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RESEARCH ARTICLE

Synthesis of some Thiadiazole and Azetidinone Derivatives as their Anti-inflammatory Activities

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ABSTRACT

(NE)-N-(2-substitutedbenzylidene)-5-(((5-((4-substitutedbenzylidene) amino-1,3,4-thiadiazol-2-yl)-thio) methyl)-1,3,4-thiadiazole-2-amine **[5a-5h]** and 3-chloro-1-(5-(((5-chloro-2-(2-subdtitutedphenyl)-4-oxoazetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)thio)-1,3,4-thiadiazole-2-yl)-4-(4-methoxyphenyl) azetidin-2-one.**[6a-6h]** were synthesized and evaluated for their anti-inflammatory activity against carrageenan induced oedema in albino rats at a dose of 50 mg/kg p.o. The structures of all these compounds were established on the basis of elemental and spectral. Moreover, the most potent compounds (NE)-N-(4-hydroxybenzylidene)-5-(((5-((4methoxy benzylidene) amino-1,3,4-thiadiazol-2-yl)-thio)methyl)-1,3,4-thiadiazole-2-amine and 3-chloro-1-(5-(((5-chloro-2-(4-hydroxyphenyl)-4-oxo azetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl)thio)-1,3,4-thiadiazole-2-yl)-4-(4-methoxyphenyl) azetidin-2-one have exhibited 37.90 and 38.65% inhibition of oedema at 50 mg/ kg p.o.

Key words: Thiadiazole and azetidinone derivatives, Anti-inflammatory; and Analgesic; activity.

INTRODUCTION

Heterocyclic bearing nitrogen, sulpher and thiadiazole moieties constitute the core structure of a number of biological interesting compounds. Literature survey revealed that 1,3,4 thiadiazole derivatives are associated with various biological activities such as anti-inflammatory [1-4], anticonvulsant [5-6], antibacterial [7,8] and antifungal [9,10]. The incorporation of azetidinone moiety in different heterocyclic nuclei markedly modulates the anti-inflammatory activity. Therefore, it was thought worthwhile to synthesized some new azetidinone derivatives[11] of thiadiazole by incorporating it at 2 and 5-position of 1,3,4-thiadiazoles nucleus with the hope to get better anti-inflammatory molecule with improved anti-inflammatory activities. All the compounds have been screened for their anti-inflammatory and analgesic activities. The structures of all compounds have been evaluated by elemental and spectral analysis (IR, and ^{1}HNMR spectrometry).

Chemistry

The substituted benzyldehyde in presence of glacial acetic acid on reaction with 5-amino-1,3,4-thiadiazole-2-thiol, it was converted into compound, 5-substitued benzylidenamino-1,3,4,-thiadiazole-2-thiols **(1a-1b).** The compound reacted when with chloroethylacetate gave compound, ethyl 2-((5-((4-substituted benzylidene) amino)-1,3,4-thiadiazole-2-yl)thio)acetate **(2a-2b)**. Furthermore, the compound when treated with thiosemicarbazide resulted into the formation of the compound. 2-(2-((5-((4-substituted benzyl idene) amino)-1,3,4-thiadiazole-2-yl)thio) acetyl) hydrazine carbo amide **(3a-3b)**. These compounds, on dehydrocyclsation with conc H_2So_4 and ammonia solution gave 5-(((5-amino-1,3,4-thiadiazole-2-yl)methyl)thio)-N-(4-substituted benzylidene)-1,3,4-thiadiazol-2-amine**(4a-4b)**. The compounds, when further reacted with substituted benzyldehyde yielded the, (NE)-N-(2-Chloro benzylidene)-5-(((5-((4-substitutedbenzylidene) amino-1,3,4-thiadiazol-2-yl)-thio) methyl)-1,3,4-thiadiazole-2-amine **(5a-5h)**. The later compounds on cylco condensation with monochloroacetyl-choride and triethylamine furnished the compound, 3-chloro-1-(5-(((5-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl) thio)-1,3,4-thiadiazole-2-yl)-4-(4-substituted phenyl)azetidin-2-one **(6a-6h)**.

