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Novel derivatives of 3-alkyl-1,5-diaryl-1*H*-1,2,4-triazoles and their pharmacological evaluation as CB_1 cannabinoid ligands

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Abstract In a previous study, we have identified 3-alkyl-1,5-diaryl-1*H*-1,2,4-triazoles to be a novel class of cannabinoid type-1 (CB_1) receptor antagonists. However, the synthesis yields for the ligands were low. Here we present an alternative synthesis pathway with improved yields. In addition, we have synthezised new structural derivatives and studied their results in competitive radioligand binding assays for cannabinoid receptors.

Keywords Cannabinoid; 1,2,4-Triazole; Binding.

Introduction

Due to the potential therapeutic effects [1] of cannabinoids that include antiemetic, analgesic, antiglaucoma, obesity treatment, alcoholism, bronchodilatation, and inflammation, a considerable number of cannabinoid ligands have been reported in recent years. Their effects are mediated through cannabinoid receptors [2–4]. So far two types of cannabinoid receptors have been cloned, namely the cannabinoid type-1 (CB_1) and cannabinoid type-2 (CB_2), which belong to the class of G-protein coupled receptors. The CB_1 receptors are spread throughout the body and the CB_2 receptors mainly in the immune system. Ligands with known affinity for the cannabinoid receptors belong to several structural classes. Pyrazoles and aminoalkylindoles (*AAI*s) are two of the most well known classes of heterocyclic ligands for the cannabinoid receptors [5–8].

In our early research program, it was found that the triazole motif exhibits cannabinoid activity [9]. We reported that 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1*H*-1,2,4-triazole (**11**) showed cannabinoid activity in *in vivo* assays. This prompted us to extend our previous investigation by synthesizing a series of 1,2,4-triazoles in order to study the influence of variable aliphatic side chains and aryl substituents. However, the synthesis route that was previously followed afforded unsatisfactory yields. 1,5-Diaryl-3-alkyl-1*H*-1,2,4-triazoles were synthesized condensing the corresponding *N*-acylbenzamides with phenylhydrazines. We therefore decided to attempt a different approach in order to improve their preparation.

We describe herein the synthesis of new 1,2,4-triazole analogues with improved yields and present initial results from radioligand binding assays as part of our investigation on cannabinoid active compounds.

Results and discussion

Synthesis

The formation of 1,2,4-triazoles from hydrazonyl chlorides has shown to be an excellent strategy [10, 11]. Thereby, 1,5-diaryl-1*H*-1,2,4-triazoles **8**–

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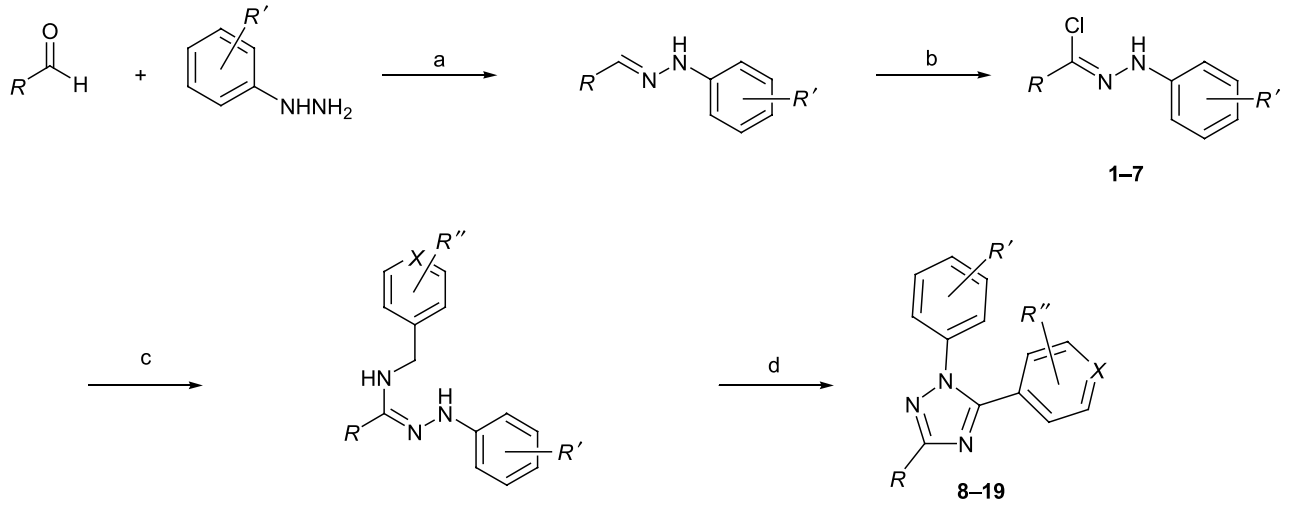


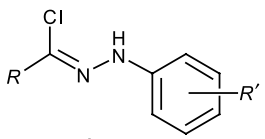
a) dry toluene, rt;
b) *NCS*/*DMS*, dry CH_2Cl_2, 0 to −78°C to room temperature;
c) benzylamine for **10**; 4-chlorobenzylamine for **8**, **9**, **11**, **15**, **18**, and **19**; 2,4-dichlorobenzylamine for **12**; 4-fluorobenzylamine for **13** and **16**; 4-(aminomethyl)pyridine for **14** and **17**, *TEA*, *Me*CN, rt;
d) aq. NaOCl, *Me*CN, room temperature (reflux for **18**).

Scheme 1

19 bearing an aliphatic substituent in position 3 were prepared as described in Scheme 1.

Condensation of aldehydes with phenylhydrazines gave the corresponding hydrazone intermediates which were used in the next step without further purification. The hydrazones were then treated at −78°C with *N*-chlorosuccinimide/dimethyl sulfide complex following *Patel*'s procedures [12] to yield

Table 1 Structures of hydrazonyl chlorides and overall yields



1–7

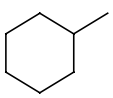
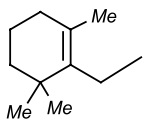
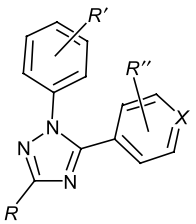
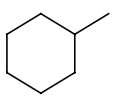
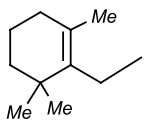
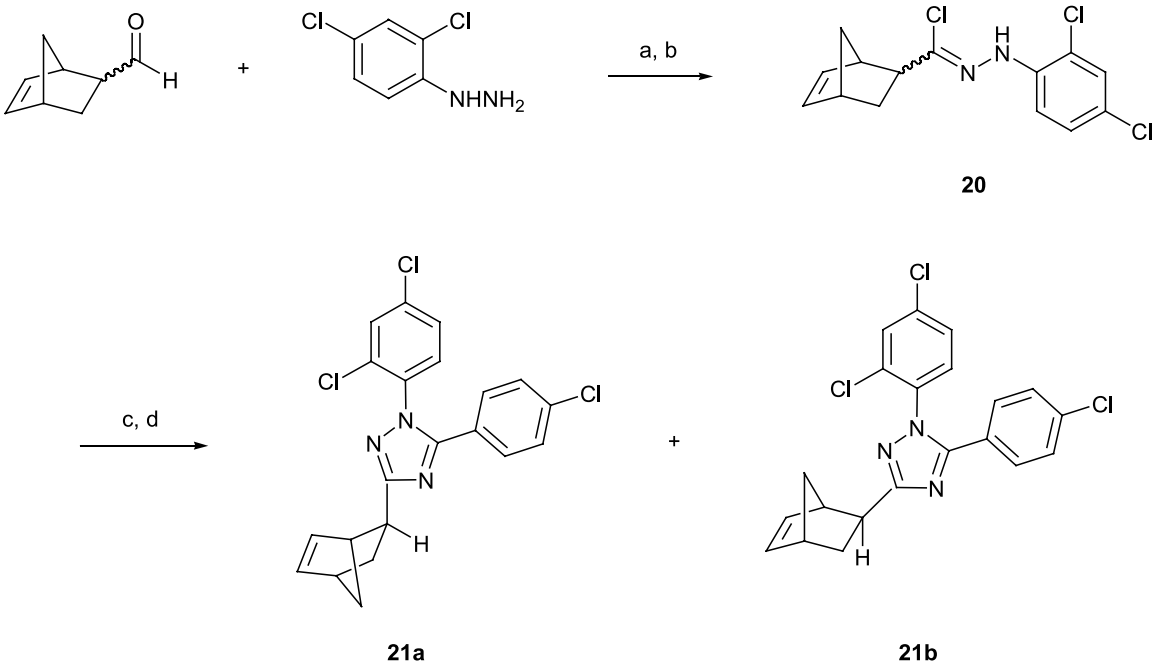
Compound	*R*	*R*′	Yield/(%)
1	CH_2CH_3	2,4-Cl_2	45
2	$CH_2(CH_2)_3CH_3$	2,4-Cl_2	5
3	$CH_2(CH_2)_4CH_3$	H	42
4	$CH_2(CH_2)_4CH_3$	2,4-Cl_2	59
5	$CH_2(CH_2)_5CH_3$	2,4-Cl_2	47
6		2,4-Cl_2	38
7		2,4-Cl_2	10

