

# Structure–activity relationships for 1-alkyl-3-(1-naphthoyl)indoles at the cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors: steric and electronic effects of naphthoyl substituents. New highly selective CB<sub>2</sub> receptor agonists

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**Abstract**—In an effort to improve indole-based CB<sub>2</sub> cannabinoid receptor ligands and also to develop SAR for both the CB<sub>1</sub> and CB<sub>2</sub> receptors, 47 indole derivatives were prepared and their CB<sub>1</sub> and CB<sub>2</sub> receptor affinities were determined. The indole derivatives include 1-propyl- and 1-pentyl-3-(1-naphthoyl)indoles both with and without a 2-methyl substituent. Naphthoyl substituents include 4- and 7-alkyl groups as well as 2-, 4-, 6-, 7-methoxy and 4-ethoxy groups. The effects of these substituents on receptor affinities are discussed and structure–activity relationships are presented. In the course of this work three new highly selective CB<sub>2</sub> receptor agonists were identified, 1-propyl-3-(4-methyl-1-naphthoyl)indole (JWH-120), 1-propyl-2-methyl-3-(6-methoxy-1-naphthoyl)indole (JWH-151), and 1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267). GTPγS assays indicated that JWH-151 is a full agonist at CB<sub>2</sub>, while JWH-120 and JWH-267 are partial agonists. Molecular modeling and receptor docking studies were carried out on a set of 3-(4-propyl-1-naphthoyl)indoles, a set of 3-(6-methoxy-1-naphthoyl)indoles and the pair of *N*-pentyl-3-(2-methoxy-1-naphthoyl)indoles. Docking studies indicated that the CB<sub>1</sub> receptor affinities of these compounds were consistent with their aromatic stacking interactions in the aromatic microdomain of the CB<sub>1</sub> receptor.

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## 1. Introduction

Nearly 40 years ago Gaoni and Mechoulam reported the elucidation of the structure of Δ<sup>9</sup>-tetrahydrocannabinol (**1**, THC) the principal psychoactive compound present in marijuana.<sup>1</sup> Subsequently, a comprehensive set of structure–activity relationships (SAR) was developed based on the dibenzopyran nucleus of THC.<sup>2–6</sup> These SAR were later extended to the very potent group of non-traditional cannabinoids developed by Pfizer, of

which CP-55,940 (**2**, DMH = 1,1-dimethylheptyl) is the prototypical example.<sup>7,8</sup>

These pharmacological effects of cannabinoids are considered to be mediated through at least two G-protein-coupled, transmembrane receptors. One of these, designated as CB<sub>1</sub>, is found predominantly in the central nervous system and is thought to be responsible for most of the overt pharmacological effects of cannabinoids.<sup>5,9–11</sup> A second receptor, designated CB<sub>2</sub>, was originally identified from macrophages present in the spleen, and is expressed primarily in the periphery.<sup>12</sup> Evidence has been presented recently for the existence of a third cannabinoid receptor, which has been detected in mouse brain.<sup>13</sup>

**Keywords:** Cannabinoids; Structure–activity relationships; Cannabinoid receptors; Aminoalkylindole.

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Some years ago in the course of a program directed toward the development of non-steroidal anti-inflammatory drugs, a group at Sterling–Winthrop reported that pravadoline (**3**), an indole derivative, unexpectedly inhibited contractions of the electrically stimulated mouse vas deferens.<sup>14</sup> Later work revealed that **3**, and a number of related compounds also inhibit adenylate cyclase, are antinociceptive and interact with a G-coupled protein in the brain. Subsequent work indicated that the G-coupled protein is the cannabinoid CB<sub>1</sub> receptor and that these aminoalkylindoles exhibit typical cannabinoid pharmacology in vivo.<sup>15,16</sup> One of the aminoalkylindoles, WIN-55,212-2 (**4**), developed by the Winthrop group is not only potent in vivo, but has high affinity for both the cannabinoid CB<sub>1</sub> and CB<sub>2</sub> receptors.<sup>17</sup>

During the course of their investigations of the aminoalkylindoles, the Winthrop group synthesized more than 100 compounds and developed some preliminary SAR.<sup>14,15,18</sup> These included the observation that a group larger than methyl at C-2 of the indole nucleus greatly attenuates potency and that a bicyclic aroyl group, usually 1-naphthoyl or a substituted 1-naphthoyl group, at C-3 is essential for potency. It was further concluded that an aminoalkyl group, usually substituted aminoethyl, attached to the indole nitrogen was essential for cannabinoid activity.

Subsequent studies by our group established that the aminoalkyl group appended to the indole nitrogen could

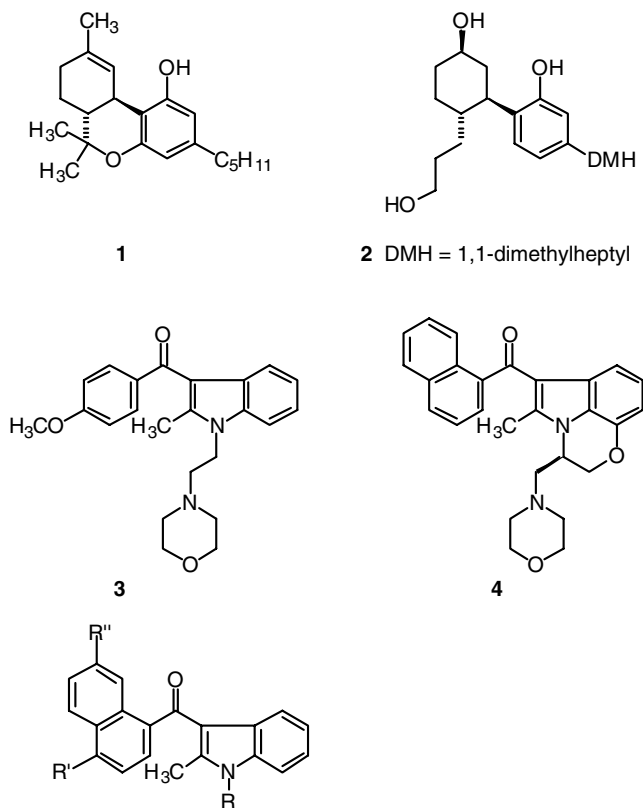
be replaced by an alkyl group to provide relatively simple indole derivatives, which exhibit typical cannabinoid pharmacology.<sup>19,20</sup> In particular, JWH-007, 1-pentyl-2-methyl-3-(1-naphthoyl)indole (**5**) has high affinity for the CB<sub>1</sub> receptor and exhibits typical cannabinoid pharmacology in vivo. The 1-propyl analog of **5**, JWH-015 (**6**) has relatively high affinity for the CB<sub>2</sub> receptor, and weak affinity for the CB<sub>1</sub> receptor.<sup>17</sup>

In an effort to develop improved indole-based CB<sub>2</sub> cannabinoid receptor ligands and also to develop SAR for both the CB<sub>1</sub> and CB<sub>2</sub> receptors a number of additional indole derivatives were prepared and their pharmacology was evaluated.<sup>21,22</sup> It was found that CB<sub>1</sub> receptor affinity is optimal with a *n*-pentyl nitrogen substituent, and decreases dramatically with *N*-alkyl substituents of three or less carbon atoms. CB<sub>1</sub> receptor affinity is also greatly attenuated with *N*-alkyl substituents longer than six carbon atoms. A 2-methyl substituent slightly decreases affinity at the CB<sub>1</sub> receptor and a 4-methoxy-1-naphthoyl group at C-3 of the indole, as in JWH-098 (**7**) enhances CB<sub>1</sub> receptor affinity. A 7-methyl-1-naphthoyl substituent in JWH-046 (**8**) and JWH-048 (**9**) has relatively little effect on either CB<sub>1</sub> or CB<sub>2</sub> receptor affinity. The SAR at the CB<sub>2</sub> receptor are somewhat similar to those at the CB<sub>1</sub> receptor, however there are a number of exceptions to these generalizations, which render it difficult to establish comprehensive SAR for these compounds at the CB<sub>2</sub> receptor.<sup>21,23</sup>

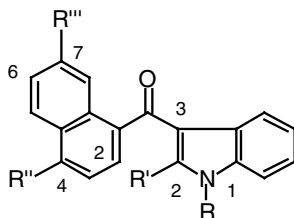
The SAR outlined above includes only indoles with an unsubstituted 3-naphthoyl substituent, or with 4-methoxy- or 7-methyl-1-naphthoyl groups. To further develop SAR for these compounds, and with the goal of preparing CB<sub>2</sub> selective ligands, a number of additional cannabimimetic indoles have been prepared and their affinities for the CB<sub>1</sub> and CB<sub>2</sub> receptors have been determined. These compounds include *N*-propyl- and *N*-pentyl-3-(1-naphthoyl)indoles in which the naphthoyl group contains various alkyl and alkoxy substituents, and the indole is either unsubstituted at C-2 or contains a 2-methyl group. The choice of the *N*-propyl substituent is based on the observation that the two most highly CB<sub>2</sub> selective indole derivatives prepared in our laboratory, JWH-015 (**6**) and JWH-046 (**8**) both contain this substitution pattern.<sup>21,23</sup> The *N*-pentyl group was chosen since this substituent almost invariably provides compounds with higher CB<sub>1</sub> receptor affinities than are observed with other nitrogen substituents.

## 2. Results

To explore the steric and electronic effects of various naphthoyl substituents, 3-(4-alkyl-1-naphthoyl), 3-(7-ethyl-1-naphthoyl), 3-(2-, 6-, 7-methoxy-1-naphthoyl), 3-(4-ethoxy-1-naphthoyl)indoles (for numbering see the structure included in Table 1), have been synthesized and their CB<sub>1</sub> and CB<sub>2</sub> receptor affinities have been determined. These indoles were prepared by modifications of established routes, either by coupling substituted 1-naphthoyl chlorides with 1-alkyl- or 1-alkyl-2-



- 5** R = C<sub>5</sub>H<sub>11</sub>, R' = H, R'' = H  
**6** R = C<sub>3</sub>H<sub>7</sub>, R' = H, R'' = H  
**7** R = C<sub>5</sub>H<sub>11</sub>, R' = OCH<sub>3</sub>, R'' = H  
**8** R = C<sub>3</sub>H<sub>7</sub>, R' = H, R'' = CH<sub>3</sub>  
**9** R = C<sub>5</sub>H<sub>11</sub>, R' = H, R'' = CH<sub>3</sub>

**Table 1.** Structures, method of synthesis, and receptor affinities (mean  $\pm$  SEM) of 3-(alkyl-1-naphthoyl)indoles

| Compound                            | $K_i$ (nM) |                                |                 |                               |                               |                             |                              |                                                     |
|-------------------------------------|------------|--------------------------------|-----------------|-------------------------------|-------------------------------|-----------------------------|------------------------------|-----------------------------------------------------|
|                                     | Synthesis  | R                              | R'              | R''                           | R'''                          | CB <sub>1</sub>             | CB <sub>2</sub>              | Ratio CB <sub>2</sub> /CB <sub>1</sub> <sup>g</sup> |
| $\Delta^9$ -THC ( <b>1</b> )        |            |                                |                 |                               |                               | 41 $\pm$ 2 <sup>a</sup>     | 36 $\pm$ 10 <sup>b</sup>     | 1.1                                                 |
| WIN-55,212-2 ( <b>4</b> )           |            |                                |                 |                               |                               | 1.9 $\pm$ 0.1 <sup>b</sup>  | 0.28 $\pm$ 0.16 <sup>b</sup> | 6.8                                                 |
| JWH-072 <sup>c</sup>                |            | C <sub>3</sub> H <sub>7</sub>  | H               | H                             | H                             | 1050 $\pm$ 55 <sup>c</sup>  | 170 $\pm$ 54 <sup>c</sup>    | 6.2                                                 |
| JWH-015 <sup>c,d</sup> ( <b>6</b> ) |            | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                             | H                             | 164 $\pm$ 22 <sup>c</sup>   | 13.8 $\pm$ 4.6 <sup>b</sup>  | 11.9                                                |
| JWH-018 <sup>c</sup>                |            | C <sub>5</sub> H <sub>11</sub> | H               | H                             | H                             | 9 $\pm$ 5 <sup>c</sup>      | 2.9 $\pm$ 2.6 <sup>c</sup>   | 3.3                                                 |
| JWH-007 <sup>c,d</sup> ( <b>5</b> ) |            | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                             | H                             | 9.5 $\pm$ 4.5 <sup>c</sup>  | 2.9 $\pm$ 2.6 <sup>c</sup>   | 3.3                                                 |
| JWH-120 ( <b>41</b> )               | B          | C <sub>3</sub> H <sub>7</sub>  | H               | CH <sub>3</sub>               | H                             | 1054 $\pm$ 31               | 6.1 $\pm$ 0.7                | 173                                                 |
| JWH-148                             | A          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | CH <sub>3</sub>               | H                             | 123 $\pm$ 8                 | 14 $\pm$ 1.0                 | 8.8                                                 |
| JWH-122 <sup>e</sup>                |            | C <sub>5</sub> H <sub>11</sub> | H               | CH <sub>3</sub>               | H                             | 0.69 $\pm$ 0.5 <sup>e</sup> | 1.2 $\pm$ 1.2                | 0.6                                                 |
| JWH-149 <sup>e</sup>                |            | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | CH <sub>3</sub>               | H                             | 5.0 $\pm$ 2.1 <sup>e</sup>  | 0.73 $\pm$ 0.03              | 6.8                                                 |
| JWH-212                             | C          | C <sub>3</sub> H <sub>7</sub>  | H               | C <sub>2</sub> H <sub>5</sub> | H                             | 33 $\pm$ 0.9                | 10 $\pm$ 1.2                 | 3.3                                                 |
| JWH-211                             | C          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H                             | 70 $\pm$ 0.8                | 12 $\pm$ 0.8                 | 5.8                                                 |
| JWH-210                             | C          | C <sub>5</sub> H <sub>11</sub> | H               | C <sub>2</sub> H <sub>5</sub> | H                             | 0.46 $\pm$ 0.03             | 0.69 $\pm$ 0.01              | 0.67                                                |
| JWH-213                             | C          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub> | H                             | 1.5 $\pm$ 0.2               | 0.42 $\pm$ 0.05              | 3.6                                                 |
| JWH-180                             | C          | C <sub>3</sub> H <sub>7</sub>  | H               | C <sub>3</sub> H <sub>7</sub> | H                             | 26 $\pm$ 2                  | 9.6 $\pm$ 2.0                | 2.7                                                 |
| JWH-189                             | C          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | C <sub>3</sub> H <sub>7</sub> | H                             | 52 $\pm$ 2                  | 12 $\pm$ 0.8                 | 4.3                                                 |
| JWH-182                             | C          | C <sub>5</sub> H <sub>11</sub> | H               | C <sub>3</sub> H <sub>7</sub> | H                             | 0.65 $\pm$ 0.03             | 1.1 $\pm$ 0.1                | 0.6                                                 |
| JWH-181                             | C          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | C <sub>3</sub> H <sub>7</sub> | H                             | 1.3 $\pm$ 0.1               | 0.62 $\pm$ 0.04              | 2.1                                                 |
| JWH-239                             | C          | C <sub>3</sub> H <sub>7</sub>  | H               | C <sub>4</sub> H <sub>9</sub> | H                             | 342 $\pm$ 20                | 52 $\pm$ 6                   | 6.6                                                 |
| JWH-241                             | C          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | C <sub>4</sub> H <sub>9</sub> | H                             | 147 $\pm$ 20                | 49 $\pm$ 7                   | 3.0                                                 |
| JWH-240                             | C          | C <sub>5</sub> H <sub>11</sub> | H               | C <sub>4</sub> H <sub>9</sub> | H                             | 14 $\pm$ 1                  | 7.2 $\pm$ 1.3                | 1.9                                                 |
| JWH-242                             | C          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | C <sub>4</sub> H <sub>9</sub> | H                             | 42 $\pm$ 9                  | 6.5 $\pm$ 0.3                | 6.5                                                 |
| JWH-076                             | A          | C <sub>3</sub> H <sub>7</sub>  | H               | H                             | CH <sub>3</sub>               | 214 $\pm$ 11                | 106 $\pm$ 46                 | 2.0                                                 |
| JWH-046 <sup>f</sup> ( <b>8</b> )   |            | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                             | CH <sub>3</sub>               | 343 $\pm$ 38 <sup>f</sup>   | 16 $\pm$ 5 <sup>f</sup>      | 21                                                  |
| JWH-048 <sup>f</sup> ( <b>9</b> )   |            | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                             | CH <sub>3</sub>               | 10.7 $\pm$ 1.0 <sup>f</sup> | 0.49 $\pm$ 0.1 <sup>f</sup>  | 22                                                  |
| JWH-235                             | B          | C <sub>3</sub> H <sub>7</sub>  | H               | H                             | C <sub>2</sub> H <sub>5</sub> | 338 $\pm$ 34                | 123 $\pm$ 34                 | 2.7                                                 |
| JWH-236                             | B          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                             | C <sub>2</sub> H <sub>5</sub> | 1351 $\pm$ 204              | 240 $\pm$ 63                 | 5.6                                                 |
| JWH-234                             | B          | C <sub>5</sub> H <sub>11</sub> | H               | H                             | C <sub>2</sub> H <sub>5</sub> | 8.4 $\pm$ 1.8               | 3.8 $\pm$ 0.6                | 2.2                                                 |
| JWH-262                             | B          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                             | C <sub>2</sub> H <sub>5</sub> | 28 $\pm$ 3                  | 5.6 $\pm$ 0.7                | 5.0                                                 |

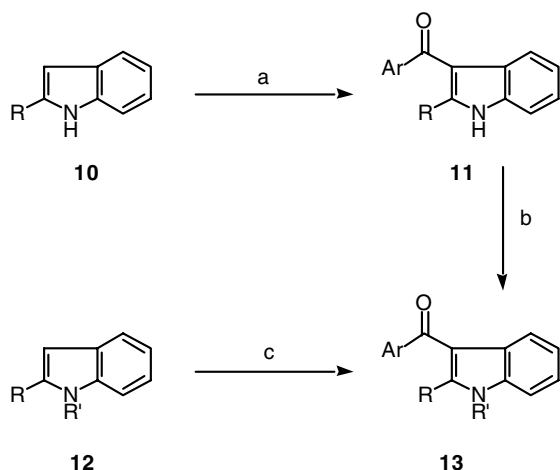
<sup>a</sup> Ref. 41.<sup>b</sup> Ref. 17.<sup>c</sup> Refs. 20,21.<sup>d</sup> Ref. 19.<sup>e</sup> Ref. 24.<sup>f</sup> Ref. 21.<sup>g</sup> Ratio is based on interspecies comparison of rat CB<sub>1</sub> and human CB<sub>2</sub>.

methylindoles or by acylation of indole or 2-methylindole, followed by *N*-alkylation (Scheme 1).<sup>14,15,18,19,24</sup>

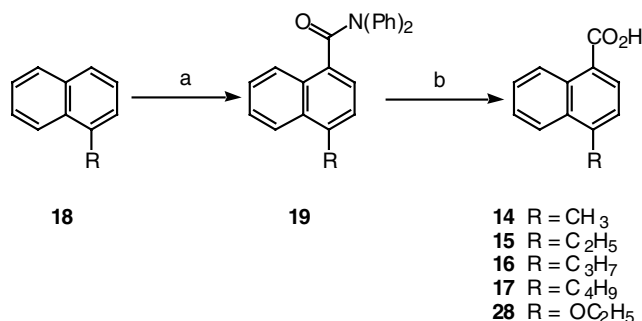
In our early work, indole (**10**, R = H) or 2-methylindole (**10**, R = CH<sub>3</sub>) was treated with methylmagnesium bromide to give the ambident indolyl anion, which upon reaction with an aroyl chloride gave the 3-acylindole (**11**, method A).<sup>19</sup> *N*-Alkylation with the appropriate primary alkyl bromide using KOH in DMSO provides the *N*-alkyl-3-acylindole. Although this sequence was satisfactory when using readily available aroyl halides, the yields in the first step were variable, the 3-acylindoles (**11**) were difficult to purify and alternative methodology was explored. Traditional aluminum chloride catalyzed Friedel–Crafts acylation of *N*-alkylindoles gave poor yields, however three variations of this classi-

cal reaction gave satisfactory to good yields. The method of choice is that reported recently by Okauchi et al. (method B) in which *N*-alkylindoles **12** are treated with dimethyl- or diethylaluminum chloride for 30 min prior to the addition of the aroyl halide.<sup>25</sup> This mild procedure provides pure products (**13**) in yields of 50–90%. The final methods are variations of a classical Friedel–Crafts procedure, but use ethylaluminum dichloride at ambient temperature for either four days (method C) or for 18 h (method D). The yields for procedures C and D are adequate, but are somewhat inferior to those using Okauchi's method (procedure B).

Of the 1-naphthoic acids required for the synthesis of the cannabimimetic 3-(4-alkyl-1-naphthoyl)indoles, only 4-methyl-1-naphthoic acid (**14**, Scheme 2) is



**Scheme 1.** Reagents and conditions: (a) MeMgBr, Et<sub>2</sub>O/THF, 0°C, then ArCOCl, reflux; (b) R'Br, KOH, DMSO, 80°C; (c) ArCOCl, Lewis acid (see text and Experimental).



