Supporting Information

Mycophenolic anilides as broad specificity inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors

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General Experimental Conditions

All reactions involving air-sensitive reagents were carried out in oven-dried glassware equipped with a magnetic stir bar and fitted with rubber septa under argon unless otherwise stated. All commercially available chemicals and reagent grade solvents were used directly without further purification unless otherwise specified. All reactions were monitored by thin-layer chromatography (TLC) on Baker-flex® silica gel plates (IB2-F) using UV-light (254 and 365 nm) detection or visualizing agents (ninhydrin or phosphomolybdic acid stain). Flash column chromatography was conducted on silica gel (230−400 mesh) using Teledyne Isco CombiFlash® Rf. NMR spectra were recorded at room temperature using a JEOL ECX-400P (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz), JEOL ECA-500 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or JEOL ECZ-600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 150 MHz) with tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) with reference to solvent signals [^{1}H-NMR: $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), DMSO-d_6 (2.50 ppm); ^{13}C-NMR: $CDCl_3$ (77.0 ppm), CD_3OD (49.15 ppm), DMSO-d_6 (39.51 ppm)]. Signal patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are given in Hz. All test compounds reported had a purity ≥95% as determined by high-performance liquid chromatography (HPLC) analyses using a Waters 1525 instrument equipped with a quaternary pump and a Proteo-C12 column (250 mm × 1 mm, 4 μm). UV absorption was monitored at λ = 220 nm. HPLC gradient went from 5% to 90% CH_3CN in H_2O (both solvents contain 0.1% trifluoroacetic acid) with a total run time of 30 min and a flow rate of 0.5 mL/min. Enantiomeric excesses were determined by chiral HPLC analysis on Chiralpak ID with UV-vis detector at 254 nm in comparison with the authentic racemates.

Method A. Waters 1525 instrument equipped with a quaternary pump and a Proteo-C12 column

(250 mm × 1 mm, 4 μm). UV absorption was monitored at λ = 220 nm. HPLC gradient went from 5% to 90% CH_3CN in H_2O (both solvents contain 0.1% trifluoroacetic acid) with a total run time of 30 min and a flow rate of 0.5 mL/min. Enantiomeric excesses were determined by chiral HPLC analysis on Chiralpak ID with UV-vis detector at 254 nm in comparison with the authentic racemates.

Method B. Waters 1525 instrument equipped with Waters 2489 UV/Visible detector. Kinetex 5u C18 100A column (250 × 4.6 mm) used for analytical and Kinetex 5u C18 100A, AXIA (250 × 21.2 mm) used for preparative purification. HPLC gradient went from 2% to 98% CH_3CN in H_2O (both solvents contain 0.1% trifluoroacetic acid) with a total run time of 30 min and a flow rate of 1 mL/min for analytical analysis and 10 mL/min for preparative purification.

Docking Protocol

Docking modeling of MPA hybrids were performed using standard protocol of AutoDock Tools-1.5.6 (http://autodock.scripps.edu), which is computed with MGLTools-1.5.4 (http://mgltools.scripps.edu). MPA hybrid ligands were created through ChemDrawBio and subjected to energy minimization using MM2 force field. The receptors of *Cp*IMPDH and hamster IMPDH were extracted from co-crystal structures of both isozymes (*Cp*IMPDH PDB: 3KHJ and hamster IMPDH PDB: 1JR1) using BIOVIA Discovery Studio Visualizer 2016 software (http:// www.3dsbiovia.com). The protocol of running Autodock Tools was used and grid boxes for docking simulation were selected based on each isozyme co-crystal structures. The docking results were analyzed using PyMoL visualization software (http:// pymol.org).

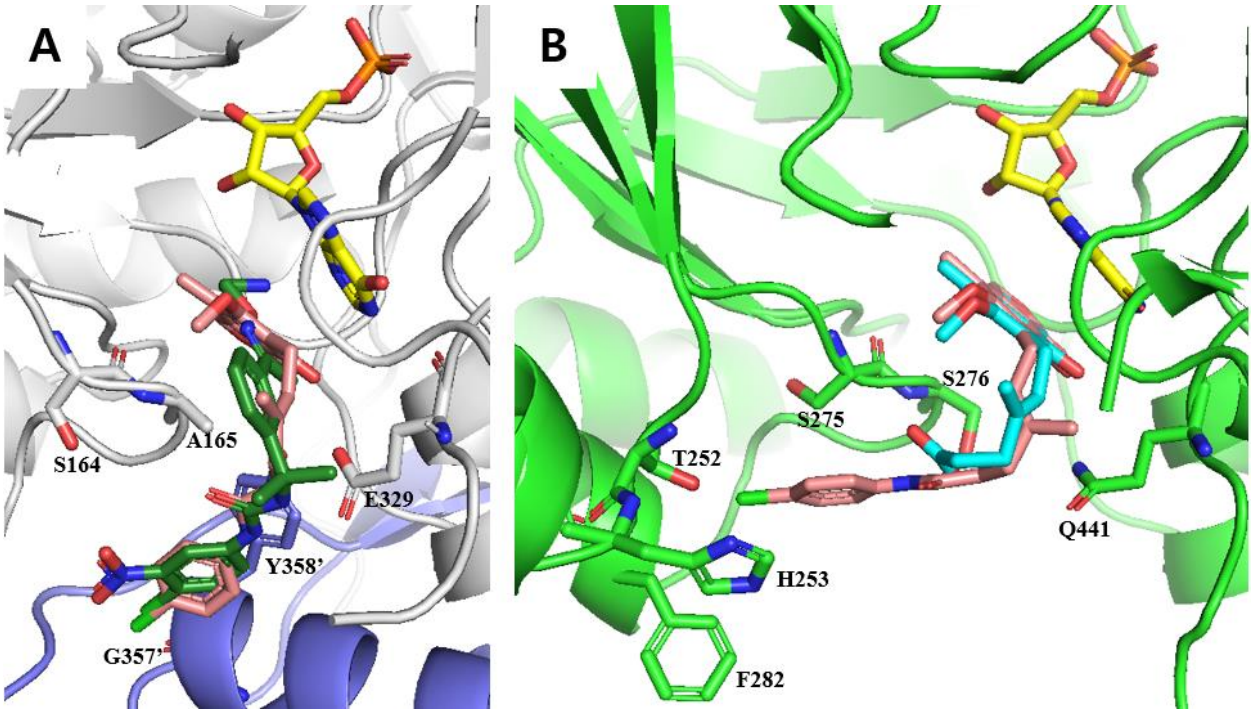
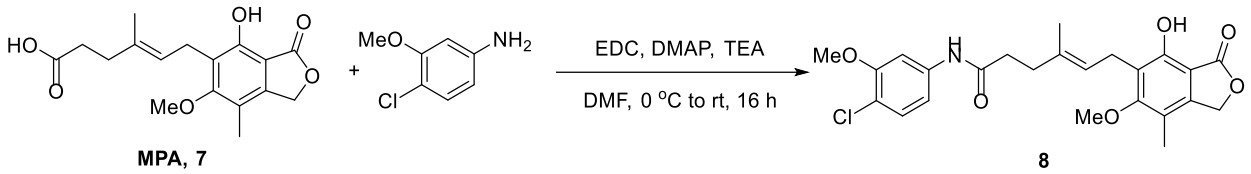


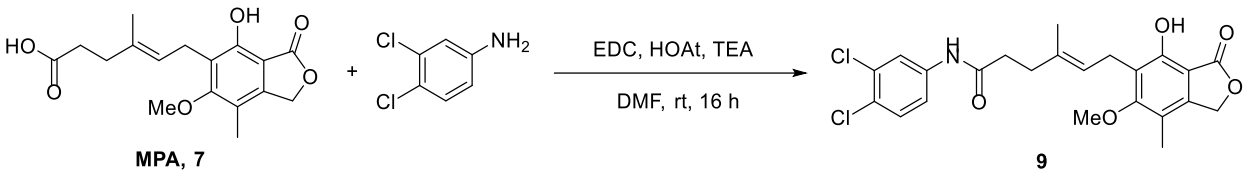
Figure S1. (**A**) Overlay of co-crystal structure of *Cp*IMPDH inhibitor **5** (dark green, PDB: 4RVB) and docked model of **12** (pink) with *Cp*IMPDH (gray, PDB: 3KHJ) and IMP (yellow). Adjacent monomer protein is shown as purple and residue numbers are differentiate by prime (’). (**B**) Overlay of co-crystal structure of hamster IMPDH in complex with IMP (yellow) and MPA (cyan, PDB: 1JR1) and docked model of **12** (pink) in hamster IMPDH.

Synthetic Procedures



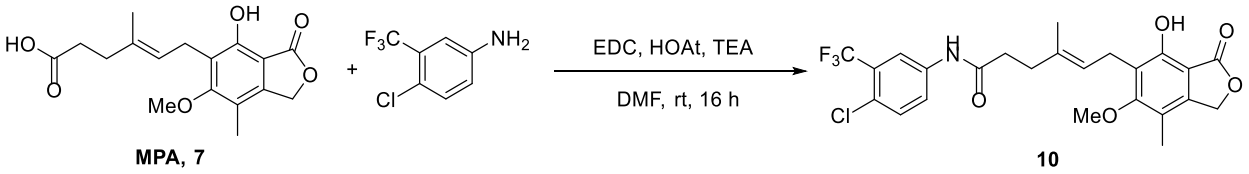
(*E*)-*N*-(4-Chloro-3-methoxyphenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (8)

To a solution of mycophenolic acid (MPA, **7**) (160.2 mg, 0.5 mmol) in anhydrous DMF (3 mL) was added EDC•HCl (143.8 mg, 0.75 mmol), DMAP (91.6 mg, 0.75 mmol), triethylamine (100 μL, 0.75 mmol) and 3-methoxy-4-chloroaniline (118.2 mg, 0.75 mmol) at 0 °C under argon. After 15 minutes, the resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **8** (40 mg, 17%) as a white solid. Note, this reaction was repeated several times with yields of 17−34%; **^{1}H-NMR** ($CDCl_3$, 400 MHz) 7.66 (s, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.34 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.61 (dd, J = 8.2, 2.2 Hz, 1H), 5.32 (t, J = 7 Hz, 1H), 5.16 (s, 2H), 3.84 (s, 3H), 3.73 (s, 3H), 3.39 (d, J = 7.6 Hz, 2H), 2.48−2.40 (m, 4H), 2.10 (s, 3H), 1.85 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) 172.9, 171.0, 163.4, 154.9, 153.4, 144.1, 137.6, 134.1, 129.6, 123.3, 121.7, 116.7, 111.7, 106.2, 104.1, 70.0, 60.9, 56.0, 36.0, 35.0, 22.6, 16.2, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 24.4 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{24}H_{26}ClNO_6Na$: 482.1350; found: 482.1341.



(*E*)-*N*-(3,4-Dichlorophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (9)

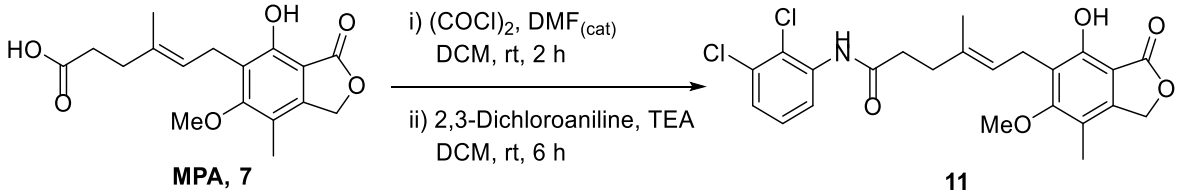
To a solution of MPA (160.2 mg, 0.5 mmol) in anhydrous DMF (3 mL) was added EDC•HCl (143.8 mg, 0.75 mmol), HOAt (102.1 mg, 0.75 mmol), triethylamine (100 μL, 0.75 mmol) and 3,4-dichloroaniline (97.2 mg, 0.6 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **9** (79 mg, 34%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 500 MHz) 7.72 (s, 1H), 7.64 (s, br, 1H), 7.61 (s, 1H), 7.27 (m, 1H), 7.18 (dd, J = 9, 2.5 Hz, 1H), 5.32 (t, J = 6.5Hz, 1H), 5.16 (s, 2H), 3.74 (s, 3H), 3.38 (d, J = 7.5 Hz, 3H), 2.47−2.38 (m, 4H), 2.10 (s, 3H), 1.84 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) 172.9, 171.0, 163.5, 153.4, 144.1, 137.2, 134.1, 132.4, 130.2, 127.1, 123.6, 121.6, 121.4, 118.9, 116.8, 106.2, 70.1, 61.0, 35.8, 35.0, 22.6, 16.1, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 26.0 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{23}H_{23}Cl_2NO_5Na$: 486.0848; found: 486.0845.



