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CORSO DI DOTTORATO DI RICERCA IN
SCIENZE CHIMICHE E SCIENZE FARMACEUTICHE

CICLO XXIX

DESIGN AND SYNTHESIS OF NOVEL CANNABINOID RECEPTOR LIGANDS

(lavoro integrativo alla tesi svolto durante il periodo di dottorato)

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Introduction

Cannabis is one of the most versatile plants used by human beings both in religious rituals and in medicine.[1] Although already known for centuries under various names, Linnaeus first had given it the name *Cannabis sativa*. On the basis on significative morphological differences, today the plant is distinct into three species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis* (Figure 1).[2]

Figure 1. Illustration of the different species of cannabis. (From Stafford P, Bigwood J, *Psychedelics Encyclopedia*, Berkeley, CA, Ronin Pub., 1992, p.159)

Different populations, over the centuries, cultivated and utilized it for various fields and O'Shaugnessy led first in vivo toxicity and efficacy studies.[3]

With the exception of studies about antibiotic properties for topical cannabinoids,[4] pharmacological studies on cannabis stayed there until 1964, when the most active constituent of the plant, Δ^9-tetrahydrocannabinol (Δ^9-THC), was discovered and isolated.[9] Δ^9-THC was found in the resin, produced by female inflorescences and for this reason with psychoactive properties, up to 15-20%.[5] The plant, and in particular its resin, contains at least 60 cannabinoids, the chemical

structure of which can be described as a dibenzo[*b*,*d*]pyran, considered as chemical "type":[6] cannabigerol type (CBG), cannabichromene type (CBC), cannabidiol type (CBD), Δ^9-THC type, Δ^8-THC type, cannabinol type (CBN), cannabicyclol of cannabitriol type, and tetrahydrocannabivarin (THCV) (Figure 2).

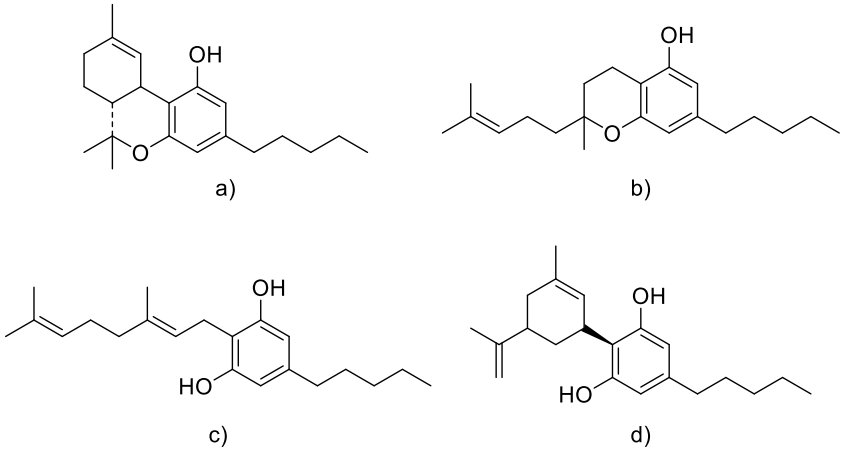


Figure 2. Phytocannabinoids from *Cannabis sativa*: (a) Δ^9-tetrahydrocannabinol, (b) cannabichromene, (c) cannabigerol and (d) cannabidiol.

However, the resin, besides to cannabinoids, contains more than 100 terpenoids and more than 20 flavonoids. Following isolation, characterization and stereochemically definition of Δ^9-THC in 1964, the endocannabinoid system (ECS) was discovered. The ECS as an important neuromodulatory system in the brain involved in a variety of physiological processes such as the development of the central nervous system (CNS), motor control, synaptic plasticity, neuroprotection,[7] regulation of the immune system,[8] nociception, regulation of food intake and energy balance.[9] ECS consists of endogenous cannabinoids [such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are the main endocannabinoids], cannabinoid receptors (CB_1 and CB_2) and enzymes responsible for the synthesis and degradation of endocannabinoids, including amide of fatty acid amide hydrolase[15] (FAAH) and monoacylglycerol lipase (MGL), that have been demonstrated to be the main

enzymes (Figure 3). The signal within this system, unlike the classic neurotransmission systems, is of retrograde type.[10]

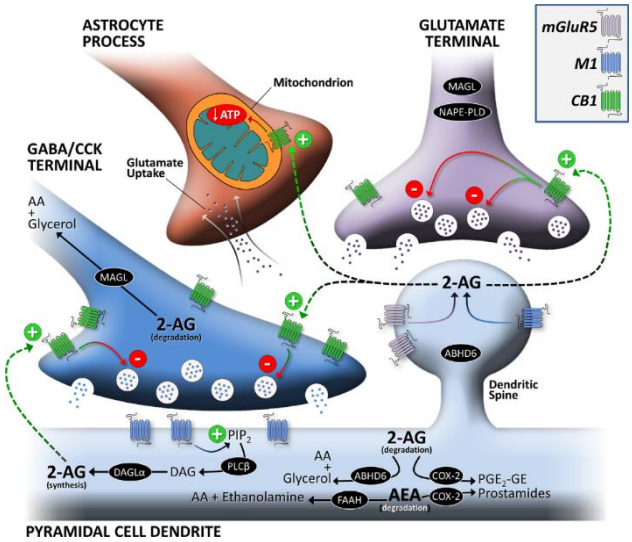


Figure 3. Overview of the localization of endocannabinoid system components at the synapse. (From: Lu HC et al, *Biol. Psychiatry*, **2016**, *79*, 517).

Regulatory effect by ECS on functions and homeostasis are modulated by CB_1 and CB_2 receptors. Both receptors belong to the large family of GPCRs,[11] with seven transmembrane domains connected by three extracellular and three intracellular loops, an extracellular N-terminal tail, and an intracellular C-terminal tail.[71] N-terminal extracellular domain possesses the sites of glycosylation, an intracellular C-terminal domain which is coupled the G protein complex and seven transmembrane α-helical regions, which bind to a wide range of ligands. The two receptors share the 44% of the amino acid sequence, demonstrating that it did not differentiated at the late stage, and an overlap of 68% at binding domains, which unfortunately makes it difficult to identify selective ligands for only one of the two receptors.[12]

CB_1 and CB_2 receptors perform their action through different cellular pathways, such as cAMP-PKA pathway,[13] PI3K-AKT pathway and kinases, in

particular the mitogen-activated protein kinase (MAP),[14] so that the activation of one receptor is able to inhibit adenylate cyclase and to activate MAP kinase.

CB_1 receptor was discovered in 1988,[15] following numerous studies on psychoactive component of Δ^9-THC. It is very abundant in the CNS, as it is found in the cortex, basal ganglia, hippocampus and cerebellum,[16] and moderate receptor levels are also present in periphery (adrenal gland, heart, lung, prostate, testis, bone marrow, thymus and spleen).[17] Its activation is responsible of the psychoactive effects associated with cannabinoids: euphoria, drowsiness, short-term memory loss, decreased motor skills, lack of concentration and disorientation;[18] at physiological level it is responsible for the modulation of cognitive processes, memory and sensory functions.

In 1992, three years after sequencing of human CB_1 receptor gene, from a collection of *c*DNA generated from a cell line of leukemia (HL60: human promyelocytic leukemia cell), CB_2 was identified,[12] which widely distributed in peripheral tissues, especially in those of immune system. Its expression was found in spleen, tonsils, thymus, in mast and blood cells,[19] suggesting that its average trigger the production and migration of cytokines, making it an excellent target for the control of pain and of inflammation.[20] Although present in lesser extent than the CB_1 in the CNS, the CB_2 is also found in both microglia both in vascular tissue,[21] and is expressed in some neurons as a result of certain pathological conditions, such as events linked to schizophrenia.[22]

With the identification of its endogenous mediators, it was possible to make sense of the concept of endocannabinoid system.[23,24] Endocannabinoids are biologically active fatty acids, among which, as previously mentioned, the most

studied are the AEA and 2-AG. In addition, unsaturated ethanolamines were described, including 2-arachidonyl glyceryl ether (noladin ether, 2-AGE), of considerable interest for its activity of CB_2 full agonist,[25] the virodhamine and *N*-arachidonoyldopamine (NADA) that bind both receptors CB[26,27]. In most of the physiological and pathological perturbations of the cell steady-state in which its function has been studied to date, the ECS has been shown to play a pro-homeostatic role, facilitated by the fact that endocannabinoids are local mediators that can be biosynthesized and released on demand and thus activate their targets only when and where needed, and, finally, absorbed into the cells via a putative transporter called AEA membrane transporter (AMT), although their lipophilic nature allows them to pass through the cell membrane.[71] As a consequence, tissue endocannabinoid levels are very often altered, and the activity of their targets modified, in nearly all chronic disorders, as an adaptive response aimed at restoring homeostasis or as a maladaptive mechanism eventually contributing to disease symptoms or progress. Thus, pharmacological manipulation of endocannabinoid levels and/or CB_1, CB_2 and TRPV1 activity, in one direction or the other (i.e. with potentiation or counteraction of endocannabinoid tone), often produces beneficial effects in animal models of diseases.[72]

A remarkable variety of cannabinomimetic molecules were designed and synthesized as a result of new knowledge on endocannabinoid system. With reference to the scaffold of the major classes, synthetic cannabinoids prepared until now can be in:[28] a) adamantane-derived indoles, b) aminoalkylindoles (AAIs), c) benzolinindoles, d) cyclohexylphenol, e) dibenzopyrans (cannabinoids “classics”, CCs), f) indazoles, g) naphthoylindoles, h) naphtylmethylindoles, i)

naphtylmethylindanes, j) naphtoylpyrroles, k) phenylacetylindoles and l) tetramethylcyclopropyl-ketoindoles (Figure 4).

