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1-Alkyl-2-aryl-4-(1-naphthoyl)pyrroles: New high affinity ligands for the cannabinoid CB_1 and CB_2 receptors

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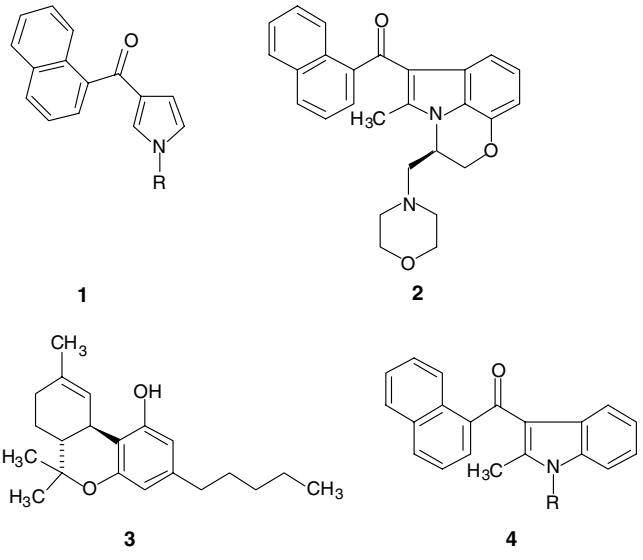
Abstract—Two series of 1-alkyl-2-aryl-4-(1-naphthoyl)pyrroles were synthesized and their affinities for the cannabinoid CB_1 and CB_2 receptors were determined. In the 2-phenyl series (**5**) the *N*-alkyl group was varied from *n*-propyl to *n*-heptyl. A second series of 23 1-pentyl-2-aryl-4-(1-naphthoyl)-pyrroles (**6**) was also prepared. Several compounds in both series have CB_1 receptor affinities in the 6–30 nM range. The high affinities of these pyrrole derivatives relative to JWH-030 (**1**, R = C_5H_{11}) support the hypothesis that these pyrroles interact with the CB_1 receptor primarily by aromatic stacking.

Several years ago we reported the synthesis, CB_1 receptor affinities, and in vivo pharmacology for a series of 1-alkyl-3-(1-naphthoyl)pyrroles (**1**, R = C_3H_7 to C_7H_{15}).[1] The 1-propyl, 1-butyl and 1-heptyl analogs have little affinity for the CB_1 receptor, however, the 1-pentyl compound (JWH-030, **1**, R = C_5H_{11}) has moderate affinity for the CB_1 receptor with $K_i = 87 \pm 3$ nM and is quite potent in vivo in the spontaneous activity and tail flick procedures. It is considerably less potent in the rectal temperature and ring immobility protocols. The 1-hexylpyrrole derivative (JWH-031, **1**, R = C_6H_{13}) has little affinity for the CB_1 receptor ($K_i = 399 \pm 109$ nM), but has moderate potency in the spontaneous activity and tail flick assays. Subsequently JWH-030 was found to inhibit the electrically stimulated contractions of the isolated mouse vas deferens.[2]

The design of these cannabimimetic pyrroles was based upon a model for a general pharmacophore that related the structures of the Sterling Winthrop aminoalkylindoles, in particular WIN-55,212-2 (**2**), with those of traditional cannabinoids such as Δ^9-tetrahydrocannabinol (Δ^9-THC, **3**).[3] In this model the phenolic hydroxyl of THC was assumed to align with the ketonic carbonyl



of WIN-55,212-2 and the cyclohexene ring of THC was overlaid upon the naphthalene portion of the aminoalkylindole. In this alignment the aminoalkyl portion of WIN-55,212-2 corresponded to the alkyl side chain of THC. This suggested that the aminoalkyl portion of **2** could be replaced by a simple alkyl group and a series of 1-alkyl-2-methyl-3-(1-naphthoyl)indoles (**4**)

Keywords: Cannabinoid; Cannabimimetic pyrroles; CB_1 receptor; CB_2 receptor.
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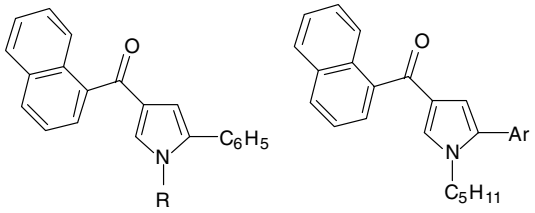
was prepared; their affinities for the CB_1 receptor and in vivo pharmacology were determined. Several of these indole derivatives have high affinity (K_i = 10–48 nM) for the CB_1 receptor and are quite potent in vivo.[3,4] 2-Methyl-1-pentyl-3-(1-naphthoyl)indole (JWH-007, **4**, R = C_5H_{11}) has the highest affinity for the CB_1 receptor of this series of indole derivatives (K_i = 10 ± 4 nM) and is quite potent in the mouse model of cannabinoid activity.

