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ScienceDirect
European Journal of Medicinal Chemistry 44 (2009) 83–90
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Original article

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

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Received 17 September 2006; received in revised form 6 March 2008; accepted 13 March 2008
Available online 1 April 2008

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.

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

1. Introduction

Quinazolinone derivatives have been found to possess potent wide spectrum of activities like antibacterial [1,2], antifungal [3–5], anticonvulsant [6] and anti-inflammatory [7–10]. It has been reported that substitution of different heterocyclic moieties at 2 or 3 position of quinazolinone nucleus modulates the anti-inflammatory activity. A large numbers of azetidinones [11,12], thiazolidinones [13,14] and oxadiazoles [15–18] were reported to possess anti-inflammatory activity. In the light of these observations this prompted us to synthesize a new series of quinazolinone derivatives by incorporation the azetidinone and thiazolidinone moieties at 3rd position of quinazolinone nucleus. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR and ^{1}H NMR). All the compounds have been screened for their anti-inflammatory activity.

2. Chemistry

Compound 2-methyl-3-aminosubstituted-3*H*-quinazolin-4-ones (**1**–**2**) were prepared according to reported method by Kumar et al. [19]. 2-Methyl-3-arylidene-amino-3*H*-quinazolin-4-one (**3**), 2-methyl-3-(*p*-chloroarylidene)-amino-3*H*-quinazolin-4-one (**4**), and 2-methyl-3-(*p*-methoxyarylidene)-amino-3*H*-quinazolin-4-one (**5**) were prepared by known method Arques et al. [20]. 2-Methyl-3-(*p*-hydroxyarylidene)-amino-3*H*-quinazolin-4-one (**6**) and 2-methyl-3-(arylidene)-amino-6-bromo-3*H*-quinazolin-4-one (**7**) were also prepared according to reported method by Roshdy et al. [21] and Sammour et. al. [22], respectively. Compounds **1**–**2** on reaction with substituted-benzaldehyde converted in to 2-methyl-3-(substituted-arylidene)aminosubstituted-3*H*-quinazolin-4-ones (**8**–**10**). On bromination in glacial acetic acid (**3**–**10**) yielded 2-bromomethyl-3-(substituted-arylidene)aminosubstituted-3*H*-quinazalin-4-ones (**11**–**18**). Further, more the reaction with 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol in pyridine gave 2-(5′-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(substituted-arylidene-amino)-substituted-3

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

0223-5234/$ - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2008.03.018

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 by the reaction of compounds **19–26** with chloroacetyl chloride and thioglycolic acid respectively.

3. Pharmacological result and discussion

All these newly synthesis compounds **19–42** were tested in vivo in order to evaluate their pharmacological activity. These compounds were screened for their anti-inflammatory profile at the dose of 50 mg/kg p.o. exhibiting substantive anti-inflammatory activity of varying degree from 16.3 to 36.3% the biological results are given in Table 1. It was observed that compound **40** showed maximum activity, which showed 36.3 inhibition of oedema. Interestedly this compound showed equal anti-inflammatory activity like standard drug phenylbutazone at the dose of 25, 50 and 100 mg/kg p.o.

Furthermore the substitution with phenyl group having chloro group at *p*-position showed better anti-inflammatory activity. Substitutions at 6 position of quinazolin-4-ones nucleus with electronegative atom increase the anti-inflammatory activity. Cyclisation of arylidene compounds into azetidinones

