Ferrocene-modified amino acids: synthesis and *in vivo* bioeffects on hippocampus*

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A method for the ferrocene modification of amino acids of natural and synthetic origin has been developed. In the *in vivo* studies, the hippocampal electrical activity under the action of ferrocenyl(phenylpyrazolyl)glycine (**1**) was assessed. A meaningful rise (up to 25% compared to the control) in the response amplitudes of the focal potentials of the hippocampal region CA1 after intraperitoneal administration of compound **1** at the dose of 2.0 mg kg^{-1} was established.

Key words: ferrocene, amino acids, synthesis, enantiomers, biological activity, brain, hippocampus.

Chemistry of ferrocene has been intensively developed for more that six decades.[1,2] However, during the first decade and a half of the XXI century a special attention was been given to the synthesis of ferrocene derivatives bearing pharmacophoric groups, namely, nucleobases, oligonucleotides, various heterocycles, amino acids, peptides, and sugars.[3—8] *In vitro* and *in vivo* studies have demonstrated that many of such ferrocenes display a large range of biological activity,[9] including antianemic,[10] antimicrobial,[11] antibacterial,[12] tuberculostatic,[13] antimalarial,[14] antitumor activities,[15—18] *etc*. Ferroceron (*o*-carboxybenzoylferrocene), being a ferrocene-based drug, is used effectively for a long time for the treatment of iron-deficiency pathologies.[19]

However, a potential of ferrocenyl-substituted amino acids as drugs for the treatment of neurodegenerative disorders 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.

Our own results[17,21—29] as well as literature data[30—33] suggest that it is ferrocene-modified amino acids that can have a considerable impact on the neurodegenerative processes. It is known, that iron-containing ferrocene moiety endows the modified compounds with a number of useful properties. First, it significantly decreases their toxicity[7,17] and improve their lipid membrane penetrating ability.[9] Moreover, it allows there compounds to exist both in salt and neutral forms[29] 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[22,27] at physiological pH values is their substantial advantage, that is to say, these compounds present a kind of mediators. 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,[6,9,17] overcomes readily the BBB (though this hypothesis did nor find sufficient experimental support yet) and can facilitate the targeted drug delivery to the brain.

Based on the commercially available ferrocene, we have developed a unique synthetic procedure and obtained a series of hitherto unknown ferrocenyl-substituted amino acids, namely, glycine, alanine, valine, tyrosine, and proline ones. This approach to ferrocenyl-substituted amino acids comprises modification of synthetically available ferrocenyl azoles[8] well-accepted in terms of biological activity. On the basis of a ferrocene-pyrazol building block

