Rational Design of Potent, Small, Synthetic Allosteric Inhibitors of Thrombin

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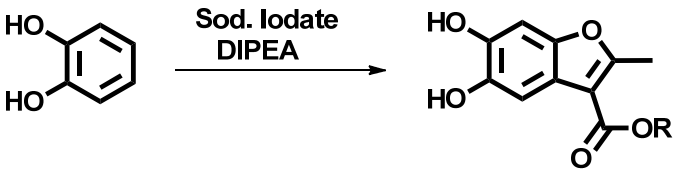
Table of Contents (Refer to Figure 2 of the paper for structures of molecules **1** – **19**)

1. **Synthesis of (1a-e)**



To the solution of catechol **(**20mM) in 75 ml of ethanol were added ester of acetoacetate (20mM) and N, N-Diisopropylethylamine (40mM). The reaction mixture was stirred for 5 min. To this mixture was added sodium iodate (20 mM) and stirred vigorously for 5 min and then 25 ml of water was added. The reaction mixture was stirred for 10 hours at room temperature and quenched with 400 ml of ethyl acetate and extracted with 150 ml of brine and 30 ml of 0.5 N HCl. The organic layer was dried over magnesium sulfate and concentrated down. The product was purified by passing through plug of silica (1 inch in height) using 2% methanol in methylene chloride. The product was concentrated and dried under vacuum to provide yield of 40%.

1a: ^{1}H NMR (Acetone-d_6, 300 MHz) δ 1.36 (t, *J* =3 Hz, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.31 (q, *J* =6 Hz, 2H, CH_2), 6.95 (s, 1H, Ar-H), 7.37 (s, 1H, Ar-H).^{13}C NMR ($CDCl_3$) δ 14.79 14.96 60.54 98.53 106.62 108.83 117.56 144.09 144.92 147.79 161.79 164.48.

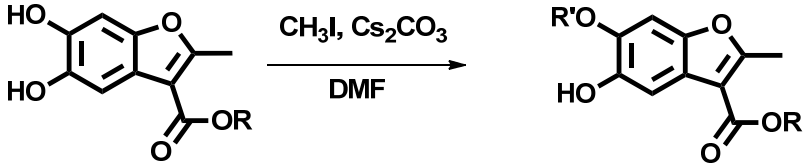
1b: ^{1}H NMR (CDCl3, 300 MHz) δ 2.65 (s, 3H), 3.97 (s, 3H), 6.99 (s, 1H), 7.43 (s, 1H).

1c: ^{1}H NMR (CDCl3, 300 MHz) δ 1.60 (s, 9H), 2.63 (s, 3H), 6.96 (s, 1H), 7.39 (s, 1H).

1d: ^{1}H NMR (CDCl3, 300 MHz) 2.63 (s, 3H), 3.41 (s, 3H), 3.72 (t, j=12 Hz, 2H), 4.46 (t, j=12 Hz, 2H), 6.96 (s, 1H), 7.39 (s, 1H).

1e: ^{1}H NMR (CDCl3, 300 MHz) 2.71 (s, 3H), 4.85 (d, 2H), 5.22 (d, 1H), 5.36 (d, 2H), 6.00 (m, 1H), 6.91 (s. 1H), 7.46 (s, 1H)

2. **Synthesis of (2a-2j)**



To a solution of **(1a-1e)** (1.44mmol) in DMF (12 ml) were added cesium carbonate (0.72mmol) and acyl or alkyl halide (1.44mmol) and stirred for 15 hours under an N_2 atmosphere. The reaction was quenched by adding 0.5N HCl and extracted with ethyl acetate. The organic extract was dried over magnesium sulfate and concentrated down and purified on silica gel (0-25% ethyl acetate in hexanes) to give product in 53% yield.

2a: ^{1}H NMR (CDCl3, 300 MHz) δ 1.46 (t, *J*=6Hz, 3H), 2.75 (s, 3H), 3.96 (s, 3H), 4.39 (q, *J* =6 Hz, 2H), 5.58 (s, 1H), 6.95 (s, 1H), 7.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.60, 14.66, 56.54, 60.43, 94.33, 106.04, 109.23, 119.19, 143.37, 145.18, 147.86, 162.87, 164.88.

2b: ^{1}H NMR (CDCl3, 300 MHz) δ 2.71 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 6.95 (s, 1H), 7.44 (s, 1H)

2c: ^{1}H NMR (CDCl3, 300 MHz) δ 1.60 (s, 9H), 2.63 (s, 3H), 3.92 (s, 3H), 6.92 (s, 1H), 7.39 (s, 1H)

2d: ^{1}H NMR (CDCl3, 300 MHz) δ 2.63 (s, 3H), 3.41 (s, 3H), 3.72 (t, j=12 Hz, 2H), 3.82 (s, 3H), 4.46 (t, j=12 Hz, 2H), 6.96 (s, 1H), 7.39 (s, 1H).

2e: ^{1}H NMR (CDCl3, 400 MHz) δ 1.45 (s, 6H,), 2.70 (s, 3H,), 4.13 (d, 2H,), 4.36 (d, 2H,), 6.93 (s, 1H,), 7.43 (s, 1H,).^{13}C NMR ($CDCl_3$) δ -14.34 14.43 14.76 31.42 36.45 60.15 65.02 76.69 77.00 77.32 94.97 105.73 109.04 118.95 143.34 144.13 147.63 162.50 162.58 164.63

2f: ^{1}H NMR (CDCl3, 300 MHz) δ 1.40 (d, *J*=1.5Hz, 6H, CH_3), 1.43 (t, *J*=1.8Hz, 3H, CH3), 2.71 (s, 3H, CH3), 4.38 (t, *j*=1.8Hz, 2H, OCH2), 4.58 (m, 1H, CH), 6.96 (s, 1H, Ar-H), 7.44 (s, 1H, Ar-H).

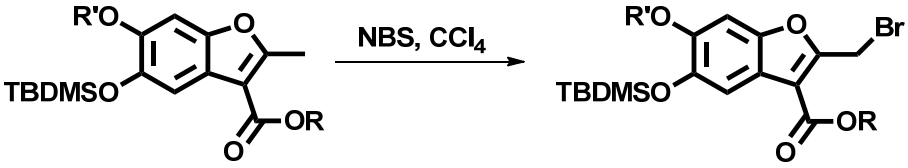
2g: ^{1}H NMR (CDCl3, 400 MHz) δ 1.45 (t, j=18 Hz, 3H), 2.71 (s, 3H), 3.76 (s, 3H), 4.36 (q, j= 18 Hz, 2H), 5.53 (s, 2H), 7.05 (s, 1H), 7.54 (s, 1H).

2h: ^{1}H NMR (CDCl3, 300 MHz) δ 1.40 (t, j=18Hz, 3H), 2.71 (s, 3H), 3.74 (m, 8H), 4.38 (q, J=18Hz, 2H), 6.95 (s, 1H), 7.58 (s, 1H).
2i: ^{1}H NMR (CDCl3, 300 MHz) δ 2.71 (s, 3H), 3.83 (s, 3H), 4.85 (d, 2H), 5.22 (d, 1H), 5.36 (d, 2H), 6.00 (m, 1H), 6.91 (s. 1H), 7.46 (s, 1H)
2j: ^{1}H NMR (CDCl3, 400 MHz) δ 1.38 (t, j= 18 Hz, 3H), 2.67 (s, 3H), 3.78 (s, 3H), 4.33 q, j= 18 Hz, 2H), 5.02 (s, 2H), 6.89 (d, j= 21 Hz, 2H), 6.98 (s, 1H), 7.32 (d, j= 21 Hz, 2H), 7.41 9s, 1H).

