

## Synthesis of 2-R-5-amino-4-(1*H*-tetrazol-5-yl)-1,3-oxazoles from 2-R-5-amino-1,3-oxazole-4-carbonitriles

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### ABSTRACT

This short communication reports about new 5-amino-4-(1*H*-tetrazol-5-yl)-1,3-oxazoles which were synthesized by [3+2] cycloaddition of 2-R-5-amino-1,3-oxazole-4-carbonitriles and trimethylsilyl azide with dibutyltin oxide present. The reaction conditions provided high yields of the products, and were tolerant to some active functional fragments in the oxazole substituents (amino, amido, and hydroxy group). In the case of 2-((4-cyano-2-phenyloxazol-5-yl)amino)-*N*-methylacetamide the by-product (*N*-((1-(2-(methylamino)-2-oxoethyl)-1*H*-tetrazol-5-yl)(1*H*-tetrazol-5-yl)methyl)-benzamide) was formed together with the expected tetrazolyloxazole.

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## 1. Introduction

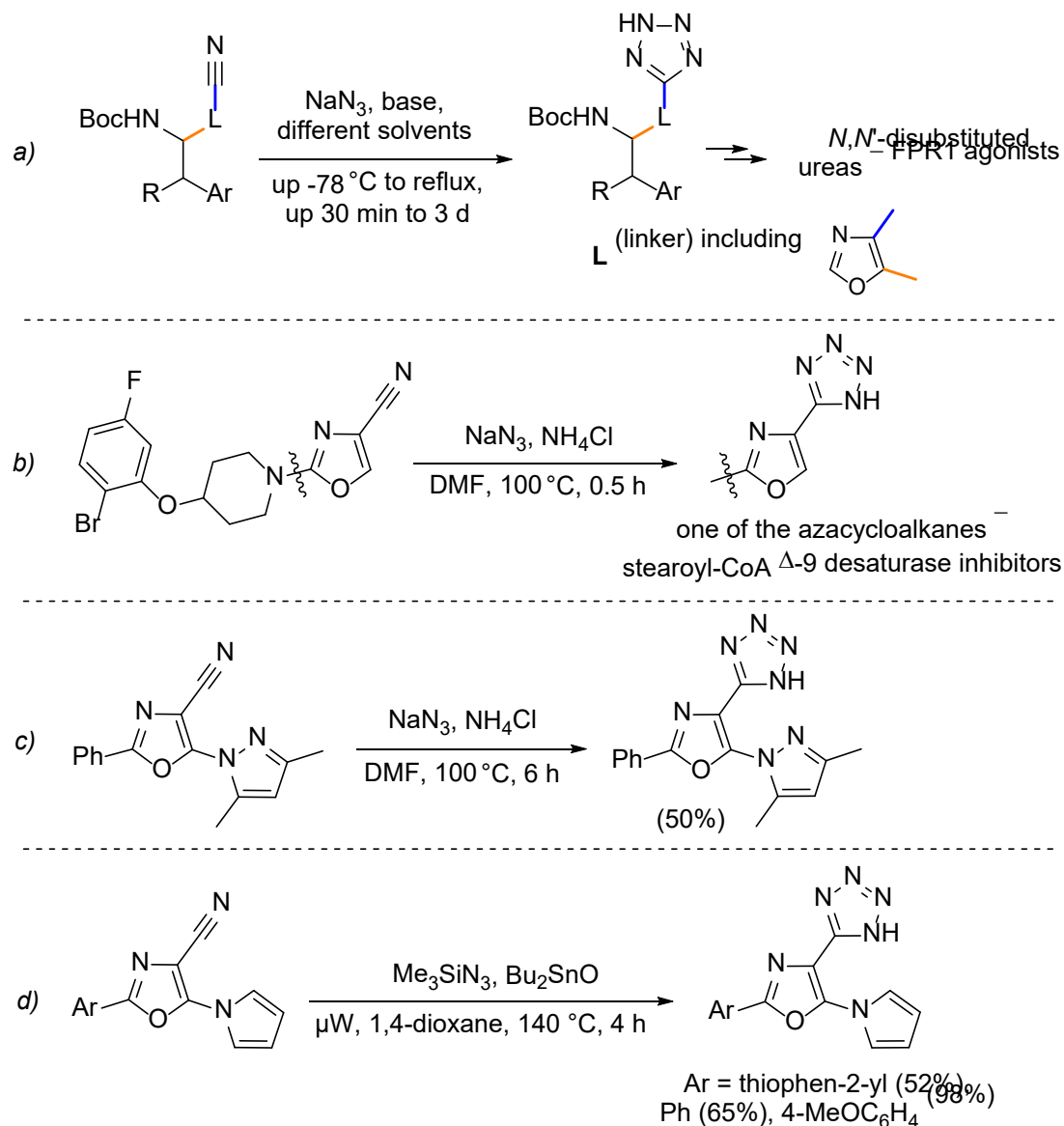
One of the current topics in tetrazole chemistry is the creation of biologically active molecules in which the tetrazole substituent plays a role of the carboxylic group metabolically stable bioisostere.<sup>1-4</sup> Tetrazole drugs are very miscellaneous, but [3+2] cycloaddition of azide anion to nitrile group is still a common method of tetrazole fragment creation.<sup>4,5</sup> This reaction is appropriate particularly for (hetero)aromatic nitriles,<sup>5</sup> and our attention has been drawn by oxazole nitriles (Scheme 1a<sup>6</sup> and 1b<sup>7</sup>). It is known that some substituted oxazoles can be considered as peptidomimetics,<sup>8</sup> and from this perspective, 5-aminooxazoles are special derivatives, because even without additional substituents there are two hidden amide fragments in such molecules.

