Supporting Information

Total synthesis of (±)-moluccanic acid methyl ester

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**Experimental section**

**General.** Unless otherwise noted, all reactions were performed in oven-dried glassware. All solvents used in the reactions were purified before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry CH₂Cl₂, dimethylformamide, methanol, ethyl acetate, benzene, and triethylamine were distilled from CaH₂. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under nitrogen atmosphere. All commercially available compounds (Acros, Aldrich, Fluka, Merck) were used without purification.

¹H and ¹³C NMR: Bruker Avance 400, spectra were recorded at 295 K in CDCl₃; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: CDCl₃ (¹H 7.25, ¹³C 77.0 ppm). HRMS (FT-ICR): Bruker Daltonic APEX 2 with electron spray ionization (ESI). Analytical LC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100-5, C-18 HD, 5 mm, 70 × 3 µm Machery Nagel, eluent: NaCl solution (5 mm)/acetonitrile, gradient: 0–10–15–17–20 min with 20–80–80–99–99% acetonitrile, flow: 0.5 mL min⁻¹. Flash chromatography: J. T. Baker silica gel 43–60 µm. Thin-layer chromatography Machery-Nagel Polygram Sil G/UV.

(4aS,6S,8aS)-6-((tert-Butyldimethylsilyl)oxy)-5,5,8a-trimethyloctahydronaphthalen-1(2H)-one (9). TBSCI (7.9 g, 52.4 mmol) was added in one portion to a stirred solution of alcohol 7 (10.0 g, 47.6 mmol) and imidazole (7.1 g, 104.8 mmol) in DMF (100 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred overnight, treated with water (200 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (200 mL), saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give enone 9 (15.0 g, 97%) as white crystals. Rᵢ = 0.68 (petroleum ether/EtOAc, 9:1). The ¹H- and ¹³C-NMR data were in complete agreement with the reported values.¹

(4bS,7S,8aR,10aS)-7-((tert-Butyldimethylsilyl)oxy)-4b,8,8-trimethyl-1,4b,5,6,7,8,8a,9,10,10a-decahydrophenanthren-3(2H)-one (10). NaH (60% suspension in mineral oil; 3.2 g, 80.0 mmol) was added portionwise to a stirred solution of ketone 9 (20.0 g, 61.5 mmol) in a THF/toluene (200 mL/80 mL) mixture at 0 °C. The resulting suspension was stirred 30 min at the same temperature

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followed by addition of ethyl formate (10 mL). The resulting mixture was allowed to warm to room temperature, stirred overnight and carefully treated with water (200 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 100 mL), dried over MgSO₄, filtered, and concentrated in vacuo.

The obtained formylketone was dissolved in CH₂Cl₂ (100 mL) and treated with triethylamine (17.2 mL, 123.0 mmol) and methyl vinyl ketone (15.4 mL, 215.2 mmol) at 0 °C. The resulting solution was stirred for 2 h at room temperature, and then diluted with water (200 mL). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo.

This residue was dissolved in methanol (100 mL) and treated with MeONa (16.6 g, 307.5 mmol). The resulting solution was stirred under reflux for 1 h, quenched with water and concentrated in vacuo. Additional 200 mL of water was added and the mixture extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo.

The residue was purified by flash chromatography (petroleum ether/EtOAc, 15:1 to 9:1) to give tricyclic enone 10 (18.1 g, 78%) as white crystals. 

