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#### 4.2.18. Introduction of three levels of molecular diversity (library D)

The levels of molecular diversity were introduced by a similar procedure as described above in the preparation of libraries A, B and C. For the first level of molecular diversity, five stock solutions, each containing 2.5 equivalents (5x) of Fmoc-protected amino acid [Fmoc-*L*-Phe-OH (496 mg, 1.28 mmol), Fmoc-*L*-4-Pal-OH (Fmoc-*L*-4-pyridinealanine-OH) (497 mg, 1.28 mmol), Fmoc-*L*-Asp(OtBu)-OH (527 mg, 1.28 mmol), Fmoc-*L*-Ser(Trt)-OH (729 mg, 1.28 mmol) or Fmoc-*L*-Tyr(2-Cl-Trt)-OH (870 mg, 1.28 mmol)], 2.5 equivalents (5x) of PyBrOP (595 mg, 1.28 mmol) and 2.5 equivalents (5x) of HOBt (175 mg, 1.28 mmol), were prepared in dry DMF (10 mL), and 5 equivalents (5x) of DIPEA (450 μL, 2.56 mmol) were added to each stock solution. To each of the 25 resins **158**, was added 2.0 mL of the appropriate stock solution. The mixtures were shaken under an argon atmosphere for 4 h at room temperature, then filtered, washed with DMF (2×), DCM (2×) and MeOH (3×), and dried under a vacuum to afford 5 groups of resins of general structure **159**. The completion of the coupling step was verified by acidic mini-cleavage and TLC analysis as described above. The cleavage of the Fmoc group of resins **159** was subsequently performed by a 1 h treatment with 2.0 mL of a solution of piperidine (20%) in DCM. The resins were then filtered, washed with DCM (3×), MeOH (3×) and DCM (1×), and dried under a vacuum to give 5 groups of resins of general structure **160**. The second level of molecular diversity was introduced using the same building blocks as for the first level except that Fmoc-*L*-4-Pal-OH was replaced by Fmoc-*L*-Ala-OH (398 mg, 1.28 mmol). The procedure described above for the introduction of the first level of molecular diversity was applied without modification. A TLC analysis after acidic mini-cleavage of a sampling of resins **161** confirmed that the introduction of the second level of molecular diversity was completed. Resins of general structure **161** were then treated with 2.0 mL of a solution of piperidine (20%) in DCM for 1 h at room temperature. The resins were filtered, washed with DCM (3×), MeOH (3×)

and DCM (1×), and dried to afford resins of general structure **162**. The third level was introduced on resins **162** by coupling carboxylic acid building block **156**. A stock solution of **156** (1.60 g, 6.40 mmol), PyBrOP (2.98 g, 6.40 mmol) and HOBt (865 mg, 6.40 mmol) was prepared in dry DMF (50 mL) and DIPEA (2.23 mL, 12.8 mmol) was added. To each of the 25 resins **162** was added 2.0 mL of the stock solution. The mixtures were shaken under argon for 4 h at room temperature, then filtered, washed with MeOH (1×), DMF (2×), DCM (3×), MeOH (3×) and DCM (1×), and dried under a vacuum to afford resins of general structure **163**. The completion of the coupling reaction was verified by acidic mini-cleavage and TLC analysis.

#### 4.2.19. Removal of protective groups (library D)

Resins **163** that were prepared with Fmoc-*L*-Ser(Trt)-OH or Fmoc-*L*-Tyr(2-Cl-Trt)-OH building blocks were treated with 2.0 mL of a solution of TFA/TIS (triisopropylsilane)/DCM, 2:1:97 for 10 min at room temperature. The resins were filtered and washed with DCM (3×), MeOH (3×) and DCM (3×). This procedure was performed twice in order to completely remove the trityl or the 2-Cl-trityl protective groups. The deprotection step was completed when the solution of acidic mini-cleavage of a sampling of resins **163** (after step e) did not become yellow anymore. The THP protective group was next removed in mild acid condition. A solution of *p*-TSA (666 mg, 3.5 mmol) dissolved in *t*-BuOH (25 mL) and DCM (25 mL) was prepared and 2.0 mL of this solution was added to each of the 25 resins **163** (after step e, if necessary). The mixtures were shaken for 24 h at room temperature. They were then filtered, washed with DCM (3×), MeOH (3×) and DCM (1×), and dried under a vacuum to afford resins **164**.

