Research Article

Synthesis of Novel 5,8-Dihydro[1,2,4]Triazolo[3,4-*B*] [1,3,4]Thiadiazepines Derivatives Involving Naphtho[2,1-*B*] Furan And Evaluation of Their Possible Pharmacological Activities

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ABSTRACT

The reaction of 2-acetylnaphtho[2,1-*b*]furan **1** with different aromatic aldehydes affords corresponding chalcones **2a-f**. These chalcones **2a-f** on reacting with 5-phenyl-4-amino-3-mercapto-1,2,4-triazole in presence of a base produces 3-phenyl-6-(naphtho [2,1-*b*] furan-2-yl)-8-(substituted)phenyl-5,8-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **3a-f**.

The structures of newly synthesized compounds have been established by elemental analysis and spectral studies. Some of the newly synthesized compounds exhibited potent antibacterial, antifungal, anti-inflammatory, analgesic, diuretic, anthelmintic and antipyretic activities.

Key words: Naphtho[2,1-*b*]furan; 5,8-Dihydro[1,2,4]triazole[3,4-*b*][1,3,4] thiadiazepines.

INTRODUCTION

The chemistry of the compounds containing the condensed N-bridged heterocyclic systems derived from 1,2,4-triazole have been explored as potential antimicrobial agents[1-5]. Similarly, triazolothiadiazepines are well known to exhibit antimicrobial, antiinflammatory, analgesic and anthelmintic activity[6-9]. Survey of literature revealed that, similar type of work involving triazolo[3,4-*b*][1,3,4]thiadiazepines and naphtho[2,1-*b*]furan, either in condensed form or in coupled form has not been reported. The naphtho[2,1-*b*]furan derivatives exhibit wide range of biological and pharmacological activities[10-12]. Hence it is thought of interest to synthesize 4-naphtho[2,1-*b*]furan-2-yl-2-(substituted)phenyl-2,5-dihydro-1*H*-1,5-benzodiazepines and and 3-phenyl-6-(naphtho[2,1-*b*]furan-2-yl)-8-(substituted) phenyl-7,8-dihydro[1,2,4]triazolo [3,4-*b*][1,3,4] thiadiazepines and evaluate them for antibacterial, antifungal, antiinflammtory, diuretic, anthelmintic and antipyretic activities.

MATERIALS AND METHODS

All the reagents were A. R. grade and used with further purification. Melting points were determined with the open capillary and are uncorrected. IR spectra recorded in KBr pellets by using JASCO FT-IR 300E spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker Supercon FT-NMR 400 MHz instrument. Chemical shifts are reported in δ (ppm) relative to TMS as internal standard.

Mass spectral data were obtained on a Jeol JMS-D 300 Mass spectrometer operating at 70 eV. Elemental analysis were performed using a Vario-EL elemental analyzer. All the reactions were monitored by TLC.

EXPERIMENTAL

Synthesis of 3-(4-Methoxyphenyl)-1-naphtho[2,1-*b*]furan-2-yl-prop-2-en-1-one 2a

To a solution of 2-acetylnaphtho[2,1-*b*]furan **1** (2.10 g, 0.01 mol) in ethanol (50 ml) containing sodium hydroxide (0.4 g, 0.01 mol), 4-methoxybenzaldehyde (1.06 g, 0.01 mol) was added and the mixture was refluxed on water bath for 2 h, and then poured into ice-cold water. The separated solid was filtered, dried and recrystallised from ethanol to give **2a**. The same method was employed to yield compounds **2b-f** using 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, benzaldehyde, 2-hydroxy benzaldehyde, and 2-chlorobenzaldehyde in place of 4-methoxybenzaldehyde.

