Supplementary Data.

Potent CYP3A4 inhibitors derived from dillapiol and sesamol.

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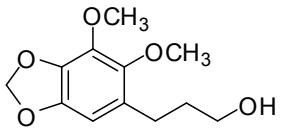
Experimental Procedures: General: All ^{1}H and ^{13}C NMR spectra were in $CDCl_3$ solutions using a Bruker AVANCE 400 spectrometer. Flash chromatography silica columns were performed using variable ratios of hexanes and ethyl acetate for the mobile phase, which were obtained from Fisher Scientific. The stationary phase silica gel used for column chromatography was Silica Flash F60 with particle size 40-63 µm (230-400 mesh) obtained from Silicycle, Quebec City. All experiments were monitored by thin-layer chromatography (TLC) using silica gel plates 60 F254, which were obtained from Merck. Results were observed by ultraviolet (UV) light and by staining with Hanessian's stain (cerium ammonium sulphate (1.0 g) and ammonium molybdate (2.5 g) in a 10% aqueous H2SO4 solution) followed by heating with a heat gun. All compounds and reagents used were commercial grade except for dillapiol, which was derived from the essential oil of *P. aduncum L.* fruit.

3-(6,7)-Dimethoxybenzo[d][1,3]dioxol-5-yl)propan-1-ol (**2**)

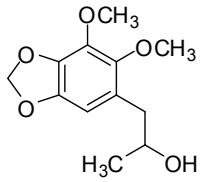


2

Compound **2** was synthesized following a typical hydroboration procedure using 3.37 mL (3.37 mmol) of borane dimethyl sulphide complex and (0.5 g, 2.25 mmol) of dillapiol in 10 mL of CH_2Cl_2. Purification by flash chromatography (6:4, hexanes: ethyl acetate) afforded **8** as a yellow oil (0.38 g, 71%). **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 1.64-1.72 (m, 2H), 2.51 (t, J= 7.4 Hz, 2H, 3.48 (t,

J= 7.3 Hz, 2H), 3.66 (s, 3H), 3.91 (s, 3H), %,77 (s, 2H), 6.25 (s1H). The ^{1}HNMR spectra matched that reported. (Majerus, S. M.Sc. Thesis. University of Ottawa 1998).

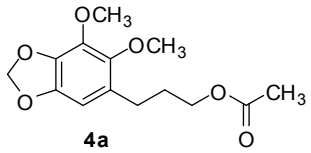
1-(6,7-dimethoxybenzo[d][1,3]dioxol-5-yl)propan-2-ol (**3**).



3

Alcohol **3** was obtained as less polar minor product from the reaction described for the preparation of **2**. Purification of the crude residue by flash chromatography (6:4, hexanes: ethyl acetate) provided **3** as a yellowish oil (0.15 g, 28%). *Alternate route for the synthesis of **3.*** Dillapiol, **1,** (1.0 g, 4.5 mmol) in THF (15 mL) was added over a period of 20 min was added to a vigorously stirred suspension of mercuric acetate (1.43 g, 4.5 mmol) in THF: water (3:1, 24 mL) at 0 ˚C. The reaction mixture was allowed to warm up to RT and stirred for 1h and then treated with an alkaline solution of $NaBH_4$ (3.6 g KOH/13mL H_2O + 1.0 g $NaBH_4$). This mixture is stirred for 1h. The liberated mercury was filtered and the filtrate was extracted with $CHCl_3$ (3 X 30mL). The combined organic extracts were dried over $MgSO_4$ filtered and evaporated to dryness under vacuum. Purification by flash chromatography (8:2, hexanes: ethyl acetate) afforded compound **3** as a yellowish liquid (0.8 g, 71%). **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 1.19 9D,j= 6.2Hz,3H), 2.13 (d, H=3.1Hz, 1H), 2,61 (dd, J= 13.6, 4.3Hz, 1H), 3.76(s, 3H), 3.95-3.99(m,1H), 4.00 (s, 3H), 5.87 (s,2H), 6.34(s,1H). The spectral data for this compound matched those reported. (Majerus, S. M.Sc. Thesis. University of Ottawa 1998).

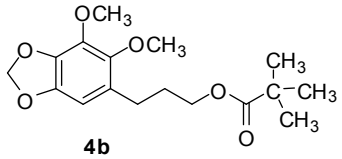
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl acetate (4a)



4a

Esterification of alcohol **2** (100 mg, 0.416 mmol) with acetic anhydride (0.1 mL, 0.924 mmol) and Et_3N (0.15 mL, 1.05 mmol) following procedure afforded 107 mg (91%) of the acetate **4a** as a brownish oil after purification by flash chromatography (8:2, hexanes: ethyl acetate). The spectral data for this compound matched those reported. Majerus, S. M.Sc. Thesis. University of Ottawa 1998.

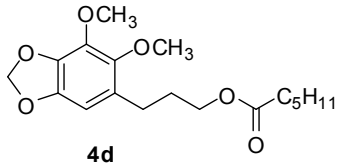
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl pivalate (4b)



4b

Esterification of **2** (100 mg, 0.416 mmol), with pivaloyl chloride (61 mg, 0.5 mmol) in dry DCM (5mL) catalyzed by DMAP (13 mg, 0.1 mmol), and Et_2N (0.15 mL, 1 mmol) was afforded ester **4b** in 75 % yield a white powder. **^{1}H-NMR** (300 MHz; $CDCl_3$) δ 1.20 (s,9H) 1.80 (m, 2H0, 2.58(dd, J= 8.6, 6.8 hz, 2H), 3.75 (s, 3H), 4.00 (s, 3H), 4.06 (t, J=6.4 Hz), 5.87,(s, 2H0, 6.32 (s, 1H0. **^{13}C NMR** (300 mHz, $CDCl_3$) δ= 178.5, 144.4, 144.3, 137.6, 135.8, 127.2, 102.5, 101.0, 63.7, 61.1, 58.8, 38.7, 29.8, 27.2, 26.4**. HRMS.** Calc`d for $C_{17}H_{24}O_6$: 324.1573. Found: 324.1553**.**

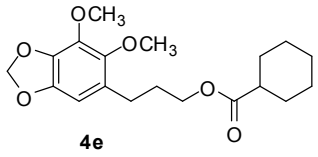
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl hexanoate (4d)



4d

Compound **4d** was obtained from 100 mg of alcohol **8** (in dry DCM (5 mL) and hexanoyl chloride (0.09 mg, 0.624 mmol) catalyzed by DMAP and triethylamine. The crude residue was purified by flash chromatography (8:2, hexane: ethyl acetate) to give compound **4d** as a yellowish oil (0.0750 g, 53%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 0.90 (t, *J* = 7.0 Hz, 3H), 1.34-1.29 (m, 4H), 1.67-1.59 (m, 2H), 1.91-1.83 (m, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.59 (dd, *J* = 8.5, 6.9 Hz, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 4.08 (t, *J* = 6.6 Hz, 2H), 6.33 (s, 1H), 5.88 (s, 2H). **^{13}C NMR** 173.9, 144.5, 144.4, 137.6, 135.8, 127.2, 102.5, 101.1, 61.1, 59.9, 56.5, 34.3, 31.3, 29.7, 26.4, 24.7, 22.3, 13.9

