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Synthesis and characterization of pyrimidine bearing 1, 3, 4-oxadiazole derivatives and their potential antifungal action

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A series of pyrimidine bearing 1, 3, 4-oxadiazole derivatives have been synthesized and evaluated for antifungal activity. All the structures of the newly synthesized compounds have been supported by IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS and CHN analysis. Most of the compounds have shown promising antifungal activity when compared with the standard drug amphotericin-B.

Keyword: Pyrimidine, oxadiazole, carbothioamide, thiosemicarbazide, antifungal activity.

1. Introduction

Literature survey has revealed the importance of pyrimidine derivatives and antimicrobial agent[1], which are found to be associated with variety of biological activities such as insecticidal, antimicrobial, antiviral etc, pyrimidine derivatives [2-8] are powerful C-C bond formation process has wide applications for the preparation of diverse aminoalkyl derivatives. It involves the condensation of a compound capable of supplying one or more active hydrogen atom with aldehyde and primary or secondary amine. Mannich bases are physiologically reactive because of the basic function rendering the molecule soluble in aqueous solvent when it is transformed into ammonium salt. Several medicinally useful mannich bases have been reviewed by Tromontini and Angiolini [9]. Besides this, considerable work has been reported on synthesis and pharmacological activities of various mannich bases for analogies, antispasmodic, anesthetic and antimalarial as well as intermediates in drug synthesis. Antiviral properties of certain thiourea and urea derivatives have been reported in which the antiviral effect is attributed to the presence of an intact NH-(C=S)-NH and NH-(C=O)-NH grouping [10]. In this direction the synthesis and pharmacological study of mannich bases of 3-and 5-mercapto derivatives of 1,2,4-triazole have been reported in literature [11-16]. Further, pyrimidine, fused heterocyclic pyrimidine derivatives and dihydropyrimidones are well known for their potential biological activity such as antiviral, antitumor, antimicrobial fungicide, algaecide and as antibiotics [17-22]. Moreover the presences of different interacted functional groups determine their great synthetic potential. In continuation of this work, herein is reported that the synthesis and *in vitro* study of antifungal activity of heterocyclic N-mannich bases of 5-(5-amino-1,3,4-oxadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one **(3)** against *Candida albicans, Penicillium sps and Aspergillus niger*. Amphotericin-B was used as standard drug. For this purpose, heterocyclic precursor DHPMs (1a-j) were synthesized by Biginelli reaction of aromatic aldehydes, ethylacetoacetate and thiourea according to the literature procedure. Subsequently, these DHPMs were used to synthesis compounds (2a-j). All the

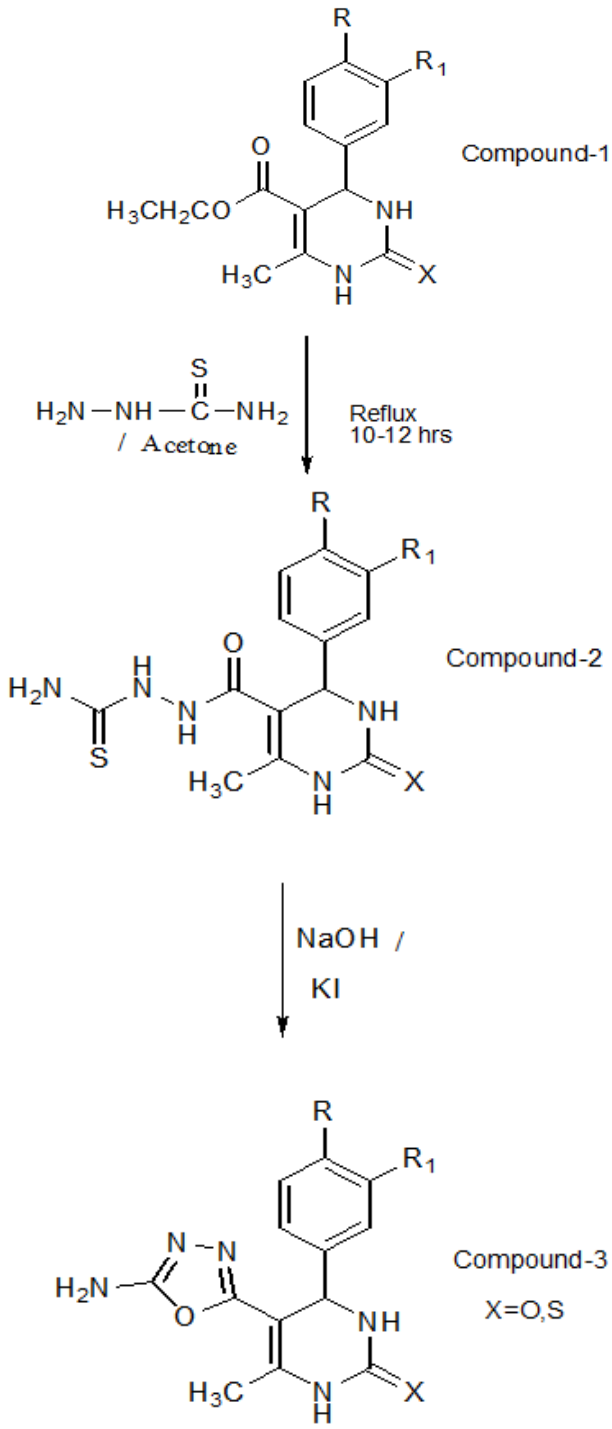
synthesised compounds were characterized by using elemental analysis, mass spectras, H^1& C^{13}-NMR spectral studies.