The participation of the CN group of 5-aminooxazole-4-carbonitrile in [3+2] cycloaddition, which leads to the formation of triazoles, has been studied only for pyrazole (Scheme 1c)<sup>9</sup> and pyrrole derivatives (Scheme 1d).<sup>10</sup> It doesn't allow us to predict the behaviour in this reaction, for example, for oxazoles with the free amino group or with the residues of functionalized amines.

Earlier we developed the effective procedure for synthesis of 5-aminooxazole-4-carbonitriles with a number of active functional groups.<sup>11</sup> The transformation of nitrile group into tetrazole cycle seemed the obvious logical step of 5-aminooxazole-4-carbonitriles modification; and in this short communication we represent our first achievements in this area.

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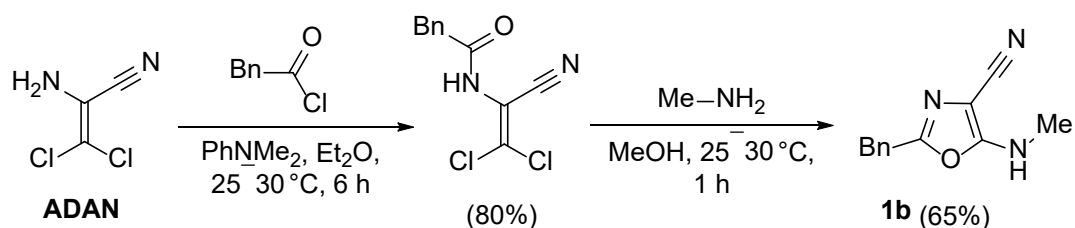
E-mail address [shablykin@gmail.com](mailto:shablykin@gmail.com) (O. Shablykin)



