Supplementary Material (ESI) for Medicinal Chemistry Communications


# Supporting Information

# Synthesis and biological evaluation of novel ferrocenyl curcuminoid derivatives

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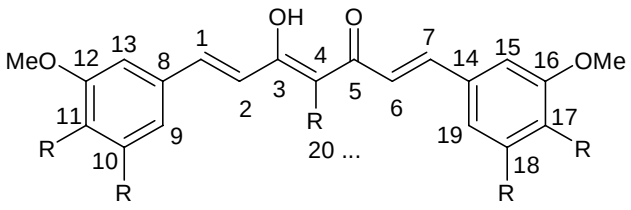
**Numbering scheme for NMR assignment of curcuminoid skeleton**




**Chemistry.** All air-sensitive reactions were carried out under argon atmosphere, using standard Schlenk and vacuum-line techniques. THF was distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Anhydrous piperidine was obtained by distillation from potassium hydroxide. All other chemical reagents and solvents were used as received without further purification. Thin layer chromatography was performed on silica gel 60 GF254. Column flash chromatography was performed on silica gel Merck 60 (40-63 μm). Melting points were measured with a Kofler device. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance300 or a Bruker Avance400 spectrometer at 20 °C at 300 MHz and 75 MHz or 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are given in ppm, referenced to the residual proton resonance of the solvents (7.26 ppm for $CDCl_3$; 5.32 ppm for $CD_2Cl_2$) and carbon resonance of the solvents (77.2 ppm for $CDCl_3$; 53.1 ppm for $CD_2Cl_2$). Mass spectra were obtained by the "Service de Spectrométrie de Masse" of the Chimie Paristech, Paris. HPLC/APCI-MS was performed with an Agilent 1100 Series liquid chromatography equipped with an automatic injector and coupled with a PESciex API 3000 mass spectrometer. The sample was introduced by Flow Injection Analysis (FIA). A solution of $H_2O$/MeOH (1/9) was used as eluant (200 $\mu L.min^{-1}$) and the injected volume of the sample was 5 μL. High-resolution mass spectroscopy was carried out by the "Groupe de spectroscopie de Masse" of the laboratory "Structure et Fonction de Molécules Bioactives" at the University of Pierre et Marie Curie, Paris. Elemental analyses were carried out by the "Service de Microanalyse" at the Institute de Chimie des Substances Naturelles (ICSN), Gif-

sur-Yvette. The organic curcuminoids **1**,[1] **2**,[1] **3**,[2] **4**[2] and **14**[3] as well as the ferrocenyl ligands 1-ferrocenyl-2-propyn-1-one,[4] α-bromoacetylferrocene[5] were prepared following literature procedures. The synthesis of the ferrocenyl curcuminoids, **5**, **6** and **7** were described earlier.[6]

**General procedure for the synthesis of 8 and 9 (series A).** An anhydrous THF solution of the appropriate curcuminoid (1 eq) was added dropwise to an oil-free suspension of NaH (1.7 eq) in anhydrous THF at 0 °C. After stirring for 30 minutes at 0 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for further 2 hours. A solution of 1-ferrocenyl-2-propyn-1-one (2 eq) in anhydrous THF was added dropwise and the reaction mixture was allowed to stir for 1-2 hours, monitored by TLC. After hydrolysis with water, the mixture was extracted with ethyl acetate, and the organic phase was dried on magnesium sulfate, filtered and evaporated under reduced pressure. The ferrocenyl-curcuminoid was purified by column flash chromatography on silica gel using hexane/ethyl acetate as eluent.

