

An Efficient Approach to the Synthesis of Hydrazinyl *Pseudo*-Peptides

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Dedicated to Prof. Fereydoun Moattar on the occasion of his 75th birthday

New hydrazinyl *pseudo*-peptides have been obtained from *Ugi* four-component reaction (4CR). The 5-hydrazinyl-5-oxopentanoic acids used as starting materials were prepared by the reaction of hydrazides with anhydrides. Mild reaction conditions, high atom economy, bond-forming efficiency, and easy workup are advantages of this approach. The products have four amide bonds and high potential for H-bonding.

Introduction. – Recently, *pseudo*-peptides have been attracting increasing attention because of their extended biological activities; in particular, they have been used in drug discovery [1 – 5]. Azapeptides are one of these modified peptides, formed through the replacement of the C^α-atom of one or more amino acid residues with an N-atom (Fig. 1). They have wide-ranging biological activities [6].

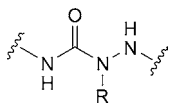


Fig. 1. General partial structure of azapeptides

To modify peptides, suitable starting materials should be selected. The replacement of one or more α -amino acid(s) by β -amino acid(s) or other functionalized carboxylic acids is one of the known approaches to synthesize pharmaceutically active peptides [7]. Using hydrazinyl carboxylic acids and α -aminoacyl benzotriazoles by means of microwave irradiation was reported by Katritzky and co-workers for the synthesis of hydrazinyl peptides [8]. Some *pseudo*-peptides containing hydrazide cores have been found to exhibit HIV protease inhibitor activities [9]. In this content, Klein and Hecht reported the synthesis of some novel *pseudo*-peptide scaffolds based on bis(thiourea) hydrazide motif, which have the ability to inhibit β -sheet aggregation [10].

Insertion of the hydrazinyl group in the structure of peptides leads to the hydrazinyl peptides. The hydrazinyl moiety in the peptide structure induces enhanced H-bonding, which affects the peptide backbone folding. In the presence of more C=O and NH functional groups, this ability, as well as their biological activities can be improved [11 –

13]. These modified peptides have been found important applications as receptor binding compounds, enzyme inhibitors, drugs, pro-drugs, and imaging agents [14].

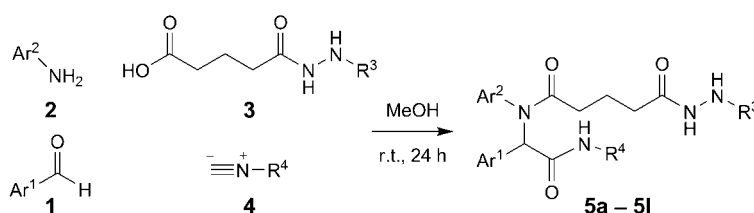
Because of their biological activities, development of novel approaches for the synthesis of the *pseudo*-peptides has been the focus of increasing attention.

The *Ugi* four-component reaction (*Ugi*-4CR) is an important method for the synthesis of *pseudo*-peptides [15]. The single-reactant-replacement (SRR) approach, which affords products with more functional groups, can be used for the synthesis of highly functionalized products.

The number of amide bonds and also the presence of lipophilic moieties in the structure of *pseudo*-peptides can affect their biological activities. With this in mind, our effort was directed to the preparation of novel *pseudo*-peptides *via Ugi*-4CR by using suitable carboxylic acid moieties.

In continuation of our work to design novel reactions based on hydrazides [16], we report herein the synthesis of novel hydrazinyl *pseudo*-peptides using 5-hydrazinyl-5-oxopentanoic acids (*Scheme*).

Scheme. Synthesis of Hydrazinyl Pseudo-Peptides through *Ugi*-4CR



Results and Discussion. – According to our synthetic plan, the carboxylic acids **3** [17] were initially synthesized through reaction of benzohydrazide and 4-methylbenzenesulfonyl hydrazide with glutaric anhydride. Previously, we used this approach for the synthesis of some fentanyl derivatives through reaction of amines with glutaric or succinic anhydride [18]. The reaction was carried out by mixing glutaric anhydride and benzohydrazide (or 4-methylbenzenesulfonyl hydrazide) in the presence of MeOH as solvent. After 30 min of stirring at room temperature, the desired product, **3a** or **3b**, were isolated in 96 and 94% yield, respectively.

The reaction of the pentanoic acid **3a**, 4-bromobenzaldehyde, 4-chloroaniline, and *tert*-butyl isocyanide in MeOH was selected as a model *Ugi*-4CR. The desired product **5a** was formed in 63% yield. The reaction has four-points of diversity. The scope of the reaction with regard to a substitution pattern in different primary amines, aromatic aldehydes, isocyanides and also two hydrazinyl-pentanoic acids was investigated. The results are compiled in the *Table*.

