γ-Lactams and pyrazoles represent nitrogen-containing heterocyclic compounds that form the key pharmacophoric motifs in a significant number of natural and synthetic compounds characterized by a broad spectrum of biological activity. For example, the active pharmaceutical ingredients of many synthetic nootropic drugs known as racetams (piracetam, Phenotropil, levetiracetam, rolipram, and others) and detoxifiers or enterosorbents (polyvinylpyrrolidone, Hemodez, Enterodex) contain the structural units of 2-pyrrolidone (Fig. 1). Pyrrolidone ring forms the structural basis of several effective investigational drug molecules (PF-07321332 (nirmatrelvir), GC376, AG-7088 (rupinavir, Rupintrivir)) applied for the treatment and prevention of COVID-19 coronavirus infection (Fig. 1).

Examples of currently approved synthetic drugs containing pyrazole rings include the anti-inflammatory drug celecoxib, the weight loss medication rimonabant, as well as fomepizole (an antidote against toxic alcohols) and others (Fig. 1).

Thus, functionalized 2-pyrrolidones containing in their molecules hetaryl substituents along with two pharmacophoric moieties – lactam and pyrazole heterocycles can be considered as key structures for targeted synthesis of pharmacological agents with various types of activity. The examples of such substituted 2-pyrrolidones has been described only in a very limited number of literature sources: 1-hetaryl-4-(pyrazol-1-ylcarbonyl)-2-pyrrolidones were obtained in good yields by cyclocondensation of...
1-hetaryl-2-oxopyrrolidine-4-carbohydrazides with 2,4-pentanedione (acac) in i-PrOH medium in the presence of a catalytic amount of hydrochloric acid\textsuperscript{14–19} (Scheme 1).

For these reasons, we were interested in studying the reactions of diastereomerically pure (3\textsuperscript{R},4\textsuperscript{S})-4-hetaryl-2-oxopyrrolidine-3-carbohydrazides 1\textsubscript{a}–\textsubscript{c}, (4\textsuperscript{R},5\textsuperscript{S})-4-hetaryl-2-oxopyrrolidine-5-carbohydrazides 2\textsubscript{a}–\textsubscript{g}, and 2-(4-aryl-2-oxopyrrolidin-1-yl)acetohydrazides 3\textsubscript{a}–\textsubscript{d} with 2,4-pentanedione. The starting materials 1\textsubscript{a}–\textsubscript{e}, 2\textsubscript{a}–\textsubscript{g}, and 3\textsubscript{a}–\textsubscript{d} were synthesized according to our previously developed procedures,\textsuperscript{20–22}

The successful completion of these reactions was found to substantially depend on the catalyst that was used. For example, the interaction of hydrazides 1\textsubscript{a}–\textsubscript{c} with 2,4-pentanedione under the conditions described in earlier publications\textsuperscript{14–19} (catalyst hydrochloric acid, solvent i-PrOH) was accompanied by rapid hydrolysis of compounds 1\textsubscript{a}–\textsubscript{c}, followed by esterification of the intermediate pyrrolidone carboxylic acids and resulting in the isolation of the respective isopropyl esters 4\textsubscript{a}–\textsubscript{c} (Scheme 2).

The use of \textit{p}-toluenesulfonic acid (TsOH) as catalyst allowed to successfully accomplish the reactions of hydrazides 1\textsubscript{a}–\textsubscript{e}, 2\textsubscript{a}–\textsubscript{g}, 3\textsubscript{a}–\textsubscript{d} with 2,4-pentanedione under identical conditions: catalyst TsOH and heating at reflux in MeOH for 30 min. The target 2-pyrrolidone pyrazole-carbonyl derivatives 5\textsubscript{a}–\textsubscript{e}, 6\textsubscript{a}–\textsubscript{g}, 7\textsubscript{a}–\textsubscript{d} were obtained in good yields (61–84\%) (Schemes 3–5).

Compounds 5\textsubscript{a}–\textsubscript{e}, 6\textsubscript{a}–\textsubscript{g}, and 7\textsubscript{a}–\textsubscript{d} were isolated as stable colorless crystals with clearly identifiable melting points. Their structures were confirmed by physicochemical methods of analysis (IR spectroscopy, one-dimensional \textit{H} \& \textit{C} NMR spectroscopy, two-dimensional \textit{H}–\textit{C} HMBC experiments, as well as by X-ray structural analysis. IR spectra of all compounds 5\textsubscript{a}–\textsubscript{e}, 6\textsubscript{a}–\textsubscript{g}, and 7\textsubscript{a}–\textsubscript{d} had similar features and were in good agreement between themselves, containing strong broadened absorption bands of carbonyl groups (at the ranges of 1727–1719 and 1700–1685 cm\textsuperscript{-1}), while IR spectra of compounds 5\textsubscript{a}–\textsubscript{e}, 6\textsubscript{a}–\textsubscript{g} showed the absorption bands of amide NH groups (at the ranges of 3219–3193 and 3114–3080 cm\textsuperscript{-1}).
\(^1\)H and \(^{13}\)C NMR spectra of compounds 5a–e, 6a–g featured one set of proton and \(^{13}\)C signals for all structural units, pointing to the presence of only one diastereomer. For example, in \(^1\)H NMR spectra of compounds 5a, 6a there were the methine proton signals of chiral centers: a 3-CH proton doublet at 5.17 ppm (\(^3\)J\(_{3,4}\) = 11.1 Hz), a 4-CH proton multiplet at 4.01–4.11 ppm (compound 5a), split doublets of 5-CH proton at 5.71 ppm (\(^3\)J\(_{5,6}\) = 8.4 Hz) and 4-CH proton at 4.07 ppm (\(^3\)J = 8.7 Hz, compound 6a). The downfield region in \(^1\)H NMR spectra of compounds 5a–e, 6a–g showed characteristic singlet signals of pyrrolidine ring 1-NH protons at 8.17–8.23 ppm (compounds 5a–e) and 8.00–8.14 ppm (compounds 6a–g).