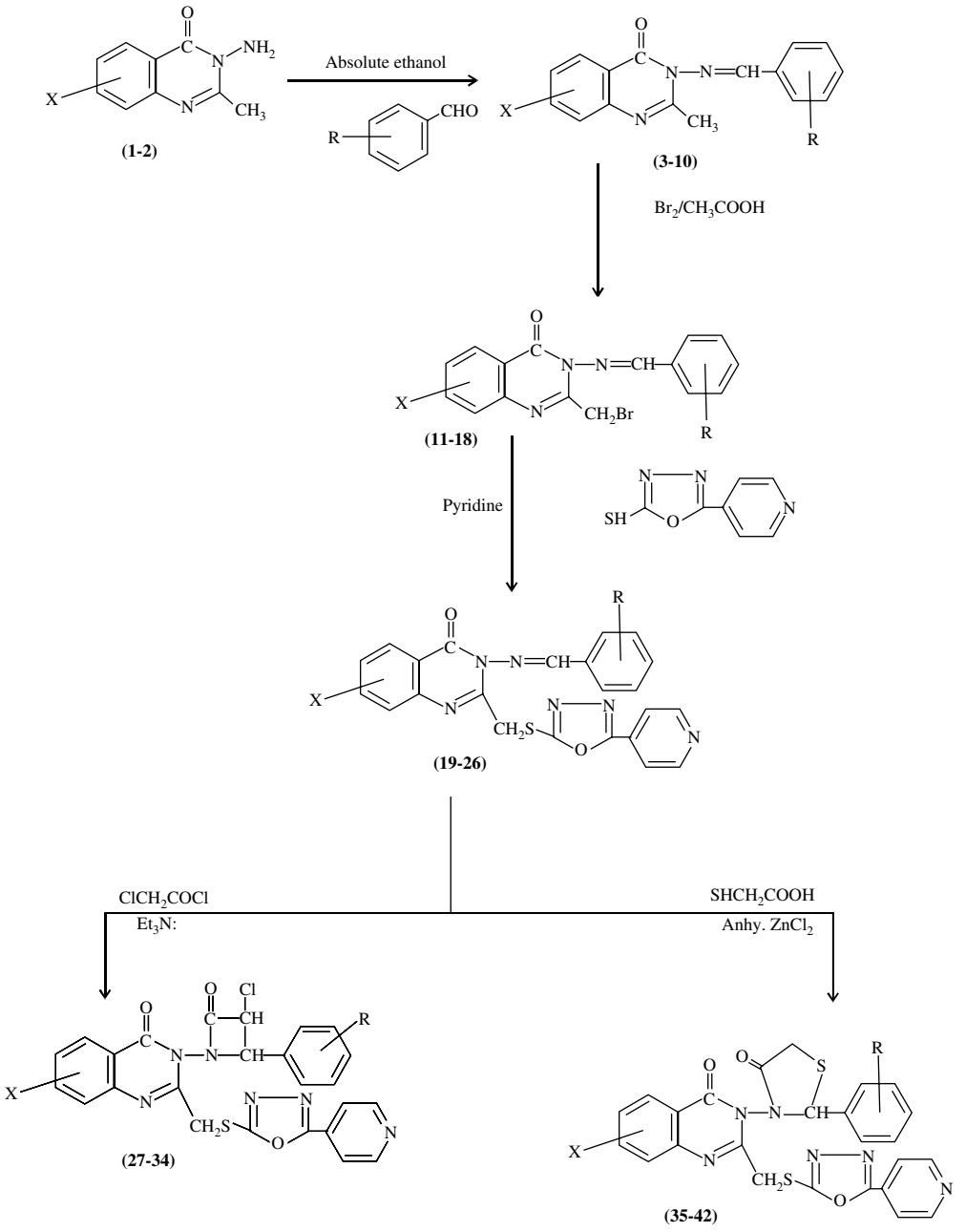

Table 1
Characterizations and anti-inflammatory activity of compounds **19–42**

Compound no.	X	R	Dose (mg/kg p.o.)	% Anti-inflammatory activity
19	H	H	50	16.3
20	H	*p*-Cl	50	23.7
21	H	*p*-OCH_3	50	20.0
22	H	*p*-OH	50	18.2
23	6 Br	H	50	19.4
24	6 Br	*p*-Cl	50	26.4
25	6 Br	*p*-OCH_3	50	24.4
26	6 Br	*p*-OH	50	22.3
27	H	H	50	25.1
28	H	*p*-Cl	50	27.9
29	H	*p*-OCH_3	50	26.1
30	H	*p*-OH	50	25.7
31	6 Br	H	50	26.3
32	6 Br	*p*-Cl	50	29.9
33	6 Br	*p*-OCH_3	50	28.6
34	6 Br	*p*-OH	50	27.4
35	H	H	50	30.1
36	H	*p*-Cl	50	34.1
37	H	*p*-OCH_3	50	33.8
38	H	*p*-OH	50	31.7
39	6 Br	H	50	31.3
40	6 Br	*p*-Cl	25	25.2
			50	36.3
			100	66.9
41	6 Br	*p*-OCH_3	50	35.3
42	6 Br	*p*-OH	50	32.7
Phenylbutazone		–	25	25.4
			50	36.8
			100	66.4

(**27–34**) enhanced the % anti-inflammatory activity of the compounds (25.1–29.9%) and into thiazolidinones (**35–42**) (30.1–36.3%), It is interesting to point out that thiazolidinones derivative showed better anti-inflammatory activity than that of azetidinones derivative.

4. Conclusion

It may be concluded that the compounds having 3-amino-2-methyl-6-bromoquinazolin-4-onyl moiety showed more protection than the compounds having 3-amino-2-methyl-quinazolin-4-onyl moiety. Further, thiazolidinones showed more potent anti-inflammatory activity in comparison to their corresponding azetidinones.

Furthermore, we also conclude that substitution with *p*-chloro phenyl group was found to increase the anti-inflammatory activity.

5. Experimental

5.1. Chemistry

Melting points were taken in open capillaries on Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel-G coated plats. Elemental analysis (C, H, N) was performed on a Perkin–Elmer 2400 analyzer and values were with in ±0.4% of the calculated. The IR spectra (cm^{-1}) were recorded in film or in potassium bromide disks on a Beckman Acculab-10-spectrophotometer (ν_{max} in cm^{-1}). The ^1H spectra were recorded on a DPX-300 MHz Bruker FT-NMR spectrometer in $CDCl_3$/DMSO-d_6 instrument.

*5.1.1. 2-Methyl-3-[(p-chloroarylidene) amino]-6-bromoquinazolin-4-one (**8**)*

Yield 70% (benzene): mp 178 °C; IR (KBr) ν_{max} in cm^{-1}: 2950 (CH_3), 1690 (C=O), 1600 (C=N), 1542 (C=C aromatic), 795 (Ar–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.52 (s, 1H, N=CH–Ar), 7.24–8.01 (m, 7H, Ar–H), 2.40 (s, 3H, CH_3). Anal. Calcd for $C_{16}H_{11}N_3OBrCl$: C, 50.99; H, 2.92; N, 11.15. Found: C, 50.79; H, 2.94; N, 11.19. MS: $[M]^+$ at *m/z* 376.5.

*5.1.2. 2-Methyl-3-[(p-methoxyarylidene) amino]-quinazolin-4-one (**9**)*

Yield 50% (ethanol): mp 155 °C; IR (KBr) ν_{max} in cm^{-1}: 3025 (CH aromatic), 2950 (CH_3), 1695 (C=O), 1602 (C=N), 1545 (C=C aromatic), 1175 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.50 (s, 1H, N=CH–Ar), 7.28–8.04 (m, 7H, Ar–H), 3.31 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3). Anal. Calcd for $C_{17}H_{14}N_3O_2Br$: C, 54.84; H, 3.76; N, 11.29. Found: C, 54.69; H, 3.78; N, 11.32. MS: $[M]^+$ at *m/z* 372.