3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl cyclohexanecarboxylate (4e)

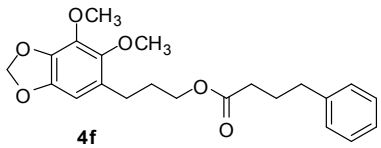


4e

Compound **4e** was prepared in 65% yield as a white powder from alcohol **2** (100 mg, 0.416 mmol), DMAP (13mg, 0.1 mmol), cyclohexanecarbonyl chloride (74 mg, 0.5 mmol), and Et_3N (0.15 mL, 1.0 mmol) in dry DCM. The product was purified by flash chromatography (8:2, hexanes: ethyl acetate). **^{1}H-NMR** (400 MHz; $CDCl_3$) δ 1.16-1.52 (m, 5H), 1.63-1.68 (m, 1H) 1.77-1.05 (m 6H0, 2.29 (tt, J= 11.2, 3.7Hz, 1H), 2.58 (dd, J= 8.6,6.8Hz, 2H, 3,75 (s,3H), 4.01 (s,3H), 4.07 (t, J=6.5Hz, 2H), 5.87 (s, 2H), 6.32 (s, 2H). **^{13}C NMR** (400 mHz, $CDCl_3$) δ 176.1, 144.5, 144.4,

137.6, 135.8, 127.2, 102.5, 101.0, 63.6, 61.2, 59.9, 43.2, 29.8. 26.4, 25.8, 25.4. HRMS. Calc`d for $C_{19}H_{26}O_6$: 350.1729. Found: 350.1717.

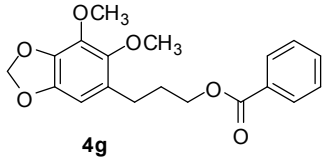
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 4-phenylbutanoate **(4f)**



4f

Alcohol **2** (100 mg, 0.416 mmol) dissolved in dry DCM (1 mL) was added to a solution of 4-phenylbutanoic acid (103 mg, 0.624 mmol) dissolved in dry DCM (3 mL) containing a catalytic amount of DMAP. Finally, DCC (146 mg, 0.707 mmol) soluble in dry DCM (1 mL) was added. The progress of the reaction was followed by analytical TLC. Purification by silica gel chromatography(8:2 hexane-ethyl acetate) afforded **4f** as a yellow oil (122 mg, 76%).**^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 1.86 (qd, *J* = 9.2, 6.5 Hz, 2H), 2.00-1.91 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.61-2.55 (m, 2H), 2.67-2.62 (m, 2H), 3.73 (s, 3H), 3.99 (s, 3H), 4.07 (t, *J* = 6.6 Hz, 2H), 5.85 (s, 2H), 6.32 (s, 1H), 7.20-7.14 (m, 3H), 7.28-7.24 (m, 2H) **^{13}C NMR** 173.6, 144.6, 144.4, 141.4, 137.7, 135.9, 128.5, 128.4, 128.4, 127.2, 125.9, 102.5, 101.1, 63.9, 61.2, 59.9, 35.2, 33.7, 29.7, 26.6, 26.4**.**

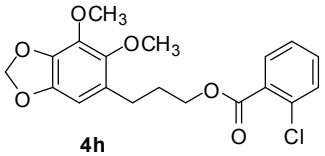
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl benzoate (4g)



4g

Compound **4g** was obtained in 33 % yield as a browinish oil starting wih 250 mg of alcohol **8**, 0.18 mL pf benzoyl chloride and 0.23 mL of Et_2N. The crude product was purified by preparative HPLC using C18 column and a solvent system consisting in 85:15 ACN:H_2O. **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.08-1.95 (m, 2H), 2.70 (dd, *J* = 8.3, 6.9 Hz, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 4.34 (t, *J* = 6.4 Hz, 2H), 5.87 (s, 2H), 6.37 (s, 1H), 7.47-7.41 (m, 2H), 7.58-7.53 (m, 1H), 8.05-8.03 (m, 2H). The spectra obtained was compared with the one previously reported. (Majerus, S. M.Sc. Thesis. University of Ottawa, 1998).

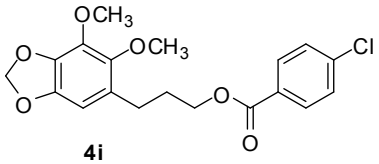
3-(6,7-dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 2-chlorobenzoate **(4h)**



4h

Compound **4h** was synthesized following the typical DCC coupling procedure using the alcohol **2** (100 mg, 0.416 mmol), dry DCM (3 mL), DMAP (5.08 mg, 0.0416 mmol), 2-chlorobenzoic acid (98 mg, 0.624 mmol), DCC (85.83 mg, 0.000416 mmol) soluble in dry DCM was added. The crude was purified by flash chromatography (8:2, hexanes: ethyl acetate) to obtain compound **60** as an orange oil (75.0 mg, 48%). **^{1}H NMR** (400 MHz, CDCl3): δ ppm 2.05-1.95 (m, 2H), 2.70-2.65 (m, 2H), 3.74 (s, 3H), 3.98 (s, 3H), 4.33 (t, *J* = 6.42 Hz, 2H), 5.85 (s, 2H), 6.34 (s, 1H), 7.31-7.26 (m, 1H), 7.44-7.36(m, 2H), 7.79 (dd, *J* = 7.71, 1.60 Hz, 1H). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 165.8, 144.5, 144.5, 137.7, 135.9, 133.6, 132.5, 131.4, 131.1, 130.4, 127.1, 126.6, 102.6, 101.1, 65.1, 61.2, 59.9, 29.7, 26.6 ppm.

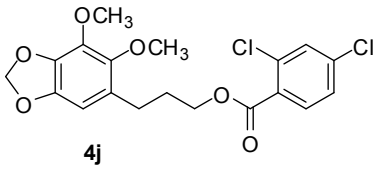
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 4-chlorobenzoate **(4i)**



4i

Reaction of alcohol **2** (100 mg, 0.416 mmol) in dry DCM (3mL), DMAP (5.08 mg, 0.0416 mmol) with 4-chlorobenzoic acid (97.76 mg, 0.624 mmol), and DCC (85.83 mg, 0.000416 mmol) gave 103 mg (65%) of **4i** as an white crystals after purification via flash chromatography (8:2, hexanes: ethyl acetate). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.00 (tt, *J* = 13.1, 6.5 Hz, 2H), 2.68-2.64 (m, 2H), 3.74 (s, 3H), 3.98 (s, 3H), 4.31 (t, *J* = 6.4 Hz, 2H), 5.85 (s, 2H), 6.33 (s, 1H), 7.41-7.36 (m, 2H), 7.95-7.92 (m, 2H). **^{13}C NMR** 165.7, 144.6, 144.4, 139.3, 138.8, 137.7, 135.9, 130.9, 128.9, 128.7, 127.1, 102.5, 101.1, 64.7, 61.2, 59.9, 29.7, 26.6

