Synthesis, Characterization, and Anti-amoebic Screening of Core-Modified 5,20-Bis{2-{[(alkyl)(alkyl′)amino]methyl}ferrocen-1-yl}-10,15-diphenyl-21,23-dithiaporphyrin (=1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-{[(alkyl)(alkyl′)amino]methyl}ferrocene]) Derivatives

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The synthesis of the first bis-ferrocenyl-substituted core-modified porphyrins, 5,20-bis{2-{[(alkyl)-(alkyl′)amino]methyl}ferrocen-1-yl}-10,15-diphenyl-21,23-dithiaporphyrin derivatives **6a**–**6j**, *via* a multi-step route is reported (*Schemes 1*, *2*, and *4*). The synthesis was carried out through acid-catalyzed ($BF_3 \cdot Et_2O$) condensation of 1,1″-[thiophene-2,5-diylbis(hydroxymethyl)]bis[2-{[(alkyl)(alkyl′)amino]methyl}ferrocenes] **4a**–**4j** with 2,2′-[thiophene-2,5-diylbis(phenylmethylene)]bis[1*H*-pyrrole] (**5b**) in presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (=4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile; DDQ). Characterization of the compounds was done at each step by means of various spectroscopic techniques. The final compounds were screened for *in vitro* anti-amoebic activity against the strain HM1:IMSS of *E. histolytica* (*Table 2*).

Introduction. – The ferrocene is an important structural motif in a great number of biologically active compounds and functional molecules [1–4]. The chemistry of bis-ferrocenyl-substituted core-modified porphyrins (=1,1″-(core-modified porphyrin-diyl)bis[ferrocenes] has remained quite unexplored, in contrast to the well-developed chemistry of ferrocene and its numerous applications in organic synthesis, homogenous catalysis, and material science [5–7]. Recently, core-modified porphyrins or modified porphyrin macrocycles obtained by replacing one of the N-atoms with a chalcogen- or C-atom has led to flurry of research activity [8–11]. The electronic environment of the porphyrin π system is expected to change by insertion of these atoms into the porphyrin core [12]. In addition, they impart different biological properties and are used as potential agents in photodynamic therapy (PDT) due to their ability to absorb long-wavelength radiation. Although the literature provides the synthesis of several ferrocenyl-substituted porphyrins [13–15], to the best of our knowledge there are no reports in the literature on the direct substitution by 2-(aminomethyl)ferrocen-1-yl groups at the *meso* position of a core-modified porphyrin ring. Herein, we report the first successful synthesis of the core-modified porphyrins **6a**–**6j** bearing two ferrocenyl moieties, each one substituted with an aminomethyl group. The synthetic methodology involves a multistep synthesis before the final condensation step. Characterization of the compounds was done at each step by means of various spectroscopic techniques.

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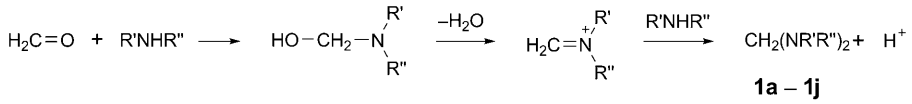
The final compounds were evaluated for their *in vitro* activity in anti-amoebic studies, globally the second leading cause of death [16][17], *i.e.*, for their *in vitro* activity, against the strain HM1:IMSS of *E. histolytica*.

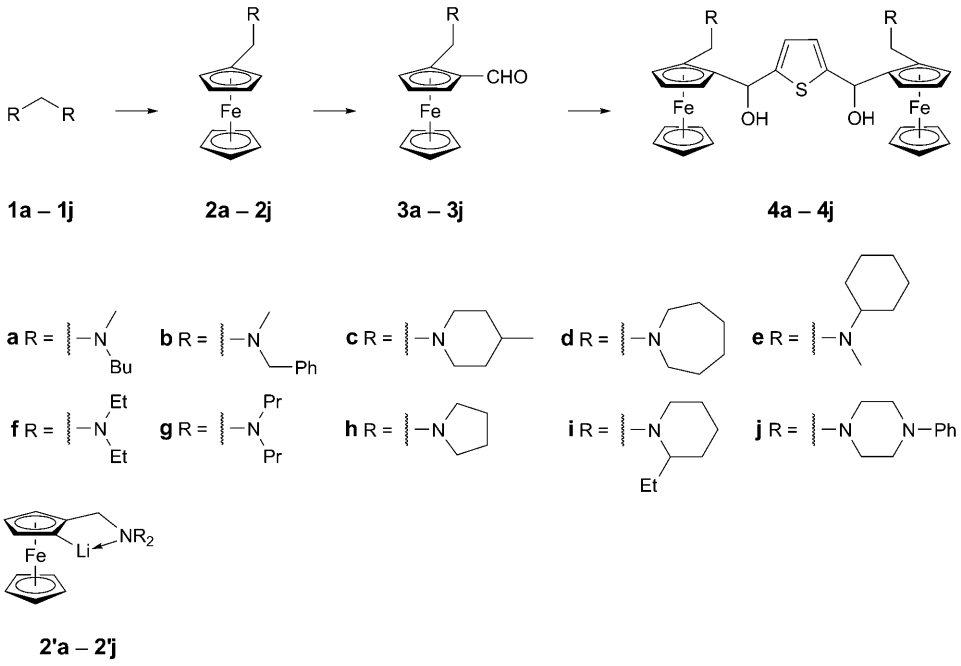
Results and Discussion. – *Synthesis.* The synthesis of bis-ferrocenyl-substituted core-modified porphyrins **6a**–**6j** required the bis[ferrocenes] **4a**–**4j** which were prepared in various steps starting by a well-known reaction of secondary amines R′NHR and HCHO to give the corresponding *N*,*N*,*N*′,*N*′-tetrasubstituted methanediamines **1a**–**1j** (*Scheme 1*).

Scheme 1



Then the 1-(aminomethyl)ferrocenes **2a**–**2j** were prepared by treating ferrocene with the corresponding diamine **1a**–**1j** in the presence of phosphoric acid (*Scheme 2*). The increase in molar ratio of phosphoric acid resulted in increasing yields of **2a**–**2j**. As ferrocene and many of its derivatives are easily oxidized in air, the reactions were carried out under Ar. The ferrocenes **2a**–**2j** were characterized by IR and ^{1}H-NMR

Scheme 2



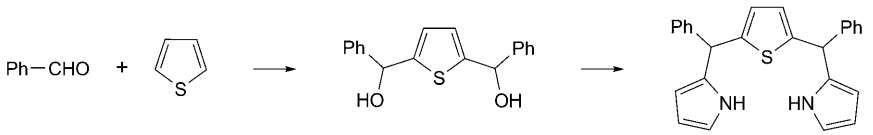
spectroscopy. The ^{1}H-NMR spectra showed a *s* in the range of δ 3.16–4.31 for the CH_2N group and two *d* in the range of δ 3.97–4.39 and 4.42–4.91 with a coupling constant *J* value around 12.6, and one *s* for five ferrocene H-atoms at δ 4.23–5.12.

The synthesis of the 1-(aminomethyl)-2-formylferrocenes **3a**–**3j** was carried out by metallation of the ferrocene ring of **2a**–**2j** in the presence of BuLi (*Scheme 2*). The lithium derivative was then condensed with DMF at room temperature under Ar in good yields. The structure of the corresponding formylferrocenes **3a**–**3j** was established on the basis of IR and ^{1}H-NMR data. The 1,2-substitution of the ferrocenes was established unambiguously by comparison of the IR data [18–20]: The IR absorption at 1000 and 1105 cm^{-1} are typical for the presence of an unsubstituted cyclopentadienyl moiety in **3a**–**3j**; indeed, these two bands are absent if both cyclopentadienyl moieties are substituted. The structures of **3a**–**3j** were further confirmed by the ^{1}H-NMR data, *i.e*, by four signals in the range for ferrocene H-atoms (2 *d* at δ 4.01–4.69 and 4.17–5.29 with coupling constant $J = 12.3$–12.9 Hz, one *m* at δ 3.89–5.29, and one *s* at δ 4.82–6.63), and by the *s* for the aldehydic H-atom at δ 8.93–9.71. Thus, the ^{1}H-NMR data confirmed the exclusive 1,2-substitution of the ferrocenes **3a**–**3j** as expected from the intermediate {2-[(amino-κN)methyl]ferrocen-1-yl}lithium compounds **2′a**–**2′j**. Indeed, this 1,2-substituted intermediate should have the maximum stability due to the possible coordination of the Li by the adjacent amino group, resulting in the formation of a 5-membered ring.

