chemical shifts were referenced to TMS (^{1}H and^{13}C-NMR).Mass spectral datawere recorded on FAB-MS instrument at 70ev with direct inlet system. Elemental analysis wasrecorded on a CarloErba 1108 elemental Analyzer, Central Drug ResearchInstitute, Lucknow, India.

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (60–120 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H, for ^{13}C, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents.

Synthesis of 4-hydroxypyrimidine-5-carbohydrazide [30] (2)*:* To a mixture of ethyl 4-hydroxy pyrimidine-5-carboxylate**(1)**(0.1 m.mol) and hydrazine hydrate (0.5 m.mol) in ethanol 10mL was refluxed for a 5 hrs at 80^{o}C. After the reaction mixture was cooled and poured into ice cold water with stirring. The progress of the reaction was monitored by TLC with acetone: ethyl acetate (7:3) as eluent. The separated solid was filtered, washed with water and recrystallized from ethanol to afford compound**(2).**Yield:71%, mp:151-3^{o}C,IR (KBr, cm^{-1}): 3495&3415 (-NH_2 stretching of acid hydrazide), 3202 (-NH stretching of acid hydrazide), 3285 (-OH Str), 1690(>C=O str of acid hydrazide), 1575(>C=N str).^{1}H NMR (DMSO-d_6, ¢ ppm): 2.24(s, 2H, Hydrazide of –NH_2), 8.65 (s, 1H, pyrimidine proton), 8.99 (s, 1H, -NCHN pyrimidine proton), 9.72 (s, H, sec amide), 11.05 (s, s, H, -OH attached to pyrimidine ring. $C_5H_6N_4O_2$ Calculated C-38.96%, H-3.92%, N-36.35% & found C-38.92%, H-3.88%, N-36.30.

Synthesis of 5-(4-hydroxypyrimidine-5-yl)-1,3,4-oxadiazole-2(3H)-thione [31] (3)

A mixture of4-hydroxypyrimidine-5-carbohydrazide**(2)** (0.1m.mol), KOH in ethanol and carbon disulfide (0.2 m.mol) were taken in a round bottom flask equipped with a chilled water condenser was refluxed on oil bath till the evaluation of hydrogen sulphide ceased. The excess of alcohol was removed by distillation. The reaction mixture was cooled at room temperature and the reaction mass was poured in to ice cooled water and neutralized with dilute

HCl. The solid precipitate was filtered, washed thoroughly with water and dried. The product further purified by re-crystallization from ethanol dioxane mixture to afford 5-(4-hydroxypyrimidine-5-yl)-1,3,4-oxadiazole-2(3H)-thione (3). Yield: 70%, mp:144-6°C. IR (KBr, cm^{-1}):3264 (-OH str), 1575(>C=N str), 1243(-C-O-C- str), 1135(C=S str)^{1}H NMR (DMSO-d_6, ¢ ppm):8.42 (s, 1H,pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.05 (s, s, H, -OH attached to pyrimidine ring), 14.7(s, H, C-SH, broad signal due to thiol-thione tautomeric form).The elemental analysis calculated(%) C-36.80, H-2.11, N-28.61 agreed well with the found(%) C-36.33, H-1.76, N-28.06.

General procedure for the synthesis of 5-(5-((4-substituted benzyl)-thio)-1,3,4-oxadiazol-2-yl)pyrimidine -4-ol (5a-f): To a stirred solution of KOH in ethanol,5-(4-hydroxypyrimidin-5-yl)-1,3,4-oxadiazole-2(3H)-thione **(3)** (0.1 m.mol) and chloromethyl benzene(4a)(0.2 mmol), was added and the reaction mixture was heated to reflux for 4hr. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulphate and the excess of solvent was removed under reduced pressure to get crude product, the crude was purified by preparative HPLC the 5-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol**(5a)** was obtained. Similar procedure was used for the synthesis of 5b-f with compound (3) and different chloro substituted benzene derivatives (4b-f).

5-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (5a) Yield:70%, mp:125-7°C,IR (KBr, cm^{-1}): 3264(-OH str), 3070(Ar-H str), 1573(>C=N str), 1295 (S-CH_2 str), 1242(oxadiazole-C-O-C- str), 711 (C-S str).^{1}H NMR (DMSO-d_6, ¢ ppm): 4.50(s, 2H, -S-CH_2), 7.25-7.47 (m, 5H, Ar-H), 8.42 (s, H, pyrimidine proton), 8.84 (s, 1H ofpyrimidine proton), 11.05 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_{10}N_4O_2S$: C-54.54%, H- 3.52%, N-19.57%& found C-54.07%, H-3.18%, N-19.09%.

5-(5-((4-methylbenzyl)thio)-1,3,4-oxadiazol-2-yl) pyrimidine-4-ol (5b)
Yield:75%, mp:117-9°C,IR (KBr, cm^{-1}): 3250(-OH str), 3088(Ar-H str), 1565(>C=N str), 1282 (S-CH_2 str), 1245 (oxadiazole -C-O-C- str), 708 (C-S str).^{1}H NMR (DMSO-d_6, ¢ ppm): 2.28, (s, 3H, -CH_3), 4.50(s, 2H, -S-CH_2), 7.16-7.35(m, 4H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.05 (s, H, -OH).AnalyticalCalculationfor $C_{14}H_{12}N_4O_2S$:C-55.99%, H-4.03%, N-18.65%& foundC-55.21%, H-3.59%, N-18.17%.

5-(5-((4-methoxybenzyl)thio)-1,3,4-oxadiazol-2-yl) pyrimidine-4-ol (5c): Yield: 65%, mp:137-9°C, IR (KBr, cm^{-1}): 3255 (-OH str), 3078(Ar-H str), 1570(>C=N str), 1290 (S-CH_2 str), 1239 (oxadiazole -C-O-C- str), 710 (C-S str).^{1}H NMR (DMSO-d_6, ¢ ppm): 3.81 (s, 3H, -OCH_3), 4.50(s, 2H, -S-CH_2), 6.98-7.24(m, 4H, Ar-H), 8.40 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.05 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{14}H_{12}N_4O_3S$: C-53.16%, H-3.82%, N-17.71%& found C-52.89%, H-3.38%, N-17.24%.

