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# POLYCYCLIC SYSTEMS CONTAINING 1,2,4-OXADIAZOLE RING 2*. 4-(1,2,4-OXADIAZOL-5-YL)PYRROLIDIN-2-ONES: SYNTHESIS AND PREDICTION OF BIOLOGICAL ACTIVITY

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*A one-pot condensation of 5-oxopyrrolidine-3-carboxylic acids, carbonyldiimidazole, and benzamidoximes leads to the formation of the novel 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-one bicyclic systems, the structures of which have been confirmed by IR and $^1$H NMR methods and by liquid chromato-mass spectrometry. The results of a PASS prediction of the biological activity of the synthesized compounds are presented.*

**Keywords:** 1,2,4-oxadiazole, pyrrolidin-2-one, biological activity, one-pot synthesis.

The intensive use of the 1,2,4-oxadiazole (isoxadiazole) system in medicinal chemistry [2-4] as bioisosteres of carboxylic acid esters and amides [5, 6] makes the question of the development and optimization of methods for their synthesis timely. There is particular interest in compounds whose molecules have an isoxadiazole ring combined with another heterocyclic pharmacophore as this may lead to compounds having a broader spectrum of biological activity.

As subjects for this investigation we chose compounds whose molecules would contain a pyrrolidin-2-one ring along with the 1,2,4-oxadiazole. It is known that the isoxadiazole system is a component of antiviral (*Picovir*) [7], antiglaucomal, cardiovascular (*Proxodolol*) [8] and other medicinal compounds [9-11]. Neurological (*Etiracetam, Memolog*) [12, 13], respiratory (*Rolipram*) [14], immunostimulatory (*Pidotimod*) [15] and other medicinal preparations [16-20] are found amongst pyrrolidin-2-one derivatives.

In [21] routes were reported for the synthesis of 3-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones based on the preparatively inconvenient reaction of substituted 3-cyanopyrrolidin-2-ones with N-hydroxybenzimidoyl chlorides or on the acid catalyzed reaction of the difficult to obtain 5-amino-4-(1,2,4-oxadiazol-5-yl)-2,3-dihydropyrroles. Information concerning the target 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones has not appeared in the literature. For their preparation we have taken advantage of the method of parallel liquid phase synthesis based on a one-pot condensation of 5-oxopyrrolidine-3-carboxylic acids, carbodiimidazole (CDI),

* For Communication 1 see [1]

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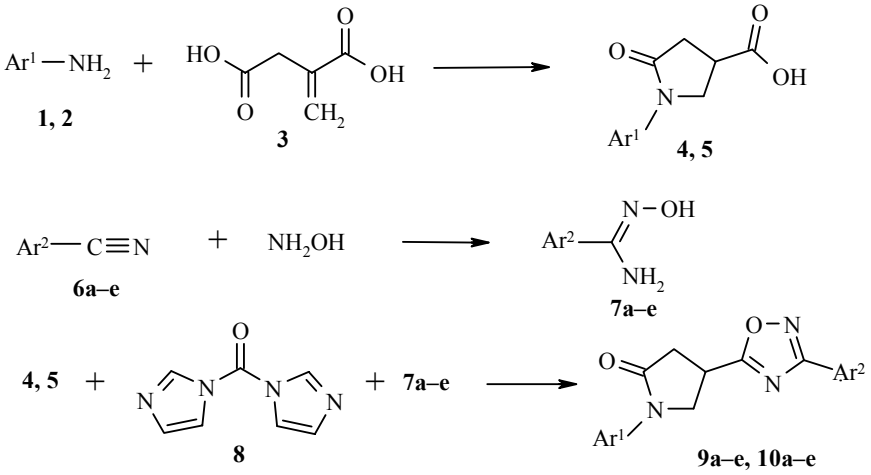
and benzamidoximes. The starting 1-aryl-5-oxopyrrolidine-3-carboxylic acids **4, 5** were prepared by the reaction of amines **1** and **2** with itaconic acid **3** as reported in [22]. The benzamidoximes **7a-e** were synthesized from the corresponding benzonitriles **6a-e** and hydroxylamine using the method [23]. Reaction of the heteryl carboxylic acids **4, 5**, CDI **8**, and benzamidoximes **7a-e** was carried out by a one-pot procedure with consecutive addition of reagents into DMF medium with variation of the temperature in the range 50-110ºC to give the 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones **9a-e, 10a-e** in 63-87% yields (Table 1). It should be noted that this method is the most universal and efficient amongst existing variations of 1,2,4-oxadiazole syntheses [24].