Although the high CB_1 receptor affinity and in vivo potency of **4** (R = C_5H_{11}) and related indoles supported the alignment that led to the development of these cannabimimetic indoles,[3,4] subsequent studies indicate that these compounds interact with the CB_1 receptor primarily by aromatic stacking.[5–7] These observations suggest that the addition of an aryl substituent to cannabimimetic pyrroles similar to JWH-030 (**1**, R = C_5H_{11}) would lead to compounds with enhanced affinity for the CB_1 receptor. In order to test this hypothesis, we have prepared two series of 1-alkyl-2-aryl-4-(1-naphthoyl)pyrroles. Initially a series of 1-alkyl-2-phenyl-4-(1-naphthoyl)pyrroles (**5**, R = C_3H_7 to C_7H_{15}) was prepared. Following the observation that four of these compounds have from moderate to high affinity for the CB_1 receptor, the effect upon receptor affinity of varying the C-2 aryl substituent while maintaining a 1-pentyl group was investigated (**6**, Ar = various aromatic groups).



5 **6**

The initial synthesis of 2-phenylpyrroles **5** was based upon that used for the preparation of pyrroles **1**.[1] 2-Phenylpyrrole was prepared in poor (22%) yield from acetophenone oxime and 1,2-dichloroethane by the procedure of Korostova et al.[8] and was converted to the 1-*p*-toluenesulfonyl derivative with *p*-toluenesulfonyl chloride in the presence of sodium hydride. Friedel–Crafts acylation with 1-naphthoyl chloride in the presence of aluminum chloride provided 2-phenyl-1-*p*-toluenesulfonyl-4-(1-naphthoyl)pyrrole (**5**, R = $C_7H_7SO_2$). Basic hydrolysis gave 2-phenyl-4-(1-naphthoyl)pyrrole (**5**, R = H), which was converted to 1-pentyl- (JWH-145, **5**, R = C_5H_{11}), 1-hexyl- (JWH-147, **5**, R = C_6H_{13}), and 1-heptyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-146, **5**, R = C_7H_{15}) upon treatment with sodium hydride and the appropriate alkyl bromide.[9]

Due to inconsistent results and poor yields in the synthesis of 2-phenylpyrrole, an alternative synthetic approach to indoles **5** was developed (Scheme 1). Bromination of 1-propyl- (**1**, R = C_3H_7) or 1-butyl-3-(1-naphthoyl)pyrrole (**1**, R = C_4H_9) with NBS, or better 1,3-dibromo-5,5-dimethylhydantoin,[10] provided the corresponding 2-bromopyrrole derivatives (**7**, R = C_3H_7 and C_4H_9), which were used in the subsequent step without further purification. Suzuki coupling[11] with phenylboronic acid under standard conditions using $(Ph_3P)_4Pd$ and Na_2CO_3, in a mixture of toluene, ethanol, and water, provided 1-propyl- (JWH-156, **5**, R = C_3H_7) and 1-butyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-150, **5**, R = C_4H_9) in 59% and 52% yield, respectively.

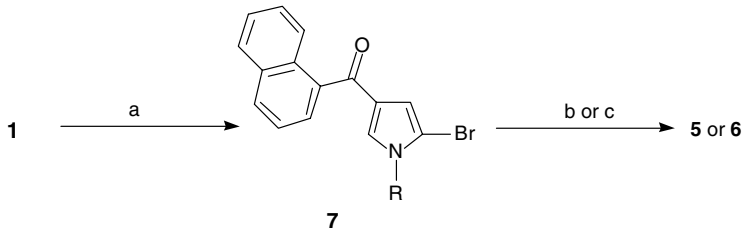
The affinities of pyrroles **5** for the CB_1 receptor were determined by measuring their ability to displace [^{3}H]CP-55,940 from its binding site in a membrane preparation from rat brain,[12] and CB_2 receptor affinities were determined by measuring the ability of the compounds to displace [^{3}H]CP-55,940 from a cloned human receptor preparation.[13] The results of these determinations are summarized in Table 1. Also included in Table 1 are the receptor affinities for WIN-55,212-2 (**1**) and Δ^9-THC (**3**).