#### 4.2.20. Generation of E<sub>2</sub> derivatives 165 by nucleophilic cleavage

To each of the 25 resins **164** was added 2.0 mL of a solution of DEA (30%) in THF. The mixtures were shaken for 45 h at room temperature. Then 1.5 mL of a solution of DEA (30%) in THF was added to each of the 25 resins and the mixtures were shaken for an additional 20 h. The mixtures were then filtered and washed with THF (3×). The filtrates were collected in preweighed tubes and evaporated in a Speedvac apparatus. Each compound was dissolved in THF, evaporated twice and dried under a vacuum pump in order to obtain the DEA-free product. The phenol derivatives **165** were obtained in the form of a yellowish viscous oil. A random sampling was done and 2 compounds were analyzed by <sup>1</sup>H NMR to verify their structure.

*16β*-(*N*-[3'-(Acetylbutyl ester)]-phenylacetyl-*L*-tyrosine-*L*-phenylalanine-aminopropyl)-3,17β-dihydroxyestra-1,3,5(10)-triene (**165**: R<sub>1</sub> = a, R<sub>2</sub> = e). <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>) δ 0.79 (s, 18-CH<sub>3</sub>), 0.85 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 1.44 (s, (CH<sub>3</sub>)<sub>3</sub>CO), 2.78 (m, 6-CH<sub>2</sub>), 2.93 and 3.12 (2m, CHCH<sub>2</sub>Ph, CHCH<sub>2</sub>PhOH and CH<sub>2</sub>NH), 3.46 and 3.48 (2s, COCH<sub>2</sub>Ph), 3.51 (s, CH<sub>2</sub>COOtBu), 3.75 (under THF peaks, 17α-CH), 4.52 (m, CHCH<sub>2</sub>Ph and CHCH<sub>2</sub>PhOH), 6.49 (d, *J* = 2.4 Hz, 4-CH), 6.55 (dd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 2.6 Hz, 2-CH), 6.65 (d, *J* = 8.5 Hz, 3'-CH and 5'-CH of 4-hydroxyphenyl),

6.94 (d,  $J = 8.5$  Hz, 2'-CH and 6'-CH of 4-hydroxyphenyl), 7.01 (d,  $J = 7.5$  Hz, 1-CH), 7.14 (m,  $9 \times$  CH of phenyl).

*16 $\beta$ -(N-[3'-(Acetylbutyl ester)]-phenylacetyl-L-serine-L-aspartic acid-aminopropyl)-3,17 $\beta$ -dihydroxyestra-1,3,5(10)-triene (165: R<sub>1</sub> = c, R<sub>2</sub> = d).* <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  0.80 (s, 18-CH<sub>3</sub>), 0.85 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 1.45 (s, (CH<sub>3</sub>)<sub>3</sub>CO), 2.78 (m, 6-CH<sub>2</sub> and CH<sub>2</sub>COOH), 3.15 (m, CH<sub>2</sub>NH), 3.54 (s, COCH<sub>2</sub>Ph), 3.62 (s, CH<sub>2</sub>COOtBu), 3.75 (under THF peaks, 17 $\alpha$ -CH), 3.75 and 3.86 (under THF peaks and dd,  $J_1 = 10.6$  Hz,  $J_2 = 5.5$  Hz, CH<sub>2</sub>OH), 4.22 (t,  $J = 6.0$  Hz, CHCH<sub>2</sub>OH), 4.75 (m, CHCH<sub>2</sub>COOH), 6.49 (d,  $J = 2.3$  Hz, 4-CH), 6.55 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.6$  Hz, 2-CH), 7.09 (d,  $J = 8.4$  Hz, 1-CH), 7.24 (m,  $4 \times$  CH of phenyl).

