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Synthesis and antimicrobial activity of chalcones of naphtho[2,1-b]furan condensed with barbituric acid

Chandrashekhar C.H, Latha K.P*, Vagdevi H. M and Vaidya V.P

*Department of Chemistry, Sahyadri Science College (Autonomous), Shimoga, Karnataka
Department of PG Studies and Research in Chemistry, Kuvempu University, Shankaraghatta,
Karnataka*

ABSTRACT

Barbitones were synthesized by the condensation of chalcones with barbituric acid. The structures of the synthesized compounds assigned on the basis of elemental analysis, IR, ¹H NMR and mass spectral studies. All the products were evaluated for their in vitro antimicrobial activity against various strains of bacteria and fungi.

Keywords: Barbitones, chalcones, Naphtho[2,1-b]furan, antimicrobial activity.

INTRODUCTION

Nitrogen containing heterocyclic compounds, such as barbitones, are known to possess a wide range of activities, such as hypnotics,¹ cardiovascular,² analgesics,³ antiviral,⁴ anticancer⁵ etc. Moreover, Furan moieties are common substructures in numerous natural products⁶. Naphthofuran derivatives have been isolated from various natural sources like *Fusarium oxysporum*⁷, *Gossypium barbadense*⁸, etc and are well known for various biological activities like antitumour⁹, antifertility¹⁰, mutagenic¹¹, growth inhibitory¹² and oestrogenic¹³. Many of the condensed heterocycles and biheterocycles enclosing naphthofuran have been reported processes wide spectrum of activities¹⁴⁻¹⁹. The starting compound, 2-acetyl naphthofuran was condensed with different aryl aldehydes to yield chalcones. These on condensation with barbituric acid in glacial acetic acid furnished the target molecules (scheme-1). The constitution of all the products were characterized using elemental analysis and IR, ¹H NMR and mass spectroscopy. All the compounds were screened for their in vitro antimicrobial activity against different strains of bacteria and fungi.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds were checked by TLC, FT-IR spectra were taken in a Perkin Elmer 157 infrared

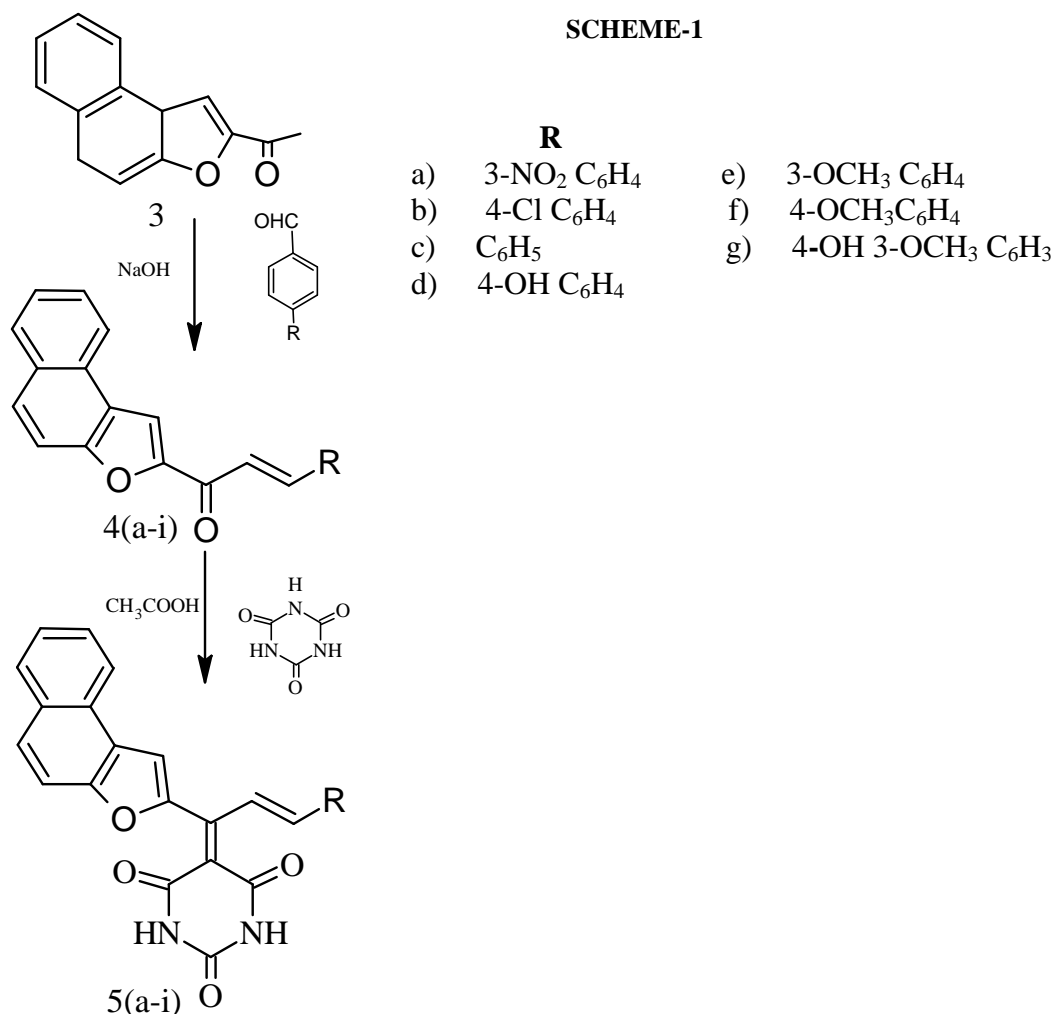
spectrophotometer. ^1H NMR spectra (300 MHz) were recorded on a Bruker supercon FT-NMR instrument using TMS as internal standard (chemical shifts in ppm).