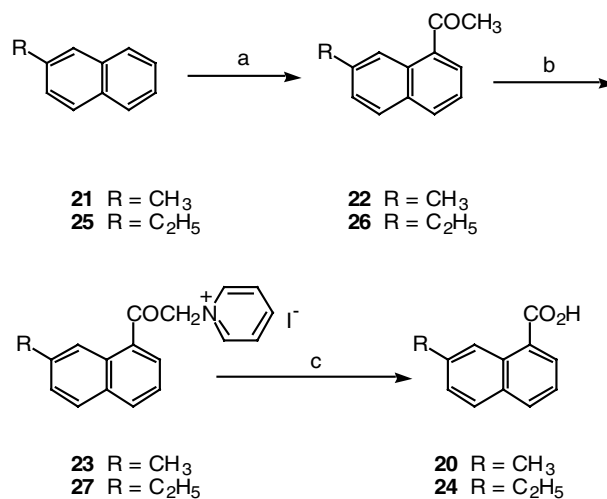
**Scheme 2.** Reagents and conditions: (a) Ph<sub>2</sub>NCOCl, AlCl<sub>3</sub>, ClCH<sub>2</sub>CH<sub>2</sub>Cl, reflux; (b) KOH, diethylene glycol, reflux, then HCl.

commercially available. 4-Ethyl- (15), 4-propyl- (16) and 4-butyl-1-naphthoic (17) acids were reported some years ago by Russian workers, who prepared them by chloromethylation of the 1-alkylnaphthalene, followed by conversion to the corresponding acetate, hydrolysis to the alcohol, and oxidation to the carboxylic acid.<sup>26</sup> A considerably more efficient approach employs Friedel–Crafts acylation of the appropriate 1-alkylnaphthalene (18, R = C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, C<sub>4</sub>H<sub>9</sub>) with *N,N*-diphenylcarbamyl chloride to give 1-naphthyl *N,N*-diphenylamides (19, R = C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, C<sub>4</sub>H<sub>9</sub>), hydrolysis of which will afford the corresponding carboxylic acid.<sup>27</sup> Although the acylation step proceeded smoothly in yields of 80–85%, hydrolysis could not be effected using the reported procedure, ethanolic sodium hydroxide at reflux. The amides were successfully hydrolyzed in 90–92% yield by treatment with potassium hydroxide in diethylene glycol at reflux.<sup>28,29</sup> Acidification then affords the 4-alkyl-1-naphthoic acids (14–17). Conversion of 4-methyl-1-naphthoic acid to 1-propyl-3-(4-methyl-1-naphthoyl)indole (JWH-120) and 2-methyl-1-propyl-3-(4-methyl-1-naphthoyl)indole (JWH-148) was carried out using methods B and A, respectively. The 1-pentyl analogs of these compounds (JWH-122, JWH-149) have been reported previously.<sup>24</sup> The conversion of acids

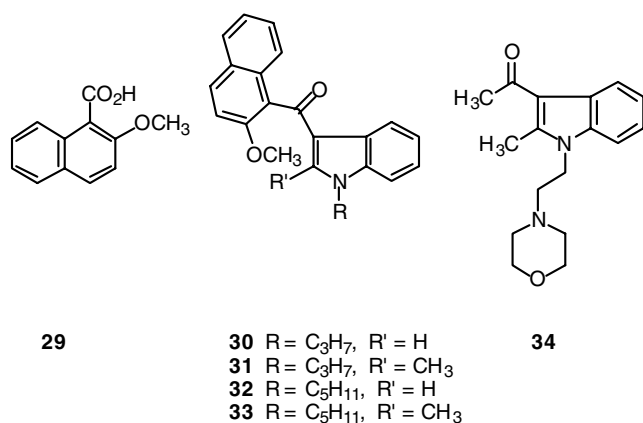
14–17 to the 3-(4-ethyl-1-naphthoyl)indoles (JWH-210–JWH-213), the 3-(4-propyl-1-naphthoyl)indoles (JWH-180–JWH-182, JWH-189) and the 3-(4-butyl-1-naphthoyl)indoles (JWH-239–JWH-242) was carried out using method C. The CB<sub>1</sub> and CB<sub>2</sub> receptor affinities of these compounds are summarized in Table 1.

7-Methyl-1-naphthoic acid (20), which had been used previously for the synthesis of JWH-046 (8) and JWH-048 (9),<sup>21</sup> was prepared by a modification of the method of Snatzke and Kunde (Scheme 3).<sup>30</sup> Friedel–Crafts acylation of 2-methylnaphthalene (21) under standard conditions using acetyl chloride and AlCl<sub>3</sub> proceeds as described to provide 1-acetyl-7-methylnaphthalene (22), however, conversion to acid 20 could not be effected using the haloform reaction under various conditions. In the King modification of the haloform reaction, ketone 22 with iodine and pyridine gave pyridinium iodide 23, which upon basic hydrolysis and acidification provided acid 20.<sup>31</sup> Conversion of this acid to 1-propyl-3-(7-methyl-1-naphthoyl)indole was carried out by method A. 7-Ethyl-1-naphthoic acid (24), which was employed for the synthesis of the 3-(7-ethyl-1-naphthoyl)indoles (JWH-234–JWH-236, JWH-262) was prepared from 2-ethylnaphthalene (25) in an analogous manner through ketone 26 and pyridinium iodide 27. Conversion of 7-ethyl-1-naphthoic acids to the 3-(7-ethyl-1-naphthoyl)indoles (JWH-234–JWH-236, JWH-262) was carried out using method B. The receptor affinities for the 3-(7-alkyl-1-naphthoyl)indoles are included in Table 1.

In the methoxynaphthoyl series, the 2-, 4-, 6-, and 7-methoxy-1-naphthoylindoles were prepared and their affinities for the CB<sub>1</sub> and CB<sub>2</sub> receptors were determined (Table 2). In addition, to evaluate steric and electronic effects upon receptor affinities, the 4-ethoxy analogs were also prepared. The 3-(4-ethoxy-1-naphthoyl)indoles were prepared from 4-ethoxy-1-naphthoic acid (28, Scheme 2), which was obtained from 1-ethoxy-naphthalene by the procedure outlined in Scheme 2.



**Scheme 3.** Reagents and conditions: (a) CH<sub>3</sub>COCl, AlCl<sub>3</sub>, ClCH<sub>2</sub>CH<sub>2</sub>Cl, rt; (b) I<sub>2</sub>, pyridine, 100 °C; (c) NaOH/H<sub>2</sub>O, reflux, then HCl.



Acid **28** was converted to the 3-(4-ethoxy-1-naphthoyl)indoles (JWH-258–JWH-261) by method B and their receptor affinities are included in Table 2. The 3-(4-methoxy-1-naphthoyl)indoles (JWH-079, JWH-094, JWH-081, JWH-098) have been reported previously

and their affinities for the CB<sub>1</sub> and CB<sub>2</sub> receptors are also included in Table 2.<sup>21,24</sup>

For the synthesis of the 3-(2-methoxy-1-naphthoyl)indoles 2-methoxy-1-naphthoic acid (**29**) was required. Acid **29** is readily available by methylation of commercially available 2-hydroxy-1-naphthoic acid followed by hydrolysis<sup>32</sup> and was converted to indoles **30–33** (JWH-265–JWH-268, Table 2) by method B. Indoles **30** (JWH-265) and **32** (JWH-267), which are unsubstituted at C-2 of the indole nucleus showed normal <sup>1</sup>H and <sup>13</sup>C NMR spectra, however in the <sup>1</sup>H spectra of the 2-methyl analogs (**31**, JWH-266, and **33**, JWH-268) the signal at  $\delta$  2.50 due to the indole 2-methyl group and an aromatic proton at  $\delta$  6.95 appeared as very broad singlets. A second aromatic proton at  $\delta$  7.13 gave rise to a somewhat broadened singlet, rather than the sharp signals characteristic of the naphthoylindoles. Also, the signals due to the 2-methyl group and one aromatic carbon were missing in the <sup>13</sup>C spectra of indoles **31** and **33**. Although it was possible that these compounds did not have the correct structures, both

**Table 2.** Structures, method of synthesis, and receptor affinities (mean  $\pm$  SEM) of 3-(alkoxy-1-naphthoyl)indoles

| Compound                     | $K_i$ (nM) |                                |                 |                  |                                |                  |                  |         | CB <sub>1</sub>               | CB <sub>2</sub>              | Ratio CB <sub>2</sub> /CB <sub>1</sub> <sup>e</sup> |
|------------------------------|------------|--------------------------------|-----------------|------------------|--------------------------------|------------------|------------------|---------|-------------------------------|------------------------------|-----------------------------------------------------|
|                              | Synthesis  | R                              | R'              | R''              | R'''                           | R''''            | R'''''           | R'''''' |                               |                              |                                                     |
| $\Delta^9$ -THC ( <b>1</b> ) |            |                                |                 |                  |                                |                  |                  |         | 41 $\pm$ 2 <sup>a</sup>       | 36 $\pm$ 10 <sup>b</sup>     | 1.1                                                 |
| WIN-55,212-2 ( <b>4</b> )    |            |                                |                 |                  |                                |                  |                  |         | 1.9 $\pm$ 0.1 <sup>b</sup>    | 0.28 $\pm$ 0.16 <sup>b</sup> | 6.8                                                 |
| JWH-265 ( <b>30</b> )        | B          | C <sub>3</sub> H <sub>7</sub>  | H               | OCH <sub>3</sub> | H                              | H                | H                | H       | 3788 $\pm$ 323                | 80 $\pm$ 13                  | 47                                                  |
| JWH-266 ( <b>31</b> )        | B          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | OCH <sub>3</sub> | H                              | H                | H                | H       | >10,000                       | 455 $\pm$ 55                 | >22                                                 |
| JWH-267 ( <b>32</b> )        | B          | C <sub>5</sub> H <sub>11</sub> | H               | OCH <sub>3</sub> | H                              | H                | H                | H       | 381 $\pm$ 16                  | 7.2 $\pm$ 0.14               | 53                                                  |
| JWH-268 ( <b>33</b> )        | B          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | OCH <sub>3</sub> | H                              | H                | H                | H       | 1379 $\pm$ 193                | 40 $\pm$ 0.6                 | 34                                                  |
| JWH-079 <sup>c</sup>         |            | C <sub>3</sub> H <sub>7</sub>  | H               | H                | OCH <sub>3</sub>               | H                | H                | H       | 63 $\pm$ 3 <sup>c</sup>       | 32 $\pm$ 6 <sup>c</sup>      | 2.0                                                 |
| JWH-094 <sup>c</sup>         |            | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                | OCH <sub>3</sub>               | H                | H                | H       | 476 $\pm$ 67 <sup>c</sup>     | 97 $\pm$ 3 <sup>c</sup>      | 4.9                                                 |
| JWH-081 <sup>c,d</sup>       |            | C <sub>5</sub> H <sub>11</sub> | H               | H                | OCH <sub>3</sub>               | H                | H                | H       | 1.2 $\pm$ 0.03 <sup>c,d</sup> | 12.4 $\pm$ 2.2 <sup>c</sup>  | 0.1                                                 |
| JWH-098 <sup>c,d</sup>       |            | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                | OCH <sub>3</sub>               | H                | H                | H       | 4.5 $\pm$ 0.1 <sup>c,d</sup>  | 1.9 $\pm$ 0.3 <sup>c</sup>   | 2.4                                                 |
| JWH-259                      | $\mu$ MB   | C <sub>3</sub> H <sub>7</sub>  | H               | H                | OC <sub>2</sub> H <sub>5</sub> | H                | H                | H       | 220 $\pm$ 29                  | 74 $\pm$ 7                   | 3.0                                                 |
| JWH-261                      | B          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                | OC <sub>2</sub> H <sub>5</sub> | H                | H                | H       | 767 $\pm$ 105                 | 221 $\pm$ 14                 | 3.5                                                 |
| JWH-258                      | B          | C <sub>5</sub> H <sub>11</sub> | H               | H                | OC <sub>2</sub> H <sub>5</sub> | H                | H                | H       | 4.6 $\pm$ 0.6                 | 10.5 $\pm$ 1.3               | 0.44                                                |
| JWH-260                      | B          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                | OC <sub>2</sub> H <sub>5</sub> | H                | H                | H       | 29 $\pm$ 0.4                  | 25 $\pm$ 1.9                 | 1.2                                                 |
| JWH-163                      | D          | C <sub>3</sub> H <sub>7</sub>  | H               | H                | H                              | OCH <sub>3</sub> | H                | H       | 2358 $\pm$ 215                | 138 $\pm$ 12                 | 17                                                  |
| JWH-151 ( <b>42</b> )        | D          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                | H                              | OCH <sub>3</sub> | H                | H       | >10,000                       | 30 $\pm$ 1.1                 | >333                                                |
| JWH-166                      | D          | C <sub>5</sub> H <sub>11</sub> | H               | H                | H                              | OCH <sub>3</sub> | H                | H       | 44 $\pm$ 10                   | 1.9 $\pm$ 0.08               | 23                                                  |
| JWH-153                      | D          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                | H                              | OCH <sub>3</sub> | H                | H       | 250 $\pm$ 24                  | 11 $\pm$ 0.5                 | 23                                                  |
| JWH-165                      | D          | C <sub>3</sub> H <sub>7</sub>  | H               | H                | H                              | H                | OCH <sub>3</sub> | H       | 204 $\pm$ 26                  | 71 $\pm$ 8                   | 2.9                                                 |
| JWH-160                      | D          | C <sub>3</sub> H <sub>7</sub>  | CH <sub>3</sub> | H                | H                              | H                | OCH <sub>3</sub> | H       | 1568 $\pm$ 201                | 441 $\pm$ 110                | 3.6                                                 |
| JWH-164                      | D          | C <sub>5</sub> H <sub>11</sub> | H               | H                | H                              | H                | OCH <sub>3</sub> | H       | 6.6 $\pm$ 0.7                 | 6.9 $\pm$ 0.2                | 0.96                                                |
| JWH-159                      | D          | C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub> | H                | H                              | H                | OCH <sub>3</sub> | H       | 45 $\pm$ 1                    | 10.4 $\pm$ 1.4               | 4.3                                                 |

<sup>a</sup> Ref. 41.

<sup>b</sup> Ref. 17.

<sup>c</sup> Ref. 21.

<sup>d</sup> Ref. 24.

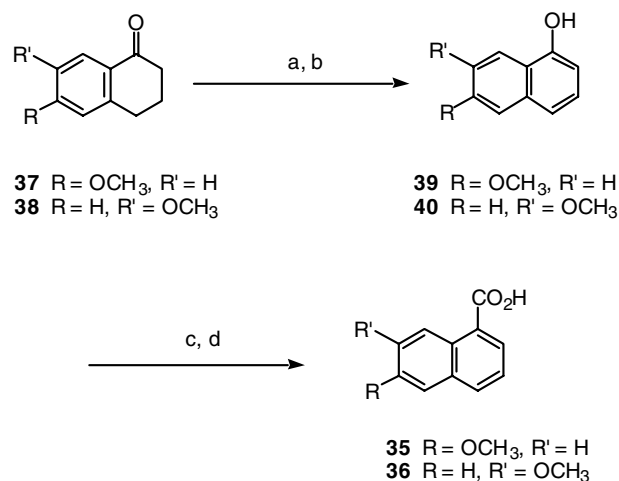
<sup>e</sup> Ratio is based on interspecies comparison of rat CB<sub>1</sub> and human CB<sub>2</sub>.

had low and high resolution mass spectra consistent with the assigned molecular formulas. The structure of 1-propyl-2-methyl-3-(2-methoxy-1-naphthoyl)indole (**31**) was confirmed by X-ray crystallography.<sup>33</sup>

It appeared probable that the anomalous NMR spectra were due to restricted rotation about the bond between C-3 of the indole nucleus and/or the naphthalene C-1 bond and the carbonyl carbon atom. Accordingly, a variable temperature study of the <sup>1</sup>H NMR spectrum of indole **31** was carried out. There was little change in the <sup>1</sup>H spectrum at 50°C, but at 75°C the signal for the C-2 methyl group had sharpened somewhat, as had that of the aromatic proton at  $\delta$  6.95, and the signal at  $\delta$  7.13 was resolved to a broadened triplet,  $J$  = 8.2 Hz. At 125°C the C-2 methyl signal was a rather sharp singlet at  $\delta$  2.46, the aromatic proton at  $\delta$  6.95 had become a well-defined triplet,  $J$  = 7.8 Hz, and the triplet at  $\delta$  7.13 appeared as a triplet of doublets,  $J$  = 0.5 and 8.2 Hz. The <sup>1</sup>H spectrum at 100°C was slightly less well resolved than that at 125°C.

A COSY spectrum of the aromatic region of indole **31** revealed that the protons, which give rise to the triplets at  $\delta$  6.95 and  $\delta$  7.13 are coupled to each other and each is coupled to one additional proton within the complex pattern between  $\delta$  7.3 and  $\delta$  7.6. The triplets at  $\delta$  6.95 and  $\delta$  7.13 can only arise from the 5,6-protons on the indole nucleus or the 6,7-naphthalene protons. Since the aromatic protons of a simple acyl indole derivative, 2-methyl-1-morpholinoethyl-3-acetylindole (**34**) appear as a series of multiplets between  $\delta$  7.26 and  $\delta$  7.97,<sup>34</sup> the triplets at  $\delta$  6.95 and  $\delta$  7.13 in indole **31** must arise from the protons at C-6 and C-7 of the naphthalene. These data confirm that the anomalies in the NMR spectra of indoles **31** and **33** are the result of restricted rotation about the bond between C-3 of the indole nucleus and/or the naphthalene C-1 bond and the carbonyl carbon atom. The energy barrier to rotation was determined using variable temperature <sup>1</sup>H NMR, and the coalescence temperature was found to be 0°C. The free energy of activation was calculated from the stopped exchange limit at –50°C and the coalescence temperature to give a rotational barrier of 13.1 kcal/mol.<sup>35</sup> An AM1 coordinate drive study shows that during rotation about the naphthalene C-1 bond and the carbonyl carbon atom the oxygen of the methoxy group has close Van der Waals' contacts with C-2 and C-3 of the indole. The maximum overlap occurs at a carbonyl oxygen–carbonyl carbon–indole C-3–indole C-2 torsion angle of –89.8°. The calculated energy difference between the global minimum energy conformer and this conformation is 9.38 kcal/mol. Single point energy calculations for the difference in energy between the global minimum energy conformer and the conformation for which maximum overlap occurs was found to be 12.86 kcal/mol at the HF 3-21G\* level. The receptor affinities of the 3-(2-methoxy-1-naphthoyl)indoles (JWH-265–JWH-268) are included in Table 2.

The 6- and 7-methoxy-1-naphthoylindoles required 6- (**35**, Scheme 4) and 7-methoxy-1-naphthoic acid (**36**), respectively, both of which were prepared a number of



**Scheme 4.** Reagents and conditions: (a) Br<sub>2</sub>, CCl<sub>4</sub>, Et<sub>2</sub>O, HCl, 0–5°C; (b) LiBr, LiCO<sub>3</sub>, DMF, reflux; (c) Tf<sub>2</sub>O, pyridine, 0°C–rt; (d) Pd(OAc)<sub>2</sub>, 1,3-diphenylphosphinopropane, Et<sub>3</sub>N, HCO<sub>2</sub>H, DMF, CO, rt.

years ago using classical chemistry. The 6-methoxy acid (**35**) was originally synthesized by Price et al. in 12% yield by the aluminum chloride catalyzed reaction of furoic acid and anisole.<sup>36</sup> 7-Methoxy-1-naphthoic acid (**36**) was described by Fieser and Holmes who prepared it from ethyl 4-(4-methoxyphenyl)butanoate via 7-methoxy-3,4-dihydro-1-naphthoic acid.<sup>37</sup> The dihydro acid was synthesized in 51% overall yield, however no yield was specified for the dehydrogenation to acid **36**. A subsequent synthesis of acid **36** utilized the reaction of 2-methoxynaphthalene with an oxalyl chloride equivalent to give a methoxyacenaphthenquinone, which was converted to acid **36** in two steps and good yield.<sup>38</sup> In our hands attempted repetition of the reaction of 2-methoxynaphthalene with the oxalyl chloride surrogate failed. Other published syntheses of both acids did not appear attractive and alternative methods of synthesis were explored.

Both 6- (**37**) and 7-methoxy-1-tetralone (**38**, Scheme 4) are commercially available, and appeared to be suitable starting materials for the synthesis of acids **35** and **36**. The initial synthetic route to 6-methoxy-1-naphthoic acid (**35**) entailed conversion of tetralone **37** to the enol triflate, followed by palladium mediated carbonylation to 6-methoxy-3,4-dihydro-1-naphthoic acid.<sup>39</sup> Dehydrogenation to acid **35** did not proceed to completion and the mixture of **35** and the dihydro acid proved exceedingly difficult to separate. The conversion of tetralones **37** and **38** to 6- (**39**) and 7-methoxy-1-naphthol (**40**), respectively, was reported some years ago by Shand and Thompson who accomplished this transformation by dehydrogenation using sulfur at 250°C.<sup>40</sup> As an alternative to thermal dehydrogenation, ketones **37** and **38** were converted to the corresponding  $\alpha$ -bromo ketones, dehydrohalogenation of which provided phenols **39** and **40**.<sup>41</sup> Conversion of these phenols to the corresponding triflates followed by palladium mediated carbonylation gave acids **35** and **36** in good yield. Acid **35** was converted to the 3-(6-methoxy-1-naphthoyl)indoles (JWH-151, JWH-153, JWH-163,

JWH-166) and acid **36** was converted to the 3-(7-methoxy-1-naphthoyl)indoles (JWH-159, JWH-160, JWH-164, JWH-165) by method D. The receptor affinities for these 3-(6- and 7-methoxy-1-naphthoyl)indoles are included in Table 2.

The affinities of the alkylnaphthoyl and alkoxynaphthoylindoles for the CB<sub>1</sub> receptor were determined by measuring their ability to displace the potent cannabinoid [<sup>3</sup>H] CP-55,940 (**2**) from its binding site in a membrane preparation from rat brain as described by Compton et al.<sup>42</sup> Affinities for the CB<sub>2</sub> receptor were determined by measuring the ability of the compounds to displace [<sup>3</sup>H] CP-55,940 from a cloned human receptor preparation using the procedure described by Showalter et al.<sup>17</sup> The results of these determinations are summarized in Tables 1 and 2. Also included in Tables 1 and 2 are the receptor affinities for Δ<sup>9</sup>-THC (**1**) and WIN-55,212-2 (**4**).

