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Synthesis and Structure–Activity Relationships of a Series of Pyrrole Cannabinoid Receptor Agonists

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Abstract—We designed and synthesized a series of pyrrole derivatives with the aim of investigating the structure–activity relationship (SAR) for the binding of non-classical agonists to CB_1 and CB_2 cannabinoid receptors. Superposition of two pyrrole-containing cannabinoid agonists, JWH-007 and JWH-161, allowed us to identify positions 1, 3 and 4 of the pyrrole nucleus as amenable to additional investigation. We prepared the 1-alkyl-2,5-dimethyl-3,4-substituted pyrroles **10a**–**e**, **11a**–**d**, **17**, **21**, **25** and the tetrahydroindole **15**, and evaluated their ability to bind to and activate cannabinoid receptors. Noteworthy in this set of compounds are the 4-bromopyrrole **11a**, which has an affinity for CB_1 and CB_2 receptors comparable to that of well-characterized heterocyclic cannabimimetics such as Win-55,212-2; the amide **25**, which, although possessing a moderate affinity for cannabinoid receptors, demonstrates that the 3-naphthoyl group, commonly present in indole and pyrrole cannabimimetics, can be substituted by alternative moieties; and compounds **10d**, **11d**, showing CB_1 partial agonist properties.

Introduction

Plant-derived and synthetic cannabimimetic agents such as Δ^9-tetrahydrocannabinol[1] (Δ^9-THC, 1, Fig. 1) bind to specific G-protein coupled cannabinoid receptors, which include the CB_1 subtype,[2] mainly present in the central and peripheral nervous systems, and the CB_2 subtype,[3] localized on immune cells. The identification, cloning, and biochemical characterization of cannabinoid receptors,[4] along with the discovery of their endogenous lipid ligands,[5] have fuelled a considerable interest in the physiology and pharmacology of the cannabinergic system.[6] Agents that modulate the activity of this system may have a broad therapeutic potential: beside acute and persistent pain conditions, additional therapeutic applications for CB_1 and CB_2 receptor agonists also may include stroke, glaucoma, multiple sclerosis and spinal cord injury.[7]

Various classes of compounds active at cannabinoid receptors have been developed, and their structure–activity relationship (SAR) properties have been extensively investigated.[8] Agonists reported in the literature belong to two main classes: (i) dibenzo[*b*,*d*]pyrane derivatives (generally referred to as 'traditional' cannabinoids), for example, **1**, HU 210[9] (**2**, Fig. 1) and structurally related molecules, for example CP 55,940[10] (**3**, Fig. 1); (ii) *N*-aminoalkyl indoles (AAIs), for example Win-55,212-2[11] (**4**, Fig. 2) and *N*-alkylindoles (non-AAIs), for example JWH-007[12] (**5a**, Fig. 2). A number of compounds having an indene or pyrrole nucleus as their basic feature has been also reported.[8b] These comprise Huffman's derivatives JWH-030 (**7a**) and **7b** (Fig. 2).[13] While the SAR of indole cannabimimetic agents have been extensively studied, much remains to be done in the area of pyrrole cannabinoids.

Molecular biology and theoretical studies have provided important insights on the pharmacophoric interactions occurring at cannabinoid receptors. The relatively high CB_1 affinity of the pentacyclic derivative JWH-161 (**6**, Fig. 2), a hybrid structure in which the elements of

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traditional and non-AAI cannabinoids are combined,[14] supports the hypothesis that a common pharmacophore exists for the two main classes of ligands.[12] According to this model, the 3-aroyl substituent of indole compounds may mimic the cyclohexene ring of Δ^9-THC (**1**), whereas the indole *N*-substituent and the 3-alkyl chain of traditional cannabinoids may engage in lipophylic interactions with the same region of the receptor.

This hypothesis was questioned by experiments with site-directed mutated receptors, which suggest that a lysine in the third transmembrane (TM3) domain of CB_1, K192, is essential for the binding of CP 55,940 (**3**), but not Win-55,212-2 (**4**).[15] However, as Huffman and co-workers pointed out, non-AAI were not included in these tests, leaving open the possibility that the *N*-alkyl group of these molecules may align to the side chain of traditional cannabinoids, whereas the morpholine group of Win-55,212-2 may bind to a different region of the receptor.[14] The CB_2 subtype offers a somewhat different scenario. In this case, K109, a lysine residue corresponding to K192 in CB_1, may not be essential for the binding of either traditional or AAI ligands. On the other hand, the double mutation K109A/S112G abolishes the binding of Δ^9-THC (**1**) and **3**, but not that of Win-55,212-2. Interestingly, the affinity of the non-AAI compound JWH-015 (**5b**, Fig. 2) is only partially affected in the singly and doubly mutated receptor.[16] Again, phenylalanine to valine mutation in the TM5 domain, F5.46, decreases the binding of Win-55,212-2.[17] It is worth noting that the CB_1 receptor affinity of Win-55,212-2 is enhanced by substitution of a valine, corresponding to CB_2 F5.46, for phenylalanine. Such mutations, however, did not affect the CB_1 and CB_2 binding of traditional cannabinoids such as HU 210 (**2**) and CP 55,940 (**3**).[17] Together with the results of docking experiments,[16,17] these observations suggest that hydrophobic aromatic interactions taking place in a region of the receptor not occupied by traditional ligands may play a crucial role in the binding of Win-55,212-2 and related compounds to CB_2 receptors, while polar interactions through K192 and S112 may contribute to the productive binding of 'traditional' ligands to CB_1 and CB_2, respectively. The decisive role of aromatic stacking interactions for cannabinoid binding has been supported by two recent investigations.[18]

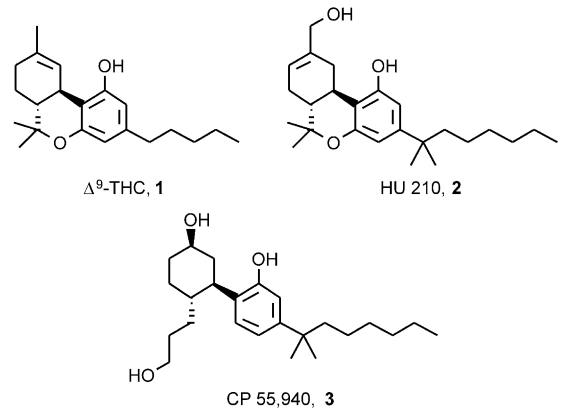


Figure 1. Representative 'traditional' cannabimimetic agents.

