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# Synthesis of New Bridgehead Substituted Azabicyclo-[2.2.1]heptane and -[3.3.1]nonane Derivatives as Potent and Selective α7 Nicotinic Ligands

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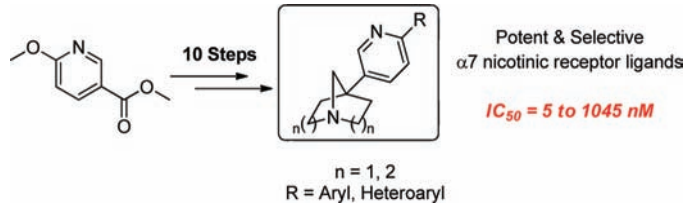
## ABSTRACT




**New azabicyclo[2.2.1]heptane and -[3.3.1]nonane derivatives containing a pyridinyl substituent at the bridgehead position have been synthesized via an efficient ten chemical steps pathway. Both chemical series were then evaluated in vitro for their affinity at α7 nicotinic receptors revealing nanomolar potency with notably excellent selectivity over the α4β2 nicotinic subtype.**

In the past decade, intense efforts from both pharmaceutical companies and academic groups have been engaged in identifying new potent and selective α7 nicotinic receptor ligands. Such compounds are expected to generate new promising treatments for cognitive dysfunction related pathologies (e.g., Schizophrenia, Alzheimer's disease).[1] A number of chemical families have been identified containing an azabicyclic moiety where the nitrogen atom is positioned at the bridgehead.[2] In most cases, these molecules possess aromatic or heteroaromatic substituents but not on the opposing bridgehead position of the azabicyclic moiety (Figure 1).

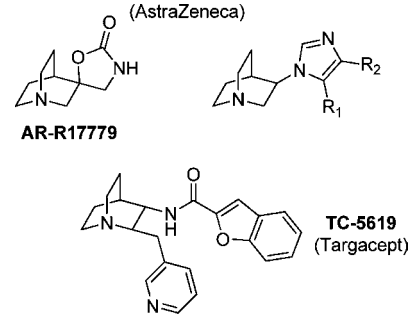



**Figure 1.** Examples of nitrogen-bridgehead azabicyclic α7 nicotinic ligands.

In the literature, few examples of azabicyclo[2.2.1]heptane derivatives of that kind, bearing an aromatic or a heteroaromatic group at the bridgehead position, are known.

Only oxadiazolyl (**B** and **C**), triazinyl (**D**), triazolyl (**E** and **F**), and tetrazolyl (**G**) groups have been described,[3] mostly

† Exploratory Unit.
‡ TSU Aging.

(1) (a) Martin, L. F.; Kem, W. R.; Freedman, R. *Psychopharmacology* **2004**, *174*, 54–64. (b) Olincy, A.; Stevens, K. E. *Biochem. Pharmacol.* **2007**, *74*, 1192–1201. (c) Dani, J. A. *Biol. Psychiatry* **2001**, *49*, 166–174. (d) Sharma, G.; Vijayaraghavan, S. *Curr. Med. Chem.* **2008**, *15*, 2921–2932.

(2) For an overview of α7 nicotinic receptor ligands possessing an azabicyclic moiety, see: (a) Romanelli, M. N.; Gratteri, P.; Guandalini, L.; Martini, E.; Bonaccini, C.; Gualtieri, F. *ChemMedChem* **2007**, *2*, 746–767. (b) Broad, L. M.; Sher, E.; Asties, P. C.; Zwart, R.; O'Neill, M. J. *Drug Future* **2007**, *32*, 161–170. (c) Mazurov, A.; Hauser, T.; Miller, C. H. *Curr. Med. Chem.* **2006**, *13*, 1657–1584.

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derived from the transformation of the ester group of the common intermediate **A** (except for **F**). Only one example of an azabicyclo[3.3.1]nonane substituted with a phenyl group at the bridgehead position (**H**) has been described with moderate yield (Figure 2).[4]