2. Results and Discussion

Compounds were synthesized as per the scheme-I, where final compound **(3)** prepared by reacting carbothioamide compound **(2)** with NaOH with KI. 5-(Carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one (compound **2)** were synthesized by reacting pyrimidine ethyl ester **(1)** with thiosemicarbazide in acetone followed by condensation reaction [23-26]. The pyrimidine ethyl ester compound **(1)** was prepared by reacting benzaldehyde, ethylacetoacetate and urea or thiourea in the presence of mineral acid followed by Biginelli reaction. The structures of the synthesized compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR, GC-MS and CHN analysis (Table-I). Formation of compound **(2)** was confirmed by the presence of N-H stretching peaks at 3365, 3241 cm^{-1} and 3116 cm^{-1} and C=O stretching peaks at 1724 cm^{-1} in IR and singlet at δ 6.50 for NH_2 group in ^{1}H-NMR spectra. Treatment of compound (2) with NaOH with KI, furnished 5-(5-amino-1, 3, 4-oxadiazole-2-yl)-3, 4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one **(3).**

The structure of **(3)** was elucidated on the basis of C-O-C linkage in the oxadiazole ring, which caused a sharp absorption band at 1020 cm^{-1} in its IR spectrum. ^{1}H-NMR spectrum showed a singlet at δ 3.98 due to NH_2 functionality confirmations of their structure were obtained through spectral and analytical data. (Physical and analytical data are given in Table-II) IR and ^{1}H-NMR spectral data revealed carbonyl absorption band at 1699 cm^{-1} of NH-CO-NH group, N-N stretching band at1089 cm^{-1} aliphatic C-H and aromatic C-H stretching at 2978 $cm^{-1}$and 3033cm^{-1} group of pyrimidine moiety **(3)**. Mass spectrum also supported the proposed structure by viewing molecular ion peak at m/z = 271 $M^{+\cdot}$

Scheme-I



5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3a.

All these compounds were screened for antifungal activity by *Candida albicans, Penicillium sps and Aspergillus niger*. Amphotericin-B was used as standard drug. Most of the synthesized compounds showed moderate to good inhibition at 10µg/ml concentration. However the activity was less compared to the standard drugs.

