Convenient synthesis of 1-substituted-4-methyl-5-oxo [1,2,4]triazolo[4,3-a]quinazolines

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Dedication to Prof. F. M. Hassan for his 70th birthday

Abstract

A new and convenient synthesis of a variety of methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio) acetamido and propanamido alkanoate 8a-h and 9a-c, respectively has been developed via azide and DCC coupling methods. Hydrazinolysis of the ester 8a-g gave the hydrazide 10a-g, which subsequently reacted with furfural to give the hydrazone 11a-f. Compounds 8-11 might show non sedative H1-antihistamines activities. Compounds 8-11 were characterized by elemental analysis, IR, mass and 1H NMR data.

Keywords: Non sedative H1-antihistamines, triazoloquinazoline; amino acids, DCC and azide coupling, hydrazone

Introduction

Triazoloquinazoline condensed derivatives constitute an important class of organic compounds with interesting biological activities. 9-Chloro-2-(2-furyl)-[1,2,4]triazolo-[1,5-c]quinazolin-5-amine, CGS 15943A I, were reported as antagonists at A2b receptors in brain preparations.1-3 Furthermore, a series of novel 1-substituted 4-aryl[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones II was reported as a new class of non sedative H1-antihistamines.4-6 Hydrazone derivatives are reported to possess antimicrobial,7-9 antitubercular,10 anticonvulsant11 and analgesic-anti-inflammatory12,13 activities. Compound III which possesses a hydrazide-hydrazone structure, is used as antimicrobial.7
In view of these facts and in continuation of our efforts in synthesizing various bioactive molecules, we have found it desirable to synthesize a series of 4-methyl-1,2,4-triazolo[4,3-\(a\)]quinazolin-5(4\(H\))-ones containing amino acid ester, hydrazide and hydrazone substituted at position 1 as non sedative H1-antihistamines.

**Results and Discussion**

Due to the ambident nucleophilic character of 4-methyl-1-thioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-\(a\)]quinazolin-5-one (1), we have recently pointed out the regioselective reaction of 1 with electrophiles\(^{14,15}\).

As described in scheme 1, the reaction of triazoloquinazoline 1 with methyl chloroacetate, chloroacetic acid and chloropropanoic acid in the presence of a base afforded the S-alkylation products 2, 5 and 6, respectively. The ester 2 and both acids 5 and 6 are excellent precursors for the simple chemical modification of triazoloquinazoline derivative 1. The ester 2 was boiled with hydrazine hydrate in methyl alcohol to afford the hydrazide 3, which subsequently converted into azide 4 by treatment with NaNO\(_2\) and HCl mixture.
The synthesis of the target thioacetyl amino acid derivatives 8a-g were efficiently formed from key intermediate ester 2 via the azide coupling method,\textsuperscript{16-18} which was reported to minimize the degree of racemization in amino acid coupling. The \textit{in situ} generated azide 4 solution in ethyl acetate reacted with amino acid methyl ester hydrochloride 7 in the presence of triethyl amine to afford the methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido) alkanoate 8a-g in good yield, scheme 2. The structure of amino acid ester S-acetamide 8a-g was chemically confirmed by an equivocal synthesis from the acid derivative 5 via DCC coupling method. The DCC coupling is one of the major tools employed in literature to introduce peptide bonds by the reaction of acid with amino acid methyl ester. Hydroxybenzotriazole (HOBT) is widely used as an additive to decrease racemization in the carbodiimide peptide coupling.\textsuperscript{19-21} Treatment of thioacetic acid 5 or thiopropanoic acid 6 with the amino acid esters hydrochloride 7 in presence of coupling reagents DCC and HOBT afforded amino acid ester S-alkanamide 8a-h and 9a-c, respectively in 58-85 % yield.
Scheme 2

The structure assignment of the amino acid ester S-alkanamide 8a-h and 9a-c is based on spectral and physicochemical analysis, Figure 1. The I.R spectrum of the glycine derivative 8a gave two bands at 3326 and 1742 cm\(^{-1}\) attributed to NH and ester C=O, respectively. Furthermore, the \(^1\)H NMR spectrum of 8a exhibits two singlet signals at \(\delta\) 3.77 and 3.71 ppm corresponding to OCH\(_3\) and NCH\(_3\), respectively. The \(^1\)H NMR for all amino acid derivatives 8a (Gly), 8c (β-Ala), 8d (Ser), 8f (Met), 8g (Val), gave a singlet centered at \(\delta\) ~4.05 ppm attributed to SCH\(_2\), figure 1.

Figure 1. Selected \(^1\)H NMR and I.R data of Methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)acetate (8a).
On the other hand, the $^1$H NMR spectrum of 8b (Ala) and 8e (Leu) shows two doublets at $\delta$ 4.12 and 4.02 ppm ($J_{AB} = 14.6$ and $14.0$ Hz) corresponding to an AB system of the prochiral hydrogen atoms of the SCH$_2$ group.$^{22,23}$

Hydrazinolysis of the amino acid ester 8a-g afforded the hydrazide 10a-g. The hydrazide 10a-g was condensed with furfural to exhibit the hydrazone 11a-g. The structure assignment for both the hydrazide and hydrazone is based on elemental analysis, IR and the $^1$H NMR spectra. The hydrazide 10a-g gave bands at 3343 and 3304 cm$^{-1}$ characteristic for NH$_2$ group. The $^1$H NMR spectrum of hydrazide 10e (Leu) shows two broad signals at $\delta$ 7.93 and $\delta$ 7.53 attributed to both NH groups in the compound. The $^1$H NMR spectra of hydrazone derivatives 11 gave an interesting $^1$H NMR pattern as represented in figure 2. Hydrazones 11 are present either in the form of a single compound structure A; 11b (Ala), and 11f (Meth) or in the form of two tautomeric mixture structure A and structure B; 11a (Gly), 11c ($\beta$-Ala), 11d (Ser) and 11e (Leu).