2-Amino-4-(4-hydroxyphenyl)-6-naphtho[2,1-*b*]furan-2-yl-nicotinonitrile **4d**

A mixture of 1-(4-methoxyphenyl)-3-(1,3-diphenyl-4-pyrazolyl)-2-propen-1-one (3.8 g, 0.01mol), barbituric acid (1.28 g, 0.01 mol) in glacial acetic acid was refluxed for 12 h in an oil bath. The contents were poured into ice and the product was isolated and crystallized from DMF. Similarly, the compounds **4** (b-g) were synthesized from **3** by reacting with appropriate aromatic aldehydes.

The required starting material 2-acetylnaphtho[2,1-*b*]furan **3** was synthesised from 2-hydroxy-1-naphthaldehyde and chloroacetone in presence of anhydrous K_2CO_3 and dry acetone by well established method in our laboratory. The synthesis of key intermediate 2-amino-4-(substituted phenyl)-6-naphtho[2,1-*b*]furan-2-yl-nicotinonitriles **4(a-g)** was accomplished by reacting 2-acetylnaphtho[2,1-*b*]furan **3** with appropriate aromatic aldehydes, with dilute NaOH. The structure of 2-amino-4-naphtho[2,1-*b*]furan-2-yl-6(4-hydroxyphenyl)nicotinonitrile **4a** was established by IR, ^1H NMR and mass spectral studies. The IR spectrum exhibited broad absorption band at 3444 cm^{-1} due to $-\text{NH}_2$ stretching frequency and a sharp absorption peak at 2202 cm^{-1} corresponds to $-\text{CN}$ stretching frequency. The formation of **4d** was confirmed by its the ^1H NMR spectrum. The presence of broad singlet (D_2O exchangeable) at δ -6.8 indicated the two protons of $-\text{NH}_2$, a multiplet between δ 7.5 - 8.5 were due to eleven aromatic protons and a peak at δ 9.8 was assigned to $-\text{OH}$ group. The mass spectra showed the molecular ion peak at m/z 377, which is consistent to its molecular weight.

SCHEME-1



RESULTS AND DISCUSSION

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas auregenosa* and *Bacillus subtilis*. The activity was carried out using cup plate method²⁴. The zone of inhibition was measured in mm. DMF was used as a vehicle and Ciproflaxacin as standard drug for comparison. The compounds were tested at 10 mg/mL concentration and each well was loaded with 50 µg/mL. All the synthesized compounds were found to exhibit moderate activity against all bacteria. The zones of inhibition are presented in Table -1

Table - 1 Antibacterial activity of the compounds

Compound	Diameter of zone of inhibition (mm*)			
	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas auregenosa</i>	<i>Bacillus subtilis</i>
5a	12	00	00	16
5b	00	00	00	15
5c	00	00	09	14
5d	00	00	00	00
5e	10	11	09	00
5f	13	08	08	15
5g	00	09	11	13
5h	00	00	00	00
5i	00	00	00	13
5j	00	10	00	15
DMF	00	00	00	00
Ciproflaxacin	25	40	43	44

Table – 2 Antifungal activity of the compounds

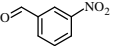
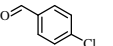

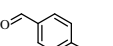
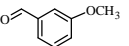
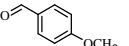
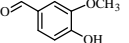
Compound	Diameter of zone of inhibition (mm*)		
	<i>Curvularia</i>	<i>Aspergillus niger</i>	<i>Candida albicans</i>
5a	00	00	00
5b	15	00	00
5c	18	00	00
5d	00	00	00
5e	10	00	00
5f	13	00	00
5g	00	00	00
5h	00	00	00
5i	00	00	00
5j	13	00	00
DMF	00	00	00
Clotrimazole	48	38	27

Antifungal activity

The synthesized compounds were evaluated *invitro* for antifungal activity by using standard agar disc diffusion method²⁴ against *Curvularia*, *Aspergillus niger* and *Candida albicans*. DMF was used as a vehicle. The compounds were tested at 10 mg/mL concentration and each well was

loaded with 50 µg/mL of the sample. Clotrimazole was used standard drug. The zones of inhibition are presented in Table-2. All synthesized compounds were found to be feebly active against fungi.

Table-3 Physical data of the compounds: 5a-j

Compound	R	Mol. Formula	Yield (%)	M.P (°C)	Elemental Analyses		
					Calcd (%)	(Found)%	
					C	H	N
5a		C ₂₄ H ₁₄ N ₄ O ₃	62	168	70.90 (70.93)	3.45 (3.47)	13.77 (13.79)
5b		C ₂₄ H ₁₄ ClN ₃ O	68	175	72.80 (72.82)	3.53 (3.56)	10.60 (10.62)
5c		C ₂₄ H ₁₅ N ₃ O	70	189	79.73 (79.76)	4.15 (4.18)	11.60 (11.63)
5d		C ₂₄ H ₁₅ N ₃ O ₂	65	183	76.34 (76.38)	3.99 (4.01)	11.11 (11.13)
5e		C ₂₅ H ₁₇ N ₃ O ₂	70	173	76.69 (76.71)	4.36 (4.38)	10.72 (10.74)
5f		C ₂₅ H ₁₇ N ₃ O ₂	65	195	76.69 (76.71)	4.35 (4.38)	10.70 (10.74)
5g		C ₂₅ H ₁₇ N ₃ O ₃	67	168	73.68 (73.70)	4.19 (4.21)	10.29 (10.31)

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