

Convenient syntheses of methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido] alkanooates and their *O*-regioisomers

Ibrahim. A. I. Ali,^{a*} Walid Fathalla,^b and S. M. El Rayes^a

^a*Department of Chemistry, Faculty of Science, Suez Canal University, Ismailia, Egypt*

^b*Department of Mathematical and Physical Sciences, Faculty of Engineering, Suez Canal University, Port Said, Egypt*
E-mail: Ibrahim3369@yahoo.com

Dedicated to Prof. El-Said H. El-Tammny

Abstract

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acet-amido] alkanooate **7**; *O*-regioisomers **12** and N-substituted dipeptides **14** were efficiently prepared by azide coupling of amino acid esters with the azide derivatives **5**, **11** and **13**, respectively. Further the N-substituted ester **7** reacted with N₂H₄.H₂O to give the hydrazide **8** which was condensed with furan-2-carbaldehyde to exhibit the hydrazone **9**.

Keywords: Quinolines, pLT antagonists, amino acids, dipeptide, azide coupling, hydrazones

Introduction

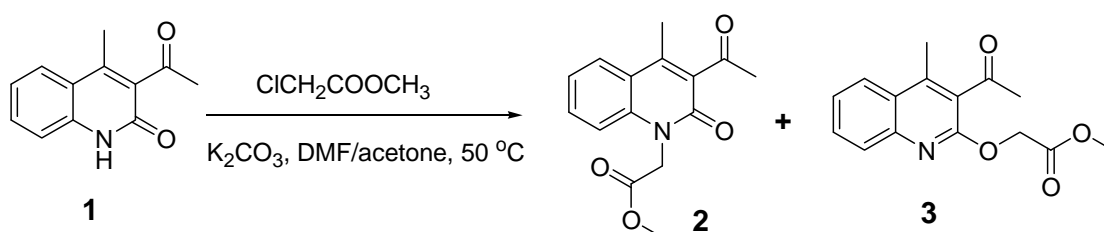
The synthesis of quinoline and its derivatives has attracted considerable attention from organic and medicinal chemists for many years.¹⁻³ The structural core of quinoline is often found in more complex natural products⁴ and is frequently associated with biological activity, such as anti-cancer,⁵ antifungal,⁶ HIV-1 integrase inhibitors,⁷ HIV protease inhibitors⁸ antileishmanial activity,⁹ NK-3 receptor antagonists¹⁰ and pLT antagonists.¹¹⁻¹³

Our objectives were to synthesize a series of quinoline derivatives substituted at position 1 and 2 by a spacer linked with a series of amino acids and dipeptides as pLT antagonists regarded as important mediators of human bronchial asthma¹⁴.

Results and Discussion

In continuation of our efforts synthesizing various amino acid coupled bioactive molecules,¹⁵⁻¹⁷ we now report the preparation of methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido] alkanoate **7** and their *O*-regioisomers **12**. The *N*-substituted amino acid coupled derivatives **7** were prepared by azide coupling from 3-acetyl-1-(2-azido-2-oxoethyl)-4-methylquinolin-2-(1*H*)-one **5**.

Treatment of *o*-aminoacetophenone with ethyl acetoacetate in Et₃N gave 3-acetyl-4-methylquinolin-2-(1*H*)-one **1**.¹⁸ The alkylation of the ambident nucleophile **1** with methyl chloroacetate in the presence of K₂CO₃ in DMF/acetone (1:1) gave a mixture of both *N*-substituted ester **2** as the major product and a low yield of *O*-regioisomer **3**, (Scheme1).¹⁸

