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DESIGN, SYNTHESIS OF SOME NOVEL 1,3,4-THIADIAZOLE DERIVATIVES ASSOCIATED WITH PYRIMIDINE CORE UNIT BY USING THIOUREA REAGENT

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Abstract
A new series of 1,3,4-Thiadiazole derivatives associated with pyrimidine core unit (7a-j) were synthesized from 4-phenylpyrimidine-2-carboxylic acid (4) with different aromatic/Heterocyclic carboxylic hydrazides (5 a-j) in the presence of $POCl_3$. Finally these 1,3,4-oxadiazole derivatives are converted into 1,3,4-thiadiazoles by using thiourea. The chemical structures of these compounds were confirmed by various physico-chemical methods viz. IR, ^{1}H-NMR, EI-Mass, ^{13}C-NMR analysis. Newly synthesized compounds were screened in vitro for their anti-microbial activity against varieties of gram-positive and gram-negative bacterial strains and fungi strains. The compounds 7j, 7i and 7e shows highly significant antimicrobial activity as compared to the standard drug.

Keywords: 1, 3, 4-Thiadiazole; Pyrimidines; cyclo-condensation, thiourea.

Introduction

The development of new antimicrobial and cytotoxic agents is one of the fundamental goals in medicinal chemistry. In recent years, there has been a concerned search for the discovery and development of potent and selective cytotoxic and antimicrobial agents.

N-heterocyclic ring systems are important for the drug design, among these Pyrimidine and 1,3,4-Thiadiazole compounds are present in several classes of natural and synthetic biologically active compounds.

A large number of organo-sulfur compounds occur in living and non living objects. They belong to open chain, alicyclic, aromatic and heterocyclic types of compounds containing sulfur atom or atoms as a part of chain/ring or both in the structure. Isolation, identification and applications of these organo-sulfur compounds are useful in scientific, technical and pharmaceutical industrial growth. During last three decades organo-sulfur chemistry developed at a much faster pace than any other branches of organic chemistry. Among the sulfur containing heterocyclic compounds, a lot of research in the field of 1,3,4- thiadizoles

has been reported. Some salient features regarding chemical reactivity, synthetic pathways and biological interest of 1, 3, 4-thiadizoles are discussed briefly as background information.
1,3,4 Thiadiazole **[1]** is five member cyclic compound with one sulphur and two nitrogen atoms in the ring **(Fig: 1)**

1,3,4-thiadiazole

(Fig: 1 structure of 1, 3, 4 thiadiazole)

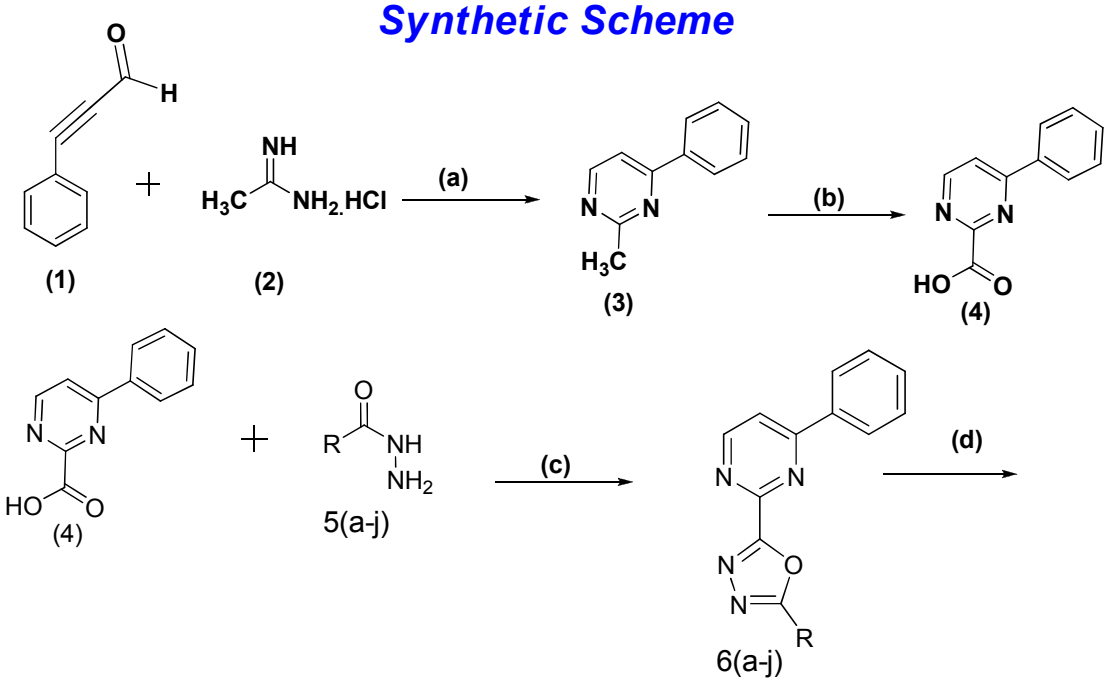
1,3,4-Thiadiazole derivatives possessed a wide range of therapeutic activities like antimicrobial [I], antifungal [II], anti-microbacterial [III], anti-leshmanial [IV], analgesic, anti-inflammatory [V] anti-depressant [VI], anti-psychotic [VII] and anti-convulsant [VIII-IX]. 1,3,4-Thiadiazole derivatives exhibited interesting in vitro [X-XII] and in vivo [XIII-XVI] anti-tumor activities. Different mechanisms of action were attributed to antitumor activity of 1,3,4-thiadiazole ring such as inhibited DNA and RNA syntheses specifically without appreciably affecting protein synthesis [XVII], inhibition of carbonic anhydrase [XVIII], phosphodiesterase-7 (PDE7) [XIX], histone deacetylase [XX] or as adenosine A3 receptor antagonists [XXI].

