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Synthesis of quinazolindionyl amino acid and dipeptide derivatives as possible antitumour agents

A. Aboelmagd,*[a] Ezzeldin M. S. Salem,[a] Ibrahim A. I. Ali,[a] and Mohamed S. Gomaa[b]

[a]Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, 41522, Egypt
[b]Department of Pharmaceutical Chemistry, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia
Email: ahmedaelmagd@gmail.com

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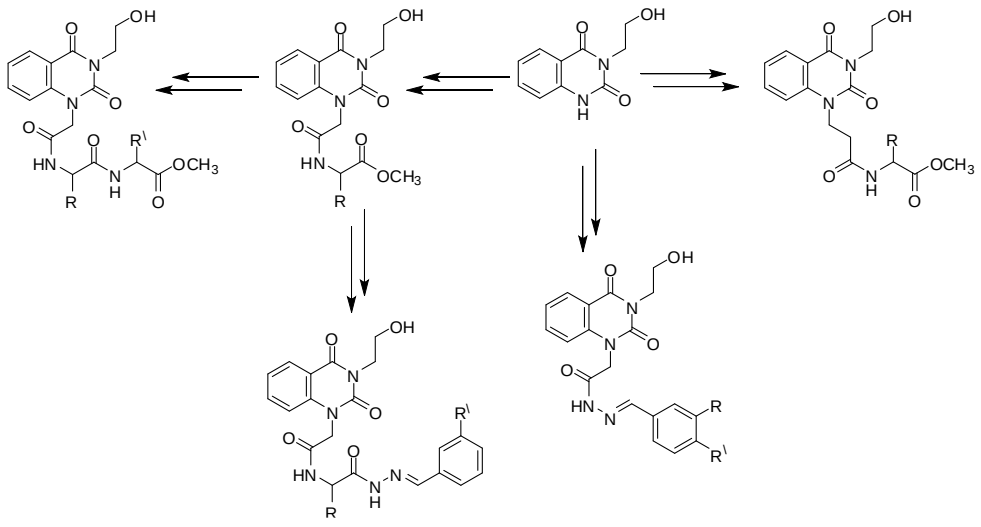
Abstract

Some physiologically active amino acid and dipeptide esters were coupled to 3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazoline at N-1 *via* acetyl/propionyl link. The C_2/C_3 anchor segments were introduced by either alkylation or Michael addition reactions with ethyl chloroacetate or methyl acrylate respectively. The occurrence of these two reactions on nitrogen N-1 rather than oxygen atom was confirmed by spectral values (^{1}H and ^{13}C NMR). Amide bond formation was performed by the azide activation procedure at 0 °C to avoid Curtius rearrangement. 21 of the newly synthesized compounds exhibited IC_{50}'s in the range of 5.63-26.9 µg/mL relative to doxorubicin (3.23 µg/mL) when tested against HepG2cell line.



Keywords: Amino acids, dipeptides, quinazolindione, hydrazones, azide method, Michael addition, antitumour activity

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Introduction

Cancer remains one of the most feared diseases all over the world, even with the huge efforts exerted on all levels to reduce and overcome it. According to the World Health Organization, it caused a quarter of all deaths in the developed world during the last decade.[1-5] Chemotherapy is a main method for the treatment of almost all types of cancer solely or with combination with another treatment approach. Despite much progress in the chemotherapy of cancer, there are several problems in cancer treatment by cytotoxic drugs that need to be solved such as the side effects arising from the indiscriminating action of the drugs on both cancerous and healthy tissues.[6-9] Quinazoline containing compounds are derived from some commercially available heterocyclic pharmaceuticals used in treatment of several types of cancer. In addition to another group still under clinical trials bearing promising results in prospects. [10-19]

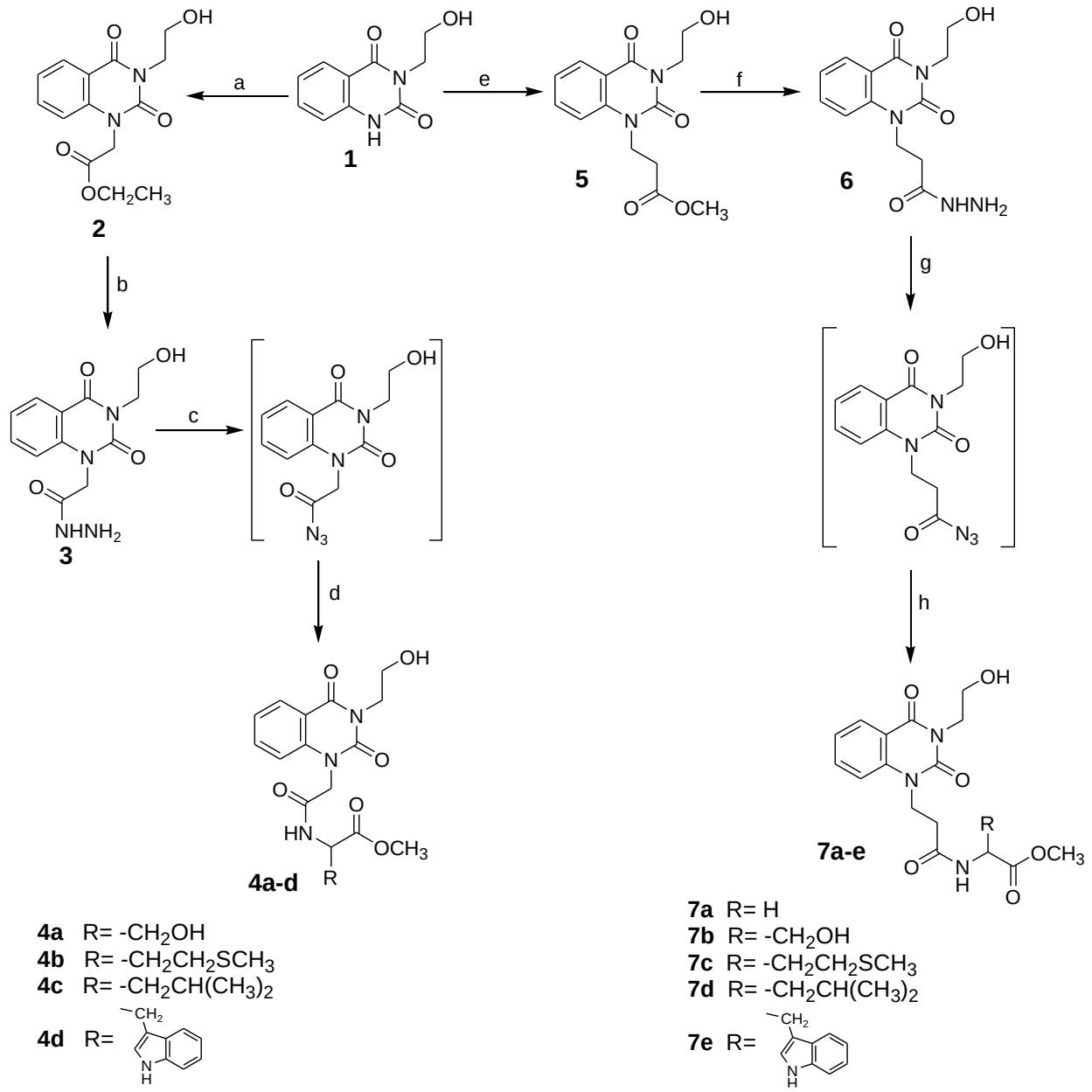
In continuation of our encouraging results on possible antitumour – active quinazoline compounds [20], the present manuscript deals with the synthesis of a series of 2,4-quinazolindione derivatives incorporating physiologically active amino acids and dipeptides at position-1, (schemes 1and 2) to evaluate their anticancer effect against human liver carcinoma cell line (HepG2), (table 1). The start compound 3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazoline **(1)** was found to be a suitable scaffold for derivatization in this study.

Results and Discussion

The key compound **1** was obtained from condensation of methyl benzoate carbamate derivative with ethanol amine according to the method described in literature.[21] In order to facilitate the introduction of the amino acid at N-1 of the quinazoline nucleus ethyl [3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)quinazolin-1-yl]acetate **(2)** was prepared by alkylation of **1** with ethyl chloroacetate in the presence of anhydrous potassium carbonate. Moreover, to investigate the effect of the length of the link between quinazoline nucleus and the amino acids on the anticancer activity some propionyl amino acid derivatives were also synthesized (Scheme 1).

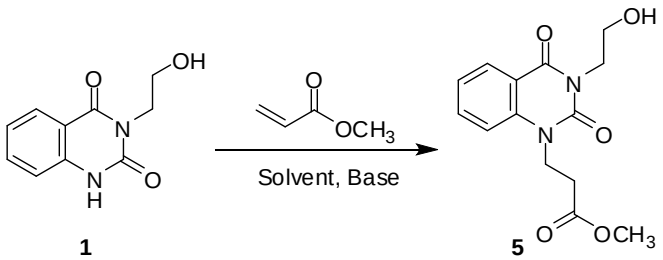
The methyl propionate derivative **5** was prepared via Michael addition of compound **1** on methyl acrylate. The reaction was conducted in different conditions to determine the most appropriate result (Scheme 2). It is obvious that compound **5** was obtained in low yield when the reaction was carried out in methanol or DMSO in the presence of triethyl amine, sodium methoxide or piperidine. However, better yield (55.6%) was achieved when the reaction was conducted in DMF with slight excess (20%) of triethyl amine and methyl acrylate.

