SYNTHESIS OF NEW PRECURSORS OF RADIOTRACERS FOR POSITRON EMISSION TOMOGRAPHY

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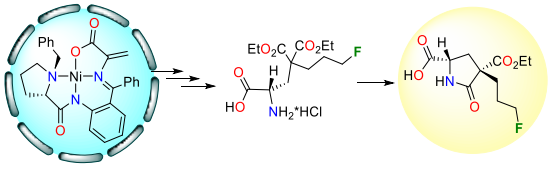
Z. T. Gugkaeva,[a] A. T. Tsaloev,[b] M. A. Moskalenko,[a] L. V.Yashkina,[a] A. F. Smolyakov,[a] V. I. Maleev,[a] and Yu. N. Belokon[a]*

[a] *Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, str. 1, Moscow, 119334 Russia*
[b] *Chemical Diversity Research Institute, ul. Rabochaya 2a, k. 1, Khimki, Moscow Oblast, 141401 Russia*

Abstract

The sequential chemical transformations of a chiral nickel(II) complex Ni-BPB-Δ-Ala affords new derivatives of fluoroglutamic acid that can be used as radiotracers in positron emission tomography.



Key words: chiral *α*-amino acids, asymmetric synthesis, Ni(II) complexes, positron emission tomography.

Introduction

Early diagnosis of malignant tumors plays a crucial role in timely treatment of cancer. To make an accurate diagnosis, the noninvasive methods are often used. In recent years, positron emission tomography (PET) has gained special popularity [1, 2]. The sensitivity and specificity of this method strongly depend on the employed radiotracer (a signaling substance) and its distribution in an organism. In the search for new appropriate candidates, it is important to take into account the properties of tumors that significantly differ tumor tissue form a healthy one. There are also certain biosynthetic requirements to these compounds. Tumors behave as peculiar "amino acid traps" and, in this respect, the development of new radiotracers based on *α*-amino acids seems to be highly promising [3, 4].

The preferred commercial standard of a radioactive isotope in PET is the fluorine isotope ^{18}F. This is caused by an optimal combination of the high specific activity (about 80 GBq/nmol) with the short half-life (less than 2 h) which is nevertheless enough for synthetic procedures. For the synthesis of radiotracers bearing the ^{18}F isotope, the following time parameters are of particular importance: an isotope label must be introduced at the latest possible stage, the complicated and long-lasting purification procedures for products must be excluded. Otherwise, the radioactivity of the isotope will considerably drop before it will be used for diagnosis. Due to these limitations, it is often impossible to synthesize [^{18}F]-radiotracers using the conventional methods of nonradioactive fluorination. At the same time, the high specific activity of the ^{18}F isotope allows for the production of [^{18}F]-radiotracers using the synthetic approaches that provide even low fluorination degrees.

The known ^{18}F-containing radiotracers of amino acid nature are mainly the derivatives of proteinogenic amino acids, such as tyrosine, phenylalanine, proline, and asparagine, although nonproteinogenic amino acids are also used in their synthesis [5–8]. All the [^{18}F]-labeled amino acids are applicable for estimating tumor boundaries.

