ORIGINAL RESEARCH ARTICLES

DESIGN, SYNTHESIS AND EVALUATION OF NOVEL AZETIDINONYL/ FORMAZONYL/ THIAZOLIDINONYLPHENOTHIAZINES AS POTENTIAL ANTI-INFLAMMATORY AGENTS

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ABSTRACT

The present study describes the synthesis, full characterization and biological evaluation of novel azetidinonyl/formazonyl/thiazolidinonylphenothiazines. The synthesis of these compounds as potential anti-inflammatory agents was carried out using a more efficient and versatile synthetic route. Various 4-substituted phenyl-1-(10'-acetylaminophenothiazinyl)-azetidin-2-ones **(9-13)**, 1-(10'-acetylimino-phenothiazinyl)-3-substituted phenyl formazans **(14-18)** and 3-(10'- acetylamino-phenothiazinyl) -2-substituted phenyl-4-thiazolidinones **(19-23)** were synthesized by reacting 10-(various substituted phenylmethyleneimino) aminoacetylphenothiazines **(4-8)** with triethylamine / acetyl chloride, benzene diazonium chloride and thioglycolic acid / anhydrous zinc chloride, respectively. The structures of these compounds have been interpreted by elemental (C, H, N) and spectral (I.R., ^{1}H-NMR and mass) analysis. All the compounds were evaluated for their anti-inflammatory activity using rat paw oedema inhibition test and were compared with standard drugs. These compounds were also screened for acute toxicity studies. Compound **22** was the most potent compound of the series, exhibiting 82.44% oedema inhibition, interestingly more potent than the standard drug - phenylbutazone. All compounds showed ALD_{50} > 1000 mg kg $^{-1}$ p.o. except compound **22,** which exhibited ALD_{50} > 2000 mg kg $^{-1}$ p.o.

Keywords: Azetidinones, formazans, thiazolidinones, phenothiazines, anti-inflammatory agents, acute toxicity

INTRODUCTION

Phenothiazine is a heterocyclic organic compound that is related to the thiazine class. Compounds bearing phenothiazine moiety possess diverse types of biological activities viz. anti-inflammatory[1-4], anticonvulsant[5-6], antimicrobial[7-8], antitubercular[9], antipsychotic[10-11], anticancer[12], etc. Azetidinones[13-15] have been observed to exhibit anti-inflammatory properties on inflammation produced by carrageenan in albino rats. Similarly, formazans[16-19] and thiazolidinones[20-27] were also reported in recent literature as anti-inflammatory agents in various experimental models. However, these compounds possess either less activity or more side-effects, due to which they are not used clinically. Incorporating these moieties- azetidinonyl, formazanyl and thiazolidinonyl at 10-position of phenothiazine nucleus might be thought to yield more potent anti-inflammatory compounds with minimum or no side effects. Thus, incorporating these moieties together, i.e. azetidinone with phenothiazine, formazan with phenothiazine and thiazolidinone with phenothiazine may yield more potent anti-inflammatory agents with minimum side effects. The present work was, therefore, aimed at synthesizing such compounds.

MATERIALS AND METHODS

Melting points of all the newly synthesized compounds were determined in open capillaries with a Thermonic melting point apparatus and are uncorrected. T.L.C. determined the homogeneity of the newly synthesized compounds on silica gel-G. The eluent was a mixture of methanol-benzene in different proportions, and spots were located by iodine. Carbon, hydrogen and nitrogen analysis were performed on C.H.N. analyzer, Carlo Erba