The chemical structures of the ester derivatives **2** and **5** were assigned by elemental analysis, ^{1}H NMR and ^{13}C NMR spectra (see the experimental part). ^{1}H NMR spectrum of compound **2** showed a singlet signal at 4.90 ppm corresponding to the two protons of the acetate moiety N$\underline{CH_2}$CO and the ^{13}C NMR spectrum of this compound displayed a signal at 44.9 ppm attributable to the carbon of the same group. Moreover, the ^{1}H NMR spectrum of the propionyl derivative **5** showed the characteristic signals of the methyl propionate moiety as a triplet signal at 4.37 ppm for the two protons of the β-carbon of the propionate (NCH_2), the two protons of the α-carbon (CH_2CO) appeared as triplet signal at 2.79 ppm, and the ^{13}C NMR spectrum exhibited signal at 31.8 ppm attributable to the α-carbon of the propionate moiety.



Scheme 1. Synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl]acetyl/propionyl amino acid methyl esters. **Reagent and conditions: a)** Ethyl chloroacetate, K_2CO_3, DMSO, 80 °C, 6 h ; **b)** $N_2H_4.H_2O$, EtOH, reflux 6 h; **c)** $NaNO_2$ / HCl, AcOH, -5 °C, stirring 0.5 h; **d)** $HCl.H_2NCHRCO_2CH_3$, Et_3N, in ethyl acetate, in refrigerator 12 h and at r.t. 12 h; **e)** Methyl acrylate, Et_3N, DMF, 70 °C, 24 h; **f)** $N_2H_4.H_2O$, MeOH, reflux 4 h; **g)** $NaNO_2$ / HCl, AcOH, -5 °C, stirring 0.5 h; **h)** $HCl.H_2NCHRCO_2CH_3$, Et_3N, in ethyl acetate, in refrigerator 12 h and at r.t. 12 h.

Spectral values published in literature for quinazolin-2,4-dione derivatives displayed the protons of $NC\underline{H_2}CO$ (in the range 4.3-5.0 ppm) and ^{13}C (in the range 44.9-46.3 ppm), whereas the protons of $NC\underline{H_2}C\underline{H_2}CO$ (in the range 4.3-4.5 ppm for the two protons of the β-carbon and 2.6-3.3 ppm for the two protons of the α-carbon). [22-26] These data revealed the occurrence of alkylation and Michael addition reactions on nitrogen atom (N-1) rather than oxygen atom. These results are based on density functional theory DFT reactivity studies which showed that the N-site has higher nucleophilicity compared to O-site. [24]



Solvent	Base	Condition	Yield
MeOH	Et_3N	reflux, 24 hrs	< 10%
MeOH	NaOMe	reflux, 24 hrs	0%
MeOH	piperidine	reflux, 24 hrs	< 10%
DMSO	Et_3N	70 ^oC, 24 hrs	< 10%
DMF	Et_3N	70 ^oC, 24 hrs	55.6%

Scheme 2. Different conditions of Michael addition of compound 1 on methyl acrylate.

Hydrazinolysis of the ester derivatives **2** and **5** in alcohol with approximately five to six equivalents of hydrazine hydrate afforded the hydrazide derivatives **3** and **6** respectively in good yields (Scheme 1). The two hydrazides **3** and **6** were characterized by their higher melting points and lower R_f values relative to the parent ester derivatives. ^1H NMR spectra of the synthesized hydrazides **3** and **6** showed the characteristic signals of the hydrazide group as two singlet signals at 9.31 ppm and 9.12 ppm for the proton of NH and at 4.27 ppm and 4.17 ppm for the two protons of NH_2 respectively. Also, ^{13}C NMR spectra displayed the disappearance of the two signals of the ethyl ester group at 62.0 ppm and 14.1 ppm and the signal of OCH_3 carbon of the ester at 52.0 ppm which confirms the formation of the hydrazides.

The [3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl] acetyl/propionyl amino acid ester derivatives **4a-d** and **7a-e** have been synthesized by the azide-coupling method from hydrazides **3** and **6**. The azides were obtained from the hydrazide derivatives **3** and **6** by treatment with nitrous acid ($NaNO_2$ / HCl) at -5 ^oC. The resulting azides are unstable at room temperature, so they were extracted by cold ethyl acetate and washed at low temperature (0 ^oC), to suppress their transformation to the isocyanate derivatives by Curtius rearrangement. [27]

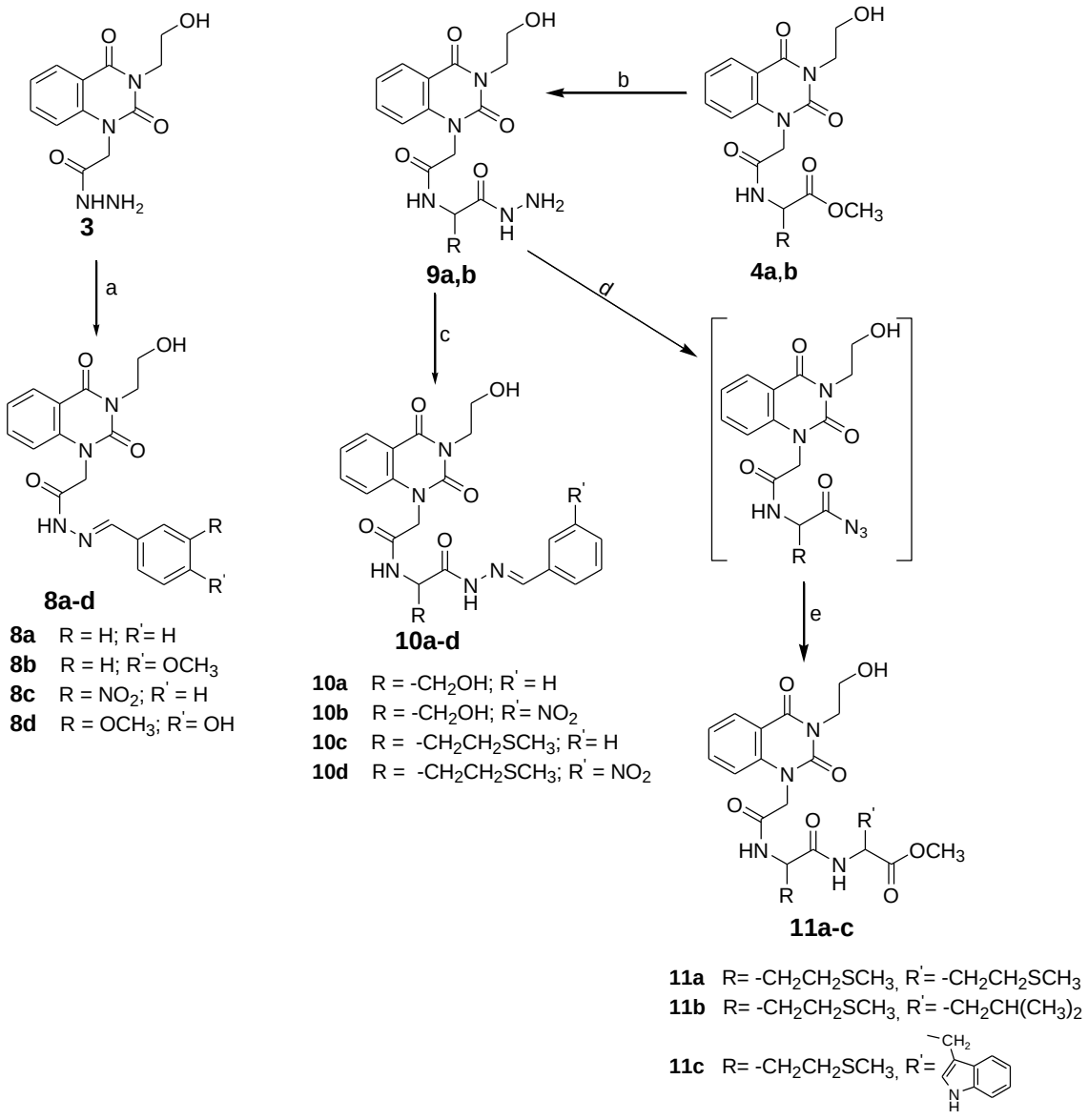
The azide solution in ethyl acetate reacted with amino acid methyl esters hydrochloride, previously treated with triethyl amine in ethyl acetate at 0 ^oC, to yield [3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1]yl acetyl/propionyl amino acid ester derivatives **4a-d** and **7a-e** in moderate yields (38-60%).

