International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Volume 8, Issue 3 (MAY-JUNE 2020), PP. 28-35

NOVEL NAPHTHOFURAN DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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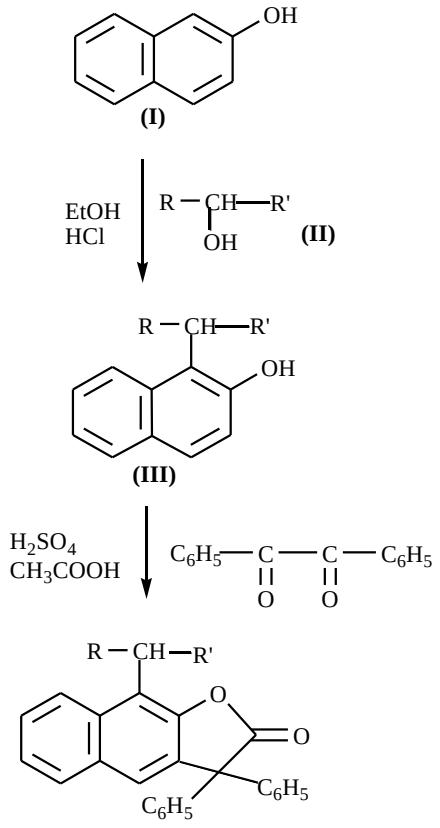
***Abstract*— Reaction of β-Naphthol (I) with amido/imido alcohols (II) in ethyl alcohol containing the catalytic quantity of conc. HCl yielded [(2-hydroxynaphthalen-1-yl)alkyl]-arylamides/imides (III) in excellent yields. Interaction of (II) with benzil in a mixture of conc. H_2SO_4 and glacial CH_3COOH (9:1) afforded the target compounds designated as [(2,3-Dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]furan-9-yl)alkyl] arylamides/imides (IV) in the yields ranging from 52 to 68%. The compounds (IV) were evaluated against five strains of fungi and four strains of bacteria, respectively. (SCHEME)**



(SCHEME)

***Index Terms*— Antimicrobial Agents, Naphthofuran Derivatives.**

I. INTRODUCTION

Furan and bezofuran derivatives as antimicrobial agents have been less extensively investigated, however, two furan derivatives viz; nitrofurazone and furazolidone are in clinical practice since a long time. These compounds are used in the treatment of burns and in the prevention of bacterial infection in skin graft procedures.[1] They are also active against various species of Salmonella, Shigella, Proteus and Enterobacter as well as Escherichia coli and Vibrio cholerae.[2] In order to study the antibacterial and antifungal activities against four strains of bacteria viz., Escherichia coli (ATCC-9637) (Ec), Pseudomonas aeruginosa (ATCCBAA-427) (Pa), Staphylococcus aureus (ATCC-25923) (Sa) and Klebsiella pneumoniae (ATCC-27736) (Kp). As well as five strains of fungi viz., Candida albicans (Ca), Cryptococcus neoformans (Cn), Trichophyton mentagrophytes (Tm), Aspergillus fumigatus (Af) and Candida parapsilosis (ATCC-22019) (Cp). The authors undertook the synthesis of some [(2,3-dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]furan-9-yl)alkyl] arylamides/imides (IV).

II. EXPERIMENTAL

The melting points of the synthesized compounds were determined in open glass capillaries in a Toshniwal Electric Apparatus (Japan) and the values reported here in are therefore, uncorrected. Percentage of the element nitrogen was determined on a Carlo Erba 1108 Elemental Analyser at Sophisticated Analytical Instrument Facility (SAIF), Central Drug Research Institute, (CDRI) Lucknow. Thin layer chromatography (TLC) was accomplished with silica-gel-G (BDH) chromatoplates of 15cm x 2cm. The spots were visualized by exposing the developed and dried plates to iodine vapours. The infrared (IR) spectra were recorded in the region 4000-450 cm-1 range using KBr discs on FTIR Perkin Elmer Spectrophotometer RXI at (CDRI), Lucknow. The nuclear magnetic resonance (NMR) spectra, (PMR and CMR) were recorded on Bruker Advance 400 MHz spectrometer at (CDRI), Lucknow using $CDCl_3$ as solvent. Tetramethyl silane (TMS) was used as an internal standard and the values of the chemical shifts are given on □-scale. The mass spectra (FAB) were recorded on JeoL SX -102 Mass spectrometer/Data system using Argon/Xenon (6 KV, 10 mA) as the FAB gas. The accelerating voltage was 10 KV and the spectra were

