Synthesis and pharmacological evaluation of new (*E*)- and (*Z*)-3-aryl-4-styryl-1*H*-pyrazoles as potential cannabinoid ligands

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DOI: http://dx.doi.org/10.3998/ark.5550190.0011.a19

Abstract

New (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles and (*Z*)- and (*E*)-3(5)-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles were prepared by alkylation of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles with a long chain alkyl bromide in basic medium. The affinity of these alkylated pyrazoles to both human CB_1 and CB_2 type cannabinoid receptors was evaluated. The results showed that some of them exhibit affinity towards CB_1 cannabinoid receptors in the nanomolar range.

Keywords: Alkylation, 3-aryl-4-styryl-1*H*-pyrazoles, radioligand, *CB_1* and *CB_2* receptors, configuration, NMR spectroscopy.

Introduction

Cannabinoids, the active component of marijuana Δ^9-THC and their analogues, exert a wide spectrum of central and peripheral effects by modulating specific CB_1 and CB_2 cannabinoid receptors acting as agonists, antagonists or inverse agonists.[1-5] Each of these activities has gained considerable attention due to their potential indication for the treatment of Alzheimer's disease,[6] obesity, epilepsy, glaucoma, motor disorders, cancer, and other pathological conditions.[7-11] Previous reports indicate that cannabinoids have also analgesic and anti-inflammatory properties.[12,13]

CB_1 and CB_2 receptors have been characterized and they are markedly different both in their distribution in the body and in their pharmacological effects. CB_1 receptors are particularly abundant in the central nervous system. In contrast, the CB_2 receptors are mainly found in the immune system. Both receptors belong to the family of G-protein coupled receptors and both inhibit adenylyl cyclase.[14-17] The physiological roles of CB_2 receptors are less know than for CB_1 receptors. However, recent work is beginning to provide evidence for the role of the CB_2 receptors in a number of biological functions, which include peripheral antinociception[18] and inhibition of tumour growth.[19-22]

A better understanding of the cannabinoid pharmacology has been possible due to the identification of endogenous ligands and the synthesis of agonists and antagonists of CB_1 and CB_2 receptors.[23] At present, different cannabinoid ligands have been identified,[24,25] which can be classified into different chemical families.[27-30] Among the different classes of synthetic compounds assuring CB_1 or CB_2 affinity and selectivity, the relevance of pyrazole derivatives has been consolidated by various studies and the pyrazole moiety is regarded as a versatile scaffold in the cannabinoid research field.[31-33] Rimonabant (SR141617A), a CB_1 antagonist/inverse agonist, and its analogue SR144528, a CB_2 antagonist/inverse agonist, are two examples of a large number of pyrazole analogues that have been developed.[31] Other examples are also known such as the analogous of 3-hexyl-1,5-diarylpyrazole (O-1877),[34] the AM251 (potent CB_1 antagonist),[35] the novel 1,4-dihydroindeno[1,2-*c*]pyrazole (selective CB_2 cannabinoid) and some other conformationally constrained pyrazoles.[36] The design of these pyrazoles, which are highly selective for the CB_2 receptor, was based on the Sanofi CB_1 and CB_2 antagonists/inverse agonists, SR141716A and SR144528.

Our group have previously reported the synthesis and characterization of *N*-alkyl-3- and 5-(2-hydroxyphenyl)pyrazoles as potential CB_1 cannabinoid ligands.[37] In order to develop additional CB_1 or CB_2 selective ligands and gain further insight into the SAR for these receptors, new (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **3a-d** and **4a-f** and (*Z*)- and (*E*)-3(5)-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles **5a-d** and **6a-f** were prepared and assayed for binding both the brain and peripheral cannabinoid receptors. The proposed pyrazoles have some pharmacophoric elements in common with Δ^9-THC, namely a lipophilic side chain and a free hydroxyl group (for derivatives **3a-d** and **4a-f**) in an effort to study the importance of hydrogen bonds. The affinity towards the CB_1-type cannabinoid receptor was evaluated in human brain tissues (frontal cortex) while the affinity towards CB_2 was evaluated using membrane fractions of human CB_2 receptor transfected cells. Emphasis is placed on separation of CB_1 activity from CB_2, since the development of compounds, which bind selectively to the CB_2 receptor, could lead to potential therapeutic agents in the immune response field.

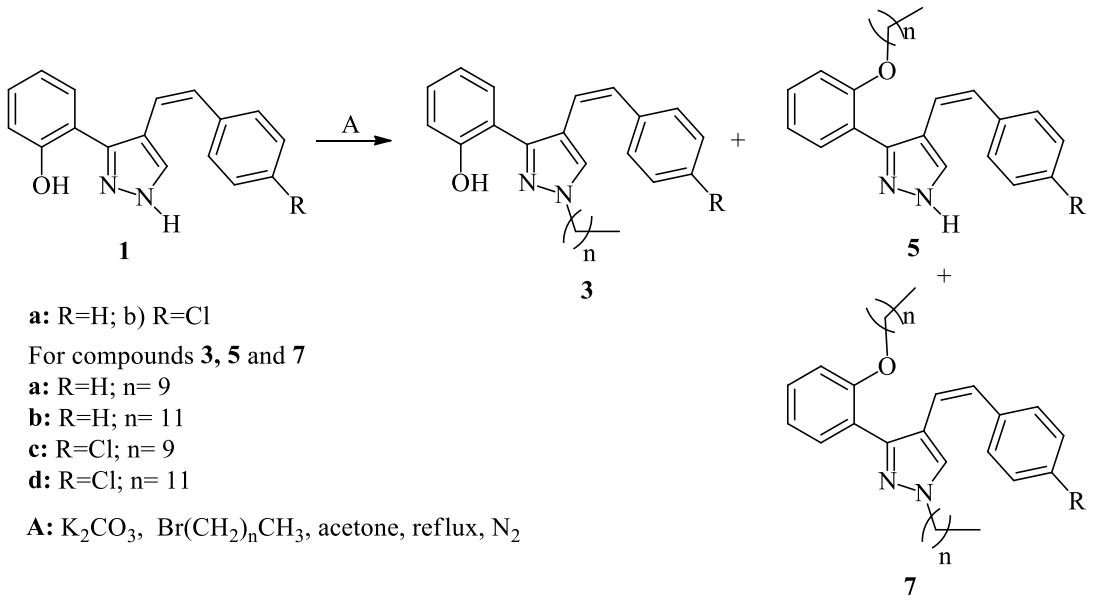
Herein we describe the synthesis, structural characterization and the evaluation of binding affinities of these new alkylpyrazoles for CB_1 and CB_2 receptors.

Results and Discussion

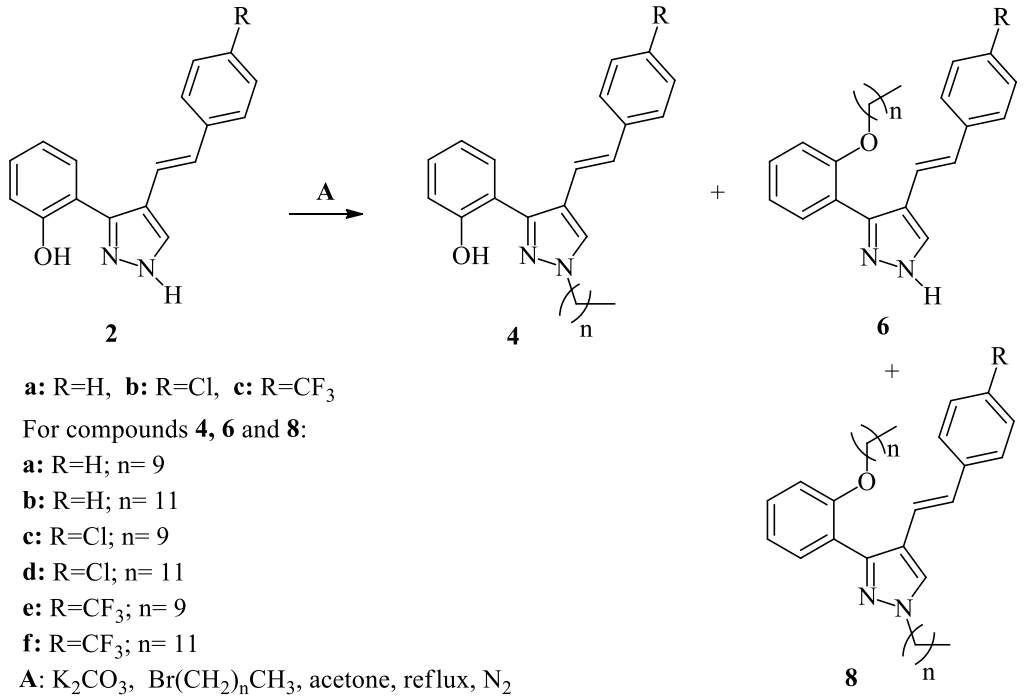
Chemistry

The alkylation of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b** and **2a-c**[38,39] with a long chain alkyl bromides in basic medium (Schemes 1 and 2) gave the corresponding (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **3a-d** and **4a-f** as the major products (43-83%) (Table 1). However, we also isolated the *O*-alkyl derivatives **5a-d** and **6a-f**, as by-products (4-18%) (Table 1). These results indicate that the *O*-alkylation of 2'-hydroxyl group is more difficult than the *N*-alkylation of pyrazole ring, probably due to the intramolecular hydrogen bond (IMHB) between hydroxyl protons with N-2. This IMHB might also be responsible for the formation of only one *N*-alkyl isomer **3a-d** and **4a-f** in the alkylation of asymmetric pyrazoles **1a,b** and **2a-c**, since it was reported that *N*-alkylation of asymmetric pyrazoles afforded a mixture of isomers.[40] In some cases we also isolated a small amount of the dialkyl derivatives **7c** and **8b,e,f** (2-7%, Table 1) (Schemes 1 and 2). The obtained mixture of pyrazoles was separated by preparative thin layer chromatography. The ^{1}H NMR analysis of the reactions mixtures proved that there was no (*Z*)→(*E*) isomerisation during the alkylation reaction.

It is known that the presence of halogens within the classical cannabinoid structure leads to large variations in the compounds' potencies and affinities mainly for the CB_1 receptors.[41] To explore the structure activity relationships and the effect of halogen substitution we synthesized some derivatives possessing a chlorine atom or a trifluoromethyl group in the *para* position of the styryl group and compared their affinities for the cannabinoid receptors (CB_1 and CB_2).



Scheme 1. Alkylation of (*Z*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b.**



Scheme 2. Alkylation of (*Z*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b.**

Table 1. Yields obtained in the alkylation of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b** and **2a-c**

Alkylation of **1a,b**						Alkylation of **2a-c**				
			Yield (%)					Yield (%)		
Compound	Substituent	n	**3**	**5**	**7**	Substituent	n	**4**	**6**	**8**
a	R = H	9	75	16	–	R= H	9	60	15	–
b	R = H	11	65	15	–	R= H	11	75	4	7
c	R = Cl	9	59	18	2	R= Cl	9	51	–	–
c						R= Cl	9	43	9	–
d	R = Cl	11	73	16	–	R= Cl	11	83	16	–
e						R= CF_3	9	77	12	5
f						R= CF_3	11	40	10	4

NMR characterisation

The main features of the ^{1}H NMR spectra of (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **3a-d** and **4a-f** and (*Z*)- and (*E*)-3(5)-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles **5a-d** and **6a-f** are: i) the triplet at δ_H 0.86-0.88 ppm assigned to the resonance of the terminal methyl group of the alkyl chain; ii) the quintet at δ_H 1.75-1.90 ppm due to the resonance of the protons linked to C-2 of the alkyl chain; iii) the triplet at δ_H 3.95-4.11 ppm attributed to the resonance of the methylene group directly linked to the nitrogen or oxygen atoms; iv) the H-5 resonance

appearing as a singlet or in some cases as a broad singlet at δ_H 7.07-7.09 ppm for **3a-d**, δ_H 7.56-7.63 ppm for **4a-f**, δ_H 7.30-7.36 ppm for **5a-d** and δ_H 7.88-7.92 ppm for **6a-f**; and v) the H-α and H-β resonances appearing as doublets or in some cases as an AB spin system at δ_H 6.52-6.55 and 6.54-6.62 ppm for **3a-d**, δ_H 7.11-7.22 and 6.76-6.82 ppm for **4a-f**, δ_H 6.43-6.44 and 6.50-6.57 ppm for **5a-d** and δ_H 7.03-7.14 and 6.88-6.96 ppm for **6a-f**. (*Z*)- and (*E*)-styrylpyrazoles can be distinguished by the coupling constant of their vinylic protons; (*Z*)-derivatives **3a-d** and **5a-d** present coupling constants of $J_{H\alpha\text{-}H\beta}$ 11.8-12.0 Hz while those of (*E*)-derivatives **4a-f** and **6a-f** are $J_{H\alpha\text{-}H\beta}$ 16.1-16.5 Hz.

