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Synthesis and analgesic activity of triazolothiadiazoles and triazolothiadiazines encompassing 3–nitronaphtho[2,1-*b*]furan

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ABSTRACT

*The required starting material 3-nitronaphtho[2,1-b]furan-2-carhohydrazide **1** was synthesized from ethy1 3-nitronaptho[2,1-b]furan-2-carboxylate. The compound **1** on reaction with carbon disulphide and hydrazine hydrate in presence of alkali produced the key intermediate 3-nitro-4-amino-5-naphtho[2,1-b]furan-2-y1-4H-1,2,4-triazole-3-thiol **2**. 1,3,4-Thiadiazole moiety was constructed on triazole ring system by adopting three different experimental protocols to obtain 3-nitronaphtho[2,1b]furan-2-yl-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thione **4,** 3-nitronaphtho[2,1-b]furan-2-yl-6-aryl-5,6-dihydro[1,2,4 triazolo[3,4-b][1,3,4]thiadiazoles **5(a-d).** and 3-nitronaphtho[2,1-b]furan-2-yl-6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **6(a-c).** To investigate the synthetic utility of compound **2** in the synthesis of bridge head six membered heterocycles, it was treated with chloroacetic acid and sodium acetate in ethanol. This reaction furnished 3-nitronaphtho[2,1-b]furan-2-y1-5H-[1,2,4]triazolo [3,4-b][1,3,4]thiadizin-6(7H)–one **3**. The newly synthesized compounds were characterized by analytical and spectral studies. All the compounds were evaluated for analgesic activity by acetic acid induced writhing method by using Swiss albino mice.*

Keywords: Naphtho[2,1-b]furan, triazole, triazolothiadiazine, triazolothiadiazole, analgesic activity.

INTRODUCTION

Many of the derivatives of naphtho[2,1-b]furan synthesized in our laboratory have been found to possess wide spectrum of pharmacological and biological activities [1-8]. It is general observation that introduction of nitro group some times enhances biological profile of the compounds to some extent. Thus nitro derivatives of naphtho[2,1-b]furan have been reported to

exhibit antipyretic[9], analgesic[10], antihypertensive[11], antiviral[12], anti-inflammatory[13], antiparasitic[14] and antimicrobial activities[15]. The biheterocyclics comprising 1,2,4-triazole, 1,3,4-thiadiazole and thiadiazines exhibit promising pharmacological activities[16-20]. Encouraged by this fact, it was contemplated to synthesize new heterocylic systems involving 3-nitronaphtho[2,1-b]furan, 1,2,4-triazole, 1,3,4-thiadiazolo thiadiazines and screen them for analgesic activity.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (cm^{-1}) were recorded in KBr pellets on FT-IR Research Spectrophotometer Schimadzu 8201 PC (4000-400 cm^{-1}) and NMR on Bruker DRX-300 (300MHz-FT-NMR with low and high temperature facility -90^0 to $+80^0$). Standard chemical shifts are given in δ ppm values. Compounds were checked for their purity by TLC on silica gel plates and spots were visualized in iodine vapour.

Synthesis of 3-nitronaphtho[2,1-b]furan-2-carbonhydrazide 1

A mixture of ethy1 3-nitronaphtho[2,1-b]furan-2-carboxylate (2.55 g, 0.01 mol) and hydrazine hydrate (2.5 ml, 99%) in ethanol (10 ml) was heated under reflux for 5 h, cooled to room temperature and the solid thus separated was filtered, washed with ethanol and recrystallised from aqueous DMF to obtain the product as solid.

Synthesis of 3-nitro-4-amino-5-naphtho[2, 1-b]furan-2-yl-4*H*-1,2,4-triazole-3-thiol 2

An ice old solution of potassium hydroxide (0.015 mol) in ethanol (50 ml) was mixed with 3-nitronaphtho[2,1-b]furan-2-carbohydrazide **1** (0.01 mol) and carbon disulphide (0.02 mol) with constant stirring. The reaction mixture was stirred further at room temperature for 12 h. The product that separated as solid was filtered and washed with dry ether. It was then refluxed with hydrazine hydrate (0.03 mol) in ethanol (50 ml) on water bath until the evolution of hydrogen sulphide ceased (about 8 h). The reaction mixture was then poured into ice-cold water, acidified with glacial acetic acid, the product that separated as solid was collected by filtration and purified by recrystallization from aqueous ethanol to obtain **2.**

