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Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4(3H)-ones

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Abstract

A series of substituted quinazolin-4(3H)-ones ($VIII_{1-12}$) have been synthesized by treating 3-amino-2-benzylamino-substituted- quinazolin-4(3H)-one VII_{1-4}, with different aldehydes. The starting material 3-amino-2-benzylamino substituted- quinazolin-4(3H)-one VII_{1-4} was synthesized by nucleophilic substitution of thiomethyl group of 3-amino-2-methylthio-substituted- quinazolin-4(3H)-one VI_{1-4} with benzylamine. The synthesized compounds $VIII_{1-12}$ was investigated for analgesic activity. All the test compounds exhibited significant analgesic activity in comparison with paracetamol.

Keywords: 2,3-disubstituted quinazolin-4(3H)-one; Paracetamol; Modeling; Analgesic activity

Abbreviations: NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; COX: Cyclooxygenase; DMSO: N,N-Dimethylformamide; PDB: Protein Data Bank; MOE: Molecular Operating Environment; MP: Melting Point.

Introduction

Quinazolines derivatives exhibited a vital role in many pharmacological activities [1-8] including anti-inflammatory, [9] antibacterial, [10] and anticonvulsant, [11] activities. Schiff's bases have generated a great deal of attention due to their interesting pharmaceutical activities include possess potent analgesic and anti-inflammatory activities [12]. In the view of these facts and to develop earlier reporting [6] quinazoline-4(3H)-ones series that drawn great attention in the field of synthetic medicinal chemistry because it shown good analgesic and anti-inflammatory activities therefore, our aim was oriented to design derivatives of existing clinically used NSAIDs that has ability to inhibit the cyclooxygenase (COX) and as a result in safety when taking paracetamol [13] because it used in medication to treat pain and fever [14] through acting by inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2 [15]. As part of our ongoing medicinal chemistry research program we found that quinazolines [6] especially quinazolin-4(3H)-ones with 2, 3-disubstitution that reported [16] to possess significant analgesic, anti-inflammatory activities. Based on these findings it is rationalized to synthesis and design new substituted quinazolin-4(3H)-ones and screen their anti-inflammatory and analgesic activities (Scheme 1).

Experimental

General

Chemistry: Melting points were measured in capillary tube on a Graffin melting point apparatus and are uncorrected. The IR spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer using KBr discs (λ_{max} in cm^{-1}). ^{1}HNMR 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. Starting Compounds 1-3 was prepared according to reported procedures [17-19].

Synthesis of substituted 3-Amino-2-mercapto Quinazolin-4(3H)-one (V)

To a vigorously stirred solution of III1-4 derivatives (0.02 mol) in and hydrazine hydrate 95% (8.6 g, 0.2 mol) that was added drop wise under cold condition. After the completion of addition, stirring was continued for 1.5 h at 50°C and the mixture was poured into ice-water. The solid obtained was filtered, washed with water, then washed with absolute ethanol and crystallized from dimethylformamide then washed with ethanol to produce compound V.

3-amino-6-bromo-2-mercaptoquinazolin-4(3H)-one (V_1): Yield: 68%; MP: 228-230°C; IR (KBr, ν, cm^{-1}): 3300 (NH_2), 2560(SH), 1700 (C=O quinazoline ring), 1570 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.02 (s, 1H, C_5-H), 7.76 (d, 1H, J = 8.30 Hz, C_7-H), 7.43 (s, 1H, J = 16.52 Hz, C_8-H), 5.21 (s, 2H, NH_2, D_2O exchangeable), 3.29 (s, 1H, SH). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 121.6, 123.2, 124.7, 132.5, 136.8, 146, 159.7, 160.7. MS (m/z): 274 (M+2, 34.58%), 272 (M+, 35, 11%). Anal. Calcd. for $C_8H_6BrN_3OS$: C, 35.31; H, 2.22; N, 15.44. Found: C, 35.17; H, 2.36; N, 15.62.

3-amino-6, 8-dibromo-2-mercaptoquinazolin-4(3H)-one (V_2): Yield: 60%; mp 237-239°C; IR (KBr, ν, cm^{-1}): 3320 (NH_2), 2567 (SH), 1690 (C=O quinazoline ring), 1573 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 7.93 (s, 1H, C_5-H), 7.71 (s, 1H, C_7-H), 5.41(s, 2H, NH_2, D_2O exchangeable), 3.21 (s, 1H, SH). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 122, 125.2, 130.2, 131.4, 139.5, 150.2, 159.4, 160.4. MS (m/z): 350 (M+4, 14.12%), 348 (M+2, 28.44%), 272 (M+, 13.89%). Anal. Calcd.

