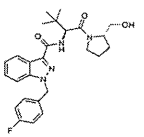
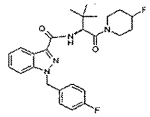
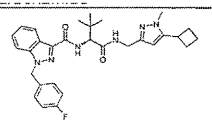
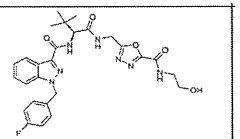
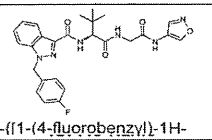
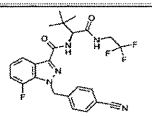
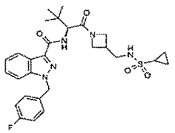
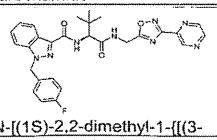
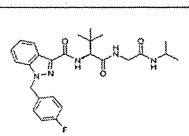
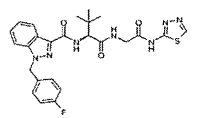
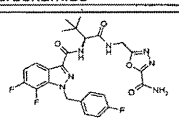
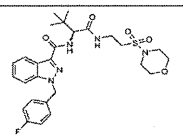
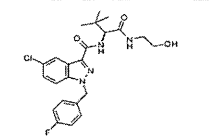
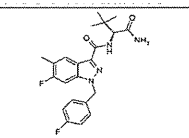
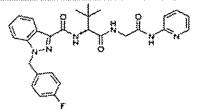
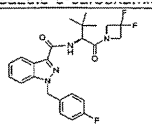
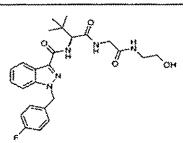
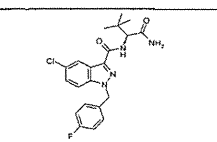
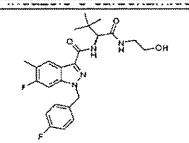
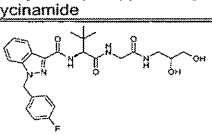
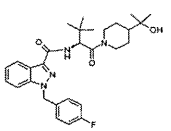
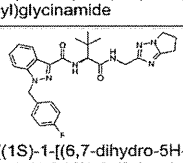
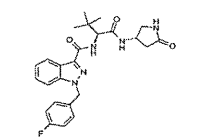
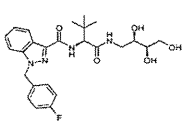
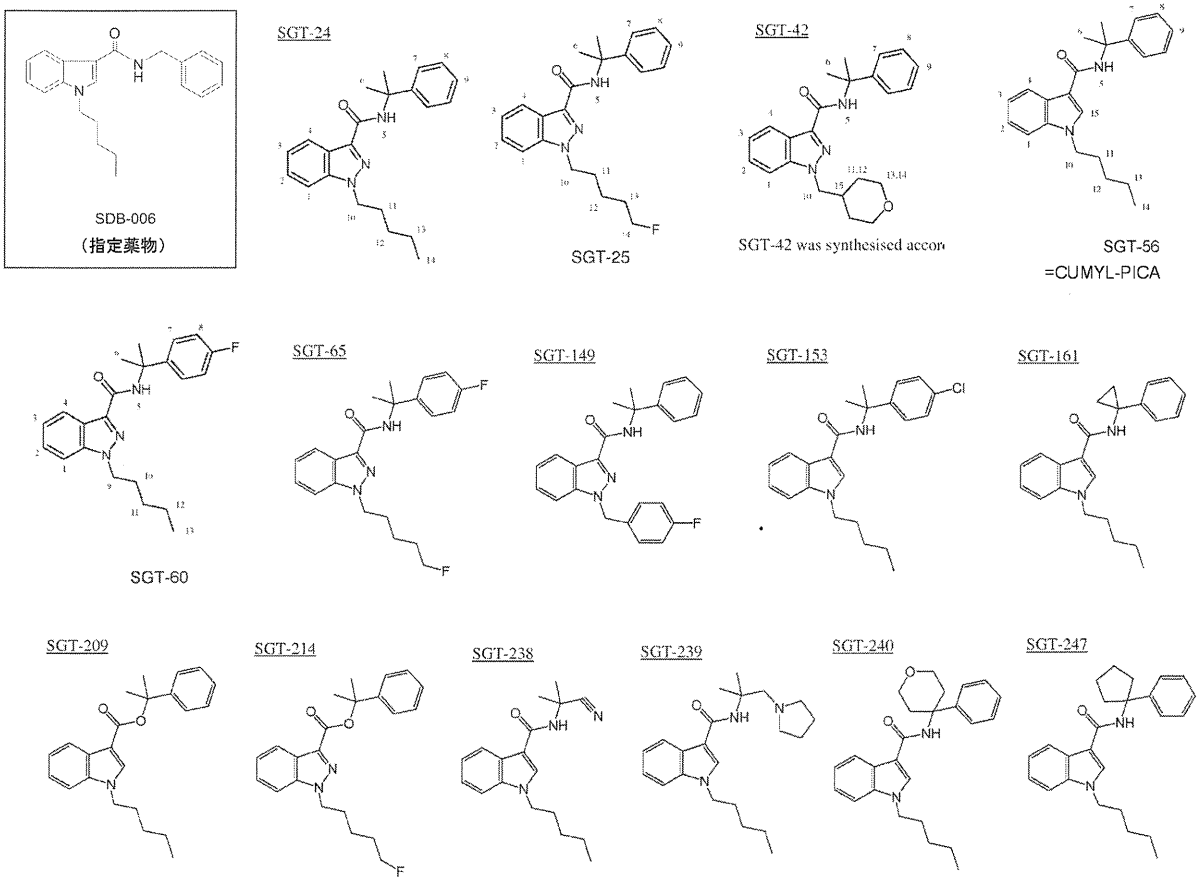
306 0.78	 1-(4-fluorobenzyl)-N-[(1S)-1-{[(2S)-2-(hydroxymethyl)-pyrrolidin-1-yl]carbonyl}-2,2-dimethylpropyl]-1H-indazole-3-carboxamide	341 3.74	 1-(4-fluorobenzyl)-N-{(1S)-1-[(4-fluoropiperidin-1-yl)-carbonyl]-2,2-dimethylpropyl}-1H-indazole-3-carboxamide	416 9.26	 N-[(1S)-1-{[(5-cyclobutyl-1-methyl-1H-pyrazol-3-yl)-methyl]carbamoyl}-2,2-dimethylpropyl]-1-(4-fluoro-benzyl)-1H-indazole-3-carboxamide	462 2.29	 1-(4-fluorobenzyl)-N-{(1S)-1-[({5-[(2-hydroxyethyl)-carbamoyl]-1,3,4-oxadiazol-2-yl}methyl)carbamoyl]-2,2-dimethylpropyl}-1H-indazole-3-carboxamide	518 --- 1.80	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-isoxazol-4-ylglycinamide
309 1.59	 1-(4-cyanobenzyl)-N-{(1S)-2,2-dimethyl-1-[(2,2,2-trifluoroethyl)carbamoyl]-propyl}-7-fluoro-1H-indazole-3-carboxamide	345 0.61	 N-{(1S)-1-[(3-{[(cyclopropyl-sulfonyl)amino]methyl}-azetidin-1-yl)carbonyl]-2,2-dimethylpropyl}-1-(4-fluoro-benzyl)-1H-indazole-3-carboxamide	418 0.78	 N-[(1S)-2,2-dimethyl-1-{[(3-pyrazin-2-yl-1,2,4-oxadiazol-5-yl)methyl]carbamoyl}-propyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide	493 0.93	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-isopropyl-glycinamide	519 0.95	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-1,3,4-thiadiazol-2-ylglycinamide
