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SYNTHESIS OF NEW 10-SUBSTITUTED PHENOTHIAZINES AS ANTIINFLAMMATORY AND ANALGESIC AGENTS.

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ABSTRACT

Some new 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl)1'-azetidinyl} thiazol-4-yl] phenothiazines (**4a-4g**) and 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl)1'-azetidinyl}oxazol-4-yl] phenothiazines **(4a'-4g'**) have been synthesized from 2-chloro-10-[2-(substitutedphenyl) methylene aminothiazol-4-yl] phenothiazines (**3a-3g**) and 2-chloro-10-[2-(substituted phenyl) methylene aminooxazol -4-yl] phenothiazines (**3a'-3g'**) respectively. The structures of all these compounds were established on the basis of elemental (C,H,N) and spectral (IR, ^{1}H-NMR and mass spectral data) analysis. All these compounds have also been tested for their antiinflammatory, analgesic activity and acute toxicity. Compound **4a'** i.e. 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(2,6-dichloro phenyl)1'-azetidinyl} oxazol-4-yl] phenothiazine was found to possess most potent antiinflammatory activity and compound **4a** i.e. 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(2, 6-dichlorophenyl) 1'-azetidinyl} thiazol-4-yl] phenothiazine showed good analgesic activity. Furthermore, these two compounds (**4a** and **4a'**) were also screened for their ulcerogenic liability.

KEY WORDS

Methylene amino phenothiazines/ Azetidinyl phenothiazines/ Antiinflammatory activity/Analgesic activity/Acute toxicity studies.

INTRODUCTION

Substitution pattern showed that substitution at 10-position on phenothiazine nucleus plays a pivital role in modulating the biological activities, viz. anti-inflammatory [1-8], analgesic [4,9-10], anti-psychotic [11-16], cardiovascular [17-18] and fungicidal [6] activities. Moreover, thiazoles, oxazoles, and azetidinones of different heterocyclic system were found to possess potent anti-inflammatory activities [19-20]. In the light of these observations it was thought worthwhile to synthesize some new 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl)1'-azetidinyl} thiazol-4-yl] pheno- thiazines (**4a-4g**) and 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substituted phenyl)1'-azetidinyl}oxazole-4-yl] phenothiazines (**4a'-4g'**) by incorporating azetidinyl thiazolyl and azetidinyl oxazolyl moieties respectively at 10-position of phenothiazine nucleus. These compounds were evaluated for anti-inflammatory,

analgesic, ulcerogenic activity and acute toxicity.

Chemistry

Compound **1** i.e. 2-chloro-10-chloroacetyl phenothiazine was prepared by the reaction of 2-chloro phenothiazine with chloroacetyl chloride in dry benzene chloroform. Compound **1** when reacted with urea and thiourea yielded compounds **2** i.e. 2-chloro-10-(2-aminothiazol-4-yl) phenothiazine and **2'** i.e. 2-chloro-10-(2-aminooxazol-4-yl) phenothiazine respectively. These compounds **2** and **2'** on reacting with substituted aldehydes gave 2-chloro-10-[2-substituted phenyl methylene amino thiazol-4-yl]phenothiazines **3a-3g** and corresponding oxazoles **3a'-3g'** respectively. The next compounds (azetidinones) i.e. 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl)1'-azetidinyl} thiazol-4-yl] phenothiazines **4a-4g** and their oxazoles **4a'-4g'** were prepared from the compounds **3a-3g** and **3a'-3g'** respectively on treatment with chloroacetyl chloride in the presence of tri ethylamine. The synthetic pathway of the above compounds is shown in Scheme-1. The structures of these compounds were elucidated by elemental (C,N,H) analysis, IR, ^{1}H-NMR and mass spectroscopic data.