**(1E,4Z,6E)-1,7-bis-(3,4-dimethoxyphenyl)-4-[(E)-1-ferrocenylprop-2-en-1-one]-3-hydroxy-hepta-1,4,6-trien-5-one (8).** The synthesis was carried out as described above by using **2** (198 mg, 0.50 mmol), sodium hydride (34 mg, 60% dispersion, 0.85 mmol) and ferrocenyl-2-propyn-1-one (237 mg, 1.00 mmol) in anhydrous THF (5 mL). After column flash chromatography (hexane/ethyl acetate 3:2), **8** was yielded as a brick red solid (80 mg, 25%). Mp: 183-185 °C. IR ($cm^{-1}$) ν 1640 (CO), 1612 (CO). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 15.2 Hz, 1H, $H_{vinyl}$), 7.79 (d, J = 15.3 Hz, 2H, H1/H7), 7.22 (d, J = 8.3 Hz, 2H, H9/H19), 7.09 (s, 2H, H13/H15), 7.09 (d, J = 15.3 Hz, 2H, H2/H6), 6.88 (d, J = 8.3 Hz, 2H, H10/H18), 6.68 (d, J = 15.1 Hz, 1H, $H_{vinyl}$), 4.83 (bs, 2H, $C_5H_4$), 4.55 (bs, 2H, $C_5H_4$), 4.18 (s, 5H, $C_5H_5$), 3.92 (s, 6H, $OCH_3$), 3.88 (s, 6H, $OCH_3$). $^{13}$C NMR (100 MHz, $CD_2Cl_2$) δ 191.5 (C22), 183.5 (C3/C5), 151.3 (C11/C17), 149.1 (C12/C16), 142.2 (C1/C7), 134.2 ($C_{vinyl}$),

128.2 (C8/C14), 127.6 ($C_{vinyl}$), 122.6 (C9/C19), 118.7 (C2/C6), 111.0 (C10/C18), 110.8 (C4), 110.2 (C13/C15), 80.4 ($C_5H_4$, $C_{ip}$), 72.5 ($C_5H_4$), 69.6 ($C_5H_5$), 69.1 ($C_5H_4$), 55.5 ($OCH_3$). MS (APCI) *m/z* 635.6 $[M+H]^+$, 633.7 $[M-H]^-$. Anal. ($C_{36}H_{34}FeO_7$) C, H.

**(1E,4Z,6E)-1,7-bis-(3,4,5-trimethoxyphenyl)-4-[(E)-1-ferrocenylprop-2-en-1-one]-3-hydroxy-hepta-1,4,6-trien-5-one (9).** The synthesis was carried out as described above by using **4** (300 mg, 0.66 mmol), sodium hydride (34 mg, 60% dispersion, 0.85 mmol) and ferrocenyl-2-propyn-1-one (313 mg, 1.31 mmol) in anhydrous THF (6 mL). After column flash chromatography (hexane/ethyl acetate 3:2) **9** was yielded as a red solid (65 mg, 14%). Mp: 99-101 °C. IR ($cm^{-1}$) ν 1647 (CO), 1615 (CO). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 15.4 Hz, 1H, $H_{vinyl}$), 7.79 (d, J = 15.4 Hz, 2H, H1/H7), 7.09 (d, J = 15.5 Hz, 2H, H2/H6), 6.81 (s, 4H, H9/H19/H13/H15), 6.63 (d, J = 15.6 Hz, 1H, $H_{vinyl}$), 4.82 (bs, 2H, $C_5H_4$), 4.55 (bs, 2H, $C_5H_4$), 4.15 (s, 5H, $C_5H_5$), 3.98 (s, 6H, $OCH_3$), 3.86 (s, 12H, $OCH_3$). $^{13}$C NMR (100 MHz, $CD_2Cl_2$) δ 191.7 (C22), 183.4 (C3/C5), 153.2 (C12/C16/C10/C18), 142.4 (C1/C7), 140.2 (C11/C17), 133.8 ($C_{vinyl}$), 130.1 (C8/C14), 128.6 ($C_{vinyl}$), 120.1 (C2/C6), 111.12 (C4), 105.4 (C13/C9/C15/C19), 80.2 ($C_5H_4$, $C_{ip}$), 72.6 ($C_5H_4$), 69.6 ($C_5H_5$), 69.1 ($C_5H_4$), 60.2 ($OCH_3$), 55.8 ($OCH_3$). MS (APCI) *m/z* 695.6 $[M+H]^+$, 693.8 $[M-H]^-$. Anal. ($C_{38}H_{38}FeO_9$) C, H.