*5.1.3. 2-Methyl-3-[(p-hydroxyarylidene) amino]-quinazolin-4-one (**10**)*

Yield 55% (ethanol): mp 135 °C; IR (KBr) ν_{max} in cm^{-1}: 3425 (Ar–OH), 2950 (CH_3), 1695 (C=O), 1600 (C=N), 1545 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.30 (s, 1H, Ar–OH), 8.56 (s, 1H, N=CH–Ar), 7.30–8.05 (m, 7H, Ar–H), 2.42 (s, 3H, CH_3). Anal. Calcd for $C_{16}H_{12}N_3O_2Br$: C, 53.63; H, 3.35; N, 11.73. Found: C, 53.81; H, 3.34; N, 11.77. MS: $[M]^+$ at *m/z* 358.

*5.1.4. 2-Bromomethyl-3-[(arylidene) amino]-quinazolin-4-ones (**11**)*

Compound **11** was synthesized by adding solution of bromine (0.02 mol) in acetic acid drop wise with constant stirring in the cold solution of compound **3** (0.01 mol). The reaction mixture was further stirred for 4 h and left for over night. The solvent was distilled off and the residue thus obtained was washed with water, filtrated, dried and recrystallized from ethanol to give compound **11**. Yield 65%: mp 137 °C; IR (KBr) ν_{max} in cm^{-1}: 2945 (CH_2), 1690 (C=O), 1595 (C=N), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.53 (s, 1H, N=CH–Ar), 7.35–8.00 (m, 9H, Ar–H), 3.69 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{12}N_3OBr$: C, 56.14; H, 3.51; N, 12.28. Found: C, 56.21; H, 3.53; N, 12.26. MS: $[M]^+$ at *m/z* 342.

The following compounds were prepared using a similar procedure as described for compound **11**.

*5.1.5. 2-Bromomethyl-3-[(p-chloroarylidene) amino]-quinazolin-4-ones (**12**)*

Yield 65% (ethanol): mp 182 °C; IR (KBr) ν_{max} in cm^{-1}: 2940 (CH_2), 1695 (C=O), 1590 (C=N), 1545 (C=C aromatic), 793 (Ar–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.56 (s, 1H, N=CH–Ar), 7.29–8.06 (m, 8H, Ar–H), 3.64 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{11}N_3OBrCl$: C, 50.99; H, 2.92; N, 11.15. Found: C, 51.11; H, 2.90; N, 11.17. MS: $[M]^+$ at *m/z* 376.5.

*5.1.6. 2-Bromomethyl-3-[(p-methoxyarylidene) amino]-quinazolin-4-ones (**13**)*

Yield 50% (benzene): mp 165 °C; IR (KBr) ν_{max} in cm^{-1}: 2944 (CH_2), 1698 (C=O), 1600 (C=N), 1540 (C=C aromatic), 1183 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.56 (s, 1H, N=CH–Ar), 7.28–8.02 (m, 8H, Ar–H), 3.66 (s, 2H, CH_2–Br), 3.36 (s, 3H, OCH_3). Anal. Calcd for $C_{17}H_{14}N_3OBr$: C, 54.84; H, 3.76; N, 11.29. Found: C, 54.96; H, 3.78; N, 11.30. MS: $[M]^+$ at *m/z* 372.

*5.1.7. 2-Bromomethyl-3-[(p-hydroxyarylidene) amino]-quinazolin-4-ones (**14**)*

Yield 55% (acetone): mp 147 °C; IR (KBr) ν_{max} in cm^{-1}: 3425 (Ar–OH), 2948 (CH_2), 1694 (C=O), 1595 (C=N), 1543 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.30 (s, 1H, Ar–OH), 8.54 (s, 1H, N=CH–Ar), 7.28–7.99 (m, 8H, Ar–H), 3.66 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{12}N_3O_2Br$: C, 53.63; H, 3.35; N, 11.73. Found: C, 51.51; H, 3.34; N, 11.75. MS: $[M]^+$ at *m/z* 358.

*5.1.8. 2-Bromomethyl-3-[(arylidene) amino]-6-bromo-quinazolin-4-ones (**15**)*

Yield 55% (methanol): mp 169 °C; IR (KBr) ν_{max} in cm^{-1}: 2950 (CH_2), 1700 (C=O), 1590 (C=N), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.59 (s, 1H, N=CH–Ar), 7.20–8.08 (m, 8H, Ar–H), 3.70 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{11}N_3OBr_2$: C, 45.61; H, 2.61; N, 9.98. Found: C, 45.73; H, 2.60; N, 10.01. MS: $[M]^+$ at *m/z* 421.

*5.1.9. 2-Bromomethyl-3-[(p-chloroarylidene) amino]-6-bromo-quinazolin-4-ones (**16**)*

Yield 60% (methanol): mp 189 °C; IR (KBr) ν_{max} in cm^{-1}: 2940 (CH_2), 1694 (C=O), 1600 (C=N), 1546 (C=C aromatic) 785 (Ar–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.62 (s, 1H, N=CH–Ar), 7.15–7.98 (m, 7H, Ar–H), 3.65 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{10}N_3OBr_2Cl$: C, 42.15; H, 2.19; N, 9.22. Found: C, 42.21; H, 2.17; N, 9.24. MS: $[M]^+$ at *m/z* 455.5.

