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Palabindela Srinivas,[a,b] Sunchu Prabhakar,[a,b] Floris Chevallier,*[a] Ekhlass Nassar,*[c] William Erb,*[a] Vincent Dorcet,[d] Viatcheslav Jouikov,*[a] Palakodety Radha Krishna*[b] and Florence Mongin[a]

Different ferrocenecarboxamides were synthesized from aminoferrocene and various acid coupling partners such as N_α-Boc-L-tryptophan and *N*-protected sugar amino acids (*N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranoic acid, *N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranoic acid and their corresponding homo- and hetero-dimers). Similarly, reactions between 2-aminoethyl ferrocenecarboxylate and *N*-protected sugar amino acids afforded compounds with a carboxamide functional group remotely positioned from the ferrocene core. The X-ray diffraction structure of one of them showed the presence of an intermolecular hydrogen bond between the amide functional groups. Carbonylamino (or carbonyloxy) and oxycarbonyl 1,2-disubstituted ferrocenes were prepared either as racemic mixtures or in enantiomerically pure (S_P) form. Their electrochemical evaluation revealed distinctive features. Interestingly, the enantiomerically pure ferrocene diester showed a large potential shift (+45 mV) in the presence of L-glutamic acid. Finally, some of the synthesized ferrocenes were evaluated for their antibacterial, antifungal and antiproliferative (MCF-7) activities.

Introduction

As a redox-active molecule, ferrocene has fascinated scientists for its applications in fields such as materials science and medicinal chemistry. The incorporation of ferrocenes in peptides[1] and carbohydrates[2] in order to achieve new properties has grown rapidly in the last few decades. Such scaffolds also proved to be bactericidal and fungicidal,[3] as well as endowed with cytotoxic[3c,4] activities. Besides, ferrocenes bearing amino acid chains at their 1,1'-positions can exhibit hydrogen bonds, hydrophobic interactions and specific conformations, and have therefore been the purpose of structural investigations.[5] Due to their ideal electrochemical properties, ferrocene derivatives are also considered as good candidates for incorporation in sensors.[1c,2a,6] Consequently, several research publications are devoted to the synthesis of functionalized ferrocenes,[7] and notably when linked to biomolecules.[8]

With the aim of identifying suitable scaffolds either for molecular recognition or endowed with bioactivities, we embarked on the synthesis of new ferrocene derivatives. Herein, we notably describe the synthesis of monosubstituted ferrocenes containing fragments based on 3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranose, 3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose and 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, and of 1,2-disubstituted ferrocenes. While electrochemistry was carried out on various ferrocene esters, structure determination by X-ray diffraction proved possible in one case. Furthermore, numerous synthesized ferrocene amides and esters were screened for their antibacterial and antifungal activity, as well as their antiproliferative potential against MCF-7.

Results and discussion

Synthesis

We first considered the access to *N*-functionalized aminoferrocenes. Towards this purpose, aminoferrocene (**1**)

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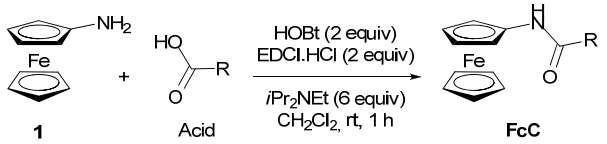
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of the compounds, ^{1}H and ^{13}C NMR spectra of the new compounds, and X-ray crystallographic data. CCDC 1475360 (**FcE-1**). See DOI: 10.1039/x0xx00000x

was prepared by (i) deprotometalation of ferrocene[9] followed by iodolysis,[10] and (ii) treatment of the iodide with phthalimide in the presence of Cu_2O in acetonitrile followed by deprotection.[11] Peptidic coupling was next performed in the presence of 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)[12] from **1** by using N_α-Boc-L-tryptophan (Boc-Trp-OH), the (*N*-protected) Sugar Amino Acids (SAA) *N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranoic acid (**SAA-1**) and *N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranoic acid (**SAA-2**), as well as the corresponding homodimers (**SAA-3** and **SAA-4**) and heterodimer (**SAA-5**) as partners, to afford the respective Ferrocene Carboxamides **FcC-0** to **FcC-5** in yields ranging from 60 to 66% (Table 1). Further, amine deprotection of **FcC-0** by trifluoroacetic acid (TFA) and peptidic coupling with Boc-Trp-OH provided **FcC-6** in 63% yield (Scheme 1).