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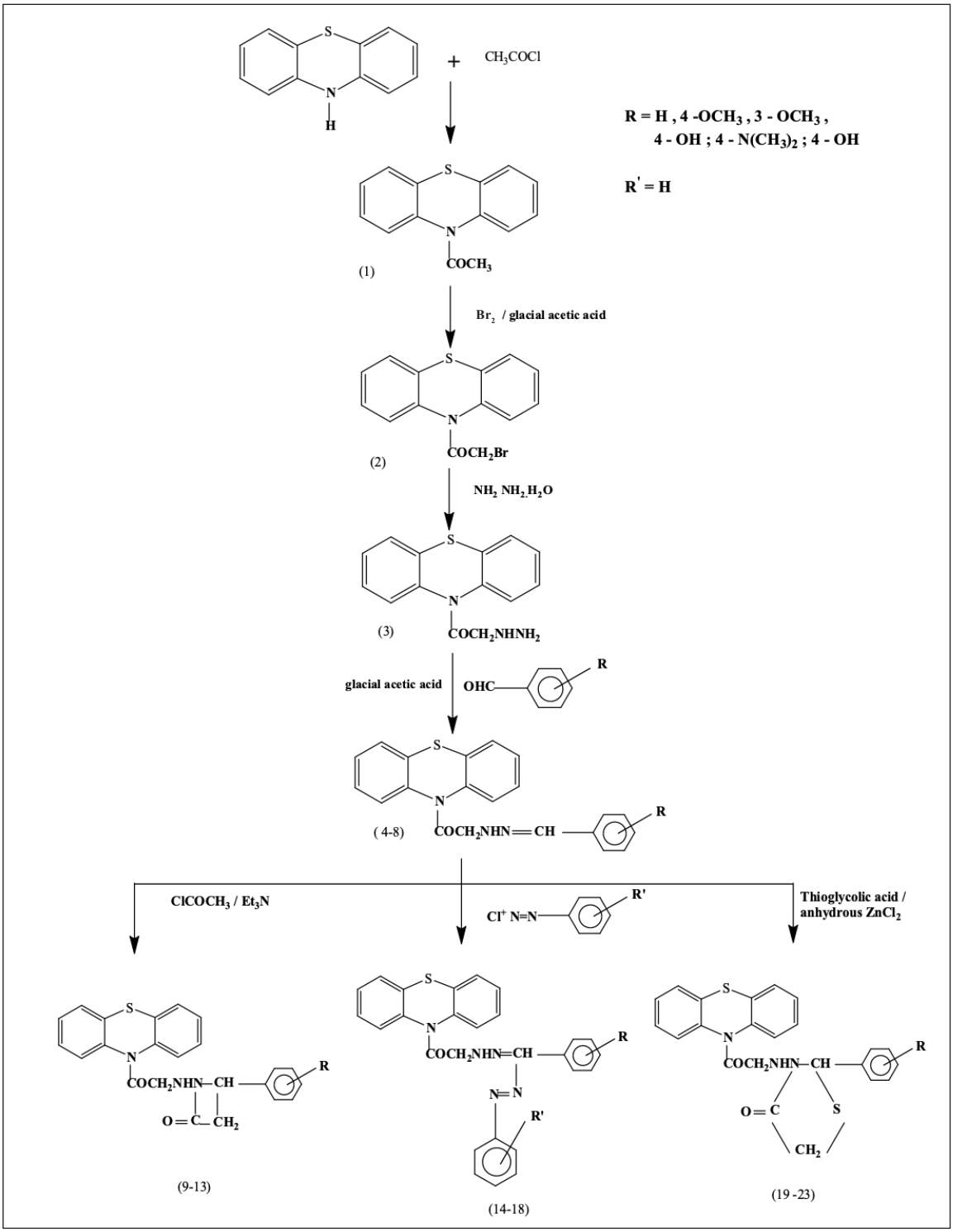
1108 analyzer. Analysies (C, H, N) were within 0.04%. The structure of the compounds was elucidated by IR, ^{1}H NMR and mass spectroscopy. The IR spectra w ere recorded on a Beckman Acculab-10 spectrophotometer (V_{max} in cm^{-1}; KBr). The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Brucker 400-FT instrument. Shimadzu 2010s mass spectrometer was used for recording mass spectra. The synthetic route for the synthesis of compounds **(1-23)** is depicted in Scheme – 1.



Scheme-1

Synthesis of 10-acetyl phenothiazine (1)

To a solution of phenothiazine (0.01 mole) in benzene (50 mL), acetyl chloride (0.01 mole) was added drop-by-drop with stirring at 0-5 ^{0}C for 1 h. The reaction mixture was stirred for 4 h at room temperature using a magnetic stirrer and kept overnight. The excess of acetyl chloride was distilled off using distillation assembly, and the residue thus obtained was washed with petroleum ether (40-60 ^{0}C) a number of times and then poured onto ice. The solid thus obtained was filtered with the help of a filtration pump and recrystallized from methanol to afford compound **1**. The physical and analytical data of compound **1** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1316 (CN), 1669 (C=O), 1610 (C-C of aromatic ring), 731 (C-S-C). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : δ 2.45 (s, 3H, $COCH_3$), 6.79-7.88 (m, 8H, Ar-H). MS : $[M]^+$ at m/z 241.

