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Synthesis and Hypoglycemic Activity of Aryl(Hetaryl)Propenoic Cyanopyrrolidine Amides

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Abstract—A series of amides based on (2S)-cyanopyrrolidine and α, β-unsaturated aryl- and hetarylcarboxylic acids have been synthesized. The dependence of the hypoglycemic activity of compounds on the structure of the aromatic fragment has been studied in the oral glucose tolerance test in mice. Amides based on (E)-3-phenylprop-2-enoic and (E)-3-(4-methoxyphenyl)prop-2-enoic acids and (2S)-cyanopyrrolidine have been shown to significantly reduce blood glucose levels in mice. The observed hypoglycemic effect at a dose of 10 mg/kg is comparable to the effect of hypoglycemic drug vildagliptin.

Keywords: diabetes mellitus type 2, cyanopyrrolidine, oral glucose tolerance test, hypoglycemic activity

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INTRODUCTION

Type 2 diabetes mellitus (DM-2) is a metabolic disease characterized by chronic hyperglycemia associated with insulin resistance of tissues. The WHO estimates that the number of patients suffering from DM-2 in 2015 had exceeded 392 million people, which is about 90% of all cases of DM [1].

Dipeptidyl peptidase-4 (DPP-4), an enzyme that cleaves peptides from the *N*-terminus of proline, plays an important role in glucose metabolism. After a meal, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are produced, which leads to a glucose-dependent increase in insulin secretion and inhibition of glucagon secretion. However, the lifetime of these incretins is extremely short because they quickly deactivate DPP-4 [2], thus leading to the prolongation of beneficial effects of GLP-1 and HIP, which is used in the treatment of DM-2. Compounds that contain the cyanopyrrolidine fragment, which has been shown [3] to bind to the active center of the enzyme, are a substantial proportion among the DPP-4 inhibitors, also called gliptins, e.g., vildagliptin (**I**) and saxagliptin (**II**) (Fig. 1). Despite the fact that presently known gliptins are used in therapeutic practice, the search for new hypoglycemic agents, which act by the same mechanism, is still relevant [4–6].

An important area of medicinal chemistry for obtaining new drugs is the synthetic transformation of natural compounds [7]. The DPP-4 inhibitors of natural origin include, in particular, compounds that contain the α,β-unsaturated styrene fragment. These compounds, i.e., caffeic acid (**III**) and resveratrol (**IV**) inhibit DPP-4 in vitro at nanomolar concentrations [8]. The main disadvantage of these compounds is the nonselective action, which complicates their targeted use as hypoglycemic agents. For example, cinnamon acids exhibit antioxidant, antihypoxic, cerebroprotective, hepatoprotective, choleretic, antiinflammatory, cytostatic, lipid-lowering, anticoagulant, antiallergic, antibacterial, antiviral, fungicidal, and other activities in addition to hypoglycemic effects [9–12]. The modification of a molecule with broad pharmacophore coverage can lead to the desired increase in the specificity of its action [13]. In our case, it seems promising to combine fragments that specifically bind to the active center of DPP-4 with molecules that have a certain affinity to the enzyme.

According to the results of molecular docking [14], resveratrol binds to the same DPP-4 site as the commercially available gliptins. In this case, one of its aromatic rings plays the role of the cyanopyrrolidine fragment and occupies the S1 pocket in the enzyme, and the remaining styrene fragment is involved in the binding to the protein due to the π–π stacking. It can be assumed that the combination of the styrene moiety

Abbreviations: GTT, glucose tolerance test; DPP-4, dipeptidyl peptidase-4; DM-2, type 2 diabetes mellitus; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

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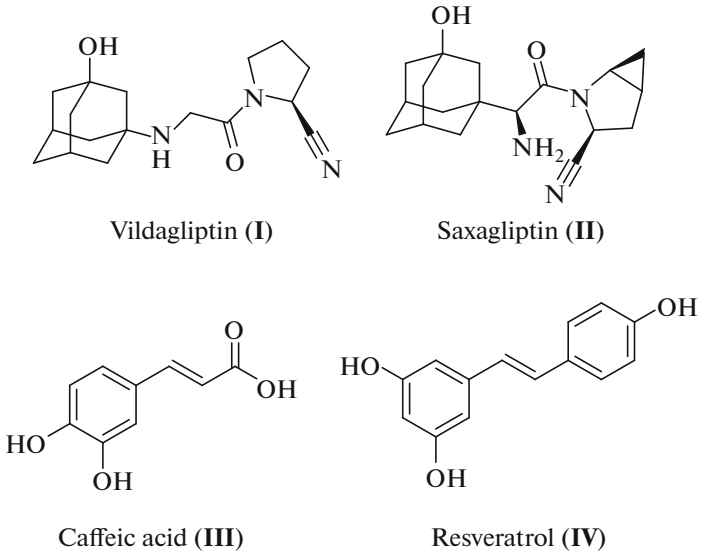


Vildagliptin (**I**) Saxagliptin (**II**)

Caffeic acid (**III**) Resveratrol (**IV**)

Fig. 1. Inhibitors of DPP-4.

of caffeic acid with resveratrol that contains the corresponding cyanopyrrolidine amide moiety will result in the compounds, which will also exhibit the hypoglycemic activity

The goal of this work was to synthesize new compounds by combining the fragment of α,β-unsaturated aromatic acids that contained the structural block of synthetic inhibitors of DPP-4 (2-cyanopyrrolidine) and to study the hypoglycemic activity of the resulting compounds.

