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Synthesis and Pharmacological Screening of some Novel Naphtho [2,1-b] furo-pyrazolines, isoxazoles and isoxazolines

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2-Acetylnaphtho [2,1-b]furan 1 was reacted with various aromatic aldehydes in presence of alkali, to produce corresponding chalcones 2a-i. These were converted into 1-phenyl-3-(naphtho[2,1-b]fur-2yl-5-aryl-2-pyrazolines 3a-i and 1-(4-nitrophenyl)-3-(naphtho[2,1-b]fur-2yl-5-aryl-2-pyrazolines 4a-i by treatment with phenyl hydrazine and 4-nitrophenyl hydrazine respectively. The reaction of chalcones 2a-i with hydroxyl amine hydrochloride in presence of sodium acetate in glacial acetic acid produced 3-(naphtho[2,1-b]fur-2yl)-5-aryl-2-isoxazoles 5a-i, whereas similar reaction in the presence of potassium hydroxide yielded 3-(naphtho[2,1-b]fur-2yl)-5-aryl-2-isoxazolines 6a and 6e. All the compounds have been characterized by elemental analysis and spectroscopic data. These novel biheterocyclic compounds have been screened for antibacterial, antifungal, anthelmintic and analgesic activities. The compound 4e showed promising antimicrobial activity, some of the compounds exhibited moderate antibacterial and antifungal activity. The only compound that showed maximum analgesic activity is 3d. Anthelmintic activity revealed the compounds 4e, 5b and 5i were as active as the standard drug.

Among the wide range of biheterocycles that have been explored for developing pharmacologically important molecules, pyrazolines[1] isoxazoles[2,3] and isoxazolines[4] play significant role in the field of medicinal chemistry. Hence in continuation of our search for pharmacologically potent naphtho[2,1-b]furans, we report here the synthesis of biheterocyclics comprising naphtho[2,1-b]furan moiety and pyrazolines, isoxazoles and isoxazolines moieties of potential use as antimicrobial, anthelmintic and analgesic agents.

2-Acetylnaphtho[2,1-b]furan 1, on reaction with various aromatic aldehydes in presence of alkali produced corresponding chalcones 2a-i i.e, 1-(naphtho[2,1-b]fur-2yl)-3-aryl-2-propen-1-ones.

The chalcones 2a-i possessing α,β-unsaturated group molecules were condensed with phenylhydrazine to produce corresponding phenylhydrazones which immediately rearranged to give 1-phenyl-3-(naphtho[2,1-b]fur-2yl)-5-aryl-2-pyrazolines (3a-i). In order to study the effect of an electron withdrawing group on pharmacological activity, 1-(4-nitrophenyl)-3-(naphtho[2,1-b]fur-2yl)-5-aryl-2-pyrazolines (4a-i), were also prepared from chalcones 2a-i and 4-nitrophenyl hydrazine in presence of acid (Scheme 1).

The acid catalysed reaction of 2a-i with hydroxylamine hydrochloride produced 3-(naphtho[2,1-b]fur-2yl)-5-aryl-isoxazoles 5a-i, whereas similar reaction in presence of base, produced corresponding isoxazolines 6a and 6e. The structures of these compounds are well supported by IR and NMR spectral data.

MATERIALS AND METHODS

Melting points were determined in capillary tube and are uncorrected. IR spectra were recorded in KBr on FTIR

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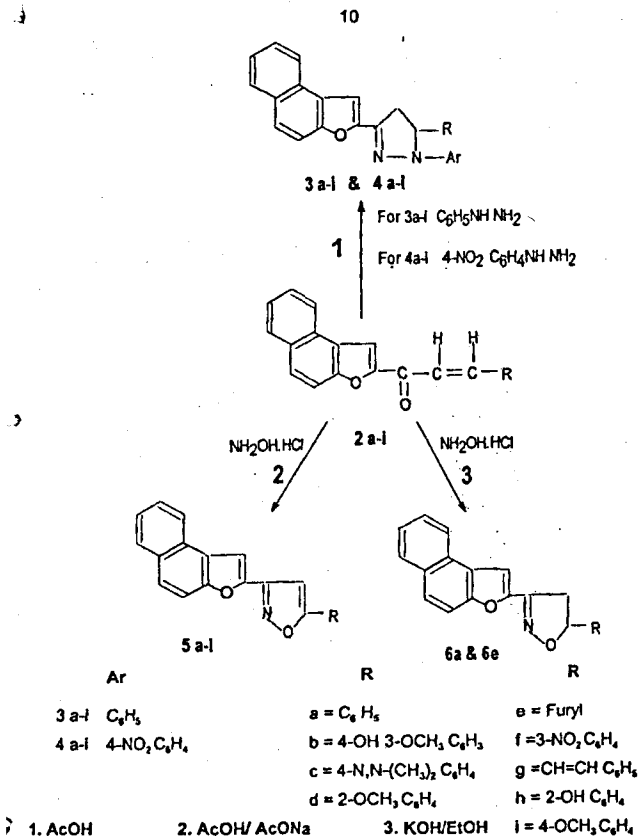

