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Synthesis of Schiff Bases from 2-Amino-4, 6-diphenyl Pyrimidines and 2-Amino-4,6-Diphenyl-5,6-Dihydro Pyrimidines and Evaluation of Antimicrobial and Anticancer Activities

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Schiff bases were prepared by the condensation of 2-amino-diaryl pyrimidines and 2-amino-diaryl-dihydro pyrimidines with substituted benzaldehydes in ethanol with 2–3 drops of H_2SO_4 as a condensing agent. The synthesised pyrimidines and their Schiff bases were futher studied for the evaluation of antimicrobial and anticancer activities.

INTRODUCTION

The biological significance of the pyrimidine derivatives has led us to the synthesis of substituted pyrimidines. As pyrimidine is a basic nucleus in DNA and RNA, it has been found to be associated with diverse biological activities[1]. Many of the Schiff bases exhibit anticancer and antitubercular activities[2] as well as anti-microbial activities. Synthesis of Schiff bases has been reported by condensation of aniline with substituted benzaldehydes[3]. Ahluwalia and coworkers[4] have synthesised 2-amino pyrimidines which were evaluated as antibacterial agents.

2-Amino-4,6-diphenyl pyrimidines and 2-amino-4,6-diphenyl-5,6-dihydro pyrimidines were prepared from dibenzoyl methanes and chalcones respectively with guanidine carbonate in ethylene glycol and DMF.

Further it was condensed with differentyl substituted aromatic aldehydes to get corresponding Schiff bases (4). Some of the compounds have been screened for anticancer, as well as for antimicrobial activities.

EXPERIMENTAL

All the melting points were determined in open capillaries and are uncorrected. The IR spectra (KBr) were recorded on Philips PV 9700 spectrophotometer. The ^{1}H-NMR spectra were recorded on Ac-Brucker 300 MHz spectrophotometer using 5 mm tubes.

General Procedure

2′-Hydroxy-5′-substituted chalcones (2) have already been reported[5].

Preparation of 2-Amino-5,6-dihydro-4,6-diaryl pyrimidine (3)

A mixture of (2) (0.01 mol) and guanidine carbonate (0.04 mol) was taken in 100 mL R.B. flask and 30 mL of DMF was added to it. The reaction mixture was refluxed for 3 h and kept overnight for completion of reaction. Then the reaction

mixture was diluted with water. The resulting solid was washed, filtered and dried. Further it was cystallized from ethanol : dioxane (4 : 1 mixture) for getting compound (3) [Table-1 Scheme I].