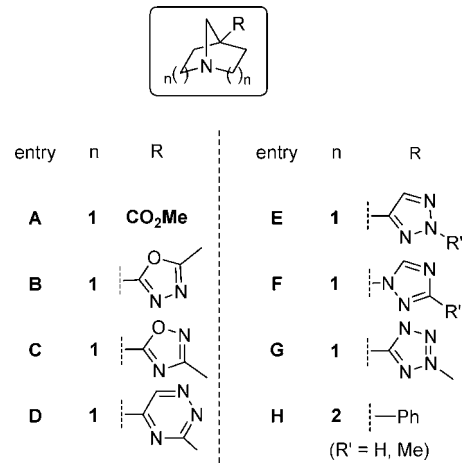



**Figure 2.** Reported bridgehead (hetero)aromatic-substituted [2.2.1]- and [3.3.1]-azabicyclic derivatives.

We wish here to report an efficient and concise synthesis of new azabicyclo[2.2.1]heptane and -[3.3.1]nonane derivatives bearing a 2-chloropyridin-5-yl substituent at the bridgehead position. These were subsequently functionalized with various substituents. To generate a library of compounds, we focused our efforts on the synthesis of both azabicyclic scaffolds **1** and **2** bearing a synthetically valuable 2-chloropyridin-5-yl group at the bridgehead position (Figure 3).

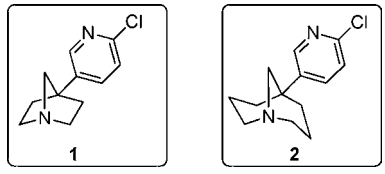
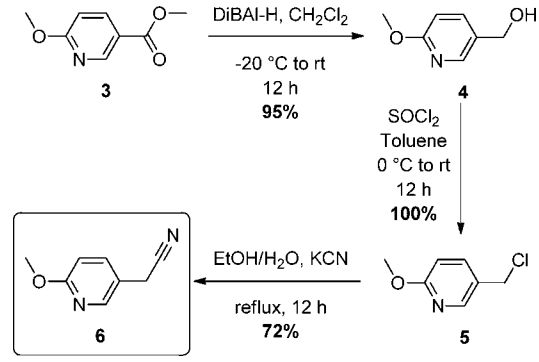



**Figure 3.** Targeted scaffolds.

Although compound **6** is commercially available, we chose to synthesize it for multigram accessibility and cost reasons. Diisobutylaluminium (DIBAL) reduction of commercially available 6-methoxynicotinic acid methyl ester **3** furnished the corresponding alcohol derivative **4** which was engaged in a chlorination step leading to the 5-chloromethyl-2-methoxy-pyridine **5**. Substitution reaction with potassium cyanide allowed access to the key synthon (6-methoxy-pyridin-3-yl)acetonitrile **6** with 68% overall yield from **3** on a multigram scale (Scheme 1).

**Scheme 1.** Synthesis of **6**




Generation of the 4-(6-chloropyridin-3-yl)-1-azabicyclo-[2.2.1]heptane scaffold **1** was then achieved in a six-step sequence described as follows: Double alkylation of **6** with ethyl bromoacetate led to compound **7** in 79% yield. Under hydrogenation conditions in the presence of Raney Nickel as a catalyst, reduction of the cyano group of **7** and concomitant intramolecular cyclization of the newly generated terminal amino group on one of the ester functions furnished the lactam **8** in 92% yield. Reduction of both lactam and ester moiety using lithium aluminum hydride (LAH) gave pyrrolidine **9** in 79% yield. Treatment of the latter with concentrated hydrobromic acid with heating led to the hydrolysis of the methoxy group of the pyridine and to the exchange of the terminal alcohol to bromide quantitatively (compound **10**). Cyclization of **10** to the target azabicyclic[2.2.1]heptane scaffold was achieved in 74% yield by treatment with potassium carbonate. Finally, action of $POCl_3$ under sealed tube conditions led to the desired key chlorinated scaffold **1** (Scheme 2).

Synthesis of scaffold **2** started with the double 1,4-addition of the above-described (6-methoxypyridin-3-yl)acetonitrile **6** on ethyl acrylate in the presence of Triton B following Uyeo's procedure[5] with Su's modifications.[6] This step afforded the compound **12** in quantitative yields. The following steps were then the same as described above for the preparation of scaffold **1** (Scheme 2).

A library of compounds were generated using scaffolds **1** and **2**. Representative examples **17a**−**g** and **18a**,**h** were synthesized via classical Suzuki−Miyaura coupling in mod-

(3) (a) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726–2735. (b) Jenkins, S. M.; Wadsworth, H. J.; Bromidge, S.; Orlek, B. S.; Wyman, P. A.; Riley, G. J.; Hawkins, J. *J. Med. Chem.* **1992**, *35*, 2392–2406. (c) Orlek, B. S.; Cassidy, F.; Clark, M. S. G.; Faulkner, R. E.; Collings, E. J.; Hawkins, J.; Riley, G. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1411–1414.

