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NEWER N-SUBSTITUTED THIADIAZOLYL/AZETIDINONYL ANTHRANILIC ACID DERIVATIVES AS POTENT ANTI-INFLAMMATORY AGENTS

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ABSTRACT:

In the present study various 5-halo-N-amino acetylamino-(2'-substitutedarylidenyl-4'-thiazolidinonyl)-benzoic acids **(16-24)** and 5-halo-N-amino acetylamino-(3'-chloro-4'-substitutedarylidenyl-2'azetidinonyl)- benzoic acids **(25-33)** have been synthesized by cyclization of compounds 5-halo-N-amino acetyl substituted arylidenyl hydrazino benzoic acids **(7-15)** via route-1 and route-2 respectively as depicted in figure. The purity of the compounds was checked by TLC. Metling points were determined in open capillaries and are uncorrected. The structure of all the synthesized compounds was characterized by C, H, N (elemental analysis) and spectral analysis (IR, NMR). Further, the above said compounds were also evaluated for anti-inflammatory and ulcerogenic activities along with acute toxicity. These compounds were found to possess varying degrees of these activities. Compound **21**, 5-bromo-N-amino acetylamino-[2'-(N,N-dimethylarylidenyl)-4'-thiazolidinonyl]- benzoic acid was found to be the most potent compound of the series, more potent than standard drug phenyl butazone, showing a protection of 55.98%, against paw edema induced by carrageenan. Most of the compounds exhibit less ulcerogenic activity and ALD_{50} >1000 mg/kg p.o. except compounds **21** and **30**, which possess ALD_{50} >2000 mg/kg p.o.

Keywords: thiazolidinones, azetidinones, anthranilic acid, anti-inflammatory activity, acute toxicity

INTRODUCTION

Inflammation is a condition in which a part of the body becomes swollen, red and sore due to injury or infection. It is an essential part of the body's healing process. It involves a series of events that can be elicited by numerous stimuli such as infectious agents, antigen-antibody interaction etc. Prednisole, dexamethasone, betamethasone etc. are the names of some of the steroids, which were considered to be the choicest anti-inflammatory drugs, almost two decades ago. Due to their severe adverse effects caused by either long term or short term steroid therapy, these have been replaced by more or less by much better and safer non-steroidal anti-inflammatory drugs (NSAIDs). The serious and enormous side effects of the use of steroids, accelerated the research towards the development of non-steroidal anti-inflammatory drugs.

Literature survey reveals that various congeners of anthranilic acid (2-amino benzoic acid) **[1-11]** comprises an important group of non-steroidal anti-inflammatory drugs (NSAIDs). Moreover, anthranilic acid (2-amino benzoic acid) derivatives has gained prominence after the discovery of mefenamic acid and meclofenamate **[12-13]** which are currently used for clinical treatment of various inflammatory diseases. Both mefenamic acid and meclofenamate are N-phenylanthranilic acid derivatives. A substantial amount of work has been done on the structural variation of this heterocyclic nucleus, which can be regarded as a subclass of drugs broadly known as nonsteroidal anti-inflammatory drugs – NSAIDs. It has also been perceived that best premier NSAIDs are acidic in nature. In view of these observations, our concentration has been directed to the variation at second position of anthranilic acid by assimilating different acidic functional five membered heterocyclic rings with perspective to synthesize new analogies with improved anti-inflammatory outcome. Moreover, survey of recent literature reveals that substitution at second position of anthranilic acid (2-amino benzoic acid) by various substituted aryl or heteroaryl moieties noticeably modulate the anti-inflammatory activity. Furthermore, considering the recent work of researchers and the structure activity relationship (SAR) various thiadiazoles **[14-19]** and azetidinones **[20-26]** have also been found to possess strong anti-inflammatory activity. Hence, it is not immaterial to speculate that incorporating these thiadiazolyl and azetidinonyl rings at the second position of anthranilic acid may enhance the anti-inflammatory activity of

such compounds. Therefore, it was thought valuable to synthesize some new N-substituted anthranilic acid derivatives by incorporating thiadiazolyl and azetidinonyl moieties with the hope to get better anti-inflammatory compounds.

EXPERIMENTAL

Chemistry

The purity and homogeneity of the compounds were checked by thin layer chromatography (TLC) using silica gel-G plates. Mixture of methanol-benzene in the ratio 2:8 was used as eluent in TLC and iodine was used to locate the spots. Melting points of all the synthesized compounds were determined on thermonic melting point apparatus. The melting points were taken in open capillary tubes and were uncorrected. C, H, N analysis for carbon, hydrogen and nitrogen was performed on Carlo Erba-1108, Heracus. Analysis (C, H, N) were within ±0.04 % of the theoretical values. The IR and ^{1}H-NMR spectra were recorded on Backman Acculab-10 spectrophotometer (ν_{max} in cm^{-1} ; KBr) and on Brucker 400-FT (in $CDCl_3$) instrument respectively.