Scheme 1

(Research Spectrophotometer series) and NMR spectra on Jeol GSX 270 FT NMR Spectrophotometer using TMS as an internal standard.

1-{Naphtho[2,1-b]fur-2yl}-3-aryl-2-propen-1-ones 2a-i:

2-Acetylnaphtho[2,1-b]furan (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°. The resultant precipitate of 2a-i was filtered, washed with ethanol, dried and recrystallised from aqueous DMF.

3-(Naphtho[2,1-b]fur-2yl)-5-aryl-2-pyrazolines 3a-i:

A mixture of chalcones, 2a-i (0.005 mol) and phenyl hydrazine (0.01 mol) in glacial acetic acid (30 ml) was refluxed on an oil-bath at 110-120° for 4 h. The reaction mixture was cooled and poured in ice-water, the resulting solid was washed with water and recrystallised from aqeous ethanol (Table 1). The same method was used to synthesise 1-(4-Nitrophenyl)-3-(naphtho[2,1-b]fur-2yl)-5-aryl-2-pyrazolines (4a-i), but here 4-nirophenyl hydrazine (0.01 mol) was used in place of phenyl hydrazine.

3-(Naphtho[2,1-b]fur-2yl)-5-aryl-2-isoxazoles 5a-i:

Anhydrous sodium acetate (0.73 g, 0.01 mol) dissolved in a minimum amount of hot acetic acid which was later added to the solution of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in ethanol (10 ml). This solution was added to a solution of 2a-i (0.01 mol) in ethanol (15 ml). The mixture was refluxed on an oil-bath for 8 h, which was concentrated and neutralised with aqueous sodium hydroxide. The product thus separated was collected by filtration and recrystallised from aqueous DMF (Table 1).

3-(Naphtho[2,1-b]fur-2yl)-5-aryl-2-isoxazolines 6a and 6e-i:

A mixture of the chalcones 2a/2e (0.01 mol), hydroxylamine hydrochloride (0.02 mol) and potassium hydroxide (0.02 mol) in ethanol (25 ml) was refluxed for 4 h. The reaction mixture was then cooled and acidified with glacial acetic acid. The resulting solid was filtered and recrystallized from 95% ethanol (Table 1).

Analgesic activity:

This method was based on acetic acid-induced writhings in mice[6,7]. Male Swiss albino mice were procured from Virus Diagnostic Laboratory, Shimoga and maintained at National College of Pharmacy were fed with standard diet and water *ad libitum*. Nine groups of six mice each (22-35 g) were selected and 0.6% acetic acid (dose 10 ml/kg) was injected intraperitoneally. The number of writhes were counted for 20 min, after 5 min of injection cf acetic acid in each mice. This reading was taken as control. Next day the same groups of mice were used for evaluating analgesic activity. Each group was administered orally with the suspension of test compound in 0.1% Tween-80 solution at the dose of 100 mg/kg body weight of the animal 1 h before injection of acetic acid. After 5 min, the mice were observed for the number of writhes for the duration of 20 min. The mean value for each group was calculated and compared with the control. Acetyl salicylic acid was used as standard for comparison of analgesic activity and the results are recorded in Table 2.

Antimicrobial activity:

The antimicrobial activity was determined by cup-plate method[8]. Pure cultures of the test microorganism were procured from the cultures maintained at National College of Pharmacy, Shimoga. The *in vitro* antimicrobial activity was carried out against 24 h culture of two

