Asian Journal of Chemistry Vol. 15, Nos. 3 & 4 (2003), 1447–1451

Synthesis and Antibacterial Activities of 1,2,3,4,6,7,8,9,10-Nonahydro-1,3,7,9,10-Pentaphenyl-5-(2-Furanyl)-2,8-Dithio-4,6-Dioxo-5H-Pyrido [2,3-d; 6,5-d'] Dipyrimidine

R. NANDHA KUMAR, T. SURESH and P.S. MOHAN*

Department of Chemistry, Bharathiar University
Coimbatore-641 046, Indian
Fax: +91-0422-422387 E-mail: rajunandha@rediffmail.com

Biologically potent pyrido dipyrimidines have been achieved from 1,3-diaryl-2-thio barbituric acid with furfural and aniline. The spectral and analytical data support the structure of the synthesized compounds and all the compounds were screened for their antibacterial activities against *Enterobacter faecalis* and *Aeromonas hydrophilla.*

Key Words: 1,3-Diaryl-2-thiobarbituric acid, pyrido-dipyrimidines, spectral, antibacterial studies.

INTRODUCTION

In the present age of pharmacogenetics too, the pyrido-dipyrimidines have been given considerable interest due to a wide spectrum of biological properties. Extensive work on the synthesis of these heterocycles was done by various routes,[1-5] owing to their physiological and pharmacological properties, biomimetic oxidations[6, 7], antibacterial[8, 9], antineoplastic activities[10], etc. Thiobarbituric 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-2-thiobarbituric acids with an amine and an aldehyde in absolute ethanol at reflux temperature for 6 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 methodsd[14, 15].

General Procedure for the Synthesis of Pyrido Dipyrimidines

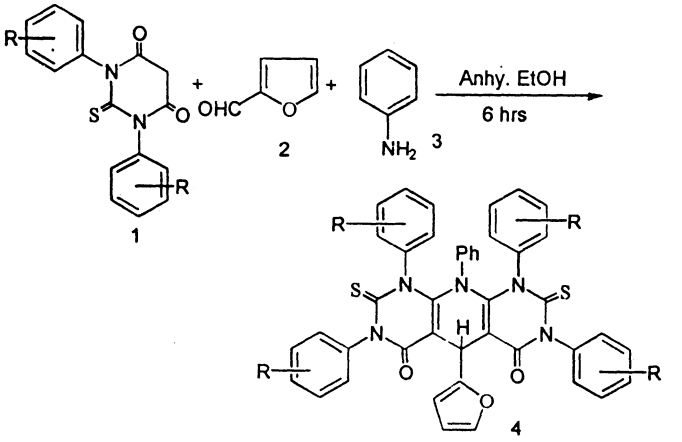
Respective 1,3-diphenyl-2-thiobarbituric acid (**1a–e**, 0.002 mol), furfural (0.001 mol) directly purchased from Merck Company and aniline (0.001 mol) after necessary purification in anhydrous ethanol (50 mL) were refluxed for about 6 h. After the completion of reaction, inferred through TLC, the reaction mixture was reduced to about half of its volume and allowed to cool. The solid separated was collected and recrystallized from $CHCl_3$-MeOH mixture.

RESULTS AND DISCUSSION

Compound **4a**, m.p. 235°C was obtained on recrystallization from $CHCl_3$: MeOH (7 : 3) in 85% yield. Its IR spectrum showed strong stretching absorption bands at 1606 cm^{-1} due to the —N—CO—N groups and 1323 cm^{-1} due to the C=S groups. The ^1H NMR spectrum revealed a sharp singlet at δ 6.7 which accounted for C_5 methine proton. All the twenty-eight aromatic proton resonances exhibited its absorption between δ 7.30–7.80 as an unresolved multiplet. The mass spectrum indicated the molecular ion peak at m/z 727. The elemental analysis further corroborated with the m.f. $C_{43}H_{29}N_5O_3S_2$. 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-(2-furanyl)-2,8-dithio-4,6-dioxo-5H-pyrido [2,3-d; 6,5-d'] dipyrimidine.

