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Synthesis of (7-methoxynaphthalen-2-yl(amino methyl) -1,3,4-thiadiazol-2-yl) phenylazetidin -2-one as anti-inflammatory agents

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ABSTRACT

N-benzylidene-5-(7-methoxynaphthalene-2-ylamino)methyl)-1,3,4-thiadiazol-2-amine(4a-4e), 3-(5-(7-methoxynaphthalen-2-ylamino)methyl)-1,3,4-thiadiazol-2-yl)-2-phenyl thia-zolidin-4-one (5a-5e) and 3-chloro-1-(5-((7-methoxynaphthalen-2-yl amino)methyl)-1,3,4-thiadiazol-2-yl)-4-phenylazetidin-2-one (6a-6e) have been synthesized in present study. The structures of these newly synthesized compounds were confirmed by their analytical and spectral data. These compounds were also evaluated for their anti-inflammatory, analgesic activities. The compound (6e) was found to exhibit potent anti-inflammatory activity as compared to the standard drugs phenylutazone. The structures of all compounds have been evaluated by elemental and spectral analysis.

Key words: Naphthalene derivatives, anti-inflammatory, analgesic activities**.**

INTRODUCTION

Gastrointestinal ulceration/inflammation is the most common toxicity observed with most of the currently used non steroidal anti-inflammatory drugs (NSAIDs). The last decade has seen the development of numerous NSAIDs with different structural classes which could be useful in the treatment of inflammatory diseases. The discovery of Nabumetone[1] exoploied the naphthalene nucleus for the synthesis of its derivatives with the hope to possess better activity than Nabumetone. Furthermore, naphthalene derivative have also been found various biological activitiyes like antibacterial[2] cardiovascular[3] and anti-inflammatory[4-10]. The substitution of different heterocyclic nuclei at β-naphthalene has been reported to possess potent anti-inflammatory activities. A large number of thiazolidinones[11-12], Azetidinones[13-14] and thiadiazoles[15-16] were reported to possess potent anti-inflammatory activity. In view above facts it was thought worthwhile to synthesis some newer naphthalene derivative by incorporating the azetidinone and thiazolidinone moiety at β-position of naphthalene nucleus with the aim to get better molecule with anti-inflammatory activity.

Chemistry

Compound 1, i.e. ethyl 2-(7-methoxynaphthalen-2-ylamino) acetate was prepared by reacting 7-ethoxynaphthalene-2-amine with chloroethylacetate in methanol. Compound 1 was then reacted with thiosemicarbazide in absolute methanol-water to give compound 2, i.e. 2-(2-(7-methoxynaphthalen-2-ylamino) acetyl) hydrazine carbothioamide. Reaction of compound 2 with H_2SO_4 and liquid ammonia in ethanol water to yield compound 3, 5-((7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-amine. On further reaction of compound 3 with various aromatic aldehyde in the presence of glacial acetic acid afforded the corresponding N-benzylidene-5-((7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-amine 4a-4e, further undergoes

cycloadditionwith thioglycolic acid in presence of anhydrous $ZnCl_2$ to afforded 3-(5-(7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-yl)-2-phenylthiazolidin-4-one 5a-5e. On the other hand, reaction between compounds 4a-4j and chloroacetylchloride in the presence of 2-3 drops of triethylamine to yielded a cyclized product, i.e. azetidinones 6a-6e, respectively.

RESULTS AND DISCUSSION

All the newly synthesized compounds of this series were tested for anti-inflammatory and analgesic activities at a dose of 50mg/kg.p.o. The results of anti-inflammatory and analgesic activities of all the compounds are statistically significant (Table II).

