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FULL PAPER

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Administration of ferrocene-modified amino acids induces changes in synaptic transmission in the CA1 area of the hippocampus

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A series of ferrocene-modified amino acid methyl esters with pyrazole linker was prepared in good to quantitative yields starting from easy accessible ferrocene pyrazole carbaldehyde and amino acids in racemic and enantio enriched forms under reductive amination conditions (NaBH$(OAc)_3$, reflux, 3 hr). The resulting enantiomers were resolved using analytical HPLC on modified cellulose or amylose as chiral selectors. *In vivo* electrophysiological experiments were performed in the CA1 field of the hippocampus on **3a** Fc-Gly, (*L*)-**3b** Fc-Ala, and (*D*)-**3b** Fc-Ala compounds. An increasing in the amplitudes of responses of local potentials (up to 25%) of the CA1 region in the studied groups was found after intraperitoneal administration of ferrocene compounds **3a** and (*D*)-**3b** compared with control rats treated with saline.

KEYWORDS

ferrocene amino acids, hippocampus, HPLC, *in vivo* electrophysiological experiment, local field potential

1 | INTRODUCTION

Chemistry of metallocenes has been intensively developed for more than six decades.[1] During the first two decades of the 21st century, special attention was paid to the synthesis and bioassay of ferrocene derivatives carrying pharmacophoric groups, namely, nucleic bases, oligonucleotides, various heterocycles, amino acids, peptides, and sugars.[2–8] *In vitro* and *in vivo* studies have demonstrated that many of such modified ferrocenes display a wide spectrum of biological activities, including antianemic,[9] antimicrobial,[10] antibacterial,[11] antimalarial,[12] tuberculostatic,[13,14] and especially antitumor activities, see recent review articles.[15–18] Ferroceron (tetrahydrate of sodium salt of *ortho*-carboxybenzoyl ferrocene), which is the first and only currently ferrocene-based drug, has been effectively used for a long time for the treatment of iron deficiency pathologies.[19] However, a potential of ferrocene-substituted amino acids as drug candidates for the treatment of disorders, especially neurodegenerative ones, is out of view of scientists. At the same time, according to the projections of the World Health Organization[20] these are precisely the disorders which will dominate in the nearest future and exceed the incidence of cancer and cardiovascular diseases.

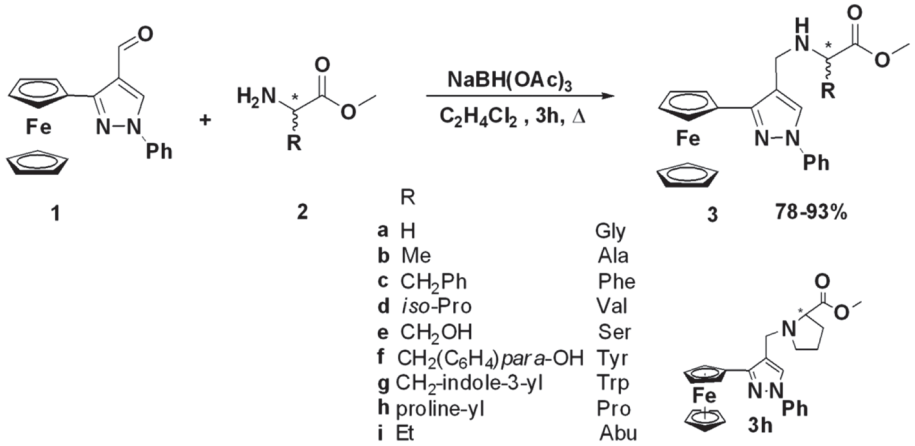
The few literary data[21–25] as well as our own biological research results,[26] suggest that it is ferrocene-modified compounds, including those based on amino acids, that can have a significant impact on

neurodegenerative processes. In addition, neurodegenerative disorders are associated with aberrant iron deposition in the brain.

It is known, that iron-containing ferrocene moiety endows the modified compounds with a number of useful properties. First, it significantly decreases their toxicity[5,17] and improve their lipid membrane penetrating ability.[7] Moreover, it allows there compounds to exist both in salt and neutral forms[27] providing their transport in a blood flow, as well as across the membranes into cytoplasm (polar medium). An ability of ferrocenyl-substituted compounds to undergo oxidation and reduction[28,29] at physiological pH values is their substantial advantage, that is to say, these compounds present a kind of mediators, moreover, they can contribute to the transmission of electrical impulses. Therefore, chemical modification of drugs intended for the treatment of brain disorders (glycine, gamma-aminobutyric acid (GABA), beta-phenyl derivatives of GABA (phenibut), other amino acids, as well as drugs used to treat Alzheimer's disease, particularly, memantin) enables one to improve the mediator properties of the existing pharmaceuticals. For instance, it is known that GABA, being a major mediator involved in the central inhibition processes activates the energetic processes in the brain, scarcely penetrates across the blood-brain barrier (BBB) and only as small as 8% of GABA-containing drug aminalon reaches the brain targets upon oral administration. A ferrocene moiety which is generally agreed to be a good vehicle[4,7,17] overcomes readily the BBB (though this hypothesis did not find sufficient experimental support[30]) and can facilitate the targeted drug delivery to the brain. Authors[24] conclude that administration of the lipophilic iron-containing ferrocene compound leads to subtle perturbations of cellular iron within the brain, potentially representing a model of iron accumulation similar to that seen in various neuropathological conditions.

It should be emphasized that biological effects of the chiral ferrocene-based compounds in an enantiomeric pure (or enantio enriched) forms earlier has virtually been studied only upon planar chiral ferrocenes.[31–33] Moreover, chemistry of such compounds is presently scarcely investigated. At the same time, these are precisely enantiomers which optimize the state of the nervous system, and are involved in the most important methylation and demethylation processes. Furthermore, the so called "thalidomide tragedy" which has been associated with the use of the drug thalidomide in a racemic form and resulted in severe birth defects, forced the world community to revise its attitude to the enantiomeric purity of drug formulations and to make the corresponding supplements to the State Pharmacopoeias. Therefore, a need in additional studies of the biological effects of individual stereoisomers is inspired by the requirements of the Pharmacopoeias of many countries or regions[34] including Pharmaceutical Committee of the Russian Federation,[35] and by the studies logic.