Subsequent addition of the formylferrocenes **3a**–**3j** to (thiophene-2,5-diyl)dilithium, obtained by 2,5-dilithiation of thiophene with excess of BuLi/TMEDA (= *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine) in excess of hexane, gave 1,1″-[thiophene-2,5-diylbis(hydroxymethylene)]bis[2-(aminomethyl)ferrocenes] **4a**–**4j** (*Scheme 2*) which were purified by column chromatography and recrystallization. The bis-ferrocenes **4a**–**4j** were single isomers as confirmed by a *s* at δ 6.64–7.51 for the thiophene H-atoms and another *s* for the hydroxymethylene moiety at δ 5.49–6.51 in the ^{1}H-NMR spectra.

The addition of benzaldehyde to (thiophene-2,5-diyl)dilithium resulted in the formation of α^2,α^5-diphenylthiophene-2,5-dimethanol (**5a**), and 2,2′-[thiophene-2,5-diylbis(phenylmethylene)]bis[1*H*-pyrrole] (**5b**) was prepared by treating **5a** with excess of 1*H*-pyrrole in the presence of $BF_3 \cdot Et_2O$ (*Scheme 3*). The data of **5a** and **5b** were in accordance with the literature [11].

Scheme 3

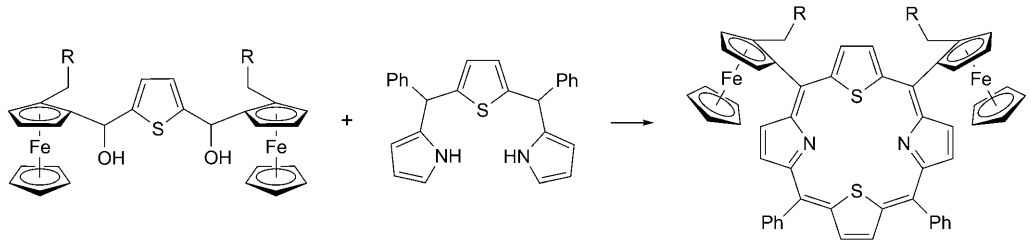


5a **5b**

The compounds **6a**–**6j**, having a *meso*-substituted porphyrin moiety with the substituted ferrocenyl groups at the 5 and 20 position and the Ph groups at the 10 and 15 position, were prepared in the dark and under Ar by the condensation of **4a**–**4j** with **5b**

in the presence of a catalytic amount of $BF_3 \cdot Et_2O$ and subsequent oxidation with DDQ (=4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile) (*Scheme 4*). The products **6a**–**6j** were purified *via* chromatography (basic alumina) and recrystallization and characterized by means of elemental analysis, IR, ^{1}H-NMR, electronic spectroscopy and mass spectrometry. All the compounds **6a**–**6j** are soluble in $CHCl_3$, MeOH, EtOH, DMF, and DMSO; and their purity was established by means of the elemental analyses and the mass spectra.

Scheme 4



4a – **4j** **5b** **6a** – **6j**

For R of **a** – **j**, see *Scheme 2*.

The IR spectra of **6a**–**6i** exhibited some prominent signals which were very helpful to deduce their structure. These include absorptions at 1652–1615 (C=N), 1211–1256 (C–N), 1110–1115 (ferrocene), 1001–1005 (ferrocene), and 907–895 cm^{-1} (ferrocene), and a very weak band at 865–845 cm^{-1} (C–S). The absence of the band near 3500–3100 cm^{-1} showed that the N-atom of the pyrrole moieties does not carry any H-atom, as expected from the aromatization of the molecule. The strong signal around 1110 cm^{-1} and a weak one around 1000 cm^{-1} established that the ferrocene moiety is present and possesses one unsubstituted cyclopentadienyl moiety [18–20]. The signal around 900 cm^{-1} was also indicative of the presence of the ferrocene moiety, and the weak band around 850 cm^{-1} confirmed the presence of the thiophene moiety.

The formation of the porphyrins **6a**–**6j** was further supported by the ^{1}H-NMR spectra. Besides the usual signals of the amino substituents, well-resolved ferrocene signals and two *d* at δ 6.31–6.57 and 6.54–6.81 with a coupling constant *J* ranging between 7.3 and 7.6 Hz of the four pyrrole H-atoms (different environment) were present. The two *s* at δ 7.31–7.91 and 7.55–805 were assigned to the four thiophene H-atoms (similar environment). The absence of signals either on the right hand side of the $SiMe_4$ signal (as found in 5,10,15,20-tetrakis[4-(*tert*-butyl)phenyl]porphyrins (TBPPs)) or beyond δ 8.69 (aromatic-NH signals are expected at $\delta > 10$) also suggested the absence of pyrrole NH atoms, in accord with the proposed structures.

The formation of the porphyrin derivatives **6a**–**6j** was further supported by the typical electronic spectra of porphyrins with one *Soret* band (λ_{max} 416–456 nm) and four Q bands (*Table 1*). Out of the four Q bands, two were intense (λ_{max} 510–520 nm and 535–576 nm), and two were less intense (λ_{max} 575–601 nm and 630–657 nm);

Table 1. *UV/VIS Band Maxima and Extinction Coefficients for* meso-*Substituted Porphyrins* **6a**–**6j**. In MeOH; λ_{max} in nm ($\varepsilon \cdot 10^{-3}$ in cm^{-1} mol^{-1} l).

Compound	*Soret* 1	Q IV	Q III	Q II	Q I
6a	416[a]) (102.3)[b])	515 (39.4)	555 (27.3)	595 (4.5)	630 (2.3)
6b	429 (120.8)	517 (29.5)	537 (16.3)	586 (3.2)	–
6c	433 (95.5)	517 (18.5)	536 (13.3)	587 (5.1)	636 (1.8)
6d	429 (87.6)	510 (35.3)	536 (29.3)	583 (5.8)	635 (2.8)
6e	448 (89.2)	519 (26.4)	535 (19.1)	586 (2.1)	642 (3.5)
6f	452 (87.4)	518 (30.5)	538 (15.5)	585 (7.9)	632 (6.8)
6g	436 (91.3)	513 (32.5)	545 (28.4)	575 (6.2)	655 (5.1)
6h	424 (84.6)	514 (31.2)	565 (20.2)	582 (3.5)	652 (4.1)
6i	456 (79.5)	511 (27.6)	576 (18.7)	593 (4.1)	–
6j	421 (87.1)	520 (20.4)	567 (17.3)	601 (7.1)	657 (6.2)

[a]) Absorption wavelength λ_{max}. [b]) Molar absorption coefficient ε (formerly called molar extinction coefficient).

even in the cases of **6b** and **6i**, the fourth Q band was not recognized. Except for **6b**, **6e**, and **6i**, all the *meso*-substituted porphyrin derivatives gave etui spectra ($\varepsilon_{IV} > \varepsilon_{III} > \varepsilon_{II} > \varepsilon_{I}$), and the relative intensities of the Q_I and Q_{II} bands exhibited a standard behavior ($\varepsilon_{II}/\varepsilon_{I} < 1$).

Anti-amoebic Activity. Preliminary experiments were carried out to determine the *in vitro* antiamoebic activity of all the compounds **6a**–**6j** against strain HM1:IMSS of *E. histolytica*, and the results were compared with the activity of metronidazole (MNZ). The IC_{50} values are shown in *Table 2*. The percent inhibition of amoebal growth was calculated from the optical densities of the control and test wells and was plotted against the logarithm of the dose of the drugs. Metronidazole had a 50% inhibitory concentration IC_{50} of 1.81 μM in our experiments (*Fig.*). The IC_{50} values for compounds **6b** (0.59 μM), **6c** (1.41 μM), **6d** (0.72 μM), **6f** (1.57 μM), **6h** (1.71 μM), and **6j** (1.56 μM) were considerably lower than that of metronidazole, corresponding to a 1.05-

Table 2. In vitro *Anti-amoebic Activity of* **6a**–**6j** *against the Strain HM1:IMSS of* E. histolytica

Compound	IC_{50} [μM]	S.D.[a]) (±)
6a	> 1.8	0.31
6b	0.59	0.51
6c	1.41	0.25
6d	0.72	0.30
6e	> 1.8	0.63
6f	1.57	0.24
6g	> 1.8	0.53
6h	1.71	0.18
6i	> 1.8	0.21
6j	1.56	0.35
Metronidazole (MNZ)	1.81	0.13

[a]) Standard deviation.

