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Synthesis, Characterization and Antimicrobial Evaluation of Some Pyrimidine Containing Mannich and Schiff bases

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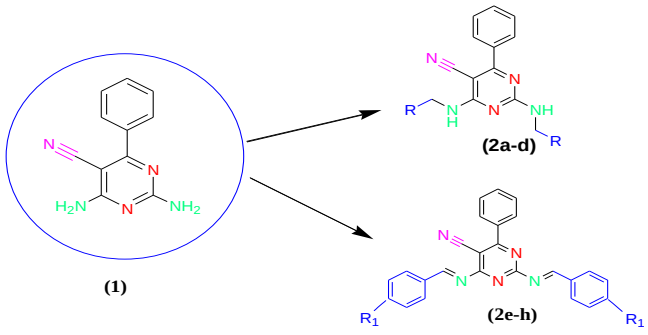
ABSTRACT

*The objective of this work is directed to synthesis of novel Mannich base and Schiff base compounds containing a pyrimidine unit. Compound **1** was prepared by one pot method using aromatic aldehyde, malanonitrile and guanidine nitrate in presence of piperidine to give 2,4-diamino-6-phenylpyrimidine-5-carbonitrile **1**. Compound **1** on reaction with secondary amines (Piperidine, morpholine, piperazine, diphenyl amine) and formaldehyde produced Mannich base **2a-d** and with different benzaldehyde using drops of glacial acetic acid as a catalyst gave Schiff bases **2e-h**. All the synthesized compounds were screened for antimicrobial activity. The structures of newly synthesized compounds were characterized by spectral and elemental analysis.*

Graphical abstract



Keywords: Pyrimidine, Schiff base, Mannich base, Antimicrobial activity.

INTRODUCTION

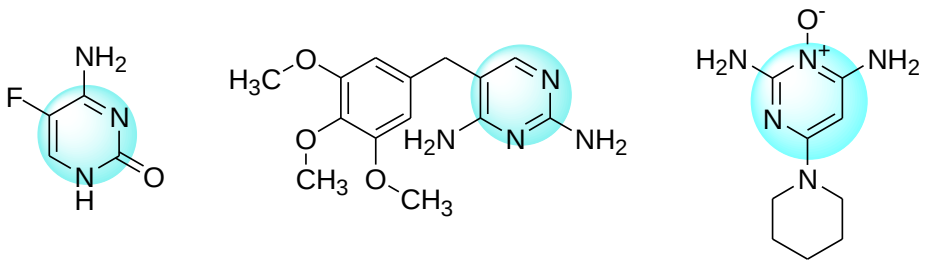
Among the nitrogen containing heterocycles pyrimidines represent a pharmaceutically important class of compounds. The pyrimidine centre has been widely studied due to its presence in numerous natural products and structurally diverse synthetic derivatives. The review of literature indicated that compound

having pyrimidine nucleus have wide range of biological activity like Flucytosine **(a)** as antifungal, Trimethoprim **(b)** as antibacterial, Minoxidil **(c)** as antihypertensive and anticonvulsant **(Figure1)**. Pyrimidine derivatives possess several interesting biological activities such as anti HIV [1], anti-tubercular, antitumor [2-3], anti-inflammatory [4-6], antimicrobial [7-10], antiviral [11], antioxidant [12] and antihistamic [13].

The chemistry of the amino alkylation of aromatic substrates by the Mannich reaction is of great interest for the synthesis and modification of biologically active compound having physical and chemical importance because the amino group can be easily converted into a variety of other functionalities. Mannich reaction offers a judicious method for introduction of basic aminoalkyl chain in various drugs and compounds. Mannich bases have gained importance due to their application in pharmaceutical chemistry. They have been encountered with anticancer [14-15], antimicrobial [16-20], anti-inflammatory [21], anticonvulsant [22-23], antioxidant [24] antitubercular [25-26] antimalarial [27] and antiproliferative activities [28]. They can also serve as anticolinsterase agent [29].