Herein, based on the commercially available ferrocene, we have developed a synthetic procedure and obtained a series of ferrocenyl-substituted amino acids with pyrazole linker, namely, glycine, alanine, phenyl alanine, valine, serine, tyrosine, tryptophan, and proline ones as methyl esters. This approach to ferrocenyl-substituted amino acids comprises modification of synthetically available ferrocenyl azoles[6] well-accepted in terms of biological activity.[36] On the basis of a ferrocene-pyrazole building block the third amino-acid moiety was attached. For this purpose, selective approaches to obtain isomeric ferrocenyl pyrazol carbaldehydes were proposed.[37,38] Their subsequent functionalization *via* the reductive amination with the amino acid methyl esters of both natural (including both *L*-, *D*- or racemic-forms), and synthetic origin using sodium



SCHEME 1 Synthesis of ferrocene-modified pyrazole amino acids methyl esters, R = H (glycine) (**a**); Me (alanine-*DL, L, D*) (**b**); CH_2Ph (phenyl alanine-*DL, L, D*) (**c**); Et (valine-*DL, L, D*) (**d**); CH_2OH (serine-*DL, L*) (**e**); 4-$HOC_6H_4CH_2$ (tyrosine-*DL, L, D*) (**f**); CH_2-3-indole (tryptophan-*DL, L*) (**g**); proline (*DL, L*) (**h**), and Et (α-amino butyric acid-*DL, L, D*)) (**i**)

triacetoxyborohydride as a reducing agent affords the ferrocene-pyrazolyl-amino acids (Scheme 1). As a result, various ferrocene-substituted amino acids in the form of methyl esters in good yields were obtained and characterized by ^{1}H, ^{13}C NMR, EI-MS, IR and microanalytical data. It should be noted that all the above reactions are well scaled up, allowing one to obtain these compounds in amounts sufficient to perform biological assays. A series of racemic (*L,D*)-ferrocene-based pyrazole amino acids methyl esters (8 pairs of ferrocene-based compounds) was separated, into enantiomers by analytical HPLC on modified cellulose or amylose as chiral selectors. Based on HPLC results, the enantiomeric purity of the final ferrocene products derived from *L*- or *D*-amino acids was evaluated. For *L*- and *D*-enantiomers the specific rotation was determined.

In the Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of sciences primary studies of a biological action of the first representatives of a series of ferrocenyl amino acids, namely, ferrocenyl (phenylpyrazolyl)-glycine methyl ester (**3a**), ferrocenyl (phenylpyrazolyl)-(*D*)-alanine, (*D*)-**3b**, and ferrocenyl (phenylpyrazolyl)-(*L*)-alanine, (*L*)-**3b**, on the hippocampus which is a part of a temporal lobe of the brain, have been performed. A significant (up to 25%) rise of the amplitudes of the hippocampal local potentials in the CA1 area upon intraperitoneal administration of ferrocene compounds **3a**, and individual enantiomer (*D*)-**3b**, at a dose of 2.0 mg kg^{-1} was established. Other enantiomer (*L*)-**3b** a significant increase in amplitude after high-frequency stimulation (up to 85%) is shown.

Thus, primary *in vivo* electrophysiological studies were carried out on the brain of animals using newly synthesized ferrocene-amino acids methyl esters in both (*L*)- and (*D*)-enantiomerically enriched forms.

2 | EXPERIMENTAL

2.1 | Starting materials and analytical instrumentations

The starting 1-phenyl-3-ferrocenyl-1*H*-pyrazolyl-4-carbaldehyde (**1**) was obtained by two-step procedure from acetyl ferrocene and phenyl hydrazine in ethanol, and the following cyclization in Vilsmeier-Haak conditions according to a well-known procedure,[37] yield 85%, m.p. 118 °C, lit. m.p.[39] 118 °C. All solvents were purified and dried by standards techniques. Sodium triacetoxyborohydride $NaBH(OAc)_3$ and amino acids (Acros Organics) were used without preliminary purification. Amino acid methyl ester hydrochlorides were obtained *via* reaction of amino acids with $SOCl_2$ in methanol.[40]

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 and 125.76 MHz, respectively, in $CDCl_3$. Chemical shifts are given in ppm relative to solvent residual protons (see Supporting Information). EI mass spectra were recorded on a Finnigan Polaris Q spectrometer (ionization energy 70 eV, the ionization chamber temperature 250 °C). IR spectra were taken on a BrukerTEM37 FTIR spectrometer (KBr pellets).

2.2 | General procedure

To a solution of 1-phenyl-3-ferrocenyl-1*H*-pyrazole-4-carbaldehyde (1.0 mmol) and an amino acid ester hydrochloride (1.2 mmol) in dried 1,2-dichloroethane (35 ml) Et_3N (0.17 ml, 1.2 mmol) was added followed by sodium triacetoxy borohydride (0.30 g, 1.4 mmol). The reaction mixture was heated under reflux for 1–3 hr controlling by TLC. After cooling it for 20 °C, 30 ml of the saturated aqueous $NaHCO_3$ solution was added. The product was extracted with dichloromethane (2×30 ml). Organic fractions were combined and washed with 30 mL of the saturated sodium chloride solution and dried over the anhydrous Na_2SO_4. The solvent was removed under the reduced pressure. The residue was purified by chromatography on silica gel, eluent $CHCl_3$—MeOH (9: 1). In some cases, the enantiomers were precipitated with 0.5 mol HCl in dioxane solution as hydrochlorides. Below are given the elemental analysis data, IR, ^{1}H and ^{13}C NMR spectroscopy as well as electron ionization mass-spectrometry data for the racemic mixtures, which are similar to the data for the individual enantiomers.

2.2.1 | Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]acetate or ferrocenyl (phenylpyrazolyl)glycine methyl ester (3a)

Yield 90%. Yellow powder, m.p. 102 °C. Found (%): C, 64.25; H, 5.38; N, 9.80. $C_{23}H_{23}FeN_3O_2$. Calculated (%): C, 64.35; H, 5.40; N, 9.79. EI-MS, m/z (I_{rel} (%)): 429 $[M]^+$ (100). ^{1}H NMR ($CDCl_3$), δ: 1.69 (br.s, 1 H, NH); 3.64 (s, 2 H, CH_2); 3.77 (s, 3 H, Me); 4.13 (s, 2 H, CH_2); 4.17 (s, 5 H, Fc); 4.33, 4.82 (both s, by 2 H, Fc); 7.28 (t, 1 H, Ph, J = 7.5 Hz); 7.45 (m, 2 H, Ph); 7.75 (d, 2 H, Ph, J = 8.0 Hz); 8.12 (s, 1 H, CH). ^{13}C NMR ($CDCl_3$), δ: 42.9, 48.9, 52.1, 67.6, 68.8, 69.4, 77.9, 116.9, 118.6, 125.9, 127.6, 129.3, 139.9, 150.1, 171.4.