The ^{1}H NMR spectra of **3a-d** and **4a-f** show a singlet at δ_H 10.39-10.83 ppm due to the OH-2' proton resonance, which is absent in the spectra of compounds **5a-d** and **6a-f**. The high frequency value of this signal is due to an intramolecular hydrogen bond between the 2'-hydroxyl proton and N-2.

The ^{13}C NMR spectra of pyrazoles **3a-d**, **4a-f**, **5a-d** and **6a-f** present many signals in the aliphatic region of the spectra corresponding to the carbon resonances of the alkyl chain: i) C-1 at δ_C 52.0-68.9 ppm the most deshielded carbon because it is directly linked to nitrogen or oxygen atoms; ii) C-2 and C-3 at respectively δ_C 29.1-30.0 and 26.0-26.5 ppm; and iii) the signal at δ_C 14.1 ppm assigned to the resonance of the terminal methyl group. The assignment of the other protonated carbons were made by using HSQC correlations while those of the quaternary carbons were unequivocally assigned through the connectivities found in the HMBC spectra (Figure 1). Some of the HMBC connectivities led to the identification of the characteristic C-3 (δ_C 137.1-148.2 ppm), C-4 (δ_C 114.7-118.4 ppm) and C-5 (δ_C 129.2–139.0 ppm) pyrazolic carbons of **3a-d**, **4a-f, 5a-d** and **6a-f** (Figure 1). The position of the alkyl chain of **3a-d**, **4a-f**, **5a-d** and **6a-f** was also confirmed by the connectivities found in their HMBC spectra; mainly those of the first methylene protons of the alkyl chain with those of C-5 of pyrazole ring for **3a-d** and **4a-f**, and those of C-2' in the case of pyrazoles **5a-d** and **6a-f** (Figure 1).

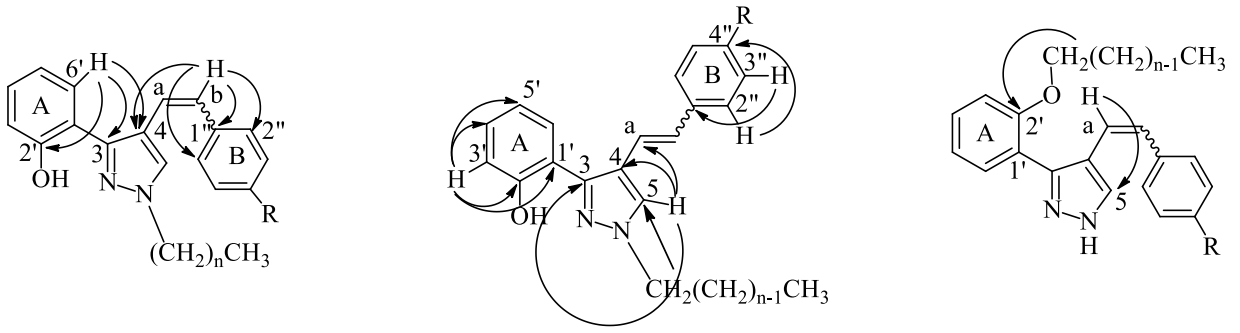


Figure 1. Main connectivities found in the heteronuclear multiple bond coherence spectra of pyrazoles **3a-d**, **4a-f**, **5a-d** and **6a-f**.

The main features of the ^{1}H and ^{13}C NMR spectra of the dialkylpyrazoles **7c** and **8b,e,f** are the number of signals in the aliphatic region of their spectra due to the presence of two alkyl

chains. The connectivities found in the HMBC spectra of these compounds also confirm the positions of the alkyl chains [$NCH_2 \rightarrow$ C-5; H-$\alpha\rightarrow$ C-5; H-6' $\rightarrow$ C-3] and [$OCH_2 \rightarrow$ C-2'].

CB_1 receptors radioligand binding assays

The pharmacological affinity for the CB_1 receptors of the prepared styrylpyrazoles was evaluated through competition binding studies against the cannabinoid selective radioligand [^{3}H]CP55-940 (1 nM). Table 2 presents the affinities of the tested compounds using SR141716A, SR144528 and AM251 as references.

In the two series of compounds **3a-d** and **4a-f**, the binding affinity for CB_1 receptor decreased for compounds having a duodecyl chain compared to compounds having a decyl chain. For instance, **4a** (K_i = 225 nM) with an alkyl chain of 10 carbons was 10 fold more affine for CB_1 receptor than the analogous of 12 carbons, **4b** (K_i = 2126 nM). However, this relationship is not maintained in the series **5a-d** and **6a-f** with the alkoxy chain of 10 or 12 carbons. Concerning the influence of the (*E*) and (*Z*) isomerism of the styryl group, compounds **4a-d** with an (*E*)-configuration showed higher binding affinities than their corresponding analogues **3a-d** having a (*Z*)-configuration. This relationship is not maintained in the series **5** and **6** except for **5c**/**6c**. Except for **6c**, a *para*-substitution (Cl or CF_3) on the phenyl of the styryl group did not improve the affinity.

Table 2. Competition binding studies for CB_1 receptor of 4-styryl-1*H*-pyrazoles **3a-d**, **4a-f**, **5a-d**, **6a-f**, **7c** and **8e** against the selective [^{3}H]CP55-940 radioligand

Compound	R	Length of the alkyl chain	CB_1 K_i (nM)	Number of determinations
SR141716A	-	-	3.73 ± 2.5	5
SR144528	-	-	935 ± 471	5
AM251	-	-	4.85 ± 1.71	5
3a	H	10	1475 ± 694	3
3b	H	12	5034 ± 3020	3
3c	Cl	10	8744 ± 3298	3
3d	Cl	12	6290 ± 393	3
4a	H	10	225 ± 209	3
4b	H	12	2126 ± 542	3
4c	Cl	10	>10000	3
4d	Cl	12	>10000	3
4e	CF_3	10	2736 ± 1552	3
4f	CF_3	12	>10000	3
5a	H	10	1378 ± 660	3
5b	H	12	173 ± 145	3
5c	Cl	10	1225 ± 522	3
5d	Cl	12	>10000	3

Table 2. Continued

Compound	R	Length of the alkyl chain	CB_1 K_i (nM)	Number of determinations
6a	H	10	8382 ± 2933	3
6b	H	12	3279 ± 1311	3
6c	Cl	10	53 ± 33	3
6d	Cl	12	>10000	3
6e	CF_3	10	2736 ± 1552	3
6f	CF_3	12	4814 ± 2647	3
7c	Cl	10	1138 ± 575	3
8e	CF_3	10	>10000	3

The most potent compound **6c** presents affinity in the nanomolar range (K_i = 53±33 nM), being 10 fold less potent than **AM251** and **SR141716A** respectively**.** This compound **6c** presents an alkyl chain of 10 carbons linked to the 2'-oxygen atom. Based on this structure we pointed out that the 2'-hydroxyl group is not necessarily involved in intermolecular hydrogen bonds with CB_1 receptors. Increasing the length of the alkyl chain to 12 carbons means loss of affinity.

(*Z*)- and (*E*)-1-alkyl-3-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles **7c** and **8e** also exhibit very low affinity for CB_1 receptors. These results suggest that it is crucial to retain a structural moiety like N*H* or O*H* to establish intermolecular hydrogen bonds with CB_1 receptors.

Several compounds of the new synthesized compounds exhibited micromolar affinity for the CB_1 cannabinoid receptor. The best result was obtained for **6c** with a K_i value of 53 ± 33 nM.

CB_2 receptors radioligand binding assays

CB_2 receptor binding studies were performed according to the procedure of *Griffin et al.*[42] using membrane fractions of human CB_2 receptor transfected cells, which ensures that only this type of receptor is present. Table 3 presents the affinities of the tested compounds using as reference WIN55,212-2 and methanandamide. The pyrazoles presented here did not show any affinity for the CB_2 receptor type, except **5c**, **6a** and **6b** that displayed low affinity for this receptor (K_i= 2000-3000 nM for *CB_2*), however **5c** and **6b** were not CB_2 selective (K_i= 1378 and 3279 nM respectively for CB_1).

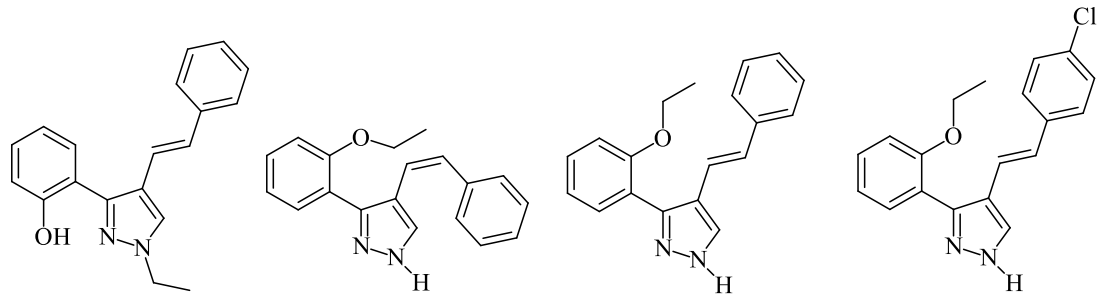
Table 3. Competition binding studies for CB_2 receptor of 4-styryl-1*H*-pyrazoles **3a-d**, **4a-f**, **5a-d** and **6a-f** against the selective [^{3}H]CP55-940 radioligand.

Compound	R	Length of the alkyl chain	CB_2 K_i (nM)	Number of determinations
WIN55,212-2	-	-	2.9 ± 1.5	3
3a	H	10	> 20000	3
3b	H	12	> 20000	3
3c	Cl	10	> 20000	3
3d	Cl	12	> 20000	3
4a	H	10	> 20000	3
4b	H	12	> 20000	3
4c	Cl	10	> 20000	3
4d	Cl	12	> 20000	3
4e	CF_3	10	> 20000	3
4f	CF_3	12	> 20000	3
5a	H	10	17300 ± 8730	3
5b	H	12	> 20000	3
5c	Cl	10	2940 ± 680	3
5d	Cl	12	>20000	3
6a	H	10	2150 ± 980	3
6b	H	12	2580 ± 1210	3
6c	Cl	10	> 20000	3
6d	Cl	12	> 20000	3
6e	CF_3	10	> 20000	3
6f	CF_3	12	> 20000	3

Conclusions

An efficient way to prepare a library of new 1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles, by alkylation of 3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles with a long chain alkyl bromides in basic medium, is described. The binding affinities of the novel (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **3a-d** and **4a-f** and other (*Z*)- and (*E*)-3(5)-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles **5a-d** and **6a-f** provide some new insights about the structural requirements for CB_1 and CB_2 binding. In general, the obtained pyrazoles present higher affinity for CB_1 type receptors than for CB_2 but in the micromolar range. (*E*)-1-Decyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole **4a**, (*Z*)-3(5)-(2-dodecyloxyphenyl)-4-styryl-1*H*-pyrazole **5b**, and (*E*)-4-(4-chlorostyryl)-3(5)-(2-decyloxyphenyl)-1*H*-pyrazole **6c** are the most potent ligands and displayed affinity for CB_1 receptors in the nanomolar range, with special emphasis for **6c** (K_i = 53±33 nM) (Figure 2). These results seems indicate that there is no

influence of the (*E*)- and (*Z*)-configuration in the obtained binding activities, but a possibility of hydrogen bond seems to be important.



4a) n=9
CB_1 = 225 ± 209 nM
CB_2 = > 20000 nM

5b) n=11
CB_1 = 173 ± 145 nM
CB_2 = > 20000 nM

6a) n=9
CB_1 = 8382 ± 2933 nM
CB_2 = 2150 ± 980 nM

6c) n=9
CB_1 = 53 ± 33 nM
CB_2 = > 20000 nM

Figure 2. Selected compounds with affinity constants for CB_1 and CB_2 ligands.