Synthesis of 3-Phenyl-6-(naphtho[2,1-*b*]furan-2-yl)-8-(substituted)phenyl-7,8-dihydro[1,2,4]triazole[3,4 -*b*][1,3,4]thiadiazepines 3a:

A mixture of 3-phenyl-1-naphtho[2,1-*b*]furan-2-yl-prop-2-en-1-one **2a** (1.09 g, 0.0033 mol) and 5-phenyl-4-amino-3-mercapto-1,2,4-triazole (0.64g, 0.0033 mol) and piperidine (0.3g, 0.004 mol) in absolute ethanol (50 ml) was refluxed on a water bath for 6 h. The contents were cooled and poured on to crushed ice and neutralized with dilute acetic acid. The solid separated was filtered, washed with water, dried and recrystallised from ethanol to give **3a**. (1.06 g, 64 %) m.p. >250 ^{0}C; ^{1}H NMR (DMSO-d_6): δ 3.8 (s, 3H, OCH_3); □□7.0- 8.5 (m, 19H, 16ArH + NH + C=CH + CHPh): ^{13}C NMR (DMSO-d_6): δ 54.91 (OCH_3); δ 112.21, 112.56, 112.63, 112.94, 113.05, 113.37, 113.50, 113.66, 113.82, 114.44, 123.42, 123.54, 123.66, 124.36, 125.50, 127.12, 127.40, 127.70, 128.18, 128.35, 128.53, 128.69, 128.86, 129.31, 129.45, 129.79, 129.95, 130.09 and 130.43 (29 carbon atoms); IR (KBr): 1597 (C=N) cm^{-1}; Calculated $C_{30}H_{22}N_4O_2S$: C, 71.69; H, 4.41; N, 11.15 %. Found: C, 71.54; H, 4.29; N, 11.02 %. M^+; 501 (m/z); 393, 374, 325, 269, 237 and 179 fragmentation pattern. The same method was employed to yield compounds 3**b-f** from **2b-f**. The IR and ^{1}H NMR spectral data of these compounds are summarized in Table 1. Physical data of these newly synthesized compounds reported in Table-2.

Evaluation of Biological and Pharmacological Activities

The compounds encompassing naphthofuran, and triazoles are known to exhibit wide spectrum of biological and pharmacological activities. Hence, it was intrigued to evaluate newly synthesized compounds for antimicrobial, anti-inflammatory, analgesic, diuretic, anthelmintic, and antipyretic activities by adopting literature procedure.

Antimicrobial activity

The *in vitro* antimicrobial activity was carried out against 24 h old cultures of two bacteria and two fungi by cup-plate method[13]. The compounds **3a-f** have been investigated for their antibacterial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Curvularia lunata*. Chloramphenicol and fluconazole were used as standards for antibacterial and antifungal activity respectively. The compounds were tested at a concentration of 0.001 mol/ml in DMF against all organisms. The zone of inhibition was compared with the standard drug after 24 h of incubation at 25 ^{0}C for antibacterial activity and 48 h at 30 ^{0}C for antifungal activity. The results are presented in Table 3.

Anti-inflammatory activity

The anti-inflammatory activity was evaluated by a rat paw edema method. This method is based on plethysmographic measurement of carrageenan-induced acute rat paw edema produced by sub plantar injection of carrageenan in hind paw of the rat[14-15]. Ibuprofen was used as standard and tween-80 (0.1%, 1 ml) solution as control for this study. The percentage inhibition of paw volume was calculated by using the formula

$$\% \text{ Inhibition} = (1 - Vt/Vc) \times 100.$$

Where, Vt = Mean increase in the paw volume in test animals group.

Vc = Mean increase in the paw volume in control group.

Analgesic activity

Analgesic activity was determined by the method based on acetic acid induced writhing in mice[16-17]. Acetyl salicylic acid (aspirin) was used as standard and Tween-80 (0.1%) solution as control. The percentage inhibition of writhing was calculated by using the formula

$$\% \text{ Inhibition} = (1-Nt/Nc) \times 100,$$

Where, Nt = Mean number of writhing in test animals

Nc = Mean number of writhing in control.

The results of anti-inflammatory activity and analgesic activities are given in Table 4.