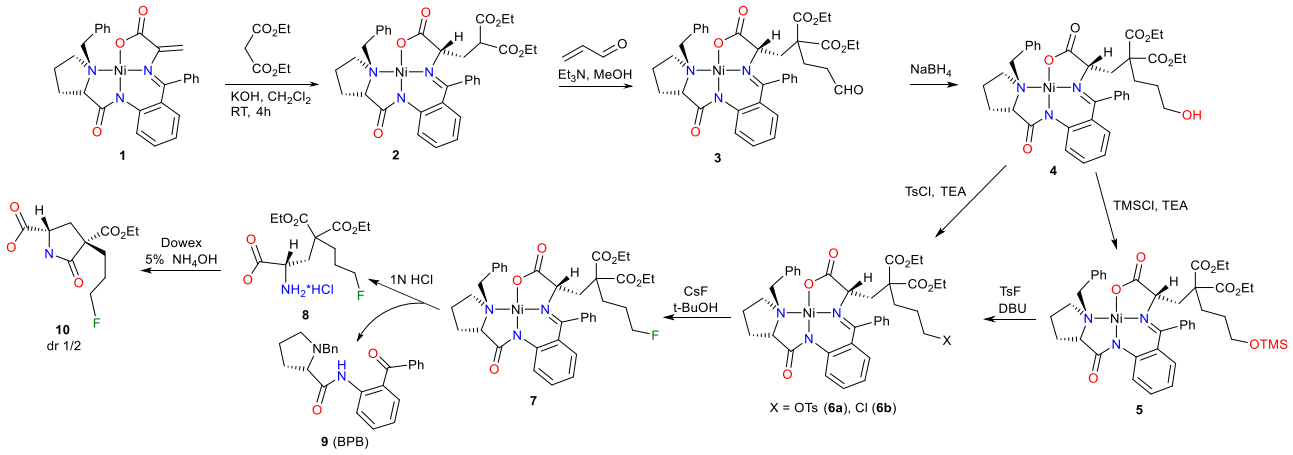
Median *et al.* [9] suggested that selective inhibition of glutamine transport by tumor cells can be used both to reduce tumor proliferation and to make a diagnosis by PET employing the glutamine-type radiotracers. The derivatives of glutamic acid and glutamine labeled with the ^{18}F isotope have been unknown until recently [10], whereas their nonradioactive analogs are well known, in particular, those bearing a fluorine atom at the *γ*-[11] or *β*-positions [12, 13]. Therefore, of particular interest is the preparation of even one new potential radiotracer of the glutamine series as well as its precursor and reference. The goal of this work was to obtain 4-(3-fluoropropyl)glutamic acid.

Results and discussion

The synthesis of new radiotracer precursors was carried out using metal complex **1** developed by Yu. N. Belokon [14, 15] based on an auxiliary recoverable chiral reagent—2-((*S*)-*N*-benzylprolino)aminobenzophenone (BPB) [16]. The detailed synthetic transformations are presented in Scheme 1.

Complex **2** was obtained by the earlier described procedure [17] and introduced into the reaction with acrolein. Product **3** was reduced with $NaBH_4$ in EtOH. This led to the formation of corresponding alcohol **4** which structure was confirmed by X-ray diffraction analysis (Fig. 1). According to its results, the amino acid residue contains two ethoxycarbonyl groups and a propanol moiety at the *γ*-carbon atom and an asymmetric center formed at the *α*-amino acid atom adopts an (*S*)-configuration.

An attempt to obtain tosyl derivative **6a** from complex **4** in one step by the treatment with *p*-toluenesulfonyl chloride in the presence of Et_3N afforded an inseparable mixture of the target compound (**6a**) with a product of substitution of the tosyl group for a chloride ion (compound **6b**). In order to exclude the formation of by-product **6b**, we first obtained trimethylsilyl derivative **5**, which then exclusively afforded compound **6a** upon interaction with TsF in the presence of DBU under mild conditions. The subsequent treatment of complex **6a** with cesium fluoride in ^{t}BuOH gave rise to corresponding fluorine



Scheme 1. Synthesis of the precursor (**7**) and references (**8**, **10**) for the new potential glutamine radiotracers.

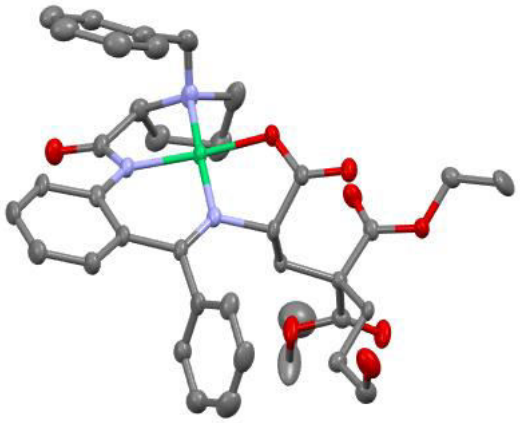


Figure 1. Molecular structure of compound **4**.

derivative **7** which was fully characterized by the ^{1}H, ^{19}F, and ^{13}C NMR as well as mass spectra. The decomposition of complex **7** upon heating in 1N HCl for 5 min furnished a hydrochloride salt of fluorine-containing amino acid **8** which can be readily separated from the auxiliary reagent, BPB, and nickel salts. The target amino acid was isolated as a free base by the conventional procedure using a DOWEX ion-exchange resin in 93% with *dr* equal to ½. New acid **10** represents a substituted pyroglutamic acid. Acids **8** and **10** were characterized by the ^{1}H, ^{13}C, and ^{19}F NMR as well as mass spectra.

