

1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles

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Abstract—A new class of cannabimimetic indoles, with 3-phenylacetyl or substituted 3-phenylacetyl substituents, has been prepared and their affinities for the cannabinoid CB₁ and CB₂ receptors have been determined. In general those compounds with a 2-substituted phenylacetyl group have good affinity for both receptors. The 4-substituted analogs have little affinity for either receptor, while the 3-substituted compounds are intermediate in their affinities. Two of these compounds, 1-pentyl-3-(2-methylphenylacetyl)indole (JWH-251) and 1-pentyl-3-(3-methoxyphenylacetyl)indole (JWH-302), have 5-fold selectivity for the CB₁ receptor with modest affinity for the CB₂ receptor. GTPγS determinations indicate that both compounds are highly efficacious agonists at the CB₁ receptor and partial agonists at the CB₂ receptor.

In the classical investigation of the structure–activity relationships (SAR) of cannabimimetic aminoalkylindoles, such as WIN-55,212-2 (1), it was found that a 3-(1-naphthoyl) substituent appended to the indole nucleus provided greater affinity for the cannabinoid CB₁ receptor than a substituted benzoyl group.¹ Nearly simultaneously, we demonstrated that the *N*-aminoalkyl group could be replaced by an alkyl group without loss of cannabinoid activity. An *n*-pentyl group on the indole nitrogen, as in JWH-018 (2), provided maximum affinity for the CB₁ receptor, and *in vivo* potency typical of traditional cannabinoids, such as Δ⁹-tetrahydrocannabinol (3, Δ⁹-THC).^{2,3} Subsequently, we prepared a number of *N*-alkyl 3-(1-naphthoyl)indole derivatives to develop SAR for cannabimimetic indoles at both the CB₁ and CB₂ receptors.^{4–7}

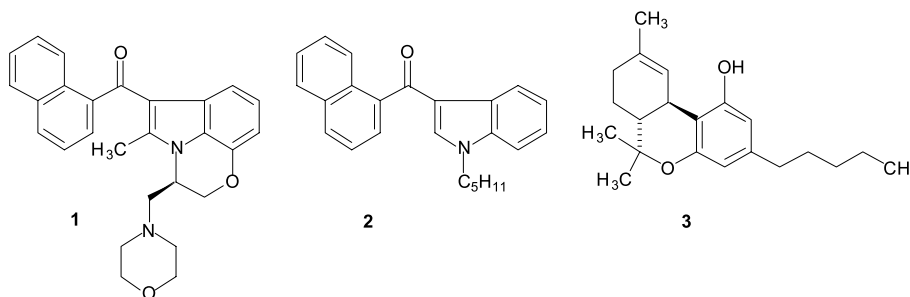
Among the compounds included in the study by the Winthrop group were aminoalkylindoles with 3-(1,2,3,4-tetrahydro-1-naphthoyl) and 3-(5,6,7,8-tetrahydro-1-naphthoyl) substituents.¹ The 3-(1,2,3,4-tetra-

hydro-1-naphthoyl) compound had moderate affinity for the CB₁ receptor and was quite potent in inhibiting the electrically induced contractions of the isolated mouse vas deferens. The compound with a 3-(5,6,7,8-tetrahydro-1-naphthoyl) substituent had considerably less affinity for the receptor, but was slightly more potent than the 1,2,3,4-tetrahydro-1-naphthoyl analog in the mouse vas deferens protocol. It was suggested that the potency of these compounds is due to the presence of a bicyclic substituent at C-3 of the indole, rather than to specific aromatic interactions. However, there now exists convincing evidence that cannabimimetic indoles, including aminoalkylindoles, interact with the CB₁ receptor primarily by aromatic stacking.^{8,9}

There appeared to be two plausible explanations for the greatly enhanced CB₁ receptor affinities of the 3-(1-naphthoyl)indoles. Either the presence of a second aromatic ring increased the magnitude of stacking interactions with the CB₁ receptor or the geometry of the naphthoyl indoles is such that the second aromatic ring (carbons 5–8) is proximate to aromatic amino acids in the receptor, which would increase the stacking interactions. To gain evidence regarding this question, we prepared a series of 1-pentyl-3-phenylacetylindoles (4, Scheme 1). These indole derivatives include compounds

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both with and without a C-2 methyl substituent (**4**, R = CH₃ or H). A variety of compounds were synthesized, including those with methyl-, methoxy-, fluoro-, chloro-, and bromophenyl substituents as well as the unsubstituted analogs.