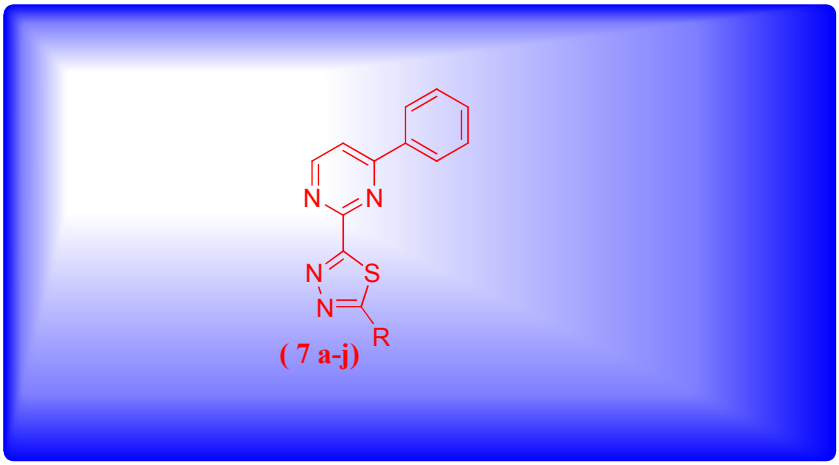
2-Amino-1,3,4-thiadiazole (ATDA, NSC4728) I (Fig. 1) and structurally related compounds had antitumor and uricogenic activity that can be prevented or reversed by nicotinamide [XXII-XXVI]. In addition, phenyl-1, 3, 4-thiadiazole derivatives were found to have anticancer activity against different human cell lines [XXVII, XXVIII]. Substitution of 1,3,4 thiadiazole ring with both amino and phenyl groups resulted in compounds with promising anticancer activity against several cell lines [XXIX].
Attributable to such biological importance, Pyrimidine core structure derivatives have grown to be the synthetic goals of many organic and medicinal chemistry researchers.

Materials and Methods

Materials and Methods Melting points of the synthesized compounds were determined in Open-glass capillaries using GUNA melting point apparatus and are uncorrected. IR Absorption spectra were recorded in the 4000-400 cm^{-1} range on a Shimadzu FTIR-8400s Using KBr pellets, ^{1}H-NMR and C^{13}NMR were recorded on Bruker-NMR, 400 MHz Spectro photometer. TLC was done on F254 grade silica-60 from SD Fine.

Synthetic Scheme



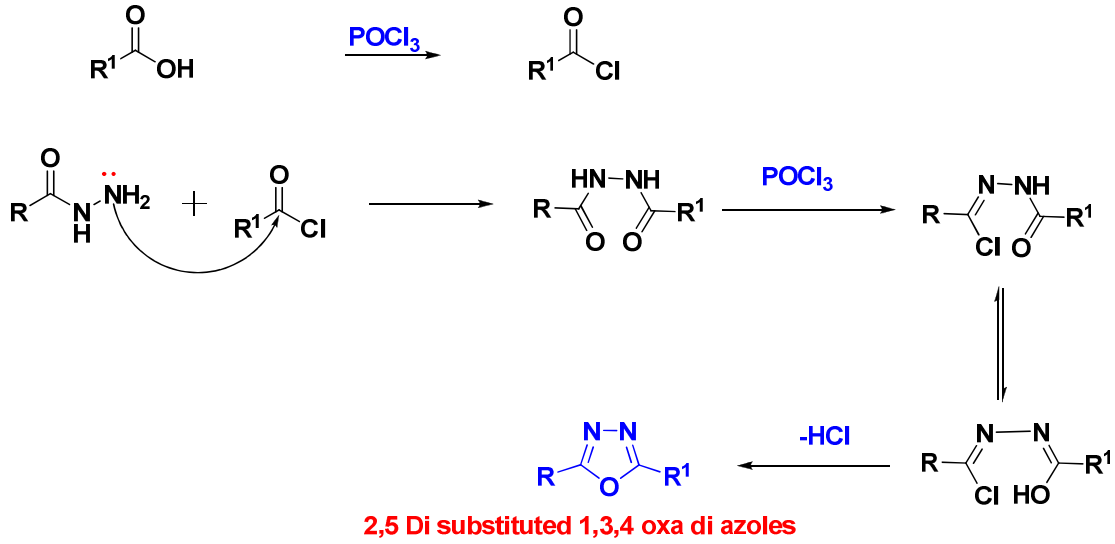


R = -Phenyl, -4 Methyl phenyl, -4 Methoxy phenyl, -4 tri fluoro methoxy phenyl, -4 Tri fluoro phenyl, -4 Nitro phenyl, -4 chloro phenyl, Thiophene 2-yl, pyrazine-2-yl, iso nicotinic acids