3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 2,4-dichlorobenzoate (4j)

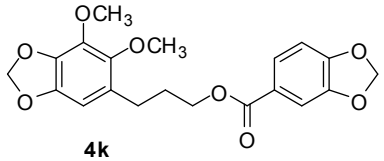


4j

Compound **4j** was obtained in 51% yield as white crystals after flash chromatography (8:2, hexanes: ethyl acetate from alcohol **2** (250 mg, 1.04 mmol) and 2,4-dichlorobenzoic acid (119.2 mg,0.624 mmol) using the typical DCC coupling method. **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.01 (qd, *J* = 8.9, 6.4 Hz, 2H), 2.68 (dd, *J* = 8.3, 6.9 Hz, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 4.34 (t, *J* = 6.4 Hz, 2H), 5.88 (s, 2H), 6.35 (s, 1H), 7.30 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* =

8.4 Hz, 1H). **^{13}C NMR** 164.9, 144.6, 144.5, 138.2, 137.7, 135.9, 134.9, 132.6, 131.0, 128.6, 126.9, 102.6, 101.1, 65.6, 61.2, 59.9, 29.7, 26.6

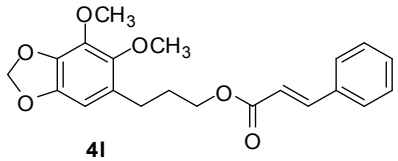
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl benzo[d][1,3]dioxole-5-carboxylate **(4k)**



4k

Esterification of alcohol **2** (100 mg, 0.416 mmol), dry DCM (3 mL)) with piperonylic acid (98 mg, 0.624 mmol), DCC (86 mg, 0.000416 mmol) and DMAP (5 mg, 0.0416 mmol) in dry DCM afforded compound **4k** as a clear oil (95 mg, 59%) after flash chromatography using 8:2 hexanes-ethyl acetate. **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 1.89-1.76 (m, 2H), 2.53-2.47 (m, 2H), 3.58 (s, 3H), 3.82 (s, 3H), 4.11 (t, *J* = 6.40 Hz, 2H), 5.69 (s, 2H), 5.84 (s, 2H), 6.18 (s, 1H), 6.65 (d, *J* = 8.18 Hz, 1H), 7.26 (d, *J* = 1.49 Hz, 1H), 7.46 (dd, *J* = 8.18, 1.57 Hz, 1H). The spectral data for this compound matched those reported. Majerus, S. M.Sc. Thesis. University of Ottawa 1998.

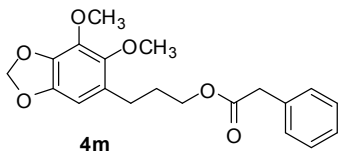
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl cinnamate **(4l)**



4l

Compound **4l** was synthesized following general procedure DCC coupling procedure starting with alcohol 2 (100 mg, 0.416 mmol) and cinnamic acid (92 mg, 0.624 mmol) was added. The crude was purified by flash column (8:2, hexanes: ethyl acetate) to obtain compound **4l** a white powder (140 mg, 91%) **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.01-1.86 (m, 2H), 2.65-2.60 (m, 2H), 3.77 (s, 3H), 4.00 (s, 3H), 4.22 (t, *J* = 6.5 Hz, 2H), 5.85 (s, 2H), 6.36 (s, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 7.37 (td, *J* = 6.4, 2.3 Hz, 3H), 7.54-7.50 (m, 2H), 7.67 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR** 167.0, 144.7, 144.6, 144.5, 137.7, 135.9, 134.5, 130.3, 128.9, 128.2, 128.1, 128.1, 127.2, 118.2, 102.6, 101.1, 64.1, 61.2, 59.9, 29.8, 26.5

3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 2-phenylacetate **(4m)**

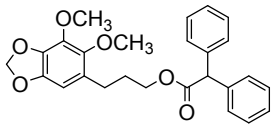


4m

Ester **29** was obtained as a white powder in 60 % yield starting with alcohol **2** (100 mg, 0.416 mmol), (5 mL), DMAP (12.7 mg, 0.104 mmol), 2-phenylacetyl chloride (77 mg, 0.5 mmol), and

Et_3N (0.145 mL, 1.04 mmol). The reaction was carried out in dry DCM. **^{1}H NMR:** (400 MHz, $CDCl_3$): δ ppm 1.91-1.80 (m, 2H), 2.57-2.51 (m, 2H), 3.63 (s, 2H), 4.01 (s, 3H), 4.10 (t, *J* = 6.5 Hz, 2H), 5.88 (s, 2H), 6.25 (s, 1H), 7.33-7.28 (m, 5H). **^{13}C NMR:** 171.6, 144.5, 144.4, 137.6, 135.8, 134.1, 129.3, 129.2, 128.5, 127.0, 102.5, 101.0, 64.3, 61.1, 59.9, 41.5, 29.6, 26.3. **HRMS:** Cal. For $C_{20}H_{22}O_6$ Exact Mass: 358.1416, obtained: 358.1432

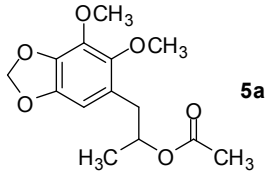
3-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propyl 2,2-diphenylacetate **(4n)**



4n

Alcohol **2** (1.5 g, 6.22 mmol), dry DCM (5mL), DMAP (190 mg, 1.56 mmol), diphenylacetyl chloride (2.2 g, 9.33 mmol) and Et_2N (5 mL, 12.44 mmol) in dry DCM gave 2.3 g (85%) of **4n** as a white powder after chromatography using 8:2, hexanes: ethyl acetate as eluent. **^{1}H NMR** (400 MHz; $CDCl_3$): δ 1.84 (qd, J= 9.2, 5.6Hz, 2H), 2.45-2.51(m, 2H) 3.67 (s,3H), 3.98 (s,3H), 4.14 (t, J= 6.5Hz, 2H), 5.02 (s, 1H), 5.85(s, 2H), 6.17(s,1H), 7.22-7.33(m, 10H). **^{13}C NMR** δ(100MHz; $CDCl_3$ 172.3, 144.4, 144.4, 138.7, 137.6, 135.8, 128.6, 128.5, 128.4, 127.5, 127.2, 126.9, 102.6, 64.6, 61.1, 59.9, 567.2, 29.6, 26.3. HRMS. Calcd for $C_{26}H_{26}O_6$: 434.1729; Found: 434.173.

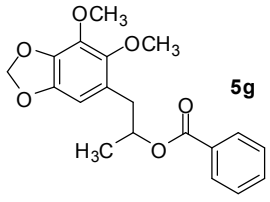
1-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propan-2-yl acetate **(5a)**



5a

Acetylation of alcohol **3** (100 mg, 0.416 mmol) with acetic anhydride (0.1 mL, 0.92 mmol), catalyzed by DMAP (12.7mg, 0.104mmol), and Et_3N (106 mg, 1.05 mmol) in dry DCM afforded the acetate **33** as a white powder in 93% yield.