**General procedure for the synthesis of 10 to 13 (series B).** The curcuminoid (1 eq) was dissolved in a minimum amount of anhydrous DMF and a solution of ferrocenecarboxaldehyde (1 eq) in anhydrous DMF containing piperidine (0.5 eq) was added dropwise. The solution was allowed to stir for 48 hours under argon atmosphere at room temperature. After hydrolysis, the mixture was extracted with ethyl acetate, and the organic

phase was dried on magnesium sulfate, filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate as eluent.

(**1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-4-[ferrocenylidene]-hepta-1,6-diene-3,5-dione (10).** The synthesis was carried out as described above by using **1** (300 mg, 0.81 mmol), piperidine (40 μL, 0.41 mmol) and ferrocenecarboxaldehyde (174 mg, 0.81 mmol). After column flash chromatography (hexane/ethyl acetate 1:1), **10** was yielded as a dark red solid (120 mg, 26%). Mp: 116-118 °C. IR ($cm^{-1}$) ν 1635 (CO), 1624 (CO). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H, H20), 7.74 (d, J = 15.8, 1H, $H_{vinyl}$), 7.45 (d, J = 16.0 Hz, 1H, $H_{vinyl}$), 7.15 (d, J = 8.1 Hz, 1H, $H_{ar}$), 7.07 (d, J = 8.3 Hz, 1H, $H_{ar}$), 7.02 (bs, 2H, H13/H15), 6.90 (dd, J = 8.2 Hz, J = 2.7 Hz, 2H, $H_{ar}$), 6.85 (d, J = 15.2 Hz, 1H, $H_{vinyl}$), 6.82 (d, J = 16.0 Hz, 1H, $H_{vinyl}$), 6.00 (bs, 2H, OH), 4.46 (bs, 4H, $C_5H_4$), 4.19 (s, 5H, $C_5H_5$), 3.91 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$). $^{13}$C NMR (100 MHz, $CD_2Cl_2$) δ 198.0 and 185.57 (C3/C5), 148.5 and 148.0 (C11/C17), 146.7 (C12/C16), 146.6 (C20), 143.4 and 141.8 (C2/C6), 136.5 (C4), 127.2 and 126.5 (C8/C14), 125.4 ($C_{vinyl}$), 123.5 and 122.8 (C9/C19), 119.4 ($C_{vinyl}$), 114.4 (C10/C18), 110.1 and 109.5 (C13/C15), 76.1 ($C_5H_4$, $C_{ip}$), 71.9 ($C_5H_4$), 71.1 ($C_5H_4$), 69.6 ($C_5H_5$), 55.7 ($OCH_3$). MS (APCI) *m/z* 565.5 $[M+H]^+$, 563.2 $[M-H]^-$. Anal. ($C_{32}H_{28}FeO_6$) C, H.

**(1E,6E)-1,7-bis(3,4-dimethoxyphenyl)-4-[ferrocenylidene]-hepta-1,6-diene-3,5-dione (11).** The synthesis was carried out as described above by using **2** (300 mg, 0.76 mmol), piperidine (37 μL, 0.38 mmol) and ferrocenecarboxaldehyde (162 mg, 0.76 mmol). After column flash chromatography (hexane/ethyl acetate 1:1), **11** was yielded as a dark red solid (121 mg, 27%). Mp: 88-90 °C. IR ($cm^{-1}$) ν 1634 (CO), 1623 (CO). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H, H20), 7.76 (d, J = 15.5 Hz, 1H, $H_{vinyl}$), 7.48 (d, J = 16.0 Hz, 1H, $H_{vinyl}$), 7.15 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H, $H_{ar}$), 7.11 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H, $H_{ar}$), 7.06 (bs,

