Synthesis, Characterization and biological evaluation of Naphthalene derivatives as NSAIDs.

Deepak Kumar

ABSTRACT: *A series of 6-bromo-2-((2-(substituted benzylidene) hydrazinyl methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-ones (4a-4e) have been synthesized via condensation of 6-bromo-2-(hydrazinyl methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-one (3) with different aromatic aldehydes. Cycloaddition of thioglycolic acid with (4a-4e) yielded 6-bromo-3-(naphthalene-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl amino)-2-(substituted phenyl) thiazolidin-4-(3H)ones (5a-5e). while compound (4a-4e) on treatment with chloro-acetylchloride in the presence of triethylamine are converted into 6-bromo-2-((3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-ylamino) methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-ones (6a-6e). The structure of all the newly synthesized compounds have been confirmed by elemental analysis and spectral studies (IR, ^{1}H-NMR and mass spectroscopy).Compounds (4a-4e, 5a-5e and 6a-6e) have been evaluated for their anti-inflammatory and analgesic activity and were compared with the standard drug phenylbutazone. The most active compound of this series is 6b.*

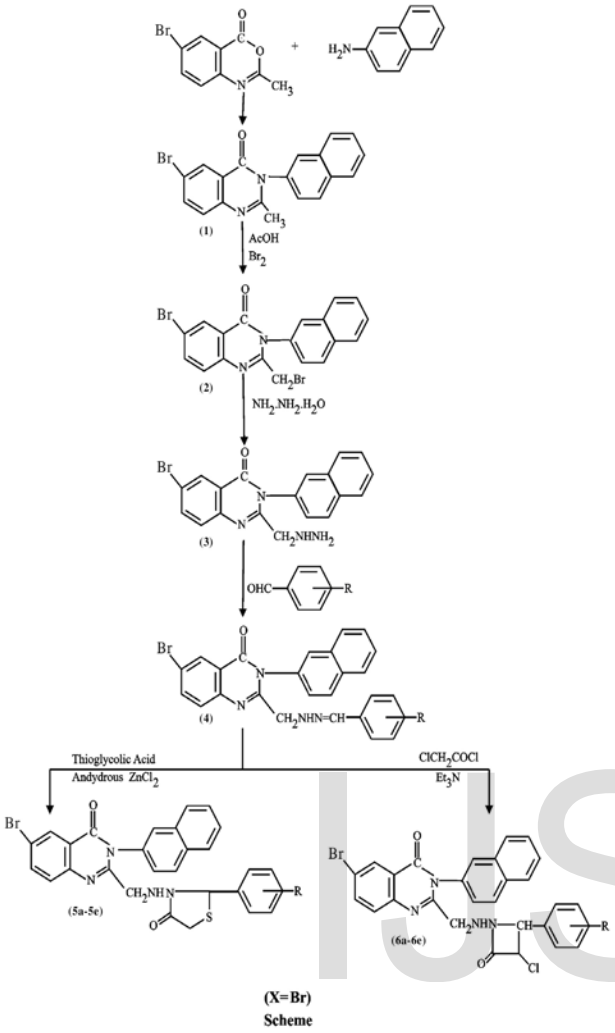
KEYWORDS: *Anti-inflammatory activity; Analgesic activity; acute toxicity; Azetidinonyl & Thiazolidinonyl quinazolinone;. Naphthalene.*

INTRODUCTION:

Nabumetone a non-acidic derivative of naphthalene is currently used for the treatment of different anti-inflammatory disorders. Substitution at β-position of naphthalene nucleus enhances the anti-inflammatory activities. Moreover, thiazole, azetidinone, and 4-oxo-thiazolidine of different heterocyclic nuclei have also been reported to possess potent anti-inflammatory activity. It was therefore, thought worthwhile to synthesize a new series of (2-oxo-azetidin-1-yl/thiazolidin-4-thiazolyl) naphthalene by incorporating the thiazolyl azetidinone and thiazolyl thiazolidinone moieties at β-position of naphthalene nucleus. These compounds will be screened for anti-inflammatory activity.