*5.1.10. 2-Bromomethyl-3-[(p-methoxyarylidene) amino]-6-bromo-quinazolin-4-ones (**17**)*

Yield 60% (benzene): mp 172 °C; IR (KBr) ν_{max} in cm^{-1}: 2948 (CH_2), 1698 (C=O), 1600 (C=N), 1546 (C=C aromatic), 1180 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 13 (s, 1H, N=CH–Ar), 7.26–8.02 (m, 7H, Ar–H), 3.62 (s, 2H, CH_2–Br), 3.35 (s, 3H, OCH_3). Anal. Calcd for $C_{17}H_{13}N_3O_2Br_2$: C, 45.23; H, 2.88; N, 9.31. Found: C, 45.40; H, 2.86; N, 9.35. MS: $[M]^+$ at *m/z* 451.

*5.1.11. 2-Bromomethyl-3-[(p-hydroxyarylidene) amino]-6-bromo-quinazolin-4-ones (**18**)*

Yield 75% (ethanol): mp 144 °C; IR (KBr) ν_{max} in cm^{-1}: 3420 (Ar–OH), 2940 (CH_2), 1694 (C=O), 1598 (C=N), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.38 (s, 1H, Ar–OH), 8.63 (s, 1H, N=CH–Ar), 7.29–8.05 (m, 7H, Ar–H), 3.67 (s, 2H, CH_2–Br). Anal. Calcd for $C_{16}H_{11}N_3O_2Br_2$: C, 43.94; H, 2.52; N, 9.61. Found: C, 43.83; H, 2.51; N, 9.62. MS: $[M]^+$ at *m/z* 437.

*5.1.12. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(arylidene-amino)-quinazolin-4-one (**19**)*

To a solution of compound **11** (0.01 mol) in pyridine (80 ml) and 5-(4-pyridinyl) 1,3,4-oxadiazole-2-thiol (0.01 mol) were refluxed for 3 h. The contents were then poured onto crushed ice bath and a solid mass, which separated out, was filtered and recrystallized from ethanol to give compound **19**. Yield 55%: mp 125 °C; IR (KBr) ν_{max} in cm^{-1}: 2935 (CH_2), 1695 (C=O), 1598 (C=N), 1635, 1610, 1580, 1420, 1070 (st. of oxadiazole), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.64 (s, 1H, N=CH–Ar), 8.21 (dd, $J = 8$ Hz, 2H, Pyr–H2), 7.30–8.02 (m, 11H, 9Ar–H, 2H, Pyr–H3), 3.10 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{16}N_6O_2S$: C, 62.73; H, 3.64; N, 19.09. Found: C, 62.89; H, 3.63; N, 19.17. MS: $[M]^+$ at *m/z* 440.

The following compounds were prepared using a similar procedure as described for compound **19**.

*5.1.13. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(p-chloro arylidene-amino)-quinazolin-4-one (**20**)*

Yield 50% (ethanol): mp 178 °C; IR (KBr) ν_{max} in cm^{-1}: 2938 (CH_2), 1698 (C=O), 1590 (C=N), 1635, 1605, 1582, 1424, 1072 (st. of oxadiazole), 1544 (C=C aromatic), 785 (Ar–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.60 (s, 1H, N=CH–Ar), 8.23 (dd, $J = 8.2$ Hz, 2H, Pyr–H2), 7.25–8.01 (m, 10H, 8Ar–H, 2Pyr–H3), 3.12 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{15}N_6O_2SCl$: C, 58.17; H, 3.16; N, 17.70. Found: C, 58.34; H, 3.18; N, 17.78. MS: $[M]^+$ at *m/z* 474.5.

*5.1.14. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(p-methoxyarylidene-amino)-quinazolin-4-one (**21**)*

Yield 52% (methanol): mp 214 °C; IR (KBr) ν_{max} in cm^{-1}: 2940 (CH_2), 1690 (C=O), 1595 (C=N), 1685, 1630, 1582, 1420, 1075 (st. of oxadiazole), 1542 (C=C aromatic), 1182 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.56 (s, 1H, N=CH–Ar), 8.25 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.26–8.05 (m, 10H, 8Ar–H, 2Pyr–H3), 3.18 (s, 2H, CH_2–S), 3.39 (s, 3H, OCH_3). Anal. Calcd for $C_{24}H_{18}N_6O_3S$: C, 61.28; H, 3.83; N, 17.87. Found: C, 61.12; H, 3.85; N, 17.94. MS: $[M]^+$ at *m/z* 470.

*5.1.15. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-3-(p-hydroxy arylidene-amino)-quinazolin-4-one (**22**)*

Yield 60% (benzene): mp 152 °C; IR (KBr) ν_{max} in cm^{-1}: 3422 (Ar–OH), 2940 (CH_2), 1690 (C=O), 1590 (C=N), 1630, 1608, 1580, 1422, 1072 (st. of oxadiazole), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.33 (s, 1H, Ar–OH), 8.61 (s, 1H, N=CH–Ar), 8.23 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.21–8.04 (m, 10H, 8Ar–H, 2Pyr–H3), 3.13 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{16}N_6O_3S$: C, 60.53; H, 3.51; N, 18.42. Found: C, 60.65; H, 3.52; N, 18.47. MS: $[M]^+$ at *m/z* 456.

*5.1.16. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(arylidene-amino)-6-bromoquinazolin-4-one (**23**)*

Yield 65% (ethanol): mp 135 °C; IR (KBr) ν_{max} in cm^{-1}: 2948 (CH_2), 1700 (C=O), 1590 (C=N), 1635, 1615, 1575, 1420, 1071 (st. of oxadiazole), 1544 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.63 (s, 1H, N=CH–Ar), 8.25 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.20–8.01 (m, 10H, 8Ar–H, 2Pyr–H3), 3.15 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{15}N_6O_2SBr$: C, 53.18; H, 2.89; N, 16.18. Found: C, 53.37; H, 2.90; N, 16.10. MS: $[M]^+$ at *m/z* 519.

