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SYNTHESIS, CHARACTERIZATION AND BIOEVALUATION OF NAPHTHOFURAN DERIVATIVES

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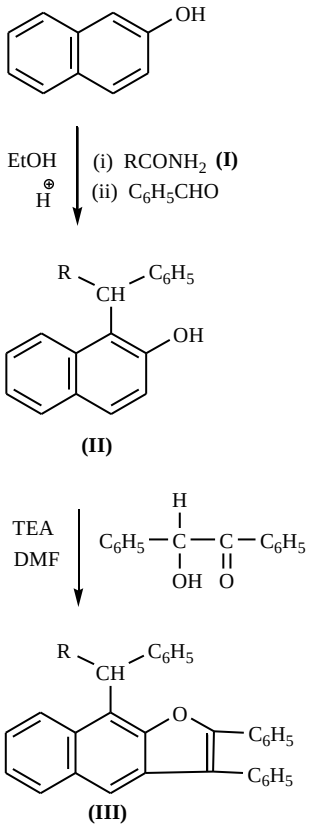
***Abstract*— Heating under reflux a mixture of β-naphthol, an amide (I) and benzaldehyde in absolute ethanol containing a catalytic quantity furnished N-[(2-Hydroxynaphthalen-1-yl)phenylmethyl]arylamides/carboxamido/methylarylamides/imides (II) in excellent yields (71 to 77%). Reaction of the compounds (II) with benzoin in dimethyl formamide (DMF) containing a catalytic quantity of triethylamine(TEA) yielded N-[(2,3-Diphenylnaphtho[2,3-b]furan-9-yl)phenylethyl]arylamides/ carboxamidomethyl-arylamides/imides (III) as target molecules in the yields ranging from 60-65%. The target molecules were bioassayed for their antimicrobial activity involving five strains of fungi and four strains of bacteria in vitro. (SCHEME)**



SCHEME

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

I. INTRODUCTION

In order to explore the possibility of finding better chemotherapeutic agents particularly the antimicrobial agents, the authors were prompted to undertake the synthesis of some naphthofuran derivatives which have shown excellent results in several health areas.[1-6] In addition, easy access to the synthesis of such compounds with higher yields encouraged the author to plan a protocol for the synthesis of the compounds of this type.

II. EXPERIMENTAL

The melting points of the compounds were determined in open glass capillary tubes in a Toshniwal Electric Apparatus (Japan) and the values reported are uncorrected. Infra red (i.r.), nuclear magnetic resonance (PMR) spectra, mass spectra and biological activity data reported in the paper were obtained from Central Drug Research Institute, Lucknow.

N- Benzoyl glycine (Hippuric acid)

Literature method was followed for the preparation of N-benzoyl glycine (hippuric acid)[7].

N-Phthaloyl glycine

The Procedure of Vogel[8] was followed for the synthesis of the titled compound.

N-(Carbamoylmethyl)-benzamide/2-(1,3-dioxoindolin-2-yl)-acetamide were synthesized following the procedures[9-10] as reported in the literature.

N-[(2-Hydroxynaphthalen-1-yl)phenylmethyl]arylamides/ carboxamido/methylarylamides/imides (II)

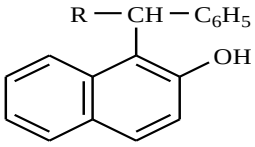
A mixture consisting of β-naphthol (0.02mole), an amide (0.02mole) and benzaldehyde (0.02mole) in absolute ethanol (100mL) containing concentrated hydrochloric acid (2mL) was heated under reflux for four hours under anhydrous reaction conditions with occasional shaking. The solution was cooled to room temperature and the solvent alcohol was distilled off. The resultant pasty mass was refrigerated overnight. It was washed with an aqueous solution of Na2CO3 and finally with water. The solid was filtered off, dried in vacuo and recrystallized

from acetone. The details of the compounds of this type are presented in the Table I.