Table 2 Structures of 3-alkyl-1,5-diaryl-1*H*-1,2,4-triazoles and overall yields



8–19

Compound	*R*	*R*′	*R*″	*X*	Yield/(%)
8	CH_2CH_3	2,4-Cl_2	4-Cl	C	48
9	$CH_2(CH_2)_3CH_3$	2,4-Cl_2	4-Cl	C	22
10	$CH_2(CH_2)_4CH_3$	H	H	C	47
11	$CH_2(CH_2)_4CH_3$	2,4-Cl_2	4-Cl	C	34
12	$CH_2(CH_2)_4CH_3$	2,4-Cl_2	2,4-Cl_2	C	31
13	$CH_2(CH_2)_4CH_3$	2,4-Cl_2	4-F	C	41
14	$CH_2(CH_2)_4CH_3$	2,4-Cl_2	H	N	26
15	$CH_2(CH_2)_5CH_3$	2,4-Cl_2	4-Cl	C	23
16	$CH_2(CH_2)_5CH_3$	2,4-Cl_2	4-F	C	35
17	$CH_2(CH_2)_5CH_3$	2,4-Cl_2	H	N	24
18		2,4-Cl_2	4-Cl	C	59
19		2,4-Cl_2	4-Cl	C	34



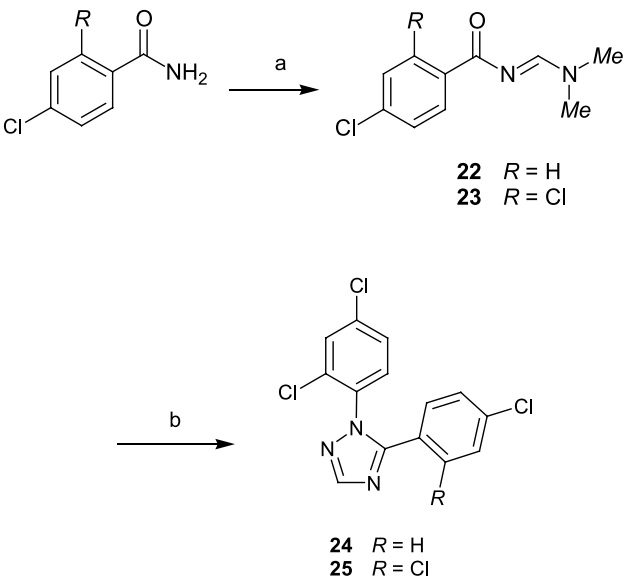
a) dry toluene, rt; b) *NCS*/*DMS*, dry CH_2Cl_2, 0 to −78°C to room temperature;
c) 4-chlorobenzylamine, *Me*CN, room temperature; d) aq. NaOCl, *Me*CN, reflux.

Scheme 2

hydrazonyl chlorides **1**–**7** in moderate yields (Table 1). The light sensitive hydrazonyl chlorides readily reacted with the corresponding benzylamines or with 4-(aminomethyl)pyridine giving crude triazenes which were then subjected to cyclization. The cyclization occurred using sodium hypochlorite as oxidizing agent at room temperature to give reasonable yields (Table 2) of the desired triazoles **8**–**17** and **19**. However, this cyclization needed to be performed under reflux conditions to obtain the triazole **18**.

In the case of the 1,5-diaryl-1*H*-1,2,4-triazole subtituted in position 3 by a norbornenyl residue (**21**) (Scheme 2), the commercial starting aldehyde, 5-norbornene-2-carboxaldehyde, was used as a mixture of *endo*/*exo* isomers in 3/1 proportion determined by ^{1}H NMR. The two resulting diastereomers **21a** and **21b** were isolated by medium pressure flash chromatography on silica gel. The structural identification of **21a** and **21b** has been further realized using two-dimensional NMR techniques (HMQC and COSY) and nuclear *Overhauser* effect measurements (*nOe*). Thereby, the structures of **21a** and **21b** have been attributed to the *endo* and to the *exo* isomers.

It is known that the nature of the alkyl side chain has a profound effect upon the pharmacological activity of most cannabinoids. Thus, C-3 unsubstituted 1,5-diaryl-1*H*-1,2,4-triazoles **24** and **25** have been prepared following Scheme 3 [13]. Amidines **22** and **23** were synthesized by refluxing the corre-



a) $(OMe)_2CHNMe_2$, reflux;
b) 2,4-dichlorophenylhydrazine, *Ac*OH 70%, 1,4-dioxane, reflux

Scheme 3

sponding benzamide with *N*,*N*-dimethylformamide dimethyl acetal. Reacting 2,4-dichlorophenylhydrazine with these amidines gave 1,2,4-triazoles **24** and **25**. Whereas **24** was obtained in moderate yield (53%), **25** was obtained in low yield (3%). This difference in reactivity is probably due to the mesomeric effects caused by chlorine atoms on position 2 of the phenyl ring. The electron density at that position is greater in the case of the 2,4-dichlorophenyl amidine (**25**) than for the 4-chlorophenyl amidine (**24**) resulting in a less reactive carbonyl group for the amidine **25**.

Regarding the 3-alkyl-1,5-diaryl-1,2,4-triazoles **8**–**19**, **21a**, and **21b**, the present method of preparation offers an improved route to this series of compounds compared to the synthesis procedures described previously for the triazole **11**. The overall yields of the previous published preparation and the present synthesis are 3.3 and 20.0% for **11**.

Binding assays

Competitive binding assays were carried out to measure the ability of this series of triazole to displace the radioligand [^{3}H]-CP55940 from CB_1 and CB_2 cannabinoid receptors. The results of these preliminary assays are reported in Table 3.

Table 3 Displacement of specific [^{3}H]-CP55940 binding (at 1 μM) in CHO cells stably transfected with human CB_1 and CB_2 receptors, expressed as percentage (%)

Compound	CB_1: Displacements[a] (%) at 1 μM	CB_2: Displacements[a] (%) at 1 μM
SR141716	100[b]	47.3[c]
WIN55212-2	100[d]	100[e]
8	23.0 ± 15.3	13.7 ± 4.2
9	53.9 ± 23	n.t.
10	22.2 ± 15.2	49.6 ± 3.6
11	64.3 ± 15.5	9.7 ± 9.2
12	62.6 ± 5.5	n.t.
13	41.5 ± 6.8	n.t.
15	56.6 ± 27.1	n.t.
17	21.0 ± 21.9	-4.1 ± 11.2
18	27.6 ± 11.3	n.t.
19	43.3 ± 4.0	n.t.
21a	36.6 ± 4.8	n.t.
21b	27.9 ± 1.6	n.t.
24	-8.1 ± 1.8	-15.1 ± 5.0

[a] Values expressed as mean of three experiments with standard deviation. n.t. = Not tested; [b] $K_i = 5.8 \pm 0.8$ nM; [c] $K_i \cong 1000$ nM; [d] $K_i = 13.1$ nM; [e] $K_i = 7.3$ nM
Displaced cannabinoid CP55940: $K_d = 0.52$ nM for CB_1 and $K_d = 0.63$ nM for CB_2

The synthesized **8**–**13**, **15**, **17**–**19**, **21a**, **21b**, and **24** showed less affinity for CB_1 receptor than the reference cannabinoid ligands SR141716 and WIN55212-2. From the tested compounds for CB_2 receptor, only one (**10**) shows a moderate binding. However, these preliminary data allow us to make observations about structure-activity relationships.