The chemical structures of the amino acid ester derivatives **4a-d** and **7a-e** were assigned by elemental analyses, ^1H and ^{13}C NMR. The ^1H NMR spectra of these compounds showed the common signals at 8.53-6.83 ppm, multiplet signals between 8.19-6.98 ppm, multiplet signals in the range 4.67-3.84 ppm and singlet signals in the range between 3.69-3.54 ppm attributed to the protons of CONH group of the peptide bond, aromatic protons of the quinazoline nucleus, the α-protons of the amino acids and the three protons of OCH_3 of the ester groups respectively. ^{13}C NMR spectrum displayed four signals in the range 172.8-150.0 ppm corresponding to the four-carbonyl carbon (CO), aromatic carbon signals between 139.4-109.3 ppm, in addition to the signals of the α-carbons of the amino acids at 51.7-51.5 ppm and the signals of OCH_3 carbons in the range 54.6-50.2 ppm. Other signals corresponding to protons and carbons of the remaining groups are reported in the experimental part.

Based upon the high anticancer activity of the two esters **4a** and **4b**, they were converted to the corresponding hydrazides with the aim to prepare some dipeptide and hydrazone derivatives with promising

antitumour action. The amino acid hydrazide derivatives **9a** and **9b** were prepared by hydrazinolysis of the corresponding esters **4a** and **4b** in methanol with six equivalents of hydrazine hydrate (Scheme2). These hydrazides are characterized by their physical data with respect to the parent esters. Moreover, the chemical structures of these hydrazides were elucidated from elemental analyses, ^{1}H NMR and ^{13}C NMR spectra (see experimental part).

The dipeptide derivatives **11a-c** have been prepared from the methionine hydrazide derivative **9b** *via* the azide coupling method (Scheme 3). The hydrazide **9b** was treated with nitrous acid at low temperature (-5 °C), to form the corresponding azide. This azide also, was found to be unstable at room temperature, which in turn was allowed to react with the amino acid methyl esters and worked up as described for the synthesis of the amino acid methyl ester derivatives **4a-d** to afford the dipeptide methyl ester derivatives **11a-c** in 31.2-41.8% yields.



8a R = H; R'= H
8b R = H; R'= OCH_3
8c R = NO_2; R' = H
8d R = OCH_3; R'= OH

10a R = $-CH_2OH$; R' = H
10b R = $-CH_2OH$; R'= NO_2
10c R = $-CH_2CH_2SCH_3$; R'= H
10d R = $-CH_2CH_2SCH_3$; R' = NO_2

11a R= $-CH_2CH_2SCH_3$, R'= $-CH_2CH_2SCH_3$
11b R= $-CH_2CH_2SCH_3$, R'= $-CH_2CH(CH_3)_2$
11c R= $-CH_2CH_2SCH_3$, R'=

Scheme 3. Synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl]acetyl hydrazone, dipeptide and amino acid hydrazone derivatives. **Reagent and conditions: a)** ArCHO, EtOH, reflux, 3 h; **b)** $N_2H_4.H_2O$, MeOH, reflux 6 h; **c)** ArCHO, EtOH, reflux, 3 h; **d) 9b,** $NaNO_2$ / HCl, AcOH, -5 °C, stirring 0.5 h; **e)** $HCl.H_2NCHRCO_2CH_3$, Et_3N, in ethyl acetate, in refrigerator 12 h and at r.t. 12 h.

^{1}H NMR spectra of the synthesized dipeptides revealed two doublets in the range 8.45-6.84 ppm for the two NH protons of the two peptide bonds. Also, exhibited other two multiplets in the range 4.75-4.42 ppm for the two α-CH protons of the two amino acids of the dipeptide. The ^{13}C NMR spectra of compounds **11a-c** showed five signals between 172.8-150.5 ppm attributable to the five carbonyl carbons. The signals of the two α-CH carbons of the two amino acids appeared between 51.7-46.9 ppm in addition to the other signals corresponding to protons and carbons of quinazoline nucleus and the individual two side chains of the amino acids of the dipeptides (see the experimental part).

Hydrazide-hydrazones have wide interest because of their diverse biological applications [28-30] including their significant role as antitumor agents. [31] Based on these findings, and in trying to find new potent anticancer agents; some quinazoline and quinazoline amino acid hydrazide-hydrazone derivatives with different aromatic aldehydes were prepared.

The hydrazone derivatives **8a-d** were obtained from condensation of hydrazide derivatives **3** with the aromatic aldehydes: benzaldehyde, m-nitrobenzaldehyde, anisaldehyde and vanillin. On the other hand, the amino acid hydrazone derivatives **10a-d** were also prepared by condensation of hydrazide derivatives **9a,** or **9b** with benzaldehyde and m-nitrobenzaldehyde. The chemical structures of the synthesized hydrazones **8a-d** and **10a-d** were assigned by ^{1}H-NMR, ^{13}C-NMR, and elemental analysis (see experimental part). ^{1}H-NMR spectra of these compounds showed their existence as an equilibrium mixture from *cis-E* and *trans-E* conformers in DMSO solution which is in agreement with previous studies on similar hydrazones. [20]

The synthesized quinazolindione derivatives were tested for their antiproliferative activity against HepG-2 (Table 1). Out of twenty-five screened novel synthesized compounds, twenty-one exhibited IC_{50}'s in the range of 5.63-26.9 µg/mL, compared to the reference drug doxorubicin (IC_{50} 3.23 µg/mL). It is evident that the benzylidene hydrazone **8c** (IC_{50} of 5.63 µg/mL) has comparable activity to doxorubicin. Moreover, the presence of free acidic proton at N-1 dramatically decreased the activity (compound **1** IC_{50} > 100 µg/mL), and the length of the link between the amino acid/dipeptide and quinazoline nucleus has no appreciable effect (compounds **4a-d** and **7a-e**).

Generally, the anticancer activity of the current tested compounds of N-1 series is more potent than the corresponding our previously published N-3 derivatives. [20]

Table 1. *In vitro* antiproliferative activity of [3-(2-Hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl] acetyl/propionyl amino acid, dipeptide and hydrazone derivatives against human liver carcinoma cell line (HepG2).

Compd.	Compound concentration (µg/mL)				IC_{50} (µg/mL)
	12.5	25	50	100	
	Inhibition (%)				
1	0	7.8	31.8	37.8	>100
3	39.5	54.5	65.9	71.4	20.8
4a	45.7	70.4	80.5	80.5	14.6
4b	25.9	63	76.7	77	20.6
4c	44.5	45.5	60.5	66.4	32.2
4d	22.2	66.7	71.5	71.9	20.3
5	27.8	74.4	77	75.3	18.1
6	37	74.8	77.8	75.2	16.6

Table 1. Continued

Compd.	Compound concentration (μg/mL)				IC_{50} (μg/mL)
	12.5	25	50	100	
	Inhibition (%)				
7a	18.8	66.3	73.9	71.9	20.9
7b	22.2	63	71.1	70.4	20.6
7c	20.9	69.2	71	76.1	20.0
7d	20.3	57.3	73.2	70.4	20.4
7e	31.5	59.3	75.9	78.9	20.6
8a	12	21.6	42.4	42.8	>100
8b	52.6	80	70	71.9	11.7
8c	68.2	76.6	82.2	83	**5.63**
8d	30	63	72.4	69.3	19.7
9a	15.6	42.7	64.1	66.7	33.5
9b	25.9	66.3	74.8	77.6	20.0
10a	21.9	42.7	58.3	59.3	36.4
10b	20.1	49	62	60.4	26.9
10c	21.9	56.2	60.4	62.5	23.3
10d	15.1	49.5	58.3	54.2	26.3
11a	25.9	71.9	71.5	71.9	19.1
11b	18.5	70.4	73	71.9	20.0
11c	22.4	62.7	77.9	77	21.1
Doxorubicin	75.2	72.5	64.0	65.6	3.23

Conclusions

The key compound 3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazoline **(1)** is a suitable scaffold for derivatization at the N-1 site to afford drugs with remarkable anticancer activity. It is hoped that the potential antiproliferative effect of the synthesized series could offer an effective treatment that is less likely to cause resistance, recurrence of cancer and less toxic to normal tissues than available drugs. Based upon the comparable activity of 3-nitrobenzylidene hydrazone derivative **8c** with doxorubicin, it is necessary to extend this study to synthesize other hydrazones, bearing different substituents on the benzylidene nucleus. The azide method seemed to be suitable activation procedure for the formation of pure amino acid and dipeptide derivatives, not contaminated with the by-product urea derivatives, when carried out at 0 ^{o}C. ^{1}H and ^{13}C NMR data supported the occurrence of alkylation and Michael addition at nitrogen (N-1) and not oxygen atom.