Synthesis of 10-bromoacetyl phenothiazine (2)

Bromine (0.8 mole) dissolved in acetic acid (20 mL) was added drop-wise to a solution of 10-acetyl phenothiazine (0.4 mole) in ethanol (50 mL) with constant stirring. The solid was separated to give 10-bromo acetyl phenothiazine. The solid product, which crystallizes out, was washed with water and dried. It was recrystallized from ethanol/water to give compound **2**, i.e. 10-bromoacetyl phenothiazine. The physical and analytical data of compound **2** is given in Table I. IR V_{max} (KBr, cm^{-1}): 1301 (CN), 1672 (C=O), 1613 (C-C of aromatic ring), 683 (C-S-C), 605 (C-Br). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : δ 3.40 (s, 2H, CH_2Br), 6.70-7.90 (m, 8H, Ar-H). MS : $[M]^+$ at m/z 320.

Synthesis of 10-hydrazinoacetyl phenothiazine (3)

Compound **2**, i.e. 10-bromoacetyl phenothiazine (0.4 mole), was taken in a round bottom flask, and a sufficient quantity of ethanol was added to dissolve it to make a clear solution. Hydrazine hydrate (0.4 mole) was added to the round bottom flask containing the solution. The reaction mixture was refluxed for 20-22 h. After completing the reaction, the excess solvent was distilled off, and the reaction mixture was poured onto ice. The solid that separated was recrystallized from methanol to give compound **3**, i.e. 10-hydrazinoacetonyl phenothiazine. The physical and analytical data of compound **3** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1275 (N-N)1305 (CN), 1670 (C=O), 1616 (C-C of aromatic ring), 690 (C-S-C), 3440 (NH_2), 3380 (NH). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : δ 6.60-7.95 (m, 8H, Ar-H), 5.56 (br, 1H, NH, exchangeable), 4.55 (hump, 2H, NH_2, exchangeable), 2.45 (d, 2H, $COCH_2NH$) . MS : $[M]^+$ at m/z 271.

Synthesis of 10-(phenylmethyleneimino) aminoacetyl phenothiazine (4)

A mixture of compound **3**, i.e. 10-hydrazinoacetyl phenothiazine (0.2 mole) and benzaldehyde (0.2 mole) in absolute methanol (50 mL) was refluxed for 8 h in the presence of glacial CH_3COOH (50 mL). The excess solvent was distilled off, and the residue thus obtained was washed with a mixture of diethyl ether and water in a ratio of 6:8 and finally recrystallized from benzene/hexane to furnish compound **4**. The physical and analytical data of compound **4** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1270 (N-N), 1305 (CN), 1670 (C=O), 1616 (C-C of aromatic ring), 690 (C-S-C), 3440 (NH_2), 3380 (NH). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : 8.60 (s, 1H, =CH-Ar), 4.5 (brs, 1H, >CH-NH), 2.45 (d, 2H, $COCH_2NH$), 7.20-8.65 (m, 13H, Ar-H). MS : $[M]^+$ at m/z 359.

Other compounds **(5-8)** of this step were also prepared similarly. Physical and analytical data of these compounds are given in Table I.

Synthesis of 4-phenyl-1-(10'-acetylaminophenothiazinyl)-azetidin-2-ones (9)

