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Synthesis and Antimicrobial Evaluation of Some New Pyrrolylnaphtho[2,1-*b*] furan Derivatives

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Abstract

A series of new (3-substitutedphenyl-5-hydroxy-5-naphtho[2,1-b]furan-2-yl-4,5-dihydro-pyrazol-1-yl)-(4-pyrrol-1-ylphenyl)methanones have been synthesized. The structures of these compounds were established on the basis of spectral data and elemental analysis.

All the compounds were evaluated for antibacterial and antifungal activities by the broth microdilution assay method. All the compounds were found moderately active.

Keywords: *Pyrrolylnaphtho[2,1-b]furans, Antimicrobial and Antifungal activity, Broth microdilution assay method.*

INTRODUCTION

There are number of biheterocycles containing nitrogen and oxygen atom which have turned out to be potential chemotherapeutic and pharmacotherapeutic agents.

Naphtho[2,1-*b*]furan derivatives are reported to possess wide spectrum of biological activities ranging from antimicrobial[1], anthelmintic[1], anticancer[2], antiviral[3] to beta adrenolytic[4] and antitumor[5].

Literature has also suggested that pyrazoline derivatives have potential antiamoebic[6], antihypertensive[7], antitubercular[8] and antidepressant[9] activities. Moreover a number of pyrrole ring containing compounds are known for their biological activities like antibacterial and antitubercular effect[10]. Thus the present communication describes the synthesis of a novel series of pyrazolylnaphthofurans linked to another biologically active pyrrole nucleus via carbonyl phenyl bridge and also their subsequent evaluation for antimicrobial and antifungal activities.

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MATERIALS AND METHODS

Melting points were determined using open capillary tube method and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on precoated silica gel 60 F_{254} plates from Merck and visualized by exposure to iodine vapors or under UV light. IR spectra were recorded using KBr disk on a Thermo Nicolet 5700 FTIR spectrophotometer and ^{1}H NMR spectra were recorded at 300 MHz on a Bruker spectrometer and their chemical shifts are reported in δ ppm units with respect to TMS as internal standard. Elemental analyses were performed for C, H, N and were within ±0.4% of theoretical values.

Synthesis of 2-acetylnaphtho[2,1-*b*]furan (3)

A mixture of 2-hydroxy-1-naphthaldehyde **2**

(5.1 g, 0.03 mol), bromoacetone (2.77 g, 0.03 mol) and anhydrous potassium carbonate (41.4 g, 0.3 mol) in dry acetone (50 ml) was heated under reflux for 24 h. The reaction mixture was filtered and potassium carbonate was washed with acetone. Evaporation of the solvent from the filtrate yielded the product which was recrystallised from ethanol to get yellow crystalline product (80%), mp: 103-105 ^{0}C.

Synthesis of 3-(substitutedphenyl)-1-naphtho[2,1-*b*]furan-2-ylprop-2-en-1-ones (4a-4f)

2-Acetylnaphtho[2,1-*b*]furan **3** (0.004 mol) was dissolved in hot ethanol (100 ml) containing sodium hydroxide (1 g). The appropriate aromatic aldehyde (0.004 mol) was added to the above solution with stirring which was continued for 12 h at 50-55^{0}C. The resultant precipitate was filtered, washed with ethanol, dried and recrystallised from appropriate solvent.

Synthesis of 2,3-dibromo-3-(substitutedphenyl) -1-naphtho[2,1-*b*]furan-2-ylpropan-1- ones (5a-5f)

To a solution of 3-(substitutedphenyl)-1-naphtho[2,1-*b*]furan-2-ylprop-2-en-1-ones **(4a-4f)** (0.001 mol) in chloroform (25 ml), bromine (0.001 mol) in chloroform (25 ml) was added slowly with stirring. After the completion of addition of bromine solution, the reaction mixture was stirred for 24 h. Excess of chloroform was distilled off under reduced pressure. The precipitated solid was filtered, dried and recrystallised from appropriate solvent. Table-1 summarizes the physical data of these compounds.

Synthesis of (3-substitutedphenyl-5-hydroxy-5-naphtho[2,1-*b*]furan-2-yl-4,5-dihydro- pyrazol-1-yl)-(4-pyrrol-1-ylphenyl)methanones (6a-6f)

The dibromides **(5a-5f)** (0.01 mol) were dissolved in absolute ethanol (75 ml) and 4-pyrrol-1-ylbenzoic acid hydrazide[10] (0.01 mol) and triethylamine (10 ml) were added to the solution. The reaction mixture was heated under reflux for 12 h on a water bath. The contents were reduced, cooled and poured on to crushed ice and kept overnight. The resulting hydroxypyrazoline was collected by filtration and recrystallised from suitable solvent. The physical data are listed in Table-1. The spectral data are mentioned in Table-2.

