ISSN 0976 – 3333

Available Online at www.ijpba.info

International Journal of Pharmaceutical & Biological Archives 2013; 4(2): 315 - 322

ORIGINAL RESEARCH ARTICLE

Several New Substituted Azetidinonyl and Thiazolidinonyl Quinazolon-4(3H)-Ones as their Anti-Inflammatory Activities

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Received 22 Dec 2012; Revised 18 Mar 2013; Accepted 29 Mar 2013

ABSTRACT

Synthesis of 2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazole-3-ylthio)-N-(substi-tutedbenzylidene) acetohydrazides **(5a-5l)**, Synthesis of 2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio]-N-(substituted benzylidene)-4-oxothiazolidin-3-yl) acetamides **(6a-6l)** and Synthesis of 2-[5-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio]-N-(3-chloro-2-(substitutedphenyl)-4-oxo azetidin-1-yl) acetamides **(7a-7l).** The active compounds of this series **6g** and **7g** were found to possess more potent anti-inflammatory activity in the comparison of phenyl butazone. The compound **6g** have shown 40.69% of inhibition of oedema. The compound **5a,** has shown least activity i.e, 10.12%. The compound **(6g)** and **(7g)** have shown the better anti-inflammatory activity i.e. 40.69 and 45.76% at a dose of 50 mg./kg.p.o. as compared to phenyl butazone at three graded doses.

Key words: Azetidinoyl, Thiazolidinoyl Derivatives, Anti-inflammatory activity.

INTRODUCTION

Recently quinazolinone nucleus has gained prominence due to the fact that this moiety contains potent anti-inflammatory (Srivastava *et al*., 2009) anti-bacterial (Alagarsamy *et al*., 2003) cardiovascular (Heiker *et al*., *et al*., 1996) agents, hypnotic (Abdal-Alim *et al*., 1993) and anti-convulsant (Abdal-Alim *et al*., 1993) biological properties. Besides, its effects on various enzyme system of the body especially those which are intimately concerned with the normal function of the central nervous system as well as cardiovascular system. Furthermore, it has been delineated that this hetero system possess variable sites (2 & 3 position) which can be suitable modified by the introduction of different pharmacophoric groups to yield useful anti-inflammatory agent which can fulfill the theoretical requirements of the drug designed. It is therefore, our contention to synthesize some quinazolinone derivatives by incorporating triazole ring at 3rd position of this nucleus. Compound **(1)** prepared according to the method of Bogert et al **(1907)**.Compound **(1)** when reacted with 6-bromo-2-methyl-4H-benzo[d] [1,3] oxazin in dry pyridine yielded compound **(2)**. Reaction of compound **(2)** with chloro acetyl chloride in dry THF to gives compound **(3)**. The later compound on reaction with hydrazine hydrate in absolute ethanol resulted into the formation of compound **(4)**. Furthermore, compound **(4)** reacted with substituted benzaldehyde in methanol to yield compound **(5a-5I)**. Compound **(6a-6I),** were synthesized by cyclo-condensation of (**5a-5I)** with thioglycolic acid in the presence of anhydrous $ZnCI_2$, while **(7a-7I)** were prepared by cycloaddition of **(5a-5I)** with chloroacetylchloride in the presence of triethylamine.

MATERIALS AND METHODS

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried borosil glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. The progress of the reaction is monitored by TLC and product are purified through recrysttalization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G

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coated plate of 0.5 mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions, and spots were visualized under iodine chamber. The IR spectra were recorded on Perkin Elmer 881 FTIR spectrophotometer (ν_{max} in cm^{-1}). The ^{1}H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Brucker DRX-400/300 FTNMR instrument. Mass spectra were determined on JEOL JMS-D-300 instrument.

5-Bromo anthranilic acid:

It was prepared according to the method of wheeler (1910) M.P. 218ºC, yield 50%, wheeler (lit. cit) reported M.P. 210º C, yield 60%.

Acetanthranil or Benzoxazinone:

6-Bromo-2-methyl-4H-benzo [d] [1,3] oxazin-4-one (1).

These were prepared according to the method of Bogert *et.al*.(1907). A mixture of 5-bromo anthranilic acid (0.01 mole) and acetic anhydride (0.02 mole) was refluxed for 2-3 hr. with occasional stirring. The excess of acetic anhydride was distilled off. On cooling, a solid separated out, which was filtered washed with petroleum ether (40º) and dried in vacuo. The acetanthranil thus synthesized is given below:

Compound	M.P. ºC	Yield
6-Bromoacetanthranils	178	85

6-Bromo-3-(5-mercapto-4H-1,2,4-triazole-3-yl)-2-methyl quanazolin-4(3H)-one (2).

