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Organometallic Nucleoside Analogues with Ferrocenyl Linker Groups: Synthesis and Cancer Cell Line Studies

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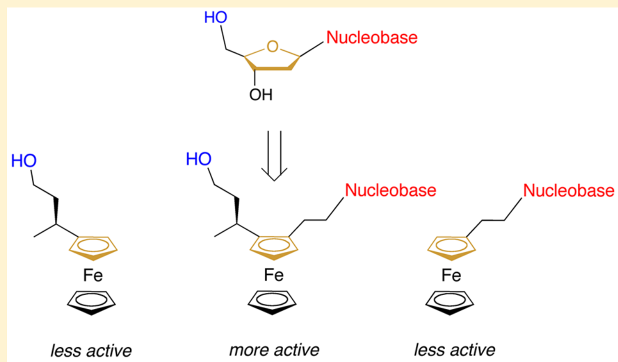
Supporting Information

ABSTRACT: Examples of organometallic compounds as nucleoside analogues are rare within the field of medicinal bioorganometallic chemistry. We report on the synthesis and properties of two chiral ferrocene derivatives containing a nucleobase and a hydroxyalkyl group. These so-called ferronucleosides show promising anticancer activity, with cytostatic studies on five different cancer cell lines indicating that both functional groups are required for optimal activity.



Nucleoside analogues have long been established as an effective class of compound that exhibits antiviral or anticancer activity.[1] Two common structural features are a nucleobase moiety and a hydroxylmethyl group (Figure 1), which together allow them to act as substrates that adversely affect processes associated with nucleic acid synthesis. These two components are typically connected by an organic linker group that is a modification or a replacement of the sugar ring, which can either be cyclic (e.g., AZT) or acyclic (e.g., acyclovir).[2] Because of their structural similarities to natural nucleosides, which can lead to resistance and side effects, there is a continuing need for a diverse range of analogues with different structural features. Ferrocene has attracted active interest in recent years within the field of medicinal and bioorganometallic chemistry,[3] with organometallic analogues and derivatives of the antimalarial drug chloroquine (ferroquine) and the breast cancer drug tamoxifen (the ferrocifen family) being the most widely known.[4] At the same time there has been a number of examples of other ferrocene containing compounds that have shown anticancer,[5] antibacterial, and antifungal properties.[6] However, although there are also some recent examples of ferrocene-conjugated nucleobases[7] and hydroxylalkyl ferrocenes[8] that exhibit anticancer activity, as far as we are aware, nucleoside analogues of the type shown in Figure 1 that are bridged solely by an organometallic linker group and show biological activity have not been reported.[9]

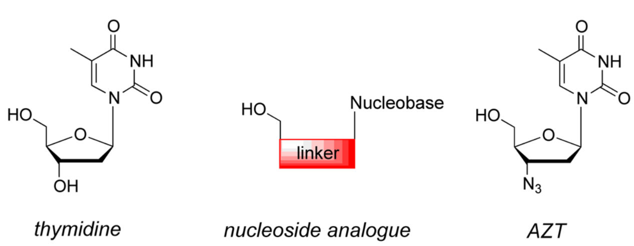


Figure 1. Representation of the structural relationship between thymidine and a nucleoside analogue that contains a variable linker group connecting a hydroxymethyl group with a nucleobase, with AZT (azidothymidine) as a specific example.

As part of our program to develop novel metal-containing analogues of DNA and its components,[10] we recently reported an organometallic nucleic acid oligomer designated as ferrocene nucleic acid (FcNA).[10b] The monomeric components of the reported form of FcNA consist of a tetrasubstituted ferrocene unit containing two alkylhydroxyl groups to allow connectivity via phosphodiesters, and two thymine nucleobases. We noticed that these monomeric compounds have the required features for a novel nucleoside analogue, where the five-membered

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sugar ring is substituted for a five-membered cyclopentadienyl ring of a ferrocene unit. Accordingly we now report bis-substituted ferrocenes **1** and **2** (so-called ferronucleosides) that contain both a nucleobase (thymine or adenine) and a hydroxyl group, along with various control compounds (Figure 2). The cell line studies reported here demonstrate the promise of these ferrocenyl derivatives as a novel class of nucleoside analogues that show anticancer activity.

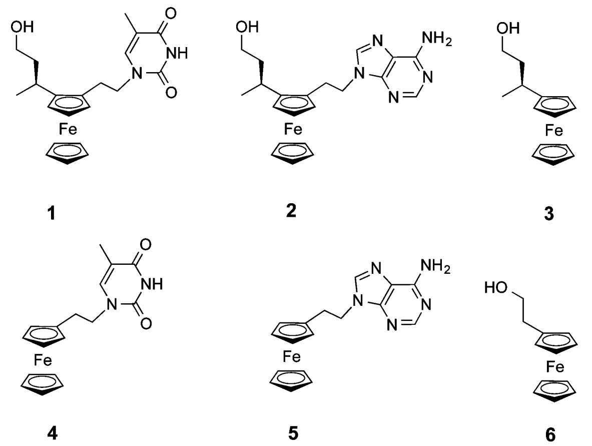

Figure 2. Ferronucleosides **1** and **2** and controls **3**−**6**.