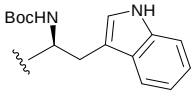
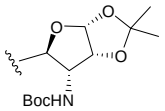
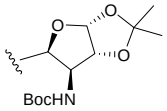
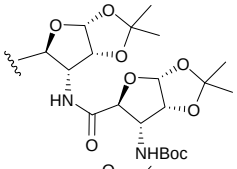
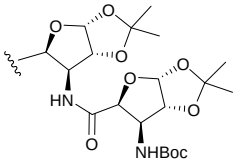
We next turned to sugar-based derivatives of ferrocenecarboxylic acid. Prepared by esterification using *N*-Boc ethanolamine and ferrocenecarboxylic acid, 2-(*tert*-butoxycarbonylamino)ethyl ferrocenecarboxylate[13] underwent amine deprotection followed by peptidic coupling with *N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-ribofuranoic acid (**SAA-1**) and *N*-Boc-3-amino-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranoic acid homodimer (**SAA-4**) to respectively furnish the Ferrocene Esters **FcE-1** (65% yield) and **FcE-4** (62% yield) (Scheme 2, Figure 1).

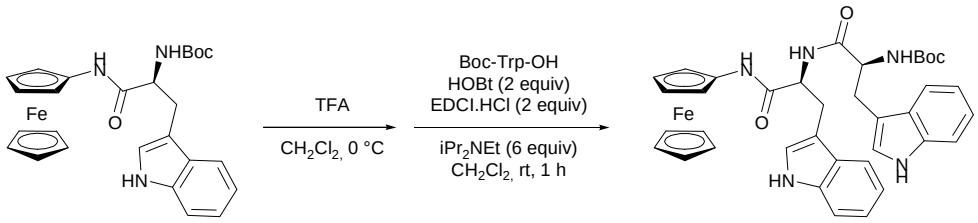
The intermolecular hydrogen bond detected between amide functions in the case of **FcE-1** led us to synthesize other 2-substituted ferrocenecarboxylic derivatives. We chose 2-iodoferrocenecarboxylic acid (**7**, Scheme 3) as the starting material. Thus, (±)-2-iodoferrocenecarboxylic acid (***rac*-7**) was generated from methyl ferrocenecarboxylate by (i) deprotonative metalation using the mixed lithium-zinc base *in situ* prepared from $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (TMP = 2,2,6,6-tetramethylpiperidino, 1.5 equiv) in THF (THF = tetrahydrofuran) at room temperature followed by iodolysis as described previously,[14] and (ii) saponification of the ester.

Table 1 Synthesis of the Ferrocene Carboxamides **FcC-0** to **FcC-5**.



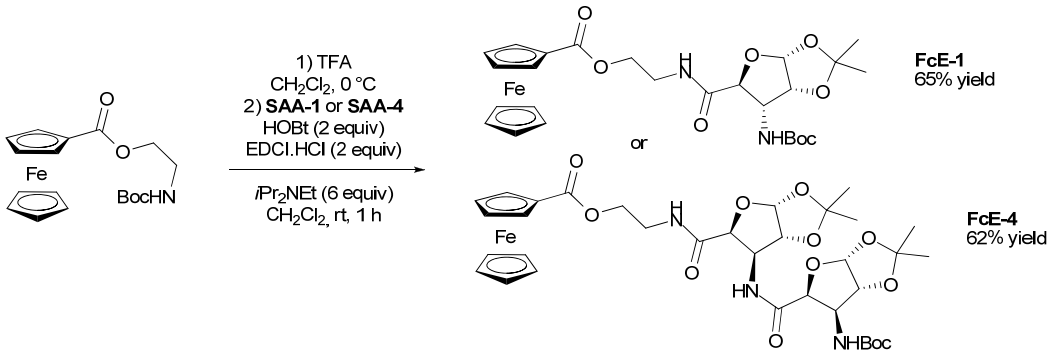
1 Acid **FcC**

Entry	Acid	-R	**FcC**, yield[a] (%)
1	Boc-Trp-OH		**FcC-0**, 66
2	**SAA-1**		**FcC-1**, 62
3	**SAA-2**		**FcC-2**, 60
4	**SAA-3**		**FcC-3**, 62
5	**SAA-4**		**FcC-4**, 63

