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Synthesis and Pharmacological Evaluation of some Potent Naphtho [2,1-*b*] furo-pyrazolyl, Oxadiazolyl and Coumaryl Derivatives

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Naphtho[2,1-*b*]furyl-2-carboxyhydrazide 1 has been condensed with various substituted acetophenones to obtain corresponding carboxy hydrazones 2, which on treatment with Vilsmeier-Haack reagent resulted in the formation of 2-[3-phenyl-4-formyl -1-carbonyl]naphtho[2,1-*b*]furan pyrazole derivatives 3a-f. The compound 1 has been converted into N-aroyl-N'-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazine 4a-c, which on cyclization with phosphorous oxychloride produced 2-[5-aroyl-1,3,4-oxadiazol-2-yl]naphtho[2,1-*b*]furans 5a-c. The compound 6 has been synthesized by the condensation of 1 with ethyl acetoacetate. Various naphtho[2,1-*b*]furan-2-[N'-(substituted benzopyran-2'-one-3'-carbonyl)]hydrazides 8a-d, have been prepared from compound 1 via compound 7. The compounds 8a-d have also been synthesized by direct condensation of 1 with 6-substituted coumarins. All newly synthesized compounds have been characterized by elemental analysis and spectral data and screened for antimicrobial, anthelmintic, antiinflammatory, analgesic and diuretic activities.

Compounds containing pyrazole moiety and 1,3,4-oxadiazole moiety find unique place in medicinal chemistry and play significant role, as they are associated with immense biological activities[1-9]. Several coumarin derivatives have been reported to possess diuretic[10], anticoagulant[11], antipyretic[12] and tranquillizing[13] activities. Many naphthofuran derivatives, synthesized in our laboratory, have been found to exhibit remarkable biological activities[14-17]. Hence, with the view that combination of naphthofuran ring and pyrazole, oxadiazole or coumarin nuclei would yield biologically more potent compounds, the present investigation has been taken up.

The starting material **1** was synthesized using a method previously reported from our laboratory[15]. The reaction sequence leading to the formation of different title compounds is outlined in Scheme 1. The reaction of **1** with various substituted acetophenones in presence of catalytic amount of sulphuric acid produced anticipated acetophenone naphtho[2,1-*b*]furan-2-carbonylhydrazones **2a-f** in an excellent yield. These hydrazones were stirred with Vilsmeier-Haack reagent (dimethyl formamide/phosphorous oxychloride) at room temperature, to form 2-[3-phenyl-4-formyl-1-carbonyl]naphtho[2,1-*b*]furanpyrazoles **3a-f** in 60-70% yield. Compound **1** on refluxing with various acyl chlorides in presence of a base, afforded N-aroyl-N'-(naphtho[2,1-*b*]furan-2-carbonyl)hydrazines **4a-c**, which underwent smooth cyclization on heating with phosphorous oxychloride and gave corresponding 2-[5-aroyl-1,3,4-oxadiazol-2-yl]naphtho[2,1-b]furans **5a-c**. Synthesis of 3-methyl-1-[(naphtho[2,1-*b*]furan-2-yl)-carbonyl]pyrazolin-5(4*H*)-one **6** was accomplished by refluxing the compound **1** and ethyl acetoacetate in ethanol using sulphuric acid as catalyst .

In order to obtain naphtho[2,1-*b*]furan-2-[N'-mono(carbethoxymalonoyl)] hydrazide **7**, the compound **1** was heated with diethyl malonate in ethanol at its reflux temperature . Further, treatment of **7** with different aromatic aldehydes in ethanol gave corresponding naphtho[2,1-*b*]furyl-2-[N,b-(benzopyran-2'-one-3'-carbonyl)]hydrazide deriva-