To a solution of 5-amino-4H-1,2,4-triazole-3-thiol (0.01 mole) in dried Pyridine (100 ml.) 6-bromo-2-methyl-4H-benzo[d][1,3] oxazin-4-one (0.02 mole) was added. The reaction mixture was refluxed separately for 6-8 hr. Excess of solvent was removed and the residue was neutralized with HCl. The solid separated out, filtered, washed and recrystallized from methanol. Compound 2: M.P: 216º C, yield 87%, mol. formula: $C_{11}H_8SN_5$ OB. Elemental analysis % Calcd. C, H, N 39.07, 2.38, 20.71 Found 39.25, 2.40, 20.54, IR (KBr) □ $\nu_{max.}$ in cm^{-1} : 3358 (N-H of triazole), 3045(C-H of Ar-H), 2920 (CH_3, C-H Stretching), 1625 (C=O of quinazolinone), 1562 (C⎓C of aromatic ring), 1485 (N-N), 735 (C-Br).^{1}H-NMR ($CDCl_3$) δ in ppm.: 10.23 (s,1H,SH exchangeable with D_2O), 9.67 (s,1H,NH of triazole ring, exchangeable with D_2O), 7.97-7.42 (m,3H,Ar-H), 1.82 (s,3H,CH_3).MS: $[M]^+$ at m/z 338.

2-(5-(6-Bromo-2-methyl-4-oxaquinazolin-3(4H)-1,2,4-triazole-3-ylthio) acetyl chloride (3).

6-Bromo-3-(5-mercapto-4H-1,2,4-triazole-3-yl)-2-methyl quinazolin-4(3H)-one (0.01 mole) in dry THF (100 ml.) was added a solution of chloro acetyl chloride (0.02 mole) in dry THF (200 ml.) at OºC drop by drop along with manual stirring for 2hr. The reaction mixture was further stirred for 2-4 hr. on the mechanical stirrer and excess of solvent was distilled off, cooled and poured onto ice. The solid thus obtained, filtered and recrystallized from methanol.Compound (3) M.P.: 225ºC, yield: 82%, mol. formula: $C_{13}H_9S_5$ - O_2ClBr.Elemental analysis % Calcd. C, H, N 37.99, 2.18, 16.88 Found 37.84, 2.20, 16.97, IR (KBr) □ $\nu_{max.}$ in cm^{-1} : 3357 (N-H), 3046 (C-H of Ar-H), 2932 (CH_3,C-H stretching), 1632 (C=O of quinazolinone), 1620 (C=N), 1553 (C⎓C of aromatic ring), 1487 (N-N), 732 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm: 9.68 (s, 1H, NH of triazole ring exchangeable with D_2O), 7.91–7.40 (m, 3H, Ar-H), 2.68 (s, 2H, -CH_2CO-), 1.85 (s, 3H, CH_3) MS: $[M]^+$ at m/z 415.

2-(5-(6-Bromo-2-methyl-4-oxaquinazolin-3 (4H)-yl)-4H-1,2,4-triazole-3-ylthio) acetohydrazide (4).

2-(5-(6-Bromo-2-methyl-4-oxaquionazolin-3(4H)-1,2,4-triazole-3-ylthio) acetyl chloride (0.01 mole) and hydrazine hydrate (99 %) (0.01 mole) in absolute ethanol (50 ml.) was refluxed for 10-12 hr. and the completion of reaction were monitored by TLC. The excess of solvent was distilled off. The reaction mixture was poured onto ice; the product thus obtained was recrystallized by ethanol. Compound (4) M.P. : 234ºC, yield : 77%, mol. formula : $C_{13}H_{12}SN_7$ O_2Br, Elemental analysis % Calcd. C, H, N 38.06, 2.95, 23.89 Found 37.82, 2.98, 23.96, IR (KBr) □ $\nu_{max.}$ in cm^{-1} : 3355 (N-H), 3052 (C-H of Ar-H), 2924 (CH_3,C-H stretching), 1650 (C=O), 1625 (C=N), 1555 (C⎓C of aromatic ring), 1495 (N-N), 1238 (C-N), 743 (C-Br). ^{1}H-NMR ($CDCl_3$) δ in ppm.: 9.64 (s,1H, NH of triazole ring exchangeable with D_2O) 7.92-7.41 (m,3H,Ar-H), 4.45 (s, 2H, $NHNH_2$), 3.12 (hump.1H,CONH exchangeable with D_2O), 2.70 (s,2H,SCH_2CO), 1.90 (s,3H,CH_3). MS: $[M]^+$ at m/z 410.

2-(5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazole-3-ylthio)-N-(2-chloro benzylidene) acetohydrazide (5a).

A mixture of 2-(5-(6-Bromo-2-methyl-4-oxo quinazolin-3 (4H)-yl)-4H-1,2,4-triazole-3-ylthio) acetohydrazide (0.01 mole) and 2-chloro benzaldehyde (0.01 mole) in methanol (50 ml.)

