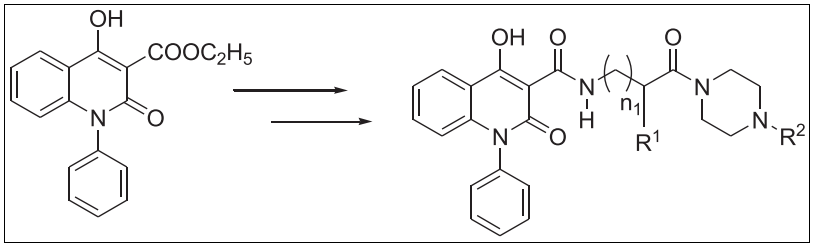
Convenient Synthesis of Piperazine Substituted Quinolones

Walid Fathalla[a]* and Pavel Pazdera[b]

[a]Physics and Mathematics Engineering Department, Faculty of Engineering, Port-Said University, Port Said, Egypt
[b]Centre for Syntheses at Sustainable Conditions and Their Management, Chemistry Department, Masaryk University, Brno, Czech Republic
*E-mail: walid3369@yahoo.com

Received March 14, 2017
DOI 10.1002/jhet.2971
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).

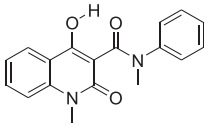


A series of 1-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonyl]-4-(substituted) piperazines **3a–c** and methyl 2-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino] alkanoates **5a–d** has been developed by the direct condensation of ethyl [4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-3-quinoline] carboxylate **2** with N^1-monosubstituted piperazine hydrochlorides or amino acid ester hydrochloride in the presence of triethyl amine. The quinolone amino acid esters **5a–d** were the key intermediate for the preparation of a series of 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino)alkylcarbony]-4-substituted piperazine derivatives **8–11 (a-d)** *via* azide coupling method with amino acid ester hydrochloride.

J. Heterocyclic Chem., **00,** 00 (2017).

INTRODUCTION

Quinolone is a very important *N*-heteroaromatic compounds known to possess a wide variety of pharmacological activities [1]. Linomide (roquinimex), immunomodulatory drug showed a wide variety of effective applications in immunotherapy of tumors [2,3], has a profound inhibitory influence in several experimental autoimmune diseases, including acute and chronic experimental allergic encephalomyelitis, and has a potential for the treatment of multiple sclerosis [4].



Roquinimex (Linomide)

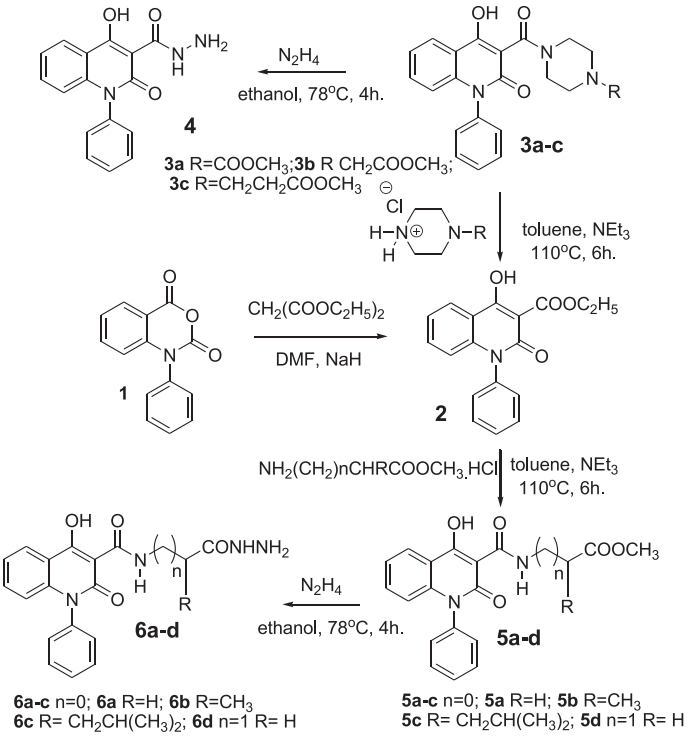
A large number of compounds conducted on piperazine ring are well known as important marketed drugs and were used in great variety of biological activities, such as antidepressant (Amoxapine [5], Befuraline [6], Buspirone [7], Flesinoxan [8], Ipsapirone [9]), antihistamine (Meclozine [10], Cinnarizine [11], Hydroxyzine [12]), antipsychotic (Perphenazine [13], Prochlorperazine [14,15]), anticancer (Imatinib [16]), analgesic, and anti-inflammatory (Antrafenine [17]).

Non-proteinogenic amino acids are major component in a number of drugs including β-lactam antibiotics [18] and glutamate antagonists [19]. These results motivated the development of a series of quinolones directly attached to biologically promising piperazine derivatives, or *via* amino acid spacer.

DISCUSSION

We now report the preparation of 1-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonyl]-4-(substituted) piperazines and 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino)alkycarbony]-4-substituted piperazine derivatives. The quinoline ester derivative **2** was prepared as reported [20] by the reaction of isatoic anhydride derivative **1** with diethyl malonate in the presence of NaH in DMF to afford the ester **2** in 74% yield. Our efforts to attach piperazine residue to quinoline ring system at position 3 were successful using the direct condensation of the piperazine derivatives with the ester. Thus, the reaction of ester **2** with N^1-monosubstituted piperazine hydrochlorides in the presence of triethyl amine in toluene under reflux condition for 6 h gave 1-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-quinolin-3-yl) carbonyl]-4-(substituted) piperazines **3a–c** in good yield (Scheme 1). N^1-Monosubstituted piperazine hydrochlorides used in this article were prepared by the direct reaction of

Scheme 1. Synthesis of 1-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydro quinolin-3-yl)carbonyl]-4-(substituted) piperazine **3a**–**c** and methyl 2-[(4-hydroxy-2-oxo-1-phenylquinolin-3-yl)carbonylamino] alkanoates **5a**–**d**.



piperazine-1-ium cation with alkyl halides or methyl acrylate by Cu^{+}, Cu^{2+}, or Al^{3+} ions supported on weakly acidic cation-exchanger resin [21,22]. Similarly, a series of amino acid quinoline derivatives **5a–d** was prepared by the reaction of ester **2** with amino acid ester hydrochloride in the presence of triethyl amine in toluene under reflux condition for 6 h gave the amino acid derivatives **5a–d** in high yield (65–89%) (Scheme 1). Both piperazine carboxylate derivatives **3a–c** and amino acid ester derivatives **5a–d** are excellent precursors for structure modification of quinoline ring system with N^1-monosubstituted piperazine *via* azide coupling method. Azide coupling method is considered as one of the important methods to couple amino acid derivatives starting from hydrazides. It was also reported that this method decreases the degree of racemization in the amino acid coupling and amine nucleophiles [23,24].

We first tried the hydrazinolysis of the piperazine derivatives **3a–c**, which represent the first step in the azide coupling method. However, the reaction of ester **3b** ($R=CH_2COOCH_3$) with hydrazine hydrate in ethanol for 4 h and gave the hydrazide **4** with an over-all elimination of the piperazine residue (Scheme 1).