It was decided to first synthesize nucleoside analogues with a 1,2-disubstituted arrangement on one Cp ring, with the other Cp ring unfunctionalized. This would enable us to utilize the synthetic chemistry already developed within the group for FcNA monomer synthesis.[10b] For the same reason, the compounds would have a three-carbon hydroxyl linker (with a methyl group on the α carbon to direct ortho-lithiation) and a two-carbon linker to the nucleobase. The synthetic route taken to make the ferronucleoside targets **1** and **2** is outlined in Scheme 1. The chirally pure Ugi amine[11] **7** was treated with *n*-BuLi and quenched with iodine to introduce the required planar 1,2-disubstitution pattern. Subsequent functional group interconversion gave **11**, to provide the chain extension giving a three carbon linker. Treatment of **11** with silyl enol ether, catalyzed by the Lewis acid boron trifluoride, gave **12** in good yield. Reduction of the ester followed by TBDPS protection gave **14**. Conversion to aldehyde **15** (via *n*-BuLi halogen exchange and quenching with DMF) enabled a Wittig reaction to be performed to form alkene **16**, with subsequent hydroboration−oxidation giving the monoprotected bis-alcohol **17** in high chiral purity (as checked by chiral HPLC analysis, overall 97% ee). The conversion of **17** to the target compounds **1** and **2** proceeded via a Mitsunobu reaction with the appropriate protected nucleobase, followed by deprotection of the protecting groups. The family of compounds was also extended by making the control compounds **3**−**6** (Figure 2) to assess the role of the alcohol and nucleobase groups, noting that **6** had previously been shown[8] to display antineoplastic activity against cervix carcinoma (HeLa) tumor cells.

The cytostatic activity of six ferrocene compounds was evaluated in comparison to the established anticancer drugs cisplatin and 5-fluorouracil (5-FU) using a proliferation activity assay carried out on three tumor cell lines: murine leukemia cells (L1210), HeLa, and human T-lymphocyte cells (CEM). The data indicate that the concomitant presence of the hydroxyl and nucleobase components is crucial to give the highest cytostatic activity, with **1** and **2** exhibiting low micromolar to submicromolar antiproliferative activity comparable with cisplatin (Table 1). In addition, **1** and **2** were almost equally as active as 5-FU in L1210 cell cultures, 2- to 5-fold less active in HeLa cell cultures, but 20- to 50-fold more active in CEM cell cultures. Compounds **1** and **2** proved to be poorly toxic to nontumorigenic human embryonic lung (HEL) fibroblast cell cultures (minimal cytotoxic concentration, >50 μM).

Cell growth studies carried out on an esophageal cancer cell line revealed that **1** inhibited growth at 6.25 μM, whereas control compounds **3** and **4** (Figure 3 and Supporting Information, respectively) had much less or no effect, even up to higher concentrations of 25 μM. The same trend was

Scheme 1. Synthetic Route toward Ferrocene Nucleoside Analogues 1 and 2

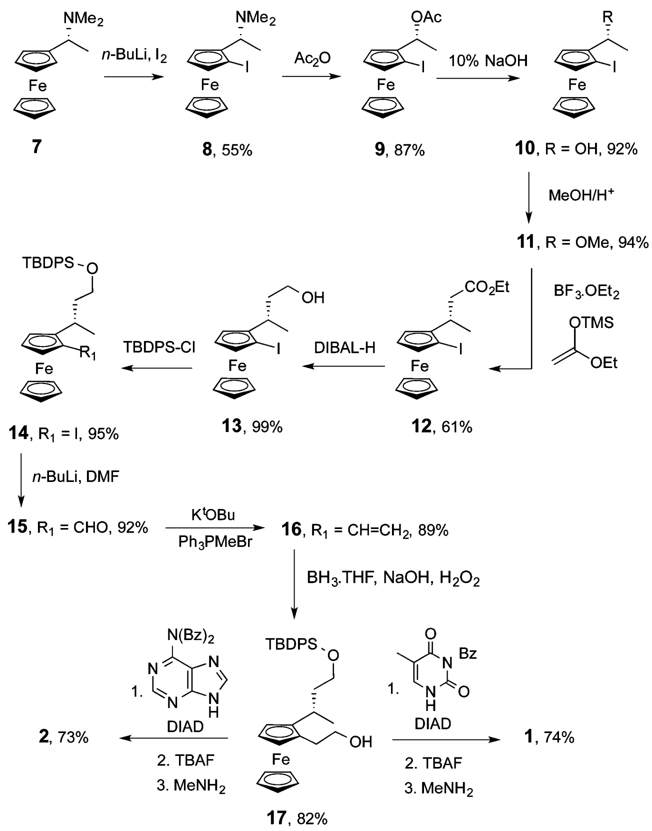

Table 1. Cytostatic activity of Compounds 1−4

compd	IC_{50} (μM)[a] L1210	CEM	HeLa
1	0.78	0.9	2.68
2	1.0	0.35	1.1
3	12	39	45
4	417	592	509
5	26	49	94
6	25	43	52
cisplatin	1	0.9	1.2
5-FU	0.33 ± 0.17	18 ± 5	0.54 ± 0.12

[a]50% inhibitory concentration, or compound concentration required to inhibit tumor cell proliferation by 50%. Data are the mean of at least two independent experiments.