In the 4-alkyl-1-naphthoyl series (Table 1), the 4-methyl-1-propyl compounds, JWH-120 (**41**) and JWH-148, have very slight ( $K_i = 1054 \pm 31$  nM) and modest ( $K_i = 123 \pm 8$  nM) affinities, respectively, for the CB<sub>1</sub> receptor. This pair of compounds is unusual in that the analog with an indole 2-methyl group (JWH-148) has significantly greater affinity for the CB<sub>1</sub> receptor than the unsubstituted compound (JWH-120). The CB<sub>2</sub> receptor affinities of these compounds are similar, for JWH-120  $K_i = 6.1 \pm 7$  nM, and for JWH-148  $K_i = 14 \pm 1.0$  nM. The 4-methyl-1-pentyl analogs, JWH-122 and JWH-149 have high affinities for both the CB<sub>1</sub> and CB<sub>2</sub> receptors. In particular, JWH-122, the compound lacking the indole C-2 methyl group, has subnanomolar affinity for the CB<sub>1</sub> receptor ( $K_i = 0.69 \pm 0.5$  nM).<sup>24</sup>

The 4-ethyl- and 4-propyl -1-naphthoylindoles (Table 1) all have uniformly high affinities for both receptors. Following the usual trend for CB<sub>1</sub> receptor affinities the 1-propyl compounds have lower affinities than the 1-pentyl analogs, and the compounds with an indole 2-methyl group have somewhat lower affinities than the unsubstituted analogs. The CB<sub>1</sub> receptor affinities for these compounds range from  $K_i = 0.46 \pm 0.03$  nM for 1-pentyl-3-(4-ethyl-1-naphthoyl)indole, JWH-210, to  $K_i = 70 \pm 0.8$  nM for 2-methyl-1-propyl-3-(4-ethyl-1-naphthoyl)indole, JWH-211. The CB<sub>1</sub> receptor affinities for the 3-(4-propyl-1-naphthoyl)indoles are comparable to those of the 4-ethyl analogs. The CB<sub>2</sub> receptor affinities for these eight 4-propyl and 4-ethyl compounds fall within a narrow range, from  $K_i = 0.62 \pm 0.04$  for 2-methyl-1-pentyl-3-(4-propyl-1-naphthoyl)indole, JWH-181, to  $K_i = 12 \pm 0.8$  for 2-methyl-1-propyl-3-(4-ethyl-1-naphthoyl)indole, JWH-211.

The 4-butyl-1-naphthoylindoles (Table 1) have significantly lower affinities for the CB<sub>1</sub> receptor than the 4-ethyl and 4-propyl-1-naphthoylindoles. In particular, the affinities of 1-propyl-3-(4-butyl-1-naphthoyl)indole, JWH-239 ( $K_i = 342 \pm 20$  nM) and its 2-methylindole analog, JWH-241 ( $K_i = 147 \pm 20$  nM) are significantly lower than the ethyl and propyl analogs. Predictably,

the CB<sub>1</sub> receptor affinities of the 1-pentyl-3-(4-butyl-1-naphthoyl)indoles are much higher than those of the 1-propyl compounds. 1-Pentyl-3-(4-butyl-1-naphthoyl)indole, JWH-240 has  $K_i = 14 \pm 1$  nM and the 2-methylindole analog, JWH-242, has  $K_i = 42 \pm 9$  nM. Again, the values for the CB<sub>2</sub> receptor affinities of the 4-butyl-1-naphthoylindoles are not nearly as diverse as the CB<sub>1</sub> affinities. The 1-propyl analogs, JWH-239 and JWH-241 have  $K_i = 52 \pm 6$  and  $49 \pm 7$  nM, respectively. The CB<sub>2</sub> receptor affinities for the 1-pentyl compounds, JWH-240 and JWH-242 are essentially identical with  $K_i = 7.2 \pm 13$  nM for JWH-240 and  $K_i = 6.5 \pm 0.3$  nM for JWH-242.

We had previously reported the CB<sub>1</sub> and CB<sub>2</sub> receptor affinities of 2-methyl-1-propyl-3-(7-methyl-1-naphthoyl)indole (**8**), JWH-046 with  $K_i = 343 \pm 38$  nM at CB<sub>1</sub> and  $K_i = 16 \pm 5$  nM at CB<sub>2</sub> (Table 1), which is comparable in its affinity for both receptors and in CB<sub>2</sub> selectivity to JWH-015 (**6**).<sup>21</sup> JWH-076, the analog of JWH-046 lacking the 2-methyl group, has slightly greater affinity for the CB<sub>1</sub> receptor than JWH-046 ( $K_i = 214 \pm 11$  nM), but considerably less affinity for the CB<sub>2</sub> receptor ( $K_i = 106 \pm 46$  nM). 2-Methyl-1-pentyl-3-(7-methyl-1-naphthoyl)indole (**9**, JWH-048) was reported previously and has  $K_i = 10.7 \pm 1$  nM for the CB<sub>1</sub> receptor and  $K_i = 0.49 \pm 0.1$  nM for the CB<sub>2</sub> receptor.<sup>21</sup> These values are very similar to those of the analog without the 7-methyl group, JWH-007 (**5**), which has  $K_i = 9.5 \pm 4.5$  nM at the CB<sub>1</sub> receptor and  $K_i = 2.9 \pm 2.6$  nM at the CB<sub>2</sub> receptor.<sup>19–21</sup>

For the 1-propyl-3-(7-ethyl-1-naphthoyl)indoles (Table 1), the 2-methyl compound, JWH-236 has considerably lower affinity than its 7-methyl homologue for both the CB<sub>1</sub> and CB<sub>2</sub> receptors with  $K_i = 1351 \pm 204$  nM at CB<sub>1</sub> and  $K_i = 240 \pm 63$  nM at CB<sub>2</sub>. The analog lacking the 2-methyl group, JWH-235 has receptor affinities very similar to those of the corresponding 7-methyl compound, with  $K_i = 338 \pm 34$  nM at CB<sub>1</sub> and  $K_i = 123 \pm 34$  nM at CB<sub>2</sub>. As expected the 1-pentyl compounds both have considerably greater affinities for both receptors than the 1-propyl analogs. For 1-pentyl-3-(7-ethyl-1-naphthoyl)indole, JWH-234,  $K_i = 8.4 \pm 1.8$  nM at CB<sub>1</sub> and  $K_i = 3.8 \pm 0.6$  nM at CB<sub>2</sub>. The 2-methyl analog has slightly less affinity for both receptors with  $K_i = 28 \pm 3$  nM at CB<sub>1</sub> and  $K_i = 5.6 \pm 0.7$  nM at CB<sub>2</sub>.

In the 3-(4-methoxy-1-naphthoyl)indole series (Table 2) the receptor affinities of all four of the 1-propyl- and 1-pentyl-3-(4-methoxy-1-naphthoyl)indoles have been reported previously.<sup>21,24</sup> The 1-propyl-2-methyl analog (JWH-094) has little affinity for the CB<sub>1</sub> receptor with  $K_i = 476 \pm 67$  nM, and only modest affinity for the CB<sub>2</sub> receptor ( $K_i = 97 \pm 3$  nM). However, JWH-079, 1-propyl-3-(4-methoxy-1-naphthoyl)indole has  $K_i = 63 \pm 3$  nM at CB<sub>1</sub> and good affinity for the CB<sub>2</sub> receptor ( $K_i = 32 \pm 6$  nM). As expected the 1-pentyl analogs have considerably higher affinity for both receptors. 1-Pentyl-3-(4-methoxy-1-naphthoyl)indole (JWH-081) has very high affinity for the CB<sub>1</sub> receptor ( $K_i = 1.2 \pm 0.03$  nM) and high affinity for the CB<sub>2</sub> receptor

( $K_i = 12.4 \pm 2.2$  nM). The 2-methyl analog (JWH-098, **7**) has slightly lower affinity for the CB<sub>1</sub> receptor with  $K_i = 4.5 \pm 0.1$  nM and somewhat higher affinity for the CB<sub>2</sub> receptor ( $K_i = 1.9 \pm 0.3$  nM).

The 3-(4-ethoxy-1-naphthoyl)indoles have from somewhat to considerably lower affinity for both receptors than the 4-methoxy analogs (Table 2). At the CB<sub>1</sub> receptor the 1-propyl compounds have  $K_i = 220 \pm 29$  nM and  $K_i = 767 \pm 105$  nM, respectively, for 1-propyl-3-(4-ethoxy-1-naphthoyl)indole (JWH-259) and 2-methyl-1-propyl-3-(4-ethoxy-1-naphthoyl)indole (JWH-261). JWH-259 has modest affinity ( $K_i = 74 \pm 7$  nM), while the 2-methyl analog (JWH-261) has even less affinity ( $K_i = 221 \pm 14$  nM) at the CB<sub>2</sub> receptor. The 1-pentyl compounds have considerably greater affinity for both receptors than the corresponding 1-propylindoles. 1-Pentyl-3-(4-ethoxy-1-naphthoyl)indole (JWH-258) has  $K_i = 4.6 \pm 0.6$  nM at CB<sub>1</sub> and  $K_i = 10.5 \pm 1.3$  nM at the CB<sub>2</sub> receptor. The 2-methyl compound, 2-methyl-1-pentyl-3-(4-ethoxy-1-naphthoyl)indole (JWH-260) has  $K_i = 29 \pm 0.4$  nM at CB<sub>1</sub> and  $K_i = 25 \pm 1.9$  nM at the CB<sub>2</sub> receptor.

None of the 1-alkyl-3-(2-methoxy-1-naphthoyl)indoles (JWH-265–JWH-268, Table 2) have significant affinity for the CB<sub>1</sub> receptor, with  $K_i = 381 \pm 16$  nM for 1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267) to  $K_i = >10,000$  nM for the 1-propyl-2-methyl analog (JWH-266). The CB<sub>2</sub> receptor affinities of this series of compounds are considerably greater than for the CB<sub>1</sub> receptor. 1-Propyl-3-(2-methoxy-1-naphthoyl)indole (JWH-265) has moderate affinity,  $K_i = 80 \pm 13$  nM, for the CB<sub>2</sub> receptor while the 2-methyl analog (JWH-266) has little affinity for the receptor,  $K_i = 455 \pm 55$  nM. 1-Pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267) has very high affinity,  $K_i = 7.2 \pm 0.14$  nM, for the CB<sub>2</sub> receptor and the 2-methyl compound (JWH-268) has somewhat less affinity with  $K_i = 40 \pm 1$  nM.

The only 6-methoxy-1-naphthoylindole with significant affinity for the CB<sub>1</sub> receptor is 1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-166, Table 2) which has good affinity with  $K_i = 44 \pm 10$  nM. The affinities of the other three members of this series for the CB<sub>1</sub> receptor range from  $K_i = 240 \pm 24$  nM for 2-methyl-1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-153) to  $K_i = >10,000$  for the 1-propyl-2-methyl analog (JWH-151, **42**). The 1-pentyl-3-(6-methoxy-1-naphthoyl)indoles (JWH-153, JWH-166) have similar and high CB<sub>2</sub> affinities with

$K_i = 11 \pm 1$  nM and  $K_i = 1.9 \pm 0.1$  nM, respectively. 1-Propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-163) has  $K_i = 138 \pm 12$  nM at CB<sub>2</sub>, while the 2-methyl compound (JWH-151, **42**) has significant affinity for the CB<sub>2</sub> receptor,  $K_i = 30 \pm 1$  nM. JWH-151 is a highly selective (>333-fold) ligand for the CB<sub>2</sub> receptor with effectively no affinity for the CB<sub>1</sub> receptor.

In the 7-methoxy-1-naphthoyl series (Table 2), neither of the 1-propyl compounds has high affinity for either the CB<sub>1</sub> or CB<sub>2</sub> receptor. 1-Propyl-3-(7-methoxy-1-naphthoyl)indole (JWH-165) has  $K_i = 204 \pm 26$  nM at the CB<sub>1</sub> receptor and  $K_i = 71 \pm 8$  nM at the CB<sub>2</sub> receptor. The 2-methyl analog (JWH-160) has  $K_i = 1568 \pm 201$  nM at CB<sub>1</sub> and  $K_i = 441 \pm 110$  nM at CB<sub>2</sub>. In contrast, 1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH-164) has  $K_i = 6.6 \pm 0.7$  nM at the CB<sub>1</sub> receptor and  $K_i = 6.9 \pm 0.2$  nM at the CB<sub>2</sub> receptor. The compound with the 2-methyl group, 2-methyl-1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH-159), has somewhat less affinity for the CB<sub>1</sub> receptor than JWH-164 with  $K_i = 45 \pm 1$  nM and similar affinity for the CB<sub>2</sub> receptor,  $K_i = 10.4 \pm 1.4$  nM.

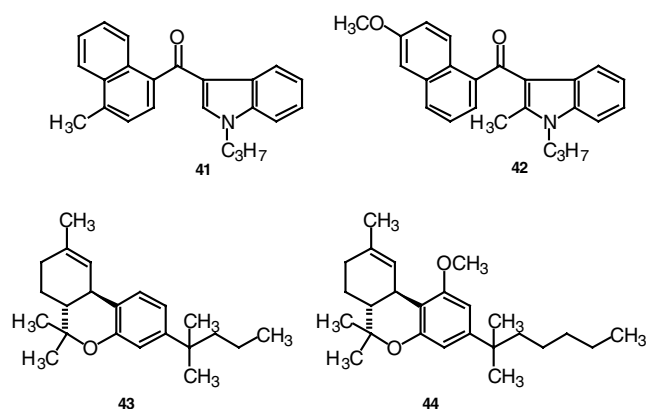
Three of the indole derivatives synthesized in the course of this SAR study are highly selective for the CB<sub>2</sub> receptor. These are 1-propyl-3-(4-methyl-1-naphthoyl)indole, JWH-120 (**41**) which is 173-fold selective, 1-pentyl-3-(2-methoxy-1-naphthoyl)indole, JWH-267 (**32**), 53-fold selective and 1-propyl-2-methyl-3-(6-methoxy-1-naphthoyl)indole, JWH-151 (**42**) which is >333-fold selective. In order to evaluate the efficacy of these compounds, their ability to stimulate GTP $\gamma$ S binding was determined. This is a functional assay, which measures G-protein coupled receptor activation using [<sup>35</sup>S]GTP $\gamma$ S binding.<sup>43</sup> Chinese Hamster Ovary (CHO) cells stably expressing the human CB<sub>2</sub> receptor were employed in this determination (see Experimental). The results of these determinations are summarized in Table 3. The stimulation is normalized to that produced by a maximally effective concentration (3  $\mu$ M) of the standard cannabinoid agonist CP-55,940 (**2**). CP-55,940 stimulated [<sup>35</sup>S]GTP $\gamma$ S binding with an  $E_{\max}$  value of  $85 \pm 6.3\%$  above basal (normalized to 100%) and an EC<sub>50</sub> value of  $0.69 \pm 0.23$  nM. In addition to indoles **32**, **41** and **42** the [<sup>35</sup>S]GTP $\gamma$ S binding for JWH-015, 1-propyl-2-methyl-3-(1-naphthoyl)indole (**6**), the lead compound for the search for CB<sub>2</sub> selective cannabimimetic indoles, was determined, and the data are included in Table 3. Also included in Table 3 are data for two

**Table 3.** EC<sub>50</sub> and  $E_{\max}$  values (mean  $\pm$  SEM) for GTP $\gamma$ S binding for CB<sub>2</sub> selective ligands

| Compound                                                                 | EC <sub>50</sub> (nM) | $E_{\max}$ (% CP-55940) |
|--------------------------------------------------------------------------|-----------------------|-------------------------|
| CP55,940 ( <b>2</b> )                                                    | $0.69 \pm 0.23$       | $100 \pm 7.4^{abc}$     |
| 2-Methyl-1-propyl-3-(1-naphthoyl)indole (JWH-015, <b>6</b> )             | $17.7 \pm 1.0$        | $65.7 \pm 6.4^d$        |
| 1-Deoxy-3-(1',1'-dimethylbutyl)- $\Delta^8$ -THC (JWH-133, <b>43</b> )   | $4.0 \pm 1.0$         | $111.5 \pm 13.6^a$      |
| 1-Methoxy-3-(1',1'-dimethylhexyl)- $\Delta^8$ -THC (JWH-229, <b>44</b> ) | $4.6 \pm 2.0$         | $75.7 \pm 8.3^{cd}$     |
| 1-Propyl-3-(4-methyl-1-naphthoyl)indole (JWH-120, <b>41</b> )            | $5.1 \pm 1.6$         | $78.1 \pm 10.7^{bcd}$   |
| 1-Pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267, <b>32</b> )           | $4.9 \pm 0.8$         | $67.3 \pm 2.9^d$        |
| 1-Propyl-2-methyl-3-(6-methoxy-1-naphthoyl)indole (JWH-151, <b>42</b> )  | $12.0 \pm 2.9$        | $108.5 \pm 13.0^{ab}$   |

Assays were carried out in human CB<sub>2</sub> receptor-expressing CHO cells.  $E_{\max}$  values are reported as percent maximal stimulation by CP-55,940 (**2**).  $E_{\max}$  values not connected by the same letter designation are significantly different ( $p < 0.05$ ).

dibenzopyran-based cannabinoids, which are highly selective for the CB<sub>2</sub> receptor, 1-deoxy-3-(1',1'-dimethylbutyl)- $\Delta^8$ -THC (JWH-133, **43**), which has excellent affinity for the CB<sub>2</sub> receptor ( $K_i = 3.4 \pm 1.0$  nM) and little affinity for the CB<sub>1</sub> receptor ( $K_i = 677 \pm 132$  nM)<sup>44</sup> and 1-methoxy-3-(1',1'-dimethylhexyl)- $\Delta^8$ -THC (JWH-229, **44**) with  $K_i = 18 \pm 2$  nM at CB<sub>2</sub> and  $K_i = 3134 \pm 110$  nM at CB<sub>1</sub>.<sup>45</sup> The results showed that  $E_{\max}$  values of most of these compounds were not significantly different from CP-55,940, although two of the indoles (**6** and **32**) were less efficacious than CP-55,940. Moreover, although **42** and **43** were not significantly different from CP-55,940, these compounds were more efficacious than **6**, **32**, and **44** (and **43** was more efficacious than **41**).



As indicated in Table 3 all six of these compounds are potent in the [<sup>35</sup>S]GTP $\gamma$ S assay with EC<sub>50</sub> values from  $4.0 \pm 1.0$  nM for JWH-133 (**43**) to  $17.7 \pm 1.0$  nM for JWH-015 (**6**). Two of these CB<sub>2</sub> receptor ligands, JWH-133 (**43**) and 1-propyl-2-methyl-3-(6-methoxy-1-naphthoyl)indole, JWH-151 (**42**) are highly efficacious with  $E_{\max}$  values of  $111.5 \pm 13.6\%$  and  $108.5 \pm 13.0\%$ , respectively, relative to CP-55,940. The other three cannabimimetic indoles, 1-propyl-2-methyl-3-(1-naphthoyl)indole, JWH-015 (**6**), 1-propyl-3-(4-methyl-1-naphthoyl)indole, JWH-120 (**41**) and 1-pentyl-3-(2-methoxy-1-naphthoyl)indole, JWH-267 (**32**), plus 1-methoxy-3-(1',1'-dimethylhexyl)- $\Delta^8$ -THC, JWH-229 (**44**) are all partial agonists relative to JWH-133 with  $E_{\max}$  values from  $65.7 \pm 6.4\%$  (JWH-015) to  $78.1 \pm 10.7\%$  (JWH-120).

### 3. Discussion

The 1-pentyl series of cannabimimetic indoles provided several important structural criteria for recognition of the CB<sub>1</sub> receptor. As noted previously, affinity for the CB<sub>1</sub> receptor is attenuated slightly by the presence of a methyl group at the 2-position of the indole. With the exception of the 1-pentyl-3-(2-methoxy-1-naphthoyl)indoles (JWH-267, **32**,  $K_i = 381 \pm 16$  nM and JWH-268, **33**,  $K_i = 1379 \pm 193$  nM) and 1-pentyl-2-methyl-3-(6-methoxy-1-naphthoyl)indole (JWH-153,  $K_i = 250 \pm 24$  nM) all of the compounds in this series

have  $K_i < 45$  nM, indicative of high affinity for the receptor. Replacing the hydrogen at C-4 of the naphthalene in JWH-018 and JWH-007 (**5**) with a methyl (JWH-122, JWH-149), ethyl (JWH-210, JWH-213) or propyl (JWH-182, JWH-181) group leads to a considerable increase in CB<sub>1</sub> receptor affinity, however a butyl group at C-4 (JWH-240, JWH-242) results in a decrease in affinity (Table 1). Neither a 7-methyl-1-naphthoyl (JWH-048, **9**) nor a 7-ethyl-1-naphthoyl (JWH-234, JWH-262) substituent has a significant effect on affinity for the CB<sub>1</sub> receptor.

With methoxynaphthoyl substituents along with retention of the *N*-pentyl group, a 2-methoxy-1-naphthoyl (JWH-267, JWH-268) substituent effectively destroys affinity for the CB<sub>1</sub> receptor while a 4-methoxy group (JWH-081, JWH-098) slightly increases affinity relative to the unsubstituted analogs (JWH-018 and JWH-007, **5**). Replacing the 4-methoxy group with a 4-ethoxy (JWH-258, JWH-260) diminishes CB<sub>1</sub> affinity somewhat. A 6-methoxy-1-naphthoyl substituent decreases affinity for the CB<sub>1</sub> receptor in the compound unsubstituted at C-2 of the indole nucleus (JWH-166,  $K_i = 44 \pm 10$  nM); while the 2-methyl analog (JWH-153) has little affinity. In contrast, the 7-methoxy analogs (JWH-164 and JWH-159) have receptor affinities comparable to those of the 4-ethoxy compounds.

