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Synthesis of urethanes and substituted ureas encompassing naphtho[2.1-b]furan and evaluation their analgesic activity

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ABSTRACT

*Ethyl naphtho[2,1-b]furan-2-carboxylate **1** was synthesized from 2-hydroxy-1-naphthaldehyde by reacting it with ethyl chloroacetate in presence of anhydrous potassium carbonate and dimethyl formamide. The ester **1** was converted to naphtho[2,1-b]furan-2-carboxyhydrazide **2** by treating it with hydrazine hydrate in alcohol. Naphtho[2,1-b]furan-2-carboxyazide **3** was obtained by reacting hydrazide **2** with nitrous acid at low temperature. The reaction of **3** with various alcohols, phenols and drugs- chloramphenicol, sulphathiazole and paracetamol resulted in the formation of new heterocyclic compounds, 2-semicarbazidonaphtho[2,1-b]furans **(4a-j)**(urethanes and substituted urea)**. The newly synthesized compounds were characterized by spectral methods and evaluated for analgesic activity by acetic acid induced writhing method and Eddy's hot plate method by using Swiss mice. Some of he compounds exhibited considerable analgesic activity.*

Key words: Urethanes, Naphtho[2.1-b]furan, Substituted urea, Analgesic activity, Eddy's hot plate.

INTRODUCTION

The compounds containing naphtho[2,1-b]furan ring system are known to possess various biological and pharmacological activities such as antimicrobial[1], anthelmintic[2], anti-inflammatory[3,4] diuretic[5], analgesic[6]. Urethanes or carbamates find application in industries as binders and adhesives. Substituted ureas are important class of compounds due to

their extensive application as agrochemicals, dyes for cellulose, detergents and synthetic intermediates [7-9]. These compounds also exhibit potent biological activities like HIV protease inhibitor [9], CCK-B receptors [10], endothelin antagonist [11]. The drugs such as chloramphenicol, sulphthiazole and paracetamol are known for their antimicrobial, analgesic, antipyretic and anti-inflammatory activities. Encouraged by these observations it was contemplated to synthesize urethanes and substituted ureas involving naphtho[2,1-b]furan, some alcohols, phenols and the drugs and evaluate them for analgesic activity.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (in cm^{-1}) were recoded in KBr on FT-IR (Research Spectrophotometer Series) and Perkin-Elmer FT-IR (Spectrum 1000), NMR spectra on Jeol GSX270FTNMR spectrophotometer using DMSO or $CDCl_3$ as solvent and TMS as an internal standard [chemical shifts are given in δ (ppm) values] and mass spectrum on Brucker Apex-11 mass spectrophotometer at 70 eV. Compounds were checked for their purity by TLC silica gel G plates using methanol-carbon tetrachloride (v/v) by varying polarity and the spots located by iodine vapour.

Ethyl naphtho[2,1-b]furan-2-carboxylate 1

2-Hydroxy-1-naphthaldehyde (8.6 g, 0.1 mol), ethyl chloroacetate (6.13 g, 0.01 mol) and anhydrous potassium carbonate (6.9 g) were refluxed in dry DMF (60 ml) for 12 hr. Potassium salts were filtered off, the filtrate was poured onto crushed ice to obtain the product as solid, which was collected by filtration and was recrystallized from ethanol.

Naphtho[2,1-b]furan-2-carboxyhydrazide 2

An aqueous solution of hydrazine hydrate (15 ml, 99%) was added to a solution of naphtho[2,1-b]furan-2-carboxylate **1** (2.4 g, 0.01 mol) in ethanol (30 ml). The reaction mixture was heated under reflux for 5 hr and cooled to room temperature. The hydrazide **2** that separated was collected and recrystallized from ethanol.

Naphtho[2,1-b]furan-2-carboxyazide 3

The solution of sodium nitrite (0.7 g) in water (3 ml) was added drop wise with stirring at 0^0C to a mixture of hydrazide **2** (2.26g, 0.01 mol) in dioxan (10 ml) and acetic acid (25 ml). The stirring was continued for 30 min. The pale yellow solid that separated was filtered, washed with ice cold water (20 ml) and then with dioxan (10 ml) It was dried in vacuum over phosphorous pentoxide.