3. Synthesis of (3a-3f)

To a solution of **(2a-2f)** (3.63mmol) in DMF (30 ml) was added imidazole (18.15mmol) and TBDMSCl (21.83mmol) and the mixture was stirred. After 16 hours the reaction mixture was quenched with water and extracted with diethyl ether. The organic layer was dried over magnesium sulfate, concentrated down and purified by flash chromatography on silica gel (0-15% EtOAc in hexanes) to obtain product in 85-90 %.
3a: ^{1}HNMR (CDCl3, 300 MHz) δ 0.17 (s, 6H), 1.01 (s, 9H), 1.46 (t, *J*=6Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.39 (q, *J* =6 Hz,, 2H, CH_2), 7.05 (s, 1H, Ar-H) and 7.41 (s, 1H, Ar-H). ^{13}C NMR ($CDCl_3$) δ -4.5, 14.47, 18.73, 22.25, 25.96, 55.99, 61.00, 95.23, 111.31, 112.77, 118.07, 143.56, 149.97, 151.43, 157.60, 163.69.
3b: ^{1}H NMR (CDCl3, 300 MHz) δ 1.16 (s, 6H), 1.02 (s, 9H), 2.70 (s, 3H), 3.83 9s, 3H), 3.91 (s, 3H), 6.93 (s, 1H), 7.37 (s, 1H)
3c: ^{1}H NMR (CDCl3, 300 MHz) δ 0.16 (s, 6H), 1.03 (s, 9H), 1.62 (s, 9H), 2.69 (s, 3H), 3.83 (s, 3H), 6.92 (s, 1H), 7.36 (s, 1H)
3d: ^{1}H NMR (CDCl3, 300 MHz) 0.13 (s, 6H), 1.01 (s, 9H), 2.63 (s, 3H), 3.41 (s, 3H), 3.72 (t, j=12 Hz, 2H), 3.82 (s, 3H), 4.46 (t, j=12 Hz, 2H), 6.96 (s, 1H), 7.39 (s, 1H)
3e: ^{1}H NMR (CDCl3, 400 MHz) δ 0.11(s, 6H,), 1.04 (s, 9H,), 1.46 (s, 6H,), 2.71 (s, 3H,), 4.03(d, 2H,), 4.35(d, 2H), 6.93(s, 1H), 7.40(s, 1H).
3f: ^{1}H NMR (CDCl3, 400 MHz) δ 0.19 (s, 6H), 1.04 (s, 9H), 1.37 (d, 6H), 1.42 (t, 3H), 2.71 (s, 3H), 4.40 (d, 2H), 6.94 (s, 1H), 7.40 (s, 1H).

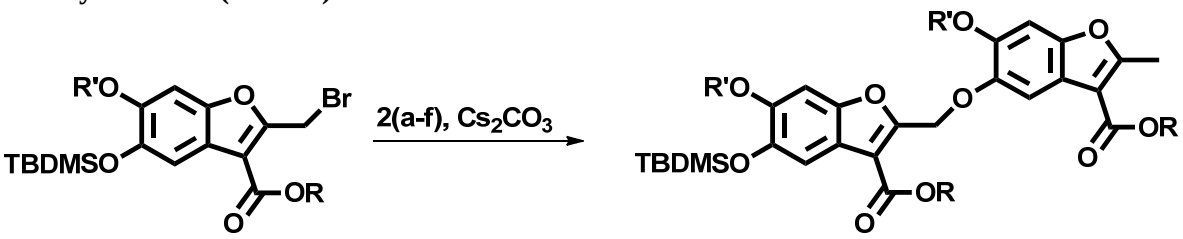
4. Synthesis of (4a-4f)



To the solution of **3a-3f** (1mM) in THF (20 ml) was added NBS (1mM) and refluxed at 65 ^{o}C under the halogen light for 1 hour. The reaction mixture was cooled and quenched with water and extracted with hexanes. The organic layer was concentrated and product was obtained in 90-95 % yield.
4a: ^{1}HNMR (CDCl3, 300 MHz) δ 0.17 (s, 6H), 1.01 (s, 9H), 1.46 (t, *J*=6Hz, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.39 (q, *J* =6 Hz,, 2H, CH_2), 4.93 (s, 2H, CH_2), 7.05 (s, 1H, Ar-H) and 7.41 (s, 1H, Ar-H).
4b: ^{1}H NMR (CDCl3, 300 MHz) δ 1.17 (s, 6H), 1.02 (s, 9H), 3.83 (s, 3H), 3.91 (s, 3H), 4.91 9s, 2H), 6.93 (s, 1H), 7.37 (s, 1H)
4c: ^{1}H NMR (CDCl3, 300 MHz) δ 0.16 (s, 6H), 1.01 (s, 9H), 1.65 (s, 9H), 3.85 (s, 3H), 4.93 (s, 2H), 6.96 (s, 1H), 7.40 (s, 1H)
4d: ^{1}H NMR (CDCl3, 300 MHz) 0.17 (s, 6H), 1.02 (s, 9H), 3.45 (s, 3H), 3.76 (t, j=12 Hz, 2H), 3.86 (s, 3H), 4.50 (t, j=12 Hz, 2H), 4.96 (s, 2H), 6.98 (s, 1H), 7.45 (s, 1H)

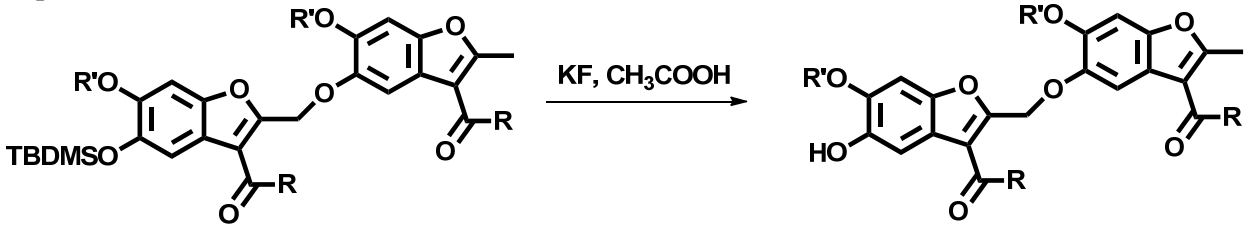
4e: ^{1}H NMR (CDCl3, 400 MHz) δ 0.11(s, 6H,), 1.04 (s, 9H,), 1.46 (s, 6H,), 4.03(d, 2H,), 4.35(d, 2H), 4.96 (s, 2H), 6.93(s, 1H), 7.40(s, 1H).
4f: ^{1}H NMR (CDCl3, 400 MHz) δ 0.17 (s, 6H,), 1.02 (s, 9H,), 1.38 (d, 6H,), 1.43 (t, 3H,), 4.48 (d, 2H,), 4.57 (s, 2H), 6.97 (s, 1H), 7.41 (s, 1H).

