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Synthesis of 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones as anti-inflammatory agent

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Abstract—*N*-Chloroacetyl-5-bromoanthranilic acid (**1**), 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-chloromethyl-6-bromoquinazolin-4-one (**2**), 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-hydrazinomethyl-6-bromoquinazolin-4-one (**3**), 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-substitutedbenzylidene aminomethyl-6-bromoquinazolin-4-ones (**4**–**11**), 2-[(4′-oxo-3′-chloro-2′-phenylazetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-ones (**12**–**19**) and 2-(4′-oxo-2′-phenyl-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-ones (**20**–**27**) have been synthesized. All the compounds have been screened for their anti-inflammatory and analgesic activities at the dose of 50 mg/kg po. Compound **21** showed maximum anti-inflammatory (38.35%) and analgesic (37.36%) activities. Compound **21** was also tested for ulcerogenic activity and the UD_{50} value was found to be 195.6 mg/kg po. The structure of all compounds has been evaluated by elemental analysis (C, H, N) and spectral analysis (IR, ^1H NMR and mass spectrometry).
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1. Introduction

Quinazolinone nucleus has been gaining prominence due to the fact that its derivatives have been found to possess wide spectrum of activities like antibacterial,[1,2] antifungal,[3] anticonvulsant[4] and anti-inflammatory.[5–8] Furthermore, Medina et al.[9] have patented quinazolinone derivative as anti-inflammatory drug. However, we have also reported substituted quinazolinone[10,11] derivatives as potent anti-inflammatory, analgesic and COX-II inhibitors. Substitution pattern by different aryl or heteroaryl moieties at 2/3 position[12,13] of quinazolinone nucleus markedly influences anti-inflammatory activities. Moreover, thiazolidinones,[14–16] azetidinones[17,18] and thiazoles[19–21] are other important pharmacodynamic heterocyclic nuclei which when incorporated in different heterocyclic templates have been reported to possess potent anti-inflammatory activity. Therien et al.[22] and Roy et al.[23] reported thiazole derivatives as Selective COX-II inhibitors. In the light of the above observation we have synthesized a new series of quinazolinone derivatives by incorporating the thiazole moiety at 3rd position, thiazolidinone and azetidinone moieties at 2nd position of the quinazolinone nucleus. All the compounds have been screened for their anti-inflammatory, analgesic and ulcerogenic activities.

2. Results

2.1. Chemistry

The starting compound 5-bromoanthranilic acid was prepared according to reported method by Wheeler et al.[24] Compound *N*-chloroacetyl-5-bromoanthranilic acid (**1**) was synthesized by the reaction of 5-bromoanthranilic acid with chloroacetylchloride in the presence of dry benzene. Further on reaction with 2-amino-4-chlorophenylthiazole,[25] compound (**1**) yielded 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-chloromethyl-6-bromoquinazolin-4-one (**2**). Treatment of compound (**2**) with 99% hydrazine hydrate afforded 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-hydrazinomethyl-6- bromoquinazolin-4-one (**3**). Compound (**3**) on reaction with substituted benzaldehyde in ethanol gave 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-substituted-benzylidenehydrazinomethyl-6-bromoquinazolin-4-ones (**4**–**11**). 3-[4′-(*p*-chlorophenyl)-

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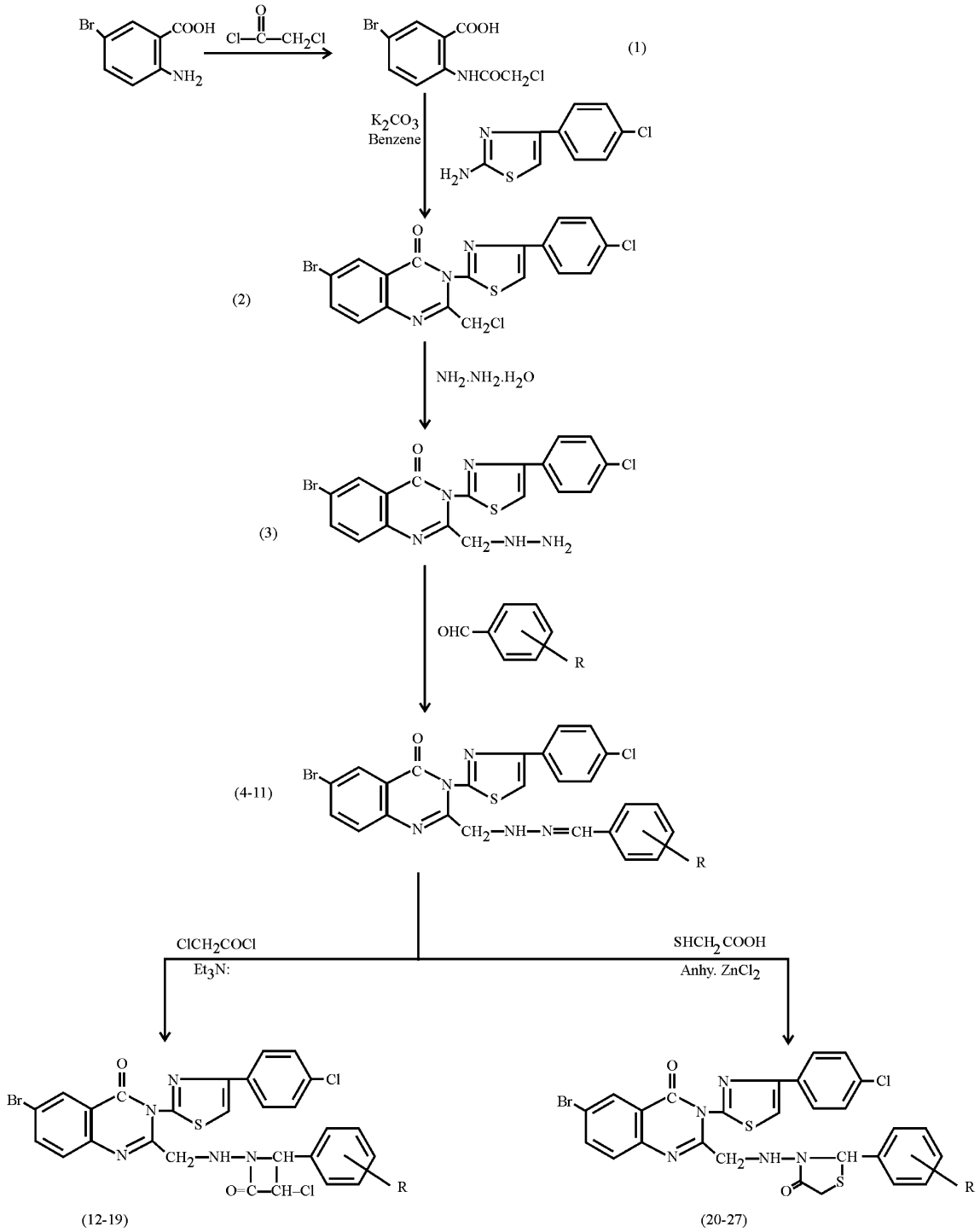

thiazol-2′-yl]-2-[(4″-oxo-2″-substitutedphenyl-3″-chloro-azetidin-1″-yl)aminomethyl]-6-bromo-quinazolin-4-ones (**12**–**19**) have been synthesized by refluxing the compounds (**4**–**11**) with chloroacetylchloride and trimethylamine in the presence of dry benzene. Treatment of (**4**–**11**) with thioglycolic acid in the presence of anhydrous $ZnCl_2$ afforded 3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-2-[(4″-oxo-2″-substitutedphenyl-thiazolidin-3″-yl)amino-methyl]-6- bromo quinazolin-4-ones (**20**–**27**). The structure of all these newly synthesized compounds was confirmed by their spectral (IR, ^{1}H NMR and mass) and analytical data. The compounds were evaluated for their anti-inflammatory, analgesic and ulcerogenic activities.

2.2. Discussion

All newly synthesized quinazolinone derivatives **4**–**27** have been tested for their anti-inflammatory activity of varying degree from 17.88% to 38.35% at a dose of 50 mg/kg per oral and the biological results are given in Table 1.

Table 1. Pharmacological evaluation of compounds **4–27**

Compound	R	Anti-inflammatory activity		Analgesic activity		UD_{50} mg/kg ip	Acute toxicity ALD_{50} mg/kg po
		Dose (mg/kg po)	% Oedema inhibitor relation	Dose (mg/kg po)	% Protection		
4	H	50	18.75	50	17.12	—	>1000
5	*o*-Cl	50	26.44	50	24.68	—	>1000
6	*p*-Cl	50	25.12	50	23.42	—	>1000
7	*o*-OCH_3	50	24.66	50	22.18	—	>1000
8	*p*-OCH_3	50	23.29	50	21.69	—	>1000
9	*p*-$N(CH_3)_2$	50	17.88	50	16.84	—	>1000
10	*p*-OH	50	20.23	50	18.96	—	>1000
11	*p*-CH_3	50	19.14	50	18.52	—	>1000
12	H	50	29.16	50	28.59	—	>1000
13	*o*-Cl	50	34.21	50	34.11	—	>1000
14	*p*-Cl	50	33.07	50	32.62	—	>1000
15	*o*-OCH_3	50	32.45	50	31.89	—	>1000
16	*p*-OCH_3	50	31.67	50	30.67	—	>1000
17	*p*-$N(CH_3)_2$	50	28.55	50	27.35	—	>1000
18	*p*-OH	50	30.65	50	29.92	—	>1000
19	*p*-CH_3	50	29.88	50	29.12	—	>1000
20	H	50	33.88	50	32.45	—	>1000
21	*o*-Cl	25	17.84	25	14.22	—	
		50	38.35	50	37.36	195.6	>1000
		100	67.45	100	61.12	—	
22	*p*-Cl	50	37.06	50	36.26	—	>1000
23	*o*-OCH_3	50	36.98	50	35.43	—	>1000
24	*p*-OCH_3	50	36.11	50	34.27	—	>1000
25	*p*-$N(CH_3)_2$	50	32.89	50	28.76	—	>1000
26	*p*-OH	50	35.13	50	333.02	—	>1000
27	*p*-CH_3	50	34.25	50	32.87	—	>1000
		25	18.46	25	16.30	—	
Phenyl-butazone	—	50	38.90	50	36.50	66.6	—
		100	66.58	100	60.23	—	

The compounds (**4–11**) of this series are characterized by the presence of azomethene linkage between 2-aminomethyl-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolinone and substituted phenyl ring. All the nine compounds of this step have shown varying degree from 17.88% to 26.44% of anti-inflammatory and 16.84% to 24.68% of analgesic activities. Compound **5**, which was substituted with chloro group at 2-position of phenyl ring, showed good anti-inflammatory activity (26.44%) and was also associated with 24.68% analgesic activity. Compound **6**, which is substituted with chloro phenyl ring, has shown a lesser degree of anti-inflammatory and analgesic activity in comparison to ortho-chloro isomer. The second step compounds are divided into two groups. The first group compounds (**12–19**) are characterized by the presence of azetidinone ring (4-membered heterocyclic ring). These compounds have shown better anti-inflammatory (28.55–34.21%) and analgesic (27.35–34.11%) activities. Out of these nine compounds, compound **13** has shown 34.21% anti-inflammatory activity and is associated with almost the same degree of analgesic (34.11%) activity. The second group compounds (**20–27**) are characterized by the presence of thiazolidinone ring (5-membered heterocyclic ring) and have shown much better both types of activity at 50 mg/kg po as compared to their parent compounds (**4–11**) and the compounds (**12–19**). Interestingly, Compound **21** which was substituted with chloro group at 2nd position of phenyl ring, has shown almost equal anti-inflammatory activity to that of phenylbutazone at 50 mg/kg po. Compound **21** and reference drug phenylbutazone were further tested at graded doses, that is, 25, 50 and 100 mg/kg po, and compound **21** showed almost equal percentage of anti-inflammatory activity at 25 and 50 mg/kg po while at 100 mg/kg po this compound showed better anti-inflammatory activity than the standard drug. On the contrary, this compound has shown better analgesic activity at 50 and 100 mg/kg po, while at 25 mg/kg po it has shown less activity than the standard drug.

