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Research paper

Design of α7 nicotinic acetylcholine receptor ligands using the (het) Aryl-1,2,3-triazole core: Synthesis, *in vitro* evaluation and SAR studies

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ABSTRACT

We report here the synthesis of a large library of 1,2,3-triazole derivatives which were *in vitro* tested as α7 nAchR ligands. The SAR study revealed that several crucial factors are involved in the affinity of these compounds for α7 nAchR such as a (*R*) quinuclidine configuration and a mono *C*-3 quinuclidine substitution. The triazole ring was substituted by a phenyl ring bearing small OMe/CH_2F groups or fluorine atom and by several heterocycles such as thiophenes, furanes, benzothiophenes or benzofuranes. Among the 30 derivatives tested, the two derivatives **10** and **39** with Ki in the nanomolar range were identified (2.3 and 3 nM respectively). They exhibited a strict selectivity toward the α4β2 nicotinic receptor (up to 1 μM) but interacted with the $5HT_3$ receptors with Ki around 3 nM. Synthesis, SAR studies and a full description of the derivatives are reported.

1. Introduction

The neurotransmitter acetylcholine (ACh) exerts its effects on the central nervous system (CNS) through two distinct muscarinic and nicotinic receptor types. The nicotinic receptors belong to the superfamily of ligand-gated transmembrane ion channels possessing homo or hetero pentameric structures and are structurally composed of 5 subunits belonging to the subfamily of α (9 subunits, α2 to α10) and/or β (β2 to β4), the heteropentameric α4β2 and homopentameric α7 subtypes being predominant [1–4]. Alpha-7 nicotinic receptors (α7 nAChR) are highly permeable to calcium and are distinguished by their tight binding to α-bungarotoxin. Previous studies indicated that α7 nAChR play important roles in modulating neurotransmission, cognition, sensory gating and anxiety [5–8]. Thus, there has been renewed interest in the use of nicotinic agonists to treat CNS diseases, and several studies show their beneficial effects on cognitive symptoms particularly in schizophrenia [9–12] and Alzheimer's disease [13,14].

Ligand families bind to the receptor directly on the active site or following an allosteric mode and researches are always in progress [15–17]. Several α7 nAChR agonists (such as EVP-6124 or GTS-21) have entered clinical trials [18]. While the promising drugs show some structural diversity, a general similarity between them can be discerned, making it possible to propose a general pharmacophoric model **I** (Fig. 1). We speculate that receptor binding could occur when a nitrogen-containing heterocycle (NCHC) is linked to a (het) Ar skeleton *via* an electron rich fraction which can reinforce the binding and form additional strong bonds [19,20]. Between the previous two components, a donor/acceptor of hydrogen bond (DAHB) is positioned. This moiety is subjected to numerous modulations (amide, urea, carbamate, oxazole, oxadiazole and furane) and achieves the required tridimensional conformations as well as the completion of the binding mode. A combination of sigma and spiranic bonds or fusion with the tertiary amine or the (het)Ar fractions are often observed to link the three key parts together. Numerous representative drugs which bind to the α7 nAchR receptor have been with a high affinity answer this general description [21–30].

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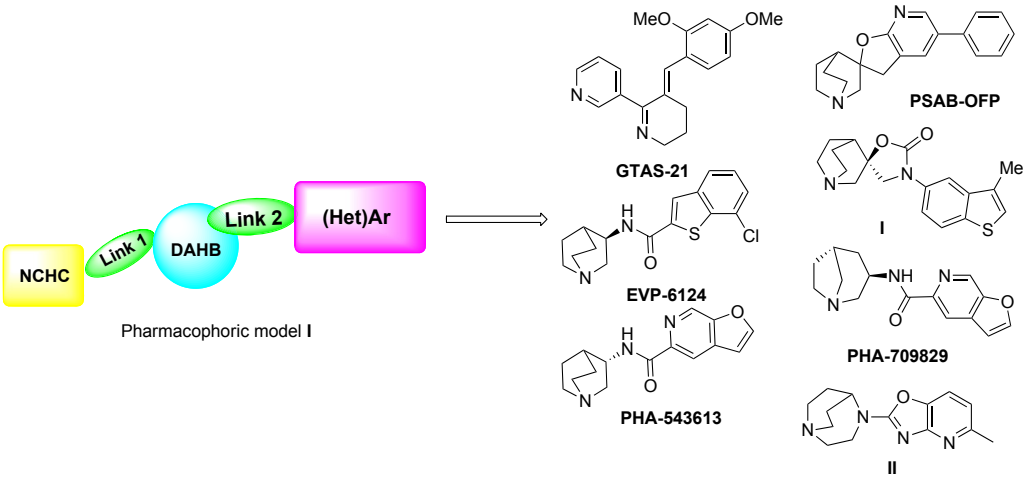


Fig. 1. Pharmacophoric model and representative α7 nAchR agonists. NCHC = nitrogen containing heterocycle. DAHB = donor and/or acceptor of hydrogen bond. Link = linker.

It seems that quinuclidine represents a chosen structure in the obtaining of drugs having potential beneficial effects in CNS disorders such as AD [31,32]. We previously reported the design of several series of α7 nAChR ligands possessing quinuclidine, tropane and quinazoline skeletons as NCHC group, as well as amide or spiranic oxazoles as links to the (het)Ar moieties. While molecules having a quinuclidine/amide enchainment remain good ligands, other NCHC series containing a tropane or a spiranic function are less efficient. Moreover, in the quinuclidine series, we speculated that the amide linker could be replaced by a small nitrogen-containing heterocycle. To investigate this possibility, we explored the use of 1,2,3-triazoles. Based on our expertise in heterocyclic bio-mimetic development [33–36], we synthesized a large library of 1,2,3-triazole derivatives of type **IIIa** and **IIIb** which were *in vitro* tested as α7 nAchR ligands (Fig. 2). From *in vitro* assays, structure–activity relationships (SAR) were depicted and the selectivity of the best ligands was assessed.

2. Chemistry

Click chemistry (Huisgen type reactions) is able to commonly build 1,2,3-triazoles from an azide and terminal alkyne in the presence of a copper catalyst. This useful chemical step is seldom described in the 3-quinuclidine triazole series, however [37,38]. The extreme instability of alkyl azides prompted us to prepare the targeted 4-(het)Ar-1,2,3-triazole quinuclidines in a single step (Scheme 1). In the presence of a catalytic amount of copper sulfate, 1*H*-imidazole-1-sulfonyl azide **1** and enantiopure commercially available (R)- or (S)-3-aminoquinuclidines of type **2**, which were both released from their respective hydrochloric acid salts using a stoichiometric amount of K_2CO_3, led after 6 h at room temperature to the enantiopure (R)- or (S)-3-azidoquinuclidine **3a** or **3b** [39]. Their rapid consumption in the presence of the alkyne **IV**, sodium ascorbate and copper catalyst led after 12 h at room temperature to the attempted final derivatives of type **IIIa**.

Several click cross couplings were first performed with commercially available alkynes (Table 1, entries 1–15). Due to the instability of **1** [40] and **3**, which required great precaution when generated, stored or used, yields did not exceed 38% whatever the nature of the aryl substituents and the quinuclidinic isomer involved in the reaction. Derivatives **4**–**29** are obtained as a single isomer. Other are racemic compounds.

Pyridine, benzofurane or benzothiophene containing terminal alkynes were commercially unavailable and thus required special preparation (Scheme 2). 2-Fluoro-3-iodopyridine was first subjected to a palladium catalyzed Sonogashira procedure in the presence of trimethylsilylacetylene to afford the alkyne **19**, which was treated with tetrabutylammonium fluoride (TBAF). After a few minutes, derivative **20** was isolated in 82% yield. Interestingly, the treatment of the crude derivative **19** with methanol in basic medium led to the simultaneous release of the trimethylsilyl group and the nucleophilic fluorine atom substitution. Compound **21** was isolated in a 75% yield. This Sonogashira/desilylation tandem procedure was next applied to several bromo aryl derivatives. Para substituted phenyl acetylenes **22**–**26** were readily obtained in moderate to good yields. Next, the 1-diazo-2-oxopropylphosphonate **27** (Bestmann Ohira reagent) easily transformed the 5-formylbenzothiophene or 5-formylbenzofurane, under a basic medium, into alkynes **28** and **29** which were obtained in very satisfactory yields.

The alkyne precursors of derivatives **IIIb** were obtained following another route. Isomerization of the triazole involves condensation of the alkyne on the commercially available quinuclidinone. This step was carried out at low temperature with a near

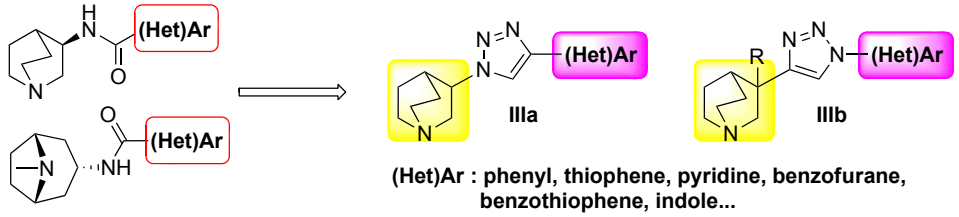
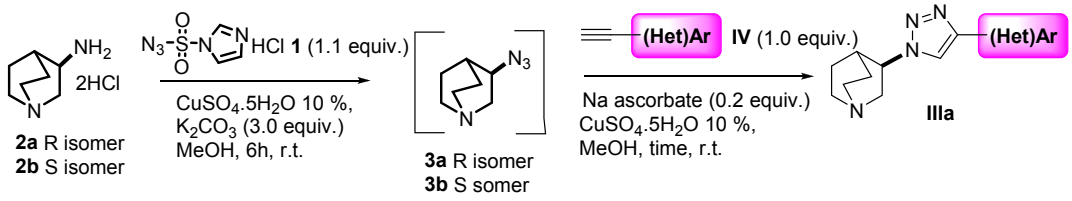


Fig. 2. Main synthetic objectives.