5. Synthesis of (11a-11f)



To the solution of **(2a-2f)** (0.3mM) and **(4a-4f)** (0.4mM) in ethyl acetate (4 ml) were added cesium carbonate (0.3mM) and anhydrous DMF (1 ml). The reaction mixture was stirred under nitrogen for 15 hours at room temperature. The reaction was quenched with methylene chloride and extracted with brine. The organic layer was dried over magnesium sulfate and concentrated down. Purification was done by using flash chromatography on silica gel using (0-20) % ethyl acetate in hexanes. The product was obtained in 60-65 % yield.
11a: ^{1}HNMR (CDCl3, 300 MHz) δ 0.17 (s, 6H), 1.01 (s, 9H), 1.46 (m, 6H), 2.71 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H)), 4.39 (m, 4H), 5.60 (s, 2H), 6.95 (s, 1H, Ar-H), 6.99 (s, 1H,), 7.42 (s, 1H), 7.55 (s, 1H). ^{13}C NMR ($CDCl_3$) δ - -4.55, 14.41, 14.73, 14.68, 18.92, 25.57, 55.77, 56.62, 60.62, 61.93, 64.47, 95.27, 98.31, 103.47, 109.31, 112.55, 112.73, 117.90, 119.98, 143.29, 146.34, 147.95, 148.08, 151.20, 150.69, 157.66, 162.67, 164.17, 164.83.
11b: ^{1}H NMR (CDCl3, 300 MHz) δ 1.16 (s, 6H), 1.02 (s, 9H), 2.71 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 3.92 9s, 3H), 5.60 (s, 2H), 6.98 (s, 1H), 7.01 (s, 1H), 7.44 9s, 1H), 7.59 (s, 1H)
11c: ^{1}H NMR (CDCl3, 300 MHz) δ 0.16 (s, 6H), 1.01 (s, 9H), 1.59 (s, 9H), 1.60 (s, 9H), 2.68 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 5.57 (s, 2H), 6.92 (s, 1H), 6.98 (s, 1H), 7.41 (s, 1H), 7.54 (s, 1H).
11d: ^{1}H NMR (CDCl3, 300 MHz) 0.17 (s, 6H), 1.02 (s, 9H), 2.71 (s, 3H), 3.43 (s, 3H), 3.71 (m, 4H), 3.83 (s, 3H), 3.86 (s, 3H), 4.45 (m, 2H), 5.59 (s, 2H), 6.97 (s, 1H), 7.00 (s, 1H), 7.47 (s, 1H), 7.64 (s, 1H).
11e: ^{1}H NMR (CDCl3, 400 MHz) δ 0.17 (s, 6H,), 1.03 (s, 9H,), 1.37 (s, 12H,), 2.70 (s, 3H,), 4.08 (d, 4H,), 4.33 (d, 4H,), 5.57 (s, 2H), 6.98 (d, 2H), 7.44 (s, 1H), 7.58 (s, 1H).
^{13}C NMR ($CDCl_3$) δ - -4.71 14.19 14.36 14.38 14.68 14.74 18.46 25.75 60.10 60.16 60.46 64.31 64.62 65.01 76.68 77.00 77.20 77.32 94.96 96.01 96.82 109.13 109.26 111.63 112.57 117.85 118.55 143.03 146.17 148.42 149.33 149.90 149.98 158.17 162.49 163.71 164.46
11f: ^{1}H NMR (CDCl3, 400 MHz) δ 0.17 (s, 6H,), 1.02 (s, 9H,), 1.34 (d, 12H,), 1.43 (m, 6H), 2.70 (s, 3H,), 4.35 (t, 4H,), 4.48 (m, 2H,), 5.54 (s, 2H), 6.98 (d, 2H), 7.44 (s, 1H), 7.58 (s, 1H).^{13}C NMR ($CDCl_3$) δ - -4.59 14.19 14.38 18.43 21.01 21.92 21.98 22.05 25.78 60.09 60.36 60.43 64.75 70.94 72.65 76.68 77.00 77.32 98.11 100.29 109.13 109.78 111.54 112.74 118.05 119.37 143.96 147.23 147.51 148.54 149.29 149.82 158.39 162.78 163.69 164.43

Deprotected form of 11a-11f



To the solution of **(11a-11f)** (0.3mM) in DMF (3 ml) were added KF (4mM) and acetic acid (10 μL). The reaction mixture was stirred for 5 hours. The reaction was quenched by methylene chloride and

extracted with brine solution. The aqueous layer was again extracted with fresh batch of methylene chloride. The organic layer was combined and dried over magnesium sulfate and concentrated in vacuum. The solid was precipitated using methanol to obtain product in 90% yield.

11a deprotected form: ^{1}HNMR (CDCl3, 300 MHz) δ 1.46 (m, 6H, CH_3), 2.71 (s, 3H), 3.80 (s, 3H), 3.85 (s, 3H)), 4.39 (m 4H, CH_2), 5.35 9S, 2H), 6.95 (s, 1H, Ar-H), 6.99 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H).

11b deprotected form: ^{1}HNMR (CDCl3, 300 MHz) δ 2.71 (s, 3H), 3.80 (s, 3H, CH_3), 3.83 (s, 3H), 3.85 (s, 3H)), 3.87 (s, 3H), 5.35 (S, 2H) 6.95 (s, 1H, Ar-H), 6.99 (s, 1H, Ar-H), 7.42 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H).

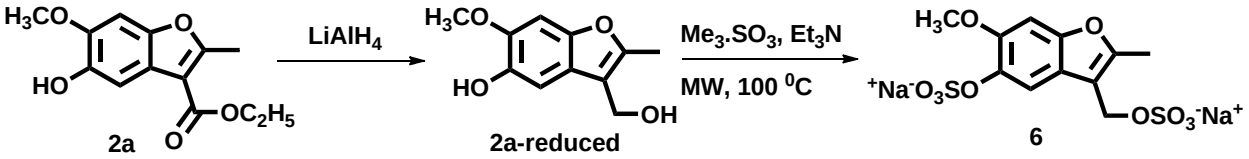
11c deprotected form: ^{1}H NMR (CDCl3, 300 MHz) δ 1.57 (s, 9H), 1.59 (s, 9H), 2.68 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 5.57 (s, 2H), 6.95 (s, 1H), 7.05 (s, 1H), 7.46 (s, 1H), 7.58 (s, 1H).

11d deprotected form: ^{1}H NMR (CDCl3, 300 MHz) 2.71 (s, 3H), 3.43 (s, 3H), 3.71 (m, 4H), 3.83 (s, 3H), 3.86 (s, 3H), 4.45 (m, 2H), 5.59 (s, 2H), 6.97 (s, 1H), 7.01 (s, 1H), 7.50 (s, 1H), 7.63 (s, 1H).

11e deprotected form: ^{1}H NMR (CDCl3, 400 MHz) δ 1.45 (m, 12H), 2.69 (s, 3H), 4.10 (m, 4H), 4.35 (m, 4H), 5.58 (s, 2H), 6.97 (s, 1H), 6.99 (s, 1H), 7.49 9s, 1H), 7.56 (s, 1H).