RESULT AND DISCUSSION

All the compounds and reference drug phenylbutazone have been examined for their antiinflammatory activity. Screening of all the compounds were performed at a dose of 50 mg/kg p.oThe antiinflammatory activity of the compounds (3a-3g), i.e. 2-chloro-10-[2-(substitutedphenyl) methylene aminothiazol-4-yl] phenothiazines varying from 10.82 to 27.03%. It is clear that when the compound was substituted with 2, 6-dichlorophenyl group (compound 3a, 27.03%) showed more potent antiinflammatory activity than compound which was substituted with 2, 6-dibromophenyl group (compound 3b, 16.22%) and with 2, 6-diiodophenyl group (compound 3c, 13.52%). The compounds 3d and 3e, substituted by 2-chloro and 2-bromophenyl groups respectively were less active (24.33%, 21.63%) than compound 3a but more active than 3b. However the compound 3f, which was substituted by 2-iodophenyl group was found to be less active (10.82%) than its disubstituted compound (3c), and compound 3g which was substituted by N,N-dimethyl amino phenyl exhibited promising antiinflammatory acitivity (18.92%).It is interestingly enough, the antiinflammatory activity of 2-chloro-10- [2-{3'-chloro-2'-oxo-4'-(substitutedphenyl) 1'- azetidinyl} thiazol-4-yl] phenothiazines (4a-4g) is more (ranging between 12.59 to 29.55%) than that of their parent compounds (3a-3g). Moreover, corresponding oxazoles, i.e. 2-chloro-10-[2-(substitutedphenyl) methylene aminooxazol-4-yl] phenothiazines (3a'-3g') showed a decrease in activity (9.24-25.21%) as compared to their corresponding thiazoles (3a-3g). The cyclised compounds (4a'-4g'), i.e. 2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl) 1'-azetidinyl} oxazol-4-yl] phenothiazines, very clearly showed an increase in antiinflammatory activity (14.69-48.56%) at a dose of 50 mg/kg. p.o. The compound which was substituted by 2, 6-dichlorophenyl group (4a') was more active (48.56%) than the reference drug phenylbutazone (39.2%) at 50 mg/kg. p.o. Considering the potentiality of compound 4a', it was tested at three graded doses, i.e. 25, 50 and 100mg/kg. p.o. This compound showed better aoctivity at all the three tested doses as compared to reference drug phenyl butozne. All these compounds were also screened for their analagesic activity at 50 mg/kg p.o. From the results it is clear that the compound **4a'** which exhibited better antiinflammatory activity and was associated with less analgesic activity (32.67%) than reference drug, while compound **4a** found to be most potent analgesic activity (39.68%) as compared to reference drug phenylbutazone. Compound **4a'** and reference drug were also tested for their ulcerogenic liability. Compound **4a'** possess less ulcerogenic liability than reference drug phenylbutazone.

Table-3 shows the biological activities of all the compounds.

From the above results, it may be concluded that methylene amino oxazoles **3a'-3g'** are less active than the corresponding thiazoles **3a-3g**, and azetidinones **4a-4g**, **4a'-4g'** are more active than their parent compounds.

Compound **4a'** which was substituted by 2,6-dichlorophenyl group is most active compound.

Experimental

General

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C,H,N were within ±0.4% of the theoretical values. IR spectra (cm^{-1}) were recorded on Beckman-Acculab 10 spectrophotometer. ^{1}H-NMR spectra were determined in $CDCl_3$/DMSO-d_6 on Brucker 300-FT instrument using TMS as internal reference standard. Mass spectra were determined on a VG-70-S instrument.

Chemistry

2-chloro-10-chloroacetyl phenothiazine 1To a solution of 2-chlorophenothiazine in benzene (dry, 100 mL), chloroacetyl chloride (0.02 mole) was added drop by drop for about 1 hr. with constant stirring. Then the reaction mixture was stirred vigrously for one hr. and after that refluxed for an hr. When the mixture was cooled, poured onto ice and kept at room temperature for about one week. The resulting mixture was filtered and recrystalised from methanol. M.P.189ºC, yield 86%.Molecular formula $C_{14}H_9Cl_2ONS$. The analytical data of this compound is given in table-2. IR (KBr): **ν_{max}** in cm^{-1}; 660 (C-Cl), 755 (C-C), 1135 (C-S), 1265 (C-N), 1540 (C=C of aromatic ring), 1720 (C=O), 3045 (aromatic C-H). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): **δ** in ppm; 3.45 (s,2H,-C$\underline{H}_2$Cl), 8.30-7.45 (m,7H,Ar-$\underline{H}$) MS: $[M]^+$ m/z **310.**

***2-chloro-10-(2-aminothiazol-4-yl) phenothiazine* 2** A mixture of 2-chloro-10-chloroacetyl phenothiazine (**1**) (0.01 mole), ethanol (50 ml) and thiourea (0.01 mole) was refluxed for about 6-8 hrs. and after refluxing allowed to stand it overnight. The solid thus seperated was filtered and washed with $NaHCO_3$ solution (2%) and then with water. After washing, dried and recrystallised from Methanol.M.P.167ºC, yield 80%. Molecular formula $C_{15}H_{10}S_2N_3Cl$. The analytical data of this compound is given in table-2. IR (KBr): ν_{max} in cm^{-1}; 665 (C-Cl), 750 (C-C) 1135 (C-S), 1260 (C-N), 1540 (C=C of aromatic ring), 1625 (C=N), 3040 (aromatic C-H), 3320 (NH_2) ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 6.30 (s, 2H, -N$\underline{H}_2$ exchangeable with D_2O), 7.95-6.90 (m, 8H, Ar-$\underline{H}$) MS: $[M]^+$ m/z 331.