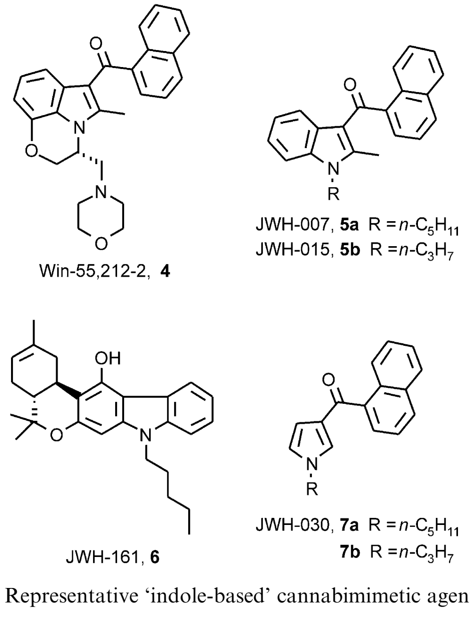


Figure 2. Representative 'indole-based' cannabimimetic agents.

In an attempt to extend Huffman's observations regarding the activity of pyrrole derivatives on CB receptors, we have prepared and tested, on CB_1 and CB_2 receptors, a series of pyrroles with chemical modifications on positions 1, 3, and 4 of the heterocycle. Our compounds were designed assuming that the pharmacophoric interactions occurring at cannabinoid receptors may be modelled by the superposition of the hybrid ligand **6** with JWH-007 (**5a**) (see Fig. 3a), so that the distal ring of the naphthoyl group of **5a** corresponds to the 'ring A' of traditional cannabimimetics.

In particular, the replacement, in compounds **10a**,**d**, **11a** of the 3-naphthoyl, the standard C-3 substituent in Huffman's pyrrolic cannabimimetics (see compounds **7a**,**b**,[13] Fig. 2), with a benzoyl group, may give information about the importance of the distal moiety of the naphthoyl group itself. In principle, this group could be replaced by fragments that fit the receptor in a similar manner. Therefore, an *N*-(2-acetylphenyl)carboxamido fragment, a planar pseudo-bicyclic substructure stabilized by an intramolecular H bond, is attached in position

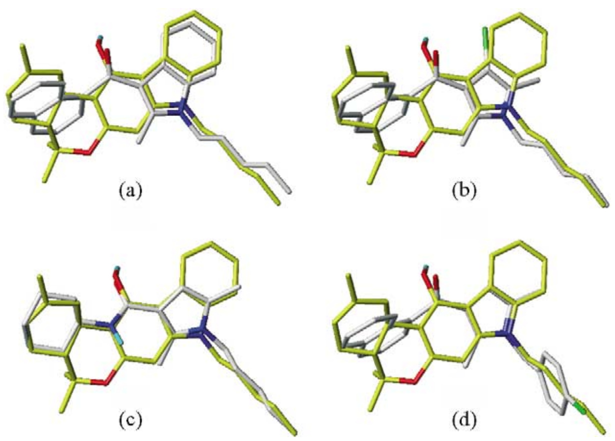
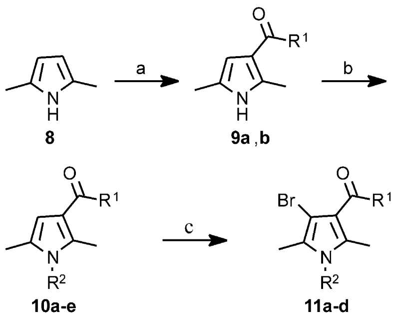


Figure 3. Superposition of **6** (yellow carbons) to **5a** (a), **11a** (b), **25** (c), **10d** (d).

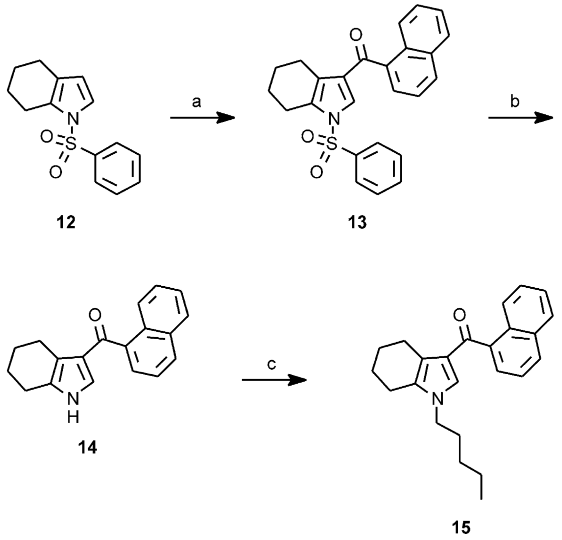
3 of compound **21**.[19] Moreover, it should be possible to place in position 3 substructures able to mimic the 'ring A' of classical cannabinoids, for example the *N*-cyclohexylcarboxamido group of compound **25** (see Fig. 3c). Lastly, we attempted to substitute the naphthalene moiety for a totally different structural element; therefore, in pyrrole **17** a linear alkyl chain is present bearing an alcoholic function, possibly interacting with the polar site of the receptor to which the 9- or 11-hydroxy residue of traditional cannabinoids are assumed to bind.

Concerning position 4, this could be substituted by a group like bromo (as in **11a–d**); these compounds, along with the 4,5,6,7-tetrahydroindole derivative **15**, in which an alkyl chain connects positions 4 and 5 of the pyrrole ring, are instrumental to further examine the concept that pyrrole derivatives may be as active as their indole congeners (**5**). It is commonly accepted that, compared to indole compounds, pyrrole cannabimimetics are endowed with a reduced affinity for CB_1 receptor. This conclusion, however, has been inferred from the analysis of a limited number of structures, namely 4,5-unsubstituted pyrroles.[20]



	R^1	R^2
a	1-naphthyl	n-C_5H_{11}
b	C_6H_5	n-C_5H_{11}
c	1-naphthyl	n-C_3H_7
d	1-naphthyl	p-$ClC_6H_4CH_2$
e	C_6H_5	p-$ClC_6H_4CH_2$

Scheme 1. Reagents and conditions: (a) $R^1C(O)Cl$, $AlCl_3$, CH_2Cl_2, 25 °C, 0.25–2 h; (b) NaH, DMF, *n*-alkylBr, 25 °C, 3 h; (c) NBS, 1,4-dioxane, AcOH, 25 °C, 0.5 h for **11a**,**b**,**d** and NBS, CH_2Cl_2, 25 °C, 3 h for **11c**.