Experimental Section

General. Melting points were determined on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. NMR spectra were recorded on Bruker Avance 300 (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) and Bruker Avance 500 (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C) spectrometers, using $CDCl_3$ as solvent if not stated otherwise. Chemical shifts (δ) are reported in ppm values (δ) and coupling constants (J) in Hz. The internal standard was TMS. ^{1}H assignments were made using two-dimensional gradient selected correlation spectroscopy (*g*COSY) and nuclear Overhauser effect spectroscopy (NOESY; 800 ms mixing time), experiments, while ^{13}C assignments were made using two-dimensional gradient selected heteronuclear single quantum coherence (*g*HSQC) and two-dimensional gradient selected heteronuclear multiple quantum coherence (*g*HMBC) (delays for one bond and long-range J C/H couplings were optimized for 145 and 7 Hz, respectively) experiments. Mass spectra (EI, 70 eV) were measured on a VG Autospec Q and M mass spectrometers. Positive-ion ESI mass spectra were acquired using a Q-TOF 2 instrument [diluting 1 μL of the sample chloroform or tetrahydrofuran (THF) solution (~10^{-5} M) in 200 μL of 0.1% formic acid/methanol solution. Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80°C and desolvation temperature at 150°C. Cone voltage was 35 V]. Mass spectra (MALDI TOF/TOF) were measured on a 4800 MALDI TOF/TOF Analyzer using α-ciano-4-hydroxycinnamic acid as a matrix. Elemental analyses were obtained with a LECO 932 CHN analyser (University of Aveiro, Portugal). Preparative thin layer chromatography was carried out with Riedel silica gel 60 DGF254, and column chromatography using Merk silica gel 60, 70-230 mesh. All chemicals and solvents used were obtained from

commercial sources and used as received or dried using standard procedures. (*Z*)- and (*E*)-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b** and **2a-c** have been prepared according to literature [38,39].

General procedure for the alkylation of (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles (1a,b) and (2a-c)

Potassium carbonate (0.40 g, 2.86 mmol) and the alkylating agent (decyl bromide or dodecyl bromide) (1.43 mmol) were added to a solution of the appropriate (*Z*)- and (*E*)-3(5)-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **1a,b** or **2a-c** (0.95 mmol) in acetone (55 mL). The mixture was refluxed with stirring and the progress of the reaction was monitored by tlc. After the starting material consumption the mixture was cooled to room temperature, the K_2CO_3 was filtered off and washed with acetone (2 x 10 mL). The solvent was evaporated to dryness and the residue taken in chloroform and purified by thin layer chromatography using a 9:1 mixture of light petroleum:ethyl acetate as eluent. Two main compounds have been isolated in all cases: (*Z*)- and (*E*)-1-alkyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **3a-d** or **4a-f** and (*Z*)- and (*E*)-3(5)-(2-alkyloxyphenyl)-4-styryl-1*H*-pyrazoles **5a-d** and **6a-f** were obtained as oils or solids which were recrystallised from ethanol. In some cases we also isolated the dialkyl-derivatives **7c** and **8b,e,f** as oils.

(*Z*)-1-Decyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (3a). Yield 75%; yellow oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.8 Hz, *N*$(CH_2)_9CH_3$], 1.24-1.29 [14H, m, *N*$(CH_2)_2(CH_2)_7CH_3$], 1.77 [2H, quint, *J* = 7.0 Hz, *N*$CH_2CH_2(CH_2)_7CH_3$], 3.98 [2H, t, *J* = 7.0 Hz, *N*$CH_2(CH_2)_8CH_3$], 6.53 (1H, AB, *J*= 11.8 Hz, H-α), 6.62 (1H, AB, *J* = 11.8 Hz, H-β), 6.90 (1H, ddd, *J* = 7.6, 7.5 and 1.2 Hz, H-5'), 7.04 (1H, dd, *J* = 8.2 and 1.2 Hz, H-3'), 7.09 (1H, s, H-5), 7.15-7.25 (4H, m, H-3",5",4",4'), 7.32 (2H, dd, *J* = 7.9 and 1.6 Hz, H-2",6"), 7.80 (1H, dd, *J* = 7.6 and 1.6 Hz, H-6'), 10.83 (1H, s, 2'-O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_9CH_3$], 22.6 [*N*$(CH_2)_8CH_2CH_3$], 26.3 [*N*$(CH_2)_2CH_2(CH_2)_6CH_3$], 29.0, 29.2, 29.38 and 29.45 [*N*$(CH_2)_3(CH_2)_4(CH_2)_2CH_3$], 29.9 [*N*$CH_2CH_2(CH_2)_7CH_3$], 31.8 [*N*$(CH_2)_7CH_2CH_2CH_3$], 52.1 [*N*$CH_2(CH_2)_8CH_3$], 115.2 (C-4), 116.8 (C-3'), 117.6 (C-1'), 119.0 (C-5'), 121.1 (C-α), 127.1 (C-4"), 127.9 (C-6'), 128.2 (C-3",5"), 128.6 (C-2",6"), 128.9 (C-4'), 129.5 (C-5), 130.5 (C-β), 137.1 (C-1"), 148.1 (C-3), 155.8 (C-2'). MS (EI): *m/z* (%) 402 ($M^{+\bullet}$, 100), 387 [$(M-CH_3)^+$, 3], 373 [$(M-C_2H_5)^+$, 6], 359 [$(M-C_3H_7)^+$, 3], 345 [$(M-C_4H_9)^+$, 5], 331 [$(M-C_5H_{11})^+$, 14], 318 (4), 311 (21), 303 [$(M-C_7H_{15})^+$, 1], 289 [$(M-C_8H_{17})^+$, 5], 276 (22), 262 (25), 248 (7), 231 (3), 218 (2), 204 (2), 202 (4), 197 (4), 185 (6), 171 (20), 156 (3), 143 (2), 128 (6), 115 (7), 102 (2), 91 (7), 78 (2), 69 (3), 55 (9). HRMS-EI *m/z* for $C_{27}H_{34}N_2O$ ($M^{+\cdot}$) calcd 402.2671, found 402.2654.

(*Z*)-1-Dodecyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (3b). Yield 65%; yellow oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.6 Hz, *N*$(CH_2)_{11}CH_3$], 1.24-1.30 [18H, m, *N*$(CH_2)_2(CH_2)_9CH_3$], 1.75 [2H, quint, *J* = 7.0 Hz, *N*$CH_2CH_2(CH_2)_9CH_3$], 3.95 [2H, t, *J* = 7.0 Hz, *N*$CH_2(CH_2)_{10}CH_3$], 6.52 (1H, AB, *J* = 11.8 Hz, H-α), 6.61 (1H, AB, *J* = 11.8, H-β), 6.89 (1H, ddd, *J* = 7.7, 7.4, 0.8 Hz, H-5'), 7.03 (1H, dd, *J* = 7.8, 0.8 Hz, H-3'), 7.07 (1H, s, H-5), 7.16-7.24 (4H, m, H-3",5",4",4'), 7.31 (2H, dd, *J* = 7.5, 1.7 Hz, H-2",6"), 7.79 (1H, dd, *J* = 7.7, 1.5 Hz, H-6'), 10.83 (1H, s, 2'-

O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_{11}$*C*H_3], 22.6 [*N*$(CH_2)_{10}$*C*H_2CH_3], 26.3 [*N*$(CH_2)_2$*C*$H_2(CH_2)_8CH_3$], 29.0, 29.3, 29.4, 29.47 and 29.53 [*N*$(CH_2)_3$(*C*$H_2)_6CH_2CH_2CH_3$], 29.9 [*N*CH_2*C*$H_2(CH_2)_9CH_3$], 31.8 [*N*$(CH_2)_9$*C*$H_2CH_2CH_3$], 52.0 [*NC*$H_2(CH_2)_{10}CH_3$], 115.1 (C-4), 116.7 (C-3'), 117.5 (C-1'), 119.0 (C-5'), 121.0 (C-α), 127.1 (C-4"), 127.8 (C-6'), 128.2 (C-3",5"), 128.6 (C-2",6"), 128.9 (C-4'), 129.4 (C-5), 130.4 (C-β), 137.1 (C-1"), 148.1 (C-3), 155.8 (C-2'). MS (EI): *m/z* (%) 430 ($M^{+\bullet}$, 100), 387 (6), 374 (2), 353 (6), 339 (22), 303 (2), 289 (5), 275 (25), 262 (27), 248 (7), 231 (3), 202 (2), 185 (5), 171 (20), 156 (2), 127 (5), 115 (5), 103 (2), 91 (6), 69 (3). HRMS-EI *m/z* for $C_{29}H_{38}N_2O$ ($M^{+\cdot}$) calcd 430.2984, found 430.2993.

(*Z*)-4-(4-Chlorostyryl)-1-decyl-3-(2-hydroxyphenyl)-1*H*-pyrazole (3c). Yield 59%; white solid (from ethanol); mp 50-51ºC. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 7.0 Hz, *N*$(CH_2)_9C$*H*$_3$], 1.19-1.29 [14H, m, *N*$(CH_2)_2$(C*H*$_2)_7CH_3$], 1.78 [2H, quint, *J* = 7.2 Hz, *N*CH_2C*H*$_2(CH_2)_7CH_3$], 4.00 [2H, t, *J* = 7.2 Hz, *NC*$H_2(CH_2)_8CH_3$], 6.55 (2H, s, H-α,β), 6.90 (1H, ddd, *J* = 7.7, 7.6, 1.2 Hz, H-5'), 7.04 (1H, dd, *J* = 8.4, 1.2 Hz, H-3'), 7.09 (1H, s, H-5), 7.18 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.22 (1H, ddd, *J* = 8.4, 7.6, 1.6 Hz, H-4'), 7.25 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.76 (1H, dd, *J* = 7.7, 1.6 Hz, H-6'), 10.80 (1H, s, 2'-O*H*). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [*N*$(CH_2)_9$*C*H_3], 22.6 [*N*$(CH_2)_8$*C*H_2CH_3], 26.3 [*N*$(CH_2)_2$*C*$H_2(CH_2)_6CH_3$], 29.0, 29.2, 29.4 and 29.5 [*N*$(CH_2)_3$(*C*$H_2)_4CH_2CH_2CH_3$], 29.9 [*N*CH_2*C*$H_2(CH_2)_7CH_3$], 31.8 [*N*$(CH_2)_7$*C*$H_2CH_2CH_3$], 52.2 [*NC*$H_2(CH_2)_8CH_3$], 114.8 (C-4), 116.8 (C-3'), 117.4 (C-1'), 119.1 (C-5'), 121.8 (C-α), 127.8 (C-6'), 128.4 (C-3",5"), 129.0 (C-4'), 129.2 (C-5), 129.4 (C-β), 129.9 (C-2",6"), 132.7 (C-4"), 135.5 (C-1"), 148.2 (C-3), 155.9 (C-2'). MS (EI): *m/z* (%) 438 ($M^{+\bullet}$, ^{37}Cl, 39), 436 ($M^{+\bullet}$, ^{35}Cl, 100), 421 [$(M\text{-}CH_3)^+$, 4], 407 [$(M\text{-}C_2H_5)^+$, 7], 379 [$(M\text{-}C_4H_9)^+$, 12], 365 [$(M\text{-}C_5H_{11})^+$, 33], 351 [$(M\text{-}C_6H_{13})^+$, 28], 337 [$(M\text{-}C_7H_{15})^+$, 2], 325 (22), 311 (86), 309 [$(M\text{-}C_{10}H_{21})^+$, 20], 296 (43), 282 (16), 260 (10), 239 (5), 215 (6), 197 (18), 185 (15), 171 (72), 140 (8), 128 (17), 115 (22), 91 ($C_7H_7^+$, 13), 69 (16). Anal. Calcd for $C_{27}H_{33}ClN_2O$: C, 74.21; H, 7.61; N, 6.41. Found: C, 73.87; H, 7.43; N, 6.34.