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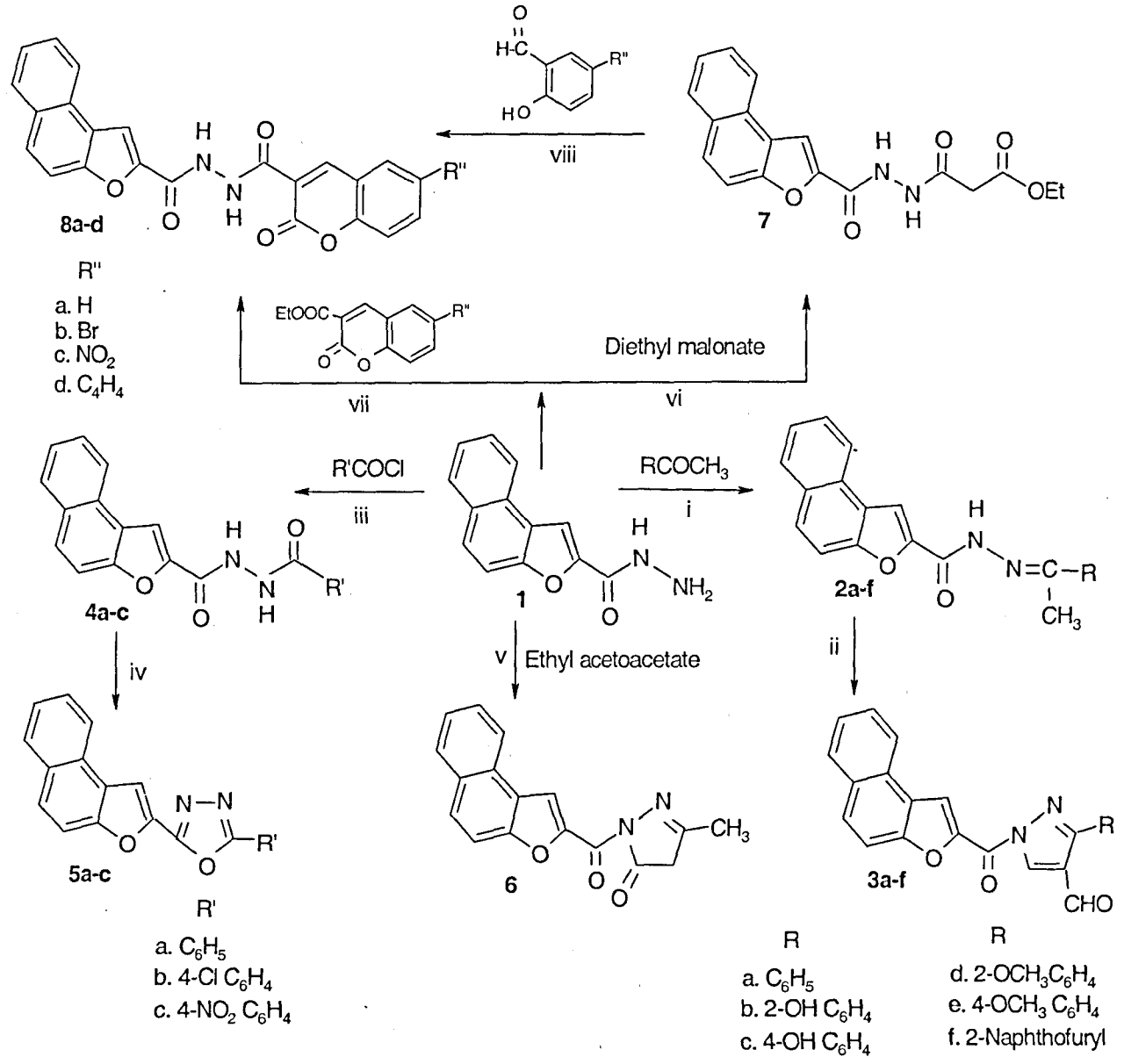
tives **8a-d.** The compounds **8a-d** were also synthesized by an alternative method which involved direct condensation of **1** with 6-substituted coumarin-3-ethyl carboxylate. The compounds obtained by this method were found to be identical with the compounds prepared by other method as indicated by superimposable IR, NMR and mixed melting point.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are uncorrected. IR were recorded on a Perkin-Elmer 297 Spectrophotometer using KBr. ^{1}H NMR were recorded on a Bruker AC 300F NMR Spectrophotometer (300 MHz) using TMS as internal standard. Chemical shifts are expressed in δ ppm. Purity of all the compounds was checked by TLC using silica gel G as an adsorbent. All the animal experiments with Wistar rats and Swiss mice were carried out at National College of Pharmacy, Shimoga and permission for conducting these experiments was obtained from Institu-