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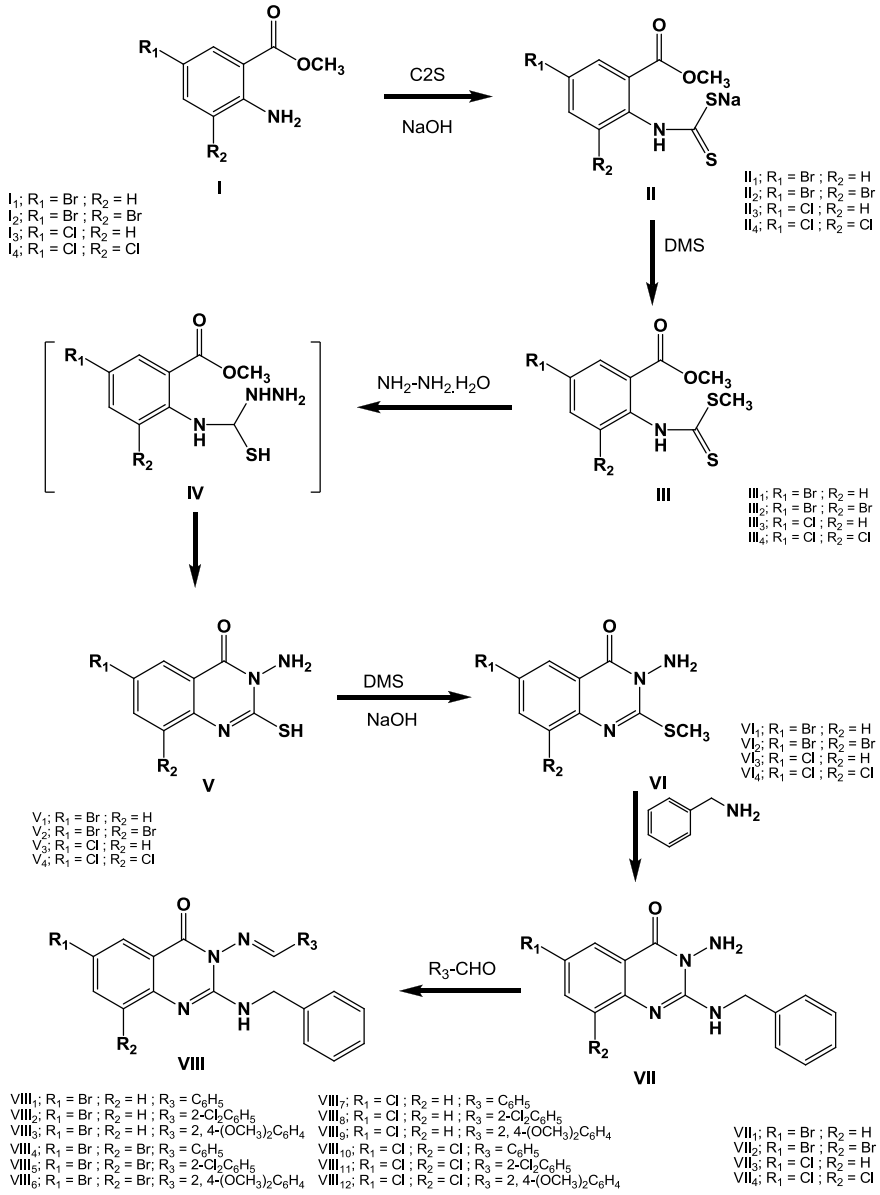

Scheme 1: Synthesis of compounds **I-VIII**.

for $C_8H_6Br_2N_3OS$: C, 27.37; H, 1.44; N, 11.97. Found: C, 27.48; H, 1.66; N, 11.72.

3-amino-6-chloro-2-mercaptoquinazolin-4(3H)-one (V_3): Yield: 75%; MP: 204-206°C; IR (KBr, ν, cm^{-1}): 3280 (NH_2), 2570 (SH), 1700 (C=O quinazoline ring), 1560 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 7.93 (s, 1H, C_5-H), 7.74 (d, 1H, J = 7.50 Hz, C_7-H), 7.61 (d, 1H, J = 8.60 Hz, C_8-H), 5.41 (s, 2H, NH_2, D_2O exchangeable), 3.34 (s, 1H, SH). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 122.3, 127.8, 127.8, 133, 133.5, 145, 159.4, 160.6. MS (m/z): 229 (M+2, 32%), 227 (M+, 7.1%). Anal. Calcd. for $C_8H_6ClN_3OS$: C, 42.20; H, 2.66; N, 18.46. Found: C, 42.46; H, 2.61; N, 18.51.

3-amino-6, 8-dichloro-2-mercaptoquinazolin-4(3H)-one (V_4): Yield: 68%; MP: 218-220°C; IR (KBr, ν, cm^{-1}): 3300 (NH_2), 2562 (SH), 1700(C=O quinazoline ring), 1572 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 7.93 (s, 1H, C_5-H), 7.70(s, 1H, C_7-H), 5.69 (s, 2H, NH_2, D_2O exchangeable), 3.20 (s, 1H, SH). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 123.7, 125.9, 129.4, 134.4, 135.2, 159.2, 159.4, 160.7. MS (m/z): 265 (M+4, 1.94%), 263 (M+2, 7.67%), 261 (M+, 10.2%). Anal. Calcd. for $C_8H_5Cl_2N_3OS$: C, 36.66; H, 1.92; N, 16.03. Found: C, 36.71; H, 1.74; N, 16.17.

