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Bis(het)aryl-1,2,3-triazole quinuclidines as α7 nicotinic acetylcholine receptor ligands: synthesis, structure affinity relationships, agonism activity, [^{18}F]-radiolabeling and PET study in rats.

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Abstract

In this paper we describe the design and synthesis of bis(Het)Aryl-1,2,3-triazole quinuclidine α7R ligands using an efficient three-step sequence including a Suzuki-Miyaura cross coupling reaction with commercially available and home-made boron derivatives. The exploration of SAR required the preparation of uncommon boron derivatives. Forty final drugs were tested for their ability to bind the target and nine of them exhibited Ki values below nanomolar concentrations. The best scores were always obtained when the 5-phenyl-2-thiophenyl core was attached to the triazole. The selectivity of these compounds towards the nicotinic α4β2 and serotoninergic 5HT3 receptors was assessed and their brain penetration was quantified by the preparation and *in vivo* evaluation of two [^{18}F] radiolabelled derivatives. It can be expected from our results that some of these compounds will be suitable for further developments and will have effects on cognitive disorders.

Introduction

The role of the brain cholinergic system is largely mediated through nicotinic receptors, which are ligand-gated ion channels composed of 5 subunits belonging to α and/or β subfamily. The rich diversity of expression and function of nicotinic receptors, with neuronal but also non-neuronal localization, and several sub-types which can interact in the control of different neurotransmission pathways, support their major and complex involvement in a large variety of physiological and cognitive functions.[1] The predominant subtypes of nicotinic receptors in human brain are the heteropentameric α4β2 and homopentameric α7 forms. The α7 nicotinic acetylcholine receptor (α7R) is of particular interest due to its involvement in various brain disorders such as schizophrenia and Alzheimer's disease,[2, 3] associated to its significant role in neuroinflammation. [4, 5]

[5] The crucial role of α7R in a number of specific functional systems and diseases has recently been extensively reviewed. [6, 7]

The in vivo exploration of α7R by a molecular imaging method such as PET (positron emission tomography) is a highly promising way to better understand the changes associated with the appearance and progression of these brain diseases but also to monitor treatment efficacy and to improve the development of new therapeutic strategies. The key step in this exploration is the availability of a suitable radiotracer, and several recent papers have reviewed the state of progress in this field (Figure 1). [8-10]

We recently designed a novel series of α7R ligands using a straightforward methodology able to selectively furnish derivatives of type **I** having a 1,2,3- triazole group attached directly to a *(R)* quinuclidine in *C*-3. [11, 12] As demonstrated by another research group, these ligands appeared suitable for therapeutic use. [13-16]

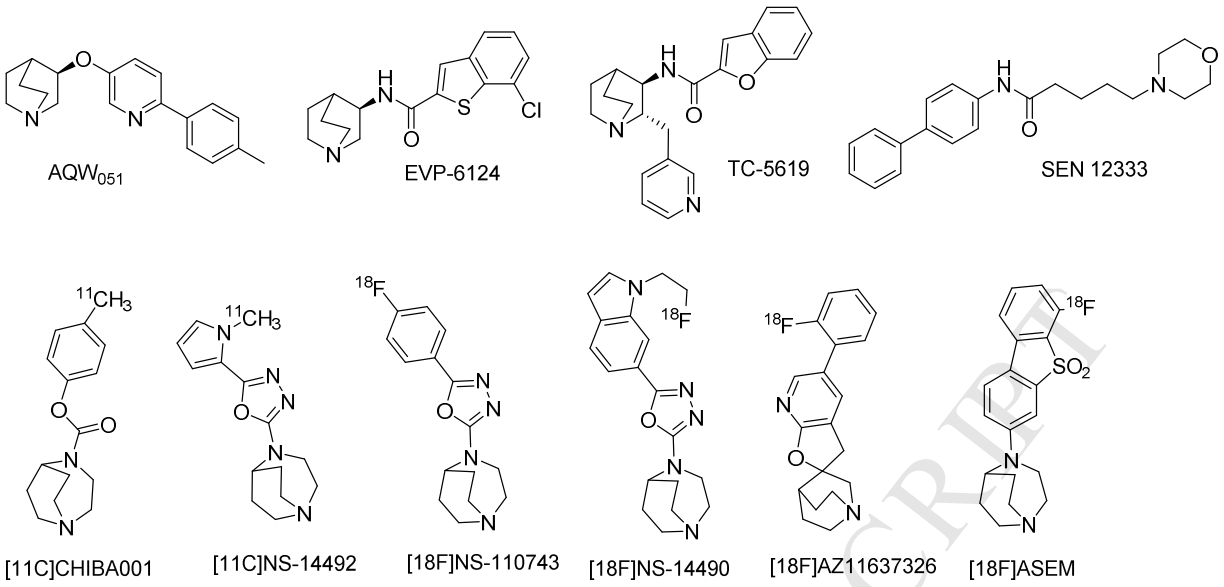


Figure 1. Some representative α7 nicotinic receptor ligands developed either for therapy or PET imaging.

SAR studies in family **I** showed that meta and para (Het)Ar substitutions were tolerated but that the best Ki values remained mainly up to 2 nM (compound **1**). Following a disruptive approach from two interesting benzothiofuran **2** and benzothiophen **3** derivatives, we developed unfused bis(Het)Ar derivatives of type **II** (Figure 2).

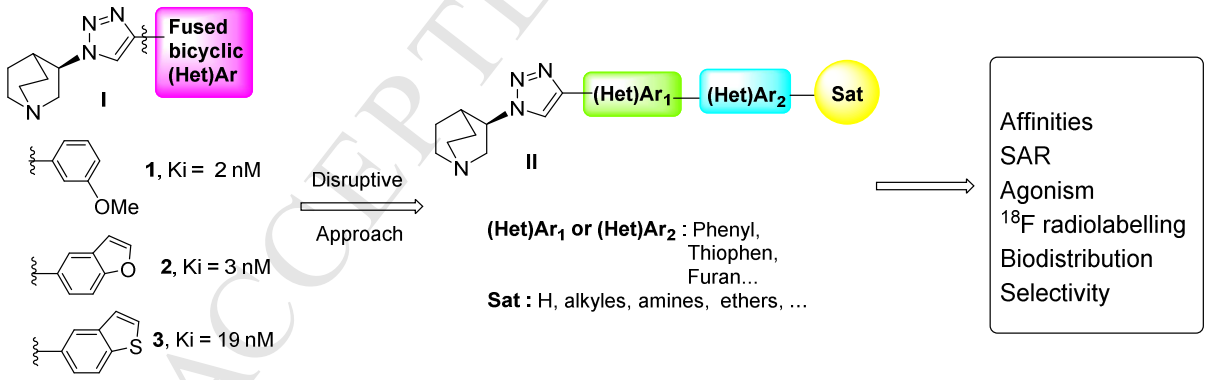


Figure 2. Drug design strategies leading to the development of the bis(Het)Ar derivatives **II**. Sat = Satellites.

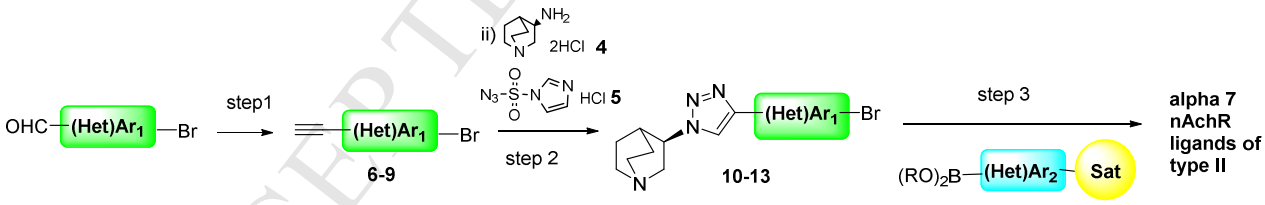
In this paper, we present the SAR evolution leading to very efficient ligands exhibiting improved inhibition constants in the (sub)nanomolar range. Each terminal (Het)Ar_2 group was additionally equipped with some satellite functions (Sat) in order to explore the SAR

diversity, and modulate the binding and hydrophilic or lipophilic balance parameters. Globally, to envision a further development of the available series, a set of 47 final derivatives was evaluated and among them some were selected to determine their agonist potency as well as their selectivity against α4β2 and 5-HT_3 receptors. The most potent fluorinated compounds were radiolabelled with ^{18}F in order to evaluate their biological properties *in vivo* in rodents and their CNS compatibility.

Results and discussion

Synthesis

The synthesis of the library of type **II** ligands was achieved from (R)-3-quinuclidine amine bis-hydrochloride **4** after three steps (Scheme 1). The first step consists in the preparation of the azide followed by direct Huisgen condensation using bromo (Het)Ar_1 terminal alkynes, leading to the regioselective synthesis of 1,2,3-triazole. The last step is the Suzuki cross coupling reaction which was carried out between borylated building blocks and the previously formed brominated intermediate**.**

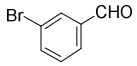
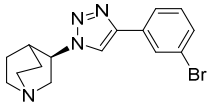
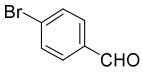
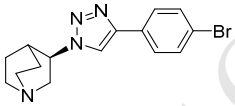
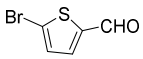
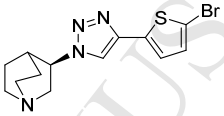
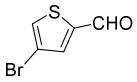
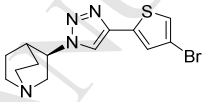


Scheme 1. Synthetic pathway to generate α7R ligands **II**.

To achieve this synthetic pathway, it was first necessary to generate a library of bromo(Het)Ar terminal alkynes (Table 1). All of them were prepared from commercially available aldehydes in the presence of the Bestmann Ohira reagent and an excess of base.[17] Acetylenes **6-9** were obtained in near stoichiometric yields and stored without any precaution. Synthesis of the regioselective triazole was achieved from the azide of **4** (which was obtained

using the highly unstable reagent **5**) and the alkynes **6-9** under classical copper catalyzed conditions to afford the brominated derivatives **10-13** in satisfying yields.[18]

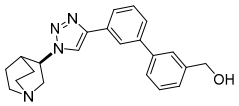
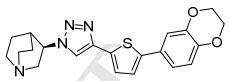
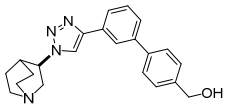
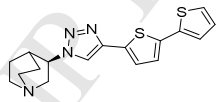
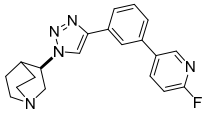
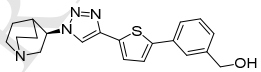
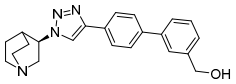
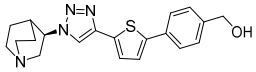
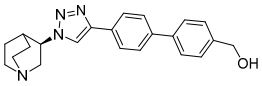
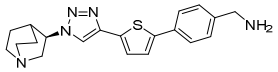
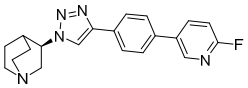
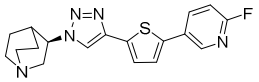
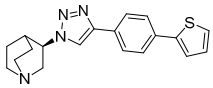
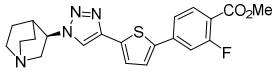
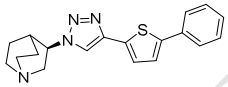
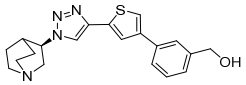
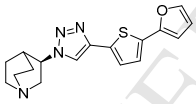
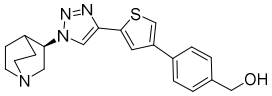
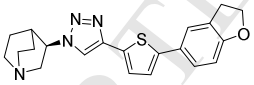
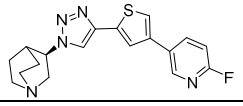
Table 1. Synthesis of compounds **10-13**.

Entry	Aldehydes	Alkynyl Compounds (Step 1[a], Yield)	Brominated Compounds (Step 2[b], Yields)
1		**6**[19] (95%)[c]	 **10** (50%)[c]
2		**7**[20] (92%)[c]	 **11** (54%)[c]
3		**8**[21] (92%)[c]	 **12** (42%)[c]
4		**9**[22] (90%)[c]	 **13** (50%)[c]

[a] Dimethyl (1-diazo-2-oxopropyl)phosphonate (1.2 eq.), K_2CO_3 (2.0 eq.), MeOH, r.t., 12 h. [b] 1*H*-Imidazole-1-sulfonyl azide (1.0 eq.), $CuSO_4.5H_2O$ 10 mol %, K_2CO_3 (3.0 eq.), MeOH, r.t., 6h and then alkyne (1.0 eq.), Na ascorbate (0.2 eq.), $CuSO_4.5H_2O$ 10 mol %, MeOH, r.t., 12h. Yields are indicated in isolated products.

The last step of the synthesis was carried out with compounds **10-13** and a set of boron derivatives. In the first place, starting from **10** or **11,** the cross coupling reactions were achieved using $Pd(PPh_3)_4$ and K_2CO_3 under microwave irradiation.[23] After 15 minutes at 150 °C, using commercially available boronic acids, the final derivatives **14-20** were obtained in yields up to 81% (Table 2, entries 1-7).

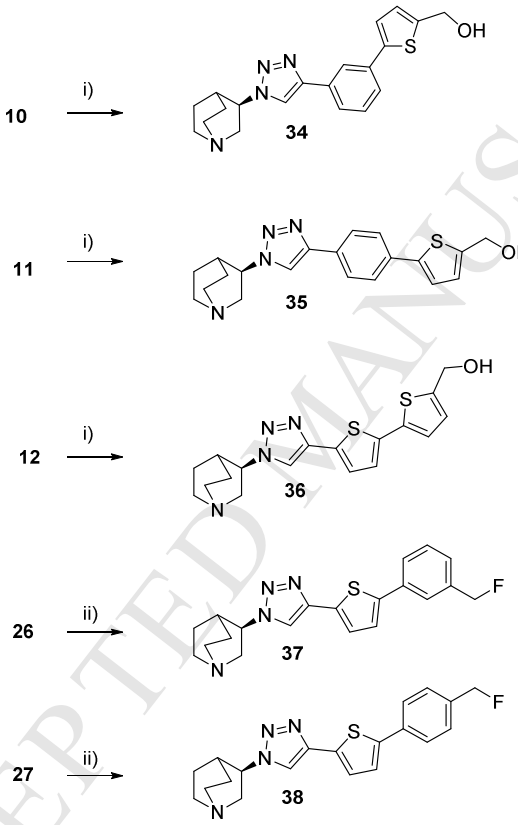
Table 2. Synthesis of the library of type **II** compounds by direct condensation of boronic acids with derivatives **10-13**.

Entry	SM	Compounds of type II (Yield)[a]		Entry	SM	Compounds of type II (Yield)[a]	
1	**10**	**14** (81%)[b]		11	**12**	**24** (91%)[c]	
2	**10**	**15** (92%)[b]		12	**12**	**25** (73%)[c]	
3	**10**	**16** (92%)[b]		13	**12**	**26** (75%)[b,d]	
4	**11**	**17** (80%)[b]		14	**12**	**27** (72%)[b,d]	
5	**11**	**18** (81%)[b]		15	**12**	**28** (77%)[c]	
6	**11**	**19** (85%)[b]		16	**12**	**29** (80%) [b,d]	
7	**11**	**20** (86%)[b]		17	**12**	**30** (85%)[c]	
8	**12**	**21** (85%)[c]		18	**13**	**31** (80%) [b,d]	
9	**12**	**22** (83%)[b]		19	**13**	**32** (79%)[c]	
10	**12**	**23** (91%)[c]		20	**13**	**33** (66%)[b,d]	

[a] Yields are indicated in isolated products. [b] Obtained with boronic derivative (1.2 eq.), $Pd(PPh_3)_4$ 10 mol %, K_2CO_3 (2.0 eq.), toluene / MeOH 2 / 1, μW, 150 °C, 15 min. [c] Obtained with boronic derivative (1.2 eq.), $PdCl_2(dppf)$ 10 mol %, Na_2CO_3 (2.0 eq.), toluene / MeOH 2 / 1, μW, 100 °C, 40 min. [d] 20 minutes microwave irradiation reaction time.

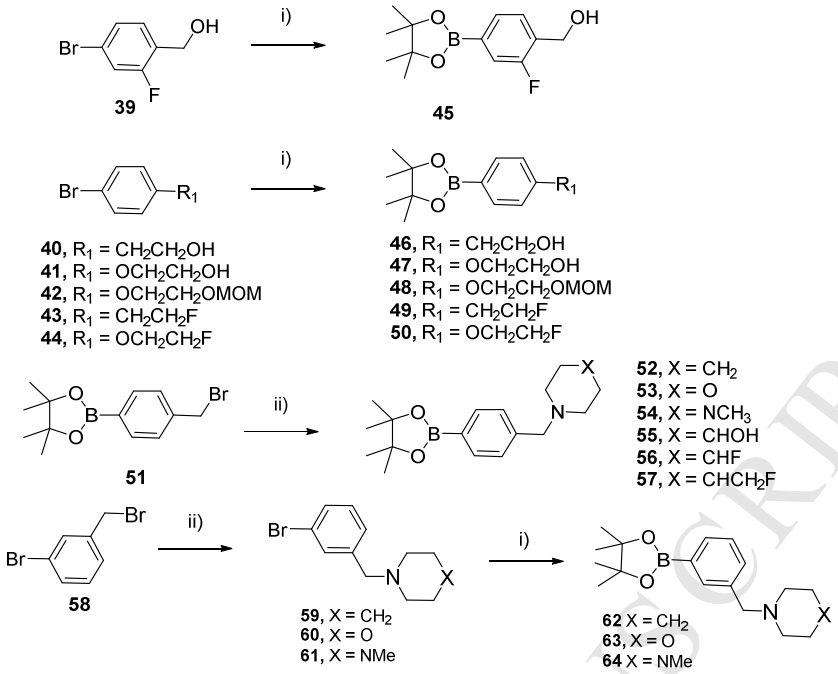
Since some yields decreased dramatically and degradation appeared, the experimental conditions were slightly modified. Several assays were carried out using only 20 minutes of irradiation or by coupling $PdCl_2(dppf)$ and Na_2CO_3 and using microwave irradiation at 110 °C to achieve satisfactory results. In the case of the bromo derivatives **12** or **13,** the two catalyzed conditions were suitable to achieve the cross coupling reactions and to furnish the derivatives **21-33** in good yields ranging from 66 to 92%. Next, we decided to extend the library of active

molecules. The bromo derivatives **10-12** were reacted with (5-formylthiophen-2-yl)boronic acid and crude material was directly involved in a formyl reduction to afford **34-36** in high yields (Scheme 2). To improve diversity, and having in hand **26** and **27**, we next decided to substitute the alcohol by a fluorine. The chosen method consisted in the direct electrophilic reaction which involved a slight excess of DAST and furnished the fluorinated derivatives **37** and **38** in moderate yields (Scheme 2).



Scheme 2. Reagents and conditions : i) formylated boronic acids (1.2 eq.), $Pd(PPh_3)_4$ 10 mol %, K_2CO_3 (2.0 eq,), toluene / MeOH 2 / 1 , µW 150 °C, 15 minutes then $NaBH_4$ (1.2 eq.), CH_2Cl_2, 0 °C, 30 min. from **10** : **34** 82%, from **11** : **35** 85%, from **12** : **36** 78%; ii) DAST (1.4 eq.), CH_2Cl_2, 0 °C, 1 h, from **26** : **37** 39%, from **27** : **38** 45%.

