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Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Quinazoline Derivatives

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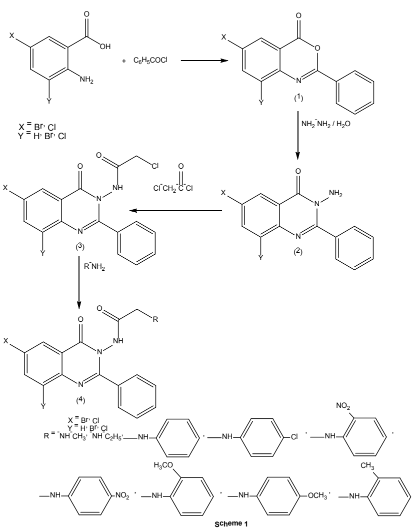
Abstract

Some new 2-(substituted)-*N*-(6-bromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamides (4.1-9), 2-(substituted)-*N*-(6,8-dibromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamides (4.10-18), 2-(substituted)-*N*-(6-chloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamides (4.19-27) and 2-(substituted)-*N*-(6,8-dichloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamides (4.28-36) were synthesized in good yield and investigated for analgesic activity. Computer aided drug design (CADD) studies were performed to rationalize the best fitting value of the prepared compounds. All the test compounds exhibited significant analgesic activity compared to reference standard diclofenac sodium. The compounds with aliphatic group (CH_3 or C_2H_5) (4.1, 2, 10, 11, 19, 20, 28 and 29) showed most potent analgesic activity of the series and it is moderately more potent compared to the reference standard diclofenac sodium.

Keywords: Analgesic; Anti-inflammatory; Quinazoline; Diclofenac sodium

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain, and fever. The most of NSAIDs act via inhibition of cyclooxygenase, thus preventing prostaglandin biosynthesis. However, this mechanism of action is also responsible for their main undesirable effects, gastrointestinal (GI) ulceration, and, less frequently, nephrotoxicity. The increase in hospitalization and deaths due to GI-related disorders parallels the increased use of NSAIDs. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. In medicinal chemistry research program, I found that quinazolines and condensed quinazolines exhibit potent central nervous system activities including analgesic [1-7], anti-inflammatory [8-11], and anticonvulsant [12,13]. Quinazolin-4(3*H*)-ones with C-2 and N-3 substitution are reported to possess significant analgesic, anti-inflammatory [14,15], and anticonvulsant activities [16]. In the present work a series of 2-(substituted)-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamides were synthesized and tested for their analgesic activity. For synthesizing the target compounds **4.1-36** the following scheme is adopted Scheme 1.



Scheme 1: Synthesizing the target compounds 4.1-36.

Experimental

All melting points were measured in capillary tube on a Graffin melting point apparatus and are uncorrected. The chemical structures of the synthesized compounds were confirmed on the basis of their spectral data (IR, ^{1}H NMR and mass spectra) and the purity was ascertained by microanalysis. The IR spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer using KBr discs (λ_{max} in cm^{-1}). ^{1}H NMR spectra were performed either on Gemini 300BB (300 MHz) or (500 MHz) and (300 MHz) for ^{13}C NMR), spectrometer, using TMS as internal standard and DMSO-d6 as solvent; the chemical shifts are reported in ppm (δ) and coupling constant (J) values are given in Hertz (Hz). Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). All of the new compounds were analyzed for C, H and N and agreed with the proposed structures within ± 0.4% of the theoretical values by the automated CHN analyzer. Mass spectra were recorded on Hewlett Packard 5988 spectrometer at the RCMB. The purity of the compounds was checked by Thin Layer Chromatography (TLC) on Merck silica gel 60 F254 precoated sheets. All analyses were performed at the Micro-analytical Unit of Cairo University, Cairo, Egypt.

Synthesis of 2-Phenyl-3,1-benzoxazin-4-one derivatives (1)

Anthranilic acid derivatives [17-19] (0.1 mol) were dissolved in pyridine (60 mL), benzoyl chloride (1.40 g, 0.2 mol) was added. The reaction mixture was stirred for an hour followed by treatment with 15 mL. of 5% sodium bicarbonate. The solid product was obtained filtered off and recrystallized from ethanol.

6-Bromo-2-Phenyl-3,1-benzoxazin-4-one (1.1): Yield: 85%; MP: 136-138°C; IR (KBr, ν, cm^{-1}): 3330 (NH), 1760 (C=O), 1600 (C=N). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 7.31-7.34 (m, 3H, Ar-H), 7.50-

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7.52 (d, 1H, Ar-H), 7.71-7.74 (m, 2H, Ar-H), 7.84-7.86 (d, 1H, Ar-H), 7.90–7.92 (d, 1H, Ar-H). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 118.7, 121.6, 124.49], 128.2, 128.3, 128.4, 128.5, 129.9, 131.2, 135.3, 138.4, 145.4, 156.5, 159.6. MS (m/z): 301/303/302, M$^+$, 100/95/20%). Anal. Calcd. For $C_{14}H_8NO_2Br$: C, 55.62; H, 2.64; N, 4.63. Found: C, 55.83; H, 2.41; N, 4.65.

6,8-Dibromo-2-Phenyl-3,1-benzoxazin-4-one (1.2): Yield: 80%; MP: 145-147°C; IR (KBr, ν, cm^{-1}): 3360 (NH), 1740 (C=O), 1620 (C=N).^{1}H NMR (300 MHz, [D6] DMSO): δ = 7.48-7.50 (m, 3H, Ar-H), 7.86-7.88 (m, 2H, Ar-H), 7.92–7.94 (d, 1H, Ar-H), 8.00-8.10 (d, 1H, Ar-H).^{13}C NMR (300 MHz, [D6] DMSO): δ = 113.2, 120.7, 121.9, 128.2, 128.2, 128.9, 128.9, 129.9 131.2, 134.2, 141.4, 156.4, 157.2, 159.5. MS (m/z): (381/383, M$^+$, 100/42%). Anal. Calcd. for $C_{14}H_7NO_2Br_2$: C, 44.09; H, 1.83; N, 3.67. Found: C, 44.36; H, 1.91; N, 3.71.