The structures of compounds **5a–5l** were deduced from their spectroscopic data and high-resolution mass spectra (HR-ESI-MS). The characteristic peaks in the range of 5.92–6.22 ppm in the ¹H-NMR spectra of the products arose from the H-atoms of the Ar¹–CH–N moieties. For instance, the ¹H-NMR spectrum of **5d** displayed a *singlet* at 6.03 ppm, and the NH H-atoms resonated at 7.44 ppm. The ¹³C-NMR spectrum revealed four distinct peaks at 165.3, 168.9, 171.1, and 171.3 ppm for the C=O groups.

Table. Synthesis of Novel Hydrazinyl Pseudo-Peptides **5a–5l** through Ugi-4CR of Aromatic Aldehydes **1**, Aromatic Primary Amines **2**, 5-Hydrazinyl-5-oxopentanoic Acids **3a** or **3b**, and Isocyanides **4^a**)

Product	Ar ¹	Ar ²	R ³	R ⁴	Yield [%] ^b
5a	4-Br-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	^t Bu	63
5b	4-Br-C ₆ H ₄	4-Cl-C ₆ H ₄	Ts	^t Bu	65
5c	5-Br-(furan-2-yl)	4-Br-C ₆ H ₄	Ts	^t Bu	66
5d	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	^t Bu	62
5e	4-Cl-C ₆ H ₄	4-Cl-C ₆ H ₄	Ts	^t Bu	65
5f	4-Me ₂ N-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	^t Bu	58
5g	4-F-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	^t Bu	65
5h	4-F-C ₆ H ₄	4-Cl-C ₆ H ₄	Ts	^t Bu	68
5i	4-F-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	Cyclohexyl	60
5j	2-(Prop-2-ynyloxy)-C ₆ H ₄	4-Cl-C ₆ H ₄	Bz	^t Bu	62
5k	2-(Prop-2-ynyloxy)-C ₆ H ₄	4-Cl-C ₆ H ₄	Ts	^t Bu	65
5l	Thiophen-2-yl	4-Br-C ₆ H ₄	Ts	^t Bu	63

^a) For the structures of the products, see the *Scheme*. ^b) Yields of isolated products.

The structure of **5j** was confirmed by single-crystal X-ray diffraction (*Fig. 2*). Both H-bond formation and π - π stacking play essential roles in the molecular association.

In the solid state, both H-atoms of the hydrazinyl moiety are involved in intermolecular H-bridges. Whereas N(10)-H of two neighboring molecules mutually form bridges to the keto O(1)-atoms of the other molecule, building pairs of molecules, N(9)-H moieties build H-bridges to crystal H₂O molecules. Both H-atoms of the crystal H₂O molecules again undergo bridging to the keto atoms O(4) and O(10) of different surrounding molecule pairs. The crystal H₂O molecules thus play a key role in interconnection of the *pseudo*-peptides (*Fig. 3*).