The synthetic routes for the synthesis of compounds **(1-33)** is depicted in **Figure-1**. The analytical and physical data of compounds **(1-33)** is given in **Table 1**.The compounds **(1-33)** were tested for their anti-inflammatory activity as well as for their acute toxicity. Phenylbutazone was used as reference drug for anti-inflammatory activity. The results of biological activity is given in **(Table 2)**.

Synthesis

The pathway for the synthesis of compounds **(1-33)** is depicted in **Figure 1**.

Synthesis of 5-halo-N-chloroacetyl amino benzoic acids (1-3)

To a well stirred solution of 2-amino benzoic acid (0.01 mol) in chloroform (dry 50ml), chloroacetyl chloride (0.02 mol) was added drop by drop at 0-5^{0}C during 1 h. The reaction mixture so formed was stirred at room temperature for 2 h. After stirring it was concentrated, cooled and poured onto ice. The solid separates out which was filtered and recrystallized from appropriate solvents to yield compounds **(1-3).** The physical and analytical data of the compounds **(1-3)** is given in **Table-1.** Compound **1**: IR (cm^{-1}, KBr): 3040 (O-H), 3120 (N-H), 3030 (C-H aromatic), 1710 (C=O), 1588 (C-C aromatic ring), 2925 (CH_2), 1215 (C-N), 690 (C-Cl). ^{1}H-NMR $CDCl_3$ δ : 7.50-6.35 (m, 3H, Ar-H), 11.45 (s, 1H, -COOH, exchangeable with D_2O), 8.60 (brs, 1H, NHCO), 3.50 (s, 2H, -CH_2Cl) (ppm).

Synthesis of 5-halo-N- amino acetyl hydrazino benzoic acids (4-6)

To a solution of 5-halo-N-chloroacetyl amino benzoic acids **(1-3)** (0.01 mol) in DMF (25 ml), hydrazine hydrate (0.01 mol) was added slowly with stirring and the reaction mixture was refluxed 2-3 h. After refluxing it was concentrated, cooled and poured into ice cold water. The separated solids were filtered and recrystallized from appropriate solvents to afford compounds **(4-6)**. The physical and analytical data of the compounds **(4-6)** is given in **Table 1**. Compound **4**: IR (cm^{-1}, KBr): 3046 (O-H), 3110 (N-H), 3025 (C-H aromatic), 1712 (C=O), 1590 (C-C aromatic ring), 2920 (CH_2), 1218 (C-N). ^{1}H-NMR $CDCl_3$ δ : 7.70-6.60 (m, 3H, Ar-H), 11.60 (s, 1H, -COOH, exchangeable with D_2O), 10.00 (s, 1H, NH exchangeable with D_2O), 8.30 (brs, 2H, NH_2 exchangeable with D_2O), 8.80 (brs, 1H, NHCO), 4.70 (s, 2H, $-COCH_2$) (ppm).

Synthesis of 5-halo-N- amino acetyl substituted arylidenyl hydrazino benzoic acids (7-15)

To a solution of 5-halo-N-acetyl amino hydrazino benzoic acids **(4-6)** (0.01 mol) in methanol in the presence of few drops of glacial acetic acid various substituted aldehydes (0.01 mol) namely 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde, 4- N,N-dimethylbenzaldehyde were refluxed for 6-8 h. The reaction mixtures were concentrated, cooled and poured onto ice. The solids which separated out were recrystallized from appropriate solvents to yield compounds **(7-15)**. The physical and analytical data of the compounds **(7-15)** is given in **Table 1**. Compound **7**: IR (cm^{-1}, KBr): 3042 (O-H), 3114 (N-H), 3020 (C-H aromatic), 1717 (C=O), 1580 (C-C aromatic ring), 2910 (CH_2), 1216 (C-N), 1620 (C=N), 735 (monosubstituted benzene ring). ^{1}H-NMR $CDCl_3$ δ : 7.65-7.20 (m, 7H, Ar-H), 11.40 (s, 1H, -COOH, exchangeable with D_2O), 9.80 (s, 1H, NH exchangeable with D_2O), 8.65 (brs, 1H, NHCO), 8.20 (d, 1H, =CH-Ar), 4.66 (s, 2H, $-COCH_2$) (ppm).

