FULL PAPER

Synthesis of *Pseudo*-Peptides Containing a Quinazolinone Skeleton *via Ugi* Four-Component Reaction

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Dedicated to Prof. *Abolghasem Najafi* on the occasion of his 75th birthday

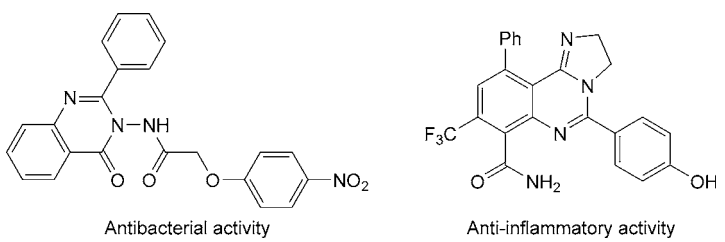
A simple and efficient synthesis of quinazolinone *pseudo*-peptide derivatives based on a new 3-amino-1,2,3,4-tetrahydro-4-oxoquinazoline-2-carboxylic acid *via Ugi* four-component reaction has been developed. This reaction was conducted under mild conditions with a broad scope of substrates.

Introduction. – Quinazolinones are a class of compounds containing the heterocyclic quinazolin-4-one scaffold which is found in a number of biologically active compounds exhibiting a broad spectrum of biological properties, such as anti-HIV [1], anticancer [2][3], antihypertensive [4 – 6], antifungal [7], antibacterial [8][9], anticonvulsant [10][11], anti-inflammatory [12][13], CNS-depressant [14], antimalarial [15], and antileishmanial activities [16]. Several bioactive natural products contain quinazolinone moieties, such as rutaecarpine [17][18], febrifugine [19], and methaqualone [20] which show potential antiplatelet, antimalarial, and sedative-hypnotic activities, respectively. The structures of two compounds containing a quinazolin(on)e skeleton and an amide functional group are shown in the *Figure*. The diverse biological activities of quinazolinone derivatives have continuously attracted the attention of biologists and natural product and synthetic chemists, resulting in a great number of methods available for their synthesis.

In recent years, isocyanide-based multicomponent reactions (IMCRs) have attracted a great deal of attention in the field of combinatorial chemistry and synthesis of *pseudo*-peptides [21 – 26] by virtue of their synthetic potential, inherent atom efficiency, convergent nature, ease of implementation, and the generation of molecular diversity. *Pseudo*-peptides open up new perspectives in drug design by providing an entire range of highly specific pharmaceuticals with high bioavailability. Existence of a dihydroquinazolinone unit in combination with additional amide bonds and lipophilic moieties due to the *pseudo*-peptide segment probably leads to better flexibility and interactions with receptors and also better permeability compared to dihydroquinazolinone itself.

Results and Discussion. – Based on the above mentioned activities of dihydroquinazolinones, the synthesis of functionalized dihydroquinazolinones was used as an efficient approach for the synthesis of biologically active compounds [27][28]. The cyclization approach was done using aldehydes, ketones, or dialkyl acetylenedicarboxylates. In this study, compound **4** was selected as target which contained the dihydroquinazolinone moiety and also a COOH group. For the synthesis of **4**, the three-component reaction of isatoic anhydride (**1**), *tert*-butyl hydrazinecarboxylate (**2**), and pyruvic acid (**3**) in the presence of different acid catalysts under various conditions was investigated (*Scheme 1*). Details of the synthesis of the quinazolinone scaffold using different catalysts are summarized in *Table 1*.

Comparison of the results showed that H_3PO_3 (20 mol-%; *Table 1*, *Entry 9*) was the best acidic catalyst, and the reaction was completed after the shortest time. The proposed mechanism for the synthesis of the 4-oxoquinazoline carboxylic acid is shown in *Scheme 2*.



Antibacterial activity Anti-inflammatory activity

Figure. *Structures of two biologically active compounds containing a quinazolin(on)e skeleton and an amide group*

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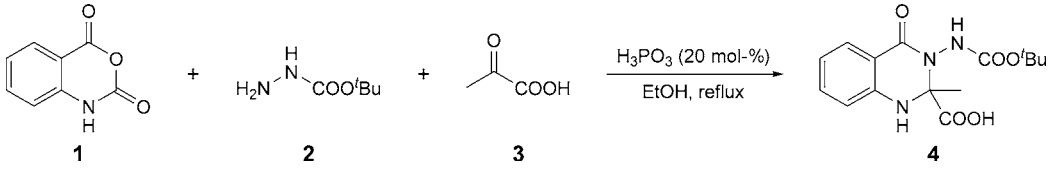
Scheme 1. *Synthesis of 4-Oxoquinazoline Carboxylic Acid* **4**



