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Synthesis and Pharmacological Evaluation of Chlorinated *N*-Alkyl-3- and -5-(2-hydroxyphenyl)pyrazoles as CB_1 Cannabinoid Ligands

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Summary. The syntheses of several new 3- and 5-(4-chloro-2-hydroxyphenyl)-5- and -3-(2,4-dichlorophenyl)-1-alkylpyrazoles are reported. These syntheses started from simple chlorophenols, 2,4-dichlorobenzaldehyde or ethyl 2,4-dichlorobenzoate in order to prepare pyrazoles bearing three and four chloro substituents in certain positions. The affinity of these compounds towards the CB_1 type cannabinoids receptors was then evaluated in human brain tissues (frontal cortex). The results showed that some of the compounds exhibit affinity towards this kind of receptors in the micromolar range.

Keywords. 3- and 5-(2-Hydroxyphenyl)-*N*-alkylpyrazoles; Chloropyrazoles; NMR spectroscopy; CB_1 cannabinoid receptors; Radioligand.

Introduction

Pyrazoles are well known five-membered heterocyclic compounds which play a major role in medicinal chemistry. Several drugs are pyrazole derivatives or include a pyrazole skeleton in its structure (Zaleplon, Cizolirtine, Celecoxib, Fomepizol, Viagra, Lesopitron, Granisetron . . .) [1]. The pyrazole moiety is regarded as a versatile scaffold in the cannabinoid research field.

The cannabinoid system has generated a great interest as therapeutic target [2, 3]. Cannabis has long been used for a variety of medical applications. In 1964, *Gaoni* and *Mechoulam* isolated and identified the main psychoactive component from *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-*THC*) [4]. The synthesized Δ^9-*THC* named dronabinol (Marinol) is licensed by the Food and Drug Administration in the USA for anti-emesis associated with cancer chemotherapy, and appetite stimulation for patients with AIDS. This drug is a nonselective cannabinoid receptor agonist. So far, two subtypes of cannabinoid receptor, CB_1 and CB_2, have been cloned. They are both G protein coupled. The CB_1 cannabinoid receptors are expressed in high abundance within the central nervous system while the CB_2 subtype is mainly associated with the immune system [5]. Even though data of different studies suggest the presence of other cannabinoid receptor subtypes, they are still uncloned. The identification of endogeneous ligands and the synthesis of agonists and antagonists of the CB_1 and CB_2 receptors have contributed to a better understanding of the cannabinoid pharmacology [6].

The emergence of potent and more selective synthetic ligands has generated interesting opportunities for the development of novel cannabinoid drugs [7, 8]. These cannabinoid ligands belong to structurally diverse classes of compounds: classical cannabinoids, nonclassical cannabinoids, eicosanoids,

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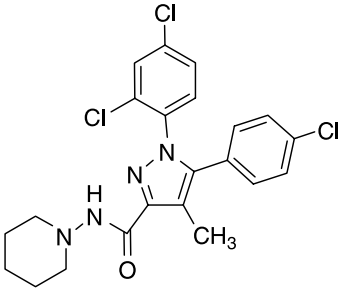
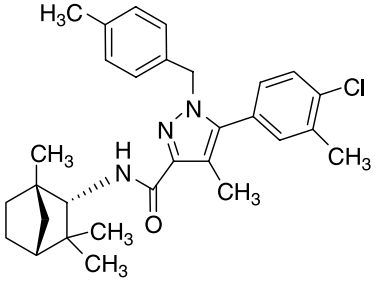
aminoalkylindoles, arylpyrazoles, and related heterocyclic compounds [8]. Arylpyrazoles play a major role in cannabinoid chemistry.

In 1994, Sanofi-Aventis reported the first CB_1 cannabinoid antagonist, the pyrazole SR141716 known under the name Rimonabant or Acomplia [9, 10]. In Europe, Acomplia was approved by EMEA in June 2006 to be used as an adjunct to diet and exercise for obese or overweight patients with associated risk factors, such as type 2 diabetes or dyslipidaeamia. In advanced clinical trials, Rimonabant shows promising therapeutic application for smoking cessation. The clinical efficacy of this pyrazole has justified the development of this class of cannabinoid ligands. As a result of these efforts, in 1997 another pyrazole, SR144528 was identified as antagonist of CB_2 receptor [11]. Even though the therapeutic applications for CB_2 receptor are not so much developed than for the CB_1 receptor, they include disorders such as rheumatoid arthritis, multiple sclerosis, psoriasis, infections and asthma. Different pharmacophore models have been described for the pyrazole class of cannabinoid ligands, they are outlined in recent reviews [12, 13]. We were interested to explore the 3,5-diarylpyrazoles as new templates for cannabinoid recognition. Based on the diverse cannabinoid structures such as the CB_1 antagonist SR141716, the 3-hexyl-1,5-diarylpyrazole O-1877 described by *Martin et al.* [13], and the *in vivo* CB_1 antagonist 1,2,4-triazole LH21 [14], we decided to synthesize a series of *N*-alkyl-3(5)-phenyl-5(3)-hydroxyphenylpyrazoles **13** and **14** and test them as CB_1 cannabinoid ligand in radioligand binding assays. The proposed pyrazoles **13** and **14** present some pharmacophoric elements in common with O-1877 and LH21: a lipophilic side chain crucial for CB_1 receptor recognition and a *para*-chlorophenyl substituent on the heterocyclic ring. In an effort to mimic hydrogen bonds provided by the carboxyamide piperidine functionality of SR151716 one of the phenyl rings has been substituted by a hydroxy group.

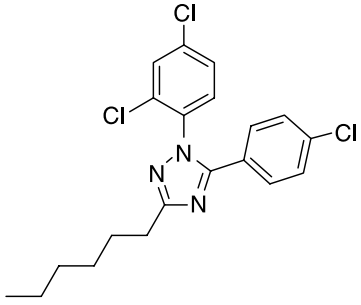
Synthetic routes to prepare the proposed new *N*-alkyl-3(5)-phenyl-5(3)-hydroxyphenylpyrazoles from β-diketones or chalcones derivatives are reported here. These new pyrazole derivatives have been tested by radioligand binding assay on membranes from post-mortem human frontal cortex.



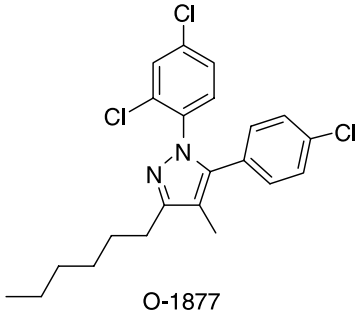
SR141716 (CB_1)
(Rimonabant, Acomplia)
$K_i(CB_1)$ = 1.98 ± 0.36 n*M* [22]



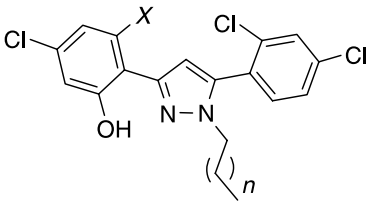
SR144528 (CB_2)



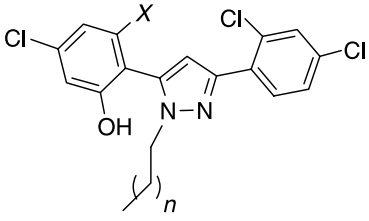
LH21
$K_i(CB_1)$ = 855 ± 296 n*M*



O-1877
$K_i(CB_1)$ = 422 ± 40 n*M*



13



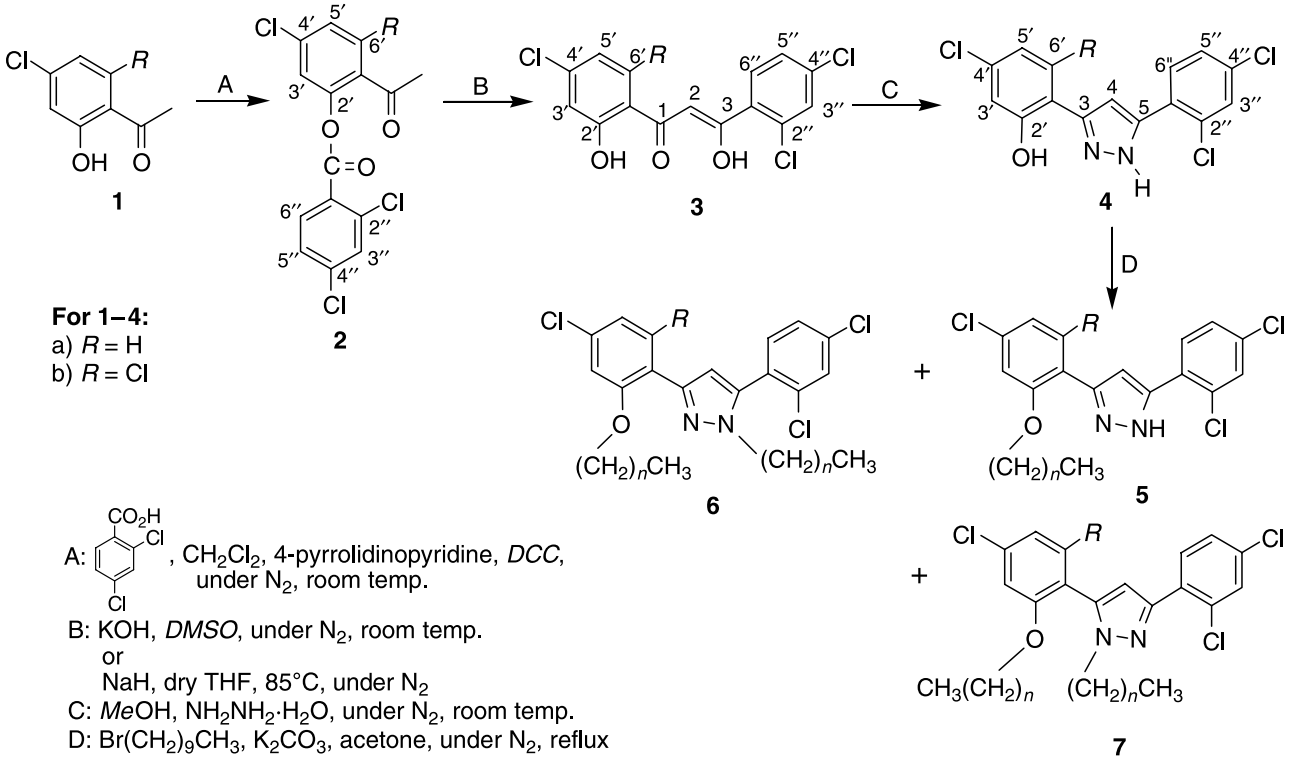
14

Results and Discussion

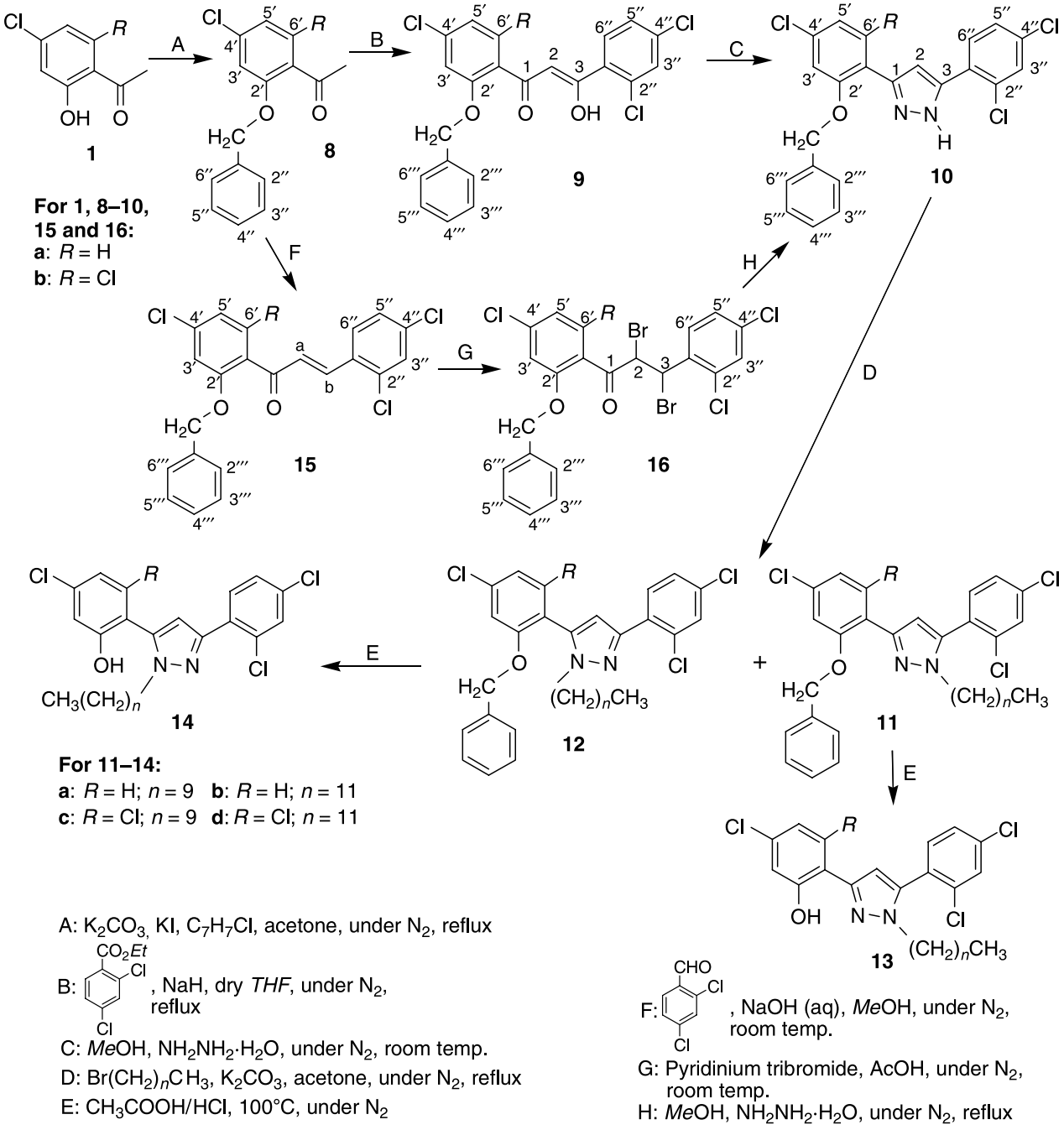
Synthesis

Our first approach to synthesize pyrazoles **13** and **14** started with the reaction of acetophenones **1a**, **1b** with 2,4-dichlorobenzoic acid, in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC) and 4-pyrrolidinopyridine to give esters **2a**, **2b**. The treatment of these esters with a concentrate solution of potassium hydroxide in *DMSO* yielded the corresponding enones **3a**, **3b** in moderate to good yields (**3a**, 68%; **3b**, 37%). However the yield of **3b** increased (64%) when the *Baker-Venkataraman* rearrangement [15–17] was done with sodium hydride in dry *THF*. The reaction of compounds **3a**, **3b** with hydrazine hydrate in methanol at room temperature yielded the corresponding pyrazoles **4a**, **4b**. The alkylation of these pyrazoles **4a**, **4b** with decyl bromide in basic medium gave 3-(4-chloro-2-decyloxyphenyl)-1-decyl-5-(2,4-dichlorophenyl)pyrazoles **6a**, **6b** as main products and 3(5)-(4-chloro-2-decyloxyphenyl)-5(3)-(2,4-dichlorophenyl)pyrazoles **5a**, **5b** and 5-(4-chloro-2-decyloxyphenyl)-1-decyl-3-(2,4-dichlorophenyl)pyrazoles **7a**, **7b** as by-products (Scheme 1). Even after several attempts with different bases, solvents, and reaction conditions we did not succeed in obtaining the desired pyrazoles **13a**, **13b** as product of the alkylation reaction of **4a**, **4b** with long chain alkyl halides.