RESULTS AND DISCUSSION

Cyanopyrrolidine tosylate (**IX**) was synthesized from commercially available L-proline (**V**) (Scheme 1). The amino group of L-proline was protected by Boc_2O in aqueous dioxane in the presence of sodium bicarbonate with the formation of acid (**VI**) [15]. Amide (**VII**) was synthesized by the reaction of *N*-Boc-protected acid (**VI**) with Boc_2O and NH_4HCO_3 in the presence of pyridine in dioxane [16]. Amide (**VII**) was dehydrated by trifluoroacetic acid anhydride in the presence of trimethylamine in methylene chloride with the formation of nitrile (**VIII**) [17]. The treatment of compound (**VIII**) with *p*-toluolsulfonic acid led to the removal of the Boc-protective group. (2*S*)-Pyrrolidine carbonitrile was isolated from the solution in the form of cyanopyrrolidine tosylate (**IX**) [18].

The series of α,β-unsaturated acids (**XIa**–**m**) was synthesized from aromatic and heteroaromatic aldehydes (**Xa**–**m**) (Scheme 2). Compounds (**XIa**–**d, g**–**i**) were prepared by the method described in [19] by the interaction of the corresponding aldehyde with malonic acid in toluol under reflux in the presence of piperidine and trimethylamine (method **A**). Compounds (**XIe, f, j**–**m**) were prepared according to the method [20] by the interaction of corresponding aldehyde with malonic acid in pyridine in the presence of catalytic amount of piperidine (method **B**) because method **A** led to either poor yields of compounds (**XIe, f**) or the formation of corresponding dicarbonic acids in the case of compounds (**XIj**–**m**). The yields of acids (**XIa**–**m**) were 45–95%.

Target (2*S*)-cyanopyrrolidine amides of (*E*)-3-((hetaryl)-2-propenoic acids (**XIIa**–**m**) were synthesized by the condensation of corresponding propenoic acids (**XIa**–**m**) with 2-cyanopyrrolidine tosylate (IX) (Scheme 2) in the presence of hexafluorophosphate of (2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium (HBTU) and trimethylamine in DMF. Amides (**XIIa**–**m**) were isolated in yields of 41–94%. Amide (**XIIa**) was described in the patent [21] (however, without any spectral data).

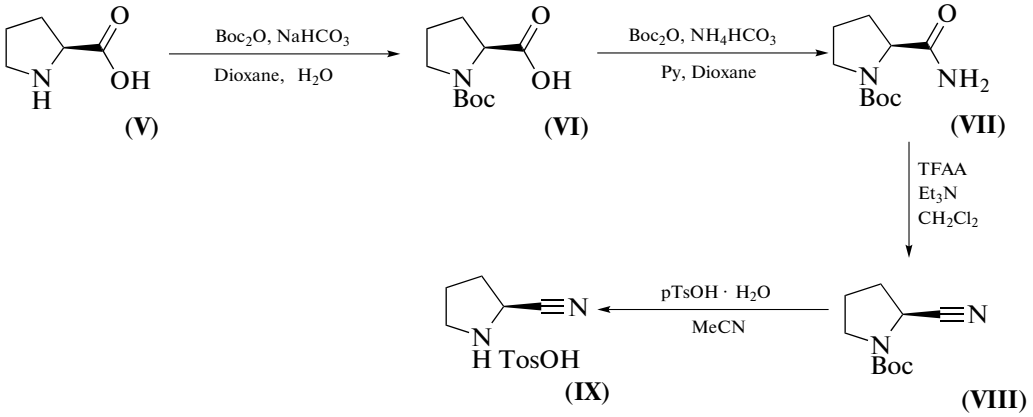
It should be noted that resulting amides (**XIIa**–**m**) exist in solution as a mixture of rotamers because of hindered rotation around the amide bond C–N, which leads to doubling of some signals in the ^{1}H NMR spectra [22].

Hypoglycemic Activity

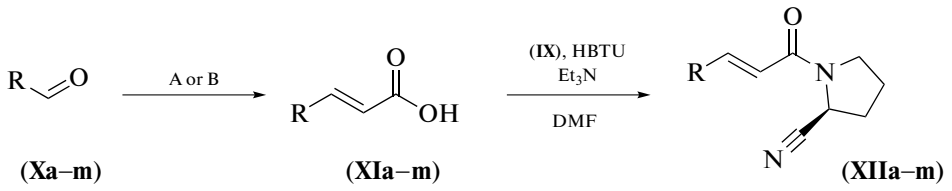
Amides (**XIIa**–**m**) were studied for their hypoglycemic activity in oral glucose tolerance test (GTT) on male CD-1 mice. The results of this test 30 and 60 min after glucose administration are presented in Fig 2. In 90 min, the glucose level was equal in mice of all groups. Vildagliptin (**I**) was used as the reference preparation. The results showed that compounds (**XIIa**) and (**XIIb**) exhibited the hypoglycemic effect comparable to that of vildagliptin.

The replacement of the methoxy group by another substituent (fluoro (**XIIc**), nitro (**XIId**),

hydroxy (**XIIf**)), an increase in the number of the methoxy groups in the aromatic fragment (**XIIg, h, i**), and the introduction of the thiophene cycle instead of benzene ring (**XIIl**) led to a loss of the hypoglycemic effect in the experiment. In some cases, these transformations led to an increase in the glucose level in blood compared to the control group (compounds (**XIIe, g, j, k, m**)).



