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Synthesis and Muscarinic Activities of *O*-[(Benzyl- or Benzoyl-pyrazolyl)propynyl]-oximes of *N*-Methylpiperidinone, 3-Tropinone, and 3-Quinuclidinone

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Dedicated to the memory of our dear colleague Dr Manfred Stud.

Abstract—The synthesis of *O*-propynyloximes of *N*-methylpiperidinone, 3-tropinone, and 3-quinuclidinone, containing several pyrazole frameworks is described, together with their muscarinic receptor affinities. Compounds derived from *N*-methylpiperidinone or 3-tropinone and *N*-(4-methoxybenzyl)- or *N*-(2,4,6-trimethylbenzoyl)pyrazole showed moderate activity for muscarinic receptors in the rat central nervous system. A semi-empirical AM1 calculation has shown that the *O*-[(benzoyl-pyrazolyl)propynyl]-oximes of tropinone fit a previously described muscarinic pharmacophoric model, revealing structural features useful for the development of new muscarinic agents.

Introduction

In recent years, considerable research efforts have been devoted to the design of muscarinic M_1 agonists for the treatment of Alzheimer's disease (AD),[1,2] a progressive and irreversible neurodegenerative disease, and one of the major challenges facing modern neuropharmacology. The potential use of muscarinic agonists is based on two complementary approaches. Firstly, the cholinergic hypothesis of memory dysfunction[3] is based on drugs that through the activation of muscarinic receptors reduce the neurotransmitter deficit and provide a palliative treatment for AD.[4] Secondly, the finding that muscarinic agonists can prevent the formation of both neurofibrillary tangles and amyloid plaques,[5] the two prominent histopathogical lesions observed in the brain of AD patients. Accordingly, it has been described that several muscarinic agonists, like xanomeline[6] and AF102B,[7] are effective in reducing tau phosphorylation through protein kinase C activation or by GSK-3β inhibition. On the other hand, other muscarinic agents, like talsaclidine[8] and CI-1017,[9] promote the non-amyloidogenic APP processing pathways decreasing the cerebrospinal fluid levels of total amyloid β-peptide in patients.[10]

Continuing with our research on different heterocyclic families (e.g., 1,2,4-thiadiazolidinones, imidazoles, and pyrazoles) of potential application in Alzheimer's disease,[11–17] and considering the muscarinic properties found in several propargylic oxime ethers,[18,19] in this work we wish to report the synthesis and muscarinic affinities of *O*-(arylpyrazolyl)propynyloximes of *N*-methylpiperidinone, tropinone, and quinuclidinone (Fig. 1, general formula I), well-known tertiary amines used in previously described muscarinic agonists.[20–22]

Results and Discussion

The synthesis of *O*-[(pyrazol-4-yl)-2-propyn-1-yl]oximes of *N*-methylpiperidinone, tropinone (8-methyl-8-azabicyclo[3.2.1]octan-3-one), and quinuclidinone (1-azabicyclo[2.2.2]octan-3-one) is outlined in Scheme 1.

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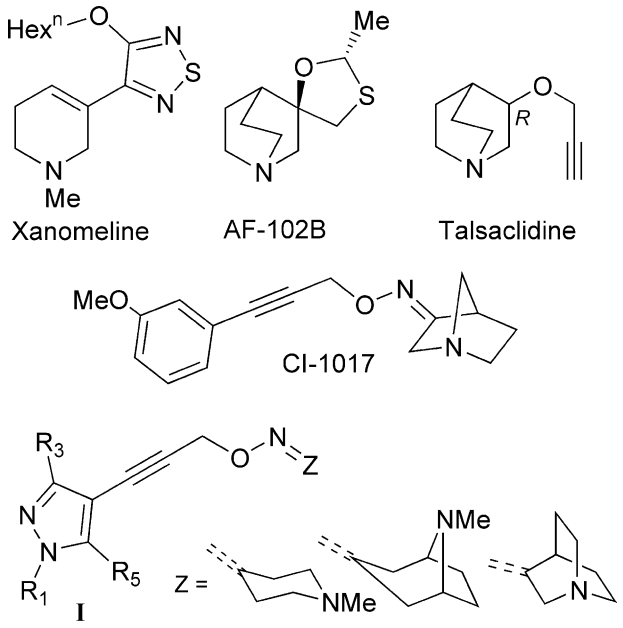


