

## Synthesis of Sulpha Drug Quinazolin -4-one Derivatives and Their Evaluation for Anti-inflammatory Activity

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**Abstract:** A rapid preparation of compounds 1-31, with the objective of discovering novel and potent anti-inflammatory agent. All the compounds exhibited anti-inflammatory and analgesic activities at the dose 50 mg/kg p.o. The compound 6-bromo-2-((2-(2-chlorophenyl)-4-oxothiazolidin-1-yl-amino) methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 29 showed better anti-inflammatory and analgesic activities at the three graded dose of 25, 50 and 100 mg/kg p.o.. The structure of all the synthesized compounds were elucidated by spectral (IR, <sup>1</sup>HNMR ) and elemental (C, H, N) analysis.

**Key words:** Quinazolin -4-ones • Azetidinones • Thiazolidinone • Sulpha drugs • Anti-inflammatory activity

### INTRODUCTION

The inflammation process involves a series of event that can be elicited by numerous stimuli (eg. infectious agents, ischemia, antigen-antibody interaction). Almost two decades ago, steroids namely prednisolone, dexamethasone, batamthansone etc were considered to be the choicest anti-inflammatory drugs. Owing to the several adverse effects caused by either short term or long term steroid therapy, these have been more or less replaced by much safer and better tolerated non steroidal anti-inflammatory drugs (NSAIDs). The seriousness and enormous after effects of steroid therapy necessitated an accelerated research towards the development of NSAIDs since the past two decades [1-2]. NSAIDs have been highly useful for treating acute, self-limited inflammatory conditions. The development of NSAIDs has helped in understanding the tissue mechanism of inflammation. The quinazolin-4-ones have been

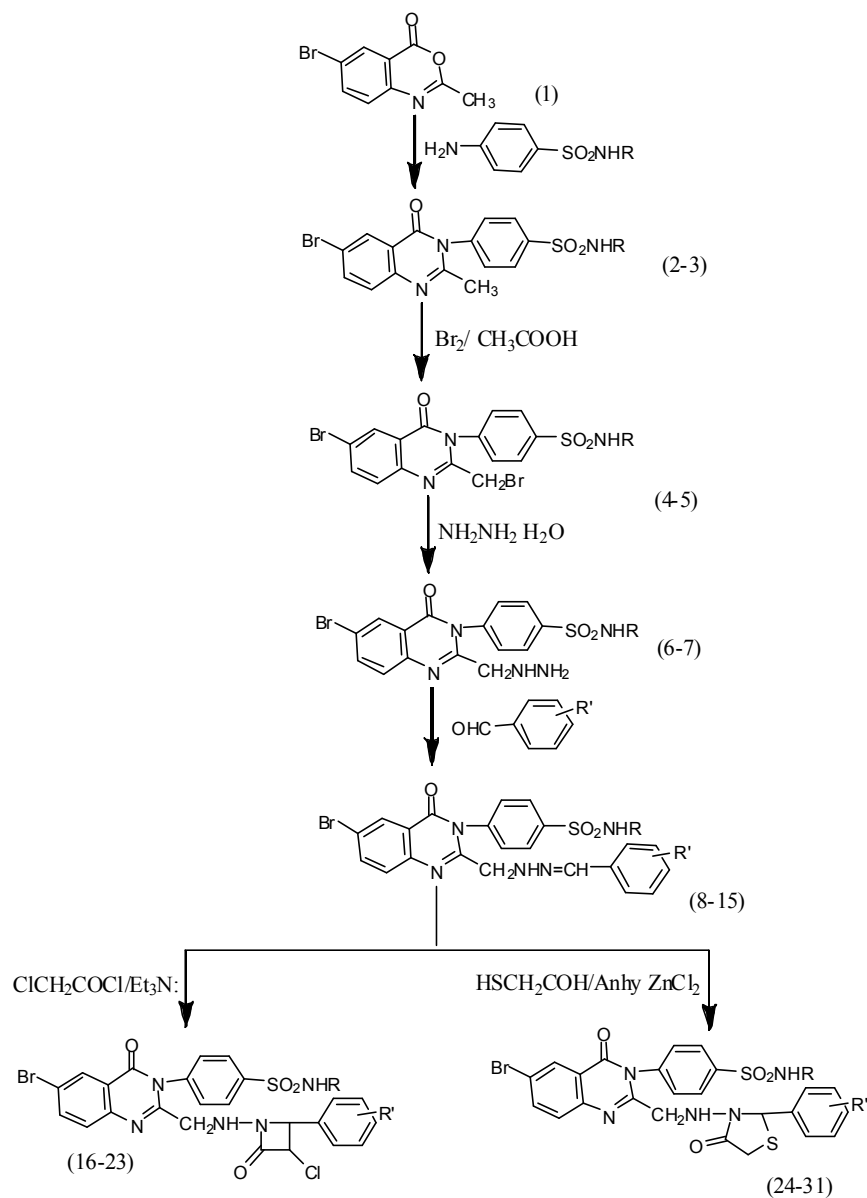
gaining prominence due to the fact that its derivatives have been found to possess wide spectrum of activities like antibacterial [3-4], antifungal [5-6], anticonvulsant [7-8] and anti-inflammatory [9-12]. It has been reported that substitution of different heterocyclic moieties at 2 or 3 position of quinazolinone nucleus modulates the anti-inflammatory activity. A large numbers of azetidinones [13-14], thiazolidinones [15-16] and oxadiazoles [17-20] were reported to possess anti-

inflammatory activity. In the light of these observations this prompted us to synthesize a new series of quinazolinone derivatives by incorporation the azetidinone and thiazolidinone moiety at 3rd position of quinazolinone nucleus.

The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR and <sup>1</sup>HNMR). All the compounds have been screened for their anti-inflammatory activity.