Schiff bases have been playing vital roles in the preparation of a large number of industrial and biologically active compounds via cycloaddition, and replacement reactions. They are also known for their diversified biological activities such as allergic inhibitors, radical scavenging, analgesic and antioxidative action, and so forth. A literature survey reveals that Schiff bases derived from various heterocyclic possess antitubercular [30], antioxidant [31], antimicrobial [32-34], anticonvulsant [35-36] and anti-inflammatory [37-38] activities. Schiff bases attract much interest both from a synthetic and biological point of view.

Although some synthetic route for compound **1** have been reported using aromatic aldehydes, malanonitrile and amidines [39-40]. Prompted by these observations, it was contemplated to synthesize some Pyrimidine containing Schiff and Mannich bases with a view to explore their potency as antimicrobial agents.



(a) **(b)** **(c)**

Figure 1 – Some Pyrimidine Containing bioactive agents

MATERIALS AND METHODS

Melting points of all synthesized compounds were taken in open capillaries and are uncorrected. The IR spectra were recorded using KBr discs on a Perkin Elmer - Spectrum RX-FTIR Spectrophotometer. The NMR spectra were carried out on a BRUKER Avance II Spectrophotometer at 400 MHz, using TMS as an internal reference and DMSO as solvent. The mass spectra were recorded on Waters, Micromass Q-TOF micro Separation. Elemental analysis was done on "Thermo Scientific (FLASH 2000) CHN Elemental Analyser." Purity of synthesized compounds was checked by TLC using silica gel plates; toluene and ethyl acetate as developing solvent, and the spots were exposed in an iodine chamber. All the compounds were synthesized according to the Reaction Scheme.

General procedure for the Synthesis of 2,4-diamino-6-phenylpyrimidine-5-carbonitrile (1): In ethanol solution of benzaldehyde 10mmol (1.06g), malanonitrile 10mmol (0.66g), guanidine nitrate 12mmol

(1.52g) was added. To this mixture piperidine in catalytic amount was added and refluxed. Refluxing was continued for 8 h and the completion of the reaction was monitored by TLC. The resultant mixture was cooled at room temperature and poured into crushed ice. The product thus separated was filtered out, washed with water, dried and recrystalized from ethanol. IR (KBr): 3478, 3344, 2214, 1650, 3034; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 4H, NH_2), 7.0-7.8 (m, 5H, Ar-H); MS: m/z 211 [M^+].

General procedure for the Synthesis of Compounds (2a-d): To a solution of 2,4-diamino-6-phenylpyrimidine-5-carbonitrile **2** 10mmol (2.11g) in ethanol, piperidine 20mmol (1.70g) and formaldehyde (2mL) were added. The reaction mixture was refluxed for 24 h. The progress of reaction was monitored by TLC. On cooling the precipitate was collected and recrystalized from ethanol.

4-Phenyl-2,6-bis-[(piperidin-1-ylmethyl)-amino]-pyrimidine-5-carbonitrile (2a): IR cm^{-1} (KBr): 3378, 3032, 2832, 2257, 1615, 1460; ^{1}H NMR (400 MHz, DMSO): δ 6.8-7.8 (m, 5H, Ar-H), 4.8 (t, 2H, N-H), 3.6 (d, 4H, CH_2), 2.3 (t, 8H, CH_2 piperidine), 1.4 (m, 12H, CH_2 piperidine); ^{13}C NMR (400 MHz, DMSO): δ 24.4, 27.1, 52.9, 72.2, 83.1, 117.9(CN), 126.4, 127.9, 128.7, 137.3, 168.2, 171.7, 176.2; MS: m/z 405 [M^+]; Anal. Calc. for $C_{23}H_{31}N_7$: C, 68.12; H, 7.70; N, 24.18. Found: C, 68.29; H, 7.61; N, 24.10.