5-(5-((4-chlorobenzyl)thio)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (5d)
Yield:77%, mp:143-5°C, IR (KBr, cm^{-1}): 3295(-OH str), 3066(Ar-H str), 1566(>C=N str), 1294 (S-CH_2 str), 1247 (oxadiazole -C-O-C- str), 703 (C-S str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 4.50 (s, 2H, -S-CH_2), 7.33-7.55 (m, 5H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton),11.05 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_9ClN_4O_2S$:C-48.68%, H-2.83%, N-11.05%& found C-48.19%, H-2.37%, N-10.56%.

5-(5-((4-(trifluoromethyl)benzyl)thio)-1,3,4-oxadiazol-2-yl)pyrimidin-4-ol (5e)
Yield:82%, mp:147-8°C, IR (KBr, cm^{-1}): 3262(-OH str), 3057 (Ar-H str), 1579 (>C=N str), 1284 (S-CH_2 str),1240 (oxadiazole -C-O-C- str), 709 (C-S str).^{1}H NMR(DMSO-d_6, ¢ ppm): 4.50 (s, 2H, -S-CH_2),7.42-7.64 (m, 5H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.05 (s, H,-OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{14}H_9F_3N_4O_2S$: C-47.46%, H-2.56%, N-15.81%& found C-47.08%, H-2.22%, N-15.35%.

5-(5-((4-nitrobenzyl)thio)-1,3,4-oxadiazol-2-yl)pyrimidin-4-ol (5f)
Yield:79%, mp:132-3°C, IR (KBr, cm^{-1}): 3255(-OH str), 3056(Ar-H str), 1579(>C=N str), 1289 (S-CH_2 str), 1246 (oxadiazole -C-O-C- str),705 (C-S str).^{1}H NMR (DMSO-d_6, ¢ ppm): 4.50 (s, 2H,-S-CH_2),7.55-7.97 (m, 5H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.05 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_9N_5O_4S$: C-47.13%,H-2.74%, N-21.14%& found C-46.75%, H-2.29%, N 20.86%.

General procedure for the synthesis of 5-(5-((4-substitutedbenzyl)sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine -4-ol (6a-f): A solution of5-(5-(benzylthio)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (**5a**)(0.1 mmol) in 50ml of glacial acetic acid were taken in 250ml of round bottomed flask with reflux condenser. The solution was heated to boiling and 8ml of 30% H_2O_2 was added refluxed for 2hrs. The product obtained was separated by filtration after room temperature. Recrystallization of the product from 95% ethanol to give 5-(5-(benzyl sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol **(6a).** The reaction procedure leading to **6a** was then extended to the synthesis of **6(b-f)**from (5b-f)respectively.

5-(5-(benzyl sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (6a): Yield:83%, mp:166-7°C, IR (KBr, cm^{-1}): 3255(-OH str), 3035(Ar-H str), 1616(N-N str), 1322&1190(O=S=O str), 1570(>C=N str), 1233(oxadiazole -C-O-C- str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 5.25 (s, 2H, -CH_2 protons), 7.25-7.47 (m, 5H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.22 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_{10}N_4O_4S$: C-49.05%, H-3.17%, N-17.60%& found C-48.48%, H-2.81%, N-17.03%.

5-(5-((4-methylbenzyl)sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (6b)
Yield:68%, mp:192-4°C,IR (KBr, cm^{-1}): 3260(-OH str), 3070(Ar-H str), 1617(N-N str), 1359&1188(O=S=O str), 1573(>C=N str), 1232(oxadiazole -C-O-C- str).^{1}H NMR (DMSO-d_6, ¢ ppm): 2.24 (s, 3H, -CH_3), 5.21 (s, 2H, -CH_2), 7.16-7.35 (m, 4H, Ar-H), 8.42 (s, 1H, pyrimidine proton),

8.84 (s, 1H, pyrimidine proton), 11.22 (s,1H,-OH). Analytical Calculation for $C_{14}H_{12}N_4O_4S$:C-50.60%, H-3.64%, N-16.86%& found C-50.12%, H-3.29%, N-16.32%.

5-(5-((4-methoxybenzyl) sulfonyl)-1, 3, 4-oxadiazol-2-yl) pyrimidine-4-ol (6c)

Yield:77%, mp:153-5°C,IR (KBr, cm^{-1}): 3256(-OH str), 3070(Ar-H str), 1614(N-N str), 1345&1174(O=S=O str), 1573(>C=N str), 1237(oxadiazole -C-O-C- str).^{1}H NMR (DMSO-d_6, ¢ ppm): 3.82 (s, 3H, -OCH_3), 5.15 (s, 2H, -CH_2), 6.98-7.24 (m, 4H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.22 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{14}H_{12}N_4O_4S$: C-48.27%, H-3.47%, N-16.08%& foundC-47.87%, H-3.11%, N-15.69%.

5-(5-((4-chlorobenzyl) sulfonyl)-1, 3, 4-oxadiazol-2-yl) pyrimidine-4-ol (6d)

Yield:69%, mp:121-3°C, IR (KBr, cm^{-1}): 3264(-OH str), 3070(Ar-H str), 1613(N-N str), 1332&1166(O=S=O str), 1577(>C=N str), 1237(oxadiazole -C-O-C- str).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.27 (s, 2H, -CH_2), 7.33-7.55 (m, 4H, Ar-H), 8.42 (s, 1H, Pyrimidine proton), 8.84 (s,1H, pyrimidine proton), 11.22 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_9ClN_4O_4S$:C-44.26%, H-2.57%, N-15.88%& found C-43.78%, H-2.32%, N-15.21%.