Experimental Section

General. Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} aluminium sheets (E. Merck, layer thickness 0.2 mm) in the following solvent systems, S_1: chloroform/methanol (95:5); S_2:

chloroform/methanol (9:1); S_3: ethyl acetate/petroleum ether (2:1); S_4: ethyl acetate/petroleum ether (1:1). The spots on thin layer plates were detected by UV lamp. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. Elemental analyses were performed on a Flash EA-1112 instrument at the Microanalytical Laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. ^{1}H and ^{13}C NMR spectra were measured on Bruker spectrometer operating at 300 and 75.0 MHz respectively, at microanalytical laboratory, Cairo University, Giza, Egypt. The starting compound 3-(2-hydroxyethyl)-2,4-di-oxo-(1H,3H)-quinazoline **1** was prepared according to the method described in literature. [21]

Synthesis of Ethyl [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetate (2). To a solution of 2-(2,4-dioxo-(1H,3H)-quinazolin-3-yl)ethanol **(1)** (2.0 g, 9.7 mmol) in DMSO (10 mL), anhydrous potassium carbonate (1.34 g, 9.7 mmol) and ethyl chloroacetate (1.1 mL, 9.7mmol) were added and stirred at 80 °C for 6 hrs. Afterwards the reaction mixture was cooled and diluted with cold water. The formed precipitate was filtered off, washed with cold water, dried, and crystallized from ethanol to afford white crystals (2.21 g, 77.8%) mp 147-149 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ 8.26 (1H, d, *J* 9.0 Hz, ArH), 7.69-7.63 (1H, t, *J* 9.0 Hz, ArH), 7.33-7.28 (1H, t, *J* 7.5 Hz, ArH), 7.00 (1H, d, *J* 9.0 Hz, ArH), 4.90 (2H, s, NCH_2CO), 4.36 (2H, t, *J* 6.0 Hz, CH_2O), 4.29-4.25 (2H, m, $O\underline{CH_2}CH_3$), 3.95-3.91 (2H, t, *J* 6.0 Hz, NCH_2), 2.35 (1H, brs, OH), 1.33 (3H, t, *J* 7.5 Hz, $OCH_2\underline{CH_3}$). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 167.6, 162.3, 151.7 (3CO), 139.6, 135.3, 129.3, 123.5, 115.5, 113.0 (Ar-C), 62.0 (OCH_2), 61.5 (OCH_2), 44.9 ($N\underline{CH_2}CO$), 44.4 (NCH_2), 14.1 (CH_3). Anal. Calcd. For $C_{14}H_{16}N_2O_5$ (292.29): C, 57.53; H, 5.52; N, 9.58; Found C, 57.78; H, 5.48; N, 9.82.

Synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl hydrazide (3). To a solution of **2** (2.0 g, 6.84 mmol) in ethanol (30 mL), hydrazine hydrate (3 mL, 48.0 mmol) was added. The reaction mixture was refluxed for 6 hrs, after cooling to room temperature the precipitated hydrazide was filtered off, washed with water, and ethanol followed by recrystallization from aqueous ethanol. White crystals (1.68 g, 88.2%), R_f = 0.31 (S_2), mp 218-221 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 9.31 (1H, s, NH), 8.08 (1H, d, *J* 7.8 Hz, ArH), 7.75 (1H, t, *J* 7.8 Hz, ArH), 7.32 (1H, t, *J* 7.5 Hz, ArH), 7.20 (1H, d, *J* 8.4 Hz, ArH), 4.85-4.75 (3H, m, NCH_2CO, OH), 4.27 (2H, s, NH_2), 4.10 (2H, t, *J* 6.5 Hz, NCH_2), 3.60-3.54 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 166.5, 161.7, 151.0 (3CO), 140.4, 135.5, 128.2, 123.2, 115.6, 114.7 (Ar-C), 58.0 (CH_2O), 45.4 ($N\underline{CH_2}CO$), 43.7 (NCH_2). Anal. Calcd. For $C_{12}H_{14}N_4O_4$ (278.26): C, 51.80; H, 5.07; N, 20.13; Found C, 51.79; H, 5.28; N, 20.38.

General method for the synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl amino acid methyl esters (4a-d). To a cold solution (-5 °C) of hydrazide **3** (0.45 g, 1.6 mmol) in acetic acid (12 mL), hydrochloric acid (5*N,* 6 mL), and water (50 mL), was added portion wise under stirring a cold solution (0 °C) of sodium nitrite (0.14 g, 2.0 mmol) in water (6 mL). After stirring at the same temperature for 30 minutes, the azide was extracted with cold ethyl acetate, and washed successively with cold water, 5 % $NaHCO_3$ and water. After drying over anhydrous sodium sulfate, the azide was used directly without further purification in the next step.

Amino acid methyl ester hydrochlorides (1.8 mmol), was stirred in ethyl acetate (50 mL) with triethyl amine (0.2 mL) at 0 °C for 20 minutes. The formed triethyl amine hydrochloride was filtered off and the filtrate was added to the previously prepared cold dried solution of the azide. Afterwards the mixture was kept 12 hrs in the refrigerator and then at room temperature for another 12 hrs. The reaction mixture was washed with 0.1*N* HCl, water, 5% $NaHCO_3$ and water then dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum and the residue was crystallized from ethyl acetate-petroleum ether to give [3-(2-hydroxyethyl)-quinazolin-2,4-dione-1-yl]acetyl amino acid methyl esters **(4a-d)**.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-serine methyl ester (4a). White crystals (0.27 g, 46.8%), R_f = 0.22 (S_1), mp 216-218 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 8.70 (1H, d, *J* 7.8 Hz, NH), 8.08 (1H, d, *J* 8.1 Hz, ArH), 7.73 (1H, t, *J* 8.1 Hz, ArH), 7.32 (1H, t, *J* 7.5 Hz, ArH), 7.18 (1H, d, *J* 8.1 Hz, ArH), 5.13-5.09 (1H, t, *J* 5.7 Hz, OH), 4.89-4.85 (2H, m, NCH_2CO), 4.79 (1H, t, *J* 5.8 Hz, OH), 4.41-4.36 (1H, m, NCH), 4.07 (2H, t, *J* 6.5 Hz, NCH_2), 3.73-3.59 (2H, m, OCH_2), 3.63 (3H, s, OCH_3), 3.59-3.55 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 171.2, 167.4, 161.6, 151.0 (4CO), 140.5, 135.5, 128.3, 123.3, 115.2, 114.8 (Ar-C), 61.6 (OCH_3), 58.0 (OCH_2), 55.2 (OCH_2), 52.3 (NCH), 45.9 ($N\underline{CH_2}CO$), 43.7 (NCH_2). Anal. Calcd. For $C_{16}H_{19}N_3O_7$ (365.34): C, 52.60; H, 5.24; N, 11.50; Found C, 52.54; H, 5.21; N, 11.61.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionine methyl ester (4b*).* White crystals (0.38 g, 57.4%), R_f = 0.41 (S_1), mp 164-166 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 8.67 (1H, d, *J* 7.5 Hz, NH), 8.08 (1H, d, *J* 7.5 Hz, ArH), 7.76-7.70 (1H, m, ArH), 7.32 (1H, t, *J* 7.5 Hz, ArH), 7.18 (1H, d, *J* 8.5 Hz, ArH), 4.84-4.74 (3H, m, NCH_2CO, OH), 4.51-4.46 (1H, m, NCH), 4.08 (2H, t, *J* 6.6 Hz, NCH_2), 3.62 (3H, s, OCH_3), 3.60-3.54 (2H, m, CH_2O), 2.50-2.45 (2H, m, CH_2S), 2.02 (3H, s, SCH_3), 2.00-1.90 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.3, 167.5, 161.6, 151.0 (4CO), 140.4, 135.5, 128.3, 123.3, 115.4, 114.7 (Ar-C), 58.0 (OCH_3), 52.4 (OCH_2), 51.4 (NCH), 46.2 ($N\underline{CH_2}CO$), 43.7 (NCH_2), 30.9 (CH_2S), 29.9 (CH_2), 15.0 (SCH_3). Anal. Calcd. For $C_{18}H_{23}N_3O_6S$ (409.46): C, 52.80; H, 5.66; N, 10.26, S, 7.83; Found C, 52.65; H, 5.69; N, 10.39, S, 7.59.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-leucine methyl ester (4c). White crystals (0.28 g, 44.5%), R_f = 0.59 (S_1), mp 114-116 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ 8.22 (1H, d, *J* 7.5 Hz, ArH), 7.70 (1H, t, *J* 7.8 Hz, ArH), 7.31-7.25 (2H, m, ArH), 6.76 (1H, d, *J* 8.4 Hz, NH), 4.90-4.78 (2H, m, NCH_2CO), 4.63-4.60 (1H, m, NCH), 4.37-4.33 (2H, t, *J* 6.6 Hz, NCH_2), 3.93-3.90 (2H, m, CH_2O), 3.67 (3H, s, OCH_3), 2.32-2.24 (1H, brs, OH), 1.63-1.49 (3H, m, CH_2, CH), 0.90-0.87 (6H, m, $2CH_3$). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 173.2, 167.0, 162.2, 151.9 (4CO), 139.7, 135.4, 128.9, 123.6, 115.4, 114.0 (Ar-C), 60.8 (OCH_3), 52.3 (OCH_2), 50.8 (NCH), 47.2 ($N\underline{CH_2}CO$), 44.2 (NCH_2), 41.0 (CH), 24.8 (CH_2), 22.7, 21.6 ($2CH_3$). Anal. Calcd. For $C_{19}H_{25}N_3O_6$ (391.24): C, 58.30; H, 6.44; N, 10.74; Found C, 57.98; H, 6.69; N, 10.97.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-tryptophane methyl ester (4d). White crystals (0.38 g, 50.3%), R_f = 0.37 (S_1), mp 128-130 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 10.91 (1H, s, Ind-NH), 8.77 (1H, d, *J* 7.8 Hz, NH), 8.06 (1H, d, *J* 7.8 Hz, ArH), 7.63 (1H, t, *J* 7.8 Hz, ArH), 7.54 (1H, d, *J* 7.8 Hz, ArH), 7.39 (1H, d, *J* 7.8 Hz, ArH), 7.29 (1H, t, *J* 7.6 Hz, ArH), 7.18 (1H, s, Ind-2-H), 7.11 (1H, t, *J* 7.5 Hz, ArH), 7.03 (1H, t, *J* 7.5 Hz, ArH), 6.86 (1H, d, *J* 8.7 Hz, ArH), 4.87-4.59 (4H, m, NCH_2CO, OH, NCH), 4.08-4.02 (2H, m, NCH_2), 3.61 (3H, s, OCH_3), 3.58-3.54 (2H, m, CH_2O) 3.23-3.09 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.4, 167.1, 161.6, 151.0 (4CO), 140.4, 136.6, 135.4, 128.2, 127.6, 124.2, 123.2, 121.4, 118.9, 118.4, 115.3, 114.5, 111.9, 109.8 (Ar-C), 58.1 (OCH_3), 53.7 (OCH_2), 52.3 (NCH), 46.0 (NCH_2CO), 43.7 (NCH_2), 27.6 (CH_2). Anal. Calcd. For $C_{24}H_{24}N_4O_6$ (464.47): C, 62.06; H, 5.21; N, 12.06; Found C, 61.91; H, 5.39; N, 11.84.