**Schemes 1.** The known examples of [3+2] cycloaddition of 5-aminooxazole-4-carbonitriles and azides (literature data).

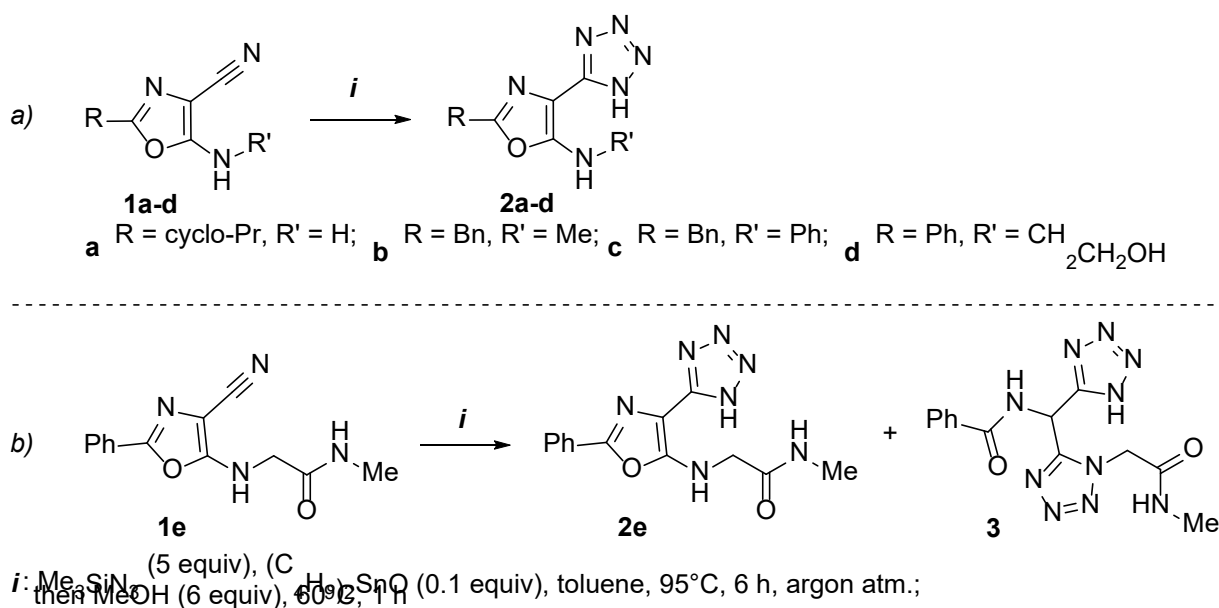
## 2. Results and Discussion

To study this problem, 5-aminooxazole-4-carbonitriles **1a-e** with cyclopropyl (**1a**), benzyl (**1b,c**) and phenyl (**1d,e**) substituents in position 2 were selected as the substrates (**Schemes 2, 3**). The amino function was represented by NH<sub>2</sub> group (**1a**), *N*-methyl (**1b**), *N*-phenyl (**1c**) and *N*-2-hydroxyethyl (**1d**) substituents, as well as the residue of *N*-methylglycinamide (**1e**). Substrate **1a** was synthesized by us using interaction of 2-aminomalononitrile tosylate and cyclopropanecarbonyl chloride; the similar synthetic scheme and also compound **1a** characterization were described in Ref.<sup>10</sup> The obtaining of initial oxazoles **1b-e** was based on 2-amino-3,3-dichloroacrylonitrile (ADAN) cyclization and described in publication;<sup>11</sup> an example of this synthetic pathway is shown in **Scheme 2** for the new compound **1b**.



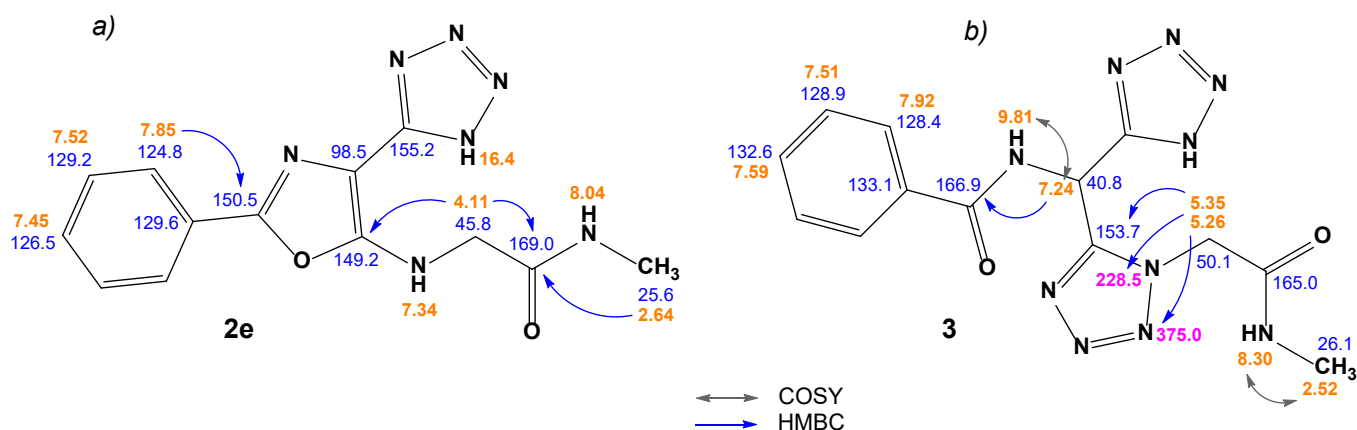
**Schemes 2.** The synthetic pathway for the compound **1b**.