5-(5-((4-(trifluoromethyl)benzyl)sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidin-4-ol (6e)

Yield:74%, mp:153-4°C,IR (KBr, cm^{-1}): 3251(-OH str), 3084(Ar-H str), 1612(N-N str), 1356&1160(O=S=O str), 1584(>C=N str), 1223(oxadiazole -C-O-C- str).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.17 (s, 2H, -CH2), 7.42-7.64 (m, 4H, Ar-H), 8.42 (s, 1H, pyrimidine proton), 8.84 (s, 1H, pyrimidine proton), 11.22 (s, H, -OH attached to pyrimidine ring).AnalyticalCalculationfor $C_{14}H_9F_3N_4O_4S$:C-43.53%, H-2.35%, N-14.50%& found C-43.07%, H-2.09%, N 14.12%.

5-(5-((4-nitrobenzyl)sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (6f)

Yield:82%, mp:172-4°C, IR (KBr, cm^{-1}): 3275(-OH str), 3077(Ar-H str), 1615(N-N str), 1345&1155(O=S=O str), 1573(>C=N str), 1243(oxadiazole -C-O-C- str).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.20 (s, 2H, -CH_2), 7.55-7.97 (m, 4H, Ar-H), 8.42 (s, 1H, pyrimidine protons), 8.82 (s, 1H, pyrimidine protons), 11.22 (s, H, -OH, attached to pyrimidine ring).AnalyticalCalculationfor $C_{13}H_9N_5O_6S$: C-42.98%, H-2.50%, N-19.28%& found C-42.32%, H-2.14%, N-18.89%.

General procedure for the synthesis of 2-(4-chloropyrimidine-5-yl)-5-((4-substituted benzyl)sulfonyl)-1,3,4-oxadiazole [32](7a-f): A mixture of 5-(5-(benzyl sulfonyl)-1,3,4-oxadiazol-2-yl)pyrimidine-4-ol (**6a**) (0.1 m.mol) treatment with acetonitrile and $POCl_3$(0.2 m.mol) it were refluxed for 18hrs. After establishing completion of the reaction, the reaction mixture was kept for 2days at room temperature and then treated with cold water. The solid obtained was filtered, washed with water and recrystallized from methanol to yield the desired product 2-(benzyl sulfonyl)-5-(4-chloropyrimidin-5-yl)-1, 3, 4-oxadiazole **(7a).** Similar procedure was adopted for the synthesis of the compounds **7b-f**from**6b-f**to give corresponding compounds.

2-(benzyl sulfonyl)-5-(4-chloropyrimidine-5-yl)-1,3,4-oxadiazole (7a)

Yield:73%, mp:191-3°C, IR (KBr, cm^{-1}): 3055(Ar-H str), 1373&1190(O=S=O str), 1594(>C=N str), 1242(oxadiazole -C-O-C- str), 672 (-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.24 (s, -CH_2 protons), 7.25-7.47 (m, 5H, Ar-H), 8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).AnalyticalCalculationfor $C_{13}H_9ClN_4O_3S$:C-46.37%, H-2.69%, N-16.64%& foundC-45.89%, H-2.13%, N-16.15%.

2-(4-chloropyrimidine-5-yl)-5-((4-methylbenzyl)sulfonyl)-1,3,4-oxadiazole (7b)

Yield:84%, mp:178-9°C, IR (KBr, cm^{-1}): 3066(Ar-H str), 1374&1184(O=S=O str), 1582(>C=N str), 1221(oxadiazole -C-O-C- str), 678 (-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm): 2.28 (s, 3H, -CH_3), 5.20 (s, -CH_2), 7.16-7.35 (m, 4H, Ar-H),8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).AnalyticalCalculationfor $C_{14}H_{11}ClN_4O_3S$: C-47.94%, H-3.16%, N-15.97%& found C-47.56%, H-2.79%, N-15.34%.

2-(4-chloropyrimidine-5-yl)-5-((4-methoxybenzyl)sulfonyl)-1,3,4-oxadiazole (7c)

Yield:65%, mp:201-3°C, IR (KBr, cm^{-1}): 3077(Ar-H str), 1373&1167(O=S=O str), 1573(>C=N str), 1225(oxadiazole -C-O-C- str), 678 (-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm): 3.81 (s, 3H, -OCH_3), 5.20 (s, -CH_2), 6.98-7.24(m, 4H, Ar-H), 8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).AnalyticalCalculationfor $C_{14}H_{11}ClN_4O_4S$:C-45.84%, H-3.02%, N-15.28%. & found C-45.27%, H-2.78%, N-14.52%.

2-((4-chlorobenzyl)sulfonyl)-5-(4-chloropyrimidine-5-yl)-1,3,4-oxadiazole (7d)

Yield:77%, mp:188-9°C, IR (KBr, cm^{-1}): 3058(Ar-H str), 1370&1165(O=S=O str), 1564(>C=N str), 1236(oxadiazole -C-O-C- str), 677(-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm):5.25 (s, -CH_2 protons), 7.33-7.55 (m, 4H, Ar-H), 8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).AnalyticalCalculationfor $C_{13}H_8Cl_2N_4O_3S$: C-42.06%, H-2.17%, N-15.09%& found C-41.69%, H-1.87%, N-14.77%.

2-(4-chloropyrimidine-5-yl)-5-((4-(trifluoromethyl)benzyl)sulfonyl)-1,3,4-oxadiazole (7e)

Yield:82%, mp:197-8°C, IR (KBr, cm^{-1}): 3062(Ar-H str), 1345&1178(O=S=O str), 1545(>C=N str), 1241(oxadiazole -C-O-C- str), 678(-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm):5.27 (s, -CH_2), 7.42-7.64 (m, 4H, Ar-H), 8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).AnalyticalCalculationfor $C_{14}H_8ClF_3N_4O_3S$: C-41.54%, H-1.99%, N-13.84%& foundC-41.08%, H-1.64%, N-13.47%.

2-(4-chloropyrimidine-5-yl)-5-((4-nitrobenzyl)sulfonyl)-1,3,4-oxadiazole (7f): Yield:65%, mp:173-5°C, IR (KBr, cm^{-1}): 3077(Ar-H str), 1342&1169(O=S=O str), 1573(>C=N str), 1236(oxadiazole -C-O-C- str), 675 (-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.20 (s, -CH_2), 7.55-7.97 (m, 4H, Ar-H), 8.97 (s, 1H, pyrimidine protons), 9.55 (s, 1H, pyrimidine protons).Analytical Calculationfor $C_{13}H_8ClN_5O_5S$:C-40.90%,

H-2.11%, N-18.35%& found C-40.43%, H-1.87%, N-17.98%.

