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МОДИФИКАЦИИ 7-ГИДРОКСИ-3-(5-ФЕНИЛ-1,3,4-ТИАДИАЗОЛ-2-ИЛ)-6-ЭТИЛХРОМОНА

Проведена модификация 7-гидрокси-3-(5-фенил-1,3,4-тиадиазол-2-ил)-6-этилхромона карбоксильной функцией путем алкилирования эфирами галогенуксусных кислот с последующим гидролизом и исследована трансформация полученной кислоты под действием гидроксиламина в 2-[2-амино-6-этил-4-оксо-3-(5-фенил-1,3,4-тиадиазол-2-ил)-4Н-7-хроменилокси]уксусную кислоту.

Ключевые слова: 7-гидрокси-3-тиадиазолилхромоны, алкилирование, рециклизация, 2-аминохромон.

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MODIFICATIONS OF 7-HYDROXY-3-(5-PHENYL-1,3,4-THIADIAZOL-2-YL)-6-ETHYLCHROMONE

To expand the range of 3-(1,3,4-thiadiazol-2-yl)chromones' polyfunctionality by introducing carboxyl and amino functions the modificaton of 7-hydroxy-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-6-ethylchromone was carried out. Alkylation of the latter with methyl 2-bromacetate or ethyl 2-chloracetate in dimethyl formamide in the presence of potassium carbonate resulted in methyl or ethyl 2-[6-ethyl-4-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4H-7-chromenyloxy]acetates. The following hydrolysis of the esters in the mixture of acetic and sulfuric acids led to 2-[6-ethyl-4-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4H-7-chromenyloxy]acetic acid. The transformation of the resulting acid under action of hydroxylamine hydrochloride was investigated. The action of hydroxylamine hydrochloride in pyridine on 2-[6-ethyl-4-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4H-7-chromenyloxy]acetic acid adduced to opening of γ-pyrone cycle and subsequent cyclization of intermediates into isoxazole derivatives, which undergo further ring opening followed by intramolecular reaction of nitrile and hydroxyl groups to form 2-[2-amino-6-ethyl-4-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4H-7-chromenyloxy]acetic acid. These transformations allowed to introduce carboxyl and amino functions into 3-(1,3,4-thiadiazol-2-yl)chromones, which in turn makes them available for use and allows to extend the spectrum of their application.

Keywords: 7-hydroxy-3-thiadiazolylchromones, alkylation, recyclization, 2-aminochromone.

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SYNTHESIS OF NEW CHIRAL α-AMINO ACID DERIVED 3,5-DISUBSTITUTED 1,2,4-TRIAZOLES

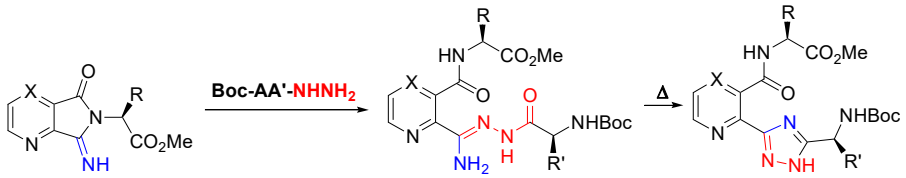
An enantio pure pyrazine-linked 3,5-disubstituted 1,2,4-triazoles, an amide bond isosteres, were synthesized by ring closure of acylated with L-α-amino acid residues N-acylamidrazone precursors. Pyrrolidine ring opening of methyl esters of (2S)-2-(imino-oxo-dihydro-6H-pyrrolo[3,4-b] (hetero)aryl)alkanoic acid bearing amino acid moiety at endo-N atom of pyrrolidine ring with Boc-protected L-Phe amino acid hydrazide was firstly shown to provide a new convenient method for preparing pyridine or pyrazine derived N-acylamidrazone intermediates in good yields. No cyclic pyrrolopyridines(pyrazines) derivatives as a result of exo-imine group substitution were found as final compounds. Pyrazine-linked 1,2,4-triazoles were successfully synthesized by thermal cyclization of N-acylamidrazone derivatives using microwave-assisted irradiation. However, pyridine-containing 1,2,4-triazoles of this type are not available from corresponding N-acylamidrazones probably due to their high thermo and solvent sensibility. Under reaction conditions they underwent decomposition followed by intramolecular cyclization giving rise starting pyrrolopyridines. (Z)/(E) isomerism of N-acylamidrazone intermediates was studied by means of NMR spectroscopy and quantum chemical calculations. It was found to be dependent on the heterocycle type. A NOE experiment for phenylalanine substituted pyridine-based N-acylamidrazone demonstrated the occurrence of Z and E rotamers due to amide-type isomerism. Theoretical calculations (B3LYP DFT with the standard 6-31G(d,p) basis set) on N-acylamidrazone isomers indicated amide bond isomerism for pyridine-linked N-acylamidrazones and C=N bond isomerism for pyrazine-linked analogues.