The UD_{50} value of compound **21** and phenylbutazone is 195.6 and 66.6 mg/kg i.p., respectively. ALD_{50} value of all the compounds is higher than 1000 mg/kg po suggesting their good safety margin.

3. Experimental

3.1. Chemistry

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, N were within ±0.4% of the theoretical values. IR spectra (cm^{-1}) were recorded on Beckman-Acculab 10 spectrophotometer. ^1H NMR spectra were determined in $CDCl_3$ on Brucker 300-FT instrument.

3.1.1. *N*-Chloroacetyl-5bromoanthranilic acid (1). 5-bromoanthranilic acid (0.01 mol) was dissolved in 100 mL of benzene with two or three drops of pyridine and chloroacetylchloride (0.02 mol) was added in dry benzene under cool condition and it was refluxed for 5 h, cooled and filtered. The solid thus obtained was recrystallized from ethanol to give **1**. (72%): mp 185 °C. IR (KBr) ν_{max} in cm^{-1}: 3490 (OH), 3125 (N–H), 3020 (C–H aromatic), 1580 (C=C), 1690 (C=O), 2950 (aliphatic C–H), 570 (C–Br), 790(C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.90 (s, 2H, C*H*$_2$–Cl), 6.80–7.25 (m, 3H, Ar–*H*), 8.90 (s, 1H, N*H* exchangeable), 10.90 (s, 1H, COO*H*, exchangeable); Anal. calcd for $C_9H_7NO_3BrCl$: C, 36.92; H, 2.39; N,4.79. Found: C,37.09; H, 2.40; N,4.83. MS: $[M]^+$ at *m*/*z* 292.5.

3.1.2. 2-Chloromethyl-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (2). *N*-Chloroacetyl-5-bromoanthranilic acid (0.01 mol) was refluxed for 2 h with 4-chlorophenylthiazole in the presence of 13 g K_2CO_3 in 100 mL of benzene under anhydrous condition. The reaction mixture was distilled and the residue was washed with hot water and the solid thus obtained was recrystallized from acetone to give **2** (55%): mp 210 °C; IR (KBr) ν_{max} in cm^{-1}: 1600 (C=N), 1690 (C=O), 3030 (C–H aromatic), 2955 (aliphatic C–H), 690 (C–S–C), 575 (C–Br), 795 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.93 (s, 2H, C*H*$_2$–Cl), 6.86–7.85 (m, 8H, 7 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{18}H_{10}N_3OBrCl_2S$: C, 46.25; H, 2.12; N, 8.99. Found: C, 46.41; H, 2.12; N, 9.07. MS: $[M]^+$ at *m*/*z* 467.

3.1.3. 2-Hydrazinomethyl-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (3). A mixture of compound **2** (0.01 mol) and hydrazine hydrate (99%, 0.02 mol) in ethanol (50 mL) was refluxed for 10 h. The excess solvent was distilled off. On cooling, a crystalline solid obtained, which was recrystallized from methanol to yield **3** (62%): mp 193 °C; IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 1590 (C=N), 1690 (C=O), 3025 (C–H aromatic), 2955 (aliphatic C–H), 690 (C–S–C), 570 (C–Br), 3350 (NH); ^1H NMR ($CDCl_3$) δ in ppm: 3.20 (d, 2H, C*H*$_2$–NH), 4.35 (br s, 2H, NH–N*H*$_2$ exchangeable), 6.80–7.90 (m, 8H, 7 proton Ar–*H* and 1 proton of thiazole), 8.15 (s, 1H, N*H*–NH$_2$ exchangeable); Anal. calcd for $C_{18}H_{13}N_5OBrClS$: C, 46.70; H, 2.81; N, 15.13. Found: C, 46.89; H, 2.83; N, 15.18. MS: $[M]^+$ at *m*/*z* 462.5.

3.1.4. 2-Benzylidenehydrazinomethyl-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (4). A mixture of compound **3** (0.01 mol) and benzaldehyde (0.01 mol) was dissolved in absolute ethanol (50 mL) in the presence of few drops of glacial acetic acid. The reaction mixture was refluxed for 8 h and poured onto crushed ice and the resultant solid was recrystallized from ethanol to yield **4**. (65%): mp 208 °C, IR (KBr) ν_{max} in cm^{-1}: 1265 (N–N), 3020 (C–H aromatic), 1600 (C=N), 1695 (C=O), 576 (C–Br), 695 (C–S–C), 3320 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 3.18 (d, 2H, C*H*$_2$–NH), 5.48 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.85–8.05 (m, 13H, 12 proton Ar–*H* and 1 proton of thiazole,), 8.20 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{25}H_{17}N_5OBrClS$: C, 54.50; H, 3.09; N, 12.72. Found: C, 54.64; H, 3.07; N, 12.69. MS: $[M]^+$ at *m*/*z* 550.5. The following compounds were prepared using a similar procedure described for **4**.

3.1.5. 2-[(*o*-Chlorobenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (5). (60%) mp 208 °C (ethanol) IR (KBr) ν_{max} in cm^{-1}: 1265 (N–N), 3025 (C–H aromatic), 1595 (C=N), 1690 (C=O), 570 (C–Br), 690 (C–S–C), 3320 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 3.20 (d, 2H, C*H*$_2$–NH), 5.52 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.80–8.06 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.16 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{25}H_{16}N_5OBrCl_2S$: C, 51.28; H, 2.73; N, 11.97. Found: C, 51.32; H, 2.68; N, 12.05. MS: $[M]^+$ at *m*/*z* 585.

3.1.6. 2-[(*p*-Chlorobenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (6). (58%) mp 223 °C (methanol) IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3025 (C–H aromatic), 1590 (C=N), 1680 (C=O), 574 (C–Br), 685 (C–S–C), 3320 (N–H), ^1H NMR ($CDCl_3$) δ in ppm: 3.25 (d, 2H, C*H*$_2$–NH), 5.56 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.85–8.09 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.20 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{25}H_{16}N_5OBrCl_2S$: C, 51.28; H, 2.73; N, 11.97. Found: C, 51.37; H, 2.74; N, 11.94. MS: $[M]^+$ at *m*/*z* 585.

3.1.7. 2-[(*o*-Methoxybenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (7). (67%) mp 225 °C (benzene) IR (KBr) ν_{max} in cm^{-1}: 1170 (C–O–C), 1265 (N–N), 3020 (C–H aromatic), 1595 (C=N), 1690 (C=O), 570 (C–Br), 680 (C–S–C), 3320 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 3.18 (d, 2H, C*H*$_2$–NH), 3.39 (s, 3H, OC*H*$_3$), 5.60 (ss, 1H, CH$_2$–NH exchangeable), 6.82–8.06 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.26 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{26}H_{19}N_5O_2BrClS$: C, 53.75; H, 3.27; N, 12.06. Found: C, 53.91; H, 3.25; N, 12.09 MS: $[M]^+$ at *m*/*z* 580.5.

3.1.8. 2-[(*p*-Methoxybenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (8). (60%) mp 231 °C (methanol) IR (KBr) ν_{max} in cm^{-1}: 1174 (C–O–C), 1268 (N–N), 3020 (C–H aromatic), 1590 (C=N), 1690 (C=O), 576 (C–Br), 680 (C–S–C), 3325 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 3.22 (d, 2H, C*H*$_2$–NH), 3.35 (s, 3H, OC*H*$_3$), 5.60 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.85–8.05 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.23 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{26}H_{19}N_5O_2BrClS$: C, 53.75; H, 3.27; N, 12.06. Found: C, 53.85; H, 3.29; N, 12.03. MS: $[M]^+$ at *m*/*z* 580.5.

3.1.9. 2-[(*p*-Dimethylaminobenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)-thiazol-2′-yl]-6-bromoquinazolin-4-one (9). (65%) mp 216 °C (DMF/water), IR (KBr) ν_{max} in cm^{-1}: 1270 (N–N), 3020 (C–H aromatic), 1595 (C=N), 1690 (C=O), 680 (C–S–C), 565 (C–Br), 3330 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 2.92 (s, 2×3H, C*H*$_3$), 3.22 (d, 2H, C*H*$_2$–NH), 5.60 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.85–8.10 (m, 12H, 11 proton Ar–*H*

and 1 proton of thiazole) 8.23 (ss, 1H, N=C*H*Ar); Anal. calcd for $C_{27}H_{22}N_6OBrClS$: C, 54.59; H, 3.71; N, 14.15. Found: C, 54.79; H, 3.73; N, 14.14. MS: $[M]^+$ at *m*/*z* 593.5.

3.1.10. 2-[(*p*-Hydroxybenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)thiazol-2′-yl]-6-bromoquinazolin-4-one (10). (62%) mp 214 °C (acetic acid), IR (KBr) ν_{max} in cm^{-1}: 3425 (OH), 1275 (N–N), 3020 (C–H aromatic), 1590 (C=N), 1690 (C=O), 570 (C–Br), 688 (C–S–C), 3325 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 3.20 (d, 2H, C*H*$_2$–NH), 5.68 (ss, 1H, –CH$_2$–N*H* exchangeable), 6.78–8.03 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.20 (ss, 1H, N=C*H*Ar), 12.40 (s, 1H, O*H*); Anal. calcd for $C_{25}H_{17}N_5O_2BrClS$: C, 52.96; H, 3.00; N, 12.36. Found: C, 53.06; H, 2.98; N, 12.40. MS: $[M]^+$ at *m*/*z* 566.5.

3.1.11. 2-[(*p*-Methoxybenzylidene)hydrazinomethyl]-3-[4′-(*p*-chlorophenyl)thiazol-2′-yl]-6-bromoquinazolin-4-one (11). (59%) mp 198 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1275 (N–N), 3025 (C–H aromatic), 1590 (C=N), 1695 (C=O), 575 (C–Br), 685 (C–S–C), 3320 (N–H); ^1H NMR ($CDCl_3$) δ in ppm: 2.85 (s, 3H, C*H*$_3$), 3.24 (d, 2H, C*H*$_2$–NH), 5.60 (ss, 1H, –CH$_2$–N*H*, exchangeable), 6.70–80.5 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 8.25 (ss,1H, N=C*H*Ar); Anal. calcd for $C_{26}H_{19}N_5OBrClS$: C, 55.27; H, 3.37; N, 12.40. Found: C, 55.38; H, 3.41; N, 12.37. MS: $[M]^+$ at *m*/*z* 564.5.