Then it was decided to develop another synthetic route that involves the protection of the 2′-O*H* group of the acetophenones **1a**, **1b** with a group that could be easily removed at the end of the synthesis and avoiding the introduction of the long chain alkyl group on this position during pyrazoles alkylation reaction (Scheme 2). The 2′-O*H* groups of the acetophenones **1a**, **1b** were protected with benzyl groups. The *Claisen* condensation of the obtained 2′-benzyloxy-4′-chloroacetophenone **8a** with ethyl 2,4-dichlorobenzoate gave diketone **9a** in low yield (21%). The pyrazole **10a** was synthesized as before through the reaction of **9a** with hydrazine hydrate and their alkylation in basic medium gave a mixture of *N*-alkylated pyrazoles **11a** and **12a**.



Scheme 1



Scheme 2

We were not able to synthesize diketone **9b** through the *Claisen* condensation of 2′-benzyloxy-4′,6′-dichloroacetophenone **8b** with ethyl 2,4-dichlorobenzoate, probably due to the steric hindrance originated by the chlorine atom in 6′-position of the acetophenone [18].

The synthetic limitations found in the synthesis of diketones **9a**, **9b** led us to search another methodology in order to prepare pyrazole derivatives **13a**–**13d** and **14a**–**14d**. This type of pyrazoles can be prepared from 2′-hydroxychalcone derivatives instead of diketones [19]. Accordingly we started the synthesis of 2′-benzyloxychalcones **15a**, **15b** through a base-catalyzed aldol condensation reaction of the 2′-benzyloxyacetophenones **8a**, **8b** with 2,4-dichlorobenzaldehyde. Since the reaction of chal-

cones with hydrazine hydrate affords 2-pyrazolines, which must be further oxidized into the expected pyrazoles, and as it is also known that the reaction of α,β-dibromochalcones with hydrazine hydrate can afford pyrazoles [20], we decided to explore this synthetic route. Due to the presence of the 2′-benzyloxy substituent, an activating group on chalcones **15a**, **15b**, the bromination with bromine is not convenient because halogenation on the activated phenyl ring can also occur, so we used pyridinium tribromide because it is less reactive. The bromination of the chalcones with pyridinium tribromide in acetic acid afforded the α,β-dibromochalcones **16a**, **16b** in very good yields (89–94%). Treatment of the appropriate α,β-dibromochalcones **16a**, **16b** with an excess of hydrazine hydrate in refluxing methanol afforded pyrazoles **10a**, **10b** in moderate yields (48–62%). The alkylation of pyrazoles **10a**, **10b** with long chain alkyl halides in basic medium gave a mixture of 3-(2-benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-alkylpyrazoles **11a**–**11d** and 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-alkylpyrazoles **12a**–**12d**, which were separated by thin layer chromatography.

The last step in the synthesis of the expected pyrazoles **13a**–**13d** and **14a**–**14d** was the deprotection of the 2′-O*H* group by the cleavage of the benzyl group in acidic conditions (CH_3COOH/HCl).

NMR Spectroscopy

The main features in the ^{1}H NMR spectra of diketones **3a**, **3b** are the typical proton resonances of the 2′-O*H* and 3-O*H* groups and H-2, appearing as singlets at $\delta_H = 10.81$–12.13, 15.10–15.53, and 6.74–7.05 ppm. Due to the electronic conjugation of compound **3a** this diketone must have a planar structure, but the presence of the 6′-Cl substituent in the case of **3b** is probably responsible for the non-coplanarity between the hydroxylated phenyl ring and the other part of the structure [20]. This effect caused a weakening of the hydrogen bond between 2′-O*H* and carbonyl (C-1) groups ($\delta_H = 10.81$ ppm for **3b** and $\delta_H = 12.13$ ppm for **3a**) and a deshielding effect on the H-2 and C-2 resonances of **3b** relative to those of **3a**.

From the ^{1}H NMR spectra of pyrazoles **4a**, **4b** in $CDCl_3$ one can observe the broad singlets at $\delta_H \sim 11$ and ~ 13 ppm, due to the N*H* and 2′-O*H* protons, respectively. Due to the low solubility of pyrazoles **4a**, **4b** in $CDCl_3$, we have done the full characterization in *DMSO*-d_6 and the 2′-O*H* proton resonance appears at $\delta_H \sim 13$ ppm. The presence of a hydrogen bond between the 2′-hydroxylic proton and N-2 are responsible for the high frequency value of the 2′-O*H* proton resonance and for the absence of prototropy, being compounds **4a**, **4b** named as 3-(4-chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)pyrazoles. Two important carbon resonances are identified from the ^{13}C NMR spectra of these pyrazoles **4a**, **4b**, those due to the C-3 ($\delta_C =$ 137.3–139.6 ppm) and C-5 ($\delta_C = 144.9$–146.3 ppm) carbon atoms, assigned unequivocally through the connectivities found in the HMBC spectra (H-6″ → C-5) and (H-4 → C-3 and C-5). The unequivocal assignment of C-5 of **10a**, **10b** was also made by the connectivities found in the HMBC spectra with H-4 and H-6″, whereas C-3 presented connectivities with H-4.

Pyrazole isomers **11a**–**11d** and **12a**–**12d** can be distinguished by the correlations found in their HMBC spectra. In the case of pyrazoles **11a**–**11d** the connectivities of C-5 with H-6″, H-4, and protons of the methylene group linked to the pyrazolic nitrogen are only compatible with the structure of 3-(2-benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-alkylpyrazoles. In the case of pyrazoles **12a**–**12d** the connectivities of H-6″ and H-4 with C-3,

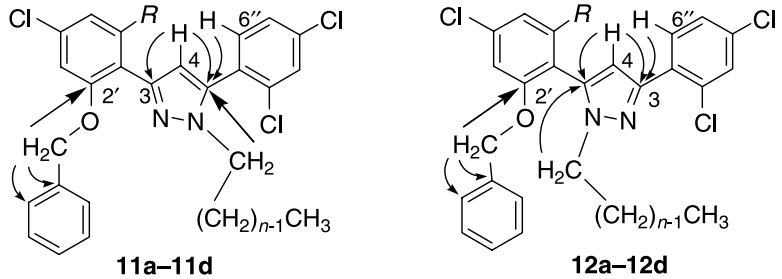


Fig. 1. Main connectivities found in the HMBC spectra of pyrazoles **11a**–**11d** and **12a**–**12d**

which do not present any correlation with aliphatic protons of the alkyl chain, conjugated with the connectivities of C-5 with H-6′ (in the case of **12a**, **12c**) and with protons of the methylene group linked to the pyrazolic nitrogen are only compatible with the structure of 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-alkylpyrazoles. Similar NMR analyses have been made in the characterization of pyrazoles **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **13a**–**13d**, and **14a**–**14d**.

Pyrazoles **13a**–**13d** and **14a**–**14d** are distinguished from their precursors **11a**–**11d** and **12a**–**12d** due to the absence in the ^{1}H NMR and ^{13}C NMR spectra of the signals typical of the benzyloxy group resonances. Instead of these signals in the ^{1}H NMR spectra one can observe a singlet due to the resonance of the 2′-O*H* proton at $\delta_H = 11.07$–12.00 ppm for pyrazoles **13a**–**13d** and $\delta_H = 5.79$–6.91 ppm for pyrazoles **14a**–**14d**.

Radioligand Binding Assays

The pharmacological affinity for the CB_1 receptors of the prepared compounds was evaluated through competition binding studies against the cannabinoid selective radioligand [^{3}H]CP55-940 (1 n*M*). The studies were performed in membranes from post-mortem human frontal cortex, a brain area that shows an important density of cannabinoid receptors. We chose to use human brain membranes in the present study because these results could be more relevant from a therapeutical vantage. WIN55212-2 (1 μM), a compound with well-established affinity for CB_1 receptors, was used to determine the non-specific binding.

Binding studies in human frontal cortex showed that all tested substances only displayed moderate or low CB_1 receptor affinity. The highest affinity was observed for pyrazole **14d** ($K_i = 3060 \pm 1820$ n*M*). Table 1 presents the affinities of the tested compounds using as reference the AM251 (*N*-piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide) which is a potent and selective CB_1 receptor antagonist.

Table 1. Competition binding studies of pyrazoles **13a**–**13d** and **14a**–**14d** against the selective [^{3}H]CP55-940 radioligand (reference = AM251)

Compound	K_i (n*M*)	*n*	Compound	K_i (n*M*)	*n*
AM251	4.85 ± 1.71	5			
13a	>10000	3	**13c**	>10000	3
14a	>10000	3	**14c**	5650 ± 3540	3
13b	>10000	3	**13d**	>10000	3
14b	>10000	3	**14d**	3060 ± 1820	3

The only compounds that presented affinity for CB_1 receptor were compounds **14c** and **14d**. Even though this affinity is considered moderate, these results suggest that the orientation of the hydroxyl group is involved in the receptor recognition. Contrary to the pyrazoles of the series **13**, the pyrazoles **14a**–**14d** do not have an intramolecular O–H···N hydrogen bond. The fact that pyrazoles **14a** and **14b** lacked receptor affinity clearly shows that the chlorine at the *ortho* position of the hydroxyphenyl ring contributes to the receptor recognition.

Conclusion

This paper reports a new and efficient synthetic methodology of novel *N*-alkyl (decyl and duodecyl) 5- and 3-(2,4-dichlorophenyl)-3- and 5-(2-hydroxyphenyl)pyrazoles **13a**–**13d** and **14a**–**14d**. Two of them show micromolar affinities towards the CB_1 receptors. Even though the CB_1 receptor affinity of **14c** (5.6 μM) and **14d** (3.1 μM) is low, it may open a new route in the search of CB_1 active compounds.

Experimental

Melting points were determined on a Reichert Thermovar apparatus fitted with a microscope. NMR spectra were recorded on a Bruker Avance 300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C), with $CDCl_3$ as solvent if not stated otherwise. Chemical shifts (δ) are reported in ppm values and coupling constants (*J*) in Hz. The internal standard was TMS. ^{1}H assignments were made using 2D *g*COSY and N*O*ESY experiments, while ^{13}C assignments were made using 2D *g*HSQC and *g*HMBC experiments. Mass spectra (EI, 70 eV) were measured on VG Autospec Q and M mass spectrometers [HRMS were in good agreement (± 0.5 ppm) with the calculated values]. Elemental analyses were obtained with a LECO 932 CHN analyser (University of Aveiro) and were in good agreement ($\pm 0.4\%$) with the calculated values. 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.

Acetophenones **1a**, **1b** were synthesised by the O-acetylation of the appropriate phenols (3-chlorophenol and 3,5-dichlorophenol) [21] which are commercial reagents obtained from Sigma-Aldrich. *Fries* rearrangement of the acetyl group gives the corresponding acetophenones **1a**, **1b** [22].

General Method for the Synthesis of 4′-Chloro-2′-(2,4-dichlorobenzoyloxy)acetophenones ***2a, 2b***

2,4-Dichlorobenzoic acid (1.26 g, 6.66 mmol), 1.37 g *N,N*-dicyclohexylcarbodiimide (6.66 mmol), and 98.70 mg 4-pyrrolidinopyridine (6.66×10^{-1} mmol) were added to a solution of the appropriate 4′-chloro-2′-hydroxyacetophenones **1a**, **1b** (6.66 mmol) in 60 cm^3 CH_2Cl_2. The mixture was stirred under nitrogen, at room temperature, for 24 h. After that period the formed urea was filtered off and washed with 2×20 cm^3 CH_2Cl_2. The organic layer was concentrated and purified by column chromatography using a 1:1 mixture of CH_2Cl_2: hexane as eluent. 4′-Chloro-2′-(2,4-dichlorobenzoyloxy)-acetophenones **2a**, **2b** were obtained in each case as white solids (recrystallised in ethanol) (**2a**, 1.85 g, 81%; **2b**, 2.06 g, 98%).

4′-Chloro-2′-(2,4-dichlorobenzoyloxy)acetophenone (**2a**, $C_{18}H_{13}NO_3$)

Mp 81–82°C; ^{1}H NMR: $\delta = 2.55$ (s, C*H*$_3$), 7.29 (d, $J = 2.0$ Hz, H-3′), 7.38 (dd, $J = 8.5$, 2.0 Hz, H-5′), 7.41 (dd, $J = 8.5$, 2.0 Hz, H-5″), 7.56 (d, $J = 2.0$ Hz, H-3″), 7.83 (d, $J = 8.5$ Hz, H-6′), 8.13 (d, $J = 8.5$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 29.2$ (*C*H$_3$), 124.5 (C-3′), 126.8 (C-5′ and C-1″), 127.4 (C-5″), 128.9 (C-1′), 131.3 (C-3″), 131.5 (C-6′), 133.4 (C-6″), 135.8 (C-2″), 139.3 and 139.5 (C-4″ and C-4′), 149.4 (C-2′), 162.6 (–*C*O$_2$), 196.2 (C=O) ppm; MS (EI): m/z (%) = 344 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 2), 342 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 2), 327 (4) 307 (2), 291 (3), 265 (7), 256 (2), 248 (5), 236 (7), 219 (6), 202 (4), 190 (4), 173 (100), 145 (20), 109 (12), 77 (5), 63 (7).