CHEMISTRY:

Started compound 5-Bromo anthranilic acid has been synthesized according to the method of wheeler (1910). Compound 6-Bromo-2-methyl-4H-benzo [1,3]oxazin-4-one (1) have also been prepared by known method of Bogert et al (1907). 6-bromo benzoxazinone on condensation with β-amino naphthalene give compound **1** which on bromination in the presence of glacial acetic acid resulted into the formation of **2**. The later compound on reaction with hydrazine hydrate yielded compound no. **3**, which on reaction with different substituted aromatic aldehyde in the presence of few drops of acetic acid, gives compound no. **4a-4e**. Compound **4a-4e** on one hand when reacted with thioglycolic acid in presence of anhydrous $ZnCl_2$ resulted into **,** 6-bromo-3-(naphthalene-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl) methylamino)-2-(substituted phenyl) thiazolidin-4-(3H)ones **5a-5e,** while compound 4a-4f on cyclo-condensation with chloro acetyl chloride in the presence of few drops of triethyl amine gives 6-bromo-2-((3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-ylamino)methyl)-3-(naphthalene-2-yl)quinazolin-4(3H)-ones **6a-6e.** Compounds 1**, 2, 3, 4a-4e, 5a-5e** and **6a-6e** were synthesized by adopting the similar method describe above.



Scheme

PHARMACOLOGY:

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 ml. 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 carrageenan treatment with the help of a plethymometer. The percent anti-inflammatory activity was calculated according to the formula given below-

$$\text{Percentage of inhibition of oedema} = (1-V_t/V_C) \times 100$$

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 [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.

PHARMACOLOGICAL RESULT AND DISCUSSION:

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

Compounds **4a-4e** has shown the varying range (29.17-36.88%) of anti-inflammatory activity. Out of these the compound which was substituted by 2-chloro phenyl **4b** was found to possess good activity (36.88%).

Compounds **5a-5e**, having thiazolidinone ring was found to possess varying degree of % of inhibition of oedema i.e. (37.28-45.85%). The compound **5b**, have exhibited 45.85% of anti-inflammatory activity, which is quite more from its parent corresponding compound **4b**. The compounds **6a-6e** is characterized by the presence of azetidinone ring (β-lactum) have shown excellent degree of % inhibition of carrageenan induced oedema. i.e.(46.10-59.64%).

The compounds, **6a-6e** which were characterized by nephthalene ring at 2nd position of quinazolinone ring and azetidinoyl ring at 3rd position of the same ring. However, it is interestingly enough, that substitution at phenyl ring plays an pivotal role to decide the anti inflammatory activity.

In addition of these moieties the compounds **4a-4e, 5a-5e** and **6a-6e** were marked by presence of bromine atom at 6th position of quinazolinone nucleus. The bromo derivatives have shown varying degree of activity, among these bromo derivatives compound **6b** has shown 59.64% inhibition of oedema respectively.

It is interesting to note that the all the compounds from 6a-6e have shown better activity than phenyl butazone. Considering the potentiality of 6b compound it is thought worthwhile to test this compound was also studied at three graded doses and it was found that at all the three graded doses compound **6b** has shown much better activity than reference drug. It is evident from the data that out of these compounds compound **6b** have shown promising activity.

Analgesic activity:

The analgesic activities of compounds **4a-4e** have shown the varying range (27.12-34.35%) of analgesic activity. Out of these, the compound which was substituted by 2-chloro group at phenyl ring was found to possess good activity (34.35). Compound **5a-5e** possesses varying degree of % of protection i.e. (36.88-43.58%). The compound **5b** have exhibited 43.58% of analgesic activity, which is quite more than parent compound **4b**. However the compounds **6a-6e** has shown range of (44.41-56.92%) of analgesic activity. All the bromo derivatives have shown better activity . All the compounds from **6a-6b** has shown better activity than reference drug. Considering the potentiality of 6b this compound have been screened at three graded doges and found to be better analgesic activity.