The *N*-propyl indoles have significantly less affinity for the CB<sub>1</sub> receptor than the corresponding *N*-pentyl compounds. Although an indole 2-methyl group usually attenuates CB<sub>1</sub> receptor affinity somewhat, in the case of the compounds with an unsubstituted naphthoyl group (JWH-015, **6**, JWH-072) and the 4-methyl-1-naphthoyl analogs (JWH-120, **41**, JWH-148) the 2-methyl compounds have CB<sub>1</sub> receptor affinities an order of magnitude greater than the unsubstituted compounds (Table 1). A similar situation exists with the 1-propyl-3-(4-butyl-1-naphthoyl)indoles (JWH-239, JWH-241); however the 2-methyl analog (JWH-241) with  $K_i = 147 \pm 20$  nM has only slightly more than two-fold greater affinity for the CB<sub>1</sub> receptor than JWH-239 with  $K_i = 342 \pm 20$  nM. With the exception of the 4-ethyl- (JWH-211, JWH-212), and 4-propyl-1-naphthoylindoles (JWH-180, JWH-189) none of the *N*-propyl-alkyl-1-naphthoyl compounds has a CB<sub>1</sub> receptor affinity less than 100 nM. In the *N*-pentyl series the 4-propyl-1-naphthoylindoles (JWH-182, JWH-181) have exceptionally high affinity for the CB<sub>1</sub> receptor, with  $K_i = 0.65 \pm 0.03$  nM and  $1.3 \pm 0.1$  nM, respectively (Table 1). These high affinities are reflected in the *N*-propyl compounds with  $K_i = 26 \pm 2$  nM for the 2H indole (JWH-180) and  $K_i = 70 \pm 0.8$  nM for the 2-methyl analog (JWH-189).

In the methoxynaphthoyl series (Table 2) the relative magnitudes of the CB<sub>1</sub> receptor affinities for the *N*-propyl indoles parallel those of the *N*-pentyl analogues. However, the compounds in this series have little affinity for the CB<sub>1</sub> receptor with affinities from 204 nM to >10,000 nM with the exception of 1-propyl-3-(4-methoxy-1-naphthoyl)indole, JWH-079, which has  $K_i = 63 \pm 3$  nM.

To gain insight into the receptor interactions responsible for the SAR of these cannabimimetic indoles at the CB<sub>1</sub> receptor, molecular modeling and receptor docking studies were carried out. NMR solution and X-ray crystallography studies showed that 3-aryloindoles can exist in two distinct conformations, which differ primarily in the orientation of the C-3 aryl system.<sup>14</sup> In the *s-trans* conformation, which predominates when the indole C-2 substituent is a hydrogen, the aryl system is near C-2, while the carbonyl oxygen is located near C-4. In the *s-cis* conformation, which predominates in 2-methylindoles, the aryl ring is located near C-4, and the carbonyl oxygen is located near C-2. Recent AM1 conformational analysis of a series of naphthoylindoles identified both *s-cis* and *s-trans* conformations for these compounds with these same trends in preferred conformation dependent on C-2 substitution.<sup>24</sup> A study of rigid C-2H and C-2-methyl naphthylidene-substituted aminoalkylindene analogs of the cannabimimetic indoles that mimic the *s-cis* (*Z*-indene) or the *s-trans* (*E*-indene) indole conformation indicated that the *E*-isomer has the higher CB<sub>1</sub> and CB<sub>2</sub> affinities and the higher pharmacological potency for both the C-2H and C-2-methyl analogs.<sup>46</sup> These results suggest that the *s-trans* conformation is the preferred conformation for the interaction of cannabimimetic indoles with both the CB<sub>1</sub> and CB<sub>2</sub> receptors.

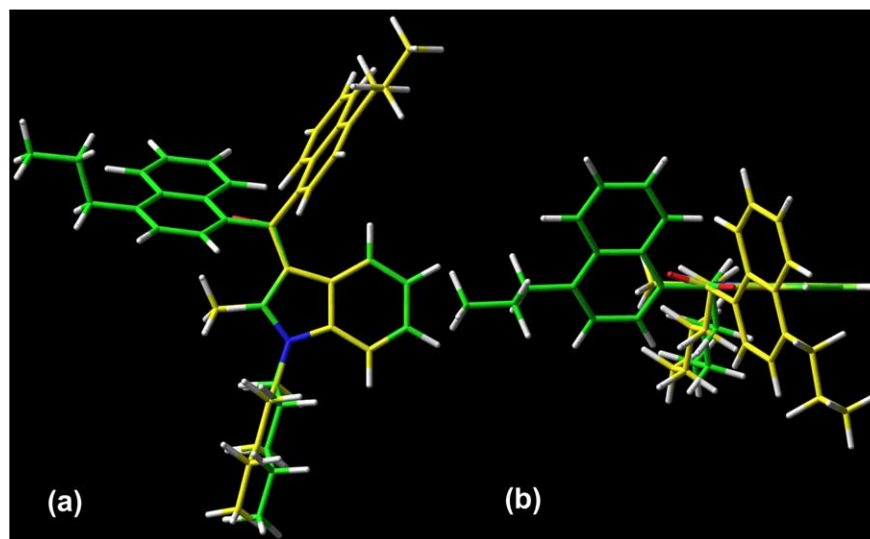
For the current modeling studies, a set of 3-(4-propyl-1-naphthoyl)indoles (JWH-180, JWH-189, JWH-182, JWH-181, Table 1) and a set of 3-(6-methoxy-1-naphthoyl)indoles (JWH-163, JWH-151, 42, JWH-166, JWH-153, Table 2) were chosen. In addition, the *N*-pentyl-3-(2-methoxy-1-naphthoyl)indoles (JWH-267, 32 and JWH-268, 33, Table 2) were examined.

AM1 conformational search results were consistent with the data discussed above which have shown that for C-

2H analogs, the *s-trans* conformation is more stable than the *s-cis* conformation, while for the C-2 methyl analogs, the situation is reversed and the *s-cis* conformation is more stable. Figure 1 illustrates the conformational differences between the global minimum energy conformer of a C-2H indole, 1-pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-182, Table 1, *s-trans* in yellow) and the 2-methylindole analog, (JWH-181, *s-cis* in green).

For 1-propyl-3-(4-propyl-1-naphthoyl)indole (JWH-180, Table 1) and 1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-163, Table 2), the C-2H analogs with *N*-propyl side chains, the global minimum energy *s-trans* conformers were found to be more stable than the lowest energy *s-cis* conformers by 0.55 and 0.56 kcal/mol, respectively. For the C-2H analogs with *N*-pentyl side chains, 1-pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-182), 1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267, 32), and 1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-166), the global minimum energy *s-trans* conformer was found to be more stable than the lowest energy *s-cis* conformer by 0.55, 0.64, and 0.54 kcal/mol, respectively.

For 2-methyl-1-propyl-3-(4-propyl-1-naphthoyl)indole (JWH-189, Table 1) and 2-methyl-1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-151, 42, Table 2) the C-2 methyl analogs, with *N*-propyl side chains, the global minimum energy *s-cis* conformers were found to be more stable than the lowest energy *s-trans* conformers by 1.28 and 1.33 kcal/mol, respectively. For the C-2-methyl analogs with *N*-pentyl side chains, 2-methyl-1-pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-181, Table 1), 2-methyl-1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-268, 33, Table 2), and 2-methyl-1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-153), the global minimum energy *s-cis* conformers were found to be



**Figure 1.** (a) The global minimum energy conformers of JWH-182 (*s-trans*; in yellow) and JWH-181 (*s-cis*; in green) are superimposed at their indole rings. (b) A top view of the global minimum energy conformers of JWH-182 (*s-trans*; in green) and JWH-181 (*s-cis*; in yellow) superimposed at their indole rings is presented here. The molecules are oriented so that the indole ring is perpendicular to the page with C-4 pointing towards the viewer and the C-2 methyl of JWH-181 pointing to the left.

more stable than the lowest energy *s-trans* conformers by 1.27, 0.59, and 1.30 kcal/mol, respectively.

Based upon recent CB<sub>1</sub> mutation studies of the aromatic microdomain formed by transmembrane helices (TMHs) 3-4-5-6 of CB<sub>1</sub> McAllister et al. suggested that the TMH 3-4-5-6 region is the binding site region for WIN-55,212-2 (**4**).<sup>47</sup> This result is consistent with CB<sub>1</sub>/CB<sub>2</sub> chimera studies, which suggested that the TMH 4-E2-TMH 5 region of CB<sub>1</sub> was important for WIN-55,212-2 binding.<sup>48</sup> 1-Pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-182) is the highest affinity analog in the series of compounds reported here ( $K_i = 0.65 \pm 0.03$  nM, Table 1). Because JWH-182 is also a highly aromatic compound structurally related to WIN-55212-2, JWH-182 was docked in the aromatic microdomain region (TMH 3-4-5-6 region) of CB<sub>1</sub>. The binding site for JWH-182 identified in these docking studies was also in the same region as that identified previously for 1-pentyl-3-(4-methoxy-1-naphthoyl)indole (JWH-081) and 2-methyl-1-pentyl-3-(4-methoxy-1-naphthoyl)indole (JWH-098).<sup>24</sup> Docking studies revealed that at the binding site, the *N*-pentyl tail of JWH-182 extends over F3.36 and the indole moiety is parallel and between TMH 5 and TMH 6. The naphthyl ring is below (intracellular to) both W5.43 and W6.48, with the 4-propyl substituent on the naphthyl ring located in an open area within the binding pocket. In this position, the indole ring has aromatic stacking interactions with W5.43 ( $d = 4.6$  Å,  $\alpha = 80^\circ$ ) and W6.48 ( $d = 6.1$  Å,  $\alpha = 60^\circ$ ). The naphthyl ring also has stacking interactions with both residues: W5.43 ( $d = 5.1$  Å,  $\alpha = 30^\circ$ ) and W6.48 ( $d = 5.7$  Å,  $\alpha = 70^\circ$ ). In this docking position, the carbonyl oxygen forms a weak hydrogen-bond with W6.48 (O–Ndbond 2.7 Å, O–H–N = 156°).

Using the docking position employed for JWH-182, the consequences of substitution at other positions on the naphthyl ring were explored. Substitution at the 2-naphthoyl position as in 1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-267,  $K_i = 381 \pm 16$  nM, Table 2) causes a great diminishment in affinity relative to the 4-methoxy-1-naphthoyl analog (JWH-182). Docking studies showed that the 2-methoxy group in JWH-267 has severe steric conflicts with W6.48 that can be relieved only by backing the ligand away from W6.48, causing the ligand to lose most of its aromatic stacking interactions.

Docking studies revealed that various substituents can be placed at C-4 of the naphthoyl moiety without any significant decrease in affinity because there is a fairly wide and deep lipophilic binding pocket in this region formed by L3.43, V3.40, L6.44, and I5.54. 1-Pentyl-3-(4-butyl-1-naphthoyl)indole (JWH-240,  $K_i = 14.1 \pm 1.3$  nM), for example, places greater bulk at C-4 of the naphthyl ring than is present in JWH-182 (4-propyl-1-naphthoyl). Docking studies indicated that the C-4 of the naphthoyl substituent can accommodate the bulkier 4-butyl substituent by a slight adjustment in the placement of the butyl substituent in order to eliminate conflict with I5.54 and L6.44.

Substitution at C-6 of the naphthyl ring results in diminished affinity for 1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-166,  $K_i = 44 \pm 10$  nM, Table 2) relative to the 4-propyl-1-naphthoyl analog (JWH-182,  $K_i = 0.65 \pm 0.03$  nM, Table 1). A methoxy substituent at C-6 in its lowest energy conformation (in the naphthyl ring plane) has some steric conflicts with L5.50 and V3.40, which can be alleviated by rotation of the 6-methoxy group  $-96^\circ$  out of the plane of the naphthyl ring into a higher energy rotameric state. The necessity for the methoxy group to assume a higher energy conformation in order to be accommodated at the binding site, likely contributes to the reduced CB<sub>1</sub> affinity of JWH-166 relative to JWH-182.

Substitution at C-7 of the naphthyl ring results in a slight reduction in affinity for 1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH-164,  $K_i = 6.6 \pm 0.7$  nM, Table 2). Docking studies show that a methoxy substituent at C-7 encounters no steric problems when it is in its minimum energy conformation (in the plane of the naphthyl ring). However, the 7-methoxy group blocks the aromatic stacking interaction between the naphthyl ring and W5.43, which is present in the 4-propyl analog (JWH-182). This loss of an aromatic stacking interaction may account for the 10-fold reduction in affinity of JWH-164 relative to JWH-182.

A study of rigid naphthylidene-substituted aminoalkylindene analogs of cannabimimetic indoles that mimic the *s-cis* (*Z*-indene) or *s-trans* (*E*-indene) conformation of the indoles indicated that the *E*-isomers (which mimic the *s-trans* conformation of the indole) have the higher CB<sub>1</sub> and CB<sub>2</sub> receptor affinities and the higher pharmacological potencies.<sup>46</sup> These results suggest that the *s-trans* conformation is the preferred conformation for the interaction of cannabimimetic indoles at both the CB<sub>1</sub> and CB<sub>2</sub> receptors. For this reason, the lowest energy *s-trans* conformer of 2-methyl-1-pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-181,  $K_i = 1.30 \pm 0.1$  nM, Table 1), rather than its global minimum energy *s-cis* conformer was used in the docking studies. Because of the use of the *s-trans* conformer as the bioactive conformation for the *N*-pentyl C-2 methyl indoles, the affinities of ligands in this series can, in general, be expected to be reduced relative to those of the corresponding C-2H indoles for which the global minimum energy conformers are *s-trans* conformers. Such a general reduction is, in fact, seen in this series (Tables 1 and 2).

Docking studies of the lowest energy *s-trans* conformer of 2-methyl-1-pentyl-3-(4-propyl-1-naphthoyl)indole (JWH-181,  $K_i = 1.30 \pm 0.1$  nM, Table 1) in the TMH 3-4-5-6 region of the CB<sub>1</sub> receptor revealed that JWH-181 sits higher (i.e., closer to extracellular) in the binding site region than does the C-2H analog (JWH-182). At this docking site, the indole ring of JWH-181 has aromatic stacking interactions with W5.43 ( $d = 4.6$  Å,  $\alpha = 90^\circ$ ) and W6.48 ( $d = 6.3$  Å,  $\alpha = 70^\circ$ ). The naphthyl moiety also has a parallel stacking interaction with W5.43 ( $d = 4.7$  Å,  $\alpha = 20^\circ$ ) and a T-stacking interaction with W6.48 ( $d = 6.1$  Å,  $\alpha = 70^\circ$ ). The carbonyl oxygen forms a hydrogen bond with W6.48 (O–N = 2.7 Å

O–H–N = 162°). The *N*-1 pentyl alkyl chain of JWH 181 can still interact with the hydrophobic binding pocket formed by L3.29, V3.32, and I6.54. The 4-position of the naphthoyl group is oriented such that substituents can reach a hydrophobic pocket formed by L3.43, V3.40, L6.44, and I5.54. This pocket can accommodate the bulkier 4-butyl substituent by a slight adjustment in the placement of the butyl substituent in order to eliminate conflict with I5.54 and L6.44.

In 2-methyl-1-pentyl-3-(2-methoxy-1-naphthoyl)indole (JWH-268, **33**,  $K_i = 1379 \pm 193$  nM, Table 2) substitution at C-2 of the naphthalene ring causes a great loss of affinity relative to JWH-181. Docking studies show that the 2-methoxy group in JWH-268 has severe steric conflicts with W6.48 that can be relieved only by backing the ligand away from W6.48, causing the ligand to lose its aromatic stacking interactions.

In the *N*-pentyl, C-2H series substitution of a methoxy group at C-6 of the naphthoyl group causes a reduction in affinity, while substitution at C-7 does not cause as extreme a reduction in CB<sub>1</sub> receptor affinity. For 1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-166, Table 2),  $K_i = 44 \pm 10$  nM; while for 1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH 164)  $K_i = 6.6 \pm 0.7$  nM. In the *N*-pentyl, C-2 methyl series, substitution at the 6- or 7-position has a more profound effect on affinity. For 2-methyl-1-pentyl-3-(6-methoxy-1-naphthoyl)indole (JWH-153)  $K_i = 250 \pm 24$  nM; and for the 7-methoxy analog (JWH-159)  $K_i = 45 \pm 1$  nM). Some of this decrease in affinity is possibly caused by the assumption of an *s-trans* conformation (see above), however, additional changes were found in the binding sites for these two analogs. Both the 6- and 7-methoxy analogs can be positioned in the same binding pocket as the C-2H indoles, however, because the molecule is higher in the binding pocket, the 6-methoxy group in JWH-153 has steric interactions with L5.50, V3.40, and W5.43 that would cause it to have reduced affinity for the CB<sub>1</sub> receptor.

Substitution at the C-7 of the naphthoyl ring system results in another lower affinity analog. 2-Methyl-1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH-159,  $K_i = 45 \pm 1$  nM, Table 2) has considerably less affinity for the CB<sub>1</sub> receptor than 1-pentyl-3-(7-methoxy-1-naphthoyl)indole (JWH-164,  $K_i = 6.6 \pm 0.7$  nM). Docking studies showed that a methoxy group at C-7 must rotate out of plane by 16° in order to avoid a steric clash with V5.46. This change from a minimum energy rotameric state for the methoxy group may contribute to the decrease in CB<sub>1</sub> affinity seen for this analog.

Compared to their *N*-pentyl congeners, each analog in the *N*-propyl series shows reduced CB<sub>1</sub> receptor affinity. In the *N*-pentyl series, the pentyl tail resides in a hydrophobic binding pocket formed by L3.29, V3.32, and I6.54. The utility of this pocket appears to lie in its ability to orient aromatic rings of the ligand for aromatic stacking interactions with the receptor. The *N*-propyl tail is too short to access this hydrophobic pocket and simultaneously allow the ligand to engage in aromatic

stacking interactions. As a result, ligands with the propyl substituent may have more difficulty in assuming the correct aromatic region orientation necessary for productive binding at the CB<sub>1</sub> receptor.

The importance of an alkyl chain of certain length (in the present case, pentyl) is very reminiscent of the classical cannabinoids for which it has been shown that C-3 alkyl chains shorter than pentyl have severely reduced CB<sub>1</sub> affinities, while those with a 1,1-dimethylheptyl side chain have optimal affinity.<sup>2–6</sup> The *N*-propyl analogs with a 4-alkyl naphthyl substituent have the highest affinities in the series. This is probably because the 4-alkyl substituent can access the other hydrophobic pocket comprised of L3.43, V3.40, L6.44, and I5.54 mentioned above for the 1-pentyl-3-(4-alkyl-1-naphthoyl)indoles. The ability of these analogs to interact with and be oriented by this pocket appears to compensate for the lack of an *N*-alkyl chain of appropriate length, and permits the proper orientation of the aromatic rings of the ligand for aromatic stacking interactions in the CB<sub>1</sub> receptor.

In contrast to the SAR at the CB<sub>1</sub> receptor, the presence of an indole 2-methyl group in most of the compounds with an unsubstituted or alkyl naphthoyl substituent has minimal effect upon CB<sub>2</sub> affinity relative to the corresponding 2H-indole, and in several cases CB<sub>2</sub> receptor affinity is increased (Table 1). In two cases the CB<sub>2</sub> receptor affinity of the 2-methyl compound is greater than six-fold that of the unsubstituted analog. For the parent compound, 2-methyl-1-propyl-3-(1-naphthoyl)indole (JWH-015, **6**),  $K_i = 13.8 \pm 4.6$  nM, while the 2H analog (JWH-072) has  $K_i = 170 \pm 54$  nM. A similar situation prevails with 2-methyl-1-propyl-3-(7-methyl-1-naphthoyl)indole (JWH-046, **8**),  $K_i = 16 \pm 5$  nM and 1-propyl-3-(7-methyl-1-naphthoyl)indole (JWH-076) with almost sevenfold less CB<sub>2</sub> receptor affinity ( $K_i = 106 \pm 46$  nM). The situation is reversed, however, for most of the methoxynaphthoyl indoles. With the exception of 1-pentyl-3-(4-methoxy-1-naphthoyl)indole (JWH-081,  $K_i = 12.4 \pm 2.2$  nM), and its 2-methyl analog (JWH-098,  $K_i = 1.9 \pm 0.3$  nM); 1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-163,  $K_i = 138 \pm 12$  nM), and its 2-methyl analog (JWH-151,  $K_i = 30 \pm 1.1$  nM), the 2H-indoles in this series have higher affinity for the CB<sub>2</sub> receptor than the 2-methylindoles (Table 2).

Although, with few exceptions, the *N*-propyl indoles have little affinity for the CB<sub>1</sub> receptor, and all have less affinity than the corresponding *N*-pentyl compound, in general, in the alkyl naphthoyl series the *N*-propyl indoles have only slightly less affinity for the CB<sub>2</sub> receptor than their *N*-pentyl congeners (Table 1). An exception to this generalization is 1-propyl-3-(1-naphthoyl)indole (JWH-072,  $K_i = 170 \pm 54$  nM) and 1-pentyl-3-(1-naphthoyl)indole (JWH-018,  $K_i = 2.9 \pm 2.6$  nM). Also, for all the 7-substituted compounds the *N*-pentyl indoles (JWH-048, JWH-234, JWH-262) have from 32 to over 300-fold greater affinity for the CB<sub>2</sub> receptor than the *N*-propyl compounds (JWH-076, JWH-235, JWH-236).

In the methoxynaphthoyl series the effects of substitution at the 2-position of the indole upon CB<sub>2</sub> receptor

affinity are similar to those at the CB<sub>1</sub> receptor, and the 2-methyl indoles have less receptor affinity than the unsubstituted compounds (Table 2). There are, however, several exceptions. 1-Pentyl-3-(4-methoxy-1-naphthoyl)indole (JWH-081,  $K_i = 12.4 \pm 2.2$  nM) has somewhat less affinity for the CB<sub>2</sub> receptor than the corresponding 2-methyl compound (JWH-098,  $K_i = 1.9 \pm 0.3$  nM). Also, 1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-163,  $K_i = 138 \pm 12$  nM) has significantly less affinity for the CB<sub>2</sub> receptor than the 2-methyl analog (JWH-151, **42**,  $K_i = 30 \pm 1.1$  nM). In the methoxy series, as in the case of the CB<sub>1</sub> affinities, the *N*-propyl indoles all have less affinity for the CB<sub>2</sub> receptor than the *N*-pentyl compounds.

