Supplementary Information

Covalent cannabinoid receptor ligands – structural insight and selectivity challenges.

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Ligand	Reported Data K_i, K_B, IC_{50} (nM) or pK_i, ± error/confidence limit range	Species, Receptor, Membrane	[^{3}H] Radioligand (concentration in nM) and K_d (nM) or reference cited to conditions used, where provided	Data reported in reference
Biaryl pyrazole				
AM251	K_i = 7.49 (6.38 – 8.78)	rCB_1R forebrain membranes	CP55,940 (0.8) As described in Drake *et al.* and Charalambous *et al.*	Lan *et al.*
	K_i = 2290 (1640 – 3190)	mCB_2R spleen		
SR141716A (Rimonabant)	K_i = 11.5 (8.45 – 13.7)	rCB_1R forebrain membranes		
	K_i = 1640 (1440 – 1850)	mCB_2R spleen		
1	IC_{50} = 56	rCB_1R forebrain membranes	CP55,940 (0.35)	Howlett *et al.*
	IC_{50} = 394 ± 124	mCB_2R spleen	CP55,940 (0.8)	
2	IC_{50} = 28	rCB_1R forebrain membranes	CP55,940 (0.35)	
	IC_{50} = 1490 ± 439	mCB_2R spleen	CP55,940 (0.8)	
3	IC_{50} = 210	rCB_1R forebrain membranes	CP55,940 (0.35)	
	IC_{50} = 1110 ± 161	mCB_2R spleen	CP55,940 (0.8)	
4	IC_{50} = 130	rCB_1R forebrain membranes	CP55,940 (0.35)	
	IC_{50} = 5970 ± 413	mCB_2R spleen	CP55,940 (0.8)	
AM6538	K_i = 3.4 ± 1.0	hCB_1R HEK293F	CP55,940 (0.79) K_d = 5.6 ± 2.3	Hua *et al.* 2016.
Aryl pyrazoles				
AM263	K_i = 23	rCB_1R brain membranes	CP55,940 (0.35) As described in *Shim et al.*	Shim *et al.*
	K_i = 26.8	mCB_2R spleen	CP55,940 (0.8) As described in Makriyannis *et al.*	Chen *et al.*
5	IC_{50} = 82	rCB_1R forebrain membranes	CP55,940 (0.35)	Howlett *et al.*
	IC_{50} = 20.7 ± 2.3	mCB_2R spleen	CP55,940 (0.8)	
6	IC_{50} = 46	rCB_1R forebrain membranes	CP55,940 (0.35)	
	IC_{50} = 22.6 ± 3.1	mCB_2R spleen	CP55,940 (0.8)	
AM10257	K_i = 13	hCB1 HEK293F	CP55,940 (0.79)	Li *et al*
	K_i = 0.075 (0.063 – 0.09)[a]	hCB_2R HEK293F [a] and Sf9 membrane	CP55,940 K_d = 0.86	
AM6731	K_i = 0.54 (0.42–0.70)	hCB2-HEK293	CP55,940 K_d = 0.62 (0.51–0.73)	Mercier *et al.*
AM1336	K_i = 0.63 (0.44 - 0.81)			
AM6720	K_i = 1.03 (0.85 –1.25)			
Tricyclic Cannabinols				
AM11542	K_i = 0.11 (0.09–0.13)	hCB_1R HEK293F	CP55,940 (0.79) K_d = 5.6 ± 2.3	Hua *et al.* 2020.
AM841	K_i = 1.14 (0.85–1.54)	hCB_1R HEK293F	CP55,940 (0.79) K_d = 5.6 ± 2.3	Hua *et al.*. 2016.
	K_i = 9.05 ± 2.06	hCB1-CHO-K1	CP55,940 (3.0) K_d = 6.7 ± 0.34	Picone *et al.*
	K_i = 1.51 (1.17–1.93)	hCB_2R HEK293	CP55,940 (0.76) K_d = 0.67 (0.51 – 0.83)	Pei *et al.*
	K_i = 4.5 (3.8-5.3)		WIN55212-2 (0.91) K_d = 3.54 (2.27 – 4.80)	