Experimental

General remarks

The ^{1}H NMR spectra were registered on a Bruker Avance 400 spectrometer (400.13 MHz). The chemical shifts were measured relative to the solvent residual proton signals ($CDCl_3$). The HRMS studies were performed on an AB Sciex TripleTOF 5600+ unit equipped with a DuoSpray ionization source (ESI). The samples were introduced into the ionization source as methanol solutions through a manual loop injection valve (20 μL). The optical rotation was measured on a Perkin–Elmer 241 polarimeter in a 5 cm cell thermally stabilized at 25 °C. The column chromatography was carried out using Kieselgel 60 (Merck) silica gel. Potassium hydroxide (99.99% Sigma-Aldrich) and Dowex 50W×2, 50–100 mesh cation-exchange resin (Acros) were purchased from commercial sources.

X-ray diffraction analysis

Single-crystal X-ray diffraction experiments were carried out with a Bruker SMART APEX II diffractometer (graphite monochromated Mo-Kα radiation, λ = 0.71073 Å, ω-scan technique). The APEX II software [18] was used for collecting frames of data, indexing reflections, determination of lattice constants, integration of intensities of reflections, scaling and absorption correction. All calculations (space group and structure determination, refinements, graphics, and structure reporting) were made using the SHELXL2014 [19] and OLEX2 [20] program packages. The structures were solved by direct methods and refined by the full-matrix least-squares technique against *F2* with the anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were placed geometrically and included in the structure factors calculations in the riding motion approximation. CCDC 2175970 contains the supplementary crystallographic data for complex **4**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk/structures.

Syntheses

Ni(II) complex of the Schiff base of BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-butanoic acid (2) [17]. Ni(II) complex **1** (10.00 g, 19.60 mmol) was dissolved in dichloromethane (40 mL). Then KOH (1.10 g, 19.60 mmol) was added to the stirred mixture in an argon atmosphere. In 5 min diethyl malonate (5.95 mL, 39.00 mmol) was added, and the reaction mixture was continued to stir for 5 h. The reaction course was monitored by TLC (SiO_2, $CHCl_3$–Me_2CO (5:1)). The resulting mixture was treated with 5% aq. acetic acid. The target product was extracted with dichloromethane. The organic layer was separated, washed with water, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eluent: $CHCl_3$–Me_2CO (5:1)). Yield: 11.80 g. (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14–1.22 (m, 6H), 2.07–2.14 (m, 1H), 2.16–2.22 (m, 2H), 2.47–2.57 (m, 1H), 2.75–2.83

(m, 1H), 2.94–3.02 (m, 1H), 3.46–3.52 (m, 1H), 3.55–3.59 (m, 2H), 3.64–3.75 (m, 1H), 3.88–3.91 (m, 1H), 3.94–4.03 (m, 3H), 4.06–4.10 (m, 2H), 4.41 (d, 1H, *J* = 12.6 Hz), 6.62 (m, 2H), 7.11–7.21 (m, 4H), 7.31–7.35 (t, 2H, *J* = 8.0 Hz), 7.50 (m, 3H), 8.06 (d, 2H, *J* = 7.4 Hz), 8.18 (d, 1H, *J* = 8.6 Hz) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* 180.42, 178.18, 171.70, 168.81, 168.28, 142.43, 133.52, 133.45, 132.42, 131.52, 129.78, 129.15, 128.88, 127.81, 127.00, 126.13, 123.53, 120.69, 70.54, 68.72, 63.26, 61.86, 61.60, 57.45, 48.24, 33.53, 30.57, 23.87, 13.96 ppm. $[\alpha]_D^{25}$ +2082 (*c* = 0.125, $CHCl_3$).