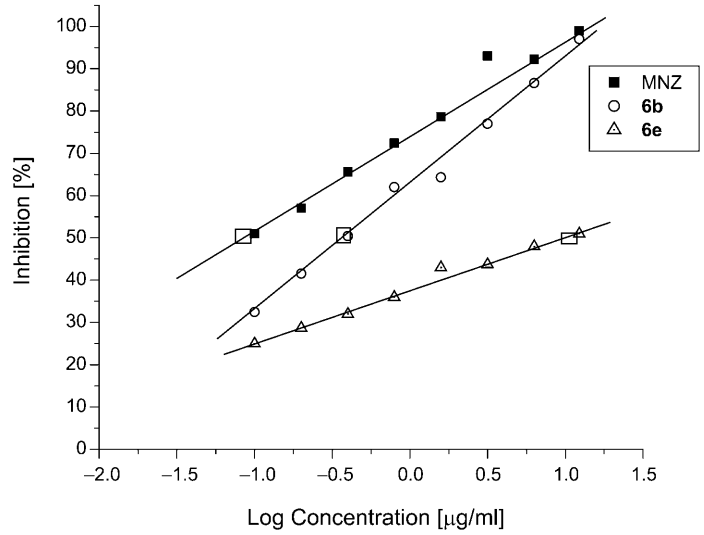


Figure. In vitro *anti-amoebic activity of metronidazole* (MNZ) *and compounds* **6b** *and* **6e** *against the Strain HM1:IMSS of* E. histolytica

to 3.05-fold increase in activity. The results were statistically evaluated by analyses of the variance. The null hypothesis was tested by the *T*-test, and the significance of the differences between the IC_{50} value(s) of metronidazole *vs.* **6a**–**6j** was evaluated. The calculated *T*-values were higher than the table values at the 4% level. Hence, the character under study was significantly influenced by the treatment. Thus, from the data available, we can say that porphyrins can act as better anti-amoebic drugs.

Conclusion. – Bis-ferrocenyl-substituted core-modified porphyrins (= 1,1″-(core-modified porphyrindiyl)bis[ferrocenes]) **6a**–**6j** were synthesized *via* an acid-catalyzed condensation of **4a**–**4j** and **5b** and subsequent oxidation with DDQ. All the compounds were characterized by spectroscopic techniques. The cell-culture studies showed that some compounds, **6a**–**6j**, possessed high *in vitro* anti-amoebic activity against *E. histolytica*. The IC_{50} values for compounds **6b**, **6c**, **6d**, **6f**, **6h**, and **6j** were considerably lower than that of metronidazole (1.81 μM), corresponding to a 1.05- to 3.05-fold increase in activity, thus these compound proved to be better inhibitors of *E. histolytica* growth.

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Experimental Part

1. *General.* Ferrocene = fc; thiophene-2,5-diyl = tp. All the reactions were carried out in the dark under Ar. All the chemicals were purchased from *Aldrich Chemical Company* (USA), and CH_2Cl_2 was

purified by treating with molecular sieves. TLC: precoated silica gel (SiO_2) *60* F_{254} aluminium plates. Flash column chromatography (FC): SiO_2 *60* Å (240–400 mesh) and basic alumina. CC = Column chromatography. UV/VIS Spectra: *Shimadzu UV-1601-PC* UV/VIS spectrophotometer; in MeOH. IR Spectra: *Perkin-Elmer 1620* FT-IR spectrophotometer; KBr pellets; $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR Spectra: *Bruker Spectrospin-DPX-300* spectrophotometer; $CDCl_3$/DMSO solns. at r.t.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. FAB-MS: *Jeol SX-102*/*DA-6000* mass spectrometer/data system; Ar/Xe (6 kV, 10 mA) as the FAB gas and 3-nitrobenzyl alcohol (NBA) as the matrix; in *m*/*z*. Elemental analyses: *Heraeus Vario-EL-III* analyzer; performed in the Central Drug Research Institute, Luckhnow; results within 0.3% of the theoretical values.

2. *Synthesis of* **1a**–**1j**. *General Procedure.* A secondary amine R′NHR″ (300 mmol) was added dropwise to a stirred 37% HCHO (150 mmol) soln. in H_2O at 0°. Subsequently, the mixture was stirred for 2 h at r.t., followed by addition of KOH pellets until two layers were separated. The org. layer was extracted with Et_2O, and the extract dried (Na_2SO_4) and concentrated: oil. The structures of the methane diamines **1a**–**1j** were confirmed by IR spectroscopy.

3. *Synthesis of* **2a**–**2j**: *General Procedure.* A mixture of ferrocene (1 equiv.), each diamine **1a**–**1j** (1 equiv.), and phosphoric acid (H_3PO_4; 1.5 equiv.) was heated in AcOH for 5 h. After cooling, the mixture was diluted with H_2O/Et_2O 5:15 (20 ml). NaOH was added to the aq. layer until the pH reached 12. The free-base derivative was extracted with CH_2Cl_2, the org. layer dried (Na_2SO_4) and concentrated, and the residue subjected to CC (SiO_2, hexane/Et_2O): **2a**–**2j** as red oils.

1-[(Butylmethylamino)methyl]ferrocene (**2a**). Yield 72%. IR: 2936 (arom. C–H), 2858 (C–H), 1638, 1582, 1450 (C=C), 1239 (C–N), 1104 (fc), 1000 (fc), 815 (fc). ^{1}H-NMR ($CDCl_3$): 1.26–1.39 (*m*, 1 Me); 1.52–1.61 (*m*, 1 CH_2); 2.71 (*m*, 1 CH_2); 3.20 (*t*, 1 CH_2); 3.34 (*s*, 1 CH_2N); 3.56 (*s*, 1 Me); 3.73 (*s*, 1 CH_2N); 4.16 (*d*, *J* = 12.6, 2 H of fc); 4.30 (*d*, *J* = 12.6, 2 H of fc); 5.30 (*s*, 5 H of fc).

1-[[Methyl(phenylmethyl)amino]methyl]ferrocene (**2b**): Yield 69%. IR: 3094 (arom. C–H), 2931 (C–H), 1650, 1558, 1456 (C=C), 1255 (C–N), 1105 (fc), 1000 (fc), 813 (fc). ^{1}H-NMR ($CDCl_3$): 2.68 (*s*, MeN); 3.56 (*s*, 1 CH_2N); 3.61 (*s*, 1 CH_2N); 4.34 (*d*, *J* = 12.6, 2 H of fc); 4.96 (*d*, *J* = 12.6, 2 H of fc); 5.18 (*s*, 5 H of fc); 6.91–7.13 (*m*, 5 arom. H).

1-[(4-Methylpiperidin-1-yl)methyl]ferrocene (**2c**): Yield 65%. IR: 3074 (arom. C–H), 2926 (C–H), 1580, 1537, 1408 (C=C), 1204 (C–N), 1103 (fc), 1002 (fc), 815 (fc). ^{1}H-NMR ($CDCl_3$): 1.99 (Me); 2.45 (*m*, CH); 2.60–2.69 (*m*, $CH(CH_2)_2$); 3.16 (*s*, 1 CH_2N); 3.55–3.63 (*m*, CH_2NCH_2); 3.97 (*d*, *J* = 12.8, 2 H of fc); 4.32 (*d*, *J* = 12.8, 2 H of fc); 4.72 (*s*, 5 H of fc).

*1-[(Hexahydro-1*H*-azepin-1-yl)methyl]ferrocene* (**2d**): Yield 67%. IR: 3038 (arom. C–H), 2903 (CH_2 stretch), 2893 (CH_2), 1569, 1493, 1483 (C=C), 1230 (C–N), 1104 (fc), 1000 (fc), 811 (fc). ^{1}H-NMR ($CDCl_3$): 2.85–2.98 (*m*, 4 CH_2); 3.82 (*s*, 1 CH_2); 4.13 (*d*, *J* = 12.9, 2 H of fc); 4.23 (*s*, 5 H of fc); 4.53–4.61 (*m*, CH_2NCH_2); 4.81 (*d*, *J* = 12.9, 2 H of fc).

