SUPPLEMENTARY INFORMATION

Substituted Aryl Benzylamines as Potent and Selective Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 3

Nigel Vicker[1,†], Helen V. Bailey[1,†], Joanna M. Day[2], Mary F. Mahon[3], Andrew Smith[1], Helena J. Tutill[2], Atul Purohit[2] and Barry V. L. Potter[1,4,*]

[1] Medicinal Chemistry, Department of Pharmacy and Pharmacology and Sterix Ltd, University of Bath, Claverton Down, Bath BA2 7AY, UK

[2] Oncology Drug Discovery & Women's Health Group, Department of Endocrinology & M Metabolic Medicine & Sterix Ltd., Imperial College London, London W2 1NY, UK

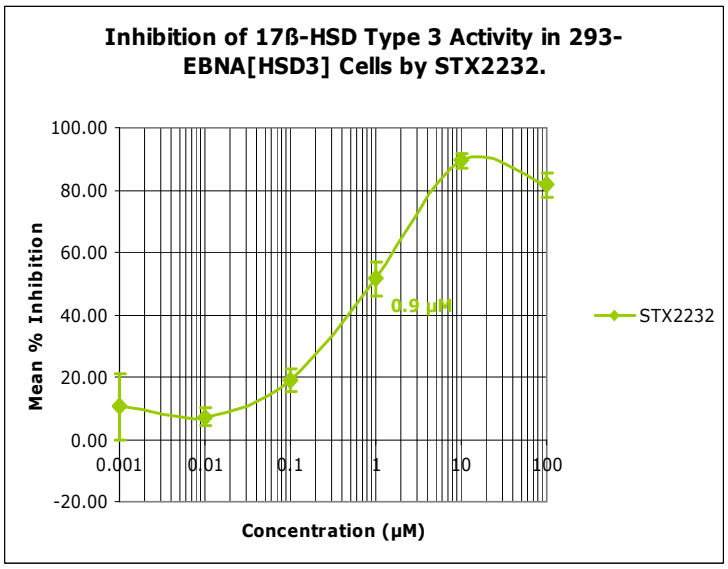
[3] Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, UK

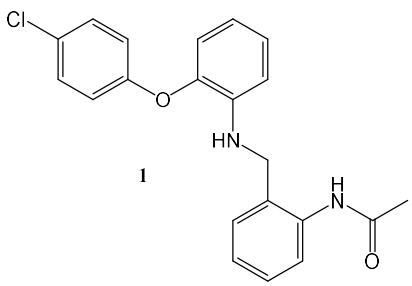
[4] Medicinal Chemistry & Drug Discovery, Department of Pharmacology, University of Oxford, Mansfield Road, Oxford, OX1 3QT, UK.

* Correspondence: barry.potter@pharm.ox.ac.uk

† Equal contribution.

Section S1. Inhibition of 17β-HSD Type 3 activity by compound **1**, (IC_{50} = 0.9 µM)





1

Figure S1. Inhibition of 17β-HSD Type 3 activity by compound **1**, (IC_{50} = 0.9 µM)

Section S2. Chiral separation of racemic **26** to give enantiomers **31** and **32.**

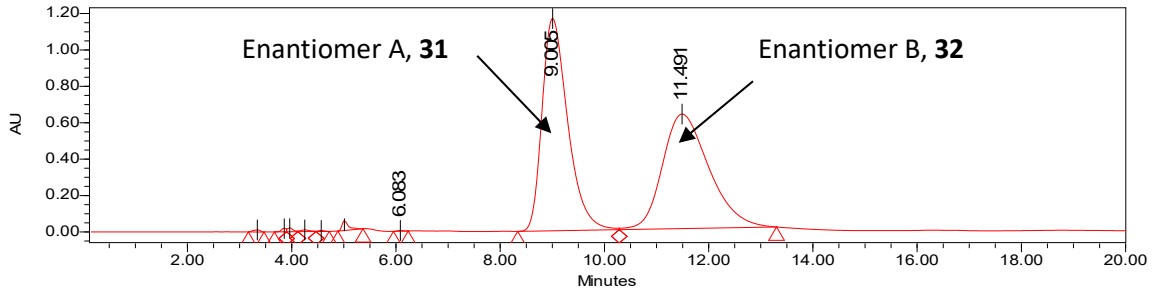


Figure S2. Chiral Separation of compound **26** to give enantiomers **31** and **32** using a Chiralcel AD-H chiral HPLC Column (80 % methanol and 20 % water at 1.0 mL/min).

