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Synthesis and Characterization of Pyrimidine bearing 1,2,4-triazole derivatives and their potential antifungal action

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Abstract: A series of pyrimidine bearing 1,2,4-triazole 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.
Key words :Pyrimidine, triazole, carbothioamide, thiosemicarbazide, antifungal activity.

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 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-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.

Results and Discussion

Compounds were synthesized as per the scheme-I, where final compound (**3)** prepared by reacting carbothioamide compound (**2)** with NaOH. 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, furnished 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1H)-one**(3).**

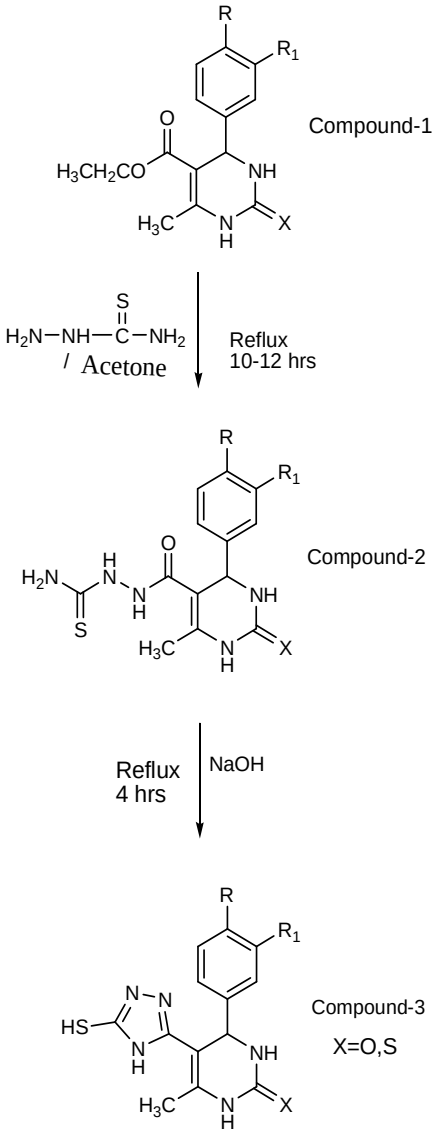
The structure of (**3)** was elucidated on the basis of C-N linkage in the triazole ring, which caused a sharp absorption band at 1373 cm^{-1} in its IR spectrum. ^{1}H-NMR spectrum showed a singlet at δ 3.21 due to SH functionality confirmations of their structure were obtained through spectral and analytical data. (Physical and analytical data are given in Table-II) IR and ^{1}H-NMR spectral data revealed carbonyl absorption band at 1654 cm^{-1} of NH-CO-NH group, N-N stretching band at1053 cm^{-1} aliphatic C-H and aromatic C-H stretching at 2968 $cm^{-1}$and 3027cm^{-1} group of pyrimidine moiety **(3)**. Mass spectrum also supported the proposed structure by viewing molecular ion peak at m/z = 287 $M^{+\cdot}$

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.

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.

Scheme-I



3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1H)-one3a.

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	$C_{13}H_{13}N_5OS$	H	H	O	287	85	120	54.41 (54.38	24.35 24.39	4.22 4.56	11.53 11.13)
3b	$C_{13}H_{12}N_5OSCl$	Cl	H	O	321	70	115	48.92 (48.62	21.44 21.80	3.39 3.76	9.54 9.95)
3c	$C_{15}H_{18}N_6OS$	$N(CH_3)_2$	H	O	330	88	220	54.74 (54.57	25.65 25.45	5.47 5.49	9.55 9.68)
3d	$C_{13}H_{12}N_6O_3S$	H	NO_2	O	332	90	118	47.18 (47.02	25.58 25.30	3.30 3.64	9.43 9.62)
3e	$C_{13}H_{13}N_5O_2S$	OH	H	O	303	84	198	51.86 (51.52	23.22 23.16	4.00 4.32	10.42 10.54)
3f	$C_{13}H_{13}N_5S_2$	H	H	S	303	82	123	51.98 (51.52	23.03 23.10	4.02 4.32	21.12 21.09)
3g	$C_{13}H_{12}N_5S_2Cl$	$N(CH_3)_2$	H	S	337	84	175	46.41 (46.32	20.31 20.77	3.78 3.59	18.83 18.97)
3h	$C_{15}H_{18}N_6S_2$	Cl	H	S	346	78	155	52.38 (52.05	24.42 24.28	5.63 5.24	18.89 18.47)
3i	$C_{13}H_{12}N_6O_2S_2$	H	NO_2	S	348	76	115	45.00 (44.86	24.04 24.14	3.26 3.47	18.69 18.37)
3j	$C_{13}H_{13}N_5OS_2$	OH	H	S	319	85	202	48.01 (48.93	21.97 21.94	4.17 4.10	20.32 20.04)

General Procedure

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

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 10-12hrs and allowed to cool and yellow solid was recrystallized from alcohol. Melting point of the compound is 140^0C 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)[305M^+].

