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

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Received 16 April 2003; accepted 13 June 2003

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 CB1 and CB2 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 pyroles 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 CB1 and CB2 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 CB1 partial agonist properties.

Introduction

Plant-derived and synthetic cannabimimetic agents such as Δ9-tetrahydrocannabinol (Δ9-THC, 1, Fig. 1) bind to specific G-protein coupled cannabinoid receptors, which include the CB1 subtype, mainly present in the central and peripheral nervous system, and the CB2 subtype, localized on immune cells. The identification, cloning, and biochemical characterization of cannabinoid receptors, along with the discovery of their endogenous lipid ligands, have fuelled a considerable interest in the physiology and pharmacology of the cannabinergic system. Agents that modulate the activity of this system may have a broad therapeutic potential: beside acute and persistent pain conditions, additional therapeutic applications for CB1 and CB2 receptor agonists may also include stroke, glaucoma, multiple sclerosis and spinal cord injury.

Various classes of compounds active at cannabinoid receptors have been developed, and their structure–activity relationship (SAR) properties have been extensively investigated. 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 2109 (2, Fig. 1) and structurally related molecules, for example CP 55,940 (3, Fig. 1); (ii) N-aminooalkyl indoles (AAIs), for example Win-55,212-2 (4, Fig. 2) and N-alkylindoles (non-AAIs), for example JWH-007 (5a, Fig. 2). A number of compounds having an indene or pyrrole nucleus as their basic feature has been also reported. These comprise Huffman’s derivatives JWH-030 (7a) and JWH-007 (7b, Fig. 2). 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 CB1 affinity of the pentacyclic derivative JWH-161 (6, Fig. 2), a hybrid structure in which the elements of...
traditional and non-AAI cannabinoids are combined, supports the hypothesis that a common pharmacophore exists for the two main classes of ligands. According to this model, the 3-aryl substituent of indole compounds may mimic the cyclohexene ring of Δ9-THC (1), whereas the indole N-substituent and the 3-alkyl chain of traditional cannabinoids may engage in lipophilic 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 CB1, K192, is essential for the binding of CP 55,940 (3), but not Win-55,212-2 (4). 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. The CB2 subtype offers a somewhat different scenario. In this case, K109, a lysine residue corresponding to K192 in CB1, 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 Δ9-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. Again, phenylalanine to valine mutation in the TM5 domain, F5.46, decreases the binding of Win-55,212-2. It is worth noting that the CB1 receptor affinity of Win-55,212-2 is enhanced by substitution of a valine, corresponding to CB1 F5.46, for phenylalanine. Such mutations, however, did not affect the CB1 and CB2 binding of traditional cannabinoids such as HU 210 (2) and CP 55,940 (3). Together with the results of docking experiments, 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 CB2 receptors, while polar interactions through K192 and S112 may contribute to the productive binding of ‘traditional’ ligands to CB1 and CB2, respectively. The decisive role of aromatic stacking interactions for cannabinoid binding has been supported by two recent investigations.

In an attempt to extend Huffman’s observations regarding the activity of pyrrole derivatives on CB receptors, we have prepared and tested, on CB1 and CB2 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, 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 1. Representative ‘traditional’ cannabimimetic agents.](image)

![Figure 2. Representative ‘indole-based’ cannabimimetic agents.](image)

![Figure 3. Superposition of 6 (yellow carbons) to 5a (a), 11a (b), 25 (c), 10d (d).](image)
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 cannabinoids are endowed with a reduced affinity for CB1 receptor. This conclusion, however, has been inferred from the analysis of a limited number of structures, namely 4,5-unsubstituted pyrroles.20