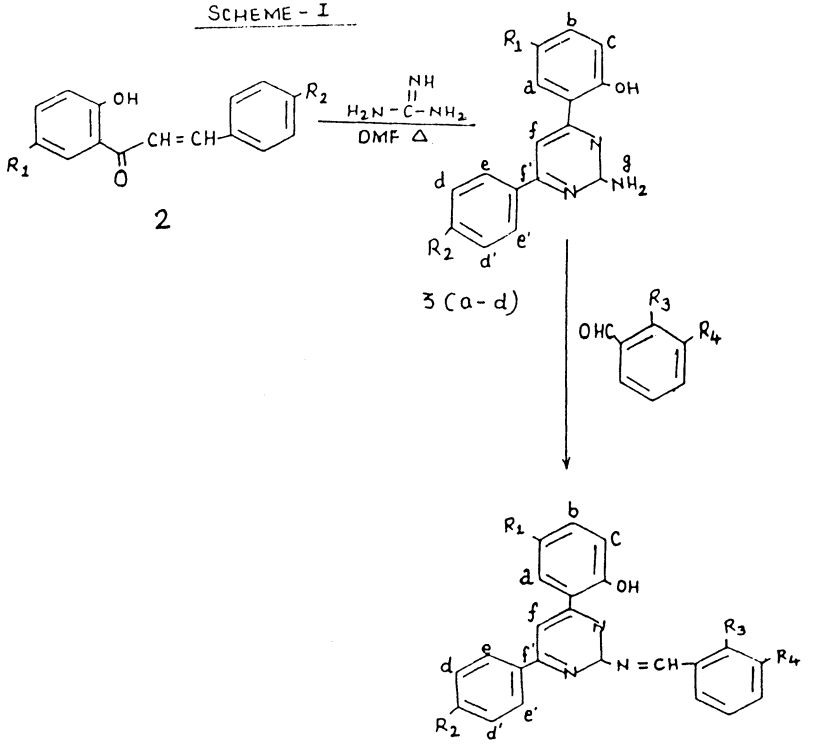
TABLE-1

Comp.	R_1	R_2	R_3	R_4	Analysis (%)			Mol formula (m.p., °C)
					C	H	N	
3a	CH_3	H	—	—	73.0	5.20	15.0	$C_{17}H_{16}N_3O$ (174)
3b	CH_3	OCH_3	—	—	71.0	5.90	13.9	$C_{18}H_{18}N_3O_2$ (221)
3c	Cl	H	—	—	65.0	4.20	14.1	$C_{16}H_{13}N_3OCl$ (211)
3d	Cl	OCH_3	—	—	60.1	4.70	13.5	$C_{16}H_{15}N_3O_2Cl$ (196)
$4a_1$	CH_3	H	H	H	78.6	5.6	11.7	$C_{24}H_{20}N_3O$ (210)
$4a_2$	CH_3	H	H	OCH_3	76.0	5.3	10.7	$C_{25}H_{22}N_3O_2$ (214)
$4a_3$	CH_3	H	NO_2	H	71.0	4.2	10.4	$C_{24}H_{19}N_4O_3$ (211)
$4a_4$	CH_3	H	H	OH	76.0	5.2	10.8	$C_{24}H_{20}N_3O_2$ (225)
$4a_5$	CH_3	H	H	$N<^{CH_3}_{CH_3}$	76.2	6.3	13.6	$C_{26}H_{25}N_4O$ (230)
$4b_1$	CH_3	OCH_3	H	H	75.9	5.6	10.6	$C_{25}H_{22}N_3O_2$ (235)
$4b_2$	CH_3	OCH_3	H	OCH_3	73.9	7.3	9.9	$C_{26}H_{24}N_3O_3$ (250)
$4b_3$	CH_3	OCH_3	NO_2	H	69.2	4.9	12.7	$C_{25}H_{21}N_4O_4$ (258)
$4b_4$	CH_3	OCH_3	H	OH	72.9	5.4	10.1	$C_{25}H_{22}N_3O_3$ (248)
$4b_5$	CH_3	OCH_3	H	$N<^{CH_3}_{CH_3}$	74.1	6.4	12.9	$C_{27}H_{27}N_4O_2$ (260)
$4c_1$	Cl	H	H	H	72.10	4.3	10.9	$C_{23}H_{17}N_3OCl$ (221)
$4c_2$	Cl	H	H	OCH_3	69.90	4.6	10.9	$C_{24}H_{19}N_3O_2Cl$ (220)
$4c_3$	Cl	H	NO_2	H	64.03	3.9	12.7	$C_{23}H_{16}N_4O_3Cl$ (218)
$4c_4$	Cl	H	H	OH	68.90	4.3	10.5	$C_{23}H_{17}N_3O_2Cl$ (227)
$4c_5$	Cl	H	H	$N<^{CH_3}_{CH_3}$	69.60	5.3	14.0	$C_{25}H_{22}N_4OCl$ (232)
$4d_1$	Cl	OCH_3	H	H	69.10	4.6	10.03	$C_{24}H_{19}N_3O_2Cl$ (228)
$4d_2$	Cl	OCH_3	H	OCH_3	68.30	4.9	9.7	$C_{25}H_{21}N_3O_3Cl$ (230)
$4d_3$	Cl	OCH_3	NO_2	H	64.90	3.7	13.1	$C_{24}H_{18}N_4O_3Cl$ (190)
$4d_4$	Cl	OCH_3	H	OH	63.40	4.2	8.9	$C_{24}H_{19}N_3O_3Cl$ (218)
$4d_5$	Cl	OCH_3	H	$N<^{CH_3}_{CH_3}$	67.30	5.6	12.1	$C_{26}H_{24}N_4O_2Cl$ (240)

(3b) IR, λ cm^{-1}: 3460 ν(OH), 3350 ν(NH), 1630 ν(C=C), 1580 ν(C=N) 1540 ν(NH bending), 1240 ν(Ar—O).