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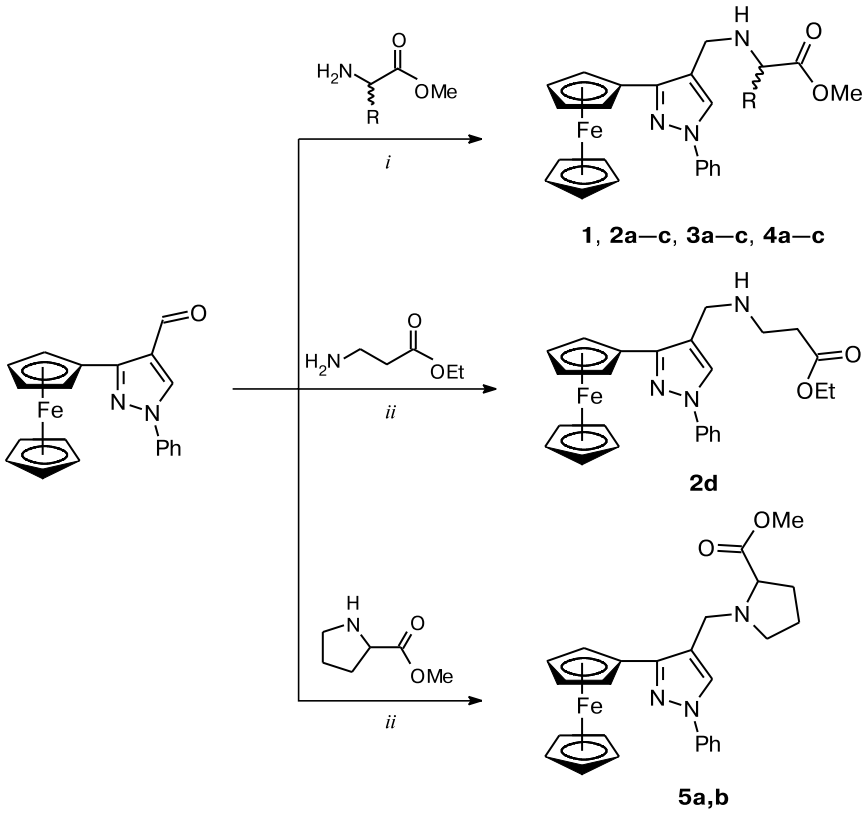
the amino-acid moiety was attached. For this purpose, selective approaches to obtain isomeric ferrocenyl pyrazol carbaldehydes were proposed.[34,35] Their subsequent functionalization *via* the reductive amination with the amino acid methyl esters of both natural (including both L-, D- or DL-forms), and synthetic origin using sodium triacetoxyborohydride as a reducing agent affords the ferrocene-pyrazol-amino acid building block (Scheme 1). As a result, various ferrocene-substituted amino acids were obtained. 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.

It should be emphasized that biological activity of the ferrocene-based compounds in an enantiomerically pure (or enriched) form earlier has virtually not been studied. 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 tradegy" 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 stereomers is inspired by the requirements of the Pharmaceutical Committee of the Russian Federation to enantiomeric purity[36] and the studies logic.

In the Institute of Higher Nervous Activity and Neurophysiology of Russian Academy of Sciences primary studies of a biological action of the first representative of a series of ferrocenyl amino acids, namely, ferrocenyl-(phenylpyrazolyl)glycine (**1**), on the hippocampus which is a part of a temporal lobe of the brain, have been performed. A significant (up to 15%) rise of the amplitude of the hippocampal focal potentials upon intraperitoneal administration of compound **1** at a dose of 2.0 mg kg^{-1} was established. Further we are planning to screen the activity of the ferrocene compounds using both racemic mixtures and the individual enantiomers.

Scheme 1



Reagents and conditions: *i.* $NaBH(OAc)_3$, $C_2H_4Cl_2$, Δ, 3 h; *ii.* $NaBH(OAc)_3$, $C_2H_4Cl_2$, Δ, 1 h.

R = H (glycine) (**1**); Me (alanine-DL, L, D) (**2a**, **2b**, **2c**, respectively); *iso*-Pro (valine-DL, L, D) (**3a**, **3b**, **3c**); 4-$HOC_6H_4CH_2$ (tyrosine-DL, L, D) (**4a**, **4b**, **4c**); β-alanine (**2d**); proline (DL, L) (**5a**, **5b**).

First ferrocenyl derivatives of amino acids such as ferrocenyl alanine (Fc-Ala) and ferrocenyl phenyl alanine (Fc-PheAla) were obtained in several steps as far back as 1957.[37] Systematic studies started in the end of 1990s and are performed nowadays though less actively (see reviews[4,6] and a book[9]).

Synthetic approaches to the ferrocene modification of amino acids are rather simple. They comprise the synthesis of Schiff bases from acetylferrocene and an amino acid.[38] However, such ferrocenyl imines are unstable compounds. They are usually reduced and then isolated as methyl or ethyl esters of the corresponding acids.[39]

To obtain ferrocenyl-modified amino acids we have previously used an approach developed for ferrocenyl-(alkyl)azoles. 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.[40]

In the present work we propose an approach to ferrocene-substituted amino acids based on modification of synthetically available ferrocenyl pyrazoles.[35,41] Reductive amination reactions between ferrocenyl pyrazoles bearing an aldehyde group in the pyrazole moiety, and esters of amino acid such as glycine, alanine, β-alanine, valine, tyrosine, and proline using sodium triacetoxyborohydride under reflux in dichloroethane afforded the target products **1**, **2a—c**, **2d**, **3a—c**, **4a—c**, and **5a**,**b**, correspondingly, in 90% yields after chromatographic purification (see Scheme 1).

