

# Supporting Information

## Optimized Protein Kinase C $\theta$ (PKC $\theta$ ) Inhibitors Reveal Only Modest Anti-Inflammatory Efficacy in a Rodent Model of Arthritis

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**Table 1.** LC/MS analytical methods

<u>Method</u>	<b>Conditions</b>
<b>1</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: MeCN (0.02% TFA) in water (0.04% TFA), from 10% to 80% within 2 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>2</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: MeCN (0.02% TFA) in water (0.04% TFA), from 30% to 90% within 2 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>3</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: MeCN (0.02% TFA) in water (0.04% TFA), from 0% to 60% within 4 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>4</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: MeCN (0.02% TFA) in water (0.04% TFA), from 10% to 80% within 4 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>5</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: acetonitrile (0.02% TFA) in water (0.04% TFA), from 5% to 95% within 1.5 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>6</b>	Column: Ultimate XB-C18, 3 $\mu$ m, 30 $\times$ 2.1 mm; Mobile phase: acetonitrile (0.02% TFA) in water (0.04% TFA), from 0% to 60% within 2 min; Flow rate: 1.2 mL/min; Wavelength: 220 nm
<b>7</b>	Column: Merck, 3 $\mu$ m, 25 $\times$ 2 mm; Mobile phase: MeCN (0.02% TFA) in water (0.04% TFA), from 5% to 95% within 0.7 min, keep at 95% for 0.4 min, keep at 5% within 0.4 min; Flow rate: 1.5 mL/min; Wavelength: 220 nm

**Table 2.** Preparative HPLC separation methods

<u>Method</u>	<b>Conditions</b>
<b>1</b>	Column: YMC-Actus Triart C18 150 $\times$ 30 mm, 5 $\mu$ m. Mobile phase: MeCN in water (0.075% TFA), from 22% to 52% in 11 min; Flow rate: 25 mL/min. Wavelength: 220 nm
<b>2</b>	Column: YMC-Actus Triart C18 150 $\times$ 30 mm, 5 $\mu$ m. Mobile phase: MeCN in water (0.075% TFA), from 25% to 45% in 11 min; Flow rate: 25 mL/min. Wavelength: 220 nm
<b>3</b>	Column: YMC-Actus Triart C18 150 $\times$ 30 mm, 5 $\mu$ m. Mobile phase: MeCN in water (0.075% TFA), from 27% to 47% in 11 min; Flow rate: 25 mL/min. Wavelength: 220 nm
<b>4</b>	Column: Phenomenex Gemini C18 200 $\times$ 25 mm, 10 $\mu$ m. Mobile phase: MeCN in water (0.05% ammonia solution), from 41% to 61% in 10 min; Flow rate: 25 mL/min. Wavelength: 220 nm
<b>5</b>	Column: YMC-Actus Triart C18 150 $\times$ 30 mm, 5 $\mu$ m. Mobile phase: MeCN in water (0.075% TFA), from 20% to 40% in 11 min; Flow rate: 25 mL/min. Wavelength: 220 nm

<u>Method</u>	<b>Conditions</b>
6	Column: Phenomenex Luna 150x25mm, 10 $\mu$ m. Mobile phase: acetonitrile in water (0.05% HCl), from 10% to 40% in 12 min; Flow rate: 25 mL/min. Wavelength: 220 nm
7	Column: YMC-pack ODS-AQ 150 x 30mm, 5 $\mu$ m. Mobile phase: acetonitrile in water (0.075% TFA), from 20% to 35% in 12 min; Flow rate: 25 mL/min. Wavelength: 220 nm

**Table 3.** Chiral SFC separation methods

<u>Method</u>	<b>Conditions</b>
1	Column: Chiralpak AD 250×30 mm I.D., 5 $\mu$ m; Mobile phase: Supercritical CO <sub>2</sub> /MeOH (0.2% NH <sub>3</sub> ·H <sub>2</sub> O) = 80/20; Flow rate: 60 mL/min; Wavelength: 220 nm
2	Column: Chiralpak AD 250×30 mm I.D., 20 $\mu$ m; Mobile phase: Supercritical CO <sub>2</sub> /EtOH (0.2% NH <sub>3</sub> ·H <sub>2</sub> O) = 65/35; Flow rate: 80 mL/min; Wavelength: 220 nm
3	Column: Chiralpak OJ 300x50mm, 10 $\mu$ m; Mobile phase: A: Supercritical CO <sub>2</sub> , B: MeOH (0.1%NH <sub>3</sub> ·H <sub>2</sub> O), A:B =75:25 at 200 mL/min; Wavelength: 220 nm
4	Column: Chiralpak AD 250×30 mm I.D., 5 $\mu$ m; Mobile phase: Supercritical CO <sub>2</sub> /MeOH (0.2% NH <sub>3</sub> ·H <sub>2</sub> O) = 80/20; Flow rate: 70 mL/min; Wavelength: 220 nm
5	Column: Chiralpak AD 250×30 mm I.D., 5 $\mu$ m; Mobile phase: supercritical CO <sub>2</sub> /EtOH = 65/35; Flow rate: 55 mL/min; Wavelength: 220 nm
6	Column: Chiralcel AD-H 250×30 mm I.D., 5 $\mu$ m. Mobile phase: EtOH (0.1% NH <sub>3</sub> ·H <sub>2</sub> O) in supercritical CO <sub>2</sub> from 40% to 60%, Flow rate: 50 mL/min. Wavelength: 220 nm

**Table 4.** SFC analytical methods

<u>Method</u>	<b>Conditions</b>
1	Column: Chiralpak AD-3 150×4.6 mm I.D., 3 $\mu$ m; Mobile phase: isopropanol (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.5 mL/min; Wavelength: 220 nm
2	Column: Chiralpak AD-3 150×4.6 mm I.D., 3 $\mu$ m; Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 4.0 mL/min; Wavelength: 220 nm
3	Column: Chiralpak AD-3 150×4.6 mm I.D., 3 $\mu$ m; Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.5 mL/min; Wavelength: 220 nm
4	Column: Chiralcel OJ-3 50x4.6mm I.D., 3 $\mu$ m Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 4 mL/min; Wavelength: 220 nm

<b>Method</b>	<b>Conditions</b>
<b>5</b>	Column: Chiralpak AS-H 150×4.6 mm I.D., 5 μm; Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> , from 5% to 40%; Flow rate: 3 mL/min; Wavelength: 220 nm
<b>6</b>	Column: Chiralpak AD-H 250×4.6 mm I.D., 5 μm Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.35 mL/min; Wavelength: 220 nm
<b>7</b>	Column: Chiralpak AS-H 250×4.6 mm I.D., 5 μm Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.35 mL/min; Wavelength: 220 nm
<b>8</b>	Column: Chiralcel OJ-H 250×4.6 mm I.D., 5 μm Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.35 mL/min; Wavelength: 220 nm
<b>9</b>	Column: Chiralpak AS-H 250×4.6 mm I.D., 5 μm Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% - 40%; Flow rate: 2.35 mL/min. Wavelength: 220 nm
<b>10</b>	Column: Chiralpak AD-3 150×4.6 mm I.D., 3 μm; Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 4.0 mL/min; Wavelength: 220 nm
<b>11</b>	Column: Chiralcel AD-H 250×4.6 mm I.D., 5 μm. Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.35 mL/min; Wavelength: 220 nm
<b>12</b>	Column: Chiralcel OD-H 150×4.6 mm I.D., 5 μm Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.35 mL/min; Wavelength: 254 nm
<b>13</b>	Column: Chiralpak AS-3 150×4.6 mm I.D., 3 μm Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.5 mL/min; Wavelength: 220 nm
<b>14</b>	Column: Chiralpak AD-3 50×4.6 mm I.D., 3 μm Mobile phase: MeOH (0.05% DEA) in CO <sub>2</sub> from 5% to 40%; Flow rate: 4 mL/min; Wavelength: 220 nm
<b>15</b>	Column: Chiralcel OJ-3 50×4.6 mm I.D., 3 μm Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 4 mL/min; Wavelength: 220 nm
<b>16</b>	Column: Chiralpak AS-H 150×4.6 mm I.D., 5 μm Mobile phase: EtOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 3 mL/min; Wavelength: 220 nm
<b>17</b>	Column: Chiralpak AS-H 150×4.6 mm I.D., 5 μm Mobile phase: MeOH (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 3 mL/min; Wavelength: 220 nm
<b>18</b>	Column: Chiralcel OJ-H 250×4.6 mm I.D., 5 μm; Mobile phase: methanol (0.05% DEA) in supercritical CO <sub>2</sub> from 5% to 40%; Flow rate: 2.5 mL/min; Wavelength: 300 nm

**6-[(1,3-Dimethyl-azetid-3-yl)-methyl-amino]-4(R)-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (11a).** A mixture of paraformaldehyde (0.016 g, 0.053 mmol) in MeOH (10 mL) and AcOH (1 mL) was heated at reflux overnight. The reaction mixture was cooled to ambient temperature and 4-methyl-6-(3-methyl-azetid-3-ylamino)-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (intermediate obtained at Step D during preparation of compound **22**, 0.020 g, 0.053 mmol) was added. The reaction mixture was stirred for 2 h. Sodium cyanoborohydride (0.013 g, 0.212 mmol) was added and the reaction mixture was stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (Table 2, Method 3) to give 6-[(1,3-dimethyl-azetid-3-yl)-methyl-amino]-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (0.015 g, 0.036 mmol, 68%) as a white solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 7.51 (m, 4H), 7.40 (m, 1H), 7.06 (m, 2H), 4.64 (m, 2H), 3.84 (m, 4H), 2.76 (s, 3H), 2.35 (s, 3H), 1.49 (m, 6H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.689 min.; MS *m/z*: 406 [M+H]<sup>+</sup>.

Racemic 6-[(1,3-dimethyl-azetid-3-yl)-methyl-amino]-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (0.12 g, 0.30 mmol) was separated by SFC (Table 3, Method 2) to give two isomers. Each isomer was treated with DCM (3 mL) and TFA (0.5 mL) and the reaction mixture was stirred at ambient temperature for 3 h. The solvent was removed *in vacuo* to give: 6-[(1,3-dimethyl-azetid-3-yl)-methyl-amino]-4(R)-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (0.068 g, 39%). <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 7.51 (m, 4H), 7.41 (m, 1H), 7.07 (m, 2H), 4.91 (m, 1H), 4.65 (m, 2H), 3.82 (m, 1H), 3.76 (m, 1H), 3.68 (m, 1H), 3.58 (m, 1H), 2.76 (s, 3H), 2.34 (s, 3H), 1.49 (m, 6H); LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.797 min.; MS *m/z*: 406.2 [M+1]<sup>+</sup>. SFC (Table 4, Method 2) R<sub>t</sub> = 1.693 min.

**(S)-2-Trifluoromethanesulfonyloxy-propionic acid ethyl ester.** To a solution of (S)-ethyl lactate (80 g, 677 mmol) in DCM (800 mL) was added trifluoromethanesulfonic anhydride (210 g, 745 mmol) at 0 °C dropwise. The solution was stirred for 15 min at 0 °C and then pyridine (58.9 g, 745 mmol) was added dropwise. The suspension was stirred for 15 min at 0 °C and the solvent was removed *in vacuo*. To the residue was added water (800 mL) and the aqueous solution was extracted with petroleum ether (3 x 800 mL). The combined organic layer was washed with brine (2 x 1500 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give (S)-2-trifluoromethanesulfonyloxy-propionic acid ethyl ester (150 g, 89%) as a brown liquid, which was used in the next step directly without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.14 - 5.28 (m, 1H) 4.21 - 4.35 (m, 1H) 1.63 - 1.73 (m, 3H) 1.25 - 1.37 (m, 3H).

**(R)-6-[(1,3-Dimethyl-azetid-3-yl)-methyl-amino]-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride (11b).** *Step A.* To a suspension of 6-nitro-4H-benzo[1,4]oxazin-3-one (intermediate obtained at Step A during preparation of compound **13r** in previous report,<sup>1</sup> 55 g, 283 mmol) in THF (1100 mL) was added KHMDS (283 L, 283 mmol, 1 M) at 0 °C, and the reaction mixture was stirred at 0 °C

for 30 min. Then (*S*)-2-trifluoromethanesulfonyloxy-propionic acid ethyl ester (142 g, 567 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 °C then warmed to ambient temperature and stirred for 2 h. Water (1000 mL) was added and the suspension was extracted with EtOAc (3 x 1000 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to give (*R*)-2-(6-nitro-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester as a yellow oil (80.0 g, 96%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.96-7.94 (m, 1H), 7.76 (d, *J* = 2.8 Hz, 1H), 7.12 (d, *J* = 9.2 Hz, 1H), 5.37-5.32 (q, *J* = 7.1 Hz, 1H), 4.78-4.68 (m, 2H), 4.28-4.23 (m, 2H), 1.68 (d, *J* = 7.6 Hz, 3H), 1.28-1.24 (t, *J* = 7.2 Hz, 3H). TLC: R<sub>f</sub> = 0.58 (eluting with 50% EtOAc in petroleum ether). SFC (Table 4, Method 6), R<sub>t</sub> = 5.39 min. [α]<sub>20</sub><sup>D</sup> = 66 (C = 0.001 g/mL in MeOH).

