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Synthesis of New 1-(But-2-ynyl)pyrazoles Containing a Pyrrolidine or Diethylamine Moiety and Their Muscarinic Properties

The synthesis of two series of 1-(but-2-ynyl)pyrazole containing a pyrrolidine or a diethylamine moiety, respectively, is described, together with their muscarinic receptor affinities.

Keywords: 1-(But-2-ynyl)pyrazoles; Muscarinic properties; Alzheimer's disease

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Introduction

Alzheimer's disease (AD), one of the major challenges facing modern neuropharmacology, is characterised by a vast degeneration of brain cholinergic function and the formation of neurofribrillary tangles and beta amyloid (Aβ) plaques [1]. Extensive efforts have been undertaken in research on cholinomimetic agents that either activate postsynaptic muscarinic receptors (e.g. arecoline, oxotremorine) or inhibit acetylcholinesterase (e.g. tacrine, donepezil), as neurotransmitter replacement therapy and potential treatment for the cognitive symptoms in AD [2]. Since recent research has revealed that muscarinic agonists can actually slow down the progress of AD, halting the formation of both neurofibrillary tangles [3] and Aβ plaques [4], current interest in these drugs has increased.

Oxotremorine (Figure 1) has long been known to act as a potent muscarinic agonist [5], moderately selective for the central nervous system, and since its discovery in 1961 numerous structural modifications have been reported, including aromatic replacement of the pyrrolidine or the pyrrolidinone ring. In this context, the derivative U-80816, in which the pyrrolidine ring of oxotremorine was replaced by an imidazolic framework, showed central cholinergic agonist effects with minimal peripheral side effects [6]. On the other hand, the replacement of the pyrrolidinone ring by an isoxazole yielded compounds that displayed selectivity between the different muscarinic receptor subtypes [7].

Continuing with our work on several heterocyclic families (e.g. 1,2,4-thiadiazolidinones, imidazoles, and pyrazoles) that display acetylcholinesterase inhibition [8–10] or muscarinic properties [11, 12], now we are interested in the synthesis of new oxotremorine-like compounds derived from pyrazoles and pyrrolidine or diethylamine (Figure 1, general formula I) as potential muscarinic agents.

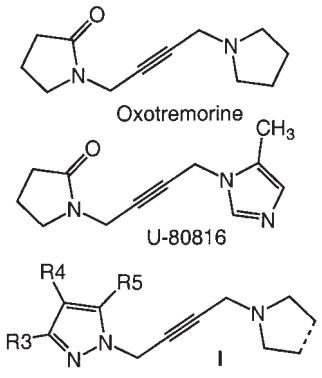

Figure 1

Results and discussion

As shown in Scheme 1, treatment of starting N-unsubstituted pyrazoles with propargyl bromide and a base yielded the corresponding acetylenic intermediates (**1**–**7**), that then were subjected to a Mannich reaction using the appropriate secondary amine, to afford the desired products **8**–**14** (**a**, **b**).

Two general methods were employed for the *N*-alkylation of the pyrazolic ring, depending on the nature of the sub-

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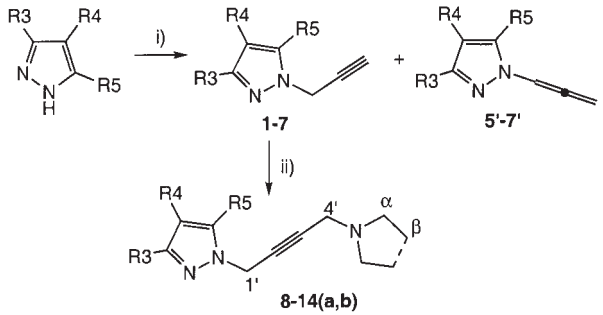

Scheme 1. (i) Propargyl bromide, base. (ii) Pyrrolidine or diethylamine, paraformaldehyde, cuprous chloride (cat.), acetic acid, dioxane.

stituent in the heterocycle. Since in the case of pyrazoles with electron-withdrawing substituents, the pyrazolate anion is easily obtained using a soft base, treatment of 3,5-bis(ethoxycarbonyl)- and 4-benzyloxy-3,5-bis-(ethoxycarbonyl)- with propargyl bromide using potassium carbonate in boiling acetone afforded acetylenic intermediates **1** and **2**, in good yields (92 and 98 %, respectively). When the above mentioned reaction conditions were applied to 3(5)-ethoxycarbonyl-4-nitro-1*H*-pyrazole of non-symmetric structure, the two possible isomers were obtained **3** (3-ethoxycarbonyl-) and **4** (5-ethoxycarbonyl-), also in good yield (39 and 60 %, respectively), as the result of the alkylation in each nitrogen atom.

However, in the case of pyrazoles with alkyl substituents, a stronger base is necessary to deprotonate the pyrazolic ring [13], but this strong base could also promote the acetylenic-allene transposition, affording the corresponding allene as the major product [14]. In fact, then 3,5-dimethylpyrazole was treated with propargyl bromide using sodium hydride as base in boiling dimethylformamide only the allene **5′** was isolated in 35 % yield.

In order to obtain the desired acetylenic intermediate as the major product, several experimental conditions were tested using the simplest 3,5-dimethylpyrazole as starting material (Table 1). The best result was obtained using aqueous sodium hydroxide 1.25 N in the presence of tetrabutylammonium bromide in a biphasic system of toluene and water.

The above optimised conditions were applied to 3(5)-methylpyrazole that, due to its non-symmetric structure, can be alkylated in one pyrazolic nitrogen atom or in the other, afforded mixtures of two isomers. In both cases, the acetylenic derivative was obtained as the major product (**6**: 30 %; **7**: 20 %), although the corresponding allene could also be isolated in minor proportions (**6′**: 6 %; **7′**: 4 %).

Table 1. Reaction between 3,5-dimethylpyrazole and propargyl bromide. Yield of isolated acetylenic (**5**) and allene derivative (**5′**).