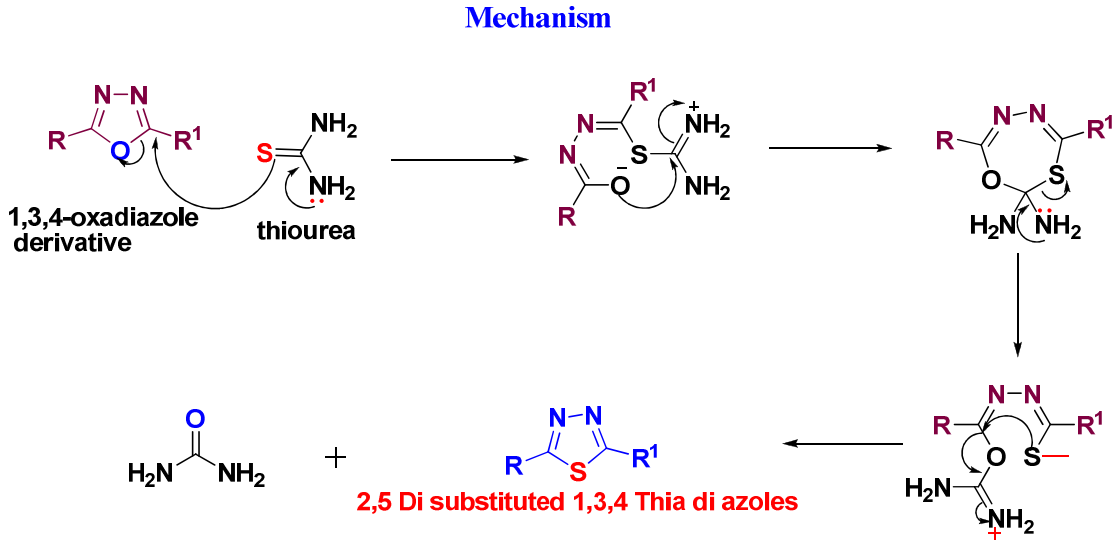
Scheme 1: Synthetic path way for compounds **7a-7j**.

Reagents and Reaction conditions: (a) Microwave irradiation, Aceto nitrile, Na_2CO_3, 90^OC, 1 hrs (b) SeO_2, Reflux, 16 hrs (c)Methanol, H_2SO_4, reflux 16 hrs (d) Hydrazine hydrate, Reflux, 10 hrs. (e) $POCl_3$, Reflux, 6 hrs (f) Thio Urea,THF, reflux

Possible Mechanism for 1,3,4-oxadiazole formation :



Possible Mechanism for 1,3,4-Thiadiazole formation :



The probable mechanism involves the formation of thiouronium salt which undergoes rearrangement to form mesomeric oxouronium salt via oxathiadiazepine derivative. Further, ring closure of oxouronium salt led to thiadiazole by the elimination of urea.

Synthesis:

Synthesis of 2-methyl-4-phenyl Pyrimidine(3):

A mixture of 3-phenylpropiolaldehyde (1.3 g, 10 m.mol) and acetimidine hydro chloride (1.418g, 15 m.mol) was stirred in dry acetonitrile (10 ml) and dry Na_2CO_3 (2.2 g, 20 m.mol) was added to it. The stirring was continued for 0.5 hr under microwave irradiation at 90 ℃ .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(100-120 mesh size silica) with elution of 10% Ethyl acetate to get pure yellow solid.
Yield: 1.36g (80 %)
m.p. 130℃-132℃
IR(KBr,cm^{-1}):3100 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.);
^{1}H NMR ($CDCl_3$-d_1, δppm): 2.5(3H, S), 8.45(1H, d), 7.8(1H, d), 7.4-7.8(5H, m);
EI-Mass: 171 (M^+, +ve mode)

Synthesis of 4-phenylpyrimidine-2-carboxylic acid (4):

A mixture of compound (3) (0.01 mol), selenium Di oxide (0.05 mol), and pyridine (10 ml) was refluxed for 2 hours. Reaction progress was monitored by TLC. After completion of compound 3, concentrated under reduced pressure, then added water (10 ml), acidified with Conc.HCl, white solid was obtained was formed, filter off, dried, to get 75 % yield.
m.p. 187-189 ℃.
IR (KBr, cm^{-1}): 3100 (Ar.C-H str.), 1628 (Ar.C-C str.), 1450 (C-N str.), 1720(C=O str.),3200(-OH Str.),1310(C-O str.);
^{1}H NMR ($CDCl_3$ & DMSO-d_6, δppm):9.35(1H,d),8.55(1H,d),7.4-7.8(5H,m),10.5(-COOH, bs);
EI-Mass: 199 (M^+, -Ve mode)