(*E*)-*N*-(4-Chloro-3-(trifluoromethyl)phenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-

dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (10)

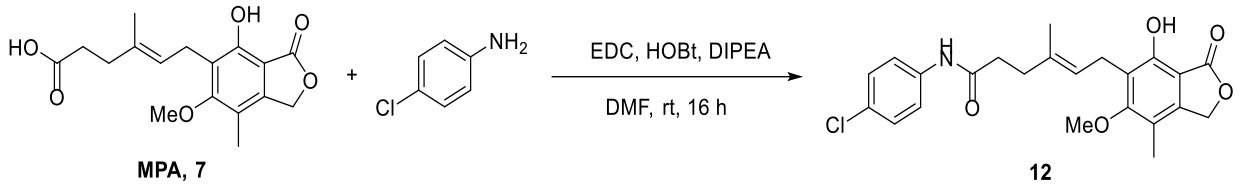
The reaction was performed using 200 mg MPA by following the procedure described for **9**, but 4-chloro-3-(trifluoromethyl)aniline was used. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **10** (250 mg, 80%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.78 (s, 1H), 7.64 (s, 1H), 7.55 (d, J = 9 Hz, 2H), 7.36 (d, J = 9.0 Hz, 1H), 5.32 (t, J = 6.4 Hz, 1H), 5.16 (s, 2H), 3.74 (s, 3H), 3.40 (d, J = 5.5 Hz, 2H), 2.45 (m, 4H), 2.10 (s, 3H), 1.85 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 172.9, 171.1, 163.5, 153.4, 144.1, 136.6, 134.1, 131.8, 128.5 (q, J = 31.3 Hz), 126.5, 123.7, 123.6, 122.4 (q, J_{CF3} = 271.3 Hz) , 121.7, 118.6 (q, J = 4.3 Hz), 116.8, 106.3, 70.1, 61.0, 35.9, 34.9, 22.6, 16.2, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 26.6 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{24}H_{23}ClF_3NO_5Na$: 520.1107; found: 520.1109.



(*E*)-*N*-(2,3-Dichlorophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (11)

To a solution of MPA (100 mg, 0.31 mmol) in anhydrous DCM (4 mL) was added oxalyl chloride (32 µL, 0.37 mmol) with two drops of DMF under argon. The resulting mixture was stirred at room temperature for 2 h and concentrated. The crude product was dissolved in anhydrous DCM (4 mL) and 2,3-dichlorolaniline (45 µL, 0.37 mmol) was added with triethylamine (52 µL, 0.37 mmol) under argon. The mixture was stirred at room temperature for 6 h and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane,

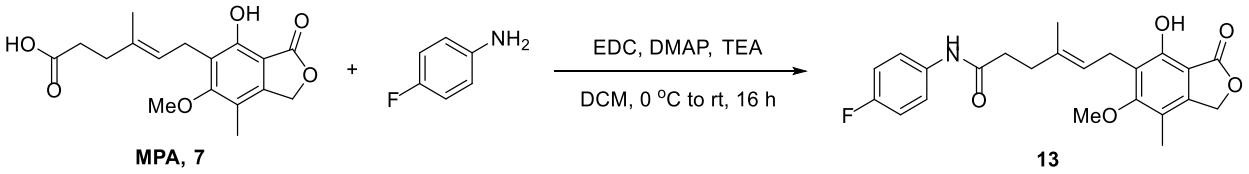
10:90 to 30:70) to afford **11** (107 mg, 73%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 400 MHz) 8.24 (q, *J* = 3.0 Hz, 1H), 7.65 (s, 1H), 7.62 (s, 1H), 7.15−7.18 (m, 2H), 5.35 (t, *J* = 7.1 Hz, 1H), 5.17 (s, 2H), 3.72 (s, 3H), 3.39 (d, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 1.86 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) 172.8, 170.8, 163.5, 153.5, 144.0, 136.1, 133.7, 132.4, 127.7, 125.0, 123.6, 121.7, 119.5, 116.7, 106.3, 70.0, 60.9, 36.3, 34.9, 22.6, 16.2, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 25.9 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{23}H_{23}Cl_2NO_5Na$: 486.0854; found: 486.0845.



(*E*)-*N*-(4-Chlorophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (12)

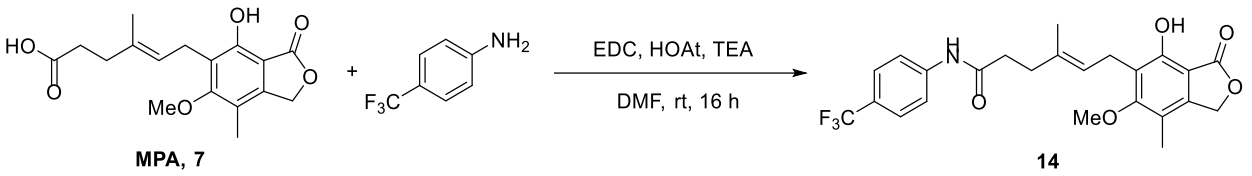
To a solution of MPA (160.2 mg, 0.5 mmol) in anhydrous DMF (3 mL) was added EDC•HCl (143.8 mg, 0.75 mmol), HOBt hydrate (101.3 mg, 0.75 mmol), 4-chloroaniline (76.5 mg, 0.6 mmol) and DIPEA (128.4 μL, 0.75 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **12** (21 mg, 24%) as a white solid. Note, this reaction was repeated several times with yields of 24–46%; **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.65 (s, 1 H), 7.38 (s, 1 H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.16 (d, *J* = 6.8 Hz, 2H), 5.31 (t, *J* =

6.8 Hz, 1H), 5.16 (s, 2H), 3.72 (s, 3H), 3.38 (d, J = 6.8 Hz, 2H), 2.45−2.39 (m, 4H), 2.09 (s, 3H), 1.84 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) 172.9, 171.0, 163.5, 153.4, 144.0, 136.3, 134.2, 128.8, 128.7, 123.3, 121.7, 120.9, 116.7, 106.2, 70.0, 61.0, 35.8, 35.0, 22.6, 16.1, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 24.8 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{23}H_{24}ClNO_5Na$: 452.1248; found: 452.1235.



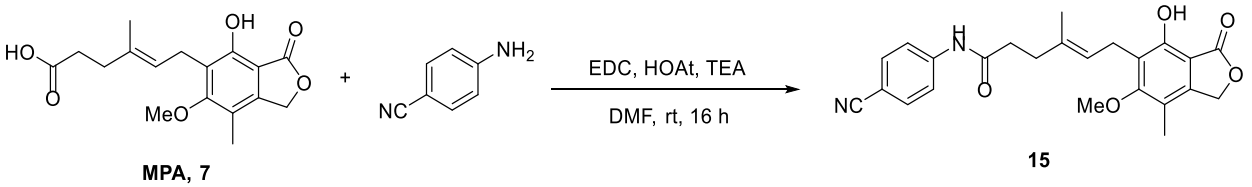
(*E*)-*N*-(4-Fluorophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (13)

The reaction was performed by following the procedure described for **8** but 4-fluoroaniline and DCM were used. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **13** (134 mg, 67%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 400 MHz) 7.66 (s, 1H), 7.34−7.31 (m, 3H), 6.95−6.90 (m, 2H), 5.33 (t, J = 6.6 Hz, 1H), 5.16 (s, 2H), 3.74 (s, 3H), 3.40 (d, J = 6.8 Hz, 2H), 2.47−2.39 (m, 4H), 2.11 (s, 3H), 1.85 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 100 MHz) 172.8, 170.9, 163.5, 159.2 (d, J_{CF} = 244.3 Hz), 153.4, 144.0, 134.3, 133.7, 123.3, 121.8, 121.7 (d, J_{CF} = 7.7 Hz), 116.7, 115.3 (d, J_{CF} = 30.2 Hz), 106.3, 70.0, 60.9, 35.7, 35.0, 22.6, 16.1, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 23.6 min. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{23}H_{25}FNO_5$: 414.1718; found: 414.1711.



(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-N-(4-(trifluoromethyl)phenyl)hex-4-enamide (14)

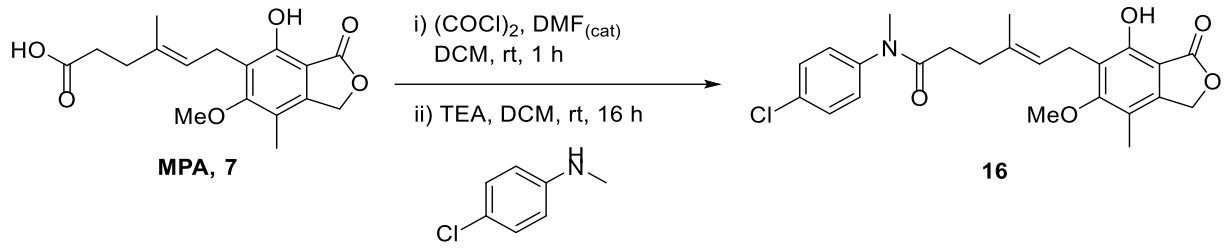
The reaction was performed by following the procedure described for **9**, but 4-(trifluoromethyl)aniline was used. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **14** (130 mg, 56%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 500 MHz) 7.68 (s, 1H), 7.53−7.49 (m, 4H), 7.38 (s, 1H), 5.34 (t, J = 6.7 Hz, 1H), 5.17 (s, 2H), 3.74 (s, 3H), 3.41 (d, J = 6.5 Hz, 2H), 2.51−2.41 (m, 4H), 2.11 (s, 3H), 1.86 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) 173.0, 171.3, 163.6, 153.5, 144.1, 140.9, 134.2, 126.0 (q, J = 4.5 Hz), 125.7 (q, J_{CF3} = 39.6 Hz), 124.0 (q, J_{CF3} = 269.2 Hz), 123.4, 121.8, 119.3, 116.8, 106.3, 70.0, 61.0, 36.0, 34.9, 22.6, 16.2, 11.5. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 25.7 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{24}H_{24}F_3NO_5Na$: 486.1507; found: 486.1499.



(*E*)-*N*-(4-Cyanophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (15)

The reaction was performed using 80 mg MPA by following the procedure described for **9**, but 4-aminobenzonitrile was used. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **15** (31 mg, 30%) as a white solid; **^{1}H-NMR** ($CDCl_3$,

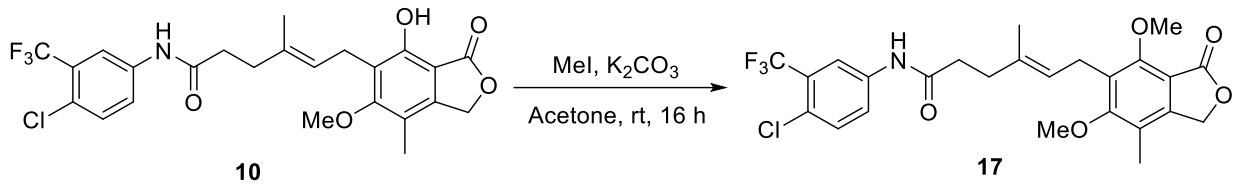
500 MHz) 7.66 (s, 1H), 7.57−7.53 (m, 4H), 5.35−5.32 (m, 1H), 5.19 (s, 2H), 3.74 (s, 3H), 3.41 (d, J = 7 Hz, 2H), 2.5−2.4 (m, 4H), 2.13 (s, 3H), 1.85 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) 172.9, 171.3, 163.5, 153.5, 144.1, 141.9, 134.2, 133.1, 123.5, 121.8, 119.4, 118.8, 116.8, 106.8, 106.4, 70.1, 61.0, 36.0, 34.8, 22.6, 16.2, 11.6. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 23.4 min. HRMS (ESI): m/z [M + Na]$^+$ calculated for $C_{24}H_{24}N_2O_5Na$: 443.1588; found: 443.1577.



(*E*)-*N*-(4-Chlorophenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-N,4-dimethylhex-4-enamide (16)

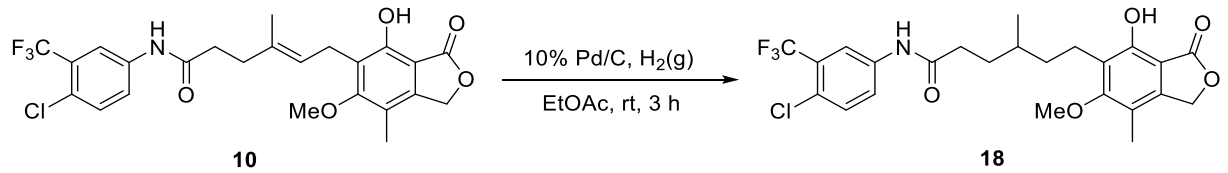
To a solution of MPA (100 mg, 0.31 mmol) in anhydrous DCM (3 mL) was added oxalyl chloride (32 μL, 0.37 mmol) with two drops of DMF under argon. The resulting mixture was stirred at room temperature for 1 h and then concentrated. The crude product was dissolved in anhydrous DCM (3 mL), then 4-chloro-*N*-methylaniline (53 mg, 0.374 mmol) and triethylamine (52 μL, 0.374 mmol) were added under argon. The mixture was stirred at room temperature for 16 h and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **16** (110 mg, 40%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.66 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.20 (s, 2H), 5.10 (t, *J* = 6.3 Hz, 1H), 3.72 (s, 3H), 3.32 (d, *J* = 6 Hz, 2H), 3.20 (s, 3H), 2.26−2.24 (m, 2H), 2.14 (m, 5H), 1.65 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 172.9, 172.5, 163.6, 153.5, 144.0, 142.6, 134.6, 133.4, 129.9, 128.6, 122.3, 122.1, 116.7, 106.3, 70.0, 61.0, 37.3, 35.2, 32.7, 22.5, 16.1, 11.6. A sample

for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 25.5 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{24}H_{26}ClNO_5Na$: 466.1394; found: 466.1392.



