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Synthesis, Characterization and Antibacterial Activities of Pyrido Dipyrimidines

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A one-pot synthesis of pyrido dipyrimidines has been achieved from 1,3-diaryl barbituric acid with furfural and aniline. The spectral and analytical data supported the structure of the synthesized compounds and all the compounds were screened for their antibacterial activities against *Enterobacteria faecalis* and *Aeromona.s hydrophilla.*

Key Words: 1,3-diaryl barbituric acid, Pyrido dipyrimidines, Spectral, Antibacterial studies.

INTRODUCTION

The synthesis of biannulated pyridines gained much importance in the field of heterocyclic chemistry. A variety of work on the synthesis of these hetercycles was done by various routes[1-5] owing to their broad spectrum of physiological and pharmacological properties, biomimetic oxidations[6, 7], antibacterial[8, 9], antineoplastic activities[10], etc. Barbituric acid has been employed as starting material for preparation of many heterocycles bearing pyrimidine nucleus.[11-13] However, earlier methods fail to provide the pyrido[2,3-d; 6,5-d']dipyrimidines with a substituent at C_5 position. This paper incorporates the synthesis of newer pyrido[2,3-d;6,5,d'] dipyrimidine derivatives of such kind by the reaction of 1,3-diaryl barbituric acids with an amine and an aldehyde in absolute ethanol at reflux temperature for 4 h.

EXPERIMENTAL

Thin layer chromatography was used to access the reactions and purity of products. m.p.s. were determined on a Boetius microheating table and Mettler-FP5 melting apparatus and are uncorrected. IR spectra were obtained on Shimadzu-8201FT instrument as KBr pellets and only noteworthy absorption levels (cm^{-1}) are listed. ^1H NMR spectra were recorded on Varian AMX-400 MHz spectrometer in $CDCl_3$ solution; chemical shifts are expressed in ppm (δ) relative TMS, coupling constants (J) in Hz and signal multiplicities are represented by s (singlet) and m (multiplet). Mass spectra were determined on a Jeol SX-102/DA-6000 mass spectrometer. CHN analyses were carried out on Carlo Erba 106 and Perkin-Elmer Model 240 analysers. The starting substrates have been prepared by earlier reported methods.[14, 15]

General Procedure for the Synthesis of pyrido dipyrimidines

Respective 1,3-diphenyl barbituric acid (**1a-e,** 0.002 mole), furfural (0.001

mole) directly purchased from Merck Company and aniline (0.001 mole) after necessary purification in anhydrous ethanol (50 mL) were refluxed for about 4 h. After the completion of reaction, inferred through TLC, the reaction mixture was reduced to about half of its volume and allowed to cool. The solid separated was collected and recrystallized from $CHCl_3$-MeOH mixutre.

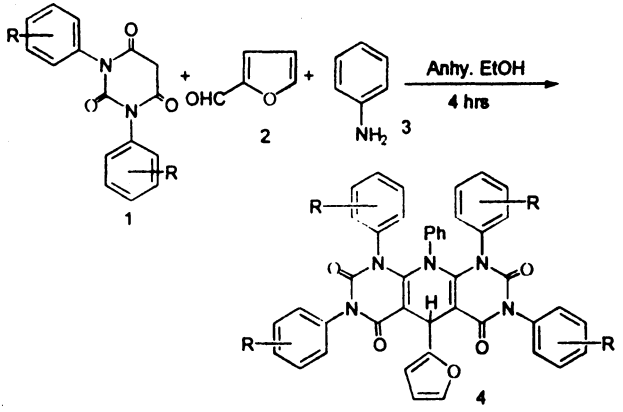
RESULTS AND DISCUSSION

Compound **4a,** (m.p. 193°C) was obtained on recrystallization from $CHCl_3$: MeOH (7 : 3) in 74% yield. The IR spectrum of this compound showed strong stretching absorption bands at 1620 cm^{-1} due to the N—CO—N groups and 1660 cm^{-1} due to the —N—CO—C groups. The ^1H NMR spectrum revealed a sharp singlet at δ 6.9 and accounted for C_5 methine proton. All the twenty-eight aromatic proton resonances exhibited its absorption between δ 7.20–7.90 as an unresolved multiplet. The mass spectrum indicated the molecular ion peak at m/z 695. The elemental analysis further corroborated the m.f. $C_{43}H_{29}N_5O_5$. All the above spectral data support the structure of **4a** as 1,2,3,4,6,7,8,9,10-nonahydro-1,3,7,9,10-pentaphenyl-5-furan-2,4,6,8-tetraoxo-5H-pyrido[2,3-d;6,5-d'] dipyrimidine.

The plausible mechanistic pathway is shown in **Scheme I.** The reaction may be proceeded *via* the formation of a bis-product through the Michael addition of 1,3-diaryl barbituric acid to the 5-arylidine-1,3-diarylbarbituric acid which further reacts with amine to give the final product. Similar series of compounds were prepared using **(1b–e)** as the starting substrates (Table-1).

