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Synthesis and pharmacological investigations of azetidinone derivatives involving naphtho[2,1-*b*]furan-2-carboxamide

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ABSTRACT

The reaction of naphtho[2,1-*b*]furan-2-carbohydrazide 2, which in turn was synthesized from ethyl naphtho[2,1-b]furan-2carboxylate 1, with various aromatic aldehydes in refluxing dioxane afforded N-[(aryl)methylene]naphtho[2,1-*b*] furan-2-carbohydrazides 3a-f. These hydrazones 3a-f on treatment with chloroacetyl chloride in presence of triethylamine produced, title compounds, azetidinone derivatives 4a-f. The structures of the newly synthesized compounds have been established by analytical and spectral studies and investigated for antibacterial, antifungal, anti-inflammatory, diuretic, anthelmintic and antipyretic activities.

Keywords: Naphtho[2,1-*b*]furan-2-carbohydrazide, carboxamide, azetidinone, antimicrobial activity, pharmacological activities.

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INTRODUCTION

Azetidin-2-one, a four membered β-lactam skeleton, has been recognized as a useful building block for the synthesis of a large number of organic molecules by exploiting its ring strain [1]. It is an essential part of the penicillin skeleton and a substructure found in β-lactamase inhibitors such as clavulanic acid or sulbactam [2]. Penams, cephems, monobactams, penems, carbapenems and triems are several structural variants of β-lactam antibiotics, which have been developed based on penicillin structure as novel approaches to antibacterial therapy [3]. Azetidinone moiety has been connected to benzo[*b*]thiophene and benzothiazole nucleus. The resulting compounds exhibited significant antimicrobial and antitubercular activity [4-5]. Certain biheterocyclics connected to azetidine ring possess excellent antibacterial and anti-inflammatory activities [6]. Some of the derivatives of azetidinone were found to be associated with antifungal [7] anti-herpes [8], and potent cholesterol absorption inhibitory activities [9-10]. Several derivatives of naphtho[2,1-b]furan derivatives synthesized in our laboratory have been reported to possess many biological and pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, diuretic, anthelmintic, antipyretic etc. [11-14].

Encouraged from these facts, and the principle that two or more biologically active heterocyclic systems enhances and/or changes the biological profile of molecules intrigued us to extend our continued efforts to synthesize more potent derivatives of naphtho[2,1-*b*]furan derivatives. We now report the synthesis of novel compounds, N-[3-chloro-2-aryl-4-oxo-azetidin-1-yl]naphtho[2,1-*b*]furan-2-carbox amides **4a-f.**

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 β(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 was performed using a Vario-EL elemental analyzer. All the reactions were monitored by TLC.

EXPERIMENTAL

Synthesis of naphtho[2,1-*b*]furan-2-carbohydrazide 2.

To a solution of 2-hydroxy-1-naphthaldehyde **1** (5.16 g, 0.03 mol) in dry N,N-dimethylformamide (25 ml), ethyl chloroacetate (3.66 g, 0.03 mol) and anhydrous potassium carbonate (12.4 g, 0.9 mol) were added and the reaction mixture was refluxed on water bath for 24 h. The reaction mixture was then poured into ice cold water, the product that separated as solid was filtered, dried and recrystallized from ethanol **2** in good yield.

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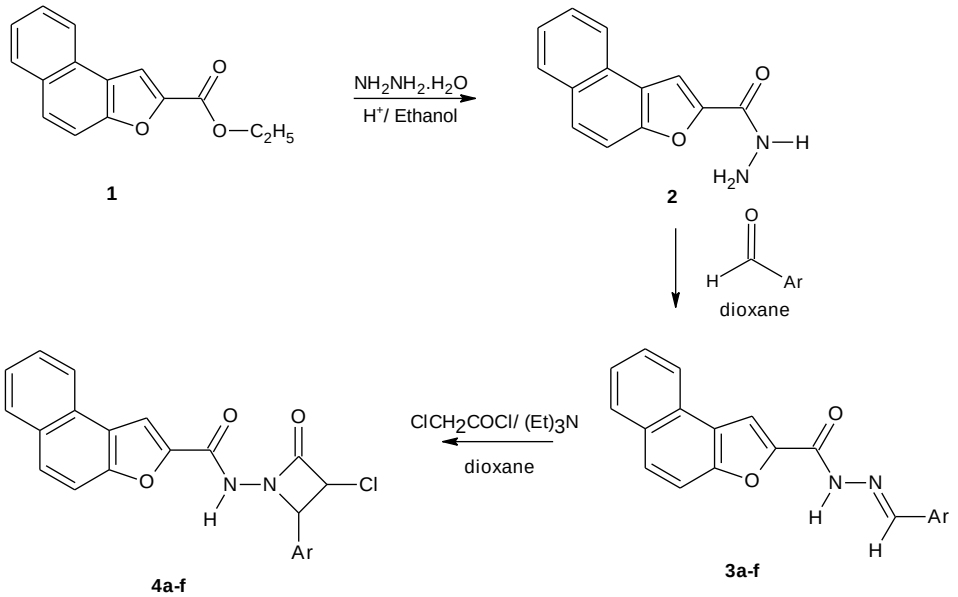
Synthesis of N-[(4-methoxyphenyl)methylene]naphtho[2,1-b]furan-2-carbohydra zide. 3b