#### 4.2.21. Generation of E<sub>2</sub> derivatives (library D) by an acid treatment

In order to remove the *tert*-butyl ester protective group, each compound **165** was put in a tube and treated for 3 h at room temperature with 2.0 mL of HCl (4M in dioxane). The reaction mixtures were then evaporated to dryness under reduced pressure and dried overnight under a vacuum pump. The crude products were dissolved in MeOH and preadsorbed on C-18 silica gel. Purification by a C-18 silica gel column (Honeywell Burdick & Jackson, solid phase systems C18 columns, size 2000 mg/8 mL (product # 9009) distributed by VWR) afforded carboxylic acid, methyl ester or a mixture of carboxylic acid and methyl ester derivatives **166–190** (2–31 mg, 2–33% overall yield from **158**). LRMS and notes on <sup>1</sup>H-NMR analysis of each library members are presented in Table 4. <sup>1</sup>H-NMR of a random sampling of four members is described as examples.

**166 (methyl ester).** <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  0.79 (s, 18-CH<sub>3</sub>), 0.95 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 2.79 (m, 6-CH<sub>2</sub>), 2.90 and 3.10 (2m,  $2 \times$  CHCH<sub>2</sub>Ph and CH<sub>2</sub>NH), 3.45 and 3.46 (2s, COCH<sub>2</sub>Ph), 3.61 (s, CH<sub>2</sub>COOCH<sub>3</sub>), 3.67 (s, COOCH<sub>3</sub>), 3.71 (d,  $J = 9.8$  Hz, 17 $\alpha$ -CH), 4.53 (t,  $J = 7.3$  Hz, COCHNH), 4.60 (m, COCHNH), 6.48 (d,  $J = 2.5$  Hz, 4-CH), 6.55 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.5$  Hz, 2-CH), 7.01 (d,  $J = 7.5$  Hz, 1-CH), 7.05 to 7.30 (m,  $14 \times$  CH of phenyl).

**180 (methyl ester).** <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  0.80 (s, 18-CH<sub>3</sub>), 1.00 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 2.75 (m, 6-CH<sub>2</sub>), 2.80, 3.00 and 3.14 (3m, CHCH<sub>2</sub>COOH, CH<sub>2</sub>PhOH) and CH<sub>2</sub>NH), 3.54 (m, COCH<sub>2</sub>Ph), 3.63 and 3.66 (2s, CH<sub>2</sub>COOCH<sub>3</sub>), 3.68 (s, COOCH<sub>3</sub>), 3.71 (d,  $J = 9.7$  Hz, 17 $\alpha$ -CH), 4.48 (m, CHCH<sub>2</sub>PhOH), 4.64 (m, CHCH<sub>2</sub>COOH), 6.49 (d,  $J = 2.5$  Hz, 4-CH), 6.55 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 2.6$  Hz, 2-CH), 6.68 (m,  $2 \times$  CH of PhOH), 7.00 to 7.25 (m, 1-CH,  $2 \times$  CH of PhOH and  $4 \times$  CH of Ph).

**184 (carboxylic acid).** <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>)  $\delta$  0.79 (s, 18-CH<sub>3</sub>), 0.95 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 2.78 (m, 6-CH<sub>2</sub>), 3.20 (m, CH<sub>2</sub>NH), 3.60 and 3.63 (2s, COCH<sub>2</sub>Ph), 3.65 and 3.69 (2s, CH<sub>2</sub>COOH), 3.71 (d,  $J = 9.9$  Hz, 17 $\alpha$ -CH), 3.79 and 3.89 (2m,  $2 \times$  CH<sub>2</sub>OH), 4.39 and

4.45 (2m, 2 × CHCH<sub>2</sub>OH), 6.49 (d,  $J = 2.4$  Hz, 4-CH), 6.55 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.5$  Hz, 2-CH), 7.09 (d,  $J = 8.4$  Hz, 1-CH), 7.24 (m, 4 × CH of Ph).