Taking into account the fact that the chiral centers in the diastereomerically pure carbohydrazides 1a–e and 2a–g were not affected during their reactions with 2,4-pentanodione, the obtained compounds 5a–e had (3R*,4S*) configuration, while compounds 6a–g had (4R*,5R*) configuration. Indeed, the spin-spin coupling constants of 3,4-CH methine protons (\(^3\)J\(_{3,4}\) = 10.7–11.2 Hz) in \(^1\)H NMR spectra of compounds 5a–e and 4,5-CH methine protons (\(^3\)J\(_{4,5}\) = 8.2–8.7 Hz) in the spectra of compounds 6a–g indicated their trans and cis orientation relative to the lactam ring plane. This orientation corresponded to (3R*,4S*) and (4R*,5R*) configurations of the chiral centers and was in good agreement with the spin-spin coupling constants established by us for the starting carbohydrazides 1a–e, 2a–g,\(^ {20–22}\) as well as the literature data available for trans- and cis-isomers of similar molecules.\(^ {23–25}\)

The formation of pyrazole ring was confirmed by the presence of characteristic ==CH proton quartet signals in \(^1\)H NMR spectra of compounds 5a–e, 6a–g, and 7a–d in the region of 5.88–6.20 ppm. These quartets showed a long range spin-spin coupling (\(^3\)J = 0.5–0.7 Hz) to the pyrazole ring methyl group protons manifested as a doublet in the region of 1.98–2.44 ppm. The methylene and methine proton signals were assigned to the pyrrolidine and pyrazole rings of compounds 5a–e, 6a–g, and 7a–d according to the results of \(^1\)H–\(^{13}\)C HMBC experiment.

The assignment of C-2,12,13 carbon signals belonging to C=O groups, as well as the 3,4,5-CH proton signals of pyrrolidine ring and ==CH proton signals of pyrazole ring in the molecules of compounds 5a–e, 6a–g, and 7a–d was performed on the basis of \(^1\)H–\(^{13}\)C HMBC data. For example, in the spectrum of compound 5a, the signal assignment relied on the correlations between 1-NH proton and C-2 carbon atom (8.19/172.1 ppm), 3-CH proton and C-12 carbon atom (5.17/170.8 ppm), as well as other spectral features (Fig. 2). Analogously, \(^1\)H–\(^{13}\)C HMBC spectrum of compound 7a was interpreted on the basis of cross peaks between the 3-CH\(_2\) protons and C-2 carbon atom (2.42 ppm, 2.73/174.3 ppm), as well as the 12-CH\(_2\) protons and C-13 carbon atom (4.74 ppm, 4.79/168.7 ppm) (Fig. 2).

The most downfield signals in \(^{13}\)C NMR spectra of compounds 5a–e, 6a–g, and 7a–d were assigned to the carbonyl carbon atoms of lactam groups (172–177 ppm) and the side chain (169–171 ppm).

The spatial structure of the obtained compounds 5a–e, 6a–g, and 7a–d was examined by X-ray structural analysis in the case of compounds 5–7 a (Figs. 3–7). According to the results of X-ray structural analysis, compounds 5–7 a crystallized in the form of racemates in centrosymmetric triclinic crystals.

The crystal structure of compound 5a contained a single molecule in the independent part of the unit cell, in which the pyrrolidine ring together with substituents at the C(3) and C(4) atoms were significantly disordered between two positions. The disordered atoms have been denoted with letters A and B. The relative configuration of the two chiral centers C(3) and C(4) in compound 5a was R* and S* (molecule A) or S* and R* (molecule B), respectively. Thus, the crystal of compound 5a can hold both enantiomers (RS/SS) or pair of diastereomers at the same position.

In the crystal structures of compounds 6a and 7a, the independent part of the unit cell contained two independent molecules of enantiomers A and B. For compound 6a, the chiral atoms C(4A) and C(5A) had S configuration, while C(4B) and C(5B) had R configuration. In the case of compound 7a, the chiral C(4A) atoms had R configuration and C(4B) had S configuration.

The lactam rings in molecules 5–7 a had the same C(4)-envelope conformation with the C(4) atom deviating from the common plane defined by the C(3)–C(2)–N(1)–C(5) atom chain. At the same time, in the disordered molecules A and B of compound 5a, the C(4) atom deviated from the C(3)–C(2)–N(1)–C(5) plane in different directions by approximately equal distances: by 0.21 Å in molecule A and by 0.28 Å in molecule B.
The phenyl and carbonylpyrazole substituents at the C(3) and C(4) chiral atoms of compound 5a assumed equatorial positions and had an anticlinal conformation relative to each other (torsion angle C(6)–C(4)–C(3)–C(12) = −99(1)°), while in the molecules of compound 6a the substituents at the C(4) and C(5) atoms were in axial and equatorial positions, respectively, and assumed an eclipsed conformation (the torsion angle C(6)–C(4)–C(5)–C(12) was equal to −10.0(4)° and −24.1(4)° in the molecules of compounds A and B, respectively). In the molecules of compound 7a, the substituents at the C(4) and N(1) atoms occupied equatorial positions.