Ulcerogenic activity:

The UD_{50} of compound **6b** is 185 mg/kg p.o. and the UD_{50} of compound **5b** is 158, while UD_{50} of phenyl butazone is 66.6. As the UD_{50} of compound **6b** is quite high then standard drug, which suggest that the compound is less ulcerogenic than phenyl butazone.

Acute Toxicity study

The ALD_{50} of all the compounds were >800 mg/kg i.p. except that of compound **6b**, which > 1400. As the values of ALD_{50} is quite high which suggest their good safety margin.

EXPERIMENTAL:

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 thermionic melting point apparatus and were uncorrected. The progress of the reaction is monitored by TLC and product are purified through recrystallization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G 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 (λ_{max} in cm.). The 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.

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

6-Bromo-2-methyl-3-(naphthalene-2-yl) quinazolin-4(3H)-one (1)

A mixture of 6-Bromo-2-methyl benzoxazin-4-one (0.01 mole) and 2-amino naphthalene (0.01 mole) in ethanol (50 ml.) were heated under reflux for 2 hr. The excess of solvent was distilled off. The reaction mixture poured onto crushed ice. The solid which was obtained, washed with water, filtered and recrystallized from Ethanol to yield the compound 1. The physical and analytical data are given in **table-I** while spectral data i.e., IR, ^{1}H-NMR, and mass are given in **table-VII.**

6-Bromo-2-(bromomethyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-one (2):

To a solution of compound 1 (0.01 mole) in acetic and to this solution bromine (0.04 mole) was added slowly and the mixture was stirred for 8 hr., during this period the solid was separated. The reaction mixture was poured into ice water and the solid thus obtained was filtered, washed with excess of water. The solid was dried and recrystallized from methanol to yield the compound 2. The physical and analytical data are given in **table-II** while spectral data i.e., IR, ^{1}H-NMR, and mass are given in **table-VII.**

6-Bromo-2-(hydrazinyl methyl)-3-(naphthalen-2-yl) quinazolin-4(3H) -one (3):

A solution of 6-Bromo-2-(bromo methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-one (0.01 mole), hydrazine hydrated (0.01 mole), were taken in acetone (50 ml), The reaction mixture was heated under reflux for 6hr. After cooling it was poured in water and the solid thus obtained was washed with excess of water and recrystallized from ethanol to yield compound 3. The physical and analytical data are given in **table-III** while spectral data i.e., IR, ^{1}H-NMR, and mass are given in **table-VII.**

6-Bromo-2-((2-(4-N,N-dimethyl aminobenzylidene) hydrazinyl) methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-ones (4a)

A mixture of 6-Bromo-2-(hydrazinyl methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-one (0.01 mole) and 4-N,N-dimethyl aminobenzaldehyde (0.01 mole) in methanol (50 ml) were heated under reflux for 4hr. The excess of solvent was distilled off. The reaction mixture poured onto crushed ice. The solid which was obtained was washed with water, filtered and recrystallized from mixture of ethanol-water to afford the compound (4a). The physical and analytical data are given in **table-IV** while spectral data i.e., IR, ^{1}H-NMR, and mass are given in **table-VII.**

Compounds **(4b-4e)** were prepared similarly and their physical and analytical data are given in **table-IV**, while spectral data i.e. IR, ^{1}H-NMR and mass and given in **table-VII.**

6-Bromo-3-(naphthalene-2-yl)-4-oxo-3,4-dihydro quinazolin-2-yl) methyl amino)-4-(substituted phenyl) thiazolidin-4(3H) ones (5a).