(*Z*)-4-(4-Chlorostyryl)-1-dodecyl-3-(2-hydroxyphenyl)-1*H*-pyrazole (3d). Yield 73%; yellow oil. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 7.0 Hz, *N*$(CH_2)_{11}C$*H*$_3$], 1.24-1.29 [18H, m, *N*$(CH_2)_2$(C*H*$_2)_9CH_3$], 1.77 [2H, quint, *J* = 7.1 Hz, *N*CH_2C*H*$_2(CH_2)_9CH_3$], 3.98 [2H, t, *J* = 7.1 Hz, *N*$CH_2(CH_2)_{10}CH_3$], 6.54 (2H, s, H-α,β), 6.89 (1H, ddd, *J* = 7.7, 7.5, 1.2 Hz, H-5'), 7.04 (1H, dd, *J* = 8.0, 1.2 Hz, H-3'), 7.08 (1H, s, H-5), 7.17 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.21 (1H, ddd, *J* = 8.0, 7.5, 1.7 Hz, H-4'), 7.24 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.75 (1H, dd, *J* = 7.7, 1.7 Hz, H-6'), 10.81 (1H, s, 2'-O*H*). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [*N*$(CH_2)_{11}$*C*H_3], 22.6 [*N*$(CH_2)_{10}$*C*H_2CH_3], 26.3 [*N*$(CH_2)_2$*C*$H_2(CH_2)_8CH_3$], 29.0, 29.3, 29.4, 29.50 and 29.53 [*N*$(CH_2)_3$(*C*$H_2)_6CH_2CH_2CH_3$], 29.9 [*N*CH_2*C*$H_2(CH_2)_9CH_3$], 31.8 [*N*$(CH_2)_9$*C*$H_2CH_2CH_3$], 52.1 [*NC*$H_2(CH_2)_{10}CH_3$], 114.7 (C-4), 116.8 (C-3'), 117.5 (C-1'), 119.0 (C-5'), 121.8 (C-α), 127.7 (C-6'), 128.4 (C-3",5"), 129.0 (C-4'), 129.2 (C-β), 129.3 (C-5), 129.9 (C-2",6"), 132.7 (C-4"), 135.5 (C-1"), 148.2 (C-3), 155.8 (C-2'). MS (EI): *m/z* (%) 466 ($M^{+\bullet}$, ^{37}Cl, 68), 464 ($M^{+\bullet}$, ^{35}Cl, 100), 435 [$(M\text{-}C_2H_5)^+$, 7], 423 (5), 407 [$(M\text{-}C_4H_9)^+$, 7], 393 [$(M\text{-}C_5H_{11})^+$, 4], 379 [$(M\text{-}C_6H_{13})^+$, 6], 365 [$(M\text{-}C_7H_{15})^+$, 12], 351 [$(M\text{-}C_8H_{17})^+$, 13], 338 [$(M\text{-}C_9H_{19})^+$, 22], 323 [$(M\text{-}C_{10}H_{21})^+$, 7], 309 [$(M\text{-}C_{11}H_{23})^+$, 36], 296 (53), 282

(12), 260 (9), 243 (4), 231 (7), 215 (4), 202 (8), 185 (10), 171 (38), 141 (6), 128 (18), 115 (20), 91 (17), 69 (23). HRMS-EI *m/z* for $C_{29}H_{37}N_2O^{35}Cl$ ($M^{+\cdot}$) calcd 464.2594, found 464.2609.

(*E*)-1-Decyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (4a). Yield 60%; yellow solid (from ethanol); mp 50-51ºC. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, *N*$(CH_2)_9$C*H*$_3$], 1.25-1.29 [14H, m, *N*CH_2CH_2(C*H*$_2)_7CH_3$], 1.87 [2H, quint, *J* = 6.9 Hz, *N*CH_2C*H*$_2(CH_2)_7CH_3$], 4.06 [2H, t, *J* = 6.9 Hz, *N*C*H*$_2(CH_2)_8CH_3$], 6.81 (1H, d, *J* = 16.2 Hz, H-β), 6.92 (1H, ddd, *J* = 7.6, 7.5, 1.2 Hz, H-5'), 7.07 (1H, dd, *J* = 8.2, 1.2 Hz, H-3'), 7.14 (1H, d, *J* = 16.2, H-α), 7.19-7.25 (2H, m, H-4',4"), 7.33 (2H, dt, *J* = 7.1, 7.0 Hz, H-3",5"), 7.44 (2H, d, *J* = 7.1 Hz, H-2",6"), 7.56 (1H, s, H-5), 7.60 (1H, dd, *J* = 7.6, 1.5 Hz, H-6'), 10.50 (1H, s, 2'-O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_9$C*H*$_3$)], 22.6 [*N*$(CH_2)_8$C*H*$_2CH_3$], 26.5 [*N*$(CH_2)_2$C*H*$_2(CH_2)_6CH_3$], 29.0, 29.2, 29.36 and 29.43 [*N*$(CH_2)_3$(C*H*$_2)_4(CH_2)_2CH_3$], 30.0 [*N*CH_2C*H*$_2(CH_2)_7CH_3$], 31.8 [*N*$(CH_2)_7$C*H*$_2CH_2CH_2CH_3$], 52.3 [*NC*$H_2(CH_2)_8CH_3$], 116.8 (C-3'), 117.6 (C-1'), 118.2 (C-4), 119.1 (C-α), 119.2 (C-5'), 126.1 (C-2",6"), 127.3 (C-4"), 128.06 (C-5), 128.09 (C-6'), 128.6 (C-3",5"), 129.0 (C-4'), 129.1 (C-β), 137.3 (C-1"), 147.3 (C-3), 155.7 (C-2'). MS (EI): *m/z* (%) 402 ($M^{+\bullet}$, 100), 387 [$(M-CH_3)^+$, 3], 373 [$(M-C_2H_5)^+$, 5], 359 [$(M-C_3H_7)^+$, 3], 345 [$(M-C_4H_9)^+$, 6], 331 [$(M-C_5H_{11})^+$, 16], 318 (4), 311 (27), 303 [$(M-C_7H_{15})^+$, 5], 289 [$(M-C_8H_{17})^+$, 5], 276 (16), 262 (32), 248 (8), 231 (3), 216 (2), 197 (3), 185 (5), 171 (31), 156 (3), 127 (4), 115 (8), 102 (2), 91 (8), 69 (3), 55 (13). Anal. Calcd for $C_{27}H_{34}N_2O$: C, 80.55; H, 8.51; N, 6.96. Found: C, 80.70; H, 8.50; N, 7.02.

(*E*)-1-Dodecyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (4b). Yield 75%; white solid (from ethanol); mp 60-61ºC. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 7.0 Hz, *N*$(CH_2)_{11}$C*H*$_3$], 1.24-1.30 [18H, m, *N*$(CH_2)_2$(C*H*$_2)_9CH_3$], 1.87 [2H, quint, *J* = 7.0 Hz, *N*CH_2C*H*$_2(CH_2)_9CH_3$], 4.07 [2H, t, *J* = 7.0 Hz, *N*C*H*$_2(CH_2)_{10}CH_3$], 6.81 (1H, d, *J* = 16.2, H-β), 6.92 (1H, ddd, *J* = 7.6, 7.5, 1.1 Hz, H-5'), 7.07 (1H, dd, *J* = 8.2, 1.1 Hz, H-3'), 7.14 (1H, d, *J* = 16.2 Hz, H-α), 7.21-7.25 (2H, m, H-4',4"), 7.33 (2H, dt, *J* = 7.8, 7.4 Hz, H-3",5"), 7.44 (2H, d, *J* = 7.4 Hz, H-2",6"), 7.57 (1H, s, H-5), 7.60 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 10.51 (1H, s, 2'-O*H*). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [*N*$(CH_2)_{11}$C*H*$_3$], 22.6 [*N*$(CH_2)_{10}$C*H*$_2CH_3$], 26.5 [*N*$(CH_2)_2$C*H*$_2(CH_2)_8CH_3$], 29.0, 29.3, 29.4, 29.5 and 29.6 [*N*$(CH_2)_3$(C*H*$_2)_6(CH_2)_2CH_3$], 30.0 [*N*CH_2C*H*$_2(CH_2)_9CH_3$], 31.8 [*N*$(CH_2)_9$C*H*$_2CH_2CH_2CH_3$], 52.3 [*NC*$H_2(CH_2)_{10}CH_3$], 116.8 (C-3'), 117.6 (C-4), 118.2 (C-1'), 119.1 (C-α), 119.2 (C-5'), 126.1 (C-2",6"), 127.3 (C-4"), 128.06 (C-5), 128.09 (C-6'), 128.6 (C-3",5"), 129.0 (C-4'), 129.1 (C-β), 137.3 (C-1"), 147.3 (C-3), 155.7 (C-2'). MS (EI): *m/z* (%) 430 ($M^{+\bullet}$, 100), 415 (1), 402 (1), 401 (3), 387 (4), 373 (4), 360 (1), 353 (4), 346 (1), 339 (18), 331 (11), 317 (10), 303 (1), 289 (4), 275 (23), 262 (25), 248 (5), 231 (2), 216 (1), 206 (1), 199 (2), 197 (3), 185 (4), 171 (22), 156 (2), 143 (1), 127 (2), 115 (5), 102 (2), 91 (5), 69 (3), 55 (10). Anal. Calcd for $C_{29}H_{38}N_2O$: C, 80.88; H, 8.89; N, 6.51. Found: C, 80.59; H, 8.50; N, 6.33.

(*E*)-4-(4-Chlorostyryl)-1-decyl-3-(2-hydroxyphenyl)-1*H*-pyrazole (4c). Yield 51%; white solid (from ethanol); mp 59-60ºC. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, *N*$(CH_2)_9$C*H*$_3$], 1.25-1.31 [18H, m, *N*(C*H*$_2)_9CH_3$], 1.90 [2H, quint, *J* = 6.8 Hz, *N*CH_2C*H*$_2(CH_2)_7CH_3$], 4.11 [2H, t, *J* = 6.8 Hz, *N*C*H*$_2(CH_2)_8CH_3$], 6.76 (1H, d, *J* = 16.1 Hz, H-β), 6.93 (1H, dt, *J* = 7.6, 1.1 Hz, H-5'), 7.07 (1H, dd, *J* = 8.1, 1.1 Hz, H-3'), 7.11 (1H, d, *J* = 16.1 Hz, H-α), 7.24 (1H, ddd, *J* = 8.1, 7.6, 1.6 Hz, H-4'), 7.30 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.36 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.56 (1H, dd, *J* =

7.6, 1.6 Hz, H-6'), 7.61 (1H, s, H-5), 10.42 (1H, br s, 2'-O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_9$*C*H_3], 22.6 [*N*$(CH_2)_8$*C*H_2CH_3], 26.5 [*N*$(CH_2)_2$*C*$H_2(CH_2)_6CH_3$], 29.1, 29.2, 29.4 and 29.5 [*N*$(CH_2)_3$(*C*$H_2)_4(CH_2)_2CH_3$], 30.0 [*N*CH_2*C*$H_2(CH_2)_7CH_3$], 31.8 [*N*$(CH_2)_7$*C*$H_2CH_2CH_2CH_3$], 52.4 [*NC*$H_2(CH_2)_8CH_3$], 116.9 (C-3'), 117.5 (C-1'), 117.9 (C-4), 119.3 (C-5'), 119.8 (C-α), 127.3 (C-2",6"), 127.7 (C-β), 128.1 (C-6', C-5), 128.8 (C-3",5"), 129.1 (C-4'), 132.9 (C-4"), 135.9 (C-1"), 147.5 (C-3), 155.7 (C-2'). MS (EI): *m/z* (%) 438 ($M^{+\bullet}$, ^{37}Cl, 43), 436 ($M^{+\bullet}$, ^{35}Cl, 100), 421 [(M-$CH_3)^+$, 4], 407 [(M-$C_2H_5)^+$, 7], 393 [(M-$C_3H_7)^+$, 4], 379 [(M-$C_4H_9)^+$, 6], 365 [(M-$C_5H_{11})^+$, 14], 351 [(M-$C_6H_{13})^+$, 17], 337 [(M-$C_7H_{15})^+$, 2], 325 [(M-$C_6H_4Cl)^+$, 12], 311 (53), 309 [(M-$C_{10}H_{21})^+$, 16], 296 (37), 282 (13), 269 (5), 260 (7), 242 (4), 231 (6), 215 (5), 202 (9), 185 (11), 171 (57), 151 (5), 140 (8), 125 (15), 115 (18), 102 (10), 91 ($C_7H_7^+$, 12), 77 (13), 69 (20), 55 (64). Anal. Calcd for $C_{27}H_{33}ClN_2O$: C, 74.21; H, 7.61; N, 6.41. Found: C, 74.58; H, 7.30; N, 6.28.

