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α-(Ferrocenyl)-aminomethanephosphonous acids. First synthesis and preparation of their esters with cholesterol and adenosine

Jarosław Lewkowski *, Monika Rzeźniczak, Romuald Skowroński

Department of Organic Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Poland

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Abstract

The series of aminophosphonous acids bearing the ferrocenyl moiety was obtained by the addition of hypophosphorous acid to Schiff bases of ferrocenecarboxaldehyde. They were subsequently condensed with cholesterol and adenosine to form their cholesteryl and adenosinyl esters. The concurrence reaction of DCC with amine nitrogen atom was observed.

Keywords: Ferrocenecarboxaldehyde; Hypophosphorous acid; Aminophosphonous acids; Adenosine; Cholesterol; Concurrence reaction

1. Introduction

The important biological function of aminophosphonic and aminophosphonous acids is well recognized [1,2]. The importance of ferrocene-derived compounds is well known too, as they have been widely employed in the molecular recognition due to their ability to make metal-centred redox systems to generate oxidized or reduced form of different properties, as described by Constable [3]. For the formation of such molecular switches containing ferrocene moiety, it was proposed to use dihydrocholesteryl ether of ferrocenedimethanol [3], derivatives of di(ferrocenylmethyl)malonate [4] and ferrocene-containing thioethers [5] as well as some derivatives of ferrocenylmethylamines [6] and ferrocenyl ligands containing the tetrathiafulvalene molecules [7]. There were also attempts to mark peptides by binding them to ferrocene-bearing amino acids. That is why, studies on the synthesis of ferrocenylalanine [8–13] and ferrocenoylalanine [14] have been performed. We contributed to this topic too, publishing the synthesis of variously substituted ferrocene-bearing aminomethanephosphonates [15,16].

Biological substances often bear in their structure a phosphorylated alcohol group. These are: phospholipids, oligonucleotides or carbohydrate phosphates [17]. The compounds of phosphorous or aminophosphonic acids with cholesterol or adenosine were not largely described. Kashman [18] presented the synthesis of *O*-cholesteryl, *O*-methyl phosphite by the reaction of dimethyl phosphite with cholesterol. Riess and co-workers [19] reported the preparation of mono- or dicholesteryl phosphites by the reaction of triethyl phosphite with cholesterol. Gibbs and Larsen [20] and Knerr et al. [17] proposed the preparation of monophosphites of cholesterol and uridine and thymidine. Stec and co-workers [21] synthesized adenosinyl and uridinyl esters of 1-aminoethanephosphonic acid.

Regarding all above, we wanted to combine properties of mentioned groups of compounds and that is why we synthesized four new (ferrocenyl)aminomethanephosphonous acids and their cholesteryl and adenosinyl esters.

2. Results and discussion

Acids **3a–d** have been synthesized by the addition of hypophosphorous acid to the azomethine bond of Schiff bases derived from ferrocenecarboxaldehyde (**2a–d**). Schiff bases **2a–d** have been already described in our previous paper [15], and they were identical to samples described there, so we do not quote their data.

* Corresponding author. Tel.: +48-426784731; fax: +48-426786583.
E-mail address: jlewkow@uni.lodz.pl (J. Lewkowski).

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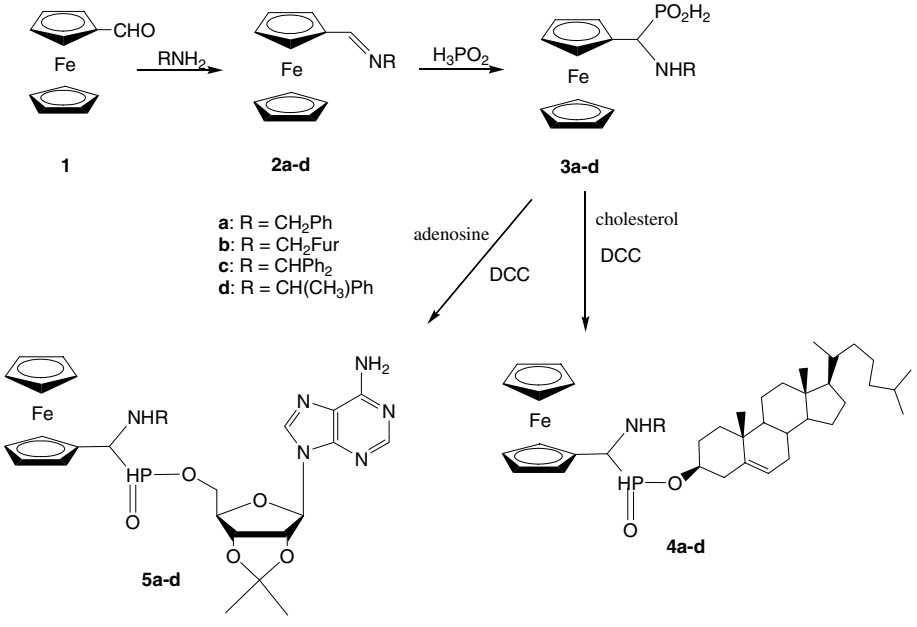
The addition of hypophosphorous acid was performed in dry 1,4-dioxane at the reflux temperature. After 3 days, we observed the precipitation of acids **3a–d**, which were isolated by filtration in 56–65% yield. They were purified by washing with cold water followed by cold methanol. The identity of compounds was confirmed by the ^{1}H and ^{31}P NMR spectroscopy, the mass spectrometry and the elemental analysis. Acids **3a–c** were obtained as racemates. In case of chiral Schiff base **2d**, the addition of hypophosphorous acid was not highly stereoselective, which was surprising in front of Hamilton, Walker and Walker's discovery [22]. Diastereoisomers formed in the 2:1 ratio, which astonishing fact was preliminarily discussed in the communication by Lewkowski [23] (Scheme 1).