Scheme 1. Synthesis of cyanopyrrolidine fragment **(IX)**.



a. R = phenyl[A]
b. R = 4-methylphenyl[A]
c. R = 4-fluorophenyl[A]
d. R = 4-nitrophenyl[A]
e. R = 3-hydroxyphenyl[B]
f. R = 4-hydroxyphenyl[B]
g. R = 2,3-dimethylphenyl[A]
h. R = 3,4-dimethylphenyl[A]
i. R = 2,3,4-trimethylphenyl[A]
j. R = 2-thienyl[B]
k. R = 3-thienyl[B]
l. R = 5-methyl-2-thienyl[B]
m. R = 4-pyridyl[B]

Scheme 2. Synthesis of (2*S*)-cyanopyrrolidine amides of (*E*)-3-((hetaryl)-2-propenoic acids (**XIIa–m**). Method A: $CH_2(COOH)_2$, piperidine, Et_3N, $PhCH_3$, Δ; method B: $CH_2(COOH)_2$, piperidine, pyridine, 67°C.

Clarification of the mechanism of hyperglycemia requires further research. One of the possible options may be an insufficient increase in insulin secretion in response to oral glucose administration, which is usually mediated by the activation of incretins (GPP-1) and (GIP) [23]. It can be assumed that compounds (**XIIe, g, j, k, m**) reduce the production of these polypeptide hormones for example by blocking the sodium-dependent glucose cotransporter (SGLT), which is important for glucose-induced secretion of GPP-1 [24].

CONCLUSIONS

Amides of α, β-unsaturated aryl and hetarylcarboxylic acids and (2*S*)-pyrrolidine carbonitrile have been synthesized. (2*S*)-Cyanopyrrolidine amide of (*E*)-3-phenyl-2-propeonic acid (**XIIa**) and (2*S*)-cyanopyrrolidine amide of (*E*)-3-(4-methoxyphenyl)-2-propenoic acid (**XIIb**) exhibited the hypoglycemic activity in GTT on mice at a dose of 10 mg/kg, which was comparable with the effect of vildagliptin (**I**). The hyperglycemic effect was observed for compounds (**XIIe, g, j, k, m**).

EXPERIMENTAL

The ^1H and ^{13}C spectra were recorded in $CDCl_3$ (where it is not specified) on AV-400 and AV-300 spectrometers (Bruker, United States), (δ, ppm; SSIC, Hz). Signals of residual protons of $CDCl_3$ were used as an internal standard (δH 7.26 ppm; δC 77.00 ppm). The IR

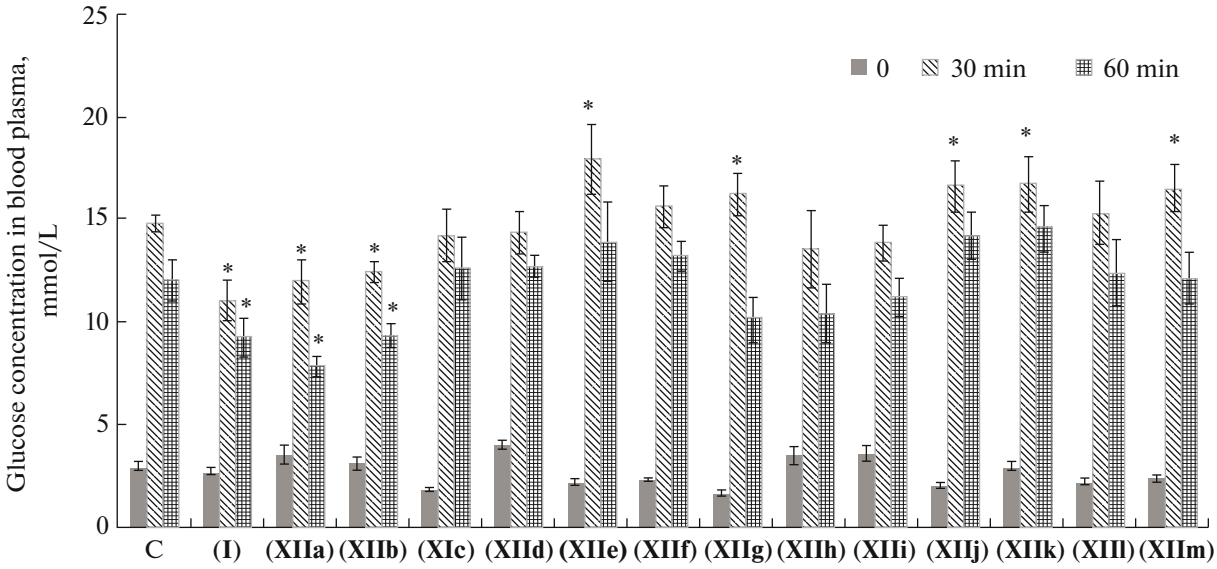


Fig. 2. Results of the glucose tolerance test. The glucose content in the plasma was measured at the beginning of the experiment and 30 and 60 minutes after its administration; the values are presented as the mean ± standard error of the mean (n = 5). C, control group. * $p < 0.05$ relative to the control.

spectra were recorded on a Bruker Tensor 27 instrument in KBr tablets (ν, cm^{-1}). The reactions were monitored by TLC on Merck silica gel 60 F254 plates in a chloroform–methanol system (10 : 1). Compounds were visualized in the iodine chamber or by UV irradiation. The column chromatography was performed on Merck silica gel (70–230 μm). The melting temperatures of the compounds were determined on a Mettler Toledo FP90 instrument and Koffler table. Initial aldehydes L-proline (Sigma-Aldrich, ≥98.5%), reactants, and solvents were obtained from commercial sources. The solvents were purified before use according to the indicated methods [25]. Compounds **(VIa–m)** and **(VII–XI)** were synthesized by the literature methods [15–20] and identified by the ^{1}H spectra.

