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

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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] alkano- ate **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 $N_2H_4.H_2O$ 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

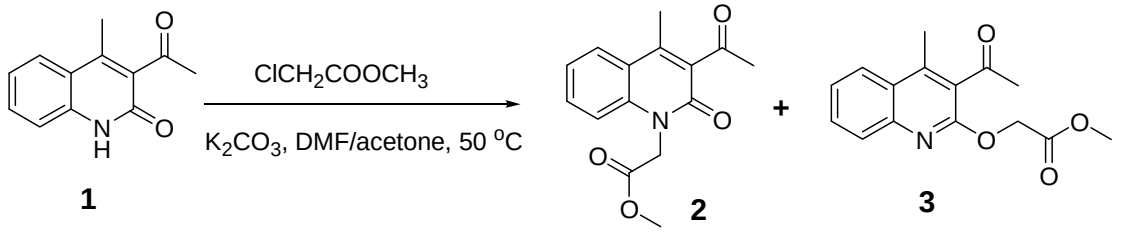
The synthesis of quinoline and its derivatives has attracted considerable attention from organic and medicinal chemists for many years.[1-3] The structural core of quinoline is often found in more complex natural products[4] and is frequently associated with biological activity, such as anti-cancer,[5] antifungal,[6] HIV-1 integrase inhibitors,[7] HIV protease inhibitors[8] antileishmanial activity,[9] NK-3 receptor antagonists[10] 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 asthma[14].

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 Et_3N 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 K_2CO_3 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]