Cannabimimetic indoles were synthesized from 1-pentylindole (**5**, R = H) or 2-methyl-1-pentylindole (**5**, R = CH₃) and the appropriate phenylacetyl chloride by the Okauchi modification of the Friedel–Crafts reaction (Scheme 1).^{7,10} In this procedure the substrate indole is stirred in dichloromethane with 1.5 equiv of dimethylaluminum chloride at 0 °C for up to 1 h. To this intermediate organoaluminum compound is added 1.5 equiv of the acyl halide.¹¹ Evidence for the formation of an organoaluminum intermediate follows from the observation that reaction of 1-pentylindole with dimethylaluminum chloride and quenching with D₂O provided 3-deuterio-1-pentylindole.

The affinities of the phenylacetylindoles for the CB₁ receptor were determined by measuring their ability to displace [³H]CP-55,940 from its binding site in a membrane preparation from rat brain,¹² and CB₂ receptor affinities were determined by measuring the ability of the compounds to displace [³H]CP-55,940 from a cloned human receptor preparation.¹³ The results of these determinations are summarized in Table 1. The receptor affinities for WIN-55,212-2 (**1**) and Δ⁹-THC (**3**) are also included in Table 1.

The receptor affinities summarized in Table 1 indicate that in general the 2-methylindoles have lower affinity for the CB₁ receptor than the 2-unsubstituted analogs. This is a general trend in the cannabimimetic indole series.^{1,3–5,7} The compounds with an unsubstituted phenylacetyl group (JWH-167 and JWH-205) have modest affinities ($K_i = 90 \pm 17$ nM and 124 ± 23 nM, respectively) for the CB₁ receptor. The 4-substituted analogs (JWH-208, JWH-209, JWH-201, JWH-202, JWH-313, JWH-316, JWH-206, JWH-207, JWH-248, and

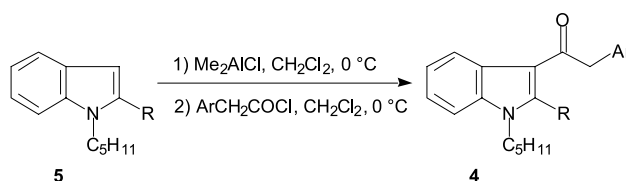
JWH-304) have uniformly low CB₁ receptor affinity ($K_i = 179$ –3363 nM).

The 3-(2-substituted phenylacetyl)indoles have good to high affinity for the CB₁ receptor. The highest affinity compounds are 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203), with $K_i = 8.0 \pm 0.9$ nM and 1-pentyl-3-(2-bromophenylacetyl)indole (JWH-249) $K_i = 8.4 \pm 1.8$ nM.

1-Pentyl-2-methyl-3-(2-methoxyphenylacetyl)indole (JWH-306), the 1-pentyl-3-(2-fluorophenylacetyl)indoles (JWH-311 and JWH-314), and the 1-pentyl-3-(2-methylphenylacetyl)indoles (JWH-251 and JWH-252) have the lowest affinities of this group of compounds with $K_i = 23$ –39 nM. The other 3-(2-substituted phenylacetyl)indoles, JWH-204, JWH-305, and JWH-250 have $K_i = 11$ –15 nM.

Those compounds with a 3-substituted phenylacetyl group have CB₁ receptor affinities intermediate between those of the 2- and 4-substituted analogs. In particular, 1-pentyl-3-(3-methoxyphenylacetyl)indole (JWH-302, $K_i = 17 \pm 2$ nM) and 1-pentyl-3-(3-chlorophenylacetyl)indole (JWH-237, $K_i = 38 \pm 10$ nM) have quite high affinity for the CB₁ receptor. The corresponding 2-methylindoles (JWH-253 and JWH-303) have significantly lower affinities than JWH-237 and JWH-302. Both 1-pentyl-3-(3-fluorophenylacetyl)indole (JWH-312) and the corresponding 2-methylindole (JWH-315) have modest and little affinity, respectively, for the CB₁ receptor.