were refluxed for 7hr, in the presence of few drops of glacial acetic acid. The progress and completion of reaction were checked by TLC. The reaction was distilled off, cooled and then poured into ice water, filtered, washed with water and dried. The solid thus obtained were recrystallized from ethanol Compound (5a) M.P: 196ºC, yield: 72%, mol. formula: $C_{20}H_{15}SN_7O_2ClBr$, Elemental analysis % Calcd. C, H, N 45.09, 2.84, 18.40 Found 45.27, 2.85, 18.47, IR (KBr) □ $\nu_{max.}$ in cm^{-1}:3360 (N-H), 3050 (Ar-CH), 2920 (CH_3 C-H stretching), 1725 (-CONH), 1710 (C=O of quinazolinone), 1680 (CO attached to CH_2),1620 (C=N), 1560 (C⎓C of aromatic ring), 1490 (N-N), 1235 (C-N), 740 (C-Br), 710 (C-Cl), ^{1}H-NMR ($CDCl_3$) δ in ppm: 8.85 (s, 1H, = CH-Ar), 7.92-7.36 (m, 7H, Ar-H), 7.15 (ss, 1H of triazole nucleus exchangeable with D_2O), 3.10 (hump, 1H, CONH exchangeable with D_2O), 2.64 (s, 2H, SCH_2CO), 2.12 (s, 3H, CH_3 attached to quinazolinone ring). MS: $[M]^+$ at m/z 533.

Compounds **(5b-5l)** were prepared similarly and their physical and analytical data are given in (T**able 1**).

2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H) -yl)-4H-1,2,4-triazol-3-ylthio]-N-(2-chloroben zylidene)-4-oxothiazolidin-3-yl)acetamide (6a) :

To a solution of the compound **(5a)** 2-(5-(6-bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazole-3-ylthio)-N-(2-chlorobenzaldehyde) acetohydrazide (0.01 mole) in ethanol (50 ml.), thioglycolic acid (0.02 mole) were added drop wise in presence of anhydrous zine chloride and the reaction mixture were refluxed for 10 hr. The completion of reaction was checked by TLC. The excess of methanol were distilled off. The cooled residual mass were diluted with ice-water, filtered washed with water, dried and recrystallized from methanol Compound (6a) M.P. 206º C, yield: 55%, mol. formula: $C_{22}H_{17}N_7O_3S_2BrCl$, Elemental analysis % Calcd. C, H, N 43.44, 2.82, 16.16 Found 43.71, 2.83, 16.10, IR (KBr) □ $\nu_{max.}$ in cm^{-1} : 3355 (NH of triazole), 3050 (Ar-CH), 2935 (CH_3, C-H stretching),2840 (CH_2), 1745 (CO thiazolidinone ring), 1730 (-CONH), 1715 (C=O of quinazolinone), 1685 (CO attached to CH_2), 1620 (C=N), 1570 (C⎓C of aromatic ring), 1485 (N-N), 1230 (C-N), 745 (C-Br), 715 (C-Cl), 695 (C-S-C).^{1}H-NMR ($CDCl_3$) δ in ppm.: 7.90-7.40 (m, 7H, Ar-H), 7.25 (ss, 1H, of triazole nucleus exchangeable with D_2O), 6.75 (s, 1H, -CH-Ar), 3.42 (s, 2H, CH_2 of thiazolidinone ring), 3.15 (hump, 1H, CONH exchangeable with D_2O), 2.70 (s, 2H, S CH_2CO), 2.15 (s, 3H, CH_3 attached to quinazolinone ring) MS: $[M]^+$ at m/z 607.

Compound **(6b-6l)** were prepared similarly and their physical and analytical data are given in (T**able 2**).

2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3-(4H)-yl)-4H-1,2,4-triazol-3-ylthio]-N-(3-chloro (2-chloro benzylidene)-4-oxoazetidin-1-yl) acet-amide (7a) :

To a solution of the compound **(5a)** 2-(5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio)-N-(2-chloro benzylidene) acetohydrazide (0.01 mole), chloro acetyl chloride were added drop wise with constant stirring in presence of triethyl amine (0.02 mole) at 0-5ºC . The reaction mixture was further refluxed for 8hr. The completion of reaction was checked by TLC and excess of ethanol was distilled off. The resulting residual mass were cooled, poured into ice water, filtered, washed with water, dried and recrystallized from methanol.

Compound (7a): M.P. 215º C, yield: 40%, mol. formula: $C_{22}H_{16}N_7O_3SBrCl_2$, Elemental analysis % Calcd. C, H, N 43.37, 2.65, 16.09 Found 43.19, 2.64, 16.18,

IR (KBr) □ □$_{max.}$ in cm^{-1} : 3360 (NH of triazole), 3065 (Ar-CH), 2925 (CH_3, C-H stretching), 1745 (CO of Azetidinone ring), 1725 (CO of quinazolinone), 1715 (CO of quinazolinone), 1685 (CO attached of CH_2), 1625 (C=N), 1565 (C⎓C of aromatic ring), 1490 (N-N),1225 (C-N), 745 (C-Br), 715 (C-Cl) ^{1}H-NMR ($CDCl_3$) δ in ppm.: 7.95-7.32 (m,7H,Ar-H), 7.21 (ss, 1H, of triazole nucleus exchangeable with D_2O), 6.74 (d, 1H, -CH-Ar), 3.92 (d, 1H, -CHCl of Azetidinone ring), 3.08 (hump,1H,CONH exchangeable with D_2O), 2.62 (S, 2H, SCH_2CO), 2.12 (S,3H,CH_3 attached to quinazolinone ring) MS: $[M]^+$ at m/z 609.