*Step B.* A solution of (*R*)-2-(6-nitro-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (80.0 g, 272.0 mmol) and Lawesson reagent (66 g, 163.0 mmol) in toluene (1000 mL) was heated at 120 °C for 3 h. The solvent was concentrated *in vacuo* and the residue purified by chromatography on silica gel (eluting with 3% EtOAc in petroleum ether) to give (*R*)-2-(6-nitro-3-thioxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (75.0 g, 89%) as a yellow solid. TLC: R<sub>f</sub> = 0.40 (eluting with 20% EtOAc in petroleum ether). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.05-8.02 (m, 1H), 7.87-7.86 (d, *J* = 2.4 Hz, 1H), 7.18-7.11 (d, *J* = 7.2 Hz, 1H), 6.72-6.71 (m, 1H), 5.12-5.03 (q, *J* = 15.6 Hz, 2H), 4.31-4.25 (m, 2H), 1.77-1.75 (d, *J* = 7.6 Hz, 3H), 1.28-1.21 (t, *J* = 7.2 Hz, 3H). SFC (Table 4, Method 6), R<sub>t</sub> = 4.045 min. [α]<sub>20</sub><sup>D</sup> = 44 (C = 0.001 g/mL in MeOH).

*Step C.* To a solution of (*R*)-2-(6-nitro-3-thioxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (150.0 g, 483.0 mmol) in EtOH (1500 mL) was added hydrazine hydrate (48.4 g, 967.0 mmol, 98%) and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was filtered and the filtrate was washed with EtOH (3 x 100 ml) to give (*R*)-4-methyl-6-nitro-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (100.0 g, 79%) as a yellow solid. TLC: R<sub>f</sub> = 0.50 (eluting with EtOAc). SFC (Table 4, Method 7) R<sub>t</sub> = 3.193 min. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 10.92 (s, 1H), 7.99-7.98 (d, *J* = 2.8 Hz, 1H), 7.89-7.86 (m, 1H), 7.24-7.21 (d, *J* = 8.8 Hz, 1H), 5.01-4.98 (q, *J* = 6.8 Hz, 1H), 4.83-4.75 (m, 2H), 1.37-1.35 (d, *J* = 6.8 Hz, 3H). [α]<sub>20</sub><sup>D</sup> = -245 (C = 0.001 g/mL in MeOH), e.e. 77%. (*R*)-4-Methyl-6-nitro-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (33 g, 142 mmol, e.e. 77%) was recrystallized in MeOH (2.1 L) to give (*R*)-4-methyl-6-nitro-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (26 g, 112 mmol, yield 79%, e.e. 97%) as a yellow solid. SFC (Table 4, Method 7), R<sub>t</sub> = 3.063 min.

*Step D.* To a solution of (*R*)-4-methyl-6-nitro-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (50 g, 191 mmol) and ammonium chloride (102 g, 1907 mmol) in MeOH (700 mL) and THF (700 mL) was added zinc powder (125 g, 1907 mmol) portionwise. The reaction mixture was stirred at 50 °C for 16 h then cooled to ambient temperature. The reaction mixture was filtered and the filter cake was washed with hot MeOH (3 x 1 L). The organic layers were combined and concentrated *in vacuo*. The residue was washed with THF (3 x 500 mL) and the organic layers combined and concentrated *in vacuo* to give (*R*)-6-amino-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (50 g, 113%

containing residual  $\text{NH}_4\text{Cl}$ ) as a brown solid which was used without further purification. TLC:  $R_f = 0.30$  (eluting with 10% MeOH in DCM).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  6.69-6.66 (m, 1H), 6.43-6.42 (d,  $J = 2.0$  Hz, 1H), 6.18-6.15 (m, 1H), 4.83 (s, 1H), 4.53-4.50 (m, 1H), 4.49-4.43 (m, 2H), 1.33-1.31 (d,  $J = 6.4$  Hz, 3H).

*Step E.* A mixture of (*R*)-6-amino-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (50 g, 172 mmol), 1-benzhydryl-3-methylazetid-3-yl methanesulfonate (95 g, 258 mmol) and  $\text{K}_2\text{CO}_3$  (47.6 g, 344 mmol) in *i*PrOH (1 L) was stirred at 90 °C for 16 h. The reaction mixture was cooled to ambient temperature, concentrated *in vacuo* and the residue was dissolved in water (1 L) and extracted with EtOAc (3 x 500 mL). The organic layers were combined, dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 30-60% EtOAc in petroleum ether) to give (*R*)-6-(1-benzhydryl-3-methyl-azetid-3-ylamino)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaz-a-phenanthren-3-one (31 g, 39%) as a yellow solid. SFC (Table 4, Method 5),  $R_t = 4.361$  min.)  $R_t = 4.36$  min. TLC:  $R_f = 0.60$  (eluting with EtOAc).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.47 (s, 1H), 7.43-7.41 (m, 4H), 7.30-7.27 (m, 4H), 7.26- 7.17 (m, 2H), 6.79-6.77 (d,  $J = 9.2$  Hz, 1H), 6.07-6.04 (m, 2H), 4.62-4.53 (m, 1H), 4.50-4.43 (m, 3H), 3.30-3.27 (m, 2H), 3.17-3.15 (m, 2H), 1.63 (s, 3H), 1.47-1.45 (d,  $J = 6.4$  Hz, 3H).

*Step F.* The solution of (*R*)-6-(1-benzhydryl-3-methyl-azetid-3-ylamino)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (20 g, 42.8 mmol) and  $\text{PdOH}_2$  (10 g, 71.2 mmol) in MeOH (400 mL) and HCl (2 mL) was stirred at 50 °C under 50 psi  $\text{H}_2$  for 48 h. The reaction mixture was cooled at ambient temperature, filtered and the filter cake was washed by hot MeOH (3 x 100 mL). The filtrate was concentrated *in vacuo* to give (*R*)-4-methyl-6-(3-methyl-azetid-3-ylamino)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one as a brown solid (18 g, 99%) which was used without further purification. TLC:  $R_f = 0.21$  (eluting with 10% MeOH in DCM). LC/MS (Table 1, Method 5)  $R_t = 0.525$  min.; MS  $m/z$ : 301  $[\text{M}+\text{H}]^+$ .

*Step G.* A mixture of (*R*)-4-methyl-6-(3-methyl-azetid-3-ylamino)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (9 g, 21.21 mmol) and paraformaldehyde (3.82 g, 127 mmol) in MeOH (300 mL) and AcOH (30 mL) was stirred at ambient temperature for 0.5 hour.  $\text{NaBH}_3\text{CN}$  (4.0 g, 63.6 mmol) was added and the reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on basified silica gel (eluting with 10% MeOH in DCM) to give (*R*)-6-[(1,3-dimethyl-azetid-3-yl)-methyl-amino]-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaz-a-phenanthren-3-one (6 g, 86 %) as a brown solid.  $^1\text{H NMR}$  ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta$  10.73 (s, 1H), 6.82-6.80 (d,  $J = 8.4$  Hz, 1H), 6.25-6.24 (d,  $J = 2.4$  Hz, 1H), 6.09-6.06 (m, 1H), 4.81-4.80 (q,  $J = 6.8$  Hz, 1H), 4.51-4.44 (m, 2H), 3.73-3.69 (m, 2H), 3.37-3.35 (m, 2H), 2.61 (s, 3H), 2.47 (s, 3H), 1.40 (s, 3H), 1.28-1.25 (d,  $J = 6.8$  Hz, 3H). LC/MS (Table 1, Method 6)  $R_t = 0.967$  min.; MS  $m/z$ : 330  $[\text{M}+\text{H}]^+$ .

*Step H.* To a mixture of (*R*)-6-[(1,3-dimethyl-azetid-3-yl)-methyl-amino]-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (3 g, 9.11 mmol) in DCM (40 mL) and MeOH (20 mL) was added *tetra*-*n*-butylammonium tribromide (6.59 g, 13.66 mmol)

portionwise. The reaction mixture was stirred at ambient temperature for 16 h then saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (10 mL) was added to quench the reaction and aqueous sodium bicarbonate (5 mL) was added to neutralize the mixture. The mixture was concentrated *in vacuo* and the residue was purified by basified silica gel column chromatography (eluting with 10% MeOH in DCM) to give (R)-7-bromo-6-[(1,3-dimethyl-azetidino-3-yl)-methyl-amino]-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (3 g, 81%) as a white solid. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 10.80 (s, 1H), 7.24 (s, 1H), 7.01 (s, 1H), 4.98-4.93 (q, *J* = 6.5 Hz, 1H), 4.59 (s, 2H), 3.73-3.50 (m, 4H), 2.63 (s, 3H), 2.48 (s, 3H), 1.53 (s, 3H), 1.28-1.27 (d, *J* = 6.8 Hz, 3H). LC/MS (Table 1, Method 6), R<sub>t</sub> = 1.061 min.; MS *m/z*: 410 [M+H]<sup>+</sup>. SFC (Table 4, Method 6), R<sub>t</sub> = 5.174 min. [α]<sub>20</sub><sup>D</sup> = -212 (C = 0.001 g/mL in MeOH).

*Step I.* A mixture of (R)-7-bromo-6-[(1,3-dimethyl-azetidino-3-yl)-methyl-amino]-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.1 g, 0.245 mmol), 2-fluorophenylboronic acid (0.041 g, 0.294 mmol), K<sub>2</sub>CO<sub>3</sub> (0.068 g, 0.490 mmol) and PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.039 g, 0.049 mmol) in 1,4-dioxane (6 mL) and water (1 mL) was stirred at 90 °C for 3 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by preparative HPLC (Table 2, Method 6) to give (R)-6-[(1,3-dimethyl-azetidino-3-yl)-methyl-amino]-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride (compound **11b**, 0.033 g, 29%) as a solid. LC/MS (Table 1, Method 4) R<sub>t</sub> = 2.100 min.; *m/z*: 424 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.43 (m, 2H), 7.30 (m, 1H), 7.34 (m, 1H), 6.95 (m, 2H), 4.95 (m, 1H), 4.64 (m, 2H), 3.93 (m, 1H), 3.87 (m, 1H), 3.80 (m, 1H), 3.71 (m, 1H), 2.61 (m, 6H), 1.50 (m, 6H). SFC (Table 4, Method 7) R<sub>t</sub> = 3.720 min.

**(R)-6-((3R,4R)-1,3-Dimethyl-piperidin-4-yl)-7-(3-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (17b).** Prepared according to the procedure of compound **17i**, step C, using (3-fluorophenyl)boronic acid (3 equiv), potassium carbonate (3 equiv), PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.2 equiv) at 90 °C overnight, 0.022 g, 43%, as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.44 (m, 1H), 7.12 (m, 3H), 6.83 (s, 1H), 6.91 (m, 1H), 4.92 (m, 1H), 4.61 (m, 2H), 3.20 (m, 1H), 2.97 (m, 1H), 2.33-2.53 (m, 7H), 1.80 (m, 2H), 1.47 (d, *J* = 6.40 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.771 min; MS *m/z*: 423 [M+H]<sup>+</sup>. SFC (Table 4, Method 9) R<sub>t</sub> = 5.612 min.

**(R)-6-((3R,4R)-1,3-Dimethyl-piperidin-4-yl)-7-(4-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (17c).** Prepared according to the procedure of compound **17i**, step C, using (4-fluorophenyl)boronic acid (1.1 equiv) and PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.1 equiv) at 90 °C overnight, 0.025 g, 48%, as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.31-7.27 (m, 2H), 7.18-7.14 (m, 2H), 6.89 (s, 1H), 6.82 (s, 1H), 4.65-4.57 (m, 3H), 3.25-3.12 (m, 2H), 2.92-2.89 (m, 1H), 2.47-2.33 (m, 6H), 1.75 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H), 0.90-0.84 (m, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.754 min; MS *m/z*: 423 [M+H]<sup>+</sup>. SFC (Table 4, Method 17) R<sub>t</sub> = 2.824 min.