**185** (mix of methyl ester and carboxylic acid). <sup>1</sup>H-NMR (400 MHz, methanol-d<sub>4</sub>) δ 0.80 (s, 18-CH<sub>3</sub>), 0.90 to 2.35 (m, CH and CH<sub>2</sub> of steroid skeleton and alkyl chain), 2.78 (m, 6-CH<sub>2</sub>), 2.90 and 3.05 (2m, CH<sub>2</sub>PhOH), 3.17 (m, CH<sub>2</sub>NH), 3.52 and 3.53 (2s, COCH<sub>2</sub>Ph), 3.58, 3.63 and 3.65 (3s, CH<sub>2</sub>COOX, × = H or CH<sub>3</sub>), 3.68 (s, COOCH<sub>3</sub>), 3.72 and 3.79 (2m, 17α-CH and CH<sub>2</sub>OH), 4.33 (m, CHCH<sub>2</sub>PhOH), 4.60 (m, CHCH<sub>2</sub>OH), 6.49 (s, 4-CH), 6.55 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 2.4$  Hz, 2-CH), 6.68 (dd,  $J_1 = 8.4$  Hz,  $J_2 = 1.8$  Hz, 2 × CH of PhOH), 7.00 to 7.35 (m, 1-CH, 2 × CH of PhOH and 4 × CH of Ph).

### 4.3. Inhibition of 17β-HSD1 in homogenated cells (enzymatic assay)

The enzymatic assays on 17β-HSD1 were performed as previously described [15,41]. HEK-293 cells transfected with 17β-HSD1 cDNA fragment were briefly sonicated in 50 mM sodium phosphate buffer (pH 7.4) containing 20% glycerol and 1mM EDTA to obtain cellular fragmentation. The cytosol fraction containing the enzyme was isolated as the supernatant after centrifugation (100,000g, 5 min, 4 °C). The enzymatic reaction was performed at 37 °C for 2 h in 1 mL of a solution which included 870 μL of 50 mM sodium phosphate buffer (pH 7.4, 20% glycerol and 1 mM EDTA), 100 μL of 1 mM NADH in phosphate buffer, 10 μL of 10 μM [<sup>14</sup>C]-estrone in ethanol (54 mCi / mmol, American Radiolabeled Chemicals Inc., St-Louis, MO, USA), 10 μL of indicated inhibitor dissolved in ethanol and 10 μL of diluted enzymatic source in phosphate buffer. Each inhibitor was assessed in duplicate at a final concentration of 1μM. Radiolabeled steroids were then extracted twice from the reaction mixture by 1 mL of diethyl ether. The organic phases were pooled and evaporated to dryness with nitrogen. Residues were dissolved in 50 μL of DCM, applied on silica gel 60 F<sub>254</sub> thin layer chromatography plates (EMD Chemicals Inc., Gibbstown, NJ, USA) and eluted with a mixture of toluene/acetone (4:1). Substrate ([<sup>14</sup>C]-E<sub>1</sub>) and metabolite ([<sup>14</sup>C]-E<sub>2</sub>) were identified by comparison with reference steroids and quantified using the Storm 860 system (Molecular Dynamics, Sunnyvale, CA, USA). The percentage of transformation of [<sup>14</sup>C]-E<sub>1</sub> into [<sup>14</sup>C]-E<sub>2</sub> was calculated as follows: % transformation = 100 × ([<sup>14</sup>C]-E<sub>2</sub>/([<sup>14</sup>C]-E<sub>2</sub> + [<sup>14</sup>C]-E<sub>1</sub>)), and subsequently, % inhibition = 100 × [(% transformation without inhibitor - % transformation with inhibitor)/% transformation without inhibitor].

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