### RESULTS AND DISCUSSION

**Chemistry:** The synthetic routes leading to the formation of titled compounds is outlined in Scheme 1. The starting compound 6-bromo-2-methyl-quinazolin-4-one 1 was prepared according to reported method by Bogert and Soil [21]. A mixture of 6-bromo-2-methyl-4H-quinazolin-4-one 1 and sulphathiazole was dissolved separately in methanol (25 ml) by warming obtained 6-bromo-2-methyl-N-(thiazol-2-yl/pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones (2-3). On bromination in glacial acetic acid 2-3 yielded 6-bromo-2-(bromomethyl)-N-(thiazol-2-yl/ pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 4-5. Further, on reaction with hydrazine hydrate gave 6-bromo-2-(hydrazinyl methyl)-N-(thiazol-2-yl/ pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 6-7. 6-bromo-2-(substituted benzylidene hydrazinyl) methyl)



Scheme 1:

-N-(thiazol-2-yl/ pyrimidin-2-yl-benzene sulfonamide) quinazolin-4(3H)-ones 8-15) were formed by mixture of compound 6 and substituted benzaldehyde. 6-bromo -2-((3-chloro-2-oxo-4-phenylazetidin-1-ylamino) methyl) -N-(thiazol-2-yl/ pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones (16-23) and 6-bromo -2-((4-oxo-2-phenylthiazolidin-3-ylamino) methyl) -N-(thiazol-2-yl/ pyrimidin-2-yl-benzene sulfonamide) quinazolin-4(3H)-ones (24-31) were synthesized by the reaction of (8-15) with chloroacetyl chloride in the presence triethyl amine and with thioglycolic acid in the presence of anhydrous  $ZnCl_2$  respectively.

**Biological Studies:** The anti-inflammatory and analgesic effects of these compounds 8-31 are reported in Table 1. The characteristic feature of this scheme is the presence of substituted phenyl at second position and thiazoly/ pyrimidinyl moiety at the third position of quinazolinone and their conversion into azetidinonyl quinazolinone (Four membered ring structure). The benzyldinyl quinazolinones 8-11 substituted with thiazole exhibited good activities than benzyldinyl quinazolinones 12-15 substituted with pyrimidine nucleus. Further, these compounds showed almost similar analgesic activity. Among these benzyldinyl

Table 1: Pharmacological evaluation of compounds 8-31

Comp. No.	R <sup>1</sup>	Dose (mg/kg p.o.)	Anti-inflammatory activity %	Analgesic Activity	Acute Toxicity ALD <sub>50</sub>
			oedema inhibitor relation	% protection	
8	H	50	17.75*	16.12*	>1000
9	2-Cl	50	25.44***	24.68**	>1000
10	2-Br	50	24.12**	23.42*	>1000
11	3-OCH <sub>3</sub> ,4-OH	50	23.66**	21.80*	>1000
12	H	50	16.29*	15.69*	>1000
13	2-Cl	50	23.88*	22.84**	>1000
14	2-Br	50	22.23**	21.96*	>1000
15	3-OCH <sub>3</sub> ,4-OH	50	20.85*	20.52*	>1000
16	H	50	30.16***	28.59***	>1000
17	2-Cl	25	18.35*	16.50*	
		50	38.21***	34.11***	>1000
		100	65.63***	60.10**	
18	2-Br	50	32.07***	31.62**	>1000
19	3-OCH <sub>3</sub> ,4-OH	50	31.45***	29.89***	>1000
20	H	50	29.67**	27.67***	>1000
21	2-Cl	50	33.10**	32.35**	>1000
22	2-Br	50	30.65***	29.92***	>1000
23	3-OCH <sub>3</sub> ,4-OH	50	29.88***	26.12***	>1000
24	H	50	31.88***	29.45***	>1000
25	2-Cl	50	36.21***	33.11***	>1000
26	2-Br	50	34.06**	30.26***	>1000
27	3-OCH <sub>3</sub> ,4-OH	50	30.98***	28.43***	>1000
28	H	50	33.11***	30.27***	>1000
29	2-Cl	25	18.51*	16.65**	
		50	39.35***	34.86***	>1000
		100	66.63***	60.65***	
30	2-Br	50	35.13***	33.02***	>1000
31	3-OCH <sub>3</sub> ,4-OH	50	34.25***	32.87***	>1000
Phenylb-utazone	-	25	18.46**	16.30*	
		50	38.90***	34.56***	-
		100	66.58***	60.23**	

\*P &lt; 0.05, \*\*P &lt; 0.01, \*\*\*P &lt; 0.001.

quinazolinones the compound 9, which was substituted with 2-chloro group at phenyl moiety at second position of quinazolinones showed good activities. It is clear from the results that the thiazolidinone derivatives 24-31 generally showed better anti-inflammatory activity in comparison to the azetidinones derivative 16-23 and benzylidene derivatives, 8-15. Out of the eight thiazolidinones 24-31, compound 29 showed most potent activity (39.35 %) which showed inhibition of oedema. Furthermore, out of eight azetidinones 16-23, compound 17 showed also very good activity (38.21 %). Compounds 17 and 29 were tested at three graded doses i.e. 25, 50 and 100 mg/kg, p.o. it 17 showed equipotent anti-inflammatory activity than the reference drug. The compounds 29 showed more anti-inflammatory activity than the reference

drug at all three graded doses respectively. It was observed that compounds 16, 20, 24 and 28 having phenyl group as substituent exhibited the less percent inhibition of oedema (30.16, 29.67, 31.88 and 33.11%), while the other compounds of this series having, 2-chloro phenyl, 2-bromo phenyl, 3-methoxy, 4-hydroxyphenyl as substituent showed better anti-inflammatory activity. Presence of 2-chlorophenyl as a substituent elicits a remarkable increase in anti-inflammatory activity. The compounds 8-15 have shown moderate to good analgesic activity. Among these compounds, compound 9 showed good activity (24.68%), which was substituted by 2-chloro phenyl ring at 2-position of quinazolinone nucleus.

The most active compound of the series was 29 which has exhibited potent analgesic activity (16.65, 34.86

and 60.65) at the dose of 25, 50 and 100 mg/kg p.o and compound 21 showed equipotent analgesic activity at the dose of 25, 50 and 100 mg/kg p.o. than standard drug Phenylbutazone. Thiazolidinones 24-31 generally showed better analgesic activity in comparison to the azetidinones 16-23. ALD<sub>50</sub> value of all the compounds are quite high more than 1000 mg/kg p.o. suggesting their good safety margin.

### Experimental

**General Chemistry:** The melting points of compounds were determined in open capillaries and are uncorrected. Homogeneity of the synthesized compounds was routinely checked by thin layer chromatography on Silica Gel-G plates. The eluent was a mixture of different polar and nonpolar solvent in different proportion and spots were located by iodine. The IR spectra were recorded on Bruker IFS-66 V FT-IR ( $\nu$  max in  $\text{cm}^{-1}$ ). The <sup>1</sup>H NMR spectra were recorded by Bruker DRX-300 FT-NMR instrument using CDCl<sub>3</sub> as solvent and tetramethyl silane (TMS) as internal reference standard. All exchangeable protons were confirmed by the addition of D<sub>2</sub>O. All Chemical shift values were recorded in ppm. Elemental analysis (C, H, N) of these newly synthesized compounds were performed on a Carlo Erba-1108 elemental analyzer.

