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Temperature-Controlled Diastereoselective Doebner/Ugi Tandem Reaction

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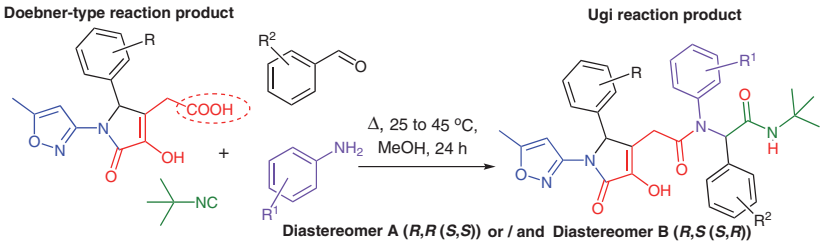

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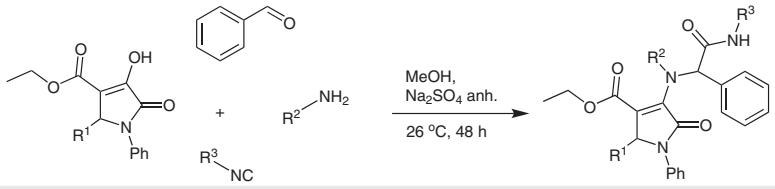
Abstract Novel peptidomimetics containing a pyrrolone fragment were synthesized by a tandem combination of Doebner and Ugi type multicomponent reactions with controlled diastereoselectivity. This approach represents a convenient synthesis in the temperature range from 25 to 45 °C. In most cases, the new method allowed each diastereomer to be isolated separately.

Keywords multicomponent reactions, Doebner reaction, Ugi reaction, peptidomimetics, pyrrolones, diastereoselectivity

Multicomponent reactions (MCRs) play an important role in the synthesis of organic molecules and they can be used to create new highly potent bioactive structures. MCRs involve the transformation of three or more starting materials into the final product in an atom- and step-economical manner in modern organic synthesis, especially in areas of drug discovery and combinatorial chemistry, allowing large libraries of organic heterocyclic compounds to be generated. In addition, MCRs are often characterized by high yields, low waste formation, and high efficiency.[1–5]

The combination of Doebner and Ugi type MCRs is a way to increase the diversity of organic compounds and to obtain peptidomimetics containing a pyrrolone moiety as a biologically privileged heterocyclic structure. The pyrrolidinone scaffold is present in numerous bioactive agents, such as the endothelin receptor antagonist oteromicyn,[6] antibiotics,[7] antimicrobials,[8] antipyretics,[9] analgesics,[10] novel tyrosinase inhibitors,[11] and molecules for the treatment of Alzheimer's disease[12] and tumors.[13,14]

Substituted pyrrolones as heterocyclic enols (acid component) containing a conjugated ester group can be functionalized via the OH group of the 3-position by an Ugi-type condensation to produce biologically relevant heterocyclic enamines (Scheme 1). Moreover, the presence of a stereogenic center in the pyrrolone ring would lead to the formation of two diastereomeric products in the Ugi reaction.[15]



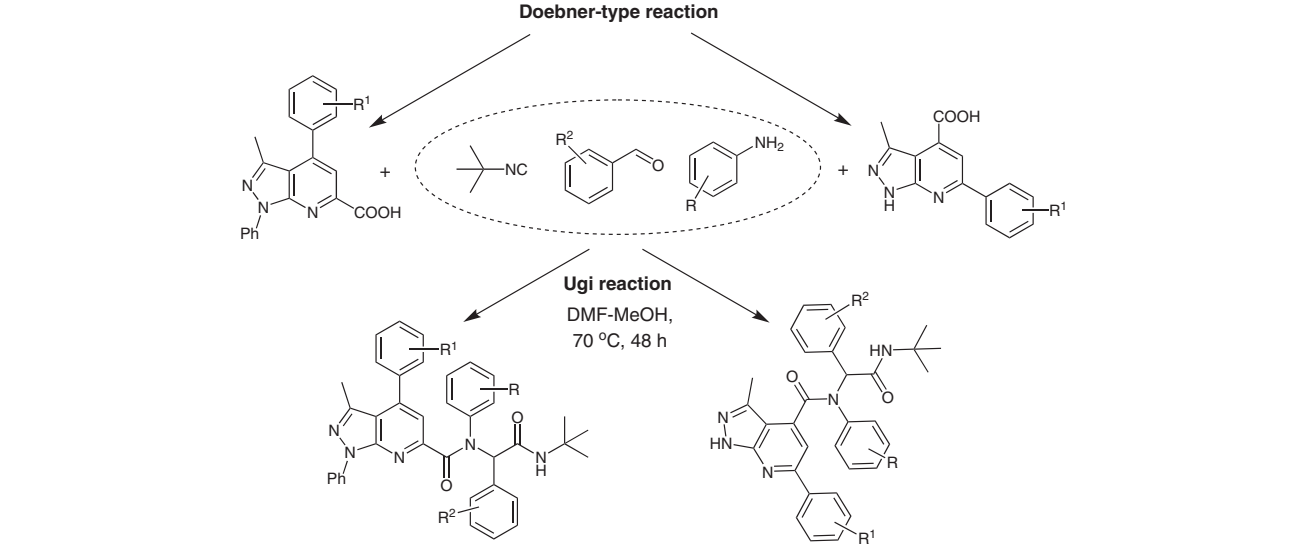
Scheme 1 Pyrrolones as acid component in the Ugi reaction

Stereoselective control of Ugi reactions remains a difficult task, and many scientific groups have sought to address this issue.[16,17] Good diastereoselectivity of MCRs is very useful to avoid the need to separate diastereomers, and to control the relative configuration of the final product.[18–20]