Keywords: azines, triazole, microwave irradiation, amide isomerism, computational study.

Introduction. The 1,2,4-triazole scaffold displays a wide range of biological activities and can be used as amide bond replacement (isosteres) that has been widely used in peptide mimicry [1-3]. This ring system can act as both hydrogen bond acceptor and donor, which make it useful in establishing intermolecular features in interactions between peptide ligands and receptors. Thus, various 1,2,4-triazoles containing chiral *α*-amino acids have been designed and synthesized. L-Tryptophane bearing 1,2,4-triazoles have been reported as ghrelin receptor (GHS-R1a) ligands [4], lysine derivatives exhibit histone deacetylase (HDAC) inhibitor activity [5] with high metabolic stability and dipeptido-1,2,4-triazole derivatives with a high level of central nervous system (CNS) activity [6].

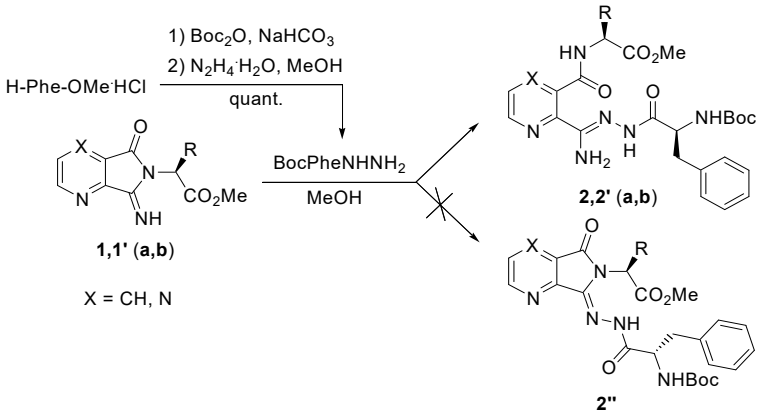
N-acylamidrazones substrates could be used as common intermediates to synthesize 1,2,4-triazoles [7]. We proposed the approach including the pyrrolidine ring opening with Boc-L-amino acid hydrazides in order to obtain *N*-acylamidrazones. This would be followed by an intramolecular condensation of the latter and formation of 3,5-disubstituted 1,2,4-triazoles (Scheme 1).

Herein, we describe the attempted synthesis of 1,2,4-triazole derived peptidomimetics including structural and computational study of *N*-acylamidrazone precursors.



Scheme 1. The proposed route to *α*-amino acid derived 1,2,4-triazoles

Results and discussion. The application of pyrrolopyridines(pyrazines) **1**,**1'**(**a**,**b**) as precursors was chosen for the synthesis of *N*-acylamidrazones and further construction of amino acid derived 1,2,4-triazoles. First, Boc-protected phenylalanine hydrazide was synthesized from phenylalanine methyl ester starting with NH_2 protection using Di-*tert*-butyl dicarbonate followed by treatment with hydrazine monohydrate giving rise the corresponding precursor in quantitative yield (Scheme 2). Second, the preparation of *N*-acylamidrazones was performed by the reaction of **1**,**1'**(**a**,**b**) with Boc-Phe-$NHNH_2$ in MeOH at room temperature (Scheme 2). No cyclic pyrrolopyridines(pyrazines) derivatives **2''** the formation of which could be expected according to a previously reported condensation of the 1-imino-1*H*-isoindol-3-amine and its pyrazine analogue with amino acid hydrazides that afforded 1*H*-isoindole- and 5*H*-pyrrolo[3,4-*b*]pyrazine-based peptidomimetics [8,9] were found.