Ni(II) complex of the Schiff base of BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-oxopentanoic acid (3). Acrolein (0.45 mL, 6.70 mmol) and Et_3N (0.63 mL, 4.50 mmol) were added to a solution of Ni(II) complex **2** (3.00 g, 4.50 mmol) in methanol (3 mL) at room temperature. The reaction course was monitored by TLC (SiO_2, $CHCl_3$–Me_2CO (5:1)). The solvent was removed under reduced pressure. The resulting residue was dissolved in chloroform (100 mL) and washed with 10% aq. acetic acid (30 mL). The organic layer was separated, washed with water (3×30 mL), dried over Na_2SO_4, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eluent: $CHCl_3$–Me_2CO (5:1)). Yield: 2.65 g (81%). ^1H NMR (400 MHz, $CDCl_3$): *δ* 9.40 (s, 1H), 8.11 (d, 2H, *J* = 8.5 Hz), 8.06 (d, 1H, *J* = 8.5 Hz), 7.56–7.55 (m, 3H), 7.39–7.33 (m, 3H), 7.22–7.13 (m, 2H), 7.11–7.07 (m, 1H), 6.72–6.66 (m, 1H), 6.58 (dd, 1H, *J* = 8.2, 1.4 Hz), 4.41 (d, 1H, *J* = 12.6 Hz), 4.23–4.08 (m, 4H), 4.00–3.92 (m, 2H), 3.73–3.67 (m, 1H), 3.62–3.58 (m, 1H), 3.54–3.50 (m, 2H), 2.86–2.79 (m, 1H), 2.63–2.52 (m, 1H), 2.37–2.30 (m, 2H), 2.16–2.09 (m, 3H), 1.96–1.90 (m, 1H), 1.75–1.68 (m, 1H), 1.28–1.23 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* 200.31, 180.61, 177.94, 170.54, 170.24, 169.27, 142.25, 133.53, 133.36, 133.14, 132.33, 131.49, 130.09, 129.46, 129.19, 128.92, 128.00, 127.75, 126.50, 123.90, 120.85, 70.48, 66.43, 63.17, 62.05, 61.63, 57.69, 55.17, 38.36, 37.50, 30.81, 23.98, 23.26, 13.93 ppm. $[\alpha]_D^{25}$ +1812 (*c* = 0.03, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{38}H_{42}N_3NiO_8$ 726.23; found 726.2322.

Ni(II) complex of the Schiff base of BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-hydroxyheptanoic acid (4). Ni(II) complex **3** (2.00 g, 2.70 mmol) was dissolved in ethanol (20 mL). Then $NaBH_4$ (0.22 g, 6.00 mmol) was added portionwise to the resulting solution. The reaction mixture was stirred at room temperature while monitoring the reaction course by TLC (SiO_2, $CHCl_3$–Me_2CO (3:1)). After full consumption of initial complex **3**, the reaction mixture was treated with 2% aq. acetic acid. The target product was extracted with chloroform. The organic layer was separated, washed with water until neutral reaction, dried over Na_2SO_4, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eluent: $CHCl_3$–Me_2CO (3:1)). Yield: 1.60 g (81%). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.11–8.07 (m, 3H), 7.55–7.52 (m, 3H), 7.38–7.28 (m, 3H), 7.21–7.08 (m, 3H), 6.68–6.64 (m, 1H), 6.55 (dd, 1H, *J* = 8.2, 1.5 Hz), 4.42 (d, 1H, *J* = 12.6 Hz), 4.18–4.14 (m, 3H), 3.96–3.92 (m, 3H), 3.69–3.60 (m, 2H), 3.53–3.48 (m, 2H), 3.33–3.25 (m, 2H), 2.86–2.80 (m, 1H), 2.26–2.51 (m, 1H), 2.30–2.21 (m, 1H), 2.16–2.11 (m, 3H), 1.66–1.58 (m, 1H), 1.27–1.21 (m, 6H), 1.06–0.97 (m, 1H), 0.31–0.19 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* 180.59, 178.19, 170.79, 170.79, 170.26, 169.86, 142.36, 133.52, 133.18, 132.29, 131.53, 129.77, 129.39, 128.96, 128.89, 128.15, 127.71, 126.54, 123.80, 120.72, 70.48, 66.82, 63.15, 62.39, 61.75, 61.51, 57.67, 55.87, 36.81, 30.81, 27.13, 26.98, 23.93, 14.01, 13.95 ppm. $[\alpha]_D^{25}$ +1558 (*c* = 0.03, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{38}H_{44}N_3NiO_8$ 728.25; found 728.2478.