There are two sources of azide anion that were successfully tested earlier for the conversion of the oxazole cyano group into tetrazole (**Scheme 1**). However, when we tried to involve compound **1a** in [3+2] cycloaddition in the manner shown in **Scheme 1b,c**, no conversion was observed. So, we chose the combination of  $\text{Me}_3\text{SiN}_3$  and  $(\text{C}_4\text{H}_9)_2\text{SnO}$  for the tetrazole synthesis. The reaction was carried out in argon atmosphere in toluene solution (**Scheme 3**). The transformation of the nitrile group of substrates **1a-d** into the tetrazole cycle in these conditions occurred with minimal side processes, and solubility of tetrazolyl oxazoles in non-polar solvents is very low; that's why the crystalline products were easily filtered off from the reaction mixture.



**Schemes 3.** The transformation of the substrates **1a-d** nitrile group into tetrazole cycle.

The process was equally successful for the four starting substances **1a-d** (**Scheme 3a**), regardless of the nature of amine residue in position 5 of the oxazole. However, a mixture of substances was obtained as the result of *N*-methylglycinamide **1e** usage in this reaction: in addition to the expected product **2e**, compound **3** with two tetrazole fragments was formed (**Scheme 3b**). Unpredictably, the competitor of nitrile group in interaction with azide was not glycinamide group (this fragment didn't undergo any changes at all), but hidden amide fragment in oxazole. Note that in  $^1\text{H}$  NMR spectra of compounds **2e** and **3** (see the Supplementary information file), the biggest differences relate to signals of  $\text{CH}_2$  link of the glycine fragment. Thus, it is a doublet with a vicinal constant due to the interaction with NH proton in the spectrum of monotetrazole **2e**, but in the spectrum of bis-tetrazole **3** these two diastereotopic protons, of course, are presented by two doublets with a geminal constant. The structures of compounds **2e**, **3** were established by NMR spectroscopy (**Fig. 1**). In particular, the location of the glycine residue in position 1 of one of the tetrazole cycle was confirmed by a NOE experiment (Supplementary information file).



**Fig. 1.** The chemical shifts of  $^1\text{H}$  and  $^{13}\text{C}$  atoms of the compound **2e** (a), and  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$  atoms of the compound **3** (b), established by COSY, NOESY, HMBC, HMQC NMR experiments

This type of recyclization of 5-aminoxazoles was not yet described in the literature,<sup>12</sup> so further studies on a wider range of substrates are needed for assumptions about its mechanism. Now we only can suppose that the formation of the additional tetrazole unit starts with a nucleophilic attack of an azide-anion on electron-depleted position 5 of the oxazole core. At least, the lability of oxazole cycle with a glycine fragment in 5th position was previously explained by the intramolecular activation of the oxazole cycle by carboxyl group;<sup>13</sup> this hypothesis is also supported by recently obtained data on recyclization of compound **1e** and other similar derivatives in acidic medium.<sup>14</sup>

The value of synthesized 5-amino-4-(1*H*-tetrazol-5-yl)-1,3-oxazoles as bioisosteres of 5-aminoxazole-4-carboxylic acids is enhanced by the fact that the last ones are relatively easily decarboxylated.<sup>15</sup>

[3+2] Cycloaddition with azide-anion doesn't have regioselectivity problem, which is so actual for the reaction with organic azide;<sup>16</sup> however, the question of tautomerism still remains. So, it is relevant to note that the 1*H*-tautomeric form of tetrazoles is shown here for simplification; but, naturally, the tetrazole proton is very mobile, and the tautomeric form is not fixed. In particular, the authors of patent<sup>7</sup> (**Scheme 1b**) reported obtaining a mixture of two products as a result of alkylation of 4-(tetrazol-5-yl)-1,3-oxazoles tetrazole fragment with a bromoacetic acid ester.

### 3. Conclusions

In conclusion, the use of trimethylsilyl azide with dibutyltin oxide is really an effective technique for the conversion of nitrile group of 2-*R*-5-amino-1,3-oxazole-4-carbonitriles into tetrazole cycle. The character of the amino function at the position 5 of oxazole-4-carbonitrile has a little effect on the products yield, even in the case of free amino group and aminoethanol residue. In addition, initial 2-*R*-5-amino-1,3-oxazole-4-carbonitriles can be easily synthesized using the method allowing for variation of the 2-*R* fragment and substituents near the amino group. Therefore, in future investigations, the number of known 5-amino-4-(1*H*-tetrazol-5-yl)-1,3-oxazoles can be significantly expanded. These substances not only have undoubted importance for medical chemistry, but they can also be a source of new heterocyclic derivatives, such as the isolated product of oxazole recyclization into the tetrazole cycle.