4′,6′-Dichloro-2′-(2,4-dichlorobenzoyloxy)acetophenone (**2b**, $C_{15}H_8Cl_4O_3$)

Mp 112–113°C; ^{1}H NMR: $\delta = 2.55$ (s, C*H*$_3$), 7.28 (d, $J =$ 1.8 Hz, H-3′), 7.38 (d, $J = 1.8$ Hz, H-5′), 7.39 (dd, $J = 8.5$, 2.1 Hz, H-5″), 7.55 (d, $J = 2.1$ Hz, H-3″), 7.92 (d, $J = 8.5$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 31.4$ (*C*H$_3$), 122.2 (C-3′), 125.9 (C-1″), 127.5 (C-5″), 127.7 (C-5′), 131.2 (C-1′), 131.5 (C-3″), 132.9 (C-6′), 133.1 (C-6″), 135.97 and 135.98 (C-2″ and C-4′), 140.0 (C-4″), 147.4 (C-2′), 162.0 (–*C*O$_2$), 198.5 (C=O) ppm; MS (EI): m/z (%) = 380 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, Cl, 1), 378 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 2), 189 (3), 173 (100), 160 (4), 145 (21), 138 (3), 109 (13), 97 (5), 84 (2), 75 (9), 62 (4).

General Method for the Synthesis of 1-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-ones ***3a, 3b***

Method A: Potassium hydroxide (1.35 g, 24.1 mmol) was added to a solution of 4′-chloro-2′-(2,4-dichlorobenzoyloxy)acetophenones **2a**, **2b** (4.82 mmol) in 15 cm^3 *DMSO*. The mixture was stirred at room temperature, under nitrogen, during half an hour for **2a** and 45 min for **2b**. After that period the mixture was poured into 20 cm^3 water and 20 g ice and was acidified with hydrochloric acid at *pH* 2–3. The formed precipitate was taken in 200 cm^3 $CHCl_3$, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the solid residue was recrystallised from hot ethanol. 1-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-ones **3a**, **3b** were obtained as yellow solids (**3a**, 1.12 g, 68%; **3b**, 0.61 g, 37%).

Method B: Sodium hydride (0.20 g, 8.46 mmol) was added to a solution of 2.00 g 4′,6′-dichloro-2′-(2,4-dichlorobenzoyloxy)acetophenone (**2b**, 5.29 mmol) in 100 cm^3 dry *THF*. The mixture was refluxed at 85°C and stirred, under nitrogen atmosphere, for 50 min. After that period the mixture was carefully poured into 100 cm^3 water and 50 g ice and was acidified with hydrochloric acid at *pH* 2–3. The formed yellow precipitate was taken in 100 cm^3 $CHCl_3$, washed with 2×100 cm^3 water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the solid residue was recrystallised in a mixture of CH_2Cl_2:cyclohexane. 1-(4,6-Dichloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one **3b** was obtained as a yellow solid (**3b**, 1.28 g, 64%).

1-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one (**3a**, $C_{15}H_9O_3Cl_3$)

Mp 153–154°C; ^{1}H NMR: $\delta = 6.74$ (s, H-2), 6.90 (dd, $J = 8.6$, 2.0 Hz, H-5′), 7.04 (d, $J = 2.0$ Hz, H-3′), 7.38 (dd, $J = 8.4$, 2.0 Hz, H-5″), 7.53 (d, $J = 2.0$ Hz, H-3″), 7.61 (d, $J = 8.6$ Hz, H-6′), 7.68 (d, $J = 8.4$ Hz, H-6″), 12.13 (s, 2′-O*H*), 15.10 (s, 3-O*H*) ppm; ^{13}C NMR: $\delta = 98.1$ (C-2), 118.4 (C-1′), 118.9 (C-3′), 120.0 (C-5′), 127.6 (C-5″), 129.7 (C-6′), 130.8 (C-3″), 131.3 (C-6″), 132.0 (C-1″), 133.1 (C-2″), 137.6 (C-4″), 142.1 (C-4′), 163.3 (C-2′), 175.0 (C-3), 195.2 (C-1) ppm; MS (EI): m/z (%) = 348 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, weak), 346 ($M^{+\bullet}$, ${}^{35}Cl + 2 \times {}^{37}Cl$, 3), 344 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 8), 342 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 8), 307 ($M^{+\bullet}$-${}^{35}Cl$, 21), 231 (5), 213 (19), 197 (27), 175 (34), 173 (51), 155 (18), 145 (23), 135 (3), 126 (6), 109 (15), 99 (9), 87 (4), 63 (12).

1-(4,6-Dichloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one (**3b**, $C_{15}H_9O_3Cl_4$)

Mp 155–156°C; ^{1}H NMR: $\delta = 6.96$ (d, $J = 2.0$ Hz, H-3′), 7.01 (d, $J = 2.0$ Hz, H-5′), 7.05 (s, H-2), 7.38 (dd, $J = 8.4$, 2.0 Hz, H-5″), 7.52 (d, $J = 2.0$ Hz, H-3″), 7.68 (d, $J = 8.4$ Hz, H-6″), 10.81 (s, 2′-O*H*), 15.53 (s, 3-O*H*) ppm; ^{13}C NMR: $\delta = 104.4$ (C-2), 117.4 (C-3′), 118.6 (C-1′), 122.7 (C-5′), 127.6 (C-5″), 130.9 (C-3″), 131.4 (C-6″), 131.8 (C-4″), 133.4 (C-2″), 133.8 (C-6′), 138.0 (C-1″), 139.6 (C-4′), 161.6 (C-2′), 177.5 (C-3), 193.0 (C-1) ppm; MS (EI): m/z (%) = 386 ($M^{+\bullet}$, $4 \times {}^{37}Cl$, weak), 384 ($M^{+\bullet}$, ${}^{35}Cl + 3 \times {}^{37}Cl$, 0.5), 382 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 1), 380 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 6), 378 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 13), 361 (3), 341(90), 325 (1), 231 (3), 251 (4), 197 (1), 189 (37), 173 (100), 162 (5), 145 (21), 123 (9), 109 (14), 97 (10), 87 (5), 75 (16), 69 (15).

General Method for the Synthesis of 3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)pyrazoles ***4a, 4b***

Hydrazine hydrate (0.07 cm^3, 1.48 mmol) was added to a solution of the appropriate 1-(4-chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-ones **3a**, **3b** (5.93×10^{-1} mmol) in 50 cm^3 methanol. The mixture was stirred at room temperature, under nitrogen atmosphere, for 6 h. After that period the mixture was poured into 150 cm^3 $CHCl_3$ and washed with 2×150 cm^3 diluted hydrochloric acid. The organic layer was concentrated and purified by

column chromatography using CH_2Cl_2 as eluent. 3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)pyrazoles **4a**, **4b** were obtained in each case as white solids (recrystallised in dichloromethane:cyclohexane) (**4a**, 80 mg, 40%; **4b**, 135 mg, 68%).

3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-pyrazole (**4a**, $C_{15}H_9Cl_3N_2O$)
Mp 224–225°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 6.92$ (dd, $J = 8.4$, 1.8 Hz, H-5′), 6.99 (d, $J = 1.8$ Hz, H-3′), 7.22 (s, H-4), 7.51 (dd, $J = 8.4$, 1.6 Hz, H-5″), 7.69 (d, $J = 1.6$ Hz, H-3″), 7.74 (d, $J = 8.4$ Hz, H-6′), 7.81 (d, $J = 8.4$ Hz, H-6″), 12.46 (s, br, 2′-O*H*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 104.7$ (C-4), 115.8 (C-1′), 116.1 (C-3′), 119.0 (C-5′), 130.3 (C-1″), 127.5 (C-5″), 128.4 (C-6′), 129.7 (C-3″), 131.5 (C-6″), 132.0 (C-4′), 132.7 (C-2″ and C-4″), 139.6 (C-3), 146.3 (C-5), 155.6 (C-2′) ppm; MS (EI): m/z (%): 344 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 3), 342 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 27), 340 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 80), 338 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 80), 311 (4), 285 (3), 275 (14), 256 (31), 239 (10), 212 (14), 191 (6), 176 (17), 149 (41), 127 (9), 118 (38), 97 (15), 83 (38), 71 (52), 57 (100).

3-(4,6-Dichloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-pyrazole (**4b**, $C_{15}H_8Cl_4N_2O$)
Mp 270–271°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 6.96$ (s, H-4 and H-3′), 7.10 (s, br, H-5′), 7.53 (d, $J = 8.4$ Hz, H-5″), 7.73 (s, br, H-3″), 7.88 (d, $J = 8.4$ Hz, H-6″), 12.88 (s, br, 2′-O*H*) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 107.4$ (C-4), 114.9 (C-3′), 116.1 (C-1′), 118.9 (C-5′), 127.6 (C-5″), 129.8 (C-3″), 131.4 (C-6″), 131.7 (C-1″), 132.7 (C-2″ and C-4″), 133.6 (C-4′), 134.1 (C-6′), 137.3 (C-3), 144.9 (C-5), 157.0 (C-2′) ppm; MS (EI): m/z (%) = 380 ($M^{+\bullet}$, $^{35}Cl + 3 \times {}^{37}Cl$, 1), 378 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 11), 376 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 50), 374 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 100), 345 (3), 309 (13), 273 (13), 246 (6), 210 (11), 174 (14), 147 (4), 138 (6), 123 (9), 109 (4), 87 (5), 73 (3), 63 (7).

*General Method for the Alkylation of 3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)pyrazoles **4a**, **4b***
Potassium carbonate (0.052 g, 0.38 mmol) and 0.027 cm^3 decyl bromide (0.13 mmol) were added to a solution of 3-(4-chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)pyrazoles **4a**, **4b** (0.13 mmol) in 20 cm^3 acetone. The mixture was refluxed with stirring during 24 h for **4a** and 72 h for **4b**. After that period the mixture was cooled to room temperature, potassium carbonate was filtered off and washed with acetone. The solvent was evaporated to dryness and the residue was taken in $CHCl_3$ and purified by thin layer chromatography using a 9:1 mixture of light petroleum:ethyl acetate as eluent. After several elutions, three spots have been collected, in each case. The spots with higher R_f value were identified as 5-(4-chloro-2-decyloxyphenyl)-1-decyl-3-(2,4-dichlorophenyl)pyrazoles **7a**, **7b** (**7a**, 15.6 mg, 20%; **7b**, 9.6 mg, 26%), the second one as 3-(4-chloro-2-decyloxyphenyl)-1-decyl-5-(2,4-dichlorophenyl) pyrazoles **6a**, **6b** (**6a**, 43.0 mg, 55.0%; **6b**, 19.6 mg, 26%), and the one with lower R_f value was identified as 3(5)-(4-chloro-2-decyloxyphenyl)-5(3)-(2,4-dichlorophenyl)pyrazoles **5a**, **5b** (**5a**, 13.6 mg, 23%; **5b**, 13.6 mg, 23%). In the case of **4b**, some starting material was recovered (11.3 mg, 23%).

3(5)-(4-Chloro-2-decyloxyphenyl)-5(3)-(2,4-dichlorophenyl)-pyrazole (**5a**, $C_{25}H_{29}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.22–1.36 [m, O(CH$_2$)$_2$(CH_2)$_7$CH$_3$], 1.77 [quint, $J = 7.0$ Hz, OCH$_2$CH_2(CH$_2$)$_7$CH$_3$], 3.99 [t, $J = 7.0$ Hz, OCH_2(CH$_2$)$_8$CH$_3$], 7.02 (d, $J = 1.9$ Hz, H-3′), 7.04 (dd, $J = 7.8$, 1.9 Hz, H-5′), 7.12 (s, H-4), 7.31 (dd, $J = 8.4$, 2.1 Hz, H-5″), 7.49 (d, $J = 2.1$ Hz, H-3″), 7.66 (d, $J = 7.8$ Hz, H-6′), 7.80 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ [O(CH$_2$)$_9$CH_3], 22.7 [O(CH$_2$)$_8$CH_2CH$_3$], 26.1, 29.2, 29.3, 29.47, 29.50 and 31.9 [OCH$_2$(CH_2)$_7$CH$_2$CH$_3$], 69.4 [OCH_2(CH$_2$)$_8$CH$_3$], 103.9 (C-4), 113.1 (C-3′), 116.1 (C-1′), 121.6 (C-5′), 127.3 (C-5″), 128.7 (C-6′), 130.1 (C-3″), 130.7 (C-1″), 131.2 (C-6″), 132.8 (C-2″), 134.0 (C-4″), 134.7 (C-4′), 140.9 (C-3), 148.1 (C-5), 155.8 (C-2′) ppm; MS (EI): m/z (%) = 484 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 0.5), 482 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 11), 480 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 33), 449 (10), 421 (7), 393 (10), 379 (3), 364 (8), 350 (46), 337 (100), 324 (9), 311 (6), 304 (11), 275 (12), 246 (6), 239 (12), 223 (2), 210 (2), 180 (3), 166 (12), 151 (3), 138 (4), 97 (2), 83 (6), 69 (15).