(*E*)-*N*-(4-Chloro-3-(trifluoromethyl)phenyl)-6-(4,6-dimethoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enamide (17)

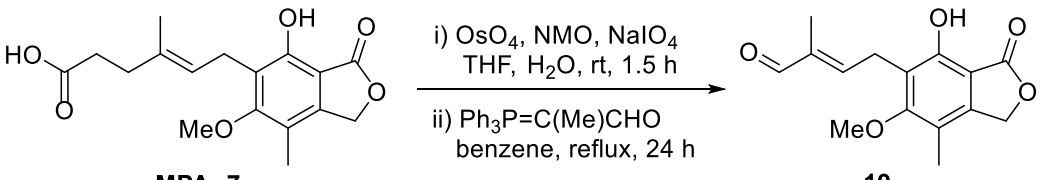
To a solution of **10** (50 mg, 0.1 mmol) in anhydrous acetone (5 mL) was added K_2CO_3 (27 mg, 2 mmol) and MeI (10 μL, 0.15 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 15:85 to 30:70) to afford **17** (33 mg, 64%) as a white solid.; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.81 (d, J = 2.1 Hz, 1H), 7.56−7.54 (m, 1H), 7.49 (s, 1H) 7.37 (d, J = 9.0 Hz, 1H), 5.25 (t, J = 6.9 Hz, 1H), 5.10 (s, 2H), 4.02 (s, 3H), 3.74 (s, 3H), 3.41 (d, J = 6.9 Hz, 2H), 2.44 (dt, J = 40.3, 7.2 Hz, 4H), 2.13 (s, 3H), 1.85 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 171.1, 169.0, 162.6, 156.5, 146.8, 136.7, 133.8, 131.8, 128.6, 128.5 (q, J_{FH} = 36 Hz), 126.5, 124.1, 123.7, 122.5 (q, J_{FH} = 272.5 Hz), 120.2, 118.7 (q, J_{FH} = 5.7 Hz), 112.5, 68.4, 62.6, 61.0, 35.9, 34.8, 23.5, 16.3, 11.5. A sample for bioassay assessment was purify using Method B. HPLC purity via Method B: ≥ 95%, t_R = 26.9 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{25}H_{25}ClF_3NO_5Na$: 534.1272; found: 534.1266.



10 **18**

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhexanamide (18)**

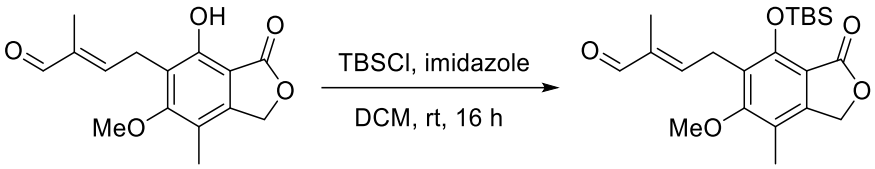
To a solution of **10** (89 mg, 0.18 mmol) in anhydrous EtOAc (10 mL) was added 10% Pd/C (w/w) under 1 atmosphere of hydrogen gas. The resulting mixture was stirred at room temperature for 3 h and then filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **18** (52 mg, 34%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.85 (d, J = 1.8 Hz, 1H), 7.74 (d, J = 8.6 Hz, 1 H), 7.44 (d, J = 9.0 Hz, 1H), 7.35 (s, 1H), 5.20 (s, 2H), 3.78 (s, 3H), 2.73−2.62 (m, 2H), 2.47−2.36 (m, 2H), 2.15 (s, 3H), 1.86−1.81 (m, 2H), 1.70−1.57 (m, 3H), 1.46−1.41 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 173.1, 171.8, 163.6, 153.6, 143.8, 136.7, 131.9, 128.0 (q, J = 30.2 Hz), 126.6, 123.6, 123.4, 122.6 (q, J_{CF3} = 270.8 Hz), 118.5 (q, J = 4.9 Hz), 116.7, 106.3, 70.1, 61.1, 35.8, 35.2, 32.5, 31.8, 20.9, 19.4, 11.6. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 27.8 min. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{25}ClF_3NO_5Na$: 522.1261; found: 522.1266.



MPA, 7 **19**

(*E*)-4-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-2-methylbut-2-enal (19)

To a solution of MPA (1.92 g, 6 mmol) and NMO (1.41 g, 12 mmol) in a 3:1 (v/v) mixture of THF/H_2O (24 mL) was added a solution of OsO_4 (50 mg, 0.2 mmol) in acetone (2 mL). The resulting mixture was stirred at room temperature for 1.5 h and then diluted with H_2O (60 mL). The mixture was cooled to 0 ºC, and a solution of $NaIO_4$ (4.28 g, 40 mL) was added in portions. The formed precipitate was filtered, washed with cold water (3 × 10 mL) and dried to give crude product (1.29 g) as a white solid. A suspension of this crude product and Ph_3P=C(Me)CHO (2.1 g, 6.6 mmol) in anhydrous benzene (25 mL) under argon was heated under reflux (90 ºC) for 24 h. The reaction mixture was concentrated and purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **19** (1.27 g, 77%) as a white solid; **^{1}H NMR** ($CDCl_3$, 500 MHz) 9.37 (1 H, s), 7.76 (1 H, br, OH), 6.52 (1 H, td, *J* = 7.0, 1.5 Hz), 5.23 (2 H, s), 3.78 (3 H, s), 3.73 (2 H, d, *J* = 7.0 Hz), 2.17 (3 H, s), 1.91 (3 H, d, *J* = 1.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 195.2, 172.6, 163.7, 153.5, 151.3, 145.1, 139.4, 118.9, 117.0, 106.6, 70.1, 61.0, 23.5, 11.6, 9.3.

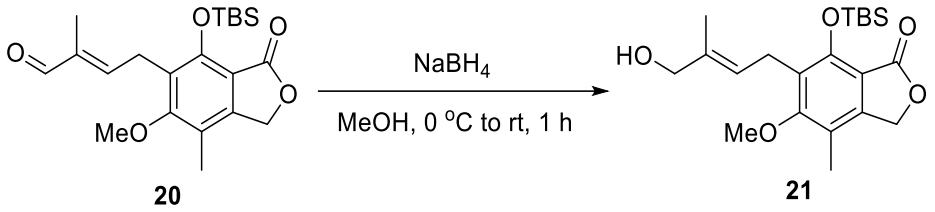


19 **20**

(*E*)-4-(4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-2-methylbut-2-enal (20)

A suspension of **19** (1.27 g, 4.6 mmol) and imidazole (1.1 g, 18.4 mmol) in anhydrous DCM (20 mL) was stirred at room temperature for 10 min, and then TBSCl (770 mg, 5.1 mmol) was added under argon. After being stirred at room temperature for 16 h, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (20 mL), and the aqueous layer was extracted with DCM (2 × 30 mL). Following neutralization with saturated aqueous $NaHCO_3$, the

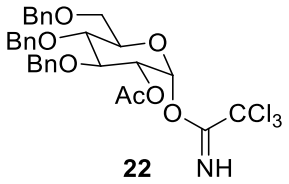
combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **20** (1.27 g, 71%) as a white solid; **^{1}H NMR** ($CDCl_3$, 500 MHz) 9.33 (1 H, s), 6.47 (1 H, td, *J* = 7.0, 1.0 Hz), 5.08 (2 H, s), 3.74 (3 H, s), 3.70 (2 H, d, *J* = 7.0 Hz), 2.16 (3 H, s), 1.85 (3 H, d, *J* = 1.0 Hz), 1.00 (9 H, s), 0.23 (6 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 194.9, 168.8, 163.0, 152.6, 151.6, 147.1, 139.1, 124.5, 118.2, 111.8, 67.6, 60.7, 25.9 (3 ×), 24.7, 18.6, 11.4, 9.3, −3.7 (2 ×).



20 **21**

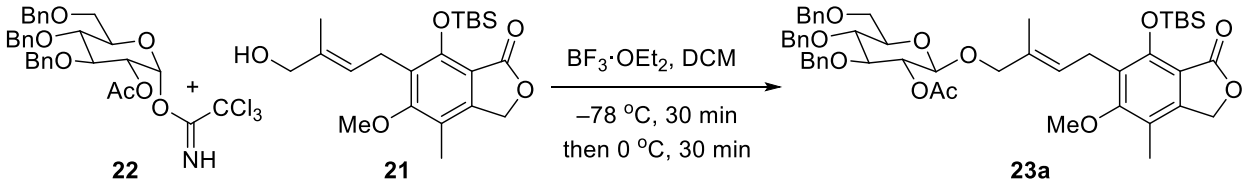
(*E*)-7-(*tert*-Butyldimethylsilyloxy)-6-(4-hydroxy-3-methylbut-2-enyl)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (21)

To a solution of **20** (100 mg, 0.26 mmol) in anhydrous MeOH (7 mL) was added $NaBH_4$ (19 mg, 0.52 mmol) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 1 h. After being quenched by the addition of saturated aqueous NH_4Cl (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **21** (94 mg, 92%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 5.42 (1 H, t, *J* = 6.5 Hz), 5.05 (2 H, s), 3.95 (2 H, s), 3.74 (3 H, s), 3.41 (2 H, d, *J* = 6.5 Hz), 2.13 (3 H, s), 1.78 (3 H, s), 1.02 (9 H, s), 0.22 (6 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 169.1, 163.1, 151.6, 146.1, 135.1, 127.2, 124.2, 118.0, 111.6, 68.6, 67.6, 60.7, 26.0 (3 ×), 23.3, 18.6, 13.9, 11.4, −3.6 (2 ×).



22

2-*O*-Acetyl-3,4,6-tri-*O*-benzyl-*α*-D-glucopyranosyl trichloroacetimidate (22) was prepared according to the previously reported method (Charette et al.[30,31]). Colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.56 (1 H, s), 7.34−7.27 (13 H, m), 7.18−7.16 (2 H, m), 6.52 (1 H, d, *J* = 4.0 Hz), 5.07 (1 H, dd, *J* = 10.0, 4.0 Hz), 4.86 (1 H, d, *J* = 11.5 Hz), 4.83 (1 H, d, *J* = 10.0 Hz), 4.77 (1 H, d, *J* = 11.5 Hz), 4.63 (1 H, d, *J* = 12.0 Hz), 4.57 (1 H, d, *J* = 10.0 Hz), 4.50 (1 H, d, *J* = 12.0 Hz), 4.09 (1 H, t, *J* = 10.0 Hz), 4.01−3.99 (1 H, m), 3.88 (1 H, t, *J* = 10.0 Hz), 3.81 (1 H, dd, *J* = 11.0, 3.5 Hz), 3.70 (1 H, dd, *J* = 11.0, 1.5 Hz), 1.93 (3 H, s).

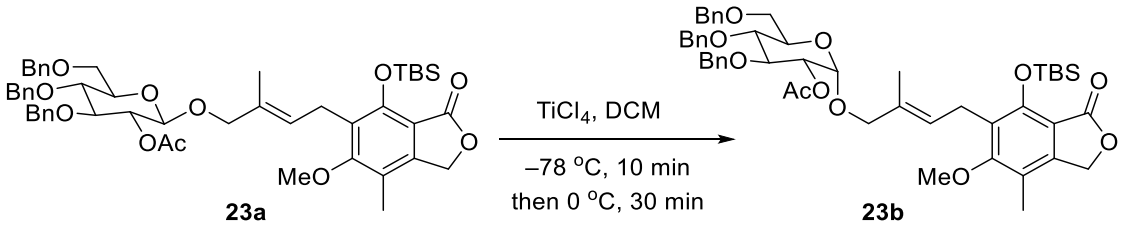


22 21 23a

(*E*)-6-(4-(2'-*O*-Acetyl-3',4',6'-tri-*O*-benzyl-*β*-D-glucopyranosyloxy)-3-methylbut-2-enyl)-7-(*tert*-butyldimethylsilyloxy)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (23a)

To a solution of **22** (460 mg, 0.72 mmol) and **21** (430 mg, 1.1 mmol) in anhydrous DCM (20 mL) was added BF_3•OEt_2 (90 μL, 0.72 mmol) at −78 ºC under argon. After being stirred at −78 ºC for 30 min, the resulting mixture was allowed to warm and stirred at 0 ºC for another 30 min. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column

