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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 CB_1 and CB_2 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 CB_1 receptor with modest affinity for the CB_2 receptor. GTPγS determinations indicate that both compounds are highly efficacious agonists at the CB_1 receptor and partial agonists at the CB_2 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 CB_1 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 CB_1 receptor, and in vivo potency typical of traditional cannabinoids, such as Δ^9-tetrahydrocannabinol (**3**, Δ^9-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 CB_1 and CB_2 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-tetrahydro-1-naphthoyl) compound had moderate affinity for the CB_1 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 CB_1 receptor primarily by aromatic stacking.[8,9]

There appeared to be two plausible explanations for the greatly enhanced CB_1 receptor affinities of the 3-(1-naphthoyl)indoles. Either the presence of a second aromatic ring increased the magnitude of stacking interactions with the CB_1 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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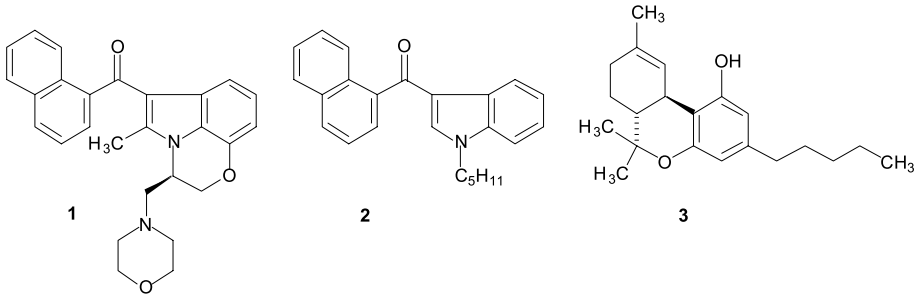


both with and without a C-2 methyl substituent (**4**, R = CH_3 or H). A variety of compounds were synthesized, including those with methyl-, methoxy-, fluoro-, chloro-, and bromophenyl substituents as well as the unsubstituted analogs.

Cannabimimetic indoles were synthesized from 1-pentylindole (**5**, R = H) or 2-methyl-1-pentylindole (**5**, R = CH_3) 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 D_2O provided 3-deuterio-1-pentylindole.

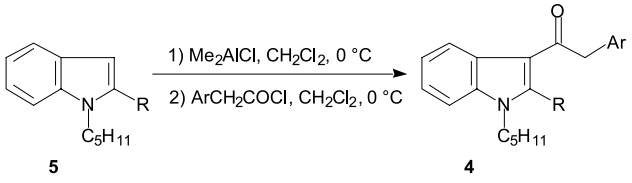
The affinities of the phenylacetylindoles for the CB_1 receptor were determined by measuring their ability to displace [^{3}H]CP-55,940 from its binding site in a membrane preparation from rat brain,[12] and CB_2 receptor affinities were determined by measuring the ability of the compounds to displace [^{3}H]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 Δ^9-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 CB_1 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 ± 17 nM and 124 ± 23 nM, respectively) for the CB_1 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 CB_1 receptor affinity (K_i = 179–3363 nM).

The 3-(2-substituted phenylacetyl)indoles have good to high affinity for the CB_1 receptor. The highest affinity compounds are 1-pentyl-3-(2-chlorophenylacetyl)indole (JWH-203), with K_i = 8.0 ± 0.9 nM and 1-pentyl-3-(2-bromophenylacetyl)indole (JWH-249) K_i = 8.4 ± 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 CB_1 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 ± 2 nM) and 1-pentyl-3-(3-chlorophenylacetyl)indole (JWH-237, K_i = 38 ± 10 nM) have quite high affinity for the CB_1 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 CB_1 receptor.

In general the CB_2 receptor affinities of this class of indoles follow the same trend as their CB_1 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 CB_2 receptor, and most of the 2-methylindoles have lower CB_2 receptor affinities than the unsubstituted analogs. However, in the 1-pentyl-3-(2-methylphenylacetyl)indoles the 2-methylindole analog (JWH-252, K_i = 19 ± 1 nM) has more than



Scheme 1.