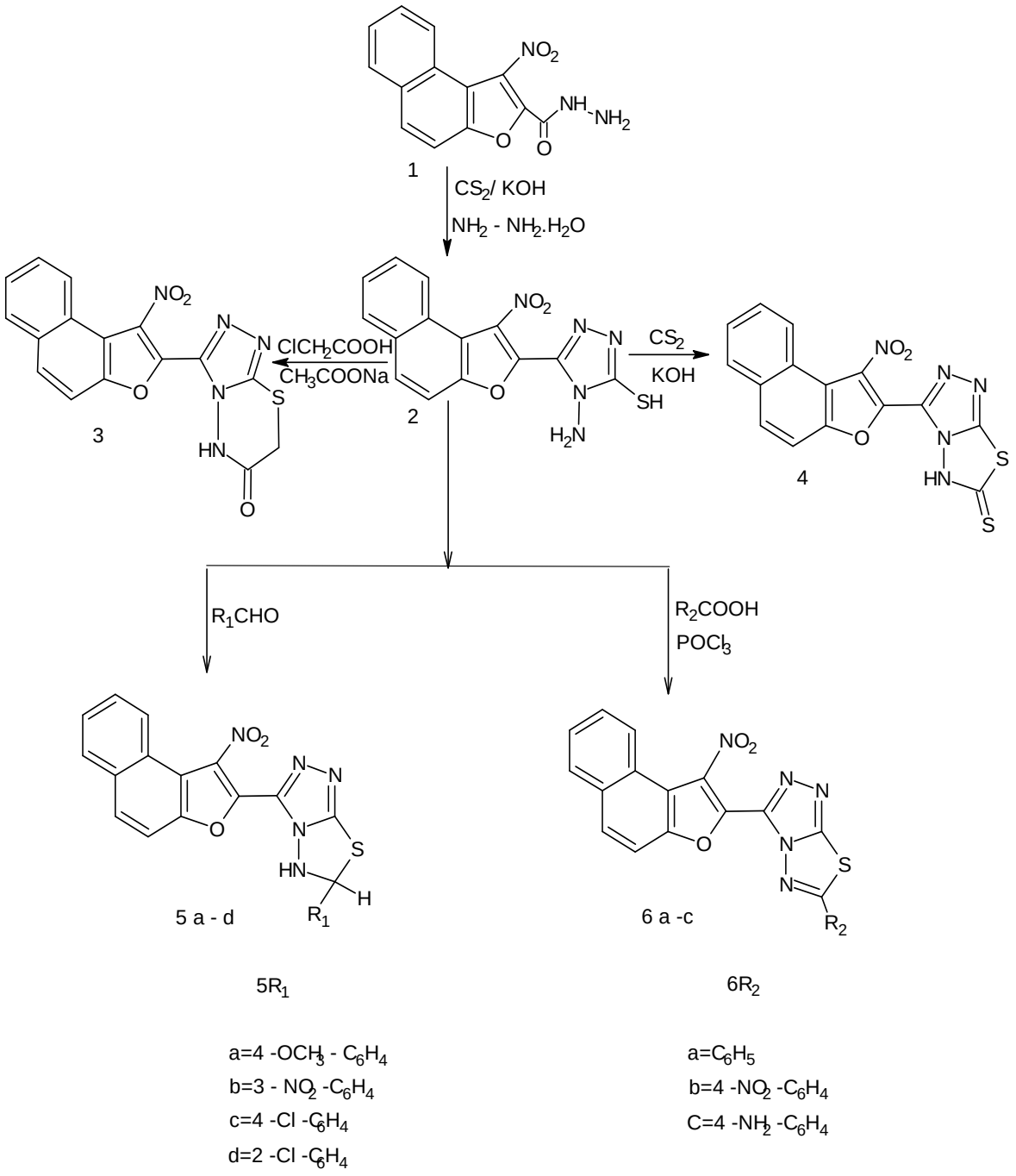
Synthesis of 3-nitronaphtho[2,1-b]furan-2-yl-5*H*-[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazin-6 (7*H*)-one 3

A mixture of **2** (0.01 mol), chloroacetic acid (0.01 mol) and fused sodium acetate (0.01 mol) in absolute ethanol (50 ml) was heated under reflux for 6 h and cooled in ice. The solid thus separated was filtered, washed thoroughly with water and purified by recrystallization from ethanol to yield **3.**

Synthesis of 3-nitronaphtho[2,1-b]furan-2-yl-5*H*[1,2,4]-triazole[3,4-b][1,3,4]thiadiazole-6 (5*H*)-thione 4