\[ R_f = 0.37 \text{ (petroleum ether/EtOAc 9:1); } ^1H \text{ NMR (400 MHz, CDCl}_3\text{): } \delta[ppm] = 0.03 \text{ (s, 3H, Si8CH}_3\text{), 0.05 \text{ (s, 3H, Si8CH}_3\text{), 0.82 \text{ (s, 3H, 88CH}_3\text{), 0.88 \text{ (s, 9H, SiC(CH}_3)_3\text{), 0.91 \text{ (s, 3H, 88CH}_3\text{), 1.02 \text{ (dd, J = 12.1, 2.8 Hz, 1H, 8a-H), 1.11 \text{ (s, 3H, 4b8CH}_3\text{, C89), 1.49–1.77 \text{(m, 7H, 1-H, 2 × 5-H, 2 × 6-H, 2 × 9-H), 1.98–2.11 \text{(m, 2H, H-1, H-10), 2.23 \text{(ddd, J = 16.4, 12.7, 5.0 Hz, 1H, 2-H), 2.36 \text{(ddd, J = 16.4, 5.0, 5.0 Hz, 1H, 2-H), 2.49–2.58 \text{(m, 1H, 10a-H), 3.17 \text{(dd, J = 10.2, 4.9 Hz, 1H, 7-H), 5.80 \text{(d, J = 1.8 Hz, 1H, 4-H); } ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{): } \delta[ppm] = –5.0 \text{ (Si8CH}_3\text{), –3.8 \text{ (Si8CH}_3\text{), 16.1 \text{ (88CH}_3\text{), 18.1 \text{(Si–C), 21.3 \text{(4b–CH}_3\text{, C-9), 25.9 \text{ (C(CH}_3)_3\text{), 27.7 \text{(C-6), 28.5 \text{(8–CH}_3\text{, 29.3 \text{(C-1), 34.2 \text{(C-10a), 34.7 \text{(C-5), 35.1 \text{(C-10), 35.9 \text{(C-2), 40.1 \text{(C-8), 40.6 \text{(C-4b), 52.2 \text{(C-8a), 78.8 \text{ (C-7), 119.8 \text{(C-4), 176.0 \text{(C-4a), 201.3 \text{(C-3); HRMS (ESI): [M+Na]'}^+ \text{ calc for C}_{23}H_{40}O_2SiNa 399.268978, found 399.268854.} \]

(2S,4aS,10aR)-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2,6-diol (11). To a solution of enone 10 (1.00 g, 2.65 mmol) in acetonitrile (50 mL) was added a solution of CuBr₂ (1.00 g, 4.48 mmol) in acetonitrile (50 mL) added dropwise over 2 h at room temperature. The resulting mixture was stirred for additional 1 h, quenched with phosphate buffer (pH = 7; 200 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (100 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1 to 1:1) to give phenol 11 (690 mg, quant.) as yellowish crystals. 

\[ R_f = 0.45 \text{ (petroleum ether/EtOAc 1:1); } ^1H \text{ NMR (400 MHz, CD}_3\text{OD): } \delta[ppm] = 0.86 \text{ (s, 3H, 1-CH}_3\text{), 1.03 \text{ (s, 3H, 1-CH}_3\text{), 1.15 \text{ (s, 3H, 4a-CH}_3\text{), 1.19–1.25 \text{(m, 1H, 10a-H), 1.35 \text{(ddd, J = 12.9, 12.9, 4.4 Hz, 1H, 4-H), 1.63–1.87 \text{(m, 4H, 2 × 3-H, 2 × 10-H), 2.22 \text{(ddd, J = 13.0, 13.5, 3.4 Hz, 1H, 4-H), 2.64–2.84 \text{(m, 2H, 2 × 9-H), 3.20 \text{(dd, J = 11.1, 5.0 Hz, 1H, 2-H), 6.47 \text{(dd, J = 8.1, 2.5 Hz, 1H, 7-H), 6.65 \text{(d, J = 2.5 Hz, 1H, 5-H), 6.79 \text{(d, J = 8.1 Hz, 1H, 8-H); } ^{13}C \text{ NMR (100 MHz, CD}_3\text{OD): } \delta[ppm] = 16.1 \text{(1-CH}_3\text{), 20.2 \text{(C-10), 25.3 \text{(4a-CH}_3\text{), 28.8 \text{(C-3, 1-CH}_3\text{, 31.0 \text{(C-9), 38.5 \text{(C-4), 39.1 \text{(C-4a), 40.1 \text{(C-1), 51.5 \text{(C-10a), 79.4 \text{(C-2), 111.8 \text{(C-5),} \]