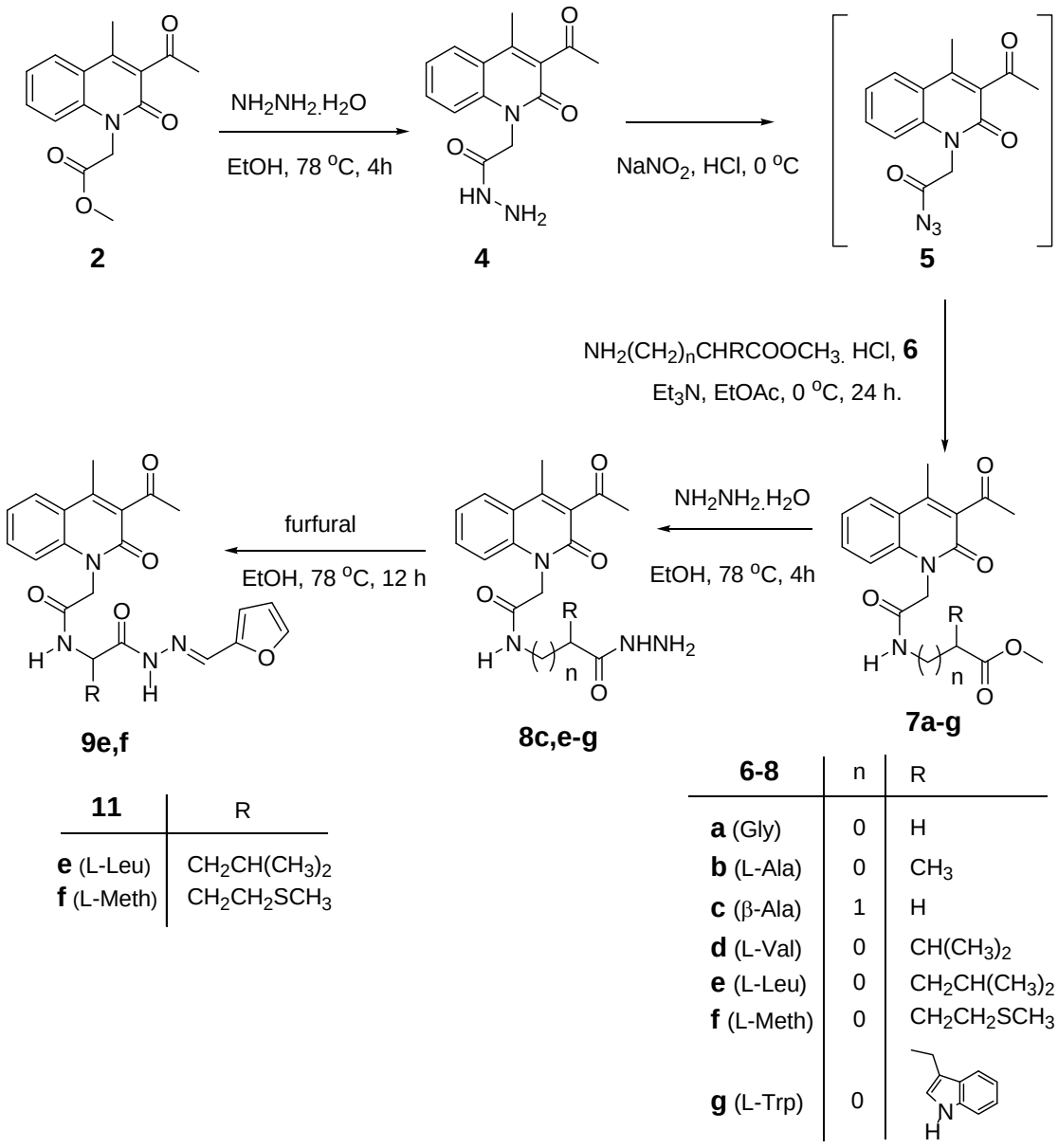


Scheme 1

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 $NaNO_2$ 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).

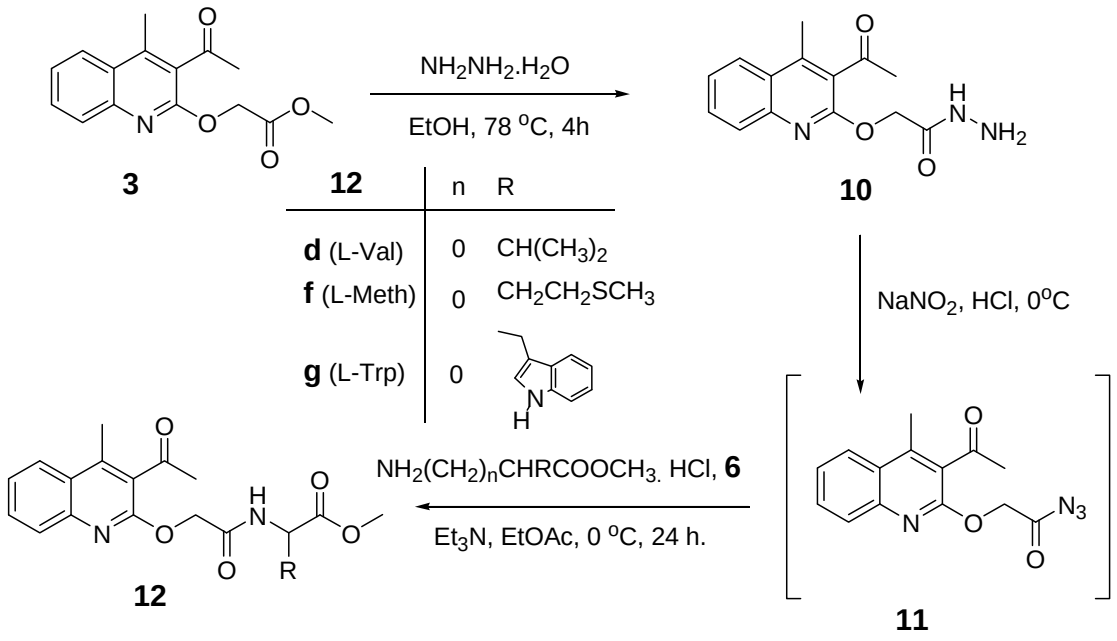


11	R
e (L-Leu)	$CH_2CH(CH_3)_2$
f (L-Meth)	$CH_2CH_2SCH_3$

6-8	n	R
a (Gly)	0	H
b (L-Ala)	0	CH_3
c (β-Ala)	1	H
d (L-Val)	0	$CH(CH_3)_2$
e (L-Leu)	0	$CH_2CH(CH_3)_2$
f (L-Meth)	0	$CH_2CH_2SCH_3$
g (L-Trp)	0	