1 **2** **3** **4**

Table 1. *Optimization of Acid Catalyst in the Synthesis of 4-Oxoquinazoline Carboxylic Acid* **4**[a])

Entry	Catalyst	Time [h]	Yield [%]
1	–	24	0
2	Al_2O_3 (20 mol-%)	24	35
3	$ZrOCl_2$	24	30
4	TsOH (20 mol-%)	24	27
5	TsOH (30 mol-%)	24	40
6	ZrO_2 nano powder (0.025 g)	24	25
7	H_3PO_3 (5 mol-%)	24	48
8	H_3PO_3 (10 mol-%)	24	65
9	H_3PO_3 (20 mol-%)	5	85

[a]) Solvent, EtOH.

Mechanistically, the reaction of isatoic anhydride (**1**) and *tert*-butyl hydrazinecarboxylate (**2**) led to ring opening of **1** and elimination of CO_2 to yield **A**, and the reaction of **A** with the activated form of pyruvic acid could form the desired imine, which could convert to iminium ion **B**. H_3PO_3 as acid catalyst plays an important role in the formation of the imine, its conversion to th e iminium form, and the following cyclization *via* nucleophilic addition of the N-atom on the iminium group affording dihydroquinazolinone carboxylic acid (**4**; *Scheme 2*).

Although functionalized quinazolinone ring systems have been found frequently in biologically active molecules, quinazolinone derivatives as MCR partners are rather under-represented. In continuation of our work to design new applications based on the *Ugi* four-component reaction (*Ugi*-4CR) [29 – 42], a carboxylic acid containing the 4-oxoquinazoline skeleton, aromatic aldehydes, primary amines, and isocyanides were used for the synthesis of *pseudo*-peptides containing the 4-oxoquinazoline moiety.

Therefore, the four-component reaction of the *N*-protected 4-oxoquinazoline carboxylic acid (**4**), benzylamine (**5a**), 4-fluorobenzaldehyde (**6b**), and cyclohexyl isocyanide (**7a**), leading to **8b** in a 9 : 1 mixture of diastereoisomers, was selected as model reaction at room temperature in EtOH (*Scheme 3*).

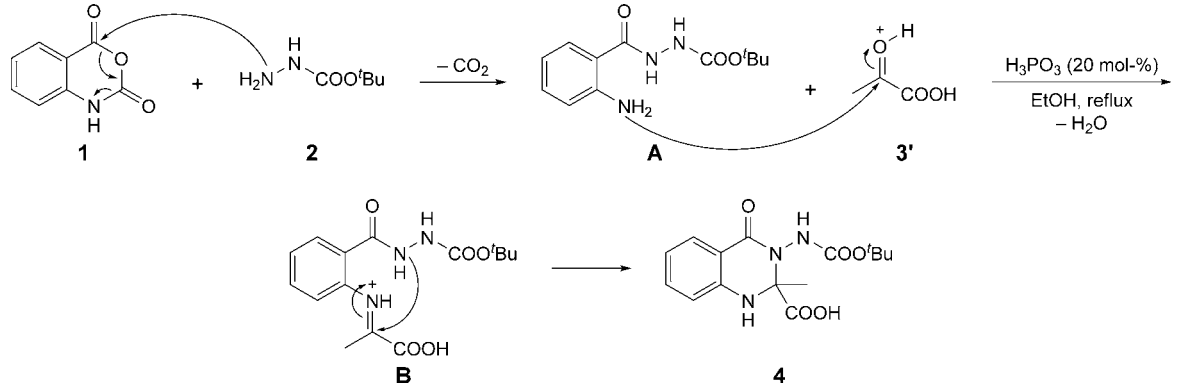
After formation of the desired 4-oxoquinazoline *pseudo*-peptide **8b**, in order to extend the chemical library with three points of diversity, we proceeded to screen the reaction of **4** with various amines, aldehydes, and isocyanides in EtOH at room temperature. The results are summarized in *Table 2*.

This synthetic approach allowed the introduction of three points of diversity within the resulting scaffolds, thus generating a small library of quinazolinone-containing *pseudo*-peptides as mixtures of diastereoisomers. In most cases, the *Ugi* reaction occurred smoothly, affording the desired purified products in good yields.