Base	Solvent	Temp./Time	**5** (%)	**5′** (%)
NaH	DMF	Reflux/4 h	–	35
NaH	DMF	25 °C/16 h	15	20
NaOH 25 N, TBAB	Tol., H_2O	25 °C/5 h	38	16
NaOH 1.25 N, TBAB	Tol., H_2O	25 °C/24 h	48	–

DMF: Dimethylformamide; TBAB: tetrabutylammonium bromide; Tol: toluene.

Both acetylenic and allenic pyrazoles showed spectroscopic data in agreement with their structures. Complete assignment of all chemical shifts, of special interest for the identification of structural isomers (**3** and **4**; **6** and **7**; **6′** and **7′**), was undertaken using two-dimensional experiments such as heteronuclear single quantum coherence (HSQC) for one-bond correlations, and heteronuclear multiple bond correlation (HMBC) for two and three bond correlations. For instance, compound **6** was identified as the 3-methylpyrazole derivative since there was a HMBC correlation between the acetylenic methylene protons (δ_H = 4.7 ppm) and the protonated pyrazolic carbon 5 (δ_C = 129 ppm). However, in the HMBC diagram of compound **7** the same methylene protons correlated with the non-protonated pyrazolic C-5 (δ_C = 138 ppm), showing that it was the 5-methylpyrazole isomer.

In the ^{1}H NMR spectra of acetylenes **1**–**7** and allenes **5′**–**7′** remarkable differences were observed, both in chemical shifts and in coupling constants (see experimental part). For example, protons belonging to the acetylenic chain showed a constant coupling of approx. 2.5 Hz, whereas the corresponding protons of the allenic derivatives displayed a higher constant (approx. 6.5 Hz).

Treatment of acetylenic intermediates **1**–**7** with pyrrolidine or diethylamine, paraformaldehyde, acetic acid, and a catalytic amount of cuprous chloride in dioxane as solvent gave the desired final oxotremorine-like pyrazoles **8**–**14** (**a**, **b**), that showed spectroscopic data in agreement with their structures, the most significant of which are collected in Table 2. In their ^{1}H-NMR spectra the two methylene groups of the butynyl chain appeared as triplets at 4.7–5.4 and 3.3–3.5 ppm, respectively, with a coupling constant of about 2 Hz. In HMBC experiments, the most deshielded triplet showed a correlation with pyrazolic C5, being assigned to CH_2(1′), whereas the

Table 2. Yields and selected ^{1}H- and ^{13}C-NMR data of oxotremorine-like pyrazoles derived from pyrrolidine (**8**–**14**) **a** and diethylamine (**8**–**14**) **b**.

					^{1}H-NMR		^{13}C-NMR						
	R3	R4	R5	Yield (%)	H1′[a]	H4′[a]	C1′	C2′	C3′	C4′	C5	Cα	Cβ
8 a	CO_2Et	H	CO_2Et	65	5.39	3.34	43.0	81.4	77.3	42.4	133.3	52.3	23.6
8 b	CO_2Et	H	CO_2Et	80	5.41	3.37	42.9	80.4	77.7	40.6	133.1	46.9	12.4
9 a	CO_2Et	OBn[b]	CO_2Et	38	5.31	3.36	44.1	79.0	77.5	43.0	134.5	52.3	23.6
9 b	CO_2Et	OBn[b]	CO_2Et	25	5.30	3.38	44.2	80.6	77.8	40.7	134.4	47.1	12.5
10 a	CO_2Et	NO_2	H	37	4.98	3.35	43.6	85.8	74.1	43.1	129.5	52.7	23.4
10 b	CO_2Et	NO_2	H	39	5.00	3.50	43.7	84.9	75.0	41.0	129.5	47.3	12.3
11 a	H	NO_2	CO_2Et	37	5.09	3.35	43.1	83.3	75.7	42.7	130.8	52.6	23.7
11 b	H	NO_2	CO_2Et	74	5.09	3.34	42.6	82.5	76.0	40.7	130.7	47.1	12.4
12 a	CH_3	H	CH_3	25	4.75	3.34	43.2	80.3	78.2	38.9	138.9	52.5	23.7
12 b	CH_3	H	CH_3	21	4.78	3.42	40.8	79.4	78.6	39.0	138.9	47.2	12.4
13 a	CH_3	H	H	29	4.86	3.43	43.2	82.0	77.1	41.5	129.3	52.7	23.7
13 b	CH_3	H	H	51	4.86	3.44	41.5	81.3	77.8	41.0	129.5	47.3	12.5
14 a	H	H	CH_3	42	4.84	3.35	43.2	81.0	78.7	39.3	138.0	52.6	23.7
14 b	H	H	CH_3	44	4.84	3.35	41.5	81.2	78.4	39.5	138.1	47.5	12.5

[a] Triplet, 2 H, *J* approx. 2 Hz; [b] Bn = $CH_2C_6H_5$.

less deshielded triplet, which displayed connectivity with the first carbon of the amine fragment (Cα), was attributed to CH_2(4′).

The affinities of synthesised oxotremorine-like pyrazoles **8**–**14** (**a**, **b**) for muscarinic receptors were determined by assessing the inhibition of specific [^{3}H]-(*R*)-quinuclidinyl benzilate ([^{3}H]-QNB) binding to rat brain membranes. In general, compounds showed IC_{50} > 100 μM, except compounds collected in Table 3 that displayed moderated affinity for muscarinic receptors in rat central nervous system, being pyrrolidine derivatives (series a) better than diethylamine analogs (series b). In general, pyrazoles with electron-withdrawing substituents displayed better results than pyrazoles with alkyl groups. It is worth mentioning that derivatives **11 a** and **11 b**, with an ethoxycarbonyl group in position 5, showed the best affinities for muscarinic receptors, whereas their corresponding isomers **10 a**, **b** with the same substituent, but in position 3, were inactive. The same effect could be observed in the couple **14 a** (5-methylpyrazole, active) and **13 a** (3-methylpyrazole, inactive). The above finding pointed out that a substituent in position 5 could be useful for the biological activity of these compounds, and this conclusion will be used in future studies.

Table 3. Muscarinic affinities using [^{3}H]-QNB as radioligand.