recorded at room temperature using m-nitrobenzyl alcohol as matrix. The peaks at m/z 136, 137, 154, 289 and 307 were of matrix.

N-(Hydroxyalkyl)-arylamides/imides (II)

The literature methods[3-6] were followed in the synthesis of the titled compounds(II).

[(2-Hydroxynaphthalen-1-yl)alkyl]-arylamides/imides (III)

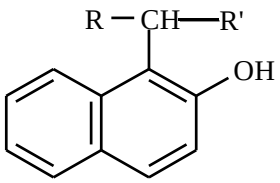
β-Naphthol (0.05mole) and (2-hydroxyalkyl)-arylamide/imide (II) (0.05mole) were dissolved in absolute

To a mixture of [(2-hydroxynaphthalen-1-yl)alkyl]-arylamides/imides (III) (0.01mole) and benzil (0.01 mole) a mixture of conc. H_2SO_4 and glacial CH_3COOH (9:1,100ml) was added slowly in installments with constant stirring. The mixture was further stirred mechanically for about four hours ethanol by warming gently and then conc. HCl (2mL) was added to this ethanolic solution. The solution thus obtained, was heated under reflux for four hours under anhydrous reaction conditions. Excess of ethanol was distilled off and the solid thus obtained, was washed with cold water, dried in air and recrystallized from acetone. The details of the compounds of this recorded in, are recorded in Table I.

[2-(2,3-Dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]furan-9-yl)alkyl] arylamides/imides (IV)

and poured into ice cold water slowly with shaking. The solid thus separated was filtered off, washed with cold water, air dried and recrystallized from diluted. ethanol. The details of the target molecules are reported in Table II.

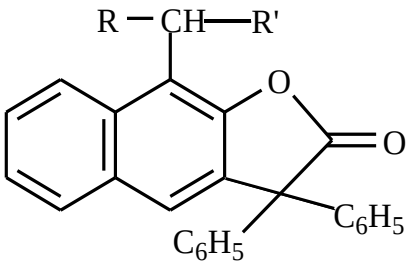
TABLE I



Physical data of [(2-hydroxynaphthalen-1-yl)alkyl]-arylamides/imides (III)

Compd. No.	R	R'	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular weight	Nitrogen %	
								Calcd.	Found
1	H	phthalimido	90-91	81	Orange	$C_{19}H_{13}NO_3$	303	4.62	4.54
2	H	phthalimidomethyl	70-71	72	Brown	$C_{20}H_{15}NO_3$	317	4.42	4.40
3	H	benzamido	80-81	82	White	$C_{18}H_{15}NO_2$	277	5.05	5.01
4	C_6H_5	benzamido	92-93	69	Brown	$C_{24}H_{19}NO_2$	353	3.97	3.93