Similar Procedure has been adopted to synthesize compounds **(7b-7l).** The physical and analytical data are given in (T**able 3**).

RESULTS AND DISCUSSION

All the compounds of this series **(5a-5l), (6a-6l)** and **(7a-7l)** have shown varying degree of anti-inflammatory activity (10.12-45.76%). The active compounds of this series **6g** and **7g** were found to possess more potent anti-inflammatory activity in the comparision of phenyl butazone. The

compound **6g** i.e. which substituted with chloro group at 2,6,-position have shown 40.69% of inhibition of oedema. The compound **5a,** which possessed chloro group at 2nd-position has shown least activity i.e., 10.12%. The compound **(6g)** 2-(5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazole-3-ylthio)-N-(2-(2,6-dichloro benzylidene)-4-oxothiazolidin-3-yl) acetamide and **(7g)** 2-(5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio)-N-(3-chloro-2-(2,6-dichloro phenyl)-4-oxoazetidin-1-yl) acetamide, have shown the better anti-inflammatory activity i.e. 40.69 and 45.76% at a dose of 50 mg./kg.p.o. as compared to phenyl butazone, showed the bar diagram of anti-inflammatory activity at three graded doses (25, 50, and 100 mg/kg p.o.) of compounds **6g**, **7g** and phenyl butazone. At all the three dose levels compounds **6g**, **7g** showed more inhibitory activity than that of phenyl butazone.

The newly synthesized compounds of the present series showed analgesic activity varying from 8.35-42.37 %. The active compound of this series **6g** and **7g** were found to possessed better analgesic activity i.e. (38.54 and 42.37 %) at the dose of 50 mg/kg p.o. Considering, potentiality of compound **6g** and **7g**, these were studied in details at three graded doses 25, 50 and 100 mg/kg p.o. The compound **7g** have shown better analgesic activity at all three graded doses of 25, 50 and 100 mg/kg p.o as compared to phenyl butazone. Compound **6g** and **7g** were also tested for their ulcerogenic activity and found to be less ulcerogenic liability as compared to phenyl butazone. UD_{50} of compound **6g** is 165.5 mg/kg i.p. and compound **7g** is 195.5 mg/kg i.p. UD_{50} of phenyl butazone is 66.6 mg./kg. i.p. Approximate lethal dose (ALD_{50}) of all compounds of the present series showed > 1000 mg/kg. p.o. The compound **6g** and **7g** have exhibited > 1400 mg./kg. p.o., it indicates a good safety margin.

Biological Study

The experiment were performed with albino rats of Charles-Foster strain of either sex, excluding pregnant females, of 60 to 90 days weighing 100 to 120 g. Food (chaw pallet) and water was given to the animals *ad libitum*. The test compounds were dissolved in propylene glycol. Indomethacin and phenylbutazone were used as reference drugs for the comparison of anti-inflammatory, analgesic and ulcerogenic activity.

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

This study was done by following the procedure of (Winter *et al*. 1962). The rats were divided into three groups (control, drug treated, and standard, drug of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline). 0.05 mn was injected under the planter aponeurosis of the right hind paw of each rat. Test compounds and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1h before the carrageen an injection. The paw volume of each rat was measured before 1 and after 3 h of carrageen an treatment with the help of a plethymometer. The percent anti-inflammatory activity was calculated according to the formula given below:

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

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

Analgesic activity

Following the method of (Berkowitz *et al*. 1977) performed this activity. 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) x 100