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-substituent is a feature similar to that of diarylpyrazolic CB2 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 CB2 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-naphthoyl)pyrrole (7a).13 Thus, 12 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-pentylpyrrole25 (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-pyrrolylcarboxylic acid ethyl ester27 (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,
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 CH₂Cl₂, 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 CB₁ receptor and the recombinant human CB₂ receptors. The former assay was conducted using rat cerebellar membranes (27,000g), and the latter using membranes of Chinese hamster ovary (CHO) cells that overexpress CB₂ receptors (Receptor Biology Inc. Perkin Elmer, Wellesley, MA, USA) using [³H]Win-55212-2 (NEN-Dupont, Boston, MA, USA, 40–60 Ci/mmol, 10 nM) as a ligand. 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 CB₁, and to slightly increase the affinity at the CB₂ receptor subtypes. This trend, illustrated by compound 10a, which is 20 times more potent than 7a in CB₂ binding affinity, persists over the entire group of our 1-alkyl-3-naphthoyl pyrrole ligands which, therefore, albeit having only a moderate preference for CB₂ receptors, show a reversed CB₁/CB₂ 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 AAs with monocyclic aryl nuclei in position 3 are far less active than their 3-(1-naphthoyl) homologues. 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 CB₁ receptor subtype, able to reproduce the binding mode of the naphthoyl group. A slightly better binding affinity, at least for the CB₂ 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 CB₂ receptor, resulting in a certain degree of CB₂ selectivity, which is consistent with literature data, even though, in our pyrroles, the CB₂/CB₁ affinity ratio enhancement caused by chain shortening is not as prominent as that found in prototypic 3-aryl indole cannabimimetics. 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 CB₁,
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 (e.g., 10a vs 10d, and 11a vs 11d).

We also investigated the intrinsic activity of selected high-affinity ligands at CB1 receptors by testing their ability to stimulate [35S]GTPγS binding in rat cerebellar membranes. Figure 4 illustrates the effects of various pyrrole-based compounds on the binding of [35S]GTPγS to rat cerebellar membranes. The compound 11a stimulates [35S]GTPγS binding with an EC50 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 (open circles). Compound 11a, which stimulates [35S]GTPγS binding with an EC50 value of 324.0 ± 20.8 nM. These findings suggest that 11a and 10a are full agonist ligands at rat CB1 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 [35S]GTPγS binding with EC50 values of 186.3 ± 42.2 and 179.3 ± 69 nM, respectively, produce only a fraction of the maximal [35S]GTPγS binding stimulation induced by Win-55,212-2. Therefore, these compounds may be considered as partial CB1 agonists. These results suggest 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 CB1/CB2 selectivity; this parallels, however, the behaviour of N-pentyl cannabimimetic indoles.31 Furthermore, the testing of several compounds that have structural elements unusual in

| No. | R1     | R2     | R3     | R4     | R5     | EC50 (nM) rCB1 | EC50 (nM) hCB2 |
|-----|--------|--------|--------|--------|--------|---------------|---------------|
| 7a  | n-C5H11 | H      | 1-Naphthyl | H      | H      | 30.5 ± 4.7    | 552 ± 314     |
| 10a | n-C5H11 | CH3    | 1-Naphthyl | H      | CH3    | 45.3 ± 7.5    | 9.85 ± 2.1    |
| 10b | n-C5H11 | CH3    | m-C6H5   | H      | CH3    | > 1000        | > 1000        |
| 10c | n-C5H11 | CH3    | 1-Naphthyl | H      | CH3    | > 1000        | 309.7 ± 20.8  |
| 10d | pClC6H4CH2 | CH3 | 1-Naphthyl | H      | CH3    | 83.7 ± 17.8   | 55.6 ± 26.5   |
| 10e | pClC6H4CH2 | CH3 | m-C6H5   | H      | CH3    | > 1000        | > 1000        |
| 11a | n-C5H11 | CH3    | 1-Naphthyl | Br     | CH3    | 13.3 ± 0.5    | 6.8 ± 1.0     |
| 11b | n-C5H11 | CH3    | m-C6H5   | Br     | CH3    | > 1000        | > 1000        |
| 11c | n-C5H11 | CH3    | 1-Naphthyl | Br     | CH3    | 780 ± 326     | 691.3 ± 101.3 |
| 11d | pClC6H4CH2 | CH3 | 1-Naphthyl | Br     | CH3    | 38 ± 7.2      | 194.5 ± 27.5  |
| 15  | n-C5H11 | H      | 1-Naphthyl | (CH3)4  | H      | 235.8 ± 6.2   | 139 ± 55      |
| 17  | n-C5H11 | CH3    | HO(CH2)3 | H      | CH3    | > 3000        | > 10,000      |
| 21  | n-C5H11 | CH3    | o(CH3CO)C6H4NH | H     | CH3    | 367.3 ± 31.2  | > 1000        |
| 25  | n-C5H11 | CH3    | o-C6H11NH | H     | CH3    | 415.5 ± 79.5  | 483.5 ± 211   |