6-Chloro-2-Phenyl-3,1-benzoxazin-4-one (1.3): Yield: 78%; MP: 124-126°C; IR (KBr, ν, cm^{-1}): 3330 (NH), 1720 (C=O), 1630 (C=N). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 7.40-7.43 (m, 4H, Ar-H), 7.61-7.63 (d, 1H, Ar-H), 7.76-7.78 (m, 2H, Ar-H), 7.94-7.96 (d, 1H, Ar-H).^{13}C NMR (300 MHz, [D6] DMSO): δ = 117.8, 127.6, 128.2, 128.3, 128.8, 128.9, 129.8, 131.3, 131.6, 132.8, 135.4, 144.3, 156.4, 159.5. MS (m/z): (257/259, M$^+$, 100/30%). Anal. Calcd. For $C_{14}H_8NO_2Cl$: C 65.24; H, 3.10; N, 5.44. Found: C, 65.41; H, 3.26; N, 5.61.

6,8-Dichloro-2-Phenyl-3,1-benzoxazin-4-one (1.4): Yield: 70%; MP: 130-132°C; IR (KBr, ν, cm^{-1}): 3340 (NH), 1730 (C=O), 1610 (C=N).^{1}H NMR (300 MHz, [D6] DMSO): δ = 7.48-7.50 (m, 3H, Ar-H), 7.76-7.78 (m, 3H, Ar-H), 7.84-7.87 (d, 2H, Ar-H). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 119.3, 128.2, 128.3, 128.9, 128.9, 129.3, 129.8, 129.9, 131.2, 134.2, 136.9, 156.4, 159.5, 166.3. MS (m/z): (291/293, M$^+$, 100/60%). Anal. Calcd. for $C_{14}H_7NO_2Cl_2$: C, 57.53; H, 2.40; N, 4.79. Found: C, 57.70; H, 2.44; N, 4.86.

Synthesis of 3-Amino-2-phenylquinazolin-4-(3*H*)-one derivatives (2)

A mixture of 2-phenyl-3,1-benzoxazin-4-one (**1**) (0.05 mol) and hydrazine hydrate (0.30 mL, 0.05 mol) in ethanol was refluxed for 3 hours. The solid product was obtained after cooling is filtered off and recrystallized from ethanol.

3-Amino-6-bromo-2-phenylquinazolin-4-(3*H*)-one (2.1): Yield: 80%; MP: 172-174°C; IR (KBr, ν, cm^{-1}): 3300 (NH_2), 1680 (C=O), 1620 (C=N) and 1600 (C=C). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.70 (s, 2H, NH_2, D_2O exchangeable), 7.21-7.23 (m, 3H, Ar- H), 7.40-7.42 (d, 1H, Ar-H), 7.63-7.66 (m, 2H, Ar-H), 7.86-7.88 (d, 1H, Ar-H), 7.94-7.96 (d, 1H, Ar-H).^{13}C NMR (300 MHz, [D6] DMSO): δ = 121.9, 123.2, 124.8, 128.2, 128.4, 128.8, 128.9, 129.0, 130.3, 132.5, 136.3, 147.8, 156.4, 160.8. MS (m/z): (315/317/316, M$^+$, 100/90/20%). Anal. Calcd. for $C_{14}H_{10}N_3OBr$: C, 53.16; H, 3.16; N, 13.29. Found: C, 53.34; H, 3.28; N, 13.43.

3-Amino-6,8-dibromo-2-phenylquinazolin-4-(3*H*)-one (2.2): Yield: 72%; MP: 186-188°C; IR (KBr, ν, cm^{-1}): 3310 (NH_2), 1700 (C=O), 1630 (C=N) and 1610 (C=C). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.60 (s, 2H, NH_2, D_2O exchangeable), 7.26-7.28 (m, 3H, Ar- H), 7.46-7.48 (m, 2H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 7.96-7.89 (d, 1H, Ar-H).^{13}C NMR (300 MHz, [D6] DMSO): δ = 113.2, 122.1, 125.4, 128.3, 128.4, 128.8, 128.9, 129.9 130.2, 131.2, 139.5, 154.5, 156.4, 160.8. MS (m/z): (395/397, M$^+$, 100/50%). Anal. Calcd. for $C_{14}H_9N_3OBr_2$: C, 42.53; H, 2.28; N, 10.63. Found: C, 42.70; H, 2.43; N, 10.41.

3-Amino-6-chloro-2-phenylquinazolin-4-(3*H*)-one (2.3): Yield: 85%; MP: 154-156°C; IR (KBr, ν, cm^{-1}): 3320 (NH_2), 1690 (C=O), 1610 (C=N) and 1600 (C=C). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.81 (s, 2H, NH_2, D_2O exchangeable), 7.31-7.34 (m, 4H, Ar- H), 7.45-7.47 (d, 1H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 7.71-7.73 (d, 1H, Ar-H).^{13}C NMR (300 MHz, [D6] DMSO): δ = 122.4, 127.8, 127.9, 128.3, 128.4, 128.7, 128.9, 128.3, 130.1, 132.9, 133.6, 146.8, 156.3, 160.6. MS (m/z): (271/273, M$^+$, 100/34%). Anal. Calcd. For $C_{14}H_{10}N_3OCl$: C 61.88; H, 3.68; N, 15.47. Found: C, 61.97; H, 3.54; N, 15.58.