The structures of the synthesized compounds were verified on the basis of their IR, ^{1}H- and ^{13}C-NMR, and HR-MS data. For instance, the ^{1}H-NMR spectrum of **8a** showed a *singlet* for the CH H-atom at δ(H) 6.19 and also a *doublet* at 7.74 for the amide NH H-atom. The ^{13}C-NMR spectrum revealed distinct peaks at δ(C) 156.8, 165.5, 167.3, and 172.6 for the carbamate and amide C=O groups. A combined analysis of ^{1}H,^{1}H-COSY allowed us to assign the signals of the ^{1}H-NMR spectrum of **8g**.

After completion of the reaction, the mixture was evaporated and the ^{1}H-NMR data of the crude product showed the presence of two diastereoisomers. The ratio of the diastereoisomers was also assigned based on the peak area in the sp^3(C–H) region at δ(H) 6.0 – 6.5 (dr = 95 : 5 for **8a**). The ratio of the diastereoisomers was also determined for the other products in the same way and are included in *Table 2*. In the case of **8j**, the two diastereoisomers showed

Scheme 2. *Proposed Mechanism for the Synthesis of 4-Oxoquinazoline Carboxylic Acid* **4**



1 **2** **A** **3'** **B** **4**

Scheme 3. *Model Reaction for the Synthesis of Quinazolinone* Pseudo-*Peptide* **8b**

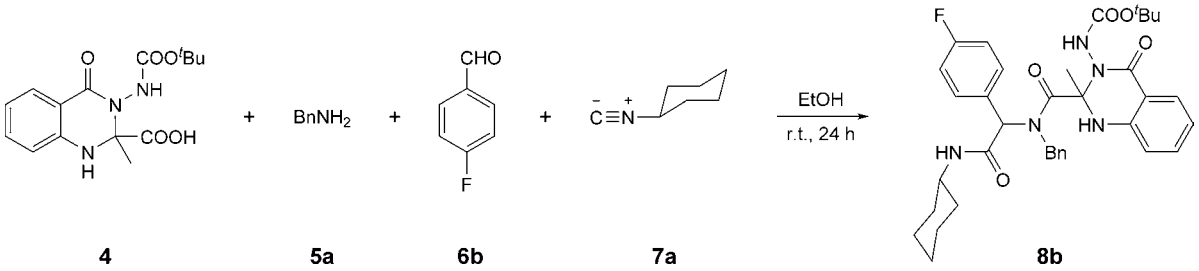
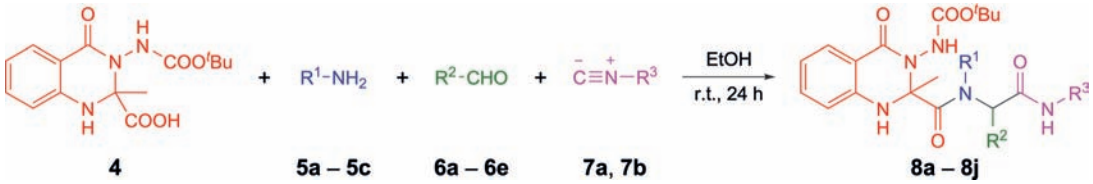


Table 2. *Synthesis of Quinazolinone* Pseudo-*Peptide Derivatives* **8a – 8j** *via* Ugi-*4CR*



Product	R^1	R^2	R^3	Yield [%][a])
8a	Bn	4-Cl–C_6H_4	cHex[b])	65 (95 : 5)
8b	Bn	4-F–C_6H_4	cHex[b])	77 (90 : 10)
8c	Bn	4-F–C_6H_4	^{t}Bu	71 (65 : 35)
8d	Bn	4-NO_2–C_6H_4	^{t}Bu	77 (53 : 47)
8e	Bn	4-NO_2–C_6H_4	cHex[b])	81 (65 : 35)
8f	Bn	4-CF_3–C_6H_4	cHex[b])	96 (60 : 40)
8g	Bn	4-Ph–C_6H_4	cHex[b])	52 (80 : 20)
8h	Ph	4-Cl–C_6H_4	cHex[b])	64 (85 : 15)
8i	Ph	4-NO_2–C_6H_4	cHex[b])	83 (75 : 25)
8j	1-Naphthyl	4-NO_2–C_6H_4	cHex[b])	56 (60 : 40)

[a]) Yield of isolated product (ratio of diastereoisomers). [b]) cHex, Cyclohexyl.

different solubilities in EtOH and could be separated by crystallization, and the major diastereoisomer was obtained in crystalline form with the other remaining dissolved in EtOH. The crystalline product was filtered and its ^{1}H-NMR spectrum showed the presence of a single diastereoisomer. Unfortunately, in all other cases the separation of the diastereoisomers was not possible. The investigation of the biological activities of the synthesized compounds is not completed yet.