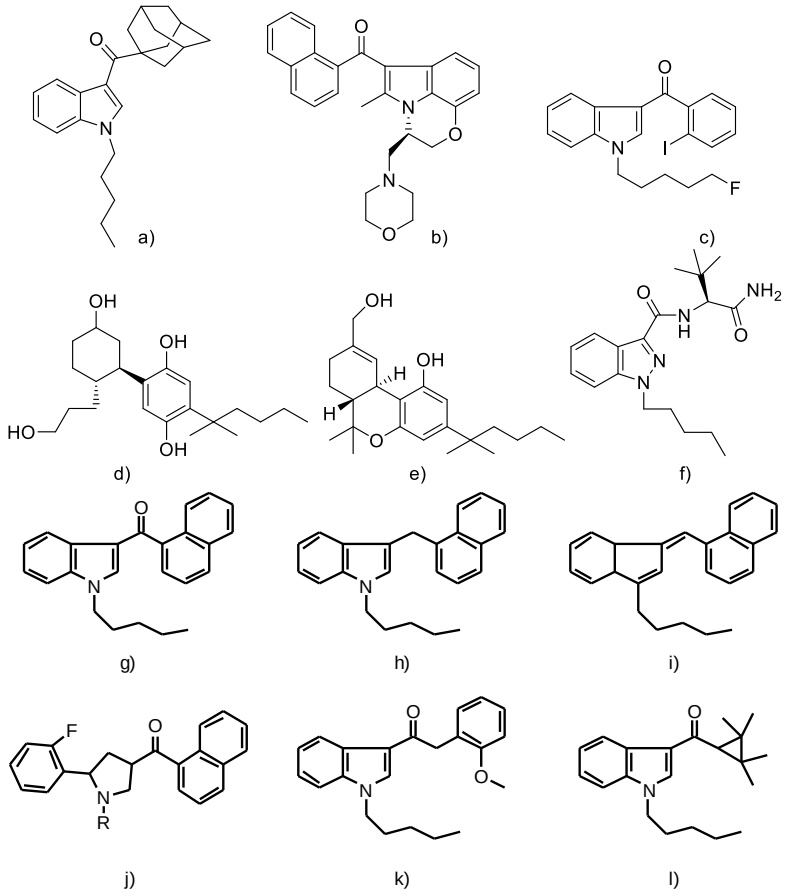


Figure 4. Main classes of synthetic cannabinoids. a) AB-001; b) WIN 55,212-2; c) AM694; d) CP 55,940; e) HU-210; f) ABD-PINACA; g) JWH-018; h) JWH-175; i) JWH-176; j) JWH-307; k) JWH-250; l) UR-144. (From: Castaneto, M. et al, *Drug Alcohol Dependence*, **2014**, *14*, 144).

In addition to the mentioned chemical classes, there are many others with considerable therapeutic interest, such as the class of diarylpyrazoles, which prove to be antagonists of the CB_1 receptor. The major limitation in the therapeutic use of non-selective cannabinoid agonists is the occurrence of psychotropic effects, which are thought to be mediated almost exclusively by the activation of the central CB_1 receptors. Therefore, selectively targeting the CB_2 receptor is one of the proposed strategies to avoid these effects and improve the benefit-to-risk ratio of such molecules.[78] Highly selective CB_2 agonists, therefore, could prevent the adverse

effects mediated by CB_1 and in order to find compounds potentially suitable for the treatment of a large number of diseases and pathological conditions such as pain,[29] neuroinflammatory conditions,[30] cardiovascular disorders, gastrointestinal disorders,[31] bone disorders[32] and cancer.[33] CB_2-selective agonists include: the synthetic "classic" cannabinoid JWH-133,[34] the bicyclic cannabinoidic analogous HU-308,[35] *N*-aminoalkylindole AM1241,[36] pyrimidines carboxamide derivative GW842166X[37] and GW833972A,[38] 5-azaindole GSK554418A,[39] the 2,2,3,3-tetramethylcyclopropanecarboxylic acid A-836339,[40,41] and dihydroindeno[1,2-c] pyrazole-3-carboxamide NESS-400,[42,43] quinoline-2,4(1H,3H)-dione derivatives,[73] proline based compounds,[75] (*S*)-piperidine compounds,[77] which have to date one of the highest affinity and selectivity discovered (Figure 5).

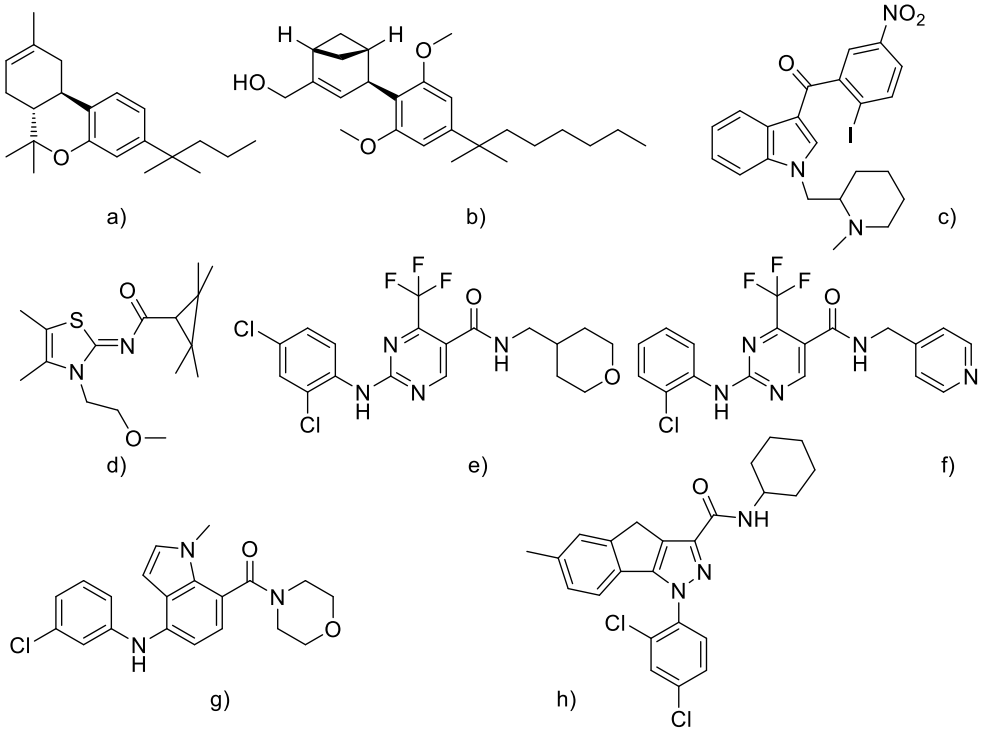


Figure 5. CB_2-selective agonists. a) JWH-133; b) HU-308; c) AM1241; d) A-836339; e) GW842166X; f) GW833972A; g) GSK554418A; h) NESS-400.

From the pharmacological point of view, CB_2 agonists demonstrate various ways of interacting with the receptor site, suggesting different binding and functional properties well represented by pharmacodynamic concepts of full, partial and inverse agonism.[74]

There is thus a considerable interest in the development of potent CB_2 receptor neutral antagonists: high-affinity ligands that lack significant agonist or inverse. The therapeutic potential of the cannabinoids has encouraged the development of several CB_2 receptor selective inverse agonists.[78] In particular, the immunomodulatory activities associated with cannabinoid CB_2 receptor inverse agonists have been demonstrated by oral administration of the inverse agonists JTE-907 and SR144528 (Figure 6).

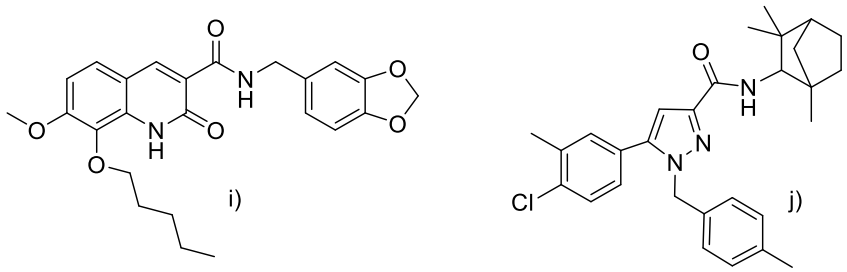


Figure 6. Chemical structures of representative CB_2 inverse agonists.

Recently, novel tricyclic pyrazoles containing a cyclopropyl or a cyclohexyl substituent were synthesized to evaluate their influence towards CB_2 receptor affinities and showed the structural requirements stated for the binding of antagonist compounds to the human CB_2 receptor.[76]

Based on SAR developed lately, Martin and coworkers[44] have proposed that the pharmacological properties unique to the cannabinoid class of drugs are produced by the interaction of Δ^9-THC with specific receptors, while cannabinoid-induced

CNS depression is a general phenomenon produced by nonspecific membrane interactions.[44]

A three point receptor model for cannabinoids has been suggested,[45] which has been modified by calculations which define a receptor essential volume for the cannabinoid receptor.[46] Inherent in all approaches to the structural requirements for cannabinoid activity is the presence of a phenolic hydroxyl group at C-1, and a lipophilic side chain at C-3.[45,46]

It turned out, however, less clear what was the location of these points of interaction within the class of AAIs, developed by researchers at Sterlin-Winthorp, because several cannabimimetic aminoalkylindoles have been described which bear no obvious structural resemblence to other active cannabinoids.[47]

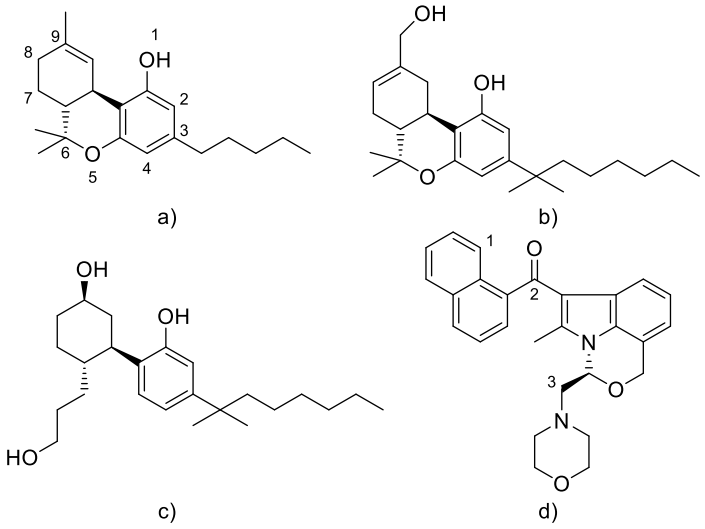


Figure 7. a) Δ^9-THC; b) HU-210; c) CP 55,940; d) WIN-55,212.