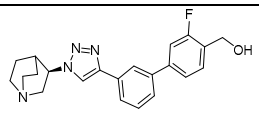
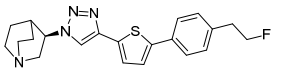
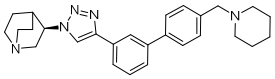
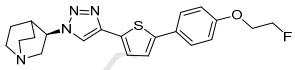
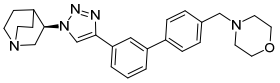
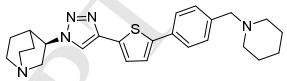
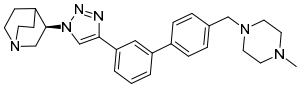
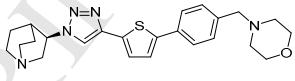
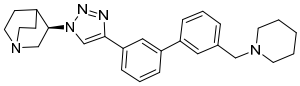
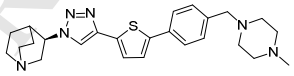
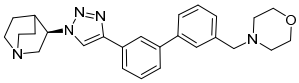
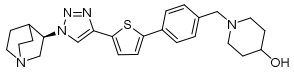
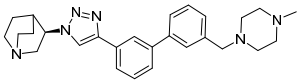
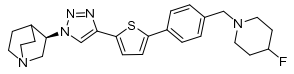
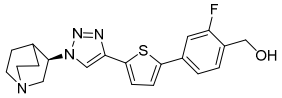
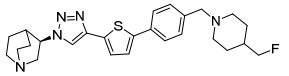
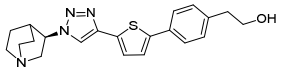
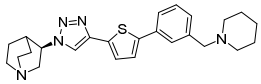
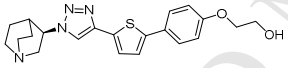
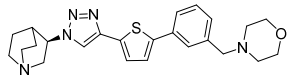
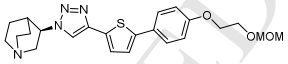
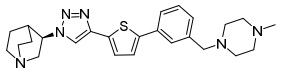
To pursue our SAR study, we performed the synthesis of the boronic ester library **45-50** which were easily prepared from bromoaryl derivatives **39-44** using $PdCl_2$dppf as catalyst and KOAc as base after 16 h heating at 90 °C (Scheme 3).[24]



Scheme 3. Reagents and conditions : i) Bis(pinacolato)diboron (1.0 eq.), $PdCl_2$dppf 10 mol %, KOAc (2.0 eq.), dioxane, 90 °C, 16 h, from **39** : **45** 76%, from **40** : **46** 65%, from **41** : **47** 63%, from **42** : **48** 74%, from **43** : **49** 72%, from **44** : **50** 75%, from **59** : **62** 70%, from **60** : **63** 65%, from **61** : **64** 78%; ii) bromomethyl derivative, Et_3N (2.0 eq.), CH_3CN, r.t., 3 h, secondary aliphatic amine (2.0 eq.), from **51** : **52** 78%, **53** 72%, **54** 75%, **55** 72%, **56** 72%, **57** 68%, from **58** : **59** 75%, **60** 80%, **61** 78%.

In addition, several nucleophilic substitutions were performed on bromomethyl derivative **51** which led directly to the boron derivatives **52-57**. However, this interesting strategy failed using 1-bromo-3-(bromomethyl)benzene **58**. To circumvent this problem, this starting material was first used in a reaction with the nucleophiles in the presence of Et_3N in acetonitrile at room temperature, to afford the resulting tertiary amine **59-61** which was next subjected to the borylation step leading to **62-64** in yields ranging between 65 and 78% after flash chromatography (Table 3). The use in palladium cross coupling reactions [25, 26] of the newly prepared boron intermediates led as expected to **81-90** in satisfactory yields.[27]

Table 3. Increase in the library size of type **II .**

Entry	SM	Compounds of type II (Yield)[a]		Entry	SM	Compounds of type II (Yield)[a]	
1	**10, 45**	**65** (75%)		12	**12, 49**	**76** (63%)	
2	**10, 52**	**66** (65%)		13	**12, 50**	**77** (63%)	
3	**10, 53**	**67** (62%)		14	**12, 52**	**78** (75%)	
4	**10, 54**	**68** (78%)		15	**12, 53**	**79** (83%)	
5	**10, 62**	**69** (68%)		16	**12, 54**	**80** (75%)	
6	**10, 63**	**70** (71%)		17	**12, 55**	**81** (68%)	
7	**10, 64**	**71** (73%)		18	**12, 56**	**82** (61%)	
8	**12, 45**	**72** (75%)		19	**12, 57**	**83** (67%)	
9	**12, 46**	**73** (75%)		20	**12, 62**	**84** (60%)	
10	**12, 47**	**74** (79%)		21	**12, 63**	**85** (63%)	
11	**12, 48**	**75** (62%)		22	**12, 64**	**86** (83%)	

SM: Starting Materials. [a] Yields are indicated in isolated products. All derivatives were obtained with bromo derivative (1.0 eq.), boronic derivative (1.2 eq.), $Pd(PPh_3)_4$ 10 mol%, K_2CO_3 (2.0 eq.), toluene / MeOH 2 / 1, μW, 150 °C, 15 min.

In vitro alpha 7 nicotinic acetylcholine receptor (α7R) binding assays

The binding competition assays against the radiolabeled α7R antagonist [^{125}I]α-bungarotoxin were performed for all final compounds on a rat brain membrane preparation. The large family of derivatives led to clear SAR trends. Table 4 summarizes the inhibition constant (Ki) obtained for the first set of type **II** derivatives. The nature of the (Het)Ar_1, (Het)Ar_2 and satellites Sat (see Scheme 1) was modified step by step and results were analyzed.

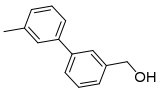
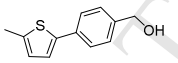
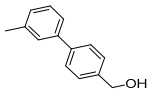
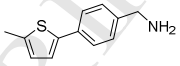
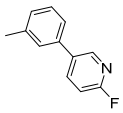
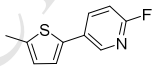
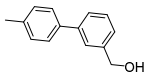
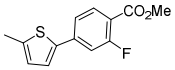
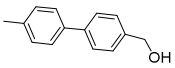
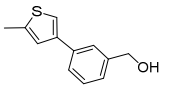
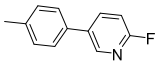
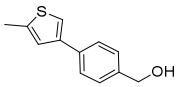
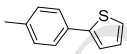
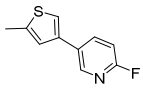
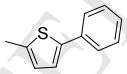
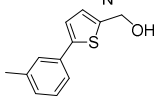
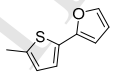
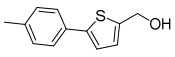
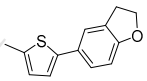
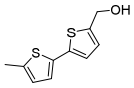
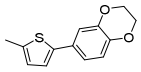
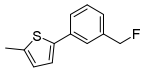
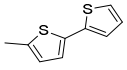
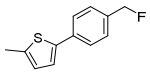
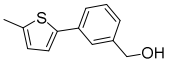
When (Het)Ar_1 was a phenyl ring and the second aromatic fraction was attached in position *C*-4, affinities were always up to 100 nM (**17-20, 35**). This loss of affinity reached a

maximum with a fluoropyridine core as **19** exhibited a Ki value up to 10^{-6} M. Conversely, moving the link between the two (Het)Ar moieties to the meta position led to a significant increase in affinity (nanomolar range), suggesting that a moderate curve in the aromatic enchainment was necessary to fit with the α7R binding site (**14-16**, **34**). Moreover, the addition of 3- or 4- hydroxymethyl groups led to **14** and **15** with a preference for the meta satellite position (Ki of 1.4 and 7 nM, respectively). Additionally, the use of a 5'-hydroxymethyl-2'-thiophenyl system led to **34** which possessed a very high affinity (Ki of 0.2 nM) whereas a 2-fluoropyridine core in (Het)Ar_2 significantly decreased this affinity (**16,** Ki of 16 nM).

As a thiophenyl skeleton appeared as a very interesting partner to enhance the affinity, we decided to link this heterocycle to the triazole, *i.e.* at the (Het)Ar_1 position. The second (Het)Ar_2 moiety was first attached in *C*-4 to furnish derivatives **31-33**. The 2-fluoropyridine compound **33** was still disappointing (Ki of 31 nM) whereas the affinity in the presence of 3- or 4- hydroxymethyl phenyl groups was better (13 and 1.5 nM, for **31** and **32,** respectively). The *C*-4 position on the (Het)Ar_2 seemed therefore to be favorable for binding, in agreement with a probable adjustment of the ligand in the active site due to the (Het)Ar_1 thiophen / phenyl switch.

When the (Het)$Ar)_1$ thiophenyl ring was linked by its *C*-5 position to a phenyl group, several (Het)Ar_2 were suitable to explore the corresponding SAR. With thiophene or dihydrobenzofurane as well as benzodioxine, Ki remained in an interesting range (**21-25**). The interactions with α7R increased strongly when hydroxy or amino methyl groups were used as supplementary functions and subnanomolar affinities were obtained for the **26, 27, 28** and **36** derivatives (0.7, 0.6, 0.3 and 0.8 nM, respectively).

Table 4. Structure affinity relationships on derivatives of type **II** (part 1).

Entry	Ki (nM)	Residues on Type II		Entry	Ki[a] (nM)	Residues on Type II	
1	1.4±0.6	**14**		14	0.6±0.2	**27**	
2	7±1	**15**		15	0.3±0.2	**28**	
3	16±4	**16**		16	13±2	**29**	
4	100±21	**17**		17	90-80	**30**	
5	175-100	**18**		18	13±3	**31**	
6	>1000	**19**		19	1.5±0.6	**32**	
7	110-160	**20**		20	31±4	**33**	
8	43±4	**21**		21	0.2±0.2	**34**	
9	10±1	**22**		22	200-120	**35**	
10	60±5	**23**		23	0.8±0.2	**36**	
11	140	**24**		24	42±2	**37**	
12	20±2	**25**		25	5±2	**38**	
13	0.7±0.3	**26**					

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

Removing the satellite hydrophilic function and using a fluorine atom, ester or fluoromethyl groups decreased the binding efficiency overall (**29, 30, 37, 38**). A first analysis of the library seemed to indicate that it was preferable to use a 3,4-biphenyl and a 2-thiophen-5-phenyl

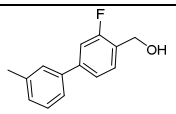
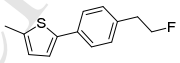
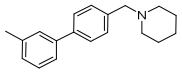
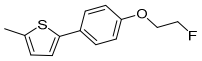
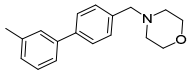
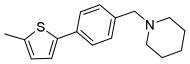
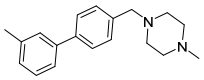
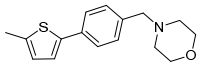
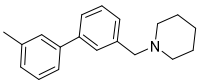
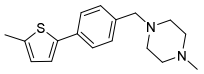
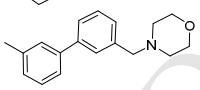
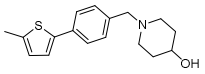
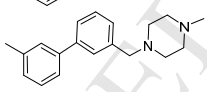
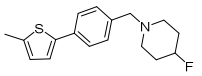
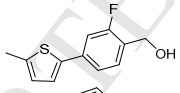
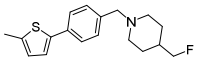
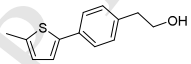
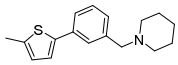
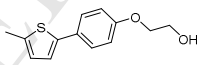
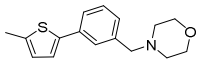
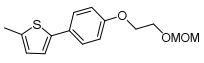
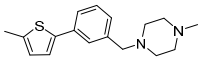
system to enhance activities. This motif induced a planar structure with a slight curve in the plane. Some flexibility was provided with quinuclidine and (Het)Ar_2 hydrophilic alcohols and methylene amine groups which enhanced interaction more than the other satellite (Sat) functions used.

In order to investigate the best Sat fractions, we focused on compounds possessing the best 1,3-biphenyl and 5-phenyl-2-thiophenyl systems. Results are summarized in Table 5. First of all, in the biphenyl series the incorporation of a fluorine atom led to a decrease in affinity as can be seen by comparing **65** to its non-fluorinated analog **15**. The same behavior was observed with thiophenyl containing molecules **72** (Ki of 12 nM vs 1.5 nM for **32**). The use of piperidine, morpholine, and piperazine on the benzylic methylene group finely tuned the activity, with the result that the para substitution remained the best in the 1,3 biphenyl series (**66-68** compared to **69-71** and **78-80** compared to **84-86**).

Noteworthy, the introduction of a hydrophilic side chain in para afforded the novel derivatives **78-80** with Ki values in the subnanomolar range. Progression in the design prompted us finally to use functionalized piperidines. Hydroxylation led to a stabilization of the activity with compound **81** at Ki = 0.3 nM.

In conclusion, the SAR studies, which helped us to define the general architecture of α7R ligands, were very fruitful and our hypothetical pharmacophoric model was fully validated as 9 molecules exhibited Ki values below nanomolar concentrations. Binding assays, realized with approximatively 40 tested derivatives, showed clearly the preference to define thiophenyl as (Het)Ar_1 and phenyl ring as (Het)Ar_2 with the best thiophene bisubstitution in *C*-2 and C-5.

Table 5. Structure affinity relationships on type **II** derivatives (part 2).

Entry	Ki (nM)	Triazole substituents on type II derivatives		Entry	Ki[a] (nM)	Triazole substituents on type II derivatives	
1	18±2	**65**		12	157±6	**76**	
2	3±0.7	**66**		13	340±88	**77**	
3	12.5±2	**67**		14	0.3±0.1	**78**	
4	1.9±0.2	**68**		15	0.9±0.2	**79**	
5	122±8	**69**		16	0.3±0.1	**80**	
6	49±11	**70**		17	0.3±0.1	**81**	
7	39±4	**71**		18	2.8±0.7	**82**	
8	12±1	**72**		19	1.4±0.2	**83**	
9	1.5±0.3	**73**		20	17±2	**84**	
10	1.7±0.2	**74**		21	16±1	**85**	
11	140	**75**		22	16±2	**86**	

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

Additionally, substitutions could be supported by the (Het)Ar_2 and by the phenyl ring in *C*-4 particularly. We proved that the choice of substitution modulates the efficacy of compound fixation. The best results were obtained with a benzylic methylene equipped with a tertiary cyclic amine with a preference for bearing an additional hydroxymethyl function in *C*-4. Based on this robust study, some sub-nanomolar active drugs were chosen for *in cellulo*

assays and some fluorinated molecules were transformed to their [^{18}F]-radiolabeled equivalents to evaluate their brain penetration and distribution *in vivo*.

In cellulo and selectivity assays

From the above SAR studies, it appeared that several compounds presented a sub-nanomolar affinity for α7R but did not possess a fluorine atom in their structure, and were thus inappropriate to be transformed into [^{18}F]-radiolabeled PET tracers. This high affinity led us to pursue the pharmacological characterization of two of these compounds (**26**, **78**) with a view to proposing them as pharmacological agents. Concurrently, we selected from our library the fluorinated compounds **29** and **38** which had a suitable affinity to be evaluated as potential [^{18}F]-PET tracers.

In a first step, we evaluated the in vitro agonism potency of these compounds by measuring the release of intracellular calcium from human SH-SY5Y cells as previously described.[28, 29] Our results showed that **26** had no effect on this release whereas compounds **29** and **38** induced a releasing effect similar to that obtained with the reference α7R agonist choline, this effect being significantly reduced (by around 50%) in the presence of the reference α7R antagonist α-bungarotoxin (Figure 3, panel A). We also observed that the compound **78** induced an 80% higher calcium release than choline, this effect being reduced by 57% in the presence of α-bungarotoxin.

In a second step, we evaluated the in vitro cell toxicity of these three α7R agonists (**29**, **38** and **78**). The results presented in Figure 3 (panel B) showed an absence of cellular toxicity for all compounds. However, it must be emphasized that compound **29** decreased cell viability by about 15% at the highest concentration (13 µM) and an acidification of the culture medium was observed.

It appeared therefore that our compound **78** possessed a high affinity for α7R (Ki of 0.3 nM), had high agonist properties and showed no cellular toxicity at the highest concentration tested (3 µM). In addition, this compound had a Ki above 10^{-6} M towards the nicotinic α4β2 receptors and 5.6 10^{-7} M towards the serotonin 5HT3 receptors, using competition assays on cells expressing human receptors with [^{3}H]cytisine and [^{3}H]BRL 43694 as reference tracers, respectively. Regarding these promising properties, further investigations should be performed in order to test the potency of **78** to improve cognitive functions as already demonstrated for other closely related structure compounds.[13, 14]

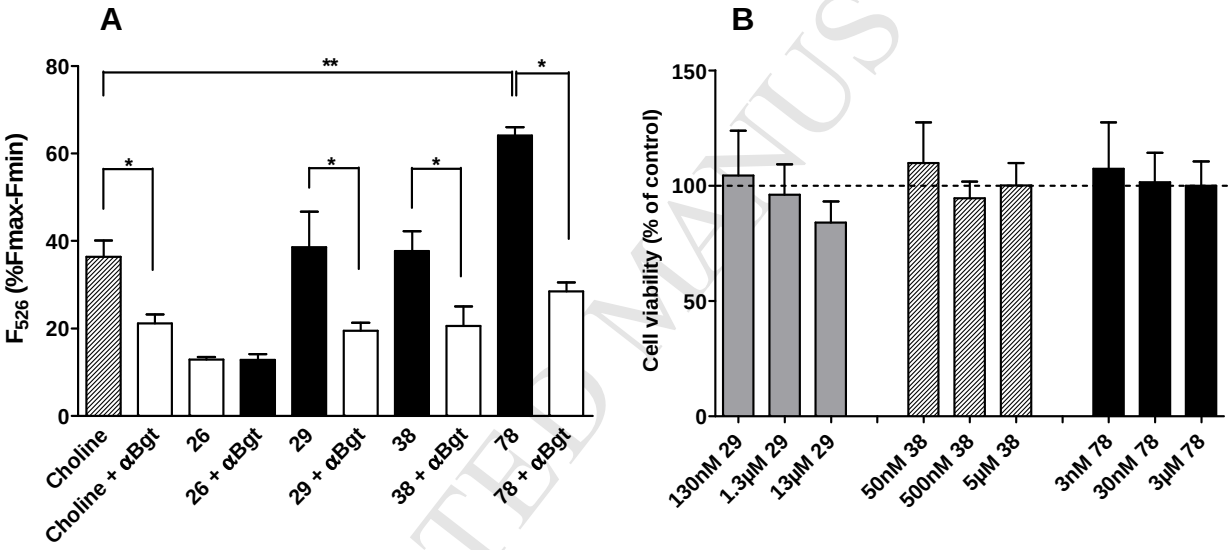
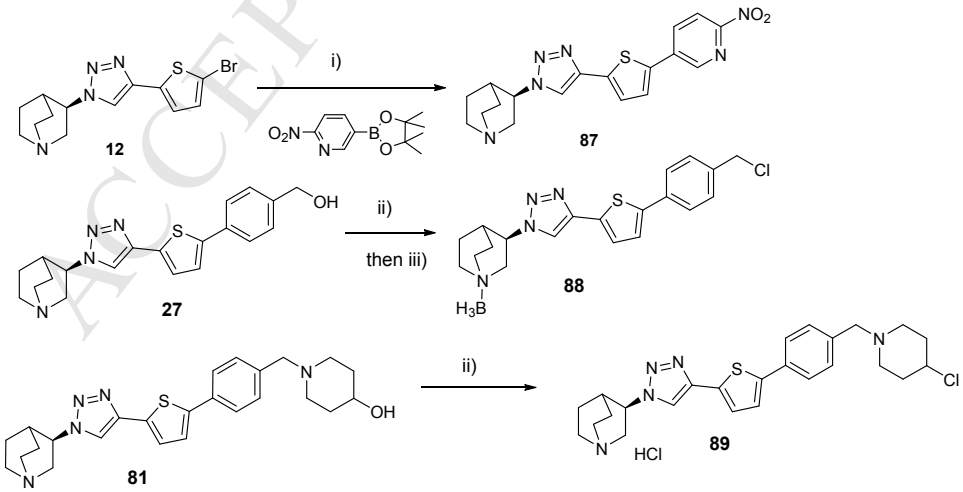


Figure 3. Panel A: Intracellular calcium release in human SH-SY5Y cells expressing native α7R. Cells were loaded with fluo-3 AM and preincubated with 100 nM α-bungarotoxin (α-Bgt) for 20 min and PNU-120596 for 1 min before stimulation with 3 mM choline or molecules **26** (7 nM), **29** (130 nM), **38** (50 nM) and **78** (3 nM), as described in the Materials and Methods. In order to normalize fluo-3 AM signals (excitation λEx = 506 nm, emission λEm = 526 nm), the maximum and minimum fluorescence from each well was determined by addition of 0.3% Triton-X100 (Fmax) followed by 100 mM $MnCl_2$ (Fmin). Drug-evoked responses were expressed as a percentage of the corresponding (Fmax-Fmin) value. Fluorescence was recorded in a Varioskan Flash spectral scanning multimode reader. Results are the mean ± SEM of 5 independent experiments in duplicate. **Panel B:** Cell viability. SH-SY5Y cells were incubated during 48 hours with increasing concentrations (10 Ki, 100 Ki and

1000 Ki) of molecules **29**, **38** and **78**. The MTS reagent was added and the reading of the optical density of the formazan was carried out after 3 hours of incubation using the Varioskan Flash spectral scanning multimode reader (490 nm). The results are expressed as percent viability compared to control cells incubated with the vehicle and represented the mean ± SEM of 4 independent experiments in triplicate.