An alternative effort to attach monosubstituted piperazine derivative to quinoline ring system could be achieved from the corresponding amino acid derivatives **5a–d** to give the target compounds 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino-alkylcarbony]-4-substituted piperazine derivatives **8–11** (**a-d**). Thus, amino acid derivatives **5a–d** was boiled with hydrazine hydrate in ethyl alcohol to afford the hydrazides **6a–d** (Scheme 1), which subsequently converted into azides **7a–d** by treatment with $NaNO_2$ and HCl mixture. The *in situ* generated azide derivatives **7a–d** in ethyl acetate was used in a *one-pot* strategy without purification nor isolation**.** The azides **7a–d** solution in ethyl acetate was reacted with *N*-methylpiperazine and 4-substituted piperazine-1-ium chloride ester derivatives in the presence of triethyl amine to afford 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino) alkylcarbony]-4-substituted piperazine derivatives **8–11** (**a–d**) in good yield (Scheme 2, Table 1).

The structure assignment of piperazine derivatives **8–11** (**a–d**) is based on ^1H and ^{13}C NMR spectroscopy as well as physicochemical analysis (Fig. 1). Thus, the ^1H NMR spectrum of **8b** ($R=COOCH_3$) exhibits two interesting singlet signals at δ 16.73 and 10.76 ppm corresponding to OH and NH groups, respectively. The ^1H NMR spectrum of **8b** exhibits an interesting doublet signal at δ 8.23 ppm due an anisotropic shielding of the neighboring carbonyl on an aromatic proton. All three chemical shifts mentioned earlier are common for all amino acid derivatives **5a–d** as well as the piperazine derivatives **8–11** (**a–d**). The ^1H NMR spectrum of **8b** also shows a doublet signal at δ 4.26 ppm typically associated with $NHCH_2$ group. The ^1H NMR spectrum of **8b** also reveals signals at δ 3.74–3.50 ppm for 11 protons corresponding to four piperazine

Scheme 2. Synthesis of 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonyl-amino)alkylcarbony]-4-substituted piperazine derivatives **8–11 (a–d)**.

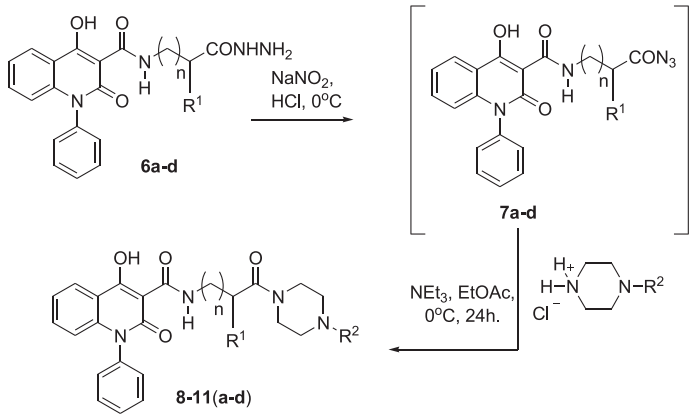


Table 1

Structures of 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino)alkylcarbony]-4-substituted piperazine derivatives **8–11 (a–d)**.

8–11	*n*	R^1	R^2	**8–11**	*n*	R^1	R^2
8a	0	H	CH_3	**10a**	0	$CH_2CH(CH_3)_2$	CH_3
8b	0	H	$COOCH_3$	**10b**	0	$CH_2CH(CH_3)_2$	$COOCH_3$
8c	0	H	CH_2COOCH_3	**10c**	0	$CH_2CH(CH_3)_2$	CH_2COOCH_3
8d	0	H	$CH_2CH_2COOCH_3$				
9a	0	CH_3	CH_3	**11a**	1	H	CH_3
9b	0	CH_3	$COOCH_3$	**11b**	1	H	$COOCH_3$
9c	0	CH_3	CH_2COOCH_3	**11c**	1	H	CH_2COOCH_3
9d	0	CH_3	$CH_2CH_2COOCH_3$	**11d**	1	H	$CH_2CH_2COOCH_3$

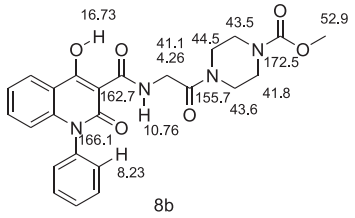


Figure 1. Selected ^1H and ^{13}C NMR spectral data of 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino)-acetyl]-4-(methoxycarbonyl) piperazine **(8b).**

CH_2 groups and OCH_3 group. The ^{13}C NMR spectrum of **8b** reveals quaternary carbon signals at δ 172.5, 166.1, 162.7, and 155.7 ppm assigned to one C=O ester group and three C=O amide groups, respectively. The ^{13}C NMR spectrum of **8b** also reveals signals at δ 44.5, 43.6, 43.5, and 41.8 ppm associated with four piperazine CH_2 groups. The ^{13}C NMR spectrum of **8b** also reveals signals at δ 52.9 and 41.1 ppm for OCH_3 and $NHCH_2$, respectively (Fig. 1).

CONCLUSION

A series of 4-hydroxy-2-oxo-1-phenylquinolin-3-yl) carbonyl]-4-(substituted) piperazines **3a–c** and methyl 2-[(4-hydroxy-2-oxo-1-phenylquinolin-3-yl)carbonyl amino] alkanoates **5a–d** has been developed by the direct condensation of ethyl [4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-3-quinoline] carboxylate **2** with N^1-monosubstituted piperazine hydrochlorides or amino acid ester hydrochloride in the presence of triethyl amine. Azide coupling method was successfully applied to attach piperazine moiety to quinoline ring system *via* amino acid spacer to afford 15 piperazine derivatives **8–11(a–d)**. However this method failed to give results to attach amino acid to quinoline ring system *via* piperazine spacer.

EXPERIMENTAL

General procedures. Solvent were purified and dried by standard procedures. The boiling range of the petroleum ether used was 40–60°C. Thin layer chromatography: silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are

uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively (Bruker AC 300) in $CDCl_3$ and DMSO solution with tetramethylsilane as an internal standard. The NMR analyses were performed at Organic Chemistry Department Masaryk University, Brno, Czech Republic. The starting ester **2** and the reagents N^1-monosubstituted piperazine hydrochlorides described in literature [20–22].

Ethyl [4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl] carboxylate (2). Condensation of diethyl malonate and isatoic anhydride derivative in the presence of sodium hydride in dry dimethylformamide led to compound **2** [20]. Yield 74%. White crystals, mp 188–189°C. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 14.45 (1H, s, OH); 8.21 (1H, d, *J* = 8.0, ArH); 7.58–7.22 (7H, m, ArH); 6.61 (1H, d, *J* = 8.0, ArH); 4.28 (2H, q, *J* = 6.0, OCH_2); 1.45 (3H, t, *J* = 6.0, CH_3). ^{13}C NMR spectrum (75.0 MHz, $CDCl_3$), δ, ppm: 172.7 (C=O ester); 172.5 (C–OH); 159.7 (C=O amide); 142.3 (C Ar); 137.6 (C Ar); 133.9 (CHAr); 130.1 (CHAr); 129.3 (CHAr); 128.8 (CHAr); 125.3 (CHAr); 122.1 (CHAr); 115.9 (CHAr); 114.7 (C Ar); 98.1 (C Ar); 62.3 (OCH_2); 14.3 (CH_3). Found, %: C, 69.65; H, 4.81; N, 4.49. For $C_{18}H_{15}NO_4$ (309.1). Calculated, %: C, 69.89; H, 4.89; N, 4.53.