1H, $H_{ar}$), 7.05 (bs, 1H, $H_{ar}$), 6.88 (d, J = 15.5 Hz, 1H, $H_{vinyl}$), 6.85 (d, J = 8.1 Hz, 1H, $H_{ar}$), 6.84 (d, J = 8.3 Hz, 1H, $H_{ar}$), 6,82 (d, J = 15.5 Hz, 1H, $H_{vinyl}$), 4.48 (bs, 2H, $C_5H_4$), 4.47 (bs, 2H, $C_5H_4$), 4.21 (s, 5H, $C_5H_5$), 3.91 (s, 6H, $OCH_3$), 3.90 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$). $^{13}C$ NMR (100 MHz, $CD_2Cl_2$) δ 197.7 and 185.53 (C3/C5), 150.9 and 150.4 (C11/C17), 148.3 and 148.2 (C12/C16), 146.0 (C20), 143.3 and 141.7 (C1/C7), 135.3 (C4), 126.9 and 126.1 (C8/C14), 125.0 ($C_{vinyl}$), 122.6 and 122.1 (C9/C19), 119.5 ($C_{vinyl}$), 110.1 (C10/C18), 109.6 and 109.1 (C13/C15), 76.2 ($C_5H_4$, $C_{ip}$), 71.2 ($C_5H_4$), 70.5 ($C_5H_4$), 69.0 ($C_5H_5$), 55.0 ($OCH_3$), 54.9 ($OCH_3$). MS (APCI) *m/z* 593.8 $[M+H]^+$. Anal. ($C_{34}H_{32}FeO_6$) C, H.

**(1E,6E)-1,7-bis-(3,5-dimethoxyphenyl)-4-[ferrocenylidene]-hepta-1,6-diene-3,5-dione (12).** The synthesis was carried out as described above by using **3** (250 mg, 0.63 mmol), piperidine (31 μL, 0.32 mmol) and ferrocenecarboxaldehyde (135 mg, 0.63 mmol). After column flash chromatography (hexane/ethyl acetate 3:1), **12** was yielded as a dark red solid (81 mg, 22%). Mp: 98-100 °C. IR ($cm^{-1}$) ν 1635 (CO), 1626 (CO). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H, H20), 7.70 (d, J = 15.6 Hz, 1H, $H_{vinyl}$), 7.44 (d, J = 15.8 Hz, 1H, $H_{vinyl}$), 7.00 (d, J = 15.2 Hz, 1H, $H_{vinyl}$), 6.91 (d, J = 15.1 Hz, 1H, $H_{vinyl}$), 6.71 (bs, 2H, $H_{ar}$), 6.66 (d, J = 1.8 Hz, 2H, $H_{ar}$), 6.49 (bs, 2H, $H_{ar}$), 4.49 (bs, 4H, $C_5H_4$), 4.21 (s, 5H, $C_5H_5$), 3.81 (s, 6H, $OCH_3$), 3.78 (s, 6H, $OCH_3$). $^{13}C$ NMR (100 MHz, $CD_2Cl_2$) δ 197.9 and 186.0 (C3/C5), 167.1 (C20), 160.7 (C12/C16/C10/C18), 145.9 and 143.1 (C1/C7), 136.1 (C4), 136.4 and 135.8 (C8/C14), 127.9 and 122.0 (C2/C6), 106.0 and 105.9 (C13/C15/C9/C19), 102.8 and 102.0 (C11/C17), 75.8 ($C_5H_4$, $C_{ip}$), 72.2 ($C_5H_4$), 71.2 ($C_5H_4$), 69.7 ($C_5H_5$), 55.1 ($OCH_3$). MS (APCI) *m/z* 593.3 $[M+H]^+$. Anal.($C_{34}H_{32}FeO_6$) C, H.