Synthesis of methyl 3-[3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionate (5). To a solution of 3-(2-hydroxyethyl**)-**2,4-dioxo-(1H,3H)-quinazoline **(1)** (2.0 g, 9.7 mmol) in DMF (20 mL), methyl acrylate (1.0 mL, 11.0 mmol) and triethyl amine (1.5 mL, 10.8 mmol) were added. The reaction mixture was stirred at 70 °C for 24 hr, afterwards cooled and diluted with cold water. The formed precipitate was filtered off, washed with cold water, dried, and crystallized from methanol to afford **5** as white crystals (1.57 g, 55.6%) mp 106-109 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ = 8.25 (1H, d, *J* 8.1 Hz, ArH), 7.72 (1H, t, *J* 7.2 Hz, ArH), 7.30-7.25 (2H, m, ArH), 4.47 (2H, t, *J* 7.5 Hz, CH_2O), 4.37 (2H, t, *J* 5.5 Hz, NCH_2), 3.94 (2H, t, *J* 5.5 Hz, NCH_2), 3.71 (3H, s, OCH_3), 2.79 (2H, t, *J* 7.5 Hz, CH_2CO), 3.50-2.90 (1H, brs, OH). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 171.5, 161.5, 150.6 (3CO), 139.7, 135.7, 128.5, 123.1, 115.5, 114.6 (Ar-C), 58.0 (OCH_2), 52.0 (OCH_3), 43.5 (NCH_2), 40.0 (NCH_2), 31.8 ($\underline{CH_2}CO$). Anal. Calcd. For $C_{14}H_{16}N_2O_5$ (292.29): C, 57.53; H, 5.52; N, 9.58; Found C, 57.37; H, 5.44; N, 9.64.

Synthesis of 3-[3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]-propionyl hydrazide (6). To a solution of ester **5** (2.0 g, 6.84 mmol) in methanol (30 mL), hydrazine hydrate (2 mL, 32.0 mmol) was added. The reaction mixture was refluxed for 4 hrs, after cooling to room temperature the precipitated hydrazide was filtered off, washed with water, and ethanol followed by recrystallization from aqueous ethanol. White crystals (1.48 g, 74.5%), R_f = 0.28 (S_2), mp 197-200 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 9.12 (1H, s, NH), 8.05 (1H, d, *J* 7.2 Hz, ArH), 7.78-7.73 (1H, t, *J* 7.6 Hz, ArH), 7.48 (1H, d, *J* 8.4 Hz, ArH), 7.30- (1H, t, *J* 7.5 Hz, ArH), 4.75 (1H, t, *J* 5.7 Hz, OH), 4.30 (2H, t, *J* 7.3 Hz, OCH_2), 4.17 (2H, s, NH_2), 4.05 (2H, t, *J* 6.3 Hz, NCH_2), 3.59-3.53 (2H, m, NCH_2), 2.44 (2H, t, *J* 7.3 Hz, CH_2CO). ^{13}C NMR (75.0 MHz, DMSO): δ 168.9, 161.1, 150.0 (3CO), 139.4, 135.2, 128.0, 122.6, 115.0, 114.1 (Ar-C), 57.5 (OCH_2), 43.0 (NCH_2), 40.0 (NCH_2), 31.3 ($\underline{CH_2}CO$). Anal. Calcd. For $C_{13}H_{16}N_4O_4$ (292.29): C, 53.42; H, 5.52; N, 19.17; Found C, 53.28; H, 5.63; N, 19.33.

General method for the synthesis of 3-[3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionyl amino acid methyl esters (7a-e). To a cold solution (-5 °C) of hydrazide **6** (0.47g, 1.6 mmol) in acetic acid (12 mL), hydrochloric acid (5*N,* 6 mL), and water (50 mL), was added portion wise under stirring a cold solution (0 °C) of sodium nitrite (0.14 g, 2.0 mmol) in water (6 mL). After stirring at the same temperature for 30 minutes, the azide was extracted with cold ethyl acetate, and washed successively with cold water, 5 % $NaHCO_3$ and water. After drying over anhydrous sodium sulfate, the azide was used directly without further purification in the next step.

Amino acid methyl ester hydrochlorides (1.8 mmol), was stirred in ethyl acetate (50 mL) with triethyl amine (0.2 mL) at 0 °C for 20 minutes. The formed triethyl amine hydrochloride was filtered off and the filtrate was added to the previously prepared cold dried solution of the azide. Afterwards the reaction mixture was treated as described above under the synthesis of the amino acid methyl ester derivatives **4a-d** to give the 3-(3-(2-hydroxyeth-yl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl)propionyl amino acid methyl esters **7a-d**.

3-[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl)propionyl glycine methyl ester (7a). White crystals (0.22 g, 39.1%), R_f = 0.33 (S_1), mp 147-150 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 8.49-8.46 (1H, m, NH), 8.06 (1H, d, *J* 7.8 Hz, ArH), 7.79 (1H, t, *J* 7.8 Hz, ArH), 7.48 (1H, d, *J* 8.4 Hz, ArH), 7.31-7.26 (1H, t, *J* 7.5 Hz, ArH), 4.76 (1H, t, *J* 5.8 Hz, OH), 4.31 (2H, t, *J* 7.5 Hz, CH_2O), 4.06 (2H, t, *J* 6.6 Hz, NCH_2), 3.84 (2H, d, *J* 6.0 Hz, NCH_2CO), 3.62 (3H, s, OCH_3), 3.62-3.54 (2H, m, NCH_2), 2.57-2.49 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 170.2, 170.1, 161.1, 150.0 (4CO), 139.4, 135.1, 128.0, 122.6, 115.0, 114.1 (Ar-C), 57.5 (OCH_2), 51.6 (OCH_3), 43.0 (NCH_2), 40.5 (NCH_2), 40.3 ($N\underline{CH_2}CO$), 32.7 ($\underline{CH_2}CO$). Anal. Calcd. For $C_{16}H_{19}N_3O_6$ (349.34): C, 55.01; H, 5.48; N, 12.03; Found C, 54.88; H, 5.52; N, 12.19.

3-[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionyl L-serine methyl ester (7b*).* White crystals (0.31 g, 49.8%), R_f = 0.21 (S_1), mp 188-190 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 8.41 (1H, d, *J* 7.5 Hz, NH), 8.07 (1H, d, *J* 7.8 Hz, ArH), 7.78 (1H, t, *J* 7.2 Hz, ArH), 7.49 (1H, d, *J* 8.4 Hz, ArH), 7.31 (1H, t, *J* 7.5 Hz, ArH), 5.01 (1H, t, *J* 5.5 Hz, OH), 4.76 (1H, t, *J* 6.0 Hz, OH), 4.37-4.26 (3H, m, CH_2O, NCH), 4.06 (2H, t, *J* 6.4 Hz, CH_2O), 3.66-3.54 (7H, m, OCH_3, $2NCH_2$), 2.59 (2H, t, *J* 7.2 Hz, CH_2CO). ^{13}C NMR (75.0 MHz, DMSO): δ 170.9, 169.8, 161.1, 150.0 (4CO), 139.4, 135.1, 127.9, 122.5, 115.0, 114.2 (Ar-C), 61.1 (OCH_2), 57.5 (OCH_2), 54.6 (OCH_3), 51.7 (NCH), 43.0 (NCH_2), 40.3 (NCH_2), 32.7($\underline{CH_2}CO$). Anal. Calcd. For $C_{17}H_{21}N_3O_7$ (379.36): C, 53.82; H, 5.58; N, 11.08; Found C, 53.69; H, 5.51; N, 11.17.