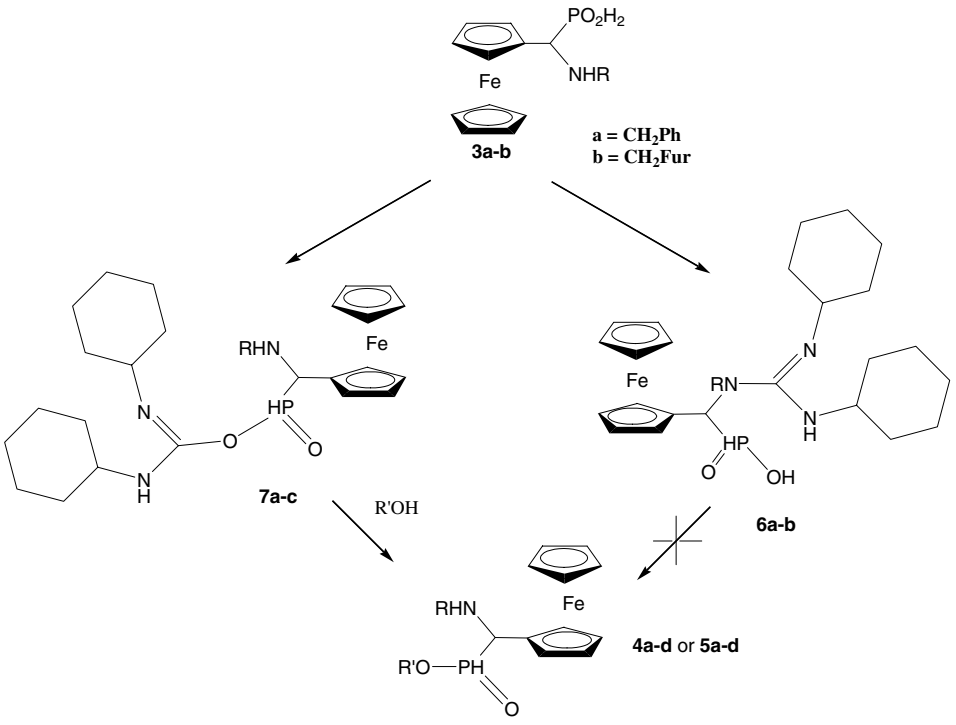
Their cholesteryl esters **4a–d** and were synthesized by the condensation of acids **3a–d** with cholesterol in the presence of dicyclohexylcarbodiimide (DCC) as a dehydrating agent in dichloromethane. After 7 days of refluxing, esters **4a–d** have been obtained in fair yields as low-melting solids (Scheme 1). They were purified by the column chromatography on cellulose powder; our tests demonstrated that obtained esters **4a–d** decomposed on silica gel as well as on neutral aluminium oxide. Moreover, too long contact of esters **4a–d** with cellulose powder resulted in decomposition, so that esters had to be flash-chromatographed. A concurrence reaction occurred in these conditions in case of *N*-benzyl and *N*-furfuryl acids **3a** and **3b**. In case of the *N*-benzyl derivative **3a**, the side product **6a** and the ester **4a** formed in a 3:1 ratio and in case of the *N*-furfuryl acid **3b**, the side product **6b** and the ester **4b** formed in a this ratio was 1:5. We isolated the esters **4a–b** by the column chromatography on cellulose powder and their purification was carried out in the same conditions.

Similar results were obtained in the course of condensation of acids **3a–d** with *O*,*O*′-iso-propylideneadenosine, which was carried out in identical conditions i.e. in dichloromethane, in the presence of dicyclohexylcarbodiimide (DCC) as a dehydrating agent (Scheme 1). Adenosinyl esters **5a–d** were obtained and, in a case of *N*-diphenylmethyl and *N*-α-methylbenzyl derivatives, corresponding esters (**5c**) and (**5d**) were exclusive products. Reactions with acids **3a** and **3b** led to desired esters **5a** and **5b** but also to side products **6a** and **6b** in a 3:1 and 1:6 (**6–4)** ratio, respectively. Adenosinyl derivatives **5c** and **5d** were characterised by the ^{1}H and ^{31}P NMR spectroscopy, the mass spectrometry and the elemental analysis. *N*-benzyl ester **5a** as well as *N*-furfuryl ester **5b** were isolated by the column chromatography on cellulose powder and they were purified in the same way. The identity of esters **4a–d** and **5a–d** was confirmed by the ^{1}H, ^{13}C and ^{31}P NMR spectroscopy, the mass spectrometry and the elemental analysis.

