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 VIII 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 in cm⁻¹). 1HNMR spectra were performed either on Gemini 300BB (300 MHz) or (500 MHz) and (300 MHz) for 13C 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 3-Amino-2-mercapto Quinazolin-4(3H)-one (V)

To a vigorously stirred solution of III-1 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 (NH₂), 2560(SH), 1700 (C=O quinazoline ring), 1570 (C=N), 1HNMR (300 MHz, [D 6] 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 = 16.32 Hz, C 8-H), 5.21 (s, 2H, NH₂, D 2O exchangeable), 3.29 (s, 1H, SH). 13C NMR (300 MHz, [D 6] DMSO): δ = 123.6, 123.2, 124.7, 132.5, 136.8, 146, 159.7, 160.7. MS (m/z): 274 (M+2, 28.44%), 348 (M+3, 28.44%), 272 (M+2, 34.58%), 272 (M+3, 34.58%), 272 (M+4, 14.12%), 348 (M+2, 28.44%), 272 (M+1, 13.89%). Anal. Calcd. for C₉H₇BrN₃OS: 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 (NH₂), 2567 (SH), 1690 (C=O quinazoline ring), 1573 (C=N). 1HNMR (300 MHz, [D 6] DMSO): δ = 7.93 (s, 1H, C 5-H), 7.71 (s, 1H, C 7-H), 5.41(s, 2H, NH₂, D 2O exchangeable), 3.21 (s, 1H, SH). 13C NMR (300 MHz, [D 6] 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+3, 13.89%). Anal. Calcd.

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Received April 20, 2016; Accepted April 28, 2016; Published May 04, 2016

Citation: Ayyad RA, Sakr HM, El-Gamal KM (2016) Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4(3H)-ones. Med chem (Los Angeles) 6: 299-305. doi:10.4172/2161-0444.1000360

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3-amino-6-chloro-2-mercaptoquinazolin-4(3H)-one (V): 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, [D$_6$] DMSO): $\delta = 7.93$ (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$_2$O exchangeable), 3.34 (s, 1H, SH). $^{13}$C NMR (300 MHz, [D$_6$] DMSO): $\delta = 122.3, 127.8, 127.8, 133.5, 145.0, 159.4, 160.6$. MS (m/z): 229 (M+2, 32%), 227 (M+, 7.1%). Anal. Calcd. for C$_8$H$_6$ClN$_3$OS: 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): 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, [D$_6$] DMSO): $\delta = 7.93$ (s, 1H, C$_5$-H), 7.70 (s, 1H, C$_7$-H), 5.69 (s, 2H, NH$_2$, D$_2$O exchangeable), 3.20 (s, 1H, SH). $^{13}$C NMR (300 MHz, [D$_6$] DMSO): $\delta = 123.7, 125.9, 129.4, 133.5, 145.0, 159.4, 160.7$. MS (m/z): 265 (M+4, 1.94%), 263 (M+2, 7.67%), 261 (M+, 10.2%). Anal. Calcd. for C$_8$H$_5$Cl$_2$N$_3$OS: 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): Yield: 80%; MP: 172-174°C; IR (KBr, ν, cm$^{-1}$): 3320 (NH$_2$), 1700 (C=O quinazoline ring), 1565 (C=N). $^1$HNMR (300 MHz, [D$_6$] DMSO): $\delta$
3-amino-6, 8-dibromo-2-(methylthio) quinazolin-4(3H)-one (VI)

Yield: 82%; MP: 154-156°C; IR (KBr, cm\(^{-1}\)): 3305 (NH), 1720 (C=O quinazoline ring), 1575 (C=N). \(^1\)HNMR (500 MHz, [D\(_6\)] DMSO): \(\delta = 7.90\) (s, 1H, \(\mathrm{C}_1\)), 7.80 (s, 1H, \(\mathrm{C}_5\)), 6.61 (s, 2H, \(\mathrm{NH}_2\), D\(_2\)O exchangeable), 2.56 (s, 3H, SH), MS (m/z): 278 (M+4, 1.11%), 276 (M+2, 4.31%), 274 (M+, 5.20%). Anal. Calcld. for C\(_{12}\)H\(_9\)ClN\(_4\): C, 59.91; H, 4.36; N, 13.37. Found: C, 59.84; H, 3.84; N, 13.64.

3-amino-6, 8-dichloro-2-(methylthio) quinazolin-4(3H)-one (VI)

Yield: 76%; MP: 171-173°C; IR (KBr, cm\(^{-1}\)): 3300 (NH), 1725 (C=O quinazoline ring), 1570 (C=N). \(^1\)HNMR (500 MHz, [D\(_6\)] DMSO): \(\delta = 8.00\) (s, 1H, \(\mathrm{C}_1\)), 7.75 (d, 1H, J = 7.0 Hz, \(\mathrm{C}_5\)), 7.27 (d, 1H, J = 7.80 Hz, \(\mathrm{C}_6\)), 3.67 (s, 2H, \(\mathrm{NH}_2\), D\(_2\)O exchangeable), 2.87 (s, 2H, \(\mathrm{CH}_2\)). Anal. Calcld. for C\(_{12}\)H\(_9\)BrN\(_4\): C, 45.01; H, 2.63; N, 13.37.