The importance of the side chain for binding to cannabinoid receptors was revealed by the triazole **24** which lacks a 4-substituent on the triazole core. This triazole did not displace [^{3}H]-CP55940 from either CB_1 or CB_2 receptors contrary to any of the 3-substituted triazoles of the present series. Increasing the length of the side chain led to a significant increase in affinity for CB_1 receptor, the ethyl derivative **8** and the heptyl derivative **15** showing displacement values of 23 and 56.6%. However, restriction of the side chain's conformation mobility by cycloalkyl substituents resulted in moderate CB_1 receptor activity. Where hexyl analogue **11** showed a value of 64.3%, cyclohexyl (**18**), cyclohexenylmethyl (**19**), and norbornenyl (**21a** and **21b**) data were 27.6, 43.3, 36.6, and 27.9%.

Regarding diaryl substitution, displacement data of the diphenyl derivative **10** (22.2%) indicated a lowering of affinity for CB_1 receptor with respect to the 2,4-dichlorophenyl analogues **11** (64.3%) and **12** (62.6%). However, it is interesting to note that **10** showed a higher affinity (49.6%) for CB_2 receptor than **11** (9.7%). Substitution of the 4-chlorophenyl group (**11**) for 2,4-dichlorophenyl (**12**) at the C5 position had no effect on the affinity for CB_1 receptor. However replacement of the 5-(4-chlorophenyl) ring substituent with either a 4-fluorophenyl or a pyridyl group resulted in lower affinities.

Conclusion

Very recently we published a study on feeding behavior and alcohol self-administration of the triazole **11** on rats [14]. A triazole named LH-21 has been shown to reduce food intake and weight gain in obese animals with major peripheral components. These effects have been shown to be mediated through CB_1 receptors even though its affinity for this receptor is considered moderate [**11** (LH-21) $K_i = 748 \pm 193$ nM [9]]. In the present study, an improved synthesis of LH-21 has been described. Different structural modifications of this triazole are reported. Regarding the preliminary biological ac-

tivity, among the tested compounds LH-21 (**11**) still showed the best [^{3}H]-CP55940 displacement value.

Experimental

Chemistry

Toluene was distilled over sodium-benzophenone, and CH_2Cl_2 was distilled over calcium chloride. The aqueous solution of NaOCl ($d = 1.206\,g/cm^3$, available chlorine 10–13%) was purchased from Aldrich. Bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde was purchased from Aldrich. Melting points were determined with a Reichert Jung Thermovar apparatus. Mass spectra were recorded using electrospray positive mode. Flash column chromatographies were run on silica gel 60 (230–400 Mesh) or on a medium pressure flash system with prepacked silica gel cartridges [Biotage Flash 40, cartridges KP-Sil 40S (4×7 cm) or 4 *M* (4×15 cm) with a particle size of 32–63 μm of 60 Å; FlashMaster Personal with prepacked cartridges FlashPack of 2, 10, 20, or 50 g]. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer. Results were within $\pm 0.4\%$ of the theoretical values. Analytical HPLC was run on a Waters 6000 with Delta Pak C 18.5 μm, 300 Å, $3.9 \times 150\,mm^2$ column, using as eluent *Me*CN/H_2O (0.05% H_3PO_4 + 0.04% *TEA*) in the proportion indicated in each case; flow rate 1 cm^3/min; 254 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Gemini 200, Varian 300, 400, and 500 unity spectrometers using *TMS* as the internal standard. All chemical shifts are reported in ppm.

*General procedure for preparing hydrazonyl chlorides **1–7** and **20***

To a solution of the corresponding aldehyde (1 equiv) in 30–100 cm^3 dry toluene was added the appropriate hydrazine (1 equiv), and the mixture was stirred at room temperature for 15 h (30 min for **3**). Removal of the solvent provided the crude hydrazone, which was used in the next step without further purification. In a round-bottom flask fitted with a dropping funnel, a solution of *NCS* (1.5 equiv) in 30–70 cm^3 dry CH_2Cl_2 was stirred with *DMS* (3 equiv) at 0°C for 30 min. A white precipitate was formed. After cooling this reaction mixture to −78°C in an acetone/dry ice bath, a solution of the hydrazone prepared above in 30–80 cm^3 dry CH_2Cl_2 was added dropwise. The resulting orange suspension was stirred for 2–3 h and then allowed to warm to room temperature (the orange suspension turned to a dark red solution). The solvent was evaporated, and the residue was dried at reduced pressure and purified by flash chromatography (*n*-hexane or cyclohexane/*Et*OA*c*, 98/2 for **3**).

N-2,4-Dichlorophenylpropyl-1-acetohydrazonyl chloride (**1**, $C_9H_9N_2Cl_3$)

Compound **1** was prepared from 0.76 cm^3 propionaldehyde (10.5 mmol), 1.79 g 2,4-dichlorophenylhydrazine (10.5 mmol), 2.02 g *NCS* (15.2 mmol), and 2.23 cm^3 *DMS* (30.3 mmol): yield 1.20 g (45%) as a transparent oil; $R_f = 0.75$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (1H, br, s, NH), 7.32 (1H, d, $J = 8.8$ Hz, 6-H), 7.26 (1H, d, $J = 2.4$ Hz, 3-H), 7.15 (1H, dd, $J = 8.8$, 2.4 Hz, 5-H), 2.65 (2H, q, $J = 7.3$ Hz, CH_2CH3), 1.26 (3H, t, $J = 7.3$ Hz, CH_2CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.7$ (1-C), 132.1 (C(Cl)=N), 128.7 (3-C), 127.9 (5-C), 124.5 (4-C), 117.7 (2-C), 115.1 (6-C), 32.6 (CH_2CH_3), 11.4 (CH_2CH_3) ppm.

N-2,4-Dichlorophenylhexyl-1-hydrazonyl chloride (**2**, $C_{12}H_{15}N_2Cl_3$)

Compound **2** was prepared from 1.74 cm^3 hexanaldehyde (14.4 mmol), 2.46 g 2,4-dichlorophenylhydrazine (14.4 mmol), 3.29 g *NCS* (24.6 mmol), and 3.62 cm^3 *DMS* (49.2 mmol): yield 226 mg (5%) as a red oil; $R_f = 0.80$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (1H, br, s, NH), 7.32 (1H, d, $J = 8.8$ Hz, 6-H), 7.16 (1H, d, $J = 2.0$ Hz, 3-H), 7.14 (1H, dd, $J = 8.8$, 2.0 Hz, 5-H), 2.61 (2H, t, $J = 7.3$ Hz, CH_2-$CH_2CH_2CH_2CH_3$), 1.70 (2H, p, $J = 7.3$ Hz, CH_2CH_2-$CH_2CH_2CH_3$), 1.37–1.30 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 0.90 (3H, br, t, $J = 6.3$ Hz, $CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.7$ (1-C), 131.2 (C(Cl)=N), 128.7 (3-C), 128.0 (5-C), 124.5 (4-C), 117.7 (2-C), 115.1 (6-C), 38.8 ($CH_2CH_2CH_2CH_2CH_3$), 30.7 ($CH_2CH_2CH_2CH_2CH_3$), 26.3 ($CH_2CH_2CH_2CH_2CH_3$), 22.3 ($CH_2CH_2CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_2CH_2CH_3$) ppm.

