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Novel and Environmental Friendly Synthesis of 4- [Phenyl amino] 6- methyl 2 - (Aza)1,3 pyrimidine and its Biological Activity

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ABSTRACT

The present work includes the synthesis of novel 4- [Phenyl amino] 6- methyl 2 - (Aza)1,3 pyrimidine by condensation of substituted primary amine and ethyl acetoacetate at 140^{0}C to form analides as intermediate. These intermediates on further reaction with guanidine hydrochloride using ethanol as solvent and converted into pyrimidines. This multicomponent reaction is of much importance due to excellent pharmacological properties of pyrimidines. The method used for the synthesis was ecofriendly and carried out in absence of solvent. Completion of reaction was confirmed by Thin layer chromatography technique. Elemental analysis, mass spectroscopy and FT-IR spectroscopy were used to characterize the prepared compounds. The antibacterial activities of the synthesized compounds were screened against standard strains of Gram positive and Gram negative bacteria using the Agar plate diffusion technique. Most of the studied compounds showed promising activities against different strains of gram positive and gram negative bacteria.

Key words: Pyrimidines compounds, Nitroso and benzoyl derivatives, antimicrobial activity, Gram positive and Gram negative strains.

INTRODUCTION

Now a days, chemists are used to carry out green synthesis by using solvent and catalyst, which are not harmful to environment. Organic reactions carried without solvent or with water have attracted much more attention, because of its usefulness, as a cheap, safe and environmental friendly solvent.

Pyrimidines does not exist in nature but in the form of its different derivatives are formed as a part of many complex systems like genetic material. Compounds containing pyrimidine ring play an important role in many biological systems, such as vitamins, several coenzymes and antibiotics where they exist in nucleic acids [1]. Pyrimidine compounds are also used as hypnotic drugs for the nervous system [2]

Pyrimidines become increasingly important mainly due to their stability, ease of preparation, structural variability and variety of applications. It has been observed that several pyrimidine derivatives shows anti-inflammatory [3] , antibacterial [4], herbicidal activities [5], anti-microbial [6], analgesic, anti-viral, anti-inflammatory [7], anti-HIV[8] , anti-tubercular [9], anti-tumour [10], anti-neoplastic [11] , anti-malarial [12], diuretic [13], cardiovascular [14] agents etc.

Keeping this in view we have synthesized new and ecofriendly pyrimidine derivatives by using facile methodology and tested them for their antibacterial activities. Pyrimidines were synthesised by the reaction of 1, 3-diketones with primary aromatic amine (According to Paal- Knorr Synthesis) and guanidine hydrochloride. The Nitroso and Acetyl derivatives of these compounds are also prepared [15, 16].

MATERIALS AND METHODS

All chemicals used for the synthesis were of analytical grade. H NMR spectra were recorded on BRUKER
AVANCE II 400 NMR Spectrometer. IR spectra were recorded by using AFFINITY-1 FTIR SPECTROPHOTOMETER. Melting points were determined by using INDO Melting Point M-AB-92 apparatus and were uncorrected. Purity of compounds and completion of reactions were checked by thin layer chromatography (TLC). The crude compounds were purified by recrystallization from ethanol. Mass spectra were also recorded.

Section A: Synthesis of 1-(N-phenyl-carboxamido)-propan-2-one:-

An equimolar (0.01 M) mixture of substituted primary amine and ethyl acetoacetate in ethanol (99% pure ethanol) was refluxed for 6-8 hrs. The reaction mixture was cooled and poured onto crushed ice while stirring continuously. Resultant solid was filtered, washed thoroughly with cold water, dried and purified by recrystalisation from ethanol to form **IIIa**. Similarly **(IIIb – IIIf)** were synthesised by above method.

NMR:[IIIa] Ar-H=δ(7.03 to 7.26ppm), NH=δ(9.21ppm), CH2= δ(3.59ppm),-CH3=δ(2.33ppm), OCH3=δ(3.87ppm)

Section B: Synthesis of 4-[amino phenyl]-5-methyl pyrimidines :-

1-[N-(2 methoxy phenyl)-carboxamido]-propan-2-one (IIIa) and guanidine hydrochloride (IV) refluxed together using alcohol as a solvent for

4-5 hrs. Neutralise the solution by addition of small amount of HCl. After completion of the reaction, the mixture was allowed to cool and pour it on crushed ice with constant stirring, which afforded crystalline solids. It was recrystallised with ethanol, m.p. 76^{0}C. Similarly compounds **(Vb – Vf)** were synthesised.

