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Microwave assisted synthesis and antifungal studies of 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*)-one**(3a-e)** 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, ^{1}H 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 antifungal activity. Most of the tested compounds show significant antifungal activity.

Keywords: Pyrimidine, Thiadiazole, Carbothiamide, Thiosemicarbazide, Antifungal activity.

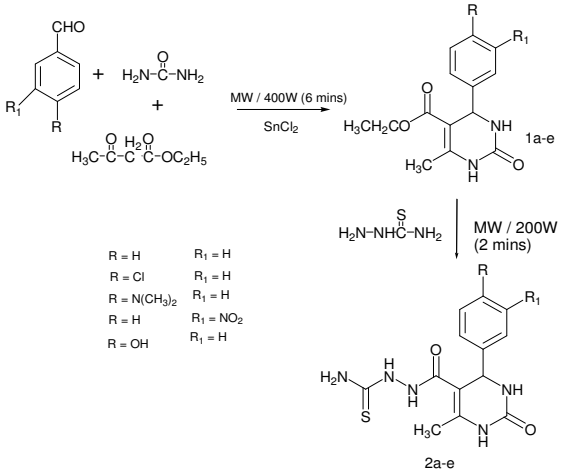
1. INTRODUCTION

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 1,3,4-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 [17-26]. 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 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*)-one **(3a-e)** against the species of *Candida tropicalis,Aspergillusterreus, Penicilliumsps*and Amphotericin-Bis used as standard drug. For this purpose, heterocyclic precursors DHPMs (1a-e) 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 (2a-e). All the synthesized compounds are characterized by using elemental analysis, mass spectra, ^{1}H&^{13}CNMR spectral studies.

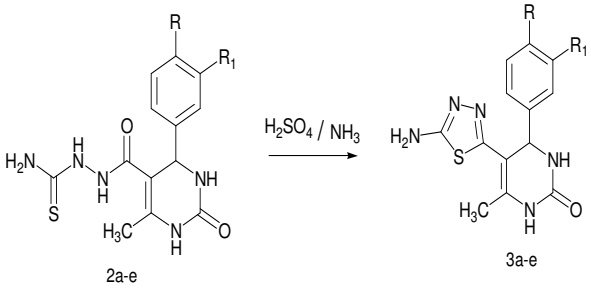
2. EXPERIMENTAL

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-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin -2(1*H*)-one (2a-e).



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

3. RESULTS AND DISCUSSION

Compounds (3a-e) are synthesized as per the scheme 1 and 2. The compound **3a** is prepared by reacting hydrazine carbothioamide compound **2a** with conc.H_2SO_4 and NH_3. Hydrazine carbothioamide compound **2a** 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 **1a** prepared by a mixture of aromatic aldehyde (0.01m), ethylacetoacetate (0.01m) and urea (0.01m) 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 **2a** is 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 δ6.50 for NH_2 group in ^{1}HNMR spectra.

Treatment of compound 2a 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**(3a-e).** The structure of **3a** is elucidated on the basis of C-S linkage in the thiadiazole ring, which causes sharp absorption band at 1225 cm^{-1} in its IR spectrum. ^{1}HNMR spectrum shows a singlet at δ4.00 due to NH_2 functional group of **3a**.

The IR spectral data reveal the carbonyl absorption band at 1689 cm^{-1} of NH-CO-NH group, N-N stretching band at1098 cm^{-1} aliphatic C-H and aromatic C-H stretching at 2976 cm^{-1} and 3027 cm^{-1} group of pyrimidine moiety **3a**. Mass spectrum also supported the proposed structure by viewing molecular ion peak at *m/z* 287 $M^{+\cdot}$.