Although the CB<sub>1</sub> receptor affinities of the methoxy naphthoyl indoles range from 1.2 nM to >10,000 nM, the range for the CB<sub>2</sub> affinities is not nearly as large (Table 2). Only four of this series of analogs have  $K_i = >100$  nM. All of these compounds, 2-methyl-1-propyl-3-(2-methoxy-1-naphthoyl)indole (JWH-266,  $K_i = 455 \pm 55$  nM), 2-methyl-1-propyl-3-(7-methoxy-1-naphthoyl)indole (JWH-160,  $K_i = 441 \pm 110$  nM), 2-methyl-1-propyl-3-(4-ethoxy-1-naphthoyl)indole (JWH-261,  $K_i = 221 \pm 14$  nM) and 1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-163,  $K_i = 138 \pm 12$  nM) are *N*-propyl indoles, which also have very weak CB<sub>1</sub> receptor affinities. However, only two *N*-propyl compounds, 1-propyl-3-(4-methoxy-1-naphthoyl)indole (JWH-079,  $K_i = 32 \pm 6$  nM) and 2-methyl-1-propyl-3-(6-methoxy-1-naphthoyl)indole (JWH-151, **42**,  $K_i = 30 \pm 1.1$  nM) have CB<sub>2</sub> receptor affinities of less than 70 nM. All of the *N*-pentyl analogs have from good to excellent affinity for the CB<sub>2</sub> receptor with  $K_i < 41$  nM (Table 2).

#### 4. Conclusions

The CB<sub>1</sub> receptor affinities for 1-pentyl- and 1-propyl-3-(1-naphthoyl)indoles with 4- and 7-alkylnaphthoyl and 2-, 4-, 6-, 7-methoxy and 4-ethoxynaphthoyl substituents indicate that receptor affinity is enhanced considerably by the presence of small alkyl groups (methyl, ethyl, propyl) at C-4. Methyl or ethyl substituents at C-7 of the naphthoyl group have little effect on affinity relative to the unsubstituted compounds. A methoxy substituent at C-4 enhances CB<sub>1</sub> receptor affinity, while a 4-ethoxy substituent has relatively little effect on affinity. 6-Methoxy-1-naphthoylindoles have attenuated CB<sub>1</sub> receptor affinities relative to the unsubstituted compounds, while a 7-methoxy substituent has little effect upon affinity. A 2-methoxy substituent effectively destroys affinity for the CB<sub>1</sub> receptor. These conclusions have been rationalized in terms of molecular modeling and receptor docking studies.

The CB<sub>2</sub> receptor affinities of these naphthoylindoles show considerably less variation than their CB<sub>1</sub> affinities. Only three compounds with alkylnaphthoyl substituents have CB<sub>2</sub> receptor affinities greater than 52 nM; the 1-propyl-3-(7-methyl or 7-ethyl-1-naphthoyl)indoles and 1-propyl-3-(7-ethyl-1-naphthoyl)indole. In the

alkoxynaphthoyl series there is no clear pattern. Most of the alkoxynaphthoyl cannabimimetic indoles have good to moderate affinity for the CB<sub>2</sub> receptor, however a 1-propyl-2-methylindole substitution pattern leads to attenuated affinity in several cases.

A 2-methyl substituent on the indole nucleus results in a decrease in affinity for either receptor relative to the unsubstituted analog. Similarly, the 1-propylindoles in general have lower affinities at both receptors than the 1-pentyl compounds. However, the differences in CB<sub>2</sub> receptor affinities as a function of *N*-substitution are less pronounced than is the case with CB<sub>1</sub> affinities. Although three new cannabimimetic indoles with potentially useful CB<sub>2</sub> selectivity have been identified, there do not appear to be sufficient data to permit the rational design of additional indole-based CB<sub>2</sub> selective ligands.

### 5. Experimental

#### 5.1. General

IR spectra were obtained using Nicolet 5DX or Magna spectrometers; <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker 300AC spectrometer. Mass spectral analyses were performed on a Hewlett–Packard 5890A capillary gas chromatograph equipped with a mass sensitive detector. HRMS data were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Ether and THF were distilled from Na-benzophenone ketyl immediately before use, and other solvents were purified using standard procedures. Column chromatography was carried out on Sorbent Technologies silica gel (32–63 μm) using the indicated solvents as eluents. All new compounds were homogeneous to TLC and <sup>13</sup>C NMR. All target compounds were homogeneous to GLC or TLC in two different solvent systems. TLC was carried out using 200 μm silica gel plates using the indicated solvents. GLC analyses were performed on the Hewlett–Packard 5890A GC/MS using a 60 m carbowax column and helium gas as a carrier. An initial column temperature of 60 °C was employed and the temperature was increased at a rate of 15 °C/min to a maximum temperature of 300 °C with a total run time of 20 min. Elemental analyses were performed by Atlantic Microlab, Norcross, GA.

**5.1.1. 1-Propyl-3-(4-methyl-1-naphthoyl)indole JWH-120 (41, method B).** To a stirred solution of 0.080 g (0.50 mmol) of 1-propylindole in 1.5 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at 0 °C under N<sub>2</sub> was added dropwise 0.75 mL (0.75 mmol) of Me<sub>2</sub>AlCl (1 M in hexanes). The solution was stirred at 0 °C for 30 min and a solution of 0.122 g (0.6 mmol) of freshly prepared 4-methyl-1-naphthoyl chloride in 1.5 mL of CH<sub>2</sub>Cl<sub>2</sub> was added. The acid chloride was prepared from 0.122 g (0.60 mmol) of 4-methyl-1-naphthoic acid to which was added dropwise 1 mL of thionyl chloride at a rate sufficient to maintain a steady evolution of gas. This solution was heated at reflux for 15 min, cooled to ambient temperature and the excess thionyl chloride was removed in vacuo to give the acid chloride, which was used without further purification.

The deep red acylation reaction mixture was stirred at 0°C until the reaction was complete as indicated by TLC (approximately 1 h). The reaction mixture was poured carefully into iced 1 M aqueous HCl and extracted with three portions of CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with three portions of aqueous NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), and the solvent was removed in vacuo to give the crude product. After chromatography (petroleum ether/ethyl acetate, 9:1) there was obtained 0.140 g (86%) of indole **41** as a white solid. Recrystallization from hexanes/ethyl acetate gave the analytical sample: mp 207–208 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.81–1.88 (m, 2H), 2.78 (s, 3H), 4.03 (t, *J* = 7.0 Hz, 2H), 7.37–7.38 (m, 5H), 7.48–7.59 (m, 3H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 8.52–8.54 (m, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.3, 19.7, 23.1, 48.7, 109.9, 117.6, 122.7, 122.9, 123.5, 124.2, 125.5, 125.8, 126.1, 126.3, 126.6, 127.0, 130.9, 132.8, 136.6, 137.0, 137.5, 137.9, 192.2; Anal. Calcd for C<sub>23</sub>H<sub>21</sub>NO: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.25; H, 6.46; N, 4.30.

**5.1.2. 2-Methyl-1-propyl-3-(4-methyl-1-naphthoyl)indole JWH-148 (method A).** To a stirred solution of 14.1 mL (42.3 mmol) of 3.0 M MeMgBr in ether, diluted with 20 mL of THF, at 0°C was added 4.62 g (35.2 mmol) of 2-methylindole in 10 mL of THF. The reaction mixture was allowed to warm to ambient temperature and a solution of 4-methyl-1-naphthoyl chloride (from 6.0 g, 35 mmol, of 4-methyl-1-naphthoic acid) in 5 mL of THF was added dropwise. The mixture was heated at reflux for 1.5 h and the reaction was quenched by the cautious addition of saturated aqueous NH<sub>4</sub>Cl. Stirring was continued until the solid precipitate was broken up and the solid was collected, and suspended in 200 mL of methanol. A solution of 3 g of KOH in 20 mL of water was added and the mixture was heated at reflux for 4 h. The precipitate was filtered off and dried to give 3.7 g (35%) of 2-methyl-3-(4-methyl-1-naphthoyl)indole as a pale brown solid, which was used in the subsequent step without further purification. For *N*-alkylation, 1.75 g (5.85 mmol) of 2-methyl-3-(4-methyl-1-naphthoyl)indole was added to a stirred suspension of 1.48 g of powdered KOH in 5 mL of DMSO and 1.44 g (11.7 mmol) of 1-bromopropane was added. The reaction mixture was stirred at 80°C for 18 h, poured into water, and extracted with three portions of ethyl acetate. The combined extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed to give the crude product. Chromatography (petroleum ether/ethyl acetate, 10:1) gave 1.62 g (81%) of JWH-148 as a white solid: mp 135–137 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.79 (sextet, *J* = 7.4 Hz, 2H), 2.44 (s, 3H), 2.74 (s, 3H), 4.04 (t, *J* = 7.3 Hz, 2H), 6.98 (t, *J* = 7.9 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 7.21–7.52 (m, 6H), 8.06 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.6, 12.7, 20.0, 23.0, 44.9, 109.6, 115.2, 121.4, 121.9, 122.2, 124.4, 125.9, 126.2, 126.4, 126.6, 127.3, 130.6, 133.0, 136.2, 136.8, 139.0, 145.5, 193.7; MS (EI) *m/z* 341 (80), 326 (43), 324 (25), 141 (100); Anal. Calcd for C<sub>24</sub>H<sub>23</sub>NO: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.39; H, 6.83; N, 4.08.

**5.1.3. *N,N*-Diphenyl-4-ethyl-1-naphthalenecarboxamide (19, R = C<sub>2</sub>H<sub>5</sub>).** A mixture of 3.00 g, (19.2 mmol) of 1-ethylnaphthalene, 4.45 g (19.2 mmol) of diphenylcarbamyl chloride, and 2.82 g (21.1 mmol) of anhydrous AlCl<sub>3</sub> in 38.4 mL of 1,2-dichloroethane was heated at reflux for 6 h. After cooling, the reaction mixture was poured onto a mixture of ice and concentrated HCl and extracted with ether. The extracts were dried (MgSO<sub>4</sub>) and the solvent was removed in vacuo. The residue was chromatographed (petroleum ether/ethyl acetate, 9:1) to give a white solid. Recrystallization gave 1.72 g (80%) of amide, which was used in the next step without further purification: mp 126–127 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.29 (t, *J* = 7.5 Hz, 3H), 3.02 (q, *J* = 7.5 Hz, 2H), 7.08–7.31 (m, 12H), 7.49–7.57 (m, 2H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.32 (d, *J* = 7.6 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 14.7, 26.0, 123.4, 124.0, 125.9, 126.1, 126.4, 127.2, 128.9, 131.0, 131.8, 132.6, 142.2, 143.2, 170.6; MS (EI) *m/z* 351 (12), 183 (100).

**5.1.4. 4-Ethyl-1-naphthoic acid (15).** A mixture of 3.70 g (10.5 mmol) of the above diphenylamide, 23.2 g of KOH and 154 mL of diethylene glycol was heated at reflux for 8 h. The reaction mixture was cooled, diluted with 1.13 L of water, and the precipitated solids filtered off. The filtrate was acidified with conc. HCl until precipitation was complete. The solid was collected and dried to give 1.90 g (90%) of acid **15**: mp 125–127 °C (lit. mp 129–130 °C, Ref. 26); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.44 (t, *J* = 7.3 Hz, 3H), 3.20 (q, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.59–7.70 (m, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 7.4 Hz, 1H), 9.21 (d, *J* = 8.6 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 14.7, 26.5, 123.8, 124.1, 125.0, 126.1, 126.6, 127.5, 131.9, 132.1, 147.5, 173.7.

**5.1.5. 1-Propyl-3-(4-ethyl-1-naphthoyl)indole, JWH-212 (method C).** 4-Ethyl-1-naphthoic acid was converted to the acid chloride by the procedure described above in the preparation of 2-methyl-1-propyl-3-(4-methyl-1-naphthoyl)indole (JWH-148). To a solution of 4-ethyl-1-naphthoyl chloride, from 0.20 g (1.00 mmol) of 4-ethyl-1-naphthoic acid in 4.0 mL of toluene was added a solution of 0.19 g (1.20 mmol) of 1-propylindole. The solution was cooled to 0°C and 0.26 mL (1.5 mmol) of 1.0 M EtAlCl<sub>2</sub> in hexanes was added dropwise with stirring. The reaction mixture was warmed to ambient temperature and stirred for 4 days. After the addition of 2.0 mL of water, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, dried (MgSO<sub>4</sub>), and concentrated in vacuo. The residue was chromatographed (petroleum ether/ether, 9:1) to give 0.190 g (56%) of JWH-212 as a yellow gum: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.45 (t, *J* = 7.5 Hz, 3H), 1.78–1.90 (m, 2H), 3.19 (q, *J* = 7.4 Hz, 2H), 4.04 (t, *J* = 7.1 Hz, 2H), 7.35–7.40 (m, 5H), 7.44–7.53 (m, 2H), 7.55–7.61 (m, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.3 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.3, 14.9, 23.1, 26.1, 48.7, 109.9, 117.7, 122.7, 122.9, 123.5, 123.8, 124.6, 125.9, 126.0, 126.2, 126.8, 127.1, 131.1, 132.0, 137.0, 137.4, 137.9,

142.5, 192.6; MS (EI)  $m/z$  341 (100), 324 (65), 312 (91); HRMS Calcd for  $C_{24}H_{23}NO$ : 341.1780, Found 341.1779.

#### 5.1.6. 1-Pentyl-3-(4-ethyl-1-naphthoyl)indole, JWH-210.

JWH-210 was prepared from 4-ethyl-1-naphthoic acid and 1-pentylindole by method C. From 0.20 g (1.00 mmol) of 4-ethyl-1-naphthoic acid and 0.22 g (1.20 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.193 g (52%) of JWH-210 as a viscous oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.88 (t,  $J$  = 6.9 Hz, 3H), 1.24–1.35 (m, 3H), 1.40–1.49 (m, 4H), 1.76–1.85 (m, 2H), 3.21 (q,  $J$  = 7.5 Hz, 2H), 4.05 (t,  $J$  = 7.2 Hz, 2H), 7.35–7.42 (m, 5H), 7.49–7.52 (m, 2), 7.55–7.64 (m, 2H), 8.16 (d,  $J$  = 8.3 Hz, 1H), 8.32 (d,  $J$  = 8.5 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  13.8, 14.8, 22.1, 26.1, 28.8, 29.4, 45.0, 109.9, 117.5, 122.6, 122.8, 123.4, 123.7, 124.0, 125.8, 126.0, 126.1, 126.7, 127.0, 131.1, 131.9, 136.9, 137.4, 137.8, 142.4, 192.2; MS (EI)  $m/z$  369 (100), 352 (64), 312 (88); HRMS Calcd for  $C_{26}H_{27}NO$ : 369.2093, Found 369.2090.

#### 5.1.7. 2-Methyl-1-propyl-3-(4-ethyl-1-naphthoyl)indole, JWH-211.

JWH-211 was prepared from 4-ethyl-1-naphthoic acid and 2-methyl-1-propylindole by method C. From 0.20 g (1.00 mmol) of 4-ethyl-1-naphthoic acid and 0.21 g (1.20 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.192 g (52%) of JWH-211 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.00 (t,  $J$  = 7.4 Hz, 3H), 1.43 (t,  $J$  = 7.5 Hz, 3H), 1.78–1.90 (m, 2H), 2.48 (s, 3H), 3.20 (q,  $J$  = 7.5 Hz, 2H), 4.10 (t,  $J$  = 7.5 Hz, 2H), 7.00 (d,  $J$  = 7.2 Hz, 1H), 7.15–7.25 (m, 2H), 7.30–7.35 (m, 2H), 7.40–7.55 (m, 3H), 8.14 (d,  $J$  = 8.4 Hz, 1H), 8.18 (d,  $J$  = 8.6 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.4, 12.5, 14.9, 22.9, 26.2, 44.8, 109.4, 115.1, 121.3, 121.8, 122.1, 123.8, 124.0, 125.8, 126.0, 126.3, 126.4, 127.1, 130.7, 132.1, 136.1, 138.8, 142.7, 145.4, 192.9; MS (EI)  $m/z$  355 (100), 338 (40), 326 (96), 298 (38); HRMS Calcd for  $C_{25}H_{25}NO$ : 354.1858, Found 354.1852.

#### 5.1.8. 2-Methyl-1-pentyl-3-(4-ethyl-1-naphthoyl)indole, JWH-213.

JWH-213 was prepared from 4-ethyl-1-naphthoic acid and 2-methyl-1-pentylindole by method C. From 0.20 g (1.00 mmol) of 4-ethyl-1-naphthoic acid and 0.24 g (1.20 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.205 g (55%) of JWH-213 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.98 (t,  $J$  = 7.0 Hz, 3H), 1.22–1.34 (t,  $J$  = 7.3 Hz, 3H), 1.42–1.49 (m, 4H), 1.84–1.94 (m, 2H), 2.56 (s, 3H), 3.28 (q,  $J$  = 7.5 Hz, 2H), 4.20 (t,  $J$  = 7.5 Hz, 2H), 7.10 (d,  $J$  = 7.3 Hz, 1H), 7.27–7.34 (m, 2H), 7.38–7.54 (m, 2H), 7.59–7.64 (m, 3H), 8.22 (d,  $J$  = 8.4 Hz, 1H), 8.26 (d,  $J$  = 8.2 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.4, 13.8, 14.9, 22.3, 26.1, 29.0, 29.2, 43.2, 109.3, 115.0, 121.2, 121.7, 122.0, 123.8, 123.9, 125.7, 125.9, 126.2, 126.3, 127.1, 130.7, 132.0, 136.0, 138.8, 142.5, 145.2, 193.6; MS (EI)  $m/z$  383 (100), 368 (59), 354 (71), 298 (43); HRMS Calcd for  $C_{27}H_{29}NO$ : 383.2249, Found 383.2246.

**5.1.9. 4-Propyl-1-naphthoic acid (16).** Acid 16 was prepared in a manner analogous to that employed for 4-ethyl-1-naphthoic acid: mp 134–135°C (lit. mp 141–142°C, Ref. 26);  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.06 (t,  $J$  = 7.3 Hz, 3H), 1.78–1.86 (m, 2H), 3.13 (t,  $J$  = 7.7 Hz, 2H), 7.41 (d,  $J$  = 7.5 Hz, 1H), 7.56–7.67 (m, 2H), 8.14 (d,  $J$  = 8.2 Hz, 1H), 8.34 (d,  $J$  = 7.5 Hz, 1H), 9.16 (d,  $J$  = 8.6 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  24.2, 23.8, 35.7, 123.9, 124.3, 124.9, 126.0, 126.6, 127.5, 131.6, 132.1, 132.3, 146.1, 172.9; MS (EI)  $m/z$  214 (59), 185 (100), 157 (20).

#### 5.1.10. 1-Propyl-3-(4-propyl-1-naphthoyl)indole, JWH-180.

JWH-180 was prepared from 4-propyl-1-naphthoic acid and 1-propylindole by method C. From 0.11 g (0.51 mmol) of 4-propyl-1-naphthoic acid and 0.098 g (0.62 mmol) of 1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.098 g (54%) of JWH-180 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.90 (t,  $J$  = 7.4 Hz, 3H), 1.08 (t,  $J$  = 7.3 Hz, 3H), 1.80–1.88 (m, 4H), 3.12 (t,  $J$  = 7.7 Hz, 2H), 4.05 (t,  $J$  = 7.1 Hz, 2H), 7.34–7.43 (m, 5H), 7.46–7.50 (m, 2H), 7.52–7.60 (m, 2H), 8.12 (d,  $J$  = 8.1 Hz, 1H), 8.24 (d,  $J$  = 8.1 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.2, 14.3, 23.1, 23.8, 35.4, 48.7, 109.9, 117.6, 122.7, 122.9, 123.5, 124.0, 124.6, 125.7, 126.0, 126.1, 126.7, 127.0, 131.2, 132.2, 137.0, 137.5, 137.9, 141.0, 192.0; MS (EI)  $m/z$  355 (100), 338 (57), 326 (52); HRMS Calcd for  $C_{25}H_{25}NO$ : 355.1936, Found 355.1924.

#### 5.1.11. 1-Pentyl-3-(4-propyl-1-naphthoyl)indole, JWH-182.

JWH-182 was prepared from 4-propyl-1-naphthoic acid and 1-pentylindole by method C. From 0.11 g (0.51 mmol) of 4-propyl-1-naphthoic acid and 0.11 g (0.62 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.099 g (50%) of JWH-182 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.86 (t,  $J$  = 6.8 Hz, 3H), 1.09 (t,  $J$  = 7.3 Hz, 3H), 1.24–1.32 (m, 4H), 1.79–1.92 (m, 4H), 3.13 (t,  $J$  = 7.7 Hz, 2H), 4.07 (t,  $J$  = 7.2 Hz, 2H), 7.35–7.44 (m, 5H), 7.46–7.50 (m, 2H), 7.52–7.60 (m, 2H), 8.13 (d,  $J$  = 8.4 Hz, 1H), 8.26 (d,  $J$  = 8.2 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  13.8, 14.3, 22.1, 23.8, 28.9, 29.5, 35.4, 47.1, 109.9, 117.6, 122.7, 122.9, 123.5, 124.0, 124.6, 125.7, 126.0, 126.1, 126.7, 127.0, 131.2, 132.2, 137.0, 137.5, 137.8, 141.0, 192.0; MS (EI)  $m/z$  383 (100), 366 (63), 326 (75); HRMS Calcd for  $C_{27}H_{29}NO$ : 383.2249, Found 383.2243.