Compound **4,** i.e. 10-(phenylmethyleneimino) aminoacetyl phenothiazine (0.01 mole), was dissolved in N,N-dimethylformamide (DMF) in a round bottom flask. Triethylamine (0.02 mole) in dioxane (40 mL) and acetyl chloride (0.02 mole) were added dropwise to the solution in the round bottom flask with constant stirring at 0-5 ^{0}C. The reaction mixture was stirred for 5 h, and precipitated amine hydrochloride was filtered off. The filtrate received was concentrated under reduced pressure and poured onto ice-cold water. The product so obtained was recrystallized from methanol to yield compound **9**. The physical and analytical data of compound **9** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1268 (N-N), 1311 (CN), 1670 (C=O), 1580 (C-C of aromatic ring), 695 (C-S-C), 3378 (NH), 2860 (CH_2), 1760(C=O of β-lactam ring). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : 8.68 (s, 1H, -CH-Ar), 4.5 (brs, 1H, -CH_2NH), 2.45 (d, 2H, $COCH_2NH$), 7.15-8.70 (m, 13H, Ar-H) 5.20 (d, 2H, J=9Hz, CH_2 of azetidinone ring). MS : $[M]^+$ at m/z 401.

Other compounds **(10-13)** of this step were also prepared similarly. Physical and analytical data of these compounds are given in Table I.

Synthesis of 1-(10'-acetylimino phenothiazinyl)-3-phenyl formazan (14)

Aniline (0.01 mole) was dissolved in 4 mL glacial acetic acid, and 3 mL of concentrated HCl was added

Table I: Physical and analytical data of compounds 1-23

Compd. No.	R	R'	M.P. (°C)	Recryt. Solvent	Yield (%)	Molecular Formula	Calcd. (Found) %		
							C	H	N
1.	-	-	185	Methanol	78	$C_{14}H_{11}ONS$	69.71 (69.73)	4.56 (4.59)	5.81 (5.78)
2.	-	-	125	Methanol	82	$C_{14}H_{10}ONSBr$	52.50 (52.79)	3.13 (3.10)	4.38 (4.37)
3.	-	-	200	Ethanol	77	$C_{14}H_{13}ON_3S$	61.99 (62.00)	4.80 (4.78)	15.50 (15.48)
4.	H	-	180	DMF	78	$C_{21}H_{17}ON_3S$	70.19 (70.17)	4.74 4.76)	11.70 11.68)
5.	4-OCH_3	-	175	Benzene/ petroleum ether	71	$C_{22}H_{19}O_2N_3S$	67.86 (67.84)	4.88 (4.90)	10.79 (10.81)
6.	3-OCH_3, 4-OH	-	160	Ethanol	69	$C_{22}H_{19}O_3N_3S$	65.19 (65.21)	4.69 (4.72)	10.37 (10.35)
7.	4-$N(CH_3)_2$	-	170	Benzene	70	$C_{23}H_{22}ON_4S$	68.66 (68.64)	5.47 (5.50)	13.93 (13.90)
8.	4-OH	-	150	Methanol	74	$C_{21}H_{17}O_2N_3S$	67.20 (67.17)	4.53 (4.51)	11.20 (11.18)
9.	H	-	210	Toluene	68	$C_{23}H_{19}O_2N_3S$	68.83 (68.81)	4.74 (4.73)	10.73 (10.72)
10.	4-OCH_3	-	190	Acetone	66	$C_{24}H_{21}O_3N_3S$	66.82 (66.79)	4.87 (4.90)	9.74 (9.73)
11.	3-OCH_3, 4-OH	-	205	DMF	69	$C_{24}H_{21}O_4N_3S$	64.43 (64.41)	4.70 (4.68)	9.39 (9.37)
12.	4-$N(CH_3)_2$	-	185	Benzene	70	$C_{25}H_{24}O_2N_4S$	67.56 (67.53)	5.40 (5.37)	12.61 12.58)
13.	4-OH	-	200	Methanol	68	$C_{23}H_{15}O_3N_3S$	66.83 (66.81)	3.63 (3.65)	10.17 (10.20)
14.	H	H	150	Toluene	65	$C_{27}H_{22}ON_5S$	69.83 (69.80)	4.74 (4.71)	15.09 (15.07)
15.	4-OCH_3	H	180	Ethanol	69	$C_{28}H_{24}O_2N_5S$	68.02 (68.00)	4.86 (4.84)	14.17 (14.15)
16.	3-OCH_3, 4-OH	H	160	Ethanol	70	$C_{28}H_{24}O_3N_5S$	65.88 (65.85)	4.70 (4.68)	13.72 (13.69)
17.	4-$N(CH_3)_2$	H	175	Acetone	65	$C_{29}H_{27}ON_6S$	68.64 (68.62)	5.32 (5.29)	16.57 (16.55)