*5.1.17. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(p-chloroarylidene-amino)-6-bromoquinazolin-4-one (**24**)*

Yield 62% (methanol): mp 197 °C; IR (KBr) ν_{max} in cm^{-1}: 2940 (CH_2), 1696 (C=O), 1599 (C=N), 1633, 1610, 1575, 1422, 1074 (st. of oxadiazole), 1540 (C=C aromatic), 790 (Ar–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.61 (s, 1H, N=CH–Ar), 8.23 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.15–8.04 (m, 9H, 7Ar–H, 2Pyr–H3), 3.09 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{14}N_6O_2SBrCl$: C, 49.86; H, 2.53; N, 15.18. Found: C, 49.98; H, 2.50; N, 15.12. MS: $[M]^+$ at *m/z* 553.5.

*5.1.18. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(p-methoxyarylidene-amino)-6-bromoquinazolin-4-one (**25**)*

Yield 55% (methanol): mp 218 °C; IR (KBr) ν_{max} in cm^{-1}: 2940 (CH_2), 1690 (C=O), 1598 (C=N), 1635, 1610, 1580, 1420, 1072 (st. of oxadiazole), 1544 (C=C aromatic), 1175 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.56 (s, 1H, N=CH–Ar), 8.22 (dd, $J = 8$ Hz, 2H, Pyr–H2), 7.25–7.99 (m, 9H, 7Ar–H, 2Pyr–H3), 3.36 (s, 3H, OCH_3), 3.12 (s, 2H, CH_2–S). Anal. Calcd for $C_{24}H_{17}N_6O_3SBr$: C, 52.46; H, 3.10; N, 15.30. Found: C, 52.32; H, 3.11; N, 15.25. MS: $[M]^+$ at *m/z* 549.

*5.1.19. 2-(5-Pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl methyl)-3-(p-hydroxyarylidene-amino)-6-bromoquinazolin-4-one (**26**)*

Yield 65% (benzene): mp 218 °C; IR (KBr) ν_{max} in cm^{-1}: 3428 (Ar–OH), 2945 (CH_2), 1695 (C=O), 1590 (C=N), 1630, 1612, 1575, 1425, 1075 (st. of oxadiazole), 1540 (C=C aromatic), 1175 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 11.30 (s, 1H, Ar–OH), 8.55 (s, 1H, N=CH–Ar), 8.24 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.21–8.04 (m, 9H, 7Ar–H, 2Pyr–H3), 3.14 (s, 2H, CH_2–S). Anal. Calcd for $C_{23}H_{15}N_6O_3SBr$: C, 51.59; H, 2.80; N, 15.70. Found: C, 51.75; H, 2.81; N, 15.76. MS: $[M]^+$ at *m/z* 535.

*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**)*

To the stirred solution of compound **19** (0.01 mol) and triethylamine (few drops) in ethanol (50 ml) was added monochloroacetyl chloride (0.014 mol) at 50 °C. The reaction mixture was stirred for 30 min at room temperature on refluxed for 6–8 h. The reaction mixture was filtered to remove triethylamine hydrochloride and the resultant solution was poured on to crushed ice with constant stirring. The solid thus obtained was recrystallized from ethanol to give compound **27**. Yield 50%: mp 137 °C; IR (KBr) ν_{max} in cm^{-1}: 2945 (CH_2), 1730 (C=O, azetidine), 1690 (C=O), 1585 (C=N), 1635, 1610, 1570, 1420, 1070 (st. of oxadiazole), 1540 (C=C aromatic), 680 (CH–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.23 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.14–8.05 (m, 11H, 9Ar–H, 2Pyr–H3), 6.20 (s, 1H, CH–Ar), 4.54 (s, 1H, CH–Cl), 3.10 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{17}N_6O_3SCl$: C, 58.08; H, 3.29; N, 16.26. Found: C, 58.27; H, 3.31; N, 16.31. MS: $[M]^+$ at *m/z* 516.5.

The following compounds were prepared using a similar procedure as described for compound **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**)*

Yield 55% (ethanol): mp 185 °C; IR (KBr) ν_{max} in cm^{-1}: 2948 (CH_2), 1735 (C=O azetidine), 1703 (C=O), 1595 (C=N), 1640, 1612, 1570, 1420, 1073 (st. of oxadiazole), 1544 (C=C aromatic), 686 (CH–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.26 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.15–8.01 (m, 10H, 8Ar–H, 2Pyr–H3), 6.25 (s, 1H, CH–Ar), 4.51 (s, 1H, CH–Cl), 3.11 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{16}N_6O_3SCl_2$: C, 54.45; H, 2.90; N, 15.24. Found: C, 54.61; H, 2.88; N, 15.19. MS: $[M]^+$ at *m/z* 551.