2.2.2 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino] propanoate or (*DL*)-ferrocenyl (phenylpyrazolyl)-alanine methyl ester (3b)

Yield 90%. Yellow powder, m.p. 94 °C. Found (%): C, 64.91; H, 5.65; N, 9.29. $C_{24}H_{25}FeN_3O_2$. Calculated (%): C, 65.02; H, 5.45; N, 9.48. EI-MS, *m*/*z* (I_{rel} (%)): 443 $[M]^+$ (87), 378 $[M - Cp]^+$ (100). IR, ν/cm^{-1}: 1731 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.31 (d, 3 H, Me, J = 6.7 Hz); 2.02 (br.s, 1 H, NH); 3.43 (q, 1 H, CH, J = 6.7 Hz); 3.68 (s, 3 H, Me); 3.70, 3.88 (both d, by 1 H, CH_2, J = 13.1 Hz); 4.02 (s, 5 H, Fc); 4.23, 4.75 (both s, by 2 H, Fc); 7.12 (t, 1 H, Ph, J = 7.2 Hz); 7.31 (m, 2 H, Ph); 7.61 (d, 2 H, Ph, J = 7.9 Hz); 7.80 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 19.2, 42.3, 51.9, 56.2, 67.2, 67.3, 68.6, 69.3, 78.0, 118.4, 119.1, 125.7, 126.8, 129.3, 140.0, 149.7, 176.0.

2.2.3 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino] propanoate, (*L*)-3b

Yield 90%. Yellow powder, m.p. 75 °C, $[\alpha]_D^{25}$ −27.2 (*c* 1.0; MeCN).

2.2.4 | (*D*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino] propanoate, (*D*)-3b

Yield 90%. Yellow powder, m.p. 74–75 °C, $[\alpha]_D^{25}$ +26.4 (c 1.0; MeCN).

2.2.5 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazol-4-yl)methyl-amino]-3-phenyl propanoate or ferrocenyl (phenylpyrazolyl)-phenylalanine methyl ester (3c)

Yield 90%. Yellow powder, m.p. 131-132 °C. Found (%): C, 69.40; H, 5.45; N, 8.15. $C_{30}H_{29}FeN_3O_2$. Calculated (%): C, 69.37; H, 5.46; N, 8.09. EI-MS, *m*/*z* (*I*rel (%)): 519 $[M]^+$ (72), 454 $[M - Cp]^+$ (100). IR, ν/cm^{-1}: 1744 (COOMe). ^1H NMR ($CDCl_3$), δ: 2.00 (br.s, 1 H, NH); 3.00 (dd, 1H, CH_2, J_1 = 8.0, J_2 = 13.0 Hz); 3.15 (dd, 1H, CH_2, J_1 = 6.0, J_2 = 13.0 Hz); 3.76 (t, 1 H, CH, J = 7.0 Hz); 3.80 (s, 3 H, Me); 3.86, 4.04 (both d, by 1 H, CH_2, J = 13.5 Hz); 4.14 (s, 5 H, Fc); 4.33, 4.79 (both s, by 2 H, Fc); 7.28-7.42 (m, 5 H +1 H, Ph); 7.49 (m, 2 H, Ph); 7.61 (s, 1 H, Pz); 7.68 (d, 2 H, Ph, J = 8.0 Hz);. ^{13}C NMR ($CDCl_3$), δ: 18.7, 19.5, 31.7, 42.8, 51.5, 66.7, 67.3, 67.4, 68.5, 69.2, 78.1, 118.4, 119.3, 125.7, 126.9, 129.3, 140.0, 149.9, 175.6.

2.2.6 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazol-4-yl)methyl-amino]-3-phenyl propanoate or ferrocenyl (phenylpyrazolyl)-phenylalanine methyl ester, (*L*)-3c

Yield 90%. Yellow powder, m.p. 130 °C, $[\alpha]_D^{25}$ −26.0 (*c* 1.0; $CHCl_3$).

2.2.7 | (*D*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazol-4-yl)methyl-amino]-3-phenyl propanoate or ferrocenyl (phenylpyrazolyl)-phenylalanine methyl ester, (*D*)-3c

Yield 91%. Yellow powder, m.p. 130 °C, $[\alpha]_D^{25}$ +26.0 (*c* 1.0; $CHCl_3$).

2.2.8 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-methylbutanoate or (*DL*)-ferrocenyl (phenylpyrazolyl)-valine methyl ester (3d)

Yield 93%. Yellow powder, m.p. 116 °C. Found (%): C, 69.40; H, 5.65; N, 8.15. $C_{26}H_{29}FeN_3O_2$. Calculated (%): C, 69.37; H, 5.63; N, 8.09. EI-MS, *m*/*z* (I_{rel} (%)): 471 $[M]^+$ (70), 406 $[M - Cp]^+$ (100). IR, ν/cm^{-1}: 1726 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.02 (d, 6 H, Me, J = 6.8 Hz); 1.96 (br s, 1 H, NH); 2.00—2.07 (m, 1 H, CH); 3.21 (d, 1 H, CH, J = 6.0 Hz); 3.74, 3.97 (both d, by 1 H, CH_2, J = 13.2 Hz); 3.79 (s, 3 H, Me); 4.12 (s, 5 H, Fc); 4.32, 4.89 (both s, by 2 H, Fc); 7.31 (t, 1 H, Ph, J = 7.4 Hz); 7.43—7.48 (m, 2 H, Ph); 7.72 (d, 2 H, Ph, J = 7.8 Hz); 7.89 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 18.7, 19.5, 31.7, 42.8, 51.5, 66.7, 67.3, 67.4, 68.5, 69.2, 78.1, 118.4, 119.3, 125.7, 126.9, 129.3, 140.0, 149.9, 175.6.