N-Phenylheptyl-1-acetohydrazonyl chloride (**3**, $C_{13}H_{19}N_2Cl$)

Compound **3** was prepared from 2.45 cm^3 heptanaldehyde (17.5 mmol), 1.73 cm^3 phenylhydrazine (17.5 mmol), 3.64 g, *NCS* (27.2 mmol), and 4.00 cm^3, *DMS* (54.4 mmol): yield 1.75 g (42%) as an orange oil; $R_f = 0.75$ (cyclohexane/*Et*OA*c*, 98/2); ^{1}H NMR ($CDCl_3$): $\delta = 7.59$ (1H, br, s, NH), 7.25 (2H, t, $J = 7.3$ Hz, 3-H), 7.03 (2H, d, $J = 7.3$ Hz, 2-H), 6.88 (1H, t, $J = 7.3$ Hz, 4-H), 2.61 (2H, t, $J = 7.3$ Hz, CH_2-$CH_2CH_2CH_2CH_2CH_3$), 1.70 (2H, p, $J = 7.3$ Hz, $CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 1.39–1.22 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.90 (3H, br, t, $J = 6.5$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 143.9$ (1-C), 129.3 (3-C), 127.8 (C(Cl)=N), 120.5 (4-C), 113.0 (2-C), 38.8 ($CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 31.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 (CH_2-$CH_2CH_2CH_2CH_2CH_3$), 26.6 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_2$-CH_2CH_3) ppm.

N-2,4-Dichlorophenylheptyl-1-acetohydrazonyl chloride (**4**, $C_{13}H_{17}N_2Cl_3$)

Compound **4** was prepared from 4.00 cm^3 heptanaldehyde (28.6 mmol), 4.86 g 2,4-dichlorophenylhydrazine (28.6 mmol), 5.31 g *NCS* (39.8 mmol), and 5.84 cm^3 *DMS* (79.6 mmol): yield 5.21 g (59%) as a transparent oil; $R_f = 0.80$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (1H, br, s, NH), 7.32 (1H, d, $J = 8.8$ Hz, 6-H), 7.26 (1H, d, $J = 2.2$ Hz, 3-H), 7.15 (1H, dd, $J = 8.8$, 2.2 Hz, 5-H), 2.61 (2H, t, $J = 7.4$ Hz, CH_2CH_2-$CH_2CH_2CH_2CH_3$), 1.69 (2H, p, $J = 7.4$ Hz, $CH_2CH_2CH_2CH_2$-CH_2CH_3), 1.40–1.20 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.88 (3H, br, t, $J = 7.0$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.7$ (1-C), 131.2 (C(Cl)=N), 128.7 (3-C), 128.0 (5-C), 124.5 (4-C), 117.7 (2-C), 115.1 (6-C), 38.8 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 31.4 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 26.5 ($CH_2CH_2CH_2CH_2CH_2$-

CH_3), 22.5 ($CH_2CH_2CH_2CH_2CH_2$-CH_3), 14.0 (CH_2CH_2-$CH_2CH_2CH_2CH_3$) ppm.

N-2,4-Dichlorophenyloctyl-1-acetohydrazonyl chloride (**5**, $C_{14}H_{19}N_2Cl_3$)

Compound **5** was prepared from 1.22 cm^3 octanaldehyde (7.8 mmol), 1.33 g 2,4-dichlorophenylhydrazine (7.8 mmol), 1.67 g *NCS* (12.5 mmol), and 1.83 cm^3 *DMS* (25.0 mmol): yield 1.19 g (47%) as a transparent oil; $R_f = 0.80$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (1H, br, s, NH), 7.32 (1H, d, $J = 8.7$ Hz, 6-H), 7.27 (1H, d, $J = 2.4$ Hz, 3-H), 7.14 (1H, dd, $J = 8.7$, 2.4 Hz, 5-H), 2.61 (2H, t, $J =$ 7.4 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.69 (2H, p, $J =$ 7.4 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.38–1.20 (8H, m, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 0,87 (3H, br, t, $J =$ 6.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.7$ (1-C), 131.1 (C(Cl)=N), 128.7 (3-C), 128.0 (5-C), 124.5 (4-C), 117.7 (2-C), 115.1 (6-C), 38.8 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 31.7 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 28.9, 28.5 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 26.6 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2$-$CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm.

N-2,4-Dichlorophenylcyclohexyl-1-acetohydrazonyl chloride (**6**, $C_{13}H_{15}N_2Cl_3$)

Compound **6** was prepared from 2.57 cm^3 cyclohexanecarboxaldehyde (21.2 mmol), 3.60 g 2,4-dichlorophenylhydrazine (21.2 mmol), 4.28 g *NCS* (32.0 mmol), and 4.71 cm^3 *DMS* (64.1 mmol): yield 2.47 g (38%) as a transparent oil; $R_f =$ 0.75 (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.08$ (1H, br, s, NH), 7.31 (1H, d, $J = 8.8$ Hz, 6-H), 7.26 (1H, d, $J = 2.2$ Hz, 3-H), 7.14 (1H, dd, $J = 8.8$, 2.2 Hz, 5-H), 2.52 (1H, tt, $J = 11.0$, 3.3 Hz, 1′-H cyclohexane), 2.05–1.98 (3H, m, H cyclohexane), 1.84–1.17 (7H, m, H cyclohexane) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.7$ (1-C), 135.2 (C(Cl)=N), 128.7 (3-C), 127.9 (5-C), 124.4 (4-C), 117.7 (2-C), 115.1 (6-C), 47.1 (1′-C), 30.6 (2′-C), 25.8 (4′-C), 25.6 (3′-C) ppm.

N-2,4-Dichlorophenyl-2-(2,6,6-trimethyl-1-cyclohexenyl)-1-acetohydrazonyl chloride (**7**, $C_{17}H_{21}N_2Cl_3$)

Compound **7** was prepared from 1.06 cm^3 2-(2,6,6-trimethyl-1-cyclohexene)-1-acetaldehyde (6.0 mmol), 1.02 g 2,4-dichlorophenylhydrazine (6.0 mmol), 1.26 g *NCS* (9.4 mmol), and 1.38 cm^3 *DMS* (18.9 mmol): yield 220 mg (10%) as a transparent oil; $R_f = 0.70$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (1H, br, s, NH), 7.28–7.15 (3H, m, H aromatics), 3.38 (2H, s, CH_2CCl), 2.00 (2H, t, $J = 5.5$ Hz, $CH_2C(CH_3)$=), 1.62 (3H, s, $CH_2C(CH_3)$=), 1.53–1.43 (4H, m, $CH_2CH_2C(CH_3)_2$), 0.99 (6H, s, $2 \times CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.8$ (1-C), 133.1 (CH_2C=), 130.3 (CH_3C=), 129.1 (3-C), 128.4 (5-C), 127.8 (C(Cl)=N), 124.4 (4-C), 117.7 (2-C), 115.3 (6-C), 40.2 ($CH_2C(CH_3)_2$), 38.3 ($CH_2C(CH_3)$=), 35.2 ($C(CH_3)_2$), 33.3 (CH_2CCl), 28.7 ($2 \times CH_3$), 21.0 (CH_3), 19.7 (CH_2) ppm.

N-2,4-Dichlorophenylbicyclo[2.2.1]hept-5-enyl-1-acetohydrazonyl chloride (**20**, $C_{14}H_{13}N_2Cl_3$)

Compound **20** was prepared from 2.13 cm^3 bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (17.8 mmol), 3.03 g 2,4-dichlorophenylhydrazine (17.8 mmol), 3.63 g *NCS* (27.2 mmol), and 4.00 cm^3 *DMS* (54.4 mmol): yield 2.02 g (36%) as a transparent oil; $R_f = 0.55$ (*n*-hexane); ^{1}H NMR ($CDCl_3$): $\delta = 8.07$ (1H, br, s, NH), 7.28 (1H, d, $J = 2.3$ Hz, 3-H), 7.25 (1H, d, $J =$ 8.8 Hz, 6-H), 7.15 (1H, dd, $J = 8.8$ Hz, 2.3, 5-H), 6.22 (1H, dd, $J = 5.6$, 2.9 Hz, 2′-H norbornene), 5.94 (1H, dd, $J = 5.6$, 2.9 Hz, 3′-H norbornene), 3.33 (1H, br, s, 4′-H norbornene), 3.25 (1H, dt, $J = 9.0$ Hz, 4.0, 5′-H norbornene), 2.95 (1H, br, s, 1′-H norbornene), 1.99 (1H, ddd, $J = 20.9$, 9.0, 3.5 Hz, 6′ec-H norbornene), 1.67 (1H, ddd, $J = 20.9$, 4.0, 2.8 Hz, 6′ax-H norbornene), 1.53–1.51 (1H, m, 7′-H norbornene), 1.37 (1H, m, 7′-H norbornene) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 138.8$ (1-C), 137.5 (2′-C), 133.8 (C(Cl)=N), 132.0 (3′-C), 128.7 (3-C), 127.9 (5-C), 124.4 (4-C), 117.6 (2-C), 115.0 (6-C), 48.9 (7′-C), 48.0 (4′-C), 46.7 (1′-C), 42.6 (5′-C), 30.1 (6′-C) ppm.

