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Preparation, characterization and biological studies of some novel ferrocenyl compounds

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Reaction of ferrocene with trichloroacetimidates in the presence of TMSOTf as a catalyst gave a series of novel ferrocenyl compounds, 1–7, in good yield and by a simple method using the Friedel–Crafts reaction. Only monosubstituted ferrocenyl compounds were obtained by flash chromatography at room temperature. Attempts to separate the disubstituted ferrocenyl compounds were unsuccessful, even in the presence of excess (2 : 1, 3 : 1 or 4 : 1) of trichloroacetimidates. The prepared compounds have been characterized by ^{1}H NMR, ^{13}C NMR, IR, UV–vis and mass spectra as well as elemental analysis. The prepared compounds showed medium to good antimicrobial activity against *Bacillus subtilis* (+ve), *Staphylococcus aureus* (+ve), *Candida albicans* (yeast), *Escherichia coli* (−ve), *Salmonella typhi* (−ve), *Aspergillus niger* (fungi) and *Fusarium solani* (fungi).

KEYWORDS: ferrocene; trichloroacetimidates; ferrocenyl carbohydrates; characterization; biological activity

INTRODUCTION

Ferrocene is a compound with excellent stability. Unlike many other organometallic compounds, it is completely stable in water and air.[1] In addition, ferrocene is 3.3×10^6 times more reactive than benzene in Friedel–Crafts acylation.[2] This high reactivity is owing to the highly nucleophilic character of the aromatic cyclopentadienyl rings in ferrocene. This reactivity was used to prepare different ferrocenyl compounds which have wide applications in catalysis,[3–6] in the design of new nonlinear optics materials,[7,8] and in preparation of newly biological active compounds.[9,10] It was reported that many ferrocenyl derivatives have good activity against several types of cancer.[11–19] The best example of these derivatives is ferrocifen, which is biologically active against some types of cancer and expected to enter phase I clinical trials soon.[11–20] A recent review has been published that summarizes the important bioorganometallic compounds (including ferrocene) and their pharmaceutical application.[20]

Preparation of ferrocenyl derivatives depends mainly on two common methods. The first method is the Friedel–Crafts acylation of ferrocene with acid halides in the presence of aluminium trichloride as catalyst,[21,22] and the second is the reaction of ferrocenoyl chloride with nucleophilic reagents.[23] The Friedel–Crafts acylation was one of the first well-documented reactions in ferrocene chemistry and also one of the first to implicate the aromatic behaviour of the ferrocene molecule.[21] The use of ferrocenoyl chloride is widespread but it presents some drawbacks. Firstly, ferrocenoyl chloride is moisture-sensitive and should be used immediately after preparation; it also exhibits thermal and photochemical instability.[24] It was also found that ferrocene can readily be metallated. This metallation method resembles the hydrogen-exchange reactions typical of aromatic hydrocarbons. *n*-Butyllithium yields mainly lithioferrocene whereas 1, 1′-dilithioferrocene can be obtained using the Bu^{n}Li.TMEDA complex. These lithiated derivatives are precursors to a wide range of substituted ferrocenyl compounds.[25,26]

Synthesis of different ferrocenyl carbohydrates attracted many authors over the last decade;[27–32] Fernandes *et al*.[27] prepared the carbohydrate-substituted cyclopentadiene at −30 °C by the reaction of 3-(*O*-tert-butyldimethylsilyl)-1,2-*O*-isopropylidene-5-*O*-(*p*-tolylsulfonyl)-a-D-xylofuranose with cyclopentadienyl sodium in dimethylformamide. Ashton *et al*.[28] have coupled aliphatic amines, incorporated with one or three (branched) acylated β-D-glucopyranosyl residues, with the acid chloride of ferrocene carboxylic acid to give four dendrimer-type, carbohydrate-coated ferrocene derivatives.[28]

In this paper, it is aimed to prepare some novel ferrocenyl compounds which may have high biological activity.