3-Amino-6,8-dichloro-2-phenylquinazolin-4-(3*H*)-one (2.4): Yield: 76%; MP: 161-163°C; IR (KBr, ν, cm^{-1}): 3300 (NH_2), 1720 (C=O), 1620 (C=N) and 1600 (C=C). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.62 (s, 2H, NH_2, D_2O exchangeable), 7.43-7.45 (m, 3H, Ar- H), 7.62-7.64 (m, 3H, Ar-H), 7.81-7.83 (d, 1H, Ar-H). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 123.8., 125.9, 128.3, 128.4, 128.7, 128.9, 128.9, 129.4, 130.2, 134.4, 135.3, 156.4, 160.75], 163.4. MS (m/z): (305/307, M$^+$, 100/40%). Anal. Calcd. for $C_{14}H_9N_3OCl_2$: C 54.90; H, 2.94; N, 13.72. Found: C, 54.93; H, 2.97; N, 13.74.

Synthesis of 2-Chloro-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl)acetamide (3)

3-Amino-2-phenylquinazoline derivatives **2** (0.01 mol) was dissolved in dioxane (20 mL), triethylamine (1.01 gm., 0.01 mol) and chloroacetyl chloride (1.12 gm., 0.01 mol) were added and the reaction mixture was stirred at room temperature for 1 hour. The stirring was continued for 2 hours with heating. Then the reaction mixture was poured into ice water and extracted with ether. The ether extract was washed with 3% sodium bicarbonate solution and dried over anhydrous magnesium sulfate; the ether was distilled off to yield **3**.

***N*-(6-bromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-chloroacetamide (3.1):** Yield: 78%; MP: 172-174°C; IR (KBr, ν, cm^{-1}): 3200 (NH), 1710 (C=O), 1680 (C=O), 1610 (C=N). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.10 (s, 2H, CH_2), 7.45-7.47 (m, 3H, Ar- H), 7.52-7.54 (d, 1H, Ar-H), 7.60-7.62 (m, 2H, Ar-H), 7.81-7.83 (d, 1H, Ar-H), 7.96-7.98 (d, 1H, Ar-H), 9.24 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 40.6, 121.8, 123.1, 124.7, 128.3, 128.4, 128.7, 128.9, 128.09130.2, 132.4, 136.4, 147.8, 156.3, 160.7, 166.38]. MS (m/z): 393/395, M$^+$, 100/28%). Anal. Calcd. for $C_{16}H_{11}N_3O_2BrCl$: C, 48.91; H, 2.80; N, 10.70. Found: C, 48.99; H, 2.97; N, 10.87.

***N*-(6,8-Dibromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-chloroacetamide (3.2):** Yield: 70%; MP: 191-193°C; IR (KBr, ν, cm^{-1}): 3190 (NH), 1690 (C=O), 1670 (C=O), 1607 (C=N), 700 (C–Cl). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.00 (s, 2H, CH_2), 7.46-7.48 (m, 3H, Ar- H), 7.57-7.59 (m, 2H, Ar-H), 7.68-7.70 (d, 1H, Ar-H), 7.94-7.96 (d, 1H, Ar-H), 9.12 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 40.6, 113.3, 122.1, 125.3, 128.3, 128.4, 128.7, 128.8, 128.9, 128.9, 130.2, 139.5, 154.4, 156.3, 160.6, 166.9. MS (m/z): 471/473, M$^+$, 100/60%). Anal. Calcd. for $C_{16}H_{10}N_3O_2Br_2Cl$: C, 40.72; H, 2.12; N, 8.91. Found: C, 40.61; H, 2.19; N, 8.84.

***N*-(6-Chloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-chloroacetamide (3.3):** Yield: 75%; MP: 165-167°C; IR (KBr, ν, cm^{-1}): 3189 (NH), 1689 (C=O), 1660 (C=O), 1607 (C=N), 700 (C–Cl). ^{1}H NMR (300 MHz, [D6] DMSO): δ = 4.20 (s, 2H, CH_2), 7.40-7.42 (m, 4H, Ar- H), 7.61-7.63 (d, 1H, Ar-H), 7.70-7.72 (m, 2H, Ar-H), 7.84-7.86 (d, 1H, Ar-H), 9.38 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 40.6, 122.3, 127.8, 127.9, 128.3, 128.4, 128.7, 128.8, 128.9, 130.2, 132.98, 133.6, 146.9, 156.3, 160.9, 166.4. MS (m/z): (347/349, M$^+$, 100/38%). Anal. Calcd. For $C_{16}H_{11}N_3O_2Cl_2$: C 55.17; H, 3.16; N, 12.07. Found: C, 55.31; H, 3.31; N, 12.33.

***N*-(6,8-Dichloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-chloroacetamide (3.4):** Yield: 68%; MP: 181-183°C; IR (KBr, ν, cm^{-1}): 3200 (NH_2), 1700 (C=O), 1620 (C=N) and 1600 (C=C), 700 (C–Cl).. ^{1}H NMR (300 MHz, [D6] DMSO): δ = 3.98 (s, 2H, CH_2), 7.42-7.44 (m, 3H, Ar- H), 7.65-7.67 (m, 3H, Ar-H), 7.80-7.82 (d, 1H, Ar-H), 9.41 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 40.5, 123.6, 125.8, 128.3, 128.4, 128.6, 128.8, 128.9, 129.4, 130.2, 134.4, 135.1, 156.3, 160.9, 163.5, 166.4. MS (m/z): (381/383/385, M^+, 100/90/32%). Anal. Calcd. for $C_{16}H_{10}N_3O_2Cl_3$: C 50.22; H, 2.61; N, 10.98. Found: C, 50.37; H, 2.69; N, 11.07.