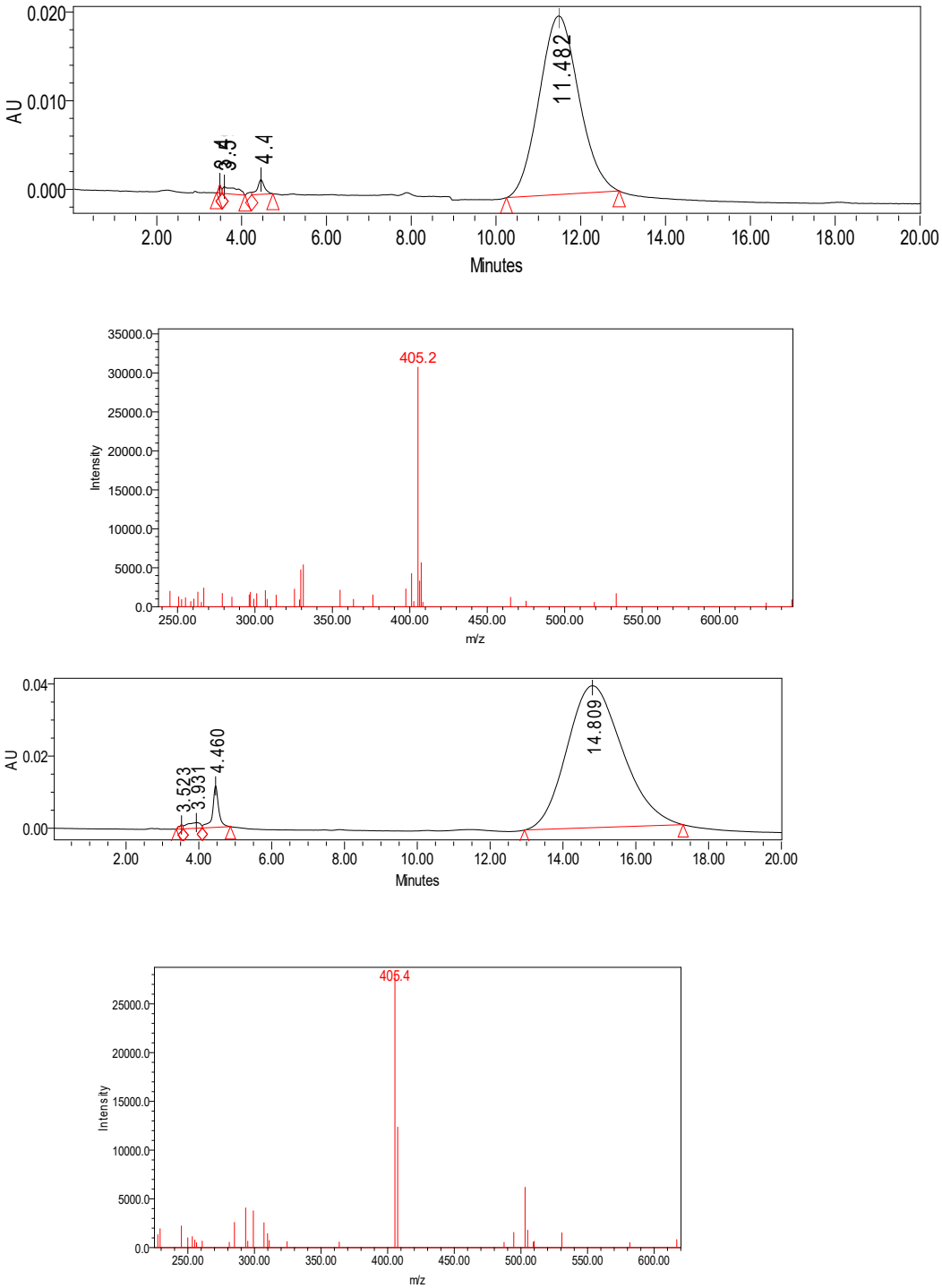


Figure S3. LCMS traces of Enantiomer A (**31**) and Enantiomer B (**32**) from the chiral separation the racemic compound **26** using a preparative Chiralcel AD-H chiral column (80 % methanol, 20 % water at 1.2 mL/min).

Section S3. X-ray data for compound **31**.

Table S1: Crystal data and structure refinement for k07farm3, compound **31**.