![Structure A](image1.png)

![Structure B](image2.png)

**Figure 2.** Selected $^1$H NMR of 2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo-[4,3-a]quinazolin-1-ylthio)acetamido)-N'-(furan-2-yl)methylene)acetohydrazide 11a.

The $^1$H NMR spectrum of 11a in DMSO gave two D$_2$O exchangeable broad signals at $\delta$ 11.26 and 8.20 ppm with similar intensities, in addition to two D$_2$O exchangeable broad signals at $\delta$ 11.46 and 3.83 ppm with larger intensities. We might conclude that the hydrazones 11a solution in DMSO are present in the form of two tautomers (structure A) and (structure B) with intramolecular hydrogen bonds of the type N–H···N=C stabilizing each form$^{22-24}$ in 1:2. ratio, respectively. The participation of the NH group in the N–H···N=C system is confirmed by a signal at $\delta$ 11.26 (structure A). Structure B is induced by enolization of the hydrazide carbonyl which gave a signal at $\delta$ 11.46 and 3.83 ppm corresponding to NH group and an exocyclic OH group, respectively. The $^1$H NMR spectrum of 11b gave two NH signals at $\delta$ 11.31 and 8.17 ppm corresponding to hydrazone in the form of structure A.
Conclusions

A variety of methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinaz-olin-1-yl-thio) acetamido and propanamido alkanoate 8a-h and 9a-c, respectively has been developed via azide and DCC coupling methods. Hydrazinolysis of amino acid esters 8a-g afforded the corresponding hydrazide 10a-g, which subsequently reacted with furfural to give the hydrazone 11a-f. Compounds 8-11 might show non sedative H1-antihistamines activities.

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. NMR spectra measured with Bruker (200 MHz). TMS (0.00 ppm) as internal standard. The mass spectra were measured with a KRATOS Analytical Kompack spectrometer. Microanalyses were performed at the Microanalytical Center, Chemistry Department, Konstanz University, Germany and Microanalytical Center, Cairo University. FTIR spectra (υ/cm-1) were taken on a Genesis (Unicam) spectrometer in potassium bromide pellets.

The starting compounds 1, 2, 5 and 6 were prepared according to the method described by Fathalla et al.14

2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ythio)aceto-hydrazide (3). To a solution of ester 2 (3.04 g, 1.0 mmol) in methyl alcohol (30 mL), hydrazine hydrate (2.4 mL, 5 mmol) was added. The reaction mixture was refluxed for 4 hours, cooled and the resultant precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazide.

White crystals (1.46 g, 48 %); mp 247-248 °C. 1H NMR (200 MHz, DMSO): δ 9.14 (1H, s, NH, D2O exchangeable), 8.56 (1H, d, J = 8.2 Hz, ArH), 8.22 (1H, d, J = 8.0 Hz, ArH), 7.93 (1H, t, J = 8.0 Hz, ArH), 7.62 (1H, t, J = 8.0 Hz, ArH), 4.25 (2H, bs, NH2, D2O exchangeable), 4.06 (2H, s, SCH2), 3.60 (3H, s, NCH3), IR (KBr) cm-1: 3332, 3262 (NH), 1725, 1681 (C=O), 1614 (C=N); Anal. Calcd. For C12H12N6O2S (304.3): C, 47.37 %; H, 3.95 %; N, 27.63 %; S, 10.54 %. Found: C, 47.41 %; H, 4.03 %; N, 27.63 %; S, 10.39 %, Mass spectrum, m/z (Iv/%): 304 (54), 273 (16), 232 (100), 231 (10), 162 (28), 145 (58), 134 (16), 90 (48).

Method A. Azide method. General procedure

To a cold solution (-5 °C) of hydrazide 3 (0.3 g, 1.0 mmol) in AcOH (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of NaN3 (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 (1.0 mmol) in ethyl acetate (20 mL) containing 0.2 mL of triethyl amine 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.

**Method B. DCC method. General procedure**

To a cold solution (-5 °C) of the amino acid methyl ester hydrochloride (1.0 mmol) in acetonitrile (6 mL) containing triethyl amine (0.14 mL, 1.0 mmol), 2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetic acid (5) (0.29 g, 1.0 mmol) or 3-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)-propanoic acid (6) (0.31 g, 1.0 mmol), dicyclohexylcarbodiimide (DCC) (0.207 g, 1.0 mmol) and hydroxybenzotriazole (HOBT) (0.135 g, 1.0 mmol) were added successively. The reaction mixture was stirred at 0 °C for one hour, at 5 °C for one hour, then at room temperature for 8 hours. The reaction mixture was set aside overnight. The precipitated dicyclohexylurea was filtered off and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, filtered and the filtrate was wash with saturated sodium chloride solution, 5% NaHCO₃, 1N HCl and saturated solution of sodium chloride then dried over anhydrous sodium sulphate. After evaporation of the solvent, the remaining oily residue was triturated with petroleum ether (b.p. 40-60 °C) at 0°C with scratching, afterwards the formed solid was filtered off and crystallized from petroleum ether/ethyl acetate.

**Methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)acetate (8a).** From GlyOCH₃·HCl 7a (0.126 g). Method A, white crystals (0.23 g, 66%); mp 120–121 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.42 (1H, d, J = 8.0 Hz, ArH), 8.22 (1H, d, J = 8.4 Hz, ArH), 8.02 (1H, bs, NH, D₂O exchangeable), 7.84 (1H, t, J = 8.4 Hz, ArH), 7.57 (1H, t, J = 8.0 Hz, ArH), 8.01 (1H, bs, NH, D₂O exchangeable), 7.85 (1H, t, J = 8.4 Hz, ArH), 7.58 (1H, t, J = 8.0 Hz, ArH), 8.01 (1H, bs, NH, D₂O exchangeable). 1H NMR (200 MHz, CDCl₃): δ 8.44 (1H, d, J = 7.8 Hz, ArH), 8.26 (1H, d, J = 8.2 Hz, ArH), 7.92 (1H, bs, NH, D₂O exchangeable), 7.85 (1H, t, J = 8.0 Hz, ArH), 7.58 (1H, t, J = 7.8 Hz, ArH), 4.63-4.48 (1H, m, CH), 4.12 (1H, d, J = 14.6 Hz, SCH₂), 4.02 (1H, d, J = 14.6 Hz, SCH₂), 3.79 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 1.42 (3H, d, J = 7.2 Hz, CH₃), IR (KBr) cm⁻¹: 3326 (NH), 1748, 1679, 1660 (C=O), 1614 (C=N); Anal. Calcd. For C₁₅H₁₅N₅O₄S (361.4): C, 49.85 %; H, 4.18 %; N, 19.38 %; Found: C, 49.63 %; H, 4.05 %; N, 19.22 %.

Method B, From 5 and GlyOCH₃·HCl 7a (0.27 g, 75%).

**Methyl 2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)propanoate (8b).** From L-AlaOCH₃·HCl 7b (0.14 g). Method A, white crystals (0.19 g, 54%); mp 114°C. ¹H NMR (200 MHz, CDCl₃): δ 8.44 (1H, d, J = 7.8 Hz, ArH), 8.26 (1H, d, J = 8.2 Hz, ArH), 7.92 (1H, bs, NH, D₂O exchangeable), 7.85 (1H, t, J = 8.0 Hz, ArH), 7.58 (1H, t, J = 7.8 Hz, ArH), 4.63-4.48 (1H, m, CH), 4.12 (1H, d, J = 14.6 Hz, SCH₂), 4.02 (1H, d, J = 14.6 Hz, SCH₂), 3.79 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 1.42 (3H, d, J = 7.2 Hz, CH₃), IR (KBr) cm⁻¹: 3326 (NH), 1748, 1679, 1660 (C=O), 1614 (C=N); Anal. Calcd. For C₁₅H₁₅N₅O₄S (375.4): C, 51.19 %; H, 4.56 5; N, 18.66 %; Found: C, 50.89 %; H, 4.41 %; N, 18.31 %.

Method B, From 5 and L-AlaOCH₃·HCl 7b (0.17 g, 46%).
Methyl 3-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)propanoate (8c). From β-AlaOCH₃·HCl 7c (0.14 g). Method A, white crystals (0.28 g, 75 %); mp 170–171 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.45 (1H, d, J = 8.0 Hz, ArH), 8.26 (1H, d, J = 8.6 Hz, ArH), 7.85 (1H, t, J = 8.4 Hz, ArH), 7.64 (1H, bs, NH, D₂O exchangeable), 7.38 (1H, t, J = 8.0 Hz, ArH), 4.04 (2H, s, SCH₂), 3.79 (3H, s, OCH₃), 3.67 (3H, s, NCH₃), 3.55 (2H, q, J = 6.6 Hz, CH₂), 2.55 (2H, t, J = 6.4 Hz, CH₂); IR (KBr) cm⁻¹: 3313 (NH), 1747, 1675, (C=O), 1612 (C=N); Anal. Calcd. For C₁₆H₁₇N₅O₄S, (375.4): C, 51.19 %; H, 4.56 %; N, 18.66 %; Found: C, 50.83 %; H, 4.34 %; N, 18.21 %.

Method B, From 5 and β-AlaOCH₃·HCl 7c (0.30 g, 82 %).

Methyl 2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)-3-hydroxypropanoate (8d). From L-SerOCH₃·HCl 7d (0.156 g). Method A, white crystals (0.18 g, 45 %); mp 198–199 °C. ¹H NMR (200 MHz, DMSO): δ 8.66 (1H, d, J = 7.2 Hz, NH, D₂O exchangeable), 8.58 (1H, d, J = 8.0 Hz, ArH), 8.28 (1H, d, J = 8.4 Hz, ArH), 7.98 (1H, t, J = 8.4 Hz, ArH), 7.65 (1H, t, J = 8.2 Hz, ArH), 5.08 (1H, t, J = 4.2 Hz, OH, D₂O exchangeable), 4.56–4.23 (1H, m, CH), 4.12 (2H, s, SCH₂), 3.73–3.48 (5H, m, OCH₃, OCH₂), 3.34 (3H, s, NCH₃), IR (KBr) cm⁻¹: 3321 (NH), 3358 (OH), 1746, 1682 (C=O), 1614 (C=N); Anal. Calcd. For C₁₆H₁₇N₅O₅S, (391.4): C, 49.10 %; H, 4.38 %; N, 17.89 %; Found: C, 48.84 %; H, 4.23 %; N, 17.75 %.