X	R		Yield, %
CH	Me	**2a**	82
CH	Bn	**2b**	97
N	Me	**2'a**	50
N	Bn	**2'b**	82

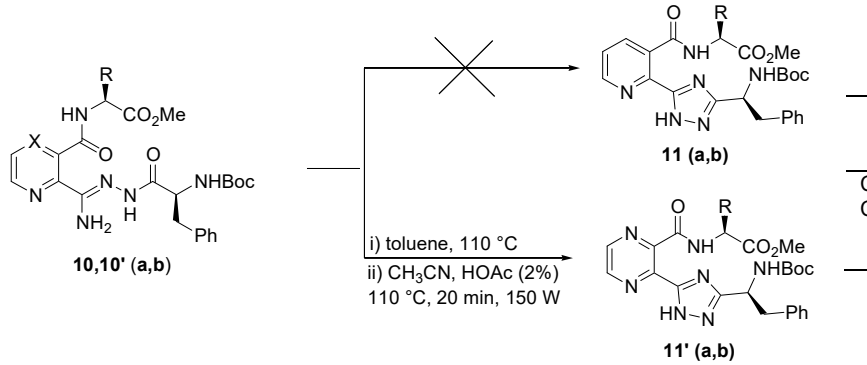
Scheme 2. Synthesis of the *N*-acylamidrazone derivatives 2,2'(a,b)

The formation of acylamidrazones **2**,**2'** proceeded *via* pyrrolidine ring opening by amino acid hydrazide, and afforded products **2a**,**b** and **2'b** in very good yields as analytically pure powders. However, we did not succeed to increase the yield of acylamidrazone **2'a** above 50%. Comparison of the reactivity of our starting material and known previously described acylamidrazone precursors towards the corresponding hydrazide nucleophiles allowed us to compare them with highly reactive epoxy imidates, the precursors of epoxy acylamidrazones [10]. Therefore, we have found a new approach towards a straightforward and mild synthesis of *N*-acylamidrazones.

The presence of two sets of signals in the ^{1}H and ^{13}C NMR spectra of the products in DMSO-d_6 and duplication of signals in IR spectra demonstrated the existence of (*Z*)/(*E*) isomerism.

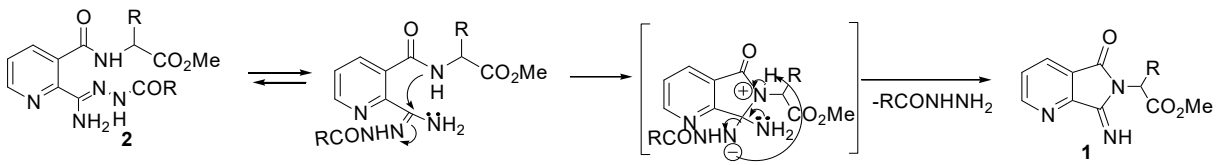
Following literature analogies, the cyclization of *N*-acylamidrazones **2**,**2'**(a,b) into the corresponding 1,2,4-triazoles was probed in different solvents (toluene, CH_3CN, THF, 1,4-dioxane, MeOH, DMF) at elevated temperatures (60–150 °C). However, we were able to convert only the pyrazine-based acylamidrazones **2'**(**a**,**b**) while in the case of the pyridine counterparts the reaction led to the pyrrolopyridines **1a**,**b** and conversion into the target 1,2,4-triazoles did not exceed 10% under any of the tested conditions (Scheme 3). The conventional cyclization of acylamidrazones **2'a**,**b** in toluene at 110 °C for 18 h furnished triazoles **3'a**,**b** in 45 and 64% yield, respectively. Alternatively, microwave assisted reaction of **2'a**,**b** and cat. HOAc in CH_3CN offered several advantages: reduced reaction time up to 20 min and increased yields up to 87% (Scheme 3).

The formation of pyrrolopyridines **1a**,**b** was suggested to be a result of termal decomposition followed by further intramolecular cyclization giving a pyrrolidine ring (Scheme 4).



