Drug Status Report

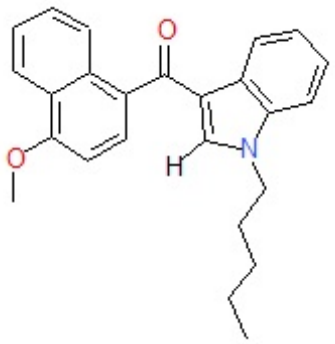
Drug: JWH-081

Drug Name Status: JWH-081 is the common name.

Chemical Name: 1-pentyl-3-(4-methoxy-1-naphtholy)indole

Other Names: 4'-methoxy-1-pentylindole; 4-methoxynaphthalen-1-yl-(1-pentylindol-3-yl)methanone

Chemical structure:



Molecular Formula: $C_{25}H_{25}NO_2$

Pharmacological class / Application: Cannabinoid receptor agonist.

International status:

US: The substance is not listed on the schedules to the US Controlled Substances Act.

United Nations: The substance is not listed on the Yellow List - List of Narcotic Drugs under International Control nor the Green List - List of Psychotropic Substances under International Control.

Canadian Status: JWH-081 is one of several synthetic cannabimimetic substances that were synthesized to assess the binding affinities of a series of 3-(alkoxy-1-naphthoyl)indoles to the CB_1 and CB_2 receptors[1]. JWH-081 has a potent binding affinity for both the CB_1 and CB_2 receptors but its affinity for the CB_1 receptor is reported to be ten times greater than that for the

[1]M M Aung et al. (2000) Influence of the –1 alkyl chain length of cannabimimetic indoles upon CB_1 and CB_2 receptor binding, Drug and Alcohol Dependence **60**:133-140.

CB_2 receptor[1,2]. Furthermore, a recent 3D-QSAR study of the selectivity of indole ligands for the CB_1 receptor identified JWH-081 as the most selective molecule for the CB_1 receptor of all the ligands that were investigated, and exceeded the selectivities observed for known potent cannabinoid agonists such as JWH-018 and JWH-015[3]. These computational data support that JWH-081 has potential as a efficacious CB_1 receptor agonist.

The efficacy of many synthetic cannabinoids, particularly those that have a high binding affinity for the CB_1 receptor, is not readily available in the literature[4]. This is mainly due to research efforts being focused upon developing drugs that do not produce unwanted psychoactive effects and hence more studies which evaluate the efficacy of substances that display a high binding affinity for the CB_2 receptor. However, unpublished *in vivo* data in the mouse has shown JWH-081 to be a highly potent CB1 receptor agonist[5].

Cannabinoid receptor agonists have been declared to be included within item 1 of Schedule II to the CDSA by virtue of being "similar synthetic preparations." Cannabinoid receptor antagonists have been declared to fall outside item 1 of Schedule II to the CDSA. Given the high affinity and high selectivity of JWH-081 for the CB_1 receptors as well as *in vivo* data showing the substance as a potent CB_1 agonist, JWH-081 should be included in item 1 of Schedule II.

Recommendation: JWH-081 is included in item 1 of Schedule II to the CDSA and is a controlled substance.

January 7th, 2010

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[2]JW Huffman et al. (2005) Structure-activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB1 and CB2 receptors: steric and electronic effects of the naphthoyl substituents. New highly selective CB2 receptor agonists. Bioorg. Med. Chem. **13**:89-112.

[3]GBL Freitas et al. (2009) Development of CoMFA and CoMSIA models of affinity and selectivity for indole ligands of cannabinoid CB1 and CB2 receptors, Eur. J. Med. Chem. **44**: 2482-2496.

[4] JW Huffman et al. (2005) 1-Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles, Bioorg. Med. Chem. Lett. **15**:4110-3.

[5]Personal communication (email correspondence attached).