Method B, From 5 and SerOCH₃·HCl 7d (0.22 g, 58 %).

Methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)-4-methylpentanoate (8e). From L-LeuOCH₃·HCl 7e (0.182 g). Method A, yellow crystals (0.14 g, 34 %); mp 144–145 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.43 (1H, d, J = 7.8 Hz, ArH), 8.26 (1H, d, J = 8.2 Hz, ArH), 7.84 (1H, t, J = 8.4 Hz, ArH), 7.73 (1H, d, NH, J = 7.8 Hz, D₂O exchangeable), 7.58 (1H, t, J = 8.2 Hz, ArH), 5.12 (1H, d, J = 4.2 Hz, OH, D₂O exchangeable), 4.62–4.51 (1H, m, CH), 4.12 (1H, d, J = 14.4 Hz, SCH₂), 3.78 (3H, s, OCH₃), 3.68 (3H, s, NCH₃), 1.69–1.53 (2H, m, CH₂), 0.98–0.83 (1H, m, CH) 0.89 (6H, d, J = 6.0 Hz, 2CH₃), IR (KBr) cm⁻¹: 3329 (NH), 3358 (OH), 1746, 1682 (C=O), 1614 (C=N); Anal. Calcd. For C₁₉H₂₃N₅O₄S, (417.5): C, 54.66 %; H, 5.55 %; N, 16.78 %; Found: C, 54.51 %; H, 5.53 %; N, 16.77 %.

Method B, From 5 and LeuOCH₃·HCl 7e (0.26 g, 64 %).

Methyl 2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)-4-(methylthio)butanoate (8f). From L-MetOCH₃·HCl 7f (0.20 g). Method A, white crystals (0.25 g, 58 %); mp 148–149 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.43 (1H, d, J = 7.8 Hz, ArH), 8.26 (1H, d, J = 8.2 Hz, ArH), 7.84 (1H, t, J = 8.4 Hz, ArH), 7.73 (1H, d, NH, J = 7.8 Hz, D₂O exchangeable), 7.58 (1H, t, J = 8.2 Hz, ArH), 7.57 (1H, d, J = 8.0 Hz, NH, D₂O exchangeable), 4.57–4.45 (1H, m, CH), 4.12 (1H, d, J = 14.4 Hz, SCh₂), 4.04 (1H, d, J = 14.4 Hz, SCH₂), 3.78 (3H, s, OCH₃), 3.68 (3H, s, NCH₃), 1.69–1.53 (2H, m, CH₂), 0.98–0.83 (1H, m, CH) 0.89 (6H, d, J = 6.0 Hz, 2CH₃), IR (KBr) cm⁻¹: 3329 (NH), 1746, 1671 (C=O), 1613 (C=N); Anal. Calcd. For C₁₈H₂₁N₅O₄S₂, (435.5): C, 49.66 %; H, 5.55 %; N, 16.78 %; Found: C, 49.51 %; H, 5.53 %; N, 16.77 %.

Method B, From 5 and MetOCH₃·HCl 7f (0.32 g, 74 %).
Methyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)-3-methylbutanoate (8g). From L-ValOCH₃·HCl 7g (0.168 g). Method A, white crystals (0.21 g, 51 %); mp 94–95 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.45 (1H, d, J = 7.8 Hz, ArH), 8.25 (1H, d, J = 8.2 Hz, ArH), 7.93 (1H, bs, NH, D₂O exchangeable), 7.84 (1H, t, J = 8.2 Hz, ArH), 7.58 (1H, t, J = 7.6 Hz, ArH), 4.53-4.46 (1H, m, CH), 4.09 (2H, s, SCH₂), 3.79 (3H, s, OCH₃), 2.29-2.12 (1H, m, CH), 0.92 (6H, d, J = 6.6 Hz, 2CH₃), IR (KBr) cm⁻¹: 3323 (NH), 1748, 1676 (C=O), 1612 (C=N); Anal. Calcd. For C₁₈H₂₁N₅O₄S (403.5): C, 53.59 %; H, 5.25 %; N, 17.36 %; Found: C, 53.36 %; H, 5.18 %; N, 17.14 %.

Ethyl-2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)acetamido)-3-methylbutanoate (8h). Method B, from 5 and DL-ValOC₂H₅·HCl 7h (0.182 g), white crystals (0.18 g, 44%), mp 98–99 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.45 (1H, d, J = 7.8 Hz, ArH), 8.24 (1H, d, J = 8.2 Hz, ArH), 7.90 (1H, bs, NH, D₂O exchangeable), 7.84 (1H, t, J = 8.2 Hz, ArH), 7.56 (1H, t, J = 7.6 Hz, ArH), 4.64-4.48 (1H, m, CH), 4.28 (2H, q, J = 7.2 Hz, CH₂), 4.11 (2H, s, SCH₂), 3.72 (3H, s, NCH₃), 2.29-2.10 (1H, m, CH), 1.22-0.92 (9H, m, 3CH₃), IR (KBr) cm⁻¹: 3299 (NH), 1743, 1681, 1659 (C=O), 1612 (C=N); Anal. Calcd. For C₁₉H₂₃N₅O₄S (417.47): C, 54.66 %; H, 5.55 %; N, 16.78 %; Found: C, 54.50 %; H, 5.42 %; N, 16.69 %. Mass spectrum, m/z (Ir/%) 419 (64), 418 (75), 417 (100), 375 (38), 345 (12), 344 (51), 273 (100), 241 (18), 162 (25), 145 (67), 90 (66).