The reaction between acids **3a–d** and DCC in the absence of any alcohol led to the unique formation of aminophosphonous acids derivatives **6a–b**. The most probably they are formed by the attack of DCC on the nitrogen atom. Normally, the mechanism of condensation of acids with alcohols passes through the intermediate **7a–d**, which forms as a result of the DCC attack on the oxygen atom. But when the nitrogen nucleophilic centre is rather accessible, the attack on it is probable. Acids **3c–d** did not react with DCC in this way probably due to the sterical hindrance of large diphenylmethyl (**3c**) or α-methylbenzyl (**3d**) groups (Scheme 2).



Scheme 1.



Scheme 2.

Acid derivatives **6a–b** were determined by the ^{1}H, ^{13}C and ^{31}P NMR spectroscopy as well as the mass spectrometry and a high resolution mass spectrometry (HRMS). They were not properly purified due to their fragility, so their combustion analysis could not be performed.

Each of esters **4a–c** and **5a–c** occurred as the mixture of four diastereoisomers, which were clearly visible on ^{31}P NMR spectra of cholesteryl esters **4a–c**, as four well-separated signals occurred. In a case of adenosinyl esters **5a–c**, they gave generally four well-shaped ^{31}P NMR signals except the *N*-benzyl derivative **5a**, which gave three signals, but one of them, this in the middle, consisted of two overlapping signals. The evidence of diastereoisomers has been also confirmed by the ^{1}H NMR spectroscopy by the presence of two or four signals of the P–H protons. In some cases two enlarged doublets instead of four ones occurred, which was due to overlapping. The same phenomenon is observed on the ^{13}C NMR spectra. All is quoted in Section 3.

Ratio of diastereoisomers of cholesteryl esters varied from 2:2:3:3 in case of *N*-diphenylmethyl derivative **4c** to even 1:1:6:6 in case of **4b**. Ratio of diastereoisomers of adenosinyl esters differed much less, as it varied from 1:1:1:1 for the *N*-benzyl derivative **5a** up to 1:1:3:3 in a case of the *N*-diphenylmethyl one **5c**. This might be caused by the chiral assistance of a cholesterol or adenosine molecule.

Much more interesting was the stereochemistry of the ester formation from *N*-(*R*)-α-methylbenzylamino(ferrocenyl)methane phosphonous acid **(3d)**, as its reaction with cholesterol as well as isopropylidene adenosine in the presence of DCC resulted in exclusively two diastereoisomers in a 1:2 ratio in both cases. This demonstrated that for each of the diastereoisomeric form of the acid **3d**, newly formed chiral centre on a phosphorus atom occurs in the 100% stereoselectivity. The chiral assistance of cholesterol or adenosine should be combined with the assistance of the (*R*)-α-methylbenzyl substituent on nitrogen. For now, the reason of such a stereoselectivity remains unclear, there are too many factors involved. This problem will be the subject of the separate theoretical study.

The separation of four diastereoisomers of esters failed due to their fragility towards silica gel or alumina; cellulose powder was not an adsorbent suitable enough to provide a good resolution of diastereoisomers.

3. Experimental

All solvents and furfural (POCh-Poland) were routinely distilled and dried prior to use. Hypophosphorous acid 50% (Aldrich) were dehydrated following the published procedure [2]. Amines, (Aldrich) as well as cholesterol (Organika S.A. Poland) were used as received. NMR spectra were recorded on a Varian Gemini 200 BB apparatus operating at 200 MHz (^{1}H NMR) and 81 MHz (^{31}P NMR). Schiff bases **2a–d** were prepared following the previously published procedure [19].

Elemental analyses were made in the Centre for Molecular and Macromolecular Science of the Polish Academy of Science in Łódź.

3.1. General procedure for the preparation of N-alkylamino(ferrocenyl)methane phosphonous acid

The Schiff base (5 mmol) was dissolved in acetonitrile (30 ml) and hypophosphorous acid (5 mmol) was added and the solution was refluxed for 1 h and then stirred for 3 days at room temperature. After this time, the precipitate was collected by filtration and washed several times with cold water to remove impurities to obtain the desired product.

3.1.1. N-benzylamino(ferrocenyl)methane phosphonous acid (**3a**)

Y = (27%); m.p.: 206–208 °C.

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.44(m, ArH, 5H); 6.68 (dd, $^1J_{PH} = 516.2$ Hz and $^3J_{HH} = 2.8$ Hz, HP, 1H); 4.30 and 4.26 (m, CH_{fer}, 2H); 4.21 (s, CH_{fer}, 5H); 4.13 (s, CH_2, 2H); 3.38 (dd, $^2J_{PH} = 10.8$ Hz and $^3J_{HH} = 2.8$ Hz, 1H).

^{31}P NMR (NaOD/D_2O, 81 MHz): δ 31.28.

EI-MS: $m/z = 369[M^+]$; $303[M^+–P(OH)_2]$; 213[Fc–CH=N^+]; 121[$CpFe^+$]; 91[$^+CH_2Ph$]; 65[Cp^+].

Elemental analysis: Anal. Found: C, 58.51; H, 5.29; N, 3.77%. Calc. for ($C_{18}H_{20}FeNO_2P$): C, 58.56; H, 5.46; N, 3.79.

3.1.2. N-furfurylamino(ferrocenyl)methane phosphonous acid (**3b**)

Y = (24%); m.p.: 194–196 °C.