Out of fifteen compounds only one compound 6bwas found to possess more potent anti-inflammatory in the comparison to phenylbutazone. Compound 6b, which was substituted with chloro group at 4 position of phenyl ring have shown 42.80% of inhibition of oedema. Compound 4a, which was possessed phenyl ring have shown least activity i.e 12.25%. The last steps of compounds 6a-6e were characterized by the presence of an azetidinone ring. All the compounds of this stage have shown promising degree (30.60-42.80) of anti-inflammatory activity. Compound 6b, has shown maximum percentage of anti-inflammatory activity i.e 42.80% at a dose of 50mg/kg.p.o.Considering, the potentiality of compound 6b, was study in detail at three graded doses 25, 50,100mg/kg.p.0. The azitidinone derivatives 6a-6e showed better anti-inflammatory activity than thiazolidinones 5a-5e haveshown moderate togood anti-inflammatory activity. Compound 4a-4e, 5a-5e, 6a-6e, and phenylbutazone were tested for their analgesic activity at 50 mg/kg/p.o and the results are given Table II. From the observations it is clear that only one compounds 6c, exhibited better analgesic activity that the standard drug phenyl butazone.

EXPERIMENTAL

General

All melting points were determined in open capillaries with the help of thermonic melting point apparatus (Campbell Elec-tronic, Mumbai, India), and are uncorrected. All the com-pounds were routinely checked for their homogeneity by thin layer chromatography (TLC) on silica gel-G (Qualigens Fine Chemicals, Mumbai, India), plates of 0.5 mm thickness and spots were located by iodine (Qualigens Fine Chemicals), elu-ent was a mixture of benzene (E. Merck, Mumbai, India) and methanol (Qualigens Fine Chemicals) in different proportions. The IR spectra were recorded on FTIR Paragon 500 (Perkin Elmer, Switzerland) and v in cm^{-1}. The ^1H NMR spectra were recorded on Bruker DRX-300 FT NMR instrument (Bruker, Switzerland) in $CDC1_3$ using tetra methyl silane (TMS) as in-ternal reference standard and chemical shift (5) are reported in parts per million (ppm). The carbon, hydrogen and nitrogen analysis were done on Carlo Erba 1108 elemental analyzer (Carlo Erba Instruments, England) at Central Drug Research Institute, Lucknow, U.P (India).

Synthesis of ethyl 2-(7-methoxynaphthalen-2-ylamino) acetate (1)

A mixture of chloroethylacetate (0.01 mole) in absolute ethanol (50 ml), was added drop-wise during 1h to a well stirred of napthalen-2-amine 0.01 mole in ethanol. The reaction mixture was stirred for 1 h, and then refluxed for 5h. The excess of solvent was distilled off, cooled, poured onto crushed ice and filtered. The solid thus obtained was recrystallized from ethanol.

Compound 1. m.p 140°C yield 80% IR (KBr) ν_{max} in cm^{-1}: 1250(C-N), 1590(C ═C of aromatic ring). 1690(C=O), 3050 (aromaticC-H), 2960 (aliphatic C-H). 3190(N-H), 'H NMR ($CDCl_3$) δ in ppm : 6.90-7.55(m,7H, Ar-H). 1.35 (t,3H,-$COOCH_2$-CH_3), 3.28 (s, 3H, Ar-OCH_3), 4.20(2H,-$COOCH_2$-CH_3), 4.60 (d,2H,NH-CH_2), 5.95 (s, 1H, NH, exchangeable with D_20). Calc. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.56; N, 5.40, (Found: C, 69.61; H, 6.57; N, 5.42 %).

Synthesis of 2-(2-(7-methoxynaphthalen-2-ylamino) acetyl) hydrazine carbothio -amide (2)

