N-Substituted-1,2,3-triazoles: synthesis, characterization and evaluation as cannabinoid ligands

Cristina G. Oliva,[a] Nadine Jagerovic,[a,*] Pilar Goya,[a] Ibon Alkorta,[a] José Elguero,[a] Rosa Cuberes,[b] and Alberto Dordal[b]

[a] *Instituto de Química Médica, CSIC, Juan de la Cierva 3, E-28006 Madrid, Spain*
[b] *Laboratorios del Dr. Esteve S. A., Av. Mare de Déu de Montserrat, 221, E-08041 Barcelona, Spain*
E-mail: nadine@iqm.csic.es

This paper is dedicated to Professor Benito Alcaide on the occasion of his 60th anniversary

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.210

Abstract

A series of new N1-, N2- and N3-substituted 1,2,3-triazole derivatives has been synthesized by cycloaddition of butyltin azide with substituted alkynes followed by a *N*-alkylation reaction. The regioisomers have been isolated and characterized using NMR techniques. GIAO/B3LYP calculations of the absolute shieldings have been performed to verify the assignments and so the structures have been unequivocally identified. The proportion in which the three isomers are obtained corresponds with the relative order of stability indicated by the energy values calculated at the B3LYP level. CB1 cannabinoid receptor binding assays have been performed but none of the compounds showed significant activity.

Keywords: 1,2,3-Triazole, *N*-alkylation, cannabinoids

Introduction

The 1,2,3-triazole ring system has been the subject of considerable research mainly due to its usefulness in synthetic organic chemistry and also because of the pharmacological properties shown by some of its derivatives. In this context, we decided to explore the 1,2,3-triazole ring system as a new scaffold for cannabinoid ligands.[1] Cannabinoids are compounds belonging to different structural families that elicit diverse biological responses by interacting with the cannabinoid receptors, of which two have been identified so far, CB1 and CB2. These receptors are involved in many biochemical processes and are thus interesting therapeutic targets.[2-4] In particular, the CB1 receptor is involved in many different food-intake related disorders such as bulimia or obesity.[5,6] Unfortunately, rimonabant (Figure 1), the first potent and selective CB1

antagonist to reach the pharmaceutical market as antiobesity agent, has been recently withdrawn due to possible depressive effects.[7] Our group reported a series of cannabinoid 1,2,4-triazoles resulting in the identification of LH-21 (Figure 1) [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-3-hexyl-1*H*-1,2,4-triazole].[8] LH-21 displays selective and neutral CB1 receptor antagonism properties with lower penetration in the brain than rimonabant.[9,10]

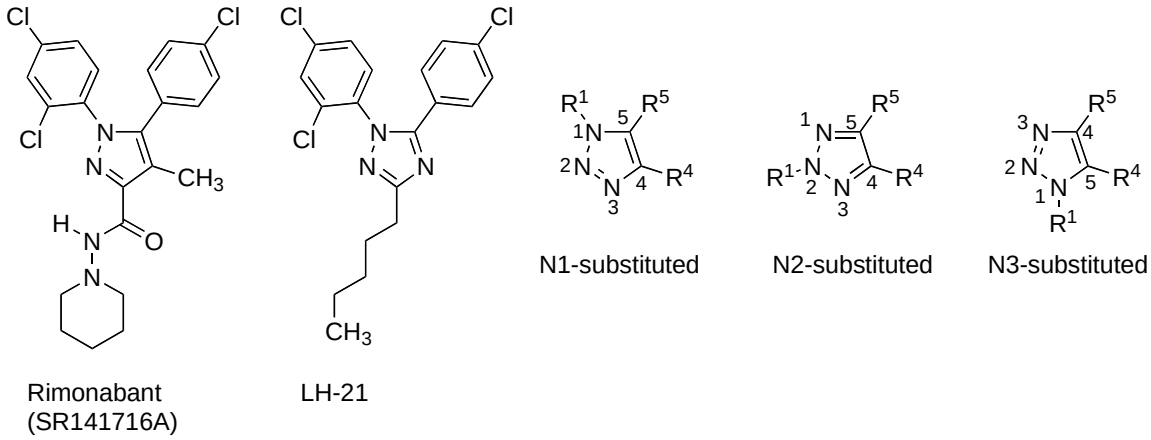


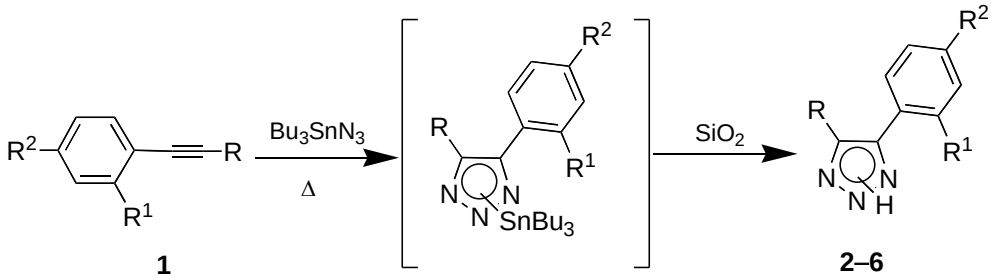
Figure 1. Structures of rimonabant and LH-21 together with the numbering of the isomers of *N*-substituted-1,2,3-triazoles.

On the basis of these findings, we have synthesized a series of 1,2,3-triazoles as LH-21 analogues. In the course of our research three reports dealing with cannabinoid 1,2,3-triazoles have appeared very recently. In one of them the 1,2,3-triazole group is reported as peptidomimetic element of mixed CB1/TRPV1 antagonists.[11] The two other reports focused on 4-alkoxycarbonyl-1,5-diaryl-1,2,3-triazoles[12] and 2-(phenoxy-carbonyl)methyl-1,2,3-triazoles[13] as CB1 cannabinoid antagonists. The results reported here deal with the preparation of 2-alkyl-1,2,3-triazoles as LH-21 analogues.

Concerning synthetic issues[14] the most classical approach to the synthesis of 1,2,3-triazoles involves thermal 1,3-dipolar cycloaddition of azides with alkynes, as initially proposed by Huisgen.[15] This reaction suffered from a lack of selectivity yielding a mixture of N1/N3- and N2-substituted 1,2,3-triazoles when azides react with unsymmetrical disubstituted alkynes.[16] The discovery of copper (I)[17] and ruthenium (II)[18] catalyzed cycloadditions opened the field of highly efficient "click chemistry" between azides and alkynes. However, using these conditions only N1/N3-substituted 1,2,3-triazole isomers can be prepared. Few methods are available for the selective preparation of N2-substituted-1,2,3-triazoles and they are limited to N2-hydroxymethyl-,[19] N2-allyl-,[21,21] or N2-aryl-1,2,3-triazoles.[22,23] We finally prepared and isolated the regioisomer N2-alkyl-1,2,3-triazoles by alkylation of N*H*-1,2,3-triazoles. N2-[*N*-(piperidin-1-yl)acetamide]-1,2,3-triazole derivatives are also reported here by comparison to rimonabant. The structural assignment of the different regioisomers was fully illustrated using NMR techniques.

Results and Discussion

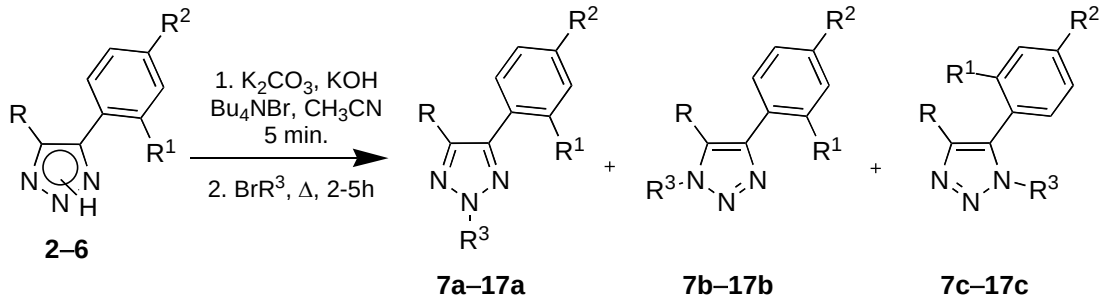
The synthesis of N*H*-1,2,3-triazoles **2-6** was achieved in acceptable yield (30-67%) by cycloaddition of tri-*n*-butyltin azide with mono- or disubstituted alkynes **1** under pressure and heating conditions (Scheme 1).[24] This procedure was convenient regarding the safety issues using tri-*n*-butyltin azide compared to the highly explosive hydrazoic acid. The tributylstannyl group could be subsequently replaced by a proton under mild conditions. The starting alkynes **1a-1d** were obtained from commercial sources and **1e** was prepared[25] in excellent yield from the corresponding 1-ethylnyl-4-methyl benzene.



1a	R = H, R^1 = H, R^2 = CH_3	**2** (40%)
1b	R = H, R^1 = H, R^2 = OCH_3	**3** (30%)
1c	R = H, R^1 = F, R^2 = Br	**4** (66%)
1d	R = Ph, R^1 = H, R^2 = Cl	**5** (54%)
1e	R = *p*-tolyl, R^1 = Cl, R^2 = Cl	**6** (67%)

Scheme 1. Synthesis of N*H*-1,2,3-triazoles **2-6.**

Triazoles **2-6** were then alkylated with the corresponding alkylbromide under basic conditions using the phase transfer catalyst Bu_4NBr[26] to afford the desired *N*-substituted-1,2,3-triazoles **7-17** (Scheme 2). *N*-Alkylation of unsymmetrical 4,5-disubstituted-1,2,3-triazoles produces a mixture of three possible regioisomers: **a** N2-, **b** N-1 and **c** N-3. Under the alkylation conditions used here two or three regioisomers have been isolated depending on the nature of the triazole substituents.



Scheme 2. Alkylation of 1,2,3-triazoles **2-6**.

The ratio of the regioisomers of **7**-**17**, determined by ^{1}H NMR is reported in Table 1. Each regioisomer has been isolated and fully identified by ^{1}H, ^{13}C, 2D-HSQC and HMBC NMR data. The only 1,2,3-triazoles that have been characterized as a mixture of two isomers are **11b**/**11c** and **17b**/**17c**.

Along the series **7**-**17**, the regioisomer N2-substituted 1,2,3-triazole, **a**, was formed as the major product. The only exception came from the alkylation of 4-(4-bromo-2-fluorophenyl)-1,2,3-triazole **4** with benzyl bromide that provided isomers **15a** and **15b** in a 45/55 ratio. It is interesting to note that the regioisomer N-3-substituted 1,2,3-triazole **7c**-**17c** was formed in small proportion or was not detected. This fact probably is a consequence of steric factors such as suggested by the results obtained for **8**, **9**, **15** and **16**. However, these factors are not valid for a higher proportion of isomer **c** over **a** in the alkylation of **7**-**14** and **17**. This difference could be explained by a mesomeric effect of the benzene substituents.

Table 1. Synthesis of N-alkyl, benzyl, and ethoxycarbonyl-1,2,3-triazoles **7**-**17**

R	R^1	R^2	R^3	t (h)	**a** (%)[a]	**b** (%)[a]	**c** (%)[a]	**a/b/c**[b]
H	H	CH_3	*n*-pentyl	5	**7a** (62)	**7b** (28)	**7c** (5)	65/29/6
H	H	OCH_3	*n*-pentyl	5	**8a** (45)	**8b** (25)		64/34/0
H	F	Br	*n*-pentyl	5	**9a** (69)	**9b** (29)		70/30/0
Ph	H	Cl	*n*-pentyl	5	**10a** (50)	**10b** (31)	**10c** (9)	55/35/10
p-tolyl	Cl	Cl	*n*-pentyl	5	**11a** (73)	**11b**[c]	**11c**[c]	80/9/11
Ph	H	Cl	*n*-heptyl	5	**12a** (64)	**12b** (18)	**12c** (9)	70/20/10
Ph	H	Cl	*p*-Br-benzyl	2	**13a** (62)	**13b** (14)	**13c** (19)	65/15/20
Ph	H	Cl	benzyl	2	**14a** (64)	**14b** (24)	**14c** (9)	65/25/10
H	F	Br	benzyl	2	**15a** (44)	**15b** (54)		45/55/0
H	F	Br	CH_2CO_2Et	5	**16a** (55)	**16b** (18)		75/25/0
Ph	H	Cl	CH_2CO_2Et	5	**17a** (60)	**17b**[c]	**17c**[c]	75/15/10

[a] Isolated yield after chromatography. [b] determined by ^{1}H NMR of the reaction mixture. [c] not isolated.

