SUPPLEMENTARY MATERIAL

Synthesis and evaluation of aporphine analogues containing C1 allyl isosteres at the *h*5-HT$_{2A}$ receptor

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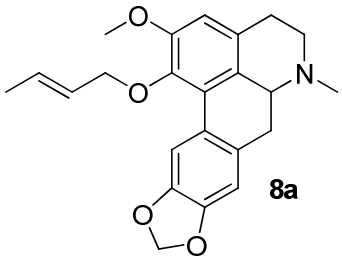
General Experimental Procedures

All moisture-sensitive and oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Dry solvents and all other reagents were purchased at the highest commercial quality from Fisher Scientific or Sigma-Aldrich and used without further purification, unless otherwise stated. HRESIMS spectra were obtained using an Agilent 6520 QTOF instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker DPX-500 spectrometer (operating at 500 MHz for ^{1}H; 125 MHz, respectively, for ^{13}C) using $CDCl_3$ as solvent. Tetramethylsilane (δ 0.00 ppm) served as an internal standard in ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) in ^{13}C NMR as solvent. Chemical shift (δ 0.00 ppm) values are reported in parts per million and coupling constants in hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Reactions were monitored by TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining with vanillin spraying reagent (2 g vanillin in 1 L of 10% H_2SO_4) followed by heating. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230-400 mesh, 0.04 - 0.063 mm particle size).

General procedure for alkylation of phenol:

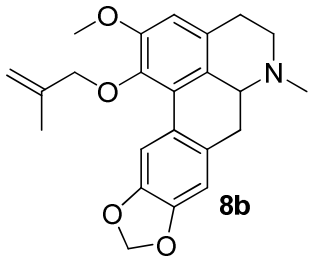
To a stirred solution of phenol **6** (1 eq.) in acetone (10 mL) was added solid K_2CO_3 (2 eq.) at rt. The resulting mixture was stirred for 5 min and then the appropriate alkyl bromide (5 eq.) was added and refluxed for 6 h. The solvent was evaporated and the resulting solid dissolved in water and extracted with dichloromethane twice (20 mL each). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography using 10% - 20% EtOAc in hexanes to afford compounds **7a** - **7k** (Yield =70 - 82%).

General procedure for BOC deprotection and reductive amination:
To a solution of the appropriate carbamate **7** (0.5 mmol) in dry dichloromethane (15 mL), was added dry zinc bromide (0.450g, 2 mmol). The reaction mixture was allowed to stir at room temperature under inert atmosphere for 45 min. Water (20 mL) was added to the reaction and the mixture extracted with dichloromethane (3×10 mL). The combined organic layer was washed with water (10 mL), then with brine (10 mL), dried over Na_2SO_4, and concentrated to give the crude amine. To a solution of this amine in dichloromethane (10 mL) was added 37% formaldehyde solution in water (0.8 mL, 10 mmol) and sodium triacetoxyborohydride (0.147g, 0.7 mmol). The reaction mixture was allowed to stir at rt for 1 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layer was washed with water (10 mL), then with brine (10 mL), dried over Na_2SO_4, and concentrated to give crude compounds **8a - 8k**, which on column chromatography over deactivated silica gel using methanol/dichloromethane (2:98) as eluant gave the purified products (Yield = 58 - 71% over two steps).



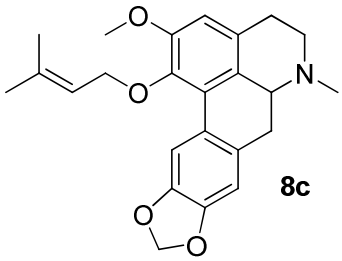
8a

(*E*)-1-(but-2-en-1-yloxy)-2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8a: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 5.99 (s, 2H), 5.65 (m, 2H), 3.16 (m, 1H), 3.01 (m, 3H), 2.69 (dd, *J1*= *J2*= 3 Hz, 1H), 2.55 (m, 5H), 2.52-2.49 (m, 2H), 1.66 (d, *J*=4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.3, 146.2, 142.9, 130.6, 130.4, 128.5, 127.5, 127.0, 125.9, 110.4, 109.3, 108.1, 100.8, 73.5, 67.8, 62.5, 55.8, 53.2, 44.0, 35.1, 29.2, 17.7; HRESIMS calculated for $C_{23}H_{26}NO_4$ ($[M+H]^+$), 380.1862, found 380.1858.