General procedure for preparing 3-alkyl-1,5-diaryl-1H-1,2,4-triazoles ***8–19***, ***21a***, *and* ***21b***

To a solution of hydrazonyl chloride (1 equiv) in 15–50 cm^3 *Me*CN were added first the corresponding benzylamine (1.2 equiv) and then, *TEA* (1.2 equiv). The mixture was stirred at room temperature for 1–4 h. Then, the solvent was removed *in vacuo* and the residue was used in the next step without further purification. To a solution of the crude triazene in 10–50 cm^3 *Me*CN were added an aqueous solution of 5–15 cm^3 NaOCl, and the mixture was stirred at room temperature (for **18** and **21** at reflux) overnight. The reaction mixture was diluted with 20–60 cm^3 *Et*OA*c* and washed with 3×30 cm^3 H_2O. The organic layer was dried over anhydrous Na_2SO_4, the solvent was evaporated, and the residue was purified by different chromatographic methods indicated in each case.

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-ethyl-1H-1,2,4-triazole (**8**, $C_{16}H_{12}Cl_3N_3$)

Compound **8** was prepared from 1.00 g **1** (4.0 mmol), 0.580 cm^3 4-chlorobenzylamine (4.8 mmol), 0.665 cm^3 *TEA* (4.8 mmol), and 10 cm^3 aq. NaOCl (flash chromatography: cyclohexane/Et_2O, 4/1): yield 674 mg (48%) as an orange solid; mp 108–110°C; $R_f = 0.40$ (cyclohexane/Et_2O, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.48$ (1H, d, $J = 2.0$ Hz, 3′-H), 7.38 (2H, d, $J = 8.7$ Hz, 2″-H), 7.40–7.34 (2H, m, 6′-H, 5′-H), 7.26 (2H, d, $J = 8.7$ Hz, 3″-H), 2.83 (2H, q, $J = 7.6$ Hz, CH_2), 1.37 (3H, t, $J = 7.6$ Hz, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 166.1 (3-C triazole), 154.3 (5-C triazole), 136.4, 136.2, 134.7, 132.6 (1′-C, 2′-C, 4′-C, 4″-C), 130.4 (6′-C), 129.9 (3′-C), 129.0, 128.8 (2″-C, 3″-C), 128.2 (5′-C), 125.9 (1″-C), 21.6 (CH_2), 12.3 (CH_3) ppm; ES-MS: m/z (%) = 352 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-pentyl-1H-1,2,4-triazole (**9**, $C_{19}H_{18}Cl_3N_3$)

Compound **9** was prepared from 210 mg **2** (0.70 mmol), 0.104 cm^3 4-chlorobenzylamine (0.80 mmol), 0.120 cm^3 *TEA* (0.80 mmol), and 5 cm^3 aq. NaOCl (medium pressure flash chromatography: *n*-hexane/*Et*OA*c*, 100/0–30/1): yield 61 mg (22%) as a white solid; mp 92–95°C; $R_f = 0.40$ (*n*-hexane/*Et*OA*c*, 8/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.46$–7.45 (1H, m, 3′-H), 7.36–7.30 (2H, m, 6′-H, 5′-H), 7.32 (2H, d,

$J = 8.8$ Hz, 2″-H), 7.23 (2H, d, $J = 8.8$ Hz, 3″-H), 2.74 (2H, t, $J = 7.7$ Hz, $CH_2CH_2CH_2CH_2CH_3$), 1.77 (2H, p, $J = 7.7$ Hz, $CH_2CH_2CH_2CH_2CH_3$), 1.36–1.27 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 0.84 (3H, br, t, $J = 7.0$ Hz, $CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.4$ (3-C triazole), 154.6 (5-C triazole), 136.8, 136.6, 134.8, 132.9 (1′-C, 2′-C, 4′-C,4″-C), 130.7 (6′-C), 130.1 (3′-C), 129.2, 129.0 (2″-C.3″-C), 128.4 (5′-C), 126.0 (1″-C), 31.6 ($CH_2CH_2CH_2CH_2CH_3$), 28.4 ($CH_2CH_2CH_2CH_2CH_3$), 28.0 ($CH_2CH_2CH_2CH_2CH_3$), 22.4 ($CH_2CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 394 ($M^+ + 1$, 100).

1,5-Diphenyl-3-hexyl-1H-1,2,4-triazole (**10**, $C_{20}H_{23}Cl_3N_3$)
Compound **10** was prepared from 1.00 g **3** (4.2 mmol), 0.549 cm^3 benzylamine (5.0 mmol), 0.700 cm^3 *TEA* (5.0 mmol), and 10 cm^3 aq. NaOCl (flash chromatography: cyclohexane/*Et*$_2$O, 4.5/1); yield 602 mg (47%) as an orange oil; $R_f = 0.50$ (*n*-hexane/*Et*OAc, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.48$–7.29 (10H, m, H aromatics), 2.80 (2H, t, $J = 7.7$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.83 (2H, p, $J = 7.7$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.47–1.29 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_2$), 0.87 (3H, br, t, $J = 6.9$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 164.7 (3-C triazole), 154.0 (5-C triazole), 138.3 (1′-C), 129.8, 128.5 (4′-C, 4″-C), 129.3 (5′-C), 128.9, 128.5 (2″-C, 3″-C), 128.1 (1″-C), 125.3 (6′-C), 31.6 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 29.2 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.5 ($CH_2CH_2CH_2CH_2CH_2CH_2$), 22.6 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 306 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole (**11**, $C_{20}H_{20}Cl_3N_3$)
Compound **11** was prepared from 500 mg **4** (1.6 mmol), 0.237 cm^3 4-chlorobenzylamine (1.9 mmol), 0.272 cm^3 *TEA* (1.9 mmol), and 10 cm^3 aq. NaOCl (flash chromatography: cyclohexane/*Et*OAc, 9/1 and medium pressure flash chromatography: cyclohexane/*Et*$_2$O, 8/1); yield 223 mg (34%) as a white solid; mp 60–63°C; $R_f = 0.50$ (*n*-hexane/*Et*OAc, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.45$–7.22 (7H, m, H aromatics), 2.75 (2H, t, $J = 7.8$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.76 (H, p, $J = 7.5$ Hz 5, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.35–1.25 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.81 (3H, br, t, $J = 6.4$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 165.4 (3-C triazole), 154.5 (5-C triazole), 136.6, 136.4, 134.8, 132.9 (1′-C, 2′-C, 4′-C, 4″-C), 130.6 (6′-C), 130.1 (3′-C), 128.4 (5′-C), 129.2, 129.0 (2″-C, 3″-C), 126.0 (1″-C), 31.2 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.3 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 408 ($M^+ + 1$, 76).