Identification code	k07farm3
Empirical formula	$C_{24}H_{23}ClN_2O_2$
Formula weight	406.89
Temperature/K	150.15
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	8.9500(1)
b/Å	10.4450(1)
c/Å	22.6800(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2120.19(4)
Z	4
ρ_{calc}g/cm^3	1.275
μ/mm^{-1}	0.202
F(000)	856.0
Crystal size/mm^3	0.35 × 0.25 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.056 to 60.074
Index ranges	$-12 \leq h \leq 12$, $-14 \leq k \leq 14$, $-31 \leq l \leq 30$
Reflections collected	42345
Independent reflections	6200 [R_{int} = 0.0403, R_{sigma} = 0.0264]
Data/restraints/parameters	6200/2/272
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	R_1 = 0.0329, wR_2 = 0.0764
Final R indexes [all data]	R_1 = 0.0388, wR_2 = 0.0796
Largest diff. peak/hole / e Å^{-3}	0.20/-0.21
Flack parameter	0.000(13)

Crystal Data for $C_{24}H_{23}ClN_2O_2$ (A_r =406.89): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.9500(1) Å, b = 10.4450(1) Å, c = 22.6800(2) Å, U = 2120.19(4) Å^3, Z = 4, T = 150 K, μ(MoK$_\alpha$) = 0.202 mm^{-1}, D_{calc} = 1.275 g cm^{-3}, 42345 reflections measured ($7.056° \leq 2\theta \leq 60.074°$), 6200 unique ($R_{int}$ = 0.0403) which were used in all calculations. The final R_1 was 0.0329 ($I \geq 2\sigma(I)$) and wR_2 was 0.0796 (all data).

H1A and H2 (attached to N1 and N2, respectively, in the structure of **k07farm3**, were located and refined at a distance of 0.9Å from the parent nitrogen atoms. The gross structure is dominated by 1-dimensional, hydrogen-bonded polymers which propagate along the *a*-axis.

Table S2: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for k07farm3. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	13382.8(5)	5596.5(5)	6077.3(2)	40.78(13)
O1	7750.0(14)	4512.2(12)	7316.4(5)	31.3(3)
O2	7183.1(13)	7843.6(12)	10379.9(6)	34.4(3)
N1	8651.4(16)	4859.8(13)	8464.9(6)	25.5(3)
N2	9268.8(15)	6827.1(13)	10065.9(6)	24.7(3)
C1	9448.2(18)	5227.0(14)	9001.4(7)	24.3(3)
C2	10980.1(19)	4564.5(15)	8993.4(7)	27.5(3)
C3	11963.0(19)	4982.8(17)	8494.9(8)	31.9(4)
C4	12551(2)	4214(2)	8098.7(10)	46.0(5)
C5	8614.9(19)	4829.2(15)	9555.5(7)	26.3(3)
C6	7902(2)	3644.8(18)	9573.5(8)	37.9(4)
C7	7206(3)	3208.2(18)	10080.4(9)	44.3(5)
C8	7245(3)	3947.0(18)	10589.3(8)	38.4(4)
C9	7942(2)	5123.3(17)	10583.1(7)	29.8(3)
C10	8614.8(17)	5579.4(15)	10067.4(7)	24.5(3)
C11	8502.2(18)	7886.2(15)	10219.5(7)	25.0(3)
C12	9337.5(19)	9135.6(16)	10186.8(8)	28.8(3)
C13	7475.1(17)	5593.9(15)	8248.0(7)	25.0(3)
C14	6683(2)	6477.9(16)	8587.6(8)	29.4(3)
C15	5513(2)	7185.3(18)	8344.4(9)	35.4(4)
C16	5100(2)	7017(2)	7760.1(10)	40.2(4)
C17	5869(2)	6131.8(19)	7417.4(9)	36.4(4)
C18	7028.8(19)	5443.8(16)	7659.6(7)	27.4(3)
C19	9074.7(19)	4848.5(16)	7041.5(7)	26.2(3)
C20	9785(2)	6019.5(16)	7114.5(7)	28.4(3)
C21	11124(2)	6255.6(17)	6817.7(8)	30.3(3)
C22	11713(2)	5320.8(17)	6455.7(7)	31.0(4)
C23	11008(2)	4153.6(17)	6382.9(8)	34.1(4)
C24	9683(2)	3912.9(17)	6679.8(8)	32.6(4)