3.1.12. 2-[(4′-Oxo-3′-chloro-2′- phenylazetidin-1′-yl)-aminomethyl]-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (12). To a solution of compound **4** (0.01 mol) and triethylamine (5–6 drops) in dry benzene (50 mL) was added in monochloroacetylchloride (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 remove triethylamine hydrogen chloride and the resultant solution was poured onto crushed ice with constant stirring. The solid thus obtained was recrystallized from methanol to yield desired compound **12** (55%), mp 224 °C, IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3020 (C–H aromatic), 1590 (C=N), 1695 (C=O), 572 (C–Br), 690 (C–S–C), 3325 (N–H), 1740 (C=O of β lactam) 670 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.26 (d, 2H, C*H*$_2$–NH), 4.60 (d, 1H, C*H*–Cl), 5.54 (ss, 1H, CH$_2$–N*H* exchangeable), 5.95 (s, 1H, N–C*H*Ar), 6.83–8.05 (m, 13H, 12 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{27}H_{18}N_5O_2BrCl_2S$: C, 51.67; H, 2.87; N, 11.16. Found: C, 51.81; H, 2.86; N, 11.18. MS: $[M]^+$ at *m*/*z* 627. The following compounds were prepared using a similar procedure described for **12**.

3.1.13. 2-[(4′-Oxo-3′-chloro-2′-{*o*-chlorophenyl}-azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (13). (50%) mp 261 °C (acetone), IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3025 (C–H aromatic), 1595 (C=N), 1695 (C=O), 570 (C–Br), 695 (C–S–C), 3320 (N–H), 1745 (C=O of β lactam) 675 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.24 (d, 2H, C*H*$_2$–NH), 4.60 (d, 1H, C*H*–Cl), 5.54 (ss, 1H, –CH$_2$–N*H* exchangeable), 5.96 (s, 1H, N–C*H*Ar), 6.75–7.98 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{27}H_{17}N_5O_2BrCl_3S$: C, 48.98; H, 2.57; N, 10.58. Found: C, 49.05; H, 2.58; N, 10.63. MS: $[M]^+$ at *m*/*z* 661.5.

3.1.14. 2-[(4′-Oxo-3′-chloro-2′-{*p*-chlorophenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (14). (53%) mp 258 °C (benzene), IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3025 (C–H aromatic), 1595 (C=N), 1695 (C=O), 575 (C–Br), 690(C–S–C), 3325 (N–H), 675 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.20 (d, 2H, C*H*$_2$–NH), 4.63 (d, 1H, C*H*–Cl), 5.56 (ss, 1H, –CH$_2$–N*H* exchangeable), 5.98 (s, 1H, N–C*H*Ar), 6.78–8.05 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole) 670 (C–Cl); Anal. calcd for $C_{27}H_{17}N_5O_2BrCl_3S$: C, 48.98; H, 2.57; N, 10.58. Found: C, 49.11; H, 2.55; N, 10.57. MS: $[M]^+$ at *m*/*z* 661.5.

3.1.15. 2-[(4′-Oxo-3′-chloro-2′-{*o*-methoxyphenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (15). (56%) mp 272 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1170 (C–O–C), 1265 (N–N), 3020 (C–H aromatic), 1600 (C=N), 1690 (C=O), 570 (C–Br), 695 (C–S–C), 3320 (N–H), 1740 (C=O of β lactam); 675 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.39 (s, 3H, OC*H*$_3$), 3.20 (d, 2H, C*H*$_2$–NH), 4.60 (d, 1H, C*H*–Cl), 5.50 (ss, 1H, –CH$_2$–N*H*, exchangeable), 5.92 (s, 1H, N–C*H*Ar), 6.60–8.03 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{20}N_5O_3BrCl_2S$: C, 51.14; H, 3.04; N, 10.65. Found: C, 51.23; H, 3.06; N, 10.62. MS: $[M]^+$ at *m*/*z* 657.

3.1.16. 2-[(4′-Oxo-3′-chloro-2′-{*p*-methoxyphenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (16). (51%) mp 264 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1165 (C–O–C), 1265 (N–N), 3020 (C–H aromatic), 1600 (C=N), 1690 (C=O), 574 (C–Br), 698 (C–S–C), 3325 (N–H), 1745 (C=O of β lactam), 680 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 3.24 (d, 2H, C*H*$_2$–NH), 3.35 (s, 3H, OC*H*$_3$), 4.63 (d, 1H, C*H*–Cl), 5.48 (ss, 1H, –CH$_2$–N*H*, exchangeable), 5.98 (s, 1H, N–C*H*Ar), 6.68-8.04 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{20}N_5O_3BrCl_2S$: C, 51.14; H, 3.04; N, 10.65. Found: C, 51.26; H, 3.03; N, 10.65. MS: $[M]^+$ at *m*/*z* 657.

3.1.17. 2-[(4′-Oxo-3′-chloro-2′-{*p*-diethylaminophenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (17). (53%) mp 257 °C (methanol), IR (KBr) ν_{max} in cm^{-1}: 1265 (N–N), 3020 (C–H aromatic), 1590 (C=N), 1700 (C=O), 570 (C–Br), 695 (C–S–C), 3325 (N–H), 1740 (C=O of β lactam), 675 (C–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 2.95 (s, $2 \times 3H$, C*H*$_3$), 3.20 (d, 2H, C*H*$_2$–NH), 4.60 (d, 1H, C*H*–Cl), 5.40(ss, 1H, –CH$_2$–N*H* exchangeable), 5.98 (s, 1H, N–C*H*Ar), 6.72–7.98 (m,12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{29}H_{23}N_6O_2BrCl_2S$: C, 51.94; H, 3.43; N, 12.54. Found: C, 51.32; H, 3.41; N, 12.57. MS: $[M]^+$ at *m*/*z* 670.

3.1.18. 2-[(4′-Oxo-3′-chloro-2′-{*p*-hydroxyphenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (18). (50%), mp234 °C (DMF/water), IR (KBr) ν_{max} in cm^{-1}: 3425 (OH),

1265 (N–N), 3020 (C–H aromatic), 1590 (C=N), 1695 (C=O), 576 (C–Br), 695 (C–S–C), 3330 (N–H), 1735 (C=O of β lactam), 675 (C–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 3.24 (d, 2H, CH_2–NH), 4.63 (d, 1H, C*H*–Cl), 5.38 (ss, 1H, –CH_2–N*H* exchangeable), 5.95 (s, 1H, N–C*H*Ar), 6.82–8.08 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole), 12.45 (s, 1H, O*H*); Anal. calcd for $C_{27}H_{18}N_5O_3BrCl_2S$: C, 50.39; H, 2.80; N, 10.89. Found: C, 50.53; H, 2.82; N, 10.91. MS: $[M]^+$ at *m*/*z* 643.

3.1.19. 2-[(4′-Oxo-3′-chloro-2′-{*p*-methylphenyl}azetidin-1′-yl)aminomethyl]-3-[4″-(*p*-chlorophenyl)thiazol-2″-yl]-6-bromoquinazolin-4-one (19). (59%) mp 222 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3025 (C–H aromatic), 1595 (C=N), 1695 (C=O), 572 (C–Br), 695(C–S–C), 3320 (N–H), 1740 (C=O of β lactam), 675 (C–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.85 (s, 3H, CH_3), 3.20 (d, 2H, CH_2–NH), 4.60 (d, 1H, C*H*–Cl), 5.32 (ss, 1H, –CH_2–N*H*, exchangeable), 5.98 (s, 1H, N–C*H*Ar), 6.75–7.98 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{20}N_5O_2BrCl_2S$: C, 52.42; H, 3.12; N, 10.94. Found: C, 52.54; H, 3.14; N, 10.96. MS: $[M]^+$ at *m*/*z* 641.

3.1.20. 2-(4′-Oxo-2′phenyl-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (20). A cool mixture of compound **4** (0.01 mol) and anhydrous $ZnCl_2$ (one pinch) in dry benzene (50 mL), thiolactic/thioglycolic acid (0.02 mol) was added dropwise 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 and poured on crushed ice. The resultant solid was recrystallized from ethanol to yield desired compound **20** (50%), mp 231 °C, IR (KBr) ν_{max} in 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 β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.81 (s, 2H, CH_2–S), 3.30 (d, 2H, CH_2–NH), 5.45(ss, 1H, –CH_2–N*H* exchangeable), 6.75–7.98 (m, 13H, 12 proton Ar–*H* and 1 proton of thiazole), 5.92 (s, 1H, N–C*H*Ar); Anal. calcd for $C_{27}H_{19}N_5O_2BrClS_2$: C, 51.88; H, 3.04; N, 11.21. Found: C, 51.99; H, 3.02; N, 11.24. MS: $[M]^+$ at *m*/*z* 624.5. The following compounds were prepared using a similar procedure described for **20**.

3.1.21. 2-(4′-Oxo-2′(*o*-chlorophenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (21). (54%) mp 244 °C (methanol), IR (KBr) ν_{max} in cm^{-1}: 1265 (N–N), 3025 (C–H aromatic), 1595 (C=N), 1690 (C=O), 570 (C–Br), 685 (C–S–C), 3325 (N–H), 1728 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.83 (s, 2H, CH_2–S), 3.35 (d, 2H, CH_2–NH), 5.40 (ss, 1H, –CH_2–N*H* exchangeable), 5.95 (s, 1H, N–C*H*Ar), 6.65–7.98 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{27}H_{18}N_5O_2BrCl_2S_2$: C, 49.16; H, 2.73; N, 10.62. Found: C, 49.32; H, 2.74; N, 10.66. MS: $[M]^+$ at *m*/*z* 659.

3.1.22. 2-(4′-Oxo-2′(*p*-chlorophenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (22). (49%) mp 239 °C (benzene), IR (KBr) ν_{max} in cm^{-1}: 1260 (N–N), 3025 (C–H aromatic), 1590 (C=N), 1690 (C=O), 570 (C–Br), 680 (C–S–C), 3325 (N–H), 1730 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.80 (s, 2H, CH_2–S), 3.35 (d, 2H, CH_2–NH), 5.35 (ss, 1H, –CH_2–N*H* exchangeable), 5.98 (s, 1H, N–C*H*Ar), 6.75–8.05 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{27}H_{18}N_5O_2BrCl_2S_2$: C, 49.16; H, 2.73; N, 10.62. Found: C, 49.27; H, 2.72; N, 10.64. MS: $[M]^+$ at *m*/*z* 659.

3.1.23. 2-(4′-Oxo-2′(*o*-methoxyphenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (23). (48%) mp 249 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1175 (C–O–C), 1250 (N–N), 3035 (C–H aromatic), 1590 (C=N), 1690 (C=O), 576 (C–Br), 675 (C–S–C), 3320 (N–H),1730 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.84 (s, 2H, CH_2–S), 3.36 (s, 3H, O–CH_3), 3.44 (d, 2H, CH_2–NH), 5.35 (ss, 1H, CH_2–N*H* exchangeable), 5.97 (s, 1H, N–C*H*Ar), 6.83–8.02 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{21}N_5O_3BrClS_2$: C, 51.34; H, 3.21; N, 10.69. Found: C, 51.53; H, 3.20; N, 10.52. MS: $[M]^+$ at *m*/*z* 654.5.