1,5-Bis(2,4-dichlorophenyl)-3-hexyl-1H-1,2,4-triazole (**12**, $C_{20}H_{19}Cl_4N_3$)
Compound **12** was prepared from 1.94 g **4** (6.3 mmol), 1.02 cm^3 2,4-dichlorobenzylamine (7.6 mmol), 1.06 cm^3 *TEA* (7.6 mmol), and 15 cm^3 aq. NaOCl (flash chromatography: cyclohexane/*Me*OH, 95/5 and medium pressure flash chromatography: cyclohexane/*Et*$_2$O, 10/1): yield 876 mg (31%) as a yellow oil; $R_f = 0.50$ (*n*-hexane/*Et*OAc, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.21 (6H, m, H aromatics), 2.84 (2H, t, $J = 7.5$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.84 (2H, p, $J =$ 7.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.35–1.25 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.87 (3H, bt, $J = 5.7$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.5$ (3-C triazole), 152.6 (5-C triazole), 137.1, 136.3, 134.4, 133.7, 132.3 (1′-C, 2′-C, 4′-C, 1″-C, 2″-C, 4″-C), 132.4, 130.3, 129.9, 129.8, 127.8, 127.2 (6′-C, 5′-C, 3′-C, 6″-C, 5″-C, 3″-C), 126.1 (1″-C), 31.4 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.8 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.3 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 22.4 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 442 ($M^+ + 1$, 78).

1-(2,4-Dichlorophenyl)-5-(4-fluorophenyl)-3-hexyl-1H-1,2,4-triazole (**13**, $C_{20}H_{20}Cl_2FN_3$)
Compound **13** was prepared from 200 mg **4** (0.65 mmol), 0.089 cm^3 4-fluorobenzylamine (0.78 mmol), 0.109 cm^3 *TEA* (0.78 mmol) and 5 cm^3 aq. NaOCl (flash chromatography: cyclohexane/*Et*$_2$O, 7/1): yield 104 mg (41%) as a brown solid; mp 43–45°C; $R_f = 0.45$ (*n*-hexane/*Et*OAc, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.50$–7.49 (1H, m, 3′-H), 7.42 (2H, dd, $J = 8.7$, 5.3 Hz, 2″-H), 7.41–7.36 (2H, m, 6′-H, 5′-H), 6.98 (2H, t, $J = 8.7$ Hz, 3″-H), 2.79 (2H, t, $J = 7.9$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81 (2H, p, $J = 7.9$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.4–1.28 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.85 (3H, br, t, $J = 6.9$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 163.6$ (1C, d, JC-F 238, 4″-C), 164.3 (3-C triazole), 154.7 (5-C triazole), 136.5, 134.9, 132.9 (1′-C, 2′-C, 4′-C), 130.6 (6′-C), 130.1 (2″-C), 130.0 (3′-C), 128.3 (5′-C), 123.8 (1″-C), 115.9 (1C, d, $J_{C\text{-}F} = 22$ Hz, 3″-C), 31.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.4 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 22.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 392 ($M^+ + 1$, 100).

4-[1-(2,4-Dichlorophenyl)-3-hexyl-1H-1,2,4-triazole-5-yl]-pyridine (**14**, $C_{19}H_{20}Cl_2N_4$)
Compound **14** was prepared from 310 mg **4** (1.0 mmol), 123 mm^3 4-(aminomethyl)pyridine (1.2 mmol), 0.169 cm^3 *TEA* (1.2 mmol), and 7 cm^3 aq. NaOCl (flash chromatography: cyclohexane/*Et*$_2$O, 2/1–1/1): yield 98 mg (26%) as a brown solid: mp 87–90°C; $R_f = 0.30$ (*n*-hexane/*Et*OAc, 1/1); ^{1}H NMR ($CDCl_3$): $\delta = 8.57$ (2H, d, $J = 6.2$ Hz, 3″-H), 7.53 (1H, t, $J = 1.3$ Hz, 3′-H), 7.41–7.40 (2H, m, 6′-H, 5′-H), 7.32 (2H, d, $J = 6.2$ Hz, 2″-H), 2.81 (2H, t, $J = 7.5$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81 (2H, p, $J = 7.5$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$), 1.43–1.22 (6H, m, $CH_2CH_2CH_2CH_2CH_2CH_3$), 0.85 (3H, br, t, $J = 7.0$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.8$ (3-C triazole), 153.0 (5-C triazole), 150.4 (3″-C), 137.0 (1″-C), 134.7, 134.4, 132.8 (1′-C, 2′-C, 4′-C), 130.7 (6′-C), 129.9 (3′-C), 128.5 (5′-C), 121.5 (2″-C), 31.4 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.9 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.3 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 28.1 ($CH_2CH_2CH_2CH_2$-

CH_2CH_3), 22.5 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 14.0 (CH_2CH_2-$CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 375 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-heptyl-1H-1,2,4-triazole (**15**, $C_{21}H_{22}Cl_3N_3$)

Compound **15** was prepared from 250 mg **5** (0.78 mmol), 0.113 cm^3 4-chlorobenzylamine (0.93 mmol), 0.130 cm^3 *TEA* (0.93 mmol), and 10 cm^3 aq. NaOCl (flash chromatography: cyclohexane/CH_2Cl_2, 2.5/1–1/3 and medium pressure flash chromatography: cyclohexane/Et_2O, 8/1): yield 75 mg (23%) as a white solid: mp 56–58°C; $R_f = 0.50$ (*n*-hexane/*EtOAc*, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.49$ (1H, br, s, 3′-H), 7.38–7.34 (2H, m, 5′-H, 6′-H), 7.36 (2H, d, $J = 8.7$ Hz, 2″-H), 7.26 (2H, d, $J = 8.6$ Hz, 3″-H), 2.78 (2H, t, $J =$ 7.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.80 (2H, p, $J =$ 7.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.33–1.24 (8H, m, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 0.83 (3H, br, t, $J =$ 6.3 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.4$ (3-C triazole), 154.5 (5-C triazole), 136.6 136.4 134.8, 132.8 (1′-C, 2′-C, 4′-C, 4″-C), 130.6 (6′-C), 130.1 (3′-C), 129.2, 129.0 (2″-C, 3″-C), 128.4 (5′-C), 126.0 (1″-C), 31.7 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 29.3 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.4 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 422 ($M^+ + 1$, 99).

1-(2,4-Dichlorophenyl)-5-(4-fluorophenyl)-3-heptyl-1H-1,2,4-triazole (**16**, $C_{21}H_{22}Cl_2FN_3$)

Compound **16** was prepared from 200 mg **5** (0.62 mmol), 0.085 cm^3 4-fluorobenzylamine (0.75 mmol), 0.104 cm^3 *TEA* (0.75 mmol), 5 cm^3 aq. NaOCl (flash chromatography: cyclohexane/Et_2O, 7/1): yield 88 mg (35%) as a brown solid: mp 45–48°C; $R_f = 0.30$ (*n*-hexane/*EtOAc*, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.51$–7.49 (1H, m, 3′-H), 7.43 (2H, dd, $J = 8.5$, 5.3 Hz, 2″-H), 7.38–7.37 (2H, m, 5′-H, 6′-H), 6.99 (2H, t, $J = 8.5$ Hz, 3″-H), 2.79 (2H, t, $J =$ 7.6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.82 (2H, p, $J =$ 7.6 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.71–1.26 (8H, m, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 0.85 (3H, br, t, $J = 6.4$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 163.6$ (1-C, d, $J_{C\text{-}F} = 24$ Hz, 4″-C), 165.3 (3-C triazole), 154.7 (5-C triazole), 136.5, 134.9, 132.9 (1′-C, 2′-C, 4′-C), 130.6 (6′-C), 130.2 (2″-C), 130.0 (3′-C), 128.3 (5′-C), 123.8 (1″-C), 115.9 (1-C, d, $J_{C\text{-}F} = 22$ Hz, 3″-C), 31.7 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 29.3 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 29.0 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.4 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.2 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 14.1 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 406 ($M^+ + 1$, 100).