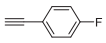
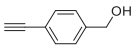
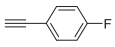
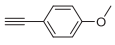
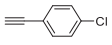
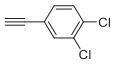
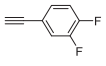
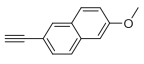
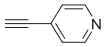


Scheme 1. General synthesis of derivatives of type **IIIa**.

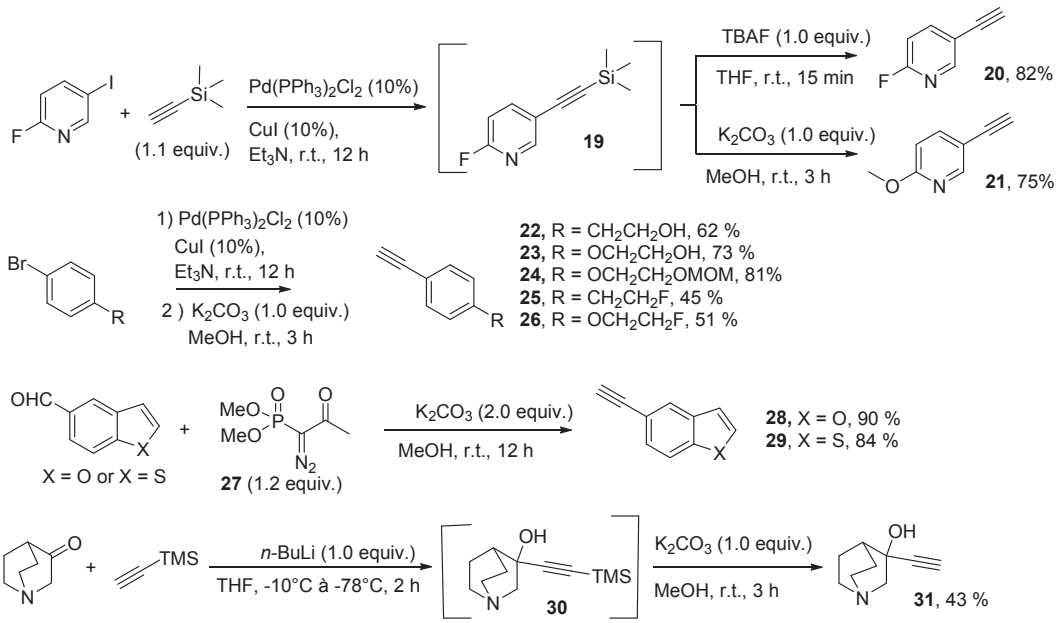
stoichiometric amount of the *in situ* formed ((trimethylsilyl)ethynyl)lithium salt. The direct trimethylsilyl (TMS) removal of **30** was achieved as described before and pure alkyne **31** was isolated in a 43% global yield [37].

As for the derivatives of type **IIIa**, the previously described condensation with novel alkynes furnished the final derivatives **32**–**42** in very high yields. The triazole building method appears to be more efficient than an inverse strategy with aliphatic alkynes

Table 1
Series of α7 nAchR ligands obtained from commercially available alkynes.

Entry	(Het)Ar alkyne IV	Product of type III, yield %[a]	Entry	(Het)Ar alkyne IV	Product of type III, yield %[a]
1		**4**, 33	14		**17**, 38
2		**5**, 29	15		**18**, 32
3		**6**, 29	16	**20**	**32**, 18
4		**7**, 22	17	**21**	**33**, 28
5		**8**, 33	18	**22**	**34**, 38
6		**9**, 21	19	**23**	**35**, 44
7		**10**, 32	20	**24**	**36**, 30
8		**11**, 28	21	**25**	**37**, 17
9		**12**, 28	22	**26**	**38**, 11
10		**13**, 17	23	**28**	**39**, 34
11		**14**, 24	24	**29**	**40**, 32
12		**15**, 21	25	**31**	**41**, 91[b]
13		**16**, 30	26	**31**	**42**, 87[b]

[a] Yields are indicated in isolated product and calculated from quinuclidine.
[b] Yields calcd. from **30**.



Scheme 2. Synthesis of unavailable terminal alkynes.

and aromatic azides.

Finally benzyl alcohols **18** and quinuclidinol **40** or **41** were subjected to a direct electrophilic fluorination with diethylaminosulfur trifluoride (DAST). This step was efficiently carried out on the three derivatives and led without any difficulties to **43**–**45** in satisfactory yields (Scheme 3).

3. Biological evaluation

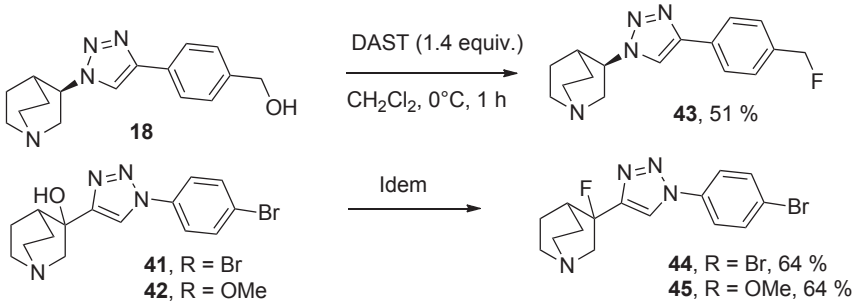
3.1. Binding to α7 nAchR and SAR

All the synthesized compounds of type **IIIa** and **IIIb** were evaluated for their inhibitory effect on the binding of [^{125}I]α-bungarotoxin as reference ligand. In our screening experiments, we obtained a Ki of 1.27 ± 0.25 nM for the α7 nAchR ligand PHA543613, in agreement with the literature data [41]. The measured affinities are reported in Table 2. In our first report we measured the inhibitory constant of the reference derivative **46** (Ki = 17 nM, entry 1) [21]. The replacement of the amide by an 1,2,3-triazole moiety appears immediately relevant as the Ki of **12** was reduced to 8 nM (entry 10). Without any halogen atom (entry 2), the Ki value remained unchanged, as was also the case when a fluorine atom was added in the three available aryl positions (entries 3–5). Unsurprisingly, two fluorine atoms in meta and para position were also well tolerated (entry 12). The change of the symmetric center (R) for the (S) configuration led to a 7-fold increase in binding strength (entry 3 *vs* 6).

A similar behavior was observed using the electron rich methoxy group when this function was positioned either on the meta or the para phenyl positions (entries 7, 8), with a slight preference for the meta substitution as the Ki of **10** reached 2.3 nM. When the methoxy group was attached in ortho, steric hindrance appeared to disrupt the flatness due to the conjugation of the triazole and the phenyl moieties which resulted in a great loss of affinity (**11**, Ki = 112 nM, entry 9).

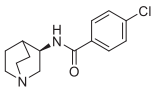
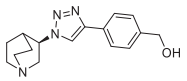
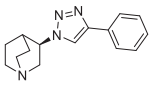
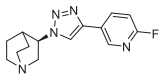
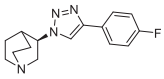
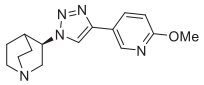
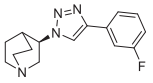
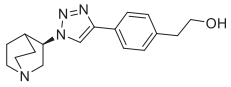
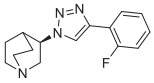
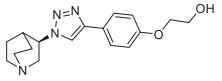
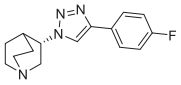
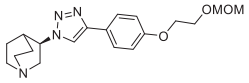
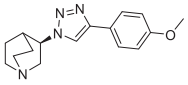
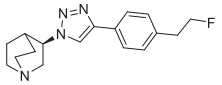
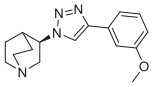
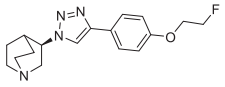
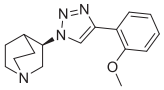
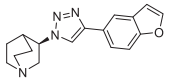
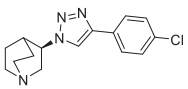
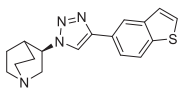
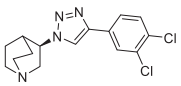
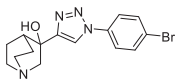
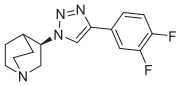
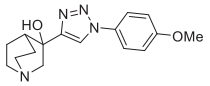
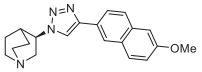
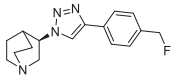
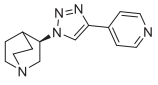
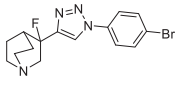
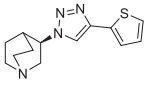
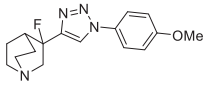
Comparing **4** *vs* **16**, **5** *vs* **32** and **9** *vs* **33**, the introduction of a pyridine instead of a phenyl group led to a strong decrease in affinity by at least tenfold. Fortunately, thiophene, benzothiophene and benzofurane heterocycles were very well tolerated as the affinity returned to the nanomolar range (entries 15, 24, 25). More precisely, an oxygen atom gave a better affinity than a sulfur atom (**39**, Ki = 3 nM f and **40** Ki = 19 nM). Finally, we replaced the (het)Ar part with a naphthyl group but steric hindrance appeared to be too high and resulted in a loss of affinity as the Ki of **15** (entry 13) then reached 200 nM.

To pursue the SAR study, we introduced small flexible side chains containing alkyl, hydroxy, ether and fluorine (entries 16, 19–23, 28). Except for compounds **18** and **43**, with Ki values of 10



Scheme 3. Electrophilic fluorination of hydroxylated derivatives **18**, **41** and **42**.

Table 2
Ki values of derivatives **IIIa** and **IIIb**.