Synthesis of substituted 3-Amino-2-methylthio Quinazolin-4(3H)-one (VI)

A solution of 3-amino-2-mercaptoquinazolin-4(3H)-one 1.93 g (0.01 mol) in sodium hydroxide 10 ml (20% w/v) was obtained by warming on a water bath. It was clarified by filtration while in warm condition, cooled and treated with dimethyl sulphate 1.26 g (0.01 mol) under constant stirring. The solution was stirred at room temperature for 12 h. The solid obtained was filtered off, washed with cold water, dried and recrystallized from chloroform/ethanol.

3-amino-6-bromo-2-(methylthio) quinazolin-4(3H)-one (VI_1): Yield: 80%; MP: 172-174°C; IR (KBr, ν, cm^{-1}): 3320 (NH_2), 1700 (C=O quinazoline ring), 1565 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ

= 8.20 (s, 1H, C_5-H), 7.82 (d, 1H, J = 8.0 Hz, C_7-H), 7.60 (d, 1H, J = 8.0 Hz, C_8-H), 6.70 (s, 2H, NH_2, D_2O exchangeable), 2.51 (s, 3H, SH_3). MS (m/z): 286 (M+2, 21.12%), 284 (M+, 22.19%). Anal. Calcd. for $C_9H_8BrN_3OS$: C, 37.78; H, 2.82; N, 14.68. Found: C, 37.92; H, 2.90; N, 14.74.

3-amino-6, 8-dibromo-2-(methylthio) quinazolin-4(3H)-one (VI_2): Yield: 72%; MP: 186-188°C; IR (KBr, ν, cm^{-1}): 3325 (NH_2), 1680 (C=O quinazoline ring), 1570 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 8.20 (s, 1H, C_5-H), 8.10 (s, 1H, C_7-H), 6.62 (s, 2H, NH_2, D_2O exchangeable), 2.55 (s, 3H, SH_3). MS (m/z): 366 (M+4, 10.12%), 364 (M+2, 20.44%), 362 (M+, 10.09%). Anal. Calcd. for $C_9H_7Br_2N_3OS$: C, 29.61; H, 1.93; N, 11.51. Found: C, 29.72; H, 1.98; N, 11.42.

3-amino-6-chloro-2-(methylthio) quinazolin-4(3H)-one (VI_3): Yield: 82%; MP: 154-156°C; IR (KBr, ν, cm^{-1}): 3305 (NH_2), 1720 (C=O quinazoline ring), 1575 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 7.90 (s, 1H, C_5-H), 7.69 (d, 1H, J = 7.60 Hz, C_7-H), 7.40 (s, 1H, J = 8.60 Hz, C_8-H), 6.72 (s, 2H, NH_2, D_2O exchangeable), 2.50 (s, 3H, SH_3). MS (m/z): 243 (M+2, 6.1%), 241 (M+, 17.9%). Anal. Calcd. for $C_9H_8ClN_3OS$: C, 44.72; H, 3.34; N, 17.39. Found: C, 44.91; H, 3.52; N, 17.56.

3-amino-6, 8-dichloro-2-(methylthio) quinazolin-4(3H)-one (VI_4): Yield: 76%; MP: 171-173°C; IR (KBr, ν, cm^{-1}): 3300 (NH_2), 1725 (C=O quinazoline ring), 1570 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 7.90 (s, 1H, C_5-H), 7.80 (s, 1H, C_7-H), 6.61 (s, 2H, NH_2, D_2O exchangeable), 2.56 (s, 3H, SH_3). MS (m/z): 278 (M+4, 1.11%), 276 (M+2, 4.31%), 274 (M+, 5.20%). Anal. Calcd. for $C_9H_7Cl_2N_3OS$: C, 39.15; H, 2.56; N, 15.22. Found: C, 39.41; H, 2.63; N, 15.39.

Synthesis of 3-Amino-2-substituted-benzylamino Quinazolin-4(3H)-one VII1-4

A mixture of benzyl amine 5.35 g (0.05 mol) and 3-amino-2-methylthio substituted-quinazolin-4(3H)-one VI_{1-4} (0.01 mol) was heated under reflux at 80°C for 36 h then the reaction mixture was cooled and treated with petroleum ether. The solid product was obtained crystallized from ethanol 95% to afford the desired products VII_{1-4}.

3-amino-2-(benzylamino)-6-bromoquinazolin-4(3H)-one (VII_1): Yield: 78%; MP: 172-174°C; IR (KBr, ν, cm^{-1}): 3400 (NH_2), 1680 (C=O quinazoline ring), 1555 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 8.40 (s, 1H, C_5-H), 8.05 (d, 1H, J = 8.0 Hz, C_7-H), 7.75 (d, 1H, J = 7.50 Hz, C_8-H), 7.4-6.81 (m, 5H, aromatic protons), 5.80 (s, 2H, NH_2, D_2O exchangeable), 4.87 (s, 2H, CH_2), 4.70 (t, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{13}BrN_4O$: C, 52.19; H, 3.80; N, 16.23. Found: C, 52.36; H, 3.56; N, 16.41.