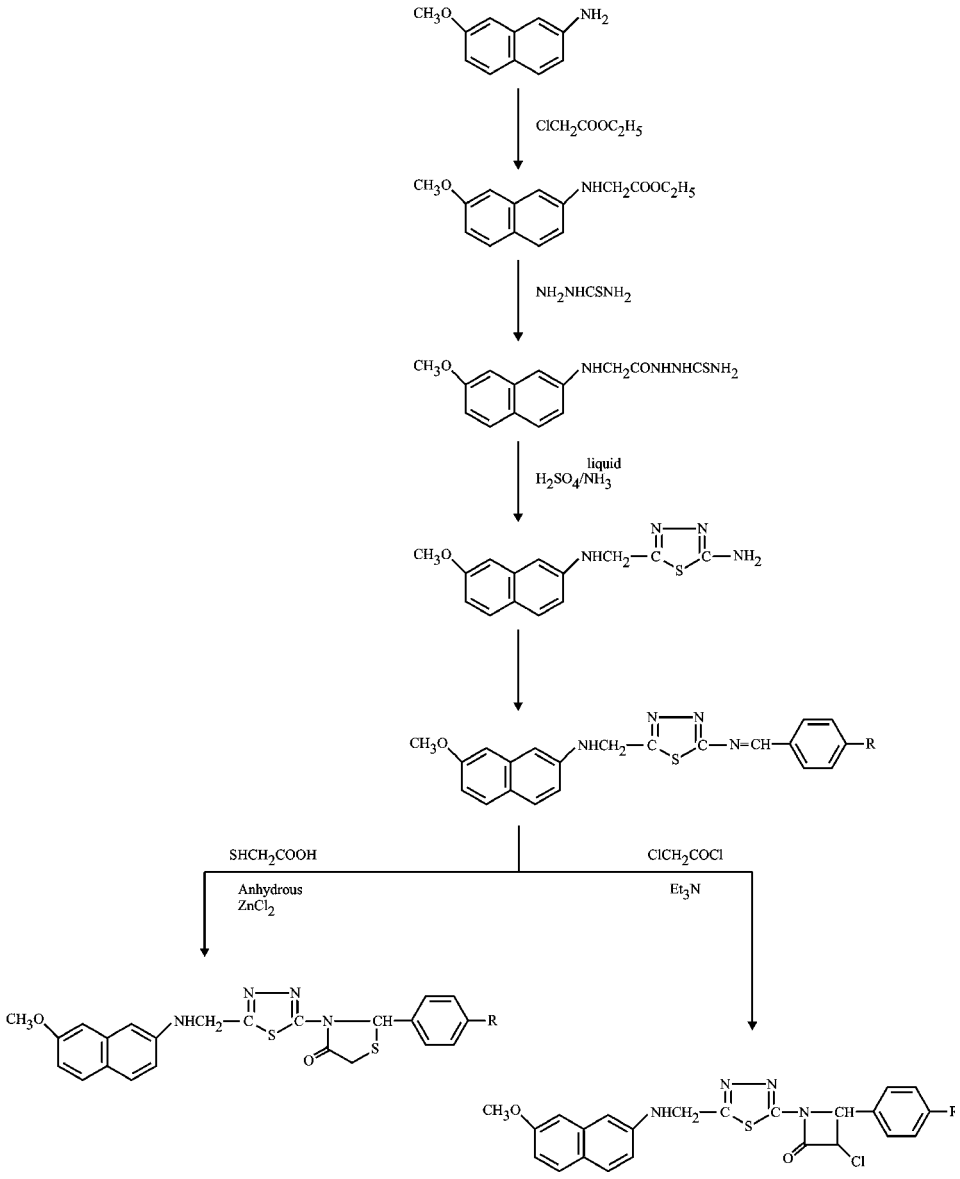
The mixture of 2-(2-(7-methoxynaphthalen-2-ylamino) acetyl)hydrazine carbo thioamide (0.02 mole) and thiosemicarbazide (0.02 mole) in methanol (50 ml) was refluxed for 10h. After reflexing, excess of solvent was distilled

off and poured into ice. The solid thus obtained was filtered, washed with water and recrystallized from methonol-water.

Compound **2**. m.p.130°C, yield 72%,.$C_{14}H_{16}N_4O_2S$. IR (KBr) ν_{max} in cm^{-1} : 1260(C-N), 3180(N-H), 3060(aromatic C-H), 1700(C=O), 2950 (aliphatic C-H), 1580(C=Cof aromatic ring), 'H N-MR($CDCl_3$) δ in ppm : 7.10-7.50 (m, 7H, Ar-H), 8.10 (m, 4H, NH NH CS NH_2, exchangeable with D_2O), 3.30 (s, 3H, Ar-OCH_3), 4.51(d,2H, NH-CH_2), 5.75(s,1H,NH exchangeable with D_2O). Calc. for $C_{14}H_{16}N_4O_2S$: C, 55.26; H, 5.26; N, 18.42, (Found: C, 55.40; H, 5.27; N, 18.50 %).