The molecules of compounds 5a, 6a in crystalline state formed centrosymmetric dimers linked by N–H···O hydrogen bonds. There were ordinary van der Waals contacts between the dimers (Fig. 6). In the crystal of compound 7a, C–H···O type bonds were observed, mediated by dispersion interactions (Fig. 7).
Compounds 5a,c, 6a,b,d, 7a,c representing each group of the obtained products were tested as potentially biologically active compounds, anticipated to have psychotropic properties. Standard pharmacological testing methods were used, which were appropriate for the given type of activity: "open field" (OF), "elevated plus maze" (EPM), "conditioned passive avoidance reflex" (CPAr), "extrapalation avoidance" (EA), and Vogel conflict test (VCT). The experiments were performed with male Wistar rats in accordance with the animal testing regulations set by the legislation of the Russian Federation and the EASC technical standards for Good Laboratory Practice (GOST R 53434-2009 and GOST R 51000.4-2011).

Compounds 5a,c, 6a,b,d, 7a,c were injected into the animals intraperitoneally (IP, physiological saline) in equimolar amounts as a single dose equal to 1/10 of the molecular mass, 30 min prior to the test. The acute toxicity level (LD50, mg/kg) of compounds 5a,c, 6a,b,d, and 7a,c was evaluated from the survival rate of white mice and exceeded 2000 mg/kg, allowing to recognize them as relatively harmless materials, belonging to the IV class of toxicity. The selected reference drug was phenibut (20 mg/kg, IP), which possesses anxiolytic and nootropic activity and is prescribed for the treatment of anxiety, cognitive, and asthenic disorders.

Statistical processing of the test results was performed using the Prism 6 program according to Shapiro–Wilks, Kruskal–Wallis, and Dunn's criteria.

The OF test characterizes the locomotor activity (by the number of traversed squares) and orienting-exploratory activity of the animals (by the sum of rearing and head-dipping acts). As shown in Table 1, compounds 5a,c, 6a,b,d, 7a,c did not produce a significant effect on the motor activity of animals in this test, pointing to the absence of psychostimulant or sedative activity associated with these compounds. It should be noted that, after the injection of compound 7c (32 mg/kg), the animals of experiment group showed a statistically significant increase in rearing and head-dipping behaviors, as well as the number of visits to the brightly lit central area (aversive for nocturnal rodents), pointing to the prevalence of orienting-exploratory activity by the animals over the aversion toward their environment (Table 1). Thus, compound 7c in the OF test showed anxiolytic activity, comparable to that of phenibut.

The EPM test was used to evaluate the anxiety level in animals by recording the total time spent, time spent in the open arm, and the number of excursions into the open arm. After a single injection of compounds 5a,c, 6a,b,d, 7a,c, only compounds 6b and 7c statistically significantly increased the number and duration of excursions into the open arms of the apparatus, amount of rearing and head-dipping behaviors in the open arms among the experiment group compared to the control group of animals. This indicated a reduction in the level of anxiety (Table 1). The anxiolytic effect of compound 7c surpassed the activity of compound 6b and was comparable to that of phenibut.

The activity of the most promising compounds 6b, 7c was also studied according to the Vogel conflict test, which is a highly specific test for evaluating the anxiolytic action of new compounds. It was established from this test that, after the injection of compounds 6b, 7c, the number of animals in the experimental group punished by withdrawal of water was statistically significantly higher compared to the control group (Table 1). Remarkably, the anxiolytic activity of compound 6b exceeded that of compound 7c, the activity of which in the EPM test was higher than in the case of compound 6b and comparable to the activity of phenibut.

Within the framework of studying compounds 5a,c, 6a,b,d, and 7a,c with regard to their psychotropic activity, their effects on the learning and memory (formation and retrieval of memory trace) were also characterized using animals in CPAR and EA tests. During the CPAR test, the animals treated with compounds 5a,c, 7c prior to the training retained the memory trace and did not enter the

Table 1. The effect of compounds 5a,c, 6a,b,d, 7a,c on animal behavior in OF, EPM, VCT, CPAR, and EA tests (M ± m)

| Compound | OF | EPM | VCT | CPAR | EA |
|----------|----|-----|-----|------|----|
|          | MA* | EB** | OA*** – frequency of entry | OA – residence time, s | Number of punished approaches | Residence time in closed arm, s. | Problem solving time, s. |
| Control  | 44.0 ± 3.2 | 13.3 ± 0.9 | 1.2 ± 0.4 | 12.4 ± 1.8 | 3.5 ± 0.7 | 126.4 ± 13.4 | 6.8 ± 1.7 |
| 5a       | 46.0 ± 3.5 | 14.0 ± 2.1 | 2.0 ± 0.5 | 24.0 ± 5.2 | **4 180.0 ± 0.0** | **4 2.5 ± 0.5** |
| 5c       | 35.0 ± 10.0 | 17.0 ± 10.0 | 1.5 ± 0.5 | 15.2 ± 9.4 | **4 180.0 ± 0.0** | **4 2.0 ± 1.0** |
| 6a       | 41.0 ± 0.9 | 13.3 ± 1.0 | 1.6 ± 0.5 | 8.9 ± 1.2 | 137.5 ± 24.0 | 4.5 ± 1.0 |
| 6b       | 35.6 ± 2.6 | 11.0 ± 0.6 | **4 2.6 ± 0.4** | **4 31.9 ± 3.3** | **4 7.3 ± 0.6** | 145.8 ± 22.6 | 4.3 ± 0.7 |
| 6d       | 38.1 ± 2.3 | 13.0 ± 0.9 | 2.1 ± 0.6 | 22.0 ± 3.0 | 140.9 ± 25.8 | 4.3 ± 0.7 |
| 7a       | 42.5 ± 9.5 | 14.5 ± 2.5 | 1.5 ± 0.5 | 10.0 ± 6.7 | 103.8 ± 24.7 | 3.5 ± 1.3 |
| 7c       | 48.5 ± 12.5 | 19.0 ± 3.5 | **4 3.0 ± 0.5** | **4 49.0 ± 9.0** | **4 5.5 ± 1.5** | **4 180.0 ± 0.0** | 3.8 ± 1.8 |
| Phenibut | 41.6 ± 4.0 | 19.0 ± 2.8 | **4 3.0 ± 0.9** | **4 45.4 ± 14.5** | **4 9.3 ± 1.2** | **4 180.0 ± 0.0** | **4 2.6 ± 0.4** |