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### 4. Experimental

#### 4.1. General Methods

All reagents and solvents were purchased from Enamine Ltd. ([www.enamine.net](http://www.enamine.net)). TLC characterization was performed with pre-coated silica gel GF254 (0.2 mm). NMR spectra of the obtained products were recorded on a Varian Unity Plus 400 spectrometer (400 MHz for <sup>1</sup>H, 101 MHz for <sup>13</sup>C), a Bruker 170 spectrometer (500 MHz for <sup>1</sup>H, 126 MHz for <sup>13</sup>C), or an Agilent ProPulse 600 spectrometer (600 MHz for <sup>1</sup>H, 151 MHz for <sup>13</sup>C); <sup>1</sup>H NMR chemical shifts were calibrated using residual undeuterated DMSO ( $\delta = 2.50$  ppm) signal. <sup>13</sup>C NMR chemical shifts are reported relative to the central DMSO ( $\delta = 39.52$  ppm) signal. Melting points were measured on a MPA100 OptiMelt automated melting point system. Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of NAS of Ukraine.

LC/MS spectra were recorded on an Agilent 1100 Series HPLC system equipped with a diode matrix with an Agilent LC/MS mass selective detector (chemical ionization). High-resolution mass spectra (HRMS) were acquired using an Agilent LC/MSD TOF mass spectrometer via electrospray ionization time of flight experiments. The preparative HPLC were performed on 1290 Infinity II LC Purification System.

Physical and spectral properties of compound **1a** see,<sup>10</sup> compound **1c** see,<sup>11</sup> compound **1d** see,<sup>17</sup> compound **1e** see.<sup>14</sup>

#### 4.2. Synthetic Procedures and Spectral Data

4.2.1. 2-Benzyl-5-(methylamino)oxazole-4-carbonitrile (**1b**). Obtained from ADAN as in publication<sup>11</sup> described. Yield 52 % (after two steps). Mp 64-65 °C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 7.99 (1H, br. q, *J* = 4.9 Hz, NH), 7.33 (2H, t, *J* = 7.2 Hz, H-3,5 Ph), 7.21-7.30 (3H, m, H-2,4,6 Ph), 3.96 (2H, s, CH<sub>2</sub>), 2.86 (3H, d, *J* = 4.9 Hz, NCH<sub>3</sub>). <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>),  $\delta$ , ppm: 162.0, 151.6, 135.2, 128.7, 128.6, 127.0, 116.2, 81.5, 33.2, 29.1. MS, *m/z* (*I*<sub>rel</sub>, %): 214 [M+H]<sup>+</sup> (100). Calculated for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>O: %, C, 67.59; H, 5.20; N, 19.71. Found, %, C 67.72; H 5.09; N 19.66.

4.2.2. General Procedure of 4-(1*H*-tetrazol-5-yl)oxazol-5-amines **2a-e** and bis-tetrazole **3** synthesis. The appropriate 5-aminoxazole-4-carbonitrile **1a-e** (4 mmol) was suspended in toluene (20 ml), then Me<sub>3</sub>SiN<sub>3</sub> (2.63 ml, 20 mmol, 5 equiv) and (C<sub>4</sub>H<sub>9</sub>)<sub>2</sub>SnO (0.10 g, 0.4 mmol, 0.1 equiv) were added under argon. The reaction mixture was heated at 95 °C (oil bath

temperature) for 6 h. After cooling to room temperature, MeOH (1.0 ml, 24.7 mmol, 6 equiv) was added. The reaction mixture was heated at 60°C for 1 h, then cooled to room temperature, and filtered; solid was washed with MTBE (5 ml) affording products **2a-d** of more than 90% purity.

For purification compounds **2a-d** were recrystallized from the mixture of MeOH – H<sub>2</sub>O 9 : 1.

The mixture of products **2e** and **3** were separated by preparative HPLC (1-6 min, 40-60% H<sub>2</sub>O / MeCN / 0.1% CF<sub>3</sub>CO<sub>2</sub>H, flow 30 mL/min).

