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Synthesis of New Amino Acid Derivatives Attached to Quinazoline Moiety as Antitumor Agents

Abdel-Rahman AH[1*], Abdel-Fattah M[2], El-Seidi MHM[2]

[1]Department of Chemistry, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt
[2]Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt

ABSTRACT

A series of peptide derivatives conjugated with a quinazoline residue were synthesized. The prepared compounds were tested for antitumor activities which displaying different degrees of antiviral activities or inhibitory actions.

Keywords: Quinazoline derivatives, Amino acids, Antitumor activity

INTRODUCTION

Quinazoline derivatives, which belong to the *N*-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [1-4], anti-inflammation [5,6], antibacterial [7-10], analgesia [5,9], antivirus [11], anticytotoxin [12], antispasm [9,13], antituberculosis [14] antioxidation [15], antimalarial [16], antihypertension [17], antiobesity [18], antipsychotic [19], antidiabetes [20]. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. In connection with our work in synthesis of new α-amino acid derivatives [21-30] and due to the pharmacological properties of amino acid derivatives prompted us to prepare new quinazoline bearing amino acid derivatives to study their antiviral activity.

MATERIALS AND METHODS

Synthetic methods, analytical and spectral data

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using Buck scientific model 500 IR spectrophotometer. The proton NMR spectra were recorded in Dimethyl Sulfoxide (DMSO-d_6) as solvent at 300 MHz, on Varian Gemini NMR Spectrophotometer using TMS as internal standard, chemical shifts are recorded as units (δ ppm). The chemical shifts are reported as Parts Per Million (ppm). Microanalyses were performed at the micro-analytical center, Cairo University. The anticancer activity of the synthesized compounds was carried out at the National Cancer Institute (NCI), Cairo, Egypt. Antiviral activity against HBV was tested at the Liver Institute, Menoufia University, and Shebin El-Koam Egypt.

Chemistry

6-Chloro-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (1)

A mixture of 2-amino-5-chlorobenzoic acid (20.52 g, 0.12 mol) in benzoyl chloride in dry pyridine (40 g, 0.3 mol) was reflux for 3 h. The excess solvents were then distilled off under reduced pressure. The reaction mixture was filtered, washed, dried and re-crystallized with absolute ethanol to afford 1 in 70% yields, M.p. 218-220°C. IR (KBr, cm^{-1}): 1720 (C=O). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.45-7.55 (m, 4H, Ar-H), 7.85-7.95 (m, 3H, Ar-H), 8.10 (s, 1H, Ar-H) ppm.

3-Amino-6-chloro-2-phenylquinazolin-4(3H)-one (2)

A mixture of 1 (2.57 g, 0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol) was refluxed in ethanol for 4 h, the reaction mixture was left to cool. A white solid product was obtained which was precipitated and crystallized from ethanol to give 2 in 78% yields, M.p. 175-177°C. IR (KBr, cm^{-1}): 3325 (NH), 1657 (C=O), 1600 (C=N). Anal. Calcd. For $C_{14}H_{10}ClN_3O$; C, 61.89; H, 3.71; N, 15.47. Found: C, 61.85; H, 3.66; N, 15.33.

6-Chloro-2-phenylquinazolin-4-ol (5)

A mixture of 1 (2.57 g, 0.01 mol) was mixed with ammonium acetate (1.54 g, 0.02 mol), then heated at 220°C, NH_3 gas was liberated during the fusion process, the mixture was left on heater for 1 h, then was left to cool. A solid product was obtained, washed by water and crystallized from ethanol to afford 5 in 90% yield, M.p. 166-168°C. IR (KBr, cm^{-1}): 3385/3176 (OH/NH), 1656 (C=O), 1618/1589 (C=N). Anal. Calcd. For $C_{14}H_9ClN_2O$; C, 65.51; H, 3.53; N, 10.91. Found: C, 65.44; H, 3.47; N, 10.78.

