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RESEARCH ARTICLE

SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1, 6-DIHYDRO PYRIDINE DERIVATIVES

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ABSTRACT

The 2-amino-4-ethyl-1,6-dihydro 6-thiophenyl pyridine-3,5- dicarbonitriles were synthesized within a single step using aldehydes, active methylene compounds and thiophenol in ethanol and piperidine system. The synthetic potential of the method was to be investigated to obtain its 4-substituted and 6-substituted derivatives. In view of this the prior method was optimized and the desired 4-sustituted and 6-substituted compounds were synthesized with 60-90% yield. Newly synthesized compounds were found to have antifungal and antihistaminic activity.

Keywords: *Aspergillus niger, Candida albicans, cinnamonitriles, DHP, thiophenol Derivatives.*

INTRODUCTION

The pyridine motif is found in various therapeutic agents and other pharmaceutical compounds. The ring system of 1, 4-DHP analogs extends its applications to the most potent CVS drugs.[1,2] The development of DHP chemistry offers numerous opportunities for further chemical modifications. [3,4,5] α, β- unsaturated nitriles have been extensively utilized in the synthesis of several new heterocyclic compounds. The synthetic potential of the α-functionally substituted cinnamonitriles forms the lightening path for the synthesis of 1, 6-DHPs. [6,7]

The 2-amino-4-ethyl-1, 6-dihydro 6-thiophenyl pyridine-3, 5- dicarbonitrile were to be synthesized. The synthetic potential of the method was to be investigated to obtain its 4-substituted and 6-substituted derivatives. The synthesized compounds were to be characterized assessed for biological activity.

MATERIALS AND METHODS

Four new compounds have been synthesized by conventional method (Scheme:1). Thin Layer Chomatography (T.L.C.) was used to assess the course of the reaction and the purity of the intermediates and the final compounds. Melting points were taken in open capillaries and are uncorrected. IR spectra of the intermediates and final compounds were recorded on Jasco FTIR-410 spectrophotometer using KBr pellet method and that of the liquid intermediates on Shimadzu IR spectrophotometer using Nujol or as a neat. H^1 NMR Spectra in $CDCl_3$/TMSO-16 were recorded on MERCURY YH-300 Model Spectrophotometer of the company VARIAN (in δ ppm) using TMS as internal standard at 300 MHz. Raw materials used are tested for their physical constants and TLC to ensure the purity. Nitrogen content of the final compounds was estimated by Kjehldal's method.

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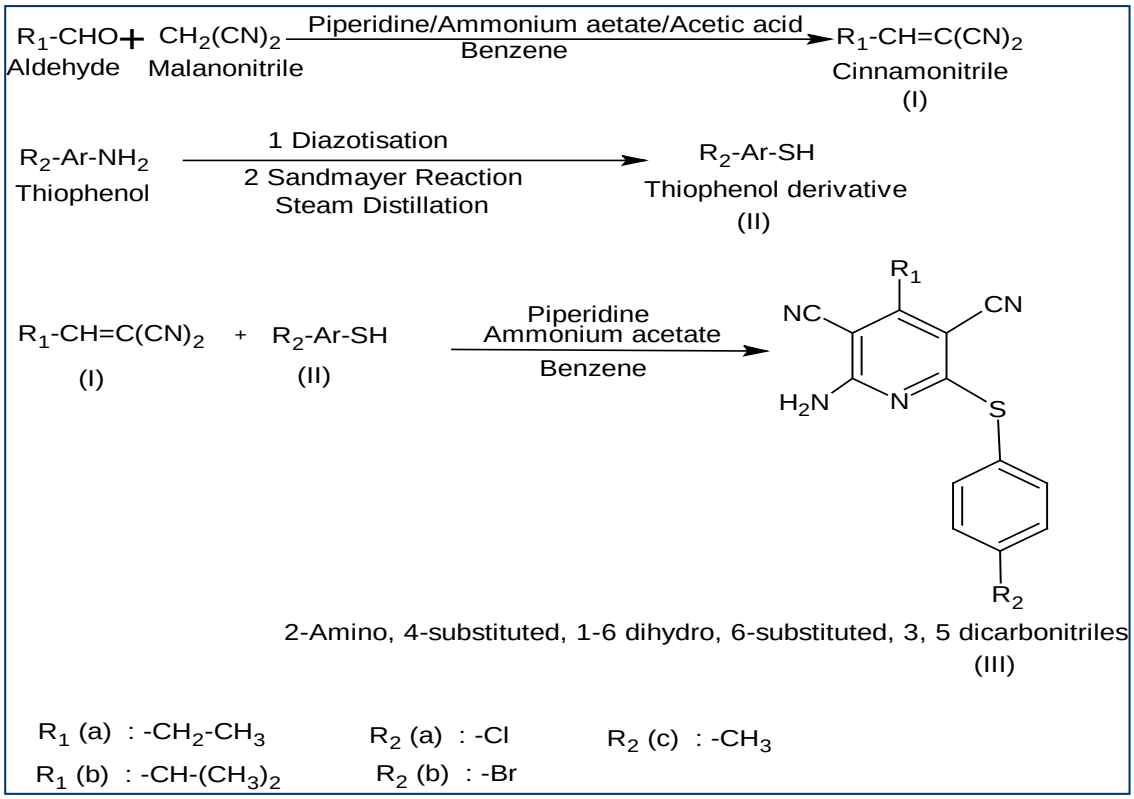
Scheme: 1