### Chemistry

**6-bromo-2-methyl quinazolin 4-one 1:** It was prepared according to the method of Bogert and Soil [21]. A mixture of 3-bromoanthranilic acid (0.01 mol) and acetic anhydride (0.02 mol) was refluxed for 2-3 h with constant stirring. The excess of acetic anhydride was distilled off on cooling a solid separated out which was filtered, washed with petroleum ether (40-60 °C) and dried to yield compound 1, m.p. 182°C (Reported m.p 184°C).

**6-bromo -2-methyl -N-(thiazol-2-yl/pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 2-3:** A mixture of 6-bromo-2-methyl-4H-quinazolin-4-one 1 and sulphathiazole (0.2 mol) was dissolved separately in methanol (25 ml) by warming. This solution was cooled at room temperature and then mixed together. The reaction content was allowed to stand at room temperature for nine days. Solvent was removed under reduced pressure and the solid residue left behind was suspended in 10% sodium carbonate solution (20 ml) and stirred for 30 min. It was then filtered, washed with water and dried to give crude product and finally recrystallized from appropriate solvent to give compounds 2-3.

**6-bromo-2-methyl-N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 2:** Yield 74% (Ethanol): m.p: 202°C; IR (KBr)  $\nu_{\text{max}}$  in [ $\text{cm}^{-1}$ ]: 610 (C-Br), 1635 (C=N), 1550 (C=C of aromatic ring), 1720 (C=O of quinazolin ring), 2865 (C-H), 3407(-NH-), <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  in ppm: 11.85(s, 1H, -NH-), 2.30 (s, 3H, CH<sub>3</sub>), 7.25-7.90 (m, 9H, Ar-H), Anal Calcd for C<sub>18</sub>H<sub>13</sub>N<sub>4</sub>O<sub>3</sub>BrS<sub>2</sub>: C, 45.29; H, 2.74; N, 11.74. Found: C, 45.50; H, 2.46; N, 11.98, MS: [M]<sup>+</sup> at m/z 475.35.

**6-bromo -2-methyl -N-(primidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 3:** Yield 74% (Acetone): m.p: 186°C; IR (KBr)  $\nu_{\text{max}}$  in [ $\text{cm}^{-1}$ ]: 609 (C-Br), 1635 (C=N), 1552 (C=C of aromatic ring), 1716 (C=O of quinazolin ring), 2864 (C-H), 3406(-NH-), <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  in ppm: 11.83 (s, 1H, -NH-), 2.32 (s, 3H, CH<sub>3</sub>), 7.26-7.94 (m, 10H, Ar-H), Anal Calcd for C<sub>19</sub>H<sub>14</sub>N<sub>5</sub>O<sub>3</sub>BrS: C, 48.32; H, 2.99; N, 14.83; Found: C, 48.70; H, 2.46; N, 14.83; MS: [M]<sup>+</sup> at m/z 472.32.

**6-bromo -2-(bromomethyl)-N-(thiazol-2-yl/ pyrimidin -2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 4-5:** Bromine (0.4 mol) in acetic acid (20 ml) was added drop wise to the solution of compound 2 (0.2 mol) in acetic acid (50 ml). The reaction mixture was poured onto crushed ice then left overnight at room temperature. The precipitate thus obtained was filtered, washed with water, dried and recrystallized from appropriate solvent to give compounds 4-5.

**6-bromo -2-(bromomethyl) -N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 4:** Yield 70% (Ethanol): m.p: 214°C; IR (KBr)  $\nu_{\text{max}}$  in [ $\text{cm}^{-1}$ ]: 610 (C-Br), 1635 (C=N), 1550 (C=C of aromatic ring), 1720 (C=O of quinazolin ring), 2865 (C-H), 3407(-NH-), <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  in ppm: 11.87 (s, 1H, -NH-), 2.70 (s, 2H, CH<sub>2</sub>Br), 7.30-7.98 (m, 9H, Ar-H), Anal Calcd for C<sub>18</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>Br<sub>2</sub>S<sub>2</sub>: C, 38.87; H, 2.17; N, 10.07; Found: C, 38.50; H, 2.46; N, 10.78; MS: [M]<sup>+</sup> at m/z 556.25.

**6-bromo-2-(bromomethyl)-N-(pyrimide-2-yl-benzenesulfonamide)quinazolin-4(3H)-one 5:** Yield 68% (Ethyl acetate): m.p: 190°C; IR (KBr)  $\nu_{\text{max}}$  in [ $\text{cm}^{-1}$ ]: 611 (C-Br), 1636 (C=N), 1555 (C=C of aromatic ring), 1722 (C=O of quinazolin ring), 2867 (C-H), 3410 (-NH-), <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$  in ppm: 11.89 (s, 1H, -NH-), 2.69 (s, 2H, CH<sub>2</sub>Br), 7.27-7.96 (m, 10H, Ar-H), Anal Calcd for C<sub>19</sub>H<sub>13</sub>N<sub>5</sub>O<sub>3</sub>Br<sub>2</sub>S: C, 41.40; H, 2.38; N, 12.71; Found: C, 41.75; H, 2.16; N, 12.86; MS: [M]<sup>+</sup> at m/z 551.21.

**6-bromo -2- (hydrazinyl methyl)-N-(thiazol-2-yl/pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 6-7:** A mixture of compound 4 (0.1 mol) and hydrazine hydrate (0.2 mol) in methanol was refluxed for 14 h. The excess of solvent was distilled off and the reaction mixture was poured onto ice. The solid thus obtained was filtered, washed with water, dried and recrystallized from appropriate solvent to give compounds 6-7.