18.	4-OH	H	195	Methanol	68	$C_{27}H_{22}O_2N_5S$	67.50 (67.47)	4.58 (4.60)	14.58 (14.61)
19.	H	-	200	THF	64	$C_{23}H_{19}O_2N_3S_2$	63.74 (63.76)	4.39 (4.41)	9.70 (9.68)
20.	4-OCH_3	-	210	Benzene/ petroleum ether	69	$C_{24}H_{21}O_3N_3S_2$	62.20 (62.17)	4.53 (4.55)	8.77 (8.80)
21.	3-OCH_3, 4-OH	-	240	DMF/ water	70	$C_{24}H_{21}O_4N_3S_2$	60.12 (60.09)	5.24 (5.27)	11.74 (11.76)
22.	4-$N(CH_3)_2$	-	235	Chloroform	73	$C_{25}H_{25}O_2N_4S_2$	62.89 (62.91)	5.24 (5.22)	11.74 (11.76)
23.	4-OH	-	220	Methanol	66	$C_{22}H_{20}O_3N_3S_2$	60.27 (60.25)	4.67 (4.64)	9.59 (9.62)

C, H, N were found within ± 0.04 %

at 0-5 ^{0}C. A solution of sodium nitrite (1 g in 5 mL water) was then added dropwise. The diazonium salt solution thus prepared was added with constant stirring to the solution of compound **4** in toluene, and the temperature was maintained below 5 ^{0}C during addition. The reaction mixture thus obtained was left at room temperature for 2-3 days and then poured into ice-cold water. Solid separates out, which was washed, filtered and recrystallized from methanol to give compound **14**. The physical and analytical data of compound **14** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1280 (C-N), 1705 (C=O), 1612 (C-C of aromatic ring), 692 (C-S-C), 3372 (NH), 1680 (C=N), 1425 (N=N). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : 2.43 (d, 2H, $COCH_2NH$), 7.10-9.15 (m, 18H, Ar-H), 4.2 (brs, 1H, -CH_2NH). MS : $[M]^+$ at m/z 464.

Other compounds **(15-18)** of this step were also prepared similarly. Physical and analytical data of these compounds are given in Table I.

Synthesis of 3-(10'-acetylamino phenothiazinyl) -2-phenyl-4-thiazolidinone (19)

Compound **4** (0.01 mole) was dissolved in dry DMF (80 mL). The solution thus obtained was stirred, and to the stirred solution was added thioglycolic acid (0.02 mole) and a small amount of anhydrous $ZnCl_2$. The reaction mixture was refluxed for 18 h. The excess solvent was distilled off, and the resulting mixture was cooled and poured onto ice-cold water. The separated solid was filtered, washed and recrystallized with methanol to yield compound **19**. The physical and analytical data of compound **19** is given in Table I. IR V_{max} (KBr, cm^{-1}) : 1270 (N-N), 1305 (C-N), 1670 (C=O), 1580 (C-C of aromatic ring), 678 (C-S-C), 3365 (NH), 1760 (C=O of β-thialactam ring). ^{1}H NMR δ ($CDCl_3$ and DMSO-d_6) : 2.41 (d, 2H, $COCH_2NH$), 7.10-8.35 (m, 13H, Ar-H), 4.4 (brs, 1H, -CH_2NH), 6.35 (t, 1H, N-CH-Ar), 3.95 (s, 2H, CH_2 of thiazolidinone ring). MS : $[M]^+$ at m/z 464 MS : m/z.

Other compounds **(20-23)** of this step were also prepared similarly. Physical and analytical data of these compounds are given in Table I.

Pharmacological evaluation

Experiments were performed on male albino rats and mice of Charles Foster strain species. The animals were kept in groups (control, treated, standard) under constant temperature (25 ± 10 ^{0}C) and 12 h of light/dark cycle. They had free access to the standard mouse diet and tap water except during the experiment. On the experiment day, animals were transferred to individual cages randomly and allowed to acclimatize for 30 minutes before administering the drug. Phenylbutazone and indomethacin were used as standard drugs. Propylene glycol was used for dissolving the newly synthesized compounds.