**(R)-6-((3R,4R)-1,3-Dimethyl-piperidin-4-yl)-4-methyl-7-o-tolyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (17d).** Prepared according to the procedure of compound **17l**, step C, using (2-methylphenyl)boronic acid (1.1 equiv), PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.1 equiv) at 90 °C overnight; 0.040 g, 78%, as a yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.80 (s, 1H), 7.30-7.22 (m, 3H), 7.13-7.06 (m, 1H), 6.91 (s, 1H), 6.71-6.65 (m, 1H), 4.98 (m, 1H), 4.67-4.57 (m, 2H), 3.20-2.75 (m, 8H), 2.00 (m, 3H), 1.75 (m, 3H), 1.35-1.33 (m, 3H), 0.86-0.77 (m, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.788 min; MS *m/z*: 419 [M+H]<sup>+</sup>. SFC (Table 4, Method 15) R<sub>t1</sub> = 0.937 min, R<sub>t2</sub> = 1.086 min (atropisomers).

**(R)-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-4-methyl-7-p-tolyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (17e).** Prepared according to the procedure of compound **17l**, step C, using *p*-tolylboronic acid (1.5 equiv), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.1 equiv) at 95 °C overnight; 0.02 g, 39%, as a yellow solid. SFC (Table 4, Method 16) R<sub>t</sub> = 3.099 min. LC/MS (Table 1, Method 4, analyzing at wavelength 220 & 254 nm) R<sub>t</sub> = 2.211 min.; MS *m/z*: 419 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.89 (s, 1H), 6.84 (s, 1H), 4.63 (m, 3H), 3.59 (m, 1H), 3.37 (m, 1H), 3.26 (m, 1H), 3.06 (m, 1H), 2.81 (s, 3H), 2.51 (m, 2H), 2.40 (s, 3H), 1.93 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 7.6 Hz, 3H)

**(R)-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-7-(3-methoxy-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triazaphenanthren-3-one (17f).** Prepared according to the procedure of compound **17l**, step C, using (3-methoxyphenyl)boronic acid (1.5 equiv) and PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.2 equiv) at 90 °C for 2 h, 0.0523 g, 70%, as a brown solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.36 (t, *J* = 8.0 Hz, 1H), 6.97 (m, 1H), 6.91 - 6.82 (m, 4H), 4.94 (m, 1H), 4.68 - 4.59 (m, 2H), 3.83 (s, 3H), 3.53 (m, 1H), 3.41 - 3.36 (m, 1H), 3.21 (m, 1H), 2.97 (m, 1H), 2.81 (m, 1H), 2.77 (s, 3H), 2.46 (m, 1H), 2.02 - 1.86 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.6 Hz, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.383 min; MS *m/z*: 435 [M+H]<sup>+</sup>. SFC (Table 4, Method 14) R<sub>t</sub> = 1.417 min.

**(R)-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-7-(4-methoxy-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (17g).** Prepared according to the procedure of compound **17l**, step C, using (4-methoxyphenyl)boronic acid (2 equiv), heating at 100 °C overnight; 0.018 g, 42%, as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.18 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.87 (s, 1H), 6.79 (s, 1H), 4.64-4.63 (m, 1H), 4.60-4.56 (m, 2H), 3.83 (s, 3H), 3.20-3.167 (m, 2H), 2.88-2.85 (m, 1H), 2.43 (s, 3H), 2.37-2.30 (m, 3H), 1.77-1.69 (m, 2H), 1.47-1.46 (m, 3H), 0.88-0.83 (m, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 2.108 min.; MS *m/z*: 435 [M+H]<sup>+</sup>. SFC: (Table 4, Method 8) R<sub>t</sub> = 7.879 min.

**(3R,4R)-3-Methyl-4-[(R)-4-methyl-3-oxo-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-piperidine-1-carboxylic acid *tert*-butyl ester.** A mixture of (3R,4R)-4-((R)-7-bromo-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-3-methyl-piperidine-1-carboxylic acid *tert*-butyl ester (intermediate obtained at Step G during preparation of compound

**17a**, 0.150 g, 0.304 mmol), 4,4,5,5,4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (0.232 g, 0.912 mmol), PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> (0.044 g, 0.061 mmol) and KOAc (0.090 g, 0.912 mmol) in EtOH (5 mL) was heated at 90 °C for 16 h. The reaction was cooled to ambient temperature. The solvent was removed *in vacuo* and the residue was purified by prep-TLC (eluting with 50% EtOAc in petroleum ether) to give (3*R*,4*R*)-3-methyl-4-[(*R*)-4-methyl-3-oxo-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3,4,10-tetrahydro-9-oxa-1,2,4*a*-triazaphenanthren-6-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (0.090 g, 55%) as a pale solid. LC/MS (Table 1, Method 7) R<sub>t</sub> = 0.967 min; MS *m/z*: 563 [M+Na]<sup>+</sup>.

**(*R*)-7-(2,6-Difluoro-phenyl)-6-((3*R*,4*R*)-1,3-dimethyl-piperidin-4-yl)-4-methyl-2,10-dihydro-9-oxa-1,2,4*a*-triazaphenanthren-3-one (17h).** Prepared according to the procedure of compound **17a** (Steps H-J). *Step H*: using (3*R*,4*R*)-3-methyl-4-[(*R*)-4-methyl-3-oxo-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,3,4,10-tetrahydro-9-oxa-1,2,4*a*-triazaphenanthren-6-yl]-piperidine-1-carboxylic acid (1 equiv), 2-bromo-1,3-difluoro-benzene (1.5 equiv), sodium carbonate (2.5 equiv) in 1,4-dioxane (78 vol equiv) and water (18 vol equiv) with PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.3 equiv) and heated at 90 °C overnight, 0.005 g, 18%, as a white solid.

*Step I*: HCl (4M in EtOAc, 2.5 equiv) at ambient temperature for 1 h, 0.005 g, 100%, as a pale solid.

*Step J*: paraformaldehyde (10 equiv) at ambient temperature for 1 h, NaBH<sub>3</sub>CN (2.4 equiv), 0.0041 g, 79%, as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): 7.50 (m, 1H), 7.13 (m, 2H), 6.96 (s, 1H), 6.89 (s, 1H), 4.96 (m, 1H), 4.67 (m, 2H), 3.58 (m, 1H), 3.09 (m, 3H), 2.82 (s, 3H), 2.51 (m, 2H), 1.96 (m, 2H), 1.51 (d, *J* = 6.40 Hz, 3H), 0.94 (m, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.656 min.; MS *m/z*: 441 [M+H]<sup>+</sup>. SFC (Table 4, Method 3) R<sub>t</sub> = 4.708 min.

**(*R*)-6-((3*R*,4*R*)-1,3-Dimethyl-piperidin-4-yl)-7-(3,4-dimethoxyphenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4*a*-triazaphenanthren-3-one (17i).** Prepared according to the procedure of compound **17l**, step C, using (3,4-dimethoxyphenyl)boronic acid (2 equiv) and PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.1 equiv) at 100 °C overnight, 0.012 g, 27%, as a solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.00 (d, *J*=8.0 Hz, 1H), 6.89 - 6.79 (m, 4H), 4.64 - 4.62 (m, 1H), 4.60 (d, *J*=5.0 Hz, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.21 (d, *J*=9.5 Hz, 2H), 2.89 (d, *J*=10.8 Hz, 1H), 2.44 (br. s., 3H), 2.41 - 2.23 (m, 3H), 1.88 - 1.66 (m, 2H), 1.47 (d, *J*=6.5 Hz, 3H), 0.86 (d, *J*=7.5 Hz, 3H). LCMS (Table 1, Method 4) R<sub>t</sub> = 2.008 min; MS *m/z*: 465 [M+H]<sup>+</sup>.

**(*R*)-7-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-6-((3*R*,4*R*)-1,3-dimethyl-piperidin-4-yl)-4-methyl-2,10-dihydro-9-oxa-1,2,4*a*-triazaphenanthren-3-one (17j).** Prepared according to the procedure of compound **17l**, step C, using (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid (2 equiv) and heated at 100 °C overnight, 0.019 g, 34%, as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 6.86 (d, *J* = 8 Hz, 2H), 6.77 (s, 1H), 6.72-6.71 (m, 2H), 4.87 (m, 1H), 4.63-4.55 (m, 2H), 4.27 (s, 4H), 3.25-3.22 (m, 2H), 2.97-2.94 (m, 1H), 2.15 (s, 3H), 2.39-2.33 (m, 3H), 1.84-1.72 (m, 2H), 1.47-1.45 (m, 3H), 0.89-0.84 (m, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.672 min.; MS *m/z*: 463 [M+H]<sup>+</sup>. SFC (Table 4, Method 16) R<sub>t</sub> = 1.586 min.

**(R)-6-((3R,4R)-1,3-Dimethyl-piperidin-4-yl)-7-(2-fluoro-4-methyl-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (17k).** To a mixture of (R)-7-bromo-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (intermediate obtained at Step B during preparation of compound **17l**, 1.25 g, 3.07 mmol), (2-fluoro-4-methylphenyl)boronic acid (0.52 g, 3.38 mmol), potassium carbonate (0.848 g, 6.16 mmol) in 1,4-dioxane (12 mL) and water (2 mL) was added PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> adduct (0.251 g, 0.307 mmol) and the reaction mixture was heated at 90 °C overnight. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 0-20% MeOH in DCM) to give (R)-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-7-(2-fluoro-4-methyl-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (1.08 g, 81%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.11-6.99 (m, 3H), 6.93 (s, 1H), 6.77 (s, 1H), 4.90-4.94 (m, 1H), 4.64-4.56 (m, 2H), 2.99-2.97 (m, 1H), 2.80 (m, 2H), 2.63-2.60 (m, 1H), 2.40 (s, 3H), 2.30-2.24 (m, 1H), 2.18 (s, 3H), 1.98-1.95 (m, 1H), 1.87-1.85 (m, 1H), 1.59-1.56 (m, 2H), 1.48 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.2 Hz, 3H). LC/MS (Table 1, Method 7) R<sub>t</sub> = 0.746 min; MS (ESI): *m/z* 437 [M+H]<sup>+</sup>. The product was treated with HCl (4M in EtOAc, 10 mL) and stirred at ambient temperature for 0.5 h. The mixture was concentrated *in vacuo* and the residue was re-crystallized from 15% DCM in EtOAc to give (R)-6-((3R,4R)-1,3-dimethyl-piperidin-4-yl)-7-(2-fluoro-4-methyl-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride (compound **17k**, 1.003 g, 86%). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.16-7.12 (m, 1H), 7.09-7.02 (m, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 4.92-4.91 (m, 1H), 4.66-4.58 (m, 2H), 3.58 (d, *J* = 11.6 Hz, 1H), 3.31-3.24 (m, 1H), 3.06-3.03 (m, 2H), 2.93-2.87 (m, 1H), 2.80 (s, 3H), 2.53-2.50 (m, 1H), 2.40 (s, 3H), 1.91 (d, *J* = 11.6 Hz, 2H), 1.48 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.769 min; MS (ESI): *m/z* 437 [M+H]<sup>+</sup>. SFC (Table 4, Method 5), R<sub>t</sub> = 3.120 min.

**3-Methyl-3-(1-trifluoromethanesulfonyloxy-vinyl)-azetidine-1-carboxylic acid *tert*-butyl ester.** *Step A.* To a solution of 3-methyl-azetidine-1,3-dicarboxylic acid mono-*tert*-butyl ester (Alfa, 10.0 g, 46.5 mmol) in THF (200 mL) was added DIEA (16.86 g, 139 mmol) and HATU (21.20 g, 55.8 mol) and the reaction mixture was stirred at ambient temperature for 1.5 h. *N,O*-Dimethylhydroxylamine (4.98 g, 51.1 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with aqueous NH<sub>4</sub>Cl (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 15% EtOAc in petroleum ether) to give 3-(methoxy-methyl-carbamoyl)-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (10.4 g, 87%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.21 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), 3.61 (d, *J* = 8.4 Hz, 2H), 3.17 (s, 3H), 1.56 (s, 3H), 1.43 (s, 9H). TLC: R<sub>f</sub> = 0.30 (eluting with 25% EtOAc in petroleum ether).

*Step B.* To a solution of 3-(methoxy-methyl-carbamoyl)-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (6.9 g, 26.7 mmol) in THF (100 mL) at -78 °C was added a

solution of methymagnesium chloride (3M in toluene, 53.4 mL, 160 mmol). The reaction mixture was stirred at -78 °C for 1 h then warmed to ambient temperature gradually and stirred for 1 h. The reaction mixture was quenched by the addition of aqueous NH<sub>4</sub>Cl solution (40 mL) and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to give 3-acetyl-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (4 g, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.16 (d, *J* = 8.4 Hz, 2H), 3.64 (d, *J* = 8.4 Hz, 2H), 2.21 (s, 3H), 1.51 (s, 3H), 1.45 (s, 9H). TLC: R<sub>f</sub> = 0.35 (eluting with 25% EtOAc in petroleum ether).