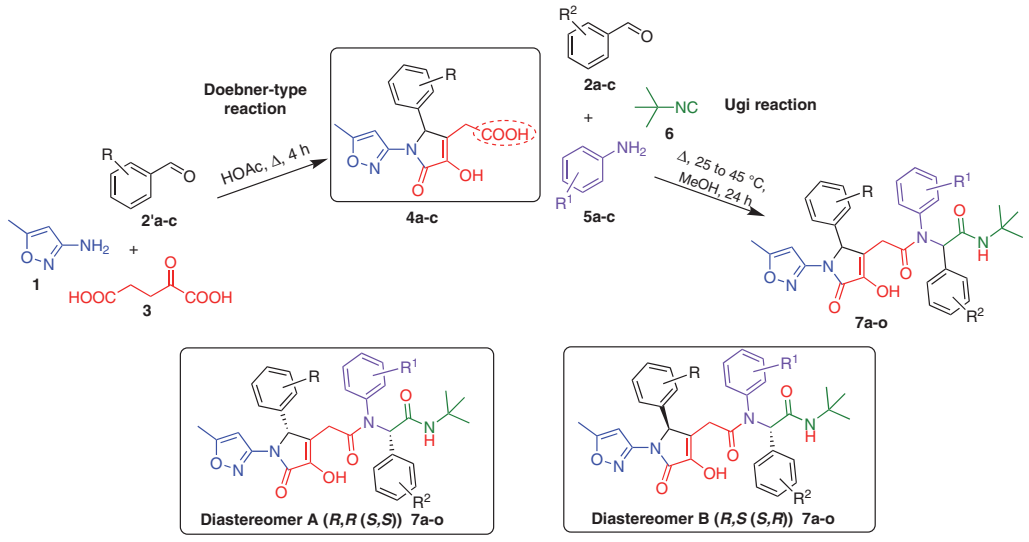
In our previous work,[21] the combination of two multicomponent reactions was studied: the pyrazolopyridine carboxylic acids obtained in the Doebner type condensation were involved in the Ugi reaction with aromatic aldehydes, amines, and *tert*-butyl isocyanide, which allowed the synthesis of new compounds containing a peptide bond and an azoloazine fragment (Scheme 2). The Ugi product, possessing two pharmacophores, namely pyrazolopyridine and peptidomimetic moieties, showed antibacterial activity.[21]

Substituted pyrrolidinones with a carboxyl-containing substituent at the 4-position, have been shown to be a privileged unit for increasing molecular diversity, and they can be introduced into subsequent MCRs. Therefore, we studied the tandem combination of three-component Doebner type reaction and four-component Ugi reaction.

Pyrrolones **4a–c** were synthesized via a three-component condensation of 3-amino-5-methylisoxazole (**1**) with aromatic aldehydes **2'a–c** and α-ketoglutaric acid (**3**) in refluxing AcOH for 4 h in 44–62% yield (Scheme 3).[22] Subse-



Scheme 2 Synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridine-4- and 1*H*-pyrazolo[3,4-*b*]pyridine-6-carboxamides via Doebner and Ugi type reaction



Scheme 3 Diastereoselective tandem Ugi/Doebner type reaction

quently, heterocycles **4** were introduced as the acidic component in the four-component Ugi reaction with aromatic aldehydes **2a–c**, aromatic amines **5a–c**, and *tert*-butyl isocyanide (**6**) in trifluoroethanol in an oil bath for 24 h at 45 °C (Scheme 3). As a result, *N*-(*tert*-butyl)-2-(2-(2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*)-pyrrol-3-yl)-*N*-(arylacetamido)-2-arylacetamides **7a–o** were isolated from the reaction.

It should be noted that under the above conditions, this Ugi reaction gave a mixture of two possible diastereomers (**A** and **B**) (Scheme 3) in a different ratio. The progress of the reaction was monitored by TLC [R_f = 0.55 (*n*-hexane/ethyl acetate, 1:2), the location and appearance of the spots of both diastereomers were practically the same]. Separation of the diastereomers by fractional crystallization or column chromatography was unsuccessful. To avoid the separation procedure for the diastereomers, we decided to develop a synthetic method that would allow the selective (or practically selective) formation of both diastereomers.

It was found that treatment of aromatic aldehyde **2** and amine **5** in methanol at 25 °C followed by the addition of acid **4** and *tert*-butyl isocyanide **6** in the temperature range from 25 to 45 °C and stirring of the resulting mixture at 45 °C for 24 h (see Experimental Section) gave only diastereomer **A** of compound **7** in yields of 24–65% (Scheme 3, Table 1). In turn, the precipitate formed from the mother liquor within a day at 20 °C was diastereomer **B** of compound **7** (20–35% yield according to the ^{1}H NMR spectroscopy data). It should be noted that the Ugi reaction in methanol at temperatures as low as 20 °C resulted in the formation of product **7** as a mixture of diastereomers **A** and **B**.

For compounds **7a**, **7d**, **7f–h**, **7j**, and **7m**, each of the diastereomers (**A** and **B**) was isolated individually. In some cases, in addition to one diastereomer, the second diastereomer was found in amounts up to 15%. Some of the peptidomimetics **7** (**7c**, **7i**, **7k**, **7l**, and **7o**) spontaneously precipitated from the reaction mixture, yielding only one diastereomer (**A** or **B**). The corresponding mother liquors were examined and the reaction solution was found to contain a mixture of both diastereomers and unreacted starting materials with some intermediates. Compounds **7b**, **7e** and **7n** were formed as a mixture of two diastereomers (diastereomer ratio was close to 1:1) irrespective of the solvent and reaction temperature. The purity of the obtained compounds **7** of both diastereomers (**A** and **B**) was determined by HPLC analysis and/or LCMS.

Diastereomers **A** and **B** have similar solubility: they are soluble in dimethyl sulfoxide, dimethyl formamide, ethanol, and dichloromethane and insoluble in toluene, ether, hexane, and water.

The purity and structures of the synthesized compounds were established by elemental analysis, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and by X-ray diffraction studies. For example, the ^{1}H NMR spectra of compounds **7a–o** exhibited the following signals: two signals for diastereotopic protons of CH_2 group at 2.14–2.24 and 3.15–3.27 ppm, protons of the *t*-butyl group at 1.22–1.25

Table 1 Synthesis of Ugi Products **7a–o** (Diastereomers **A** and **B**)