General procedure for preparation of 1-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydro quinolin-3-yl)carbonyl]-4-(substituted) piperazine (3a–c). N^1-monosubstituted piperazine hydrochlorides (1.2 mmol) and ethyl 1,2-dihydro-4-hydroxy-1-phenyl-2-oxo-3-quinolinecarboxylate **2** (0.31 g, 1.0 mmol) and triethyl amine (0.15 mL, 1.5 mmol) were dissolved in 100 mL of dry toluene. The reaction mixture was refluxed, and an amount of approximately 60 mL of the volatiles was distilled off at atmospheric pressure for 6 h using a dean stark system. After cooling, the reaction mixture was evaporated under reduced pressure and the resultant solid was crystalized from ethanol.

1-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonyl]-4-(methoxy-carbonyl) piperazine (3a). 0.30 g, Yield 74%. White crystals, mp 179–180°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, d, *J* = 8.0, ArH); 7.67–7.28 (7H, m, ArH); 6.66 (1H, d, *J* = 8.0, ArH); 3.76–3.54 (11H, m, $4CH_2$, OCH_3). ^{13}C NMR spectrum, δ, ppm: 170.3 (C=O ester); 168.9 (C–OH); 159.9 (C=O amide); 155.8 (C=O ester); 141.6 (C Ar); 137.5 (C Ar); 132.9 (CHAr); 130.2 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 124.8 (CHAr); 122.3 (CHAr); 115.9 (CHAr); 115.3 (C Ar); 101.6 (C Ar); 52.8 (OCH_3); 47.2 (CH_2–piperazine); 46.7 (CH_2–piperazine); 43.7 (CH_2–piperazine); 43.4 (CH_2–piperazine). Found, %: C, 64.74; H, 5.12; N, 10.27. For $C_{22}H_{21}N_3O_5$ (407.2). Calculated, %: C, 64.86; H, 5.20; N, 10.31.

1-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonyl]-4-(2-methoxy-2-oxoethyl) piperazine (3b). 0.35 g, Yield 84%. White crystals, mp 80–81°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.21 (1H, d, *J* = 8.0, ArH); 7.67–7.49 (3H, m, ArH); 7.31–7.21 (4H, m, ArH); 6.63 (1H, d, *J* = 8.0, ArH); 3.81–3.63 (7H, m, $2CH_2$, OCH_3), 3.61 (2H, s, CH_2), 2.79–2.71 (4H, m, $2CH_2$). ^{13}C NMR spectrum, δ, ppm: 170.1 (C=O ester); 169.0 (C–OH); 168.2 (C=O amide); 160.0 (C=O ester); 141.6 (C Ar); 137.6 (C Ar); 132.7 (CHAr); 130.2 (CHAr); 129.1 (CHAr); 128.9 (CHAr); 124.8 (CHAr); 122.2 (CHAr); 115.8 (CHAr); 115.4 (C Ar); 101.9 (C Ar); 58.8 (NCH_2); 52.9 (CH_2-piperazine); 52.7 (CH_2–piperazine); 51.8 (OCH_3); 47.2 (CH_2–piperazine); 46.8 (CH_2–piperazine). Found, %: C, 65.39; H, 5.40; N, 9.86. For $C_{23}H_{23}N_3O_5$ (421.2). Calculated, %: C, 65.55; H, 5.50; N, 9.97.

1-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonyl]-4-(3-methoxy-3-oxopropyl) piperazine (3c). 0.29 g, Yield 67%. White crystals, mp 205–206°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.23 (1H, d, *J* = 8.0, ArH); 7.41–7.25 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 3.78–3.53 (7H, m, $2CH_2$, OCH_3); 3.48–2.91 (8H, m, $4CH_2$). ^{13}C NMR spectrum, δ, ppm: 172.2 (C=O ester); 169.2 (C–OH); 168.3 (C-amide); 160.0 (C=O ester); 141.6 (C Ar); 137.6 (C Ar); 132.8 (CHAr); 130.2 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 124.8 (CHAr); 122.3 (CHAr); 115.9 (CHAr); 115.4 (C Ar); 101.7 (C Ar); 53.2 (NCH_2); 53.0 (CH_2–piperazine); 52.7 (CH_2 piperazine); 51.8 (OCH_3); 47.3 (CH_2 piperazine); 46.6 (CH_2 piperazine); 31.4 ($\underline{C}H_2COOCH_3$). Found, %: C, 66.01; H, 5.68; N, 9.47. For $C_{24}H_{25}N_3O_5$ (435.2). Calculated, %: C, 66.19; H, 5.79; N, 9.65.

[4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3yl] carbohydrazide (4). To a solution of piperazine derivative **3b** (0.42 g, 1.0 mmol) in ethyl alcohol (15 mL), hydrazine hydrate 100% (0.1 mL, 2.0 mmol) was added. The reaction mixture was refluxed for 4 h, cooled and the resultant precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide **5**.

0.18 g, Yield 62%. White crystals, mp 209–210°C. ^{1}H NMR spectrum (300 MHz, DMSO-*d6*), δ, ppm (*J*, Hz): 10.78 (1H, s, NH); 8.15 (1H, d, *J* = 8.0, ArH); 7.70–7.52 (5H, m, ArH); 7.38–7.18 (5H, m, ArH); 6.53 (1H, d, *J* = 8.0, ArH); 4.86 (2H, bs, NH_2). ^{13}C NMR spectrum (75.0 MHz, DMSO-*d6*), δ, ppm: 171.7 (C=O ester); 168.4 (C–OH); 161.2 (C=O amide); 141.0 (C Ar); 137.4 (C Ar); 134.2 (CHAr); 130.5 (CHAr); 129.6 (CHAr); 129.4 (CHAr); 124.8 (CHAr); 123.2 (CHAr); 116.3 (CHAr); 115.2 (C Ar). Found, %: C, 64.96; H, 4.38; N, 14.12. For $C_{16}H_{13}N_3O_3$ (295.1). Calculated, %: C, 65.08; H, 4.44; N, 14.23.

General procedure for preparation of methyl 2-[(4-hydroxy-2-oxo-1-phenylquinolin-3-yl)carbonylamino] alkanoates (5a–d). Amino acid ester hydrochlorides (1.2 mmol) and ethyl 1,2-dihydro-4-hydroxy-1-phenyl-2-oxo-3-quinolinecarboxylate **2** (0.31 g, 1.0 mmol) and

triethyl amine (mL, 1.2 mmol) were dissolved in 100 mL of dry toluene. The reaction mixture was refluxed, and an amount of approximately 60 mL of the volatiles was distilled off at atmospheric pressure for 6 h using a dean stark system. After cooling, the reaction mixture was evaporated under reduced pressure and the resultant solid was crystallized from ethanol.