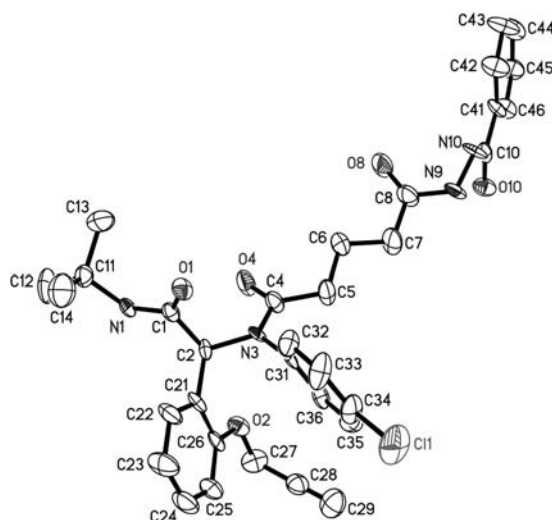


Fig. 2. ORTEP Presentation of the structure of compound 5j

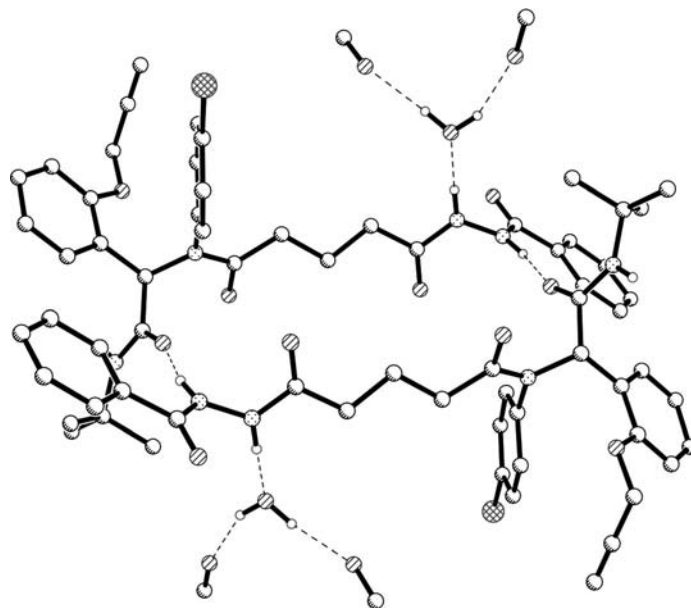


Fig. 3. Intramolecular and intermolecular H-bonding in hydrazinyl pseudo-peptide **5j**

In all cases, the products have four amide bonds. In the case of **5j** and **5k**, an additional alkyne bond provides opportunity for further cyclization. The presence of four amide bonds in the structure increases the activity and also rigidity of the products.

The molecular aggregation is usually mediated through low-energy interactions. The main forces involved in construction and controlling the size and shape of these supramolecular structures are the electrostatic interactions, *Van der Waals* bonds, H-bonds, and π -stacking forces.

As shown in Fig. 4, spherical structures (300 nm in diameter) are produced in the three-component solvent mixture (1,1,1,3,3,3-hexafluoroisopropanol/MeOH/H₂O 1:4:5), confirming highly ordered self-aggregation of compound **5c**. The presence of aromatic moieties and H-bonds could be responsible for the stabilization and formation of the spherical structures of molecules.

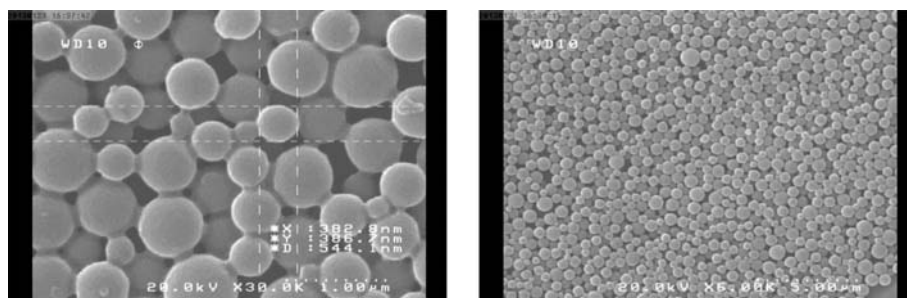


Fig. 4. SEM Micrographs of compound **5c**

Conclusions. – In conclusion, we have developed an efficient procedure for the preparation of some novel hydrazinyl *pseudo*-peptides. Both high yields and bond-forming efficiencies, in addition to tolerance of various groups toward the reaction conditions, are important advantages of this protocol. This method may have interesting implications on the construction of structurally diverse molecules, which contain four amide bonds and find applications in combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

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Experimental Part

General. M.p.: *Electrothermal 9100* apparatus; uncorrected. IR Spectra: *ABB FT-IR FTLA 2000* spectrometer; as KBr disks. ^1H - and ^{13}C -NMR spectra: *Bruker DRX-300 Avance* spectrometer at 300 and 75 MHz, resp.; in (D_6)DMSO; chemical shifts, δ , in ppm; and coupling constants (J) in Hz; HR-MS: Mass-ESI-POS (*Apex Qe-FT-ICR* instrument) spectrometer; in m/z (relative intensity). Scanning electron microscopy: *Hitachi 4160*.

General Procedures for the Synthesis of Acids **3a and **3b**** [17]. The pentanoic acids **3a** and **3b** were prepared as described in [17]. A mixture of benzohydrazide (or 4-methylbenzenesulfonohydrazide (20 mmol)) and glutaric anhydride (22 mmol) in CHCl_3 (100 ml) was stirred at r.t. overnight. The progress of the reaction was monitored by TLC (hexane/AcOEt 1:3). Then, the solvent was evaporated, and the resulting crude product was recrystallized from AcOEt/hexane to give pure products **3a** and **3b**.