2.2.9 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-methylbutanoate (HCl) or (*L*)-ferrocenyl (phenylpyrazolyl)-valine methyl ester hydrochloride, (*L*)-3d

Yield 90%. Yellow powder, m.p. 136 °C, $[\alpha]_D^{25}$-18.0 (*c* 1.0; $CHCl_3$).

2.2.10 | (*D*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-methylbutanoate × HCl or (*D*)-ferrocenyl (phenylpyrazolyl)-valine methyl ester hydrochloride, (*D*)-3d

Yield 90%. Yellow powder, m.p. 137 °C, $[\alpha]_D^{25}$ +17.9 (*c* 1.0; $CHCl_3$).

2.2.11 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-hydroxypropanoate or (*DL*)-ferrocenyl (phenylpyrazolyl)-serine methyl ester, 3e

Yield 87%. Yellow powder, m.p. 170 °C. Found (%): C, 62.84; H, 5.55; N, 9.20. $C_{24}H_{25}FeN_3O_3$. Calculated (%): C, 62.76; H, 5.49; N, 9.15. EI-MS, *m*/*z* (I_{rel} (%)): 459 $[M]^+$ (100), 394 $[M - Cp]^+$ (84). IR, ν/cm^{-1}: 1737 (COOMe). ^1H NMR ($CDCl_3$), δ: 2.70 (br.s, 2 H); 3.58-3.72 (m, 2 H, CH_2); 3.78 (s, 3 H, Me); 3.83, 4.05 (both d, by 1 H, CH_2, J = 13.2 Hz); 3.85 (m, 1H, CH); 4.11 (s, 5 H, Fc); 4.32 (s, 2 H, Fc); 4.83 (both s, by 1 H, Fc); 7.23 (d, 1 H, Ph, J = 7.3 Hz); 7.42-7.47 (m, 2 H, Ph); 7.70 (d, 2 H, Ph, J = 7.8 Hz); 7.90 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 42.4, 52.2, 62.0, 62.7, 67.2, 67.3, 68.6, 69.3, 77.8, 118.5, 118.7, 125.8, 126.8, 129.3, 139.8, 149.8, 173.3.

2.2.12 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-hydroxypropanoate or (*L*)-ferrocenyl (phenylpyrazolyl)-serine methyl ester, (*L*)-3e

Yield 87%. Yellow powder, m.p. 165-166 °C, $[\alpha]_D^{25}$ −12.5 (*c* 1.0; $CHCl_3$).

2.2.13 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-(4-hydroxyphenyl)propanoate or (*DL*)-ferrocenyl (phenylpyrazolyl)-tyrosine methyl ester, 3f

Yield 90%. Yellow powder, m.p. 170 °C. Found (%): C, 67.40; H, 5.40; N, 7.85. $C_{30}H_{29}FeN_3O_3$. Calculated (%): C, 67.30; H, 5.46; N, 7.85. EI-MS, *m*/*z* (I_{rel} (%)): 535 $[M]^+$ (34), 470 $[M - Cp]^+$ (58). IR, ν/cm^{-1}: 1732 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.95 (br s, 1 H, NH); 2.83 (dd, 1H, CH_2, J_1 = 8.0, J_2 = 13.5 Hz); 2.97 (dd, 1H, CH_2, J_1 = 5.3, J_2 = 13.5 Hz); 3.64 (m, 1 H, CH); 3.73 (s, 3 H, Me); 3.78, 3.96 (both d, by 1 H, CH_2, J = 13.7 Hz); 4.06 (s, 5 H, Fc); 4.26, 4.72 (both s, by 2 H, Fc); 6.69, 7.03 (both d, by 2 H, Ph, J = 7.8 Hz); 7.18 (t, 1 H, Ph, J = 7.2 Hz); 7.37-7.42 (m, 2 H, Ph); 7.55 (s, 1 H, Pz); 7.57 (d, 2 H, Ph, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 29.8, 38.9, 42.5, 52.1, 62.5, 67.3, 67.6, 68.8, 69.4, 77.8, 115.7, 118.8, 118.9; 126.0, 127.3, 128.5; 129.4, 130.4; 139.8, 150.1, 155.3; 175.3.

2.2.14 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-(4-hydroxyphenyl)propanoate × HCl or (*L*)-ferrocenyl (phenylpyrazolyl)-tyrosine methyl ester hydrochloride, (*L*)-3f

Yield 90%. Yellow powder, m.p. 182 °C, $[\alpha]_D^{25}$ −11.2 (*c*0.81; $CHCl_3$).

2.2.15 | (*D*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-(4-hydroxyphenyl)propanoate × HCl or (*D*)-ferrocenyl (phenylpyrazolyl)-tyrosine methyl ester hydrochloride, (*D*)-3f

Yield 89%. Yellow powder, m.p. 182 °C, $[\alpha]_D^{25}$ +11.1 (*c* 0.74.; $CHCl_3$).

2.2.16 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-(1H-indole-3-yl)propanoate or (*DL*)-ferrocenyl (phenylpyrazolyl)-tryptophan methyl ester (3g)

Yield 80%. Orange powder, m.p.(decomp.) 178 °C. Found (%): C, 68.75; H, 5.45; N, 10.10. $C_{32}H_{30}FeN_4O_2$. Calculated (%): C, 68.82; H, 5.41; N, 10.03. EI-MS, *m*/*z* (I_{rel} (%)): 558 $[M]^+$ (60), 493 $[M - Cp]^+$ (46). IR, ν/cm^{-1}: 1736 (COOMe). ^1H NMR ($CDCl_3$), δ: 2.17 (br s, 1 H, NH); 3.10 (dd, 1H, CH_2, J_1 = 8.2, J_2 = 14.3 Hz); 3.31 (dd, 1H, CH_2, J_1 = 4.8, J_2 = 14.3 Hz); 3.76 (s, 3 H, Me); 3.79, 4.01 (both d, by 1 H, CH_2, J = 13.9 Hz); 3.86 (d, 1 H, CH, J_1 = 4.8, J_2 = 8.2 Hz); 4.05 (s, 5 H, Fc); 4.20, 4.26, 4.63, 4.72 (all s, by 1 H, Fc); 7.03 (s, 1 H, Ar); 7.14-7.24 (m, 3 H, Ar); 7.34-7.52 (m, 5 H, Ph); 7.70 (d, 1 H, Pz, J = 7.7 Hz); 8.36 (s, 1 H, NH-indole);. ^{13}C NMR ($CDCl_3$), δ: 29.5, 42.5, 51.9, 61.1, 67.1, 67.3, 68.6, 69.2, 78.0, 111.0, 111.3, 118.3, 118.7, 119.0, 119.5, 122.1; 123.2, 125.6, 126.6, 127.2, 129.2; 136.2; 139.8, 149.7, 175.3.