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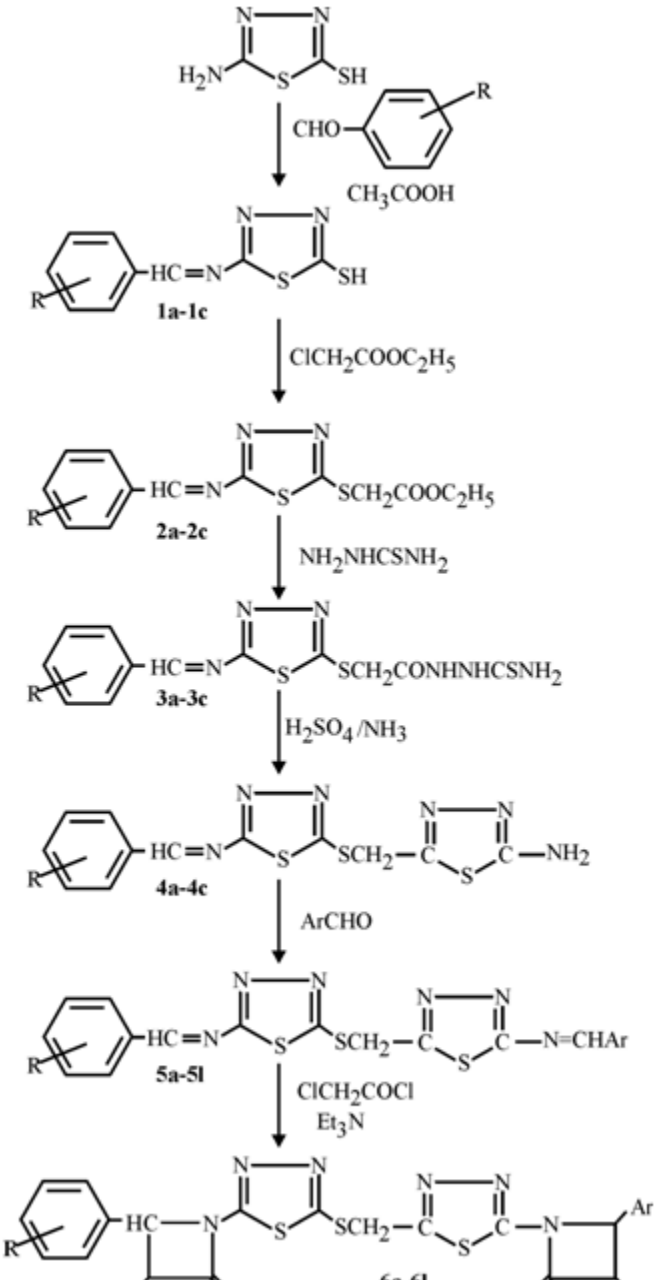

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Biological activities

Anti-inflammatory activity:

Preliminary study at all the three tested doses (25, 50, 100, mg/kg) were compared with standard drug, phenyl butazone and acetyl salicylic acid. These compounds were administered either by oral or intraperitoneal route. Rats of either sex weighing 60-130 were divided into groups of 6 animals each. A freshly prepared suspension of carrageenin (1.0% in 0.9%saline) 0.05 ml, was injected under the planter aponeurosis of right paw of the rat by the method of Winter et a[12]. One group was kept as control and the animals of other group were pretreated with the test drugs suspended in gum acacia, given orally 1 h before the carrageenin injection. The volume of foot bwas measured before one and 3 h after carrageenin treatment by the micropipette method The mean increase of paw volume in each group was measured and percentage anti-inflammatory activity was calculated according to the formula given below–

Percentage of inhibition of oedema = (1–Vt/Vc) × 100

Where Vt and Vc are the volumes of oedema in drug treated and the control groups. Phenylbutazone was used as the standard drug for comparison.

Analgesic activity

This activity was performed by following the method of Berkowitz et al.[13] This method is based on the property of the test compound to antagonize the phenyl quinone-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) × 100

EXPERIMENTAL

General

All melting points were determined in open capillaries with the help of thermonic melting point apparatus (Campbell Electronic, Mumbai, India), and are uncorrected. All the compounds 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 CDC13 using tetra methyl silane (TMS) as internal 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).

The starting material 5-amino-1,3,4-thiadiazole-2-thiol was obtained from sigma company (Reported m.p. 235°C)

Synthesis of 5-((2-chlorobenzylidene)amino-1,3,4,-thiadizole-2-thiol [1a].