Methyl 2-(3-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)propanamido)acetate (9a). Method B, from 6 and GlyOCH₃·HCl 7a (0.126 g). yellow crystals (0.31 g, 85 %); mp 92–93 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.37 (1H, d, J = 8.0 Hz, ArH), 7.78 (1H, d, J = 8.2 Hz, ArH), 7.63 (1H, t, J = 8.2 Hz, ArH), 7.50 (1H, t, J = 8.0 Hz, ArH), 7.09 (1H, bs, NH, D₂O exchangeable), 4.11 (2H, d, J = 5.4 Hz, CH₂), 3.75 (3H, s, OCH₃), 3.72 (3H, s, NCH₃), 3.59 (2H, t, J = 7.1 Hz, SCH₂), 2.86 (2H, t, J = 7.1 Hz, CH₂), IR (KBr) cm⁻¹: 3303 (NH), 1742, 1677 (C=O), 1608 (C=N); Anal. Calcd. For C₁₆H₁₇N₅O₄S (375.4): C, 51.19 %; H, 4.56 %; N, 18.66 %; Found: C, 51.03 %; H, 4.38 %; N, 18.43 %.

Methyl 3-(3-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)propanamido)propanoate (9b). Method B, From 6 and β-AlaOCH₃·HCl 7c (0.14 g), white crystals (0.30 g, 79 %); mp 105–106 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.42 (1H, d, J = 8.0 Hz, ArH), 7.81 (1H, d, J = 8.4 Hz, ArH), 7.67 (1H, t, J = 8.4 Hz, ArH), 7.54 (1H, t, J = 8.0 Hz, ArH), 6.65 (1H, bs, NH, D₂O exchangeable), 4.16 (2H, d, J = 5.4 Hz, CH₂), 3.75 (3H, s, OCH₃), 3.72 (3H, s, NCH₃), 3.59 (2H, t, J = 7.1 Hz, SCH₂), 2.80 (2H, t, J = 7.1 Hz, CH₂), 2.61 (2H, t, J = 7.1 Hz, CH₂), IR (KBr) cm⁻¹: 3312 (NH), 1748, 1665 (C=O), 1614 (C=N); Anal. Calcd. For C₁₇H₁₉N₅O₄S (389.4): C, 52.43 %; H, 4.92 %; N, 17.98 %; Found: C, 52.24 %; H, 4.76 %; N, 17.74 %.

Methyl 2-(3-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-yl-thio)propanamido)-3-hydroxypropanoate (9c). Method B, From 6 and L-SerOCH₃·HCl 7d (0.156 g). yellow crystals (0.29 g, 72 %); mp 129–130 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.39 (1H, d, J = 8.0 Hz, ArH), 8.24 (1H, d, J = 7.2 Hz, NH, D₂O exchangeable), 7.78 (1H, d, J = 8.4 Hz, ArH), 7.68 (1H, t, J = 8.4 Hz, ArH), 7.56 (1H, t, J = 8.0 Hz, ArH), 6.74 (1H, t, J = 4.2 Hz, OH, D₂O...
exchangeable), 4.56-4.23 (1H, m, CH), 3.78 (3H, s, OCH₃), 3.59 (3H, s, NCH₃), 3.52 (2H, t, \(J = 7.1\) Hz, SCH₂), 2.86 (2H, t, \(J = 7.1\) Hz, CH₂) ; 1.96 (2H, t, \(J = 5.2\) Hz, CH₂O), IR (KBr) cm⁻¹: 3318 (NH), 3475 (OH), 1742, 1676 (C=O), 1612 (C=N); Anal. Calcd. For C₁₇H₁₉N₅O₅S, (405.4): C, 50.36 %; H, 4.72 %; N, 17.27 %; Found: C, 50.34 %; H, 4.68 %; N, 17.14 %.

**Hydrazide. General method**

To a solution of thioacetyl amino acid derivatives 8a-g (1.0 mmol) in methyl 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-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetamido) acetohydrazide (10a). Colorless crystals (0.3 g, 82 %); mp 243–244 °C. ¹H NMR (200 MHz, CDCl₃): δ 8.45 (1H, d, \(J = 7.9\) Hz, ArH), 8.23 (1H, d, \(J = 8.0\) Hz, ArH), 7.97 (1H, bs, NH, D₂O exchangeable), 7.83 (1H, t, \(J = 8.0\) Hz, ArH), 7.68 (1H, bs, NH, D₂O exchangeable), 7.59 (1H, t, \(J = 8.0\) Hz, ArH), 4.14 (2H, s, SCH₂), 4.09 (2H, d, \(J = 5.4\) Hz, NHCH₂), 3.68 (3H, s, NCH₃), IR (KBr) cm⁻¹: 3324, 3277, 3090 (NH), 1695, 1671 (C=O), 1612 (C=N); Anal. Calcd. For C₁₄H₁₅N₇O₃S (361.4): C, 46.53 %; H, 4.18 %; N, 27.13 %; Found: C, 46.48 %; H, 4.06 %; N, 26.94 %.