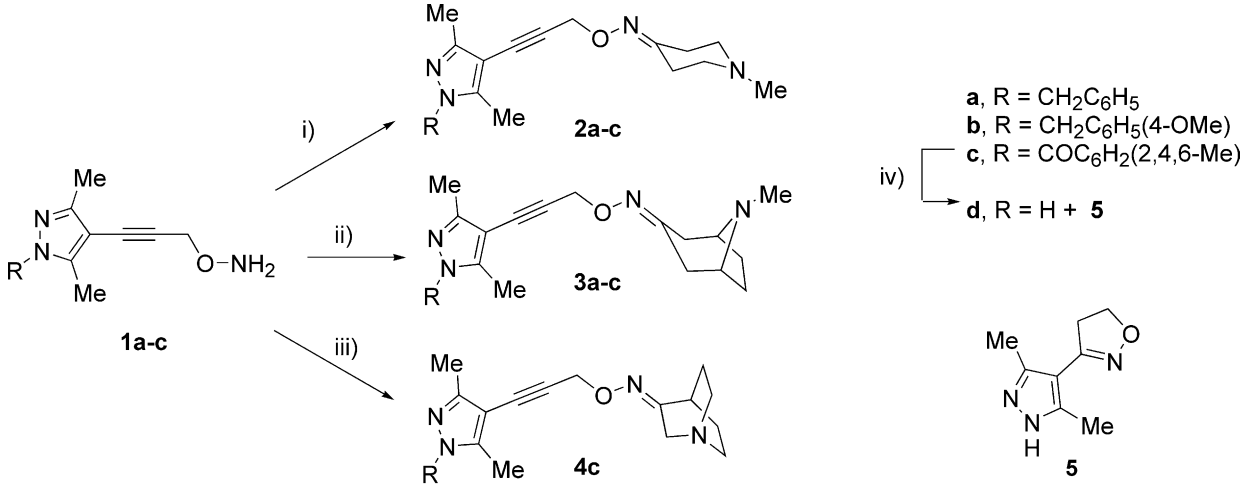
Figure 1.

O-(*N*-Substituted-pyrazolylpropynyl)-hydroxylamines **1a–c** were synthesized in good yields using an optimised Pd/Cu-catalyzed cross-coupling reaction of 4-iodopyrazoles with 2-propyn-1-ol, followed by a Mitsunobu transformation with *N*-hydroxyphthalimide and subsequent hydrazinolysis, as previously described by us.[23,24] Condensation of the above *N*-substituted pyrazole intermediates **1a–c**, with different ketones in methanol at room temperature afforded the corresponding *O*-(*N*-substituted-pyrazolylpropynyl)-oximes **2a–c**, **3a–c** and **4c** in good yields (40–69%).

Finally, removal of the 2,4,6-trimethylbenzoyl group in the pyrazole nitrogen of **2–4c** gave the corresponding *N*H-substituted derivatives **2–4d**. However, preliminary experiments using 5 M aq NaOH in refluxing methanol, as previously described for related pyrazoles,[25] afforded the isoxazoline **5** as the major product. The formation of this compound can be explained as the result of the hydrolysis of the imine double bond, followed by an intramolecular addition of the amine to the triple bond.[24] Since it is known that the addition of hydroxylamines to triple bonds is more favourable in strong basic or acidic media and high temperatures, and with the aim to obtain the *N*H-pyrazole oximes **2–4d** as the major products, milder experimental conditions were tested. The best results were obtained when **2–4c** were treated with 1 equiv of aq HCl 1 M in methanol at 50 °C during 1 h, obtaining the desired *N*H-pyrazole derivatives in moderate yields (**2d**: 33%; **3d**: 44%; **4d**: 50%), although minor amounts of the isoxazoline **5** were also isolated in all cases (see Experimental).