General procedure for the Synthesis of 2-(4-hydrazinylpyrimidine-5-yl)-5-((4-substituted benzyl) sulfonyl)-1, 3, 4-oxadiazole [33[3] (8a-f)

A mixture of 2-(benzyl sulfonyl)-5-(4-chloropyrimidine-5-yl)-1,3,4-oxadiazole (**7a**)(0.1m.mol) and hydrazine hydrate in ethanol(0.2m.mol) was refluxed for a 5 hrs. After the reaction mixture was cooled and poured into ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 2-(benzylsulfonyl)-5-(4-hydrazinylpyrimidin-5-yl)-1,3,4-oxadiazole **(8a)**. The similar experimental procedure was adopted for the synthesis of compounds **8(b-f)** from **7(b-f).**

2-(benzylsulfonyl)-5-(4-hydrazinylpyrimidin-5-yl)-1,3,4-oxadiazole (8a)

Yield:80%, mp:166-7°C, IR (KBr, cm^{-1}): 3499&3413 (-NH_2str), 3207(-NHstr), 3057(Ar-H), 1576(>C=N str), 1325&1190(O=S=O str), 1243(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 4.21 (s, 2H, hydrazide -NH_2), 5.25 (s, 2H, -CH_2 group), 7.31-7.57 (m, 5H, Ar-H), 8.02 (s, 1H, hydrazide -NH), 8.11 (s, 1H, pyrimidine protons), 8.45 (s, 1H, pyrimidine protons). AnalyticalCalculationfor $C_{13}H_{12}N_6O_3S$:C-46.98%, H-3.64%, N-25.95%& found C-46.32%, H-3.49%, N-25.28%.

2-(4-hydrazinylpyrimidin-5-yl)-5-((4-methylbenzyl)sulfonyl)-1,3,4-oxadiazole (8b)

Yield:76%, mp:184-6°C, IR (KBr, cm^{-1}): 3496&3411 (-NH_2str), 3204(-NH str), 3044(Ar-H), 1589(>C=N str), 1331&1188(O=S=Ostr), 1276(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm):2.29 (s, 2H, -CH_3), 4.21 (s, 2H, hydrazide -NH_2), 5.25 (s, 2H, -CH_2), 7.21-7.69 (m, 5H, Ar-H), 8.02 (s, 1H, hydrazide-NH), 8.15 (s, 1H, pyrimidine protons), 8.47 (s, 1H, pyrimidine protons). AnalyticalCalculationfor $C_{14}H_{14}N_6O_3S$: C-48.55%, H-4.07%, N-24.26%& found C-48.08%, H-3.81%, N-23.78%.

2-(4-hydrazinylpyrimidin-5-yl)-5-((4-methoxybenzyl)sulfonyl)-1,3,4-oxadiazole (8c)

Yield:69%, mp:195-7°C, IR (KBr, cm^{-1}): 3497&3415 (-NH_2), 3215(-NH), 3071(Ar-H), 1605(>C=N str), 1327&1191(O=S=O str), 1282(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 3.81 (s, 3H, -OCH_3), 4.25 (s, 2H,hydrazide -NH_2), 5.21 (s, 2H, -CH_2), 6.95-7.22 (m, 4H, Ar-H), 8.02 (s, H,hydrazide-NH), 8.15 (s, 1H, pyrimidine protons), 8.47 (s, 1H, pyrimidine protons). Analytical Calculation for $C_{14}H_{14}N_6O_4S$: C-46.40%, H-3.89%, N-23.19%& foundC-45.86%, H-3.34%, N-22.73%.

2-((4-chlorobenzyl) sulfonyl)-5-(4-hydrazinylpyrimidin-5-yl)-1,3,4-oxadiazole (8d): Yield: 74%, mp: 223-4°C, IR (KBr, cm^{-1}): 3492&3416 (-NH_2str), 3218(-NH str), 3083(Ar-H), 1611(>C=Nstr), 1325&1186(O=S=O str), 1294(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 4.27 (s, 2H, hydrazide -NH_2), 5.24 (s, 2H, -CH_2), 7.23-7.52 (m, 4H, Ar-H), 8.0 (s, 1H, hydrazide-NH), 8.17 (s, 1H, pyrimidine protons), 8.45 (s, 1H, pyrimidine protons). Analytical Calculation for $C_{13}H_{11}ClN_6O_3S$: C-42.57%, H-3.02%, N-22.91%& found C-41.95%, H-2.67%, N-22.24%.

2-(4-hydrazinylpyrimidin-5-yl)-5-((4-(trifluoromethyl)benzyl)sulfonyl)-1,3,4-oxadiazole (8e)

Yield:82%, mp:211-3°C, IR (KBr, cm^{-1}): 3498&3417 (-NH_2), 3211(-NH), 3060(Ar-H), 1599(>C=N), 1322&1190(O=S=O), 1305(oxadiazole -C-O-C-),^{1}H NMR (DMSO-d_6, ¢ ppm): 4.24(s, 2H, hydrazide -NH_2), 5.24 (s, 2H, -CH_2), 7.20-7.59 (m, 4H, Ar-H), 7.95 (s, 1H, hydrazide-NH), 8.11 (s, 1H, pyrimidine protons), 8.47 (s, 1H, pyrimidine protons). AnalyticalCalculationfor $C_{14}H_{11}F_3N_6O_3S$:C-42.00%, H-2.77%, N-20.99%& found C-41.41%, H-2.24%, N-20.45%.