Synthesis of 5-halo-N-amino acetylamino-(2'-substitutedarylidenyl-4'-thiazolidinonyl)- benzoic acids (16-24)

To a cooled mixtures of 5-halo-N- amino acetyl substituted arylidenyl hydrazino benzoic acids **(7-15)** (0.01 mol) and anhydrous $ZnCl_2$ (0.02 mol) in DMF (50 ml), thioglycolic (0.02 mol) was added dropwise with stirring at ambient temperature and the mixtures were kept for 48 h at room temperature and refluxed for 12 h. The reaction mixtures were cooled, filtered, washed with water and poured into ice cold

water. The resulting solids thus obtained were recrystallized with appropriate solvents to afford compounds **(16-24)**. The physical and analytical data of the compounds **(16-24)** is given in **Table 1**. Compound **16**: IR (cm^{-1}, KBr): 3045 (O-H), 3108 (N-H), 3015 (C-H aromatic), 1720 (C=O), 1586 (C-C aromatic ring), 2920 (CH_2), 1220 (C-N), 676 (C-S-C), 730 (monosubstituted benzene ring), 1760 (C=O of β-thialactam ring). ^{1}H-NMR $CDCl_3$ δ : 7.60-7.10 (m, 7H, Ar-H), 11.30 (s, 1H, -COOH, exchangeable with D_2O), 9.70 (s, 1H, NH exchangeable with D_2O), 8.50 (brs, 1H, NHCO), 4.72 (s, 2H, -$COCH_2$), 3.90 (s, 2H, CH_2 of thiazolidinone), 6.35 (t, 1H, N-CH-Ar) (ppm).

Synthesis of 5-halo-N-amino acetylamino-(3'-chloro-4'-substitutedarylidenyl-2'azetidinonyl)- benzoic acids (25-33)

To the well stirred solutions 5-halo-N- amino acetyl substituted arylidenyl hydrazino benzoic acids **(7-15)** (0.02 mol), in dioxane (50 ml), chloroacetyl chloride (0.02 mol) and few drops of triethylamine were added with constant stirring at 0-5^{0}C during 15 min. . The reaction mixtures were stirred for about 3 h at room temperature. The solid triethylamine hydrochloride formed was filtered and removed. The solutions (filterates) were heated under reflux for 5h. The solvent was evaporated under reduced pressure. The solid products so obtained were washed with water, filtered and dried. The resulting solids which separated out were recrystallized from appropriate solvents to yield compounds **(25-33)**. The physical and analytical data of the compounds **(25)** is given in **Table 1**. Compound **25**: IR (cm^{-1}, KBr): 3048 (O-H), 3120 (N-H), 3026 (C-H aromatic), 1712 (C=O), 1585 (C-C aromatic ring), 2916 (CH_2), 1212 (C-N), 740 (monosubstituted benzene ring), 1745 (CO of β-lactam), 635 (C-Cl). ^{1}H-NMR $CDCl_3$ δ : 7.75-7.30 (m, 7H, Ar-H), 11.10 (s, 1H, -COOH, exchangeable with D_2O), 9.85 (s, 1H, NH exchangeable with D_2O), 8.50 (brs, 1H, NHCO), 4.62 (s, 2H, -$COCH_2$), 5.45 (d, 1H, -CH-Ar, azetidinone ring), 5.18 (d, 1H, CH-Cl) (ppm).

Pharmacology

Anti-inflammatory activity: Anti-inflammatory activity was performed by paw edema inhibition test on albino rats following the method of Winter *et al* **[27]**. Individual cages were used for rats. One percent carrageenan suspension was prepared in 0.9% NaCl solution and 0.2 ml of it was injected subutaneously into the platar aponeurosis of hind paw after 30 minutes. Water plethysmometer socrel was used to measure the paw volume. Paw volume was again measured after 3 h. The mean increase

of the paw volume at each time interval was compared with that of the control group at the identical time intervals and the percent inhibition of edema values were calculated using the formula:

Percentage of anti-inflammatory activity = 1 – (V_t/V_c) X 100

Where, V_t = test groups

V_c = control groups

Ulcerogenic activity: Newly synthesized compounds were checked for their ulcerogenic liabilities by the method of Verma *et al* **[28]**. Prior to the administration of the drug the albino rats were fasted for 24 h. After 8 h of drug treatment, all the animals were sacrificed and then their small intestines and stomachs were examined microscopically to assess the shedding of epithelium, incidence of hyperemia, frank and petechial haemorrhages and discrete or erosion ulceration with or without perforation. The appearance of any of these specifications was considered to be the confirmation of ulcerogenic activity.