RESULTS AND DISCUSSION

The main aim of this work was to synthesize 3-substitutedphenyl-5-hydroxy-5-naphtho[2,1-*b*]furan-2-yl-4,5-dihydro-pyrazol-1-yl)-(4-pyrrol-1-ylphenyl)methanones. Initially 3-(substitutedphenyl)-1-naphtho[2,1-*b*]furan-2-ylprop-2-en-1-ones were synthesized from the reaction of 2-acetylnaphtho[2,1-*b*]furan and corresponding aromatic aldehydes in presence of a strong base. The chalcones **(4a-4f)** on treatment with bromine in chloroform underwent addition of bromine and produced corresponding dibromo compounds **(5a-5f).** The titled compounds **(6a-6f)** were obtained by condensing 4-pyrrol-1-ylbenzoic acid hydrazide with dibromides **(5a-5f)** under reflux in absolute ethanol.

The structures of the newly synthesized compounds **(6a-6f)** were confirmed by their spectral data. IR spectra of above compounds (**6a-6f)** showed sharp bands around 3400-3450 cm^{-1}(-OH stretch), 2250-2350 cm^{-1} (-CH from Ar-H stretch) and 1620-1632 cm^{-1} (-C=O stretch). Their structure was further supported

by their ^{1}H NMR spectral data which exhibited a sharp singlet around 4.44-4.60 δ ppm which was assigned for the proton of hydroxyl group. The methylene protons of hydroxypyrazoline ring appeared as two doublets in the region of δ 5.28 and 5.48. Subsequent purification yielded final compounds in moderate to higher yields. Elemental analysis also supported the structures assigned. Physical data of the synthesized compounds are listed in Table-1. The spectral data are mentioned in Table-2. Some of these compounds have shown good antibacterial activity.

Biological evaluation

All the newly synthesized compounds were evaluated for antibacterial activity by broth microdilution assay method[11] against the Gram-positive bacteria *Staphylococcus aureus* (ATCC 11632), *Streptococuus faecalis* (ATCC 14506) and *Bacillus subtilis* (ATCC 60511), the Gram-negative bacteria *Klebsiella pneumoniae* (ATCC 10031), *Escherichia coli* (ATCC 10536) and *Pseudomonas aeruginosa* (ATCC 10145). Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. The tubes were inoculated with 10^{5} cfu ml^{-1} (colony forming unit/ml) and incubated at 37 °C for 18 h. Ciprofloxacin and Norfloxacin were used as standard drugs. The antifungal activity of synthesized compounds was performed by broth microdilution assay method[11] using fungi *Aspergillus niger* and *Candida albicans*. Flucanazole used as standard drug. The data of activity is summarized in Table-3.

CONCLUSION

Pyrrolylnaphtho[2,1-*b*]furan derivatives presented herein showed antibacterial and antifungal activities. Compounds **(6a-f)** were highly active against Gram-positive bacteria. They exhibited activity against pathogenic Gram-negative bacteria and fungi at higher concentration, while compounds **6b** and **6c** specifically exhibited excellent antibacterial activity even at lower concentration showing importance of halogenated compounds.

Suitable molecular modification of these compounds may generate potent antimicrobial agents in future.

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Table 1: Physical data of the synthesized compounds