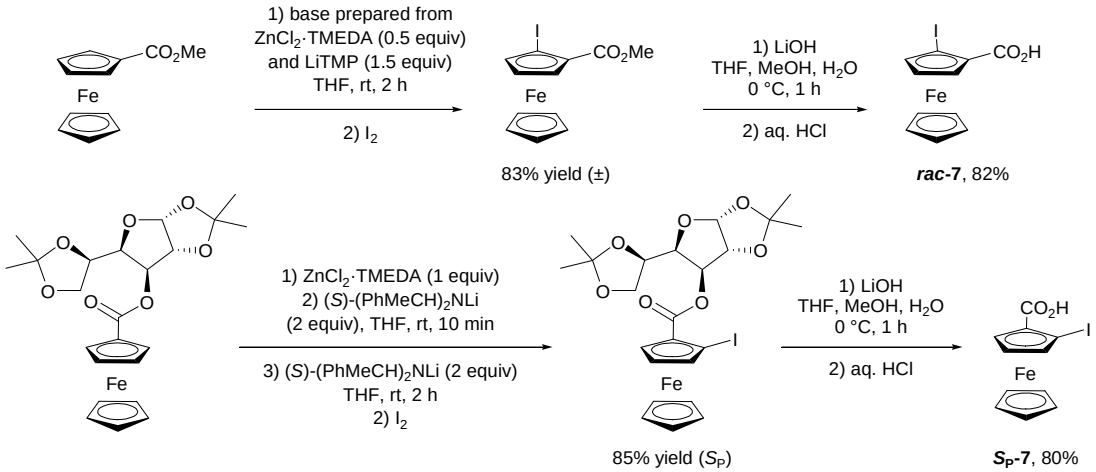


FcC-0 **FcC-6**, 63% yield

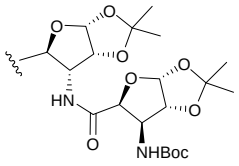
Scheme 1 Synthesis of the Ferrocene Carboxamide **FcC-6**.



Scheme 2 Synthesis of the Ferrocene Esters **FcE-1** and **FcE-4**.

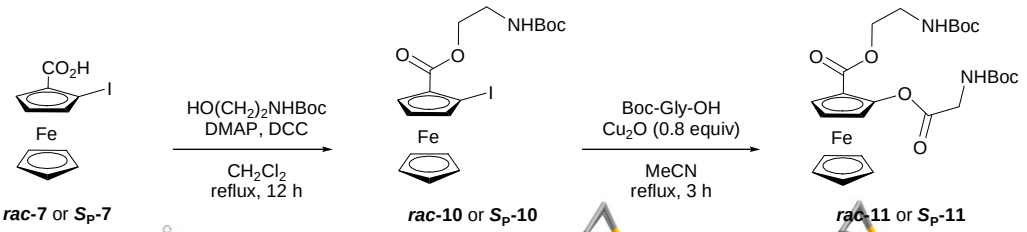


Scheme 3 Synthesis of 2-iodoferrocenecarboxylic acid either as a racemic mixture (***rac*-7**, top) or enantiomerically pure (**S_P-7**, bottom).

6	**SAA-5**		**FcC-5**, 63

[a] Yield after purification by column chromatography.

Corresponding S_P-2-iodoferrocenecarboxylic acid (**S_P-7**)[15] was synthesized from 3-*O*-(ferrocenecarbonyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose by (i) deprotonative metalation in THF using lithium (*S*)-bis(1-phenylethyl)amide (2 x 2 equiv at 10 min interval) through a *double asymmetric induction* process in the presence of $ZnCl_2$·TMEDA (1 equiv) as *in situ* trap, followed by iodolysis as described previously,[16] and (ii) saponification of the ester.



Scheme 5 Synthesis of ferrocene diester **11** either as racemic mixture or enantiomerically pure.