To a mixture of 6-Bromo-2-(2-(4-N,N-dimethyl aminobenzylidene)hydrazinyl)methyl)-3-(naphthalene-2-yl)quinazolin-4(3H)-one (0.01 mole) and thioglycolic acid (0.02 mole) was added drop wise in the presence of anhydrous $ZnCl_2$ and the reaction mixture was refluxed for 10hr. The reaction mixture was concentrated, cooled and poured into ice water, and filtered. The resulting solid was recrystallized from acetic acid to yield the compound (5a.) The physical and analytical data are given in **table-V** while spectral data i.e., IR, ^{1}H-NMR, and mass are given in **table-VII.** Compounds **(5b-5e)** were prepared similarly and their physical and analytical data are given in **table-V**, while spectral data i.e. IR, ^{1}H-NMR and mass and given in **table-VII.**

6-Bromo-2-((3-chloro-4-(substituted phenyl)-4-oxoazetidin-1-yl amino) methyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-ones (6a)

To a solution of 6-Bromo-2-(2-(4-N,N-dimethyl aminobenzylidene) hydrazinyl) methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-one (0.01 mole) and 2-3 drops of triethyl amine and chloracetyl chloride (0.02 mole) were added under

stirring for 1hr. The reaction mixture were stirred and refluxed for 8hr. After refluxing, the reaction mixture was distilled off, cooled and poured onto ice. Solid thus obtained was filtered and recrystallize from acetone to afford compound (6a). Compounds **(6b-6e)** were prepared similarly and their physical and analytical data are given in **table-VI**, while spectral data i.e. IR, ^{1}H-NMR and mass and given in **table-VII.**

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Table-I, Physical and analytical data of 6-Bromo-2-methyl-3-(naphthalene-2-yl) quinazolin-4(3H)-one (1)

Comp.	M.P °C	Yield %	Recrysta -llization solvent	Molecular Formula	Elemental analysis					
					% C		% H		% N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1	150	95	Ethanol	$C_{19}H_{13}BrN_2O$	62.48	62.63	03.59	03.61	07.67	7.65

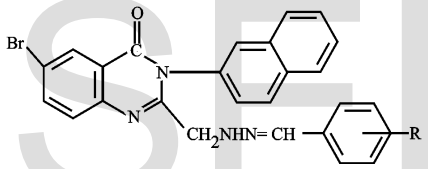
Table-II, Physical and analytical data of 6-Bromo-2-(bromomethyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-one (2)

Comp.	M.P. °C	Yield %	Recrysta -llization solvent	Molecular Formula	Elemental analysis					
					% C		% H		% N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
2	196	92	Acetic Acid	$C_{19}H_{12}Br_2N_2O$	51.38	51.55	02.72	02.74	6.31	6.30

Table-III , Physical and analytical data of 6-Bromo-2-(hydrazinyl methyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-one (3)

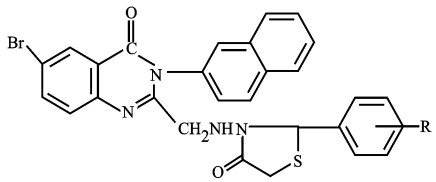
Comp.	M.P. °C	Yield %	Recrysta -llization Solvent	Molecular Formula	Elemental analysis					
					% C		% H		% N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
3	224	88	Methanol	$C_{19}H_{15}BrN_4O$	57.74	57.96	03.83	03.85	14.17	14.20

Table-IV: Physical and analytical data of 6-bromo-2-((2-(substituted benzylidene) hydrazinyl methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)-ones (4b-4e)



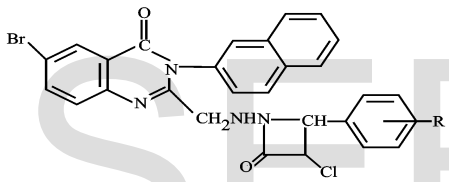
Comp.	R	M.P °C	Yield %	Recrysta -llization Solvent	Molecular Formula	Elemental analysis %					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	4-$N(CH_3)_2$	230	78	Acetone	$C_{28}H_{24}BrN_5O$	63.88	64.65	04.60	04.61	13.30	13.33
4b	2-Cl	220	80	Ethanol	$C_{26}H_{18}BrClN_4O$	60.31	60.19	03.50	03.51	10.82	10.86
4c	4-Cl	235	75	Ethanol	$C_{26}H_{18}BrClN_4O$	60.31	60.53	03.50	03.49	10.82	10.81
4d	4-OH	242	78	Acetone	$C_{26}H_{19}BrN_4O_2$	62.54	62.80	03.84	03.82	11.22	11.18
4e	3-NO_2	248	80	DMF	$C_{26}H_{18}BrN_5O_3$	59.28	59.28	03.43	03.42	13.25	13.28