Compd.	Mol. formula	Mol. Wt. Wt.	M. P. ^{0} C (Solvent of Recrystn.)	Yield %	Elemental analysis Found (Calcd) %		
					C	H	N
5a	$C_{21}H_{14}Br_2O_2$	458.14	185-187 (DMF-Water)	55	55.40 (55.05)	3.10 (3.08)	-
5b	$C_{21}H_{12}Br_2C_{12}O_2$	527.03	198-200 (DMF-Water)	59	47.48 (47.86)	2.31 (2.29)	-
5c	$C_{21}H_{13}Br_3O_2$	524.02	210-212 (DMF-Water)	63	46.60 (46.97)	2.46 (2.44)	-
5d	$C_{21}H_{13}Br_2NO_4$	503.14	270-272 (DMF-Water)	67	50.54 (50.13)	2.62 (2.60)	2.76 (2.78)
5e	$C_{21}H_{14}Br_2O_3$	474.14	230-232 (DMF-Water)	70	53.48 (53.20)	2.99 (2.98)	-
5f	$C_{23}H_{19}Br_2NO_2$	501.21	205-207 (DMF-Water)	65	55.48 (55.12)	3.84 (3.82)	2.77 (2.79)
6a	$C_{32}H_{23}N_3O_3$	497.54	214-216 (Ethanol)	58	77.65 (77.25)	4.68 (4.66)	8.47 (8.45)
6b	$C_{32}H_{21}Cl_2N_3O_3$	566.43	215-217 (Ethanol)	55	67.53 (67.85)	3.76 (3.74)	7.44 (7.42)
6c	$C_{32}H_{22}BrN_3O_3$	576.44	244-246 (Ethanol)	54	66.42 (66.68)	3.84 (3.85)	7.31 (7.29)
6d	$C_{32}H_{22}N_4O_5$	542.54	281-283 (Ethanol)	60	70.48 (70.84)	4.06 (4.09)	10.31 (10.33)
6e	$C_{32}H_{23}N_3O_4$	513.54	263-265 (Ethanol)	70	74.76 (74.84)	4.53 (4.51)	8.20 (8.18)
6f	$C_{34}H_{28}N_4O_3$	540.61	222-224 (Ethanol)	66	75.22 (75.54)	5.24 (5.22)	10.39 (10.36)

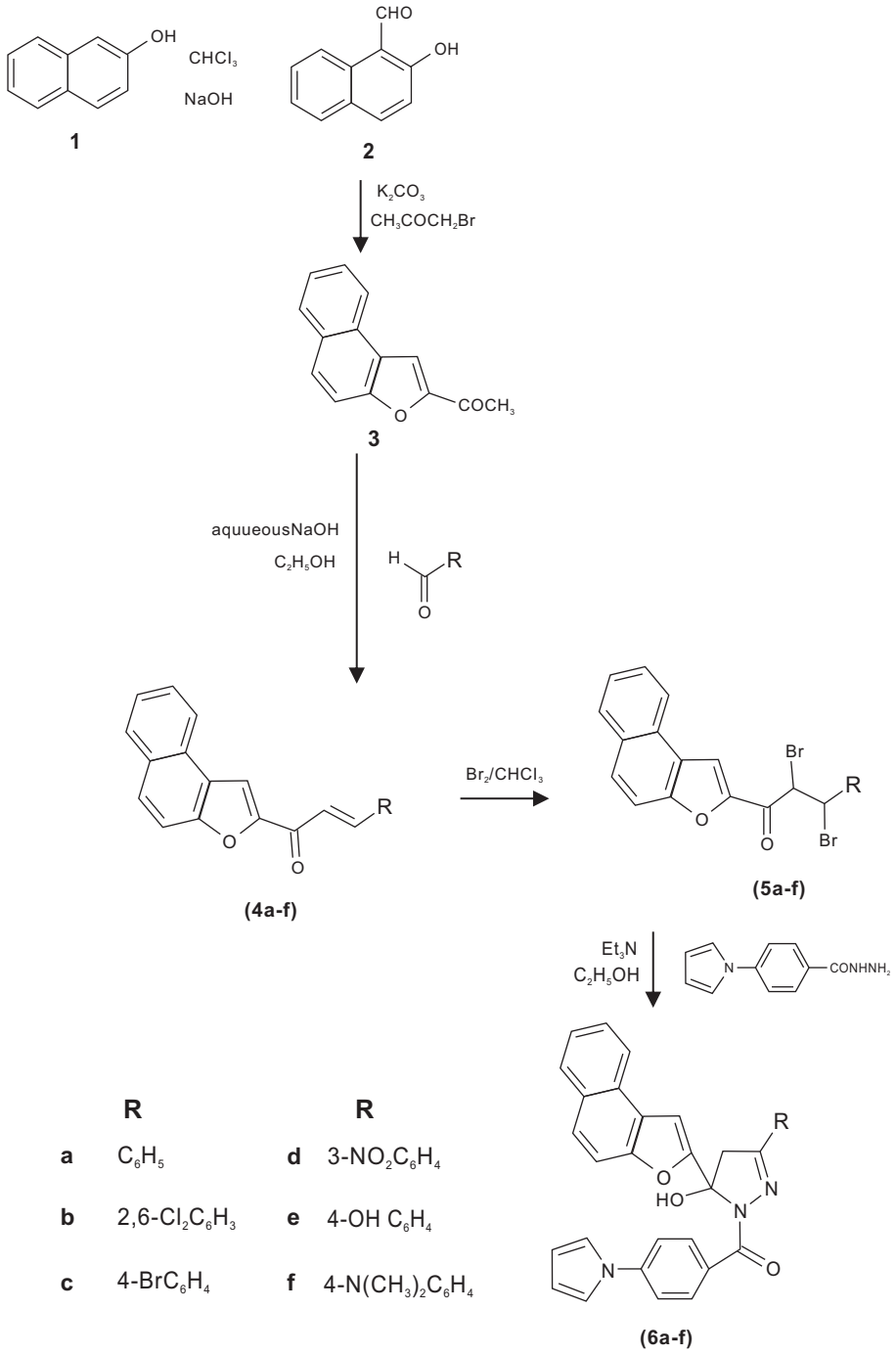
Table 2: Spectral data of the synthesized compounds