Table S3: Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for k07farm3. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	32.8(2)	51.5(3)	38.1(2)	6.6(2)	5.33(18)	7.7(2)
O1	36.5(6)	30.2(6)	27.2(6)	-4.3(5)	2.1(5)	-7.5(5)
O2	20.7(5)	34.6(6)	47.9(8)	-7.4(6)	1.2(5)	1.4(5)

N1	29.2(7)	25.9(6)	21.5(6)	-1.8(5)	1.5(5)	1.9(5)
N2	20.6(6)	27.6(6)	26.0(6)	-4.1(5)	1.0(5)	-0.3(5)
C1	30.6(7)	22.1(7)	20.4(7)	0.0(6)	0.8(6)	-1.5(6)
C2	30.8(7)	25.1(7)	26.8(7)	1.9(6)	-1.5(6)	1.2(6)
C3	29.3(8)	30.2(8)	36.2(9)	2.1(7)	2.1(7)	0.3(7)
C4	45.6(11)	44.3(11)	48.2(11)	-4.0(9)	15.5(9)	-0.4(9)
C5	32.8(8)	24.3(7)	21.9(7)	1.4(6)	1.7(6)	-1.1(6)
C6	59.6(12)	27.0(8)	27.2(8)	-2.2(7)	8.8(8)	-9.1(8)
C7	69.0(14)	30.4(9)	33.3(9)	1.4(7)	13.7(10)	-14.3(9)
C8	53.4(12)	35.6(9)	26.3(8)	4.6(7)	9.6(8)	-4.4(8)
C9	32.8(8)	34.1(8)	22.6(7)	-1.0(6)	1.1(6)	1.7(7)
C10	23.9(7)	25.8(7)	23.7(7)	-0.1(6)	-0.5(5)	0.8(6)
C11	22.5(7)	28.8(8)	23.8(7)	-3.4(6)	-4.1(6)	1.6(6)
C12	26.6(7)	28.3(8)	31.6(8)	-2.8(6)	-1.4(7)	-0.1(6)
C13	25.4(7)	23.7(7)	26.0(7)	2.9(6)	2.0(6)	-4.2(6)
C14	28.9(8)	29.2(8)	30.2(8)	0.2(6)	5.6(7)	-2.5(7)
C15	29.0(9)	31.4(8)	45.9(10)	2.8(8)	8.2(8)	1.9(7)
C16	27.2(8)	40.9(10)	52.5(12)	11.0(9)	-2.5(8)	1.5(8)
C17	32.8(9)	41.7(10)	34.8(9)	6.4(8)	-6.7(8)	-6.0(8)
C18	28.3(7)	27.1(8)	26.6(7)	0.8(6)	1.2(6)	-5.3(6)
C19	31.4(8)	28.6(8)	18.6(7)	1.0(6)	-2.9(6)	-0.4(6)
C20	34.4(8)	27.1(8)	23.7(7)	-1.9(6)	-0.3(6)	-0.2(6)
C21	34.5(8)	28.6(8)	27.8(8)	1.4(7)	-1.3(7)	-0.5(7)
C22	29.4(8)	37.6(9)	26.0(7)	5.6(7)	0.1(6)	6.6(7)
C23	41.1(9)	30.7(9)	30.4(8)	-2.8(7)	-0.7(7)	8.5(7)
C24	41.5(9)	27.0(8)	29.3(8)	-2.3(6)	-4.3(7)	0.5(7)

Table S4: Bond Lengths for k07farm3.

Atom	**Atom**	**Length/Å**	**Atom**	**Atom**	**Length/Å**
Cl1	C22	1.7474(18)	C8	C9	1.378(3)
O1	C18	1.403(2)	C9	C10	1.399(2)
O1	C19	1.385(2)	C11	C12	1.506(2)
O2	C11	1.236(2)	C13	C14	1.396(2)
N1	C1	1.462(2)	C13	C18	1.402(2)
N1	C13	1.392(2)	C14	C15	1.395(3)
N2	C10	1.429(2)	C15	C16	1.387(3)
N2	C11	1.348(2)	C16	C17	1.390(3)
C1	C2	1.536(2)	C17	C18	1.377(2)
C1	C5	1.519(2)	C19	C20	1.388(2)

C2	C3	1.498(2)	C19	C24	1.387(2)
C3	C4	1.315(3)	C20	C21	1.397(2)
C5	C6	1.392(2)	C21	C22	1.380(2)
C5	C10	1.401(2)	C22	C23	1.383(3)
C6	C7	1.385(3)	C23	C24	1.386(3)
C7	C8	1.389(3)			

Table S5: Bond Angles for k07farm3.