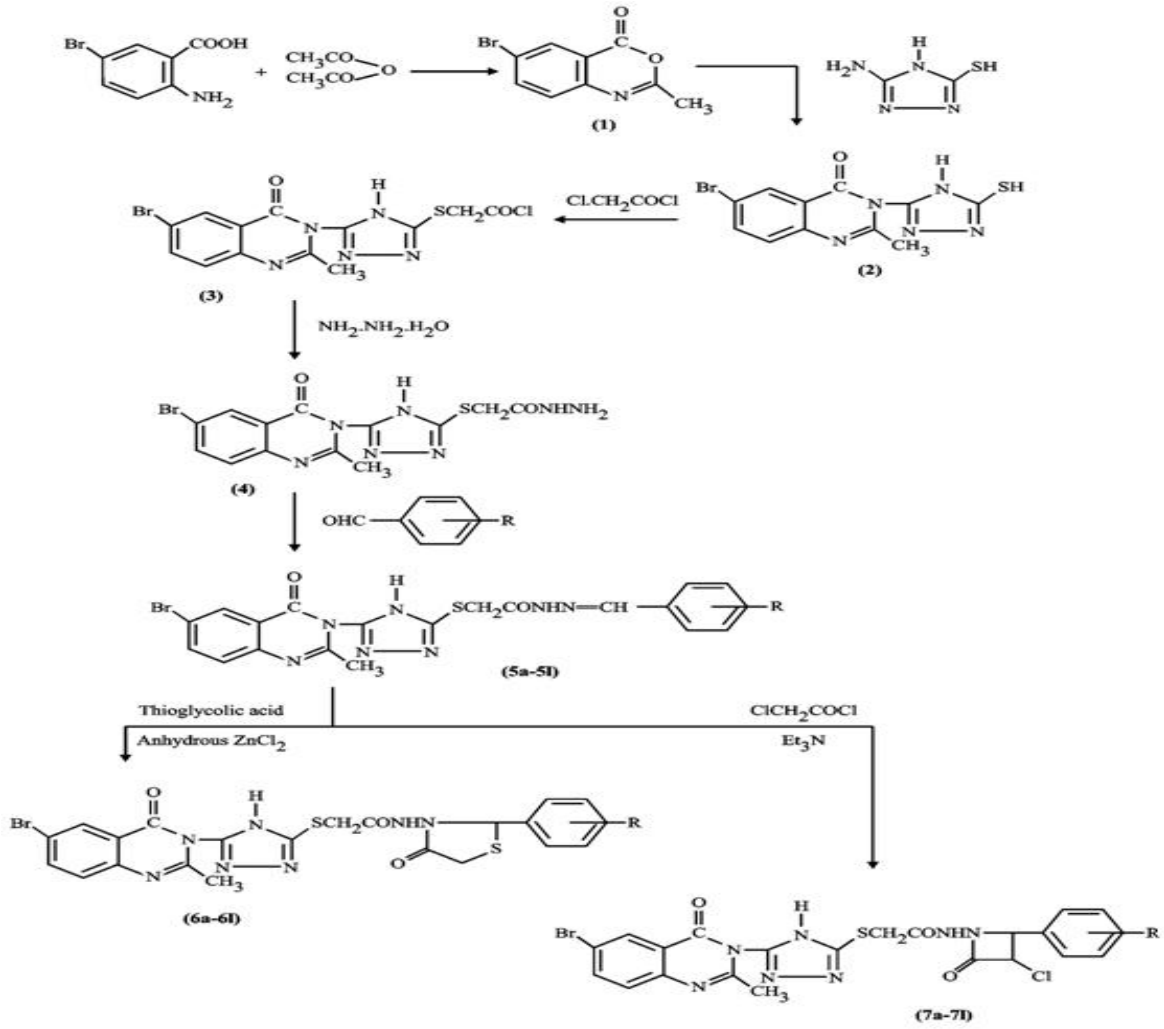
Ulcerogenic activity

Ulcerogenic liabilities of newly synthesized compounds were checked with method of (Verma *et al* 1981). Albino rats were fasted for 24 h prior to drug administration. All animals were sacrificed 8 h after drug treatment, and their stomachs and small intestines were microscopically examined to assess the incidence of hyperemia, shedding of epithelium, Petechial and frank hemorrhages 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.

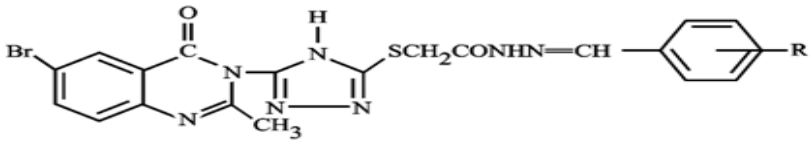
Acute Toxicity study

The test compounds were investigated for their acute toxicity (ALD_{50}) in albino mice, according to the method of (Smith *et al*, 1960). The test compounds were given orally at different dose levels in separate groups of animals. After 24 h of drug administration, percent mortality in each group was observed. ALD_{50} was calculated from the data obtained.



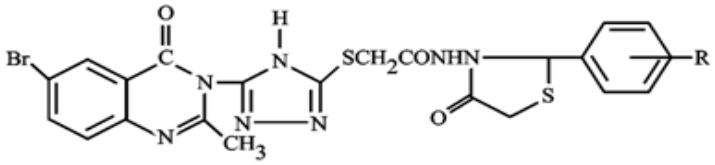
Scheme - I

Table 1: Physical and analytical data of (E)-2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazole-3-ylthio)-N-(substituted benzylidene) acetohydrazides (5b-5l)