Entry	Compound of type III		Ki (nM)[a]	Entry	Compound of type III		Ki (nM)[a]
1	**46** [7]		17 ± 5	16	**18**		10 ± 3
2	**4**		8 ± 4	17	**32**		469 ± 6
3	**5**		15 ± 4	18	**33**		105 ± 29
4	**6**		10 ± 1	19	**34**		130 ± 20
5	**7**		13 ± 3	20	**35**		215 ± 10
6	**8**		114 ± 38	21	**36**		225 ± 15
7	**9**		11 ± 1	22	**37**		230 ± 10
8	**10**		2.3 ± 1	23	**38**		190 ± 10
9	**11**		112 ± 26	24	**39**		3 ± 1
10	**12**		8 ± 3	25	**40**		19 ± 1
11	**13**		19 ± 6	26	**41**		>10^3
12	**14**		10 ± 4	27	**42**		>10^3
13	**15**		196 ± 21	28	**43**		21 ± 7
14	**16**		141 ± 41	29	**44**		150 ± 4
15	**17**		9.5 ± 3	30	**45**		>10^3

[a] Values are expressed as an average of 3 values from 3 independent experiments ± SEM.

and 21 nM respectively, all the other derivatives displayed an affinity over 100 nM. The incorporation of a long and flexible (hetero) alkyl side chain was detrimental to the biological target interaction and the occupancy of the corresponding pocket site. Finally, the preparation of type **IIIb** derivatives led to disappointing results. The 3-hydroxy or 3-fluoro quinuclidine derivatives **41**, **42**, **44** and **45**, which present a triazole isomerization, can be considered as quite inactive compounds. Compound **44** was the only one that could be considered as a weak α7 nAchR ligand. This SAR analysis confirmed the strong effect of the 3D triazole environment as well as of the nitrogen triazole positions on the interaction with the biological target.

Overall, the SAR study indicated that several crucial factors are involved in the affinity for α7 nAchR. Derivatives of type **IIIa** with a (*R*) configuration were preferred. Phenyl, thiophene, benzothiophene and benzofurane could be attached to the triazole and led to compounds with 3–19 nM affinity. In the phenyl series, OMe and CH_2OH groups proved suitable to modulate the ligand efficiency. To date, derivatives **10** and **39** were the best two ligands we found in the **IIIa** series.

3.2. Selectivity

It appeared from the above results that two compounds had a much higher affinity for α7 nAchR than the others, i.e. compounds **10** and **39**, with a Ki of 2.3 and 3 nM, respectively. The affinity of these two compounds was therefore evaluated in the CEREP profiling, using cells transfected with human recombinants on the α4β2 sub-type of nicotinic receptors and on the 5-HT_3 receptors which are structural homologs of α7 nAchR. Compounds **10** and **39** showed a very high selectivity toward α4β2 nicotinic receptors as no interaction was detected down to 1 μM. However, both bound to the 5-HT_3 receptors with a Ki around 3 nM. Our best derivatives can therefore be considered as full dual 5-HT_3/α7 receptor ligands and could be of real interest for the development of innovative treatments for CNS disorders as these two targets have been fully validated to treat such pathologies [42]. Indeed, a non-selective indole derivative of our quinuclidine series [43] named **IND8** which exhibited a K_d of 0.12 μM against α7 nAChR, 0.052 μM against 5-and α4β2 nicotinic receptor subtype (Ki = 0.75 μM) [43], respectively, showed promising improvements in cognitive tests in a mouse model of amnesia.

4. Conclusions

We have reported herein the synthesis and SAR study in the quinuclidin-1,2,3-triazole series. Compounds were synthetized in only a few steps and scale up is possible to ensure further *in vivo* developments. The synthesis mainly involved the preparation of quinuclidin 3-azide, several terminal alkynes and a key Huisgen reaction. However, other reactions were performed on pre-built ligands. A series of 30 new compounds were designed and tested for their potent α7 nAChR affinity. The SAR study clearly showed that the quinuclidine/triazole/(het)Ar association is highly valuable for the design of very active derivatives. Four derivatives **4**, **18**, **19** and **39** bind the receptor with inhibition constants less than 10 nM. Additionally, the leaders **10** and **38** exhibit full selectivity towards the α4β2 receptor subtype (up to 1 μM) but bind to 5-HT_3 receptors in an interesting nanomolar range. *In vivo* behavioral experiments using these compounds in animal models are in progress.

5. Experimental section

5.1. Chemistry

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 MHz or 400 MHz instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all coupling constant (*J*) values are in Hertz (Hz). The following abbreviations were used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet doublet). Melting points are uncorrected. IR absorption spectra were obtained on a Perkin–Elmer PARAGON 1000 PC and values are reported in cm^{-1}. HRMS were recorded on a Bruker maXis mass spectrometer by the "Federation de Recherche" ICOA/CBM (FR2708) platform. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualized by UV light at 254 nm and 356 nm. Column chromatographies were performed using silica gel 60 (0.063–0.200 mm, Merck). Microwave irradiation was carried out in sealed 2–5 mL vessels placed in a Biotage Initiator system using a standard absorbance level (300 W maximum power). The temperatures were measured externally by an IR probe that determined the temperature on the surface of the vial and could be read directly from the instrument screen. The reaction time was measured from when the reaction mixture reached the stated temperature for temperature-controlled experiments. Pressure was measured by a non-invasive sensor integrated into the cavity.

5.1.1. General procedure A for the synthesis of derivatives *IIIa*

Under argon, to a solution containing 3-aminoquinuclidine bis-hydrochloride salt **2** (212 mg, 1.00 mmol) and 1*H*-imidazole-1-sulfonyle azide **1** (232 mg, 1.10 mmol) in MeOH (6 mL) was portion wise added K_2CO_3 (415 mg, 3.00 mmol) and next a catalytic amount of $CuSO_4$, $5H_2O$ (25 mg, 0.10 mmol). The reaction mixture was stirred at room temperature for 6 h and then concentrated under reduced pressure. The crude solid was solubilized in Et_2O (10 mL), filtered and the precipitate washed with an additional amount of Et_2O (10 mL). The combined organic layers were reduced under reduced pressure and the (R) intermediate **3a** used in the next step. After addition of MeOH (6 mL), the desired terminal alkyne **4** (1.00 mmol) and next $CuSO_4$, $5H_2O$ (25 mg, 0.10 mmol), sodium ascorbate (40 mg, 0.20 mmol) were successively added. The reaction mixture was stirred for 12 h at room temperature. Volatiles were evaporated under reduced pressure and the residue purified by flash chromatography. When some traces of imidazole were observed, EtOAc (20 mL) was added. After washing with water (2 × 10 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the pure derivative of type **IIIa**.

5.1.2. (R)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)quinuclidine *4*

Compound **4** was obtained from ethynylbenzene following the general procedure A and isolated as a white solid in 33% yield. R_f: 0.29 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 132–134 °C; IR (ATR, Diamond): ν (cm^{-1}) 973, 1023, 1043, 1060, 1072, 1211, 1227, 1411, 1453, 1482, 2870, 2937; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.45–1.61 (m, 1H), 1.68–1.79 (m, 1H), 1.82–1.92 (m, 1H), 2.32 (q, *J* = 3.1 Hz, 1H), 2.90–3.10 (m, 3H), 3.15–3.35 (m, 1H), 3.56 (dd, *J* = 2.2 Hz, *J* = 9.9 Hz, 1H), 3.62 (dd, *J* = 2.2 Hz, *J* = 9.9 Hz, 1H), 3.81 (dd, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H), 4.69–4.79 (m, 1H), 7.29–7.37 (m, 1H), 7.39–7.47 (m, 2H), 7.81–7.86 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.9 (CH_2), 25.6 (CH_2), 28.3 (CH), 47.0 (CH_2), 47.4 (CH_2), 52.4 (CH_2), 58.0 (CH), 119.4 (CH), 125.9 (2 × CH), 128.4 (CH), 129.1 (2 × CH), 130.7 (C_q), 147.9 (C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{19}N_4$ $[M+H]^+$: 255.1610, found: 255.1613.

5.1.3. (R)-3-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)quinuclidine *5*

Compound **5** was obtained from 1-ethynyl-4-fluorobenzene following the general procedure A and isolated as a white solid in 29% yield. R_f: 0.37 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 180–182 °C; IR (ATR, Diamond): ν (cm^{-1}) 973, 1014, 1044, 1060, 1160, 1225, 1453, 1495, 1560, 2375, 2869, 2936; ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.49–1.62 (m, 2H), 1.81–1.94 (m, 2H), 2.31–2.36 (m, 1H), 2.94–3.08 (m, 3H), 3.12–3.26 (m, 1H), 3.57–3.71 (m, 2H), 3.91–4.02 (m, 1H), 7.34 (t, *J* = 8.6 Hz, 2H), 7.94 (dd, *J* = 5.3 Hz, *J* = 8.6 Hz, 2H), 8.83 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.7 (CH_2), 23.8 (CH_2), 27.1 (CH), 45.9 (CH_2), 46.1 (CH_2), 50.8 (CH_2), 56.3 (CH), 115.8 (d, *J* = 22.0 Hz, 2 × CH), 121.0 (CH), 127.1 (d, *J* = 8.0 Hz, 2 × CH), 127.3 (d, *J* = 3.0 Hz, C_q), 145.4 (C_q), 161.7 (d, *J* = 244.0 Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}FN_4$ $[M+H]^+$:

273.1516, found: 273.1508.

5.1.4. (R)-3-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)quinuclidine **6**

Compound **6** was obtained from 1-ethynyl-3-fluorobenzene following the general procedure **A** and isolated as a white solid in 29% yield. R_f: 0.31 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 120–122 °C; IR (ATR, Diamond): ν (cm^{-1}) 1041, 1061, 1148, 1214, 1266, 1315, 1345, 1449, 1487, 1589, 1620, 2869, 2936; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.40–1.55 (m, 1H), 1.60–1.72 (m, 1H), 1.73–1.86 (m, 2H), 2.28 (q, J = 3.1 Hz, 1H), 2.84–3.00 (m, 3H), 3.08–3.22 (m, 1H), 3.50 (ddd, J = 2.0 Hz, J = 9.8 Hz, J = 14.5 Hz, 1H), 3.70 (dd, J = 5.0 Hz, J = 14.5 Hz, 1H), 4.60–4.70 (m, 1H), 7.03 (td, J = 2.3 Hz, J = 8.3 Hz, 1H), 7.33–7.44 (m, 1H), 7.52–7.63 (m, 1H), 7.59 (s, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.8 (CH), 112.8 (d, J = 22.0 Hz, CH), 115.1 (d, J = 22.0 Hz, CH), 119.6 (CH), 121.5 (d, J = 3.0 Hz, CH), 130.6 (d, J = 8.0 Hz, CH), 133.0 (d, J = 8.0 Hz, C_q), 146.8 (d, J = 3.0 Hz, C_q), 163.4 (d, J = 246.0 Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}FN_4$ $[M+H]^+$: 273.1516, found: 273.1516.