Synthesis of *N*-(4-Oxo-2-phenylquinazolin-3(3*H*)-yl) acetamide derivative (4)

A mixture of 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl) acetamide (**3**) (0.01 mol), anhydrous potassium carbonate (200 mg), and amine derivatives (0.01 mol) in dioxane (15 mL) was refluxed for 12 hours The reaction mixture was then poured into crushed ice. The solid product was obtained filtered off, washed with water, dried, and recrystallized from ethanol (Table 1).

N-(6-Bromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(ethylamino) acetamide (4.2)

IR (KBr, ν, cm^{-1}): 3330 (NH), 3230 (NH), 1710 (C=O), 1680 (C=O), 1610 (C=N).^{1}H NMR (500 MHz, [D6] DMSO): δ = 0.98-1.00 (t, 3H, CH_3), 2.50-2.52 (m, 2H, CH_2-CH_3), 3.30 (s, 2H, CH_2-NH) 7.18-7.20 (m, 3H, Ar-H), 7.60-7.62(d, 1H, Ar-H), 7.80-7.83 (m, 2H, Ar-H), 7.98-8.00 (d, 1H, Ar-H), 8.20-8.22 (d, 1H, Ar-H), 8.42 (s, 1H, NH), 8.65 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 14.3, 19.6, 40.7, 120.8, 121.9, 123.2, 128.2, 128.3, 128.6, 128.8, 128.9, 130.3, 132.4, 136.4, 147.8, 156.6, 160.8, 176.7. MS (m/z): 400/402/403 M^+, 100/95 /20%).

N-(6-Bromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(2-nitrophenylamino)acetamide (4.5)

IR (KBr, ν, cm^{-1}): 3380 (NH), 3190 (NH), 1725 (C=O), 1700 (C=O), 1615 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 3.60 (s, 2H, CH_2-NH) 7.28-7.30 (m, 2H, Ar-H), 7.58-7.62(m, 5H, Ar-H), 7.80-7.82 (m, 2H, Ar-H), 8.00-8.02 (m, 2H, Ar-H), 8.12-8.14 (d, 1H, Ar-H), 8.50 (s, 1H, NH), 8.62 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 56.4, 111.8, 118.5, 121.8, 123.2, 124.7, 125.9, 128.2, 128.2, 128.6, 128.8, 128.9, 130.3, 131.8 132.4, 135.6, 136.3, 145.6, 147.6, 156.4, 160.7, 170.4.. MS (m/z): 493/495/495 M^+, 100/90/24%).

N-(6,8-Dibromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(phenylamino)acetamide (4.12)

IR (KBr, ν, cm^{-1}): 3360 (NH), 3240 (NH), 1705 (C=O), 1640 (C=O), 1598 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 3.70 (s, 2H, CH_2-NH) 6.65-6.68 (m, 3H, Ar-H), 7.16-7.18(m, 2H, Ar-H), 7.48-7.50 (m, 3H, Ar-H), 7.62-7.46 (d, 1H, Ar-H), 7.76-7.78 (m, 2H, Ar-H), 8.10 (d, 1H, Ar-H), 8.51 (s, 1H, NH), 8.62 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 57.4, 113.4, 113.6, 113.7, 120.9, 122.1, 125.4, 128.4, 128.6, 128.9, 128.9, 128.9, 129.6, 130.3, 131.4, 139.7, 147.8, 154.5, 156.5, 160.8, 160.7, 170.6. MS (m/z): (528/526/530, M^+, 100/52/46%).

N-(6,8-Dibromo-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(*o*-tolylamino)acetamide (4.18)

IR (KBr, ν, cm^{-1}): 3400 (NH), 3200 (NH), 1700 (C=O), 1660 (C=O), 1590 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 2.04(s, 3H, CH_3) 3.68 (s, 2H, CH_2-NH) 6.62-6.64 (m, 2H, Ar-H), 6.83-6.85(m, 1H, Ar-H), 7.10-7.12 (d, 1H, Ar-H), 7.43-7.45 (m, 3H, Ar-H), 7.66-7.68 (d, 1H, Ar-H), 7.78-7.80 (m, 2H, Ar-H), 8.05-8.07 (d, 1H, Ar-H), 8.40 (s, 1H, NH), 8.60 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 17.8, 57.6, 113.3, 117.2, 121.9, 122.2, 122.3, 125.4, 126.7, 127.2, 128.3, 128.4, 128.4, 128.7, 128.9, 130.3, 131.4, 139.5, 146.7, 154.5, 156.2, 160.7, 170.3. MS (m/z): (542/544/540, M^+, 100/50/48%).

N-(6-Chloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(ethylamino) acetamide (4.20)

IR (KBr, ν, cm^{-1}): 3350 (NH), 3228 (NH), 1712 (C=O), 1655 (C=O), 1600 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 1.00-1.02 (t, 3H, CH_3), 2.48-2.50 (m, 2H, CH_2-CH_3), 3.34 (s, 2H, CH_2-NH) 7.40-7.43 (m, 4H, Ar-H), 7.58-7.60(d, 1H, Ar-H), 7.82-7.84 (m, 2H, Ar-H), 7.94-7.96 (d, 1H, Ar-H), 8.45 (s, 1H, NH), 8.60 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 15.4, 44.5, 54.9, 122.3, 127.8, 127.8, 128.3, 128.4, 128.6, 128.9, 128.9, 130.3, 132.9, 133.6, 146.8, 156.3, 160.8, 170.4. MS (m/z): (356/358, M^+, 100/32%).