3.1.24. 2-(4′-Oxo-2′(*p*-methoxyphenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (24). (53%) mp 252 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1170 (C–O–C), 1250 (N–N),3035 (C–H aromatic), 1600 (C=N), 1690 (C=O), 570 (C–Br), 670 (C–S–C), 3322 (N–H), 1730 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.86 (s, 2H, CH_2–S), 3.32 (s, 3H, O–CH_3), 3.46 (d, 2H, CH_2–NH), 5.39 (ss, 1H, –CH_2–N*H* exchangeable), 5.96 (s, 1H, N–C*H*Ar), 6.79–8.03 (m,12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{21}N_5O_3BrClS_2$: C, 51.34; H, 3.21; N, 10.69. Found: C, 51.49; H, 3.23; N, 10.73. MS: $[M]^+$ at *m*/*z* 654.5.

3.1.25. 2-(4′-Oxo-2′(*p*-diethylaminophenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (25). (51%) mp 228 °C (DMF/water), IR (KBr) ν_{max} in cm^{-1}: 1255 (N–N), 3030 (C–H aromatic), 1605 (C=N), 1700 (C=O), 572 (C–Br), 675(C–S–C), 3320 (N–H), 1725 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.83 (s, 2H, CH_2–S), 2.95 (s, 2 × 3H, CH_3), 3.34 (d, 2H, CH_2–NH), 5.36 (ss, 1H, –CH_2–N*H* exchangeable), 5.95 (s, 1H, N–C*H*Ar), 6.85–8.05 (m,12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{29}H_{24}N_6O_2BrClS_2$: C, 52.13; H, 3.59; N, 12.61. Found: C, 52.38; H, 3.60; N, 12.61. MS: $[M]^+$ at *m*/*z* 667.5.

3.1.26. 2-(4′-Oxo-2′(*p*-hydoxyphenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromoquinazolin-4-one (26). (45%) mp 226 °C (acetic acid), IR (KBr) ν_{max} in cm^{-1}: 3420 (OH), 1250 (N–N), 3036 (C–H aromatic), 1600 (C=N), 1690 (C=O), 570 (C–Br), 670 (C–S–C), 3325 (N–H), 1730 (C=O of β thialactam); ^{1}H NMR ($CDCl_3$) δ in ppm: 2.83 (s, 2H, CH_2–S), 3.36 (d, 2H, CH_2–NH), 5.33 (ss, 1H, –CH_2–N*H* exchangeable), 5.94 (s, 1H, N–C*H*Ar), 6.79–8.06 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole) 12.42 (s, 1H, O*H*); Anal. calcd for $C_{27}H_{19}N_5O_3BrClS_2$: C, 50.58; H, 2.97; N, 10.93. Found: C, 50.82; H, 2.99; N, 10.91. MS: $[M]^+$ at *m*/*z* 640.5.

3.1.27. 2-(4′-Oxo-2′(*p*-methoxyphenyl)-thiazolidin-3′-yl-aminomethyl)-3-[4″-(*p*-chlorophenyl)-thiazol-2″-yl]-6-bromo-quinazolin-4-one (27). (50%) mp 206 °C (ethanol), IR (KBr) ν_{max} in cm^{-1}: 1255 (N–N), 3030 (C–H aromatic), 1595 (C═N), 11705 (C═O), 570 (C–Br), 670 (C–S–C), 3335 (N–H), 1740 (C═O of β thialactam); ^{1}HNMR ($CDCl_3$) δ in ppm: 2.76 (s, 3H, CH_3), 2.88 (s, 2H, CH_2–S), 3.33 (d, 2H, C*H*$_2$–NH), 5.38 (ss, 1H, –CH_2–N*H* exchangeable), 5.96 (s, 1H, N–C*H*Ar), 6.72–7.98 (m, 12H, 11 proton Ar–*H* and 1 proton of thiazole); Anal. calcd for $C_{28}H_{21}N_5O_2BrClS_2$: C, 52.62; H, 3.29; N, 10.96. Found: C, 52.84; H, 3.29; N, 11.01. MS: $[M]^+$ at *m*/*z* 638.5.

3.2. Pharmacological evaluation

The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70–95 days weighing 100–150 g. Acute toxicity was tested in albino mice (15–25 g). Food (chaw pallet) and water were given to the animals ad libitum. The compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

3.3. Anti-inflammatory activity

This study was done by following the procedure of Winter et al.[26] The rats were divided into three groups (control, drugs treated and standard drugs) of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline), 0.05 mL, was injected under the plantar aponeurosis of the right hind paw of each rat. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1 h before the carrageenan injection. The paw volume of each rat was measured before 1 h and after 3 h of carrageenan treatment with the help of a plethysmometer. 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 volumes of oedema in drug, treated and control groups, respectively.

3.4. Analgesic activity

Acetic acid writhing test was performed on mice by following the method of Davis at el.[27] Test compounds were given to the animals at the dose of 50 mg/kg, 30 min later the animals were injected interperitoneally with 0.25 mL/mouse of 0.5% acetic acid. The mean number of writhes for each experimental group and percentage decrease compared with that of the control group were calculated after 60 min.

3.5. Ulcerogenic activity

Ulcerogenic liabilities of newly synthesized compounds were checked by the method of Verma et al.[28] Albino rats were fasted for 24 h prior to drug administration. All animals were sacrificed 8 h after drug treatment and then their stomachs and small intestines were microscopically examined to assess the incidence of hyperaemia, shedding of epithelium, petechial and frank haemorrhages 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.

3.6. Acute toxicity study

Approximate lethal dose (ALD_{50}) of compound was determined in albino mice. After 24 h of drug administration, percent mortality in each group was observed and from the data obtained ALD_{50} was calculated by the method of Smith.[29]

References and notes

1. Ghorab, M. M.; Abdel Hamide, S. G.; El-Hakim, A. E. *Indian J. Heterocycl. Chem.* **1995**, *5*, 115.
2. Reddy, P. N. S.; Vasanatha, T. V.; Naga Raja, Ch. *Indian J. Chem.* **1999**, *38B*, 40.
3. Rao, A. D.; Shankar, C. R.; Rao, A. B.; Reedy, V. M. *Indian J. Chem.* **1986**, *25B*, 665.
4. Archana; Srivastava, V. K.; Ramesh Chandra; Ashok Kumar. Indian J. Chem. **2002**, 41B, 2371.
5. Sarvanana, J.; Mohan, S.; Manjjunatha, K. S. *Indian J. Heterocycl. Chem.* **1998**, *8*, 55.
6. Rani, Preeti; Archana; Srivastava, V. K.; Kumar, Ashok *Indian J. Chem.* **2002**, *41B*, 2642.
7. Bekhit, A. A.; Habib, N. S.; Park, Ji Young *Chem. Abstr.* **2005**, *142*, 114000f.
8. Kumar, A.; Singh, S.; Saxena, A. K.; Shanker, K. *Indian J. Chem.* **1988**, *27B*, 443.
9. Medina Julino, C.; Johanson Michael, G.; Li, An-Rong; Lu, Jiwen; Huang Alan, Xi; Zhu, Liusheng; Marcus Andrew, P.; PCT Int Appl. WO. 02 83,143. Chem. Abstr. **2002**, 137, 337907e.
10. Kumar, Ashok; Sharma, Shalabh; Bajaj, Kiran; Bansal, Deepti; Sharma, Shipra; Archana; Saxena, K. K.; Lata, S.; Gupta, B.; Srivastava, V. K. *Indian J. Chem.* **2003**, *42B*, 1979.
11. Kumar, Ashok; Sharma, Shalabh; Archana; Bajaj, Kiran; Sharma, Shipra; Panwar, Hemant; Singh, Tripti; Srivastava, V. K. *Bioorg. Med. Chem.* **2003**, *11*, 5293.
12. Kumar, A.; Verma, R. S.; Jaju, B. P.; Sinha, J. N. *J. Indian Chem. Soc.* **1990**, *69*, 920.
13. Singh, I. P.; Saxena, A. K.; Sinha, J. N.; Bhatnagar, K. P.; Shanker, K. *Indian J. Chem.* **1984**, *23B*, 592.
14. Goel, B.; Ram, T.; Tyagi, R.; Bansal, E.; Kumar, A.; Mukerjee, D.; Shina, J. N. *Eur. J. Med. Chem.* **1999**, *33*, 265.
15. Srivastava, S. K.; Yadav, R.; Srivastava, S. D. *Indian J. Chem.* **2004**, *42B*, 399.
16. Mishra, Suma; Srivastava, S. K.; Srivastava, S. D. *Indian J. Chem.* **1997**, *36B*, 826.
17. Agarwal, R.; Agarwal, C.; Singh, C.; Mishra, V. S. *Indian J. Chem.* **1989**, *28B*, 893.
18. Srivastava, S. K.; Srivastava, S. L.; Srivastava, S. D. *Indian J. Chem.* **2000**, *39B*, 464.
19. Baddi, M. M.; Mahajanshetti, C. S. *Indian J. Chem.* **1997**, *36B*, 1074.
20. Holla, B.; Shivarama; Malini, K. V.; Sooryanarayana, Rao B.; Sarajini, B. K; Suchetha, Kumari N. Eur. J. Med. Chem. **2003**, 38, 313.

21. Mohan, S.; Attimarad, Mahesh *Indian J. Heterocycl. Chem.* **2004**, *13*, 339.
22. Therien, Michel; Brideau, Christine; Chan, Chi Chung; Wanda, A.; Gauthier, Cromlish Jacques Yves; Gordon, Robert; Greig, Gillian; Korgman, Stocia; Lau, Sheuk Kun; Leblanc, Yves; Li, Chun-Sing; O' Neill, Gary P.; Riendeau, Denis; Roy, Patrick; Wang, Zhaoyin; Lijing Xu; Prasit, Petpiboon *Bioorg. Med. Chem. Lett.* **1997**, *7*, 47.
23. Roy, P.; Leblanc, Y.; Ball, R. G.; Brideau, C.; Chan, C. C.; Chauret, N.; Cromlish, W.; Ethier, D.; Gauthier, J. Y.; Gordon, R.; Greig, G.; Guay, J.; Kargman, S.; Lau, C. K.; Neill, G. O'.; Silva, J.; Therien, M.; Van staden, C.; Wong, E.; Xu, L.; Prasit, P. *Bio-org. Med. Chem. Lett.* **1997**, *7*, 57.
24. Wheelar, A. A.; Dats, W. M. *J. Am. Chem. Soc.* **1910**, *32*, 770.
25. Caroll King, L.; Robert, J.; Hlaracek, J. *Am. Chem. Soc.* **1950**, *72*, 3722.
26. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. NY* **1962**, *111*, 544.
27. Davis, J. E.; Kellet, D. N.; Pennington, J. C. *Arch. Int. Pharmacodyn. Ther.* **1976**, *221*, 274.
28. Verma, M.; Sinha, J. N.; Gujrati, V. R.; Bhalla, T. N.; Bhargava, K. S.; Shanker, K. *Pharmacol. Res. Commun.* **1981**, *13*, 967.
29. Smith, Q. E.. In *Pharmacological Screening test progress in Medicinal Chemistry*; Butterworth: London, 1960; Vol. I.