i. EtOH/H+ ii. DMF/$POCl_3$ iii. NaOH iv. $POCl_3$ v. EtOH/H+ vi. EtOH vii. EtOH/H+ viii. Pipyridine

Scheme 1

tional Animals Ethics Committee (CPCSEA Regd. No. 144).

Synthesis of acetophenone naphtho[2,1-*b*]furan-2-carbonylhydrazone 2a General procedure:

To a solution of **1** (2.26 g) in hot methanol (30 ml), acetophenone (1.2 g) and a drop of concentrated sulphuric acid were added. The reaction mixture was refluxed for 1 h and cooled. The solid separated was filtered and recrystallized from ethanol.

Synthesis of 2-(3-phenyl-4-formylpyrazole -1-carbonyl) naphtho[2,1-*b*]furan 3a:

To the Vilsmeier-Haack reagent prepared from dimethyl formamide (10 ml) and phosphorous oxychloride (1.1 ml), the hydrazone **2a** (1.3 g) was added and the reaction mixture was stirred at room temperature for 2 h and poured into crushed ice. The solid thus separated was filtered and recrystallised from methanol. Similarly compounds **3b-f** were prepared by using corresponding hydrazones **2b-f.**

TABLE 1: CHARACTERISATION DATA OF COMPOUNDS 2a-f, 3a-f, 4a-c, 5a-c, 6, 7 AND 8a-d.

Compd	R	Mol. formula	Yield %	m.p.	N% Found	N% Cald
2a	$-C_6H_5$	$C_{21}H_{16}N_2O_2$	85	190	8.48	8.53
2b	2-OH C_6H_4	$C_{21}H_{16}N_2O_3$	70	235	8.18	8.14
2c	4-OH C_6H_4	$C_{21}H_{16}N_2O_3$	70	220	8.18	8.14
2d	2-$OCH_3C_6H_4$	$C_{22}H_{18}N_2O_3$	60	210	7.75	7.82
2e	4-$OCH_3C_6H_4$	$C_{22}H_{18}N_2O_3$	68	195	7.75	7.82
2f	$-C_{12}H_7O$	$C_{27}H_{18}N_2O_3$	55	225	6.65	6.69
3a	$-C_6H_5$	$C_{23}H_{14}N_2O_3$	60	240	7.55	7.65
3b	2-OH C_6H_4	$C_{23}H_{14}N_2O_4$	60	220	7.32	7.33
3c	4-OH C_6H_4	$C_{23}H_{14}N_2O_4$	80	198	7.30	7.33
3d	2-$OCH_3C_6H_4$	$C_{24}H_{16}N_2O_4$	70	230	7.04	7.07
3e	4-$OCH_3C_6H_4$	$C_{24}H_{16}N_2O_4$	75	237	7.02	7.07
3f	$-C_{12}H_7O$	$C_{29}H_{16}N_2O_4$	60	226	6.60	6.67
4a	$-C_6H_5$	$C_{20}H_{14}N_2O_3$	80	230	8.40	8.48
4b	4-Cl C_6H_4	$C_{20}H_{13}N_2O_3Cl$	90	210	7.66	7.68
4c	4-NO_2 C_6H_4	$C_{20}H_{13}N_3O_5$	85	217	11.12	11.20
5a	$-C_6H_5$	$C_{20}H_{12}N_2O_2$	40	164	8.80	8.97
5b	4-Cl C_6H_4	$C_{20}H_{11}N_2O_2Cl$	40	234	8.06	8.08
5c	4-NO_2 C_6H_4	$C_{20}H_{11}N_3O_4$	50	225	11.70	11.76
6	-	$C_{17}H_{12}N_2O_3$	80	208	9.50	9.58
7	-	$C_{18}H_{16}N_2O_5$	70	222	8.16	8.23
8a	-H	$C_{23}H_{14}N_2O_5$	60	218	7.00	7.04
8b	-Br	$C_{23}H_{13}N_2O_5Br$	60	250	5.80	5.87
8c	$-NO_2$	$C_{23}H_{13}N_3O_7$	50	267	9.46	9.48
8d	$-C_4H_4$	$C_{27}H_{16}N_2O_5$	50	230	6.20	6.25