**1, 4, 9** $Ar^1$ = Ph; **2, 5, 10** $Ar^1$ = 4-$MeC_6H_4$; **6, 7, 9, 10 a** $Ar^2$ = Ph, **b** $Ar^2$ = 2-$MeC_6H_4$, **c** $Ar^2$ = 3-$ClC_6H_4$, **d** $Ar^2$ = 2-$FC_6H_4$, **e** $Ar^2$ = 4-$MeOC_6H_4$

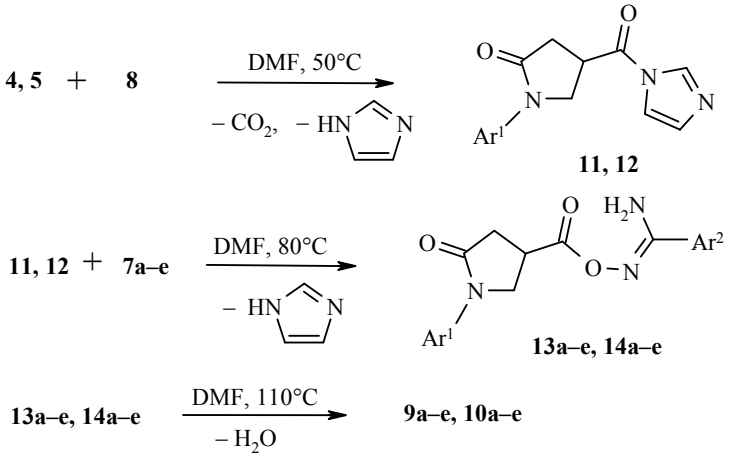
TABLE 1. Characteristics of 1-$Ar^1$-4-(3-$Ar^2$-1,2,4-Oxadiazol-5-yl)-pyrrolidin-2-ones **9a-e, 10a-e**

| Com-pound | Empirical formula | Found N, % / Calculated N, % | mp, °C | Yield, % |
|---|---|---|---|---|
| **9a** | $C_{18}H_{15}N_3O_2$ | 13.81 / 13.76 | 118-119 | 65 |
| **9b** | $C_{19}H_{17}N_3O_2$ | 13.12 / 13.16 | 124-125 | 73 |
| **9c** | $C_{18}H_{14}ClN_3O_2$ | 12.38 / 12.37 | 130-131 | 60 |
| **9d** | $C_{18}H_{14}FN_3O$ | 13.08 / 13.00 | 105-106 | 59 |
| **9e** | $C_{19}H_{17}N_3O_3$ | 12.59 / 12.53 | 143-144 | 63 |
| **10a** | $C_{19}H_{17}N_3O_2$ | 13.17 / 13.16 | 103-104 | 87 |
| **10b** | $C_{20}H_{19}N_3O_2$ | 12.67 / 12.60 | 116-117 | 77 |
| **10c** | $C_{19}H_{16}ClN_3O_2$ | 11.80 / 11.88 | 145-146 | 73 |
| **10d** | $C_{19}H_{16}FN_3O$ | 12.53 / 12.46 | 95-96 | 65 |
| **10e** | $C_{20}H_{19}N_3O_3$ | 12.01 / 12.03 | 142-143 | 63 |

Thanks to the possibility of introducing a series of different benzamidoximes into the condensation with the one activated 5-oxopyrrolidine-3-carboxylic acid with the same reaction conditions for the majority of reactants and variation of substituents in the starting reagents the method is readily adapted to parallel liquid phase synthesis. This allowed the preparation of a larger group of 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones in high yield, in a short time, and generally without further purification.

The mechanism of the three-component one-pot condensation with consecutive addition of reagents comprises three stages, the progress of which is controlled by the temperature factor. In the first step at 50ºC in dry DMF activation of the carboxylic acids **4, 5** by the CDI **8** occurs to give the acid imidazolides **11, 12**.