3-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetamido) propanehydrazide (10c). Colorless crystals (0.34 g, 91 %); mp 244–245 °C. ¹H NMR (200 MHz, DMSO): δ 9.12 (1H, s, NH, D₂O exchangeable), 8.54 (1H, d, \(J = 8.0\) Hz, ArH), 8.46 (1H, d, \(J = 7.2\) Hz, NH, D₂O exchangeable), 8.26 (1H, d, \(J = 7.8\) Hz, ArH), 7.97 (1H, t, \(J = 7.8\) Hz, ArH), 7.63 (1H, t, \(J = 7.8\) Hz, ArH), 4.32-4.13 (3H, m, CH, NH₂), 4.05 (2H, s, SCH₂), 3.59 (3H, s, NCH₃), 1.15 (3H, d, \(J = 7.0\) Hz, CH₃), IR (KBr) cm⁻¹: 3332, 3288, 3090 (NH), 1693, 1668 (C=O), 1614 (C=N); Anal. Calcd. For C₁₅H₁₇N₇O₃S (375.4): C, 47.99 %; H, 4.56 %; N, 26.12 %; Found: C, 47.86 %; H, 4.51 %; N, 26.11 %.

2-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetamido)-3-hydroxypropanehydrazide (10d). Colorless crystals (0.25 g, 64 %); mp 222–223 °C. ¹H NMR (200 MHz, DMSO): δ 9.12 (1H, bs, NH, D₂O exchangeable), 8.56 (1H, d, \(J = 8.2\) Hz, ArH), 8.35
(1H, d, J = 8.6 Hz, NH, D2O exchangeable), 8.28 (1H, d, J = 8.0 Hz, ArH), 7.98 (1H, t, J = 7.9 Hz, ArH), 7.64 (1H, t, J = 8.0 Hz, ArH), 4.87 (1H, t, J = 5.2 Hz, OH, D2O exchangeable), 4.37-4.13 (3H, m, CH, NH2), 4.10 (2H, s, SCH2), 3.60 (3H, s, NCH3), 3.52 (2H, t, J = 5.8 Hz, CH2), IR (KBr) cm⁻¹: 3343, 3304, 3072 (NH), 1691, 1673 (C=O), 1613 (C=N); Anal. Calcd. For C15H17N7O4S (391.4): C, 46.03 %; H, 4.38 %; N, 25.05 %; Found: C, 45.94 %; H, 4.26 %; N, 25.03 %.

2-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetamido)-4-methylpentanehydrazide (10e). Colorless crystals (0.28 g, 69 %); mp 194–195 °C. 1H NMR (200 MHz, CDCl3): δ 8.36 (1H, d, J = 7.9 Hz, ArH), 8.19 (1H, d, J = 8.0 Hz, ArH), 7.57 (1H, bs, NH, D2O exchangeable), 7.52 (1H, t, J = 8.0 Hz, ArH), 4.48-4.35 (1H, m, CH), 3.99 (2H, s, SCH2), 3.71 (3H, s, NCH3), 1.79-1.46 (3H, m, CH2, CH), 0.84 (6H, d, J = 6.0 Hz, 2CH3), IR (KBr) cm⁻¹: 3301, 3289, 3055 (NH), 1680, 1660 (C=O), 1612 (C=N); Anal. Calcd. For C18H23N7O3S (417.5): C, 51.78 %; H, 5.55 %; N, 23.49 %; Found: C, 51.67 %; H, 5.41 %; N, 23.48 %.

2-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acetamido)-4-(methylthio)butanehydrazide (10f). Colorless crystals (0.24 g, 56 %); mp 216–217 °C. 1H NMR (200 MHz, DMSO): δ 9.11(1H, s, NH, D2O exchangeable), 8.53 (1H, d, J = 8.2 Hz, ArH), 8.36 (1H, d, J = 7.2 Hz, NH, D2O exchangeable), 8.23 (1H, d, J = 8.0 Hz, ArH), 7.94 (1H, t, J = 8.0 Hz, ArH), 7.64 (1H, t, J = 8.2 Hz, NH, D2O exchangeable), 4.36-4.10 (3H, m, CH, NH2), 4.12 (2H, s, SCH2), 3.72 (2H, t, J = 7.2 Hz, CH2), 3.60 (3H, s, NCH3), 2.47 (2H, t, J = 7.2 Hz, CH2), 2.05 (3H, s, SCH3), IR (KBr) cm⁻¹: 3328, 3295, 3070 (NH), 1691, 1678 (C=O), 1614 (C=N); Anal. Calcd. For C17H21N7O3S2 (435.5): C, 46.88 %; H, 4.86 %; N, 22.51 %; Found: C, 46.63 %; H, 4.74 %; N, 22.48 %.

Condensation with furfural. General method
To a solution of hydrazide 10 (1.0 mmol) in absolute ethyl alcohol (30 mL), furfural (0.09 mL, 1.0 mmol) was added. The reaction mixture was refluxed for 12 hours. The reaction mixture...
was cooled and the formed precipitate was filtered off, washed with ethanol and ether then crystallized from aqueous ethanol to yield the hydrazone 11.