*Step C.* To a -78°C solution of 3-acetyl-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (6.3 g, 29.5 mmol) in toluene (200 mL) was added a solution of KHMDS (1M in THF, 44.3 mL, 44.3 mmol). The reaction mixture was warmed to ambient temperature gradually and stirred for 3 h. The reaction mixture was cooled to -78 °C and a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (15.82 g, 44.3 mmol) in toluene (50 mL) was added. The reaction mixture was warmed to ambient temperature gradually and stirred overnight. The reaction mixture was quenched by the addition of aqueous NH<sub>4</sub>Cl solution (100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 1-10% EtOAc in petroleum ether) to give 3-methyl-3-(1-trifluoromethanesulfonyloxy-vinyl)-azetidine-1-carboxylic acid *tert*-butyl ester (6 g, 59%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.30 (d, *J* = 4.8 Hz, 1H), 5.09 (d, *J* = 4.8 Hz, 1H), 4.06 (d, *J* = 8.4 Hz, 2H), 3.69 (d, *J* = 8.8 Hz, 2H), 1.56 (s, 3H), 1.45 (s, 9H). TLC: R<sub>f</sub> = 0.50 (eluting with 20% EtOAc in petroleum ether).

**(*R*)-4-Methyl-6-[methyl-(3-methyl-azetid-3-yl)-amino]-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (19).** *Step A.* A mixture of 6-bromo-4-methyl-7-trifluoromethyl-2-(2-trimethylsilyl-ethoxymethyl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2.0 g, 4.05 mmol), *tert*-butyl 3-amino azetidine-1-carboxylate (0.904 g, 4.85 mmol), diacetoxypalladium (0.091 g, 0.405 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2.64 g, 8.10 mmol) and BINAP (0.252 g, 0.405 mmol) in toluene (10 mL) was heated at reflux for 10 h. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to give 3-methyl-3-[4-methyl-3-oxo-7-trifluoromethyl-2-(2-trimethylsilyl-ethoxymethyl)-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-ylamino]-azetidine-1-carboxylic acid *tert*-butyl ester (2.2 g, 91%) as a pale yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.16 (s, 1H), 5.96 (br s, 1H), 5.13 (q, *J* = 9.2 Hz, 2H), 4.61 (m, 1H), 4.56 (q, *J* = 13.2 Hz, 2H), 4.41 (br s, 1H), 4.04 (m, 2H), 3.95 (d, *J* = 12.4 Hz, 2H), 3.68 (m, 2H), 1.66 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.46 (s, 9H), 0.99 (m, 2H), 0.02 (s, 9H). LC/MS (Table 1, Method 1) R<sub>t</sub> = 1.458 min.; MS *m/z*: 622 [M+23]<sup>+</sup>.

*Step B.* A mixture of 3-methyl-3-[4-methyl-3-oxo-7-trifluoromethyl-2-(2-trimethylsilyl-ethoxymethyl)-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-ylamin

o]-azetidine-1-carboxylic acid *tert*-butyl ester (0.250 g, 0.417 mmol) and paraformaldehyde (neat, 0.250 g, 8.34 mmol) in *i*PrOH (5 mL) and AcOH (0.5 mL) was stirred at 110 °C for 2 d. The reaction mixture was cooled to ambient temperature and the solvent was removed *in vacuo*. MeOH (5 mL), AcOH (2.5 mL) and NaBH<sub>3</sub>CN (0.524 g, 8.34 mmol) were added. The reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was cooled to ambient temperature and solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 5-10% EtOAc in petroleum ether) to give 3-methyl-3-{methyl-[4-methyl-3-oxo-7-trifluoromethyl-2-(2-trimethylsilylanyl-ethoxymethyl)-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-amino}-azetidine-1-carboxylic acid *tert*-butyl ester (0.135 g, 53%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.25 (s, 1H), 6.72 (s, 1H), 5.10 (m, 2H), 4.65 (m, 1H), 4.66 (q, *J* = 13.2 Hz, 2H), 4.03 (d, *J* = 8.8 Hz, 1H), 3.90 (d, *J* = 12.4 Hz, 1H), 3.66 (t, 2H), 3.58 (t, 2H), 2.68 (s, 3H), 1.48 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.42 (s, 9H), 0.99 (m, 2H), 0.00 (s, 9H). LC/MS (Table 1, Method 2) R<sub>t</sub> = 1.331 min.; MS *m/z*: 636 [M+23]<sup>+</sup>.

*Step C.* To a solution of 3-methyl-3-{methyl-[4-methyl-3-oxo-7-trifluoromethyl-2-(2-trimethylsilylanyl-ethoxymethyl)-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-amino}-azetidine-1-carboxylic acid *tert*-butyl ester (0.586 g, 0.360 mmol) in DCM (4 mL) was added TFA (0.8 mL) and the reaction mixture was stirred at ambient temperature for 1.5 h. The solvent was removed *in vacuo*, 1,4-dioxane (1 mL) and aqueous ammonium hydroxide (25%, 1 mL) were added and the reaction mixture was stirred for 1.5 h at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by HPLC (Table 2, Method 1) and further separated by chiral SFC (Table 3, Method 1) to give (*R*)-4-methyl-6-[methyl-(3-methyl-azetidin-3-yl)-amino]-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (compound 19, 0.033 g, 7%) as a pale solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz): δ 7.31 (s, 1H), 7.10 (s, 1H), 4.93 (m, 1H), 4.67 (q, *J* = 13.2 Hz, 2H), 4.37 (m, 2H), 3.75 (d, *J* = 11.2 Hz, 2H), 2.82 (s, 3H), 1.63 (s, 3H), 1.47 (d, *J* = 6.4 Hz, 3H). LC/MS (Table 1, Method 3) R<sub>t</sub> = 2.319 min.; MS *m/z*: 384 [M+H]<sup>+</sup>. SFC (Table 4, Method 1) R<sub>t</sub>: 6.57 min.

**(*R*)-4-Methyl-6-[methyl-(1,3-dimethyl-azetidin-3-yl)-amino]-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (20).** To a mixture of (*R*)-4-methyl-6-(3-methyl-azetidin-3-ylamino)-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid<sup>1</sup> (0.120 g, 0.250 mmol) in MeOH (5 mL) and AcOH (0.5 mL) was added paraformaldehyde (neat, 0.060 g, 2 mmol). The reaction mixture was stirred at ambient temperature for 30 min then NaBH<sub>3</sub>CN (0.126 g, 2 mmol) was added and the reaction mixture was heated at 50 °C for 5 h. The reaction mixture was cooled to ambient temperature and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC (Table 2, Method 5) and further separated by chiral SFC (Table 3, Method 4) to give (*R*)-4-methyl-6-[methyl-(1,3-dimethyl-azetidin-3-yl)-amino]-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (compound 20, 0.020 g, 12%) as a white solid. LC/MS (Table 1, Method 3) R<sub>t</sub> = 1.672 min; MS *m/z*: 384 [M+H]<sup>+</sup>. SFC (Table 4, Method 3) R<sub>t</sub> = 5.89 min.

**(R)-6-[(1,3-Dimethyl-azetidin-3-yl)-methyl-amino]-4-methyl-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (21).** (R)-4-Methyl-6-(3-methyl-azetidin-3-ylamino)-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride<sup>1</sup> (0.440 g, 1.191 mmol) was dissolved in MeOH (10 mL) and the pH was adjusted to 7 by addition of aqueous NH<sub>3</sub>.H<sub>2</sub>O. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in MeOH (4 mL) and AcOH (0.4 mL). Paraformaldehyde (10 mg/mL in MeOH, 35.8 mL, 11.91 mmol) was added and the reaction mixture was stirred at 70 °C for 2 h. NaBH<sub>3</sub>CN (0.749 g, 11.91 mmol) was added and the reaction mixture was stirred at 70 °C for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0-15% EtOAc in petroleum ether). Further purification by preparative HPLC (Table 2, Method 7) and prep-TLC (eluting with 17% MeOH in EtOAc) gave (R)-6-[(1,3-dimethyl-azetidin-3-yl)-methyl-amino]-4-methyl-7-trifluoromethyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (compound 21, 0.0035 g, 1%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.21 (s, 1H), 6.95 (s, 1H), 4.74 (m, 1H), 4.57 (m, 2H), 4.23 (m, 1H), 4.10 (m, 1H), 3.89 (m, 2H), 2.74 (m, 6H), 1.53 (s, 3H), 1.36 (d, *J* = 6.4 Hz, 3H). LC/MS (Table 1, Method 4) R<sub>t</sub> = 1.289 min.; MS m/z: 398 [M+H]<sup>+</sup>. SFC (Table 4, Method 18) R<sub>t</sub> = 5.23 min.

**1-Benzhydryl-3-methyl-azetidin-3-ol.** To a 0 °C solution of methylmagnesium bromide (3M in ethyl ether, 263 mL, 790 mmol) and THF (800 mL) was added a solution of 1-benzhydryl-azetidin-3-one (75 g, 316 mmol) in THF (300 mL) rapidly with vigorous stirring. The reaction mixture was stirred for 10 min, then warmed to ambient temperature and stirred for 2 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride (1 L), diluted with water (1 L) and extracted with EtOAc (3 x 1 L). The organic portion was washed with brine (500 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 10-20% EtOAc in petroleum ether) to give 1-benzhydryl-3-methyl-azetidin-3-ol (65 g, 81%) as a white solid. TLC: R<sub>f</sub> = 0.40 (eluting with 30% EtOAc in petroleum ether). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.43-7.41 (d, *J* = 7.6 Hz, 4H), 7.29-7.26 (m, 4H), 7.22-7.19 (m, 2H), 4.36 (s, 1H), 3.2-3.19 (d, *J* = 1.8 Hz, 2H), 3.00-2.98 (d, *J* = 7.2 Hz, 2H), 1.53 (s, 3H).

**Methanesulfonic acid 1-benzhydryl-3-methyl-azetidin-3-yl ester.** Methanesulfonyl chloride (57 g, 497 mmol) was added dropwise to a 0 °C solution of 1-benzhydryl-3-methylazetidin-3-ol (70 g, 276 mmol) and triethylamine (53.1 g, 525 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (700 mL) and the reaction mixture was stirred for 3 h. The reaction mixture was filtered and the filter cake was washed with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The organic layers were combined, washed with water (3 x 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo* to give 1-benzhydryl-3-methylazetidin-3-yl methanesulfonate (90 g, 98%) as a brown solid which was used without further purification. TLC: R<sub>f</sub> = 0.57 (eluting with 30% EtOAc in petroleum ether). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 7.45-7.43 (d, *J* = 7.6 Hz, 4H), 7.33-7.29 (m, 4H), 7.28-7.23 (m, 2H), 4.55 (s, 1H), 3.66-3.46 (m, 4H), 3.07 (s, 3H), 1.94 (s, 3H).

**6-(1,3-Dimethyl-azetidin-3-ylamino)-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid (22).** *Step A.* A mixture of  $K_2CO_3$  (0.238 g, 1.722 mmol), 6-amino-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one<sup>1</sup> (0.20 g, 0.861 mmol), and 1-benzhydryl-3-methylazetidin-3-yl methanesulfonate (0.428 g, 1.292 mmol) in propan-2-ol (10 mL) was stirred at 80 °C overnight. The solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0 to 50% EtOAc in petroleum ether) to give 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.234 g, 58%). <sup>1</sup>H NMR (400MHz,  $CDCl_3$ ):  $\delta$  8.05 (br s, 1H), 7.36 (m, 4H), 7.19 (m, 4H), 7.11 (m, 2H), 6.70 (d,  $J = 8.4$  Hz, 1H), 5.97 (m, 2H), 4.53 (q,  $J = 6.8$  Hz, 1H), 4.37 (d,  $J = 12.0$  Hz, 2H), 4.28 (s, 1H), 3.70 (br s, 1H), 3.24 (m, 2H), 3.07 (m, 2H), 1.45 (s, 3H), 1.38 (d,  $J = 6.8$  Hz, 3H). LC/MS (Table 1, Method 1)  $R_t = 0.948$  min; MS  $m/z$ : 468  $[M+H]^+$ .