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.56 (m, CH_{fur}, 1H); 6.47 (m, CH_{fur}, 2H); 6.61 (dd, $^1J_{PH} = 516.2$ Hz and $^3J_{HH} = 2.8$ Hz, HP, 1H); 4.30 and 4.26 (m, CH_{fer}, 4H); 4.21 (s, CH_{fer}, 5H); 4.13 (s, CH_2, 2H); 3.38 (dd, $^2J_{PH} = 10.8$ Hz and $^3J_{HH} = 2.8$ Hz, 1H).

^{31}P NMR (NaOD/D_2O, 81 MHz): δ 30.34.

EI-MS: $m/z = 359[M^+]$; $293[M^+–P(OH)_2]$; 213[Fc–CH=N^+]; 121[$CpFe^+$]; 81[$^+CH_2Fur$]; 65[Cp^+].

Elemental analysis: Anal. Found: C, 53.20; H, 5.03; N, 3.94%. Calc. for ($C_{16}H_{18}NO_3PFe$): C, 53.51; H, 5.05; N, 3.90.

3.1.3. N-diphenylmethylamino(ferrocenyl)methane phosphonous acid (**3c**)

Y = (26%); m.p.: 191–194 °C.

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.35(m, ArH, 10H); 7.31 (dd, $^1J_{PH} = 523.9$ Hz and $^3J_{HH} = 2.8$ Hz, HP, 1H); 5.62 (s, CH, 1H); 4.30 and 4.26 (m, CH_{fer}, 2H); 4.21 (s, CH_{fer}, 5H); 3.38 (dd, $^2J_{PH} = 10.8$ Hz and $^3J_{HH} = 2.8$ Hz, 1H).

EI-MS: $m/z = 445[M^+]$; $379[M^+–P(OH)_2]$; 213[Fc–CH=N^+]; 121[$CpFe^+$]; 167[$^+CHPh_2$]; 65[Cp^+].

^{31}P NMR (NaOD/D_2O, 81 MHz): δ 28.52.

Elemental analysis: Anal. Found: C, 64.52; H, 5.30; N, 3.32%. Calc. for ($C_{24}H_{24}FeNO_2P$): C, 64.74; H, 5.43; N, 3.15%.

3.1.4. N-(R)-α-methylbenzylamino(ferrocenyl)methane phosphonous acid (**3d**)

m.p. = 215–217 °C.

^{1}H NMR (NaOD/D_2O, 200 MHz): δ 7.23 (m, CH_{fur}, 1H); 6.47 (m, CH_{fur}, 2H); *6.67* (dd, $^1J_{PH} = 521.6$ Hz and $^3J_{HH} = 1.6$ Hz, HP, 1H); 6.58 (dd, $^1J_{PH} = 514.9$ Hz and $^3J_{HH} = 1.6$ Hz, HP, 1H); 4.19 and *4.13* (2quart, $J = 6.7$ Hz); 4.00 and 3.92 (m, CH_{fer}, 4H); 3.78 (s, CH_{fer}, 5H); *3.23* and 3.13 (dd, $^2J_{PH} = 9.8$ Hz and $^3J_{HH} = 1.6$ Hz, 1H, CHP); 1.32 and *1.16* (2d, $J = 6.7$ Hz, 3H, CH_3).

^{31}P NMR (NaOD/D_2O, 81 MHz): δ 28.52 and *26.04* (*2:1*).

EI-MS: $m/z = 383[M^+]$; $317[M^+–P(OH)_2]$; 213[Fc–CH=N^+]; 121[$CpFe^+$]; 91[$^+CH_2Ph$]; 65[Cp^+].

Elemental analysis: Anal. Found:C, 59.17; H, 5.86; N, 3.59%. Calc. for ($C_{19}H_{22}FeNO_2P$): C, 59.55; H, 5.79; N, 3.66.

3.2. Cholesteryl and isopropylidene adenosinyl amino(ferrocenyl)methane phosphonite. Typical procedure

To a suspension of aminophosphonous acid **3a–d** (0.005 mol) in dichloromethane (30 ml), 0.005 mol of an appropriete alcohol (cholesterol or isopropylidene adenosine) and 0.005 mol (1.03 g) of DCC were added. The mixture was then refluxed for 10 h with vigorous stirring, then stirred overnight at room temperature and the procedure repeated during next 7 days. After, the mixture was filtered, the solid residue washed with dichloromethane and then discarded. The filtrate was evaporated, the residue was re-dissolved in chloroform, shaken with charcoal, filtered then chromatographed on cellulose powder and evaporated to obtain the pure product **3a–d** and **4a–d**.

