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A Novel Approach to the Synthesis of Some Naphthofuran Derivatives Bearing Polar Substituents for Studying their Antimicrobial Activity

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Abstract: ***β-Naphthol on reaction with N-(hydroxyalkyl)-arylamides/ imides (1) in ethanol containing catalytic amount of conc. HCl furnishes N-(2-hydroxy-naphthalen-1-yl-alkyl)-arylamides/ imides (2) which on treatment with benzoin in dioxan containing triethylamine (TEA) affords N-(2, 3- diphenyl-naphtho [2, 3-b] furan-9-yl-alkyl)- arylamides/ imides (3). Compounds 3 have been evaluated for their antimicrobial activity involving four bacterial and six fungal strains.***

Keywords: Antimicrobial resistance, nitrofurazone, amidoalkylation

1. Introduction

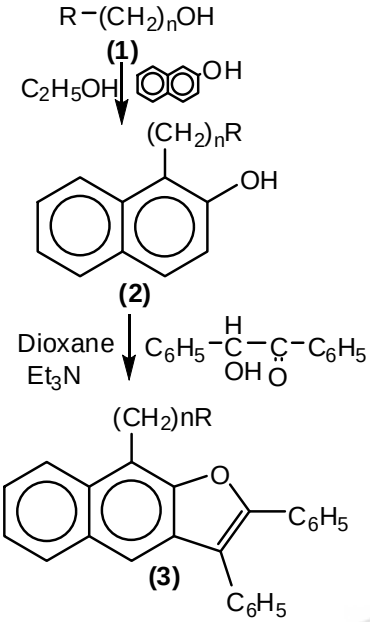
The antimicrobial resistance has increased rapidly worldwide during the past few years giving rise to a growing necessity for antimicrobial resistance surveillance programme and an urgent need for new and more effective agents. In recent past several reports have emerged regarding the study of resistant bacterial and fungal strains. Emergence of antimicrobial resistance has led the researchers to design and develop new chemical agents of greater 74potentials. Amongst various synthetic compounds furan derivatives have been demonstrated to be potential biologic entities against several bacterial strains. Some of nitrofuran derivatives are being used extensively. Thus, nitrofurazone which is the semicarbazones of 5- nitro- 2- furaldehyde is used topically in the treatment of burns and in prevention of bacterial infection in skin graft procedures[1]. Furazolidine is the hydrazone from the 5-nitro-2-furaldehyde and 3-amino-oxazoli-dinone is active against various species of salmonella, *Escherichia coli* and *Vibrio cholerae*[2]. In addition, the hydrazone prepared from 5-nitro-2-furaldehyde and 1-amino-hydantoin is known as nitrofurantoin. It is active against many gram positive and gram-negative bacteria at concentration of 5-10 µg/ ml. It accumulates in urine in sufficient concentration for treatment of urinary tract infections. Chickens and rats fed nitrofurantoin produced metabolites in urine from which a small amount of corresponding 4-hydroxy derivative was isolated[3]. It has been suggested that nucleic acids, especially t-RNA, are the primary targets in nitrofuran mutagenesis and carcinogenesis. Thus, incubation of labeled 2- amino-4 (5-nitro- 2- furyl) - thiazole with rodent liver preparation led to the covalent attachment of metabolites to added yeast t-RNA. Enzymatic hydrolysis of the product gave two covalently adducts[4]. Very recently 4- styryl- 9- (p- phenyl-phenyl) furo- (2', 3': 5, 6) benzo [1, 2- b] pyran- 2- ones were found antivirally active against *Japanese encephalitis virus* and *Herpes simplex virus* type-I in vitro[5]. These valid observations prompted the authors to undertake the synthesis of some furan derivatives 3a-d (**Scheme-I**) in order to study their antibacterial and antifungal activities *in vitro* involving the standardized method as recommended by National Committee on clinical laboratory standards (NCCLS).

2. Results and Discussion

Reaction of N-(2-hydroxynaphthalen-1-yl-alkyl)-arylamides/ imides (**2**) with benzoin in dioxan solvent containing catalytic amount of triethylamine (TEA) afforded N-(2, 3-diphenyl-naphtho [2, 3-b] furan-9-yl-alkyl) aryl-amides/ imides (**3**) in the yields varying from 62 to 70%. These compounds **3** were characterized on the basis of elemental analysis, IR, ^{1}HNMR, ^{13}CNMR and mass spectral data. IR spectrum of the compound **3b** exhibited characteristic absorption bands at 1700 and 1130 cm^{-1} due to tertiary amido and cyclic ether groups, respectively. The ^{1} HNMR spectrum of the compounds **3b** displayed signals at 6.35 – 7.75 for aromatic protons, a triplet at 3.75 for methylene protons attached with carbon and another triplet at 4.15 for methylene protons attached with carbon and another triplet at 4.15 for methylene protons attached with nitrogen atom. In the ^{13}CNMR spectrum **3b** showed signals at 170.5 due to tertiary amido carbonyl carbon and at 141.6, 139.2, 137.5, 133.6, 130.4, 127.2, 126.4, 125.4, 123.3, 121.6, 119.2, 116.4, 115.2, 112.0 for aromatic carbons. Signals at 42.2 and 45.4 were due to methylene carbons attached with carbon and nitrogen, respectively. In the mass spectrum of **3b**, a base peak appeared at m/z 160.