#### 5.1.12. 2-Methyl-1-propyl-3-(4-propyl-1-naphthoyl)indole, JWH-189.

JWH-189 was prepared from 4-propyl-1-naphthoic acid and 2-methyl-1-propylindole by method C. From 0.12 g (0.56 mmol) of 4-propyl-1-naphthoic acid and 0.12 g (0.67 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.12 g (60%) of JWH-189 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.97–1.08 (m, 6H), 1.80–1.88 (m, 4H), 2.48 (s, 3H), 3.13 (t,  $J$  = 7.6 Hz, 2H), 4.10 (t,  $J$  = 7.5 Hz, 2H), 7.00 (d,  $J$  = 7.6 Hz, 1H), 7.15–7.25 (m, 2H), 7.30–7.38 (m, 2H), 7.40–7.56 (m, 3H), 8.13 (d,  $J$  = 8.5 Hz, 1H), 8.25 (d,  $J$  = 8.3 Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.4, 12.9, 14.2, 22.9, 23.8, 35.4, 44.8, 109.4, 121.3,

122.0, 122.1, 122.9, 124.1, 125.2, 125.7, 126.0, 126.4, 127.4, 128.0, 130.9, 132.3, 136.0, 139.1, 141.1, 145.7, 192.9; MS (EI)  $m/z$  369 (100), 352 (40), 326 (87); HRMS Calcd for  $C_{26}H_{27}NO$ : 369.2093, Found 369.2088.

**5.1.13. 2-Methyl-1-pentyl-3-(4-propyl-1-naphthoyl)-indole, JWH-181.** JWH-181 was prepared from 4-propyl-1-naphthoic acid and 2-methyl-1-pentylindole by method C. From 0.11 g (0.51 mmol) of 4-propyl-1-naphthoic acid and 0.12 g (0.62 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.11 g (54%) of JWH-181 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.93 (t,  $J = 7.4$  Hz, 3H), 1.05 (t,  $J = 7.3$  Hz, 3H), 1.36–1.40 (m, 4H), 1.80–1.87 (m, 4H), 2.48 (s, 3H), 3.13 (t,  $J = 7.6$  Hz, 2H), 4.12 (t,  $J = 7.6$  Hz, 2H), 7.00 (d,  $J = 7.5$  Hz, 1H), 7.15–7.22 (m, 2H), 7.30–7.35 (m, 2H), 7.40–7.55 (m, 3H), 8.13 (d,  $J = 8.5$  Hz, 1H), 8.17 (d,  $J = 8.4$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.5, 13.9, 14.2, 22.4, 23.8, 29.1, 29.3, 35.4, 43.3, 109.3, 115.1, 121.3, 121.8, 122.1, 124.1, 125.2, 125.6, 126.3, 126.4, 127.1, 130.8, 132.2, 136.0, 138.8, 141.0, 145.3, 193.8; MS (EI)  $m/z$  397 (100), 382 (56), 354 (81); HRMS Calcd for  $C_{28}H_{31}NO$ : 397.2406, Found 397.2394.

**5.1.14. 4-Butyl-1-naphthoic acid (17).** Acid 17 was prepared in a manner analogous to that employed for 4-ethyl-1-naphthoic acid: mp 136–137 °C (lit. mp 148–148.5 °C, Ref. 26);  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.99 (t,  $J = 7.3$  Hz, 3H), 1.42–1.54 (m, 2H), 1.73–1.81 (m, 2H), 3.14 (t,  $J = 7.7$  Hz, 2H), 7.41 (d,  $J = 7.3$  Hz, 1H), 7.56–7.67 (m, 2H), 8.14 (d,  $J = 8.2$  Hz, 1H), 8.33 (d,  $J = 7.5$  Hz, 1H), 9.15 (d,  $J = 8.2$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  14.0, 22.9, 32.8, 33.4, 123.9, 124.3, 124.9, 126.0, 126.6, 127.5, 131.6, 132.1, 132.3, 146.3, 172.9; MS (EI)  $m/z$  228 (53), 185 (100), 157 (36).

**5.1.15. 1-Propyl-3-(4-butyl-1-naphthoyl)indole, JWH-239.** JWH-239 was prepared from 4-butyl-1-naphthoic acid and 1-propylindole by method C. From 0.18 g (0.79 mmol) of 4-butyl-1-naphthoic acid and 0.15 g (0.95 mmol) of 1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.19 g (62%) of JWH-239 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.90 (t,  $J = 7.4$  Hz, 3H), 1.02 (t,  $J = 7.3$  Hz, 3H), 1.46–1.58 (m, 2H), 1.71–1.88 (m, 4H), 3.15 (t,  $J = 7.8$  Hz, 2H), 4.04 (t,  $J = 7.1$  Hz, 2H), 7.35–7.43 (m, 5H), 7.46–7.50 (m, 2H), 7.52–7.60 (m, 2H), 8.14 (d,  $J = 8.3$  Hz, 1H), 8.27 (d,  $J = 8.2$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.3, 14.0, 22.9, 23.1, 32.9, 33.1, 48.7, 109.9, 117.6, 122.7, 122.9, 123.5, 124.0, 124.5, 125.7, 126.0, 126.2, 126.7, 127.0, 131.2, 132.1, 137.0, 137.4, 137.9, 141.3, 192.3; MS (EI)  $m/z$  369 (100), 352 (70), 340 (53); HRMS Calcd for  $C_{26}H_{27}NO$ : 369.2093, Found 369.2094.

**5.1.16. 1-Pentyl-3-(4-butyl-1-naphthoyl)indole, JWH-240.** JWH-240 was prepared from 4-butyl-1-naphthoic acid and 1-pentylindole by method C. From 0.17 g (0.75 mmol) of 4-butyl-1-naphthoic acid and 0.17 g (0.89 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.17 g (58%) of JWH-240 as a gum:  $^1H$  NMR (300 MHz,

$CDCl_3$ )  $\delta$  0.87 (t,  $J = 6.8$  Hz, 3H), 1.03 (t,  $J = 7.3$  Hz, 3H), 1.24–1.35 (m, 4H), 1.47–1.59 (m, 2H), 1.76–1.86 (m, 4H), 3.16 (t,  $J = 7.8$  Hz, 2H), 4.06 (t,  $J = 7.2$  Hz, 2H), 7.34–7.42 (m, 5H), 7.45–7.53 (m, 2H), 7.56–7.60 (m, 2H), 8.15 (d,  $J = 8.4$  Hz, 1H), 8.28 (d,  $J = 8.3$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  13.8, 14.0, 22.1, 22.9, 28.8, 29.4, 32.9, 33.1, 47.0, 109.9, 117.6, 122.7, 122.9, 123.4, 124.0, 124.5, 125.7, 126.0, 126.1, 126.7, 127.0, 131.2, 132.1, 137.0, 137.4, 137.8, 141.3, 192.3; MS (EI)  $m/z$  397 (100), 380 (59), 340 (82); HRMS Calcd for  $C_{28}H_{31}NO$ : 397.2406, Found 397.2400.

**5.1.17. 2-Methyl-1-propyl-3-(4-butyl-1-naphthoyl)indole, JWH-241.** JWH-241 was prepared from 4-butyl-1-naphthoic acid and 2-methyl-1-propylindole by method C. From 0.18 g (0.79 mmol) of 4-butyl-1-naphthoic acid and 0.16 g (0.95 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.18 g (62%) of JWH-241 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.97–1.03 (m, 6H), 1.44–1.56 (m, 2H), 1.77–1.90 (m, 4H), 2.49 (s, 3H), 3.16 (t,  $J = 7.7$  Hz, 2H), 4.13 (t,  $J = 7.9$  Hz, 2H), 7.02 (d,  $J = 7.4$  Hz, 1H), 7.16–7.25 (m, 2H), 7.30–7.36 (m, 2H), 7.42–7.56 (m, 3H), 8.13 (d,  $J = 8.5$  Hz, 1H), 8.25 (d,  $J = 8.3$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.4, 12.5, 14.0, 22.8, 22.9, 32.9, 33.1, 44.8, 109.4, 115.0, 121.3, 121.7, 122.1, 124.0, 125.0, 125.7, 125.9, 126.2, 126.4, 127.1, 130.8, 132.2, 136.1, 138.8, 141.3, 145.4, 193.7; MS (EI)  $m/z$  383 (100), 366 (34), 326 (95); Calcd for  $C_{27}H_{29}NO$ : 383.2249, Found 383.2246.

**5.1.18. 2-Methyl-1-pentyl-3-(4-butyl-1-naphthoyl)indole, JWH-242.** JWH-242 was prepared from 4-butyl-1-naphthoic acid and 2-methyl-1-pentylindole by method C. From 0.17 g (0.75 mmol) of 4-butyl-1-naphthoic acid and 0.18 g (0.89 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ether, 9:1) 0.17 g (56%) of JWH-242 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.92 (t,  $J = 6.9$  Hz, 3H), 1.00 (t,  $J = 7.3$  Hz, 3H), 1.39–1.45 (m, 4H), 1.47–1.55 (m, 2H), 1.74–1.84 (m, 4H), 2.48 (s, 3H), 3.16 (t,  $J = 7.7$  Hz, 2H), 4.12 (t,  $J = 7.6$  Hz, 2H), 7.02 (t,  $J = 7.4$  Hz, 1H), 7.16–7.26 (m, 2H), 7.32–7.36 (m, 2H), 7.40–7.56 (m, 3H), 8.14 (d,  $J = 8.5$  Hz, 1H), 8.18 (d,  $J = 8.5$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.5, 13.9, 14.0, 22.4, 22.8, 29.1, 29.3, 32.9, 33.1, 43.3, 109.3, 121.3, 121.8, 122.1, 124.0, 125.1, 125.7, 125.9, 126.2, 126.4; MS (EI)  $m/z$  411 (89), 396 (60), 354 (100); Calcd for  $C_{29}H_{33}NO$ : 411.2562, Found 411.2563.

**5.1.19. 1-Propyl-3-(7-methyl-1-naphthoyl)indole, JWH-076 (method A).** JWH-076 was prepared from 1-propylindole and 7-methyl-1-naphthoyl chloride by method B. From 0.186 g (0.65 mmol) of 3-(7-methyl-1-naphthoyl)indole and 0.5 mL (5.5 mmol) of 1-bromopropane there was obtained after chromatography (petroleum ether/ethyl acetate, 1:3) 0.207 g (97%) of JWH-076 as a tan gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.90 (t,  $J = 7.3$  Hz, 3H), 1.85 (q,  $J = 7.3$  Hz, 2H), 2.44 (s, 3H), 4.05 (t,  $J = 7.2$  Hz, 2H), 7.35–7.47 (m, 6H), 7.62 (d,  $J = 6.8$  Hz, 1H), 7.81 (d,  $J = 8.3$  Hz, 1H), 7.92 (d,  $J = 8.1$  Hz, 1H), 7.98 (s, 1H), 8.52 (t,  $J = 5.4$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.3, 21.9, 23.1, 48.7,

110.0, 117.6, 122.8, 123.0, 123.5, 124.8, 125.9, 127.0, 127.9, 128.6, 129.7, 130.9, 132.0, 136.7, 137.0, 138.0, 138.4, 192.3; MS (EI) *m/z* 327 (82), 310 (43), 298 (58), 186 (100).

**5.1.20. 7-Ethyl-1-naphthoic Acid (24).** To a mixture of 9.56 g of  $\text{AlCl}_3$  (64 mmol) and 4.05 mL of acetyl chloride (57 mmol) was added, with stirring, 21.3 mL of 1,2-dichloroethane. To this light brown solution was added dropwise a solution of 10.0 g (64 mmol) of 2-ethylnaphthalene in 7.1 mL of 1,2-dichloroethane. The reaction mixture was allowed to stand at ambient temperature for 18 h, diluted with dichloromethane, and shaken with dilute aqueous HCl. After washing with saturated aqueous  $\text{NaHCO}_3$  and water, the organic phase was dried ( $\text{MgSO}_4$ ) and the solvents were removed in vacuo. Chromatography (petroleum ether/ethyl acetate, 95:5) gave 9.88 g (86%) of 1-acetyl-7-ethylnaphthalene (**26**) as a colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.33 (t,  $J = 7.6$  Hz, 3H), 2.72 (s, 3H), 2.83 (q,  $J = 7.5$  Hz, 2H), 7.39–7.50 (m, 2H), 7.79 (d,  $J = 8.4$  Hz, 1H), 8.56 (s, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  15.5, 29.5, 30.0, 123.4, 123.8, 127.5, 128.3, 128.7, 130.3, 132.4, 132.7, 134.6, 144.3, 202.1.

A solution of 8.7 g (44 mmol) of iodine in 15 mL of pyridine was added to 8.70 g (44 mmol) of 1-acetyl-7-ethylnaphthalene, and the solution was stirred at 100 °C for 30 min. After cooling to ambient temperature the precipitated pyridinium salt was suspended in methanol and collected by filtration. After drying in vacuo at 45 °C there was obtained 23.5 g of salt **27** as a brown solid, which was added to 250 mL of water without further purification and 20 g of solid NaOH were added. The reaction mixture was heated at reflux for 2 h, cooled to ambient temperature and acidified with 10% aqueous HCl to give 7.56 g of acid **24** as dark purple crystals. Recrystallization from aqueous methanol gave 5.74 g (65%) of product as a brown solid. For further purification, to a solution of 1.0 g of acid in 15 mL of methanol was added 3 mL of  $\text{H}_2\text{SO}_4$  and the reaction mixture was heated at reflux for 2 h. The reaction mixture was concentrated in vacuo, diluted with ether, washed with water, and dried ( $\text{MgSO}_4$ ). The solvent was removed in vacuo to give a brown oil, which was chromatographed (petroleum ether/ethyl acetate, 95:5) to give 0.42 g (42%) of ester as a colorless oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.29 (t,  $J = 7.6$  Hz, 3H), 2.84 (q,  $J = 7.3$  Hz, 2H), 3.98 (s, 3H), 7.39 (t,  $J = 7.6$  Hz, 1H), 7.38 (d,  $J = 8.0$  Hz, 1H), 7.77 (d,  $J = 8.4$  Hz, 1H), 7.94 (d,  $J = 8.1$  Hz, 1H), 8.07 (d,  $J = 7.7$  Hz, 1H), 8.74 (s, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  15.5, 29.5, 51.9, 123.5, 126.3, 127.2, 128.4, 130.2, 131.6, 132.3, 133.0, 143.9, 168.0.

To a suspension of 1.66 g (8.4 mmol) of ester in 50 mL of water was added 10 g of KOH and the mixture was heated at reflux for 18 h. After acidification with conc. HCl to pH 5 the precipitated solid was filtered out to give, after drying in vacuo, 1.32 g (80%) of 7-ethyl-1-naphthoic acid (**24**) as an off white solid, which was used in subsequent steps without further purification. Recrystallization from petroleum ether gave fine white needles:

mp 117–120 °C (lit. mp 126 °C, Ref. 49):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.37 (t,  $J = 7.5$  Hz, 3H), 2.90 (q,  $J = 7.5$  Hz, 2H), 7.44–7.51 (m, 2H), 7.85 (d,  $J = 8.4$  Hz, 1H), 8.06 (d,  $J = 8.2$  Hz, 1H), 8.38 (dd,  $J = 1.0, 7.2$  Hz, 1H), 8.88 (s, 1H).

**5.1.21. 1-Propyl-3-(7-ethyl-1-naphthoyl)indole, JWH-235.** JWH-235 was prepared from 7-ethyl-1-naphthoic acid by method B. From 0.150 g (0.75 mmol) of 7-ethyl-1-naphthoic acid and 0.08 g (0.50 mmol) of 1-propylindole there was obtained 0.150 g (88%) of JWH-235 as a pale brown oil after chromatography (petroleum ether/ethyl acetate, 95:5):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.83 (t,  $J = 7.3$  Hz, 3H), 1.21 (t,  $J = 7.5$  Hz, 3H), 1.70–1.83 (m, 2H), 2.72 (q,  $J = 7.5$  Hz, 2H), 3.95 (t,  $J = 7.1$  Hz, 2H), 7.20–7.38 (m, 5H), 7.42 (d,  $J = 7.2$  Hz, 1H), 7.58 (dd,  $J = 7.2, 0.8$  Hz, 1H), 7.80 (d,  $J = 8.3$  Hz, 1H), 7.88 (d,  $J = 8.3$  Hz, 1H), 8.01 (s, 1H), 8.53–8.56 (m, 1);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  11.2, 15.6, 22.9, 29.2, 48.6, 110.0, 117.4, 122.7, 122.8, 123.4, 123.5, 123.6, 125.9, 126.9, 127.3, 128.1, 129.6, 130.9, 132.2, 137.0, 138.0, 138.4, 142.8, 192.1; MS (EI) *m/z* 341 (100), 312 (80); HRMS Calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}$ : 341.1760, Found 341.1779.

**5.1.22. 1-Pentyl-3-(7-ethyl-1-naphthoyl)indole, JWH-234.** JWH-234 was prepared from 7-ethyl-1-naphthoic acid and 1-pentylindole by method B. From 0.150 g (0.75 mmol) of 7-ethyl-1-naphthoic acid and 0.094 g (0.5 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 95:5) 0.100 g (54%) of JWH-234 as a pale brown oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 (t,  $J = 7.0$  Hz, 3H), 1.21–1.46 (m, 7H), 1.75–1.84 (m, 2H), 2.73 (q,  $J = 7.6$  Hz, 2H), 4.05 (t,  $J = 7.2$  Hz, 2H), 7.34–7.41 (m, 5H), 7.45 (d,  $J = 7.2$  Hz, 1H), 7.61 (dd,  $J = 7.2, 1.0$  Hz, 1H), 7.83 (d,  $J = 8.3$  Hz, 1H), 7.92 (d,  $J = 8.3$  Hz, 1H), 8.00 (s, 1H), 8.51–8.53 (m, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 15.7, 22.1, 28.7, 29.3, 29.5, 47.1, 109.9, 117.6, 122.8, 122.9, 123.5, 123.6, 123.7, 126.0, 127.0, 127.4, 128.1, 129.7, 131.0, 132.3, 137.0, 137.9, 138.5, 143.0, 192.2; MS (EI) *m/z* 369 (75), 352 (40), 312 (50), 207 (100); HRMS Calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}$ : 369.2091, Found 369.2093.

**5.1.23. 2-Methyl-1-propyl-3-(7-ethyl-1-naphthoyl)indole, JWH-236.** JWH-236 was prepared from 7-ethyl-1-naphthoic acid and 2-methyl-1-propylindole by method B. From 0.150 g (0.75 mmol) of 7-ethyl-1-naphthoic acid and 0.087 g (0.5 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 95:5) 0.163 g (92%) of JWH-236 as a pale brown oil:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.98 (t,  $J = 7.3$  Hz, 3H), 1.21 (t,  $J = 7.6$  Hz, 3H), 1.76–1.88 (m, 2H), 2.47 (s, 3H), 2.72 (q,  $J = 7.6$  Hz, 2H), 4.08 (t,  $J = 7.4$  Hz, 2H), 7.00 (t,  $J = 7.3$  Hz, 1H), 7.17 (t,  $J = 7.3$  Hz, 1H), 7.24 (d,  $J = 7.6$  Hz, 1H), 7.31 (d,  $J = 8.2$  Hz, 1H), 7.36–7.51 (m, 2H), 7.52 (d,  $J = 6.0$  Hz, 1H), 7.83 (d,  $J = 8.2$  Hz, 1H), 7.92 (d,  $J = 8.2$  Hz, 1H), 7.96 (s, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  11.4, 12.5, 15.5, 22.9, 29.2, 44.8, 109.4, 114.9, 121.3, 121.8, 122.1, 123.4, 124.0, 126.0, 127.1, 127.3, 128.1, 129.8, 130.6, 132.3, 136.1, 139.7, 142.9, 145.5, 193.6; MS (EI)

*m/z* 355 (100), 338 (40); HRMS Calcd for  $C_{25}H_{25}NO$ : 355.1936, Found 355.1936.

**5.1.24. 2-Methyl-1-pentyl-3-(7-ethyl-1-naphthoyl)indole, JWH-262.** JWH-262 was prepared from 7-ethyl-1-naphthoic acid and 2-methyl-1-pentylindole by method B. From 0.150 g (0.75 mmol) of 7-ethyl-1-naphthoic acid and 0.100 g (0.5 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 95:5) 0.167 g (87%) of JWH-262 as a pale brown oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.89 (t,  $J$  = 6.9 Hz, 3H), 1.21 (t,  $J$  = 7.6 Hz, 3H), 1.26–1.43 (m, 4H), 1.74–1.79 (m, 2H), 2.47 (s, 3H), 2.71 (q,  $J$  = 7.6 Hz, 2H), 4.09 (t,  $J$  = 7.5 Hz, 2H), 6.99 (t,  $J$  = 7.3 Hz, 1H), 7.16 (t,  $J$  = 7.3 Hz, 1H), 7.24 (d,  $J$  = 8.0 Hz, 1H), 7.30 (d,  $J$  = 8.0 Hz, 1H), 7.36–7.48 (m, 2H), 7.52 (dd,  $J$  = 7.1, 1.2 Hz, 1H), 7.83 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 7.97 (s, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.5, 13.9, 15.5, 22.3, 29.0, 29.3, 43.3, 53.3, 109.3, 114.9, 121.1, 121.7, 122.1, 123.4, 124.0, 126.0, 127.1, 127.2, 128.1, 129.7, 130.5, 132.5, 135.9, 139.6, 142.9, 145.4, 193.6; MS (EI) *m/z* 383 (100), 368 (50), 297 (50); HRMS Calcd for  $C_{27}H_{29}NO$ : 382.2175, Found 382.2175.