3-amino-2-(benzylamino)-6, 8-dibromoquinazolin-4(3H)-one (VII_2): Yield: 70%; MP: 191-193°C; IR (KBr, ν, cm^{-1}): 3395 (NH_2), 1690(C=O quinazoline ring), 1560 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 8.1-7.2 (m, 7H, aromatic protons), 5.60 (s, 2H, NH_2, D_2O exchangeable), 4.90 (s, 2H, CH_2), 4.40 (t, 1H, NH, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{12}Br_2N_4O$: C, 42.48; H, 2.85; N, 13.21. Found: C, 42.66; H, 2.96; N, 13.39.

3-amino-2-(benzylamino)-6-chloroquinazolin-4(3H)-one (VII_3): Yield: 75%; MP: 160-162°C; IR (KBr, ν, cm^{-1}): 3390 (NH_2), 1688 (C=O quinazoline ring), 1540 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 8.20 (s, 1H, C_5-H), 8.0 (d, 1H, J = 7.0 Hz, C_7-H), 7.75 (d, 1H, J = 7.0 Hz, C_8-H), 7.71-7.2 (m, 5H, aromatic protons), 5.40 (s, 2H, NH_2, D_2O exchangeable), 4.60 (s, 2H, CH_2), 4.60 (t, 1H, NH, D_2O exchangeable). MS (m/z): 302 (M+2, 3.2%), 300 (M+, 3.3%). Anal. Calcd. for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63. Found: C, 60.01; H, 4.46; N, 18.91.

3-amino-2-(benzylamino)-6, 8-dichloroquinazolin-4(3H)-one (VII_4): Yield: 68%; MP: 168-170°C; IR (KBr, ν, cm^{-1}): 3370 (NH_2), 1694(C=O quinazoline ring), 1558 (C=N). ^{1}HNMR (500 MHz, [D6] DMSO): δ = 8.23-7.50 (m, 7H, aromatic protons), 5.80 (s, 2H, NH_2, D_2O exchangeable), 4.80 (t, 1H, NH, D_2O exchangeable), 4.60 (s, 2H, CH_2). MS (m/z): 338 (M+4, 1.8%), 336 (M+2, 7.2%), 334 (M+, 9.01%). Anal. Calcd. for $C_{15}H_{12}Cl_2N_4O$: C, 53.75; H, 3.61; N, 16.72. Found: C, 53.86; H, 3.76; N, 16.86.

Synthesis of substituted- 2-Benzylamino-3-(substituted benzylidene amino) quinazolin-4(3H)-one $VIII_{1-12}$

General procedure: A mixture of 3-amino-2-benzylamino substituted quinazolin-4(3H)-one VII_{1-4} (0.01 mol) and different aromatic aldehydes derivative (0.01 mol) in acetic acid was refluxed for 30 hrs. After completion of reaction (TLC) the reaction mixture was poured into crushed ice and the solid obtained was crystallized from ethanol 95% to obtain pure compounds $VIII_{1-12}$.

2-(benzylamino)-3-(benzylideneamino)-6-bromoquinazolin-4 (3H)-one ($VIII_1$): Yield: 82%; MP: 165-167°C; IR (KBr, ν, cm^{-1}): 3015 (CH-aromatic), 1688 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.65 (s, 1H, CH), 8.20-7.20 (m, 13H, aromatic protons), 4.90 (s, 1H, NH, D_2O exchangeable), 4.10 (s, 2H, CH_2). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 45, 121.8, 123.1, 124.7, 126.8, 126.9, 126.9, 128.5, 128.5, 128.8, 128.8, 129.3, 129.3, 131.2, 132.2, 133.7, 136.5, 137, 146, 153.4, 154.2, 162.3. MS (m/z): 434 (M+2, 2.5%), 432 (M+, 2.51%). Anal. Calcd. for $C_{22}H_{17}BrN_4O$: C, 60.98; H, 3.95; N, 12.93. Found: C, 60.84; H, 3.84; N, 12.97.

2-(benzylamino)-6-bromo-3-(2-chlorobenzylide neamino) quinazolin-4(3H)-one ($VIII_2$): Yield: 72%; MP: 187-189°C; IR (KBr, ν, cm^{-1}): 3010 (CH-aromatic), 1690 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.50 (s, 1H, CH), 8.30-7.20 (m, 12H, aromatic protons), 4.70 (s, 1H, NH, D_2O exchangeable), 3.90 (s, 2H, CH_2). MS (m/z): 469(M+2, 7.4%), 467(M+, 12.3%). Anal. Calcd. for $C_{22}H_{16}BrClN_4O$: C, 56.49; H, 3.45; N, 11.98. Found: C, 56.71; H, 3.67; N, 11.84.

2-(benzylamino)-6-bromo-3-(2,4-dimethoxybenzylideneamino)-quinazolin-4(3H)-one ($VIII_3$): Yield: 68%; MP: 205-207°C; IR (KBr, ν, cm^{-1}): 3012 (CH-aromatic), 1685 (C=O quinazoline ring), 1551 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.90 (s, 1H, CH), 8.00-7.20 (m, 11H, aromatic protons), 4.68(s, 1H, NH, D_2O exchangeable), 3.92(s, 2H, CH_2), 3.74 (s, 6H, OCH_3). MS (m/z): 494 (M+2, 34.2%), 496(M+, 34.3%). Anal. Calcd. for $C_{24}H_{21}BrN_4O_3$: C, 58.43; H, 4.29; N, 11.36. Found: C, 58.57; H, 4.37; N, 11.54.