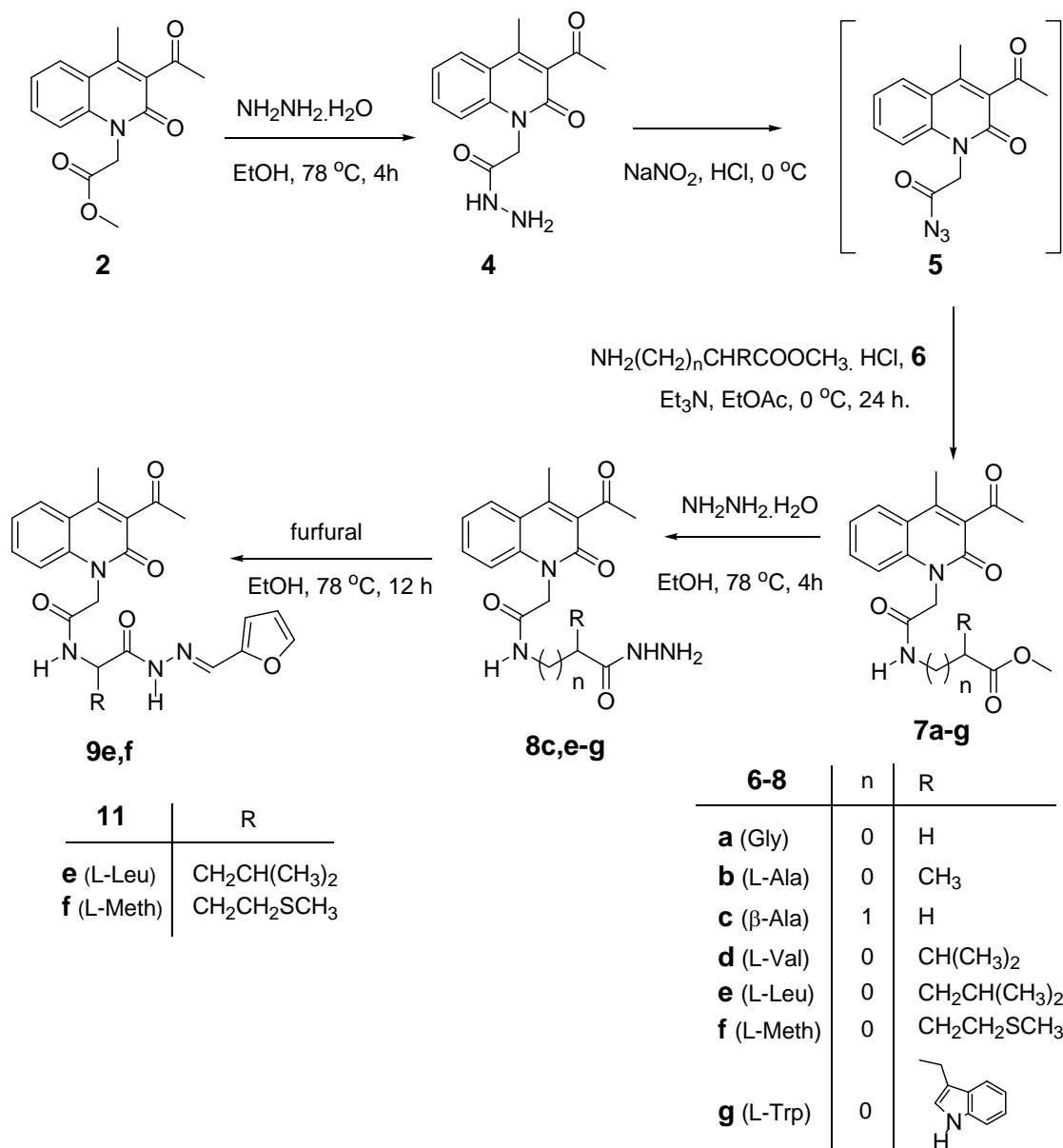


Scheme 1

Both esters **2** and **3** are excellent key intermediates for the simple chemical modification of quinoline derivative **1**. The ester **2** was boiled with hydrazine hydrate in ethyl alcohol to afford the hydrazide **4**, which subsequently converted into azide **5** by treatment with NaNO₂ and HCl mixture.

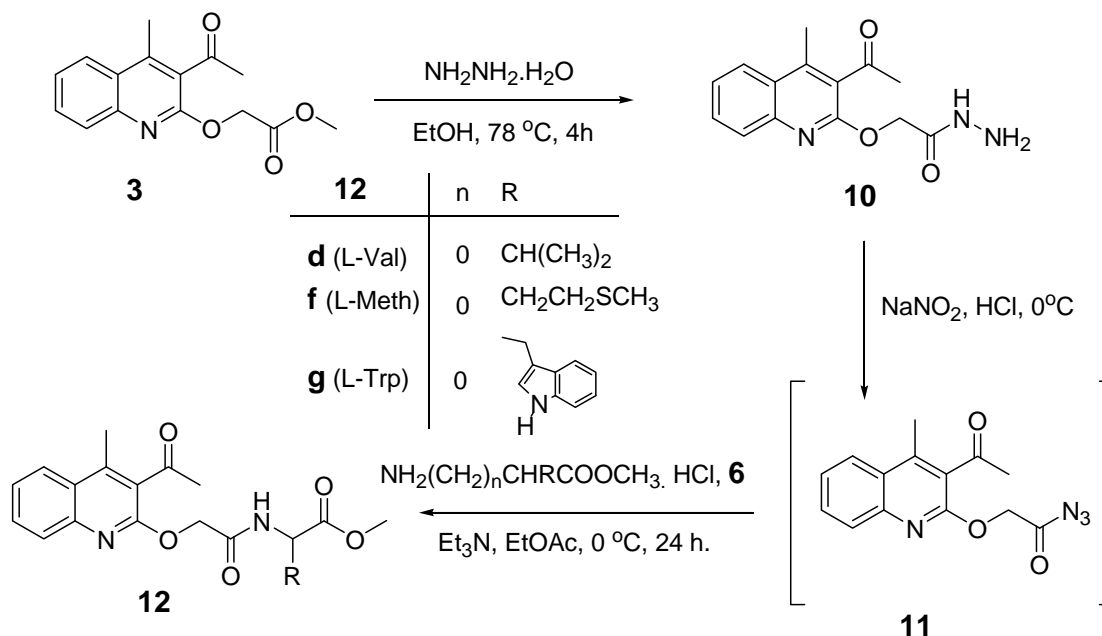
The synthesis of the target amino acid derivatives **7a-g** were efficiently formed from key intermediate ester **2** *via* the azide coupling method,^{15,19,20} which was reported to minimize the degree of racemization in amino acid coupling. The *in situ* generated azide **5** solution in ethyl acetate reacted with amino acid methyl ester hydrochloride **6** in the presence of triethyl amine to afford the methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido] alkanoate **7a-g** in good yield (Scheme 2).