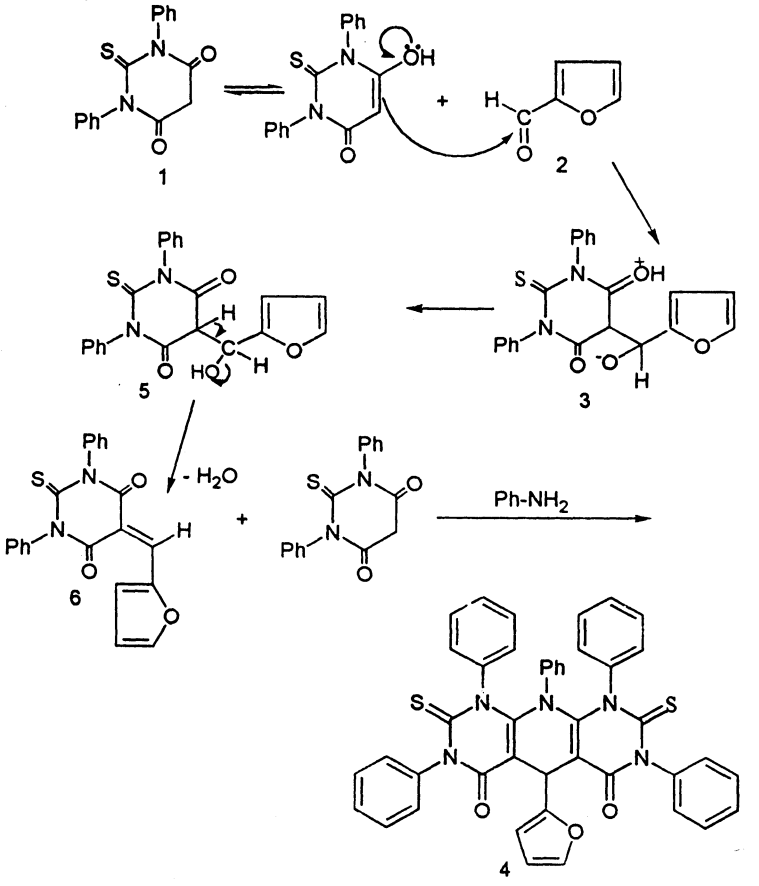
The plausible mechanistic pathway is shown in **Scheme I.** The reaction may be proceeded *via* the formation of a bis-product through the Michael addition of 1,3-diaryl-2-thiobarbituric acid to the 5-arylidine-1,3-diaryl-2-thiobarbituric acid which further react with amine to give the final product. Similar series of compounds were prepared using **(1b-e)** as the starting substrates (Table-1).

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 (5.0 g), peptone (5.0 g), beef extract powder (3.0 g), yeast extract powder (3.0 g), agar (20.0 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.



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-1

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

Comp.	m.p. (°C)	Yield (%)	IR γ_{max} (cm^{-1})	m.f. (m.w.)	Analysis (%) Calcd.	Found	^{1}H-NMR (δ/ppm)
4a	235	85	1323 1606	$C_{43}H_{29}N_5O_3S_2$ (727.87)	C 70.96 H 04.02 N 09.62	70.81 04.10 09.51	δ 6.7 (s, 1H, —CH) δ 7.3–7.8 (m, 28H, Ar—H)
4b	223	72.5	1325 1612	$C_{47}H_{37}N_5O_3S_2$ (783.97)	C 72.01 H 04.76 N 08.93	71.89 04.60 08.85	δ 2.3 (s, 12H, 4 × CH_3) δ 6.6 (s, 1H, —CH) δ 7.5–8.1 (m, 24H, Ar—H)
4c	174	82	1323 1616	$C_{47}H_{37}N_5O_3S_2$ (783.97)	C 72.01 H 04.76 N 08.93	72.10 04.72 08.91	δ 2.45 (s, 12H, 4 × CH_3) δ 6.8 (s, 1H, —CH) δ 7.1–7.85 (m, 24H, Ar—H)
4d	195	69.5	1310 1623	$C_{47}H_{37}N_5O_7S_2$ (847.97)	C 66.57 H 04.39 N 08.26	66.51 04.43 08.35	δ 3.9 (s, 12H, 4 × OCH_3) δ 6.9 (s, 1H, —CH) δ 7.4–8.2 (m, 24H, Ar—H)
4e	163	63	1290 1595	$C_{43}H_{25}N_5O_3S_2Cl_4$ (865.65)	C 59.66 H 02.91 N 08.09	59.53 02.79 08.01	δ 6.8 (s, 1H, —CH) δ 7.3–8.1 (m, 24H, Ar—H)

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	9	5	11
4b	3	8	6	12
4c	4	10	5	9
4d	5	11	6	11
4e	5	13	7	15
Streptomycin	9	16	12	19

From the graph (Fig. 1) it is clear that the toxicity increases with increase in concentration of test solution containing new compounds. All the compounds are active, but they did not reach the effectiveness of conventional bacterostatic streptomycin. The effectiveness may be due to the sulfur and other heterocyclic atoms present in the compound. 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 Micheal addition. The antibacterial studies of all compounds show their biological importance.