Synthesis of 5-((7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-amine (3)

A mixture of compound **2** (0.02 mole) and conc. H_2SO_4 (20 ml) was kept overnight at room temperature. Then the reaction mixture was poured into cold water and neutralized with liquid ammonia and filtered. The product this obtained was



Scheme 1:

recrystallized from ethanol-water and the purity of product was checked by TLC. Compound **3** : m.p. 145°C, yield 65%, $C_{14}H_{14}N_4OS$. IR (KBr) ν_{max} in cm^{-1} : 3155 (N-H), 3350(NH_2), 2940(C-H aliphatic), 1585(C=C of aromatic ring), 3050(aromatic C-H), 1710(C=O), 1590(C=N), 1220(C-N), 1040(N-N), 735(C-S-C), ^{1}H-NMR($CDCl_3$) δ in ppm: 7.15-7.65(m, 7H, Ar-H), 6.30(bs, 2H, NH_2 exchangeable with D_2O), 3.35 (s, 3H, Ar-OCH_3), 4.58(d, 2H, NH-CH_2), 5.82 (s, 1H, NH, exchangeable with D_2O). Calc. for $C_{14}H_{14}N_4OS$: C, 58.74; H, 4.89; N, 19.58, (Found: C, 58.94; H, 4.90; N, 19.50 %).

Synthesis of N-benzylidene-5- ((7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-amine (4a-4e)

A mixture of compound **3** (0.01 mole) and proper aromatic aldehydes (0.01 mole) in methanol (50 ml) was refluxed for 6h, in presence of few drops of glacial acetic acid. The progress and completion of reaction was monitored by T.LC. The reaction was distilled off, cooled and than poured into crushed ice water and filtered, washed with water and dried. The product thus obtained was recrystallized from suitable solvent, physical and analytical data of compounds 4a-4e are given in Table I

Compound. 4a:m.p. 152°C, yield 70%, IR (KBr) ν_{max} in cm^{-1}: 3185(N-H), 2945(C-H aliphatic), 1580(C =C of aromatic ring), 3040(aromatic C-H), 1210(C-N), 1045(N-N), 725(C-S-C), ^{1}H-NMR ($CDCl_3$) δ in ppm: 7.05-7.76 (m, 11H, Ar-H), 4.62(d, 2H, NH-CH_2), 5.96(s, 1H, NH, exchangeable), 8.10(d, 1H, =CH-Ar), 3.34(s, 3H, Ar-OCH_3).Calc. for $C_{21}H_{18}N_4OS$: C, 67.36; H, 4.85; N, 14.96, (Found: C, 67.50; H, 4.86; N, 15.02 %).

Synthesis of 3-(5-(7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadia- zol-2-yl)-2-phenylthiazolidin-4-one (5a-5e)

To a cold mixture of compound 4a (0.01 mol) in ethanol (50 ml), thioglycolic acid (0.02 mole) was added drop-wise in the presence of anhydrous $ZnCl_2$ and the reaction mixture was refluxed for 12 h. The reaction mixture were concentrated, cooled and poured into ice water, and filtered. The resulting solid was recrystallised from suitable solvent, physical and analytical data of compounds 5a are given in Table I. Compound 5a. m.p. 135°C, yield 57%, IR (KBr) ν_{max} in cm^{-1} : 3180(N-H), 2950(C-H aliphatic), 1590(C =C of aromatic ring), 3050(aromatic C-H), 1585(C-N), 1205(C-N), 1040(N-N), 735(C-S-C), 1710(C=O), 1490 (C-N of-N-CH-Ar) 'H-NMR ($CDCl_3$) δ in ppm: 6.90-7.84 (m, 11H, Ar-H), 4.58(d, 2H, NH-CH_2), 6.01(s, 1H, NH, exchangeable), 3.41(s, 3H, Ar-OCH_3), 4.38(d, 1H, =CH-N), 2.85(s, 2H, CH_2). Calc. for $C_{23}H_{20}N_4O_2S_2$ C, 61.59; H, 4.14; N, 12.49, (Found: C, 61.71; H, 4.51; N, 12.55 %).