TABLE 1: CHARACTERISTIC DATA OF 3a-i, 4a-i, 5a-i, 6a and 6e

Compd	R	mol.formula	yield %	m.p °C	N%	
					Found	Cald
3a	C_6H_5	$C_{27}H_{20}N_2O$	65	175	7.50	7.22
3b	4-OH 3-OCH_3 C_6H_3	$C_{28}H_{22}N_2O_3$	64	180	6.40	6.45
3c	4-N, $N(CH_3)_2$ C_6H_4	$C_{29}H_{25}N_3O$	56	185	9.70	9.74
3d	2-OCH_3 C_6H_4	$C_{28}H_{22}N_2O_2$	64	180	6.67	6.70
3e	Furyl	$C_{25}H_{18}N_2O_2$	60	200	7.20	7.41
3f	3-NO_2 C_6H_4	$C_{27}H_{19}N_3O_3$	65	245	9.20	9.70
3g	CH=CH-C_6H_5	$C_{29}H_{22}N_2O$	58	145	6.26	6.76
3h	2-OH C_6H_4	$C_{27}H_{20}N_2O_2$	58	165	7.04	6.94
3i	4-OCH_3 C_6H_4	$C_{28}H_{22}N_2O_2$	60	208	6.20	6.70
4a	C_6H_5	$C_{27}H_{19}N_3O_3$	62	195	9.52	9.70
4b	4-OH 3-OCH_3 C_6H_3	$C_{28}H_{21}N_3O_5$	65	175	8.70	8.77
4c	4-N,$N(CH_3)_2$ C_6H_4	$C_{29}H_{24}N_4O_3$	58	240	11.04	11.76
4d	2-OCH_3 C_6H_4	$C_{28}H_{21}N_3O_4$	54	250	9.66	9.07
4e	Furyl	$C_{25}H_{17}N_3O_4$	62	245	9.25	9.93
4f	3-NO_2 C_6H_4	$C_{27}H_{18}N_4O_5$	59	235	11.02	11.72
4g	CH=CH-C_6H_5	$C_{29}H_{21}N_3O_3$	56	225	8.89	9.15
4h	2-OH C_6H_4	$C_{27}H_{19}N_3O_4$	60	230	9.05	9.35
4i	4-OCH_3 C_6H_4	$C_{28}H_{21}N_3O_4$	58	238	8.80	9.07
5a	C_6H_5	$C_{21}H_{13}NO_2$	56	180	4.30	4.50
5b	4-OH 3-OCH_3 C_6H_3	$C_{22}H_{15}NO_4$	62	210	3.74	3.92
5c	4-N,$N(CH_3)_2$ C_6H_4	$C_{23}H_{18}N_2O_2$	59	120	7.72	7.91
5d	2-OCH_3 C_6H_4	$C_{22}H_{15}NO_3$	65	180	4.08	4.11
5e	Furyl	$C_{19}H_{11}NO_3$	59	190	4.05	4.65
5f	3-NO_2 C_6H_4	$C_{21}H_{12}N_2O_4$	54	210	7.27	7.87
5g	CH=CH- C_6H_5	$C_{23}H_{15}NO_2$	52	250	4.02	4.16
5h	2-OH C_6H_4	$C_{21}H_{13}NO_3$	50	190	4.02	4.28
5i	4-OCH_3 C_6H_4	$C_{22}H_{15}NO_3$	60	210	4.20	4.11
6a	C_6H_5	$C_{21}H_{15}NO_2$	62	215	4.40	4.47
6e	Furyl	$C_{19}H_{13}NO_3$	60	210	4.05	4.62

*All compounds gave satisfactory C and H analysis.

TABLE 2: ANALGESIC ACTIVITY OF SOME SELECTED COMPOUNDS

Compd	Dose mg/kg	Mean no. of writhing		% Protection
		Without the administration of drug	With the administration of drug	
Std	150	47.00±2.50	11.80±1.27	74.9
3b	100	28.83±4.66	10.00±2.36	65.3
3d	100	37.67±2.75	0.8.00±1.91	78.8
4d	100	33.00±2.35	14.00±1.65	57.6
4f	100	36.80±3.49	12.50±1.78	66.9
5c	100	40.00±2.73	14.33±3.88	64.2
5f	100	38.16±2.40	10.00±2.27	73.8
6a	100	39.00±4.56	10.66±2.57	72.7
6e	100	39.80±3.74	18.00±2.13	54.8

values are mean±SEM., No. of animals in each group : 06

bacteria and two fungi. The bacteria used were *Staphylococcus aureus* and *Klebsiella pneumoniae* while the fungi used were *Aspergillus niger* and *Candida albicans*. The compounds were tested at a concentration of 0.001 mol/ml in dimethyl formamide against both the organisms. Ciprofloxacin (0.001 mol/ml) and ciclopirox olamine (0.001 mol/ml) were used as standards for comparison of antibacterial and antifungal activities respectively. The zone of inhibition was compared with the standard drug after 24 h of incubation at 37° for antibacterial activity and 72 h at 25° for antifungal activity. The results are recorded in Table 3.

