Supporting Information

Highly Potent First Examples of Dual Aromatase-Steroid Sulfatase Inhibitors based on a Biphenyl Template

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- D) Crystallographic statistics of data collection and refinement for the hCA II - **23** complex (PDB code: 2wd3.pdb).

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[∇] This article is dedicated to Professor Michael John Reed, BSc, MSc, PhD, DSc, FRCPath (1944–2009)

A) ^{13}C NMR data

5-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-hydroxybiphenyl-2-carbonitrile 19. δ_{C} (67.9 MHz, DMSO- d_6) 52.0, 109.8, 116.1, 119.2, 127.0, 128.6, 129.6, 130.5, 134.8, 142.4, 145.3, 145.5, 152.6 and 158.8.

5'-((1*H*-1,2,4-triazol-1-yl)methyl)-2'-cyanobiphenyl-4-yl sulfamate 20. δ_{C} (67.9 MHz, DMSO- d_6) 51.9, 110.1, 118.8, 123.1, 128.1, 129.9, 130.8, 134.9, 136.3, 142.6, 144.3, 145.3, 151.1 and 152.7.

5'-((1*H*-1,2,4-triazol-1-yl)methyl)-2'-cyanobiphenyl-4-yl dimethylsulfamate 21. δ_{C} (67.9 MHz, CDCl_3) 38.9, 52.7, 111.5, 117.9, 122.2, 127.0, 129.2, 130.3, 134.5, 135.9, 140.3, 143.6, 145.0, 150.9 and 152.9.

5-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-2-carbonitrile 22. δ_{C} (100.6 MHz, DMSO- d_6) 51.4, 109.4, 116.8, 118.4, 120.0, 127.1, 128.6, 129.3, 129.3, 130.0, 134.3, 142.0, 143.4, 144.8, 152.1 and 153.9.

5'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-2'-cyanobiphenyl-4-yl sulfamate 23. δ_{C} (67.9 MHz, DMSO- d_6) 51.9, 110.3, 118.6, 124.5, 127.3, 128.5, 129.4, 130.2, 131.2, 134.9, 137.4, 142.6, 142.9, 145.3, 147.0 and 152.7.

5'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-2'-cyanobiphenyl-4-yl dimethylsulfamate 24. δ_{C} (67.9 MHz, CDCl_3) 40.0, 52.7, 111.5, 117.6, 123.8, 127.3, 127.5, 128.5, 129.2, 131.0, 134.6, 136.6, 140.4, 143.6, 143.7, 146.8 and 153.0.

5-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-chloro-3'-hydroxybiphenyl-2-carbonitrile 25. δ_{C} (67.9 MHz, DMSO- d_6) 51.9, 110.0, 117.1, 118.7, 120.8, 121.2, 128.1, 129.6, 130.8, 134.9, 137.9, 142.6, 144.4, 145.3, 152.7 and 153.7.

5'-((1*H*-1,2,4-triazol-1-yl)methyl)-4-chloro-2'-cyanobiphenyl-3-yl sulfamate 26. δ_{C} (67.9 MHz, DMSO- d_6) 51.4, 109.5, 109.6, 118.0, 124.1, 127.5, 128.1, 129.5, 131.0, 134.5, 137.6, 142.3, 142.6, 144.8, 146.1 and 152.2.

3-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-hydroxybiphenyl-4-carbonitrile 28. δ_{C} (67.9 MHz, DMSO- d_6) 51.0, 110.5, 114.2, 116.5, 117.7, 118.3, 127.6, 128.4, 130.9, 134.5, 139.8, 140.2, 145.5, 145.6, 152.7 and 158.6.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-cyanobiphenyl-3-yl sulfamate 29. δ_{C} (67.9 MHz, DMSO- d_6) 51.0, 111.3, 117.5, 121.5, 123.3, 125.9, 127.9, 128.9, 131.3, 134.7, 140.2, 140.3, 144.3, 145.5, 151.3 and 152.7.

3-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-hydroxybiphenyl-4-carbonitrile 30. δ_{C} (100.6 MHz, DMSO- d_6) 51.0, 109.2, 116.5, 117.8, 126.5, 127.5, 128.8, 134.3, 139.9, 145.4, 152.6 and 159.0 (two overlapping resonances).