* MA – motor activity (number of squares traversed in the experimental apparatus).
** EB – exploratory behavior (total number rearing and head-dipping acts).
*** OA – the open arm of the EPM apparatus.

The differences were statistically significant compared to the control group, at p < 0.05.
closed arm with electrode floor at 7 days after the training (Table 1). Along with that, the animals treated with compounds 5a,c solved the extrapolation task significantly faster during the EA test compared to the control group (Table 1). Thus, according to the results of both tests, from the series of compounds 5a,c, 6a,b,d, and 7a,c we selected compounds 5a,c that improved the formation and retrieval of memory trace in experimental animals and showed nootropic effects.

In conclusion, the results of this study allowed us to develop an effective method for the preparation of previously unknown diastereomerically pure 3(5)-(3,5-dimethyl-1H-pyrazol-1-yl)-2-pyrrolidones – new members of the racetam family containing the pharmacophoric lactam and pyrazole rings.

Experimental

IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer for samples in KBr pellets. One-dimensional 1H, 13C, 15N NMR spectra and two-dimensional 1H–13C HMQC and 1H–13C HMBC spectra were acquired on a Jeol ECX400A spectrometer at the working frequencies of 400 MHz (for 1H nuclei), 100 MHz (for 13C nuclei), and 40 MHz (for 15N nuclei) for samples in DMSO-d6 solutions. The residual non-deuterated solvent signals (for 1H nuclei) or deuterated solvent signals (for 13C nuclei) were used as standards, while 15N NMR chemical shifts were recorded relative to MeNO2. Elemental analysis was performed on a EuroVector EA3000 (CHN Dual) analyzer. The reaction progress and purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates using 9:1:2 i-PrOH–NH4OH–H2O mobile phase and visualization under UV light (λ = 254 nm).

The synthesis of (3R*,4S*)-4-aryl-2-pyrrolidin-3-carboxylic acids 1a–e (4R*,5R*)-4-aryl-2-pyrrolidin-3-carboxylic acids 2a–g, and 2-[4-aryl-2-pyrrolidon-1-yl]acetohydrazides 3a–d was accomplished by following published procedures.20–22

Synthesis of isopropyl (3R*,4S*)-4-aryl-2-oxopyrrolidine-3-carboxylates 4a–e (General method). A mixture of the appropriate 4-aryl-2-oxopyrrolidine-3-carboxylic acid 1a–e (5 mmol), 2,4-pentanedione (15 mmol), and 6 N HCl (0.25 ml) in i-PrOH (20 ml) was refluxed at 2 h. The solvent was evaporated at reduced pressure (15–20 mmHg) by 2/3 of the initial volume, and the residue was treated with H2O (4 ml). The crystalline product was filtered off, air-dried, and recrystallized from MeOH.

Isopropyl (3R*,4S*)-2-oxo-4-phenylpyrrolidine-3-carboxylate (4a) was obtained from carbohydrazide 1a (1095 mg, 5 mmol). Yield 1000 mg (81%), colorless crystals, mp 124–125°C (MeOH). IR spectrum, ν, cm−1: 1729, 1689 (C=O), 3209, 3100 (NH). 1H NMR spectrum, δ, ppm (J, Hz): 1.08 (3H, d, 3J = 6.2, CH3); 1.14 (3H, d, 3J = 6.2, CH3); 3.22 (1H, t, J = 9.4, 5-CH2); 3.54 (1H, d, 3J = 11.1, 3-CH); 3.59 (1H, t, J = 8.9, 5-CH2); 3.80–3.90 (1H, m, 4-CH); 4.88 (1H, sept, 3J = 6.2, OCH); 7.18–7.25 (1H, m, H-4 Ph); 7.26–7.33 (4H, m, H-2,3,5,6 Ph); 8.11 (1H, s, NH). 13C NMR spectrum, δ, ppm: 22.0 (CH3); 22.1 (CH3); 44.9 (C-4); 47.1 (C-5); 55.7 (C-3); 68.7 (OCH); 127.7 (C-4 Ph); 127.8 (C-2,6 Ph); 129.2 (C-3,5 Ph); 140.3 (C-1 Ph); 169.8 (C-12); 171.9 (C-2). Found, %: C 68.07; H 7.08; N 5.64. C14H17NO3. Calculated, %: C 68.00; H 6.93; N 5.66.