2-(benzylamino)-3-(benzylideneamino)-6, 8-dibromoquinazolin-4(3H)-one ($VIII_4$): Yield: 74%; MP: 171-173°C; IR (KBr, ν, cm^{-1}): 3010 (CH-aromatic), 1680 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.50 (s, 1H, CH), 8.25-7.20 (m, 12H, aromatic protons), 4.71 (s, 1H, NH, D_2O exchangeable), 4.00 (s, 2H, CH_2). MS (m/z): 512.2 (M+2, 21.6%), 510(M+, 22.3%). Anal. Calcd. for $C_{22}H_{16}Br_2N_4O$: C, 51.59; H, 3.15; N, 10.94. Found: C, 51.68; H, 3.34; N, 11.12.

2-(benzylamino)-6,8-dibromo-3-(2-chlorobenzylid eneamino) quinazolin-4(3H)-one ($VIII_5$): Yield: 77%; MP: 192-194°C; IR (KBr, ν, cm^{-1}): 3012 (CH-aromatic), 1692 (C=O quinazoline ring), 1555 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 9.10 (s, 1H, CH), 7.90-6.80 (m, 11H, aromatic protons), 4.65 (s, 1H, NH, D_2O exchangeable), 3.90 (s, 2H, CH_2). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 45, 113.2, 122, 125.4, 126.7, 126.7, 126.9, 127.2, 128.5, 128.5, 130.5, 131.4, 132.4, 133.5, 134.5, 137.5, 137.9, 139.5, 143.5, 150.3, 153.5, 162.3. MS (m/z):

583 (M+4, 11.2%), 548(M+2, 22.7%), 5546 (M+, 72.44%). Anal. Calcd. for $C_{22}H_{15}Br_2ClN_4O$: C, 48.34; H, 2.77; N, 10.25. Found: C, 48.41; H, 2.86; N, 10.35.

2-(benzylamino)-6, 8-dibromo-3-(2, 4-dimethoxybenzylid eneamino)-quinazolin-4(3H)-one ($VIII_6$): Yield: 86%; MP: 231-233°C; IR (KBr, ν, cm^{-1}): 3009 (CH-aromatic), 1690 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.85 (s, 1H, CH), 8.20-7.20 (m, 10H, aromatic protons), 4.65 (s, 1H, NH, D_2O exchangeable), 3.95 (s, 2H, CH_2), 3.66 (s, 6H, OCH_3). MS (m/z): 572 (M+2, 51.01%), 570(M+, 52.5%). Anal. Calcd. for $C_{24}H_{20}Br_2N_4O_3$: C, 50.37; H, 3.52; N, 9.79. Found: C, 50.52; H, 3.58; N, 9.83.

2-(benzylamino)-3-(benzylideneamino)-6-chloroquin azolin-4(3H)-one ($VIII_7$): Yield: 80%; MP: 159-161°C; IR (KBr, ν, cm^{-1}): 3010 (CH-aromatic), 1690 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.90 (s, 1H, CH), 8.30-7.16 (m, 12H, aromatic protons), 4.65 (s, 1H, NH, D_2O exchangeable), 3.90 (s, 2H, CH_2). MS (m/z): 425 (M+2, 11.39%), 423(M+, 34.3%). Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O$: C, 62.42; H, 3.81; N, 13.24. Found: C, 62.56; H, 3.92; N, 13.36.

2-(benzylamino)-6-chloro-3-(2-chlorobenzylidene amino) quinazolin-4(3H)-one ($VIII_8$): Yield: 71%; mp 172-174°C; IR (KBr, ν, cm^{-1}): 3018 (CH-aromatic), 1690 (C=O quinazoline ring), 1557 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.97 (s, 1H, CH), 8.33-7.25 (m, 11H, aromatic protons), 4.68 (s, 1H, NH, D_2O exchangeable), 3.95 (s, 2H, CH_2). MS (m/z): 458 (M+2, 19.3%), 456(M+, 58.3%). Anal. Calcd. for $C_{22}H_{15}Cl_3N_4O$: C, 57.73; H, 3.30; N, 12.24. Found: C, 57.87; H, 3.42; N, 12.27.

2-(benzylamino)-6-chloro-3-(2,4-dimethoxybenzylide neamino)-quinazolin-4(3H)-one ($VIII_9$): Yield: 80%; MP: 212-214°C; IR (KBr, ν, cm^{-1}): 3010 (CH-aromatic), 1688 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.96 (s, 1H, CH), 8.20-7.00 (m, 11H, aromatic protons), 4.65 (s, 1H, NH, D_2O exchangeable), 3.87 (s, 2H, CH_2), 3.62(s, 6H, OCH_3). MS (m/z): 450 (M+2, 3.19%), 448(M+, 10.1%). Anal. Calcd. for $C_{24}H_{21}ClN_4O_3$: C, 64.21; H, 4.68; N, 12.48. Found: C, 64.35; H, 4.81; N, 12.60.