4-Phenyl-2,6-bis-[(morpholin-1-ylmethyl)-amino]-pyrimidine-5-carbonitrile (2b): IR cm^{-1} (KBr): 3370, 3038, 2854, 2245, 1612, 1458; ^{1}H NMR (400 MHz, DMSO): δ 7.1-7.6 (m, 5H, Ar-H), 4.5 (t, 2H, N-H), 3.4 (d, 4H, CH_2), 2.4 (t, 8H, CH_2, morpholine), 3.4 (t, 8H,CH_2, morpholine); ^{13}C NMR (400 MHz, DMSO): δ 52.4, 72.1, 73.7, 83.4, 118.2(CN), 126.3, 127.7, 128.5, 137.2, 168.6, 171.4, 176.6; MS: m/z 409 [M^+]; Anal. Calc. for $C_{21}H_{27}N_7O_2$: C, 61.60; H, 6.65; N, 23.94. Found: C, 61.48; H, 6.86; N, 23.85.

4-Phenyl-2,6-bis-[(NN-diphenyl-1-ylmethyl)-amino]-pyrimidine-5-carbonitrile (2c): IR cm^{-1} (KBr): 3368, 3045, 2830, 2247, 1618, 1450; ^{1}H NMR (400 MHz, DMSO): δ 6.7-7.7 (m, 25H, Ar-H), 4.3 (t, 2H, N-H), 3.8 (d, 4H, CH_2); ^{13}C NMR (400 MHz, DMSO): δ 72.4, 83.2, 115.7, 118.1(CN), 126.1, 127.8, 128.4, 137.6, 141.5, 168.1, 171.5, 176.4; MS: m/z 573 [M^+]; Anal. Calc. for $C_{37}H_{31}N_7$: C, 77.46; H, 5.45; N, 17.09. Found: C, 77.54; H, 5.32; N, 17.14.

4-Phenyl-2,6-bis-[(piperazin-1-ylmethyl)-amino]-pyrimidine-5-carbonitrile (2d): IR cm^{-1} (KBr): 3354, 3040, 2828, 2252, 1612, 1447; ^{1}H NMR (400 MHz, DMSO): δ 6.8-7.5 (m, 5H, Ar-H), 4.6 (t, 2H, N-H), 3.5 (d, 4H, CH_2), 2.6-2.8 (m, 16H, CH_2 piperazine), 2.2 (t, 2H, NH piperazine); ^{13}C NMR (400 MHz, DMSO): δ 51.3, 54.6, 72.6, 83.1, 118.4(CN), 126.1, 127.5, 128.7, 137.3, 168.4, 171.7, 176.8; MS: m/z 407 [M^+]; Anal. Calc. for $C_{21}H_{29}N_9$: C, 61.89; H, 7.17; N, 30.93. Found: C, 61.95; H, 7.23; N, 30.82.

General procedure for the Synthesis of Compounds (2e-h): 2,4-diamino-6-(phenyl)pyrimidine-5-carbonitrile **1** 10mmol (2.11g) and benzaldehyde 20mmol (2.12g) were dissolved in 50 mL of ethanol. To this, glacial acetic acid was added in a catalytic amount. The mixture was refluxed for 9 h. The progress of reaction was monitored by TLC. Reaction mixture was poured into crushed ice. The product was separated by filtration, and recrystalized from ethanol.

2-[benzylideneamino]-4-[benzylideneamino]-6-phenylpyrimidine-5-carbonitrile (2e): IR cm^{-1} (KBr): 3052, 2250, 1650, 1580; ^{1}H NMR (400 MHz, DMSO): δ 7.3-7.9 (m, 15H, Ar-H), 8.1 (s, 2H, =C-H); ^{13}C NMR (400 MHz, DMSO): δ 96.4, 117.9(CN), 128.4, 129.5, 131.6, 137.5, 165.1, 173.1, 185.6; MS: m/z 387 [M^+]; Anal. Calc. for $C_{25}H_{17}N_5$: C, 68.12; H, 7.70; N, 24.18. Found: C, 68.28; H, 7.62; N, 24.10.