11f deprotected form: ^{1}H NMR (CDCl3, 400 MHz) δ 1.38 (d, 12H,), 1.47 (m, 6H), 2.70 (s, 3H,), 4.37 (t, 4H,), 4.39 (t, 4H,), 5.57 (s, 2H,), 7.02 (d, 2H), 7.50 (s, 1H), 7.57 (s, 1H).^{13}C NMR ($CDCl_3$) δ – 14.31 14.37 14.38 21.99 22.05 60.11 60.53 64.64 72.40 72.71 76.69 77.01 77.21 77.32 96.70 100.36 106.03 109.12 109.60 111.67 118.50119.39 143.83 144.45 147.15 147.46 148.66 149.25 158.69 162.79 163.67 164.43

6. Synthesis of 6 from 2a



To the solution of **2a** (0.5mM) in toluene was added lithium aluminum hydride (2.5mM) and stirred for 4 hours at RT. The reaction was quenched by adding water. The reaction mixture was extracted with ethyl ether twice. The organic layer was concentrated under vacuum and purified by flash chromatography using ethyl acetate in hexanes (0-40%). The reduced form of **2a** is sulfated by method described previously in this paper.

2a-reduced : ^{1}H NMR (CDCl3, 300 MHz) δ 2.75 (s, 3H), 3.96 (s, 3H), 5.58 (s, 2H), 6.98 (s, 1H), 7.36 (s, 1H).

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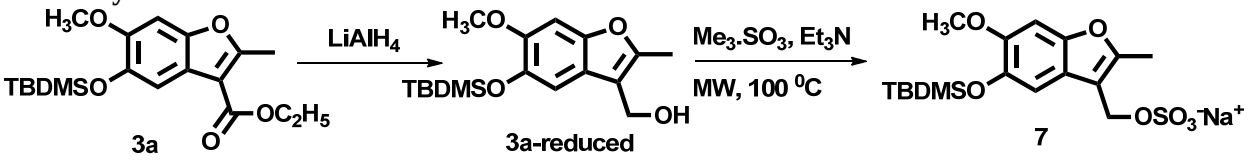
7. Synthesis of 7 from 3a:

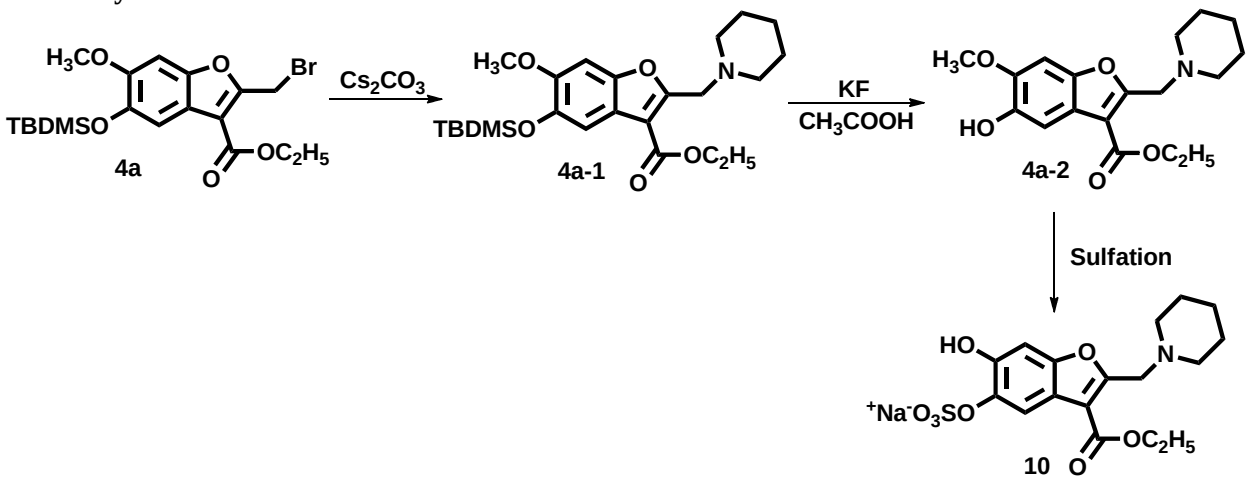


To the solution of **3a** (0.5 mM) in toluene was added lithium aluminum hydride (4 mM) and stirred for 4 hours at RT. The reaction was quenched by adding water. The reaction mixture was extracted with ethyl ether twice. The organic layer was concentrated under vacuum and purified by flash chromatography using ethyl acetate in hexanes (0-40%). The reduced form of **3a** is sulfated by method described previously in this paper.

3a-reduced: ^{1}H NMR (CDCl3, 300 MHz) δ 0.44 (s, 6H), 1.02 (s, 9H), 2.75 (s, 3H), 3.96 (s, 3H), 5.58 (s, 2H), 6.98 (s, 1H), 7.36 (s, 1H).^{13}C NMR (CDCl3) δ - -4.48, 12.29, 18.70, 26.02, 55.88, 56.04, 95.47, 109.94, 114.31, 120.84, 142.03, 149.32, 149.40, 151.81.

7: Provided in main article.

8. Synthesis of 10 from 4a



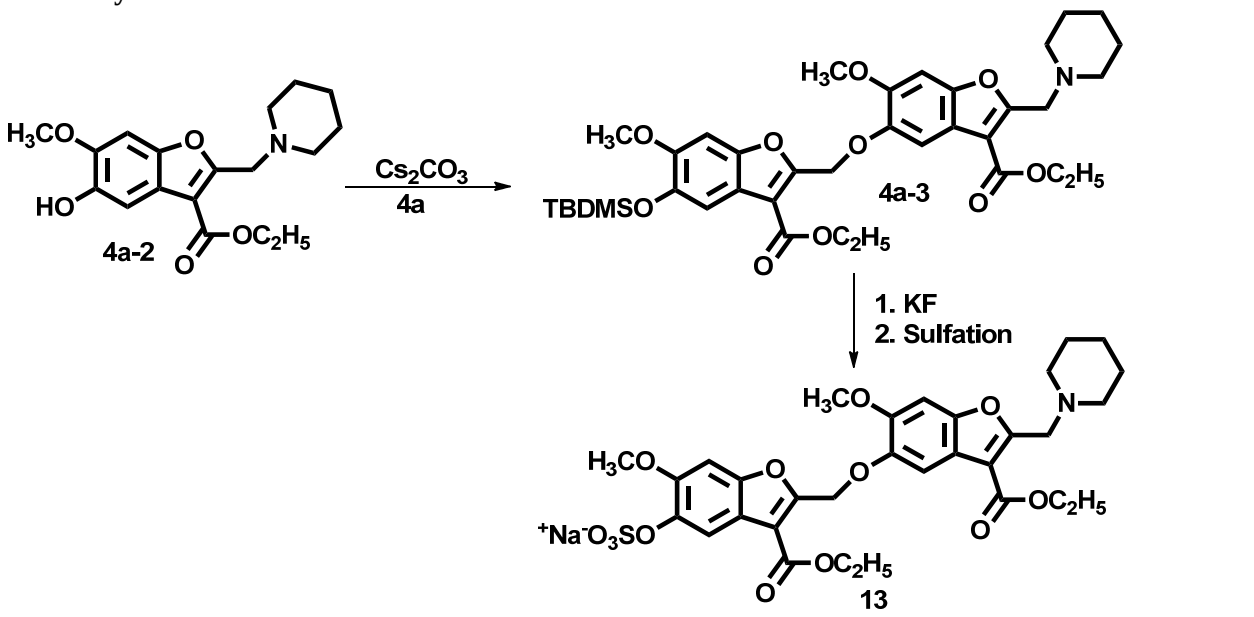
To the solution of **4a** (0.3mM) in DMF was added Morpholine (0.4 mM) and cesium carbonate (0.4 mM) and stirred for 8 hrs at RT. The reaction was quenched by adding methylene chloride and extracted with brine. The organic layer was concentrated down and purified by flash chromatography using ethyl acetate in hexanes (0-40%). To the solution of intermediate **4a-1** (0.3 mM) in DMF (3 ml) were added KF (4 mM) and acetic acid (10 µL). The reaction mixture was stirred for 5 hours. The reaction was quenched by methylene chloride and extracted with brine solution. The organic layer was combined and dried over magnesium sulfate and concentrated down. The solid was precipitated using methanol to obtain intermediate **4a-2** in 90% yield. Compound 10 was obtained by sulfation reaction previously described.