***2-chloro-10-(2-aminooxazol-4-yl) phenothiazine* 2'** A mixture of 2-chloro-10-chloroacetyl phenothiazine (**1**) (0.01 mole), ethanol (50 mL) and urea (0.01 mole) was refluxed for about 6-8 hrs. allowed it to stand overnight. The separated solid was filtered and washed with 2% solution of $NaHCO_3$ and then with water, dried and recrystallised from ethanol/water. M.P. 225ºC, yield 72% Molecular Formula $C_{15}H_{10}N_3SOCl$. The analytical data of the compound is given in table-2. IR (KBr): ν_{max} in cm^{-1}; 660(C-Cl) , 755 (C-C), 1065 (C-O-C), 1145 (C-S), 1265 (C-N), 1535 (C=C of aromatic ring), 1615 (C=N), 3045 (aromatic C-H), 3320 (NH_2). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 6.30 (s, 2H, -N$\underline{H}_2$ exchangeable with D_2O), 7.95-6.95 (m, 8H, Ar-$\underline{H}$) MS:$[M]^+$ m/z 315.

***2-chloro-10-[2-(substitutedphenyl) methylene aminothiazol-4-yl] phenothiazines* 3a-3g** To a solution of 2-chloro-10-(2-aminothiazol-4-yl)phenothiazine (**2**) (0.01 mole) and proper benzaldehyde (0.01 mole) in ethanol (50mL) and few drops of and glacial acetic acid were added. The mixtures were heated under reflux for about 15-20 hrs. The solvents were distilled off and the residues were washed with pet. ether, and recrystallised from suitable solvents. Compounds **3a-3g** were prepared starting from 2,6-dichloro benzaldehyde, 2,6-dibromobenzaldehyde, 2,6-diiodobenzaldehyde, 2-chlorobenzaldehyde, 2-bromobenzaldehyde, 2-iodobenzaldehyde, N,N-dimethylaminobenzaldehyde respectively. The physical and analytical data of these compounds **3a-3g** are given in tables-1 and 2. Compound **3a** ($C_{22}H_{12}N_3Cl_3S_2$): IR (KBr): ν_{max} in cm^{-1}; 675(C-Cl) , 755 (C-C), 1140 (C-S), 1260 (C-N), 1535 (C=C of aromatic ring), 1550 (C=N), 3060 (aromatic C-H). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 7.75-6.40 (m, 11H, Ar-$\underline{H}$), 8.3 (s, 1H, N=C$\underline{H}$-Ar). MS:$[M]^+$m/z 488.

2-chloro-10-[2-(substitutedphenyl) methylene aminooxazol-4-yl] phenothiazines 3a'-3g' To a solution of 2-chloro-10-(2-aminooxazol-4-yl) phenothiazine (**2'**) (0.01 mole) and appropriate benzaldehyde (0.01 mole) in ethanol (50mL) and few drops of and glacial acetic acid were added. The mixtures were refluxed for about 15-20 hrs. Now the reaction mixtures were cooled, filtered and the residues were washed with $NaHCO_3$ solution (2%) and then with water, dried and recrystallised from suitable solvents to give compounds **3a'-3g'**. The physical and analytical data of all these compounds are given in tables-1 and 2. Compound **3a'** ($C_{22}H_{12}N_3Cl_3OS$): IR (KBr): ν_{max} in cm^{-1}; 670(C-Cl) , 750 (C-C), 1070 (C-O-C),1140 (C-S), 1265 (C-N), 1530 (C=C of aromatic ring), 1545 (C=N), 3040 (aromatic C-H). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 7.75-6.45 (m, 11H, Ar-H), 8.2 (s, 1H, N=CH-Ar). MS: $[M]^+$m/z 472