(*E*)-4-(4-Chlorostyryl)-1-dodecyl-3-(2-hydroxyphenyl)-1*H*-pyrazole (4d). Yield 83%; white solid (from ethanol); mp 65-66ºC. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, *N*$(CH_2)_{11}$CH_3], 1.25-1.32 [18H, m, *N*$(CH_2)_2$(C$H_2)_9CH_3$], 1.90 [2H, quint, *J* = 6.9 Hz, *N*CH_2C$H_2(CH_2)_9CH_3$], 4.11 [2H, t, *J* = 6.9 Hz, *NC*$H_2(CH_2)_{10}CH_3$], 6.76 (1H, d, *J* = 16.2 Hz, H-β), 6.93 (1H, dt, *J* = 7.6, 0.9 Hz, H-5'), 7.07 (1H, dd, *J* = 7.9, 0.9 Hz, H-3'), 7.11 (1H, d, *J* = 16.2, H-α), 7.24 (1H, ddd, *J* = 7.9, 7.6, 1.5 Hz, H-4'), 7.30 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.36 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.56 (1H, dd, *J* = 7.6, 1.5 Hz, H-6'), 7.61 (1H, s, H-5), 10.41 (1H, s, 2'-O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_{11}$*C*H_3], 22.6 [*N*$(CH_2)_{10}$*C*H_2CH_3], 26.5 [*N*$(CH_2)_2$*C*$H_2(CH_2)_8CH_3$], 29.1, 29.2, 29.4 and 29.5 [*N*$(CH_2)_3$(*C*$H_2)_6CH_2CH_2CH_3$], 30.0 [*N*CH_2*C*$H_2(CH_2)_9CH_3$], 31.8 [*N*$(CH_2)_9$*C*$H_2CH_2CH_2CH_3$], 52.4 [*NC*$H_2(CH_2)_{10}CH_3$], 116.9 (C-3'), 117.5 (C-1'), 117.9 (C-4), 119.3 (C-5'), 119.8 (C-α), 127.3 (C-2",6"), 127.7 (C-β), 128.08 (C-6'), 128.09 (C-5), 128.8 (C-3",5"), 129.1 (C-4'), 132.9 (C-4"), 135.9 (C-1"), 147.5 (C-3), 155.7 (C-2'). MS (EI): *m/z* (%) 466 ($M^{+\bullet}$, ^{37}Cl, 39), 464 ($M^{+\bullet}$, ^{35}Cl, 100), 421 [(M-$C_3H_7)^+$, 3], 379 [(M-$C_6H_{13})^+$, 3], 365 [(M-$C_7H_{15})^+$, 9], 339 (17), 309 [(M-$C_{11}H_{23})^+$, 20], 296 [(M-$C_{12}H_{25})^+$, 22], 282 (6), 260 (3), 231 (2), 202 (2), 185 (4), 171 (24), 154 (2), 125 (4), 91 (2), 69 (4). Anal. Calcd for $C_{29}H_{37}ClN_2O$: C, 74.89; H, 8.02; N, 6.02. Found: C, 74.56; H, 7.87; N, 6.16.

(*E*)-1-Decyl-3-(2-hydroxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (4e). Yield 77%; yellow oil. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 6.7 Hz, *N*$(CH_2)_9$CH_3], 1.25-1.31 [14H, m, *N*$(CH_2)_2$(C$H_2)_7CH_3$], 1.89 [2H, quint, *J* = 7.0 Hz, *N*CH_2C$H_2(CH_2)_7CH_3$], 4.11 [2H, t, *J* = 7.0 Hz, *NC*$H_2(CH_2)_8CH_3$], 6.82 (1H, d, *J* = 16.2 Hz, H-β), 6.94 (1H, ddd, *J* = 7.6, 7.3, 1.2 Hz, H-5'), 7.08 (1H, dd, *J* = 7.9, 1.2 Hz, H-3'), 7.22 (1H, d, *J* = 16.2 Hz, H-α), 7.25 (1H, ddd, *J* = 7.9, 7.6, 1.8 Hz, H-4'), 7.32 (2H, d, *J* = 8.5 Hz, H-2",6"), 7.58 (2H, d, *J* = 8.5 Hz, H-3",5"), 7.54 (1H, dd, *J* = 7.3, 1.8 Hz, H-6'), 7.63 (1H, s, H-5), 10.42 (1H, s, 2'-O*H*). δ_C ($CDCl_3$, 75.47 MHz) 14.1 [*N*$(CH_2)_9$*C*H_3)], 22.6 [*N*$(CH_2)_8$*C*H_2CH_3], 26.5 [*N*$(CH_2)_2$*C*$H_2(CH_2)_6CH_3$], 29.1, 29.2, 29.4, 29.5 and 29.6 [*N*$(CH_2)_3$(*C*$H_2)_4(CH_2)_2CH_3$], 30.0 [*N*CH_2*C*$H_2(CH_2)_7CH_3$], 31.8 [*N*C$H_2(CH_2)_6$*C*$H_2CH_2CH_2CH_3$], 52.5 [*NC*$H_2(CH_2)_8CH_3$], 117.0 (C-3'), 117.4 (C-1'), 117.7 (C-4), 119.4 (C-5'), 121.8 (C-α), 124.2 (q, *J* = 270.3 Hz, *C*F_3), 125.6 (q, *J* = 3.8 Hz, C-3",5"), 126.2 (C-2", 6"), 127.4 (C-β), 128.1 (C-6'), 128.3 (C-5), 129.2 (q, *J* = 31.8 Hz, C-4"), 129.3 (C-4'), 140.9 (C-1"), 147.7 (C-3), 155.7 (C-2'). MS (EI): *m/z* (%) 470 ($M^{+\bullet}$, 100), 451 (9), 413 [(M-

$C_4H_9)^+$, 7], 399 [(M-$C_5H_{11})^+$, 21], 371 [(M-$C_7H_{15})^+$, 21], 357 [(M-$C_8H_{17})^+$, 7], 343 [(M-$C_9H_{19})^+$, 41], 330 (49), 311 (32), 299 (41), 202 (5), 185 (10), 171 (56), 159 (6), 115 (7), 91 ($C_7H_7^+$, 7), 69 (11). HRMS-EI *m/z* for $C_{28}H_{33}N_2O^{19}F_3$ ($M^{+\cdot}$) calcd 470.2545, found 470.2547.

(*E*)-1-Dodecyl-3-(2-hydroxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (4f). Yield 40%; white solid (from ethanol); mp 34-35ºC. δ_H ($CDCl_3$) 0.86 [3H, t, *J* = 6.7 Hz, *N*$(CH_2)_{11}CH_3$], 1.25-1.31 [18H, m, *N*$(CH_2)_2(CH_2)_9CH_3$], 1.89 [2H, quint, *J* = 6.8 Hz, *N*$CH_2CH_2(CH_2)_9CH_3$], 4.10 [2H, t, *J* = 6.8 Hz, *N*$CH_2(CH_2)_{10}CH_3$], 6.82 (1H, d, *J* = 16.2 Hz, H-β), 6.94 (1H, ddd, *J* = 7.6, 7.3, 1.2 Hz, H-5'), 7.08 (1H, dd, *J* = 7.9, 1.2 Hz, H-3'), 7.22 (1H, d, *J* = 16.2 Hz, H-α), 7.25 (1H, ddd, *J* = 7.9, 7.6, 1.6 Hz, H-4'), 7.50 (2H, d, *J* = 8.5 Hz, H-2",6"), 7.54 (1H, dd, *J* = 7.3, 1.6 Hz, H-6'), 7.57 (2H, d, *J* = 8.5 Hz, H-3",5"), 7.63 (1H, s, H-5), 10.39 (1H, s, 2'-O*H*). δ_C ($CDCl_3$) 14.1 [*N*$(CH_2)_{11}CH_3$)], 22.6 [*N*$(CH_2)_{10}CH_2CH_3$], 26.5 [*N*$(CH_2)_2CH_2(CH_2)_8CH_3$], 29.1, 29.3, 29.4, 29.5 and 29.6 [*N*$(CH_2)_3(CH_2)_6(CH_2)_2CH_3$], 30.0 [*N*$CH_2CH_2(CH_2)_9CH_3$], 31.9 [*N*$CH_2(CH_2)_8CH_2CH_2CH_3$], 52.5 [*N*$CH_2(CH_2)_{10}CH_3$], 117.0 (C-3'), 117.4 (C-1'), 117.7 (C-4), 119.3 (C-5'), 121.7 (C-α), 124.2 (q, *J* = 271.7 Hz, *C*F_3), 125.7 (q, *J* = 3.8 Hz, C-3",5"), 126.2 (C-2",6"), 127.4 (C-β), 128.1 (C-6'), 128.3 (C-5), 129.0 (q, *J* = 32.4 Hz, C-4"), 129.2 (C-4'), 140.9 (C-1"), 147.7 (C-3), 155.7 (C-2'); MS (EI): *m/z* (%) 498 ($M^{+\bullet}$, 100), 479 [(M-$F)^+$, 9], 469 [(M-$C_2H_5)^+$, 5], 455 [(M-$C_3H_7)^+$, 8], 441 [(M-$C_4H_9)^+$, 9], 427 [(M-$C_5H_{11})^+$, 6], 413 [(M-$C_6H_{13})^+$, 8], 399 [(M-$C_7H_{15})^+$, 20], 385 [(M-$C_8H_{17})^+$, 18], 371 [(M-$C_9H_{19})^+$, 2], 357 [(M-$C_{10}H_{21})^+$, 8], 344 (16), 330 (28), 316 (8), 274 (1), 231 (2), 202 (3), 185 (6), 171 (25), 146 (3), 115 (5), 91 (5), 69 (10). HRMS-EI *m/z* for $C_{30}H_{37}N_2O^{19}F_3$ ($M^{+\cdot}$) calcd 498.2858, found 498.2869.

(*Z*)-3(5)-(2-Decyloxyphenyl)-4-styryl-1*H*-pyrazole (5a). Yield 16%; yellow oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, *O*$(CH_2)_9CH_3$], 1.25-1.45 [14H, m, *O*$CH_2CH_2(CH_2)_7CH_3$], 1.85 [2H, quint, *J* = 7.0 Hz, *O*CH_2CH_2 $(CH_2)_7CH_3$], 4.07 [2H, t, *J* = 7.0 Hz, *O*$CH_2(CH_2)_8CH_3$], 6.43 (1H, d, *J* = 12.0, H-α), 6.57 (1H, d, *J* = 12.0 Hz, H-β), 7.01 (1H, d, *J* = 8.3 Hz, H-3'), 7.04 (1H, dd, *J* = 7.7, 7.1 Hz, H-5'), 7.17-7.21 (1H, m, H-4"), 7.26 (2H, dt, *J* = 7.6, 6.8 Hz, H-3",5"), 7.27-7.32 (1H, m, H-4'), 7.36 (1H, s, H-5), 7.39 (2H, d, *J* = 6.8 Hz, H-2",6"), 7.70 (1H, dd, *J* = 7.7, 1.6 Hz, H-6'). δ_C ($CDCl_3$) 14.1 [*O*$CH_2(CH_2)_8CH_3$], 22.6 [*O*$CH_2(CH_2)_7CH_2CH_3$], 26.1 [*O*$(CH_2)_2CH_2(CH_2)_6CH_3$], 29.2, 29.26, 29.30, 29.49, 29.50 [*O*$CH_2CH_2CH_2(CH_2)_4(CH_2)_2CH_3$], 31.8 [*O*$CH_2(CH_2)_6CH_2CH_2CH_3$], 68.9 [*O*$CH_2(CH_2)_8CH_3$], 112.3 (C-3'), 115.4 (C-4), 118.2 (C-1'), 120.9 (C-5'), 121.2 (C-α), 126.4 (C-β), 127.0 (C-4"), 128.2 (C-3",5"), 128.6 (C-2",6"), 129.5 (C-4'), 130.3 (C-6'), 137.5 (C-3), 137.6 (C-1"), 139.0 (C-5), 155.8 (C-2'). MS (EI): *m/z* (%) 402 ($M^{+\bullet}$, 100), 373 [(M-$C_4H_9)^+$, 2], 359 [(M-$C_5H_{11})^+$, 2], 345 [(M-$C_6H_{13})^+$, 2], 331 [(M-$C_7H_{15})^+$, 2], 311 (4), 289 [(M-$C_{10}H_{21})^+$, 2], 275 [(M-$C_{11}H_{23})^+$, 7], 261 [(M-$C_{12}H_{25})^+$, 27], 245 [(M-$C_{12}H_{25}O)^+$, 7], 231 (4), 216 (3), 202 (4), 185 (11), 171 (45), 155 (2), 128 (3), 115 (8), 102 (3), 91 (7), 77 (5), 55 (11). HRMS-EI *m/z* for $C_{27}H_{34}N_2O$ ($M^{+\cdot}$) calcd 402.2671, found 402.2657.