Various *N*-acylheteroarylhydrazones (NAH) have been synthesized and were found to possess very interesting biological activities.^{21,22} Hydrazinolysis of the amino acid ester **7c,e-g** afforded the hydrazide **8c,e-g**. The hydrazide **8e,f** was condensed with furan-2-carbaldehyde to exhibit the hydrazone **9e,f** (Scheme 2).



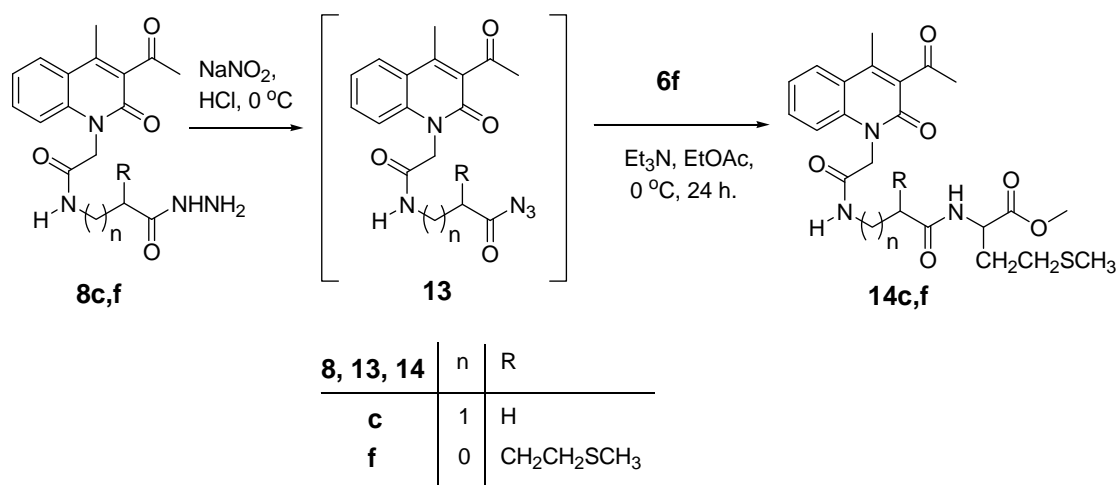
Scheme 2

Similarly, amino acid derivatives **12d,f,g** were efficiently formed from key intermediate ester **3** via the azide coupling method. The ester **3** was boiled with hydrazine hydrate in ethyl alcohol to afford the hydrazide **10**. The hydrazide **10** was treated with NaNO_2 and HCl mixture to yield the O-substituted azide derivative **11**. The *in situ* generated azide **11** solution in ethyl acetate reacted with amino acid methyl ester hydrochloride **6** in the presence of triethyl amine to afford **12**, (Scheme 3).



Scheme 3

Further development of azide coupling was obtained by the synthesis of *N*-substituted dipeptide derivatives **14**. The hydrazide **8** was treated with NaNO₂ and HCl mixture to produce the azide **13**. The *in situ* generated azide **13c,f** solution in ethyl acetate reacted with methionine methyl ester hydrochloride **6c,f** in the presence of triethyl amine to afford the dipeptide **14** (Scheme 4).



Scheme 4

The structure assignment of the *N*-substituted amino acid esters **7**; their *O*-regio isomer **12** and the *N*-substituted dipeptide **14** is based on ¹H NMR spectral and physicochemical analysis,

Figure 1. The ^1H NMR spectra clearly confirm the alkylation site for all isolated *O*- and *N*-substituted derivatives. Thus, the ^1H NMR spectrum of **7d** gave a singlet signal at 4.96 ppm typically associated with NCH_2 . Further more, the ^1H NMR spectrum of **7d** exhibited two singlets and a doublet at 2.45, 2.57 and 7.09 ppm associated with Me, COMe and NH groups, respectively.

The ^1H NMR spectrum of the *N*-substituted dipeptide **14** exhibits signals at δ 3.71, 2.60, 2.40 and 2.24 ppm corresponding to NCH_2 , Me, COMe and NH, respectively.

However, the *O*-substituted derivatives **12d,f,g** gave completely different ^1H NMR patterns. Thus, the ^1H NMR spectrum of **12d** showed an interesting two doublets centered at 5.14 and 5.01 ppm ($J_{\text{AB}} = 15.4$ Hz) corresponding to an AB system of the prochiral hydrogen atoms of the OCH_2 group.¹⁷ Additionally, three signals; two singlets and a doublet at 2.60, 2.66 and 6.89 associated with Me, COMe and NH groups, respectively. The chemical shift of Me group is downfield due to a better conjugation of the quinoline ring system compared to that of **7d**.

