Supplementary Material: Discovery of Vibegron: A Potent and Selective β_3 Adrenergic Receptor Agonist for the Treatment of Overactive Bladder

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β_3 Adrenergic Receptor Agonists, Overactive Bladder, Vibegron

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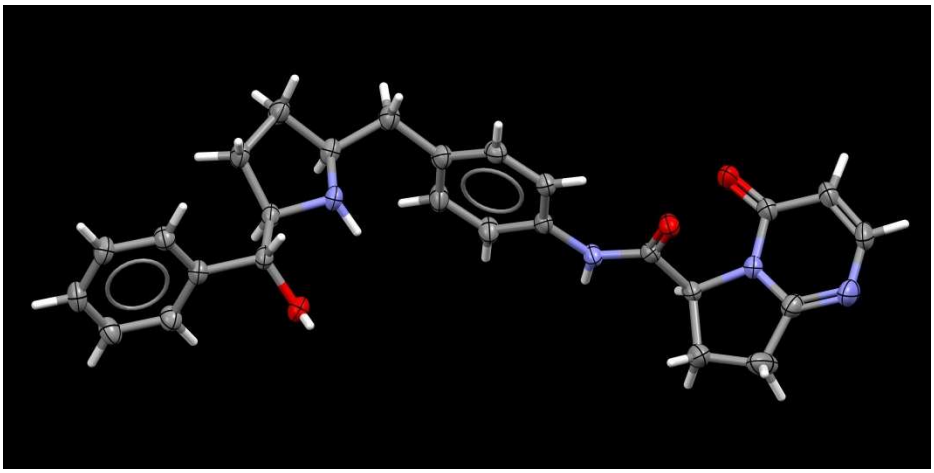
A) **Crystal data and structure refinement for Compound 7 (Vibegron) [CCDC 1421635)]**

A single crystal grown from acetonitrile and water by slow evaporation was selected for single crystal X-ray data analysis. The crystal was a prismatic needle with dimensions of 0.41mm x 0.13mm x 0.06mm. Data collection was performed at 100K on an Oxford Gemini system with a Cu radiation source. The unit cell was determined to be monoclinic in space group $P2_1$ with one molecule in the asymmetric unit. Crystallographic data is summarized in Table 1. Absolute configuration was supported by anomalous-dispersion effects in diffraction measurements on the crystal yielding a Flack parameter of -0.07(17). Results supported that the stereochemistry of Compound 7 was as shown in Scheme 1. Figure 1 shows an ORTEP representation of Compound 7 with thermal ellipsoid set at the 50% probability level. Full structural details have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1421635).

Figure A1: ORTEP representation of Compound 7 (Vibegron) with thermal ellipsoids set at the 50% probability level.



Scheme A1: Scheme showing the absolute configuration of Compound **7** (Vibegron).

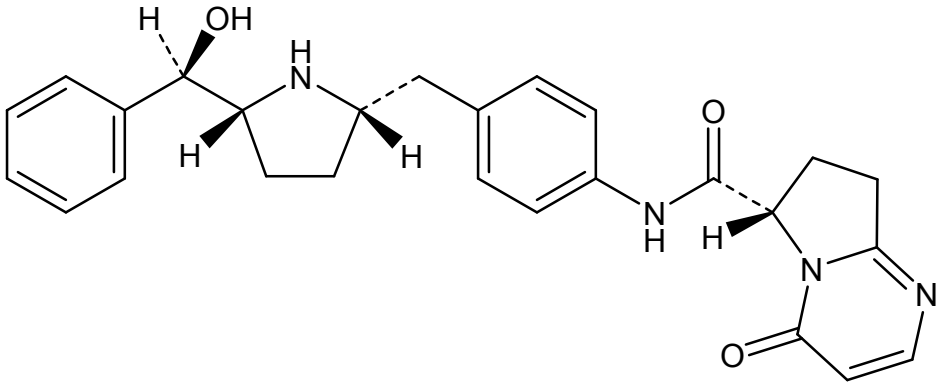


Table A1. Crystal data and structure refinement for Compound 7 (Vibegron)

Empirical formula	$C_{26}H_{28}N_4O_3$	
Formula weight	444.53	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.832 (8) Å	α= 90°
	b = 6.3650 (19) Å	β= 95.35 (3)°
	c = 15.531 (4) Å	γ = 90°
Volume	1164.6(9) $Å^3$	
Z	2	
Density (calculated)	1.268 Mg/m^3	
Absorption coefficient	0.680 mm^{-1}	
F(000)	472	
Crystal size	0.06 x 0.12 x 0.41 mm^3	
Theta range for data collection	2.855 to 66.6034°.	
Index ranges	-14<=h<=13, -6<=k<=7, -18<=l<=18	
Reflections collected	19109	
Independent reflections	3758 [R(int) = 0.0308]	
Completeness to theta = 66.6°	98.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.960 and 0.748	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3758 / 4 / 299	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0315, wR2 = 0.0837	
R indices (all data)	R1 = 0.0327, wR2 = 0.0847	
Absolute structure parameter	0.07(17)	
Largest diff. peak and hole	0.262 and -0.195 $e.Å^{-3}$	

B) Algorithm for cLog D determinations.

Calculated Log D determinations (cLog D) were determined as AlogD pH7.4 – AlogP + cLogP, using software from ACD (AlogD and AlogP) and Biobyte (cLogP).