Compd.	*IR (cm^{-1})*	*^{1}H-NMR (δ, ppm)*	*Mass (m/e)*
2	3560 (-OH str.), 2375 (-Ar.CH str.), 1642 (-CHO str.)	13.00 (s, 1H, -CHO), 10.30 (s, 1H, -OH), 6.90-8.20 (m, 6H, -Ar-CH).	-
3	2322 (-Ar.CH str.), 1674 (-CO str.)	8.60 (s, 1H, -C_3-H), 8.10 (t, 2H, -$C_{8,}C_9$-H), 8.4 (d, 1H, -C_7-H), 7.80 (d, 1H, -C_4-H), 7.70 (t, 1H, -C_6-H), 7.60 (t, 1H, -C_5-H), 2.60 (s, 3H, -$COCH_3$).	210 (M^+), 211 (M+1)
4a	2392 (-Ar.CH str.), 1660 (-CO str.)	7.00-8.50 (m, 13H, -Ar-CH), 6.00 (s, 2H, -CH=CH).	298 (M^+), 299 (M+1)
6a	3390 (-OH str.), 2336 (-Ar.CH str.), 1620 (-CO str.)	7.60-8.50 (m, 16H, -Ar-CH), 7.00 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.30 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.30 (d, 2H, -CH_2), 4.60 (s, 1H, -OH).	497 (M^+), 498 (M+1)
6b	3410 (-OH str.), 2380 (-Ar.CH str.), 1632 (-CO str.)	7.28-8.62 (m, 14H, -Ar-CH), 6.96 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.32 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.26 (d, 2H, -CH_2), 4.54 (s, 1H, -OH).	566 (M^+), 567 (M+1)
6c	3420 (-OH str.), 2344 (-Ar.CH str.), 1626 (-CO str.)	7.19-7.94 (m, 15H, -Ar-CH), 6.95 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.19 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.24 (d, 2H, -CH_2), 4.44 (s, 1H, -OH).	-
6d	3442 (-OH str.), 2358 (-Ar.CH str.), 1628 (-CO str.)	7.18-8.62 (m, 15H, -Ar-CH), 6.90 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.22 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.36 (d, 2H, -CH_2), 4.68 (s, 1H, -OH).	-
6e	3452 (-OH str.), 2392 (-Ar.CH str.), 1622 (-CO str.)	6.84-7.98 (m, 15H, -Ar-CH), 6.95 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.19 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.48 (d, 2H, -CH_2), 5.02 (s, 1H, -OH at phenyl), 4.54 (s, 1H, -OH).	-
6d	3450 (-OH str.), 2358 (-Ar.CH str.), 1616 (-CO str.)	6.62-8.12 (m, 15H, -Ar-CH), 6.88 (s, 2H, pyrrole-$C_{2,}C_5$-H), 6.32 (s, 2H, pyrrole-$C_{3,}C_4$-H), 5.34 (d, 2H, -CH_2), 4.48 (s, 1H, -OH), 2.84 (s, 6H, -$2CH_3$).	-

Table 3: Antibacterial and Antifungal activity of synthesized compounds

	MIC values (µg/ml)							
	Antibacterial activity							
	Gram-positive organisms			Gram-negative organism			Antifungal activity	
	S. aureus	S. faecalis	B. subtilis	K. pneumoniae	E. coli	P. aeruginosa	A. niger	C. albicans
6a	125	125	62.5	500	500	500	>500	500
6b	16	62.5	62.5	500	500	500	>500	500
6c	31.25	62.5	125	500	500	500	>500	500
6d	125	125	125	500	500	500	>500	500
6e	125	125	125	500	500	500	>500	500
6f	125	125	125	500	500	500	>500	500
Ciprofloxacin	<5	<5	≤1	≤1	≤1	>5	-	-
Norfloxacin	<5	<5	≤1	≤1	≤1	>5	-	-
Flucanazole	-	-	-	-	-	-	0.25	0.25