NMR (3b): ($CDCl_3$ + DMSO-d_6): δ (2.34, S, 3H, Ar—CH_3), (3.8, S, 3H,

SCHEME - I



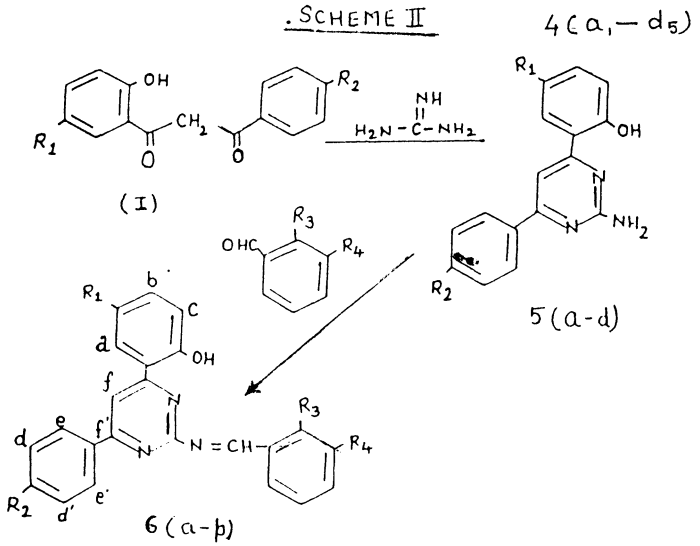
Ar—OCH_3), (6.62, S, 2H, NH_2), (7.11, dd, 1H, H_f), (6.82, d, 2H, Hb, Hc), (7.52, S, 1H, Ha), (7.77, S, 1H, H_f), (7.006, d, 2H, Hd′, He′), (8.1, d, 2H, Hd, He), (13.83, S, 1H, Ar—OH).

2-Imino-benzal 5,6-dihydro 4,6-diaryl pyrimidines (4)

A mixture of (3) (0.001 mol) and substituted aromatic aldehyde (0.001 mol) was taken in ethanol (10 mL) in R.B. flask. A drop of conc. H_2SO_4 was added to it. The reaction mixture was refluxed for about 1/2 h on water bath. A bright yellow coloured compound separated was filtered hot. The compound was recrystallized from ethanol (Table-1) (Scheme II).

($4b_5$) IR, λ cm^{-1}-3340 ν(OH), 1685 ν(C=N), 1620 ν(C=C), 1585 ν(C=N streching), 1250 ν(Ar—O)

NMR ($4b_5$): ($CDCl_3$ + DMSO-d_6) – δ (2.36, S, 3H, Ar—CH_3), (3.91, S, 3H, Ar—OCH_3), (5.15, b, 6H, $N<\begin{matrix}CH_3\\CH_3\end{matrix}$), (6.96, d, 1H, Hb), (7.1, d, 2H, Hd, He), (7.27, d, 1H, Hc), (7.68, S, H, N=CH), (7.80, S, H, Ha), (7.86, S, 1H, Hf), (7.15, d, 2H, Hd′, He′), (8.35, b, 1H, NH).



Preparation of 2-amino-4,6-diaryl pyrimidine (5)

A mixture of (I) (0.01 mol) and guanidine carbonate (0.04 mol) was taken in 100 mL R.B. flask and ethylene glycol was added to it. The reaction mixture was refluxed for 3 h and kept overnight for completion of reaction. Then the reaction mixture was diluted with water. The resulting solid was washed, filtered and dried. Further it was crystallised.

IR (KBr) cm^{-1} (5b): 3350 ν(N—H), 1630 ν(C=C), 1580 ν(C=N—), 1540 ν(N—H bending), 1580 ν(C=N—), Stretching in cyclic system).

(5b) ^1H NMR δ ($CDCl_3$ + DMSO-d_6): 3.83 (OCH_3), 6.07 (NH_2), 6.44–8.05 (Ar—H), 14.34 (O—H), 7.37 (Ar—H of pyrimidine).

2-Imino-benzal,4,6-diaryl pyrimidines (6)

A mixture of (5) (0.001 mol) and substituted aromatic aldehyde (0.001 mol) was taken in ethanol (10 mL) in R.B. flask. A drop of conc. H_2SO_4 was added to it. The reaction mixture was refluxed for about 1/2 h on water bath. A bright yellow coloured compound separated was filtered hot. The compound was recrystallized from ethanol.