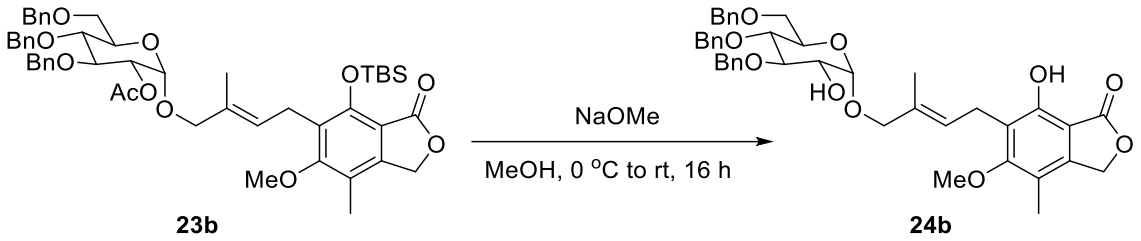
chromatography on silica gel (EtOAc/hexane, 10:90 to 15:85 to 20:80) to afford **23a** (550 mg, 88%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.33−7.24 (13 H, m), 7.18−7.16 (2 H, m), 5.41 (1 H, t, *J* = 6.5 Hz), 5.03 (2 H, s), 4.98 (1 H, dd, *J* = 9.5, 8.0 Hz), 4.78 (1 H, d, *J* = 11.5 Hz), 4.77 (1 H, d, *J* = 11.0 Hz), 4.65 (1 H, d, *J* = 11.5 Hz), 4.61 (1 H, d, *J* = 12.0 Hz), 4.53 (1 H, d, *J* = 11.0 Hz), 4.51 (1 H, d, *J* = 12.0 Hz), 4.30 (1 H, d, *J* = 8.0 Hz), 4.15 (1 H, d, *J* = 12.0 Hz), 3.94 (1 H, d, *J* = 11.0 Hz), 3.72−3.65 (6 H, m), 3.59 (1 H, t, *J* = 9.0 Hz), 3.43−3.41 (2 H, m), 3.34−3.30 (1 H, m), 2.13 (3 H, s), 1.92 (3 H, s), 1.74 (3 H, s), 1.04 (9 H, s), 0.24 (6 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 169.4, 169.1, 163.1, 151.5, 146.2, 138.1, 137.9, 137.8, 131.2, 128.3 (4 ×), 128.3 (2 ×), 128.0 (2 ×), 127.8, 127.7 (2 ×), 127.7 (3 ×), 127.5, 127.3, 127.0, 118.0, 111.6, 98.8, 82.9, 77.9, 74.9 (2 ×), 74.9, 74.3, 73.3, 73.0, 68.4, 67.6, 60.7, 26.0 (3 ×), 23.4, 20.8, 18.7, 13.9, 11.4, −3.6, −3.7.



(*E*)-6-(4-(2'-*O*-Acetyl-3',4',6'-tri-*O*-benzyl-*α*-D-glucopyranosyloxy)-3-methylbut-2-enyl)-7-(*tert*-butyldimethylsilyloxy)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (23b)

To a solution of **23a** (95 mg, 0.11 mmol) in anhydrous DCM (10 mL) was added $TiCl_4$ (24 μL, 0.22 mmol) dropwise at −78 °C under argon. After being stirred at −78 °C for 10 min, the resulting mixture was allowed to warm and stirred at 0 °C for another 30 min. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with DCM (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica

gel (EtOAc/hexane, 10:90 to 20:80) to afford **23b** (94 mg, 99%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.33−7.24 (13 H, m), 7.14−7.12 (2 H, m), 5.46 (1 H, dd, *J* = 6.5, 6.0 Hz), 5.06 (2 H, s), 4.96 (1 H, d, *J* = 3.5 Hz), 4.87−4.73 (4 H, m), 4.62 (1 H, d, *J* = 12.0 Hz), 4.48 (1 H, d, *J* = 11.0 Hz), 4.47 (1 H, d, *J* = 12.0 Hz), 4.02−3.98 (2 H, m), 3.83−3.63 (8 H, m), 3.42 (2 H, d, *J* = 6.5 Hz), 2.14 (3 H, s), 1.98 (3 H, s), 1.75 (3 H, s), 1.03 (9 H, s), 0.24 (3 H, s), 0.24 (3 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 170.2, 169.1, 163.1, 151.6, 146.2, 138.6, 138.0, 137.9, 131.1, 128.3 (6 ×), 127.9 (2 ×), 127.8 (2 ×), 127.7, 127.6, 127.5, 127.4 (2 ×), 127.2, 126.9, 118.0, 111.6, 94.3, 80.3, 77.7, 75.3, 75.0, 73.4 (2 ×), 72.7, 70.3, 68.2, 67.6, 60.7, 26.0 (3 ×), 23.4, 20.8, 18.7, 14.0, 11.4, −3.6 (2 ×).

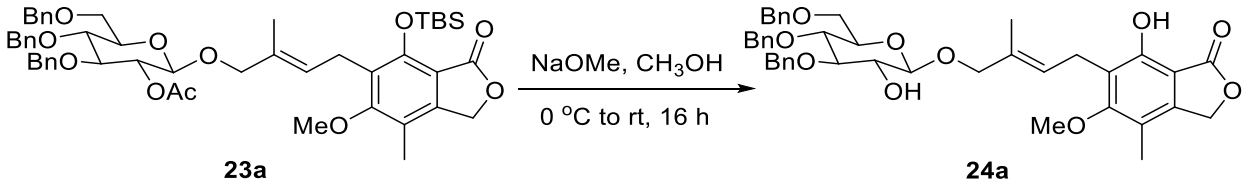


23b **24b**

(*E*)-6-(4-(3',4',6'-Tri-*O*-benzyl-*α*-D-glucopyranosyloxy)-3-methylbut-2-enyl)-7-hydroxy-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (24b)

To a solution of **23b** (450 mg, 0.52 mmol) in MeOH (10 mL) was added NaOMe (280 mg, 5.2 mmol) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 16 h. After being neutralized by the addition of Dowex 50W × 8 (H^+), the reaction mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 30:70) to afford **24b** (285 mg, 77%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.70 (1 H, br, OH), 7.38−7.24 (13 H, m), 7.13−7.11 (2 H, m), 5.52 (1 H, t, *J* = 7.0 Hz), 5.16 (2 H, s), 4.93 (1 H, d, *J* = 11.0 Hz), 4.88 (1 H, d, *J* = 3.5 Hz), 4.82 (1 H, d, *J* = 11.0 Hz), 4.80 (1 H, d, *J* = 11.0 Hz), 4.62 (1 H, d, *J* = 12.0 Hz), 4.47 (1 H, d, *J* =

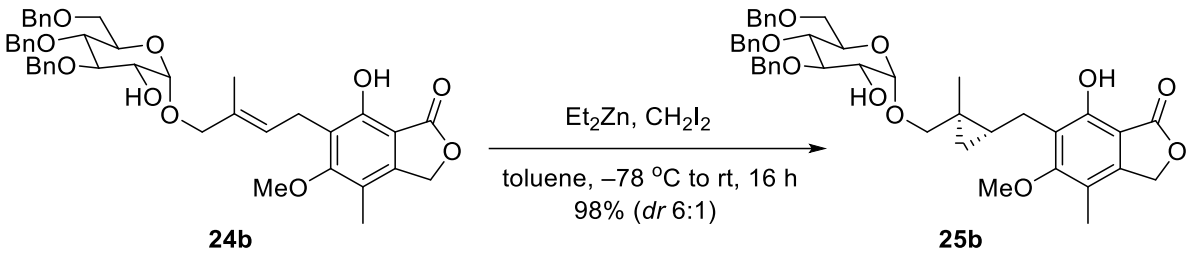
12.0 Hz), 4.46 (1 H, d, *J* = 11.0 Hz), 4.07 (1 H, d, *J* = 11.0 Hz), 3.88 (1 H, d, *J* = 11.0 Hz), 3.78−3.70 (7 H, m), 3.65−3.61 (2 H, m), 3.42 (2 H, d, *J* = 7.0 Hz), 2.13 (3 H, s), 1.84 (3 H, s); **^{13}C NMR** ($CDCl_3$, 125 MHz) 172.8, 163.5, 153.5, 144.2, 138.6, 138.0, 137.8, 131.4, 128.3 (6 ×), 127.9 (2 ×), 127.8 (2 ×), 127.8 (2 ×), 127.6, 127.6, 127.5, 126.6, 121.2, 116.7, 106.3, 96.9, 83.5, 77.2, 75.2, 74.9, 73.4, 73.3, 72.9, 70.4, 70.0, 68.3, 60.9, 22.3, 14.2, 11.5.



23a **24a**

(*E*)-6-(4-(3',4',6'-Tri-*O*-benzyl-*β*-D-glucopyranosyloxy)-3-methylbut-2-enyl)-7-hydroxy-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (24a)

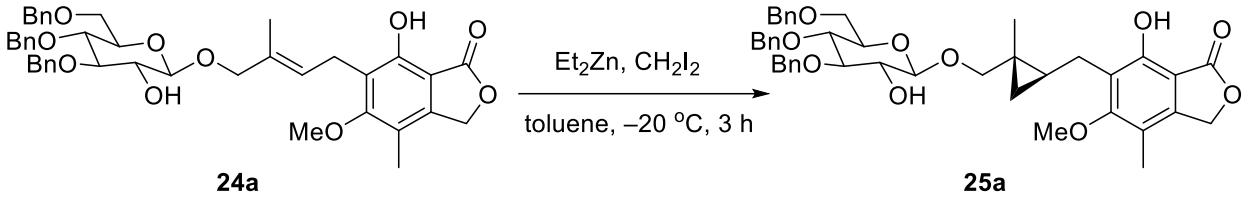
The reaction was performed by following the procedure described for **24b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75 to 30:70) to afford **24a** (240 mg, 55% from **23a**) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.70 (1 H, s, OH), 7.38−7.24 (13 H, m), 7.17−7.15 (2 H, m), 5.53 (1 H, t, *J* = 6.8 Hz), 5.15 (2 H, s), 4.93 (1 H, d, *J* = 11.2 Hz), 4.84−4.81 (2 H, m), 4.61−4.49 (3 H, m), 4.25−4.21 (2 H, m), 4.00 (1 H, d, *J* = 12.0 Hz), 3.75 (3 H, s), 3.70−3.53 (5 H, m), 3.44 (2 H, d, *J* = 6.8 Hz), 3.34−3.31 (1 H, m), 2.34 (1 H, s, OH), 2.13 (3 H, s), 1.86 (3 H, s); **^{13}C NMR** ($CDCl_3$, 100 MHz) 172.9, 163.6, 153.5, 144.2, 138.6, 138.1, 138.0, 131.7, 128.4 (2 ×), 128.4 (2 ×), 128.3 (2 ×), 128.0 (2 ×), 127.9 (2 ×), 127.7 (3 ×), 127.7, 127.6, 126.9, 121.4, 116.7, 106.4, 100.8, 84.6, 77.5, 75.1, 75.0, 75.0, 74.9, 74.6, 73.4, 70.0, 68.7, 61.0, 22.4, 14.2, 11.5.



6-((1*S*,2*R*)-(2-(3',4',6'-Tri-*O*-benzyl-*α*-D-glucopyranosyloxy)methyl-2-methylcyclopropyl)methyl)-7-hydroxy-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (25b)

To a solution of **24b** (250 mg, 0.35 mmol) in anhydrous toluene (4 mL) was added Et_2Zn (1.0 M in hexane, 3.6 mL, 3.6 mmol) at −30 °C under argon. After 15 min of stirring at −30 °C, the reaction mixture was cooled to −78 °C, and a solution of CH_2I_2 (960 mg, 3.6 mmol) in anhydrous toluene (1 mL) was added dropwise. The resulting mixture was then allowed to slowly warm to room temperature over 1 h and stirred at room temperature for another 16 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc. Following neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 25:75) to afford a mixture of two cyclopropane diastereomers (249 mg, 98%) with a ratio of 6:1. Further purifications by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) afforded desired diastereomer **25b** (120 mg) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.72 (1 H, br, OH), 7.41−7.27 (13 H, m), 7.16−7.14 (2 H, m), 5.15 (2 H, s), 4.97 (1 H, d, *J* = 11.0 Hz), 4.88 (1 H, d, *J* = 3.5 Hz), 4.82 (2 H, d, *J* = 11.0 Hz), 4.60 (1 H, d, *J* = 12.0 Hz), 4.49 (1 H, d, *J* = 11.0 Hz), 4.47 (1 H, d, *J* = 12.0 Hz), 3.74−3.69 (7 H, m), 3.63−3.61 (2 H, m), 3.44 (1 H, d, *J* = 10.5 Hz), 3.19 (1 H, d, *J* = 10.5 Hz), 2.85 (1 H, dd, *J* = 13.5, 5.0 Hz), 2.53 (1 H, dd, *J* = 13.5, 8.5 Hz), 2.13−2.08 (4 H, m), 1.26 (3 H, s), 0.96−0.92 (1 H, m), 0.57 (1 H, dd, *J* = 8.5, 5.0 Hz), 0.29 (1 H, t, *J* = 5.0 Hz); **^{13}C NMR** ($CDCl_3$,

125 MHz) 173.0, 163.8, 153.7, 144.1, 138.8, 138.2, 137.9, 128.4 (3 ×), 128.3 (2 ×), 128.1 (2 ×), 127.9 (2 ×), 127.8 (3 ×), 127.7, 127.6, 127.6, 122.9, 116.6, 106.4, 97.8, 83.8, 77.2, 76.8, 75.3, 75.1, 73.4, 73.2, 70.4, 70.0, 68.4, 61.0, 22.4, 21.6, 20.2, 17.5, 16.2, 11.6.