3(5)-(4,6-Dichloro-2-decyloxyphenyl)-5(3)-(2,4-dichlorophenyl)pyrazole (**5b**, $C_{25}H_{29}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ [t, $J = 6.8$ Hz, O(CH$_2$)$_9$CH_3], 1.22–1.36 [m, O(CH$_2$)$_2$(CH_2)$_7$CH$_3$], 1.77 [quint, $J = 6.9$ Hz, OCH$_2$CH_2(CH$_2$)$_7$CH$_3$], 3.99 [t, $J = 6.9$ Hz, OCH_2(CH$_2$)$_8$CH$_3$], 6.89 (d, $J = 2.0$ Hz, H-3′), 7.15 (d, $J = 2.0$ Hz, H-5′), 7.20 (s, H-4), 7.29 (dd, $J = 8.4$, 2.1 Hz, H-5″), 7.49 (d, $J = 2.1$ Hz, H-3″), 7.78 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ [O(CH$_2$)$_9$CH_3], 22.7 [O(CH$_2$)$_8$CH_2CH$_3$], 25.9, 28.9, 29.2, 29.3, 29.5, 29.7, and 31.9 [OCH$_2$(CH_2)$_7$CH$_2$CH$_3$], 69.8 [OCH_2(CH$_2$)$_8$CH$_3$], 109.1 (C-4), 111.6 (C-3′), 116.9 (C-1′), 122.7 (C-5′), 127.3 (C-5″), 130.1 (C-3″), 130.4 (C-1″), 131.2 (C-6″), 132.7 (C-2″), 134.0 (C-4″), 134.4 (C-6′), 135.1 (C-4′), 136.6 (C-3), 146.9 (C-5), 157.8 (C-2′) ppm; MS (EI): m/z (%) = 519 ($M^{+\bullet}$, $^{35}Cl + 3 \times {}^{37}Cl$, 0.5), 517 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 3), 515 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 14), 513 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 28), 512 (10), 482 (9), 440 (8), 428 (10), 414 (4), 400 (9), 386 (41), 373 (100), 355 (11), 337 (15), 326 (13), 308 (11), 286 (3), 273 (17), 258 (3), 244 (9), 212 (7), 210 (14), 200 (17), 187 (4), 174 (11), 123 (5), 97 (3), 83 (7), 69 (20).

3-(4-Chloro-2-decyloxyphenyl)-1-decyl-5-(2,4-dichlorophenyl)pyrazole (**6a**, $C_{35}H_{50}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ [t, $J = 6.8$ Hz, NCH$_2$(CH$_2$)$_8$CH_3], 0.88 [t, $J = 6.8$ Hz, OCH$_2$(CH$_2$)$_8$CH_3], 1.17–1.28 [m, N(CH$_2$)$_2$(CH_2)$_7$CH$_3$ and O(CH$_2$)$_2$(CH_2)$_7$CH$_3$], 1.78 [quint, $J = 6.9$ Hz, N(CH$_2$)$_2$(CH_2)$_7$CH$_3$], 1.83 [quint, $J = 6.5$ Hz, OCH$_2$CH_2(CH$_2$)$_7$CH$_3$], 3.95 [t, $J = 6.9$ Hz, NCH_2(CH$_2$)$_8$CH$_3$], 4.01 [t, $J = 6.5$ Hz, OCH_2(CH$_2$)$_8$CH$_3$], 6.82 (s, H-4), 6.93 (d, $J = 2.0$ Hz, H-3′), 6.98 (dd, $J = 8.3$, 2.0 Hz, H-5′), 7.29 (d, $J = 8.3$ Hz, H-6″), 7.35 (dd, $J = 8.3$, 2.0 Hz, H-5″), 7.54 (d, $J = 2.0$ Hz, H-3″), 8.00 (d, $J = 8.3$ Hz, H-6′) ppm; ^{13}C NMR: $\delta = 14.1$ [N(CH$_2$)$_9$CH_3 and O(CH$_2$)$_9$CH_3], 22.6 [N(CH$_2$)$_8$CH_2CH$_3$], 22.7 [O(CH$_2$)$_8$CH_2CH$_3$], 26.2, 26.4, 29.0, 29.2, 29.26, 29.30, 29.34, 29.46, 29.51, 29.6, and 31.8 [NCH$_2$(CH_2)$_7$CH$_2$CH$_3$ and OCH$_2$(CH_2)$_7$CH$_2$CH$_3$], 49.8 [NCH_2(CH$_2$)$_8$CH$_3$], 68.6 [OCH_2(CH$_2$)$_8$CH$_3$], 108.5 (C-4), 112.5 (C-3′), 120.6 (C-5′), 120.8 (C-1′), 127.1 (C-5″), 129.0 (C-6′),

129.8 (C-3″), 132.8 (C-6″ and C-1″), 133.7 (C-4′), 135.2 (C-2″), 135.6 (C-4″), 139.1 (C-5), 146.4 (C-3), 156.6 (C-2′) ppm; MS (EI): m/z (%) = 624 ($M^{+\bullet}$, $^{35}Cl + 2 \times ^{37}Cl$, 4), 622 ($M^{+\bullet}$, $2 \times ^{35}Cl + ^{37}Cl$, 24), 620 ($M^{+\bullet}$, $3 \times ^{35}Cl$, 64), 619 (62), 603 (3), 583 (12), 561 (8), 548 (5), 533 (13), 519 (2), 505 (14), 491 (100), 478 (21), 457 (12), 434 (5), 408 (7), 392 (9), 378 (5), 364 (13), 352 (36), 337 (23), 317 (11), 304 (5), 275 (5), 239 (4), 212 (3), 180 (6), 149 (4), 97 (5), 84 (49), 69 (28).

3-(4,6-Dichloro-2-decyloxyphenyl)-1-decyl-5-(2,4-dichlorophenyl)pyrazole (**6b**, $C_{35}H_{49}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ [t, $J = 6.8$ Hz, $N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 1.17–1.28 [m, $N(CH_2)_2(CH_2)_7CH_3$ and $O(CH_2)_2(CH_2)_7CH_3$], 1.62 [m, $NCH_2CH_2(CH_2)_7CH_3$ and $OCH_2CH_2(CH_2)_7CH_3$], 3.89 [t, $J = 7.1$ Hz, $NCH_2(CH_2)_8CH_3$], 3.97 [t, $J = 7.2$ Hz, $OCH_2(CH_2)_8CH_3$], 6.28 (s, H-4), 6.82 (d, $J = 1.7$ Hz, H-3′), 7.09 (d, $J = 1.7$ Hz, H-5′), 7.31–7.37 (m, H-5″ and H-6″), 7.54 (d, $J = 0.8$ Hz, H-3″) ppm; ^{13}C NMR: $\delta = 14.1$ [$N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 22.7 [$N(CH_2)_8CH_2CH_3$ and $O(CH_2)_8CH_2CH_3$], 25.9, 26.3, 29.0, 29.1, 29.29, 29.35, 29.46, 29.50, 29.59, 29.63, 30.3 and 31.9 [$NCH_2(CH_2)_7CH_2CH_3$ and $OCH_2(CH_2)_7CH_2CH_3$], 49.8 [$NCH_2(CH_2)_8CH_3$], 69.1 [$OCH_2(CH_2)_8CH_3$], 109.0 (C-4), 111.3 (C-3′), 121.5 (C-5′), 121.8 (C-1′), 127.1 (C-5″), 128.9 (C-1″), 129.8 (C-3″), 132.8 (C-6″), 134.5 (C-4′), 135.3 (C-2″), 135.6 (C-4″), 135.7 (C-6′), 138.7 (C-5), 143.8 (C-3), 159.0 (C-2′) ppm; MS (EI): m/z (%) = 659 ($M^{+\bullet}$, $^{35}Cl + 3 \times ^{37}Cl$, 0.5), 657 ($M^{+\bullet}$, $2 \times ^{35}Cl + 2 \times ^{37}Cl$, 5), 655 ($M^{+\bullet}$, $3 \times ^{35}Cl + ^{37}Cl$, 21), 653 ($M^{+\bullet}$, $4 \times ^{35}Cl$, 41), 652 (19), 638 (2), 619 (12), 584 (5), 568 (12), 554 (2), 540 (11), 526 (89), 512 (21), 490 (10), 466 (9), 442 (6), 412 (4), 400 (9), 386 (27), 370 (13), 371 (17), 357 (11), 308 (5), 273 (6), 246 (3), 214 (7), 212 (3), 200 (6), 188 (3), 174 (6), 149 (6), 97 (5), 85 (15), 69 (33).

5-(4-Chloro-2-decyloxyphenyl)-1-decyl-3-(2,4-dichlorophenyl)pyrazole (**7a**, $C_{35}H_{50}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ [t, $J = 6.7$ Hz, $N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 1.17–1.25 [m, $N(CH_2)_2(CH_2)_7CH_3$ and $O(CH_2)_2(CH_2)_7CH_3$], 1.70 [quint, $J = 6.7$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 1.74 [quint, $J = 6.8$ Hz, $OCH_2CH_2(CH_2)_7CH_3$], 3.96 (t, $J = 6.8$ Hz, $OCH_2(CH_2)_8CH_3$], 3.98 (t, $J = 6.7$ Hz, $NCH_2(CH_2)_8CH_3$], 6.74 (s, H-4), 6.98 (d, $J = 1.9$ Hz, H-3′), 7.01 (dd, $J = 8.5$, 1.9 Hz, H-5′), 7.21 (d, $J = 8.5$ Hz, H-6′), 7.28 (dd, $J = 8.6$, 2.4 Hz, H-5″), 7.45 (d, $J = 2.4$ Hz, H-3″), 7.87 (d, $J = 8.6$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ [$N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 22.7 [$N(CH_2)_8CH_2CH_3$ and $O(CH_2)_8CH_2CH_3$], 25.9, 26.5, 28.9, 29.1, 29.2, 29.3, 29.4, 29.5, 30.2, 31.8, and 31.9 [$NCH_2(CH_2)_7CH_2CH_3$ and $OCH_2(CH_2)_7CH_2CH_3$], 50.0 [$NCH_2(CH_2)_8CH_3$], 68.9 [$OCH_2(CH_2)_8CH_3$], 107.9 (C-4), 112.9 (C-3′), 118.5 (C-1′), 120.6 (C-5′), 127.1 (C-5″), 129.9 (C-3″), 131.1 (C-6″), 131.3 (C-1″), 132.3 (C-6′), 132.6 (C-2″), 133.3 (C-4″), 135.9 (C-4′), 139.5 (C-5), 146.7 (C-3), 157.2 (C-2′) ppm; MS (EI): m/z (%) = 624 ($M^{+\bullet}$, $^{35}Cl + 2 \times ^{37}Cl$, 3), 622 ($M^{+\bullet}$, $2 \times ^{35}Cl + ^{37}Cl$, 19), 620 ($M^{+\bullet}$, $3 \times ^{35}Cl$, 55), 619 (34), 603 (4), 589 (10), 561 (11), 533 (25), 519 (2), 505 (10), 493 (77), 491 (75), 479 (30), 477 (25), 463 (12), 437 (4), 423 (7), 407 (9), 379 (7), 365 (28), 351 (55), 338 (31), 317 (14), 304 (8), 275 (5), 239 (4), 210 (3), 172 (5), 138 (4), 97 (4), 85 (15), 69 (26), 57 (100).

5-(4,6-Dichloro-2-decyloxyphenyl)-1-decyl-3-(2,4-dichlorophenyl)pyrazole (**7b**, $C_{35}H_{49}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ [t, $J = 6.6$ Hz, $N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 1.18–1.33 [m, $N(CH_2)_2(CH_2)_7CH_3$ and $O(CH_2)_2(CH_2)_7CH_3$], 1.63 [quint, $J = 7.2$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 1.74 [quint, $J = 6.4$ Hz, $OCH_2CH_2(CH_2)_7CH_3$], 3.88 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_8CH_3$], 3.93 [t, $J = 6.4$ Hz, $OCH_2(CH_2)_8CH_3$], 6.74 (s, H-4), 6.88 (d, $J = 1.9$ Hz, H-3′), 7.14 (d, $J = 1.9$ Hz, H-5′), 7.28 (dd, $J = 8.6$, 2.3 Hz, H-5″), 7.45 (d, $J = 2.3$ Hz, H-3″), 7.88 (d, $J = 8.6$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ [$N(CH_2)_9CH_3$ and $O(CH_2)_9CH_3$], 22.7 [$N(CH_2)_8CH_2CH_3$ and $O(CH_2)_8CH_2CH_3$], 25.8, 26.4, 28.8, 29.09, 29.14, 29.3, 29.4, 29.49, 29.52, 30.1, 31.8, and 31.9 [$NCH_2(CH_2)_7CH_2CH_3$ and $OCH_2(CH_2)_7CH_2CH_3$], 50.0 [$NCH_2(CH_2)_8CH_3$], 69.2 [$OCH_2(CH_2)_8CH_3$], 108.6 (C-4), 111.2 (C-3′), 118.1 (C-1′), 121.5 (C-5′), 127.0 (C-5″), 129.9 (C-3″), 131.1 (C-6″), 131.3 (C-1″), 132.7 (C-2″), 133.3 (C-4″), 135.6 (C-5), 136.3 (C-6′), 136.4 (C-4′), 146.7 (C-3), 158.7 (C-2′) ppm; MS (EI): m/z (%) = 660 ($M^{+\bullet}$, $^{35}Cl + 3 \times ^{37}Cl$, 1), 658 ($M^{+\bullet}$, $2 \times ^{35}Cl + 2 \times ^{37}Cl$, 6), 656 ($M^{+\bullet}$, $3 \times ^{35}Cl + ^{37}Cl$, 27), 654 ($M^{+\bullet}$, $4 \times ^{35}Cl$, 50), 653 (26), 639 (4), 637 (3), 619 (20), 597 (10), 595 (8), 581 (20), 569 (26), 567 (20), 555 (3), 541 (8), 539 (6), 527 (63), 525 (48), 513 (23), 511 (16), 491 (11), 479 (6), 455 (6), 443 (8), 415 (7), 401 (25), 387 (48), 351 (17), 338 (8), 309 (5), 273 (5), 239 (3), 214 (6), 185 (5), 172 (9), 138 (4), 97 (5), 85 (17), 69 (32), 57 (100).

*General Method for the Synthesis of 2′-Benzyloxy-4′-chloroacetophenones **8a**, **8b***
Potassium carbonate (10.84 g, 78.4 mmol), 6.51 g potassium iodide (39.2 mmol), and 3.38 cm^3 benzyl chloride (29.4 mmol) were added to a solution of the appropriate 4′-chloro-2′-hydroxyacetophenone **1a**, **1b** (24.5 mmol) in 25 cm^3 acetone. The mixture was refluxed with stirring for 16 h. After that period the mixture was poured into 100 cm^3 water and 100 g ice and the formed precipitate was filtered off, taken in 100 cm^3 $CHCl_3$, and washed with 100 cm^3 water. The solvent was evaporated and the solid residue was crystallized in hot ethanol. 2′-Benzyloxy-4′-chloroacetophenones **8a**, **8b** were obtained in each case as white solids (**8a**, 3.74 g, 59%; **8b**, 5.52 g, 92%).