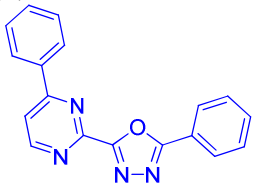
Synthesis of Different carboxylic acid hydrazides (5 a-j):

A mixture of carboxylic acids (0.05 mol), Sulphuric acid (catalytic), and Methanol (10 volumes, 100mL) was refluxed for 2 hours. Reaction progress was monitored by TLC. After completion of reaction Concentrated under reduced pressure, then added Na_2CO_3 Solution (10 ml), white solid was formed, filter off, dried, to get 75 % yield.
The corresponding carboxylic Esters (1 equivalent) are converted into acid hydrazides by using hydrazine hydrate (2 equivalents) in Ethanol solvent under reflux conditions to get corresponding hydrazides (5 a-j). and recrystallization by using Ethanol.

Synthesis of
2-phenyl-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6a),
2-(4-phenylpyrimidin-2-yl)-5-p-tolyl-1,3,4-oxadiazole (6b),
2-(4-methoxyphenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6c),
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazole (6d),
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-oxadiazole (6e),
2-(4-nitrophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6f),
2-(4-chlorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6g),
2-(4-phenylpyrimidin-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (6h),
2-(4-phenylpyrimidin-2-yl)-5-(pyrazin-2-yl)-1,3,4-oxadiazole (6i),
2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1,3,4-oxadiazole (6j):

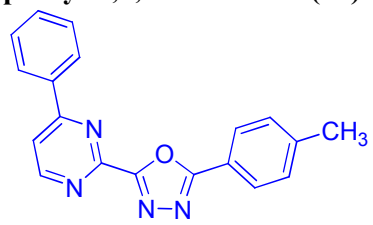
A mixture of compound 4 (2.5 g, 12.487m.mol), compound 5a (1.7 g, 12.487m.mol) and $POCl_3$ (10 mL) was heated under reflux for 5-6 h. The excess $POCl_3$ was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution and then with water, dried and recrystallized from ethanol to get 6a.

2-phenyl-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6a)



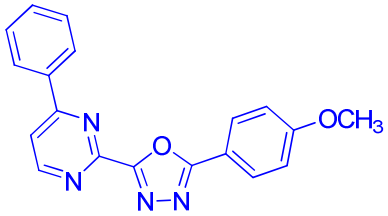
(6a)

Yield 3 g (80%); white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.65(1H,d), 7.95(1H, d),7.41-7.89(10H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 115.5,125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1629 (C=N), 3110 (Ar.C-H str.), 1450 (C-N str.),1354 (C-O-C).
EI-Mass: 301.101(M$^+$, +ve mode)
2-(4-phenylpyrimidin-2-yl)-5-p-tolyl-1,3,4-oxadiazole (6b)



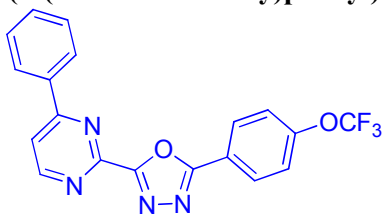
(6b)

Yield 3.2 g (82%); white crystals;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 2.35 (2H,s,-CH$_3$),8.85(1H,d),8.04(1H,d),7.95(2H,d), 7.35(2H,d),7.41-7.89(5H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 23.5 (-CH$_3$), 115.5, 127.5, 128.89, 130.55, 134.55,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1639 (C=N), 3100 (Ar.C-H str.), 2940 (C-H str.,-CH$_3$), 1350 (C-O-C).
EI-Mass: 315.341(M$^+$, +ve mode)
2-(4-methoxyphenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6c)



(6c)

Yield 3.5 g (85%); white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 3.85 (3H,s,-OCH$_3$),8.85(1H,d),8.04(1H,d),7.15(2H,d), 8.15(2H,d),7.41-7.89(5H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 55.5(OCH$_3$), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1639 (C=N), 3100 (Ar.C-H str.), 2940 (C-H str.,-CH$_3$), 1350 (C-O-C).
EI-Mass: 331.341(M$^+$, +ve mode).
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethoxy)phenyl)-1,3,4-oxadiazole (6d)

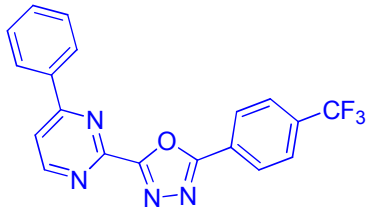


(6d)

Yield 3.85 g (80%); white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H,d),8.05(1H,d),8.15(2H,d), 7.15(2H,d),7.41-7.89(5H,m).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 129.7 (O-**C**F$_3$), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1320 (-C-F str.),1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 383.081(M^+, -ve mode).