S3
(2S,4aS,10aR)-6-((tert-Butyldimethylsilyl)oxy)-1,1,4a-trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (12). TBSCI (140 mg, 0.93 mmol) was added in one portion to a stirred solution of phenol 11 (220 mg, 0.85 mmol) and imidazole (125 mg, 1.86 mmol) in THF (10 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight, diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give mono-TBS-protected compound 12 (290 mg, 91%) as colorless oil. Rf = 0.43 (petroleum ether/EtOAc, 4:1); ¹H NMR (400 MHz, CD₃OD): δ[ppm] = 0.15 (2 × s, 6H, Si(CH₃)₂), 0.87 (s, 3H, 18CH₃), 0.96 (s, 9H, C(CH₃)₃), 1.05 (s, 3H, 1-CH₃), 1.16 (s, 3H, 4a-CH₃), 1.25 (dd, J = 12.2, 2.1 Hz, 1H, 10a-H), 1.45 (dd, J = 12.8, 12.8, 4.7 Hz, 1H, 4-H), 1.69–1.90 (m, 4H, 2 × 3-H, 2 × 10-H), 2.22 (dd, J = 12.9, 12.9, 3.5 Hz, 1H, 4-H), 2.67–2.88 (m, 2H, 2 × 9-H, 2 × 10-H), 6.53 (dd, J = 8.3, 2.5 Hz, 1H, 7-H), 6.67 (d, J = 2.3 Hz, 1H, 5-H), 6.84 (d, J = 8.3 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CD₃OD): δ[ppm] = -4.2 (Si(CH₃)₂), 16.1 (1-CH₃), 19.1 (SiC), 20.2 (C-10), 25.4 (4a-CH₃), 26.3 (C(CH₃)₃), 28.8 (C-3, 1-CH₃), 31.1 (C-9), 38.4 (C-4), 38.7 (C-4a), 40.1 (C-1), 51.4 (C-10a), 79.4 (C-2), 116.8 (C-5), 118.6 (C-7), 129.0 (C-8a), 130.8 (C-8), 151.7 (C-4b), 154.8 (C-6); HRMS (ESI): [M+H]⁺ calcd for C₂₃H₃₉O₂Si 375.271383, found 375.271019.

(4aS,10aR)-6-((tert-Butyldimethylsilyl)oxy)-1,1,4a-trimethyl-1,4,4a,9,10,10a-hexahydrophenanthren-2(3H)-one (13). Dess-Martin reagent² (500 mg, 1.17 mmol) was added to a stirred suspension of alcohol 12 (400 mg, 1.07 mmol) and Na₂CO₃ (400 mg) in CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, quenched with saturated Na₂S₂O₃ (5 mL) followed by addition of saturated NaHCO₃ (20 mL) solution. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 12:1 to 6:1) to give ketone 13 (400 mg, quant.) as colorless oil. Rf = 0.77 (petroleum ether/EtOAc, 4:1); ¹H NMR (400 MHz, CD₃OD): δ[ppm] = 0.15 (s, 6H, Si(CH₃)₂), 0.96 (s, 9H, Si(CH₃)₃), 1.11 (s, 3H, 1-CH₃), 1.41–1.82 (m, 2H, 2 × 3-H, 2 × 10-H), 2.35–2.60 (m, 5H, 2 × 3-H, 2 × 10-H), 6.10–6.40 (m, 2H, 7-H, 5-H), 6.53–6.83 (m, 2H, 8-H, 8a-H), 7.00–7.20 (m, 1H, 6-H); ¹³C NMR (100 MHz, CD₃OD): δ[ppm] = 18.1 (1-CH₃), 20.4 (10a-CH₃), 21.7 (SiC), 26.3 (4a-CH₃), 27.0 (C(CH₃)₃), 28.8 (C-3, 1-CH₃), 31.1 (C-9), 38.4 (C-4), 38.7 (C-4a), 40.1 (C-1), 51.4 (C-10a), 79.4 (C-2), 116.8 (C-5), 118.6 (C-7), 129.0 (C-8a), 130.8 (C-8), 151.7 (C-4b), 154.8 (C-6); HRMS (ESI): [M+H]⁺ calcd for C₂₃H₃₉O₂Si 375.271383, found 375.271019.