2′-Benzyloxy-4′-chloroacetophenone (**8a**, $C_{15}H_{13}ClO_2$)
Mp 58–59°C; ^{1}H NMR: $\delta = 2.56$ (s, CH_3), 5.14 (s, OCH_2), 7.00 (dd, $J = 8.3$, 1.8 Hz, H-5′), 7.04 (d, $J = 1.8$ Hz, H-3′), 7.37–7.48 (m, $OCH_2C_6H_5$), 7.72 (d, $J = 8.3$ Hz, H-6′) ppm; ^{13}C NMR: $\delta = 32.1$ (C-2), 71.0 (OCH_2), 113.3 (C-3′), 121.2 (C-5′), 126.8 (C-1′), 127.7 (C-2″,6″), 128.5 (C-4″), 128.8 (C-3″,5″), 131.7 (C-6′), 135.4 (C-1″), 139.4 (C-4′), 158.5 (C-2′), 198.4 (C=O) ppm; MS (EI): m/z (%) = 262 ($M^{+\bullet}$, ^{37}Cl, 5), 260 ($M^{+\bullet}$, ^{35}Cl, 14), 204 (2), 217 (3), 155 (5), 141 (2), 126 (4), 92 (15), 91 (100), 77 (5), 65 (18).

2′-Benzyloxy-4′,6′-dichloroacetophenone (**8b**, $C_{15}H_{12}Cl_2O_2$)
Mp 87–88°C; ^{1}H NMR: $\delta = 2.51$ (s, CH_3), 5.08 (s, OCH_2), 6.89 (d, $J = 1.6$ Hz, H-5′), 7.03 (d, $J = 1.6$ Hz, H-3′), 7.32–7.42 (m, $OCH_2C_6H_5$) ppm; ^{13}C NMR: $\delta = 31.8$ (C-2), 71.0 (OCH_2), 109.3 (C-1′), 111.7 (C-3′), 122.1 (C-5′), 127.2 (C-

2″,6″), 128.5 (C-4″), 128.8 (C-3″,5″), 130.7 (C-6′), 135.2 and 135.8 (C-1″ and C-4′), 156.0 (C-2′), 200.3 (C=O) ppm; MS (EI): m/z (%) = 297 ($M^{+\bullet}$, $^{35}Cl + {}^{37}Cl$, 2), 295 ($M^{+\bullet}$, $2 \times {}^{35}Cl$, 3), 294 (5), 279 (3), 175 (2), 188 (6), 175 (4), 160 (11), 132 (3), 111 (5), 97 (7), 91 (100), 77 (6), 65 (28).

1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one (**9a**, $C_{22}H_{15}Cl_3O_3$)

Ethyl 2,4-dichlorobenzoate (2.51 g, 11.5 mmol) and 0.28 g sodium hydride (1.5 mmol) were added to a solution of 2.0 g 2′-benzyloxy-4′-chloroacetophenone (**8a**, 7.67 mmol) in 50 cm^3 dry *THF*. The mixture was refluxed with stirring for 2 h, then another batch of ethyl 2,4-dichlorobenzoate (0.1 mmol) was added and the mixture was stirred for 1 h more. After that period the mixture was carefully poured into 100 cm^3 water and 100 g ice and was acidified with diluted hydrochloric acid at *pH* 5. The obtained precipitate was filtered off and crystallised from ethanol. 1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one **9a** was obtained as a yellow solid (699 mg, 21%). Mp 122–123°C; ^{1}H NMR: $\delta = 5.12$ (s, OCH_2), 6.96 (s, H-2), 7.06 (s, br, H-3′), 7.08 (dd, $J = 9.0$, 1.9 Hz, H-5′), 7.16 (dd, $J = 8.4$, 1.8 Hz, H-5″), 7.24 (d, $J = 8.4$ Hz, H-6″), 7.39 (d, $J = 1.8$ Hz, H-3″), 7.35–7.38 and 7.41–7.44 (m, $OCH_2C_6H_5$), 7.95–7.98 (m, H-6′) ppm; ^{13}C NMR: $\delta = 71.3$ (OCH_2), 103.1 (C-2), 113.4 (C-3′), 121.4 (C-6′), 122.4 (C-1′), 127.1 (C-5′), 128.1 (C-2‴,6‴), 128.6 (C-4‴), 128.8 (C-3‴,5‴), 130.4 (C-3″), 130.9 (C-6″), 131.5 (C-5″), 132.9 (C-1″), 134.7 (C-2″), 135.2 (C-1‴), 136.8 (C-4″), 139.3 (C-4′), 158.3 (C-2′), 180.8 (C-3), 186.8 (C-1) ppm; MS (EI): m/z (%) = 436 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 1%), 434 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 3), 432 (2), 416 (17), 397 (8), 379 (2), 343 (6), 328 (28), 307 (9), 277 (20), 269 (1), 259 (51), 244 (70), 215 (6), 199 (2), 181 (3), 173 (100), 155 (36), 145 (24), 126 (10), 110 (7), 99 (10), 91 (20), 75 (3), 65 (11).

3(5)-(2-Benzyloxy-4-chlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazole (**10a**, $C_{22}H_{15}Cl_3N_2O$)

Hydrazine hydrate (0.10 cm^3, 2.02 mmol) was added to a solution of 0.35 g 1-(4-chloro-2-benzyloxyphenyl)-3-(2,4-dichlorophenyl)-3-hydroxyprop-2-en-1-one **9a** (8.07×10^{-1} mmol) in 75 cm^3 methanol. The mixture was stirred at room temperature for 8 h. After that period the mixture was poured into 150 cm^3 $CHCl_3$, washed with 2×150 cm^3 acidified water, dried over anhydrous sodium sulfate, concentrated, and purified by thin layer chromatography using CH_2Cl_2 as eluent. 3(5)-(2-Benzyloxy-4-chlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazole **10a** was crystallised from ethanol and obtained as a white solid (329 mg, 95%). Mp 128–129°C; ^{1}H NMR (500.13 MHz): $\delta = 5.11$ (s, OCH_2), 7.00 (dd, $J =$ 8.3, 1.9 Hz, H-5′), 7.06 (d, $J = 1.9$ Hz, H-3′), 7.09 (s, H-4), 7.20 (dd, $J = 8.4$, 2.2 Hz, H-5″), 7.37–7.41 (m, $OCH_2C_6H_5$), 7.42 (d, $J = 2.2$ Hz, H-3″), 7.61 (d, $J = 8.3$ Hz, H-6′), 7.67 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR (125.67 MHz): $\delta = 71.3$ (OCH_2), 104.3 (C-4), 113.3 (C-3′), 116.5 (C-1′), 121.8 (C-5′), 127.1 (C-5″), 127.9 (C-2‴,6‴), 128.7 (C-6′), 128.9 (C-4‴), 129.1 (C-3‴,5‴), 129.9 (C-3″), 130.4 (C-1″), 131.1 (C-6″), 132.6 (C-4″), 133.9 (C-2″), 134.6 (C-4′), 135.0 (C-1‴), 140.7 (C-3), 147.6 (C-5), 155.4 (C-2′) ppm; MS (EI): m/z (%) = 434 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 3), 432 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 17), 430 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 37), 428 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 40), 351 (7), 338 (4), 239 (5), 210 (6), 176 (8), 166 (5), 92 (15), 91 (100), 65 (12).

*General Method for the Synthesis of 3(5)-(2-Benzyloxy-4-chlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazoles **10a**, **10b***

Hydrazine hydrate (0.12 cm^3, 2.48 mmol) was added to a solution of the appropriate 1-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2,3-dibromopropan-1-one **16a**, **16b** (0.33 mmol) in 30 cm^3 methanol. The mixture was refluxed with stirring, under nitrogen atmosphere, for 2:30 h. After that period the mixture was poured into 50 cm^3 $CHCl_3$, washed with 2×50 cm^3 acidified water, and dried over anhydrous sodium sulfate. The organic layer was concentrated and purified by thin layer chromatography using CH_2Cl_2 as eluent. The 3(5)-(2-benzyloxy-4-chlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazoles **10a**, **10b** were obtained in each case as white solids (**10a**, 87.7 mg, 62%; **10b**, 69.1 mg, 48%).

3(5)-(2-Benzyloxy-4,6-dichlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazole (**10b**, $C_{22}H_{14}N_2OCl_4$)

Mp 70–71°C; ^{1}H NMR: $\delta = 4.91$ (s, OCH_2), 6.83 (d, $J =$ 1.9 Hz, H-5′), 7.03 (s, H-4), 7.07 (dd, $J = 8.4$, 2.1 Hz, H-5″), 7.08 (d, $J = 1.9$ Hz, H-3′), 7.22 (s, $OCH_2C_6H_5$), 7.40 (d, $J = 2.1$ Hz, H-3″), 7.45 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 71.1$ (OCH_2), 109.0 (C-4), 111.9 (C-3′), 117.7 (C-1′), 122.7 (C-5′), 127.0 (C-2‴,6‴), 127.04 (C-5″), 128.2 (C-4‴), 128.6 (C-3‴,5‴), 129.9 (C-3″), 131.1 (C-6″), 132.6 (C-1″), 134.0 (C-2″), 134.7 (C-4″), 135.1 and 135.2 (C-4′ and C-6′), 136.6 (C-3), 145.9 (C-5), 157.3 (C-2′) ppm; MS (EI): m/z (%) = 468 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 2), 466 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 10), 464 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 19), 427 (1), 387 (2), 261 (3), 200 (1), 91 (100), 65 (2).

*General Method for the Synthesis of 3-(2-Benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**11a**) and 5-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**12a**)*

Potassium carbonate (0.14 g, 1.05 mmol) and 0.11 cm^3 decyl bromide (0.52 mmol) were added to a solution of 0.15 g 3(5)-(2-benzyloxy-4-chlorophenyl)-5(3)-(2,4-dichlorophenyl)pyrazole (**10a**, 0.35 mmol) in 20 cm^3 acetone. The mixture was refluxed with stirring for 24 h. After that period the mixture was cooled to room temperature, the potassium carbonate was filtered off and washed with 2×20 cm^3 acetone. The solvent was evaporated to dryness and the residue taken in $CHCl_3$ and purified by thin layer chromatography using a 9:1 mixture of light petroleum ether:ethyl acetate as eluent. Two compounds have been isolated, the first one coming out of the column was the 3-(2-benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**11a**) and the second one the 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**12a**), both obtained as yellow oils (**11a**, 94.4 mg, 47%; **12a**, 81.3 mg, 41%).

3-(2-Benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**11a**, $C_{32}H_{35}N_2OCl_3$)

^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.17–1.28 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.76 [quint, $J = 6.7$ Hz, $NCH_2CH_2(CH_2)_7CH_3$],

3.95 [t, $J = 7.3$ Hz, $NCH_2(CH_2)_8CH_3$], 5.14 (s, OCH_2), 6.77 (s, H-4), 7.02 (d, $J = 1.9$ Hz, H-3′), 7.03 (dd, $J = 7.0$, 1.9 Hz, H-5′), 7.29–7.38 (m, $OCH_2C_6H_5$ and H-6″), 7.44 (dd, $J = 7.9$, 1.6 Hz, H-5″), 7.52 (d, $J = 1.6$ Hz, H-3″), 7.99 (d, $J = 7.0$ Hz, H-6′) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.6 [$N(CH_2)_8CH_2CH_3$], 26.4, 29.0, 29.3, 29.4, 29.5, 30.3, and 31.8 [$NCH_2(CH_2)_8CH_2CH_3$], 49.8 [$NCH_2(CH_2)_8CH_3$], 70.7 (OCH_2), 108.7 (C-4), 113.3 (C-3′), 121.3 (C-5′), 121.4 (C-1′), 127.1 (C-5″), 127.3 (C-2‴,6‴), 128.0 (C-4‴), 128.5 (C-3‴,5‴), 128.9 (C-1″), 129.4 (C-6′), 129.8 (C-3″), 132.7 (C-6″), 133.7 (C-4′), 135.1 (C-2″), 135.5 (C-4″), 136.4 (C-1‴), 139.2 (C-5), 146.3 (C-3), 156.2 (C-2′) ppm; MS (EI): m/z (%) = 574 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 3), 572 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 20), 570 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 47), 534 (5), 491 (10), 463 (4), 443 (28), 428 (23), 407 (6), 393 (4), 365 (6), 351 (15), 337 (10), 273 (2), 261 (4), 210 (2), 176 (2), 91 (100), 65 (9).

5-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**12a**, $C_{32}H_{35}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.12–1.28 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.73 [quint, $J = 6.6$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 3.98 [t, $J = 7.3$ Hz, $NCH_2(CH_2)_8CH_3$], 5.08 (s, OCH_2), 6.77 (s, H-4), 7.04 (d, $J = 1.9$ Hz, H-3′), 7.05 (dd, $J = 8.2$, 1.9 Hz, H-5′), 7.24–7.34 (m, $OCH_2C_6H_5$, H-5″ and H-6′), 7.45 (d, $J = 2.1$ Hz, H-3″), 7.85 (d, $J = 8.2$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.6 [$N(CH_2)_8CH_2CH_3$], 26.4, 29.0, 29.2, 29.4, 29.5, 30.2, and 31.8 [$NCH_2(CH_2)_7CH_2CH_3$], 50.1 [$NCH_2(CH_2)_8CH_3$], 70.6 (OCH_2), 108.0 (C-4), 113.7 (C-3′), 118.9 (C-1′), 121.2 (C-5′), 126.8 (C-2‴,6‴), 127.1 (C-5″), 128.0 (C-4‴), 128.6 (C-3‴,5‴), 129.9 (C-3″), 131.16 (C-6″), 131.22 (C-1″), 132.4 (C-6′), 132.6 (C-2″), 133.4 (C-4″), 135.8 and 135.9 (C-1‴ and C-4′), 139.3 (C-5), 146.8 (C-3), 156.7 (C-2′) ppm; MS (EI): m/z (%) = 574 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 5), 572 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 31), 570 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 67), 568 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 65), 553 (2), 534 (8), 491 (13), 479 (10), 443 (11), 393 (4), 351 (14), 337 (11), 275 (2), 243 (3), 180 (2), 105 (2), 91 (100), 69 (4).

