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# (+)-3-[2-(Benzo[*b*]thiophen-2-yl)-2-oxoethyl]-1-azabicyclo[2.2.2]-octane as potent agonists for the α7 nicotinic acetylcholine receptor

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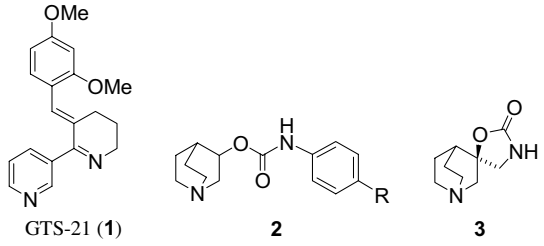
**Abstract**—A series of 3-substituted 1-azabicyclo[2.2.2]octanes was discovered as the α7 nicotinic acetylcholine (α7) receptor agonists. It was found that (+)-3-[2-(benzo[*b*]thiophen-2-yl)-2-oxoethyl]-1-azabicyclo[2.2.2]octane (+)-**15b** has potent agonistic activity for the α7 receptor.


Neuronal nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated cation channels, composed of various combinations of α and β subunits (α2-10, β2-4). Recent advances in molecular biology suggest that neuronal nicotinic receptors play important roles in cognition, schizophrenia, sensory gating, and anxiety.[1–5] Although the subtypes which mediate nicotine's CNS actions are largely unknown, the distribution and abundance of the α7 and the α4β2 subtypes in the CNS suggest these subtypes may be involved in at least some of these functions.[6] Therefore, α7 nicotinic acetylcholine receptor agonists are thought to be potential pharmacological targets.

In recent investigations of the α7 receptor, a number of compounds were reported as α7 receptor agonists (Fig. 1). One example is GTS-21 (**1**), which acts as a partial agonist at the α7 receptor.[7] It has been reported to be 'functionally' selective α7 receptor agonists; however GTS-21 possesses a higher affinity for the α4β2 receptor than for the α7 receptor, and it acts as an antagonist toward the α4β2 receptor.[8] On the other hand, by screening our library compounds, 1-azabicyclo[2.2.2]octane derivative **4** was identified to have moderate affinity for the α7 receptor. Furthermore, carbamate derivatives **2**[9] and **3**[10] were also reported as α7 receptor agonists. We hypothesized that the 1-azabicyclo[2.2.2]octane derivatives, bearing an aromatic part and a spacer group at the 3-position, may be involved in α7 receptor agonistic activity (Fig. 2).



GTS-21 (**1**) **2** **3**

**Figure 1.** α7 nicotinic acetylcholine receptor agonists.

In this paper, we describe a synthetic approach and the SAR of 3-substituted 1-azabicyclo[2.2.2]octane derivatives. We found that (+)-3-[2-(benzo[*b*]thiophen-2-yl)-2-oxoethyl]-1-azabicyclo[2.2.2]octane (+)-**15b** is a potent agonist for the α7 receptor.

The synthesis of 3-substituted 1-azabicyclo[2.2.2]octane derivatives is shown in Scheme 1.[11] Ester derivative **4**

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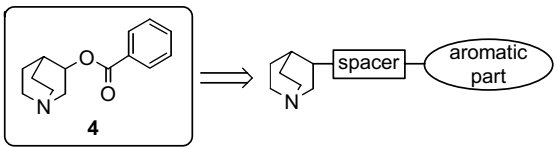


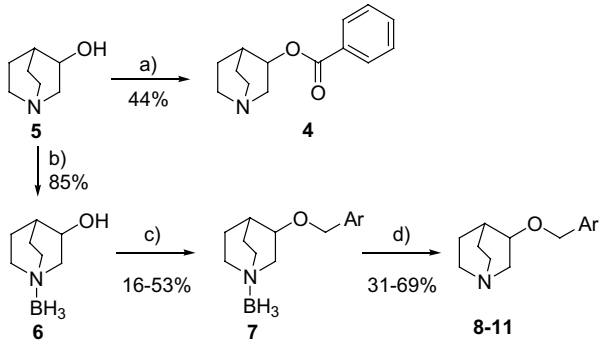

**Figure 2.** Synthetic strategy for the α7 nicotinic acetylcholine receptor agonist.

was synthesized by the coupling of 3-hydroxy-1-azabicyclo[2.2.2]octane **5** and benzoyl chloride in the presence of pyridine. Ether derivatives **8**–**11** were prepared by the reaction of 3-hydroxy-1-azabicyclo[2.2.2]octane-borane complex **6** with arylmethyl chloride using sodium hydride, and subsequent treatment with 3*N*-hydrochloric acid. The enantiomers of **11** were obtained in the same manner as chiral **5**.[12]