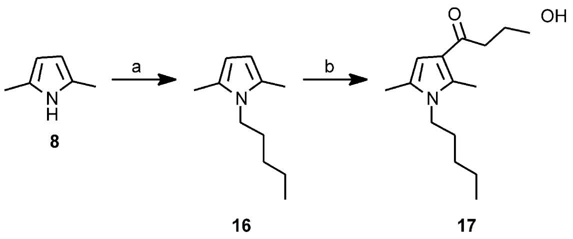


Scheme 2. Reagents and conditions: (a) $R^1C(O)Cl$, $AlCl_3$, CH_3NO_2, CH_2Cl_2, 25 °C, 4 h; (b) KOH, H_2O–MeOH, reflux, 20 h; (c) NaH, DMF, n-$C_5H_{11}Br$, 25 °C, 5 h.

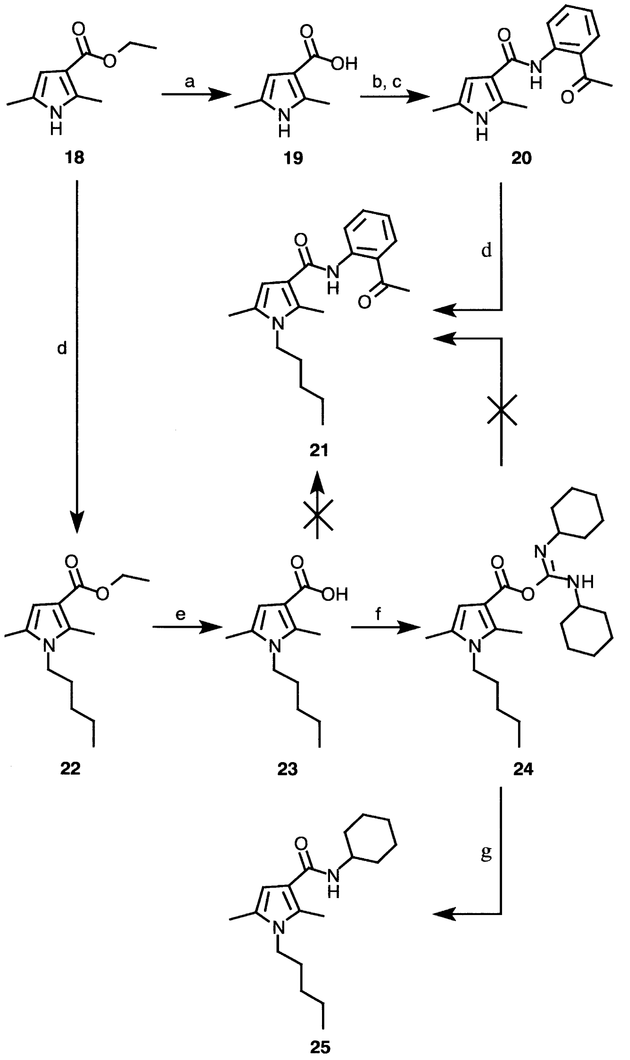
Another region of cannabinoid receptors, which is of crucial importance for ligand binding, is the one corresponding in our topographical model to the alkyl chain attached to the pyrrole nitrogen. Compounds in which a group bearing an aromatic ring replaces the typical alkyl chain substituent may provide useful information about the steric tolerance of this region. Therefore, we prepared compounds **10d**,**e** and **11d**, whose *p*-chlorobenzyl *N*-substitutent is a feature similar to that of diarylpyrazolic CB_2 antagonist SR144528.[8c] However, most of our compounds retain an *N*-pentyl chain, a group known to afford optimal cannabinoid binding to non-AAI and pyrrole ligands;[20,21] an *N*-propylic chain was inserted in some cases (**10c**, **11c**), since this shortened alkyl fragment is reported to confer CB_2 selectivity to AAI compounds.[22]

Result and discussion

Compounds **10a–e** and **11a–d** were synthesized in a straightforward manner according to Scheme 1. Thus, aroylation of 2,5-dimethylpyrrole (**8**) in the presence of aluminum chloride, followed by *N*-alkylation, afforded compounds **10a–e**; pyrroles **10a–d** were then brominated with *N*-bromosuccinimide to give **11a–d**. The synthesis of 4,5,6,7-tetrahydroindole derivative **15** (Scheme 2), also proceeding smoothly, followed the same route employed by Huffman and co-workers for the preparation of 1-pentyl-3-(1-naphtoyl)pyrrole (**7a**).[13] Thus, **12**[23] was regioselectively acylated,[24] deprotected by alkaline treatment, and eventually alkylated in standard conditions to give **15**. Compound **17** was obtained from 2,5-dimethyl-1-pentylpyrrole[25] (**16**), prepared by the already mentioned *N*-alkylation procedure, and γ-butyrolactone in polyphosphoric acid, according to the method of Moussavi et al.[26] (Scheme 3). Compounds **21** and **25** were prepared as outlined in Scheme 4. Thus, 2,5-dimethyl-3-pyrrole carboxylic acid ethyl ester[27] (**18**), prepared following a literature procedure for the synthesis of the methyl ester analogue of **18**,[28] yielded, after hydrolysis, the carboxylic acid **19**,[29] which was transformed into the amide **20** via acid chloride. Finally,



Scheme 3. Reagents and conditions: (a) NaH, DMF, n-$C_5H_{11}Br$, 25 °C, 3 h; (b) PPA, γ-butyrolactone, 135 °C, 24 h.

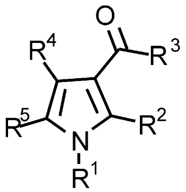


Scheme 4. Reagents and conditions: (a) see Ref. 29; (b) ClC(O)-C(O)Cl, CH_2Cl_2, DMF, 25 °C, 2 h; (c) 2′-$NH_2C_6H_4C(O)CH_3$, 25 °C, 6 h; (d) NaH, DMF, *n*-$C_5H_{11}Br$, 20 h for **21** or 3 h for **22**; (e) LiOH–H_2O in H_2O, EtOH, reflux, 24 h; (f) 2′-$NH_2C_6H_4C(O)CH_3$, CH_2Cl_2, DCC, 25 °C, 24 h; (g) xylene, Et_3N, reflux, 15 h.

N-alkylation of **20** gave the desired compound **21**. We originally conceived an alternative synthesis of this compound (Scheme 4); thus, compound **24**, a putative immediate precursor of **21**, was obtained from **18** by *N*-alkylation, hydrolysis, and treatment with dicyclohexylcarbodiimide. Even after prolonged heating, however, **24** did not react with 2′-aminoacetophenone, giving instead an intramolecular rearrangement to *N*-cyclohexylcarboxamido pyrrole **25**. We also attempted to convert **23** to **21** via acid chloride. Unfortunately, by treating **23** with oxalyl chloride/DMF in CH_2Cl_2, followed by 2′-aminoacetophenone, we obtained, after workup, a mixture in which no trace of the desired amide **21**, and of unreacted starting material **23**, was present.