All compounds gave satisfactory C and H analysis.

Synthesis of N-aroyl-N¹-(naphtho[2,1-*b*]furan-2-carbonyl) hydrazine 4a:

A mixture of compound **1** (2.26 g) and benzoyl chloride (1.4 g) was stirred at room temperature, followed by addition of aqueous sodium hydroxide (5 ml, 0.01 N) dropwise to a stirred mixture, stirring was continued for 1 h. The mixture was then poured into water, filtered, dried and recrystallised from ethanol. Other compounds **4b-c** in the series were prepared similarly by using appropriately substituted benzoyl chloride.

Synthesis of 2-(5-aroyl-1,3,4-oxadiazol-2-yl)naphtho[2,1-*b*]furan 5a:

Compound **4a** (3.3 g) was refluxed with phosphorous oxychloride (15 ml) for 3 h, cooled and poured into crushed ice with stirring. The solid thus separated was filtered and recrystallised from methanol. The compounds **5b-c** were prepared by adopting same procedure from **4b-c.**

Synthesis of 3-methyl-1-[(naphtho[2,1-*b*]furan-2-yl)-carbonyl]pyrazolin-5(4H)-one 6:

To a solution of ethyl acetoaectate (1.2 g) in methanol (25 ml) catalytic amount of concentrated sulphuric acid and compound **1** (2.26 g) were added and refluxed for 2 h, cooled and poured into ice cold water, solid separated was filtered, dried and recrystallised from ethanol.

Synthesis of naphtho[2,1-*b*]furan-2-[N¹-mono (carbethoxy malonoyl)]hydrazide 7:

A mixture of compound **1** (0.904 g) and diethyl malonate (0.64 g) was refluxed for 4 h in methanol (20 ml), cooled and poured into ice cold water. The solid separated was filtered, dried and recrystallised from ethanol.

Synthesis of naphtho[2,1-*b*]furan-2-[N¹-(substitutedbenzopyran-2'-one-3'-carboxyl)] carboxy hydrazide 8a-d General procedure:

To a solution of appropriate salicylaldehydes (1.1 g) in ethanol (20 ml) compound **7** (3.4 g) was added and the mixture was refluxed for 4 h in presence of catalytic amount of piperidine. The mixture was cooled and poured into cold water, solid separated was filtered, dried and recrystallised from ethanol. Physical and analytical data of all the compounds are given in the Table 1. The structures of all compounds were confirmed by IR and PMR data (Table 2).

Antimicrobial activity:

The *in vitro* antimicrobial activity was carried out against 24 h cultures of two bacteria and one fungus. The bacteria used were *Staphylococcus aureus* and *Klebsiella pneumoniae* and the fungus used was *Aspergillus niger.* Pure cultures of the test microorganisms were procured from the culture maintained at Biotechnology Department, Kuvempu University, Jnana Sahyadri, Shankaraghatta-577 451. The antimicrobial activity was performed using the agar cup-plate method[17]. Nutrient agar and potato dextrose agars were used

TABLE 2: SPECTRAL DATA OF COMPOUNDS.