The most active of these indoles is WIN-55.212 (compound d, Figure 6), which acts in vitro at the same binding site as Δ^9-THC [47] and shows in vivo activity in the mouse model, which is comparable to Δ^9-THC (compound d, Figure 7). In addition, with refence to Δ^9-THC (CB_1 K_i = 41 nM, CB_2 K_i = 36 nM), WIN-55,212-2

has better affinity for CB_2 (K_i = 0,28 nM) and CB_1 (K_i = 1,89 nM), acting as agonist in vitro assays.

Indole WIN-55,212 does not contain a phenolic hydroxyl, nor is it obvious which portion of this molecule corresponds to the lipophilic side chain present in active cannabinoids described previously.[48]

To reconcile the structural features inherent in WIN-55,212 with those of more traditional cannabinoids, and perhaps to develop other cannabimimetic indoles, Huffman et al. proposed that morpholine unit of WIN55,212-2 corresponds with pentyl side chain of Δ^9-THC.[48] With the aim to evaluate this theory, they synthesized a series of compounds 1-alkyl-2-methyl-3-(1-naphthoyl)indoles (**4**) and a series of 3-acyl-2-methyl-l-(4-morpholinoethyl) derivatives (**5**): when the structures are superimposed, the side chain of the cannabinoids and the nitrogen substituent of the indole correspond well with each other (Figure 8).

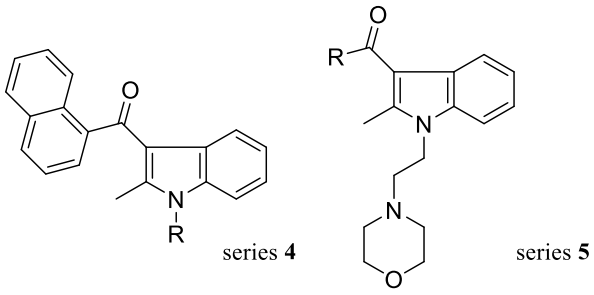


Figure 8. Analogous of WIN 55,212-2.

Series **5** was found to be free of activity, and it has shown that a cyclic amino group on the N-1 is not necessary for the activity. The replacement with a *n*-pentyl group led to JWH-018 (compound a, Figure 9), with a better affinity towards the CB_1 receptor (K_i = 9 nM) and good power in the tetrad tests.[49] This is what is discussed with the provisions of the SAR of the classical and bicyclic cannabinoids, in which

the length and branching of the carbon chain at C-3, that it was assumed corresponded to the substituent on the nitrogen of AAIs, it is able of influencing CB_1 affinity and in vivo potency.[49]

Subsequently, following Huffman et al. studies and in order to extend SARs, a large series of indole and pyrrole were synthesized.[49] On analyzing the overlaid structures of Δ^9-THC and these indoles, it was clear that benzenoid ring of the indole did not correspond with any of the atoms in the Δ^9-THC structure.[49] To test this hypothesis it was proposed an analogous series of pyrroles that led to compounds with affinity for the CB_1 and significantly reduced power receptors, except for the *n*-pentylpyrrole.[56] JWH-030 it is the only one of the pyrrole series to possess a reasonable affinity (K_i = 87 nM), although low power (>70 µM/kg) (compound b, Figure 9).[48]

With regard to CB_2 subtype, the situation appears completely different. In fact, the mutation of the aminoacid residue K109, does not appear to be essential for the binding of any of the above two classes, unless the mutation is not overlapped the serine residue 112 (double mutation K109A/S112G), thus causing a total loss of binding for the Δ^9-THC and CP 55,940 but not for WIN-55,212-2 and its analogous indole JWH-015 (Figure 10 c).

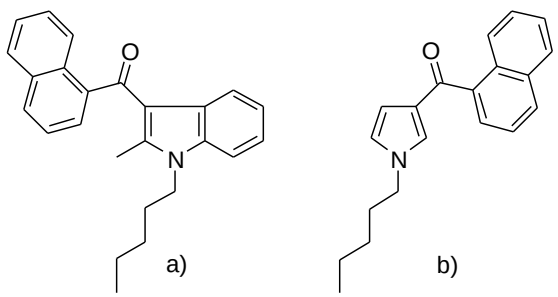


Figure 9. a) JWH-018, b) JWH-030.

In addition to the above-mentioned studies,[48] an increasing number of compounds with indole, indene or pyrrole ring were synthesized. Although it was very clear about the SAR of cannabinomimetic agents with indole structure, just as had been done with regard to those with pyrrole structure.

Since the 2000s, Tarzia et al.[50] developed a series of pyrrole derivatives, variously substituted in positions 1, 2 and 4,[49] to obtain novel selective ligands towards the CB_2 using both the results previously obtained with this chemical class[48] and the definition of the key aminoacids necessary for the interaction with CB receptors. In fact, as a result of receptor mutation studies, it was clarified that lysine^{192} (K192) residue might be important for the binding of cannabinoids, present in the third transmembrane domain (TM3) of CB receptors might be important for ligand recognition, was certainly necessary for the binding of compound CP 55,940 but not for WIN-55.212-2 (Figure 7).[51]

With regard to the CB_2 receptor, the situation is completely different. In fact, the mutation of the aminoacid residue K109, corresponding to Lys^{192} of CB_1 receptor, does not appear to be essential for the binding of any of the above two classes. The serine residue, unique to the CB_2 receptor, was then mutated to glycine in the K109A mutant. This double mutant, K109A/S112G, retains the ability to bind aminoalkylindoles but loses affinity for classical cannabinoids. Distinct cellular localization of the mutant receptors observed with immunofluorescence also suggests differences in receptor function.[52] In particular, receptor docking studies revealed that in CB_1 versus CB_2, CP-55,940 is oriented differently in the binding pocket. The results of these studies[52,53] suggest that, for this class of compounds, are established interactions of the aromatic group of the receptor in a region not occupied by the

traditional ligands, but responsible of the binding of WIN-55.212 or related compounds to the CB_2 receptor, also highlighting the importance of aromatic stacking interaction in the mechanisms of receptor binding.

Therefore, the pyrrole series was designed following as lead compound the hybrid ligand JWH-161 (a), with the indole JHW-007 (b), so that the naphthoyl group (Figure 10) could correspond to cyclohexene of cannabiminometic (a) (Figure 10 and Figure 11).

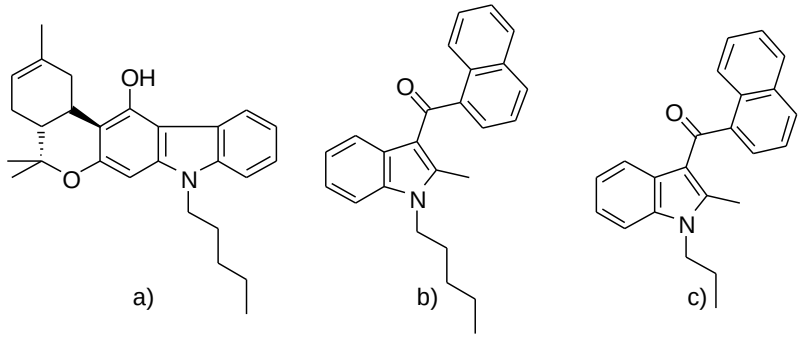


Figure 10. a) JWH-161; b) JWH-007; c) JWH-015.

The replacement of naphthoyl group in C-3 position in pyrrole series was necessary in order to obtain information about the importance of the presence or not of this group in the ligand. It was therefore decided to replace this group with others who could adapt to the receptor in a similar way, as *N*-(2-acetylphenyl)carboxamide (a), or with a fragments capable of mimic the ring A of the classical cannabinoids, such as *n*-cyclohexyl carboxamide (b).

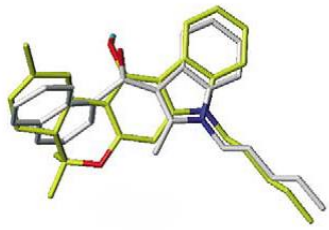


Figure 11. Superposition of JWH-161 (yellow carbons) e JWH-007 (grey carbons). (From: Tarzia G et al, *Bioorg & Med Chem*, **2003**; *11*, 3966).

The analogues designed have shown, however, a marked decrease of affinity, losing it completely when naphthoyl group was substituted with one alcohol, so that this could interact with the same receptor site to which they bind the residual hydroxyl of the classical cannabinoids (c) (Figure 12).

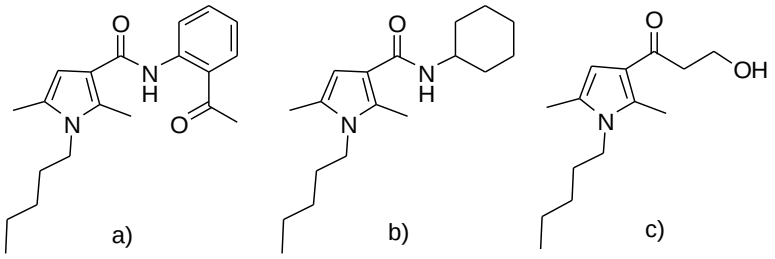


Figure 12. Analogues of naphthoyl group.

This part of the molecule was then replaced with a benzyl group (compounds b and f) that, as already noted for the class of amminoalchilindoles, it resulted harmful for the affinity.[54] Regarding other portions explored, substitution at position 4 can cause different effects based on the chosen group; while a bromine atom produces a weak increasing of affinity for both receptors (compound e), the introduction of a cycle between positions 4 and 5 of the pyrrole is responsible of the opposite effect (compound i). (Figure 13).

Another crucial region for binding to the receptor was represented by the substitution on the pyrrole nitrogen, for which a change of the length of hydrocarbon chain of the substituent or the presence of aromatic substituents would allow to obtain information about the steric tolerance of the receptor. *N*-pentyl derivatives (compounds a and e) are slightly less potent than the corresponding analogues *n*-propyl (compounds c and g), but more selective against CB_2 receptor. Instead, replacements of the linear alkyl chain with groups of different nature, either steric or electronic, such as *p*-chlorobenzene, means that the affinity for CB receptors and

power do not change (d and h compounds), even further to the introduction of a bromine atom in position 4 (see a vs d, e vs h), as instead happens in *n*-alkylpyrrole derivatives.