Table-V: Physical and analytical data of 6-bromo-3-(naphthalene-2-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl amino)-2-(substituted phenyl) thiazolidin-4-(3H)ones(5b-5e)



Comp.	R	M.P °C	Yield %	Recrysta -llization Solvent	Molecular Formula	Elemental analysis %					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	4-N(CH_3)$_2$	275	70	Ethanol	$C_{30}H_{26}BrN_5O_2S$	60.00	60.20	04.36	04.35	11.66	11.64
5b	2-Cl	264	76	Ethanol	$C_{28}H_{20}BrClN_4O_2S$	56.82	56.66	03.41	03.43	09.47	9.49
5c	4-Cl	260	68	Acetic Acid	$C_{28}H_{20}BrClN_4O_2S$	56.82	56.65	03.41	03.42	09.47	9.48
5d	4-OH	268	70	DMF-water	$C_{28}H_{21}BrN_4O_3S$	58.64	58.80	03.69	03.67	09.77	9.76
5e	3-NO_2	259	69	Methanol	$C_{28}H_{20}BrN_5O_4S$	55.82	55.68	03.35	03.37	11.62	11.65

Table-VI: Physical and analytical data of 6-bromo-2-((3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-ylamino) methyl)-3-(naphthalene-2-yl) quinazolin-4(3H)–ones(6b-6e)



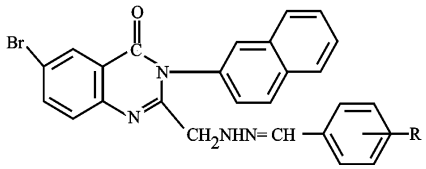
Comp.	R	M.P. °C	Yield %	Recrysta -llization Solvent	Molecular Formula	Elemental analysis %					
						% C		% H		% N	
						Calcd	Found	Calcd	Found	Calcd	Found
6a	4-N(CH_3)$_2$	264	60	DMF-water	$C_{30}H_{25}BrClN_5O_2$	59.76	59.61	04.18	04.19	11.62	11.65
6b	2-Cl	254	65	Acetone	$C_{28}H_{19}BrCl_2N_4O_2$	56.59	56.68	03.22	03.20	09.43	09.41
6c	4-Cl	250	60	Ethanol	$C_{28}H_{19}BrCl_2N_4O_2$	56.59	56.70	03.22	03.21	09.43	09.42
6d	4-OH	243	63	Ethanol	$C_{28}H_{20}BrClN_4O_3$	58.40	58.25	03.50	03.52	09.73	09.75
6e	3-NO_2	262	58	Acetic Acid	$C_{28}H_{19}BrClN_5O_4$	55.60	55.46	03.17	03.18	11.58	11.60

Table-VII: Spectral Data of compounds 1, 2, 3 , (4a-4e), (5a-5e), and (6a-6e).