Table I: Physical and analytical data of compounds- (2a-j)

S. No.	M. Formula	R	R_1	X	M. Wt	Yield(%)	M. p (^{0}C)	Calculated./Found (%)			
								C	N	H	S
2a	$C_{13}H_{15}N_5O_2S$	H	H	O	305	85	140	51.17 (51.94	22.50 22.24	4.94 4.85	10.47 10.94)
2b	$C_{13}H_{14}N_5O_2SCl$	Cl	H	O	339	70	145	46.05 (46.30	20.65 20.94	4.15 4.60	9.42 9.49)
2c	$C_{15}H_{20}N_6O_2S$	$N(CH_3)_2$	H	O	348	78	170	52.35 (52.79	24.42 24.77	5.84 5.83	9.28 9.85)
2d	$C_{13}H_{14}N_6O_4S$	H	NO_2	O	350	81	132	44.60 (44.06	24.00 24.07	4.02 4.43	9.13 9.22)
2e	$C_{13}H_{15}N_5O_3S$	OH	H	O	321	83	160	48.62 (48.75	21.18 21.19	4.70 4.32	9.95 9.36)
2f	$C_{13}H_{15}N_5OS_2$	H	H	S	321	65	143	48.63 (48.46	21.80 21.97	4.70 4.55	19.91 20.10)
2g	$C_{13}H_{14}N_5OS_2Cl$	$N(CH_3)_2$	H	S	355	72	110	43.90 (43.41	19.72 19.42	3.97 4.09	18.00 18.06)
2h	$C_{15}H_{20}N_6OS_2$	Cl	H	S	364	75	148	49.47 (49.00	23.08 23.26	5.49 5.22	17.56 17.69)
2i	$C_{13}H_{14}N_6O_3S_2$	H	NO_2	S	366	70	125	42.65 (42.59	22.95 23.00	3.85 3.54	17.46 17.72)
2j	$C_{13}H_{15}N_5O_2S_2$	OH	H	S	337	78	118	46.32 (46.53	20.77 21.03	4.47 4.70	18.96 19.06)

Table II: Physical and analytical data of compounds-(3a-j)

S. No.	M. Formula	R	R_1	X	M.Wt	Yield (%)	M.p (^{0}C)	Calculated. /Found (%)			
								C	N	H	S
3a	$C_{13}H_{13}N_5O_2$	H	H	O	271	89	176	57.52 (57.59	25.80 25.82	4.07 4.83	0.00 0.00)
3b	$C_{13}H_{12}N_5O_2$ Cl	Cl	H	O	305	86	198	51.28 (51.07	22.76 22.95	3.64 3.96	0.00 0.00)
3c	$C_{15}H_{18}N_6O_2$	$N(CH_3)_2$	H	O	314	88	205	57.51 (57.34	26.71 26.75	5.25 5.77	0.00 0.00)
3d	$C_{13}H_{12}N_6O_4$	H	NO_2	O	316	73	136	49.89 (49.39	26.46 26.82	3.86 3.82	0.00 0.00)
3e	$C_{13}H_{13}N_5O_3$	OH	H	O	287	84	125	54.10 (54.38	24.95 24.38	4.57 4.56	0.00 0.00)
3f	$C_{13}H_{13}N_5OS$	H	H	S	287	80	190	54.23 (54.38	24.52 24.39	4.55 4.56	11.00 11.13)
3g	$C_{15}H_{18}N_6OS$	$N(CH_3)_2$	H	S	330	78	148	48.81 (48.62	21.97 21.80	3.24 3.76	10.33 9.95)
3h	$C_{13}H_{12}N_5OS$ Cl	Cl	H	S	321	81	183	54.01 (54.57	25.29 25.45	5.80 5.49	10.03 9.68)
3i	$C_{13}H_{12}N_6O_3S$	H	NO_2	S	332	76	180	47.87 (47.02	25.08 25.30	3.47 3.64	9.96 9.62)
3j	$C_{13}H_{13}N_5O_2S$	OH	H	S	303	82	172	51.69 (51.52	23.19 23.16	4.22 4.32	10.26 10.54)

3. Experimental section

Melting points were determined using open capillary method and are uncorrected. The compounds were checked for homogeneity by TLC on silicagel-G. The IR spectra were recorded on FT-IR Thermo Nicolet Avatar 370 spectrophotometer using KBr disc method. The ^{1}H-NMR and ^{13}C-NMR were recorded on Bruker Avance III 400 MHz – FTNMR spectrophotometer using DMSO-d_6. Elemental analyses were recorded on Elemental Vario EL III. The mass spectrums were recorded on Joel GC-mate spectrometer. All compounds gave satisfactory micro analytical results. Pyrimidine (**1**) was prepared by reported method.