N-(6-Chloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(4-chlorophenylamino)acetamide (4.22)

IR (KBr, ν, cm^{-1}): 3360 (NH), 3236 (NH), 1730 (C=O), 1675 (C=O), 1590 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 3.68 (s, 2H, CH_2-NH) 6.48-6.50 (d, 2H, Ar-H), 7.40-7.42(d, 2H, Ar-H), 7.50-7.53 (m, 4H, Ar-H), 7.68-7.70 (d, 1H, Ar-H), 7.85-7.87 (m, 2H, Ar-H), 7.92-7.94 (d, 1H, Ar-H), 8.40 (s, 1H, NH). 8.58 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 57.4, 114.9, 114.9, 122.2, 126.3, 127.8, 127.8, 128.2, 128.3, 128.7, 128.9, 128.9, 129.7, 129.7, 130.3, 132.9, 133.6, 145.7, 146.7, 156.3, 160.9, 170.4. MS (m/z): (438/440/439, M^+, 100/60/22%).

N-(6,8-Dichloro-4-oxo-2-phenylquinazolin-3(3*H*)-yl)-2-(methylamino)acetamide (4.28)

IR (KBr, ν, cm^{-1}): 3345 (NH), 3218 (NH), 1720 (C=O), 1660 (C=O), 1596 (C=N). ^{1}H NMR (500 MHz, [D6] DMSO): δ = 3.20 (s, 2H, CH_2-NH) 3.40 (s, 3H, CH_3), 7.48-7.50 (m, 4H, Ar-H), 7.82-7.84 (m, 3H, Ar-H), 8.45 (s, 1H, NH). 8.61 (s, 1H, NH).^{13}C NMR (300 MHz, [D6] DMSO): δ = 57.5, 79.1, 123.7, 125.9, 128.3, 128.3, 128.7, 128.9, 128.9, 129.4, 130.2, 134.4, 135.3, 156.3, 160.7, 163.5, 170.4. MS (m/z): (376/378/377, M^+, 100/60/20%).

Pharmacology

The synthesized compounds were evaluated for analgesic activity. The test compounds and the standard drugs were administered in the form of a suspension (1% carboxy methyl cellulose as a vehicle) by oral route. Each group consisted of six animals. The animals were maintained in colony cages at 25 ± 2°C, relative humidity of 45-55%, under a 12 hours light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use.

Analgesic activity

The analgesic activity was performed by the tail-flick technique [20,21] using albino mice (25-35 g) of either sex selected by the random sampling technique. Diclofenac sodium at a dose level of 10 mg/ kg was administered orally as a reference drug for comparison. The test compounds at a dose level of 10 mg/kg were administered orally. The reaction time was recorded at 30 minutes, 1, 2, and 3 hours after the treatment, and cut-off time was 10 seconds. The results are presented in Table 2. The percent analgesic activity (PAA) was calculated by the following formula:

$$PAA=[T_2-T_1/10-T_1] \times 100$$

Where T_1 is the reaction time (s) before treatment and T_2 is the reaction time (s) after treatment.