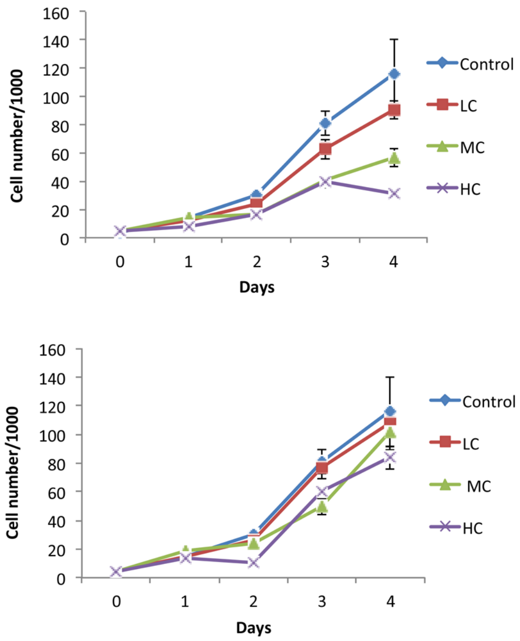

Figure 3. Growth curves for **1** (top) and **3** (bottom) at three different concentrations (LC = 6.25 μM, MC = 12.5 μM, HC = 25 μM) over 4 days in cancer cell line OE 19 (n = 3 ± SD).

observed for the adenine **2** and its control **5** (see Supporting Information data). Once again the data indicate that both functional groups (the hydroxyl and the nucleobase) are required for the best cytostatic activities, which is comparable to cisplatin under these conditions.

Assays of cellular viability (MTT assay) and cell proliferation (BrdU assay) were then performed on colorectal cancer cell lines. The results after a 48 h exposure (Figure 4) revealed that

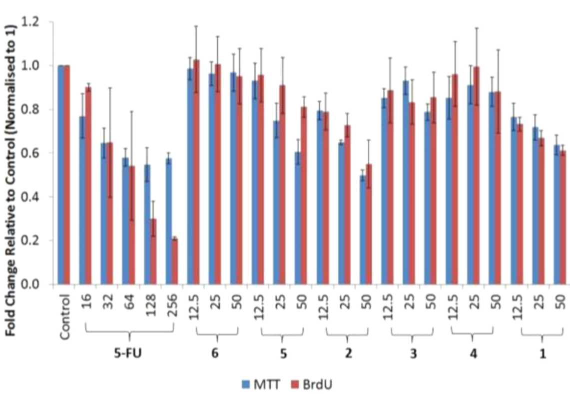

Figure 4. Cellular viability (MTT, blue) and cell proliferation (BrdU, red) assays on colorectal cell lines (48 h).

1 and **2** had antineoplastic activities approaching that 5-FU, whereas the other compounds were less effective. Encouragingly, an AMES assay to investigate the potential mutagenicity of these ferrocenyl derivatives revealed that the compounds were inactive.

In conclusion, novel ferrocenyl nucleoside analogues **1** and **2** appear to exhibit cytostatic activities that are comparable under the conditions used to commercially establish anticancer drugs such as cisplatin and 5-FU. Control studies indicate that the presence of a hydroxyl and a nucleobase group is required for optimal activity. This suggests a mechanistic role for these novel bioorganometallic compounds involving an adverse effect on nucleic acid synthesis, as is the case for nucleobase analogue drugs containing organic linker groups.[12] We are currently planning to carry out further studies to reveal the mode of action of these ferronucleosides and to highlight stereochemical and structure−activity relationships for improving biological activity and specificity.

■ EXPERIMENTAL SECTION

General Information. Unless stated otherwise, all reactions were performed under an Ar atmosphere. Compound **6** was prepared as described previously.[8] All tested compounds had a purity of ≥95%, as shown by HPLC (see Supporting Information for data and conditions used).

(R,S_p)-1-(α-N,N-Dimethylaminoethyl)-2-iodoferrocene (8). The Ugi amine **7**[11] (4.00 g, 15.56 mmol) was dissolved in Et_2O (50 mL) at room temperature. n-BuLi (12 mL, 30 mmol) was added and the mixture stirred overnight. The mixture was cooled to −78 °C, and iodine (9.52 g, 37.51 mmol), dissolved in THF (60 mL), was added over 10 min. The mixture was stirred at −78 °C for 90 min before being warmed to room temperature, at which point it was stirred for an additional 90 min before being quenched at 0 °C with sodium thiosulfate$_{(aq)}$ (50 mL, 25% w/v). After dilution with Et_2O (30 mL), the layers were separated and the aqueous layer was further extracted with Et_2O (3 × 50 mL). The combined organic fractions were dried over $MgSO_4$. The solvent was removed in vacuo before purification via flash column chromatography (5% MeOH, 5% TEA in DCM) to yield product (3.18 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (dd, J = 2.4, 1.4 Hz, 1H), 4.24 (t, J = 2.6 Hz, 1H), 4.15 (dd, J = 2.7, 1.3 Hz, 1H), 4.12 (s, 5H), 3.62 (q, J = 6.8 Hz, 1H), 2.15 (s, 6H), 1.50 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 90.21 (ipso Cp), 74.32 (Fc), 71.67 (Fc), 68.19 (Fc), 65.59 (Fc), 57.59 (CH*), 45.49 (ipso Cp), 41.22 (CH_3), 16.01 (CH_3). MS (ES) (m/z) calcd for $C_{14}H_{18}N^{56}FeI$ 382.9833, found 382.9820. IR (cm^{-1}): 3078 (=C−H), 2931 (CH_2), 2878 (CH_2), 2809 (CH_2), 1446 (CH_3), 1371 (CH_3), 1243, 1087, 821 (CH=CH), 732 (CH Ar). Mp: 58−60 °C.