*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**)*

Yield 40% (methanol): mp 196 °C; IR (KBr) ν_{max} in cm^{-1}: 2950 (CH_2), 1732 (C=O azetidine), 1700 (C=O), 1600 (C=N), 1635, 1610, 1580, 1425, 1070 (st. of oxadiazole), 1540 (C=C aromatic), 683 (CH–Cl); ^1H NMR ($CDCl_3$) δ in ppm: 8.25 (dd, $J = 8$ Hz, 2H, Pyr–H2), 7.28–8.00 (m, 10H, 8Ar–H, 2Pyr–H3), 6.22 (s, 1H, CH–Ar), 4.56 (s, 1H, CH–Cl), 3.36 (s, 3H, OCH_3), 3.14 (s, 2H, CH_2–S). Anal. Calcd for $C_{26}H_{19}N_6O_4SCl$: C, 57.09; H, 3.48; N, 15.37. Found: C, 57.21; H, 3.50; N, 15.43. MS: $[M]^+$ at *m/z* 546.5.

*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**)*

Yield 45% (methanol): mp 166 °C; IR (KBr) ν_{max} in cm^{-1}: 3425 (Ar–OH), 2940 (CH_2), 1738 (C=O azetidine), 1700 (C=O), 1600 (C=N), 1635, 1615, 1580, 1420, 1075 (st. of oxadiazole), 1540 (C=C aromatic), 689 (CH–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 11.33 (s, 1H, Ar–OH), 8.26 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.17–8.02 (m, 10H, 8Ar–H, 2Pyr–H3), 6.24 (s, 1H, CH–Ar), 4.54 (s, 1H, CH–Cl), 3.16 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{17}N_6O_4SCl$: C, 56.34; H, 3.19; N, 15.77. Found: C, 56.52; H, 3.17; N, 15.72. MS: $[M]^+$ at *m/z* 532.5.

*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**)*

Yield 52% (benzene): mp 147 °C; IR (KBr) ν_{max} in cm^{-1}: 2947 (CH_2), 1735 (C=O azetidine), 1690 (C=O), 1595 (C=N), 1640, 1615, 1570, 1420, 1070 (st. of oxadiazole), 1540 (C=C aromatic), 675 (CH–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.28 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.20–8.05 (m, 10H, 8Ar–H, 2Pyr–H3), 6.23 (s, 1H, CH–Ar), 4.51 (s, 1H, CH–Cl), 3.08 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{16}N_6O_3SClBr$: C, 50.38; H, 2.69; N, 14.11. Found: C, 50.29; H, 2.68; N, 14.18. MS: $[M]^+$ at *m/z* 595.5.

*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**)*

Yield 55% (ethanol): mp 182 °C; IR (KBr) ν_{max} in cm^{-1}: 2945 (CH_2), 1735 (C=O azetidine), 1690 (C=O), 1590 (C=N), 1635, 1620, 1560, 1420, 1065 (st. of oxadiazole), 1545 (C=C aromatic), 673 (CH–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.29 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.26–8.05 (m, 9H, 7Ar–H, 2Pyr–H3), 6.25 (s, 1H, CH–Ar), 4.53 (s, 1H, CH–Cl), 3.12 (s, 2H, CH_2-S). Anal. Calcd for $C_{25}H_{15}N_6O_3SCl_2Br$: C, 47.62; H, 2.38; N, 13.33. Found: C, 47.73; H, 2.37; N, 13.25. MS: $[M]^+$ at *m/z* 630.

*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**)*

Yield 40% (acetic acid): mp 191 °C; IR (KBr) ν_{max} in cm^{-1}: 2953 (CH_2), 1738 (C=O azetidine), 1695 (C=O), 1590 (C=N), 1640, 1615, 1560, 1425, 1068 (st. of oxadiazole), 1548 (C=C aromatic), 1180 (C–O–C), 675 (CH–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.26 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.22–8.00 (m, 9H, 7Ar–H, 2Pyr–H3), 6.21 (s, 1H, CH–Ar), 4.54 (s, 1H, CH–Cl), 3.39 (s, 3H, OCH_3), 3.15 (s, 2H, CH_2–S). Anal. Calcd for $C_{26}H_{18}N_6O_4SClBr$: C, 49.88; H, 2.88; N, 13.43. Found: C, 49.97; H, 2.91; N, 13.32. MS: $[M]^+$ at *m/z* 625.5.

*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**)*

Yield 55% (methanol): mp 153 °C; IR (KBr) ν_{max} in cm^{-1}: 3420 (Ar–OH), 2945 (CH_2), 1730 (C=O azetidine), 1705 (C=O), 1600 (C=N), 1642, 1615, 1560, 1420, 1073 (st. of oxadiazole), 1540 (C=C aromatic), 670 (CH–Cl); ^{1}H NMR ($CDCl_3$) δ in ppm: 11.35 (s, 1H, Ar–OH), 8.28 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.20–8.05 (m, 9H, 7Ar–H, 2Pyr–H3), 6.28 (s, 1H, CH–Ar), 4.56 (s, 1H, CH–Cl), 3.11 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{16}N_6O_4SClBr$: C, 49.06; H, 2.62; N, 13.74. Found: C, 49.21; H, 2.63; N, 13.79. MS: $[M]^+$ at *m/z* 611.5.

*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**)*

To a cool mixture of compound **19** (0.01 mol) and anhydrous $ZnCl_2$ (1 pinch) in ethanol (50 ml), thioglycolic acid (0.014 mol) was added drop wise with stirring at ambient temperature and refluxed for 12 h. The reaction mixture was filtered. The filtrate was concentrated, poured on crushed ice. The resultant solid was recrystallized from methanol to give compound **35**. Yield 55%: mp 119 °C; IR (KBr) ν_{max} in cm^{-1}: 1750 (C=O thiazolidin), 1690 (C=O), 1595 (C=N), 1635, 1620, 1565, 1422, 1075 (st. of oxadiazole), 1542 (C=C aromatic); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.25 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.20–8.01 (m, 11H, 9Ar–H, 2Pyr–H3), 6.24 (s, 1H, CH–Ar), 3.60 (s, 2H, CH_2 of thiazolidin), 3.14 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{18}N_6O_3S_2$: C, 58.37; H, 3.50; N, 16.34. Found: C, 58.55; H, 3.48; N, 16.41. MS: $[M]^+$ at *m/z* 514.

