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Microwave assisted synthesis and antibacterial studies of 5-amino thiadiazole substituted pyrimidine compounds

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Abstract
Simple synthetic methods of 5-(5-amino-1,3,4-thiadiazol-2yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-thione (3f-j) are described. Compound 1 is converted to carbothiamide 2 by reacting compound 1 with thiosemicarbazide in catalytic amount of acetone is irradiated with help of domestic microwave oven (200W) for 2 minutes. Compound 2 is act as a key intermediate for the final compounds. The compound 2 is converted to corresponding thiadiazole 3 by treatment with conc.H_2SO_4 and NH_3. Structural elucidation is accomplished by IR, ^1H and ^{13}CNMR, Elemental analysis and GC-Mass spectral data of the synthesized compounds. Few of these Pyrimidine derivatives have been evaluated for their possible antibacterial activity. Most of the tested compounds show significant antibacterial activity.

Keywords: Pyrimidine, thiadiazole, carbothiamide, thiosemicarbazide, antibacterial 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 amino alkyl 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, 3, 4-thiadiazole 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 antibacterial activity of heterocyclic N-Mannich bases of 5-(5-amino-1,3,4-thiadiazol-2yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-thione (3f-j) against *Streptococcus faecalis (Gram +ve), Bacillus sps (Gram +ve) and Escherichia coli (Gram -ve)* and Ciprofloxacin is used as standard drug. For this purpose, heterocyclic precursors DHPMs (1f-j) are synthesized by microwave irradiation of aromatic aldehydes, ethylacetoacetate and thiourea according to the literature procedure [27, 28]. Subsequently, these DHPMs are used to synthesis compounds (2f-j). All the synthesized compounds are characterized by using elemental analysis, mass spectra, ^1H& [13] CNMR spectral studies.

Results and Discussion
Compounds (3f-j) are synthesized as per the scheme 1 and 2. The compound 3f is prepared by reacting hydrazine carbothioamide compound 2f with conc.H_2SO_4 and NH_3.

Hydrazine carbothioamide compound 2f is synthesized by reacting pyrimidine ethyl ester 1 with thiosemicarbazide is irradiated in a domestic microwave oven (200W) for 2 minutes [29]. The reaction mixture is allowed to cool and the obtained solid is recrystallized from ethanol.

The pyrimidine ethyl ester compound 1f prepared by a mixture of aromatic aldehyde (0.01mol), ethylacetoacetate (0.01mol) and urea (0.01mol) is mixed thoroughly with 0.15 mole of tin (II) chloride as catalyst in a conical flask. The content of the flask is irradiated in a domestic microwave oven (400W) for 6 minutes. The completion of the reaction is monitored by TLC.

The structures of the synthesized compounds are confirmed by IR, ^{1}H and [13] C-NMR, GC-MS and CHN analysis. Formation of compound 2f is confirmed by the presence of N-H stretching peaks at 3328, 3172 cm^{-1} and 3106 cm^{-1} and C=S stretching peaks at 1669 cm^{-1} in IR and singlet at δ 6.68 for NH_2 group in $^{1}HNMR$ spectra. Treatment of compound 2f with conc.H_2SO_4 and NH_3, furnished 5-(5-amino-1,3,4-thiadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-one(3f-j). The structure of 3f is elucidated on the basis of C-S linkage in the thiadiazole ring, which causes sharp absorption band at 1195 cm^{-1} in its IR spectrum. $^{1}HNMR$ spectrum shows a singlet at δ4.03 due to NH_2 functional group of 3f.

The IR spectral data reveals the carbonyl absorption band at 1282 cm^{-1} of NH-CS-NH group, N-N stretching band at1001 cm^{-1} aliphatic C-H and aromatic C-H stretching at 2979 cm^{-1} and 3033 cm^{-1} group of pyrimidine moiety 3f. Mass spectrum also supported the proposed structure by viewing molecular ion peak at *m/z* 303$M^{+\cdot}$

Table 1: Physical and analytical data of compounds (2f-j)

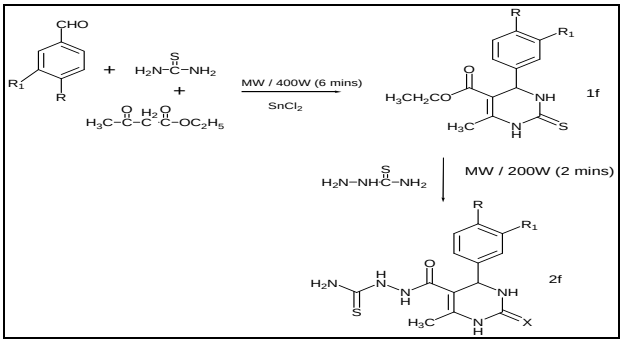
Compd.	Mol. Formula	R	R_1	X	Mol. Wt	Yield (%)	m.p (^{0}C)	Calcd. /Found (%)			
								C	N	H	S
2f	$C_{13}H_{15}N_5OS_2$	H	H	S	321	65	143	48.63 (48.46	21.80 21.97	4.70 4.55	19.91 20.10)
2g	$C_{13}H_{14}N_5OS_2Cl$	$N(CH_3)_2$	H	S	355	72	110	43.90 (43.41	19.72 19.42	3.97 4.09	18.00 18.06)
2h	$C_{15}H_{20}N_6OS_2$	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 2: Physical and analytical data of compounds (3f-j)