Radiolabeling and stability studies

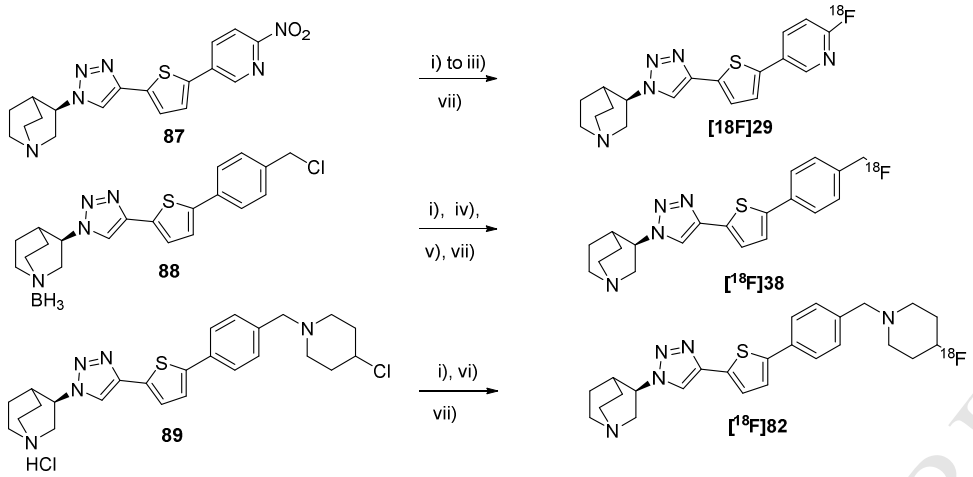
In order to obtain potential PET tracers labeled with fluor-18, – chemistry efforts were developed to - prepare the precursors - allowing a nucleophilic substitution (Scheme 4). The 2-nitropyridine derivative **87** was obtained from **12** using the Suzuki-Miyaura conditions depicted in Table 2 with some changes in temperature (110 °C) and reaction time (1h30) to achieve complete conversion. After purification the final product was isolated in a 77% yield. For nucleophilic aliphatic substitution, the chlorine was choosen as leaving group. Thus, the corresponding precursors were prepared by direct chlorination of **27** and **81** using $SOCl_2$ in dichloromethane –with a catalytic amount of DMF. While derivative **89** was obtained in satisfactory yield, reaction with the benzylic alcohol **27** failed. To circumvent this problem, quinuclidine was first protected on the nitrogen atom using $BH_3.Me_2S$ complex and then $SOCl_2$ was used to obtain the borylated derivative **88** in 80% yield.



Scheme 4. Reagents and conditions : i) 2-nitro-5-pyridineboronic acid pinacol ester (1.2 eq.), $Pd(PPh_3)_4$ 10 mol %, K_2CO_3 (2.0 eq.), toluene / MeOH 2 / 1, μW, 110 °C, 1h30, 77%, ii)

from **81** : $SOCl_2$ (2.0 eq.), DMF cat., CH_2Cl_2, r.t., 12 h, **89** 80% and from **27**: $SOCl_2$ (2.0 eq.), DMF cat., CH_2Cl_2, r.t., 12 h then BH_3Me_2S (1.0 eq.), CH_2Cl_2 / THF (9/1), -10 °C, 1h, **88** 80%.

The synthesis of the radiotracer **[^{18}F]29** was achieved through a two-step radiolabeling procedure (Scheme 5). First nucleophilic substitution occurred on the pyridine ring ~~and~~ followed by a reduction of the nitro group of the ~~excess~~ of precursor's excess ~~was performed~~ to allow a fast and efficient purification of **[^{18}F]29**. After purification via semi preparative high performance liquid chromatography (HPLC), **[^{18}F]29** was obtained in about 7.4% radiochemical yield (n = 5, decay-corrected) with a radiochemical purity (RCP) greater than 95% and a molar activity (MA) of 41−73 GBq/μmol. **[^{18}F]38** was obtained in a one-pot multistep reaction from the chlorinated analog **88**. Chlorine was substituted by $^{18}F^-$ followed by a removal of the BH_3 protective group on the quinuclidine under acidic conditions. As for **[^{18}F]29, [^{18}F]38** was purified by HPLC and ~~was~~ obtained in 24% radiochemical yield (n = 4, decay-corrected). RCP was greater than 95% and MA was 39-86 GBq/μmol. The total synthesis time was about 100 min for **[^{18}F]29** and 90 min for **[^{18}F]38**. [^{18}F]**29** was formulated classically in a sodium chloride 0.9%/ethanol solution suitable for *in vivo* injection to animals. In this medium, a fast degradation of **[^{18}F]38** was observed but **[^{18}F]38** remained stable in pure ethanol up to 4h. Thus, **[^{18}F]38** was extemporaneously prepared in an injectable form prior to animal experiments. The stability of both compounds in rat plasma was checked up to 4 hours and the purity was greater than 95% at the latest time point.



Scheme 5. Nucleophilic radiosynthesis of potent compounds with ^{18}F starting from their corresponding precursors. Reagents and conditions: i) [^{18}F]KF / $K_{2.2.2}$, DMSO, 150 °C, 10 min ; ii) $SnCl_2$ /HCl, 15min ; iii) aq. NaOH 0.6N; iv) [^{18}F]KF / $K_{2.2.2}$, DMSO, 115 °C, 15 min ; v) HCl/acetone, 10 min ; vi) [^{18}F]KF / $K_{2.2.2}$, DMSO, µW 100 W, 5 min.

Surprisingly, we were not able to prepare **[^{18}F]82** by thermal heating but only under microwave activation. Even with these harsh conditions, 100 W for 5 min, the amount of **[^{18}F]82** was not sufficient to prepare it for *in vivo* evaluation.

In vivo brain biodistribution and imaging studies

After checking that they had low in vitro toxicity (Figure 3B), good stability and radiochemical purity (>95%), we evaluated the in vivo properties of **[^{18}F]29** and **[^{18}F]38** in rodents (Figures 4 and 5).

In a first step of experiments, we measured the uptake of each tracer in several rat brain regions. These regions were chosen according to their known α7R density in the rodent brain, i.e. high in the frontal cortex and hippocampus, intermediate in the hypothalamus and striatum, and low in the cerebellum (Davies ARL et al. Neuropharmacology 1999, 38:679-690; Whiteaker P et al. Eur J Neurosci 1999, 11:2689-2696). Each tracer was intravenously (i.v.) injected in a group of control rats (n=6) and in another group of rats (n=6) that received 15 min before the tracer injection, an i.v. injection of the high affinity α7R antagonist

methyllycaconitine (MLA; Wonnacott S et al. Methods Neurosci 1993, 12:263-275) at the dose of 1 mg/kg. It was previously showed that this experimental design allows blocking the in vivo accumulation of α7R radiotracer in the rat brain (Maier DL et al. Neuropharmacology 2011, 61:161-171). The radioactivity uptake was measured in each dissected brain region at 1 hour post-injection. Although we did not prove that this radioactivity was exclusively related to the parent tracers, this can be expected as we previously checked that they were stable up to 4 hours in rat plasma.

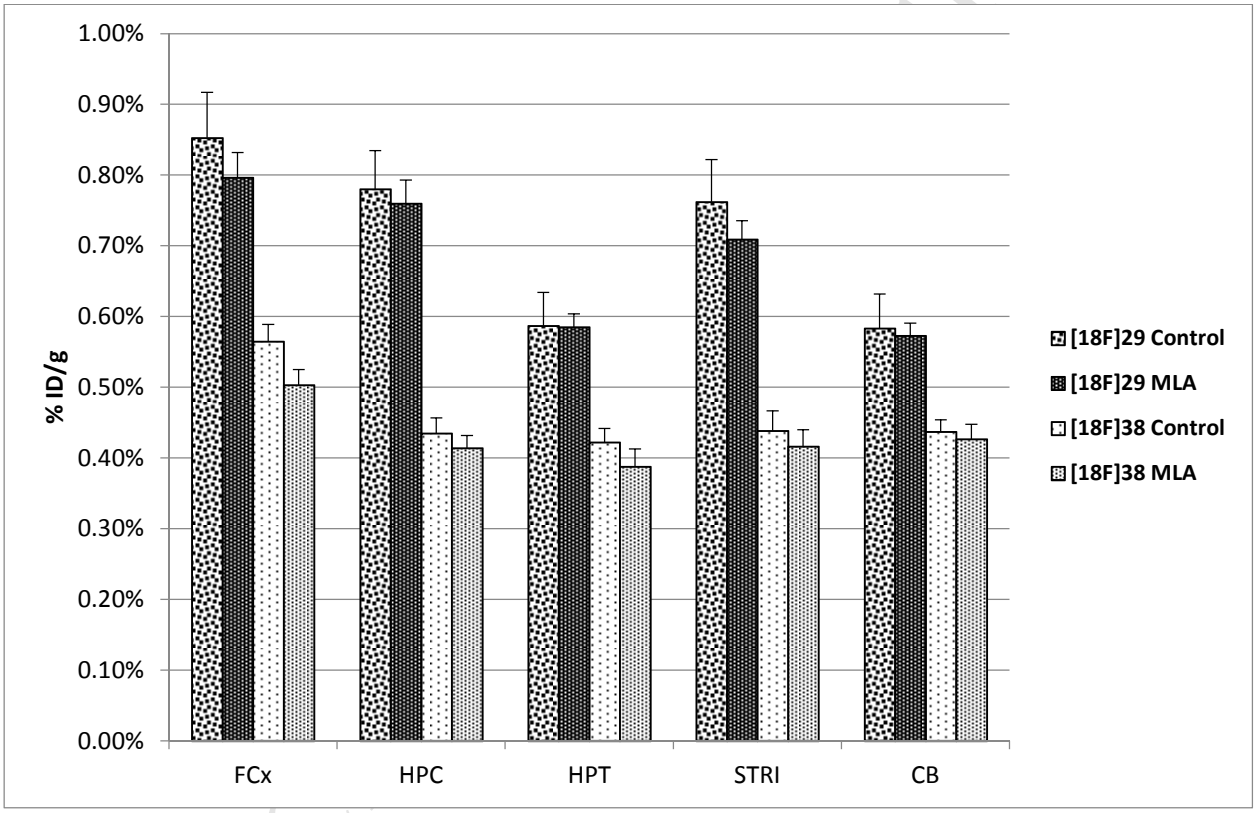


Figure 4. Brain biodistribution study in rats. Rats (n = 6 group) received an i.v. injection of either **[^{18}F]29** or **[^{18}F]38** preceded (MLA) or not (Control) by an i.v. injection of methyllycaconitine (1.0 mg/kg). They were sacrificed at 1 h post-injection of the tracer and the radioactivity was measured in different dissected brain regions. The results are expressed as mean percentage of injected dose per gram of tissue (%ID/g) ± SEM. FCx, frontal cortex; HPC, hippocampus; HPT, hypothalamus; STRI, striatum; CB, cerebellum.

The brain biodistribution studies (Figure 4) showed that in control rats, both **[^{18}F]29** and **[^{18}F]38** were able to pass through the blood-brain barrier, with a range value of 0.4 to 0.8%ID/g tissue, depending on the brain region. Indeed, it is known that suitable radiotracers for central nervous system exploration show typically values from 0.5% ID/g tissue in the rodent brain (Wong DF & Pomper MG Mol Imaging Biol 2003, 5:350-362.) However, a significantly higher level of accumulation was observed for **[^{18}F]29** than for **[^{18}F]38** ($p<0.05$) in all the brain regions explored (Cx: 0.85±0.06 *vs* 0.56±0.02 %ID/g; HPC: 0.78±0.05 *vs* 0.43±0.02 %ID/g; HPT: 0.59±0.05 *vs* 0.42±0.02 %ID/g; STRI: 0.76±0.06 *vs* 0.44±0.03 %ID/g; CB: 0.58±0.05 *vs* 0.44±0.02 %ID/g). The ratio of accumulation in the structures *vs* cerebellum, considered to reflect non-specific binding, was slightly above 1 in the Cx (1.47±0.03), HPC (1.34±0.04) and STRI (1.31±0.02) for **[^{18}F]29** and only in the Cx (1.29±0.04) for **[^{18}F]38**. However, pre-injection of the antagonist α7R MLA did not significantly modify the brain accumulation of either tracer, whatever the region considered. It can be pointed out that in contrast to this last result, the uptake of other described α7R tracers have been obtained in rodent brain with MLA, the selective α7R ligand SSR180711, or nicotine (Maier et al. 2011; Gao et al. 2013).

The imaging study (Figure 5) illustrated the overall higher brain uptake for [^{18}F]**29** than for [^{18}F]**38**, with a quite homogeneous distribution of both tracers between the different regions.

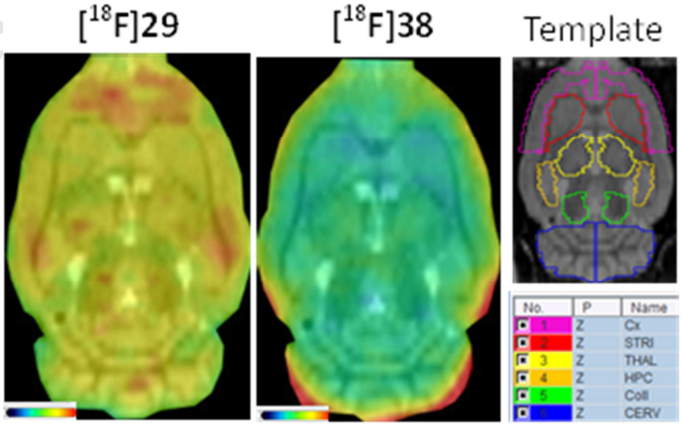


Figure 5. Representative sagittal PET brain image of [^{18}F]29 and [^{18}F]38. The rats received a bolus i.v. injection of 37 MBq of **[^{18}F]29** or **[^{18}F]38**. The acquisition lasted 71 min and the images were reconstructed using a 2-D OSEM algorithm. Images represent the sum of the last frames corresponding to 49-71 min of acquisition after tracer injection. Brain regions are represented on the template (PMOD Technologies, Zurich, Switzerland; www.pmod.com). Cx, cortex; STRI, striatum; THAL, thalamus; HPC, hippocampus; Coll, colliculus; CERV, cerebellum.

Our *in vivo* results thus indicated that although they passed through the BBB after i.v. injection, neither **[^{18}F]29** nor **[^{18}F]38** specifically accumulated in brain regions rich in α7R and were not significantly displaced by the α7R antagonist MLA. This disappointing result did not appear to be due to a lack of specificity of our compounds, as we measured a Ki above 10^{-6} M towards the nicotinic α4β2 receptors for both **29** and **38**, and a Ki of 4.4 10^{-7} M and above 10^{-6} M towards the serotonin 5HT3 receptors for **29** and **38**, respectively. Although many attempts have been performed to develop suitable [^{18}F]-labeled PET tracers for brain α7R imaging, to date only [^{18}F]ASEM (Figure 1) has proved to be really useful.[30-33] This is probably related to the very high affinity of this compound (Ki of 0.4 nM)[34] compared to ours (13 and 5 nM) that allows ASEM to bind in vivo to α7R despite their low brain density in rodent as well as in human brain.[35-37]

Conclusion

We have prepared a library of bis(Het)Aryl-1,2,3-triazole quinuclidine α7R ligands using an efficient strategy involving a Suzuki-Miyaura cross coupling reaction. The exploration of SAR required the preparation of uncommon boron derivatives. Forty final drugs were tested for their ability to bind the target and nine of them exhibited Ki below nanomolar concentrations. The best scores were always obtained when the 5-phenyl-2-thiophenyl core was attached to the triazole. Furthermore, the introduction of phenyl substituents in para led to

a set of very efficient derivatives, in particular compound **78** which has a very high affinity for α7R (Ki of 0.3 nM), is selective towards the nicotinic α4β2 and serotoninergic 5HT3 receptors, and is a potent agonist of the target. It can be expected that this compound will have a strong effect on cognitive disorders, as such effects have already been obtained with agonists possessing much poorer affinity (around 100 nM) for α7R.[13]

Regarding the interest of our compounds as [^{18}F]-labeled PET tracers, they have not the requisite properties compared to [^{18}F]ASEM, probably due to their lower affinity. This point is indeed a key parameter for a good in vivo tracer of α7R, due to their low density in the brain.[1, 15]

Experimental part

Chemistry

^{1}H 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. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). 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 lid.

The chromatographic purity of the final compounds was determined using an Agilent Technology 1260 Infinity HPLC system with a C-18 column (Agilent ZORBAX Eclipse plus C18 3.5 μm, 4.6 mm × 100 mm) operating at 30 °C. Elution was carried out using acetonitrile containing 0.1% formic acid as mobile phase A and water containing 0.1% formic acid as mobile phase B. Elution conditions: at 0 min, phase A 10% + phase B 90%; at 5 min, phase A 50% + phase B 50%; at 7 min phase A 50% + phase B 50%, at 7.1 min, phase A 10% + phase B 90%; at 20 min, phase A 10% + phase B 90%. The flow-rate of the mobile phase was 0.9 mL/min, and the injection volume of the sample was 2 μL. Peaks were detected at 254 nm and 300 nm. Purity of all the tested compounds was found to be >95% unless otherwise stated.

General procedure A to obtain ethynyl derivatives: To a solution of dimethyl 1-diazo-2-oxopropylphosphonate (1.15 g, 6.00 mmol) in MeOH (60 mL) were added the corresponding aldehydes (5.00 mmol) and K_2CO_3 (1.38 g, 10.0 mmol). The reaction mixture was stirred at room temperature for 12 h. After removing the volatiles without any heating, alkynes **6-9** were purified by flash chromatography using a mixture of petroleum ether and EtOAc 99/1 as eluent.