All new compounds showed combustion analysis and spectroscopic data (MS, ^{1}H NMR and ^{13}C NMR) in agreement with their structures. Due to the non-symmetric structure of the quinuclidine ring, the *O*-propargyloxime **4c** was obtained as a mixture of *Z*/*E* isomers, which could not be separated on a preparative scale. From the ^{1}H NMR spectrum of the mixture an approximate 3:2 ratio was calculated. Using HSQC and HMBC experiments all proton and carbon chemical shifts were assigned for both constituents and the assignment of the *Z*/*E* structure to each compound was made possible by means of a combination of NOE experiments and molecular modelling calculations. A positive NOE was observed between the signal at $\delta_H = 3.44$ ppm of the minor isomer, belonging to the methylene in C-2 of the quinuclidine ring, and the singlet at $\delta_H = 4.79$ ppm, assigned to the methylene of the propargylic chain. Conversely, the corresponding signals of the major isomer, resonating at $\delta_H = 3.61$ and 4.82 ppm, did not exhibit any NOE effect.

With the aim of unambiguously assigning of the *Z*- or *E*-configuration to the two isomers, semi-empirical AM1 molecular calculations were carried out, using the SYBYL program implemented on a Silicon Graphics workstation. As it can be observed in Figure 2, where the optimised structures have been depicted, the distance between the methylenes involved in the observed NOE is 3.0 Å for the *Z*-isomer, pointing out that this is



Scheme 1. (i) *N*-Methyl-4-piperidinone, MeOH, rt, 24 h; (ii) 3-tropinone, MeOH, rt, 24 h; (iii) 3-quinuclidinone, MeOH, rt, 24 h; (iv) HCl 1 M, MeOH, 50 °C, 1 h.

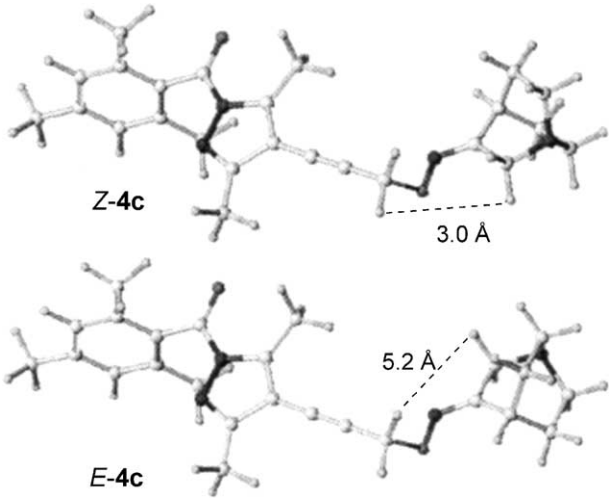


Figure 2. Optimised structures of *Z*- and *E*- isomers of **4c**, using AM1 method.

the minor component of the mixture. On the other hand, the major component could be the *E*-isomer, where the larger distance between the same methylenes (5.2 Å) precludes the NOE effect.

The affinities of synthesised pyrazolylpropynyl oximes **2a**–**d**, **3a**–**d** and **4c**,**d** for muscarinic receptors were determined by assessing the inhibition of specific [^{3}H]-(*R*)-quinuclidinyl benzylate ([^{3}H]-QNB) binding to rat cortical membranes, where M_1 receptors predominate, and the results are collected in Table 1. In general, the tested compounds showed moderate affinities for muscarinic receptors, in the range 10–80 μM, 3c being the best compound with an IC_{50} close to the structurally related CI-1017.[26]

From data collected in Table 1, one can deduce that the nature of both the tertiary amine and the pyrazole *N*-substituent have some effects in the muscarinic affinities. In relation to the amine, the best results were obtained with compounds **3a**–**d**, derived from tropinone, a relatively flexible bicyclic amine. Regarding the pyrazole *N*-substituent, the best affinities were obtained with aromatic moieties, in particular with the 2,4,6-trimethylbenzoyl group (series **c**), probably due to the formation of additional non-covalent bonds between this aromatic fragment and the receptor.

Table 1. Muscarinic affinities using [^{3}H]-QNB as radioligand

Compd	IC_{50} (μM)
2a	>100
2b	>100
2c	19.3±5.4
2d	86.2±1.23
3a	32.7±15.8
3b	17.6±6.8
3c	10.2±1.1
3d	20.1±0.31
4c	42.8±19.6
4d	>100
CI-1017[a]	6.9

[a]Taken from ref 26.