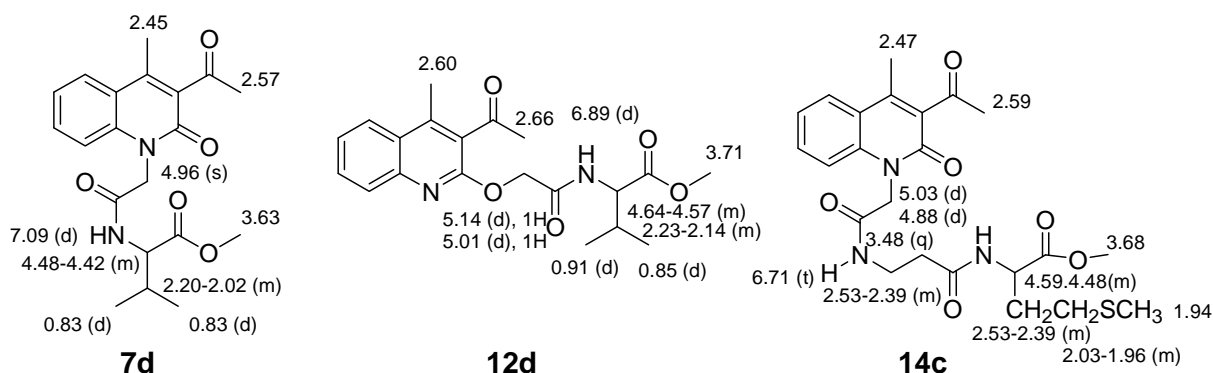


Figure 1. Selected ^1H NMR spectral data of amino acid derivatives **7d**, **12d** and dipeptides **14c**.

Experimental Section

General Procedures. Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 °C. Thin layer chromatography (TLC): silica gel 60 F₂₅₄ plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. ^1H NMR spectra measured with Bruker (200 MHz). TMS (0.00 ppm) as internal standard. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory, Faculty of Science, Suez Canal University, Ismailia, Egypt.

The starting compounds **1-4**, **10** were prepared according to described method.¹⁸

General procedure for the azide method

To a cold solution (-5 °C) of hydrazide (**4**, **8** or **10**) (1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of NaNO₂ (0.87 g, 1.0 mmol) in cold water (3 mL). After stirring at -5 °C for 15 min, the yellow syrup was formed. The azide was extracted in cold ethyl acetate (30 mL), washed with cold 3 % NaHCO₃, H₂O and finally dried (Na₂SO₄). A solution of amino acid esters hydrochloride **6** (1.0 mmol) in ethyl acetate (20 mL) containing 0.2 mL of Et₃N was added to the azide solution. The mixture was kept at -5 °C for 24 h, then at 25 °C for another 24 h, followed by washing with 0.5 N HCl, water, 3 % solution of NaHCO₃ and finally dried (Na₂SO₄). The solution was evaporated to dryness, and the residue was recrystallized from petroleum ether/ ethyl acetate to give the desired product.

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]acetate (7a).

From azide **5** and GlyOMe·HCl **6a**. White crystals (0.29 g, 88 %); mp 200-201 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.83 (1H, d, *J* = 8.0 Hz, ArH), 7.68–7.55 (2H, m, ArH), 7.34 (1H, t, *J* = 8.0 Hz, ArH), 6.99 (1H, bs, NH, D₂O exchangeable), 4.99 (2H, s, NCH₂), 4.00 (2H, d, *J* = 5.4 Hz, NHCH₂), 3.68 (3H, s, OMe), 2.59 (3H, s, COMe), 2.47 (3H, s, Me), Anal. Calcd. For C₁₇H₁₈N₂O₅ (330.3): C, 61.81; H, 5.49; N, 8.48; Found: C, 61.67; H, 5.41; N, 8.43.

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido] propionate (7b).

From azide **5** and L-AlaOMe·HCl **6b**. White crystals (0.28 g, 81 %); mp 161-162 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.84 (1H, d, *J* = 8.2 Hz, ArH), 7.68–7.53 (2H, m, ArH), 7.33 (1H, t, *J* = 8.2 Hz, ArH), 6.95 (1H, d, *J* = 6.2 Hz, NH, D₂O exchangeable), 5.01 (1H, d, *J* = 15.6 Hz, NCH₂), 4.90 (1H, d, *J* = 15.6 Hz, NCH₂), 4.60–4.45 (1H, m, CH), 3.66 (3H, s, OMe), 2.60 (3H, s, COMe), 2.47 (3H, s, Me), 1.37 (3H, d, *J* = 7.0, Me). Anal. Calcd. For C₁₈H₂₀N₂O₅ (344.4): C, 62.78; H, 5.85; N, 8.13; Found: C, 62.64; H, 5.79; N, 8.06.

Methyl 3-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido] propionate (7c).

From azide **5** and β-AlaOMe·HCl **6c**. White crystals (0.30 g, 87 %); mp 188-189 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.82 (1H, d, *J* = 8.2 Hz, ArH), 7.65–7.48 (2H, m, ArH), 7.23–7.36 (1H, m, ArH), 6.86 (1H, bs, NH, D₂O exchangeable), 4.90 (2H, s, NCH₂), 3.57 (3H, s, OMe), 3.54–3.42 (2H, m, NHCH₂), 2.58 (3H, s, COMe), 2.48 (2H, t, *J* = 6.2 Hz, CH₂), 2.45 (3H, s, Me). Anal. Calcd. For C₁₈H₂₀N₂O₅ (344.4): C, 62.78; H, 5.85; N, 8.13; Found: C, 62.72; H, 5.81; N, 8.04.

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]-3-methylbutanoate (7d).

From azide **5** and L-ValOMe·HCl **6d**. White crystals (0.26 g, 70 %); mp 204-205 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.81 (1H, d, *J* = 8.4 Hz, ArH), 7.65–7.48 (2H, m, ArH), 7.31 (1H, m, ArH), 7.09 (1H, d, *J* = 7.2 Hz, NH, D₂O exchangeable), 4.96 (2H, s, NCH₂), 4.48–4.42 (1H, m, CH), 3.63 (3H, s, OMe), 2.57 (3H, s, COMe), 2.45 (3H, s, Me), 2.20–2.02 (1H, m, CH), 0.83 (6H, 2d, *J* = 6.0, 2xMe). Anal. Calcd. For C₂₀H₂₄N₂O₅ (372.4): C, 64.50; H, 6.50; N, 7.52; Found: C, 64.38; H, 6.43; N, 7.43.