(*Z*)-3(5)-(2-Dodecyloxyphenyl)-4-styryl-1*H*-pyrazole (5b). Yield 15%; yellow oil. δ_H ($CDCl_3$) 0.88 [3H, t, *J* = 6.7 Hz, *O*$(CH_2)_{11}CH_3$], 1.24-1.43 [18H, m, *O*$(CH_2)_2(CH_2)_9CH_3$], 1.84 [2H, quint, *J* = 7.0 Hz, *O*$CH_2CH_2(CH_2)_9CH_3$], 4.06 [2H, t, *J* = 7.0 Hz, *O*$CH_2(CH_2)_{10}CH_3$], 6.43 (1H, d, *J* = 12.0 Hz, H-α), 6.57 (1H, d, *J* = 12.0 Hz, H-β), 7.00 (1H, d, *J* = 8.3 Hz, H-3'), 7.03 (1H, ddd, *J* =

7.6, 7.5, 1.0 Hz, H-5'), 7.17-7.22 (1H, m, H-4"), 7.26 (2H, dt, *J* = 7.0, 7.4 Hz, H-3",5"), 7.32 (1H, ddd, *J* = 8.3, 7.5, 1.8 Hz, H-4'), 7.36 (1H, br s, H-5), 7.39 (2H, d, *J* = 7.0 Hz, H-2",6"), 7.69 (1H, dd, *J* = 7.6, 1.8 Hz, H-6'). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_{10}CH_3$], 22.6 [$O(CH_2)_{10}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_8CH_3$], 29.2, 29.3, 29.48, 29.54 and 29.6 [$OCH_2CH_2CH_2(CH_2)_6CH_2CH_2CH_3$], 31.9 [$O(CH_2)_9CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_{10}CH_3$], 112.3 (C-3'), 115.5 (C-4), 118.2 (C-1'), 120.9 (C-5'), 121.2 (C-α), 127.0 (C-4"), 128.2 (C-3",5"), 128.5 (C-2",6"), 129.4 (C-β), 129.5 (C-4'), 130.3 (C-6'), 137.6 (C-3), 138.7 (C-5,1"), 155.8 (C-2'). MS (EI): *m/z* (%) 430 ($M^{+\bullet}$, 100), 415 [$(M-CH_3)^+$, 1], 401 [$(M-C_2H_5)^+$, 2], 373 [$(M-C_4H_9)^+$, 3], 339 (4), 289 [$(M-C_{10}H_{21})^+$, 2], 275 [$(M-C_{11}H_{23})^+$, 7], 261 [$(M-C_{12}H_{25})^+$, 25], 245 (6), 231 (3), 202 (3), 185 (10), 171 (43), 128 (3), 115 (8), 102 (3), 91 (7), 78 (2), 69 (5), 55 (16). Anal. Calcd for $C_{29}H_{38}N_2O$: C, 74.56; H, 7.82; N, 6.21. Found: C, 74.25; H, 7.87; N, 6.16.

(*Z*)-4-(4-Chlorostyryl)-3(5)-(2-decyloxyphenyl)-1*H*-pyrazole (5c). Yield 18%; yellow oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.6 Hz, $O(CH_2)_9CH_3$], 1.21-1.40 [14H, m, $OCH_2CH_2(CH_2)_7CH_3$], 1.81 [2H, quint, *J* = 6.6 Hz, $OCH_2CH_2(CH_2)_7CH_3$], 4.06 [2H, t, *J* = 6.6 Hz, $OCH_2(CH_2)_8CH_3$], 6.44 (1H, d, *J* = 11.9 Hz, H-α), 6.50 (1H, d, *J* = 11.9 Hz, H-β), 7.01 (1H, dd, *J* = 8.0, 2.2 Hz, H-3'), 7.05 (1H, ddd, *J* = 8.2, 7.6, 2.2 Hz, H-5'), 7.20 (2H, d, *J* = 8.4 Hz, H-3",5"), 7.29 (2H, d, *J* = 8.4 Hz, H-2",6"), 7.30-7.36 (2H, m, H-4',5), 7.64 (1H, dd, *J* = 7.6, 1.5 Hz, H-6'). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_8CH_3$], 22.6 [$OCH_2(CH_2)_7CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_6CH_3$], 29.0, 29.2, 29.3 and 29.5 [$OCH_2CH_2CH_2(CH_2)_4(CH_2)_2CH_3$], 31.8 [$OCH_2(CH_2)_6CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_8CH_3$], 112.3 (C-3'), 115.0 (C-4), 118.0 (C-1'), 120.4 (C-5'), 121.9 (C-α), 128.2 (C-β), 128.4 (C-2",6"), 129.4 (C-4'), 129.8 (C-3",5"), 130.2 (C-6'), 132.6 (C-4"), 136.1 (C-1"), 138.2 (C-3), 138.6 (C-5), 155.8 (C-2'). MS (EI): *m/z* (%) 438 ($M^{+\bullet}$, ^{37}Cl, 14), 436 ($M^{+\bullet}$, ^{35}Cl, 44), 423 (4), 314 (6), 313 (32), 295 [$(M-C_{10}H_{21})^+$, 2], 281 (7), 279 [$(M-OC_{10}H_{21})^+$, 7], 260 (10), 231 (5), 200 (7), 199 (26), 186 (27), 171 (100), 160 (14), 141 (10), 139 (21), 111 (8). HRMS-EI *m/z* for $C_{27}H_{33}N_2O^{35}Cl$ ($M^{+\cdot}$) calcd 436.2281, found 436.2269.

(*Z*)-4-(4-Chlorostyryl)-3(5)-(2-dodecyloxyphenyl)-1*H*-pyrazole (5d). Yield 16%; yellow oil. δ_H ($CDCl_3$, 500.13 MHz) 0.88 [3H, t, *J* = 6.7 Hz, $O(CH_2)_{11}CH_3$], 1.24-1.43 [18H, m, $O(CH_2)_2(CH_2)_9CH_3$)], 1.84 [2H, quint, *J* = 7.0 Hz, $OCH_2CH_2(CH_2)_9CH_3$)], 4.06 [2H, t, *J* = 7.0 Hz, $OCH_2(CH_2)_{10}CH_3$)], 6.44 (1H, AB, *J* = 12.0 Hz, H-α), 6.50 (1H, AB, *J* = 12.0 Hz, H-β), 7.00 (1H, d, *J* = 8.3 Hz, H-3'), 7.03 (1H, ddd, *J* = 8.2, 7.4, 0.9 Hz, H-5'), 7.20 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.30 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.32 (1H, ddd, *J* = 8.3, 8.2, 1.5 Hz, H-4'), 7.35 (1H, s, H-5), 7.65 (1H, dd, *J* = 7.4, 1.5 Hz, H-6'). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [$OCH_2(CH_2)_{10}CH_3$], 22.7 [$O(CH_2)_{10}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_8CH_3$], 29.2, 29.3 29.5, 29.59, 29.61 [$OCH_2CH_2CH_2(CH_2)_6(CH_2)_2CH_3$], 31.9 [$OCH_2(CH_2)_8CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_{10}CH_3$], 112.3 (C-3'), 115.0 (C-4), 117.5 (C-1'), 120.9 (C-5'), 121.9 (C-α), 128.2 (C-β), 128.4 (C-2",6"), 129.6 (C-4'), 129.9 (C-3",5"), 130.2 (C-6'), 132.5 (C-4"), 136.1 (C-1"), 138.0 (C-3), 138.9 (C-5), 155.8 (C-2'). MS (EI): *m/z* (%) 466 ($M^{+\bullet}$, ^{37}Cl, 47), 464 ($M^{+\bullet}$, ^{35}Cl, 100), 309 (5), 295 [$(M-C_{12}H_{25})^+$, 20], 279 [$(M-OC_{12}H_{25})^+$, 4], 260 (6), 231 (4), 202 (6), 185 (10), 171 (46), 125 (7), 91 (7), 69 (11). HRMS-EI *m/z* for $C_{29}H_{37}N_2O^{35}Cl$ ($M^{+\cdot}$) calcd 464.2594, found 464.2577.

(*E*)-3(5)-(2-Decyloxyphenyl)-4-styryl-1*H*-pyrazole (6a). Yield 15%, white solid (from ethanol); mp 43-44ºC. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 7.0 Hz, $O(CH_2)_9CH_3$], 1.24-1.39 [14H, m, $OCH_2CH_2(CH_2)_7CH_3$], 1.82 [2H, quint, *J* = 7.1 Hz, $OCH_2CH_2(CH_2)_7CH_3$], 4.07 [2H, t, *J* = 7.1 Hz, $OCH_2(CH_2)_8CH_3$], 6.95 (1H, d, *J* = 16.3 Hz, H-β), 7.05 (1H, dd, *J* = 8.0, 1.0 Hz, H-3'), 7.07 (1H, d, *J* = 16.3 Hz, H-α), 7.08 (1H, ddd, *J* = 7.7, 7.6, 1.0 Hz, H-5'), 7.22 (1H, dd, *J* = 7.6, 1.3, H-4"), 7.33 (2H, t, *J* = 7.6, 7.3 Hz, H-3",5"), 7.37 (1H, ddd, *J* = 8.0, 7.7, 1.7 Hz, H-4'), 7.45 (2H, dd, *J* = 7.3, 1.3 Hz, H-2",6"), 7.52 (1H, dd, *J* = 7.6, 1.7 Hz, H-6'), 7.90 (1H, br s, H-5). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [$OCH_2(CH_2)_8CH_3$], 22.7 [$O(CH_2)_8CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_6CH_3$], 29.2, 29.3, 29.48 and 29.52 [$OCH_2CH_2CH_2(CH_2)_4(CH_2)_2CH_3$], 31.9 [$O(CH_2)_7CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_8CH_3$], 112.5 (C-3'), 118.1 (C-1'), 118.2 (C-4), 120.1 (C-α), 121.1 (C-5'), 126.0 (C-2",6"), 127.1 (C-4"), 127.9 (C-β), 128.6 (C-3",5"), 129.8 (C-4'), 130.6 (C-6'), 136.3 (C-1"), 137.2 (C-5), 137.8 (C-3), 156.0 (C-2'). *m/z* (ESI-MS) 403 $[M+H]^+$. HRMS-ESI *m/z* for $C_{27}H_{35}N_2O$ $[(M+H)^+]$ calcd 403.27439, found 403.27408.

(*E*)-3(5)-(2-Dodecyloxyphenyl)-4-styryl-1*H*-pyrazole (6b). Yield 4%; yellow oil. δ_H ($CDCl_3$) 0.88 [3H, t, *J* = 6.7 Hz, $O(CH_2)_{11}CH_3$], 1.23-1.38 [18H, m, $O(CH_2)_2(CH_2)_9CH_3$], 1.79 [2H, quint, *J* = 7.0 Hz, $OCH_2CH_2(CH_2)_9CH_3$], 4.04 [2H, t, *J* = 7.0 Hz, $OCH_2(CH_2)_{10}CH_3$], 6.93 (1H, d, *J* = 16.5 Hz, H-β), 7.01-7.06 (1H, m, H-5'), 7.06 (1H, d, *J* = 16.5 Hz, H-α), 7.07 (1H, dd, *J* = 7.5, 0.9 Hz, H-3'), 7.21 (1H, dd, *J* = 7.3, 1.6 Hz, H-4"), 7.29-7.34 (2H, m, H-3",5"), 7.32-7.39 (1H, m, H-4'), 7.44 (2H, dd, *J* = 7.2, 1.6 Hz, H-2",6"), 7.50 (1H, dd, *J* = 7.6, 1.7 Hz, H-6'), 7.88 (1H, br s, H-5). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_{10}CH_3$], 22.7 [$O(CH_2)_{10}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_8CH_3$], 29.1, 29.2, 29.28, 29.31, 29.45 and 29.54 [$O(CH_2)_3(CH_2)_6(CH_2)_2CH_3$], 29.6 [$OCH_2CH_2(CH_2)_9CH_3$], 31.9 [$O(CH_2)_9CH_2CH_2CH_3$], 68.8 [$OCH_2(CH_2)_{10}CH_3$], 112.5 (C-3'), 118.4 (C-4), 119.5 (C-1',α), 121.0 (C-5'), 126.0 (C-2",6"), 127.0 (C-4"), 127.7 (C-β), 128.6 (C-3",5"), 129.7 (C-4'), 130.7 (C-6'), 137.3 (C-5), 137.8 (C-3,1"), 156.0 (C-2'). MS (EI): *m/z* (EI, %) = 430 ($M^{+\bullet}$, 100), 402 (3), 373 [$(M-C_4H_9)^+$, 3], 341 (5), 317 [$(M-C_8H_{17})^+$, 4], 295 (7), 275 [$(M-C_{11}H_{23})^+$, 9], 261 [$(M-C_{12}H_{25})^+$, 29], 245 (8), 231 (5), 202 (6), 185 (16), 171 (58), 160 (6), 143 (10), 128 (12), 115 (16), 105 (6), 91 (27), 77 (9), 55 (23). HRMS-EI *m/z* for $C_{29}H_{38}N_2O$ ($M^{+\cdot}$) calcd 430.2984, found 430.2984.