With the aim of obtaining some information about the possible interactions of the new ligands with the muscarinic receptor, a molecular modelling study was performed with the best product **3c**, and the results were compared with a M_1 pharmacophoric model, described by Wermuth and colleagues.[27] According to such a model, the authors proposed a cationic head, like a quaternary or physiologically protonable nitrogen, surrounded by a lipophilic environment such as a tropane framework, and an electronegative dipole, usually part of a planar function, like an ester or an oxime. Both functions must be almost in the same plane, with an intercharge distance of 5±0.05 Å.

Using the semi-empirical method AM1, in this work compound **3c**, derived from 2,4,6-trimethylbenzoylpyrazole and 3-tropane, was optimised (Fig. 3). From the geometrical data, we could observe that the protonated tertiary amine from the tropane framework and the oxime group were almost in the same plane, and that the distance HN^+...O was 4.95 Å. In addition, the aromatic substituent of the pyrazole was located outside this plane, where the carbonyl oxygen was more accessible by the receptor, and therefore it could act as hydrogen acceptor in an additional hydrogen bonding that probably improves its muscarinic affinity.

Since it is possible to introduce a great variety of substituents in the pyrazole nitrogen, containing different hydrogen acceptor heteroatoms, the *O*-[(pyrazolyl)propynyl]-oximes of tropinone can be considered as useful structures in the search for new muscarinic agents of potential application in Alzheimer's disease.

Experimental

Chemistry

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. *O*-(*N*-Substituted-pyrazolylpropynyl)-hydroxylamines **1a**–**c** were obtained as previously described by us.[23,24] Chromatographic separations were performed on silica gel, using either flash column chromatography (CC, using Kieselgel 60 Merck of 230–400 mesh) or 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 or Varian XL-300 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. Unequivocal assignments of chemical shifts were undertaken using two-dimensional experiments such as

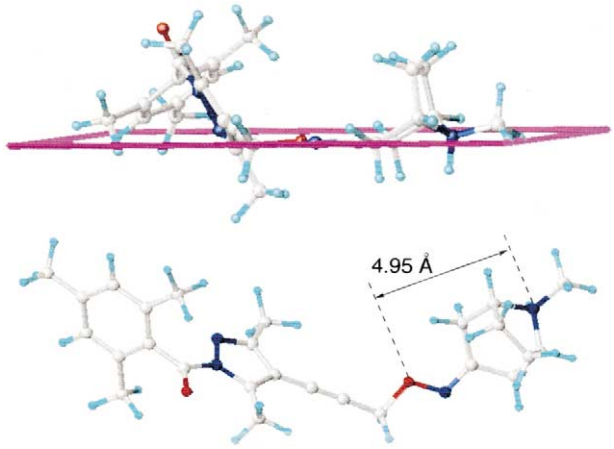


Figure 3. Oxime **3c**, optimised by AM1 method.

HSQC (Heteronuclear Single Quantum Coherance) for one-bond correlations, and HMBC (Heteronuclear Multiple Bond Correlation) for two- and three-bond correlations. Significant ^{13}C NMR data are collected in Table 2. Mass spectra (MS) were obtained by electronic impact at 70 eV in a Hewlett-Packard 5973 spectrometer with direct insertion probe. 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 procedure for the synthesis of 2a–c, 3a–c and 4c

A mixture of the corresponding 1-substituted 3,5-dimethyl-4-(1-hydroxyamino-2-propyn-3-yl)-1*H*-pyrazole **1a–c** (1 mmol) and the ketone (1 mmol) in dry methanol (5 mL) was stirred at room temperature during 24 h. Then, the solvent was evaporated to dryness and the residue was dissolved in water (10 mL) and made basic by slow addition of potassium carbonate. The resulting aqueous solution was extracted with dichloromethane (3×10 mL), and the organic layer was washed with water (10 mL), dried with Na_2SO_4 and evaporated to dryness in vacuo. The residual syrups were purified by chromatography on silica gel, as showed for individual products.