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Therefore, the ferrocenyl compounds (**1–7**) were prepared by the reaction of ferrocene with different derivatives of trichloroacetimidates in presence of TMSOTf as a catalyst and using Friedel–Crafts reaction. The first four compounds belong to ferrocenyl carbohydrates (**1–4**), whereas compounds **5–7** are ferrocenyl compounds containing alkane-derivatives. Compounds **1–7** were purified by flash chromatography at room temperature and characterized by several spectroscopic tools, e.g. ^{1}H NMR, ^{13}C NMR, IR, UV–vis and mass spectra as well as elemental analysis. The prepared compounds showed medium to good antimicrobial activity against *Bacillus subtilis* (+ve), *Staphylococcus aureus* (+ve), *Candida albicans* (yeast), *Escherichia coli* (−ve), *Salmonella typhi* (−ve), *Aspergillus niger* (fungus) and *Fusarium solani* (fungus).

EXPERIMENTAL

The solvents used in the article were purified and dried in the usual way. The boiling range of the petroleum ether used was 35–65 °C. Thin-layer chromatography (TLC) was carried out using silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) and was detected by UV lamp. Melting points were determined on a Büchi 510 melting-point apparatus and were uncorrected. The yields refer to analytically pure ferrocene and were not optimized. ^{1}H NMR was recorded in $CDCl_3$ with a Bruker AC 250 (250 MHz) and using TMS (0.00 ppm) or the signals of the deuterated solvent as internal standard. MALDI-MS were measured with a KRATOS Analytical Compact, using 2,5-dihydroxybenzoic acid (DHB) as matrix. Electronic absorptions were recorded on a Shimadzu UV240 automatic spectrophotometer in $CHCl_3$. Trichloroacetimidates were prepared according to the method described in the literature.[33]

General procedure for reaction of trichloro-acetimidates with ferrocene

Trichloroacetimidates (1.4 mmol) dissolved in dry dichloromethane (20 ml) was added to ferrocene (0.26 g, 1.4 mmol) dissolved in dry dichloromethane (20 ml) at room temperature with stirring and under nitrogen atmosphere. Then the catalyst TMSOTf (13 µl, 0.06 mmol) was added with continuous stirring and the reaction mixture was left for 20–90 min. After that, the reaction mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuum. The reaction products were separated and purified at room temperature by flash chromatography using petroleum ether : ethyl acetate (8 : 1). After evaporation of the solvent, the products were separated as yellow to reddish-yellow powders.

*Ferrocenyl 2,3,4,6-tetra-O-benzyl-α-D-mannopyranoside (**1**)*

Reddish-yellow powder (0.53 g, 53%); m. p. 105 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.62$ (m, 2 H, 6-H, 6′-H), 3.72 (m, 1 H, 5-H), 3.82 (m, 1 H, 2-H), 4.00 (dd, $J_{4,3} = J_{4,5} = 9.5$ Hz, 1 H, 4-H), 4.12 (m, 2 H, Cp rings), 4.23 (m, 7 H, Cp rings), 4.41 (m, 1 H, 3-H), 4.53 (d, $J_{gem} = 11.9$ Hz, 1 H, CHPh), 4.60 (m, 2 H, 2 CHPh), 4.70 (m, 2 H, 2 CHPh), 4.77 (d, $J_{gem} = 11.5$ Hz, 1 H, CHPh), 4.81 (d, $J_{gem} = 11.5$ Hz, 1 H, CHPh), 4.98 (d, $J_{gem} = 11.0$ Hz, 1 H, CHPh), 5.26 (d, $J_{1,2} = 1.1$ Hz, 1 H, 1-H), 7.18–7.51 (m, 20 H, Ar-H). MS (MALDI, positive mode, matrix DHB): $m/z = 707.8$. $C_{44}H_{44}O_5Fe$ (708.68) calcd: C, 74.57, H, 6.26; found: C, 74.26, H, 6.43. UV–vis: 440 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3078 (w), 1385 (w), 1109 (m), 1005 (m), 817 (m) and 490 (m).