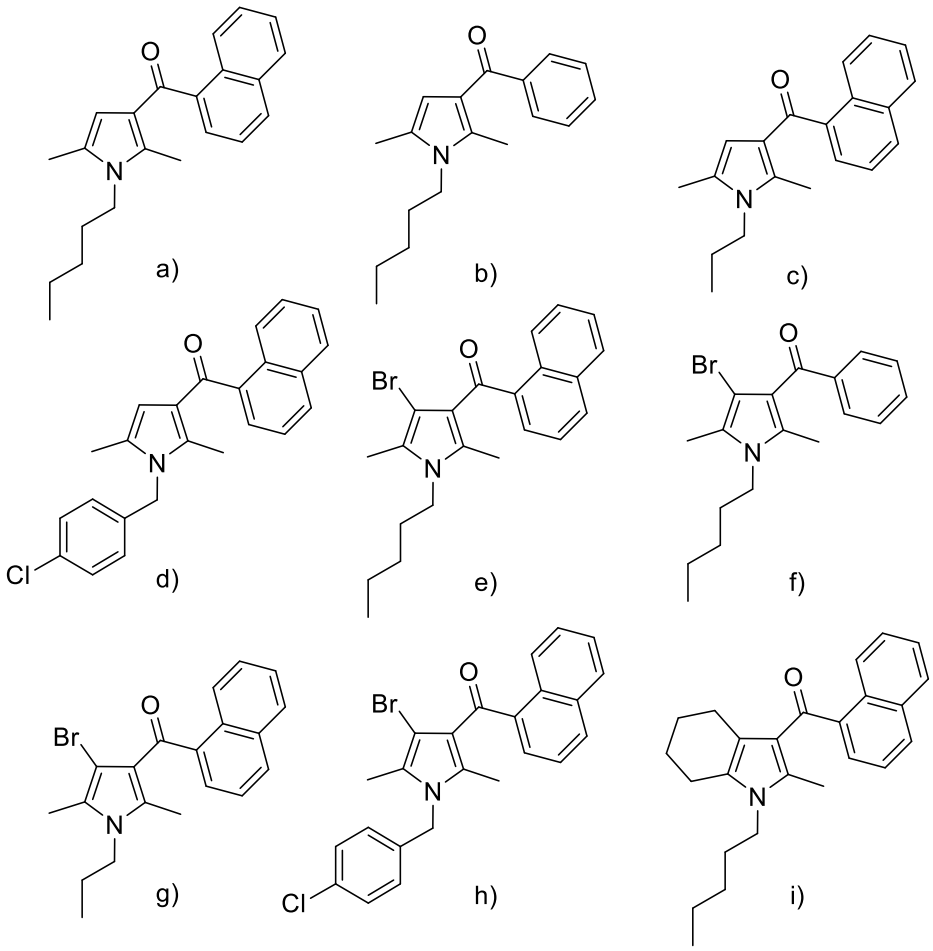


Figure 13. Pyrroles analogues.

This study, therefore, allowed to strengthen further the SAR for the pyrrole class, also suggesting how, in the conversion from naphthoylindoles to naphthoylpyrroles, the presence of a suitable lipophilic substituent can offset the loss of the benzene portion in the indole. In addition, the fact that the compound d behaves as a partial agonist suggests that the substituent on the nitrogen in this series of compounds can interact with an area of the receptor involved in the modulation of the affinity of binding.

Following the results obtained with the series of 2,5-dimethyl-3-ketopyrroles[54] and basing on the affinity obtained by compounds a, d and e (Figure 13) and on the selectivity obtained from the compound a (CB_1/CB_2 = 4.6), it was decided to design and synthesize compounds potentially active as agonists/antagonists CB_2 peripheral. The strategy chosen was to provide selective ligands for CB_2 receptors and to optimize them to get a good cLogP = 3÷5 e tPSA ≥ 50. Topological polar surface area (tPSA) makes use of functional group contributions based on a large database of structures, and it is a convenient measure of the polar surface area that avoids the need to calculate ligand 3D structure or to decide which is the relevant biological conformation or conformations.[79] Assuming that the variation/enlargement of the naphthoyl portion of the molecule is important in order to obtain the abolition of the affinity towards CB_1 receptor, it was decided to incorporate the same variations at the C-3 in the four series of pyrrole derivatives chosen, represented by the following substitution in the *n*-1: a) *n*-pentyl; b) *n*-propyl; c) *p*-chlorobenzyl; d) morpholinoethyl.

Of all compounds synthesized in the series, just some can be considered CB_1/CB_2 ligands. In particular, it appears that the most promising compounds are characterized by a *n*-pentyl group and a 3-ketoaryl or 3-ketoarylalkyl one. The reference compound selected as starting point for further investigations and for parameters optimization was URB1256, that showed selectivity towards CB_2 receptor. Therefore, in order to optimize the lead compound URB1256, some possible analogues were studied (Figure 15).

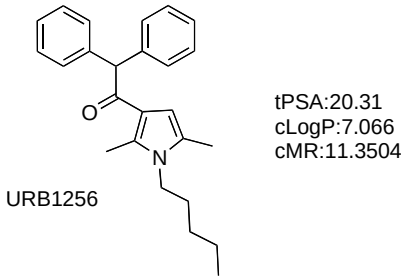


Figure 14. Chemical structure of **URB1256**.

The proposed structures could provide further information concerning the importance of the 3-position of the pyrrole ring. Moreover, these novel pyrroles show higher calculated cLogP and lower tPSA respect of URB1256. For this reason the molecules in Figure 15 could have a low penetration of the blood brain barrier (BBB) and could be given by oral administration.

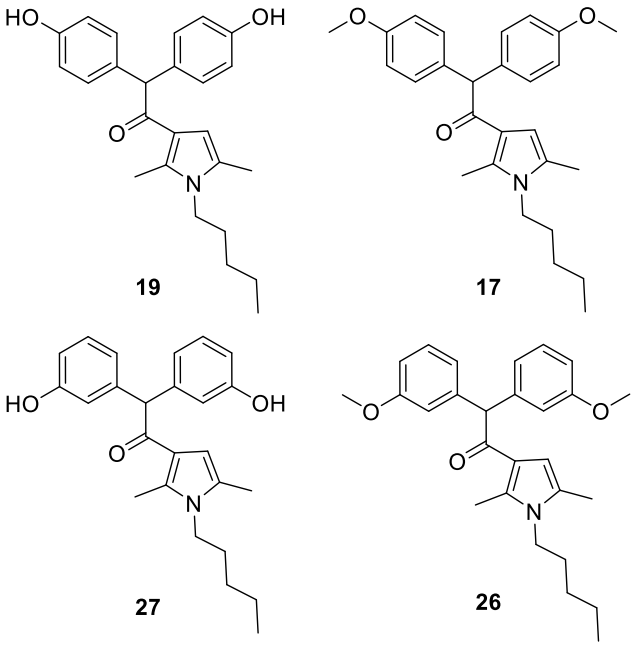
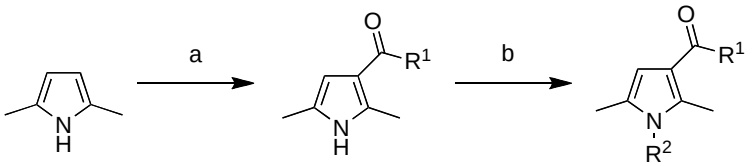


Figure 15. Possible analogues of URB1256.

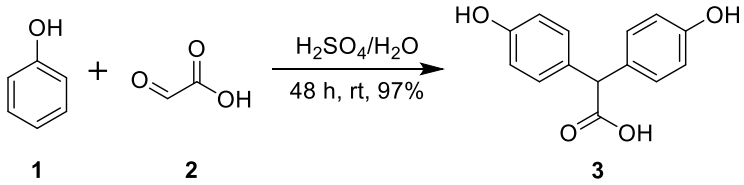
Results and discussion

Compound **17**, **19**, **26** and **27** were synthesized following the Scheme 1[54] that provides for the following steps: 1) Friedel-Crafts acylation of 2,5-dimethylpyrrole, after synthesis of the appropriate aryl chloride; 2) alkylation of the nitrogen atom.



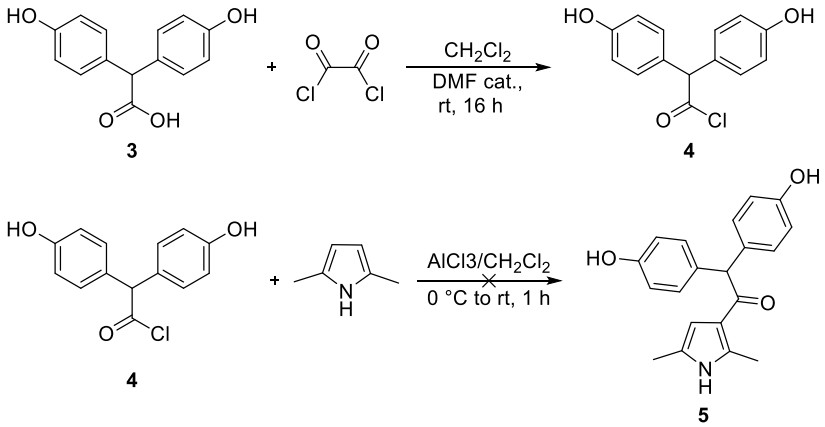
Scheme 1. Reagents and conditions: (a) $R^1C(O)Cl$, $AlCl_3$, CH_2Cl_2, 25 °C, 0.25-2 h; (b) NaH, DMF, *n*-alchilBr, 25 °C, 3 h. (From: Tarzia G. et al., *Bioorg Med Chem*, **2003**, *11*, 3967).

To synthesize compound **17**, it was firstly prepared non-commercial available aryl 2,2-(4-hydroxyphenyl) acetic acid **3** as described in Scheme 2.



Scheme 2. Synthesis of compound **3**.