**6-bromo -2-(hydrazinyl methyl) -N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 6:** yield 64% (Ethanol): m.p. 222°C; IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1635 (C=N), 1550 (C=C of aromatic ring), 1720 (C=O of quinazolin ring), 2865 (C-H), 3407 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.87 (s, 1H, -NH-), 2.66 (s, 2H,  $\text{CH}_2$ ), 6.45 (s, 2H, -NH<sub>2</sub> exchangeable with D<sub>2</sub>O), 7.30-7.98 (m, 9H, Ar-H), 5.45 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), Anal Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>6</sub>O<sub>3</sub>BrS<sub>2</sub>: C, 42.61; H, 2.98; N, 16.56; Found: C, 42.30; H, 2.43; N, 16.75; MS:  $[\text{M}]^+$  at m/z 507.38.

**6-bromo -2- (hydrazinyl methyl) -N-(pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 7:** Yield 60% (Methanol): m.p. 210°C; IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1636 (C=N), 1552 (C=C of aromatic ring), 1722 (C=O of quinazolin ring), 2866 (C-H), 3410 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.83 (s, 1H, -NH-), 2.64 (s, 2H,  $\text{CH}_2$ ), 6.46 (s, 2H, -NH<sub>2</sub> exchangeable with D<sub>2</sub>O), 7.30-7.98 (m, 10H, Ar-H), 5.52 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), Anal Calcd for C<sub>19</sub>H<sub>16</sub>N<sub>7</sub>O<sub>3</sub>BrS: C, 45.43; H, 3.21; N, 19.52; Found: C, 45.20; H, 3.47; N, 19.75; MS:  $[\text{M}]^+$  at m/z 502.34.

**6-bromo-2-(Substitutedbenzylidenehydrazinyl) methyl) -N-(thiazol-2-yl/ pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 8-15:** A mixture of compound 6 (0.01 mol) and substituted benzaldehyde (0.01 mol) was dissolved in absolute ethanol (50 ml) in the present of few drops of glacial acetic acid. The reaction mixture was refluxed for 10 h and poured onto crushed ice and resultant solid was recrystallized from appropriate solvent to give compounds 8-15.

**6-bromo -2-((2-benzylidenehydrazinyl) methyl) -N-(thiazol-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 8:** Yield 60% (Ethanol): mp. 212°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1636 (C=N), 1552 (C=C of aromatic ring), 1722 (C=O of quinazolin ring), 2866 (C-H), 3410 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.83 (s, 1H, -NH-), 2.76 (s, 2H,  $\text{CH}_2$ ), 5.48 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 7.35-8.02 (m, 14H, Ar-H), 8.20 (ss, 1H, N=CHAr), Anal Calcd for C<sub>25</sub>H<sub>19</sub>N<sub>6</sub>O<sub>3</sub>BrS<sub>2</sub>: C, 50.42; H, 3.22; N, 14.11; Found: C, 50.20; H, 3.50; N, 14.75; MS:  $[\text{M}]^+$  at m/z 595.49.

**6-bromo -2-((2-(2-chlorobenzylidene) hydrazinyl) methyl) -N-(thiazol-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 9:** 56% (Benzene): m.p. 223°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1645 (C=N), 1560 (C=C of aromatic ring), 1727 (C=O of quinazolin ring), 2875 (C-H), 3418 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.91 (s, 1H, -NH-), 2.85 (s, 2H,  $\text{CH}_2$ ), 5.56 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 7.40-8.12 (m, 13H, Ar-H), 8.30 (ss, 1H, N=CHAr), Anal Calcd for C<sub>25</sub>H<sub>18</sub>N<sub>6</sub>O<sub>3</sub>BrClS<sub>2</sub>: C, 47.67; H, 2.88; N, 13.34; Found: C, 47.13; H, 2.50; N, 13.75; MS:  $[\text{M}]^+$  at m/z 629.94.

**6-bromo-2-((2-(2-bromobenzylidene)hydrazinyl) methyl) -N-(thiazol-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 10:** Yield 52% (Acetone): m.p. 212°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1640 (C=N), 1557 (C=C of aromatic ring), 1725 (C=O of quinazolin ring), 2868 (C-H), 3414 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.87 (s, 1H, -NH-), 2.76 (s, 2H,  $\text{CH}_2$ ), 5.48 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 7.35-8.02 (m, 13H, Ar-H), 8.21 (ss, 1H, N=CHAr), Anal Calcd for C<sub>25</sub>H<sub>18</sub>N<sub>6</sub>O<sub>3</sub>Br<sub>2</sub>S<sub>2</sub>: C, 44.52; H, 2.69; N, 12.46; Found: C, 44.80; H, 2.50; N, 12.76; MS:  $[\text{M}]^+$  at m/z 674.39.

**6-bromo -2-((2-(4-hydroxy-3-methoxybenzylidene) hydrazinyl) methyl) -N-(thiazol-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 11:** Yield 50% (DMF/Water): m.p. 212°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1636 (C=N), 1552 (C=C of aromatic ring), 1722 (C=O of quinazolin ring), 2866 (C-H), 3410 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.83 (s, 1H, -NH-), 2.76 (s, 2H,  $\text{CH}_2$ ), 3.39 (s, 3H, OCH<sub>3</sub>), 5.48 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 7.35-8.02 (m, 12H, Ar-H), 8.20 (ss, 1H, N=CHAr), 11.78 (s, 1H, OH); Anal Calcd for C<sub>26</sub>H<sub>21</sub>N<sub>6</sub>O<sub>5</sub>BrS<sub>2</sub>: C, 48.68; H, 3.30; N, 13.10; Found: C, 48.25; H, 3.58; N, 13.65; MS:  $[\text{M}]^+$  at m/z 641.52.

**6-bromo -2-((2-benzylidenehydrazinyl) methyl)-N-(pyrimidin-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 12:** Yield 48% (Ethanol): m.p. 224°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1631 (C=N), 1548 (C=C of aromatic ring), 1722 (C=O of quinazolin ring), 2860 (C-H), 3406 (-NH-),  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.80 (s, 1H, -NH-), 2.70 (s, 2H,  $\text{CH}_2$ ), 5.42 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 7.30-8.02 (m, 15H, Ar-H), 8.21 (ss, 1H, N=CHAr), Anal Calcd for C<sub>26</sub>H<sub>20</sub>N<sub>7</sub>O<sub>3</sub>BrS: C, 52.89; H, 3.41; N, 16.61; Found: C, 52.25; H, 3.55; N, 16.74; MS:  $[\text{M}]^+$  at m/z 589.05.