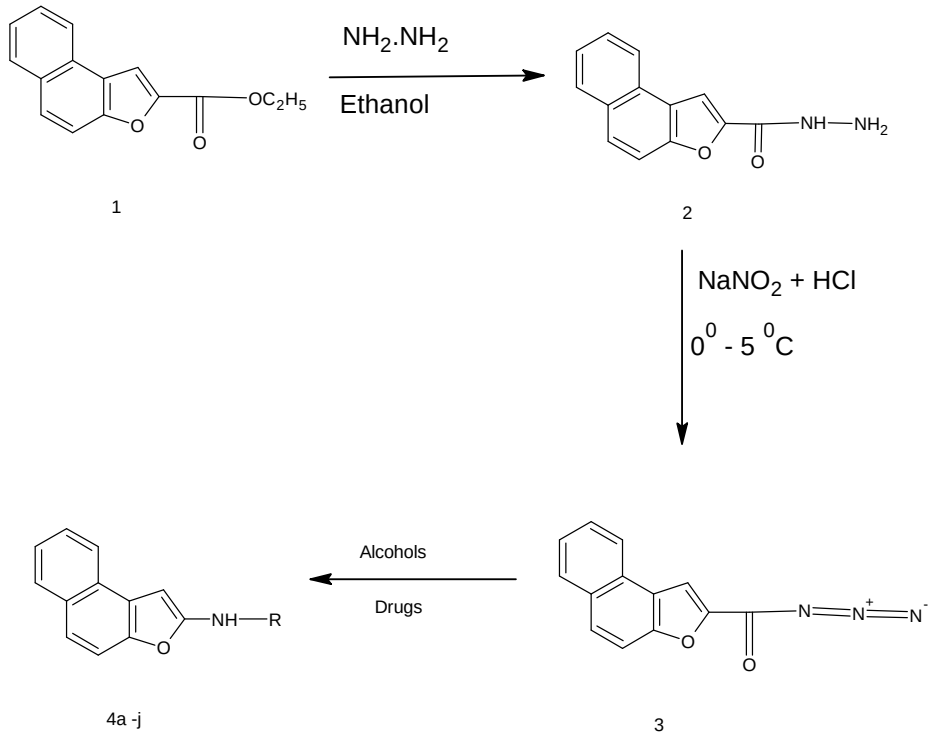
2- Semicarbazido naphtho[2,1-b]furans (4a-j)

A mixture of naphtho[2,1-b]furan-2- carboxyazide **3** (0.005 mol) was refluxed with methanol, ethanol, 2-propanol, and 2-butanol respectively for 5 hrs each. The solids **(4a-d)** obtained were recovered after evaporation of alcohols. Similarly azide **3** (0.005 mol) was treated with chloramphenicol (0.005 mol), sulphathiazole (0.005 mol) and paracetamol (0.005 mol), the mixture was ground well and heated on a water bath for 4 hrs. The solid obtained (**4e-g**) were recrystallized from appropriate solvents. Naphtho[2,1-b]furan-2-carboxyazide **3** (0.005 mol) was treated with phenol (0.005 mol), p-nitrophenol (0.005 mol), methyl salicylate (0.005 mol) in an oil bath at 220^o C for 2 to 3 hours. The reaction mixture was treated with aqueous solution of

sodium hydroxide (10 %) , filtered and washed with water and the solid compounds thus obtained **(4h-j)** were recryllaized from ethanol.

The sequence of the reaction is depicted in the scheme

Scheme



	R		R
a	$-OCH_3$	f	$-C_9H_7S_2N_3O_3$
b	$-OC_2H_5$	h	$-OC_6H_5$
c	$-OC_3H_7$	i	$-OC_6H_4.NO_2(p)$
d	$-OC_4H_9$	j	$-OC_8H_7O_2$
e	$-OC_{10}H_9N_2O_3Cl_2$		

The physical characterization data of all the compounds has been summarized in Table 1

Table 1- Physical characterization data of the compounds

Compd.	R	Molecular formula	m.p.^{o}C	yield %	Found%(calculated)		
					C	H	N
1	-	$C_{15}H_{12}O_3$	77		74.52 (75.00)	4.91 (5.00)	
2	-	$C_{13}H_{10}N_2O_2$	100	78	68.95 (69.03)	4.36 (4.42)	12.19 (12.39)
3	-	$C_{13}H_7N_3O_2$	165	70	65.68 (65.82)	2.85 (2.95)	17.62 (17.72)
4a	-OCH_3	$C_{14}H_{11}NO_3$	160	62	69.59 (69.71)	4.59 (4.56)	5.68 (5.81)
4b	-OC_2H_5	$C_{15}H_{13}NO_3$	145	60	70.48 (70.59)	4.98 (5.10)	5.49 (5.49)
4c	-OC_3H_7	$C_{16}H_{15}NO_3$	205	72	71.20 (71.37)	5.49 (5.58)	5.09 (5.20)
4d	-OC_4H_9	$C_{17}H_{17}NO_3$	147	59	71.97 (72.08)	5.89 (6.00)	4.88 (4.95)
4e	-$OC_{10}H_9N_2O_3Cl_2$	$C_{23}H_{17}N_3O_6Cl_2$	144	65	54.79 (56.89)	3.30 (3.38)	8.29 (8.36)
4f	-$C_9H_7S_2N_3O_3$	$C_{22}H_{16}N_4O_4S_2$	118	84	56.49 (56.89)	3.39 (3.45)	11.97 (12.07)
4g	-OC_8H_8NO	$C_{21}H_{16}N_2O_4$	>250	61	69.80 (70.00)	4.32 (4.44)	7.68 (7.78)
4h	-OC_6H_5	$C_{19}H_{13}NO_3$	120	62	75.00 (75.24)	4.19 (4.29)	4.55 (4.62)
4i	-$OC_6H_4.NO_2$(p)	$C_{19}H_{12}N_2O_5$	98	65	65.39 (65.52)	3.39 (3.44}	7.79 (8.05)
4j	-$OC_8H_7O_2$	$C_{21}H_{15}NO_5$	155	68	69.50 (69.80)	4.01 (4.16)	3.78 (3.88)