Based upon the high CB_1 and CB_2 receptor affinities of 1-pentyl- (JWH-145, **5**, R = C_5H_{11}) and 1-hexyl-2-phenyl-4-(1-naphthoyl)pyrrole (JWH-147, **5**, R = C_6H_{13}) a second series of 2-aryl-4-(1-naphthoyl)pyrroles was syn-

Table 1. Receptor affinities (mean ± SEM) of 1-alkyl-2-phenyl-4-(1-naphthoyl)pyrroles (**5**), WIN-55,212-2 (**2**), and Δ^9-THC (**3**)

	K_i (nM)	
	CB_1	CB_2
WIN-55,212-2 (**2**)	1.9 ± 0.1[a]	0.28 ± 0.16[a]
Δ^9-THC (**3**)	41 ± 2[b]	36 ± 10[a]
1-Alkyl Group, R		
Propyl, JWH-156	404 ± 18	104 ± 18
Butyl, JWH-150	60 ± 1	15 ± 2
Pentyl, JWH-145	14 ± 2	6.4 ± 0.4
Hexyl, JWH-147	11 ± 1	7.1 ± 0.2
Heptyl, JWH-146	21 ± 2	62 ± 5

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



7

Scheme 1. Reagents and conditions: (a) NBS, or 1,3-dibromo-5,5-dimethylhydantoin, THF, −78 °C; (b) $(Ph_3P)_4Pd$, Na_2CO_3, $C_6H_5CH_3$, C_2H_5OH, H_2O, reflux; (c) $Pd(OAc)_2$, $(o\text{-}CH_3C_6H_4)_3P$, K_2CO_3, $(C_4H_9)_4NBr$, $C_6H_5CH_3$, H_2O, reflux.

thesized in order to obtain data regarding the structure–activity relationships of this class of cannabinoids at both receptors. For this series of compounds an *N*-pentyl substituent was employed and the aryl group was varied. The pentyl group was selected since JWH-030 (**1**, R = C_5H_{11}) has the highest CB_1 receptor affinity in the original series of cannabimimetic pyrroles and JWH-145 (**5**, R = C_5H_{11}) has high affinity for both receptors.

The original synthetic design for pyrroles **6** was based upon the route initially employed for the synthesis of the 2-phenylpyrroles (**5**), but was to employ an efficient alternative synthesis of 1-*p*-toluenesulfonyl-2-arylpyrroles.[14] However, with the exception of 1-*p*-toluenesulfonyl-2-phenylpyrrole (**5**, R = $C_7H_7SO_2$), Friedel–Crafts reaction of other 1-*p*-toluenesulfonyl-2-arylpyrroles with 1-naphthoyl chloride under a variety of conditions afforded either complex mixtures of regioisomers or the undesired 2-aryl-5-(1-naphthoyl) compound.[15] Pyrroles **6** were successfully synthesized by a modification of the procedure outlined in Scheme 1 using JWH-030 (**1**, R = C_5H_{11}) as the starting material. Bromination with 1,3-dibromo-5,5-dimethylhydantoin gave 1-pentyl-2-bromo-4-(1-naphthoyl)pyrrole (**7**, R = C_5H_{11}) plus a small amount of the 3-bromo-4-(1-naphthoyl) isomer, from which **7**, R = C_5H_{11} was isolated in 70% yield.