2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acet-amido)-N'-(furan-2-yl)methylene)acetohydrazide (11a). Colorless crystals (0.39 g, 90 %); mp 281–282 °C. ¹H NMR (200 MHz, DMSO): δ 11.46 (1H, bs, NH, D₂O exchangeable, structure B), 11.26 (1H, bs, NH, D₂O exchangeable, structure A), 8.68-8.46 (2H, m, ArH), 8.29 (1H, d, J = 8.0 Hz, ArH), 8.20 (1H, bs, NH, D₂O exchangeable, structure A), 8.0 (1H, t, J = 8.0 Hz, ArH), 7.84 (2H, d, J = 8.0 Hz, CH furyl), 7.65 (1H, t, J = 8.0 Hz, ArH), 6.82-6.79 (1H, m, CH furyl), 6.78-6.51 (1H, m, CH furyl), 4.15 (4H, s, NHCH₂, SCH₂), 3.82 (1H, bs, NH, D₂O exchangeable, structure B), 3.62 (3H, s, NCH₃), IR (KBr) cm⁻¹: 3305, 3209 (NH), 3427 (OH), 1698, 1670 (C=O), 1612 (C=N); Anal. Calcd. For C₁₉H₁₇N₇O₄S, (439.4): C, 51.93 %; H, 3.90 %; N, 22.31 %; Found: C, 51.78 %; H, 3.84 %; N, 22.26 %. Mass spectrum, m/z (Ir/%): 441 (14, M+2), 440 (12, M+1), 439 (11, M), 330 (67), 302 (15), 273 (22), 245 (31), 232 (100), 222 (100), 208 (8), 200 (9), 174 (26), 166 (17), 160 (14), 152 (30), 145 (26), 137 (15), 131 (11), 109 (13), 104 (19), 99 (17), 94 (8), 76 (8), 74 (8), 66 (6).

N-[1-(Furan-2-ylmethylene-hydrazinocarbonyl)-ethyl]-2-(4-methyl-5-oxo-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinazolin-1-ylsulfanyl)-acetamide (11b). Colorless crystals (0.43 g, 95 %); mp 254-255 °C. ¹H NMR (200 MHz, DMSO): δ 11.31 (1H, s, NH, D₂O exchangeable, structure A), 8.71-8.46 (2H, m, ArH), 8.27 (1H, d, J = 8.0 Hz, ArH), 8.17 (1H, s, NH, D₂O exchangeable, structure A), 7.97 (1H, t, J = 8.1 Hz, ArH), 7.84 (1H, t, J = 7.4 Hz, CH furyl), 7.63 (1H, t, J = 7.4 Hz, ArH), 6.96-6.81 (1H, m, CH furyl), 6.67-6.53 (1H, m, CH furyl), 4.33-4.22 (1H, m, CH), 4.07 (2H, s, SCH₂), 3.60 (3H, s, NCH₃), 1.23 (3H, t, J = 7.0 Hz, CH₃), IR (KBr) cm⁻¹: 3305, 3230 (NH), 1691, 1676 (C=O), 1614 (C=N); Anal. Calcd. For C₂₀H₁₉N₇O₄S (453.5): C, 52.97 %; H, 4.22 %; N, 21.62 %; Found: C, 52.86 %; H, 4.11 %; N, 21.29 %. Mass spectrum, m/z (Ir/%): 444 (14, M+2), 440 (12, M+1), 439 (11, M), 330 (67), 302 (15), 273 (22), 245 (31), 232 (100), 222 (100), 208 (8), 200 (9), 174 (26), 166 (17), 160 (14), 152 (30), 145 (26), 137 (15), 131 (11), 109 (13), 104 (19), 99 (17), 94 (8), 76 (8), 74 (8), 67 (6).

3-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acet-amido)-N'-(furan-2-yl)methylene)propanehydrazide (11c). Colorless crystals (0.36 g, 81 %); mp 245–246 °C. ¹H NMR (200 MHz, DMSO): δ 11.46 (1H, s, NH, D₂O exchangeable, structure A), 8.71-8.46 (2H, m, ArH), 8.27 (1H, d, J = 8.0 Hz, ArH), 8.17 (1H, s, NH, D₂O exchangeable, structure A), 7.97 (1H, t, J = 8.1 Hz, ArH), 7.84 (1H, t, J = 7.4 Hz, CH furyl), 7.63 (1H, t, J = 7.4 Hz, ArH), 6.96-6.81 (1H, m, CH furyl), 6.67-6.53 (1H, m, CH furyl), 4.33-4.22 (1H, m, CH), 4.07 (2H, s, SCH₂), 3.60 (3H, s, NCH₃), 2.53 (2H, t, J = 7.0 Hz, CH₃), IR (KBr) cm⁻¹: 3321, 3295 (NH), 1691, 1683 (C=O), 1614 (C=N); Anal. Calcd. For C₂₀H₁₉N₇O₄S (453.5): C, 52.97 %; H, 4.22 %; N, 21.62 %; Found: C, 52.92 %; H, 4.13 %; N, 21.44 %.