1-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propan-2-yl benzoate **(5g)**



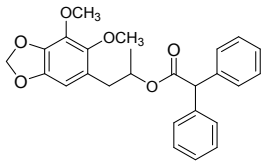
5g

Alcohol **3** (100 mg, 0.416 mmol) in dry DCM was reacted with), benzoyl chloride (0.106 mL, 1.04 mmol), catalyzed by dry DCM (5 mL), DMAP (13 mg, 0.104 mmol and Et_3N (0.145 mL, 1.04

mmol). The yield of benzoate ester **5g,** a white powder was 100 mg (70%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 1.32 (d, *J* = 6.3 Hz, 3H), 2.84 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.95 (dd, *J* = 13.6, 7.0 Hz, 1H), 3.78 (s, 3H), 3.97 (s, 3H), 5.43-5.27 (m, 1H), 5.84 (dd, *J* = 5.4, 1.5 Hz, 2H), 6.41 (s, 1H), 7.5-7.4 (m, 3H), 8.01 (td, *J* = 8.5, 1.6 Hz, 2H). **^{13}C NMR** 166.1, 145.1, 144.4, 137.6, 136.4, 132.7, 130.8, 129.5, 128.3, 123.5, 103.6, 101.2, 7, 71.9, 61.2, 59.9, 36.1, 19.7.

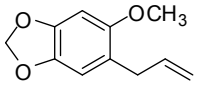
1-(6,7-Dimethoxybenzo[d][1,3]dioxol-5-yl)propan-2-yl 2,2-diphenylacetate **(5n)**

31



Reaction of diphenylacetyl chloride (116 mg, 0.5 mmol),) with alcohol **3** 100 mg, 0.416 mmol) in dry DCM catalyzed by DMAP (12.7 mg, 0.104 mmol and Et_3N (0.145 mL, 1.04 mmol) yielded 150.3 mg, (83%) of the diphenyl ester **5n** as a white powder. **^{1}H NMR** 400 MHz, $CDCl_3$): δ ppm 1.32 (d, *J* = 6.3 Hz, 3H), 2.71 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.77 (dd, *J* = 13.8, 7.6 Hz, 1H), 3.78 (s, 3H), 3.97 (s, 3H), 4.95(s, 1H), 5.23-5.15 (m, 1H), 5.84 (dd, *J* = 5.4, 1.5 Hz, 2H), 6.41 (s, 1H), 7.32-7.17 (m, 10H).**^{13}C NMR** 171.9, 144.9, 144.3, 138.8, 138.8, 137.5, 136.3, 128.7, 128.5, 128.5, 128.4, 127.1, 127.0, 123.4, 103.5, 101.1, 72.0, 61.1, 59.9, 57.3, 35.9, 19.7. **HRMS:** calc. $C_{26}H_{26}O_6$: 434.1729, Found: 434.17462

5-Allyl-6-methoxybenzo[d][1,3]dioxole **(8b)**

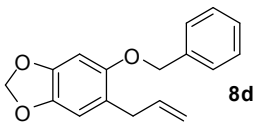


8b

Methylation of 500 mg (2.8 mmol) of the phenol **37** dry acetone (5mL), containing 582 mg, (4.2 mmol) of potassium and 20.26 mL (4.2 mmol) of methyl iodide afforded 485 (92%) mg of **38** as a light colorless oil after chromatography. The spectra corresponds to the one reported in literature[62].

^{1}H NMR (400 MHz, CDCl3): δ ppm 3.29 (d, 2H, J=5.3 Hz), 3.75 (s, 3H), 5.01 (dd, 1H, J=10.6 Hz, J=1.2 Hz), 5.18 (dd, 1H, J=17.3 Hz, J=1.4 Hz), 5.87 (s, 2H), 5.98-5.89 (m, 3H), 6.51 (s, 1H), 6.65 (s, 1H)

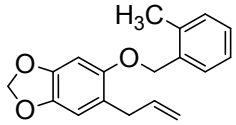
5-Allyl-6-(benzyloxy)benzo[d][1,3]dioxole **(8d)**



8d

Reaction of **37** (500 mg, 2.8 mmol) in 3 ml of dry THF with NaH (100.8 mg, 4.2 mmol) followed by benzyl bromide (0.44 mL, 3.64 mmol) gave 715mg (95%) of the benzyl ether **8d** as off white needles. Compound has been synthesized before[63].**^{1}H NMR** (400 MHz, CDCl3): δ ppm 3.35 (td, *J* = 6.6, 1.3 Hz, 2H), 5.00 (s, 2H), 5.05-4.99 (m, 2H), 5.89 (s, 2H), 5.98-5.88 (m, 1H), 6.57 (s, 1H), 6.67 (s, 1H), 7.42-7.30 (m, 5H). **^{13}C NMR** 151.0, 146.2, 141.4, 137.3, 137.2, 128.5, 127.9, 127.3, 121.5, 115.4, 109.689, 101.0, 96.5, 71.5, 34.2.

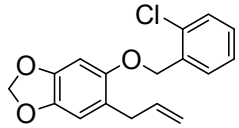
5-Allyl-6-(2,5-dimethoxybenzyl)oxy)benzo[d][1,3]dioxole **(8e)**



8e

Alkylation of the phenol **7** (1.67 g, 9.37 mmol) with 2-methylbenzyl bromide (194 mg, 0.84 mmol) in dry acetone (20 mL) to which had been added K_2CO_3 (4.56 g, 3.3mmol) gave **8e** as white crystals (1.56g, 78%) after flash chromatography (8:2, hexanes: ethyl acetate). **^{1}H NMR** (400 MHz, CDCl3): δ ppm 7.41-7.39(d, J= 7.25Hz, 1H), 7.24-7.18(m, 3H), 6.66(s, 1H), 6.59(s, 1H), 5.94-5.87(m, 3H), 5.03-4.98(m, 2H), 4.94(s, 2H), 3.32(d, J=6.61Hz, 2H), 2.35(s, 3H) **^{13}C NMR :** 151.15, 146.22, 141.32, 137.24, 136.24, 135.17, 130.26, 128.15, 128.02, 125.99, 121.49, 115.41, 109.69, 101.01, 96.35, 69.93, 34.07, 18.85

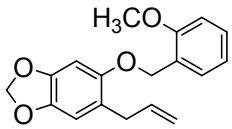
5-Allyl-6-((2-chlorobenzyl)oxy)benzo[d][1,3]dioxole **(8f)**



8f

This compound was prepared using **21b** (0.5 g, 2.81 mmol), in 20 ml of Acetone, potassium carbonate (1.16 g, 8.41 mmol) was added and stirred for 10 minutes before the addition of 4-chlorobenzyl bromide (0.43ml, 2.81mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (0.43 g, Rf= 0.70 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$* 400ppm 7.58-7.57(d, J= Hz, 1H), 7.40-7.38(m, 4H), 6.69(s, 1H), 6.59(s, 1H), 6.02-5.95(m, 1H), 5.88(s, 2H), 5.08(s, 4H), 3.41(d, J=6.55Hz, 2H)**^{13}C NMR** (100MHz, *$CDCl_3$*□□□ ppm 150.77, 146.36, 141.59, 137.21, 135.08, 132.43, 129.34, 128.89, 128.58, 126.98, 121.45, 115.52, 109.74, 101.11, 96.43, 68.58, 34.27