*General Method for the Synthesis of **11b–11d** and **12b–12d***
3-(2-Benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole **11b–11d** and 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole **12b–12d** were prepared by a procedure similar to that of **11a** and **12a**, except the amount of dodecyl bromide (2.2 molar equiv) and reaction time (48 h). Two compounds have also been isolated in each case, the 3-(2-benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole **11b–11d** and the 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole **12b–12d**, both obtained as oils (**11b**, 56.4 mg, 27%; **12b**, 81.4 mg, 39%; **11c**, 15.6 mg, 8%; **12c**, 143.0 mg, 73%; **11d**, 22.5 mg, 11%; **12d**, 155.0 mg, 76%).

3-(2-Benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole (**11b**, $C_{34}H_{39}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.7$ Hz, CH_3), 1.17–1.29 [m, $N(CH_2)_2(CH_2)_9CH_3$], 1.76 [quint, $J = 6.5$ Hz, $NCH_2CH_2(CH_2)_9CH_3$], 3.95 [t, $J = 7.4$ Hz, $NCH_2(CH_2)_{10}CH_3$], 5.14 (s, OCH_2), 6.77 (s, H-4), 7.02 (d, $J = 1.9$ Hz, H-3′), 7.03 (dd, $J = 8.9$, 1.9 Hz, H-5′), 7.24 (d, $J = 8.3$ Hz, H-6″), 7.30–7.37 (m, $OCH_2C_6H_5$), 7.44 (dd, $J = 8.3$, 1.9 Hz, H-5″), 7.52 (d, $J = 1.9$ Hz, H-3″), 7.99 (d, $J = 8.9$ Hz, H-6′) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.7 [$N(CH_2)_{10}CH_2CH_3$], 26.5, 29.0, 29.3, 29.4, 29.5, 29.6, 30.3, and 31.9 [$NCH_2(CH_2)_9CH_2CH_3$], 49.8 [$NCH_2(CH_2)_{10}CH_3$], 70.7 (OCH_2), 108.7 (C-4), 113.3 (C-3′), 121.3 (C-5′), 121.4 (C-1′), 127.1 (C-5″), 127.3 (C-2‴,6‴), 128.0 (C-4‴), 128.5 (C-3‴,5‴), 128.9 (C-1″), 129.4 (C-6′), 129.8 (C-3″), 132.7 (C-6″), 133.7 (C-4′), 135.1 (C-2″), 135.5 (C-4″), 136.4 (C-1‴), 139.2 (C-5), 146.3 (C-3), 156.2 (C-2′) ppm; MS (EI): m/z (%) = 602 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 5), 600 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 32), 598 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 71), 596 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 70), 562 (7), 519 (12), 507 (12), 485 (4), 442 (13), 428 (12), 407 (6), 393 (5), 365 (3), 353 (21), 352 (10), 351 (23), 338 (14), 322 (11), 275 (3), 243 (4), 212 (3), 176 (4), 138 (3), 105 (3), 91 (100), 69 (8).

5-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole (**12b**, $C_{34}H_{39}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.12–1.28 (m, $N(CH_2)_2(CH_2)_9CH_3$), 1.73 [quint, $J = 6.8$ Hz, $NCH_2CH_2(CH_2)_9CH_3$], 3.98 [t, $J = 7.4$ Hz, $NCH_2(CH_2)_{10}CH_3$], 5.08 (s, OCH_2), 6.77 (s, H-4), 7.07 (d, $J = 2.0$ Hz, H-3′), 7.05 (dd, $J = 7.8$, 2.0 Hz, H-5′), 7.24–7.32 (m, $OCH_2C_6H_5$ and H-5″), 7.25 (d, $J = 7.8$ Hz, H-6′), 7.45 (d, $J = 2.1$ Hz, H-3″), 7.84 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.6 [$N(CH_2)_{10}CH_2CH_3$], 26.4, 29.0, 29.3, 29.4, 29.5, 29.6, 30.3, and 31.9 [$NCH_2(CH_2)_9CH_2CH_3$], 50.1 [$NCH_2(CH_2)_{10}CH_3$], 70.6 (OCH_2), 108.0 (C-4), 113.7 (C-3′), 118.9 (C-1′), 121.2 (C-5′), 126.8 (C-2‴,6‴), 127.1 (C-5″), 128.0 (C-4‴), 128.6 (C-3‴,5‴), 129.9 (C-3″), 131.16 (C-6″), 131.22 (C-1″), 132.4 (C-6′), 132.6 (C-2″), 133.4 (C-4″), 135.8 and 135.9 (C-1‴ and C-4′), 139.2 (C-5), 146.8 (C-3), 156.7 (C-2′) ppm; MS (EI): m/z (%) = 602 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 5), 600 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 32), 598 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 71), 596 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 70), 562 (7), 555 (7), 519 (12), 507 (9), 485 (4), 443 (23), 428 (18), 407 (6), 393 (5), 365 (6), 351 (15), 337 (10), 322 (11), 317 (3), 275 (3), 261 (3), 243 (4), 210 (2), 174 (3), 138 (2), 91 (100), 69 (5).

3-(2-Benzyloxy-4,6-dichlorophenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**11c**, $C_{32}H_{34}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.9$ Hz, CH_3), 1.14–1.34 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.74 [quint, $J = 6.3$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 3.98 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_8CH_3$], 5.04 (s, OCH_2), 6.33 (s, H-4), 6.93 (d, $J = 1.9$ Hz, H-3′), 7.15 (d, $J = 1.9$ Hz, H-5′), 7.28–7.31 (m, $OCH_2C_6H_5$), 7.33–7.35 (m, H-5″), 7.55 (d, $J = 1.3$ Hz, H-3″), 7.69 (m, H-6″).

5-(2-Benzyloxy-4,6-dichlorophenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**12c**, $C_{32}H_{34}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.12–1.25 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.73 [quint, $J = 6.6$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 3.89 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_8CH_3$], 5.07 (s, OCH_2), 6.77 (s, H-4), 6.98 (d, $J = 1.8$ Hz, H-5′), 7.18 (d, $J = 1.8$ Hz, H-3′), 7.26–7.52 (m, $OCH_2C_6H_5$), 7.30 (dd, $J = 8.2$, 2.0 Hz, H-5″), 7.46 (d, $J = 2.0$ Hz, H-3″), 7.86 (d, $J = 8.2$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.7 [$N(CH_2)_8CH_2CH_3$], 26.3,

29.0, 29.3, 29.4, 29.5, 30.3, and 31.9 [$NCH_2(CH_2)_7CH_2CH_3$], 49.9 [$NCH_2(CH_2)_8CH_3$], 70.7 (OCH_2), 109.0 (C-4), 112.0 (C-3′), 122.2 (C-5′ and C-1′), 126.6 (C-2‴,6‴), 127.2 (C-5″), 127.7 (C-4‴), 128.3 (C-3‴,5‴), 128.8 (C-6″), 129.8 (C-3″), 132.8 (C-1″), 134.6 (C-6′), 135.3 (C-2″), 135.7 (C-4″), 136.0 (C-4′), 136.2 (C-1‴), 139.0 (C-5), 143.7 (C-3), 158.4 (C-2′) ppm; MS (EI, 70 eV): m/z (%) = 610 ($M^{+\bullet}$, $^{35}Cl + 3 \times {}^{37}Cl$, 1), 608 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 4), 606 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 18), 604 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 35), 569 (3), 527 (6), 513 (5), 475 (4), 463 (4), 398 (2), 386 (7), 372 (8), 357 (8), 309 (2), 273 (2), 214 (2), 172 (3), 105 (2), 91 (100), 69 (4).

3-(2-Benzyloxy-4,6-dichlorophenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole (**11d**, $C_{34}H_{38}N_2OCl_4$)
^{1}H NMR: $\delta = 0.88$ [t, $J = 6.8$ Hz, $N(CH_2)_{11}CH_3$], 1.11–1.29 [m, $N(CH_2)_2(CH_2)_9CH_3$], 1.73 [quint, $J = 6.6$ Hz, $NCH_2CH_2(CH_2)_9CH_3$], 3.89 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_{10}CH_3$], 5.07 (s, OCH_2), 6.77 (s, H-4), 6.98 (d, $J = 1.8$ Hz, H-3′), 7.18 (d, $J = 1.8$ Hz, H-5′), 7.19–7.27 (m, $OCH_2C_6H_5$), 7.30 (dd, $J = 8.3$, 2.0 Hz, H-5″), 7.46 (d, $J = 2.0$ Hz, H-3″), 7.86 (d, $J = 8.3$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.7 [$N(CH_2)_{10}CH_2CH_3$], 26.4, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7, 30.0, and 31.9 [$NCH_2(CH_2)_9CH_2CH_3$], 50.0 [$NCH_2(CH_2)_8CH_3$], 70.7 (OCH_2), 108.7 (C-4), 112.0 (C-3′), 118.5 (C-1′), 122.2 (C-5′), 126.5 (C-2‴,6‴), 127.1 (C-5″), 128.1 (C-4‴), 128.6 (C-3‴,5‴), 129.9 (C-3″), 131.2 (C-6″), 132.8 and 133.4 (C-2″, C-4″ and C-1″), 135.4 (C-5 and C-1‴), 136.3 (C-6′), 136.6 (C-4′), 146.9 (C-3), 158.1 (C-2′) ppm; MS (EI, 70 eV): m/z (%) = 638 ($M^{+\bullet}$, $^{35}Cl + 3 \times {}^{37}Cl$, 0,5), 636 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 2), 634 ($M^{+\bullet}$, $^{35}Cl + 3 \times {}^{37}Cl$, 8), 632 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 16), 603 (1), 597 (4), 589 (1), 555 (2), 547 (1), 543 (4), 541 (5), 533 (3), 519 (4), 505 (2), 477 (8), 464 (4), 455 (2), 443 (3), 401 (3), 387 (6), 374 (5), 358 (2), 351 (3), 338 (2), 309 (1), 261 (2), 172 (2), 91 (100), 69 (4), 55 (10).

5-(2-Benzyloxy-4,6-dichlorophenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole (**12d**, $C_{34}H_{38}N_2OCl_4$)
^{1}H NMR: $\delta = 0.88$ (t, $J = 6.7$ Hz, CH_3), 1.12–1.29 [m, $N(CH_2)_2(CH_2)_9CH_3$], 1.73 [quint, $J = 6.4$ Hz, $NCH_2CH_2(CH_2)_9CH_3$], 3.89 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_{10}CH_3$], 5.06 (s, OCH_2), 6.77 (s, H-4), 6.98 (d, $J = 1.8$ Hz, H-3′), 7.18 (d, $J = 1.8$ Hz, Hz, H-5′), 7.25–7.31 (m, $OCH_2C_6H_5$), 7.20 (dd, $J = 7.9$, 2.0 Hz, H-5″), 7.46 (d, $J = 2.1$ Hz, H-3″), 7.86 (d, $J = 7.9$ Hz, H-6″) ppm; MS (EI, 70 eV): m/z (%) = 636 ($M^{+\bullet}$, $2 \times {}^{35}Cl + 2 \times {}^{37}Cl$, 3), 634 ($M^{+\bullet}$, $3 \times {}^{35}Cl + {}^{37}Cl$, 3), 632 ($M^{+\bullet}$, $4 \times {}^{35}Cl$, 25), 597 (6), 555 (5), 519 (6), 505 (2), 477 (15), 441 (4), 401 (5), 371 (9), 351 (4), 309 (2), 273 (2), 261 (4), 244 (2), 214 (2), 174 (4), 136 (1), 105 (2), 91 (100), 69 (4).

General Method for the Synthesis of 3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-alkylpyrazoles ***13a–13d***
Hydrochloric acid (0.7 cm^3) and 3.2 cm^3 acetic acid were added to the appropriate 3-(2-benzyloxy-4-chlorophenyl)-5-(2,4-dichlorophenyl)-1-alkylpyrazole **11a–11d** (0.48 mmol). The mixture was stirred at 100°C, under nitrogen atmosphere, for 48 h. After that period the mixture was poured into 20 cm^3 water and 30 g ice and the organic layer was extracted with 2×20 cm^3 $CHCl_3$. The organic layer was then purified by thin layer chromatography using a 9:1 mixture of light petroleum:ethyl acetate as eluent. 3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-alkylpyrazoles **13a–13d** were obtained in each case as oils (**13a**, 181.0 mg, 79%; **13b**, 137 mg, 80%; **13c**, 124 mg, 73%; **13d**, 146 mg, 73%).

3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**13a**, $C_{25}H_{29}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.18–1.28 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.77 [quint, $J = 6.8$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 3.92 [t, $J = 7.1$ Hz, $NCH_2(CH_2)_8CH_3$], 6.57 (s, H-4), 6.86 (dd, $J = 8.3$, 2.1 Hz, H-5′), 7.03 (d, $J = 2.1$ Hz, H-3′), 7.28 (d, $J = 8.3$ Hz, H-6″), 7.37 (dd, $J = 8.3$, 2.0 Hz, H-5″), 7.44 (d, $J = 8.3$ Hz, H-6′), 7.56 (d, $J = 2.0$ Hz, H-3″), 11.07 (s, 2′-OH) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.6 [$N(CH_2)_8CH_2CH_3$], 26.3, 28.9, 29.2, 29.3, 29.4, 29.7, and 31.8 [$NCH_2(CH_2)_7CH_2CH_3$], 49.7 [$NCH_2(CH_2)_8CH_3$], 103.5 (C-4), 115.2 (C-1′), 117.2 (C-3′), 119.5 (C-5′), 126.9 (C-6″), 127.4 (C-5″), 127.7 (C-1″), 130.0 (C-3″), 132.7 (C-6′), 134.1 (C-4′), 135.1 (C-2″), 136.3 (C-4″), 140.1 (C-5), 149.7 (C-3), 156.7 (C-2′) ppm; MS (EI): m/z (%) = 485 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 4), 483 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 16), 481 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 24), 480 (99), 478 (100), 443 (10), 421 (6), 393 (17), 380 (3), 365 (7), 351 (63), 338 (47), 317 (13), 304 (8), 275 (7), 248 (2), 239 (5), 212 (5), 185 (2), 176 (7), 138 (3), 99 (3), 69 (7), 55 (29).