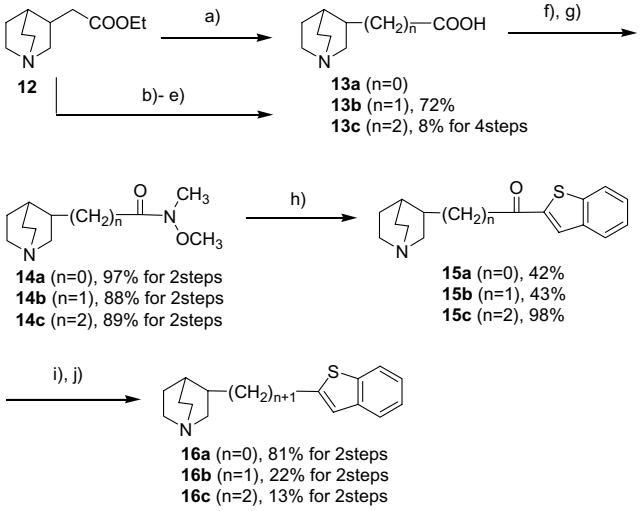
The synthesis of benzo[*b*]thiophene derivatives is shown in Scheme 2. Carboxylic acid derivatives **13a**,**b** were prepared by a previously reported method.[13,14] Compound **13c** was synthesized from ester **12** in 4 steps. Compounds **13a**–**c** were treated with $SOCl_2$ to give the corresponding acid chlorides. Subsequent treatment with *N*,*O*-dimethylhydroxylamine afforded Weinreb amides **14a**–**c**.

Ketone derivatives **15a**–**c** were synthesized from **14a**–**c** using 2-lithiobenzo[*b*]thiophene. **15a**–**c** were reduced with $NaBH_4$ to afford alcohol derivatives, followed by treatment with NaI/TMSCl to give compounds **16a**–**c**.[15] Resolution of **15b** was accomplished via the D- or L-malate salt.[16] Enantiomers of **16b** were obtained by the reduction of the enantiomers of **15b**.

Table 1 summarizes the binding affinity of 3-substituted 1-azabicyclo[2.2.2]octanes for α-Bungarotoxin binding inhibition.[17] The ester derivative **4** had moderate affinity. The ether derivative **8** had almost the same potency for the α7 receptor as ester derivative **4**. The introduction of an α or β-naphthyl moiety as the aromatic part dramatically enhanced the α7 receptor binding affinity (**9** and **10**). Moreover, the replacement of the naphthyl part with the benzo[*b*]thiophen-2-yl part, also known as a bioisostere of naphthyl part, increased the affinity for the α7 receptor. (*S*)-**11** showed a potent affinity almost 20-fold more than (*R*)-**11**.

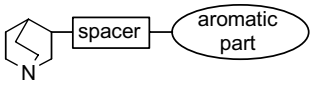



**Scheme 1.** (a) Benzoyl chloride, pyridine; (b) $BH_3$–THF; (c) NaH, arylmethyl chloride, DMF; (d) 3*N*-HCl, acetone.




**Scheme 2.** (a) *c*HCl, reflux; (b) $LiAlH_4$; (c) $SOCl_2$; (d) NaCN/DMSO; (e) *c*HCl, reflux; (f) $SOCl_2$; (g) $HNCH_3(OCH_3)$–HCl, $Et_3N$; (h) 2-Lithiobenzo[*b*]thiophene, −78 °C; (i) $NaBH_4$; (j) TMSCl, NaI/$CH_3CN$.