We used radioligand displacement assays to evaluate the affinity of compounds **10a–e**, **11a–d**, **15**, **17**, **21**, **25** for the native rat CB_1 receptor and the recombinant human CB_2 receptors. The former assay was conducted using rat cerebellar membranes (27,000*g*), and the latter using membranes of Chinese hamster ovary (CHO) cells that overexpress CB_2 receptors (Receptor Biology Inc. Perkin Elmer, Wellesley, MA, USA) using [^{3}H]Win-55212-2 (NEN-Dupont, Boston, MA, USA, 40–60 Ci/mmol, 10 nM) as a ligand.[5a] A summary of these results is provided in Table 1. *N*-Pentyl-3-naphthoylpyrroles **10a**, **11a**, **15**, which can be regarded as congeners of Huffman's pyrrole derivative **7a** (Fig. 2), retain a moderate to good affinity for CB receptors. In particular, the concomitant presence of a C-2 and a C-5 methyl substituent, a distinctive feature of the present series of pyrrole ligands influencing the conformational equilibrium of the *N*-alkyl group, appears to be tolerated at CB_1, and to slightly increase the affinity at the CB_2, receptor subtypes. This trend, illustrated by compound **10a**, which is 20 times more potent than **7a** in CB_2 binding affinity, persists over the entire group of our 1-alkyl-3-naphthoyl pyrrole ligands which, therefore, albeit having only a moderate preference for CB_2 receptors, show a reversed CB_1/CB_2 selectivity, compared with Huffman's derivative **7a**. Substituents in position 4 cause different effects, depending on their nature: in agreement with the topographic model depicted in Fig. 3b, introduction of a bromo group produces a slight increase in binding affinity for both receptor subtypes (see **10a**), whereas an unfavourable effect is produced by the tetramethylene chain linking positions 4 and 5 of compound **15**. The substitution of the 3-(1-naphthoyl) group for a benzoyl one is detrimental for affinity (**10b**,**e**, **11b**), and this is consistent with the previous observation that AAIs with monocyclic aroyl nuclei in position 3 are far less active than their 3-(1-naphthoyl) homologues.[11,30] The replacement of the C-3 naphthoyl substituent with groups of different structural characteristics provides compounds with reduced affinity for the cannabinoid receptors (**21**, **25**), or a complete loss of binding (**17**). In particular, the *N*-(2-acetylphenyl)carboxamido group of **21** is only in part, and only with CB_1 receptor subtype, able to reproduce the binding mode of the naphthoyl group. A slightly better binding affinity, at least for the CB_2 subtype, was obtained with compound **25**. This supports our hypothesis of a cycloalkyl fragment mimicking the cyclohexene ring of classical cannabinoids, according to the model of Figure 3c. Finally, the attempt to reproduce the interactions afforded by the hydroxy group of classical cannabinoids by means of a hydroxyalkyl chain (**17**) was unsuccessful. The *N*-propyl derivatives **10c** and **11c** proved to be less potent than the corresponding *N*-pentyl analogues **10a** and **11a**. The decrease of affinity is less marked for the CB_2 receptor, resulting in a certain degree of CB_2 selectivity, which is consistent with literature data,[18,20] even though, in our pyrroles, the CB_2/CB_1 affinity ratio enhancement caused by chain shortening is not as prominent as that found in prototypic 3-aroyl indole cannabimimetics.[31] Interestingly, the replacement of the *N*-linear alkyl chain by a substituent of different steric and electronic nature, that is, a *p*-chlorobenzyl group, yields compounds (**10d**, **11d**) that retain a certain affinity for cannabinoid receptors. Indeed, such derivatives, especially relative to CB_1

Table 1. Binding affinity values at rat native CB_1 and human recombinant CB_2 receptors



No.	R^1	R^2	R^3	R^4	R^5	EC_{50} (nM) rCB_1	EC_{50} (nM) hCB_2
7a	n-C_5H_{11}	H	1-Naphthyl	H	H	30.5±4.7	552±314
10a	n-C_5H_{11}	CH_3	1-Naphthyl	H	CH_3	45.3±7.5	9.85±2.1
10b	n-C_5H_{11}	CH_3	C_6H_5	H	CH_3	>1000	>1000
10c	n-C_3H_7	CH_3	1-Naphthyl	H	CH_3	>1000	309.7±20.8
10d	pClC$_6$H$_4$CH$_2$	CH_3	1-Naphthyl	H	CH_3	83.7±17.8	55.6±26.5
10e	pClC$_6$H$_4$CH$_2$	CH_3	C_6H_5	H	CH_3	>1000	>1000
11a	n-C_5H_{11}	CH_3	1-Naphthyl	Br	CH_3	13.3±0.5	6.8±1.0
11b	n-C_5H_{11}	CH_3	C_6H_5	Br	CH_3	>1000	>1000
11c	n-C_3H_7	CH_3	1-Naphthyl	Br	CH_3	780±326	691.3±101.3
11d	pClC$_6$H$_4$CH$_2$	CH_3	1-Naphthyl	Br	CH_3	38±7.2	194.5±27.5
15	n-C_5H_{11}	H	1-Naphthyl	$(CH_2)_4$		235.8±6.2	139±55
17	n-C_5H_{11}	CH_3	$HO(CH_2)_3$	H	CH_3	>3000	>10,000
21	n-C_5H_{11}	CH_3	o(CH$_3$CO)C$_6$H$_4$NH	H	CH_3	367.3±31.2	>1000
25	n-C_5H_{11}	CH_3	c-C$_6$H$_{11}$NH	H	CH_3	415.5±79.5	483.5±211

Results are expressed as the mean±SEM of at least three independent experiments.

binding, are more potent than the short alkyl chain analogues **10c**, **11c**. The binding mode of **10d** and **11d** may be somewhat different from that of the remaining *N*-alkylpyrroles, as suggested by the fact that introduction of a bromo group in position 4 does not increase potency (cfr. **10a** vs **10d**, and **11a** vs **11d**).