**6-bromo -2-((2-(2-chlorobenzylidene) hydrazinyl) methyl) -N-(pyrimidin-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 13:** Yield 45% (Acetone): m.p. 206°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1638 (C=N), 1552 (C=C of aromatic ring), 1726 (C=O of quinazolin ring), 2865 (C-H), 3414 (-NH-),

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.86 (s, 1H,  $-\text{NH}-$ ), 2.84 (s, 2H,  $\text{CH}_2$ ), 5.55 (ss, 1H,  $-\text{CH}_2-\text{NH}$  exchangeable), 7.39-8.10 (m, 14H, Ar-H), 8.30 (ss, 1H,  $\text{N}=\text{CHAr}$ ); Anal. Calcd for  $\text{C}_{26}\text{H}_{19}\text{N}_7\text{O}_3\text{BrClS}$ : C, 49.97; H, 3.06; N, 15.69; Found: C, 49.23; H, 3.50; N, 15.75; MS:  $[\text{M}]^+$  at  $m/z$  623.01.

**6-bromo-2-((2-(2-bromobenzylidene)hydrazinyl) methyl) -N-(pyrimidin-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 14:** Yield 40% (Methanol): m.p. 232°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 1640 (C=N), 1550 (C=C of aromatic ring), 1723 (C=O of quinazolin ring), 2864 (C-H), 3411 ( $-\text{NH}-$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.83 (s, 1H,  $-\text{NH}-$ ), 2.80 (s, 2H,  $\text{CH}_2$ ), 5.51 (ss, 1H,  $-\text{CH}_2-\text{NH}$  exchangeable), 7.36-8.07 (m, 14H, Ar-H), 8.25 (ss, 1H,  $\text{N}=\text{CHAr}$ ); Anal. Calcd for  $\text{C}_{26}\text{H}_{19}\text{N}_7\text{O}_3\text{Br}_2\text{S}$ : C, 46.65; H, 2.86; N, 14.65; Found: C, 46.80; H, 2.45; N, 14.78; MS:  $[\text{M}]^+$  at  $m/z$  669.35.

**6-bromo-2-((2-(4-hydroxy-3-methoxybenzylidene)hydrazinyl) methyl) -N-(pyrimidin-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 15:** Yield 36% (Acetone): m.p. 220°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 1641 (C=N), 1552 (C=C of aromatic ring), 1725 (C=O of quinazolin ring), 2867 (C-H), 3415 ( $-\text{NH}-$ );  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 11.86 (s, 1H,  $-\text{NH}-$ ), 2.78 (s, 2H,  $\text{CH}_2$ ), 3.42 (s, 3H,  $\text{OCH}_3$ ), 5.52 (ss, 1H,  $-\text{CH}_2-\text{NH}$  exchangeable), 7.38-8.10 (m, 13H, Ar-H), 8.27 (ss, 1H,  $\text{N}=\text{CHAr}$ ), 11.80 (s, 1H, OH); Anal. Calcd for  $\text{C}_{27}\text{H}_{22}\text{N}_7\text{O}_3\text{BrS}$ : C, 50.95; H, 3.48; N, 15.40; Found: C, 50.25; H, 3.78; N, 15.15; MS:  $[\text{M}]^+$  at  $m/z$  636.48.

**6-bromo-2-((3-chloro-2-oxo-4-phenylazetidin-1-ylamino) methyl) -N-(thiazol-2-yl/ pyrimidin-2-yl-benzenesulfonamide) quinazolin-4(3H)-ones 16-23:** To a solution of compound 8 (0.01 mol) and triethylamine (5-6 drops) in methanol (50 ml) was added in mono chloro acetyl chloride (0.015 mol) at 50°C. The reaction mixture was stirred for 40 min. at room temperature and refluxed for 7 h. the reaction mixture was filtered to removed triethyl amine hydrogen chloride and the resultant solution was poured onto crushed ice with constant stirring. The solid thus obtained was recrystallized from appropriate solvent to give compounds 16-23.

**6-bromo-2-((3-chloro-2-oxo-4-phenylazetidin-1-ylamino)methyl)-N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 16:** 57%, mp. 224°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 670 (C-Cl), 572 (C-Br), 690 (C-S-C), 1260 (N-N), 1590 (C=N), 1695 (C=O), 1740 (C=O of azetidinone), 3020 (C-H aromatic), 3325 (N-H);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.26 (d, 2H,  $\text{CH}_2-\text{NH}$ ), 4.60 (d, 1H,  $\text{CH}-\text{Cl}$ ), 5.54 (ss, 1H,  $\text{CH}_2-\text{NH}$

exchangeable), 5.95 (s, 1H,  $\text{N}-\text{CHAr}$ ), 6.83-8.05 (m, 14H, 12 proton Ar-H and 2 proton of thiazole), 11.85 (s, 1H,  $-\text{NH}-\text{SO}_2$ ); Anal. Calcd for  $\text{C}_{27}\text{H}_{20}\text{N}_6\text{O}_4\text{BrClS}_2$ : C, 48.26; H, 3.00; N, 12.51; Found: C, 48.80; H, 2.86; N, 12.20; MS:  $[\text{M}]^+$  at  $m/z$  669.99.

The following compounds (17-23) were prepared using a similar procedure mentioned for compound (16). The physical and spectral data of these compounds are giving below

**6-bromo-2-((3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-ylamino) methyl) -N-(thiazol-2-yl-benzene sulfonamide) quinazolin-4(3H)-one 17:** Yield 50% (Acetone): mp. 248°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 675 (C-Cl), 577 (C-Br), 696 (C-S-C), 1265 (N-N), 1594 (C=N), 1700 (C=O), 1745 (C=O of azetidinone), 3026 (C-H aromatic), 3331 (N-H);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.29 (d, 2H,  $\text{CH}_2-\text{NH}$ ), 4.64 (d, 1H,  $\text{CH}-\text{Cl}$ ), 5.60 (ss, 1H,  $\text{CH}_2-\text{NH}$  exchangeable), 5.98 (s, 1H,  $\text{N}-\text{CHAr}$ ), 6.90-8.12 (m, 13H, 11 proton Ar-H and 2 proton of thiazole), 11.88 (s, 1H,  $-\text{NH}-\text{SO}_2$ ); Anal. Calcd for  $\text{C}_{27}\text{H}_{19}\text{N}_6\text{O}_4\text{BrCl}_2\text{S}_2$ : C, 45.91; H, 2.71; N, 11.90; Found: C, 45.50; H, 2.46; N, 11.20; MS:  $[\text{M}]^+$  at  $m/z$  703.95.