(*E*)-4-(4-Chlorostyryl)-3(5)-(2-decyloxyphenyl)-1*H*-pyrazole (6c). Yield 9%; oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, $O(CH_2)_9CH_3$], 1.24-1.42 [m, 14H, $OCH_2CH_2(CH_2)_7CH_3$], 1.80 [2H, quint, *J* = 6.9 Hz, $OCH_2CH_2(CH_2)_7CH_3$], 4.06 [2H, t, *J* = 6.9 Hz, $OCH_2(CH_2)_8CH_3$], 6.88 (1H, d, *J* = 16.5 Hz, H-β), 7.03 (1H, d, *J* = 16.5 Hz, H-α), 7.04 (1H, dd, *J* = 7.3, 1.4 Hz, H-3'), 7.08 (1H, ddd, *J* = 7.9, 7.6, 1.4 Hz, H-5'), 7.28 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.36 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.37 (1H, ddd, *J* = 7.9, 7.3, 1.6 Hz, H-4'), 7.49 (1H, dd, *J* = 7.6, 1.6 Hz, H-6'), 7.89 (1H, br s, H-5). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_8CH_3$], 22.7 [$OCH_2(CH_2)_7CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_6CH_3$], 29.1, 29.3, 29.47 and 29.51 [$OCH_2CH_2CH_2$ $(CH_2)_4(CH_2)_2CH_3$], 31.9 [$O(CH_2)_7CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_8CH_3$], 112.5 (C-3'), 117.5 (C-4), 118.1 (C-1'), 120.1 (C-α), 121.1 (C-5'), 126.4 (C-β), 127.2 (C-2",6"), 128.7 (C-3",5"), 129.9 (C-4'), 130.6 (C-6'), 132.5 (C-4"), 136.3 (C-1"), 137.1 (C-3), 137.4 (C-5), 156.0 (C-2'). MS (EI): *m/z* (%) 438 ($M^{+\bullet}$,^{37}Cl, 42), 436 ($M^{+\bullet}$,^{35}Cl, 100), 402 [$(M-Cl)^+$, 1], 365 [$(M-C_5H_{11})^+$, 2], 328 (2), 309 [(M-

$C_9H_{19})^+$, 5], 295 [(M-$C_{10}H_{21})^+$, 20], 260 (6), 241 (2), 231 (4), 214 (2), 202 (4), 185 (10), 171 (58), 160 (5), 149 (2), 127 (2), 115 (5), 102 (2), 77 (3), 69 (6), 57 (17). HRMS-EI *m/z* for $C_{27}H_{33}N_2O^{35}Cl$ ($M^{+\cdot}$) calcd 436.2281, found 436.2273.

(*E*)-4-(4-Chlorostyryl)-3(5)-(2-dodecyloxyphenyl)-1*H*-pyrazole (6d). Yield 16%; white solid (from ethanol); mp 104-105ºC. δ_H ($CDCl_3$) 0.88 [3H, t, *J* = 6.8 Hz, $O(CH_2)_{11}CH_3$], 1.24-1.37 [18H, m, $OCH_2CH_2(CH_2)_9CH_3$], 1.81 [2H, quint, *J* = 7.0 Hz, $OCH_2CH_2CH_2(CH_2)_8CH_3$], 4.06 [2H, t, *J* = 7.0 Hz, $OCH_2(CH_2)_{10}CH_3$], 6.89 (1H, d, *J* = 16.4 Hz, H-β), 7.03 (1H, d, *J* = 16.4 Hz, H-α), 7.05 (1H, dd, *J* = 8.4, 1.0 Hz, H-3'), 7.08 (1H, ddd, *J* = 7.9, 7.5, 1.0 Hz, H-5'), 7.28 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.36 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.38 (1H, ddd, *J* = 8.4, 7.5, 1.8 Hz, H-4'), 7.49 (1H, dd, *J* = 7.9, 1.8 Hz, H-6'), 7.89 (1H, s, H-5). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_{10}CH_3$], 22.7 [$OCH_2(CH_2)_9CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_8CH_3$], 29.2, 29.30, 29.34 and 29.5 [$O(CH_2)_3(CH_2)_6(CH_2)_2CH_3$], 29.6 [$OCH_2CH_2(CH_2)_9CH_3$], 31.9 [$O(CH_2)_9CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_{10}CH_3$], 112.5 (C-3'), 117.5 (C-4), 118.1 (C-1'), 120.1 (C-α), 121.1 (C-5'), 126.4 (C-β), 127.2 (C-2",6"), 128.7 (C-3",5"), 129.9 (C-4'), 130.6 (C-6'), 132.5 (C-4"), 136.3 (C-1"), 137.4 (C-3,5), 156.0 (C-2'). *m/z* (MALDI TOF/TOF-MS) 465 $[M+H]^+$. Anal. Calcd for $C_{29}H_{37}ClN_2O$: C, 74.89; H, 8.02; N, 6.02. Found: C, 75.21; H, 7.92; N, 6.05.

(*E*)-3(5)-(2-Decyloxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (**6e).** Yield 12%; yellow oil. δ_H ($CDCl_3$, 500.13 MHz) 0.87 [3H, t, *J* = 7.0 Hz, $O(CH_2)_9CH_3$], 1.25-1.39 [14H, m, $O(CH_2)_2(CH_2)_7CH_3$], 1.78 [2H, quint., *J* = 6.9 Hz, $OCH_2CH_2(CH_2)_7CH_3$], 4.05 [2H, t, *J* = 6.9 Hz, $OCH_2(CH_2)_8CH_3$], 6.94 (1H, d, *J* = 16.3, H-β), 7.05 (1H, d, *J* = 8.1 Hz, H-3'), 7.08 (1H, ddd, *J* = 7.7, 7.5 and 0.8 Hz, H-5'), 7.13 (1H, d, *J* = 16.3 Hz, H-α), 7.39 (1H, ddd, *J* = 8.1, 7.7 and 1.7 Hz, H-4'), 7.47 (1H, dd, *J* = 7.5 and 1.7 Hz, H-6'), 7.51 (2H, d, *J* = 8.3 Hz, H-2",6"), 7.56 (2H, d, *J* = 8.3 Hz, H-3",5"), 7.90 (1H, s, H-5). δ_C ($CDCl_3$, 125.77 MHz) 14.1 [$OCH_2(CH_2)_8CH_3$], 22.6 [$O(CH_2)_8CH_2CH_3$], 26.0 [$O(CH_2)_2CH_2(CH_2)_6CH_3$], 29.1, 29.3, 29.47 and 29.51 [$OCH_2CH_2CH_2(CH_2)_3(CH_2)_3CH_3$], 31.8 [$O(CH_2)_7CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_8CH_3$], 112.5 (C-3'), 117.3 (C-4), 118.1 (C-1'), 121.0 (C-5'), 122.0 (C-α), 122.4 (q, *J* = 270.8 Hz, CF_3), 125.5 (q, *J* = 3.8 Hz, C-3",5"), 125.9 (C-β), 126.0 (C-2",6"), 128.6 (q, *J* = 32.4 Hz, C-4"), 130.1 (C-4'), 130.7 (C-6'), 137.0 (C-5), 138.1 (C-3), 141.3 (C-1"), 156.1 (C-2'). *m/z* (ESI-MS) 471 $[M+H]^+$. HRMS-ESI *m/z* for $C_{28}H_{34}N_2O^{19}F_3$ [$(M+H)^+$] calcd 471.26177, found 471.26122.

(*E*)-3(5)-(2-Dodecyloxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (6f). Yield 10%; yellow oil. δ_H ($CDCl_3$, 500.13 MHz) 0.88 [3H, t, *J* = 6.8 Hz, $O(CH_2)_{11}CH_3$], 1.23-1.41 [18H, m, $O(CH_2)_2(CH_2)_9CH_3$], 1.80 [2H, quint, *J* = 7.1 Hz, $OCH_2CH_2(CH_2)_9CH_3$], 4.07 [2H, t, *J* = 7.1 Hz, $OCH_2(CH_2)_{10}CH_3$], 6.96 (1H, d, *J* = 16.3 Hz, H-β), 7.06 (1H, dd, *J* = 8.3, 0.8 Hz, H-3'), 7.09 (1H, ddd, *J* = 7.7, 7.5, 0.8 Hz, H-5'), 7.14 (1H, d, *J* = 16.3 Hz, H-α), 7.39 (1H, ddd, *J* = 8.3, 7.7, 1.7 Hz, H-4'), 7.48 (1H, dd, *J* = 7.5, 1.7 Hz, H-6'), 7.52 (2H, d, *J* = 8.3 Hz, H-2",6"), 7.57 (2H, d, *J* = 8.3 Hz, H-3",5"), 7.92 (1H, br s, H-5). δ_C ($CDCl_3$) 14.1 [$OCH_2(CH_2)_{10}CH_3$], 22.7 [$O(CH_2)_{10}CH_2CH_3$], 26.1 [$O(CH_2)_2CH_2(CH_2)_8CH_3$], 29.1, 29.3, 29.47 and 29.6 [$OCH_2CH_2CH_2(CH_2)_6(CH_2)_2CH_3$], 31.9 [$O(CH_2)_9CH_2CH_2CH_3$], 68.9 [$OCH_2(CH_2)_{10}CH_3$], 112.6 (C-3'), 117.8 (C-4), 117.9 (C-1'), 121.1 (C-5'), 122.0 (C-α), 123.5 (q, *J* = 235.6 Hz, CF_3), 125.5

(q, *J* = 3.8 Hz, C-3",5"), 126.0 (C-2",6"), 126.1 (C-β), 128.0 (q, *J* = 32.5 Hz, C-4"), 130.1 (C-4'), 130.6 (C-6'), 137.5 (C-5), 137.8 (C-3), 141.3 (C-1"), 156.1 (C-2'). MS (EI): *m/z* (%) 498 ($M^{+\bullet}$, 57), 343 [(M-$C_{11}H_{23}$)$^+$, 18], 331 (24), 330 [(M-$C_{12}H_{25}$)$^+$, 35], 329 (37), 313 [(M-$C_{12}H_{25}O$)$^+$, 10], 172 (10), 171 (100), 160 (7), 145 (5), 124 (4), 96 (2), 64 (13). HRMS-EI *m/z* for $C_{30}H_{37}N_2O^{19}F_3$ ($M^{+\cdot}$) calcd 498.2858, found 498.2874.

(*Z*)-4-(4-Chlorostyryl)-1-decyl-3-(2-decyloxyphenyl)-1*H*-pyrazole (7c). Yield 2%; oil. δ_H ($CDCl_3$) 0.87 [6H, t, *J* = 6.6 Hz, *N*(CH_2)$_9$C*H*$_3$ and *O*(CH_2)$_9$C*H*$_3$], 1.20-1.33 [28H, m, *N*(CH_2)$_2$(C*H*$_2$)$_7$$CH_3$) and *O*($CH_2$)$_2$(C*H*$_2$)$_7$$CH_3$], 1.60 [2H, quint, *J* = 7.3 Hz, *N*CH_2C*H*$_2$(CH_2)$_7$$CH_3$], 1.92 [2H, quint, *J* = 7.1 Hz, *O*CH_2C*H*$_2$(CH_2)$_7$$CH_3$], 3.91 [2H, t, *J* = 7.3 Hz, *N*C*H*$_2$(CH_2)$_8$$CH_3$], 4.15 [2H, t, *J* = 7.1 Hz, *O*C*H*$_2$(CH_2)$_8$$CH_3$], 6.94 (1H, ddd, *J* = 7.7, 7.5, 1.2 Hz, H-5'), 7.07 (1H, dd, *J* = 8.2, 1.2 Hz, H-3'), 7.20-7.28 (1H, m, H-4'), 7.32 (2H, d, *J* = 8.6 Hz, H-3",5"), 7.38 (2H, d, *J* = 8.6 Hz, H-2",6"), 7.56 (1H, dd, *J* = 7.7, 1.6 Hz, H-6'), 7.64 (1H, br s, H-5). MS (EI): *m/z* (%) 578 ($M^{+\bullet}$, ^{37}Cl, 4), 576 ($M^{+\bullet}$, ^{35}Cl, 16), 449 (15), 436 (100), 435 (26), 407 (5), 393 (3), 379 (5), 365 (18), 351 (16), 323 (6), 311 (50), 309 (60), 296 (57), 295 (36), 282 (14), 260 (13), 199 (7), 185 (13), 171 (82). HRMS-EI *m/z* for $C_{37}H_{53}N_2O^{35}Cl$ ($M^{+\cdot}$) calcd 576.3846, found 576.3823.