Comp. No.	X	Y	R	Yield %	m.p. °C	Mol. F./Mol. Wt.	Elemental analysis		
							C	H	N
4.1	Br	H	-$NHCH_3$	80	178-180	$C_{17}H_{15}N_4O_2Br$ 387	52.71 52.94	3.87 3.96	14.47 14.62
4.2	Br	H	-NHC_2H_5	82	183-185	$C_{18}H_{17}N_4O_2Br$ 401	53.86 53.89	4.24 4.32	13.96 13.91
4.3	Br	H	-NHC_6H_5	78	188-190	$C_{22}H_{17}N_4O_2Br$ 449	58.80 58.92	3.79 3.96	12.47 12.59
4.4	Br	H	-NH-4-(Cl)C_6H_4	75	195-197	$C_{22}H_{16}N_4O_2BrCl$ 483.50	54.60 54.73	3.31 3.34	11.58 11.70
4.5	Br	H	-NH-2-(NO_2)C_6H_4	72	208-210	$C_{22}H_{16}N_5O_4Br$ 494	53.44 53.38	3.24 3.27	14.17 14.24
4.6	Br	H	-NH-4-(NO_2)C_6H_4	75	212-214	$C_{22}H_{16}N_5O_4Br$ 494	53.44 53.61	3.24 3.35	14.17 14.30
4.7	Br	H	-NH-2-(OCH_3)C_6H_4	76	193-195	$C_{23}H_{19}N_4O_3Br$ 479	57.62 57.68	3.97 3.84	11.69 11.78
4.8	Br	H	-NH-4-(OCH_3)C_6H_4	74	195-197	$C_{23}H_{19}N_4O_3Br$ 479	57.62 57.70	3.97 4.08	11.69 11.82
4.9	Br	H	-NH-2-(CH_3)C_6H_4	75	186-188	$C_{23}H_{19}N_4O_2Br$ 463	59.61 59.73	4.10 4.33	12.09 12.27
4.10	Br	Br	-$NHCH_3$	70	223-225	$C_{17}H_{14}N_4O_2Br_2$ 466	43.78 43.90	3.00 3.24	12.02 12.31
4.11	Br	Br	-NHC_2H_5	75	233-235	$C_{18}H_{16}N_4O_2Br_2$ 480	45.00 45.08	3.33 3.39	11.66 11.82
4.12	Br	Br	-NHC_6H_5	78	237-239	$C_{22}H_{16}N_4O_2Br_2$ 528	50.00 49.91	3.03 3.10	10.60 10.74
4.13	Br	Br	-NH-4-(Cl)C_6H_4	76	241-243	$C_{22}H_{15}N_4O_2Br_2Cl$ 562.5	46.93 47.01	2.66 2.90	9.95 9.74
4.14	Br	Br	-NH-2-(NO_2)C_6H_4	74	253-255	$C_{22}H_{15}N_5O_4Br_2$ 573	46.07 46.21	2.62 2.68	12.22 12.31
4.15	Br	Br	-NH-4-(NO_2)C_6H_4	75	251-253	$C_{22}H_{15}N_5O_4Br_2$ 573	46.07 46.24	2.62 2.71	12.22 12.38
4.16	Br	Br	-NH-2-(OCH_3)C_6H_4	78	228-230	$C_{23}H_{18}N_4O_3Br_2$ 558	49.46 49.70	3.23 3.50	10.04 10.08
4.17	Br	Br	-NH-4-(OCH_3)C_6H_4	80	230-232	$C_{23}H_{18}N_4O_3Br_2$ 558	49.46 49.68	3.23 3.37	10.04 10.12
4.18	Br	Br	-NH-2-(CH_3)C_6H_4	77	212-214	$C_{23}H_{18}N_4O_2Br_2$ 542	50.92 50.74	3.32 3.38	10.33 10.50
4.19	Cl	H	-$NHCH_3$	78	152-154	$C_{17}H_{15}N_4O_2Cl$ 342.5	59.56 59.62	4.38 4.61	16.35 16.40
4.20	Cl	H	-NHC_2H_5	82	158-160	$C_{18}H_{17}N_4O_2Cl$ 356.5	60.59 60.74	4.77 4.82	15.70 15.79
4.21	Cl	H	-NHC_6H_5	74	164-166	$C_{22}H_{17}N_4O_2Cl$ 404.5	65.27 65.38	4.20 4.09	13.84 13.92
4.22	Cl	H	-NH-4(Cl)C_6H_4	75	183-185	$C_{22}H_{16}N_4O_2Cl_2$ 439	60.14 60.30	3.64 3.82	12.75 12.91
4.23	Cl	H	-NH-2(NO_2)C_6H_4	72	191-193	$C_{22}H_{16}N_5O_4Cl$ 449.5	58.73 58.80	3.56 3.61	15.57 15.41
4.24	Cl	H	-NH-4(NO_2)C_6H_4	74	190-192	$C_{22}H_{16}N_5O_4Cl$ 449.5	58.73 58.86	3.56 3.77	15.57 15.60
4.25	Cl	H	-NH-2(OCH_3)C_6H_4	80	194-196	$C_{23}H_{19}N_4O_3Cl$ 434.5	63.52 63.74	4.37 4.61	12.88 12.93
4.26	Cl	H	-NH-4(OCH_3)C_6H_4	78	207-209	$C_{23}H_{19}N_4O_3Cl$ 434.5	63.52 63.60	4.37 4.56	12.88 12.87
4.27	Cl	H	-NH-2(CH_3)C_6H_4	80	176-178	$C_{23}H_{19}N_4O_2Cl$ 418.5	65.95 65.87	4.54 4.66	13.38 13.52
4.28	Cl	Cl	-$NHCH_3$	78	180-182	$C_{17}H_{14}N_4O_2Cl_2$ 377	54.11 54.20	3.71 3.89	14.85 14.93
4.29	Cl	Cl	-NHC_2H_5	85	191-193	$C_{18}H_{16}N_4O_2Cl_2$ 391	55.24 55.49	4.09 4.20	14.32 14.37
4.30	Cl	Cl	-NHC_6H_5	78	205-207	$C_{22}H_{16}N_4O_2Cl_2$ 439	60.14 60.22	3.64 3.59	12.75 12.81
4.31	Cl	Cl	-NH-4-(Cl)C_6H_4	76	218-220	$C_{22}H_{15}N_4O_2Cl_3$ 473.5	55.76 55.90	3.17 3.41	11.83 11.88
4.32	Cl	Cl	-NH-2-(NO_2)C_6H_4	75	235-237	$C_{22}H_{15}N_5O_4Cl_2$ 484	54.55 54.70	3.10 3.26	14.46 14.51
4.33	Cl	Cl	-NH-4-(NO_2)C_6H_4	74	234-236	$C_{22}H_{15}N_5O_4Cl_2$ 484	54.55 54.43	3.10 3.18	14.46 14.58

4.34	Cl	Cl	$-NH-2(-OCH_3)C_6H_4$	80	247-249	$C_{23}H_{18}N_4O_3Cl_2$ 469	58.85 58.93	3.84 3.96	11.94 12.10
4.35	Cl	Cl	$-NH-4-(OCH_3)C_6H_4$	82	245-247	$C_{23}H_{18}N_4O_3Cl_2$ 469	58.85 58.87	3.84 3.90	11.94 11.98
4.36	Cl	Cl	$-NH-2-(CH_3)C_6H_4$	78	234-236	$C_{23}H_{18}N_4O_2Cl_2$ 453	60.93 60.87	3.97 4.13	12.36 12.50

Table 1: The physical data and elemental analysis of compounds (4).