Analgesic activity

Analgesic activity of the synthesized compounds was assessed by adopting two methods,

1. Acetic acid induced writhing method.
2. Eddy's hot plate method.

Acetic acid induced writhing method:

Colony bred albino mice (Swiss strain) of either sex weighing 22-35 g were used to evaluate analgesic activity. It was determined as described by the method based on acetic acid induced writhing response in mice.

For this experiment 42 mice were used and they were divided into 7 groups containing 6 animals each. All the animals received 0.6% v/v of 100 mg/kg body weight of acetic acid intraperitoneally and number of writhing was recorded after 10 min up to next 15 min. The same groups of animals were used next day for evaluating analgesic activity.

Group 1 received 0.5ml Tween-80 (0.1%) and served as control, group II received 100 mg/kg body weight of acetylsalicylic acid (aspirin) orally and served as standard. The remaining 5 groups received various test compounds at a dose of 100 mg/kg body weight orally in the form of suspension in 0.1% Tween-80. After 1 hr, all the animals received 0.6% of 100 mg/kg body

weight of acetic acid intraperitoneally. The writhing were counted similarly as in the previous day. The results are presented in Table 2.

Table 2- Analgesic activity of synthesized compounds by acetic acid induced writhing method

Compound	Dose	Mean number of writhing	% protection
Control	100	80	
Standard	100	30	62.50
4a	100	50	30.00
4b	100	40	50.00
4c	100	39	51.25
4d	100	65	18.75
4e	100	60	25.00
4f	100	30	62.50
4g	100	35	56.25
4g	100	40	50.00
4h	100	35	56.25
4i	100	45	43.75
4j	100	36	55.00
Acetic acid:1%V/V(inject 1ml/100g body weight of the animal) Aspirin:100mg/kg bodyweight			

Animal : Albino mice
No. of animals per group: 03 (25-35 g)
Route of administration : Intraperitoneal
Standard drug used : Acetyl salicylic acid (100mg/kg body weight)
Control : Acetic acid 1% v/v (inject 1ml/100g body weight of the animal)

Table 3- Analgesic activity of synthesized compounds by Eddy's Hot Plate Method

Compound	Reaction time (sec) after drug administration		
	30 min ± SEM	60 min ± SEM	90 min ± SEM
4a	5.02 ± 0.44	6.20 ± 0.60	8.25 ± 0.51
4b	5.40 ± 0.30	6.70 ± 0.56	8.55 ± 0.32
4c	8.50 ± 0.24	9.55 ± 0.55	11.35 ± 0.38
4d	6.75 ± 0.48	7.75 ± 0.48	9.75 ± 0.48
4e	8.25 ± 0.48	9.50 ± 0.29	10.50 ± 0.29
4f	8.73 ± 0.20	9.50 ± 0.65	11.50 ± 0.29
4g	7.10 ± 0.25	8.26 ± 0.65	9.12 ± 0.66
4h	7.00 ± 0.41	8.25 ± 0.48	10.00 ± 0.41
4i	7.22 ± 0.24	8.33 ± 0.52	9.40 ± 0.39
4j	7.25 ± 0.48	8.50 ± 0.65	10.25 ± 0.48
Diclofenac sodium	8.00 ± 0.41	9.50 ± 0.29	11.50 ± 0.65

±SEM = Standard Error Mean
Animal : Mice (Swiss strain) weighing between 25-35 g
Standard drug used : Diclofenac sodium (50mg/kg body weight)
Gum acacia : (1%)
Method : Eddy's hot plate

Eddy's hot plate method:
All the compounds were tested for their analgesic activity by using Eddy's hot plate technique. Mice (Swiss strain) of either sex weighing between 25-35 g were used for the experiment.

Diclofenac sodium at the dose of 5 mg/kg body weight as suspension in 1% gum acacia was used as standard. In this method heat is used as a source of pain.