4a-1: ^{1}H NMR (CDCl3, 400 MHz) δ 1.44 (t, j=18Hz, 4H,), 2.63 (s, 4H,), 3.74 (s, 4H,), 4.11 (s, 2H,), 4.39 (q, j=18Hz, 3H,), 7.02 (s, 1H,), 7.48 (s, 1H).

4a-2: ^{1}H NMR (CDCl3, 400 MHz) δ 1.45 (t, j=18 Hz, 3H,), 2.67 (m, 4H,), 3.76 (m, 4H,), 3.94 (s, 3H,), 4.15 (s, 2H,), 4.40 (q, j=18Hz, 3H,), 7.03 (s, 1H), 7.48 (s, 1H).

10: Provided in paper

9. Synthesis of 13 from 4a



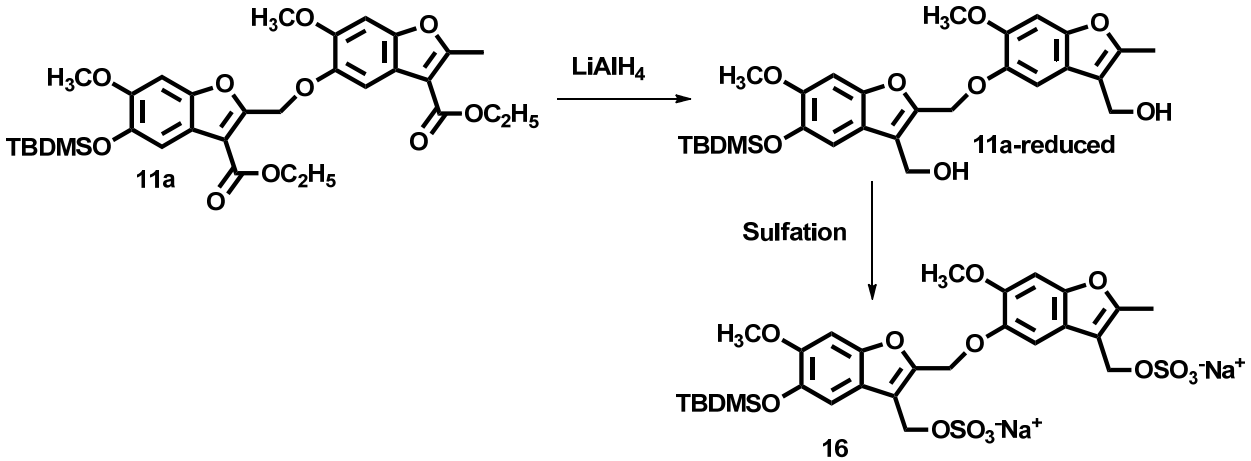
To the solution of **4a-2** (0.3 mM) and **4a** (0.4 mM) in ethyl acetate (4 ml) were added cesium carbonate (0.3 mM) and anhydrous DMF (1 ml). The reaction mixture was stirred under nitrogen for 15 hours at room temperature. The reaction was quenched with methylene chloride and extracted with brine. The organic layer was dried over magnesium sulphate and concentrated down. Purification was done by using flash chromatography on silica gel using (0-70) % ethyl acetate in hexanes. The product **4a-3** was obtained in 60% yield. The deprotection step followed by sulfation (performed as explained previously) yielded the product **13.**

4a-3: ^{1}H NMR (CDCl3, 400 MHz) δ 0.17 (s, 6H,), 1.03 (s, 9H,), 1.39 (m, 6H,), 2.62 (m, 4H,), 3.65 (m, 4H,), 3.73 (s, 3H,), 3.82 (s, 3H), 4.36 (m, 6H), 5.61 (s, 2H), 7.00 (s, 1H), 7.06 (s, 1H), 7.45 (s, 1H), 7.62 (s, 1H).

4a-3 (deprotected form): ^{1}H NMR (CDCl3, 400 MHz) δ 1.38 (m, 6H,), 2.60 (m, 3H,), 3.71 (m, 4H,), 3.91 (s, 3H,), 3.93 (s, 3H), 4.37 (m, 6H,), 5.62 (s, 2H,), 7.02 (s, 1H), 7.05 (s, 1H), 7.49 (s, 1H), 7.59 (s, 1H).

13: Provided in paper.

10. Synthesis of 16 from 11a

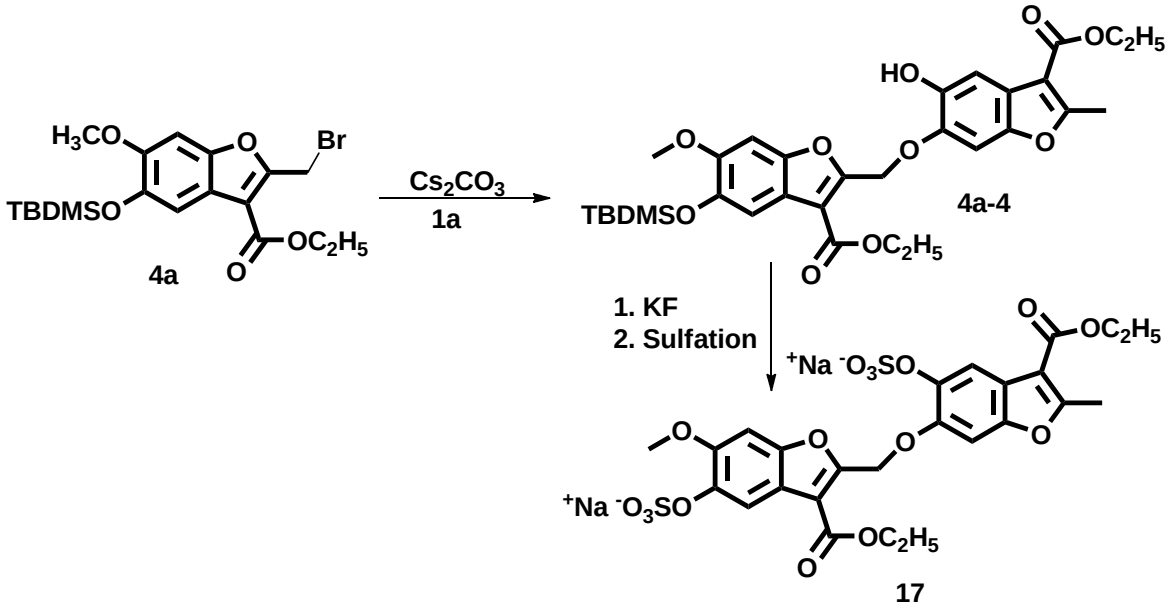


To the solution of 11a (200 mg, 0.32 mMol) in 10 ml of dry THF was added LiAlH4 (65 mg, 1.6 mMol) and stirred for 6 hours under nitrogen. After completion, reaction was quenched by adding 30 ml of water and extracted with 100 ml of ethyl ether twice. Organic layer is concentrated down and purified using flash chromatography using ethyl acetate in hexanes (0-50%). The reduced form of 11a is sulfated using the general sulfation procedure explained previously.