*Ferrocenyl 2.3, 5.6-di-O-isopropylidene-α-D-mannofuranoside (**2a**)*

Reddish-yellow powder (0.14 g, 23%); m.p. 92 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 1.25, 1.36, 1.40, 1.60$ (4 CH_3), 3.77 (dd, $J_{6,5} = 3.5$, $J_{gem} = 8.0$ Hz, 1 H, 6-H), 3.97 (m, 2 H, 6′-H, 4-H), 4.07 (m, 1 H, 5-H), 4.18 (s, 7 H, Cp rings), 4.41 (m, 2 H, Cp rings), 4.82 (m, 1 H, 2-H), 5.00 (m, 2 H, 1-H, 3-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 25.1, 25.3, 26.4, 27.4$ (4 CH_3), 66.7 (C_6), 67.2, 67.5 (Cp rings), 68.6 (C_5), 68.8, 68.9 (Cp rings), 73.5 (C_3), 80.7 (C_2), 81.4 (C_4), 109.3 (C_1). MS (MALDI, positive mode, matrix DHB): $m/z = 427.4$. UV–vis: 444 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3086 (w), 1390 (w), 1104 (m), 1002 (m), 812 (m) and 494 (m).

*Ferrocenyl 2.3, 5.6-di-O-isopropylidene-β-D-mannofuranoside (**2b**)*

Reddish-yellow powder (0.16 g, 26%); m. p. 92 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 1.29, 1.39, 1.47, 1.48$ (4 CH_3), 3.60 (dd, $J_{6,5} = 3.7$, $J_{gem} = 7.2$ Hz, 1 H, 6-H), 4.15 (m, 8 H, 6′-H, Cp rings), 4.31 (m, 2 H, Cp rings), 4.38 (m, 1 H, 5-H), 4.45 (m, 1 H, 2-H), 4.65 (dd, $J = 3.5$, $J = 6.1$ Hz, 1 H, 3-H), 4.80 (m, 1 H, 1-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 25.2, 25.5, 25.9, 26.7$ (4 CH_3), 66.6 (C_6), 67.9, 68.5, 68.6 (Cp rings), 68.8 (C_5), 73.1 (C_3), 80.7 (C_2), 81.0 (C_4), 82.0 (C_1). MS (MALDI, positive mode, matrix DHB): $m/z = 427.6$. UV–vis: 443 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3080 (w), 1403 (w), 1117 (m), 1011 (m), 822 (m) and 492 (m).

*Ferrocenyl 2,3,4,6-tetra-O-benzyl-α-D-galactopyranoside (**3**)*

Reddish-yellow powder (0.54 g, 55%); m. p. 112 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.70$ (m, 2 H, 6-H, 6′-H), 3.90 (m, 1 H, 3-H), 4.00 (m, 1 H, 2-H), 4.15 (m, 4 H, Cp rings), 4.19 (m, 5 H, Cp rings), 4.37 (m, 2 H, 4-H, 5-H), 4.50 (m, 1 H, CHPh), 4.55 (m, 3 H, 3 CHPh), 4.59 (d, $J_{1,2} = 3.3$ Hz, 1 H, 1-H), 4.68 (d, $J_{gem} = 11.8$ Hz, 1 H, CHPh), 4.80 (m, 2 H, 2 CHPh), 5.03 (d, $J_{gem} = 11.8$ Hz, 1 H, CHPh). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 65.9, 67.3, 67.8, 68.9$ (Cp rings), 69.9 (C_6), 72.9 (C_5), 73.8, 74.8, 75.2, 76.7 (CH_2), 78.2 (C_4), 81.5 (C_2), 84.5 (C_3), 88.2 (C_1), 127.6, 127.7, 127.9, 128.1, 128.3, 128.6, 130.9, 138.2, 138.5, 138.8, 139.2 (Ar-C). MS (MALDI, positive mode, matrix DHB): $m/z = 707.4$. $C_{44}H_{44}O_5Fe$. 0.5 H_2O (716.68) calcd: C, 73.74, H, 6.32; found: C, 73.44, H, 6.47. UV–vis: 444 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3073 (w), 1406 (w), 1097 (m), 998 (m), 815 (m) and 488 (m).