Acute toxicity activity (ALD_{50}): Approximate lethal dose of all the newly synthesized compounds was determined. Procedure of Smith **[29]** was followed for determining the acute toxicity of the synthesized compounds. Albino mice were used to perform this activity. Animals were divided in a groups of 10 animals. The test compounds are suspended in propylene glycol and were given orally at different dose levels. Percent mortality in each group was observed after 24 h of drug administration. From the data so obtained ALD_{50} was calculated.

RESULTS AND DISCUSSION

The physico-chemical data of all the synthesized compounds is depicted in **Table-1**. All the synthesized compounds **(1-33)** were also screened for their anti-inflammatory, cyclooxygenase-II (COX-II) and ulcerogenic activity. The compounds were also screened also screened for their acute toxicity. The compounds wre tested at a dose of 50 mg/kg p.o. and were compared with the standard drug phenyl butazone. The pharmacological data of compounds **(1-33)** is given in **Table 1**.

The series was characterized by the incorporation of two moieties that are thiazolidinone and azetidinone, at the 2nd position of anthranilic acid to develop more potent and safer anti-inflammatory drugs. Compounds **(1-3)** i.e.5-halo-N-chloroacetyl amino benzoic acids, were found to exhibit mild anti-inflammatory activity ranging from 21.89% to 24.66%. A little increase in anti-inflammatory was observed in step-2 compounds i.e. compounds 5-halo-N- amino

acetyl hydrazino benzoic acids **(4-6)**. These compounds **(4-6)** exhibited 22.66% to 27.48% inhibition of edema induced by carrageenan when tested. Somewhat enhanced anti-inflammatory activity was observed in compounds 5-halo-N- amino acetyl substituted arylidenyl hydrazino benzoic acids **(7-15)**. These compounds **(7-15)** exhibited activity between 26.22% to 35.12%. Further, cyclization of compounds **(7-15)**, via route-1 was found to be fruitful in enhancing the anti-inflammatory activity. Cyclization of compounds **(7-15)** was done by treating them with thioglycolic acid in presence of anhydrous $ZnCl_2$ into five membered ring compounds i.e. 5-halo-N-amino acetylamino-(2'-substitutedarylidenyl-4'-thiazolidinonyl)- benzoic acids **(16-24)**. These compounds showed high percentage protection ranging from 33.28% to 55.98%. Compound **21**, 5-bromo-N-amino acetylamino-[2'-(N,N-dimethylarylidenyl)-4'-thiazolidinonyl]- benzoic acid was found to be the most potent compound of the series, which showed protection of 55.98%, against edema induced by carrageenan. This compound showed more potent activity than the standard drug phenyl butazone. Standard drug phenyl butazone was reported to exhibit 36.4%, edema inhibition. Being the most potent compound of the series, this compound **21**, was further analyzed in detail at three graded doses of 25, 50 and 100 mg/kg p.o. for its anti-inflammatory activity and was found to possess 28.36%, 55.98% and 60.12% oedema inhibition respectively. Standard drug was also studied in detail at those three graded doses. On comparing the results of the two, it was found that both standard drug as well as compound **21**, showed almost similar activity at lower dose of 25 mg/kg p.o. But when results at higher doses of 50 and 100 mg/kg p.o. are compared, compound **21** was found to be more potent. Compound **21**, showed anti-inflammatory activity of 55.98% and 60.12% whereas standard drug was found to possess activity of 36.4% and 58.4% at doses of 50 and 100 mg/kg p.o. respectively.

Furthermore, compounds **(7-15)** were cyclized through route-2 by the addition of chloro acetylchloride and triethylamine to give four membered ring compounds 5-halo-N-amino acetylamino-(3'-chloro-4'-substitutedarylidenyl-2'azetidinonyl)-benzoic acids **(25-33)**. A good percentage protection between 30.25% to 48.65% was shown by these compounds. Out of nine compounds **(25-33)**, the most potent compound was found to be compound **30**. This compound 5-bromo-N-amino acetylamino-[3'-chloro-4'-(N',N'-

dimethylarylidenyl-2'azetidinonyl]-benzoic acid **(30)**, exhibited anti-inflammatory activity of 48.65%, which is more than that exhibited by standard drug (36.40%) when compared. Considering the potential nature of this compound 30, it was studied further in detail at three graded doses of 25, 50 and 100 mg/kg p.o. and was found to inhibit 20.20%, 48.65% and 58.02% of edema produced by carrageenan. Standard drug when studied at these three graded doses was found to possess 28.42%, 36.4% and 58.4% edema inhibition. On comparing the results of the two, it was noted that at blower dose, standard drug showed more potent activity whereas on increasing the dose to 50 mg/kg p.o. compound **30** exhibit more potent activity than standard drug. But if results at a higher dose of 100 mg/kg p.o. are compared, both the standard drug as well as compound 30, elicited almost similar protection against edema.