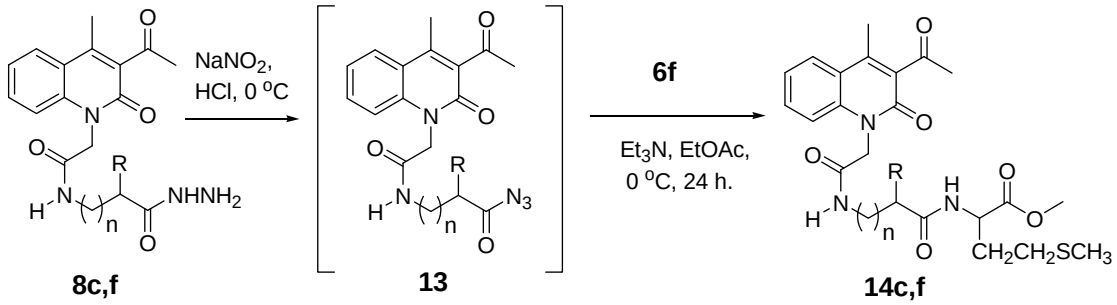
Scheme 2

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 $NaNO_2$ 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).



8, 13, 14	n	R
c	1	H
f	0	$CH_2CH_2SCH_3$

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 ^{1}H NMR spectral and physicochemical analysis,

Figure 1. The ^{1}H NMR spectra clearly confirm the alkylation site for all isolated *O*- and *N*-substituted derivatives. Thus, the ^{1}H NMR spectrum of **7d** gave a singlet signal at 4.96 ppm typically associated with NCH_2. Further more, the ^{1}H 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 ^{1}H 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 ^{1}H NMR patterns. Thus, the ^{1}H NMR spectrum of **12d** showed an interesting two doublets centered at 5.14 and 5.01 ppm (J_{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**.

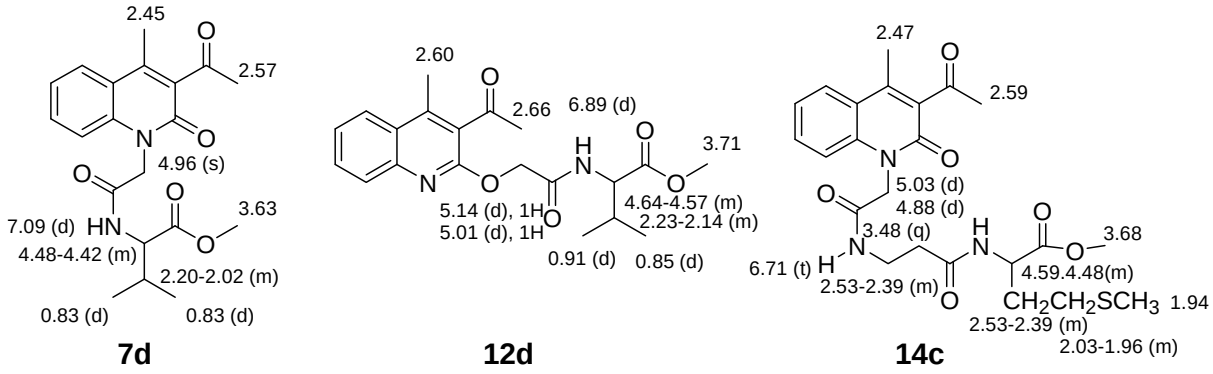


Figure 1. Selected ^{1}H NMR spectral data of amino acid derivatives **7d**, **12d** and dipeptides **14c**.