It is known that sodium triacetoxyborohydride $NaBH(OAc)_3$ is often used in the reductive aminations. 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.[42] We have found that $NaBH(OAc)_3$ effectively reduces Fc-formylpyrazol in reaction with monoaminotetraphenyl porphyrine to form the $—CH_2—NH—$ bond in the corresponding ferrocenyl porphyrine.[43]

Thus, ferrocenyl pyrazol derivatives of amino acids 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, β-alanine, valine, tyrosine, and proline, a variety of ferrocenyl-substituted amino acids both in a racemic forms and in L- and D-forms were obtained in high yields.

Antitumor activity of ferrocene compounds is presently under active investigation,[5,15—18] and the authors have also succeeded in this field.[17,21] However, for the moment there are only few publications concerning the influence of the ferrocenyl-substituted compounds on the brain.[30—33,44] This subject is only beginning to attract the attention of scientists working in the field of organometallic chemistry. In particular, in animal (rodent) studies it was established[30] that oral (*e.g.* dietary) administration of (3,5,5-trimethylhexanoyl)ferrocene did not result in accumulation of iron in the brain tissues. In a recent work,[44] *N*-phenylferrocene carboxamide FcC(O)NH-Ph was used only as a starting compound to be radiolabeled with ^{99m}Tc through substituting iron for ^{99m}Tc. Iron-free technetium-labeled compound was subsequently administrated to anesthesized animals (rats) with the purpose to investigate the accumulation of the radioactive product in different parts on the brain.

The influence of ferrocenyl-substituted amino acids obtained by us on the efficiency of interneuronal interactions was studied by the *in vivo* recording the hippocampal focal potentials. Hippocampus is a key structure involved in the learning and memory processes.[45] 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.[46]

Electrophysiological studies were carried out on the anesthesized Wistar rats weighting 350 g. The animals were anesthesized with ethylcarbamate (1.75 g kg^{-1}; IP). 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 commissura (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 an 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 stimili 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 responces 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 commissura (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 study was performed 30 min before the drug treatment, within 1 h after the injection and within 1 h after the high-frequency stimulation (Fig. 1).

During the testing of the ferrocenyl(phenylpyrazolyl)-glycine methyl ester (**1**) at a dose of 2.0 mg kg^{-1} (in a DMSO—H_2O solution) two groups of animals were studied. It was shown that response amplitudes of the focal