Table 1. Binding affinity values at rat native CB1 and human recombinant CB2 receptors.

In summary, our results extend previously established SARs for indole and pyrrole cannabimimetics. In particular, we identified a 3-naphthyl pyrrole 11a, which displays a binding affinity and intrinsic activity comparable to that of 3-naphthyl 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 CB1/CB2 selectivity; this parallels, however, the behaviour of N-pentyl cannabimimetic indoles.31 Furthermore, the testing of several compounds that have structural elements unusual in
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 cannabinoid receptors involved in modulating ligand efficacy.

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, Erba analyzers). TLC analyses were performed on precoated silica gel on aluminium sheets (Kieselgel 60 F254, 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 (M+ -1) are given.1H NMR spectra were recorded on a Bruker AC 200 spectrometer using CDCl3 as solvent; chemical shifts (δ scale) are reported in part per million (ppm) relative to the central peak of the solvent; coupling constants (J values) are given in hertz (Hz). IR spectra were obtained on a Shimadzu FT-8300, or a Nicolet Avatar, spectrometer; 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 package33 and their geometry was optimized using the standard Tripos force field,34 with the Powell method35 to an energy gradient of 0.01 Kcal/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 the convenient pyrrole 8, 9a,b, 14, 18, 20 (5 mmol) in dry DMF (12.5 mL) under N2 atmosphere, NaH (0.173 g of an 80% mineral oil dispersion, 5.75 mmol) was added. When H2 evolution had ceased, the opportune 1-bromoisocyanate 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-bromoisocyanate (2.88 mmol; 1.44 mmol in the case of 16) were added and the mixture again allowed to react for 1 h. CH2Cl2 and H2O were then cautiously added and the organic layer washed with H2O, dried (Na2SO4) 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,c,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-1H-pyrrol-3-yl)(naphthalen-1-yl)methanone (9a). Light-yellow crystals. Yield: 39% (1.459 g). Mp 163–164°C (EtOAc) (lit.: 165–167°C).36

(2,5-Dimethyl-1H-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 1-bromoalkane (2.88 mmol; 1.44 mmol in the case of 16) and the opportune 1-bromoalkane (5.75 mmol) was added. When H2 evolution had ceased, the opportune 1-bromoalkane (5.75 mmol) 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-bromoisocyanate (2.88 mmol; 1.44 mmol in the case of 16) were added and the mixture again allowed to react for 1 h. CH2Cl2 and H2O were then cautiously added and the organic layer washed with H2O, dried (Na2SO4) 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,c,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-1H-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 (CDCl3): 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): 1613, 1616 cm−1. Anal. calcd for C22H25NO (319.45): C, 82.72; H, 7.89; N, 4.36. Found: C, 82.76; H, 7.93; N, 4.36.