5-Amino-1,3,4-thiadiazole-2-thiol (0.01 mole), 2-chlorobenzyldehyde (0.02 mole) and acetic acid in benzene (50 ml) was refluxed for 15 hr. The solvent was removed under reduced pressure and the viscous mass was poured over ice water filtered and recrystallized from methanol and water.

Compound 1a: *M.P*. 120°C, *Yield* 72 % ,IR (KBr) ν_{max} in cm^{-1}: 3340 (NH_2), 1045 (N-N), 1620 (C=N), 2545 (SH), 725 (C-S-C), 635 (C-Cl), 1550 (C=C of aromatic ring). ^{1}HNMR ($CDCl_3$) δ□in ppm: 7.20-8.10 (m,4H,ArH), 8.40 (s,1H,N=CH-Ar), 2.92 (s,1H,SH). MS: $[M]^+$ at m/z 255. Anal. Calcd for $C_9H_6ClN_3S_2$: C, 42.27; H, 2.34; N, 16.43. Found : C, 42.35; H, 3.61; N, 16.48.

Synthesis of 5-((4-methoxybenzylidene)amino-1,3,4,-thiadizole-2-thiol [1b].

Compound 1b: *M.P*. 112°C, *Yield* 68 %,.IR (KBr) ν_{max} in cm^{-1}: 3330 (NH_2), 1050 (N-N), 1615 (C=N), 2540 (SH), 720 (C-S-C), 1545 (C=C of aromatic ring). ^{1}HNMR ($CDCl_3$) δ□in ppm: 3.36 (s, 3H, $ArOCH_3$), 7.22-8.12 (m, 4H, ArH), 8.45 (s,1H,N=CH-Ar), 2.85 (s,1H,SH). MS: $[M]^+$ at m/z 251. Anal. Calcd for $C_{10}H_9N_3OS_2$: C, 47.81; H, 3.59; N, 16.74. Found : C, 47.98; H, 3.60; N, 16.68.

Synthesis of ethyl 2-((5-((2-chlorobenzylidene) amino)-1,3,4-thiadiazole 2-yl)thio) acetate. [2a].

5-substitutedbenzylideneamino-1,3,4-thiadiazol-2-thiol (0.02mole) and chloroethyl acetate (0.02 mole) in methanol (50 ml) was refluxed for 12 hr. The solvent was removed under reduced pressure and the viscous mass was poured over crushed ice filtered and recrystallized methanol and water.

Compound 2a: *M.P*. 138°C, *Yield* 68%, IR (KBr) ν_{max} in cm^{-1}: 3335 (NH_2), 1045 (N-N), 1610 (C=N), 725 (C-S-C), 635 (C-Cl), 1550 (C=C of aromatic ring), 1725 (C=O of ester), 2840 (CH_2).^{1}HNMR ($CDCl_3$) δ□in ppm: 1.25 (t,3H,$COOCH_2CH_3$), 3.90-4.10 (s,2H,SCH_2) (q,2H,$COOCH_2CH_3$), 7.15-8.05 (m,4H,ArH), 8.45 (s,1H,N=CH-Ar). MS: $[M]^+$ at m/z 341.Anal. Calcd for $C_{13}H_{12}ClN_3O_2S_2$: C, 49.86; H, 4.45; N, 12.46. Found : C,50.04; H, 4.46; N,12.42.

Synthesis of ethyl 2-((5-((4-methoxybenzylidene) amino)-1,3,4-thiadiazole 2-yl) thio)acetate. [2b].

Compound 2b: *M.P*. 132°C, *Yield* 65%, IR (KBr) ν_{max} in cm^{-1}: 3340 (NH_2), 1050 (N-N), 1615 (C=N), 730 (C-S-C), 1555 (C=C of aromatic ring), 1730 (C=O of ester), 2840 (CH_2).^{1}HNMR ($CDCl_3$) δ in ppm: 1.25 (t, 3H, $COOCH_2CH_3$), 3.40 (s, 3H, ArO, CH_3), 3.90-4.10 (s,2H,SCH_2) (q,2H,$COOCH_2CH_3$), 7.15-8.05 (m,4H,ArH), 8.45 (s,1H,N=CH-Ar). MS: $[M]^+$ at m/z 337.Anal. Calcd for $C_{14}H_{15}N_3O_3S_2$: C, 49.86; H, 4.45; N, 12.46. Found : C,50.04; H, 4.46; N,12.42.