(R,S_p)-1-(α-Acetoxyethyl)-2-iodoferrocene (9). Compound **8** (3.26 g, 8.51 mmol) and acetic anhydride (25.68 mL, 272.17 mmol) were heated at 50 °C for 2 h. The acetic anhydride was removed under high vacuum (0.1 mmHg) and the residue purified via flash column chromatography (10% EtOAc in hexane) to yield the yellow-brown oily product (2.94 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (q, J = 6.4 Hz, 1H), 4.51 (dd, J = 2.6, 1.4 Hz, 1H), 4.33 (dd, J = 2.8, 1.4 Hz, 1H), 4.28 (t, J = 2.6 Hz, 1H), 4.15 (s, 5H), 2.01 (s, 3H), 1.66 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.30 (C=O), 87.54 (ipso Cp), 75.63 (Fc), 71.76 (Fc), 69.71 (Fc), 68.94 (Fc), 65.80 (CH*), 44.03 (ipso Cp), 21.16 (CH_3), 18.66 (CH_3). MS (ES) calcd for $C_{14}H_{15}O_2{}^{56}FeI$ 397.9466, found 397.9471. IR (cm^{-1}): 3095 (=C−H), 2972 (CH_2), 2928 (CH_2), 2866 (CH_2), 1729 (C=O), 1445 (CH_3), 1371 (CH_3), 1085, 820 (CH=CH), 703 (CH Ar).

(R,S_p)-1-(α-Hydroxyethyl)-2-iodoferrocene (10). Compound **9** (2.937 g, 7.37 mmol) was dissolved in EtOH (35 mL). NaOH$_{(aq)}$ (30 mL, 10% w/v) was added, and the mixture was heated at 95 °C for 15 min. After the mixture was cooled to room temperature, the organic layer was extracted with EtOAc (2 × 40 mL). The organic layers were dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified via flash column chromatography (25% EtOAc in hexane) to yield the yellow oily product (2.43 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (qd, J = 6.5, 2.8 Hz, 1H), 4.46 (dd, J = 2.5, 1.4 Hz, 1H), 4.29 (dd, J = 2.7, 1.3 Hz, 1H), 4.25 (t, J = 2.6 Hz, 1H), 4.14 (s, 5H), 1.88 (d, J = 3.6 Hz, 1H), 1.62 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 91.61 (ipso Cp), 75.01 (Fc), 71.59 (Fc), 68.72 (Fc), 66.51 (Fc), 64.98 (CH*), 43.62 (ipso Cp), 21.31 (CH_3). MS (ES) (m/z) calcd for $C_{12}H_{13}O^{56}FeI$ 355.9361, found 355.9352. IR (cm^{-1}): 3255 (OH), 3093 (=C−H), 2967 (CH_2), 2920 (CH_2), 1445 (CH_3), 1369 (CH_3), 1099 (C−OH), 816 (CH=CH), 684 (CH=CH).

(R,S_p)-1-(α-Methoxyethyl)-2-iodoferrocene (11). Compound **10** (2.43 g, 6.83 mmol) was dissolved in a MeOH/AcOH (20 mL, 9:1) mixture, and the solution was stirred at room temperature for 48

h. The reaction was quenched with water (10 mL) and extracted with DCM (2 × 20 mL). The combined organic fractions were dried over $MgSO_4$, the solvent was removed in vacuo, and the residue was purified via flash column chromatography (25% EtOAc in hexane) to yield the yellow oily product (2.37 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (dd, *J* = 2.4, 1.4 Hz, 1H), 4.34 (q, *J* = 6.5 Hz, 1H), 4.29−4.25 (m, 2H), 4.13 (s, 5H), 3.26 (s, 3H), 1.64 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 89.78 (ipso Cp), 74.78 (Fc), 74.22 (Fc), 71.66 (Fc), 68.86 (Fc), 65.35 (CH*), 56.00 (CH_3), 39.48 (ipso Cp), 19.63 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{13}H_{15}O^{56}FeI$ 369.9517, found 369.9513. IR (cm^{-1}): 3094 (═C−H), 2974 (CH_2), 2926 (CH_2), 2871 (CH_2), 2815 (CH_2), 1448 (CH_3), 1371 (CH_3), 1085 (C−O−C), 820 (CH═CH).

(S,S_p)-1-[α-Methyl(2-ethylpropanoate)]-2-iodoferrocene (12). Compound **11** (2.37 g, 6.42 mmol) and 1-ethoxyvinyloxytrimethylsilane (8.234 g, 51.37 mmol) were dissolved in DCM (30 mL). The mixture was cooled to −78 °C, and $BF_3{\cdot}OEt_2$ (1.77 mL, 14.12 mmol) was then added dropwise. The mixture was stirred for 15 min at −78 °C before being warmed to room temperature and quenched with saturated $NaHCO_3$ (40 mL). The organic layer was separated, and the aqueous layer was further extracted with DCM (40 mL). The combined organic fractions were dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified via flash column chromatography (10% EtOAc in hexane) to yield the yellow oily product (1.676 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 2.4, 1.4 Hz, 1H), 4.18−4.08 (m, 7H + 2H), 3.14−3.05 (m, 1H), 2.53 (dd, *J* = 15.0, 3.7 Hz, 1H), 2.11 (dd, *J* = 15.0, 10.3 Hz, 1H), 1.43 (d, *J* = 6.9 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.00 (C═O), 94.07 (ipso Cp), 74.12 (Fc), 71.52 (Fc), 67.84 (Fc), 64.58 (Fc), 60.26 (CH_2), 44.08 (ipso Cp), 43.19 (CH_2), 30.72 (CH*), 18.90 (CH_3), 14.27 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{16}H_{19}O_2{}^{56}FeI$ 425.9779, found 425.9782.