*Step B.* To a solution of 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.250 g, 0.535 mmol) in DCM (10 mL) and MeOH (10 ml), was added *tetra*-N-butylammonium tribromide (0.258 g, 0.535 mmol) in portions at ambient temperature. The resulting yellow solution was stirred for 0.5 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 50% EtOAc in petroleum ether) to give 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-7-bromo-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.180 g, 62%) as an off-white solid. <sup>1</sup>H NMR ( $CDCl_3$ , 400 MHz):  $\delta$  8.77 (br s, 1H), 7.35 (m, 4H), 7.20 (m, 4H), 7.12 (m, 2H), 7.04 (s, 1H), 5.84 (s, 1H), 4.46 (q,  $J = 6.4$  Hz, 1H), 4.40 (s, 2H), 4.37 (s, 1H), 4.24 (br s, 1H), 3.29 (m, 2H), 3.06 (m, 2H), 1.56 (s, 3H), 1.30 (d,  $J = 6.4$  Hz, 3H). TLC:  $R_f = 0.6$  (eluting with 50% EtOAc in petroleum ether).

*Step C.* To a mixture of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.175 g, 0.214 mmol), 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-7-bromo-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.220 g, 0.403 mmol),  $K_2CO_3$  (0.167 g, 1.208 mmol),  $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$  (0.066 g, 0.081 mmol) and phenylboronic acid (0.123 g, 1.006 mmol) in water (0.5 mL) and 1,4-dioxane (3 mL) was stirred at 100 °C overnight. The mixture was cooled to ambient temperature, the solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0 to 50% EtOAc in petroleum ether) to give 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.120 g, 55%). <sup>1</sup>H NMR ( $CDCl_3$ , 400 MHz):  $\delta$  8.09 (br s, 1H), 7.31 (m, 7H), 7.19 (m, 6H), 7.12 (m, 2H), 6.73 (s, 1H), 5.85 (s, 1H), 4.54 (q,  $J = 6.8$  Hz, 1H), 4.49 (d,  $J = 12.8$  Hz, 2H), 4.32 (s, 1H), 3.96 (br s, 1H), 3.22 (m, 2H), 2.93 (m, 2H), 1.52 (s, 3H), 1.37 (d,  $J = 6.8$  Hz, 3H). TLC:  $R_f = 0.5$  (eluting with 50% EtOAc in petroleum ether).

*Step D.* To a solution of 6-(1-benzhydryl-3-methyl-azetidin-3-ylamino)-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.10 g, 0.18 mmol) in THF (20 mL), MeOH (20 mL), and aqueous HCl (12 N, 0.3 mL) was added  $Pd(OH)_2/C$  (10%, 0.02 g, 0.014 mmol) and the solution was heated at 50 °C under  $H_2$  (55 psi) for 4 h. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was evaporated *in vacuo* to give 4-methyl-6-(3-methyl-azetidin-3-ylamino)-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.08 g, 80%).

thren-3-one (0.095 g, purity 57%, 82%), which was used in the next step directly without further purification. LC/MS (Table 1, Method 1)  $R_t = 0.890$  min; MS  $m/z$ : 378.1  $[M+1]^+$ .

*Step E.* A solution of 4-methyl-6-(3-methyl-azetidino-3-ylamino)-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.095 g, purity 57 %, 0.15 mmol) and paraformaldehyde (0.015 g, 0.45 mmol) in MeOH (10 mL) and HOAc (1 mL) was heated at 80 °C for 2 h. NaBH<sub>3</sub>CN (0.019 g, 0.30 mmol) was added to the solution and the mixture was stirred at 80 °C for 0.5hr. The reaction mixture was cooled to ambient temperature. The solvent was removed *in vacuo* and the residue was washed with aqueous saturated Na<sub>2</sub>CO<sub>3</sub> solution (2 mL). The aqueous phase was extracted with EtOAc (4 x 20 mL). The combined organic layer was dried, filtered and concentrated to give crude 6-(1,3-dimethyl-azetidino-3-ylamino)-2-hydroxymethyl-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.060 g, 0.14 mmol), which was used in the next step without further purification. LC/MS (Table 1, Method 1)  $R_t = 0.924$  min; MS  $m/z$ : 392.1  $[M+1]^+$ .

*Step F.* A solution of 6-(1,3-dimethyl-azetidino-3-ylamino)-2-hydroxymethyl-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.060 g, 0.16 mmol) in NH<sub>4</sub>OH (5 mL) and 1,4-dioxane (5 mL) was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC (Table 2, Method 2) to give 6-(1,3-dimethyl-azetidino-3-ylamino)-4-methyl-7-phenyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one trifluoroacetic acid salt (compound 22, 0.022 g, 27%) as a solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta$  7.44 (m, 5H), 6.84 (s, 1H), 6.03 (d,  $J = 14.8$  Hz, 1H), 4.82 (m, 1H), 4.58 (s, 2H), 4.29 (m, 2H), 4.06 (m, 2H), 2.97 (s, 3H), 1.60 (d,  $J = 5.6$  Hz, 3H), 1.48 (m, 3H); LC/MS (Table 1, Method 4)  $R_t = 1.722$  min; MS  $m/z$ : 392.1  $[M+1]^+$ .

**(R)-6-[(R)-1-(1,3-Dimethyl-azetidino-3-yl)-ethyl]-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (23).** *Step A.* To a mixture of PdCl<sub>2</sub>(dppf) (4.94 g, 6.75 mmol) and 4,4,4',4',5,5,5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (20.58 g, 81 mmol), (R)-6-bromo-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (intermediate obtained at Step D during preparation of compound 17a, 20 g, 67.5 mmol) in 1,4-dioxane (200 mL) was added potassium acetate (13.26 g, 135 mmol) and the reaction mixture was stirred at 90 °C for 4 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 50-100% EtOAc in petroleum ether, then eluting with 1-10% MeOH in EtOAc) to give (R)-4-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (23 g, 99%) as a brown solid. SFC (Table 4, Method 10)  $R_t = 6.51$  min. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.44-7.36 (m, 2H), 7.05-6.95 (m, 1H), 4.85-4.75 (m, 1H), 4.65-4.55 (d,  $J = 1.28$  Hz, 2H), 1.45 (d,  $J = 6.8$  Hz, 3H), 1.35 (s, 12H). LC/MS (Table 1, Method 7)  $R_t = 0.823$  min.; MS  $m/z$ : 344  $[M+H]^+$ .

*Step B.* A mixture of (R)-4-methyl-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2 g, 5.83 mmol), 3-methyl-3-(1-trifluoromethanesulfonyloxy-vinyl)-azetidino-1-carboxylic acid *tert*-butyl ester (3.02 g, 8.74 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.235 g, 11.66 mmol) and Pd(Ph<sub>3</sub>P)<sub>4</sub> (3.37 g, 2.91 mmol) in

1,4-dioxane (20 mL) and water (5 mL) was stirred at 90 °C overnight. The reaction mixture was cooled to ambient temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 0-30% EtOAc in petroleum ether) to give 3-methyl-3-[1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-vinyl]-azetidine-1-carboxylic acid *tert*-butyl ester (0.610 g, 25%) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.10 (br s., 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 1H), 5.33 (s, 1H), 5.10 (s, 1H), 4.74 (m, 1H), 4.67 - 4.56 (d, *J* = 15.2 Hz, 2H), 4.11 (m, 2H), 3.79 (m, 2H), 1.61 (d, *J* = 15.2 Hz, 3H), 1.55 (m, 3H), 1.46 (s, 9H). LC/MS (Table 1, Method 7) *R*<sub>t</sub> = 0.867 min.; *m/z*: 413 [M+H]<sup>+</sup>.

*Step C.* A mixture of 3-methyl-3-[1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-vinyl]-azetidine-1-carboxylic acid *tert*-butyl ester (0.5 g, 1.212 mmol) and Pd/C (10%, 0.258 g, 0.242 mmol) in MeOH (10 mL) was stirred under H<sub>2</sub> at ambient temperature for 1 h. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give 3-methyl-3-[1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-azetidine-1-carboxylic acid *tert*-butyl ester (0.484 g, 96%) as a solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz): δ 8.08 (br s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 4.78 (m, 1H), 4.63 - 4.56 (m, 2H), 3.84 (m, 2H), 3.57 (d, *J* = 8.0 Hz, 1H), 3.35 (d, *J* = 8.0 Hz, 1H), 2.98 (m, 1H), 1.66 - 1.49 (m, 12H), 1.27 (d, *J* = 7.3 Hz, 3H), 1.21 (s, 3H). LC/MS (Table 1, Method 7) *R*<sub>t</sub> = 0.858 min.; MS *m/z*: 415 [M+H]<sup>+</sup>. Chiral SFC separation (Table 3, Method 6) gave two diastereomers: 3-methyl-3-[(*R*)-1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-azetidine-1-carboxylic acid *tert*-butyl ester (diastereomer 1, 0.179 g, 36%, LC/MS (Table 1, Method 7) *R*<sub>t</sub> = 0.868 min.; MS *m/z*: 437 [M+Na]<sup>+</sup>, SFC (Table 4, Method 11) *R*<sub>t</sub> = 9.201 min. and 3-methyl-3-[(*S*)-1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-azetidine-1-carboxylic acid *tert*-butyl ester (diastereomer 2, 0.228 g, 47%, LC/MS (Table 1, Method 7) *R*<sub>t</sub> = 0.872 min.; MS *m/z*: 437 [M+Na]<sup>+</sup>, SFC (Table 4, Method 11) *R*<sub>t</sub> = 9.819 min.

*Step D.* To a solution of 3-methyl-3-[(*R*)-1-((*R*)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-azetidine-1-carboxylic acid *tert*-butyl ester (diastereomer 1, 0.283 g, 0.683 mmol) in AcOH (1 mL) was added a solution of bromine (0.070 mL, 1.366 mmol) in AcOH (1 mL) dropwise and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was quenched by the addition of saturated aqueous Na<sub>2</sub>O<sub>3</sub> solution and aqueous NaHCO<sub>3</sub> solution was added to adjust to pH 7-8. MeOH (5 mL), Et<sub>3</sub>N (0.146 g, 1.439 mmol) and di-*tert*-butyl dicarbonate (0.188 g, 0.864 mmol) were added in sequence and the reaction mixture was stirred at ambient temperature for 1.5 h. The aqueous solution was extracted with EtOAc (3 x 10 mL) and the combined organic phase was washed with saturated brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by prep-TLC (eluting with 50% EtOAc in petroleum ether) to give 3-[(*R*)-1-((*R*)-7-bromo-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (0.128 g, 36%) as a solid.

LC/MS (Table 1, Method 7)  $R_t = 0.913$  min.; MS  $m/z$ : 437  $[M+H-56]^+$  and 439  $[M+H-56]^+$ .  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.26 (br s, 1H), 7.25 (s, 1H), 6.70 (s, 1H), 4.75 - 4.70 (m, 1H), 4.60 (d,  $J = 12.8$  Hz, 2H), 3.98 - 3.91 (m, 2H), 3.55 (m, 2H), 3.44 (d,  $J = 8.4$  Hz, 1H), 1.52 (d,  $J = 6.8$  Hz, 3H), 1.46 (s, 9H), 1.32 - 1.27 (m, 6H).

*Step E.* To a solution of 3-[(*S*)-1-((*R*)-7-bromo-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl)-ethyl]-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (0.08 g, 0.162 mmol), (2-fluorophenyl)boronic acid (0.027 g, 0.195 mmol) and sodium carbonate (0.034 g, 0.324 mmol) in 1,4-dioxane (2.0 mL) and water (0.5 mL) was added  $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$  (0.013 g, 0.016 mmol) and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was cooled to ambient temperature and filtered. The filtrate was partitioned between EtOAc (30 mL) and water (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by prep-TLC (eluting with 5% MeOH in dichloromethane) to give 3-[(*R*)-1-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-ethyl]-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (0.083 g, 100%).  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  8.12 (br s, 1H), 7.37 (m, 1H), 7.08 - 7.26 (m, 3H), 6.84 - 6.91 (m, 1H), 6.79 (m, 1H), 4.73 - 4.87 (m, 1H), 4.59 - 4.68 (m, 2H), 3.57 (m, 1H), 3.44 - 3.51 (m, 1H), 3.33 - 3.41 (m, 1H), 3.25 (m, 1H), 2.86 (m, 1H), 1.55 (d,  $J = 6.8$  Hz, 3H), 1.35 - 1.47 (m, 9H), 1.22 - 1.35 (m, 3H), 1.07 - 1.21 (m, 3H). LC/MS (Table 1, Method 7)  $R_t = 0.883$  min; MS (ESI):  $m/z$  531  $[M+\text{Na}]^+$  and 453  $[M+H-56]^+$ .