Synthesis of 2-(2-((5-((2-chlorobenzylidene) amino)-1,3,4-thiadiazole-2-yl)thio)acetyl) hydrazine carboamide. [3a].

5-substitutedbenzylideneamino-2-thiocarbethoxy methyl-1,3,4-thiadiazole (0.02 mole) and thiosemi carbazide (0.02 mole) in benzene (50 ml) was refluxed for 12 hr. The solvent was removed under pressure and the viscous mass poured over ice-water, filtered and recryltallized from methanol and water.

Compound 3a: *M.P*. 154°C, *Yield* 60%, IR (KBr) ν_{max} in cm^{-1}: 3340 (NH_2), 1055 (N-N), 1620 (C=N), 735 (C-S-C), 635 (C-Cl), 1560 (C=C of aromatic ring), 1715 (C=O of amides), 2845 (CH_2).^{1}HNMR ($CDCl_3$) δ□in ppm: 3.88 (s, 2H, SCH_2), 7.18-8.12 (m,4H,ArH), 8.42 (s,1H,N=CH-Ar), 8.68 (m,4H,NH-NH-CS-NH_2). MS: $[M]^+$ at m/z 382. Anal. Calcd for $C_{12}H_{11}ClN_6OS_3$: C, 40.83; H, 3.66; N, 21.98. Found : C,40.76; H, 3.67; N,21.91.

Synthesis of 2-(2-((5-((4-methoxybenzylidene) amino)-1,3,4-thiadiazole-2-yl)thio)acetyl) hydrazine carboamide. [3b].

Compound 3b: *M.P*. 160°C, *Yield* 58%, IR (KBr) ν_{max} in cm^{-1}: 3340 (NH_2), 1055 (N-N), 1620 (C=N), 735 (C-S-C), 1560 (C=C of aromatic ring), 1715 (C=O of amides), 2845 (CH_2).^{1}HNMR ($CDCl_3$) δ□in ppm: 3.42 (s, 3H, $ArOCH_3$), 3.88 (s, 2H, SCH_2), 7.18-8.12 (m,4H,ArH), 8.42 (s,1H,N=CH-Ar), 8.68 (m,4H,NH-NH-CS-NH_2). MS: $[M]^+$ at m/z 402. Anal. Calcd for $C_{12}H_{11}ClN_6OS_3$: C, 35.82; H, 2.72; N, 20.89. Found : C,35.88; H, 2.73; N,20.93.

Synthesis of 5-(((5-amino-1,3,4-thiadiazole-2-yl)methyl)thio)-N-(2-chloro benzylidene)-1,3,4-thiadiazol-2-amine. [4a].

A mixture of 5-substitutedbenzylideneamino-2-(thiosemicarbazidocarbonyl methyl thio)-1,3,4-thidiazoles (0.02 mole) and conc. H_2SO_4 (25 ml) was kept over night at room temperature. Then, the reaction mixture was poured into cold water and neutralized with liquid ammonia and filtered. The

product thus obtained was recryltallized from ethanol and water.

Compound 4a: *M.P.* 145°C, *Yield* 55%, IR (KBr) ν_{max} in cm^{-1}: 3335 (NH_2), 1045 (N-N), 1610 (C=N), 725 (C-S-C), 630 (C-Cl), 1650 (C=C of aromatic ring), 2850 (CH_2).^{1}HNMR ($CDCl_3$) δ □in ppm: 7.98-7.46 (m, 4H, ArH), 4.25 (bs, 2H, NH_2), 3.90 (s, 2H, SCH_2), 8.25(s, 1H, N=CH-Ar). MS: $[M]^+$ at m/z 368. Anal. Calcd for $C_{12}H_9ClN_6S_3$: C, 39.07; H, 2.44; N, 22.80. Found : C,39.15; H,2.45; N, 22.85.

Synthesis of 5-(((5-amino-1,3,4-thiadiazole-2-yl) methyl)thio)-N-(4-methoxy benzylidene)-1,3,4-thiadiazol-2-amine. [4b].