**(1E,6E)-1,7-bis-(3,4,5-trimethoxyphenyl)-4-[ferrocenylidene]-hepta-1,6-diene-3,5-dione (13).** The synthesis was carried out as described above by using **4** (300 mg, 0.66

mmol), piperidine (32 μL, 0.33 mmol) and ferrocenecarboxaldehyde (141 mg, 0.66 mmol). After column flash chromatography (hexane/ethyl acetate 3:2), **13** was yielded as a dark red solid (119 mg, 28%). Mp: 104-106 °C. IR ($cm^{-1}$) ν 1635 (CO), 1602 (CO). $^{1}H$ NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H, H20), 7.72 (d, J = 14.5 Hz, 1H, $H_{vinyl}$), 7.43 (d, J = 15.3 Hz, 1H, $H_{vinyl}$), 6.90 (d, J = 14.7 Hz, 1H, $H_{vinyl}$), 6.87 (d, J = 15.6 Hz, 1H, $H_{vinyl}$), 6.78 (s, 2H, $H_{ar}$), 6.75 (s, 2H, $H_{ar}$), 4.49 (bs, 4H, $C_5H_4$), 4.22 (s, 5H, $C_5H_5$), 3.88 (s, 6H, $OCH_3$), 3.86 (s, 6H, $OCH_3$), 3.85 (s, 6H, $OCH_3$). $^{13}C$ NMR (100 MHz, $CD_2Cl_2$) δ 197.8 and 185.7 (C3/C5), 153.1 (C12/C16/C10/C18), 140.0 (C20), 143.3 and 142.4 (C1/C7), 140.3 and 140.1 (C11/C17), 136.5 (C4), 129.9 and 129.2 (C8/C14), 126.8 and 120.8 (C2/C6), 105.3 (C13/C15/C9/C19), 75.9 ($C_5H_4$, $C_{ip}$), 72.0 ($C_5H_4$), 71.1 ($C_5H_4$), 69.6 ($C_5H_5$), 60.2 ($OCH_3$), 55.8 ($OCH_3$), 55.7 ($OCH_3$). MS (APCI) *m/z* 653.6 $[M+H]^+$. Anal. ($C_{36}H_{36}FeO_8$) C, H.

**General procedure for the synthesis of 15 and 16 (series C).** An anhydrous THF solution of the appropriate curcuminoid (1 eq) was added dropwise to an oil-free suspension of NaH (1.7 eq) in anhydrous THF at 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirring was continued for 2 hours. A solution of α-bromoacetylferrocene (2 eq) in anhydrous THF was added dropwise and the reaction mixture was heated for 4 hours at 50 °C, and then stirred overnight at room temperature. After hydrolysis with water, the mixture was extracted with ethyl acetate, and the organic phase was dried on magnesium sulfate, filtered and evaporated under reduced pressure. The ferrocenyl curcuminoid was purified by column flash chromatography on silica gel using hexane/ethyl acetate as eluent.

**(1E,6E)-1,7-bis(3,4-dimethoxyphenyl)-4-[1-ferrocenylethanone]-hepta-1,6-dien-3,5-dione (15).** The synthesis was carried out as described above by using **2** (300 mg, 0.76

mmol), sodium hydride (52 mg, 60% dispersion, 1.29 mmol) and α-bromoacetylferrocene (465 mg, 1.51 mmol) in anhydrous THF (8 mL). After column flash chromatography (hexane/ethyl acetate 3:2) **15** was yielded as an orange solid (107 mg, 44%). Mp: 133-135°C. IR ($cm^{-1}$) ν 1661 (CO). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 15.8 Hz, 2H, H1/H7), 7.14 (d, J = 8.1 Hz, 2H, H9/H19), 7.06 (s, 2H, H13/H15), 6.83 (d, J = 8.1 Hz, 2H, H10/H18), 6.81 (d, J = 15.8 Hz, 2H, H2/H6), 4.94 (t, J = 6.6 Hz, 1H, H4), 4.81 (bs, 2H, $C_5H_4$), 4.49 (bs, 2H, $C_5H_4$), 4.27 (s, 5H, $C_5H_5$), 3.88 (s, 6H, $OCH_3$), 3.86 (s, 6H, $OCH_3$), 3.50 (d, J = 6.5 Hz, 2 H, H20). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 201.3 (C21), 194.6 (C3/C5), 151.7 (C11/C17), 149.2 (C12/C16), 144.6 (C1/C7), 127.2 (C8/C14), 123.6 (C9/C19), 122.7 (C2/C6), 111.1 (C10/C18), 110.0 (C13/C15), 78.0 ($C_5H_4$, $C_{ip}$), 72.4 ($C_5H_4$), 70.4 ($C_5H_5$), 69.3 ($C_5H_4$), 57.7 (C4), 56.0 ($OCH_3$), 55.9 ($OCH_3$), 38.8 (C20). MS (APCI) *m/z* 623.6 $[M+H]^+$, 622.7 $[M-H]^-$. Anal. ($C_{35}H_{34}FeO_7$) C, H.