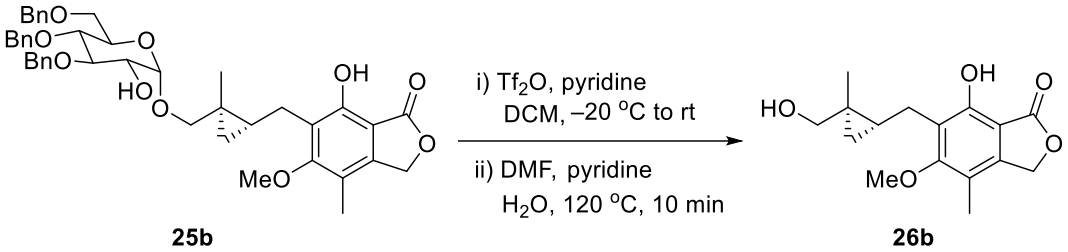


24a **25a**

6-((1*R*,2*S*)-(2-(3',4',6'-Tri-*O*-benzyl-*β*-D-glucopyranosyloxy)methyl-2-methylcyclopropyl)methyl)-7-hydroxy-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (25a)

To a solution of **24a** (200 mg, 0.28 mmol) in anhydrous toluene (0.6 mL) was added Et_2Zn (1.0 M in hexane, 2.8 mL, 2.8 mmol) under argon. After 30 min of stirring, the reaction mixture was cooled to −20 °C, and a solution of CH_2I_2 (756 mg, 2.8 mmol) in anhydrous toluene (1.4 mL) was added dropwise. The resulting mixture was stirred at −20 °C for another 3 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc. Following neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **25a** (154 mg, 76%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) 7.73 (1 H, br, OH), 7.38−7.22 (13 H, m), 7.18−7.15 (2 H, m), 5.14 (2 H, s), 4.96 (1 H, d, J = 11.6 Hz), 4.83 (1 H, d, J = 11.2 Hz), 4.82 (1 H, d, J = 11.6 Hz), 4.60−4.49 (3 H, m), 4.30 (1 H, d, J = 6.8 Hz), 3.76 (3 H, s), 3.74−3.53 (6 H, m), 3.44−3.42 (1 H, m), 3.27 (1 H, d, J = 10.0 Hz), 2.88 (1 H, dd, J = 14.0, 5.2 Hz), 2.66 (1 H, br, OH), 2.52 (1 H, dd, J = 14.0, 8.8 Hz), 2.13 (3 H, s), 1.30 (3 H, s), 1.04−0.97 (1 H, m), 0.57 (1 H, dd, J = 9.2, 4.4 Hz), 0.30 (1 H, t, J = 5.2 Hz); **^{13}C NMR** ($CDCl_3$, 100 MHz) 173.1, 164.0, 153.8, 144.3, 138.9,

138.3 (2 ×), 128.5 (3 ×), 128.5 (3 ×), 128.4 (2 ×), 128.1 (3 ×), 127.9 (2 ×), 127.8, 127.7, 123.2, 116.8, 106.5, 102.2, 84.7, 78.5, 77.7, 75.2 (2 ×), 75.1, 75.1, 73.5, 70.2, 69.0, 61.2, 22.5, 21.3, 20.3, 17.6, 16.3, 11.8.

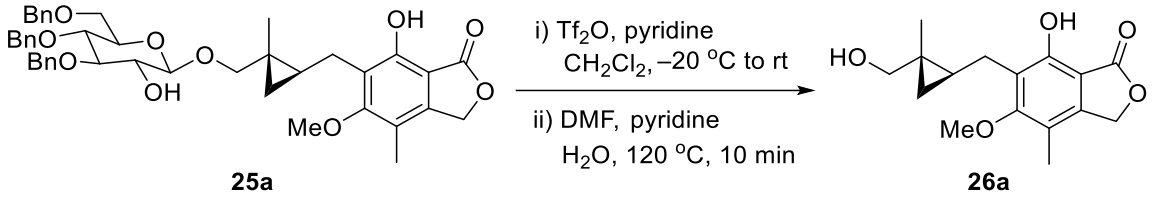


25b **26b**

7-Hydroxy-6-(((1*S*,2*R*)-2-(hydroxymethyl)-2-methylcyclopropyl)methyl)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (26b)

To a solution of **25b** (120 mg, 0.17 mmol) in DCM (1 mL) was added pyridine (80 µL, 1.0 mmol) in one portion followed by Tf_2O (135 µL, 0.85 mmol) dropwise at −20 °C under argon. After 40 min of stirring at −20 °C, an additional amount of Tf_2O (27 µL, 0.17 mmol) was added to the solution, and the resulting mixture was stirred at room temperature for another 2 h. The reaction mixture was then cooled to 0 °C, quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered through a short pad of silica gel and concentrated (bath temperature <30 °C) to afford the triflate derivative as the crude product. To a solution of this crude product in DMF (1 mL) was added pyridine (150 µL) and H_2O (300 µL) at room temperature. The resulting mixture was stirred at 120 °C for 10 min and then allowed to cool to room temperature. The mixture was partitioned between 1 N $HCl_{(aq)}$ and EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60 to 50:50 to 60:40) to afford **26b** (45

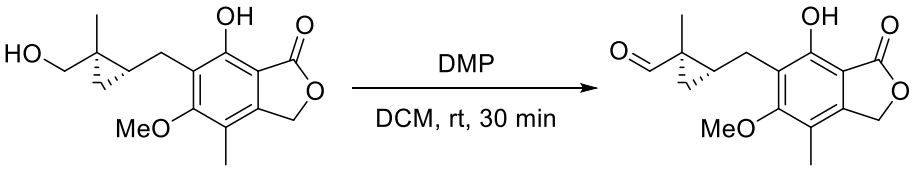
mg, 93%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 5.20 (2 H, s), 3.87 (3 H, s), 3.30 (1 H, d, *J* = 10.5 Hz), 3.27 (1 H, d, *J* = 10.5 Hz), 2.99 (1 H, dd, *J* = 14.5, 5.0 Hz), 2.62 (1 H, dd, *J* = 14.5, 8.5 Hz), 2.28 (3 H, s), 1.23 (3 H, s), 0.96−0.91 (1 H, m), 0.53 (1 H, dd, *J* = 8.5, 5.5 Hz), 0.20 (1 H, t, *J* = 5.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 166.9, 163.2, 147.0, 142.3, 131.4, 126.0, 114.2, 71.6, 68.2, 61.5, 24.4, 23.1, 21.4, 17.0, 15.5, 12.0.



25a **26a**

7-Hydroxy-6-(((1*R*,2*S*)-2-(hydroxymethyl)-2-methylcyclopropyl)methyl)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (26a)

The reaction was performed by following the procedure described for **26b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 40:60 to 60:40) to afford **26a** (14 mg, 81% from **25a**) as a colorless oil.

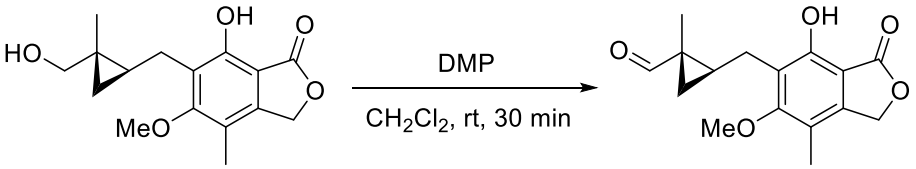


26b **27b**

(1*R*,2*R*)-2-((4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropanecarbaldehyde (27b)

To a solution of **26b** (45 mg, 0.15 mmol) and Dess-Martin periodinane (130 mg, 0.3 mmol) was added anhydrous DCM (2 mL) under argon. The reaction was stirred at room temperature for 30 min. After being quenched by the addition of 1 M $Na_2S_2O_{3(aq)}$, the aqueous layer was extracted

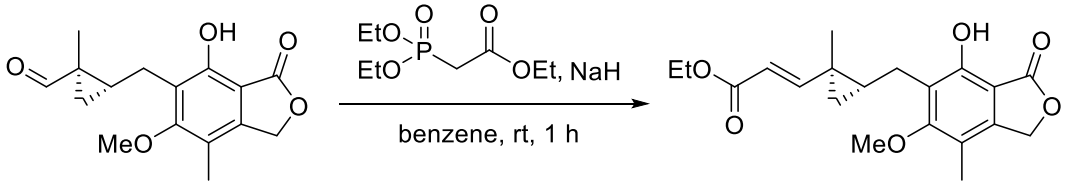
with EtOAc (2 × 10 mL). Following neutralization with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **27b** (36 mg, 83%) as a colorless oil; **^{1}H NMR** ($CDCl_3$, 500 MHz) 8.62 (1 H, s), 5.22 (2 H, s), 3.87 (3 H, s), 3.05 (1 H, dd, *J* = 14.0, 5.0 Hz), 2.72 (1 H, dd, *J* = 14.0, 9.5 Hz), 2.29 (3 H, s), 1.68−1.62 (1 H, m), 1.35 (3 H, s), 1.28 (1 H, dd, *J* = 9.5, 5.0 Hz), 0.84 (1 H, dd, *J* = 7.0, 5.0 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 201.8, 166.6, 163.2, 147.6, 142.3, 129.7, 126.2, 114.4, 68.2, 61.5, 32.3, 24.0, 23.6, 19.7, 12.1, 11.2.



26a **27a**

(1*S*,2*S*)-2-((4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropanecarbaldehyde (27a)

The reaction was performed by following the procedure described for **27b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **27a** (5.7 mg, 99% from **26a**) as a colorless oil.

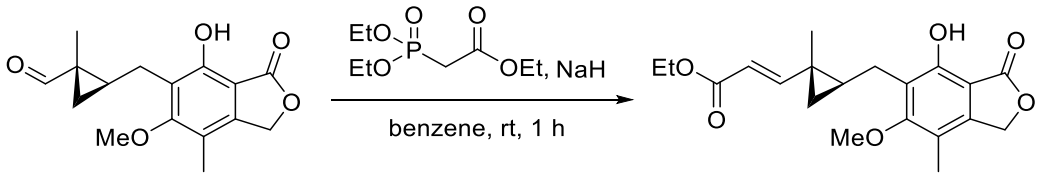


27b **28b**

(*E*)-Ethyl 3-((1*R*,2*S*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-

yl)methyl)-1-methylcyclopropyl)acrylate (28b)

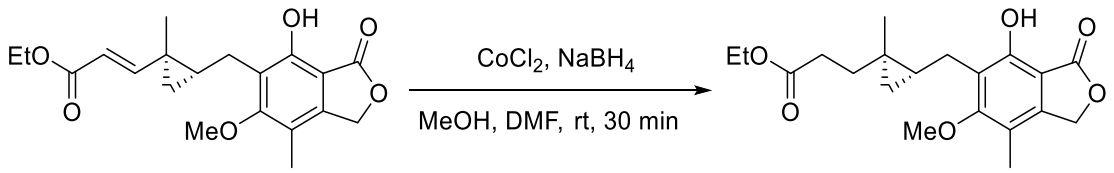
To a solution of NaH (60%, 21 mg, 0.53 mmol) in anhydrous benzene (1 mL) was added triethyl phosphonoacetate (61 mg, 0.27 mmol) under argon. After 10 min of stirring, a solution of **27b** (36 mg, 0.12 mmol) in anhydrous benzene (1 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched by the addition of 1 N $HCl_{(aq)}$ and then extracted with EtOAc. Following neutralization with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **28b** (22 mg, 51%) as a white solid; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.70 (1 H, s, OH), 6.44 (1 H, d, *J* = 16.0 Hz), 5.73 (1 H, d, *J* = 16.0 Hz), 5.21 (2 H, s), 4.15 (2 H, q, *J* = 7.0 Hz), 3.78 (3 H, s), 2.92 (1 H, dd, *J* = 13.5, 4.5 Hz), 2.61 (1 H, dd, *J* = 13.5, 8.5 Hz), 2.16 (3 H, s), 1.39−1.36 (1 H, m), 1.34 (3 H, s), 1.26 (3 H, t, *J* = 7.0 Hz), 0.94 (1 H, dd, *J* = 9.0, 4.5 Hz), 0.77 (1 H, dd, *J* = 6.0, 4.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 172.9, 167.2, 163.8, 158.6, 153.6, 144.3, 122.0, 116.7, 115.7, 106.4, 70.1, 61.0, 60.0, 27.5, 23.1, 22.7, 22.4, 15.4, 14.3, 11.7.



27a **28a**

(*E*)-Ethyl 3-((1*S*,2*R*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)acrylate (28a)

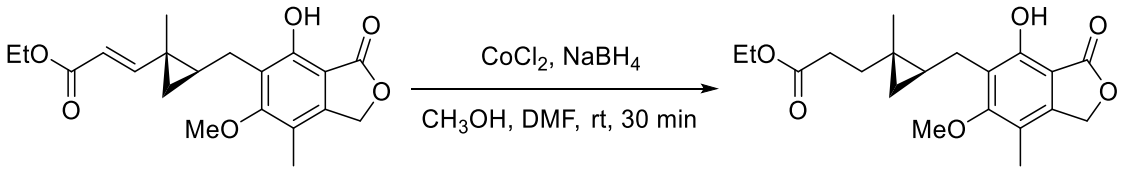
The reaction was performed by following the procedure described for **28b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **28a** (5 mg, 57% from **27a**) as a white solid.