Entry	Starting materials						Product	Yield (%)	
	R	Pyrrolone	R^1	Amine	R^2	Aldehyde		Diastereomer	
								A	**B**
1	4-Cl	**4a**	4-OCH_3	**5a**	4-Cl	**2a**	**7a**	49	29
2	4-Cl	**4a**	4-Cl	**5b**	4-Cl	**2a**	**7b**	41[a]	
3	4-Cl	**4a**	4-CH_3	**5c**	4-Cl	**2a**	**7c**	41	–
4	4-Cl	**4a**	4-OCH_3	**5a**	4-OCH_3	**2b**	**7d**	65	20
5	4-Cl	**4a**	4-Cl	**5b**	4-OCH_3	**2b**	**7e**	89[a]	
6	4-Cl	**4a**	4-CH_3	**5c**	4-OCH_3	**2b**	**7f**	45	23
7	4-Cl	**4a**	4-OCH_3	**5a**	4-CO-OCH_3	**2c**	**7g**	42	35
8	4-Cl	**4a**	4-Cl	**5b**	4-CO-OCH_3	**2c**	**7h**	45	35
9	4-Cl	**4a**	4-CH_3	**5c**	4-CO-OCH_3	**2c**	**7i**	34[a]	24
10	4-OCH_3	**4b**	4-OCH_3	**5a**	4-OCH_3	**2b**	**7j**	41	33
11	4-OCH_3	**4b**	4-Cl	**5b**	4-Cl	**2a**	**7k**	45	–
12	4-OCH_3	**4b**	4-CH_3	**5c**	4-Cl	**2a**	**7l**	49	–
13	4-CO-OCH_3	**4c**	4-OCH_3	**5a**	4-OCH_3	**2b**	**7m**	40	21
14	4-CO-OCH_3	**4c**	4-Cl	**5b**	4-OCH_3	**2b**	**7n**	73[a]	
15	4-CO-OCH_3	**4c**	4-CH_3	**5c**	4-OCH_3	**2b**	**7o**	64	–

[a] Mixture of two diastereomers.

ppm (diastereomer **A**) and 1.28–1.29 ppm (diastereomer **B**), a singlet for the CH group of pyrrolone at 5.53–5.59 ppm, a singlet for the CH group at the aldehyde moiety (5.93–5.99 ppm), a singlet for CH group of the isoxazole fragment (6.68–6.75 ppm), singlet protons for the NH group in the 7.58–7.93 ppm, peaks for aromatic protons in the range of 5.90–7.98 ppm, a singlet for the enol OH group in pyrrolone at 9.88–10.04 ppm and signals for terminal functional groups in appropriate regions of the spectra. Broad and double signals of some aromatic protons may indicate the presence of rotamerism. Indeed, temperature NMR experiments for compound **7j** confirmed the presence of rotamers in solution due to the hindered rotation around the amide C–N bond.[23–26]

The structure of compounds **7a–o** for each diastereomer **A** and **B** was additionally proven by X-ray analysis of compound **7d** (Figure 1 and Figure 2).

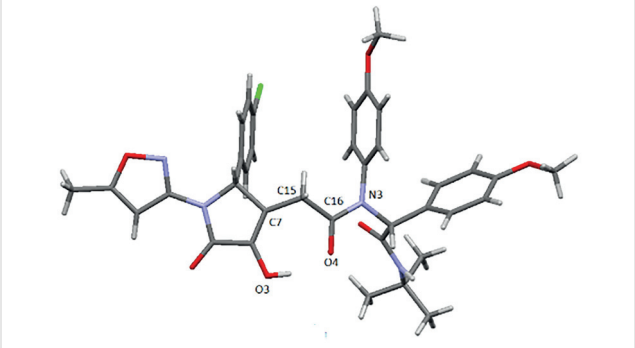


Figure 1 Molecular structure of *N*-(*tert*-butyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(4-methoxyphenyl)acetamido)-2-(4-methoxyphenyl)acetamide (**7d**). *R*,*R* (*S*,*S*)-Diastereomer **A** obtained from X-ray diffraction data.

X-ray diffraction analysis of diastereomer **B** (compound **7d**) (Figure 2) was described in our previous work.[27] Diastereomer **A** of compound **7d** was crystallized as a non-solvated structure in contrast to the diastereomer **B**, which was found to be a methanol solvate in the crystal structure. Comparison of the molecular structures of these diastereomers revealed only one significant difference related to the conformation of the substituent on the C7 atom. The C16(=O4)–N3 carbamide group in diastereomer **B** is located in the *–ac* position with respect to the C6–C7 endocyclic bond [C6–C7–C15–C16 = –107.2 (3)°] due to rotation around the C7–C15 bond. The hydroxyl group forms an intermolecular hydrogen bond with the methanol solvent molecule. In diastereomer **A**, the carbamide group is in an intermediate position between *sp* and *+sc* in relation to the C6–C7 endocyclic bond [C6–C7–C15–C16 = 33.1 (6)°]. This orientation is stabilized by the intramolecular hydrogen bond O3–H3···O4 [the H3···O4 distance is 1.78 Å, the O3–H3···O4 angle is 159°].

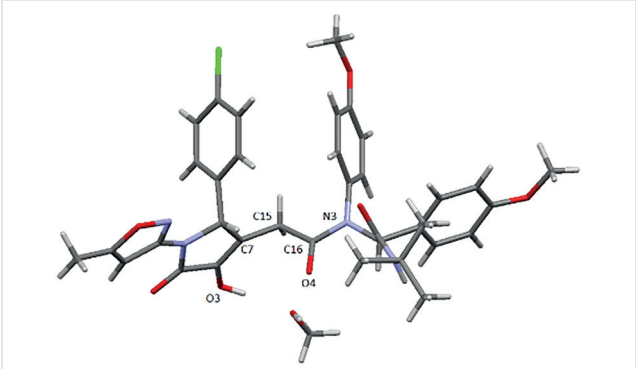


Figure 2 Molecular structure of *N*-(*tert*-butyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(4-methoxyphenyl)acetamido)-2-(4-methoxyphenyl)acetamide (**7d**). *R*,*S* (*S*,*R*)-Diastereomer **B** obtained from X-ray diffraction data.

In summary, a procedure based on the tandem combination of Doebner and Ugi reactions has been developed in which the formation of pyrrolone-containing peptidomimetics selectively generates both possible diastereomers of the target compounds in most cases. This treatment is carried out by regulating the solvent and temperature to control selectivity. The optimal conditions are methanol as solvent and heating temperature between 25 and 45 °C.

The starting pyrrolones **4a–c** were synthesized according to a described procedure.[22] The aromatic aldehydes **2a–c**, aromatic amines **5a–c**, and *tert*-butyl isocyanide (**6**) are commercially available. All solvents were obtained from commercial suppliers and used without additional purification. Melting points of all synthesized compounds were determined with a Stuart SMP10 electronic melting-point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were performed in DMSO-d_6 at 400 MHz (100 MHz for ^{13}C) with a Varian MR-400 spectrometer. Mass spectra were measured with a Shimadzu LCMS-2020, Waters Quatro Micro API mass spectrometer, mass spectrometer VG 70-70EQ with primary FAB ion source and LC /MSD Agilent 1100 with ESI. Elemental analysis was performed with a Euro Vector EA-3000. Thin-layer chromatography was performed on precoated TLC films Alugram (layer 0.20 mm silica gel). HPLC analysis was performed with a Shimadzu LC -2030 3D Plus.