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Synthesis and anti-inflammatory activity of newer quinazolin-4-one derivatives

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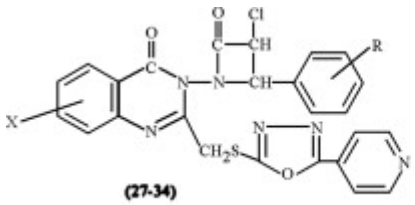
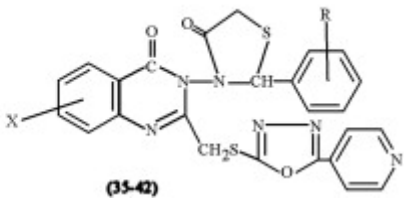
Abstract

2-Methyl-3-aminosubstituted-3*H*-quinazolin-4-ones (**1**–**2**), 2-methyl-3-(substituted-arylidene-amino)-substituted-3*H*-quinazolin-4-ones (**3**–**10**), 2-bromomethyl-3-(substituted-arylidene-amino)-substituted-3*H*-quinazolin-4-ones (**11**–**18**), 2-(5′-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(substituted-arylidene-amino)-substituted-3*H*-quinazolin-4-ones (**19**–**26**), 3-(3-chloro-2-oxo-4-substituted-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-substituted-3*H*-quinazolin-4-ones (**27**–**34**) and 3-(4-oxo-2-substituted-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-substituted-3*H*-quinazolin-4-ones (**35**–**42**) were synthesized in present study. All the compounds exhibited anti-inflammatory activity at the dose 50 mg/kg p.o. varying degree from 16.3 to 36.3% inhibition of oedema. Compound **40** showed same activity at 25, 50 and 100 mg/kg p.o. like standard drugs. The structure of all these newly synthesized compounds was confirmed by their analytical (C, H, N) and spectral (IR and ^{1}H NMR) data.

Graphical abstract

In the present study, we have synthesized new substituted-quinazolin-4-one derivatives and screened for their anti-inflammatory activity. The compound **40** has shown almost equipotent activity to that of standard drug.





Keywords: Quinazolin-4-ones; Azetidinones; Thiazolidinones; Oxadiazoles; Anti-inflammatory activity

Article Outline

- 5.1.16. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(arylidene-amino)-6-bromoquinazolin-4-one (**23**)
- 5.1.17. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(*p*-chloroarylidene-amino)-6-bromoquinazolin-4-one (**24**)
- 5.1.18. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(*p*-methoxyarylidene-amino)-6-bromoquinazolin-4-one (**25**)
- 5.1.19. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(*p*-hydroxyarylidene-amino)-6-bromoquinazolin-4-one (**26**)
- 5.1.20. 3-(3-Chloro-2-oxo-4-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-ones (**27**)
- 5.1.21. 3-(3-Chloro-2-oxo-4-{*p*-chloroaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-one (**28**)
- 5.1.22. 3-(3-Chloro-2-oxo-4-{*p*-methoxyaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-ones (**29**)
- 5.1.23. 3-(3-Chloro-2-oxo-4-{*p*-hydroxyaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-ones (**30**)
- 5.1.24. 3-(3-Chloro-2-oxo-4-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-ones (**31**)
- 5.1.25. 3-(3-Chloro-2-oxo-4-{*p*-chloroaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-ones (**32**)
- 5.1.26. 3-(3-Chloro-2-oxo-4-{*p*-methoxyaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-ones (**33**)
- 5.1.27. 3-(3-Chloro-2-oxo-4-{*p*-hydroxyaryl}-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-ones (**34**)
- 5.1.28. 3-(4-Oxo-2-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-one (**35**)
- 5.1.29. 3-(4-Oxo-2-{*p*-chloroaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-one (**36**)

Table 1. Characterizations and anti-inflammatory activity of compounds **19**–**42**

View Within Article

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[1]Part of Ph.D. thesis work.

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Synthesis and Antiinflammatory Activity of 2-[5'-(4-Pyridinyl)-1',2',3'-oxadiazol-2-yl-thiomethyl]-3-substituted-aryl-6-substituted-quinazolin-4-ones

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In present study, a novel series of quinazolin-4-ones derivatives *viz.*, 2-methyl-3-substituted aryl-6-substituted quinazolin-4-ones (**4-18**), 2-bromomethyl-3-substitutedaryl-6-substuted quinazolin-4-ones (**19-33**), 2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-yl-thiomethyl]-3-substituted aryl-6-substituted quinazolin-4-ones (**34-48**) have been synthesized. The structures of all these newly synthesized compounds were confirmed by their analytical and spectral data. The compounds were evaluated for their antiinflammatory activity. Compound **43** showed maximum antiinflammatory (36.25 %) activity at the dose of 50 mg/kg p.o.

Key Words: Quinazolin-4-ones, 1',3',4'-Oxadiazoles, Antiinflammatory activity.

INTRODUCTION

Quinazolinone derivatives have been found to possess potent wide spectrum of activities like antibacterial[1,2], anticonvulsant[3-5] and antiinflammatory[6-10]. It is also reported that substitution of halo group at 6th[8] and 8th[6] position in this nucleus enhances its antiinflammatory action. A large number of oxadiazoles[11-15] are reported to possess potent antiinflammatory activity. This prompted us to syntheses a new series of quinazolinone derivatives by incorporating the oxadiazole moiety at 2nd position of the quinazolinone nucleus. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR, ^{1}H NMR and mass spectrometry). All the compounds have been screened for their antiinflammatory activity.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. Analytical data of C, H, N were with in ± 0.4 % of the theoretical values. IR spectra (cm^{-1}) were recorded on Beckman-Acculab 10 spectrophotometer. ^{1}H NMR spectra were determined in $CHCl_3$ on Brucker 300-FT instrument.

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Synthesys of compounds

5-Bromoanthranilic acid and 5-iodoanthranilic acid: These compounds were prepared according to reported methods by Wheeler *et al.*[16] and Klemme *et al.*[17], respectively.

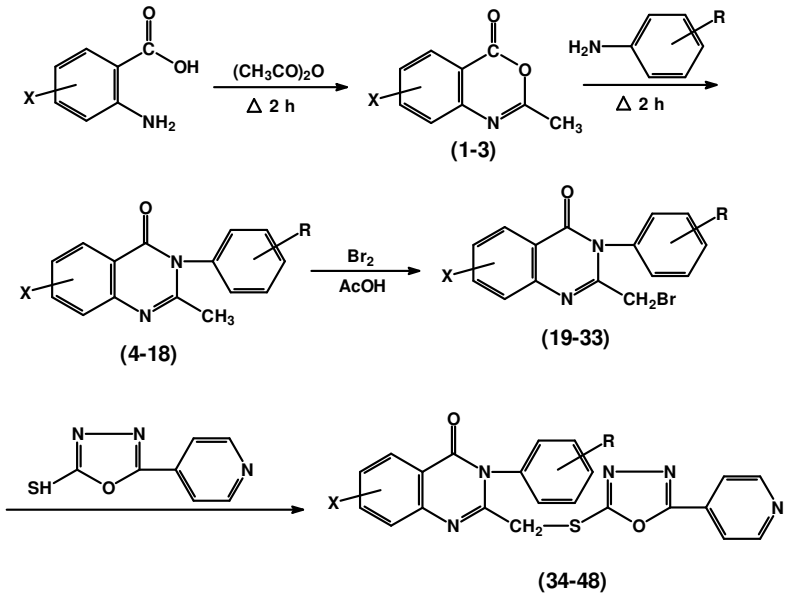
2-Methyl-6-substituted benzoxazin-4-one (1-3): These compounds were synthesized by known method[18].

A mixture of substituted anthranilic acid (0.19 mol) and acetic anhydride (142 mL, 99 %, 1.5 mol) was heated under reflux for 2 h. The excess of acetic anhydride was then distilled off under reduced pressure, on cooling the flask the residue solidified. The benzoxazinone was dissolved in hot dry ethyl acetate and the filtrate was treated with *n*-hexane just to remove turbidity and chilled in a ice bath and was dried *in vacuo* over calcium chloride.

2-Methyl-3-substituted aryl-6-substituted quinazolin-4-ones (4-18): A mixture of **1-3** (0.01 mol) and substituted aniline (0.01 mol) were heated on a free flame for 10-20 min. On cooling a jelly like mass was obtained. The analytical data of the compounds are given in Table-1. Compound **8**: m.p. 97 ºC, yield 55 %, m.f. $C_{16}H_{14}N_2O_2$, IR (KBr, ν_{max}, cm^{-1}): 1525 (C-N), 1460 (C-C of aromatic ring), 1580 (C=N), 1695 (C=O), 3020 (C-H aromatic), 2810-2930 (aliphatic C-H). ^{1}H NMR ($CDCl_3$) δ in ppm : 2.27 (s, 3H, CH_3), 3.41 (s, 3H, OCH_3), 7.26-7.90 (m, 8H, Ar-H): MS: m/z 266 $[M]^+$.

2-Bromomethyl-3-substituted aryl-6-substituted quinazolin-4-ones (19-33): Compounds (**19-33**) were synthesized by adding a solution of bromine (0.02 mol) in acetic acid dropwise with constant stirring in the cold solution of compounds (**4-18**) (0.01 mol). The reaction mixture was further stirred for 4 h. The solvent was distilled off and the residue thus obtained was washed with petroleum ether (40-60 ºC). The analytical data of the compounds are given in Table-1. Compound **23**: m.p. 141 ºC, yield 55 %, molecular formula $C_{16}H_{13}N_2O_2Br$, IR (KBr, ν_{max}, cm^{-1}): 1525 (C-N), 1465 (C-C of aromatic ring), 1580 (C=N), 1695 (C=O), 3025 (C-H aromatic), 765 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm : 3.40 (s, 3H, OCH_3), 2.89, (s, 2H, CH_2Br), 7.36-8.36 (m, 8H, Ar-H): MS: m/z 345 $[M]^+$.

2-[5'-(4-pyridinyl)-1',3',4'-oxadiazol-2'-ylthiomethyl]-3-substituted aryl-6-substituted quinazolin-4-ones (34-48): The solutions of (**19-33**) (0.03 mol) in pyridine (80 mL) and 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol (0.03 mol) were refluxed for 3 h. The contents were then poured onto crushed ice and solid masses were obtained (**Scheme-I**). The analytical data of the compounds are given in Table-1. Compound **38**: m.p. 163 ºC, yield 55 %, m.f. $C_{23}H_{17}N_5O_3S$. IR (KBr, ν_{max}, cm^{-1}): 1180 (C-O-C), 1525 (C-N), 1460 (C-C of aromatic ring), 1575 (C=N), 1690 (C=O), 1640, 1615, 1570, 1415, (ring str. of oxadiazole nucleus), 1065 (C-O str. of oxadiazole nucleus), 1270 (N-N). ^{1}H NMR ($CDCl_3$) δ in ppm: 2.75 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3), 8.01-8.70 (4H, pyridinyl ring). 7.26-8.33 (m, 8H, Ar-H): MS: m/z 443 $[M]^+$.



Scheme-I

Pharmacological evaluation: The experiments were performed with albino rats of the Charles-Foster strain of either sex, excluding pregnant females, of 70 to 95 d weighing 60 to 160 g. Acute toxicity was tested in albino mice (120-125 g). Food (chaw pallet) and water was given to the animals *ad libitum*. The test compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

Antiinflammatory activity: Antiinflammatory activity performed by carrageenan-induced paw oedema test in rats was done by following the procedure of Winter *et al.*[19]. The rats were divided into three groups (control, drugs treated and standard drugs) 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. The compound and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively, 1h before the carrageenan injection. The paw volume of each rat was measured before 1 and after 3 h of carrageenan treatment with the help of a plethysmo-meter. The percent antiinflammatory 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 paw volume of rats of the treated and control group, respectively. Results obtained were statistically analyzed.

