



0960-894X(94)E0009-4

Design, Synthesis and Pharmacology of Cannabimimetic Indoles

John W. Huffman* and Dong Dai

Department of Chemistry, Clemson University, Clemson, SC 29634-1905, USA

Billy R. Martin and David R. Compton

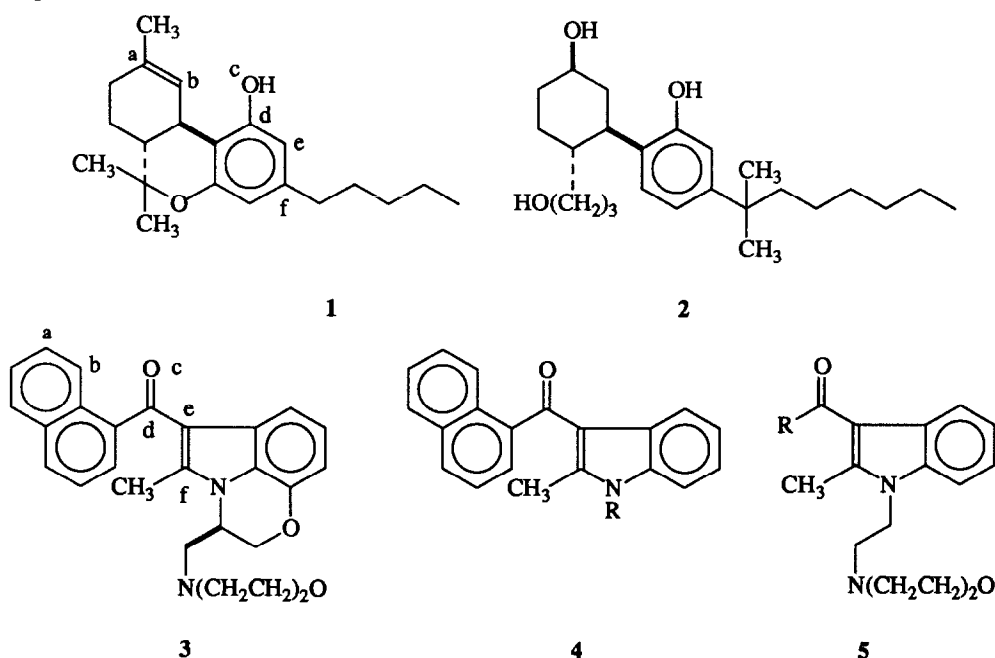
Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University,
Richmond, Virginia 23298-0613, USA

Abstract: Molecular modeling has been employed to design a new group of cannabimimetic 1-alkyl-2-methyl-3-(1-naphthoyl)indoles. Cannabinoid activity was evaluated *in vivo* in the mouse and *in vitro* by determining the binding to the cannabinoid receptor. Maximum activity was found for the 1-butyl, pentyl and hexyl analogs. A rationalization for the alignment of these indoles with traditional cannabinoids is presented.

In the thirty years since Gaoni and Mechoulam described the isolation and elucidation of structure of Δ^9 -THC (1, Δ^9 -tetrahydrocannabinol)¹ a comprehensive set of structure activity relationships for cannabinoids has been developed.² In the past few years, however, several nontraditional cannabinoids have been prepared, which include *inter alia*, a series of 3-arylcyclohexanols, such as CP-55,940 (2) and related compounds.³ Although structural similarities between THC (1) and analog 2 are apparent, several cannabimimetic aminoalkylindoles have been described recently which bear no obvious structural resemblance to other active cannabinoids.⁴ The most active of these indoles is WIN-55,212 (3), which acts *in vitro* at the same binding site as THC⁴ and shows *in vivo* activity in the mouse model which is comparable to THC.⁵ A three point receptor model for cannabinoids has been suggested,⁶ which has been modified by calculations which define a receptor essential volume for the cannabinoid receptor.⁷ Inherent in all approaches to the structural requirements for cannabinoid activity is the presence of a phenolic hydroxyl group at C-1, and a lipophilic side chain at C-3.^{2,6,7} Indole 3 does not contain a phenolic hydroxyl, nor is it obvious which portion of this molecule corresponds to the lipophilic side chain present in active cannabinoids described previously.

To reconcile the structural features inherent in indole 3 with those of more traditional cannabinoids, and perhaps to develop other cannabimimetic indoles, a study was initiated using the program PCModel.⁸ The structure of THC was simplified by reducing the length of the side chain to four atoms, and the morpholine unit of indole 3 was changed to a dimethylamino. For THC the nonaromatic rings were assumed to be in the half chair conformation, and side chain conformations within 1 Kcal/mole of the apparent global minimum were considered. For indole 3 several rotational isomers about the bonds to the carbonyl carbon and the aromatic rings were investigated, and the minimum energy conformation of the dimethylamino (morpholino) group was employed. Various atoms of the ring systems were compared and the relative alignments of the lipophilic side

chains and appropriate portions of indole **3** were compared visually. The best fit was found to be the alignment indicated in structures **1** and **3**, in which the 1, 2, 3, 9 and 10 carbons and phenolic oxygen of the cannabinoid correspond with the corresponding carbons and ketonic oxygen of the indole (The lettering indicated on structures **1** and **3** indicates which atoms were aligned for comparison.). When the structures were superimposed using this alignment, the side chain of the cannabinoids and the nitrogen substituent of the indole corresponded well with each other.