(S,S_p)-1-[α-Methyl-(3-(hydroxyl)propyl)]-2-iodoferrocene (13). Compound **12** (1.592 g, 3.73 mmol) was dissolved in Et_2O (50 mL), and the solution was cooled to 0 °C. After standing for 5 min, diisobutylaluminum hydride (11.2 mL, 11.2 mmol) was added slowly at that temperature. The mixture was stirred at 0 °C for 1 h before the reaction was quenched with saturated sodium potassium tartrate in water (30 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (30 mL). The combined organic fractions were dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was purified via flash column chromatography (50% EtOAc in hexane) to yield the product (1.413 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 2.4, 1.4 Hz, 1H), 4.17 (td, *J* = 2.6, 0.6 Hz, 1H), 4.13 (s, 5H), 4.06 (dd, *J* = 2.7, 1.3 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.78−2.69 (m, 1H), 1.72−1.52 (m, 2H), 1.41 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 95.87 (ipso Cp), 73.76 (Fc), 71.47 (Fc), 67.87 (Fc), 64.18 (Fc), 60.84 (CH_2), 44.73 (ipso Cp), 42.09 (CH_2), 29.81 (CH*), 19.69 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{14}H_{17}O^{56}FeI$ 383.9674, found 383.9678. IR (cm^{-1}): 3282 br (OH), 3088 (═CH Fc), 2971 (CH_2), 2932 (CH_2), 2854 (CH_2), 1556, 1452 (CH_2), 1376 (CH_3), 680 (C═C). Mp: 96−98 °C.

(S,S_p)-1-[α-Methyl-(3-(*tert*-butyldiphenylsilyloxy)propyl)]-2-iodoferrocene (14). Compound **13** (1.413 g, 3.67 mmol) was dissolved in DCM (20 mL) at room temperature. TEA (0.77 mL, 5.52 mmol), *tert*-butyldiphenylsilyl chloride (1.44 mL, 5.51 mmol), and DMAP (catalytic amount) were added to the mixture. The solution was then stirred overnight at room temperature before quenching with water (10 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic fractions were dried over Na_2SO_4, the solvent was removed in vacuo, and the residue was purified via flash column chromatography (10% EtOAc in hexane) to yield a yellow oily product (2 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.43−7.32 (m, 6H), 4.38 (dd, *J* = 2.4, 1.3 Hz, 1H), 4.10 (s, 5H + 1H), 4.00 (dd, *J* = 2.7, 1.3 Hz, 1H), 3.70−3.65 (m, 2H), 2.77−2.68 (m, 1H), 1.88−1.80 (m, 1H), 1.43−1.34 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.63 (Ph), 134.10 (ipso Ph), 134.05 (ipso Ph), 129.47 (Ph), 127.58 (Ph), 96.25 (ipso Cp), 73.81 (Fc), 71.38 (Fc), 67.61 (Fc), 64.27(Fc), 62.10 (CH_2), 44.45 (ipso Cp), 41.60 (CH_2), 30.03 (CH*), 26.94 (^{t}Bu), 19.24 (ipso ^{t}Bu), 18.91 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{30}H_{35}O^{56}FeISiNa$ 622.0851, found 622.0846. IR (cm^{-1}): 3071 (═CH Fc), 2958 (CH_2), 2929 (CH_2), 2856 (CH_2), 1472 (CH_2), 1387 (CH_3), 1361, 1106, 1085, 821 (CH Ar TBDPS), 700 (C═C).

(S,S_p)-1-[α-Methyl-(3-(*tert*-butyldiphenylsilyloxy)propyl)]-2-formylferrocene (15). Compound **14** (2.182 g, 3.51 mmol) was dissolved in Et_2O (30 mL). The mixture was cooled to −78 °C, and *n*-BuLi (2.32 mL, 7.01 mmol) was added. After 30 min, DMF (0.68 mL, 8.76 mmol) was added, and the mixture was stirred at −78 °C for another 30 min before being allowed to warm to room temperature before quenching with water (20 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined ethereal fractions were dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified via flash column chromatography (10% EtOAc in hexane) to yield the red oily product (1.686 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.68−7.59 (m, 4H), 7.42−7.33 (m, 6H), 4.75 (dd, *J* = 2.7, 1.4 Hz, 1H), 4.48 (t, *J* = 2.6 Hz, 1H), 4.43 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.21 (s, 5H), 3.61 (t, *J* = 7.1, 2H), 3.21−3.10 (m, 1H), 1.73−1.50 (m, 2H), 1.34 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.25 (C═O), 135.55 (Ph), 133.94 (ipso Ph), 133.80 (ipso Ph), 129.55 (Ph), 127.61 (Ph), 99.14 (ipso Cp), 76.31 (ipso Cp), 71.04 (Fc), 70.80 (Fc), 70.03 (Fc), 68.89 (Fc), 61.75 (CH_2), 43.28 (CH_2), 27.90 (CH*), 26.89 (^{t}Bu), 22.66 (ipso ^{t}Bu), 19.17 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{31}H_{36}O_2{}^{56}FeSiNa$ 547.1732, found 547.1727. IR (cm^{-1}): 3071 (═CH Fc), 2958 (CH_2), 2929 (CH_2), 2856 (CH_2), 1673 (C═O), 1589 (C═N), 1427 (CH_2), 1376 (^{t}Bu), 1106 (Si-OR), 1086 (Si-OR), 821 (CH Ar Ph), 700 (C═C).