Table 1. Receptor affinities (mean ± 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 ± 0.1[a]	0.28 ± 0.16[a]	6.8
Δ^9-THC (**3**)		41 ± 2[b]	36 ± 10[a]	1.1
Phenylacetyl, JWH-167	H	90 ± 17	159 ± 14	0.57
Phenylacetyl, JWH-205	CH_3	124 ± 23	180 ± 9	0.69
2-Methylphenylacetyl, JWH-251	H	29 ± 3	146 ± 36	0.20
2-Methylphenylacetyl, JWH-252	CH_3	23 ± 3	19 ± 1	1.2
4-Methylphenylacetyl, JWH-208	H	179 ± 7	570 ± 127	0.31
4-Methylphenylacetyl, JWH-209	CH_3	746 ± 49	1353 ± 270	0.55
2-Methoxyphenylacetyl, JWH-250	H	11 ± 2	33 ± 2	0.33
2-Methoxyphenylacetyl, JWH-306	CH_3	25 ± 1	82 ± 11	0.30
3-Methoxyphenylacetyl, JWH-302	H	17 ± 2	89 ± 15	0.19
3-Methoxyphenylacetyl, JWH-253	CH_3	62 ± 10	84 ± 12	0.74
4-Methoxyphenylacetyl, JWH-201	H	1064 ± 21	444 ± 14	2.4
4-Methoxyphenylacetyl, JWH-202	CH_3	1678 ± 63	645 ± 6	2.6
2-Fluorophenylacetyl, JWH-311	H	23 ± 2	39 ± 3	0.60
2-Fluorophenylacetyl, JWH-314	CH_3	39 ± 2	76 ± 4	0.51
3-Fluorophenylacetyl, JWH-312	H	72 ± 7	91 ± 20	0.79
3-Fluorophenylacetyl, JWH-315	CH_3	430 ± 24	182 ± 23	2.4
4-Fluorophenylacetyl, JWH-313	H	422 ± 19	365 ± 92	1.2
4-Fluorophenylacetyl, JWH-316	CH_3	2862 ± 670	781 ± 105	3.7
2-Chlorophenylacetyl, JWH-203	H	8.0 ± 0.9	7.0 ± 1.3	1.1
2-Chlorophenylacetyl, JWH-204	CH_3	13 ± 1	25 ± 1	0.52
3-Chlorophenylacetyl, JWH-237	H	38 ± 10	106 ± 2	0.36
3-Chlorophenylacetyl, JWH-303	CH_3	117 ± 10	138 ± 12	0.85
4-Chlorophenylacetyl, JWH-206	H	389 ± 25	498 ± 37	0.78
4-Chlorophenylacetyl, JWH-207	CH_3	1598 ± 134	3723 ± 10	0.43
2-Bromophenylacetyl, JWH-249	H	8.4 ± 1.8	20 ± 2	0.42
2-Bromophenylacetyl, JWH-305	CH_3	15 ± 1.8	29 ± 5	0.52
4-Bromophenylacetyl, JWH-248	H	1028 ± 39	657 ± 19	1.6
4-Bromophenylacetyl, JWH-304	CH_3	3363 ± 332	2679 ± 688	1.2

[a] Ref. 13.
[b] Ref. 12.

7-fold greater affinity for the CB_2 receptor than the unsubstituted compound (JWH-251, K_i = 146 ± 36 nM).

In contrast to most cannabimimetic indoles, which tend to show selectivity for the CB_2 receptor,[4,6,7,13] two of these phenylacetylindoles show 5-fold selectivity for the CB_1 receptor. One of them, 1-pentyl-3-(2-methylphenylacetyl)indole, JWH-251, has good affinity for the CB_1 receptor (K_i = 29 ± 3 nM) with modest affinity for the CB_2 receptor (K_i = 146 ± 36 nM). The other, 1-pentyl-3-(3-methoxyphenylacetyl)indole, JWH-302, also has good affinity (K_i = 17 ± 2 nM) for the CB_1 receptor, and fair affinity for the CB_2 receptor (K_i = 89 ± 15 nM). To evaluate the efficacy of these compounds, their ability to stimulate [^{35}S]GTPγS binding at CB_1 and CB_2 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 GTPγS binding at CB_1, with approximately equal values of EC_{50} (29 nM) and are high efficacy agonists with E_{max} of greater than 90% (Table 2). Although the affinities of these compounds at CB_2 are approximately one-fifth that of their affinities for the CB_1 receptor, both significantly stimulate GTPγS binding at the CB_2 receptor. Surprisingly, their potencies for CB_2 receptor activation were similar to those seen with CB_1: for JWH-251, EC_{50} = 8.3 ± 0.8 nM and for JWH-302, EC_{50} = 24.4 ± 6.9 nM. At the CB_2 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 CB_2 receptor. Two of these indole derivatives,

Table 2. EC_{50} and E_{max} values (mean ± SEM) for stimulation by GTPγS binding of CB_1 and CB_2 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 ± 5.5	97.6 ± 1.5	8.3 ± 0.8	47.0 ± 2.4
1-Pentyl-3-(3-methoxyphenylacetyl)indole (JWH-302)	29.3 ± 0.8	91.5 ± 2.9	24.4 ± 6.9	33.5 ± 2.9

[a] Stimulation values are from data normalized to stimulation produced by a maximally effective concentration of a standard full agonist: 10 μM WIN-55,212-2 for CB_1 and 3 μM CP-55,940 for CB_2 receptors.

JWH-251 and JWH-302, are moderately selective for the CB_1 receptor and are full agonists at this receptor. Selective agonists for the CB_1 receptor are relatively rare and although these compounds are also partial agonists at the CB_2 receptor, they may serve as the prototypes for additional CB_1 receptor selective agonists. In addition, the high CB_1 receptor affinities of several of these compounds combined with the efficacies of JWH-251 and JWH-302 suggest that the increased potency of cannabimimetic 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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