We also investigated the intrinsic activity of selected high-affinity ligands at CB_1 receptors by testing their ability to stimulate [^{35}S]GTPγS binding in rat cerebellar membranes. Figure 4 illustrates the effects of various pyrrole-based compounds on the binding of [^{35}S]GTPγS to rat cerebellar membranes. The compound **11a** stimulates [^{35}S]GTPγS binding with an EC_{50} value of 140.3±8.2 nM (mean±SEM, $n=9$) and a maximal degree of stimulation (238±18%) identical to that of Win-55,212-2 (Fig. 4). We obtained similar results with compound **10a**, which stimulates [^{35}S]GTPγS binding with an EC_{50} value of 324.0±20.8 nM. These findings suggest that **11a** and **10a** are full agonist ligands at rat CB_1 with an efficacy comparable to that of known cannabimimetic agents.[32] By contrast, the compounds **11d** (Fig. 4) and **10d** (data not shown), which enhance [^{35}S]GTPγS binding with EC_{50} values of 186.3±42.2 and 179.3±69 nM, respectively, produce only a fraction of the maximal [^{35}S]GTPγS binding stimulation induced by Win-55,212-2. Therefore, these compounds may be considered as partial CB_1 agonists. These results support the idea that it is possible to modulate the pharmacological properties of cannabimimetic pyrroles by suitable elaboration of their *N*-substituents. Finally, the compounds **21** and **10c** are very weak at stimulating [^{35}S]GTPγS binding (EC_{50} values 4052±4 and 4004±603 nM, respectively). This failure may be due either to their modest affinity for CB_1 receptors and/or to a lack of efficacy.

In summary, our results extend previously established SARs for indole and pyrrole cannabimimetics. In particular, we identified a 3-naphthoyl pyrrole **11a**, which displays a binding affinity and intrinsic activity comparable to that of 3-naphthoyl indoles. This suggests that a suitable lipophylic group, attached to position 4 of the pyrrole nucleus, can compensate for the lack of contribution of the benzo moiety present in indole compounds. The steric and electronic characters of this substituent seem to be strictly defined, as may be inferred from the reduced affinity of 4,5,6,7-tetrahydroindole **15**. Compound **11a**, the most active of our series, does not display a significant CB_1/CB_2 selectivity; this parallels, however, the behaviour of *N*-pentyl cannabimimetic indoles.[31] Furthermore, the testing of several compounds that have structural elements unusual in

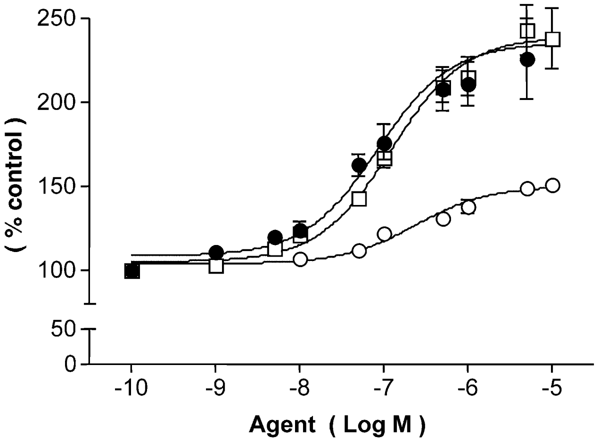


Figure 4. Effects of various cannabinoid receptor ligands on [^{35}S]-GTPγS binding to rat cerebellar membranes. Shown are the effects of Win-55,212-2 (closed circles), **11a** (open squares) and **11d** (open circles).

heterocyclic cannabinoid ligands provided further insights to the topography of cannabinoid receptor binding sites. Lastly, the fact that the *N*-chlorobenzyl compound **10d** behaves as a partial agonist, indicates that the standard linear alkyl chain of non-AAI can be substituted with groups that interact with an area of the receptor involved in modulating ligand efficacy.

Conclusions

Some of the pyrrole derivatives described in this study exhibit interesting affinity and efficacy profiles for cannabinoid receptors. Functional tests indicate that these compounds may behave as full or partial agonists at the CB_1 receptor subtype, depending on the presence of specific substituents. Further investigations will be necessary to optimize the affinity and efficacy of the present class of compounds, and to explore in more detail their SAR properties.

Experimental

Chemistry

All chemicals were purchased from Aldrich in the highest quality commercially available. Solvents were RP grade, unless otherwise indicated. Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck). TLC analyses were performed on precoated silica gel on aluminium sheets (Kieselgel 60 F_{254}, Merck). Melting points were determined on a Büchi SMP-510 capillary melting point apparatus, unless otherwise indicated, and are uncorrected. EI-MS analyses (70 eV) were recorded with a Fisons Trio 1000 spectrometer; only molecular ions (M^+) and base peaks are given. ^1H NMR spectra were recorded on a Bruker AC 200 spectrometer using $CDCl_3$ as solvent; chemical shifts (δ scale) are reported in part per million (ppm) relative to the central peak of the solvent; coupling costants (*J* values) are given in hertz (Hz). IR spectra were obtained on a Shimadzu FT-8300, or a Nicolet Avatar, spectometer; absorbances are reported in ν (cm^{-1}). Elemental analyses were performed on a Carlo Erba analyzers.

Molecular modeling

Three-dimensional models of the molecules were built with Sybyl 6.7 software package[33] and their geometry was optimized using the standard Tripos force field,[34] with the Powell method[35] to an energy gradient of 0.01 *K*cal/mol Å, ignoring the electrostatic contribution.

General procedure for the synthesis of 3-aroyl-2,5-dimethylpyrroles (9a,b). To a stirred, cooled (0 °C) solution of 2,5-dimethylpyrrole (**8**) (15 mmol) and the opportune aroyl chloride (15 mmol) in CH_2Cl_2 (15 mL), $AlCl_3$ (2 g; 15 mmol) was cautiously added. The mixture was stirred at room temperature for 15 min, quenched with a cooled saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 6:4) gave **9a**,**b**.

(2,5-Dimethyl-1*H*-pyrrol-3-yl)(naphthalen-1-yl)methanone (9a).[36] Light-yellow crystals. Yield: 39% (1.459 g). Mp 163–164 °C (EtOAc) (lit.: 165–167 °C).[36]

(2,5-Dimethyl-1*H*-pyrrol-3-yl)(phenyl)methanone (9b).[37] Pale brown amorphous solid. Yield: 28% (0.839 g). MS (EI) is in agreement with literature.[37]

General procedure for the synthesis of 1-alkyl-2,5-dimethyl-3,4-(un)substituted pyrroles (10a–e, 15, 16, 21, 22). To a stirred, cooled (0 °C) solution of the convenient pyrrole **8**, **9a**,**b**, **14**, **18**, **20** (5 mmol) in dry DMF (12.5 mL) under N_2 atmosphere, NaH (0.173 g of an 80% mineral oil dispersion, 5.75 mmol) was added. When H_2 evolution had ceased, the opportune 1-bromoalkane was added (5.75 mmol). After stirring the mixture for 2 h at room temperature a further amount of NaH (0.087 g, 2.88 mmol; 0.043 g, 1.44 mmol in the case of **16**) and 1-bromoalkane (2.88 mmol; 1.44 mmol in the case of **16**) were added and the mixture again allowed to react for 1 h. CH_2Cl_2 and H_2O were then cautiously added and the organic layer washed with H_2O, dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 9:1; 85:15 for **10a**; 8:2 for **10c**,**e** and **22**; 95:5 for **16**) gave **10a**,**b**,**d**,**e**, **15**, and **21** as solids, and **10c**, **16**, **22** as oils. In the case of **21** a few modifications to the procedure were adopted; thus, only 5 mmol of NaH was employed, and after the addition of 1-bromopentane (5 mmol) the mixture was allowed to react for 20 h, then worked up as above (chromatography: cyclohexane/EtOAc 8:2, then 1:1).