3-[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionyl L-methionine methyl ester (7c*).* White crystals (0.26 g, 37.9%), R_f = 0.36 (S_1), mp 126-129 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ 8.19 (1H, d, *J* 7.8 Hz, ArH), 7.69 (1H, t, *J* 7.8 Hz, ArH), 7.39 (1H, d, *J* 8.4 Hz, ArH), 7.26 (1H, t, *J* 7.8 Hz, ArH), 6.83 (1H, d, *J* 8.1 Hz, NH), 4.67-4.64 (1H, m, NCH), 4.45 (2H, t, *J* 7.1 Hz, CH_2O), 4.32 (2H, t, *J* 5.5 Hz, NCH_2), 3.90 (2H, t, *J* 5.5 Hz, NCH_2), 3.69 (3H,

s, OCH_3), 2.74-2.66 (3H, m, OH, CH_2S), 2.47 (2H, t, *J* 7.2 Hz, CH_2CO), 2.04 (3H, s, SCH_3), 2.03-1.92 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 172.2, 169.9, 162.2, 151.5 (4CO), 139.3, 135.4, 129.0, 123.2, 115.5, 113.7 (Ar-C), 61.1 (OCH_2), 52.4 (OCH_3), 51.5 (NCH), 44.1 (NCH_2), 40.3 (NCH_2), 34.0 (CH_2S), 31.3 (CH_2CO), 29.9 (CH_2), 15.3 (SCH_3). Anal. Calcd. For $C_{19}H_{25}N_3O_6S$ (423.48): C, 53.89; H, 5.95; N, 9.92, S, 7.57; Found C, 53.80; H, 5.88; N, 10.06, S, 7.49.

3-[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionyl L-leucine methyl ester (7d*).* White crystals (0.35 g, 53.7%), R_f = 0.38 (S_1), mp 114-117 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 8.40 (1H, d, *J* 7.8 Hz, NH), 8.05 (1H, d, *J* 7.8 Hz, ArH), 7.77 (1H, t, *J* 7.8 Hz, ArH), 7.47 (1H, d, *J* 8.4 Hz, ArH), 7.30 (1H, t, *J* 7.5 Hz, ArH), 4.76 (1H, t, *J* 6.0 Hz, OH), 4.30-4.25 (3H, m, NCH, CH_2O), 4.06 (2H, t, *J* 6.6 Hz, NCH_2), 3.60 (3H, s, OCH_3), 3.58-3.54 (2H, m, NCH_2), 2.55-2.50 (2H, m, CH_2), 1.48-1.45 (3H, m, CH_2, CH), 0.85 (3H, d, *J* 6.0 Hz, CH_3), 0.80 (3H, d, *J* 6.0 Hz, CH_3). ^{13}C NMR (75.0 MHz, DMSO): δ 172.8, 169.8, 161.0, 150.0 (4CO), 139.4, 135.1, 127.9, 122.5, 115.0, 114.2 (Ar-C), 57.5 (CH_2O), 51.7 (NCH), 50.2 (OCH_3), 43.0 (NCH_2), 40.3 (NCH_2), 32.8 ($\underline{CH_2}CO$), 24.1 (CH_2), 22.5, 21.2 ($2CH_3$). Anal. Calcd. For $C_{20}H_{27}N_3O_6$ (405.44): C, 59.25; H, 6.71; N, 10.36; Found C, 59.13; H, 6.68; N, 10.50.

3-[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]propionyl L-tryptophane methyl ester (7e*).* White crystals (0.46 g, 59.7%), R_f = 0.31 (S_1), mp 123-130 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 10.84 (1H, s, Ind-NH), 8.53 (1H, d, *J* 7.5 Hz, NH), 8.07 (1H, d, *J* 7.8 Hz, ArH), 7.72 (1H, t, *J* 7.8 Hz, ArH), 7.50 (1H, d, *J* 7.8 Hz, ArH), 7.42-7.25 (3H, m, ArH), 7.14 (1H, s, Ind-2-H), 7.09-6.98 (2H, m, ArH), 4.77 (1H, t, *J* 6.0 Hz, OH), 4.55-4.50 (1H, m, NCH), 4.30-4.20 (2H, m, CH_2O), 4.07 (2H, t, *J* 6.6 Hz, NCH_2), 4.02-3.54 (5H, m, OCH_3, NCH_2), 3.12-3.03 (2H, m, CH_2), 2.54-2.49 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.2, 169.6, 161.1, 150.0 (4CO), 139.3, 136.0, 135.1, 128.0, 127.0, 123.6, 122.5, 120.9, 118.3, 117.9, 115.0, 114.1, 111.4, 109.3 (Ar-C), 57.5 (CH_2O), 53.1 (OCH_3), 51.7 (NCH), 43.1 (NCH_2), 40.3 (NCH_2), 32.7 ($\underline{CH_2}CO$), 27.1 (CH_2). Anal. Calcd. For $C_{25}H_{26}N_4O_6$ (478.50): C, 62.75; H, 5.48; N, 11.71; Found C, 62.67; H, 5.42; N, 11.87.

General procedure for the synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl arylidene hydrazone derivatives (8a-d). A mixture of hydrazide **3** (0.3 g, 1.08 mmol) and aromatic aldehyde (1.1 mmol) was refluxed in ethanol (20 mL) for 3 hours. After cooling to room temperature, the resulting solid was filtered off, washed with cold ethanol and recrystallized from aqueous ethanol.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl benzylidene hydrazone (8a*).* White crystals (0.36g, 91.2%), R_f = 0.74 (S_2), mp 268-271 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 11.76, 11.75 (1H, 2s, NH), 8.24-8.07 (2H, m, ArH, CH), 7.77-7.69 (3H, m, ArH), 7.48-7.27 (5H, m, ArH), 5.33, 4.91 (2H, 2s, NCH_2CO), 4.81-4.77 (1H, m, OH), 4.09 (2H, t, *J* 6.6 Hz, NCH_2), 3.61-3.57 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 168.5, 161.6, 151.0 (3CO), 144.7 (CH), 140.7, 135.7, 134.42, 130.5, 129.2, 127.4, 123.2, 115.1 (Ar-C), 58.0 (OCH_2), 45.1 ($N\underline{CH_2}CO$), 43.6 (NCH_2). Anal. Calcd. For $C_{19}H_{18}N_4O_4$ (366.37): C, 62.29; H, 4.95; N, 15.29; Found C, 62.11; H, 4.89; N, 15.52.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl 4-methoxybenzylidene hydrazone (8b). White crystals (0.38 g, 90.7%), R_f = 0.76 (S_2), mp 263-265 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 11.62, 11.59 (1H, 2s, NH), 8.09 (1H, d, *J* 7.8 Hz, ArH), 8.18, 8.01 (1H, 2s, CH), 7.73-7.62 (3H, m, ArH), 7.37-7.26 (2H, m, ArH), 7.02 (2H, d, *J* 8.7 Hz, ArH), 5.30, 4.89 (2H, 2s, NCH_2CO), 4.82-4.78 (1H, m, OH), 4.09 (2H, t, *J* 6.6 Hz, NCH_2), 3.80 (3H, s, OCH_3) 3.61-3.55 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 167.7 160.7, 150.5 (3CO), 144.0 (CH), 147.2, 140.2, 135.1, 128.6, 127.7, 126.5, 122.7, 114.8, 114.2 (Ar-C), 57.5 (OCH_2), 55.2 (OCH_3), 44.6 ($N\underline{CH_2}CO$), 43.1 (NCH_2). Anal. Calcd. For $C_{20}H_{20}N_4O_5$ (396.40): C, 60.60; H, 5.09; N, 14.13; Found C, 60.51; H, 4.96; N, 14.25.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl 3′-nitrobenzylidene hydrazone (8c). Yellowish white crystals (0.41 g, 92.5%), R_f = 0.63 (S_2), mp 263-265 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 12.00 (1H, s, NH), 8.57 (1H, s, ArH), 8.37, 8.20 (1H, 2s, CH), 8.27-8.23 (2H, m, ArH), 8.10 (1H, d, *J* 7.8 Hz, ArH), 7.77-7.69 (2H, m,

ArH), 7.37-7.27 (2H, m, ArH), 5.38, 4.94 (2H, 2s, NCH_2CO), 4.81-4.77 (1H, m, OH), 4.09 (2H, t, *J* 6.6 Hz, NCH_2), 3.61-3.55 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 168.8, 161.6, 151.0 (3CO), 148.7 (Ar-C), 142.4 (CH), 140.6, 136.4, 135.6, 133.5, 130.8, 128.3, 124.6, 123.2, 121.5, 115.1 (Ar-C), 58.0 (OCH_2), 45.2 ($N\underline{CH_2}CO$), 43.6 (NCH_2). Anal. Calcd. For $C_{19}H_{17}N_5O_6$ (411.37): C, 55.47; H, 4.17; N, 17.02; Found C, 55.39; H, 4.15; N, 17.18.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl 3′-methoxy-4′-hydroxybenzylidene hydrazone (8d). White crystals (0.39 g, 88.9%), R_f = 0.43 (S_2), mp 287-289 °C. ^1H NMR (300.0 MHz, DMSO): δ 11.58, 11.55 (1H, 2s, NH), 9.49 (1H, s, OH), 8.09 (1H, d, *J* 7.8 Hz, ArH), 8.11, 7.95 (1H, 2s, CH), 7.74 (1H, t, *J* 7.8 Hz, ArH), 7.34-7.29 (3H, m, ArH), 7.13-7.09 (1H, m, ArH), 6.85-6.82 (1H, m, ArH), 5.31, 4.88 (2H, 2s, NCH_2CO), 4.82-4.78 (1H, m, OH), 4.09 (2H, t, *J* 6.5 Hz, NCH_2), 3.82 (3H, s, OCH_3) 3.61-3.55 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 167.6 161.1, 150.5 (3CO), 148.8, 147.8 (Ar-C), 144.6 (CH), 140.2, 135.1, 127.8, 125.3, 122.7, 121.4, 115.4, 114.6, 109.5 (Ar-C), 57.5 (OCH_2), 55.5 (OCH_3), 44.7 ($N\underline{CH_2}CO$), 43.1 (NCH_2). Anal. Calcd. For $C_{20}H_{20}N_4O_6$ (412.40): C, 58.25; H, 4.89; N, 13.59; Found C, 58.09; H, 4.81; N, 13.66.