*Step F.* A solution of 3-[(*R*)-1-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-ethyl]-3-methyl-azetidine-1-carboxylic acid *tert*-butyl ester (0.073 g, 0.144 mmol) in HCl (4M in EtOAc, 1 mL) was stirred at ambient temperature for 1 h. The reaction mixture was concentrated *in vacuo* to give (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-[(*R*)-1-(3-methyl-azetidin-3-yl)-ethyl]-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.06 g, 100%), which was used directly in the next step without further purification.  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ , 400 MHz):  $\delta$  7.45 (m, 1H), 7.16 - 7.34 (m, 3H), 6.90 - 6.96 (m, 1H), 6.86 (s, 1H), 4.92 - 4.98 (m, 1H), 4.57 - 4.68 (m, 2H), 4.24 (m, 1H), 3.69 - 3.76 (m, 1H), 3.46 - 3.55 (m, 1H), 3.38 (m, 1H), 2.97 (m, 1H), 1.36 - 1.51 (m, 6H), 1.20 - 1.27 (m, 3H). LC/MS (Table 1, Method 7)  $R_t = 0.673$  min; MS (ESI):  $m/z$  409  $[M+H]^+$ .

*Step G.* To a solution of (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-[(*R*)-1-(3-methyl-azetidin-3-yl)-ethyl]-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.04 g, 0.098 mmol) in AcOH (0.5 mL) and MeOH (5 mL) was added paraformaldehyde (0.029 g, 0.979 mmol) and the resulting mixture was stirred at ambient temperature for 1 h.  $\text{NaBH}_3\text{CN}$  (0.015 g, 0.245 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. Aqueous  $\text{NaHCO}_3$  (10 mL) was added and the aqueous solution was extracted with EtOAc (3 x 30 mL). The combined organic phase was dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by prep-HPLC (Table 2, Method 4) to give (*R*)-6-[(*R*)-1-(1,3-dimethyl-azetidin-3-yl)-ethyl]-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (compound **23**, 0.017 g, 40%) as a white solid.  $^1\text{H}$

NMR (CD<sub>3</sub>OD, 400 MHz):  $\delta$  7.40 - 7.48 (m, 1H), 7.15 - 7.32 (m, 3H), 6.91 (s, 1H), 6.84 (s, 1H), 4.83 (m, 1H), 4.58 - 4.69 (m, 2H), 2.87 - 3.19 (m, 3H), 2.73 - 2.87 (m, 2H), 2.10 - 2.22 (m, 3H), 1.50 (m, 3H), 1.25 - 1.35 (m, 3H), 1.13 - 1.23 (m, 3H). LC/MS (Table 1, Method 4)  $R_t$  = 1.858 min; MS  $m/z$ : 423 [M+H]<sup>+</sup>. SFC (Table 4, Method 2)  $R_t$  = 1.592 min.

**(R)-7-(2-Fluoro-phenyl)-4-methyl-6-((S)-1-methyl-pyrrolidin-3-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (24).** *Step A.* To a mixture of

7-bromo-4H-benzo[1,4]oxazin-3-one<sup>1</sup> (59.7 g, 263 mmol) in THF (700 mL) was added KHMDS (1M in THF, 263 mL, 263 mmol) dropwise at 0 °C and the reaction mixture was stirred for 30 min. (S)-Ethyl 2-(((trifluoromethyl)sulfonyl)oxy)propanoate (132 g, 526 mmol) was added and the reaction mixture was allowed to warm to ambient temperature and stirred for 2 h. The reaction mixture was quenched with water (1000 mL). The organic phase was separated and the aqueous solution was extracted with EtOAc (4 x 500 mL). The combined organic phase was washed with brine (1 L), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (eluting with 5-15% EtOAc in petroleum ether) to give (R)-2-(7-bromo-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (80 g, 93%) as a brown liquid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.27-7.23 (m, 2H), 7.22-7.09 (m, 1H), 5.14-5.12 (m, 1H), 4.66 (s, 2H), 4.10-4.05 (m, 2H), 1.46 (d,  $J$  = 6.8 Hz, 3H), 1.16-1.08 (m, 3H). TLC:  $R_f$  = 0.5 (eluting with 12.5% EtOAc in petroleum ether). SFC (Table 4, Method 6)  $R_t$  = 4.626 min.

*Step B.* A solution of (R)-2-(7-bromo-3-oxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (80 g, 244 mmol) and Lawesson reagent (59.1 g, 146 mmol) in toluene (900 mL) was heated at reflux for 3 h then cooled to ambient temperature. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica gel (eluting with 5-10% EtOAc in petroleum ether) to give (R)-2-(7-bromo-3-thioxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (60 g, 71%) as a yellow liquid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.28-7.21 (m, 1H), 7.15-7.12 (m, 1H), 6.80-6.78 (m, 1H), 6.71-6.69 (m, 1H), 5.00-4.89 (m, 2H), 4.25-4.17 (m, 2H), 1.70-1.68 (m, 3H), 1.19-1.15 (m, 3H). TLC:  $R_f$  = 0.7 (eluting with 12.5% EtOAc in petroleum ether). SFC (Table 4, Method 12)  $[\alpha]_D^{20}$  = 20.79 (C = 0.002 g/mL in MeOH)  $R_t$  = 3.097 min.

*Step C.* To a mixture of (R)-2-(7-bromo-3-thioxo-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propionic acid ethyl ester (60 g, 174 mmol) in EtOH (800 mL) was added hydrazine hydrate (98%, 17.4 g, 349 mmol) and the reaction mixture was stirred at ambient temperature overnight. The precipitate was collected by filtration and washed with cold EtOH (3 x 80 mL) to give (R)-7-bromo-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (32.5 g, 59%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  10.77 (s, 1H), 7.19-7.17 (m, 3H), 4.76-4.74 (m, 1H), 4.61-4.60 (m, 2H), 1.26 (d,  $J$  = 6.4 Hz, 3H). TLC:  $R_f$  = 0.2 (eluting with 33% EtOAc in petroleum ether). SFC: (Table 4, Method 7)  $[\alpha]_D^{20}$  = -342.08 (C = 0.002 g/mL in MeOH)  $R_t$  = 5.934 min.

*Step D.* A mixture of (R)-7-bromo-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (5.0 g, 16.88 mmol), (2-fluorophenyl)boronic acid (3.54 g, 25.32 mmol), K<sub>2</sub>CO<sub>3</sub> (4.67 g, 33.78 mmol) and Pd(dppf)<sub>2</sub>Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> (2.76 g, 3.37 mmol) in

1,4-dioxane (60 mL) and water (10 mL) was stirred at 90 °C for 2 h. The reaction mixture was cooled to ambient temperature and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 10-50% EtOAc in petroleum ether) to give (R)-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2.5 g, 46%) as a red solid. LCMS (Table 1, Method 7)  $R_t = 0.813$  MS  $m/z$ : 312[M+H]<sup>+</sup>. TLC:  $R_f = 0.3$  (eluting with 33% EtOAc in petroleum ether).

*Step E.* To a solution of (R)-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2.4 g, 7.71 mmol) in TFA (20 mL) was added NBS (1.37 g, 7.71 mmol) in portions. The reaction mixture was stirred at ambient temperature for 3 h then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 10-50% EtOAc in petroleum ether) to give (R)-6-bromo-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2.2 g, 73%) as a colorless solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD),  $\delta$  7.28-7.22 (m, 2H), 7.24-7.18 (m, 3H), 6.97 (s, 1H), 4.87-4.83 (m, 1H), 4.70-4.62 (m, 2H), 1.51-1.49 (d,  $J = 6.8$  Hz, 3H). TLC:  $R_f = 0.3$  (eluting with 33% EtOAc in petroleum ether).

*Step F.* A mixture of (R)-6-bromo-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (0.300 g, 0.769 mmol), 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (prepared from *tert*-butyl 3-oxopyrrolidine-1-carboxylate by treatment with LiHMDS and N-phenyl-N-(phenylsulfonyl)benzenesulfonamide to form the triflate followed by Pd-catalyzed conversion to the boronate ester, 0.454 g, 1.538 mmol), Pd(dppf)Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> complex (0.063 g, 0.077 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.213 g, 1.538 mmol) in 1,4-dioxane (6 mL) and water (1 mL) was heated at 100 °C for 15 h. The reaction mixture was cooled to ambient temperature. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (eluting with 15% EtOAc in petroleum ether) to give 3-[(R)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (0.240 g, 65%) as a pale solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>):  $\delta$  8.47-8.00 (m, 1 H), 7.41-7.30 (m, 1 H), 7.23-7.14 (m, 2 H), 7.12-7.04 (m, 1 H), 6.99-6.83 (m, 2 H), 5.39-5.20 (m, 1 H), 4.87-4.76 (m, 1 H), 4.71-4.56 (m, 2 H), 4.40-4.18 (m, 1 H), 4.17-4.00 (m, 3 H), 1.57-1.55 (m, 3 H), 1.46 (s, 9 H). LC/MS (Table 1, Method 7)  $R_t = 0.901$  min; MS  $m/z$ : 423 [M+H-56]<sup>+</sup>.

*Step G.* A suspension of 3-[(R)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-2,5-dihydro-pyrrole-1-carboxylic acid *tert*-butyl ester (0.205 g, 0.428 mmol) and Pd/C (10%, 0.091 g, 0.086 mmol) in MeOH (10 mL) was stirred at ambient temperature under an atmosphere of H<sub>2</sub> for 2 h. After filtration, the filtrate was evaporated *in vacuo* and the residue was purified by preparative TLC (eluting with 30% EtOAc in petroleum ether) to give 3-[(R)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.141 g, 69%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.10 (m, 1H), 7.32 (m, 1H), 7.15 (m, 3H), 6.93-6.82 (m, 2H), 4.81 (m, 1H), 4.65 (m, 2H), 3.62 (m, 2H), 3.23 (m, 3H), 2.17 (s, 2H), 1.56 (m, 3H), 1.48 (br s, 9H). LC/MS (Table 1, Method 7)  $R_t = 0.921$  min; MS  $m/z$ : 425 [M+H-56]<sup>+</sup>.

3-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.141 g, 0.295 mmol) was purified by SFC (Table 3, Method 5) to give two isomers.

**Isomer 1:**

(*S*)-3-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester, SFC (Table 4, Method 1)  $R_t = 6.218$  min, 0.070 g, 50%, as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.12-8.01 (m, 1 H), 7.46-7.33 (m, 1 H), 7.27-7.10 (m, 3 H), 6.90 (s, 2 H), 4.87-4.72 (m, 1 H), 4.70-4.56 (m, 2 H), 3.88-3.53 (m, 2 H), 3.43-3.06 (m, 3 H), 2.29-1.80 (m, 2 H), 1.58-1.53 (m, 3 H), 1.49 (br s, 9H). LC/MS (Table 1, Method 7)  $R_t = 0.916$  min; MS  $m/z$ : 425 [M+H] $^+$ .

**Isomer 2:**

(*R*)-3-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester. SFC (Table 4, Method 1)  $R_t = 7.149$  min, 0.040 g, 29%, as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.30-8.11 (m, 1H), 7.47-7.35 (m, 1H), 7.26-7.13 (m, 3H), 6.96-6.86 (m, 2H), 4.90-4.75 (m, 1H), 4.73-4.53 (m, 2H), 3.73-3.48 (m, 2H), 3.36-3.00 (m, 3H), 2.32-1.82 (m, 2H), 1.59 (m, 3H), 1.49 (br s, 9H). LC/MS (Table 1, Method 7)  $R_t = 0.915$  min; MS  $m/z$ : 425 [M+H] $^+$ .

*Step H.* A mixture of (*S*)-3-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**Isomer 1**, 0.100 g, 0.208 mmol) in HCl (4M in EtOAc, 2 mL) was stirred at ambient temperature for 1 h. The solvent was removed *in vacuo* to give (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-(*S*)-pyrrolidin-3-yl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (0.079 g, 91%) as a white solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.52-7.42 (m, 1 H), 7.35-7.28 (m, 2 H), 7.24 (m, 2 H), 6.94-6.87 (m, 1 H), 5.03-4.96 (m, 1 H), 4.70-4.61 (m, 2 H), 3.56 (m, 3 H), 3.17 (m, 2 H), 2.16 (m, 2 H), 1.51 (m, 3 H). LC/MS (Table 1, Method 3)  $R_t = 2.333$  min; MS  $m/z$ : 381[M+H] $^+$ . SFC: (Table 4, Method 8)  $R_t = 6.98$  min.