***2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl) 1'-azetidinyl} thiazol-4-yl] phenothiazines* 4a-4g** In the solution of compounds **3a-3g** i.e. 2-chloro-10-[2-(substitutedphenyl) methylene aminothiazol-4-yl] phenothiazines (0.01 mole) and chloroacetyl chloride (0.02 mole) in benzene (dry 50 mL), triethylamine (3-4 drops) was added dropwise, constantly stirred for one hr. The reaction mixtures were more stirred by magnetic stirrer for about 4 hrs. and refluxed for one hr. The reaction mixture was cooled and then poured into ice cold water, filtered and recrystallised from proper solvents giving compounds **4a-4g**. The physical and analytical data of all these compounds are given in tasbles-1 and 2. Compound **4a** ($C_{24}H_{13}N_3S_2Cl_4O$): IR (KBr): ν_{max} in cm^{-1}; 665(C-Cl) , 760 (C-C), 1145 (C-S), 1260 (C-N), 1530 (C=C of aromatic ring), 1545 (C=N), 1710 (C=O), 3045 (aromatic C-H). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 4.65 (d,1H,CH-N), 6.40 (d,1H,CH-Cl), 7.75-6.55 (m, 11H, Ar-H). MS:$[M]^+$ m/z 565

***2-chloro-10-[2-{3'-chloro-2'-oxo-4'-(substitutedphenyl) 1'-azetidinyl}oxazol-4-yl] henothiazines* 4a'-4g'** In the solution of compounds **3a'-3g'** i.e. 2-chloro-10-[2-(substitutedphenyl) methylene aminooxazol-4-yl] phenothiazines (0.01 mole) and chloroacetyl chloride (0.02 mole) in benzene (dry 50 mL), triethyl amine (3-4 drops) was added dropwise with constant stirring for one hr. The reaction mixtures were more stirred by magnetic stirrer for about 4-5 hrs. and refluxed for two hr., cooled and then poured into ice cold water. The solids thus obtained were filtered and recrystallised from suitable solvents to give compounds **4a'-4g'**. Their physical and analytical data are given in tables-1 and 2. Compound **4a'**($C_{24}H_{13}N_3SCl_4O_2$): IR (KBr): ν_{max} in cm^{-1}; 670 (C-Cl) , 760 (C-C), 1070 (C-O-C), 1145 (C-S), 1260 (C-N), 1530 (C=C of aromatic ring), 1545 (C=N), 1710 (C=O), 3045 (aromatic C-H). ^{1}H-NMR ($CDCl_3$+DMSO-d_6): δ in ppm; 4.65 (d,1H,CH-N), 6.40 (d,1H,CH-Cl), 7.75-6.50 (m, 11H, Ar-H). MS:$[M]^+$ m/z 549

Biological Study

All the synthesised compounds were evaluated for anti-inflammatory activity against albino rats of either sex, excluding pregnant females. These compounds were also examined for analgesic, ulcerogenic activity and acute toxicity.

Anti-inflammatory activity Preliminary study at all the three tested doses (25,50,100, mg/kg) were compared with standard drug, phenyl butazone. These compounds were administered either by oral or intraperitoneal route. Rats of either sex weighing 60-110 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 al. [21]. 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 hr before the carrageenin injection. The volume of foot was measured before one and 3 hour after carrageenin treatment with the help of a plethysmometer. The percent anti-inflammatory activity was calculated according to the formula given below–

Percentage of inhibition of oedema = $(1–V_t/V_c) \times 100$

Where V_t and V_c 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. [22]. 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 hr 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.

Ulcerogenic Activity Ulcerogenic activity of all these compounds were checked by the method of Djahanguiri [23]. Adult albino rats of either sex were divided into group of 10 animals each. Pregnancy was excluded in the female rats and they were fasted 24 hours prior to the administration of drugs. Water was allowed at libitum to the animals. The compounds (which have shown the promising anti-inflammatory activity) and phenyl butazone were given intraperitoneally and the animals sacrificed 8 hours after drug treatment. The stomach, duodenum and jejunum were removed and examined for any evidence of shedding of epithelium, red spots below skin and bleeding and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Acute Toxicity Study Approximate 50% lethal dose (ALD_{50}) of the promising compounds was determined in albino mice. The drugs were injected by intraperitoneal (i.p.) route at different dose levels in separate groups of animals. After 24 hours of drug administration, percent mortality in each group was observed. From the data obtained, ALD_{50} was calculated by the method of Smith [24]

Table – 1

Physical data of compounds 3a-3g, 4a-4g, 3a'-3g', 4a'-4g'.