(4aS,10aR)-6-Hydroxy-1,1,4a-trimethyl-1,4,4a,9,10,10a-hexahydrophenanthren-2(3H)-one (5). pTsOH monohydrate (23 mg, 0.12 mmol) was added to a stirred solution of ketone 13 (30 mg, 0.08 mmol) in methanol (2 mL) at room temperature. The resulting solution was stirred overnight at the same temperature, poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 6:1 to 2:1) to give phenol 5 (20 mg, quant.) as colorless oil. R$_f$ = 0.19 (petroleum ether/EtOAc, 4:1); $^1$H NMR (400 MHz, CD$_3$OD): $\delta_{ppm} = 1.12$ (s, 3H, 18CH$_3$), 1.14 (s, 3H, 18CH$_3$), 1.25 (s, 3H, 4aCH$_3$), 1.65–1.93 (m, 4H, 10aH, 3H, 2 × 10H), 2.34 (ddd, $J = 13.1, 7.8, 4.3$ Hz, 1H, 3H), 2.55–2.86 (m, 4H, 2 × 4H, 2 × 9H), 6.52 (dd, $J = 8.3, 2.5$ Hz, 1H, 7H), 6.69 (d, $J = 2.5$ Hz, 1H, 5H), 6.79 (d, $J = 8.3$ Hz, 1H, 8H); $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta_{ppm} = 21.5$ (18CH$_3$, C810), 27.4 (1H, 3H, 2 × 10H), 29.2 (4aCH$_3$), 31.1 (C89), 35.6 (C84), 38.7 (C84a), 38.7 (C83), 48.9 (C81), 52.0 (C810a), 112.7 (C85), 114.4 (C7), 126.9 (C8a), 130.8 (C8), 149.6 (C4b), 156.4 (C6), 220.2 (C2); HRMS (ESI): [M–H]$^-$ calcld for C$_{17}$H$_{21}$O$_2$ 257.154703, found 257.154736.
3H, 5-CH₃), 1.47 (s, 3H, 11b-CH₃), 1.56 (s, 3H, 5-CH₃), 1.70–1.76 (m, 2H, 2 × 6-H), 1.96 (ddd, J = 14.2, 6.0, 3.8 Hz, 1H, 1-H), 2.22–2.34 (m, 2H, 1-H, 5a-H), 2.53–2.80 (m, 4H, 2 × 2-H, 2 × 7-H), 6.58 (dd, J = 8.3, 2.5 Hz, 1H, 9-H), 6.66 (d, J = 2.3 Hz, 1H, 11-H), 6.84 (d, J = 8.3 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = –4.4 (Si(CH₃)₃), 18.9 (SiC), 24.8 (C-6), 25.7 (C(CH₃)₃), 26.4 (5-CH₃), 26.5 (11b-CH₃), 30.1 (C-7), 30.2 (5-CH₃), 32.7 (C-2), 39.0 (C-1), 39.5 (C-11b), 49.3 (C-5a), 85.8 (C-5), 117.9 (C-9), 118.1 (C-11), 126.5 (C-7a), 129.1 (C-8), 149.4 (C-11a), 154.1 (C-11b), 174.1 (C-3); HRMS (ESI): [M+H]+ calcd for C₂₃H₂₇O₃Si 389.250648, found 389.250822.

![Diagram](image)

**Methyl 3-((1S,2R)-7-hydroxy-2-(2-hydroxypropan-2-yl)-1-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (15) and methyl 3-((1S,2S)-7-hydroxy-1-methyl-2-(prop-1-en-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)propanoate (2).** pTsOH monohydrate (2.03 g, 10.7 mmol) was added in one portion to a stirred solution of lactone 14 (520 mg, 1.34 mmol) in methanol (10 mL) at room temperature. The resulting solution was stirred overnight, treated with saturated NaHCO₃ solution (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated NaCl solution (30 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1 to 4:1) to give the two esters 15 and 2 (15: 320 mg, 60%); (2: 160 mg, 30%) as colorless oils.

**2: Rf = 0.33 (petroleum ether/EtOAc, 4:1);** ^1^H NMR (400 MHz, CDCl₃): δ[ppm] = 1.19 (s, 3H, 1-CH₃), 1.77 (s, 3H, C(CH₃)₂=CH₂), 1.56 (s, 3H, 5-CH₃), 1.80–2.15 (m, 5H, 2’-H, 2 × 3’-H, 2 × 3-H), 2.21–2.29 (m, 1H, 2’-H), 2.38 (dd, J = 11.4, 3.0 Hz, 1H, 2-H), 2.68–2.75 (m, 2H, 2 × 4-H), 3.61 (s, 3H, OCH₃), 4.69 (br s, 1H, =CH₂), 4.94 (br s, 1H, =CH₂), 6.61 (dd, J = 8.1, 2.5 Hz, 1H, 6-H), 6.75 (d, J = 2.5 Hz, 1H, 5-H), 6.89 (d, J = 8.1 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 22.8 (CH₂C=CH₂), 24.7 (C-3), 27.8 (1-CH₃), 29.5 (C-2’, C-4), 34.6 (C-3’), 41.1 (C-1), 47.0 (C-2), 51.7 (OCH₃), 112.9 (C-8), 113.3 (C-6), 114.3 (C=CH₂), 129.1 (C-4a), 130.1 (C-5), 144.5 (C-8a), 146.6 (C=CH₂), 154.0 (C-7), 175.0 (ester); HRMS (ESI): [M+Na]+ calcd for C₁₃H₂₄O₃Na 311.161766, found 311.161980.