5.1.5. (R)-3-(4-(2-fluorophenyl)-1H-1,2,3-triazol-1-yl)quinuclidine **7**

Compound **7** was obtained from 1-ethynyl-2-fluorobenzene following the general procedure **A** and isolated as a white solid in 22% yield. R_f: 0.42 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 94–98 °C; IR (ATR, Diamond): ν (cm^{-1}) 970, 1045, 1068, 1227, 1328, 1452, 1487, 1644, 2932, 3142, 3352; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.41–1.55 (m, 1H), 1.63–1.74 (m, 1H), 1.76–1.88 (m, 2H), 2.30 (q, J = 3.1 Hz, 1H), 2.87–3.00 (m, 3H), 3.10–3.24 (m, 1H), 3.50 (ddd, J = 2.2 Hz, J = 9.8 Hz, J = 14.4 Hz, 1H), 3.75 (dd, J = 4.7 Hz, J = 14.4 Hz, 1H), 4.63–4.72 (m, 1H), 7.09–7.18 (m, 1H), 7.22–7.34 (m, 2H), 7.98 (d, J = 3.7 Hz, 1H), 8.32 (dd, J = 2.2 Hz, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.8 (CH_2), 58.6 (CH), 115.8 (d, J = 22.0 Hz, CH), 118.8 (d, J = 13.0 Hz, C_q), 122.4 (d, J = 13.0 Hz, CH), 124.8 (d, J = 3.0 Hz, CH), 128.0 (d, J = 3.0 Hz, CH), 129.5 (d, J = 8.0 Hz, CH), 141.2 (C_q), 159.4 (d, J = 248.0 Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}FN_4$ $[M+H]^+$: 273.1516, found: 273.1529.

5.1.6. (S)-3-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)quinuclidine **8**

Compound **8** was obtained from 1-ethynyl-4-fluorobenzene and (S) intermediate **3b** following the general procedure **A** and isolated as a white solid in 33% yield. R_f: 0.37 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 139–141 °C; IR (ATR, Diamond): ν (cm^{-1}) 974, 1022, 1042, 1060, 1160, 1225, 1330, 1400, 1494, 1560, 1612, 2869, 2936; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.39–1.54 (m, 1H), 1.60–1.74 (m, 1H), 1.75–1.88 (m, 2H), 2.26–2.36 (m, 1H), 2.84–2.98 (m, 3H), 3.07–3.21 (m, 1H), 3.48 (ddd, J = 2.3 Hz, J = 9.8 Hz, J = 14.4 Hz, 1H), 3.70 (dd, J = 5.1 Hz, J = 14.4 Hz, 1H), 4.59–4.68 (m, 1H), 7.11 (t, J = 8.6 Hz, 2H), 7.77 (s, 1H), 7.79–7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.7 (CH), 116.0 (d, J = 22.0 Hz, 2 × CH), 118.9 (CH), 127.1 (d, J = 3.0 Hz, C_q), 127.6 (d, J = 8.0 Hz, 2 × CH), 146.9 (C_q), 162.8 (d, J = 247.0 Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}N_4F$ $[M+H]^+$: 273.1516, found: 273.1509.

5.1.7. (R)-3-(4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **9**

Compound **9** was obtained from 1-ethynyl-4-methoxybenzene following the general procedure **A** and isolated as a white solid in 21% yield. R_f: 0.33 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 122–124 °C; IR (ATR, Diamond): ν (cm^{-1}) 1029, 1060, 1106, 1177, 1249, 1307, 1454, 1497, 1561, 1618, 2870, 2937, 3399; ^1H NMR (250 MHz, DMSO-d_6): δ (ppm) 1.38–1.50 (m, 2H), 1.72–1.82 (m, 2H), 2.19–2.26 (m, 1H), 2.74–2.92 (m, 3H), 2.96–3.17 (m, 1H), 3.33–3.62 (m, 2H), 3.83 (s, 3H), 4.74–4.83 (m, 1H), 7.05 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.6 (CH_2), 25.2 (CH_2), 27.6 (CH), 46.3 (CH_2), 46.6 (CH_2), 51.8 (CH_2), 55.1 (CH_3), 57.2 (CH), 114.2 (2 × CH), 119.9 (CH), 123.5 (C_q), 126.5 (2 × CH), 146.1 (C_q), 158.9 (C_q); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_4O$ $[M+H]^+$: 285.1715, found: 285.1726.

5.1.8. (R)-3-(4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **10**

Compound **10** was obtained from 1-ethynyl-3-methoxybenzene following the general procedure **A** and isolated as pale yellow viscous oil in 32% yield. R_f: 0.45 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); IR (ATR, Diamond): ν (cm^{-1}) 1040, 1158, 1243, 1282, 1321, 1455, 1483, 1584, 1610, 2872, 2942; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.39–1.54 (m, 1H), 1.61–1.72 (m, 1H), 1.73–1.85 (m, 2H), 2.27–2.37 (m, 1H), 2.84–2.98 (m, 3H), 3.08–3.22 (m, 1H), 3.48 (ddd, J = 2.2 Hz, J = 9.8 Hz, J = 14.5 Hz, 1H), 3.71 (dd, J = 4.8 Hz, J = 14.5 Hz, 1H), 3.85 (s, 3H), 4.59–4.68 (m, 1H), 6.85–6.90 (m, 1H), 7.28–7.38 (m, 2H), 7.44–7.47 (m, 1H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.3 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.8 (CH_2), 55.6 (CH_3), 58.6 (CH), 110.9 (CH), 114.4 (CH), 118.2 (CH), 119.4 (CH), 130.1 (CH), 132.1 (C_q), 147.6 (C_q), 160.2 (C_q); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_4O$ $[M+H]^+$: 285.1715, found: 285.1719.

5.1.9. (R)-3-(4-(2-methoxyphenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **11**

Compound **11** was obtained from 1-ethynyl-2-methoxybenzene following the general procedure **A** and isolated as a white solid in 28% yield. R_f: 0.50 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 120–122 °C; IR (ATR, Diamond): ν (cm^{-1}) 969, 1017, 1043, 1067, 1120, 1240, 1322, 1434, 1488, 1583, 2864, 2927; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.37–1.52 (m, 1H), 1.63–1.74 (m, 1H), 1.75–1.85 (m, 2H), 2.28–2.39 (m, 1H), 2.85–2.99 (m, 3H), 3.10–3.24 (m, 1H), 3.46 (ddd, J = 2.2 Hz, J = 9.8 Hz, J = 14.3 Hz, 1H), 3.75 (dd, J = 5.2 Hz, J = 14.3 Hz, 1H), 3.94 (s, 3H), 4.59–4.68 (m, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.08 (td, J = 1.1 Hz, J = 7.6 Hz, 1H), 7.31 (ddd, J = 1.8 Hz, J = 7.6 Hz, J = 8.3 Hz, 1H), 8.08 (s, 1H), 8.35 (dd, J = 1.8 Hz, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.8 (CH_2), 55.6 (CH_3), 58.4 (CH), 111.0 (CH), 120.0 (C_q), 121.3 (CH), 122.7 (CH), 127.8 (CH), 129.0 (CH), 143.1 (C_q), 155.8 (C_q); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_4O$ $[M+H]^+$: 285.1723, found: 285.1715.

5.1.10. (R)-3-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **12**

Compound **12** was obtained from 1-ethynyl-4-chlorobenzene following the general procedure **A** and isolated as a white solid in 28% yield. R_f: 0.41 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 144–146 °C; IR (ATR, Diamond): ν (cm^{-1}) 971, 1014, 1060, 1092, 1190, 1202, 1324, 1401, 1433, 1452, 1468, 1484, 2868, 2939, 3110; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40–1.50 (m, 1H), 1.60–1.73 (m, 1H), 1.74–1.87 (m, 2H), 2.28–2.39 (m, 1H), 2.84–3.00 (m, 3H), 3.08–3.22 (m, 1H), 3.49 (ddd, J = 2.2 Hz, J = 9.9 Hz, J = 14.3 Hz, 1H), 3.70 (dd, J = 5.0 Hz, J = 14.3 Hz, 1H), 4.55–4.71 (m, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 7.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.7 (CH), 119.2 (CH), 127.1 (2 × CH), 129.3 (2 × CH), 129.4 (C_q), 134.1 (C_q), 146.7 (C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{18}N_4Cl$ $[M+H]^+$: 289.1220, found: 289.1211.

*5.1.11. (R)-3-(4-(3,4-dichlorophenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **13***

Compound **13** was obtained from 1-ethynyl-3,4-dichlorobenzene following the general procedure **A** and isolated as a white solid in 17% yield. R_f: 0.33 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 108–110 °C; IR (ATR, Diamond): ν (cm^{-1}) 986, 1029, 1044, 1133, 1231, 1324, 1457, 1561, 1606, 2871, 2942, 3385; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.41–1.57 (m, 1H), 1.59–1.74 (m, 1H), 1.76–1.87 (m, 2H), 2.28 (q, J = 3.0 Hz, 1H), 2.86–3.00 (m, 3H), 3.08–3.22 (m, 1H), 3.44–3.57 (m, 1H), 3.70 (dd, J = 5.0 Hz, J = 14.4 Hz, 1H), 4.61–4.71 (m, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.65 (dd, J = 1.9 Hz, J = 8.4 Hz, 1H), 7.84 (s, 1H), 7.91 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.1 (CH_2), 26.0 (CH_2), 28.3 (CH), 47.1 (CH_2), 47.4 (CH_2), 52.7 (CH_2), 58.7 (CH), 119.7 (CH), 125.0 (CH), 127.6 (CH), 130.9 (C_q), 131.0 (CH), 132.1 (C_q), 133.2 (C_q), 145.6 (C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{17}N_4Cl_2$ $[M+H]^+$: 323.0830, found: 323.0827.