5-(2-Benzoylhydrazinyl)-5-oxopentanoic Acid (3a**)** [17]. Yield: 240 mg (96%). White solid. M.p. 170–172°. R_f (33% AcOEt/hexane) 0.45. IR (KBr): 3259, 3034, 2964, 1711, 1613. ^1H -NMR: 1.66–1.81 (m , CH_2); 2.22 (t , $J = 7.5$, CH_2); 2.29 (t , $J = 7.5$, CH_2); 7.45–7.58 (m , 3 arom. H); 7.85 (d , $J = 7.5$, 2 arom. H); 9.86 (s , NH); 10.28 (s , NH); 12.08 ($br. s$, COOH). ^{13}C -NMR: 20.5; 32.4; 32.8; 127.4; 128.5; 131.8; 132.5; 165.5; 171.2; 174.2. HR-ESI-MS: 523.1799 ($[2M + \text{Na}]^+$, $\text{C}_{24}\text{H}_{28}\text{N}_4\text{NaO}_8^+$; calc. 523.1805).

5-[2-[(4-Methylphenyl)sulfonyl]hydrazinyl]-5-oxopentanoic Acid (3b**)** [17]. Yield: 282 mg (94%). White solid. M.p. 142–144°. R_f (33% AcOEt/hexane) 0.35. IR (KBr): 3388, 3343, 3065, 2947, 1695. ^1H -NMR: 1.62–1.72 (m , CH_2); 2.06–2.12 (m , 2 CH_2); 2.40 (s , Me); 7.33 (d , $J = 8.0$, 2 arom. H); 7.76 (d , $J = 8.0$, 2 arom. H). ^{13}C -NMR: 21.5; 21.7; 33.4; 33.6; 129.6; 130.5; 136.3; 145.6; 173.2; 176.6. HR-ESI-MS: 623.1452 ($[2M + \text{Na}]^+$, $\text{C}_{24}\text{H}_{32}\text{N}_4\text{NaO}_{10}\text{S}_2^+$; calc. 623.1458).

General Procedure for the Synthesis of the Hydrazinyl Pseudo-Peptides **5a–5l**. Aldehyde **1** (1 mmol) and amine **2** (1 mmol) were dissolved in MeOH (5 ml), and the mixture was stirred at r.t. for 30 min. Pentanoic acid **3a** or **3b** (1 mmol) was, then, added, and stirring was continued for 15 min, followed by addition of isocyanide **4** (1 mmol). The mixture was stirred for 24 h. The progress of the reaction was monitored by TLC. Then, the solvent was evaporated, the resulting mixture was washed with sat. NaHCO_3 (10 ml), and the crude was extracted with AcOEt (2×10 ml), and the org. phase was separated and dried (Na_2SO_4). The solvent was evaporated, and the residue was washed with $^3\text{Pr}_2\text{O}$ to give pure products **5a–5l** (yields 58–68%). In the case of **5j**, a single crystal was obtained by recrystallizing from EtOH.

5-(2-Benzoylhydrazinyl)-N-[1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl]-N-(4-chlorophenyl)-5-oxopentanamide (5a**)**. Yield: 395 mg (63%). White solid. M.p. 189–191°. R_f (33% AcOEt/hexane) 0.31. IR (KBr): 3316, 3150, 2970, 1692. ^1H -NMR: 1.22 (s , ^tBu); 1.65–1.82 (m , CH_2); 1.97–2.10 (m , 2 CH_2); 6.02 (s , CHN); 6.90 (d , $J = 7.2$, 4 arom. H); 7.25–7.36 (m , 3 arom. H, NH); 7.47–7.56 (m , 4 arom. H); 7.80–7.86 (m , 3 arom. H); 9.77 (s , NH); 10.24 (s , 1 NH). ^{13}C -NMR: 22.8; 28.4; 32.4; 33.7; 50.4; 62.9; 120.9; 127.4; 128.4; 130.9; 131.8; 132.1; 132.5; 132.8; 135.2; 138.6; 165.4; 168.8; 171.3; 171.4. HR-ESI-MS: 627.1377 ($[M + \text{H}]^+$, $\text{C}_{30}\text{H}_{33}^{79}\text{Br}^{35}\text{ClN}_4\text{O}_4^+$; calc. 627.1368), 649.1192 ($[M + \text{Na}]^+$, $\text{C}_{30}\text{H}_{32}^{79}\text{Br}^{35}\text{ClN}_4\text{NaO}_4^+$; calc. 649.1193), 665.0931 ($[M + \text{K}]^+$, $\text{C}_{30}\text{H}_{32}^{79}\text{Br}^{35}\text{ClN}_4\text{KO}_4^+$; calc. 665.0933).