General method of the synthesis of amides (XIIa–m). The mixture of corresponding acid **(XIa–m)** (1 mmol), cyanopyrrolidine tosylate **(IX)** (0.27 g, 1 mmol), and Et_3N (0.28 mL, 2 mmol) in DMF (10 mL) were stirred in an inert atmosphere at room temperature for 24 h. The reaction mixture was poured into 40 mL of water, and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed successively by water (10 mL) and saturated sodium chloride (10 mL) and dried over $MgSO_4$. The precipitate was filtered off, and the solution was evaporated under reduced pressure. The residue was purified by column chromatography using a chloroform-methanol mixture (10 : 1) as an eluent.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-phenyl-2-propenoic acid (XIIa). White powder; yield, 43%; mp, 131.8°C, decomp. $[\alpha]_D^{27.4}$ −129 (c 0.24, $CHCl_3$). IR spectrum: 2241 (–C≡N). ^{1}H NMR (400 MHz): 2.10–2.49 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.57–3.88 (2 H, m, $CH_2C\underline{H}_2N$), 4.79 (0.2 H, d, J 6.9, C<u>H</u>CN), 4.87 (0.8 H, d, J 5.9, C<u>H</u>CN), 6.66 (1 H, d, J 15.4, ArCH-C<u>H</u>CO), 6.77 (1 H, d, J 15.6, ArCHC<u>H</u>CO), 7.35–7.44 (3 H, m, Ph-3,4,5), 7.50–7.60 (2 H, m, Ph-2,6), 7.79 (1 H, d, J 15.4, ArC<u>H</u>CHCO). ^{13}C NMR (126 MHz): 25.1 ($CH_2\underline{C}H_2CH_2CHCN$), 30.0 ($CH_2CH_2\underline{C}H_2CHCN$), 46.3 ($CH_2\underline{C}H_2N$), 46.6 (<u>C</u>HCN), 116.8 (ArCH<u>C</u>HCO), 118.4 (CN), 128.0 (Ph-3,5), 128.8 (Ph-2,6), 130.2 (Ph-4), 134.6 (Ph-1), 144.3 (Ar<u>C</u>HCH), 164.9 (ArCHCH<u>C</u>O). Found: m/z 226.1109 $[M]^+$. $C_{14}H_{14}N_2O$. Calc.,M 226.1106. Found, %: C 74.46; H 6.27; N 12.35. $C_{14}H_{14}N_2O$. Calc., %: C 74.31; H 6.24; N 12.38.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(4-methoxyphenyl)- 2-propenoic acid (XIIb). White powder; yield, 65%; mp, 107.2°C, decomp. $[\alpha]_D^{27.4}$ −114 (c 0.18, $CHCl_3$). IR spectrum: 2235 (–C≡N). ^{1}H NMR (400 MHz): 2.09–2.45 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.57–3.65 (1 H, m, $CH_2C\underline{H}_2N$), 3.77–3.85 (4 H, m, $CH_2C\underline{H}_2N$, Ph-4-O<u>CH</u>$_3$), 4.85 (1 H, d, J 5.6, C<u>H</u>CN), 6.51 (1 H, d, J 15.4, ArCHC<u>H</u>CO), 6.62 (1 H, d, J 14.9, ArCH-C<u>H</u>CO), 6.89 (2 H, d, J 8.7, Ph-3,5), 7.48 (2 H, d, J 8.6, Ph-2,6), 7.73 (1 H, d, J 15.4, ArC<u>H</u>CHCO). ^{13}C NMR (101 MHz): 25.1 ($CH_2\underline{C}H_2CH_2CHCN$), 29.9 ($CH_2CH_2\underline{C}H_2CHCN$), 46.2 ($CH_2\underline{C}H_2N$), 46.6 (<u>C</u>HCN), 55.3 (Ph-6-O<u>C</u>H$_3$), 114.2 (Ph-3,5), 114.3 (ArCH<u>C</u>HCO), 118.5 (CN), 127.3 (Ph-1), 129.7 (Ph-2,6), 143.8 (Ar<u>C</u>HCH), 161.2 (Ph-4), 165.2 (ArCHCH<u>C</u>O). Found: m/z 256.1217 $[M]^+$. $C_{15}H_{16}N_2O_2$. Calc.: M 256.1212. Found, %: C 70.27; H 6.31; N 10.95. $C_{15}H_{16}N_2O_2$. Calc., %: C 70.29; H 6.29; N 10.93.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(4-fluorophenyl)- 2-propenoic acid (XIIc). White powder; yield,