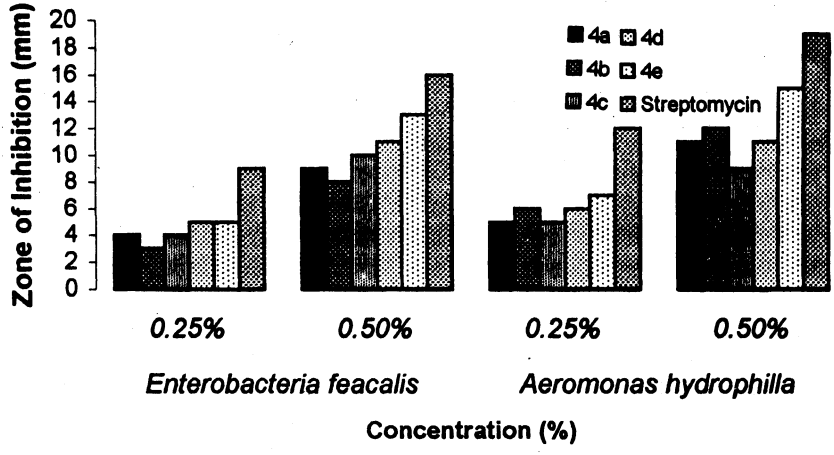


Fig. 1

ACKNOWLEDGEMENTS

The authors (RNK and TS) thank CSIR, New Delhi for the award of Senior Research Fellowship; SIF, Indian Institute of Science, Bangalore and Central Drug and Research Institute, Lucknow supported the spectral details. We gratefully acknowledge Mr. P.M. Ayyaswamy and Prof. Lakshmana Perumal Swamy, Division of Microbiology, Department of Environmental Sciences, Bharathiar University, Coimbatore for their Anthibacterial activities.

REFERENCES

1. K. Hirota, Y. Kitade and S. Senda, *J. Heterocyclic Chem.*, **22**, 345 (1985).
2. K. Tanaka, T. Okada and F. Yoneda, *Tetrahedron. Lett.*, **25**, 1741 (1984).
3. V.K. Ahluwalia, R. Agarwal and R. Chandra, *Indian J. Chem.*, **28B**, 964 (1989).
4. R.N. Kumar, S. Thamarai Selvi and P.S. Mohan, *Heterocyclic Commun.*, **6, 5,** 457 (2000).
5. R.N. Kumar, T. Suresh, A. Mythili and P.S. Mohan, *Heterocyclic Commun.*, **1, 2,** 193 (2001)
6. N. Tomohisa and Y. Hirotake, *J. Chem. Soc., Perkin Trans.* I, **16**, 2101 (1992).
7. N. Tomohisa and S. Yoshiharu, *Synthesis*, **9**, 93 (1983).
8. K.B. Beranadette and A.W. Judith, *J. Heterocyclic Chem.*, **12**, 1221 (1975).
9. J.A. Bares, N.J. Kurlick, S.E. Shaffer and M.G. Varner, *J. Med. Chem. Chim. Ther.*, **15**, 571 (1980).
10. A. Krewtzberger and E. Kreutzberger, *Arch. Pharm.*, **318**, 821 (1985).
11. P. Molina, M.J. Vilaplanna and A. Paston, *Synthesis*, 827 (1992).
12. F. Yonedo, H. Yamato and M. Ono, *J. Am. Chem. Soc.*, **103**, 5943 (1981).
13. V.K. Ahluwalia and U.S. Das, *Indian J. Chem.*, **35B**, 852 (1996).
14. S.C. Nagam, G.S. Saharia and H.R. Sharma, *Def. Sci. J.*, **31**, 15 (1981).
15. I.N.D. Das and S. Dutt, *Proc. Indian Acad. Sci.*, **8A**, 145 (1938).
16. C.H. Collins and P.M. Lyne, Microbial Methods, University Park Press, Baltimore (1970).
17. R. Nandha Kumar, H. Vishwanathan, T. Suresh and P.S. Mohan, *Fitoterapia*, **73**, 734 (2002).
18. P.G. Lawrence, P.L. Harold and O.G. Francis, *Antibiot. Chemother.*, 1597 (1980).

(*Received*: 2 January 2003; *Accepted*: 18 April 2003) AJC-3046