Compounds **(1-33)** were also evaluated for their ulcerogenic activity. The compounds were found to possess varying degree of hyperemia ranging from 20% to 100%. At the same time these compounds **(1-33)** were found to be associated with low degree of ulcer production (10% to 40% of animals). Compounds **9, 12, 15, 18, 21, 24, 27, 30** and **33** have shown a very low degree of ulcer production. All these compounds **(1-33)** were also evaluated for ALD_{50}. All the compounds exhibited a high value of ALD_{50} which is greater than 1000 mg/kg p.o. except compound **21** and **30**, which showed ALD_{50} greater than 2000 mg/kg p.o., thereby suggesting a good safety margin of these compounds.

Table 1: Physical and analytical data of compounds (1-33)

Compd. No.	X	R	M.P. (^{0}C)	Recryst. solvent	Yield (%)	Molecular Formula	Calcd. (Found) %		
							C	H	N
1.	H	-	85	methanol	54	$C_9H_8NO_3Cl$	54.13 (54.10)	4.01 (3.99)	7.01 (6.98)
2.	Br	-	98	ethanol	68	$C_9H_7NO_3BrCl$	36.92 (36.89)	2.39 (2.42)	4.78 (4.81)
3.	I	-	105	ethanol	65	$C_9H_7NO_3ICl$	31.81 (31.79)	2.06 (2.09)	4.12 (4.09)
4.	H	-	100	ethanol	56	$C_9H_{11}N_3O_3$	51.67 (51.70)	5.26 (5.23)	20.09 (20.11)
5.	Br	-	110	methanol	58	$C_9H_{10}N_3O_3Br$	37.50 (37.48)	3.47 (3.50)	14.58 (14.62)
6.	I	-	125	methanol	55	$C_9H_{10}N_3O_3I$	32.23 (32.19)	2.98 (3.01)	12-53 (12.55)
7.	H	4-OH	130	benzene	50	$C_{16}H_{15}N_3O_4$	61.34 (61.36)	4.79 (4.82)	13.41 (13.39)
8.	H	4-OCH_3	150	acetone	45	$C_{17}H_{17}N_3O_4$	62.38 (62.41)	5.19 (5.22)	12.84 (12.87)
9.	H	4-$N(CH_3)_2$	115	benzene	52	$C_{18}H_{20}N_4O_3$	63.52 (63.49)	5.88 (5.91)	16.47 (16.50)
10.	Br	4-OH	145	DMF	48	$C_{16}H_{14}N_3O_4Br$	48.97 (49.00)	3.57 (4.01)	10.71 (10.69)