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]-4-methylpentanoate (7e).

From azide **5** and L-LeuOMe·HCl **6e**. White crystals (0.29 g, 75 %); mp 119-120 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.84 (1H, d, *J* = 8.0 Hz, ArH), 7.63–7.52 (2H, m, ArH), 7.34 (1H, m, ArH), 6.83 (1H, d, *J* = 7.8 Hz, NH, D₂O exchangeable), 4.96 (2H, s, NCH₂), 4.62–4.53 (1H, m, CH),

Methyl 2-[2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]-4-methylsulfanyl butanoate (7f). From azide **5** and L-MetOMe·HCl **6f**. White crystals (0.27 g, 67 %); mp 156-157 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.83 (1H, d, *J* = 8.0 Hz, ArH), 7.68–7.51 (2H, m, ArH), 7.32 (1H, t, *J* = 8.0 Hz, ArH), 7.16 (1H, d, *J* = 7.6 Hz, NH, D₂O exchangeable), 4.97 (2H, s, NCH₂), 4.71–4.61 (1H, m, CH), 3.66 (3H, s, OMe), 2.59 (3H, s, COMe), 2.46 (3H, s, Me), 2.40 (2H, t, *J* = 7.2 Hz, CH₂), 2.19-2.03 (2H, m, CH₂) 1.97 (3H, s, SMe). Anal. Calcd. For C₂₀H₂₄N₂O₅S (404.5): C, 59.39; H, 5.98; N, 6.93; Found: C, 59.22; H, 5.78; N, 6.85.

Methyl 2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]-3-(1H-indol-3-yl) propanoate (7g). From azide **5** and L-TrpOMe·HCl **6g**. White crystals 0.25 g, 54 %; mp 138-139 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.42 (1H, s, NH, D₂O exchangeable), 7.74 (1H, d, *J* = 8.2 Hz, ArH), 7.57 (1H, t, *J* = 8.0 Hz, ArH), 7.42 (1H, d, *J* = 8.2 Hz, ArH), 7.35–7.21 (3H, m, ArH), 7.04 (1H, t, *J* = 8.0 Hz, ArH), 6.94–6.81 (3H, m, ArH, NH), 4.96 (1H, d, *J* = 15.4 Hz, NCH₂), 4.90 (1H, d, *J* = 15.4 Hz, NCH₂), 4.17–4.06 (1H, m, CH), 3.59 (3H, s, OMe), 3.23–3.01 (2H, m, CH₂), 2.51 (3H, s, COMe), 2.43 (3H, s, Me). Anal. Calcd. For C₂₆H₂₅N₃O₅ (459.5): C, 67.96; H, 5.48; N, 9.14; Found: C, 67.78; H, 5.34; N, 9.01.

Methyl 2-[2-(3-acetyl-4-methyl-quinolin-2-yloxy)acetamido]-3-methylbutanoate (12d). From azide **11** and L-ValOMe·HCl **6d**. White crystals (0.24 g, 64 %); mp 138-139 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.94 (1H, d, *J* = 8.2 Hz, ArH), 7.84 (1H, d, *J* = 8.2 Hz, ArH), 7.68 (1H, t, *J* = 8.1 Hz, ArH), 7.48 (1H, t, *J* = 8.1 Hz, ArH), 6.89 (1H, d, *J* = 8.6 Hz, NH, D₂O exchangeable), 5.14 (1H, d, *J* = 15.4 Hz, OCH₂), 5.01 (1H, d, *J* = 15.4 Hz, NCH₂), 4.64–4.57 (1H, m, CH), 3.71 (3H, s, OMe), 2.66 (3H, s, COMe), 2.60 (3H, s, Me), 2.23–2.14 (1H, m, CH), 0.91 (3H, d, *J* = 6.8 Hz, Me), 0.85 (3H, d, *J* = 6.8 Hz, Me). Anal. Calcd. For C₂₀H₂₄N₂O₅ (372.4): C, 64.50; H, 6.50; N, 7.52; Found: C, 64.41; H, 6.47; N, 7.49.

Methyl 2-[2-(3-acetyl-4-methyl-quinolin-2-yloxy)acetamido]-4-methylsulfanyl butanoate (12f). From azide **11** and L-MetOCH₃·HCl **6f**. White crystals (0.23 g, 57 %); mp 95-96 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.90 (1H, d, *J* = 8.1 Hz, ArH), 7.79 (1H, d, *J* = 8.1 Hz, ArH), 7.64 (1H, t, *J* = 8.2 Hz, ArH), 7.44 (1H, t, *J* = 8.2 Hz, ArH), 7.11 (1H, d, *J* = 7.6 Hz, NH, D₂O exchangeable), 5.12 (1H, d, *J* = 15.2 Hz, NCH₂), 4.96 (1H, d, *J* = 15.2 Hz, NCH₂), 4.77–4.67 (1H, m, CH), 3.70 (3H, s, OMe), 2.63 (3H, s, COMe), 2.55 (3H, s, Me), 2.39 (2H, t, *J* = 7.0 Hz, CH₂), 2.20-1.92 (5H, m, CH₂, SMe). Anal. Calcd. For C₂₀H₂₄N₂O₅S (404.5): C, 59.39; H, 5.98; N, 6.93; Found: C, 59.27; H, 5.83; N, 6.71.