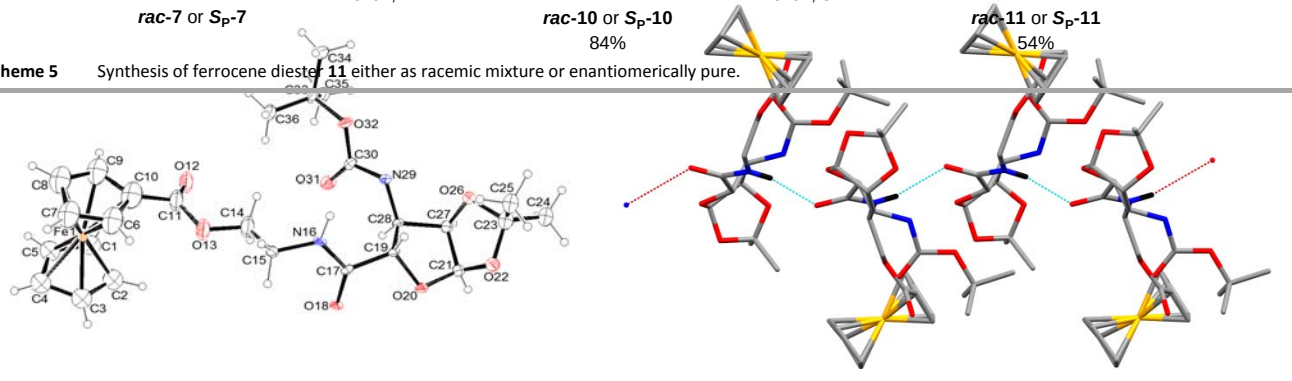


Fig. 1 Left: ORTEP diagram (30% probability) of **FcE-1**. Right: visualization of the intermolecular hydrogen bond (2.996 Å); H atoms bound to C atoms are omitted for clarity.

Both 2-substituted ferrocenecarboxamides ***rac*-8** and ***S*$_P$-8** were synthesized in 84% yield, respectively from ***rac*-7** and ***S*$_P$-7**, by HOBt/EDCI-mediated peptidic coupling[12] using ethyl glycinate hydrochloride (H-Gly-OEt.HCl) as partner. Treatment with *N*-protected glycine Boc-Gly-OH in the presence of Cu_2O at acetonitrile reflux[11] led to the substitution products ***rac*-9** and ***S*$_P$-9** in 50% yield (Scheme 4).

Ferrocene diesters ***rac*-11** and ***S*$_P$-11** were similarly obtained by substitution from respectively ***rac*-10** and ***S*$_P$-10** after esterification of ***rac*-7** and ***S*$_P$-7** with *N*-Boc ethanolamine under classical conditions (Scheme 5).[17]

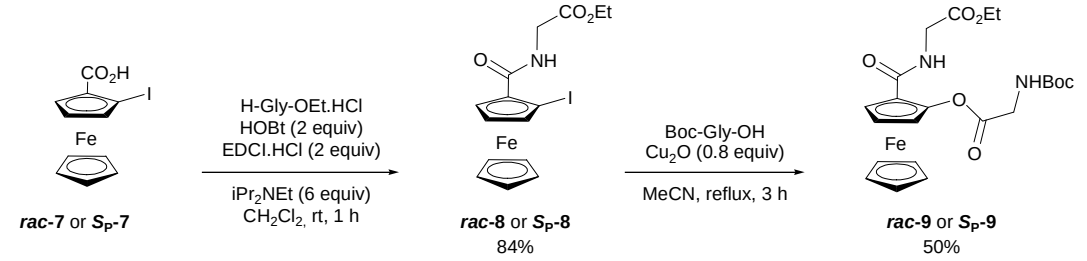
Electrochemistry

The synthesized ferrocene conjugates being redox-active, we explored the electrochemical properties of **FcE-1**, **FcE-4**, ***rac*-9**, ***S*$_P$-9**, ***rac*-11** and ***S*$_P$-11** by voltammetry aiming to explore the suitability of this analytical method for the study of their behavior and intermolecular interactions with biomolecules.