The heterocyclic carboxylic acid imidazolides are generally stable in inert solvents (in the absence of moisture). In the following step the introduction of the benzamidoximes **7a-e** into the reaction medium at 80ºC gives the O-(heterylcarbonyl)benzamidoximes **13a-e, 14a-e**, the formation of which is not in doubt as shown by the authors of previous studies and also their separation in individual cases (when the cyclization to the 1,2,4-oxadiazole ring does not occur spontaneously) [25, 26]. In the final step the increase in temperature to 110ºC causes cyclization to give the 1,2,4-oxadiazole ring.




The structure of the compounds obtained was confirmed by IR and $^1$H NMR spectroscopic methods and also by liquid chromato-mass spectrometry. The IR spectra of the samples show characteristic C=O stretching absorption bands for the pyrrolidin-2-one ring at 1689-1702 cm$^{-1}$. The synthesized 4-(1,2,4-oxadiazol-5-yl)-pyrrolidin-2-ones **9, 10** have a chiral C-4 atom as a result of which the methylene protons on the C-3 and C-5 atoms are diastereotopic. This causes a complex $^1$H NMR spectroscopic picture for the pyrrolidin-2-one fragment protons, especially for the H-4 proton which is obscured by the H-3 proton signals to form a three-proton multiplet at 4.20-4.75 ppm. The signals for the H-5 protons are seen at 2.85-3.25 ppm (2H), also as a multiplet. The spectroscopic characteristics of compounds **9, 10** are given in Table 2.

Compound **10e** was studied by liquid chromato-mass spectrometry. Upon chromatography of the sample ultraviolet (UV, 254 nm) and evaporative light scattering light (ELSD) detectors showed a clear region of maximum absorption. The mass spectrum of the compound corresponding to this retention time showed a high intensity peak for the molecular ion of **10e** and low intensity fragments indicating a stable molecule.

The biological activity of the synthesized 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones was predicted using the PASS C&T computer system (Prediction Activity Spectra for Substances: Complex and Training) [27, 28].

The results of the PASS prediction showed that compounds in this series are potential antagonists of GABA A receptors, histamine N-methyltransferase inhibitors, and antagonists of benzodiazepine receptors. They can show arrhythmic, antiepileptic, anxiolytic, antispasmodic, neuroprotecting, psychotropic, and nootropic activity and affect cognitive dysfunction.