*Ferrocenyl 2,3,5-tri-O-benzyl-α-arabinoside (**4**)*
Reddish-yellow powder(0.5 g, 61%); m.p. 106 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.59$ (m, 2 H, 5-H, 5′-H), 4.09 (m, 8 H, Cp rings, 4-H), 4.21 (m, 4 H, Cp rings, 2-H, 3-H), 4.55 (m, 6 H, 3 CH_2Ph), 4.82 (s, 1 H, 1-H), 7.31 (m, 15 H, Ar-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 67.3$ (C_6), 67.7 (C_5), 68.2, 68.3, 68.7 (Cp rings), 70.2, 71.8, 73.4 (3 CH_2), 81.4 (C_3), 85.3 (C_2), 89.4 (C_1), 127.6, 127.7, 127.8, 128.3, 128.4, 137.7 (Ar-C). MS (MALDI, positive mode, matrix DHB): $m/z = 587.8$. $C_{36}H_{36}O_4Fe$ (588.52) calcd: C, 73.47, H, 6.16; found: C, 73.59, H, 6.49. UV–vis: 443 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3083 (w), 1389 (w), 1119 (m), 1019 (m), 827 (m) and 496 (m).

*N-Phthalimidomethylferrocene (**5**)*
Yellow powder (0.33 g, 69%); m.p. 108 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 4.07$ (m, 2 H, Cp rings), 4.17 (m, 5 H, Cp rings), 4.34 (m, 2 H, Cp rings), 4.58 (s, 2 H, CH_2), 7.60–7.82 (m, 4 H, Ar-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 68.1$, 68.5 (Cp rings), 69.4 (CH_2), 122.9, 131.9, 133.6 (Ar-C), 167.7 (CO). EI-MS ($C_{19}H_{15}O_2Fe$): $m/z = 345.2$. $C_{19}H_{15}NO_2Fe$. $0.75H_2O$ (353.18) calcd: C, 63.62, H, 4.46, N, 3.91 found: C, 63.57, H, 4.47, N, 4.11. UV–vis: 443 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3082 (w), 1399 (w), 1118 (m), 1014 (m), 825 (m) and 487 (m).

*Diphenylmethylferrocene (**6**)*
Yellow powder (0.30 g, 60%); m.p. 109 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.92$ (s, 7 H, Cp rings), 4.07 (s, 2 H, Cp rings), 5.07 (s, 1 H, CH), 7.15 (m, 10 H, Ar-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 67.7$, 68.8 (Cp rings), 91.6 (CH), 126.1, 128.1, 128.8 (Ar-C). EI-MS ($C_{23}H_{20}Fe$): $m/z = 352.3$. UV–vis: 443 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3088 (w), 1412 (w), 1112 (m), 998 (m), 822 (m) and 494 (m).

*3-Ferrocenyl-2-allyl-2,3-dihydro-isoindol-1-one (**7**)*
Yellow powder (0.28 g, 56%); m.p. 102 °C, ^{1}H-NMR (250 MHz, $CDCl_3$): $\delta = 3.70$ (m, 2 H, NCH_2), 4.10 (m, 1 H, Cp rings), 4.30 (m, 7 H, Cp rings), 4.65 (m, 1 H, Cp rings), 5.20 (m, 2 H, CH_2), 5.40 (s, 1 H, CH), 5.80 (m, 1 H, CH), 7.50–7.90 (m, 4 H, Ar-H). ^{13}C-NMR (62.8 MHz, $CDCl_3$): $\delta = 42.2$ (CH_2), 58.7 (CH_2), 67.7, 68.1 (Cp rings), 116.9 (CH), 123.4, 123.6, 128.2, 131.0, 133.4 (Ar-C), 167.4 (CO). EI-MS: $m/z = 357.3$. UV–vis: 443 nm. IR (KBr pellets, cm^{-1}): ferrocenyl group, 3088 (w), 1418 (w), 1119 (m), 1008 (m), 827 (m) and 496 (m).

Antimicrobial studies

Preparation of the discs
A 60 μg sample from the compounds (dissolved in 0.01 ml $CHCl_3$) was added with the help of a micropipette on a paper disc cut prepared from blotting paper (5 mm diameter). The discs were left at room temperature until dry and then applied to the microorganisms grown agar plates.