3.2.1. Cholesteryl N-benzylamino(ferrocenyl)methane phosphonite (**4a**)

Y = 1.07 g (29%); oily liquid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.32 (m, PhH, 5H); 6.94 and 6.86 (2d, $^1J_{PH} = 546.3$ Hz, HP, 1H); 5.34 (m, CH–$O_{cholest}$, 1H); 4.26 and 4.17 (m, CH_{fer}, 4H); 4.10 (s, CH_{fer}, 5H); 3.53 (m, CH=$C_{cholest}$, 1H); 2.26 (m, CH_2, 2H); 2.03–1.06 (m, $CH_{cholest}$, 24H); 0.99 (s, CH_3, 3H); 0.91 (d, $J = 9.4$ Hz, CH_3, 3H); 0.85 (d, $J = 6.6$ Hz, CH_3, 3H); 0.66 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.0 ($C_{cholest}$); 141.5 (C_{ipso}); 129.6 (C_{ortho}); 130.4 and 129.6 (2d, $^1J_{CP} = 105.6$ Hz, C–P); 129.2 (C_{meta}); 129.0 (C_{para}); 122.8 ($CH_{cholest}$); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 67.1 ($CH_{cholest}$); 49.1 (CH_2); 48.2, 46.4, 42.8, 40.5, 39.5 ($C_{cholest}$); 39.9, 39.7, 32.9, 32.7, 31.8, 30.2, 25.3, 21.6, 20.9 ($CH_2^{cholest}$); 48.2, 46.4, 42.8, 29.6,

29.4, 28.5 ($CH_{cholest}$); 22.3, 20.3, 18.5 ($CH_3^{cholest}$). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 35.26, 35.14, 34.90, 34.86 (4:4:1:1).

FAB-MS: $m/z = 737[M^+]$; $304[M^+–HP(O)OC_{27}H_{45}]$; 213[Fc–CH=NH]; 107 [$^+CH_2Ph$].

Elemental analysis: Anal. Found: C, 72.94; H, 9.02; N, 2.11%. Calc. for ($C_{45}H_{64}NO_2PFe$): C, 73.25; H, 8.74; N, 1.90.

3.2.2. Cholesteryl N-furfurylamino(ferrocenyl)methane phosphonite (**4b**)

Y = 2.05 g (56%); oily liquid.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.43 (m, $^5H_{fur}$, 1H); 6.83 and 6.75 (2d, $^1J_{PH} = 543.9$ Hz, HP, 1H); 6.37 (m, $^3H_{fur}$, 1H); 6.32 (m, $^4H_{fur}$, 1H); 5.37 (m, CH–$O_{cholest}$, 1H); 4.26 and 4.18 (m, CH_{fer}, 4H); 4.10 (s, CH_{fer}, 5H); 3.53 (m, CH=$C_{cholest}$, 1H); 2.28 (m, CH_2, 2H); 2.08-1.06 (m, $CH_{cholest}$, 24H); 1.01 (s, CH_3, 3H); 0.91 (d, $J = 9.4$ Hz, CH_3, 3H); 0.87 (d, $J = 6.8$ Hz, CH_3, 3H); 0.68 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.5 (C^2_{fur}); 149.0 ($C_{cholest}$); 143.1 (C^5_{fur}); 129.8 and 129.0 (2d, $^1J_{CP} = 104.6$ Hz, C–P); 111.2 (C^3_{fur}); 111.0 (C^4_{fur}); 122.8 ($CH_{cholest}$); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 67.1 ($CH_{cholest}$); 47.19 (CH_2); 48.2, 46.4, 42.8, 40.5, 39.5 ($C_{cholest}$); 39.9, 39.7, 32.9, 32.7, 31.8, 30.2, 25.3, 21.6, 20.9 ($CH_2^{cholest}$); 48.2, 46.4, 42.8, 29.6, 29.4, 28.5 ($CH_{cholest}$); 22.3, 20.3, 18.5 ($CH_3^{cholest}$). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 36.23, 36.05, 35.98, 35.85. (6:6:1:1).

FAB-MS: $m/z = 727[M^+]$; $294[M^+–HP(O)OC_{27}H_{45}]$; 213[Fc–CH=NH]; 81 [$^+CH_2Fur$]; 65.1[$Cp^+$].

Elemental analysis: Anal. Found: C, 70.66; H, 8.40; N, 1.75%. Calc. for ($C_{43}H_{62}NO_3PFe$): C, 70.96; H, 8.59; N, 1.92.

3.2.3. Cholesteryl N-diphenylmethylamino(ferrocenyl)methane phosphonite (**4c**)

Y = 2.89 g (71%); m.p.: 65–67 °C.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.51-07.22 (m, ArH, 10H); 7.20 and 7.00 (2d, $^1J_{PH} = 548.4$ Hz, HP, 1H); 5.34 (s, CH, 1H); 4.30 and 4.26 (m, CH_{fer}, 2H); 4.21 (s, CH_{fer}, 5H); 4.13 (s, CH, 1H); 3.63 (m, CH=$C_{cholest}$, 1H); 2.44 (m, CH_2, 2H); 2.04–1.02 (m, $CH_{cholest}$, 24H); 0.99 (s, CH_3, 3H); 0.91 (d, $J = 9.4$ Hz, CH_3, 3H); 0.87 (d, $J = 6.8$ Hz, CH_3, 3H); 0.68 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.0 ($C_{cholest}$); 143.5 (C_{ipso}); 129.0 (C_{meta}); 129.0 and 128.2 (2d, $^1J_{CP} = 105.6$ Hz, C–P); 128.4 (C_{ortho}); 127.0 (C_{para}); 122.8 ($CH_{cholest}$); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 67.1 ($CH_{cholest}$); 56.4 (CH); 48.2, 46.4, 42.8, 40.5, 39.5 ($C_{cholest}$); 39.9, 39.7, 32.9, 32.7, 31.8, 30.2, 25.3, 21.6, 20.9 ($CH_2^{cholest}$); 48.2, 46.4, 42.8, 29.6, 29.4, 28.5 ($CH_{cholest}$); 22.3, 20.3, 18.5 ($CH_3^{cholest}$). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 33.65, 33.58, 32.81, 32.74 (2:2:3:3).