TABLE 2. Spectroscopic Characteristics of Compounds **9a-e, 10a-e**

| Compound | IR spectrum, $\nu_{C=O}$, $cm^{-1}$ | $^1H$ NMR spectrum, δ, ppm (*J*, Hz) |
|---|---|---|
| **9a** | 1702 | 2.85-3.25 (2H, m, H-5); 4.15-4.45 (3H, m, H-4,3); 7.14 (1H, t, $J_{4,3}$ = 7.6, *p*-H $Ar^1$); 7.39 (2H,t, $J_{3,2}$ = 8.2, *m*-H $Ar^1$); 7.50-7.60 (3H, m, *p*-, *m*-H $Ar^2$); 7.65 (2H, d, $J_{2,3}$ = 8.2, *o*-H $Ar^1$); 8.00 (2H, dd, $J_{2,3}$ = 7.9, $J_{2,6}$ = 1.9, *o*-H $Ar^2$) |
| **9b** | 1702 | 2.52 (3H, s, $CH_3$); 2.85–3.20 (2H, m, H-5); 4.15-4.45 (3H, m, H-4,3); 7.14 (1H, t, $J_{4,3}$ = 7.6, *p*-H $Ar^1$); 7.30-7.50 (5H, m, *m*-H $Ar^1$, *p*-, *m*-H $Ar^2$); 7.65 (2H, d, $J_{2,3}$ = 8.2, *o*-H $Ar^1$); 7.92 (1H, d, $J_{2,3}$ = 7.4, *o*-H $Ar^2$) |
| **9c** | 1700 | 2.85-3.20 (2H, m, H-5); 4.15-4.45 (3H, m, H-4,3); 7.15 (1H, t, $J_{4,3}$ = 7.6, *p*-H $Ar^1$); 7.47 (2H, t, $J_{3,2}$ = 8.2, *m*-H $Ar^1$); 7.55-.75 (4H, m, *o*-H $Ar^1$, *p*-, *m*-H $Ar^2$); 7.95 (2H, m, *o*-H $Ar^2$) |
| **9d** | 1699 | 2.95-3.10 (2H, m, H-5); 4.15-4.40 (3H, m, H-4,3); 7.15 (1H, t, $J_{4,3}$ = 7.6, *p*-H $Ar^1$); 7.32-7.49 (4H, m, *m*-H $Ar^1$, *m*-H $Ar^2$); 7.59-7.70 (3H, m, *p*-H $Ar^2$, *o*-H $Ar^1$); 8.05 (1H, dt, $J_{2,3}$ = 7.8, $J_{2,6<F>}$ = 2.6, *o*-H $Ar^2$) |
| **9e** | 1694 | 2.85-3.20 (2H, m, H-5); 3.80 (3H, s, $OCH_3$); 4.15-4.35 (3H, m, H-4,3); 7.05-7.20 (3H, m, *p*-H $Ar^1$, *m*-H $Ar^2$); 7.38 (2H, t, $J_{3,2}$ = 8.2, *m*-H $Ar^1$); 7.65 (2H, d, $J_{2,3}$ = 8.2, *o*-H $Ar^1$); 7.93 (2H, d, $J_{2,3}$ = 9.0, *o*-H $Ar^2$) |
| **10a** | 1689 | 2.26 (3H, s, $CH_3$); 2.95-3.20 (2H, m, H-5); 4.15-4.35 (3H, m, H-4,3); 7.19 (2H, d, $J_{3,2}$ = 8.1, *m*-H $Ar^1$); 7.50-7.61 (5H, m, *o*-H $Ar^1$, *m*-, *p*-H $Ar^2$); 8.08 (2H, dd, $J_{2,3}$ = 7.9, $J_{2,6}$ = 1.9, *o*-H $Ar^2$) |
| **10b** | 1693 | 2.26 (3H, s, $CH_3$); 2.52 (3H, s, $CH_3$); 2.85-3.20 (2H, m, H-5); 4.12-4.40 (3H, m, H-4,3); 7.19 (2H, d, $J_{3,2}$ = 8.1, *m*-H $Ar^1$); 7.35-7.48 (3H, m, *m*-, *p*-H $Ar^2$); 7.54 (2H, d, $J_{2,3}$ = 8.1, *o*-H $Ar^1$); 7.91 (1H, d, $J_{2,3}$ = 7.4, *o*-H $Ar^2$) |
| **10c** | 1695 | 2.27 (3H, s, $CH_3$); 2.90-3.15 (2H, m, H-5); 4.10-4.35 (3H, m, H-4,3); 7.19 (2H, d, $J_{3,2}$ = 8.1, *m*-H $Ar^1$); 7.50-7.71 (4H, m, *o*-H $Ar^1$, *m*-, *p*-H $Ar^2$); 7.94-8.02 (2H, m, *o*-H $Ar^2$) |
| **10d** | 1698 | 2.27 (3H, s, $CH_3$); 2.85-3.20 (2H, m, H-5); 4.10-4.40 (3H, m, H-4,3); 7.19 (2H, d, $J_{3,2}$ = 8.1, *m*-H $Ar^1$); 7.35-7.73 (5H, m, *o*-H $Ar^1$, *m*-, *p*-H $Ar^2$); 8.05 (2H, dt, $J_{2,3}$ = 7.8, $J_{2,6<F>}$ = 2.5, *o*-H $Ar^2$) |
| **10e** | 1702 | 2.25 (3H, s, $CH_3$); 2.85-3.15 (2H, m, H-5); 3.80 (3H, s, $OCH_3$); 4.10-4.40 (3H, m, H-4,3); 7.09 (2H, d, $J_{3,2}$ = 9.0, *m*-H $Ar^2$); 7.18 (2H, d, $J_{3,2}$ = 8.1, *m*-H $Ar^1$); 7.52 (2H, d, $J_{2,3}$ = 8.1, *o*-H $Ar^1$); 7.93 (2H, d, $J_{2,3}$ = 9.1, *o*-H $Ar^2$) |

Hence we have developed a preparative method for novel biheterocyclic compounds containing 1,2,4-oxadiazole and pyrrolidin-2-one rings (4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones) which is based on a one-pot condensation of 5-oxopyrrolidine-3-carboxylic acids, carbodiimidazole, and benzamidoximes. We have also presented the results of computer modelling of their biological activity.