The following compounds were prepared using a similar procedure as described for compound **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**)*

Yield 50% (methanol): mp 163 °C; IR (KBr) ν_{max} in cm^{-1}: 1745 (C=O thiazolidin), 1700 (C=O), 1590 (C=N), 1640, 1615, 1570, 1420, 1078 (st. of oxadiazole), 1540 (C=C aromatic); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.25 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.16–8.02 (m, 10H, 8Ar–H, 2 Pyr–H3), 6.26 (s, 1H, CH–Ar), 3.65 (s, 2H, CH_2 of thiazolidin), 3.10 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{17}N_6O_3S_2Cl$: C, 54.69; H, 3.10; N, 15.31. Found: C, 54.82; H, 3.12; N, 15.28. MS: $[M]^+$ at *m/z* 548.5.

*5.1.30. 3-(4-Oxo-2-{p-methoxyaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-one (**37**)*

Yield (40%) (ethanol): mp 155 °C; IR (KBr) ν_{max} in cm^{-1}: 1755 (C=O thiazolidin), 1695 (C=O), 1590 (C=N), 1640, 1620, 1560, 1425, 1070 (st. of oxadiazole), 1544 (C=C aromatic); ^{1}H NMR ($CDCl_3$) δ in ppm: 8.27 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.26–8.02 (m, 10H, 8Ar–H, 2Pyr–H3), 6.20 (s, 1H, CH–Ar), 3.64 (s, 2H, CH_2 of thiazolidin), 3.39

(s, 3H, OCH_3), 3.16 (s, 2H, CH_2–S). Anal. Calcd for $C_{26}H_{20}N_6O_4S_2$: C, 57.35; H, 3.68; N, 15.44. Found: C, 57.14; H, 3.71; N, 15.52. MS: $[M]^+$ at *m/z* 544.

*5.1.31. 3-(4-Oxo-2-{p-hydroxyaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-quinazolin-4-one (**38**)*

Yield 48% (ethanol): mp 178 °C; IR (KBr) ν_{max} in cm^{-1}: 3330 (Ar–OH), 1751 (C=O thiazolidin), 1700 (C=O), 1600 (C=N), 1644, 1615, 1565, 1425, 1077 (st. of oxadiazole), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.35 (s, 1H, Ar–OH), 8.22 (dd, $J = 8$ Hz, 2H, Pyr–H2), 7.18–8.02 (m, 10H, 8Ar–H, 2Pyr–H3), 6.24 (s, 1H, CH–Ar), 3.65 (s, 2H, CH_2 of thiazolidin), 3.09 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{18}N_6O_4S_2$: C, 56.60; H, 3.40; N, 15.85. Found: C, 56.41; H, 3.43; N, 15.92. MS: $[M]^+$ at *m/z* 530.

*5.1.32. 3-(4-Oxo-2-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-one (**39**)*

Yield 52% (acetone): mp 162 °C; IR (KBr) ν_{max} in cm^{-1}: 1753 (C=O thiazolidin), 1690 (C=O), 1595 (C=N), 1641, 1615, 1565, 1424, 1070 (st. of oxadiazole), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.27 (dd, $J = 8$ Hz, 2H, Pyr–H2), 7.21–8.021 (m, 10H, 8Ar–H, 2Pyr–H3), 6.24 (s, 1H, CH–Ar), 3.61 (s, 2H, CH_2 of thiazolidin), 3.12 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{17}N_6O_3S_2Br$: C, 50.59; H, 2.87; N, 14.16. Found: C, 50.77; H, 2.85; N, 14.14. MS: $[M]^+$ at *m/z* 593.

*5.1.33. 3-(4-Oxo-2-{p-chloroaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-one (**40**)*

Yield 56% (benzene): mp 202 °C; IR (KBr) ν_{max} in cm^{-1}: 1755 (C=O thiazolidin), 1705 (C=O), 1590 (C=N), 1635, 1617, 1565, 1423, 1075 (st. of oxadiazole), 1543 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 8.29 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.19–8.04 (m, 9H, 8Ar–H, 2Pyr–H3), 6.23 (s, 1H, CH–Ar), 3.64 (s, 2H, CH_2 of thiazolidin), 3.09 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{16}N_6O_3S_2BrCl$: C, 47.81; H, 2.55; N, 13.39. Found: C, 47.72; H, 2.57; N, 13.32. MS: $[M]^+$ at *m/z* 627.5.

*5.1.34. 3-(4-Oxo-2-{p-methoxyaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6bromoquinazolin-4-one (**41**)*

Yield 40% (ethanol): mp 210 °C; IR (KBr) ν_{max} in cm^{-1}: 1750 (C=O thiazolidin), 1690 (C=O), 1600 (C=N), 1640, 1615, 1560, 1420, 1073 (st. of oxadiazole), 1540 (C=C aromatic), 1175 (C–O–C); ^1H NMR ($CDCl_3$) δ in ppm: 8.24 (dd, $J = 8.6$ Hz, 2H, Pyr–H2), 7.20–8.01 (m, 9H, 7Ar–H, 2Pyr–H3), 6.21 (s, 1H, CH–Ar), 3.66 (s, 2H, CH_2 of thiazolidin), 3.37 (s, 3H, OCH_3), 3.15 (s, 2H, CH_2–S). Anal. Calcd for $C_{26}H_{19}N_6O_4S_2Br$: C, 50.08; H, 3.05; N, 13.48. Found: C, 50.21; H, 3.03; N, 13.51. MS: $[M]^+$ at *m/z* 622.