FAB-MS: $m/z = 813[M^+]$; $380[M^+–HP(O)OC_{27}H_{45}]$; 213[Fc–CH=NH]; 167 [$^+CHPh_2$]; 121 [$CpFe^+$]; 65.1 [$Cp^+$].

Elemental analysis: Anal. Found: C, 75.21; H, 8.42; N, 1.93%. Calc. for ($C_{51}H_{68}FeNO_2P$): C, 75.26; H, 8.42; N, 1.72.

3.2.4. Cholesteryl N-(R)-α-methylbenzylamino(ferrocenyl)methane phosphonite (**4d**)

Y = 2.37 g (63%); m.p.: 100–102 °C.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.43-7.33 (m, ArH, 5H); 7.05 and 7.01 (2d, $^1J_{PH} = 537.1$ Hz, HP, 1H); 5.40 and 5.37 (m, CH–$O_{cholest}$, 1H); 4.27 and 4.19 (m, CH_{fer}, 4H); 4.14 (s, CH_{fer}, 5H); 3.60 (2m, CH–N, 1H); 3.67 (d, $^1J_{PH} = 13.7$ Hz, 1H); 3.52 (m, C=$CH^{cholest}$, 1H); 2.28 (m, $CH_2C–O^{cholest}$, 2H); 2.03–1.11 (m, $CH^{cholest}$ and CH_3 33H); 1.00 (s, CH_3, 3H); 0.90 (d, $J = 9.2$ Hz, CH_3, 3H); 0.87 (d, $J = 6.6$ Hz, 2xCH_3, 6H); 0.67 (s, CH_3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 149.0 ($C_{cholest}$); 141.53 (C_{ipso}); 129.6 (C_{ortho}); 125.4 and 124.8 (2d, $^1J_{CP} = 105.6$ Hz, C–P); 129.2 (C_{meta}); 129.0 (C_{para}); 122.8 ($CH_{cholest}$); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 67.1 ($CH_{cholest}$); 49.4 (CH); 48.2, 46.4, 42.8, 40.5, 39.5 ($C_{cholest}$); 39.9, 39.7, 32.9, 32.7, 31.8, 30.2, 25.3, 21.6, 20.9 ($CH_2^{cholest}$); 48.2, 46.4, 42.8, 29.6, 29.4, 28.5 ($CH_{cholest}$); 24.6 (CH_3); 22.3, 20.3, 18.5 ($CH_3^{cholest}$). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 35.72, 35.37 (1:2).

FAB-MS: $m/z = 751[M^+]$; $318[M^+–HP(O)OC_{27}H_{45}]$; 213[Fc–CH=NH]; 105 [$^+CH(CH_3)Ph$]; 65.1[$Cp^+$].

Elemental analysis: Anal. Found: C, 73.40; H, 8.56; N, 1.93%. Calc. for ($C_{46}H_{66}FeNO_2P$): C, 73.49; H, 8.85; N, 1.86.

3.2.5. O,O′-iso-propylideneadenosinyl N-benzylamino-(ferrocenyl)methane phosphonite (**5a**)

Y = 0.82 g (25%); m.p.: 66–69 °C.

^1H NMR ($CDCl_3$, 200 MHz): δ 8.34 (s, $AdenH_2$, 1H); 8.15 (s, $AdenH_8$, 1H); 7.35 (m, PhH, NH_2, 7H); 7.13 and 6.98 (2d, $^1J_{PH} = 550.3$ Hz, HP, 1H); 6.12 (m, H^1_{ryb}, 1H); 5.33 (m, H^3_{ryb}, 1H); 4.97 (m, H^2_{ryb}, 1H); 4.26 and 4.17 (m, H^1_{ryb}, CH_{fer}, 5H); 4.12 (s, CH_{fer}, 5H); 3.56 (m, $CH_2^{ryb,}$, 2H); 1.54 and 1.32 (2s, CH_3, 2x3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9 (C_{ade}); 152.0 (CH_{ade}); 147.9 (CH_{ade}); 144.8 (C_{ade}); 141.5 (C_{ipso}); 129.6 (C_{ortho}); 130.4 and 129.3 (2d, $^1J_{CP} = 105.6$ Hz, C–P); 129.2 (C_{meta}); 129.0 (C_{para}); 128.4 (CH_{ade}); 85.0, 75.7, 72.8, 70.5 (CH_{ryb}); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 60.5 (CH_2^{ryb}); 49.1 (CH_2). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 37.95, 37.68, 37.41 (*1:2:1*).

FAB-MS: $m/z = 658[M^+]$; $304[M^+–HP(O)OAden]$; 213[Fc–CH=NH]; $135[C_5H_5N_5^+]$ 91[$^+CH_2Ph$].

Elemental analysis: Anal. Found: C, 56.84; H, 5.31; N, 12.73%. Calc. for ($C_{31}H_{35}FeN_6O_5P$): C, 56.55; H, 5.36; N, 12.76.

3.2.6. O,O′-iso-propylideneadenosinyl N-furfurylamino (ferrocenyl)methane phosphonite (**5b**)

Y = 2.01 g (62%); m.p.: 86–89 °C.