X	R		Isolated yield(i), %	Isolated yield(ii), %
CH	Me	**3a**	-	-
CH	Bn	**3b**	-	-
N	Me	**3'a**	45	85
N	Bn	**3'b**	64	87

Scheme 3. Synthesis of the target amino acid-derived 1,2,4-triazoles



Scheme 4. Suggested mechanism of intramolecular cyclization for pyridine-based compounds 2

Structural and thermodynamic studies of acylamidrazones 2,2'

In the ^{1}H and ^{13}C NMR spectra of acylamidrazone derivatives **2**,**2'**, two sets of signals are observed in DMSO-d_6 for most of the protons and carbons. This indicates that compounds exist as a mixture of *Z* and *E* isomers. Our literature survey has revealed that acylamidrazones can display amide hydrazone (**A**) – hydrazide imide (**B**) tautomerism because of C=N bond or they can exist as *Z* and *E* isomers due to C=N or amide bond isomerism (Fig. 1) [11-13]. From these observations the problem of resonance assignment has become apparent.

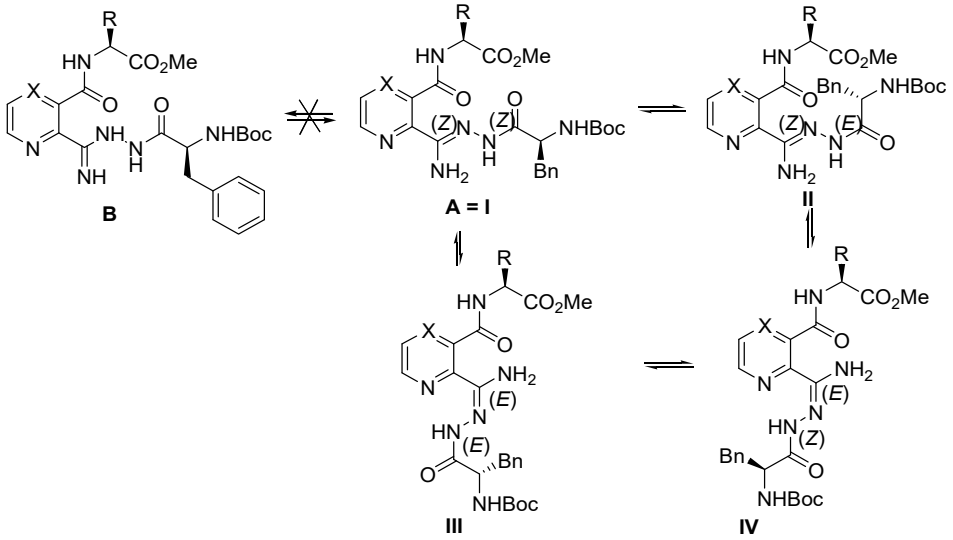


Fig. 1. Possible isomerism of *N*-acylamidrazones 2,2'

Two sets of signals were observed in the ^{1}H NMR spectra for most of the protons of compounds **2**,**2'** indicating the presence of only two forms. We abandon plausible tautomeric forms **A** and **B** as two singlets due to observation of NH_2 signals in the ^{1}H NMR spectra corresponding to each isomer. A NOESY experiment was performed for assignment of two populations. A NOE effect between the NH-N= and the NH_2 protons of compound **2b** was observed for each conformation and supported the occurrence of *Z* and *E* rotamers due to amide-type isomerism (Fig. 2).

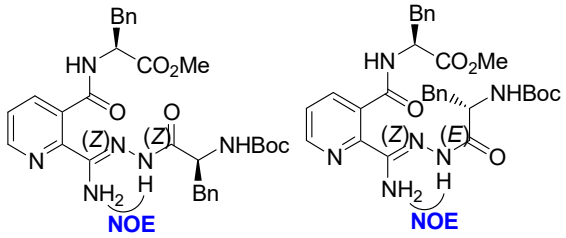


Fig. 2. NOE effects in a mixture of *Z* and *E* amide isomers of 2b

However, the NH-N= protons in the rest of the series (**2a**, **2'a**, **2'b**) appeared with the same chemical shifts, thus we were unable to prove amide isomerism for these compounds. Moreover, no correlations were found in NOESY spectra that could help to assign proton signals to either *Z* or *E* isomers. In order to find the most stable structures, calculations were performed on all conformers of compounds and the results are listed in Table 1.