Ni(II) complex of the Schiff base derived from BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-trimethylsiloxyheptanoic acid (5). Et_3N (0.57 mL, 4.11 mmol) was added to a stirred solution of Ni(II) complex **4** (1.50 g, 2.06 mmol) in dichloromethane (10 mL). Then TMSCl (0.50 mL, 4.11 mmol) was slowly added dropwise to the resulting mixture at 0 °C. The reaction course was monitored by TLC (SiO_2, EtOAc). After full consumption of initial complex **4**, hexane (5 mL) was added and the reaction mixture was filtered through zeolite. The filtrate was evaporated to dryness. The resulting residue was dissolved in CCl_4 and filtered again. The residue obtained after evaporation of the filtrate was purified by column chromatography on silica gel (eluent: EtOAc). Yield: 1.50 g (91%). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.10 (d, 2H, *J* = 7.5 Hz), 8.06 (d, 1H, *J* = 8.8 Hz), 7.53–7.49 (m, 3H), 7.35 (t, 1H, *J* = 7.6 Hz), 7.30–7.28 (m, 1H), 7.19 (t, 1H, *J* = 7.4 Hz), 7.13 (t, 1H, *J* = 7.7 Hz), 7.07–7.05 (m, 1H), 6.65 (t, 1H, *J* = 7.5 Hz), 6.57–6.55 (m, 1H), 4.42 (d, 1H, *J* = 12.6 Hz), 4.21–4.07 (m, 5H), 3.92 (dd, 1H, *J* = 11.6, 4.9 Hz), 3.76–3.69 (m, 1H), 3.62–3.58 (m, 1H), 3.51–3.48 (m, 2H), 3.31–3.28 (m, 1H), 3.19 (t, 1H, *J* = 6.4 Hz), 2.85–2.77 (m, 1H), 2.58–2.50 (m, 1H), 2.29–2.26 (m, 1H), 2.21–2.02 (m, 3H), 1.43–1.38 (m, 1H), 1.29–1.22 (m, 6H), 1.01–0.94 (m, 1H), 0.09 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* 180.64, 177.84, 170.89, 169.82, 142.34, 133.49, 133.31, 133.15, 132.17, 131.55, 129.97, 129.35, 128.88, 128.81, 128.04, 127.62, 126.67, 123.84, 120.71, 70.43, 66.87, 63.02, 62.21, 61.63, 61.35, 57.61, 55.99, 37.40, 30.84, 27.25, 26.89, 23.98, 14.00, 13.96 ppm. $[\alpha]_D^{25}$ +1720 (*c* = 0.02, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{41}H_{52}N_3NiO_8Si$ 800.29; found 800.2872.