4. General Procedure

4.1 Synthesis of 5-(Carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one2a.

General procedure for the synthesis of compounds (2a-j), an equimolar mixture of compound **1** (0.01 mole) and thiosemicarbazide (0.01 mole) in acetone was refluxed for 10-12 hrs and allowed to cool and yellow solid was recrystallized from alcohol. Melting point of the compound is 140 ^{0}C yield 85%.

H^{1}-NMR (DMSO-d_6) – **δ** 2.251(s, 3H, CH_3), 5.152(J= 3.2Hz, d, 1H, CH), 6.501 (s, 2H, NH_2), 7.213 – 7.336 (m,5H, Ar-H), 7.702 (J= 2.8Hz, d, 1H, NH), 8.175 (J= 6.4Hz, d, 2H, NHx2), 9.149 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) – **δ** 17.72, 59.17, 99.33, 126.21, 127.23, 128.34, 148.25, 151.71, 152.16, 165.33, 178.40. FT-IR(cm^{-1}) - 3365, 3241, 3116 (NH), 3079 (Ar-H), 2978 (CH), 1724 (C=O), 1598 (C=N), 1385 (C-N), 1219 (C=S), 1089 (N-N). GCMS: (m/z) [305 M^{+}].

4.2 Synthesis of 5-(Carbothioamide)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 2b.

H^{1}-NMR (DMSO-d_6) **δ** -2.251 (s, 3H, CH_3), 5.146 (J= 3.6Hz, d, 1H, CH), 6.530 (s, 2H, NH_2), 7.239 – 7.260 (dd, 2H, Ar-H), 7.377-7.399 (dd, 2H,Ar-H), 7.733 (J= 1.2Hz, d, 1H, NH), 8.096 (J= 2Hz, d, 2H, NHx2), 9.204 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** -17.75, 59.22, 98.87, 128.15, 128.34, 131.74, 143.74, 148.64, 151.92, 165.18, 178.43. FT-IR(cm^{-1})-3376, 3240, 3118 (NH), 3029 (Ar-H), 2978 (CH), 1724 (C=O), 1597 (C=N), 1340 (C-N), 1220 (C=S), 1090 (N-N). GCMS: (m/z) [339 M^{+}].

4.3 Synthesis of 5-(Carbothioamide)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-ethyl-4-phenylpyrimidin-2(1H)-one 2c.

H^{1}-NMR (DMSO-d_6) – **δ** 2.226 (s, 3H, CH_3), 2.846 (s, 6H, N(CH_3)$_2$), 5.5036(J= 3.2Hz, d, 1H, CH), 6.130 (s, 2H, NH_2), 6.650 (J= 8.8Hz, d, 2H, Ar-H), 7.036 (J= 8.8Hz, d, 2H, Ar-H) 7.534 (J= 2.8Hz, d, 2H, NHx2), 9.036 (J= 1.2Hz, d, 1H, NH), 9.866 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) –**δ** 17.67, 53.29, 59.06, 99.93, 112.20, 126.85, 132.61, 149.73, 151.27, 165.46, 178.43. FT-IR(cm^{-1})- 3365, 3241, 3116 (NH), 3053 (Ar-H), 2978 (CH), 1724 (C=O), 1598 (C=N), 1340 (C-N), 1219 (C=S), 1089 (N-N). GCMS: (m/z) [349 M^{+}].

4.4 Synthesis of 5-(Carbothioamide)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 2d.

H^{1}-NMR (DMSO-d_6) **δ** - 2.276(s, 3H, CH_3), 5.309 (J= 4Hz, d, 1H, CH), 6.970 (s, 2H, NH_2), 7.656-7.760 (m, 4H, Ar-H), 7.826 (J= 3.7Hz, d, 2H, NHx2), 9.345 (J= 2.4Hz, d, 1H, NH), 9.872 (s,1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.81, 58.61, 98.35, 129.61, 130.19, 132.95, 147.65, 147.73, 149.36, 151.62, 151.73, 165.04, 178.44. FT-IR(cm^{-1})- 3377, 3239, 3117 (NH), 3029 (Ar-H), 2977 (CH), 1719 (C=O), 1561 (C=N), 1365 (C-N), 1219 (C=S), 1091 (N-N). GCMS: (m/z) [350 M^{+}].