**2-Cyclopropyl-4-(1H-tetrazol-5-yl)oxazol-5-amine (2a)**. Yield 58 %. Mp 174-175°C. <sup>1</sup>H NMR spectrum (500 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 16.09 (1H, br. s, NH tetrazole), 6.76 (2H, s, NH<sub>2</sub>), 1.91-2.08 (1H, m, CH), 0.94-1.02 (2H, m), 0.88 (2H, s). <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 155.0 (C tetrazole), 154.8 (C-2 oxazole), 149.5 (C-5 oxazole), 96.5 (C-4 oxazole), 8.1 (CH *cycloPr*), 7.0 (2 CH<sub>2</sub>). Calculated for C<sub>7</sub>H<sub>9</sub>N<sub>6</sub>O: *m/z* 193.0835. Found: *m/z* 193.0967 [M+H]<sup>+</sup>.

**2-Benzyl-N-methyl-4-(1H-tetrazol-5-yl)oxazol-5-amine (2b)**. Yield 72 %. Mp 155 °C decomp. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 16.16 (1H, br. s, NH tetrazole), 7.22-7.32 (5H, m, Ph), 6.83 (1H, q, *J* = 4.5 Hz, NH), 4.09 (2H, s, CH<sub>2</sub>), 2.94 (3H, d, *J* = 4.5 Hz, NCH<sub>3</sub>). <sup>13</sup>C NMR spectrum (101 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 155.9 (C tetrazole), 152.2 (C-2 oxazole), 149.4 (C-5 oxazole), 135.8 (C-1 Ph), 128.7 (C-3,5 Ph), 128.7 (C-2,6 Ph), 126.9 (C-4 Ph), 95.7 (C-4 oxazole), 33.5 (CH<sub>2</sub>), 29.7 (CH<sub>3</sub>). Calculated for C<sub>12</sub>H<sub>13</sub>N<sub>6</sub>O: *m/z* 257.1146. Found: *m/z* 257.1260 [M+H]<sup>+</sup>.

**2-Benzyl-N-phenyl-4-(1H-tetrazol-5-yl)oxazol-5-amine (2c)**. Yield 81 %. Mp 219-220°C. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 4.20 (2H, s, CH<sub>2</sub>), 6.92 (1H, t, *J* = 7.2 Hz, H-4 Ph), 7.12 (2H, d, *J* = 7.8 Hz, H-2,6 Ph), 7.20-7.31 (3H, m, H-3,5 Ph and H-4 Ph'), 7.31-7.40 (4H, m, H-2,3,5,6 Ph'), 9.08 (1H, s, NH); tetrazole NH signal is very broad due to exchanging processes, and cannot be determined precisely. <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 156.1 (C tetrazole), 148.8 (C-2 oxazole), 140.8 (C-5 oxazole), 135.4 (C-1 Ph), 129.1 (2 CH Ph), 128.8 (2 CH Ph), 128.7 (2 CH Ph), 128.2 (C-1 Ph), 127.1 (C-4 Ph), 121.3 (C-4 Ph), 116.6 (2 CH Ph), 105.9 (C-4 oxazole), 33.7 (CH<sub>2</sub>). Calculated for C<sub>17</sub>H<sub>15</sub>N<sub>6</sub>O: *m/z* 319.1303. Found: *m/z* 319.1319 [M+H]<sup>+</sup>.

**2-((2-Phenyl-4-(1H-tetrazol-5-yl)oxazol-5-yl)amino)ethanol (2d)**. Yield 63 %. Mp 174 °C decomp. <sup>1</sup>H NMR spectrum (400 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 16.30 (1H, br. s, NH tetrazole), 7.87 (2H, br. d, *J* = 6.0 Hz, H-2,6 Ph), 7.38-7.57 (3H, m, H-3-5 Ph), 7.03 (1H, br. t, *J* = 6.0 Hz, NH), 4.96 (1H, br. s, OH), 3.65 (2H, s, CH<sub>2</sub>), 3.57 (2H, s, CH<sub>2</sub>). <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 155.7 (C tetrazole), 150.3 (C-2 oxazole), 149.4 (C-5 oxazole), 129.6 (C-1 Ph), 129.1 (C-3,5 Ph), 126.6 (C-4 Ph), 124.8 (C-2,6 Ph), 97.96 (C-4 oxazole), 60.2 (OCH<sub>2</sub>), 45.7 (NCH<sub>2</sub>). Calculated for C<sub>12</sub>H<sub>13</sub>N<sub>6</sub>O<sub>2</sub>: *m/z* 273.1095. Found: *m/z* 273.1141 [M+H]<sup>+</sup>.