Diuretic activity

The diuretic activity was evaluated on albino rats (Wistar strain) by literature method[18]. For this study aqueous solution of tween-80 (0.1%, 5 ml) served as control and frusemide as standard.

Anthelmintic activity

Anthelmintic activity was evaluated by using *Pheritima posthuma* (class-Annelida and order-Oligichaeta). The technique adopted was that described by Giand et al[19-20]. For this study 25 ml of 0.1% Tween-80 prepared in 6% dextrose solution was served as control. Albendazole suspended in 6% dextrose solution served as standard.

Antipyretic activity

The antipyretic activity was carried out on colony bred albino male rats as by a modified yeast induced hyperpyrexia method[21]. Tween–80 used as control and paracetamol as standard drug. All values are expressed as mean ± SEM. The results of diuretic, anthelmintic and antipyretic activities are presented in Table 5.

RESULT AND DISCUSSION

The key starting material 2-acetylnaphtho[2,1-*b*]furan **1** was synthesized by the reaction of 2-hydroxy-1-naphthaldehyde with chloroacetone in presence of potassium carbonate[19]. 2-Acetylnaphtho[2,1-*b*]furan on treatment with different aromatic aldehydes in presence of sodium hydroxide produced appropriate chalcones **2a-f.** The selection of aromatic aldehydes was based upon presence of electron withdrawing and electron donating groups which could enable to study structure activity relationship during the evaluation of pharmacological activities. These chalcones **2a-f** on reaction with 5-phenyl-4-amino-1,2,4-triazole in presence of piperidine and ethanol resulted in the formation of the products which were identified as 3-phenyl-6-(naphtho[2,1-*b*]furan-2-yl)-8-(substituted)phenyl-7,8-dihydro[1,2,4] triazole[3,4-*b*][1,3,4]thiadiazepines 3**a-f**, on the basis of analytical and spectral studies. The sequence of the reaction is depicted in scheme-1.

The newly synthesized compounds were evaluated for antimicrobial activity. The zone of inhibition was measured in mm and results are presented in Table **3**. The compounds **3c, 3e-f,** displayed significant antibacterial activity against both organisms. Rest of the compounds exhibited substantial activity against both the organisms. It is observed that electron withdrawing groups resulted in enhancement of activity. The compounds **3c-f** exhibited promising antifungal activity, whereas remaining compounds are found to be considerably active. In this case also electron withdrawing groups have much more pronounced effect on antifungal activity.

Anti-inflammatory activity of the synthesized compounds was investigated by carrageenan induced rat paw edema method on albino rats (Wistar strain) using ibuprofen as standard drug. The percentage of inhibition edema was calculated in each case and is presented in Table-4. The compounds 3**(a-b)** and **3d** exhibited excellent activity, having percentage inhibition of 57.66, 59.67, 61.69 comparable with that of standard drug having percentage inhibition of 79.59, while rest of the compounds were found to be moderately active. The presence of electron donating groups resulted in increase of activity to greater extent.

Acetic acid induced writing method was adopted to evaluate analgesic activity of the synthesized compounds. The experiment was carried out on albino mice (Swiss strain) using aspirin as standard and % protection was calculated for each compound as well as standard, which is presented in Table-4.

The results indicated that compounds **3a-d** possess substantial analgesic activity and remaining compounds exhibited significant activity. The activity is independent of the substituent present in the molecule. The mechanism of action of all the tested compounds at present could not be ascertained and needs detailed investigation.

Diuretic activity was evaluated on albino rats (Wistar strain) using Frusamide as standard drug. Lipschitz values were calculated and presented in Table **5**. The compounds **3a**, **3c**, **3e**, were found to display promising activity having T/S value 0.55, 0.58, 0.58 compared with that of standard and remaining compounds possessed moderate activity. Diuretics are drugs that increase the rate of urine flow. However, clinically useful diuretics also increase the rate of excretion of Na^+ and accompanying anion, usually Cl^-. The standard drug Frusemide used in this case, contains furan ring in its structure, hence the diuretic effect of the test compounds may due to the presence of naphthofuran moiety in their structures. The results are reported in Table 4.