Comp	IR (KBr) λ max in cm^{-1}	^{1}H-NMR ($CDCl_3$) δ in ppm	MS:$[M]^+$ m/z
1	3150 (CH-Ar), 2925 (CH_3, C-H Stretching), 1705 (C=O of quinazolinone ring) 1552 (C⎓C of aromatic ring), 1225 (C-N), 710 (C-Br).	8.04-6.95 (m, 10H, Ar-H), 2.08 (s, 3H, CH_3)	365
2	3160 (CH-Ar), 2930 (CH_3, C-H Stretching), 1700 (C=O of quinazolinone ring), 1545 (C⎓C of aromatic ring), 1235 (C-N), 712 (C-Br).	7.95-6.85 (m, 10H, Ar-H), 2.20 (s, 2H, CH_2Br)	444
3	3155 (CH-Ar), 2935 (CH_3, C-H Stretching), 1710 (C=O of quinazolinone ring), 1540 (C⎓C of aromatic ring), 1240 (C-N), 720 (C-Br).	7.98-6.85 (m, 10H, Ar-H), 4.82 (brs, 3H, NH.NH_2 exchangeable with D_2O), 3.22 (d, 2H, CH_2NH)	395
4a	3315 (N-H), 3170 (Ar-CH), 2925 (CH_3, C-H stretching), 1730 (C=O of quinazolinone ring), 1590 (C=N), 1530 (C⎓C of aromatic ring), 1245 (C-N).	9.52 (brs, 1H, $NHCH_2$), 8.26 (ss, 1H, N=CH-Ar), 7.85-6.83 (m, 14H, Ar-H), 3.27 (d, 2H, CH_2NH), 1.28 (s, 6H, Ar-N $(CH_3)_2$	513
4b	3325 (N-H), 3170 (Ar-CH), 2940 (CH_3, C-H stretching), 1720 (C=O of quinazolinone ring), 1530 (C⎓C of aromatic ring), 1585 (C=N), 1240 (C-N), 745 (C-Cl).	9.56 (brs, 1H, $NHCH_2$), 8.30 (ss, 1H, N=CH-Ar), 7.90-6.89 (m, 14H, Ar-H), 3.30 (d, 2H, CH_2NH)	499
4c	3335 (N-H), 3175 (Ar-CH), 2945 (CH_3, C-H stretching), 1725 (C=O of quinazolinone ring), 1590 (C=N), 1535 (C⎓C of aromatic ring), 1245 (C-N), 745 (C-Cl).	9.55 (brs, 1H, $NHCH_2$), 8.29 (ss, 1H, N=CH-Ar), 7.89-6.87 (m, 14H, Ar-H), 3.29 (d, 2H, CH_2NH)	529
4d	3325 (N-H), 3170 (Ar-CH), 2930 (CH_3, C-H stretching), 1725 (C=O of quinazolinone ring), 1585 (C=N), 1530 (C⎓C of aromatic ring), 1235 (C-N).	9.54 (brs, 1H, $NHCH_2$), 9.25 (ss, 1H, OH), 8.28 (ss, 1H, N=CH-Ar), 7.88-6.79 (m, 14H, Ar-H), 3.30 (d, 2H, CH_2NH)	528
4e	3325 (N-H), 3165 (Ar-CH), 2940 (CH_3, C-H stretching), 1725 (C=O of quinazolinone ring), 1595 (C=N) 1535 (C⎓C of aromatic ring), 1240 (C-N).	9.52 (brs, 1H, $NHCH_2$), 8.27 (ss, 1H, N=CH-Ar), 7.86-6.82 (m, 14H, Ar-H), 3.28 (d, 2H, CH_2NH)	526
5a	3340 (N-H), 3155 (Ar-CH), 2940 (CH_3, C-H stretching), 1740 (C=O of thiazolidinone), 1720 (C=O of quinazolinone ring), 1565 (C=N), 1540 (C⎓C of aromatic ring), 1220 (C-N), 670 (C-S-C).	9.60 (brs, 1H, $NHCH_2$), 7.80-6.79 (m, 14H, Ar-H), 4.57 (s, 1H, CH-Ar), 3.68 (s, 2H of thiazolidinone), 3.34 (d, 2H, CH_2NH), 1.28 (s, 6H, Ar-N$(CH_3)_2$	601
5b	3355 (N-H), 3160 (Ar-CH), 2960 (CH_3, C-H stretching), 1750 (C=O of thiazolidinone), 1730 (C=O of quinazolinone ring), 1565 (C=N), 1530 (C⎓C of aromatic ring), 1230 (C-N), 755 (C-CI), 685 (C-S-C).	9.70 (brs, 1H, $NHCH_2$), 7.90-6.85 (m, 14H, Ar-H), 4.57 (s, 1H, CH-Ar) 3.73 (s, 2H of thiazolidinone), 3.39 (d, 2H, CH_2NH)	592
5c	3345 (N-H), 3165 (Ar-CH), 2940 (CH_3, C-H stretching), 1745 (C=O of thiazolidinone), 1725 (C=O of quinazolinone ring), 1580 (C=N), 1540 (C⎓C of aromatic ring), 1235 (C-N), 740(C-CI), 675 (C-S-C).	9.65 (brs, 1H, $NHCH_2$), 7.86-6.80 (m, 14H, Ar-H), 4.52 (s, 1H, CH-Ar) 3.70 (s, 2H, CH_2 of thiazolidinone), 3.38 (d, 2H, CH_2NH)	592
5d	3350 (N-H), 3165 (Ar-CH), 2945 (CH_3, C-H stretching), 1745 (C=O of thiazolidinone), 1720 (C=O of quinazolinone ring), 1580 (C=N), 1545 (C⎓C of aromatic ring), 1235 (C-N), 680 (C-S-C).	9.60 (brs, 1H, $NHCH_2$), 9.33 (S, 1H, OH), 7.84-6.85 (m, 14H, Ar-H), 4.54 (s, 1H, CH-Ar) 3.67 (s, 2H, CH_2 of thiazolidinone), 3.33 (d, 2H, CH_2NH)	573
5e	3345 (N-H), 3145 (Ar-CH), 2935 (CH_3, C-H stretching), 1745 (C=O of thiazolidinone), 1720 (C=O of quinazolinone ring), 1565 (C=N), 1540 (C⎓C of aromatic ring), 1240 (C-N), 675 (C-S-C).	9.55 (brs, 1H, $NHCH_2$), 7.86-6.82 (m, 14H, Ar-H), 4.53 (s, 1H, CH-Ar) 3.65 (s, 2H, CH_2 of thiazolidinone), 3.33 (d, 2H, CH_2NH)	602
6a	3355 (N-H), 3145 (Ar-CH), 3020 (CH-Ar), 2945 (CH_3, C-H stretching), 1740 (C=O of Azetidinone), 1720 (C=O of quinazolinone ring), 1565 (C=N), 1525 (C⎓C of aromatic ring), 1225 (C-N), 755 (C-Cl).	9.67 (brs, 1H, $NHCH_2$), 7.90-6.85 (m, 14H, Ar-H), 6.66 (s, 1H, CH-Cl), 4.62 (s, 1H, CH-Ar), 3.32 (d, 2H, CH_2NH), 1.30 (s, 6H, Ar-N $(CH_3)_2$	603
6b	3380 (N-H), 3160 (Ar-CH), 3045 (CH-Ar), 2965 (CH_3, C-H stretching), 1770 (C=O of Azetidinone), 1740 (C=O of quinazolinone ring), 1575 (C=N), 1540 (C⎓C of aromatic ring), 1245 (C-N), 775 (C-Cl).	9.78 (brs, 1H, $NHCH_2$), 7.95-6.90 (m, 14H, Ar-H), 6.75 (s, 1H, CH-Cl), 4.72 (s, 1H, CH-Ar), 3.43 (d, 2H, CH_2NH)	594
6c	3370 (N-H), 3155 (Ar-CH), 3045 (CH-Ar), 2970 (CH_3, C-H stretching), 1765 (C=O of Azetidinone), 1735 (C=O of quinazolinone ring), 1570 (C=N), 1535 (C⎓C of aromatic ring),	9.76 (brs, 1H, $NHCH_2$), 7.93-6.88 (m, 14H, Ar-H), 6.73 (s, 1H, CH-Cl), 4.69 (s, 1H, CH-Ar), 3.41 (d, 2H, CH_2NH)	594