4.5 Synthesis of 5-(Carbothioamide)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 2e.

H^{1}-NMR (DMSO-d_6) –**δ** 2.233 (s, 3H, CH_3), 5.049(J= 3.2Hz, d, 1H, CH), 6.176 (s, 2H, NH_2), 6.676-6.698 (dd, 2H, Ar-H), 7.019-7.040 (dd, 2H,Ar-H), 7.572 (J= 2.4Hz, d, 2H, NHx2), 7.956 (s, 1H, OH), 9.065 (J= 1.2Hz, d, 1H, NH), 9.868 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) –**δ** 17.69, 59.07, 99.80, 114.96, 127.37, 135.40, 151.66, 152.19, 156.50, 165.39, 178.43. FT-IR(cm^{-1})-

3515 (OH), 3377, 3234, 3151 (NH), 2997 (Ar-H), 2904 (CH), 1684 (C=O), 1596 (C=N), 1367 (C-N), 1268 (C=S), 1098 (N-N). GCMS: (m/z) [321 M^+].

4.6 Synthesis of 5-(Carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 2f.

H^1-NMR (DMSO-d_6) – **δ** 2.292 (s, 3H, CH_3), 5.176 (J= 3.6Hz, d, 1H, CH), 6.681 (s, 2H, NH_2), 7.211-7.366 (m, 5H, Ar-H), 7.981 (J= 4Hz, d, 2H, NHx2), 9.887 (J=1.2Hz, d, 1H, NH), 10.308 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **-δ** 17.47, 59.54, 100.75, 126.35, 127.62, 128.50, 143.47, 144.95, 165.10, 178.47, 183.94. FT-IR(cm^{-1}) -3328, 3172, 3106 (NH), 2979 (Ar-H), 2936 (CH), 1669(C=O), 1573 (C=N), 1327 (C-N), 1283 (C=S), 1117 (N-N). GCMS: (m/z) [321M^+].

4.7 Synthesis of 5-(Carbothioamide)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 2g.

H^1-NMR (DMSO-d_6) **-δ** 2.296 (s, 3H, CH_3), 5.174 (J= 2Hz, d, 1H, CH), 7.023 (s, 2H, NH_2), 7.209-7.243 (dd,2H, Ar-H), 7.413-7.503 (dd, 2H, Ar-H), 8.295 (J=0.8Hz, d, 2H, NHx2), 9.648 (J= 2.8Hz, d, 1H, NH), 10.363 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **-δ** 17.48, 59.63, 100.34, 128.27, 128.52, 142.33, 145.28, 164.96, 178.43, 183.89. FT-IR (cm^{-1})- 3377, 3327, 3236 (NH), 3158 (Ar-H), 2996 (CH), 1731 (C=O), 1596 (C=N), 1335 (C-N), 1281 (C=S), 1041 (N-N). GCMS: (m/z) [355M^+].

4.8 Synthesis of 5-(Carbothioamide)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 2h.

H^1-NMR (DMSO-d_6)-**δ** 2.277 (s, 3H, CH_3), 2.855 (s, 6H, $N(CH_3)_2$), 5.048 (J=4Hz, d, 1H, CH), 6.305 (s, 2H, NH_2), 6.663 (J=8.8Hz, d, 2H, Ar-H), 7.016 (J=8.8Hz, d, 2H, Ar-H), 9.509 (J=1.6Hz, d, 2H, NHx2), 9.887 (s, 1H, NH), 10.197 (J=0.8Hz, d, 1H, NH). C^{13}-NMR (DMSO-d_6) **-δ** 17.48, 53.53, 59.43, 101.27, 112.16, 127.08, 131.19, 149.93, 151.56, 165.25, 178.47, 183.93. FT-IR(cm^{-1})- 3377, 3356, 3168 (NH), 3105 (Ar-H), 2981 (CH), 1669 (C=O), 1577 (C=N), 1366 (C-N), 1285 (C=S), 1117 (N-N). GCMS: (m/z) [364 M^+].