Comp.	R	M.P. [°C]	Yield [%]	Recrystallize solvent	Molecular formula
3a	2,6-$(Cl)_2C_6H_3$	198	48	ethanol/ water	$C_{22}H_{12}N_3Cl_3S_2$
3b	2,6-$(Br)_2C_6H_3$	193	42	benzene	$C_{22}H_{12}N_3S_2Br_2Cl$
3c	2,6-$(I)_2C_6H_3$	182	43	ethanol	$C_{22}H_{12}N_3S_2I_2Cl$
3d	2-Cl-C_6H_4	184	47	methanol/water	$C_{22}H_{13}N_3S_2Cl_2$
3e	2-Br-C_6H_4	179	49	acetone	$C_{22}H_{13}N_3S_2BrCl$
3f	2-I-C_6H_4	176	45	benzene/hexane	$C_{22}H_{13}N_3S_2ICl$
3g	4-$N(CH_3)_2$-C_6H_4	187	44	methanol	$C_{24}H_{19}N_4S_2Cl$
4a	2,6-$(Cl)_2C_6H_3$	237	32	ethanol/water	$C_{24}H_{13}N_3S_2Cl_4O$
4b	2,6-$(Br)_2C_6H_3$	232	27	benzene/pet.ether	$C_{24}H_{13}N_3S_2Br_2Cl_2O$
4c	2,6-$(I)_2C_6H_3$	223	28	ethanol	$C_{24}H_{13}N_3S_2I_2Cl_2O$
4d	2-Cl-C_6H_4	230	25	acetic acid	$C_{24}H_{14}N_3S_2Cl_3O$
4e	2-Br-C_6H_4	221	32	methanol/water	$C_{24}H_{14}N_3S_2BrCl_2O$

4f	2-I-C_6H_4	212	34	ethanol/water	$C_{24}H_{14}N_3S_2ICl_2O$
4g	4-N$(CH_3)_2$-C_6H_4	228	29	acetone	$C_{26}H_{20}N_4S_2Cl_2O$
3a'	2,6-$(Cl)_2C_6H_3$	188	47	ethanol	$C_{22}H_{12}N_3Cl_3SO$
3b'	2,6-$(Br)_2C_6H_3$	183	49	ethanol/water	$C_{22}H_{12}N_3Br_2SClO$
3c'	2,6-$(I)_2C_6H_3$	178	45	methanol	$C_{22}H_{12}N_3I_2SClO$
3d'	2-Cl-C_6H_4	181	52	acetone	$C_{22}H_{13}N_3Cl_2SO$
3e'	2-Br-C_6H_4	175	51	acetic acid	$C_{22}H_{13}N_3BrSClO$
3f'	2-I-C_6H_4	172	48	ethanol	$C_{22}H_{13}N_3ISClO$
3g'	4-N$(CH_3)_2$-C_6H_4	185	54	benzene/pet.ether	$C_{24}H_{19}N_4SClO$
4a'	2,6-$(Cl)_2C_6H_3$	231	34	ethanol	$C_{24}H_{13}N_3SCl_4O_2$
4b'	2,6-$(Br)_2C_6H_3$	226	31	methanol/water	$C_{24}H_{13}N_3SBr_2Cl_2O_2$
4c'	2,6-$(I)_2C_6H_3$	220	35	acetic acid	$C_{24}H_{13}N_3SI_2Cl_2O_2$
4d'	2-Cl-C_6H_4	229	38	methanol	$C_{24}H_{14}N_3SCl_3O_2$
4e'	2-Br-C_6H_4	218	36	benzene	$C_{24}H_{14}N_3SBrCl_2O_2$
4f'	2-I-C_6H_4	210	32	ethanol/water	$C_{24}H_{14}N_3SICl_2O_2$
4g'	4-N$(CH_3)_2$-C_6H_4	224	31	acetone	$C_{26}H_{20}N_4SCl_2O_2$

Table-2

Analytical data of compounds 1,2,2', 3a,-3g, 4a-4g, 3a'-3g', 4a'-4g'.

Comp.	R	Elemental analysis					
		C%		H%		N%	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
1	-	54.19	54.20	2.90	2.89	4.51	4.50
2	-	54.29	54.36	3.01	3.02	12.66	12.62
2'	-	57.05	54.94	3.16	3.15	13.31	13.33
3a	2,6-$(Cl)_2C_6H_3$	54.04	54.13	2.46	2.45	8.59	8.61
3b	2,6-$(Br)_2C_6H_3$	45.71	45.76	2.07	2.06	7.27	7.28
3c	2,6-$(I)_2C_6H_3$	39.31	39.26	1.78	1.79	6.25	6.24
3d	2-Cl-C_6H_4	58.14	58.02	2.86	2.85	9.25	9.23
3e	2-Br-C_6H_4	52.95	53.02	2.60	2.61	8.42	8.40
3f	2-I-C_6H_4	48.39	48.42	2.38	2.39	7.69	7.70
3g	4-N$(CH_3)_2$-C_6H_4	62.27	62.19	4.10	4.11	12.10	12.09