Compound	IC_{50} (μM)
8 a	57.6 ± 15.0
11 a	45.2 ± 20.0
11 b	40.6 ± 6.4
14 a	80.2 ± 5.9
carbachol[a]	5.5 ± 1.0

[a] Taken from Ref. [15].

From this study we can conclude that oxotremorine-like pyrazoles derived from pyrrolidine (series a), especially with an electron-withdrawing substituent in the pyrazolic position 5, show moderate activity for muscarinic receptors in the rat central nervous system.

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Experimental

Chemistry

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. The following pyrazoles were synthesised according to the literature: 3,5-bis(ethoxycarbonyl)-1*H*-pyrazole [16] and 4-benzyloxy-3,5-bis(ethoxycarbonyl)-1*H*-pyrazole [17]. Chromatographic separations were performed on silica gel, using the following techniques: flash column chromatography (CC, using Kieselgel 60 Merck of 230–400 mesh) and preparative centrifugal thin layer chromatography (CTLC, on a circular plate coated with a 1 mm layer of Kieselgel 60 PF_{254} gipshaltig, Merck, using a Chromatotron®). Compounds were detected with UV light (254 nm), iodine chamber, or ninhydrin.

Nuclear magnetic resonance spectra were recorded in $CDCl_3$ solutions, using Varian Unity-500, Varian XL-300, and Gemini-200 spectrometers. Typical spectral parameters for ^{1}H NMR were: spectral width 10 ppm, pulse width 9 μs (57°), data size 32 K. The acquisition parameters in decoupled ^{13}C NMR spectra were: spectral width 16 kHz, acquisition time 0.99 s, pulse width 9 μs (57°), data size 32 K. Chemical shifts are reported in δ values (ppm) relative to internal Me_4Si and *J* values are reported in hertz. Other experiments such HSQC (Heteronuclear Single-Quantum Coherence) and HMBC (Heteronuclear Multiple Bond Correlation) were obtained in standard conditions. Mass spectra (MS) were obtained by electronic impact (EI) at 70 eV in a Hewlett-Packard 5973 spectrometer (with direct insertion probe) and by atmospheric pressure chemical ionisation (APCI) or electrospray in a Hewlett-Packard MSD 1100 spectrometer. Elemental analyses were carried out in a Perkin-Elmer 240C equipment in the Centro de Química Orgánica 'Manuel Lora-Tamayo' (CSIC) and the results are within ± 0.4 % of the theoretical values.

General procedures for the N-alkylation of pyrazoles

Method A: A mixture of the corresponding pyrazole (10 mmol), propargyl bromide (10 mmol), and K_2CO_3 (10 mmol) in acetone (50 mL) was refluxed for 2–5 hours. Then, crude material was poured into crushed ice (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic solution was dried (Na_2SO_4) and evaporated to dryness *in vacuo* and the residual syrup was purified by chromatography on silica gel, as showed for individual products.

Method B: A mixture of pyrazole (10 mmol), propargyl bromide (10 mmol), and tetrabutylammonium bromide (2 mmol) in toluene (25 mL) was treated with 1.25 N aq. sodium hydroxide (25 mL) at room temperature or reflux, as indicated in each case, until a TLC control did not show starting materials. Then, the organic phase was separated, the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL) and the resulting organic solution was dried and evaporated to dryness *in vacuo*, to give syrups that were purified by chromatography on silica gel, as indicated in each case.

3,5-Bis(ethoxycarbonyl)-1-prop-2-ynyl-1H-pyrazole (**1**)

Reagents and conditions: 3,5-bis(ethoxycarbonyl)-1*H*-pyrazole (500 mg, 2.4 mmol), propargyl bromide (356 mg, 267 μL, 2.4 mmol), K_2CO_3 (332 mg, 2.4 mmol), refluxing acetone, 2 hours (Method A). Purification: CC, hexane:ethyl acetate (4 : 1), R_f = 0.4. Yield 550 mg (92 %). Colourless syrup. Anal. Calcd for $C_{12}H_{14}N_2O_4$ (250.25): C, 57.94; H, 5.64; N, 11.19. Found: C, 57.68; H, 5.72; N, 11.21. ^{1}H-NMR ($CDCl_3$), δ: 7.36 (s, 1 H), 5.42 (d, 2 H, *J* = 2.4 Hz), 4.40 (q, 2 H, *J* = 7.1 Hz), 4.38 (q, 2 H, *J* = 7.1 Hz), 2.38 (t, 1 H, *J* = 2.4 Hz), 1.38 (t, 6 H, *J* =

7.1 Hz). ^{13}C-NMR ($CDCl_3$), δ: 161.3, 158.7, 142.8, 133.4, 114.2, 76.7, 73.9, 61.7, 61.3, 42.5, 14.3, 14.1.

4-Benzyloxy-3,5-bis(ethoxycarbonyl)-1-prop-2-ynyl-1H-pyrazole (**2**)

Reagents and conditions: 4-benzyloxy-3,5-bis(ethoxycarbonyl)-1*H*-pyrazole (193 mg, 0.6 mmol), propargyl bromide (89 mg, 67 µL, 0.6 mmol), K_2CO_3 (84 mg, 0.6 mmol), refluxing acetone, 3 hours (Method A). Purification: CC, hexane : ethyl acetate (1 : 1), R_f = 0.7. Yield 210 mg (98 %). Colourless syrup. Anal. Calcd for $C_{19}H_{20}N_2O_5$ (356.39): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.15; H, 5.72; N, 7.90. ^{1}H-NMR ($CDCl_3$), δ: 7.48–7.29 (m, 5 H), 5.31 (d, 2 H, *J* = 2.5 Hz), 5.11 (s, 2 H), 4.40 (q, 2 H, *J* = 7.2 Hz), 4.33 (q, 2 H, *J* = 7.2 Hz), 2.38 (t, 1 H, *J* = 2.5 Hz), 1.36 (t, 6 H, *J* = 7.2 Hz), 1.32 (t, 6 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 160.5, 158.4, 147.6, 136.4, 134.8, 128.2, 128.1, 128.0, 124.8, 77.5, 76.8, 73.9, 61.4, 61.0, 43.5, 14.3, 13.9.