3.1. General Procedure

3.1.1. Synthesis of 5-(hydrazine carbothioamide)-3,4-dihydro-6-methyl-4-phenylpyrimidin-2(1*H*)-one2a

An equimolar mixture of compound1 (0.01m) and thiosemicarbazide (0.01m) 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 (2a-e) are listed in Table1. Melting point of the compound is 140^{0}C yield 85%. ^{1}HNMR (400 MHz, 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); ^{13}CNMR (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.(%) ($C_{13}H_{15}O_2N_5S$), 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.

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

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 (3a-e) are listed in Table 2.Melting point 175^{0}c, Yield 92%. ^{1}HNMR(400MHz, DMSO-d_6) δ2.258 (s, 3H, CH_3), 4.004 (s, 2H, NH_2), 5.159 (J= 3.2Hz, d, 1H, CH),7.227-7.347 (m,5H, Ar-H), 7.701 (*J*=2Hz, d, 1H, NH), 9.151 (s, 1H, NH).^{13}CNMR(400MHz, DMSO-d_6) δ 17.03, 59.15, 99.30, 126.20, 127.20, 128.34, 144.82, 148.27, 152.10, 165.32. FT-IR(KBr) 3354, 3227, 3110 (NH), 3027 (Ar-H), 2976 (CH), 1689 (C=O), 1460(C=N), 1225 (C-S), 1378 (C-N), 1098 (N-N)cm^{-1}. GCMS: *m/z*[287 M$^+$].

3.1.3. Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-chlorophenyl)-3,4-dihydro-6-methylpyrimidin-2(1*H*)-one 3b.

^{1}HNMR(400MHz, DMSO-d_6) δ2.257(s, 3H, CH_3), 4.003 (s, 2H, NH_2), 5.154 (*J*= 3.2Hz, d, 1H,CH),7.247-7.274 (dd,2H, Ar-H), 7.379- 7.413 (dd, 2H, Ar-H) 7.738 (*J*= 3.2Hz, d, 1H, NH), 9.209 (s, 1H, NH). ^{13}CNMR (400MHz, DMSO-d_6) δ17.75, 59.21, 98.88, 126.15, 128.33,131.78, 143.75,148.63, 151.93, 165.18. FT-IR(KBr) 3542, 3242, 3114 (NH), 3037 (Ar-H), 2977 (CH), 1713(C=O), 1529 (C=N), 1290 (C-N), 1223 (C-S), 1089 (N-N)cm^{-1}. GCMS:*m/z*[322 M$^+$].

3.1.4. Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-(dimethylamino)phenyl)-3,4-dihydro-6-methylpyrimidin-2(1*H*)-one 3c.

^{1}HNMR (400MHz, DMSO-d_6) δ 2.238 (s, 3H, CH_3), 2.856 (s, 6H, $N(CH_3)_2$), 3.996 (s, 2H,NH_2), 5.048(*J*=3.2Hz, d, 1H, CH), 6.660(*J*=8.8Hz,d,2H, Ar-H), 7.048 (*J*=8.4Hz,d, 2H, Ar-H), 7.556(2.4Hz, d, 1H, NH), 9.053 (s, 1H, NH). ^{13}CNMR(400MHz, DMSO-d_6) δ17.68, 53.30,59.04, 99.94,112.19, 126.85, 132.62, 147.46, 149.74, 152.27, 165.46. FT-IR(KBr) 3357,3242, 3110 (NH), 3018 (Ar-H), 2977 (CH), 1721 (C=O), 1526 (C=N), 1221(C-S), 1093 (N-N)cm^{-1}.GCMS: *m/z* [331 M$^+$].