General Procedure for the preparation of the esters 3 and 6

Ethyl chloroacetate (1.4 g, 0.01 mol) was added to a solution of 2 and/or 5 (0.01 mol) in dry acetone (30 ml) and anhydrous K_2CO_3 (1.38 g, 0.01 mol). The reaction mixture was heated under reflux for 6 h, poured on crushed-ice, filtered off and recrystallized from ethanol to give the corresponding esters.

Ethyl 2-(6-chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)acetate (3)

Yield 84% yield, M.p. 160-162°C. IR (KBr, cm^{-1}): 3404-3202 (NH), 1753, 1669 (2 × C=O), 1596 (C=N). Anal. Calcd. For $C_{18}H_{16}ClN_3O_3$; C, 60.42; H, 4.51; N, 11.74. Found: C, 60.33; H, 4.44; N, 11.61.

Ethyl 2-(6-chloro-2-phenylquinazolin-4-yloxy)acetate (6)

Yield 85% yield, M.p. 185-187°C. IR (KBr, cm^{-1}): 1751 (C=O), 1605 (C=N). Anal. Calcd. For $C_{18}H_{15}ClN_2O_3$; C, 63.07; H, 4.41; N, 8.17. Found: C, 62.97; H, 4.32; N, 8.10.

General procedure for the preparation of the acid hydrazides 4 and 7

A solution of the respective esters (0.01 mol) in absolute ethanol (30 ml) and hydrazine hydrate (1.5 g, 0.03 mol) was refluxed for 3 h. The solvent was removed under reduced pressure and the remaining precipitate was collected, dried, and recrystallized from ethanol to afford the acid hydrazides as pale yellow powders.

2-(6-Chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)acetohydrazide (4)

Yield 87% yield, M.p. 168-170°C. IR (KBr, cm^{-1}): 3325 (NH), 1674 (C=O), 1615 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.50 (s, 2H, CH_2), 7.20 (m, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.93 (m, 2H, Ar-H), 8.20 (m, 1H, Ar-H), 8.40 (m, 1H, Ar-H), 8.77 (m, 1H, Ar-H), 12.92 (brs, 3H, NH, NH_2) ppm. Anal. Calcd. For $C_{16}H_{14}ClN_5O_2$; C, 55.90; H, 4.10; N, 20.37. Found: C, 55.80; H, 4.00; N, 20.17.

2-(6-Chloro-2-phenylquinazolin-4-yloxy)acetohydrazide (7)

Yield 91% yield, Mp 210-212°C. IR (KBr, cm^{-1}): 3440-3220 (NH), 1664 (C=O), 1605 (C=N). Anal. Calcd. For $C_{16}H_{143}ClN_4O_2$; C, 58.45; H, 3.99; N, 17.04. Found: C, 58.31; H, 3.79; N, 16.91.

General procedure for the preparation of quinazoline bearing amino acid esters 8, 9, 12, and 13

A solution of 4 and/or 7 (0.80 mmol) in AcOH (6 ml), 1*N* HCl, (3 ml) and H_2O (25 ml) was cooled in an ice-bath (-5°C). $NaNO_2$ (0.87 g, 12.60 mmol) in cold H_2O (3 ml) was added with stirring. After stirring at -5°C for 15 min, the yellow syrup was formed. The azide was taken in cold ethyl acetate (30 ml), washed with $NaHCO_3$ (3%) (30 ml), H_2O (30 ml) and dried (Na_2SO_4). A solution of the appropriate amino acid ethyl ester hydrochloride (0.90 mmol) in ethyl acetate (20 ml) containing Et_3N (0.2 ml) was stirred at 0°C for 20 min, filtered, and the filtrate was added to the azide solution. The mixture was kept at -5°C for 12 h, then at room temperature for another 12 h, followed by washing with 0.5*N* HCl (30 ml), $NaHCO_3$ (3%) (30 ml), H_2O (30 ml) and dried (Na_2SO_4). The filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using PE:EE=5:1 to afford the corresponding peptides.

