Asian Journal of Chemistry Vol. 10, No. 4 (1998), 976–979

Synthesis of Pyrimidine and Piperazine Based Medicinal Compounds

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2-Amino pyrimidines on condensation with piperazine in presence of formaldehyde in acidic alcohol leads to the formation of 1,4-di[2-aminodiaryl pyrimidine] 1,4-dimethyl piperazine. All the compounds were purified and analysed using physical and chemical methods and were further confirmed by spectral studies. The antibacterial effect was studied by using the cup-plate (N. agar) technique on four different strains of bacteria. The synthesised compounds were further studied for the evaluation of anti-AIDS, anticancer and antileprosy activities also.

INTRODUCTION

Piperazine is used as piperazine hydrate and piperazine citric acid in the treatment of filaria. Pyrimidine which is a basic unit of DNA and RNA, has been utilised with different substituents in the treatment of cancer, AIDS and certain other diseases. In continuation of our work, it was thought interesting to combine these two important nuclei, *i.e.*, pyrimidine and piperazine and develop certain new compounds for their better activity as medicine in the treatment of different diseases.

The reaction of $—NH_2$ or —NH— group with formaldehyde takes place, leading to a condensation product. When reaction is carried out, the following type of compound is reported in most of the cases.[1]

$$—NH_2 + HCHO + H_2N— \rightarrow —NH—CH_2—NH—$$

2-Amino pyrimidines (I) are condensed with piperazine and formaldehyde in presence of acidic alcohol (acidified by conc. HCl) to get 1,4-di-[2-amino-diaryl pyrimidine] 1,4-dimethyl piperazine (II).

The compounds thus synthesised in the series described below are tested for their antimicrobial activities of cup-plate method[2] using DMF as solvent against *S. aureus*, *B. subtilis*, *E. coli* and *Pr. mirabilis* at 100 μg/mL. The zone of inhibition with respect to the controlled, *i.e.*, ciprofloxacin are illustrated in Table-1 and physical data and yield in Table-2.

The compounds have also been screened at TAARF for their antituberculosis activity. Compound II a is found to have 91% activity and it will be further screened by TAARF on the resistant tuberculosis strains. The compounds were also screened for their anticancer activities and were found to be sufficiently active but not to the level of getting the status of a drug. Anti AIDS activity are confirmed negative.

TABLE-1
ANTIMICROBIAL ACTIVITY OF PYRIMIDINE PIPERAZINE DERIVATIVES (II)
(Zone of inhibittion in cm)

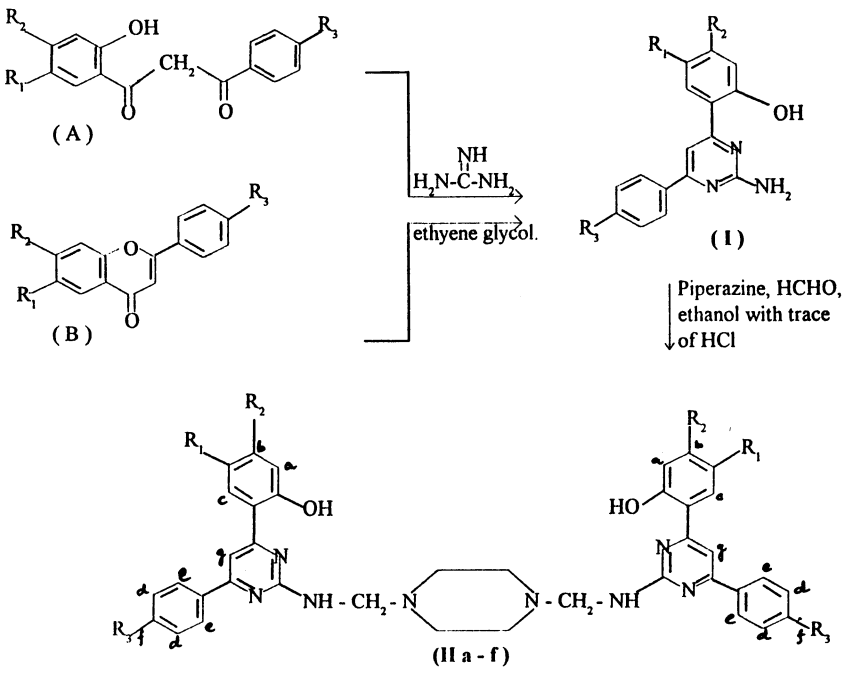
S. No.	Compound	*E. coli*	*Pr. mirabilis*	*S. aureus*	*B. subtilis*
1.	IIa	0.5	n.i	0.6	n.i
2.	IIb	n.i	0.5	0.7	n.i
3.	IIc	0.4	0.4	0.3	0.3
4.	IId	0.3	0.4	0.6	0.3
5.	IIe	1.5	1.5	0.9	1.2
6.	IIf	0.6	0.5	0.8	0.5