Carbon disulphide (0.015 mol) was added drop wise with constant stirring to a solution of **2** (0.01 mol) in ethanolic potassium hydroxide solution (0.01 mol in 50 ml). The reaction mixture was heated on a steam bath for about 12 h until the evolution of hydrogen sulplhide ceased. The reaction mixture was concentrated to one fourth of its volume and poured into ice and acidified with dilute hydrochloric acid. The precipitate thus obtained was filtered, washed with water and purified by recrystallization from pet ether: chloroform (6:4) to get **4.**

SCHEME - 1



5R$_1$

a=4 -OCH$_3$ - C$_6$H$_4$
b=3 - NO$_2$ -C$_6$H$_4$
c=4 -Cl -C$_6$H$_4$
d=2 -Cl -C$_6$H$_4$

6R$_2$

a=C$_6$H$_5$
b=4 -NO$_2$ -C$_6$H$_4$
C=4 -NH$_2$ -C$_6$H$_4$

Synthesis of 3-nitronaphtho[2,1-b]furan -2-yl-6-aryl-5,6-dihydro[1,2,4]triazolo [3,4-b][1, 3, 4]-thiadiazoles 5a-d

The compound **2** (0.01 mol) and anisaldehyde (0.01 mol) were dissolved in DMF (20 ml) and refluxed for 10 h. The reaction mixture was then poured into ice cold water, the solid separated was filtered and purified by recrystallization from absolute ethanol to obtain **5a**. Similarly the compounds **5b-d** were synthesized from **2**, by using appropriate aldehydes.

Synthesis of 3-nitronaphtho[2,1-b]furan-2-yl-6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles, 6a-c

A mixture of **2** (0.01 mol), benzoic acid (0.01 mol) and phosphorous oxychloride (10 ml) was heated in an oil bath at 120^0 C for 1 h. The reaction mixture was then cooled, poured into ice cold water and neutralized with aqueous potassium carbonate solution. The solid thus separated was filtered, washed thoroughly with water and purified by recrystallization from ethanol to yield **6a.** Similarly **6 b-c** were prepared from **2** by using different substituted aromatic acids. The sequence of the reaction is depicted in the scheme.

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

Table 1- Physical characterization data of compounds

Compd.	R1/R2	Molecular formula	m.p. ^{0}C	Yield	Found%(calculated)		
					C	H	N
2	----	$C_{14}H_9N_5O_3S$	218	61	51.29 (51.37)	2.68 (2.75)	21.36 (21.40)
3	----	C_{16}-$H_9N_5O_4S$	195	89	52.25 (52.31)	2.32 (2.45)	19.02 (19.07)
4	----	C_{15}-$H_7N_5O_3S_2$	191	90	48.69 (48.78)	1.76 (1.89)	18.85 (18.97)
5a	4-OCH_3-C_6H_4	C_{22}-$H_{15}N_5O_4S$	216	83	59.28 (59.32)	3.15 (3.37)	15.35 (15.73)
5b	3-NO_2-C_6H_4	C_{21}-$H_{12}N_6O_5S$	>250	72	57.19 (57.27)	2.68 (2.72)	19.01 (19.09)
5c	4-C1-C_6H_4	C_{21}-$H_{12}N_5O_3SC1$	153	69	56.03 (56.06)	2.64 (2.66)	15.54 (15.57)
5d	2-C1-C_6H_4	C_{21}-$H_{12}N_5O_3SCl$	150	76	56.01 (56.06)	2.61 (2.66)	15.52 (15.57)
6a	C_6H_5	C_{21}-$H_{11}N_5O_3S$	184	64	61.00 (61.01)	2.54 (2.66)	16.87 (16.94)
6b	4-NO_2-C_6H_4	C_{21}-$H_{10}N_6O_5S$	222	73	55.01 (55.02)	2.15 (2.18)	18.29 (18.34)
6c	4-NH_2-C_6H_4	C_{21}-$H_{12}N_6O_3S$	158	59	58.79 (58.87)	2.78 (2.80)	19.58 (19.62)

Analgesic activity

Acetic acid induced writhing method:

Colony bred albino mice (Swiss strain) of either sex weighing 20-30 g were used to evaluate analgesic activity. It was determined as described by the method based on acetic acid induced writhing response in mice [21].

For this experiment, 72 mice were used and they were divided into 12 groups containing 6 animals each. All the animals received 0.6% v/v of 10 ml/kg body weight of acetic acid intraperitoneally and number of writhing was recorded after 5 min up to next 10 min. The same group of animals was used next day for evaluating analgesic activity.