1-[(Cyclohexylmethylamino)methyl]ferrocene (**2e**): Yield 79%. IR: 3007 (arom. C–H), 2905 (Me stretch), 2892 (CH_2), 1592, 1561, 1494 (C=C), 1216 (C–N), 1105 (fc), 1002 (fc), 817 (fc). ^{1}H-NMR ($CDCl_3$): 2.43–2.52 (*m*, $(CH_2)_5$); 2.71 (*s*, Me); 3.89 (*s*, 1 CH_2); 4.08–4.17 (*m*, CHN–); 4.32 (*s*, 5 H of fc); 4.47 (*d*, *J* = 12.3, 2 H of fc); 4.52 (*d*, *J* = 12.3, 2 H of fc).

1-[(Diethylamino)methyl]ferrocene (**2f**): Yield 75%. IR: 3032 (arom. C–H), 2937 (Me stretch), 2893 (CH_2), 1602, 1586, 1430 (C=C), 1205 (C–N), 1101 (fc), 1002 (fc), 817 (fc). ^{1}H-NMR ($CDCl_3$): 1.94 (*t*, 2 Me); 3.4 (*m*, $(CH_2)_2N$); 3.8 (*s*, CH_2); 4.12 (*d*, *J* = 12.4, 2 H of fc); 4.42 (*d*, *J* = 12.4, 2 H of fc); 4.81 (*s*, 5 H of fc).

1-[(Dipropylamino)methyl]ferrocene (**2g**): Yield 68%. IR: 3025 (arom. C–H), 2928 (Me stretch), 2840 (CH_2), 1593, 1548, 1410 (C=C), 1215 (C–N), 1104 (fc), 1000 (fc), 815 (fc). ^{1}H-NMR ($CDCl_3$): 1.92 (*t*, 2 Me); 2.52–2.63 (*m*, 2 CH_2); 3.37 (*t*, $(CH_2)_2N$); 4.31 (*s*, 1 CH_2N); 4.31 (*d*, *J* = 12.6, 2 H of fc); 4.82 (*d*, *J* = 12.6, 2 H of fc); 5.12 (*s*, 5 H of fc).

1-[(Pyrrolidin-1-yl)methyl]ferrocene (**2h**): Yield 77%. IR: 3063 (arom. C–H), 2890 (CH_2), 1610, 1559, 1435 (C=C), 1238 (C–N), 1107 (fc), 1000 (fc), 813 (fc). ^{1}H-NMR ($CDCl_3$): 2.63–2.72 (*m*, $(CH_2)_2$); 3.89–3.95 (*m*, $(CH_2)_2N$); 4.1 (*s*, 1 CH_2N); 4.39 (*d*, *J* = 12.6, 2 H of fc); 4.82 (*s*, 5 H of fc); 4.91 (*d*, *J* = 12.6, 2 H of fc).

1-[(2-Ethylpiperidin-1-yl)methyl]ferrocene (**2i**): Yield 67%. IR: 3078 (arom. C–H), 2956 (Me), 2841 (CH_2), 1613, 1586, 1513 (C=C), 1221 (C–N), 1103 (fc), 1001 (fc), 815 (fc). ^{1}H-NMR ($CDCl_3$): 1.75

(*t*, 1 Me); 2.13 (*m*, 4 CH_2); 3.61 (*m*, CHN); 3.89 (*t*, 1 CH_2N); 4.44 (*s*, 1 CH_2N); 4.52 (*d*, *J* = 12.8, 2 H of fc); 4.87 (*s*, 5 H of fc); 4.95 (*d*, *J* = 12.8, 2 H of fc).

1-[(4-Phenylpiperazin-1-yl)methyl]ferrocene (**2j**): Yield 77%. IR: 3051 (arom. C–H), 2880 (CH_2), 1615, 1549, 1432 (C=C), 1256 (C–N), 1106 (fc), 1002 (fc), 811 (fc). ^{1}H-NMR ($CDCl_3$): 2.38–2.70 (*m*, 2 CH_2NCH_2); 4.7 (*s*, 1 NCH_2); 4.63 (*d*, *J* = 12.8, 2 H of fc); 4.91 (*s*, 5 H of fc); 5.32 (*d*, *J* = 12.8, 2 H of fc); 6.53–7.12 (*m*, 5 H of Ph).

3. *Synthesis of* **3a**–**3j**. *General Procedure*. Each ferrocene **2a**–**2j** (1 equiv.) in anh. Et_2O (20 ml) was treated with BuLi in hexane (1.25 equiv.) under Ar at r.t. with continous stirring. The reaction was completed in 16 h. The soln. obtained was treated with *N*,*N*-dimethylformamide (1.25 equiv.) under Ar at r.t. After 4 h, the compound was hydrolyzed by addition of H_2O. The aq. phase was washed with small portions of Et_2O, the combined Et_2O extract dried (Na_2SO_4) and concentrated, and the obtained red oil purified by CC (SiO_2, Et_2O/hexane): **3a**–**3j** as red oils.

1-[(Butylmethylamino)methyl]-2-formylferrocene (**3a**): Yield 53%. IR: 2916 (arom. C–H), 2867 (C–H), 1723 (C=O), 1630, 1542, 1435 (C=C), 1234 (C–N), 1114 (fc), 1003 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 1.28–1.37 (*m*, 1 Me); 1.43–1.49 (*m*, 1 CH_2); 1.92–2.05 (*m*, 1 CH_2); 3.32 (*t*, 1 CH_2); 3.47 (*s*, 1 Me); 3.58 (*s*, 1 CH_2N); 4.01 (*d*, *J* = 12.8, 1 H of fc); 4.17 (*d*, *J* = 12.8, 1 H of fc); 5.15–5.29 (*m*, 1 H of fc); 6.63 (*s*, 5 H of fc); 9.35 (*s*, CHO).

1-Formyl-2-{[methyl(phenylmethyl)amino]methyl}ferrocene (**3b**): Yield 69%. IR: 3086 (arom. C–H), 2976 (C–H), 1721 (C=O), 1630, 1535, 1474 (C=C), 1237 (C–N), 1112 (fc), 1002 (fc), 905 (fc). ^{1}H-NMR ($CDCl_3$): 2.73 (*s*, MeN); 3.23 (*s*, 1 CH_2N); 3.48 (*s*, 1 CH_2N); 3.92–4.03 (*m*, 1 H of fc); 4.25 (*d*, *J* = 12.9, 1 H of fc); 4.39 (*d*, *J* = 12.9, 1 H of fc); 5.92 (*s*, 5 H of fc); 9.36 (*s*, CHO).

1-Formyl-2-[(4-methylpiperidin-1-yl)methyl]ferrocene (**3c**): Yield 69%. IR: 3035 (arom. C–H), 2963 (C–H), 1733 (C=O), 1586, 1533, 1426 (C=C), 1227 (C–N), 1113 (fc), 1002 (fc), 899 (fc). ^{1}H-NMR ($CDCl_3$): 1.43 (*d*, Me); 2.41 (*m*, 1 CH); 2.52–2.61 (*m*, $CH(CH_2)_2$); 3.23–3.37 (*m*, CH_2NCH_2); 3.43 (*s*, 1 CH_2); 4.13 (*d*, *J* = 12.4, 1 H of fc); 4.19 (*d*, *J* = 12.4, 1 H of fc); 4.52–4.61 (*m*, 1 H of fc); 5.13 (*s*, 5 H of fc); 8.93 (*s*, CHO).

*1-Formyl-2-[(hexahydro-1*H*-azepin-1-yl)methyl]ferrocene* (**3d**): Yield 68%. IR: 3046 (arom. C–H), 2923 (CH_2 stretch), 2884 (CH_2), 1728 (C=O), 1576, 1498, 1480 (C=C), 1246 (C–N), 1113 (fc), 1004 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.73–2.87 (*m*, 4 CH_2); 3.49 (*s*, 1 CH_2N); 4.43–4.50 (*m*, CH_2NCH_2); 4.52–4.61 (*m*, 1 H of fc); 4.63 (*d*, *J* = 12.4, 1 H of fc); 4.79 (*d*, *J* = 12.4, 1 H of fc); 5.61 (*s*, 5 H of fc); 9.71 (*s*, CHO).