8b

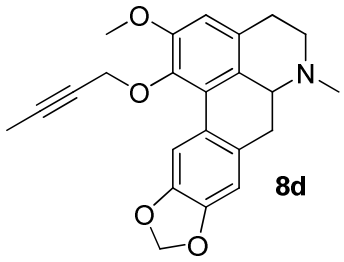
2-methoxy-6-methyl-1-((2-methylallyl)oxy)-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8b: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 1H), 6.78 (s, 1H), 6.61 (s, 1H), 5.99 (s, 2H), 5.06 (s, 1H), 4.94 (s, 1H), 4.25 (d, *J*=11 Hz, 1H), 4.09 (d, *J*=11 Hz, 1H), 3.87 (s, 3H), 3.19 (m, 1H), 3.11-2.98 (m, 3H), 2.70 (dd, *J1*= *J2*=3 Hz, 1H), 2.58-2.55 (m, 5H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 146.3, 142.2, 141.7, 130.4, 128.3, 127.3, 125.5, 113.0, 110.7, 109.3, 108.1, 100.8, 62.4, 55.9, 53.1, 43.8, 34.9, 28.9, 19.9; HRESIMS calculated for $C_{23}H_{26}NO_4$ ($[M+H]^+$), 380.1862, found 380.1859.



8c

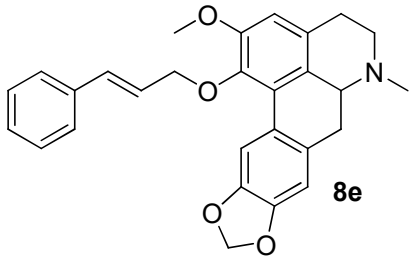
2-methoxy-6-methyl-1-((3-methylbut-2-en-1-yl)oxy)-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8c: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 6.76 (s, 1H), 6.59 (s, 1H), 5.99 (s, 2H), 5.43 (t, *J* = 8

Hz, 1H), 4.53 (m, 1H), 4.31 (dd, *J1*= *J2*=8 Hz, 1H), 4.23 (dd, *J1*= *J2*=8 Hz, 1H), 3.17 (m, 1H), 3.05-2.97 (m, 3H), 2.69 (m, 1H), 2.55 (s, 3H), 2.52-2.49 (m, 2H), 1.69 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 146.3, 146.1, 143.0, 138.3, 130.6, 128.4, 127.7, 127.1, 126.0, 120.3, 110.4, 109.4, 108.0, 100.7, 68.9, 62.5, 55.8, 53.2, 43.9, 35.1, 29.1, 25.7, 17.6; ; HRESIMS calculated for $C_{24}H_{28}NO_4$ ($[M+H]^+$), 394.2018, found 394.2010.



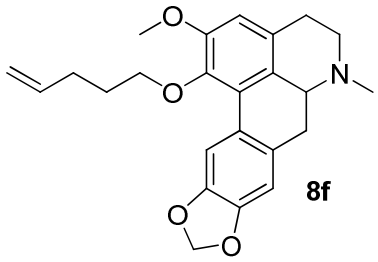
8d

1-(but-2-yn-1-yloxy)-2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8d: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 6.75 (s, 1H), 6.60 (s, 1H), 5.99 (m, 2H), 4.50-4.40 (m, 2H), 3.88 (s, 3H), 3.16 (m, 1H), 3.04 (m, 1H), 3.02-2.97 (m, 2H), 2.71-2.67 (dd, *J1*=*J2*=3Hz, 1H), 2.55 (s, 3H), 2.52-2.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 146.4, 146.3, 142.1, 130.6, 129.0, 127.9, 127.2, 125.8, 110.5, 109.6, 108.0, 100.8, 83.3, 74.7, 62.5, 60.5, 55.8, 53.2, 44.0, 35.2, 29.2; HRESIMS calculated for $C_{23}H_{24}NO_4$ ($[M+H]^+$), 378.1705, found 378.1700.