Methyl 2-[2-(3-acetyl-4-methyl-quinolin-2-yloxy)acetamido]-3-(1H-indol-3-yl) propanoate (12g). From azide **11** and L-TrpOMe·HCl **6g**. White crystals (0.24 g, 52 %); mp 83-84 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.22 (1H, s, NH, D₂O exchangeable), 7.92 (1H, d, *J* = 8.2 Hz, ArH), 7.79 (1H, d, *J* = 8.1 Hz, ArH), 7.67 (1H, t, *J* = 8.2 Hz, ArH), 7.52–7.41 (2H, m, ArH), 7.25 (1H, d, *J* = 8.2 Hz, ArH), 7.08 (1H, t, *J* = 8.2 Hz, ArH), 6.98–6.86 (3H, m, ArH, NH), 5.15–4.93 (3H, m, NCH₂, CH), 3.65 (3H, s, OMe), 3.32 (2H, t, *J* = 4.6 Hz, CH₂), 2.52 (3H, s, COMe), 2.31 (3H,

Methyl 2-{3-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)acetamido]-propanamido}-4-methylsulfanyl butanoate (14c). From azide **13c** and L-Met-OMe·HCl **6f**. White crystals (0.30 g, 63 %); mp 204-205 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.84 (1H, d, *J* = 8.0 Hz, ArH), 7.64 (1H, t, *J* = 8.0 Hz, ArH), 7.45 (1H, d, *J* = 8.0 Hz, ArH), 7.34 (1H, t, *J* = 8.0 Hz, ArH), 7.22 (1H, d, *J* = 7.6 Hz, NH, D₂O exchangeable), 6.71 (1H, t, *J* = 7.0 Hz, NH, D₂O exchangeable), 5.03 (1H, d, *J* = 15.8 Hz, NCH₂), 4.88 (1H, d, *J* = 15.8 Hz, NCH₂), 4.53 (1H, q, *J* = 7.0 Hz, CH), 3.68 (3H, s, OMe), 3.47 (2H, q, *J* = 6.4 Hz, NHCH₂), 2.59 (3H, s, COMe), 2.53–2.39 (7H, m, Me, CH₂, CH₂), 2.03–1.94 (5H, m, SMe, CH₂). Anal. Calcd. For C₂₃H₂₉N₃O₆S (475.6): C, 58.09; H, 6.15; N, 8.84; Found: C, 58.01; H, 6.12; N, 8.80.

Methyl 2-{2-[2-(3-acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-acetamido]-4-methylsulfanylbutanamido}-4-methylsulfanylbutanoate (14f). From azide **13f** and L-MetOMe·HCl **6f**. White crystals (0.32 g, 60 %); mp 162-163 °C. ¹H NMR (200 MHz, CDCl₃): δ 7.83 (1H, d, *J* = 8.0 Hz, ArH), 7.64 (1H, t, *J* = 8.0 Hz, ArH), 7.44 (1H, d, *J* = 8.0 Hz, ArH), 7.40–7.29 (2H, m, ArH, NH), 6.93 (1H, t, *J* = 8.4 Hz, NH, D₂O exchangeable), 4.97 (2H, s, NCH₂), 4.63 (2H, m, 2CH), 3.73 (3H, s, OMe), 2.57 (3H, s, COMe), 2.51–2.38 (7H, m, Me, CH₂, CH₂), 2.12–1.91 (10H, m, 2xSMe, 2CH₂). Anal. Calcd. For C₂₅H₃₃N₃O₆S₂ (535.7): C, 56.05; H, 6.21; N, 7.84; Found: C, 55.87; H, 6.10; N, 7.73.