**6-bromo-2-((3-chloro-2-(2-Bromophenyl)-4-oxoazetidin-1-ylamino) methyl) -N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 18:** Yield 46% (Acetic Acid): m.p. 195°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 673 (C-Cl), 575 (C-Br), 694 (C-S-C), 1262 (N-N), 1592 (C=N), 1702 (C=O), 1742 (C=O of azetidinone), 3023 (C-H aromatic), 3335 (N-H);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.27 (d, 2H,  $\text{CH}_2-\text{NH}$ ), 4.62 (d, 1H,  $\text{CH}-\text{Cl}$ ), 5.60 (ss, 1H,  $\text{CH}_2-\text{NH}$  exchangeable), 5.94 (s, 1H,  $\text{N}-\text{CHAr}$ ), 6.85-8.10 (m, 13H, 11 proton Ar-H and 2 proton of thiazole), 11.86 (s, 1H,  $-\text{NH}-\text{SO}_2$ ); Anal. Calcd for  $\text{C}_{27}\text{H}_{19}\text{N}_6\text{O}_4\text{Br}_2\text{ClS}_2$ : C, 43.19; H, 2.55; N, 11.19; Found: C, 43.55; H, 2.20; N, 11.60; MS:  $[\text{M}]^+$  at  $m/z$  747.90.

**6-bromo-2-((3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-ylamino) methyl) -N-(thiazol-2-yl-benzenesulfonamide) quinazolin-4(3H)-one 19:** Yield 40% (pet ether): m.p. 210°C, IR (KBr)  $\nu_{\text{max}}$  in  $[\text{cm}^{-1}]$ : 671 (C-Cl), 573 (C-Br), 692 (C-S-C), 1260 (N-N), 1591 (C=N), 1705 (C=O), 1745 (C=O of azetidinone), 3025 (C-H aromatic), 3337 (N-H);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.25 (d, 2H,  $\text{CH}_2-\text{NH}$ ), 3.45 (s, 3H,  $\text{OCH}_3$ ), 4.64 (d, 1H,  $\text{CH}-\text{Cl}$ ), 5.61 (ss, 1H,  $\text{CH}_2-\text{NH}$  exchangeable), 5.94 (s, 1H,  $\text{N}-\text{CHAr}$ ), 6.82-8.08 (m, 12H, 10 proton Ar-H and 2 proton of thiazole), 11.84 (s, 1H,  $-\text{NH}-\text{SO}_2$ ), 11.95 (s, 1H, OH); Anal. Calcd for  $\text{C}_{28}\text{H}_{22}\text{N}_6\text{O}_6\text{BrClS}_2$ : C, 46.84; H, 3.09; N, 11.70; Found: C, 46.50; H, 3.45; N, 11.30; MS:  $[\text{M}]^+$  at  $m/z$  715.99.

**6-bromo-2-((3-chloro-2-oxo-4-phenylazetidin-1-ylamino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 20:** Yield 43% (Benzene): m.p. 262°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 670 (C-Cl), 573 (C-Br), 693 (C-S-C), 1260 (N-N), 1591 (C=N), 1697 (C=O), 1738 (C=O of azetidinone), 3018 (C-H aromatic), 3325 (N-H);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.23 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 4.57 (d, 1H,  $\text{CH-Cl}$ ), 5.50 (ss, 1H,  $\text{CH}_2\text{-NH}$  exchangeable), 5.92 (s, 1H, N- $\text{CHAr}$ ), 6.80-8.02 (m, 15H, 12 proton Ar-H and 3 proton of pyrimidine), 11.82 (s, 1H,  $\text{-NH-SO}_2$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{21}\text{N}_7\text{O}_4\text{BrClS}$ : C, 50.42; H, 3.17; N, 14.70; Found: C, 50.85; H, 3.80; N, 14.30; MS:  $[\text{M}]^+$  at m/z 666.93.

**6-bromo-2-((3-chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl-amino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 21:** Yield (35%), (Methanol), m.p. 245°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 678 (C-Cl), 577 (C-Br), 696 (C-S-C), 1265 (N-N), 1594 (C=N), 1708 (C=O), 1745 (C=O of azetidinone), 3028 (C-H aromatic), 3340 (N-H);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.29 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 4.65 (d, 1H,  $\text{CH-Cl}$ ), 5.62 (ss, 1H,  $\text{CH}_2\text{-NH}$  exchangeable), 5.97 (s, 1H, N- $\text{CHAr}$ ), 6.92-8.15 (m, 14H, 11 proton Ar-H and 3 proton of pyrimidine), 11.88 (s, 1H,  $\text{-NH-SO}_2$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{20}\text{N}_7\text{O}_4\text{BrCl}_2\text{S}$ : C, 47.95; H, 2.87; N, 13.98; Found: C, 47.55; H, 2.25; N, 13.35; MS:  $[\text{M}]^+$  at m/z 701.38.

**6-bromo-2-((3-chloro-2-(2-Bromophenyl)-4-oxoazetidin-1-yl-amino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 22:** Yield (32%), (Acetone), m.p. 195°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 676 (C-Cl), 574 (C-Br), 690 (C-S-C), 1260 (N-N), 1592 (C=N), 1705 (C=O), 1736 (C=O of azetidinone), 3022 (C-H aromatic), 3335 (N-H);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.25 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 4.62 (d, 1H,  $\text{CH-Cl}$ ), 5.60 (ss, 1H,  $\text{CH}_2\text{-NH}$  exchangeable), 5.93 (s, 1H, N- $\text{CHAr}$ ), 6.87-8.13 (m, 14H, 11 proton Ar-H and 3 proton of pyrimidine), 11.85 (s, 1H,  $\text{-NH-SO}_2$ ); Anal. Calcd for  $\text{C}_{27}\text{H}_{20}\text{N}_7\text{O}_4\text{Br}_2\text{ClS}$ : C, 45.09; H, 2.70; N, 13.15; Found: C, 45.50; H, 2.25; N, 13.70; MS:  $[\text{M}]^+$  at m/z 745.83.