Conclusions. – In conclusion, we have described an efficient approach for the synthesis of quinazolinone *pseudo*-peptide derivatives *via Ugi*-4CR, with a carboxylic acid that contains a quinazolinone skeleton. This reaction shows several advantages including high atom economy, high yields of products, and an easy experimental workup procedure.

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Experimental Part

General. Thin layer chromatography (TLC): precoated silica gel *60* F_{254} plates (SiO_2). M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *ABB FT-IR FTLA 2000* spectrometer; KBr; $\tilde{\nu}$ in cm^{-1}. ^{1}H-, ^{13}C-, and 2D-NMR spectra: *Bruker DRX-300 AVANCE* spectrometer (300 and 75 MHz for ^{1}H- and ^{13}C, resp.); in (D_6)DMSO or $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS: *Mass-ESI-POS* (*Apex Qe-FT-ICR* instrument) spectrometer; in *m*/*z*.

Synthesis of Quinazolinone Carboxylic Acid (**4**). Isatoic anhydride (**1**; 1 mmol, 0.163 g), *tert*-butyl hydrazinecarboxylate (**2**; 1 mmol, 0.132 g), and H_3PO_3 (20 mol-%, 0.0164 g) were added in a round-bottom flask. Then, EtOH (10 ml) was added, and the mixture was heated for 1 h under reflux. When the reaction was complete (TLC (hexane/AcOEt 3 : 1)), pyruvic acid (**3**; 1.2 mmol, 840 µl) was added to the mixture. The stirred mixture was heated under reflux for 4 h. After completion of the reaction (TLC (hexane/AcOEt 3 : 1)), the precipitate was filtered and dried.

*3-[(*tert*-Butoxycarbonyl)amino]-1,2,3,4-tetrahydro-2-methyl-4-oxoquinazoline-2-carboxylic Acid* (**4**). Yield: 272 mg (85%). Colorless powder. M.p. 193 – 196°. IR: 3322 (NH), 2800 – 3340 (COOH), 1746 (C=O), 1642 (C=O). ^{1}H-NMR ((D_6)DMSO): 1.40 (*s*, ^{t}Bu); 1.62 (*s*, Me); 6.60 – 6.79 (*m*, 2 arom. H); 7.28 (*t*, *J* = 7.2, 1 arom. H); 7.58 (*d*, *J* = 7.2, 1 arom. H); 7.60 (*s*, NH); 8.42 (*s*, NH (amide)); 13.13 (*s*, COOH). ^{13}C-NMR ((D_6)DMSO): 21.9; 27.9; 76.2; 79.6; 113.5; 114.1; 117.7; 127.7; 133.8; 146.0; 155.7; 162.8; 173.0. HR-ESI-MS: 344.12177 ($[M+Na]^+$, $C_{15}H_{19}N_3NaO_5^+$; calc. 344.12169), 360.09571 ($[M+K]^+$, $C_{15}H_{19}KN_3O_5^+$; calc. 360.09563).

General Procedure for the Synthesis of **8a – 8j**. Subsequently, to a soln. of aldehyde **6** (1 mmol) in EtOH (5 ml) was added the primary amine **5** (1 mmol), and the mixture was stirred at r.t. for 1 h. Then, carboxylic acid **4** (1 mmol) was added, and stirring was continued for

15 min, followed by addition of isocyanide **7** (1 mmol). The mixture was stirred for 24 h at r.t. Progress of the reaction was monitored by TLC (hexane/AcOEt 1:2). The formed precipitate was filtered off, washed with EtOH/H_2O 2:1, and dried. The product was a mixture of two diastereoisomers. The ratios of the diastereoisomers are shown in *Table 2*. An attempt was made to separate the two diastereoisomers by crystallization from MeOH/H_2O 4:1.