General procedure B for the synthesis of arylated quinuclinine triazoles: Under argon, to a solution containing 3-aminoquinuclidine bishydrochloride salt **4** (212 mg, 1.00 mmol) and 1*H*-imidazole-1-sulfonyle azide **5** (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 intermediate used in the next step. After addition of MeOH (6 mL), the desired terminal alkynes **6-9** (1.0 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 residual imidazole moiety were observed, EtOAc (20 mL) was added. After extraction with water (2 x 10 mL), the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford the pure derivative of type **IV** (**10-13**).

(*R*)-3-[4-(3-Bromophenyl)-1*H*-1,2,3-triazol-1-yl]quinuclidine 10. Compound **10** was obtained from 1-bromo-3-ethynylbenzene following the general procedure **B** and isolated as a white solid in a 50% yield. R_f : 0.18 (CH_2Cl_2/MeOH : 97/3 + NH_4OH 10%) ; Mp : 188-190 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 970, 1020, 1041, 1060, 1069, 1233, 1341, 14237 1455, 1470, 1603, 2868, 2938 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.44-1.50 (m, 1H), 1.61-1.65 (m, 1H), 1.73-1.87 (m, 2H), 2.27 (q, *J* = 3.2 Hz, 1H), 2.86-3.00 (m, 3H), 3.09-3.17 (m, 1H), 3.49 (ddd, *J* = 2.2 Hz, *J* = 9.8 Hz, *J* = 14.4 Hz, 1H), 3.68 (dd, *J* = 14.4 Hz, *J* = 3.6 Hz, 1H), 4.63-4.65 (m, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.98 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.5 (CH), 119.3 (CH), 122.9 (C_q), 124.1 (CH), 128.6 (CH), 130.4 (CH), 131.0 (CH), 132.6 (C_q), 146.1 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{15}H_{18}N_4Br$ $[M+H]^+$: 333.0715, found: 333.0709.

(*R*)-3-(4-(4-Bromophenyl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 11. Compound **11** was obtained from 1-bromo-4-ethynylbenzene following the general procedure **B** and isolated as a white solid in a 54% yield. R_f : 0.32 (CH_2Cl_2/MeOH 80/20 + NH_4OH 10%) ; Mp : 158-160 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 972, 1009, 1043, 1060, 1070, 1186, 1218, 1315, 1424, 1451, 1479, 2867, 2936 ; ^{1}H NMR (250 MHz, $CDCl_3$) : δ (ppm) 1.40-1.57 (m, 1H), 1.60-1.72

(m, 1H), 1.72-1.86 (m, 2H), 2.28 (q, *J* = 3.1 Hz, 1H), 2.86-3.00 (m, 3H), 3.07-3.22 (m, 1H), 3.49 (ddd, *J* = 2.2 Hz, *J* = 9.8 Hz, *J* = 14.5 Hz, 1H), 3.69 (dd, *J* = 5.0 Hz, *J* = 14.4 Hz, 1H), 4.58-4.71 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.81 (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), 119.3 (CH), 122.2 (C_q), 127.4 (2 CH), 129.8 (C_q), 132.2 (2 CH), 146.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{15}H_{18}N_4Br$ $[M+H]^+$: 333.0715, found: 333.0722.

(*R*)-3-(4-(5-Bromothiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 12. Compound **12** was obtained from 2-bromo-5-ethynylthiophene following the general procedure **B** and isolated as a white solid in a 42% yield. R_f : 0.46 (CH_2Cl_2/MeOH 80/20 + NH_4OH 1 %) ; Mp : 146-148 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 972, 1041, 1057, 1215, 1322, 1433, 1496, 1645, 2867, 2934, 3356 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.44-1.51 (m, 1H), 1.59- 1.69 (m, 1H), 1.71 -1.87 (m, 2H), 2.25 (q, *J* = 3.0 Hz, 1H), 2.83-2.99 (m, 3H), 3.07-3.16 (m, 1H), 3.47 (ddd, *J* = 2.2 Hz, *J* = 9.8 Hz, *J* = 14.4 Hz, 1H), 3.66 (ddd, *J* = 1.6 Hz, *J* = 5.1 Hz, *J* = 14.4 Hz, 1H), 4.57-4.63 (m, 1H), 7.00 (d, *J* = 3.8 Hz, 1H), 7.08 (d, *J* = 3.8 Hz, 1H), 7.69 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.1 (CH_2), 28.3 (CH), 47.0 (CH_2), 47.4 (CH_2), 52.7 (CH_2), 58.7 (CH), 112.1 (Cq), 118.7 (CH), 124.3 (CH), 130.6 (CH), 134.8 (Cq), 142.1 (Cq) ; HRMS (EI-MS): *m/z* calcd. for $C_{13}H_{16}N_4SBr$ $[M+H]^+$: 339.0279, found: 339.0283.

(R)-3-(4-(4-Bromothiophen-2-yl)-1*H*-1,2,3-triazol-1yl)quinuclidine (13). Compound **13** was obtained from 4-bromo-2-ethynylthiophene following the general procedure **B** and isolated as a white solid in a 50% yield. R_f : 0.24 (CH_2Cl_2/MeOH 98/2 + NH_4OH 1 %) ; Mp: 106-108 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 786, 988, 1054, 1226, 1326, 1452, 1497, 2870, 2938, 3107; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.52 (m, 1H), 1.61-1.69 (m, 1H), 1.76-1.85 (m, 2H), 2.26 (q, *J* = 3.2 Hz, 1H), 2.85-3.00 (m, 3H), 3.09-3.16 (m, 1H), 3.49 (ddd, *J* = 2.1 Hz, *J* = 10.0 Hz, *J* = 14.4 Hz, 1H), 3.66 (dd, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H), 4.60-4.65

(m, 1H), 7.19 (s, 1H), 7.26 (s, 1H), 7.74 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 19.9 (CH_2), 25.9 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.6 (CH), 110.2 (C_q), 118.7 (CH), 122.1 (CH), 126.4 (CH), 134.3 (C_q), 141.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{13}H_{16}N_4SBr$ $[M+H]^+$: 339.0276, found: 339.0273.

General procedure C for the synthesis of derivatives of type II. : To a mixture of derivative of type **IV** (50 mg, 0.147 mmol) in toluene (1.5 mL) and EtOH (0.75 mL) were successively added the desired boronic ester or acid of type **V** (0.176 mmol, 1.2 eq.), K_2CO_3 (0.294 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (0.0147 mmol, 10 mol %). The reaction mixture was degassed with Ar and irradiated under microwave for 20 minutes at 150 °C. Alternatively $PdCl_2$(dppf) 10 mol %, could be used as catalyst. In this case the base was switched to Na_2CO_3 (2.0 eq.) and the irradiation performed for 40 minutes at 100 °C. In both cases, after cooling, the volatiles were removed under reduced pressure and the crude material purified by flash chromatography (CH_2Cl_2/MeOH 80/20 + NH_4OH 0.1 mL).

(*R*)-(3'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-3-yl)methanol 14. Compound **14** was obtained from compound **10** and (3-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 81% yield. R_f : 0.18 (CH_2Cl_2/MeOH 97/3 + NH_4OH 1 mL) ; Mp: 201-203 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 793, 984, 1042, 1262, 1326, 1423, 1436, 1612, 1697, 1719, 2870, 2943, 3133 ; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.34-1.48 (m, 2H), 1.69-1.75 (m, 2H), 2.20 (q, *J* = 2.8 Hz, 1H), 2.75-2.79 (m, 3H), 2.94-3.01 (m, 1H), 3.35-3.48 (m, 2H), 4.58 (d, *J* = 5.6 Hz, 2H), 4.72-4.79 (m, 1H), 5.25 (d, *J* = 5.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.51-7.63 (m, 3H), 7.66 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 8.85 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ(ppm) 20.0 (CH_2), 25.7 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.0 (CH_2), 52.2 (CH_2), 57.8 (CH), 63.3 (CH_2), 121.5 (CH), 123.8 (CH), 124.5 (CH), 125.2 (CH), 125.5 (CH),

126.2 (CH), 126.5 (CH), 129.1 (CH), 129.9 (CH), 131.9 (C_q), 140.1 (C_q), 141.3 (C_q), 143.7 (C_q), 146.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{22}H_{25}N_4O$ $[M+H]^+$: 361.2023, found: 361.2024.

(*R*)-(3'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-4-yl)methanol 15. Compound **15** was obtained from compound **10** and (4-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 92% yield. R_f : 0.18 (CH_2Cl_2/MeOH9 7/3 + NH_4OH 10%) ; Mp : 214-216 °C ; IR (ATR, Diamond): ν (cm^{-1}): 793, 972, 1041, 1222, 1320, 1451, 1481, 1660, 2868, 2939, 3077 ; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.3-1.49 (m, 2H), 1.70-1.74 (m, 2H), 2.20 (q, *J* = 2.8 Hz, 1H), 2.74-2.78 (m, 3H), 2.94-3.01 (m, 1H), 3.38-3.46 (m, 2H), 4.55 (s, 2H), 4.74-4.78 (m, 1H), 5.23 (br s, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.87 (d, *J* = 7.6 Hz, 1H), 8.14 (s, 1H), 8.85 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.0 (CH_2), 25.7 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.0 (CH_2), 52.3 (CH_2), 57.8 (CH), 63.0 (CH_2), 121.5 (CH), 123.7 (CH), 124.3 (CH), 126.3 (CH), 126.8 (2 CH), 127.4 (2 CH), 129.9 (CH), 131.9 (C_q), 138.6 (C_q), 141.0 (C_q), 142.5 (C_q), 146.5 (C_q) ; HRMS (EI -MS): *m/z* calcd. for $C_{22}H_{25}N_4O$ $[M+H]^+$: 361.2023, found: 361.2023.

(*R*)-3-(4-(3-(6-Fluoropyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 16. Compound **16** was obtained from compound **10** and (6-fluoropyridin-3-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 82% yield. R_f : 0.23 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 164-166°C ; IR (ATR, Diamond) ν (cm^{-1}) : 789, 980, 1061, 1208, 1344, 1454, 1473, 1590, 2865, 2940, 3059 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.42-1.55 (m, 1H), 1.65-1.70 (m, 1H), 1.75-1.87 (m, 2H), 2.30 (q, *J* = 3.2 Hz, 1H), 2.88-2.97 (m, 3H), 3.12-3.19 (m, 1H), 3.51 (ddd, *J* = 2.2 Hz, *J* = 9.8 Hz, *J* = 14.4 Hz, 1H), 3.72 (dd, *J* = 4.0 Hz, *J* = 14.4 Hz, 1H), 4.66-4.68 (m, 1H), 7.01 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz,

1H), 7.48-7.54 (m, 2H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.89 (s, 1H), 8.01-8.06 (m, 2H), 8.46 (d, *J* = 2.0 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0 (CH_2), 25.9 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.5 (CH), 109.4 (d, *J* = 37.0 Hz, CH), 119.2 (CH), 124.3 (CH), 125.3 (CH), 126.7 (CH), 129.6 (CH), 131.6 (C_q), 134.5 (d, *J* = 4.0 Hz, C_q), 137.4 (C_q), 139.8 (d, *J* = 8.0 Hz, CH), 145.8 (d, *J* = 15.0 Hz, CH), 147.0 (C_q), 163.2 (d, *J* = 238.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{21}N_5F$ $[M+H]^+$: 350.1775, found: 350.1777.

(*R*)-(4'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-3-yl)methanol 17. Compound **17** was obtained from compound **11** and (3-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 80% yield. R_f : 0.18 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp: 207-209 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 792, 982, 1038, 1225, 1324, 1437, 1455, 1603, 2874, 2941, 3367 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.32-1.52 (m, 2H), 1.67-1.74 (m, 2H), 2.20 (q, *J* = 2.8 Hz, 1H), 2.73-2.80 (m, 3H), 2.96-3.05 (m, 1H), 3.36-3.50 (m, 2H), 4.58 (s, 2H), 4.76-4.78 (m, 1H), 5.25 (br s, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.67 (s, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.97 (d, *J* = 8.2 Hz, 2H), 8.79 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 20.0 (CH_2), 25.7 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.0 (CH_2), 52.2 (CH_2), 57.8 (CH), 63.3 (CH_2), 121.4 (CH), 124.9 (CH), 125.2 (CH), 126.1 (3 CH), 127.4 (2 CH), 129.1 (CH), 130.4 (C_q), 139.8 (C_q), 139.9 (C_q), 143.7 (C_q), 146.2 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{22}H_{25}N_4O$ $[M+H]^+$: 361.2023, found: 361.2026.

(*R*)-(4'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-4-yl)methanol 18. Compound **18** was obtained from compound **11** and (4-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 81% yield. R_f : 0.18 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp: 250-252 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 798, 973, 1042, 1223, 1344, 1429, 1451, 1661, 2869, 2938, 3119 ; ^{1}H NMR (400 MHz, DMSO-

d$_6$) : δ (ppm) 1.36-1.49 (m, 2H), 1.69-1.75 (m, 2H), 2.20 (q, *J* = 2.8 Hz, 1H), 2.73-2.80 (m, 3H), 2.96-3.03 (m, 1H), 3.35-3.49 (m, 2H), 4.54 (d, *J* = 3.2 Hz, 2H), 4.75-4.77 (m, 1H), 5.21 (br s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.96 (d, *J* = 8.4 Hz, 2H), 8.78 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-*d*$_6$) : δ (ppm) 20.0 (CH_2), 25.7 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.0 (CH_2), 52.3 (CH_2), 57.8 (CH), 63.0 (CH_2), 121.3 (CH), 126.1 (2 CH), 126.6 (2 CH), 127.3 (2 CH), 127.4 (2 CH), 130.2 (C_q), 138.3 (C_q), 139.7 (C_q), 142.3 (C_q), 146.2 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{22}H_{25}N_4O$ $[M+H]^+$: 361.2023, found: 361.2027.

(*R*)-3-(4-(4-(6-Fluoropyridin-3-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 19. Compound **19** was obtained from compound **11** and (6-fluoropyridin-3-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 85% yield. R_f : 0.22 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp: 181-183 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 811, 987, 1039, 1253, 1372, 1474, 1590, 2871, 2942, 3115 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.47-1.53 (m, 1H), 1.67-1.85 (m, 3H), 2.30 (q, *J* = 3.2 Hz, 1H), 2.88-3.02 (m, 3H), 3.13-3.20 (m, 1H), 3.51 (ddd, *J* = 2.2 Hz, *J* = 9.8 Hz, *J* = 14.2 Hz, 1H), 3.72 (dd, *J* = 4.0 Hz, *J* = 14.2 Hz, 1H), 4.66-4.69 (m, 1H), 7.01 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 8.01 (td, *J* = 8.2 Hz, *J* = 2.4 Hz, 1H), 8.45 (d, *J* = 2.4 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 58.5 (CH), 109.5 (d, *J* = 37.0 Hz, CH), 119.2 (CH), 126.3 (2 CH), 127.4 (2 CH), 130.6 (C_q), 134.2 (d, *J* = 4.0 Hz, C_q), 136.2 (C_q), 139.5 (d, *J* = 8.0 Hz, CH), 145.6 (d, *J* = 15.0 Hz, CH), 146.8 (C_q), 163.1 (d, *J* = 238.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{21}N_5F$ $[M+H]^+$: 350.1775, found: 350.1778.

(*R*)-3-(4-(4-(Thiophen-2-yl)phenyl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 20. Compound **20** was obtained from compound **11** and thiophen-2-ylboronic acid following the general

procedure **B** and isolated as a white solid in a 86% yield. R_f : 0.17 (CH_2Cl_2/MeOH 97/3 + NH_4OH 1 mL) ; Mp : 214-216 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 791, 988, 1042, 1222, 1314, 1404, 1450, 1493, 2867, 2937, 3120 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.54 (m, 1H), 1.65-1.83 (m, 3H), 2.29 (q, *J* = 2.8 Hz, 1H), 2.87-3.01 (m, 3H), 3.12-3.20 (m, 1H), 3.50 (ddd, *J* = 3.2 Hz, *J* =10.0 Hz, *J* = 14.4 Hz, 1H), 3.72 (dd, *J* = 3.2 Hz, *J* = 14.4 Hz, 1H), 4.64-4.66 (m, 1H), 7.10 (dd, *J* = 3.6 Hz, *J* = 5.0 Hz, 1H), 7.29 (dd, *J* = 1.2 Hz, *J* = 5.0 Hz, 1H), 7.33-7.37 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.83-7.87 (m, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 58.4 (CH), 118.9 (CH), 123.2 (CH), 124.9 (CH), 126.0 (2 CH), 126.2 (2 CH), 128.1 (CH), 129.6 (C_q), 134.1 (C_q), 143.9 (C_q), 147.1 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{19}H_{21}N_4S$ $[M+H]^+$: 337.1481, found: 337.1485.

(*R*)-3-(4-(5-Phenylthiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 21. Compound **21** was obtained from compound **12** and phenylboronic acid following the general procedure **C** and isolated as a white solid in a 80% yield. R_f : 0.25 (CH_2Cl_2/MeOH 98/2 + NH_4OH 1 mL) ; Mp : 184-186 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 789, 982, 1060, 1209, 1323, 1404, 1455, 1498, 1590, 2866, 2940, 3059 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.43-1.55 (m, 1H), 1.62-1.80 (m, 3H), 2.28 (q, *J* = 2.8 Hz, 1H), 2.85-3.03 (m, 3H), 3.12-3.19 (m, 1H), 3.50 (ddd, *J* = 2.8 Hz, *J* = 10.0 Hz, *J* = 14.4 Hz, 1H), 4.70 (dd, *J* = 4.0 Hz, *J* = 14.4 Hz, 1H), 4.62-4.65 (m , 1H), 7.27-7.32 (m, 2H), 7.35-7.41 (m, 3H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.75 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.3 (CH), 118.4 (CH), 123.5 (CH), 124.9 (CH), 125.6 (2 CH), 127.6 (CH), 128.9 (2 CH), 132.2 (C_q), 134.0 (C_q), 142.6 (C_q), 143.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{19}H_{21}N_4S$ $[M+H]^+$: 337.1481, found: 337.1484.

(*R*)-3-(4-(5-(Furan-2-yl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 22. Compound **22** was obtained from compound **12** and furan-2-ylboronic acid following the general procedure **C** and isolated as a white solid in a 83% yield. R_f : 0.27 (CH_2Cl_2/MeOH 80/20 + NH_4OH 1 mL) ; Mp : 180-182 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 977, 1070, 1442, 1647, 2939, 3243 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.44-1.53 (m, 1H), 1.64-1.73 (m, 1H), 1.76-1.88 (m, 2H), 2.28 (q, *J* = 3.0 Hz, 1H), 2.87-3.01 (m, 3H), 3.10-3.20 (m, 1H), 3.49 (ddd, *J* = 2.1 Hz, *J* = 9.8 Hz, *J* = 14.4 Hz, 1H), 3.68 (ddd, *J* = 1.5 Hz, *J* = 5.0 Hz, *J* = 14.4 Hz, 1H), 4.61-4.66 (m, 1H), 6.46 (dd, *J* = 1.8 Hz, *J* = 3.4 Hz, 1H), 6.54 (d, *J* = 3.4 Hz, 1H), 7.21 (d, *J* = 3.8 Hz, 1H), 7.31 (d, *J* = 3.8 Hz, 1H), 7.41-7.42 (m, 1H), 7.73 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.1 (CH_2), 28.3 (CH), 47.1 (CH_2), 47.4 (CH_2), 52.8 (CH_2), 58.7 (CH), 105.6 (CH), 112.0 (CH), 118.6 (CH), 123.1 (CH), 124.8 (CH), 131.8 (C_q), 133.4 (C_q), 142.0 (CH), 142.6 (C_q), 149,3 (C_q) ; HRMS (EI-MS) : *m/z* calcd. for $C_{17}H_{19}N_4OS$ $[M+H]^+$: 327.1280, found: 327.1284.