(**1E,4Z,6E)-1,7-bis-(3-methoxy-4-(tetrahydro-2H-pyran-2-yloxy)phenyl)-4-[1-ferrocenylethanone]-hepta-1,6-dien-3,5-dione (16).** The synthesis was carried out as described above by using **14** (600 mg, 1.18 mmol), sodium hydride (67 mg of 60% dispersion, 1.68 mmol) and α-bromoacetylferrocene (515 mg, 1.68 mmol) in anhydrous THF (6 mL). After column flash chromatography (hexane/ethyl acetate 2:1) **16** was yielded as a dark yellow solid (430 mg, 48%). Mp: 80-82 °C IR ($cm^{-1}$) ν 1664 (CO), 1579 (CO). $^1$H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 15.8 Hz, 2H, H1/H7), 7.18-7.08 (m, 6H, H13/H15/H9/H19/H10/H18), 6.85 (d, J = 15.8 Hz, 2H, H2/H6), 5.44 (t, J = 3.1 Hz, 2H, CH), 4.96 (t, J = 6.6 Hz, 1H, H4), 4.83 (t, J = 1.9 Hz, 2H, $C_5H_4$), 4.53 (t, J = 1.9 Hz, 2H, $C_5H_4$), 4.31 (s, 5H, $C_5H_5$), 3.85 (s, 6H, $OCH_3$), 3.60-3.55 (m, 2H, $CH_2$), 3.48 (d, J = 6.8 Hz, 2H, H20), 2.03-1.94 (m, 2H, $CH_2$), 1.90-1.86 (m, 4H, $CH_2$), 1.72-1.57 (m, 8H, $CH_2$). $^{13}$C NMR (75 MHz, $CD_2Cl_2$): δ 200.4 (C21), 194.2 (C3/C5), 150.0 (C11/C17), 148.8 (C12/C16), 143.8

(C1/C7), 128.0 (C8/C14), 122.9 and 122.7 (C2/C6/C9/C19), 116.4 (C10/C18), 111.0 (C13/C15), 97.2 (CH), 77.9 ($C_5H_4$, $C_{ip}$), 72.0 ($C_5H_4$), 69.7 ($C_5H_5$), 68.9 ($C_5H_4$), 61.9 ($CH_2$), 57.1 (C4), 55.7 ($OCH_3$), 38.4 (C20), 29.9 ($CH_2$), 24.8 ($CH_2$), 18.5 ($CH_2$). MS (APCI) *m/z* 761.8 $[M-H]^-$, 797.5 $[MCl]^-$. Anal. ($C_{43}H_{46}FeO_9$) C, H.