**N-methyl-2-((2-phenyl-4-(1H-tetrazol-5-yl)oxazol-5-yl)amino)acetamide (2e)**. Yield 34 %. Mp 163 °C decomp. <sup>1</sup>H NMR spectrum (500 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 16.40 (1H, br. s, NH tetrazole), 8.04 (1H, br. q, *J* = 4.4 Hz, NHCH<sub>3</sub>), 7.85 (2H, d, *J* = 7.4 Hz, H-2,6 Ph), 7.52 (2H, t, *J* = 7.4 Hz, H-3,5 Ph), 7.45 (1H, t, *J* = 7.4 Hz, H-4 Ph), 7.34 (1H, br. t, *J* = 5.8 Hz, NHCH<sub>2</sub>), 4.11 (2H, d, *J* = 5.8 Hz, CH<sub>2</sub>), 2.64 (3H, d, *J* = 4.4 Hz, CH<sub>3</sub>). <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 169.0 (C=O), 155.2 (C tetrazole), 150.5 (C-2 oxazole), 149.2 (C-5 oxazole), 129.6 (C-1 Ph), 129.2 (C-3,5 Ph), 126.5 (C-4 Ph), 124.8 (C-2,6 Ph), 98.5 (C-4 oxazole), 45.8 (CH<sub>2</sub>), 25.6 (CH<sub>3</sub>). Calculated for C<sub>13</sub>H<sub>14</sub>N<sub>7</sub>O<sub>2</sub>: *m/z* 300.1204. Found: *m/z* 300.1317 [M+H]<sup>+</sup>.

**N-((1-(2-(methylamino)-2-oxoethyl)-1H-tetrazol-5-yl)(1H-tetrazol-5-yl)methyl)benzamide (3)**. Yield 28 %. Mp 262 °C decomp. <sup>1</sup>H NMR spectrum (600 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 9.81 (1H, d, *J* = 7.5 Hz, NHCH), 8.30 (1H, br. q, *J* = 4.5, Hz NHCH<sub>3</sub>), 7.92 (2H, d, *J* = 7.5 Hz, H-2,6 Ph), 7.59 (1H, t, *J* = 7.5 Hz, H-4 Ph), 7.51 (2H, t, *J* = 7.5 Hz, H-3,5 Ph), 7.24 (1H, d, *J* = 7.5 Hz, CH), 5.35 (1H, d, *J* = 16.7 Hz, CHH), 5.26 (1H, d, *J* = 16.7 Hz, CHH), 2.52 (3H, d, *J* = 4.5 Hz, CH<sub>3</sub>); tetrazole NH signals are very broad due to exchanging processes, and cannot be determined precisely. <sup>13</sup>C NMR spectrum (126 MHz, DMSO-*d*<sub>6</sub>), δ, ppm: 166.9 (PhC=O), 165.0 (CH<sub>2</sub>C=O), 153.7 (C tetrazole), 133.1 (C-1 Ph), 132.6 (C-4 Ph), 128.9 (C-3,5 Ph), 128.4 (C-2,6 Ph), 50.1 (CH<sub>2</sub>), 40.8 (CH), 26.1 (CH<sub>3</sub>). Calculated for C<sub>13</sub>H<sub>15</sub>N<sub>10</sub>O<sub>2</sub>: *m/z* 343.1374. Found: *m/z* 343.1413 [M+H]<sup>+</sup>.

## References

- Zou Y., Liu L., Liu J., and Liu G. (2020) Bioisosteres in drug discovery: focus on tetrazole. *Future Med. Chem.*, 12 (2) 91-93.
- Bredael K., Geurs S., Clarisse D., De Bosscher K., and D'hooghe M. (2022) Carboxylic Acid Bioisosteres in Medicinal Chemistry: Synthesis and Properties. *J. Chem.*, 2022 Article ID 2164558.
- Dhiman N., Kaur K., and Jaitak V. (2020) Tetrazoles as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies. *Bioorg. Med. Chem.*, 28 (15) 115599.
- Malik M. A., Wani M. Y., Al-Thabaiti S. A., and Shiekh R. A. (2014) Tetrazoles as carboxylic acid isosteres: chemistry and biology. *J. Incl. Phenom. Macro.*, 78 (1-4) 15-37.