We have calculated at the B3LYP/6-311++G(d,p) level (see Computational details) the energies of the three isomers **10a** (–1360.77472 hartrees, E_{rel} = 0.0 kJ mol^{-1}), **10b** (E_{rel} = 23.9 kJ mol^{-1}) and **10c** (E_{rel} = 27.0 kJ mol^{-1}). The order of stability is the same that the proportion of isomers reported in Table 1 (50%, 31%, 9%).

In order to illustrate the structural assignment of these regioisomers, 2D NMR studies of compound **10** are described here. 2D ^{1}H-^{13}C HMBC NMR analysis performed on the major regioisomer indicated the lack of correlations between the H-1' signal of the pentyl chain (δ = 4.36 ppm, t, $^{3}J_{1',2'}$ = 7.0 Hz, 2 H) and the C-5 and C-4 signals of the 1,2,3-triazole ring (δ = 144.2 and 142.9 ppm) allowing the identification of **10a** (Figure 2). On the spectra of the two other

isolated regioisomers, **10b** and **10c**, these correlations were observed between the H-1' signal (δ = 4.17 ppm, t, $^{3}J_{1',2'}$ = 7.3 Hz, 2 H) and C-5 signal (δ = 133.7 ppm) for one of them and the H-1' signal (δ = 4.18 ppm, t, $^{3}J_{1',2'}$ = 7.4 Hz, 2 H) and the C-5 signal (δ = 132.4 ppm) for the other one (Figure 3) but they did not allow the identification of **10b** and **10c**. Furthermore, support for localization of the pentyl chain was provided on one hand by correlations between C-4 (δ = 143.1 ppm) and C_{para} (δ = 133.3 ppm) signals with the H_{ortho} signal (δ = 7.44 ppm, dt, $^{3}J_{o,m}$ = 8.6 Hz, $^{4}J_{m,m}$ = $^{5}J_{o,m}$ = 2.2 Hz, 2 H) in the case of the regioisomer **10b** (Figure 3). On the other hand, correlations between C-5 (δ = 132.4 ppm) and $C_{para'}$ (δ = 135.9 ppm) signals with $H_{ortho'}$ signal (δ = 7.29-7.24 ppm, m, 5 H) were consistent with the regioisomer **10c** (experimental data on Scheme 3).

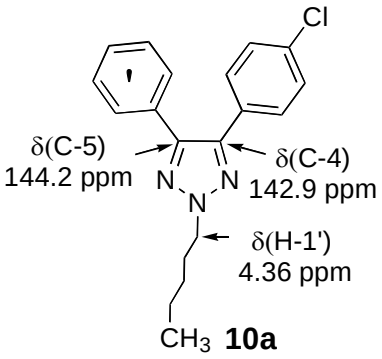


Figure 2. Lack of correlation between H-1' and C-5 and C-4 signals of **10a** from HMBC spectrum.

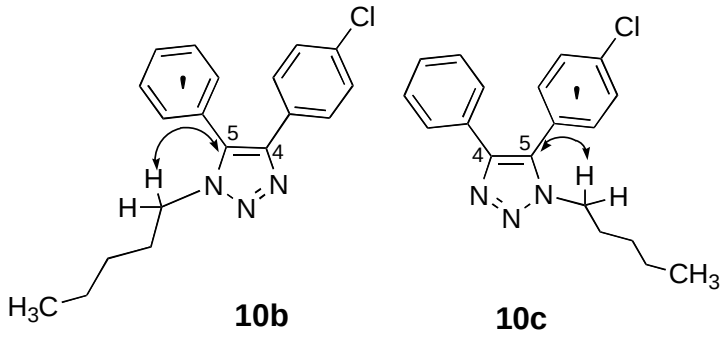
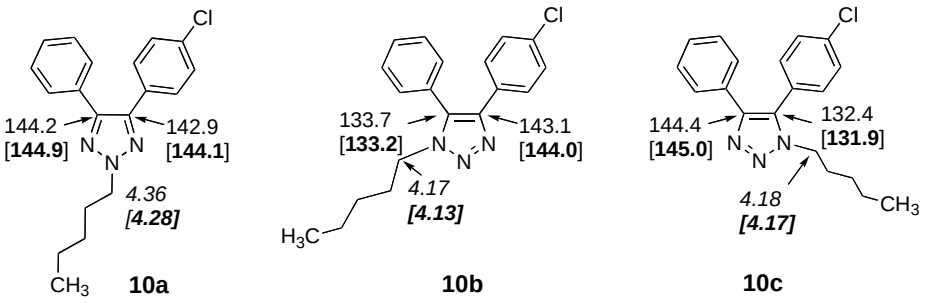


Figure 3. Correlation between H-1' and C-5 signals of **10b** and **10c** (HMBC NMR spectrum).

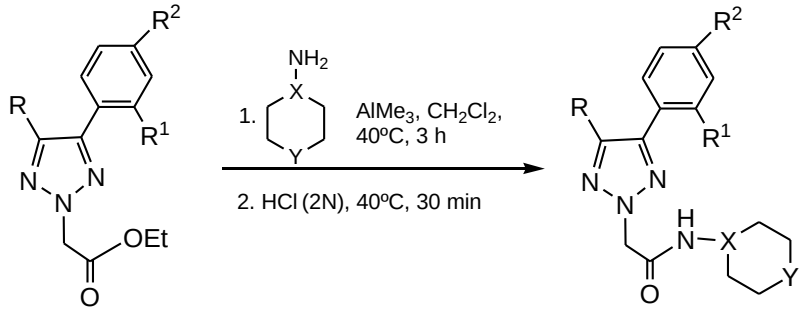
We have carried out GIAO/ B3LYP/6-311++G(d,p) calculations of absolute shieldings on the three isomers to verify the assignments (see Computational details). First we have examined the ^{13}C chemical shifts. As we have shown in previous works, the carbon atoms bearing chlorine substituents are underestimated.[27] Thus to compare the experimental chemical shifts (δ, ppm) with the calculated absolute shieldings (σ, ppm) these three atoms were described with a dummy

variable. The resulting equation is: $\delta^{13}C = (176.4\pm0.4) - (0.987\pm0.004)\ \sigma^{13}C - (8.5\pm0.9)$ CCl, n = 57, $R^2 = 0.999$. This equation, similar to those we have published,[28] corresponds to the fitted values (in bold) for the carbon atoms of the triazole ring (the most sensitive to positional isomerism):



Scheme 3. Experimental and calculated (in bold) chemical shifts. ^{1}H data in italic.

Then, we have examined the ^{1}H NMR chemical shifts. In this case we have averaged the calculated values of isochronous protons by rotation (H_{ortho}, H_{para}, CH_2 and CH_3). Using the assigned signals, we found $\delta^1H = (31.0\pm0.4) - (0.970\pm0.013)\ \sigma^1H$, n = 27, $R^2 = 0.995$, identical to that we have observed for other compounds.[29] The fitted values of the first methylene group (1') are given in Scheme 3.



16a	R = Ph, R^1 = H, R^2 = Cl, X = N, Y = CH_2	**18** (38%)
17a	R = H, R^1 = F, R^2 = Br, X = N, Y = CH_2	**19** (44%)
16a	R = Ph, R^1 = H, R^2 = Cl, X = N, Y = O	**20** (70%)
17a	R = H, R^1 = F, R^2 = Br, X = N, Y = O	**21** (64%)
16a	R = Ph, R^1 = H, R^2 = Cl, X = CH, Y = CH_2	**22** (56%)
17a	R = H, R^1 = F, R^2 = Br, X = CH, Y = CH_2	**23** (42%)

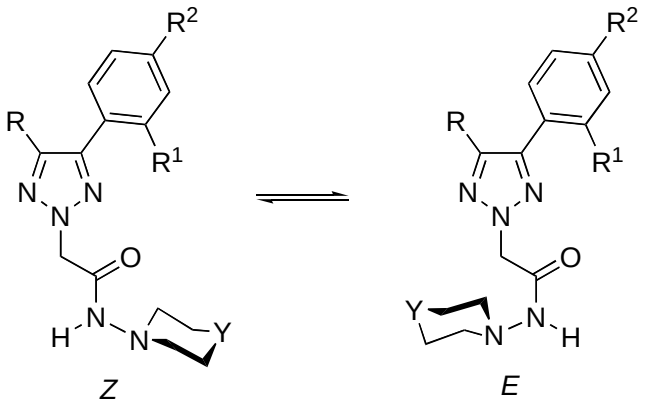
Scheme 5. 2-Acetamide-1,2,3-triazoles **18**-**23**.

Carboxamides of related diaryl pyrazoles, such as rimonabant, are of particular interest in the field of cannabinoid ligands. Therefore we decided to synthesize 2-acetamide-1,2,3-triazoles **18**-

23. These were prepared starting from 2-ethoxycarbonylmethyl-1,2,3-triazoles **16a** and **17a** as described in Scheme 4. The esters **16a** and **17a** were treated with dimethylaluminum amides prepared from trimethylaluminum and the corresponding amine following a procedure previously used by us for conversion of ethyl esters to carboxylic acid hydrazides under mild conditions.

^{1}H and ^{13}C NMR data of **18**-**21** (Table 2) suggested the existence of two conformers. The fact that the amide N–C bonds have a partial double-bond character causes a substantial rotational barrier that enables the *cis*(*E*)-*trans*(*Z*) interconversion resulting in magnetic non-equivalence between protons of the two rotamers.[31] This *E*-*Z* isomerism often plays an important role in receptor affinity due to possible hydrogen bonding patterns. Amides in solution show a preference for the *Z*-isomer that may be explained by possible steric interactions.

Table 2. ^{1}H NMR and ^{13}C NMR data and ratio of amide rotamers **18**-**21**



Cpds	M/m[a]	^{1}H NMR δ (ppm)		^{13}C NMR δ (ppm)			
		NH	*CH*$_2$CO	CO	*CH*$_2$CO	N-*CH*$_2$CH$_2$	N-CH$_2$-*CH*$_2$
18	80/20	9.35 (m) 9.03 (M)	5.46 (M) 5.08 (m)	168.1 (M) 162.8 (m)	56.7 (m) 56.2 (M)	57.3 (M) 56.3 (m)	26.0 (M) 25.8 (m)
19	80/20	6.71 (m) 6.35 (M)	5.45 (M) 5.15 (m)	167.9 (M) 162.9 (m)	57.2 (m) 55.6 (M)	58.1 (M) 56.8 (m)	25.6 (M) 25.1 (m)
20	70/30	9.54 (m) 9.15 (M)	5.55 (M) 5.13 (m)	167.6 (M) 162.5 (m)	55.8 (m) 55.5 (M)	55.7 (M) 54.7 (m)	65.9 (M) 65.8 (m)

Table 2. Continued

Cpds	M/m[a]	^{1}H NMR δ (ppm)		^{13}C NMR δ (ppm)			
		NH	*CH*$_2$CO	CO	*CH*$_2$CO	N-*CH*$_2$CH$_2$	N-CH$_2$-*CH*$_2$
21	70/30	9.45 (m) 9.10 (M)	5.53 (M) 5.10 (m)	167.5 (M) 162.4 (m)	55.9 (m) 55.6 (M)	55.7 (M) 54.7 (m)	65.9 (M) 65.8 (m)

M = major conformer; m = minor conformer; [a] The ratio of the conformers has been determined by ^{1}H NMR.