2-(4-hydrazinylpyrimidin-5-yl)-5-((4-nitrobenzyl)sulfonyl)-1,3,4-oxadiazole (8f)

Yield: 68%, mp: 184-6°C, IR (KBr, cm^{-1}): 3496&3418 (-NH_2), 3219(-NH), 3091(Ar-H), 1580(>C=N str), 1327&1187(O=S=O str), 1311(oxadiazole-C-O-Cstr). ^{1}H NMR (DMSO-d_6, ¢ ppm): 4.21 (s, 2H, hydrazide-NH_2), 5.19 (s, 2H, -CH_2), 7.55-8.02 (m, 4H, Ar-H), 8.11 (s, 1H, hydrazide-NH), 8.23 (s, 1H, pyrimidine protons), 8.56 (s, 1H, pyrimidine protons). Analytical Calculation for $C_{13}H_{11}N_7O_5S$: C-41.38%, H-2.94%, N-25.98%& found C-40.81%, H-2.48%, N-25.62%.

General procedure for the Synthesis of 2-((4- substituted benzyl)sulfonyl)-5-(3-(4-(substitutedphenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole [33] (9a-l): A mixture of 2-(benzyl sulfonyl)-5-(4-hydrazinyl pyrimidin-5-yl)-1,3,4-oxadiazole **(8a)**(0.2m.mol) and substituted benzoic acid were taken in $POCl_3$(0.4m.mol) and heated to reflux for 6hrs. The reaction mass was concentrated under reduced pressure and then quenched in ice. The solid 2-(benzylsulfonyl)-5-(3-(4-(trifluoromethyl) phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4-oxadiazole **(9a)** was filtered off, washed with water, dried and recrystallized from ethanol solvent. The similar experimental procedure was adopted for the synthesis of compounds **9(b-l)**.

2-(benzylsulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9a)

Yield: 65%, mp: 218-9°C, IR (KBr, cm^{-1}): 3082(Ar-H), 1559(>C=N str), 1327&1187(O=S=O str), 1305(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 5.23 (s, 2H, -CH_2 group), 7.35-7.54 (m, 9H, Ar-H), 9.05 (s, 1Hof pyrimidine proton), 9.34 (s, 1H of pyrimidine ring). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 130.7, 131.1, 128.2, 126.9, 152.1, 137.9, 127.4, 126.1, 132.1, 124.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}&C_{20}, C_{17}&C_{19},C_{18}, C_{21}, respectively. Analytical Calculation for $C_{21}H_{13}F_3N_6O_3S$: C-51.85%, H-2.69%, N-17.28%& found C-51.08%, H-2.12%, N-16.72%.

2-((4-methylbenzyl)sulfonyl)-5-(3-(4-(trifluoromethyl) phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9b): Yield: 85%, mp:222-4°C, IR (KBr, cm^{-1}): 3097(Ar-H), 1591(>C=N str), 1325&1190 (O=S=Ostr), 1318(oxadiazole -C-O-C str).^{1}H NMR (DMSO-d_6, ¢ ppm): 2.26 (s, 3H, -CH_3), 5.19 (s, 2H, -CH_2), 7.22-7.45 (m, 8H, Ar-H), 9.01 (s, 1H ofpyrimidine proton), 9.33 (s, 1H of pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 126.9, 129.1, 128.9, 135.9,

21.8, 152.1, 137.9, 127.4, 125.9, 132.1, 124.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17}&C_{21}, C_{18}&C_{20},C_{19}, C_{22} respectively. Analytical Calculation for $C_{22}H_{15}F_3N_6O_3S$: C-52.80%, H-3.02%, N-16.79%& found C-52.13%, H-2.68%, N-16.11%.

2-((4-methoxybenzyl)sulfonyl)-5-(3-(4-(trifluoro methyl) phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9c): Yield:70%, mp:207-8°C, IR (KBr, cm^{-1}): 3055(Ar-H), 1564(>C=N str), 1322&1195 (O=S=O str), 1311(oxadiazole -C-O-C str),1144(-OCH_3-Ar str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 3.82 (s, 3H, -OCH_3 group), 5.16 (s, 2H, -CH_2), 7.10-7.32 (m, 8H, Ar-H), 9.04 (s, 1H of pyrimidine proton), 9.38 (s, 1H of pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 121.9, 130.7, 115.9, 158.9, 56.2, 152.1, 137.9, 126.4, 125.6, 131.9 & 124.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17}&C_{21}, C_{18}&C_{20},C_{19}, C_{22} respectively.

Analytical Calculation for $C_{22}H_{15}F_3N_6O_4S$:C-51.16%, H-2.93%, N-16.27%& found C-50.69%, H-2.58%, N-15.77%.

2-((4-chlorobenzyl)sulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9d): Yield:60%, mp:197-9°C, IR (KBr, cm^{-1}): 3079(Ar-H), 1583(>C=N str), 1320&1185 (O=S=O str), 1282(oxadiazole -C-O-C str), 674 (-C-Cl).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.22(s, 2H, -CH_2), 7.42-7.66 (m, 8H, Ar-H), 9.07 (s, 1H, pyrimidine proton), 9.33 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 127.9, 130.7, 129.6, 131.9, 152.1, 137.9, 126.4, 125.6, 131.9, 124.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16} & C_{20}, C_{17}&C_{19},C_{18}, C_{21} respectively.

Analytical Calculation for $C_{21}H_{12}ClF_3N_6O_3S$:C-48.42%, H-2.32%, N-16.13%& found C-47.77%, H-2.01%, N-15.77%.

2-((4(trifluoromethyl)benzyl)sulfonyl)-5-(3(4(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9e): Yield:85%, mp:223-5°C, IR (KBr, cm^{-1}): 3050 (Ar-H), 1606(>C=N str), 1318&1188(O=S=O str), 1266(oxadiazole -C-O-C str),^{1}H NMR (DMSO-d_6, ¢ ppm): 5.29(s, 2H, -CH_2), 7.45-7.79 (m, 8H, Ar-H), 9.05 (s, 1H, pyrimidine proton), 9.29 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 132.9, 130.7, 125.9, 128.9, 124.6, 152.1, 137.9, 126.4, 125.6, 131.9 & 125.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17}&C_{21}, C_{18}&C_{20},C_{19}, C_{22} respectively.

Analytical Calculation for $C_{22}H_{12}F_6N_6O_3S$:C-47.66%, H-2.18%, N-15.16%& found C-47.12%, H-1.81%, N-14.78%.