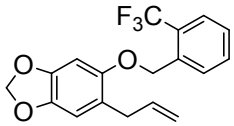
5-Allyl-6-((2-methoxybenzyl)oxy)benzo[d][1,3]dioxole **(8g)**



8g

This compound was prepared using **7** (0.5 g, 2.81 mmol), in 20 ml of Acetone, potassium carbonate (1.16 g, 8.41 mmol) was added and stirred for 10 minutes before the addition of 4-methoxy benzyl bromide (0.43ml, 2.81mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (0.45 g, Rf= 0.80 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm 7.51-7.49(d, J=7.14Hz, 1H), 7.33-7.29(m, 1H), 7.03-7.01(m, 1H), 6.99-6.90(d, J=3.08 Hz, 1H), 6.70-6.65(m, 2H), 6.03-5.89(m, 1H), 5.88(s, 2H), 5.07(m, 4H), 3.87(s, 3H), 3.29-3.28(d, J= 5.48Hz, 2H)**^{13}C NMR** (100MHz, *$CDCl_3$*) δ ppm 156.72, 151.29, 146.28, 141.29, 137.44, 128.80, 128.29, 125.78, 121.50, 120.60, 115.36, 110.13, 109.57, 101.00, 96.68, 66.65, 55.32, 34.31

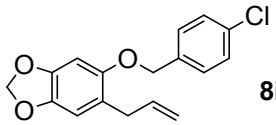
5-Allyl-6-((2-trifluoromethyl)benzyl)oxy)benzo[d][1,3]dioxole **(8h)**



8h

This compound was prepared using **7** (0.5 g, 2.81 mmol), in 20 ml of Acetone, potassium carbonate (1.16 g, 8.41 mmol) was added and stirred for 10 minutes before the addition of 2-triflurobenzyl bromide (0.43ml, 2.81mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (0.41 g, Rf= 0.75 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm 7.75-7.73(d, J=7.79Hz, 1H), 7.67-7.65(d, J=7.79Hz, 1H), 7.57-7.53(t, J=7.48Hz, 1H), 7.41-7.38(t, J=7.54Hz, 1H), 6.66(s, 1H), 6.50(s, 1H), 5.98-5.91(m, 1H), 5.87(s, 2H), 5.17(s, 2H), 5.06-5.01(m, 2H), 3.37-3.35(d J=6.55Hz, 2H)**^{13}C NMR** (100MHz, *$CDCl_3$*) δ ppm 150.59, 146.32, 141.59, 137.09, 132.15, 128.31, 127.59, 125.88, 125.82, 121.38, 115.50, 109.78, 101.09, 96.32, 67.43, 67.40, 34.19

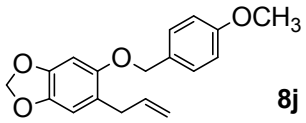
5-Allyl-6-((4-chlorobenzyl)oxy)benzo[d][1,3]dioxole **(8i)**



8i

This compound was prepared using **7** (0.2 g, 1.12 mmol), in 15 ml of Acetone, potassium carbonate (0.465 g, 3.37 mmol) was added and stirred for 10 minutes before the addition of *para*-chloro benzyl chloride (0.181 g, 1.12mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (0.12 g, Rf= 0.25 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$* ppm 7.32(s, 4H), 6.64(s, 1H), 6.51(s, 1H), 5.94-5.87(m, 1H), 5.85(s, 2H), 5.03-4.99(m, 2H), 4.93(s, 2H), 3.32-3.30(d, J= 6.69 Hz, 2H) **^{13}C NMR** (100MHz, *$CDCl_3$* ppm 159.15, 150.78, 146.28, 141.59, 137.17, 129.60, 129.52, 129.49, 124.52, 124.38, 124.23, 124.19, 121.67, 115.41, 115.18, 109.65, 101.05, 96.63, 65.40, 65.36, 34.14

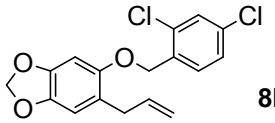
5-Allyl-6-((4-methoxybenzyl)oxy)benzo[d][1,3]dioxole **(8j)**



8j

This compound was prepared using **21b** (2.91 g, 16.33 mmol), in 30 ml of Acetone, potassium carbonate (6.77 g, 48.9 mmol) was added and stirred for 10 minutes before the addition of 4 methoxy benzyl bromide (2.2ml, 16.16mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white powder (2.6g, Rf= 0.7 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$* ppm 7.32-7.30 (d, J= 8.69Hz, 2H), 6.89-6.87 (d, J= 8.68Hz, 2H), 6.63 (s, 1H), 6.55(s, 1H), 5.98-5.78 (m, 1H), 5.86(s, 2H), 5.03-4.98(m, 2H), 4.90(s, 2H), 3.80(s, 3H), 3.31-3.29(d, J= 6.61Hz, 2H)**^{13}C NMR** (100 MHz, *$CDCl_3$* ppm 159.35, 151.06, 146.18, 141.31, 137.25, 129.34, 128.95, 121.58, 115.35, 113.92, 109.61, 100.97, 96.67, 71.37, 55.30, 34.17

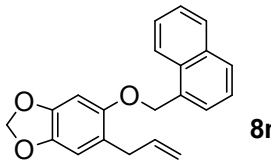
5-Allyl-6-((2,4-dichlorobenzyl)oxy)benzo[d][1,3]dioxole **(8k)**



8k

This compound was prepared using **7** (0.2 g, 1.12 mmol), in 15 ml of Acetone, potassium carbonate (0.613 g, 4.44 mmol) was added and stirred for 10 minutes before the addition of 2,4 dichloro benzyl chloride (1.15ml, 1.11mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (195mg, Rf= 0.80 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm 7.48-7.46 (d, J=8.35, 1H), 7.39(d, J=2.05, 1H), 7.27-7.26(m, 1H), 6.65(s, 1H), 6.52(s, 1H), 5.88(m, 3H), 5.03-4.99(m, 4H), 3.34-3.32(dt, J=6.51, 6.51, 6.51 Hz, 2H)**^{13}C NMR** (100MHz, *$CDCl_3$*) δ ppm 150.51, 146.34, 141.72, 137.04, 134.03, 133.68, 133.01, 129.44, 129.16, 127.30, 121.47, 115.51, 109.79, 101.12, 96.41, 68.10, 34.18

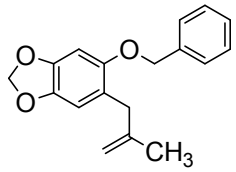
5-Allyl-6-((naphthalen-1-ylmethoxy)benzo[d][1,3]dioxole **(8m)**