N-[1-(4-Bromophenyl)-2-(tert-butylamino)-2-oxoethyl]-N-(4-chlorophenyl)-5-[2-[(4-methylphenyl)sulfonyl]hydrazinyl]-5-oxopentanamide (**5b**). Yield: 440 mg (65%). White solid. M.p. 206–208°. R_f (33% AcOEt/hexane) 0.31. IR (KBr): 3371, 3288, 2970, 1670. $^1\text{H-NMR}$: 1.22 (s, 'Bu); 1.47–1.51 (m, CH_2); 1.73–1.85 (m, 2 CH_2); 2.36 (s, Me); 5.98 (s, CHN); 6.96 (d, $J=8.1$, 2 arom. H); 7.25–7.36 (m, 7 arom. H, NH); 7.60 (d, $J=8.1$, 2 arom. H); 7.78 (br. s, 2 arom. H); 9.67 (s, NH); 9.82 (s, 1 NH). $^{13}\text{C-NMR}$: 21.0; 22.8; 28.4; 32.1; 33.4; 50.4; 62.8; 120.9; 127.6; 128.5; 129.2; 130.8; 132.1; 132.8; 135.1; 136.1; 138.6; 143.1; 168.8; 170.5; 171.2. HR-ESI-MS: 677.1202 ($[M+H]^+$, $\text{C}_{30}\text{H}_{35}^{79}\text{Br}^{35}\text{ClN}_4\text{O}_5\text{S}^+$; calc. 677.1195), 699.1017 ($[M+Na]^+$, $\text{C}_{30}\text{H}_{34}^{79}\text{Br}^{35}\text{ClN}_4\text{NaO}_5\text{S}^+$; calc. 699.1020), 715.0756 ($[M+K]^+$, $\text{C}_{30}\text{H}_{34}^{79}\text{Br}^{35}\text{ClKN}_4\text{O}_5\text{S}^+$; calc. 715.0759).

N-[1-(5-Bromofuran-2-yl)-2-(tert-butylamino)-2-oxoethyl]-N-(4-bromophenyl)-5-[2-[(4-methylphenyl)sulfonyl]hydrazinyl]-5-oxopentanamide (**5c**). Yield: 470 mg (66%). Yellow solid. M.p. 118°. R_f (33% AcOEt/hexane) 0.33. IR (KBr): 3295, 3250, 3083, 2970, 1671. $^1\text{H-NMR}$: 1.23 (s, 'Bu); 1.45–1.50 (m, CH_2); 1.73–1.86 (m, 2 CH_2); 2.36 (s, Me); 5.98 (s, CHN); 6.06 (br. s, 1 H (furanlyl)); 6.29 (d, $J=1.8$, 2 H (furanlyl)); 7.30 (d, $J=7.8$, 2 arom. H); 7.36–7.46 (m, 4 arom. H); 7.60 (d, $J=7.8$, 2 arom. H); 7.88 (s, NH); 9.84 (br. s, 2 NH). $^{13}\text{C-NMR}$: 20.5; 21.0; 28.3; 32.0; 33.1; 50.5; 57.8; 112.4; 113.8; 121.1; 121.3; 127.6; 129.2; 131.5; 138.9; 143.1; 151.1; 166.0; 170.4; 171.0. HR-ESI-MS: 711.0491 ($[M+H]^+$, $\text{C}_{28}\text{H}_{32}^{79}\text{Br}_2\text{N}_4\text{O}_6\text{S}^+$; calc. 711.0482), 733.0312 ($[M+Na]^+$, $\text{C}_{28}\text{H}_{32}^{79}\text{Br}_2\text{N}_4\text{NaO}_6\text{S}^+$; calc. 733.0307), 749.0048 ($[M+K]^+$, $\text{C}_{28}\text{H}_{32}^{79}\text{Br}_2\text{KN}_4\text{O}_6\text{S}^+$; calc. 749.0046).