where n.i. = no inhibition

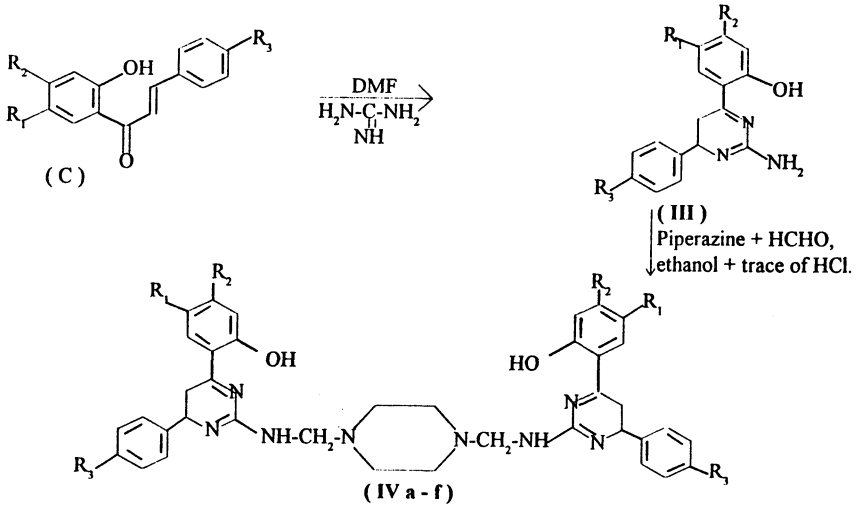
TABLE-2
PHYSICAL DATA AND YIELD OF SYNTHESISED COMPOUNDS

S. No.	Compound*	R_1	R_2	R_3	Mol. formula (Yield %)	N % Found (Calcd)
1.	IIa	CH_3	H	H	$C_{40}H_{40}N_8O_2$ (70)	16.70 (16.86)
2.	IIb	CH_3	H	OCH_3	$C_{42}H_{46}N_8O_4$ (60)	15.50 (15.42)
3.	IIc	Cl	H	H	$C_{38}H_{34}N_8O_2Cl_2$ (65)	15.50 (15.88)
4.	IId	Cl	H	OCH_3	$C_{40}H_{38}N_8O_2Cl_2$ (50)	15.50 (15.27)
5.	IIe	H	OCH_3	H	$C_{40}H_{40}N_8O_4$ (78)	16.00 (16.09)
6.	IIf	H	OCH_3	OCH_3	$C_{42}H_{44}N_8O_6$ (55)	14.70 (14.81)
7.	IVa	CH_3	H	H	$C_{40}H_{42}N_8O_2$ (75)	16.90 (16.81)
8.	IVb	CH_3	H	OCH_3	$C_{42}H_{48}N_8O_4$ (60)	15.10 (15.38)
9.	IVc	Cl	H	H	$C_{38}H_{36}N_8O_4Cl_2$ (68)	15.00 (15.15)
10.	IVd	Cl	H	OCH_3	$C_{40}H_{40}N_8O_4Cl_2$ (80)	14.50 (14.60)
11.	IVe	H	OCH_3	H	$C_{40}H_{42}N_8O_4$ (63)	16.00 (16.04)
12.	IVf	H	OCH_3	OCH_3	$C_{42}H_{46}N_8O_6$ (59)	14.80 (14.77)

*All compounds decomposed at *ca.* 250°C.



Scheme-I



Scheme-II

EXPERIMENTAL

All the melting points are uncorrected. The IR spectra are recorded on Perkin-Elmer spectrophotometer and NMR on Brucher AC 300F NMR spectrometer (300 MHz)

Preparation

(i) *Preparation of 2-amino-4, 6-diaryl pyrimidine (I):* A mixture of A or B (Scheme-I) (0.01 mol), guanidine carbonate (0.02 mol) and 30 mL ethylene glycol in an R.B. flask was refluxed for 3 h and the reaction mixture was kept overnight.[3,4] It was diluted with water, filtered, dried and further recrystallised from ethanol.[5]

(ii) *Preparation of 1,4-di(2-amino-4,6-diaryl pyrimidine)-1,4-dimethyl piperazine(II):* A mixture of (I) (0.01 mol), piperazine (0.01 mol), formaldehyde (0.03 mol) and 30 mL ethanol with traces of conc. HCl was taken in an R.B flask and refluxed for 1 h. The compound was extracted from the reaction mixture itself. It was filtered and further recrystallised from ethanol, *e.g.*, IIa.

IR: ν_{max} (cm^{-1}) 3500–3300 ν(—OH, NH), 3010 ν(Ar—C—H), 2960 (CH_3), 1590, 1578 (phenyl ring), 1515 (C—N stretching).

^{1}H NMR: (δ) 2.6 (6 =CH), 3.4 (2 —CH_3), 4.0 (2H), 4.4 (2H), 6.9 (2 N—H), 7.4 (10 Ar H), 7.9 (2H), 8.4 (2H), 13.9 (2H of OH).

(iii) *Preparation of 2-amino-4,6-diaryl-5,6-dihydro pyrimidine (III):* (Scheme-II) A mixture of (C, 0.01 mol), guanidine carbonate (0.02 mol) and 30 mL dimethyl formamide in an R.B. flask was refluxed for 4 h. The reaction mixture was kept overnight. It was then diluted with cold water, filtered, dried and further recrystallised from ethanol.[6]

(iv) *Preparation of 1,4-di (2-amino-4,6-diaryl-5,6-dihydro pyrimidine) 1,4-dimethyl piperazine (IV):* A mixture of (III) (0.01 mol), piperazine (0.01 mol), formaldehyde (0.03 mol) and 30 mL ethanol with traces of conc. HCl was taken in an R.B. flask and refluxed for 1 h. The compound was extracted from the reaction mixture itself, filtered, dried and further recrystallised from ethanol, *e.g.*, IV a.

IR: ν_{max} (cm^{-1}) 3550 ν(OH), 3120 ν(NH), 3020 ν(Ar C—H), 2960 (CH_3), 1580–1550 (phenyl ring), 1510 (C—N stretching).

ACKNOWLEDGEMENTS

The authors thank UGC, New Delhi for the major research grant, RSIC Chandigarh and RSIC Nagpur for spectral (IR and NMR) analysis, and also Environment Engineering Department, VRCE for carrying out antimicrobial activity.

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(*Received*: 8 May 1998; *Accepted:* 15 June 1998) AJC-1523