Synthesis of cinnamonitriles (Ia and Ib):

Equimolar quantities of aldehydes and malanonitriles were dissolved in benzene. 0.04 mol of ammonium acetate in 0.08 mol of acetic acid and few drops of piperidine were added. The mixture was refluxed under a constant water separator for 40 minutes. Cooled, washed with water and distilled in vacuum.

Synthesis of thiophenol derivatives (IIa-c):

The thiophenol were prepared by the diazotization of the respective amine followed by the substitution of diazonium group by halo or cyano group in the presence of cuprous salts, the reaction is well known as Sandmeyer reaction

General Procedure for the synthesis of titled compounds (IIIa-d):

The equimolar quantities of alkylidene malononitriles (Ia/b) and thiophenol derivative (IIa/b/c) were dissolved in benzene. Ammonium acetate in acetic acid and few drops of piperidine were added. The mixture was refluxed under constant water separator for 12-14 hrs. Excess of benzene was distilled out and the reaction mixture was cooled and poured on to ice. Filtered and recrystallized.

Characterization of the synthesized compounds is given in (Table: 1).

Table: 1

	Compound synthesized	mp/bp(^{0}C)	Yield (%)	IR (cm^{-1})	NMR (δ)
1. 6.	2-Amino-4-ethyl-1,6-dihydro-6-(4-Bromo-thiophenyl) pyridine-3,5-dicarbonitrile **(IIIa)**	84	76.77	3408, 2923(Ar str), 2856(CH2-CH3 Str), 2206(R-CN str), 2856(CH2-CH3 Bending) 1377 (Ar-NH2 Str), 1010, 1080 (CN str), 725(CS str), 603Ar C-Br str).	7.2-7.56 (4H, Doublet of doublet, Aromatic protons), 3.602 (Singlet of NH2 proton), 1.2, 1.5 (-R), 0 (TMS).
2. 7.	2-Amino-4-isopropyl-1,6-dihydro-6-(4-Bromo-thiophenyl) pyridine-3,5-dicarbonitrile **(IIIb)**	92	89.44	3072, 2923 (Ar C-H str), 2852 (CH2-CH3 Str), 2206 (R-CN str), 1468 (CH2-CH3 Bending) 1383 (Ar-NH2 Str), 1005, 1079 (CN str), 722, 691 (CS str), 624 (Ar C-Br str).	7.2-7.428 (4H, Doublet of doublet, Aromatic protons), 3.55 (Singlet of NH2 proton), 1.250 (-R), 0 (TMS).