(6d) IR (KBr) cm^{-1} : 1685 ν(C=N); 1620 ν(C=C); 1585 ν(C=N— stretching in cyclic system)

Absence of N—H stretching band which appears at 3350 cm^{-1} in 5d is a clear indication that the condensation has taken place. A strong and sharp band appearing at 1685 cm^{-1} again supports the condensation between (5b) and benzaldehyde.

^1H NMR, δ (DMSO-d_6): 3.87 (OCH_3), 3.90 (OCH_3), 7.54 (N—CH), 7.79 (Ar—H of pyrimidine), 6.5–8.06 (Ar—H).

The physical data of compounds 5 and 6 are presented in Table-2.

Anti-microbrial Activity

The synthesised compounds were tested for antimicrobial activity by using DMF as solvent against *S. aureus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae* at 100 μg. The zone of inhibition with respect to controlled medium is illustrated in Table-3. The sensitivity of the compounds against the said microbs was compared with standered drug as penicilin. Zone of inhibition was measured in mm.

TABLE-2
PHYSICAL DATA OF COMPOUNDS 5 AND 6

Comp. No.	R	R_1	R_2	R_3	R_4	m.p. (°C)	Yield (%)
5a	OCH_3	H	H	—	—	180	62
5b	OCH_3	H	H	—	—	225	60
5c	H	CH_3	H	—	—	180	80
5d	H	Cl	H	—	—	201	80
6a	OCH_3	H	H	H	H	263	95
6b	OCH_3	H	H	H	OCH_3	265	92
6c	OCH_3	H	H	NO_2	H	267	95
6d	OCH_3	H	OCH_3	H	H	267	95
6e	OCH_3	H	OCH_3	H	OCH_3	265	95
6f	OCH_3	H	OCH_3	NO_2	H	270	90
6g	H	CH_3	H	H	H	210	90
6h	H	CH_3	H	H	OCH_3	240	90
6i	H	CH_3	H	NO_2	H	195	90
6j	H	CH_3	H	H	OH	225	90
6k	H	CH_3	H	H	$N<^{CH_3}_{CH_3}$	230	90
6l	H	Cl	H	H	H	205	90
6m	H	Cl	H	H	OCH_3	218	90
6n	H	Cl	H	NO_2	H	215	90
6o	H	Cl	H	H	OH	223	90
6p	H	Cl	H	H	$N<^{CH_3}_{CH_3}$	217	90

TABLE-3

Comp.	*E. coli*	*S. aureus*	*P. aeruginosa*	*K. pneumoniae*
3c	n.i.	n.i	n.i.	8
$4d_1$	6	8	n.i.	7
$4d_2$	6	7	n.i.	n.i.
$4d_3$	6	6	n.i.	6
$4d_4$	6	8	n.i.	n.i.

n.i. = not inhibited; all zone of inhibition are in mm.

TABLE-4

Comp	*E. coli*	*S. aureus*	*B. subtilis*	*P. aerugenosa*	*K. Pneumoniae*
5a	4	5	5.0	—	—
5b	n.i.	1	n.i.	—	—
5c	11	n.i.	—	10	7.0
5d	n.i.	n.i.	—	n.i.	n.i.
6a	5	6.4	10.3	—	—
6b	4	4.2	5.0	—	—
6c	4	5.4	10.5	—	—
6d	7	6.0	10.2	—	—
6e	4	5.2	4.9	—	—
6f	5	6.2	8.3	—	—
6g	6	6.0	—	n.i.	n.i.
6h	6	6.0	—	n.i.	6.0
6i	6	7.0	—	7.0	7.0
6j	—	—	—	—	—
6k	—	—	—	—	—
6l	6	10.0	—	46.0	8.0
6m	n.i.	n.i.	—	n.i.	9.0
6n	n.i.	6.0	—	n.i.	6.0
6o	—	—	—	—	—
6p	—	—	—	—	—

n.i = not inhibited; all zone of inhibition are in mm.

Compounds were found to be inactive on primary screen for their anti-cancer evaluation tests (CRI, Maryland USA).

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