**5.1.25. 1-Propyl-3-(4-ethoxy-1-naphthoyl)indole, JWH-259.** JWH-259 was prepared from 4-ethoxy-1-naphthoic acid and 1-propylindole by method B. From 0.13 g (0.6 mmol) of 4-ethoxy-1-naphthoic acid and 0.080 g (0.5 mmol) of 1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 9:1) 0.15 g (86%) of JWH-259 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.85 (t,  $J$  = 7.3 Hz, 3H), 1.55 (t,  $J$  = 6.9 Hz, 3H), 1.75–1.82 (m, 2H), 3.97 (t,  $J$  = 7.1 Hz, 2H), 4.20 (q,  $J$  = 6.9 Hz, 2H), 6.74 (d,  $J$  = 7.9 Hz, 1H), 7.29–7.37 (m, 4H), 7.45–7.47 (m, 2H), 7.60 (d,  $J$  = 7.9 Hz, 1H), 8.29–8.32 (m, 1H), 8.34–8.38 (m, 1H), 8.46–8.48 (m, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.2, 14.7, 23.0, 48.5, 63.8, 102.7, 109.9, 117.6, 122.1, 122.5, 122.7, 123.3, 125.4, 125.5, 125.6, 125.7, 127.2, 127.9, 131.1, 132.1, 136.9, 137.4, 156.3, 191.7; HRMS Calcd for  $C_{24}H_{23}NO_2$ : 357.1725, Found 357.1728.

**5.1.26. 1-Pentyl-3-(4-ethoxy-1-naphthoyl)indole, JWH-258.** JWH-258 was prepared from 4-ethoxy-1-naphthoic acid and 1-pentylindole by method B. From 0.13 g (0.6 mmol) of 4-ethoxy-1-naphthoic acid and 0.094 g (0.5 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 9:1) 0.17 g (90%) of JWH-258 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.83 (t,  $J$  = 6.6 Hz, 3H), 1.26–1.29 (m, 4H), 1.56 (t,  $J$  = 6.9 Hz, 3H), 1.75–1.82 (m, 2H), 4.03 (t,  $J$  = 7.1 Hz, 2H), 4.22 (q,  $J$  = 6.9 Hz, 2H), 6.77 (d,  $J$  = 7.9 Hz, 1H), 7.22–7.38 (m, 4H), 7.47–7.50 (m, 2H), 7.62 (d,  $J$  = 7.9 Hz, 1H), 8.29–8.33 (m, 1H), 8.35–8.39 (m, 1H), 8.46–8.48 (m, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  13.8, 14.7, 22.1, 28.8, 29.4, 46.9, 63.9, 102.8, 109.9, 117.6, 122.1, 122.5, 122.8, 123.3, 125.4, 125.5, 125.7, 125.8, 127.2, 127.9, 131.1, 132.1, 136.9, 137.3, 156.3, 191.7; HRMS Calcd for  $C_{26}H_{27}NO_2$ : 385.2038, Found 385.2042.

**5.1.27. 2-Methyl-1-propyl-3-(4-ethoxy-1-naphthoyl)indole, JWH-261.** JWH-261 was prepared from 4-ethoxy-1-naphthoic acid and 2-methyl-1-propylindole by method B. From 0.13 g (0.6 mmol) of 4-ethoxy-1-naphthoic acid and 0.087 g (0.5 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 9:1) 0.17 g (90%) of JWH-261 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  1.04 (t,  $J$  = 7.2 Hz, 3H), 1.64 (t,  $J$  = 6.8 Hz, 3H), 1.84–1.91 (m, 2H), 2.54 (s, 3H), 4.11 (t,  $J$  = 7.2 Hz, 2H), 4.29 (q,  $J$  = 6.8 Hz, 2H), 6.82 (d,  $J$  = 7.9 Hz, 1H), 7.10 (t,  $J$  = 7.5 Hz, 1H), 7.24 (t,  $J$  = 7.2 Hz, 1H), 7.30–7.44 (m, 2H), 7.55–7.58 (m, 2H), 7.65 (d,  $J$  = 7.9 Hz, 1H), 8.38–8.41 (m, 1H), 8.47–8.50 (m, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.3, 12.3, 14.6, 22.8, 44.6, 63.6, 103.2, 109.3, 115.1, 121.1, 121.4, 121.8, 122.1, 125.3, 125.4, 125.7, 127.1, 127.3, 128.4, 131.8, 132.0, 135.9, 144.6, 156.4, 193.0; HRMS Calcd for  $C_{25}H_{25}NO_2$ : 368.3411, Found 368.3403.

**5.1.28. 2-Methyl-1-pentyl-3-(4-ethoxy-1-naphthoyl)indole, JWH-260.** JWH-260 was prepared from 4-ethoxy-1-naphthoic acid and 2-methyl-1-pentylindole by method B. From 0.13 g (0.6 mmol) of 4-ethoxy-1-naphthoic acid and 0.10 g (0.5 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 9:1) 0.18 g (90%) of JWH-260 as a gum:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.89 (t,  $J$  = 6.9 Hz, 3H), 1.34–1.36 (m, 4H), 1.56 (t,  $J$  = 6.9 Hz, 3H), 1.74–1.81 (m, 2H), 2.47 (s, 3H), 4.07 (t,  $J$  = 7.4 Hz, 2H), 4.22 (q,  $J$  = 6.9 Hz, 2H), 6.75 (d,  $J$  = 7.9 Hz, 1H), 6.99 (t,  $J$  = 7.5 Hz, 1H), 7.15 (t,  $J$  = 8.1 Hz, 1H), 7.22–7.30 (m, 2H), 7.45–7.50 (m, 2H), 7.55 (d,  $J$  = 7.9 Hz, 1H), 8.26–8.29 (m, 1H), 8.36–8.39 (m, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.4, 13.9, 14.7, 22.3, 29.0, 29.3, 43.2, 63.8, 103.2, 109.3, 112.2, 115.2, 121.4, 121.9, 122.1, 125.3, 125.5, 125.7, 127.2, 127.3, 128.5, 131.8, 132.1, 135.9, 144.6, 156.5, 193.1; HRMS Calcd for  $C_{27}H_{29}NO_2$ : 399.2193, Found 399.2198.

**5.1.29. 1-Propyl-3-(2-methoxy-1-naphthoyl)indole, JWH-265 (30).** Indole **30** was prepared from 2-methoxy-1-naphthoic acid and 1-propylindole by method B. From 0.150 g (0.75 mmol) of 2-methoxy-1-naphthoic acid and 0.075 g (0.47 mmol) of 1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 7:3) 0.113 g (70%) of 1-propyl-3-(2-methoxy-1-naphthoyl)indole (**30**) as white crystals: mp 117–119 °C;  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.77 (t,  $J$  = 7.4 Hz, 3H), 1.70 (sept,  $J$  = 7.2 Hz, 2H), 3.79 (s, 3H), 3.86 (t,  $J$  = 6.8 Hz, 2H), 7.21–7.31 (m, 7H), 7.68–7.71 (m, 1H), 7.75–7.78 (m, 1H), 7.87 (d,  $J$  = 9.0 Hz, 1H), 8.44 (s, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.0, 22.8, 48.4, 56.5, 109.9, 113.4, 117.9, 122.5, 122.6, 123.2, 123.7, 124.5, 125.1, 126.3, 126.8, 127.7, 128.6, 130.2, 131.8, 136.9, 137.9, 153.3, 190.7; MS (EI) *m/z* 343 (100), 326 (50), 172 (43); HRMS Calcd for  $C_{23}H_{21}NO_2$ : 343.1572, Found 343.1577.

**5.1.30. 1-Pentyl-3-(2-methoxy-1-naphthoyl)indole, JWH-267 (32).** Indole **32** was prepared from 2-methoxy-1-naphthoic acid and 1-pentylindole by method B. From

0.150 (0.75 mmol) of 2-methoxy-1-naphthoic acid and 0.090 g (0.48 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 7:3) 0.107 g (60%) of **32** as a viscous yellow gum:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.81 (t,  $J = 6.9$  Hz, 3H), 1.18–1.26 (m, 4H), 1.75 (quintet,  $J = 7.1$  Hz, 2H), 3.86 (s, 3H), 3.99 (t,  $J = 7.2$  Hz, 2H), 7.24–7.37 (m, 7H), 7.68–7.72 (m, 1H), 7.80–7.83 (m, 1H), 7.92 (d,  $J = 9.1$  Hz, 1H), 8.41 (s, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 22.0, 28.7, 29.2, 47.0, 56.5, 109.9, 113.4, 118.0, 122.6, 122.7, 123.2, 123.8, 124.6, 125.2, 126.4, 126.8, 127.7, 128.6, 130.2, 131.8, 136.9, 137.9, 153.4, 190.8; MS (EI)  $m/z$  37 (100), 354 (61), 200 (55); HRMS Calcd for  $\text{C}_{25}\text{H}_{25}\text{NO}_2$ : 371.1885, Found 371.1876.

**5.1.31. 2-Methyl-1-propyl-3-(2-methoxy-1-naphthoyl)-indole, JWH-266 (31).** Indole **31** was prepared from 2-methoxy-1-naphthoic acid and 2-methyl-1-propylindole by method B. From 0.150 g (0.75 mmol) of 2-methoxy-1-naphthoic acid and 0.086 g (0.50 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 7:3) 0.100 g (58%) of **31** as a yellow solid: mp 124–125°C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.86 (t,  $J = 7.3$  Hz, 3H), 1.57–1.73 (m, 2H), 3.73 (s, 3H), 3.92 (t,  $J = 6.7$  Hz, 2H), 7.08 (s, 3H), 7.17–7.30 (m, 7H), 7.58–7.60 (m, 1H), 7.74–7.76 (m, 1H), 7.87 (d,  $J = 9.1$  Hz, 1H);  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 25°C)  $\delta$  0.88 (br s, 3H), 1.61–1.78 (m, 2H), 3.78 (s, 3H), 4.08–4.23 (m, 2H), 7.13 (br s, 1H), 7.24–7.64 (m, 6H), 7.93–7.98 (m, 1H), 8.10 (d,  $J = 9.1$  Hz, 1H);  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 125°C)  $\delta$  0.88 (t, 6.8 Hz, 3H), 1.71–1.80 (m, 2H), 2.36 (s, 3H), 3.80 (s, 3H), 4.17 (t,  $J = 7.4$  Hz, 2H), 6.95 (t,  $J = 7.8$  Hz, 1H); 7.14 (td,  $J = 0.5$ , 8.2 Hz, 1H), 7.32–7.39 (m, 2H), 7.47–7.58 (m, 4H), 7.91–7.96 (m, 1H), 8.06 (d,  $J = 9.2$  Hz, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  11.0, 22.8, 44.4, 56.4, 109.3, 115.2, 121.4, 121.9, 122.2, 123.7, 123.9, 125.2, 126.3, 126.8, 127.7, 128.7, 130.0, 131.0, 135.9, 145.7, 152.8, 191.4; MS (EI)  $m/z$  357 (44), 326 (100); HRMS Calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}_2$ : 357.1729, Found 357.1734.

**5.1.32. 2-Methyl-1-pentyl-3-(2-methoxy-1-naphthoyl)-indole, JWH-267 (33).** Indole **33** was prepared from 2-methoxy-1-naphthoic acid and 2-methyl-1-pentylindole by method B. From 0.150 g (0.75 mmol) of 2-methoxy-1-naphthoic acid and 0.094 g (0.47 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 7:3) 0.109 g (60%) of **33** as a yellow solid: mp 39–40°C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.81 (t,  $J = 7.0$  Hz, 3H), 1.35–1.36 (m, 4H), 1.59–1.63 (m, 2H), 3.83 (s, 3H), 4.08 (t,  $J = 7.0$  Hz, 2H), 7.15 (s, 3H), 7.25–7.38 (m, 7H), 7.64–7.67 (m, 1H), 7.80–7.84 (m, 1H), 7.94 (d,  $J = 9.0$  Hz, 1H); 2-Methyl-1-pentyl-3-(2-methoxy-1-naphthoyl)indole at 25;  $^1\text{H}$  NMR (500 MHz, toluene- $d_8$ , 25°C)  $\delta$  0.72 (t,  $J = 7.4$  Hz, 3H), 0.87–0.96 (m, 2H), 0.96–1.07 (m, 2H), 1.18–1.27 (m, 2H), 2.15–2.74 (br, 3H), 3.32 (s, 3H), 3.41 (t,  $J = 6.85$  Hz, 2H), 6.88–7.25 (m, 7H), 7.60–7.64 (m, 1H), 7.65 (d,  $J = 9.2$  Hz, 1H), 7.97 (d,  $J = 7.8$  Hz, 1H);  $^1\text{H}$  NMR (500 MHz, toluene- $d_8$ , 100°C)  $\delta$  0.72 (t,  $J = 7.4$  Hz, 3H), 0.97–1.11 (m, 4H), 1.30–1.39 (m, 2H),

2.34 (s, 3H), 3.41 (s, 3H), 3.54 (t,  $J = 8.7$  Hz, 2H), 6.89 (br s, 1H), 6.95–7.12 (m, 6H), 7.60 (d,  $J = 7.3$  Hz, 1H), 7.64 (d,  $J = 10.2$  Hz, 1H), 7.90 (d,  $J = 8.2$  Hz, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 22.3, 29.0, 29.2, 43.2, 56.7, 109.3, 113.6, 116.0, 122.1, 122.2, 122.4, 123.9, 124.2, 125.2, 126.3, 127.0, 127.8, 128.9, 130.2, 131.2, 138.6, 152.9, 191.3; MS (EI)  $m/z$  385 (34), 354 (100), 185 (46); HRMS Calcd for  $\text{C}_{26}\text{H}_{27}\text{NO}_2$ : 385.2042, Found 385.2040.

**5.1.33. 6-Methoxy-1-naphthoic acid (35).** To a solution of 2.3 g (13.2 mmol) of 6-methoxy-1-naphthol<sup>40,41</sup> in 50 mL of pyridine was added dropwise at 0°C 2.6 mL (15.5 mmol) of trifluoromethanesulfonic anhydride. The solution was warmed to ambient temperature, stirred for 18 h, quenched with water and extracted with ether. The combined ethereal extracts were washed with 10% aqueous HCl until the aqueous solution was acidic. The solution was dried ( $\text{MgSO}_4$ ) and the solvent was removed in vacuo. The residue was chromatographed (petroleum ether/ethyl acetate, 12:1) to give 3.4 g (84%) of triflate as a yellow oil, which was used in the subsequent step without further purification:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.92 (s, 3H), 7.16 (d,  $J = 2.4$  Hz, 1H), 7.27 (dd,  $J = 8.7$ , 2.4 Hz, 2H), 7.41 (t,  $J = 8.1$  Hz, 1H), 7.95 (d,  $J = 9.0$  Hz, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  55.4, 106.0, 115.3, 116.6, 120.7, 120.9, 121.6, 122.4, 125.8, 127.2, 136.5, 145.8, 158.7; MS (EI)  $m/z$  306 (25), 173 (55), 145 (100).

To a solution of 0.96 g (3.18 mmol) of 6-methoxy-1-naphthyl trifluoromethanesulfonate in 30 mL of DMF was added 0.034 g (0.15 mmol) of  $\text{Pd}(\text{OAc})_2$ , 0.040 g (0.010 mmol) of 1,3-bis(diphenylphosphino)propane and 1.20 g of triethylamine. The mixture was flushed with carbon monoxide for 25 min, 3.1 mL of 96% formic acid was added dropwise and the reaction was stirred at ambient temperature for 6 h under an atmosphere of CO, diluted with water, and extracted with ethyl acetate. The organic extracts were washed with five portions of brine, followed by two portions of aqueous  $\text{NaHCO}_3$ . The bicarbonate extracts were combined, cautiously neutralized with 10% aqueous HCl, and extracted with ether. The ethereal extracts were washed with water, dried ( $\text{MgSO}_4$ ), and the solvent was removed in vacuo to give 0.42 g (65%) of acid **35** as a yellow powder. Recrystallization from ethyl acetate/petroleum ether gave pale yellow needles: mp 185–186°C (lit. mp 180–180.5°C, Ref. 36);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.89 (s, 3H), 7.29 (dd,  $J = 6.9$ , 2.4 Hz, 1H), 7.41 (d,  $J = 2.4$  Hz, 1H), 7.53 (t,  $J = 7.8$  Hz, 1H), 7.98 (d,  $J = 6.1$  Hz, 1H), 8.05 (d,  $J = 8.1$  Hz, 1H), 8.79 (d,  $J = 9.1$  Hz, 1H);  $^{13}\text{C}$  NMR (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  55.2, 106.7, 120.0, 125.4, 126.1, 127.1, 127.5, 127.6, 131.8, 135.2, 157.1, 168.8; MS (EI)  $m/z$  202 (100), 159 (35), 109 (50).

**5.1.34. 1-Propyl-3-(6-methoxy-1-naphthoyl)indole, JWH-163 (method D).** To a solution of 0.18 g (0.90 mmol) of 6-methoxy-1-naphthoic acid (**35**) in 10 mL of dichloromethane was added dropwise 0.44 mL (5.0 mmol) of oxalyl chloride. The solution was stirred at room temperature for 1 h, then heated at reflux for 1 h. After

cooling, the solvent and residual oxalyl chloride were removed in vacuo. The residue was dissolved in 5 mL of toluene and added to a solution of 0.20 g (1.3 mmol) of 1-propylindole in 4 mL of toluene at 0°C. To this solution was added dropwise 0.82 mL (1.5 mmol) of 1.8 M EtAlCl<sub>2</sub>. The mixture was allowed to warm to ambient temperature and stirred for 18 h. After quenching with water, the reaction mixture was extracted with ether. The ethereal extracts were washed with water, dried (MgSO<sub>4</sub>) and the solvent was removed in vacuo. The residue was chromatographed (petroleum ether/ethyl acetate, 8:1) to give 0.19 g of JWH-163 as a colorless solid: mp 139–140°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.87 (t, *J* = 7.3 Hz, 3H), 1.81 (sextet, *J* = 7.3 Hz, 2H), 3.91 (s, 3H), 4.01 (t, *J* = 7.2 Hz, 2H), 7.12 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.18 (d, *J* = 2.54 Hz, 1H), 7.30–7.39 (m, 4H), 7.44–7.52 (m, 2H), 7.82 (dd, *J* = 7.5, 1.6 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 8.47–8.50 (m, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.3, 23.0, 48.7, 55.2, 106.0, 110.0, 117.4, 119.3, 122.7, 122.8, 123.5, 123.6, 125.1, 126.1, 126.9, 127.5, 128.7, 135.1, 137.0, 138.0, 139.0, 157.7, 192.1; Anal. Calcd for C<sub>23</sub>H<sub>21</sub>NO<sub>2</sub>: C, 80.44; H, 6.16; N, 4.08; Found: C, 80.30; H, 6.17; N, 3.99.

**5.1.35. 1-Pentyl-3-(6-methoxy-1-naphthoyl)indole, JWH-166.** JWH-166 was prepared from 6-methoxy-1-naphthoic acid and 1-pentylindole by method D. From 0.19 g (0.9 mmol) of acid and 0.24 g (1.3 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.29 g (81%) of JWH-166 as an oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.85 (t, *J* = 6.9 Hz, 3H), 1.23–1.33 (m, 4H), 1.75–1.85 (m, 2H), 3.98 (s, 3H), 4.05 (t, *J* = 7.3 Hz, 2H), 7.12 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.33–7.40 (m, 4H), 7.47–7.52 (m, 2H), 7.83 (dd, *J* = 7.4, 1.9 Hz, 1H), 8.10 (d, *J* = 9.1 Hz, 1H), 8.45–8.48 (m, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 13.8, 22.1, 28.9, 29.4, 47.1, 55.3, 106.1, 110.0, 117.5, 119.4, 122.8, 122.9, 123.5, 123.7, 125.1, 126.2, 127.0, 127.6, 128.7, 135.1, 137.0, 137.8, 139.0, 157.7, 192.1; MS (EI) *m/z* 371 (90), 354 (75), 314 (65), 214 (100); HRMS Calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>2</sub>: 371.1885, Found 371.1885.

**5.1.36. 2-Methyl-1-propyl-3-(6-methoxy-1-naphthoyl)indole, JWH-151 (42).** Indole 42 was prepared from 6-methoxy-1-naphthoic acid and 2-methyl-1-propylindole by method D. From 0.19 g (0.9 mmol) of acid and 0.22 g (1.3 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.19 g (56%) of 42 as an oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.99 (t, *J* = 7.5 Hz, 3H), 1.79–1.86 (m, 2H), 2.47 (s, 3H), 3.92 (s, 3H), 4.09 (t, *J* = 7.5 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.09 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.14–7.20 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.40–7.49 (m, 2), 7.85 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.4, 12.5, 22.9, 44.8, 55.2, 106.1, 109.4, 114.9, 119.5, 121.2, 121.8, 122.1, 123.4, 125.7, 127.1, 127.2, 128.7, 135.2, 136.1, 140.5, 145.5, 157.7, 193.5; MS (EI) *m/z* 357 (100), 340 (40), 207 (98); HRMS Calcd for C<sub>24</sub>H<sub>23</sub>NO<sub>2</sub>: 357.1729, Found 357.1721.

**5.1.37. 2-Methyl-1-pentyl-3-(6-methoxy-1-naphthoyl)indole, JWH-153.** JWH-153 was prepared from 6-methoxy-1-naphthoic acid and 2-methyl-1-pentylindole by method D. From 0.20 g (1.0 mmol) of acid and 0.24 g (1.2 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 12:1) 0.23 g (60%) of JWH-153: mp 114.5–116°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.35–1.38 (m, 4H), 1.74–1.79 (m, 2H), 2.46 (s, 3H), 3.92 (s, 3H), 4.10 (t, *J* = 7.6 Hz, 2H), 6.98 (t, *J* = 6.6 Hz, 1H), 7.08 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.13–7.20 (m, 3), 7.29 (d, *J* = 8.4 Hz, 1H), 7.39–7.48 (m, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 8.98 (d, *J* = 9.0 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 12.4, 13.8, 22.3, 29.0, 29.3, 43.3, 55.2, 106.1, 109.4, 114.9, 119.5, 121.2, 121.8, 122.1, 123.4, 125.6, 125.7, 127.1, 127.2, 128.7, 135.1, 136.0, 140.4, 145.4, 157.7, 193.4; Anal. Calcd for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>: C, 81.01; H, 7.06; N, 3.63; Found: C, 80.80; H, 7.18; N, 3.62.

