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1-Alkyl-3-(1-naphthoyl)pyrroles: A New Class of Cannabinoid

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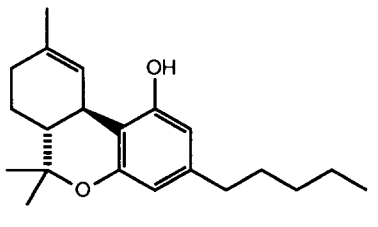
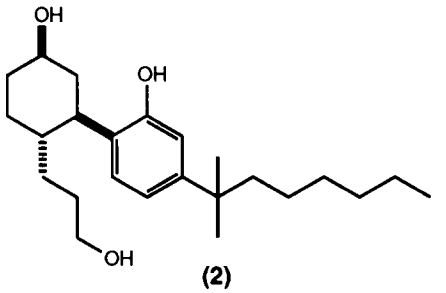
Abstract: The design and synthesis of a series of 1-alkyl-3-(1-naphthoyl)pyrroles is described. Molecular modeling studies were employed to aid in the design of these compounds. During the course of the synthesis the Friedel-Crafts reactions of N-aryl sulfonyl pyrroles were reinvestigated. The title compounds (**4**) were subjected to pharmacological evaluation and the data obtained have enabled these pyrroles to be classified as cannabinoids.

In 1964, Gaoni and Mechoulam described the isolation and structure elucidation of Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**).[1] Compounds possessing this tricyclic dibenzopyran ring system are considered to be *classical* cannabinoids, for which a comprehensive set of structure-activity relationships have been developed.[2] More recently, several *non-traditional* cannabinoids have been synthesized, including a series of 3-arylcyclohexanols, such as CP-55,940 (**2**) and related compounds,[3] as well as several cannabimimetic aminoalkylindoles, such as WIN-55,212.[4]



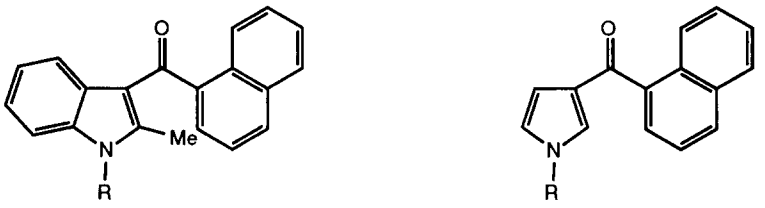
(1)



(2)

Very recently, Huffman *et al.* described a series of cannabimimetic indoles (**3**).[5] These compounds represent a significant series of non-classical cannabinoids in that they are structurally very different from Δ^9-THC (**1**), but display excellent cannabinoid activity both *in vivo* and *in vitro* and hence must be interacting with the same receptor. One of these analogues (**3**, R=^{n}pentyl) is significantly more potent than Δ^9-THC (**1**). The target structures for the indoles were designed using the modeling package, PCModel.[6] On analyzing the overlaid structures of Δ^9-THC (**1**) and these indoles, it was apparent that the benzenoid ring of the indole was

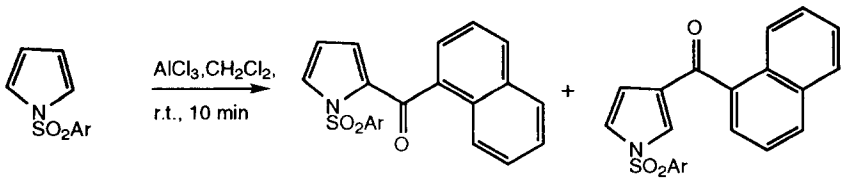
extraneous, since it did not correspond with any of the atoms in the Δ^9-THC structure. To test this hypothesis it was proposed that an analogous series of pyrroles (**4**) could be produced by effectively removing the benzenoid ring, and evaluating the pharmacology of the two series. The methyl group at the 2-position in the indole series (**3**) was omitted from the pyrrole series (**4**) since it has been found that this substitution did not appear to affect the activity of the indoles.[7]



R=Alkyl

(3) **(4)**

To synthesise the target compounds (**4**), a route to 3-acyl pyrroles followed by N-alkylation was required. The nitrogen atom in pyrrole was functionalized with various aryl sulfonyl directing groups, using standard conditions,[8] giving the N-sulfonyl compounds (**5**). Pyrroles normally give 2-acylated products under Friedel-Crafts conditions, but N-aryl sulfonyl derivatives have been reported to give exclusively the 3-substituted product.[9] However, on reacting both N-tosyl and N-phenyl sulfonyl pyrrole using the published conditions, ($AlCl_3$, CH_2Cl_2, 1-naphthoyl chloride) an approximately equimolar mixture of the 2-product (**6**) and the desired 3-isomer (**7**) was obtained, (Scheme 1) the separation of which required tedious column chromatography. The isomers could be distinguished by their ^1H nmr spectra, since the 2-naphthoyl compound gives characteristic signals for 3-H (δ 6.57, dd, J=3.7, 1.6 Hz) and 4-H (δ 6.27, t, J=3.7 Hz), whereas the 3-isomer shows signals for 4-H (δ 6.83, dd, J=3.0, 1.4 Hz) and 5-H (δ 7.20, dd, J=3.0, 2.2 Hz). This nmr assignment was confirmed by the X-ray crystal structure of 2-naphthoyl-N-tosylpyrrole (**6**).[10]