It was found that isomeric forms **I** and **II** corresponding to *Z*/*E* amide isomers, have the lowest energies for pyridine derivatives **2a,b**, therefore are the most stable in *vacuo* according to the calculations which is in agreement with experimental data for compound **2b**. However, pyrazine counterparts **2'a** and **2'b** showed *Z*/*E* isomerism around C=N bond, as it follows from the lowest energies values for conformers **II** and **III** (Table 1). In accord with previous calculations, the *E* amide isomer has the lowest energy in all series. The obtained energy differences (ΔE) between **I** and **II** for **2a,b** and **II** and **III** for **2'a,b** were in the range 2.49-4.91 kcal/mol and depended mainly on the heterocycle (higher for pyridine derivatives **2a,b** and lower for pyrazine derivatives **2'a,b**).

Table 1

Absolute and relative energies (in atomic units and kcal/mol, respectively) for isomers of *N*-acylamidrazones calculated at B3LYP level of theory using 6-31G(d,p) basis set

R	X		E_I [a.u.]	E_{II} [a.u.]	E_{III} [a.u.]	E_{IV} [a.u.]	ΔE [kcal/mol]
Me	CH	**2a**	-1751.286540	-1751.294366	-1751.280429	-1751.277908	4.91
Bn	CH	**2b**	-1982.258785	-1982.265883	-1982.256207	-1982.252817	4.45
Me	N	**2'a**	-1767.328071	-1767.335808	-1767.331841	-1767.326273	2.49
Bn	N	**2'b**	-1998.299683	-1998.306963	-1998.300874	-1998.298101	3.82

Note: Energies include both electronic and thermal energies. Geometries were obtained by energy minimization at the stated level of theory. ΔE was calculated as a difference between energies of the most stable configurations (highlighted values).

We have also attempted to determine isomeric ratio of compounds in DMSO-d_6 and to test the effect of solvent polarity (Table 4). Surprisingly, a partial decomposition of the pyridine derivatives **2a,b** occurred after adding $CDCl_3$ (Table 2, Scheme 4). The proton signals of the pyrrolopyridines **1a,b** appears in a mixture DMSO-d_6/$CDCl_3$ and becomes predominant with increasing the ratio up to 1:3. The instant formation of **1a,b** was also detected by LCMS analysis.

Table 2

Influence of solvent polarity on the *E/Z* isomeric ratio of compounds 2,2'

DMSO-d_6/$CDCl_3$	1:0	1:1	1:3
	E/Z ratio		
2a	1/0.63	-[a]	-[b]
2b	1/0.56	-[c]	-[d]
	Z/E ratio		
2'a	1/0.70	1/0.66	1/0.50
2'b	1/0.67	1/0.69	1/0.55

[a]Mixture containing **2a** and **1a** (~45%); [b]Mixture containing **2a** and **1a** (~65%); [c]Mixture containing **2b** and **1b** (~35%); [d]Mixture containing **2b** and **1b** (~55%).

We proposed the route suggested for termal decomposition of **2a,b** which depicted in Scheme 4. Such an effect is negligible (<5%) in case of the pyrazine analogues **2'** and the proportion of *Z* conformer decreasing with increasing solvent polarity. From these results, it is clear that in polar solvent like DMSO-d_6 all compounds are stabilized by hydrogen bonding with solvent molecules. We suggested hydrogen bonding between NH-amide and nitrogen of the pyrazine ring that can stabilize the pyrazine derivatives in non hydrogen bonding solvents, precluding intramolecular cyclization into the precursors **1'**.

Conclusions. A new straightforward and mild synthesis of amino acid derived *N*-acylamidrazones *via* pyrrolidine ring opening by hydrazide of amino acid was identified. The (*Z*)/(*E*) isomerism was found to be dependent on the heterocycle type, and was studied by NMR spectroscopy and quantum chemical calculations. Althought, pyrazine-based *N*-acylamidrazones studied appeared the effective precursors for microwave-assisted cyclodehydration into the corresponding chiral *α*-amino acid-derived 1,2,4-triazoles, we were not able to obtain pyridine-linked 1,2,4-triazoles due to high thermo and solvent sensibility.

Experimental part. Microwave-assisted reactions were performed using CEM Focused Microwave™ Synthesis System, Model Discover, in a septa capped 10 mL reaction vessels with stirring. Melting points were measured on a Buchi M–560 Melting Point apparatus. IR spectra were recorded with a Bruker Alpha Platinum ATR Spectrometer. NMR spectra were measured with a Bruker Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C) with TMS as standard.