X-ray Crystallography

The colorless crystals of diastereomer **A** ($C_{36}H_{37}ClN_4O_7$) are triclinic. At 293 K, a = 10.3733(17), b = 12.0572(13), c = 16.474(2) Å, α = 73.728(10)°, β = 74.040(13)°, γ = 82.795(11)°, V = 1899.1(5) Å^3, M_r = 673.14, Z = 2, space group *P*-1, d_{calc} = 1.177 g/cm^3, μ(MoK$_\alpha$) = 0.150 mm^{-1}, F(000) = 708. Intensities of 13448 reflections (6674 independent, R_{int} = 0.087) were measured with an «Xcalibur-3» diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 50°). The structure was solved by direct methods using the SHELXTL package.[28] Positions of the hydrogen atoms were located from electron density difference maps and refined by the 'riding' model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refine-

ment against F^2 in anisotropic approximation for non-hydrogen atoms using 6674 reflections was converged to wR_2 = 0.216 (R_1 = 0.073 for 2969 reflections with $F>4\sigma(F)$, S = 0.971).

CCDC 2250972 (molecule **7**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Ugi Products 7a–o; General Procedure

A mixture of aldehyde **2** (0.29 mmol) and amine **5** (0.29 mmol) in MeOH (2 mL) was stirred at 25 °C for 50 min. Then pyrrolone **4** (0.29 mmol) and *tert*-butyl isocyanide **6** (0.29 mmol) were added at 25 °C, successively, and the temperature was increased to 45 °C. The resulting mixture was stirred at 45 °C for 24 h. The reaction was monitored by TLC (R_f = 0.55; *n*-hexane/EtOAc 1:2). The formed white precipitate was immediately filtered off from the warm reaction mixture and dried in vacuum (diastereomer **A**). The mother liquor was allowed to stand at 20 °C for 1 day, and the resulting precipitate was filtered and dried in vacuum (diastereomer **B**).

N-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(4-methoxyphenyl)acetamido)acetamide (7a)

Diastereomer ***A***

Yield 96 mg (49%); white solid; mp 249–251 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, OH), 7.72 (s, 1 H, NH), 6.10–7.56 (m, 12 H, ArH), 6.73 (s, 1 H, CH isoxazole), 5.98 (s, 1 H, CH), 5.58 (s, 1 H, CH pyrrolone), 3.62 (s, 3 H, OCH_3), 3.28 (d, J = 17.6 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.18 (d, J = 17.6 Hz, 1 H, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.7, 168.5, 165.1, 158.2, 156.1, 142.5, 135.2, 134.6, 132.7, 132.3, 131.9, 131.8, 131.5, 129.1, 128.7, 127.8, 122.8, 113.4, 94.9, 63.1, 60.6, 55.1, 50.4, 30.4, 28.4, 12.1.

MS (ESI): m/z = 677 (100) $[M + H]^+$, 604 (50).

Anal. Calcd for $C_{35}H_{34}Cl_2N_4O_6$: C, 62.04; H, 5.06; N, 8.27. Found: C, 62.0; H, 5.09; N, 8.22.

Diastereomer ***B***

Yield 57 mg (29%); light-yellow solid; mp 217–219 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1 H, OH), 7.80 (s, 1 H, NH), 6.40–7.46 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 5.94 (s, 1 H, CH), 5.54 (s, 1 H, CH pyrrolone), 3.62 (s, 3 H, OCH_3), 3.19 (d, J = 17.3 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.22 (d, J = 17.3 Hz, 1 H, CH_2), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.8, 168.6, 165.2, 158.2, 156.1, 142.4, 135.2, 134.5, 132.5, 132.2, 131.8, 131.7, 131.6, 128.7, 128.6, 127.8, 123.5, 113.4, 94.9, 63.1, 60.8, 55.1, 50.4, 30.2, 28.4, 12.0.

MS (ESI): m/z = 677 $[M + H]^+$, 604 (40).

Anal. Calcd for $C_{35}H_{34}Cl_2N_4O_6$: C, 62.04; H, 5.06; N, 8.27. Found: C, 62.07; H, 5.11; N, 8.24.

N-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(*N*-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)acetamido)acetamide (7b)

Mixture of diastereomers **A**/**B** (diastereomeric ratio 50:50).

Yield 81 mg (41%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 0.5 H-**B**, OH), 9.98 (s, 0.5 H-**A**, OH), 7.87 (s, 0.5 H-**B**, NH), 7.80 (s, 0.5 H-**A**, NH), 6.33–7.60 (m, 12 H, ArH), 6.75 (s, 0.5 H-**B**, CH isoxazole), 6.73 (s, 0.5 H-**A**, CH isoxazole), 6.02 (s, 0.5 H-**A**, CH), 5.98 (s, 0.5 H-**B**, CH), 5.61 (s, 0.5 H-**A**, CH pyrrolone), 5.54 (s, 0.5 H-**B**, CH pyrrolone), 3.19–3.25 (m, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.20–2.26 (m, 1 H, CH_2), 1.29 (s, 4.5 H-**B**, *t*-Bu), 1.25 (s, 4.5 H-**A**, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 170, 168.7, 168.0, 167.9, 165.2, 164.9, 156.1, 156.0, 142.5, 138.1, 137.9, 135.2, 135.1, 134.2, 132.7, 132.5, 132.4, 132.3, 131.9, 131.8, 129.1, 128.7, 128.6, 128.4, 127.9, 123.0, 123.1, 122.2, 94.9, 63.1, 63.0, 60.8, 60.6, 50.5, 50.4, 30.5, 30.4, 28.4, 12.1.

MS (ESI): m/z (%) = 683 (100) $[M + H]^+$.

Anal. Calcd for $C_{34}H_{31}Cl_3N_4O_5$: C, 59.88; H, 4.58; N, 8.22. Found: C, 59.84; H, 4.54; N, 8.27.