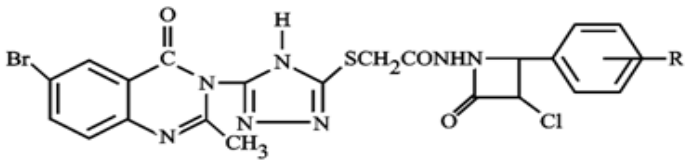
Comp.	R	M.P. (ºC)	Yield (%)	Recrysta-llization solvent	Molecular formula	Elemental analysis (%)					
						C %		H %		N %	
						Calcd.	Found	Calcd.	Found	Calcd	Found
5b	4-Cl	201	67	Ethanol	$C_{20}H_{15}SN_7O_2ClBr$	45.09	45.27	2.84	2.85	18.40	18.47
5c	2-Br	222	65	Acetone	$C_{20}H_{15}SN_7O_2ClBr_2$	41.62	41.78	2.62	2.63	16.98	17.05
5d	4-Br	242	63	Benzene	$C_{20}H_{15}SN_7O_2ClBr_2$	41.62	41.78	2.62	2.63	16.98	17.05
5e	2,4-Cl_2	220	60	Methanol	$C_{20}H_{14}SN_7O_2Cl_2Br$	42.35	42.18	2.49	2.48	17.28	17.21
5f	2,4-Br_2	248	55	DMF Water	$C_{20}H_{14}SN_7O_2Br_3$	36.61	36.46	2.15	2.14	14.94	14.88
5g	2,6-Cl_2	228	65	Ethanol	$C_{20}H_{14}SN_7O_2Cl_2Br$	42.35	42.18	2.49	2.48	17.28	17.21
5h	2,6-Br_2	252	55	Benzene	$C_{20}H_{14}SN_7O_2Br_3$	36.61	36.46	2.15	2.14	14.94	14.88
5i	2-OCH_3	197	61	Acetone	$C_{21}H_{18}SN_7O_3Br$	47.74	47.93	3.43	3.44	18.56	18.63
5j	4-OCH_3	188	63	Methanol	$C_{21}H_{18}SN_7O_3Br$	47.74	47.55	3.43	3.42	18.56	18.49
5k	2-CH_3	176	58	Ethanol	$C_{21}H_{18}SN_7O_2Br$	49.23	49.43	3.54	3.55	19.14	19.22
5l	4-CH_3	182	56	Ethanol	$C_{21}H_{18}SN_7O_2Br$	49.23	49.03	3.54	3.53	19.14	19.02

Table 2: 2-[5-(6-Bromo-2-methyl-4-oxoquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio]-N-(substituted benzyli-dene)-4-oxothiazolidin-3-yl) acetamides (6b-6l)



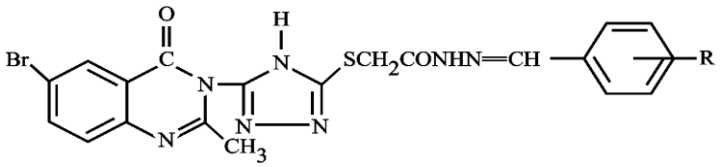
Comp.	R	M.P. (ºC)	Yield (%)	Recrysta-llization solvent	Molecular formula	Elemental analysis (%)					
						C %		H %		N %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
6b	4-Cl	211	50	Acetone	$C_{22}H_{17}N_7O_3S_2BrCl$	43.54	43.71	2.82	2.83	16.16	16.22
6c	2-Br	217	48	Benzene	$C_{22}H_{17}N_7O_3S_2Br_2$	40.57	40.41	2.63	2.62	15.05	15.11
6d	4-Br	228	45	DMF Water	$C_{22}H_{17}N_7O_3S_2Br_2$	40.57	40.41	2.63	2.62	15.05	15.11
6e	2,4-Cl_2	230	49	Ethanol	$C_{22}H_{16}BrCl_2N_7O_3S_2$	41.20	41.36	2.51	2.50	15.29	15.35
6f	2,4-Br_2	258	43	Benzene	$C_{22}H_{16}N_7O_3S_2Br_3$	36.18	36.04	2.21	2.22	13.43	13.38
6g	2,6-Cl_2	238	46	Ethanol	$C_{22}H_{16}BrCl_2N_7O_3S_2$	41.20	41.36	2.51	2.50	15.29	15.35
6h	2,6-Br_2	248	41	Acetone	$C_{22}H_{16}N_7O_3S_2Br_3$	36.18	36.04	2.21	2.22	13.43	13.38
6i	2-OCH_3	192	48	Benzene	$C_{23}H_{20}N_7O_4S_2Br$	45.85	45.67	3.35	3.34	16.27	16.33
6j	4-OCH_3	183	45	Ethanol	$C_{23}H_{20}N_7O_4S_2Br$	45.85	45.67	3.35	3.34	16.27	16.33
6k	2-CH_3	181	40	DMF Water	$C_{23}H_{20}N_7O_3S_2Br$	47.10	47.29	3.44	3.45	16.72	16.68
6l	4-CH_3	187	42	Acetone	$C_{23}H_{20}N_7O_3S_2Br$	47.10	47.29	3.44	3.45	16.72	16.68

Table 3: 2-[5-(6-Bromo-2-methyl-4-oxcquinazolin-3(4H)-yl)-4H-1,2,4-triazol-3-ylthio]-N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) acetamides (7b-7l)