Pharmacological Activity

All the four compounds **3a-d** were bio-evaluated for their antibacterial activity against four bacterial strains viz., *Klebsiella pneumonia*, *Escherichia coli*, *Candida Pseud albicans*, *Cryptococcus neoformans*, *Sporothrix schenkii*, *Trichophyton mentagrophyte*, ATCC-22019). The investigational compounds were tested for their antifungal activity in RPMI 1640 medium and antibacterial activity in Mueller Hinton Broth (MHB) by the National Committee on clinical laboratory standards methods[6].*omonas aeruginosa* and *Staphylococcus aureus*. These compounds were also assayed for their antifungal activity against six fungal strains viz., [7]*Aspergillus fumigatus* and *Candida parapsilosis*



Out of four compounds investigated for their antimicrobial activity only one compound (**3a**) showed measurable degree of activity against *Escherichia coli* and *Trichophyton mentagrophyte in vitro* while other three compounds (**3b**, **3c** and **3d**) could not provoke any noticeable degree of antimicrobial activity at the same concentration level.

3. Experimental

The melting points of the compounds were determined in open glass capillaries in a Toshniwal melting point apparatus and therefore the recorded values are uncorrected. IR spectra in KBr were recorded on Perkin-Elmer 157 spectrophotometer in region ν_{max} 4000-400 cm^{-1} and ^{1}HNMR and ^{13}CNMR spectra were recorded on Brooker DRX 300 MHz spectrometer using $CDCl_3$ as solvent (TMS as nternal standard with chemical shift in δ ppm). Mass spectrum (FAB) was recorded in Jeol SX 102/ DA-600 mass spectrometer using Argon (6KV, 10 mA) as the FAB gas.

N- Hydroxymethyl phthalimide, N- (2- hydroxyethyl) phthalimide, N- hydroxymethyl salicylamido and N- hydroxymethyl nicotinamide (**1**) were synthesized following the literature methods[8, 11].

N- (2- Hydroxynaphthlene- 1- yl- alkyl)-arylamides/ imides (2)

This synthesis involved the amido/ imidoalkylation reaction following the procedure of Einhorn[12]. Thus, a mixture of finely powdered β-naphthol (0.05 mole) and an amido/ imidoalcohol (0.05 mole) in absolute ethanol (100 ml) containing catalytic amount of concentrated hydrochloric acid (2.0 ml) was heated under reflux for five hours. Subsequently, the solvent was distilled off and the residual solid mass was washed repeatedly with cold water. It was dried in vacuo and recrystallized from acetone. The compounds thus synthesized, are recorded in **Table-I**.

Table 1: Characterization data of N-(2-hydroxy-naphthalen-1-yl-alkyl)-arylamides/ imides (2) and N- (2, 3- diphenyl-naphtho [2, 3-b] furan- 9- yl- alkyl) arylamides/ imides (3)

Compd.	R	n	m. p. (°C)	Yield (%)	Molecular formula	Nitrogen (%)	
						Found	Calcd.
2a	Phthalimido	1	84 – 85	65	$C_{19}H_{13}NO_3$	4.62	4.45
2b	Phthalimido	2	75 – 76	62	$C_{20}H_{15}NO_3$	4.41	4.30
2c	Salicylamido	1	80 – 81	84	$C_{18}H_{15}NO_3$	4.77	4.60
2d	Nicotinamido	1	86	67	$C_{17}H_{14}N_2O_2$	10.07	10.00
3a	Phthalimido	1	66	70	$C_{33}H_{21}NO_3$	2.92	2.80
*3b	Phthalimido	2	76 – 77	65	$C_{34}H_{23}NO_3$	2.83	2.70
3c	Salicylamido	1	85	62	$C_{32}H_{23}NO_3$	2.98	2.78
3d	Nicotinamido	1	81 – 82	68	$C_{31}H_{22}N_2O_3$	6.16	6.10

***IR (KBr) ($\sqrt{}_{max}$ in cm^{-1}):** 1700 (tert. Amide C=O), 1130 (C-O-C)

***^{1}HNMR ($CDCl_3$) (δ ppm):** 6.35 – 8.75 (m, 19H, ArH), 3.75 (t, 2H, CH_2-C, J 7.00), 4.15 (t, 2H, CH_2-N, J 7.00)

***^{13}CNMR ($CDCl_3$) (δ ppm):** 42.2, 45.4, 99.5, 112, 115.2, 116.4, 119.2, 121.6, 123.3, 125.6, 126.4, 127.2, 130.4, 133.6, 137.5, 139.2, 141.6, 170.5

***Mass (m/z) (FAB):** M^+ 493, 160 (base peak), 105, 125, 141, 146, 174, 315, 319, 333

N- (2, 3- Diphenylnaphtho [2, 3- b] furan- 9- yl) alkyl) arylamides/ imides (3)

A mixture of N- (2- hydroxynaphthalen- 1- yl- alkyl)-arylamide/ imide (**2**) (0.01 mole) and benzoin (0.01 mole) in dioxan (50 ml) containing triethyl amine (TEA) (5 ml) was heated under reflux for six hours under anhydrous reaction conditions. The resultant solution on cooling to room temperature solidified and filtered off. It was washed with cold water (100 ml) containing diluted hydrochloric acid (10 ml) repeatedly and dried in vacuo. The crude compound on re-crystallization from ethanol afforded analytically pure sample N- (2, 3- Diphenyl- naphtho [2, 3- b] furan- 9- yl-alkyl) arylamides/ imides (**3**) thus synthesized, are presented in **Table-I** along with their characterization data.

4. Conclusion

The investigational compounds were tested for their antifungal activity in RPMI 1640 medium and antibacterial activity in Mueller Hinton Broth (MHB) by the National Committee on clinical laboratory standards methods *omonas aeruginosa* and *Staphylococcus aureus*. These compounds were also assayed for their antifungal activity against six fungal strains viz., *Candida parapsilosis*, and *Candida*

parapsilosi From the biological activity data report it is apparent that all the target compounds are antibacterially active against two strains of bacteria viz. *Trichophyton mentagrophyte* and *E. coli* while four such compounds have displayed quite promising antibacterial activity against bacteria

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