328 0.71	 N-[(1S)-1-{[(5-carbamoyl-1,3,4-oxadiazol-2-yl)-methyl]carbamoyl}-2,2-dimethylpropyl]-6,7-difluoro-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide	357 2.93	 N-[(1S)-2,2-dimethyl-1-{[2-(morpholin-4-ylsulfonyl)-ethyl]carbamoyl}propyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide	428 0.89	 5-chloro-1-(4-fluorobenzyl)-N-{(1S)-1-[(2-hydroxyethyl)-carbamoyl]-2,2-dimethyl-propyl}-1H-indazole-3-carboxamide	509 0.45	 N-[(1S)-1-carbamoyl-2,2-dimethylpropyl]-6-fluoro-1-(4-fluorobenzyl)-5-methyl-1H-indazole-3-carboxamide	520 1.88	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-pyridin-2-yl-glycinamide
330 0.20	 N-{(1S)-1-[(3,3-difluoro-azetidin-1-yl)carbonyl]-2,2-dimethylpropyl}-1-(4-fluoro-benzyl)-1H-indazole-3-carboxamide	376 1.52	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-(2-hydroxy-ethyl)glycinamide	429 0.44	 N-[(1S)-1-carbamoyl-2,2-dimethylpropyl]-5-chloro-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide	511 0.68	 6-fluoro-1-(4-fluorobenzyl)-N-{(1S)-1-[(2-hydroxyethyl)-carbamoyl]-2,2-dimethyl-propyl}-5-methyl-1H-indazole-3-carboxamide	523 5.22 4.28	 N-{[1-(4-fluorobenzyl)-1H-indazol-3-yl]carbonyl}-3-methyl-L-valyl-N-[(2R)-2,3-dihydroxypropyl]glycinamide
338 3.43	 1-(4-fluorobenzyl)-N-[(1S)-1-{[4-(1-hydroxy-1-methylethyl)-piperidin-1-yl]carbonyl}-2,2-dimethylpropyl]-1H-indazole-3-carboxamide	415 8.69	 N-{(1S)-1-[(6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazol-2-ylmethyl)carbamoyl]-2,2-dimethylpropyl}-1-(4-fluoro-benzyl)-1H-indazole-3-carboxamide	459 2.78	 N-[(1S)-2,2-dimethyl-1-{[(3S)-5-oxopyrrolidin-3-yl]-carbamoyl}propyl]-1-(4-fluoro-benzyl)-1H-indazole-3-carboxamide	516 4.28	 N-[(1S)-2,2-dimethyl-1-{[(2R,3R)-2,3,4-trihydroxy-butyl]carbamoyl}propyl]-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide		