The ^{1}H NMR spectra of **18**-**21** showed two signals for N*H* and two signals for CH$_2$CO. The rotamers ratios reported in Table 2 have been determined according to ^{1}H NMR signal integration. The ^{13}C NMR data of **18**-**21** were in agreement with the presence of these two rotamers with two signals for each of the following carbons: CO, CH$_2$ and piperidine- and morpholine-C-2' and C-3'. In the case of the cyclohexyl derivatives **22** and **23**, no chemical shift differences have been shown in ^{1}H or in ^{13}C NMR spectra.

These ratios correspond, respectively, to 3.4 (Y = CH$_2$) and 2.1 kJ mol^{-1} (Y = O). To assign the *E*/*Z* isomers to the M/m ones, we have carried out calculations at the B3LYP/6-311++G(d,p) level of the energies and these minimized geometries of absolute shieldings [GIAO/ B3LYP/6-311++G(d,p)]. In all cases, the *Z* isomers are more stable that the E ones by about 14 kJ mol^{-1} for X = CH$_2$ (**18**, **19**) and 12 kJ mol^{-1} for X = O (**20**, **21**), overestimated by rapport to the experimental values in solution but in the same order. Thus, it appears that *Z* = *M* and *E* = *m*.

Respect to the cyclohexyl conformation of the derivative **22**, it has been determined that the amide group occupies an equatorial position. It was confirmed by the detection of large coupling constant ^3J between the axial H-1' (δ = 3.82 ppm) and the neighboring axial H-2' (δ = 1.63 ppm) in the ^{1}H NMR spectrum ($^3J_{1ax',2ax'}$ = 10.2 Hz). This is also the minimum energy conformation.

The comparison of experimental chemical shifts (δ, ppm) with calculated absolute shieldings (σ, ppm) was performed to confirm the assignment of position and rotation isomers. The only atom that is sensitive and reliable is the ^{13}C of the C=O group. This carbon is sensitive because for this signal a large difference ($\Delta\sigma \approx 5$ ppm) between the *E* and *Z* isomers is observed and it is reliable because the other protons of Table 2 included those of the NH depend on the concentration and cannot be used. We have transformed the σ^{13}C into δ^{13}C using the equation $\delta^{13}C = 175.7 - 0.963\ \sigma^{13}C$.[28] With the *Z* = *M* and *E* = *m* assignment, we found δ^{13}Cexp. = (1.020±0.001)* δ^{13}Ccalcd., n = 8, R^2 = 0.971 (the opposite assignment yields and absurd relationship with an intercept of 330 ppm!). Therefore, the assignment based on the energies has been confirmed by the chemical shifts.

Biological activity

To explore the biological activity of the 1,2,3-triazoles presented here, competitive binding assays have been performed in membranes from HEK-293 EBNA cells expressed with human CB_1 cannabinoid receptor. Therefore, the ability of **7a-11a**, **13a-17a**, **7b-10b**, **14b**, **15b**, **10c**, **18-22** to bind this receptor has been evaluated by measuring the displacement of the radioligand [^{3}H]-CP55940 from CB_1 receptor. None of the evaluated compounds showed significant affinity for CB_1 cannabinoid receptor. They displaced [^{3}H]-CP55940 in less than 45% indicating a low affinity.

Conclusions

New di- and trisubstituted derivatives of 1,2,3-triazoles have been synthesized and evaluated as cannabinoid ligands. Although the 1,2,3-triazole ring has recently proved to be an interesting cannabinoid scaffold,[12,13] none of the 1,2,3-triazoles evaluated here showed significant affinity for the CB_1 cannabinoid receptor. Nevertheless, some interesting results concerning synthesis and reactivity of this ring system have been found. The diversity of chemical structures of the 1,2,3-triazole family and their useful biological activities make these compounds attractive targets in synthetic organic and medicinal chemistry.

Experimental Section

General. All starting materials were commercially available research grade chemicals and used without further purification. Dichloromethane was distilled over $CaCl_2$. Silical gel 60 F_{254} (Merck) was used for TLC, and the spots were detected with UV light (254 nm). Flash column chromatography was carried out on silica gel 60 (Merck). Melting points were determined on a Reichert Jung Thermovar apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini [200 MHz (^{1}H), 50 MHz (^{13}C)] spectrometer, Varian Inova 300 or 400 [(300 MHz (^{1}H), 75 MHz (^{13}C) or 400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer and Varian Unity 500 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer with TMS as internal reference. Multiplicity were denoted by s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), quin (quintet), dd (double doublet) and m (multiplet). Mass spectra were determined on a MSD-Serie 1100 Hewlett Packard apparatus. Elemental analyses were performed with a Heraeus CHN-O Rapid analyser. Analyses indicated by the symbols of the elements or functions were within ± 0.4 % of the theoretical values.

2,4-Dichloro-1-(4-methylphenyl)ethynylbenzene (1e). To a mixture of palladium diacetate (42.6 mg, 0.19 mmol), triphenylphosphine (99.7 mg, 0.38 mmol), CH_3CN (8.6 mL) and H_2O (0.9 mL) in a Schlenk tube was added under nitrogen a well-stirred mixture of 1-ethynyl-4-

methylbenzene (0.24 mL, 1.9 mmol), 1,4-dichloro-2-iodobenzene (0.51 mL, 3.8 mmol), triethylamine (0.66 mL, 4.7 mmol), tetrabutylammonium hydrogen sulfate (645.1 mg, 1.9 mmol), CH_3CN (8.6 mL) and H_2O (0.9 mL). The reaction was stirred at room temperature for 3 h. The mixture was then hydrolyzed by H_2O (15 mL) and extracted with Et_2O (3 X 15 mL). The combined organic extracts were dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a solid, which was purified by column chromatography (cyclohexane) and recrystallized from cyclohexane to give the alkyne **1e**. White solid (491.2 mg, 99%); m.p. 69–71 ºC. ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.57 (d, $^4J_{3,5}$ = 2.6 Hz, 1 H, H-3), 7.51 (d, $^3J_{o,m}$ = 8.2 Hz, 2 H, H$_o$), 7.37 (d, $^3J_{5,6}$ = 8.5 Hz, 1 H, H-6), 7.24 (dd, $^3J_{5,6}$ = 8.5 Hz, $^4J_{3,5}$ = 2.6 Hz, 1 H, H-5), 7.21 (d, $^3J_{o,m}$ = 8.2 Hz, 2 H, H$_m$), 2.42 (s, 3 H, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ = 139.1 (C-2), 134.0 (C$_p$), 132.4 (C-6), 132.1 (C-4), 131.6 (C$_o$), 130.1 (C-3), 129.0 (C$_m$), 128.9 (C-5), 124.7 (C-1), 119.2 (C$_{ipso}$), 95.9 (C-1'), 84.3 (C-2'), 21.4 (CH_3) ppm. ESI-MS: m/z (%) = 264 (21), 262 (88), 260 (100) [M$^+$]; 225 (30) [M$^+$-35]; 189 (75) [M$^+$-71]. Anal. Calcd. for $C_{15}H_{10}Cl_2$: C, 68.99; H, 3.86. Found: C, 69.07; H, 4.12.

Synthesis of triazoles 2-6. General procedure

A mixture of tri-*n*-butyltin azide (0.86 mL, 3.15 mmol) with the appropriate alkyne **1** (3 mmol) was heated at 150 ºC for 70 h in a sealed glass bottle. The resulting solution was purified by column chromatography (cyclohexane/AcOEt, 5:1) and recrystallized from (cyclohexane/AcOEt) to give the desired triazoles.

4-(4-Methylphenyl)-1H(2*H*)-[1,2,3]triazole (2). Yellow solid (191.0 mg, 40%); m.p. 139–141 ºC. ^{1}H NMR (200 MHz, DMSO-*d*$_6$, 25 ºC): δ = 14.91 (sw, 1 H, NH), 8.08 (s, 1 H, H-5), 7.61 (d, $^3J_{o,m}$ = 7.8 Hz, 2 H, H$_o$), 7.11 (d, $^3J_{o,m}$ = 7.8 Hz, 2 H, H$_m$), 2.21 (s, 3 H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-*d*$_6$, 25 ºC): δ = 147.4 (C-4), 137.7 (C$_p$), 129.3 (C$_m$, C-5), 129.1 (C$_{ipso}$), 125.4 (C$_o$), 20.8 (CH_3) ppm. ESI-MS: m/z (%) = 182 [M$^+$+Na]; 160 [M$^+$+1]. Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70, N, 26.40. Found: C, 67.81; H, 5.75; N 26.49.

4-(4-Methoxyphenyl)-1H(2H)-[1,2,3]triazole (3). Yellow solid (157.7 mg, 30%); m.p. 163–165 ºC. ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.91 (s, 1 H, H-5), 7.76 (d, $^3J_{o,m}$ = 8.0 Hz, 2 H, H$_o$), 7.00 (d, $^3J_{o,m}$ = 8.0 Hz, 2 H, H$_m$), 3.87 (3 H, s, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 159.5 (C$_p$), 147.5 (C-4), 126.5 (C-5), 127.3 (C$_o$), 123.1 (C$_{ipso}$), 114.7 (C$_m$), 55.5 (CH_3) ppm. ESI-MS: m/z (%) = 198 [M$^+$+Na]; 177 [M$^+$+2]; 176 [M$^+$+1]. Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18, N, 23.99. Found: C, 61.85; H, 5.15; N 24.09.

4-(4-Bromo-2-fluorophenyl)-1*H*(2*H*)-[1,2,3]triazole (4). Yellow solid (477.1 mg, 66%); m.p. 139–141 ºC. ^{1}H NMR (200 MHz, DMSO-*d*$_6$, 25 ºC): δ = 11.33 (sw, 1 H, NH), 8.13 (s, 1 H, H-5), 7.87 (dd, $^3J_{5',6'}$ = 8.3 Hz, $^4J_{6',F}$ = 8.1 Hz, 1 H, H-6'), 7.57 (dd, $^3J_{3',F}$ = 10.6 Hz, $^4J_{3',5'}$ = 2.0 Hz, 1 H, H-3'), 7.41 (ddd, $^3J_{5',6'}$ = 8.3 Hz, $^4J_{3',5'}$ = 2.0 Hz, $^5J_{5',F}$ = 0.6 Hz, 1 H, H-5') ppm; ^{13}C NMR (75 MHz, DMSO-*d*$_6$, 25 ºC): δ = 158.9 (d, $^1J_{2',F}$ = 252.5 Hz, C-2'), 132.3 (C-4), 129.6 (C-5), 128.6 (C-6'), 128.5 (C-5'), 121.5 (C-4'), 119.8 (d, $^2J_{3',F}$ = 38.8 Hz, C-3'), 118.1 (C-1') ppm. ESI-MS: m/z (%) = 244, 242 [M$^+$+1]. Anal. Calcd. for $C_8H_5BrFN_3$: C, 39.70; H, 2.08, N, 17.36. Found: C, 39.82; H, 2.12; N 17.15.

4-(4-Chlorophenyl)-5-phenyl-1*H*(2*H*)-[1,2,3]triazole (5). White solid (413.2 mg, 54%); m.p. 124–126 ºC. ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.51-7.46 (m, 4 H, H_o, $H_{o'}$), 7.38-7.35 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.31 (dt, $^3J_{o,m}$ = 8.6 Hz, $^4J_{m,m}$ = $^5J_{o,m}$ = 2.2 Hz, 2 H, H_m) ppm; ^{13}C NMR (50.5 MHz, $CDCl_3$, 25 ºC): δ = 142.4 (C-5), 142.0 (C-4), 134.6 (C_p), 129.6 ($C_{ipso'}$), 129.4 (C_o), 128.9 (C_m, $C_{p'}$), 128.8 ($C_{m'}$), 128.6 (C_{ipso}), 128.2 ($C_{o'}$) ppm. ESI-MS: m/z (%) = 278 [M^++Na], 256 [M^+]. Anal. Calcd. for $C_{14}H_{10}ClN_3$: C, 67.76; H, 3.94, N, 16.43. Found: C, 67.93; H, 3.84; N 16.36.