(R)-3-{4-[5-(2,3-Dihydro-benzofuran-5-yl)-thiopen-2-yl]-[1,2,3]triazol-1-yl}-1-aza-bicyclo [2.2.2]octane (23). Compound **23** was obtained from compound **12** and (2,3-dihydrobenzofuran-5-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 91% yield. R_f : 0.35 (CH_2Cl_2/MeOH + 95/5 /NH_4OH 10%) ; Mp : 146-148°C ; IR (ATR, Diamond) ν (cm^{-1}) : 801, 978, 1023, 1048, 1241, 1325, 1450, 1487, 1603, 2800, 2857, 2934; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.48 (s,1H), 1.68 (s, 1H), 1.82 (m, 2H), 2.27 (s, 1H), 2.95 (d, *J* = 10.6 Hz, 3H), 3.1 (m, 1H), 3.15-3.26 (t, *J* = 7.7 Hz, 2H), 3.46-3.52 (t, *J* = 13.2 Hz, 1H), 3.68-3.72 (dd, , *J* = 5.0 Hz, *J* = 13.2 Hz, 1H), 4.58-4.62 (t, *J* = 7.70 Hz, 3H), 6.78-6.80 (d, *J* = 8.9 Hz, 1H), 7.12-7.13 (d, *J* = 3.4 Hz, 1H), 7.30-7.31 (d, *J* = 4.2 Hz, 1H), 7.37-7.39 (d, *J* = 8.9 Hz, 1H), 7.45 (s, 1H), 7.72 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26..0 (CH_2), 28.2 (CH), 29.7 (CH_2), 47.0 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 58.5 (CH), 71.6 (CH_2), 109.7 (CH), 118.4 (CH), 122.4 (CH), 122.7 (CH), 125.0 (CH), 126.1

(CH), 127.0 (Cq), 128.0 (Cq), 130.9 (Cq), 142.9 (Cq), 144.5 (Cq); HRMS (EI-MS) : *m/z* calcd. for $C_{21}H_{23}N_4OS$ $[M+H]^+$: 378.4941, found 379.1590.

(R)-3-{4-[5-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-thiopen-2-yl]-[1,2,3]triazol-1-yl}-1-aza-bicyclo[2.2.2]octane 24. Compound **24** was obtained from compound **12** and (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 66% yield. R_f : 0,42 (CH_2Cl_2/MeOH 95/5 + NH_4OH 10%) Mp : 212-214°C ; IR (ATR, Diamond) ν (cm^{-1}) : 800, 845, 1067, 1253, 1283, 1305, 1499, 1580, 2870, 2934; ^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.67-1.97 (m, 4H), 2.26-2.28 (m, 1H), 2.85-2.99 (m, 3H), 3.10-3.17 (m, 1H), 4.44-3.51 (m,1H), 3.66 (dd, *J*= 4.5 Hz , *J*= 14.1 Hz, 1H), 4.28 (s, 4H), 4.62 (m, 1H), 6.86-6.88 (d, *J* = 8.2 Hz, 1H), 7.09 (dd, *J* = 2.8 Hz, *J* = 8.5 Hz, 1H), 7.13-7.15 (m, 2H), 7.30 (d, *J* = 8.20 Hz, 1H), 7.71 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.1 (CH_2), 28.2 (CH), 47.0 (CH_2), 47.4 (CH_2), 52.7 (CH_2), 58.6 (CH), 64.5 (2 CH_2), 114.7 (CH), 117.8 (CH), 118.4 (CH), 119.2 (CH), 122.9 (CH), 125.0 (CH),127.9 (Cq),131.5 (Cq), 142.8 (Cq),143.5 (Cq), 143.7 (Cq), 143.8 (Cq); HRMS (EI-MS) : *m/z* calcd. for $C_{21}H_{22}N_4O_2S$ m/z = 394.4930, found 395.1536.

(*R*)-3-(4-(2,2'-Bithiophen-5-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 25. Compound **25** was obtained from compound **12** and thiophen-2-ylboronic acid following the general procedure **C** and isolated as a white solid in a 73% yield. R_f : 0.25 (CH_2Cl_2/MeOH 80/20 + NH_4OH 10%) ; Mp : 182-184 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 1042, 1067, 1210, 1340, 1425, 1454, 1503, 1584, 2867, 2937 ; ^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.44-1.54 (m, 1H), 1.63-1.74 (m, 1H), 1.76-1.88 (m, 2H), 2.26-2.30 (m, 1H), 2.86-3.00 (m, 3H), 3.10-3.20 (m, 1H), 3.45-3.54 (m, 1H), 3.70 (dd, *J* = 4.6 Hz, *J* = 14.3 Hz, 1H), 4.60-4.67 (m, 1H), 7.03 (dd, *J* = 3.8 Hz, *J* = 4.9 Hz, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.19-7.24 (m, 2H), 7.28 (d, *J* = 3.6 Hz, 1H), 7.73 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.1 (CH_2), 28.3 (CH), 47.1 (CH_2),

47.4 (CH_2), 52.7 (CH_2), 58.7 (CH), 118.6 (CH), 124.0 (CH), 124.3 (CH), 124.7 (CH), 124.8 (CH), 128.1 (CH), 131.8 (C_q), 137.1 (C_q), 137.3 (C_q), 142.6 (C_q) ; HRMS (EI-MS) : *m/z* calcd. for $C_{17}H_{19}N_4S_2$ $[M+H]^+$: 343.1051, found: 343.1055.

(*R*)-(3-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl)methanol 26. Compound **26** was obtained from compound **12** and 3-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 75% yield. R_f : 0.17 (CH_2Cl_2/MeOH 98/2+ NH_4OH 10%) ; Mp : 181-183 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 796, 988, 1040, 1226, 1323, 1452, 1488, 2870, 2938, 3108 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.35-1.50 (m, 2H), 1.66-1.81 (m, 2H), 2.20-2.22 (m, 1H), 2.72-2.87 (m, 3H), 2.93-3.05 (m, 1H), 3.34-3.51 (m, 2H), 4.57 (s, 2H), 4.74-4.81 (m, 1H), 5.33 (br s, 1H), 7.28 (d, *J* = 12.0 Hz, 1H), 7.39 (t, *J* = 12.0 Hz, 1H), 7.46 (d, *J* = 6.0 Hz, 1H), 7.53 (d, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 12.0 Hz, 1H), 7.65 (s, 1H), 8.70 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ(ppm) 20.0 (CH_2), 25.7 (CH_2), 28.0 (CH), 46.7 (CH_2), 47.0 (CH_2), 52.2 (CH_2), 57.9 (CH), 63.0 (CH_2), 120.8 (CH), 123.5 (CH), 123.9 (CH), 124.6 (CH), 125.6 (CH), 126.2 (CH), 129.3 (CH), 132.8 (C_q), 133.6 (C_q), 141.8 (Cq), 142.8 (C_q), 144.0 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{23}N_4OS$ $[M+H]^+$: 367.1587, found: 367.1590.

(*R*)-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl)methanol 27. Compound **27** was obtained from compound **12** and 4-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 72% yield. R_f : 0.17 (CH_2Cl_2/MeOH 80/20+ NH_4OH 10%) ; Mp : 253-255 °C ; IR (ATR, Diamond): ν (cm^{-1}) : 983, 1041, 1214, 1306, 1355, 1416, 1454, 1502, 2823, 2872, 2941, 3110 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.38-1.52 (m, 2H), 1.72-1.80 (m, 2H), 2.20-2.26 (m, 1H), 2.76-2.85 (m, 3H), 2.96-3.05 (m, 1H), 3.34-3.51 (m, 2H), 4.56 (d, *J* = 4.8 Hz, 2H), 4.76-4.82 (m, 1H), 5.27 (t, *J* = 4.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 3.1 Hz, 1H), 7.54 (d, *J* =

3.1 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 2H), 8.72 (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), 57.6 (CH), 62.5 (CH_2), 120.3 (CH), 123.9 (CH), 124.9 (2 CH), 125.1 (CH), 127.1 (2 CH), 131.9 (C_q), 132.1 (C_q), 141.4 (C_q), 142.2 (2 C_q) ; HRMS (EI-MS) : *m/z* calcd. for $C_{20}H_{23}N_4OS$ $[M+H]^+$: 367.1593, found: 367.1609.

(*R*)-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl)methanamine 28. Compound **28** was obtained from compound **12** and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine following the general procedure **C** and isolated as a white solid in a 77% yield. R_f : 0.17 (CH_2Cl_2/MeOH 80/20 + NH_4OH 10%) ; Mp : > 260 °C ; IR (ATR, Diamond): ν (cm^{-1}) : 697, 789, 988, 1027-1040, 1227, 1347, 1434, 1583, 2874, 2935, 3100 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ(ppm) 1.37-1.58 (m, 3H), 1.65-1.87 (m, 3H), 2.27 (q, *J* = 3.0 Hz , 1H), 2.89-2.99 (m, 3H), 3.10-3.17 (m, 1H), 3.45-3.51 (m, 1H), 3.68 (dd, *J* = 3.6 Hz, *J* = 14.4 Hz, 1H), 3.89 (s, 2H), 4.62-4.64 (m, 1H), 7.25-7.27 (m, 1H), 7.33-7.35 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 2H), 8.74 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.2 (CH_2), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 58.6 (CH), 118.4 (CH), 123.4 (CH), 124.9 (CH), 125.8 (2 CH), 127.7 (2 CH), 132.0 (C_q), 132.7 (C_q), 142.6 (C_q), 142.9 (C_q), 143.7 (C_q) ; HRMS (EI-MS) : *m/z* calcd. for $C_{20}H_{24}N_5S$ $[M+H]^+$: 366.1747, found: 366.1744.

(*R*)-3-(4-(5-(6-Fluoropyridin-3-yl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 29. Compound **29** was obtained from compound **12** and (6-fluoropyridin-3-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 80% yield. R_f : 0.20 (CH_2Cl_2/MeOH 98/2 + NH_4OH 10%) ; Mp : 163-165 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 784, 801, 986, 1077, 1241, 1320, 1387, 1447, 1526, 1581, 2871, 2939, 3127 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ(ppm) 1.46-1.52 (m, 1H), 1.64-1.71 (m, 1H), 1.74-1.87 (m, 2H), 2.28 (q, *J* = 2.8

Hz, 1H), 2.86-3.00 (m, 3H), 3.10-3.14 (m, 1H), 3.46 (ddd, *J* = 14.4 Hz, *J* = 10.0 Hz, *J* = 2.0 Hz, 1H), 3.66 (dd, *J* = 4.0 Hz, *J* = 14.4 Hz, 1H), 4.63-4.65 (m, 1H), 6.96 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 3.8 Hz, 1H), 7.35 (d, *J* = 3.8 Hz, 1H), 7.78 (s, 1H), 7.97 (td, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H), 8.46 (d, *J* = 2.2 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 25.9 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.6 (CH), 109.7 (d, *J* = 38.0 Hz, CH), 118.6 (CH), 124.7 (CH), 124.9 (CH), 128.4 (d, *J* = 5.0 Hz, C_q), 133.6 (C_q), 138.2 (d, *J* = 8.0 Hz, CH), 138.3 (C_q), 142.1 (C_q), 144.3 (d, *J* = 14.0 Hz, CH), 162.8 (d, *J* = 239.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{18}H_{19}N_5SF$ $[M+H]^+$: 356.1340, found: 356.1343.

Methyl (*R*)-2-fluoro-4-(5-(1-(quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl) benzoate 30. Compound **30** was obtained from compound **12** and (3-fluoro-4-(methoxycarbonyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 85% yield. R_f : 0.20 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 250-252 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 785, 926, 1090, 1262, 1326, 1422, 1472, 1612, 1703, 1718, 2870, 2943, 3133 ; ^{1}H NMR (250 MHz, $CDCl_3$) : δ(ppm) 1.30-1.52 (m, 2H), 1.63-1.81 (m, 2H), 2.20 (q, *J* = 2.8 Hz, 1H), 2.71-3.03 (m, 4H), 3.33-3.50 (m, 2H), 3.87 (s, 3H), 4.71-4.83 (m, 1H), 7.51 (d, *J* = 3.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.70-7.81 (m, 2H), 7.93 (t, *J* = 8.0 Hz, 1H), 8.76 (s, 1H) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) : δ(ppm) 19.6 (CH_2), 25.4 (CH_2), 27.9 (CH), 46.5 (CH_2), 46.8 (CH_2), 51.8 (CH_2), 52.3 (CH_3), 58.3 (CH), 113.2 (d, *J* = 38.0 Hz, CH), 116.7 (d, *J* = 10.0 Hz, C_q), 119.5 (CH), 120.9 (d, *J* = 6.0 Hz, CH), 125.5 (CH), 125.9 (CH), 132.8 (CH), 134.1 (C_q), 140.4 (d, *J* = 15.0 Hz, C_q), 140.9 (d, *J* = 3.0 Hz, C_q), 142.2 (C_q), 162.3 (d, *J* = 258.0 Hz, C_q), 164.7 (d, *J* = 4.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{21}H_{22}N_4FO_2S$ $[M+H]^+$: 413.1442, found: 413.1444.

(*R*)-(3-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-3-yl)phenyl)methanol 31. Compound **31** was obtained from compound **13** and 3-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 80% yield. R_f : 0.21 (CH_2Cl_2/MeOH 98/2 + NH_4OH) 1% ; Mp : 211-213 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 787, 996, 1041, 1162, 1233, 1324, 1437, 1455, 1603, 2868, 2937, 3367; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.43-1.58 (m, 1H), 1.62-1.90 (m, 3H), 2.26-2.32 (m, 1H), 2.47 (br s, 1H), 2.83-3.01 (m, 3H), 3.09-3.19 (m, 1H), 3.46 (ddd, *J* = 3.6 Hz, *J* = 12.0 Hz, *J* = 15.6 Hz, 1H), 3.66 (dd, *J* = 7.6 Hz, *J* = 15.6 Hz, 1H), 4.60-4.69 (m, 1H), 4.76 (s, 2H), 7.32 (d, *J* = 12.2 Hz, 1H), 7.38-7.44 (m, 2H), 7.56 (dd, *J* = 2.2 Hz, *J* = 12.2 Hz, 1H), 7.66 (s, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.78 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 19.9 (CH_2), 25.8 (CH_2), 28.0 (CH), 46.8 (CH_2), 47.1 (CH_2), 52.5 (CH_2), 58.4 (CH), 65.0 (CH_2), 118.5 (CH), 119.9 (CH), 123.2 (CH), 124.8 (CH), 125.3 (CH), 125.8 (CH), 129.0 (CH), 133.7 (C_q), 135.7 (C_q), 141.8 (C_q), 142.5 (2 C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{23}N_4OS$ $[M+H]^+$: 367.1587, found: 367.1591.

(*R*)-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-3-yl)phenyl)methanol 32. Compound **32** was obtained from compound **13** and 4-(hydroxymethyl)phenyl)boronic acid following the general procedure **C** and isolated as a white solid in a 79% yield. R_f : 0.18 (CH_2Cl_2/MeOH 98/2 + NH_4OH 10%) ; Mp : 196-198 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 749, 785, 981, 1042, 1061, 1211, 1325, 1413, 1452, 1534, 2870, 2941, 3116 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.34-1.50 (m, 2H), 1.66-1.78 (m, 2H), 2.19 (q, *J* = 2.8 Hz, 1H), 2.74-2.83 (m, 3H), 2.94-3.01 (m, 1H), 3.40 (d, *J* = 7.2 Hz, 2H), 4.51 (s, 2H), 4.75-4.79 (m, 1H), 5.20 (br s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.80 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 0.8 Hz, 1H), 8.70 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 19.9 (CH_2), 25.6 (CH_2), 28.0 (CH), 46.7 (CH_2), 47.0 (CH_2), 52.3 (CH_2), 57.8 (CH), 63.0 (CH_2), 120.1 (CH), 120.7 (CH), 123.3 (CH), 126.0 (2 CH), 127.4 (2 CH), 133.7 (C_q), 134.3 (C_q), 142.0

(C_q), 142.1 (C_q), 142.2 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{23}N_4OS$ $[M+H]^+$: 367.1587, found: 367.15889.

(*R*)-3-(4-(4-(6-Fluoropyridin-3-yl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 33. Compound **33** was obtained from compound **12** and (6-fluoropyridin-3-yl)boronic acid following the general procedure **C** and isolated as a white solid in a 77% yield. R_f : 0.20 (CH_2Cl_2/MeOH 98/2 + NH_4OH 10%) ; Mp : 136-138 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 793, 972, 1055, 1219, 1310, 1402, 1459, 1589, 2868, 2938, 3115 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.46-1.53 (m, 1H), 1.65-1.73 (m, 1H), 1.77-1.87 (m, 2H), 2.30 (q, *J* = 2.8 Hz, 1H), 2.87-3.01 (m, 3H), 3.11-3.18 (m, 1H), 3.51 (ddd, *J* = 14.4 Hz, *J* = 10.0 Hz, *J* = 2.0 Hz, 1H), 3.70 (dd, *J* = 4.0 Hz, *J* = 14.4 Hz, 1H), 4.65-4.68 (m, 1H), 6.98 (dd, *J* = 2.8 Hz, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.63 (s, 1H), 7.81 (s, 1H), 7.98 (td, *J* = 8.4 Hz, *J* = 2.8 Hz, 1H), 8.46 (d, *J* = 1.6 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 19.9 (CH_2), 25.9 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.6 (CH), 109.6 (d, *J* = 38.0 Hz, CH), 118.7 (CH), 120.7 (CH), 122.5 (CH), 129.5 (d, *J* = 5.0 Hz, C_q), 134.7 (C_q), 138.0 (C_q), 138.8 (d, *J* = 7.0 Hz, CH), 142.1 (C_q), 145.0 (d, *J* = 15.0 Hz, CH), 162.8 (d, *J* = 238.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{18}H_{19}N_5SF$ $[M+H]^+$: 356.1340, found: 356.1342.

General procedure D. Compounds **34-36** were obtained after two successive steps. First the cross coupling reaction was achieved using procedure **C** from **10, 11 or 12** following the general procedure **C** and using the corresponding formylated boronic acids (1.2 eq.), $Pd(PPh_3)_4$ 10 mol %, K_2CO_3 (2.0 eq.) in a mixture of toluene / MeOH 2 / 1 under microwave irradiation at 150 °C for 15 minutes. After aqueous treatment and drying, the crude material was subjected to a using sodium borohydride (1.2 eq.) at 0 °C for 15 minutes. Afterwards, water and CH_2Cl_2 were added. After extraction of the aqueous layers three times, the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under

reduced pressure. The residues were purified by flash chromatography using CH_2Cl_2/MeOH and 10% of NH_4OH as eluent to afford derivatives 34-36.

(*R*)-(5-(3-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)phenyl)thiophen-2-yl)methanol 34. Compound **34** was obtained from compound **10** following the general procedure **D** and isolated as a white solid in a 82% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3 NH_4OH 10%) ; Mp : 176-178 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 795, 981, 1029, 1206, 1373, 1416, 1450, 1608, 2877, 2942, 3070 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.32-1.51 (m, 2H), 1.65-1.82 (m, 2H), 2.29 (q, *J* = 2.8 Hz, 1H), 2.73-2.80 (m, 3H), 2.95-3.02 (m, 1H), 3.39-3.49 (m, 2H), 4.65 (s, 2H), 4.72-4.81 (m, 1H), 5.54 (br s, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 7.42 (d, *J* = 3.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 8.11 (s, 1H), 8.85 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 20.0 (CH_2), 25.7 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.0 (CH_2), 52.3 (CH_2), 57.8 (CH), 58.8 (CH_2), 121.6 (CH), 122.0 (CH), 123.8 (CH), 124.4 (CH), 124.8 (CH), 125.6 (CH), 130.1 (CH), 132.0 (C_q), 135.0 (C_q), 142.1 (C_q), 146.1 (C_q), 146.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{23}N_4OS$ $[M+H]^+$: 367.1587, found: 367.1589.