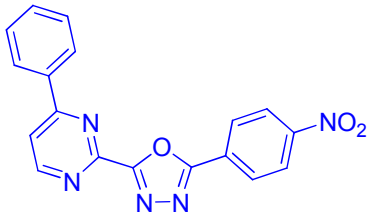
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoro methyl) phenyl)-1, 3, 4-oxadiazole (6e):



(6e)

Yield 3.68 g (80%); white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H, d), 8.05(1H, d), 8.15(2H, d), 7.85(2H, d), 7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 124.7 (**C**F$_3$), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1340 (-C-F str.), 1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 369.081(M^+, +ve mode).

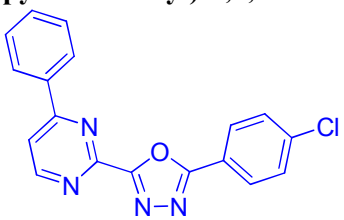
2-(4-nitrophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6f)



(6f)

Yield 3.234g (75%); yellow solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H, d), 8.05(1H, d), 8.25(2H, d), 8.65(2H, d), 7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1330 & 1540 (-N-O symmetrical and unsymmetrical str.in nitro group), 1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 344.086(M^+, -ve mode).

2-(4-chlorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-oxadiazole (6g):

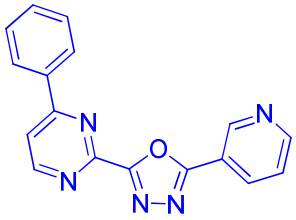


(6g)

Yield 3.347g (80%); white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 7.35(2H, d), 7.41-7.95(5H, m).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 750 (-C-Cl str.), 1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 335.75 (M^+, +ve mode), 337.75 (M+2 peak),3:1 ratio it indicates molecule contain one chlorine atom.

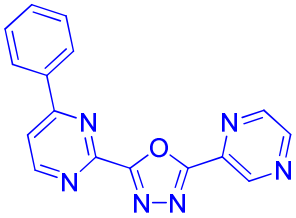
2-(4-phenylpyrimidin-2-yl)-5-(pyridin-3-yl)-1,3,4-oxadiazole (6h)



(6h)

Yield 3.085g (82%); white solid;
^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 9.35(1H, s), 7.6(1H,d),8.85(1H,d),7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 152.6,158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 302.095(M^+, +ve mode).

2-(4-phenylpyrimidin-2-yl)-5-(pyrazin-2-yl)-1,3,4-oxadiazole (6i)



(6i)

Yield 3.0585g (81%); white solid;
^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 9.25(1H, s), 8.85(2H,s),7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 152.6,158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1649 (C=N), 3100 (Ar.C-H str.), 1350 (C-O-C).
EI-Mass: 303.095(M^+, +Ve mode).

2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1, 3, 4-oxadiazole (6j):

(6j)

IR (KBr, cm^{-1}): 940 (-C-S-C str.), 3108 (Ar.C-H str.), 1620 (Ar.C-C str.), 1555 (C=N str.), 1350 (C-O-C).
^{1}H NMR (DMS0-d_6, ppm): δ 8.65(1H,d), 7.93(1H,d),7.4-7.8(5H,m),7.65(1H, d,), 7.15(1H, d,); 7.75 (1H, d).
^{13}C NMR (100 MHz; $CDCl_3$): δC 125.5, 128.89, 130.55, 133.45,141,149, 155.45, 158.8, 162.34, 165.45.

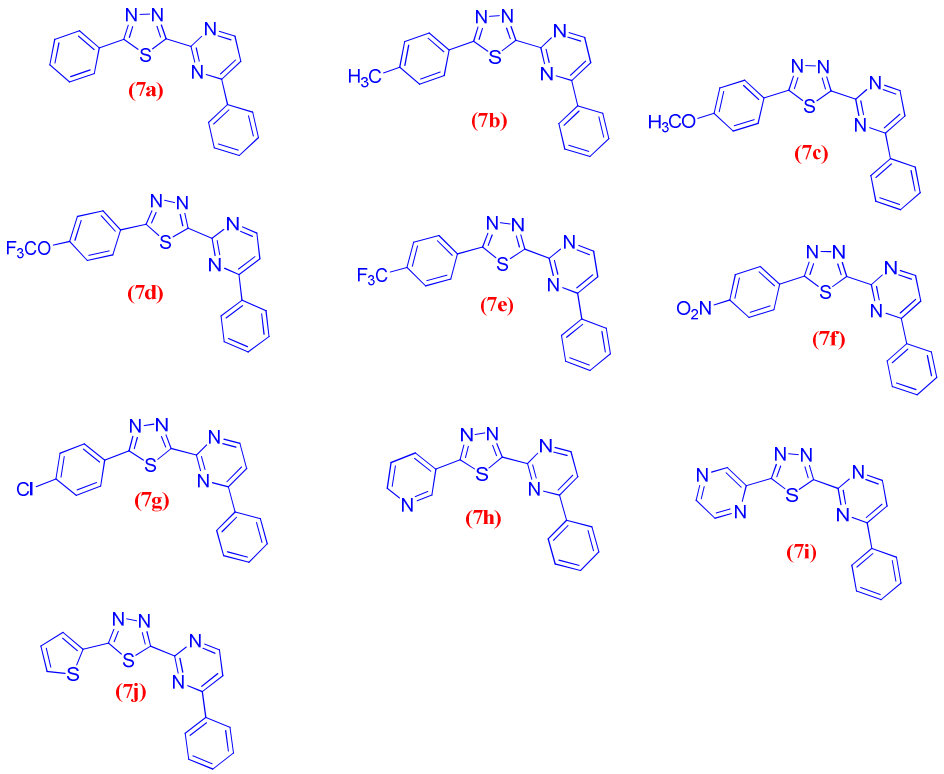
EI-Mass: 307 (M^+, +ve mode)