Methyl 2-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydro-quinolin-3-yl)carbonylamino] acetate (5a). 0.31 g, Yield 88%. White crystals, mp 194–195°C.^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.67 (1H, s, OH); 10.55 (1H, bs, NH); 8.26 (1H, d, *J* = 9.0, ArH); 7.64–7.29 (7H, m, ArH); 6.69 (1H, d, *J* = 8.0, ArH); 4.20 (2H, d, *J* = 6.0, CH_2); 3.78 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 171.4 (C–OH); 169.4 (C=O amide); 162.9 (C=O amide); 141.0 (C Ar); 137.1 (C Ar); 133.5 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.7 (CHAr); 116.1 (CHAr); 115.8 (C Ar); 96.9 (C Ar); 52.4 (OCH_3); 40.9 (CH_2). Found, %: C, 64.57; H, 4.42; N, 7.81. For $C_{19}H_{16}N_2O_5$ (352.1). Calculated, %: C, 64.77; H, 4.58; N, 7.95.

Methyl 2-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino] propanoate (5b). 0.24 g, Yield 65%. White crystals, mp 150–151°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.81 (1H, s, OH); 10.48 (1H, d, *J* = 6.0, NH); 8.24 (1H, d, *J* = 8.0, ArH); 7.62–7.28 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 4.74–4.67 (1H, m, CH); 3.76 (3H, s, OCH_3); 1.51 (3H, d, *J* = 6.0, CH_3). ^{13}C NMR spectrum, δ, ppm: 172.8 (C=O ester); 172.6 (C–OH); 171.8 (C=O amide); 170.7 (C=O amide); 162.9 (C=O amide); 141.0 (C Ar); 137.1 (C Ar); 133.4 (CHAr); 130.3 (CHAr); 129.2 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.7 (CHAr); 116.1 (CHAr); 115.9 (C Ar); 96.8 (C Ar); 52.4 (OCH_3); 48.0 (CH); 18.3 (CH_3). Found, %: C, 65.54; H, 4.84; N, 7.48. For $C_{20}H_{18}N_2O_5$ (366.1). Calculated, %: C, 65.57; H, 4.95; N, 7.65.

Methyl 2-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino] 4-methylpentanoate (5c). 0.33 g, Yield 89%. White crystals, mp 190–191°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.20 (1H, s, OH); 10.31 (1H, bs, NH); 8.26 (1H, d, *J* = 8.0, ArH); 7.64–7.28 (7H, m, ArH); 6.66 (1H, d, *J* = 8.0, ArH); 3.77–3.69 (5H, m, CH_2, OCH_3); 2.67 (2H, t, *J* = 6.0, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.9 (C=O ester); 171.8 (C–OH); 171.3 (C=O amide); 163.0 (C=O amide); 140.9 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.6 (CHAr); 116.0 (CHAr); 96.8 (C Ar); 51.8 (OCH_3); 34.9 (CH_2); 33.9 (CH_2). Found, %: C, 65.40; H, 4.86; N, 7.59. For $C_{20}H_{18}N_2O_5$ (366.1). Calculated, %: C, 65.57; H, 4.95; N, 7.65.

Methyl 3-[(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino] propanoate (5d). 0.31 g, Yield 75%. White crystals, mp 120–121°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.48 (1H, s, OH); 10.14 (1H, bs, NH); 8.25 (1H, d, *J* = 8.0, ArH); 7.63–7.28 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 3.66 (3H, s, OCH_3); 3.42 (2H, q, *J* = 6.0, CH_2); 2.32 (2H, t, *J* = 6.0, CH_2); 1.69–1.41 (6H, m, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 173.9 (C=O ester); 173.0 (C–OH); 172.9 (C=O amide); 171.0 (C=O amide); 163.1 (C=O amide); 140.8 (C Ar); 137.2 (C Ar); 133.2 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.6 (CHAr); 116.2 (CHAr); 116.0 (C Ar); 96.7 (C Ar); 51.4 (OCH_3); 38.9 (C-Leu); 33.9 (CH_2-Leu); 29.0 (CH_2-Leu); 26.5 (CH_3); 24.6 (CH_3). Found, %: C, 67.59; H, 5.84; N, 6.77. For $C_{23}H_{24}N_2O_5$ (408.2). Calculated, %: C, 67.63; H, 5.92; N, 6.86.

General method for the preparation of 2-[2-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino] alkanehydrazides (6a–d). To a solution of methyl-2-[2-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carboxamido] alkanoate **5a–d** (1.0 mmol) in absolute ethyl alcohol (30 mL), hydrazine hydrate 100% (0.24 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 h; afterwards, it was left overnight at room temperature. The formed precipitate was filtered off, washed with aqueous ethanol and ether, then crystallized from ethanol to yield the hydrazide.

2-[(4-Hydroxy-2-oxo-1-phenyl1,2-dihydroquinolin-3-yl) carbonylamino] ethanhydrazide (6a). 0.27 g, Yield 78%. White crystals, mp 270–271°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.38 (1H, bs, NH); 9.38 (1H, bs, NH); 8.13 (1H, d, *J* = 8.0, ArH); 7.65–7.60 (4H, m, ArH); 7.38–7.36 (3H, m, ArH); 6.57 (1H, d, *J* = 8.0, ArH); 4.48 (3H, bs, NH_2); 4.15 (2H, d, *J* = 6.0, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.3 (C=O ester); 171.0 (C–OH); 167.5 (C=O amide); 162.1 (C=O amide); 141.2 (C Ar); 137.5 (C Ar); 134.4 (CHAr); 130.5 (CHAr); 129.7 (CHAr); 129.4 (CHAr); 125.0 (CHAr); 123.1 (CHAr); 116.4 (CHAr); 115.4 (C Ar); 96.8 (C Ar); 41.2 (CH_2). Found, %: C, 61.24; H, 4.48; N, 15.73. For $C_{18}H_{16}N_4O_4$ (352.1). Calculated, %: C, 61.36; H, 4.58; N, 15.90.

2-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino] propan-hydrazide (6b). 0.24 g, Yield 65%. White crystals, mp 230–231°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.44 (1H, bs, NH); 9.41 (1H, bs, NH); 8.12 (1H, d, *J* = 8.0, ArH); 7.63–7.55 (4H, m, ArH); 7.35–7.28 (3H, m, ArH); 6.51 (1H, d, *J* = 8.0, ArH); 5.25 (3H, bs, NH_2); 4.53–4.46 (1H, m, CH); 1.31 (3H, d, *J* = 6.0, CH_3). ^{13}C NMR spectrum, δ, ppm: 173.0 (C=O ester); 171.2 (C–OH); 169.9 (C=O amide); 162.9 (C=O amide); 141.2 (C Ar); 138.0 (C Ar); 133.6 (CHAr); 130.4 (CHAr); 129.9 (CHAr); 129.1 (CHAr); 125.2 (CHAr); 122.6 (CHAr); 116.0 (CHAr); 115.6 (C Ar); 97.3 (C Ar); 47.3 (CH); 19.4 (CH_3). Found, %: C, 62.12; H, 4.87; N, 15.17. For $C_{19}H_{18}N_4O_4$ (366.1). Calculated, %: C, 62.29; H, 4.95; N, 15.29.