1-[(Cyclohexylmethylamino)methyl]-2-formylferrocene (**3e**): Yield 58%. IR: 3036 (arom. C–H), 2938 (Me stretch), 2897 (CH_2), 1729 (C=O), 1613, 1573, 1467 (C=C), 1234 (C–N), 1114 (fc), 1002 (fc), 901 (fc). ^{1}H-NMR ($CDCl_3$): 2.33–2.47 (*m*, $(CH_2)_5$); 2.64 (*s*, Me); 3.67 (*s*, CH_2N); 3.92–3.98 (*m*, CHN); 4.49 (*d*, *J* = 12.8, 1 H of fc); 4.57 (*d*, *J* = 12.8, 1 H of fc); 4.63–4.71 (*m*, 1 Hof fc); 5.12 (*s*, 5 H of fc); 9.25 (*s*, CHO).

1-[(Diethylamino)methyl]-2-formylferrocene (**3f**): Yield 69%. IR: 3036 (arom. C–H), 2916 (Me stretch), 2894 (CH_2), 1732 (C=O), 1613, 1597, 1447 (C=C), 1238 (C–N), 1115 (fc), 1004 (fc), 904 (fc). ^{1}H-NMR ($CDCl_3$): 1.83 (*t*, 2 Me); 3.53 (*m*, $N(CH_2)_2$); 3.72 (*s*, CH_2N); 4.43–4.59 (*m*, 1 H of fc); 4.69 (*d*, *J* = 12.3, 1 H of fc); 4.83 (*d*, *J* = 12.3, 1 H of fc); 5.31 (*s*, 5 H of fc); 9.61 (*s*, CHO).

1-[(Dipropylamino)methyl]-2-formylferrocene (**3g**): Yield 52%. IR: 3067 (arom. C–H), 2956 (Me stretch), 2826 (CH_2), 1727 (C=O), 1586, 1567, 1428 (C=C), 1231 (C–N), 1113 (fc), 1001 (fc), 905 (fc). ^{1}H-NMR ($CDCl_3$): 1.86 (*t*, 2 Me); 2.69–2.78 (*m*, 2 CH_2); 3.58 (*t*, $(CH_2)_2N$); 4.21 (*s*, CH_2N); 4.44 (*d*, *J* = 12.8, 1 H of fc); 4.78–4.86 (*m*, 1 H of fc); 4.93 (*d*, *J* = 12.8, 1 H of fc); 5.95 (*s*, 5 H of fc); 9.09 (*s*, CHO).

1-Formyl-2-[(pyrrolidin-1-yl)methyl]ferrocene (**3h**): Yield 58%. IR: 3037 (arom. C–H), 2873 (CH_2), 1731 (C=O), 1593, 1578, 1426 (C=C), 1228 (C–N), 1112 (fc), 1003 (fc), 905 (fc). ^{1}H-NMR ($CDCl_3$): 2.39–2.47 (*m*, $(CH_2)_2$); 4.02–4.11 (*m*, $(CH_2)_2N$); 4.17 (*s*, 1 CH_2N); 4.23 (*d*, *J* = 12.4, 1 H of fc); 4.63–4.71 (*m*, 1 H of fc); 5.03 (*d*, *J* = 12.4, 1 H of fc); 6.23 (*s*, 5 H of fc); 9.39 (*s*, CHO).

1-[2-Ethylpiperidin-1-yl)methyl]-2-formylferrocene (**3i**): Yield 54%. IR: 3069 (arom. C–H), 2913 (Me), 2886 (CH_2), 1733 (C=O), 1618, 1572, 1487 (C=C), 1234 (C–N), 1115 (fc), 1000 (fc), 902 (fc). ^{1}H-NMR ($CDCl_3$): 1.79 (*t*, Me); 2.32 (*m*, 4 CH_2); 3.48 (*m*, CHN); 3.91 (*t*, 1 CH_2N); 4.16 (*s*, 1 CH_2N); 4.43–4.49 (*m*, 1 H of fc); 4.39 (*d*, *J* = 12.6, 1 H of fc); 4.82 (*s*, 5 H of fc); 4.91 (*d*, *J* = 12.6, 1 H of fc); 9.71 (*s*, CHO).

1-Formyl-2-[(4-phenylpiperazin-1-yl)methyl]ferrocene (**3j**): Yield 64%. IR: 3043 (arom. C–H), 2897 (CH_2), 1710 (C=O), 1615, 1553, 1422 (C=C), 1234 (C–N), 1101 (fc), 1004 (fc), 902 (fc). ^{1}H-NMR ($CDCl_3$): 2.30–2.65 (*m*, 2 CH_2NCH_2); 4.5 (*s*, 1 CH_2N); 4.75 (*d*, *J* = 12.8, 2 H of fc); 4.70–4.78 (*m*, 1 H of fc); 4.85 (*s*, 5 H of fc); 5.12 (*d*, *J* = 12.8, 2 H of fc); 6.20–6.33 (*m*, 5 H of Ph); 9.89 (*s*, CHO).

4. *Synthesis of* **4a**–**4j**. *General Procedure.* Thiophene (1 equiv.) was added to a soln. of BuLi (3 equiv.) and *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA; 3 equiv.) in hexane under Ar. The mixture was heated under reflux for 2 h, cooled to r.t., and transferred to a dropping funnel. The (thiophene-2,5-diyl)dilithium suspension was then added dropwise, at 0° under Ar, to a formylferrocene **3a**–**3j** (3 equiv.) in THF (dried over basic alumina and degassed with Ar for 15 min). After the addition, the mixture was allowed to warm to r.t. followed by the addition of 1M aq. NH_4Cl. The aq. phase was extracted with Et_2O (3×), the combined org. phase washed with H_2O and brine, dried ($MgSO_4$), and concentrated, and the crude red oil purified by CC (SiO_2, Et_2O/hexane): **4a**–**4j** as red oils.

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(butylmethylamino)methyl]ferrocene] (**4a**): Yield 17%. IR: 3237 (O–H), 2915 (arom. C–H), 2885 (C–H), 1602, 1583, 1495 (C=C), 1237 (C–N), 1112 (fc), 1001 (fc), 901 (fc). ^{1}H-NMR ($CDCl_3$): 1.16–1.23 (*m*, 2 Me); 1.28–1.33 (*m*, 2 CH_2); 1.69–1.76 (*m*, 2 CH_2); 3.53 (*s*, 2 Me); 3.64 (*t*, 2 CH_2); 4.01 (*s*, 2 CH_2); 4.08 (*d*, *J* = 12.3, 2 H of fc); 4.23 (*d*, *J* = 12.3, 2 H of fc); 4.39 (*s*, 2 CHO*H*); 5.32–5.39 (*m*, 2 H of fc); 5.93 (*s*, 10 H of fc); 6.11 (*s*, 2 C*H*OH); 6.64 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-{[methyl(phenylmethyl)amino]methyl}ferrocene] (**4b**): Yield 22%. IR: 3320 (O–H), 3065 (arom. C–H), 2935 (C–H), 1595, 1574, 1501 (C=C), 1228 (C–N), 1113 (fc), 1004 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.94 (*s*, 2 MeN); 3.16 (*s*, 2 CH_2N); 3.51 (*s*, 2 CH_2N); 3.81–3.93 (*m*, 2 H of fc); 4.12 (*d*, *J* = 12.2, 2 H of fc); 4.31 (*d*, *J* = 12.2, 2 H of fc); 5.39 (*s*, 10 H of fc); 5.21 (*s*, 2 CHO*H*); 6.12 (*s*, 2 C*H*OH); 7.23 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(4-methylpiperidin-1-yl)methyl]ferrocene] (**4c**): Yield 25%. IR: 3320 (O–H), 3076 (arom. C–H), 2934 (C–H), 1605, 1583, 1495 (C=C), 1210 (C–N), 1115 (fc), 1001 (fc), 902 (fc). ^{1}H-NMR ($CDCl_3$): 1.21 (*d*, 2 Me); 1.91 (*m*, 2 CH); 2.36–2.51 (*m*, 2 CH(CH_2)$_2$); 3.05–3.21 (*m*, 2 CH_2NCH_2); 3.56 (*s*, 2 CH_2N); 4.10 (*d*, *J* = 12.5, 2 H of fc); 4.27 (*d*, *J* = 12.5, 2 H of fc); 4.53 (*s*, 2 CHO*H*); 4.71–4.78 (*m*, 2 H of fc); 5.49 (*s*, 10 H of fc); 5.49 (*s*, 2 C*H*OH); 7.31 (*s*, 2 H of tp).