Synthesis of Compounds **2,2'**(**a,b**); General Procedure:

Methanolic (25 mL) suspension of the methyl ester of a (2*S*)-2-(imino-oxo-dihydro-6*H*-pyrrolo[3,4-*b*] (hetero)aryl)-alkanoic acid **1**, **1'** (1 mmol) and Boc-(*S*)Phe-$NHNH_2$ (1.1 mmol) was stirred overnight at r.t. Then, the precipitate was filtered off, washed with cold methanol (10 mL) and dried *in vacuo*.

*Methyl (2S)-2-[({2-[amino((Z)-2-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazono)methyl]pyridin-3-yl}carbonyl)amino]propanoate (**2a**)*

White solid; yield: 0.420 g (82%); mp 188-189 °C. IR: ν_{max} = 3435, 3318, 3062, 3027, 2982, 1738, 1688, 1660, 1634, 1590, 1526, 1455, 1390, 1294, 645 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.86 and 9.75 (2×s, 1H, NH-N=), 8.77 and 8.54 (2×d, *J* = 6.0, 7.0 Hz, 1H, NH), 8.68 – 8.59 (m, 1H, H_{Ar}), 7.87 and 7.78 (dd, *J* = 7.7, 1.5 Hz, 1H, H_{Ar}), 7.57 and 7.54 (2×dd, *J* = 7.8, 4.9 Hz, 1H, H_{Ar}), 7.33 - 7.08 (m, 5H, 5×H_{Ar}), 7.01 and 6.21 (2×d, *J* = 8.4 Hz, 1H, NHBoc), 6.58 and 6.53 (2×s, 2H, NH_2), 4.90 – 4.78 and 4.30 – 4.19 (2×m, 1H, C<u>H</u>NHBoc), 4.69 – 4.59 and 4.59 – 4.48 (2×m, 1H, C<u>H</u>CH_3), 3.63 and 3.60 (2×s, 3H, OCH_3), 2.99 – 2.70 (m, 2H, CH_2), 1.38 – 1.17 (m, 12H, $(CH_3)_3$ and CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.4 (172.0), 167.6, 167.3, 167.1, 155.3 (154.8), 148.5 (148.7), 148.5 (149.5), 147.3 (144.1), 138.1 (137.8), 136.8 (136.6), 132.0, 129.2 (129.5), 128.0 (127.8), 126.2 (126.0), 123.8 (123.7), 77.9 (77.8), 54.9 (52.3), 51.7 (51.8), 48.3 (47.9), 37.8 (36.2), 28.1, 16.7 (16.7).

*Methyl (2S)-2-[({2-[amino((Z)-2-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazono)methyl]pyridin-3-yl}carbonyl)amino]-3-phenylpropanoate (**2b**)*

White solid; yield: 0.570 g (97%); mp 183-185 °C. IR: ν_{max} = 3449, 3320, 3063, 3024, 2971, 2930, 1737, 1690, 1662, 1631, 1563, 1524, 1454, 1392, 1267, 1250, 1201, 699, 651 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.91 and 9.87 (2×s, 1H, NH-N=), 9.03 (d, *J* = 6.6 Hz, 1H, NH), 8.67 – 8.58 (m, 1H, H_{Ar}), 7.74 and 7.66 (2×d, *J* = 6.6, 7.5 Hz, 1H, H_{Ar}), 7.56 – 7.46 (m, 1H, H_{Ar}), 7.33 – 7.08 (m, 10H, 10×H_{Ar}), 7.00 and 6.11 (2×d, *J* = 8.5 Hz, 1H, NHBoc), 6.62 and 6.55 (2×s, 2H, NH_2), 4.85 – 4.68 (m, 1H, CH), 4.79 – 4.68 and 4.32 – 4.28 (2,×m, 1H, CH), 3.52 and 3.45 (2×s, 3H, OCH_3), 3.20 – 2.71 (m, 4H, 2×CH_2), 1.30 and 1.27 (2×s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.9 (171.8), 167.5, 167.3, 167.0, 155.2 (154.7), 149.1, 148.7, 148.0, 144.3, 138.1 (137.8), 137.4 (136.9), 137.1 (136.6), 131.7, 129.6, 129.2, 128.1, 128.0, 127.7, 126.4, 126.2, 126.2, 125.9, 123.8 (123.7), 77.9 (77.7), 54.5 (54.7), 53.8 (52.4), 51.4, 37.9 (37.1), 36.7 (36.1), 28.0.