28b **29b**

Ethyl 3-((1*R*,2*S*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanoate (29b)

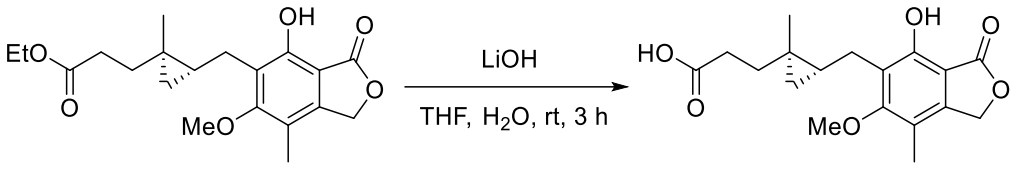
To a solution of **28b** (22 mg, 0.06 mmol) in MeOH (1 mL) was added $CoCl_2$•$6H_2O$ (30 mg, 0.12 mmol) under argon. After 30 min of stirring, a solution of $NaBH_4$ (30 mg, 0.79 mmol) in DMF (300 μL) was added to the solution. The resulting mixture was stirred at room temperature for another 30 min and then quenched by the addition of H_2O (5 mL). The solid was removed by filtration, and the aqueous layer was extracted with EtOAc (2 × 20 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to afford **29b** (19 mg, 87%) as a white solid; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.68 (1 H, s, OH), 5.20 (2 H, s), 4.10 (2 H, q, *J* = 7.0 Hz), 3.78 (3 H, s), 2.83 (1 H, dd, *J* = 13.5, 5.0 Hz), 2.48 (1 H, dd, *J* = 13.5, 8.5 Hz), 2.35−2.31 (2 H, m), 2.15 (3 H, s), 1.61−1.55 (1 H, m), 1.47−1.41 (1 H, m), 1.24 (3 H, t, *J* = 7.0 Hz), 1.15 (3 H, s), 0.88−0.84 (1 H, m), 0.39 (1 H, dd, *J* = 8.5, 4.5 Hz), 0.18 (1 H, t, *J* = 4.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 174.0, 173.1, 163.8, 153.7, 143.9, 123.2, 116.6, 106.3, 70.1, 61.0, 60.2, 36.4, 32.0, 23.7, 22.9, 19.7, 19.2, 17.2, 14.2, 11.7.



28a **29a**

Ethyl 3-((1*S*,2*R*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanoate (29a)

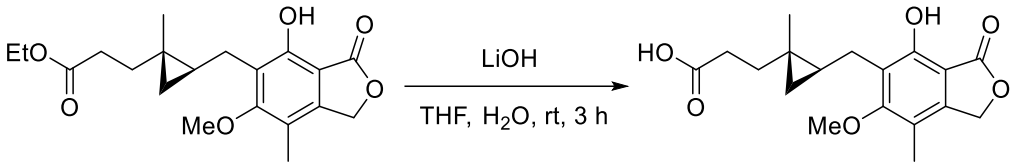
The reaction was performed by following the procedure described for **29b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80) to afford **29a** (5 mg, 62% from **28a**) as a white solid.



29b **30b**

3-((1*R*,2*S*)-2-((4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanoic acid (30b)

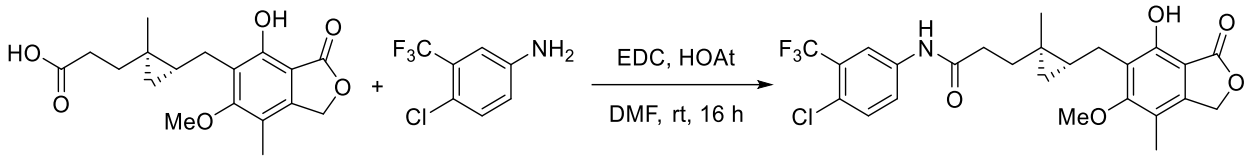
To a solution of **29b** (16 mg, 0.044 mmol) in THF (2 mL) and H_2O (2 mL) was added LiOH•H_2O (15 mg, 0.35 mmol), and the mixture was stirred at room temperature for 3 h. After being quenched with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **30b** (12.5 mg, 85%) as a white solid; **^{1}H NMR** ($CDCl_3$, 500 MHz) 5.20 (2 H, s), 3.77 (3 H, s), 2.83 (1 H, dd, *J* = 13.0, 6.0 Hz), 2.49 (1 H, dd, *J* = 13.0, 9.0 Hz), 2.40−2.37 (2 H, m), 2.15 (3 H, s), 1.67−1.58 (1 H, m), 1.47−1.41 (1 H, m), 1.16 (3 H, s), 0.91−0.87 (1 H, m), 0.42 (1 H, dd, *J* = 8.5, 4.5 Hz), 0.19 (1 H, t, *J* = 4.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 179.8, 173.1, 163.8, 153.7, 143.9, 123.2, 116.6, 106.3, 70.1, 61.0, 36.1, 31.7, 23.7, 22.9, 19.6, 19.3, 17.1, 11.7.



29a **30a**

3-((1*S*,2*R*)-2-((4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanoic acid (30a)

The reaction was performed by following the procedure described for **30b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 30:70 to 40:60) to afford **30a** (4 mg, 86% from **29a**) as a white solid.

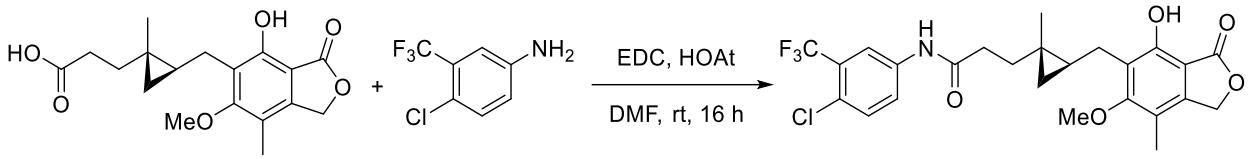


30b **31b**

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-3-((1*R*,2*S*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanamide (31b)**

To a solution of **30b** (11 mg, 0.033 mmol), 4-chloro-3-(trifluoromethyl)aniline (8 mg, 0.04 mmol) and HOAt (6 mg, 0.04 mmol) in anhydrous DMF (1 mL) was added EDC•HCl (8 mg, 0.04 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (1 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **31b** (12 mg, 71%) as a white foam; **^{1}H NMR** ($CDCl_3$, 500 MHz) 7.83 (1 H, d, *J* = 2.0 Hz), 7.71−7.69 (2 H, m), 7.47 (1 H, s), 7.41 (1 H, d, *J* = 8.5 Hz), 5.18 (2 H, d, *J* = 2.5 Hz), 3.77 (3 H, s), 2.79 (1 H, dd, *J* = 14.0, 5.5 Hz), 2.54 (1 H, dd, *J* = 14.0,

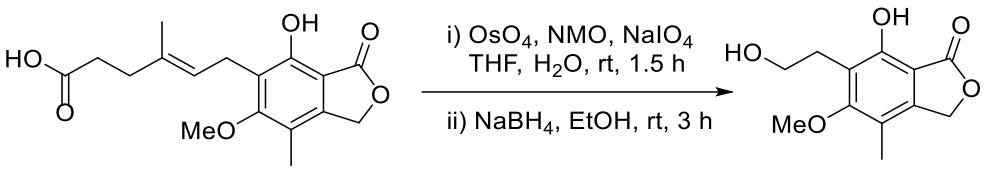
8.0 Hz), 2.43−2.39 (2 H, m), 2.14 (3 H, s), 1.76−1.70 (1 H, m), 1.54−1.48 (1 H, m), 1.19 (3 H, s), 0.92−0.86 (1 H, m), 0.46 (1 H, dd, J = 8.5, 4.5 Hz), 0.22 (1 H, t, J = 4.5 Hz); **^{13}C NMR** ($CDCl_3$, 125 MHz) 173.2, 171.8, 163.9, 153.6, 144.0, 136.8, 131.9, 128.6 (q, J_{CF3} = 31.8 Hz), 126.5, 123.5, 123.2, 122.5 (q, J_{CF3} = 270.4 Hz), 118.5 (q, J_{CF3} = 6.1 Hz), 116.7, 106.3, 70.1, 61.1, 36.7, 35.2, 23.7, 22.9, 19.8, 19.6, 17.4, 11.7. A sample for bioassay assessment was purified using Method A. HPLC purity via Method A: ≥ 95%, t_R = 27.6 min; HPLC Chiralpak ID (hexane/*i*-PrOH, 90:10; flow rate: 0.75 mL/min) 88% *ee*, t_R = 34.4 min. HRMS (ESI): m/z [M + Na]$^+$ calculated for $C_{25}H_{25}ClF_3NO_5Na$: 534.1274; found: 534.1266.



30a **31a**

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)-3-((1*S*,2*R*)-2-((4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)methyl)-1-methylcyclopropyl)propanamide (31a)**

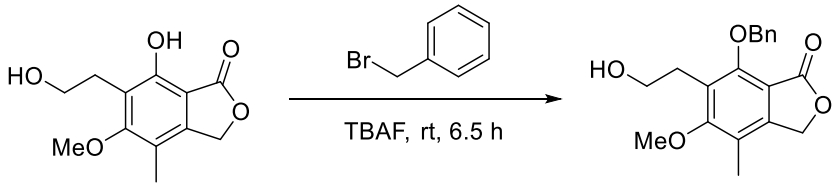
The reaction was performed by following the procedure described for **31b**. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 25:75) to afford **31a** (5 mg, 81% from **30a**) as a white foam. A sample for bioassay assessment was purify using Method A. HPLC purity via Method A: ≥ 95%, t_R = 27.6 min; HPLC Chiralpak ID (hexane/*i*-PrOH, 90:10; flow rate: 0.75 mL/min) 99% *ee*, t_R = 24.9 min. HRMS (ESI): m/z [M + H]$^+$ calculated for $C_{25}H_{26}ClF_3NO_5$: 512.1443; found: 512.1446.



MPA, 7 **33**

2-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetaldehyde (33)

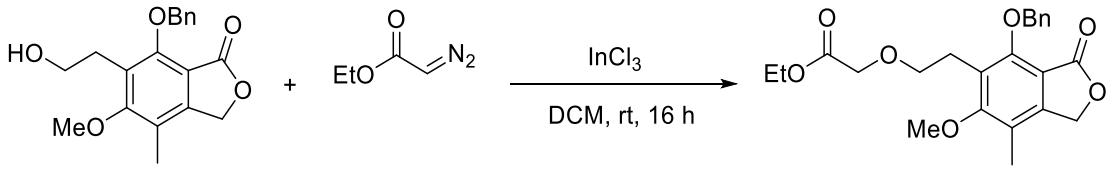
To a solution of MPA (1.92 g, 6 mmol) and NMO (1.41 g, 12 mmol) in a 3:1 (v/v) mixture of THF/H_2O (24 mL) was added a solution of OsO_4 (50 mg, 0.2 mmol) in acetone (2 mL). The resulting mixture was stirred at room temperature for 1.5 h, and then diluted with H_2O (60 mL). The mixture was cooled to 0 ºC, and a solution of $NaIO_4$ (4.28 g, 3.33 mmol) in H_2O (40 mL) was added in portions. The formed precipitate was filtered, washed with cold water (3 × 10 mL) and dried to give a white solid. This intermediate (50 mg, 0.2 mmol) in EtOH (2 mL) was added $NaBH_4$ (18.9 mg, 0.5 mmol) under argon. The resulting mixture was stirred at room temperature for 3 h and then quenched by the addition of 3N HCl until pH 7. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **33** (36 mg, 75%) as a white solid. Note, this reaction was repeated several times with yields of 70–81%; **^{1}H-NMR** ($CDCl_3$, 500 MHz) 5.20 (s, 2H), 3.87 (t, J = 6.5 Hz, 2H), 3.80 (s, 3H), 3.00 (t, J = 6.2 Hz, 2H), 2.17 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) 172.6, 163.9, 154.0, 144.9, 119.8, 116.8, 106.7, 69.9, 62.4, 61.1, 26.9, 11.6.



33 **34**

7-(Benzyloxy)-6-(2-hydroxyethyl)-5-methoxy-4-methylisobenzofuran-1(3*H*)-one (34)

To a solution of **33** (400 mg, 1.68 mmol) in neat TBAF (6.8 mL, 23.5 mmol) was added benzyl bromide (220 μL, 1.85 mmol) under argon. The resulting mixture was stirred at room temperature for 6.5 h and then quenched by the addition of saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **34** (473 mg, 82%) as a white solid. Note, this reaction was repeated several times with yields of 81–89%; **^{1}H-NMR** ($CDCl_3$, 500 MHz) 7.50–7.48 (m, 2H), 7.40–7.34 (m, 3H), 5.32 (s, 2H), 5.18 (s, 2H), 3.79 (s, 3H), 3.70 (q, J = 5.7 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.21 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) 169.0, 163.1, 155.4, 147.4, 136.8, 128.7, 128.5, 128.4, 126.6, 120.2, 112.9, 77.4, 68.4, 62.8, 61.0, 27.9, 11.6.