(S,R_p)-1-[α-Methyl-(3-(*tert*-butyldiphenylsilyloxy)propyl)]-2-vinylferrocene (16). Trimethylmethylphosphonium bromide (1.722 g, 4.82 mmol), potassium *tert*-butoxide (0.541 g, 4.82 mmol, and a catalytic amount of dibenzo-18-crown-6-ether were dissolved in THF (20 mL). The mixture was stirred for 30 min, and then **15** (1.686 g, 3.21 mmol), dissolved in THF (30 mL), was added to the mixture. The mixture was stirred overnight at room temperature, before quenching with water (10 mL) and extracting with Et_2O (2 × 20 mL). The combined ethereal fractions were dried over Na_2SO_4, solvent was removed in vacuo, and the residue was purified via flash column chromatography (5% EtOAc in hexane) to yield the product as a yellow oil (1.497 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4H), 7.44−7.33 (m, 6H), 6.62 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.34 (dd, *J* = 17.5, 1.8 Hz, 1H), 5.01 (dd, *J* = 10.8, 1.7 Hz, 1H), 4.43 (dd, *J* = 2.5, 1.4 Hz, 1H), 4.12 (t, *J* = 2.6 Hz, 1H), 4.06 (dd, *J* = 2.5, 1.4 Hz, 1H), 4.03 (s, 5H), 3.62 (dd, *J* = 7.2, 5.4 Hz, 2H), 2.94−2.86 (m, 1H), 1.72−1.61 (m, 1H), 1.45−1.37 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.59 (Ph), 134.08 (ipso Ph), 134.02 (ipso Ph), 133.50 (CH vinyl), 129.49 (Ph), 127.56 (Ph), 110.96 (CH_2 vinyl), 94.84 (ipso Cp), 81.37 (ipso Cp), 69.66 (Fc), 66.55 (Fc), 66.27 (Fc), 64.08 (Fc), 61.89 (CH_2), 42.80 (CH_2), 27.65 (CH*), 26.89 (^{t}Bu), 19.23 (ipso ^{t}Bu), 18.92 (CH_3). MS (ES) (*m*/*z*) calcd for $C_{32}H_{38}O^{56}FeSi$ 522.2041, found 522.2055. IR (cm^{-1}): 3072 (═CH Fc), 2958 (CH_2) 2930 (CH_2), 2857 (CH_2), 1625 (Ar Ph), 1589, 1427 (CH_2), 1388 (CH_3), 1105 (Si-OR), 1086 (Si-OR), 821 (CH Ar), 699 (vinyl/C═C).

(S,R_p)-1-[α-Methyl-(3-(*tert*-butyldiphenylsilyloxy)propyl)]-[2-(hydroxyl)ethyl]ferrocene (17). Compound **16** (1.497 g, 2.87 mmol) was dissolved in THF (30 mL). $BH_3{\cdot}THF$ (1 M, 8.2 mL, 8.2 mmol) was then added dropwise at room temperature and the mixture stirred for 2 h. EtOH (9.76 mL), NaOH (3M, 9.76 mL, 29.28 mol), and H_2O_2 (30 wt % in water, 7.17 mL, 63.24 mol) were then successively added, and the mixture was stirred for 1 h at room temperature. The reaction mixture was extracted with DCM (30 mL), washed with brine (20 mL), and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified via flash column chromatography (10% EtOAc in hexane) to yield the yellow oily product (1.434 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.43−7.36 (m, 6H), 4.11−4.09 (m, 1H), 4.05 (s, 5H), 4.00 (t, *J* = 2.5 Hz, 1H), 3.97 (dd, *J* = 2.5, 1.3 Hz, 1H), 3.75 (tq, *J* = 6.8, 2.6 Hz, 2H), 3.67−3.63 (m, 2H), 2.77−2.68 (m, 1H), 2.66−2.49 (m, 2H), 1.74−1.66 (m, 1H), 1.43−1.32 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.56 (Ph), 133.96 (ipso Ph), 129.59 (Ph), 127.63 (Ph), 95.01 (ipso Cp), 82.31 (ipso Cp), 69.03 (Fc), 67.36 (Fc), 65.39 (Fc), 65.15 (Fc), 63.00 (CH_2), 61.98 (CH_2), 42.43 (CH_2), 30.93 (CH_2), 27.51 (CH*), 26.91 (^{t}Bu), 19.37 (CH_3), 19.22 (ipso ^{t}Bu). MS (ES) (m/z) calcd for $C_{32}H_{40}O_2{}^{56}FeSiNa$ 563.2045, found 563.2039. IR (cm^{-1}): 3378 br (OH), 3072 (=CH Fc), 2930 (CH_2), 2857 (CH_2), 1589, 1472 (CH_3), 1427 (CH_2), 1388 (^{t}Bu), 1361, 1105 (Si-OR), 1086 (Si-OR), 819 (CH Ar Ph), 705 (C=C). HPLC: retention time 16.85 min; chiral AD column, 1% IPA in hexane, isocratic over 40 min (1 mL/min), 97% ee.