Atom	**Atom**	**Atom**	**Angle/°**	**Atom**	**Atom**	**Atom**	**Angle/°**
C19	O1	C18	117.88(12)	N1	C13	C14	123.61(15)
C13	N1	C1	121.24(13)	N1	C13	C18	119.36(15)
C11	N2	C10	122.65(13)	C14	C13	C18	117.03(15)
N1	C1	C2	107.91(12)	C15	C14	C13	120.90(17)
N1	C1	C5	112.18(13)	C16	C15	C14	120.71(17)
C5	C1	C2	108.95(13)	C15	C16	C17	119.11(17)
C3	C2	C1	113.69(13)	C18	C17	C16	119.83(18)
C4	C3	C2	124.94(18)	C13	C18	O1	118.33(14)
C6	C5	C1	119.47(14)	C17	C18	O1	119.17(15)
C6	C5	C10	118.21(15)	C17	C18	C13	122.43(16)
C10	C5	C1	122.18(14)	O1	C19	C20	124.18(15)
C7	C6	C5	121.54(17)	O1	C19	C24	115.05(15)
C6	C7	C8	119.69(18)	C24	C19	C20	120.76(16)
C9	C8	C7	119.91(17)	C19	C20	C21	119.41(16)
C8	C9	C10	120.46(16)	C22	C21	C20	119.29(17)
C5	C10	N2	120.55(14)	C21	C22	Cl1	120.13(15)
C9	C10	N2	119.27(14)	C21	C22	C23	121.37(17)
C9	C10	C5	120.16(15)	C23	C22	Cl1	118.50(14)
O2	C11	N2	122.20(15)	C22	C23	C24	119.49(16)
O2	C11	C12	121.33(15)	C23	C24	C19	119.67(17)
N2	C11	C12	116.48(14)				

Table S6: Hydrogen Bonds for k07farm3.

D	**H**	**A**	**d(D-H)/Å**	**d(H-A)/Å**	**d(D-A)/Å**	**D-H-A/°**
N2	H2	O2[1]	0.898(7)	1.921(7)	2.8185(18)	178(2)

[1]1/2+X,3/2-Y,2-Z

Table S7: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for k07farm3.

Atom	*x*	*y*	*z*	U(eq)
H1	9250(20)	4560(20)	8180(7)	37(5)
H2	10206(12)	6910(20)	9930(9)	38(6)
H1A	9595	6176	9004	29
H2A	11497	4743	9370	33
H2B	10827	3628	8966	33
H3	12178	5871	8462	38
H4A	12361	3320	8116	55
H4B	13165	4553	7795	55
H6	7893	3124	9230	46
H7	6703	2407	10080	53
H8	6793	3642	10941	46
H9	7967	5628	10931	36
H12A	8788	9735	9935	43
H12B	10333	8987	10020	43
H12C	9435	9498	10584	43
H14	6943	6599	8990	35
H15	4993	7788	8582	43
H16	4303	7501	7596	48
H17	5595	6002	7017	44
H20	9364	6654	7364	34
H21	11625	7051	6865	36
H23	11427	3522	6131	41
H24	9194	3111	6636	39

Crystal structure determination of [k07farm3]

Refinement model description. Number of restraints - 2, number of constraints - unknown. Details:

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1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2. Restrained distances
 H1-N1 = H2-N2
 0.9 with sigma of 0.005
3.a Ternary CH refined with riding coordinates:
 C1(H1A)
3.b Secondary CH2 refined with riding coordinates:
 C2(H2A,H2B)
3.c Aromatic/amide H refined with riding coordinates:
 C3(H3), C6(H6), C7(H7), C8(H8), C9(H9), C14(H14), C15(H15), C16(H16),
 C17(H17), C20(H20), C21(H21), C23(H23), C24(H24)
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3.d X=CH2 refined with riding coordinates:
 C4(H4A,H4B)
3.e Idealised Me refined as rotating group:
 C12(H12A,H12B,H12C)
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This report has been created with Olex2, compiled on 2018.05.29 svn.r3508 for OlexSys.

Crystallographic data for **31** been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 2088971. A copy of these data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax (+44) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk.2088971.