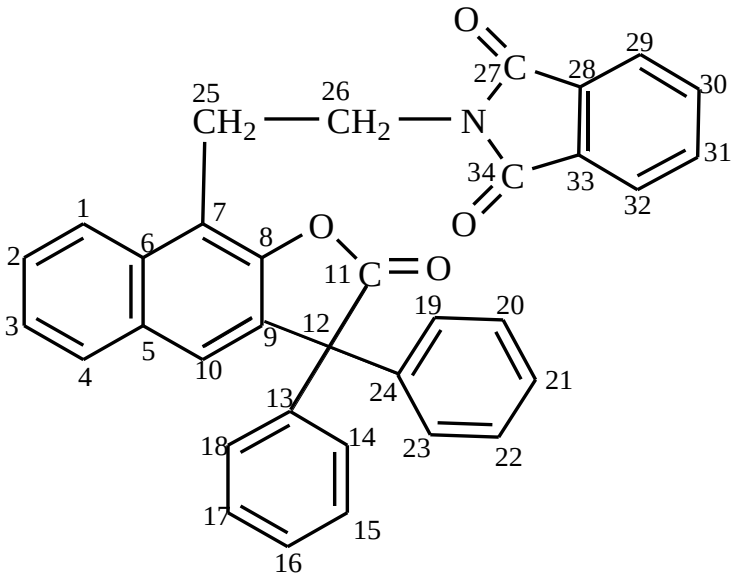
Table II



Physical data of [(2,3-dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]-furan-9-yl)alkyl] arylamides/imides (IV)

Compd. No.	R	R'	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular weight	Nitrogen %	
								Calcd.	Found
1	H	phthalimido	76	68	Brown	$C_{33}H_{21}NO_4$	495	2.83	2.75
2	H	phthalimidomethyl	80	59	Green	$C_{34}H_{23}NO_4$	509	2.75	2.70
3	H	benzamido	90	64	Brown	$C_{32}H_{23}NO_3$	469	2.99	2.96
4	phenyl	benzamido	110	52	Grey	$C_{38}H_{27}NO_3$	545	2.57	2.55

IR, ^{1}HNMR and ^{13}CNMR spectral data of [(2,3-dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]-furan-9-yl)ethyl]isoindoline-1,3-dione (Compound 2 of Table II)



IR (KBr) cm^{-1}: 1673.4 (imide C=O), 1817.4 (β-lactone C=O), 1212.7 (C–O–C, cyclic).

^{1}H NMR (CDCl$_3$) δ ppm: 7.257-7.984 (m, 19H, Ar<u>H</u>), 1.235 (t, 2H, C–C<u>H</u>$_2$, J=5.55Hz), 2.362 (s, 2H, N–C<u>H</u>$_2$, J=4.55Hz).