Synthesis of

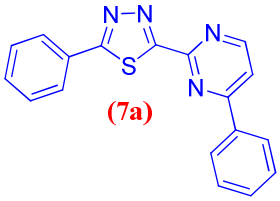
2-phenyl-5-(4-phenylpyrimidin-2-yl)-1,3,4-Thiadiazole (7a),
2-(4-phenylpyrimidin-2-yl)-5-p-tolyl-1,3,4-thiadiazole (7b),
2-(4-methoxyphenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7c),
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole (7d),
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazole (7e),
2-(4-nitrophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7f),
2-(4-chlorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7g),
2-(4-phenylpyrimidin-2-yl)-5-(pyridin-3-yl)-1,3,4-thiadiazole (7h),
2-(2, 5-difluorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7i),
2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1,3,4-thiadiazole (7j):

In a sealed test tube, a mixture of 6a (1.5 g, 5 m.mol), Thiourea (1.53 g, 20m.mol) dissolved in dry Tetrahydrofuran(THF) (5 ml) was taken. The contents were heated at 140-150℃ in an oil bath for 25-28 h. after the reaction was completed, it was extracted with dichloromethane. The organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. The resultant solid was recrystallized from methanol to get 8a.

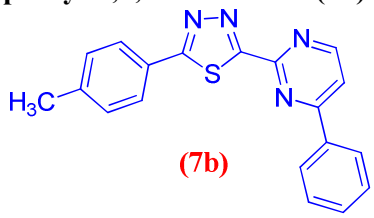
Novel 1,3,4-Thiadiazole derivatives 7(a-j)



2-phenyl-5-(4-phenylpyrimidin-2-yl)-1,3,4-Thiadiazole (7a)

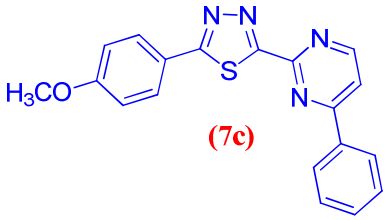


Yield 80%; white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.85(1H,d), 7.95(1H, d),7.41-7.89(10H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 115.5,125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 3026.92 (Ar.C-H str.), 1565.87 (C=N str.),696.67 (C-S-C).
EI-Mass: 317.40(M$^+$, +ve mode)
2-(4-phenylpyrimidin-2-yl)-5-p-tolyl-1,3,4-thiadiazole (7b)



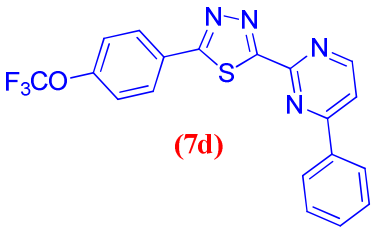
(7b)

Yield 68%, white crystals;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 2.35 (2H,s,-CH$_3$),8.85(1H,d),8.04(1H,d),7.95(2H,d), 7.35(2H,d),7.41-7.89(5H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 23.5 (-CH$_3$), 115.5, 127.5, 128.89, 130.55, 134.55,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1562.55 (C=N), 305.78 (Ar.C-H str.), 2981.73 (C-H str.,-CH$_3$), 696.14(C-S-C).
EI-Mass: 331.341(M$^+$, +ve mode)
2-(4-methoxyphenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7c)



(7c)

Yield 75%; white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 3.85 (3H,s,-OCH$_3$),8.85(1H,d),8.04(1H,d),7.15(2H,d), 8.15(2H,d),7.41-7.89(5H,m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 55.5(OCH$_3$), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1567.48 (C=N), 3023.93 (Ar.C-H str.), 2981.56 (C-H str.,-CH$_3$), 697 (C-S-C).
EI-Mass: 347.406(M$^+$, +ve mode).
2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole (7d)

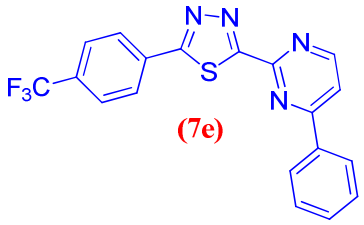


(7d)

Yield 70%, white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H,d),8.05(1H,d),8.15(2H,d), 7.15(2H,d),7.41-7.89(5H,m).