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),1340(C-N),1220(C=S),1090(N-N). GCMS: (m/z)[339M^+].

Synthesis of 5-(Carbothioamide)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-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, 53.29,59.06,99.93,112.20,126.85,151.27,165.46,178.43.FT-IR(cm^{-1})-365,3241,3116(NH),3053(Ar-H), 2978 (C=O),1340(C-N),1219(C=S),1089(N-N). GCMS:(m/z)[349M^+].

Synthesis of 5-(Carbothioamide)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1 H)-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**-17.81,58.61,98.35,129.61,130.19,132.95,147.65,147.73,149.36,151.62,51.73,165.04, 178.44.FT-IR(cm^{-1})-3377,3239,3117(NH),3029(Ar-H),2977(CH),1719(C=O),1365(C-N),1219(C=S), 1091(N-N).GCMS:(m/z)[350M^+].

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,H,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, 135.40,156.50,165.39,178.43.FT-IR(cm^{-1})-515(OH),3234, 3151(NH),2997(Ar-H),1684 (C=O),1367 (C-N),1268(C=S),1098(N-N).GCMS:(m/z)[321M^+].

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).C^{13}-NMR(DMSO-d_6)-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})-328,3172,3106(NH),2999(Ar-H), 2936 (CH),1669 (C=O),1573(C=N),1327 (C-N),1283(C=S),1117(N-N). GCMS:(m/z)[321M^+].

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).C^{13}-NMR(DMSO-d_6)-**δ**17.48,59.63,128.2, 145.2, 164.96,183.89. FT-IR(cm^{-1})-3377,3236(NH),3158(Ar-H),2996(CH),1731(C=O),1281(C=S), 1041 (N-N).GCMS: (m/z)[355M^+].

Synthesis of 5-(Carbothioamide)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl-4-phenyl pyrimidin-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)[364M^+].

Synthesis of 5-(Carbothioamide)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2 (1 H)-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})-3379,3175(NH),3088(Ar-H),1727(C=O),1233(C=S). GCMS:(m/z) [366M^+].

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** .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)[337M^+].

General procedure for Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidin-2(1H)-one3a.

General procedure for the synthesis of compounds (3a-j), carbothioamide**2** (0.01 mole) was added into 8% NaOH it was heated under refluxed for 4hrs. The reaction mixture was cooled to room temperature and acidified with dilute acetic acid then filtered and washed well with water and purified by recrystallization from alcohol as shiny crystals. Melting point 120^0C, yield 85%. H^1-NMR(DMSO-d_6)**δ**-2.304(s,3H,CH_3),3.217(s,1H,SH),5.507(J=3.6Hz,d,1H,CH),6.975(s,1H,NH),7.268–7.338 (m,5H ,ArH),7.766(J=2.4Hz,d,1H,NH),9.217(s,1H,NH).C^{13}-NMR(DMSO-d_6)**δ**-17.74,59.14,99.24,126.22, 127.21,128.33,144.84,152.15,155.11,165.32.FT-IR(cm^{-1})-3423,3258,(NH),3027(Ar-H),2968(CH), 2235 (SH),1654(C=O),1590(C=N),1373(C-N), 1057 (N-N). GCMS: (m/z)[287 M^+].

Synthesis of 4-(4-chlorophenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-Methyl pyrimidin-2(1H)-one3b. H^1-NMR(DMSO-d_6)**δ**-2.259(s,3H,CH_3),3.153(s,1H,SH), 5.156 (J=2.4Hz, d, 1H, CH),7.004(s,1H,NH),7.365–8.214(m,4H,Ar-H),9.286(J=3.1Hz,d,1H,NH),9.973 (s,1H,NH).C^{13}-NMR (DMSO-d_6)**δ**-7.76,59.25,98.85,128.15,128.33,128.65,128.88,131.76,133.17, 134.21,140.89, 165.18, 178.12.FT-IR(cm^{-1})-3436,3276(NH),3036(Ar-H),2978(CH),2265(S-H),1682 (C=O),1526(C=N), 1322 (C-N),1090(N-N).GCMS:(m/z)[321M^+].