3-Ethoxycarbonyl-4-nitro-1-prop-2-ynyl-1H-pyrazole (**3**) *and 5-ethoxycarbonyl-4-nitro-1-prop-2-ynyl-1H-pyrazole* (**4**)

Reagents and conditions: 3(5)-ethoxycarbonyl-4-nitro-1*H*-pyrazole (900 mg, 4.9 mmol), propargyl bromide (734 mg, 550 µL, 4.9 mmol), K_2CO_3 (672 mg, 4.9 mmol), refluxing acetone, 2 hours (Method A). Purification: CC, hexane : ethyl acetate (3 : 1).

3: R_f = 0.5. Yield 424 mg (39 %). Colourless syrup. Anal. Calcd for $C_9H_9N_3O_4$ (223.19): C, 48.43; H, 4.06; N, 18.83. Found: C, 48.59; H, 3.97; N, 18.90. ^{1}H-NMR ($CDCl_3$), δ: 7.93 (s, 1 H), 5.03 (d, 2 H, *J* = 2.7 Hz), 4.34 (q, 2 H, *J* = 7.2 Hz), 2.46 (t, 1 H, *J* = 2.7 Hz), 1.29 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 157.5, 135.2, 134.5, 130.6, 75.2, 74.9, 63.2, 42.0, 13.4.

4: R_f = 0.4. Yield 663 mg (60 %). Colourless syrup. Anal. Calcd for $C_9H_9N_3O_4$ (223.19): C, 48.43; H, 4.06; N, 18.83. Found: C, 48.31; H, 4.17; N, 18.72. ^{1}H-NMR ($CDCl_3$), δ: 8.42 (s, 1 H), 4.99 (d, 2 H, *J* = 2.5 Hz), 4.40 (q, 2 H, *J* = 7.2 Hz), 2.49 (t, 1 H, *J* = 2.5 Hz), 1.29 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 159.8, 139.1, 134.1, 129.7, 77.6, 73.8, 62.5, 43.2, 13.8.

3,5-Dimethyl-1-prop-2-ynyl-1H-pyrazole (**5**) [18]

Reagents and conditions: 3,5-dimethyl-1*H*-pyrazole (1.5 g, 15.6 mmol), propargyl bromide (2.3 g, 1.7 mL, 15.6 mmol), tetrabutylammonium bromide (1.26 g, 4.0 mmol), NaOH 1.25 N (10 mL), toluene (50 mL), room temperature, 24 hours (Method B). Eluent: hexane : ethyl acetate (5 : 1), R_f = 0.5. Yield 1.0 g (48 %). Colourless syrup. Anal. Calcd for $C_8H_{10}N_2$ (134.18): C, 71.61; H, 7.51; N, 20.87. Found: C, 71.50; H, 7.34; N, 21.16. ^{1}H-NMR ($CDCl_3$), δ: 5.74 (s, 1 H), 4.68 (d, 2 H, *J* = 2.5 Hz), 2.28 (t, 1 H, *J* = 2.5 Hz), 2.21 (s, 3 H), 2.13 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 147.9, 139.0, 105.8, 77.4, 72.9, 38.4, 13.3, 10.8. EM (EI, 70 eV), *m/z* : 133 (100 %), 134 (M^+, 56 %).

3,5-Dimethyl-1-propa-1,2-dienyl-1H-pyrazole (**5′**)

To a suspension of NaH (104 mg, 2.6 mmol) and 3,5-dimethyl-1*H*-pyrazole (250 mg, 2.6 mmol) in DMF (10 mL), a solution of propargyl bromide (0.3 mL, 2.6 mmol) in DMF (2 mL) was added, and the mixture was refluxed for 4 hours. Solvent was evaporated to dryness and the crude material was redisolved in CH_2Cl_2 (20 mL), washed with H_2O (20 mL) and the organic solution was dried (Na_2SO_4) and evaporated to dryness, yielding a syrup that was purified on a silica gel column, using CH_2Cl_2 : CH_3OH (10 : 1) as eluent. From fractions of R_f = 0.6 allene **5′** was isolated as a pure colourless syrup (120 mg, 35 % yield). Anal. Calcd for $C_8H_{10}N_2$ (134.18): C, 71.61; H, 7.51; N, 20.87. Found: C, 71.48; H, 7.44; N, 21.08. ^{1}H-NMR ($CDCl_3$), δ: 6.91 (t, 1 H, *J* = 6.4 Hz), 5.77 (s, 1 H), 5.47 (d, 2 H, *J* = 6.4 Hz), 2.18 (s, 3 H), 2.15 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 202.8, 149.2, 139.3, 106.6, 98.4, 86.8, 13.3, 11.3.

3-Methyl-1-prop-2-ynyl-1H-pyrazole (**6**), *5-methyl-1-prop-2-ynyl-1H-pyrazole* (**7**), *3-methy-1-propa-1,2-dienyl-1H-pyrazole* (**6′**), *and 5-methyl-1-propa-1,2-dienyl-1H-pyrazole* (**7′**)

Reagents and conditions: 3(5)-methyl-1*H*-pyrazole (1.0 g, 11.6 mmol), propargyl bromide (1.34 g, 1.0 mL, 11.6 mmol), tetrabutylammonium bromide (748 mg, 2.3 mmol), NaOH 1.25 N (16 mL), toluene (60 mL), room temperature, 48 hours (Method B). A flash column chromatography using as eluent mixtures of hexane:ethyl acetate of increasing polarity, 50 : 1 (ca. 250 mL), 25 : 1 (ca. 250 mL), 14.1 (ca. 200 mL), and 7 : 1 (ca. 200 mL), gave two fractions, each composed of a mixture of two compounds. The first band afforded the allenic isomers **6′** and **7′** (190 mg), and the second band yielded the mixture of the acetylenic intermediates **6** and **7** (830 mg).

The mixture of **6′** and **7′** was then separated into its single components by a centrifugal circular thin layer chromatography, using the following mixtures of hexane:ethyl acetate, 100 : 1 (ca. 100 mL), 75 : 1 (ca. 50 mL), and 50 : 1 (ca. 50 mL).