(S,R_p)-1-[α-Methyl-(3-(hydroxy)propyl)]-2-[(thyminyl)ethyl]-ferrocene (1). Triphenylphosphine (137 mg, 0.516 mmol), 3-benzoylthymine[13] (95 mg, 0.447 mmol), and **17** (0.186 g, 0.344 mmol) were dissolved in THF (10 mL) and stirred for 10 min at room temperature. The flask was then covered with foil, and DIAD (0.11 mL, 0.516 mmol) was added at room temperature before the mixture was heated at 65 °C for 2 h. The mixture was evaporated, extracted with EtOAc (30 mL), washed with brine (20 mL) followed by water (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified via flash column chromatography (30% EtOAc in hexane) to give the fully protected product (219 mg, 85%). Deprotection was achieved first by stirring the compound in 5 mL of TBAF for 2 h before the solvent was removed. The mixture was then redissolved in methylamine (33 wt % in ethanol, 2 mL) and stirred at room temperature for an addition 30 min. The methylamine was evaporated and the crude was purified via flash column chromatography (5% MeOH in DCM) to give the product as a yellow oil (105 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.07 (d, J = 1.2 Hz, 1H), 4.16−4.02 (m, 8H), 3.99−3.88 (m, 1H), 3.74−3.55 (m, 3H), 2.96−2.47 (m, 4H), 1.95 (d, J = 1.1 Hz, 3H), 1.75−1.64 (m, 1H), 1.56−1.46 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.22 (C=O), 151.11 (C=O), 140.41 (CH-thymine), 111.00 (ipso thymine), 95.36 (ipso Fc), 80.77(ipso Fc), 69.30 (CH Cp), 67.63 (CH Cp), 65.97 (CH Cp), 65.37 (CH Cp), 60.27 (CH_2), 49.84 (CH_2), 43.24 (CH_2), 27.99 (CH_2), 27.07 (CH), 19.25 (CH_3 thymine), 12.30 (CH_3). MS (ES) (m/z) calcd for $C_{21}H_{26}N_2O_3Na^{56}Fe$ 433.1191, found 433.1182. IR (cm^{-1}): 3520−3291 br (OH), 2957 (CH), 1677 (C=O).

(S,R_p)-1-[α-Methyl-(3-(hydroxy)propyl)]-2-[2-(-adenin-9-yl)-ethyl]ferrocene (2). Triphenylphosphine (0.291 g, 1.109 mmol), N,N-6-dibenzoyladenine[14] (0.381 g, 1.109 mmol), and **17** (0.300 g, 0.555 mmol) were dissolved in THF (10 mL) and stirred for 10 min at room temperature. The flask was then covered with foil, and DIAD (0.24 mL, 1.109 mmol) was added at room temperature before the mixture was warmed to 65 °C for 2 h. The mixture was evaporated, extracted with EtOAc (30 mL), washed with brine (20 mL) followed by water (20 mL), and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified via flash column chromatography (30% EtOAc in hexane) to give the protected product (0.343 g, 72%). Deprotection was achieved first by stirring the compound in TBAF (5 mL, 1M) for 2 h. The solvent was then removed and the residue redissolved in methylamine (33 wt % in ethanol, 2 mL) and stirred at room temperature for an additional 30 min. The methylamine was then evaporated and the crude mixture purified via flash column chromatography to give the product as a yellow solid (170 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.17 (s, 1H), 7.21 (s, 2H), 4.41−4.33 (m, 2H+1H (OH)), 4.11 (s, 5H), 4.02 (d, J = 2.4 Hz, 2H), 3.99 (t, J = 2.4 Hz, 1H), 3.42−3.28 (m, 2H), 2.97−2.75 (m, 2H), 2.75−2.67 (m, 1H), 1.53−1.45 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H + 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.95 (ipso adenine), 152.43 (CH adenine), 149.39 (ipso adenine), 140.71 (CH adenine), 118.75 (ipso adenine), 94.43 (ipso Cp), 81.89 (ipso Cp), 68.80 (Cp), 66.46 (Cp), 64.92 (Cp), 64.74 (Cp), 58.66 (CH_2), 43.10 (CH_2), 42.43 (CH_2), 27.98 (CH_2), 27.10 (CH*), 19.38 (CH_3). MS (ES) (m/z) calcd for $C_{21}H_{26}N_5O^{56}Fe$ 420.1487, found 420.1484. IR (cm^{-1}): 3348 br (OH), 3270 (NH_2), 3240 (NH_2), 3098 (=CH Fc), 2955 (CH_2), 2926 (CH_2), 2871 (CH_2), 1674 (C=N), 1604 (NH_2), 1574 (NH_2), 1305 (OH), 1076 (C−O), 814 (CH Ar). Mp: 90 °C-92 °C.