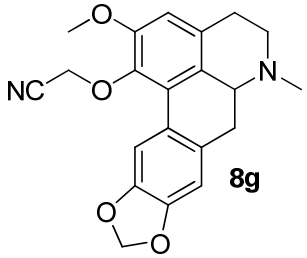
8e

1-(cinnamyloxy)-2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8e: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.25-7.23 (m, 5H), 6.76 (s, 1H), 6.62 (s, 1H), 6.50 (m, 1H), 6.33 (m, 1H), 5.96 (s, 2H), 4.56-4.52 (dd, *J1*=*J2*=6 Hz, 1H), 4.40-4.36 (dd, *J1*=*J2*=7 Hz, 1H), 3.96 (s, 3H), 3.16 (m, 1H), 3.07-2.95 (m, 3H), 2.71-2.68 (dd, *J1*=*J2*=3 Hz, 1H), 2.54 (s, 3H), 2.53-2.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.0, 146.3, 142.8, 136.7, 133.1, 130.7, 128.7, 127.7, 127.6, 127.3, 126.5, 125.8,125.4, 110.5, 109.5, 108.1, 100.5, 62.5, 55.9, 53.2, 43.9, 35.1, 29.2; HRESIMS calculated for $C_{28}H_{28}NO_4$ ($[M+H]^+$), 442.2018, found 442.2015.



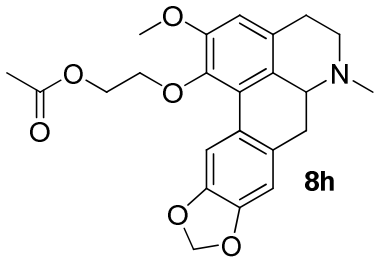
8f

2-methoxy-6-methyl-1-(pent-4-en-1-yloxy)-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8f: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 6.77 (s, 1H), 6.60 (s, 1H), 5.98 (s, 2H), 5.81 (m, 1H), 4.98 (m, 2H), 3.88 (s, 3H), 3.85 (m, 1H), 3.74-3.64 (m, 2H), 3.15 (m, 1H), 3.01 (m, 3H), 2.70 (d, *J*=4 Hz, 1H), 2.55 (s, 3H), 2.53-2.50 (m, 2H), 2.22-2.12 (m, 2H), 1.83-1.76 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.5, 143.6, 138.3, 130.7, 128.4, 127.3, 125.7, 114.6, 110.6, 109.2, 108.1, 100.8, 72.5, 62.5, 55.8, 53.3, 44.0, 35.1, 30.2, 29.8, 29.4, 29.2; HRESIMS calculated for $C_{24}H_{28}NO_4$ ($[M+H]^+$), 394.2018, found 394.2014.



8g

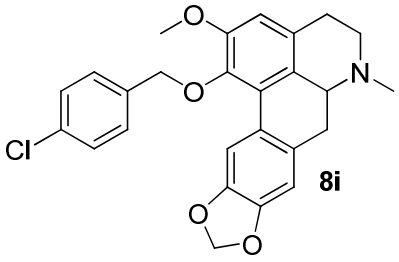
2-((2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinolin-1-yl)oxy)acetonitrile, 8g: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 6.73 (s, 1H), 6.64 (s, 1H), 6.01 (s, 2H), 4.59 (s, 2H), 3.92 (s, 3H), 3.16 (m, 1H), 3.04-2.97 (m, 3H), 3.15 (m, 1H), 2.72 (d, *J*=3 Hz, 1H), 2.70 (d, *J*=4 Hz, 1H), 2.55 (s, 3H), 2.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 146.8, 146.6, 141.1, 131.3, 130.6, 127.5, 124.5, 115.4, 110.7, 108.7, 101.0, 72.5, 62.3, 57.1, 55.8, 53.0, 43.9, 35.0, 29.2; HRESIMS calculated for $C_{21}H_{21}N_2O_4$ ($[M+H]^+$), 365.1501, found 365.1492.