3. 8.	2-Amino-4-ethyl-1,6-dihydro-6-(4-thiocresyl) pyridine-3,5-dicarbonitrile **(IIIc)**	76	83.59	3449, 2917 (Ar str), 2855 (CH2-CH3 Str), 2360 (R-CN str), 1487 (CH2-CH3 Bending) 1397 (Ar-NH2 Str), 1013 (CN str), 619, 669 (CS str).	7.072-7.370 (4H, Doublet of doublet, Aromatic protons), 3.62 (Singlet of NH2 proton), 1.313 (-R), 0 (TMS).
4. 9.	2-Amino-4-ethyl-1,6-dihydro-6-(4-chloro-thiophenyl) pyridine-3,5-dicarbonitrile **(IIId)**	87	62.01	3076, 2920 (Ar C-H str), 2850 (CH2-CH3 Str), 2203 (R-CN str), 1472 (CH2-CH3 Bending) 1385 (Ar-NH2 Str), 1009, 1093 (CN str), 740(CS str), 626 (Ar C-Cl str).	7.1-7.4 (4H, Doublet of doublet, Aromatic protons), 3.476 (Singlet of NH2 proton), 1.248 (-R), 0 (TMS).

RESULT AND DISCUSSION

BIOLOGICAL ACTIVITY

Antifungal Activity [8,9]:

Nutrient Agar I. P. (MMO12-HiMedia) was used for testing the antifungal activity. The synthesized compounds were screened *in-vitro* for antifungal activity against the organisms *Aspergillus niger* and *Candida albicans* using diffusion assay (paper disc method) technique in which each sterile disc of Whatman's filter paper of 3 mm diameter was dipped into the compounds (IIIa-d) solution separately using DMF as the universal organic solvent. The discs were placed on to the surface of the solid media inoculated with 0.5ml of growing culture of test microorganisms in each separate plate. Ketoconazole (10µg/ml) was used as a standard drug. The plates were kept in refrigerator for 15 mins to allow diffusion of the drugs from the disc into the media and were then incubated at 37°C. After 24 has of incubation the results are reported in table: 2.

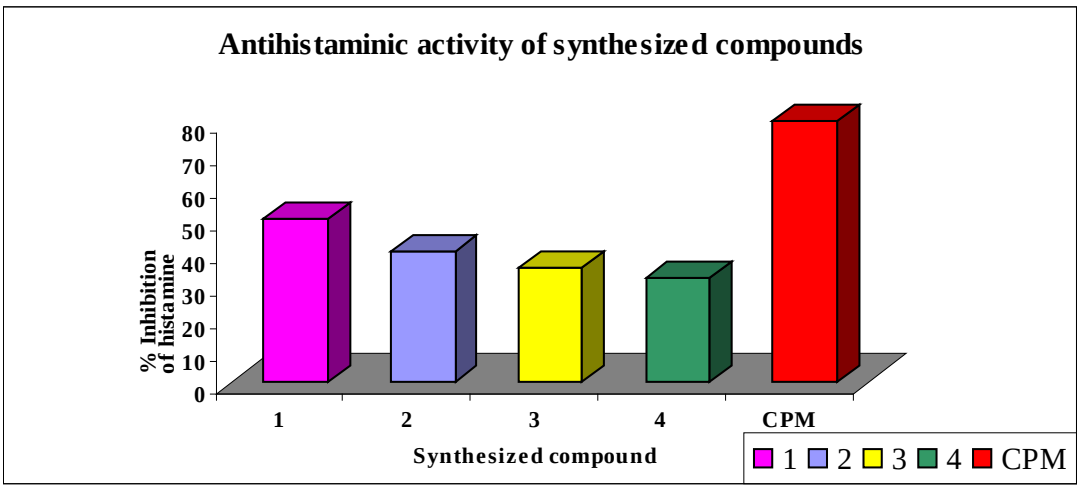
Table: 2

Sr. No.	Compound	Dilutions (µg/ml)	A. niger (mm)	C. albicans (mm)
1.	IIIa	2000	17	11
		1500	10	--
		1000	9	--
		Standard 10	15	21
2.	IIIb	2000	16	--
		1500	15	---
		1000	15	--
		Standard 10	16	24
3.	IIIc	2000	12	10
		1500	--	9
		1000	--	8
		Standard 10	14	20
4.	IIId	2000	15	10
		1500	--	8
		1000	--	--
		Standard 10	18	20

Antihistaminic activity [10]:

The synthesized compounds were evaluated for their antihistaminic activity *in vitro* by recording concentration response curve of histamine using isolated tissue preparation of *guinea pig* ileum. *Guinea pigs* (400-600 g) overnight fasted were used. The animals were sacrificed and the 2-3 cm long, a small fragment of ileum was cut, tied with the tread at top and the bottom ends without closing the lumen. Mounted the tissue in the organ bath containing Tyrone solution at 32-35°C and bubbled with air. A tension of 0.5 g is applied and the tissue is allowed to equilibrate for 30 mins. The drugs were added and the concentration response curve was recorded. The Chlorpheneramine (10 µg/ml) was used as the standard. Histamine (1mg/ml) was used. The % inhibition of the histamine was recorded in the graph No .1

Graph: 1



The four derivatives of 2-amino-4-ethyl-1,6-dihydro 6-thiophenyl pyridine-3,5- dicarbonitrile were successfully with the novel method with 60-90% yield.

All the synthesized compounds were found to be active against *A. niger* and *C. albicans*. The results revealed that all the tested compounds exhibit moderate to strong activity against these microorganisms.

The antihistaminic activity results were reported as % inhibition of the histamine. The % inhibition of the standard was 80%. Height of the histamine was 10mm. It was observed that all the compounds were having less blocking activity that that of the standard.

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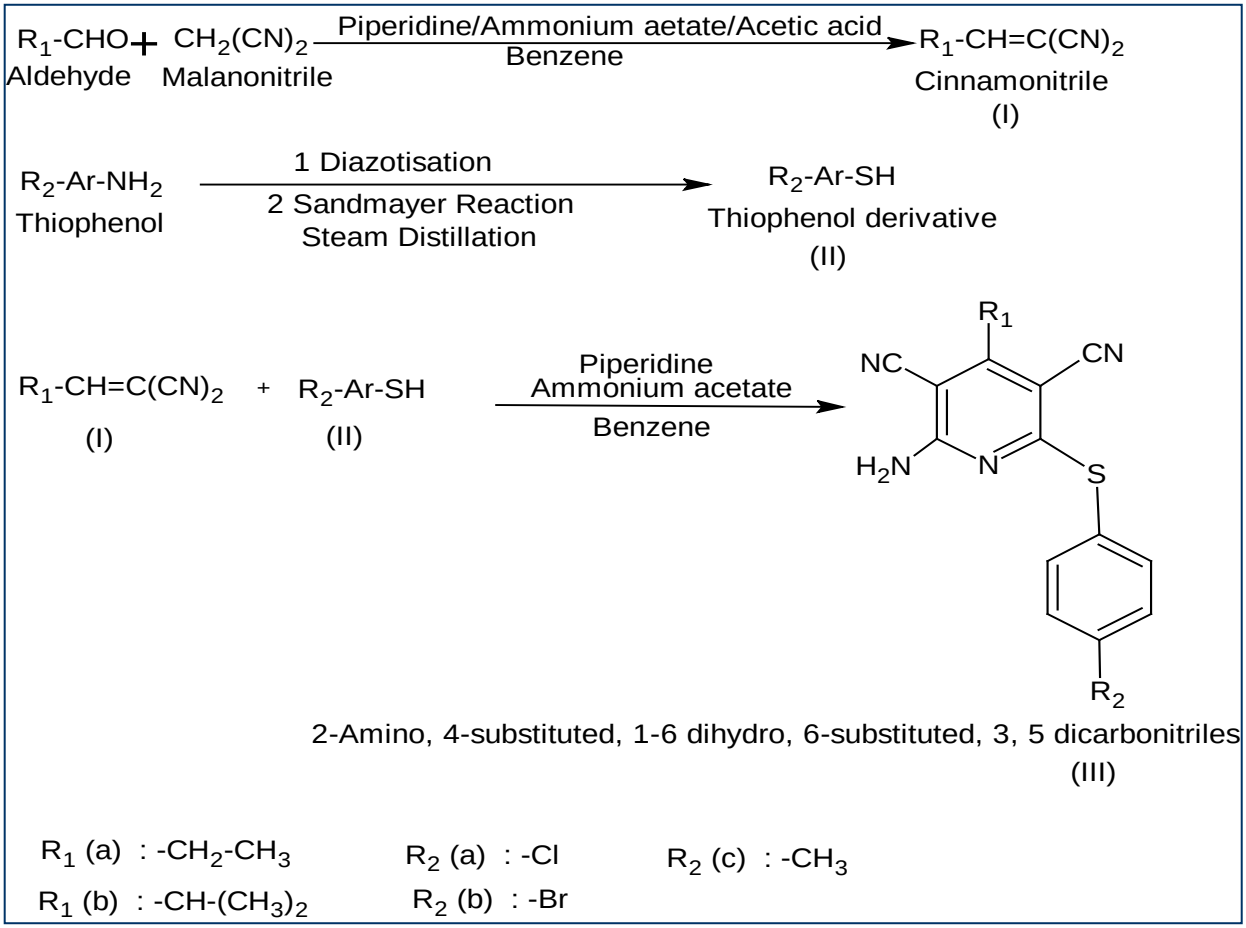
REFERENCES