1-Methyl-4-piperidone, *O*-[3-(1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl)-2-propyn-1-yl]oxime (2a). Following the general method, compound **1a** (55 mg, 0.22 mmol) and 1-methyl-4-piperidone (25 mg, 0.22 mmol) afforded a syrup, which was purified by CC eluting with EtOAc–MeOH 3:1. Fractions of $R_f = 0.2$ gave oxime **2a** as a colourless oil (55 mg, 73%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–6.99 (m, 5H, benzyl), 5.15 (s, 2H, CH_2–Bn), 4.82 (s, 2H, C≡C–CH_2–O), 2.62 (t, 2H, $J = 6.0$ Hz, H3 piperidine), 2.55 (t, 2H, $J = 5.4$ Hz, H6 piperidine), 2.46 (t, 2H, $J = 6.0$ Hz, H2 piperidine), 2.34 (t, 2H, $J = 5.4$ Hz, H5 piperidine), 2.27 (s, 6H, N–CH_3 + 3-CH_3 pyrazole), 2.17 (s, 3H, 5-CH_3 pyrazole). MS *m*/*z* 223 (100%), 350 ($M^{+\cdot}$, 4%). Anal. calcd for $C_{21}H_{26}N_4O$ (350.46): C, 71.97; H, 7.48; N, 15.99. Found: C, 71.82; H, 7.60; N, 16.03.

1-Methyl-4-piperidone, *O*-{3-[3,5-dimethyl-1-(*p*-methoxybenzyl)-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (2b). From **1b** (28 mg, 0.098 mmol) and 1-methyl-4-piperidinone (11 mg, 0.098 mmol) a syrup was obtained, which was purified by CTLC, using EtOAc–MeOH (10:1) as eluent. Fractions of $R_f = 0.2$ afforded **2b** as a pure syrup (27 mg, 72%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, 2H, $J = 8.7$ Hz, H2.6 benzyl), 6.80 (d, 2H, $J = 8.7$ Hz, H3.5 benzyl), 5.10 (s, 2H, CH_2–Bn), 4.83 (s, 2H, C≡C–CH_2–O–), 3.75 (s, 3H, OCH_3), 2.66 (t, 2H, $J = 6.0$ Hz, H3 piperidine), 2.54 (t, 2H, $J = 5.8$ Hz, H6 piperidine), 2.48 (t, 2H, $J = 6.0$ Hz, H2 piperidine), 2.38 (t, 2H, $J = 5.8$ Hz, H5 piperidine), 2.31 (N–CH_3), 2.26 (s, 3H, 3-CH_3 pyrazole), 2.18 (s, 3H, 5-CH_3 pyrazole). MS *m*/*z* 121 (100%), 380 ($M^{+\cdot}$, 5%). Anal. calcd for $C_{22}H_{28}N_4O_2$ (380.48): C, 69.45; H, 7.42; N, 14.73. Found: C, 69.25; H, 7.36; N, 14.81.

1-Methyl-4-piperidone, *O*-{3-[1-(2,4,6-trimethylbenzoyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (2c). Following the general method, from **1c** (187 mg, 0.6 mmol) and 1-methyl-4-piperidone (68 mg, 0.6 mmol) a syrup was obtained, which was purified by CC eluting with EtOAc–MeOH (15:1). From the fractions of $R_f = 0.4$ oxime **2c** was obtained as a colourless oil (168 mg, 69%). ^1H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 2H, C_6H_2), 4.83 (s, 2H, C≡C–CH_2–O–), 2.68 (s, 3H, 3-CH_3 pyrazole), 2.65 (t, 2H, $J = 5.9$ Hz, H3 piperidine), 2.52 (t, 2H, $J = 5.4$ Hz, H6 piperidine), 2.46 (t, 2H, $J = 5.9$ Hz, H2 piperidine), 2.37 (t, 2H, $J = 5.4$ Hz, H5 piperidine), 2.39 (s, 3H, N–CH_3), 2.27 (s, 3H, 4-CH_3 benzoyl), 2.16 (s, 3H, 5-CH_3 pyrazole), 2.08 (s, 6H, 2.6-CH_3

Table 2. Selected ^{13}C NMR data (δ, ppm)