Animals were individually placed on a hot plate maintained at constant temperature (55^0C) and the reaction of animals such as paw licking or jump response (whichever appears first) was taken as the end point. Test compounds at the dose of 5 mg/kg body weight were given as suspension in 1% gum acacia orally to animals and observed the reaction time of animals on the hot plate at 15, 30, 60 and 90 minutes after administration of the compounds. A cut off-time of 15 seconds was taken as maximum analgesic response to avoid injury to the paws. The results are presented in Table 3.

RESULTS AND DISCUSSION

The starting material ethyl naphtho[2,1-b]furan2-carboxylate **1** was prepared by the reaction between 2-hydroxy-1-naphthaldehyde and ethyl chloroacetate in presence of anhydrous potassium carbonate and dimethylformamide. The IR spectrum of **1** exhibited ester carbonyl absorption at 1737 cm^{-1}. The ^{1}H NMR spectrum of **1** showed expected multiplet between δ 7.2 and 8.2, quartet centered at 4.49 (J=7.03 Hz) and triplet centered at 1.47 (J =7.02 Hz) integrating for seven, two and three protons respectively

The electron impact mass spectrum of **1** showed the molecular ion peak at m/z 240 consistent with the molecular weight in high intensity attributing to the strong conjugated ring system.

Naphtho[2,1-b]furan-2-carboxyhydrazide **2** was obtained by the condensation of **1** with hydrazine hydrate (99%) in absolute ethanol. The structure of **2** was established by its IR spectrum, exhibiting characteristic peaks at 3127 cm^{-1} and 3200 cm^{-1} due to NH and NH_2 absorption and at 1684 cm^{-1}due to C=O group. The structure was well supported by its ^{1}H NMR spectrum showing peaks at δ 8.3 (s, 1H, NH), δ 7.2-8.2 (m, 7H, ArH) and δ 3.3 (s, b. 2H, NH_2).

The carboxyhydrazide **2** on treatment with acetic acid and sodium nitrite in dioxan at 0-5^0 produced naphtho[2,1-b]furan-2-carboxyazide **3**. The IR spectrum of which exhibited peaks at 2144 and 1684 cm^{-1} accounting for absorption due to $N=N^+=N^-$ and C=O groups respectively confirmed the assigned structure. ^{1}H NMR spectrum showing peak in the region of δ 7.25-8.2 (m, 7H, ArH) indicated the presence of only aromatic protons giving additional support to the structure.

The azide **3** served as an excellent intermediate for the synthesis of title compounds. For this purpose Curtius rearrangement was thought to be an efficient route. Thus azide **3** was treated with different alcohols such as methanol, ethanol, 2-propanol, 2-butanol and phenols such as phenol, p-nitrophenol, methyl salicylate. To extend the similar reaction to synthesize analogs of drugs, the azide **3** was treated with drugs like chloramphenicol, sulphathiazole and paracetamol to investigate the effect of naphthofuran moiety on these drugs regarding their analgesic activity.

The compounds **4a-j** exhibited characteristic absorption band between 1675 and 1689 cm^{-1} due to NH-C=O functionality in their IR spectra. The ^{1}H NMR spectra of some representative compounds were recorded to confirm the structure assigned. The ^{1}H NMR spectrum of

compound **4a** showed signals at δ 3.42 (s, 3H, -OCH_3), 7.5-8.3 (m, 7H, ArH) and at 11.7 (s, 1H, -NH), **4g** exhibited peaks at δ 1.39 (s, 3H, -CH_3), at 7.4- 8.7 (m, 11H, ArH), at 11.67 (s, 1H, -NH), and at 11.91 (s, 1H, -NH) and **4i** showed signals at δ 7.5-8.86 (m, 11H, ArH) and at 10.91 (s, 1H, -NH). The mass spectrum of the compounds **4a-j** exhibited molecular ion peak corresponding to their molecular weights.

Analgesic efficacy of the newly synthesized compounds was evaluated by two methods. The first method was based on acetic induced writhing in mice, which shows the action on peripheral nervous system and the second method adopted was Eddy's hot plate method, which measures the action on central nervous system. The results indicated that the compound **4f** exhibited equipotent activity when compared with the standard drug aspirin, the compounds **4g** and **4j** showed considerable activity where as remaining compounds were found to be less active, in acetic acid induced writhing method. On the other hand results of Eddy's hot plate method, none of the compounds exhibited promising analgesic activity. Thus it can be concluded that some of the newly synthesized compounds acted on peripheral nervous system, where as no effect was observed on central nervous system.

For carrying out experiments with animals, approval from Institutional Animal Ethics Committee in accordance with "Principles of Laboratory Animal Care" was obtained as per certificate No.1625, 2003-04 issued to Sonia College of Pharmacy, Dharwad, Karnataka.

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