- 5 Vishwakarma R., Gadipelly C., and Mannepalli L. K. (2022) Advances in Tetrazole Synthesis – An Overview. *ChemistrySelect*, 7 (29) e202200706.
- 6 Takahashi H., Watanabe H., Fujii K., Shibasaki M., Kawashima M., Kamiya M., and Ohata K. (2016) Urea derivative or pharmacologically acceptable salt thereof. WO Patent 2016189877.
- 7 Lachance N., Li C. S., Leclerc J.-P., and Ramtohul Y. K. (2009) Novel heteroaromatic compounds as inhibitors of stearoyl-coenzyme A delta-9 desaturase. WO Patent 200973973.
- 8 Apostol T.-V., Chifiriuc M. C., Nitulescu G. M., Oлару O. T., Barbuceanu S.-F., Socea L.-I., Pahontu E. M., Karnezan C. M., and Marutescu L. G. (2022) In Silico and In Vitro Assessment of Antimicrobial and Antibiofilm Activity of Some 1,3-Oxazole-Based Compounds and Their Isosteric Analogues. *Appl. Sci.*, 12 (11) 5571.
- 9 Shablykin O. V., Brovarets V. S., and Drach B. S. (2007) New transformations of 5-Hydrazino-2-phenyl-1,3-oxazole-4-carbonitrile. *Russ. J. Gen. Chem.*, 77 (5) 936-939.
- 10 Spencer J., Patel H., Amin J., Callear S. K., Coles S. J., Deadman J. J., Furman C., Mansouri R., Chavatte P., and Millet R. (2012) Microwave-mediated synthesis and manipulation of a 2-substituted-5-amino-oxazole-4-carbonitrile library. *Tetrahedron Lett.*, 53 (13) 1656-1659.
- 11 Merzhyievskiy D. O., Shablykin O. V., Shablykina O. V., Kozytskiy A. V., Rusanov E. B., Moskvina V. S., and Brovarets V. S. (2021) Functionalized 5-Amino-4-cyanoxazoles, their Hetero- and Macrocyclic Derivatives: Preparation and Synthetic Applications. *Eur. J. Org. Chem.*, 2021 (47) 6511-6523.
- 12 Shablykin O. V., Brovarets V. S., and Shablykina O. V. (2024) Recyclization of 5-Amino-oxazoles as a Route to new Functionalized Heterocycles (Developments of V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry of the NAS of Ukraine). *Chem. Rec.*, 24 (2) e202300264.
- 13 Zhao G., Sun X., Bienayme H., and Zhu J. (2001) Activation of a terminal carboxylic acid by an internal oxazole: A novel synthesis of macrocyclodepsipeptide. *J. Am. Chem. Soc.*, 123 (27) 6700-6701.
- 14 Shablykin O. V., Merzhyievskiy D. O., Brovarets V. S., and Shishkina S. V. (2023) New oxazole to oxazole recyclization. *Chem. Heterocycl. Comp.*, 59 (6-7) 521-524.
- 15 Clerin D., and Fleury J.-P. (1973) Hétérocyclization des  $\alpha$ -acylaminoamides. II. – Sur l'hétérocyclization des amides  $\alpha$ -acylaminés tertiaires. *Bull. Soc. Chim. Fr.*, (11) 3134-3142.
- 16 Dresler E., Woliński P., Wróblewska A., Jasiński R. (2023) On the Question of Zwitterionic Intermediates in the [3+2] Cycloaddition Reactions between Aryl Azides and Ethyl Propiolate. *Molecules*, 28 (24) 8152.
- 17 Kozachenko A. P., Shablykin O. V., and Brovarets V. S. (2012) Synthesis of 4-alkyl-2-aryl-1,3-oxazole[5,4-*d*]pyrimidine-7(4*H*)-thiones and 6-alkyl-2-aryl-1,3-oxazole[5,4-*d*]pyrimidin-7(6*H*)-ones from 2-arylamino-3,3-dichloroacrylonitriles. *Russ. J. Gen. Chem.*, 82 (4) 739-743.



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