2-((4-nitrobenzyl)sulfonyl)-5-(3-(4-(trifluoromethyl)phenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9f): Yield:75%, mp:242-4°C, IR (KBr, cm^{-1}): 3077(Ar-H), 1624(>C=N str), 1329&1194 (O=S=Ostr), 1283 (oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 5.18(s, 2H, -CH_2), 7.64-8.16 (m, 8H, Ar-H), 9.02 (s, 1H, pyrimidine proton), 9.36 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 136.9, 130.7, 123.9, 144.9, 152.1, 137.9, 126.1, 126.9, 131.9, 125.6 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}&C_{20}, C_{17}&C_{19},C_{18}, C_{21} respectively.

Analytical Calculation for $C_{21}H_{12}F_3N_7O_5S$:C-47.46%, H-2.28%, N-18.45%& found C-46.79%, H-1.82%, N-18.12%.

2-(benzylsulfonyl)-5-(3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9g): Yield:69%, mp:221-3°C, IR (KBr, cm^{-1}): 3060(Ar-H), 1603(>C=N str), 1333&1186(O=S=O str), 1274(oxadiazole -C-O-C str).^{1}H NMR (DMSO-d_6, ¢ ppm): 5.22(s, 2H, -CH_2), 7.44-7.67 (m, 9H, Ar-H), 8.99 (s, 1H, pyrimidine proton), 9.26 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 129.9, 130.7, 128.9, 126.7, 152.1, 141.9, 127.4, 125.9 , 148.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}&C_{20}, C_{17}&C_{19}, C_{18} respectively.

Analytical Calculation for $C_{20}H_{13}N_7O_5S$:C-51.83%, H-2.83%, N-21.16%& found C-51.16%, H-2.38%, N-20.88%.

2-((4-methylbenzyl) sulfonyl)-5-(3-(4-nitrophenyl)-[1, 2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9h) Yield:81%, mp:213-5°C, IR (KBr, cm^{-1}): 3044(Ar-H), 1646(>C=N str), 1321&1199(O=S=O str), 1300(oxadiazole -C-O-C str). ^{1}H NMR (DMSO-d_6, ¢ ppm): 2.28 (s, 3H –CH3), 5.20(s, 2H, -CH_2), 7.24-7.55(m, 9H, Ar-H), 9.02 (s, 1H, pyrimidine proton), 9.29 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 126.9, 129.7, 128.9, 21.9, 152.1, 141.9, 127.4, 125.9 , 148.3corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17} & C_{21}, C_{18}&C_{20},C_{19}respectively.

Analytical Calculation for $C_{21}H_{15}N_7O_5S$: C-52.83%, H-3.17%, N-20.54 %& found C-52.17%, H-2.91%, N-20.08%.

2-((4-methoxybenzyl)sulfonyl)-5-(3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]pyrimidine-8-yl)-1,3,4-oxadiazole (9i) Yield:77%, mp: 195-7°C, IR (KBr, cm^{-1}): 3083(Ar-H), 1655(>C=N str), 1323&1196(O=S=Ostr), 1305(oxadiazole -C-O-C str),1162(-OCH_3-Ar).^{1}H NMR (DMSO-d_6, ¢ ppm): 3.81 (s, 3H -OCH_3), 5.19 (s, 2H, -CH_2), 7.21-7.47 (m, 9H, Ar-H), 9.05 (s, 1H, pyrimidine proton), 9.31 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 121.9, 129.7, 115.9, 158.4, 56.2, 152.1, 141.9, 127.4, 125.9, 148.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17}&C_{21}, C_{18}&C_{20},C_{19}respectively.

Analytical Calculation for $C_{21}H_{15}N_7O_6S$:C-51.11%, H-3.06%, N-19.87%& found C-50.66%, H-2.79%, N-19.21%.

2-((4-chlorobenzyl) sulfonyl)-5-(3-(4-nitrophenyl)-[1, 2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4-oxadiazole (9j) Yield: 68%, mp: 254-6°C, IR (KBr, cm^{-1}): 3071(Ar-H), 1611(>C=Nstr), 1324&1189(O=S=O str),1280(oxadiazole -C-O-C str),679(-C-Cl). ^{1}H NMR (DMSO-d_6, ¢ ppm): 5.15 (s, 2H, -CH_2), 7.52-7.79 (m, 8H, Ar-H), 9.04 (s, 1H, pyrimidine proton), 9.38 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 127.9, 130.8, 128.7, 132.7, 152.1, 141.9, 127.4, 125.9 , 148.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7,

C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}&C_{20}, C_{17}&C_{19},C_{18} respectively.

Analytical Calculation for $C_{20}H_{12}ClN_7O_5S$: C-48.25%, H-2.43%, N-16.69%& found C-47.87%, H-2.07%, N-16.13%.

2-(3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-8-yl)-5-((4(trifluoromethyl)benzyl)sulfonyl)-1,3,4-oxadiazole (9k): Yield:80%, mp:222-4^oC, IR (KBr, cm^{-1}): 3091(Ar-H), 1601(>C=N str), 1333&1189(O=S=O str), 1292(oxadiazole -C-O-Cstr). ^1H NMR (DMSO-d_6, ¢ ppm): 5.21 (s, 2H, -CH_2), 7.46-7.83 (m, 8H, Ar-H), 9.03 (s, 1H, (s, 1H, pyrimidine proton), 9.37 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 132.9, 129.7, 125.7, 128.3, 124.4, 152.1, 141.9, 127.4, 125.9, 148.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10} & C_{12}, C_{11}, C_{14}, C_{15}, C_{16}, C_{17}&C_{21}, C_{18}&C_{20},C_{19} respectively.

Analytical Calculation for $C_{21}H_{12}F_3N_7O_5S$:C-47.46%, H-2.28%, N-18.45%& found C-47.13%, H-1.92%, N-18.11%.