(**1E,4Z,6E)-1,7-bis-(3-methoxy-4-hydroxyphenyl)-4-[1-ferrocenylethanone]-hepta-1,6-dien-3,5-dione (17). 16** (2801 mg, 0.37 mmol) was dissolved in dichloromethane (2 mL) and diluted with absolute ethanol (5 mL). PPTS (92 mg, 0.37 mmol) was added in one portion to the stirred solution and stirring was continued for 3 hours at room temperature, monitored by TLC. Water (15 mL) was then added for hydrolysis and the aqueous layer was extracted with dichloromethane (15 mL). The combined organic extracts were washed once with water (20 mL) and brine (20 mL), dried on magnesium sulfate, filtered and evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (2:1) as eluent, yielding **17** as an orange solid (142 mg, 65%). Mp: 90-92 °C. IR ($cm^{-1}$) ν 1659 (CO), 1585 (CO). $^1$H NMR (300 MHz, $CD_2Cl_2$): δ 7.66 (d, J = 16.0 Hz, 2H, H1/H7), 7.15 (bd, J = 8.3 Hz, 2H, H9/H19), 7.12 (s, 2H, H13/H15), 6.91 (d, J = 8.1 Hz, 2H, H10/H18), 6.81 (d, J = 15.8 Hz, 2H, H2/H6), 6.02 (bs, 2H, OH), 4.92 (t, J = 6.8 Hz, 1H, H4), 4.85 (bs, 2H, $C_5H_4$), 4.55 (bs, 2H, $C_5H_4$), 4.33 (s, 5H, $C_5H_5$), 3.91 (s, 6H, $OCH_3$), 3.46 (d, J = 6.8 Hz, 2H, H20). $^{13}$C NMR (75 MHz, $CD_2Cl_2$): δ 200.7 (C21), 194.3 (C3/C5), 148.4 (C11/C17), 146.7 (C12/C16), 144.1 (C1/C7), 126.4 (C8/C14), 123.5 (C2/C6), 122.2 (C9/C19), 114.4 (C10/C18), 109.6 (C13/C15), 77.8 ($C_5H_4$, $C_{ip}$), 72.1 ($C_5H_4$), 69.7 ($C_5H_5$), 68.9 ($C_5H_4$), 57.1 (C4), 55.7 ($OCH_3$), 38.4 (C20). MS (APCI) *m/z* 595.3 $[M+H]^+$, 593.4 $[M-H]^-$, 629.6 $[MCl]^-$. Anal. ($C_{33}H_{30}FeO_7$) C, H.

**Table S1.** Elemental analysis of compounds **8-13** and **15-17**

| Compound | Calculated | | Found | |
|---|---|---|---|---|
| | C [%] | H [%] | C [%] | H [%] |
| **8** $C_{36}H_{34}FeO_7$ | 68.14 | 5.40 | 67.23 | 5.27 |
| **9** $C_{38}H_{38}FeO_9$ | 65.71 | 5.41 | 65.16 | 5.53 |
| **10** $C_{32}H_{28}FeO_6$ | 68.1 | 5.00 | 65.59 | 5.31 |
| **11** $C_{34}H_{32}FeO_6$ | 68.93 | 5.44 | 68.32 | 5.94 |
| **12** $C_{34}H_{32}FeO_6$ | 68.93 | 5.44 | 66.22 | 5.68 |
| **13** $C_{36}H_{36}FeO_8$ | 66.26 | 5.56 | 65.64 | 5.61 |
| **15** $C_{35}H_{34}FeO_7$ | 67.53 | 5.51 | 66.15 | 5.36 |
| **16** $C_{43}H_{46}FeO_9$ | 67.72 | 5.45 | 66.72 | 6.24 |
| **17** $C_{33}H_{30}FeO_7$ | 66.68 | 5.09 | 65.76 | 5.62 |

**Table S2.** HRMS (ESI) purity data of compounds **8-10** and **15-17**

| Compound | Calculated *m/z* | Found m/z |
|---|---|---|
| **8** $C_{36}H_{34}FeO_7Na^+$ | 657.15462 | 657.15352 |
| **9** $C_{38}H_{38}FeO_9Na^+$ | 717.17575 | 717.17645 |
| **10** $C_{32}H_{28}FeO_6Na^+$ | 587.11275 | 587.11227 |
| **12** $C_{34}H_{32}FeO_6Na^+$ | 615.14405 | 615.14409 |
| **15** $C_{35}H_{34}FeO_7Na^+$ | 645.15462 | 645.15467 |
| **16** $C_{43}H_{46}FeO_9Na^+$ | 785.23835 | 785.24015 |
| **17** $C_{33}H_{30}FeO_7Na^+$ | 617.12332 | 617.12286 |