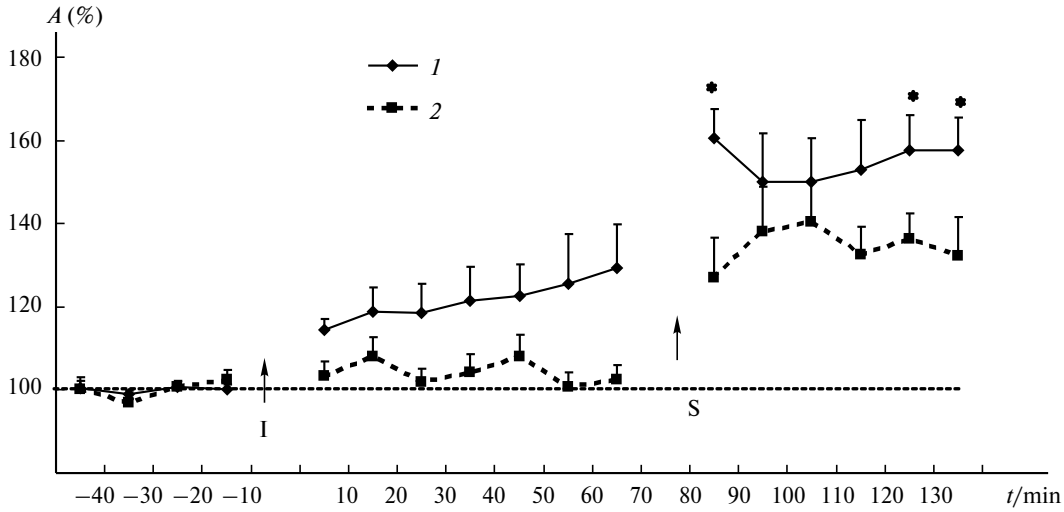


Fig. 1. A change in the amplitude of the focal potentials of the hippocampal field CA1as a response on the VHC testing stimulation within 60 min after administrating the ferrocene-containing preparation (compound **1**, a dose of 2 mg kg^{-1}, IP) and within 60 min after high-frequency stimulation; *1* is a ferrocene-modified preparation, *2* is a saline solution, I is a preparation administration, S is a high-frequency stimulation, *t* is a duration of a test, *A* is a response amplitude as a percentage of the background level (AM±SEM are presented). Meaningful values ($p < 0.05$) are designated (*) in assessment of the group differences according to the t-test.

potentials of the hippocampal field CA1 in the tested animals injected with a ferrocene-containing preparation (compound **1**) at the concentration of 2 mg kg^{-1} ($n = 5$) rised from 15% to 25% compared to the saline-treated control animals ($n = 3$) (see Fig. 1). Within 60 min after the beginning of recordings in the group of rats injected with the preparation, the response amplitude following the high-frequency stimulation was significanty 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).

In such a manner a pronouced response of the hippocampal region of the brain to the ferrocene-containing preparation was detected. Naturally, there is a need in further studies with varying the dose 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 most important 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 focal potentials in the hippocampal region CA1 was detected. The result 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 ferrocenyl compounds act in a low dose range.

Primary biological studies revealed the involvement of the ferrocene based compounds in the synaptic plasticity of a brain region.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 spectrometer at 500.13 and 125.76 MHz, respectively, in $CDCl_3$. Mass spectra were recorded on a Finnigan Polaris Q spectrometer (ionization energy 70 eV, the ionization chamber temperature 250 °C). IR spectra were recorded on a UR-20 (Karl Zeiss) spectrometer (KBr pellets). Sodium triacetoxyborohydride $NaBH(OAc)_3$ and amino acids (Acros Organics) were used without preliminary purification. Amino acid methyl and ethyl ester hydrochlorides were obtained by reaction of amino acids with $SOCl_2$ in methanol or ethanol, respectively.[47]

Synthesis of ferrocene-substituted pyrazolyl amino acids (general procedure). To a solution of 1-phenyl-3-(ferrocenyl)pyrazol-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 triacetoxyborohydride (0.3 g, 1.4 mmol). The reaction mixture was heated under reflux for 1—3 h. 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). Below are given the elemental analysis data, IR, ^1H and ^{13}C NMR spectroscopy as well as mass-spectrometry data for the racemic mixtures, which are similar to the data for the individual enantiomers.

Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)methylamino]acetate or ferrocenyl(phenylpyrazolyl)glycine methyl ester (1). 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. MS, *m/z* (I_{rel} (%)): 429 $[M]^+$ (100). ^1H 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.

(DL)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]propanoate or (DL)-ferrocenyl(phenylpyrazolyl)-alanine methyl ester (2a). 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. 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.

(L)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]propanoate (2b). Yield 90%. Yellow powder, m.p. 75 °C, $[\alpha]_D^{25}$ −27.2 (*c* 1.0; MeCN).

(D)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]propanoate (2c). Yield 90%. Yellow powder, m.p. 74—75 °C, $[\alpha]_D^{25}$ +26.4 (*c* 1.0; MeCN).