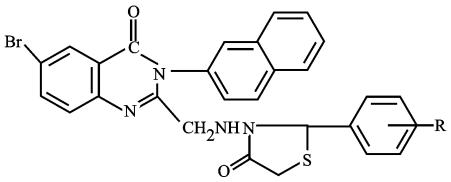
	1235 (C-N), 770 (C-Cl).		
6d	3350 (N-H), 3165 (Ar-CH), 3035 (CH-Ar), 2955 (CH_3, C-H stretching), 1745 (C=O of Azetidinone), 1730 (C=O of quinazolinone ring), 1565 (C=N), 1530 (C⋯C of aromatic ring), 1240 (C-N), 760 (C-Cl).	9.70 (brs, 1H, $NHCH_2$), 7.98-6.93 (m, 14H, Ar-H), 6.72 (s, 1H, CH-Cl), 4.67 (s, 1H, CH-Ar), 3.39 (d, 2H, CH_2NH), 9.32 (ss, 1H, OH)	576
6e	3360 (N-H), 3150 (Ar-CH), 3045 (CH-Ar), 2950 (CH_3, C-H stretching), 1750 (C=O of Azetidinone), 1735 (C=O of quinazolinone ring), 1525 (C⋯C of aromatic ring), 1240 (C-N), 765 (C-Cl).	9.64 (brs, 1H, $NHCH_2$), 7.90-6.85 (m, 14H, Ar-H), 6.66 (s, 1H, CH-Cl), 4.69 (s, 1H, CH-Ar), 3.38 (d, 2H, CH_2NH)	605