(2,5-Dimethyl-1-pentyl-1*H*-pyrrol-3-yl)(naphthalen-1-yl)-methanone (10a). White crystals. Yield: 95% (1.518 g). Mp 48–50 °C (cyclohexane). MS (EI): *m*/*z* 319 (M^+), 155 (100). ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H); 1.37 (m, 4H); 1.68 (m, 2H); 2.14 (s, 3H); 2.61 (s, 3H); 3.79 (t, 2H); 5.84 (d, 1H); 7.48 (m, 4H); 7.89 (m, 2H); 8.11 (m, 1H) ppm. IR (nujol): 1631, 1616 cm^{-1}. Anal. calcd for $C_{22}H_{25}NO$ (319.45): C, 82.72; H, 7.89; N, 4.38. Found: C, 82.76; H, 7.93; N, 4.36.

(2,5-Dimethyl-1-pentyl-1*H*-pyrrol-3-yl)(phenyl)methanone (10b). White crystals. Yield: 90% (1.211 g). Mp 55–56 °C (after trituration with petroleum ether/Et_2O 9:1). MS (EI): *m*/*z* 269 (M^+, 100). ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H); 1.36 (m, 4H); 1.67 (m, 2H); 2.22 (s, 3H); 2.59 (s, 3H); 3.80 (t, 2H); 6.07 (s, 1H); 7.42 (m, 3H); 7.79 (m, 2H) ppm. IR (nujol): 1625 cm^{-1}. Anal. calcd for $C_{18}H_{23}NO$ (269.39): C, 80.26; H, 8.61; N, 5.20. Found: C, 79.81; H, 8.63; N, 5.13.

(2,5-Dimethyl-1-propyl-1*H*-pyrrol-3-yl)(naphthalen-1-yl)-methanone (10c). Yellow oil. Yield: 82% (1.194 g). MS (EI): *m*/*z* 291 (M^+, 100). ^1H NMR ($CDCl_3$): δ 1.01 (t, 3H); 1.71 (m, 2H); 2.14 (s, 3H); 2.61 (s, 3H); 3.77 (t, 2H); 5.84 (s, 1H); 7.48 (m, 4H); 7.88 (m, 2H); 8.12 (m, 1H) ppm. IR ($CHCl_3$): 1627, 1618 cm^{-1}. Anal. calcd for

$C_{20}H_{21}NO$ (291.39): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.22; H, 7.40; N, 4.87.

1-(4-Chlorobenzyl)-2,5-dimethyl-1*H*-pyrrol-3-yl naphthalen-1-yl methanone (10d). Pale yellow crystals. Yield: 83% (1.552 g). Mp 105–106 °C (*i*-Pr_2O). MS (EI): *m/z* 373 (M^+), 125 (100). ^1H NMR ($CDCl_3$): δ 2.06 (s, 3H); 2.51 (s, 3H); 5.06 (s, 2H); 5.97 (s, 1H); 6.89 (d, 2H); 7.27–7.64 (m, 6H); 7.91 (m, 2H); 8.16 (m, 1H) ppm. IR ($CHCl_3$): 1628 cm^{-1}. Anal. calcd for $C_{24}H_{20}ClNO$ (373.88): C, 77.10; H, 5.39; N, 3.82. Found: C, 77.00; H, 5.38; N, 3.82.

[1-(4-Chlorobenzyl)-2,5-dimethyl-1*H*-pyrrol-3-yl](phenyl)-methanone (10e). White crystals. Yield: 92% (1.491 g). Mp 93–95 °C (cyclohexane). MS (EI): *m/z* 323 (M^+), 125 (100). ^1H NMR ($CDCl_3$): δ 2.13 (d, 3H, $J=0.74$ Hz); 2.50 (s, 3H); 5.07 (s, 2H); 6.18 (d, 1H, $J=0.74$ Hz); 6.88 (d, 2H); 7.29–7.50 (m, 5H); 7.82 (m, 2H) ppm. IR (Nujol): 1624 cm^{-1}. Anal. calcd for $C_{20}H_{18}ClNO\cdot 0.25H_2O$ (328.33): C, 73.17; H, 5.68; N, 4.27. Found: C, 72.99; H, 5.55; N, 4.22.

(Naphthalen-1-yl)(1-pentyl-4,5,6,7-tetrahydro-1*H*-indol-3-yl)methanone (15). Pale yellow amorphous solid. Yield: 77% (1.329 g). MS (EI): *m/z* 345 (M^+), 155 (100). ^1H NMR ($CDCl_3$): δ 0.95 (t, 3H); 1.42 (m, 4H); 1.71 (m, 2H); 1.87 (m, 4H); 2.40 (t, 2H); 2.67 (t, 2H); 4.43 (t, 2H); 6.26 (s, 1H); 7.51 (m, 4H); 7.89 (m, 2H); 8.09 (m, 1H) ppm. IR (nujol): 1617 cm^{-1}. Anal. calcd for $C_{24}H_{27}NO$ (345.48): C, 83.44; H, 7.88; N, 4.05. Found: C, 83.57; H, 8.03; N, 4.05.

2,5-Dimethyl-1-pentyl-1*H*-pyrrole (16). Colorless oil. Yield: 20% (0.165 g). MS (EI): *m/z* 165 (M^+), 108 (100). The product was not fully characterized, owing to the impossibility to obtain a pure sample of it (apparently, 16 is not stable in our chromatographic conditions).

2,5-Dimethyl-1-pentyl-1*H*-pyrrol-3-carboxylic acid (2-acetylphenyl)amide (21). White crystals. Yield: 50% (0.816 g). Mp 78–79 °C (petroleum ether). MS (EI): *m/z* 326 (M^+), 192 (100). ^1H NMR ($CDCl_3$): δ 0.93 (t, 3H); 1.35 (m, 4H); 1.51 (m, 2H); 2.27 (s, 3H); 2.62 (s, 3H); 2.70 (s, 3H); 3.77 (t, 2H); 6.41 (s, 1H); 7.05 (t, 1H); 7.55 (t, 1H); 7.91 (d, 1H); 8.95 (d, 1H), 12.10 (br s, 1H) ppm. IR (KBr): 3274, 1668, 1645, 1606 cm^{-1}. Anal. calcd for $C_{20}H_{26}N_2O_2$ (326.44): C, 73.59; H, 8.03; N, 8.58. Found: C, 74.12; H, 7.78; N, 8.92.