Preparation of agar plates
Minimal agar was used for the growth of specific microbial species. For the preparation of agar plates for *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi* (bacteria) nutrient agar (2.30 g) obtained from Panreac Quimica SA (Spain) was suspended in freshly distilled water (100 ml), and for *Candida albicans* (yeast), *Aspergillus niger* and *Fusarium solani* (fungi) potato dextrose agar medium (3.9 g/100 ml) was obtained from Merck. It was allowed to soak for 15 min and then boiled in a water bath until the agar was completely dissolved. The mixture was autoclaved for 15 min at 120 °C and then poured into previously washed and sterilized Petri dishes and stored at 30 °C for inoculation.

Procedure of inoculation
Inoculation was done with the help of a platinum wire loop, which was heated to red-hot in a flame, cooled and then used for the application of the microbial strains.

Application of the discs
Sterilized forceps were used for the application of the paper disc on previously inoculated agar plates. When the discs were applied, they were incubated at 37 °C for 24 h for bacteria and yeast and at 28 °C for 48 h for fungi. The zone of inhibition around the disc was then measured in mm.[34]

RESULTS AND DISCUSSION

The reaction of ferrocene with trichloroacetimidates in presence of TMSTOf as a catalyst gave the ferrocenyl carbohydrates (**1–4**) and the other ferrocenyl compounds (**5–7**) with a good yield ranging from 23 to 69% (Fig. 1). All the prepared compounds were separated as yellow to reddish yellow powders. Compounds **1–7** were stable in air, soluble in MeOH, DMF, CH_2Cl_2 and $CHCl_3$ and were purified by flash chromatography. The elemental analysis confirmed that the reaction proceeded by 1 : 1 molar ratio between the reactants. However, our attempts to prepare disubstituted ferrocenyl derivatives were unsuccessful, even in the presence of excess (2 : 1 or 3 : 1 or 4 : 1) of trichloroacetimidates. This result reflects that it is easy to substitute one hydrogen atom in ferrocene to form the monosubstituted ferrocenyl compounds due to the higher nucleophilic character of ferrocene, but it is difficult to obtain the disubstituted ferrocenyl derivatives. The reaction time was ranging from 20 to 90 min and it depended on the substituted moiety.

Two isomers (α- and β-isomers) of compound **2** were separated by flash chromatography in 23 and 26% yield. The structure of each isomer was characterized by the usual methods.

^{1}H NMR spectra

All compounds were characterized by ^{1}H NMR; some of them were characterized by ^{13}C NMR. The NMR spectra of compounds (**1–7**) were carried out in $CDCl_3$ at room

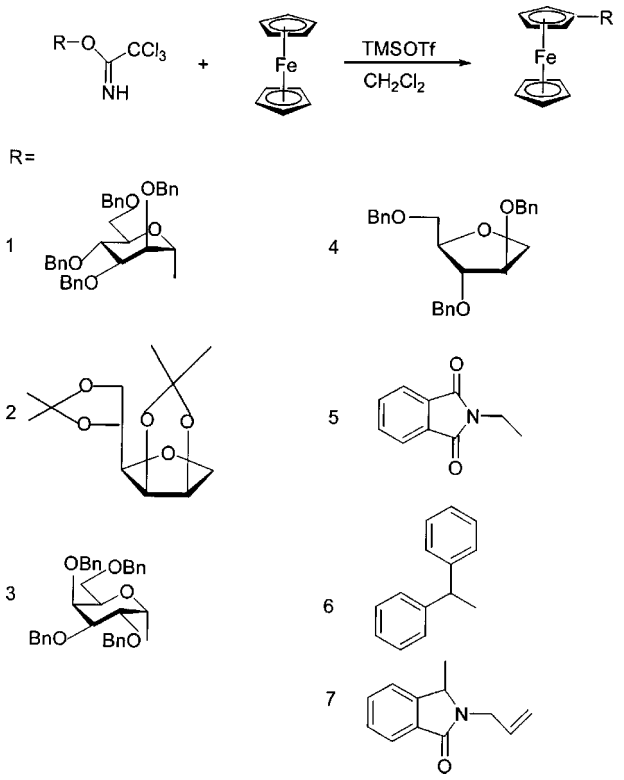

Figure 1. Preparation of the ferrocenyl compounds.