3-(4-Chloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole (**13b**, $C_{27}H_{33}N_2OCl_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.17–1.31 [m, $N(CH_2)_2(CH_2)_9CH_3$], 1.77 [quint, $J = 6.7$ Hz, $NCH_2CH_2(CH_2)_9CH_3$], 3.92 [t, $J = 7.1$ Hz, $NCH_2(CH_2)_{10}CH_3$], 6.57 (s, H-4), 6.85 (dd, $J = 8.4$, 2.1 Hz, H-5′), 7.02 (d, $J = 2.1$ Hz, H-3′), 7.28 (d, $J = 8.3$ Hz, H-6″), 7.36 (dd, $J = 8.3$, 2.0 Hz, H-5″), 7.44 (d, $J = 8.4$ Hz, H-6′), 7.55 (d, $J = 2.0$ Hz, H-3″), 11.06 (s, 2′-OH) ppm; ^{13}C NMR: $\delta = 14.1$ (CH_3), 22.6 [$N(CH_2)_{10}CH_2CH_3$], 26.3, 28.9, 29.29, 29.31, 29.5, 29.6, 29.7, and 31.9 [$NCH_2(CH_2)_9CH_2CH_3$], 49.6 [$NCH_2(CH_2)_{10}CH_3$], 103.5 (C-4), 115.2 (C-1′), 117.2 (C-3′), 119.5 (C-5′), 126.9 (C-6″), 127.4 (C-5″), 127.7 (C-1″), 129.9 (C-3″), 132.7 (C-6′), 134.1 (C-4′), 135.1 (C-2″), 136.3 (C-4″), 140.1 (C-5), 149.7 (C-3), 156.6 (C-2′) ppm; MS (EI): m/z (%) = 512 ($M^{+\bullet}$, $3 \times {}^{37}Cl$, 6), 510 ($M^{+\bullet}$, $^{35}Cl + 2 \times {}^{37}Cl$, 41), 508 ($M^{+\bullet}$, $2 \times {}^{35}Cl + {}^{37}Cl$, 95), 506 ($M^{+\bullet}$, $3 \times {}^{35}Cl$, 96), 491 (3), 477 (9), 471 (13), 463 (13), 449 (13), 435 (8), 421 (11), 407 (25), 393 (28), 380 (5), 365 (13), 353 (100), 351 (100), 338 (70), 317 (21), 304 (10), 275 (12), 239 (10), 212 (8), 176 (13), 138 (7), 99 (5), 83 (10), 69 (14).

3-(4,6-Dichloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-decylpyrazole (**13c**, $C_{25}H_{28}N_2OCl_4$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, CH_3), 1.19–1.28 [m, $N(CH_2)_2(CH_2)_7CH_3$], 1.79 [quint, $J = 6.6$ Hz, $NCH_2CH_2(CH_2)_7CH_3$], 3.96 [t, $J = 7.2$ Hz, $NCH_2(CH_2)_8CH_3$], 6.98 (d, $J = 2.1$ Hz,

H-3′), 7.00 (d, $J = 2.1$ Hz, H-5′), 7.18 (s, H-4), 7.33 (d, $J = 8.2$ Hz, H-6″), 7.39 (dd, $J = 8.2$, 2.0 Hz, H-5″), 7.58 (d, $J = 2.0$ Hz, H-3″), 11.98 (s, 2′-O*H*) ppm; ^{13}C NMR: $\delta = 14.1$ (*C*H$_3$), 22.6 [N(CH$_2$)$_8$*C*H$_2$CH$_3$], 26.3, 28.9, 29.2, 29.3, 29.4, 29.7, and 31.8 [NCH$_2$(*C*H$_2$)$_7$CH$_2$CH$_3$], 49.8 [N*C*H$_2$(CH$_2$)$_8$CH$_3$], 109.0 (C-4), 114.5 (C-1′), 116.2 (C-3′), 121.5 (C-5′), 127.4 (C-5″), 127.6 (C-1″), 130.0 (C-3″), 132.6 (C-6′), 132.8 (C-6″), 133.6 (C-4′), 135.2 (C-2″), 136.5 (C-4″), 139.6 (C-5), 146.8 (C-3), 158.2 (C-2′) ppm; MS (EI): m/z (%) = 522 (M$^{+\bullet}$, 4 × ^{37}Cl, 5), 520 (M$^{+\bullet}$, ^{35}Cl + 3 × ^{37}Cl, 6), 518 (M$^{+\bullet}$, 2 × ^{35}Cl + 2 × ^{37}Cl, 23), 516 (M$^{+\bullet}$, 3 × ^{35}Cl + ^{37}Cl, 14), 514 (M$^{+\bullet}$, 4 × ^{35}Cl, 55), 497 (4), 485 (8), 477 (13), 471 (6), 457 (10), 441 (8), 443 (26), 435 (1), 429 (25), 415 (3), 401 (9), 392 (15), 387 (100), 378 (14), 374 (75), 365 (13), 355 (6), 351 (19), 338 (6), 309 (7), 273 (7), 252 (1), 239 (4), 212 (2), 200 (6), 185 (13), 123 (4), 99 (3), 83 (6), 69 (17), 55 (53).

3-(4,6-Dichloro-2-hydroxyphenyl)-5-(2,4-dichlorophenyl)-1-dodecylpyrazole (**13d**, C$_{27}$H$_{32}$N$_2$OCl$_4$)
^{1}H NMR (500.13 MHz): $\delta = 0.87$ (t, $J = 7.0$ Hz, C*H*$_3$), 1.18–1.30 [m, N(CH$_2$)$_2$(C*H*$_2$)$_9$CH$_3$], 1.79 [quint, $J = 6.5$ Hz, NCH$_2$C*H*$_2$(CH$_2$)$_9$CH$_3$], 3.96 [t, $J = 7.2$ Hz, NC*H*$_2$(CH$_2$)$_{10}$CH$_3$], 6.98 (d, $J = 2.1$ Hz, H-3′), 7.00 (d, $J = 2.1$ Hz, H-5′), 7.18 (s, H-4), 7.33 (d, $J = 8.2$ Hz, H-6″), 7.39 (dd, $J = 8.2$, 2.0 Hz, H-5″), 7.58 (d, $J = 2.0$ Hz, H-3″), 12.00 (s, br, 2′-O*H*) ppm; ^{13}C NMR (125.67 MHz): $\delta = 14.1$ (*C*H$_3$), 22.7 [N(CH$_2$)$_{10}$*C*H$_2$CH$_3$], 26.4, 29.0, 29.3, 29.5, 29.6, 29.7, and 31.9 [NCH$_2$(*C*H$_2$)$_9$CH$_2$CH$_3$], 49.8 [N*C*H$_2$(CH$_2$)$_{10}$CH$_3$], 109.0 (C-4), 114.5 (C-1′), 116.2 (C-3′), 121.5 (C-5′), 127.5 (C-5″), 127.6 (C-1″), 130.0 (C-3″), 132.7 (C-6′), 132.9 (C-6″), 133.6 (C-4′), 135.2 (C-2″), 136.5 (C-4″), 139.6 (C-5), 146.9 (C-3), 158.3 (C-2′) ppm; MS (EI): m/z (%) = 548 (M$^{+\bullet}$, ^{35}Cl + 3 × ^{37}Cl, 1), 546 (M$^{+\bullet}$, 2 × ^{35}Cl + 2 × ^{37}Cl, 12), 544 (M$^{+\bullet}$, 3 × ^{35}Cl + ^{37}Cl, 49), 542 (M$^{+\bullet}$, 4 × ^{35}Cl, 100), 527 (2), 507 (10), 485 (10), 469 (5), 457 (8), 443 (17), 441 (14), 429 (20), 415 (3), 401 (10), 387 (100), 373 (64), 351 (14), 338 (6), 309 (8), 286 (2), 273 (12), 248 (3), 237 (12), 218 (2), 208 (9), 185 (7), 174 (11), 164 (100), 137 (65), 117 (74), 104 (26), 90 (19), 77 (26).

General Method for the Synthesis of 5-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-alkylpyrazoles ***14a–14d***
Hydrochloric acid (0.7 cm^3) and 3.2 cm^3 acetic acid were added to the appropriate 5-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-1-alkylpyrazole **12a–12d** (0.48 mmol). The mixture was stirred at 100°C, under nitrogen atmosphere, for 48 h. After that period the mixture was poured into 20 cm^3 water and 30 g ice and the organic layer was extracted with 2 × 20 cm^3 CHCl$_3$. The organic layer was then purified by thin layer chromatography using a 9:1 mixture of light petroleum:ethyl acetate as eluent. 5-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-alkylpyrazoles **14a–14d** were obtained in each case (**14a**, 140.0 mg, 61%, white solid; **14b**, 92.0 mg, 38%, oil; **14c**, 71.0 mg, 29%, white solid; **14d**, 172.0 mg, 70%, white solid).

5-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**14a**, C$_{25}$H$_{29}$N$_2$OCl$_3$)
Mp 87–88°C; ^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, C*H*$_3$), 1.19–1.29 [m, N(CH$_2$)$_2$(C*H*$_2$)$_7$CH$_3$], 1.78 [quint, $J = 7.0$ Hz, NCH$_2$C*H*$_2$(CH$_2$)$_7$CH$_3$], 4.02 [t, $J = 7.4$ Hz, N*C*H$_2$(CH$_2$)$_8$CH$_3$], 5.79 (s, br, 2′-O*H*), 6.84 (s, H-4), 7.02 (dd, $J = 8.1$, 2.0 Hz, H-5′), 7.04 (d, $J = 2.0$ Hz, H-3′), 7.17 (d, $J = 8.1$ Hz, H-6′), 7.30 (dd, $J = 8.4$, 2.1 Hz, H-5″), 7.47 (d, $J = 2.1$ Hz, H-3″), 7.83 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (*C*H$_3$), 22.6 [N(CH$_2$)$_8$*C*H$_2$CH$_3$], 26.4, 29.0, 29.2, 29.37, 29.45, 30.4, and 31.8 [NCH$_2$(*C*H$_2$)$_7$CH$_2$CH$_3$], 49.8 [N*C*H$_2$(CH$_2$)$_8$CH$_3$], 107.8 (C-4), 115.3 (C-1′), 116.6 (C-3′), 121.0 (C-5′), 127.3 (C-5″), 130.1 (C-3″), 130.4 (C-1″), 131.2 (C-6″), 131.4 (C-6′), 132.7 (C-2″), 134.0 (C-4″), 136.4 (C-4′), 137.1 (C-5), 147.7 (C-3), 154.3 (C-2′) ppm; MS (EI): m/z (%) = 484 (M$^{+\bullet}$, 3 × ^{37}Cl, 2), 482 (M$^{+\bullet}$, ^{35}Cl + 2 × ^{37}Cl, 15), 480 (M$^{+\bullet}$, 2 × ^{35}Cl + ^{37}Cl, 39), 478 (M$^{+\bullet}$, 3 × ^{35}Cl, 40), 463 (5), 451 (7), 435 (6), 421 (9), 407 (23), 393 (25), 379 (3), 365 (12), 353 (100), 352 (63), 338 (79), 317 (17), 304 (6), 290 (3), 275 (9), 239 (10), 224 (2), 212 (8), 176 (15), 152 (6), 123 (6), 111 (4), 91 (20), 69 (17).

5-(4-Chloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole (**14b**, C$_{27}$H$_{33}$N$_2$OCl$_3$)
^{1}H NMR: $\delta = 0.87$ (t, $J = 6.8$ Hz, C*H*$_3$), 1.14–1.29 [m, N(CH$_2$)$_2$(C*H*$_2$)$_9$CH$_3$], 1.73 [quint, $J = 6.1$ Hz, NCH$_2$C*H*$_2$(CH$_2$)$_9$CH$_3$], 4.01 [t, $J = 7.3$ Hz, NC*H*$_2$(CH$_2$)$_{10}$CH$_3$], 6.76 (s, H-4), 6.91 (d, $J = 1.9$ Hz, H-3′), 6.96 (dd, $J = 8.2$, 1.9 Hz, H-5′), 7.15 (d, $J = 8.2$ Hz, H-6′), 7.25 (dd, $J = 8.4$, 2.1 Hz, H-5″), 7.45 (d, $J = 2.1$ Hz, H-3″), 7.74 (d, $J = 8.4$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (*C*H$_3$), 22.7 [N(CH$_2$)$_{10}$*C*H$_2$CH$_3$], 26.4, 29.0, 29.3, 29.4, 29.5, 29.6, 30.3, and 31.9 [NCH$_2$(*C*H$_2$)$_9$CH$_2$CH$_3$], 49.9 [N*C*H$_2$(CH$_2$)$_{10}$CH$_3$], 107.9 (C-4), 115.6 (C-1′), 116.5 (C-3′), 120.7 (C-5′), 127.2 (C-5″), 130.0 (C-3″), 130.4 (C-1″), 131.2 (C-6″), 131.7 (C-6′), 132.8 (C-2″), 134.1 (C-4″), 136.2 (C-4′), 138.5 (C-5), 147.5 (C-3), 154.6 (C-2′) ppm; MS (EI): m/z (%) = 512 (M$^{+\bullet}$, 3 × ^{37}Cl, weak signal), 510 (M$^{+\bullet}$, ^{35}Cl + 2 × ^{37}Cl, 3), 508 (M$^{+\bullet}$, 2 × ^{35}Cl + ^{37}Cl, 8), 506 (M$^{+\bullet}$, 3 × ^{35}Cl, 8), 463 (2), 421 (2), 393 (4), 365 (2), 351 (20), 338 (17), 317 (5), 304 (3), 275 (2), 239 (2), 176 (3), 118 (2), 69 (8).