Experimental Section

General Procedures. Solvent were purified and dried in the usual way. The boiling range of the petroleum ether used was 40-60 ^{o}C. Thin layer chromatography (TLC): silica gel 60 F_{254} 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. ^{1}H 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 $NaNO_2$ (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 % $NaHCO_3$, H_2O and finally dried (Na_2SO_4). A solution of amino acid esters hydrochloride **6** (1.0 mmol) in ethyl acetate (20 mL) containing 0.2 mL of Et_3N 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 $NaHCO_3$ and finally dried (Na_2SO_4). 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.99 (2H, s, NCH_2), 4.00 (2H, d, *J* = 5.4 Hz, $NHC\underline{H}_2$), 3.68 (3H, s, OMe), 2.59 (3H, s, COMe), 2.47 (3H, s, Me), Anal. Calcd. For $C_{17}H_{18}N_2O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 5.01 (1H, d, *J* = 15.6 Hz, NCH_2), 4.90 (1H, d, *J* = 15.6 Hz, NCH_2), 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 $C_{18}H_{20}N_2O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.90 (2H, s, NCH_2), 3.57 (3H, s, OMe), 3.54−3.42 (2H, m, $NHC\underline{H}_2$), 2.58 (3H, s, COMe), 2.48 (2H, t, *J*= 6.2 Hz, CH_2), 2.45 (3H, s, Me). Anal. Calcd. For $C_{18}H_{20}N_2O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.96 (2H, s, NCH_2), 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 $C_{20}H_{24}N_2O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.96 (2H, s, NCH_2), 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.97 (2H, s, NCH_2), 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, CH_2), 2.19-2.03 (2H, m, CH_2) 1.97 (3H, s, SMe). Anal. Calcd. For $C_{20}H_{24}N_2O_5S$ (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-(1*H*-indol-3-yl) propanoate (7g). From azide **5** and L-TrpOMe·HCl **6g**. White crystals 0.25 g, 54 %); mp 138-139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.42 (1H, s, NH, D_2O 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, NCH_2), 4.90 (1H, d, *J* = 15.4 Hz, NCH_2), 4.17−4.06 (1H, m, CH), 3.59 (3H, s, OMe), 3.23−3.01 (2H, m, CH_2), 2.51 (3H, s, COMe), 2.43 (3H, s, Me). Anal. Calcd. For $C_{26}H_{25}N_3O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 5.14 (1H, d, *J* = 15.4 Hz, OCH_2), 5.01 (1H, d, *J* = 15.4 Hz, NCH_2), 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 $C_{20}H_{24}N_2O_5$ (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-MetOCH$_3$·HCl **6f**. White crystals (0.23 g, 57 %); mp 95-96 °C. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 5.12 (1H, d, *J* = 15.2 Hz, NCH_2), 4.96 (1H, d, *J* = 15.2 Hz, NCH_2), 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, CH_2), 2.20-1.92 (5H, m, CH_2, SMe). Anal. Calcd. For $C_{20}H_{24}N_2O_5S$ (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-(1*H*-indol-3-yl) propanoate (12g). From azide **11** and L-TrpOMe·HCl **6g**. White crystals (0.24 g, 52 %); mp 83-84 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.22 (1H, s, NH, D_2O 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, NCH_2, CH), 3.65 (3H, s, OMe), 3.32 (2H, t, *J* = 4.6 Hz, CH_2), 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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 6.71 (1H, t, *J* = 7.0 Hz, NH, D_2O exchangeable), 5.03 (1H, d, *J* = 15.8 Hz, NCH_2), 4.88 (1H, d, *J* = 15.8 Hz, NCH_2), 4.53 (1H, q, *J* = 7.0 Hz, CH), 3.68 (3H, s, OMe), 3.47 (2H, q, *J* = 6.4 Hz, $NHC\underline{H}_2$), 2.59 (3H, s, COMe), 2.53−2.39 (7H, m, Me, CH_2, CH_2), 2.03−1.94 (5H, m, SMe, CH_2). Anal. Calcd. For $C_{23}H_{29}N_3O_6S$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): 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, D_2O exchangeable), 4.97 (2H, s, NCH_2), 4.63 (2H, m, 2CH), 3.73 (3H, s, OMe), 2.57 (3H, s, COMe), 2.51−2.38 (7H, m, Me, CH_2, CH_2), 2.12−1.91 (10H, m, 2xSMe, $2CH_2$). Anal. Calcd. For $C_{25}H_{33}N_3O_6S_2$ (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. ^{1}H NMR (200 MHz, DMSO): δ 9.16 (1H, s, NH, D_2O exchangeable), 8.54 (1H, d, *J* = 8.2 Hz, NH, D_2O 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, NCH_2), 4.91 (1H, d, *J* = 16.6 Hz, NCH_2), 4.28 (2H, bs, NH_2, D_2O exchangeable), 3.55-3.51 (2H, m, $NHCH_2$), 2.51 (3H, s, COMe), 2.42−2.36 (5H, m, CH_2CO, Me). Anal. Calcd. For $C_{17}H_{20}N_4O_4$ (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. ^{1}H NMR (200 MHz, DMSO): δ 9.24 (1H, s, NH, D_2O exchangeable), 8.52 (1H, d, *J* = 8.0 Hz, NH, D_2O 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, NCH_2), 4.91 (1H, d, *J* = 16.4 Hz, NCH_2), 4.35−4.26 (3H, m, CH, NH_2), 2.51 (3H, s, COMe), 2.38 (3H, s, Me), 1.64−1.46 (3H, m, CH_2, CH), 0.91 (3H, d, *J* = 6.2 Hz, Me), 0.82 (3H, d, *J* = 6.0 Hz, Me). Anal. Calcd. For $C_{20}H_{26}N_4O_4$ (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. ^{1}H NMR (200 MHz, DMSO): δ 9.26 (1H, s, NH, D_2O exchangeable), 8.61 (1H, d, *J* = 8.2 Hz, NH, D_2O 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, NCH_2), 4.98 (1H, d, *J* = 16.8 Hz, NCH_2), 4.37−4.24 (3H, m, CH, NH_2), 2.54 (3H, s, COMe), 2.48 (3H, s, Me), 2.40 (2H, t, *J* = 7.0 Hz, CH_2), 2.06 (3H, s, Me), 1.92−1.81 (2H, m, CH_2). Anal. Calcd. For $C_{19}H_{24}N_4O_4S$ (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-(1*H*-indol-3-yl)ethyl] acetamide (8g). White crystals (0.30 g, 65 %); mp 274-275 °C. ^{1}H NMR (200 MHz, DMSO): δ 10.93 (1H, s, NH, D_2O exchangeable), 9.38 (1H, s, NH, D_2O exchangeable), 8.71 (1H, d, *J* = 8.0 Hz, NH, D_2O 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, NCH_2), 4.72 (1H, d, *J* = 16.4 Hz, NCH_2), 4.62−4.46 (1H, m, CH), 4.32 (2H, s, NH_2), 3.23−2.93 (2H, m, CH_2), 2.54 (3H, s, COMe), 2.47 (3H, s, Me). Anal. Calcd. For $C_{19}H_{24}N_4O_4S$ (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. ^{1}H NMR (200 MHz, DMSO): δ 11.48 (1H, s, NH, D_2O exchangeable, structure B), 11.32 (1H, s, NH, D_2O exchangeable, structure A), 8.52 (1H, d, *J* = 7.2 Hz, NH, D_2O exchangeable), 8.11 (1H, s, NH, D_2O 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, D_2O exchangeable, structure A), 5.03 (2H, s, NCH_2), 4.41−4.29 (1H, m, CH), 2.46 (3H, s, COMe), 2.38 (3H, s, Me), 1.82−1.42 (3H, m, CH_2, CH), 0.94 (3H, d, *J* = 6.4 Hz, Me), 0.87 (3H, d, *J* = 6.4 Hz, Me). Anal. Calcd. For $C_{25}H_{28}N_4O_5$ (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. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.52 (1H, s, NH, D_2O exchangeable, structure B), 11.43 (1H, s, NH, D_2O exchangeable, structure A), 8.77 (1H, d, *J* = 8.0 Hz, NH, D_2O exchangeable), 8.14 (1H, s, NH, D_2O 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, D_2O exchangeable, structure A), 5.07 (2H, s, NCH_2), 4.51−5.38 (1H, m, CH), 2.53 (3H, s, COMe), 2.41−2.31 (3H, s, Me, CH_2), 2.18−1.79 (5H, m,

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