Ethyl-3-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)methyl-amino]propanoate or ferrocenyl(phenylpyrazolyl)-β-alanine ethyl ester (2d). Yield 87%. Yellow powder, m.p. 112 °C. Found (%): C, 65.70; H, 5.85; N, 9.10. $C_{25}H_{27}FeN_3O_2$. Calculated (%): C, 65.65; H, 5.95; N, 9.19. MS, *m/z* (I_{rel} (%)): 457 $[M]^+$ (67), 392 $[M - Cp]^+$ (100). IR, ν/cm^{-1}: 1732 (COOEt). ^1H NMR ($CDCl_3$), δ: 1.25 (t, 3 H, Me, J = 7.0 Hz); 1.70 (br s, 1 H, NH); 2.59, 3.05 (both t, by 2 H, CH_2, J = 6.5 Hz); 3.97 (s, 2 H, CH_2); 4.12 (s, 5 H, Fc); 4.14 (m, 2 H, CH_2); 4.32, 4.82 (both s, by 2 H, Fc); 7.22 (t, 1 H, Ph, J = 7.7 Hz); 7.42 (m, 2 H, Ph); 7.71 (d, 2 H, Ph, J = 7.8 Hz); 7.90 (s, 1 H, Pz). ^{13}C NMR ($CDCl_3$), δ: 14.0, 30.6, 41,4, 41.7, 61.3, 68.1, 68.9, 69.5, 76.7, 110.2, 118.7, 126.5, 129.3, 129.7, 139.3, 150.7, 170.2.

(DL)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]-3-methylbutanoate or (DL)-ferrocenyl(phenyl-pyrazolyl)valine methyl ester (3a). 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. 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.

(L)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]-3-methylbutanoate (3b). Yield 90%. Yellow powder, m.p. 136 °C, $[\alpha]_D^{25}$ −18.0 (*c* 1.0; $CHCl_3$).

(D)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]-3-methylbutanoate (3c). Yield 90%. Yellow powder, m.p. 137 °C, $[\alpha]_D^{25}$ +17.9 (*c* 1.0; $CHCl_3$).

(DL)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]-3-(4-hydroxyphenyl)propanoate or (DL)-ferrocenyl(phenylpyrazolyl)tyrosine methyl ester (4a). 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. MS, *m/z* (I_{rel} (%)): 535 $[M]^+$ (34), 470 $[M - Cp]^+$ (58). IR, ν/$см^{-1}$: 1732 (COOMe). ^1H NMR ($CDCl_3$), δ: 1.95 (br s, 1 H, NH); 2.83 (dd, 1 H, CH_2, J_1 = 8.0 Hz, J_2 = 13.5 Hz); 2.97 (dd, 1 H, CH_2, J_1 = 5.3 Hz, J_2 = 13.5 Hz); 3.64 (m, 1 H, CH); 3.63 (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, Ar, 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, 139.0, 150.1, 155.3, 175.3.

(L)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)methylamino]-3-(4-hydroxyphenyl)propanoate (4b). Yield 90%. Yellow powder, m.p. 182 °C, $[\alpha]_D^{25}$ −11.2 (*c* 0.81; $CHCl_3$).

(D)-Methyl-2-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methylamino]-3-(4-hydroxyphenyl)propanoate (4c). Yield 89%. Yellow powder, m.p. 182 °C, $[\alpha]_D^{25}$ +11.1 (*c* 0.74; $CHCl_3$).

(DL)-Methyl-1-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methyl]pyrrolidine-2-carboxylate or ferrocenyl(phenylpyr-azolyl)proline methyl ester (5a). 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. 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 (d, 1 H, CH_2, J = 13.5 Hz); 4.08 (d, 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: 219, 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.

(L)-Methyl-1-[(1-phenyl-3-ferrocenyl-1*H*-pyrazol-4-yl)-methyl]pyrrolidine-2-carboxylate or ferrocenyl(phenylpyrazol-yl)proline methyl ester (5b). Yield 80%. Yellow powder, m.p. 140 °C, $[\alpha]_D^{25}$ +20.6 (*c* 1.07; $CHCl_3$).

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