Table - 1: Physical and analytical data of compounds (2a-e)

Compd.	Mol. Formula	R	R_1	X	Mol. Wt	Yield (%)	m.p (^{0}C)	Calcd. /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)

Table - 2: Physical and analytical data of compounds (3a-e)

Compd	Mol. Formula	R	R_1	X	Mol. Wt	Yield (%)	m.p (^{0}C)	Calcld./Found (%)			
								C	N	H	S
3a	$C_{13}H_{13}N_5OS$	H	H	O	287	92	175	54.38 (54.35	24.39 24.64	4.56 4.56	11.13 11.68)
3b	$C_{13}H_{12}N_5OSCl$	Cl	H	O	321	85	170	48.63 (48.28	21.80 21.79	3.76 3.50	9.95 6.68)
3c	$C_{15}H_{18}N_6OS$	$N(CH_3)_2$	H	O	330	86	210	54.57 (54.34	25.45 25.67	5.49 5.60	9.96 9.62)
3d	$C_{13}H_{12}N_6O_3S$	H	NO_2	O	332	82	162	47.02 (47.51	25.30 25.85	3.64 3.88	9.62 9.21)
3e	$C_{13}H_{13}N_5O_2S$	OH	H	O	303	83	220	51.51 (51.11	23.10 23.02	4.32 4.89	10.54 10.07)

Table - 3: Antifungal activities of compounds (3a-e)

Compound	Candida tropicalis	Penicilliumsps	Aspergillusterreus
Control	0	0	0
3a	6	-	21
3b	24	9	25
3c	12	5	13
3d	8	6	15
3e	9	8	10

3.1.5. Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(3-nitrophenyl)-3,4-dihydro-6-methyl pyrimidin-2(1*H*)-one 3d

^{1}HNMR(400MHz, DMSO-d_6) δ2.066(s, 3H, CH_3), 3.805 (s, 2H, NH_2), 5.098(*J*=3.2Hz,d, 1H,CH),7.036-7.802 (m, 4H, Ar-H), 8.482 (*J*=3.2Hz, d, 1H, NH), 9.126 (s, 1H, NH).^{13}CNMR(400MHz, DMSO-d_6) δ 17.81, 59.35, 98.35, 122.29, 123.87, 132.94, 133.40, 146.96, 147.73,148.38,149.36, 165.03, 178.39. FT-IR(KBr) 3429, 3396, 3245 (NH), 3153 (Ar-H), 2980 (CH), 1705 (C=O), 1526 (C=N), 1348 (C-N), 1294 (C-S), 1094 (N-N)cm^{-1}. GCMS: *m/z*[332 M$^+$].

3.1.6. Synthesis of 5-(5-amino-1,3,4-thiadiazole-2-yl)-4-(4-hydroxyphenyl)-3,4-dihydro-6-methylpyrimidin-2(1*H*)-one 3e

^{1}HNMR (400MHz, DMSO-d_6) δ 2.237(s, 3H, CH_3), 3.991 (s, 2H, NH_2),5.051(*J*=3.2Hz, d, 1H,CH),6.887-7.115 (m, 4H, Ar-H), 7.563 (*J*=1.6Hz, d, 1H, NH), 9.074 (s, 1H, NH), 10.296(br,1H, OH). ^{13}CNMR(400MHz, DMSO-d_6) δ17.69, 59.08, 99.79, 114.97, 127.36, 129.67, 135.22,147.65, 155.32, 156.51, 165.40.

FT-IR(KBr) 3607 (OH), 3429, 3396, 3245 (NH), 3030(Ar-H), 2980 (CH), 1705 (C=O), 1526 (C=N), 1348 (C-N), 1294 (C-S), 1094 (N-N)cm^{-1}. GCMS: *m/z*[303 M$^+$].

3.2. Antifungal studies

Among the newly synthesized pyrimidine derivatives are screened for their antifungal activity *in vitro*against the species of *Candida tropicalis, Aspergillus terreus and Penicillium spps*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 18hrs at 37^{0}C. Amphotericin-Bis used as a standard and the results are shown in table 3. Most of the tested compounds show moderate to good inhibition.

4. CONCLUSION

The investigation of antifungal screening data reveals that, all the tested compounds show moderate to good inhibition at 50µg/mL concentration. Especially, the compound 3b shows very good activity than the others. However the activity of compound 3a, 3b, 3c and 3d against *Aspergillus terreus* inhibition is more compared to the standard drug.

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