2.2.17 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-3-(1H-indole-3-yl)propanoate or (*L*)-ferrocenyl (phenylpyrazolyl)-tryptophan methyl ester, (*L*)-3g

Yield 78%. Yellow powder, m.p.(decomp.) 190 °C, $[\alpha]_D^{25}$ −11.1 (*c* 1.0; $CHCl_3$).

2.2.18 | (*DL*)-Methyl-1-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methyl] pyrrolidine-2-carboxylate or (*DL*)-ferrocenyl (phenylpyrazolyl)-proline methyl ester (3h)

Yield 80%. Yellow powder, m.p. 140 °C. Found (%): C, 66.51; H, 5.85; N, 8.90. $C_{26}H_{27}FeN_3O_2$. Calculated (%): C, 66.53; H, 5.80; N, 8.95. EI-MS, *m/z* (I_{rel} (%)): 469 $[M]^+$ (100). IR, ν/cm^{-1}: 1744 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.92-2.09 (m, 3 H); 2.21-2.32 (m, 1 H); 2.54-2.63 (m, 1 H); 3.22-3.27 (m, 1 H); 3.38-3.43 (m, 1 H); 3.75 (s, 3 H, Me); 3.81, 4.08 (both d, by 1 H, CH_2, J = 13.5 Hz); 4.17 (s, 5 H, Fc); 4.36 (s, 2 H, Fc);4.95, 4.98 (both s, by 1 H, Fc); 7.28 (t, 1 H, Ph, J = 7.5 Hz); 7.48-7.53 (m, 2 H, Ph); 7.76 (d, 2 H, Ph, J = 7.8 Hz); 7.92 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 21.9, 28.3, 47.0, 47.1, 52.8, 64.0, 66.7, 68.5, 69.2, 111.2, 118.4, 126.0, 129.0, 130.2; 139.0, 150.2, 167.0.

2.2.19 | (*L*)-Methyl-1-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methyl] pyrrolidine-2-carboxylate × HCl or (*L*)-ferrocenyl (phenylpyrazolyl)-proline methyl ester hydrochloride, (*L*)-3h

Yield 80%. Yellow powder, m.p. 156 °C, $[\alpha]_D^{25}$ +20.6 (*c* 1.07; $CHCl_3$).

2.2.20 | (*DL*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-butanoate × HCl or (*DL*)-ferrocenyl (phenylpyrazolyl)-amino butyric methyl ester hydrochloride (3i)

Yield 90%. Yellow powder, m.p. 130-131 °C. Found (%): C, 65.60; H, 6.01; N, 9.10. $C_{25}H_{27}FeN_3O_2$. Calculated (%): C, 65.65; H, 5.95; N, 9.19. EI-MS, *m/z* (I_{rel} (%)): 457 $[M]^+$ (74), 392 $[M - Cp]^+$ (100). IR, ν/cm^{-1}: 1730 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.05 (t, 3 H, Me, J = 7.4 Hz); 1.72 (br s, 1 H, NH); 1.77—1.88 (m, 2 H, CH_2); 3.44 (t, 1 H, CH, J = 6.5 Hz); 3.82, 4.05 (both d, by 1 H, CH_2, J = 13.3 Hz); 3.84 (s, 3 H, Me); 4.17 (s, 5 H, Fc); 4.38, 4.91 (both s, by 2 H, Fc); 7.28 (t, 1 H, Ph, J = 7.3 Hz); 7.48—7.52 (m, 2 H, Ph); 7.77 (d, 2 H, Ph, J = 7.8 Hz); 7.95 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 10.3, 26.7, 42.4, 51.7, 62.2, 67.2, 67.3, 68.5, 69.2, 78.0, 118.4, 119.2, 125.7, 126.8, 129.2, 139.9, 149.8, 175.7.

2.2.21 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-butanoate or (*L*)-ferrocenyl (phenylpyrazolyl)-amino butyric methyl ester, (*L*)-3i

Yield 90%. Yellow powder, m.p. 120 °C, $[\alpha]_D^{25}$ –41.2 (*c* 0.73; $CHCl_3$).

2.2.22 | (*L*)-Methyl-2-[(1-phenyl-3-ferrocenyl-1H-pyrazole-4-yl)methylamino]-butanoate or (*D*)-ferrocenyl (phenylpyrazolyl)-amino butyric methyl ester, (*D*)-3i

Yield 90%. Yellow powder, m.p. 120 °C, $[\alpha]_D^{25}$ +38.7 (*c* 0.70; $CHCl_3$).

2.3 | HPLC chromatographic separations of enantiomers

Chiralcel OD and Chiralpak AS-H chiral columns (250 × 4.6 mm, 5 μm) were used. The HPLC system (Advanced Separation Technologies, Inc., Whippany, NJ, USA), Bruker LC 31 with a UV 254 detector was operated at a flow rate of 1.0 ml min^{-1} and an ambient temperature.

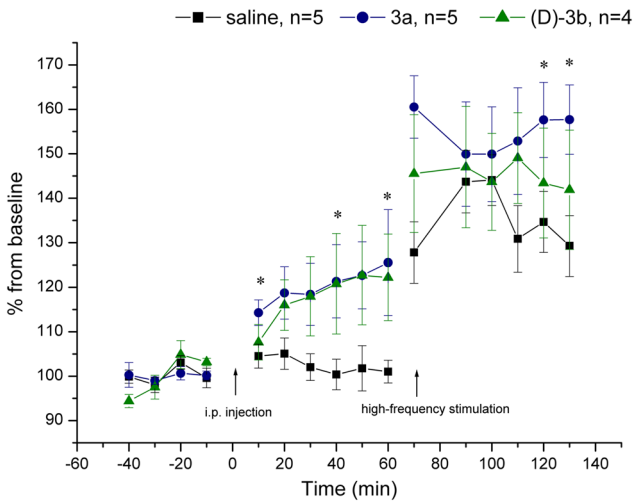


FIGURE 1 Effects of **3a** and (*D*)-**3b** on field excitatory postsynaptic potential (fEPSP) in the hippocampal CA1 region. The time course of fEPSP in **3a** (blue line, n=5), (*D*)-**3b** (green line, n=4) and saline (black line, n=5) for 60 min after intraperitoneal injection (i.p. injection) and after high frequency stimulation (HFS) in anaesthetized rats. Each point represents the mean ± S.E.M. percentage of basal fEPSP amplitude at 0 min; (*), significant differences against the saline group, $p<0.05$