tert-*Butyl [2-{Benzyl[1-(4-chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8a**). Yield: 428 mg (65%; mixture of two diastereoisomers A/B 95:5). Colorless powder. M.p. 237 – 239°. IR: 3399 (NH), 3343 (NH), 2932 (CH), 1756 (C=O), 1679 (C=O). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 95:5): 0.80 – 1.90 (*m*, CH_2 (cHex), A and B); 1.42 (*s*, ^{t}Bu); 1.95 (*s*, Me); 3.56 – 3.80 (*m*, CH (cHex), A and B); 4.45 (br. *s*, 1 H of PhCH_2, A); 4.65 (*d*, *J* = 16.7, 1 H of PhCH_2, B); 5.16 (*d*, *J* = 7.2, 1 H of PhCH_2, A); 5.52 (*d*, *J* = 16.7, 1 H of PhCH_2, B); 6.19 (*s*, CH); 6.34 (br. *s*, ^{t}BuOC(O)N*H*); 6.45 – 6.70 (*m*, 3 arom. H); 6.73 (*s*, 1 arom. H); 6.84 (*t*, *J* = 7.2, 2 arom. H); 6.92 (*d*, *J* = 6.9, 3 arom. H); 7.25 (*d*, 3 arom. H); 7.27 (*s*, NH); 7.74 (*d*, NH (amide)). ^{13}C-NMR ((D$_6$)DMSO): 21.7; 24.7; 25.4; 28.1; 32.5; 48.7; 52.7; 67.3; 78.9; 81.6; 117.4; 117.9; 121.2; 127.3; 127.5; 127.8; 128.6; 128.7; 129.9; 130.8; 132.9; 134.0; 135.6; 143.1; 156.8; 165.5; 167.3; 172.6. HR-ESI-MS: 660.29490 ([*M* + H]$^+$, $C_{36}H_{43}ClN_5O_5^+$; calc. 660.29472); 682.27684 ([*M* + Na]$^+$, $C_{36}H_{42}ClN_5NaO_5^+$; calc. 682.27667); 698.25079 ([*M* + K]$^+$, $C_{36}H_{42}ClKN_5O_5^+$; calc. 698.25061).

tert-*Butyl [2-{Benzyl[2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8b**). Yield: 495 mg (77%; mixture of two diastereoisomers A/B 90:10). Colorless powder. M.p. 220 – 222°. IR: 3384 (NH), 3319 (NH), 3065 (CH), 1757 (C=O), 1687 (C=O), 1707 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 90:10): 0.75 – 1.90 (*m*, CH_2 (cHex)); 1.43 (*s*, ^{t}Bu); 1.94 (*s*, Me); 3.45 – 3.70 (*m*, CH (cHex)); 4.45 (*s*, 1 H of PhCH_2, A); 4.63 (*d*, *J* = 16.1, 1 H of PhCH_2, B); 5.15 (*s*, 1 H of PhCH_2, A); 5.51 (*d*, *J* = 16.1, 1 H of PhCH_2, B); 6.18 (*s*, CH); 6.31 (br. *s*, NH (amide)); 6.95 – 7.42 (*m*, 13 arom. H); 7.27 (*s*, NH); 7.73 (br. *s*, CON*H*–cHex). ^{13}C-NMR ((D$_6$)DMSO): 21.5; 24.6; 25.3; 28.1; 32.4; 48.5; 52.6; 78.7; 81.6; 81.6; 114.9; 115.3; 115.6; 117.2; 120.4; 126.7; 127.3; 127.9; 128.5; 130.2; 131.5; 133.9; 135.6; 143.3; 157.0; 165.9; 167.6; 172.9. HR-ESI-MS: 644.32455 ([*M* + H]$^+$, $C_{36}H_{43}FN_5O_5^+$; calc. 644.32427); 666.30654 ([*M* + Na]$^+$, $C_{36}H_{42}FN_5NaO_5^+$; calc. 666.30622); 682.28053 ([*M* + K]$^+$, $C_{36}H_{42}FKN_5O_5^+$; calc. 682.28016).

tert-*Butyl [2-{Benzyl[2-(*tert*-butylamino)-1-(4-fluorophenyl)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8c**). Yield: 438 mg (71%; mixture of two diastereoisomers A/B 65:35). Colorless powder. M.p. 226 – 228°. IR: 3326 (NH), 1742 (C=O), 1652 (C=O), 1506 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 65:35): 1.15 (*s*, 9 H, ^{t}Bu, A); 1.30 (*s*, 9 H, ^{t}Bu, B); 1.41 (*s*, 18 H, ^{t}Bu, A and B); 1.66 (*s*, Me, A); 1.83 (*s*, Me, B); 3.95 (*d*, *J* = 16.7, 1 H of PhCH_2, B); 4.43 (*d*, *J* = 17.2, 1 H of PhCH_2, A); 4.90 (*d*, *J* = 16.7, 1 H of PhCH_2, B); 5.41 (*d*, *J* = 17.2, 1 H of PhCH_2, A); 5.64 (*s*, NH); 6.12 (br. *s*, CH, A); 6.20 (br. *s*, CH, B); 6.27 (br. *s*, ^{t}BuN*H*); 6.42 – 7.71 (*m*, NH, 11 arom. H); 7.75 (*d*, *J* = 7.2, 1 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 14.1; 20.7; 27.9; 28.2; 50.5; 50.7; 78.4; 79.8; 114.5; 116.6; 125.2; 125.5; 126.3; 127.0; 127.2; 128.3; 131.2; 131.4; 131.8; 134.0; 138.0; 143.9; 155.5; 159.8; 163.1; 168.8. HR-ESI-MS: 618.30885 ([*M* + H]$^+$, $C_{34}H_{41}FN_5O_5^+$; calc. 618.30862); 640.29082 ([*M* + Na]$^+$, $C_{34}H_{40}FN_5NaO_5^+$; calc. 640.29057); 656.26478 ([*M* + K]$^+$, $C_{34}H_{40}FKN_5O_5^+$; calc. 656.26451).