In general the CB₂ receptor affinities of this class of indoles follow the same trend as their CB₁ affinities (Table 1). That is, the 2-substituted phenylacetyl compounds have the greatest affinity, followed by the 3-substituted analogs. The 3-(4-substituted phenylacetyl)indoles have negligible affinity for the CB₂ receptor, and most of the 2-methylindoles have lower CB₂ receptor affinities than the unsubstituted analogs. However, in the 1-pentyl-3-(2-methylphenylacetyl)indoles the 2-methylindole analog (JWH-252, $K_i = 19 \pm 1$ nM) has more than



Scheme 1.

Table 1. Receptor affinities (mean $\pm$ SEM) of 1-pentyl-3-phenylacetylindoles

3-Substituent	R	K_i (nM)		
		CB ₁	CB ₂	Ratio CB ₁ /CB ₂
WIN-55,212-2 (1)		1.9 $\pm$ 0.1 ^a	0.28 $\pm$ 0.16 ^a	6.8
Δ^9 -THC (3)		41 $\pm$ 2 ^b	36 $\pm$ 10 ^a	1.1
Phenylacetyl, JWH-167	H	90 $\pm$ 17	159 $\pm$ 14	0.57
Phenylacetyl, JWH-205	CH ₃	124 $\pm$ 23	180 $\pm$ 9	0.69
2-Methylphenylacetyl, JWH-251	H	29 $\pm$ 3	146 $\pm$ 36	0.20
2-Methylphenylacetyl, JWH-252	CH ₃	23 $\pm$ 3	19 $\pm$ 1	1.2
4-Methylphenylacetyl, JWH-208	H	179 $\pm$ 7	570 $\pm$ 127	0.31
4-Methylphenylacetyl, JWH-209	CH ₃	746 $\pm$ 49	1353 $\pm$ 270	0.55
2-Methoxyphenylacetyl, JWH-250	H	11 $\pm$ 2	33 $\pm$ 2	0.33
2-Methoxyphenylacetyl, JWH-306	CH ₃	25 $\pm$ 1	82 $\pm$ 11	0.30
3-Methoxyphenylacetyl, JWH-302	H	17 $\pm$ 2	89 $\pm$ 15	0.19
3-Methoxyphenylacetyl, JWH-253	CH ₃	62 $\pm$ 10	84 $\pm$ 12	0.74
4-Methoxyphenylacetyl, JWH-201	H	1064 $\pm$ 21	444 $\pm$ 14	2.4
4-Methoxyphenylacetyl, JWH-202	CH ₃	1678 $\pm$ 63	645 $\pm$ 6	2.6
2-Fluorophenylacetyl, JWH-311	H	23 $\pm$ 2	39 $\pm$ 3	0.60
2-Fluorophenylacetyl, JWH-314	CH ₃	39 $\pm$ 2	76 $\pm$ 4	0.51
3-Fluorophenylacetyl, JWH-312	H	72 $\pm$ 7	91 $\pm$ 20	0.79
3-Fluorophenylacetyl, JWH-315	CH ₃	430 $\pm$ 24	182 $\pm$ 23	2.4
4-Fluorophenylacetyl, JWH-313	H	422 $\pm$ 19	365 $\pm$ 92	1.2
4-Fluorophenylacetyl, JWH-316	CH ₃	2862 $\pm$ 670	781 $\pm$ 105	3.7
2-Chlorophenylacetyl, JWH-203	H	8.0 $\pm$ 0.9	7.0 $\pm$ 1.3	1.1
2-Chlorophenylacetyl, JWH-204	CH ₃	13 $\pm$ 1	25 $\pm$ 1	0.52
3-Chlorophenylacetyl, JWH-237	H	38 $\pm$ 10	106 $\pm$ 2	0.36
3-Chlorophenylacetyl, JWH-303	CH ₃	117 $\pm$ 10	138 $\pm$ 12	0.85
4-Chlorophenylacetyl, JWH-206	H	389 $\pm$ 25	498 $\pm$ 37	0.78
4-Chlorophenylacetyl, JWH-207	CH ₃	1598 $\pm$ 134	3723 $\pm$ 10	0.43
2-Bromophenylacetyl, JWH-249	H	8.4 $\pm$ 1.8	20 $\pm$ 2	0.42
2-Bromophenylacetyl, JWH-305	CH ₃	15 $\pm$ 1.8	29 $\pm$ 5	0.52
4-Bromophenylacetyl, JWH-248	H	1028 $\pm$ 39	657 $\pm$ 19	1.6
4-Bromophenylacetyl, JWH-304	CH ₃	3363 $\pm$ 332	2679 $\pm$ 688	1.2

^a Ref. 13.^b Ref. 12.