**Evaluation of cytotoxicity in murine B16 melanoma cells and normal NIH 3T3 cells.** Murine B16 melanoma cells and NIH 3T3 cells were grown in Dulbecco minimal essential medium (DMEM) containing 2 mM L-glutamine, 10% foetal bovine serum, 100 U/mL penicillin and 100 μg/mL streptomycin (37 °C, 5% $CO_2$). All compounds were initially dissolved in DMSO at a stock concentration of 2.5 mg/mL and were further diluted in cell culture medium. Exponentially growing B16 cells were plated onto 96-well plates at 5000 cells per well (4000 cells for NIH 3T3 cells) in 100 μl of culture medium. 24 hours after plating, 100 μl of medium containing the compound of interest at final concentrations ranging from 0 to 100 μM were added to the wells (in triplicate) containing the cells, and incubated for 48 h at 37 °C and 5% $CO_2$. After the 48 hour exposure period to the test compounds, cell viability was evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltatrazolium bromide) test[7] and absorbance was read at 562 nm in a microplate reader (BioKinetics Reader, EL340). Appropriate controls with DMEM only and MTT were run to substract background absorbance. Results are presented as percent of controls containing 1% DMSO, which was not cytotoxic at this concentration. The concentration of compound that inhibited cell viability by 50% (inhibitory concentration for 50% of cells, or $IC_{50}$) was determined using the GraphPad Prism software. Results are presented as the mean of 3 determinations.

**Inhibition of tubulin polymerization (ITP).** Tubulin assembly in microtubules was carried out using the fluorescent dye DAPI (4',6-diamidino-2-phenylindole)[8] in a 96-well plate format as described by Barron *et al.*[9] and Bane *et al.*[10] The standard assay was performed as follows: wells were charged with tubulin (Cytoskeleton, 97% pure, final concentration 1 mg/ml) in PME buffer (100 mM PIPES (1,4-piperazinebis(ethanesulfonic acid); 1 mM $MgSO_4$; 2 mM EGTA) with 10 μM DAPI and varying concentrations of the test compounds using colchicine as an internal control. After a preincubation time of 45 min at

room temperature, 5 µl of 1 mM GTP was added to each well to initiate tubulin polymerization, and the plate was then transferred to a thermostated Victor plate reader at 37 °C for an additional 2 hours. Fluorescence was then read at the excitation wavelength of 360 nm and emission of 450 nm. The percent inhibition was determined as follows: 1 - (ΔF(sample)/ΔF(control) X 100, where ΔF control = F(no inhibition) - F(complete inhibition), and ΔF sample = F(sample)-F(complete inhibition with colchicine). The $IC_{50}$ for compound-induced inhibition of tubulin polymerization is the concentration of compound at which the extent of inhibition of polymerization is 50% of the maximum value, as determined from the semi-logarithmic plot of percent inhibition as a function of the drug concentration using the GraphPad Prism software.

**Effect on the morphology of transformed HUVEC cells (EA.hy 926 cells).** To assess the effects of the compounds on the morphology of endothelial cells, we used the EA.hy 926 endothelial cell line which is derived from the fusion of human umbilical vein endothelial cells (HUVEC) with the permanent human cell line A549.[11] The EA.hy 926 cell line is considered as one of the best immortalized HUVEC cell lines because these cells express most of the biochemical markers of parental HUVEC.[12] EA.hy 926 cells, originally obtained from Dr Cora-Jean S. Edgell (Pathology Department, University of North Carolina, Chapel Hill, NC 27599-7525, USA) were used with her permission, and were grown in DMEM containing 2 mM L-glutamine, 10% foetal bovine serum, 100 U/mL penicillin and 100 µg/mL streptomycin (37 °C, 5% $CO_2$). Exponentially growing EA.hy 926 cells were plated onto 96 well plates at 5000 cells/100 µl/ well. 24 hours after plating, the medium was aspirated, and 100 µl of medium containing the test compound was added to the well containing the cells (in triplicate) in 10-fold dilutions, and incubated for 2 hours. After the 2 hour-incubation period,

digital photographs were taken of representative centre areas of each well at a magnification of 100X and 200X.

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