*5.1.12. (R)-3-(4-(3,4-difluorophenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **14***

Compound **14** was obtained from 1-ethynyl-3,4-difluorobenzene following the general procedure **A** and isolated as a white solid in 24% yield. R_f: 0.33 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 122–124 °C; IR (ATR, Diamond): ν (cm^{-1}) 969, 989, 1025, 1045, 1059, 1207, 1281, 1449, 1508, 1606, 2869, 2942; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.40–1.55 (m, 1H), 1.59–1.74 (m, 1H), 1.75–1.88 (m, 2H), 2.26–2.30 (m, 1H), 2.85–2.99 (m, 3H), 3.07–3.20 (m, 1H), 3.48 (ddd, J = 2.1 Hz, J = 9.7 Hz, J = 14.4 Hz, 1H), 3.69 (dd, J = 4.8 Hz, J = 14.4 Hz, 1H), 4.59–4.68 (m, 1H), 7.14–7.26 (m, 1H), 7.50–7.57 (m, 1H), 7.66 (ddd, J = 2.1 Hz, J = 7.6 Hz, J = 11.2 Hz, 1H), 7.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.8 (CH_2), 58.8 (CH), 114.9 (d, J = 18.0 Hz, CH), 117.9 (d, J = 18.0 Hz, CH), 119.4 (CH), 121.9 (q, J = 5.0 Hz, CH), 128.0 (q, J = 5.0 Hz, C_q), 146.0 (C_q), 150.3 (q, J = 248.0 Hz, C_q), 150.8 (q, J = 248.0 Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{17}F_2N_4$ $[M+H]^+$: 291.1421, found: 291.1423.

*5.1.13. (R)-3-(4-(6-methoxynaphthalen-2-yl)-1H-1,2,3-triazol-1-yl)quinuclidine **15***

Compound **15** was obtained from 2-ethynyl-6-methoxynaphthalene following the general procedure **A** and isolated as a white solid in 21% yield. R_f: 0.29 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 186–188 °C; IR (ATR, Diamond): ν (cm^{-1}) 906, 1025, 1123, 1162, 1210, 1262, 1344, 1394, 1454, 1479, 1612, 1630, 2869, 2932; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42–1.56 (m, 1H), 1.65–1.76 (m, 1H), 1.77–1.88 (m, 2H), 2.31 (q, J = 3.1 Hz, 1H), 2.86–3.02 (m, 3H), 3.10–3.24 (m, 1H), 3.52 (ddd, J = 2.1 Hz, J = 9.7 Hz, J = 14.4 Hz, 1H), 3.73 (dd, J = 5.2 Hz, J = 14.4 Hz, 1H), 3.93 (s, 3H), 4.58–4.75 (m, 1H), 7.14 (s, 1H), 7.16–7.20 (m, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.89 (s, 1H), 7.91 (dd, J = 1.7 Hz, J = 9.0 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 55.6 (CH_3), 58.7 (CH), 106.0 (CH), 119.0 (CH), 119.5 (CH), 124.5 (CH), 124.6 (CH), 126.1 (C_q), 127.6 (CH), 129.2 (C_q), 129.9 (CH), 134.6 (C_q), 148.0 (C_q), 158.1 (C_q); HRMS (ESI): *m/z* calcd. for $C_{20}H_{23}N_4O$ $[M+H]^+$: 335.1872, found: 335.1866.

*5.1.14. (R)-3-(4-(pyridin-4-yl)-1H-1,2,3-triazol-1-yl)quinuclidine **16***

Compound **16** was obtained from 4-ethynylpyridine following the general procedure **A** and isolated as a white solid in 30% yield. R_f: 0.21 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 150–152 °C; IR (ATR, Diamond): ν (cm^{-1}) 991, 1041, 1058, 1073, 1208, 1227, 1325, 1413, 1430, 1562, 1613, 2869, 2935; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42–1.56 (m, 1H), 1.60–1.76 (m, 1H), 1.77–1.88 (m, 2H), 2.29 (q, J = 3.1 Hz, 1H), 2.86–3.00 (m, 3H), 3.07–3.25 (m, 1H), 3.50 (ddd, J = 2.1 Hz, J = 9.7 Hz, J = 14.5 Hz, 1H), 3.71 (dd, J = 5.0 Hz, J = 14.4 Hz, 1H), 4.63–4.72 (m, 1H), 7.73 (d, J = 6.0 Hz, 2H), 7.95 (s, 1H), 8.66 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 59.0 (CH), 120.1 (2 × CH), 120.7 (CH), 138.2 (C_q), 145.3 (C_q), 150.7 (2 × CH); HRMS (ESI): *m/z* calcd. for $C_{14}H_{18}N_5$ $[M+H]^+$: 256.1562, found: 256.1550.

*5.1.15. (R)-3-(4-(thiophen-2-yl)-1H-1,2,3-triazol-1-yl)quinuclidine **17***

Compound **17** was obtained from 2-ethynylthiophene following the general procedure **A** and isolated as a white solid in 38% yield. R_f: 0.42 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 137–139 °C; IR (ATR, Diamond): ν (cm^{-1}) 931, 973, 1027, 1042, 1062, 1159, 1212, 1295, 1316, 1432, 1451, 2867, 2937, 3074; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.38–1.53 (m, 1H), 1.59–1.72 (m, 1H), 1.73–1.85 (m, 2H), 2.26 (q, J = 3.1 Hz, 1H), 2.83–2.98 (m, 3H), 3.06–3.20 (m, 1H), 3.47 (ddd, J = 2.0 Hz, J = 9.7 Hz, J = 14.5 Hz, 1H), 3.68 (dd, J = 5.0 Hz, J = 14.5 Hz, 1H), 4.57–4.66 (m, 1H), 7.07 (dd, J = 3.6 Hz, J = 5.0 Hz, 1H), 7.25–7.30 (m, 1H), 7.38 (dd, J = 1.1 Hz, J = 3.6 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.3 (CH), 47.1 (CH_2), 47.4 (CH_2), 52.8 (CH_2), 58.7 (CH), 118.7 (CH), 124.3 (CH), 125.2 (CH), 127.8 (CH), 133.2 (C_q), 142.9 (C_q); HRMS (ESI): *m/z* calcd. for $C_{13}H_{17}N_4S$ $[M+H]^+$: 261.1174, found: 261.1185.

*5.1.16. (R)-(4-(1-(quinuclidin-3-yl)-1H-1,2,3-triazol-4-yl)phenyl) methanol **18***

Compound **18** was obtained from (4-ethynylphenyl)methanol following the general procedure **A** and isolated as a white solid in 32% yield. R_f: 0.11 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 200–202 °C; IR (ATR, Diamond): ν (cm^{-1}) 978, 1017, 1041, 1059, 1221, 1337, 1428, 1450, 1610, 2878, 2939, 3127, 3353; ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.39–1.56 (m, 2H), 1.71–1.82 (m, 2H), 2.22 (q, J = 3.0 Hz, 1H), 2.77–2.87 (m, 3H), 2.95–3.08 (m, 1H), 3.34–3.55 (m, 3H), 4.62 (d, J = 4.4 Hz, 1H), 4.74–4.83 (m, 1H), 5.25 (t, J = 4.4 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.87 (d, J = 8.3 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 19.6 (CH_2), 25.3 (CH_2), 27.6 (CH), 46.3 (CH_2), 46.6 (CH_2), 51.9 (CH_2), 57.4 (CH), 62.6 (CH_2), 120.6 (CH), 124.9 (2 × CH), 126.8 (2 × CH), 129.3 (C_q), 142.1 (C_q), 146.1 (C_q); HRMS (ESI): *m/z* calcd. for $C_{16}H_{21}N_4O$ $[M+H]^+$: 285.1715, found: 285.1702.

*5.1.17. 5-Ethynyl-2-fluoropyridine **20***

To a degassed solution of 2-fluoro-5-iodopyridine (4.00 g, 17.9 mmol) in triethylamine (30 mL) were successively added ethynyl(trimethyl)silane (2.78 mL, 19.7 mmol), copper iodide (340 mg, 1.79 mmol) and $Pd(PPh_3)_2Cl_2$ (1.25 g, 1.79 mmol). The reaction mixture was stirred at room temperature for 12 h. After cooling to room temperature, water (100 mL) was added and the organic material was extracted with Et_2O (5 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure to obtain **19** as a crude solid material. The crude derivative **19** was dissolved in THF (50 mL) and a TBAF solution (17.9 mL, 1 M in THF) was added dropwise. After 15 min, solvents were removed under reduced pressure and the residue was purified under flash chromatography to afford the alkyne **20** (petroleum ether/EtOAc 95/5) as a red oil in 82% yield. R_f: 0.49 (petroleum ether/EtOAc: 95/5); IR (ATR, Diamond): ν (cm^{-1}) 927, 1020, 1130, 1240, 1365, 1477, 1575, 3074; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.19 (s, 1H), 6.90 (dd, J = 3.0 Hz, J = 8.5 Hz, 1H), 7.85 (ddd, J = 2.3 Hz, J = 7.6 Hz, J = 8.5 Hz, 1H), 8.34 (d, J = 2.3 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) 79.2 (CH), 80.7 (d, J = 1.0 Hz, C_q), 109.6 (d, J = 38.0 Hz, CH), 117.3 (d, J = 5.0 Hz, C_q), 144.4 (d, J = 8.0 Hz, CH), 151.4 (d, J = 15.0 Hz, CH), 163.1 (d, J = 243.0 Hz, C_q); MS (IS): *m/z* for C_7H_5NF $[M+H]^+$: 122.0.