^1H NMR ($CDCl_3$, 200 MHz): δ 8.35 (s, $AdenH_2$, 1H); 8.17 (s, $AdenH_8$, 1H); 7.61 (m, $^5H_{fur}$, 1H); 7.38 (s, NH_2,

2H); 7.21 and 7.09 (2d, $^1J_{PH} = 554.6$ Hz, HP, 1H); 6.41 (m, $^3H_{fur}$, 1H); 6.31 (m, $^4H_{fur}$, 1H); 6.12 (m, H^1_{ryb}, 1H); 5.34 (m, H^3_{ryb}, 1H); 4.97 (m, H^2_{ryb}, 1H); 4.24 (m, H^1_{ryb}, 1H); 4.10 (s, CH_{fer}, 5H); 4.00 and 3.94 (m, CH_{fer}, 4H); 3.56 (m, $CH^{ryb,}_2$, 2H); 1.54 and 1.32 (2s, CH_3, 2x3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9 (C_{ade}); 152.0 (CH_{ade}); 149.53 (C^2_{fur}); 147.9 (CH_{ade}); 144.8 (C_{ade}); 143.09 (C^5_{fur}); 129.8 and 128.7 (2d, $^1J_{CP} = 104.6$ Hz, C–P); 128.4 (CH_{ade}); 111.2 (C^3_{fur}); 111.0 (C^4_{fur}); 85.0, 75.7, 72.8, 70.5 (CH_{ryb}); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 60.5 (CH^{ryb}_2); 47.2 (CH_2). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 43.03, 42.87, 42.69, 42.53 (*2:2:1:1*).

FAB-MS: $m/z = 648[M^+]$; 294[M^+–HP(O)OAden]; 213[Fc–CH=NH]; 81 [$^+CH_2$Fur]; 65.1[Cp^+].

Elemental analysis: Anal. Found: C, 53.94; H, 5.31; N, 12.73%. Calc. for ($C_{29}H_{33}FeN_6O_6P$): C, 53.72; H, 5.13; N, 12.96.

3.2.7. *O,O′-iso-propylideneadenosinyl N-diphenylmethylamino(ferrocenyl)methane phosphonite (**5c**)*

Y = 2.39 g (65%); m.p.: 104–107 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.34 (s, $AdenH_2$, 1H); 8.15 (s, $AdenH_8$, 1H); 7.45–7.35 (m, ArH, 10H); 6.78, 6.66, 6.61 and 6.58 (4d, $^1J_{PH} = 570.4$, 579.3, 585.6 and 592.0 Hz, HP, 1H); 6.21 (m, H^1_{ryb}, 1H); 5.43 (m, H^3_{ryb}, 1H); 5.07 (m, H^2_{ryb}, 1H); 4.30 (m, H^1_{ryb}, 1H); 4.18 and 4.12 (m, CH_{fer}, 4H); 4.06 and 4.04 (2s, CH_{fer}, 5H); 3.56 (m, $CH^{ryb,}_2$, 2H); 1.54 and 1.32 (2s, CH_3, 2x3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9 (C_{ade}); 152.0 (CH_{ade}); 147.9 (CH_{ade}); 144.8 (C_{ade}); 143.53 (C_{ipso}); 129.0 (C_{meta}); 129.0 and 128.4 (2d, $^1J_{CP} = 105.6$ Hz, C–P); 128.4 (C_{ortho}); 126.99 (C_{para}); 128.4 (CH_{ade}); 85.0, 75.7, 72.8, 70.5 (CH_{ryb}); 70.9 (C_{fer}); 69.3 (Cp); 69.0 (C_{fer}); 68.7 (C_{fer}); 60.5 (CH^{ryb}_2); 56.4 (CH). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 37.80, 37.53, 37.23, 37.14 (*1:1:3:3*).

FAB-MS: $m/z = 734[M^+]$; 380[M^+–HP(O)OAden]; 213[Fc–CH=NH]; 167 [$^+CHPh_2$].

Elemental analysis: Anal. Found: C, 60.24; H, 5.51; N, 11.73%. Calc. for ($C_{51}H_{68}FeNO_2P$): C, 60.50; H, 5.35; N, 11.44.

3.2.8. *O,O′-iso-propylideneadenosinyl N-(R)-α-methylbenzylamino(ferrocenyl)methane phosphonite (**5d**)*