2,5-Dimethyl-1-pentyl-1*H*-pyrrol-3-carboxylic acid ethyl ester (22). Yellow oil. Yield: 88% (1.046 g). MS (EI): *m/z* 237 (M^+), 108 (100). ^1H NMR ($CDCl_3$): δ 0.92 (t, 3H); 1.33 (m, 7H); 1.62 (m, 2H); 2.20 (s, 3H); 2.52 (s, 3H); 3.74 (t, 2H); 4.24 (q, 2H); 6.25 (s, 1H) ppm. IR (neat): 1694 cm^{-1}. The product tends to decompose on standing.

General procedure for the synthesis of 1-alkyl-3-aroyl-4-bromo-2,5-dimethylpyrroles (11a,b,d)

To a stirred solution of the convenient pyrrole 10a,b,d (1 mmol) in a 2:1 solution of dioxane and glacial acetic acid (4.5 mL), *N*-bromosuccinimmide (0.178 g, 1 mmol) was added portionwise and the reactants were stirred at room temperature for 30 min. The mixture was then poured onto a cooled (0 °C), dilute solution of NaOH, and extracted with CH_2Cl_2. The combined organic layers were washed with 2 N HCl and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 85:15) and recrystallization gave 11a,b,d.

(4-Bromo-2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-yl)(naphthalen-1-yl)methanone (11a). White crystals. Yield: 15% (0.060 g). Mp 74–77 °C (Et_2O/petroleum ether). MS (EI): *m/z* 398 (M^+), 318 (100). ^1H NMR ($CDCl_3$): δ 0.93 (t, 3H); 1.35 (m, 4H); 1.65 (m, 2H); 2.22 (s, 3H); 2.31 (s, 3H); 3.82 (t, 2H); 7.52 (m, 4H); 7.87 (m, 2H); 8.22 (m, 1H) ppm. IR (nujol): 1627, 1618 cm^{-1}. Anal. calcd for $C_{22}H_{24}BrNO$ (398.34): C, 66.34; H, 6.07; N, 3.52. Found: C, 66.32; H, 6.12; N, 3.48.

(4-Bromo-2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-yl)(phenyl)-methanone (11b). White crystals. Yield: 22% (0.077 g). Mp 80–81 °C (Et_2O/petroleum ether). MS (EI): *m/z* 348 (M^+), 105 (100). ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H); 1.37 (m, 4H); 1.65 (m, 2H); 2.24 (s, 3H); 2.28 (s, 3H); 3.82 (t, 2H); 7.42 (m, 3H); 7.77 (m, 2H) ppm. IR (nujol): 1617 cm^{-1}. Anal. calcd for $C_{18}H_{22}BrNO$ (348.28): C, 62.08; H, 6.37; N, 4.02. Found: C, 61.88; H, 6.36; N, 3.99.

[4-Bromo-1-(4-chlorobenzyl)-2,5-dimethyl-1*H*-pyrrol-3-yl](naphthalen-1-yl)methanone (11d). White crystals. Yield: 41% (0.186 g). Mp 119–121 °C (subl.) (CH_2Cl_2/petroleum ether). MS (EI): *m/z* 372, 125 (100). ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H); 2.20 (s, 3H); 5.07 (s, 2H); 6.89 (d, 2H); 7.32–7.65 (m, 6H); 7.93 (m, 2H); 8.28 (m, 1H) ppm. IR (KBr): 1628 cm^{-1}. Anal. calcd for $C_{24}H_{19}BrClNO\cdot 0.05CH_2Cl_2$ (457.62): C, 63.25; H, 4.25; N, 3.06. Found: C, 63.16; H, 4.19; N, 3.10.

Synthesis of (4-bromo-2,5-dimethyl-1-propyl-1*H*-pyrrol-3-yl)(naphthalen-1-yl)methanone (11c). To a stirred solution of 10c (0.293 g, 1 mmol) in CH_2Cl_2 (6 mL), *N*-bromosuccinimmide (0.178 g, 1 mmol) was added portionwise and the reactants were allowed to react at room temperature for 3 h. The mixture was then poured onto a cooled (0 °C) 2N NaOH solution, and extracted with CH_2Cl_2. The combined organic layers were washed with 2 N HCl and brine, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 9:1) and recrystallization gave 11c as a white solid. Yield: 94% (0.348 g). Mp 92 °C (with decomposition, EtOH). MS (EI): *m/z* 370 (M^+), 290 (100). ^1H NMR ($CDCl_3$): δ 0.99 (t, 3H); 1.70 (m, 2H); 2.22 (s, 3H); 2.31 (s, 3H); 3.80 (t, 2H); 7.51 (m, 4H); 7.91 (m, 2H); 8.23 (m, 1H) ppm. IR (neat): 1634 cm^{-1}. Anal. calcd for $C_{20}H_{20}BrNO\cdot 0.25c\text{-}C_6H_{12}$ (391.33): C, 65.99; H, 5.92; N, 3.58. Found: C, 65.65; H, 5.70; N, 3.64.

Synthesis of (1-benzenesulfonyl-4,5,6,7-tetrahydro-1*H*-indol-3-yl)(naphthalen-1-yl)methanone (13). To a stirred solution of $AlCl_3$ (0.320 g, 2.4 mmol) in CH_3NO_2 (1.6 mL), a solution of 4,5,6,7-tetrahydro-1-phenylsulphonylindole (12) (0.523 g, 2 mmol) in CH_2Cl_2 (13 mL), then 1-naphthoyl chloride (0.458 g, 0.36 mL, 2.4 mmol) were added and the reactants were allowed to react at room temperature for 4 h. The mixture was then poured onto ice and H_2O and extracted with CH_2Cl_2. The combined organic layers were washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 85:15) gave **13** as a pale brown foamy solid. Yield: 44% (0.366 g). MS (EI): *m*/*z* 415 (M^+), 274 (100). ^1H NMR ($CDCl_3$): δ 1.80 (m, 4H); 2.37 (t, 2H); 3.06 (t, 2H); 6.31 (s, 1H); 7.39–7.76 (m, 8H); 7.93 (m, 2H); 8.30 (m, 2H) ppm. The product tends to decompose on standing.