tert-*Butyl [2-{Benzyl[2-(*tert*-butylamino)-1-(4-nitrophenyl)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8d**). Yield: 495 mg (77%; mixture of two diastereoisomers A/B 53:47). Colorless powder. M.p. 232 – 235°. IR: 3393 (NH), 3331 (NH), 2973 (CH), 1756 (C=O), 1665 (C=O), 1527 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 53:47): 1.07 (*s*, 9 H, ^{t}Bu, A); 1.29 (*s*, 9 H, ^{t}Bu, B); 1.40 (*s*, 18 H, ^{t}Bu, A and B); 1.72 (*s*, Me, A); 1.84 (*s*, Me, B); 3.97 (*d*, *J* = 14.5, 1 H of PhCH_2, A); 4.72 (*d*, *J* = 16.1, 1 H of PhCH_2, B); 4.97 (*d*, *J* = 14.5, 1 H of PhCH_2, A); 5.44 (*d*, *J* = 16.1, 1 H of PhCH_2, B); 5.63 (*s*, NH); 6.11 (br. *s*, CH); 6.26 (br. *s*, ^{t}BuN*H*); 6.38 – 8.12 (*m*, NH (amide), 13 arom. H). ^{13}C-NMR ((D$_6$)DMSO): 23.3; 27.9; 28.2; 33.0; 50.6; 62.2; 64.1; 79.4; 79.9; 114.9; 117.2; 122.7; 125.4; 125.7; 126.8; 127.1; 127.5; 130.2; 130.9; 134.0; 137.4; 143.9; 156.5; 164.1; 167.6; 168.7; 170.7. HR-ESI-MS: 645.30315 ([*M* + H]$^+$, $C_{34}H_{41}N_6O_7^+$; calc. 645.30312).

tert-*Butyl [2-{Benzyl[2-(cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8e**). Yield: 542 mg (81%; mixture of two diastereoisomers A/B 65:35). Colorless powder. M.p. 206 – 208°. IR: 3372 (NH), 3304 (NH), 1749 (C=O), 1656 (C=O), 1615 (C=O), 1524 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 65:35): 0.74 – 1.96 (*m*, CH_2 (cHex), A and B); 1.42 (*s*, ^{t}Bu, A and B); 1.69 (*s*, Me, A and B); 3.45 – 3.70 (*m*, CH (cHex), A and B); 3.98 (*d*, *J* = 16.2, 1 H of PhCH_2, A); 4.98 (*d*, *J* = 16.2, 1 H of PhCH_2, B); 5.27 (*d*, *J* = 16.2, 1 H of PhCH_2, A); 5.39 (*d*, *J* = 15.2, 1 H of PhCH_2, A); 6.17 (*s*, CH, A and B); 6.34 (*d*, *J* = 6.9, CON*H*–cHex, A and B); 6.52 – 8.23 (*m*, NH, 13 arom. H, A and B); 8.30 (br. *s*, NH (amide), A and B). ^{13}C-NMR ((D$_6$)DMSO): 23.2; 24.5; 25.1; 27.9; 31.9; 47.9; 48.3; 64.0; 79.2; 79.9; 122.6; 123.9; 127.0; 127.0; 127.6; 128.0; 128.4; 129.0; 134.2; 139.0; 141.6; 148.6; 155.6; 160.4; 163.0; 166.7; 170.9. HR-ESI-MS: 671.31888 ([*M* + H]$^+$, $C_{36}H_{43}N_6O_7^+$; calc. 671.31877); 693.30083 ([*M* + Na]$^+$, $C_{36}H_{42}N_6NaO_7^+$; calc. 693.30072); 709.27478 ([*M* + K]$^+$, $C_{36}H_{42}KN_6O_7^+$; calc. 709.27466).