Fig. 2D



Compound	CB_1 EC50 (nM)	CB_2 EC50 (nM)
SGT-24	0.15	0.41
SGT-25	< 0.1 #	0.37
SGT-42	0.10	0.59
SGT-56	0.66	13
SGT-60	0.17	0.69
SGT-65	< 0.1 #	0.61
SGT-149	< 0.1 #	0.21
SGT-153	0.72	5.7
SGT-161	2.8	29
SGT-209	N.C. ##	N.C. ##
SGT-214	2200	94
SGT-238	2500	6300
SGT-239	200	440
SGT-240	3.6	11
SGT-247	10	4.7

EC50 value below the lowest test concentration. Concentration-response curve shows more than 50 % effect at the lowest validated testing concentration.

EC50 value not calculable. Concentration-response curve shows less than 25% effect at the highest validated testing concentration.

Fig. 3

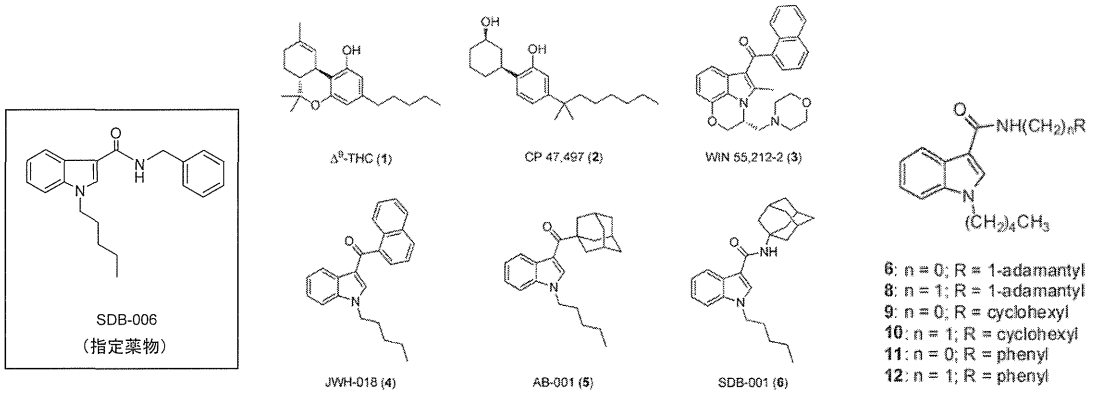


Table 1. Functional Activity of Δ^9-THC, WIN 55,212-2, and 5–12 at Rat CB_1 and Human CB_2 Receptors