N-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(*p*-tolyl)acetamido)acetamide (7c)

Diastereomer ***A***

Yield 78 mg (41%); white solid; mp 228–230 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.0 (s, 1 H, OH), 7.73 (s, 1 H, NH), 6.58–7.60 (m, 12 H, ArH), 6.73 (s, 1 H, CH isoxazole), 6.0 (s, 1 H, CH), 5.58 (s, 1 H, CH pyrrolone), 3.27 (d, J = 17.8 Hz, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, J = 17.8 Hz, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.6, 168.3, 165.0, 156.0, 142.5, 137.1, 136.4, 135.2, 134.5, 132.7, 132.3, 131.8, 130.2, 129.0, 128.9, 128.6, 127.8, 122.8, 94.9, 63.1, 60.6, 50.4, 30.4, 28.4, 20.5, 12.0.

MS (ESI): m/z (%) = 661 (100) $[M + H]^+$.

Anal. Calcd for $C_{35}H_{34}Cl_2N_4O_5$: C, 63.54; H, 5.18; N, 8.47. Found: C, 63.60; H, 5.14; N, 8.51.

N-(*tert*-Butyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(4-methoxyphenyl)acetamido)-2-(4-methoxyphenyl)acetamide (7d)

Diastereomer ***A***

Yield 127 mg (65%); white solid; mp 251–253 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.99 (s, 1 H, OH), 7.58 (s, 1 H, NH), 5.96–7.63 (m, 12 H, ArH), 6.70 (s, 1 H, CH isoxazole), 5.94 (s, 1 H, CH), 5.59 (s, 1 H, CH pyrrolone), 3.65 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.27 (d, J = 17.6 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, J = 17.6 Hz, 1 H, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 169.4, 168.5, 165.1, 158.6, 158.1, 156.1, 142.5, 135.3, 132.8, 131.9, 131.4, 129.1, 128.7, 127.4, 123.1, 113.4, 113.3, 113.2, 95.0, 63.4, 60.8, 55.2, 55.0, 50.3, 30.6, 28.5, 12.1.

MS (ESI): m/z (%) = 673 (82) $[M + H]^+$, 600 (70).

Anal. Calcd for $C_{36}H_{37}ClN_4O_7$: C, 64.23; H, 5.54; N, 8.32. Found: C, 64.18; H, 5.49; N, 8.37.

Diastereomer ***B***.

Yield 40 mg (20%); white solid; mp 191–193 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.99 (s, 1 H, OH), 7.66 (s, 1 H, NH), 6.36–7.52 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 5.88 (s, 1 H, CH), 5.54 (s, 1 H, CH pyrrolone), 3.63 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.17 (d, J = 17.4 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.21 (d, J = 17.4 Hz, 1 H, CH_2), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR spectrum (100 MHz, DMSO-d_6): δ = 170.1, 169.4, 168.5, 158.4, 158.0, 156.1, 142.4, 135.2, 132.5, 131.9, 131.5, 131.3, 128.7, 128.6, 127.3, 123.6, 113.3, 113.2, 113.1, 94.9, 63.3, 60.8, 55.0, 54.9, 50.3, 30.3, 28.4, 12.1.

MS (ESI): *m*/*z* (%) = 673 (38) [M + H]$^+$, 600 (41), 695 (100) [M + Na]$^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_7$: C, 64.23; H, 5.54; N, 8.32. Found: C, 64.15; H, 5.45; N, 8.4.

_N_-(*tert*-Butyl)-2-(_N_-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1_H_-pyrrol-3-yl)acetamido)-2-(4-methoxyphenyl)acetamide (7e)

Mixture of diastereomers **A**/**B** (diastereomeric ratio 40:60).

Yield 175 mg (89%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (s, 0.6 H-**B**, OH), 10.02 (s, 0.4 H-**A**, OH), 7.80 (s, 0.6 H-**B**, NH), 7.73 (s, 0.4 H-**A**, NH), 6.30–7.65 (m, 12 H, ArH), 6.76 (s, 0.6 H-**B**, CH isoxazole), 6.73 (s, 0.4 H-**A**, CH isoxazole), 5.98 (s, 0.4 H-**A**, CH), 5.93 (s, 0.6 H-**B**, CH), 5.62 (s, 0.4 H-**A**, CH pyrrolone), 5.55 (s, 0.6 H-**B**, CH pyrrolone), 3.64 (s, 3 H, OCH_3), 3.10–3.32 (m, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.17–2.27 (m, 1 H, CH_2), 1.29 (s, 5H-**B**, *t*-Bu), 1.25 (s, 4 H-**A**, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 170.5, 169.8, 169.7, 168.4, 168.3, 165.7, 159.0, 156.5, 142.9, 138.8, 138.7, 135.8, 135.7, 133.2, 133.0, 132.9, 132.6, 132.5, 131.7, 129.6, 129.1, 128.8, 128.7, 127.4, 123.7, 122.9, 113.8, 95.4, 63.7, 55.4, 50.8, 30.9, 28.9, 12.6.

MS (ESI): *m*/*z* (%) = 677 (64) [M + H]$^+$.

Anal. Calcd for $C_{35}H_{34}Cl_2N_4O_6$: C, 62.04; H, 5.06; N, 8.27. Found: C, 61.98; H, 5.01; N, 8.31.

_N_-(*tert*-Butyl)-2-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1_H_-pyrrol-3-yl)-_N_-(*p*-tolyl)acetamido)-2-(4-methoxyphenyl)acetamide (7f)

*Diastereomer***A**.

Yield 85 mg (45%); white solid; mp 245–247 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.99 (s, 1 H, OH), 7.58 (s, 1 H, NH), 6.48–7.47 (m, 12 H, ArH), 6.72 (s, 1 H, CH isoxazole), 5.94 (s, 1 H, CH), 5.58 (s, 1 H, CH pyrrolone), 3.64 (s, 3 H, OCH_3), 3.25 (d, *J* = 17.4 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.17 (d, *J* = 17.4 Hz, 1 H, CH_2), 2.12 (s, 3 H, CH_3), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 169.2, 168.2, 165.1, 158.5, 156.1, 142.4, 136.8, 136.6, 135.3, 132.7, 131.3, 130.2, 129.0, 128.8, 128.6, 127.3, 123.0, 113.2, 94.9, 63.3, 60.7, 55.0, 50.3, 30.5, 28.5, 20.5, 12.1.

MS (ESI): *m*/*z* (%) = 657 (100) [M + H]$^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_6$: C, 65.8; H, 5.68; N, 8.53. Found: C, 65.88; H, 5.62; N, 8.59.

*Diastereomer***B**.