*5.1.18. 5-Ethynyl-2-methoxypyridine **21***

The crude alkyne **19** (*vide supra*) was dissolved in MeOH (60 mL) in the presence of K_2CO_3 (2.47 g, 17.9 mmol) for 3 h at room temperature. Solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc 95/5) to afford **21** as a pale yellow oil in 75% yield. R_f: 0.72 (petroleum ether/EtOAc: 96/4); IR (ATR, Diamond): ν (cm^{-1}) 1021, 1126, 1251, 1284, 1305, 1367, 1488, 1559, 1600, 3290; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.10 (s, 1H), 3.94 (s, 3H), 6.69 (d, $J = 8.6$ Hz, 1H), 7.63 (dd, $J = 2.3$ Hz, $J = 8.6$ Hz, 1H), 8.30 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 53.9 (CH_3), 78.8 (CH), 80.9 (C_q), 110.9 (CH), 112.1 (C_q), 141.8 (CH), 151.0 (CH), 163.9 (C_q); MS (IS): *m/z* for C_8H_8NO $[M + H]^+$: 134.0.

*5.1.19. 2-(4-Ethynylphenyl)ethanol **22** [43]*

Compound **22** [39] was obtained from 2-(4-bromophenyl) ethanol as described for **21** and was isolated as a white solid in 62% yield. R_f: 0.40 (petroleum ether/EtOAc: 80/20); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.51–1.65 (m, 1H), 2.84–2.90 (m, 2H), 3.07 (s, 1H), 3.83–3.89 (m, 2H), 7.19 (d, $J = 8.3$ Hz, 2H), 7.44 (d, $J = 8.3$ Hz, 2H); MS (IS): *m/z* for $C_{10}H_{11}O$ $[M + H]^+$: 147.0.

*5.1.20. 2-(4-Ethynylphenoxy)ethanol **23** [44]*

Compound **23** [40] was obtained from 2-(4-bromophenoxy) ethanol as described for **21** and was isolated as a white solid in 73% yield. R_f: 0.20 (petroleum ether/EtOAc: 80/20); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.15–2.18 (m, 1H), 3.00 (s, 1H), 3.94–3.97 (t, $J = 4.5$ Hz, 2H), 4.05–4.09 (m, 2H), 6.85 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 8.3$ Hz, 2H); MS (IS): *m/z* for $C_{10}H_{11}O_2$ $[M + H]^+$: 163.0.

*5.1.21. 1-Ethynyl-4-(2-(methoxymethoxy)ethoxy)benzene **24***

Compound **24** was obtained from 1-bromo-4-(2-(methoxymethoxy)ethoxy)benzene as described for **20** and was isolated as a white solid in 81% yield. R_f: 0.70 (petroleum ether/EtOAc: 80/20); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.05 (s, 1H), 3.39 (s, 3H), 3.87–3.90 (m, 2H), 4.10–4.16 (m, 2H), 4.70 (s, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.39 (d, $J = 8.7$ Hz, 2H); MS (IS): *m/z* for $C_{12}H_{15}O_3$ $[M + H]^+$: 207.0.

*5.1.22. 1-Ethynyl-4-(2-fluoroethyl)benzene **25***

Compound **25** was obtained from 1-bromo-4-(2-fluoroethyl) benzene as described for **20** and was isolated as a white solid in 45% yield. R_f: 0.20 (petroleum ether/EtOAc: 80/20); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.99 (dt, $J = 6.4$ Hz, $J = 23.7$ Hz, 2H), 3.12 (s, 1H), 4.61 (dt, $J = 6.4$ Hz, $J = 46.8$ Hz, 2H), 7.17 (d, $J = 8.3$ Hz, 2H), 7.41 (d, $J = 8.3$ Hz, 2H); MS (IS): *m/z* for $C_{10}H_{10}F$ $[M + H]^+$: 149.0.

*5.1.23. 1-Ethynyl-4-(2-fluoroethoxy)benzene **26***

Compound **26** was obtained from 1-bromo-4-(2-fluoroethoxy) benzene as described for **20** and was isolated as a white solid in 51% yield. R_f: 0.20 (EP/AcOEt: 80/20); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.99 (dt, $J = 6.6$ Hz, $J = 23.7$ Hz, 2H), 3.08 (s, 1H), 4.60 (dt, $J = 6.6$ Hz, $J = 47.0$ Hz, 2H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.41 (d, $J = 7.8$ Hz, 2H); MS (IS): *m/z* for $C_{10}H_{10}FO$ $[M + H]^+$: 165.0.

*5.1.24. 5-Ethynylbenzo[b]furane **28***

To a solution of dimethyl 1-diazo-2-oxopropylphosphonate **27** (1.15 g, 6.0 mmol) in anhydrous MeOH (60 mL) were successively added 5-formylbenzofuran (730 mg, 5.0 mmol) and K_2CO_3 (1.38 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 12 h. After a careful removal of solvent under reduced pressure, the crude material was purified by flash chromatography to furnish compound **28** as a white solid in 90% yield. R_f: 0.52 (petroleum ether/EtOAc: 95/5); M.p. 66–68 °C; IR (ATR, Diamond): ν (cm^{-1}) 882, 1029, 1107, 1118, 1195, 1265, 1329, 1436, 1460, 3290; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.03 (s, 1H), 6.75 (d, $J = 2.2$ Hz, 1H), 7.43–7.46 (m, 2H), 7.64 (d, $J = 2.2$ Hz, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 76.0 (CH), 84.2 (C_q), 106.7 (CH), 111.7 (CH), 116.8 (C_q), 125.6 (CH), 127.7 (C_q), 128.6 (CH), 146.1 (CH), 155.0 (C_q); MS (IS): *m/z* for $C_{10}H_7O$ $[M + H]^+$: 143.1.

*5.1.25. 5-Ethynylbenzo[b]thiophene **29***

Compound **29** was obtained from 5-formylbenzothiophene as described for **28** as a white solid in 84% yield. R_f: 0.40 (petroleum ether/EtOAc: 99/1); M.p. 55–57 °C; IR (ATR, Diamond): ν (cm^{-1}) 1050, 1088, 1222, 1258, 1324, 1411, 1431, 3082, 3101, 3277; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) 3.11 (s, 1H), 7.31 (d, $J = 5.5$ Hz, 1H), 7.43–7.51 (m, 2H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 76.9 (CH), 84.1 (C_q), 118.1 (C_q), 122.6 (CH), 123.8 (CH), 127.6 (CH), 127.7 (2 × CH), 139.6 (C_q), 140.3 (C_q); MS (IS): *m/z* for $C_{10}H_7S$ $[M + H]^+$: 159.1.

*5.1.26. 3-Ethynylquinuclidin-3-ol **31** [35]*

A solution of ethynyl(trimethyl)silane (4.44 mL, 31.4 mmol) in dry THF (30 mL) was cooled at −10 °C and solution of *n*-BuLi (12.6 mL, 2.5 M in hexane) was dropwise added. After 10 min at this temperature, the reaction mixture was cooled at −78 °C and a solution of 3-quinuclidone (3.74 g, 29.9 mmol) in THF (70 mL) was slowly added. The cold bath was removed just after the introduction of the ketone and after one hour of reaction at room temperature, brine (70 mL) was added. After extraction with EtOAc (2 × 35 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude silylated derivative **30** was dissolved again in MeOH (60 mL) in the presence of K_2CO_3 (3.89 g, 28.1 mmol). The novel reaction mixture was reduced under vacuum and the residue purified by flash chromatography (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%). The pure alkyne derivative **31** [45] was isolated as a white solid with a global yield of 43% (calcd from 3-quinuclidinone). R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 201–203 °C; IR (ATR, Diamond): ν (cm^{-1}) 989, 1024, 1048, 1071, 1138, 1154, 1317, 1455, 2596, 2754, 2873, 2934, 2950, 2965, 3216; ^1H NMR (250 MHz, MeOD): δ (ppm) 1.38–1.53 (m, 1H), 1.61–1.75 (m, 1H), 1.93–2.10 (m, 3H), 2.73–2.84 (m, 4H), 2.88 (d, $J = 13.8$ Hz, 1H), 2.89 (s, 1H), 3.13 (d, $J = 13.8$ Hz, 1H); MS (IS): *m/z* for $C_9H_{14}NO$ $[M + H]^+$: 152.8.

*5.1.27. (R)-3-(4-(6-fluoropyridin-3-yl)-1H-1,2,3-triazol-1-yl) quinuclidine **32***

Compound **32** was obtained from 5-ethynyl-2-fluoropyridine **20** following the general procedure **A** and isolated as a white solid in 18% yield. R_f: 0.32 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 147–149 °C; IR (ATR, Diamond): ν (cm^{-1}) 976, 1024, 1044, 1060, 1237, 1316, 1429, 1471, 1552, 1593, 2870, 2935; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45–1.54 (m, 1H), 1.63–1.72 (m, 1H), 1.74–1.90 (m, 2H), 2.29 (q, $J = 3.1$ Hz, 1H), 2.87–3.02 (m, 3H), 3.11–3.20 (m, 1H), 3.51 (ddd, $J = 2.0$ Hz, $J = 9.8$ Hz, $J = 14.4$ Hz, 1H), 3.71 (dd, $J = 5.1$ Hz, $J = 14.4$ Hz, 1H), 4.63–4.69 (m, 1H), 7.02 (dd, $J = 2.9$ Hz, $J = 8.5$ Hz, 1H), 7.87 (s, 1H), 8.28–8.37 (m, 1H), 8.60 (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.2 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.9 (CH), 110.1 (d, $J = 38.0$ Hz, CH), 119.4 (CH), 125.3 (d, $J = 5.0$ Hz, C_q), 138.7 (d, $J = 8.0$ Hz, CH), 143.8 (C_q), 144.9 (d, $J = 15.0$ Hz, CH), 163.5 (d, $J = 240.0$ Hz, C_q); HRMS (ESI): *m/z* calcd. for $C_{14}H_{17}N_5F$ $[M + H]^+$: 274.1468, found: 274.1465.