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-cyanobiphenyl-4-yl sulfamate 31. δ_{C} (100.6 MHz, DMSO- d_6) δ 50.9, 110.7, 117.5, 123.4, 127.6, 128.5, 129.1, 134.5, 136.7, 140.2, 144.4, 145.4, 151.2 and 152.6.

3-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-4-carbonitrile 32. δ_{C} (100.6 MHz, DMSO- d_6) 50.5, 109.5, 117.2, 117.2, 120.6, 126.4, 126.9, 127.5, 128.4, 129.6, 134.0, 139.5, 143.5, 144.9, 152.1 and 154.1.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-4'-cyanobiphenyl-4-yl sulfamate 33. δ_{C} (67.9, DMSO- d_6) δ 51.0, 111.5, 117.5, 124.9, 127.7, 127.8, 127.9, 129.1, 129.6, 134.7, 137.9, 140.2, 143.1, 145.5, 147.0 and 152.6.

5-((1*H*-1,2,4-triazol-1-yl)methyl)biphenyl-3-carbonitrile 34. δ_C (67.9 MHz, CDCl₃) 52.5, 113.8, 118.1, 127.1, 128.8, 129.2, 129.6, 130.7, 130.9, 136.9, 138.1, 143.4, 143.5 and 152.8.

5-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-fluorobiphenyl-3-carbonitrile 35. δ_C (67.9 MHz, CDCl₃) 52.5, 113.9, 116.2-116.4, 118.0, 128.8-128.9, 129.6, 130.5-130.7, 134.3, 137.0, 142.5, 143.4, 152.8, 162.0-164.5.

5-((1*H*-1,2,4-triazol-1-yl)methyl)biphenyl-3,4'-dicarbonitrile 36. δ_C (67.9 MHz, CDCl₃) 52.3, 112.7, 114.3, 117.6, 118.2, 127.8, 130.7, 130.9, 133.0, 137.5, 141.5, 142.4, 143.5, 152.9.

5-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-hydroxybiphenyl-3-carbonitrile 37. δ_C (67.9 MHz, DMSO-*d*₆) 51.3, 112.2, 115.9, 118.6, 128.1, 128.2, 128.9, 129.2, 130.3, 138.4, 141.7, 144.6, 152.0, 158.1.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-5'-cyanobiphenyl-4-yl sulfamate 38. δ_C (67.9 MHz, DMSO-*d*₆) 51.2, 112.5, 118.5, 122.9, 128.5, 130.0, 130.7, 131.3, 136.0, 138.7, 140.7, 144.7, 150.5 and 152.2.

5-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-3-carbonitrile 39. δ_C (67.9 MHz, DMSO-*d*₆) 52.2, 109.5, 112.3, 117.1, 118.5, 120.5, 126.6, 128.2, 129.2, 129.4, 129.8, 130.6, 138.4, 140.3, 144.6, 152.0.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-5'-cyanobiphenyl-4-yl sulfamate 40. δ_C (67.9 MHz, DMSO-*d*₆) 51.2, 112.5, 118.3, 124.2, 126.9, 127.2, 128.9, 130.2, 131.1, 131.5, 137.1, 138.6, 139.3, 144.6, 146.3 and 152.1.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)biphenyl-4-ol 42. δ_C (100 MHz, DMSO-*d*₆) 2.6 (CH₂), 116.2, 126.0, 126.0, 126.3, 128.2, 129.6, 130.9, 137.3, 141.0, 144.8, 152.2, 157.8;

3'-((1*H*-1,2,4-triazol-1-yl)methyl)biphenyl-4-yl sulfamate 43. δ_C (100.6 MHz, DMSO-*d*₆) 52.7, 123.5, 126.4, 126.4, 127.8, 128.8, 130.1, 137.8, 138.8, 140.2, 145.0, 150.5 and 152.5.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chlorobiphenyl-4-yl sulfamate 45. δ_C (67.9 MHz, DMSO-*d*₆) 52.5, 124.8, 127.0, 127.1, 127.6, 128.2, 129.0, 130.0, 137.7, 138.7, 139.9, 144.9, 146.1 and 152.4 (one overlapping resonance).