The synthesized compounds were screened for anthelmintic activity the time required paralysis and death of the worm were noted in each case. It was observed that none of the compounds exhibited considerable anthelmintic activity. Outer layer of the earthworm is a mucilaginous layer and composed of polysaccharides. This layer, being slimy, enables the earthworms to move freely. Any damage to the muco polysaccharide membrane will expose the outer layers, and this restricts its movement and can

cause paralysis. This action may lead to death of the worm and will be expelled out from the body. None of the compounds seems to have such an effect on earthworms.

Antipyretic activity of the synthesized compounds was determined by yeast induced hyperpyrexia method on albino rats (Wistar strain) using paracetamol as standard drug. Decrease in rectal temperature was recorded in each case. The results indicated that compound **3a-d** exhibited excellent antipyretic activity showing the decrease in temperature to the extent of 0.5 ^{0}C. Rest of the compounds were either moderately active or less active. Chlorine atom which is present in position 4 increased the activity to considerable activity. The test compounds possess a significant antipyretic effect in yeast-induced elevation of body temperature in rats and this may be due to combined anti-inflammatory and analgesic effects.

CONCLUSION

A number of 3-phenyl-6-(naphtho[2,1-*b*]furan-2-yl)-8-(substituted)phenyl-7,8-dihydro [1,2,4]triazole[3,4-*b*][1,3,4]thiadiazepines **3a-f**, were synthesized and characterized by analytical and spectral studies. The newly synthesized compounds were evaluated for antibacterial, antifungal, antiinflammtory, analgesic, diuretic, anthelmintic, and antipyretic activities. The results obtained hitherto indicated, that introduction of benzodiazepine and triazolethiadiazepine moiety enhances the activity to considerable extent. In many cases, presence of electron withdrawing groups results in increase of activity and in few cases electron donating methoxy group has marked influence in enhancing activity.

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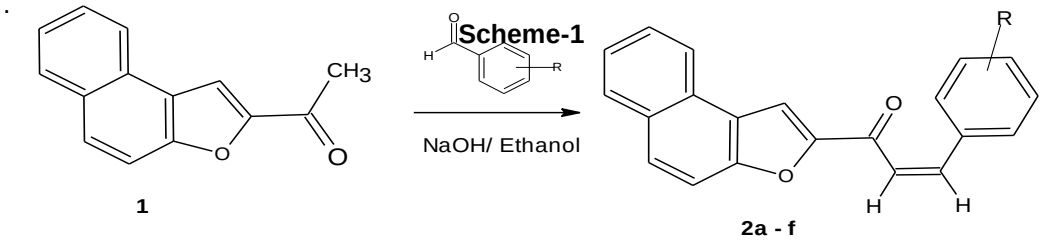

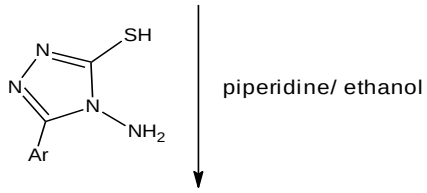

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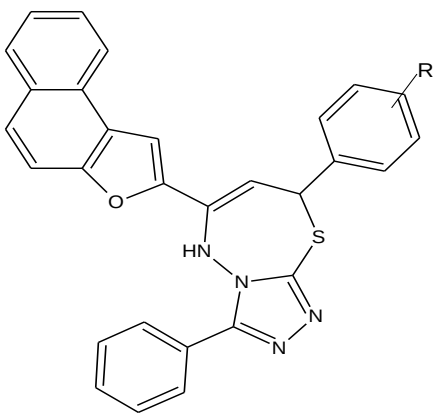
b	4-Cl
c	4-NO_2
d	-H
e	2-OH
f	2-Cl