Isopropyl (3R*,4S*)-(4-(4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (4b) was obtained from carbohydrazide 1b (1165 mg, 5 mmol). Yield 980 mg (75%), colorless crystals, mp 114–116°C (MeOH). IR spectrum, ν, cm−1: 1734, 1700 (CO); 3215, 3112 (NH). 1H NMR spectrum, δ, ppm (J, Hz): 1.08 (3H, d, 3J = 6.2, CH3); 1.14 (3H, d, 3J = 6.2, CH3); 2.23 (3H, s, CH3 Ph); 3.17 (1H, t, J = 9.5, 5-CH2); 3.48 (1H, d, 3J = 11.1, 3-CH); 3.51–3.58 (1H, m, 5-CH2); 3.74–3.84 (1H, m, 4-CH); 4.86 (1H, sept, 3J = 6.2, OCH); 7.10 (2H, d, J = 8.0, H Ph); 7.17 (2H, d, J = 8.0, H Ph); 8.07 (1H, s, NH). 13C NMR spectrum, δ, ppm: 21.1 (CH3 Ph); 22.0 (CH3); 22.1 (CH3); 45.1 (C-4); 47.1 (C-5); 55.8 (C-3); 68.7 (CH); 127.6 (CH2 Ph); 129.7 (CH Ph); 136.8 (C Ph); 137.2 (C Ph); 169.9 (C-12); 171.9 (C-2). Found, %: C 68.72; H 7.22; N 5.38. C14H19NO3. Calculated, %: C 68.94; H 7.33; N 5.36.

Isopropyl (3R*,4S*)-4-(4-methoxyphenyl)-2-oxopyrrolidine-3-carboxylate (4c) was obtained from carbohydrazide 1c (1245 mg, 5 mmol). Yield 1165 mg (84%), colorless crystals, mp 110–112°C (MeOH). IR spectrum, ν, cm−1: 1733, 1699 (CO); 3215, 3110 (NH). 1H NMR spectrum, δ, ppm (J, Hz): 1.08 (3H, d, 3J = 6.2, CH3); 1.14 (3H, d, 3J = 6.2, CH3); 2.23 (3H, s, CH3 Ph); 3.17 (1H, t, J = 9.5, 5-CH2); 3.47 (1H, d, 3J = 11.1, 3-CH); 3.50–3.56 (1H, m, 5-CH2); 3.69 (3H, s, CH3O); 3.72–3.82 (1H, m, 4-CH); 4.86 (1H, sept, 3J = 6.2, OCH); 6.85 (2H, d, J = 8.7, H-3,5 Ph); 7.21 (2H, d, J = 8.7, H-2,6 Ph); 8.06 (1H, s, NH). 13C NMR spectrum, δ, ppm: 22.0 (CH3); 22.1 (CH3); 44.9 (C-4); 47.3 (C-5); 55.6 (CH2O); 55.9 (C-3); 68.7 (CH); 114.5 (C-3,5 Ph); 128.9 (C-2,6 Ph); 132.1 (C-1 Ph); 158.9 (C-4 Ph); 169.9 (C-12); 171.9 (C-2). Found, %: C 64.81; H 6.79; N 5.38. C14H18O2N4. Calculated, %: C 64.97; H 6.91; N 5.05.

Synthesis of 3-(3,5-dimethyl-1H-pyrazole-1-carboxyloxy)-4-pyrrolidin-2-ones 5a–e, 6a–g and aryl-1-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-4-pyrrolidin-2-ones 7a–d (General method). A mixture of the appropriate compound 2a–g, 3a–d (5 mmol), 2,4-pentanedione (15 mmol), and p-toluenesulfonic acid (1 mmol) in MeOH (15 ml) was heated at reflux for 30 min. The solvent was evaporated at reduced pressure (15–20 mmHg) by 2/3 of the initial volume, and the residue was treated with H2O (4 ml). The crystalline product was filtered off and air-dried.

(3R*,4S*)-3-(3,5-Dimethyl-1H-pyrazole-1-carboxyloxy)-4-pyrrolidin-2-one (5a) was obtained from carbohydrazide 1a (1095 mg, 5 mmol). Yield 1090 mg (77%), colorless crystals, mp 143–145°C (i-PrOH). IR spect-
from hydrazide

(1H, d, J = 11.1, 3-CH3); 6.19 (1H, q, J = 6.7, 16-CH3); 7.20 (2H, d, J = 8.0, H Ph); 8.19 (1H, s, NH). 13C NMR spectrum, δ ppm (C-17); 121.0 (C-15); 170.8 (C-12). Found, %: C 67.76; H 5.97; N 14.81. C16H19N3O2. Calculated, %: C 67.83; H 6.05; N 14.83.

(3R,4S*)-3-(3,5-Dimethyl-1H-pyrazole-1-carbonyl)-4-(4-methylphenyl)pyrrolidin-2-one (5b) was obtained from hydrazide 1b (1165 mg, 5 mmol). Yield 1025 mg (69%), colorless crystals, mp 141–143°C (i-PrOH). IR spectrum, υ cm⁻¹: 3412, 3342 (NH); 1725, 1703, 1699 (C=O); 1519, 1460, 1440 (C=O); 3212, 3192 (OH). 1H NMR spectrum, δ ppm (J, Hz): 1.19 (3H, s, 15-CH3); 2.42 (3H, d, J = 10.8, 17-CH3); 3.28 (1H, t, J = 9.4, 5-CH2); 3.64 (1H, ddd, J = 9.4, 8.2, 1.9, 3-CH); 3.97–4.07 (1H, m, 4-CH); 5.15 (1H, d, J = 11.1, 3-CH3); 6.17 (1H, q, J = 6.5, 16-CH3); 7.07 (2H, d, J = 8.0, H Ph); 7.20 (2H, d, J = 8.0, H Ph); 8.19 (1H, s, NH). 13C NMR spectrum, δ ppm (C-17); 147.4 (C Ph); 21.1 (CH3); 45.3 (C-4); 54.1 (C-3); 112.8 (C-16); 127.7 (C-4 Ph); 128.9 (C-2,5 Ph); 140.3 (C-1 Ph); 144.0 (C-17); 152.6 (C-15); 170.8 (C-12). Found, %: C 67.76; H 5.97; N 14.81.