4.9 Synthesis of 5-(Carbothioamide)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 2i.

H^1-NMR (DMSO-d_6) **-δ** 2.498 (s, 3H, CH_3), 4.931 (J= 1.2Hz, d, 1H, CH), 6.557(s, 2H, NH_2), 7.540-7.817 (m, 4H, Ar-H), 8.178 (J=0.8Hz, d, 2H, NHx2), 8.566 (J=2.4Hz, d, 1H, NH), 9.855 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **-δ** 17.49, 60.26, 98.35, 122.96, 123.05, 129.73, 135.27, 141.64, 149.51, 151.64, 168.09, 175.39, 183.85. FT-IR(cm^{-1})-3379, 3273, 3175(NH), 3088 (Ar-H), 2982 (CH), 1727)C=O), 1530 (C=N), 1315 (C-N), 1233 (C=S), 1117 (N-N). GCMS: (m/z) [366 M^+].

4.10 Synthesis of 5-(Carbothioamide)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 2j.

H^1-NMR (DMSO-d_6) **-δ** 2.277 (s, 3H, CH_3), 5.063 (J= 3.6Hz, d, 1H, CH), 6.120 (s, 2H, NH_2), 6.699-6.720 (t, 2H, Ar-H), 6.999-7.070 (q, 2H, Ar-H), 7.500 (s, 1H, Ar-H), 7.965 (J=3.5Hz, d, 2H, NHx2), 9.528 (J=1.6Hz, d, 1H, NH), 9.883 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **-δ** 17.50, 59.47, 101.12, 115.17, 127.61, 134.08, 144.42, 151.68, 165.18, 178.38, 183.83. FT-IR(cm^{-1}) -3429 (OH), 3245, 3179, 3079(NH), 3036 (Ar-H), 2988 (CH), 1715 (C=O), 1597 (C=N), 1314 (C-N), 1259 (C=S), 1082 (N-N). GCMS: (m/z) [337 M^+].

5. General procedure for Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3a.

General procedure for the synthesis of compounds (3a-j), carbothioamide **2** (0.01 mole) was added into 10% NaOH with cooling and shaking. Then Iodine solution in KI was added gradually and shaking until the Iodine color persisted. This reaction mixture was heated continuously for 5hrs and it was concentrated the residue, its cooled and poured onto ice cold water. This solution was filtered and acidified with 10% HCl to isolate the product. It was filtered washed with cold water and little amount

of CS_2 was added. The product was recrystallized from alcohol. Melting point 176^0c, Yield 89%.

H^1-NMR (DMSO-d_6) **δ**- 2.264 (s, 3H, CH_3), 3.987 (s, 2H, NH_2), 5.167 (J= 3.2Hz, d, 1H, CH), 7.245 – 7.347 (m,5H, Ar-H), 7.717 (J=1.6Hz, d, 1H, NH), 9.165 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ**- 17.73, 59.14, 99.29, 126.22, 127.21, 128.33, 142.03, 144.83, 148.28, 152.14, 165.31. FT-IR (cm^{-1})- 3375, 3242, 3115 (NH), 3033 (Ar-H), 2978 (CH), 1699 (C=O), 1598 (C=N), 1340 (C-N), 1089 (N-N), 1020 (C-O). GCMS: (m/z) [271 M^+].

5.1 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3b.

H^1-NMR (DMSO-d_6) **δ** - 2.255 (s, 3H, CH_3), 3.997 (s, 2H, NH_2), 5.152 (J=3.6 Hz,d,1H, CH), 7.243 – 7.299 (m, 4H, Ar-H), 7.735 (J=2.8Hz, d, 1H, NH), 9.207 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** -17.76, 59.21, 98.85, 128.15, 128.34, 131.77, 143.76, 148.65, 151.94, 165.17. FT-IR(cm^{-1}) - 3376, 3244, 3116 (NH), 2980 (Ar-H), 2956 (CH), 1723 (C=O), 1534 (C=N), 1367 (C-N), 1170 (C-O), 1087 (N-N). GCMS: (m/z) [305 M^+].

5.2 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3c.