3 was obtained by condensation of phenol **1** and glyoxylic acid **2** with sulfuric acid and water,[55] then treated with oxalyl chloride[56] and dimethylformamide in catalytic amount to obtain the corresponding acyl chloride **4** that was instantly added to a solution of 2,5-dimethylpyrrole and aluminium chloride (Scheme 3).[51]



Scheme 3. First attempt of Friedel-Crafts acylation.

Unfortunately, the Friedel-Crafts acylation did not proceed, probably due to the high reactivity of phenols mojety present in the acyl chloride.

Therefore, **3** was protected with several groups as shown in Figure 16.

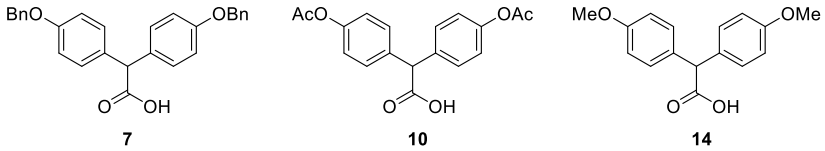
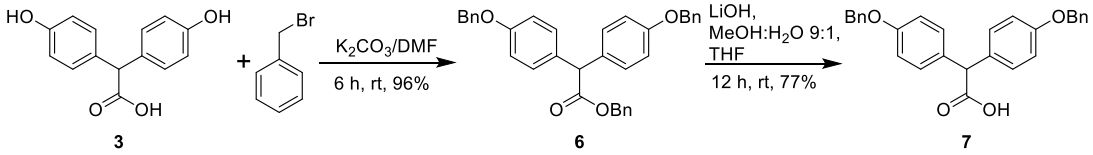


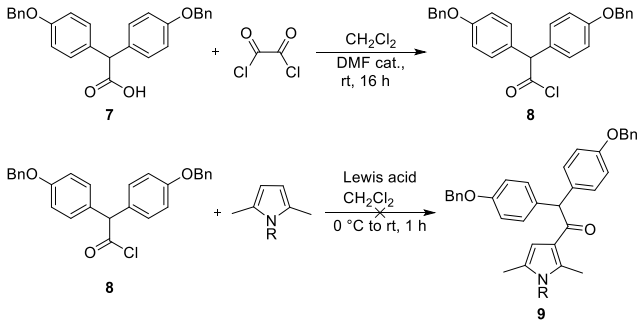
Figure 16. Protection of **3**.

O-Benzyl protected phenol **7** were synthesized as described in Scheme 4.



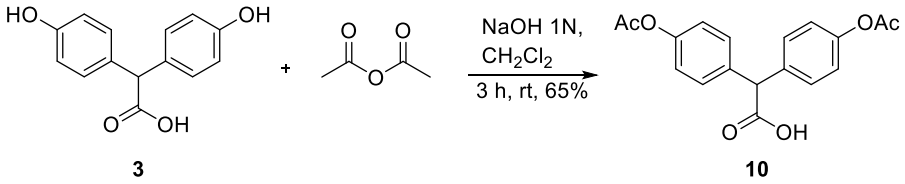
Scheme 4.

Compound **3** was treated under argon atmosphere with potassium carbonate and benzyl bromide[57] in anhydrous dimethylformamide to obtain the intermediate **6**. Benzyl ester **6** was hydrolized with methanol/water in ratio 9:1, lithium hydroxide, into a solution of tetrahydrofuran for 12 h at room temperature (Scheme 4) to give the desired acidic product **7**.[58] **7** was then treated to obtain the corresponding acyl chloride **8** with oxalyl chloride in dichloromethane and dimethylformamide catalytic amount for 16 h. Thus, **8** was added to a solution of 2,5-dimethylpyrrole in the presence of a Lewis acid. Aluminum chloride or diethylaluminium chloride were used as catalysts during the Friedel-Crafts acylation, but unsuccessfully (Scheme 5).



Schema 5. Friedel-Crafts acylation with -OBn groups. R = H, *n*-pentyl.

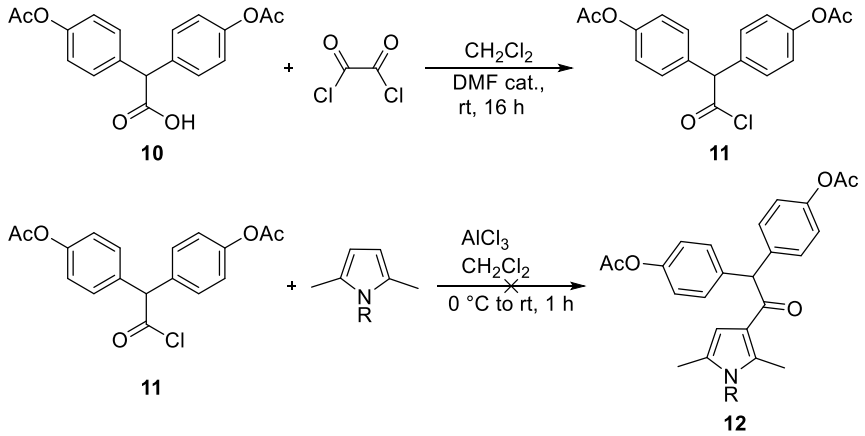
Moreover, this reaction was carried out both with NH-free pyrrole and with 1-pentylpyrrole, but the acylation did not proceed, probably because of the steric hyndrance of benzyl esters. Therefore, phenols were protected with acetyl groups (Scheme 6).[58]



Scheme 6. Acetylation of **3**.

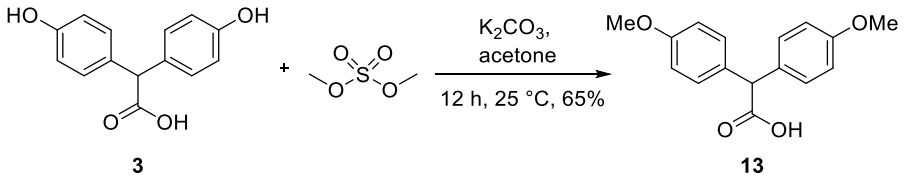
To give 2,2-bis(4-acetoxyphenyl)acetic acid (**10**), compound **3** was treated with a solution of acetic anhydride, sodium hydroxide 1N and dichloromethane.

10 was converted to the corresponding acyl chloride **11**, as described above, that was directly added to a solution of 2,5-dimethylpyrrole derivative in the presence of aluminium chloride (Scheme 7). The acylation reaction has not led to the expected product, probably because of the formation of complexes between aluminium chloride and carbonyl group of the acetyl moiety.



Scheme 7. Friedel-Crafts acylation with -OAc groups. R = H, *n*-pentyl.

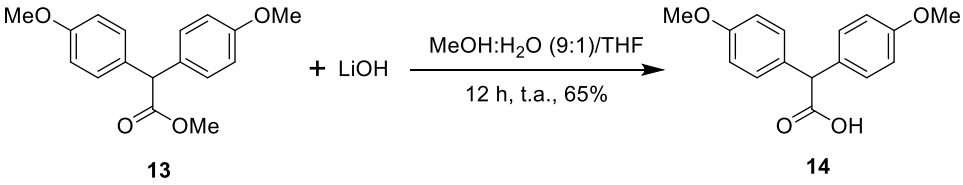
Finally, one last protection strategy was chosen, by using methoxy group (Scheme 8).



Scheme 8. Methylation of compound **3**.

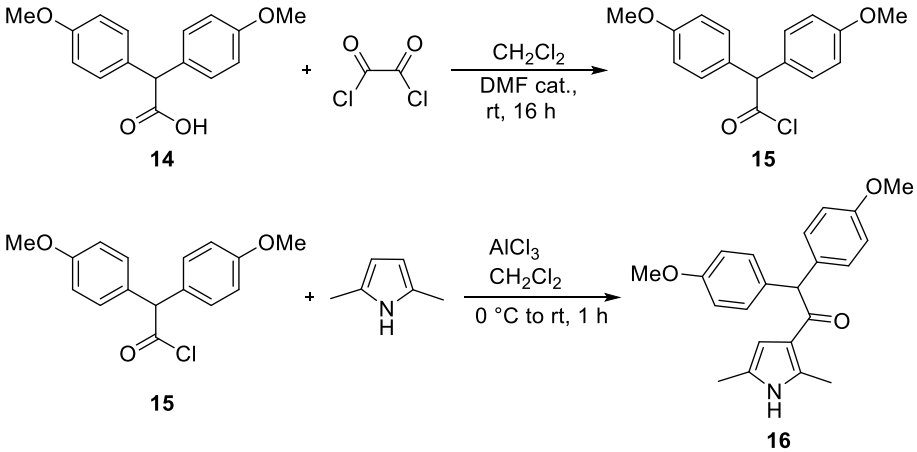
2,2-bis(4-methoxyphenyl)acetic acid **13** was prepared from **3** by treatment with dimethyl sulphate and potassium carbonate in acetone at 25 °C for 12 h (Scheme 8).[60]

The same hydrolysis method followed in Scheme 4 was used to achieve the desired acid **14** with a yield of 65% (Scheme 9).



Scheme 9. Hydrolysis of methyl ester.

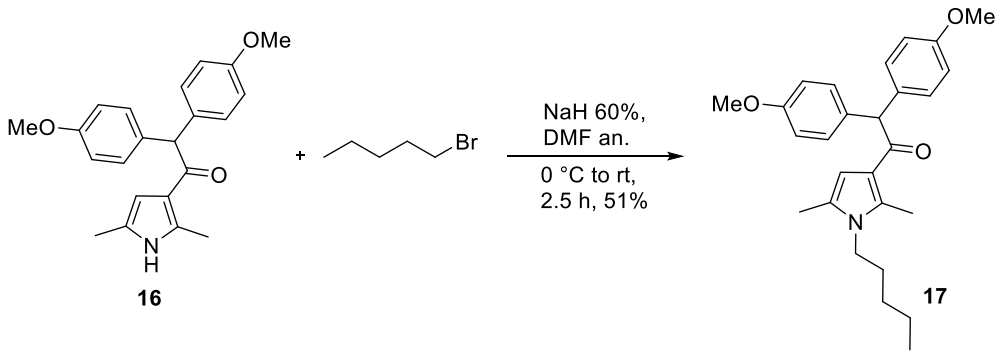
At this point, therefore, the Friedel-Crafts acylation was carried out. Freshly prepared **15** was added to a 2,5-dimethylpirrole with aluminium chloride and dichloromethane at 0 °C (Scheme 10).