N-[(2,3-Diphenylnaphtho[2,3-b]furan-9-yl)phenylethyl]aryl amides/carboxamidomethyl-arylamides/imides (III)

N-[(2-Hydroxynaphthalen-1yl)phenylmethyl]arylamides/ carboxamido/methylarylamide/imide (II) (0.01mol) and benzoin (0.01mol) were dissolved in dimethyl formamide (100mL) by constant stirring. Subsiquently, triethylamine(TEA) (5mL) was added to this mixture and stirred for half an hour. The resultant reaction mixture was heated under reflux for five hours in anhydrous reaction conditions. Excess of dimethyl formamide and triethylamine were removed by distillation under diminished pressure. The solid thus obtained, was washed with diluted HCL and finally with water. It was filtered off, air dried and recrystallized from ethanol. The physical data of such compounds are summarized in Table II.

TABLE I



Physical data of N-[(2-hydroxynaphthalen-1-yl)phenylmethyl]arylamides/carboxamido/methylarylamides/imides(II)

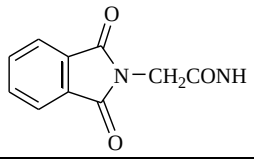
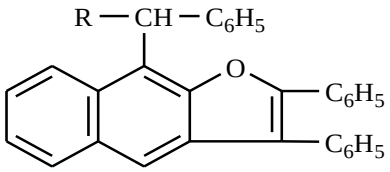
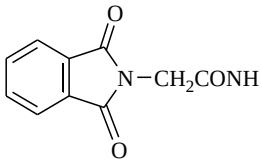
Compd. No.	R	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular weight	Nitrogen %	
							Calcd.	Found
1.	C_6H_5CONH	92	71	Brown	$C_{24}H_{19}NO_2$	353	3.97	3.96
2.	$C_6H_5CONHCH_2CONH$	95	75	Orange	$C_{26}H_{22}N_2O_3$	410	6.82	6.72
3.		106	77	Yellow	$C_{27}H_{20}N_2O_4$	436	6.42	6.32