6′: Colourless syrup, yield 84 mg (6 %), R_f = 0.7 (hexane : ethyl acetate, 20 : 1). Anal. Calcd for $C_7H_8N_2$ (120.15): C, 69.98; H, 6.70; N, 23.31. Found: C, 69.59; H, 7.05; N, 23.36. ^{1}H-NMR ($CDCl_3$), δ: 7.38 (t, 1 H, *J* = 2.3 Hz), 7.06 (t, 1 H, *J* = 6.4 Hz), 6.09 (d, 1 H, *J* = 2.3 Hz), 5.56 (d, 2 H, *J* = 6.4 Hz), 2.26 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 202.5, 149.2, 129.3, 105.3, 98.2, 86.5, 13.2.

7′: Colourless syrup, yield 35 mg (4 %), R_f = 0.6 (hexane : ethyl acetate, 20 : 1). Anal. Calcd for $C_7H_8N_2$ (120.15): C, 69.98; H, 6.70; N, 23.31. Found: C, 69.77; H, 7.00; N, 23.23. ^{1}H-NMR ($CDCl_3$), δ: 7.40 (d, 1 H, *J* = 1.7 Hz), 7.04 (t, 1 H, *J* = 6.5 Hz), 6.00 (d, 1 H, *J* = 1.7 Hz), 5.51 (d, 2 H, *J* = 6.5 Hz), 2.27 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 203.1, 138.6, 138.1, 106.6, 98.7, 87.0, 11.5.

Centrifugal circular thin layer chromatography of the mixture of the acetylenic intermediates **6** and **7**, using as eluent hexane: ethyl acetate of increasing polarity, 50 : 1 (ca. 100 mL), 25 : 1 (ca. 100 mL), and 7 : 1 (ca. 50 mL), allowed the isolation of both compounds.

6: Colourless syrup, yield 413 mg (30 %), R_f = 0.3 (hexane : ethyl acetate, 7 : 1). Anal. Calcd for $C_7H_8N_2$ (120.15): C, 69.98; H, 6.70; N, 23.31. Found: C, 69.80; H, 7.01; N, 23.31. ^{1}H-NMR ($CDCl_3$), δ: 7.31 (d, 1 H, *J* = 1.7 Hz), 5.906 (d, 1 H, *J* = 1.7 Hz), 4.68 (d, 2 H, *J* = 2.6 Hz), 2.36 (t, 1 H, *J* = 2.6 Hz), 2.12 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 148.8, 129.1, 105.3, 76.7, 74.0, 40.7, 13.1. EM (EI, 70 eV), *m/z* : 119 (100 %), 120 (M^+, 53 %).

7: Colourless syrup, yield 293 mg (20 %), R_f = 0.2 (hexane : ethyl acetate, 7 : 1). Anal. Calcd for $C_7H_8N_2$ (120.15): C, 69.98; H, 6.70; N, 23.31. Found: C, 70.01; H, 6.82; N, 23.17. ^{1}H-NMR ($CDCl_3$), δ: 7.29 (d, 1 H, *J* = 2.0 Hz), 5.94 (d, 1 H, *J* = 2.0 Hz), 4.75 (d, 2 H, *J* = 2.5 Hz), 2.31 (t, 1 H, *J* = 2.5 Hz), 2.25 (s, 3 H). ^{13}C-NMR ($CDCl_3$), δ: 138.6, 138.0, 105.8, 77.0, 73.2, 38.7, 10.7. EM (EI, 70 eV), *m/z* : 119 (100 %), 120 (M^+, 52 %).

General method for preparing 1-(4-pyrrolidin-1-yl-but-2-ynyl)-pyrazoles (series a) and diethyl-[4-(1H-pyrazol-1-yl)-but-2-ynyl]-amines (series b)

To a mixture of paraformaldehyde (10 mmol), acetic acid (10 mmol), and copper (I) chloride (0.18 mmol) in anhydrous dioxane (20 mL), a solution of the amine (10 mmol) in dioxane (10 mL) was added, and the resulting mixture was stirred to

room temperature for 30 minutes. Then, a solution of the corresponding 1-prop-2-ynyl-1*H*-pyrazole (10 mmol) in dry dioxane (10 mL) was added and the mixture was refluxed for 2–10 hours. Solvent was evaporated to dryness *in vacuo* and the resulting crude material was redissolved in water (50 mL), neutralized with aq. K_2CO_3, extracted with CH_2Cl_2 (3 × 50 mL) and dried with Na_2SO_3. Evaporation of the organic layer yielded crude syrups that were purified on column chromatography (CC) or centrifugal thin layer chromatography (CTLC), as indicated for individual products.

3,5-Bis(ethoxycarbonyl)-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**8 a**)

Reagents and conditions: **1** (70 mg, 0.26 mmol), pyrrolidine (24 µL, 0.28 mmol), paraformaldehyde (8 mg, 0.28 mmol), acetic acid (15 µL, 0.28 mmol), CuCl (0.5 mg, 0.005 mmol), refluxing dioxane 4 hours. Purification: CTLC (ethyl acetate : methanol, 8 : 1). Yield 60 mg (65 %). Colourless syrup. Anal. Calcd for $C_{17}H_{23}N_3O_4$ (333.39): C, 61.25; H, 6.95; N, 12.60. Found: C, 61.31; H, 6.73; N, 19.88. ^{1}H-NMR ($CDCl_3$), δ: 7.32 (s, 1 H), 5.39 (t, 2 H, *J* = 1.9 Hz), 4.32 (q, 4 H, *J* = 7.1 Hz), 3.34 (t, 2 H, *J* = 1.9 Hz), 2.50 (t, 4 H, *J* = 6.6 Hz), 1.72 (q, 4 H, *J* = 6.6 Hz), 1.35 (t, 6 H, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$), δ: 161.3, 158.6, 142.5, 133.3, 114.1, 81.4, 77.3, 61.5, 61.2, 52.3, 43.0, 42.4, 23.6, 14.2, 14.1.