8m

This compound was prepared using **7** (0.5 g, 2.81 mmol), in 20 ml of Acetone, potassium carbonate (1.16 g, 8.41 mmol) was added and stirred for 10 minutes before the addition of 2-bromoethyl napthalene (0.42ml, 2.81mmol) and refluxed for 6 hours. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (0.43 g, Rf= 0.80 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$*) δ ppm 8.03-7.90(m, 1H), 7.88-7.83(m, 2H), 7.58-7.43(m, 4H), 6.69-6.67(d, J=3.08 Hz, 2H), 5.89 (m, 3H), 5.41(s, 2H), 4.99-4.95(m, 2H), 3.29-3.28(d, J=6.59 Hz, 2H)**^{13}C NMR** (100MHz, *$CDCl_3$*) δ ppm 151.10, 146.26, 141.43, 137.25, 133.72, 132.64, 131.42, 128.84, 128.70, 126.35, 126.17, 125.91, 125.35, 123.72, 121.63, 115.41, 109.74, 101.06, 96.48, 70.09, 34.08

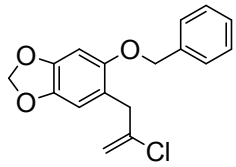
5-(benzyloxy)-6-(2-methlyallyl)benzo[d][1,3]dioxole **(8n)**



8n

This compound was prepared using **7** (2g, 9.38 mmol), in 20 ml of Acetone, potassium carbonate (4 g, 28.16 mmol) was added and stirred for 10 minutes before the addition of benzyl bromide (1.11ml, 9.39mmol)) and refluxed for 8 hours. The reaction mixture was extracted with EtOAc and water. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product (3.14 g) was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (1.3g, Rf= 0.75 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$* ppm 7.39-7.30(m, 5H), 6.70(s, 1H), 6.56(s, 1H), 5.89(s, 2H), 5.19(s, 1H), 5.04 (s, 1H), 4.98(s, 2H), 3.59(s, 2H)**^{13}C NMR** (100 MHz, *$CDCl_3$* ppm 151.57, 147.08, 141.33, 137.05, 128.56, 127.93, 127.28, 118.12, 113.04, 110.17, 101.18, 96.42, 71.44, 39.37

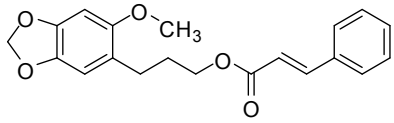
5-(benzyloxy)-6-(2-chloroallyl)benzo[d][1,3]dioxole **(8o)**



8o

This compound was prepared using **7** (2g, 9.38 mmol), in 20 ml of Acetone, potassium carbonate (4 g, 28.16 mmol) was added and stirred for 10 minutes before the addition of benzyl bromide (1.11ml, 9.39mmol)) and refluxed for 8 hours. The reaction mixture was extracted with EtOAc and water. The reaction mixture was extracted with EtOAc and water. The phenol was washed with 10% NaOH. The crude product (3.14 g) was purified via gradient column chromatography (2.5% EtOAc in hexanes) resulting as a white solid (1.3g, Rf= 0.75 in 2:8 EtOAc:Hexanes).**^{1}H NMR** (400 MHz, *$CDCl_3$* ppm 7.39-7.30(m, 5H), 6.70(s, 1H), 6.56(s, 1H), 5.89(s, 2H), 5.19(s, 1H), 5.04 (s, 1H), 4.98(s, 2H), 3.59(s, 2H)**^{13}C NMR** (100 MHz, *$CDCl_3$* ppm 151.57, 147.08, 141.33, 137.05, 128.56, 127.93, 127.28, 118.12, 113.04, 110.17, 101.18, 96.42, 71.44, 39.37

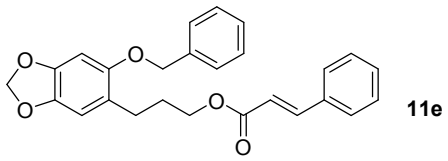
3-(6-Methoxybenzo[d][1,3]dioxol-5-yl)propyl cinnamate **(11d)**



11d

Acylation of **45** (100 mg, 0.48 mmol) with cinnamoyl chloride (106 mg, 0.71 mmol) and DMAP (9 mg, 0.071) in dry DCM (2 mL), yielded 122mg (75%) **48** as a white powder. **^{1}H NMR** (400 MHz, CDCl3): δ ppm 2.03-1.90 (m, 2H), 2.69-2.63 (m, 2H), 3.75 (s, 3H), 4.21 (t, *J* = 6.6 Hz, 2H), 5.87 (s, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.51 (s, 1H), 6.66 (s, 1H), 7.41-7.36 (m, 3H), 7.56-7.51 (m, 2H), 7.68 (d, *J* = 16.0 Hz, 1H). **^{13}C NMR:** 167.1, 152.3, 146.2, 144.6, 140.8, 134.5, 130.2, 128.9, 128.1, 121.8, 118.3, 109.8, 100.9, 94.7, 64.2, 56.3, 29.1, 26.6

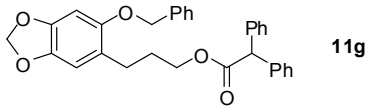
3-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)propyl cinnamate **(11e)**



11e

Compound **11** (100 mg, 0.35 mmol) in dry DCM (2 mL) containing DMAP (4 mg, 0.035 mmol) was reacted with cinnamoyl chloride (77 mg, 0.524 mmol) to obtain compound 139 mg (96%) of **11e** as a white powder (139 mg, 96%). **^{1}H NMR** (400 MHz, CDCl3): δ ppm 2.04-1.96 (m, 2H), 2.77-2.71 (m, 2H), 4.23 (t, *J* = 6.48 Hz, 2H), 5.02 (s, 2H), 5.89 (s, 2H), 6.43 (d, *J* = 16.02 Hz, 1H), 6.59 (s, 1H), 6.70 (s, 1H), 7.55-7.27 (m, 10H), 7.67 (d, *J* = 16.03 Hz, 1H). **^{13}C NMR** 167.1, 151.3, 146.2, 145.9, 144.6, 141.2, 137.3, 130.2, 128.9, 128.6, 128.1, 127.8, 127.1, 122.4, 118.2, 109.8, 100.9, 96.3, 71.2, 64.2, 29.2, 26.8

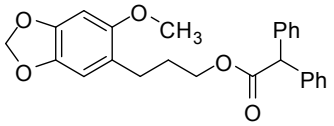
3-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)propyl 2,2-diphenylacetate **(11g)**



11g

Compound **11g** was synthesized by adding 121mg diphenylacetyl chloride (0.52mmol) dissolved in DCM to 100 mg (0.35 mmol) of **11**, DMAP (10 mg, 0.1 mmol)and Et_3N (121 mg, 0.52 mmol), in 2 ML of dry DCM. Purification of the crude by preparative HPLC H_2O: ACN (85%) afforded compound **11g** as a white powder (52 mg, 35%). **^{1}H NMR** (400 MHz, CDCl3): δ ppm 1.92-1.81 (m, 2H), 2.57-2.51 (m, 2H), 4.12 (t, *J* = 6.5 Hz, 2H), 4.94 (s, 2H), 4.99 (s, 1H), 5.86 (s, 2H), 6.47 (s, 1H), 6.51 (s, 1H), 7.40-7.24 (m, 15H)**^{13}C NMR** 172.5, 151.2, 146.2, 141.0, 138.8, 137.3, 129.1, 128.6, 128.6, 128.5, 127.9, 127.7, 127.4, 127.4, 127.2, 127.1, 122.2, 109.9, 100.9, 96.2, 71.1, 64.8, 57.2, 28.9, 26.7. **HRMS** calc. $C_{31}H_{28}O_5$: 480.1937, obtained: 480.19419