If the indole nitrogen in cannabimimetic indoles corresponds to C-1' of cannabinoids and the substituent on the nitrogen corresponds to the remaining atoms of the side chain, it is predicted that 1-alkyl-2-methyl-3-(1-naphthoyl)indoles such as **4** should show cannabinoid activity. Modeling studies identical to those described above were carried out using **1**, again with a *n*-butyl substituent at C-3, and **4**, R=*n*-C₃H₇. Excellent correspondence between the cannabinoid side chain and the nitrogen substituent of **4** was observed. A corollary to this hypothesis is that the naphthoyl substituent, or an alternative group which occupies a similar region in space is essential to cannabinoid activity.^{5,7}

To test this hypothesis a series of acyl indoles related to **4** containing various substituents on nitrogen as well as two indoles related to **5** possessing 3-acyl-2-methyl-1-(4-morpholinoethyl) structures have been prepared and their pharmacology has been evaluated. The 3-acylindoles (R=CH₃ and R=(CH₃)₂C=CH) were prepared by Friedel-Crafts acylation of 2-methyl-1-(4-morpholinylethyl)indole.^{9,10} Indole derivatives **4** (Table 1) were prepared from 2-methyl-3-(1-naphthoyl)indole⁹ and the appropriate alkyl halide or tosylate. For primary groups alkylation was carried out using KOH in DMSO and the appropriate alkyl bromide. The 2-heptyl derivatives were prepared from the corresponding tosylates with KH in DMSO. The unoptimized yields

with primary halides were from 38% to 54% ; however the 2-heptyl derivatives gave elimination as the major reaction path and the purified alkylation products were obtained in only 17% to 19% yield.

All of the indoles were evaluated *in vitro* by measuring their ability to displace [^3H] CP-55,940 (2) from its binding site in a membrane preparation as described by Compton *et al.*¹¹ The K_I values for the indole derivatives, CP-55,940 (2), Δ^9 -THC (1) and WIN-55,212 (3) are presented in Table 1. Several of the indole derivatives were also evaluated *in vivo* in a mouse model of cannabimimetic activity.^{5,12} These evaluations include measures of spontaneous activity, antinociception, hypothermia, and catalepsy. It has been shown that an average of the ED_{50} values for these four behavioral procedures correlate well with K_I ¹¹ and the *in vivo* data in Table 1 are presented as these averages. Data for compounds 1, 2 and 3 are also included in Table 1.

Table 1. Pharmacology of Indoles 4 and 5, and Cannabinoids 1, 2 and 3.

Entry	Compound	K_I (nM)	<i>in vivo</i> (ED_{50} , $\mu\text{M/Kg}$)
1	4 R = 2-Phenylethyl	1250 $\pm$ 250	>257
2	4 R = 2-Cyclohexylethyl	46 $\pm$ 13	65.8
3	4 R = n-Propyl	164 $\pm$ 22	not det.
4	4 R = n-Butyl	22 $\pm$ 1.5	not det.
5	4 R = n-Pentyl	9.5 $\pm$ 4.5	2.62
6	4 R = n-Hexyl	48 $\pm$ 13	14.0
7	4 R = n-Heptyl	>10,000	>189
8	4 R = RS-2 Heptyl	33 $\pm$ 11	35.6
9	4 R = R-2-Heptyl	81 $\pm$ 41	21.5
10	4 R = S-2-Heptyl	72 $\pm$ 32	not det.
11	5 R = CH_3	>10,000	>350
12	5 R = $(\text{CH}_3)_2\text{C}=\text{CH}$	>10,000	>103
13	1 Δ^9 -THC	41 ^a	4.70 ^a
14	2 CP-55,940	0.924 ^a	0.55 ^c
15	3 WIN-55,212	24 ^d	6.53 ^b

a. Ref. 11. b. Ref. 5. c. Ref 12(b). d. Ref. 15. not det. = not determined.

As predicted by the hypothesis developed using PCModel those 3-acylindoles (5) which lack a naphthoyl substituent at C-3, were devoid of cannabinoid activity (entries 11, 12). However, in agreement with the hypothesis, the 1-alkylindoles in which the nitrogen substituent provides a chain of four to six carbons show both *in vitro* and *in vivo* activity comparable to both THC and WIN-55,212 (entries 4 -10, 13, 15). It is known that in traditional cannabinoids activity normally requires a side chain of four to seven carbons.^{2a} Since the modeling studies indicate that the indole nitrogen corresponds to C-1' of the cannabinoid, then these results are consistent with the theory of structural alignment proposed above. It is also interesting to note that the racemic 1-(2-heptyl) analog and both enantiomers have the same (within experimental error) *in vitro* activity (entries 8 - 10). Also, the n-heptyl derivative (entry 7) is devoid of activity, although the next lower homolog is quite active. The n-heptyl compound would correspond to an octyl side chain on a traditional cannabinoid and consequently would be expected to have little, if any, activity.