To a solution of naphtho[2,1-*b*]furan-2-carbohydrazide **2** (2.26 g, 0.01 mol) in dioxane (15 ml), 4-methoxybenzaldehyde (1.36 g, 0.01 mol) was added; the mixture refluxed on water bath for 2 h, and poured into ice-cold water. The product that separated as solid was filtered, dried, and recrystallised from dioxane. (2.34 g, 68 %). Similarly the compounds **3a**, **3c-f** were synthesized by using benzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde and furfural, in place of 4-methoxybenzaldehyde.

Synthesis of N-[3-chloro-2-(methoxyphenyl)-4-oxo-azetidin-1-yl]naphtho[2,1-b] furan-2-carboxamide 4b

A stirred solution of chloroacetyl chloride (0.6 ml, 0.0055 mol) in dioxane (10 ml) was cooled to –10 ^{0}C using ice-salt bath. To this, triethyl amine (0.5 g, 0.005 mol) was added drop wise maintaining the temperature below 0 ^{0}C, while white solid separated out. A solution of N-[(4-methoxyphenyl)methylene]naphtho[2,1-*b*]furan-2-carbohydrazide **3b** (0.86 g, 0.0025 mol) in dioxane (10 ml) was then added drop wise regulating the temperature <0 ^{0}C. After the addition was over the reaction mixture was refluxed for 16 h and was then poured into ice cold water to obtain the product **4b** as solid, which was filtered, dried and recrystallised from dioxane. The compounds **4a**, **4c-f** were synthesized by the same method. The sequence of reactions is presented in the scheme-1



1 2 4a-f 3a-f

Ar
a. C_6H_5
b. 4-OCH_3-C_6H_4
c. 2-Cl-C_6H_4
d. 4-Cl-C_6H_4
e. 4-NO_2-C_6H_4
f. Furfuryl

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The physical and analytical data of the synthesized compounds is presented in Table-1

Table 1- Physical and analytical data of the synthesized compounds

Comp.	R	M.p. ^{0}C	Yield (%)	Mol. Formula	Found (Calcd.) %		
					C	H	N
3a	-C_6H_5	235	60	$C_{20}H_{14}N_2O_2$	76.36 (76.42)	4.39 (4.49)	8.85 (8.91)
3b	4-OCH_3-C_6H_4	243	68	$C_{21}H_{16}N_2O_3$	73.1 (73.2)	4.5 (4.6)	8.0 (8.1)
3c	2-Cl- C_6H_4	249	66	$C_{20}H_{13}N_2O_2Cl$	68.79 (68.87)	3.68 (3.76)	7.89 (8.03)
3d	4-Cl- C_6H_4	251	71	$C_{20}H_{13}N_2O_2Cl$	68.78 (68.87)	3.69 (3.76)	7.95 (8.03)
3e	4-NO_2- C_6H_4	257	65	$C_{20}H_{13}N_3O_4$	66.79 (66.85)	3.57 (3.65)	11.59 (11.69)
3f	Furfural	238	69	$C_{18}H_{12}N_2O_3$	70.98 (71.05)	3.89 (3.97)	9.16 (9.21)
4a	C_6H_5	251	60	$C_{22}H_{15}N_2O_3Cl$	67.56 (67.61)	3.79 (3.87)	7.00 (7.17)
4b	4-OCH_3- C_6H_4	262	72	$C_{23}H_{17}N_2O_4Cl$	65.5 (65.6)	3.9 (4.0)	6.5 (6.6)
4c	2-Cl- C_6H_4	260	68	$C_{22}H_{14}N_2O_3Cl_2$	62.05 (62.13)	3.26 (3.32)	6.51 (6.59)
4d	4-Cl- C_6H_4	265	68	$C_{22}H_{14}N_2O_3Cl_2$	62.08 (62.13)	3.22 (3.32)	6.49 (6.59)
4e	4-NO_2- C_6H_4	268	62	$C_{22}H_{14}N_3O_5Cl$	60.56 (60.63)	3.17 (3.24)	9.57 (9.64)
4f	Furfural	249	70	$C_{20}H_{13}N_2O_4Cl$	62.96 (63.03)	3.38 (3.44)	7.27 (7.36)

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 [15]. The compounds **4a-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 2.