Acute toxity: Approximate lethal dose (ALD_{50}) of all the compounds were investigated by the method of Smith[20].

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS **4-48**

Compd.	X	R	m.p. (ºC)	Recrystalliation solvent	Yield (%)	m.f.	Found (Calcd.) (%)		
							C	H	N
4	H	H	85	Ethanol	70	$C_{15}H_{12}N_2O$	76.40 (76.27)	5.16 (5.08)	11.92 (11.86)
5	H	2-Cl	83	Methanol	65	$C_{15}H_{11}N_2OCl$	66.78 (66.54)	4.01 (4.07)	10.43 (10.35)
6	H	4-Cl	86	Ethanol	70	$C_{15}H_{11}N_2OCl$	66.70 (66.54)	4.10 (4.07)	10.46 (10.35)
7	H	2-OCH_3	91	Methanol	85	$C_{16}H_{14}N_2O_2$	72.38 (72.18)	5.34 (5.26)	10.58 (10.53)
8	H	4-OCH_3	97	Ethanol	55	$C_{16}H_{14}N_2O_2$	72.41 (72.18)	5.32 (5.26)	10.62 (10.53)
9	6-I	H	137	Ethanol	50	$C_{15}H_{11}N_2OI$	49.50 (49.72)	3.18 (3.04)	7.96 (7.73)
10	6-I	2-Cl	156	Ethanol	50	$C_{15}H_{10}N_2OClI$	45.54 (45.40)	2.43 (3.52)	7.18 (7.06)
11	6-I	4-Cl	164	Ethanol	68	$C_{15}H_{10}N_2OClI$	45.61 (45.40)	2.61 (2.52)	7.23 (7.06)
12	6-I	2-OCH_3	180	Methanol	55	$C_{16}H_{13}N_2O_2I$	49.21 (48.98)	3.28 (3.32)	7.32 (7.14)
13	6-I	4-OCH_3	186	Ethanol	65	$C_{16}H_{13}N_2O_2I$	49.18 (48.98)	3.23 (3.32)	7.29 (7.14)
14	6-Br	H	123	Benzene	56	$C_{15}H_{11}N_2OBr$	57.26 (57.14)	3.23 (3.49)	8.94 (8.89)
15	6-Br	2-Cl	142	Ethanol	45	$C_{15}H_{10}N_2OBrCl$	51.78 (51.50)	2.69 (2.86)	8.07 (8.01)
16	6-Br	4-Cl	149	DMF/water	55	$C_{15}H_{10}N_2OBrCl$	57.81 (51.50)	2.71 (2.86)	8.05 (8.01)
17	6-Br	2-OCH_3	171	Ethanol	60	$C_{16}H_{13}N_2O_2Br$	55.36 (55.56)	5.58 (3.77)	8.32 (8.12)
18	6-Br	4-OCH_3	178	DMF	65	$C_{16}H_{13}N_2O_2Br$	55.41 (55.56)	5.54 (3.77)	8.29 (8.12)
19	H	H	98	Ethanol	65	$C_{15}H_{11}N_2OBr$	57.42 (57.14)	3.65 (3.49)	9.02 (8.89)
20	H	2-Cl	147	Ethanol	70	$C_{15}H_{10}N_2OBrCl$	51.63 (51.50)	2.72 (2.86)	8.08 (8.01)
21	H	4-Cl	152	Acetic acid	62	$C_{15}H_{10}N_2OBrCl$	51.65 (51.50)	2.69 (2.86)	8.03 (8.01)
22	H	2-OCH_3	134	Acetone/Pet. Ether	68	$C_{16}H_{13}N_2O_2Br$	55.79 (55.65)	3.82 (3.77)	8.22 (8.12)
23	H	4-OCH_3	141	Ethanol	55	$C_{16}H_{13}N_2O_2Br$	55.81 (55.65)	3.81 (3.77)	8.25 (8.12)
24	6-I	H	142	Methanol	66	$C_{15}H_{10}N_2OBrI$	40.26 (40.82)	2.19 (2.27)	6.16 (6.35)
25	6-I	2-Cl	163	Methanol	54	$C_{15}H_9N_2OBrClI$	38.01 (37.85)	2.08 (1.89)	5.67 (5.89)

Compd.	X	R	m.p. (ºC)	Recrystalliation solvent	Yield (%)	m.f.	Found (Calcd.) (%)		
							C	H	N
26	6-I	4-Cl	167	DMF/water	60	$C_{15}H_9N_2OBrClI$	37.96 (37.85)	2.10 (1.89)	5.63 (5.89)
27	6-I	2-OCH_3	208	Rectified Spirit	65	$C_{16}H_{12}N_2O_2BrI$	41.98 (40.76)	2.88 (2.55)	6.09 (5.94)
28	6-I	4-OCH_3	222	Ethanol	50	$C_{16}H_{12}N_2O_2BrI$	41.93 (40.76)	2.79 (2.55)	6.13 (5.94)
29	6-Br	H	95	Benzene	58	$C_{15}H_{10}N_2OBr_2$	57.33 (57.14)	3.64 (3.49)	9.03 (8.89)
30	6-Br	2-Cl	148	Methanol	52	$C_{15}H_9N_2OBr_2Cl$	51.68 (51.50)	2.79 (2.86)	8.10 (8.01)
31	6-Br	4-Cl	155	Ethanol	65	$C_{15}H_9N_2OBr_2Cl$	51.63 (51.50)	2.71 (2.86)	8.07 (8.01)
32	6-Br	2-OCH_3	210	DMF/water	57	$C_{16}H_{12}N_2O_2Br_2$	55.83 (55.56)	3.81 (3.77)	8.24 (8.12)
33	6-Br	4-OCH_3	216	Ethanol	54	$C_{16}H_{12}N_2O_2Br_2$	55.79 (55.56)	3.83 (3.77)	8.21 (8.12)
34	H	H	112	Ethanol	50	$C_{22}H_{15}N_5O_2S$	63.81 (63.92)	3.59 (3.63)	16.99 (16.94)
35	H	2-Cl	178	Ethanol	45	$C_{22}H_{14}N_5O_2SCl$	59.08 (58.99)	3.08 (3.13)	15.59 (15.64)
36	H	4-Cl	284	Methanol	40	$C_{22}H_{14}N_5O_2SCl$	58.77 (58.99)	3.16 (3.13)	15.57 (15.64)
37	H	2-OCH_3	155	Benzene	38	$C_{23}H_{17}N_5O_3S$	62.51 (62.30)	3.79 (3.84)	15.83 (15.80)
38	H	4-OCH_3	163	DMF	55	$C_{23}H_{17}N_5O_3S$	62.44 (62.30)	3.87 (3.84)	15.85 (15.80)
39	6-I	H	189	Ethanol	56	$C_{22}H_{14}N_5O_2IS$	48.69 (48.98)	2.64 (2.60)	12.92 (12.99)
40	6-I	2-Cl	197	Acetic acid	44	$C_{22}H_{13}N_5O_2IClS$	46.18 (46.03)	2.29 (2.27)	12.23 (12.21)
41	6-I	4-Cl	215	Methanol	51	$C_{22}H_{13}N_5O_2IClS$	46.15 (46.03)	2.25 (2.27)	12.25 (12.21)
42	6-I	2-OCH_3	221	Methanol	52	$C_{23}H_{16}N_5O_3IS$	48.40 (48.51)	2.86 (2.81)	12.33 (12.30)
43	6-I	4-OCH_3	227	Acetone	57	$C_{23}H_{16}N_5O_3IS$	46.48 (48.51)	2.83 (2.81)	12.31 (12.30)
44	6-Br	H	135	Ethanol	58	$C_{22}H_{14}N_5O_2BrS$	55.78 (55.66)	2.81 (2.85)	14.19 (14.23)
45	6-Br	2-Cl	185	Ethanol	49	$C_{22}H_{13}N_5O_2BrClS$	50.05 (50.14)	2.41 (2.47)	13.35 (13.29)
46	6-Br	4-Cl	198	Benzene	52	$C_{22}H_{13}N_5O_2BrClS$	50.23 (50.14)	2.44 (2.47)	13.35 (13.29)
47	6-Br	2-OCH_3	217	DMF	46	$C_{23}H_{16}N_5O_3BrS$	52.85 (52.87)	3.14 (3.06)	13.34 (13.41)
48	6-Br	4-OCH_3	223	Acetic acid	50	$C_{23}H_{16}N_5O_3BrS$	52.92 (52.87)	3.12 (3.06)	13.38 (13.41)

RESULTS AND DISCUSSION

All newly synthesized quinazolinones (**19-48**) have shown antiinflammatory activity of varying degree from 12.45 to 36.25 % and biological results are given in Table-2. All compounds of this series have been evaluated for their antiinflammatory activity against carrageenan induced rat hind

TABLE-2
ANTIINFLAMMATORY ACTIVITY OF TITLED COMPOUNDS (**19-48**)

Compd.* no.	X	R	Dose mg/kg p.o.	%Decrease in paw oedema antiinfammatory activity
19	H	H	50	12.45
20	H	2-Cl	50	18.79
21	H	4-Cl	50	17.55
22	H	2-OCH_3	50	15.56
23	H	4-OCH_3	50	14.78
24	6-I	H	50	14.50
25	6-I	2-Cl	50	19.97
26	6-I	4-Cl	50	18.25
27	6-I	2-OCH_3	50	17.67
28	6-I	4-OCH_3	50	16.88
29	6-Br	H	50	16.35
30	6-Br	2-Cl	50	21.27
31	6-Br	4-Cl	50	20.57
32	6-Br	2-OCH_3	50	19.48
33	6-Br	4-OCH_3	50	18.75
34	H	H	50	22.25
35	H	2-Cl	50	24.72
36	H	4-Cl	50	23.25
37	H	2-OCH_3	50	21.35
38	H	4-OCH_3	50	20.98
39	6-I	H	50	25.23
40	6-I	2-Cl	50	27.24
41	6-I	4-Cl	50	26.45
42	6-I	2-OCH_3	50	26.68
			25	17.20
43	6-I	4-OCH_3	50	36.25
			100	69.21
44	6-Br	H	50	25.67
45	6-Br	2-Cl	50	24.75
46	6-Br	4-Cl	50	24.95
47	6-Br	2-OCH_3	50	27.33
48	6-Br	4-OCH_3	50	26.59
			25	18.30
Phenylbutazone	-	-	50	36.80
			100	64.50

*ALD_{50} values of all compounds were found to be >1000 mg/kg p.o.

paw oedema test at a dose of 50 mg/kg per oral. The compounds (**19-33**) have shown modulate antiinflammatory activity (12.45-21.27 %). Further oxadiazole substituted compounds (**34-48**) have shown better antiinflammatory (21.35-36.25 %) activity than compounds (**19-33**) at the dose of 50 mg/kg p.o. Among these, compound **43** have shown most potent activity, which showed 36.25 % inhibition of oedema. This compound elicited almost equal activity like the standard drug phenylbutazone (36.8 % inhibition at 50 mg/kg p.o.).This compound was further screened for antiinflammatory activity at three graded doses that is 25, 50 and 100 mg/kg p.o. Interestingly, this compound showed better antiinflammatory activity than the standard drug at the dose of 100 mg/kg p.o.