Y = 2.32 g (69%); m.p.: 111–114 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.35 (s, $AdenH_2$, 1H); 8.16 (s, $AdenH_8$, 1H); 7.45–7.35 (m, ArH, 10H); 6.76 and 6.65 (4d, $^1J_{PH} = 569.1$, 571.3, 567.6 and 572.0 Hz, HP, 1H); 6.21 (m, H^1_{ryb}, 1H); 5.43 (m, H^3_{ryb}, 1H); 5.07 (m, H^2_{ryb}, 1H); 4.30 (m, H^1_{ryb}, 1H); 4.18 and 4.12 (m, CH_{fer}, 4H); 4.06 and 4.04 (2s, CH_{fer}, 5H); 3.60 (2m, CH–N, 1H); 3.56 (m, $CH^{ryb,}_2$, 2H); 1.54 and 1.32 (2s, CH_3, 2x3H); 1.12 (d, $J = 9.2$ Hz, CH_3, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 154.9 (C_{ade}); 152.0 (CH_{ade}); 147.9 (CH_{ade}); 144.8 (C_{ade}); 141.5 (C_{ipso}); 129.6 (C_{ortho}); 125.4 and 124.2 (d, $^1J_{CP} = 105.6$ Hz, C–P); 129.2 (C_{meta}); 129.0 (C_{para}); 128.4 (CH_{ade}); 85.0, 75.7, 72.8, 70.5 (CH_{ryb}); 70.9 (C_{fer}); 69.3 (Cp); 68.9 (C_{fer}); 68.7 (C_{fer}); 60.5 (CH^{ryb}_2); 49.4 (CH); 24.6 (CH_3). ^{31}P NMR ($CDCl_3$, 81 MHz): δ 38.12, 37.83 (1:2).

FAB-MS: $m/z = 672[M^+]$; 318[M^+–HP(O)OAden]; 213[Fc–CH=NH]; 107 [$^+CH(CH_3)Ph$].

Elemental analysis: Anal. Found: C, 57.24; H, 5.34; N, 12.73%. Calc. for ($C_{32}H_{37}FeNO_2P$): C, 57.15; H, 5.55; N, 12.50.

3.3. *N′,N″-dicyclohexyl-N-guanidyno)(ferrocenyl)methane phosphonous acid. Typical procedure*

To a suspension of aminophosphonous acid **3a–d** (0.005 mol) in dichloromethane (30 ml), 0.005 mol (1.03 g) of DCC were added. The mixture was then refluxed for 10 hours with vigorous stirring, then stirred overnight at room temperature and the procedure repeated during next 7 days. After, the mixture was filtered through the cellulose powder pad and evaporated to obtain the product **6a–b**.

3.3.1. *N′,N″-dicyclohexyl-N-benzyl-guanidyno)(ferrocenyl)methane phosphonous acid (**6a**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43 (m, PhH, 10H); 6.83 (d, $^1J_{PH} = 543.9$ Hz, HP, 1H); 4.28 (m, CH_2, 2H); 4.26 and 4.18 (m, CH_{fer}, 4H); 4.10 (s, CH_{fer}, 5H); 1.40 and 1.35 (2m, $H_{cyclohex}$, 2×11H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.73 ($C_{guanidine}$); 141.53 (C_{ipso}); 129.63 (C_{ortho}); 130.38 (d, $^1J_{CP} = 105.6$ Hz, C–P); 129.16 (C_{meta}); 128.99 (C_{para}); 70.92 (C_{fer}); 69.27 (Cp); 68.96 (C_{fer}); 68.69 (C_{fer}); 49.07 (CH_2); 34.94, 34.00 ($C_{cyclohex}$); 25.68, 25.48, 25.02, 24.91, 24.72 ($C_{cyclohex}$).

^{31}P NMR ($CDCl_3$, 81 MHz): δ 16.36 (large signal).

FAB-MS: $m/z = 576[M^+]$; 511[M^+–P(OH)$_2$]; 495[M^+–CH_2Ph]; 420[M^+–CH_2Ph-P(OH)$_2$]; 294 [$^+$Fc–CH–NH-CH_2Ph]; 213 [294 [Fc–CH–NH^+].

HRMS: Found: 575.51998; Calc. for ($C_{31}H_{42}FeN_3O_2P$): 575.52009.

3.3.2. *N′,N″-dicyclohexyl-N-furfuryl-guanidyno)(ferrocenyl)methane phosphonous acid (**6b**)*

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.51 and 7.36 (m, $^5H_{fur}$, 2H); 6.83 (d, $^1J_{PH} = 534.2$ Hz, HP, 2H); 6.49 (m, $^3H_{fur}$, $^4H_{fur}$, 2H); 6.31 (m, $^3H_{fur}$, 1H); 6.28 (m, $^4H_{fur}$, 1H); 4.61 (m, CH_2, 2H); 4.17 and 4.15 (m, CH_{fer}, 24H); 4.09 (s, CH_{fer}, 5H); 1.40 and 1.35 (2m, $H_{cyclohex}$, 2×11H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 156.84 ($C_{guanidine}$); 149.53 (C^2_{fur}); 143.09 (C^5_{fur}); 129.80 (d, $^1J_{CP} = 104.6$ Hz, C–P); 111.16 (C^3_{fur}); 110.99 (C^4_{fur}); 70.92 (C_{fer}); 69.27 (Cp); 68.96 (C_{fer}); 68.69 (C_{fer}); 49.07 (CH_2); 34.94, 34.00 ($C_{cyclohex}$); 25.68, 25.48, 25.02, 24.91, 24.72 ($C_{cyclohex}$).

^{31}P NMR ($CDCl_3$, 81 MHz): δ 13.91.

FAB-MS: $m/z = 566[M^+]$; 501[M^+–$P(OH)_2$]; 485 [M^+–CH_2Fur]; 420[M^+–CH_2Fur-$P(OH)_2$]; 294 [$^+$Fc–CH–NH-CH_2Fur]; 213 [Fc–CH–NH^+].

HRMS: Found: 565.48145; Calc. for ($C_{29}H_{40}FeN_3O_3P$): 565.48125.

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