Hydrazide. General method

To a solution of quinoline amino acid derivatives **7c,e,f,g** (1.0 mmol) in ethyl alcohol (30 mL), hydrazine hydrate (0.24 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 hours; afterwards it was left overnight at room temperature. The formed precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-(2-hydrazinocarbonyl-ethyl) acetamide (8c). White crystals (0.33 g, 95 %); mp 291-292 °C. ¹H NMR (200 MHz, DMSO): δ 9.16 (1H, s, NH, D₂O exchangeable), 8.54 (1H, d, *J* = 8.2 Hz, NH, D₂O exchangeable), 8.05 (1H, d, *J* = 8.0 Hz, ArH), 7.49 (1H, t, *J* = 7.8 Hz, ArH), 7.38–7.26 (2H, t, *J* = 8.2 Hz, ArH), 5.12 (1H, d, *J* = 16.4 Hz, NCH₂), 4.91 (1H, d, *J* = 16.6 Hz, NCH₂), 4.28 (2H, bs, NH₂, D₂O exchangeable), 3.55-3.51 (2H, m, NHCH₂), 2.51 (3H, s, COMe), 2.42–2.36 (5H, m, CH₂CO, Me). Anal. Calcd. For C₁₇H₂₀N₄O₄ (344.2): C, 59.29; H, 5.85; N, 16.27; Found: C, 59.04; H, 5.67; N, 16.05.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-(1-hydrazinocarbonyl-3-methylbutyl) acetamide (8e). White crystals (0.30 g, 78 %); mp 266-267 °C. ¹H NMR (200 MHz, DMSO): δ 9.24 (1H, s, NH, D₂O exchangeable), 8.52 (1H, d, *J* = 8.0 Hz, NH, D₂O exchangeable), 7.93 (1H, d, *J* = 8.0 Hz, ArH), 7.63 (1H, t, *J* = 7.8 Hz, ArH), 7.38–7.29 (2H, t, *J* = 8.2 Hz, ArH), 5.10 (1H, d, *J* = 16.4 Hz, NCH₂), 4.91 (1H, d, *J* = 16.4 Hz, NCH₂), 4.35–4.26 (3H, m, CH, NH₂), 2.51 (3H, s, COMe), 2.38 (3H, s, Me), 1.64–1.46 (3H, m, CH₂, CH), 0.91 (3H, d, *J* = 6.2 Hz, Me), 0.82 (3H, d, *J* = 6.0 Hz, Me). Anal. Calcd. For C₂₀H₂₆N₄O₄ (386.4): C, 62.16; H, 6.78; N, 14.50; Found: C, 62.03; H, 6.56; N, 14.38.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-(1-hydrazinocarbonyl-3-methylsulfanylpropyl) acetamide (8f). White crystals (0.36 g, 89 %); mp 276-277 °C. ¹H NMR (200 MHz, DMSO): δ 9.26 (1H, s, NH, D₂O exchangeable), 8.61 (1H, d, *J* = 8.2 Hz, NH, D₂O exchangeable), 7.96 (1H, d, *J* = 8.0 Hz, ArH), 7.66 (1H, t, *J* = 8.0 Hz, ArH), 7.41–7.37 (2H, d, *J* = 8.2 Hz, ArH), 5.12 (1H, d, *J* = 16.8 Hz, NCH₂), 4.98 (1H, d, *J* = 16.8 Hz, NCH₂), 4.37–4.24 (3H, m, CH, NH₂), 2.54 (3H, s, COMe), 2.48 (3H, s, Me), 2.40 (2H, t, *J* = 7.0 Hz, CH₂), 2.06 (3H, s, Me), 1.92–1.81 (2H, m, CH₂). Anal. Calcd. For C₁₉H₂₄N₄O₄S (404.5): C, 56.42; H, 5.98; N, 13.85; Found: C, 56.38; H, 5.84; N, 13.79.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-[1-hydrazinocarbonyl-2-(1H-indol-3-yl)ethyl] acetamide (8g). White crystals (0.30 g, 65 %); mp 274-275 °C. ¹H NMR (200 MHz, DMSO): δ 10.93 (1H, s, NH, D₂O exchangeable), 9.38 (1H, s, NH, D₂O exchangeable), 8.71 (1H, d, *J* = 8.0 Hz, NH, D₂O exchangeable), 7.91 (1H, d, *J* = 8.0 Hz, ArH), 7.66 (1H, d, *J* = 8.0 Hz, ArH), 7.52–7.23 (3H, m, ArH), 7.15–6.98 (3H, m, ArH), 6.88 (1H, d, *J* = 8.2 Hz, ArH), 5.21 (1H, d, *J* = 16.4 Hz, NCH₂), 4.72 (1H, d, *J* = 16.4 Hz, NCH₂), 4.62–4.46 (1H, m, CH), 4.32 (2H, s, NH₂), 3.23–2.93 (2H, m, CH₂), 2.54 (3H, s, COMe), 2.47 (3H, s, Me). Anal. Calcd. For C₁₉H₂₄N₄O₄S (459.5): C, 65.35; H, 5.48; N, 15.24; Found: C, 65.22; H, 5.34; N, 15.18.

Condensation with furan-2-carbaldehyde. General method

To a solution of hydrazide **8e,f** (1.0 mmol) in absolute ethyl alcohol (30 mL), furan-2-carbaldehyde (0.09 mL, 1.0 mmol) was added. The reaction mixture was refluxed for 12 hours, cooled and the formed precipitate was filtered off and crystallized from ethanol to yield the hydrazone **9e,f**.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-[1-(furan-2-ylmethylene-hydrazinocarbonyl)-3-methylbutyl] acetamide (9e).¹⁶ White crystals (0.34 g, 73 %); mp 265-266 °C. ¹H NMR (200 MHz, DMSO): δ 11.48 (1H, s, NH, D₂O exchangeable, structure B), 11.32 (1H, s, NH, D₂O exchangeable, structure A), 8.52 (1H, d, *J* = 7.2 Hz, NH, D₂O exchangeable), 8.11 (1H, s, NH, D₂O exchangeable, structure B), 7.95–7.78 (2H, m, ArH), 7.61 (1H, s, CH furan-2-yl), 7.42–7.23 (2H, m, ArH), 6.85 (1H, dd, *J*_{gem} = 3.6, *J*_{1',2'} = 14.8 Hz, CH furan-2-yl), 6.63–6.59 (1H, m, CH furan-2-yl), 5.21 (1H, s, OH, D₂O exchangeable, structure A), 5.03 (2H, s, NCH₂), 4.41–4.29 (1H, m, CH), 2.46 (3H, s, COMe), 2.38 (3H, s, Me), 1.82–1.42 (3H, m, CH₂, CH), 0.94 (3H, d, *J* = 6.4 Hz, Me), 0.87 (3H, d, *J* = 6.4 Hz, Me). Anal. Calcd. For C₂₅H₂₈N₄O₅ (464.5): C, 64.64; H, 6.08; N, 12.06; Found: C, 64.58; H, 6.05; N, 11.89.