11a-reduced: ^{1}HNMR (CDCl3, 300 MHz) δ 0.17 (s, 6H), 1.01 (s, 9H), 2.71 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H)), 5.51 (2, 2H), 5.55 (s, 2H), 5.60 (s, 2H), 6.95 (s, 1H, Ar-H), 6.99 (s, 1H,), 7.42 (s, 1H), 7.55 (s, 1H).

16: Provided in main article.

11. Synthesis of 17 from 4a and 1a



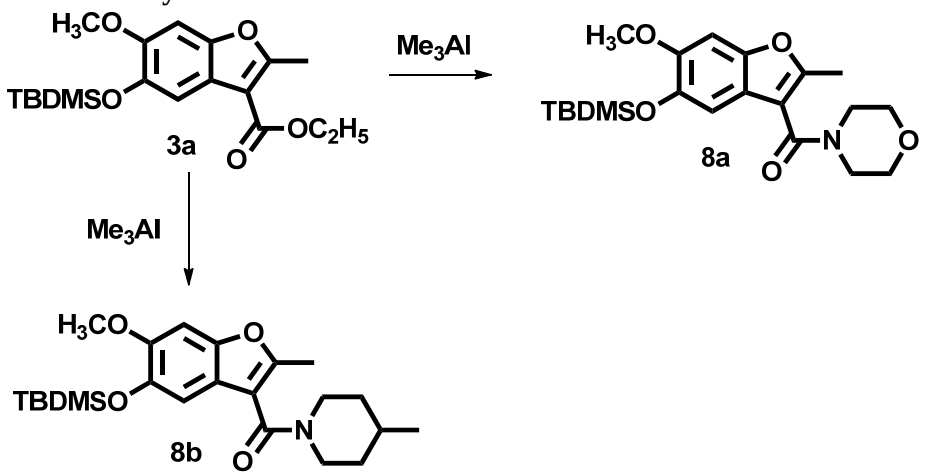
To the solution of **1a** (0.3 mM) and **4a** (0.4 mM) in ethyl acetate (4 ml) were added cesium carbonate (0.3 mM) and anhydrous DMF (1 ml). The reaction mixture was stirred under nitrogen for 15 hours at room temperature. The reaction was quenched with methylene chloride and extracted with brine. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Purification was done by using flash chromatography on silica gel using (0-70) % ethyl acetate in hexanes. The product **4a-4** was obtained in 60% yield. The deprotection step followed by sulfation step (performed as explained previously) yielded the product **17.**

4a-4: ^{1}H NMR (CDCl3, 400 MHz) δ .03 (s, 6H), 0.04 (s, 6H), 0.96 (s, 9H), 0.97 (s, 9H), 1.36 (m, 6H), 2.72 (s, 3H), 3.81 (s, 3H), 4.15 (m, 4H), 5.34 (s, 2H), 6.78 (s, 1H), 6.80 (s, 1H), 7.22 (s, 1H), 7.37 (s, 1H).

Deprotected 4a-4: ^{1}H NMR (CDCl3, 400 MHz) δ 1.36 (m, 6H), 2.70 (s, 3H), 3.86 (s, 3H), 4.35 (m, 4H), 5.54 (s, 2H), 6.98 (s, 1H), 7.00 (s, 1H), 7.42 (s, 1H), 7.57 (s, 1H).

17: Provided in main article.

12. Synthesis of 8a & 8b from 3a



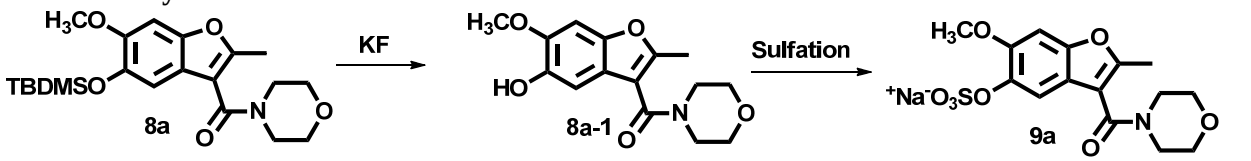
To the solution of trimethyl aluminum (1.5mM) in THF was added Morpholine or 4-methyl Piperidine (1.5mM). The solution was stirred for 1 hour at RT. The solution of **3a** (1mM) in THF was added to drop wise to above solution over the time of 30 mins. The reaction mixture was stirred at 70 ^{o}C

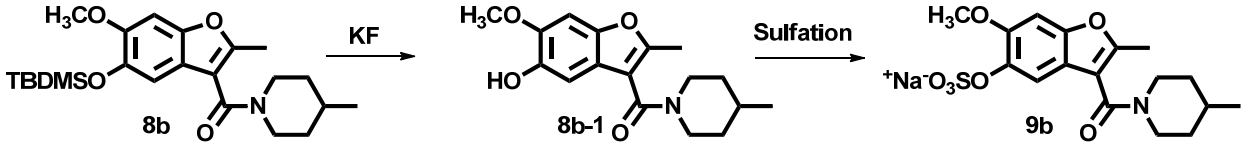
for 24 hours. The reaction was quenched by adding ethyl acetate and extracted with brine. The organic layer is concentrated down and purified by flash chromatography using ethyl acetate and hexanes (0-70 %).

8a: ^{1}H NMR (CDCl3, 400 MHz) δ 0.13 (s, 6H,), 1.00 (s, 9H,), 2.48 (s, 3H,), 3.64 (m, 8H,), 3.78 (s, 3H,), 6.84 (s.1H,), 6.93 (s, 1H).

8b: ^{1}H NMR (CDCl3, 400 MHz) δ 0.11 (s, 6H), 0.97 (d, j= 18 Hz, 3H), 0.98 (s, 9H), 1.65 (m, 4H), 2.44 (s, 3H), 2.88 (m, 2H), 2.98 (m, 2H), 3.80 (s, 3H), 6.86 (s, 1H), 6.93 (s, 1H).

13. Synthesis of 9a and 9b





The deprotection step followed by sulfation step (performed as explained previously) yielded the product **9a** and **9b**.