(2,5-Dimethyl-1-pentyl-1H-pyrrol-3-yl)(phenyl)methanone (10b). White crystals. Yield: 90% (1.211 g). Mp 55–56°C (after trituration with petroleum ether/Et2O 9:1). MS (EI): m/z 269 (M+ ), 100. 1H NMR (CDCl3): δ 0.94 (t, 3H); 1.36 (m, 4H); 1.67 (m, 2H); 2.22 (s, 3H); 2.59 (s, 3H); 3.80 (s, 1H); 7.42 (m, 3H); 7.79 (m, 2H) ppm. IR (nujol): 1625 cm−1. Anal. calcd for C18H23NO (269.39): C, 82.76; H, 7.93; N, 4.36. Found: C, 82.76; H, 7.93; N, 4.36.

(2,5-Dimethyl-1-propyl-1H-pyrrol-3-yl)(naphthalen-1-yl)methanone (10c). Yellow oil. Yield: 82% (1.194 g). MS (EI): m/z 291 (M+ ), 100. 1H NMR (CDCl3): 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 (CHCl3): 1627, 1618 cm−1. Anal. calcd for
(1-Chlorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl naphthalen-1-yl methanone (10d). 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-bromosuccinimide (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 CH2Cl2. The combined organic layers were washed with 2 N HCl and brine, dried (Na2SO4), 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-1H-pyrrol-3-yl)(naphthalen-1-yl) methanone (11a). White crystals. Yield: 15% (0.060 g). Mp 74–77°C (Et2O/petroleum ether). MS (EI): m/z 398 (M+), 318 (100). 1H NMR (CDCl3): δ 0.93 (3 H), 1.35 (4 H), 1.65 (m, 2 H), 2.22 (3 H), 2.31 (3 H), 3.82 (3 H), 7.52 (4 H), 7.87 (4 H), 8.22 (m, 2 H) ppm. IR (nujol): 1627, 1618 cm⁻¹. Anal. calculated for C22H23BrNO: C, 77.07; H, 5.59; N, 3.48.

(4-Bromo-2,5-dimethyl-1-pentyl-1H-pyrrol-3-yl)(phenyl)methanone (11b). White crystals. Yield: 22% (0.077 g). Mp 80–81°C (Et2O/petroleum ether). MS (EI): m/z 348 (M+), 105 (100). 1H NMR (CDCl3): δ 0.94 (3 H), 1.37 (m, 4 H), 1.65 (m, 2 H), 2.24 (3 H), 2.28 (3 H), 3.82 (3 H), 7.24 (m, 4 H), 7.77 (m, 2 H) ppm. IR (nujol) (1617 cm⁻¹. Anal. calculated for C16H23BrNO: 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-1H-pyrrol-3-yl)(naphthalen-1-yl)methanone (11d). White crystals. Yield: 41% (0.186 g). Mp 119–121°C (subl.) (CH2Cl2/petroleum ether). MS (EI): m/z 372, 125 (100). 1H NMR (CDCl3): δ 0.94 (3 H), 1.37 (m, 4 H), 1.65 (m, 2 H), 2.24 (3 H), 2.28 (3 H), 3.82 (3 H), 7.24 (m, 4 H), 7.77 (m, 2 H) ppm. IR (KBr): 1628 cm⁻¹. Anal. calculated for C16H23BrNO: 348.28 C, 62.08; H, 6.37; N, 4.02. Found: C, 63.16; H, 6.19; N, 3.10.

Synthesis of (4-bromo-2,5-dimethyl-1-propyl-1H-pyrrol-3-yl)(naphthalen-1-yl)methanone (11c). To a stirred solution of 10c (0.293 g, 1 mmol) in CH2Cl2 (6 mL) N-bromosuccinimide (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) 2 N NaOH solution, and extracted with CH2Cl2. The combined organic layers were washed with 2 N HCl and brine, dried (Na2SO4), 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 (CDCl3): δ 0.99 (3 H), 1.70 (m, 2 H), 2.22 (3 H), 2.31 (3 H), 3.80 (t, 2 H), 7.51 (m, 4 H), 7.91 (m, 2 H), 8.23 (m, 1 H) ppm. IR (neat): 1634 cm⁻¹. Anal. calculated for C20H19BrNO: 0.5C6H12 (391.33): C, 65.99; H, 5.92; N, 3.58. Found: C, 65.65; H, 5.70; N, 3.64.