**15: Rf = 0.10 (petroleum ether/EtOAc, 4:1);** ^1^H NMR (400 MHz, CDCl₃): δ[ppm] = 1.29 (s, 3H, C(CH₃)₂), 1.35 (s, 3H, 1-CH₃), 1.47 (s, 3H, C(CH₃)₂), 1.50–1.76 (m, 3H, 2 × 3-H, 2-H), 1.92–2.10 (m, 3H, 2 × 3’-H, 2’-H), 2.17 (s, 1H, OH), 2.56–2.69 (m, 2H, 2’-H, 4-H), 2.82–2.88 (m, 1H, 4-H), 3.60 (s, 3H, OCH₃), 6.58 (dd, J = 8.3, 2.5 Hz, 1H, 6-H), 6.79 (d, J = 2.3 Hz, 1H, 8-H), 6.85 (d, J = 8.3 Hz, 1H, 5-H); ¹³C NMR (100 MHz, CDCl₃): δ[ppm] = 24.5 (C-3), 26.8 (C(CH₃)₂), 27.2 (1-CH₃), 29.6 (C-4), 30.7 (C(CH₃)₂), 33.2 (C-2’), 36.6 (C-3’), 43.4 (C-1), 48.7 (C-2), 51.8 (OCH₃), 75.5 (C(CH₃)₂), 112.9 (C-6), 113.2 (C-8), 129.6 (C-4a), 129.8 (C-5), 146.4 (C-8a), 154.4 (C-7), 176.3 (C-1’); HRMS (ESI): [M+Na]+ calcd for C₁₃H₂₆O₄Na 329.172330, found 329.172482.

**Cell proliferation assay.** L-929 mouse fibroblast and KB-3-1 human cervix carcinoma cell lines were obtained from DSMZ, Germany. Potoroo kidney cell line PtK2 was from ATCC, USA. L-929 and KB-3-1 were cultivated at 37°C and 10% CO₂ in DME medium (high glucose) supplemented with 10% fetal calf serum, PtK2 in MEM with non-essential amino acids. Cell culture reagents came from Life Technologies Inc. (GIBCO BRL). Growth inhibition was measured in 96-well plates. 60 µL of serial dilutions of the test compounds were given to aliquots of 120 µL of the suspended cells (50,000 mL⁻¹). After 5 d, metabolic activity in each well was determined using an
MTT assay. The values were related to control cells and the IC$_{50}$ was determined from the resulting concentration dependent activity curves.

**Impedance measurement profiling.** The impedance measurements were performed with small modifications on a RT-CES system (xCelligence) from Acea Biosciences (Roche), which has been described previously. For time-dependent cell response profiling, 60 μL of media was added to 96-well E-Plate to obtain background readings followed by the addition of 120 μL cell suspension of L-929 cells. After each step, the E-Plates were incubated for 30 min at room temperature and then placed on the reader in the incubator for continuous recording of impedance as reflected by cell index. After 24 h of incubation the cells were treated with the compounds. To prepare the compounds for screening each stock solution (10 mM in DMSO) was diluted with cell media to get a final test concentration of the IC$_{90}$ and less than 0.1 % DMSO. 1 μL of each prepared solution was then transferred into the 96-well E-Plate. Each E-plate contained also wells with DMSO only as a solvent control. All measurements were performed in triplicates and run for 5 d. The time-dependent cellular response profiles (TCRP) were recorded by the Roche RTCA Software, Version 1.2. Data processing and mining workflow was implemented in the statistical programming language R, Version 2.12.2 (R Development Core Team, 2011). The following additional R packages were used in addition: class, gplots and MASS. For the development of the R code the integrated development environment R Studio, Version 0.94.92, was used. The workflow starts by importing the raw impedance data which is provided by the RTCA software as cell index (CI) data. The CI is already background corrected and is calculated as follows (Eq. 1):

\[
CI(t) = \frac{R_t - R_b}{Z_n}
\]

where CI(t) is the cell index at time point t, $R_t$ is defined as measured electrode impedance of the well with the cells in the medium at a certain time point and $R_b$ as measured background impedance of the well with the cell medium alone. $Z_n$ is a frequency factor which corrects for different frequencies of the alternating voltage the xCelligence system can use, the standard setting is $Z_n = 15$. The raw data were imported into R and normalized as suggested by Abassi and colleagues by dividing the cell indices for each time point after compound addition by the cell index at a reference time point (Eq. 2).

\[
NCI = \frac{CI_t}{CI_{(reference)}}
\]

The reference compounds and the test compounds with unknown mode of action were measured as triplicates which were randomly distributed over the microtiter plates (using sampling without replacement in R) to avoid batch effects.