4-[1-(2,4-Dichlorophenyl)-3-heptyl-1H-1,2,4-triazole-5-yl]-pyridine (**17**, $C_{20}H_{22}Cl_2N_4$)

Compound **17** was prepared from 400 mg **5** (1.2 mmol), 0.152 cm^3 4-(aminomethyl)pyridine (1.5 mmol), 0.207 cm^3 *TEA* (1.5 mmol), 7 cm^3 aq. NaOCl (flash chromatography: cyclohexane/Et_2O, 2/1–1.7/1): yield 116 mg (24%) as a brown solid: mp 93–97°C; $R_f = 0.40$ (*n*-hexane/*EtOAc*, 1/1); ^{1}H NMR ($CDCl_3$): $\delta = 8.58$ (2H, d, $J = 6.1$ Hz, 3″-H), 7.53 (1H, t, $J = 1.3$ Hz, 3′-H), 7.41–7.40 (2H, m, 5′-H, 6′-H), 7.31 (2H, d, $J = 6.1$ Hz, 2″-H), 2.80 (2H, t, $J =$ 7.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.81 (2H, p, $J =$ 7.5 Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 1.27–1.20 (8H, m, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 0.84 (3H, br, t, $J = 6.4$ Hz, $CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.8$ (3-C triazole), 153.0 (5-C triazole), 150.4 (3″-C), 137.0 (1″-C), 134.8, 134.5, 132.8 (1′-C, 2′-C, 4′-C), 130.7 (6′-C), 129.9 (3′-C), 128.5 (5′-C), 121.5 (2″-C), 31.7 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 29.2 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 28.9 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.3 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 28.1 ($CH_2CH_2CH_2CH_2$-$CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_2CH_2CH_2CH_3$) ppm; ES-MS: m/z (%) = 389 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-cyclohexyl-1H-1,2,4-triazole (**18**, $C_{20}H_{18}Cl_3N_3$)

Compound **18** was prepared from 1.21 g **6** (4.0 mmol), 0.580 cm^3 4-chlorobenzylamine (4.8 mmol), 0.660 cm^3 *TEA* (4.8 mmol), 15 cm^3 aq. NaOCl (recrystallized from *Me*CN): yield 948 mg (59%) as a white solid: mp 118–120°C; ^{1}H NMR ($CDCl_3$): $\delta = 7.50$ (1H, br, s, 3′-H), 7.39–7.37 (4H, m, 5′-H, 6′-H, 2‴-H), 7.27 (2H, d, $J = 8.6$ Hz, 3‴-H), 2.83 (1H, tt, $J = 11.4$, 3.4 Hz, 1″-H cyclohexane), 2.14–2.09 (2H, m, 2″-H cyclohexane), 1.86–1.81 (2H, m, 3″-H cyclohexane), 1.73–1.67 (2H, m, 3′′-H cyclohexane), 1.49–1.23 (2H, m, 4″-H cyclohexane) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 169.1$ (3-C triazole), 154.3 (5-C triazole), 136.5, 136.3, 134.9, 132.9 (1′-C, 2′-C, 4′-C, 4‴-C), 130.6 (6′-C), 130.1 (3′-C), 129.2, 128.9 (2‴-C, 3‴-C), 128.3 (5′-C), 126.1 (1‴-C), 37.7 (1″-C), 31.8 (2″-C), 26.0 (4″-C), 25.9 (3″-C). ES-MS: m/z (%) = 406 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-[(2,6,6-trimethyl-1-cyclohexene)-1-methyl]-1H-1,2,4-triazole (**19**, $C_{24}H_{24}Cl_3N_3$)

Compound **19** was prepared from 215 mg **7** (0.6 mmol), 0.087 cm^3 4-chlorobenzylamine (0.7 mmol), 0.100 cm^3 *TEA* (0.7 mmol), 10 cm^3 aq. NaOCl (medium pressure flash chromatography: cyclohexane/Et_2O, 8/1): yield 94 mg (34%) as an orange oil; $R_f = 0.60$ (cyclohexane/*EtOAc*, 5/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.49$ (1H, t, $J = 1.3$ Hz, 3′-H), 7.37 (2H, d, $J = 8.9$ Hz, 2″-H), 7.36–7.35 (2H, m, 5′-H, 6′-H), 7.27 (2H, d, $J = 8.9$ Hz, 3″-H), 3.75 (2H, s, CH_2CCl), 2.00 (2H, t, $J = 6.1$ Hz, $CH_2C(CH_3)$=), 1.71 (3H, s, $CH_2C(CH_3)$=), 1.64–1.56 (2H, m, $CH_2CH_2C(CH_3)$=), 1.48–1.40 (2H, m, $CH_2CH_2C(CH_3)_2$), 1.03 (6H, s, $2 \times CH_3$) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 165.1$ (3-C triazole), 154.1 (5-C triazole), 136.4, 136.1, 135.0, 132.8 (1′-C, 2′-C, 4′-C, 4″-C), 133.1 (CH_2C=), 130.6 (6′-C), 130.3 (CH_3C=), 130.2 (3′-C), 129.2, 128.9 (2″-C, 3″-C), 128.3 (5′-C), 126.2 (1″-C), 39.6 ($CH_2C(CH_3)_2$), 35.0 ($C(CH_3)_2$), 32.8 ($CH_2C(CH_3)$=), 28.4 ($2 \times CH_3$), 27.7 (CH_2C=), 20.6 (CH_3), 19.4 (CH_2) ppm; ES-MS: m/z (%) = 460 ($M^+ + 1$, 95); HPLC: *Me*CN/H_2O, 50/50, τ_R % = 6.55 min (89%).

3-(Bicyclo[2.2.1]hept-5-enyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole (endo) (**21a**, $C_{21}H_{16}Cl_3N_3$) and *3-(bicyclo [2.2.1]hept-5-enyl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole (exo)* (**21b**, $C_{21}H_{16}Cl_3N_3$)

Compound **21a** and **21b** were prepared from 1.05 g **20** (3.3 mmol), 0.490 cm^3 4-chlorobenzylamine (4.0 mmol), 0.560 cm^3 *TEA* (4.0 mmol), 10 cm^3 aq. NaOCl (medium pressure flash chromatography: cyclohexane/Et_2O, 8/1): yield 523 mg (38%) **21a** as a white solid and 111 mg (8%) **21b** as a white solid.

21a: mp 103–104°C; $R_f = 0.70$ (cyclohexane/*Et*OAc, 4/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.49$ (1H, t, $J = 1.3$ Hz, 3′-H), 7.36–7.35 (2H, m, 5′-H, 6′-H), 7.35 (2 H, d, $J = 8.8$ Hz, 2‴-H), 7.27 (2H, d, $J = 8.8$ Hz, 3‴-H), 6.20 (1H, dd, $J = 5.6$, 3.0 Hz, 2″-H norbornene), 5.85 (1H, dd, $J = 5.6$, 2.8 Hz, 3″-H norbornene), 3.50 (1H, dt, $J = 9.1$, 4.0 Hz, 5″ec-H norbornene), 3.42 (1H, br, s, 4″-H norbornene), 2.95 (1H, br, s, 1″-H norbornene), 2.21–2.15 (1H, m, 6″ec-H norbornene), 1.67–1.63 (1H, m, 6″ax-H norbornene), 1.53–1.50 (1H, m, 7″-H norbornene), 1.45–1.45 (1H, m, 7″-H norbornene) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 167.5$ (3-C triazole), 154.2 (5-C triazole), 137.2 (2″-C), 136.4, 136.2, 134.8, 132.9 (1′-C, 2′-C, 4′-C, 4‴-C), 132.9 (3″-C), 130.6 (6′-C), 130.1 (3′-C), 129.2, 128.9 (2‴-C, 3‴-C), 128.3 (5′-C), 126.1 (1‴-C), 49.5 (7″-C), 46.9 (4″-C), 42.7 (1″-C), 37.6 (5″-C), 30.7 (6″-C) ppm; ES-MS: m/z (%) = 416 ($M^+ + 1$, 95).