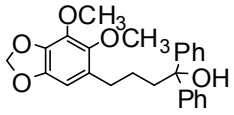
3-(6-(Benzyloxy)benzo[d][1,3]dioxol-5-yl)propyl benzoate **(11f)**



11f

Reaction of **9** (100 mg, 0.35 mmol) with 120 mg (0.52 mmol) of diphenylacetyl chloride in dry DCM catalyzed by 10 mg (0.1 mmol) of DMAP, gave **11f** which was purified by column chromatography (hexanes: ethyl acetate, 8:2) afforded compound **11f** as a white powder (87 mg, 62%). **^{1}H NMR** (400 MHz, CDCl3): δ ppm 1.88-1.81 (m, 2H), 2.52-2.47 (m, 2H), 3.68 (s, 3H), 4.13 (t, *J* = 6.5 Hz, 2H), 5.02 (s, 1H), 5.86-5.86 (m, 2H), 6.46 (d, *J* = 1.0 Hz, 2H), 7.34-7.23 (m, 10H). **^{13}C NMR** 172.5, 152.2, 146.2, 140.6, 138.7, 128.6, 128.5, 127.2, 121.5, 109.8, 100.9, 94.6, 64.7, 57.2, 56.2, 28.9, 26.5. **HRMS** Calc. for $C_{25}H_{24}O_5$ 404.1624, obtained: 404.1635

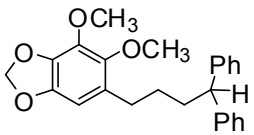
Compound **13**.



13

n-Buli (1.25 mL, 2.0M) was added drop wise a cooled (-78˚C) solution of dillapiol **1** (0.4 g, 1.8mmol) in dry THF (10mL) The reaction mixture was stirred for 30 min, allowed to warm up to 0˚C and kept at 0˚C for another 30 min. After this time the reaction mixture was cooled to -78˚C for 5 minutes and then benzophenone (0.4264 g, 1.3 mmol) was added. The resulting mixture was stirred for 5 minutes then quenched with saturated NH_4Cl solution (3 mL) and extracted with Et_2O (3 X 20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude was purified by Flash chromatography (8:2, hexanes: ethyl acetate) to provide compound **2** as a white powder (598mg, 82%). **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 1.60 (s, 2H), 2.60 (s, 1H), 3.24 (d, *J* = 7.3 Hz, 2H), 3.69 (s, 3H), 4.01 (s, 3H), 5.89 (s, 3H), 6.49 (s, 1H), 6.78 (d, *J* = 16.0 Hz, 1H), 7.28-7.25 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.49 (d, *J* = 7.6 Hz, 4H). **^{13}C NMR** δ(100MHz; $CDCl_3$) 46.2, 60.0, 61.5, 77.4, 98.6, 101.3, 124.0, 124.2, 126.1, 126.9, 128.2, 129.2, 137.1, 137.5, 144.5, 145.0 146.6

Compound **14.**

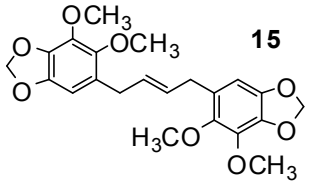


14

A solution of **2** (250mg, 0.62mmol) in toluene (1 mL) containing a catalytic amount of *p*-toluensulfonic acid (PTSA) was heated to boiling using a heating gun. The reaction mixture was allowed to cool and toluene was removed using roto-evaporation. The residue was purified by flash chromatography (9:1, hexanes: ethyl acetate) to give the dehydration product as a

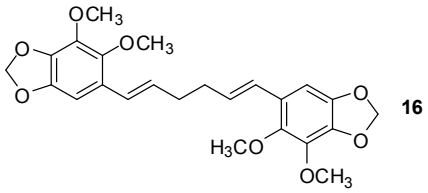
yellowish powder (93.4g, 81%). **^{1}H NMR** (400 MHz; $CDCl_3$): δ 3.82 (s, 3H), 4.05 (s, 3H), 5.91 (s, 2H), 6.56 (s, 1H), 6.79 (dd, *J* = 15.6, 11.0 Hz, 1H), 6.99 (dd, *J* = 24.3, 13.3 Hz, 2H), 7.48-7.28 (m, 11H). This intermediate (44.7mg, (0.116mmol) was dissolved in 2 mL of methanol (2 mL) containing a catalytic amount of Pd/C and exposed to hydrogen via an inflated balloon for 24 h. The reaction mixture was filtered and the solvent evaporated. The crude product was purified by flash chromatography (8:2, hexanes: ethyl acetate) to yield 96%) of compound 1**4** as clear oil **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 1.44-1.53 (m, 2H), 2.02-2.11(m,2H) 2.52 (t J=7.7Hz), 2H), 3.65(s, 3H), 3.89 (s,3H), 5.84(s,2H), 6.25 (s,1H), 7.11-7.26(m, 10H). **^{13}C NMR** δ(100Mhz, $CDCl_3$): δ 146.6, 145.0, 144.4, 129.2, 128.3, 128.2, 128.2, 126.9, 126.1, 124.1, 123.9, 101.3, 98.5, 61.5, 60.1, 46.2.

Compound (**15).**



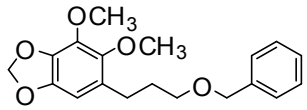
Grubbs II catalyst (30 mg, 0.135 mmol) was added to a solution of dillapiol (200 mg, 0.9 mmol) dissolved in dry DCM,. The mixture was kept under nitrogen and refluxed for 72h. The crude residue was purified by flash chromatography (9:1, hexane: ethyl acetate) to give 64 mg (57%) of 1**6** as a thick brownish oil. **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 3.26 (dd, 3.6, 1.4Hz, 4H), 3.73 (s, 6H), 4.01(s, 6H), 5.57 (ddd, J=5.0, 3.5,1.3Hz, 2H), 5.88, s, 4H), 4.34 (s, 2H). **^{13}C NMR** δ(100Mhz, $CDCl_3$): δ 144.6, 144.2, 137.6, 135.8, 130.1, 126.8, 102.7, 101.1, 61.3, 59.9, 32.6.