2.4 | Electrophysiological experiments

Electrophysiological studies were carried out on the anesthetized Wistar rats weighting 350 g. The animals were anesthetized with ethylcarbamate (1.75 g kg^{-1}; intraperitoneally). Electrodes for the electric stimulation were implanted according to the following stereotaxic coordinates: hippocampal sector CA1 AP 2.7, L is 1.5; ventral hippocampal commissure (VHC) AP 1.3, L is 1.0 with the rat´s skull position at the same horizontal level. Bipolar electrodes made from 80 μm diameter nichrome wire were used for recording and stimulation. Penetration depth of the stimulation and recording electrodes was assessed from the recorded response measurements (optimal ratio of amplitude and stimulating current). To record the focal potentials of the field CA1 VHC was stimulated with 50-100 μs rectangular pulses. A series of ten paired stimulus presentations was applied (interstimulus interval in a pair was 30 ms, pulse pair interval was 20 s). Optimal parameters for the stimulating current varied from 100 to 400 μA. Efficiency of the synaptic transmission was assessed from the change in the amplitude characteristics of the induced responses of the hippocampal field CA1 on the testing stimulation of the VHC. Long term potentiation presenting an interneuronal synaptic transmission was induced by the high-frequency stimulation of the ventral hippocampal commissure (five stimulus sets each comprising four repeats of five stimuli with the 100 Hz stimulation frequency and an interval of 200 μs; an interval between the stimulus sets was 30 s). Electrophysiological studies were performed 30 min before the drug treatment, within 1 h after the injection and within 1 h after the high-frequency stimulation (Figure 1, 2).

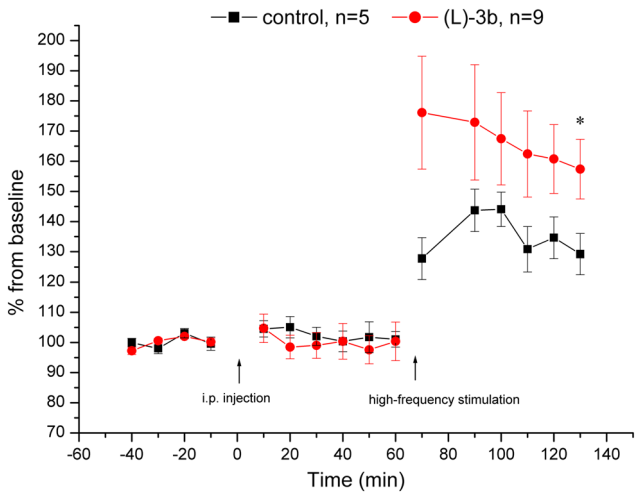


FIGURE 2 Effects of (*L*)-**3b** on field excitatory postsynaptic potential (fEPSP) in the hippocampal CA1 region. The time course of fEPSP in (*L*)-**3b** (red line, n=9) and saline (black line, n=5) for 60 min after intraperitoneal injection (i.p. injection) and after high frequency stimulation (HFS) in anaesthetized rats. Each point represents the mean ± S.E.M. percentage of basal fEPSP amplitude at 0 min; (*), significant differences against the saline group, $p<0.05$

3 | RESULTS AND DISCUSSIONS

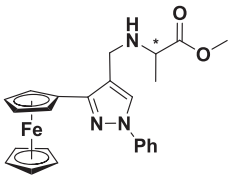
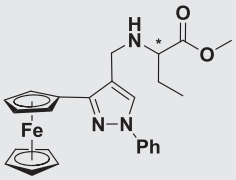
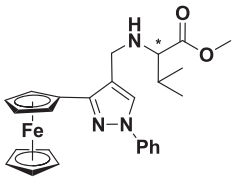
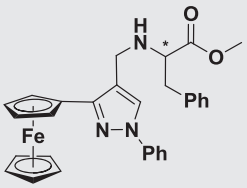
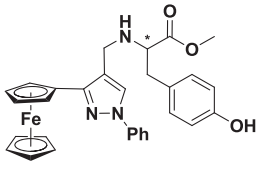
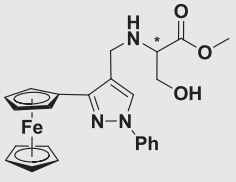
In this article, new ferrocene-based amino acids methyl esters with a pyrazole linker were synthesized in racemic and enantiomerically enriched forms. It is known that aberrant iron deposition in the brain is associated with neurodegenerative disorders. We would like to find out whether the synthesized ferrocene amino acids affect the hippocampus, and whether the action of individual enantiomers is different.

First ferrocene derivatives of amino acids such as ferrocenyl alanine (Fc-Ala) and ferrocenyl phenylalanine (Fc-Phe) were obtained by Schlögl in several steps as far back as 1957.[41] Systematic studies started in the end of 1990s and are performed nowadays though less actively (see reviews[2,4] and a book[7]). Synthetic approaches to the ferrocene modification of amino acids are rather simple. They comprise the synthesis of Schiff bases from acetylferrocene or formylferrocene and an amino acid.[42] However, such ferrocenyl imines are unstable compounds. They are usually reduced and then isolated as methyl or ethyl esters of the corresponding acids.[43] Starting from ferrocene carboxylic acid through ferrocenoyl benzotriazole ester, Kraatz synthesized ferrocene amino acid derivatives.[4,44,45] To obtain ferrocene-modified amino acids previously reported an approach developed for ferrocenylalkyl azoles.[46] Starting from ferrocenyl alcohols FcCH (OH)R and ethyl esters of glycine and β-alanine under acidic catalysis in aqueous organic medium the corresponding products were obtained.[46] Recently Ziegler and co-workers elaborated new synthetic route to ferrocene complexes of such type using a sulfonamide linking strategy.[47,48] Ferrocene-based pyrazole-containing amino acids were successfully prepared by Vukićević and co-workers, and evaluated as promising antitumor agents.[49] In a recent review, ferrocene conjugates with several natural amino acids were subjected to the detailed conformational and DFT analyses in order to determine the turn-inducing potential of ferrocene scaffolds in the corresponding peptidomimetics.[50]