*1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(hexahydro-1*H*-azepin-1-yl)methyl]ferrocene]* (**4d**): Yield 19%. IR: 3250 (O–H), 3018 (arom. C–H), 2956 (CH_2 stretch), 2905 (CH_2), 1593, 1520, 1465 (C=C), 1235 (C–N), 1115 (fc), 1001 (fc), 907 (fc). ^{1}H-NMR ($CDCl_3$): 1.69–1.81 (*m*, 8 CH_2); 3.95 (*s*, 2 CH_2N); 4.13–4.20 (*m*, 2 CH_2NCH_2); 4.32–4.40 (*m*, 2 H of fc); 4.49 (*d*, *J* = 12.9, 2 H of fc); 4.81 (*d*, *J* = 12.9, 2 H of fc); 5.31 (*s*, 10 H of fc); 5.43 (*s*, 2 CHO*H*); 6.19 (*s*, 2 C*H*OH); 6.97 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(cyclohexylmethylamino)methyl]ferrocene] (**4e**): Yield 15%. IR: 3356 (O–H), 3057 (arom. C–H), 2940 (Me stretch), 2886 (CH_2), 1615, 1575, 1567 (C=C), 1225 (C–N), 1113 (fc), 1005 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 1.93–2.07 (*m*, 2 $(CH_2)_5$); 2.34 (*s*, 2 Me); 3.87 (*s*, 2 CH_2N); 4.12–4.19 (*m*, CHN); 4.32 (*d*, *J* = 12.2, 2 H of fc); 4.48 (*d*, *J* = 12.2, 2 H of fc); 4.51–4.59 (*m*, 2 H of fc); 4.97 (*s*, 10 H of fc); 5.43 (*s*, 2 CHO*H*); 6.71 (*s*, 2 C*H*OH); 7.05 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(diethylamino)methyl]ferrocene] (**4f**): Yield 16%. IR: 3410 (O–H), 3018 (arom. C–H), 2936 (Me stretch), 2886 (CH_2), 1633, 1576, 1513 (C=C), 1247 (C–N), 1113 (fc), 1002 (fc), 904 (fc). ^{1}H-NMR ($CDCl_3$): 1.73 (*t*, 4 Me); 3.19 (*m*, 2 $(CH_2)_2N$); 3.75 (*s*, 2 CH_2N); 4.51–4.58 (*m*, 2 H of fc); 4.65 (*d*, *J* = 12.4, 2 H of fc); 4.73 (*s*, 2 CHO*H*); 4.79 (*d*, *J* = 12.4, 2 H of fc); 5.21 (*s*, 10 H of fc); 6.15 (*s*, 2 C*H*OH); 6.95 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(dipropylamino)methyl]ferrocene] (**4g**): Yield 19%. IR: 3313 (O–H), 3045 (arom. C–H), 2956 (Me stretch), 2854 (CH_2), 1565, 1510, 1438 (C=C), 1241 (C–N), 1115 (fc), 1004 (fc), 906 (fc). ^{1}H-NMR ($CDCl_3$): 1.32 (*t*, 4 Me); 2.51–2.58 (*m*, 4 CH_2); 3.25 (*t*, 2 $(CH_2)_2N$); 4.03 (*s*, 2 CH_2N); 4.23 (*d*, *J* = 12.2, 2 H of fc); 4.62–4.73 (*m*, 2 H of fc); 4.81 (*d*, *J* = 12.2, 4 H of fc); 5.09 (*s*, 2 CHO*H*); 5.32 (*s*, 10 H of fc); 6.51 (*s*, 2 C*H*OH); 7.51 (*s*, 2 H of tp).

1,1″-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(pyrrolidin-1-yl)methyl]ferrocene] (**4h**): IR: 3276 (O–H), 3031 (arom. C–H), 2895 (CH_2), 1597, 1536, 1481 (C=C), 1235 (C–N), 1110 (fc), 1006 (fc), 899 (fc). ^{1}H-NMR ($CDCl_3$): 2.13–2.27 (*m*, $(CH_2)_2$); 3.71–3.85 (*m*, 2 $(CH_2)_2N$); 4.03 (*s*, 2 CH_2N);

4.19 (*d*, *J* = 12.4, 2 H of fc); 4.42–4.51 (*m*, 2 H of fc); 5.17 (*d*, *J* = 12.4, 2 H of fc); 5.42 (*s*, 2 CHO*H*); 5.49 (*s*, 10 H of fc); 6.38 (*s*, 2 C*H*OH); 7.19 (*s*, 2 H of tp).

1,1''-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(2-ethylpiperidin-1-yl)methyl]ferrocene] (**4i**): Yield 16%. IR: 3319 (O–H), 3053 (arom. C–H), 2905 (CH_2), 1635, 1546, 1483 (C=C), 1235 (C–N), 1109 (fc), 1005 (fc), 901 (fc). ^{1}H-NMR ($CDCl_3$): 1.56 (*t*, Me); 2.43 (*m*, 4 CH_2); 3.71 (*m*, CHN); 3.82 (*t*, 1 CH_2N); 4.31 (*s*, 1 CH_2N); 4.47 (*d*, *J* = 12.6, 2 H of fc); 4.53 (*d*, *J* = 12.6, 2 H of fc); 4.61–4.68 (*m*, 2 H of fc); 4.79 (*s*, 2 CHO*H*); 4.83 (*s*, 10 H of fc); 6.42 (*s*, 2 C*H*OH); 6.97 (*s*, 2 H of tp).

1,1''-[Thiophene-2,5-diylbis(hydroxymethylene)]bis[2-[(4-phenylpiperazin-1-yl)methyl]ferrocene] (**4j**): Yield 21%. IR: 3236 (O–H), 3011 (arom. C–H), 2885 (CH_2), 1591, 1533, 1482 (C=C), 1233 (C–N), 1112 (fc), 1004 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.28–2.55 (*m*, 2 CH_2NCH_2); 4.27 (*s*, 1 CH_2N); 4.39 (*d*, *J* = 12.7, 2 H of fc); 4.50–4.62 (*m*, 2 H of fc); 4.82 (*s*, 10 H of fc); 4.91 (*d*, *J* = 12.7, 2 H of fc); 4.96 (*s*, 2 CHO*H*); 6.38 (*s*, 2 C*H*OH); 6.49–6.74 (*m*, 5 H of Ph); 7.08 (*s*, 2 H of tp).

5. *α^2,α^5-Diphenylthiophene-2,5-dimethanol* (**5a**). As described in *Sect. 4*, with benzaldehyde instead of a formylferrocene **3a**–**3j**. Concentration of the dried org. phase gave **5a** (32%). White crystals. IR: 3033 (arom. C–H), 2928 (Me stretch), 1536, 1511, 1468 (C=C). ^{1}H-NMR ($CDCl_3$): 2.93 (*s*, 2 CHO*H*); 4.92 (*s*, 2 C*H*OH); 7.03 (*s*, 2 H of tp); 7.14 (*t*, 2 H of Ph); 7.49 (*d*, 4 H of Ph); 7.52 (*dd*, 4 H of Ph).

6. *2,2'-[Thiophene-2,5-diylbis(phenylmethylene)]bis[1*H*-pyrrole]* (**5b**). Compound **5a** was dissolved in excess 1*H*-pyrrole (10.6 ml), and Ar was bubbled through it. $BF_3 \cdot Et_2O$ (0.1 ml) was added, and the resulting mixture was stirred for 1 h. The reaction was stopped by the addition of CH_2Cl_2 (100 ml) followed by 40% NaOH soln. (25 ml). The org. layer was washed with H_2O (3 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and concentrated. The excess 1*H*-pyrrole was removed *in vacuo* at r.t. The residual oil was purified by CC (SiO_2, hexane/AcOEt 75 : 25) to give a yellow oil, which was recrystallized from AcOEt/hexane: 0.74 g (46%) of **5b**. White solid. M.p. 98–100°. IR: 3411 (OH), 3045 (arom. C–H), 1576, 1532, 1401 (C=C). ^{1}H-NMR ($CDCl_3$): 3.87 (*s*, 2 CH); 5.79 (*d*, 2 H of pyr); 6.06–6.10 (*m*, 2 H of pyr); 6.37–6.42 (*m*, 2 H of pyr); 7.04 (*s*, 2 H of tp); 7.16–7.27 (*m*, 10 H of Ph). FAB-MS: 395 ($[M+H]^+$, $C_{26}H_{23}N_2S^+$).