(R)-(5-(4-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)phenyl)thiophen-2-yl)methanol 35. Compound **35** was obtained from compound **11** following the general procedure **D** and isolated as a white solid in a 85% yield. R_f : 0.12 (CH_2Cl_2/MeOH/NH_4OH : 96/3/1) ; Mp : 232-234°C ; IR (ATR, Diamond) ν (cm^{-1}) : 791, 979, 1032, 1204, 1328, 1447, 1500, 1661, 2871, 2939, 3124 ; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.34-1.47 (m, 2H), 1.68-1.74 (m, 2H), 2.19 (q, *J* = 2.8 Hz, 1H), 2.71-2.79 (m, 3H), 2.94-3.02 (m, 1H), 3.31-3.47 (m, 2H), 4.64 (d, *J* = 5.2 Hz, 2H), 4.72-4.76 (m, 1H), 5.51 (t, 1H, *J* = 5.2 Hz), 6.96 (d, 1H, *J* = 3.6 Hz), 7.39 (d, *J* = 3.6 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 8.75 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6): 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), 57.9 (CH), 58.9 (CH_2), 121.4 (CH), 123.6 (CH), 125.7 (CH), 125.9 (2 CH), 126.2 (2 CH), 130.3 (Cq), 133.8 (Cq), 142.1 (Cq), 146.2 (Cq), 146.7 (Cq); HRMS (EI-MS) : calcd. for $C_{20}H_{23}N_4SO$ m/z = 367.15871, found m/z = 367.15900.

(*R*)-(5'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[2,2'-bithiophen]-5-yl)methanol 36. Compound **36** was obtained from compound **12** a following the general procedure **D** and isolated as a white solid in a 78% yield. R_f : 0.25 (CH_2Cl_2/MeOH 80/20 + NH_4OH 10%) ; Mp : 200-202 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 791, 988, 1028, 1226, 1347, 1445, 1583, 2934 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.35-1.46 (m, 2H), 1.69-1.74 (m, 2H), 2.19 (q, *J* = 3.6 Hz, 1H), 2.73-2.80 (m, 3H), 2.93-3.00 (m, 1H), 3.34-3.46 (m, 2H), 4.63 (s, 2H), 4.71-4.80 (m, 1H), 5.56 (br s, 1H), 6.93 (d, *J* = 3.6 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.26 (d, *J* = 3.6 Hz, 1H), 7.38 (d, *J* = 3.6 Hz, 1H), 8.69 (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), 52.3 (CH_2), 58.1 (CH), 58.8 (CH_2), 120.9 (CH), 124.0 (CH), 124.5 (CH), 125.3 (CH), 125.5 (CH), 132.2 (C_q), 135.5 (C_q), 136.2 (C_q), 141.7 (C_q), 146.6 (C_q) ; HRMS (EI-MS) : *m/z* calcd. for $C_{18}H_{20}N_4OS_2$ $[M+H]^+$: 373.1151, found: 373.1153.

General procedure E : The title alcohol (0.5 mmol) was dissolved in CH_2Cl_2 at 0 °C. DAST reagent (1.4 eq.) was added dropwise and the reaction mixture stirred for 1 hour at this temperature. An aqueous saturated solution of $NaHCO_3$ was added. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH with NH_4OH 10% as eluent.

(*R*)-3-(4-(5-(3-(Fluoromethyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 37. Compound **37** was obtained from alcohol **26** following the general procedure **D** and isolated as a white solid in a 39% yield. R_f : 0.25 (CH_2Cl_2/MeOH 98/2+ NH_4OH 10%) ; Mp :

144-146 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 792, 971, 1041, 1211, 1364, 1452, 1588, 1606, 2165, 2869, 2939 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.46-1.54 (m, 1H), 1.65-1.80 (m, 3H), 2.27-2.31 (m, 1H), 2.88-2.98 (m, 3H), 3.11-3.18 (m, 1H), 3.50 (ddd, *J* = 2.0 Hz, *J* = 9.6 Hz, *J* = 14.4 Hz, 1H), 3.71 (dd, *J* = 3.6 Hz, *J* = 14.4 Hz, 1H), 4.62-4.66 (m, 1H), 5.43 (d, *J* = 47.6 Hz, 2H), 7.29-7.31 (m, 2H), 7.36 (d, *J* = 3.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.61-7.63 (m, 2H), 7.76 (s, 1H) ; ^{13}C NMR (100 MHz, CDCl3) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.5 (CH), 84.3 (d, *J* = 166.0 Hz, CH_2), 118.5 (CH), 123.9 (CH), 124.5 (d, *J* = 6.0 Hz, CH), 124.9 (CH), 125.9 (d, *J* = 3.0 Hz, CH), 126.4 (d, *J* = 6.0 Hz, CH), 129.2 (CH) , 132.6 (C_q), 134.4 (C_q), 137.0 (d, *J* = 17.0 Hz, C_q), 142.5 (C_q), 143.1 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{22}N_4FS$ $[M+H]^+$: 369.1543, found: 369.1545.

(*R*)-3-(4-(5-(4-(fluoromethyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine

38. Compound **38** was obtained from alcohol **27** following the general procedure **E** and isolated as a white solid in a 45% yield. R_f : 0.25 (CH_2Cl_2/MeOH 98/2 NH_4OH 10%) ; Mp : 199-201 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 962, 1042, 1060, 1219, 1376, 1414, 1454, 1502, 1601, 2163, 2321, 2937 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.54 (m, 1H), 1.66-1.70 (m, 1H), 1.77-1.90 (m, 2H), 2.30 (q, *J* = 3.2 Hz, 1H), 2.88-2.98 (m, 3H), 3.12-3.19 (m, 1H), 3.50 (ddd, *J* = 2.0 Hz, *J* = 9.6 Hz, *J* = 14.4 Hz, 1H), 3.71 (dd, *J* = 3.6 Hz, *J* = 14.4 Hz, 1H), 4.64-4.67 (m, 1H), 5.40 (d, *J* = 47.6 Hz, 2H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 3.6 Hz, 1H), 7.40 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 25.9 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.5 (CH), 84.2 (d, *J* = 166.0 Hz, CH_2), 118.4 (CH), 123.9 (CH), 124.9 (CH), 125.8 (2 CH), 128.2 (d, *J* = 6.0 Hz, 2 CH), 132.6 (C_q), 134.5 (d, *J* = 4.0 Hz, C_q), 135.4 (d, *J* = 17.0 Hz, C_q), 142.5 (C_q), 143.1 (C_q); HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{22}N_4FS$ $[M+H]^+$: 369.1543, found: 369.1544.

(*R*)-(2-Fluoro-4-(5-(1-(quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl) methanol 65. Compound **65** was obtained from **10** and **45** following the general procedure **C** and isolated as a white solid in a 75% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 228-230 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 803, 863, 1036, 1127, 1213, 1356, 1420, 1617, 2871, 2943 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.32-1.54 (m, 2H), 1.63-1.85 (m, 2H), 2.20 (q, *J* = 3.2 Hz, 1H), 2.68-2.87 (m, 3H), 2.87-3.05 (m, 1H), 3.36-3.42 (m, 2H), 4.57 (s, 2H), 4.69-4.84 (m, 1H), 5.32 (br s, 1H), 7.45-7.61 (m, 5H), 8.71 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 20.1 (CH_2), 25.8 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.1 (CH_2), 52.3 (CH_2), 57.0 (d, *J* = 4.0 Hz, CH_2), 58.1 (CH), 111.8 (d, *J* = 23.0 Hz, CH), 121.0 (CH), 121.5 (d, *J* = 2.0 Hz, CH), 125.6 (CH), 125.7 (CH), 128.9 (d, *J* = 15.0 Hz, Cq), 127.3 (d, *J* = 5.0 Hz, CH), 133.5 (C_q), 134.6 (d, *J* = 9.0 Hz, C_q), 141.1 (C_q), 141.7 (C_q), 160.4 (d, *J* = 243.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{22}N_4OSF$ $[M+H]^+$: 385.1493, found: 385.1494.

(*R*)-3-(4-(4'-(Piperidin-1-ylmethyl)-[1,1'-biphenyl]-3-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 66. Compound **66** was obtained from from **10** and **52** following the general procedure **C** and isolated as a white solid in a 65% yield. R_f : 0.20 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 140-142 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 795, 995, 1106, 1318, 1455, 1608, 2757, 2870, 2934 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.84 (m, 10H), 2.29 (q, *J* = 2.8 Hz, 1H), 2.34-2.54 (m, 4H), 2.89-2.97 (m, 3H), 3.12-3.19 (m, 1H), 3.47-3.53 (m, 3H), 3.71 (dd, *J* = 5.2 H, *J* = 14.4 Hz, 1H), 4.65-4.67 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.55-7.61 (m, 3H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.86 (s, 1H), 8.07 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 24.4 (CH_2), 26.0 (2 CH_2), 26.1 (CH_2), 28.2 (CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 54.5 (2 CH_2), 58.5 (CH), 63.5 (CH_2), 119.1 (CH), 124.3 (CH), 124.4 (CH), 126.8 (CH), 126.9 (2 CH), 129.3 (CH), 129.7 (2 CH), 131.1 (C_q), 137.9 (C_q), 139.4 (C_q), 141.7 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{27}H_{33}N_5$ $[M+H]^+$: 428.2809, found: 428.2806.

(*R*)-4-((3'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-4-yl)methyl) morpholine 67. Compound **67** was obtained from **10** and **53** following the general procedure **C** and isolated as a white solid in a 62% yield. R_f : 0.15 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 162-164 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 797, 866, 1007, 1115, 1324, 1454, 1611, 2809, 2868, 2942 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.53 (m, 1H), 1.68-1.87 (m, 3H), 2.31 (q, *J* = 2.8 Hz, 1H), 2.50 (t, *J* = 4.2 Hz, 4H), 2.91-3.03 (m, 3H), 3.14-3.20 (m, 1H), 3.49-3.57 (m, 3H), 3.72-3.76 (m, 5H), 4.67-4.69 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.87 (s, 1H), 8.08 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.0 (CH_2), 28.2 (CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 53.7 (2 CH_2), 58.4 (CH), 63.1 (CH_2), 67.0 (2 CH_2), 119.1 (CH), 124.4 (CH), 124.5 (CH), 126.8 (CH), 127.1 (2 CH), 129.3 (CH), 129.6 (2 CH), 131.2 (C_q), 137.2 (C_q), 139.7 (C_q), 141.6 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{26}H_{32}N_5O$ $[M+H]^+$: 430.2601, found: 430.2597.

(*R*)-3-(4-(3'-((4-Methylpiperazin-1-yl)methyl)-[1,1'-biphenyl]-3-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 68. Compound **68** was obtained from **10** and **54** following the general procedure **C** and isolated as a white solid in a 78% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 146-148 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 699, 798, 1014, 1161, 1210, 1347, 1452, 2794, 2937 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.43-1.49 (m, 1H), 1.66-1.88 (m, 3H), 2.30-2.50 (m, 12H), 2.87-3.01 (m, 3H), 3.11-3.22 (m, 1H), 3.47-3.56 (m, 3H), 3.72 (dd, *J* = 5.0 Hz, *J* = 14.6 Hz, 1H), 4.63-4.71 (m, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.55-7.62 (m, 3H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.87 (s, 1H), 8.08 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.0 (CH_2), 28.2 (CH), 46.1 (CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 53.1 (2 CH_2), 55.1 (2 CH_2), 58.4 (CH), 62.7 (CH_2), 119.1 (CH), 124.4 (CH), 124.5 (CH), 126.8 (CH), 127.0 (2 CH), 129.3 (CH), 129.6 (2 CH), 131.1 (C_q), 137.6

(C_q), 139.5 (C_q), 141.6 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{27}H_{35}N_6$ $[M+H]^+$: 443.2918, found: 443.2911.

(*R*)-3-(4-(3'-(Piperidin-1-ylmethyl)-[1,1'-biphenyl]-3-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 69. Compound **69** was obtained from **10** and **62** following the general procedure **C** and isolated as a white solid in a 68% yield. R_f : 0.18 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 155-157 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 701, 760, 795, 1040, 1155, 1342, 1454, 1604, 2792, 2868, 2933 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.87 (m, 10H), 2.28 (q, *J* = 2.8 Hz, 1H), 2.40-2.54 (m, 4H), 2.86-3.03 (m, 3H), 3.12-3.21 (m, 1H), 3.46-3.54 (m, 3H), 3.71 (dd, *J* = 5.2 H, *J* = 14.4 Hz, 1H), 4.63-4.68 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.47-7.60 (m, 4H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 8.09 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 24.4 (CH_2), 26.0 (2 CH_2), 26.1 (CH_2), 28.2 (CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 54.6 (2 CH_2), 58.5 (CH), 63.9 (CH_2), 119.2 (CH), 124.5 (CH), 124.6 (CH), 125.7 (CH), 127.0 (CH), 128.0 (CH), 128.5 (CH), 128.6 (CH), 129.2 (CH), 131.1 (C_q), 139.2 (C_q), 140.6 (C_q), 141.9 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{27}H_{34}N_5$ $[M+H]^+$: 428.2809, found: 428.2807.

(*R*)-4-((3'-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)-[1,1'-biphenyl]-3-yl)methyl)morpholine 70. Compound **70** was obtained from **10** and **63** following the general procedure **C** and isolated as a white solid in a 71% yield. R_f : 0.15 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 120-122 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 700, 782, 860, 1007, 1113, 1330, 1455, 1604, 2809, 2868, 2942 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.45-1.53 (m, 1H), 1.66-1.89 (m, 3H), 2.30 (q, *J* = 2.8 Hz, 1H), 2.48 (t, *J* = 4.2 Hz, 4H), 2.88-3.02 (m, 3H), 3.13-3.21 (m, 1H), 3.49-3.57 (m, 3H), 3.67-3.76 (m, 5H), 4.65-4.69 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.47-7.62 (m, 4H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.88 (s, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 25.9 (CH_2), 28.2 (CH), 46.9

(CH_2), 47.3 (CH_2), 52.6 (CH_2), 53.7 (2 CH_2), 58.4 (CH), 63.5 (CH_2), 67.0 (2 CH_2), 119.2 (CH), 124.5 (CH), 124.5 (CH), 126.1 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 131.1 (C_q), 138.4 (C_q), 140.8 (C_q), 141.8 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{26}H_{32}N_5O$ $[M+H]^+$: 430.2601, found: 430.2597.

(*R*)-3-(4-(3'-((4-Methylpiperazin-1-yl)methyl)-[1,1'-biphenyl]-3-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 71. Compound **71** was obtained from **10** and **64** following the general procedure **C** and isolated as a white solid in a 73% yield. R_f : 0.15 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 150-152 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 700, 810, 1005, 1140, 1281, 1455, 1604, 2796, 2937 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.41-1.50 (m, 1H), 1.64-1.86 (m, 3H), 2.24-2.29 (m, 4H), 2.35-2.61 (m, 8H), 2.85-2.98 (m, 3H), 3.11-3.18 (m, 1H), 3.47 (ddd, *J* = 2.1 Hz, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H), 3.56 (s, 2H), 3.71 (dd, *J* = 3.2 Hz, *J* = 12.8 Hz, 1H), 4.62-4.66 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.45-7.59 (m, 4H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.86 (s, 1H), 8.08 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.0 (CH_2), 28.2 (CH), 46.0 (CH_2), 46.9 (CH_3), 47.3 (CH_2), 52.6 (CH_2), 53.1 (2 CH_2), 55.1 (2 CH_2), 58.4 (CH), 63.1 (CH_2), 119.2 (CH), 124.5 (CH), 124.6 (CH), 125.9 (CH), 127.0 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.2 (CH), 131.1 (C_q), 138.8 (C_q), 140.7 (C_q), 141.8 (C_q), 147.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{27}H_{34}N_6$ $[M+H]^+$: 443.2918, found: 443.2911.

(*R*)-(2-Fluoro-4-(5-(1-(quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl) methanol 72. Compound **72** was obtained from **12** and **45** following the general procedure **C** and isolated as a white solid in a 75% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 228-230 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 803, 863, 1036, 1127, 1213, 1356, 1420, 1617, 2871, 2943 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.32-1.54 (m, 2H), 1.63-1.85 (m, 2H), 2.20 (q, *J* = 3.2 Hz, 1H), 2.68-2.87 (m, 3H), 2.87-3.05 (m, 1H), 3.36-3.42 (m, 2H),

4.57 (s, 2H), 4.69-4.84 (m, 1H), 5.32 (br s, 1H), 7.45-7.61 (m, 5H), 8.71 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 20.1 (CH_2), 25.8 (CH_2), 28.1 (CH), 46.8 (CH_2), 47.1 (CH_2), 52.3 (CH_2), 57.0 (d, J = 4.0 Hz, CH_2), 58.1 (CH), 111.8 (d, J = 23.0 Hz, CH), 121.0 (CH), 121.5 (d, J = 2.0 Hz, CH), 125.6 (CH), 125.7 (CH), 128.9 (d, J = 15.0 Hz, Cq), 127.3 (d, J = 5.0 Hz, CH), 133.5 (C_q), 134.6 (d, J = 9.0 Hz, C_q), 141.1 (C_q), 141.7 (C_q), 160.4 (d, J = 243.0 Hz, C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{20}H_{22}N_4OSF$ $[M+H]^+$: 385.1493, found: 385.1494.

(*R*)-2-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenyl)ethan-1-ol 73. Compound **73** was obtained from **12** and **45** following the general procedure **C** and isolated as a white solid in a 75% yield. R_f : 0.12 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 198-200 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 800, 922, 1040, 1218, 1317, 1454, 1500, 2873, 2942 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.38-1.44 (m, 2H), 1.69-1.75 (m, 2H), 2.19 (q, J = 3.2 Hz, 1H), 2.73-2.80 (m, 5H), 2.94-2.99 (m, 1H), 3.35-3.47 (m, 2H), 3.63 (t, J = 7.2 Hz, 2H), 4.68-4.77 (m, 2H), 7.28 (d, J = 7.6 Hz, 2H), 7.43-7.48 (m, 2H), 7.60 (d, J = 7.6 Hz, 2H), 8.68 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 20.1 (CH_2), 25.8 (CH_2), 28.1 (CH), 39.1 (CH_2), 46.8 (CH_2), 47.1 (CH_2), 52.3 (CH_2), 58.0 (CH), 62.5 (CH_2), 120.8 (CH), 124.2 (CH), 125.5 (2 CH), 125.6 (CH), 130.1 (2 CH), 131.7 (C_q), 132.5 (C_q), 139.8 (C_q), 141.9 (C_q), 142.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{21}H_{25}N_4SO$ $[M+H]^+$: 381.1744, found: 381.1744.

(*R*)-2-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)phenoxy)ethan-1-ol 74. Compound **74** was obtained from **12** and **47** following the general procedure **C** and isolated as a white solid in a 79% yield. R_f : 0.14 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 216-218 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 795, 833, 976, 1050, 1175, 1245, 1454, 1500, 1606, 2870, 2940 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.42-1.54 (m, 1H), 1.63-1.88 (m, 4H), 2.28 (q, J = 3.2 Hz, 1H), 2.86-3.01 (m, 3H), 3.11-3.19 (m, 1H), 3.45-3.51 (m, 1H), 3.68

(dd, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H), 3.98 (t, *J* = 4.5 Hz, 2H), 4.12 (t, *J* = 4.5 Hz, 2H), 4.60-4.67 (m, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 4.0 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.72 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 58.5 (CH), 61.4 (CH_2), 69.4 (CH_2), 115.0 (2 CH), 118.3 (CH), 122.6 (CH), 124.9 (CH), 127.1 (2 CH), 127.4 (C_q), 131.3 (C_q), 142.7 (C_q), 143.7 (C_q), 158.4 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{21}H_{24}N_4SO_2$ $[M+H]^+$: 397.1693, found: 397.1694.