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(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(4-methoxyphenyl)pyrrolidin-2-one (6f) was obtained from hydrazide 2e (249 mg, 1 mmol). Yield 222 mg (71%), colorless crystals, mp 178–180°C (i-PrOH). IR spectrum, ν, cm⁻¹: 1723, 1696 (C=O), 3208, 3106 (NH). δ ppm (J, Hz): 7.20 (3H, d, J = 7.8, 4-CH); 7.10 (1H, d, J = 7.9, 3-CH); 4.12 (2H, t, J = 7.8, 4-CH); 3.74 (3H, s, CH₃); 1.19 (3H, d, J = 6.7, 2-CH₃); 2.44 (3H, s, 16-CH₃); 1.05 (3H, s, 15-CH₃); 1.02 (3H, d, J = 6.9, 6-CH₃); 0.87 (3H, d, J = 6.7, 5-CH₃); 0.85 (3H, d, J = 6.5, 5-CH₃). Found, %: C 69.24; H 6.75; N 14.07.

(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(3-nitrophenyl)pyrrolidin-2-one (6e) was obtained from hydrazide 2d (160 mg, 0.5 mmol). Yield 106 mg (67%), colorless crystals, mp 157–159°C (PrOH). IR spectrum, ν, cm⁻¹: 328; 3087 (NH), 3060 (C=H). δ ppm (J, Hz): 7.57 (1H, d, J = 7.2, 4-CH); 7.13 (1H, d, J = 7.2, 3-CH); 7.07 (1H, d, J = 7.4, 5-CH); 7.03 (1H, d, J = 7.6, 5-CH); 6.97 (1H, d, J = 7.8, 6-CH); 6.62 (1H, d, J = 7.9, 6-CH); 6.94 (1H, d, J = 8.0, 5-CH); 6.39 (1H, d, J = 8.1, 4-CH). Found, %: C 65.57; H 6.04; N 13.12.

(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(4-methylphenyl)pyrrolidin-2-one (6d) was obtained from hydrazide 2c (249 mg, 1 mmol). Yield 222 mg (71%), colorless crystals, mp 205–207°C (i-PrOH). IR spectrum, ν, cm⁻¹: 1723, 1699 (C=O), 3195, 3094 (NH). δ ppm (J, Hz): 7.46 (1H, d, J = 7.8, 4-CH); 7.15 (1H, d, J = 7.9, 3-CH); 4.12 (2H, t, J = 7.8, 4-CH); 3.74 (3H, s, CH₃); 1.19 (3H, d, J = 6.7, 2-CH₃); 2.44 (3H, s, 16-CH₃); 1.05 (3H, s, 15-CH₃); 1.02 (3H, d, J = 6.9, 6-CH₃); 0.87 (3H, d, J = 6.7, 5-CH₃); 0.85 (3H, d, J = 6.5, 5-CH₃). Found, %: C 69.24; H 6.75; N 14.07.

(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(4-phenyl)pyrrolidin-2-one (6c) was obtained from hydrazide 2b (249 mg, 1 mmol). Yield 222 mg (71%), colorless crystals, mp 210–212°C (i-PrOH). IR spectrum, ν, cm⁻¹: 1723, 1696 (C=O), 3201, 3094 (NH). δ ppm (J, Hz): 7.46 (1H, d, J = 7.8, 4-CH); 7.15 (1H, d, J = 7.9, 3-CH); 4.12 (2H, t, J = 7.8, 4-CH); 3.74 (3H, s, CH₃); 1.19 (3H, d, J = 6.7, 2-CH₃); 2.44 (3H, s, 16-CH₃); 1.05 (3H, s, 15-CH₃); 1.02 (3H, d, J = 6.9, 6-CH₃); 0.87 (3H, d, J = 6.7, 5-CH₃); 0.85 (3H, d, J = 6.5, 5-CH₃). Found, %: C 69.24; H 6.75; N 14.07.

(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(3-nitrophenyl)pyrrolidin-2-one (6b) was obtained from hydrazide 2a (249 mg, 1 mmol). Yield 222 mg (71%), colorless crystals, mp 197–199°C (MeOH). IR spectrum, ν, cm⁻¹: 1723, 1696 (C=O), 3195, 3094 (NH). δ ppm (J, Hz): 7.46 (1H, d, J = 7.8, 4-CH); 7.15 (1H, d, J = 7.9, 3-CH); 4.12 (2H, t, J = 7.8, 4-CH); 3.74 (3H, s, CH₃); 1.19 (3H, d, J = 6.7, 2-CH₃); 2.44 (3H, s, 16-CH₃); 1.05 (3H, s, 15-CH₃); 1.02 (3H, d, J = 6.9, 6-CH₃); 0.87 (3H, d, J = 6.7, 5-CH₃); 0.85 (3H, d, J = 6.5, 5-CH₃). Found, %: C 69.24; H 6.75; N 14.07.