4-(2,4-Dichlorophenyl)-5-(4-methylphenyl)-1*H*(2*H*)-[1,2,3]triazole (6). White solid (611.1 mg, 67%); m.p. 54–56 ºC. ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 13.56 (sw, 1 H, NH), 7.45 (d, $^4J_{3',5'}$ = 2.2 Hz, 1 H, H-3'), 7.39 (d, $^3J_{5',6'}$ = 8.3 Hz, 1 H, H-6'), 7.36-7.33 (m, 3 H, H-5', H_o), 7.12 (d, $^3J_{o,m}$ = 7.8 Hz, 2 H, H_m), 2.26 (s, 3 H, CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.2 (C-5), 140.4 (C-4), 138.7 (C_p), 132.7 (C-2'), 132.6 (C-4'), 131.8 (C-3'), 131.7 (C-1'), 131.1 (C-6'), 130.3 (C-5'), 129.5 (C_m), 126.8 (C_o), 126.3 (C_{ipso}), 21.4 (CH_3) ppm. ESI-MS: m/z (%) = 307 (14), 305 (70), 303 (89) [M^+]; 270 (46), 268 (100) [M^+-35]; 233 (47) [M^+-70]; 213 (60) [M^+-90]. Anal. Calcd. for $C_{15}H_{11}Cl_2N_3$: C, 59.23; H, 3.65; N, 13.81. Found: C, 59.65; H, 3.85; N, 13.09.

Preparation of triazoles 7-17 by *N*-alkylation of 2–6. General procedure

To a solution of 1,2,3-triazole **2-6** (0.5 mmol) in acetonitrile (3 mL) was added K_2CO_3 (83.0 mg, 0.6 mmol), KOH (84.0 mg, 1.5 mmol) and Bu_4NBr (4.0 mg, 0.013 mmol). The mixture was stirred for 5 min. at r.t. Then the appropriate alkyl bromide (0.6 mmol) was added and the mixture was stirred at reflux for 5 h for **7-12, 16-17** and for 2 h for **13-15**. The resulting solution was filtered and the remaining solid material was washed with Et_2O (20 mL). Evaporation of the solvent afforded an oil residue. From the oily crude the different regioisomers were separated by column chromatography eluting with cyclohexane/AcOEt (20:1) to get the isomers **7a-15a** then eluting with cyclohexane/ AcOEt (10:1) to separate the isomers **7b-15b** and **7c-15c**. The regioisomers **16-17** were separated by column chromatography eluting with cyclohexane/AcOEt (10:1) to get the isomers **16a-17a** then eluting with cyclohexane/AcOEt (5:1) to obtain the isomer **16b**.

2-Pentyl-4-(4-methylphenyl)-2*H*-[1,2,3]triazole (7a). Colourless oil (71.1 mg, 62%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.69 (s, 1 H, H-5), 7.59 (d, $^3J_{o,m}$ = 8.0 Hz, 2 H, H_o), 7.18 (d, $^3J_{o,m}$ = 8.0 Hz, 2 H, H_m), 4.35 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 2.29 (s, 3 H, CH_3), 1.91 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.29-1.21 (m, 4 H, H-3', H-4'), 0.82 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 147.4 (C-4), 138.0 (C_p), 130.0 (C-5), 129.4 (C_m), 127.6 (C_{ipso}), 125.7 (C_o), 55.0 (C-1'), 29.5 (C-2'), 28.6 (C-3'), 22.1 (C-4'), 21.2 (CH_3), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 229 (100) [M^+]; 186 (73) [M^+-43]; 131 (52) [M^+-98]; 118 (51) [M^+-111]; 116 (59) [M^+-113]. Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.28; H, 8.53; N 18.13.

1-Pentyl-4-(4-methylphenyl)-1*H*-[1,2,3]triazole (7b). White solid (32.6 mg, 28%); m.p. 73–75 ºC (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.64 (d, $^3J_{o,m}$ = 8.2 Hz, 2 H,

H_o), 7.62 (s, 1 H, H-5), 7.14 (d, $^3J_{o,m}$ = 8.2 Hz, 2 H, H_m), 4.28 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 2.29 (s, 3 H, CH_3), 1.85 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.29-1.18 (m, 4 H, H-3', H-4'), 0.82 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 147.7 (C-4), 137.8 (C_p), 129.4 (C_m), 127.8 (C_{ipso}), 125.5 (C_o), 119.0 (C-5), 50.3 (C-1'), 30.0 (C-2'), 28.5 (C-3'), 22.0 (C-4'), 21.2 (CH_3), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 229 (50) [M^+]; 159 (43) [M^+-70]; 131 (100) [M^+-98]. Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.48; H, 8.47; N 18.01.

1-Pentyl-5-(4-methylphenyl)-1*H*-[1,2,3]triazole (7c). White solid (5.7 mg, 5%); m.p. 102−104 ºC (cyclohexane/AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.56 (s, 1 H, H-4), 7.19-7.16 (m, 4 H, H_o, H_m), 4.26 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 2.33 (s, 3 H, CH_3), 1.73 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.27-1.15 (m, 4 H, H-3', H-4'), 0.74 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 139.5 (C_p), 137.7 (C-5), 132.9 (C-4), 129.7 (C_m), 128.6 (C_o), 124.3 (C_{ipso}), 48.2 (C-1'), 29.8 (C-2'), 28.5 (C-3'), 22.0 (C-4'), 21.3 (CH_3), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 229 (16) [M^+]; 131 (100) [M^+-98]; 116 (67) [M^+-113]. Anal. Calcd. for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found: C, 73.74; H, 8.25; N 18.01.

4-(4-Methoxyphenyl)-2-pentyl-2*H*-[1,2,3]triazole (8a). Yellow solid (55.2 mg, 45%); m.p. 52−54 ºC (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.75 (s, 1 H, H-5), 7.71 (d, $^3J_{o,m}$ = 9.0 Hz, 2 H, H_o), 6.96 (d, $^3J_{o,m}$ = 9.0 Hz, 2 H, H_m), 4.43 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 3.85 (s, 3 H, CH_3), 2.00 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.38-1.26 (m, 4 H, H-3', H-4'), 0.91 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (50.5 MHz, $CDCl_3$, 25 ºC): δ = 159.7 (C_p), 147.3 (C-4), 130.0 (C-5), 127.1 (C_o), 123.3 (C_{ipso}), 114.2 (C_m), 55.3 (CH_3), 55.0 (C-1'), 29.5 (C-2'), 28.6 (C-3'), 22.1 (C-4'), 13.9 (C-5') ppm. ESI-MS: m/z (%) = 245 (100) [M^+]; 202 (52) [M^+-43]; 133 (54) [M^+-112]; 132 (88) [M^+-113]. Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.65; H, 8.12; N 16.97.

4-(4-Methoxyphenyl)-1-pentyl-1*H*-[1,2,3]triazole (8b). Yellow solid (30.7 mg, 25%); m.p. 100−102 ºC (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.76 (d, $^3J_{o,m}$ = 8.7 Hz, 2 H, H_o), 7.67 (s, 1 H, H-5), 6.96 (d, $^3J_{o,m}$ = 8.7 Hz, 2 H, H_m), 4.38 (t, $^3J_{1',2'}$ = 7.2 Hz, 2 H, H-1'), 3.85 (s, 3 H, CH_3), 1.95 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.2 Hz, 2 H, H-2'), 1.39-1.33 (m, 4 H, H-3', H-4'), 0.91 (t, $^3J_{4',5'}$ = 6.7 Hz, 3 H, H-5') ppm; ^{13}C NMR (50.5 MHz, $CDCl_3$, 25 ºC): δ = 159.5 (C_p), 147.5 (C-4), 126.9 (C_o), 123.5 (C_{ipso}), 118.6 (C-5), 114.2 (C_m), 56.3 (CH_3), 50.0 (C-1'), 30.0 (C-2'), 28.6 (C-3'), 22.1 (C-4'), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 245 (76) [M^+]; 175 (93) [M^+-70]; 147 (100) [M^+-98]; 132 (79) [M^+-113]. Anal. Calcd. for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.42; H, 7.97; N 17.40.

4-(4-Bromo-2-fluorophenyl)-2-pentyl-2*H*-[1,2,3]triazole (9a). Colourless oil (107.7 mg, 69%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.84 (d, $^5J_{5,F}$ = 3.8 Hz, 1 H, H-5), 7.80 (dd, $^3J_{5'',6}$ = 8.5 Hz, $^4J_{6'',F}$ = 8.0 Hz, 1 H, H-6''), 7.29-7.18 (m, 2 H, H-3'', H-5''), 4.37 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 1.92 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.34-1.31 (m, 4 H, H-3', H-4'), 0.82 (t, $^3J_{4',5'}$ = 6.7 Hz, 3 H, H-5') ppm; ^{13}C NMR (50.5 MHz, $CDCl_3$, 25 ºC): δ = 159.4 (d, $^1J_{2'',F}$ = 254.7 Hz, C-2''), 140.9 (C-4), 133.4 (d, $^4J_{5,F}$ = 12.5 Hz, C-5), 129.1 (d, $^3J_{6'',F}$ = 4.4 Hz, C-6''), 127.8 (d, $^4J_{5'',F}$ = 3.5 Hz, C-5''), 121.8 (d, $^3J_{4'',F}$ = 9.9 Hz, C-4''), 119.6 (d, $^2J_{3'',F}$ = 25.1 Hz, C-3''), 117.7 (d, $^2J_{1'',F}$ = 12.6

Hz, C-1''), 55.1 (C-1'), 29.4 (C-2'), 28.6 (C-3'), 22.1 (C-4'), 13.9 (C-5') ppm. ESI-MS: m/z (%) = 313, 311 (100) [M^+]; 285, 283 (72) [M^+-28]; 270, 268 (89) [M^+-43]; 256, 254 (56) [M^+-57]; 244, 242 (56) [M^+-71]; 243, 241 (57) [M^+-70]; 215, 213 (70) [M^+-98]; 202, 200 (55) [M^+-111]; 200, 198 (49) [M^+-113]. Anal. Calcd. for $C_{13}H_{15}BrFN_3$: C, 50.02; H, 4.84; N, 13.46. Found: C, 50.28; H, 4.48; N 13.73.

4-(4-Bromo-2-fluorophenyl)-1-pentyl-1*H*-[1,2,3]triazole (9b). Yellow solid (45.3 mg, 29%); m.p. 71–73 ºC (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 8.12 (t, $^3J_{5'',6''}$ = $^4J_{6'',F}$ = 8.2 Hz, 1 H, H-6''), 7.82 (d, $^5J_{5\text{-}F}$ = 3.8 Hz, 1 H, H-5), 7.35-7.15 (m, 2 H, H-3'', H-5''), 4.33 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 1.89 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.33-1.26 (m, 4 H, H-3', H-4'), 0.84 (t, $^3J_{4',5'}$ = 6.9 Hz, 3 H, H-5') ppm; ^{13}C NMR (50.5 MHz, $CDCl_3$, 25 ºC): δ = 158.7 (d, $^1J_{2'',F}$ = 258.7 Hz, C-2''), 140.2 (d, $^3J_{4,F}$ = 3.1 Hz, C-4), 128.7 (d, $^3J_{6'',F}$ = 6.1 Hz, C-6''), 128.0 (d, $^4J_{5'',F}$ = 3.9 Hz, C-5''), 122.5 (d, $^4J_{5,F}$ = 13.9 Hz, C-5), 121.4 (d, $^3J_{4'',F}$ = 8.9 Hz, C-4''), 119.2 (d, $^2J_{3'',F}$ = 25.1 Hz, C-3''), 117.9 (d, $^2J_{1'',F}$ = 13.0 Hz, C-1''), 50.4 (C-1'), 29.9 (C-2'), 28.5 (C-3'), 22.0 (C-4'), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 313, 311 (71) [M^+]; 243, 241 (52) [M^+-70]; 215, 213 (100) [M^+-98]; 202, 200 (66) [M^+-111]. Anal. Calcd. for $C_{13}H_{15}BrFN_3$: C, 50.02; H, 4.84; N, 13.46. Found: C, 50.19; H, 4.96; N 13.17.