temperature using TMS as internal standard. The results are in accordance with the expected structures. The ^{1}H NMR spectra of compounds **1–7** showed two multiplets for the α- and β-protons for the substituted cyclopentadienyl ring appearing at ca. 4.20 and 4.10 ppm, and a five-proton singlet for the unsubstituted cyclopentadienyl ring in the range 3.90–4.00 ppm.[28] The other signals of the phenyl group in compound **5–7** were found in the expected region, 6.90–7.90 ppm.[33]

In the ^{13}C NMR spectra, the compounds displayed a signal at ca. 68.6 ppm assigned to the unsubstituted cyclopentadienyl ring and three signals at ca. 69.4, 73.3 and 78.6 ppm due to the substituted ring. The signals of the phenyl group in compounds **5–7** were found in the expected regions at ca. 119.2, 127.4, 131.2 and 153.5 ppm.[28] The signals of the CH and CH_2 in compounds **5–7** agree well with other results.[33]

IR spectra

The major bands in the IR spectrum of the ferrocenyl compounds (**1–7**) were found at about 3078, 1412, 1111, 1005, 817 and 490 cm^{-1}. The band at 3078 cm^{-1} was assigned to the C–H stretching band. The band at 1412 cm^{-1} was assigned to the asymmetric C–C stretching band. The 1111 cm^{-1} band was due to the asymmetric ring breathing vibration. The two bands located at 1005 and 817 cm^{-1} were assigned to parallel and perpendicular C–H bands, respectively. The last band at 490 cm^{-1} was assigned to the Fe–Cp stretching frequency.[35–38]

Table 1. Antimicrobial activity data for the prepared compounds

Compound	B.s.	S.a.	C.a.	E.c.	S.t.	A.n.	F.s.
Ferrocene	−	−	+	−	+	−	++++
1	−	+	+	+	+	−	++
2a	+	+	++	+	+	+	+
2b	++	+++	+	+	+++	+	++
3	−	+	++	−	++	+	+
4	+	+	++	−	−	+	+
5	+	−	+	+	+	−	+
6	−	+	++	+	++	+	+
7	+	+	++	−	+	−	+

Inhibition zone diameter in mm (% inhibition): +, 6–9 (33–50%); ++, 10–12 (55–67%); +++, 13–15 (72–83%); ++++, 16–18 (89–100%). Percentage inhibition values were relative to inhibition zone (18 mm) with 100% inhibition.

Electronic spectra

The electronic absorption spectra of compounds **1–7** were nearly the same. A broad and weak band was observed for every compound at ca. 443 nm. This band was attributed to the transition of the 3d electron on iron to either non-bonding or antibonding orbitals of the cyclopentadienyl ring.[38]

On the basis of the physical and spectral data of the prepared compounds (**1–7**) discussed above and also by comparison with other ferrocenyl compounds,[28] the structure of the compounds is illustrated in Fig. 1.

Antimicrobial properties

The prepared compounds were evaluated for their antimicrobial activity against the strains *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhi* (bacteria), *Candida albicans* (yeast), *Aspergillus niger* and *Fusarium solani* (fungi). The compounds were tested at concentration 60 μg/mL in $CHCl_3$ solution using the paper disc diffusion method.[39,40] The diameters of the susceptibility zones were measured in mm and the results are reproduced in Table 1. The susceptibility zones measured were the clear zones around the discs inhibiting the microbial growth. The prepared compounds have medium activity against the mentioned microbes. In comparison with other results[34,36] obtained for different ferrocenyl complexes under the same conditions, the results show that the ferrocenyl complexes are more active than the prepared compounds under investigation. The higher activity of the complexes may be due to the effect of chelation, which increases the powerful and potent bactericidal agents, thus killing more microorganisms than the prepared compounds (**1–7**). On the other hand, such ferrocenyl carbohydrates **1–4** or the other ferrocenyl compounds **5–7** may have significant activity against other diseases or cancers, and we plan further tests in the future.

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