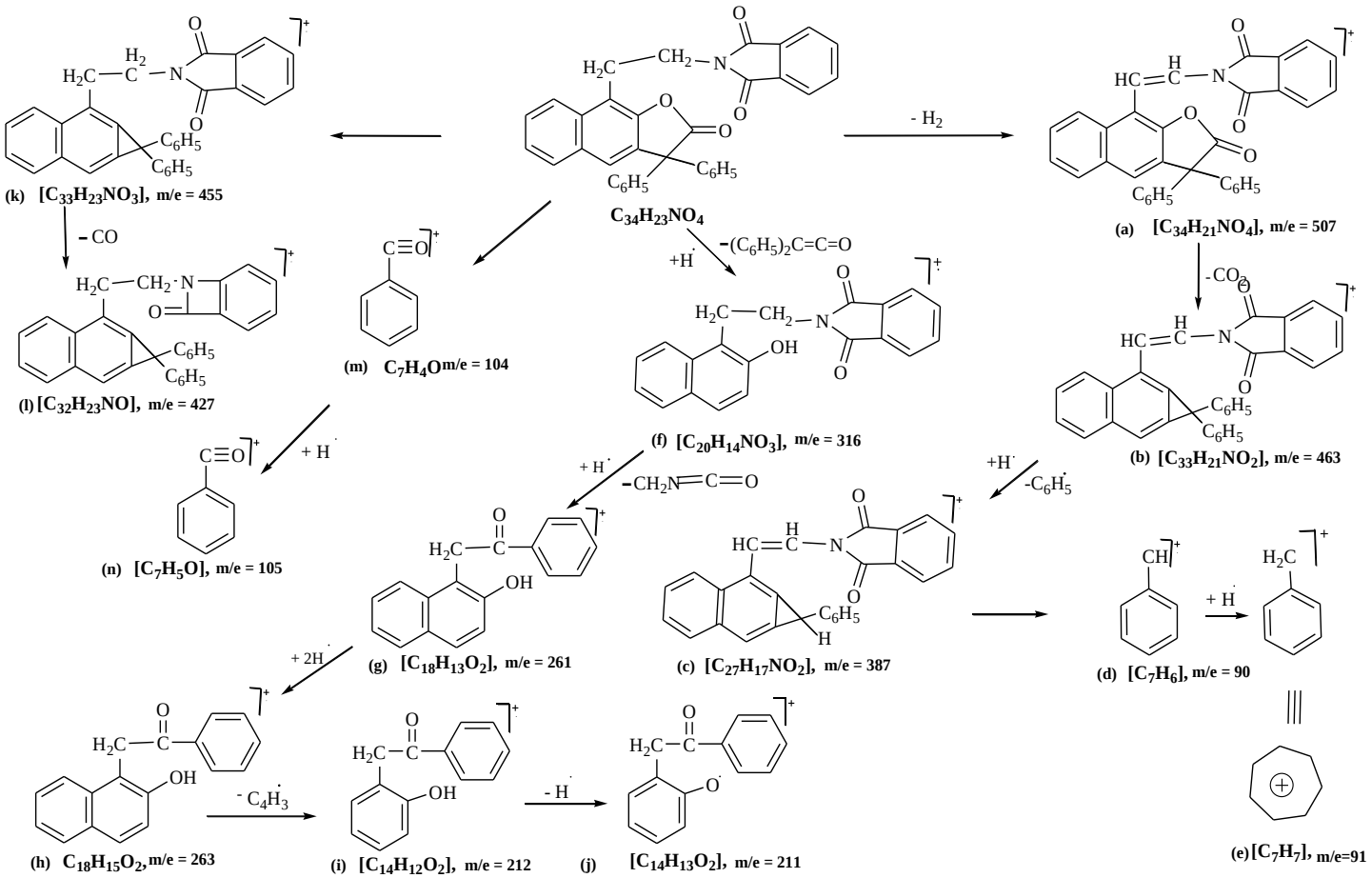
^{13}C NMR (CDCl$_3$) δ ppm: 45.541 (C–25), 50.262 (C–26) 123.080, 1123.341, 123.559, 131.030, 131.811, 132.253, 133.892, 134.389, 135.143 (C–1 to C–10), (C–13 to C–18), (C–19 to C–24), (C–28 to C–33), 169.275 (C–27, C–34), 175.25 (C-11).

Important mass spectral peaks of [(2,3-dihydro-2-oxo-3,3-diphenyl naphtho[2,3-b]-furan-9-yl)ethyl]isoindoline-1,3-dione

Fragments	**Molecular formula**	**m/e**
(a)	$C_{34}H_{21}NO_4$	507
(b)	$C_{33}H_{21}NO_2$	463
(c)	$C_{27}H_{17}NO_2$	387
(d)	C_7H_6	90
(e)	C_7H_7	91
(f)	$C_{20}H_{14}NO_3$	316
(g)	$C_{18}H_{13}O_2$	261
(h)	$C_{18}H_{15}O_2$	263
(i)	$C_{14}H_{11}O_2$	212
(j)	C_6H_5	77
(k)	$C_{33}H_{23}NO_2$	455
(l)	$C_{32}H_{23}NO$	427
(m)	C_7H_4O	104
(n)*	C_7H_5O	105

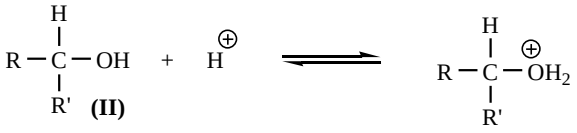
M^+ was not observed; *base peak

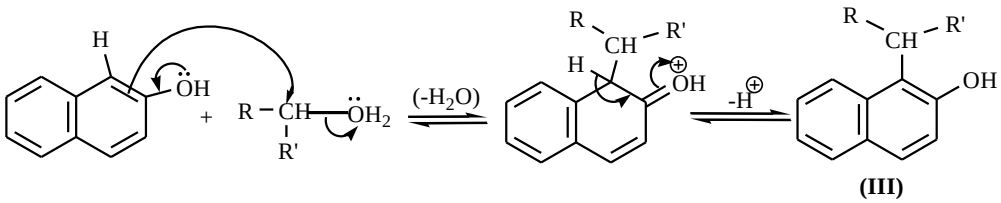
Mass spectral pattern of [(2,3-dihydro-2-oxo-3,3-diphenylnaphtho[2,3-b]-furan-9-yl)ethyl]isoindoline-1,3-dione