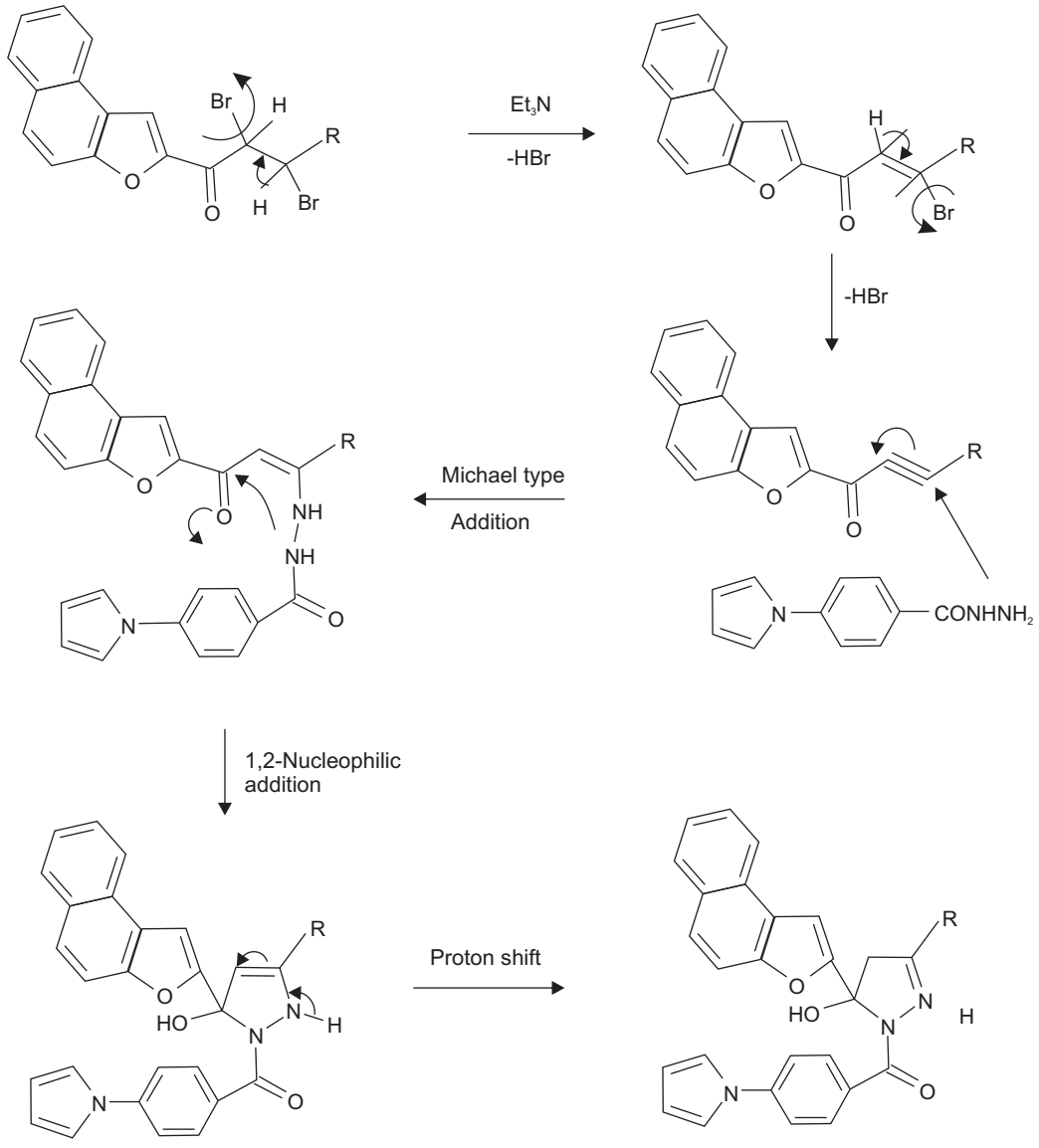
SCHEME



	R		R
a	C_6H_5	**d**	3-$NO_2C_6H_4$
b	2,6-$Cl_2C_6H_3$	**e**	4-OH C_6H_4
c	4-BrC_6H_4	**f**	4-$N(CH_3)_2C_6H_4$

SCHEME

Mechanism for the formation of (3-substitutedphenyl-5-hydroxy-5-naphtho[2,1-*b*]furan-2-yl -4,5-dihydro-pyrazol-1-yl)-(4-pyrrol-1-ylphenyl)methanones **(6a-f)**



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