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

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ABSTRACT

Simple synthetic methods of 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidine-2(1H)-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 oxadiazole **3** by treatment with NaOH follow by KI. Structural elucidation is accomplished by IR, ¹H and ¹³CNMR, 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, Oxadiazole, Carbothiamide, Antibacterial activity, Microwave.

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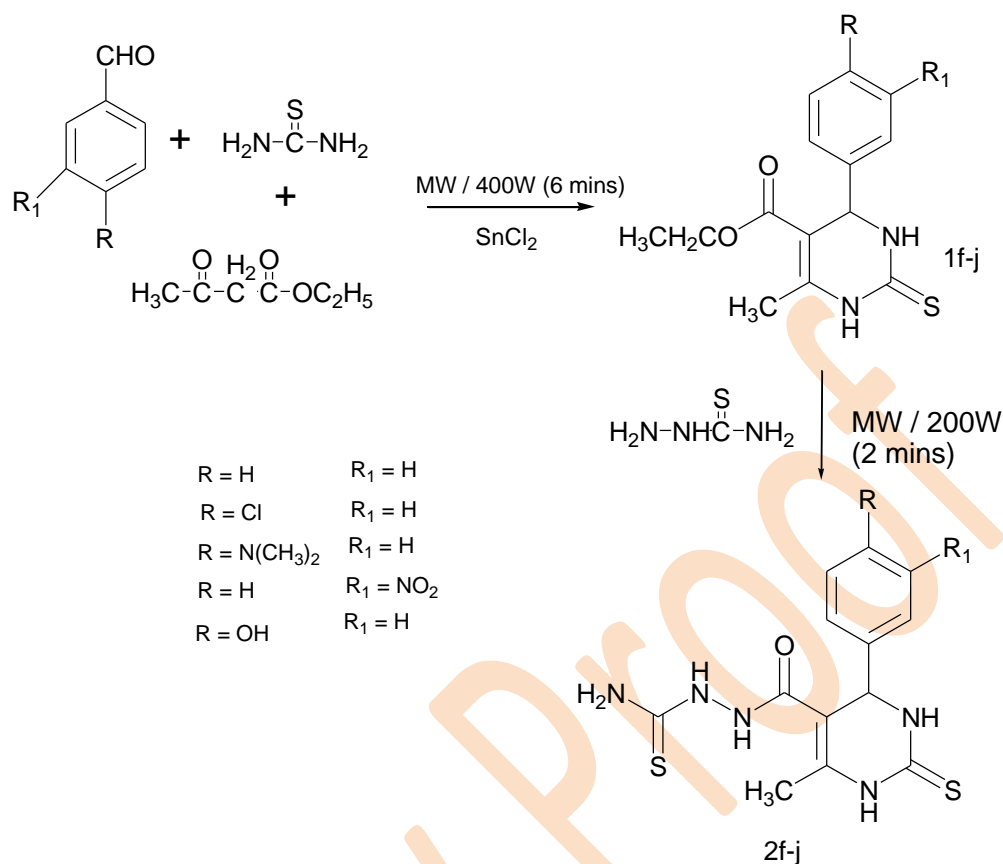
INTRODUCTION

Literature survey has revealed the importance of pyrimidine derivatives and antimicrobial agent¹, which are found to be associated with variety of biological activities such as insecticidal, antimicrobial, antiviral etc, pyrimidine derivatives²⁻⁸ 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 Angiolini⁹. 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 grouping¹⁰. In this direction the synthesis and pharmacological study of Mannich bases of 3-and 5-mercapto derivatives of 1,3,4-oxadiazole have been reported in literature¹¹⁻¹⁶. Further, pyrimidine, fused heterocyclic pyrimidine derivatives and dihydropyrimidones are well known for their potential biological activity such as antiviral, antitumor, antimicrobial fungicide, algacide and as antibiotics¹⁷⁻²⁶. 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-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidine-2(1H)-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 & ¹³CNMR spectral studies.