2-(2-(4,5-dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acet-amido)-N'-(furan-2-yl)methylene)-3-hydroxypropanehydrazide (11d). Colorless crystals (0.37 g, 79 %); mp 242–243 °C. ¹H NMR (200 MHz, DMSO): δ 11.38 (1H, s, NH, D₂O exchangeable, structure B), 8.86-8.66 (2H, m, ArH), 8.28 (1H, d, J = 8.0 Hz, ArH), 7.84 (1H, t, J = 8.0 Hz, ArH), 6.82-6.79 (1H, m, CH furyl), 6.78-6.51 (1H, m, CH furyl), 4.15 (4H, s, NHCH₂, SCH₂), 3.62 (3H, s, NCH₃), 2.53 (2H, t, J = 7.0 Hz, CH₃), IR (KBr) cm⁻¹: 3321, 3295 (NH), 1691, 1683 (C=O), 1612 (C=N); Anal. Calcd. For C₂₀H₁₉N₇O₄S (453.5): C, 52.97 %; H, 4.22 %; N, 21.62 %; Found: C, 52.92 %; H, 4.13 %; N, 21.44 %.
B), 11.30 (1H, s, NH, D_2O exchangeable, structure A), 8.56 (1H, d, J = 8.0 Hz, ArH), 8.24 (1H, d, J = 8.0 Hz, ArH), 8.21 (1H, bs, NH, D_2O exchangeable, structure A), 7.98-7.63 (3H, m, 2ArH, CH furyl), 6.98-6.87 (1H, m, CH furyl), 6.69-6.57 (1H, m, CH furyl), 5.18-5.03 (1H, m, OH, D_2O exchangeable), 4.43-4.23 (1H, m, CH), 4.12 (2H, m, SCH_2), 3.70-3.56 (5H, m, NCH_3, OCH_2), 3.12 (1H, bs, OH, structure B), IR (KBr) cm\(^{-1}\): 3265, 3215 (NH), 1680, 1656 (C=O), 1614 (C=N); Anal. Calcd. For C_{20}H_{19}N_{7}O_{5}S (469.5): C, 51.17 %; H, 4.08 %; N, 20.88 %; Found: C, 50.94 %; H, 4.01 %; N, 20.65 %. Mass spectrum, m/z (Ir/%): 292 (5), 290 (19), 289 (16), 273 (16), 245 (50), 232 (100), 203 (14), 200 (31), 162 (50), 159 (14), 145 (62), 137 (6), 130 (6), 129 (6), 109 (6), 104 (26), 94 (37), 74 (13), 67 (7). 66 (21).

2-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acet-amido)-N’-((furan-2-yl)methylene)-4-methylpentanehydrazide (11e). Colorless crystals (0.45 g, 92 %); mp 230–231 °C. \(^{1}\)H NMR (200 MHz, DMSO): \(\delta\) 11.37 (1H, s, NH, D_2O exchangeable, structure B), 11.25 (1H, s, NH, D_2O exchangeable, structure A), 8.60 (1H, d, J = 8.0 Hz, ArH), 8.35-8.20 (1H, m, ArH), 8.16 (1H, s, NH, D_2O exchangeable, structure B), 8.05-7.55 (3H, m, 2ArH, CH furyl), 6.84 (1H, dd, \(J_{\text{gem}} = 3.2\), \(J_{1,2} = 13.2\) Hz, CH furyl), 6.64-6.55 (1H, m, CH furyl), 4.36-4.28 (1H, m, CH), 4.07 (2H, s, SCH_2), 3.60 (3H, s, NCH_3), 1.62-1.34 (3H, m, CH, CH_2), 0.86 (6H, dd, \(J = 6.0\) Hz, 2CH_3), IR (KBr) cm\(^{-1}\): 3263, 3203 (NH), 1682, 1650 (C=O), 1612 (C=N); Anal. Calcd. For C_{23}H_{25}N_{7}O_{4}S (495.6): C, 55.74 %; H, 5.08 %; N, 19.79 %; Found: C, 55.68 %; H, 5.04 %; N, 19.67 %. Mass spectrum, m/z (Ir/%): 497 (9, M+1), 496 (11, M), 386 (21), 273 (34), 288 (2), 264 (5), 245 (18), 232 (100), 229 (3), 222 (27), 200 (61), 187 (4), 159 (29), 156 (12), 155 (18), 145 (71), 137 (18), 109 (10), 104 (34), 94 (39), 76 (4), 74 (6), 67 (3).

2-(2-(4,5-Dihydro-4-methyl-5-oxo-[1,2,4]triazolo[4,3-a]quinazolin-1-ylthio)acet-amido)-N'-(furan-2-yl)methylene)-4-(methylthio)butanehydrazide (11f). Colorless crystals (0.43 g, 85 %); mp 252–253 °C. \(^{1}\)H NMR (200 MHz, DMSO): \(\delta\) 11.36 (1H, s, NH, D_2O exchangeable, structure A), 11.25 (1H, s, NH, D_2O exchangeable, structure A), 8.60 (1H, d, J = 8.0 Hz, ArH), 8.19 (1H, s, NH, D_2O exchangeable, structure A), 7.97 (1H, t, J = 8.2 Hz, ArH), 7.84 (1H, t, J = 7.0 Hz, ArH), 7.63 (1H, t, J = 7.6 Hz, ArH), 6.88 (1H, dd, \(J_{\text{gem}} = 3.0\), \(J_{1,2} = 13.1\) Hz, CH furyl), 6.67-6.58 (1H, m, CH furyl), 4.36-4.24 (1H, m, CH), 4.08 (2H, s, SCH_2), 3.60 (3H, s, NCH_3), 2.51 (2H, t, J = 7.4 Hz, CH_2), 2.46-2.38 (2H, m, CH_2), 2.05 (3H, s, SCH_3), IR (KBr) cm\(^{-1}\): 3262, 3219 (NH), 1657, 1646 (C=O), 1612 (C=N); Anal. Calcd. For C_{22}H_{23}N_{7}O_{4}S_2 (513.6): C, 51.45 %; H, 4.51 %; N, 19.09 %; Found: C, 51.28 %; H, 4.49 %; N, 19.01 %. Mass spectrum, m/z (Ir/%): 516 (9, M+2), 515 (11, M+1), 514 (32, M), 404 (58), 376 (4), 288 (19), 282 (37), 273 (54), 248 (7), 245 (24), 240 (31), 232 (100), 205 (1), 200 (48), 174 (32), 173 (25), 159 (24), 145 (68), 137 (11), 109 (4), 104 (34), 94 (22), 74 (8), 67 (6).

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