4'-((1*H*-1,2,4-triazol-1-yl)methyl)-2'-cyanobiphenyl-4-yl sulfamate 48. δ_C (67.9 MHz, DMSO-*d*₆) 51.4, 110.9, 118.8, 123.0, 130.8, 131.2, 133.7, 133.8, 136.1, 137.4, 143.5, 145.2, 151.1 and 152.5.

4-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-2-carbonitrile 49. δ_C (67.9 MHz, DMSO-*d*₆) 51.4, 111.2, 116.9, 118.6, 120.6, 128.8, 130.3, 130.4, 130.5, 132.9, 133.3, 136.6, 143.4, 144.2, 152.2 and 153.8.

4'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-2'-cyanobiphenyl-4-yl sulfamate 50. δ_C (100.6 MHz, DMSO-*d*₆) 50.8, 110.5, 118.0, 123.9, 126.7, 128.9, 130.8, 130.8, 133.2, 133.3, 136.7, 137.3, 141.6, 144.6, 146.5 and 152.1.

6-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-3-carbonitrile 52. δ_C (67.9 MHz, DMSO-*d*₆) 49.8, 110.9, 116.6, 118.4, 119.9, 128.9, 129.3, 129.4, 130.4, 131.3, 133.8, 139.1, 140.7, 144.9, 152.0 and 153.2.

2'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-5'-cyanobiphenyl-4-yl sulfamate 53. δ_C (100.6 MHz, DMSO-*d*₆) 49.7, 111.1, 118.3, 123.6, 126.6, 129.2, 129.5, 131.1, 132.1, 133.7, 137.0, 139.2, 139.7, 145.0, 146.0 and 152.0.

2-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-4'-hydroxybiphenyl-3-yl)-2-methylpropanenitrile 55. δ_C (100.5 MHz, DMSO-*d*₆) 28.8, 37.3, 52.5, 116.3, 122.9, 123.3, 125.0, 125.5, 128.5, 130.5, 138.0, 141.8, 143.0, 144.9, 152.3 and 158.0.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-5'-(2-cyanopropan-2-yl)biphenyl-4-yl sulfamate 56. δ_C (100.5 MHz, DMSO-*d*₆) 28.7, 37.3, 52.3, 123.3, 123.8, 124.6, 124.9, 126.3, 128.8, 138.3, 140.9, 143.3, 144.9, 150.5 and 152.4 (one overlapping signal).

2-(5-((1*H*-1,2,4-triazol-1-yl)methyl)-3'-chloro-4'-hydroxybiphenyl-3-yl)-2-methylpropanenitrile 57. δ_C (69.5 MHz, DMSO-*d*₆) 28.8, 37.4, 52.5, 117.6, 120.9, 123.1, 124.1, 125.1, 125.9, 127.1, 128.6, 131.9, 138.2, 140.5, 143.2, 144.9, 152.4 and 153.6.

3'-((1*H*-1,2,4-triazol-1-yl)methyl)-3-chloro-5'-(2-cyanopropan-2-yl)biphenyl-4-yl sulfamate 58. δ_C (67.9 MHz, DMSO-*d*₆) 28.8, 37.4, 52.4, 124.0, 124.8, 125.0, 125.3, 126.7, 127.4, 127.7, 129.4, 138.4, 139.5, 139.6, 143.4, 145.0, 146.3 and 152.5.

B) Combustion analysis data

Compd.	Formula	Found			Calculated		
		C	H	N	C	H	N
19	C ₁₆ H ₁₂ N ₄ O	69.3	4.4	20.2	69.6	4.4	20.3
22	C ₁₆ H ₁₁ ClN ₄ O	61.6	3.5	17.8	61.8	3.6	18.0
23	C ₁₆ H ₁₂ ClN ₅ O ₃ S	49.3	3.1	17.6	49.3	3.1	18.0
24	C ₁₈ H ₁₆ ClN ₅ O ₃ S	51.3	3.8	16.7	51.7	3.9	16.8
25	C ₁₆ H ₁₁ ClN ₄ O	62.0	3.7	18.0	61.8	3.6	18.0
28	C ₁₆ H ₁₂ N ₄ O	69.2	4.4	19.9	69.6	4.4	20.3
31	C ₁₆ H ₁₃ N ₅ O ₃ S	54.0	3.9	19.3	54.1	3.7	19.7
32	C ₁₆ H ₁₁ ClN ₄ O	61.4	3.6	17.5	61.8	3.6	18.0
37	C ₁₆ H ₁₂ N ₄ O	69.4	4.4	20.1	69.6	4.4	20.3
39	C ₁₆ H ₁₁ ClN ₄ O	62.0	3.8	17.1	61.8	3.6	18.0
40	C ₁₆ H ₁₂ ClN ₅ O ₃ S	49.6	3.2	17.4	49.3	3.1	18.0
42	C ₁₅ H ₁₃ N ₃ O	71.5	5.3	16.6	71.7	5.2	16.7
47	C ₁₆ H ₁₂ N ₄ O	69.3	4.4	20.2	69.6	4.4	20.3