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Table 2- Antimicrobial activity data of the compounds 4a-f

Compd.	Zone of Inhibition in mm			
	Antibacterial activity		Antifungal activity	
	P. aerugenosa	*S. aureus*	*A. niger*	*C. lunata*
Standard	24	26	24	22
4a	16	18	15	17
4b	15	16	16	15
4c	15	16	18	17
4d	18	17	16	18
4e	16	14	17	17
4f	17	16	17	16

Anti-inflammatory activity

The anti-inflammatory activity was evaluated by a rat paw edema method. Edema represents the early phase of inflammation and carrageenan-induced paw edema is the simplest and most widely used model for studying the anti-inflammatory activity of chemical compounds. 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 [16, 17]. For this study, albino rats (Wistar strain) of either sex, weighing between 100-200 g, were used and divided into 14 groups, of 4 animals each. The group I served as control and received tween-80 (0.1%, 1 ml) solution orally. The group II received ibuprofen in tween-80 (0.1%, 1 ml) at a dose of 40 mg/kg body weight and served as standard. The groups III – XIV received orally the test compounds mentioned at the dose of 30 mg/kg body weight in tween-80 (0.1%, 1 ml) solution. These drugs were administered 1 h before the injection of an irritant, carrageenan. After 1 h all the animals were injected subcutaneously with a suspension of carrageenan in tween-80 (0.1%, 0.05 ml) solution to the left hind paw in the sub plantar region and the paw volume was measured immediately. After 3 h the paw volume was measured in control, in standard and in test groups.

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 [18-19]. Colony bred albino mice (Swiss strain) of either sex weighing 25-35 g were used to evaluate analgesic activity. For this experiment mice were divided into 14 groups of 6

animals each. The group I served as control and received 0.5 ml of Tween-80 (0.1%) solution orally. The group II received acetyl salicylic acid (aspirin) 150 mg/kg body weight and served as standard. The groups III – XIV were treated with 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 h the all the animals were injected with 0.6% of 10 ml/kg body weight acetic acid intraperitoneally and the number of writhing were recorded after 5 min for 20 min.

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 3.

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

Compd.	Anti-inflammatory activity		Analgesic activity
	Group	Inhibition (%) of edema after 3 hrs	% Protection
Control	I	-----	-----
Standard	II	79.59	71.05
4a	III	44.89	46.42
4b	IV	52.04	58.90
4c	V	56.12	47.11
4d	VI	47.96	55.01
4e	VII	48.97	56.18
4f	VIII	51.02	49.51

Diuretic activity

The diuretic activity was evaluated on albino rats (Wistar strain) by literature method [20]. Rats of either sex, weighing between 100-200 g were divided into 14 groups, each containing 6 animals. Group I served as control and received aqueous solution of tween-80 (0.1%, 5 ml). Group II received 40 mg/kg body weight of frusemide in tween-80 (0.1%, 5 ml) in distilled water orally and served as standard. The groups III - XIV received orally the test compounds at the dose of 30 mg/kg body weight in tween-80 (0.1%, 5 ml). Each group of animals was kept in different metabolic cages provided with a wire mesh at the bottom and a funnel to collect urine. Sieves made up of stainless steel were placed on the funnel to retain feces. The rats were fed with standard diet and water *ad libitum*. Food and water were withdrawn 24 h prior to the experiment. Urine excreted was collected after 5 h.

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 [21] with slight

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modification [22]. The worms were procured from local supplier at the time of carrying out the experiment. The worms were washed with water to remove adhering materials and were sorted out for uniform size and length. The worms were kept in 6% dextrose solution for acclimatization. The worms with normal motility were selected for the experiment. Petri dishes of equal size were selected and in each Petri dishes, 25 mg of the test compounds in 0.1% Tween-80 suspension were placed and the volume made up to 25 ml with 6% dextrose solution. In another Petri dish 25 ml of 0.1% Tween-80 prepared in 6% dextrose solution was placed which served as control. Albendazole suspended in 6% dextrose solution was placed which served as standard. In each Petri dishes 4 worms were placed. The time taken by each worm for paralysis and for the death was noted by placing the worms in water maintained at 50 ^{0}C.