Diethyl-{4-[3,5-bis(ethoxycarbonyl)-1H-pyrazol-1-yl]-but-2-ynyl}-amine (**8 b**)

Reagents and conditions: **1** (100 mg, 0.4 mmol), diethylamine (45 µL, 0.4 mmol), paraformaldehyde (13 mg, 0.4 mmol), acetic acid (24 µL, 0.4 mmol), CuCl (0.8 mg, 0.008 mmol), refluxing dioxane 2 hours. Purification: CC (ethyl acetate), R_f = 0.2. Yield 103 mg (80 %). Colourless syrup. Anal. Calcd for $C_{17}H_{25}N_3O_4$ (335.41): C, 60.88; H, 7.51; N, 12.53. Found: C, 60.92; H, 7.65; N, 12.69. ^{1}H-NMR ($CDCl_3$), δ: 7.35 (s, 1 H), 5.41 (s, 2 H), 4.36 (q, 4 H, *J* = 7.2 Hz), 3.37 (s, 2 H), 2.45 (q, 4 H, *J* = 7.1 Hz), 1.38 (t, 6 H, *J* = 7.2 Hz), 0.99 (t, 6 H, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$), δ: 161.2, 158.5, 142.4, 133.1, 114.1, 80.4, 77.7, 61.4, 61.1, 46.9, 42.9, 40.6, 14.2, 14.0, 12.4. EM (IE 70 eV), *m/z* : 123 (100 %), 335 (M^+, 1 %).

4-Benzyloxy-3,5-bis(ethoxycarbonyl)-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**9 a**)

Reagents and conditions: **2** (100 mg, 0.28 mmol), pyrrolidine (26 µL, 0.31 mmol), paraformaldehyde (9.3 mg, 0.31 mmol), acetic acid (17 µL, 0.31 mmol), CuCl (0.6 mg, 0.006 mmol), refluxing dioxane 4 hours. Purification: CC (ethyl acetate : methanol, 20 : 1), R_f = 0.4. Yield 28 mg (38 %). Colourless syrup. Anal. Calcd for $C_{24}H_{29}N_2O_5$ (425.51): C, 67.75; H, 6.89; N, 6.58. Found: C, 67.65; H, 6.73; N, 6.55. ^{1}H-NMR ($CDCl_3$), δ: 7.47–7.28 (m, 5 H), 5.31 (t, 2 H, *J* = 2.0 Hz), 5.10 (s, 2 H), 4.36 (q, 2 H, *J* = 7.2 Hz), 4.32 (q, 2 H, *J* = 7.2 Hz), 3.36 (t, 2 H, *J* = 2.0 Hz), 2.52 (t, 4 H, *J* = 6.6 Hz), 1.73 (q, 4 H, *J* = 6.6 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 160.7, 158.4, 147.7, 136.5, 134.5, 128.3, 128.2, 128.1, 124.9, 79.0, 77.6, 77.5, 61.4, 61.1, 52.3, 44.1, 43.0, 23.6, 14.3, 14.1.

Diethyl-{4-[4-benzyloxy-3,5-bis(ethoxycarbonyl)-1H-pyrazol-1-yl]-but-2-ynyl}-amine (**9 b**)

Reagents and conditions: **2** (97 mg, 0.27 mmol), diethylamine (31 µL, 0.30 mmol), paraformaldehyde (9 mg, 0.30 mmol), acetic acid (16 µL, 0.30 mmol), CuCl (0.6 mg, 0.006 mmol), refluxing dioxane 4 hours. Purification: CC (ethyl acetate), R_f = 0.3. Yield 30 mg (25 %). Colourless syrup. Anal. Calcd for $C_{24}H_{31}N_2O_5$ (427.52): C, 67.43; H, 7.31; N, 6.55. Found: C, 67.25; H, 7.40; N, 6.75. ^{1}H-NMR ($CDCl_3$), δ: 7.47–7.29 (m, 5 H), 5.30 (t, 2 H, *J* = 1.7 Hz), 5.11 (s, 2 H), 4.40 (q, 2 H, *J* = 7.2 Hz), 4.33 (q, 2 H, *J* = 7.2 Hz), 3.38 (t, 2 H, *J* = 1.7 Hz), 2.45 (q, 4 H, *J* = 7.2 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.33 (t, 3 H, *J* = 7.2 Hz), 0.99 (q, 4 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 160.7, 158.4, 147.7, 136.5, 134.4, 128.3, 128.2, 128.1, 124.9, 80.6, 77.8, 77.6, 61.5, 61.2, 47.1, 44.2, 40.7, 14.3, 14.1, 12.5.

3-Ethoxycarbonyl-4-nitro-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**10 a**)

Reagents and conditions: **3** (100 mg, 0.49 mmol), pyrrolidine (41 µL, 0.49 mmol), paraformaldehyde (15 mg, 0.49 mmol), acetic acid (27 µL, 0.49 mmol), CuCl (1 mg, 0.01 mmol), refluxing dioxane 3 hours. Purification: CC (ethyl acetate : methanol, 10 : 1), R_f = 0.2. Yield 51 mg (37 %). Colourless syrup. Anal. Calcd for $C_{14}H_{18}N_4O_4$ (306.32): C, 54.89; H, 5.92; N, 18.29. Found: C, 54.95; H, 5.73; N, 18.10. ^{1}H-NMR ($CDCl_3$), δ: 8.38 (s, 1 H), 4.98 (s, 2 H), 4.39 (q, 2 H, *J* = 7.2 Hz), 3.35 (s, 2 H), 2.56 (t, 4 H, *J* = 6.4 Hz), 1.34 (q, 4 H, *J* = 6.4 Hz), 1.30 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 159.8, 139.0, 134.1, 129.5, 85.8, 74.1, 62.3, 52.7, 43.6, 43.1, 23.4, 13.8. EM (electrospray): 307 (MH^+).