Yield 43 mg (23%); white solid; mp 205–207 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.0 (s, 1 H, OH), 7.68 (s, 1 H, NH), 6.35–7.50 (m, 12 H, ArH), 6.74 (s, 1 H, CH isoxazole), 5.90 (s, 1 H, CH), 5.54 (s, 1 H, CH pyrrolone), 3.63 (s, 3 H, OCH_3), 3.16 (d, *J* = 17.6 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, *J* = 17.6 Hz, 1 H, CH_2), 2.12 (s, 3 H, CH_3), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 169.4, 168.3, 165.3, 158.4, 156.1, 142.4, 136.8, 136.8, 135.2, 132.6, 131.3, 130.3, 128.8, 128.7, 128.6, 127.3, 123.6, 113.2, 95.0, 63.4, 60.9, 55.0, 50.4, 30.4, 28.5, 20.6, 12.1.

MS (ESI): *m*/*z* (%) = 657 (100) [M + H]$^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_6$: C, 65.8; H, 5.68; N, 8.53. Found: C, 65.84; H, 5.61; N, 8.61.

Methyl 4-(2-(*tert*-Butylamino)-1-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1_H_-pyrrol-3-yl)-_N_-(4-methoxyphenyl)acetamido)-2-oxoethyl)benzoate (7g)

*Diastereomer***A**.

Yield 85 mg (42%); white solid; mp 240–242 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, OH), 7.80 (s, 1 H, NH), 6.12–7.77 (m, 12 H, ArH), 6.73 (s, 1 H, CH isoxazole), 6.06 (s, 1 H, CH), 5.59 (s, 1 H, CH pyrrolone), 3.79 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.29 (d, *J* = 17.1 Hz, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.21 (d, *J* = 17.1 Hz, 1 H, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.6, 168.4, 165.9, 165.1, 158.2, 156.0, 142.5, 141.0, 135.2, 132.7, 131.9, 131.5, 131.0, 130.5, 129.1, 128.7, 128.6, 122.8, 113.5, 94.9, 63.5, 60.6, 55.1, 52.1, 50.4, 30.3, 28.4, 12.1.

MS (ESI): *m*/*z* (%) = 701 (100) [M + H]$^+$.

Anal. Calcd for $C_{37}H_{37}ClN_4O_8$: C, 63.38; H, 5.32; N, 7.99. Found: C, 63.29; H, 5.37; N, 8.02.

Diastereomer ***B***.

Yield 71 mg (35%); white solid; mp 157–159 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.01 (s, 1 H, OH), 7.84 (s, 1 H, NH), 6.46–7.76 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 6.02 (s, 1 H, CH), 5.54 (s, 1 H, CH pyrrolone), 3.79 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.21 (d, *J* = 17.6 Hz, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.25 (d, *J* = 17.6 Hz, 1 H, CH_2), 1.29 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0, 168.6, 168.4, 165.8, 165.0, 158.2, 156.0, 142.5, 141.0, 135.6, 131.6, 131.5, 131.1, 130.4, 129.4, 128.6, 128.5, 122.7, 121.2, 113.4, 94.9, 63.5, 60.7, 55.1, 52.1, 50.4, 30.3, 28.4, 12.0.

MS (ESI): *m*/*z* = 701 [M + H]$^+$.

Methyl 4-(2-(*tert*-Butylamino)-1-(_N_-(4-chlorophenyl)-2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1_H_-pyrrol-3-yl)acetamido)-2-oxoethyl)benzoate (7h)

*Diastereomer***A**.

Yield 92 mg (45%); white solid; mp 227–229 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.0 (s, 1 H, OH), 7.87 (s, 1 H, NH), 6.40–7.78 (m, 12 H, ArH), 6.73 (s, 1 H, CH isoxazole), 6.10 (s, 1 H, CH), 5.61 (s, 1 H, CH pyrrolone), 3.79 (s, 3 H, OCH_3), 3.23 (d, *J* = 17.0 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.25 (d, *J* = 17.0 Hz, 1 H, CH_2), 1.25 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.4, 168.0, 165.8, 165.2, 164.9, 156.0, 142.5, 140.6, 138.0, 135.1, 132.6, 132.3, 130.4, 129.1, 128.7, 128.6, 128.4, 123.0, 122.2, 94.9, 63.4, 60.8, 52.0, 50.5, 30.3, 28.3, 12.0.

MS (ESI): *m*/*z* (%) = 705 (100) [M + H]$^+$.

Anal. Calcd for $C_{36}H_{34}Cl_2N_4O_7$: C, 61.28; H, 4.86; N, 7.94. Found: C, 61.21; H, 4.90; N, 8.04.

*Diastereomer***B**.

Yield 71 mg (35%); light-yellow solid; mp 170–172 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.93 (s, 1 H, NH), 7.01–7.81 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 6.06 (s, 1 H, CH), 5.53 (s, 1 H, CH pyrrolone), 3.78 (s, 3 H, OCH_3), 3.24 (d, *J* = 17.3 Hz, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.24 (d, *J* = 17.3 Hz, 1 H, CH_2), 1.29 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.0, 168.4, 168.2, 165.8, 165.5, 156.1, 142.9, 140.6, 138.0, 135.3, 132.6, 132.5, 132.3, 130.4, 129.1, 128.8, 128.7, 128.6, 128.4, 122.6, 94.9, 63.4, 60.8, 52.1, 50.5, 30.3, 28.4, 12.0.

MS (ESI): *m*/*z* (%) = 705 (100) $[M + H]^+$.

Anal. Calcd for $C_{36}H_{34}Cl_2N_4O_7$: C, 61.28; H, 4.86; N, 7.94. Found: C, 61.21; H, 4.91; N, 7.89.

Methyl 4-(2-(*tert*-Butylamino)-1-(2-(2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(*p*-tolyl)acetamido)-2-oxoethyl)benzoate (7i)

*Diastereomer**B**.*

Yield 48 mg (24%); white solid; mp 178–180 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1 H, OH), 7.85 (s, 1 H, NH), 6.75–7.75 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 6.03 (s, 1 H, CH), 5.54 (s, 1 H, CH pyrrolone), 3.78 (s, 3 H, OCH_3), 3.20 (d, *J* = 17.3 Hz, 1 H, CH_2), 2.33 (s, 3 H, CH_3), 2.22 (d, *J* = 17.3 Hz, 1 H, CH_2), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.4, 165.8, 165.2, 156.0, 142.5, 140.8, 141.0, 137.1, 136.4, 135.1, 132.5, 130.4, 130.2, 128.9, 128.7, 128.6, 128.5, 123.4, 94.9, 63.5, 60.8, 52.1, 50.5, 30.2, 28.4, 20.4, 12.0.