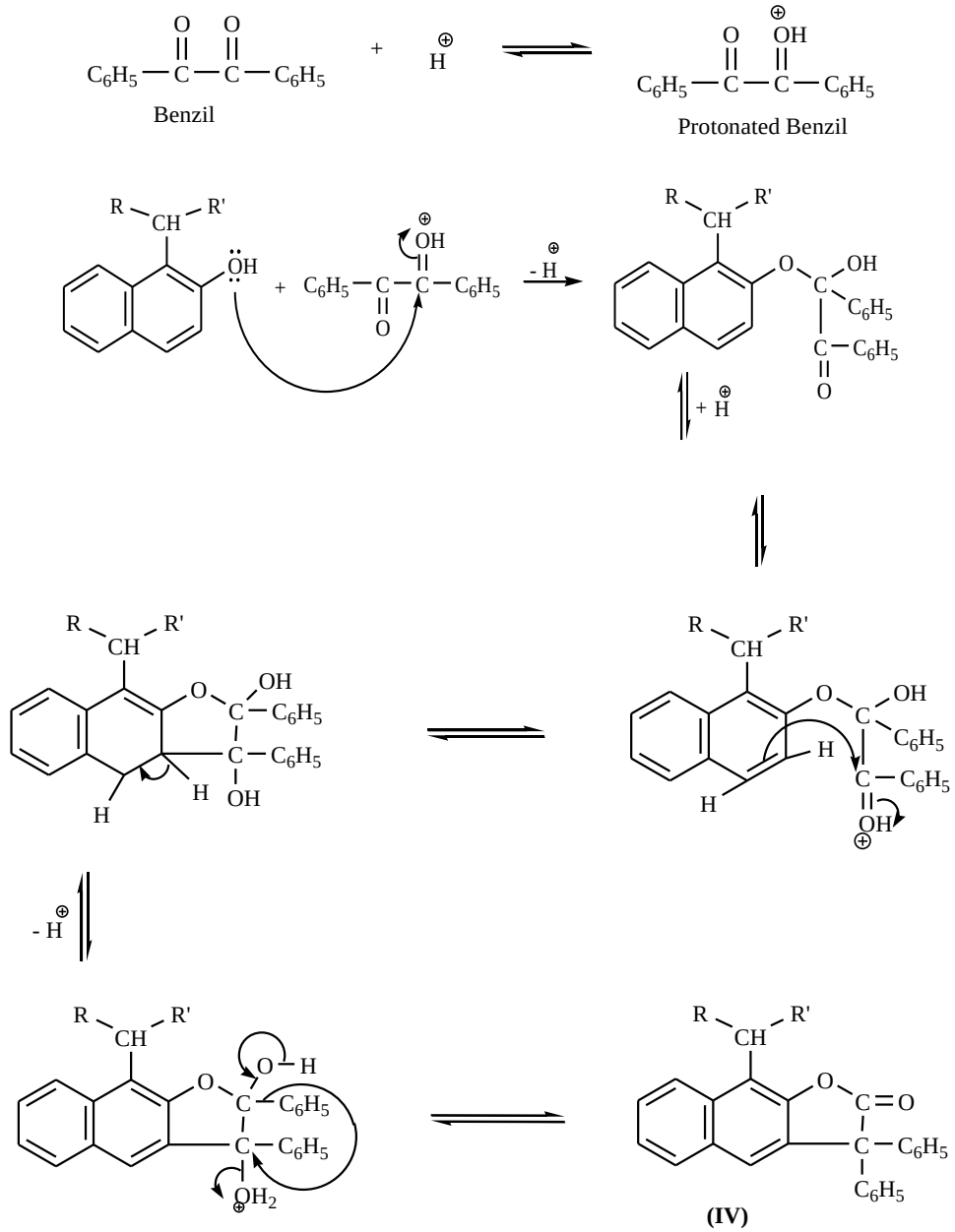
An attempt has been made to explain the mechanistic details for the formation of the target molecules (TM).