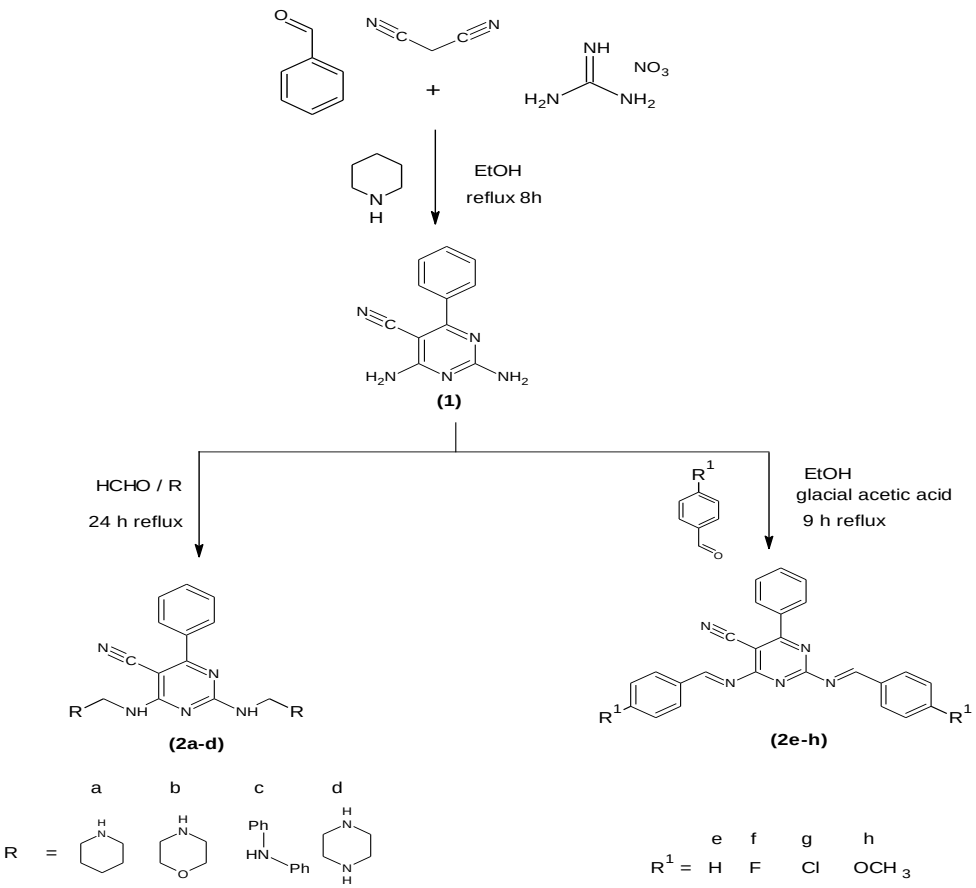
2-[benzylideneamino]-4-[benzylideneamino]-6-(4-fluorophenyl)pyrimidine-5-carbonitrile (2f): IR cm^{-1} (KBr): 3055, 2248, 1652, 1575; ^{1}H NMR (400 MHz, DMSO): δ 7.4-7.8 (m, 13H, Ar-H), 8.3 (s, 2H, =C-H); ^{13}C NMR (400 MHz, DMSO): δ 96.5, 114.3, 118.3, 124.6, 128, 129.4, 131.4, 137.8, 163.6, 165.3, 173.5, 185.8 ; MS: m/z 423 [M^+]; Anal. Calc. for $C_{25}H_{15}F_2N_5$: C, 70.92; H, 3.57; N, 16.54. Found: C, 70.84; H, 3.62; N, 16.57.

2-[benzylideneamino]-4-[benzylideneamino]-6-(4-chlorophenyl)pyrimidine-5-carbonitrile (2g): IR cm^{-1} (KBr): 3048, 2257, 1650, 1585; ^1H NMR (400 MHz, DMSO): δ 7.2-7.6 (m, 13H, Ar-H), 8.2 (s, 2H, =C-H); ^{13}C NMR (400 MHz, DMSO): δ 96, 118.1, 126.8, 128.7, 129.5, 131.6, 137.4, 165.2, 173.2, 185.6; MS: m/z 447 [M^+]; Anal. Calc. for $C_{25}H_{15}Cl_2N_5$: C, 65.80; H, 3.31; N, 15.35. Found: C, 65.74; H, 3.42; N, 15.30.