Methyl 2-[2-(6-chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)acetamido]acetate (8)

Yield 74% yield, M.p. 217-219°C. IR (KBr, cm^{-1}): 3395 (NH), 1748, 1659 (2 × C=O), 1598 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.11 (m, 7H, 2 × CH_2, OCH_3), 7.19 (m, 1H, Ar-H), 7.56 (m, 2H, Ar-H), 7.95 (m, 2H, Ar-H), 8.18 (m, 1H, Ar-H), 8.41 (m, 1H, Ar-H), 8.79 (m, 1H, Ar-H), 9.00 (brs, 1H, NH), 12.92 (brs, 2H, NH_2) ppm. Anal. Calcd. For $C_{19}H_{17}ClN_4O_4$; C, 56.93; H, 4.28; N, 13.98. Found: C, 56.80; H, 4.18; N, 13.80.

(S)-Methyl 2-[2-(6-chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)acetamido]-4-methylpentanoate (9)

Yield 65% yield, M.p. 230-232°C. IR (KBr, cm^{-1}): 3391-3214 (NH), 1766-1654 (2xC=O), 1602 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.15 (d, 6H, *J*=5.5 Hz, 2 × CH_3), 2.00 (m, 1H, CH), 3.03 (m, 7H, 2 × CH_2, OCH_3), 3.95 (s, 2H, CH_2), 7.18 (m, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.90 (m, 2H, Ar-H), 8.20 (m, 1H, Ar-H), 8.40 (m, 1H, Ar-H), 8.69 (m, 1H, Ar-H), 12.95 (s, 1H, NH). ppm. Anal. Calcd. For $C_{23}H_{25}ClN_4O_4$; C, 60.46; H, 5.51; N, 12.26. Found: C, 60.36; H, 5.40; N, 12.10.

Methyl 2-[2-(6-chloro-2-phenylquinazolin-4-yloxy)acetamido]acetate (12)

Yield 76% yield, M.p. 233-235°C. IR (KBr, cm^{-1}): 3395 (NH), 1748, 1659 (2 × C=O), 1622 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.99-3.20 (m, 7H, 2 × CH_2, OCH_3), 7.19 (m, 1H, Ar-H), 7.53 (m, 2H, Ar-H), 7.92 (m, 2H, Ar-H), 8.23 (m, 1H, Ar-H), 8.42 (m, 1H, Ar-H), 8.70 (m, 1H, Ar-H), 12.96 (s, 1H, NH) ppm. Anal. Calcd. For $C_{19}H_{16}ClN_3O_4$; C, 59.15; H, 4.18; N, 10.89. Found: C, 59.00; H, 4.10; N, 10.70.

(S)-Methyl 2-[2-(6-chloro-2-phenylquinazolin-4-yloxy)acetamido]-4-methylpentanoate (13)

Yield 68% yield, Mp 239-241°C. IR (KBr, cm^{-1}): 3325 (NH), 1674 (C=O), 1615 (C=N). ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.14 (d, 6H, *J* = 5.5 Hz, 2 × CH_3), 1.60 (m, 1H, CH), 3.07 (m, 4H, 2 × CH_2), 3.35 (m, 3H, OCH_3), 3.95 (s, 1H, CH), 7.19 (m, 1H, Ar-H), 7.50 (m, 2H, Ar-H), 7.80 (m, 2H, Ar-H), 8.22 (m, 1H, Ar-H), 8.41 (m, 1H, Ar-H), 8.68 (m, 1H, Ar-H), 12.94 (s, 1H, NH) ppm. Anal. Calcd. For $C_{23}H_{24}ClN_3O_4$; C, 62.51; H, 5.47; N, 9.51. Found: C, 62.41; H, 5.40; N, 9.43.

General procedure for the preparation of the hydrazides 10, 11, 14, and 15

A mixture of the above esters (10 mmol) and $N_2H_4.H_2O$ (1.25 g, 25 mmol) in ethanol (30 ml) was heated under reflux for 3 h. The excess of ethanol was removed under reduced pressure and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from ethanol to give the corresponding hydrazides in 69-89% yields.