General method for the synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl amino acid hydrazide (9a, b). To a solution of **4a** or **4b** (5.0 mmol) in methanol (30 mL), hydrazine hydrate (2 mL, 32.0 mmol) was added. The reaction mixture was refluxed for 6 hrs, after cooling to room temperature the precipitated hydrazide was filtered off, washed with water, and ethanol followed by recrystallization from aqueous ethanol to give the 3-(2-hydroxyethyl)-2,4-dioxo-(1H,3H)-quinazolin-1-yl-acetyl amino acid hydrazides **9a** and **9b**.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-serine hydrazide (9a). White crystals (1.35 g, 87.0%), R_f = 0.19 (S_2), mp 235 °C (dec). ^1H NMR (300.0 MHz, DMSO): δ 9.16 (1H, s, NH), 8.38 (1H, d, *J* 7.8 Hz, NH), 8.05 (1H, d, *J* 7.8 Hz, ArH), 7.72 (1H, t, *J* 7.9 Hz, ArH), 7.29-7.22 (2H, m, ArH), 4.92-4.76 (4H, m, OH, NCH_2CO, OH), 4.35-4.20 (3H, m, NCH, NH_2), 4.07 (2H, t, *J* 5.8 Hz, NCH_2), 3.65-3.50 (4H, m, $2CH_2O$). ^{13}C NMR (75.0 MHz, DMSO): δ 168.9, 166.68, 161.1, 150.6 (4CO), 140.1, 135.1, 127.8, 122.8, 114.7, 114.5 (Ar-C), 61.7 (OCH_2), 57.6 (OCH_2), 54.1 (NCH), 45.6 ($N\underline{CH_2}CO$), 43.2 (NCH_2). Anal. Calcd. For $C_{15}H_{19}N_5O_7$ (365.34): C, 49.31; H, 5.24; N, 19.17; Found C, 49.22; H, 5.18; N, 19.38.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionine hydrazide (9b). White crystals (1.5 g, 75.1%), R_f = 0.32 (S_2), mp 245-247 °C. ^1H NMR (300.0 MHz, DMSO): δ 9.17 (1H, s, NH), 8.47 (1H, d, *J* 8.1 Hz, NH), 8.07 (1H, d, *J* 7.2 Hz, ArH), 7.73 (1H, t, *J* 7.5 Hz, ArH), 7.31-7.21 (2H, m, ArH), 4.95-4.80 (2H, m, NCH_2CO), 4.78 (1H, t, *J* 5.8 Hz, OH), 4.45-4.30 (1H, m, NCH), 4.24 (2H, s, NH_2), 4.07 (2H, t, *J* 6.3 Hz, NCH_2), 3.59-3.53 (2H, m, CH_2O), 2.45-2.36 (2H, m, CH_2S), 2.01 (3H, s, SCH_3), 1.92-1.76 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 170.0, 166.6, 161.1, 150.5 (4CO), 140.1, 134.9, 127.8, 122.7, 114.8, 114.3 (Ar-C), 57.5 (OCH_2), 50.6 (NCH), 45.7 ($N\underline{CH_2}CO$), 43.1 (NCH_2), 31.9 (CH_2S), 29.4 (CH_2), 14.5 (SCH_3). Anal. Calcd. For $C_{17}H_{23}N_5O_5S$ (409.46): C, 49.87; H, 5.66; N, 17.10, S, 7.83; Found C, 49.68; H, 5.59; N, 17.32, S, 7.64.

General procedure for the synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl amino acid arylidene hydrazone derivatives (10a-d). A mixture of **9a** or **9b** (0.54 mmol) and aromatic aldehyde (0.55 mmol) was refluxed in ethanol (20 mL) for 6 hours. After cooling to room temperature, the resulting solid was filtered off, washed with cold ethanol and recrystallized from aqueous ethanol.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-serinyl benzylidene hydrazone (10a). White crystals (0.21g, 79.8%), R_f = 0.39 (S_2), mp 245-247 °C. ^1H NMR (300.0 MHz, DMSO): δ 11.48, 11.42 (1H, 2s, NH), 8.60-8.50 (1H, m, NH), 8.23, 7.98 (1H, 2s, CH), 8.06 (1H, d, , *J* 7.5 Hz, ArH), 7.70-7.60 (3H, m, ArH), 7.43-7.35 (3H, m, ArH), 7.30-7.20 (2H, m, ArH), 5.35-5.28, 4.50-4.40 (1H, 2m, NCH), 5.13, 5.00 (1H, 2m, OH), 4.89 (2H, s, NCH_2CO), 4.80 (1H, t, *J* 5.8 Hz, OH), 4.08-4.04 (2H, t, *J* 6.0 Hz, NCH_2), 3.71-3.57 (4H, m, $2CH_2O$). ^{13}C NMR (75.0

MHz, DMSO): δ 170.9, 166.5, 161.1, 150.6 (4CO), 147.2 (CH), 143.3, 140.1, 135.1, 134.1, 130.0, 128.7, 127.8, 127.0, 126.7, 122.8, 114.8, 114.4 (Ar-C), 61.5, 61.1 (OCH_2), 57.6 (CH_2O), 54.6, 52.6 (NCH), 45.6 ($N\underline{CH_2}CO$), 43.2 (NCH_2). Anal. Calcd. For $C_{22}H_{23}N_5O_6$ (453.45): C, 58.27; H, 5.11; N, 15.44; Found C, 58.13; H, 5.06; N, 15.57.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-serinyl 3'-nitro-benzylidene hydrazone (10b*).* Yellowish white crystals (0.24g, 87.5%), R_f = 0.31 (S_2), mp 231-233 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 12.00-11.60 (1H, brs, NH), 8.65-8.59 (1H, m, NH), 8.49, 8.40 (1H, 2s, CH), 8.34 (1H, s, ArH), 8.24-8.17 (1H, m, ArH), 8.08-7.90 (2H, m, ArH), 7.71-7.63 (2H, m, ArH), 7.29-7.16 (2H, m, ArH), 5.40-5.25, 5.10-5.00 (1H, 2m, NCH), 4.89 (2H, s, NCH_2CO), 4.85-4.75 (1H, m, OH), 4.57-4.40(1H, m, OH), 4.18-4.00 (2H, m, NCH_2), 3.75-3.65 (2H, m, CH_2O), 3.60-3.50 (2H, m, CH_2O). ^{13}C NMR (75.0 MHz, DMSO): δ 171.2, 166.8, 161.1, 150.6 (4CO), 148.1 (Ar-C), 145.1 (CH), 144.7, 141.1, 140.1, 136.0, 135.1, 133.2, 130.3, 127.8, 124.1, 122.7, 120.9, 114.7, 114.3 (Ar-C), 61.5, 61.0 (OCH_2), 57.5 (CH_2O), 54.6, 52.3 (NCH), 45.6 ($N\underline{CH_2}CO$), 43.2 (NCH_2). Anal. Calcd. For $C_{22}H_{22}N_6O_8$ (498.45): C, 53.01; H, 4.45; N, 16.86; Found C, 52.95; H, 4.38; N, 17.02.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionyl benzylidene hydrazone (10c). White crystals (0.21g, 85.1%), R_f = 0.50 (S_2), mp 255-258 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 11.51, 11.39 (1H, 2s, NH), 8.66, 8.59 (1H, 2d, *J* 8.1 Hz, NH), 8.22, 7.98 (1H, 2s, CH), 8.06 (1H, d, *J* 7.5 Hz, ArH), 7.73-7.60 (3H, m, ArH), 7.43-7.32 (3H, m, ArH), 7.30-7.17 (2H, m, ArH), 5.41-5.30, 4.55-4.45 (1H, 2m, NCH), 4.92-4.75 (3H, m, OH, NCH_2CO), 4.07 (2H, t, *J* 6.0 Hz, NCH_2), 3.60-3.50 (2H, m, CH_2O), 2.55-2.42 (2H, m, CH_2S), 2.04, 2.00 (3H, 2s, SCH_3), 1.95-1.80 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.5, 166.7, 161.1, 150.5 (4CO), 147.4 (CH), 143.6, 140.0, 135.0, 134.0, 129.8, 128.7, 127.7, 127.0, 126.7, 122.7, 114.9, 114.3 (Ar-C), 57.5 (CH_2O), 51.2, 48.7 (NCH), 45.7 ($N\underline{CH_2}CO$), 43.1 (NCH_2), 31.9, 30.4 (CH_2S), 29.8, 29.5 (CH_2), 14.7 (SCH_3). Anal. Calcd. For $C_{24}H_{27}N_5O_5S$ (497.57): C, 57.93; H, 5.47; N, 14.08; S, 6.44; Found C, 57.81; H, 5.40; N, 14.23; S, 6.31.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionyl 3'-nitrobenzylidene hydrazone (10d). Yellowish white crystals (0.18g, 69.2%), R_f = 0.53 (S_2), mp 245-247 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 11.80, 11.62 (1H, 2s, NH), 8.70, 8.64 (1H, 2d, *J* 8.1 Hz, NH), 8.49, 8.33 (1H, 2s, CH), 8.24-8.17 (1H, m, ArH), 8.11-8.01 (3H, m, ArH), 7.74-7.64 (2H, m, ArH), 7.27-7.11 (2H, m, ArH), 5.50-5.35, 4.59-4.48 (1H, 2m, NCH), 4.90-4.75 (3H, m, OH, NCH_2CO), 4.15-4.00 (2H, m, NCH_2), 3.65-3.55 (2H, m, CH_2O), 2.57-2.46 (2H, m, CH_2S), 2.05, 2.00 (3H, 2s, SCH_3), 2.00-1.80 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.8, 166.7, 161.1, 150.5 (4CO), 148.1 (CH), 141.4, 140.0, 135.8, 135.0, 133.0, 130.3, 127.7, 124.0, 122.7, 120.7, 114.8, 114.2 (Ar-C), 57.5 (CH_2O), 51.2, 48.5 (NCH), 45.7 ($N\underline{CH_2}CO$), 43.1 (NCH_2), 31.5, 30.4 (CH_2S), 29.9, 29.5 (CH_2), 14.7 (SCH_3). Anal. Calcd. For $C_{24}H_{26}N_6O_7S$ (54.56): C, 53.13; H, 4.83; N, 15.49; S, 5.91; Found C, 52.97; H, 4.77; N, 15.68; S, 5.86.