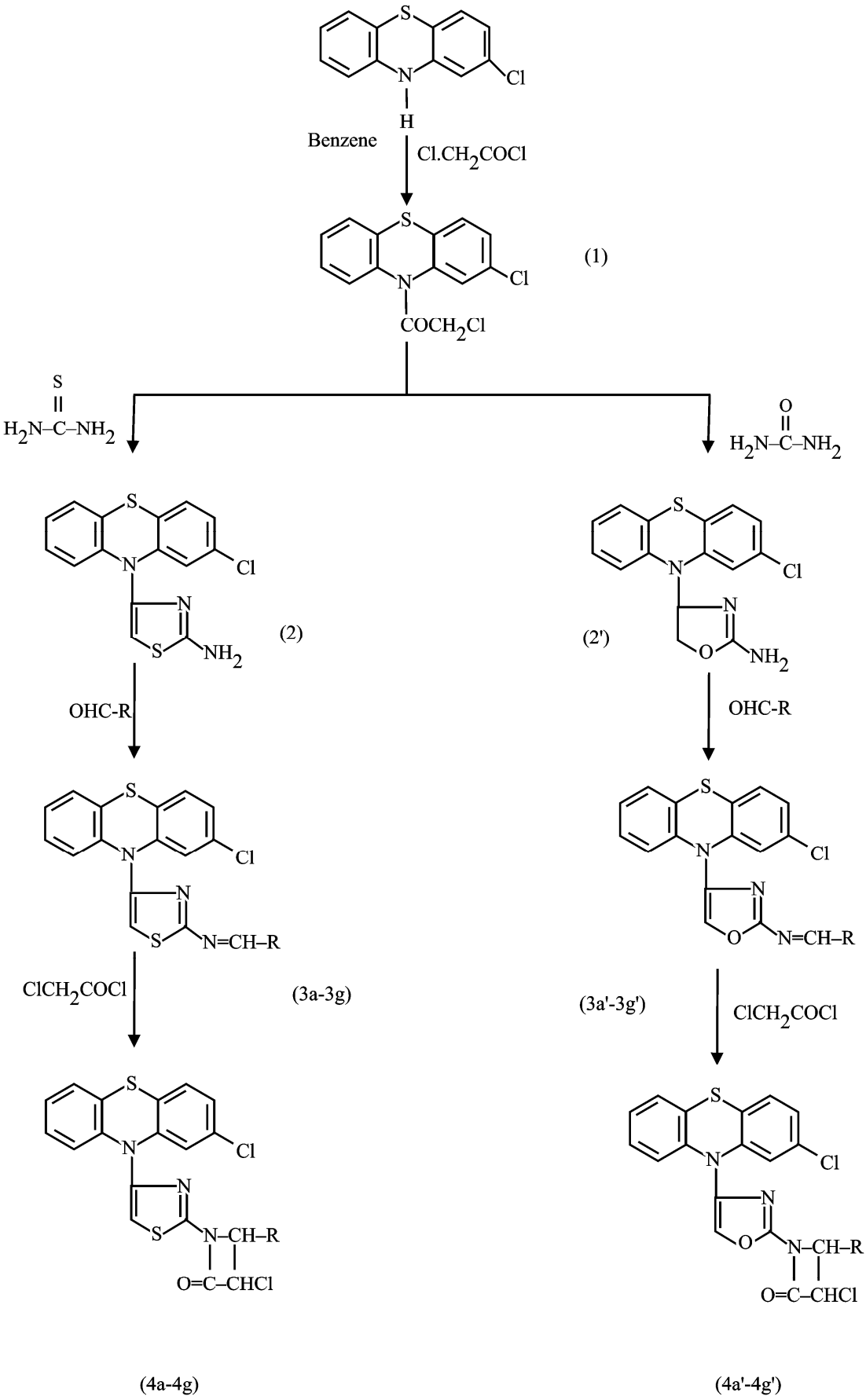
4a	2,6-$(Cl)_2C_6H_3$	50.97	51.11	2.30	2.31	7.43	7.42
4b	2,6-$(Br)_2C_6H_3$	44.03	44.12	1.98	1.99	6.42	6.44
4c	2,6-$(I)_2C_6H_3$	38.50	38.39	1.73	1.72	5.61	5.60
4d	2-Cl-C_6H_4	54.28	54.42	2.64	2.63	7.91	7.89
4e	2-Br-C_6H_4	50.08	50.13	2.43	2.42	7.30	7.31
4f	2-I-C_6H_4	46.30	46.21	2.25	2.26	6.75	6.77
4g	4-$N(CH_3)_2$-C_6H_4	57.88	57.76	3.71	3.70	10.38	10.37
3a'	2,6-$(Cl)_2C_6H_3$	55.87	55.95	2.53	2.52	8.88	8.90
3b'	2,6-$(Br)_2C_6H_3$	47.01	47.09	2.13	2.12	7.47	7.46
3c'	2,6-$(I)_2C_6H_3$	40.27	40.18	1.83	1.84	6.40	6.41
3d'	2-Cl-C_6H_4	60.27	60.12	2.96	2.95	9.58	9.60
3e'	2-Br-C_6H_4	54.71	54.68	2.69	2.70	8.70	8.68
3f'	2-I-C_6H_4	49.85	49.93	2.45	2.46	7.93	7.95
3g'	4-$N(CH_3)_2$-C_6H_4	64.50	44.61	4.25	4.24	12.54	12.52
4a'	2,6-$(Cl)_2C_6H_3$	52.45	52.53	2.36	2.37	7.65	7.67
4b'	2,6-$(Br)_2C_6H_3$	45.14	15.21	2.03	2.02	6.58	5.57
4c'	2,6-$(I)_2C_6H_3$	39.34	39.27	1.77	1.76	5.73	5.72
4d'	2-Cl-C_6H_4	55.97	56.04	2.72	2.71	8.16	8.18
4e'	2-Br-C_6H_4	51.52	51.42	2.50	2.51	7.51	7.53
4f'	2-I-C_6H_4	47.52	47.48	2.31	2.30	6.93	6.91
4g'	4-$N(CH_3)_2$-C_6H_4	59.65	59.61	3.82	3.83	10.70	10.73