Table 1: Physical data of synthesised pyrimidines (Va to Vf)

SrNo	1-(N-phenyl-carboxamido)-propan-2-one **(III)**	4- [Phenyl amino] 6- methyl 2 -(Aza)1,3 pyrimidine **(V)**	MOL. FORMULA	MP (°C)	YIELD (%)	ELEMENTAL ANALYSIS			
						C	H	N	O
1	1-[N-(2 methoxy phenyl)-carboxamido]-propan-2-one **(IIIa)**	4- [2 methoxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Va)**	$C_{12}H_{14}N_4O$	76	82	61.88 (62.60)	5.67 (6.08)	23.56 (24.34)	6.14 (6.95)
2	1-[N-(3 methoxy phenyl)-carboxamido]-propan-2-one **(IIIb)**	4- [3 methoxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Vb)**	$C_{12}H_{14}N_4O$	110	78	61.45 (62.60)	5.26 (6.08)	23.78 (24.34)	6.56 (6.95)
3	1-[N-(4 methoxy phenyl)-carboxamido]-propan-2-one **(IIIc)**	4- [4 methoxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Vc)**	$C_{12}H_{14}N_4O$	76	86	62.21 (62.60)	5.21 (6.08)	24.01 (24.34)	6.38 (6.95)
4	1-[N-(2 hydroxy phenyl)-carboxamido]-propan-2-one **(IIId)**	4- [2 hydroxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Vd)**	$C_{11}H_{12}N_4O$	174	63	60.08 (61.11)	5.34 (5.55)	24.46 (25.92)	6.77 (7.40)
5	1-[N-(3 hydroxy phenyl)-carboxamido]-propan-2-one **(IIIe)**	4- [2 hydroxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Ve)**	$C_{11}H_{12}N_4O$	>300	80	59.98 (61.11)	4.85 (5.55)	23.18 (25.92)	6.80 (7.40)
6	1-[N-(4 hydroxy phenyl)-carboxamido]-propan-2-one **(IIIf)**	4- [2 hydroxy Phenyl amino] 6-methyl 2 (Aza) 1,3 pyrimidine **(Vf)**	$C_{11}H_{12}N_4O$	204	75	60.21 (61.11)	5.71 (5.55)	24.76 (25.92)	7.91 (7.40)

Analytical results (NMR & IR):

(1) 4- [2 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Va) : Ar-H=δ(6.87 to 7.07ppm), NH=δ(9.43 ppm), -CH= δ(3.47ppm),-CH_3=δ(2.22ppm), -OCH_3=δ(3.47ppm) ; IR: Ar-OCH_3Str = 1035.84 cm-1, N-H Str.=3282.02 cm-1, C=N Str. =1532.51cm-1, C-N Str. =1329.01 cm-1, C=O Str. = 1712.86 cm-1.

(2) 4- [3 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Vb) : Ar-H=δ (6.48 to 6.96 ppm), NH=δ (9.48ppm), -CH= δ (3.43ppm),-CH_3=δ (2.18ppm), -OCH_3=δ(3.49ppm)

; IR: Ar-OCH_3Str = 1065.04 cm-1, N-H Str.=3078.21 cm-1, C=N Str. =1526.23cm-1, C-N Str. =1350.17 cm-1, C=O Str. = 1731.46 cm-1

(3) 4- [4 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Vc) : Ar-H=δ (7.04 to 7.07 ppm), NH=δ (9.33ppm), -CH= δ (3.34 ppm), -CH_3=δ (2.06 ppm), -OCH_3=δ (3.66 ppm)

; IR: Ar-OCH_3Str = 1053.32 cm-1, N-H Str.=3065.68 cm-1, C=N Str. =1518.10cm-1, C-N Str. =1344.57 cm-1, C=O Str. = 1720.93 cm-1

(4) 4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Vd): Ar-H=δ (6.85 to 7.12ppm), NH=δ (9.08ppm), -CH= δ (3.34ppm),-CH_3=δ (2.24ppm), -OH=δ (9.24ppm)

; IR: Ar-OCH_3Str = 1016.98 cm-1, N-H Str.=3287.51 cm-1, C=N Str. =1520.45cm-1, C-N Str. =1362.37 cm-1, C=O Str. = 1731.23 cm-1

(5) 4- [3 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Ve) : Ar-H=δ(6.83 to 7.14ppm), NH=δ(9.13 ppm), -CH= δ(3.58 ppm),-CH_3=δ(2.13 ppm), -OH=δ(9.53 ppm)