*Methyl (2S)-2-[({3-[amino((Z)-2-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazono)methyl]pyrazin-2-yl}carbonyl)amino]propanoate (**2'a**)*

White solid; yield: 0.257 g (50%); mp 191-192 °C. IR: ν_{max} = 3440, 3319, 3066, 2982, 2931, 1737, 1687, 1666, 1635, 1596, 1543, 1525, 1453, 1295, 1165, 648 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.91 and 9.80 (2×s, 1H, NH-N=), 8.86 – 8.65 (m, 3H, H_{Ar} and NH), 7.35 – 7.08 (m, 5H, 5×H_{Ar}), 7.03 and 6.38 (2×d, *J* = 8.0 Hz, 1H, NHBoc), 6.61 (s, 2H, NH_2), 4.88 – 4.75 and 4.32 – 4.16 (2×m, 1H, C<u>H</u>NHBoc), 4.68 – 4.52 (m, 1H, C<u>H</u>CH_3), 3.64 and 3.57 (2×s, 3H, OCH_3), 2.99 – 2.61 (m, 2H, CH_2), 1.39 – 1.20 (m, 12H, $(CH_3)_3$ and CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.2, 172.9, 172.3, 167.3, 165.4, 164.9, 155.3 (154.9), 148.3, 147.3, 146.6, 145.6, 145.0, 143.2 (143.8), 143.8 (143.0), 138.1, 129.2 (129.4), 128.0 (127.8), 126.2 (125.9), 77.9 (77.7), 54.8 (52.5), 51.7, 48.1 (47.7), 37.8 (36.2), 28.1, 16.9.

*Methyl (2S)-2-[({3-[amino((Z)-2-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-phenylpropanoyl}hydrazono)methyl]pyrazin-2-yl}carbonyl)amino]-3-phenylpropanoate (**2'b**)*

White solid; yield: 0.483 g (82%); mp 171-174 °C. IR: ν_{max} = 3488, 3432, 3320, 3062, 3028, 2980, 1747, 1687, 1664, 1634, 1601, 1538, 1519, 1449, 1385, 1163, 698 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 9.93 and 9.32 (2×s, 1H, NH-N=), 8.83 – 8.71 (m, 2H, H_{Ar} and 0.4H, NH), 8.69 (d, *J* = 2.3 Hz, 0.6H, NH), 7.34 – 7.08 (m, 10H, 10×H_{Ar}), 7.02 and 6.32 (d, *J* = 8.4 Hz, 1H, NHBoc), 6.63 (s, 2H, NH_2), 4.79 (dd, *J* = 13.2, 6.3 Hz, 1H, CH), 4.82 – 4.74 and 4.35 – 4.22 (2×m, 1H, C<u>H</u>NHBoc), 3.52 and 3.44 (2×s, 3H, OCH_3), 3.25 – 2.63 (m, 4H, 2×CH_2), 1.28 and 1.26 (2×s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 172.1, 171.7, 171.3, 167.3, 165.3, 164.6, 155.3 (154.9), 147.7, 146.5, 146.1, 145.3, 144.1, 143.6, 143.5, 143.1, 138.1 (138.2), 137.1 (136.6), 129.4, 129.2, 128.1, 128.0, 127.7, 126.5, 126.3, 126.2, 125.9, 77.9 (77.7), 54.3 (54.7), 53.6 (52.6), 51.45 (51.6), 37.9, 36.8, 36.1, 28.0.

Synthesis of Compounds **3'a,b**; General Procedure:

A 5 mL CEM microwave process vessel was charged with **2'** (**a**,**b**; 0.2 mmol) in CH_3CN (5 mL) with addition of cat. HOAc (2%) and the vessel was capped. The mixture was stirred and

heated under microwave conditions (150 W) at 110 °C for 20 min. The solution was then concentrated under vacuo and purified by NP-HPLC with a gradient of MeOH (1-5% v/v) in $CHCl_3$ to yield 1,2,4-triazoles **3'a**,**b**.