Compound 4b: *M.P.* 152°C, *Yield* 60%, IR (KBr) ν_{max} in cm^{-1}: 3335 (NH_2), 1045 (N-N), 1610 (C=N), 725 (C-S-C), 1650 (C=C of aromatic ring), 2850 (CH_2).^{1}HNMR ($CDCl_3$) δ □in ppm: 7.98-7.46 (m, 4H, ArH), 4.25 (bs, 2H, NH_2), 3.90 (s, 2H, SCH_2), 3.41 (s, 3H, Ar-OCH_3), 8.25(s, 1H, N=CH-Ar). MS: $[M]^+$ at m/z 364. Anal. Calcd for $C_{13}H_{12}ON_6S_3$: C, 42.86; H, 3.29; N, 23.07. Found : C,42.74; H,3.28; N, 23.13.

Synthesis of (NE)-N-(2-Chlorobenzylidene)-5-(((5-((2-chlorobenzylidene)amino-1,3,4-thiadia-zol-2-yl)-thio)methyl)-1,3,4-thiadiazole-2-amine [5a].

To a cold solution of compound **4a** and ethanol (0.02 mole) was added substitutedbenzyldehyde (0.03 mole) drop wise with stirring at ambient temperature refluxed for 16-18 hr. The reaction mixture was concentrated, cooled and poured into ice water. The resulting solids was recrystallized from DMF and water.

Compound 5a: *M.P.* 184°C, *Yield* 50%, IR(KBr) ν_{max} in cm^{-1}: 1610 (N-N), 1605 (C=N), 730 (C-S-C), 635 (C-Cl), 1645 (C=C of aromatic ring), 2855 (CH_2).^{1}HNMR ($CDCl_3$) δ □in ppm: 8.12-7.26 (m, 8H, Ar-H), 9.98 (ss,1H, phenolic proton), 3.95 (s,2H,SCH_2), 3.41 (s,3H,ArOCH_3), 8.38 (s,2H,2 x N=CH-Ar). MS: $[M]^+$ at m/z 456. Anal. Calcd for $C_{19}H_{13}ClN_6S_3$.: C, 49.95; H, 2.85; N,18.40. Found : 49.86; H,2.86; N, 18.42.

Compounds **(5a-5h)** were prepared similarly and their characterization data are given in (**Table 1**) respectively.

Synthesis of 3-chloro-1-(5-(((5-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl) -1,3,4-thiadia zol-2-yl)methyl)thio)-1,3,4-thiadiazole-2-yl)-4-(2-chlorophenyl) azetidin-2-one. [6a].

To a solution of compound **5a** (0.02 mole) in absolute benzene (100 ml) 2-3 drops of triethylamine and chloroacetylchloride (0.04 mole) were added drop by drop during 1 hr and refluxed for an hour. The reaction mixture was cooled and poured onto ice. The solid thus obtained was filtered and recrystallized from acetone.

Compound 6b: *M.P.* 208°C, *Yield* 54%, IR(KBr) ν_{max} in cm^{-1}: 1065 (N-N), 1615 (C=N), 735 (C-S-C), 1650 (C=C of aromatic ring), 2860 (CH_2), 1720 (C=O of β-lactam ring), 640 (C-Cl). ^{1}HNMR ($CDCl_3$) δ □in ppm: 8.22-7.32 (m, 8H, Ar-H), 9.96 (s,s, 1H phenolic proton), 3.98 (s,2H,SCH_2), 3.39 (s,3H,Ar-OCH_3), 5.90 (s,2H,2 x CH-Ar), 3.75 (s,2H,2xCHCl).MS: $[M]^+$ at m/z 609. Anal. Calcd for $C_{23}H_{15}Cl_3N_6O_2S_3$..: C, 45.28; H,2.46; N,13.78. Found : 45.35; H,2.47; N, 13.82.

Compounds **(6a-6h)** were prepared similarly and their characterization data are given in (**Table 2**) respectively.