2-*(6-Chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)-N-(2-hydrazinyl-2-oxoethyl)acetamide (10)*

Yield 69% yield, M.p. 243-245°C. IR (KBr, cm^{-1}): 3390 (NH), 1657 (C=O), 1619 (C=N). Anal. Calcd. For $C_{18}H_{17}ClN_6O_3$; C, 53.94; H, 4.27; N, 20.97. Found: C, 53.80; H, 4.18; N, 20.88.

(S)-2-(6-Chloro-4-oxo-2-phenylquinazolin-3(4H)-ylamino)-N-(1-hydrazinyl-4-methyl-1-oxopentan-2-yl)acetamide (11)

Yield 79% yield, M.p. 250-252°C. IR (KBr, cm^{-1}): 3390 (NH), 1658 (C=O), 1620 (C=N). Anal. Calcd. For $C_{22}H_{25}ClN_6O_3$; C, 57.83; H, 5.51; N, 18.39. Found: C, 57.80; H, 5.41; N, 18.22.

2-(6-Chloro-2-phenylquinazolin-4-yloxy)-N-(2-hydrazinyl-2-oxoethyl)acetamide (14)

Yield 83% yield, M.p. 255-257°C. IR (KBr, cm^{-1}): 3390 (NH), 1657 (C=O), 1620 (C=N). Anal. Calcd. For $C_{18}H_{16}ClN_5O_3$; C, 56.04; H, 4.18; N, 18.15. Found: C, 55.90; H, 4.00; N, 18.00.

(S)-2-(6-Chloro-2-phenylquinazolin-4-yloxy)-N-(1-hydrazinyl-4-methyl-1-oxopentan-2-yl)acetamide (15)

Yield 89% yield, M.p. 266-268°C. IR (KBr, cm^{-1}): 3381 (NH), 1648 (C=O), 1620 (C=N). Anal. Calcd. For $C_{22}H_{24}ClN_5O_3$; C, 59.79; H, 5.47; N, 15.85. Found: C, 59.60; H, 5.40; N, 15.73.

***In vitro* antitumor activity**

Measurement of potential cytotoxicity by SRB assay

Some of the newly synthesized compounds have been evaluated for their potential cytotoxicity testing against breast cancer (MCF7) using the method of Skehan and Storeng [31]. Cells were plated in 96-multiwell plate (10^4 cells well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentration of the compound under test (0, 1, 2.5, 5 and 10 µg/ml) were added to the cell monolayer triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37°C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed and stained with Sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Ethylenediaminetetraacetic Acid (Tris-EDTA) buffer. Color intensity was measured in an Enzyme-linked Immunosorbent Assay (ELISA) reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specific compound. The IC_{50} percent control of infected and uninfected response values were calculated for the various active compounds were reported in Table 1. Doxorubicin (DOX) was used as positive standard. Compounds having IC_{50} < 5 µg/ml are considered potentially active and exposed to further in *vivo* studies.

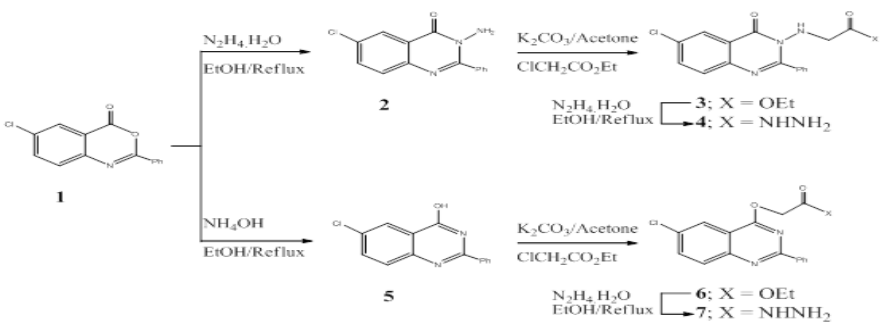
The results obtained in Table 1 showed that all compounds possess the highly significant effect against MCF7 and this is might be due to the presence of such N-C=O and amino acid moieties in addition to quinazoline moiety.