**6-bromo-2-((3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-yl-amino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 23:** Yield (30%), (DMF/Water), m.p. 210°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 671 (C-Cl), 573 (C-Br), 692 (C-S-C), 1260 (N-N), 1591 (C=N), 1705 (C=O), 1745 (C=O of azetidinone), 3025 (C-H aromatic), 3337 (N-H);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 3.25 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 3.45 (s, 3H,  $\text{OCH}_3$ ), 4.64 (d, 1H,  $\text{CH-Cl}$ ), 5.61 (ss, 1H,  $\text{CH}_2\text{-NH}$  exchangeable), 5.94 (s, 1H, N- $\text{CHAr}$ ),

6.82-8.08 (m, 13H, 10 proton Ar-H and 3 proton of pyrimidine), 11.84 (s, 1H,  $\text{-NH-SO}_2$ ), 11.95 (s, 1H, OH); Anal. Calcd for  $\text{C}_{28}\text{H}_{23}\text{N}_7\text{O}_6\text{BrClS}$ : C, 48.85; H, 3.25; N, 13.75; Found: C, 48.40; H, 3.65; N, 13.30; MS:  $[\text{M}]^+$  at m/z 712.96.

**6-bromo-2-((4-oxo-2-phenylthiazolidin-3-ylamino)methyl)-N-(thiazol-2-yl/pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-ones 24-31:** A cool mixture of compound 8 (0.01 mol) and anhydrous  $\text{ZnCl}_2$  (one pinch) in dry benzene (50 ml), thioglycolic acid (0.02 mol) was added drop wise with stirring at ambient temperature and the reaction mixture was kept for 3 days at room temperature and then refluxed for 14 h. The reaction mixture was filtered. The filtrate was concentrated poured on crushed ice. The resultant solid was recrystallized from appropriate solvent to give compounds 24-31.

**6-bromo-2-((4-oxo-2-phenylthiazolidin-3-yl-amino)methyl)-N-(thiazol-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 24:** Yield 60% (Ethanol), m.p. 209-211°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1260 (N-N), 3030 (C-H aromatic), 1590 (C=N), 1700 (C=O), 572 (C-Br), 680 (C-S-C), 3330 (N-H), 1730 (C=O of thiazolidinone ring);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 2.81 (s, 2H,  $\text{CH}_2\text{-S}$ ), 3.30 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 5.45 (ss, 1H,  $\text{-CH}_2\text{-NH}$  exchangeable), 5.92 (s, 1H, N- $\text{CHAr}$ ), 6.75-7.98 (m, 14H, 12 proton Ar-H and 2 proton of thiazole), 11.80 (s, 1H,  $\text{-NH-SO}_2$ ); Anal. calcd for  $\text{C}_{27}\text{H}_{21}\text{N}_6\text{O}_4\text{BrS}_3$ : C, 48.43; H, 3.16; N, 12.55; Found: C, 48.85; H, 3.02; N, 12.20; MS:  $[\text{M}]^+$  at m/z 669.59.

**6-bromo-2-((2-(2-chlorophenyl)-4-oxothiazolidin-1-yl-amino)methyl)-N-(thiazol-2-yl-benzene sulfonamide) quinazolin-4(3H)-one 25:** Yield 55% (Acetone), m.p.: 242°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1267 (N-N), 3036 (C-H aromatic), 1595 (C=N), 1710 (C=O), 578 (C-Br), 687 (C-S-C), 3330 (N-H), 1735 (C=O of thiazolidinone ring);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  in ppm: 2.86 (s, 2H,  $\text{CH}_2\text{-S}$ ), 3.39 (d, 2H,  $\text{CH}_2\text{-NH}$ ), 5.49 (ss, 1H,  $\text{-CH}_2\text{-NH}$  exchangeable), 5.97 (s, 1H, N- $\text{CHAr}$ ), 6.80-8.05 (m, 13H, 11 proton Ar-H and 2 proton of thiazole), 11.85 (s, 1H,  $\text{-NH-SO}_2$ ); Anal. calcd for  $\text{C}_{27}\text{H}_{20}\text{N}_6\text{O}_4\text{BrClS}_3$ : C, 46.06; H, 2.86; N, 11.94. Found: C, 46.45; H, 3.02; N, 11.20. MS:  $[\text{M}]^+$  at m/z 704.04.

**6-bromo-2-((2-(2-bromophenyl)-4-oxothiazolidin-1-ylamino)methyl)-N-(thiazol-2-yl-benzene sulfonamide) quinazolin-4(3H)-one 26:** Yield 50% (Methanol), m.p.: 215°C, IR (KBr)  $\nu_{\max}$  in  $[\text{cm}^{-1}]$ : 1263 (N-N), 3032 (C-H

aromatic), 1594 (C=N), 1705 (C=O), 575 (C-Br), 685 (C-S-C), 3332 (N-H), 1733 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.84 (s, 2H, CH<sub>2</sub>-S), 3.32 (d, 2H, CH<sub>2</sub>-NH), 5.47 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.95 (s, 1H, N-CHAr), 6.77-8.00 (m, 13H, 11 proton Ar-H and 2 proton of thiazole), 11.83 (s, 1H, -NH-SO<sub>2</sub>??); Anal. calcd for C<sub>27</sub>H<sub>20</sub>N<sub>6</sub>O<sub>4</sub>Br<sub>2</sub>S<sub>3</sub>: C, 43.33; H, 2.69; N, 11.23; Found: C, 43.80; H, 2.42; N, 11.45; MS: [M]<sup>+</sup> at m/z 748.49.

**6-bromo-2-((2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-1-ylamino)methyl)-N-(thiazol-2-ylbenzene sulfonamide) quinazolin-4(3H)-one 27:** Yield 42% (Ethanol), m.p: 225°C, IR (KBr) ν<sub>max</sub> in [cm<sup>-1</sup>]: 1264 (N-N), 3035 (C-H aromatic), 1596 (C=N), 1708 (C=O), 575 (C-Br), 684 (C-S-C), 3330 (N-H), 1735 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.84 (s, 2H, CH<sub>2</sub>-S), 3.35 (d, 2H, CH<sub>2</sub>-NH), 3.40 (s, 3H, OCH<sub>3</sub>), 5.47 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.93 (s, 1H, N-CHAr), 6.70-7.95 (m, 12H, 10 proton Ar-H and 2 proton of thiazole), 11.82 (s, 1H, -NH-SO<sub>2</sub>??), 11.90 (s, 1H, OH); Anal. calcd for C<sub>28</sub>H<sub>23</sub>N<sub>6</sub>O<sub>6</sub>BrS<sub>3</sub>: C, 46.99; H, 3.24; N, 11.74; Found: C, 46.55; H, 3.05; N, 11.30; MS: [M]<sup>+</sup> at m/z 715.62.