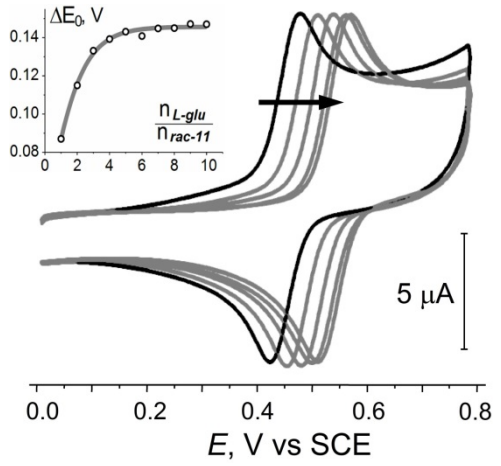
Being oxidized at a glassy carbon (GC) disk electrode in CH_3CN/0.1 M Bu_4NBF_4, all these ferrocene derivatives show reversible oxidation signals (Figure 2) with E_0 slightly superior to that of non-substituted ferrocene (0.31 V vs SCE[18], Table 2). Their peak currents i_p are proportional to the substrate concentration while $i_p/v^{1/2}$ is invariant with the scan rate, attesting diffusional character of the process.[19] From comparison with the i_p of one-electron oxidation of ferrocene,[20] the electron stoichiometry was found to be n = 1 in all cases.

Figure 2 Voltammetry of ***rac*-11** (2 mmol L^{-1}) alone (black), and the shift of its oxidation signal (grey) in the presence of L-glutamic acid (1, 2, 3 and 8 equiv) at a GC disk electrode in CH_3CN/0.1 M Bu_4NBF_4. Scan rate v = 200 mV s^{-1}. T = 22 °C.

Interestingly, the voltammogram of racemic ***rac*-9** looks different compared to other curves in this series (Figure 3, a). First derivative voltammogram allows distinguishing two close electron transfers (each with n ≅ 0.5) with 36 mV difference between E_0^1 and E_0^2 (Figure 3, b). First oxidation of ***rac*-9** (E_0^1 = 0.385 V) occurs at practically same potential as that of pure ***S*$_P$-9** (E_0 = 0.380 V) suggesting that it is related to the electron withdrawal from the same stereoisomer; second step at slightly more positive potentials thus corresponds to the oxidation of its enantiomer (***R*$_P$-9**) present in the 50:50 ratio. It is to note that in the pair ***rac*-11** and ***S*$_P$-11** this feature is not observed. Since the ferrocene derivatives ***rac*-11** and ***S*$_P$-11** are 1,2-carboxy-substituted while ***rac*-9** and ***S*$_P$-9** have an amido-substituent in place of one carboxy group, one can suppose that some intramolecular NH···O=C coordination via an 8-membered cyclic structure might account for this; the fact that both oxidations (at E_0^1 and E_0^2) of ***rac*-9** and ***S*$_P$-9** occur at less positive potentials than those of ***rac*-11** and ***S*$_P$-11** (Table 2) is probably also related to this difference.



Scheme 4 Synthesis of 2-substituted ferrocenecarboxamides **8** and **9** either as racemic mixtures or enantiomerically pure.



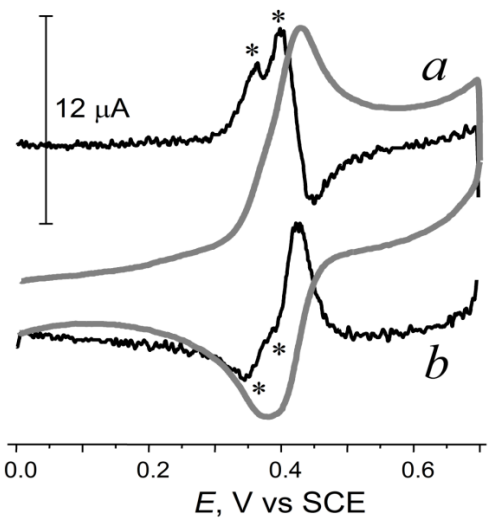


Figure 3 (a, grey) Cyclic voltammogram of ***rac*-9** (2 mmol L^{-1}) at a glassy carbon (GC) disk electrode in CH_3CN/0.1 M Bu_4NBF_4. (b, black) First derivative; two redox pairs are marked with asterisks. v = 200 mV s^{-1}. T = 22 °C.

Table 2 Oxidation potentials of substituted ferrocenes.[a]

Compound		E_0, V vs SCE
1	**FcE-1**	0.355
2	**FcE-4**	0.395
3	***rac*-9**	0.385, 0.420
4	***S*$_P$-9**	0.380
5	***rac*-11**	0.435
6	***S*$_P$-11**	0.390

[a] GC electrode, CH_3CN/0.1 M Bu_4NBF_4. v = 100 mV s^{-1}.