Table 1: The IC_{50} (µg/ml) of some of the selected new compounds against MCF7

Compound	IC_{50} µg/ml	Compound	IC_{50} µg/ml
DOX	2.97	DOX	2.97
2	4.50	9	4.00
3	4.17	10	3.88
4	5.00	11	3.45
5	4.15	12	4.10
6	3.50	13	4.70
7	11.0	14	3.90
8	4.90	15	3.90

RESULTS AND DISCUSSION

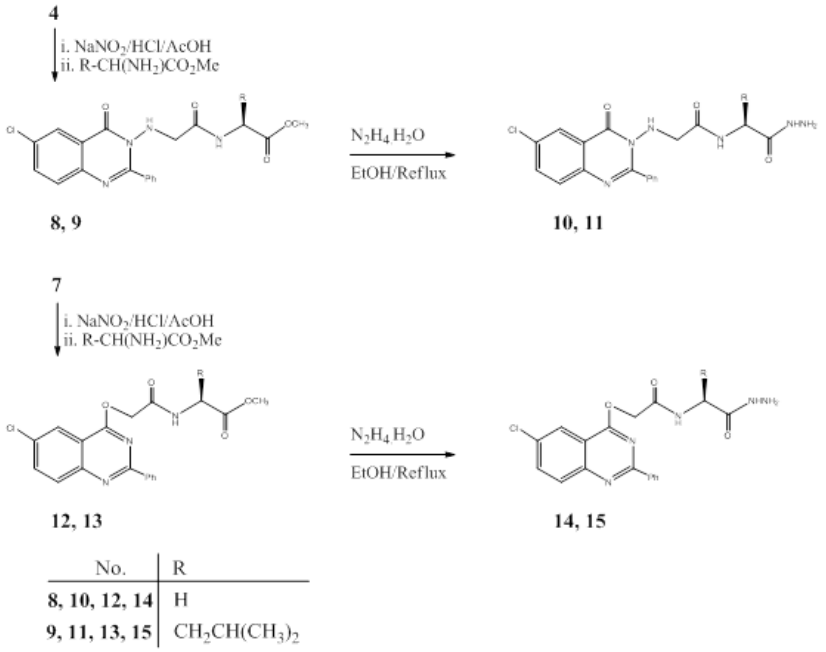
In the present investigation, 6-chloro-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (1) was prepared in 70% yield by refluxing of 2-amino-5-chlorobenzoic acid in benzoyl chloride in dry pyridine. Refluxing of 1 either with hydrazine hydrate or with ammonium hydroxide afforded 2 and 5 in 78% and 90%, respectively. Quinazoline derivatives 2 and/or 5 were treated with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dry acetone to afford the corresponding ethyl esters 3 and 6 in 84% and 85%, respectively. Hydrazinolysis of 3 and 6 was carried out by refluxing with hydrazine hydrate in ethanol to give the corresponding acid hydrazides 4 and 7 in 87% and 91% yield, respectively. The structures were confirmed by their IR, ^1H NMR and elemental analyses (Scheme 1).



Scheme 1: Acid hydrazides

These hydrazides 4 and 7 were selected as starting materials for the coupling reaction with the appropriate acylated amino acids, *via* the azide-coupling method. Thus, treatment of 4 and/or 7 at -5°C in acetic acid and 1*N* HCl with sodium nitrite afforded the inseparable azide derivative. The yellow syrupy azide compound was then treated, *in situ*, with the appropriate amino acid methyl esters in ethyl acetate containing triethyl amine at 0°C to give, after neutralization, the desired peptides 8, 9, 12 and 13 in 65-76% yields. The structures of these peptides were assigned from their IR, ^{1}H NMR and elemental analyses (Scheme 2).

Treating of 8, 9, 12, or 13 with hydrazine hydrate in ethanol at reflux temperature afforded the corresponding hydrazides 10, 11, 14 or 15 in 69\-89% yields. The structures of the hydrazide derivatives were confirmed by their IR, ^{1}H NMR and elemental analyses (Scheme 2).



No.	R
8, 10, 12, 14	H
9, 11, 13, 15	$CH_2CH(CH_3)_2$

Scheme 2: Peptides

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