(*R*)-3-(4-(5-(4-(2-(Methoxymethoxy)ethoxy)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 75. Compound **75** was obtained **12** and **48** following the general procedure **C** and isolated as a white solid in a 62% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 196-198 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 797, 920, 1040, 1112, 1250, 1452, 1502, 1607, 2870, 2940 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.41-1.53 (m, 1H), 1.64-1.86 (m, 3H), 2.26 (q, *J* = 3.0 Hz, 1H), 2.85-2.99 (m, 3H), 3.08-3.18 (m, 1H), 3.40-3.50 (m, 4H), 3.68 (dd, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H), 3.90 (t, *J* = 4.5 Hz, 2H), 4.17 (t, *J* = 4.5 Hz, 2H), 4.59-4.64 (m, 1H), 4.72 (s, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.32 (d, *J* = 3.6 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.71 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 55.3 (CH_3), 58.5 (CH), 65.9 (CH_2), 67.5 (CH_2), 96.6 (CH_2), 115.0 (2 CH), 118.3 (CH), 122.5 (CH), 124.9 (CH), 127.0 (2 CH), 127.2 (C_q), 131.2 (C_q), 142.7 (C_q), 143.8 (C_q), 158.5 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{23}H_{29}N_4O_3S$ $[M+H]^+$: 441.1955, found: 441.1956.

(*R*)-3-(4-(5-(4-(2-Fluoroethyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 76. Compound **76** was obtained from **12** and **49** following the general procedure **C** and isolated as a white solid in a 63% yield. R_f : 0.16 (CH_2Cl_2/MeOH 98/2+ NH_4OH 10%) ; Mp : 207-209 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 798, 922, 1042-1072, 1218, 1356, 1451, 1500,

2866, 2935 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.49-1.53 (m, 1H), 1.67-1.87 (m, 3H), 2.29 (q, *J* = 3.2 Hz, 1H), 2.91-3.16 (m, 6H), 3.48-3.54 (m, 1H), 3.71 (dd, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H), 4.59-4.74 (m, 3H), 7.27-7.37 (m, 4H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.76 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.1 (CH_2), 28.1 (CH), 36.6 (d, *J* = 20.0 Hz, CH_2), 46.9 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 58.5 (CH), 83.9 (d, *J* = 168.0 Hz, CH_2), 118.4 (CH), 123.4 (CH), 124.9 (CH), 125.7 (2 CH), 128.9 (2 CH), 132.1 (C_q), 132.6 (C_q), 136.7 (d, *J* = 5.0 Hz, C_q), 142.6 (C_q), 143.6 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{21}H_{24}N_4SF$ $[M+H]^+$: 383.1700, found: 383.1699.

(*R*)-3-(4-(5-(4-(2-fluoroethoxy)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 77. Compound **77** was obtained from **12** and **50** following the general procedure **C** and isolated as a white solid in a 63% yield. R_f : 0.16 (CH_2Cl_2/MeOH 98/2+ NH_4OH 10%) ; Mp : 215-217 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 797, 883, 920, 1050, 1180, 1250, 1450, 1500, 1607, 2868, 2940 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.44-1.56 (m, 1H), 1.67-1.89 (m, 3H), 2.29 (q, *J* = 3.2 Hz, 1H), 2.88-3.02 (m, 3H), 3.13-3.19 (m, 1H), 3.47-3.54 (m, 1H), 3.70 (dd, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H), 4.26 (dt, *J* = 4.0 Hz, *J* = 28.2 Hz, 2H), 4.63-4.66 (m, 1H), 4.73 (t, *J* = 4.0 Hz, 1H), 4.85 (t, *J* = 4.0 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.75 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 58.5 (CH), 67.2 (d, *J* = 20.0 Hz, CH_2), 81.9 (d, *J* = 169.0 Hz, CH_2), 115.1 (2 CH), 118.3 (CH), 122.7 (CH), 124.9 (CH), 127.0 (2 CH), 127.7 (C_q), 131.4 (C_q), 142.7 (C_q), 143.6 (C_q), 158.1 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{21}H_{24}N_4SOF$ $[M+H]^+$: 399.1649, found: 399.1648.

(*R*)-3-(4-(5-(4-(Piperidin-1-ylmethyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 78. Compound **78** was obtained from **12** and **52** following the general procedure **C** and isolated as a white solid in a 75% yield. R_f: 0.21 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ;

Mp : 230-232 °C ; IR (ATR, Diamond) ν (cm^{-1}): 792, 995, 1103, 1215, 1366, 1415, 1451, 1662, 2866, 2934, 3120 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.38-1.52 (m, 3H), 1.56-1.62 (m, 4H), 1.64-1.88 (m, 3H), 2.28 (q, *J* = 2.8 Hz, 1H), 2.32-2.49 (m, 4H), 2.86-3.01 (m, 3H), 3.11-3.18 (m, 1H), 3.45-3.52 (m, 3H), 3.69 (dd, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H), 4.62-4.64 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.33-7.35 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 24.3 (CH_2), 25.9 (2 CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 54.5 (2 CH_2), 58.5 (CH), 63.4 (CH_2), 118.3 (CH), 123.2 (CH), 124.9 (CH), 125.4 (2 CH), 129.7 (2 CH), 131.8 (C_q), 132.6 (C_q), 138.3 (C_q), 142.6 (C_q), 143.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{31}N_5S$ $[M+H]^+$: 434.2373, found: 433.2374.

(*R*)-4-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)benzyl)morpholine 79. Compound **79** was obtained from **12** and **53** following the general procedure **C** and isolated as a white solid in a 83% yield. R_f : 0.21 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 222-224 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 791, 987, 1040, 1220, 1345, 1451, 1498, 1662, 2803, 2868, 2938 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.41-1.53 (m, 1H), 1.62-1.86 (m, 3H), 2.27 (q, *J* = 2.8 Hz, 1H), 2.45-2.28 (m, 4H), 2.28-3.00 (m, 3H), 3.10-3.19 (m, 1H), 3.46-3.50 (m, 3H), 3.66-3.72 (m, 5H), 4.61-4.64 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.33-7.36 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 53.6 (2 CH_2), 58.5 (CH), 63.0 (CH_2), 37.0 (2 CH_2), 118.3 (CH), 123.4 (CH), 124.9 (CH), 125.5 (2 CH), 129.7 (2 CH), 132.0 (C_q), 133.0 (C_q), 137.4 (C_q), 142.6 (Cq), 143.6 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{24}H_{29}N_5OS$ $[M+H]^+$: 436.2165, found: 436.2166.

(*R*)-3-[4-(5-(4-((4-Methylpiperazin-1-yl)methyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 80. Compound **80** was obtained from **12** and **54** following the general

procedure **C** and isolated as a white solid in a 75% yield. R_f : 0.20 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 214-216 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 792, 973, 1040, 1222, 1347, 1450, 1661, 2869, 2939, 3120 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.42-1.53 (m, 1H), 1.62-1.85 (m, 3H), 2.27-2.70 (m, 12H), 2.84-3.00 (m, 3H), 3.10-3.18 (m, 1H), 3.45-3.52 (m, 3H), 3.69 (dd, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H), 4.61-4.64 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.33-7.35 (m, 3H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.74 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.0 (CH_3), 46.9 (CH_2), 47.2 (CH_2), 52.6 (2 CH_2), 53.1 (2 CH_2), 55.1 (CH_2), 58.5 (CH), 62.6 (CH_2), 118.3 (CH), 123.3 (CH), 124.9 (CH), 125.5 (2 CH), 129.7 (2 CH), 131.9 (C_q), 132.8 (C_q), 137.9 (C_q), 142.6 (Cq), 143.7 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{33}N_6S$ $[M+H]^+$: 449.2482, found: 449.2484.

(*R*)-1-(4-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)benzyl)piperidin-4-ol 81. Compound **81** was obtained from **12** and **55** following the general procedure **C** and isolated as a white solid in a 68% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 242-244 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 683, 786-801, 977, 1073, 1214, 1319, 1450-1470, 1501, 2797, 2869, 2941, 3207 ; ^{1}H NMR (400 MHz, DMSO-d_6) : δ (ppm) 1.35-1.48 (m, 4H), 1.69-1.74 (m, 4H), 2.04 (t, *J* = 10.0 Hz, 2H), 2.20 (q, *J* = 3.0 Hz, 1H), 2.66-2.81 (m, 5H), 2.92-3.01 (m, 1H), 3.26-3.45 (m, 5H), 4.54 (br s, 1H), 4.73-4.79 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 3.6 Hz, 1H), 7.50 (d, *J* = 3.6 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 8.69 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ(ppm) 20.1 (CH_2), 25.8 (CH_2), 28.1 (CH), 34.9 (2 CH_2), 46.8 (CH_2), 47.1 (CH_2), 51.3 (2 CH_2), 52.3 (CH_2), 58.0 (CH), 62.2 (CH_2), 66.8 (CH), 120.8 (CH), 124.5 (CH), 125.5 (2 CH), 125.6 (CH), 129.9 (2 CH), 132.5 (C_q), 132.7 (C_q), 138.9 (C_q), 141.9 (C_q), 142.6 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{31}N_5OS$ $[M+H]^+$: 450.2322, found: 450.2320.

(*R*)-3-(4-(5-(4-((4-Fluoropiperidin-1-yl)methyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 82. Compound **82** was obtained from **12** and **56** following the general procedure **C** and isolated as a white solid in a 61% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 227-229 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 684, 789, 923, 1039, 1211, 1323, 1417-1472, 1501, 2868, 2940 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.42-1.50 (m, 1H), 1.64-1.96 (m, 7H), 2.27 (q, *J* = 3.2 Hz, 1H), 2.37 (t, *J* = 5.5 Hz, 2H), 2.59 (t, *J* = 5.5 Hz, 2H), 2.89-3.00 (m, 3H), 3.10-3.17 (m, 1H), 3.45-3.51 (m, 3H), 3.68 (dd, *J* = 4.5 Hz, *J* = 14.5 Hz, 1H), 4.61-4.78 (m, 2H), 7.27-7.34 (m, 4H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.1 (CH_2), 26.0 (CH_2), 28.1 (CH), 31.5 (d, *J* = 20.0 Hz, 2 CH_2), 47.0 (CH_2), 47.3 (CH_2), 49.5 (d, *J* = 6.0 Hz, 2 CH_2), 52.7 (CH_2), 58.5 (CH), 62.6 (CH_2), 88.6 (d, *J* = 172.0 Hz, CH), 118.4 (CH), 123.4 (CH), 124.9 (CH), 125.6 (2 CH), 129.6 (2 CH), 132.0 (C_q), 132.9 (C_q), 138.1 (C_q), 142.6 (C_q), 143.7 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{31}N_5FS$ $[M+H]^+$: 452.2279, found: 452.2276.

(*R*)-3-(4-(5-(4-((4-(Fluoromethyl)piperidin-1-yl)methyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 83. Compound **83** was obtained from **12** and **57** following the general procedure **C** and isolated as a white solid in a 67% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 225-227 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 790, 986, 1029, 1223, 1365, 1416-1471, 1500, 2868, 2942 ; ^{1}H NMR (250 MHz, $CDCl_3$) : δ (ppm) 1.31-1.50 (m, 3H), 1.68-1.81 (m, 6H), 1.99 (t, *J* = 6.7 Hz, 2H), 2.27 (q, *J* = 3.2 Hz, 1H), 2.91-2.93 (m, 5H), 3.11-3.18 (m, 1H), 3.45-3.57 (m, 3H), 3.68 (dd, *J* = 4.5 Hz, *J* = 14.5 Hz, 1H), 4.26 (dd, *J* = 5.6 Hz, *J* = 47.2 Hz, 2H), 4.57-4.69 (m, 1H), 7.27-7.34 (m, 4H), 7.57 (d, *J* = 4.7 Hz, 2H), 7.74 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 27.8 (d, *J* = 6.0 Hz, 2 CH_2), 28.1 (CH), 36.7 (d, *J* = 19.0 Hz, CH), 47.0 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 53.1 (2 CH_2), 58.5 (CH), 63.0 (CH_2), 87.9 (d, *J* = 168.0 Hz, CH), 118.4 (CH), 123.4 (CH), 124.9

(CH), 125.5 (2 CH), 129.7 (2 CH), 132.0 (C_q), 132.8 (C_q), 138.2 (C_q), 142.7 (C_q), 143.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{26}H_{33}N_5FS$ $[M+H]^+$: 465.2435, found: 465.2434.

(*R*)-3-(4-(5-(3-(Piperidin-1-ylmethyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 84. Compound **84** was obtained from **12** and **62** following the general procedure **C** and isolated as a white solid in a 60% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 170-172 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 698, 806, 1040, 1119, 1210, 1368, 1441, 1602, 2752, 2934 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.40-1.47 (m, 3H), 1.51-1.90 (m, 7H), 2.28 (q, *J* = 3.2 Hz, 1H), 2.42 (t, *J* = 4.4 Hz, 4H), 2.87-3.01 (m, 3H), 3.11-3.19 (m, 1H), 3.46-3.54 (m, 3H), 3.48 (dd, *J* = 4.8 Hz, *J* = 14.6 Hz, 1H), 4.59-4.68 (m, 1H), 7.25-7.37 (m, 4H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.60 (s, 1H), 7.75 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 24.4 (CH_2), 26.0 (2 CH_2), 26.1 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.7 (CH_2), 54.5 (2 CH_2), 58.5 (CH), 63.7 (CH_2), 118.4 (CH), 123.6 (CH), 124.2 (CH), 124.9 (CH), 126.4 (CH), 128.5 (CH), 128.7 (CH), 132.1 (C_q), 133.9 (C_q), 139.5 (C_q), 142.7 (C_q), 144.0 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{32}N_5S$ $[M+H]^+$: 434.2373, found: 434.2367.

(*R*)-4-(3-(5-(1-(Quinuclidin-3-yl)-1*H*-1,2,3-triazol-4-yl)thiophen-2-yl)benzyl)morpholine 85. Compound **85** was obtained from **12** and **63** following the general procedure **C** and isolated as a white solid in a 63% yield. R_f : 0.16 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 162-164 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 782, 916, 1011, 1113, 1212, 1348, 1454, 1603, 2800, 2870, 2936 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.46-1.52 (m, 1H), 1.66-1.87 (m, 3H), 2.29 (q, *J* = 3.2 Hz, 1H), 2.48 (t, *J* = 4.4 Hz, 4H), 2.88-3.01 (m, 3H), 3.12-3.17 (m, 1H), 3.46-3.54 (m, 3H), 3.67-3.74 (m, 5H), 4.61-4.70 (m, 1H), 7.26-7.36 (m, 4H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.61 (s, 1H), 7.76 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.3 (CH_2), 52.6 (CH_2), 53.6 (2 CH_2), 58.5 (CH), 63.2 (CH_2),

67.0 (2 CH), 118.4 (CH), 123.6 (CH), 124.5 (CH), 124.9 (CH), 126.3 (CH), 128.5 (CH), 128.9 (CH), 132.2 (C_q), 134.1 (C_q), 138.7 (C_q), 142.6 (C_q), 143.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{24}H_{30}N_5OS$ $[M+H]^+$: 436.2166, found: 436.2164.

(*R*)-3-(4-(5-(3-((4-Methylpiperazin-1-yl)methyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl) quinuclidine 86. Compound **86** was obtained from **12** and **64** following the general procedure **C** and isolated as a white solid in a 83% yield. R_f : 0.20 (CH_2Cl_2/MeOH 97/3 + NH_4OH 10%) ; Mp : 155-157 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 788, 923, 1013, 1279, 1347, 1453, 1506, 2793, 2870, 2938, 3306 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.42-1.60 (m, 1H), 1.65-1.92 (m, 3H), 2.24-2.32 (m, 4H), 2.37-2.73 (m, 8H), 2.86-2.99 (m, 3H), 3.08-3.22 (m, 1H), 3.45-3.56 (m, 3H), 3.70 (dd, *J* = 5.2 Hz, *J* = 14.5 Hz, 1H), 4.60-4.70 (m, 1H), 7.26-7.38 (m, 4H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.61 (m, 1H), 7.76 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) : δ (ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.0 (CH_3), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 53.1 (2 CH_2), 55.1 (2 CH), 58.5 (CH), 62.8 (CH_2), 118.3 (CH), 123.6 (CH), 124.4 (CH), 124.8 (CH), 126.3 (CH), 128.4 (CH), 128.8 (CH), 132.1 (C_q), 133.9 (C_q), 139.1 (C_q), 142.6 (C_q), 143.8 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{33}N_6S$ $[M+H]^+$: 449.2482, found: 449.2479.

(*R*)-3-(4-(5-(6-Nitropyridin-3-yl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine 87. Compound **87** was obtained from **12** and 2-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine following the general procedure **C** at 110 °C for 1h30 and isolated as a white solid in a 77% yield. R_f : 0.20 (CH_2Cl_2/MeOH 98/2 + NH_4OH 10%) ; Mp : 160-162 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 788, 987, 1013, 1216, 1278, 1347, 1413, 1453, 1528, 2794, 2938, 3307 ; ^{1}H NMR (250 MHz, $CDCl_3$) : δ (ppm) 1.48-1.57(m, 1H), 1.65-1.69 (m, 1H), 1.73-1.90 (m, 2H), 2.30 (q, *J* = 2.8 Hz, 1H), 2.85-3.02 (m, 3H), 3.09-3.19 (m, 1H), 3.49 (ddd, *J* = 2.8 Hz, *J* = 10.0 Hz, *J* = 14.4 Hz, 1H), 3.70 (dd, *J* = 4.4 Hz, *J* = 14.4 Hz, 1H), 4.63-4.71 (m, 1H), 7.45

(d, *J* = 3.2 Hz, 1H), 7.54 (d, *J* = 3.2 Hz, 1H), 7.84 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) : δ(ppm) 20.0 (CH_2), 26.0 (CH_2), 28.1 (CH), 46.9 (CH_2), 47.2 (CH_2), 52.6 (CH_2), 58.3 (CH), 118.5 (CH), 119.0 (CH), 125.4 (CH), 127.3 (CH), 135.2 (CH), 135.7 (C_q), 136.6 (C_q), 136.7 (C_q), 141.6 (C_q), 145.0 (CH), 155.0 (C_q) ; HRMS (EI-MS): *m/z* calcd. for $C_{18}H_{19}N_6O_2S$ $[M+H]^+$: 383.1285, found: 383.1286.

(R)-3-[4-[5-[4-(chloromethyl)phenyl]-2-thienyl]-1*H*-1,2,3-triazol-1-yl]quinuclidine 88.