5-(2-Benzoylhydrazinyl)-N-[2-(tert-butylamino)-1-(4-chlorophenyl)-2-oxoethyl]-N-(4-chlorophenyl)-5-oxopentanamide (**5d**). Yield: 361 mg (62%). White solid. M.p. 185–187°. R_f (33% AcOEt/hexane) 0.32. IR (KBr): 3305, 3064, 2970, 1661. $^1\text{H-NMR}$: 1.22 (s, 'Bu); 1.72–1.74 (m, CH_2); 1.92–2.09 (m, 2 CH_2); 6.03 (s, CHN); 7.04 (d, $J=8.1$, 2 arom. H); 7.21 (d, $J=8.1$, 4 arom. H); 7.44 (br. s, NH); 7.48 (d, $J=6.6$, 2 arom. H); 10.03 (br. s, 2 NH). $^{13}\text{C-NMR}$: 22.8; 28.4; 32.4; 33.7; 50.4; 62.8; 127.4; 127.9; 128.4; 131.8; 132.1; 132.2; 132.6; 132.8; 134.7; 138.6; 165.3; 168.9; 171.1; 171.3. HR-ESI-MS: 583.1883 ($[M+H]^+$, $\text{C}_{30}\text{H}_{33}\text{Cl}_2\text{N}_4\text{O}_4^+$; calc. 583.1873), 605.1697 ($[M+Na]^+$, $\text{C}_{30}\text{H}_{32}^{35}\text{Cl}_2\text{N}_4\text{NaO}_4^+$; calc. 605.1698), 621.1437 ($[M+K]^+$, $\text{C}_{30}\text{H}_{32}^{35}\text{Cl}_2\text{N}_4\text{KO}_4^+$; calc. 621.14382).

N-[2-(tert-Butylamino)-1-(4-chlorophenyl)-2-oxoethyl]-N-(4-chlorophenyl)-5-[2-[(4-methylphenyl)sulfonyl]hydrazinyl]-5-oxopentanamide (**5e**). Yield: 411 mg (65%). White solid. M.p. 202–205°. R_f (33% AcOEt/hexane) 0.33. IR (KBr): 3288, 3194, 2971, 1666. $^1\text{H-NMR}$: 1.22 (s, 'Bu); 1.47–1.52 (m, CH_2); 1.78–1.97 (m, 2 CH_2); 2.36 (s, Me); 6.00 (s, CHN); 7.02 (d, $J=8.1$, 2 arom. H); 7.20 (d, $J=8.1$, 4 arom. H); 7.31 (d, $J=7.8$, 4 arom. H); 7.60 (d, $J=7.8$, 2 arom. H); 7.78 (s, NH); 9.90 (br. s, 2 NH). $^{13}\text{C-NMR}$: 20.6; 21.1; 22.8; 28.4; 32.1; 33.4; 50.3; 62.8; 127.6; 127.9; 128.5; 129.2; 131.8; 132.1; 132.8; 134.7; 136.1; 138.6; 143.1; 168.9; 170.5; 171.2. HR-ESI-MS: 633.1710 ($[M+H]^+$, $\text{C}_{30}\text{H}_{35}^{35}\text{Cl}_2\text{N}_4\text{O}_5\text{S}^+$; calc. 633.1700).

5-(2-Benzoylhydrazinyl)-N-[2-(tert-butylamino)-1-[4-(dimethylamino)phenyl]-2-oxoethyl]-N-(4-chlorophenyl)-5-oxopentanamide (**5f**). Yield: 343 mg (58%). White solid. M.p. 137–139°. R_f (33% EtOAc/hexane) 0.32. IR (KBr): 3303, 2968, 1686. $^1\text{H-NMR}$: 1.22 (s, 'Bu); 1.71–1.73 (m, CH_2); 1.97–2.09 (m, 2 CH_2); 2.77 (s, Me_2N); 5.92 (s, CHN); 6.43 (d, $J=8.4$, 2 arom. H); 6.81 (d, $J=8.4$, 2 arom. H); 7.21 (br. s, NH); 7.44–7.55 (m, 7 arom. H); 7.84 (d, $J=7.5$, 2 arom. H); 9.75 (s, NH); 10.22 (s, 1 NH). $^{13}\text{C-NMR}$: 20.7; 28.5; 32.5; 33.7; 50.1; 59.7; 63.2; 111.4; 122.4; 127.4; 128.2; 128.4; 130.7; 131.7; 132.5; 132.9; 139.1; 149.4; 165.4; 169.9; 170.3; 171.3. HR-ESI-MS: 592.2697 ($[M+H]^+$, $\text{C}_{32}\text{H}_{39}^{35}\text{ClN}_5\text{O}_4^+$; calc. 592.2685), 614.2508 ($[M+Na]^+$, $\text{C}_{32}\text{H}_{38}^{35}\text{ClN}_5\text{NaO}_4^+$; calc. 614.2510), 630.2249 ($[M+K]^+$, C_{3