Table-3

Biological activities of compounds 3a-3g, 4a-4g, 3a'3g', 4a',4g'.

Comp.	R	Anti-inflammatory activity		Analgesic activity		Ulcerogenic liability (UD_{50}) [mg/kg i.p.]	ALD_{50}
		Dose [mg/kg p.o.]	% Inhibition of oedema	Dose [mg/kg p.o.]	% Protection		
3a	2,6-$(Cl)_2C_6H_3$	50	27.03	50	25.86	-	>800
3b	2,6-$(Br)_2C_6H_3$	50	16.22	50	15.42	-	>800
3c	2,6-$(I)_2C_6H_3$	50	13.52	50	12.98	-	>800
3d	2-Cl-C_6H_4	50	24.33	50	23.17	-	>800
3e	2-Br-C_6H_4	50	21.63	50	19.75	-	>800
3f	2-I-C_6H_4	50	10.82	50	11.39	-	>800
3g	4-$N(CH_3)_2$-C_6H_4	50	18.92	50	17.24	-	>800
4a	2,6-$(Cl)_2C_6H_3$	50	29.55	50	39.68	-	>800
4b	2,6-$(Br)_2C_6H_3$	50	18.46	50	16.87	-	>800

4c	2,6-$(I)_2C_6H_3$	50	12.59	50	10.39	-	>800
4d	2-Cl-C_6H_4	50	25.85	50	23.49	-	>800
4e	2-Br-C_6H_4	50	22.73	50	20.85	-	>800
4f	2-I-C_6H_4	50	14.68	50	13.18	-	>800
4g	4-$N(CH_3)_2$-C_6H_4	50	19.95	50	17.75	-	>800
3a'	2,6-$(Cl)_2C_6H_3$	50	25.21	50	23.51	-	>800
3b'	2,6-$(Br)_2C_6H_3$	50	14.68	50	13.15	-	>800
3c'	2,6-$(I)_2C_6H_3$	50	9.24	50	7.89	-	>800
3d'	2-Cl-C_6H_4	50	23.12	50	21.74	-	>800
3e'	2-Br-C_6H_4	50	19.65	50	17.36	-	>800
3f '	2-I-C_6H_4	50	12.14	50	10.78	-	>800
3g'	4-$N(CH_3)_2$-C_6H_4	50	18.18	50	16.64	-	>800
4a'	2,6-$(Cl)_2C_6H_3$	25 50 100	35.93 48.56 71.42	25 50 100	24.38 32.67 58.42	124.6	>1000
4b'	2,6-$(Br)_2C_6H_3$	50	22.43	50	20.29	-	>800
4c'	2,6-$(I)_2C_6H_3$	50	14.69	50	11.98	-	>800
4d'	2-Cl-C_6H_4	50	27.95	50	26.47	-	>800
4e'	2-Br-C_6H_4	50	25.14	50	23.85	-	>800
4f'	2-I-C_6H_4	50	18.04	50	16.76	-	>800
4g'	4-$N(CH_3)_2$-C_6H_4	50	24.31	50	23.08	-	>800
Phenyl butazone		25 50 100	15.3 39.2 65.8	25 50 100	13.70 37.18 62.34	66.6	