tert-*Butyl [2-(Benzyl{2-(cyclohexylamino)-1-[4-(trifluoromethyl)-phenyl]-2-oxoethyl}carbamoyl)-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]carbamate* (**8f**). Yield: 632 mg (96%; mixture of two diastereoisomers A/B 60:40). Colorless powder. M.p. 228 – 230°. IR: 3322 (NH), 1757 (C=O), 1643 (C=O), 1623 (C=O), 1547 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 60:40): 0.79 – 1.98 (*m*, CH_2 (cHex), A and B); 1.53 (*s*, ^{t}Bu, A and B); 1.72 (*s*, Me, A and B); 3.58 – 3.72 (*m*, CH (cHex), A and B); 3.95 (*s*, *J* = 15.0, 1 H of PhCH_2, A); 4.67 (*d*, *J* = 12.0, 1 H of PhCH_2, B); 4.97 (*d*, *J* = 15.0, 1 H of PhCH_2, A); 5.47 (*d*, *J* = 12.0, 1 H of PhCH_2, B); 6.13 (br. *s*, CH, A); 6.30 (br. *s*, CH, B); 6.48 – 7.97 (*m*, NH, 13 arom. H, A and B); 8.12 (br. *s*, NH (amide), A); 8.62 (br. *s*, NH (amide), B). ^{13}C-NMR ((D$_6$)DMSO): 24.5; 25.1; 27.9; 30.3; 31.9; 42.3; 48.0; 77.7; 79.3; 79.8; 116.5; 125.2; 125.6; 126.7; 126.9; 128.1; 128.6; 128.7; 129.9; 130.2; 133.3; 134.6; 139.6; 147.6; 154.9; 155.5; 165.1; 167.7. HR-ESI-MS: 694.32169 ([*M* + H]$^+$, $C_{37}H_{43}F_3N_5O_5^+$; calc. 694.32108); 716.30363 ([*M* + Na]$^+$, $C_{37}H_{42}F_3N_5NaO_5^+$; calc. 716.30303); 732.27772 ([*M* + K]$^+$, $C_{37}H_{42}F_3KN_5O_5^+$; calc. 732.27696).

tert-*Butyl [2-{Benzyl[1-(biphenyl-4-yl)-2-(cyclohexylamino)-2-oxoethyl]carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]-carbamate* (**8g**). Yield: 364 mg (52%; mixture of two diastereoisomers A/B 80:20). Colorless powder. M.p. 228 – 230°. IR: 3462 (NH), 3299 (NH), 1724 (C=O), 1666 (C=O), 1489 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 80:20): 0.85 – 1.92 (*m*, CH_2 (cHex), A and B); 1.42 (*s*, ^{t}Bu, A); 1.44 (*s*, ^{t}Bu, B); 1.71 (*s*, Me, A and B); 3.48 – 3.67 (*m*, CH (cHex), A and B); 4.28 (*d*, *J* = 15.1, 1 H of PhCH_2, A and B); 4.79 (*d*, *J* = 15.1, 1 H of PhCH_2, A and B); 5.40 (*s*, NH, A and B); 6.48 (br. *s*, CH, B); 6.64 (br. *s*, CH, A); 6.68 – 8.02 (*m*, 13 arom. H, A and B); 7.80 (*d*, *J* = 7.2, NH (amide), B); 8.08 (*d*, *J* = 7.2, NH (amide), A). HR-ESI-MS: 702.36517 ([*M* + H]$^+$, $C_{42}H_{48}N_5O_5^+$; calc. 702.36500); 724.34713 ([*M* + Na]$^+$, $C_{42}H_{47}N_5NaO_5^+$; calc. 724.34694); 740.32113 ([*M* + K]$^+$, $C_{42}H_{47}KN_5O_5^+$; calc. 740.32088).

tert-*Butyl [2-{[1-(4-Chlorophenyl)-2-(cyclohexylamino)-2-oxoethyl](phenyl)carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]carbamate* (**8h**). Yield: 414 mg (64%; mixture of two diastereoisomers A/B 85:15). Colorless powder. M.p. 195 – 197°. IR: 3324 (NH), 3244 (NH), 1766 (C=O), 1633 (C=O), 1502 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 85:15): 0.80 – 1.83 (*m*, CH_2 (cHex), A and B); 1.40 (*s*, ^{t}Bu, A and B); 1.54 (*s*, Me, A and B); 3.32 – 3.64 (*m*, CH (cHex), A and B); 5.70 (br. *s*, CH, B); 5.90 (br. *s*, CH, A); 6.30 (br. *s*, *J* = 6.9, CON*H*–cHex, A and B); 6.35 – 7.28 (*m*, 13 arom. H, A and B); 7.84 (br. *s*, NH (amide), A and B). ^{13}C-NMR ((D$_6$)DMSO): 24.4; 24.6; 25.2; 28.0; 32.2; 47.8; 65.3; 79.6;