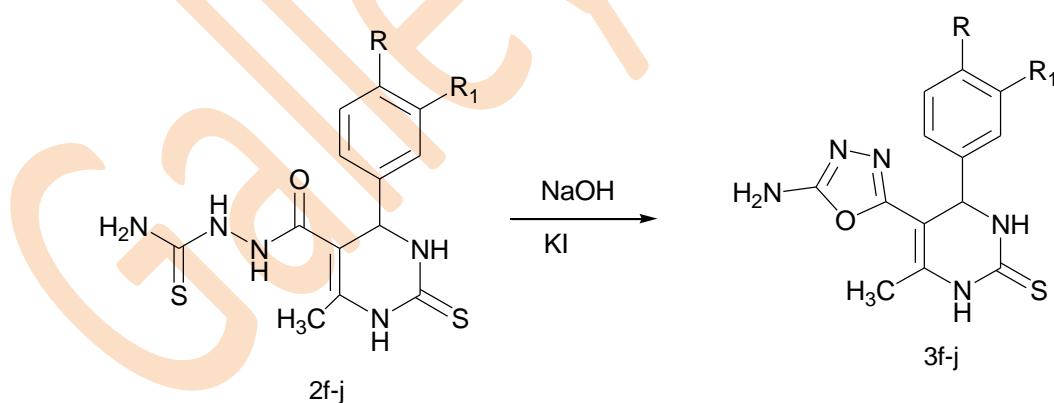
EXPERIMENTAL SECTION

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 ¹H and ¹³CNMR 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 method²⁷.



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



Scheme 2: Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidine-2(1H)-thione (3f-j).

RESULTS AND DISCUSSION

Compounds (3f-j) are synthesized as per the scheme 1 and 2. The compound 3a is prepared by reacting hydrazine carbothioamide compound 2f with NaOH follow by KI. Hydrazine

carbothioamide compound **2f** is synthesized by reacting pyrimidine ethyl ester **1** with thiosemicarbazide is irradiated in a domestic microwave oven (200W) for 2 minutes²⁹. 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 thiourea (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, ¹H and ¹³C-NMR, GC-MS and CHN analysis. Formation of compound **2f** is confirmed by the presence of N-H stretching peaks at 3365, 3241 cm⁻¹ and 3116 cm⁻¹ and C=S stretching peaks at 1219 cm⁻¹ in IR and singlet at δ 6.50 for NH₂ group in ¹HNMR spectra.

Treatment of compound **2f** with NaOH follow by KI, furnished 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidine-2(1H)-thione(**3f-j**). The structure of **3f** is elucidated on the basis of C-O-C linkage in the oxadiazole ring, which causes a sharp absorption band at 1027 cm⁻¹ in its IR spectrum. ¹H NMR spectrum showed a singlet at δ 4.023 due to NH₂ functionality confirmations of the structure **3f**.

The IR and ¹H NMR spectral data revealed C=S carbonyl absorption band at 1197 cm⁻¹ of NH-CO-NH group, N-N stretching band at 1117 cm⁻¹ aliphatic C-H and aromatic C-H stretching at 2969 cm⁻¹ and 3072 cm⁻¹ for pyrimidine moiety **3**. Mass spectrum also supports the proposed structure by viewing molecular ion peak at *m/z* 287 M⁺.