MS (ESI): *m*/*z* (%) = 685 (100) $[M + H]^+$, 612 (50).

Anal. Calcd for $C_{37}H_{37}ClN_4O_7$: C, 64.86; H, 5.44; N, 8.18. Found: C, 64.8; H, 5.49; N, 8.25.

*Mixture of diastereomers **A**/**B** (diastereomeric ratio 50:50).*

Yield 67 mg (34%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1 H, OH), 7.86 (s, 0.5 H-**B**, NH), 7.78 (s, 0.5 H-**A**, NH), 6.69–7.77 (m, 12 H, ArH), 6.75 (s, 0.5 H-**B**, CH isoxazole), 6.73 (s, 0.5 H-**A**, CH isoxazole), 6.07 (s, 0.5 H-**A**, CH), 6.03 (s, 0.5 H-**B**, CH), 5.58 (s, 0.5 H-**A**, CH pyrrolone), 5.54 (s, 0.5 H-**B**, CH pyrrolone), 3.79 (s, 3 H, OCH_3), 3.18–3.28 (m, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.18–2.24 (m, 1 H, CH_2), 2.11 (s, 3 H, CH_3), 1.28 (s, 4.5 H-**B**, *t*-Bu), 1.23 (s, 4.5 H-**A**, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 170.0, 168.4, 168.3, 168.2, 165.8, 165.2, 165.0, 156.0, 142.5, 142.4, 141.0, 140.9, 137.1, 137.0, 136.4, 136.3, 135.2, 135.1, 132.7, 132.5, 130.4, 130.2, 129.0, 128.8, 128.7, 128.6, 123.3, 122.7, 94.9, 63.5, 60.8, 60.6, 52.0, 50.4, 50.3, 30.3, 30.2, 20.4, 12.0.

MS (ESI): *m*/*z* (%) = 685 (100) $[M + H]^+$.

Anal. Calcd for $C_{37}H_{37}ClN_4O_7$: C, 64.86; H, 5.44; N, 8.18. Found: C, 64.82; H, 5.47; N, 8.25.

***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(2-(4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(4-methoxyphenyl)acetamido)acetamide (7j)**

*Diastereomer**A**.*

Yield 80 mg (41%); white solid; mp 239–241 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.90 (s, 1 H, OH), 7.72 (s, 1 H, NH), 5.90–7.62 (m, 12 H, ArH), 6.70 (s, 1 H, CH isoxazole), 5.99 (s, 1 H, CH), 5.52 (s, 1 H, CH pyrrolone), 3.72 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.25 (d, *J* = 17.1 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, *J* = 17.1 Hz, 1 H, CH_2), 1.22 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.5, 165.2, 165.0, 158.2, 156.0, 142.5, 135.6, 134.6, 132.3, 132.0, 131.9, 131.6, 129.4, 127.8, 123.4, 122.8, 121.1, 113.4, 94.9, 63.1, 60.7, 55.1, 55.4, 30.4, 28.4, 12.0.

MS (ESI): *m*/*z* (%) = 673 (80) $[M + H]^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_7$: C, 64.23; H, 5.54; N, 8.32. Found: C, 64.31; H, 5.51; N, 8.39.

*Diastereomer**B**.*

Yield 64 mg (33%); light-yellow solid; mp 210–212 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.90 (s, 1 H, OH), 7.78 (s, 1 H, NH), 6.40–7.48 (m, 12 H, ArH), 6.72 (s, 1 H, CH isoxazole), 5.95 (s, 1 H, CH), 5.47 (s, 1 H, CH pyrrolone), 3.75 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.17 (d, *J* = 17.3 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.22 (d, *J* = 17.3 Hz, 1 H, CH_2), 1.28 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 168.8, 168.6, 165.2, 158.2, 156.1, 142.4, 135.2, 134.5, 132.5, 132.2, 131.8, 131.7, 131.6, 128.7, 128.6, 127.8, 123.5, 113.4, 94.9, 63.1, 60.8, 55.1, 50.4, 30.2, 28.4, 12.0.

MS (ESI): *m*/*z* (%) = 673 (100) $[M + H]^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_7$: C, 64.23; H, 5.54; N, 8.32. Found: C, 64.29; H, 5.50; N, 8.37.

***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(N-(4-chlorophenyl)-2-(4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)acetamido)acetamide (7k)**

*Diastereomer**A**.*

Yield 88 mg (45%); white solid; mp 253–255 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1 H, OH), 7.85 (s, 1 H, NH), 6.08–7.75 (m, 12 H, ArH), 6.70 (s, 1 H, CH isoxazole), 6.02 (s, 1 H, CH), 5.53 (s, 1 H, CH pyrrolone), 3.72 (s, 3 H, OCH_3), 3.29 (d, *J* = 17.1 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, *J* = 17.1 Hz, 1 H, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 168.5, 168.1, 165.1, 159.1, 156.1, 142.2, 138.0, 134.2, 132.5, 132.4, 132.2, 131.8, 128.5, 128.4, 128.0, 127.6, 123.1, 114.0, 95.1, 63.0, 60.8, 55.1, 50.4, 30.5, 28.4, 12.0.

MS (ESI): *m*/*z* (%) = 677 (100) $[M + H]^+$.

Anal. Calcd for $C_{35}H_{34}Cl_2N_4O_6$: C, 62.04; H, 5.06; N, 8.27. Found: C, 62.11; H, 5.01; N, 8.31.

***N*-(*tert*-Butyl)-2-(4-chlorophenyl)-2-(2-(4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl)-*N*-(*p*-tolyl)acetamido)acetamide (7l)**

*Diastereomer**A**.*

Yield 93 mg (49%); white solid; mp 223–225 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.88 (s, 1 H, OH), 7.71 (s, 1 H, NH), 6.68–7.20 (m, 12 H, ArH), 6.70 (s, 1 H, CH isoxazole), 6.01 (s, 1 H, CH), 5.51 (s, 1 H, CH pyrrolone), 3.73 (s, 3 H, OCH_3), 3.24 (d, *J* = 17.8 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.18 (d, *J* = 17.8 Hz, 1 H, CH_2), 2.13 (s, 3 H, CH_3), 1.22 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.9, 168.6, 168.5, 165.2, 159.2, 156.1, 142.2, 137.1, 136.4, 134.6, 132.3, 131.9, 130.2, 128.8, 128.4, 127.8, 127.7, 123.6, 114.1, 95.1, 63.0, 60.8, 55.2, 50.4, 30.4, 28.4, 20.5, 12.1.