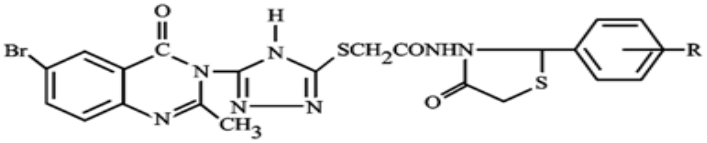
Comp.	R	M.P (ºC)	Yield (%)	Recrysta-llization solvent	Molecular formula	Elemental analysis (%)					
						C %		H %		N %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
7b	4-Cl	221	35	Benzene	$C_{22}H_{16}N_7O_3SBrCl_2$	43.37	43.18	2.65	2.64	16.09	16.17
7c	2-Br	213	30	Acetone	$C_{22}H_{16}N_7O_3SBr_2Cl$	40.42	40.51	2.47	2.48	15.00	15.08
7d	4-Br	221	32	Methanol	$C_{22}H_{16}N_7O_3SBr_2Cl$	40.42	40.48	2.47	2.48	15.00	15.09
7e	2,4-Cl_2	237	28	Ethanol	$C_{22}H_{15}N_7O_3SBrCl_3$	41.05	41.18	2.35	2.31	15.23	15.21
7f	2,4-Br_2	253	30	Methanol	$C_{22}H_{15}N_7O_3SClBr_3$	36.07	36.22	2.06	2.05	13.38	13.30
7g	2,6-Cl_2	234	33	Acetone	$C_{22}H_{15}N_7O_3SBrCl_3$	41.05	41.16	2.35	2.33	15.23	15.28
7h	2,6-Br_2	243	29	Benzene	$C_{22}H_{15}N_7O_3SClBr_3$	36.07	36.25	2.06	2.05	13.38	13.29
7i	2-OCH_3	204	26	Methanol	$C_{23}H_{19}N_7O_4SClBr$	45.67	45.80	3.17	3.15	16.21	16.13
7j	4-OCH_3	184	23	Methanol	$C_{23}H_{19}N_7O_4SClBr$	45.67	45.51	3.17	3.16	16.21	16.13
7k	2-CH_3	186	25	DMF Water	$C_{23}H_{19}N_7O_3SBrCl$	46.91	46.80	3.25	3.26	16.65	16.69
7l	4-CH_3	191	30	Benzene	$C_{23}H_{19}N_7O_3SBrCl$	46.91	46.75	3.25	3.27	16.65	16.68

Table 4: Anti-inflammatory, analgesic and toxicity data of compounds (5a-5j)



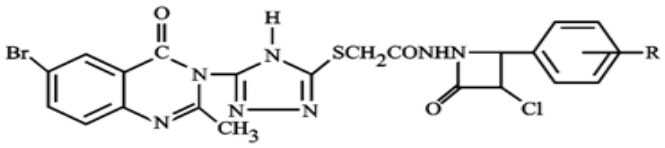
Comp.	R	Anti-Inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg. i.p.)	Acute Toxicity ALD_{50} (mg./kg. p.o)
		Dose (mg./kg. p.o.)	% Inhibition of oedema	Dose (mg./kg. p.o.)	% Protection		
5a	2-Cl	50	10.12*	50	08.35*	-	> 1000
5b	4-Cl	50	16.15*	50	14.27*	-	> 1000
5c	2-Br	50	17.38*	50	15.26*	-	> 1000
5d	4-Br	50	18.76*	50	16.52*	-	> 1000
5e	2,4-Cl_2	50	14.82*	50	12.38*	-	> 1000
5f	2,4-Br_2	50	13.52*	50	11.40*	-	> 1000
5g	2,6-Cl_2	50	15.18*	50	13.45*	-	> 1000
5h	2,6-Br_2	50	12.92*	50	10.19*	-	> 1000
5i	2-OCH_3	50	16.65*	50	14.60*	-	> 1000
5j	4-OCH_3	50	14.38*	50	12.52*	-	> 1000
5k	2-CH_3	50	17.72*	50	15.14*	-	> 1000
5l	4-CH_3	50	13.23*	50	11.38*	-	> 1000

Table 5: Anti-inflammatory, analgesic and toxicity data of compounds (6a-6j)



Comp.	R	Anti-Inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg. i.p.)	Acute Toxicity ALD_{50} (mg./kg. p.o)
		Dose (mg./kg. p.o.)	% Inhibition of oedema	Dose (mg./kg. p.o.)	% Protection		
6a	2-Cl	50	21.18**	50	18.64*	-	> 1000
6b	4-Cl	50	26.47**	50	24.60**	-	> 1000
6c	2-Br	50	27.58**	50	24.38**	-	> 1000
6d	4-Br	50	28.24**	50	26.92**	-	> 1000
6e	2,4-Cl_2	50	30.19**	50	29.53**	-	> 1000
6f	2,4-Br_2	50	22.49**	50	20.63**	-	> 1000
6g	2,6-Cl_2	25 50 100	19.30** 40.69*** 71.62***	25 50 100	16.93** 38.54*** 62.39***	165.50	> 14000
6h	2,6-Br_2	50	26.83**	50	24.48**	-	> 1000
6i	2-OCH_3	50	23.39**	50	22.11**	-	> 1000
6j	4-OCH_3	50	25.63**	50	22.40**	-	> 1000
6k	2-CH_3	50	27.16**	50	25.61**	-	> 1000
6l	4-CH_3	50	22.36**	50	20.81*	-	> 1000

Table 6: Anti-inflammatory, analgesic and toxicity data of compounds (7a-7j)