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

Compd	Mol. Formula	R	R ₁	X	Mol. Wt	Yield (%)	m.p (°C)	Calcld. /Found (%)			
								C	N	H	S
2f	C ₁₃ H ₁₅ ON ₅ S ₂	H	H	S	321	75	142-143	48.63 (48.46)	21.80 (21.97)	4.70 (4.55)	19.91 (20.10)
2g	C ₁₃ H ₁₄ ON ₅ ClS ₂	Cl	H	S	355	66	109-111	43.90 (43.41)	19.72 (19.42)	3.97 (4.09)	18.00 (18.06)
2h	C ₁₃ H ₁₅ O ₂ N ₅ S ₂	OH	H	S	337	78	117-119	46.32 (46.53)	20.77 (21.03)	4.47 (4.70)	18.96 (19.06)
2i	C ₁₅ H ₂₀ ON ₆ S ₂	N(CH ₃) ₂	H	S	364	74	147-149	49.47 (49.00)	23.08 (23.26)	5.49 (5.22)	17.56 (17.69)
2j	C ₁₃ H ₁₄ O ₃ N ₆ S ₂	H	NO ₂	S	366	60	124-126	42.65 (42.59)	22.95 (23.00)	3.85 (3.54)	17.46 (17.72)

Table 2: Physical and analytical data of compounds (3f-j)

Compd	Mol. Formula	R	R ₁	X	Mol.Wt	Yield (%)	m.p (°C)	Calcd. /Found (%)			
								C	N	H	S
3f	C ₁₃ H ₁₃ ON ₅ S	H	H	S	287	76	189-191	54.23 (54.38)	24.52 24.39	4.55 4.56	11.00 11.13
3g	C ₁₃ H ₁₂ ON ₅ Cl S	Cl	H	S	321	81	182-184	54.01 (54.57)	25.29 25.45	5.80 5.49	10.03 9.68
3j	C ₁₃ H ₁₃ O ₂ N ₅ S	OH	H	S	303	82	171-173	51.69 (51.52)	23.19 23.16	4.22 4.32	10.26 10.54
3h	C ₁₅ H ₁₈ ON ₆ S	N(CH ₃) ₂	H	S	330	68	147-149	48.81 (48.62)	21.97 21.80	3.24 3.76	10.33 9.95
3i	C ₁₃ H ₁₂ O ₃ N ₆ S	H	NO ₂	S	332	65	179-181	47.87 (47.02)	25.08 25.30	3.47 3.64	9.96 9.62

GENERAL PROCEDURE

Synthesis of 5-(hydrazine carbothioamide)-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1H)-thione (2f).

An equimolar mixture of compound **1** (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 140°C yield 85%. ¹HNMR (400MHz, DMSO-*d*₆) δ 2.251 (s, 3H), 5.152 (d, *J* = 3.2Hz, 1H), 6.501 (s, 2H), 7.213–7.336 (m, 5H), 7.702 (d, *J* = 2.8Hz, 1H), 8.175 (d, *J* = 6.4Hz, 2H), 9.149 (s, 1H); ¹³CNMR (400MHz, 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 (KBr) 3365, 3241, 3116 (NH), 3079 (Ar-H), 2978 (CH), 1724 (C=O), 1385 (C-N), 1219 (C=S), 1089 (N-N) cm⁻¹; GCMS: *m/z* 305 [M⁺]. Elemental Anal.(%) (C₁₃H₁₅O₂N₅S), Calculated; C 51.17, H 4.94, N 22.50, S 10.47. Found; C 51.10, H 4.85, N 22.24, S 10.94.

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

General procedure for Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-phenylpyrimidine-2(1H)-thione, (**3f**), for the compounds (**3f-j**) are listed in Table 2, carbothioamide **2** (0.01 mol) is added into 10% NaOH with cooling and shaking. Then Iodine solution in KI is added gradually and shaking until the Iodine color persisted. This reaction mixture is heated continuously for 5 hr and it is concentrated the residue, its cooled and poured onto ice cold water. This solution is filtered and acidified with 10% HCl to isolate the product. It is filtered and washed with cold water and little amount of CS₂ is added. The product is purified by recrystallization from alcohol. ¹H NMR(DMSO-*d*₆):δ 2.304(s,3H,CH₃), 4.029(s,2H,NH₂), 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); ^{13}C 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(KBr): 3328, 3172(NH), 3072(Ar-H), 2969(CH), 1573(C=N), 1370(C-N), 1197(C=S), 1117(N-N), 1027 cm^{-1} (C-O); GCMS: m/z [287 M^+].

Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-6-methyl pyrimidine-2(1H)-thione (3g): ^1H NMR(DMSO- d_6): δ 2.297(s,3H, CH_3), 4.022(s,2H, NH_2), 5.171($J=3.6$ Hz,d,1H,CH), 7.222-7.258(dd,2H,Ar-H), 7.424-7.453(dd,2H,Ar-H), 9.645($J=2$ Hz,d,NH), 10.361(s,1H,NH); ^{13}C 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(KBr): 3437, 3327, 3171(NH), 3104(Ar-H), 2982(CH), 1573(C=N), 1334(C-N), 1197(C=S), 1092(N-N), 1030 cm^{-1} (C-O); GCMS: m/z [321 M^+].

Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-4-(4-hydroxyphenyl)-6-methylpyrimidine-2(1H)-thione (3h): ^1H NMR(DMSO- d_6): δ 2.279(s,3H, CH_3), 3.994 (s,2H, NH_2), 5.066($J=3.6$ Hz,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($J=1.6$ Hz,d,1H,NH), 10.216(s,1H,NH); ^{13}C 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(KBr): 3477(OH), 3325, 3171, 3104(NH), 2985(Ar-H), 2903(CH), 1597(C=N), 1315(C-N), 1196(C=S), 1083(N-N), 1027 cm^{-1} (C-O); GCMS: m/z [303 M^+].

Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methylpyrimidine-2(1H)-thione (3i): ^1H NMR(DMSO- d_6): δ 2.285(s,3H, CH_3), 2.933(s,6H, $\text{N}(\text{CH}_3)_2$), 4.018(s,2H, NH_2), 5.104($J=3.6$ Hz,d,1H,CH), 7.022($J=8.8$ Hz,d, 2H,Ar-H), 7.114-7.463(m,2H,Ar-H), 9.561($J=1.6$ Hz,d,1H,NH), 10.253(s,1H,NH); ^{13}C 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(KBr): 3482, 3326, 3173(NH), 3032(Ar-H), 2981 (CH), 1576(C=N), 1329(C-N), 1182(C=S), 1117(N-N), 1022 cm^{-1} (C-O); GCMS: m/z [330 M^+].

Synthesis of 5-(5-amino-1,3,4-oxadiazol-2-yl)-3,4-dihydro-6-methyl-4-(3-nitrophenyl) pyrimidin-2(1H)-thione (3j): ^1H NMR(DMSO- d_6): δ 2.323(s,3H, CH_3), 4.033(s,2H, NH_2), 5.339($J=4$ Hz,d,1H,CH), 7.663-7.696(dd,2H,Ar-H), 8.081-8.242(m,3H,Ar-H), 9.757($J=1.2$ Hz,d, 1H,NH), 10.493(s,1H,NH); ^{13}C 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(KBr): 3437, 3179(NH), 3027(Ar-H), 2988(CH), 1532(C=N), 1344(C-N), 1189(C=S), 1102(N-N), 1039 cm^{-1} (C-O); GCMS: m/z [332 M^+].

ANTIBACTERIAL STUDIES

Among the newly synthesized pyrimidine derivatives are screened for their antibacterial activity *in vitro* against the species of *Streptococcus faecalis*, *Bacillus sps* and *Escherichia coli*, using agar well disk diffusion method. The test compounds are dissolved in DMSO to get a solution of 10µg/mL concentration. The inhibition zones are measured in millimeters at the end of an incubation period of 18 hrs at 37⁰C. 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	10	8	7
3g	5	18	7
3h	3	8	6
3i	8	14	6
3j	4	12	6

CONCLUSION

The investigation of antibacterial screening data reveals that, all the tested compounds show moderate to good inhibition at 10µg/ml concentration. Especially, the compound **3f** and **3g** shows very good activity than the others and also the compound **3i** show moderate inhibition against all the three species.

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