Suzuki coupling of **7**, R = C_5H_{11} with four substituted arylboronic acids (*p*-methoxyphenyl, *p*-methylphenyl, *p*-chlorophenyl, and *m*-chlorophenyl) under the conditions used for the preparation of JWH-156, (**5**, R = C_3H_7) and JWH-150 (**5**, R = C_4H_9) gave poor (10–26%) yields of pyrroles **6**. A modified Suzuki procedure reported by Badone, which employs $Pd(OAc)_2$, tri-*o*-tolylphosphine, and K_2CO_3 in aqueous toluene with a phase transfer catalyst,[16] was used to prepare 19 additional substituted pyrroles in yields of 24–83%. With one exception these compounds were synthesized using commercially available boronic acids, however *o*-butylphenylboronic acid is not commercially available and was prepared in four steps from *o*-bromobenzaldehyde.[15] For purification the boronic acid was converted to the potassium tetrafluoroborate salt.[17] Coupling of **7**, R = C_5H_{11} with this tetrafluoroborate salt was carried out by the modified Suzuki procedure, with $(Ph_3P)_4Pd$ as catalyst to give **6**, Ar = *o*-butylphenyl (JWH-373) in 76% yield.

The affinities of 2-arylpyrroles **6** for the CB_1 and CB_2 receptors were determined by the same methods that were employed for the series of 2-phenylpyrroles (**5**) and are listed in Table 2.[12,13] Those 2-arylpyrroles (**6**) with small *ortho*-substituents on the 2-aryl group (JWH-370, JWH-365, JWH-292, JWH-307, and JWH-369) and the unsubstituted analog (JWH-145, **5**, R = C_5H_{11}) have uniformly high affinity for the CB_1 receptor (K_i = 5.6–29 nM). An exception is the *o*-trifluoromethylphenyl derivative, JWH-372 (**6**, Ar = *o*-trifluoromethylphenyl), which has $K_i = 77 \pm 2$ nM. The trifluoromethyl group is inductively a strong electron-withdrawing substituent with approximately the same van der Waals radius as a methyl group, Thus, this decreased CB_1 receptor affinity would appear to be due to electronic effects rather than steric effects. 1-Pentyl-2-(2-butylphenyl)-4-(1-naphthoyl)pyrrole (JWH-373, **6**, Ar = *o*-butylphenyl) has decreased CB_1 receptor affinity ($K_i = 60 \pm 3$ nM). This effect is probably due to the steric bulk of the butyl group. With the exception of the *o*-trifluoromethylphenyl analog (JWH-372) there is little difference in the CB_1 and CB_2 receptor affinities of the 2-arylpyrroles with an *ortho*-substituted phenyl group. At the CB_2 receptor, JWH-372 is an exception with greater than 9-fold selectivity for the CB_2 receptor.

Other than the *meta*-fluoro analog (JWH-368, **6**, Ar = *m*-fluorophenyl, $K_i = 16 \pm 1$ nM) those pyrroles with a *meta*-substituted phenyl substituent in the 2-position have from somewhat to significantly lower CB_1 receptor affinities than the *ortho*-substituted analogs. The two compounds with strongly electron-withdrawing substituents, *m*-trifluoromethylphenyl (JWH-363) and *m*-nitrophenyl (JWH-293) pyrroles, both have very modest CB_1 receptor affinities ($K_i = 245 \pm 5$ nM and 100 ± 5 nM, respectively). The two compounds with electron-releasing groups (JWH-346 and JWH-367) and the *m*-chloro analog (JWH-246) have somewhat attenuated CB_1 receptor affinities relative to the *ortho*-substituted compounds. This entire series of pyrroles with a *m*-substituted phenyl group in the 2-position exhibit some (1.7- to 4.4-fold) selectivity for the CB_2 receptor.

Table 2. Receptor affinities (mean ± SEM) of 1-pentyl-2-aryl-4-(1-naphthoyl)pyrroles (**6**)