2-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino]-4-methyl pentanhydrazide (6c). 0.31 g, Yield 76%. White crystals, mp 170–171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.15 (1H, bs, NH); 8.84 (1H, bs, NH); 8.14 (1H, d, *J* = 8.0, ArH); 7.64–7.57 (4H, m, ArH); 7.39–7.36 (3H, m, ArH); 6.57 (1H, d, *J* = 8.0, ArH); 3.54 (2H, q, *J* = 6.0, CH_2); 2.01 (2H, t, *J* = 6.0, CH_2); 1.54–1.25 (6H, m, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 171.9 (C–OH); 170.9 (C=O amide); 163.1 (C=O amide); 141.1 (C Ar); 137.5 (C Ar); 134.4 (CHAr); 130.5 (CHAr); 129.7 (CHAr); 125.0 (CHAr); 123.1 (CHAr); 116.4 (CHAr); 96.8 (C Ar); 38.9 (C-Leu); 33.7 (CH_2-Leu); 28.9 (CH_2-Leu); 26.5 (CH_3); 25.3 (CH_3). Found, %: C, 64.57; H, 5.85; N, 13.61. For $C_{22}H_{24}N_4O_4$ (408.2). Calculated, %: C, 64.69; H, 5.92; N, 13.72.

3-[(4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino] propanhydrazide (6d). 0.31 g, Yield 84%. White crystals, mp 245–246°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.24 (1H, bs, NH); 9.04 (1H, bs, NH); 8.14 (1H, d, *J* = 8.0, ArH); 7.66–7.57 (4H, m, ArH); 7.38–7.35 (3H, m, ArH); 6.56 (1H, d, *J* = 8.0, ArH); 3.57 (2H, q, *J* = 6.0, CH_2); 2.36 (2H, t, *J* = 6.0, CH_2). ^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 171.0 (C–OH); 170.0 (C=O amide); 163.7 (C=O amide); 141.2 (C Ar); 137.5 (C Ar); 134.4 (CHAr); 130.5 (CHAr); 129.7 (CHAr); 129.4 (CHAr); 125.0 (CHAr); 123.0 (CHAr); 116.2 (CHAr); 115.6 (CHAr); 96.5 (C Ar); 35.5 (CH_2); 33.1 (CH_2). Found, %: C, 62.11; H, 4.73; N, 15.06. For $C_{19}H_{18}N_4O_4$ (366.1). Calculated, %: C, 62.29; H, 4.95; N, 15.29.

General procedure for the preparation of 1-[2-((4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)carbonylamino) alkylcarbony]-4-substituted piperazine derivatives 8–11 (a–d). To a cold solution (−5°C) of quinoline hydrazides **6a–d (**1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of $NaNO_2$ (0.1 g, 1.5 mmol) in cold water (3 mL). After stirring at −5°C for 15 min to afford a yellowish syrup, the reaction mixture was extracted with cold ethyl acetate (30 mL), washed with cold 3% $NaHCO_3$, H_2O, and finally dried (Na_2SO_4) to give the *in situ* generated ethyl acetate solution of azide **7a–d**. A prepared cold solution of *N*-methyl piperazine and N^1-monosubstituted piperazine hydrochlorides (1.0 mmol) in ethyl acetate (20 mL) and triethyl amine (0.1 mL, 1.0 mmol) was added to the azide solution **7a–d**. The mixture was kept at −5°C for 24 h, then at 25°C for another 24 h, followed by washing with 3% solution of $NaHCO_3$ and dried (Na_2SO_4). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ ethyl acetate to give **8–11** (**a–d**).

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-acetyl]-4-methylpiperazine (8a). 0.19 g, Yield 45%. White crystals, mp 210–211°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.79 (1H, s, OH); 10.76 (1H, bs, NH); 8.23 (1H, d, *J* = 8.0, ArH); 7.60–7.28 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 4.26 (2H, d, *J* = 6.0, CH_2), 3.69 (2H, t, *J* = 6.0, CH_2); 3.51 (2H, t, *J* = 6.0, CH_2); 2.48 (4H, t, *J* = 6.0, $2CH_2$); 2.34 (3H, s, CH_3).^{13}C NMR spectrum, δ, ppm: 174.5 (C=O ester); 172.4 (C–OH); 170.9 (C=O amide); 165.7 (C=O amide); 162.7 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.1 (CHAr); 129.2 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.5 (CHAr); 116.1 (CHAr); 115.8 (C Ar); 97.1 (C Ar); 54.5 (CH_2-piperazine); 54.2 (CH_2-piperazine); 45.6 (CH_3); 44.2 (CH_2-piperazine); 41.6 (CH_2-piperazine); 41.0 ($NHCH_2$). Found, C, 65.33; H, 5.46; N, 13.07. For $C_{23}H_{24}N_4O_4$ (420.2). Calculated, %: C, 65.70; H, 5.75; N, 13.33.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-acetyl]-4-(methoxycarbonyl) piperazine (8b). 0.36 g, Yield 78%. White crystals, mp 240–241°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.73 (1H, s, OH); 10.76 (1H, bs, NH); 8.23 (1H, d, *J* = 8.0, ArH); 7.60–7.27 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 4.26 (2H, d, *J* = 6.0, CH_2), 3.74–3.50 (11H, m, $4CH_2$, OCH_3).^{13}C NMR spectrum, δ, ppm: 172.5 (C=O ester); 170.0 (C–OH); 166.1 (C=O amide); 162.7 (C=O amide); 155.7 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.4 (CHAr); 130.1 (CHAr); 129.2 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.5 (CHAr); 116.1 (CHAr); 115.8 (C Ar); 97.0 (C Ar); 52.9 (OCH_3); 44.5 (CH_2-piperazine); 43.6 (CH_2-piperazine); 43.5 (CH_2-piperazine); 41.8 (CH_2-piperazine); 41.1 ($NHCH_2$). Found, C, 61.73; H, 5.01; N, 11.75. For $C_{24}H_{24}N_4O_6$ (464.2). Calculated, %: C, 62.06; H, 5.21; N, 12.06.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-acetyl]-4-(2-methoxy-2-oxoethyl) piperazine (8c). 0.31 g, Yield 65%. White crystals, mp 180–181°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.75 (1H, s, OH); 10.76 (1H, bs, NH); 8.20 (1H, d, *J* = 8.0, ArH); 7.58–7.28 (7H, m, ArH); 6.64 (1H, d, *J* = 8.0, ArH); 4.25 (2H, d, *J* = 6.0, CH_2), 3.77–3.52 (7H, m, $2CH_2$, OCH_3); 3.26 (2H, s, CH_2); 2.59 (4H, t, *J* = 6.0, $2CH_2$).^{13}C NMR spectrum, δ, ppm: 172.5 (C=O ester); 170.9 (C–OH); 170.4 (C=O amide); 165.6 (C=O amide); 162.7 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.4 (CHAr); 130.1 (CHAr); 129.2 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.5 (CHAr); 116.0 (CHAr); 115.8 (C Ar); 97.0 (C Ar); 58.9 (NCH_2); 52.6 (CH_2 piperazine); 52.4 (CH_2 piperazine); 51.7 (OCH_3); 44.5 (CH_2 piperazine); 41.5 (CH_2 piperazine); 41.0 ($NHCH_2$). Found, %: C, 62.58; H, 5.32; N, 11.49. For $C_{25}H_{26}N_4O_6$ (478.2). Calculated, C, 62.75; H, 5.48; N, 11.71.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-acetyl]-4-(3-methoxy-3-oxopropyl) piperazine (8d). 0.30 g, Yield 61%. White crystals, mp 165–166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.80 (1H, s, OH); 10.75 (1H, bs, NH); 8.23 (1H, d, *J* = 8.0, ArH);