Synthesis of 3- chloro-1-(5-((7-methoxynaphthalen-2-ylamino) methyl)-1,3,4-thiadiazol-2-yl)-4-phenylthiazolidin-2-one (6a-6e)

To a solution of compound 4a (0.01 mol) in absolute ethanol) (100 ml) 2-3 drops of triethylamine and chloroacetylchloride (0.02 mole) were added under stirring 1 h. The reaction mixture were stirred and refluxed for 10 h. After refluxing, these reaction mixtures were distilled off, cooled and poured onto ice. Solid thus obtained was filtered and recrystallized from suitable solvent, physical and analytical data of compounds (6a-6e) are given in Table I.

Compound 6a

m.p. 133°C, yield 55%, .IR (KBr) ν_{max} in cm^{-1} : 3180(N-H), 2950 (C-H aliphatic), 1585 (C =C of aromatic ring), 3050 (aromatic C-H), 1610(C-N), 1215 (C-N), 1050 (N-N), 1710 (C=O), 690 (C-Cl). 'H NMR ($CDCl_3$) δ in ppm: 7.10-7.80 (m, 11H, Ar-H), 4.55(d, 2H, NH-CH_2), 5.95(s, 1H, NH, exchangeable), 3.39(s, 3H, Ar-OCH_3), 6.42 (d, 1H, =CH-Cl), 4.42(d, 1H, CH-N). Calc. for $C_{23}H_{19}ClN_4O_2S$: C, 61.26; H, 4.25; N, 12.42, (Found: C, 61.23; H, 4.24; N, 12.35 %).

Biological Studies

The experiment were performed with albino rats of Charles-Foster strain of either sex, excluding pregnant females, of 60 to 90 days weighing 90-120 g. Acute toxicity was tested in albino mice (15-29g). Food (Chaw pallet) and water was given to the animals ad libitum. The compounds were dissolved in propylene glycol.

Anti-inflammatory activity against carrageenan-induced rat's paw oedema

This study was done by following the procedure of Winter et al.[17]. The rats were divided into three groups (control, drug treated, and standard, drug of six animals each. A freshly

Table 1: Physical and analytical data of compound (4a-4e), (5a-5e) and (6a-6e)

Compd. No.	R	m.p. (°C)	Yield %	Recrystalization solvent	Molecular Formula	Elemental Analysis					
						%C		%H		%N	
						Calcd	Found	Calcd	Found	Caled	Found
4a	C_6H_5	152	70	Ethanol	$C_{21}H_{18}N_4OS$	67.36	67.50	4.85	4.86	14.96	15.02
4b	4-ClC_6H_4	131	65	Acetic-Acid	$C_{21}H_{17}ClN_4OS$	61.68	61.80	4.19	4.20	13.70	13.76
4c	4-OHC_6H_4	165	58	Ethanol	$C_{21}H_{18}N_4O_2S$	64.60	64.72	4.65	4.66	14.35	14.29
4d	4-$CH_3C_6H_4$	142	55	Methanol	$C_{22}H_{20}N_4OS$	68.02	68.18	5.19	5.18	14.42	14.48
4e	4-$OCH_3C_6H_4$	138	60	DMG	$C_{22}H_{20}N_4O_2S$	65.33	65.46	4.98	4.99	13.85	13.90
5a	C_6H_5	135	57	Acetone	$C_{23}H_{20}N_4O_2S_2$	61.59	61.71	4.49	4.51	12.49	12.55
5b	4-ClC_6H_4	141	53	Methanol	$C_{23}H_{19}ClN_4O_2S_2$	57.19	57.06	3.96	3.95	11.60	11.53
5c	4-OHC_6H_4	132	55	Ethanol	$C_{23}H_{20}N_4O_3S_2$	59.46	59.55	4.36	4.37	12.06	12.12
5d	4-$CH_3C_6H_4$	103	60	Acetic-Acid	$C_{24}H_{22}N_4O_2S_2$	62.31	62.45	4.79	4.80	12.11	12.19
5e	4-$OCH_3C_6H_4$	127	62	Ethanol	$C_{24}H_{22}N_4O_3S_2$	60.23	60.36	4.63	4.64	11.71	11.75
6a	C_6H_5	133	55	Methanol	$C_{23}H_{19}ClN_4O_2S$	61.26	61.13	4.25	4.24	12.42	12.35
6b	4-ClC_6H_4	145	50	DMG	$C_{23}H_{17}Cl_2N_3OS$	60.80	60.95	3.77	3.78	9.25	9.30
6c	4-OHC_6H_4	125	48	Ethanol	$C_{23}H_{18}ClN_3O_2S$	63.37	63.50	4.16	4.15	9.64	9.60
6d	4-$CH_3C_6H_4$	116	40	Acetic-Acid	$C_{24}H_{20}ClN_3OS$	66.43	66.55	4.65	4.66	9.68	9.75
6e	4-$OCH_3C_6H_4$	109	45	Benzene	$C_{24}H_{20}ClN_3O_2S$	64.06	64.20	4.48	4.50	9.34	9.40