	Pyrazole			Propargylic chain			Tertiary amine							
	C-3	C-4	C-5	C-1	C-2	C-3	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
2a	150.2	101.9	142.5	61.9	78.3	88.9	—	54.6	25.5	157.6	31.5	55.9	—	—
2b	150.2	101.8	142.4	62.0	78.3	88.7	—	54.4	25.3	157.8	31.3	55.3	—	—
2c	154.1	107.8	146.4	61.5	76.1	91.8	—	54.4	25.4	157.8	31.4	55.3	—	—
2d	147.1	127.2	147.1	62.0	77.5	89.8	—	54.3	25.3	165.4	31.4	55.2	—	—
3a	150.2	101.9	142.5	62.0	75.7	89.0	60.0	36.9	156.9	31.9	60.8	27.4	26.6	—
3b	150.1	101.8	142.3	61.9	78.2	88.8	59.9	36.9	156.9	31.9	60.6	27.3	26.4	—
3c	154.1	107.8	146.3	61.6	76.0	91.9	59.9	36.8	156.9	31.8	60.7	27.2	26.3	—
3d	143.4	128.1	143.4	62.0	78.7	90.3	60.0	36.4	165.2	31.9	60.4	27.4	26.5	—
***Z*-4c**	154.1	107.8	146.3	61.7	76.3	91.7	—	53.4	162.0	28.5	24.4	46.8	46.8	24.4
***E*-4c**	154.1	107.8	146.3	61.8	76.2	91.6	—	52.1	164.5	28.5	25.9	47.1	47.1	25.9
4d	147.4	128.0	147.4	62.1	77.8	88.9	—	52.3	165.3	28.7	26.2	47.2	47.2	26.2

benzoyl). MS *m/z* 147 (100%), 406 ($M^{+\cdot}$, 5%). Anal. calcd for $C_{28}H_{30}N_4O_2$ (406.52): C, 70.91; H, 7.44; N, 13.78. Found: C, 70.84; H, 7.55; N, 13.80.

3-Tropinone, *O*-{3-[1-benzyl-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (3a). From **1a** (55 mg, 0.22 mmol) and 3-tropinone (30 mg, 0.22 mmol), and following the general method, a syrup was obtained, which was purified by CC eluting with EtOAc–MeOH (3:1). Fractions of $R_f = 0.2$ afforded oxime **3a** as a pure syrup (23 mg, 28%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29–6.99 (m, 5H, benzyl), 5.15 (s, 2H, CH_2–Bn), 4.81 (s, 2H, C≡C–CH_2–O), 3.27 (m, 1H, H1 tropane), 3.20 (m, 1H, H5 tropane), 2.93 (m, 1H, $H4_{eq}$ tropane), 2.53 (m, 1H, $H2_{eq}$ tropane), 2.33 (N–CH_3), 2.25 (s, 3H, 3-CH_3 pyrazole), 2.20 (m, 1H, $H4_{ax}$ tropane), 2.16 (s, 3H, 5-CH_3 pyrazole), 2.12 (m, 1H, $H2_{ax}$ tropane), 2.09 (m, 1H, $H6_{eq}$ tropane), 1.95 (m, 1H, $H7_{eq}$ tropane), 1.57 (m, 1H, $H6_{ax}$ tropane), 1.44 (m, 1H, $H7_{ax}$ tropane). Anal. calcd for $C_{23}H_{28}N_4O$ (376.49): C, 73.37; H, 7.50; N, 14.88. Found: C, 73.25; H, 7.62; N, 14.60.

3-Tropinone, *O*-{3-[1-(*p*-methoxybenzyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (3b). Following the general method, **1b** (28 mg, 0.098 mmol) and 3-tropinone (14 mg, 0.098 mmol) afforded a syrup, which was purified by CTLC using EtOAc–MeOH (5:1) as eluent. From fractions of $R_f = 0.1$ oxime **3b** was isolated as a colourless oil (20 mg, 50%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.99 (d, 2H, $J = 8.1$ Hz, H2.6 Bn), 6.80 (d, 2H, $J = 8.1$ Hz, H3.5 Bn), 5.10 (s, 2H, CH_2–Bn), 4.83 (s, 2H, C≡C–CH_2–O–), 3.74 (s, 3H, OCH_3), 3.30 (m, 1H, H1 tropane), 3.23 (m, 1H, H5 tropane), 2.95 (m, 1H, $H4_{eq}$ tropane), 2.56 (m, 1H, $H2_{eq}$ tropane), 2.35 (N–CH_3), 2.25 (s, 3H, 3-CH_3 pyrazole), 2.18 (s, 3H, 5-CH_3 pyrazole), 2.17 (m, 1H, $H4_{ax}$ tropane), 2.12 (m, 1H, $H2_{ax}$ tropane), 2.08 (m, 1H, $H6_{eq}$ tropane), 1.98 (m, 2H $H7_{eq}$ tropane), 1.59 (m, 1H, $H6_{ax}$ tropane), 1.49 (m, 1H, $H7_{ax}$ tropane). Anal. calcd for $C_{24}H_{30}N_4O_2$ (406.52): C, 70.91; H, 7.44; N, 13.78. Found: C, 70.82; H, 7.30; N, 13.85.