*Step I.* A mixture of (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-(*S*)-pyrrolidin-3-yl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (0.050 g, 0.131 mmol) and formaldehyde (0.024 g, 0.789 mmol) in MeOH (5 mL) and AcOH (0.5 mL) was stirred at ambient temperature for 3 h.  $\text{NaBH}_3\text{CN}$  (0.020 g, 0.317 mmol) was added and the reaction mixture was stirred for 2 h. The solvent was removed *in vacuo* and the residue was purified by prep-TLC (eluting with 15% MeOH in DCM) to give (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-((*S*)-1-methyl-pyrrolidin-3-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (compounds **24**, 0.030 g, 58%) as a pale solid.  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.51-7.35 (m, 2H), 7.39-7.35 (m, 2H), 7.34-7.26 (m, 1H), 7.26-7.19 (m, 1H), 6.91-6.83 (m, 1H), 5.18-4.98 (m, 1H), 4.72-4.57 (m, 2H), 3.90-3.35 (m, 4H), 3.31-3.07 (m, 1H), 3.06-2.87 (m, 3H), 2.58-2.10 (m, 2H), 1.52 (m, 3H). LC/MS (Table 1, Method 3)  $R_t = 2.362$  min; MS  $m/z$ : 395 [M+H] $^+$ . SFC (Table 4, Method 5)  $R_t = 3.09$  min.

**(*R*)-7-(2-Fluoro-phenyl)-4-methyl-6-((*R*)-1-methyl-pyrrolidin-3-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (25).** Prepared according to the procedure of **24** (steps H and I) using: *Step H:* (*R*)-3-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-

tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester (intermediate obtained at Step G during the preparation of Compound **24**, Isomer **2**, 0.100 g, 0.208 mmol) and HCl (4M in EtOAc, 40 equiv) at ambient temperature for 1 h; 0.020 g, 36%, as a white solid. *Step I*: formaldehyde (6 equiv), MeOH (13 vol equiv), AcOH (1.3 vol equiv) and NaBH<sub>3</sub>CN (6 equiv) at ambient temperature for 2 h; 0.015 g, 12%, as a pale solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 7.51-7.41 (m, 1H), 7.36 (s, 1H), 7.33-7.26 (m, 2H), 7.25-7.19 (m, 1H), 6.86 (s, 1H), 5.12-5.02 (m, 1H), 4.64 (m, 2H), 3.56-3.35 (m, 3H), 3.32-3.16 (m, 2H), 2.98-2.73 (m, 3H), 2.54-2.04 (m, 2H), 1.57-1.46 (m, 3H). LC/MS (Table 1, Method 3) R<sub>t</sub> = 2.334 min; MS *m/z*: 395 [M+H]<sup>+</sup>. SFC: (Table 4, Method 5) R<sub>t</sub> = 1.99 min.

**(R)-7-(2-Fluoro-phenyl)-4-methyl-6-(1-methyl-piperidin-4-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (26).** *Step A.* A mixture of

(*R*)-6-bromo-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (2.0 g, 5.13 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2*H*)-carboxylate (2.38 g, 7.69 mmol), Pd(dppf)<sub>2</sub>Cl<sub>2</sub>-CH<sub>2</sub>Cl<sub>2</sub> (0.84 g, 1.03 mmol) and K<sub>2</sub>CO<sub>3</sub> (1.42 g, 10.25 mmol) in 1,4-dioxane (21 mL) and water (7 mL) was heated at 90 °C overnight. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluting with 10-50% EtOAc in petroleum ether) to give

4-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (1.6 g, 61%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.64 (br s, 1H), 7.36-7.20 (m, 3H), 7.19-7.05 (m, 2H), 6.99 (s, 1H), 6.81 (s, 1H), 5.49 (br s, 1H), 4.79 (q, *J* = 6.4 Hz, 1H), 4.72-4.57 (m, 2H), 3.88 (br s, 2H), 3.35 (m, 2H), 2.06 (br s, 2H), 1.60-1.57 (m, 3H), 1.47 (s, 9H). LC/MS (Table 1, Method 1) R<sub>t</sub> = 1.267 min.; MS *m/z*: 493[M+1]<sup>+</sup>.

*Step B.* To a suspension of Pd/C (10%, 0.324 g, 3.05 mmol) in MeOH (30 mL) was added 4-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (1.5 g, 3.05 mmol) and the reaction mixture was stirred at 50 °C under H<sub>2</sub> (50 psi) overnight. The reaction mixture was cooled to ambient temperature, filtered and the filtrate was concentrated *in vacuo* to give 4-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (1.2 g, 80%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ 7.49-7.38 (m, 1H), 7.31-7.16 (m, 3H), 7.09 (s, 1H), 6.82 (s, 1H), 5.00-4.94 (m, 1H), 4.68-4.57 (m, 2H), 4.24-4.07 (m, 2H), 2.58 (m, 3H), 1.76 (m, 2H), 1.67-1.56 (m, 2H), 1.50-1.46 (m, 12H). LC/MS (Table 1, Method 7) R<sub>t</sub> = 0.926 min.; MS *m/z*: 495[M+1]<sup>+</sup>.

*Step C.* To HCl (1M in EtOAc, 10 mL) was added 4-[(*R*)-7-(2-fluoro-phenyl)-4-methyl-3-oxo-2,3,4,10-tetrahydro-9-oxa-1,2,4a-triaza-phenanthren-6-yl]-piperidine-1-carboxylic acid *tert*-butyl ester (1 g, 2.20 mmol) and the reaction mixture was stirred at ambient temperature for 1 h. The solvent was removed *in vacuo* to give (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-piperidin-4-yl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride (0.65 g, 81%) as a yellow solid. <sup>1</sup>H NMR (400 MHz,

CD<sub>3</sub>OD)  $\delta$  7.51-7.41 (m, 1H), 7.32-7.27 (m, 2H), 7.23 (t,  $J$  = 9.0 Hz, 1H), 7.03 (s, 1H), 6.87 (s, 1H), 5.01-4.95 (m, 1H), 4.70-4.60 (m, 2H), 3.50-3.38 (m, 2H), 3.01-2.69 (m, 3H), 2.05 (m, 2H), 1.90 (m, 2H), 1.52 (m, 3H). LCMS (Table 1, Method 4)  $R_t$  = 2.351 min; MS  $m/z$ : 395 [M+H]<sup>+</sup>.

*Step D.* To a solution of MeOH (10 mL) and acetic acid (1 mL) was added (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-piperidin-4-yl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (0.300, 0.761 mmol) and paraformaldehyde (0.228 g, 7.61 mmol) and the reaction mixture was stirred at ambient temperature for 4 h. Then sodium cyanoborohydride (0.096 g, 1.52 mmol) was added and the reaction mixture was stirred for 30 min. The solvent was removed *in vacuo* and the residue was purified by prep-TLC (eluting with 10% MeOH in DCM) to give (*R*)-7-(2-fluoro-phenyl)-4-methyl-6-(1-methyl-piperidin-4-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (compound **26**, 0.160 g, 51%) as a white solid. <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  7.50-7.41 (m, 1H), 7.32-7.26 (m, 2H), 7.25-7.19 (m, 1H), 7.09 (s, 1H), 6.86 (s, 1H), 5.02-4.93 (m, 1H), 4.70-4.59 (m, 2H), 3.63-3.46 (m, 2H), 3.04-2.89 (m, 2H), 2.84 (s, 3H), 2.76 (m, 1H), 2.28-2.01 (m, 3H), 1.96-1.83 (m, 1H), 1.52 (d,  $J$  = 6.4 Hz, 3H). LCMS (Table 1, Method 4)  $R_t$  = 1.617 min; MS  $m/z$ : 409 [M+H]<sup>+</sup>. SFC (Table 4, Method 13)  $R_t$  = 3.630 min.

**3,3-Dimethyl-4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester.** To a -78 °C mixture of 3,3-dimethyl-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (2.0 g, 8.80 mmol) in THF (20 mL) was added LiHMDS (1M in THF, 14.96 mL, 14.96 mmol) dropwise and the mixture was stirred at ambient temperature for 0.5 h. 2-[N,N-Bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (4.15 g, 10.56 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The mixture was quenched with saturated aqueous NH<sub>4</sub>Cl (20 mL), extracted with EtOAc (3 x 20 mL). The combined organic extract was washed with brine (50 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a yellow oil. The residue was purified by column chromatography on silica gel (eluting with 10% EtOAc in petroleum ether) to give 3,3-dimethyl-4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (2.2 g, 69%) as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.70 - 5.60 (m, 1H), 4.20 - 3.98 (m, 2H), 3.45-3.30 (m, 2H), 1.49 - 1.46 (m, 9H), 1.15 (s, 3H), 1.11 (s, 3H). TLC:  $R_f$  = 0.7 (eluting with 20% EtOAc in petroleum ether).

**(*R*)-7-(2-Fluoro-phenyl)-4-methyl-6-((*R*)-1,3,3-trimethyl-piperidin-4-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (**29**).** Prepared according to the procedure of compound **17a** (steps E-J). *Step E:* using K<sub>2</sub>CO<sub>3</sub> (2 equiv), 3,3-dimethyl-4-trifluoromethanesulfonyloxy-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (1.3 equiv) in 1,4-dioxane (16 vol equiv) and water (2.7 vol equiv) with PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub>-adduct (0.1 equiv) at 90 °C for 2 h, 1.2 g, 44%, as a white solid. Chiral separation was performed after Step F. *Step F:* heated at 50 °C overnight, 1.2 g, 100%, as a white solid. Chiral SFC separation (Table 3, Method 3) gave two isomers: **isomer 1**, SFC (Table 4, Method 2),  $R_t$  = 5.45 min., 0.53 g, 44%, as a white solid; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  6.98 - 6.70 (m, 3H), 4.81 - 4.80 (m, 1H), 4.60 - 4.47 (m, 2H), 4.30 - 4.20 (m, 1H),

3.85 - 3.76 (m, 1H), 2.96 - 2.47 (m, 3H), 2.28 - 1.93 (m, 2H), 1.52 - 1.39 (m, 12H), 0.81 (d,  $J = 19.3$  Hz, 6H); LC/MS (Table 1, Method 4; monitoring at wavelength: 220 nm & 254 nm)  $R_t = 3.188$  min.; MS  $m/z$ : 429  $[M+H]^+$ , and isomer 2, SFC (Table 4, Method 2),  $R_t = 6.41$  min., 0.56 g, 47%, as a white solid;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.07 (s, 1H), 6.93 (d,  $J = 8.3$  Hz, 1H), 6.75 (d,  $J = 8.3$  Hz, 1H), 6.66 (s, 1H), 4.80 - 4.70 (m, 1H), 4.65 - 4.49 (m, 2H), 4.48 - 4.15 (m, 1H), 4.06 - 3.72 (m, 1H), 2.91 - 2.40 (m, 3H), 2.10 - 2.05 (m, 1H), 1.53 - 1.47 (m, 12H), 0.80 (d,  $J = 10.5$  Hz, 6H). LC/MS (Table 1, Method 4; monitoring at wavelength: 220 nm & 254 nm)  $R_t = 3.177$  min.; MS  $m/z$ : 429  $[M+H]^+$ . Step G: with isomer 1, DCM (30 vol equiv),  $Br_2$  (1.3 equiv) at 0 °C for 50 min. Step H: (2-fluorophenyl)boronic acid (1.5 equiv). Step I: ambient temperature for 30 min. Step J: paraformaldehyde (6 equiv), MeOH (38 vol equiv) and AcOH (3.8 vol equiv) at ambient temperature for 30 min then  $NaBH_3CN$  (3 equiv) at ambient temperature for 0.5 h followed by treatment with HCl (4M in EtOAc, 22 equiv); 0.044 g, 59%, as a white solid.  $^1H$  NMR (400 MHz,  $CD_3OD$ ):  $\delta$  7.49-7.40 (m, 1H), 7.38-7.18 (m, 3H), 6.99-6.85 (m, 2H), 4.87-4.80 (m, 1H), 4.71-4.61 (m, 2H), 3.67-3.57 (m, 1H), 3.17 (d,  $J = 12.5$  Hz, 1H), 3.02 (t,  $J = 9.7$  Hz, 1H), 2.88-2.84 (m, 3H), 2.81-2.64 (m, 2H), 2.55-2.38 (m, 1H), 2.04 (d,  $J = 14.8$  Hz, 1H), 1.54-1.47 (m, 3H), 1.15 (d,  $J = 3.8$  Hz, 3H), 0.50 (d,  $J = 16.8$  Hz, 1H) LC/MS (Table 1, Method 3)  $R_t = 2.805$  min.; MS  $m/z$ : 437  $[M+H]^+$ . SFC (Table 4, Method 2)  $R_t = 1.406$  min.