Detection and removal of outliers was carried out using the median polishing procedure. The central idea of the data mining concept is to use cubic smoothing splines for the approximation of the

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impedance data and as dimension reduction technique. This approach has the benefit of avoiding the curse of dimensionality and the Runge phenomenon that occurs for high polynomials, while keeping the complexity of the data set. The smooth.spline function of R was used for TCRP approximation. As set of descriptors the spline basis coefficients were extracted to construct a distance matrix that was used for hierarchical cluster analysis. A heatmap was constructed that displays the Z-transformed values of the 22 descriptors (= basis spline coefficients). Hierarchical cluster analysis of the reference compounds together with the compound of unknown mode of action was carried out. Co-clustering of the compound of unknown mode of action with reference compounds with known activity class label is used to predict the mode of action.

![Figure S1](image.png)

**Figure S1.** Compound 2 and 11 were tested for their influence on impedance kinetics of L-929 cells cultured in 96-well plates. Impedance curves were mathematically analysed and compared with reference compounds.

**Cell staining.** PtK2 cells were grown on glass cover slips (13 mm diameter) in 4-well plates and incubated with the compounds 2 at 20 µg mL⁻¹ for 18 h. For staining microtubules cells were fixed with cold MeOH/acetone (1:1) for 10 min, and primary mouse anti-α-tubulin and secondary antibodies anti-mouse Alexa Fluor 488 were incubated for 45 min. For staining actin filaments cells were fixed with 3.7% paraformaldehyde for 10 min, followed by incubation with 0.1% Triton-X100 for 5 min. F-actin was labelled then using phalloidin Alexa Fluor 594. Nuclei and chromosomes were stained using DAPI. Cells were washed with phosphate-buffered saline (PBS) between each step. Cover slips were mounted in anti fade mounting medium (Molecular Probes) and images taken with a Zeiss Axiohot fluorescence microscope using appropriate filter sets. The following antibodies were used for cell staining: rat anti-GRP94 and anti-rat Alexa Fluor 488.
Figure S2. Potoroo kidney cells PtK2 were incubated with 2 (69 µM) (right) or the vehicle only (left) for 24 h and stained for microtubules. With compound 2 we observed weak and bended mitotic spindles.
$^1$H NMR (400 MHz) spectrum of tricyclic enone 10 in CDCl$_3$

$^{13}$C NMR (100 MHz) spectrum of tricyclic enone 10 in CDCl$_3$
$^1$H NMR (400 MHz) spectrum of phenol 11 in CD$_3$OD

$^{13}$C NMR (100 MHz) spectrum of phenol 11 in CD$_3$OD
$^{1}H$ NMR (400 MHz) spectrum of aryl silyl ether 12 in CD$_3$OD

$^{13}$C NMR (100 MHz) spectrum of aryl silyl ether 12 in CD$_3$OD
$^1$H NMR (400 MHz) spectrum of ketone 13 in CD$_3$OD

$^{13}$C NMR (100 MHz) spectrum of ketone 13 in CD$_3$OD
$^1$H NMR (400 MHz) spectrum of ketone 5 in CD$_3$OD

$^{13}$C NMR (100 MHz) spectrum of ketone 5 in CD$_3$OD
$^1$H NMR (400 MHz) spectrum of lactone 14 in CDCl$_3$

$^{13}$C NMR (100 MHz) spectrum of lactone 14 in CDCl$_3$
$^1$H NMR (400 MHz) spectrum of hydroxy ester 15 in CDCl$_3$

$^{13}$C NMR (100 MHz) spectrum of hydroxy ester 15 in CDCl$_3$
$^1$H NMR (400 MHz) spectrum of (±)-moluccanic acid methyl ester (2) in CDCl$_3$

$^{13}$C NMR (100 MHz) spectrum of (±)-moluccanic acid methyl ester (2) in CDCl$_3$