*5.1.28. (R)-3-(4-(6-methoxypyridin-3-yl)-1H-1,2,3-triazol-1-yl) quinuclidine **33***

Compound **33** was obtained from 5-ethynyl-2-methoxypyridine **21** following the general procedure **A** and isolated as a white solid in 28% yield. R_f: 0.28 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 155–157 °C; IR (ATR, Diamond): ν (cm^{-1}) 973, 1027, 1215, 1254,

1282, 1325, 1420, 1481, 1555, 1614, 1729, 2869, 2938; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.40–1.55 (m, 1H), 1.62–1.74 (m, 1H), 1.75–1.88 (m, 2H), 2.27 (q, *J* = 3.0 Hz, 1H), 2.84–3.00 (m, 3H), 3.08–3.22 (m, 1H), 3.42–3.56 (m, 1H), 3.72 (dd, *J* = 4.3 Hz, *J* = 14.3 Hz, 1H), 3.97 (s, 3H), 4.58–4.69 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 8.07 (dd, *J* = 2.2 Hz, *J* = 8.6 Hz, 1H), 8.56 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 53.8 (CH_3), 58.8 (CH), 111.3 (CH), 118.7 (CH), 120.5 (C_q), 136.5 (CH), 144.3 (CH), 145.0 (C_q), 164.2 (C_q); HRMS (ESI): *m/z* calcd. for $C_{15}H_{20}N_5O$ $[M+H]^+$: 286.1668, found: 286.1681.

5.1.29. (R)-2-(4-(1-(quinuclidin-3-yl)-1H-1,2,3-triazol-4-yl)phenyl) ethanol **34**

Compound **34** was obtained from alkyne **22** following the general procedure **A** and isolated as a white solid in 38% yield. R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 95/5 + 1%); M.p. 148–150 °C; IR (ATR, Diamond): ν (cm^{-1}) 788, 815, 917, 1038, 1153, 1265, 1452, 1502, 1613, 2853, 2930; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44–1.51 (m, 1H), 1.64–1.71 (m, 1H), 1.75–1.84 (m, 2H), 2.17 (br s, 1H), 2.27 (q, *J* = 3.0 Hz, 1H), 2.88–2.98 (m, 5H), 3.09–3.16 (m, 1H), 3.42–3.48 (m, 1H), 3.67 (dd, *J* = 4.8 Hz, *J* = 14.4 Hz, 1H), 3.88 (t, *J* = 6.5 Hz, 2H), 4.61–4.66 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.77–7.79 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.9 (CH_2), 25.9 (CH_2), 28.1 (CH), 39.0 (CH_2), 46.8 (CH_2), 47.2 (CH_2), 52.5 (CH_2), 58.2 (CH), 63.4 (CH_2), 118.8 (CH), 125.9 (2 × CH), 128.8 (C_q), 129.5 (2 × CH), 138.8 (C_q), 147.4 (C_q); HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}N_4O$ $[M+H]^+$: 299.1872, found: 299.1870.

5.1.30. (R)-2-(4-(1-(quinuclidin-3-yl)-1H-1,2,3-triazol-4-yl) phenoxy)ethanol **35**

Compound **35** was obtained from alkyne **23** following the general procedure **A** and isolated as a white solid in 44% yield. R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 95/5 + 1%), M.p. 168–170 °C; IR (ATR, Diamond): ν (cm^{-1}) 694, 822, 925, 1040, 1155, 1267, 1458, 1530, 1602, 2836, 2950; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.34–1.47 (m, 2H), 1.67–1.78 (m, 2H), 2.17 (q, *J* = 3.0 Hz, 1H), 2.71–2.79 (m, 3H), 2.93–3.00 (m, 1H), 3.32–3.47 (m, 2H), 3.73 (d, *J* = 3.0 Hz, 2H), 4.02 (t, *J* = 5.0 Hz, 2H), 4.70–4.74 (m, 1H), 4.87 (br s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 8.60 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.1 (CH_2), 25.8 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.1 (CH_2), 52.4 (CH_2), 57.8 (CH_2), 60.0 (CH_2), 70.0 (CH), 115.2 (2 × CH), 120.3 (CH), 123.9 (C_q), 126.9 (2 × CH), 146.5 (C_q), 158.8 (C_q); HRMS (ESI): *m/z* calcd. for $C_{17}H_{23}N_4O_2$ $[M+H]^+$: 315.1815, found: 315.1817.

5.1.31. (R)-3-(4-(4-(2-(methoxymethoxy)ethoxy)phenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **36**

Compound **36** was obtained from alkyne **24** following the general procedure **A** and isolated as a white solid in 30% yield. R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 95/5 + 1%); M.p. 125–127 °C; IR (ATR, Diamond): ν (cm^{-1}) 610, 789, 802, 917, 989, 1041, 1109, 1153, 1249, 1452, 1497, 1613, 2865, 2940; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45–1.56 (m, 1H), 1.67–1.88 (m, 3H), 2.26 (q, *J* = 3.0 Hz, 1H), 2.89–2.98 (m, 3H), 3.10–3.17 (m, 1H), 3.40 (s, 3H), 3.43–3.51 (t, *J* = 12.6 Hz, 1H), 3.67–3.72 (dd, *J* = 4.3 Hz, *J* = 14.1 Hz, 1H), 3.90–3.92 (t, *J* = 3.1 Hz, 2H), 4.17–4.20 (t, *J* = 5.1 Hz, 2H), 4.61–4.63 (m, 1H), 4.72 (s, 2H), 6.97–6.99 (d, *J* = 9.1 Hz, 2H), 7.72 (s, 1H), 7.74–7.76 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.9 (CH_2), 25.9 (CH_2), 27.9 (CH), 46.8 (CH_2), 47.1 (CH_2), 52.5 (CH_2), 55.1 (CH_3), 58.1 (CH), 65.7 (CH_2), 67.2 (CH_2), 96.4 (CH_2), 114.7 (2 × CH), 117.9 (CH), 123.4 (C_q), 126.7 (2 × CH), 147.2 (C_q), 158.5 (C_q), HRMS (ESI): *m/z* calcd. for $C_{19}H_{27}N_4O_3$ $[M+H]^+$: 359. 2078, found: 359.2081.

5.1.32. (R)-3-(4-(4-(2-fluoroethyl)phenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **37**

Compound **37** was obtained from alkyne **25** following the general procedure **A** and isolated as a white solid in 17% yield. R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 95/5 + 1%); M.p. 108–110 °C; IR (ATR, Diamond): ν (cm^{-1}) 612, 662, 781, 802, 834, 969, 1014, 1161, 1180, 1261, 1655, 2118, 2940, 2958; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.45–1.51 (m, 1H), 1.67–1.88 (m, 3H), 2.28 (q, *J* = 3.2 Hz, 1H), 2.94–3.09 (m, 5H), 3.11–3.23 (m, 1H), 3.48–3.54 (m, 1H), 3.73 (d, *J* = 12.2 Hz, 1H), 4.57–4.73 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.78–7.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8 (CH_2), 25.8 (CH_2), 28.0 (CH), 36.4 (CH_2), 36.6 (CH_2), 46.9 (d, *J* = 36.0 Hz, CH_2), 52.4 (CH_2), 58.1 (CH), 83.8 (d, *J* = 168.0 Hz, CH_2), 118.7 (CH), 125.7 (2 × CH), 129.0 (C_q), 129.3 (2 × CH), 137.0 (d, *J* = 6.0 Hz, C_q), 147.2 (C_q); HRMS (ESI): *m/z* calcd. for $C_{17}H_{22}FN_4$ $[M+H]^+$: 301.1822, found: 301.1824.

5.1.33. (R)-3-(4-(4-(2-fluoroethoxy)phenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **38**

Compound **38** was obtained from alkyne **26** following the general procedure **A** and isolated as a white solid in 11% yield. R_f: 0.35 (CH_2Cl_2/MeOH + NH_4OH: 95/5 + 1%); M.p. 126–128 °C; IR (ATR, Diamond): ν (cm^{-1}) 618, 787, 802, 837, 888, 926, 1047, 1072, 1107, 1249, 1316, 1428, 1489, 1617, 1688, 2867, 2938, 3120; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42–1.51 (m, 1H), 1.65–1.83 (m, 3H), 2.26 (q, *J* = 3.2 Hz, 1H), 2.85–3.00 (m, 3H), 3.10–3.17 (m, 1H), 3.44–3.51 (m, 1H), 3.69 (dd, *J* = 4.6 Hz, *J* = 14.6 Hz, 1H), 4.25 (dt, *J* = 4.4 Hz, *J* = 27.6 Hz, 2H), 4.61–4.64 (m, 1H), 4.77 (dt, *J* = 4.4 Hz, *J* = 47.2 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.73 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.8 (CH_2), 25.8 (CH_2), 27.9 (CH), 46.7 (CH_2), 47.1 (CH_2), 52.5 (CH_2), 58.2 (CH), 67.0 (d, *J* = 21.0 Hz, CH_2), 81.7 (d, *J* = 170.0 Hz, CH_2), 114.8 (2 × CH), 118.1 (CH), 123.8 (C_q), 126.8 (2 × CH), 147.1 (C_q), 158.2 (C_q); HRMS (ESI): *m/z* calcd. for $C_{17}H_{22}FN_4O$ $[M+H]^+$: 317.1772, found: 317.1774.

5.1.34. (R)-3-(4-(benzofuran-5-yl)-1H-1,2,3-triazol-1-yl) quinuclidine **39**

Compound **39** was obtained from alkyne **28** following the general procedure **A** and isolated as a white solid in 34% yield. R_f: 0.34 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 180–182 °C; IR (ATR, Diamond): ν (cm^{-1}) 989, 1029, 1062, 1109, 1194, 1221, 1321, 1455, 1497, 2870, 2935; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44–1.53 (m, 1H), 1.67–1.77 (m, 1H), 1.78–1.89 (m, 2H), 2.30 (q, *J* = 3.0 Hz, 1H), 2.88–3.00 (m, 3H), 3.12–3.22 (m, 1H), 3.46–3.55 (m, 1H), 3.73 (dd, *J* = 4.3 Hz, *J* = 14.3 Hz, 1H), 4.63–4.69 (m, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.76 (dd, *J* = 1.6 Hz, *J* = 8.6 Hz, 1H), 7.82 (s, 1H), 8.10 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.6 (CH), 107.0 (CH), 111.9 (CH), 118.6 (CH), 118.8 (CH), 122.6 (CH), 125.9 (C_q), 128.2 (C_q), 145.9 (CH), 148.2 (C_q), 155.1 (C_q); HRMS (ESI): *m/z* calcd. for $C_{17}H_{19}N_4O$ $[M+H]^+$: 295.1559, found: 295.1557.