Anti-inflammatory activity

The method of Winter et al.[28] was used for performing paw oedema inhibition test on albino rats. Rats were transferred to individual cages, and after 30 minutes, 0.2 mL of 1 % carrageenan suspension in 0.9 % NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw, and a water plethysmometersocrel measured the paw volume and then was measured again after 3 h. The mean increase of paw volume at each time interval was compared with that of the control group at

Table II: Pharmacological evaluation of compounds 1 to 23

Compd. No.	R	R'	Anti-inflammatory activity		ALD_{50} (mg kg^{-1} p.o.)
			Dose (mg kg^{-1} p.o.)	% oedema inhibition relative to control	
1.	-	-	50	11.12*	>1000
2.	-	-	50	15.34**	>1000
3.	-	-	50	17.67*	>1000
4.	H	-	50	22.22**	>1000
5.	4-OCH_3	-	50	24.23*	>1000
6.	3-OCH_3, 4-OH	-	50	38.70*	>1000
7.	4-$N(CH_3)_2$	-	50	43.64**	>1000
8.	4-OH	-	50	37.67*	>1000
9.	H	-	50	37.64**	>1000
10.	4-OCH_3	-	50	39.38**	>1000
11.	3-OCH_3, 4-OH	-	50	46.72**	>1000
12.	4-$N(CH_3)_2$	-	50	55.32***	>1000
13.	4-OH	-	50	44.68**	>1000
14.	H	H	50	40.98**	>1000
15.	4-OCH_3	H	50	46.32**	>1000
16.	3-OCH_3, 4-OH	H	50	52.60**	>1000
17.	4-$N(CH_3)_2$	H	50	59.56***	>1000
18.	4-OH	H	50	48.99**	>1000
19.	H	-	50	45.98**	>1000
20.	4-OCH_3	-	50	49.23**	>1000
21.	3-OCH_3, 4-OH	-	50	51.20***	>1000
22.	4-$N(CH_3)_2$	-	25 50 100	39.62** 60.48*** 82.44***	>2000
23.	4-OH	-	50	52.68***	>1000
Phenyl butazone	-	-	25 50 100	28.42 36.40 58.40	
Indomethacin	-	-	5.0 7.0 10.0	52.20 63.10 93.20	

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

the same time intervals, and per cent inhibition values were calculated by the formula given below:

% anti-inflammatory activity = 1-(Vt/Vc) x 100

where Vt and Vc are tested and control groups, respectively

Acute toxicity study

The approximate lethal dose (ALD_{50}) of compounds was determined in albino mice. The test compounds were given orally at different dose levels in groups of 10 animals. After 24 h of drug administration, per cent mortality in each group was observed and from the data obtained, ALD_{50} was calculated by the method of Smith[29].

RESULTS

Anti-inflammatory activity in rats

Random screening of compounds **(1-23)** was performed at 50 mg kg $^{-1}$ p.o. for their anti-inflammatory activity. Compound **22** was found to be the most potent compound of the series. Due to the potentiality of compound **22**, it was studied further at three graded doses of 25, 50 and 100 mg kg^{-1} p.o.

Acute toxicity

All the compounds of the present series exhibited $ALD5_{50}$ greater than 1000 mg kg $^{-1}$ p.o., thereby indicating a good safety margin. However, compound **22** exhibited ALD_{50} greater than 2000 mg kg $^{-1}$ p.o.

DISCUSSION

In this work, a number of compounds with good anti-inflammatory action were synthesized the obtained compounds were tested as anti-inflammatory agents, and the obtained results were compared with the activity shown by the standard drug. The synthesized compounds were tested at a dose of 50 mg kg^{-1} given orally, and the dose was decided by taking 1/20th of the ALD_{50} value.