In a recent publication, Semus and Martin have concluded, on the basis of modeling studies, that the phenolic hydroxyl group of cannabinoids hydrogen bonds to the receptor.¹³ However, in neither the indoles described in Table 1, nor WIN-55,212 can this occur. It appears quite probable that in both cannabimimetic indoles, and possibly traditional cannabinoids, that the receptor serves as a hydrogen bond donor to the cannabinoid, similar to the mechanism proposed and evaluated by Reggio *et al.*¹⁴

In summary, modeling experiments have been employed to design a new group of cannabimimetic indoles which possess activity comparable to that of traditional cannabinoids. These readily available compounds demonstrate this activity both *in vitro* and *in vivo*, provide additional evidence that the cannabinoid receptor hydrogen bonds to the substrate, and suggest a possible structural alignment between cannabimimetic indoles and traditional cannabinoids.

Acknowledgements. The work at Clemson was supported by grant DA03590, and that at Virginia Commonwealth University by grant DA03672, both from the National Institute on Drug Abuse, as well as by the Virginia Commonwealth Center on Drug Abuse (VCU). We thank Dr. Richard H. Wallace of the University of Alabama for assistance in obtaining high resolution mass spectral data.

REFERENCES AND NOTES

1. Gaoni, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1964**, *86*, 1646.
2. (a) Razdan, R. K. *Pharmacol. Rev.* **1986**, *38*, 75. (b) Mechoulam, R.; Devane, W. A.; Glaser, R. Cannabinoid Geometry and Biological Behavior. In *Marijuana/Cannabinoids: Neurobiology and Neuropsychology*; Murphy, L.; Bartke, A.; CRC Press, Boca Raton 1992; pp 1-33.
3. Johnson, M. R.; Melvin, L. S. The Discovery of Nonclassical Cannabinoid Analgetics. In *Cannabinoids as Therapeutic Agents*, Mechoulam, R.; CRC Press, Boca Raton, 1986, pp 121-145.
4. D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. A.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M.; Beghin, N. C.; Chippari, S. M.; Grego, J. D.; Kullnig, R. K.; Daley, G. T. *J. Med. Chem.* **1992**, *35*, 124.
5. Compton, D. R.; Gold, L. H.; Ward, S. J.; Balster, R. L.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 1118.
6. Devane, W. A.; Dysarz, F. A. III; Johnsson, M. R.; Melvin, L. S.; Howlett, A. C. *Mol. Pharmacol.* **1988**, *34*, 605.
7. Reggio, P. H.; Panu, A. M.; Miles, S. *J. Med. Chem.* **1993**, *36*, 1761.
8. PCModel is a modified MM2/MMP1 program which incorporates the MODEL graphical interface and which permits the direct comparison of several structures. PCModel is marketed by Serena Software, Bloomington, IN.
9. Bell, M. R.; D'Ambra, T. E.; Kumar, V.; Eissanstat, M. A.; Herrmann, J. L.; Wetzel, J. R.; Rosi, D.; Phillion, R. E.; Daum, S. J.; Hlasta, D. J.; Kullnig, R. K.; Ackerman, J. H.; Haubrich, D. R.; Luttinger, D. A.; Baizman, E. R.; Miller, M. S.; Ward, S. J. *J. Med. Chem.* **1991**, *34*, 1099.
10. All new compounds were characterized by ¹H and ¹³C NMR and gave either acceptable analytical or HRMS data. Purity was established by TLC and ¹³C NMR.
11. Compton, D. R.; Rice, K. C.; De Costa, B. R.; Razdan, R. K.; Melvin, L. S.; Johnson, M. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 218.
12. (a) Martin, B. R.; Compton, D. R.; Little, P. J.; Martin, T. J.; Beardsley, P. M. Pharmacological Evaluation of Agonistic and Antagonistic Activity of Cannabinoids. In *Structure Activity Relationships in Cannabinoids*, Rapaka, R. S.; Makriyannis, A. NIDA Research Monograph 79, National Institute on Drug Abuse, Rockville, MD, 1987, pp 108-122. (b) Little, P. J.; Compton, D. R.; Johnson, M. R.; Melvin, L. S.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1046.
13. Semus, S. F.; Martin, B. R. *Life Sci.* **1990**, *46*, 1781.
14. Reggio, P. H.; Seltzman, H. H.; Compton, D. R.; Martin, B. R. *Mol. Pharmacol.* **1990**, *38*, 854.
15. Jansen, E. M.; Haycock, D. A.; Ward, S. J.; Seybold, V. S. *Brain Res.* **1992**, *575*, 93.

(Received in USA 23 November 1993; accepted 17 December 1993)