(E)-4,5-Dimethoxy-6-(4-phenylbut-1-enyl)benzo[d][1,3]dioxole ***(16)***



Compound **16** was obtained unexpectedly when the lithio derivative of dillapiol (see preparation of compound **13** was reacted with benzyl bromide. The crude reaction mixture was purified by flash chromatography (8:2, hexanes: ethyl acetate). Compound **16** was obtained as clear oil in 28 % yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.39-2.36 (m, 4H), 3.73 (s, 6H), 4.00 (s, 6H), 5.88 (s, 4H), 6.12-6.03 (m, 2H), 6.63 (s, 2H), 6.63 (d, J= 16.0Hz, 2H). **^{13}C NMR:** 145.1, 144.1, 137.5, 136.6, 129.6, 124.7, 124.2, 101.2, 98.4, 61.5, 60.1, 33.2

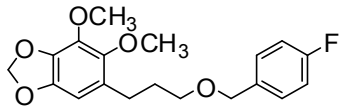
6-(3-(Benzyloxy)propyl)-4,5-dimethoxybenzo[d][1,3]dioxole **(17a)**



17a

This compound was prepared by refluxing the sodium salt of the precursor and benzyl bromide in dry THF (3 mL) for 12 h. Usual workup followed by flash chromatography (9:1, hexane: ethyl acetate) gave compound **17a** as a pale yellow oil (60mg, 43%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 2.03 (qd, *J* = 8.9, 6.5 Hz, 2H), 2.72-2.68 (m, 2H), 3.76 (s, 3H), 4.01 (s, 3H), 4.34 (t, *J* = 6.4 Hz, 2H), 5.87 (s, 2H), 6.37 (s, 1H), 7.48-7.41 (m, 2H), 7.58-7.53 (m, 1H), 8.05-8.03 (m, 2H). **^{13}C NMR** 166.6, 144.6, 144.5, 137.7, 135.9, 132.8, 130.5, 129.6, 128.3, 127.2, 102.6, 101.1, 64.5, 61.2, 59.9, 29.8, 26.6

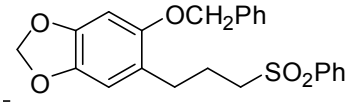
6-(3-((4-fluorobenzyl)oxy)propyl)-4,5-dimethoxybenzo[d][1,3]dioxole **(17b)**



17b

Compound **16f** was synthesized following the procedure used for compound **17a** but using *p*-fluorobenzyl bromide in place of benzyl bromide**.** The crude product was purified by flash chromatography (8:2, hexane: ethyl acetate) to give compound **17b** as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ ppm 1.90-1.78 (m, 2H), 2.62-2.58 (m, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 3.74 (s, 3H), 4.00 (s, 3H), 4.44 (s, 2H), 5.85 (s, 2H), 6.32 (s, 1H), 7.05-6.97 (m, 2H), 7.29 (dd, *J* = 8.4, 5.6 Hz, 2H). **^{13}C NMR** 163.5, 160.9, 144.5, 144.3, 129.4, 129.3, 127.9, 115.3, 115.1, 102.6, 101.1, 72.1, 69.7, 61.2, 59.9, 30.7, 26.5.

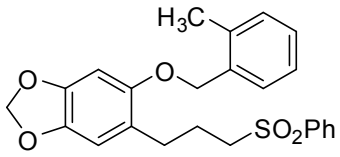
5-Benzyloxy-6-(3-sulfonylphenyl)propylbenzo[d][1,3]dioxole (**18**)



This compound was prepared via the following sequence: Hydroboration of **8d** which gave the expected primary alcohol as the major product. Subsequent tosylation, displacement with PhS(-)NA(+) and finally oxidation with MCPBA following standard procedures afforded 18.

Compound 18. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) 1,26 (t: J=7,1 Hz, 1H), 1,97 (q: J=7,4 Hz, 2H), 2,63 (t: J=7,2 Hz, 2H), 3,01-3,10 (m, 2H), 4,92 (s, 2H), 5,88 (s, 2H), 6,52 (s, 1H), 6,55 (s, 1H), 7,28-7,41 (m, 5H), 7,52 (t: J=7,52 Hz, 2H), 7,62 (t,t: J=7,44 Hz, J=1,48 Hz, 1H), 7,86 (d,t: J=8,5 Hz, J=1,7 Hz). **^{13}C NMR** δ(ppm) 23,13, 28,57, 55,49, 71,04, 96,05, 101,01, 109,67, 120,74, 127,18, 127,89, 127,96, 128,54, 129,12, 133,47, 136,89, 139,08, 141,10, 146,50, 151,18.

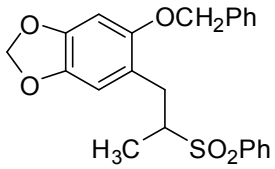
Compound **19**



This compound was prepared following the same overall procedure as for **18** starting with **11.**

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1,15-1,34(m, 2H), 2,15 (s, 2H), 2,22-2,42 (m, 1H), 2,82-3,25 (m, 1H), 4,57-4,92 (m, 1H), 5,27 (s, 2H), 6,90-8,21 (m, 5*H*)

5-Benzyloxy-6-(2-methyl-3-sulfonylphenyl) propyl benzo[d][1,3]dioxole (**20**)



This compound was prepared following the same overall procedure as for **18** starting with the minor hydroboration product obtained from **8d**.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1,10 (d: J = 6,7 Hz, 3H), 2,35-2.25 (m, 1H), 2,51 (d,d: J=11,1 Hz, 4,3 Hz, 1H), 2,56 (d,d: J=11,1 Hz, 5,5Hz, 1H), 2,89 (d,d: J=14,3 Hz, 8,9 Hz, 1H), 3,15 (d,d: J=14,3 Hz, 3,4 Hz, 1H), 4,87 (d,d: J=11,8 Hz, 17,0 Hz, 2H), 5,88 (s, 2H), 6,46 (s, 1H), 6,47 (s, 1H), 7,29-7,41 (m, 5H), 7,46 (t: J=7,8 Hz, 2H), 7,58 (t,t: J = 7,5 Hz, 1,2 Hz, 1H), 7,74-7,78 (m, 2H). **^{13}C NMR** (400 MHz, $CDCl_3$): δ (ppm) 19,96, 29,82, 37,20, 53,77, 71,04, 96,01, 101,04, 110,33, 119,80, 127,14, 127,75, 127,91, 128,59, 129,05, 133,26, 136,96, 139,80, 141,04, 146,54, 151,40.

Bioassays

This part of the work carried out by with Suqi Liu (Department of Biology)

1. A CYP 3A4 assay will be used for fast screening the active compounds

Enzyme inhibition assays are conducted with a cloned CYP3A4 isozyme. The method described by Foster and co-workers[57] was used for this isozyme. Assays will be performed in clear-bottom, opaque-welled microtiter plates. Wells are designated as either “Control,” “Blank,” “Test,” or “Test-Blank.” Control wells consist of ddH_2O and NADPH (*β*-nicotinamide adenine dinucleotide phosphate) solution; blank wells consist of ddH_2O and buffer solution; test wells consist of the derivatives of dillapiol at a particular concentration and NADPH solution; and test-blank wells consist of the corresponding derivative compounds and buffer solution. Enzyme solution will be added to all wells. A Millipore Cytofluor 4000 Fluorescence Measurement System set to 485-nm

excitation filter (20-nm bandwidth) will be used to analyze each plate. Percent inhibition calculations were based on differences in fluorescence between the control/blank wells and test/test blank wells. All assays were performed under gold fluorescent lighting.