(S)-1-[α-Methyl-(3-(hydroxy)propyl)]ferrocene (3). (S)-3-Ethoxy-1-methyl-3-oxopropylferrocene[15] (220 mg, 0.733 mmol) was dissolved in diethyl ether (10 mL). $LiAlH_4$ (56 mg, 1.466 mmol) was added carefully, and the resulting suspension was left to stir for 1 h. The reaction was quenched with saturated sodium potassium tartrate (10 mL), extracted with diethyl ether (2 × 20 mL), dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified via flash column chromatography to give the product as a yellow oil (100 mg, 58%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 5H), 4.09−4.04 (m, 4H), 3.67 (q, J = 6.2 Hz, 2H), 2.74−2.53 (m, 1H), 1.85−1.61 (m, 2H), 1.27 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 95.41 (ipso Cp), 68.51 (CH Cp), 67.22 (CH Cp), 67.12 (CH Cp), 67.07 (CH Cp), 65.70 (CH Cp), 61.12 (CH_2), 41.47 (CH_2), 29.62 (CH), 20.64 (CH_3). MS (ES) (m/z) calcd for $C_{14}H_{18}O_2{}^{56}Fe$ 258.0707, found 258.0708. IR (cm^{-1}): 3512−3146 br (OH), 2933 (CH), 1052 (C−O).

1-(Thyminyl)ethylferrocene (4). Triphenylphosphine (348 mg, 1.30 mmol), N-3-benzoylthymine[13] (223 mg, 1.04 mmol), and 2-ferrocenylethanol[16] (200 mg, 0.87 mmol) were dissolved in THF (10 mL) and stirred for 10 min at room temperature. The flask was then covered with foil, and DIAD (0.28 mL, 1.30 mmol) was added at room temperature before the mixture was heated at 65 °C for 2 h. The solvent was then evaporated and the residue extracted with EtOAc (30 mL), washed with brine (20 mL) and water (20 mL), and dried over Na_2SO_4, before the solvent was removed in vacuo. Deprotection was achieved by treating the crude mixture with methylamine solution (33 wt % in ethanol, 5 mL) for 30 min. The solvent was then evaporated in vacuo and the residue purified via flash column chromatography (40% EtOAc in hexane) to give the product (176 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 6.70 (d, J = 1.2 Hz, 1H), 4.15 (s, 5H), 4.13−4.09 (m, 2H), 4.04 (t, J = 1.8 Hz, 2H), 3.79 (t, J = 7.1 Hz, 2H), 2.73 (t, J = 7.1 Hz, 2H), 1.85 (d, J = 1.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$ trace of MeOD) δ 216.94 (ipso thymine), 193.73 (C=O), 181.71 (C=O), 141.17 (CH-thymine), 83.57 (ipso-Cp), 68.63(CH-Cp), 68.37(CH-Cp), 67.94 (CH-Cp), 50.20 (CH_2), 29.17 (CH_2), 11.98 (CH_3). MS (ES) (m/z) calcd for $C_{17}H_{18}N_2O_2{}^{56}Fe$ 338.0718, found 338.0720. Mp: degraded at 235 °C. IR (cm^{-1}): 3146 (NH), 2999 (CH), 1683 (C=O), 1644 (NH bending).

1-[2-(Adenin-9-yl)ethyl]ferrocene (5). Triphenylphosphine (0.383 g, 1.46 mmol), N,N-6,6-dibenzoyladenine[14] (0.500 g, 1.46 mmol), and 2-ferrocenylethanol[16] (0.201 g, 0.73 mmol) were dissolved in THF (10 mL) and stirred for 10 min at room temperature. The flask was then covered with foil, and DIAD (0.24 mL, 1.18 mmol) was added at room temperature before the mixture was warmed to 65 °C for 2 h. The mixture was evaporated, extracted with EtOAc (30 mL), washed with brine (20 mL) followed by water (20 mL), and then dried over Na_2SO_4. The solvent was removed in vacuo and purified via flash column chromatography (40% EtOAc in hexane) to give the bis-protected product (0.134 g, 33%). Deprotection was achieved by dissolving the compound (0.055 g, 0.1 mmol) in methylamine (33 wt % in ethanol, 3 mL) and stirring at room temperature for 30 min. The methylamine was then evaporated and the residue purified via flash column chromatography (95/5 DCM/MeOH) to give the product as a yellow solid (0.019 g, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (s, 1H), 8.05 (s, 1H), 7.17 (s, 2H), 4.31 (dd, J = 8.2, 6.8 Hz, 2H), 4.15 (s, 5H), 4.08−4.02 (m, 4H), 2.85 (t, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.89 (ipso adenine), 152.35 (CH adenine), 149.40 (ipso adenine), 140.76 (CH adenine), 118.73 (ipso adenine), 84.39 (ipso Cp), 69.00 (Fc), 68.55 (Fc), 43.75 (CH_2), 29.34 (CH_2). MS (ES) (m/z) calcd for $C_{17}H_{18}N_5{}^{56}Fe$ 348.0912, found 348.0920 ($M^+ + H^+$). IR (cm^{-1}): 3399 (NH_2), 3316 (NH_2), 3084 (=CH Fc), 2980 (CH_2), 2931 (CH_2), 2907 (CH_2), 1653 (C=C), 1596 (NH_2), 1435 (CH_2), 1245, 797 (CH Ar). Mp: 142 °C (dec).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra for **1−5** and **8−17**, HPLC data for **1−6** and **17**, cell study procedures, and cell growth data for

2, 4, and 5 on an esophageal cancer cell line. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

DCM, dichloromethane; DIAD, diisopropyl azodicarboxylate; DMSO, dimethyl sulfoxide; TEA, triethylamine; DMAP, 4-dimethylaminopyridine; *n*-BuLi, *n*-butyllithium; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; BrdU, bromodeoxyuridine; THF, tetrahydrofuran

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