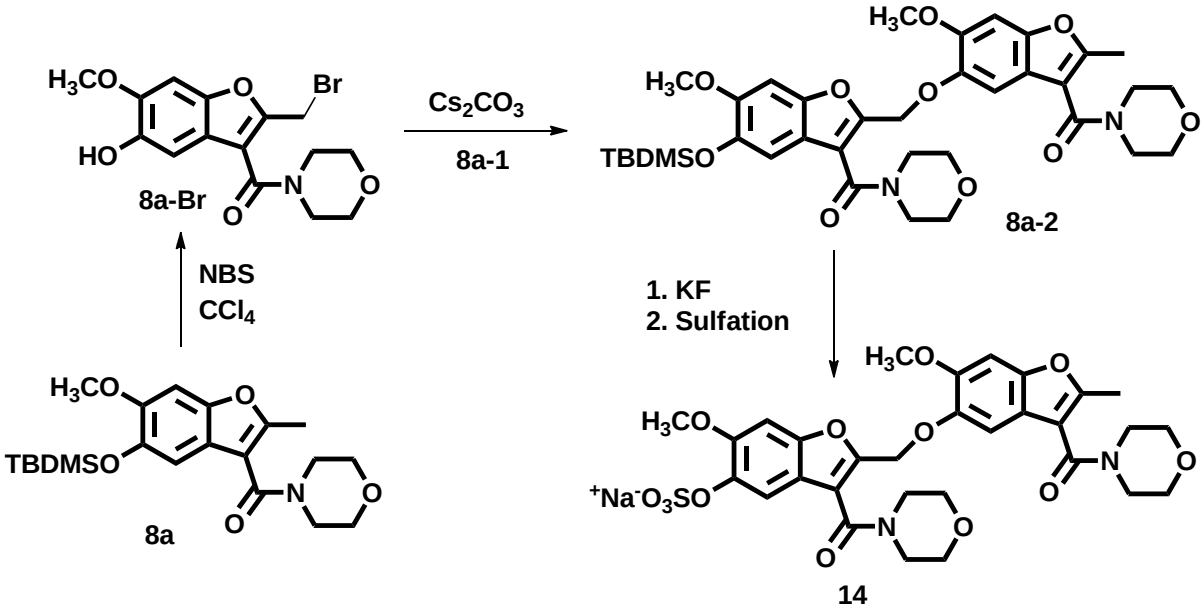
8a-1: ^{1}H NMR (CDCl3, 400 MHz) δ 2.48 (s, 3H,), 3.69 (m, 8H,), 3.91 (s, 3H,), 6.91 (s, 1H,), 6.94 (s, 1H,).

8b-1: ^{1}H NMR (CDCl3, 400 MHz) δ 0.97 (d, j= 18 Hz, 3H), 1.67 (m, 4H), 2.46 (s, 3H), 2.88 (m, 2H), 2.98 (m, 2H), 3.80 (s, 3H), 6.86 (s, 1H), 6.93 (s, 1H).

9a: Provided in main article.

9b: Provided in main article.

14. Synthesis of 14 from 8a



To the solution of **8a** (1 mM) in THF (20 ml) was added NBS (1 mM) and the mixture was refluxed at 65 ^{o}C under the halogen light for 1 hour. The reaction mixture was cooled and extracted using hexanes and water. The organic layer was concentrated and product **8a-Br** was obtained in 90% yield. To the solution of **8a-1** (0.3 mM) and **8a-Br** (0.4 mM) in ethyl acetate (4 ml) were added cesium carbonate (0.3 mM) and anhydrous DMF (1 ml). The reaction mixture was stirred under nitrogen for 15 hours at room temperature. The reaction was quenched with methylene chloride and extracted with brine. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Purification was done by using flash chromatography on silica gel using (0-70) % ethyl acetate in hexanes. The product **4a-4** was obtained in 60% yield. The deprotection step followed by sulfation step (performed as explained previously) yielded the product **14.**

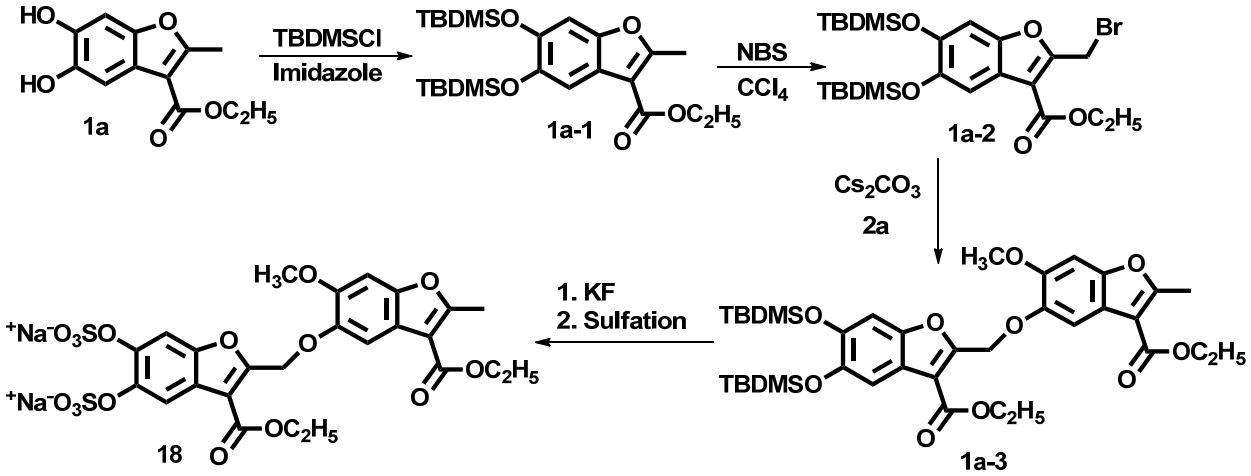
8a-br: ^{1}H NMR (CDCl3, 400 MHz) δ 0.14 (s, 6H), 1.01 (s, 9H), 3.72 (m, 8H), 3.85 (s, 3H), 4.69 (s.2H), 6.85 (s, 1H), 6.99 (s, 1H).

8a-2: ^{1}H NMR (CDCl3, 400 MHz) δ 0.14 (s, 6H), 1.01 (s, 9H), 2.49 (s, 3H,), 3.74 (m, 16H), 3.85 (s, 3H,), 3.87 (s, 3H), 5.24 (s, 2H,), 6.90 (s, 1H,), 7.00 (s, 1H), 7.02 (s.1H,), 7.11 (s, 1H).

8a-2 (deprotected form): ^{1}H NMR (CDCl3, 400 MHz) δ 2.48 (s, 3H,), 3.74 (m, 16H), 3.87 (s, 3H,), 3.96 (s, 3H), 5.25 (s, 2H,), 6.99 (s, 1H,), 7.04 (s, 1H), 7.09 (s.1H,), 7.12 (s, 1H).

14: Provided in main article.

15. Synthesis of 18 from 1a



The protection of free phenolic groups of **1a** with TBDMSCl (as per procedure for synthesis of **3a-3f)** followed by introduction of bromo group (as per procedure for synthesis of **4a-4f**) lead to synthesis of intermediate **1a-2.** Coupling intermediate **1a-2** with **2a** using the procedure described above (synthesis of **5a-5f**) lead to formation of intermediate **1a-3.** The deprotection step followed by sulfation step (performed as explained previously) yielded the product **18.**

1a-1: ^{1}H NMR (CDCl3, 400 MHz) δ 0.12 (s, 12H,), 1.05 (s, 18H,), 1.37 (t, j= 18 Hz, 3H), 2.71 (s, 3H,), 4.40 (q, j= 18 Hz, 2H), 6.95 (s, 1H), 7.30 (s, 1H).