*Methyl (2S)-2-({[3-(5-{(1S)-1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-1H-1,2,4-triazol-3-yl)pyrazin-2-yl]carbonyl}amino)propanoate (**3'a**)*

Light-yellow solid; yield: 0.084 g (85%); mp 177-180 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.04 (s, 1H, H_{Ar}), 8.76 (d, J = 6.3 Hz, 1H, NH_{amide}), 8.69 (s, 1H, H_{Ar}), 7.25 – 7.09 (m, 6H, $NH_{triazole}$ and 5×H_{Ar}), 5.66 (d, J = 6.4 Hz, 1H, NHBoc), 5.42 – 5.27 (m, 1H, C<u>H</u>NHBoc), 4.79 (*pseudo*-p, J = 7.2 Hz, 1H, C<u>H</u>CH_3), 3.82 (s, 3H, OCH_3), 3.45 – 3.23 (m, 2H,), 1.59 (d, J = 7.1 Hz, 3H, CH_3), 1.37 (s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 164.7, 164.4, 155.9, 152.9, 147.9, 143.2, 142.6, 141.5, 137.6, 130.3, 128.9, 127.2, 80.2, 53.5, 50.8, 49.6, 41.7, 29.0, 18.7.

*Methyl (2S)-2-({[3-(5-{(1S)-1-[(tert-butoxycarbonyl)amino]-2-phenylethyl}-1H-1,2,4-triazol-3-yl)pyrazin-2-yl]carbonyl}amino)-3-phenylpropanoate (**3'b**)*

Yellow solid; yield: 0.099 g (87%); mp 152-154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.96 (d, J = 1.4 Hz, 1H, H_{Ar}), 8.71 – 8.49 (m, 2H, NH_{amide} and H_{Ar}), 7.33 – 7.04 (m, 11H, $NH_{triazole}$ and 10×H_{Ar}), 5.49 (d, J = 8.5 Hz, 1H, NHBoc), 5.40 – 5.19 (m, 1H, C<u>H</u>NHBoc), 5.06 (dd, J = 13.9, 6.2 Hz, 1H, C<u>H</u>$COOCH_3$), 3.77 (s, 3H, OCH_3), 3.41 – 3.14 (m, 4H, 2×CH_2), 1.37 (s, 9H, $(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 164.8, 155.8, 153.6, 147.5, 142.9, 142.7, 142.2, 137.7, 136.1, 130.2, 129.8, 129.3, 128.8, 128.0, 127.1, 80.0, 54.7, 53.2, 50.8, 41.7, 38.5, 28.9. LC/MS: m/z = 572 $[M+H]^+$.

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СИНТЕЗ НОВИХ ХІРАЛЬНИХ *α*-АМІНОКИСЛОТНИХ ПОХІДНИХ 3,5-ДИЗАМІЩЕНИХ 1,2,4-ТРИАЗОЛІВ

Енантіомерно чисті азино-зв'язані 3,5-дизаміщені 1,2,4-триазоли синтезовані термальною циклізацією при мікрохвильовому опроміненні. Розкриття піролідинового кільця гідразидом амінокислоти дає новий зручний метод одержання прекурсорів N-ациламідразонів. Ізомери останніх вивчені ЯМР-спектроскопією та комп'ютерними розрахунками.

Ключові слова: азини, триазол, мікрохвильове опромінення, амідна ізомерія, комп'ютерні розрахунки.

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СИНТЕЗ НОВЫХ ХИРАЛЬНЫХ *α*-АМИНОКИСЛОТНЫХ ПРОИЗВОДНЫХ 3,5-ДИЗАМЕЩЕННЫХ 1,2,4-ТРИАЗОЛОВ

Енантиомерно чистые азино-связанные 3,5-дизамещенные 1,2,4-триазолы синтезированы термальною циклизацией при микроволновом облучении. Раскрытие пирролидинового кольца гидразидом аминокислоты дает новый удобный метод получения прекурсоров N-ациламидразонов. Изомеры последних изучены ЯМР-спектроскопией и компьютерными расчетами.

Ключевые слова: азины, триазол, микроволновое облучение, амидная изомерия, компьютерные расчеты.