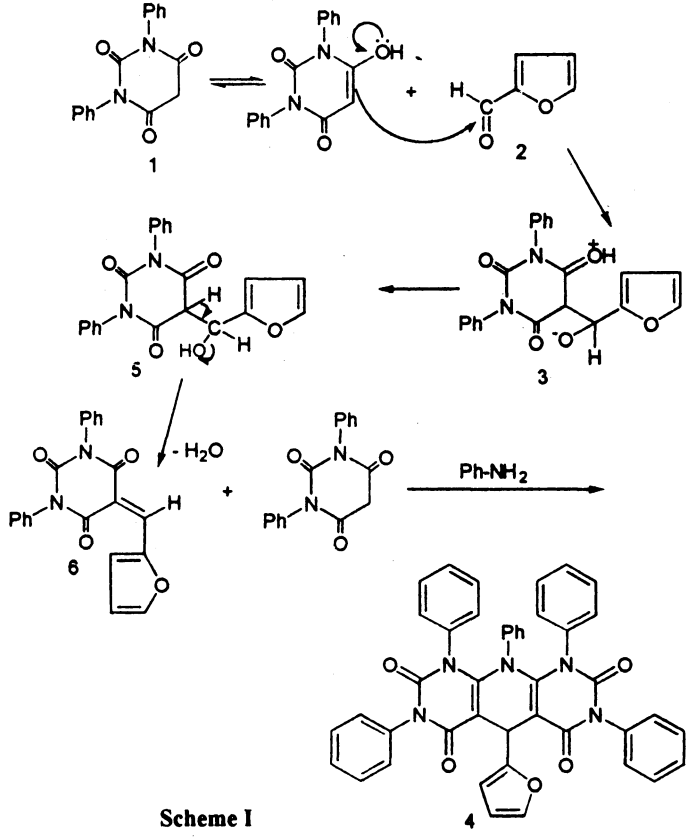
TABLE-1
PHYSICAL AND SPECTRAL DATA OF COMPOUNDS **4a–e**

Compds.	m.p. (°C)	Yield (%)	IR ν_{max} (cm^{-1})	m.f. (m.w.)	Analysis (%)		^1H-NMR δ/ppm
					Calcd.	Found	
4a	193	74	1660	$C_{43}H_{29}N_5O_5$	C 74.23	74.11	δ 6.9 (s, 1H, —CH)
			1620	(695.73)	H 4.20	4.25	δ 7.2–7.9 (m, 28H, Ar—H)
					N 10.07	10.21	
4b	234	78.5	1670	$C_{47}H_{37}N_5O_5$	C 75.09	75.01	δ 2.3 (s, 12H, 4 × CH_3)
			1630	(751.84)	H 4.96	4.81	δ 6.6 (s, 1H, —CH)
					N 9.31	9.12	δ 7.1–8.0 (m, 24H, Ar—H)
4c	210	82	1679	$C_{47}H_{37}N_5O_5$	C 75.09	74.98	δ 2.4 (s, 12H, 4 × CH_3)
			1627	(751.84)	H 4.96	4.92	δ 6.7 (s, 1H, —CH)
					N 9.31	9.23	δ 7.3–7.7 (m, 24H, Ar—H)
4d	156	62	1680	$C_{47}H_{37}N_5O_9$	C 69.20	69.11	δ 3.92 (s, 6H, 2 × OCH_3)
			1638	(815.84)	H 4.57	4.68	δ 4.01 (s, 6H, 2 × OCH_3)
					N 8.58	8.49	δ 6.68 (s, 1H, —CH)
							δ 6.9–7.8 (m, 24H, Ar—H)
4e	182	58.5	1675	$C_{43}H_{25}N_5O_5Cl_4$	C 61.96	61.82	δ 6.8 (s, 1H, —CH)
			1623	(833.51)	H 3.02	3.12	δ 7.2–8.2 (m, 24H Ar—H)
					N 8.40	8.53	



a) R = H b) R = 2-CH_3 c) R = 4–CH_3 d) R = 2–OCH_3 e) R = 4-Cl

The Mechanism



Scheme I

Antibacterial Studies

Antibacterial screening for the *in vitro* growth inhibitory activity against *Enterobacteria faecalis* and *Aeromonas hydrophilla* were done for the compounds

by using the disc diffusion method.[16, 17] Bacteria were cultured in nutrient agar medium and used as inoculum for study. Bacterial cells were swabbed on to nutrient agar medium [prepared from NaCl (5 g), peptone (5 g), beef extract powder (3 g), yeast extract powder (3.0 g), agar (20 g) in 100 mL distilled water; pH = 7.5 ± 0.2)] in petri plates. The compounds to be tested were dissolved in chloroform to a final concentration of 0.25% and 0.5% and soaked in filter paper discs of 5 mm diameter and 1 mm thickness. These discs were placed on the already seeded plates and incubated at 35 ± 2°C for 24 h. The diameter (mm) of the inhibition zone around each disc was measured after 24 h and results are listed in Table-2. Streptomycin was used as standard.

TABLE-2
ANTIBACTERIAL ACTIVITY OF COMPOUNDS (**4a–e**)

Compound	Diameter of zone of inhibition in mm			
	Enterobacteria faecalis		*Aeromonas hydrophilla*	
	0.25%	0.5%	0.25%	0.5%
4a	–	4	–	3
4b	–	5	–	2
4c	4	7	–	4
4d	6	11	4	9
4e	7	12	5	11
Streptomycin	9	16	12	19

According to the observation, the toxicity increases with increase in concentration of test solution containing new compounds. Although all the compounds are active, they did not reach the effectiveness of conventional bacterostatic streptomycin. Generally zone of inhibition was more significant against *Enterobacteria faecalis* than *Aeromonas hydrophilla.* The variation in effectiveness of different compounds against different organisms depends either on impermeability of cells of the microbes or diffusion in ribosomes of microbial cells.[18]

Conclusion

In conclusion, we have demonstrated the synthesis of newer pyrido dipyrimidines in one-pot method through Michael addition. The antibacterial studies of all compounds show their biological importance.

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