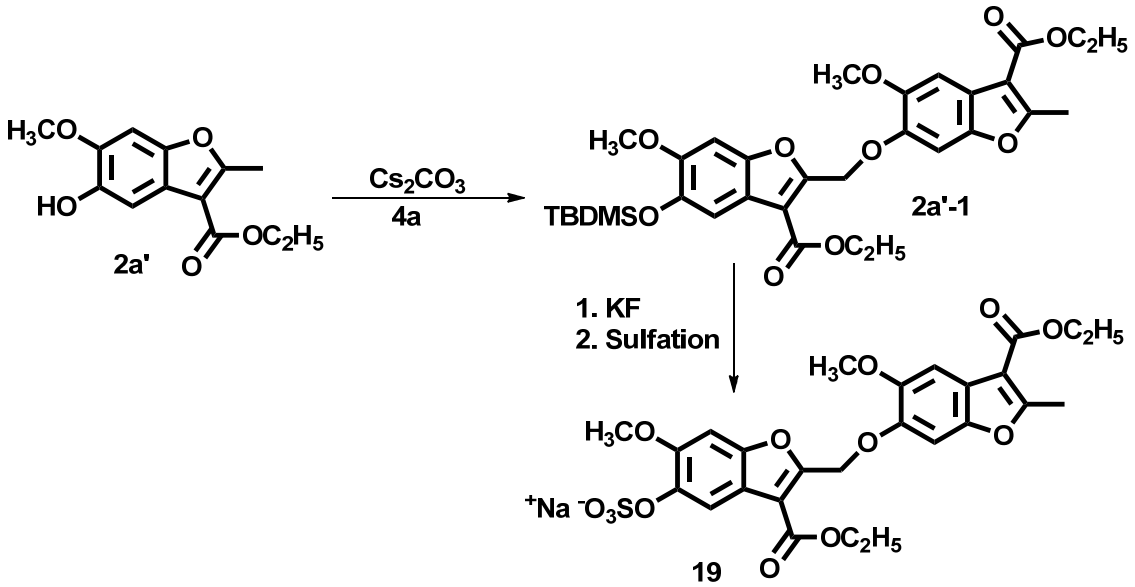
1a-2: ^{1}H NMR (CDCl3, 400 MHz) δ 0.10 (s, 12H), 1.05 (s, 18H), 1.34 (t, j= 18 Hz, 3H), 4.21 (q, j= 18 Hz, 2H), 6.99 (s, 1H), 7.23 (s, 1H).

1a-3: ^{1}H NMR (CDCl3, 400 MHz) δ .04 (s, 6H), 0.09 (s, 6H),1.01 (s, 9H), 1.05 (s, 9H), 1.43 (m, 6H), 2.62 (s, 3H), 3.81 (s, 3H), 4.15 (m, 4H), 5.34 (s, 2H), 6.88 (s, 1H), 6.96 (s, 1H), 7.22 (s, 1H), 7.37 (s, 1H).

1a-3 (deprotected form): ^{1}H NMR (CDCl3, 400 MHz) δ 1.35 (m, 6H), 2.71 (s, 3H), 3.84 (s, 3H), 4.37 (m, 4H), 5.52 (s, 2H), 6.98 (s, 1H), 7.12 (s, 1H), 7.35 (s, 1H), 7.47 (s, 1H).

18: Provided in main article.

16. Synthesis of 19



To the solution of **2a'** (0.3 mM) and **4a** (0.4 mM) in ethyl acetate (4 ml) were added cesium carbonate (0.3 mM) and anhydrous DMF (1 ml). The reaction mixture was stirred under nitrogen for 15 hours at room temperature. The reaction was quenched with methylene chloride and extracted with brine. The organic layer was dried over magnesium sulphate and concentrated in vacuo. Purification was done by using flash chromatography on silica gel using (0-70) % ethyl acetate in hexanes. The product **2a'-1** was obtained in 60% yield. The deprotection step followed by sulfation step (performed as explained previously) yielded the product **19. (Note: 2a'** is obtained as side product in synthesis of **2a** from **1a).**
2a': ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (t, *J*=6Hz, 3H), 2.75 (s, 3H), 3.94 (s, 3H), 4.40 (q, *J* =6 Hz, 2H, CH_2), 7.03 (s, 1H), 7.43 (s, 1H).
2a'-1: ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.16 (s, 6H), 1.01 (s, 9H), 1.41 (m, 6H), 2.70 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H)), 4.39 (m, 4H), 5.60 (s, 2H), 6.99 (s, 1H), 7.21 (s, 1H), 7.43 (s, 1H), 7.44 (s, 1H).^{13}C NMR ($CDCl_3$) δ - -4.50, 14.46, 14.63, 14.78, 18.72, 25.97, 55.97, 56.62, 60.42, 60.93, 63.47, 95.47, 98.39, 103.77, 109.21, 112.25, 112.73, 117.90, 119.98, 143.29, 146.34, 147.95, 148.08, 150.20, 150.99, 157.66, 162.77, 164.07, 164.79.
2a'-1 (deprotected form): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (t, j=6 Hz, 6H), 2.72 (s, 3H), 3.92 (s, 6H), 4.39 (m, 4H), 5.60 (s, 2H), 7.00 (s, 1H), 7.19 (s, 1H), 7.41 (s, 1H), 7.44 (s, 1H).^{13}C NMR ($CDCl_3$) δ – 14.57, 14.63, 14.77, 56.52, 56.65, 60.42, 61.01, 63.57, 94.71, 98.55, 103.83, 106.24, 109.21, 112.35, 118.39, 120.08, 143.81, 146.34, 147.95, 148.12, 149.07, 157.99, 162.82, 164.06, 164.80.
19: Provided in main article.

17. Determination of Purity by HPLC

HPLC analysis was carried out on a Jasco chromatography system using Varian's dynamax microsorb C4 column of size 250×10 mm. The mobile phase consisted of acetonitrile – water mixture run at a constant flow rate of 3 mL/min. Absorbance of the analyte was recorded by Jasco MD-2010 plus UV-VIS detector at 300 nm. The mobile phase gradient was 5% acetonitrile in water for the first 5 min increasing to 50% in the next 10 min, then further

increase to 100% acetonitrile in the next 5 min, which was maintained for the next 10 min, followed by re-equilibration.

Purity of Sulfated benzofurans analyzed by gradient RP-HPLC

Sulfated Benzofuran	Retention time (mins)	% purity
5a	16.21	98.12
5b	15.38	98.09
5c	16.64	98.56
5d	14.69	96.56
5e	15.85	98.34
5f	16.32	97.87
5g	12.23	78.11
5h	11.60	76.85
5i	16.31	95.15
5j	16.04	98.08
9a	11.22	98.27
9b	11.72	97.59
10	13.34	98.52
12a	12.72	99.01
12b	12.01	96.64
12c	13.37	96.22
12d	11.20	95.37
12e	12.97	99.05
12f	13.50	97.52
13	10.34	98.43
14	11.1	98.15
15	8.01	99.13
17	8.34	97.59
18	8.61	98.36
19	12.65	98.27