7. *Synthesis of* **6a**–**6j**. *General Procedure.* Compounds **5b** (1 equiv.) was dissolved in CH_2Cl_2 (1 l) and degassed under Ar for 20 min. DDQ (0.5 equiv.) was added, and the reaction vessel was covered with Al foil followed by purging the system with Ar. In the dark, $BF_3 \cdot Et_2O$ (0.2 ml) was added, and the resulting mixture was heated at reflux for 1 h. The mixture was allowed to cool and concentrated, and the residue was redissolved in a minimum of CH_2Cl_2. The resulting soln. was purified by chromatography on basic Al_2O_3 eluted with CH_2Cl_2. The first red band was collected, and the product was washed with acetone. The crude product was then recrystallized from CH_2Cl_2/MeOH to gave **6a**–**6j** as purple solids. M.p. > 300°.

1,1''-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(butylmethylamino)methyl]ferrocene] (**6a**): Yield 16%. IR: 2947 (arom. C–H), 2836 (C–H), 1652 (C=N), 1596, 1565, 1495 (C=C), 1256 (C–N), 1110 (fc), 1001 (fc), 895 (fc). ^{1}H-NMR ($CDCl_3$): 1.34–1.39 (*m*, 2 Me); 1.45–1.51 (*m*, 2 CH_2); 2.13–2.18 (*m*, 2 CH_2); 3.05 (*t*, 2 CH_2); 3.56 (*s*, 2 Me); 3.78 (*s*, CH_2N); 4.05 (*d*, *J* = 12.8, 2 H of fc); 4.10 (*d*, *J* = 12.8, 2 H of fc); 5.20–5.28 (*m*, 2 H of fc); 5.93 (*s*, 10 H of fc); 6.56 (*d*, *J* = 7.3, 2 H of pyr); 6.63 (*d*, *J* = 7.3, 2 H of pyr); 7.82 (*s*, 2 H of tp); 7.94 (*s*, 2 H of tp); 8.51–8.69 (*m*, 10 arom. H). FAB-MS: 1063.25 ($[M+H]^+$; calc. 1062.17). Anal. calc. for $C_{64}H_{62}Fe_2N_4S_2$: C 72.30, H 5.88, N 5.27; found: C 72.38, H 5.97, N 5.32.

1,1''-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-{[methyl(phenylmethyl)amino]methyl}-ferrocene] (**6b**): Yield 9%. IR: 3056 (arom. C–H), 2925 (C–H), 1635 (C=N), 1576, 1549, 1510 (C=C), 1211 (C–N), 1114 (fc), 1003 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.71 (*s*, 2 MeN); 3.38 (*s*, 2 CH_2N); 3.76 (*s*, 2 CH_2N); 4.35 (*d*, *J* = 12.9, 2 H of fc); 4.65–4.76 (*m*, 2 H of fc); 4.82 (*d*, *J* = 12.9, 2 H of fc); 5.03 (*s*, 10 H of fc); 6.46 (*d*, *J* = 7.6, 2 H of pyr); 6.54 (*d*, *J* = 7.6, 2 H of pyr); 7.87 (*s*, 2 H of tp); 7.93 (*s*, 2 H of tp); 8.49–8.58 (*m*, 10 arom. H). FAB-MS: 1131.46 ($[M+H]^+$; calc. 1130.14). Anal. calc. for $C_{70}H_{58}Fe_2N_4S_2$: C 74.32, H 5.17, N 4.95; found: C 74.43, H 5.31, N 5.14.

1,1''-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(4-methylpiperidin-1-yl)methyl]ferrocene] (**6c**): Yield 7%. IR: 3065 (arom. C–H), 2943 (C–H), 1648 (C=N), 15605, 1583, 1465 (C=C), 1248 (C–N), 1111 (fc), 1002 (fc), 901 (fc). ^{1}H-NMR ($CDCl_3$): 1.65 (*d*, 2 Me); 2.68 (*m*, 2 CH); 2.38–2.46 (*m*, 2 CH(CH_2)$_2$); 2.30–3.41 (*m*, 2 CH_2NCH_2); 3.99 (*s*, 2 CH_2N); 4.29 (*d*, *J* = 12.9, 2 H of fc); 4.35–4.44 (*m*,

2 H of fc); 4.68 (*d*, *J* = 12.9, 2 H of fc); 5.39 (*s*, 10 H of fc); 6.31 (*d*, *J* = 7.6, 2 H of pyr); 6.61 (*d*, *J* = 7.6, 2 H of pyr); 7.91 (*s*, 2 H of tp); 8.05 (*s*, 2 H of tp); 8.36–8.48 (*m*, 10 arom. H). FAB-MS: 1085.37 ($[M+H]^+$; calc. 1084.15). Anal. calc. for $C_{66}H_{60}Fe_2N_4S_2$: C 73.05, H 5.57, N 5.16; found: C 73.18, H 5.71, N 5.36.