Benzene
Cl.CH2COCl
(1)
COCH2Cl
H2N–C(=S)–NH2
H2N–C(=O)–NH2
(2)
(2')
OHC-R
N=CH–R
ClCH2COCl
(3a-3g)
(3a'-3g')
N–CH–R
O=C–CHCl
(4a-4g)
(4a'-4g')

Scheme-I

REFERENCES

[1] M. Verma, V.R. Gujrati, A.K. Saxena, K. Shanker, Indian J. Chem. **1981**, 58(11), 1119.

[2] E. Bansal, A. Kumar, Orient J. Chem. **1999**, 15, 489-494.

[3] A. Kumar, T. Ram, B.Goel, E. Bansal, V.K. Srivastava, Boll Chim Farm. **1998**, 137, 152-156.

[4] S. Mishra, S.K. Srivastava, S.D. Srivastava, Indian J.Chem. **1997**, 36B, 826-830.

[5] M.K. El – said, S.M. El – Moghazy Aly, F.A. Romeih, F.F. Barsom, A.B. Hassan, Egypt J. Pharm. Sci. **1991**, 32(1-2), 251-261.

[6] J. Jain, S.Srivastava, S.Kumar, Indian J. Chem. **1994**, 71(11), 691-692.

[7] A. Kumar, R.S. Verma, K.K. Saxena, V.K. Srivastava, Indian J. Chem. **1994**, 71(10), 641-642.

[8] R. Tilak, R. Tyagi, B. Goel, K.K. Saxena, V.K. Srivastava, A.Kumar, Indian Drugs, **1998**, 35(4), 216-221.

[9] C.R. Courvoisier, Soc. Biol. 151, 1378 (1957), Jacob Robert, U.S. Pat. 2,837, 518 (1958 to Rhonepoulene); M.I. **1976** 9th Ed., 782.

[10] Y.S. Sadanadan, P. Leelavathi, Indian J. Chem. **1991**, 30B(1), 85.

[11] R.J. Baldessarini, Goodman and Gilman's, Pergamon Press, Maxwell Macmillan Internal, **1992**, Vol. I, 8th Ed., 386-401.

[12] R.J. Baldessarini, Goodman and Gilman's, The pharmacological basis of therapeutics, **2001**, 10th ed., 447-484.

[13] V. Singh, R.Khanna, V.K. Srivastava, G. Palit, K. Shanker, Arzenium forsch. **1992**, 42(3), 277-280.

[14] N. Jaiswal, R.K. Jaiswal, J.P. Barthwal, K. Kishor, Indian J. Chem. **1981**, 20B(3), 252-253.

[15] C. Corral, J. Lizzavetzky. G. Quintanilla, J. Heterocycl. Chem. **1978**, 15(6), 969-975.

[16] J.A.J. Den Hartog, G.M. Visser, B.J. Van Steen, M.T.M. Tulp, E. Roneken, C.G. Kruse, J.H.M. Lange, Chem. Abstr. **1999**,131(11), 144595u.

[17] A. Kumar, S.Gurtu, J.C. Agarwal, J.N. Sinha, K.P. Bhargava, K. Shanker, Indian J. Chem. **1983**, 60, 609-610.

[18] J. Gante, H.E. Rajunz, Orth. Dieter. Schilp. Hans. Jochen. Schorscher Ernst (Merck Patent G.m.b.H.), Ger. Offen, 2,917, 650 (Cl.CO7D 417/06), 13 Nov. 1980, Appl. 02 May (1979).

[19] A. Kumar, C.S. Rajput, S.K. Bhati, Bioorganic Med. Chem, **2007**, 15, 3089-3096.

[20] I.P. Singh, S. Gurtu, A.Kumar, J.N. Sinha, K.P. Bhargava, K. Shanker, Archiv. der Pharmazie, **1984**, 317, 904.

[21] C.A. Winter, E.A. Risley, G.W. Nuss, Proc. Soc. Exp. Biol. **1962**, 111, 544-550.

[22] B.A. Berkowitz, A.D. Finck, S.H. Ngai, J. Pharmacol. Exp. Ther. **1977**, 203, 539-547.

[23] B. Djahanjuiri J. Pharm. Pharmacol, **1969**, 21, 341-345.

[24] Q.E. Smith, Pharmacological Screening Test Progress in Medicinal Chemistry. I, Butterworths, London **1960**, 1-33.