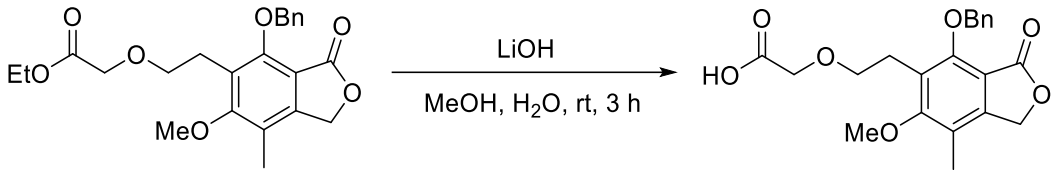


34 **35**

Ethyl 2-(2-(4-(benzyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)ethoxy)acetate (35)

To a solution of **34** (575 mg, 1.75 mmol) in DCM (2 mL) was added ethyl diazoacetate (450 μL, 3.5 mmol) and $InCl_3$ (150 mg, 0.65 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (50 mL). Note, this reaction did not go to completion. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and

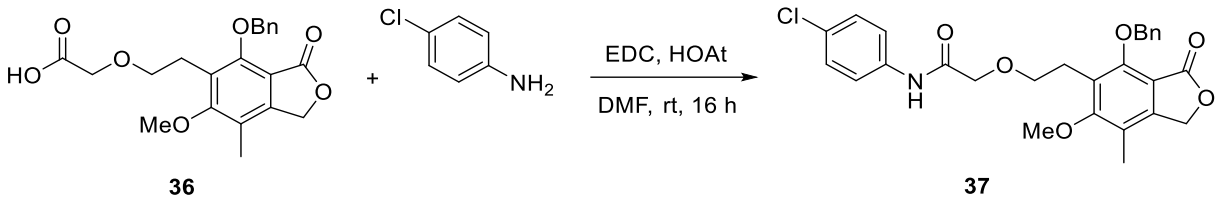
concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 30:70) to afford **35** (470 mg, 57%) as a light yellow solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.51 (d, *J* = 6.9 Hz, 2H), 7.38–7.31 (m, 3H), 5.31 (s, 2H), 5.15 (s, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.97 (s, 2H), 3.80 (s, 3H), 3.61 (t, *J* = 7.5 Hz, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 2.18 (s, 3H), 1.24 (t, *J* = 6.9 Hz, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 170.3, 169.1, 163.3, 155.7, 147.3, 137.0, 128.7, 128.5, 128.2, 125.9, 120.1, 112.6, 70.6, 68.4, 68.2, 61.2, 60.7, 29.7, 25.0, 14.1, 11.6.



35 **36**

2-(2-(4-(Benzyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)ethoxy)acetic acid (36)

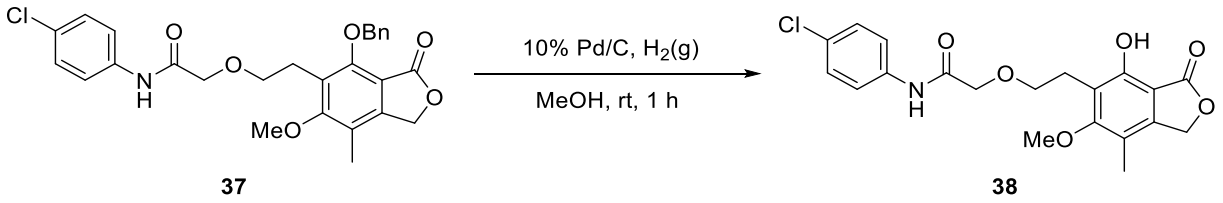
To a solution of **35** (412 mg, 0.99 mmol) in MeOH (7 mL) and H_2O (3 mL) was added LiOH (209 mg, 4.97 mmol). The resulting mixture was stirred at room temperature for 3 h and then quenched by the addition of H_2O (50 mL) and 2N HCl until pH 2. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **36** (365 mg, 95%) as a white solid. Note, this reaction was repeated several times with yields of 76–95%; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.48–7.46 (m, 2H), 7.38–7.33 (m, 3H), 5.33 (s, 2H), 5.17 (s, 2H), 3.97 (s, 2H), 3.79 (s, 3H), 3.59 (t, *J* = 6.9 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H), 2.19 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 173.6, 169.0, 163.1, 155.5, 147.5, 136.9, 128.7, 128.5, 128.3, 125.6, 120.2, 112.7, 77.4, 70.9, 68.4, 67.6, 61.1, 24.9, 11.6.



36 **37**

2-(2-(4-(Benzyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)ethoxy)-*N*-(4-chlorophenyl)acetamide (37)

To a solution of **36** (11 mg, 0.03 mmol) in anhydrous DMF (2 mL) was added EDC•HCl (8.4 mg, 0.043 mmol), HOAt (6 mg, 0.043 mmol) and 4-chlororoaniline (4 mg, 0.032 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 20:80 to 30:70) to afford **37** (12 mg, 80%) as a white solid. Note, this reaction was repeated several times with yields of 65–80%; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 8.49 (s, 1H), 7.50–7.45 (m, 4H), 7.36–7.31 (m, 3H), 7.26 (m, 2H), 5.34 (s, 2H), 5.18 (s, 2H), 3.89 (s, 2H), 3.82 (s, 3H), 3.62 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H), 2.20 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 168.9, 167.6, 163.0, 155.5, 147.7, 136.6, 135.9, 129.1, 128.9, 128.7, 128.5, 128.5, 126.5, 120.9, 120.4, 113.1, 77.6, 70.8, 70.0, 68.4, 61.0, 25.1, 11.7.

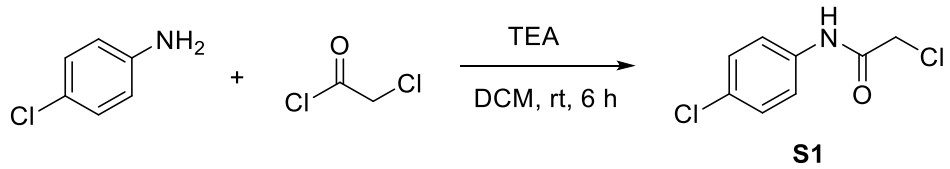


37 **38**

***N*-(4-Chlorophenyl)-2-(2-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-**

5-yl)ethoxy)acetamide (38)

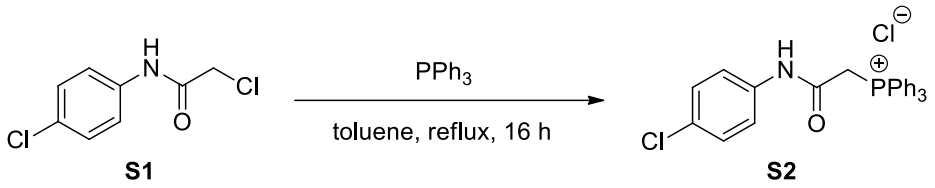
To a solution of **37** (90 mg, 0.18 mmol) in MeOH (25 mL) was added 10% Pd/C (w/w) under 1 atmosphere of hydrogen gas. The resulting mixture was stirred at room temperature for 1 h and then filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 10:90 to 30:70) to afford **38** (20 mg, 27%) as a white solid. Note, this reaction was repeated several times with yields of 27–56%; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 8.51 (s, 1H), 7.50–7.48 (m, 2H), 7.30–7.28 (m, 2H), 5.21 (s, 2H), 4.03 (s, 2H), 3.84 (s, 3H), 3.79 (t, J = 6.3 Hz, 2H), 3.06 (t, J = 6.3 Hz, 2H), 2.15 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 172.7, 168.0, 164.0, 153.7, 145.0, 135.8, 129.4, 129.0, 120.8, 119.2, 116.9, 106.7, 70.4, 70.1, 70.0, 61.1, 24.1, 11.7. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 23.8 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{20}H_{20}ClNO_6Na$: 428.0873; found: 428.0871.



S1

2-Chloro-*N*-(4-chlorophenyl)acetamide (S1)

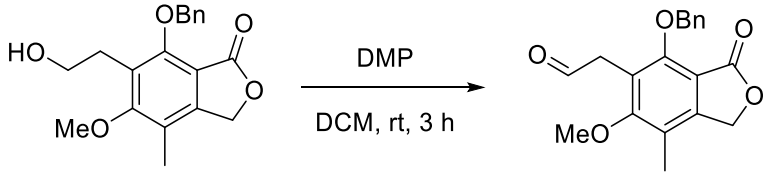
To a solution of 4-chloroaniline (500 mg, 3.92 mmol) in DCM (5 mL) was added chloroacetyl chloride (374 μL, 4.7 mmol) and triethylamine (710 μL, 5.1 mmol) under argon. The resulting mixture was stirred at room temperature for 6 h and then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **S1** (620 mg, 77%) as a light yellow solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 8.23 (s, 1H), 7.51 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 4.20 (s, 2H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 163.8, 135.3, 130.4, 129.3, 121.4, 42.9.



S1 S2

(2-((4-Chlorophenyl)amino)-2-oxoethyl)triphenylphosphonium (S2)

To a solution of **S1** (400 mg, 1.95 mmol) in toluene (25 mL) was added PPh_3 (565 mg, 2.16 mmol) and refluxed under argon. The resulting mixture was refluxed for 16 h and then allowed to cool to room temperature. After concentration, the precipitate was filtered, washed with toluene (3 × 10 mL) and dried to afford **S2** (602 mg, 71%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 12.12 (s, 1H), 7.86–7.83 (m, 6H), 7.78 (td, *J* = 7.5, 1.0 Hz, 3H), 7.65 (td, *J* = 7.8, 3.6 Hz, 6H), 7.60 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 5.23 (d, J = 14.5 Hz, 2H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 160.8, 160.7, 136.6, 135.1, 135.1, 134.1, 134.0, 130.2, 130.1, 129.3, 128.5, 121.4, 118.4, 117.8, 33.4, 33.1.

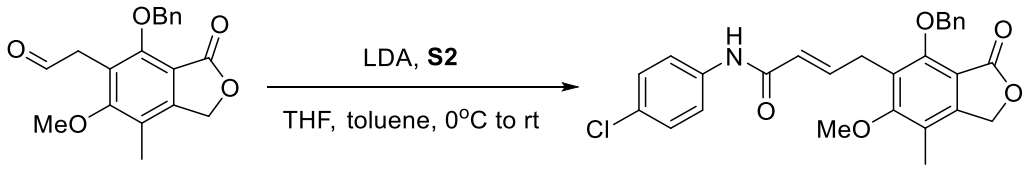


34 40b

2-(4-(Benzyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetaldehyde (40b)

To a solution of **34** (30 mg, 0.09 mmol) in DCM (2 mL) was added Dess-Martin periodinane (DMP, 46.6 mg, 0.11 mmol) at room temperature under argon. The resulting mixture was stirred at room temperature for 3 h and then concentrated. The residue was purified by column

chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **40b** (24 mg, 80%) as a white solid. Note, this reaction was repeated several times with yields of 80–88%; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 9.55 (t, *J* = 1.5 Hz, 1H), 7.42–7.40 (m, 2H), 7.38–7.33 (m, 3n), 5.33 (s, 2H), 5.21 (s, 2H), 3.71 (s, 3H), 3.67 (d, *J* = 1.2 Hz, 2H), 2.21 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 199.0, 168.8, 162.9, 155.2, 148.5, 136.5, 128.9, 128.5, 128.5, 121.2, 120.1, 112.7, 77.4, 68.4, 60.8, 39.7, 11.6.

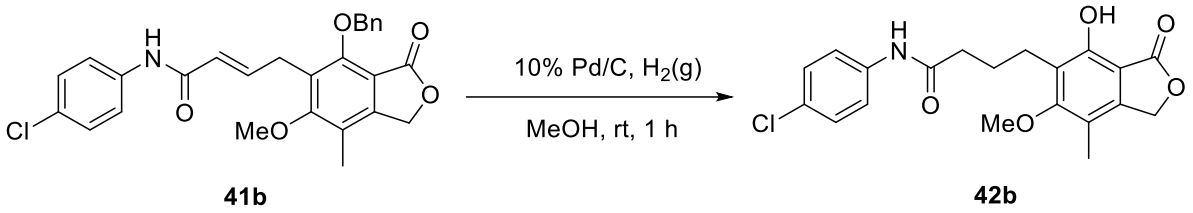


40b **41b**

(*E*)-4-(4-(Benzyloxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-*N*-(4-chlorophenyl)but-2-enamide (41b)

To a solution of **40b** (50 mg, 0.12 mmol) in THF (2 mL) at 0 °C was added LDA (2M in THF, 77 μL, 0.15 mmol) under argon. The resulting mixture was stirred at 0 °C for 1 h and then **S2** (100 mg, 0.214 mmol) in toluene (1 mL) was added dropwise. The mixture was allowed to warm to room temperature and stir for 16 h before being quenched by the addition of NH_4Cl and H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **41b** (19 mg, 51%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.46–7.44 (m, 4H), 7.38–7.34 (m, 3H), 7.28–7.25 (m, 5H), 6.99 (dt, *J* = 15.6, 6.2 Hz, H), 6.94 (s, 1H), 5.59 (d, *J* = 15.6 Hz, 1H), 5.33 (s, 2H), 5.19 (s, 2H), 3.78 (s, 3H), 3.52 (d, *J* = 6.2 Hz, 2H), 2.21 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 169.0, 162.8, 155.4, 147.8, 143.9, 137.0, 136.4, 129.0, 128.5, 128.5, 128.3,

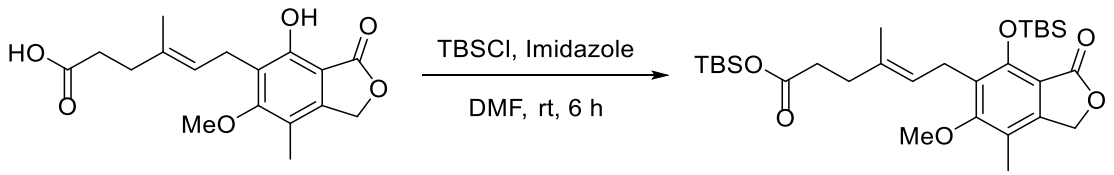
125.7, 124.4, 121.0, 120.8, 120.3, 112.7, 68.4, 61.3, 27.1, 11.6.