Synthesis of 4-(4-(dimethylamino)phenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methylpyrimidin-2(1H)-one3c. H^1-NMR(DMSO-d_6)**δ**-2.226(s,3H,CH_3),2.846(s,6H, N(CH_3)$_2$),2.992 (s,1H,SH),5.035(J=3.2Hz,d,1H,CH),6.353(s,1H,NH),6.650(J=8.4Hz,d,1H,Ar-H),6.765(J=8.8Hz,d, 1H, Ar -H),7.026-7.062(dd,2H,Ar-H),8.475(J=15.2Hz,d,1H,NH),9.051 (s,1H,NH). C^{13}-NMR(DMSO-d_6) **δ**-17.68, 53.29,59.05,99.91,111.67,126.85,129.46,149.73, 152.26,159.76,165.46. FT-IR(cm-1)-3244, 3112(NH),3010(Ar-H),2976(CH),2376(SH),1709(C=O),1524(C=N),1365(C-N),1089(N-N). GCMS: (m/z) [330M^+].

Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-(3-nitrophenyl) pyrimidin-2(1H)-one3d. H^1-NMR(DMSO-d_6)**δ**-2.285(s,3H,CH_3),2.973(s,1H,SH),5.319(J=2.4Hz,d,1H,CH), 7.182(s,1H,NH),7.643-7.721(m,4H,Ar-H),7.940 (J=2.4Hz,d,1H,Ar-H),8.110(J=15.6Hz,d,1H,Ar-H),

8.178(J=2.3Hz,d,1H,NH),9.408(s,1H,NH).C^{13}-NMR(DMSO-d_6)**δ**-17.80,59.38,98.36,120.96, 122.31, 130.19,132.98,139.08,146.96,147.72,149.41,151.85,165.07.FT-IR(cm^{-1})-3440,3335NH), 3090(Ar-H), 2966(CH),2385(SH),1687(C=O),1560(C=N),1346(C-N),1088(N-N).GCMS:(m/z) [$332M^+$].

Synthesis of 3,4-dihydro-4-(4-hydroxyphenyl)-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl py rimidin-2(1H)-one3e.H^1-NMR(DMSO-d_6)**δ**-2.340(s,3H,CH_3),3.226(s,1H,SH),5.738 (J=8.8Hz, d,1H, CH),7.282(s,1H,NH),7.664(J=8.8Hz,d,2H,Ar-H),7.853-7.857(dd,1H,Ar-H),8.031 (J=8Hz,d,1H,Ar-H), 8.080(J=1.2Hz,d,1H,NH),9.918(s,1H,NH),11.276(s,1H,OH).C^{13}-NMR(DMSO-d_6)**δ**-17.76, 59.22, .85, 115.53,125.10,129.01,140.89,142.77,159.22,177.44.FT-IR(cm^{-1})-3468, 3359(NH),3128(OH),3015(Ar-H),2925(CH),2335(SH),1609(C=O),1547(C=N),1388(C-N),1097(N-N).GCMS-(m/z)[$303M^+$].

Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-phenylpyrimidine-2 (1 H) -thione3f.H^1-NMR (DMSO-d_6)**δ** -2.289(s,3H,CH_3),3.112(s,1H,SH),5.376(J=2.4Hz,d, 1H,CH), 7.498 (s,1H,NH),7.594(dd, 2H, Ar-H),7.778-7.962(dd, 2H, Ar-H),8.112(J=4Hz,d,1H,NH), 9.694 (s, 1H, NH).C^{13}-NMR(DMSO-d_6)**δ** -17.76,59.22,98.85,127.24,128.62,129.81,134.13,142.38, 165.18, 177. 99. -IR(cm^{-1})-3421,3252(NH),3054(Ar-H),2982(CH),2336(SH), 1590(C=N),1372(C-N), 1293 (C=S), 1067 (N-N).GCMS: (m/z)[$303M^+$].

Synthesis of 4-(4-chlorophenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl pyr imidine-2(1H)-thione3g.H^1-NMR(DMSO-d_6)**δ**-2.310(s,3H,CH_3),3.065(s,1H,SH),5.356(J=2.4Hz, d,1H,CH),7.199(s,1H,NH),7.460(J=8.4Hz,d,1H,Ar-H),7.590(J=8.4Hz,d,1H,Ar-H),7.840(J=8.4Hz, d,1H,Ar-H),7.904(J=11.6Hz,d,1H,Ar-H),8.177(J=2.4Hz,d,1H,NH),8.715(s,1H,NH).C^{13}-NMR (DMSO -d_6)**δ**-17.76,59.21,98.85,128.66,128.89,129.05,129.99,133.18,134.19,140.89,178.12.FT-IR(cm^{-1})-3437,3280(NH),3065(Ar-H),2994(CH),2372(SH),1525(C=N),1367(C-N),1283(C=S),1016(N-N). GCMS:(m/z)[$337M^+$].