MS (ESI): *m*/*z* (%) = 657 (100) $[M + H]^+$.

Anal. Calcd for $C_{36}H_{37}ClN_4O_6$: C, 65.8; H, 5.68; N, 8.53. Found: C, 65.83; H, 5.61; N, 8.59.

Methyl 4-(3-(2-((2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)(4-methoxyphenyl)amino)-2-oxoethyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)benzoate (7m)

*Diastereomer**A**.*

Yield 80 mg (40%); white solid; mp 215–217 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.1 (s, 1 H, OH), 7.60 (s, 1 H, NH), 6.02–7.94 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 5.95 (s, 1 H, CH), 5.68 (s, 1 H, CH pyrrolone), 3.83 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 3.27 (d, *J* = 17.6 Hz, 1 H, CH_2), 2.31 (s, 3 H, CH_3), 2.16 (d, *J* = 17.6 Hz, 1 H, CH_2), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 169.3, 168.4, 165.9, 165.1, 158.5, 158.1, 156.1, 142.5, 141.8, 131.8, 131.6, 131.3, 131.1, 129.6, 129.5, 127.4, 122.8, 113.3, 113.2, 94.9, 63.3, 61.0, 55.1, 55.0, 52.2, 50.3, 30.5, 28.5, 12.1.

MS (ESI): *m*/*z* (%) = 697 (82) $[M + H]^+$.

Anal. Calcd for $C_{38}H_{40}N_4O_9$: C, 65.51; H, 5.79; N, 8.04. Found: C, 65.58; H, 5.73; N, 8.10.

*Diastereomer**B***.

Yield 42 mg (21%); light-yellow solid; mp 163–165 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.1 (s, 1 H, OH), 7.70 (s, 1 H, NH), 6.38–7.94 (m, 12 H, ArH), 6.77 (s, 1 H, CH isoxazole), 5.89 (s, 1 H, CH), 5.67 (s, 1 H, CH pyrrolone), 3.87 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3), 3.18 (d, *J* = 17.8 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.19 (d, *J* = 17.8 Hz, 1 H, CH_2), 1.29 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 169.5, 168.5, 166.0, 165.3, 158.4, 158.0, 156.1, 142.4, 141.8, 131.9, 131.6, 131.3, 129.5, 129.3, 127.3, 127.1, 123.4, 113.3, 113.1, 94.9, 63.3, 61.2, 55.0, 54.9, 52.2, 50.3, 30.4, 28.5, 12.1.

MS (ESI): *m*/*z* (%) = 697 (100) $[M + H]^+$.

Anal. Calcd for $C_{38}H_{40}N_4O_9$: C, 65.51; H, 5.79; N, 8.04. Found: C, 65.54; H, 5.71; N, 8.11.

Methyl 4-(3-(2-((2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)(4-chlorophenyl)amino)-2-oxoethyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)benzoate (7n)

Mixture of diastereomers **A**/**B** (diastereomeric ratio 50:50).

Yield 148 mg (73%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.1 (s, 0.5 H-**B**, OH), 10.0 (s, 0.5 H-**A**, OH), 7.81 (s, 0.5 H-**B**, NH), 7.74 (s, 0.5 H-**A**, NH), 6.20–7.94 (m, 12 H, ArH), 6.79 (s, 0.5 H-**B**, CH isoxazole), 6.76 (s, 0.5 H-**A**, CH isoxazole), 5.99 (s, 0.5 H-**A**, CH), 5.93 (s, 0.5 H-**B**, CH), 5.71 (s, 0.5 H-**A**, CH pyrrolone), 5.69 (s, 0.5 H-**B**, CH pyrrolone), 3.87 (s, 1.5 H-**B**, OCH_3), 3.83 (s, 1.5 H-A, OCH_3), 3.64 (s, 1.5 H-**A**, OCH_3), 3.63 (s, 1.5 H-**B**, OCH_3), 3.17–3.34 (m, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.14–2.26 (m, 1 H, CH_2), 1.30 (s, 4.5H-**B**, *t*-Bu), 1.25 (s, 4.5 H-**A**, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2; 170.1; 169.3; 169.2; 167.8; 165.9; 165.8; 165.2; 165.0; 158.6; 158.5; 156.1; 142.5; 141.7; 138.3; 138.1; 132.4; 132.1; 131.3; 131.2; 129.5; 129.3; 128.2; 127.4; 127.0; 126.9; 123.0; 122.3; 113.3; 94.9; 63.3; 63.2; 61.2; 61.0; 54.9; 52.2; 50.4; 50.3; 30.7; 30.5; 28.4; 12.0.

MS (FAB): *m*/*z* (%) = 701 (12) $[M + H]^+$, 723 (48) $[M + Na]^+$.

Anal. Calcd for $C_{37}H_{37}ClN_4O_8$: C, 63.38; H, 5.32; N, 7.99. Found: C, 63.44; H, 5.29; N, 8.04.

Methyl 4-(3-(2-((2-(*tert*-Butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)(*p*-tolyl)amino)-2-oxoethyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)benzoate (7o)

*Diastereomer**A***.

Yield 126 mg (64%); white solid; mp 224–226 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.04 (s, 1 H, OH), 7.62 (s, 1 H, NH), 6.04–7.92 (m, 12 H, ArH), 6.75 (s, 1 H, CH isoxazole), 5.98 (s, 1 H, CH), 5.67 (s, 1 H, CH pyrrolone), 3.85 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.25 (d, *J* = 17.7 Hz, 1 H, CH_2), 2.32 (s, 3 H, CH_3), 2.18 (d, *J* = 17.7 Hz, CH_2), 2.11 (s, 3 H, CH_3), 1.23 (s, 9 H, *t*-Bu).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.1, 169.2, 168.1, 165.8, 165.0, 158.4, 156.1, 142.9, 142.4, 141.8, 136.8, 131.3, 129.5, 129.4, 128.7, 127.3, 127.2, 122.7, 113.1, 94.8, 63.3, 61.0, 54.9, 52.2, 50.2, 30.5, 28.4, 20.5, 12.0.

MS (Mass-FAB): *m*/*z* (%) = 681 (13) $[M + H]^+$.

Anal. Calcd for $C_{38}H_{40}CN_4O_8$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.09; H, 5.88; N, 8.27.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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