RESULTS AND DISCUSSION

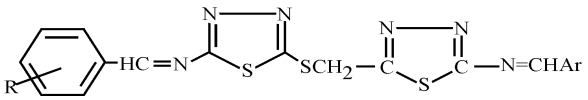
All the sixteen newly synthesized compounds of this series were tested for anti-inflammatory, and analgesic, activity, at a dose of 50-mg/kg p.o. The first step compounds i.e **(5a-5g)** have shown anti-inflammatory activity ranging from 16.50 to 22.30%. The compound **5b**, which was substituted with chloro group at 4- position of phenyl ring have shown 18.35% of inhibition of oedema. The compound **5a,** which possessed phenyl ring have shown least activity i.e 16.50. However, the compound **5f,** which was subsituted with chloro group at 2-position of phenyl ring connected via-N=CH-linkage at 5'-position of thiadiazole nucleus exhibited maximum inhibit of oedema (28.02%). This compound was found to be most potent among **(5a-5g)**. The compound, which was subsituted with 2-hydroxyl group on phenyl ring, has shown moderate degree of anti-inflammatory activity (19.32).

The second step compounds were characterized by the presence of an azetidinone ring (β-lactum). All the compound of this stage have shown modrate to potent degree (27.12 to 34.60%) of anti-inflammatory activity. The compound **6f,** has shown the maximum percentage of anti-inflammatory activity i.e 37.64 at a dose of 50 mg/kg p.o. Considering, potentiality of compound **5f** and **6f,** these were studied in details at three graded doses 25,50,100 mg/kg p.o. The compound **5f** exhibited better anti-inflammatory activity at all the three doses of 25, 50 and 100 mg/Kg p.o as compared to phenylbutazone. Figure-I showed the bar diagram of anti-inflammatory activity at three graded doses (25, 50 and 100) mg/kg p.o) of

compounds **5f** and **6f** and phenylbutazone. At all the three dose levels compound **5f** and **6f** showed good acivity than that of phenylbutazone.

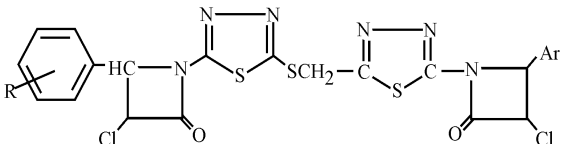
The compounds of first step **(5a-5g)** have shown moderate to good analgesic activity. The compound **5f,** which was substituted by 2-methoxy phenyl ring at 5-position of thiadiazole nucleus along with 4-chlorophenyl at 5' -position of thiadiazole nucleus, exhibited (39.89%) most potent analgesic activity. On cyclisation of these compounds **(5a-5g)** with chloroacetylchloride in the presence of triethylamine resulted ito the formation of azetidinones **(6a-6g)**. The most active compound of this series was **6f,** which has shown potent analgesic activity 42.82% at a dose of 50mg/kg p.o. Considering the potentiality of compounds **5f** and 6**f**, hese compounds were studied in details at of 25, 50 and 100 mg/kg p.o. and exhibited better activity than standard drug phenylbutazone.

Table 1: Physical and analytical data of 5-substitutedbenzylideneamino-2-[5'-(substituted benzylideneamino-1',3',4'- thiadiazol-2'-yl)-thiomethyl]-1,3,4-thiadiazoles (5a-5g)



Comp No.	R	Ar	M.P (0ºC)	Yield	Recrystalization solvent	Molecular formula	Elemental Analysis					
							% C		% H		% N	
							Calcd	Found	Calcd	Found	Calc	Found
5a	2-Cl	C6H5	168	55	Ethanol-water	C19H13ClN6S3	49.95	49.80	2.85	2.86	18.40	18.42
5b	2-Cl	4-ClC6H4	162	50	Ethanol-water	C19H12Cl2N6S3	46.43	46.60	2.44	2.45	7.10	7.12
5c	2-Cl	4-CH3C6H4	164	64	Acetone	C20H15ClN6S3	51.00	51.17	3.18	3.19	17.86	18.82
5d	2-Cl	4-OHC6H4	158	50	Methanol-water	C19H13ClN6OS3	48.25	48.42	2.75	2.77	17.78	17.84
5e	4-OCH3	C6H5	172	65	Ethanol-water	C20H16N6OS3	53.09	53.23	3.54	3.55	18.58	18.51
5f	4-OCH3	4-ClC6H4	175	60	Acetic acid	C20H15ClN6OS3	49.33	49.51	3.08	3.09	17.20	17.25
5g	4-OCH3	4-CH3C6H4	178	55	Methanol -water	C21H18N6OS3	54.07	53.88	3.86	3.88	18.02	18.05
5h	4-OCH3	4-OHC6H4	181	50	DMF	C20H16N6O2S3	51.28	51.33	3.41	3.42	17.95	18.02