; IR: Ar-OCH_3Str = 1043.26 cm-1, N-H Str.=3071.71 cm-1, C=N Str. =1534.53cm-1, C-N Str. =1376.17 cm-1, C=O Str. = 1745.87 cm-1

(6) 4- [4 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine (Vf) : Ar-H=δ(6.67 to 7.32ppm), NH=δ(9.04ppm), -CH= δ(3.66ppm),-CH_3=δ(2.21ppm), -OH=δ(9.76 ppm)

; IR: Ar-OCH_3Str = 1027.56 cm-1, N-H Str.=3066.13cm-1, C=N Str. =1521.90cm-1, C-N Str. =1355.57 cm-1, C=O Str. = 1712.43 cm-1

Section C: Derivatives of pyrimidines:

a) *Nitroso derivative of pyrimidines*:-

Va, Vb, Vc, Vd, Ve, Vf (0.01 M) was made into solution with conc. HCl. Cool this solution at 0-5° C. To this acidic solution 5ml of 20% sodium nitrite was added with continuous stirring. The reaction mixture was allowed to stand for half an hrs for completion of reaction. It was filtered through Buchner funnel and washed with water [17 – 18] . Recrystalised with ethanol to form **VIa –VIf**. Physical data were shown in Table 2.

Table 2: Physical data of synthesised Nitroso derivatives of pyrimidines (VIa to VIf)

Sr No	4- [Phenyl amino] 6- methyl 2 - (Aza) 1,3 pyrimidine	4- [Phenyl amino] 6- methyl 2 - (Aza) 3 Nitroso pyrimidine	MOL. FORMULA	MP (°C)	ELEMENTAL ANALYSIS			
					C	H	N	O
1	4- [2 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{12}H_{13}N_5O_2$	156	54.68 (55.59)	4.73 (5.01)	26.96 (27.02)	11.82 (12.35)
2	4- [3 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [3 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{12}H_{13}N_5O_2$	128	54.93 (55.59)	4.28 (5.01)	26.83 (27.02)	12.08 (12.35)
3	4- [4 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [4 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{12}H_{13}N_5O_2$	120	55.12 (55.59)	5.38 (5.01)	26.48 (27.02)	11.66 (12.35)
4	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{11}H_{11}N_5O_2$	112	53.18 (53.87)	4.13 (4.48)	28.62 (28.57)	13.28 (13.06)
5	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{11}H_{11}N_5O_2$	187	53.29 (53.87)	4.22 (4.48)	28.36 (28.57)	12.94 (13.06)
6	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Nitroso pyrimidine	$C_{11}H_{11}N_5O_2$	146	53.63 (53.87)	4.04 (4.48)	28.47 (28.57)	12.77 (13.06)

b) *Benzoyl derivative of pyrimidines*:

Va, Vb, Vc, Vd, Ve, Vf (0.01 M) of compound was mixed with NaOH solution .The reaction mixture was cooled on ice bath. Approximately 2ml Benzoyl Chloride was added drop wise and shake. Allow the reaction mixture to settle down. Filter the mixture [19-20] .Recrystallised with ethanol to form **VIIa – VIIf**. Physical data were shown in Table 3.

Table 3: Physical data of synthesised Benzoyl derivatives of pyrimidines (VIIa to VIIf)

Sr.No	4- [Phenyl amino] 6-methyl 2 - (Aza) 1,3 pyrimidine	4- [Phenyl amino] 6-methyl 2 - (Aza) 3 Benzoyl pyrimidine	MOL. FORMULA	MP (°C)	ELEMENTAL ANALYSIS			
					C	H	N	O
1	4- [2 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{18}H_{17}N_4O_2$	128	65.79 (67.28)	6.03 (5.29)	17.12 (17.44)	9.65 (9.96)
2	4- [3 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [3 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{18}H_{17}N_4O_2$	120	66.62 (67.28)	5.73 (5.29)	17.24 (17.44)	9.42 (9.96)
3	4- [4 methoxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [4 methoxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{18}H_{17}N_4O_2$	118	66.86 (67.28)	5.77 (5.29)	17.18 (17.44)	9.73 (9.96)
4	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{17}H_{15}N_4O_2$	86	65.23 (66.44)	4.43 (4.88)	18.11 (18.24)	10.21 (10.42)
5	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{17}H_{15}N_4O_2$	138	65.78 (66.44)	4.62 (4.88)	18.08 (18.24)	9.79 (10.42)
6	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 1,3 pyrimidine	4- [2 hydroxy Phenyl amino] 6- methyl 2 (Aza) 3 Benzoyl pyrimidine	$C_{17}H_{15}N_4O_2$	92	66.13 (66.44)	4.71 (4.88)	18.30 (18.24)	10.13 (10.42)

Section D: Antimicrobial Activity:

Preparation of sample:

0.001 g/ 1 mg was taken and dissolved in 1 ml of DMSO.