Table 2: Biological data of compounds (4a-4e), (5a-5e), and (6a-6e)

Compounds	R	Anti–inflammatory activity		Analgesic activity	
		Dose (mg/kg p.o.)	% oedema inhibitor relation	Dose (mg/ kg / p.o)	% protection
4a	C_6H_5	50	12.25	50	10.15
4b	4-ClC_6H_4	50	20.32	50	18.18
4c	4-OHC_6H_4	50	14.48	50	12.52
4d	4-$CH_3C_6H_4$	50	16.19	50	14.27
4e	4-$OCH_3C_6H_4$	50	18.44	50	16.22
5a	C_6H_5	50	21.65	50	19.98
5b	4-ClC_6H_4	50	23.66	50	21.62
5c	4-OHC_6H_4	50	25.78	50	23.13
5d	4-$CH_3C_6H_4$	50	16.17	50	24.05
5e	4-$OCH_3C_6H_4$	50	28.02	50	26.34
		50	30.60	50	28.28
6a6b	$C_6H_5$4-ClC_6H_4	25	25.75	25	20.12
		50	42.80	50	38.45
		100	68.21	100	60.84
6c	4-OHC_6H_4	50	34.88	50	31.08
6d	4-$CH_3C_6H_4$	50	31.50	50	29.72
6e	4-$OCH_3C_6H_4$	50	32.10	50	27.60
	Controld	25	26.76	25	14.26
	Phenyl	50	36.80	50	32.50
	butazone	100	64.68	100	54.58

*P < 0.05, **P < 0.01, ***P < 0.001.

Propylene glycol standard for control group.

prepared suspension of carrageenan (1% in 0.9% saline). 0.05 ml was injected under the planter aponeurosis of the right hind paw of each rat. Test compounds and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively. 1 h before the carrageenan injection. The paw volume of each rat was measured before 1 and after 3 h of carrageenan treatment with the help of a plethymometer. The percent anti-inflammatory activity was calculated according to the formula given below-

Percentage of inhibition of oedema=$(1-V_t/V_c)$ x 100

Where, V_t and V_c are the mean increase in paw volume of rats of the treated and the control group, respectively. Results obtained were statistically analyzed.

Analgesic activity

This activity was performed by following the method of Berkowitz et al[18]. This method is based on the property of the test compound to antagonize the phenyl quinine-induced pain syndrome in mice. Groups of five mice were injected intraperitonely with 0.25 ml of a 0.02% solution of phenylquinone in ethanol (5%) 1 h after of oral administration of the test compound. The number of writhes induced in each mouse was counted for 5 min (between 5 and 10 min) after injection of an irritant. The analgesic effect was expressed as percent protection in comparison to control.

% Protection = (1-mean no. of writhes in mice of test groups/mean number of writhes in mice of control group) x 100

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