2-(benzylamino)-3-(benzylideneamino)-6,8-dichloro quinazolin-4(3H)-one ($VIII_{10}$): Yield: 87%; MP: 201-203°C; IR (KBr, ν, cm^{-1}): 3010 (CH-aromatic), 1680 (C=O quinazoline ring), 1550 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.65 (s, 1H, CH), 8.30-7.20 (m, 12H, aromatic protons), 4.73 (s, 1H, NH, D_2O exchangeable), 3.80 (s, 2H, CH_2). MS (m/z): 427(M+4, 5.9%), 425 (M+2, 12.1%), 423(M+, 42.1%). Anal. Calcd. for $C_{22}H_{16}Cl_2N_4O$: C, 62.42; H, 3.81; N, 13.24. Found: C, 62.55; H, 3.61; N, 13.39.

2-(benzylamino)-6,8-dichloro-3-(2-chlorobenzylidene amino) quinazolin-4(3H)-one ($VIII_{11}$): Yield: 79%; MP: 207-209°C; IR (KBr, ν, cm^{-1}): 3020 (CH-aromatic), 1688 (C=O quinazoline ring), 1557 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.96 (s, 1H, CH), 8.35-7.25 (m, 11H, aromatic protons), 4.73 (s, 1H, NH, D_2O exchangeable), 4.01 (s, 2H, CH_2). MS (m/z): 461 (M+4, 14.2%), 459(M+2, 17.2%), 457(M+, 14.7%). Anal. Calcd. for $C_{22}H_{15}Cl_3N_4O$: C, 57.73; H, 3.30; N, 12.24. Found: C, 57.82; H, 3.49; N, 12.39.

2-(benzylamino)-6,8-dichloro-3-(2,4-dimethoxy benzylideneamino)-quinazolin-4(3H)-one ($VIII_{12}$): Yield: 78%; MP: 231-233°C; IR (KBr, ν, cm^{-1}): 3009 (CH-aromatic), 1688 (C=O quinazoline ring), 1542 (C=N). ^{1}HNMR (300 MHz, [D6] DMSO): δ = 8.76 (s, 1H, CH), 8.13-7.02 (m, 10H, aromatic protons), 4.35 (s, 1H, NH, D_2O exchangeable), 3.93 (s, 2H, CH_2), 3.46 (s, 6H, OCH_3). ^{13}C NMR (300 MHz, [D6] DMSO): δ = 49, 56, 56, 101.6, 106.8, 109.2, 123.7, 126, 126.8, 127, 127, 128.7, 128.7, 129.4, 133.1, 134.3, 135.2, 137.8, 143.4, 153.5, 159.3, 159.6, 162.4, 164. MS (m/z): 487 (M+4, 1.1%), 485(M+2, 5.7%), 483 (M+, 7.7%). Anal. Calcd. for $C_{24}H_{20}Cl_2N_4O_3$: C, 59.64; H, 4.17; N, 11.59. Found: C, 59.80; H, 4.27; N, 11.70.

Pharmacology

All the newly synthesized compounds $VIII_{1-12}$ were preliminarily evaluated for their analgesic and Anti-inflammatory activities (using writhing test) using paracetamol as writhing protective stander. The analgesic activity of the newly synthesized compounds $VIII_{1-12}$ compared to paracetamol (Sigma Chemical Co., St. Louis, MO, USA) as a reference was measured after and 30, 60, 90, 120, 150, and 180 after p-benzoquinone (Aldrich) subcutaneous injection. All the tested compounds significantly showed highly percentage of protection against writhing compared with the control untreated group.

Analgesic screening

Adult albino mice of either sex weighing 20-25 gm which was obtained from animal house of Department of Pharmacology, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt. Mice's were divided into twelve groups; each group consists of six mice's per cage. The mice's were kept under constant temperature 30°C and 12 hours light/dark cycle. All animals were acclimatized in the animal facility for at least two weeks prior the experiments. The animals were kept fastened for 24 hours prior to the experiment, but they were allowed free access to water [20,21]. The animal experiments described below comply with the ethical principles and guidelines for the care and use of laboratory animals adopted by the National Egyptian Community. The equipment used was Dial micrometer model (120 - 1206 Baty, Sussex, England). The test compounds as well Paracetamol were suspended in water by the aid of few drops of Tween-80 (Sigma) to produce 2% suspension. And p-benzoquinone (Aldrich) was dissolved in water for injection containing a few drops of Tween-80 to produce 0.02% solution and was used as writhing inducer.

Analgesic activity

The analgesic action of some newly synthesized compound was determined using the writhing method on mice [22]. The mice were randomly arranged in groups each of 10 animal's one group was kept as control. The animals of another group were given paracetamol subcutaneously in a dose of 30 mg/kg body weight. Mice of the other groups were blindly injected subcutaneously with test compounds in a dose of 150 mg/kg body weight. After 30 minutes, each animal of each group was injected with 0.25 ml of 0.02% aqueous solution of p-benzoquinone and was observed for writhing after 30, 60, 90, 120, 150 and 180 minutes. Animals protected from writhing were recorded in each group and the analgesic potency of the test compounds was determined as percentage of protection against writhing. The results are presented in Table 1.