Aryl group, Ar	K_i (nM)	
	CB_1	CB_2
Phenyl, JWH-145	14 ± 2	6.4 ± 0.4
ortho-isomers		
o-Methylphenyl, JWH-370	5.6 ± 0.4	4.0 ± 0.5
o-Ethylphenyl, JWH-365	17 ± 1	3.4 ± 0.2
o-Butylphenyl, JWH-373	60 ± 3	69 ± 2
o-Methoxyphenyl, JWH-292	29 ± 1	20 ± 1
o-Fluorophenyl, JWH-307	7.7 ± 1.8	3.3 ± 0.2
o-Chlorophenyl, JWH-369	7.9 ± 0.4	5.2 ± 0.3
o-Trifluoromethylphenyl, JWH-372	77 ± 2	8.2 ± 0.2
meta-isomers		
m-Methylphenyl, JWH-346	67 ± 6	39 ± 2
m-Methoxyphenyl, JWH-367	53 ± 2	23 ± 1
m-Fluorophenyl, JWH-368	16 ± 1	9.1 ± 0.7
m-Chlorophenyl, JWH-246	70 ± 4	16 ± 1
m-Trifluoromethylphenyl, JWH-363	245 ± 5	71 ± 1
m-Nitrophenyl, JWH-293	100 ± 5	41 ± 4
para-isomers		
p-Methylphenyl, JWH-244	130 ± 6	18 ± 1
p-Ethylphenyl, JWH-364	34 ± 3	29 ± 1
p-Butylphenyl, JWH-371	42 ± 1	64 ± 2
p-Methoxyphenyl, JWH-243	285 ± 40	41 ± 3
p-Fluorophenyl, JWH-308	41 ± 1	33 ± 2
p-Chlorophenyl, JWH-245	276 ± 4	25 ± 2
p-Trifluoromethylphenyl, JWH-348	218 ± 19	53 ± 1
Others		
1-Naphthyl, JWH-309	41 ± 3	49 ± 7
2-Naphthyl, JWH-347	333 ± 17	169 ± 17
3-Pyridyl, JWH-366	191 ± 12	24 ± 1

For those pyrroles **6** with a *para*-substituted phenyl substituent, the compounds with small electron donating substituents (JWH-244 and JWH-243) as well as the *p*-chloro (JWH-245) and *p*-trifluoromethyl (JWH-348) analogs have little affinity for the CB_1 receptor with K_i = 130–276 nM. However, the *p*-ethyl (JWH-244), *p*-butyl (JWH-371), and *p*-fluoro (JWH-308) analogs have considerably greater and nearly equal affinity with K_i = 34–42 nM. The CB_2 receptor affinities of this group of 1-pentyl-2-aryl-4-(1-naphthoyl)pyrroles (**6**) fall in a relatively narrow range with K_i = 18–64 nM.

Three examples of pyrroles **6** containing aromatic substituents at C-2 other than phenyl were also prepared. The analog with a 1-naphthyl moiety (JWH-309) has relatively high affinity for the CB_1 receptor with $K_1 = 41 \pm 3$ nM, while the 2-naphthyl analog (JWH-347) has little affinity with $K_i = 333 \pm 17$ nM. The 2-(3-pyridyl) compound (JWH-366) also has modest affinity for the CB_1 receptor with $K_i = 191 \pm 12$ nM. The pyridyl (JWH-366) and the 1-naphthyl (JWH-309) compounds have relatively high affinity for the CB_2 receptor with $K_i = 24 \pm 1$ and 49 ± 7 nM, respectively. The 2-naphthyl compound (JWH-347) has little affinity for the CB_2 receptor ($K_i = 169 \pm 17$ nM).

The enhanced CB_1 receptor affinities of pyrroles **5** ($R = C_5H_{11}$ to C_7H_{15}) and **6** containing various aryl substituents, relative to JWH-030 (**1**, $R = C_5H_{11}$), provide additional evidence in support of the hypothesis that cannabimimetic pyrroles as well as their indole counterparts interact with the CB_1 receptor primarily by aromatic stacking.[5–7] In pyrroles **6** a small *ortho* electron-releasing substituent slightly enhances CB_1 receptor affinity relative to JWH-145 (**5**, $R = C_5H_{11}$) with an unsubstituted phenyl group. An inductively electron withdrawing, but electron releasing by resonance, fluoro or chloro substituent also enhances CB_1 receptor affinity.[18] Larger or strongly electron-withdrawing groups attenuate affinity. Other than fluorine a *meta*- or *para*-substituent diminishes CB_1 receptor affinity, however a *p*-ethyl or *p*-butylphenyl group has only a slight effect. This would tend to indicate that at least some of the decrease in affinity for the *meta*- and *para*-substituted compounds is due to steric effects inasmuch as a fluorine atom is only slightly larger than a hydrogen. The variation in CB_1 receptor affinities of pyrroles **6** would appear to be due to a subtle combination of steric and electronic effects. With the exception of the 2-naphthyl analog (JWH-347) there is relatively little variation in CB_2 receptor affinities for pyrroles **6**, with K_i = 3.4–71 nM.

Acknowledgments

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