11.	**Br**	**4-OCH_3**	**185**	**DMF**	**54**	**$C_{17}H_{16}N_3O_4Br$**	**50.24 (50.27)**	**3.94 (3.98)**	**10.34 (10.37)**
12.	**Br**	**4-$N(CH_3)_2$**	**198**	**benzene**	**40**	**$C_{18}H_{19}N_4O_3Br$**	**51.55**	**4.53 (4.55)**	**13.36 (13.38)**
13.	**I**	**4-OH**	**200**	**ethanol**	**45**	**$C_{16}H_{14}N_3O_4I$**	**43.73 (43.75)**	**3.18 (3.21)**	**9.56 (9.59)**
14.	**I**	**4-OCH_3**	**210**	**acetone**	**40**	**$C_{17}H_{16}N_3O_4I$**	**45.03 (45.05)**	**3.53 (3.56)**	**9.27 (9.30)**
15.	**I**	**4-$N(CH_3)_2$**	**240**	**acetone**	**48**	**$C_{18}H_{19}N_4O_3I$**	**46.35 (46.36)**	**4.07 (4.10)**	**12.01 (11.99)**
16.	**H**	**4-OH**	**160**	**Ethanol**	**54**	**$C_{18}H_{17}N_3O_5S$**	**55.81 (55.78)**	**4.39 (4.42)**	**10.85 (10.88)**
17.	**H**	**4-OCH_3**	**175**	**ethanol**	**55**	**$C_{19}H_{19}N_3O_5S$**	**56.85 (56.88)**	**4.73 (4.75)**	**10.47 (10.51)**
18.	**H**	**4-$N(CH_3)_2$**	**185**	**methanol**	**40**	**$C_{20}H_{22}N_4O_4S$**	**57.97 (57.99)**	**5.31 (5.28)**	**13.52 (13.49)**
19.	**Br**	**4-OH**	**205**	**ethanol**	**42**	**$C_{18}H_{16}N_3O_5BrS$**	**46.35 (46.37)**	**3.43 (3.46)**	**9.01 (8.98)**
20.	**Br**	**4-OCH_3**	**240**	**ethanol**	**46**	**$C_{19}H_{18}N_3O_5BrS$**	**47.50 (47.47)**	**3.75 (3.77)**	**8.75 (8.78)**
21.	**Br**	**4-$N(CH_3)_2$**	**260**	**methanol**	**45**	**$C_{20}H_{21}N_4O_4BrS$**	**48.68 (48.70)**	**4.25 (4.28)**	**11.35 (11.38)**
22.	**I**	**4-OH**	**225**	**acetone**	**50**	**$C_{18}H_{16}N_3O_5IS$**	**42.10 (42.08)**	**3.11 (3.09)**	**8.18 (8.21)**
23.	**I**	**4-OCH_3**	**210**	**benzene**	**42**	**$C_{19}H_{18}N_3O_5IS$**	**43.26 (43.28)**	**3.41 (3.38)**	**7.96 (7.99)**
24.	**I**	**4-$N(CH_3)_2$**	**280**	**pet. ether**	**38**	**$C_{20}H_{21}N_4O_4IS$**	**44.44 (44.41)**	**3.88 (3.91)**	**10.37 (10.40)**
25.	**H**	**4-OH**	**182**	**toluene**	**36**	**$C_{18}H_{16}N_3O_5Cl$**	**55.45 (55.48)**	**4.10 (4.07)**	**10.78 (10.81)**
26.	**H**	**4-OCH_3**	**168**	**ethanol**	**40**	**$C_{19}H_{18}N_3O_5Cl$**	**47.58 (47.61)**	**4.46 (4.49)**	**10.40 (10.37)**
27.	**H**	**4-$N(CH_3)_2$**	**154**	**pet. ether**	**42**	**$C_{20}H_{21}N_4O_4Cl$**	**57.62 (57.59)**	**5.04 (5.08)**	**13.44 (13.47)**
28.	**Br**	**4-OH**	**180**	**DMF**	**38**	**$C_{18}H_{15}N_3O_5BrCl$**	**46.10 (46.08)**	**3.20 (3.17)**	**8.96 (8.99)**
29.	**Br**	**4-OCH_3**	**175**	**benzene**	**40**	**$C_{19}H_{17}N_3O_5BrCl$**	**47.25 (47.27)**	**3.52 (3.49)**	**8.70 (8.67)**
30.	**Br**	**4-$N(CH_3)_2$**	**145**	**DMF**	**44**	**$C_{20}H_{20}N_3O_4BrCl$**	**49.84 (49.81)**	**4.15 (4.18)**	**8.72 (8.69)**
31.	**I**	**4-OH**	**200**	**methanol**	**45**	**$C_{18}H_{15}N_3O_5ICl$**	**41.90 (41.87)**	**2.90 (2.87)**	**8.14 (8.16)**
32.	**I**	**4-OCH_3**	**248**	**ethanol**	**42**	**$C_{19}H_{17}N_3O_5ICl$**	**43.05 (43.08)**	**3.21 (3.18)**	**7.93 (7.95)**
33.	**I**	**4-$N(CH_3)_2$**	**280**	**benzene**	**45**	**$C_{20}H_{20}N_3O_4ICl$**	**49.84 (49.81)**	**4.15 (4.17)**	**8.72 (8.69)**

C, H, N were found within ± 0.04%

Table 2: Pharmacological evaluation of compounds (1-33)