(*E*)-1-Dodecyl-3-(2-dodecyloxyphenyl)-4-styryl-1*H*-pyrazole (8b). Yield 7%; oil. δ_H ($CDCl_3$) 0.88 [3H, t, *J* = 6.6 Hz, *N*(CH_2)$_{11}$C*H*$_3$], 0.88 [3H, t, *J* = 6.6 Hz, *O*(CH_2)$_{11}$C*H*$_3$], 1.11-1.33 [36H, m, *N*(CH_2)$_2$(C*H*$_2$)$_9$$CH_3$) and *O*($CH_2$)$_2$(C*H*$_2$)$_9$$CH_3$)], 1.62 [2H, quint, *J* = 6.5 Hz, *N*CH_2C*H*$_2$(CH_2)$_9$$CH_3$], 1.92 [2H, quint, *J* = 7.2 Hz, *O*CH_2C*H*$_2$(CH_2)$_9$$CH_3$], 3.93 [2H, t, *J* = 6.5 Hz, *N*C*H*$_2$(CH_2)$_{10}$$CH_3$], 4.14 [2H, t, *J* = 7.2 Hz, *O*C*H*$_2$(CH_2)$_{10}$$CH_3$], 6.68 (1H, d, *J* = 16.3 Hz, H-α), 6.84 (1H, d, *J* = 16.3 Hz, H-β), 7.00-7.48 (8H, m, H-3',4',5',2",3",4",5",6"), 7.60 (1H, dd, *J* = 7.5, 1.6 Hz, H-6'), 7.66 (1H, s, H-5). *m/z* (ESI-MS) 599 $[M+H]^+$. HRMS-ESI *m/z* for $C_{41}H_{63}N_2O$ $[(M+H)^+]$ calcd 599.49349, found 599.49349.

(*E*)-1-Decyl-3-(2-decyloxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (8e). Yield 5%; oil. δ_H ($CDCl_3$) 0.87 [6H, t, *J* = 6.7 Hz, *N*(CH_2)$_9$C*H*$_3$ and *O*(CH_2)$_9$C*H*$_3$], 1.08-1.35 [28H, m, *N*(CH_2)$_2$(C*H*$_2$)$_7$$CH_3$ and *O*(CH_2)$_2$(C*H*$_2$)$_7$$CH_3$], 1.62 [2H, quint, *J* = 6.7 Hz, *N*CH_2C*H*$_2$(CH_2)$_7$$CH_3$], 1.93 [2H, quint, *J* = 7.1 Hz, *O*CH_2C*H*$_2$(CH_2)$_7$$CH_3$], 3.93 [2H, t, *J* = 6.7 Hz, *N*C*H*$_2$(CH_2)$_8$$CH_3$], 4.15 [2H, t, *J* = 7.1 Hz, *O*C*H*$_2$(CH_2)$_8$$CH_3$], 6.68 (1H, d, *J* = 16.5 Hz, H-α), 6.94 (1H, d, *J* = 16.5 Hz, H-β), 6.97 (1H, dd, *J* = 7.2, 0.8, H-3'), 7.03 (1H, ddd, *J* = 7.8, 7.5, 0.8 Hz, H-5'), 7.37 (1H, ddd, *J* = 7.8, 7.2, 1.8 Hz, H-4'), 7.41 (2H, d, *J* = 8.2 Hz, H-2",6"), 7.43 (1H, dd, *J* = 7.5, 1.8 Hz, H-6'), 7.50 (2H, d, *J* = 8.2 Hz, H-3",5"), 7.68 (1H, s, H-5). MS (EI): *m/z* (%) 610 ($M^{+\bullet}$, 48), 591 [(M-F)$^+$, 6], 553 [(M-C_4H_9)$^+$, 6], 539 [(M-C_5H_{11})$^+$, 13], 525 [(M-C_6H_{13})$^+$, 10], 498 (5), 497 [(M-C_8H_{17})$^+$, 15], 484 [(M-C_9H_{19})$^+$, 32], 483 (100), 470 [(M-$C_{10}H_{21}$)$^+$, 39], 469 (38), 451 (22), 399 (8), 357 (8), 344 (13), 343 (26), 329 (44), 309 (53), 199 (6), 173 (12), 171 (34), 145 (6). HRMS-EI *m/z* for $C_{38}H_{53}N_2O^{19}F_3$ ($M^{+\cdot}$) calcd 610.4110, found 610.4121.

(*E*)-1-Dodecyl-3-(2-dodecyloxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (8f). Yield 4%; oil. δ_H ($CDCl_3$) 0.87 [3H, t, *J* = 6.7 Hz, *N*(CH_2)$_{11}$C*H*$_3$], 0.88 [3H, t, *J* = 6.8 Hz, *O*(CH_2)$_{11}$C*H*$_3$], 1.08-1.35 [36H, m, *N*(CH_2)$_2$(C*H*$_2$)$_9$$CH_3$) and *O*($CH_2$)$_2$(C*H*$_2$)$_9$$CH_3$)], 1.60 [2H, quint, *J* = 7.2 Hz, *N*CH_2C*H*$_2$(CH_2)$_9$$CH_3$], 1.91 [2H, quint, *J* = 7.4 Hz, *O*CH_2C*H*$_2$(CH_2)$_9$$CH_3$],

3.93 [2H, t, *J* = 7.2 Hz, $NCH_2(CH_2)_{10}CH_3$], 4.15 [2H, t, *J* = 7.4 Hz, $OCH_2(CH_2)_{10}CH_3$], 6.68 (1H, d, *J* = 16.6 Hz, H-α), 6.94 (1H, d, *J* = 16.6 Hz, H-β), 7.03 (1H, ddd, *J* = 7.5, 7.3, 0.9 Hz, H-5'), 7.04 (1H, d, *J* = 7.3 Hz, H-3'), 7.34-7.37 (1H, m, H-4'), 7.38 (2H, d, *J* = 8.2 Hz, H-2",6"), 7.43 (1H, dd, *J* = 7.5, 1.8 Hz, H-6'), 7.50 (2H, d, *J* = 8.2 Hz, H-3",5"), 7.69 (1H, s, H-5). MS (EI): *m/z* (%) = 667 ($M^{+\bullet}$, 100), 623 [$(M-C_3H_7)^+$, 3], 581 [$(M-C_6H_{13})^+$, 3], 553 [$(M-C_8H_{17})^+$, 5], 539 [$(M-C_9H_{19})^+$, 3], 525 [$(M-C_{10}H_{21})^+$, 6], 512 [$(M-C_{11}H_{22})^+$, 9], 499 (24), 481 [$(M-C_{12}H_{25}O)^+$, 5], 469 (3), 441 (4), 399 (5), 369 (4), 357 (6), 343 (15), 331 (12), 313 (6), 301 (4), 275 (3), 233 (3), 211 (5), 197 (8), 185 (11), 171 (23), 159 (7), 120 (6). HRMS-ESI *m/z* for $C_{42}H_{62}N_2O^{19}F_3$ [$(M+H)^+$] calcd 667.48088, found 667.48073.

CB_1 receptors radioligand binding assays

Preparation of membranes. Brain membranes were prepared by established methods[23] from the prefrontal cortex of human brains obtained at autopsy in the ''Instituto Vasco de Medicina Legal'', Bilbao, Spain. All tissue samples were collected under an approved protocol from each institution's Human Studies Committee. Briefly, the tissue samples were homogenized in 5 mL of ice-cold Tris sucrose with EDTA buffer (5mM Tris–HCl, 250mM sucrose, 1 nM EDTA, pH, 7.4; and 0.1% BSA). The homogenates were centrifuged at 3000 rpm for 10 min, and the supernatants were then recentrifuged at 18000 rpm for 10 min. The resulting pellet was incubated at 37ºC for 15 min to remove the endogenous cannabinoids. After that, the pellet was washed twice and resuspended in buffer without BSA.

[^{3}H]CP55-940 Binding assay

Total [^{3}H]CP55-940 binding was measured in 0.55 mL aliquots (50mM Tris–HCl, EDTA, pH 7.4 with 0.1% BSA) of human brain cortical membranes that were incubated with [^{3}H]CP55-940 (1 nM) for 60 min at 30ºC in the absence or presence of competing compounds (10^{-12}-10^{-3} M, 10 concentrations). Non-specific binding was estimated in the presence of 10^{-6} M WIN55212-2. Incubations were terminated by diluting the samples with 5 mL ice-cold Tris–incubation buffer with 0.1% BSA (4ºC). Membrane bound [^{3}H]CP55-940 was separated by vacuum filtration through Whatman GF/C glass fiber filters. The filters were then rinsed twice with 5 mL of incubation buffer and transferred to minivials containing 3–5 mL of OptiPhase ''HiSafe'' II cocktail and counted for radioactivity by liquid scintillation spectrometry.

Analysis of binding data

Analysis of competition experiments to obtain the inhibition constant (Ki) was performed by non-linear regression using the EBDA-LIGAND program. All experiments were analyzed assuming a one-site model of radioligand binding.

CB_2 receptors radioligand binding assays

CB_2 receptor binding studies were performed according to the procedure of *Griffin et al.*[42] using membrane fractions of human CB_2 receptor transfected cells, which ensures that only this type of

receptor is present. HEK293EBNA membranes were purchased from Perkin-Elmer Life and Analytical Sciences (Boston, MA). HEK293EBNA membranes were resuspended in Tris buffer (50 mM Tris-HCl, 2.5 mM EGTA, 5 mM $MgCl_2$, 1 mg/mL BSA fatty acid free, pH 7.5). Fractions of the final membrane suspension (about 0.18 mg/mL of protein) were incubated at 30°C for 90 min with 0.33 nM [^{3}H]-CP55-940 (139.6 Ci/mmol), in the presence or absence of several concentrations of the competing drug, in a final volume of 0.6 mL of assay buffer (50 mM Tris-HCl, 2.5 mM EGTA, 5 mM $MgCl_2$, 1 mg/mL BSA fatty acid free, pH 7.5). Nonspecific binding was determined in the presence of 10 μM WIN 55,212-2. Silanized tubes were used throughout the experiment to minimize receptor-binding loss due to tube adsorption. The reaction was terminated by rapid vacuum filtration with a filter mate Harvester apparatus (Perkin-Elmer) through Filtermat A GF/C filters pre-soaked in 0.05% polyethylenimine (PEI). The filters were washed nine times with ice-cold buffer (50 mM Tris-HCl, 2.5 mM EGTA, 5 mM $MgCl_2$, 1 mg/mL BSA fatty acid free, pH 7.5), and bound radioactivity was measured with a 1450 LSC & Luminescence counter Wallac MicroBeta TriLux (Perkin-Elmer). The binding assay showed the appropriate sensitivity to CB_2 ligands. Thus, WIN55,212-2 and methanandamide inhibited the binding with K_i values of 2.1 and 96 nM, respectively. For all binding experiments, competition binding curves were analyzed by using an iterative curve-fitting procedure GraphPad (Prism), which provided IC_{50} values for test compounds. K_i values were determined by the method of *Cheng* and *Prusoff*.[43] Table 3 presents the affinities of the tested compounds using as reference WIN55,212-2 and methanandamide.

Acknowledgements

Thanks are due to the University of Aveiro, "Fundação para a Ciência e a Tecnologia" and FEDER for funding the Organic Chemistry Research Unit. One of us VLM Silva is also grateful to "Fundação para a Ciência e a Tecnologia" and FSE for a PhD grant (SFRH/BD/6647/2001). Financial support from the Bizkaiko Foru Aldundia (EKINBERRI 7/12/EK/2005/65) and the Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM to LFC and from FCT-CSIC bilateral convention (2007PT0038) to NJ, AMSS, MCYT (SAF2006-13391-C03-02) and CANNAB-CM (S-SAL-0261-2006) is also grateful. We thank the staff members of the Instituto Vasco de Medicina Legal for their cooperation in the study.

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