94%; mp, 125.0°C, decomp. $[\alpha]_D^{27.4}$ −111 (c 0.19, $CHCl_3$). IR spectrum: 2237 (−C≡N). ^{1}H NMR (400 MHz): 2.05–2.53 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.54–3.92 (2 H, m, $CH_2C\underline{H}_2N$), 4.79 (0.2 H, d, *J* 6.4, C<u>H</u>CN), 4.87 (0.8 H, d, *J* 5.6, C<u>H</u>CN), 6.58 (0.8 H, d, *J* 15.4, ArCHC<u>H</u>CO), 6.64–6.74 (0.2 H, m, ArCHC<u>H</u>CO), 7.07 (2 H, t, *J* 8.5, Ph-3,5), 7.46–7.61 (2 H, m, Ph-2,6), 7.75 (1 H, d, *J* 15.4, ArC<u>H</u>CHCO). ^{13}C NMR (75 MHz): 25.0 ($CH_2\underline{C}H_2CH_2CHCN$), 29.9 ($CH_2CH_2\underline{C}H_2CHCN$), 46.2 ($CH_2\underline{C}H_2N$), 46.6 (<u>C</u>HCN), 115.9 (Ph-3,5), 116.6 (ArCH<u>C</u>HCO), 118.4 (CN), 129.8 (Ph-2,6), 130.8 (Ph-1), 142.8 (Ar<u>C</u>HCH), 163.7 (Ph-4), 164.7 (ArCHCH<u>C</u>O). Found: *m/z* 244.1008 $[M]^+$. $C_{14}H_{14}FN_2O$. Calc., M 244.1012. Found, %: C 68.90; H 5.37; N 11.49. $C_{14}H_{13}N_2OF$. Calc., %: C 68.84; H 5.36; N 11.47.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(4-nitrophenyl)-2-propenoic acid (XIId). Light yellow powder; Yield, 56%; mp, 166.9°C, decomp. $[\alpha]_D^{24.3}$ −129 (*c* 0.4, $CHCl_3$). IR spectrum: 1400 (NO_2), 1537 (NO_2), 2239 (−C≡N). ^{1}H NMR (400 MHz): 2–2.51 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.56–3.94 (2 H, m, $CH_2C\underline{H}_2N$), 4.82 (0.2 H, d, *J* 7.3, C<u>H</u>CN), 4.88 (0.8 H, d *J* 6.4, C<u>H</u>CN), 6.79 (0.8 H, d, *J* 15.6, ArCHC<u>H</u>CO), 6.89 (0.2 H, d *J* 15.2, ArCHC<u>H</u>CO), 7.68 (2 H, d, *J* 8.7, Ph-2,6), 7.81 (1 H, d, *J* 15.6, ArC<u>H</u>CHCO), 8.24 (2 H, d, *J* 8.7, Ph-3,5). ^{13}C NMR (126 MHz): 25.1 ($CH_2\underline{C}H_2CH_2CHCN$), 30.0 ($CH_2CH_2\underline{C}H_2CHCN$), 46.4 ($CH_2\underline{C}H_2N$), 46.8 (<u>C</u>HCN), 118.1 (CN), 121.0 (ArCH<u>C</u>HCO), 124.1 (Ph-2,6), 128.6 (Ph-3,5), 140.7 (Ph-1), 141.4 (Ar<u>C</u>HCH), 148.3 (Ph-4), 163.9 (ArCHCH<u>C</u>O). Found: *m/z* 244.1008 $[M]^+$. $C_{14}H_{13}N_3O_3$. Calc.: M 271.0957. Found, %: C 62.11; H 4.84; N 15.50. $C_{14}H_{13}N_3O_3$. Calc., %: C 61.99; H 4.83; N 15.49.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(3-hydroxyphenyl)-2-propenoic acid (XIIe). Light beige powder; yield, 41%; mp, 143.2°C, decomp. $[\alpha]_D^{27.4}$ −85 (*c* 0.19, $CHCl_3$). IR spectrum: 2239 (−C≡N). ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6:1/2): 2.01–2.34 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.57–3.85 (2 H, m, $CH_2C\underline{H}_2N$), 4.77 (1 H, t, *J* 5.2, C<u>H</u>CN), 5.22 (0.2 H, dd, *J* 6.6, 2.6, Ph-3-O<u>H</u>), 6.68 (0.8 H, d, *J* 15.4, ArCHC<u>H</u>CO), 6.74–6.79 (1 H, m, Ph-4), 6.84 (0.2 H, d, *J* 15.2, ArCHC<u>H</u>CO), 6.93–7.00 (2 H, m, Ph-2,6), 7.09–7.16 (1 H, m, Ph-3), 7.49 (1 H, d, *J* 15.4, ArC<u>H</u>CHCO), 9.25 (0.8 H, s, Ph-3-O<u>H</u>). ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-d_6:1/2): 24.9 ($CH_2\underline{C}H_2CH_2CHCN$), 29.6 ($CH_2CH_2\underline{C}H_2CHCN$), 45.8 ($CH_2\underline{C}H_2N$), 46.4 (<u>C</u>HCN), 114.7 (Ph-2), 117.3 (ArCH<u>C</u>HCO), 118.4 (Ph-4), 119.3 (Ph-6), 119.4 (CN), 129.9 (Ph-5), 136.0 (Ph-1), 142.5 (Ar<u>C</u>HCH), 157.8 (Ph-2), 164.3 (ArCHCH<u>C</u>O). Found: *m/z* 242.1053 $[M]^+$. $C_{14}H_{14}N_2O_2$. Calc.: M 242.1055. Found, %: C 69.63; H 5.85; N 11.58. $C_{14}H_{14}N_2O_2$. Calc., %: C 69.41; H 5.82; N 11.56.