TABLE II

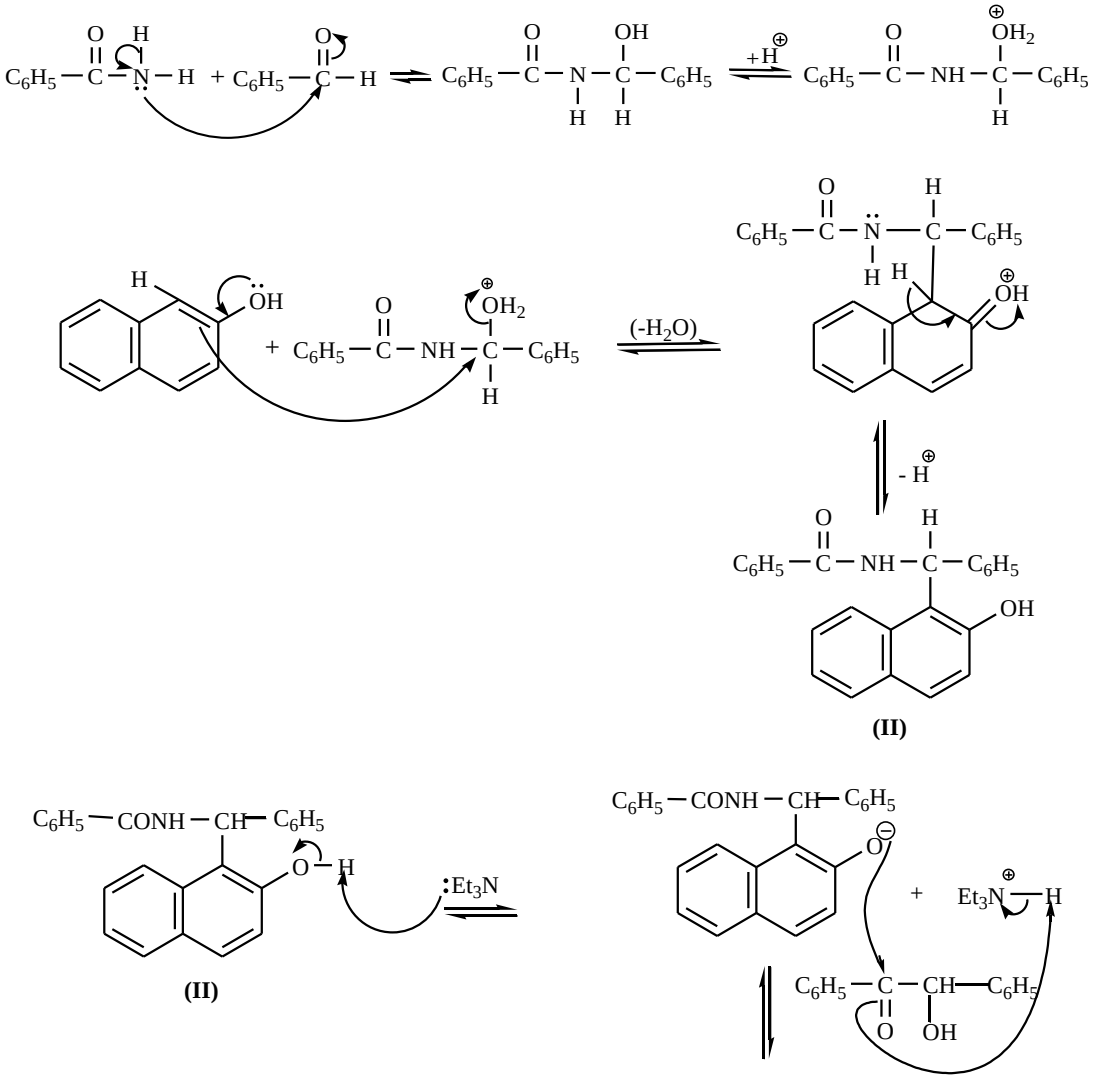


Physical data of N-[(2,3-diphenylnaphtho[2,3-b]furan-9-yl) phenyl-methyl]arylamides/carboxamido-methyl-arylamides/imides (III)

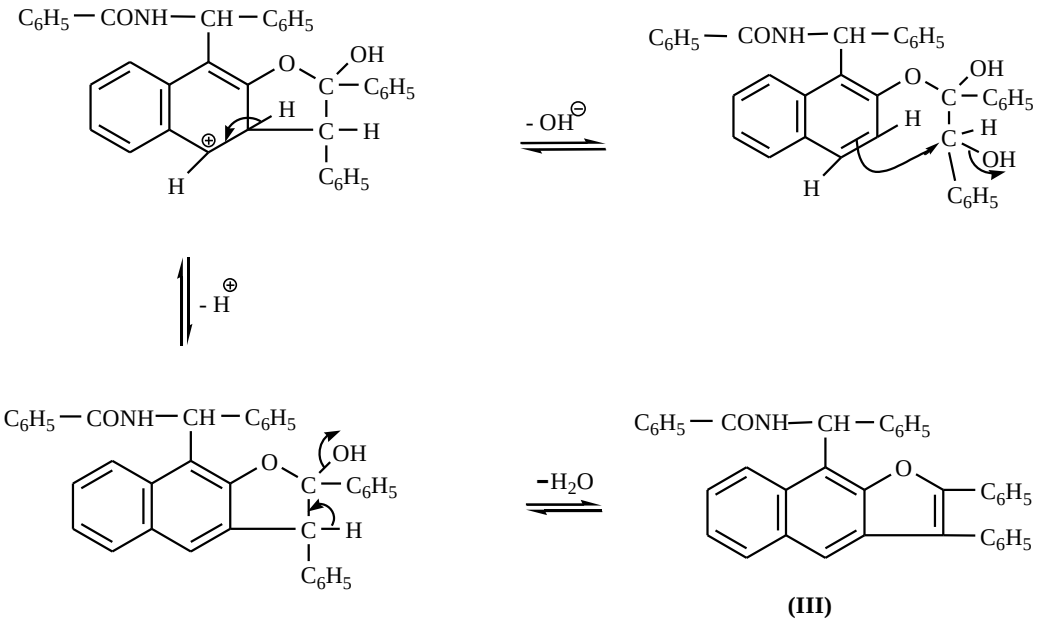
Compd. No.	R	m.p. (°C)	Yield (%)	Colour	Molecular formula	Molecular weight	Nitrogen %	
							Calcd.	Found
1.	C_6H_5CONH	80	65	Grey	$C_{38}H_{27}NO_2$	529	2.65	2.58
2.	$C_6H_5CONHCH_2CONH$	82	62	Brown	$C_{40}H_{30}N_2O_3$	586	4.78	4.70
3.		80-81	60	Orange	$C_{41}H_{28}N_2O_4$	612	4.57	4.51