Compd	IR (KBr) (ν_{max} in cm^{-1})	PMR (δ ppm)
2a	3442 (NH), 1672 (C=O), 1570 (C=N).	($CDCl_3$): 9.56 (s, NH) 7.25-8.19 (m, 12H, ArH), 2.47 (s, CH_3).
3a	1694 (C=O, Aldehyde), 1620 (C=O), 1554 (C=N).	($CDCl_3$): 9.2 (s, 1H, CHO), 7.25-8.32 (m,13H, ArH).
4a	3440 (NH), 1690 (C=O), 1629 (C=N).	(DMSO-d_6): 7.32-8.17 (m, 12H, ArH, 2H, NHNH,).
5	1636 (C=N), 1274 (C-O-C).	($CDCl_3$): 6.77-8.16 (m, 12H, ArH).
6	1665 (C=O), 1595 (C=N).	($CDCl_3$): 7.5-8.17 (m,7H,ArH), 2.2 (s, CH_2) 1.3 (s,CH_3).
7	3443 (NH), 1740, 1628,1597 (C=O and-COO-).	(DMSO-d_6): 8-8.2 (dd, NHNH). 7–8 (m, 7H, ArH), 3.9 (s, 2H), 3.7 (q, 2H), 1.13 (t, 3H)
8a	3438 (NH), 1739 (ring-O-C=O), 1627 (C=O).	(DMSO-d_6): 6.792-8.7 (m, 12H, ArH and 2H, NHNH).

to culture the bacteria and fungus respectively. The compounds were tested at a concentration of 0.005 mol/ml in DMF solution. Solutions of streptomycin (0.005 mol/ml) and griseofulvin (0.005 mol/ml) were prepared in sterilized water and used as standards for comparison of antibacterial and antifungal activities, respectively. The diameter of the zone of inhibition at the end of the 24 h incubation for bacteria and fungus was measured. Each experiment was repeated thrice and the average of the three independent determinations was recorded. The results are summarized in

TABLE 3: ANTIMICROBIAL AND ANTHELMINTIC ACTIVITIES OF 2a-f, 3a-f, 4a-c, 5a-c, 6, 7 AND 8a-d.

Compd.	Zone of inhibition (mm*)			Anthelmintic activity (min)	
	S. aureus	*K. pneumoniae*	*A. niger*	Paralysis (t)	Death (t)
2a	3.0	35	28	120	-
2b	8	20	24	100	100
2c	6.4	10	12	90	120
2d	-	18	22	80	130
2e	13.3	15	18	-	-
2f	9.6	22	24	80	100
3b	9	18	21	90	120
3a	4.2	15	17	100	-
3c	-	-	10	-	130
3d	-	-	08	100	-
3e	14	20	12	90	120
3f	10	22	28	-	140
4a	-	24	24	110	120
4b	-	20	25	-	95
4c	12	16	18	100	-
5a	16	26	24	-	130
5b	7	-	35	90	120
5c	3.6	23	16	100	110
6	-	13	-	130	165
7	4.8	42	54	160	180
8a	14	26	32	-	-
8b	-	24	27	120	150
8c	12	18	56	60	90
8d	16	32	34	20	90
Control	-	-	-	-	-
Std	12	26	24	90	90

*Including diameter of the well, (-) – No activity.

the Table 3.

Anthelmintic activity:

Anthelmintic activity was evaluated on earthworms (*Pheritima posthuma, Order-Annelida, Class-oligochaeta)* by following the reported method[17]. The worms were collected from a local supplier at Shimoga at the time of carrying out anthelmintic activity. The worms were sorted for uniform length and size. They were washed with normal saline to remove the adhering material and were kept in 6% dextrose solution for 15 min and those with normal mobility were used for the test. The compounds were tested at a dose of 0.005 mol/ml suspension in 0.1% Tween-80 solution in saline. Mebendazole was used as standard drug at dose of (0.005 mol/ml) suspension in 0.1% Tween-80 solution in saline. Petridishes of nearly equal size were taken and two worms were placed in each petridish. Normal saline (20 ml), Tween-80 solution and mebendazole suspension were poured in to separate petridishes as a control, blank and standard, respectively. The suspension of the test compounds (20 ml) was taken in different petridishes and time was noted as zero time. Time for paralysis (loss of movement) and time taken for deaths were recorded (Table 3).