C) HPLC data

High performance liquid chromatography (HPLC) analysis was performed using a Waters Symmetry C₁₈-column (4.6 x 150 mm, 3.5 μ m pore size) or a Waters Sunfire C₁₈-column (4.6 x 150 mm, 3.5 μ m pore size) on a Waters 717 with autosampler and PDA detector.

Compound	Purity	t _R (min)	Solvent system (FR: Flow rate)	Column
20	99%	2.41	Isocratic 70%MeCN:30%H ₂ O, FR: 0.8mL/min	Symmetry
21	97%	2.26	Isocratic 70%MeCN:30%H ₂ O, FR: 0.8mL/min	Sunfire
26	99%	1.24	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
28	99%	1.96	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Symmetry
29	99%	1.86	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Symmetry
30	95%	1.83	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
32	98%	2.07	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Symmetry
33	99%	2.26	Isocratic 70%MeCN:30%H ₂ O, FR: 0.8mL/min	Symmetry
34	99%	1.52	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
35	96%	1.51	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
36	99%	1.42	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
37	99%	1.33	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
38	99%	1.29	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
39	99%	1.38	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
40	99%	1.31	Isocratic 90%MeCN/10%H ₂ O, FR: 1.0mL/min	Sunfire
43	99%	1.45	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
44	96%	1.98	Isocratic 80%MeCN:20%H ₂ O, FR: 1.0mL/min	Sunfire
45	99%	2.69	Isocratic 70%MeCN/30%H ₂ O, FR: 0.8mL/min	Symmetry
47	97%	1.23	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
48	99%	1.15	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
49	99%	1.33	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
50	99%	1.17	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
52	95%	1.29	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
53	99%	1.42	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Sunfire
55	98%	3.25	Isocratic 70%MeCN:30%H ₂ O, FR: 0.8mL/min	Symmetry
56	98%	3.21	Isocratic 70%MeCN:30%H ₂ O, FR: 0.8mL/min	Symmetry
57	95%	1.92	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Symmetry
58	99%	1.84	Isocratic 90%MeCN:10%H ₂ O, FR: 1.0mL/min	Symmetry

D) Crystallographic statistics of data collection and refinement for the hCA II - 23 complex.

	Complex with inhibitor 23
Data collection	
Resolution range (Å)	50 – 1.80
Space group	P2 ₁
Unit cell dimensions (Å)	42.1, 41.2, 72.3
Highest-resolution shell (Å)	1.86 - 1.80
Total no. of reflections	103023
No. of unique reflections	22577
Completeness (%)	81.5 (62.0)
R_{sym} (%)	0.067 (0.093)
$I/\sigma(I)$	10.0 (6.0)
Refinement	
No. of refined protein residues	4 - 260
No. of refined water molecules	290
No. of refined zinc atoms	1
No. of refined inhibitor molecules	2
Resolution range in refinement (Å)	20.6 – 1.80
R_{free}	0.19
Test set size (%)	5.0
R_{cryst}	0.15
Rms deviations	
Bond lengths (Å)	0.011
Bond angles (deg)	1.392
Average B value (Å ²)	12.2
Zn ²⁺ B-factor (Å ²)	7.1
Primary ligand B-factor range (Å ²)	5.0 – 14.4
Secondary ligand B-factor range (Å ²)	15.4 – 21.1

Water <i>B</i> -factor Average ($\text{\AA}^2$)	26.2
Ramachandran plot	
Most favoured (%)	88.4
Additionally allowed (%)	11.1
Generously allowed (%)	0.5
Disallowed (%)	0