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(4-hydroxyphenyl)-2-propenoic acid (XIIf). White powder; yield, 44%, mp, 137.6°C, decomp. $[\alpha]_D^{27.4}$ −72 (c 0.2, $CHCl_3$). IR spectrum: 2240 (−C≡N). ^{1}H NMR (400 MHz): 2.05–2.42 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.51–3.76 (2 H, dt, *J* 7.9, $CH_2C\underline{H}_2N$), 4.76–4.87 (1 H, m, C<u>H</u>CN), 6.44 (0.8 H, d, *J* 15.4, ArCHC<u>H</u>CO), 6.57 (0.2 H, d, *J* 15.2, ArCHC<u>H</u>CO), 6.90 (2 H, d, *J* 8.5, Ph-3,5), 7.36 (2 H, d, *J* 8.5, Ph-2,6), 7.66 (1 H, d, *J* 15.3, ArC<u>H</u>CHCO), 8.67 (1 H, br.s, Ph-4-O<u>H</u>). ^{13}C NMR (101 MHz): 24.8 ($CH_2\underline{C}H_2CH_2CHCN$), 29.6 ($CH_2CH_2\underline{C}H_2CHCN$), 46.1 ($CH_2\underline{C}H_2N$), 46.3 (<u>C</u>HCN), 114.8 (ArCH<u>C</u>HCO), 115.7 (Ph-3,5), 119.5 (CN), 125.7 (Ph-1), 130.1 (Ph-2,6), 142.4 (Ar<u>C</u>HCH), 159.4 (Ph-4), 164.6 (ArCHCH<u>C</u>O). Found: *m/z* 242.1051 $[M]^+$. $C_{14}H_{14}N_2O_2$. Calc., M 242.1055. Found, %: C 69.50; H 5.84; N 11.58. $C_{14}H_{14}N_2O_2$. Calc., %: C 69.41; H 5.82; N 11.56.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(2,3-dimethoxyphenyl)-2-propenoic acid (XIIg). White powder; yield, 69%; mp, 134–136°C; $[\alpha]_D^{27.4}$ −31 (c 0.26, $CHCl_3$). IR spectrum: 2237 (−C≡N). ^{1}H NMR (400 MHz): 2.10–2.44 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.58–3.67 (1 H, m, $CH_2C\underline{H}_2N$), 3.78 - 3.90 (7 H, m, $CH_2C\underline{H}_2N$, Ph-2,3-O$C\underline{H}_3$), 4.77 (0.2 H, d, *J* 7.7, C<u>H</u>CN), 4.87 (0.8 H, d, *J* 5.9, C<u>H</u>CN), 6.77 (0.9 H, d, *J* 15.7, ArCHC<u>H</u>CO), 6.93 (1.1 H, d, *J* 7.9, ArCHC<u>H</u>CO, Ph-6), 7.03–7.09 (1 H, m, Ph-5), 7.12 (1 H, d, *J* 7.1, Ph-4), 8.02 (1 H, d, *J* 15.7, ArC<u>H</u>CHCO). ^{13}C NMR (101 MHz): 25.1 ($CH_2\underline{C}H_2CH_2CHCN$), 30.0 ($CH_2CH_2\underline{C}H_2CHCN$), 46.3 ($CH_2\underline{C}H_2N$), 46.6 (<u>C</u>HCN), 55.8 (Ph-3-O$\underline{C}H_3$), 61.1 (Ph-2-O$\underline{C}H_3$), 113.7 (ArCH<u>C</u>HCO), 118.5 (CN), 118.6 (Ph-4), 119.8 (Ph-5), 124.1 (Ph-6), 128.8 (Ph-1), 139.2 (Ar<u>C</u>HCH), 148.5 (Ph-3), 153.2 (Ph-2), 165.2 (ArCHCH<u>C</u>O). Found: *m/z* 286.1315 $[M]^+$. $C_{17}H_{20}N_2O_4$. Calc.: M 286.1317. Found, %: C 67.05; H 6.36; N 9.79. $C_{16}H_{18}N_2O_3$. Calc., %: C 67.12; H 6.34; N 9.78.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(3,4-dimethoxyphenyl)-2-propenoic acid (XIIh). White powder; yield, 48%; mp,, 139–140°C; $[\alpha]_D^{27.4}$ −98 (c 0.22, $CHCl_3$). IR spectrum: 2235 (−C≡N). ^{1}H NMR (400 MHz): 2.10–2.47 (4 H, m, $CH_2C\underline{H}_2C\underline{H}_2CHCN$), 3.57–3.71 (1 H, m, $CH_2C\underline{H}_2N$), 3.79–3.98 (7 H, m, $CH_2C\underline{H}_2N$, Ph-3,4-OCH_3), 4.76–4.83 (0.2 H, m, C<u>H</u>CN), 4.87 (0.8 H, d, *J* 5.5, C<u>H</u>CN), 6.50 (0.8 H, d, *J* 15.4, ArCHC<u>H</u>CO), 6.55–6.63 (0.2 H, m, ArCHC<u>H</u>CO), 6.86 (1 H, d, *J* 8.3, Ph-5), 7.02 (1 H, s, Ph-2), 7.13 (1 H, d, *J* 7.9, Ph-6), 7.72 (1 H, d, *J* 15.4, ArC<u>H</u>CHCO). ^{13}C NMR (75 MHz): 25.1 ($CH_2\underline{C}H_2CH_2CHCN$), 30.0 ($CH_2CH_2\underline{C}H_2CHCN$), 46.2 ($CH_2\underline{C}H_2N$), 46.6 (<u>C</u>HCN), 55.9 (Ph-3,4-O$\underline{C}H_3$), 110.1 (ArCH<u>C</u>HCO), 111.1 (Ph-5), 114.5 (Ph-2), 118.5 (CN), 122.3 (Ph-6), 127.6 (Ph-1), 144.2 (Ar<u>C</u>HCH), 149.1 (Ph-3), 151.0