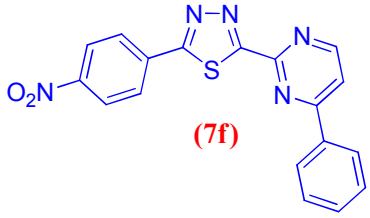
^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.7 (O-**C**F_3), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1340 (-C-F str.),1569 (C=N), 3100 (Ar.C-H str.), 694.34 (C-S-C).
EI-Mass: 399.377(M^+, -ve mode).

2-(4-phenylpyrimidin-2-yl)-5-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazole (7e)



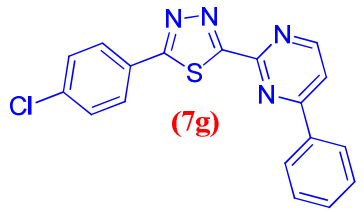
(7e)

Yield 65%; white solid;
^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.75(1H, d), 8.05(1H, d), 8.15(2H, d), 7.85(2H, d), 7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 126.7 (**C**F_3), 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1340 (-C-F str.), 1549 (C=N), 3100 (Ar.C-H str.), 948.26 (C-S-C).
EI-Mass: 385.38(M^+, +ve mode).
2-(4-nitrophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7f)



(7f)

Yield 65%; yellow solid;
^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.75(1H, d), 8.05(1H, d), 8.25(2H, d), 8.65(2H, d), 7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1335 & 1548(-N-O symmetrical and unsymmetrical str.in nitro group), 1549 (C=N), 3100 (Ar.C-H str.), 945.26 (C-S-C).
EI-Mass: 360.063(M^+, -ve mode).
2-(4-chlorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7g)

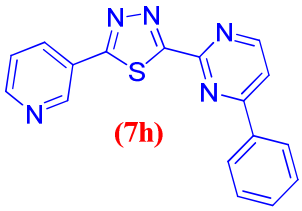


(7g)

Yield 80%; white solid;
^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 7.35(2H, d), 7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 158.8, 162.34, 165.65 (aromatic carbons);

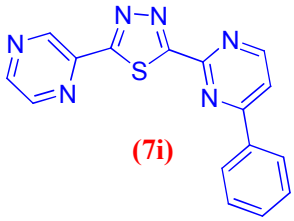
IR (KBr, cm^{-1}): 745.26 (-C-Cl str.), 1564 (C=N), 3100 (Ar.C-H str.), 965 (C-S-C).
EI-Mass: 351.75 (M^+, +ve mode), 353.75 (M+2 peak),3:1 ratio it indicates molecule contain one chlorine atom.

2-(4-phenylpyrimidin-2-yl)-5-(pyridin-3-yl)-1,3,4-thiadiazole (7h)



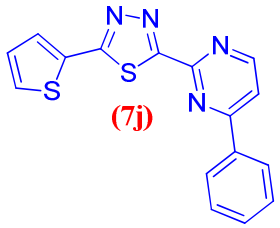
(7h)

Yield 75%; white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 9.35(1H, s), 7.6(1H,d),8.85(1H,d),7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 152.6,158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1549 (C=N), 3100 (Ar.C-H str.), 950 (C-S-C).
EI-Mass: 318.368(M^+, +ve mode).
2-(2, 5-difluorophenyl)-5-(4-phenylpyrimidin-2-yl)-1,3,4-thiadiazole (7i)



(7i)

Yield 80%; white solid;
^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 8.75(1H, d), 8.05(1H, d), 7.25(2H, d), 9.25(1H, s), 8.85(2H,s),7.41-7.95(5H, m).
^{13}C NMR (100 MHz, DMSO-d$_6$): δ = 115.5, 125.5, 128.89, 130.55, 133.45,141,149, 152.6,158.8, 162.34, 165.65 (aromatic carbons);
IR (KBr, cm^{-1}): 1649 (C=N), 3100 (Ar.C-H str.), 940 (C-S-C).
EI-Mass: 319.095(M^+, +Ve mode).
2-(4-phenylpyrimidin-2-yl)-5-(thiophen-2-yl)-1,3,4-thiadiazole (7j)



(7j)

IR (KBr, cm^{-1}): 740 (-C-S-C str.), 3108 (Ar.C-H str.), 1620 (Ar.C-C str.), 1555 (C=N str.), 945.26 (C-S-C).
^{1}H NMR (DMS0-d$_6$, ppm): δ 8.65(1H,d), 7.93(1H,d),7.4-7.8(5H,m),7.65(1H, d,), 7.15(1H, d,); 7.75 (1H, d).