7.59–7.25 (7H, m, ArH); 6.65 (1H, d, J = 8.0, ArH); 4.24 (2H, d, J = 6.0, CH_2), 3.76–3.46 (7H, m, $2CH_2$, OCH_3); 2.73 (2H, t, J = 6.0, CH_2); 2–54-2.47 (6H, m, $3CH_2$).^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 172.4 (C–OH); 170.9 (C=O amide); 165.6 (C=O amide); 162.7 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.1 (CHAr); 129.2 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.5 (CHAr); 116.1 (CHAr); 115.8 (C Ar); 97.1 (C Ar); 53.3 (NCH_2); 52.8 (CH_2 piperazine); 52.4 (CH_2 piperazine); 51.7 (OCH_3); 44.6 (CH_2 piperazine); 41.9 (CH_2 piperazine); 41.0 ($NHCH_2$); 32.0 ($\underline{C}H_2COOMe$). Found, %: C, 63.26; H, 5.64; N, 11.23. For $C_{26}H_{28}N_4O_6$ (492.2). Calculated, %: C, 63.40; H, 5.73; N, 11.38.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-2-methylacetyl]-4-methylpiperazine (9a). 0.18 g, Yield 41%. White crystals, mp 190–191°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 16.9 (1H, s, OH); 10.59 (1H, d, J = 6.0, NH); 8.32 (1H, d, J = 8.0, ArH); 7.63–7.28 (7H, m, ArH); 6.64 (1H, d, J = 8.0, ArH); 5.14–4.96 (1H, m, CH); 3.85–3.52 (4H, m, $2CH_2$); 2.58–2.49 (4H, m, $2CH_2$); 2.45 (3H, s, CH_3); 1.48 (3H, t, J = 6.0, CH_3).^{13}C NMR spectrum, δ, ppm: 172.7 (C=O ester); 170.1 (C–OH); 169.9 (C=O amide); 162.7 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.2 (CHAr); 129.3 (CHAr); 129.1 (CHAr); 125.1 (CHAr); 122.5 (CHAr); 116.1 (CHAr); 115.9 (C Ar); 96.9 (C Ar); 54.9 (CH_2 piperazine); 54.5 (CH_2 piperazine); 45.8 (CH); 45.2 (NCH_3); 44.0 (CH_2 piperazine); 42.2 (CH_2 piperazine); 18.4 (CH_3). Found, %: C, 66.14; H, 5.82; N, 12.64. For $C_{24}H_{26}N_4O_4$ (434.2). Calculated, %: C, 66.34; H, 6.03; N, 12.89.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-2-methylacetyl]-4-(methoxycarbonyl) piperazine (9b). 0.24 g, Yield 51%. White crystals, mp 220–221°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 16.82 (1H, s, OH); 10.67 (1H, d, J = 6.0, NH); 8.24 (1H, d, J = 8.0, ArH); 7.62–7.28 (7H, m, ArH); 6.65 (1H, d, J = 8.0, ArH); 5.10–5.01 (1H, m, CH); 3.80–3.46 (11H, m, $4CH_2$, OCH_3); 1.45 (3H, t, J = 6.0, CH_3).^{13}C NMR spectrum, δ, ppm: 172.7 (C=O ester); 170.3 (C–OH); 170.2 (C=O amide); 162.7 (C=O amide); 155.8 (C=O amide); 141.1 (C Ar); 137.1 (C Ar); 133.4 (CHAr); 130.1 (CHAr); 129.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.6 (CHAr); 116.1 (CHAr); 115.8 (C Ar); 96.8 (C Ar); 52.8 (OCH_3); 45.4 (CH_2 piperazine); 45.2 (CH); 43.9 (CH_2 piperazine); 43.6 (CH_2 piperazine); 42.0 (CH_2 piperazine), 18.3 (CH_3). Found, %: C, 62.67; H, 5.26; N, 11.52. For $C_{25}H_{26}N_4O_6$ (478.2). Calculated, %: C, 62.75; H, 5.48; N, 11.71.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-2-methylacetyl]4-(2-methoxy-2-oxoethyl) piperazine (9c). 0.29 g, Yield 59%. White crystals, mp 155–156°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 16.92 (1H, s, OH); 10.98 (1H, d, J = 6.0, NH); 8.20 (1H, d, J = 8.0, ArH); 7.58–7.25 (7H, m, ArH); 6.62 (1H, d, J = 8.0, ArH); 5.08–4.98 (1H, m, CH); 3.79–3.60 (7H, m, $2CH_2$, OCH_3); 3.25 (2H, s, CH_2); 2.64–2.54 (4H, m, $2CH_2$); 1.42 (3H, t, J = 6.0, CH_3).^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 170.3 (C–OH); 170.1 (C=O amide); 169.8 (C=O amide); 162.6 (C=O amide); 141.1 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.2 (CHAr); 129.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.5 (CHAr); 116.0 (CHAr); 115.8 (C Ar); 96.9 (C Ar); 58.9 (CH_2); 52.8 (CH_2 piperazine); 52.5 (CH_2 piperazine); 51.7 (OCH_3); 45.3 (CH_2 piperazine); 45.0 (CH); 42.0 (CH_2 piperazine); 18.4 (CH_3). Found, %: C, 63.17; H, 5.48; N, 11.11. For $C_{26}H_{28}N_4O_6$ (492.2). Calculated, %: C, 63.40; H, 5.73; N, 11.38.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-2-methylacetyl]-4-(3-methoxy-3-oxopropyl) piperazine (9d). 0.20 g, Yield 39%. White crystals, mp 150–151°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 16.92 (1H, s, OH); 10.66 (1H, d, J = 6.0, NH); 8.17 (1H, d, J = 8.0, ArH); 7.57–7.25 (7H, m, ArH); 6.51 (1H, d, J = 8.0, ArH); 5.05–4.96 (1H, m, CH); 3.66–3.55 (7H, m, $2CH_2$, OCH_3); 2.71 (2H, t, J = 6.0, CH_2); 2.52–2.47 (6H, m, $3CH_2$); 1.40 (3H, t, J = 6.0, CH_3).^{13}C NMR spectrum, δ, ppm: 172.6 (C=O ester); 172.6 (C–OH); 170.1 (C=O amide); 169.8 (C=O amide); 162.6 (C=O amide); 141.0 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.2 (CHAr); 129.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.0 (CHAr); 122.5 (CHAr); 116.0 (CHAr); 115.8 (C Ar); 96.8 (C Ar); 53.3 (NCH_2); 52.9 (CH_2 piperazine); 52.4 (CH_2 piperazine); 51.7 (OCH_3); 45.3 (CH_2 piperazine); 45.1 (CH); 42.0 (CH_2 piperazine); 31.9 ($\underline{C}H_2COOCH_3$); 18.4 (CH_3). Found, %: C, 63.78; H, 5.83; N, 10.77. For $C_{27}H_{30}N_4O_6$ (506.2). Calculated, %: C, 64.02; H, 5.97; N, 11.06.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)4-methylpentylcarbonyl]-4-methylpiperazine (10a). 0.18 g, Yield 37%. White crystals, mp 105–106°C. ^{1}H NMR spectrum, δ, ppm (J, Hz): 17.42 (1H, s, OH); 10.06 (1H, bs, NH); 8.14 (1H, d, J = 8.0, ArH); 7.55–7.21 (7H, m, ArH); 6.57 (1H, d, J = 8.0, ArH); 3.44–3.33 (6H, m, $3CH_2$); 2.37–2.23 (9H, m, $2CH_2$, CH_3, CH_2-Leu); 1.59–1.26 (6H, m, $2CH_3$).^{13}C NMR spectrum, δ, ppm: 174.3 (C=O ester); 172.9 (C–OH); 171.2 (C=O amide); 170.9 (C=O amide); 162.9 (C=O amide); 140.7 (C Ar); 137.2 (C Ar); 133.2 (CHAr); 130.2 (CHAr); 129.0 (CHAr); 125.0 (CHAr); 122.5 (CHAr); 116.1 (CHAr); 116.0 (C Ar); 96.5 (C Ar); 54.8 (CH_2 piperazine); 54.4 (CH_2 piperazine); 45.6 (CH_2 piperazine); 45.0 (NCH_3); 41.0 (CH_2 piperazine); 38.9 (CH_2); 32.9 (CH_2); 29.1 (CH_2); 26.8 (CH_3); 24.8 (CH_3). Found, %: C, 67.86; H, 6.53; N, 11.64. For $C_{27}H_{32}N_4O_4$ (476.2). Calculated, %: C, 68.05; H, 6.77; N, 11.76.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)4-methylpentylcarbonyl]-4-(methoxycarbonyl) piperazine (10b). 0.27 g,Yield 52%. White crystals, mp