Synthesis of (1-benzensulfonyl-4,5,6,7-tetrahydro-1H-indol-3-yl)(naphthalen-1-yl)methanone (13). To a stirred solution of AlCl3 (0.320 g, 2.4 mmol) in CH2NO2 (1.6 mL), a solution of 4,5,6,7-tetrahydro-1-phenylsulphonylindole (12) (0.523 g, 2 mmol) in CH2Cl2 (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 H₂O and extracted with CH₂Cl₂. The combined organic layers were washed with 5% aqueous NaHCO₃, dried (Na₂SO₄), 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 (CDCl₃): 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-1H-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 5.8 mixture of H₂O and MeOH (3 mL) was refluxed for 20 h, and then concentrated. The residue was dissolved in H₂O/CH₂Cl₂, and the organic layer cautiously washed with 2N HCl, dried (Na₂SO₄), 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 (CDCl₃): 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 (KBr): 3318, 3254, 1612 cm⁻¹. Anal. calcd for C₁₉H₁₇NO 1.80 (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-1H-pyrrole-3-carboxylic acid (23). To a stirred solution of 22 (0.237 g, 1 mmol) in EtOH (8 mL), LiOH·H₂O (0.168 g, 4 mmol) in H₂O (2 mL) was added, and the reactants refluxed for 24 h. The mixture was then cooled to room temperature, poured onto H₂O, washed with EtOAc to remove side products, acidified with 2N HCl, and extracted with EtOAc. The organic layers were dried (Na₂SO₄), 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 (CDCl₃): 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.

Acknowledgements

This work was supported by grants from MIUR (Ministero dell’Istruzione, dell’Università e della Ricerca); Universities of Parma and Urbino; and the National Institute of Drug Abuse (S.K. and D.P.). The CCE (Centro di Calcolo Elettronico) and CIM (Centro Interfacolta Misure) of the University of Parma are gratefully acknowledged for supplying the Sybyl software. Thanks are due to Dr. Giuseppe Gatti for assistance with NMR characterization of compound 21.
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19. In order to ascertain this hypothesis, additional 1H NMR experiments were carried out on compound 21 in CDCl3 solution. The amide proton resulted considerably deshielded (δ 12.10), showing that it is involved in a hydrogen bond. Moreover, the observed NH chemical shift was independent on the concentration in the 0.4–12 μM range, suggesting a purely intramolecular lock of the NH proton to the carbonyl of the 2'-acetoyl group. Finally, concerning the strength of the bond, we measured the temperature coefficient of the chemical shift, Δδ/ΔT: the observed value of –0.003 ppm K–1 (CDCl3 solution, in the 298–328 K temperature range) is typical of a very strong intramolecular hydrogen bond: (a) Urry, D. W.; Ohnishi, T. In Peptides, Polypeptides and Proteins; Blout, E. R., Bovey, F. A.; Goodman, M. and Lotan, N., Eds.; Wiley-Interscience: New York, 1974; p 230. (b) Urry, D. W.; Long, M. M. CRC Crit. Rev. Biochem. 1976, 4, 1. (c) Gehlin, S. H.; Dado, G. P.; Liang, G.-B.; Adams, B. R. J. Am. Chem. Soc. 1991, 113, 1164.
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The above text is a list of references and notes, likely from a scientific document, detailing various studies and experiments related to biological chemistry. It includes references to specific compounds, their properties, and the conditions under which they were studied. The text is in English and is formatted in a standard academic style, with citations to support each point. The references cover a range of topics, from chemical synthesis to pharmacological effects, and are cited using the numerical referencing system. The notes provide additional context and details, such as experimental conditions and methodologies. The text is a valuable resource for researchers in the field of medicinal chemistry and related sciences.