8h

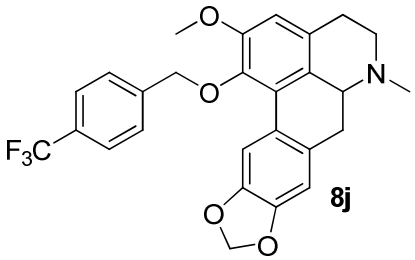
methyl 3-((2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinolin-1-yl)oxy)propanoate, 8h: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.77 (s, 1H), 6.61 (s, 1H),

5.97 (s, 2H), 4.32 (m, 1H), 4.23 (m, 1H), 4.11(m, 1H), 3.91 (m, 1H), 3.82 (s, 3H), 3.16 (m, 1H), 3.05 (m, 1H), 3.01 (dd, *J1*=*J2*=4 Hz, 2H), 2.69 (dd, *J1*=*J2*=3 Hz, 1H), 2.55 (s, 3H), 2.54 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 151.8, 146.3, 142.8, 130.8, 128.9, 127.3, 125.4, 114.6, 110.6, 109.5, 108.2, 100.8, 63.7, 62.4, 55.8, 53.2, 43.9, 35.1, 30.2, 29.2, 20.7; HRESIMS calculated for $C_{23}H_{26}NO_6$ ($[M+H]^+$), 412.1760, found 412.1755.



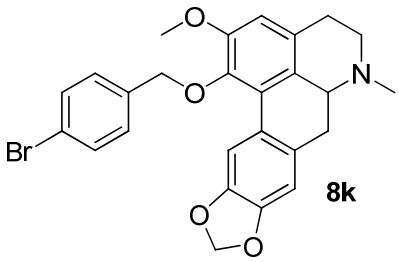
8i

1-((4-chlorobenzyl)oxy)-2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8i: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.21-7.17 (m, 4H), 6.17 (s, 1H), 6.59 (s, 1H), 5.96 (s, 2H), 4.79 (d, *J*=10 Hz, 1H), 4.65 (d, *J*=11 Hz, 1H), 3.85 (s, 3H), 3.14 (m, 1H), 3.01 (m, 1H), 2.93 (m, 2H), 2.66 (m, 1H), 2.52 (s, 3H), 2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.2, 142.4, 135.6, 133.7, 130.7, 130.2, 129.0, 128.2, 127.3, 125.5, 110.6, 109.6, 108.1, 100.9, 77.1, 73.9, 62.5, 55.9, 53.2, 44.0, 35.1, 29.3; HRESIMS calculated for $C_{26}H_{25}ClNO_4$ ($[M+H]^+$), 450.1472, found 450.1470.



8j

2-methoxy-6-methyl-1-((4-(trifluoromethyl)benzyl)oxy)-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8j: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.49 (d, *J*=8 Hz, 2H), 7.37 (d, *J*=8 Hz, 2H), 6.69 (s, 1H), 6.61 (s, 1H), 5.94 (s, 2H), 4.89 (d, *J*=10 Hz, 1H), 4.73 (d, *J*=15 Hz, 1H), 3.86 (s, 3H), 3.15 (m, 1H), 3.03 (m, 1H), 2.93 (m, 2H), 2.67 (m, 1H), 2.52 (s, 3H), 2.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 146.2, 142.3, 140.9, 130.7, 130.0, 129.7, 129.1, 128.8, 127.9, 125.4, 124.9, 110.6, 109.4, 108.2, 100.9, 73.8, 62.4, 55.8, 53.1, 43.9, 35.0, 29.3; HRESIMS calculated for $C_{26}H_{25}F_3NO_4$ ($[M+H]^+$), 484.1736, found 484.1733.



8k

1-((4-bromobenzyl)oxy)-2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-[1,3]dioxolo[4',5':4,5]benzo[1,2-g]benzo[de]quinoline, 8k: Gummy Solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.24-7.22 (d, *J*= 7 Hz, 2H), 7.17-7.16 (d, *J*= 7 Hz, 2H), 6.73 (s, 1H), 6.57 (s, 1H), 5.96 (s, 2H), 4.08-4.07 (m, 1H), 3.88-3.87 (m, 1H), 3.82 (s, 3H), 3.15 (m, 1H), 2.98 (m, 1H), 2.95 (m, 2H), 2.68-2.65 (m, 1H), 2.52 (s, 3H), 2.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 146.3, 143.4, 138.3, 130.6, 128.8, 128.2, 127.3, 126.1, 125.7, 110.6, 109.2, 108.1, 100.8, 73.6, 55.8, 53.2, 43.9, 36.6, 35.0, 29.1; HRESIMS calculated for $C_{26}H_{25}BrNO_4$ ($[M+H]^+$), 494.0967, found. 494.0958.