130–131°C ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.38 (1H, s, OH); 10.12 (1H, bs, NH); 8.23 (1H, d, *J* = 8.0, ArH); 7.61–7.26 (7H, m, ArH); 6.63 (1H, d, *J* = 8.0, ArH); 3.71–3.40 (11H, m, 4CH_2, OCH_3); 3.10 (2H, q, *J* = 6.0, CH_2); 2.30 (2H, t, *J* = 6.0, CH_2); 1.59–1.26 (6H, m, 2CH_3).^{13}C NMR spectrum, δ, ppm: 173.0 (C=O ester); 171.6 (C–OH); 171.0 (C=O amide); 163.1 (C=O amide); 156.0 (C=O amide); 140.8 (C Ar); 137.2 (C Ar); 133.2 (CHAr); 130.3 (CHAr); 129.2 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.6 (CHAr); 116.2 (CHAr); 116.0 (C Ar); 96.6 (C Ar); 52.8 (OCH_3); 45.8 (CH_2 piperazine); 45.3 (CH_2 piperazine); 43.6 (CH_2 piperazine); 41.3 (CH_2 piperazine); 38.9 (CH_2); 33.0 (CH_2); 29.1 (CH_2); 26.8 (CH_3); 24.3 (CH_3). Found, %: C, 64.44; H, 6.03; N, 10.54. For $C_{28}H_{32}N_4O_6$ (520.2). Calculated, %: C, 64.60; H, 6.20; N, 10.76.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)4-methylpentylcarbonyl]-4-(2-methoxy-2-oxoethyl) piperazine (10c). 0.22 g, Yield 41%. White crystals, mp 170–171°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.75 (1H, s, OH); 10.76 (1H, bs, NH); 8.20 (1H, d, *J* = 8.0, ArH); 7.58–7.28 (7H, m, ArH); 6.64 (1H, d, *J* = 8.0, ArH); 4.25 (2H, d, *J* = 6.0, CH_2), 3.71–3.23 (7H, m, 2CH_2, OCH_3); 3.23 (2H, s, CH_2); 2.55–2.27 (4H, t, *J* = 6.0, 2CH_2); 1.63–1.40 (6H, m, 2CH_3) .^{13}C NMR spectrum, δ, ppm: 174.2 (C=O ester); 173.0 (C–OH); 171.4 (C=O amide); 171.0 (C=O amide); 162.4 (C=O amide); 155.8 (C=O amide); 140.8 (C Ar); 137.2 (C Ar); 133.2 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.6 (CHAr); 116.0 (CHAr); 116.0 (C Ar); 96.8 (C Ar); 58.9 (CH_2); 52.9 (CH_2 piperazine); 52.6 (CH_2 piperazine); 51.7 (OCH_3); 45.3 (CH_2 piperazine); 41.1 (CH_2 piperazine); 38.9 (CH_2); 33.0 (CH_2); 29.1 (CH_2); 26.8 (CH_3); 24.8 (CH_3). Found, %: C, 64.83; H, 6.28; N, 10.31. For $C_{29}H_{34}N_4O_6$ (534.3). Calculated, C, 65.15; H, 6.41; N, 10.48.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)ethyl-carbonyl]-4-methylpiperazine (11a). 0.26 g, Yield 60%. White crystals, mp 165–166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.35 (1H, s, OH); 10.17 (1H, bs, NH); 8.26 (1H, d, *J* = 8.0, ArH); 7.62–7.28 (7H, m, ArH); 6.66 (1H, d, *J* = 8.0, ArH); 3.78–3.64 (4H, m, 2CH_2); 3.48 (2H, t, *J* = 6.0, CH_2); 2.66 (2H, t, *J* = 6.0, CH_2); 2.45–2.31 (7H, m, 2CH_2, CH_3).^{13}C NMR spectrum, δ, ppm: 172.9 (C=O ester); 171.3 (C–OH); 169.0 (C=O amide); 162.9 (C=O amide); 140.9 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.9 (CHAr); 116.0 (CHAr); 115.9 (C Ar); 96.8 (C Ar); 54.9 (CH_2 piperazine); 54.5 (CH_2 piperazine); 45.9 (CH_2 piperazine); 45.2 (NCH_3); 41.6 (CH_2 piperazine); 35.4 (CH_2); 32.8 (CH_2). Found, %: C, 66.24; H, 5.97; N, 12.74. For $C_{24}H_{26}N_4O_4$ (434.2). Calculated, %: C, 66.34; H, 6.03; N, 12.89.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)-ethylcarbonyl]- 4-(methoxycarbonyl) piperazine (11b). 0.39 g, Yield 81%. White crystals, mp 200–201°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.22 (1H, s, OH); 10.31 (1H, bs, NH); 8.25 (1H, d, *J* = 8.0, ArH); 7.62–7.26 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 3.78–3.71 (5H, m, CH_2, OCH_3); 3.60 (2H, t, *J* = 6.0, CH_2); 3.51–3.38 (6H, m, 3CH_2); 2.67 (2H, t, *J* = 6.0, CH_2).^{13}C NMR spectrum, δ, ppm: 171.9 (C=O ester); 171.2 (C–OH); 169.3 (C=O amide); 155.8 (C=O amide); 140.9 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.3 (CHAr); 129.1 (CHAr); 129.0 (CHAr); 125.2 (CHAr); 122.6 (CHAr); 116.1 (CHAr); 116.0 (C Ar); 96.8 (C Ar); 52.8 (OCH_3); 45.1 (CH_2 piperazine); 43.7 (CH_2 piperazine); 43.3 (CH_2 piperazine); 41.3 (CH_2 piperazine); 35.3 (CH_2), 32.9 (CH_2). Found, %: C, 62.61; H, 5.36; N, 11.59. For $C_{25}H_{26}N_4O_6$ (478.2). Calculated, %: C, 62.75; H, 5.48; N, 11.71.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)ethyl-carbonyl]-4-(2-methoxy-2-oxoethyl) piperazine (11c). 0.39 g, Yield 78%. White crystals, mp 120–121°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.29 (1H, s, OH); 10.18 (1H, bs, NH); 8.23 (1H, d, *J* = 8.0, ArH); 7.64–7.26 (7H, m, ArH); 6.65 (1H, d, *J* = 8.0, ArH); 3.68–3.21 (9H, m, 2CH_2, $NHC\underline{H}_2$, OCH_3); 3.12 (4H, t, *J* = 6.0, 2CH_2); 2.68 (2H, t, *J* = 6.0, CH_2).^{13}C NMR spectrum, δ, ppm: 173.2 (C=O ester); 172.7 (C–OH); 170.5 (C=O amide); 169.2 (C=O amide); 162.4 (C=O amide); 140.3 (C Ar); 137.2 (C Ar); 133.3 (CHAr); 130.3 (CHAr); 129.0 (CHAr); 125.1 (CHAr); 122.9 (CHAr); 116.1 (CHAr); 115.9 (C Ar); 96.8 (C Ar); 58.6 (CH_2 piperazine); 53.1 (CH_2 piperazine); 51.4 (OCH_3); 44.6 (CH_2 piperazine); 41.8 (CH_2 piperazine); 35.5 (CH_2), 32.2 (CH_2). Found, %: C, 63.26; H, 5.54; N, 11.21. For $C_{26}H_{28}N_4O_6$ (492.2). Calculated, %: C, 63.40; H, 5.73; N, 11.38.