Formation of (III) has been suggested on the basis of the following plausible mechanism. β-Naphthol is a strong nucleophile and undergoes amido/imidoalkylation reaction in acidic medium.





The compound (III) on reaction with benzil undergoes a rearrangement reaction to give the product (IV) formation of which has been suggested on the basis of the following probable mechanism.



III. BIOLOGICAL ACTIVITY

Two Fold Serial Dilution Technique was adopted in order to screen these compounds for their antifungal and antibacterial activities in vitro as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Minimum inhibitory concentration (MIC) was determined in µg/mL against each fungus and bacterium up to a maximum concentration of 50µg/mL. For antifungal activity fluconazole was choosen as standard drug having MIC values of 0.5, 1.0, 1.0, 2.0 and 1.0µg/mL against Ca, Cn, Tm, Af and Cp respectively while for antibacterial activity gentamycin was selected as the standard drug having MIC values of 0.18, 25, 6.25 and 0.18µg/mL against Ec, Pa, Sa and Kp respectively.

TABLE-III
Antifungal activity data of compounds (IV)

Compd. No.	R	R'	Minimum inhibitory concentration (MIC) in µg/ml				
			Ca	Cn	Tm	Af	Cp
1	H	phthalimido	25	>50	12.5	25	>50
2	H	phthalimidomethyl	50	>50	25	50	>50
3	H	benzamido	50	50	25	50	>50
4	phenyl	benzamido	>50	>50	25	50	>50

IV. RESULT AND DISCUSSION(A)

The antifungal activity data incorporated in Table III clearly indicate that only the compound no. 1 having R=H and R'=phthalimido substituents is highly active against Trichophyton mentagrophytes (Tm) as it has MIC value of 12.5 against this fungus and a low level of antifungal activity against Candida albicans (Ca), and Aspergillus fumigatus (Af) (MIC values were 25 in each case). Other compounddisplayed less degree of antifungal activity. It is interesting to observe here that a minor alteration in the molecular structure of such compounds may cause profound effect on the biological activity. Thus, compound no.1 containing R=H and R'= phthalimido substituents was active against Tm while the compound no.2 having R=H and R'=N-methyl phthalimido substituents is not as active as compound no.1. it is inferred that compound no.1 finds a better fit at the receptor site against Tm than the other compounds of the series.

TABLE-III
Antibacterial activity data of compounds (IV)

Compd. No.	R	R'	Minimum inhibitory concentration (MIC) in µg/ml			
			Ec	Pa	Sa	Kp
1	H	phthalimido	>50	50	25	25
2	H	phthalimidomethyl	>50	50	>50	>50
3	H	benzamido	>50	>50	12.5	12.5
4	phenyl	benzamido	>50	>50	25	25

V. RESULT AND DISCUSSION(B)

Only one compound out of the four compounds tested against four bacterial strains exhibited measurable degree of antiviral activity against Staphylococcus aureus (Sa) and Klebsiella pneumoniae (Kp) as is evident from the antibacterial data recorded in Table-IV. Thus the compound no.3 R=H and R'=benzamido groups has MIC value of 12.5 for both the bacteria viz; Sa and Kp, however, this compound could not provoke any measurable degree of antibacterial activity against Ec and Pa (MIC values were >50 for both the compounds). When hydrogen atom is replaced by a phenyl group, antibacterial activity is diminished to half (compound no. 4). MIC values for compound no.4 were 25 for Sa and Kp. However, more data are required to ascertain the biological potential of these compounds.

VI. ACKNOWLEDGMENT

The authors express their thanks to the Head, Chemistry Department, Lucknow University, Lucknow for providing necessary laboratory facilities and the Director CDRI, Lucknow for providing elemental, spectral and biological activity data.

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