Comp. 4	**% Analgesic Activity[a]**			
	Time (minutes)			
	30	**60**	**120**	**180**
4.1	34 ± 1.62^b	37 ± 1.41^c	40 ± 1.91^c	30 ± 1.32^b
4.2	35 ± 1.28^c	41 ± 1.42^c	53 ± 1.05^b	31 ± 1.53^b
4.3	30 ± 1.51^b	33 ± 1.26^c	36 ± 1.51^c	29 ± 1.63^b
4.4	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.5	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.6	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.7	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.8	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.9	25 ± 1.11^b	27 ± 1.01^b	30 ± 1.20^b	26 ± 1.73^b
4.10	34 ± 1.62^b	37 ± 1.41^c	40 ± 1.91^c	30 ± 1.32^b
4.11	35 ± 1.28^c	41 ± 1.42^c	53 ± 1.05^b	31 ± 1.53^b
4.12	30 ± 1.51^b	33 ± 1.26^c	36 ± 1.51^c	29 ± 1.63^b
4.13	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.14	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.15	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.16	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.17	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.18	25 ± 1.11^b	27 ± 1.01^b	30 ± 1.20^b	26 ± 1.73^b
4.19	34 ± 1.62^b	37 ± 1.41^c	40 ± 1.91^c	30 ± 1.32^b
4.20	35 ± 1.28^c	41 ± 1.42^c	53 ± 1.05^b	31 ± 1.53^b
4.21	30 ± 1.51^b	33 ± 1.26^c	36 ± 1.51^c	29 ± 1.63^b
4.22	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.23	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.24	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.25	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.26	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.27	25 ± 1.11^b	27 ± 1.01^b	30 ± 1.20^b	26 ± 1.73^b
4.28	34 ± 1.62^b	37 ± 1.41^c	40 ± 1.91^c	30 ± 1.32^b
4.29	35 ± 1.28^c	41 ± 1.42^c	53 ± 1.05^b	31 ± 1.53^b
4.30	30 ± 1.51^b	33 ± 1.26^c	36 ± 1.51^c	29 ± 1.63^b
4.31	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.32	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.33	28 ± 1.13^b	29 ± 1.21^b	32 ± 1.06^c	22 ± 1.44^b
4.34	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.35	29 ± 1.51^b	31 ± 1.30^b	36 ± 1.41^b	28 ± 1.32^c
4.36	25 ± 1.11^b	27 ± 1.01^b	30 ± 1.20^b	26 ± 1.73^b
Control	2 ± 0.23	4 ± 0.30	4 ± 0.29	2 ± 0.51
Diclofenac	38 ± 1.23^c	43 ± 1.42^c	46 ± 1.08^c	35 ± 1.15^b

[a]Data expressed as mean ± SD from six different experiments done in duplicate; Significance levels: [b]*p*<0.5 and [c]*p*<0.01 as compared to the respective control; control refers to no treatment (vehicle only).

Table 2: The analgesic effect of diclofenac sodium and test compounds (4) in mice.

Molecular modeling

Docking studies were carried out to examine the analgesic effect of compounds **4.1-36**.

Preparation of the target protein

The protein target needs to be prepared and modeled according to the format requirements of the docking algorithms used. Thus the required protein was downloaded from protein data bank (PDB) (code 4COX) using Discovery Studio 2.5 software. Water molecules were removed from downloaded protein. Crystallographic disorders and unfilled valence atoms were corrected using alternate conformations and valence monitor options. Protein was subjected to energy minimization by applying CHARMM force fields for charge, and MMFF94 force field for partial charge. Inflexibility of structure is obtained by creating fixed atom constraint. The binding site of the protein was defined and prepared for docking.

Tested compounds preparation

The designed compounds 2D structures were sketched using ChemBioDraw Ultra 14.0 and saved in MDL-SDfile format. SDfile opened, 3D structures were protonated and energy minimized by applying CHARMM force fields for charge, and MMFF94 force field for partial charge, then prepared for docking by optimization of the parameters.

Results and Discussion

The synthetic route depicted in Scheme 1 outlines the chemistry part of the present work. The key intermediate 3-amino-2-phenylquinazoline-4-(3*H*)-one (**2**) was synthesized by a straightforward method; 5-bromoanthranilic acid, 3,5-dibromoanthranilic acid, 5-chloroanthranilic acid and 3,5-dichloroanthranilic acid was treated with benzoyl chloride in the presence of pyridine to give benzoxazin-4-one (**1**) which was condensed with hydrazine hydrate in ethanol to yield the desired 3-amino-2-phenylquinazoline-4-(3*H*)-one (**2**). The 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl)acetamide (**3**) was prepared by the reaction between 3-amino-2-phenylquinazoline-4-(3*H*)-one (**2**) and chloroacetyl chloride in dioxane in the presence of triethylamine. The IR spectrum of **3** showed intense peaks at 3200 cm^{-1} for NH, 1710 1680, cm^{-1} for carbonyl (C = O), 1610 cm^{-1} for (C = N). The ^{1}H NMR spectrum of **3** showed a singlet at δ=3.98-4.20 ppm due to a CH_2 group and for aromatic protons in the range δ=7.40–7.98 ppm and there is a singlet around 9.12-9.41 due to NH.

The target compounds, 2-(substituted)-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl)acetamide **4.1-36**, were obtained in a good yield through the nucleophilic displacement of the chloride substituted of **3** with a variety of amines, using dioxane as solvent. The formation of target compounds is indicated by the disappearance of the C–Cl stretching peak of the starting material and the appearance of NH at 3380-3330 cm-1 in the IR spectra of the compounds. The ^{1}HNMR spectra showed signals for substituents at C-3 and a two singlet around δ=8.4 and 8.5 ppm due to two NH groups, and a multiplet at δ=6.62–7.94 ppm was observed for aromatic protons. The mass spectra of the title compounds showed molecular ion peaks corresponding to their molecular formulae. In the mass spectrum of compounds **4.1-36**, a common peak at *m/z*=144 corresponding to a quinazolin-4-one moiety appeared. The $^{35}Cl/^{37}Cl$ isotope peaks were observed in the mass spectra of all the compounds containing Cl, confirming the presence of a chlorine atom in the compounds. The relative intensities of these $^{35}Cl/^{37}Cl$ peaks in comparison with the molecular ion peak were in the ratio of 1:3. Elemental (C, H, N) analyses satisfactorily confirmed elemental composition and purity of the synthesized compounds.

The analgesic activity was performed by the tail-immersion technique using albino mice (Table 2). The results of analgesic testing indicate that the test compounds exhibited moderate analgesic activity at 30 minutes of reaction time and an increase in activity at 1 hour which reached a peak level at 2 hours, and declining activity was observed at 3 hours (Tables 2 and 3). Compounds **4.2, 11, 20** and **29** with ethyl substituent showed good activity, when the ethyl group was replaced by aryl substituents showed a decrease in activity compared to the aliphatic as methyl and ethyl groups.