Scheme 10. Friedel-Crafts acylation.

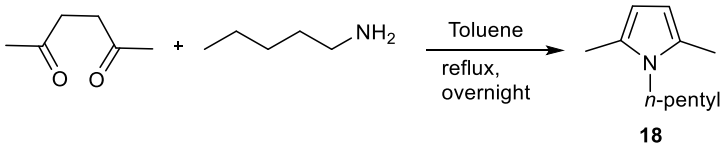
The reaction was followed for 1 h, and after work-up and chromatography purification, the desired dimethoxy acylated product **16** was obtained, although with very low yield (10%).

We proceeded, therefore, with alkylation of NH-free pyrrole, in order to obtain the compound **17**. The reaction was carried out under nitrogen atmosphere, with 60% sodium hydride, *n*-pentyl bromide and anhydrous dimethylformamide (Scheme 11).



Scheme 11. *N*-alkylation of **16**.

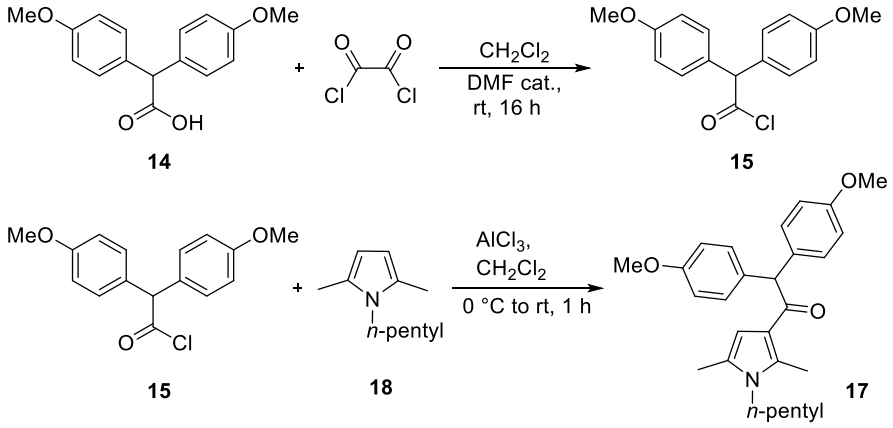
With the aim to increase the yield, 1-pentylpyrrole was prepared by Paal-Knoor condensation[61] (quantitative yield) (Scheme 12).



Scheme 12. Synthesis of **18**.

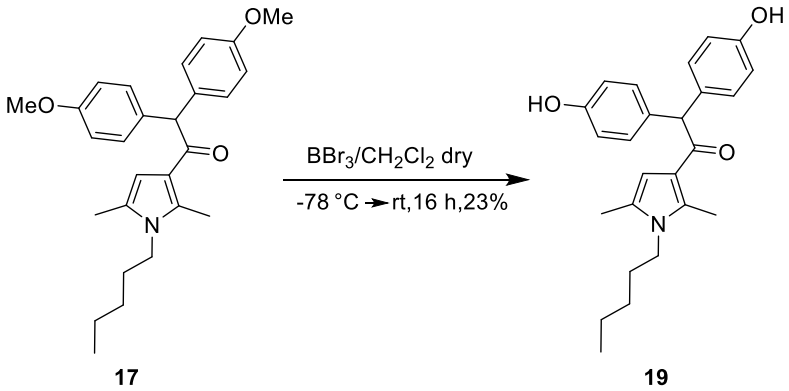
1-pentylpyrrole **18** was directly treated with acyl chloride **11**, aluminium in dichloromethane at 0 °C (Scheme 13) giving the corresponding compound **17** in very low yield (Scheme 14).

Both synthetic route to prepare **17** showed very low yields, however the second procedure is slightly better in terms of yield (11% vs 5% over two steps) (Scheme 14).



Scheme 14. Friedel-Crafts acylation.

Compound **19** was prepared from compound **17** as shown in Scheme 15.



Scheme 15. Deprotection of **17** and production of final derivative **19**.

Compound **17** was treated with boron tribromide[62] in anhydrous dichloromethane, to obtain 1-(2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-il)-2,2-bis(4-metoxyphenyl)etan-1-one **19** with 23% yield (Scheme 15).

With the aim of studying the SAR based on activity and potency and to elucidate the relationship between the position of the substituents and the values of cLogP and tPSA, two analogous of **20** and **21** were synthesized (Figure 17).

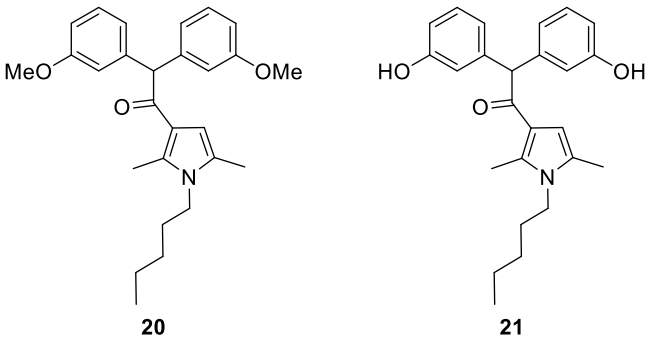
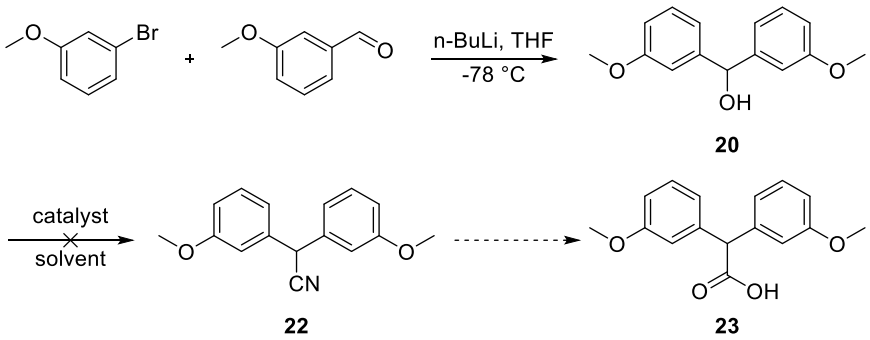


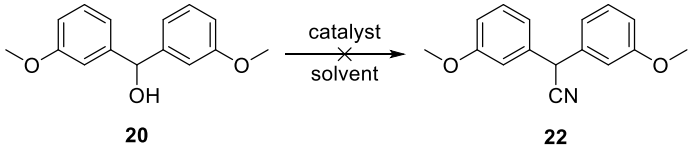
Figure 17. Analogous *m*-substituited derivatives.

To synthesize **27**, the acid **23** should be prepared, as described in Scheme 16. Intermediate **20** was prepared by treatment of *m*-bromoanisole and *m*-methoxyaldehyde *n*-buthyl lithium in tetrahydrofuran at -78 °C. Unfortunately, the alcohol **20** did not react with several cyanating agents, as described in literature.[63]



Scheme 16. First scheme for the synthesis of 2,2-bis(3-methoxyphenyl)acetic acid **23**.

The first three attempts were carried out by using as cyanating agent the trimethylsilyl cyanide,[64,65,66] although varying reaction conditions, such as the catalysts, solvent and/or temperature, the reaction did not proceed. Moreover, the use of tetrabutylammonium cyanide, in the presence of dichlorodicyanoquinone and triphenylphosphine[67] has not led to the desired product **22** (Scheme 17).

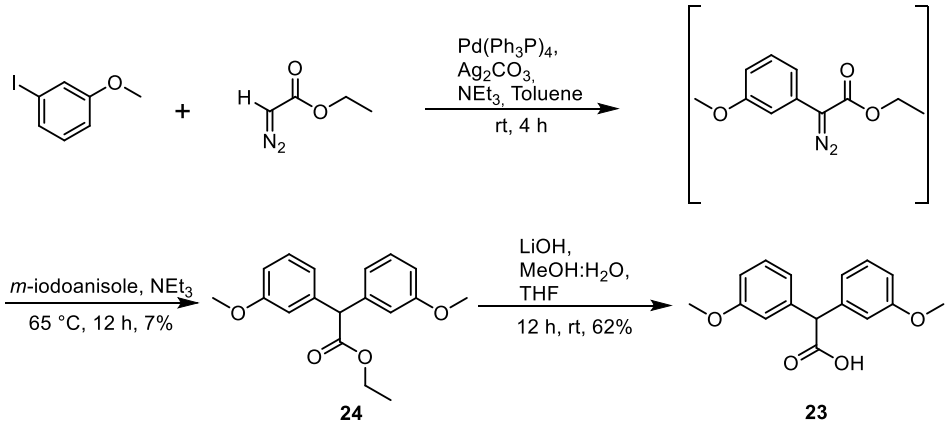


Scheme 17. Synthesis of 2,2-bis(3-methoxyphenyl)acetonitrile **22**.

Table 1. Conditions for the synthesis of compound **22**.

Protocol	Reagents and Conditions	Yield
A	$(CH_3)_3SiCN$, $Zn(OTf)_2$, CH_3NO_2, 100 °C, 5 h	–
B	$(CH_3)_3SiCN$, $InBr_3$, CH_2Cl_2 an., rt., 0,5 h	–
C	$(CH_3)_3SiCN$, Montmorillonite K10, CH_2Cl_2 an., rt., 3 h	–
D	PPh_3, DDQ, *n*-Bu_4NCN, CH_3CN, rt., 20 h	–

At this point, the synthetic scheme to prepare **23** was changed using an alternative method as described in Scheme 18.