2-(3-Acetyl-4-methyl-2-oxo-1,2-dihydroquinolin-1-yl)-N-[1-(furan-2-ylmethylene-hydrazinocarbonyl)-3-methylsulfanylpropyl] acetamide (9f).¹⁶ White crystals (0.28 g, 58 %); mp 269-270 °C. ¹H NMR (200 MHz, CDCl₃): δ 11.52 (1H, s, NH, D₂O exchangeable, structure B), 11.43 (1H, s, NH, D₂O exchangeable, structure A), 8.77 (1H, d, *J* = 8.0 Hz, NH, D₂O exchangeable), 8.14 (1H, s, NH, D₂O exchangeable, structure B), 7.97–7.82 (2H, m, ArH), 7.63 (1H, s, CH furan-2-yl), 7.46–7.25 (2H, m, ArH), 6.94–7.88 (1H, m, CH furan-2-yl), 6.66–6.56 (1H, m, CH furan-2-yl), 5.25 (1H, s, OH, D₂O exchangeable, structure A), 5.07 (2H, s, NCH₂), 4.51–5.38 (1H, m, CH), 2.53 (3H, s, COMe), 2.41–2.31 (3H, s, Me, CH₂), 2.18–1.79 (5H, m,

References

1. Balasubramanian, M.; Keay, J. G. In Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds., *Comprehensive Heterocyclic Chemistry II*; Vol. 5, Pergamon: Oxford, 1996.
2. De, D.; Byers, L. D.; Krogstad, D. J. *J. Heterocycl. Chem.* **1997**, *34*, 315.
3. Thomas, L.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491.
4. Kouznetsov, V.; Mendez, L.; Gomes, C. *Curr. Org. Chem.* **2005**, *9*, 141.
5. Elderfield, R. C.; Le Von, E. F. *J. Org. Chem.* **1960**, *25*, 1576.
6. Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. *Bioorg. Med. Chem.* **2006**, *14*, 3592.
7. Bénard, C.; Zouhiri, F.; Normand-Bayle, M.; Danet, M.; Desmaële, D.; Leh, H.; Mouscadet, J-F.; Mbemba, G.; Thomas, C-M.; Bonnenfant, S.; Le Bretc, M.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2473.
8. Garrouste, P.; Pawlowski, M. Tonnaire T.; Sicsic, S.; Dumy, P.; De Rosny, E.; Reboud-Ravaux, M.; Fulcrand, P.; Martinez, J. *Eur. J. Chem.* **1998**, *33*, 423.
9. Desrivot, J.; Herrenknecht, C.; Ponchel, G.; Garbi, N.; Prina, E.; Fournet, A.; Bories, C.; Figadère, B.; Hocquemiller, R.; Loiseau, P. M. *Biomed. Pharmacother.* **2007**, *61*, 441.
10. Borioni, A.; Mustazza, C.; Sestili, I.; Sbraccia, M.; Turchetto, L.; Rosaria Del Giudice, M. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 17.
11. Sprecher, A.; Gerspacher, M.; Beck, A.; Kimmel, S.; Wiestner, H.; Anderson, G. P.; Niederhauser, U.; Subramanian, N.; Bray, M. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 965.
12. Galemmo, R. A.; Gavai, A.; Huang, F-C. *Curr. Opin. Ther. Patents* **1992**, 811.
13. Musser, J. H.; Kreft, A. F. *Drugs Fut.* **1990**, *15*, 73.
14. Ford-Hutchinson AW. *Adv. Prostagandin, Thromboxane, and Leukotriene Res.* **1995**, *23*, 69.
15. Fathalla, W.; Ali, I. A. I. *Heteroatom Chem.* **2007**, *18*, 637.
16. Fathalla, W.; El Rayes, S. M.; Ali, I. A. I. *ARKIVOC* **2007**, (xvi), 173.
17. El Rayes, S. M.; Ali, I. A. I.; Fathalla, W. *ARKIVOC* **2008**, (xi), 86.
18. Helmy, H. MSc Thesis, Faculty of Science, Suez Canal University, Ismailia, Egypt, 2003.
19. Sahin, G.; Palaska, E.; Ekizoglu, M.; Ozalp, M. *Farmaco* **2002**, *57*, 539.
20. Ali, I. A. I.; Al-Masoudi, I. A.; Saeed, B.; Al-Masoudi, N. A.; La Colla, P. *Heteroatom Chem.* **2005**, *16*, 148.
21. Todeschini, A. R.; Miranda, A. L. P.; Silva, K. C. M.; Parrini, S. C.; Barreiro, E. J. *Eur. J. Med. Chem.* **1997**, *33*, 189.
22. Lima, P. C.; Lima, L. M.; Silva, K. C. M.; Leda, P. H. O.; Miranda, A. L. P.; Fraga, C. A. M.; Barreiro, E. J. *Eur. J. Med. Chem.* **2000**, *35*, 187.