*1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(hexahydro-1*H*-azepin-1-yl)methyl]ferrocene]* (**6d**): Yield 13%. IR: 3065 (arom. C–H), 2953 (CH_2 stretch), 2893 (CH_2), 1628 (C=N), 1597, 1545, 1595 (C=C), 1233 (C–N), 1115 (fc), 1002 (fc), 899 (fc). ^{1}H-NMR ($CDCl_3$): 2.49–2.56 (*m*, 8 CH_2); 3.94 (*s*, 2 CH_2); 4.35–4.45 (*m*, 2 CH_2NCH_2); 4.55–4.62 (*m*, 2 H of fc); 4.74 (*d*, *J* = 12.4, 2 H of fc); 4.84 (*d*, *J* = 12.4, 2 H of fc); 5.19 (*s*, 10 H of fc); 6.57 (*d*, *J* = 7.4, 2 H of pyr); 6.72 (*d*, *J* = 7.4, 2 H of pyr); 7.51 (*s*, 2 H of tp); 7.55 (*s*, 2 H of tp); 8.06–8.19 (*m*, 10 arom. H). FAB-MS: 1087.43 ($[M+H]^+$; calc. 1086.17). Anal. calc. for $C_{66}H_{62}Fe_2N_4S_2$: C 72.91, H 5.75, N 5.15; found: C 72.98, H 5.83, N 5.27.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(cyclohexylmethylamino)methyl]ferrocene] (**6e**): Yield 8%. IR: 3013 (arom. C–H), 2945 (Me stretch), 2868 (CH_2), 1633 (C=N), 1605, 1545, 1508 (C=C), 1219 (C–N), 1113 (fc), 1002 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.35–2.43 (*m*, 2 $(CH_2)_5$); 2.61 (*s*, 2 Me); 3.56 (*s*, 2 CH_2); 3.81–3.89 (*m*, 2 CHN); 4.39–4.47 (*m*, 2 H of fc); 4.65 (*d*, *J* = 12.9, 2 H of fc); 4.71 (*d*, *J* = 12.9, 2 H of fc); 5.36 (*s*, 10 H of fc); 6.42 (*d*, *J* = 7.5, 2 H of pyr); 6.58 (*d*, *J* = 7.5, 2 H of pyr); 7.31 (*s*, 2 H of tp); 7.81 (*s*, 2 H of tp); 8.36–8.48 (*m*, 10 arom. H). FAB-MS: 1115.41 ($[M+H]^+$; calc. 1114.20). Anal. calc. for $C_{68}H_{66}Fe_2N_4S_2$: C 73.23, H 5.97, N 5.02; found: C 73.61, H 6.13, N 5.13.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(diethylamino)methyl]ferrocene] (**6f**): Yield 11%. IR: 3054 (arom. C–H), 2857 (Me stretch), 2857 (CH_2), 1633 (C=N), 1580, 1536, 1485 (C=C), 1248 (C–N), 1115 (fc), 1004 (fc), 904 (fc). ^{1}H-NMR ($CDCl_3$): 1.72 (*t*, 4 Me); 3.58 (*m*, 2 $(CH_2)_2N$); 3.60 (*s*, 2 CH_2); 4.25 (*d*, *J* = 12.3, 2 H of fc); 4.56 (*d*, *J* = 12.3, 2 H of fc); 4.62 (*s*, 10 H of fc); 4.71–4.79 (*m*, 2 H of fc); 6.49 (*d*, *J* = 12.6, 2 H of pyr); 6.69 (*d*, *J* = 12.6, 2 H of pyr); 7.53 (*s*, 2 H of tp); 7.67 (*s*, 2 H of tp); 8.13–8.25 (*m*, 10 arom. H). FAB-MS: 1035.56 ($[M+H]^+$; calc. 1034.14). Anal. calc. for $C_{62}H_{58}Fe_2N_4S_2$: C 71.94, H 5.65, N 5.41; found: C 71.88, H 5.74, N 5.49.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(dipropylamino)methyl]ferrocene] (**6g**): Yield 13%. IR: 3048 (arom. C–H), 2920 (Me stretch), 2865 (CH_2), 1642 (C=N), 1505, 1536, 1498 (C=C), 1223 (C–N), 1115 (fc), 1005 (fc), 905 (fc). ^{1}H-NMR ($CDCl_3$): 1.65 (*t*, 4 Me); 2.88–2.96 (*m*, 4 CH_2); 3.11 (*t*, 2 $(CH_2)_2N$); 4.05 (*s*, 2 CH_2N); 4.35 (*d*, *J* = 12.8, 2 H of fc); 4.56 (*d*, *J* = 12.8, 4 H of fc); 4.73–4.79 (*m*, 2 H of fc); 4.97 (*s*, 10 H of fc); 6.51 (*d*, *J* = 7.3, 2 H of pyr); 6.81 (*d*, *J* = 7.3, 2 H of pyr); 7.43 (*s*, 2 H of tp); 7.82 (*s*, 2 H of tp); 8.19–8.32 (*m*, 10 arom. H). FAB-MS: 1091.62 ($[M+H]^+$; calc. 1090.20). Anal. calc. for $C_{66}H_{66}Fe_2N_4S_2$: C 72.64, H 6.10, N 5.13; found: C 72.56, H 6.23, N 5.18.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(pyrrolidin-1-yl)methyl]ferrocene] (**6h**): Yield 9%. IR: 3038 (arom. C–H), 2895 (CH_2), 1628 (C=N), 1610, 1511, 1472 (C=C), 1215 (C–N), 1115 (fc), 1005 (fc), 905 (fc). ^{1}H-NMR ($CDCl_3$): 2.57–2.61 (*m*, 2 $(CH_2)_2$); 4.19–4.25 (*m*, 2 $(CH_2)_2N$); 4.36 (*s*, 2 CH_2N); 4.39 (*d*, *J* = 12.4, 2 H of fc); 4.55–4.64 (*m*, 2 H of fc); 4.95 (*d*, *J* = 12.4, 2 H of fc); 5.92 (*s*, 10 H of fc); 6.39 (*d*, *J* = 7.4, 2 H of pyr); 6.74 (*d*, *J* = 7.4, 2 H of pyr); 7.54 (*s*, 2 H of tp); 7.86 (*s*, 2 H of tp); 8.21–8.35 (*m*, 10 arom. H). FAB-MS: 1031.57 ($[M+H]^+$; calc. 1030.10). Anal. calc. for $C_{62}H_{54}Fe_2N_4S_2$: C 72.22, H 5.28, N 5.43; found: C 72.32, H 5.43, N 5.56.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(ethylpiperidin-1-yl)methyl]ferrocene] (**6i**): Yield 8%. IR: 3069 (arom. C–H), 2913 (CH_2), 1618, 1572, 1487 (C=C), 1234 (C–N), 1115 (fc), 1000 (fc), 902 (fc). ^{1}H-NMR ($CDCl_3$): 1.63 (*t*, 2 Me); 2.28 (*m*, 8 CH_2); 3.76 (*m*, 2 CHN); 3.82 (*t*, 2 CH_2N); 4.39 (*d*, *J* = 12.6, 2 H of fc); 4.53 (*s*, 2 CH_2N); 4.61–4.68 (*m*, 2 H of fc); 4.82 (*d*, *J* = 12.6, 2 H of fc); 4.91 (*s*, 10 H of fc); 6.48 (*d*, *J* = 7.5, 2 H of pyr); 6.78 (*d*, *J* = 7.5, 2 H of pyr); 7.37 (*s*, 2 H of tp); 7.76 (*s*, 2 H of tp); 8.39–8.47 (*m*, 10 arom. H). FAB-MS: 1115.48 ($[M+H]^+$; calc. 1114.20). Anal. calc. for $C_{68}H_{66}Fe_2N_4S_2$: C 73.23, H 5.97, N 5.02; found: C 73.34, H 6.09, N 5.15.

1,1″-(10,15-Diphenyl-21,23-dithiaporphine-5,20-diyl)bis[2-[(4-phenylpiperazin-1-yl)methyl]ferrocene] (**6j**): Yield 12%. IR: 3011 (arom. C–H), 2885 (CH_2), 1591, 1533, 1482 (C=C), 1233 (C–N), 1112 (fc), 1004 (fc), 903 (fc). ^{1}H-NMR ($CDCl_3$): 2.30–2.64 (*m*, 4 CH_2NCH_2); 4.30 (*s*, 2 CH_2N); 4.41 (*d*, *J* = 12.7, 2 H of fc); 4.58–4.71 (*m*, 2 H of fc); 4.91 (*s*, 10 H of fc); 5.01 (*d*, *J* = 12.7, 2 H of fc); 6.39 (*d*, *J* = 7.4, 2 H of pyr); 6.68 (*d*, *J* = 7.4, 2 H of pyr); 7.44 (*s*, 2 H of tp); 7.89 (*s*, 2 H of tp); 8.36–8.45 (*m*, 10 arom. H). FAB-MS: 1213.33 ($[M+H]^+$; calc. 1212.08). Anal. calc. for $C_{74}H_{64}Fe_2N_6S_2$: C 73.26, H 5.32, N 6.93; found: C 73.41, H 5.39, N 7.06.

8. *Anti-amoebic Activity.* The compounds **6a**–**6j** were screened *in vitro* for anti-amoebic activity against the strain HM1:IMSS of *E. histolytica* by the microdilution method [21]. *E. histolytica* trophozoites were cultured in TYIS-33 growth medium [22], in wells of a 96 microtiter plate (*Costar*). The test compounds were dissolved in DMSO (40 µl). The maximum concentration of DMSO in the test did not exceed 0.1% at which level no inhibition of amoebal growth occurred [23][24]. Enough culture medium was added to obtain a concentration of 1 mg/ml. Stock solns. of the compounds were prepared freshly before use at a concentration of 0.1 mg/ml. Two-fold serial dilutions were made. Each test included metronidazole as a standard amoebic drug, control wells (culture medium plus amoeba), and a blank (culture medium only). The number of amoeba per milliliter was estimated with a haemocytometer, and trypan blue exclusion was used to confirm viability. The cell suspension used was diluted to 10^5 organisms/ml by adding fresh medium, and 170 µl of this suspension was added to the test and control wells in the plate. An inoculum of $1.7 \cdot 10^4$ organisms/well was chosen, so that confluent but not excessive growth took place. The plates were sealed, gassed for 10 min with N_2, and incubated at 37° for 72 h. After incubation, the growth of the amoeba was checked with a low-power microscope. The culture medium was removed by inverting the plate and shaking gently. The plates were immediately washed with 0.9% aq. NaCl soln. at 37°. This procedure was performed quickly, and the plate was not allowed to cool, to prevent the detachment of amoebae. The plate was allowed to dry at r.t., and the amoebae were fixed with chilled MeOH by keeping it in an ice bath for 15 min, dried, and stained with 0.5% aq. eosin soln. for 15 min. The stained plate was washed once with ordinary H_2O, and then twice with dist. H_2O, and allowed to dry. Then, 0.1N aq. NaOH soln. (200 µl) was added to each well to dissolve the protein and to release the dye (eosine). The optical density of the resulting soln. in each well was determined at 490 nm with a microplate reader. The inhibition (%) of amoebal growth was calculated from the optical densities of the control and test wells, and plotted against the logarithm of the dose of the drug tested. Linear-regression analysis was used to determine the best-fitting straight line (*Fig.*) from which IC_{50} values were determined. The experiments were performed thrice for each compound tested.

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