3.1 | Synthesis

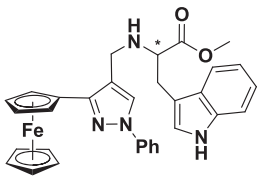
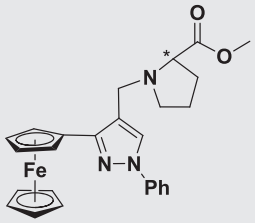
In this paper, we propose an approach to ferrocene-substituted amino acids based on synthetically available

TABLE 1 Enantiomeric resolution of **3 (b-d)**, **3i**, and **3 (e-h)** racemic mixtures on columns Chiralcel OD and Chiralpak AS-H, respectively

Molecule[a] and compound number	HPLC data[b]		
	Retention factor, k'_1	Retention factor, k'_2	Separation factor, α
 **3b**	2.17	2.83	1.30
 **3i**	1.75	2.98	1.70
 **3d**	1.16	1.72	1.48
 **3c**	4.90	6.63	1.35
Molecule[a] and compound number	HPLC data[c]		
	Retention factor, k'_1	Retention factor, k'_2	Separation factor, α
 **3f**	5.60	6.37	1.14
 **3e**	4.15	4.80	1.16

(Continues)

TABLE 1 (Continued)

 3g	4.37	4.90	1.12
 3h	0.84	1.29	1.54

[a]* in the structures means the stereogenic center.
[b]Mobile phase, hexane–isopropanol 90:10 (v/v).
[c]Mobile phase, hexane–isopropanol –TEA 90:10:0.01 (v/v/v).

ferrocenyl pyrazoles[32,33,39] using a reductive amination strategy. The interaction of ferrocenyl pyrazoles bearing an aldehyde group in the pyrazole moiety with amino acid esters, such as glycine, alanine, phenyl alanine, valine, serine, tryptophan, tyrosine, proline, and 2-aminobutyric acid, using sodium triacetoxyborohydride in dichloroethane under reflux conditions afforded the target products in 78-93% yields after chromatographic purification (Scheme 1). When *L*- or *D*-amino acids were used, the corresponding final products were isolated in enantiomerically enriched forms (see Experimental). Their purity is confirmed by the HPLC method. In the reactions of racemic amino acids, the final products are isolated as racemic mixtures.

It is known that sodium triacetoxyborohydride NaBH $(OAc)_3$ is often used in the reductive amination reaction. Being a milder reductive agent compared to, e.g., sodium borohydride or lithium aluminium hydride, it is effective in the carbonyl and aldehyde group reduction, with the C=C multiple bonds, cyano or nitro groups remaining intact.[51] We have found that NaBH $(OAc)_3$ effectively reduced Fc-formylpyrazole in reaction with mono-aminotetraphenyl porphyrine to form the -CH_2-NH- bond in the corresponding ferrocenyl porphyrine.[52]

Thus, ferrocenyl pyrazole derivatives of amino acids methyl esters were synthesized *via* the reductive amination using sodium triacetoxyborohydride according to Scheme 1. As a result, starting from methyl esters of amino acids such as glycine, alanine, phenylalanine, valine, serine, tyrosine, tryptophan, proline and 2-aminobutiric acid, a number of ferrocenyl-substituted amino acids methyl esters in racemic forms and in *L*- and *D*-forms were obtained in high yields.

3.2 | HPLC resolution

In addition to enantio enriched Fc-derived amino acids, racemic mixtures were obtained. The synthesized eight ferrocene derivatives **3b–i** contain one asymmetric carbon atom in their structures and give racemic mixtures of two enantiomers (Table 1). It is logical to suppose that the two enantiomers may possess different biological activities. So we separated the racemic mixtures into two enantiomers using high-performance liquid chromatography (HPLC). Earlier, this method of separation was successfully used for racemic ferrocene compounds with different simple substituents,[53] the chiral sorbents based upon β- and γ-cyclodextrins turned out to be effective in these cases. To separate mixtures of racemic ferrocene derivatives having bulky substituents such as azoles[29] including thiazoles[54] and nitro-imidazoles[55] we used modified cellulose or amylose as chiral stationary phases.

The enantiomeric resolution analytical data are summarized in Table 1. It should be noted that the stereogenic centre in these compounds is located on the periphery of the molecule far from the ferrocene core.

We successfully separated all 8 pairs of investigated compounds. Enantiomeric purity confirmed for *L*- and *D*-enantiomers. The recognition mechanism on cellulose or amylose is apparently connected, with formation of

specific hydrogen bonds between the strongly basic nitrogen atom of the NH-group, on the one hand, and carbamate units on the modified cellulose or amylose, on the other hand. Some interesting conformities should be marked. First, retention factors k'_1 and k'_2 for compounds **3b**, **3d** and **3i** with aliphatic substituents R (Table 1) decrease with a growing or branching chain length of R, excluding k'_2 for **3i**. For example, for **3b** and **3d** from k'_1 2.17 and k'_2 2.83 (R = methyl) to 1.16 and 1.72 (R = *iso*-propyl), respectively; bulky phenyl substituent significantly increases both k'_1 and k'_2 values, for compound **3c** to 4.90 and 6.63, respectively (R = CH_2-phenyl). The separation factors α for these compounds are significant, and for compound **3i**, where R = ethyl, reaches maximum value α = 1.7, that is, the enantiomers on the sorbent (column Chiralcel OD) are well separated.