(4R*,5R*)-5-(3,5-Dimethyl-1H-pyrazol-1-carbonyl)-4-(4-methylphenyl)pyrrolidin-2-one (6a) was obtained from hydrazide 2 (1065 mg, 4 mmol). Yield 918 mg (70%), colorless crystals, mp 173–175°C (MeOH). IR spectrum, ν, cm⁻¹: 1723, 1696 (C=O), 3193, 3087 (NH). δ NMR spectrum, δ ppm (J, Hz): 7.46 (1H, d, J = 7.8, 4-CH); 7.15 (1H, d, J = 7.9, 3-CH); 4.12 (2H, t, J = 7.8, 4-CH); 3.74 (3H, s, CH₃); 1.19 (3H, d, J = 6.7, 2-CH₃); 2.44 (3H, s, 16-CH₃); 1.05 (3H, s, 15-CH₃); 1.02 (3H, d, J = 6.9, 6-CH₃); 0.87 (3H, d, J = 6.7, 5-CH₃); 0.85 (3H, d, J = 6.5, 5-CH₃). Found, %: C 69.24; H 6.75; N 14.07.
18-CH$_3$): 2.70 (1H, dd, $^2J = 16.7$, $^3J = 9.0$, 3-CH$_2$); 3.41 (1H, dd, $J = 9.1$, $J = 7.5$, 5-CH$_2$); 3.52–3.64 (1H, m, 4-CH$_3$); 3.77 (1H, dd, $J = 9.1$, $J = 8.4$, 5-CH$_3$); 4.72 (1H, d, $^2J = 18.3$, 12-CH$_2$); 4.78 (1H, d, $^2J = 18.3$, 12-CH$_2$); 6.20 (1H, q, $^3J = 0.7$, 17-CH); 7.11 (2H, d, $J = 8.0$, H Ph); 7.19 (2H, d, $J = 8.0$, H Ph). $^{13}$C NMR spectrum, δ, ppm: 14.0 (16-CH$_3$); 14.3 (18-CH$_3$); 21.1 (CH$_3$ Ph); 37.0 (C-4); 38.6 (C-3); 46.0 (C-12); 54.9 (C-5); 111.9 (C-17); 127.3 (C Ph); 129.7 (C Ph); 136.3 (C Ph); 140.2 (C Ph); 144.2 (C-18); 152.9 (C-16); 168.7 (C-13); 174.4 (C-2). Found, %: C 69.14; H 6.85; N 13.59. C$_{18}$H$_{21}$N$_3$O$_2$. Calculated, %: C 69.43; H 6.60; N 13.49.

1-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-oxoethyl]-4-(4-methoxyphenyl)pyrrolidin-2-one (7c) was obtained from hydrazide 3e (789 mg, 3 mmol). Yield 647 mg (66%), colorless crystals, mp 125–127°C (i-PrOH). IR spectrum, ν, cm$^{-1}$: 1740, 1684 (C=O). $^1$H NMR spectrum, δ, ppm (J, Hz): 2.16 (3H, s, 16-CH$_3$); 2.38 (1H, d, $^2J = 16.6$, $^3J = 8.8$, 3-CH$_2$); 2.44 (3H, s, CH$_3$ O Ph); 2.68 (1H, dd, $^2J = 16.6$, $^3J = 9.0$, 3-CH$_2$); 3.39 (1H, dd, $^3J = 0.5$, 18-CH$_3$); 3.50–3.62 (1H, m, 4-CH$_3$); 7.19 (1H, d, $J = 9.1$, $J = 8.5$, 5-CH$_2$); 4.72 (1H, d, $^2J = 18.3$, 12-CH$_2$); 4.78 (1H, d, $^2J = 18.3$, 12-CH$_2$); 6.20 (1H, q, $^3J = 0.5$, 17-CH); 6.70 (2H, d, $J = 8.7$, H-3,5-CH$_2$); 7.23 (2H, d, $J = 8.7$, H-2,6 Ph). $^{13}$C NMR spectrum, δ, ppm: 14.0 (16-CH$_3$); 14.3 (18-CH$_3$); 36.7 (C-4); 38.7 (C-3); 45.9 (C-12); 55.1 (C-5); 55.6 (CH$_3$ O Ph); 111.9 (C-17); 114.5 (C, Ph); 128.5 (C-2,6 Ph); 135.1 (C-1 Ph); 144.2 (C-18); 152.9 (C-16); 156.8 (C-4 Ph); 168.7 (C-13); 174.4 (C-2). Found, %: C 65.68; H 6.47; N 12.81. C$_{18}$H$_{21}$N$_3$O$_2$. Calculated, %: C 66.04; H 6.47; N 12.84.

Supplementary information file containing IR spectra, $^1$H and $^{13}$C NMR spectra of all synthesized compounds 5a–e, 6a–g, 7a–d, as well as $^1$H, $^{13}$C HMOC and $^{1}$H–$^{13}$C HMBC spectra of compounds 5a,c, 6a,b, 7a and crystallographic data of structures 5–7 a is available at the journal website http://link.springer.com/journal/10593.

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References

1. Berestovitskaya, V. M.; Tyurenkov, I. N.; Vasilyeva, O. S.; Perfilova, V. N.; Ostroglyadov, E. S.; Bagmetova, V. V. Rateyotnaya: method manifold biochemistry and biological activity (Racem: methods of synthesis and biological activity [in Russian]); Asterton: St. Petersburg, 2016.

2. Kucukguzel, S. G.; Senkardes, S. Eur. J. Med. Chem. 2015, 97, 786.

3. Caruano, J.; Muccioli, G. G.; Robiette, R. Org. Biomol. Chem. 2016, 14, 10134.

4. Mert, S.; Kasamoqullan, R.; Ica, T.; Colak, F.; Altun, A.; Ok, S. Eur. J. Med. Chem. 2014, 78, 86.

5. Faria, J. V.; Vegg, P. F.; Miguita, A. G. C.; dos Santos, M. S.; Boechat, N.; Bernardino, A. M. R. Bioorg. Med. Chem. 2017, 25, 5891.