3-Tropinone, *O*-{3-[1-(2,4,6-trimethylbenzoyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl} oxime (3c). From **1c** (405 mg, 1.3 mmol) and 3-tropinone (181 mg, 1.3 mmol) a residue was obtained, which was chromatographied using CC and EtOAc–MeOH (5:1) as eluent. From fractions of $R_f = 0.2$ compound **3c** was obtained as a colourless oil (321 mg, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.77 (s, 2H, H C_6H_2), 4.75 (s, 2H, –C≡C–CH_2–O–), 3.32 (m, 1H, H1 tropane), 3.26 (m, 1H, H5 tropane), 2.95 (m, 1H, $H4_{eq}$ tropane), 2.67 (s, 3H, 3-CH_3 pyrazole), 2.59 (m, 1H, $H2_{eq}$ tropane), 2.34 (s, 3H, N–CH_3), 2.27 (s, 3H, 4-CH_3 benzoyl), 2.18 (m, 1H, $H4_{ax}$ tropane), 2.15 (s, 3H, 5-CH_3 pyrazole), 2.14 (m, 1H, $H2_{ax}$ tropane), 2.08 (s, 6H, 2.6-CH_3 benzoyl), 2.00 (m, 2H, $H6_{eq}$ tropane), 1.94 (m, 1H, $H7_{eq}$ tropane), 1.54 (m, 1H, $H6_{ax}$ tropane), 1.48 (m, 1H, $H7_{ax}$ tropane). MS *m/z* 147 (100%), 432 ($M^{+\cdot}$, 23%). Anal. calcd for $C_{26}H_{32}N_4O_2$ (432.56): C, 72.19; H, 7.46; N, 12.95. Found: C, 71.96; H, 7.58; N, 13.02.

3-Quinuclidinone, *O*-{3-[1-(2,4,6-Trimethylbenzoyl)-3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (4c). Following the general method, **1c** (202 mg, 0.65 mmol) and 3-quinuclidinone hydrochloride (105 mg, 0.65 mmol) a syrup was obtained, which was purified by CC using EtOAc–MeOH (6:1) as eluent. Fractions of $R_f = 0.4$ afforded **4c** (140 mg, 52%) as a mixture of isomers *E*/*Z* (in ratio 3:2). ^{1}H NMR ($CDCl_3$, 500 MHz)[28] δ 6.80 (s, 4H, C_4H_2), 4.82 (s, 2H, C≡C–CH_2–O–*E*-**4c**), 4.79 (s, 2H, C≡C–CH_2–O–*Z*-**4c**), 3.61 (s, 2H, H2 quinuclidine *E*-**4c**), 3.44 (s, 2H, H2 quinuclidine *Z*-**4c**), 2.90 (m, 4H, H6,7 quinuclidine *E*-**4c**), 2.83 (m, 4H, H6,7 quinuclidine *Z*-**4c**), 2.64 (s, 6H, 3-CH_3 pyrazole), 2.58 (m, 2H, H4 quinuclidine), 2.23 (s, 6H, 4-CH_3 benzoyl), 2.12 (s, 6H, 5-CH_3 pyrazole), 2.05 (s, 12H, 2.6-CH_3 benzoyl), 1.77 (m, 2H, H5,8 quinuclidine *E*-**4c**), 1.69 (m, 2H, H5,8 quinuclidine *Z*-**4c**).

General procedure for the synthesis of 2–4d

The corresponding *N*-(2,4,6-trimethylbenzoyl)-pyrazole oximes **2**–**4c** (1 mmol) in methanol (2 mL) was treated with HCl 1 M (1 mmol) at 50 °C during 1 h. After cooling, the solvent was evaporated to dryness in vacuo and the syrup was dissolved in H_2O (2 mL). The mixture was carefully neutralised with K_2CO_3 and extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with water (10 mL), dried with Na_2SO_4 and evaporated to dryness, and the residues were purified by chromatography on silica gel. In all cases, the first eluted product was the isoxazoline **5** (mp = 168–169 °C)[24] and the second one was the corresponding NH-pyrazole oxime **2**–**4d**.