Comp.	R	Anti-Inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg. i.p.)	Acute Toxicity ALD_{50} (mg./kg. p.o)
		Dose (mg./kg. p.o.)	% Inhibition of oedema	Dose (mg./kg. p.o.)	% Protection		
7a	2-Cl	50	30.68**	50	27.30**	-	> 1000
7b	4-Cl	50	34.27***	50	32.62***	-	> 1000
7c	2-Br	50	36.56***	50	34.54***	-	> 1000
7d	4-Br	50	37.52***	50	35.48***	-	> 1000
7e	2,4-Cl_2	50	35.63***	50	32.62***	-	> 1000
7f	2,4-Br_2	50	32.45**	50	30.59**	-	> 1000
7g	2,6-Cl_2	25 50 100	20.82** 45.76*** 75.30***	25 50 100	18.25** 42.37*** 65.48***	195.50	> 14000
7h	2,6-Br_2	50	33.37***	50	30.54***	-	> 1000
7i	2-OCH_3	50	31.28**	50	29.40**	-	> 1000
7j	4-OCH_3	50	34.22***	50	32.16***	-	> 1000
7k	2-CH_3	50	32.35**	50	29.27**	-	> 1000
7l	4-CH_3	50	35.53***	50	33.61***	-	> 1000
Phenyl butazone		25 50 100	17.50** 38.80*** 68.60***	25 50 100	15.80** 36.50*** 60.50***	66.60	

*P < 0.05; **P < 0.01; ***P <0.001
Propylene glycol standard for control group

ACKNOWLEDGEMENT

Elemental and spectral analysis of the compounds was obtained from sophisticated, Analytical Instrumentation Facility Chandigarh, Punjab and CDRI, Lucknow, India.

REFERENCES

1. Abdal-Alim; Abdel Alim M.; EI-Shorbagi, Nasser A.; El-Gendy, Mahmoud A.; El-Shareif, Hosny A.H.: Quinazolinone derivatives of biological interest. V. Novel 4(3H)-quinazolinones with sedative-hypnotic, anti-convulsant and anti-inflammatory activities: *Collect. Czech. Chem. Commun.*, **1993**, 58 (8): 1963-1968.
2. Alagarsamy V.; Mahukumar V.; Pavalarani N.; Vasanthanathan P.; Rivathi R., Synthesis, analgesic, anti-inflammatory and antibacterial activities of some novel 2,3-disubstituted quinazolin-4(3H)-ones, *Biol. Pharm. Bull.*, **2003**, 26(4): 557-559.
3. Alagarsamy V.; Rajesh R.; Rameseshu M.; Vijay K.S.; Ramseshu K.V. and Duraiananda K.T., Synthesis, analgesic, anti-inflammatory and antibacterial activities of some novel 2-methylthio-3-substituted quinazolin-4-(3H)-ones, *Biol. Pharm. Bull.*; **2004**, 27(5): 652-656.

4. Alagarsamy V.; Soloman V.R.; Dhanabal K., Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H-quinazolin-4-one as analgesic, anti-inflammatory agents, *Bio-Org. Med. Chem*.; **2007**, 15(1): 235-241.
5. Amin, K.M.; Kamel M.M.; Anwar M.M.; Khedr M.; Syam Y.M.: Synthesis, biological evaluation and molecular doking of novel series of spiro {(2H, 3H) quinazoline 2,1-cyclohexan] -4 (1H)-one derivatives, *Eur J.med. chem* .**2010**, 45(6) : 2117-2131.
6. Bekhit, A.A.; Habib, N.S.; Park, Ji Young: Synthesis of some thiazolyl and thiadiazolyl derivatives of 4-(3H)-quinazolinone as anti-inflammatory, anti-microbial agents: *Bolletino Chemico Farmaceutico,* **2004,** 143(1): 34-39.
7. Berkowitz R. A.; Finck A. D.; Ngai S. H.; *Pharmacol Exp. Ther.* **1977**, 203, 539-547.
8. Heiker, Fred R.; Niewoehner, Ulrich; Hartwig, Wolfgang; Schuetz, Helmuth; Bischoff, Erwin; Perzborn, Elisabeth; Schramm, Matthias: Preparation of 2,8-disubstituted quinazolinones as anti-inflammatory and cardiovascular agents : *Chem., Abstr.* **1996**,125(13), 168013e.
9. Smith Q. E.: Pharmacological Screening Tests Progressive, Medicinal Chemistry, **1960,** Vol. I. Butterworth's, London.1-32.
10. Srivastava, M.; Salahuddin, M.D.; Santra Kumar, S.M.; Synthesis and anti-inflammatory activity of some novel 3-(6-substituted-1, 3, benzothiol-2-yl)- 2 [{(4-substituted phenyl) amino} methyl] quinazolins-4 (3H)- ones: *Eur. J. Med. chem.*, **2009**, 6:1055-1062
11. Verma, M.; Sinha, J. N.; Gujrati, V. R.; Bhalla, T. N.; Bhargava, K. P.; Shanker, K.: A new potent anti-inflammatory quinazolone: *Pharmacol. Res. Commun.*, **1981**, 13(10): 967-979.
12. Winter C. A ; Risley E. A.; and Nuss G. W. : Carrageenan induced oedema in hind paw of the rat an as assay for anti-inflammatory drugs. *Proc. Soc. Exp. Biol. N. Y.* **1962**, 111, 544-550.