Table 2: Physical and analytical data of 5-[4'-oxo-3'-chloro-2'-substitutedphenyl-azetidin-1'-yl]-2-[{5"-(4'''-oxo-3''' chloro-2'''-aryl-azetidin-1'''-yl)-1",3",4"-thiadiazol -2"-yl}-thiomethyl]-1,3,4-thiadiazoles (6a-6l)



Comp No.	R	Ar	M.P (0ºC)	Yield	Recrystalizatio n solvent	Molecular formula	Elemental Analysis					
							% C		% H		% N	
							Calcd	Found	Calcd	Found	Calcd	Found
6a	2-Cl	C_6H_5	191	50	Acetone	$C_{23}H_{15}Cl_3N_6O_2S_3$	45.28	45.34	2.46	2.45	13.78	13.82
6b	2-Cl	4-ClC_6H_4	188	54	Acetic acid	$C_{23}H_{14}Cl_4N_6O_2S_3$	42.86	43.02	2.17	2.18	13.04	13.08
6c	2-Cl	4-$CH_3C_6H_4$	184	55	Ethanol-water	$C_{24}H_{17}Cl_3N_6O_2S_3$	46.19	46.36	2.73	2.72	13.47	13.52
6d	2-Cl	4-OHC_6H_4	196	50	Ethanol-water	$C_{23}H_{15}Cl_3N_6O_3S_3$	44.12	44.28	2.39	2.39	13.42	13.47
6e	4-OCH_3	C_6H_5	183	55	DMF	$C_{24}H_{18}Cl_2N_6O_3S_3$	47.60	47.68	2.97	2.99	13.88	13.92
6f	4-OCH_3	4-ClC_6H_4	199	48	Methanol-water	$C_{24}H_{17}Cl_3N_6O_3S_3$	45.03	45.19	2.66	2.65	13.13	13.18
6g	4-OCH_3	4-$CH_3C_6H_4$	205	50	Methanol-water	$C_{25}H_{20}Cl_2N_6O_3S_3$	48.46	48.64	3.23	3.24	13.57	13.59
6h	4-OCH_3	4-OHC_6H_4	212	54	Acetone	$C_{24}H_{18}Cl_2N_6O_4S_3$	46.37	46.46	2.90	2.92	13.52	13.56

Table 3: Biological activities of compounds 5a-5h and 6a-6h

Compd. No	R	Ar	Anti-inflammatory activity		Analgesic activity	
			Dose (mg/kg/p.o.)	% inhibition of oedema	Dose (mg/kgp.o)	% Protection
5a	2-Cl	C_6H_5	50	16.50	50	13.20
5b	2-Cl	4-ClC_6H_4	50	18.35	50	20.10
5c	2-Cl	4-$CH_3C_6H_4$	50	17.10	50	12.10
5d	2-Cl	4-OHC_6H_4	50	18.05	50	13.70
5e	4-OCH_3	C_6H_5	50	20.15	50	25.12
5f	4-OCH_3	4-ClC_6H_4	25 50 100	19.70 37.90 60.50	25 50 100	24.60 39.90 55.20
5g	4-OCH_3	4-$CH_3C_6H_4$	50	21.80	50	31.20
5g	4-OCH_3	4-OHC_6H_4	50	22.30	50	22.50
6a	2-Cl	C_6H_5	50	27.70	50	29.60
6b	2-Cl	4-ClC_6H_4	50	33.10	50	32.60
6c	2-Cl	4-$CH_3C_6H_4$	50	29.60	50	18.13
6d	2-Cl	4-OHC_6H_4	50	31.40	50	21.70
6e	4-OCH_3	C_6H_5	50	30.70	50	33.80
6f	4-OCH_3	4-ClC_6H_4	25 50 100	20.50 38.65 62.25	25 50 100	36.70 42.82 59.60
6g	4-OCH_3	4-$CH_3C_6H_4$	50	31.20	50	26.43

6h	4-OCH_3	4-OHC_6H_4	50	32.80	50	33.30
Phenyl butazoe	-	-	25 50 100	16.75 36.80 58.59	25 50 100	24.48 39.27 51.26

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