	rCB$_1$		hCB$_2$		
compd	pEC$_{50}$ ± SEM (EC$_{50}$, nM)	max ± SEM (% WIN 55,212-2)	pEC$_{50}$ ± SEM (EC$_{50}$, nM)	max ± SEM (% WIN 55,212-2)	CB$_1$ selectivity[a]
1 (Δ^9-THC)	7.24 ± 0.12 (58)	78 ± 5	n.d.	13 (at 10 μM)	
3 (WIN 55,212–2)	7.57 ± 0.14 (27)		6.93 ± 0.1 (117)		4.3
5 (AB-001)	7.46 ± 0.16 (35)	105 ± 8	7.32 ± 0.12 (48)	86 ± 6	1.4
6 (SDB-001)	7.47 ± 0.12 (34)	98 ± 6	7.54 ± 0.11 (29)	91 ± 5	0.9
7 (AB-002)	7.43 ± 0.13 (37)	90 ± 6	7.05 ± 0.13 (89)	82 ± 7	2.4
8 (SDB-002)	7.37 ± 0.12 (43)	84 ± 6	7.24 ± 0.26 (57)	23 ± 4	1.3
9 (SDB-003)	7.43 ± 0.16 (37)	93 ± 7	6.99 ± 0.08 (102)	95 ± 5	2.7
10 (SDB-004)	7.79 ± 0.19 (16)	94 ± 8	6.67 ± 0.09 (216)	71 ± 5	13.1
11 (SDB-005)	7.68 ± 0.11 (21)	99 ± 6	6.86 ± 0.12 (140)	74 ± 6	6.7
12 (SDB-006)	7.73 ± 0.11 (19)	85 ± 5	6.88 ± 0.22 (134)	68 ± 9	7.2

[a] CB_1 selectivity expressed as the ratio of CB_2 EC_{50} to CB_1 EC_{50}. n.d. = not determined.

Fig. 4

TABLE 1

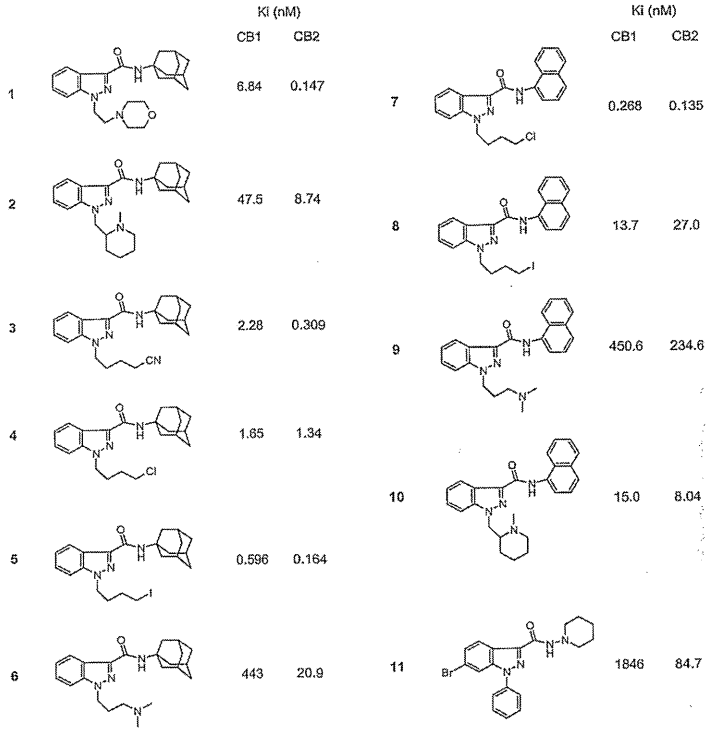
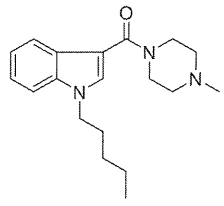
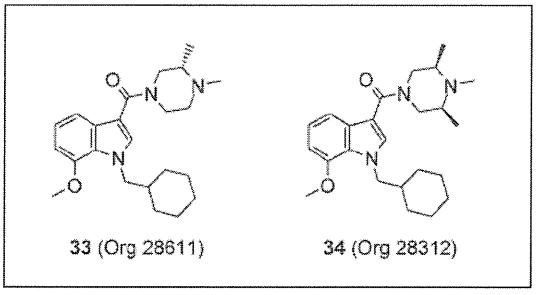