Diethyl-[4-(3-ethoxycarbonyl-4-nitro-1H-pyrazol-1-yl)-but-2-ynyl]-amine (**10 b**)

Reagents and conditions: **3** (100 mg, 0.49 mmol), diethylamine (50 µL, 0.49 mmol), paraformaldehyde (15 mg, 0.49 mmol), acetic acid (27 µL, 0.49 mmol), CuCl (1 mg, 0.01 mmol), refluxing dioxane 3 hours. Purification: CC (ethyl acetate : methanol, 10 : 1), R_f = 0.5. Yield 54 mg (39 %). Colourless syrup. Anal. Calcd for $C_{14}H_{20}N_4O_4$ (308.34): C, 54.56; H, 6.54; N, 18.17. Found: C, 54.31; H, 6.69; N, 18.22. ^{1}H-NMR ($CDCl_3$), δ: 8.39 (s, 1 H), 5.00 (s, 2 H), 4.39 (q, 2 H, *J* = 7.2 Hz), 3.50 (s, 2 H), 2.52 (q, 4 H, *J* = 7.2 Hz), 1.35 (t, 3 H, *J* = 7.2 Hz), 1.04 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 159.8, 139.0, 134.1, 129.5, 84.9, 75.0, 62.5, 43.7, 47.3, 41.0, 13.9, 12.3. EM (electrospray): 309 (MH^+).

5-Ethoxycarbonyl-4-nitro-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**11 a**)

Reagents and conditions: **4** (90 mg, 0.4 mmol), pyrrolidine (37 µL, 0.44 mmol), paraformaldehyde (13 mg, 0.44 mmol), acetic acid (24 µL, 0.44 mmol), CuCl (0.8 mg, 0.008 mmol), refluxing dioxane 5 hours. Purification: CC (ethyl acetate : methanol, 20 : 1), R_f = 0.4. Yield 45 mg (37 %). Colourless syrup. Anal. Calcd for $C_{14}H_{18}N_4O_4$ (306.32): C, 54.89; H, 5.92; N, 18.29. Found: C, 55.03; H, 5.73; N, 18.20. ^{1}H-NMR ($CDCl_3$), δ: 7.97 (s, 1 H), 5.09 (s, 2 H), 4.43 (q, 2 H, *J* = 7.2 Hz), 3.35 (s, 2 H), 2.51 (m, 4 H), 1.73 (m, 4 H), 1.33 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 157.9, 135.4, 135.2, 130.8, 83.3, 75.7, 63.4, 52.6, 43.1, 42.7, 23.7, 13.7. EM (electrospray): 307 (MH^+).

Diethyl-[4-(5-ethoxycarbonyl-4-nitro-1H-pyrazol-1-yl)-but-2-ynyl]-amine (**11 b**)

Reagents and conditions: **4** (90 mg, 0.40 mmol), diethylamine (45 µL, 0.44 mmol), paraformaldehyde (13 mg, 0.44 mmol), acetic acid (24 µL, 0.44 mmol), CuCl (0.8 mg, 0.008 mmol), refluxing dioxane 5 hours. Purification: CC (ethyl acetate : methanol, 10 : 1), R_f = 0.5. Yield 92 mg (74 %). Colourless syrup. Anal. Calcd for $C_{14}H_{20}N_4O_4$ (308.34): C, 54.56; H, 6.54; N, 18.17. Found: C, 54.66; H, 6.29; N, 18.31. ^{1}H-NMR ($CDCl_3$), δ: 7.97 (s, 1 H), 5.09 (s, 2 H), 4.45 (q, 2 H, *J* = 7.2 Hz), 3.34 (s, 2 H), 2.45 (q, 4 H, *J* = 7.2 Hz), 1.36 (t, 3 H, *J* = 7.2 Hz), 0.96 (t, 3 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 157.8, 135.3, 135.1, 130.7, 82.5, 76.0, 63.3, 47.1, 42.6, 40.7, 13.6, 12.4. EM (electrospray): 309 (MH^+).

3,5-Dimethyl-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**12 a**)

Reagents and conditions: **5** (150 mg, 1.12 mmol), pyrrolidine (102 µL, 1.23 mmol), paraformaldehyde (37 mg, 1.23 mmol), acetic acid (67 µL, 1.23 mmol), CuCl (2 mg, 0.02 mmol), refluxing dioxane 4 hours. Purification: CC (ethyl acetate : methanol, 20 : 1), R_f = 0.2. Yield 60 mg (25 %). Colourless syrup. Anal. Calcd for $C_{13}H_{19}N_3$ (217.31): C, 71.85; H, 8.81; N, 19.34. Found: C, 71.92; H, 8.56; N, 19.52. ^{1}H-NMR ($CDCl_3$), δ: 5.78 (s, 1 H), 4.75 (t, 2 H, *J* = 2.0 Hz), 3.34 (t, 2 H, *J* = 2.0 Hz), 2.56–2.48 (m, 4 H), 2.26 (s, 3 H), 2.17 (s, 3 H), 1.78–1.71 (m, 4 H). ^{13}C-NMR ($CDCl_3$), δ: 147.7, 138.9, 105.7, 80.3, 78.2, 52.5, 43.2, 38.9, 23.7, 13.4, 11.0.

Diethyl-[4-(3,5-dimethyl-1H-pyrazol-1-yl)-but-2-ynyl]-amine (**12 b**)

Reagents and conditions: **5** (109 mg, 0.44 mmol), diethylamine (55 µL, 0.48 mmol), paraformaldehyde (15 mg, 0.5 mmol), acetic acid (26 µL, 0.48 mmol), CuCl (1 mg, 0.01 mmol), refluxing dioxane 5 hours. Purification: CC (ethyl acetate : methanol, 10 : 1), R_f = 0.2. Yield 20 mg (21 %). Colourless syrup. Anal. Calcd for $C_{13}H_{21}N_3$ (219.33): C, 71.19; H, 9.65; N, 19.16. Found: C, 71.32; H, 9.47; N, 19.21. ^{1}H-NMR ($CDCl_3$), δ: 5.79 (s, 1 H), 4.78 (t, 2 H, *J* = 2.0 Hz), 3.42 (t, 2 H, *J* = 2.0 Hz), 2.52 (q, 4 H, *J* = 7.2 Hz), 2.28 (s, 3 H), 2.19 (s, 3 H), 1.03 (t, 6 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 147.7, 138.9, 105.7, 79.4, 78.6, 47.2, 40.8, 39.0, 13.4, 12.4, 11.0.