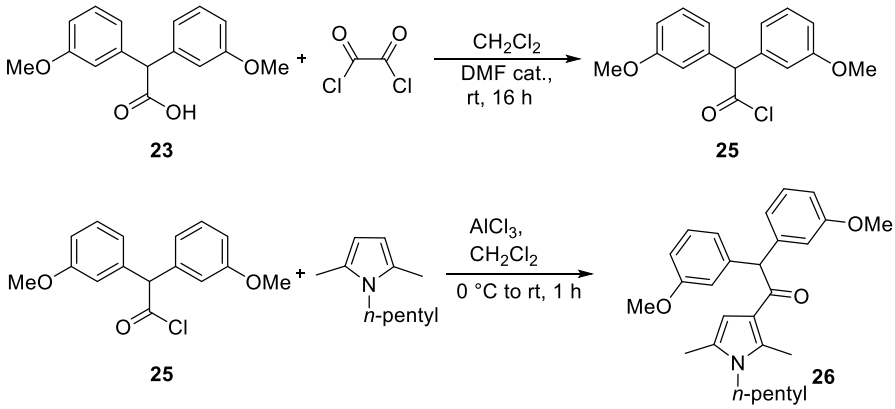


Scheme 18. Method II for the synthesis of 2,2-bis(3-methoxyphenyl)acetic acid **23**.

Firstly, α,α-diaryl ester **24** was prepared by using a one-pot tandem cross-coupling palladium catalysed reaction of *m*-iodoanisole and ethyl diazoacetate, using palladium tetrakis(triphenylphosphine), silver carbonate, triethylamine in toluene with a 7% yield (Scheme 18).[68] Compound **24** was then hydrolyzed to obtain the carboxylic acid **23**, the intermediate precursor suitable for the Friedel-Crafts acylation.

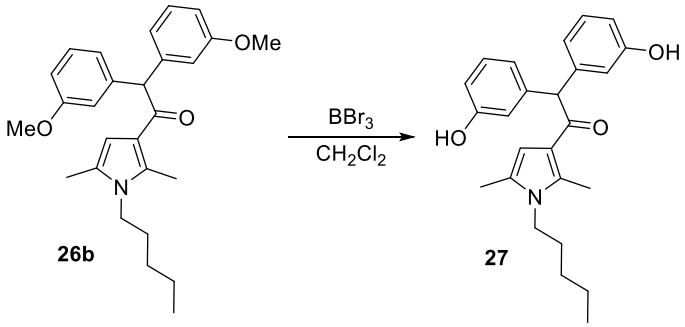
Compound **26** was prepared with the same procedure followed for the *p*-OMe derivative **17**. Thus, **25** was freshly prepared by treatment of the acid **23** with oxalyl chloride, dimethylformamide and dichloromethane, and instantly used in the subsequent Friedel-Crafts acylation. 2,5-dimethyl-1-pentyl-1*H*-pyrrole was used as

reactant in the Friedel-Craft acylation, and the corresponding product **26** was obtained with 25% yield (Scheme 19).



Scheme 19. Acylation of Friedel-Crafts. **26b** R = *n*-pentyl, 25%.

Finally, to synthesize **27**, two protocols were explored to remove *m*-OMe protecting groups on **26** (Scheme 20 and Table 2).



Scheme 20. Attempts of removal *m*-OMe protecting groups.

Table 2.

Entry	Conditions	Conversion
1	BBr_3, CH_2Cl_2, -78 to rt, 12 h	–
2	BBr_3, CH_2Cl_2, -78 to reflux, 2 h	–

Further investigations are now ongoing to obtain the final product **27**.

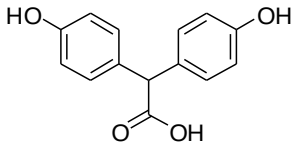
Then, all the product will be tested in vitro models of CB_1 e CB_2 receptors to evaluate affinity and potency.

Chemicals, materials and methods

All reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI in highest quality commercially available. The solvents are capable of RP. The melting point was determined with Büchi B-540 apparatus. The structure of intermediates and the final product were evaluated in an unequivocal way through MS, ^{1}H NMR, ^{13}C NMR, IR and $[\alpha]^{20}$D. MS (ESI) spectra were recorded with a Waters Micromass ZQ spectrometer in a positive mode using a nebulizing nitrogen gas at 400 L/min and a temperature of 250 ºC, cone flow 40 mL/min, capillary 3.5 Kvolts and cone voltage 60 V; the revelation was performed either in ESI (+) and ESI (-), from 100 to 800 units of mass, which spectrophotometrically using diode array spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 400 or 50, instrument, and analyzed using the WIN-NMR software package. Chemical shifts were measured by using the central peak of the solvent. Purification of the crude material was carried out by column chromatography on silica gel "flash" (230-400 mm, Merck. TLC analyses were performed on precoated aluminum oxide on aluminum sheets (60 F254, neutral; Merck). IR spectra were obtained with a Nicolet Avatar 360 spectrophotometer.

Experimental section

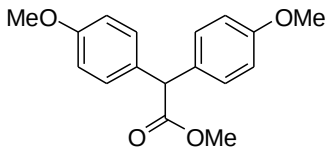
Synthesis of 2,2-bis(4-hydroxyphenyl)acetic acid (3)



To a solution of phenol (3.82 mL, 43.45 mmol) in concentrated H_2SO_4 (594 µL) and H_2O (1.22 mL), was added ad room temperature, glyoxylic acid (2 g, 43.45 mmol)

and the mixture was stirred for 48 h. H_2O, ice and a solution of saturated $NaHCO_3$ (38 mL) were added, and poured into a solution of NaOH 35% to pH = 8.0 and extracted with EtOAc. The aqueous layer was treated with HCl 37% to pH = 1. Extraction with EtOAc gave **3** as white solid. Yield 97% (10.3 g, 42.15 mmol). P.f. 212-213 °C (EtOAc). MS (ESI): 243 ($M-H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 4.77 (s, 1H, Ar_2-C*H*), 6.69 (d, 4H, *J* = 8 Hz, Ar-*H*), 7.07 (d, 4H, *J* = 8.0 Hz, Ar-*H*), 9.29 (s, 2H, O*H*), 12.43 (s, 1H, COO*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 55.2, 115.5, 129.8, 130.8, 156.5, 174.6 ppm. IR (Nujol) ν = 3063, 2990, 1421, 1262 cm^{-1}. The physico-chemical data are in agreement with those reported in the literature.[55]

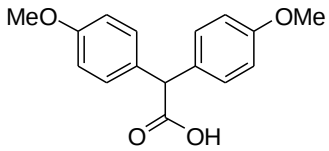
Synthesis of methyl 2,2-bis(4-methoxyphenyl)acetate (13)



Compound **3** (2.57 g, 10.54 mmol) was dissolved in $CH_3C(O)CH_3$ (25.8 mL) at room temperature and $(CH_3)_2SO_4$ (2.49 mL, 26.35 mmol) and K_2CO_3 (4.37 g, 31.62 mmol) were added. The mixture was stirred for 12 h and then filtered over Celite®, washed with $CH_3C(O)CH_3$ and evaporated under vacuum. The purification of the by flash column chromatography (cyclohexane/EtOAc 9:1) gave **13** (2.112 g, 7.38 mmol) as white solid. Yield 70%. P.f. 65-66 °C (EtOAc/petroleum ether). MS (ESI): 287 ($M+H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H, OC*H*$_3$), 3.79 (s, 6H, Ar-OC*H*$_3$), 4.94 (s, 1H, Ar-C*H*), 6.86 (d, 4H, *J* = 8.0 Hz, Ar-*H*), 7.22 (d, 4H, *J* = 8.0 Hz, Ar-*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 26.9, 52.3, 55.4, 114.2, 129.5, 131.1, 158.6, 173.5 ppm. IR (Nujol) ν =2958, 2921, 2843, 2721, 2357, 2332, 1454, 1380, 1151,

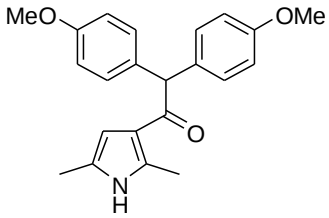
722 cm^{-1}. The physico-chemical data are in agreement with those reported in the literature.[69]

Synthesis of 2,2-bis(*p*-metoxyphenyl)acetic acid (14)



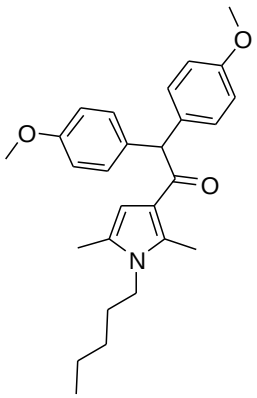
To a stirred solution of **13** (2 g, 6.99 mmol) in MeOH/H_2O 9:1 (23.2 mL) at room temperature LiOH (0.59 g, 13.98 mmol) and THF (2.2 mL) were added. The mixture was stirred for 12 h, diluited with EtOAc and extracted with H_2O. The aqueous layer was treated with HCl 1N until pH= 2 and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to give **14** (1.24 g, 4.54 mmol) as white solid. Yield 5%. P.f. 201-202 °C (EtOAc/petroleum ether). MS (ESI): 273 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 6H, OC*H*$_3$), 4.96 (s, 1H, Ar$_2$C*H*), 6.87 (d, 4H, *J* = 8 Hz, Ar-*H*), 7.24 (d, 4H, *J* = 8 Hz, Ar-*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 55.2, 55.3, 114.0, 129.7, 130.4, 158.9, 177.9 ppm. IR (Nujol) ν = 3182, 2962, 2921, 2855, 2725, 1707, 1458, 1368, 718 cm^{-1}. The physico-chemical data are in agreement with those reported in the literature.[69]

Synthesis of 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)-2,2-bis(4-metoxyphenyl)etan-1-one (16)



To a stirred, cooled (0 °C) solution of 2,5-dimethylpyrrole (119 µL, 1.169 mmol) in CH_2Cl_2 (3.24 mL) and the aroyl chloride **15** (339 mg, 1.169 mmol) in CH_2Cl_2 (15 mL), $AlCl_3$ (156 mg; 1.169 mmol) was cautiously added. The mixture was stirred at room temperature for 1 h, 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 8:4) gave **16** as colorless oil. Yield 10% (41 mg, 0.169 mmol). MS (ESI): 350 ($M+H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H, C*H*$_3$), 2.52 (s, 3H, C*H*$_3$), 3.77 (s, 6H, OC*H*$_3$), 5.59 (s, 1H, Ar-C*H*), 6.14 (s, 1H, Ar-*H*), 6.84 (d, 4H, *J* = 8 Hz, Ar-*H*), 7.21 (d, 4H, *J* = 8.0 Hz, Ar-*H*), 7.90 (brs, 1H, N*H*) ppm. IR (Nujol) ν = 3378, 3182, 2712, 2361, 1466, 1384 cm^{-1}.