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AM4073	K_i = 3.3 (1.9 – 5.7)	hCB$_2$R HEK293	CP55,940 K_d = 2.1 (1.8−2.3) As described in Pei *et al.*	Zhou *et al.*
AM4099	K_i = 12.6 (9.0 – 17.5)			
7	K_i = 0.4 ± 0.1	rCB$_1$R brain membranes	CP55,940 As described in Nikas *et al.*	Jiang *et al.*
	K_i = 1.1 ± 0.1	mCB$_2$R HEK293		
	K_i = 1.0 ± 0.2	hCB$_2$R HEK293		
8	K_i = 37.6 ± 0.6	rCB$_1$R brain membranes		
	K_i = 14.6 ± 2.1	mCB$_2$R HEK293		
	K_i = 4.2 ± 0.3	hCB$_2$R HEK293		
9	K_i = 0.41 ± 0.05	rCB$_1$R brain membranes		
	K_i = 0.8 ± 0.1	mCB$_2$R HEK293		
	K_i = 1.40 ± 0.06	hCB$_2$R HEK293		
AM993	K_i = 18.6	rCB$_1$R brain membranes	CP55,940 As described in Nikas *et al.*	Ogawa *et al.*
	K_i = 38.4	mCB$_2$R HEK293		
	K_i = 24.8	hCB$_2$R HEK293		
AM994	K_i = 35.4	rCB$_1$R brain membranes		
	K_i = 31.7	mCB$_2$R HEK293		
	K_i = 13.1	hCB$_2$R HEK293		
AM10509	K_i = 2.3	rCB$_1$R brain membranes	CP55,940 As described in Ogawa *et al.*	Ho *et al.*
	K_i = 2.9	mCB$_2$R HEK293		
	K_i = 3.1	hCB$_2$R HEK293		
AM10504	K_i = 4.8	rCB$_1$R brain membranes		
	K_i = 9.5	mCB$_2$R HEK293		
	K_i = 3.6	hCB$_2$R HEK293		
AM967	K_i = 1254	rCB$_1$R brain membranes	CP55,940 As described in Krishnamurthy *et al.*	Dixon *et al.*
	K_i = 34.2	mCB$_2$R HEK293		
	K_i = 124.8	hCB$_2$R HEK293		
10	K_i = 156.6	rCB$_1$R brain membranes		
	K_i = 152.1	mCB$_2$R HEK293		
	K_i = 124.8	hCB$_2$R HEK293		
HU-308	K_i > 10000	rCB1 brain (synaptosomal) membranes	HU-243	Hanuš *et al.*
	K_i = 22.7 ± 3.9	hCB$_2$R COS-7	HU-243	

Ligand	Reported Data K_i, K_B, IC_{50} (nM) or pK_i, ± error/confidence limit range	Species, Receptor, Membrane	[^{3}H] Radioligand (concentration in nM) and K_d (nM) or reference cited to conditions used, where provided	Data reported in reference
11	K_i = 2670	hCB_1R CHO	CP55,940 As described in Soethoudt *et al.* 2017.	Westphal *et al.*
	K_i = 158	mCB_2R CHO		
	K_i = 13.1	hCB_2R CHO		
12	K_i = 1130	hCB_1R CHO		
	K_i = 40	mCB_2R CHO		
	K_i = 3.7	hCB_2R CHO		
13	K_i = 357	hCB_1R CHO		
	K_i = 417	mCB_2R CHO		
	K_i = 96	hCB_2R CHO		
RO7239315	K_i = 3890	hCB_1R CHO	CP55,940 As described in Soethoudt *et al.* 2017.	Westphal *et al.* Soethoudt *et al.* 2018.
	K_i = 88	mCB_2R CHO		
	K_i = 9.3	hCB_2R CHO		
Aryl Pyridinyl				
LE101	pK_i = <5	hCB_1R CHOK	CP55,940 As described in Mukhopadhyay *et al.*	Soethoudt *et al.* 2018
	pK_i = 7.5 ± 0.1	hCB_2R CHOK		
LEI121	pK_i = <5	hCB_1R CHOK	CP55,940	Soethoudt *et al.* 2018.
	pK_i = 7.2 ± 0.4	hCB_2R CHOK	CP55,940 (1.5) As described in Dixon *et al.*	
LEI120	pK_i = 6.9 ± 0.3	hCB_2R CHOK	CP55,940 (1.5) As described in Dixon *et al.*	Soethoudt *et al.* 2018.
Indole Carboxamides				
ORG27569	K_B = 217.3 (170.3 – 277.2) α = 6.95	hCB_1R HEK293	CP55,940 As described in Ahn *et al.*	Ahn. *et al.*

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