Antipyretic activity

The antipyretic activity was carried out on colony bred albino male rats as by a modified yeast induced hyperpyrexia method [23]. The rats weighing 150-170 g were selected and divided into 10 groups each having 6 animals. The normal rectal temperature and its hourly variation were recorded at the beginning of the experiment using a digital tele-thermometer. The rats were maintained at constant temperature of 24-25 ^{0}C for 24 h before pyrexia was induced by subcutaneous injections of 2 ml of 15% Brewer's yeast suspension in saline solution. After 18 h of yeast injection the animals developed 0.5 ^{0}C or more rise in rectal temperature were distributed in to different group of 6 each and test drugs, each groups at the dose of 100 mg/kg were administered orally as a suspension in Tween-80. Group I received tween–80 as control and group-II received paracetamol as standard drug. The decrease in rectal temperature was noted using tele-thermometer at 1 h intervals up to 3 h. All values are expressed as mean $\pm$ SEM.

The results of diuretic, anthelmintic and antipyretic activities are presented in Table 4.

Table 4- Diuretic, Anthelmintic and Antipyretic activities of the compounds 3a-f

Compd.	Group	Diuretic activity	Anthelmintic activity		Antipyretic activity		
		T/S (Lipschitz value)	Time in minutes		Mean rectal temperature		Decrease in temperature
					0 hr	3 hr	
			Mean time of paralysis	Mean death time			
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	143	282	37.9	37.6	0.3
3b	IV	0.48	155	170	38.1	37.8	0.3
3c	V	0.55	136	250	---	---	---
3d	VI	0.58	133	274	38.6	38.3	0.3
3e	**VII**	0.52	120	253	38.4	38.1	0.3
3f	VIII	0.58	152	258	---	---	---

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RESULTS AND DISCUSSION

The starting material, ethyl naphtho[2,-b]furan-2-caroxyalate **1** was synthesized by well established method in our laboratory[24]. The ester was converted into naphtho[2,1-*b*]furan-2-carbohydrazide **2** by reacting it with hydrazine hydrate. The synthesis of N-[(aryl)methylene]naphtho[2,1-*b*]furan-2-carbohydrazide 3**a-f** was carried out by refluxing equimolar amount of naphtho[2,1-*b*]furan-2-carbohydrazide **2** with various aromatic aldehydes containing electron withdrawing and electron donating groups. The structure assigned to **3b** has been established by spectral studies: ^{1}H NMR (DMSO-d_6): δ 4.2 (s, 3H, OCH_3); 7.6- 8.5 (m, 11H, ArH); δ 8.6 (s, 1H, N=CH); 10.4 (s, 1H, CONH); 10.8 (s, 1H, HO-C=N, tautomeric protons); IR (KBr): 1653 (C=O), 1603 (C=N) cm^{-1}. The spectral data of compounds 3**a** and 3**c-f** is presented in Table 5. These hydrazones (**3a-f**) on treatment with chloroacetyl chloride in presence of triethylamine at 0 ^{0}C furnished the desired products, N-[3-chloro-2-aryl-4-oxo-azetidin-1-yl]naphtho[2,1-*b*]furan-2-carboxamides **4a-f.** The IR spectrum of **4b** exhibited the sharp absorption bands at 1709 cm^{-1} due to amide carbonyl group and at 1657 cm^{-1} due to carbonyl group of β-lactum ring. The ^{1}H NMR (DMSO-d_6) spectrum of **4b** exhibited peaks at δ3.8 (s, 3H, OCH_3); 7.0-8.5 (m, 13H, 11ArH+ CHPh+CHCl); 12.1 (s, 1H, CONH); Similarly ^{13}C NMR (DMSO-d_6) spectra was recorded which showed peaks at: δ 161.72, 161.06, 152.43, 148.50, 147.67, 131.71, 130.17, 129.92, 128.84, 128.37, 127.59, 127.28, 126.88, 126.69, 125.38, 123.61, 122.67, 114.41, 112.46, 110.10, 54.75, 23.61, 18.49; MS: 421 (M+1);.

The spectral data of remaining compounds i.e**. 3a,** and **3c-f**, **4a,** and **4c-f** is presented in Table 5.