2-((4-nitrobenzyl) sulfonyl)-5-(3-(4-nitrophenyl)-[1, 2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4-oxadiazole (9l)

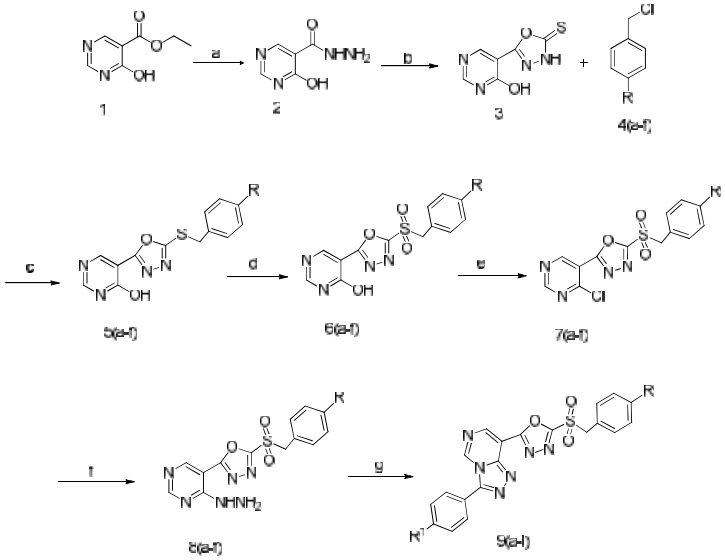
Yield:75%, mp: 192-3^oC, IR (KBr, cm^{-1}): 3066(Ar-H), 1620(>C=Nstr), 1323&1198(O=S=O str), 1308(oxadiazole -C-O-C str).^1H NMR (DMSO-d_6, ¢ ppm): 5.25 (s, 2H, -CH_2), 7.79-8.14 (m, 8H, Ar-H), 9.02 (s, 1H, (s, 1H, pyrimidine proton), 9.33 (s, 1H, pyrimidine proton). ^{13}C NMR in DMSO-d_6 : 141.8, 149.3, 132.5, 152.9, 165.7, 106.3, 69.3, 136.2, 131.3, 124.5, 145.4, 152.1, 141.9, 127.4, 125.9, 148.3 corresponding to C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9&C_{13}, C_{10}&C_{12}, C_{11}, C_{14}, C_{15}, C_{16}&C_{20}, C_{17}&C_{19}, C_{18} respectively.

Analytical Calculation for $C_{20}H_{12}N_8O_7S$:C-47.25%, H-2.38%, N-22.04% & found C-46.89%, H-1.88%, N-21.39%.

3. Results and Discussion

The antibacterial activity of newly synthesized compounds 9a-l were screened against *Staphylococcus aureus* NCCS 2079 and *Bacillus cereus* NCCS 2106 (gram-positive bacteria) and *Escherichia coli* 2065, Pseudomonas aeruginosa NCCS2200 (gram-negative bacteria). Novel synthesized compounds were used at the concentration of 250µg/disc using DMSO solvent. The amoxicillin 10µg/disc was used as standard to antibacterial activity. Similarly the compoundswere screened for antifungal activity against Aspergillus Niger NCCCS1196 and Candida albicans NCCS34471. The ketoconazole 50µg/disc were used as standard to study antifungal activity. Novel synthesized compounds were used at the concentration of 50µg/disc using DMSO solvent. In the series of nitro substituted compounds were showed more, both antibacterial and antifungalactivities than trifluoro substituted compounds. The results were showed in Table-1 and Fig-1&2.

Docking was carried out using GOLD (Genetic Optimization of Ligand Docking) software which is based on Genetic Algorithm (GA). This method allows as partial flexibility of protein and full flexibility of ligand. The compounds are docked to the active site of protein. After docking, the individual binding possess of each ligand were observed and their interactions with the protein were studied.The docking studies of newly synthesized compounds 2-((4- substituted benzyl)sulfonyl)-5-(3-(4-(substituted phenyl)-[1,2,4]triazolo[4,3-c]pyrimidin-8-yl)-1,3,4 oxadiazole (9a-l). Among these compounds9b, 9d, 9e, 9h, 9jand 9k were carried out as model compounds on phytase protein to study the anti-fungal activity of pyrimidine moiety bearing 1,2,4-triazole-1,3,4-oxadiazole sulphonyls derivatives. Based on protein-ligand interaction, GOLD score fitness was evaluated and the 1,2,4-triazole-1,3,4-oxadiazole sulphonyls derivatives having high GOLD score fitness exhibits high anti-fungal activity (Fig-3). The order of anti-fungal activity based on docking studies are 9k>9d>9j>9b>9h>9e (Fig-4, Table-2).



Scheme-1

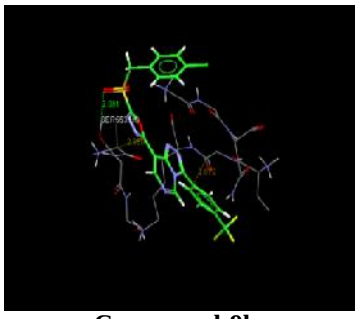
Reagents & Conditions:

(a) Ethanol, hydrazine hydrate (b) KOH & CS_2, ethanol(c) KOH&Ethanol(d) H_2O_2/Glacial acetic acid, (e) Acetonitrile, $POCl_3$, Reflux(f) Ethanol, hydrazine hydrate(g) various 4-substituted benzoic acids, $POCl_3$

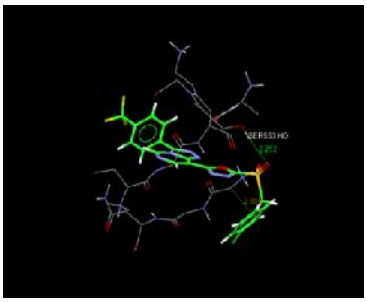
Comp	**9a**	**9b**	**9c**	**9d**	**9e**	**9f**	**9g**	**9h**	**9i**	**9j**	**9k**	**9l**
R	H	CH_3	OCH_3	Cl	CF_3	NO_2	H	CH_3	OCH_3	Cl	CF_3	NO_2
R^1	CF_3	CF_3	CF_3	CF_3	CF_3	CF_3	NO_2	NO_2	NO_2	NO_2	NO_2	NO_2