H^1-NMR (DMSO-d_6) **δ** - 2.227 (s, 3H, CH_3), 2.848 (s, 6H, $N(CH_3)_2$), 3.986 (s, 2H, NH_2), 5.038 (J=4.4Hz, d, 1H, CH), 6.658 (J=8.8Hz, d, 2H, Ar-H), 7.022 – 7.058 (m, 2H, Ar-H) 7.539 (J=2.8Hz, d, 1H, NH), 9.041 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.68, 53.28, 59.05, 99.89, 112.29, 126.86, 132.76, 134.25, 147.50, 149.65, 152.25, 165.46. FT-IR(cm^{-1})- 3380, 3245, 3114 (NH), 2953 (Ar-H), 2811 (CH), 1719 (C=O), 1560 (C=N), 1384 (C-N), 1091 (N-N), 1025 (C-O). GCMS: (m/z) [314 M^+].

5.3 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3d.

H^1-NMR (DMSO-d_6) **δ**- 2.283 (s, 3H, CH_3), 4.039 (s, 2H, NH_2), 5.314 (J=3.6Hz, d, 1H, CH), 7.699-8.142 (m, 4H, Ar-H), 8.722 (J=10.4Hz, d, 1H, NH), 9.310 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.81, 59.35, 98.35, 122.26, 130.10, 130.14, 132.94, 146.96, 147.70, 148.30, 149.35, 151.77, 165.02. FT-IR (cm^{-1})- 3566, 3440, 3335 (NH), 3090 (Ar-H), 2966 (CH), 1707 (C=O), 1526 (C=N), 1316 (C-N), 1088 (N-N), 1007 (C-O). GCMS: (m/z) [316 M^+].

5.4 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-one 3e.

H^1-NMR (DMSO-d_6) **δ** - 2.286 (s, 3H, CH_3), 4.046 (s, 2H, NH_2), 5.100 (J= 3.6Hz, d, 1H, CH), 6.765-7.793 (q, 2H, Ar-H), 7.013-7.033 (q, 2H, Ar-H), 9.187 (J= 1.2Hz, d, 1H, NH), 9.347 (s, 1H, NH), 10.296 (s, 1H, OH). C^{13}-NMR (DMSO-d_6) **δ** -17.69, 59.07, 99.78, 114.96, 127.36, 135.41, 136.72, 148.10, 151.98, 152.17, 165.25. FT-IR (cm^{-1}) - 3291 (OH), 3218, 3121 (NH), 3021 (Ar-H), 2981 (CH), 1692 (C=O), 1514 (C=N), 1316 (C-N), 1101 (N-N), 1023 (C-O). GCMS-(m/z) [287 M^+].

5.5 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 3f.

H^1-NMR (DMSO-d_6) **δ** - 2.304 (s, 3H, CH_3), 4.029 (s, 2H, NH_2), 5.191 (J= 3.6Hz, d, 1H, CH), 7.224-7.373 (m, 5H, Ar-H), 9.634 (J= 1.6, d, 1H, NH), 10.314 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.13, 59.54, 100.76, 126.36, 127.62, 128.49, 143.48, 144.95, 165.11, 174.28. FT-IR(cm^{-1})- 3328, 3172 (NH), 3072 (Ar-H), 2979 (CH), 1573 (C=N), 1370 (C-N), 1197 (C=S), 1117 (N-N), 1027 (C-O). GCMS: (m/z) [287 M^+].

5.6 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 3g.

H^1-NMR (DMSO-d_6) **δ** - 2.297 (s, 3H, CH_3), 4.022 (s, 2H, NH_2), 5.171 (J=3.6Hz, d, 1H, CH), 7.222-7.258(dd,2H, Ar-H), 7.424-7.453 (dd, 2H, Ar-H), 9.645 (J=2Hz, d, NH), 10.361 (s,1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.15, 59.61, 100.33, 128.27, 128.52, 128.63, 128.87, 142.35, 145.30, 164.96, 174.28. FT-IR(cm^{-1})- 3437, 3327, 3171 (NH), 3104 (Ar-H), 2982 (CH),

1573 (C=N), 1334 (C-N), 1197 (C=S), 1092 (N-N), 1030 (C-O). GCMS: (m/z) [321 M^+].

5.7 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 3h.