Preparation of inoculums:

Stock cultures were maintained at 4oC on slants of nutrient agar. Active cultures of experiment were prepared by transferring a loop full of cells from the stock cultures to test tube of Muller-Hinton broth (MHB) for bacteria that were incubated for 24 hrs at 37°C .

Screening of Bacteria:

The disk diffusion method was used for antimicrobial activity. The nutrient agar were poured in Petri plates and allowed it to solidify. The above prepared microbial cultures were spread uniformly on the surface of the agar. The diffused disks of each sample are placed on the agar. Plates were then incubated at 37°C for 24hrs [21-23] .

Antimicrobial results were shown in Table 4.

Table 4: Results of Antimicrobial Testing for Synthesised compounds (Va to Vf)

Results of antimicrobial activity of synthesised pyrimidines were graphically represented as shown in figure 1.

Name of Organism	Zone of Inhibition in mm					
	Va	Vb	Vc	Vd	Ve	Vf
Salmonella typhi	16	--	24	26	28	18
Staphylococcus aureous	20	28	24	24	18	18
Bacillus subtilis	18	32	20	16	24	20
Klebsiella shigella	24	24	28	--	36	24
Proteus vulgaris	24	28	18	24	34	24

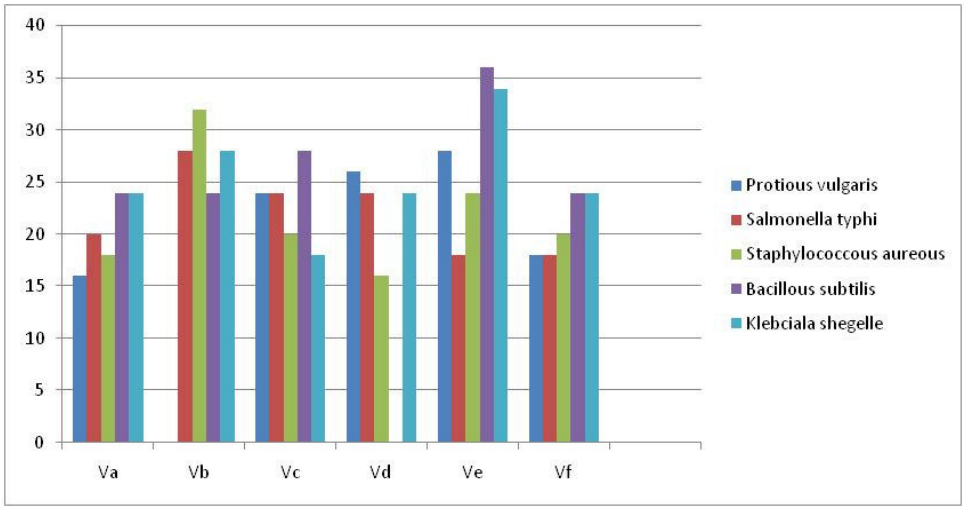

Figure 1: Graphical representation of Antimicrobial Activity Results

RESULTS AND DISCUSSION

Novel 4- [Phenyl amino] 6- methyl 2 -(Aza)1,3 pyrimidine were synthesised according to procedure explained above in experimental section. Structural Conformations were carried out by H NMR, IR and Mass spectroscopic data. Simultaneously, Nitroso and benzoyl derivatives also prepared by simple techniques.

Antimicrobial activities of some synthesised compounds were determined by Agar Plate diffusion technique. Compounds were examined for antimicrobial activities against gram +ve and gram –ve strains. The diameter of inhibition zone around each disc was measured in mm. Results shows, various compounds gives good antimicrobial activity for selected gram +ve and gram –ve strains. In feature these pyrimidines and its derivatives are used as drugs. Similarly further studies were carried out for other strains of organisms.

CONCLUSION

Novel pyrimidines were successfully synthesised via multicomponent reaction starting from primary amines and ethyl acetoacetate. These compounds were ecofriendly, non-hazardous and biologically active. From antimicrobial results we can conclude that, these substituted pyrimidines were most useful in medicinal chemistry and further studies in pharmaceutical and microbiological studies.

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