(Ph-4), 165.1 (ArCHCHCO). Found: *m/z* 286.1320 $[M]^+$. $C_{17}H_{20}N_2O_4$. Calc.: M 286.1317. Found, %: C 67.14; H 6.37; N 9.77. $C_{16}H_{18}N_2O_3$. Calc., %: C 67.12; H 6.34; N 9.78.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(2,3,4-trimethoxyphenyl)-2-propenoic acid (XIIi). Light yellow oil; yield, 66%; mp, 87°C, decomp. $[\alpha]_D^{27.4}$ −23 (c 0.24, $CHCl_3$). IR spectrum: 2243 (−C≡N). ^{1}H NMR (400 MHz): 2.11–2.45 (4 H, m, $CH_2CH_2CH_2CHCN$), 3.55–3.67 (1 H, m, CH_2CH_2N), 3.75–3.95 (10 H, m, CH_2CH_2N, Ph-2,3,4-OCH_3), 4.77 (0.2 H, d, *J* 7.4, CHCN), 4.88 (0.8 H, d, *J* 5.4, CHCN), 6.63-6.76 (1.8 H, m, ArCHCHCO,Ph-5), 6.89 (0.2 H, d, *J* 15.3, ArCHCHCO), 7.21 (1 H, d, *J* 8.7, Ph-6), 7.88 (1 H, d, *J* 15.6, ArCHCHCO). ^{13}C NMR (101 MHz): 25.1 ($CH_2CH_2CH_2CHCN$), 30.0 ($CH_2CH_2CH_2CHCN$), 46.2 (CH_2CH_2N), 46.6 (CHCN), 56.0 (Ph-2-OCH_3), 60.8 (Ph-3-OCH_3), 61.1 (Ph-4-OCH_3), 107.4 (ArCHCHCO), 116.1 (Ph-5), 118.5 (CN), 121.6 (Ph-1), 124.1 (Ph-6), 139.6 (ArCHCH), 142.4 (Ph-3), 153.4 (Ph-4), 155.3 (Ph-2), 165.6 (ArCHCHCO). Found: *m/z* 316.1424 $[M]^+$. $C_{17}H_{20}N_2O_4$. Calc.: M 316.1423. Found, %: C 64.71; H 6.38; N 8.88. $C_{17}H_{20}N_2O_4$. Calc., %: C 64.54; H 6.37; N 8.86.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(2-thienyl)-2-propenoic acid (XIIj). Beige powder; yield, 59%; mp, 123.2°C, decomp. $[\alpha]_D^{27.4}$ −160 (c 0.21, $CHCl_3$). IR spectrum: 2236 (−C≡N). ^{1}H-NMR (400 MHz): 2.09–2.45 (4 H, m, $CH_2CH_2CH_2CHCN$), 3.55–3.85 (2 H, m, CH_2CH_2N), 4.77 (0.8 H, d, *J* 6.3, CHCN), 4.85 (0.2 H, d, *J* 5.4, CHCN), 6.43 (0.8 H, d, *J* 15.0, ArCHCHCO), 6.53 (0.2 H, d, *J* 14.6, ArCHCHCO), 7.04 (1 H, dd, *J* 5.0, 3.6, Th-3), 7.25 (1 H, br.s, Th-2), 7.35 (1 H, d, *J* 5.0, Th-4), 7.88 (1 H, d, *J* 15.0, ArCHCHCO). ^{13}C NMR (126 MHz): 25.2 ($CH_2CH_2CH_2CHCN$), 30.3 ($CH_2CH_2CH_2CHCN$), 46.1 (CH_2CH_2N), 46.4 (CHCN), 113.9 (ArCHCHCO), 118.2 (CN), 128.5 (Th-3), 129.0 (Th-2), 137.2 (ArCHCH), 130.5 (Th-4), 140.3 (Th-1), 164.8 (ArCHCHCO). Found: *m/z* 232.0674 $[M]^+$. $C_{12}H_{12}N_2OS$. Calc.: M 232.0670. Found, %: C 62.14; H 5.23; N 12.01. $C_{12}H_{12}N_2OS$. Calc., %: C 62.04; H 5.21; N 12.06.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(5-methyl-2-thienyl)-2-propenoic acid (XIIk). Yellow powder; yield, 56%; mp, 137.1°C, decomp. $[\alpha]_D^{27.4}$ −195 (c 0.17, $CHCl_3$). IR spectrum: 2237 (−C≡N). ^{1}H NMR (300 MHz): 2.09–2.42 (4 H, m, $CH_2CH_2CH_2CHCN$), 2.49 (3 H, s, Th-4-CH_3), 3.53–3.84 (2 H, m, CH_2CH_2N), 4.85 (1 H, d, *J* 7.3, CHCN), 6.29 (0.8 H, d, *J* 15.0, ArCHCHCO), 6.38 (0.2 H, d, *J* 15.4, ArCHCHCO), 6.67 - 6.75 (1 H, m, Th-3), 7.06 (1 H, d, *J* 3.5, Th-2), 7.80 (1 H, d, *J* 15.0, ArCHCHCO). ^{13}C NMR (126 MHz): 15.8 (Th-4-OCH_3), 25.0 ($CH_2CH_2CH_2CHCN$), 30.0 ($CH_2CH_2CH_2CHCN$), 46.2 (CH_2CH_2N), 46.6 (CHCN), 114.1 (ArCHCHCO), 118.5 (CN), 126.5 (Th-3), 132.0 (Th-2), 137.0 (ArCHCH), 137.7 (Th-4), 143.6 (Th-1), 164.9 (ArCHCHCO). Found: *m/z* 246.0831 $[M]^+$. $C_{13}H_{14}N_2OS$. Calc.: M 246.0827. Found, %: C 63.38; H 5.73; N 11.39. $C_{13}H_{14}N_2OS$. Calc., %: C 63.39; H 5.73; N 11.37.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(3-thienyl)-2-propenoic acid (XIIl). Gray powder; yield, 62%; mp, 151.2°C, decomp. $[\alpha]_D^{27.4}$ −250 (c 0.19, $CHCl_3$). IR spectrum: 2240 (−C≡N). ^{1}H NMR (400 MHz): 2.04–2.45 (4 H, m, $CH_2CH_2CH_2CHCN$), 3.50–3.85 (1 H, m, CH_2CH_2N), 4.74–4.90 (1 H, m, CHCN), 6.46 (0.2 H, d, *J* 15.4, ArCHCHCO), 6.58 (0.8 H, d, *J* 15.2, ArCHCHCO), 7.22–7.37 (2 H, m, Th-4,5), 7.48 (1 H, d, *J* 1.5, Th-2), 7.73 (1 H, d, *J* 15.3, ArCHCHCO). ^{13}C NMR (126 MHz): 25.0 ($CH_2CH_2CH_2CHCN$), 29.9 ($CH_2CH_2CH_2CHCN$), 46.2 (CH_2CH_2N), 46.5 (CHCN), 116.5 (ArCHCHCO), 118.4 (CN), 125.0 (Th-2), 126.8 (Th-3), 128.0 (Th-4), 137.5 (ArCHCH), 137.6 (Th-2), 165.0 (ArCHCHCO). Found: *m/z* 232.0673 $[M]^+$. $C_{12}H_{12}N_2OS$. Calc.: M 232.0670. Found, %: C 62.08; H 5.23; N 12.07. $C_{12}H_{12}N_2OS$. Calc., %: C 62.04; H 5.21; N 12.06.