Fig. 5



MEPIRAPIM
（指定薬物）



33 (Org 28611)　　34 (Org 28312)

Table 3　Profile of CB1 agonists in *in vitro* hCB1 and hCB2 binding assays

	CB1 pKi	CB2 pKi
CP 55,940	9.5	9.5
WIN 55,212-2	7.9	8.6
Org 28611	8.9	8.8
Org 28312	8.9	9.1

Fig. 6

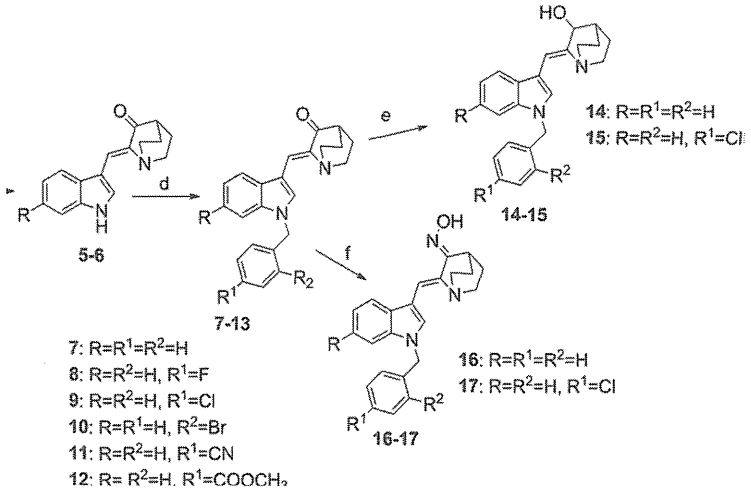
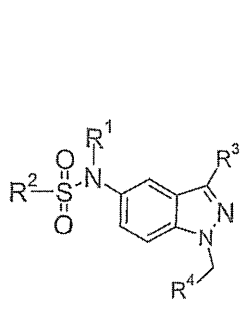


Table 1
K_i values for (*Z*)-2-(*N*-benzylindol-3-ylmethylene) quinuclidin-3-ones (7–13) at CB1 and CB2 receptors

Compound	K_i (nM)	
	CB1	CB2
7	135 ± 44.1	11.7 ± 5.55
8	9.23 ± 0.64	1.33 ± 0.45
9	31.7 ± 9.25	20.3 ± 7.43
10	629 ± 201	333 ± 157
11	55.3 ± 8.89	114 ± 36.2
12	953 ± 162	588 ± 237
13	85.7 ± 15.9	2.50 ± 0.49
14	540 ± 64.2	55.3 ± 3.10
15	85.3 ± 42.5	113 ± 2.03
16	357 ± 52.2	68.6 ± 7.27
17	95.7 ± 2.03	107 ± 8.75

Fig. 7



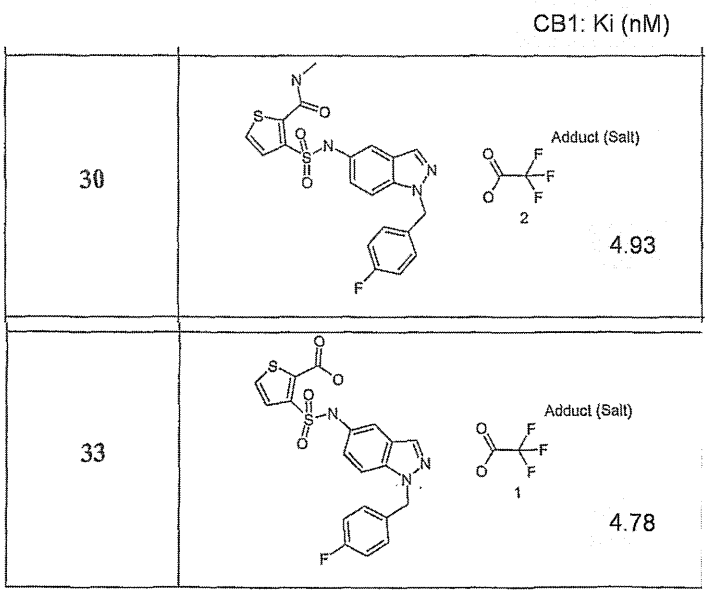


Fig. 8