5-(4,6-Dichloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-decylpyrazole (**14c**, C$_{25}$H$_{28}$N$_2$OCl$_4$)
Mp 67–68°C; ^{1}H NMR: $\delta = 0.88$ (t, $J = 6.8$ Hz, C*H*$_3$), 1.18–1.28 [m, N(CH$_2$)$_2$(C*H*$_2$)$_7$CH$_3$], 1.75 [quint, $J = 6.5$ Hz, NCH$_2$C*H*$_2$(CH$_2$)$_7$CH$_3$], 3.86–4.00 [m, NC*H*$_2$(CH$_2$)$_8$CH$_3$], 6.85 (s, H-4), 6.91 (s, br, 2′-O*H*), 6.93 (d, $J = 2.0$ Hz, H-3′), 7.11 (d, $J = 2.0$ Hz, H-5′), 7.29 (dd, $J = 8.5$, 2.1 Hz, H-5″), 7.47 (d, $J = 2.1$ Hz, H-3″), 7.84 (d, $J = 8.5$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (*C*H$_3$), 22.6 [N(CH$_2$)$_8$*C*H$_2$CH$_3$], 26.4, 29.0, 29.1, 29.3, 29.4, 29.5, 30.0, and 31.8 [NCH$_2$(*C*H$_2$)$_7$CH$_2$CH$_3$], 50.1 [N*C*H$_2$(CH$_2$)$_8$CH$_3$], 108.7 (C-4), 115.0 (C-3′), 115.1 (C-1′), 121.7 (C-5′), 127.2 (C-5″), 130.1 (C-3″), 130.3 (C-1″), 131.1 (C-6″), 132.7 (C-2″), 133.9 (C-4″), 134.0 (C-5), 135.7 (C-4′), 136.7 (C-6′), 147.7 (C-3), 155.8 (C-2′) ppm; MS (EI): m/z (%) = 520 (M$^{+\bullet}$, ^{35}Cl + 3 × ^{37}Cl, 1), 518 (M$^{+\bullet}$, 2 × ^{35}Cl + 2 × ^{37}Cl, 4), 516 (M$^{+\bullet}$, 3 × ^{35}Cl + ^{37}Cl, 7),

514 ($M^{+\bullet}$, $4\times{}^{35}Cl$, 29), 497 (2), 479 (9), 457 (6), 441 (16), 429 (23), 415 (2), 401 (8), 387 (100), 374 (73), 351 (28), 340 (11), 338 (10), 324 (3), 317 (5), 309 (7), 282 (2), 273 (9), 248 (1), 246 (4), 239 (4), 224 (1), 216 (5), 210 (9), 200 (7), 187 (11), 185 (14), 174 (13), 172 (15), 159 (6), 147 (3), 138 (6), 136 (7), 123 (9), 111 (4), 99 (3), 87 (4), 83 (5), 75 (6), 69 (18), 55 (40).

5-(4,6-Dichloro-2-hydroxyphenyl)-3-(2,4-dichlorophenyl)-1-dodecylpyrazole (**14d**, $C_{27}H_{32}N_2OCl_4$)
^{1}H NMR: $\delta = 0.88$ (t, $J = 6.7$ Hz, CH_3), 1.16–1.29 [m, N(CH$_2$)$_2$(CH_2)$_9$CH$_3$], 1.74 [quint, $J = 6.4$ Hz, NCH$_2$CH_2(CH$_2$)$_9$CH$_3$], 3.84–4.00 [m, NCH_2(CH$_2$)$_{10}$CH$_3$], 6.88 (d, $J = 1.9$ Hz, H-3′), 6.92 (s, br, 2′-O*H*), 7.10 (d, $J = 1.9$ Hz, H-5′), 7.28 (dd, $J = 8.5$, 2.2 Hz, H-5″), 7.46 (d, $J = 2.2$ Hz, H-3″), 7.81 (d, $J = 8.5$ Hz, H-6″) ppm; ^{13}C NMR: $\delta = 14.1$ (*C*H$_3$), 22.7 [N(CH$_2$)$_{10}$*C*H$_2$CH$_3$], 26.4, 29.0, 29.3, 29.4, 29.5, 29.6, 30.0, and 31.9 [NCH$_2$(*C*H$_2$)$_9$CH$_2$CH$_3$], 50.1 [N*C*H$_2$(CH$_2$)$_8$CH$_3$], 108.8 (C-4), 114.9 (C-3′), 115.1 (C-1′), 121.6 (C-5′), 127.2 (C-5″), 130.1 (C-3″), 130.2 (C-1″), 131.2 (C-6″), 132.8 (C-4″), 134.1 (C-2″), 134.3 (C-5), 135.7 (C-4′), 136.7 (C-6′), 147.7 (C-3), 155.9 (C-2′) ppm; MS (EI): m/z (%) = 548 ($M^{+\bullet}$, $^{35}Cl + 3\times{}^{37}Cl$, 1), 546 ($M^{+\bullet}$, $2\times{}^{35}Cl + 2\times{}^{37}Cl$, 11), 544 ($M^{+\bullet}$, $3\times{}^{35}Cl + {}^{37}Cl$, 38), 542 ($M^{+\bullet}$, $4\times{}^{35}Cl$, 93), 507 (21), 485 (12), 469 (4), 457 (7), 443 (19), 429 (15), 415 (2), 401 (6), 385 (65), 374 (45), 351 (10), 341 (4), 309 (3), 281 (9), 248 (3), 223 (8), 207 (4), 185 (13), 172 (10), 159 (4), 149 (6), 123 (5), 111 (3), 97 (6), 83 (11), 69 (40), 55 (100).

General Method for the Synthesis of 1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2-propen-1-ones ***15a, 15b***
Sodium hydroxide (1.23 g, 30.7 mmol) in 2.0 cm^3 water and 0.16 g 2,4-dichlorobenzaldehyde (0.92 mmol) were added to a solution of the appropriate 2′-benzyloxy-4′-chloroacetophenone **8a**, **8b** (0.77 mmol) in 20 cm^3 methanol. The mixture was stirred at room temperature, under nitrogen atmosphere, for 2 h. After that period the mixture was poured into 50 cm^3 water and 50 g ice and acidified at *pH* 2 with hydrochloric acid. The organic layer was extracted with chloroform, concentrated, and purified by thin layer chromatography using a 1:1 mixture of light petroleum:CH_2Cl_2 as eluent. The 1-(2-benzyloxy-3,4-dichlorophenyl)-3-(4-chlorophenyl)-2-propen-1-ones **15a**, **15b** were obtained in each case as yellow solids (crystallised in ethanol) (**15a**, 311 mg, 97%; **15b**, 270 mg, 88%).

1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2-propen-1-ones (**15a**, $C_{22}H_{15}Cl_3O_2$)
Mp 156–158°C; ^{1}H NMR: $\delta = 5.13$ (s, OCH_2), 6.99 (d, $J = 8.5$ Hz, H-6″), 7.03 (dd, $J = 8.5$, 1.8 Hz, H-5″), 7.07 (dd, $J = 8.2$, 1.8 Hz, H-5′), 7.10 (d, $J = 1.8$ Hz, H-3′), 7.31–7.44 (m, H-2‴,3‴,4‴5‴,6‴), 7.39 (d, $J = 1.8$ Hz, H-3″), 7.41 (d, $J = 15.8$ Hz, H-α), 7.76 (d, $J = 8.2$ Hz, H-6′), 7.95 (d, $J = 15.8$ Hz, H-β) ppm; ^{13}C NMR: $\delta = 71.2$ (O*C*H$_2$), 113.3 (C-3′), 121.6 (C-5′), 126.9 (C-1′), 127.3 (C-5″), 128.0 (C-2‴,6‴), 128.2 (C-6″), 128.6 (C-4‴), 128.8 (C-3‴,5‴), 129.3 (C-α), 129.8 (C-3″), 131.9 (C-1″), 132.4 (C-6′), 135.3 (C-1‴), 135.89 (C-2″), 135.92 (C-4″), 137.1 (C-β), 139.6 (C-4′), 158.3 (C-2′), 189.7 (C=O) ppm; MS (EI): m/z (%) = 420 ($M^{+\bullet}$, $^{35}Cl + 2\times{}^{37}Cl$), 418 ($M^{+\bullet}$, $2\times{}^{35}Cl + {}^{37}Cl$, 2), 416 ($M^{+\bullet}$, $3\times{}^{35}Cl$, 2), 381 (15), 325 (9), 291 (3), 257 (3), 248 (11), 227 (1), 199 (4), 170 (3), 155 (6), 135 (4), 126 (1), 99 (4), 91 (100), 75 (2), 65 (11).

1-(2-Benzyloxy-4,6-dichlorophenyl)-3-(2,4-dichlorophenyl)-2-propen-1-one (**15b**, $C_{22}H_{15}O_2Cl_4$)
Mp 161–162°C; ^{1}H NMR: $\delta = 5.06$ (s, OCH_2), 6.86 (d, $J = 16.2$ Hz, H-α), 6.93 (d, $J = 1.6$ Hz, H-5′), 7.09 (d, $J = 1.6$ Hz, H-3′), 7.25–7.37 (m, H-2‴,3‴,4‴,5‴,6‴,5″), 7.43 (d, $J = 2.1$ Hz, H-3″), 7.55 (d, $J = 8.5$ Hz, H-6″), 7.65 (d, $J = 16.2$ Hz, H-β) ppm; ^{13}C NMR: $\delta = 70.9$ (O*C*H$_2$), 111.9 (C-3′), 122.2 (C-5′), 127.0 (C-2‴,6‴), 127.1 (C-1′), 127.6 (C-5″), 128.2 (C-4‴), 128.57 (C-6″), 128.62 (C-3‴,5‴), 129.7 (C-α), 130.0 (C-3″), 131.1 (C-1″), 132.3 (C-6′), 135.2 (C-1‴), 135.7 (C-2″), 136.2 (C-4′), 136.9 (C-4″), 140.9 (C-β), 156.9 (C-2′), 192.3 (C=O) ppm; MS (EI): m/z (%) = 456 ($M^{+\bullet}$, $2\times{}^{35}Cl + 2\times{}^{37}Cl$, weak signal), 454 ($M^{+\bullet}$, $3\times{}^{35}Cl + {}^{37}Cl$, 2), 452 ($M^{+\bullet}$, $4\times{}^{35}Cl$, 5), 415 (47), 393 (3), 361 (33), 335 (6), 325 (17), 305 (6), 291 (12), 262 (21), 248 (100), 233 (15), 199 (13), 189 (38), 172 (20), 160 (7), 146 (3), 135 (25), 125 (5), 109 (4), 99 (14), 91 (7).

General Method for the Synthesis of 1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2,3-dibromopropan-1-ones ***16a, 16b***
Pyridinium tribromide (0.24 g, 0.76 mmol) was added to a solution of the appropriate 1-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2-propen-1-one **15a**, **15b** (0.51 mmol) in 10 cm^3 acetic acid. The mixture was stirred at room temperature, under nitrogen atmosphere, for 4:30 h. After that period the mixture was poured into 20 cm^3 water and 30 g ice. The obtained solid was filtered off, taken in chloroform, and washed with water. The solvent was evaporated to dryness and the solid residue was crystallised in ethanol. The 1-(2-benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2,3-dibromopropan-1-one **16a**, **16b** were obtained in each case as white powders (**16a**, 261 mg, 89%; **16b**, 267 mg, 94%).

1-(2-Benzyloxy-4-chlorophenyl)-3-(2,4-dichlorophenyl)-2,3-dibromopropan-1-one (**16a**, $C_{22}H_{15}Br_2Cl_3O_2$)
Mp 141–142°C; ^{1}H NMR (*DMSO*-d$_6$; 55°C): $\delta = 5.38$ (s, OCH_2), 5.95 (d, $J = 11.5$ Hz, H-3), 6.32 (d, $J = 11.5$ Hz, H-2), 7.10 (d, $J = 8.1$ Hz, H-6″), 7.24 (dd, $J = 8.4$, 1.9 Hz, H-5′), 7.35 (dd, $J = 8.1$, 2.2 Hz, H-5″), 7.51–7.64 (m, OCH$_2$C$_6$*H*$_5$), 7.54 (d, $J = 1.9$ Hz, H-3′), 7.65 (d, $J = 2.1$ Hz, H-3″), 7.92 (d, $J = 8.4$ Hz, H-6′) ppm; ^{13}C NMR (*DMSO*-d$_6$; 55°C): $\delta = 43.5$ (C-3), 49.3 (C-2), 71.4 (O*C*H$_2$), 114.4 (C-3′), 121.4 (C-5′), 122.1 (C-1′), 128.2 (C-5″), 128.8 (C-3‴,5‴,4‴), 129.1 (C-2‴,6‴), 129.3 (C-3″), 130.4 (C-6″), 133.0 (C-6′ and C-2″), 133.5 (C-1″), 134.5 (C-4″), 135.3 (C-1‴), 140.5 (C-4′), 158.7 (C-2′), 190.0 (C-1) ppm.

1-(2-Benzyloxy-4,6-dichlorophenyl)-3-(2,4-dichlorophenyl)-2,3-dibromopropan-1-one (**16b**, $C_{22}H_{14}O_2Br_2Cl_4$)
Mp 148–149°C; ^{1}H NMR (*DMSO*-d$_6$; 45°C): $\delta = 5.23$ (s, OCH_2), 5.82 (d, $J = 11.0$ Hz, H-3), 6.08 (d, $J = 11.0$ Hz,

H-2), 7.24 (d, $J = 1.5$ Hz, H-5′), 7.33 (d, $J = 1.5$ Hz, H-3′), 7.35–7.44 (m, H-3‴,5‴,4‴), 7.51 (dd, $J = 9.0$, 1.5 Hz, H-5″), 7.54–7.58 (m, H-2‴,6‴ and H-6″), 7.64 (d, $J = 1.5$ Hz, H-3″) ppm; ^{13}C NMR (*DMSO*-d_6; 45°C): $\delta = 40.3$ (C-3), 51.2 (C-2), 70.6 (OCH_2), 112.7 (C-3′), 121.2 (C-5′), 123.7 (C-1′), 127.7 (C-2‴,6‴), 128.2 (C-5″), 128.5 (C-4‴), 128.6 (C-3‴,5‴), 128.7 (C-3″), 129.5 (C-6″), 133.6 (C-2″), 134.4 (C-1″), 135.0 (C-1‴), 135.8 (C-6′ and C-4″), 137.4 (C-4′), 155.9 (C-2′), 189.6 (C-1) ppm.

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 cm^3 of ice-cold *Tris* sucrose with *EDTA* buffer (5 m*M Tris*–HCl, 250 m*M* sucrose, 1 n*M 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 37°C 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 cm^3 aliquots (50 m*M Tris*–HCl, *EDTA*, *pH* 7.4 with 0.1% BSA) of human brain cortical membranes that were incubated with [^{3}H]CP55-940 (1 n*M*) for 60 min at 30°C 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 cm^3 ice-cold *Tris*–incubation buffer with 0.1% BSA (4°C). 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 cm^3 of incubation buffer and transferred to minivials containing 3–5 cm^3 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 (K_i) was performed by non-linear regression using the EBDA-LIGAND program. All experiments were analyzed assuming a one-site model of radioligand binding.

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