R_f (33% AcOEt/hexane) 0.31. IR (KBr): 3291, 3195, 3081, 2972, 1661. $^1\text{H-NMR}$ 1.21 (s, 'Bu); 1.48–1.50 (m, CH_2); 1.77–1.84 (m, 2 CH_2); 2.35 (s, Me); 5.98 (s, CHN); 6.92–7.02 (m, 4 arom. H); 7.20–7.39 (m, 5 arom. H, NH); 7.59 (d, $J = 7.5$, 2 arom. H); 7.75 (br. s, 2 arom. H); 9.85 (br. s, 2 NH). $^{13}\text{C-NMR}$: 20.6; 21.0; 28.3; 32.0; 33.4; 50.3; 62.7; 114.6; 114.9; 127.6; 128.4; 129.2; 132.0; 132.8; 135.9; 138.6; 143.2; 169.1; 170.6; 171.1. HR-ESI-MS: 617.2013 ($[M + \text{H}]^+$, $\text{C}_{30}\text{H}_{35}^{35}\text{ClFN}_4\text{O}_5\text{S}^+$; calc. 617.1995), 639.1820 ($[M + \text{Na}]^+$, $\text{C}_{30}\text{H}_{34}^{35}\text{ClFN}_4\text{NaO}_5\text{S}^+$; calc. 639.1820), 655.1562 ($[M + \text{K}]^+$, $\text{C}_{30}\text{H}_{34}^{35}\text{ClFKN}_4\text{O}_5\text{S}^+$; calc. 655.1560).

5-(2-Benzoylhydrazinyl)-N-(4-chlorophenyl)-N-[2-(cyclohexylamino)-1-(4-fluorophenyl)-2-oxoethyl]-5-oxopentanamide (**5i**). Yield: 355 mg (60%). White solid. M.p. 220–222°. R_f (33% AcOEt/hexane) 0.33. IR (KBr): 3261, 3070, 2932, 1655. $^1\text{H-NMR}$: 1.00–1.90 (m, 5 CH_2 of cyclohexyl, CH_2); 1.97–2.10 (m, 2 CH_2); 3.56–3.59 (m, CHN); 6.05 (s, CHN); 6.94–7.08 (m, 6 arom. H); 7.23 (br. s, NH); 7.45–7.58 (m, 4 arom. H); 7.80 (d, $J = 7.5$, 2 arom. H); 8.02 (d, $J = 7.5$, 1 arom. H); 9.76 (br. s, NH); 10.23 (br. s, NH). $^{13}\text{C-NMR}$: 20.7; 24.4; 24.6; 25.2; 32.1; 32.2; 32.4; 33.6; 47.9; 62.5; 114.6; 114.9; 127.4; 128.4; 131.7; 132.1; 132.2; 132.6; 132.8; 138.6; 159.8; 163.0; 165.4; 168.6; 170.3. HR-ESI-MS: 593.2333 ($[M + \text{H}]^+$, $\text{C}_{32}\text{H}_{34}^{35}\text{ClFN}_4\text{O}_4^+$; calc. 593.2325), 615.2151 ($[M + \text{Na}]^+$, $\text{C}_{32}\text{H}_{34}^{35}\text{ClFN}_4\text{NaO}_4^+$; calc. 615.2150), 631.1892 ($[M + \text{K}]^+$, $\text{C}_{32}\text{H}_{34}^{35}\text{ClFKN}_4\text{O}_4^+$; calc. 631.1890).

5-(2-Benzoylhydrazinyl)-N-[2-(tert-butylamino)-2-oxo-1-[2-(prop-2-yn-1-yloxy)phenyl]ethyl]-N-(4-chlorophenyl)-5-oxopentanamide (**5j**). Yield: 373 mg (62%). White solid. M.p. 130–133°. R_f (33% AcOEt/hexane) 0.32. IR (KBr): 3288, 3201, 3091, 2969, 1656. $^1\text{H-NMR}$: 1.25 (s, 'Bu); 1.73–1.75 (m, CH_2); 1.93–2.10 (m, 2 CH_2); 3.68 (s, $\equiv\text{CH}$); 4.83 (s, OCH_2); 6.19 (s, NH); 6.67 (t, $J = 7.2$, 1 arom. H); 6.81 (d, $J = 7.2$, 1 arom. H); 6.90 (d, $J = 7.8$, 1 arom. H); 7.10 (t, $J = 7.8$, 1 arom. H); 7.15 (br. s, NH); 7.45–7.55 (m, 5 arom. H); 7.84 (m, 4 arom. H); 9.90 (br. s, 2 NH). $^{13}\text{C-NMR}$: 22.8; 28.5; 32.5; 33.7; 50.3; 55.4; 58.6; 78.5; 79.2; 111.4; 120.3; 124.1; 127.4; 128.2; 128.4; 129.1; 129.8; 131.8; 132.5; 138.8; 155.1; 165.4; 169.5; 170.9; 171.3. HR-ESI-MS: 603.2381 ($[M + \text{H}]^+$, $\text{C}_{33}\text{H}_{36}^{35}\text{ClN}_4\text{O}_5^+$; calc. 603.2369), 625.2198 ($[M + \text{Na}]^+$, $\text{C}_{33}\text{H}_{35}^{35}\text{ClN}_4\text{NaO}_5^+$; calc. 625.2194).