**(R)-6-((3R,4R)-1-Ethyl-3-methyl-piperidin-4-yl)-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-ro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride (30).** To a solution of (R)-7-(2-fluoro-phenyl)-4-methyl-6-((3R,4R)-3-methyl-piperidin-4-yl)-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one (intermediate obtained at Step F during preparation of compound 17a, 0.03 g, 0.073 mmol) in MeOH (2 mL) and acetaldehyde (0.049 g, 0.441 mmol) was added and the reaction mixture was stirred at ambient temperature for 3 h.  $NaBH_3CN$  (0.014 g, 0.22 mmol) was added and the reaction mixture was stirred at ambient temperature for 0.5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative TLC (eluting with 10% MeOH in dichloromethane) to give (R)-6-((3R,4R)-1-ethyl-3-methyl-piperidin-4-yl)-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one. The product was stirred with HCl (4M in EtOAc, 10 mL) for 30 min then the reaction mixture was concentrated *in vacuo* to give (R)-6-((3R,4R)-1-ethyl-3-methyl-piperidin-4-yl)-7-(2-fluoro-phenyl)-4-methyl-2,10-dihydro-9-oxa-1,2,4a-triaza-phenanthren-3-one hydrochloride acid (compound 30, 0.0204 g, 24%) as a white solid.  $^1H$  NMR (400 MHz,  $CD_3OD$ ):  $\delta$  7.44-7.21 (m, 4H), 6.90-6.84 (m, 2H), 4.86-4.85 (m, 1H), 4.63-4.62 (m, 2H), 3.60 (s, 1H), 3.12-2.77 (m, 6H), 2.45 (s, 1H), 1.97-1.89 (m, 2H), 1.48 (m, 3H), 1.30-1.29 (m, 3H), 0.90 (m, 3H). LC/MS (Table 1, Method 4)  $R_t = 1.851$  min.; MS  $m/z$ : 437  $[M+H]^+$ . SFC (Table 4, Method 4),  $R_t = 1.052$  min.

### **PKC $\alpha$ protein expression, purification and crystallization method:**

Human PKC $\alpha$  (6His-[PKC $\alpha$  (2-317)]-(TEV)-GIS-[PKC $\alpha$  (318-672) C619S]) was expressed in Sf9 cells (Invitrogen, Grand Island, NY). The protein was purified with a Ni-column, the protein cleaved with TEV protease and N-terminal portion of the protein captured on a second Ni-column while the desired C-terminal portion was eluted. The C-terminal portion was then

further purified by SEC (running buffer, 20mM Tris pH 8.0, 150mM NaCl, 5%(v/v) glycerol and 1 mM TCEP) and concentrated to 11 mg/mL. Compound **28** powder was dissolved in DMSO to give a 100 mM stock solution. Compound **28** was added to protein to give a final solution of 2% (v/v) DMSO, 2 mM compound and allowed to incubate at room temperature for 1h. Prior to crystallization magnesium chloride was added to give 2 mM and DTT to give 10 mM. Crystals grew after one day in vapor diffusion with the reservoir containing 25% (w/v) PEG 3350, 0.1 M Bis-Tris pH 5.5, 0.2 M magnesium chloride. The crystals were cryo protected using the reservoir solution with 10% (v/v) propylene glycol and diffraction data was collected at the Advanced Photon Source (Argonne National Laboratories, Argonne, IL) under gaseous nitrogen at 100K.

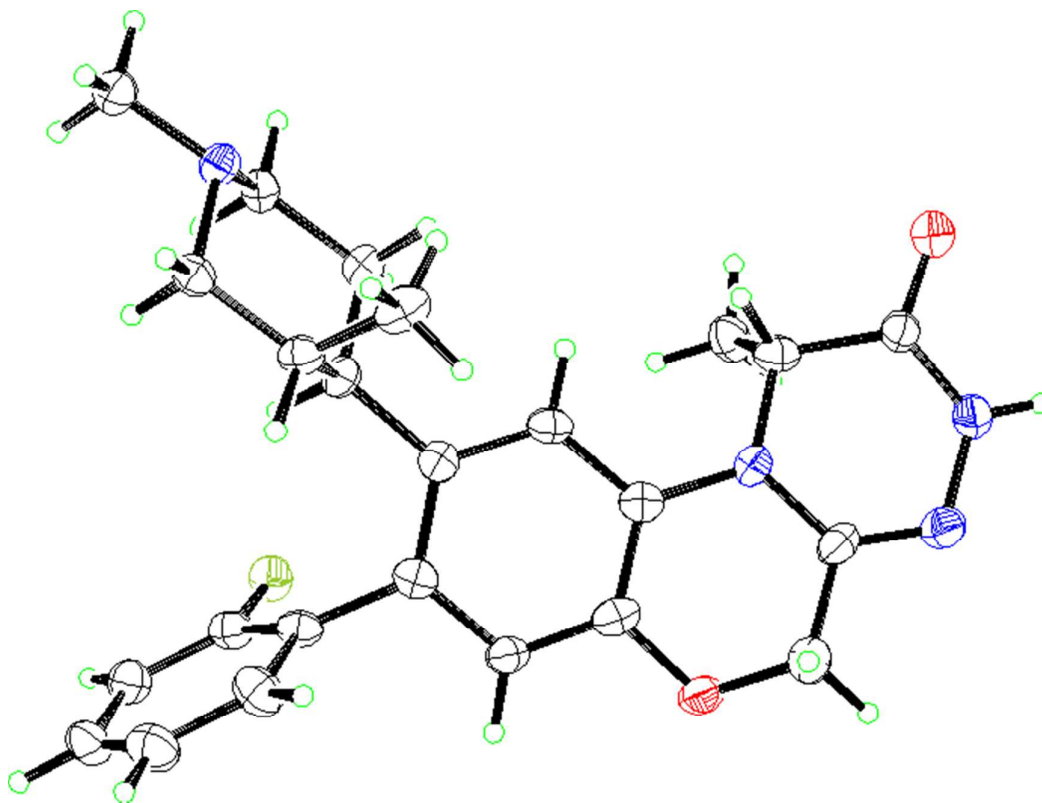
**Table 5:** Crystallographic statistics for PKC $\theta$ /Compound **11a** and PKC $\alpha$ /Compound **28** complexes

Structure	PKC $\theta$ /Compound <b>11a</b>	PKC $\alpha$ /Compound <b>28</b>
<b>PDB entry</b>	4RA5 <sup>a</sup>	4RA4 <sup>b</sup>
<b>Data Collection</b>		
<b>Resolution (Å)</b>	73.77–2.61	77.67–2.63
<b>(Highest shell, Å)</b>	2.81–2.61	2.64–2.63
<b>Space Group</b>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	C2 <sub>1</sub>
<b>Unit Cell Lengths (a, b, c; Å)</b>	74.82, 77.03, 147.6	112.4, 44.47, 85.50 $\beta$ = 114.7
<b>Unique reflections</b>	26348	11659
<b>Overall Statistics (Highest Shell)</b>		
<b>R<sub>sym</sub> (%)</b>	0.047 (0.444)	0.077 (0.557)
<b>I/<math>\sigma</math><sub>I</sub></b>	21.11 (3.71)	13.8 (3.2)
<b>Data completeness (%)</b>	99.1 (99.3)	99.6 (99.1)
<b>Mean multiplicity</b>	4.0 (3.9)	4.3 (4.7)
<b>Refinement</b>		
<b>Reflections used in refinement (working/test)</b>	25436 / 912	11609 / 553
<b>R<sub>cryst</sub> (%)</b>	22.8	18.6
<b>R<sub>free</sub> (%)</b>	27.7	26.4
<b>R.m.s. deviations, bond lengths (Å), bond angles (°)</b>	0.009, 1.12	0.010, 1.23

<sup>a</sup> Data collected at the Swiss Light Source (Proteros Biostructures GmbH). Data was processed by XDS.<sup>2</sup> Model building was performed using the program COOT.<sup>3</sup> Refinement was performed by the software package CCP4.<sup>4</sup>

<sup>b</sup> Data collected at IMCA-CAT beamline 17-ID. Data was processed by AUTOPROC.<sup>5</sup> Model building was performed using the program COOT.<sup>3</sup> Refinement was performed by the software packages CCP4<sup>4</sup> and BUSTER.<sup>6</sup>

### Small molecule X-ray of Compound 17a.



The single crystal X-ray diffraction experiment was performed on a Bruker SMART system equipped with an APEX2 CCD camera. Data were collected at 100 K with graphite-monochromated CuK $\alpha$  radiation ( $\lambda = 1.54178 \text{ \AA}$ ). The data was collected and processed using SaintPlus.<sup>7</sup> The structure was solved using direct methods that generated non-hydrogen atoms. All hydrogen atoms were located in Fourier-difference electron density maps and included in geometrically constrained riding positions with the exception of the hydrogen atoms associated with the alcoholic oxygen atoms which were initially located from the difference map but refined with inter atomic distance restraints. Refinement was achieved with the use of SHELX-97.<sup>8</sup>

### Receptors measured in the bioprofiling panel:

5HT1A, 5HT2A, 5HT2B, 5HT2C, A1, AT1, Alpha1A, Alpha2A, B2, Beta1, CB1, Cav1.2 (L-type), D2L, ETA, ETB, H1, M2, Opiod mu, PPAR $\gamma$ , Kv11.1 (hERG)

### Kinases measured in the in-house panel of kinases:

ACVR1, ALK, AMP, Abl, Akt1, Aurora1, Aurora2, BTK, CAMK1D, CAMK2A, CAMKK2, CDK2, CDK7, CDK8, CDK9, CDK11, CLK2, cMET, CSF1R, Ck1 alpha1, DDR1, DYRK1B, DYRK1A, EGFR, Erk2, FAK, FGFR1, Flt1, Fyn, GRK5, Gsk3a, Gsk3b, IGF1R, IKKE, InsR, JAK2, JAK3, JNK1, JNK2, Kdr, LTK, Lck, MAP2K3, MAP3K10, MAP4K2, MAP4K4, MEK1, MEK2, MST1, Nek2, p38 alpha, PAK4KD, PDGFRA V561D, PDGFRB, PKA, PKCtheta, PKCzeta, PKG1A, Pim1, Pim2, Plk3, Prkcn, RET, Rock1, Rock2, Rsk2, SGK1, STK16, STK33, Src, Syk, TAOK2, TBK1, TNK2, TYRO3, TrkA, TrkB, TrkC, Wee1, ZipK.

### CEREP panel of receptors:

5-HT transporter, 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub>, 5-HT<sub>3</sub>, 5-HT<sub>5A</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>, A1, A2A, A3, alpha 1, alpha 2, AT1, AT2, B2, BB, beta 1, beta 2, BZD (central), BZD (peripheral), Ca<sup>2+</sup> (L, verapamil site), CB1, CCK1, CCK2, CCR1, CGRP, CI-channel (GABA-gated), CXCR2, D<sub>1</sub>, D<sub>2S</sub>, D<sub>3</sub>, D<sub>4.4</sub>, D<sub>5</sub>, delta 2 (DOP), dopamine transporter, EP2, ETA, ETB, GABA (non-selective), GAL1, GAL2, GR, H<sub>1</sub>, H<sub>2</sub>, IP, kappa (KOP), KV channel, M<sub>1</sub>, M<sub>2</sub>, M<sub>3</sub>, M<sub>4</sub>, M<sub>5</sub>, MAO0A, MC4, MT<sub>1</sub>, mu (MOP), Na<sup>+</sup> channel (site 2), NK1, NK2, NK3, NOP (ORL1), norepinephrine transporter, NTS1, P2X, P2Y, PAC1, PCP, PDGF, PPARgamma, sigma (non-selective), SKCa channel, sst (non-selective), TNF-alpha, V1a, VPAC1, Y1, Y2.

**Conscious mouse CV model:** Male CD1 mice were instrumented with telemetry transmitters and then allowed to recover. Mice were housed individually in a temperature and humidity controlled room with a standard light cycle (light; 6am-6pm, dark; 6pm-6am). The pre-dose baseline period was recorded for 1 h. Animals were then oral dosed with compound **17h** (30 mg/kg in 0.5% HPMC/0.02% Tween 80 in water vehicle; 0.5mL/kg; n=5). Dosing is designated as time zero on the graphs. Measurements were recorded every 3 min for the 24 h period following dosing and are presented as 1 h averages on the graphs. No satellite bleeds were taken for PK analysis. The vehicle mice were the same group of animals dosed two weeks after compound **17h** dosing.

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