(4) Badger, G. M.; Cook, J. W.; Walker, T. *J. Chem. Soc.* **1949**, 1141–1144.

(5) Hazama, N.; Irie, H.; Mizutani, T.; Shingu, T.; Takada, M.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 2947–2953.

(6) Su, D.-S.; Lim, J. L.; Markowitz, M. K.; Wan, B.-L.; Murphy, K. L.; Reiss, D. R.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Pettibone, D. J.; Tang, C.; Prueksaritanont, T.; Freidinger, R. M.; Bock, M. G. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3006–3009.

**Scheme 2.** Synthesis of Scaffold **1** and **2**

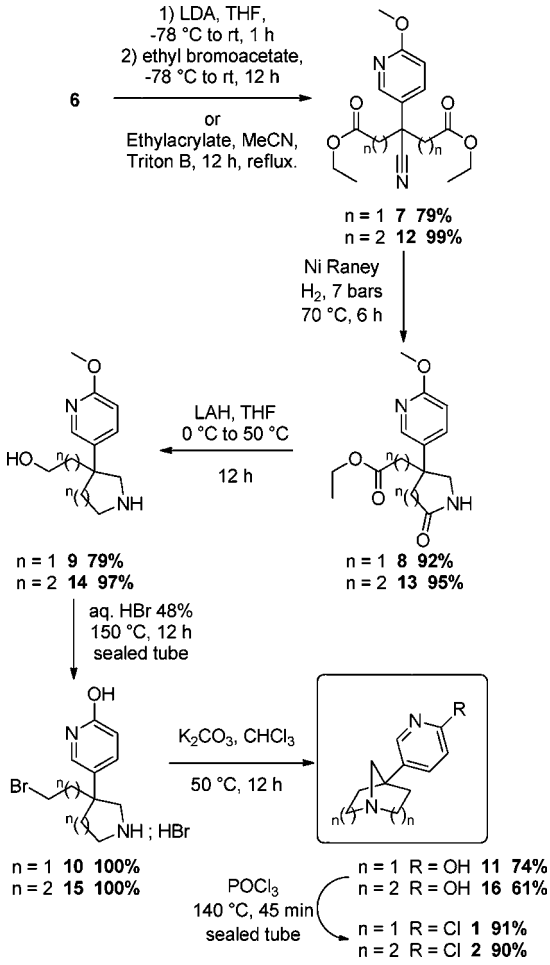
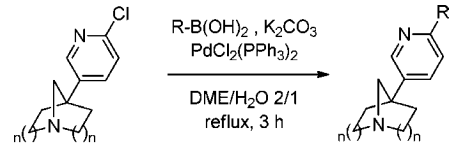
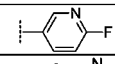
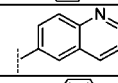
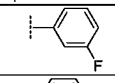
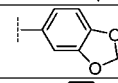
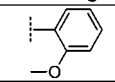
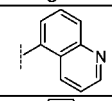
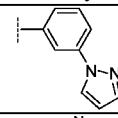
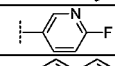
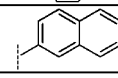



**Table 1.** Suzuki−Miyaura Coupling Reaction on **1** and **2**




n = 1 **1**
n = 2 **2**

n = 1 **17a-g**
n = 2 **18a, h**

| compound | R | yield (%) |
|---|---|---|
| **17a** |  | **54** |
| **17b**[a,c] |  | **61** |
| **17c**[b] |  | **68** |
| **17d** |  | **79** |
| **17e** |  | **55** |
| **17f** |  | **72** |
| **17g**[a] |  | **42** |
| **18a** |  | **37** |
| **18h** |  | **46** |

[a] Boronic acid pinacol ester was used instead of boronic acid. [b] Subsequent salification was performed providing **17c** as its hydrobromide salt. [c] Subsequent salification was performed providing **17b** as its hydrochloride salt.

erate to good yields. Compounds **17b** and **17e** were subsequently salified to hydrochloride and hydrobromide salt, respectively, to obtain satisfactory purity (Table 1).