1-Methyl-4-piperidone, *O*-{[3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (2d). Following the general method, **2c** (60 mg, 0.15 mmol) afforded a syrup, which was purified by CC using EtOAc–MeOH (1:1) as eluent. Fractions of $R_f = 0.7$ gave isoxazoline **5** (4.6 mg, 19%) and fractions of $R_f = 0.2$ afforded oxime **2d** as a colourless oil (13 mg, 33%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.85 (s, 2H, C≡C–CH_2–O–), 3.45 (br. s, 1H, NH), 2.67 (t, 2H, $J = 5.6$ Hz, H3 piperidine), 2.53 (t, 2H, $J = 5.4$ Hz, H6 piperidine), 2.47 (t, 2H, $J = 5.6$ Hz, H2 piperidine), 2.37 (t, 2H, $J = 5.4$ Hz, H5 piperidine), 2.32 (s, 3H, N–CH_3), 2.02 (s, 6H, 3.5-CH_3 pyrazole). Anal. calcd for $C_{14}H_{20}N_4O$ (260.34): C, 64.59; H, 7.74; N, 21.52. Found: C, 64.62; H, 7.55; N, 21.45.

3-Tropinone, *O*-{[3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl} oxime (3d). Following the general method, from **3c** (62 mg, 0.14 mmol) a syrup was obtained, which was purified by CTLC using EtOAc–MeOH (5:1) as eluent. Besides isoxazoline **5** (5.7 mg, 24%), NH–pyrazole oxime **3d** was isolated as a pure oil (18 mg, 44%) of $R_f = 0.2$. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (br. s, 1H, NH), 4.86 (s, 2H, C≡C–CH_2–O–), 3.35 (m, 1H, H1 tropane), 3.30 (m, 1H, H5 tropane), 2.97 (m, 1H, $H4_{eq}$ tropane), 2.60 (m, 1H, $H2_{eq}$ tropane), 2.39 (s, 3H, N–CH_3), 2.28 (s, 6H, 3.5-CH_3 pyrazole), 2.20 (m, 1H, $H4_{ax}$ tropane), 2.16 (m, 1H, $H2_{ax}$ tropane), 2.01 (m, 2H, $H6,7_{eq}$ tropane), 1.59 (m, 1H, $H6_{ax}$ tropane), 1.49 (m, 1H, $H7_{ax}$ tropane). MS *m/z* 286 ($M^{+\cdot}$, 3%). Anal. calcd for $C_{16}H_{22}N_4O$ (286.38): C, 67.11; H, 7.74; N, 19.56. Found: C, 67.25; H, 7.63; N, 19.40.

3-Quinuclidinone, *O*-{[3,5-dimethyl-1*H*-pyrazol-4-yl]-2-propyn-1-yl}oxime (*Z,E*-4d). Following the general method, *Z,E*-**4c** (26 mg, 0.06 mmol) afforded a syrup which was purified by CTLC using hexane–EtOAc–MeOH (4:4:1) as eluent. First fractions gave isoxazoline **5** (3 mg, 29%) and fractions of $R_f = 0.1$ afforded oxime *Z,E*-**4d** as a colourless oil (8.5 mg, 50%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.84 (s, 2H, C≡C–CH_2–O–), 4.09 (s, 1H, NH), 3.62 (s, 2H, H2 quinuclidine), 2.90 (m, 4H, H6,7 quinuclidine), 2.60 (m, 1H, H4 quinuclidine), 2.29 (s, 6H, 3.5-CH_3 pyrazole), 1.80 (m, 4H, H5,8 quinuclidine).

Pharmacology

Muscarinic receptor binding studies were carried out by evaluating the abilitity of compounds **2a**–**d**, **3a**–**d**, and **4c**,**d** as free bases, to compete with 50 pM [^{3}H]-(*R*)-quinuclidinyl benzylate in a suspension of brain membranes, as previously described.[29] 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.

Molecular modelling studies

Molecular modelling studies were performed using a SYBYL software[30] implemented in a Silicon Graphics working station. Input geometries were taken from the standard ones within SYBYL program. Semi-empirical calculations were carried out using the AM1 method[31] in MOPAC v5.0 program package[32] and full geometry optimisations were performed with the Fletcher–Power algorithm.

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