Synthesis of 3-Amino-2-substituted-benzylimino Quinazolin-4(3H)-one VIII-1

A mixture of benzyl amine 5.35 g (0.05 mol) and 3-amino-2-methylthio substituted-quinazolin-4(3H)-one pentafluorobenzamide (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 VIII-1.
-1,2,3,4-tetramethoxybenzene amino)-quinazolin-4(3H)-one (VIII): Yield: 80%; MP: 212-214°C; IR (KBr, ν, cm$^{-1}$): 3018 (CH-aromatic), 1690 (C=O quinazoline ring), 1557 (C=N). 1$^1$HNMR (300 MHz, D$_6$ DMSO): δ = 8.96 (s, 1H, CH), 8.20-7.20 (m, 11H, aromatic protons), 4.65 (s, 1H, NH, D$_2$O exchangeable), 3.80 (s, 2H, CH$_2$). MS (m/z): 452 (M+2, 12.1%), 444 (M+1, 34.8%). Anal. Calcd. for C$_{19}$H$_{17}$N$_2$O: C, 54.77; H, 3.55; N, 12.71. Found: C, 54.81; H, 3.59; N, 12.69.

2-(benzylamino)-6-chloro-3-(2-chlorobenzylidene amino)-quinazolin-4(3H)-one (VIII): Yield: 79%; MP: 207-209°C; IR (KBr, ν, cm$^{-1}$): 3020 (CH-aromatic), 1688 (C=O quinazoline ring), 1557 (C=N). 1$^1$HNMR (300 MHz, D$_6$ DMSO): δ = 8.96 (s, 1H, CH), 8.35-7.25 (m, 11H, aromatic protons), 4.73 (s, 1H, NH, D$_2$O exchangeable), 3.80 (s, 2H, CH$_2$). MS (m/z): 461 (M+4, 14.2%), 453 (M+2, 17.2%), 451 (M+1, 42.1%). Anal. Calcd. for C$_{19}$H$_{15}$ClN$_2$O: C, 57.73; H, 3.61; N, 13.29. Found: C, 57.62; H, 3.63; N, 13.28.

2-(benzylamino)-6-chloro-3-(2-chlorobenzyldene amino)-quinazolin-4(3H)-one (VIII): Yield: 78%; MP: 231-233°C; IR (KBr, ν, cm$^{-1}$): 3009 (CH=O, 1688 (C=O quinazoline ring), 1542 (C=N). 1$^1$HNMR (300 MHz, D$_6$ DMSO): δ = 8.76 (s, 1H, CH), 8.13-7.02 (m, 10H, aromatic protons), 4.35 (s, 1H, NH, D$_2$O exchangeable), 3.93 (s, 2H, CH$_2$), 3.46 (s, 6H, OCH$_3$). 1$^3$C NMR (300 MHz, D$_6$ DMSO): δ = 136, 135, 127, 121, 120, 112, 109, 107, 56, 49. Anal. Calcd. for C$_{28}$H$_{22}$ClN$_4$O$_3$: C, 60.71; H, 4.71; N, 11.59. Found: C, 60.68; H, 4.72; N, 11.70.
The present work involves the synthesis of new derivatives of substituted 2-Benzylamino-3-(substituted benzylidene amino) quinazolin-4(3H)-one VIII via starting with key intermediates through bromination and chlorination of methylanthranilate using reported method [17-19] to get compound I. Compound I underwent reaction with carbon disulfide and sodium hydroxide to afford II, that suspected to dimethylsulfate resulting the compound III that when reacted with hydrazine hydrate it yielded compound IV. The structures of such new compounds were confirmed by both elemental and spectral analyses. The IR spectra of titled compounds VIII showed the presence of aromatic carbonyl peak around 1600 cm⁻¹ which belong to NH and NH stretching moreover, in some compounds containing two halogen the 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 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 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, VIII, VIII, and VIII showed good binding energies ranging from -37.18 to -39.12 kcal/mol (Table 2).

The proposed binding mode of compound VIII, (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 Å with Ser530. The chloride atom formed a further hydrogen bond with a distance of 2.30 Å with the acidic proton of Arg120. Furthermore, the compound formed Pi-sigma interaction with Phe518 and with ser353. The proposed binding mode of compound VIII (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 Å with ser530. One bromide atom of the ring formed a further hydrogen bond with a distance of 2.37 Å 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 VIII (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 Å with Ser530. The

### Table 1: The analgesic effect of paracetamol and tested compounds VIII in mice.

| Comp. No. VIII | Dose mg/kg | % of mice showing abolished writhing Time (minutes) |
|---------------|------------|-----------------------------------------------|
|               | 30 | 60 | 90 | 120 | 150 | 180 |
| Paracetamol (control) | 20 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |
| VIII | 150 | 100 | 100 | 100 | 100 | 100 |

Citation: Ayyad RA, Sakr HM, El-Gamal KM (2016) Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4(3H)-ones. Med chem (Los Angeles) 6: 299-305. doi:10.4172/2161-0444.1000360
The biological analgesic screening was performed in Pharmacology Department, Faculty of Pharmacy Al-Azher University, Cairo, Egypt. For carrying out the analgesic activity for testing compounds. And I would like to thanks all members of Pharmacology Department, Faculty of Pharmacy Al-Azher University, Cairo, Egypt.

**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<sub>1-12</sub> 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.

| Compound | ΔG<sup>1</sup> | Compound | ΔG<sup>2</sup> | Compound | ΔG<sup>3</sup> | Compound | ΔG<sup>4</sup> |
|----------|--------------|----------|--------------|----------|--------------|----------|--------------|
| VIII<sub>1</sub> | -40.42 | VIII<sub>2</sub> | -42.08 | VIII<sub>3</sub> | -40.99 | VIII<sub>4</sub> | -40.86 |
| VIII<sub>5</sub> | -43.80 | VIII<sub>6</sub> | -43.80 | VIII<sub>7</sub> | -39.84 | VIII<sub>8</sub> | -39.12 |
| VIII<sub>9</sub> | -39.96 | VIII<sub>10</sub> | -37.33 | VIII<sub>11</sub> | -37.18 | VIII<sub>12</sub> | -37.18 |

**Table 2:** ΔG for ligand VIII<sub>1-12</sub>

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

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