**6-bromo-2-((4-oxo-2-phenylthiazolidin-3-ylamino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 28:** Yield 35% (Acetone), m.p: 230°C, IR (KBr) ν<sub>max</sub> in [cm<sup>-1</sup>]: 1258 (N-N), 3025 (C-H aromatic), 1590 (C=N), 1700 (C=O), 570 (C-Br), 677 (C-S-C), 3325 (N-H), 1728 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.80 (s, 2H, CH<sub>2</sub>-S), 3.25 (d, 2H, CH<sub>2</sub>-NH), 5.40 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.90 (s, 1H, N-CHAr), 6.70-7.90 (m, 15H, 12 proton Ar-H and 3 proton of pyrimidine), 11.75 (s, 1H, -NH-SO<sub>2</sub>??); Anal. calcd for C<sub>27</sub>H<sub>22</sub>N<sub>7</sub>O<sub>4</sub>BrS<sub>2</sub>: C, 50.61; H, 3.34; N, 14.75; Found: C, 50.85; H, 3.65; N, 14.25; MS: [M]<sup>+</sup> at m/z 664.55.

**6-bromo-2-((2-(2-chlorophenyl)-4-oxothiazolidin-1-ylamino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 29:** Yield 50% (Methanol), m.p. 254-256°C, IR (KBr) ν<sub>max</sub> in [cm<sup>-1</sup>]: 1262 (N-N), 3030 (C-H aromatic), 1595 (C=N), 1708 (C=O), 576 (C-Br), 685 (C-S-C), 3332 (N-H), 1734 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.84 (s, 2H, CH<sub>2</sub>-S), 3.35 (d, 2H, CH<sub>2</sub>-NH), 5.50 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.95 (s, 1H, N-CHAr), 6.77-8.10 (m, 14H, 11 proton Ar-H and 3 proton of pyrimidine), 11.85 (s, 1H, -NH-SO<sub>2</sub>??); Anal. calcd for C<sub>28</sub>H<sub>21</sub>N<sub>7</sub>O<sub>4</sub>BrClS<sub>2</sub>: C, 48.11; H, 3.03; N, 14.03; Found: C, 48.80; H, 3.35; N, 14.40; MS: [M]<sup>+</sup> at m/z 699.

**6-bromo-2-((2-(2-bromophenyl)-4-oxothiazolidin-1-ylamino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 30:** Yield 30% (Acetone), m.p: 186°C, IR (KBr) ν<sub>max</sub> in [cm<sup>-1</sup>]: 1260 (N-N), 3028 (C-H aromatic), 1593 (C=N), 1705 (C=O), 575 (C-Br), 680 (C-S-C), 3328 (N-H), 1730 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.82 (s, 2H, CH<sub>2</sub>-S), 3.32 (d, 2H, CH<sub>2</sub>-NH), 5.48 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.90 (s, 1H, N-CHAr), 6.78-8.05 (m, 14H, 11 proton Ar-H and 3 proton of pyrimidine), 11.82 (s, 1H, -NH-SO<sub>2</sub>??); Anal. calcd for C<sub>28</sub>H<sub>21</sub>N<sub>7</sub>O<sub>4</sub>Br<sub>2</sub>S<sub>2</sub>: C, 45.24; H, 2.85; N, 13.19; Found: C, 45.75; H, 2.50; N, 13.50; MS: [M]<sup>+</sup> at m/z 743.45.

**6-bromo-2-((2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-1-ylamino)methyl)-N-(pyrimidin-2-ylbenzenesulfonamide) quinazolin-4(3H)-one 31:** Yield 32% (Methanol): m.p: 248-251°C, IR (KBr) ν<sub>max</sub> in [cm<sup>-1</sup>]: 1265 (N-N), 3035 (C-H aromatic), 1590 (C=N), 1702 (C=O), 570 (C-Br), 685 (C-S-C), 3330 (N-H), 1732 (C=O of thiazolidinone ring); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ in ppm: 2.83 (s, 2H, CH<sub>2</sub>-S), 3.28 (d, 2H, CH<sub>2</sub>-NH), 3.42 (s, 3H, OCH<sub>3</sub>), 5.47 (ss, 1H, -CH<sub>2</sub>-NH exchangeable), 5.90 (s, 1H, N-CHAr), 6.75-7.98 (m, 13H, 10 proton Ar-H and 3 proton of pyrimidine), 11.85 (s, 1H, -NH-SO<sub>2</sub>??), 11.92 (s, 1H, OH); Anal. calcd for C<sub>29</sub>H<sub>24</sub>N<sub>7</sub>O<sub>6</sub>BrS<sub>2</sub>: C, 49.02; H, 3.40; N, 13.80; Found: C, 49.45; H, 3.15; N, 13.25; MS: [M]<sup>+</sup> at m/z 710.58.

**Pharmacology:** The compounds were tested for their anti-inflammatory and analgesic activities as well as for acute toxicity. The test compounds were suspended in 0.5% gum acacia in water and administered orally. The experiment were performed with albino rates 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 *adlibidum*. The tested compounds were dissolved in propylene glycol. Phenyl butazone and aspirine were used as reference drugs for the comparison of anti-inflammatory and analgesic activities.

**Anti-inflammatory Activity:** Anti-inflammatory activity against carrageenan-induced rat's paw oedema was determined by the method of Winter *et al.* [22]. This study was conducted on albino rats of either sex (100-150g). The rats were divided into groups of five animals each. Compounds were screened for anti-inflammatory activity at 50 mg/kg p.o.. The percentage of anti-inflammatory activity was calculated according to the following formula.



$$\% \text{ Anti-inflammatory activity} = 1 - \frac{V_d}{V_c} \times 100$$

Where,  $V_d$  and  $V_c$  are the volume of oedema in drug treated and control group, respectively.

**Analgesic Activity:** This activity was performed method of Berkowitz *et al.* [23]. 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 intraperitoneally 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 mice was counted for 5 min after injection of an irritant. The analgesic effect was expressed as percent protection in comparison to control.

$$\% \text{ protection} = \left( 1 - \frac{\text{mean no. of writhes in mice of test groups}}{\text{mean number of writhes in mice of control group}} \right) \times 100$$

**Acute Toxicity:** Acute Lethal dose ( $ALD_{50}$ ) of all the compounds were investigated by the method of Smith, Q.E. [24].

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