All the newly synthesized compounds, i.e. compounds **(1-23)**, have been evaluated for anti-inflammatory and acute toxicity studies. After the investigation of anti-inflammatory screening (Table II), it has been noticed that the newly synthesized compounds exhibited moderate to good inhibition in the paw oedema inhibition test. The principal feature of the compounds of this series is the substitution by different heterocyclic moieties at the 10th- position of the phenothiazine nucleus. Compounds **1**, **2** and **3** of the series were tested at a dose of 50 mg kg^{-1} p.o. and showed 11.12, 15.34 and 17.67 per cent oedema inhibition relative to control. Further, the series was characterized by incorporating various substituted aldehydes in compound **3**, which lead to the synthesis of compounds (**4 - 8)**. Compounds **(4-8)** were also screened for anti-inflammatory activity and acute toxicity. All the compounds **(4-8)** exhibited moderate anti-inflammatory activity of 22.22 %, 24.23 %, 38.70 %, 43.64 % and 36.67 % having benzaldehyde, 4-methoxy benzaldehyde, 3-methoxy-4-hydroxy benzaldehyde, 4-*N, N*-dimethyl benzaldehyde and 4-hydroxy benzaldehyde substitutions, respectively.

Route-1 of the series was characterized by the addition of azetidinonyl moiety in compounds **(4-8)**, leading to the formation of compounds **(9 -13)**. These compounds exhibited an increase in per cent oedema inhibition varying from 37.64 % to 55.32 % relative to control when screened for anti-inflammatory activity. Among compounds **(9-13)**, compound **9** with phenyl ring showed the least activity of 37.64 %, whereas compound **12**, having 4-*N*, *N*-dimethyl phenyl group in its molecular framework, exhibited maximum activity of 55.32 per cent. Compounds **10**, **11** and **13** having 4-methoxy phenyl, 3-methoxy-4-hydroxy phenyl and 4-hydroxy phenyl groups exhibited 39.38%, 46.72 % and 44.68 % oedema inhibition, respectively. Furthermore, the addition of formazanyl moiety in compounds **(4-8)** via route-2 is a crucial feature of compounds **(14-18)**. These compounds were found to possess anti-inflammatory activity ranging from 40.98 % to 59.56 % at a dose of 50 mg kg^{-1} p.o. Compound **14** with phenyl group and compound **17** with 4-*N*, *N*-dimethyl group on azetidinone ring was found to possess minimum and maximum activity of 40.98 % and 59.56 %, respectively. Compounds **15**, **16** and **18** with 4-methoxy phenyl group, 3-methoxy-4-hydroxy phenyl group and 4-hydroxy phenyl groups on azetidinone ring exhibited 46.32 %, 52.60 % and 48.99 % oedema inhibition, respectively. Cyclization of compounds **(4-8)** into compounds **(19-23)** via route-3 due to incorporation of thiazolidinonyl ring is the characteristic feature of these compounds. These compounds revealed promising anti-inflammatory activity ranging from 45.98 % to 60.48 %. Compounds **19**, **20**, **21** and **23** having phenyl group, 4-methoxy phenyl group, 3-methoxy-4-hydroxy phenyl group and 4-hydroxy phenyl group at thiazolidinone ring exhibited activity of 45.98 %, 49.23 %, 51.20 % and 52.68 % oedema inhibition respectively when tested at a dose of 50 mg kg $^{-1}$ p.o. Compound **22** was found to be the most potent compound of the series having an unexpectedly high anti-inflammatory activity (60.48 %) and ALD_{50} value (>2000 mg kg $^{-1}$ p.o.). It was further investigated in detail

at three graded doses of 25 mg kg $^{-1}$ p.o., 50 mg kg^{-1} p.o. and 100 mg kg $^{-1}$ p.o. thereby exhibiting 39.62 %, 60.48 % and 82.44 % oedema inhibition, respectively.

CONCLUSION

The results of the present study indicated that all the synthesized phenothiazine derivatives exhibited anti-inflammatory activity with less toxicity. Among all the 23 compounds, compound **22** was found to significantly influence the activity, which may be due to substituents present on the ring. On analyzing the pharmacological data of the compounds of this study, it may be concluded that :

* Remarkable increase in activity was observed by introducing azetidinone ring, formazan moiety and thiazolidinone ring.
* Thiazolidinone containing compounds showed more potent compounds than their corresponding azetidinones and formazans.
* Compounds having 4-*N, N*-dimethyl phenyl group as substituent elicited the most potent anti-inflammatory activity.

The present work indicates that further clinical research on these phenothiazine derivatives can lead to the development of anti-inflammatory drugs that can be used for the clinical treatment of inflammation.

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