4-(4-Chlorophenyl)-2-pentyl-5-phenyl-2*H*-[1,2,3]triazole (10a). Colorless oil (81.5 mg, 50%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.46-7.37 (m, 4 H, $H_{o'}$, H_o), 7.30-7.20 (m, 5 H, $H_{m'}$, $H_{p'}$, H_m), 4.36 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 1.95 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.32-1.25 (m, 4 H, H-3', H-4'), 0.83 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.2 (C-5), 142.9 (C-4), 134.1 (C_p), 130.9 ($C_{ipso'}$), 130.0 (C_{ipso}), 129.4 (C_o), 128.7 (C_m), 128.6 ($C_{m'}$), 128.3 ($C_{p'}$), 128.2 ($C_{o'}$), 55.6 (C-1'), 29.9 (C-2'), 29.1 (C-3'), 22.6 (C-4'), 14.6 (C-5') ppm. ESI-MS: m/z (%) = 327 (42), 325 (100) [M^+]; 296 (58) [M^+-29]; 282 (51) [M^+-43]; 227 (60) [M^+-98]; 165 (56) [M^+-160]. Anal. Calcd. for $C_{19}H_{20}ClN_3$: C, 70.04; H, 6.19; N, 12.90. Found: C, 70.44; H, 6.10; N 12.76.

4-(4-Chlorophenyl)-1-pentyl-5-phenyl-1*H*-[1,2,3]triazole (10b). White solid (50.5 mg, 31%); m.p. 85–87 ºC (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.54-7.48 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.44 (dt, $^3J_{o,m}$ = 8.6 Hz, $^4J_{o,o}$ = $^5J_{o,m}$ = 2.2 Hz, 2 H, H_o), 7.29 (m, 2 H, $H_{o'}$), 7.19 (dt, $^3J_{o,m}$ = 8.6 Hz, $^4J_{m,m}$ = $^5J_{o,m}$ = 2.2 Hz, 2 H, H_m), 4.17 (t, $^3J_{1',2'}$ = 7.3 Hz, 2 H, H-1'), 1.76 (quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.3 Hz, 2 H, H-2'), 1.24-1.12 (m, 4 H, H-3', H-4'), 0.80 (t, $^3J_{4',5'}$ = 6.5 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 143.1 (C-4), 133.7 (C-5), 133.3 (C_p), 129.8 ($C_{p'}$, $C_{o'}$), 129.5 (C_{ipso}), 129.4 ($C_{m'}$), 128.6 (C_m), 127.9 (C_o, $C_{ipso'}$), 48.2 (C-1'), 29.7 (C-2'), 28.4 (C-3'), 21.9 (C-4'), 13.7 (C-5') ppm. ESI-MS: m/z (%) = 327 (12), 325 (34) [M^+]; 229 (34), 227 (100) [M^+-98]; 228 (44), 226 (90) [M^+-99]; 165 (46) [M^+-160]. Anal. Calcd. for $C_{19}H_{20}ClN_3$: C, 70.04; H, 6.19; N, 12.90. Found: C, 69.94; H, 6.18; N 12.65.

5-(4-Chlorophenyl)-1-pentyl-4-phenyl-1*H*-[1,2,3]triazole (10c). White solid (14.7 mg, 9%); m.p. 110–112 ºC (cyclohexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.52-7.47 (m, 4 H, H_o, $H_{m'}$), 7.29-7.24 (m, 5 H, $H_{o'}$, H_p, H_m), 4.18 (t, $^3J_{1',2'}$ = 7.4 Hz, 2 H, H-1'), 1.78 (2H, quin, $^3J_{1',2'}$ = $^3J_{2',3'}$ = 7.4 Hz, H-2'), 1.33-1.20 (4H, m, H-3', H-4'), 0.83 (3H, t, $^3J_{4',5'}$ = 6.8 Hz, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.4 (C-4), 135.9 ($C_{p'}$), 132.4 (C-5), 131.3 ($C_{o'}$),

130.7 (C_{ipso}), 129.7 ($C_{m'}$), 128.5 (C_m), 127.8 (C_p), 126.8 (C_o), 126.7 ($C_{ipso'}$), 48.3 (C-1'), 29.7 (C-2'), 28.5 (C-3'), 22.0 (C-4'), 13.8 (C-5') ppm. ESI-MS: m/z (%) = 327 (10), 325 (27) [M^+]; 229 (34), 227 (100) [M^+-98]; 228 (36), 226 (67) [M^+-99]; 165 (45) [M^+-160]. Anal. Calcd. for $C_{19}H_{20}ClN_3$: C, 70.04; H, 6.19; N, 12.90. Found: C, 70.29; H, 6.05; N 12.35.

4-(2,4-Dichlorophenyl)-2-pentyl-5-(4-methylphenyl)-2*H*-[1,2,3]triazole (11a). Colourless oil (136.6 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.43 (d, $^4J_{3'',5''}$ = 2.4 Hz, 1 H, H-3''), 7.39 (d, $^3J_{5'',6''}$ = 8.4 Hz, 1 H, H-6''), 7.33-7.32 (m, 3 H, H-5'', H_o), 7.11 (d, $^3J_{o,m}$ = 8.0 Hz, 2 H, H_m), 4.47 (t, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 2.32 (s, 3 H, CH_3), 2.05 (quin, $^3J_{1',2'} = {}^3J_{2',3'}$ = 7.0 Hz, 2 H, H-2'), 1.38-1.35 (m, 4 H, H-3', H-4'), 0.91 (t, $^3J_{4',5'}$ = 7.0 Hz, 3 H, H-5') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 145.2 (C-5), 140.4 (C-4), 138.1 (C_p), 132.8 (C-1''), 132.7 (C-2''), 132.6 (C-4''), 131.8 (C-3''), 131.0 (C6''), 130.1 (C5''), 129.3 (C_m), 127.8 (C_{ipso}), 126.6 (C_o), 55.3 (C-1'), 29.5 (C-2'), 28.7 (C-3'), 22.1 (C-4'), 21.3 (CH_3), 13.9 (C-5') ppm. ESI-MS: m/z (%) = 377 (16), 375 (78), 373 (100) [M^+]; 330 (59) [M^+-43]; 275 (62) [M^+-98]; 213 (43) [M^+-161]; 118 (68) [M^+-255]. Anal. Calcd. for $C_{20}H_{21}Cl_2N_3$: C, 64.18; H, 5.65; N, 11.23. Found: C, 64.21; H, 5.46; N 11.08.

4-(4-Chlorophenyl)-2-heptyl-5-phenyl-2*H*-[1,2,3]triazole (12a). Colourless oil (113.2 mg, 64%). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.52-7.46 (m, 4 H, H_o, $H_{o'}$), 7.37-7.30 (m, 5 H, $H_{m'}$, $H_{p'}$, H_m), 4.44 (t, $^3J_{1',2'}$ = 7.2 Hz, 2 H, H-1'), 2.02 (quin, $^3J_{1',2'} = {}^3J_{2',3'}$ = 7.2 Hz, 2 H, H-2'), 1.39-1.26 (m, 8 H, H-3', H-4', H-5', H-6'), 0.86 (t, 3 H, $^3J_{6',7'}$ = 7.2 Hz, H-7') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.2 (C-5), 142.9 (C-4), 134.1 (C_p), 130.9 ($C_{ipso'}$), 129.7 (C_{ipso}), 129.4 (C_o), 128.8 (C_m), 128.6 ($C_{m'}$), 128.4 ($C_{p'}$), 128.2 ($C_{o'}$), 55.2 (C-1'), 31.6 (C-5'), 29.8 (C-2'), 28.7 (C-4'), 26.5 (C-3'), 22.4 (C-6'), 14.0 (C-7') ppm. ESI-MS: m/z (%) = 355 (35), 353 (97) [M^+]; 282 (87) [M^+-71]; 256 (50) [M^+-98]; 229 (35), 227 (100) [M^+-128]; 165 (79) [M^+-188]. Anal. Calcd. for $C_{21}H_{24}ClN_3$: C, 71.27; H, 6.84; N, 11.87. Found: C, 71.63; H, 6.97; N 11.68.

4-(4-Chlorophenyl)-1-heptyl-5-phenyl-1H-[1,2,3]triazole (12b). White solid (31.8 mg, 18%); m.p. 64–66 ºC (cyclohexane/AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.47-7.44 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.40 (dt, $^3J_{o,m}$ = 8.4 Hz, $^4J_{o,o} = {}^5J_{o,m}$ = 2.2 Hz, 2 H, H_o), 7.25-7.22 (m, 2 H, $H_{o'}$), 7.16 (dt, $^3J_{o,m}$ = 8.4 Hz, $^4J_{m,m} = {}^5J_{o,m}$ = 2.2 Hz, 2 H, H_m), 4.12 (t, $^3J_{1',2'}$ = 7.2 Hz, 2 H, H-1'), 1.17 (quin, $^3J_{1',2'} = {}^3J_{2',3'}$ = 7.2 Hz, 2 H, H-2'), 1.18-1.13 (m, 8 H, H-3', H-4', H-5', H-6'), 0.78 (t, 3 H, $^3J_{6',7'}$ = 7.2 Hz, H-7') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 143.1 (C-4), 133.8 (C-5), 133.4 (C_p), 129.9 ($C_{o'}$), 129.8 ($C_{p'}$), 129.6 (C_{ipso}), 129.4 ($C_{m'}$), 128.6 (C_m), 127.9 (C_o, $C_{ipso'}$), 48.3 (C-1'), 31.4 (C-5'), 30.0 (C-2'), 28.5 (C-4'), 26.3 (C-3'), 22.4 (C-6'), 14.0 (C-7') ppm. ESI-MS: m/z (%) = 355 (10), 353 (28) [M^+]; 229 (35), 227 (100) [M^+-128]; 228 (45), 226 (86) [M^+-129]. Anal. Calcd. for $C_{21}H_{24}ClN_3$: C, 71.27; H, 6.84; N, 11.87. Found: C, 71.32; H, 7.91; N 11.80.

5-(4-Chlorophenyl)-1-heptyl-4-phenyl-1*H*-[1,2,3]triazole (12c). Colourless oil (15.9 mg, 9%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.46-7.41 (m, 4 H, H_o, $H_{m'}$), 7.21-7.17 (m, 5 H, $H_{o'}$, H_p, H_m), 4.12 (t, $^3J_{1',2'}$ = 7.2 Hz, 2 H, H-1'), 1.71 (quin, $^3J_{1',2'} = {}^3J_{2',3'}$ = 7.2 Hz, 2 H, H-2'), 1.18-1.14 (m, 8 H, H-3', H-4', H-5', H-6'), 0.77 (t, 3 H, $^3J_{6',7'}$ = 7.2 Hz, H-7') ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.3 (C-4), 135.9 ($C_{p'}$), 132.5 (C-5), 131.3 ($C_{o'}$), 130.7 (C_{ipso}), 129.8 ($C_{m'}$), 128.5 (C_m), 127.8 (C_p), 126.9 (C_o), 126.8 ($C_{ipso'}$), 48.3 (C-1'), 31.4 (C-5'), 30.0 (C-2'), 28.5 (C-4'),

26.4 (C-3'), 22.4 (C-6'), 14.0 (C-7') ppm. ESI-MS: m/z (%) = 355 (7), 353 (19) [M^+]; 229 (35), 227 (100) [M^+-128]; 228 (38), 226 (65) [M^+-129]. Anal. Calcd. for $C_{21}H_{24}ClN_3$: C, 71.27; H, 6.84; N, 11.87. Found: C, 71.40; H, 6.80; N 11.98.