All ferrocene derivatives were systematically oxidized in the presence of a number of amino acids (L-alanine, L-phenylalanine, L-proline, L-glutamic acid, L-aspartic acid, *N*-α-acetyl-L-histidine and *trans*-4-hydroxy-L-proline) that might possibly be complementary to their peptide chains. Although some alteration of the oxidation potentials E_0 was in fact observed, e.g. for **FcE-1**, ***rac*-9** and ***S*$_P$-9**, the ΔE_0 values were not large enough to serve as a reliable analytical signal. For instance, ***S*$_P$-9** showed ΔE_0 of +25, +12 and +10 mV in the presence of L-glutamic acid, L-histidine and L-phenylalanine, respectively; for ***rac*-11**, maximal value of ΔE_0 = +20 mV was observed in the presence of L-phenylalanine. At the same time, **FcE-4** did not show any shift in E_0 within the experimental uncertainty ($\Delta E_0 \cong 5$ mV).

In contrast, ***S*$_P$-11** and ***rac*-11** reveal a pronounced shift of E_0 (Figure 2) upon addition of L-glutamic acid. Its maximal value (for ***rac*-11**, ΔE_0 = 140 mV) is attained at the molar ratio superior to 1:1 (Figure 2, inset) indicating some dynamic equilibrium between the complexed and free forms in the solution. At this point, the origin of such important shift in the presence of L-glutamic acid is not yet clear. Nevertheless, on the basis of precedents in the literature concerning binding properties of 1,1'- and 1,3-disubstituted ferrocenes and their impact on the oxidation E_0,[21] a more important inductive effect of the ferrocene substituents, due to ***S*$_P$-11** acting as a polytopic ligand, could be advanced to rationalize this result.

Biological evaluation

The synthesized Ferrocene Carboxamides **FcC-0** to **FcC-3**, **FcC-5** and **FcC-6**, and Ferrocene Esters **FcE-1** and **FcE-4** were screened for their antibacterial activity against Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria, and for their antifungal activity against *Candida albicans* (Table 3). The tested compounds were found to have a moderate effect against Gram-negative bacteria (*E. coli*) except in the case of **FcE-4** for which an activity similar to that of ciprofloxacin was detected. A moderate effect was similarly noted against Gram-positive bacteria (*Staphylococcus aureus*) for most of the compounds evaluated; in the case of **FcC-1** and **FcE-4**, an activity similar to that of ciprofloxacin was observed. For their antifungal activity, **FcE-1** and **FcE-4** gave the best results against *Candida albicans* when compared with the reference drug (nystatin).

Table 3 Bactericidal and fungicidal activity of the compounds **FcC-0** to **FcC-3**, **FcC-5**, **FcC-6**, **FcE-1**, **FcE-4**, ciprofloxacin and nystatin.[a]

Compound	*Escherichia coli*	*Staphylococcus aureus*	*Candida albicans*
FcC-0	+++	++	----
FcC-1	+++	++++	++
FcC-2	++	+++	----
FcC-3	+++	++	++
FcC-5	++	++	----
FcC-6	++	+++	----
FcE-1	++	+++	++++
FcE-4	++++	++++	++++
ciprofloxacin	++++	++++	----
nystatin	----	----	++++

[a] The diameters of zones of inhibition are given in mm. Stock solution: 5 μg in 1 mL of DMF; 0.1 mL of stock solution in each hole of each paper disk. +: <15 mm; ++: 15–24 mm; +++: 25–34 mm; ++++: 35–44 mm, etc.

A study has also been carried out to investigate the cytotoxic potential of the derivatives **FcC-0** to **FcC-3** and **FcC-6** (Table 4). The antiproliferative activity of the derivatives was determined using breast cancer cell line MCF-7, which is an invasive differentiated mammary epithelial breast cancer cell line used worldwide to screen and compare the antiproliferative activity of new molecules vs standard anticancer compounds. The compounds **FcC-1** and **FcC-2** showed low activity while **FcC-0**, **FcC-3** and **FcC-6** were found to be more effective and exhibited an activity slightly lower than that of the reference standard doxorubicin. The compounds **FcC-0** and **FcC-6**, made from N_α-Boc-L-tryptophan, proved more active than the sugar-based derivatives.