General method for the synthesis of [3-(2-hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl dipeptide methyl esters (11a-c). To a cold solution (-5 °C) of hydrazide **9b** (0.65 g, 1.6 mmol) in acetic acid (12 mL), hydrochloric acid (5*N,* 6 mL), and water (50 mL), was added portion wise under stirring a cold solution (0 °C) of sodium nitrite (0.14 g, 2.0 mmol) in water (6 mL). After stirring at the same temperature for 30 minutes, the azide was extracted with cold ethyl acetate, and washed successively with cold water, 5 % $NaHCO_3$ and water. After drying over anhydrous sodium sulphate, the azide was used directly without further purification in the next step.

The amino acid methyl ester hydrochlorides (1.8 mmol), was stirred in ethyl acetate (50 mL) with triethyl amine (0.2 mL) at 0 °C for 20 minutes. The formed triethyl amine hydrochloride was filtered off and the filtrate was added to the previously prepared cold dried solution of the azide. The reaction mixture was treated as described above under the synthesis of the amino acid methyl ester derivatives **4a-d** to afford the dipeptide ester derivatives **11a-c**.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionyl L-methionine methyl ester (11a). White crystals (0.32 g, 37.7%), R_f = 0.47 (S_1), mp 171-173 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ 8.13 (1H, d, *J* 8.1 Hz, ArH), 7.61-7.50 (2H, m, ArH, NH), 7.27-7.18 (2H, m, ArH), 7.12 (1H, d, *J* 8.5 Hz, NH), 4.79-4.69 (2H, m, NCH_2CO), 4.68-4.58 (2H, m, 2NCH), 4.26 (2H, t, *J* 5.2 Hz, NCH_2), 3.95-3.80 (2H, m, CH_2O), 3.71 (3H, s, OCH_3), 3.22-2.10 (1H, brs, OH), 2.53-2.42 (4H, m, $2CH_2S$), 2.05-1.94 (10H, m, $2SCH_3$, $2CH_2$). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 172.3, 170.9, 167.2, 162.0, 151.7 (5CO), 139.7, 135.4, 128.9, 123.5, 115.4, 113.5 (Ar-C), 60.6 (OCH_3), 52.4 (OCH_2), 51.5, 47.0 (2NCH), 46.7 ($N\underline{CH_2}CO$), 44.2 (NCH_2), 31.0 ($2CH_2S$), 29.8 ($2CH_2$), 15.2, 15.0 ($2SCH_3$). Anal. Calcd. For $C_{23}H_{32}N_4O_7S_2$ (540.65): C, 51.09; H, 5.97; N, 10.36, S, 11.86; Found C, 50.97; H, 6.01; N, 10.52, S, 11.61.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionyl L-leucine methyl ester (11b). White crystals (0.34 g, 41.8%), R_f = 0.53 (S_1), mp 156-158 °C. ^{1}H NMR (300.0 MHz, $CDCl_3$): δ 8.17 (1H, d, *J* 7.8 Hz, ArH), 7.65-7.59 (1H, t, *J* 7.8 Hz, ArH), 7.43 (1H, d, *J* 7.8 Hz, NH), 7.26 (1H, t, *J* 7.5 Hz, ArH), 7.14 (1H, d, *J* 8.4 Hz, ArH), 6.84 (1H, d, *J* 8.1 Hz, NH), 4.84-4.79 (2H, m, NCH_2CO), 4.75-4.65 (1H, m, NCH), 4.58-4.45 (1H, m, NCH), 4.29 (2H, t, *J* 5.5 Hz, NCH_2), 3.89 (2H, t, *J* 5.1 Hz, CH_2O), 3.70 (3H, s, OCH_3), 3.20-2.85 (1H, brs, OH), 2.56-2.51 (2H, t, *J* 6.9 Hz, CH_2S), 2.03 (3H, s, SCH_3), 2.02-1.96 (2H, m, CH_2), 1.62-1.48 (3H, m, CH_2, CH), 0.92-0.86 (6H, m, $2CH_3$). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 172.8, 170.6, 166.9, 162.1, 151.8 (5CO), 139.7, 135.4, 129.1, 123.6, 115.5, 113.6 (Ar-C), 60.8 (OCH_3), 52.1 (OCH_2), 50.9, 46.9 (2NCH), 44.3 ($N\underline{CH_2}CO$), 40.9 (NCH_2), 30.9 (CH_2S), 30.1 (CH), 29.8 (CH_2), 24.7 (CH_2), 22.7, 21.6 ($2CH_3$) 14.9 (SCH_3). Anal. Calcd. For $C_{24}H_{34}N_4O_7S$ (522.61): C, 55.16; H, 6.56; N, 10.72, S, 6.14; Found C, 54.98; H, 6.64; N, 10.93, S, 6.05.

[3-(2-Hydroxyethyl)-2,4-dioxo-(1*H*,3*H*)-quinazolin-1-yl]acetyl L-methionyl L-tryptophane methyl ester (11c). White crystals (0.29 g, 31.2%), R_f = 0.41 (S_1), mp 166-169 °C. ^{1}H NMR (300.0 MHz, DMSO): δ 10.83 (1H, s, Ind-NH), 8.45 (1H, d, *J* 8.1 Hz, NH), 8.38 (1H, d, *J* 7.2 Hz, NH), 8.07 (1H, d, *J* 7.8 Hz, ArH), 7.69-7.62 (1H, m, ArH), 7.49 (1H, d, *J* 7.5 Hz, ArH), 7.35-7.27 (2H, m, ArH), 7.18-7.10 (2H, m, ArH, Ind-2-H), 7.07-6.98 (2H, m, ArH), 4.81-4.75 (3H, m, NCH_2CO, OH), 4.59-4.42 (2H, m, 2NCH), 4.08-4.03 (2H, t, *J* 6.6 Hz, NCH_2), 3.62-3.54 (2H, m, CH_2O), 3.56 (3H, s, OCH_3), 3.15-3.09 (2H, m, CH_2), 2.49-2.38 (2H, m, CH_2S), 2.01 (3H, s, SCH_3), 1.93-1.79 (2H, m, CH_2). ^{13}C NMR (75.0 MHz, DMSO): δ 172.0, 170.8, 166.5, 161.1, 150.5 (5CO), 140.0, 136.0, 135.0, 128.2, 127.7, 126.9, 123.6, 122.7, 118.3, 117.8, 114.8, 114.2, 111.3, 109.1 (Ar-C), 57.5 (OCH_3), 53.1 (OCH_2), 51.7 (NCH), 45.7 ($N\underline{CH_2}CO$), 43.1 (NCH_2), 32.0 (CH_2S), 29.2 (CH_2), 26.7 (CH_2), 14.5 (SCH_3). Anal. Calcd. For $C_{29}H_{33}N_5O_7S$ (595.67): C, 58.47; H, 5.58; N, 11.76, S, 5.38; Found C, 58.22; H, 5.67; N, 11.89, S, 5.29.

In vitro antiproliferative activity

Cytotoxicity of the newly synthesized compounds was tested against human liver carcinoma cell line (HepG2) using the method of Skehan et al. [32]

A preliminary investigation was performed at 100 µg/mL. Based upon this study the inactive compounds were excluded. The data of the in vitro antiproliferative activity are presented in Table 1.

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of the new compounds can be found in the supplementary material file.

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