2-[benzylideneamino]-4-[benzylideneamino]-6-(4-methoxyphenyl) pyrimidine-5-carbonitrile (2h): IR cm^{-1} (KBr): 3058, 2832, 2253, 1655, 1572; ^1H NMR (400 MHz, DMSO): δ 6.9-7.6 (m, 13H, Ar-H), 8.1 (s, 2H, =C-H), 3.2 (s, 6H, OCH_3); ^{13}C NMR (400 MHz, DMSO): δ 58.1(OCH_3), 96.3, 113.2, 117.8, 122.4, 126, 128.1, 129.6, 137.6, 165.7, 173.3, 185.3**;** MS: m/z 456 [M^+]; Anal. Calc. for $C_{27}H_{21}N_5O_2$: C, 72.47; H, 4.73; N, 15.65. Found: C, 72.53; H, 4.59; N, 15.73.

ANTIMICROBIAL ACTIVITY

All the synthesized derivatives **2a-h** were screened for their antibacterial activity against Gram positive bacteria *S. aureus, S. pyogenes*, Gram negative bacteria *E. coli, P. aeroginosa* and fungal strain *C. albicans* and *A. clavatus* for antifungal activity. **Cefixime** was used as a standard drug for antibacterial activity while **Griseofulvin** was used as a standard drug for antifungal activity. All the compounds were dissolved in dimethyl sulfoxide (DMSO) to give a concentration of50 µgmL^{-1}. Muller-Hinton agar medium was used as culture medium. The method employed was agar disc diffusion method. The zones of inhibition were measured in mm.



Reaction Scheme

RESULTS AND DISCUSSION

Chemistry- In the present work the synthesis of some new Mannich and Schiff bases **2a-h** were achieved from 2,4-diamino-6-phenylpyrimidine-5-carbonitrile **1**, the synthetic route used is shown in Reaction Scheme. All the physical properties are shown in **(Table 1)**. Compound **1** was prepared in 85% yield by reaction of aromatic aldehyde and malanonitrile with guanidine nitrate in the presence of piperidine. The structure of compound **1** was confirmed by spectral studies. The IR spectra of compound **1** showed strong absorption bands in the region 3478, 3344 cm^{-1} for NH_2 and 2257 cm^{-1} for CN group. ^1H NMR spectra of compound **1** has shown broad singlet corresponding to NH_2 at δ 4.2 ppm. In first route compound **1** was treated with formaldehyde and different secondary amines viz. piperidine, morpholine, diphenylamine, and piperazine to give its Mannich bases in a good yield **2a-d**. These products were confirmed by spectral and analytical studies. IR spectra of compounds **2a-d** were elucidated by disappearance of two absorption peaks of NH_2 group of the compound **1** and appearance of new absorption peaks at 2832 and 3375 cm^{-1} corresponding to CH_2 and NH respectively. The ^1H NMR spectrum revealed characteristic -N-CH_2-N- protons as a doublet between δ 3.4-3.8 ppm and triplet at around δ 4.3-4.8 ppm assigned to the N-H protons. CH_2 peak of piperidine, morpholine, and piperazine was appeared in the range of δ 2.3-3.4 ppm. Compound **2d** also showed signal at around δ 2.2 ppm for N-H proton of piperazine. In another route compound **1** was condensed with various substituted benzaldehydes in catalytic amount of acetic acid in ethanol media to yield a new series of corresponding Schiff bases **2e-h**. The structure of the prepared schiff bases was confirmed by IR and ^1H NMR studies. The IR spectrum of compound **2e-h**, showed new absorption stretching band of C=N group in the region 1650–1655 $cm^{-1}$and also band at 3055 cm^{-1} of C-H stretching of H-C=N group appeared. The ^1H-NMR spectrum of compound **2e-h** showed the singlet between δ 8.1-8.3 ppm suggested the attribution of the proton of the CH=N which confirmed the synthesis of Schiff bases. The singlet derived from –OCH_3 group in compound **2h** was recorded at δ 3.2 ppm integrating three protons. The mass spectrum also supports the proposed structure by viewing molecular ion peaks of all compounds.