**5.1.38. 7-Methoxy-1-naphthoic acid (36).** The trifluoromethanesulfonate ester of 7-methoxy-1-naphthol was prepared by the procedure employed for the preparation of the triflate of 6-methoxy-1-naphthol. From 2.30 g (15.5 mmol) of 7-methoxy-1-naphthol (40)<sup>40,41</sup> there was obtained after chromatography (petroleum ether/ethyl acetate, 12:1) 3.40 g (84%) of triflate as a colorless oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.91 (s, 3H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.27 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 55.4, 106.0, 115.3, 116.6, 120.7, 120.9, 121.6, 122.4, 125.8, 127.2, 136.5, 145.8, 158.7; MS (EI) *m/z* 306 (25), 173 (55), 145 (100).

Acid 36 was prepared from 7-methoxy-1-naphthyl trifluoromethanesulfonate by the procedure used for the preparation of acid 35. From 0.96 g (3.18 mmol) of triflate there was obtained, after recrystallization from ethyl acetate/petroleum ether, 0.35 g (54%) of acid 36: mp 185–186° (lit. mp 169–170°C Ref. 37); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 3.89 (s, 3H), 7.29 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 6.1 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 8.79 (d, *J* = 9.1 Hz, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 55.2, 106.7, 120.0, 125.4, 126.1, 127.1, 127.5, 127.6, 131.8, 135.2, 157.1, 168.8; MS (EI) *m/z* 202 (100), 159 (35), 109 (50).

**5.1.39. 1-Propyl-3-(7-methoxy-1-naphthoyl)indole JWH-165.** JWH-165 was prepared from 7-methoxy-1-naphthoic acid and 1-propylindole by method D. From 0.18 g (0.9 mmol) of acid and 0.24 g (1.2 mmol) of 1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.19 g (64%) of JWH-165: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.90 (t, *J* = 8.1 Hz, 3H), 1.85 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 4.05 (t, *J* = 7.2 Hz, 2H), 7.17 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.24–7.41 (m, 5H), 7.61–7.65 (m, 2H), 7.78 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 8.47–8.50 (m, 1H); <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 11.3, 23.1, 48.7, 55.3, 103.9, 110.0, 117.5, 119.4, 122.1, 122.7, 122.9, 123.5, 127.1, 129.4, 129.6, 130.0, 132.1, 137.0, 137.4,

137.8, 158.4, 192.2; MS (EI)  $m/z$  343 (100), 326 (60), 314 (55), 207 (85); HRMS Calcd for  $C_{23}H_{21}NO_2$ : 343.1572, Found 343.1581.

**5.1.40. 1-Pentyl-3-(7-methoxy-1-naphthoyl)indole, JWH-164.** JWH-164 was prepared from 7-methoxy-1-naphthoic acid and 1-pentylindole by method D. From 0.19 g (1.0 mmol) of acid and 0.24 g (1.2 mmol) of 1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.21 g (66%) of JWH-164:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.83 (t,  $J = 7.5$  Hz, 3H), 1.18–1.32 (m, 4H), 1.77–1.86 (m, 2H), 3.82 (s, 3H), 4.08 (t,  $J = 7.2$  Hz, 2H), 7.18 (dd,  $J = 9.0$ , 2.5 Hz, 1H), 7.34–7.42 (m, 5H), 7.61–7.65 (m, 2H), 7.79 (d,  $J = 9.0$  Hz, 1H), 7.89 (d,  $J = 8.1$  Hz, 1H), 8.46–8.51 (m, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  13.8, 22.1, 28.9, 29.5, 47.1, 55.3, 103.9, 110.0, 117.5, 119.4, 122.1, 122.2, 122.7, 122.9, 123.5, 127.1, 129.4, 129.6, 130.0, 132.1, 137.0, 137.4, 137.7, 158.4, 192.2; MS (EI)  $m/z$  371 (100), 314 (55), 214 (45), 207 (65); HRMS Calcd for  $C_{25}H_{25}NO_2$ : 371.1885, Found 371.1893.

**5.1.41. 2-Methyl-1-propyl-3-(7-methoxy-1-naphthoyl)indole, JWH-160.** JWH-160 was prepared from 7-methoxy-1-naphthoic acid and 2-methyl-1-propylindole by method D. From 0.18 g (0.9 mmol) of acid and 0.24 g (1.2 mmol) of 2-methyl-1-propylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.20 g (66%) of JWH-160 as a viscous oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.99 (t,  $J = 7.3$  Hz, 3H), 1.77–1.90 (m, 2H), 2.50 (s, 3H), 3.79 (s, 3H), 4.10 (t,  $J = 7.5$  Hz, 2H), 7.03 (t,  $J = 7.8$  Hz, 1H), 7.16–7.24 (m, 3H), 7.32 (t,  $J = 7.1$  Hz, 2H), 7.54–7.60 (m, 2H), 7.80 (d,  $J = 8.9$  Hz, 1H), 7.90 (d,  $J = 7.8$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  11.4, 12.5, 22.9, 44.8, 55.2, 103.7, 109.4, 115.3, 119.3, 121.2, 121.7, 122.1, 122.6, 127.2, 127.4, 129.5, 129.7, 130.1, 131.7, 136.1, 138.5, 145.1, 158.5, 193.8; MS (EI)  $m/z$  357 (100), 340 (40), 300 (15); HRMS Calcd for  $C_{24}H_{23}NO_2$ : 357.1729, Found 357.1720.

**5.1.42. 2-Methyl-1-pentyl-3-(7-methoxy-1-naphthoyl)indole, JWH-159.** JWH-159 was prepared from 7-methoxy-1-naphthoic acid and 2-methyl-1-pentylindole by method D. From 0.18 g (0.9 mmol) of acid and 0.24 g (1.2 mmol) of 2-methyl-1-pentylindole there was obtained after chromatography (petroleum ether/ethyl acetate, 8:1) 0.19 g (43%) of JWH-159 as a viscous oil:  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  0.91 (6.9, 3H), 1.18–1.26 (m, 4H), 1.80 (t,  $J = 7.3$  Hz, 2H), 2.50 (s, 3H), 3.79 (s, 3H), 4.12 (t,  $J = 7.5$  Hz, 2H), 7.01 (t,  $J = 7.8$  Hz, 1H), 7.15–7.24 (m, 3H), 7.32 (t,  $J = 7.8$  Hz, 2H), 7.55–7.59 (m, 2H), 7.80 (d,  $J = 8.9$  Hz, 1H), 7.89 (d,  $J = 7.9$  Hz, 1H);  $^{13}C$  NMR (75.5 MHz,  $CDCl_3$ )  $\delta$  12.5, 13.9, 22.4, 29.1, 29.4, 43.4, 55.3, 103.7, 109.4, 115.0, 119.3, 121.2, 121.7, 122.1, 122.6, 127.2, 127.4, 129.5, 129.7, 130.1, 131.7, 136.0, 138.5, 145.0, 158.5, 193.8; MS (EI)  $m/z$  385 (45), 328 (82), 207 (100); HRMS Calcd for  $C_{26}H_{27}NO_2$ : 385.2041, Found 385.2039.

## 5.2. Receptor binding experiments

**5.2.1. Materials.** Frozen whole brains of male Sprague–Dawley rats were obtained from Harlan (Dublin, VA).

CP 55,940 was provided by Pfizer (Groton, CT). [ $^3H$ ]CP 55,940 was purchased from NEN Life Science Products, Inc. (Boston, MA). Lipofectamine reagent was purchased from Life Technologies (Gaithersburg, MD). Human CB<sub>2</sub> cDNA was provided by Dr. Sean Munro (MRC Lab, Cambridge, UK). DMEM and geneticin was purchased from (GIBCO BRL, Grand Island, NY). Fetal clone II was purchased from Hyclone Laboratories, Inc. (Logan, UT). Aquasil was purchased from Pierce (Rockford, IL). GF/C glass-fiber filters (2.4 cm) were purchased from Baxter (McGaw Park, IL). Polyethylenimine and bovine serum albumin were purchased from Sigma Chemical Co. (St. Louis, MO). Scintillation vials and Budget Solve scintillation fluid were purchased from RPI Corp. (Mount Prospect, IL).

**5.2.2. Development of hCB<sub>2</sub>-CHO cell line.** Chinese hamster ovary cells were maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal clone II and 5% CO<sub>2</sub> at 37°C in a Forma incubator. Cell lines were created by transfection of CB<sub>2</sub>pcDNA3 into CHO cells by the Lipofectamine reagent. Stable transformants were selected in growth medium containing geneticin (1 mg/mL, reagent). Colonies of about 500 cells were picked (about two weeks post-transfection) and allowed to expand, then tested for expression of receptor mRNA by northern blot analysis. Cell lines containing moderate to high levels of receptor mRNA were tested for receptor binding properties. Transfected cell lines were maintained in DMEM with 10% fetal clone II plus 0.3–0.5 mg/mL geneticin and 5% CO<sub>2</sub> at 37°C in a Forma incubator.

**5.2.3. Membrane preparation.** hCB<sub>2</sub>-CHO cells were harvested in phosphate-buffered saline containing 1 mM EDTA and centrifuged at 500g. Cell pellets (for CB<sub>2</sub>) or whole rat brains (for CB<sub>1</sub>) were homogenized in 10 mL of solution A (50 mM Tris–HCl, 320 mM sucrose, 2 mM EDTA, 5 mM MgCl<sub>2</sub>, pH 7.4). The homogenate was centrifuged at 1600g (10 min), the supernatant saved, and the pellet washed three times in solution A with subsequent centrifugation. The combined supernatants were centrifuged at 100,000g (60 min). The (P<sub>2</sub> membrane) pellet was resuspended in 3 mL of buffer B (50 mM Tris–HCl, 1 mM EDTA, 3 mM MgCl<sub>2</sub>, pH 7.4) to yield a protein concentration of approximately 1 mg/mL. The tissue preparation was divided into equal aliquots, frozen on dry ice, and stored at –70°C.

## 5.3. Competition binding assays

**5.3.1. CB<sub>1</sub> assay.** [ $^3H$ ]CP-55,940 binding to P<sub>2</sub> membranes was conducted as described elsewhere,<sup>50</sup> except whole brain (rather than cortex only) was used. CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). Displacement curves were generated by incubating drugs with 1 nM of [ $^3H$ ]CP-55,940. [ $^3H$ ]CP 55,940 bound to rat brain membranes with a  $K_D$  value of  $0.68 \pm 0.07$  nM and a  $B_{max}$  value of  $1.7 \pm 0.11$  pmol/mg. The assays were performed

in triplicate, and the results represent the combined data from three individual experiments.

**5.3.2. CB<sub>2</sub> assay.** Binding was assayed by a modification of Compton et al.<sup>42</sup> CP-55,940 and all cannabinoid analogs were prepared by suspension in assay buffer from a 1 mg/mL ethanolic stock without evaporation of the ethanol (final concentration of no more than 0.4%). The incubation was initiated by the addition of 40–50 µg membrane protein to silanized tubes containing [<sup>3</sup>H]CP-55,940 (102.9 Ci/mmol) and a sufficient volume of buffer C (50 mM Tris–HCl, 1 mM EDTA, 3 mM MgCl<sub>2</sub>, and 5 mg/mL fatty acid free BSA, pH 7.4) to bring the total volume to 0.5 mL. The addition of 1 µM unlabelled CP-55,940 was used to assess non-specific binding. Following incubation (30 °C for 1 h), binding was terminated by the addition of 2 mL of ice cold buffer D (50 mM Tris–HCl, pH 7.4, plus 1 mg/mL BSA) and rapid vacuum filtration through Whatman GF/C filters (pretreated with polyethyleneimine (0.1%) for at least 2 h). Tubes were rinsed with 2 mL of ice cold buffer D, which was also filtered, and the filters subsequently rinsed twice with 4 mL of ice cold buffer D. Before radioactivity was quantitated by liquid scintillation spectrometry, filters were shaken for 1 h in 5 mL of scintillation fluid. [<sup>3</sup>H]CP 55,940 bound to hCB<sub>2</sub>-CHO cells membranes with a  $K_D$  value of  $0.45 \pm 0.07$  nM and a  $B_{\max}$  value of  $2.93 \pm 0.06$  pmol/mg.

**5.3.3. Data analysis.** Competition assays were conducted with 1 nM [<sup>3</sup>H]CP-55,940 and 6 concentrations (0.1 nM to 10 µM displacing ligands). Displacement IC<sub>50</sub> values were originally determined by unweighted least-squares linear regression of log concentration–percent displacement data and then converted to  $K_i$  values using the method of Cheng and Prusoff.<sup>51</sup> All experiments were performed in triplicate and repeated 3–6 times. All data are reported as mean values  $\pm$  SEM.

## 5.4. [<sup>35</sup>S]GTPγS binding experiments

**5.4.1. Materials.** All chemicals were from Sigma (St. Louis, MO) except the following: [<sup>35</sup>S]GTPγS (1250 Ci/mmol) was purchased from New England Nuclear Group (Boston, MA), GTPγS from Boehringer Mannheim (New York, NY), and DMEM/F-12 from Fischer Scientific (Pittsburgh, PA). Whatman GF/B glass fiber filters were purchased from Fisher Scientific (Pittsburgh, PA).

**5.4.2. Membrane preparations.** Chinese Hamster Ovary (CHO) cells stably expressing the human CB<sub>2</sub> receptor (CB<sub>2</sub>-CHO) were cultured in a 50:50 mixture of DMEM and Ham F-12 supplemented with 100 U/mL penicillin, 100 Bg/mL streptomycin, 0.25 mg/mL G418, and 5% fetal calf serum. Cells were harvested by replacement of the media with cold phosphate-buffered saline containing 0.4% EDTA followed by agitation. Membranes were prepared by homogenization of cells in 50 mM Tris–HCl, 3 mM MgCl<sub>2</sub>, 1 mM EGTA, pH 7.4, centrifugation at 50,000g for 10 min at 4 °C, and resuspension in the same buffer at 1.5 mg/mL. Membranes were stored at –80 °C until use.

**5.4.3. [<sup>35</sup>S]GTPγS binding assay.** Prior to assays, samples were thawed on ice, centrifuged at 50,000g for 10 min at 4 °C, and resuspended in Assay Buffer (50 mM Tris–HCl (pH 7.4), 3 mM MgCl<sub>2</sub>, 0.2 mM EGTA, and 100 mM NaCl). Reactions containing 10 Bg of membrane protein were incubated for 1.5 h at 30 °C in Assay Buffer containing 10 µM GDP, 0.1 nM [<sup>35</sup>S]GTPγS, 0.1% bovine serum albumin, and various concentrations of agonist. Non-specific binding was determined in the presence of 20 µM unlabeled GTPγS. Reactions were terminated by rapid vacuum filtration through GF/B glass fiber filters, and radioactivity was measured by liquid scintillation spectrophotometry at 95% efficiency for <sup>35</sup>S.

**5.4.4. Data analysis.** Nonspecific [<sup>35</sup>S]GTPγS binding was subtracted from all data. Basal [<sup>35</sup>S]GTPγS binding is defined as specific [<sup>35</sup>S]GTPγS binding in the absence of drug. Net-stimulated [<sup>35</sup>S]GTPγS binding is defined as [<sup>35</sup>S]GTPγS binding in the presence of drug minus basal. Percent stimulation is expressed as (net stimulated [<sup>35</sup>S]GTPγS binding/basal)  $\times$  100%. The net stimulation produced by each concentration of every test compound was normalized to that obtained by a maximally effective concentration of CP-55,940 (3 µM), which was included in one triplicate of each individual experiment as an internal standard, according to the following equation. Percent maximal CP-55,940 stimulation = (net stimulated [<sup>35</sup>S]GTPγS binding by test compound/net stimulated [<sup>35</sup>S]GTPγS binding by 3 µM CP-55,940)  $\times$  100%. In this way, individual concentration-effect curves of the percent maximal CP-55,940 stimulation produced by each test compound were obtained and subjected to non-linear regression analysis. All data are reported as mean  $E_{\max}$  or EC<sub>50</sub> values  $\pm$  SEM of 3–6 experiments, each performed in triplicate. Nonlinear regression analysis was conducted by iterative fitting of the concentration-effect curves using JMP (SAS for Macintosh: Cary, NC). Statistically significant differences among  $E_{\max}$  values were determined by analysis of variance followed by post-hoc analysis with the unpaired, two-tailed Student's *t*-test using JMP.

## 5.5. Molecular modeling

**5.5.1. Conformational analysis.** The structures of the *N*-propyl-C-2H series analogs: JWH-163 and JWH-180; the *N*-propyl-C-2 methyl series analogs: JWH-151 and JWH-189; the *N*-pentyl-C-2H series analogs: JWH-166, JWH-182, JWH-267; and the *N*-pentyl C-2-methyl series analogs: JWH-153, JWH-181, and JWH-268 were built in the Spartan molecular modeling program (V4.1.1; Wavefunction, Inc. Irvine, CA). Each structure was minimized using the AM1, semi-empirical method. For each minimized structure, AM1 conformational searches were then performed for rotation about the carbonyl to indole C-3 and carbonyl to naphthoyl C-1 bonds.

**5.5.2. Coordinate drive.** In order to describe the energy barrier for rotation about the carbonyl oxygen–carbonyl carbon–naphthalene C-1–naphthalene C-2 torsion angle in JWH-268 (**33**), an AM1 coordinate drive study was undertaken using Spartan. The torsion angle was driven

from its global minimum energy value of  $99.47^\circ$  to  $-80.49^\circ$  in  $10^\circ$  increments. The single point energies of the lowest energy and highest energy conformers identified during this drive were calculated at the HF 3-21G\* level using Spartan.

**5.5.3. CB<sub>1</sub> receptor docking studies. Amino acid numbering system.** In the discussion of receptor residues that follows, the amino acid numbering scheme proposed by Ballesteros and Weinstein<sup>52</sup> is used. In this numbering system, the most highly conserved residue in each transmembrane helix (TMH) of Class A GPCRs is assigned a locant of.<sup>50</sup> This number is preceded by the TMH number and may be followed in parentheses by the sequence number. All other residues in a TMH are numbered relative to this residue. In this numbering system, for example, the most highly conserved residue in TMH 2 of the CB<sub>1</sub> receptor is D2.50(163). The residue that immediately precedes it is A2.49 (162).

**5.5.4. Ligand/CB<sub>1</sub> R\* complex.** Because agonists are thought to have higher affinity for the activated form of GPCRs,<sup>53</sup> agonist ligands in the work reported here were docked in a model of the activated state (R\*) of CB<sub>1</sub>. This R\* CB<sub>1</sub> model was created by modification of our rhodopsin-based model of the inactive (R) form of CB<sub>1</sub> and guided by the biophysical literature on the R to R\* transition. A complete discussion of the creation of both our CB<sub>1</sub> R and R\* models can be found in our published work.<sup>47,54</sup>

A recent CB<sub>1</sub> mutation study has suggested that residues F3.36, W5.43, and W6.48 are part of the binding site of the aminoalkylindole, WIN55, 212-2.<sup>47</sup> These results are consistent with the earlier work of Shire, which showed that the TMH4-E2-TMH<sub>5</sub> region of CB<sub>1</sub> contains residues critical for the binding of SR141716A and WIN55,212-2.<sup>55</sup> Because the indoles studied here are structurally related to the aminoalkylindoles, we chose to dock the indoles studied here in the same region of CB<sub>1</sub> (i.e., the TMH3-4-5-6 region). Each ligand was docked in the CB<sub>1</sub> TMH 3-4-5-6 region using interactive computer graphics. For all analogs studied, the lowest energy *s-trans* conformer of each ligand was used for docking studies.<sup>46</sup> The energy of the CB<sub>1</sub> R\* TMH bundle/ligand complex was minimized using the AMBER\* united atom force field in Macromodel 6.5 (Schrodinger Inc., Portland, OR). A distance dependent dielectric, 8.0 Å extended non-bonded cutoff (updated every 10 steps), 20.0 Å electrostatic cutoff, and 4.0 Å hydrogen bond cutoff were used. The first stage of the calculation consisted of 2000 steps of Polak–Ribier conjugate gradient (CG) minimization in which a force constant of 225 kJ/mol was used on the helix backbone atoms in order to hold the helix backbones fixed, while permitting the side chains to relax. The second stage of the calculation consisted of 100 steps of CG in which the force constant on the helix backbone atoms was reduced to 50 kJ/mol in order to allow the helix backbones to adjust. Stages one and two were repeated with the number of CG steps in stage two incremented from 100 to 500 steps until a gradient of 0.001 kJ/(mol Å<sup>2</sup>) was reached. Explicit hydrogens were included on all aromatic amino acid

residues in order to better simulate aromatic stacking interactions.<sup>56</sup>

Each resultant receptor/ligand complex was analyzed for the presence of hydrogen bonding and aromatic stacking interactions. Aromatic stacking interactions were identified using Burley and Petsko's criteria.<sup>56</sup> These investigators reported that aromatic–aromatic stacking interactions in proteins operate at distances (*d*) of 4.5–7.0 Å between ring centroids. The angle ( $\alpha$ ) between normal vectors of interacting aromatic rings typically is between  $30^\circ$  and  $90^\circ$ , producing a 'tilted-T' or 'edge-to-face' arrangement of interacting rings. Residues and/or ligand regions were designated here as participating in an aromatic stacking interaction if they had centroid to centroid distances between 4.5 and 7.0 Å. These interactions were further classified as 'tilted-T' arrangements if  $30^\circ \leq \alpha \leq 90^\circ$  and as parallel arrangements for  $\alpha < 30^\circ$ . In interactions where  $\alpha = 0^\circ$ , arrangements were also identified as offset or not offset, as Hunter and co-workers have shown that off-set parallel stacks are more energetically favorable.<sup>57</sup>

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