Ni(II) complex of the Schiff based of BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-tosyloxyheptanoic acid (6). DBU (0.43 g, 2.80 mmol) and TsF (0.46 g, 2.70 mmol) were added to a solution of Ni(II) complex **5** (1.50 g, 1.90 mmol) in acetonitrile (30 mL). The reaction mixture was stirred at room temperature for 48 h and then treated with 2% aq. acetic acid. The target product was extracted with chloroform. The organic layer was separated, washed several times with water until neutral reaction, dried over Na_2SO_4, and evaporated to dryness, The residue obtained was purified by column chromatography on silica gel (eluent: EtOAc). Yield: 1.40 g (83%). ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.10 (d, 2H, *J* = 7.6 Hz), 8.04 (d, 1H, *J* = 8.6 Hz), 7.79 (d, 2H, *J* = 7.9 Hz), 7.59–7.49 (m, 3H), 7.40–7.34 (m, 4H), 7.30 (br. s, 1H), 7.20 (t, 1H, *J* = 7.5 Hz), 7.14 (t, 1H, *J* = 7.8 Hz), 7.04 (d, 1H, *J* = 7.5 Hz), 6.66 (t, 1H, *J* = 7.6 Hz), 6.57 (d, 1H, *J* = 7.9 Hz), 4.42 (d, 1H, *J* = 12.7 Hz), 4.21–4.05 (m, 4H), 4.02–3.93 (m, 1H), 3.87 (dd, 1H, *J* = 11.7, 4.3 Hz), 3.73–3.56 (m, 4H), 3.50 (d, 2H, *J* = 12.8 Hz), 2.84–2.76 (m, 1H), 2.59–2.49 (m, 1H), 2.48 (s, 3H), 2.32–2.23 (m, 1H), 2.13–2.10 (m, 2H), 1.97–1.90 (m, 1H), 1.49–1.40 (m, 1H), 1.23–1.71 (m, 6H), 1.18–1.11 (m, 1H), 0.27–0.14 (m, 1H) ppm. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): *δ* 180.53, 177.90, 170.47, 170.25, 169.28, 144.77, 142.31, 133.47, 133.18, 132.89, 132.27, 131.53, 130.43, 129.88, 129.39, 129.17, 128.91, 127.94, 127.89, 127.59, 126.59, 123.88, 120.78, 70.44, 69.90, 66.54, 63.09, 61.91, 61.51, 57.63,

55.67, 37.29, 30.84, 26.74, 23.99, 23.40, 21.65, 13.97, 13.94 ppm. $[\alpha]_D^{25}$ +1363 (*c* = 0.02, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{45}H_{50}N_3NiO_{10}S$ 882.26; found 882.2564.

Ni(II) complex of the Schiff base of BPB and (*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-fluoroheptanoic acid (7). A stirred mixture of complex **6a** (1.00 g, 1.10 mmol) and CsF (2.00 g, 12.00 mmol) in ^{t}BuOH was heated at 50 °C in an argon atmosphere for 72 h. The resulting mixture was treated with dichloromethane and washed with water. The organic layer was separated, washed with water, and evaporated to dryness. The residue obtained was purified by column chromatography on silica gel (eluent: EtOAc). Yield: 0.70 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, 2H, *J* = 7.4 Hz), 8.05 (d, 1H, *J* = 8.6 Hz), 7.52 (br. s, 3H), 7.38–7.32 (m, 3H), 7.20 (t, 1H, *J* = 7.4 Hz), 7.14 (t, 1H, *J* = 7.7 Hz), 7.07 (br. s, 1H), 6.66 (t, 1H, *J* = 7.5 Hz), 6.58–6.56 (m, 1H), 4.42 (d, 1H, *J* = 12.6 Hz), 4.25–4.07 (m, 5H), 4.02–3.98 (m, 2H), 3.92 (dd, 1H, *J* = 11.9, 4.3 Hz), 3.76 (t, 1H, *J* = 12.9 Hz), 3.62–3.58 (m, 1H), 3.50 (d, 2H, *J* = 12.5 Hz), 2.85–2.79 (m, 1H), 2.62–2.51 (m, 1H), 2.33–2.25 (m, 1H), 2.18–2.06 (m, 3H), 1.57–1.51 (m, 1H), 1.27–1.23 (m, 6H), 0.91–0.88 (m, 1H), 0.29–0.14 (m, 1H) ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 180.54, 177.93, 170.70, 169.98, 169.53, 142.42, 133.48, 133.32, 133.15, 132.25, 131.54, 129.97, 129.40, 128.91, 128.02, 127.70, 126.63, 123.88, 120.77, 84.17, 82.41, 70.44, 66.65, 63.07, 61.84, 61.53, 57.63, 55.77, 37.47, 30.84, 24.00, 13.99 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ –217.85 ppm. $[\alpha]_D^{25}$ +1823 (*c* = 0.03, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{38}H_{43}FN_3NiO_7$ 730.24; found 730.2433.