5.1.35. (R)-3-(4-(benzo[b]thiophen-5-yl)-1H-1,2,3-triazol-1-yl) quinuclidine **40**

Compound **40** was obtained from alkyne **29** following the general procedure **A** and isolated as a white solid in 32% yield. R_f: 0.32 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 178–180 °C; IR (ATR, Diamond): ν (cm^{-1}) 1023, 1047, 1202, 1223, 1323, 1440, 2866, 2933; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.44–1.53 (m, 1H), 1.66–1.76 (m, 1H), 1.77–1.88 (m, 2H), 2.30 (q, *J* = 3.0 Hz, 1H), 2.86–3.00 (m, 3H), 3.11–3.21 (m, 1H), 3.50 (ddd, *J* = 2.1 Hz, *J* = 9.8 Hz, *J* = 14.5 Hz, 1H), 3.70 (dd, *J* = 5.0 Hz, *J* = 14.5 Hz, 1H), 4.62–4.69 (m, 1H), 7.37 (d, *J* = 5.4 Hz, 1H), 7.47 (d, *J* = 5.4 Hz, 1H), 7.80 (dd, *J* = 1.1 Hz, *J* = 8.4 Hz, 1H), 7.86 (s, 1H), 7.92 (d, *J* = 8.4 Hz,

1H), 8.33 (d, J = 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.2 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.6 (CH), 119.1 (CH), 120.8 (CH), 122.4 (CH), 123.1 (CH), 124.2 (CH), 127.2 (C_q), 127.4 (CH), 139.6 (C_q), 140.2 (C_q), 147.9 (C_q); HRMS (ESI): m/z calcd. for $C_{17}H_{19}N_4S$ $[M+H]^+$: 311.1330, found: 311.1322.

5.1.36. 3-(1-(4-Bromophenyl)-1H-1,2,3-triazol-4-yl)quinuclidin-3-ol **41**

Compound **41** was obtained from alkyne **31** following the general procedure **A** and isolated as a white solid in 91% yield. R_f: 0.22 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 214–216 °C; IR (ATR, Diamond): ν (cm^{-1}) 994, 1040, 1214, 1320, 1445, 1496, 2871, 2927, 3112; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.42–1.58 (m, 3H), 2.15–2.31 (m, 2H), 2.72–3.04 (m, 4H), 3.08 (d, J = 14.3 Hz, 1H), 3.32 (br s, 1H), 3.62 (dd, J = 1.3 Hz, J = 14.3 Hz, 1H), 7.59–7.68 (m, 4H), 7.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.8 (CH_2), 23.1 (CH_2), 33.7 (CH), 46.4 (CH_2), 47.1 (CH_2), 62.3 (CH_2), 69.7 (C_q), 119.0 (CH), 122.1 (2 × CH), 122.7 (C_q), 133.1 (2 × CH), 136.1 (C_q), 155.1 (C_q); HRMS (ESI): m/z calcd. for $C_{15}H_{18}BrN_4O$ $[M+H]^+$: 349.0664, found: 349.0657.

5.1.37. 3-(1-(4-Methoxyphenyl)-1H-1,2,3-triazol-4-yl)quinuclidin-3-ol **42**

Compound **42** was obtained from alkyne **31** following the general procedure **A** and isolated as a white solid in 87% yield. R_f: 0.22 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 174–176 °C; IR (ATR, Diamond): ν (cm^{-1}) 992, 1049, 1133, 1231, 1305, 1439, 1517, 2873, 2928, 2998, 3112, 3348; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.42–1.58 (m, 3H), 2.17–2.31 (m, 2H), 2.76–2.95 (m, 3H), 2.96–3.14 (m, 2H), 3.20–3.43 (m, 1H), 3.61 (dd, J = 1.6 Hz, J = 14.4 Hz, 1H), 3.86 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H), 7.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 21.2 (CH_2), 23.3 (CH_2), 33.7 (CH), 46.5 (CH_2), 47.1 (CH_2), 55.8 (CH_3), 62.4 (CH_2), 69.7 (C_q), 115.0 (2 × CH), 119.2 (CH), 122.4 (2 × CH), 130.7 (C_q), 154.5 (C_q), 160.0 (C_q); HRMS (ESI): m/z calcd. for $C_{16}H_{21}N_4O_2$ $[M+H]^+$: 301.1665, found m/z = 301.1669.

5.1.38. (R)-3-(4-(4-(fluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl) quinuclidine **43**

To a solution of alcohol **18** (140 mg, 0.500 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added dropwise the DAST (92 μL, 0.70 mmol). After 1 h, a saturated aqueous $NaHCO_3$ solution (20 mL) was added. After extraction, the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (CH_2Cl_2/MeOH + NH_4OH: 90/10 + 1%) to afford **43** as a white solid with a 51% yield. R_f: 0.41 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 148–150 °C; IR (ATR, Diamond): ν (cm^{-1}) 974, 1010, 1060, 1212, 1317, 1382, 1407, 1453, 1500, 2870, 2940; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.41–1.56 (m, 1H), 1.62–1.74 (m, 1H), 1.76–1.94 (m, 2H), 2.30 (q, J = 3.0 Hz, 1H), 2.86–3.00 (m, 3H), 3.09–3.24 (m, 1H), 3.50 (ddd, J = 2.0 Hz, J = 9.6 Hz, J = 14.6 Hz, 1H), 3.72 (dd, J = 5.1 Hz, J = 14.5 Hz, 1H), 4.61–4.70 (m, 1H), 5.41 (d, J = 47.8 Hz, 2H), 7.44 (dd, J = 1.6 Hz, J = 8.6 Hz, 2H), 7.84 (s, 1H), 7.88 (dd, J = 1.0 Hz, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.3 (CH_2), 26.2 (CH_2), 28.4 (CH), 47.1 (CH_2), 47.5 (CH_2), 52.9 (CH_2), 58.7 (CH), 84.5 (d, J = 166.0 Hz, CH_2), 119.4 (CH), 126.1 (2 × CH), 128.2 (d, J = 6.0 Hz, 2 × CH), 131.4 (d, J = 3.0 Hz, C_q), 136.2 (d, J = 17.0 Hz, C_q), 147.3 (C_q); HRMS (ESI): m/z calcd. for $C_{16}H_{20}N_4F$ $[M+H]^+$: 287.1672, found: 287.1660.

5.1.39. 3-Fluoro-3-(1-(4-bromophenyl)-1H-1,2,3-triazol-4-yl) quinuclidine **44**

Compound **44** was obtained as described for **43** starting from **41** as a white solid in 64% yield. R_f: 0.52 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); M.p. 127–129 °C; IR (ATR, Diamond): ν (cm^{-1}) 991, 1018, 1038, 1075, 1222, 1246, 1321, 1453, 1497, 2869, 2933; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.46–1.68 (m, 2H), 1.69–1.84 (m, 1H), 2.05–1.19 (m, 1H), 2.28–2.35 (m, 1H), 2.76–2.92 (m, 1H), 2.93–3.06 (m, 3H), 3.29 (dd, J = 15.2 Hz, J = 30.5 Hz, 1H), 3.82 (dd, J = 15.2 Hz, J = 24.8 Hz, 1H), 7.59–7.69 (m, 4H), 8.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.6 (d, J = 8.0 Hz, CH_2), 22.3 (d, J = 6.0 Hz, CH_2), 32.9 (d, J = 24.0 Hz, CH), 46.5 (CH_2), 47.0 (CH_2), 59.7 (d, J = 24.0 Hz, CH_2), 93.4 (d, J = 177.0 Hz, C_q), 119.6 (d, J = 5.0 Hz, CH), 122.1 (2 × CH), 122.8 (C_q), 133.1 (2 × CH), 136.0 (C_q), 151.0 (d, J = 32.0 Hz, C_q); HRMS (ESI): m/z calcd. for $C_{15}H_{17}BrFN_4$ $[M+H]^+$: 351.0621, found: 351.0637.

5.1.40. 3-Fluoro-3-(1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl) quinuclidine **45**

Compound **45** was obtained as described for **43** starting from **42** as a pale viscous oil in 64% yield. R_f: 0.54 (CH_2Cl_2/MeOH + NH_4OH: 80/20 + 1%); IR (ATR, Diamond): ν (cm^{-1}) 992, 1043, 1110, 1175, 1254, 1306, 1462, 1518, 1611, 2961, 3392; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 1.45–1.62 (m, 2H), 1.64–1.82 (m, 1H), 2.02–2.19 (m, 1H), 2.28–2.36 (m, 1H), 2.74–2.90 (m, 1H), 2.91–3.04 (m, 3H), 3.28 (dd, J = 15.2 Hz, J = 30.5 Hz, 1H), 3.75–3.83 (m, 1H), 3.85 (s, 3H), 7.01 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.7 (d, J = 8.0 Hz, CH_2), 22.4 (d, J = 8.0 Hz, CH_2), 32.9 (d, J = 24.0 Hz, CH), 46.5 (CH_2), 47.0 (CH_2), 55.8 (CH_3), 59.7 (d, J = 24.0 Hz, CH_2), 93.4 (d, J = 175.0 Hz, C_q), 115.0 (2 × CH), 119.9 (d, J = 4.0 Hz, CH), 122.4 (2 × CH), 130.6 (C_q), 150.4 (d, J = 32.0 Hz, C_q), 160.1 (C_q); HRMS (ESI): m/z calcd for $C_{16}H_{20}FN_4O$ $[M+H]^+$: 303.1621, found: 303.1623.

5.2. In vitro biological evaluations

The measurement of Ki towards α7 nAChR was performed on a membrane preparation from rat frontal cortices according to a previously described method [19–21]. Stable α-bungarotoxin was obtained from Tocris Bioscience (R&D Systems, Lille, France) and [^{125}I]α-bungarotoxin (specific activity 81.4 TBq/mmol) from Perkin–Elmer (Courtaboeuf, France). The IC_{50} values were determined graphically for each compound and the Ki calculated [46]. Selectivity experiments towards the α4β2 and 5-HT_3 receptors were performed by CEREP (Poitiers, France) on cells transfected with human recombinants using as reference ligands [^{3}H]cytisine and [^{3}H]BRL 43694, respectively.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.11.001.

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