Compd. No.	X	R	Mean increase in paw volume ± S. E.	Anti-inflammatory Activity		Ulcerogenic Activity			ALD_{50} (mg/kg p.o.)
				Dose (mg/kg p.o.)	% Decrease in Oedema	Dose (mg/kg p.o.)	% of Animals with hyperemia	% of animals with ulcer	
1.	**H**	**-**	**0.210±0.002**	**50**	**21.98****	**300**	**60***	**20**	**>1000**
2.	**Br**	**-**	**0.401±0.004**	**50**	**24.66****	**300**	**70*****	**30**	**>1000**
3.	**I**	**-**	**0.342±0.003**	**50**	**23.24***	**300**	**70****	**20**	**>1000**
4.	**H**	**-**	**0.376±0.012**	**50**	**22.66****	**300**	**60****	**20**	**>1000**
5.	**Br**	**-**	**0.385±0.011**	**50**	**27.48*****	**300**	**60*****	**30**	**>1000**
6.	**I**	**-**	**0.342±0.004**	**50**	**26.52*****	**300**	**60****	**20**	**>1000**
7.	**H**	**p-OH**	**0.365±0.006**	**50**	**26.22***	**300**	**50*****	**20**	**>1000**
8.	**Br**	**p-OCH_3**	**0.336±0.001**	**50**	**28.34*****	**300**	**50****	**30**	**>1000**
9.	**I**	**p-$N(CH_3)$**	**0.372±0.002**	**50**	**30.48****	**300**	**40*****	**10**	**>1000**
10.	**H**	**p-OH**	**0.388±0.001**	**50**	**28.33****	**300**	**60****	**20**	**>1000**
11.	**Br**	**p-OCH_3**	**0.333±0.003**	**50**	**27.77*****	**300**	**40*****	**20**	**>1000**
12.	**I**	**p-$N(CH_3)$**	**0.346±0.001**	**50**	**35.12*****	**300**	**40****	**10**	**>1000**
13.	**H**	**p-OH**	**0.372±0.011**	**50**	**28.64****	**300**	**50****	**20**	**>1000**
14.	**Br**	**p-OCH_3**	**0.420±0.002**	**50**	**30.52*****	**300**	**20***	**20**	**>1000**

15.	**I**	**p-N(CH_3)**	**0.299±0.001**	**50**	**32.48****	**300**	**70****	**10**	**>1000**
16.	**H**	**p-OH**	**0.285±0.003**	**50**	**33.28***	**300**	**90****	**40**	**>1000**
17.	**Br**	**p-OCH_3**	**0.333±0.005**	**50**	**36.42***	**300**	**70****	**30**	**>1000**
18.	**I**	**p-N(CH_3)**	**0.322±0.004**	**50**	**42.72****	**300**	**80****	**10**	**>1000**
19.	**H**	**p-OH**	**0.320±0.001**	**50**	**35.48*****	**300**	**70*****	**20**	**>1000**
20.	**Br**	**p-OCH_3**	**0.346±0.001**	**50**	**41.10****	**300**	**90****	**20**	**>1000**
21.	**I**	**p-N(CH_3)**	**0.344±0.002** **0.392±0.003** **0.382±0.001**	**25** **50** **100**	**28.36**** **55.98***** **60.12*****	**100** **200** **300**	**30**** **60***** **100*****	**10** **10** **10**	**>2000**
22.	**H**	**p-OH**	**0.388±0.004**	**50**	**35.13****	**300**	**50***	**30**	**>1000**
23.	**Br**	**p-OCH_3**	**0.349±0.003**	**50**	**42.27****	**300**	**60****	**20**	**>1000**
24.	**I**	**p-N(CH_3)**	**0.329±0.001**	**50**	**50.12****	**300**	**40****	**10**	**>1000**
25.	**H**	**p-OH**	**0.289±0.002**	**50**	**30.25*****	**300**	**80****	**20**	**>1000**
26.	**Br**	**p-OCH_3**	**0.298±0.004**	**50**	**33.33*****	**300**	**70****	**20**	**>1000**
27.	**I**	**p-N(CH_3)**	**0.3010.003**	**50**	**38.62*****	**300**	**60****	**10**	**>1000**
28.	**H**	**p-OH**	**0.312±0.003**	**50**	**37.41****	**300**	**100****	**20**	**>1000**
29.	**Br**	**p-OCH_3**	**0.322±0.001**	**50**	**39.42***	**300**	**70*****	**20**	**>1000**
30.	**I**	**p-N(CH_3)**	**0.342±0.005** **0.373±0.001** **0.362±0.002**	**25** **50** **100**	**20.20**** **48.65***** **58.02*****	**100** **200** **300**	**60**** **80***** **90*****	**10** **10** **20**	**>2000**
31.	**H**	**p-OH**	**0.321±0.001**	**50**	**37.72****	**300**	**50****	**20**	**>1000**
32.	**Br**	**p-OCH_3**	**0.378±0.002**	**50**	**39.98*****	**300**	**30*****	**20**	**>1000**
33.	**I**	**p-N(CH_3)**	**0.321±0.003**	**50**	**42.12*****	**300**	**60*****	**10**	**>1000**
Phenyl butazone				**25** **50** **100**	**28.42** **36.40** **58.40**				