Compound **27** (1.0 mmol) was dissolved in CH_2Cl_2 at 0 °C. $SOCl_2$ reagent (2.0. eq.) was added dropwise and the reaction mixture was stirred for 12 hours at room temperature. The mixture was concentrated under reduced pressure and the crude solid was solubilized in Et_2O (10 mL) and filtered. The precipitate was washed with an additional amount of Et_2O (5 x 10 mL) and evaporated under reduced pressure. The obtained compound (1.0 mmol) was dissolved in a mixture of CH_2Cl_2/THF (9/1) and $BH_3.Me_2S$ (1.00 mmol) was added dropwise at -10 °C. The reaction mixture was stirred for 1 hour at this temperature. The mixture was concentrated under reduced pressure and the crude solid was solubilized in Et_2O (10 mL) and filtered. The crude material was purified by flash chromatography using CH_2Cl_2 with NH_4OH 10% as eluent to afford the desired compound **88** as a grey solid in a 80% yield. R_f : 0.4 (CH_2Cl_2/MeOH/NH_4OH : 97/2/1) ; Mp : 195°C ; IR (ATR, Diamond) : ν (cm^{-1}) : 797, 973, 1042, 1229, 1319, 1455, 1600, 1694, 2880, 3392 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.71-1.92 (m, 2H), 2.00-2.08 (m, 2H), 2.48-2.51 (m, 1H), 3.07-3.17 (m, 3H), 3.34 – 3.65 (m, 2H), 3.95-4.02 (m, 1H), 4.63 (s , 2H), 4.82 – 4.89 (m, 1H), 7.31 (d, 1H, *J* = 3.6 Hz), 7.37 (d, 1H, *J* = 3.6 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 7.62 (d, 2H, *J* = 8.4 Hz), 7.78 (s, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 19.5 (CH_2), 24.3 (CH_2), 27.9 (CH), 45.9 (CH_2), 53.0 (CH_2), 53.4 (CH_2), 56.8 (CH_2), 57.1 (CH),118.7 (CH), 124.1 (CH), 125.4 (CH), 126.0 (2 CH), 129.3 (2

CH), 131.9 (C_q), 134.1 (C_q), 136.9 (C_q), 143.1 (C_q), 143.4 (C_q) ; HRMS (EI-MS) : calcd. for $C_{20}H_{22}N_4SCl$ m/z = 385.1248, found m/z = 385.1249.

(R)-3-(4-(5-(4-((4-chloropiperidin-1-yl)methyl)phenyl)thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)quinuclidine hydrochloride 89. Compound **81** (1.0 mmol) was dissolved in CH_2Cl_2 at 0 °C. $SOCl_2$ reagent (2.0. eq.) was added dropwise and the reaction mixture was stirred for 12 hours at room temperature. The mixture was concentrated under reduced pressure and the crude solid was solubilized in Et_2O (10 mL) and filtered. The precipitate was washed with an additional amount of Et_2O (5 x 10 mL) and evaporated under reduced pressure to afford the pure derivative **89** as a white solid in a 80% yield. R_f : 0.3 (CH_2Cl_2/MeOH 97/3+ NH_4OH 10%) ; Mp : 206-208 °C ; IR (ATR, Diamond) ν (cm^{-1}) : 613, 801, 990, 1075, 1188, 1364, 1452, 1601-1727, 2868, 2952, 3397 ; ^{1}H NMR (400 MHz, CDCl3) : δ (ppm) 1.47-1.56 (m, 1H), 1.67-1.98 (m, 6H), 2.09-2.17 (m, 1H), 2.29-2.32 (m, 3H), 2.70-2.82 (m, 2H), 2.90-3.02 (m, 3H), 3.14-3.22 (m, 1H), 3.49-3.57 (m, 3H), 3.70-3.75 (m, 1H), 4.63-4.70 (m, 3H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.35-7.37 (m, 3H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.77 (s, 1H) ; ^{13}C NMR (100 MHz, DMSO-d_6) : δ (ppm) 20.0 (CH_2), 25.9 (CH_2), 28.1 (CH), 30.8 (2 CH_2), 35.5 (CH_2), 46.9 (CH_2), 47.3 (CH_2), 50.5 (CH_2), 52.6 (CH), 57.4 (CH_2), 58.5 (CH),62.5 (CH), 118.4 (CH), 123.4 (CH), 124.9 (2 CH), 125.6 (CH), 129.6 (2 CH), 129.8 (C_q), 132.0 (C_q), 132.9 (C_q), 137.8 (C_q), 142.7 (C_q), 143.7 (C),160.6 (C) ; HRMS (EI-MS): *m/z* calcd. for $C_{25}H_{31}N_5ClS$ $[M+H]^+$: 468.1983 , found: 468.1981.

Radiochemistry

No-carrier-added aqueous ^{18}F-fluoride ion was produced on a cyclotron (PET trace, GE Healthcare) by irradiation of enriched ^{18}O H_2O with protons via the $^{18}O(p,n)^{18}F$ nuclear reaction. ^{18}F-Fluoride was transferred to a modified TRACERlab FX-FN Pro (GE) synthesizer and passed through an anion-exchange resin (Waters Sep-Pak Accell Light QMA

cartridge in the carbonate form). Trapped ^{18}F-fluoride was isolated by elution with a solution of aqueous eluent solution containing K_2CO_3 (7.0 mg in 300 mL of pure water), acetonitrile (300 mL), and 22.0 mg of Kryptofix-222 (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). Azeotropic drying by addition of ACN (1 mL) was performed. The evaporation was performed at 90 °C under helium flow and vacuum, and the operation was repeated twice prior to nucleophilic substitution.

Description for [^{18}F]**29:** The corresponding nitro precursor **87** (1.7 mg) dissolved in DMSO (1.0 mL) was added to the reactor. The solution was heated to 150 °C for 10 min, then concentrated *via* evaporation of the solvent and reactor was cooled to 30 °C. A solution of tin chloride (28 mg) in MeOH (320 µL) was added followed by the addition of HCl, 5N (320 µL). The reaction was stirred for 15 min at 30 °C and then diluted with 7 mL of 0.5 N NaOH. The crude solution was passed through a Sep-pak Plus cartridge (Waters). The reactor and cartridge were rinsed with water (5 mL) and the crude compound was eluted from the cartridge with CAN (1.5 mL). The crude product was injected onto a Gemini C_{18} column (Phenomenex, 10 x 250 mm, 10 mm) and purification occurred at 4 mL/ min using NH_4OAc 0.1M (0.2% Et_3N)/ACN (62:38) as mobile phase. The radioactive peak corresponding to [^{18}F]**29** was collected and diluted with water (30 mL). The radioactive product was trapped on a *t*C_{18} cartridge (Waters Sep-Pak Accell Light tC_{18} cartridge). The cartridge was rinsed with water (5 mL) and [^{18}F]**33** was eluted from the *t*C_{18} with EtOH (0.5 mL). Formulation was completed by addition of 0.9% NaCl solution (4.5 mL).

Description for [^{18}F]**38**: Derivative **88** (2.0 mg) dissolved in DMSO (350 µL) was added to the reactor. The solution was heated to 115°C for 10 min, then cooled to 30 °C. A solution of HCl, 10N (160 µL) in acetone (160 µL) was added and the solution was stirred 10 min at 30 °C. Then the mixture was diluted with 0.2 N NaOH solution (6 mL)and the crude solution was passed through a Sep-pak Plus cartridge (Waters). The reactor and cartridge were rinsed

with water (5 mL) and the crude compound was eluted from the cartridge with DMSO (1.5 mL). The crude product was injected onto a Gemini C_{18} column (Phenomenex, 10 x 250 mm, 10 mm) and purification occurred at 4 mL/ min using NH_4OAc 0.1M (0.2% Et_3N)/ACN (45:55) as mobile phase. The radioactive peak corresponding to **[^{18}F]38** was collected and diluted with water (40 mL). The radioactive product was trapped on a *t*C_{18} cartridge (Waters Sep-Pak Accell Light tC_{18} cartridge). The cartridge was rinsed with water (5 mL) and [^{18}F]**38** was eluted from the *t*C_{18} with EtOH (0.5 mL).

Radiochemical and plasmatic stabilities of the radiotracers.

For quality control the stabilities of the radiotracers were checked by HPLC (Ultimate 3000, Thermo) equipped with a radiodetector (Pet metabolite, Bioscan) on a Gemini C_{18} column (Phenomenex 4.6x250 mm 5µ) up to four hours. For radiochemical purities 20 µl of the final solution obtained in the tracer lab FXFN pro were loaded onto the HPLC. For plasma stability, 100 µL of the radiotracer solution was mixed with 1 mL of rat plasma and incubated at 37°C. Five hundred µL of acetonitrile were added then the organic layer was taken out, filtered and 20 µL were loaded onto the HPLC. The stability was checked at 30 min, 1 hour, 2 hour and 4 hour, and experiments were repeated twice with different radiotracer preparations.

Biological evaluations

Experiments were performed on male Wistar rats weighing 250-300 g (Centre d'Elevage R. Janvier, Le Genest St Isle, France). All animal use procedures were conducted in accordance with the requirements of the European Community Council Directive 2010/63/EU for the care of laboratory animals and with the authorization of the Regional Ethical Committee. Rats were kept in a temperature (23 ± 0.5°C) and humidity (43 ± 8%) controlled environment under a 12 h light-dark cycle with food and water available *ad libitum*. All efforts were made

to minimize animal suffering and discomfort. Stable α-bungarotoxin and methyllycaconitine were 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).

In vitro binding assays

Affinity for α7 receptors

Animals were killed by decapitation on the day of the assay and both frontal cortices of each animal were removed on ice and weighed (2 rats were used for each experiment). The tissue was homogenized in 10 vol of a pH 7.4 HEPES 15 mM buffer containing 120 mM NaCl, 5.4 mM KCl, 0.8 mM $MgCl_2$ and 1.8 mM $CaCl_2$ using an Ultraturrax T25. After 45,000×*g* centrifugation at 4°C for 10 min (J2-21M/E, Beckman), the supernatant was eliminated and the pellet was suspended in 2 mL of the same buffer. The protein concentration was measured according to Bradford using bovine serum albumin as standard. For competition studies, [^{125}I]α-bungarotoxin (2 nM) was incubated in the presence or not of each tested compound (10^{-6} to 10^{-10} M) with 25 µg protein in a total volume of 1 mL in a pH 7.4 Tris-HCl buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$ and 2.5 mM $CaCl_2$) for 3 h at 22°C. Nonspecific binding was determined in the presence of 1 µM α-bungarotoxin. After incubation, samples were diluted in 3 mL of Tris-HCl buffer at 4°C and then rapidly filtered through Whatman GF/C fiber filters soaked with 0.05% polyethylenimine (Sigma, St Quentin-Fallavier, France). The filters were washed twice with 3 mL of 4°C buffer, and the residual radioactivity was measured in a γcounter (2480 Gamma counter Wizard, Perkin Elmer).The IC_{50} values were determined graphically for each compound and the Ki calculated.[38]

Affinity for α4β2 and 5-HT3 receptors

In vitro competition experiments were conducted by CEREP (Le Bois l'Eveque, 86600 Celle L'Evescault, France) according to their standard assay protocols (see http://www.cerep.fr/cerep/users/pages/catalog/search/catalog.asp, Ref 3029 and 0411).

Agonism properties

Materials

Reagents for cell culture including Minimum Essential Media (MEM), Ham's F12 Nutrient Mixture (F12), 5,000 units of penicillin (base) and 5,000 µg of streptomycin (base)/mL (PS) mixture, 0.05% Trypsin-EDTA (1X) phenol red, Fetal Bovine Serum certified (FBS), Fluo-3, AM Calcium Indicator, Pluronic® F-127 were purchased from Gibco-Invitrogen (ThermoFisher Scientific distributor, Illkirch, France). Sterile filtered dimethylsulfoxide Hybri-Max® (DMSO), all−*trans*−Retinoic acid (ATRA), Triton X-100 and all reagent-grade chemicals for buffers were purchased from Sigma (St Quentin Fallavier, France) or Merck France (Fontenay Sous Bois, France). Specific chemical products for α7R such as α-bungarotoxin, PNU 120596 were purchased from Tocris (Bio-Techne distributor, Lille, France). The CellTiter 96® AQueous One Solution Cell Proliferation Assay (MTS) was provided by Promega (Charbonnieres-les-bains, France).

SH-SY5Y culture

In this study, we used the human neuroblastoma cell line SH-SY5Y that expresses the nicotinic acetylcholine receptors (AChRs) including the α7R.[39, 40] The cell line SH-SY5Y obtained from American Tissue Type Collection (ATTC) were propagated in minimum essential medium (MEM) mixed with F12 (1:1, v/v), supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% penicillin/streptomycin (PS). The cells were cultured in 96-well plates (5,000 cells per well) and maintained in a humidified 5% CO_2 atmosphere at 37 °C. Cells were differentiated into neural cells by incubating with 10 µM retinoic acid (ATRA) for 7 days as previously described.[41, 42]

Cell treatment and calcium fluorimetry

To determine the agonist properties of the molecules to the α7R, increases in intracellular calcium (Ca^{2+}) in SH-SY5Y cells were monitored by measuring changes in fluorescence in cells loaded with fluo-3AM, as previously described.[27,28] In brief, cells cultured in 96-well plates were washed twice with Tyrode's salt solution (TSS, in mM: NaCl, 137.0; KCl, 2.7; $MgCl_2$, 1.0; $CaCl_2$ $2H_2O$, 2.5; NaH_2PO_4 H_2O, 0.2; $NaHCO_3$, 12.0; glucose, 5.5; pH 7.4). Then, cells were incubated with 10 µM fluo-3 AM and 0.02% Pluronic® F127 for 1 h at room temperature (r.t.) in the dark. Pluronic® F127, a nonionic surfactant polyol, was used to help disperse fluo-3 AM in the culture medium. Therefore, a mixture 1:1 (v/v) of fluo-3 AM and Pluronic® F127 was prepared in TSS solution (100 µL/well). After incubation and washing the cells twice with TSS, cells were pre-incubated during 20 min at r.t. with 80 µl TSS, with or without antagonist (100 nM α-bungarotoxin or its vehicle H_2O_{UHQ}). One minute prior to the end of pre-incubation, 10 µL of PNU 120596 as a positive allosteric modulator of α7R were added to the cells. Basal fluorescence (excitation λEx = 506 nm, emission λEm = 526 nm) was recorded in a Varioskan Flash spectral scanning multimode reader (ThermoFisher Scientific distributor, Illkirch, France). Then 10 µL of molecules at 10 Ki (compounds **26**, **29**, **38** and **78**) or their vehicles (DMSO at 1% for compound **29** and 0.1% for other compounds) were added and the change in fluorescence was recorded. Choline at 3 mM was used as a known agonist of α7R. Under all conditions examined, increases in fluorescence reached a maximum level within 10 s and this response was sustained over the remainder of the time course of the experiment. In order to normalize fluo-3 signals, the maximum and minimum fluorescence from each well was determined by addition of 0.3% Triton-X100 (Fmax) followed by 100 mM $MnCl_2$ (Fmin). Drug-evoked responses were expressed as a percentage of the corresponding (Fmax-Fmin) value. None of the drugs or vehicles used altered the basal level of fluorescence.

Cell viability

Following the results of the calcium release assay, we tested the toxicity of the molecules **29**, **38** and **78** by measuring cell viability. SH-SY5Y cells were cultured in the same conditions as those described above. The cells were incubated for 48 hours with each molecule at increasing concentrations equal to 10, 100 and 1000 times the Ki. A range of increasing concentrations of cells was added to the plate to define the number of live cells. Assays were performed by adding 20 µL of MTS directly to culture wells, incubating for 3 hours and then recording absorbance at 490 nm with the Varioskan Flash spectral scanning multimode reader (ThermoFisher Scientific distributor, Illkirch, France). The quantity of formazan product as measured by the amount of 490 nm absorbance was directly proportional to the number of living cells in culture. Results were expressed as the percentage of cells incubated in the respective vehicle.

In vivo brain biodistribution and imaging studies

Rats were injected i.v. under isofurane gas anesthesia in the penis vein with 0.3 mL of either **[^{18}F]29** (7.3 ± 0.44 MBq) or **[^{18}F]38** (6.5±0.46 MBq) in the control groups (n= 6/group). In the MLA groups (n=6), injection of the tracer was preceded (15 min) by i.v. injection of methyllycaconitine (MLA, 1 mg/kg). Rats were killed by decapitation at 1 h post injection of the tracer. The whole brain was quickly removed and dissected into segments consisting of the frontal cortex, hippocampus, hypothalamus, striatum, and cerebellum. Samples were weighed and radioactivity was measured in the same γ counter as above (counting efficiency of 48% for ^{18}F), and the percent injected dose per gram of tissue (%ID/g) was calculated by comparison with samples to standard dilutions of the injected solution.

For PET imaging studies, rats received an i.v. injection of 37 MBq of either **[^{18}F]29** or **[^{18}F]38.** Acquisitions were made on a microPET-CT SuperArgus system (Sedecal, Madrid, Spain) which has an effective axial/trans axial field of view (FOV) of 4.8/6.7 cm, a spatial

resolution less than 2 mm and a sensitivity above 2.5% in the whole FOV. Animals were anesthetized with isoflurane (Baxter, France), at 4-5% in O_2 for induction and then 1.5-2% during scanning. For imaging, each rat was placed on a thermo-regulated bed (Minerve, France) in the prone position with a nose cone. The brain was positioned on the center of the FOV. Before PET acquisition, a 5-minute computed tomography (CT) scan was acquired for attenuation correction. A bolus injection of 37 MBq of tracer was administered into the tail vein. During the 71 minutes of PET acquisition, the respiratory rate and body temperature were monitored and kept as constant as possible.

Supporting information

Supplementary data to this article can be found online.

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Abbreviations used

5-HT3: serotonin receptor of type 3

ACN: acetonitrile

α7R: alpha 7 nicotinic acetylcholine receptor

ATR: Attenuated Total Reflection

ATRA: retinoic acid

PET : positron emission tomography

CB: cerebellum

CT: computed tomography

Cx: cortex

DAST: diethylaminosulfur trifluoride

DMF : dimethylformamide

DMSO: dimethylsulfoxide

EI-MS: electrospray ionization – mass spectroscopy

EtOAc : Ethyl acetate

EtOH : ethanol

FOV: field of view

(Het)Ar: heteroaromatic

HPC: hippocampus

HPLC: high performance liquid chromatography

HPT: hypothalamus

IR: infrared spectroscopy

HRMS: high resolution mass spectroscopy

IS: Ion Spray

Ki: inhibitory constant

MEM: minimum essential medium

μL : microliter

μM : micromolar

mL: milliliter

μW: Microwave

mg: milligramme

MA : Molar Activity

MLA: methyllycaconitine

MOM: methyl methylether

Mp: melting point

nM: nanomolar

NMR: nuclear magnetic resonance

pM: picomolar

R_f: retention factor

Rflx: reflux

r.t.: room temperature

SAR: structure activity relationships

Satd : Saturated

Sat: satellite

STRI: striatum

TSS: Tyrode's salt solution

vs : versus

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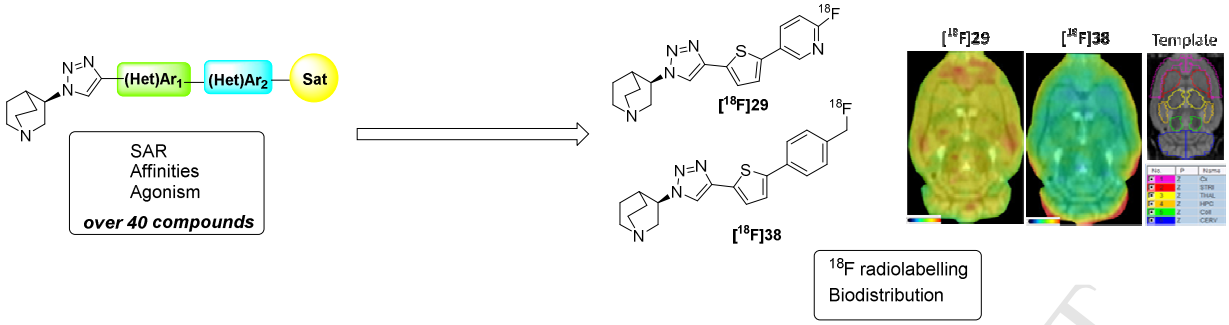
TABLE OF CONTENTS GRAPHIC



Highlights

47 new potent triazole/quinuclidinic alpha 7 nAChR ligand have been synthesized.
Identified leads exhibited a affinity in the subnanomolar range (10 cpds with 0.2<Ki<1 nM) .
Leads exhibit strict selectivity toward the α4β2 nicotinic and 5-HT3 receptors
Brain penetration and distribution was evaluated by preparing [^{18}F] radiolabelled derivatives
Rational design, synthesis, SAR are depicted