Synthesis of 4-(4-(dimethylamino)phenyl)-3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-me thylpyrimidine-2(1H)-thione3h.H^1-NMR(DMSO-d_6)**δ**-2.283(s,3H,CH_3),2.864(s,6H,$N(CH_3)_2$), 3.098(s,1H,SH),5.058(J=3.6Hz,d,1H,CH),6.881(s,1H,NH),7.522(J=8.8Hz,d,2H,Ar-H),7.766(J=9.2 Hz, d, 1H,Ar-H),7.641-7.734(t,1H,Ar-H),7.951(J=9.2Hz,d,1H, Ar-H),9.506(J=3.6Hz,d,1H,Ar-H), 10.195(s,1H,NH).C^{13}-NMR(DMSO-d_6)**δ**-17.07,53.49,59.44,101.27,121.39,127.08,128.57,129.46, 131.18,149.94,151.39,165.26.FT-IR(cm^{-1})-3415,3150(NH),3056(Ar-H),2981(CH),2386(SH),1521(C =N),1365(C-N),1229(C=S),1030(N-N).GCMS:(m/z)[$346M^+$].

Synthesis of 3,4-dihydro-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl-4-(3-nitrophenyl) pyrimi dine-2(1H)-thione3i.H^1-NMR(DMSO-d_6)**δ**-2.093(s,3H,CH_3),3.088(s,1H,SH),5.113(J=4Hz,d,1H, CH),6.624(s,1H,NH),7.064(J=7.6Hz,d,1H,Ar-H),7.451-7.831(m,1H,Ar-H),8.333(J=16Hz,d,1H,NH), 11.317(s,1H,NH).C^{13}-NMR(DMSO-d_6)**δ**-17.81,59.35,98.35,115.79,128.80, 129.13,133.11, 134.25, 134.48,140.96,143.52,162.02,177.82.FT-IR(cm^{-1})-3326,3176(NH),3010(Ar-H),2986(CH), 2386(SH),1585 (C=N), 1320(C-N), 1279(C=S),1089(N-N).GCMS:(m/z)[$348M^+$].

Synthesis of 3,4-dihydro-4-(4-hydroxyphenyl)-5-(5-mercapto-4H-1,2,4-triazol-3-yl)-6-methyl pyr imidine-2(1H)-thione3j.H^1-NMR(DMSO-d_6)**δ**-2.526(s,3H,CH_3),3.120(s,1H,SH), 5.295(J=3.2Hz, d, 1H, CH),6.764-6.798(m,2H,Ar-H),7.590-7.625(m,2H,Ar-H),7.802(s,1H,NH),7.991(J=2.7 Hz,d,1H, NH),9.858(s,1H,NH),11.221(s,1H,OH).C^{13}-NMR(DMSO-d_6)-17.81,59.35,98.35,115.52,125.11, 129.00,132.94,133.57,142.77,159.22,177.46.FT-IR(cm^{-1})-468,3360(NH),3191(OH),3015(ArH), 2810(CH),2471(SH),1586(C=N),1384(C-N),1265(C=S),1097(N-N).GCMS:(m/z)[$319M^+$].

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 10µg/ml concentration. The inhibition zones were measured in millimeters at the end of an incubation period of 18hrs at 37^0C. 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.

Table-III-Antifungal activities of compounds (3a-j)
Antifungal activity in (mm) Std. Amphotericin-B (18mm)

Compound	*Candida albicans*	*Penicillium sps*	*Aspergillus niger*
Control(DMSO)	0	0	0
3a	12 mm	13mm	10mm
3b	10mm	10mm	6mm
3c	-	7mm	5mm
3d	-	-	5mm
3e	7mm	6mm	7mm
3f	9mm	8mm	8mm
3g	11mm	15mm	10mm
3h	8mm	10mm	6mm
3i	10mm	9mm	7mm
3j	6mm	8mm	5mm
Concentration was 10µg/ml @ 10% DMSO; "-" and"0" no inhibition zone.			

The investigation of antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 10µg/ml concentration. Especially all the compounds showed very good activity against *Aspergillus niger* than the others. However the activity was less compared to the standard drug.

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