The obtained results indicated that all studied ligands have similar position and orientation inside the putative binding site of the COX II enzyme. The selected compounds (**4.10**, **4.28** and **4.11**) showed good binding energies ranging from –40.14 to -55.91 kcal/mol. The proposed binding mode of compound **4.10** (affinity value of –55.91 kcal/mol and 2 H-bonds) is shown in Figure 1. It formed two hydrogen bonds with a distance of 1.79 and 2.35 A° with Lue352 and Ser353 respectively. Furthermore, the compound formed Pi-Pi interaction with Phe518. The proposed binding mode of compound **4.28** (affinity value of –55.14 kcal/mol and 2 H-bonds) is shown in Figure 2. It formed two hydrogen bonds with a distance of 2.15 and 2.45 A° with Lue352 and Ser353 respectively. Furthermore, the compound formed Pi-Pi interaction with Phe518. The proposed binding mode of compound **4.11** (affinity value of –54.50 kcal/mol and 1 H-bonds) is shown in Figure 3. It formed a hydrogen bond with a distance of 2.43 A° with Ser353. Furthermore, the compound formed Pi-Pi interaction with Phe518.

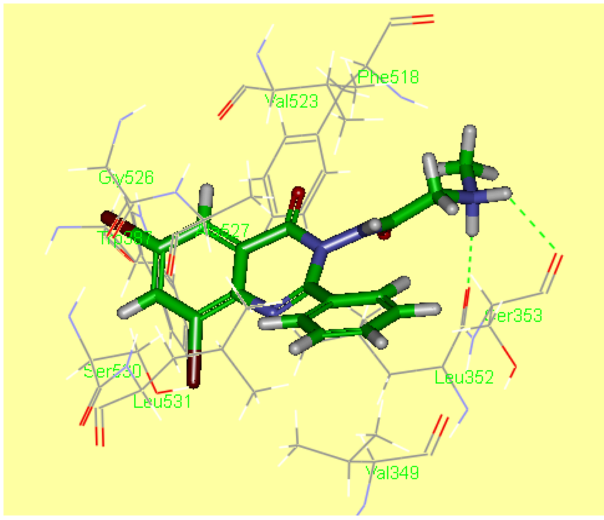

Figure 1: Binding mode of compound 4.10.

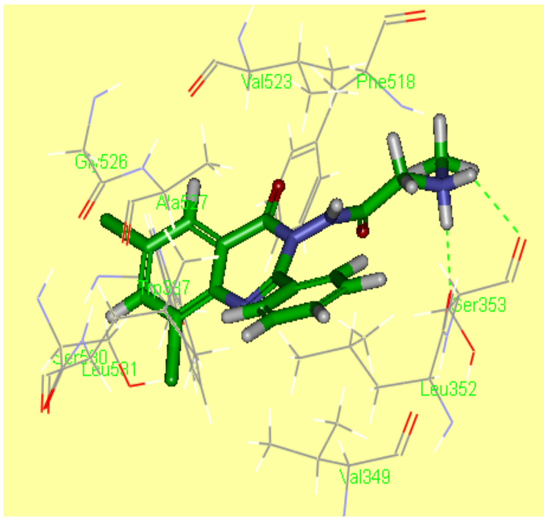

Figure 2: Binding mode of compound 4.28.

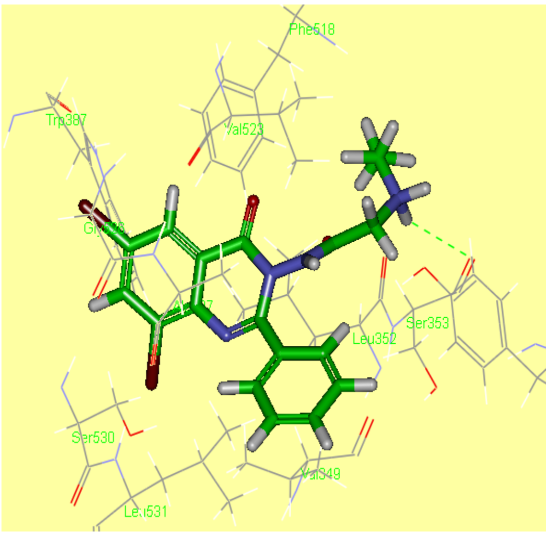

Figure 3: Binding mode of compound 4.11.

Comp.	ΔG	Comp.	ΔG
4.1	-45.42	**4.19**	-44.05
4.2	-43.32	**4.20**	-43.26
4.3	-44.19	**4.21**	-44.08
4.4	-50.01	**4.22**	-54.01
4.5	-49.29	**4.23**	-43.31
4.6	-51.25	**4.24**	-48.55
4.7	-49.91	**4.25**	-47.88
4.8	-47.09	**4.26**	-42.17
4.9	-40.14	**4.27**	-50.31
4.10	-55.91	**4.28**	-55.14
4.11	-54.50	**4.29**	-48.59
4.12	-51.05	**4.30**	-49.49
4.13	-48.17	**4.31**	-41.68
4.14	-53.12	**4.32**	-42.29
4.15	-43.87	**4.33**	-50.44
4.16	-43.55	**4.34**	-40.39
4.17	-40.94	**4.35**	-44.56
4.18	-52.32	**4.36**	-43.52

Table 3: ΔG for ligands 4.1-4.36.

Conclusion

In the present study, the synthesis of a new series of 2-(substituted)-*N*-(4-oxo-2-phenylquinazolin-3(3*H*)-yl)acetamides (**4.1-36**) has been described. The results of the analgesic activity showed a moderate enhancement of activity. The compounds with ethyl side chain (**4.2, 11, 20 and 29**) emerged as the most active compound. Hence this series could be developed as a novel class of analgesic agents. Further structural modification is planned to obtain compounds with increased analgesic and anti-inflammatory activities with minimal ulcerogenic behavior.

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