Table-VIII: Biological data of 6-Bromo-2-((2-(2-Substituted benzylidene) hydrazinyl) methyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-ones (4a-4e)



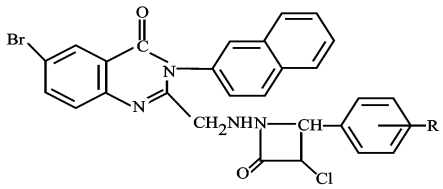
Comp.	R	Anti-inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg. i.p)	Acute Toxicity ALD_{50} (mg./kg. p.o.)
		Dose (mg./kg. p.o)	% Inhibition of oedema	Dose (mg./kg. p.o)	% Protection		
4a	4-$N(CH_3)_2$	50	29.17*	50	27.12*	-	>800
4b	2-Cl	50	36.88*	50	34.35*	-	>800
4c	4-Cl	50	34.12*	50	32.51*	-	>800
4d	4-OH	50	30.43*	50	27.92*	-	>800
4e	3-NO_2	50	31.64*	50	28.89*	-	>800

Table-IX: Biological data of 6-Bromo-3-(naphthalen-2-yl)-4-oxo-3,4-dihydroquinazoline-2-yl) methyl amino)-2-(substituted phenyl) thiadiazolin-4(3H)-ones (5a-5e)



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	4-$N(CH_3)_2$	50	37.28*	50	36.90*	-	>800
5b	2-Cl	50	45.85**	50	43.58**	158	>800
5c	4-Cl	50	44.05**	50	42.17**	-	>800
5d	4-OH	50	40.37*	50	38.30*	-	>800
5e	3-NO_2	50	39.72*	50	36.88*	-	>800

Table-X: Biological data of 6-Bromo-2-((3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl amino) methyl)-3-(naphthalen-2-yl) quinazolin-4(3H)-ones (6a-6e)



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	4-$N(CH_3)_2$	50	46.10**	50	44.41**	-	>800
6b	2-Cl	25 50 100	41.36** 59.64*** 82.85***	25 50 100	39.52** 56.92*** 76.88***	185	>1400
6c	4-Cl	50	54.38***	50	52.20***	-	>800
6d	4-OH	50	51.58**	50	49.16**	-	>800
6e	3-NO_2	50	52.17***	50	49.78**	-	>800
Pheny Buta--zone		25 50 100	17.50** 38.80*** 68.60***	25 50 100	15.80** 36.50*** 60.50***	66.6	

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