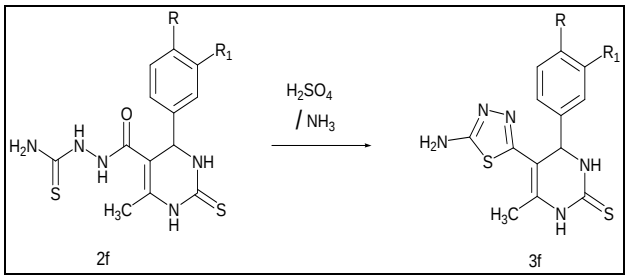
Compd	Mol. Formula	R	R_1	X	Mol.Wt	Yield (%)	m.p (^{0}C)	Calcd. /Found (%)			
								C	N	H	S
3f	$C_{13}H_{13}N_5S_2$	H	H	S	303	75	185	51.52 (51.45	23.10 23.95	4.32 4.35	21.09 21.15)
3g	$C_{15}H_{18}N_6S_2$	$N(CH_3)_2$	H	S	346	85	188	52.05 (52.44	24.28 24.84	5.24 5.39	18.47 18.54)
3h	$C_{13}H_{12}N_5S_2Cl$	Cl	H	S	337	70	161	46.32 (46.15	20.77 20.44	3.58 3.31	18.97 18.40)
3i	$C_{13}H_{12}N_6O_2S_2$	H	NO_2	S	348	72	150	44.86 (44.64	24.14 24.57	3.47 3.51	18.37 18.39)
3j	$C_{13}H_{13}N_5OS_2$	OH	H	S	319	82	130	48.93 (48.53	22.06 22.50	4.10 4.01	20.04 20.28)

Experimental section

Melting points are determined using open capillary method and are uncorrected. The compounds are checked for homogeneity by TLC on silica gel-G. The IR spectra are recorded on FT-IR Thermo Nicolet Avatar 370 spectrophotometer using KBr disc method. The ^{1}H and ^{13}C-NMR are recorded on Bruker Avance-III 400MHz FTNMR spectrometer using DMSO-d_6. Elemental analyses are recorded on Elemental Vario EL III instrument. The mass spectrums are recorded on Joel GC-mate spectrometer. All compounds given satisfactory micro analytical results. Pyrimidine (**1)** is prepared by reported method[27].



Scheme 1: Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-Phenyl pyrimidin-2(1*H*)-thione (3f-j).



Scheme 2: Synthesis of 5-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-thione (3f-j).

General Procedure

Synthesis of 5-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-thione 2f.

An equimolar mixture of compound1 (0.01mol) and thiosemicarbazide (0.01mol) with catalytic amount of acetone is irradiated in a domestic microwave oven (200W) for 2 minutes. The reaction mixture is allowed to cool and the obtained solid is recrystallized from ethanol. The compounds prepared in this manner (2f-j) are listed in Table 1. Melting point of the compound is 143^0C, yield 65%. ^{1}HNMR(400MHz,DMSO-d_6) δ2.292(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). ^{13}CNMR(400MHz,DMSO-d_6) δ17.47, 59.54, 100.75, 126.35, 127.62, 128.50, 143.47, 144.95, 165.10, 178.47, 183.94. FT-IR(KBr)3328, 3172, 3106(NH), 2999(Ar-H), 2936(CH), 1669(C=O), 1573(C=N), 1327(C-N), 1283(C=S), 1117(N-N)cm^{-1}. GCMS:*m/z* [321M$^+$].

General procedure for Synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-3,4-dihydro-6-methyl-4-henylpyrimidin-2(1*H*)-thione 3f.

The compound 2 (0.01mol) is dissolved with cooling in 4ml conc.H_2SO_4 and kept at room temperature for overnight, stirred it occasionally and then poured onto crushed ice then resulting suspension is kept in ammonical solution for 2hrs, filtered and recrystallized from ethanol as white crystals. The compounds prepared (3f-j) are listed in Table 2. Melting point 185^0C, Yield75%. ^{1}HNMR(400MHz,DMSO-d_6) δ2.301 (s,3H,CH_3), 4.030(s,2H,NH_2), 5.189(*J*=4Hz,d,1H,CH), 7.222-7.372(m,4H,Ar-H), 9.634(*J*=1.6 Hz,d,1H,NH), 9.074(s,1H,NH). ^{13}CNMR(400MHz,DMSO-d_6) δ17.12, 59.57, 100.75, 126.35, 127.65, 128.51, 143.44, 144.95, 165.12, 174.23. FT-IR(KBr)3328, 3174, 3106(NH), 3033(Ar-H), 2979(CH), 1574(C=N), 1384(C-N), 1282(C=S), 1195(C-S), 1001(N-N)cm^{-1}. GCMS:*m/z* [303M$^+$].

Synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl pyrimidin-2(1*H*)-thione 3g.

^{1}HNMR(400MHz,DMSO-d_6) δ2.301(s,3H,CH_3),4.027(s,2H,NH_2), 5.179(*J*=3.6Hz,d,1H,CH), 7.227-7.254(dd,2H,Ar-H), 7.419-7.440(dd,2H,Ar-H), 9.653(*J*=2Hz,d, 1H,NH), 10.369(s,1H,NH). ^{13}CNMR(400MHz,DMSO-d_6) δ17.14, 59.62, 100.30, 128.28, 128.54, 132.24, 142.34, 145.32, 164.97, 174.24. FT-IR(KBr)3327, 3174, 3104(NH), 3030(Ar-H), 2982(CH), 1573(C=N), 1380(C-N), 1281(C=S), 1196(C-S), 1092(N-N)cm^{-1}. GCMS:*m/z* [337M$^+$].

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methyl pyrimidin-2(1*H*)-thione 3h. ^{1}HNMR(400MHz,DMSO-d_6) δ2.284(s,3H,CH_3), 2.864(s, 6H,N(CH_3)$_2$), 4.018(s,2H,NH_2), 5.059(*J*=2.8Hz,d,1H,CH), 6.671(*J*=9.2Hz,d,2H,Ar-H), 7.024 (*J*=8.8Hz,d,2H,Ar-H), 9.515(*J*=3.2Hz,d,1H,NH), 10.202(s,1H,NH). ^{13} CNMR(400MHz,DMSO-d_6) δ17.07, 53.48, 59.43, 101.25, 112.16, 127.08, 131.18, 144.24, 149.93, 165.25, 173.84. FT-IR(KBr)3326, 3164(NH), 2982(Ar-H), 2882(CH), 1593(C=N), 1360(C-N), 1281(C=S), 1191(C-S), 1100(N-N)cm^{-1}. GCMS: *m/z* [346M$^+$].

Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl pyrimidin-2(1*H*)-thione 3i. ^{1}HNMR(400MHz,DMSO-d_6) δ2.301(s,3H,CH_3), 4.027(s,2H,NH_2), 5.342(*J*=2.8Hz,d,1H,CH), 7.236(*J*=8.4Hz,d,2H,Ar-H), 7.429(*J*=8.4Hz,d,2H,Ar-H), 7.682-7.856 (dd,2H,Ar-H), 8.165(*J*=2.4Hz,d,1H,NH), 9.655(s,1H,NH). ^{13}CNMR(400MHz,DMSO-d_6)δ17.83, 59.35, 99.35, 123.87, 130.07, 133.04, 134.40, 136.16, 149.38, 151.06, 165.83, 178.39.
FT-IR(KBr) 3424, 3326, 3176(NH), 3016(Ar-H), 2986(CH), 1593(C=N), 1343(C-N), 1296(C=S), 1193(C-S), 1102(N-N)cm^{-1}. GCMS: *m/z* [348M$^+$].

Synthesis of 5-(5-amino-1, 3, 4-thiadiazole-2-yl)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methyl pyrimidin-2(1*H*)-thione 3j. ^{1}HNMR(400MHz,DMSO-d_6) δ2.229(s,3H,CH_3), 4.014(s,2H,NH_2), 5.075(*J*=8.4Hz,d,1H,CH), 7.386-8.051(m,4H,Ar-H), 8.562(*J*=5.2Hz,d,1H,NH), 10.224(s,1H, NH), 11.221(s,1H,OH). ^{13}CNMR(400MHz,DMSO-d_6) δ17.06, 59.32, 90.20, 115.11, 115.51, 125.42, 127.86, 129.00, 134.36, 152.51, 164.92. FT-IR (KBr) 3545, 3187, 3134(NH), 3080(Ar-H), 2980(CH), 1511(C=N), 1329(C-N), 1285(C=S), 1186(C-S), 1113(N-N)cm^{-1}. GCMS:*m/z* [319M$^+$].

Antibacterial studies

Among the newly synthesized pyrimidine derivatives are screened for their antibacterial activity *in vitro* against the species of *Streptococcus faecalis (Gram +ve), Bacillus sps (Gram +ve) and Escherichia coli (Gram -ve)* using agar well disk diffusion method. The test compounds are dissolved in DMSO to get a solution of 50µg/ml concentration. The inhibition zones are measured in millimeters at the end of an incubation period of 18 hrs at 37^0C. Ciprofloxacin is used as a standard and the results are shown in Table 3. Most of the tested compounds show moderate to good inhibition.

Table 3: Antibacterial activities of compounds (3f-j)

Compound	Streptococcus faecalis(+ve)	Bacillus sps (+ve)	Escherichia coli(-ve)
Control	0	0	0
3f	7	7	6
3g	12	6	7
3h	7	8	6
3i	10	12	10
3j	9	14	14

Conclusion

The investigation of antibacterial screening data reveals that, all the tested compounds show moderate to good inhibition at 50µg/ml concentration. Especially the compounds 3g, 3i and 3j show very good activity than the others. However the activity is less compared to the standard drug.

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