Anthelmintic activity:

The earthworms (*Pheritima posthuma*, order-annelida, class-Oligochaeta) were collected from a local supplier at Shimoga at the time of carrying out anthelmintic activity. The activity was evaluated on earthworms by a reported method[9]. The worms were washed with normal saline to remove the adhering material and sorted for uniform length and size. They were kept in 6% dextrose solution for 15 min and those with normal motility were used to evaluate anthelmintic activity. The compounds were tested at a dose of 0.001 mol/ml suspension in 0.1% Tween-80 solution. Petridishes of equal size were taken, 20 ml of 6% dextrose, Tween-80 solution and piperazine citrate were poured into separate petridishes as a control, blank and standard, respectively. The suspension of test compounds (20 ml) in 0.1 % Tween-80 solution was taken in different petridishes and two worms were placed in each petridish. The time taken by worm to become motionless was noted as paralysis time and the time taken for complete death of worms was also recorded. The results are reported in Table 3.

RESULTS AND DISSCUSSION

In the IR spectra of compounds 3a-i, no peak was observed between 1645-1635 cm^{-1} indicating the absence of C=O group. Instead new peaks were observed at 1605-1600 cm^{-1} due to C=N, 1340-1315 cm^{-1} due to CH_2 of pyrazolines and 1240-1220 cm^{-1} due to C-N stretching frequencies. The formation of pyrazolines has been further substantiated by the PMR spectrum (DMSO-d_6) of 3e which showed peak at δ 3.65 (2H, dd, CH_2 of pyrazoline ring), δ 4.9 (1H, t, CH of pyrazoline ring) and δ 7.2-8.2 (15H, m, aromatic protons).

Analgesic activity study reveals that the compound 3d is found to be more active than the standard drug (acetyl salicylic acid), while other compounds exhibit moderate activity. Investigation of antimicrobial activity reveals that compound 4e shows promising activity against all the four organisms whereas compounds 5c and 6e were active against *S. aureus* and 3f and 4g are active against *K. pneumoniae*. Determination of

TABLE 3: ANTIMICROBIAL AND ANTHELMINTIC ACTIVITIES OF 3a-i, 4a-i, 5a-i, 6a and 6e

	Antibacterial activity zone of inhibition in mm*		Antifungal activity zone of inhibition in mm*		Anthelmintic activity (min)	
Compd	*S.aureus*	*K. pneumoniae*	*A. niger*	*C. albicans*	Paralysis	Death
3a	12	20	—	10	Nil	Nil
3b	14	18	—	08	100	130
3c	16	18	20	12	90	140
3d	11	16	24	28	Nil	Nil
3e	—	—	22	24	120	160
3f	22	26	20	25	Nil	Nil
3g	12	14	16	18	100	140
3h	14	16	20	24	Nil	Nil
3i	13	15	26	28	130	160
4a	18	12	20	24	85	105
4b	—	—	10	12	140	160
4c	14	16	18	22	Nil	Nil
4d	08	10	15	18	Nil	Nil
4e	26	28	26	24	80	100
4f	11	14	15	17	100	130
4g	18	26	26	28	80	Nil
4h	14	16	22	22	90	140
4i	11	12	—	08	Nil	Nil
5a	—	09	10	14	120	Nil
5b	15	18	20	18	80	100
5c	29	16	28	25	95	125
5d	14	16	18	24	120	Nil
5e	16	18	28	22	Nil	Nil
5f	12	—	—	08	140	160
5g	14	—	12	15	Nil	Nil
5h	10	18	14	19	100	120
5i	16	17	22	22	80	90
6a	19	23	22	28	140	160
6e	28	16	25	27	90	130
Std	24	26	24	22	80	100
Saline	—	—	—	—	Nil	Nil

*Including diameter of the well, Control (DMF) = No activity

antifungal activity shows that compounds 3d, 3i, 4g, 5c, 5e and 6e are active against both the organisms, whereas 3e, 3f, 3h, 4a and 6a active against *C. albicans*. When anthelmintic activity on *Pheritima posthuma* was carried out, compounds 4e, 5b and 5i showed equipotent activity, whereas the rest of the compounds are less active than the standard drug. From these results one could conclude that all the activities are independent of either electron withdrawing group or electron donating group in the molecules.

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