21b: mp 137–139°C; $R_f = 0.75$ (cyclohexane/*Et*OAc, 4/1); ^{1}H NMR ($CDCl_3$): $\delta = 7.45$ (1H, br, s, 3′-H), 7.35–7.31 (4H, m, 5′-H, 6′-H, 2‴-H), 7.22 (2H, d, $J = 8.6$ Hz, 3‴-H), 6.14 (2H, br, s, 2″-H, 3″-H norbornene), 3.08 (1H, br, s, 4″-H norbornene), 2.92 (1H, br, s, 1″-H norbornene), 2.78 (1H, dd, $J = 8.5$, 3.9 Hz, 5″ax-H norbornene), 2.21–2.11 (1H, m, 6″ec-H norbornene), 1.67 (1H, d, $J = 8.3$ Hz, 7″-H norbornene), 1.58–1.46 (1H, m, 6″ax-H norbornene), 1.35 (1H, d, $J = 8.3$ Hz, 7″-H norbornene) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 168.5$ (3-C triazole), 154.4 (5-C triazole), 137.7 (2″-C), 136.5, 136.3, 134.8, 132.8 (1′-C, 2′-C, 4′-C, 4‴-C), 136.2 (3″-C), 130.6 (6′-C), 130.1 (3′-C), 129.2, 128.9 (2‴-C, 3‴-C), 128.3 (5′-C), 126.0 (1‴-C), 48.3 (7″-C), 46.0 (4″-C), 42.0 (1″-C), 37.8 (5″-C), 31.4 (6″-C). ES-MS: m/z (%) = 416 ($M^+ + 1$, 100).

*General procedure for preparing N′-acyl-N,N-dimethylamidines **22** and **23***

A suspension of the corresponding benzamide in 4 cm^3 *N,N*-dimethylformamide dimethyl acetal was stirred at reflux for 2 h. Then, the mixture was cooled, upon which a white solid precipitated. The solid was collected by filtration, dried under reduced pressure and recrystallized from *n*-hexane.

4-Chloro-N-[(dimethylamino)methylene]benzamide
(**22**, $C_{10}H_{11}ClN_2O$)

Compound **22** was prepared from 1.00 g 4-chlorobenzamide (6.4 mmol): yield 1.11 g (82%) as a white solid: mp 103–104°C; ^{1}H NMR ($CDCl_3$): $\delta = 8.59$ (1H, s, CH=N), 8.17 (2H, d, $J = 8.7$ Hz, 2-H), 7.34 (2H, d, $J = 8.7$ Hz, 3-H), 3.16 (3H, s, CH_3), 3.14 (3H, s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 176.6$ (CO), 160.8 (CH=N), 137.9 (4-C); 135.3 (1-C), 131.1, 128.1 (2-C, 3-C), 41.3 (CH_3), 35.2 (CH_3) ppm; ES-MS: m/z (%) = 211 ($M^+ + 1$, 100).

2,4-Dichloro-N-[(dimethylamino)methylene]benzamide
(**23**, $C_{10}H_{10}Cl_2N_2O_2$)

Compound **23** was prepared from 1.00 g 2,4-dichlorobenzamide (5.3 mmol): yield 1.24 g (96%) as a white solid: mp 71–72°C; ^{1}H NMR ($CDCl_3$): $\delta = 8.55$ (1H, s, CH=N), 7.87 (1H, d, $J = 8.4$ Hz, 6-H), 7.38 (1H, d, $J = 2.1$ Hz, 3-H), 7.22 (1H, dd, $J = 8.4$, 2.1 Hz, 5-H), 3.16 (3H, s, CH_3), 3.13 (3H, s, CH_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 176.8$ (CO), 160.7 (CH=N), 135.4 (2-C), 133.8 (1-C), 132.3 (6-C), 130.3 (3-C), 126.5 (5-C), 41.5 (CH_3), 35.4 (CH_3) ppm; ES-MS: m/z (%) = 245 ($M^+ + 1$, 100).

5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole
(**24**, $C_{14}H_8Cl_3N_3$)

To a solution of 914 mg 2,4-dichlorophenylhydrazine hydrochloride (4.3 mmol) in 1 cm^3 5*N* NaOH and 4 cm^3 1,4-dioxane were added 8 cm^3 70% aq. *Ac*OH and 750 mg **22** (3.6 mmol). The mixture was stirred at reflux for 1 h and then 15 cm^3 H_2O were added precipitating an orange solid. The solid was collected by filtration, washed with H_2O, dried under reduced pressure, and recrystallized from *Et*OH, affording 618 mg **24** as an orange solid (53%): mp 135–136°C; ^{1}H NMR ($CDCl_3$): $\delta = 8.11$ (1H, s, 3-H triazole), 7.53 (1H, t, $J = 1.3$ Hz, 3′-H), 7.39 (2H, d, $J = 8.9$ Hz, 2″-H), 7.39–7.38 (2H, m, 5′-H, 6′-H), 7.29 (2H, d, $J = 8.9$ Hz, 3″-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 154.4$ (5-C triazole), 152.2 (3-C triazole), 136.9, 136.7, 134.6, 132.8 (1′-C, 2′-C, 4′-C, 4″-C), 130.8 (6′-C), 130.0 (5′-C), 129.2, 129.1 (2″-C, 3″-C), 128.5 (3′-C), 125.7 (1″-C) ppm; ES-MS: m/z (%) = 324 ($M^+ + 1$, 100).

1,5-Bis(2,4-dichlorophenyl)-1H-1,2,4-triazole
(**25**, $C_{14}H_7Cl_4N_3$)

To a solution of 210 mg 2,4-dichlorophenylhydrazine hydrochloride (1.0 mmol) in 0.2 cm^3 5*N* NaOH and 2 cm^3 1,4-dioxane were added 2 cm^3 70% aq. *Ac*OH and 200 mg **23** (0.8 mmol). The mixture was stirred at reflux for 5 h, and then 20 cm^3 H_2O were added, precipitating an orange solid. The solid was collected by filtration, washed with H_2O, dried, and purified by medium pressure chromatography (cyclohexane/*Et*OAc, 6/1) to give 8 mg **25** (3%) as a white solid: mp 107–111°C; $R_f = 0.50$ (cyclohexane/*Et*OAc, 6/1); ^{1}H NMR ($CDCl_3$): $\delta = 8.21$ (1H, s, 3-H triazole), 7.27–7.46 (6H, m, H aromatics). ^{13}C NMR ($CDCl_3$): $\delta = 152.7$ (5-C triazole), 152.4 (3-C triazole), 137.4, 136.7, 134.6 (1′-C, 2′-C, 4′-C), 133.6, 132.3 (2″-C, 4″-C), 132.4, 130.5, 130.1, 129.8, 128.0, 127.3 (6′-C, 5′-C, 3′-C, 5″-C, 6″-C, 3″-C) ppm; ES-MS: m/z (%) = 360 ($M^+ + 1$, 100); HPLC: *Me*CN/H_2O, 90/10, τ_R = 19.06 min (93%).

Binding assays

Membranes from HEK-293 EBNA cells with human CB_1 or CB_2 cannabinoid receptor expressed were supplied by Perkin Elmer. The receptor concentration was 3.5 pmol/mg proteins and the protein concentration was 6.4 mg/cm^3. The binding assays were performed as described by *Ross* [15] with modifications. The commercial membrane was diluted (1:60) with the binding buffer (50 mM *Tris*Cl, 5 m*M* $MgCl_2$, 2.5 m*M* *EDTA*, 0.5 mg/cm^3 BSA, *pH* = 7.4). The radioligand used

was [^{3}H]-CP55940 (PerkinElmer) at 0.135 n*M* and the final volume was 200 mm^3. The incubation was initiated with the addition of 160 mm^3 membrane and the incubation time was 90 min at 30°C. After incubation, the membrane was collected onto pre-treated glass fiber filters (Schleicher & Schnell 3362), with polyethylenimine 0.5%. The filter was washed four times with 1 cm^3 washing buffer (50 m*M Tris*Cl, $pH = 7.4$) and then filter sections were transferred to vials and 5 cm^3 Ecoscint H liquid scintillation cocktail were added to each vial. Vials were allowed to set for several hours and then quantified by liquid scintillation spectrophotometry (Wallac Winspectral 1414). Non-specific binding was determined with 10 μM WIN55212-2. Competition binding data were analyzed by using the LIGAND program [16] and assays were performed in triplicate determinations for each point.

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