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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).

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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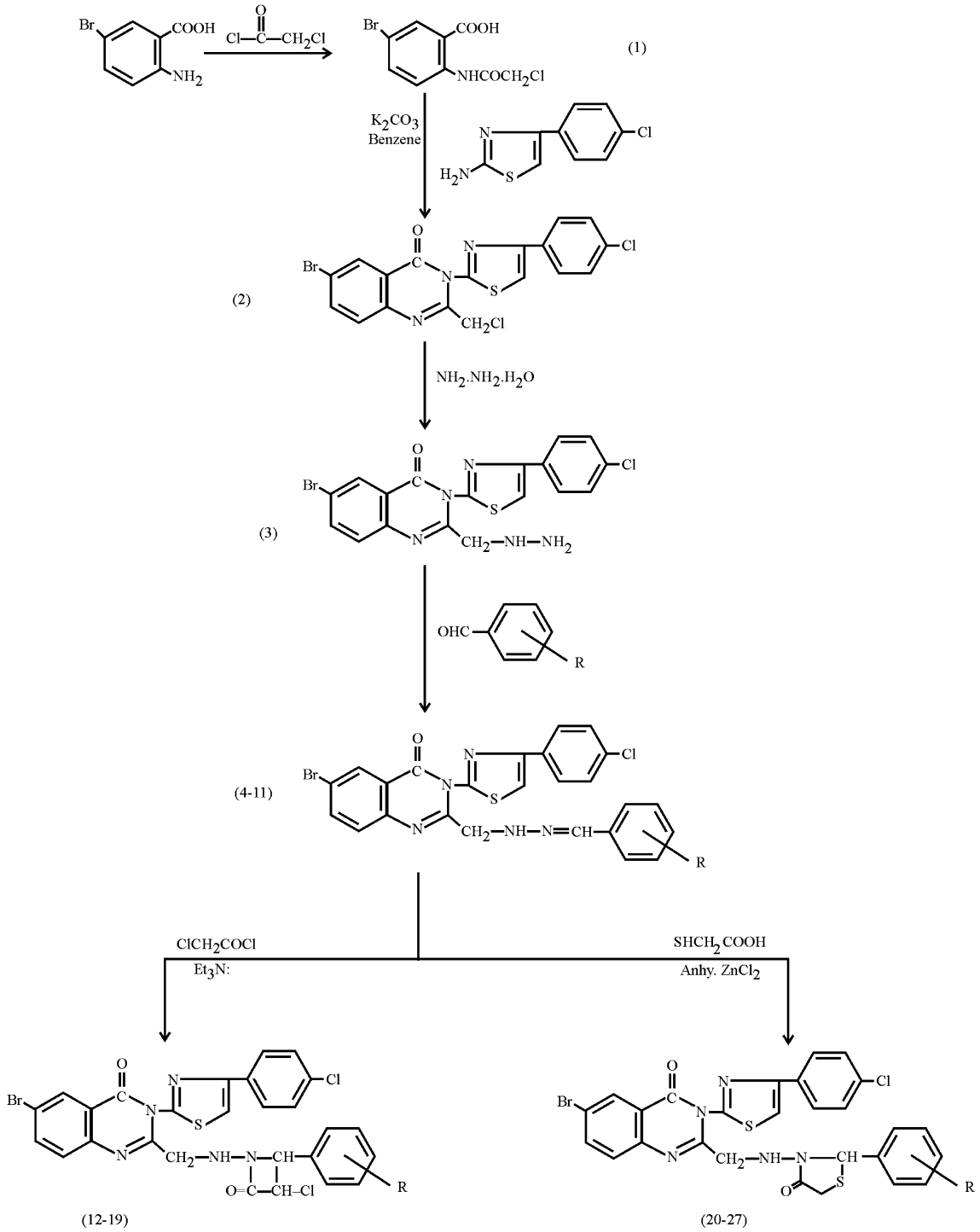

thiazol-2′-yl]-2-[(4″-oxo-2″-substitutedphenyl-3″-chloro-azetidin-1″-yl)aminomethyl]-6-bromo-quinazolin-4-ones (**12**–**19**) have been synthesized by refluxing the compounds (**4**–**11**) with chloroacetylchloride and trimethylamine in the presence of dry benzene. Treatment of (**4**–**11**) with 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]

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