3a-f

Table 1: IR and NMR Spectral data of 3-Phenyl-6-(naphtho[2,1-*b*]furan-2-yl)-8-(substituted)phenyl-5,8-dihydro[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepines. 3a-f

Comp.	R	IR (KBr) cm^{-1} C=N	^{1}H NMR in ppm
3b	4-Cl	1605	δ 7.2-8.6 (m, 19H, 16ArH + NH + C=CH + CHPh)
3c	4-NO_2	1586	δ 7.1-8.6 (m, 19H, 16ArH +NH +C=CH + CHPh)
3d	H	1610	δ 7.0-8.4 (m, 20H, 17ArH + NH +C=CH + CHPh)
3e	2-OH	1602	δ 5.3 (b, 1H, OH), δ 7.3-8.8 (m, 19H, 16ArH +NH+ C=CH +CHPh)
3f	2-Cl	1615	δ 7.1-8.5 (m, 18H, 15ArH + NH + C=CH + CHPh)

Table 2: Physical data of new synthesized compounds

Comp.	R	M.p.^{0}C	Yield (%)	Mol. formula	Found (Calcd) %		
					C	H	N
3a	4-OCH_3	>250	64	$C_{30}H_{22}N_4O_2S$	71.54 (71.69)	4.29 (4.41)	11.02 (11.15)
3b	4-Cl	248	70	$C_{29}H_{19}N_4OSCl$	68.60 (68.70)	3.65 (3.78)	10.96 (11.05)
3c	4-NO_2	>250	68	$C_{29}H_{19}N_5O_3S$	67.21 (67.30)	3.69 (3.70)	13.45 (13.53)
3d	H	225	71	$C_{29}H_{20}N_4OS$	73.62 (73.71)	4.19 (4.27)	11.77 (11.86)
3e	2-OH	>250	71	$C_{29}H_{20}N_4O_2S$	71.16 (71.29)	4.03 (4.13)	11.31 (11.47)
3f	2-Cl	242	67	$C_{29}H_{19}N_4OSCl$	68.60 (68.70)	3.66 (3.78)	10.92 (11.05)

Table 3: Antimicrobial activity data of the compounds 3a-f

Comp	Zone of Inhibition in mm			
	Antibacterial activity		Antifungal activity	
	P. aerugenosa	*S.aureus*	*A. niger*	*C. lunata*
Standard	24	26	22	24
DMF	Nil	Nil	Nil	Nil
3a	16	17	16	17
3b	18	17	17	17
3c	17	17	19	18
3d	20	19	19	17
3e	19	18	20	19
3f	20	19	17	19

Table 4: Anti-inflammatory and Analgesic activity of the compounds 3a-f

Comp.	Anti-inflammatory activity		Analgesic activity
	Group	Inhibition (%) of edema after 3 hrs	% Protection
Control	I	----	----
Standard	II	75.80	71.00
3a	III	51.61	58.67
3b	IV	40.72	55.63
3c	V	45.56	60.00
3d	VI	45.56	62.98
3e	VII	55.64	54.42
3f	VIII	40.67	53.41

Table 5: Diuretic, Anthelmintic and Antipyretic activities of the compounds 3a-f

Comp.	Group	Diuretic activity	Anthelmintic activity		Antipyretic activity		
		T/S	Time in minutes		Mean rectal temperature		Decrease in temperature
			Mean time of paralysis	Mean death time	0 hr	3 hr	
Control	I	0.27	------	-----	38.7	38.5	0.2
Standard	II	1.00	33	46	38.4	37.7	0.7
3a	III	0.62	109	117	38.5	38.2	0.3
3b	IV	0.51	120	147	37.7	37.4	0.3
3c	V	0.58	115	123	37.8	37.5	0.3
3d	VI	0.48	95	121	38.0	37.7	0.3
3e	VII	0.69	176	184	37.9	37.6	0.3
3f	VIII	0.48	124	145	38.0	37.8	0.2

T/S: Lipschitz value

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