Table-1: Antimicrobial activities

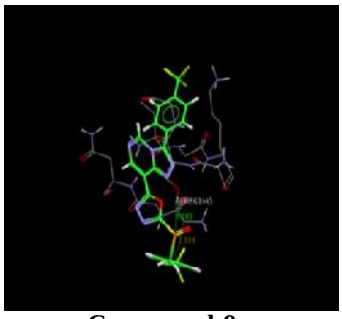
Comp	**Zone of inhibition (nm)**					
	Antibacterial activity				**Antifungal activity**	
	Gram +ve		***Gram -ve***		***Gram +ve***	***Gram -ve***
	SA	***BC***	***EC***	***PA***	***AN***	***CA***
9a	12	06	08	10	11	07
9b	10	04	06	09	09	05
9c	09	ND	04	08	06	ND
9d	13	07	09	11	12	08
9e	15	09	11	12	14	10
9f	16	10	12	14	15	12
9g	13	09	10	11	13	10
9h	12	08	09	10	12	08
9i	11	05	08	09	10	06
9j	15	10	12	14	14	11
9k	16	11	13	15	15	13
9l	17	12	14	16	17	15
Amoxicillin	21	27	24	22	--	--
ketoconazole	--	--	--	--	22	25



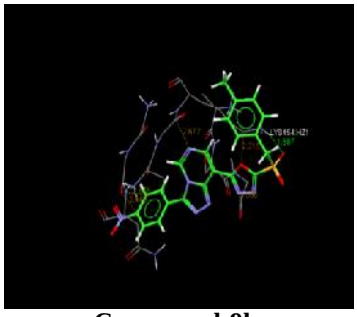
Compound-9b



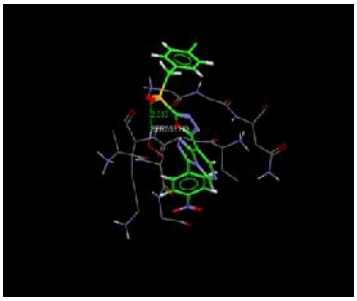
Compound-9d



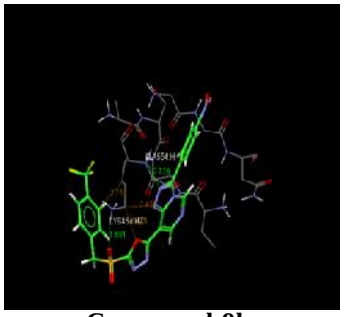
Compound-9e



Compound-9h



Compound-9j



Compound-9k

Figure 1: Docking images of modal compounds

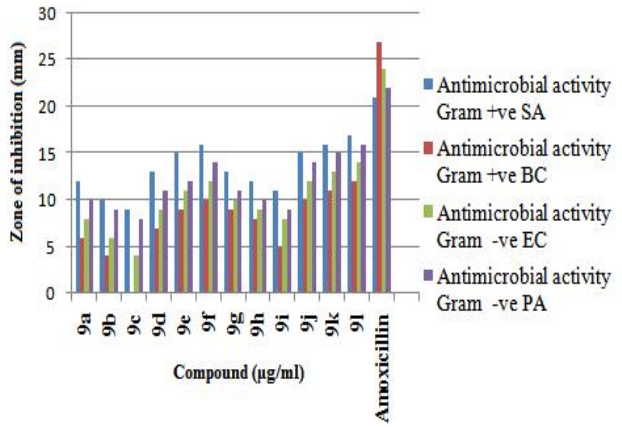


Figure2: Antibacterial activity

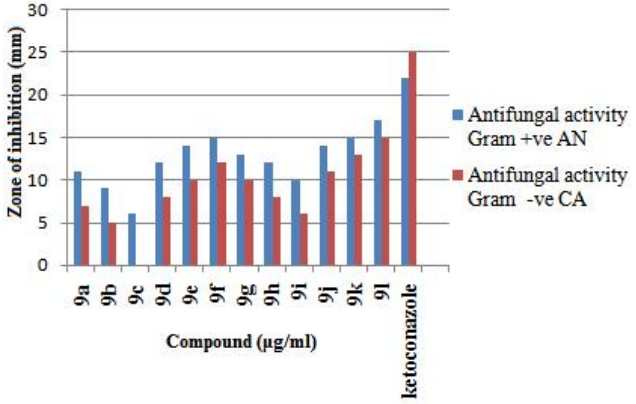


Figure 3: Antifungal activity

Table 2: Docking results of 9b,d,e,h, j&k on Protein phytase

Comp	Fitness	S(hb_ext)	S(vdw_ext)	S(hb_int)	S(int)
9b	43.57	2.00	34.59	0.00	-6.00
9d	44.27	1.83	34.67	0.00	-5.24
9e	42.97	2.00	35.12	0.00	-7.31
9h	43.44	6.00	30.52	0.00	-4.52
9j	44.11	2.00	34.42	0.00	-5.21
9k	44.49	6.00	31.92	0.00	-5.40

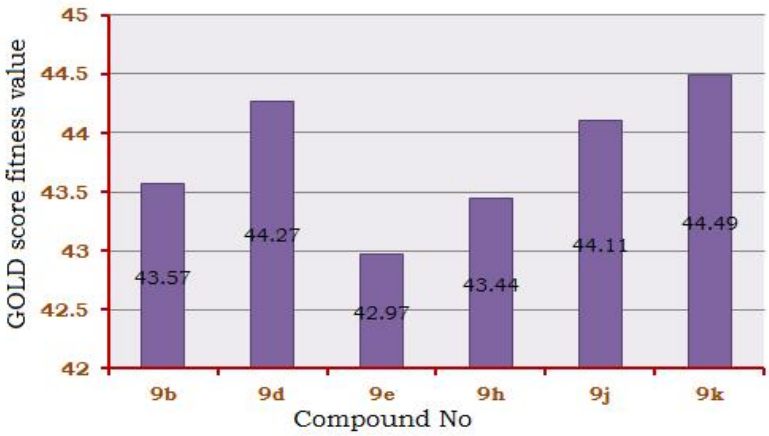


Figure 4: Comparative Gold score fitness values

4. Acknowledgment

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