6. Ansari, A.; Ali, A.; Asif, M.; Shamsuzzaman New J. Chem. 2017, 1, 16.

7. Mashkovskiy, M. D. Lekarstvennye sredstva (Drugs [in Russian]); Novaya Volna: Moscow, 2012, 16th Ed.

8. (a) Granik, V. G. Lekarstva (farmakologicheski, biokhimicheskii i khimicheskii aspekt) (Drugs (pharmacological, biochemical and chemical aspects) [in Russian]); Vuzovskaya Kniga: Moscow, 2006, 2nd Ed., p. 149. (b) Granik, V. G. Lekarstva (farmakologicheski, biokhimicheskii i khimicheskii aspekt) (Drugs (pharmacological, biochemical and chemical aspects) [in Russian]); Vuzovskaya Kniga: Moscow, 2006, 2nd Ed., p. 153. (c) Granik, V. G. Lekarstva (farmakologicheski, biokhimicheskii i khimicheskii aspekt) (Drugs (pharmacological, biochemical and chemical aspects) [in Russian]); Vuzovskaya Kniga: Moscow, 2006, 2nd Ed., p. 360.

9. Gouliaev, A. H.; Monster, J. B.; Vedso, M.; Senning, A. Org. Prep. Proced. Int. 1995, 27, 273.

10. Malykh, A. G.; Sadaie, M. R. Drugs 2010, 70, 287.

11. Hoffman, R. L.; Kania, R. S.; Brothers, M. A.; Davies, J. F.; Ferre, R. A.; Gajiwala, K. S.; He, M.; Hogan, R. J.; Kozinski, K.; Li, L. Y.; Lockner, J. W.; Lou, J.; Marra, M. T.; Mitchell, L. J., Jr.; Murray, B. W.; Nieman, J. A.; Noell, S.; Planken, S. P.; Rowe, T.; Ryan, K.; Smith III, G. J.; Solowij, J. E.; Steppan, C. M.; Taggart, B. J. Med. Chem. 2020, 63, 12725.

12. Vandycck, K.; Deval, J. Curr. Opin. Virol. 2021, 49, 36.

13. Zhang, L.; Lin, D.; Kusoy, V.; Nian, Y.; Ma, Q.; Wang, J.; von Brunn, A.; Leyssen, P.; Lanko, K.; Neys, J.; de Wilde, A.; Snijder, E. J.; Liu, H.; Hilgenfeld, R. J. Med. Chem. 2020, 63, 4562.

14. Vaickelioniene, R.; Mickevicius, V. Chem. Heterocyc. Compd. 2006, 42, 753.

15. Mickevicius, V.; Vaickelionienė, R. Chem. Heterocyc. Compd. 2008, 44, 170.

16. Brokaite, K.; Mickevicius, V.; Mikulskiene, G. Chem. Heterocyc. Compd. 2006, 42, 1158.

17. Sapijanskaitė, B.; Mickevicius, V. Chem. Heterocyc. Compd. 2008, 44, 807.

18. Mickevicius, V.; Vaickelionienė, R.; Jonuškienė, I.; Mikulskienė, G.; Kantmireni, K. Monat. Chem. 2009, 140, 1513.

19. Anusevičius, K.; Jonuškienė, I.; Sapijanskaitė, B.; Kantmireni, K.; Mickevičius, V. Res. Chem. Intermed. 2016, 42, 6975.

20. Gorodnicheva, N. V.; Vasil'eva, O. S.; Ostroglyadov, E. S.; Baichurin, R. I.; Makarenko, S. V.; Karamov, F. A.; Lodochnikova, O. A.; Litvinov, I. A. Russ. Chem. Bull. 2020, 69, 470.

21. Gorodnicheva, N. V.; Ostroglyadov, E. S.; Vasil'eva, O. S.; Pelipko, V. V.; Gurzhii, V. V.; Berestovitskaya, V. M.; Lipina, E. S. Russ. J. Org. Chem. 2016, 52, 1616.

22. Vasil'eva, O. S.; Berestovitskaya, B. M.; Tyurenkov, I. N.; Ostroglyadov, E. S.;Perfilova, V. N.; Gorodnicheva, N. V.; Yaremchuk, A. I. Russ. Chem. Bull. 2017, 66, 1491.

23. Monteoya-Balbás, I. J.; Valentín-Guevara, B.; López-Mendoza, E.; Linzaga-Elizalde, I.; Ordoñez, M.; Roman-Bravo, P. Molecules 2015, 20, 22028.

24. Pachaly, P. Chem. Ber. 1971, J04, 412.

25. Pachaly, P. Chem. Ber. 1971, J04, 429.

26. Klimochkin, Y. N.; Tkachenko, I. M.; Reznikov, A. N.; Bakerlin, D. A.; Abrosimova, E. E.; Kurkin, D. V.; Tyurenkov, I. N. Russ. J. Bioorg. Chem. 2021, 47, 1276.

27. APEX2 (Version 2.1); Bruker AXS, Inc.: Madison, 2006.

28. SADABS; Bruker AXS, Inc.: Madison, 1997.

29. Sheldrick, G. Acta Crystallogr., Sect. A Found. Adv. 2015, A71, 3.

30. Sheldrick, G. Acta Crystallogr., Sect. C: Struct. Chem. 2015, C71, 3.

31. Spek, A. Acta Crystallogr., Sect. A: Found. Crystallogr. 1990, A46, 34.

32. Farrugia, L. J. Appl. Crystallogr. 2012, 45, 849.