Table 1: Physical properties of synthesized compounds

Compounds	Reflux time (h)	Mol. formula	Mol. weight	mp (°C)	Yield (%)
1	8	$C_{11}H_9N_5$	211.20	240-242	85
2a	24	$C_{23}H_{31}N_7$	405.53	140-142	87
2b	20	$C_{21}H_{27}N_7O_2$	407.51	135-136	68
2c	19	$C_{37}H_{31}N_7$	409.48	148-152	84
2d	21	$C_{21}H_{29}N_9$	573.68	142-145	76
2e	9	$C_{25}H_{17}N_5$	387.43	120-123	88
2f	7	$C_{25}H_{15}F_2N_5$	423.41	117-120	71
2g	10	$C_{25}H_{15}Cl_2N_5$	447.48	112-115	55
2h	8	$C_{27}H_{21}N_5O_2$	456.32	122-124	65

APPLICATIONS

Antimicrobial activity- The results of antimicrobial screening of the compounds were reported as zone of inhibition **(Table 2)**. Biological studies revealed that pyrimidine containing Mannich base and Schiff base **2a-h** derivatives were showing good to moderate antimicrobial activity against all the bacterial and fungal strains. Amongst compounds morpholine containing compound **2b** exhibited potent antibacterial and

antifungal activity as compared to reference drug. Compound **2h** showed good activity against *S. aureus* while against *S. pyogenes* it is moderately active. Compound **2e** also exhibited moderate activity against *S. aureus* and *E. coli*. In antifungal activity compound **2f** exhibited excellent activity against both the species while the compounds **2d, 2e, 2g** and **2h** exhibited moderate to potent activity.

Table-2 Antimicrobial activity of synthesized compounds: Zone of inhibition in mm (activity index)^{std}

Compounds	Antibacterial Strains				Antifungal Strains	
	Gram Positive		*Gram Negative*			
	Staphylococcus aureus	***Streptococus pyogenes***	***Escherichia coli***	***Pseudomonas aeruginosa***	***Candida albicans***	***Aspergillus clavatus***
2a	16 (0.76)	16 (0.69)	13 (0.52)	16 (0.68)	14 (0.64)	19 (0.68)
2b	20 (0.95)	18 (0.78)	22 (0.88)	18 (0.75)	18 (0.82)	24 (0.86)
2c	17 (0.81)	17 (0.74)	18 (0.72)	12 (0.50)	15 (0.68)	16 (0.57)
2d	15 (0.71)	16 (0.69)	17 (0.68)	18 (0.75)	18 (0.82)	23 (0.82)
2e	17 (0.81)	15 (0.65)	20 (0.80)	17 (0.71)	17 (0.77)	20 (0.71)
2f	13 (0.62)	14 (0.60)	15 (0.60)	14 (0.58)	20 (0.91)	25 (0.89)
2g	14 (0.66)	15 (0.65)	16 (0.64)	16 (0.68)	18 (0.80)	22 (0.78)
2h	18 (0.86)	19 (0.82)	19 (0.76)	18 (0.75)	17 (0.77)	19 (0.68)
Cefixime	21	23	25	24	-	-
Griseofulvin	-	-	-	-	22	28

(Activity index)^{std} = zone of inhibition of the sample/zone of inhibition of the standard

CONCLUSIONS

In conclusion, a series of new pyrimidine containing Mannich and Schiff bases **2a-h** were synthesized in good yield, characterized by different spectral studies and their antimicrobial activity have been evaluated. The activity studies revealed that derivative carrying morpholine containing Mannich base **2b** and 4-methoxy group containing Schiff base **2h** have shown excellent antibacterial activity, whereas fluoro group carrying Schiff base **2f** has shown highest antifungal activity. The good inhibition by compound **2f** could be attributed to the presence of an electron withdrawing fluoro group.

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