(5) **(6)** **(7)**

Ar=*p*-MeC_6H_4
=C_6H_5

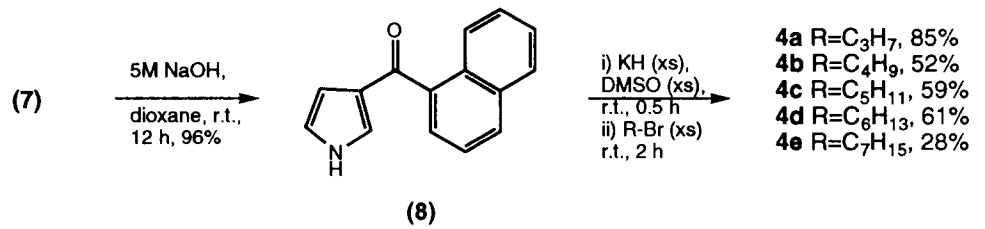
Scheme 1

This result prompted reinvestigation of the Friedel-Crafts reaction of N-aryl sulfonyl pyrroles using benzoyl chloride as the acylating agent.[9] Mixtures of the 2- and 3-isomers were obtained once again when using

dichloromethane as the solvent, but interestingly only the 3-benzoyl derivative was obtained when 1,2-dichloroethane was employed. However, on using 1-naphthoyl chloride in 1,2-dichloroethane, mixtures of the two possible products were obtained.

This problem was resolved by adapting the conditions of Anderson,[11] which utilize nitromethane as a co-solvent which results in the complete dissolution of the aluminum chloride. In this case, the desired 3-naphthoyl compound **(7)** was obtained, in modest, although unoptimized yield (41%), as the exclusive product. This result may be explained by the fact that the presence of the nitromethane leads to the formation of a relatively completely disassociated acylium ion, a hard electrophile, which would favor 3- over 2-attack.[12] Problems were encountered initially due to the presence of 1-naphthoic acid as a by-product of the acylation, which contaminated even chromatographed material. However, the acid was easily removed by incorporating a simple base wash into the isolation procedure.

Removal of the directing group on the nitrogen proved somewhat capricious, though the optimum conditions finally gave the unsubstituted pyrrole **(8)** in 96% yield, using 5M NaOH (aq) in dioxane.[8] (Scheme 2) Initially alkylation of **(8)** was attempted using the method developed for the indole series **(3)**,[5] which involved heating the indoles at 80°C overnight with KOH in DMSO. However, these conditions proved to be far too harsh for the pyrroles, which suffered extensive decomposition. A milder method was required and N-alkylation was achieved by using potassium dimsyl as the base and an excess of the corresponding alkyl bromide, at room temperature in DMSO, to give the target series of compounds **(4a-e)**.[13]



Scheme 2

Pharmacology of the pyrroles **(4a-e)** was evaluated using standard cannabinoid assays both *in vivo* and *in vitro*. The *in vitro* pharmacological data were obtained by measuring the ability of the compounds to displace the very active cannabinoid [^{3}H] CP-55,940 **(2)** from its binding site in a membrane preparation as described by Compton *et al.*[14] The N-propyl compound **(4a)** was essentially inactive (K_I >10 000 nM) and the N-butyl pyrrole **(4b)** was only weakly active (K_I=666 nM). The N-pentyl derivative **(4c)** was the most active in the series (K_I=87 nM) and displayed significant cannabinoid activity, comparable to Δ^9-THC (K_I=41 nM).[14] The N-hexyl **(4d)** and N-heptyl **(4e)** pyrroles were slightly less active than the pentyl compound, but did bind to the cannabinoid receptor, with K_I values of 324 and 309 nM respectively.

The *in vivo* pharmacology was evaluated using the mouse tetrad model of cannabimimetic activity[15] which consists of measuring spontaneous activity (SA), antinociception (as tail flick, TF), rectal temperature (RT) and catalepsy (as ring immobility, RI). For another series of non-classical cannabinoids the average of the ED_{50} values for these four behavioral procedures has been shown to correlate well with the K_I.[14] For the propyl **(4a)**

and butyl **(4b)** compounds, on the basis of the relatively poor ability to bind to the receptor, the *in vivo* pharmacology was not evaluated. For the other compounds **(4c-e)** significant *in vivo* activity was obtained. The average ED_{50} value for Δ^9-THC was 4.7 μM/kg [14] and the values determined here for the pyrroles **(4c-e)** were 20.2, 26.8 and 19.4 μM/kg respectively, which indicates that these compounds are active cannabinoids, although somewhat less potent than Δ^9-THC.

In summary, modeling experiments were employed to design a new and structurally unique class of cannabimimetic pyrroles which possess activity comparable to that of traditional cannabinoids. The demonstration of cannabinoid activity for pyrrole derivatives is completely without precedent. Synthesis of these compounds also led to a reinvestigation of the Friedel-Crafts chemistry of N-aryl sulfonyl pyrroles, which demonstrated that the use of nitromethane as a co-solvent with dichloromethane gives exclusively the 3-acylated product.

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