X-Ray Crystal-Structure Determination. Colorless crystals (plate); dimensions, $0.24 \times 0.06 \times 0.01$ mm; crystal system, triclinic, space group, $\text{P}\bar{1}$, $Z = 2$, $a = 9.859(4)$ Å, $b = 10.204(4)$ Å, $c = 18.089(7)$ Å, $\alpha = 73.884(8)^\circ$, $\beta = 83.878(9)^\circ$, $\gamma = 71.071(9)^\circ$, $V = 1653.5(11)$ Å³, $\rho = 1.248$ g/cm³, $T = 200(2)$ K, $\theta_{\text{max}} = 19.59^\circ$, radiation, $\text{MoK}\alpha$, $\lambda = 0.71073$ Å; 0.5° ω -scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 2.13 and a completeness of 99.9% to a resolution of 1.06 Å; 6193 reflections measured; 2904 unique ($R(\text{int}) = 0.0878$); 1456 observed ($I > 2\sigma(I)$), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS [19a] based on the *Laue* symmetry of the reciprocal space, $\mu = 0.16$ mm^{−1}, $T_{\text{min}} = 0.96$, $T_{\text{max}} = 1.00$; structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package [19b], 403 parameters refined, H-atoms were treated using appropriate riding models, except those at the crystal water O(11), which were refined restrained, goodness-of-fit, 1.05 for observed reflections, final residual values, $R^1(F) = 0.076$, $wR(F^2) = 0.149$ for observed reflections; residual electron density, -0.27 to 0.32 eÅ^{−3}. CCDC-950020 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

N-[2-(tert-Butylamino)-2-oxo-1-[2-(prop-2-yn-1-yloxy)phenyl]ethyl]-N-(4-chlorophenyl)-5-[2-[(4-methylphenyl)sulfonyl]hydrazinyl]-5-oxopentanamide (**5k**). Yield: 424 mg (65%). White solid. M.p. 176–178°. R_f (33% AcOEt/hexane) 0.31. IR (KBr): 3320, 3249, 3068, 2968, 1684, 1649. $^1\text{H-NMR}$: 1.24 (s, 'Bu); 1.47–1.52 (m, CH_2); 1.73–1.91 (m, 2 CH_2); 2.36 (s, Me); 3.64 (s, $\equiv\text{CH}$); 4.81 (s, OCH_2); 6.15 (s, CHN); 6.66 (t, $J = 7.5$, 1 arom. H); 6.80 (d, $J = 6.6$, 1 arom. H); 6.88 (d, $J = 8.0$, 1 arom. H); 7.10 (t, $J = 7.8$, 1 arom. H); 7.30–7.39 (m, 4 arom. H); 7.

H, 1 H of thienyl); 7.60 (*d*, *J* = 7.8, 1 arom. H); 7.80 (*s*, NH); 9.70 (*br. s*, NH); 9.85 (*br. s*, 1 NH). ¹³C-NMR: 21.1; 22.8; 28.3; 32.0; 33.4; 50.4; 58.5; 120.9; 123.3; 126.3; 127.5; 127.6; 129.1; 129.2; 131.3; 132.1; 133.1; 136.0; 137.4; 138.8; 143.1; 168.4; 170.5; 170.9. HR-ESI-MS: 649.1161 (*[M + H]*⁺, C₂₈H₃₃⁷⁹BrN₄O₅S₂⁺; calc. 649.1149), 671.0973 (*[M + Na]*⁺, C₂₈H₃₃⁷⁹BrN₄NaO₅S₂⁺; calc. 671.0973), 687.0713 (*[M + K]*⁺, C₂₈H₃₃⁷⁹BrKN₄O₅S₂⁺; calc. 687.0713).

Scanning Electron Microscopy. The self-aggregation of compound **5c** was studied by dissolving 2 mg of the sample in 1 ml of the solvent system 1,1,1,3,3,3-hexafluoroisopropanol/MeOH/*mili Q* H₂O 1:4:5. The scanning electron micrographs (SEM; *Hitachi 4160*, Japan) of the assembled constructions were obtained after 4 h.

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