In vitro evaluation of these compounds as α7 nicotinic receptor ligands was then performed on tissues from rat brain following Marks and Collins' protocol.[7]

All examples possessed potent α7 nicotinic receptor affinities with $IC_{50}$ values from 5 nM (**17g**) to 1.045 $\mu$M (**17f**). More precisely, six of nine examples (**17a**−**d**, **17g**, **18h**) exhibited activity with $IC_{50}$ below 50 nM. These primary activities are comparable or better than the in vitro activity of the **SSR180711**, an α7 nicotinic receptor partial agonist we previously developed (advanced clinical phases), used as our reference drug compound.[8] In terms of structure−activity relationship, an influence of the size of the azabicyclic moiety has been observed by comparing $IC_{50}$ of **17a** with its superior homologue **18a**. The latter appeared to be 10-fold less potent but still had affinity in the hundred-nanomolar range. This trend which should be confirmed with a wider range of analogues is the subject of a future study. The functional activity of examples from this publication is under study and will be published elsewhere.

Selectivity versus the α4$\beta$2 nicotinic receptor, the other major nicotinic receptor subtype present in the brain, was also evaluated following a protocol described by Anderson and Hall.[9] Of the five tested compounds, three (**17c**−**e**) were inactive as ligand on the α4$\beta$2 nicotinic receptor ($IC_{50}$ > 10 000 nM), whereas compounds **17b** and **17g** exhibited α4$\beta$2 nicotinic receptor affinity with $IC_{50}$ values, respectively, of 4150 and 1960 nM. In these cases, α7 selectivity versus the α4$\beta$2 subtype is more than 100-fold (Table 2).

In summary, we have developed an efficient and concise synthesis of two new chemical series of pyridinyl bridge-

(7) (a) Marks, M. J.; Collins, A. C. *Mol. Pharmacol.* **1982**, *22*, 554–564. (b) Marks, M. J.; Stitzel, J. A.; Romm, E.; Wehner, J. M.; Collins, A. C. *Mol. Pharmacol.* **1986**, *30*, 427–436.

(8) For more informations on the **SSR180711**, see: (a) Biton, B.; et al. *Neuropsychopharmacology* **2007**, *32*, 1–16. (b) Pichat, P.; et al. *Neuropsychopharmacology* **2007**, *32*, 17–34.

(9) (a) Anderson, D. J.; Arneric, S. P. *Eur. J. Pharmacol.* **1994**, *253*, 261–267. (b) Hall, M.; Zerbe, L.; Leonard, S.; Freedman, R. *Brain Res.* **1993**, *600*, 127–133.

**Table 2.** In Vitro Evaluation of Compounds **17a**−**g** and **18a**,**h** as α7 Nicotinic Receptor Ligands and Selectivity vs the α4β2 Subtype[a]

| compound | α7 receptor $IC_{50}$ (nM) ± SD | α4β2 receptor $IC_{50}$ (nM) |
|---|---|---|
| **SSR180711** | 30 ± 5 | >10 000 |
| **17a** | 23 | n.d. |
| **17b** | 37 | 4150 |
| **17c** | 14 | >10 000 |
| **17d** | 9 | >10 000 |
| **17e** | 596 ± 19 | >10 000 |
| **17f** | 1045 ± 146 | n.d. |
| **17g** | 5 ± 0.3 | 1960 |
| **18a** | 260 | n.d. |
| **18h** | 21 | n.d. |

[a] SD: Standard deviation. The results with no SD were only performed once but with **SSR180711** as the internal reference drug compound exhibiting reproducible values; n.d.: not determined; α7 ligands: in vitro evaluation was performed on OFA male rat brain tissues in the presence of [$^3$H]-α-bungarotoxine at 1 nM concn; α4β2 ligands, in vitro evaluation was performed on Sprague Dawley rat brain tissues in the presence of [$^3$H]-cytisine at 1 nM concn.

head substituted azabicyclo[2.2.1]heptane and -[3.3.1]nonane. We were therefore able to generate a library of compounds from scaffolds **1** and **2** by means of a Suzuki−Miyaura coupling reaction. These final compounds were then evaluated by in vitro biological tests and exhibited highly potent activity (nanomolar range) as α7 nicotinic ligands with an excellent selectivity versus the α4β2 nicotinic receptor. This synthesis opens an efficient general access to (hetero)aromatic bridgehead substituted azabicyclo-[2.2.1]heptane and -[3.3.1]nonane with the nitrogen atom at the opposing bridgehead position.

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**Supporting Information Available:** Experimental procedures and structural characterization data for all compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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