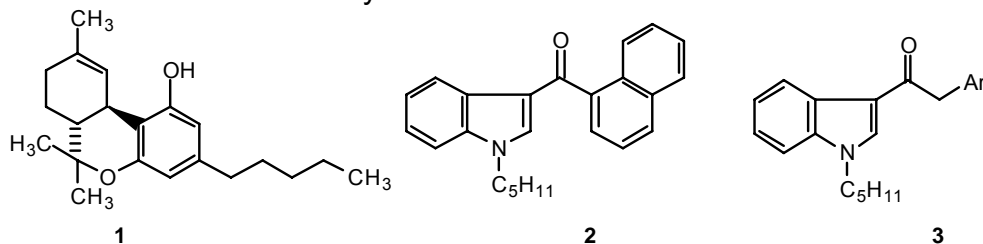


## Synthesis of Cannabimimetic Indoles

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The principal psychoactive component of *cannabis sativa* (marijuana) is  $\Delta^9$ -tetrahydrocannabinol (THC, **1**). Other classes of compounds structurally dissimilar to **1** also exhibit typical cannabinoid pharmacology. A very structurally diverse group of these non-traditional cannabinoids is the cannabimimetic indoles, of which, JWH-018, 1-pentyl-3-(1-naphthoyl)indole (**2**), is an example. This compound has approximately five times greater affinity for the cannabinoid central nervous system (CB<sub>1</sub>) receptor than THC and is more potent *in vivo*. To investigate the structural features that are necessary for optimal activity our group has synthesized more than 100 indole derivatives. Several of these compounds show selectivity for the peripheral (CB<sub>2</sub>) cannabinoid receptor. Many of these compounds have been prepared by summer undergraduate research students, and the pharmacology has been carried out by our collaborators at Virginia Commonwealth University.



Recently we found that two 1-pentyl-3-acylacetylindoles (**3**, Ar = 2-methylphenyl and 3-methoxyphenyl) show modest selectivity for the CB<sub>1</sub> receptor. Although CB<sub>2</sub> selectivity is not unusual, there are very few CB<sub>1</sub> selective agonists. Using these two compounds as leads, summer undergraduate research students will synthesize additional compounds in this series. Specifically, those compounds in which Ar = 2-ethylphenyl, 3-ethylphenyl, 2-ethoxyphenyl and 3-ethoxyphenyl will be prepared and their affinities for the CB<sub>1</sub> and CB<sub>2</sub> receptors will be determined. The synthetic sequence is three steps from indole and the appropriate arylacetic acid. The first steps are *N*-alkylation of the indole and conversion of the acid to the acid chloride. Modified Friedel Crafts acylation, followed by purification provides the target compounds. A number of other compounds in this series (**3**, Ar = various substituted phenyl groups) have been prepared by summer undergraduate research students. Subsequent work will include the synthesis of indole derivatives similar to **3** in which the indole nitrogen substituent is varied. The synthesis of additional compounds in this series will be dictated by the results of the pharmacological evaluation of the compounds described above.