*5.1.35. 3-(4-Oxo-2-{p-hydroxyaryl}-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-6-bromoquinazolin-4-one (**42**)*

Yield 55% (ethanol): mp 169 °C; IR (KBr) ν_{max} in cm^{-1}: 3425 (Ar–OH), 1755 (C=O thiazolidin), 1695 (C=O), 1592 (C=N), 1645, 1615, 1565, 1424, 1070 (st. of oxadiazole), 1540 (C=C aromatic); ^1H NMR ($CDCl_3$) δ in ppm: 11.35 (s, 1H, Ar–OH), 8.21 (dd, $J = 8.3$ Hz, 2H, Pyr–H2), 7.16–8.00 (m, 9H, 7Ar–H, 2Pyr–H3), 6.26 (s, 1H, CH–Ar), 3.60 (s, 2H, CH_2 of thiazolidin), 3.11 (s, 2H, CH_2–S). Anal. Calcd for $C_{25}H_{17}N_6O_4S_2Br$: C, 49.26; H, 2.79; N, 13.33. Found: C, 49.20; H, 2.80; N, 13.37. MS: $[M]^+$ at *m/z* 609.

5.2. Biological activity

The experiments were performed with albino rats of the Charles–Foster stain of either sex, excluding pregnant females, of 70–95 days weighting 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. All the compounds were dissolved in propylene glycol. Phenylbutazone drug was used as reference drug.

5.2.1. Anti-inflammatory activity

This study was done by following the procedure of Winter et al. [23]. The rats were divided into 3 groups (control, drugs treated and standard drugs) of 6 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 percent anti-inflammatory activity was calculated according to the formula as given below:

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

where V_t and V_c are the volume of oedema in right paw of rats in the drug treated and control group, respectively.

5.2.2. Acute toxicity

Approximate lethal doses (ALD50) of all the compounds were investigated by the method of Smith [24]. All the compounds were studied for acute toxicity ALD_{50} value were found to be >1000 mg/kg p.o.

References

[1] R.K. Saksena, P. Kant, Indian J. Chem Soc. 61 (8) (1984) 722–724.
[2] M.I. Husain, S. Shakla, Indian J. Chem. 25B (1986) 552–555.
[3] A.K.S. Gupta, H.K. Misra, Chem. Abstr. 94 (17) (1981) 759.
[4] A.D. Rao, C.R. Shankar, A.B. Rao, V.M. Reddy, Indian J. Chem. 25B (1986) 665–667.
[5] A. Vyas, H.S. Joshi, H. Parkh, Chem. Abstr. 123 (1995) 913.
[6] Archana, V.K. Srivastava, Ramesh Chandra, Ashok Kumar, Eur. J. Med. Chem. 37 (2002) 873–882.
[7] N.A. Gangwal, B. Narasimhan, V.K. Mourya, A.S. Dhake, Indian J. Heterocycl. Chem. 12 (2) (2002) 201–204.
[8] Ashok Kumar, Shalab Sharma, Archana, Kiran Bajaj, Shipra Sharma, Hemant Panwar, Tripti Sigh, V.K. Srivastava, Bioorg. Med. Chem. 11 (2003) 5293–5299.

[9] G. Daidone, B. Maggio, D. Raffa, S. Plescia, M.L. Bajardi, A. Caruso, V.M.C. Cutuli, M. Amico Roxas, Eur. J. Med. Chem. 29 (9) (1994) 707–711.
[10] A.A. Bekhit, N.S. Habib, J.Y. Park, Chem. Abstr. 142 (2005) 114000f.
[11] R. Agarwal, C. Agarwal, C. Singh, V.S. Mishra, Indian J. Chem. 28B (1989) 893–896.
[12] S.K. Srivastava, S.L. Srivastava, S.D. Srivastava, Indian J. Chem. 39B (2000) 464–467.
[13] S.K. Srivastava, R. Yadav, S.L. Srivastava, Indian J. Chem. 42B (2004) 399–405.
[14] Suma Mishra, S.K. Srivastava, S.D. Srivastava, Indian J. Chem. 36B (1997) 826–830.
[15] A. Mohmmad, A. Oberoi, A. Shah, Indian J. Chem. 38B (1999) 237–239.
[16] F.A. Omar, N.M. Mahfouz, M.A. Rahman, Eur. J. Med. Chem. 31 (10) (1996) 819–825.
[17] L.V.G. Nargund, G.R.N. Reddy, V. Hariprasad, J. Pharm. Sci. 83 (2) (1994) 246–248.
[18] B.R. Rani, U.T. Bhalerau, M.F. Rahman, Indian J. Chem. 29B (1990) 995–998.
[19] A. Kumar, S. Singh, A.K. Saxena, K. Shanker, Indian J. Chem. 27B (1988) 443–447.
[20] A. Arques, P. Molina, A. Soler, Synthesis 9 (1980) 702–704.
[21] S.M. Roshdy, K.M. Ghoneim, M. Khalifa, Pharmazie 30 (4) (1975) 210–213.
[22] A. Sammour, A. Rabie, M. Elhashash, M. Sayed, Egypt. J. Chem. 19 (4) (1976) 571–588.
[23] C.A. Winter, E.A. Risley, G.M. Nuss, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–550.
[24] Q.E. Smith, Pharmacological Screening Test Progress in Medicinal Chemistry, vol. I, Butterworth, London, 1960.