1. Hantzsch A., Ann. Chem., 1882. 1, p. 215.
2. Eisner U. and Kuthan J., Chem. Rev., 1972. 1, p. 72.
3. Nefzi A., Ostresh J. M., Houghten R. A., The Current Status of Heterocyclic Combinatorial Libraries, Chem. Rev., 1997. 97, p. 449-472.
4. Roth H. J., Kleeman A., Pharmaceutical Chemistry. New York: John Wiley and sons; 1998.
5. Gogfraind T., Miller R., Wibo M., Pharmacol. Rew., 1986. 38, p. 321-330.
6. A.H.H. Elghandour, M.K.A. Ibrhim, F.M.M. Ali and S.M.M. Elshikh, Indian J. of Chem.. Vol 36 B, Jan 1997. p. 79-82.
7. Elnagdi M. H., El-Fahham H. A. and Elgomeie G. E. H., Heterocycles. 1983. 20, p. 519.
8. Indian Pharmacopoeia. **Vol-II** 3rd ed. 1985. A-88.
9. R. Cruickshank, Duguid J. P., Swain R. H., Medical Microbiology, Churchil Livingstone, **2**, 1998. p. 190-202.
10. Kulkarni S. K., Experimental Pharmacology, Nirali Prakashan.

Scheme: 1



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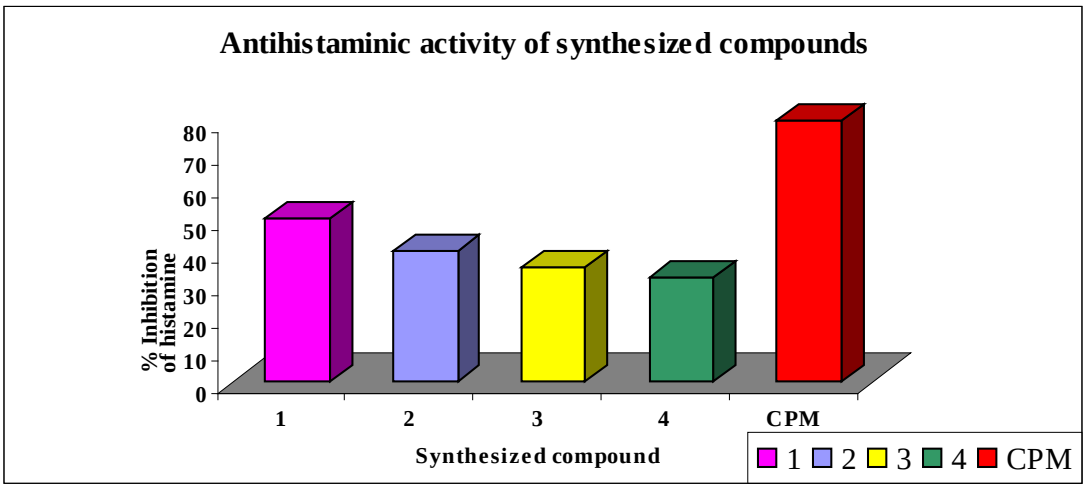
		1000	15	--
		Standard 10	16	24
7.	IIIc	2000	12	10
		1500	--	9
		1000	--	8
		Standard 10	14	20
8.	IIId	2000	15	10
		1500	--	8
		1000	--	--
		Standard 10	18	20

Graph: 1



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