Group I received 0.1ml of 0.6% acetic acid and served as control, group II received 30mg/kg body weight of Tremadol orally and served as standard. The remaining 10 groups received various test compounds at a dose of 300 mg/kg body weight orally in the form of suspension in 50% DMSO. After 1 hr, all the animals received 0.6% of 10 ml /kg body weight of acetic acid intraperitoneally. The writhings were counted similarly as in the previous day. The results are presented in table 2.

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

Compound	Mean no of writhing ± SEM	% protection
Control	31.00 ± 4.32	
Standard Tremadol	8.00 ± 1.224	71.42
2	16.50±10.234	41.07
3	15.66±0.6582	44.28
4	24.5±0.4082	12.50
5a	15.33±4.508	46.42
5b	11.66±4.514	58.35
5c	20.00±4.082	27.39
5d	8.78±5.448	68.75
6a	9.33±2.507	66.67
6b	10.50±11.672	50.00
6c	10.00±3.265	16.00

Index for analgesic activity
Method : Acetic acid induced writhing
Animals : Swiss albino mice
No of animals per group : 06
Route of administration : Intraperitoneal
Standard : Tremadol

RESULTS AND DISCUSSION

For the synthesis of the title compounds, 2-aminothiol functionality was thought to be the most appropriate. Thus, the required 4-amino-5-naphtho[2,1-b]furan-2-y1-4H-1,2,4,-triazole--3-thiol **2** was synthesized by the reaction of naphtho[2,1-b]furan-2-carboxyhydrazide **1** with carbon disulphide and hydrazine hydrate in presence of ethanolic potassium hydroxide. Formation of **2** was evident by the absence of carbony1 absorption frequency in the IR spectrum. 1, 3, 4-Thiadiazole moiety was constructed on triazole ring system by adopting three different synthetic strategies. The first method involved the reaction of **2** with alkaline carbon disulphide to obtain compound 3-nitronaphtho[2,1-b]furan-2-yl-5H-[1,2,4]triazole [3,4-b] [1,3,4] thiadiazole -6(5H)-thione 4 . As expected, ^{1}H NMR spectrum of **4** exhibited only two signals, one as a multiplet between δ 7.56 and 8.18 due to six aromatic protons and another as a broad singlet at δ 10.84 due to – NH proton. IR and mass spectral data of **4** was consistent with the assigned structure. Fragmentation pattern was also in accordance with theoretical expectation.

The second synthetic strategy involved the reaction between compound **2** and substituted aromatic aldehydes in presence of DMF which resulted in the formation of a series of compounds 3-nitronaphtho[2,1-b]furan-2-yl-6-arly-5-6-dihydro[1,2,4]triazolo[3,4-b][1,3,4] thiadiazoles **5a-d**. In the ^{1}H NMR spectrum of compound **5a**, one D_2O exchangeable singlet at δ 11.0 integrating for two protons of $–NH_2$ group was observed. In addition it showed another signal as a multiplet at δ 6.86-8.62 integrating for seven protons, which may be attributed to six aromatic protons and one CH proton.

In the third approach, the triazole **2** was reacted with various aromatic carboxylic acids in the presence of phosphorous oxychloride which resulted in the formation of 3-nitronaphtho[2,1-b]furan-2-yl-6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **6(a-c).** The ^{1}H NMR spectrum of **6c** exhibited two signals, one as a broad singlet at δ 6.61 due to two protons of $–NH_2$ group and another one as a multiplet at δ 7.59-8.03 due to ten aromatic protons.

To demonstrate the synthetic utility of **2,** in the synthesis of various bridgehead six membered heterocycles, the compound **2** was refluxed with chloroacetic acid and fused sodium acetate in ethanol. This reaction yielded 3-nitronaphtho[2,1-b]furan-2-yl-5H[1,2,4] triazolo [3,4-b][1,3,4] thiadiazin-6(7H)-one **3**. The appearance of absorption band at 1625 cm^{-1} due to ring carbonyl in the IR spectrum of **3** confirmed the ring closure.

The synthesized compounds were screened for analgesic activity by acetic acid induced writhing method by using albino mice. The activity was compared with that of standard drug tremadol. The results revealed that revealed that activity of 3-nitro substituted derivative was less than that of the unsubstituted naphthofuran derivatives.

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 Sophia College of Pharmacy, Dharwad, Karnataka.

CONCLUSION

The present work describes a novel and simple approach for the synthesis of various bridgehead heterocycles such as triazolothiadiazoles and triazolothiadiazines linked to 3–nitronaphtho[2,1-b]furan. The pharmacological profile of the synthesized novel compounds revealed that the analgesic activity of 3-nitro substituted derivatives was less than that of the unsubstituted naphthofuran derivatives.

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