41b **42b**

(*E*)-*N*-(4-Chlorophenyl)-4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)but-2-enamide (42b)

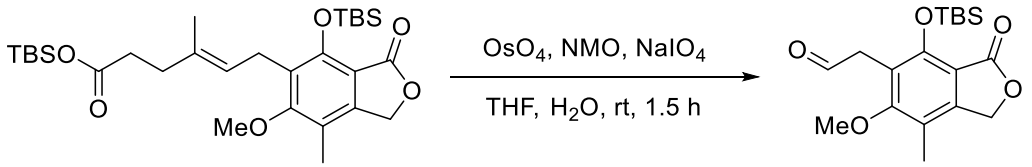
To a solution of **41b** (18mg, 0.037 mmol) in MeOH (10 mL) was added 10% Pd/C (w/w) under 1 atmosphere of hydrogen gas. The resulting mixture was stirred at room temperature for 1 h and then filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **42b** (6.7 mg, 46%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.52 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 5.20 (s, 2H), 3.78 (s, 3H), 2.78 (t, J = 6.6 Hz, 2H), 2.39 (t, J = 6.6 Hz, 2H), 2.16 (s, 3H), 2.04 (t, J = 7.2 Hz, 2H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 172.9, 171.6, 163.8, 153.6, 144.5, 136.3, 129.3, 129.0, 121.9, 121.0, 116.9, 106.5, 70.1, 61.2, 36.7, 25.0, 22.6, 11.6. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 23.8 min. HRMS (ESI): m/z $[M + Na]^+$ calculated for $C_{20}H_{20}ClNO_5Na$: 412.0918; found: 412.0922.



MPA, 7 **39**

(*E*)-*tert*-Butyldimethylsilyl 6-(4-((tert-butyldimethylsilyl)oxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate (39)

To a solution of MPA (200 mg, 0.62 mmol) in DMF (3 mL) was added imidazole (380 mg, 5.6 mmol) and TBSCl (470 mg, 3.1 mmol) under argon. The resulting mixture was stirred at room temperature for 6 h and then quenched by the addition of H_2O (100 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 30:70) to afford **39** (225 mg, 66%) as a clear oil; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 5.18 (t, *J* = 6.4 Hz, 1H), 5.05 (s, 2H), 3.73 (s, 3H), 3.37 (d, *J* = 6.0 Hz, 2H), 2.39–2.35 (m, 2H), 2.27–2.24 (m, 2H), 2.14 (s, 3H), 1.74 (s, 3H), 1.01 (s, 9H), 0.89 (s, 9H), 0.22 (s, 6H), 0.17 (s, 6H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 173.9, 169.3, 163.2, 151.8, 146.1, 133.9, 127.7, 123.3, 118.0, 111.7, 67.7, 60.8, 34.7, 34.6, 26.1, 25.6, 23.7, 18.8, 17.6, 16.4, 11.5, –3.46, –4.84.

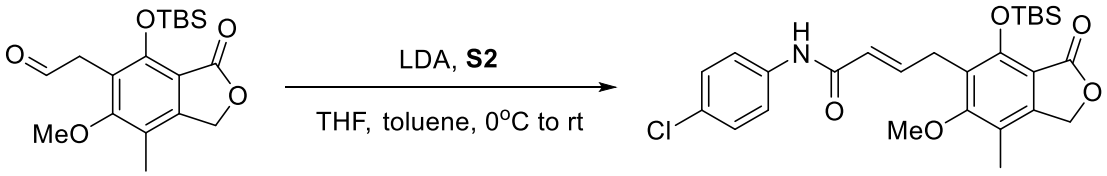


39 **40a**

2-(4-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetaldehyde (40a)

To a solution of **39** (225 mg, 0.41 mmol) and NMO (96 mg, 0.82 mmol) in a 3:1 (v/v) mixture of THF/H_2O (2.5 mL) was added a solution of OsO_4 (4 mg, 0.033 mmol) in acetone (0.5 mL). The resulting mixture was stirred at room temperature for 1.5 h, and then diluted with H_2O (3 mL). The mixture was cooled to 0 ºC, and a solution of $NaIO_4$ in H_2O (4 mL) was added in portions. After 6 h, mixture was quenched by H_2O (4 mL) and extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered

and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 10:90 to 30:70) to afford **40a** (100 mg, 70%); **^{1}H-NMR** ($CDCl_3$, 600 MHz) 9.63 (s, 1H), 5.12 (s, 2H), 3.73 (s, 5H), 2.19 (s, 3H), 1.03 (s, 9H), 0.23 (s, 6H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 199.1, 168.8, 163.2, 152.1, 148.0, 119.7, 118.0, 112.0, 67.8, 60.5, 39.7, 26.0, 18.7, 11.5, –3.5.

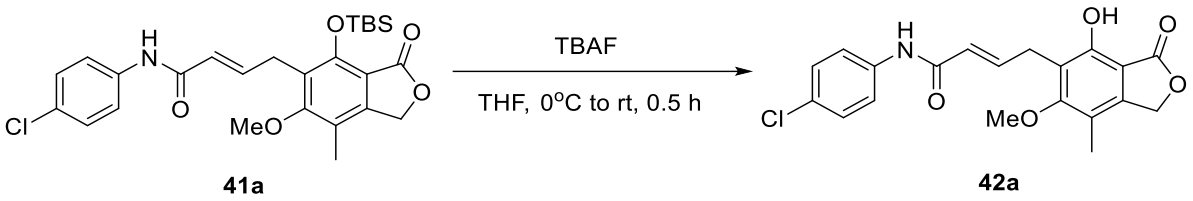


40a **41a**

(*E*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-*N*-(4-chlorophenyl)but-2-enamide (41a)

To a solution of **40a** (50 mg, 0.14 mmol) in THF (2 mL) at 0 °C was added LDA (2M in THF, 142.7 µL, 0.29 mmol) under argon. The resulting mixture was stirred at 0 °C for 1 h. After 1 h, **S2** (100 mg, 0.214 mmol) in toluene (1 mL) was added into the mixture dropwise. The mixture was allowed to warm to room temperature and was stirred 16 h before being quenched by the addition of NH_4Cl and H_2O (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **41a** (105 mg, 73%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.49 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.12 (dt, J = 15.0, 5.9 Hz, 1H), 5.72 (d, J = 15.0 Hz, 1H), 5.08 (s, 2H), 3.76 (s, 3H), 3.62 (d, J = 5.4 Hz, 2H), 2.17 (s, 3H), 1.01 (s, 9H), 0.25 (s, 6H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 169.2, 163.8, 163.2, 152.0, 147.2, 144.1, 136.7, 129.1, 129.0,

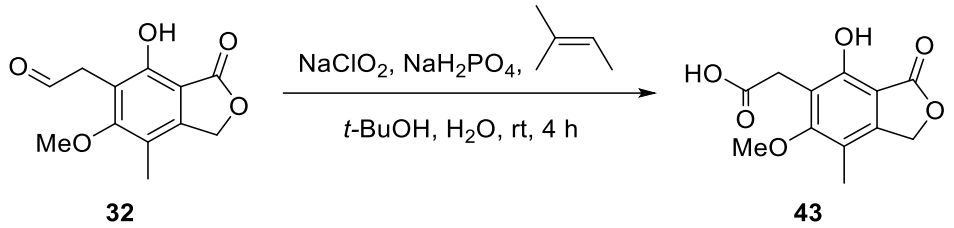
124.3, 124.1, 121.0, 118.3, 111.7, 67.8, 61.2, 27.1, 26.1, 18.8, 11.6, –3.4, –3.6.



41a **42a**

(*E*)-*N*-(4-Chlorophenyl)-4-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)but-2-enamide (42a)

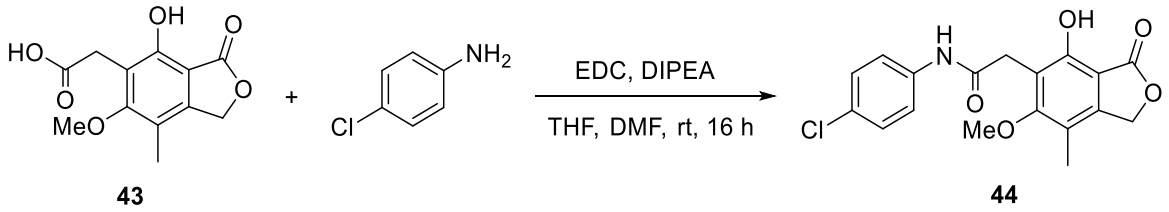
To a solution of **41a** (50 mg, 0.1 mmol) in THF (2 mL) at 0 ºC was added TBAF (110 µL, 0.11 mmol) under argon. The resulting mixture was stirred at room temperature for 15 minutes. After completion of the reaction, the mixture was quenched by the addition of H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **42a** (8.7 mg, 22%) as a white solid; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 7.72 (s, 1H), 7.48 (d, J = 7.8 Hz, 2H), 7.28 (s, 1H), 7.26 (d, J = 9.0 Hz, 2H), 7.13–7.08 (dt, J = 15.0, 5.9 Hz, 1H), 5.86 (d, J = 15.0 Hz, 1H), 5.21 (s, 2H), 3.79 (s, 3H), 3.61 (d, J = 6 Hz, 2H), 2.17 (s, 3H); **^{13}C-NMR** ($CDCl_3$, 150 MHz) 172.7, 163.7, 153.6, 145.1, 143.5, 136.5, 129.1, 129.0, 124.3, 120.9, 118.6, 117.0, 106.5, 70.1, 61.3, 26.0, 11.6. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 23.6 min. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{20}H_{19}ClNO_5$: 388.0945; found: 388.0946.



32 **43**

2-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetic acid (43)

To a solution of **32** (50 mg, 0.22 mmol) in *t*-BuOH (2 mL) was added 2-methyl-2-butene (1 mL), $NaClO_2$ (57 mg, 0.635 mmol) and a solution of NaH_2PO_4 (76 mg, 0.635 mmol) in H_2O (2 mL). The resulting mixture was stirred at room temperature for 4 h. After completion of the reaction, the mixture was quenched by the addition of H_2O (20 mL) and 1N HCl until pH 2. The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (MeOH/DCM, 1:99 to 5:95) to afford **43** (40 mg) as a semi-pure clear oil; **^{1}H-NMR** ($CDCl_3$, 600 MHz) 5.23 (s, 2H), 3.81 (s, 3H), 3.78 (s, 2H), 2.17 (s, 3H). This material was used directly in the next reaction without further purification.



43 **44**

***N*-(4-Chlorophenyl)-2-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)acetamide (44)**

To a solution of **43** (40 mg, 0.16 mmol) in anhydrous THF/DMF (2/0.2 mL) was added EDC•HCl (45 mg, 0.24 mmol), 4-chloroaniline (25 mg, 0.19 mmol) and DIPEA (53 µL, 0.32 mmol) under argon. The resulting mixture was stirred at room temperature for 16 h and then concentrated.

After the addition of H_2O (100 mL), the aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/DCM, 5:95 to 10:90) to afford **44** (22 mg, 38%) as a white solid.; **^{1}H NMR** ($CDCl_3$, 600 MHz) 8.04 (s, 1H), 7.89 (s, 1H), 7.44 (d, J = 9.0 Hz, 2H), 7.26 (d, J = 9.6 Hz, 2H), 5.25 (s, 2H), 3.90 (s, 3H), 3.80 (s, 2H), 2.20 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) 172.5, 168.3, 163.8, 152.9, 145.8, 136.5, 129.1, 128.9, 120.9, 117.7, 116.2, 106.9, 70.2, 61.8, 33.0, 11.7. A sample for bioassay assessment was purified using Method B. HPLC purity via Method B: ≥ 95%, t_R = 22.4 min. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{18}H_{17}ClNO_5$: 362.0793; found: 362.0790.