REFERENCES

1. M.M. Ghorab, S.G. Abdel Hamide and A.E. El-Hakim, *Indian J. Heterocycl. Chem.*, **5**, 115 (1995),
2. P.N.S. Reddy, T.V. Vasanatha and Ch. N. Raja, *Indian J. Chem.*, **38B**, 40 (1999).
3. F.W. James, L.R. Terry, E.S. Merk, A.C. James and D.G. Thomas, *J. Med. Chem.*, **33**, 16 (1998).
4. Archana, V.K. Srivastava, R. Chandra and A. Kumar, *Indian J. Chem.*, **41B**, 2371 (2002).
5. O.A.R. El-Naser and B.S. El-Sayed, *Arzeim-Forsch/Drug Res.*, **44**, 915 (1994).
6. A. Kumar, S. Sharma, K. Bajaj, D. Bansal, S. Sharma, Archana, K.K. Saxena, S. Lata, B. Gupta and V.K. Srivastava, *Indian J. Chem.*, **42B**, 1979 (2003).
7. J. Sarvanana, S. Mohan and K.S. Manjjunatha, *Indian J. Heterocycl. Chem.*, **8**, 55 (1998).
8. P. Rani, Archana, V.K. Srivastava and A. Kumar, *Indian J. Chem.*, **41B**, 2642 (2002),
9. A. Kumar, R.S. Verma, B.P. Jaju and J.N. Sinha, *J. Indian Chem. Soc.*, **69**, 920 (1990).
10. A. Veerachamy, R. Viswas, M. Ramseshu and V.R. Kona, *Biol. Pharm. Bull.*, **28**, 1091 (2005).
11. A. Mohammad, A. Oberoi and A. Shah, *Indian J. Chem.*, **38B**, 237 (1999).
12. F.A. Omar, N.M. Mohfouz and M.A.D. Rahman, *Eur. J. Med. Chem.*, **31**, 819 (1996).
13. A.D. Rao, C.R. Shankar, A.B. Rao and V.M. Reddy, *Indian J. Chem.*, **25B**, 665 (1986).
14. M.S.Y. Khan, G. Chawla and A. Mueed, *Indian J. Chem.*, **43B**, 1302 (2004).
15. Y.M.S. Khan and M. Akhtor, *Indian J. Chem.*, **43B**, 900 (2003).
16. A.A. Wheelar and W.M. Oats, *J. Am. Chem. Soc.*, **32**, 770 (1910).
17. C.J. Klemme and J.H. Hunter, *J. Org. Chem.*, **5**, 227 (1940).
18. M.T. Bogert and H.A. Soli, *J. Am. Chem. Soc.*, **29**, 517 (1907).
19. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. NY*, **111**, 544 (1962).
20. Q.E. Smith, Pharmacological Screening Test Progress in Medicinal Chemistry, Butterworth, London, Vol. 1 (1960).

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Synthesis and Antiinflammatory Activity of Some New Indolyl Substituted Quinazolin-4-(3*H*)-ones

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A series of 2-methyl-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**1-2**), 2-chloroacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**3-4**), 2-hydrazinoacetylmethylene-3-(2'-substituted-indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**5-6**), 2-(substituted phenylmethyleneimino)aminoacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**7-14**) and 2-(substituted phenylaminomethyleneacetyl-4'-oxo-3'-thiazalidinyl)-3-(2"-substituted indol-3"-yl)-substituted quinazolin-4(3*H*)-ones (**15-22**) have been synthesized. The compounds were screened for their antiinflammatory activity and were compared with the standard drug phenylbutazone. Out of these compounds the most active was 2-(*p*-chlorophenyl aminomethylacetyl-4'-oxo-1'-thiazolidinyl)-3-(indol-3"-yl)-6,8-dibromo quinazokin-4(3*H*)-one (**19**). The structures of these compounds have been confirmed by elemental and spectral analysis.

Key Words: Synthesis, Substituted Quinazolin-4-(3*H*)-ones, Antiinflammatory activity.

INTRODUCTION

Quinazolin-4(3*H*)-ones have been reported a variety of biological activities such as antibacteral[1,2], antifungal[3], anticonvulsant[4] and anti-inflammatory[5-8]. However the substitution pattern in the quinazolinone nucleus at 2/3 position by different heterocyclic moieties markedly modulates their antiinflammatory activity. Many indole[9-12] and thiazolidinone[13,14] derivatives have also been reported to possess potent antiinflammatory activity. Incorporating thus moieties in 2/3 position of quinazolinone nucleus might be thought to yield more potent antiinflammatory and substitution at 2/3 position further results in protection against inflammations. These findings prompted us to synthesize a new series of quinazolinones with a hope to get a better antiinflammatory activity.

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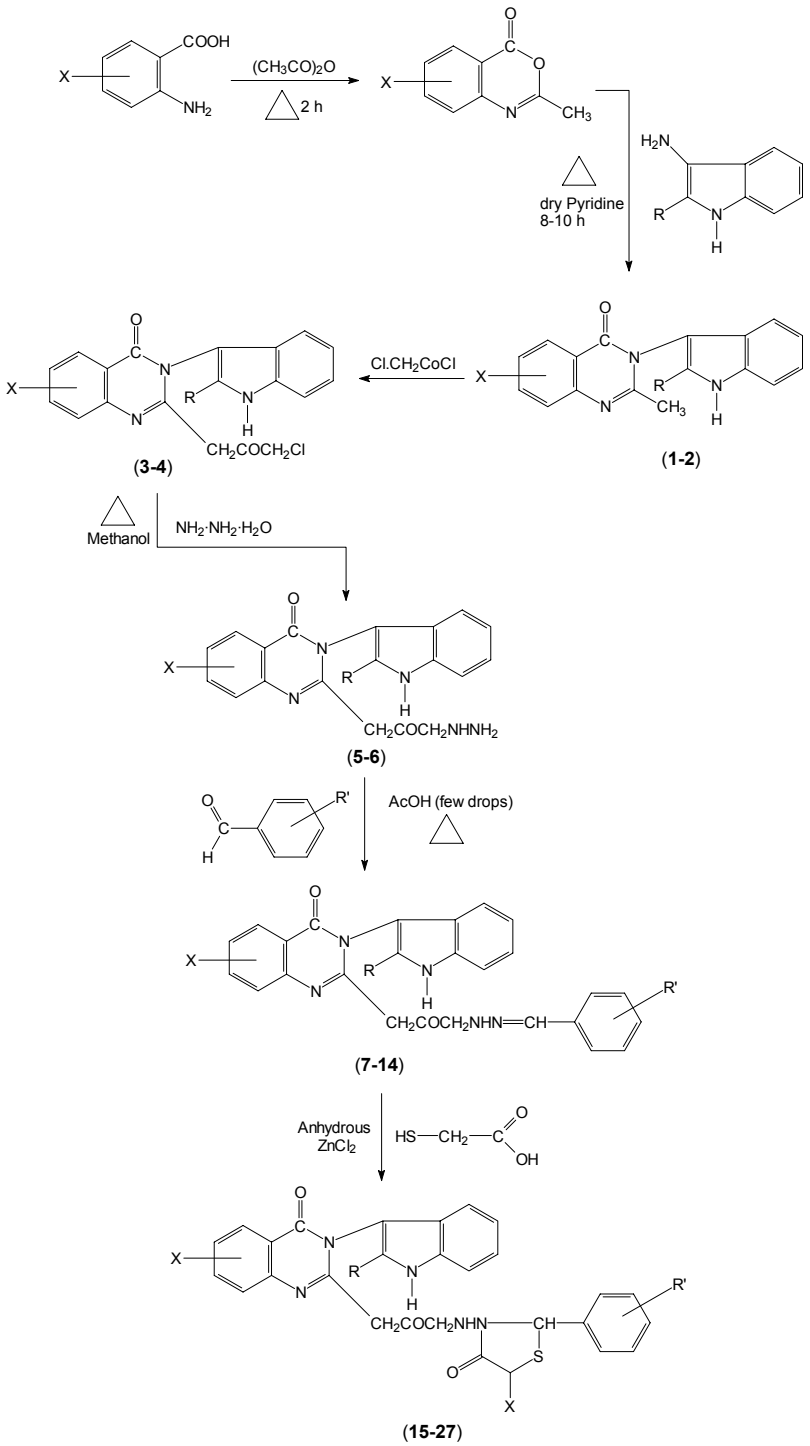
COOH
X
NH2
(CH3CO)2O
2 h
O
C
O
X
N
CH3
dry Pyridine
8-10 h
H2N
R
N
H
O
C
N
X
R
N
H
N
CH3
(1-2)
Cl.CH2CoCl
CH2COCH2Cl
(3-4)
Methanol
NH2·NH2·H2O
CH2COCH2NHNH2
(5-6)
R'
AcOH (few drops)
CH2COCH2NHN=CH
(7-14)
Anhydrous
ZnCl2
HS—CH2—C
OH
S
(15-27)

Scheme-I

The starting compound substituted anthranilic acid was prepared according to reported method by Wheeler *et al.*[15]. Compound 2-methyl-substituted benzoxazines was also synthesized by known method[16]. 2-Methyl-3-(2'-substituted indol-3'-yl-substituted quinazolin-4(3*H*)-ones (**1-2**), were prepared by the reaction of 2-methyl substituted benzoxazines with 2-substituted-3-aminoindoles in dry pyridine. On treatment with chloroacetyl chloride compounds (**1-2**) yielded the compounds (**3-4**). 2-hydrazinoacetyl methylene-3-(2'-substitutedindol-3'-yl)-substituted quinazolin-4(3H)-ones (**5-6**) were obtained by the reaction of compounds (**3-4**) with hydrazine hydrate. Furthermore reaction with substituted benzaldehyde in the presence of glacial acetic acid compounds (**5-6**) converted into 2-(substituted phenylmethyleneimino)aminoacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**7-14**). Thioglycolic acid reacted with compound (**7-14**) in the presence of anhydrous $ZnCl_2$ to yield. 2-(Substituted phenylaminomethylacetyl{4'-oxo-3'-thiazolidinyl}-3-(2"-substituted indol-3"-yl)-substituted quinazolin-4(3*H*)-ones (**15-22**). The structures of all newly synthesized compounds were confirmed by spectral and analytical data.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. The homogeneity of all compounds were checked by using silica gel-G plates. IR spectra were located in KBr on Beckman Acculab-10-spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra in $CDCl_3$ on Bruker-400-FT and Bruker-300-FT instrument (chemical shift in δ ppm). Analysis (C,H,N) were within ± 0.4 % of theoretical values.

2-Methyl-3-(indol-3'-yl)-6-bromoquinazolin-4(3H) one (1): A mixture of 3-aminoindole (0.01 mol) and 6-bromo benzoxazone (0.02 mol) in dry pyridine (80 mL) was refluxed for 12 h. After refluxing, excess of solvent was removed and the residue neutralized with HCl. The solid separated out was washed with water and recrystallized from benzene to yield compound **1**. m.p. 210 ºC, yield 80 % molecular formula $C_{17}H_{12}N_3OBr$.

IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1690 (C=0), 1605 (C=N), 570 (C-Br), 2960 (CH aliphatic). ^1H NMR ($CDCl_3$) δ in ppm: 7.90-8.50 (m, 8H, Ar-H), 8.95 (s, 1H, NH) 2.20 (s, 3H, CH_3).

Compound 2 was prepared using a similar procedure described for **1**. Physical data are given in Table-1.

2-Chloroacetylmethylene-3-(indol-3'-yl)-6-bromoquinazolin-4-(3*H*)-one (3): To a solution of 2-methyl-3-(indol-3'-yl)-6-bromoquinazolin-4-(3*H*)-one (**2**) (0.01 mol) in dry THF (100 mL) was added at 0 ºC temperature in chloroacetyl chloride drop by drop along with manual stirring for 5 h. The reaction mixture was further stirred for 6 h at room temperature.

TABLE-1
PHYSICAL† AND PHARMACOLOGICAL PROPERTIES OF COMPOUND **1-22**

Compd. no.	X	R	R^1	m.p. (ºC)	Yield (%)	Recrystallization solvent	m.f.	Antiinflammatory (%)*
1	6 Br	H	-	210	80	Benzene	$C_{17}H_{12}N_3OBr$	-
2	6,8-di Br	C_2H_5	-	260	75	Methanol	$C_{19}H_{15}N_3OBr_2$	-
3	6 Br	H	-	172	72	Methanol	$C_{19}H_{13}N_3O_2Br$	-
4	6,8-di Br	C_2H_5	-	240	70	Ethanol	$C_{21}H_{16}N_3O_2Br_2$	-
5	6 Br	H	-	220	75	Methanol	$C_{19}H_{16}N_5O_2Br$	-
6	6,8-di Br	C_2H_5	-	255	70	Acetic acid	$C_{21}H_{19}N_5O_2Br_2$	-
7	6 Br	H	4-Cl	180	62	Ethanol	$C_{26}H_{19}N_5O_2BrCl$	29.24
8	6 Br	H	4-OH	175	60	Methanol	$C_{26}H_{20}N_5O_3BrCl$	27.56
9	6 Br	H	4-OCH_3	190	60	Acetic acid	$C_{27}H_{22}N_5O_3BrCl$	28.44
10	6 Br	H	4-OCH_3	198	58	Ethanol	$C_{27}H_{22}N_5O_2Br$	26.18
11	6,8-di Br	C_2H_5	4-Cl	230	56	Benzene	$C_{28}H_{22}N_5O_2Br_2Cl$	34.32
12	6,8-di Br	C_2H_5	4-OH	225	62	Ethanol	$C_{28}H_{23}N_5O_3Br_2$	32.22
13	6,8-di Br	C_2H_5	4-OCH_3	218	60	Methanol	$C_{29}H_{25}N_5O_3Br_2$	33.68
14	6,8-di Br	C_2H_5	4-CH_3	208	55	Acetone	$C_{29}H_{25}N_5O_2Br_2$	30.48
15	6 Br	H	4-Cl	215	45	Benzene	$C_{28}H_{21}N_5O_3SBr_2$	36.18
16	6 Br	H	4-OH	220	52	Acetic acid	$C_{28}H_{22}N_5O_4SBr$	34.12
17	6 Br	H	4-OCH_3	140	48	Ethanol	$C_{29}H_{24}N_5O_4SBr$	35.44
18	6 Br	H	4-OCH_3	250	50	Acetone	$C_{29}H_{24}N_5O_3SBr$	32.56
19	6,8-di Br	C_2H_5	4-Cl	260	46	Methanol	$C_{30}H_{24}N_5O_3SBr_2Cl$	38.34
20	6,8-di Br	C_2H_5	4-OH	242	45	Benzene	$C_{30}H_{25}N_5O_4SBr_2$	35.82
21	6,8-di Br	C_2H_5	4-OCH_3	205	50	Ethanol	$C_{31}H_{27}N_5O_4SBr_2$	36.84
22	6,8-di Br	C_2H_5	4-CH_3	224	48	Benzene	$C_{31}H_{27}N_5O_3SBr_2$	34.89
	Phenylbutazane		–	–	–	–	–	37.22

†Elemental analysis for C, H, N was obtained for all compounds with ± 0.4 % of the theoretical values; *Dose 50 mg/kg p.o.

After stirring, excess of solvent was distilled off, cooled poured onto crushed ice and filtered. The solid thus obtained was recrystallized from methanol to yield 3. m.p. 172 ºC, yield 72 %, m.f. $C_{19}H_{13}N_3O_2BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3260 (NH), 2950 (CH-aliphatic), 1700 (C=O), 1595 (C=N), 580 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm: 7.95-8.60 (m, 8H, Ar-H), 9.05 (s, 1H, NH), 3.95 (s, 2H, CH_2), 4.15 (s, 2H, CH_2Cl).

Compound 4 was prepared using a similar procedure described for 3 and physical data are given in Table-1.

2-(*p*-Chlorophenylmethylenimino)aminoacetylmethylene-3-(indol-3'-yl)-6-bromo-quinazolin-4-(3*H*)-one (7): A mixture of compound **5** (0.01 mol) and *p*-chlorobenzaldehydle (0.01 mol) in methanol (60 mL) was refluxed for 8 h in presence of glacial acetic acid (4 mL). The excess of solvent was distilled off and the residue thus obtained washed with diethyl either and recrystallized from ethanol to yield **7**. m.p. 180 ºC, yield 62 %, m.f. $C_{29}H_{19}N_5O_2BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3280 (NH), 1700 (C=O), 1590 (C=N), 2970 (CH aliphatic), 570 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm: 7.80-8.60 (m, 12H, Ar-H), 9.05 (s, 1H, NH), 4.12 (d, 2H, CH_2NH), 3.90 (d, 2H, CH_2-CO), 5.65 (t, 1H, NH-N=CH), 6.05 (s, 1H, =CH-Ar).

All the compounds (**8-14**) of this step were prepared using a similar procedure described for **7** and physical data are given in Table-1.

2-(*p*-Chlorophenylaminomethylacetyl-4'-oxo-3'-thiazolidinyl)-3-(indol-3''-yl)-6-bromo quinazolin-4-(3*H*)-one (15): A mixture of compound **7** (0.01 mol) and thioglycolic acid (0.01 mol) in the presence of anhydrous $ZnCl_2$ and absolute ethanol (80 mL) was refluxed for 16 h. The solvent was removed under reduced pressure. The solid thus obtained was treated with saturated solution of $NaHNO_3$ and then washed with water, dried over anhydrous sodium sulphate. The product finally obtained was recrystallized from methanol to give **15**. Compound **19**: m.p. 215 ºC, yield 45 %, m.f. $C_{28}H_{21}N_5O_3BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3275 (NH), 1705 (C=O), 1600 (C=N), 2975 (CH aliphatic), 570 (C-Br), 690 (C-S-C). ^{1}HNMR ($CDCl_3$) δ in ppm: 7.15-8.50 (m, 12H, Ar-H), 9.15 (s, 1H, NH), 4.16 (s, 2H, CH_2NH), 3.85 (d, 2H, CH_2), 5.60 (t, 1H, NH-N), 6.12 (s, 1H, CH), 3.65 (s, 2H, CH_2 of β-thiolactam ring).

All the compounds (**16-22**) of this step were prepared using a procedure described for **15** and physical data are given in Table-1.

Antiinflammatory activity against carragunan induced hind paw oedema in rats was determined by the method of Winter *et al.*[17]. This study was conducted on albino rats of either sex (100-175 g). The rats were divided into groups of five animals each. Compounds were screened for anti-inflammatory activity at 50 mg/kg per oral. The percentage of antiinflammatory activity was calculated according to the following formula.

$$\text{Antiinflammatory activity (\%)} = 1 - \frac{V_t}{V_c} \times 100$$

where V_t and V_c are the volume of oedema in drug treated and control group, respectively. Phenylbutazone was used as a reference drug for comparative evaluation.

RESULTS AND DISCUSSION

Compound **7-22** have been tested for their antiinflammatory activity at the dose of 50 mg/kg p.o. of varying degree from 26.18 to 88.34 % and biological result are given in Table-1. Among these compounds, compound **19** found to possess most potent antiinflammatory activity than other compounds. Compound **7-14** exhibited mild to moderate antiinflammatory activity (26.18 to 34.32 %). The cyclization of these derivatives into their corresponding thiazolidinones (**15-22**) enhanced antiinflammatory activity (32.56 to 38.34 %). It is observed that compound (**10**) having *p*-methylphenyl group as substitutent showed least activity (26.18 %). While compound (**19**) substituted with 4-chlorophenyl ring exhibited the maximum activity (38.34 %). This compound showed better antiinflammatory activity (38.34 %) at the dose of 50 mg/kg p.o. than that of standard drug phenyl butazone (37.22 %).

REFERENCES

1. M.M. Gharab, Abdel, S.G. Hamide and A.E. El-Hakim, *Indian J. Heterocycl. Chem.*, **5**, 115 (1995).
2. P.S.N. Reddy, T.V. Vasantha and C.N. Raju, *Indian J. Chem.*, **38B**, 40 (1999).
3. P. Paneerseelvam, R.V.P. Chandran and S.K. Sridhar, *Indian J. Pharm. Sci.*, **65**, 268 (2003).
4. F.J. Wolfe, L.T. Ratham, M.C. Sleevi, J.A. Campbell and T.D. Greenwood. *J. Med. Chem.*, **33**, 161 (1990).
5. A. Kumar, R.S. Verma, B.P. Jaju and J.N. Sinha, *J. Indian Chem. Soc.*, **67**, 920 (1990).
6. J.S. Mohan and K.S. Manjunatha, *Indian J. Heterocycl. Chem.*, **8**, 115 (1998).
7. R. Tyagi, B. Goel, V.K. Srivastava and A. Kumar, *Chem. Abstr.*, **131**, 129966x (1999).
8. L.A. Lerry, J.B. Michael, B.J. Charles, E.G. Don and C.U. David, *Chem. Abstr.*, **135**, 196553t (2001).
9. R. Sharma, *Chem. Abstr.*, **136**, 134670d (2002).
10. V.N. Sonar, Y.S. Khadar and N. Sreenivasulu, *Indian J. Heterocycl. Chem.*, **10**, 299 (2001).
11. E. Bansal, V.K. Srivastava and A. Kumar, *Indian J. Chem.*, **39B**, 357 (2000).
12. Mohd. Amir, N. Dhar and S.K. Tiwari, *Indian J. Chem.*, **36B**, 96 (1997).
13. S. Mishra, S.K. Srivastava and S.D. Srivastava, *Indian J. Chem.*, **36B**, 826 (1997).
14. S.K. Srivastava, R. Yadav and S.D. Srivastava, *Indian J. Chem.*, **43B**, 399 (2004).
15. A.A. Wheeler and W.M. Dats, *J. Am. Chem. Soc.*, **32**, 770 (1910).
16. M.T. Bogert and H.A. Soil, *J. Am. Chem. Soc.*, **29**, 517 (1907).
17. C.A. Winter, E.A. Rislesy and G.W. Nuss, *Proc. Soc. Exp. Biol.*, **111**, 544 (1962).

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