1-[2-((4-Hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl) carbonylamino)ethyl-carbonyl]-4-(3-methoxy-3-oxopropyl) piperazine (11d). 0.24 g, Yield 48%. White crystals, mp 95–96°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 17.23 (1H, s, OH); 10.26 (1H, bs, NH); 8.21 (1H, d, *J* = 8.0, ArH); 7.60–7.25 (7H, m, ArH); 6.63 (1H, d, *J* = 8.0, ArH); 3.69–3.43 (9H, m, 3CH_2, OCH_3); 2.76–2.42 (10H, m, 5CH_2).^{13}C NMR spectrum, δ, ppm: 172.8 (C=O ester); 172.6 (C–OH); 171.2 (C=O amide); 168.9 (C=O amide); 162.9 (C=O amide); 141.0 (C Ar); 137.2 (C Ar); 133.2 (CHAr); 130.2 (CHAr); 129.1 (CHAr); 125.1 (CHAr); 122.6 (CHAr); 116.0 (CHAr); 116.0 (C Ar); 96.7 (C Ar); 53.4 (CH_2); 52.9 (CH_2 piperazine); 52.4 (CH_2 piperazine); 51.6 (OCH_3); 45.3 (CH_2 piperazine); 41.5 (CH_2 piperazine); 35.3 (CH_2); 32.76 (CH_2); 32.04 (CH_2). Found, %: C, 63.78; H, 5.81; N, 10.84. For $C_{27}H_{30}N_4O_6$ (506.2). Calculated, %: C, 64.02; H, 5.97; N, 11.06.

Acknowledgments. We would like to Thank Department of Organic Chemistry Faculty of Science Masaryk University, Brno, Czech Republic, and Ministry of High Education, Egypt, for funding this research proposal. We would like to thank Dr. D. Herova, PhD., for technical support.

REFERENCES AND NOTES

[1] Gurnos, J. Chemistry of Heterocyclic Compounds: Quinolines, Part I. John Wiley and Sons: New York, 2008; Vol 32.

[2] Kalland, T. Cancer Res 1986, 46, 3018.

[3] Robinson, C.; Castaner, J. Drugs Future 1995, 20, 19.

[4] Anderson, O.; Lycke, J.; Tollesson, P. O.; Svenningsson, A.; Runmarker, B.; Linde, A. S.; Astrom, M.; Gjorstrup, P.; Ekholm, S. Neurology 1996, 47, 895.

[5] Kinney, J. L.; Evans, R. L Clin Pharm 1982, 1, 417.

[6] Gastpar, M.; Gastpar, G.; Gilsdorf, U. B. Pharmacopsychiatry 1985, 18, 351.

[7] Trivedi, M. H.; Fava, M.; Wisniewski, S. R.; Thase, M. E.; Quitkin, F.; Warden, D.; Ritz, L.; Nierenberg, A. A.; Lebowitz, B. D.; Biggs, M. M.; Luther, J. F.; Shores-Wilson, K.; Rush, A. J. N Engl J Med 2006, 354, 1243.

[8] Schoeffter, P. Br J Pharmacol 1988, 95, 975.

[9] Fanelli, R. J.; Schuurman, T.; Glaser, T.; Traber, J. Prog Clin Biol Res 1990, 361, 461.

[10] Dahl, E.; Offer-Ohlsen, D.; Lillevold, P. E.; Sandvik, L. Clin Pharmacol & Ther 1984, 36, 116.

[11] Nicholson, A. N.; Stone, B. M.; Turner, C. M. Aviat Space Environ Med 2002, 73, 570.

[12] Simons, F. E.; Simons, K. J.; Frith, E. M. J Allergy Clin Immunol 1984, 73, 69.

[13] Anderson, P.; Knoben, J. E.; Troutman, W. G. Handbook of clinical drug data; McGraw-Hill: New York, 2002; p 807.

[14] Rees, L. British Med J 1960, 2, 522.

[15] Benson, A. J. Aerospace Med 1969, 40, 589.

[16] Gambacorti-Passerini, C. Lancet Oncol 2008, 9, 600.

[17] Manoury, P. M.; Dumas, A. P.; Najer, H.; Branceni, D.; Prouteau, M.; Lefevre-Borg, F. M. J Med Chem 1979, 22, 554.

[18] Townsend, C. A.; Brown, A. M. J Am Chem Soc 1983, 105, 913.

[19] Moloney, M. G. Nat Prod Rep 1999, 16, 485.

[20] Cappola, G. M.; Hartmann, G. E. J Heterocyclic Chem 1979, 16, 1605.

[21] Herova, D.; Pazdera, P. Curr Org Synth 2015, 12, 173.

[22] Herova, D.; Pazdera, P. Monat für Chem 2015, 146, 653.

[23] Han, S.-Y.; Kim, Y.-A. Tetrahedron 2004, 60, 2447.

[24] Ali, I. A. I.; Al-Masoudi, I. A.; Saeed, B.; Al-Masoudi, N. A.; La Colla, P. Heteroatom Chem 2005, 16, 148.