3-Methyl-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**13 a**)

Reagents and conditions: **6** (105 mg, 0.9 mmol), pyrrolidine (80 µL, 0.96 mmol), paraformaldehyde (29 mg, 0.96 mmol), acetic acid (53 µL, 0.96 mmol), CuCl (1.8 mg, 0.018 mmol), refluxing dioxane 10 hours. Purification: CC (ethyl acetate : methanol, 15 : 1). Yield 52 mg (29 %). Colourless syrup. Anal. Calcd for $C_{12}H_{17}N_3$ (203.29): C, 70.90; H, 8.43; N, 20.67. Found: C, 71.25; H, 8.16; N, 20.59. ^{1}H-NMR ($CDCl_3$), δ: 7.45 (1H, d, *J* = 2.1 Hz), 6.01 (1 H, d, *J* = 2.1 Hz), 4.86 (t, 2 H, *J* = 2.0 Hz), 3.43 (t, 2 H, *J* = 2.0 Hz), 2.59–2.50 (m, 4 H), 2.24 (s, 3 H), 1.78–1.71 (m, 4 H). ^{13}C-NMR ($CDCl_3$), δ: 149.0, 129.3, 105.4, 82.0, 77.1, 52.7, 43.2, 41.5, 23.7, 13.5. EM (electrospray), *m/z* : 204 (MH^+).

Diethyl-[4-(3-methyl-1H-pyrazol-1-yl)-but-2-ynyl]-amine (**13 b**)

Reagents and conditions: **6** (29 mg, 0.24 mmol), diethylamine (27 µL, 0.26 mmol), paraformaldehyde (7.8 mg, 0.26 mmol), acetic acid (13 µL, 0.26 mmol), CuCl (0.5 mg, 0.005 mmol), refluxing dioxane 3 hours. Purification: CC (ethyl acetate : methanol, 15 : 1). Yield 25 mg (51 %). Colourless syrup. Anal. Calcd for $C_{12}H_{19}N_3$ (205.30): C, 70.20; H, 9.33; N, 20.47. Found: C, 70.35; H, 9.46; N, 20.19. ^{1}H-NMR ($CDCl_3$), δ: 7.47 (1 H, d, *J* = 2.2 Hz), 6.03 (1 H, d, *J* = 2.2 Hz), 4.86 (t, 2 H, *J* = 2.0 Hz), 3.44 (t, 2 H, *J* = 2.0 Hz), 2.51 (q, 4 H, *J* = 7.2 Hz), 2.25 (s, 3 H), 1.04 (t, 6 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 149.0, 129.2, 105.4, 81.3, 77.8, 47.3, 41.5, 41.0, 13.5, 12.5.

5-Methyl-1-(4-pyrrolidin-1-yl-but-2-ynyl)-1H-pyrazole (**14 a**)

Reagents and conditions: **7** (97 mg, 0.8 mmol), pyrrolidine (74 µL, 0.90 mmol), paraformaldehyde (27 mg, 0.90 mmol), acetic acid (48 µL, 0.90 mmol), CuCl (1.6 mg, 0.016 mmol), refluxing dioxane 10 hours. Purification: CC (ethyl acetate : methanol, 15 : 1). Yield 68 mg (42 %). Colourless syrup. Anal. Calcd for $C_{12}H_{17}N_3$ (203.29): C, 70.90; H, 8.43; N, 20.67. Found: C, 70.61; H, 8.39; N, 21.00. ^{1}H-NMR ($CDCl_3$), δ: 7.33 (d, 1 H, *J* = 1.6 Hz), 5.98 (d, 1 H, *J* = 1.6 Hz), 4.84 (t, 2 H, *J* = 2.0 Hz), 3.35 (t, 2 H, *J* = 2.0 Hz), 2.56–2.50 (m, 4 H), 2.31 (s, 3 H), 1.78–1.71 (m, 4 H). ^{13}C-NMR ($CDCl_3$), δ: 138.6, 138.0, 105.8, 81.0, 78.7, 52.6, 43.2, 39.3, 23.7, 11.0, EM(electrospray), *m/z* : 204 (MH^+).

Diethyl-[4-(5-methyl-1H-pyrazol-1-yl)-but-2-ynyl]-amine (**14 b**)

Reagents and conditions: **7** (40 mg, 0.33 mmol), diethylamine (38 µL, 0.37 mmol), paraformaldehyde (11 mg, 0.37 mmol), acetic acid (20 µL, 0.37 mmol), CuCl (0.7 mg, 0.007 mmol), refluxing dioxane 3 hours. Purification: CC (ethyl acetate : methanol, 15 : 1). Yield 30 mg (44 %). Colourless syrup. Anal. Calcd for $C_{12}H_{19}N_3$ (205.30): C, 70.20; H, 9.33; N, 20.47. Found: C, 70.42; H, 9.21; N, 20.37. ^{1}H-NMR ($CDCl_3$), δ: 7.35 (1 H, d, *J* = 1.6 Hz), 6.00 (1 H, d, *J* = 1.6 Hz), 4.84 (t, 2 H, *J* = 2.0 Hz), 3.35 (t, 2 H, *J* = 2.0 Hz), 2.49 (q, 4 H, *J* = 7.2 Hz), 2.30 (s, 3 H), 1.07 (t, 6 H, *J* = 7.2 Hz). ^{13}C-NMR ($CDCl_3$), δ: 138.6, 138.1, 105.8, 81.2, 78.4, 47.5, 41.5, 39.5, 12.5, 11.2.

Pharmacology

Muscarinic receptor binding studies were carried out by evaluating the ability of compounds **8**–**14** (**a**, b), as free bases, to compete with 50 pM [^{3}H]-(*R*)-quinuclidinyl benzilate in a suspension of brain membranes, as previously described [19]. The IC_{50} values were determined from displacement curves and the values are here reported as means ± SEM of three independent experiments, each performed in triplicate.

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