IR (KBr) cm^{-1}: 1212 (C–O–C), 1670 (imide C=O), 1682 (amide C=O).
^{1}H NMR (CDCl$_3$) δ ppm: 7.25-7.75 (m, 13H, ArH), 4.55 (s, N–CH$_2$–CO), 4.41 (s, CH–C$_6$H$_5$).
Mass (FAB): M$^+$ 612, Base peak 160, other peaks appeared at m/z 77, 90, 91.

The formation of target compound (**III**) can be suggested on the basis of the following mechanism.(taking benzamide as one of three amides used)



(II)

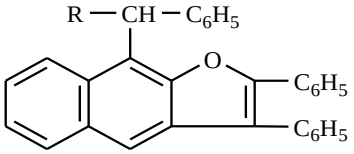


(III)

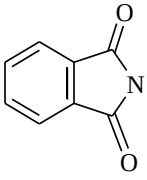
III. BIOLOGICAL ACTIVITY

All the three final compounds (III) were screened for their antifungal and antiviral activity involving two Fold Serial Dilution Technique as recommended by the National Committee for Clinical Laboratory Standards (NCCLS). Biological activity protocol involved five fungal and four bacterial strains. The fungal strains included were Candida albicans (Ca), Cryptococcus neoformans (Cn), Trichophyton mentagrophytes (Tm), Aspergillus fumigatus (Af) and Candida parapsilosis (Cp). The bacterial strains used for evaluation were Escherichia coli (Ec), Pseudomonas aeruginosa (Pa), Staphylococcus aureus (Sa) and Klebsiella pneumoniae (Kp). The antifungal and antibacterial activity and antibacterial activity data of the target compounds (III) are recorded in the Table-III.

TABLE III



Antimicrobial data of compound no. (III)

Compd. No.	**R**	**A**ntifungal activity (MIC in µg/ml)					**A**ntibacterial activity (MIC in µg/ml)			
		Ca	**Cn**	**Tm**	**Af**	**Cp**	**Ec**	**Pa**	**Sa**	**Kp**
1	C_6H_5CONH	50	50	12.5	>50	50	>50	>50	>50	50
2	$C_6H_5CONHCH_2CONH$	>50	>50	50	50	>50	>50	50	25	25
3		50	50	25	>50	50	>50	>50	>50	>50

IV. RESULT AND DISCUSSION

Biological activity data incorporated in Table III demonstrate that the compound no.1 having R= C6H5CONH group is antifungally active against only one fungas. This compound has a MIC value of 12.5 against Trichophyton mentagrophytes (Tm) while against all the four fungi no measurable level of antifungal activity was observed. The compound no. 2 containing R= C6H5CONHCH2CONH was completely devoid of antifungal activity against all the five fungi. The compound no.3 having a phthalimido-acetamido group showed a slight activity against Tm (MIC 25) but no observable activity was demonstrated by four other fungi. Regarding antibacterial activity the compound no. 2 showed lower level of activity against Sa and Kp (MIC 25 in each case). Because of the investigation of the limited number of compounds for their antibacterial activity, it is not possible to predict the potentials of such compounds in this health area.

V. ACKNOWLEDGEMENT

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