Hydrochloride salt of (2*S*)-2-amino-4,4-bis(ethoxycarbonyl)-7-fluoroheptanoic acid (8). 1 N HCl (10.00 mL) was added to a suspension of Ni(II) complex **7** (0.40 g, 0.54 mmol) in methanol (10 mL). The stirred reaction mixture was heated at 50 °C until a red color of the initial complex disappeared. The solvent was removed under reduced pressure. After addition of water (5 mL), the resulting solution was washed with dichloromethane (5×50 mL). The aqueous layer was separated and evaporated at 40 °C. After addition of dioxane (10 mL), the stirred mixture was heated to 70 °C, and filtered in a hot state to separate the undissolved admixtures. The filtrate was evaporated to dryness. The precipitate formed after addition of dioxane (10 mL) was filtered off and rinsed with dioxane. Yield: 0.18 g (95%). ^{1}H NMR (400 MHz, D_2O): δ 4.43 (br. s, 1H), 4.31 (br. s, 1H), 4.09 (d, 4H, *J* = 6.7 Hz), 3.97 (br. s, 1H), 3.51 (br. s, 1H), 2.47–2.28 (m, 2H), 2.01–1.97 (m, 2H), 1.62–1.44 (m, 2H), 1.10–1.05 (m, 6H) ppm. ^{13}C{^{1}H} NMR (101 MHz, D_2O): δ 171.76, 171.76, 85.06, 83.57, 66.76, 63.40, 63.40, 63.19, 50.03, 33.26, 29.74, 24.84, 12.97 ppm. ^{19}F NMR (376 MHz, D_2O): δ –218.31 ppm. $[\alpha]_D^{25}$ +5.5 (*c* = 1.36, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{13}H_{23}FNO_6$ 308.15; found 308.1510.

(2*S*,4*S*)-4-Ethoxycarbonyl-4-(3-fluoropropyl)-5-oxo-pyrrolidine-2-carboxylic acid (10). Amino acid **8** (0.18 g, 0.49 mmol) was dissolved in water (5 mL). The resulting solution was passed through a Dowex cation-exchange column in the H^+ form, eluted with 5% aq. NH_4OH, and evaporated to dryness. Yield: 0.12 g (93%), *dr* 1/2. ^{1}H NMR (400 MHz, D_2O): δ 4.52–4.49 (m, 1H), 4.41–4.37 (m, 1H), 4.20–4.06 (m, 3H), 2.89 (dd, 1H, *J* = 13.7, 8.6 Hz), 2.63 (dd, 1H, *J* = 13.8, 4.2 Hz), 2.47 (dd, 1H, *J* = 13.8, 9.7 Hz), 2.03–1.94 (m, 2H), 1.80–1.60 (m, 3H), 1.21–1.14 (m, 3H) ppm. ^{13}C{^{1}H} NMR (101 MHz, D_2O): δ 178.64, 177.05, 172.40, 85.45, 62.96, 55.97, 55.45, 54.78, 34.18, 33.83, 29.37, 29.02, 25.12, 13.09, 13.03 ppm. ^{19}F NMR (376 MHz, D_2O): δ –217.73, –217.77 ppm. $[\alpha]_D^{25}$ +4 (*c* = 0.35, MeOH). HRMS (ESI): m/z $[M+H]^+$ calcd. for $C_{11}H_{18}FNO_5$ 262.11; found 262.1101.

Conclusions

Hence, the efficient synthetic approaches to enantiomerically pure amino acid **8** and its derivative **10** were suggested. These compounds are promising candidates for the application as radiotracers in PET. Once again it was demonstrated that nickel complex Ni-BPB-ΔAla **1** has great potential as a chiral building block for further modifications. It protects the carboxy and amino groups and determines the stereo and regioselectivities of reactions by its chiral environment.

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Corresponding author

* E-mail: yubel@ineos.ac.ru. Tel: +7(499)135-5047 (Yu. N. Belokon)

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