Molecular Modeling

Docking studies were carried out to examine the analgesic effect of compounds $VIII_{1-12}$ which subjected to docking using Molecular Operating Environment (MOE) program [23] on the 3D structure of the cyclooxygenase-2 enzyme (COX-2) in a trial to predict their analgesic action drugs and the aim of the flexible docking calculations is prediction of correct binding geometry for each binder.

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

Comp. No. VIII	Dose mg/kg	% of mice showing abolished writhing						Comp. No. VIII	Dose mg/kg	% of mice showing abolished writhing					
		Time (minutes)								Time (minutes)					
		30	60	90	120	150	180			30	60	90	120	150	180
Paracetamol (control)	20	100	100	100	100	100	100	Paracetamol (control)	20	100	100	100	100	100	100
$VIII_1$	150	100	100	100	100	100	100	$VIII_7$	150	100	100	100	100	100	100
$VIII_2$	150	100	100	100	100	100	100	$VIII_8$	150	100	100	100	100	100	100
$VIII_3$	150	100	100	100	100	100	100	$VIII_9$	150	100	100	100	100	100	100
$VIII_4$	150	100	100	100	100	100	100	$VIII_{10}$	150	100	100	100	100	100	100
$VIII_5$	150	100	100	100	100	100	100	$VIII_{11}$	150	100	100	100	100	100	100
$VIII_6$	150	100	100	100	100	100	100	$VIII_{12}$	150	100	100	100	100	100	100

Table 1: The analgesic effect of paracetamol and tested compounds $VIII_{1-12}$ in mice.

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 ChemBio Draw Ultra 14.0 and saved in MDL-SDfile format. SD file 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 present work, involves the synthesis of new derivatives of substituted- 2-Benzylamino-3-(substituted benzylidene amino) quinazolin-4(3H)-one $VIII_{1-12}$ via starting with key intermediates through bromination and chlorination of methylanthranilate using reported method [17-19] to get compound I_{1-4}. Compound I_{1-4} underwent reaction with carbon disulfide and sodium hydroxide to afford II_{1-4} that suspected to dimethylsulfate resulting the compound III_{1-4} that when reacted with hydrazine hydrate it yielded compound V_{1-4}. The structures of such new compounds were confirmed by both elemental and spectral analyses. The IR spectra of V_{1-4} in KBr showed carbonyl stretching around 1700 cm^{-1} in addition, to NH_2 stretching around 3300 cm^{-1}. The ^1H NMR spectra of V_{1-4} in DMSO-d6, showed singlet of one proton, at 3.20-3.29 ppm due to SH group and NH_2 group appeared as abroad singlet at 5.21-5.69 ppm which is D_2O exchangeable moreover, In the ^{13}C-NMR spectra of these compounds showed C=O peak at about 160 ppm corresponded to carbonyl groups of quinazoline ring that confirm the cyclization of intermediate IV into V. Consequently compound VI was obtained from V upon treatment with dimethyl sulfate in sodium hydroxide and the structure of the resulting compounds clearly confirmed from ^{1}HNMR spectra that showed disappearance of SH signal and appearance of singlet signal around 2.5 ppm belong SCH_3. Frequently, replacement of alkylthio group at 2-position with benzyl amine in simple electrophilic substitution reaction it produce new quinazoline compounds VII_{1-4} where the elemental analysis and spectral data confirm the existence of this substitution reaction where the ^{1}HNMR of new compound contain two signals one at 4.40-4.80 ppm and another one at 5.40-5.80 ppm that exchangeable with D_2O which belong to NH and NH_2 respectively, also the structure of some the compounds were established from the spectral data of the resulting compounds. The title compounds substituted-2-Benzylamino-3-(substituted benzylidene amino) quinazolin-4(3H)-one $VIII_{1-12}$ were obtained by the condensation of amino group of 3-amino-2-substituted-benzylamino Quinazolin-4(3H)-one VII_{1-4} with a different aromatic aldehydes that afford new Schiff's bases. The assignment of the produced Schiff's bases were based on spectral and elemental analysis where ^{1}H-NMR spectrum of all the compounds $VIII_{1-12}$ showed disappearance of signal due to NH_2 group in addition, the ^{1}H-NMR spectrum of all the compounds $VIII_{1-12}$ exhibit singlet of one proton around 8.50-8.97 ppm which belong the (N=CH) proton. The IR spectrum of titled compounds $VIII_{1-12}$ showed the presence of peak carbonyl (C=O), NH and Aryl groups. Because titled compounds contain halogen atom(s) its mass spectrum showed molecular ion peaks corresponding to their molecular formula in addition, to its isotopic peak moreover, in some compounds containing two halogen the mass spectrum showed peaks of M+, M+2, and M+4 that clearly observed and consequently, proven the resulting product. Finally, the structure of the newly synthesized product compounds $VIII_{1-12}$ was proven on the basis of their elemental and spectral data. From the previous mentioned discussion it was observed that our synthetic strategies adopted to obtain the newly synthesized quinazolin-4(3H)-one depending using whether simple synthetic procedure or simple reagent(s). The results of analgesic testing indicate that the test compounds exhibited excellent significant analgesic activity and docking study revealed that the synthesized compounds have potential analgesic activity and can be further optimized and developed as a lead compound. The rationalized steps depend on ligand based drug design particularly a molecular hybridization approach that involves the coupling of two or more groups with relevant biological properties.