Synthesis of (naphthalen-1-yl)(4,5,6,7-tetrahydro-1*H*-indol-3-yl)methanone (14). A stirred suspension of **13** (0.332 g, 0.8 mmol) and KOH (0.090 g, 1.6 mmol) in a 5:8 mixture of H_2O and MeOH (3 mL) was refluxed for 20 h, and then concentrated. The residue was dissolved in H_2O/CH_2Cl_2, and the organic layer cautiously washed with 2 N HCl, dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 9:1) and recrystallization gave **14** as a yellow solid. Yield: 71% (0.148 g). Mp 196–198 °C (EtOAc). MS (EI): *m*/*z* 275 (M^+, 100). ^1H NMR ($CDCl_3$): δ 1.81 (m, 4H); 2.47 (t, 2H); 2.72 (t, 2H); 6.40 (d, 1H); 7.52 (m, 3H); 7.73 (m, 1H); 7.93 (m, 2H); 8.22 (m, 1H); 9.47 (br s, 1H) ppm. IR (nujol): 3263, 1578 cm^{-1}. Anal. calcd for $C_{19}H_{17}NO$ (275.35): C, 82.88; H, 6.22; N, 5.09. Found: C, 82.67; H, 6.05; N, 5.16.

Synthesis of 1-(2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-yl)-4-hydroxybutan-1-one (17). To a stirred solution of **16** (0.495 g, 3 mmol) in polyphosphoric acid (6 mL), γ-butyrolactone (0.258 g, 0.24 mL, 3 mmol) was added, and the reactants heated at 135 °C for 24 h. The mixture was then cooled at room temperature, poured onto H_2O and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), and concentrated. Purification of the crude material residue by column chromatography (cyclohexane/EtOAc 9:1, then 1:1) gave **17** (0.036 g) as a pale brown oil, together with a consistent amount of unreacted **16** (0.294 g). Yield 12%, calculated on the reacted **16**. MS (EI): *m*/*z* 251 (M^+), 192 (100). ^1H NMR ($CDCl_3$): δ 0.92 (t, 3H); 1.34 (m, 4H); 1.60 (m, 2H); 1.94 (m, 2H); 2.21 (s, 3H); 2.55 (s, 3H); 2.73 (br d, 1H); 2.89 (t, 2H); 3.75 (m, 4H); 6.23 (s, 1H) ppm. IR ($CHCl_3$): 3393, 1636 cm^{-1}. The purity of the sample was ascertained by NMR.

Synthesis of 2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-acetylphenyl)amide (20). To a stirred, cooled (0 °C), suspension of 2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid (**19**) (0.696 g, 5 mmol) in CH_2Cl_2 (60 mL), oxalyl chloride (0.762 g, 0.52 mL, 6 mmol) was added, followed by a catalytic amount of DMF; the mixture was warmed to room temperature, stirred for 2 h, and, after addition of 1-(2-aminophenyl) ethanone (1.014 g, 0.90 mL, 7.5 mmol), stirred for another 6 h, and eventually concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 8:2, then 7:3) and recrystallization gave **20** as a white solid. Yield: 22% (0.282 g). Mp 180–182 °C (EtOH). MS (EI): *m*/*z* 256 (M^+), 122 (100). ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H); 2.59 (s, 3H); 2.70 (s, 3H); 6.39 (s, 1H); 7.07 (t, 1H); 7.56 (t, 1H); 7.90 (br s, 1H); 7.92 (d, 1H); 8.95 (d, 1H); 12.13 (br s, 1H) ppm. IR (KBr): 3308, 3276, 1653, 1641, 1608 cm^{-1}. Anal. calcd for $C_{15}H_{16}N_2O_2$ (256.30): C, 70.29; H, 6.29; N, 10.93. Found: C, 70.59; H, 6.12; N, 11.10.

Synthesis of 2,5-dimethyl-1-pentyl-1*H*-pyrrole-3-carboxylic acid (23). To a stirred solution of **22** (0.237 g, 1 mmol) in EtOH (8 mL), $LiOH{\cdot}H_2O$ (0.168 g, 4 mmol) in H_2O (2 mL) was added, and the reactants refluxed for 24 h. The mixture was then cooled to room temperature, poured onto H_2O, washed with EtOAc to remove side products, acidified with 2 N HCl, and extracted with EtOAc. The organic layers were dried (Na_2SO_4), and concentrated. Recrystallization of the residue gave **23** as a white solid. Yield: 72% (0.151 g). Mp 163–165 °C (EtOH) (with decarboxylation). MS (EI): *m*/*z* 209 (M^+), 152 (100). ^1H NMR ($CDCl_3$): δ 0.92 (t, 3H); 1.35 (m, 4H); 1.63 (m, 2H); 2.21 (s, 3H); 2.53 (s, 3H); 3.75 (t, 2H); 6.31 (d, 1H) ppm. IR (KBr): 2994-2587, 1648 cm^{-1}.

Synthesis of 2,5-dimethyl-1-pentyl-1*H*-pyrrole-3-carboxylic acid cyclohexyl amide (25). To a stirred, cooled (0 °C) solution of **23** (0.126 g, 0.6 mmol) and 1-(2-aminophenyl) ethanone (0.081 g, 0.07 mL, 0.6 mmol) in CH_2Cl_2 (6 mL), DCC (0.124 g, 0.6 mmol) was added, and the mixture allowed to react at room temperature for 24 h. After addition of EtOAc, the mixture was filtered, and the filtrate washed with $NaHCO_3$ saturated solution. The organic layer was dried (Na_2SO_4), and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 8:2) afforded pure 1,3-dicyclohexyl-2-(2,5-dimethyl-1-pentyl-1*H*-pyrrole-3-carbonyl)isourea (**24**) [MS (EI): *m*/*z* 415 (M^+), 192 (100)], which was dissolved in xylene (1.2 mL), added of Et_3N (0.6 mL), refluxed overnight under stirring, and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 8:2) and recrystallization gave **25** as pale yellow solid. Yield: 38% (0.066 g). Mp 88–89 °C (petroleum ether). MS (EI): *m*/*z* 290 (M^+), 192 (100). ^1H NMR ($CDCl_3$): δ 0.91 (t, 3H); 1.07–1.68 (m, 14H); 1.98 (m, 2H); 2.20 (s, 3H); 2.55 (s, 3H); 3.73 (t, 2H); 3.88 (m, 1H); 5.52 (br d, 1H); 5.91 (s, 1H) ppm. IR (KBr): 3318, 3254, 1612 cm^{-1}. Anal. calcd for $C_{18}H_{30}N_2O$ (290.45): C, 74.44; H, 10.41; N, 9.64. Found: C, 74.43; H, 10.51; N, 9.64.

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