## EXPERIMENTAL

IR spectra were taken for KBr tablets on an IR-75 spectrophotomer. $^1H$ NMR spectra were recorded on a Varian VXR-400 instrument (400 MHz) using DMSO-$d_6$ solvent and TMS as internal standard. Melting points for compounds **9a-e, 10a-e** were measured on a Buchi (Switzerland) model B-520 apparatus. TLC monitoring of the course of the reaction and the purity of the products was carried out on Sorbfil AFV-UV plates using $CHCl_3$ as eluent. Elemental analysis for nitrogen was performed using the Dumas method.

Liquid chromato-mass spectrometer for compound **10e** was performed on a PE SCIEX API 150 EX instrument using UV (254 nm) and ELSD detectors.

**1-Phenyl-5-oxopyrrolidine-3-carboxylic Acid (4)**. Aniline **1** (13.95 g, 150 mmol) and itaconic acid **3** (19.5 g, 150 mmol) were placed in a 100 ml volume flask and heated for 2 h at 115-120ºC. The crystalline mass melted with effervescence. At the end of the reaction the effervescence had ceased and droplets of water ran down the walls of the flask. The hot solution was poured into iced water (20 ml) and the organic layer formed was triturated with a glass rod to crystallization. The product was filtered and washed on the filter with cold water (100 ml). For further purification the obtained 5-oxopyrrolidine-3-carboxylic acid was dissolved with heating in 10% NaOH solution (100 ml) and refluxed for 10 min with activated carbon (2-3 g). The carbon was filtered off and washed with hot water (15-20 ml) and the mother liquor was cooled and acidified with HCl to acid Congo reaction. The separated product **4** was filtered off and washed with cold water to neutral reaction. Mp 168-169ºC, yield 54%.

**1-(4-Methylphenyl)-5-oxopyrrolidine-3-carboxylic Acid (5)**. From *p*-toluidine **2** and acid **3** similarly to give compound **5** with mp 182-183ºC, yield 67%.

**2-Methylbenzamidoxime (7b)**. Ethanol (100 ml) was placed in a 150 ml volume flask and $NH_2OH \cdot HCl$ (13.90 g, 200 mmol) and KOH (11.20 g, 200 mmol) were added. The 2-methylbenzonitrile **6b** (17.55 g, 150 mmol) was then added and the reaction mixture was refluxed for 4-5 h. At the end of the reaction (TLC monitoring) the mixture was poured into a beaker containing iced water (200 ml). The target compound was formed as a crystalline precipitate which was filtered, washed on the filter with cold water and then dried to give the benzamidoxime **7b** with mp 142-143ºC, yield 68%.

**Benzamidoximes 7c-e** were prepared similarly from the corresponding benzonitriles (mp, yield given): **7c** (116-117ºC, 70%); **7d** (89-90ºC, 53%), **7e** (105ºC, 89%).

**Benzamidoxime 7a**. The reaction mixture was additionally diluted with water (100 ml), extracted with ethyl acetate (3×50 ml), and the organic layer was dried over $MgSO_4$, solvent distilled off *in vacuo*, and the residue treated with hexane with glass rod trituration. The benzamidoxime **7a** did not form a crystalline precipitate and had mp 79-80ºC, yield 48%.

**1-Phenyl-4-(3-phenyl-1,2,4-oxadiazol-5-yl)pyrrolidin-2-one (9a)**. CDI **8** (0.195 g, 1.2 mmol) was added to a solution of compound **4** (0.205 g, 1 mmol) in dry DMF (3 ml) and held for 20 min at 50ºC. The acid imidazolide formed was treated with the benzamidoxime **7a** (0.164 g, 1.2 mmol) and the mixture was held for 30 min at 80ºC. The reaction temperature was then raised to 110ºC and held for a further 3 h. At the end of the reaction the mixture was diluted with water (10 ml) and the solid product **9a** was filtered off, washed on the filter with water, and dried.

**The target products 9b-e, 10a-e** were prepared similarly using the corresponding combination of starting 1-aryl-5-oxopyrrolidine-3-carboxylic acids **4,5** and benzamidoximes **7a-e**.

The indicated method allows the synthesis of analytically pure 4-(1,2,4-oxadiazol-5-yl)pyrrolidin-2-ones **9a-e, 10a-e**.

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