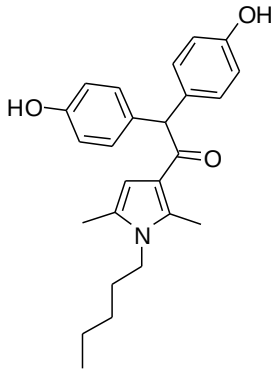
Synthesis of 1-(2,5-dimethy-1-pentyl-1*H*-pyrrol-3-yl)-2,2-bis(4-metoxyphenyl) etan-1-one (17)



To a stirred, cooled (0 °C) solution of pyrrole **16** (110 mg, 0.38 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, 1-pentylpyrrole was added (0.4 mmol). 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 95:5) gave **17** as yellow oil. Yield 51% (18 mg). MS (ESI): 420 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, *J* = 6.8 Hz, C*H*$_3$), 1.26-1.37 (m, 4H, C*H*$_2$), 1.58-1.68 (m, 2H, C*H*$_2$), 2.16 (s, 3H, C*H*$_3$), 2.56 (s, 3H, C*H*$_3$), 3.70 (t, 2H, *J* = 8.0 Hz, C*H*$_2$), 3.77 (s, 6H, OC*H*$_3$), 5.61 (s, 1H, Ar-C*H*), 6.20 (s, 1H, Ar-*H*), 6.84 (d, 4H, *J* = 8 Hz, Ar-*H*), 7.22 (d, 4H, *J* = 8 Hz, Ar-*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 12.0, 12.3, 13.9, 22.3, 29.0, 30.1, 43.5, 55.2, 59.1, 107.9, 113.8, 119.5, 127.2, 130.0, 133.0, 136.4, 158.2, 195.0 ppm. IR (Nujol) ν = 3174, 2725, 2655, 1650, 1597, 1454, 1372, 1172, 1029 cm^{-1}.

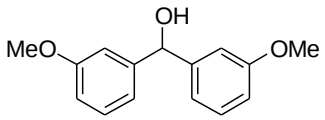
Synthesis of 1-(2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-yl)-2,2-bis(4-hydroxyphenyl) etan-1-one (19)



To a stirred solution of **17** (30 mg, 0.071 mmol) in dry CH_2Cl_2 (582 µL), cooled to -78 °C, under N_2 atmosphere, was added BBr_3 (73 µL, 0.426 mmol) in dry CH_2Cl_2 (275 µL). The suspension was stirred at room temperature for 16 h. The reaction was quenched with a solution of HCl 10% and extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 7:3) gave **19** brown solid. Yield 53% (15 mg, 0.038 mmol). P.f 190-191 °C (EtOAc/petroleum ether). MS (ESI): 392 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, *J* = 6.8 Hz, C*H*$_3$), 1.25-1.36 (m, 4H, C*H*$_2$), 1.57-1.61 (m, 2H, C*H*$_2$), 2.15 (s, 3H, C*H*$_3$), 2.55 (s, 3H, C*H*$_3$), 3.68-3.72

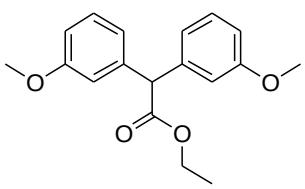
(m, 2H, CH_2), 5.62 (s, 1H, Ar_2-C*H*), 6.23 (s, 1H, Ar-*H*), 6.64 (d, 4H, *J* = 8.0 Hz, Ar-*H*), 7.01 (d, 4H, *J* = 8.0 Hz, Ar-*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 12.2, 12.3, 13.9, 22.3, 29.0, 29.7, 30.1, 43.5, 59.0, 108.1, 115.4, 119.5, 127.5, 130.2, 132.5, 136.7, 154.3 ppm. IR (Nujol) ν = 2953, 2921, 2855, 2357, 1462, 1380, 409 $cm^{-1.}$

Synthesis of bis(3-metoxyphenyl)methanol (20)



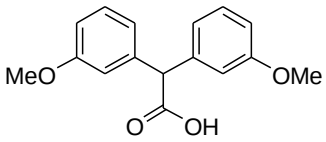
A stirred solution of 1-bromo-3-metoxybenzene (202 µL, 1.617 mmol) in dry THF (2 mL) was cooled to -78 °C and *n*-BuLi (647 µL) was added. After 30 min *m*-anisaldehyde (1.79 µL) in THF dry (2.4 mL) was added and the reaction mixture was stirred at -78 °C for 4 h. *i*-PrOH was added and the reaction was heated to room temperature. H_2O was added and the reaction was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (cyclohexane/EtOAc 9:1) gave **20** as colorless oil. Yield 12% (43 mg, 0.177 mmol). MS (ESI): 245 ($M+H^+$): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 6H, Ar-OCH_3), 5.79 (s, 1H, Ar_2-C*H*OH), 6.81 (dd, 2H, Ar-*H*), 6.96 (m, 4H, Ar-*H*), 7.26 (t, 2H, *J* = 8 Hz, Ar-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 55.2, 76.06, 112.1, 113.0, 118.8, 129.5, 145.3, 159.7 ppm. IR (Nujol) ν = 3047, 2929, 2843, 2373, 1450, 1266 cm^{-1}. The physico-chemical data are in agreement with those reported in the literature.[70]

Synthesis of ethyl 2,2-bis(3-metoxyphenyl) acetate (24)



$Pd(PPh_3)_4$ (101 mg, 0.0875 mmol), *m*-iodoanisole (183 µL, 1.54 mmol), $AgCO_3$ (192 mg, 0.7 mmol), and Et_3N (245 µL, 3.542 mmol) were suspended in toluene (2 mL) in a 10 mL schlenk tube under N_2. Then $N_2CHC(O)CH_2CH_3$ (223 µL, 1.75 mmol) was added. After stirring at room temperature for 4 h, *m*-iodoanisole (29 µL, 2.82 mmol) and Et_3N (186 µL, 1.848 mmol) were added and the solution was heated at 65 °C for 12 h. Then the catalyst and solids were removed by filtering through a short path of silica gel, eluting with EtOAc. The volatile compounds were removed in vacuo and the residue was purified by flash chromatography (petroleum ether/EtOAc 9:1) to give **24** as a white solid. Yield 7% (111 mg, 0.368 mmol). MS (ESI): 301 ($M+H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.21 (d, J = 8.0 Hz, 2H), 6.91-6.87 (m, 4H), 6.79 (d, J = 8.0 Hz, 2H), 4.94 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.76 (s, 6H), 1.25 (t, J = 7.1 Hz, 3H) ppm. IR (Nujol) ν = 2922, 2850, 1734, 1599, 1490, 1260, 1158, 1047, 746, 695 cm^{-1}. The physico-chemical data are in agreement with those reported in the literature.[68]

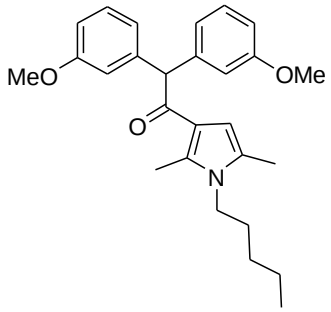
Synthesis of 2,2-bis(3-metoxyphenyl) acetic acid (23)



To a stirred solution of **24** (120 mg, 0.399 mmol) in MeOH/H_2O 9:1 (1.32 mL) was added, at room temperature LiOH (28.5 mg, 0.679 mmol) and THF (131 µL). The mixture was stirred for 12 h, then diluted with EtOAc and extracted with H_2O. The aqueous layer was treated with a solution of HCl 1N until pH = 2, extracted with EtOAc, dried over Na_2SO_4 and evaporated under vacuum to give **23** as white solid. Yield 90% (98 mg, 0.359 mmol). MS (ESI): 271 ($M-H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 6H, OCH_3), 5.00 (s, 1H, Ar_2CH), 6.83 (d, 2H, Ar-*H*), 6.89-6.95 (m,

4H, Ar-*H*), 7.26 (t, 2H, *J* = 8 Hz, Ar-*H*) ppm. 55.2, 56.7, 112.8, 114.4, 121.3, 129.5, 139.5, 155.9, 177.3 ppm. IR (Nujol) ν = 3182, 2962, 2921, 2855, 2725, 1707, 1458,1368,718 cm^{-1}.

Synthesis of 1-(2,5-dimethyl-1-pentyl-1*H*-pyrrol-3-yl)-2,2-bis(3-metoxyphenyl) etan-1-one (26)



To a stirred, cooled (0 °C) solution of 2,5-dimethyl-1-pentyl pyrrole (54.5 mg, 0.330 mmol) in CH_2Cl_2 (868 µL) and the aroyl chloride **25** (96 mg, 0.330 mmol) in CH_2Cl_2 (15 mL), $AlCl_3$ (44 mg, 0.330) was cautiously added. The mixture was stirred at room temperature for 3 h, 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 8:4) gave **26** as yellow oil. Yield 25% (34.58 mg, 0.0825 mmol). MS (ESI): 420 ($M+H^+$). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, *J* = 6.8 Hz, C*H*$_3$), 1.28-1.36 (m, 4H, C*H*$_2$), 1.58 (m, 2H, C*H*$_2$), 2.16 (s, 3H, C*H*$_3$), 2.56 (s, 3H, C*H*$_3$), 3.68-3.74 (m, 2H, C*H*$_2$), 3.77 (s, 6H, C*H*$_3$), 5.65 (s, 1H, Ar_2CH), 6.22 (s, 1H, Ar-*H*), 6.75-6.77 (m, 2H, Ar-*H*), 6.87-6.92 (m, 4H, Ar-*H*), 7.21 (t, 2H, *J* = 8.0 Hz, Ar-*H*) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) *δ*: 12.0, 12.3, 13.9, 22.3, 28.9, 30.1, 43.5, 55.2, 60.8, 107.9, 111.9, 115.0, 119.5, 121.6, 127.3, 129.2, 135.4, 141.7, 159.5, 193.9 ppm. IR (Nujol) ν = 3174, 2725, 2655, 1650, 1597, 1454, 1372, 1172, 1029 cm^{-1}.

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