Analgesic activity:

Acetic acid-induced writhing in mice was used to evaluate analgesic activity[18]. Swiss albino mice of either sex were procured from Virus Diagnostic Laboratory, Shimoga and maintained at National College of Pharmacy and 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 was counted for 20 min, after 5 min of injection of 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. Statistical analysis was carried out using student 't' test. The results are expressed in ±SEM. Acetyl salicylic acid was used as standard for comparison of analgesic activity and the results are recorded in Table 4.

Diuretic activity:

The activity was evaluated on Wistar rats using an earlier reported method[19]. The rats weighing 140-220 g were divided into 4 groups of 6 animals each and placed in metabolic cages, which were provided with a wire mesh at the bottom and a funnel to collect urine. Sieves made up of stainless steel were placed in the funnel to retain feces. Rats were fed with standard diet and water *ad libitum.* Food and water were withdrawn 24 h prior to the experiment. The test compounds were administered orally at a dose of 30 mg/kg

TABLE 4: ANALGESIC ACTIVITY OF SOME NAPHTHO[2,1-*b*]FURO PYRAZOLES, OXADIAZOLES AND COUMARINES.

Compd	Dose (mg/kg)	Mean no. of writhing		% Protection
		Control	Treatment	
Std	100	47.0±2.50	11.8±1.27	74.9
3a	100	30.8±2.76	12.3±1.58	60.0
3b	100	31.5±2.08	15.5±2.28*	50.8
5b	100	34.8±1.51	16.8±2.64*	51.7
5c	100	33.2±1.87	14.5±1.54*	56.3
8a	100	36.3±2.40	14.7±1.89*	52.3
8b	100	33.5±2.12	15.3±2.23*	54.2
8c	100	36.5±1.41	16.5±0.11	54.8
8d	100	34.5±2.28	11.8±1.27	55.6

Values are expressed as mean ± SEM, Number of animals used in each group is 6: *P<0.5, % of protection = Nc-Nt / Nc x 100, N_c = Number of writhing in control, N_t = Number of writhing in test compounds.

body weight suspended in 0.1% Tween-80. Another set of 2 groups served as standard and received 40 mg/kg body weight of frusemide (aqueous solution) orally. The remaining 2 groups served as control and received only 0.1 % Tween-80 solution. Sodium chloride solution (0.9%) at a dose of 5 ml/100 g body weight was given to all the animals by gavage before the experiment. Urine excretion was recorded after 5 h and the values are tabulated in Table 5.

RESULTS AND DISCUSSION

The results of antimicrobial activity revealed that compounds **2a, 7** and **8d** were found to be active against *K. pneumoniae,* whereas other compounds were moderately active against both the bacteria. The compounds **2a, 3f, 5b, 7** and **8a-d** exhibited more antifungal activity against *A, niger* than the standard.

Amongst the compounds screened for analgesic activity only the compound **3a** was found to show moderate activity. Evaluation of anthelmintic activity indicated that the compounds **8c** and **8d** showed equipotent activity when compared with standard. Screening result of diuretic activity revealed that the only compounds **8a** and **8c** exhibited moderate activity. All the above result indicated that presence of coumarin moiety along with naphtho[2,1-b]furan ring enhance the activities.

TABLE 5: DIURETIC ACTIVITY OF SOME NAPHTHO[2,1-*b*]FURO COUMARINS.

Compd.	Volume of urine collected after 5 h	T/S (Lipschitzvalues)[19]
Std	29.0	1.0
8a	20.7	0.7
8b	17.8	0.6
8c	18.2	0.6
8d	13.6	0.5
Control	08.0	0.3

Index for diuretic activity. Number of animals used :6. Standard- frusemide, T- Urine collected for test compound, S-Urine collected for standard drug, Control- 0.1% Tween-80.

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