7-fold greater affinity for the CB₂ receptor than the unsubstituted compound (JWH-251, K_i = 146 $\pm$ 36 nM).

In contrast to most cannabimimetic indoles, which tend to show selectivity for the CB₂ receptor,^{4,6,7,13} two of these phenylacetylindoles show 5-fold selectivity for the CB₁ receptor. One of them, 1-pentyl-3-(2-methylphenylacetyl)indole, JWH-251, has good affinity for the CB₁ receptor (K_i = 29 $\pm$ 3 nM) with modest affinity for the CB₂ receptor (K_i = 146 $\pm$ 36 nM). The other, 1-pentyl-3-(3-methoxyphenylacetyl)indole, JWH-302, also has good affinity (K_i = 17 $\pm$ 2 nM) for the CB₁ receptor, and fair affinity for the CB₂ receptor (K_i = 89 $\pm$ 15 nM). To evaluate the efficacy of these compounds, their ability to stimulate [³⁵S]GTP γ S binding at CB₁ and CB₂ was determined.^{7,14} The results of these determinations are summarized in Table 2, where the stimulation produced at each receptor is normalized to a standard

cannabinoid full agonist. JWH-251 and JWH-302 both stimulate GTP γ S binding at CB₁, with approximately equal values of EC₅₀ (29 nM) and are high efficacy agonists with E_{max} of greater than 90% (Table 2). Although the affinities of these compounds at CB₂ are approximately one-fifth that of their affinities for the CB₁ receptor, both significantly stimulate GTP γ S binding at the CB₂ receptor. Surprisingly, their potencies for CB₂ receptor activation were similar to those seen with CB₁: for JWH-251, EC₅₀ = 8.3 $\pm$ 0.8 nM and for JWH-302, EC₅₀ = 24.4 $\pm$ 6.9 nM. At the CB₂ receptor, however, both compounds are partial agonists with E_{max} values of less than 50%.

The 1-pentyl-3-phenylacetylindoles constitute a new class of cannabimimetic indoles, which in contrast to most compounds of this general type show little selectivity for the CB₂ receptor. Two of these indole derivatives,

Table 2. EC₅₀ and E_{max} values (mean $\pm$ SEM) for stimulation by GTP γ S binding of CB₁ and CB₂ for JWH-251 and JWH-302

Compound	CB ₁ ^a		CB ₂ ^a	
	EC ₅₀ (nM)	E_{max} (%)	EC ₅₀ (nM)	E_{max} (%)
1-Pentyl-3-(2-methylphenylacetyl)indole (JWH-251)	29.0 $\pm$ 5.5	97.6 $\pm$ 1.5	8.3 $\pm$ 0.8	47.0 $\pm$ 2.4
1-Pentyl-3-(3-methoxyphenylacetyl)indole (JWH-302)	29.3 $\pm$ 0.8	91.5 $\pm$ 2.9	24.4 $\pm$ 6.9	33.5 $\pm$ 2.9

^a Stimulation values are from data normalized to stimulation produced by a maximally effective concentration of a standard full agonist: 10 μ M WIN-55,212-2 for CB₁ and 3 μ M CP-55,940 for CB₂ receptors.

JWH-251 and JWH-302, are moderately selective for the CB₁ receptor and are full agonists at this receptor. Selective agonists for the CB₁ receptor are relatively rare and although these compounds are also partial agonists at the CB₂ receptor, they may serve as the prototypes for additional CB₁ receptor selective agonists. In addition, the high CB₁ receptor affinities of several of these compounds combined with the efficacies of JWH-251 and JWH-302 suggest that the increased potency of cannabinimimetic 3-(1-naphthoyl)indoles relative to their benzoyl congeners is caused by their molecular geometry rather than the presence of a second aromatic ring.

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