(2*S*)-Cyanopyrrolidine amide of (*E*)-3-(4-pyridyl)-2-propenoic acid (XIIm). Gray powder; yield, 62%; mp, 158.7°C, decomp. $[\alpha]_D^{27.4}$ −93 (c 0.21, $CHCl_3$). IR spectrum: 2238 (−C≡N). ^{1}H NMR (300 MHz): 2.06–2.50 (4 H, m, $CH_2CH_2CH_2CHCN$), 3.53–3.89 (2 H, m, CH_2CH_2N), 4.77–4.89 (1 H, m, CHCN), 6.80 (0.2 H, d, *J* 15.4, ArCHCHCO), 6.92 (0.8 H, d, *J* 15.4, ArCHCHCO), 7.34 (2 H, d, *J* 6.0, Py-3,5), 7.66 (1 H, d, *J* 15.5, ArCHCHCO), 8.62 (2 H, d, *J* 6.0, Py-2,6). ^{13}C NMR (101 MHz): 24.9 ($CH_2CH_2CH_2CHCN$), 29.7 ($CH_2CH_2CH_2CHCN$), 46.2 (CH_2CH_2N), 46.5 (CHCN), 118.0 (CN), 121.2 (ArCHCHCO), 121.6 (Py-3,5), 141.0 (ArCHCH), 141.5 (Py-4), 150.3 (Py-2,6), 163.7 (ArCHCHCO). Found: *m/z* 227.1055 $[M]^+$. $C_{13}H_{13}N_3O$. Calc.: M 227.1059. Found, %: C 68.74; H 5.75; N 18.54. $C_{12}H_{12}N_2OS$. Calc., %: C 68.70; H 5.77; N 18.49.

Biological Tests

We used male CD-1 mice (25–30 g). The animals were obtained from the vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences and were kept in standard conditions with free access to food and water. All experiments were conducted in accordance with the European Convention for the Protection of Animals used for Experimental and Other Scientific Purposes, 1986. After quarantine, the animals were randomized by weight and divided into groups of five mice each. All test compounds were mixed with a few drops of Tween 80 or DMSO, dissolved in distilled water, and orally administered in mice on an empty stomach (hun-

ger for 12 h) 5 h before oral glucose load (2.5 g/kg). Control animals received only water with Tween 80 or DMSO. The blood glucose level was measured using the ONE TOUCH Select glucometer (LIFESCAN Inc., United States) before dosing (0) and 30, 60, 90 minutes after glucose administration. Vildagliptin (Galvus, Novartis) was used as a positive control. Statistical analysis was performed using the Mann–Whitney *U*-test. The value $P < 0.05$ was considered statistically significant.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

The authors state that there is no conflict of interests.

Statement on the Welfare of Animals

All applicable international, national and institutional guidelines for the care and use of animals have been observed.

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