79.9; 113.5; 114.2; 114.5; 117.5; 127.4; 127.7; 132.2; 133.4; 133.7; 137.8; 143.9; 146.4; 154.8; 155.4; 155.6; 163.2; 168.2; 173.4. HR-ESI-MS: 646.28029 ($[M+H]^+$, $C_{35}H_{41}ClN_5O_5^+$; calc. 646.27907).

tert-*Butyl [2-{[2-(Cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl](phenyl)carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]carbamate* (**8i**). Yield: 544 mg (83%; mixture of two diastereoisomers A/B 75 :25). Yellow powder. M.p. 205 – 208°. IR: 3328 (NH), 3253 (NH), 1768 (C=O), 1675 (C=O), 1523 (C=C). ^{1}H-NMR ((D$_6$)DMSO; mixture of two diastereoisomers A/B 75 :25): 0.79 – 1.96 (*m*, CH$_2$ (cHex), A and B); 1.40 (*s*, ^{t}Bu, A and B); 1.57 (*s*, Me, A and B); 3.38 – 3.62 (*m*, CH (cHex), A and B); 5.84 (br. *s*, CH, B); 6.00 (*s*, CH, A); 6.24 (br. *s*, CON*H*–cHex, B); 6.31 (br. *s*, CON*H*–cHex, A); 6.42 – 8.44 (*m*, NH (amide), 9 arom. H, A and B); 8.20 (*d*, *J* = 8.7, 2 arom. H, A and B); 8.37 (*d*, *J* = 8.7, 2 arom. H, A and B); 8.81 (*s*, NH, A and B). ^{13}C-NMR ((D$_6$)DMSO): 24.4; 24.5; 25.1; 27.9; 32.1; 47.9; 65.5; 78.7; 79.8; 114.4; 116.9; 122.4; 122.6; 127.4; 127.9; 131.6; 133.4; 137.3; 142.7; 143.8; 146.5; 155.5; 155.6; 161.9; 164.6; 167.4; 170.5. HR-ESI-MS: 657.30344 ($[M+H]^+$, $C_{35}H_{41}N_6O_7^+$; calc. 657.30312); 679.28537 ($[M+Na]^+$, $C_{35}H_{40}N_6NaO_7^+$; calc. 679.28507); 695.25935 ($[M+K]^+$, $C_{35}H_{40}KN_6O_7^+$; calc. 695.25901).

tert-*Butyl [2-{[2-(Cyclohexylamino)-1-(4-nitrophenyl)-2-oxoethyl](naphthalen-1-yl)carbamoyl}-1,4-dihydro-2-methyl-4-oxoquinazolin-3(2*H*)-yl]carbamate* (**8j**). Yield: 403 mg (56%; mixture of two diastereoisomers A/B 60 :40). Yellow powder. M.p. 224 – 227°. IR: 3394 (NH), 1746 (C=O), 1689 (C=O), 1593 (C=C).

In this case, the two diastereoisomers were separated by crystallization from MeOH/H$_2$O 4 :1 to give 205 mg (0.28 mmol) of pure diastereoisomer A.

^{1}H-NMR ((D$_6$)DMSO; pure diastereoisomer A): 0.90 – 1.89 (*m*, CH$_2$ (cHex)); 1.40 (*s*, ^{t}Bu); 1.57 (*s*, Me); 3.56 – 3.72 (*m*, CH (cHex)); 6.67 (*s*, CH); 6.73 (*d*, *J* = 7.2, CON*H*–cHex); 7.16 – 8.33 (*m*, 11 arom. H); 8.31 (*d*, *J* = 8.2, 2 H of 4-NO$_2$–C$_6$H$_4$); 8.40 (*d*, *J* = 8.2, 2 H of 4-NO$_2$–C$_6$H$_4$); 8.90 (*s*, NH (amide)). ^{13}C-NMR ((D$_6$)DMSO): 22.1; 25.0; 26.8; 27.9; 42.7; 47.1; 62.9; 77.5; 82.2; 113.2; 119.1; 123.3; 124.1; 126.2; 126.6; 127.7; 128.4; 129.7; 133.5; 141.6; 147.4; 148.9; 153.3; 155.9; 158.1; 162.5; 165.0; 166.5; 170.8. HR-ESI-MS: 707.31869 ($[M+H]^+$, $C_{39}H_{43}N_6O_7^+$; calc. 707.31877).

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