3.3 | Biological tests. Electrophysiological measurements in the CA1 area of the hippocampus

Antitumor activity of ferrocene compounds is presently under active investigations,[15–18] and the authors have also succeeded in this field.[28,29,54,55] However, at the moment there are only a few publications on the effects of the ferrocene-substituted compounds on the brain.[21–25,56,57] This subject is only beginning to attract the attention of scientists working in the field of organometallic chemistry. In particular, in animal (rats) studies it was established that oral (e.g. dietary) administration of (3,5,5-trimethylhexanoyl)ferrocene did not result in accumulation of iron in the brain tissues.[21] *In vivo* experiments have investigated ferrocene-thiazolidinones as anxiolytics, that is, anxiety-inhibiting substances.[22] It has been found that the high dose-dependent anxiolytic activity of the synthesized ferrocene-thiazolidinones may be associated with their preferred interaction with the benzodiazepine-binding site of the GABA receptors. In other experiments, when ferrocene was exposed, in hippocampal slices *ex vivo* a significant accumulation of iron was found.[57]

For electrophysiological studies, we used ferrocene derivatives of glycine, *L*- and *D*-alanine. These are the first representatives of the synthesized series. Moreover, both glycine and alanine are used in medical practice. The role of *L*-amino acids in biological processes is well known, in contrast to *D*-amino acids. It seemed to us important and necessary to study both *L*-and *D*-alanine ferrocene compounds, the more so this necessary requirement is indicated in the pharmacopoeias of European and other countries to investigate the bio-effects of all stereoisomers. Also, in a recent article by Dr. Armstrong and colleagues, the possible role of *D*-amino acids (*D*-serine and *D*-asparagine) in stimulating the proliferation of breast cancer was indicated.[58]

Herein, impact of ferrocene-substituted alanine amino acid obtained in *D*- and *L*-forms, (*D*)-ferrocenyl (phenylpyrazolyl)-alanine methyl ester, (*D*)-**3b**, and (*L*)-ferrocenyl (phenylpyrazolyl)-alanine methyl ester, (*L*)-**3b**, as well as ferrocenyl (phenylpyrazolyl)-glycine, **3a** on the efficiency of interneuronal interactions was studied by the *in vivo (in vivo* means on alive, anaesthetized animals) recording the hippocampal local field potentials (LFP).

The local field potential (LFP) is an electrophysiological signal generated by a summed electrical current flowing from many neighboring neurons in a small amount of nervous tissue. Introduction of a ferrocene-containing compound, a good redox mediator, can produce an increase in the amplitudes of local field potentials. This will mean that such ferrocene-based compounds are involved in the synaptic plasticity of the brain area. Hippocampus is a key structure involved in the learning and memory processes.[57] One of the common model of processes taking place in the hippocampus during learning is a development of a long-term potentiation of the synaptic transmission in the hippocampal sector CA1.[59]

The response amplitudes of the local potentials of the hippocampal field means that a bipolar nichrome electrode was lowered into the CA1 region of the hippocampus to record field excitatory postsynaptic potentials (fEPSPs). The fEPSP amplitude in the CA1 field evoked by stimulation of the ventral hippocampal commissure (VHC). Thus, fEPSP characteristics can change under different experimental conditions. Here we injected the ferrocene-based compounds which increased amplitudes of fEPSP in the CA1 hippocampal area.

During the testing of the ferrocenyl (phenylpyrazolyl)-glycine methyl ester (**3a**) and (*D*)-ferrocenyl (phenylpyrazolyl)-alanine methyl ester, (*D*)-**3b**, at a dose of 2.0 mg kg^{-1} (in a DMSO—H_2O solution, intraperitoneally) two groups of animals were studied and one control group (animals were injected with saline). It was shown that response amplitudes of the focal potentials of the hippocampal field CA1 in the tested animals injected with ferrocene-containing compounds (number of animals in a first group, n = 5, in a second group, n = 4) raised from 15% to 25% compared to the saline-treated control animals (n = 5) (see Figure 1). That is, the effects of the introduction at the first hour of both substances are almost the same, only compound (*D*)-**3b** is slower goes to the level of 20% of the control. It can be argued that the compounds **3a** and (*D*)-**3b** cause long-term changes in synaptic plasticity.

Within 60 min after the beginning of recordings in the group of rats injected with the compound **3a** (Fc-glycine-based), the response amplitude following the high-frequency stimulation (HFS) was significantly higher compared to that for the saline-injected control group animals (157.7±7.9% и 132.25±9.3%, respectively; $p < 0.05$ according to the t-test). However, additional stimulation with the introduction of compound (*D*)-**3b** (Fc-alanine-based) has a lesser effect, but higher than in control and at one level about 145%.

Overall, our results suggest that compounds **3a** and (*D*)-**3b** enhanced the amplitudes of basal synaptic transmission and long-term potentiation (LTP) as compared to control animals.

Figure 2 shows the data for administration from compound (*L*)-**3b** ($n = 9$). In this group of animals (Wistar rats), nine animals were tested, the largest number, and five in the control group ($n = 5$). It can be seen that during the first hour after injection, the effect is at the control level, in contrast to the action of the *D*-enantiomer (up to 25% in compare to control). After high-frequency stimulation (the second hour) a rather significant increase (up to 180%) is shown. Although the error bars after high-frequency stimulation are large (the red line) the high level of error bars is normal after HFS in *in vivo* electrophysiological experiments.[60–62]

Thus, the effects of ferrocene enantiomers on the CA1 hippocampal region are considerably different. One stereoisomer has a significant effect, while the other has a minor effect on the CA1 zone of the hippocampus. Overall, this result is not surprising. The biological actions of enantiomers are usually different. That is why it is important to study the actions of each enantiomer, which is required in the research of drug candidates and is fixed in the pharmacopoeias.

Thus, pronounced responses of the hippocampal region of the brain to the ferrocene-containing compounds were detected *in vivo*. Naturally, there is a need in further studies with varying the doses and the ferrocene preparations *per se* to accumulate the statistical data and to review the results. However, it should be noted that the chosen class of the ferrocene-modified amino acids displays a biological action on the region of the brain, i.e. hippocampus. The biological model was well chosen and a significant change (an increase of 15–25% compared to the control) in the amplitude of the local potentials in the hippocampal region CA1 was detected. The results obtained on choosing a dose (2.0 mg kg^{-1}) based on a considerable experience of other biological studies performed by us suggests that the ferrocene compounds can act in a low dose range.

4 | CONCLUSION

Using the reductive amination strategy, a series of ferrocene-containing amino acid esters with pyrazole linkers were obtained, both in racemic form and in the form of individual enantiomers in high yields. For the first time primary electrophysiological studies of ferrocene-modified amino acids were carried out *in vivo*. It was found that after 60 min after intraperitoneal administration of the studied compounds, effects were registered in the CA1 zone of the hippocampus, i.e. in the brain of animals. Moreover, these effects are different for the (*L*)- and (*D*)-enantiomers. Biological studies have revealed the involvement of ferrocene-based compounds in the synaptic plasticity of the CA1 hippocampus brain region.

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CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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