Table 4 Cytotoxic activity of the compounds **FcC-0** to **FcC-3**, **FcC-6** and doxorubicin against MCF-7.[a]

Compound	IC_{50} (µg/mL)
FcC-0	4.6
FcC-1	11.3
FcC-2	10.0
FcC-3	6.0
FcC-6	4.4
doxorubicin	3.5

[a] IC50 is defined as the concentration which results in a 50% decrease in the cell number as compared with that of the control structures in the absence of an inhibitor.

Conclusions

Various ferrocene-based amides and esters were synthesized and screened for their antibacterial and antifungal activity, as well as their cytotoxic potential against MCF-7. All the ferrocene derivatives studied by voltammetry exhibit reversible oxidation at close potentials reflecting quite weak (inductive) influence of the substituent on the redox-active ferrocene unit. Quite surprisingly, two stereoisomers of racemic ***rac*-9** in the acetonitrile solution show close but distinct individual oxidation steps of their ferrocene units while those of ***rac*-11** are not redox-distinguishable. In general, analytical response of ferrocene as redox marker in these molecules is not specific to external amino acids. If one cannot expect strong variation in oxidation E_0 with single coordination (no strong variation of the electronic effects of the substituents, neither difference in diffusion coefficients), things might be different with ditopic ligands.[21] The specific response of ***S*$_P$-11** for the presence of L-glutamic acid certainly merits further consideration.

Experimental

General

All reagents were obtained commercially unless otherwise noted. All reactions were performed in oven-dried glassware (Schlenk tubes) under an argon atmosphere (Air Liquide). All solvents were dried and distilled by standard procedures. Flash column chromatography separations were achieved on silica gel (Merck-Geduran Si 60, 63-200 µm).

3-Amino-3-deoxy-*N*-(*tert*-butoxycarbonyl)-1,2-*O*-isopropylidene-α-D-xylofuranuronic acid (**SAA-2**) as well as the N-Boc protected furanoid sugar amino acids **SAA-3** and **SAA-5** were prepared as described previously.[22]

Melting points were measured on a Kofler apparatus. Optical rotations were measured on a Perkin Elmer 341 polarimeter (λ = 589 nm). Nuclear magnetic resonance spectra were acquired on a Bruker Avance III 300 (300 and 75 MHz for ^{1}H and ^{13}C, respectively) spectrometer. Chemical shifts (δ) in ppm were referenced to the solvent residual peak (^{1}H) or to the central peak of the solvent signal (^{13}C).[23] High-resolution mass spectra were recorded on Micromass MS/MS ZABSpecTOF and Bruker MicrOTOF-Q II mass spectrometers.

X-ray data of compound **FcE-1** were collected with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å) at T = 150(2) K using D8 VENTURE Bruker AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[24] and then refined with full-matrix least-square methods based on F^2 (SHELX-97).[25] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[26]

Cyclic voltammetry has been carried out using a PAR 263 potentiostat in a standard 15 mL three-electrode cell fitted with a glassy carbon disk (2.5 mm) working electrode, Pt wire as a counter electrode and a saturated calomel electrode separated from the analyte by an electrolytic bridge filled with the same solution (CH_3CN/0.1 M Bu_4NBF_4). CH_3CN (Aldrich) was distilled from CaH_2 and the supporting salt Bu_4NBF_4 (Acros) was used as received.

General procedure for peptidic coupling[12]

To a stirred, cooled (0 °C) solution of carboxylic acid (1.0 mmol) in CH_2Cl_2 (5 mL) were successively added HOBt (270 mg, 2.0 mmol) and EDCI hydrochloride (383 mg, 2.0 mmol). After 15 min, a solution of amine (1.0 mmol) and *N*,*N*-diisopropylethylamine (775 mg, 6.0 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture. The reaction was stirred for 1 h at room temperature before addition of an aqueous saturated solution of NH_4Cl (20 mL) and $CHCl_3$ (20 mL). The organic layer was successively washed with 1 M HCl (20 mL), water (20 mL), aqueous saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

In vitro antimicrobial and antifungal activity, and cytotoxicity

The assays were performed as reported previously.[27]

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