H^1-NMR (DMSO-d_6) **δ** - 2.285 (s, 3H, CH_3), 2.933 (s, 6H, $N(CH_3)_2$), 4.018 (s, 2H, NH_2), 5.104 (J=3.6, d, 1H, CH), 7.022 (J=8.8Hz, d, 2H, Ar-H), 7.114-7.463 (m, 2H, Ar-H), 9.561 (J=1.6Hz, d, 1H, NH), 10.253 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.11, 53.44, 59.52, 100.93, 127.34, 130.33, 144.66, 148.47, 151.67, 155.19, 165.17, 174.03. FT-IR (cm^{-1})- 3482, 3326, 3173 (NH), 3032 (Ar-H), 2981 (CH), 1576 (C=N), 1329 (C-N), 1182 (C=S), 1117 (N-N), 1022 (C-O). GCMS: (m/z) [330M^+].

5.8 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 3i.

H^1-NMR (DMSO-d_6) **δ** - 2.323 (s, 3H, CH_3), 4.033 (s, 2H, NH_2), 5.339 (J= 4Hz, d, 1H, CH), 7.663-7.696 (dd, 2H, Ar-H), 8.081-8.242 (m, 3H, Ar-H), 9.757 (J= 1.2Hz, d, 1H, NH), 10.493 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.19, 59.75, 99.86, 121.12, 122.66, 130.36, 132.97, 145.47, 145.94, 147.80, 164.82, 174.52. FT-IR(cm^{-1})- 3437, 3179 (NH), 3027 (Ar-H), 2988 (CH), 1532 (C=N), 1344 (C-N), 1189 (C=S), 1102 (N-N), 1039 (C-O). GCMS: (m/z) [332 M^+].

5.9 Synthesis of 5-(5-amino-1,3,4-oxadiazole-2-yl)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1H)-thione 3j.

H^1-NMR (DMSO-d_6) **δ** - 2.279 (s, 3H, CH_3), 3.994 (s, 2H, NH_2), 5.066 (J= 3.6Hz, d, 1H, CH), 6.701-6.722 (dd, 2H, Ar-H), 7.002-7.033 (dd, 2H, Ar-H), 9.402 (s, 1H, OH), 9.526 (J= 1.6Hz, d, 1H, NH), 10.216 (s, 1H, NH). C^{13}-NMR (DMSO-d_6) **δ** - 17.09, 59.46, 101.13, 115.12, 127.61, 134.09, 144.43, 156.86, 165.18, 173.87. FT-IR(cm^{-1})- 3477 (OH), 3325, 3171, 3104 (NH), 2985 (Ar-H), 2903 (CH), 1597 (C=N), 1315 (C-N), 1196 (C=S), 1083 (N-N), 1027 (C-O). GCMS: (m/z) [303 M^+].

Table III: Antifungal activities of compounds (3a-j) Antifungal activity in (mm) Std. Amphotericin-B (25mm)

Compound	*Candida albicans*	*Penicillium sps*	*Aspergillus niger*
Control (DMSO)	0	0	0
3a	23 mm	-	-
3b	7mm	8mm	9mm
3c	6mm	6mm	9mm
3d	6mm	7mm	12mm
3e	7mm	8mm	8mm
3f	5mm	9mm	7mm
3g	8mm	8mm	7mm
3h	-	7mm	6mm
3i	-	5mm	6mm
3j	-	6mm	6mm

Concentration was 10µg/ml @ 10% DMSO; "-" and"0" no inhibition zone.

6. Antifungal studies

Among the newly synthesized pyrimidine derivatives were screened for their antifungal activity *in vitro* against the species of *Candida albicans, Penicillium sps and Aspergillus niger,* using agar well disk diffusion method. The test compounds were dissolved in DMSO to get a solution of 10 µg/ml concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 18 hrs at 37 ^{0}C. Amphotericin-B was used as a reference and the results were shown in Table-III. Most of the tested compounds showed antifungal activity comparable with that of the standard drug amphotericin-B. The investigation of antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 10 µg/ml concentration. Especially the compounds showed very good activity against *Penicillium sps* and *Aspergillus niger* than the

others. However the activity was less compared to the standard drug.

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