2-(4-Bromobenzyl)-4-(*p*-chlorophenyl)-5-phenyl-2*H*-[1,2,3]triazole (13a). White solid (131.6 mg, 62%); m.p. 104–106 ºC (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.52-7.45 (m, 6 H, H_o, $H_{o'}$, $H_{m''}$), 7.38-7.34 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.33-7.29 (m, 4 H, H_m, $H_{o''}$), 5.57 (s, 2 H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 145.1 (C-5), 143.9 (C-4), 134.3 ($C_{ipso''}$), 134.0 (C_p), 131.9 ($C_{m''}$), 130.5 ($C_{ipso'}$), 129.9 ($C_{o''}$), 129.5 (C_o), 129.3 (C_{ipso}), 128.8 (C_m), 128.7 ($C_{m'}$), 128.6 ($C_{p'}$), 128.2 ($C_{o'}$), 122.5 ($C_{p''}$), 58.1 (CH_2) ppm. ESI-MS: m/z (%) = 427 (36), 425 (97), 423 (78) [M^+]; 228 (47), 226 (100) [M^+-199]; 171 (82), 169 (80) [M^+-255]. Anal. Calcd. for $C_{21}H_{15}ClBrN_3$: C, 59.39; H, 3.56; N, 9.89. Found: C, 59.10; H, 3.72; N 9.38.

1-(4-Bromobenzyl)-4-(*p*-chlorophenyl)-5-phenyl-1*H*-[1,2,3]triazole (13b). White solid (29.7 mg, 14%); m.p. 120–122 ºC (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.49-7.44 (m, 5 H, $H_{m'}$, $H_{m''}$, $H_{p'}$), 7.38 (dt, $^3J_{o,m}$ = 8.4 Hz, $^4J_{o,o}$ = $^5J_{o,m}$ = 2.4 Hz, 2 H, H_o), 7.22 (dt, $^3J_{o,m}$ = 8.4 Hz, $^4J_{m,m}$ = $^5J_{o,m}$ = 2.4 Hz, 2 H, H_m), 7.15-7.11 (m, 2 H, $H_{o'}$), 6.89 (d, $^3J_{o'',m''}$ = 8.4 Hz, 2 H, $H_{o''}$), 5.34 (s, 2 H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 144.1 (C-4), 134.1 ($C_{ipso''}$), 133.9 (C-5), 133.6 (C_p), 131.9 ($C_{m''}$), 130.0 ($C_{p'}$), 129.9 ($C_{o'}$, C_{ipso}), 129.4 ($C_{m'}$), 129.2 ($C_{o''}$), 128.7 (C_m), 127.9 (C_o), 127.4 ($C_{ipso'}$), 122.4 ($C_{p''}$), 51.8 (CH_2) ppm. ESI-MS: m/z (%) = 425 (6) [M^+]; 228 (37), 226 (100) [M^+-199]; 171 (52), 169 (54) [M^+-255]. Anal. Calcd. for $C_{21}H_{15}ClBrN_3$: C, 59.39; H, 3.56; N, 9.89. Found: C, 59.42; H, 3.91; N 9.53.

1-(4-Bromobenzyl)-5-(*p*-chlorophenyl)-4-phenyl-1*H*-[1,2,3]triazole (13c). White solid (40.3 mg, 19%); m.p. 164–166 ºC (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC): δ = 7.54-7.50 (m, 2 H, $H_{m''}$), 7.43-7.39 (m, 4 H, H_o, $H_{m'}$) 7.31-7.26 (m, 3 H, H_m, H_p), 7.06 (dt, $^3J_{o',m'}$ = 8.6 Hz, $^4J_{o',o'}$ = $^5J_{o',m'}$ = 2.0 Hz, 2 H, $H_{o'}$) 6.92 (d, $^3J_{o'',m''}$ = 8.5 Hz, 2 H, $H_{o''}$), 5.35 (s, 2 H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 145.0 (C-4), 136.3 ($C_{p'}$), 134.1 (C-5), 134.0 ($C_{ipso''}$), 131.9 ($C_{m''}$), 131.4 ($C_{o'}$), 130.4 (C_{ipso}), 129.7 ($C_{m'}$), 129.1 ($C_{o''}$), 128.6 (C_m), 128.0 (C_p), 126.7 (C_o), 126.1 ($C_{ipso'}$), 122.3 ($C_{p''}$), 58.1 (CH_2) ppm. ESI-MS: m/z (%) = 425 (10) [M^+]; 228 (39), 226 (100) [M^+-199]; 171 (49), 169 (51) [M^+-255]. Anal. Calcd. for $C_{21}H_{15}ClBrN_3$: C, 59.39; H, 3.56; N, 9.89. Found: C, 59.22; H, 3.88; N 9.77.

2-Benzyl-4-(4-chlorophenyl)-5-phenyl-2*H*-[1,2,3]triazole (14a). White solid (110.7 mg, 64%); m.p. 110–112 ºC (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.52-7.45 (m, 4 H, H_o, $H_{o'}$), 7.46-7.42 (m, 2 H, $H_{o''}$), 7.40-7.32 (m, 8 H, $H_{m''}$, $H_{p''}$, $H_{m'}$, $H_{p'}$, H_m), 5.62 (s, 2 H, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC): δ = 145.1 (C-5), 143.9 (C-4), 135.4 ($C_{ipso''}$), 134.5 (C_p), 131.0 ($C_{ipso'}$), 129.8 (C_{ipso}, C_o), 129.1 ($C_{o''}$), 129.0 (C_m), 128.9 ($C_{m'}$), 128.7 ($C_{p''}$), 128.6 ($C_{p'}$), 128.5 ($C_{o'}$) 128.4 ($C_{m''}$), 59.0 (CH_2) ppm. ESI-MS: m/z (%) = 347 (58), 345 (100) [M^+]; 226 (79) [M^+-119]; 91 (99) [M^+-254]. Anal. Calcd. for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.68; H, 4.75; N 12.10.

1-Benzyl-4-(4-chlorophenyl)-5-phenyl-1*H*-[1,2,3]triazole (14b). White solid (41.4 mg, 24%); m.p. 145–147 ºC (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.51-7.46 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.44-7.40 (m, 2 H, H_o), 7.26-7.20 (m, 5 H, $H_{m''}$, $H_{p''}$, $H_{m'}$), 7.14-7.10 (m, 2 H, $H_{o'}$), 7.03-7.00

(m, 2 H, $H_{o''}$), 5.40 (s, 2 H, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 143.5 (C-4), 135.2 ($C_{ipso''}$), 134.0 (C-5), 133.1 (C_p), 130.0 (C_{ipso}, $C_{o'}$), 129.8 ($C_{p'}$), 129.4 ($C_{o''}$), 129.3 ($C_{m'}$), 128.6 (C_m, $C_{m''}$), 128.2 ($C_{p''}$), 127.9 ($C_{ipso'}$), 127.5 ($C_{o''}$), 52.1 (CH_2) ppm. ESI-MS: m/z (%) = 347 (20), 345 (51) [M^+]; 228 (58), 226 (100) [M^+-119]; 91 (96) [M^+-255]. Anal. Calcd. for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.82; H, 4.90; N 11.93.

1-Benzyl-5-(4-chlorophenyl)-4-phenyl-1*H*-[1,2,3]triazole (14c). White solid (15.5 mg, 9%); m.p. 177–179 ºC (cyclohexane). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.57-7.52 (m, 2 H, H_o), 7.43-7.39 (d, $^3J_{m',o'}$ = 8.4 Hz, 2 H, $H_{m'}$), 7.30-7.28 (m, 6 H, $H_{o''}$, $H_{p''}$, H_m, H_p), 7.10-7.06 (m, 4 H, $H_{o'}$, $H_{m''}$), 5.43 (s, 2 H, CH_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ = 144.8 (C-4), 136.0 ($C_{p'}$), 135.2 ($C_{ipso''}$), 132.7 (C-5), 131.4 ($C_{o'}$), 130.6 (C_{ipso}), 129.5 ($C_{m'}$), 128.8 ($C_{m''}$), 128.5 (C_m), 127.9 (C_p), 127.3 ($C_{p''}$), 127.3 ($C_{o''}$), 126.7 (C_o), 126.3 ($C_{ipso'}$), 52.1 (CH_2) ppm. ESI-MS: m/z (%) = 347 (14), 345 (36) [M^+]; 228 (43), 226 (95) [M^+-119]; 91 (100) [M^+-255]. Anal. Calcd. for $C_{21}H_{16}ClN_3$: C, 72.93; H, 4.66; N, 12.15. Found: C, 72.98; H, 4.94; N 11.83.

2-Benzyl-4-(4-bromo-2-fluorophenyl)-2*H*-[1,2,3]triazole (15a). White solid (73.1 mg, 44%); m.p. 104–106 ºC (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 7.97 (d, $^5J_{5,F}$ = 3.9 Hz, 1 H, H-5), 7.88 (t, $^3J_{5',6'}$ = $^4J_{6',F}$ = 8.3 Hz, 1 H, H-6'), 7.40-7.34 (m, 7 H, H_o, H_m, H_p, H-3', H-5'), 5.60 (s, 2 H, CH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ = 159.8 (d, $^1J_{2',F}$ = 254.1 Hz, C-2'), 141.9 (d, $^3J_{4,F}$ = 1.5 Hz, C-4), 135.3 (C_{ipso}), 134.4 (d, $^4J_{5,F}$ = 11.4 Hz, C-5), 129.5 (d, $^3J_{6',F}$ = 4.4 Hz, C-6'), 129.1 (C_o) 128.7 (C_p), 128.3 (C_m), 128.1 (d, $^4J_{5',F}$ = 3.8 Hz, C-5'), 122.3 (d, $^3J_{4',F}$ = 9.9 Hz, C-4'), 119.9 (d, $^2J_{3',F}$ = 25.2 Hz, C-3'), 117.8 (d, $^2J_{1',F}$ = 13.0 Hz, C-1'), 59.1 (CH_2) ppm. ESI-MS: m/z (%) = 333 (83), 331 (80) [M^+]; 214 (44), 212 (43) [M^+-119]; 91 (100) [M^+-241]. Anal. Calcd. for $C_{15}H_{11}BrFN_3$: C, 54.24; H, 3.34; N, 12.65. Found: C, 53.98; H, 3.21; N 12.42.

1-Benzyl-4-(4-bromo-2-fluorophenyl)-1*H*-[1,2,3]triazole (15b). White solid (89.7 mg, 54%); m.p. 146–148 ºC (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ = 8.17 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{6',F}$ = 7.8 Hz, 1 H, H-6'), 7.83 (d, $^5J_{5,F}$ = 3.4 Hz, 1 H, H-5), 7.39-7.34 (m, 4 H, H-5', H_m, H_p), 7.30-7.24 (m, 3 H, H-3', H_o), 5.57 (s, 2 H, CH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ =158.7 (d, $^1J_{2',F}$ = 251.7 Hz, C-2'), 140.6 (d, $^3J_{4,F}$ = 3.1 Hz, C-4), 134.5 (C_{ipso}), 129.1 (C_m), 128.8 (C_p), 128.7 (d, $^3J_{6',F}$ = 4.6 Hz, C-6'), 127.9 (C_o, C-5'), 122.6 (d, $^4J_{5,F}$ = 12.2 Hz, C-5), 121.6 (d, $^3J_{4',F}$ = 11.0 Hz, C-4'), 119.2 (d, $^2J_{3',F}$ = 25.2 Hz, C-3'), 117.8 (d, $^2J_{1',F}$ = 12.9 Hz, C-1'), 54.2 (CH_2) ppm. ESI-MS: m/z (%) = 333 (35), 331 (34) [M^+]; 304 (50), 302 (49) [M^+-29]; 214 (75), 212 (73) [M^+-119]; 197 (50) [M^+-137]; 91 (100) [M^+-241]. Anal. Calcd. for $C_{15}H_{11}BrFN_3$: C, 54.24; H, 3.34; N, 12.65. Found: C, 54.15; H, 3.45; N 12.38.