Table 5- The spectral data of remaining compounds i.e. 3a, and 3c-f, 4a, and 4c-f

Comp.	Ar	IR (KBr) cm^{-1}		^{1}H NMR in ppm
		C=N	C=O	
3a	- C_6H_5	1585	1678	δ 7.1-8.5 (m, 12H, ArH), δ 8.6 (s, 1H, NCH), δ 9.5 (s, 1H, CONH)
3c	2-Cl- C_6H_4	1620	1690	δ 7.3-8.3 (m, 11H, ArH), δ 8.8 (s, 1H, NCH), 10.6 (s, 1H, CONH)
3d	4-Cl- C_6H_4	1610	1680	δ 7.5-8.6 (m, 11H, ArH), δ 8.9 (s, 1H, NCH), 10.0 (s, 1H, CONH)
3e	4-NO_2- C_6H_4	1598	1675	δ 7.2-8.6 (m, 11H, ArH), δ 8.8 (s, 1H, NCH), δ 10.5 (s, 1H, CONH)
3f	Furfural	1609	1685	δ 7.1-8.2 (m, 10H, ArH), δ 8.6 (s, 1H, NCH), δ 10.3 (s, 1H, CONH)
		C=O Amide	C=O Keto	
4a	C_6H_5	1585	1678	δ 7.0-8.7 (m, 14H, 12ArH + CHPh + CHCl), δ12.1 (s, 1H, NHCO)
4c	2-Cl- C_6H_4	1620	1690	δ 7.1-8.6 (m, 13H, 11ArH+ CHPh+ CHCl), δ 11.8 (s, 1H, NHCO)
4d	4-Cl- C_6H_4	1725	1666	δ 7.2-8.6 (m, 13H, 11ArH + CHPh + CHCl), δ 12.3 (s, 1H, NHCO)
4e	4-NO_2- C_6H_4	1700	1675	δ 7.1-8.7 (m, 13H, 11ArH + CHPh + CHCl), δ11.9 (s, 1H, NHCO)
4f	Furfural	1609	1685	δ 7.0-8.4 (m, 12H, 10ArH + CHPh + CHCl), δ 12.1 (s, 1H, NHCO)

The compounds encompassing naphthofuran, and azetidinone 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.

The newly synthesized compounds were evaluated for antimicrobial activity by cup-plate method. Antibacterial activity was carried out against *Pseudomonas aerugenosa* and *Staphylococcus aureus* using Chloramphenicol as standard drug, Zone of inhibition was measured in mm and results are presented in Table 2. The compounds **4a,** and **4d,** displayed significant activity against both *P. aerugenosa* and *S. aureus.* Rest of the compounds exhibited substantial activity against both the organisms. It is observed that electron withdrawing groups resulted in enhancement of activity. For antifungal activity *Aspergillus niger* and *Curvularia lunata* were used as test organisms and fluconazole as standard drug. The compounds **4c**, and **4e**, exhibited promising activity against *A. niger* and *C. lunata*, whereas remaining compounds are found to be considerable 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 3. Electron donating methoxy group resulted in increase of activity to greater extent. The anti-inflammatory effect is believed to be biphasic. The initial phase is due to the release of histamine, serotonin and kinin in the 1^{st} h after the administration of carrageenan; a more pronounced 2^{nd} phase is attributed to the release of bradykinin, protease, prostaglandin, and lysozyme. The later phase is reported to be sensitive to most of the clinically effective anti-inflammatory agents [25]. The present results suggest that the mechanism of action of tested compounds require further investigation.

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 **4b, 4d,** and **4e** possess substantial analgesic activity and remaining compounds exhibited significant activity. The activity is independent of the substituents present in the molecule. Any injury or tissue damage is associated with pain and inflammation. Analgesics can act on peripheral or central nervous system. Peripherally acting analgesics act by blocking the generation of impulses at chemoreceptor site of pain, while centrally acting analgesics not only raise the threshold of pain, but also alter the psychological response to pain and suppress the patient's anxiety and apprehension. The mechanism of action of all the tested compounds at present could not be ascertained and needs detailed investigation.

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CONCLUSION

A number of N-[3-chloro-2-aryl-4-oxo-azetidin-1-yl] naphtha [2,1-b]furan-2-carboxamides **4a-f** were synthesized and characterized by analytical and spectral studies. The newly synthesized compounds were evaluated for antibacterial, antifungal, anti-inflammatory, analgesic, diuretic, anthelmintic, and antipyretic activities. The results obtained hitherto indicated, that combination of naphtha [2,1-b] furan and azetidinone ring systems enhances the activity to a 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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