Docking Discussion

The obtained results indicated that all studied ligand have similar position and orientation inside the putative binding site of the COX -2 enzyme. The selected compounds $VIII_{12}$, $VIII_9$, $VIII_3$, and $VIII_{11}$ showed good binding energies ranging from -37.18 to -39.12 kcal/mol (Table 2).

The proposed binding mode of compound $VIII_2$ (affinity value of -43.80 kcal/mol and 2 H-bonds) is shown in Figure 1. One carbonyl group formed a hydrogen bond with a distance of 2-12 A° with Ser530. The chloride atom formed a further hydrogen bond with a distance of 2.30 A° with the acidic proton of Arg120. Furthermore, the compound formed Pi-sigma interaction with Phe518 and with ser353. The proposed binding mode of compound VIII4 (affinity value of -42.08 kcal/mol and 2 H-bonds) is shown in Figure 2. One carbonyl group formed a hydrogen bond with a distance of 1.80 A° with ser530. One bromide atom of the ring formed a further hydrogen bond with a distance of 2.37 A° with the acidic proton of Arg120. Furthermore, the compound formed Pi-sigma interaction with Phe518, Trp387 and with Ser353. The proposed binding mode of compound VIII8 (affinity value of -39.12 kcal/mol and 2 H-bonds) is shown in Figure 3. One carbonyl group formed a hydrogen bond with a distance of 2.09 A° with Ser530. The

Compound	ΔG	Compound	ΔG	Compound	ΔG	Compound	ΔG
$VIII_1$	-40.42	$VIII_4$	-42.08	$VIII_7$	-40.99	$VIII_{10}$	-40.86
$VIII_2$	-43.80	$VIII_5$	-43.80	$VIII_8$	-39.84	$VIII_{11}$	-39.12
$VIII_3$	-39.09	$VIII_6$	-39.96	$VIII_9$	-37.33	$VIII_{12}$	-37.18
Paracetamol ΔG=49.12							

Table 2: ΔG for ligand $VIII_{1-12}$.

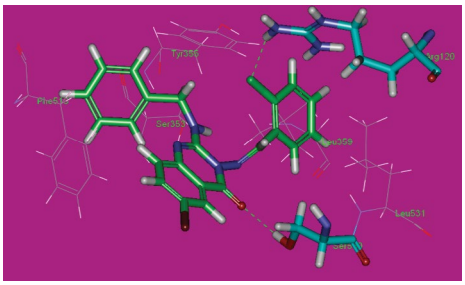

Figure 1: Binding mode of comp. $VIII_2$.

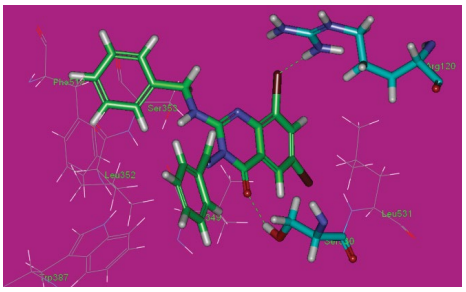

Figure 2: Binding mode of comp. $VIII_4$.

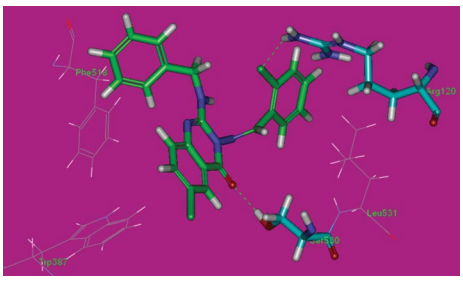

Figure 3: Binding mode of comp. VIII.

chloride atom of the side chain formed a further hydrogen bond with a distance of 2.32 A° with the acidic proton of Arg120. Furthermore, the compound formed Pi-sigma interaction with Phe518 and with Trp387 (Figure 4).

Conclusions

We have synthesized newly derivatives of disubstituted quinazolin-4(3H)-ones that showed analgesic activity. From the data obtained in Table 1 it was found that all derivative $VIII_{1-12}$ have excellent significant analgesic activity. In addition to, the molecular docking for all compounds was performed on the active site of COX-2 enzyme in a trial to predict their mode of action as analgesic drugs, in which the compounds showed several interactions leading to the conclusion that they might exert their action through inhibition of COX-2 enzyme. The biological analgesic screening was performed in Pharmacology Department, Faculty of Pharmacy Al-Azher University, Cairo, Egypt.

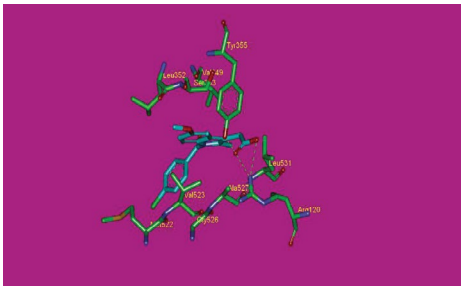

Figure 4: Binding mode of paracetamol.

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