4-(4-Bromo-2-fluorophenyl)-2-(ethoxycarbonyl)methyl-2*H*[1,2,3]-triazole (16a). White solid (90.2, 55%); m.p. 107–109 ºC (cyclohexane/Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 8.04 (d, $^5J_{5,F}$ = 4.0 Hz, 1 H, H-5), 7.89 (dd, $^3J_{6',5'}$ = 8.5 Hz, $^4J_{6',F}$ = 7.2 Hz, 1 H, H-6'), 7.37 (d, $^3J_{5',6'}$ = 8.5 Hz, $^3J_{3',F}$ = 8.5 Hz, 2 H, H-5', H-3'), 5.27 (s, 2 H, CH_2), 4.28 (q, $^3J_{1'',2''}$ = 7.0 Hz, 2 H, H-1''), 1.30 (t, $^3J_{1'',2''}$ = 7.0 Hz, 3 H, H-2'') ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ = 166.5 (CO), 159.5 (d, $^1J_{2',F}$ = 254.7 Hz, C-2'), 142.3 (d, $^3J_{4,F}$ = 2.3 Hz, C-4), 134.7 (d, $^4J_{5,F}$ = 12.4 Hz, C-5), 129.3 (d, $^3J_{6',F}$ = 4.6 Hz, C-6'), 127.9 (d, $^4J_{5',F}$ = 4.1 Hz, C-5'), 122.3 (d, $^3J_{4',F}$ = 9.2 Hz, C-4'), 119.6 (d, $^2J_{3',F}$ = 25.1 Hz, C-3'), 117.2 (d, $^2J_{1',F}$ = 12.0 Hz, C-1'), 62.1 (CH_2), 55.6 (C-1''), 14.0 (C-

2'') ppm. ESI-MS: m/z (%) = 329 (100), 327 (99) [M^+]; 256 (93), 258 (92) [M^+-73]; 202 (34), 200 (43) [M^+-129]. Anal. Calcd. for $C_{12}H_{11}BrFN_3O_2$: C, 43.92; H, 3.38; N, 12.81. Found: C, 43.74; H, 3.50; N 12.68.

4-(4-Bromo-2-fluorophenyl)-1-(ethoxycarbonyl)methyl-1*H*-[1,2,3]triazole (16b). White solid (29.5, 18%); m.p. 115–117 ºC (cyclohexane/Et_2O). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 8.17 (t, $^3J_{5',6'} = {}^4J_{6',F}$ = 8.2 Hz, 1 H, H-6'), 8.18 (d, $^5J_{5,F}$ = 3.6 Hz, 1 H, H-5), 7.41-7.33 (m, 2 H, H-3', H-5'), 5.25 (s, 2 H, CH_2), 4.29 (q, $^3J_{1'',2''}$ = 7.2 Hz, 2 H, H-1''), 1.31 (t, $^3J_{1'',2''}$ = 7.2 Hz, 3 H, H-2'') ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ = 166.1 (CO), 158.7 (d, $^1J_{2',F}$ = 251.0 Hz, C-2'), 140.8 (C-4), 128.7 (d, $^3J_{6',F}$ = 4.1 Hz, C-6'), 128.0 (d, $^4J_{5',F}$ = 3.6 Hz, C-5'), 124.2 (d, $^4J_{5,F}$ = 13.0 Hz, C-5), 121.8 (d, $^3J_{4',F}$ = 9.5 Hz, C-4'), 119.3 (d, $^2J_{3',F}$ = 24.6 Hz, C-3'), 117.4 (d, $^2J_{1',F}$ = 12.8 Hz, C-1'), 62.5 (CH_2), 50.9 (C-1''), 14.0 (C-2'') ppm. ESI-MS: m/z (%) = 329 (35), 327 (35) [M^+]; 229 (51), 227 (61) [M^+-100]; 214 (100), 212 (68) [M^+-115]. Anal. Calcd. for $C_{12}H_{11}BrFN_3O_2$: C, 43.92; H, 3.38; N, 12.81. Found: C, 44.22; H, 3.45; N 12.54.

4-(4-Chlorophenyl)-2-(ethoxycarbonyl)methyl-5-phenyl-2*H*-[1,2,3]triazole (17a). White solid (104.1 mg, 60%); m.p. 94–96º C (cyclohexane/AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ = 7.54-7.47 (m, 4 H, $H_{o'}$, H_o), 7.38-7.35 (m, 3 H, $H_{m'}$, $H_{p'}$), 7.32 (dt, $^3J_{o,m}$ = 8.8 Hz, $^4J_{m,m} = {}^5J_{o,m}$ = 2.2 Hz, 2 H, H_m), 5.17 (2 H, s, CH_2), 4.19 (q, $^3J_{1',2'}$ = 7.0 Hz, 2 H, H-1'), 1.21 (t, $^3J_{1',2'}$ = 7.0 Hz, 3H, H-2') ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 166.6 (CO), 145.6 (C-5), 144.4 (C-4), 134.4 (C_p), 130.4 ($C_{ipso'}$), 129.5 (C_o), 129.1 (C_{ipso}), 128.7 (C_m), 128.6 ($C_{p'}$, $C_{m'}$), 128.3 ($C_{o'}$), 62.1 (CH_2), 55.6 (C-1'), 14.1 (C-2') ppm. ESI-MS: m/z (%) = 343 (41), 341 (95) [M^+]; 270 (45), 268 (100) [M^+-73]; 104 (50) [M^+-237]. Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72; N, 12.29. Found: C, 62.99; H, 5.01; N 12.08.

Synthesis of compounds 18-23. General procedure

To a solution of amine (0.75 mmol) in dry CH_2Cl_2 (0.50 mL) was added dropwise under nitrogen a solution of trimethylaluminium in heptane 2M (0.38 mL, 0.75 mmol). The mixture was stirred at room temperature for 1 h. **16a-17a** (0.3 mmol) in dry CH_2Cl_2 (0.5 mL) was added under nitrogen and the solution was warmed to 40ºC for 2 h. The reaction mixture was raised to 0 ºC and poured carefully (exothermic reaction) into HCl (2N, 4.68 mL). The resultant mixture was stirred at 40ºC for 0.5 h. The aqueous layer was then extracted with 3 x 10 mL CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and the oily residue was purified by column chromatography eluting with cyclohexane/AcOEt (1:1). RMN signals of **18-21** were described to majority conformer.

4-(4-Chlorophenyl)-5-phenyl-2-(piperidin-1-yl-carbamoyl)methyl-2*H*-[1,2,3]triazole (18). White solid (45.1 mg, 38%); m.p. 204–206 ºC (toluene). ^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC): δ = 9.03 (s, 1 H, NH), 7.49-7.38 (m, 9 H, H_{ar}), 5.46 (s, 2 H, CH_2), 3.02 (sw, 2 H, H-2ec'), 2.71-2.69 (m, 2 H, H-2ax'), 2.40 (sw, 1 H, H-4ec'), 1.56-1.52 (m, 5 H, H-3', H-4ax') ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 ºC): δ = 168.1 (CO), 144.6 (C-5), 143.3 (C-4), 133.8 (C_p), 131.1 ($C_{ipso'}$), 130.2 (C_o), 129.5 ($C_{p'}$, C_m, $C_{m'}$), 129.3 (C_{ipso}), 128.6 ($C_{o'}$), 57.3 (C-2'), 56.2 (CH_2), 26.0

(C-3'), 23.4 (C-4') ppm. ESI-MS: m/z (%) = 395 (9) [M^+]; 99 (100) [M^+-296]; 84 (87) [M^+-311]. Anal. Calcd. for $C_{21}H_{22}ClN_5O$: C, 63.71; H, 5.60; N, 17.69. Found: C, 63.43; H, 6.00; N 17.24.

4-(4-Bromo-2-fluorophenyl)-2-(piperidin-1-yl-carbamoyl)methyl-2*H*-[1,2,3]triazole (19). White solid (50.5 mg, 44%); m.p. 235–237 ºC (toluene). ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ = 8.01 (d, $^5J_{5,F}$ = 2.1 Hz, 1 H, H-5), 7.87 (t, $^3J_{6',5'}$ = $^4J_{6',F}$ = 8.3 Hz, 1 H, H-6'), 7.32 (d, $^3J_{3',F}$ = 8.3 Hz, $^3J_{5',6'}$ = 8.3 Hz, 2 H, H-3', H-5'), 6.35 (sw, 1 H, NH), 5.45 (s, 2 H, CH_2), 3.12 (sw, 2 H, H-2ec''), 2.68 (sw, 1 H, H-4ec''), 2.34 (sw, 2 H, H-2ax''), 1.72-1.63 (m, 5 H, H-3'', H-4ax'') ppm; ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ = 167.9 (CO), 159.5 (d, $^1J_{2',F}$ = 254.0 Hz, C-2'), 142.1 (C-4), 134.5 (d, $^4J_{5,F}$ = 11.4 Hz, C-5), 129.4 (d, $^3J_{6',F}$ = 4.6 Hz, C-6'), 127.9 (d, $^4J_{5',F}$ = 3.1 Hz, C-5'), 122.1 (d, $^3J_{4',F}$ = 9.9 Hz, C-4'), 119.6 (d, $^2J_{3',F}$ = 25.2 Hz, C-3'), 117.5 (d, $^2J_{1',F}$ = 13.0 Hz, C-1'), 58.1 (C-2''), 55.6 (CH_2), 25.6 (C-3''), 22.8 (C-4'') ppm. ESI-MS: m/z (%) = 383, 381 (9) [M^+]; 99 (100) [M^+-283]; 83 (92) [M^+-299]. Anal. Calcd. for $C_{15}H_{17}BrFN_5O$: C, 47.13; H, 4.48; N, 18.32. Found: C, 46.97; H, 4.77; N 18.18.

4-(4-Chlorophenyl)-5-phenyl-2-(morpholin-4-yl-carbamoyl)methyl-2*H*-[1,2,3] triazole (20). White solid (83.5 mg, 70%); m.p. 230–232 ºC (toluene). ^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC): δ = 9.15 (s, 1 H, NH), 7.49-7.42 (m, 9 H, H_{ar}), 5.55 (s, 2 H, CH_2), 3.77-3.52 (m, 4 H, H-3'), 2.95-2.63 (m, 4 H, H-2') ppm; ^{13}C NMR (100 MHz, DMSO-d_6, 25 ºC): δ =167.6 (CO), 143.9 (C-5), 142.6 (C-4), 133.1 (C_p), 130.4 ($C_{ipso'}$), 129.5 ($C_{p'}$, C_o), 128.9 (C_m), 128.8 ($C_{m'}$), 128.6 (C_{ipso}), 127.9 ($C_{o'}$), 65.9 (C-3'), 55.7 (C-2'), 55.5 (CH_2) ppm. ESI-MS: m/z (%) = 399 (14), 397 (39) [M^+]; 270 (23), 268 (61) [M^+-129]; 104 [M^+-293] (56); 101 [M^+-296] (100); 86 [M^+-311] (67). Anal. Calcd. for $C_{20}H_{20}ClN_5O_2$: C, 60.38; H, 5.07; N, 17.60. Found: C, 60.15; H, 5.31; N 17.43.