^{13}C NMR (100 MHz; $CDCl_3$): δC 125.5, 128.89, 130.55, 133.45,141,149, 155.45, 158.8, 162.34, 165.45.
EI-Mass: 323.035 (M^+, +ve mode)

Biological Activity:

Antibacterial studies

The newly prepared compounds were screened for their antibacterial activity against Bacillus subtilis, Staphylococcus aureus, Klebsiella pneumonia and Escherichia coli (clinical isolate) bacterial strains by disc diffusion method [**15, 16**]. A standard inoculums (1-2×107 c.f.u./ml 0.5 McFarland standards) were introduced on to the surface of sterile agar plates, and a sterile glass spreader was used for even distribution of the inoculums. The disks measuring 6 mm in diameters were prepared from what man no. 1 filter paper and sterilized by dry heat at 140 ℃ for 1 h. The sterile disks previously soaked in a known concentration of the test compounds were placed in nutrient agar medium. Solvent and growth controls were kept. **Amoxicillin** (30 µg) was used as positive control and the disk poured in DMSO was used as negative control and the test compounds were dissolved in DMSO at concentration of 100 and 50 µg/ml. The plates were inverted and incubated for 24 h at 37 ℃. The susceptibility was assessed on the basis of diameter of zone of inhibition against Gram-positive and Gram-negative strains of bacteria. Inhibition of zone of measured and compared with controls. The bacterial zone of inhibition values are given in (**Table1**). The order of activity was **7e>7j>7i> 7h>7g>7d>7f>7b>7c>7a.**

Table 1: Anti-bacterial activity of Novel 1, 3, 4-thiadiazole derivatives associated with pyrimidine core unit 7(a-j):

Zone of inhibition measure in mm								
Synthesised Compounds	**Gram positive**				**Gram negative**			
	Bacillus sub tilis		**Staphylocouccus aurous**		**Klebsiella pneumonia**		**Escherichia coli**	
	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
7a	6	3	7.5	5	8	6	9.5	6
7b	8.5	6.5	9.0	6.5	10.15	8	11	8
7c	7.5	3.5	8	7	9.5	7	10.5	7.5
7d	10	8	11.1	9.5	12	11	13.5	11
7e	14.5	11.5	17	14	17.3	14	18.5	14
7f	9.5	7	9.5	7.5	12	10	12.5	10.5
7g	11	9.5	11.5	8.5	12.5	12	13	11.5
7h	11.5	9	12.5	11	14.5	11.5	15.5	12
7i	12.9	10.5	14.9	11.5	15.9	13.9	17.0	12.9
7j	13.8	11.2	15.5	12.5	16.9	14.2	17.9	13.5
Amoxicillin	15.9	12.5	17.3	14	17.6	14.5	19.5	15.5
Control (**DMSO**)	---	---	----	-----	----	-----	-----	-----

Antifungal studies

The newly prepared compounds were screened for their antifungal activity against **Candida albicans** and **Aspergillus flavus** in DMSO by agar diffusion method [**17**]. Sabourauds agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting p^H 5.7. Normal saline was used to make suspension of corresponding species. Twenty millilitres of agar media was poured into each Petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h using an agar punch, wells were made and each well was labelled. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The fungal activity of each compound was compared with **Flucanazole** as a standard drug. Inhibition zone were measured and compared with the controls. The fungal zone of inhibition values are given in (**Table 2**).

Table 2: Anti-fungal activity of Novel 1, 3, 4-thiadiazole derivatives associated with pyrimidine core unit 7(a-j):

Zone of inhibition measure in mm				
Synthesised Compounds	**Candida albicans**		**Aspergillus flavus**	
	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
7a	6.5	4.5	7	4
7b	8.5	6.5	9.0	6.5
7c	7.5	3.5	8	7
7d	10	8	11.1	9.5
7e	20	15	17	13.3
7f	9.5	7	9.5	7.5
7g	11	9.5	11.5	8.5
7h	13	11.5	10.5	8
7i	15.5	12.6	14.5	11.5
7j	19.5	14.5	16.5	13
Flucanazole	21	16	18.5	14
Control (**DMSO**)	---	---	---	---

Results and Discussion

Chemistry

In the present work, 1, 3, 4-Thiadiazole derivatives containing Pyrimidine nucleus unit 7(a-j) were synthesized and characterized on the basis of spectral (^{1}H NMR, C^{13}NMR, EI-Mass and IR) analyses. Synthetic chemistry involves conversion of corresponding aromatic acids to respective Methyl esters and further converted to carbohydrazides (5 a-j) by refluxing with pyrimidine carboxylic acid (compound 4) in $POCl_3$ to get 1,3,4-oxadiazole derivatives 6(a-j)[XXX]. These 1,3,4-oxadiazole derivatives 6(a-j) into 1,3,4-Thiadiazoles by using thiourea reagent [XXXI].

Conclusion

A new series of 2-(4-phenylpyrimidin-2-yl)-5-p-substituted-1, 3, 4-Thiadiazole derivatives

(7a-j) were synthesized. These Novel Pyrimidine derivatives screening For Anti-microbial studies. Among these some compounds exhibit excellent biological activity.

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