*p <0.05, **p<0.01, ***p<0.001**

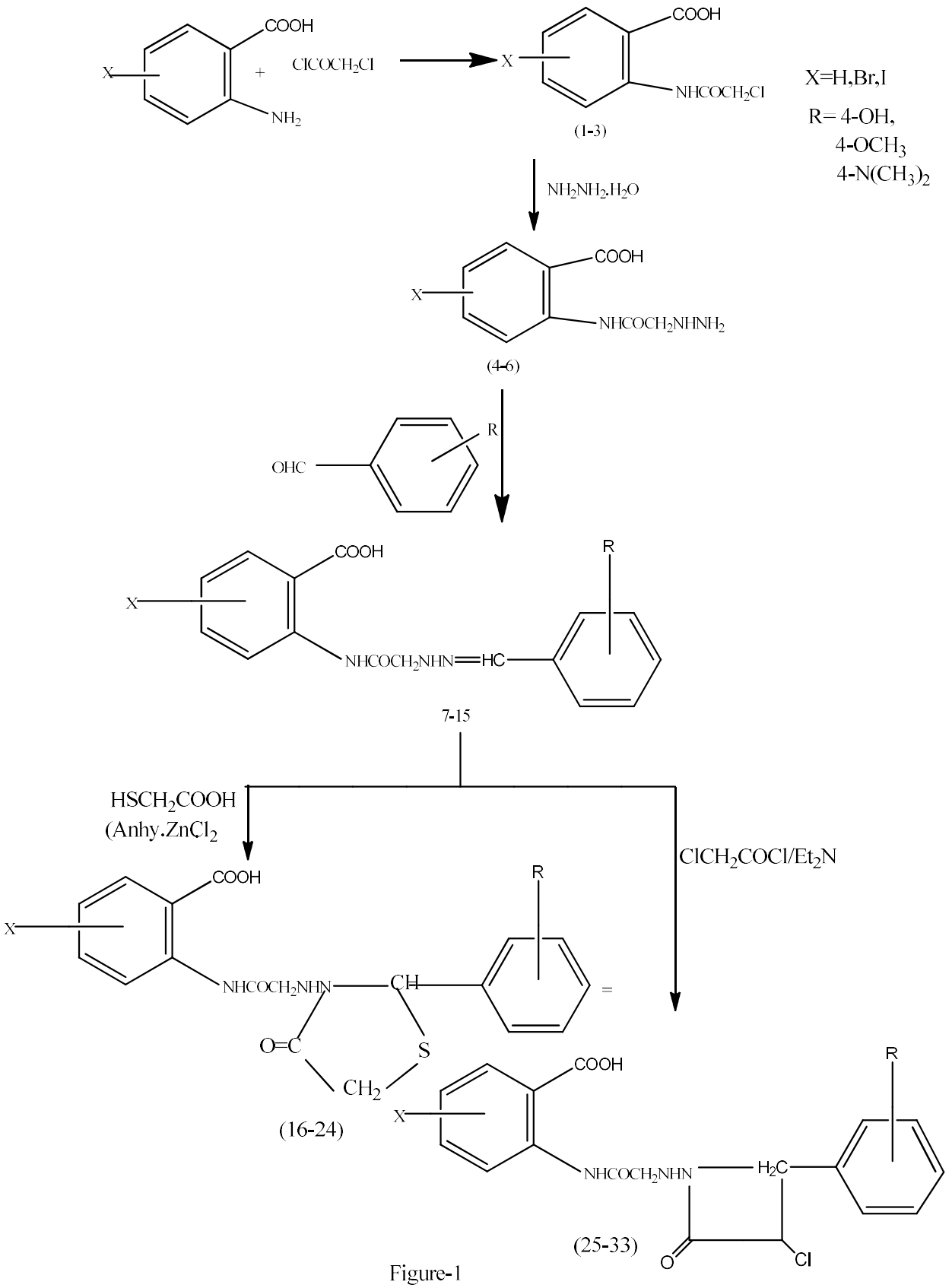
COOH
X
ClCOCH2Cl
NH2
NHCOCH2Cl
(1-3)
X=H,Br,I
R= 4-OH,
4-OCH3
4-N(CH3)2
NH2NH2.H2O
NHCOCH2NHNH2
(4-6)
OHC
R
NHCOCH2NHN=HC
7-15
HSCH2COOH
(Anhy.ZnCl2
ClCH2COCl/Et2N
NHCOCH2NHN
CH
O=C
S
CH2
(16-24)
H2C
O
Cl
(25-33)

Figure-1

CONCLUSION

On comparing the entire pharmacological data of these compounds of the series i.e. compounds **(1-33)**, it may be concluded that-

1. Bromo substituted derivatives were found to be more potent than their corresponding derivatives.
2. Presence of 4-N,N-dimethyl phenyl ring in compounds was found to enhance the anti-inflammatory activity in comparison to presence of 4-hydroxy pheny ring and 4-methoxy phenyl ring.
3. Thiazolidinones were found to be more potent than the corresponding azetidinones.

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Conflict of interest

There is no conflict of interest among authors.

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