4-(4-Bromo-2-fluorophenyl)-2-(morpholin-4-yl-carbamoyl)methyl-2*H*-[1,2,3]triazole (21). White solid (73.8 mg, 64%); m.p. 254–256 ºC (toluene). ^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC): δ = 9.10 (s, 1 H, NH), 8.16 (d, $^5J_{5,F}$ = 3.3 Hz, 1 H, H-5), 7.85 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{6',F}$ = 7.8 Hz, 1 H, H-6'), 7.73 (dd, $^3J_{3',F}$ = 10.3 Hz, $^4J_{3',5'}$ = 2.0 Hz, 1 H, H-3'), 7.53 (dd, $^3J_{6',5'}$ = 8.3 Hz, $^4J_{5',3'}$ = 2.0 Hz, 1 H, H-5'), 5.53 (s, 2 H, CH_2), 3.61-3.59 (m, 4 H, H-3''), 2.77-2.75 (m, 4 H, H-2'') ppm; ^{13}C NMR (125 MHz, DMSO-d_6, 25 ºC): δ = 167.5 (CO), 158.8 (d, $^1J_{2',F}$ = 253.3 Hz, C-2'), 140.7 (C-4), 133.7 (d, $^4J_{5,F}$ = 9.9 Hz, C-5), 129.4 (d, $^3J_{6',F}$ = 4.1 Hz, C-6'), 128.3 (d, $^4J_{5',F}$ = 3.1 Hz, C-5'), 121.6 (d, $^3J_{4',F}$ = 9.8 Hz, C-4'), 119.7 (d, $^2J_{3',F}$ = 24.4 Hz, C-3'), 117.3 (d, $^3J_{1',F}$ = 13.0 Hz, C-1'), 65.9 (C-3''), 55.7 (C-2''), 55.6 (CH_2) ppm. ESI-MS: m/z (%) = 385, 383 (4) [M^+]; 300, 298 (7) [M-85]; 256, 254 (11) [M-129]; 202, 200 (16) [M-185]; 200, 198 (16) [M-183]; 101 (100) [M-283]. Anal. Calcd. for $C_{14}H_{15}BrFN_5O_2$: C, 43.77; H, 3.94; N, 18.23. Found: C, 43.94; H, 3.90; N 18.62.

4-(4-Chlorophenyl)-5-phenyl-2-(cyclohexyl-carbamoyl)methyl-2*H*-[1,2,3]triazole (22). White solid (66.3 mg, 56%); m.p. 192–194 ºC (cyclohexane). ^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ =7.52-7.50 (m, 2 H, $H_{o'}$), 7.48 (d, $^3J_{o,m}$ = 8.3 Hz, 2 H, H_o), 7.39-7.38 (m, 3 H, $H_{m'}$, $H_{p'}$) 7.33 (d, $^3J_{o,m}$ = 8.3 Hz, 2 H, H_m), 6.14 (d, $^3J_{NH,1ax'}$ = 6.6 Hz, 1 H, NH), 5.14 (s, 2 H, CH_2), 3.82 (tq, $^3J_{1ax',2ax'}$ = 10.2 Hz, $^3J_{1ax',2eq'}$ = $^3J_{NH,1ax'}$ = 6.6 Hz, 1 H, H-1ax'), 1.88 (m, 2 H, H-2eq'), 1.63 (m, 2 H, H-2ax'), 1.57 (m, 1 H, H-4eq'), 1.36 (m, 2 H, H-3eq'), 1.17 (m, 3 H, H-3ax', H-4ax') ppm; ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ = 164.3 (CO), 145.8 (C-5), 144.5 (C-4), 134.7 (C_p), 130.0

($C_{ipso'}$), 129.4 (C_o), 128.9 (C_{ipso}, C_m), 128.7 ($C_{p'}$, $C_{m'}$), 128.2 ($C_{o'}$), 57.7 (CH_2), 48.4 (C1'), 32.6 (C-2'), 25.3 (C-4'), 24.5 (C-3') ppm. ESI-MS: m/z (%) = 396 (36), 394 (82) [M^+]; 314 (27), 312 (62) [M^+-82]; 271 (42), 269 (96) [M^+-182]; 214 (44), 212 (100) [M^+-182]; 138 (48) [M^+-257]; 104 (70) [M^+-291]. Anal. Calcd. for $C_{22}H_{23}ClN_4O$: C, 66.91; H, 5.87; N, 14.19. Found: C, 66.82; H, 6.08; N 14.02.

4-(4-Bromo-2-fluorophenyl)-2-(cyclohexyl-carbamoyl)methyl-2*H*-[1,2,3]triazole (23). White solid (48.0 mg, 42%); m.p. 228–230 ºC (toluene). ^{1}H NMR (500 MHz, DMSO-d_6, 25 ºC): δ = 8.25 (d, $^3J_{NH,1''}$ = 7.5 Hz, 1 H, NH), 8.15 (d, $^5J_{5,F}$ = 3.4 Hz, 1 H, H-5), 7.85 (dd, $^4J_{6',F}$ = 9.2 Hz, $^3J_{6',5'}$ = 8.3 Hz, 1 H, H-6'), 7.72 (d, $^3J_{3',F}$ = 10.3 Hz, 1 H, H-3'), 7.52 (d, $^3J_{6',5'}$ = 8.3 Hz, 1H, H-5'), 5.15 (s, 2 H, CH_2), 3.53-3.52 (m, 1 H, H-1''), 1.76-1.51 (m, 4 H, H-2''), 1.28-1.06 (m, 6 H, H-3'', H-4''); ^{13}C NMR (125 MHz, DMSO-d_6, 25 ºC): δ =164.0 (CO), 158.9 (d, $^1J_{2',F}$ = 253.3 Hz, C-2'), 140.8 (C-4), 133.8 (d, $^4J_{5,F}$ = 9.9 Hz, C-5), 129.5 (d, $^3J_{6',F}$ = 3.8 Hz, C-6'), 128.3 (d, $^4J_{5',F}$ = 3.1 Hz, C-5'), 121.7 (d, $^3J_{4',F}$ = 9.9 Hz, C-4'), 119.7 (d, $^2J_{3',F}$ = 25.2 Hz, C-3'), 117.2 (d, $^3J_{1',F}$ = 13.0 Hz, C-1'), 56.9 (CH_2), 47.8 (C-1''), 32.3 (C-2''), 25.1 (C-4''), 24.4 (C-3'') ppm. ESI-MS: m/z (%) = 382 (27), 380 (27) [M^+]; 257 (98), 255 (98) [M^+-126]; 200 (69), 198 (69) [M^+-182]; 83 (68) [M^+-283]; 55 (78) [M^+-327]. Anal. Calcd. for $C_{16}H_{18}BrFN_4O$: C, 50.41; H, 4.76; N, 14.70. Found: C, 50.72; H, 4.58; N 14.95.

Computational details

The geometry of the systems has been fully optimized at the B3LYP/6-31G(d) computational level.[32,33] Frequency calculation has been carried out at the same computational level to confirm that the structures obtained correspond to energetic minima.[34] A further geometry optimization has been performed at the B3LYP/6-311++G(d,p) level.[35] These geometries have been used to calculated the absolute chemical shielding within the GIAO approximation[36] at the B3LYP/6-311++G(d,p) computational level. All these calculations were carried out using the facilities of Gaussian 03.[37]

Acknowledgements

PG, NJ and CGO are grateful to the Spanish National Health Program (SAF2006-13391-C03-02 and SAF2009-12422-C02-02) and RETICS RTA (RD06/001/0014), and the program CANNAB-CM (S-SAL-0261-2006).

References

1. Jagerovic, N.; Gómez de la Oliva, C.; Goya, P.; Dordal, A.; Cuberes, R. Eur. Pat. Appl. 0380 290, 2006.
2. Graham, E. S.; Ashton, J. C.; Glass, M. *Front. Biosci.* **2009**, *14*, 944.

3. Jagerovic, N.; Fernandez-Fernandez, C.; Goya, P. *Curr. Top. Med. Chem.* **2008**, *8*, 205.
4. Marriott, K. S.; Huffman, J. W. *Curr. Top. Med. Chem.* **2008**, *8*, 187.
5. Viveros, M. P.; de Fonseca, F. R.; Bermudez-Silva, F. J.; McPartland, J. M. *Endocr. Metab. Immune Disord. Drug Targets* **2008**, *8*, 220.
6. Di Marzo, V. *Drug Discov. Today* **2008**, *13*, 1026.
7. Le Foll, B.; Gorelick, D.A.; Goldberg, S.R. *Psychopharmacology* **2009**, *205*, 171.
8. Jagerovic, N.; Hernández-Folgado, L.; Alkorta, I.; Goya, P.; Navarro, M.; Serrano, A.; Rodríguez de Fonseca, F.; Dannert, M.T.; Alsasua, A.; Suardiaz, M.; Pascual, D.; Martín, M. I. *J. Med. Chem.* **2004**, *47*, 2939.
9. Pavón, F. J.; Bilbao, A.; Hernández-Folgado, L.; Cippitelli, A.; Jagerovic, N.; Abellan, G.; Rodríguez-Franco, M. I.; Serrano, A.; Macias, M.; Gómez, R.; Navarro, M.; Goya, P.; Rodríguez de Fonseca, F. *Neuropharmacology* **2006**, *51*, 358.
10. Pavón, F. J.; Serrano, A.; Pérez-Valero, V.; Jagerovic, N.; Hernandez-Folgado, L.; Bermudez-Silva, F.J.; Macias, M.; Goya, P; de Fonseca, F. R. *J. Neuroendocrinol.* **2008**, *20*, 116.
a. Appendino, G.; Bacchiega, S.; Minassi, A.; Cascio, M. G.; De Petrocellis, L.; Di Marzo V. *Angew. Chem. Int. Ed.* **2007**, *46*, 9312.
11. Shu, H.; Izenwasser, S.; Wade, D.; Stevens, E. D; Trudell, M. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 891.
12. Hou, D.-R.; Alam, S.; Kuan, T.-C.; Ramanathan, M.; Lin, T.-P.; Hung, M.-S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1022.
13. Tomé, A. C. *Sci. Synth.* **2004**, *13*, 415.
14. Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.
15. Huisgen, R.; Knorr, R.; Mobius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014.
16. Kolb, J. H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128.
17. Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
18. Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171.
19. Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786.
20. Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett.* **2007**, *9*, 1809.
21. Tang, W. J., Hu, Y. Z. *Synth. Commun.* **2006**, *36*, 2461.
22. Krivopalov V. P.; Shkurko O. P. L. *Russ. Chem. Rev.* **2005**, *74*, 339.
23. Hitomi, T.; Kozima, S. *J. Organomet. Chem.* **1977**, *127*, 273.
24. Nguefack, J. F.; Bolitt, V., Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527.
25. Pardo, C; Graf, S.; Ramos, M.; Sesmilo, E.; Elguero, *J. Org. Prep. Proced. Int.* **2000**, *32*, 385.
26. I. Alkorta, J. Elguero, *Computational NMR Spectroscopy*, in J. Grunenberg, Ed. 2010, in press.
27. Blanco, F.; Alkorta, I.; Elguero, J. *Magn. Reson. Chem.* **2007**, *45*, 797.

28. Silva, A. M. S.; Sousa, R. M. S.; Jimeno, M. L.; Blanco, F.; Alkorta, I.; Elguero, J. *Magn.Reson. Chem*. **2008**, *46*, 859.
29. Jagerovic N.; Hernandez-Folgado, L.; Alkorta, I.; Goya, P.; Martín, M. I.; Dannert, M. T.; Alsasua, A.; Frigola, J.; Cuberes, M. R.; dordal, A.; Holenz, J. *Eu. J. Med. Chem.* **2006**, *41*, 114.
30. Dugave, C.; Demange, L. *Chem. Rev*. **2003**, *103*, 2475.
31. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. Becke, A. D. *J. Chem. Phys*. **1993**, *98*, 5648. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
32. Hariharan, P. A.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
33. McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc*. **1972**, *94*, 2625.
34. Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys*. **1971**, *54*, 724. Frisch, M. J.; Pople, J. A.; Krishnam, R.; Binkley, J. S. *J. Chem. Phys*. **1984**, *80*, 3265.
35. Ditchfield, R. *Mol. Phys*. **1974**, *27*, 789. London, F. *J. Phys. Radium* **1937**, *8*, 397.
36. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C. and Pople, J. A. *Gaussian 03*, Gaussian, Inc., Pittsburgh PA, 2003.