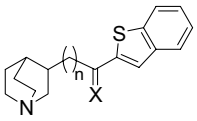
**Table 1.** Binding affinities of 1-azabicyclo[2.2.2]octane derivatives for the α7 nicotinic acetylcholine receptor




| Compound No. | Spacer | Aromatic part | α7 affinity ($IC_{50}$; μmol/L) |
|---|---|---|---|
| **4** | –OCO– | Ph | 2.6 |
| **8** | $-OCH_2-$ | Ph | 3.7 |
| **9** | $-OCH_2-$ | 2-Naphthyl | 0.15 |
| **10** | $-OCH_2-$ | 1-Naphthyl | 0.73 |
| **11** | $-OCH_2-$ |  | 0.059 |
| (*R*)-**11** | $-OCH_2-$ |  | 0.515 |
| (*S*)-**11** | $-OCH_2-$ |  | 0.026 |
| GTS-21 (**1**) | | | 0.76 |

The benzo[*b*]thiophene derivative (*S*)-**11** showed potent affinity for the α7 receptor; however, this compound showed poor bioavailability (data not shown). We estimated that this defect might be contributed to the arylmethyl ether part of compound **11**. Thus next, the conversion of the oxygen atom to a carbon atom was examined. To investigate the optimum length between the 1-azabicyclo[2.2.2]octane part and the aromatic part, the spacer length was changed from one carbon to three carbons, and the results are shown in Table 2. In this series, ethylene derivative **16b** was observed to have the most potent affinity. Corresponding ketone analogue **15b** reduced the affinity for the α7 receptor. Elongation (**15c**, **16c**) or reduction (**15a**, **16a**) of the spacer length resulted in the reduction in affinity for the α7 receptor. Alkylene analogues **16a**–**c** had a higher affinity than their corresponding ketone analogues **15a**–**c**.

**Table 2.** Binding affinities of benzo[*b*]thiophen-2-yl derivatives



| Compound No. | *n* | X | α7 affinity ($IC_{50}$; μmol/L) |
|---|---|---|---|
| **15a** | 0 | O | 0.95 |
| **16a** | 0 | $H_2$ | 0.11 |
| **15b** | 1 | O | 0.15 |
| **16b** | 1 | $H_2$ | 0.023 |
| **15c** | 2 | O | 1.7 |
| **16c** | 2 | $H_2$ | 0.37 |

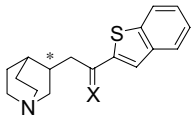
Next, we evaluated the pharmacokinetics on the compounds **15b**, **16a**, and **16b**, which have potent or modest affinity for the α7 receptor. Methylene analogue **16a** was not detected in the rat plasma (30 mg/kg, p.o.); however, two carbon analogues **15b** (Cmax; 270 ng/mL, 30 mg/kg, p.o.) and **16b** (Cmax; 450 ng/mL, 30 mg/kg, p.o.) showed modest PK profile.

The enantiomers of selected compounds (**15b** and **16b**) were synthesized and evaluated for the α7 binding affinities (Table 3). A comparison of the enantiomers of **15b** confirmed that (+)-**15b** was slightly preferred over (−)-**15b**. On the other hand, ethylene analogue (−)-**16b** was conversely 3-fold more potent than (+)-**16b**.

Finally, agonistic activities of these four compounds (each enantiomer of **15b** and **16b**) were evaluated by electrophysiological measurement of the α7 receptor mediated response using PC12 cells. The assay was assessed by the measurement of relative inward current towards 10 mmol/L choline in PC12 cells.[18] Figure 3 shows the agonistic activities of each enantiomer and GTS-21 (**1**). The results indicate that neither (−)-**15b** nor (−)-**16b** show agonistic activity. (+)-**16b** showed slight agonistic activity at 100 μmol/L, however this was abolished at 1000 μmol/L. (+)-**15b** showed dose-dependent agonistic activity, which was more potent than GTS-21 (**1**) at lower concentrations. Consequently, (+)-**15b** was the most potent agonist in this evaluation.

In summary, we have identified the potent α7 receptor agonists. We showed that in this series, (+)-3-[2-(benzo[*b*]thiophen-2-yl)-2-oxoethyl]-1-azabicyclo-[2.2.2]-octane (+)-**15b** has potent agonistic activity for the α7 receptor. (+)-**15b** would be a useful tool to investigate the pharmacophore of the α7 nicotinic acetylcholine receptor.

**Table 3.** Binding affinities of chiral benzo[*b*]thiophene-2-yl derivatives



| Compound No. | X | α7 affinity ($IC_{50}$; μmol/L) |
|---|---|---|
| (+)-**15b** | O | 0.13 |
| (−)-**15b** | O | 0.17 |
| (+)-**16b** | $H_2$ | 0.065 |
| (−)-**16b** | $H_2$ | 0.22 |

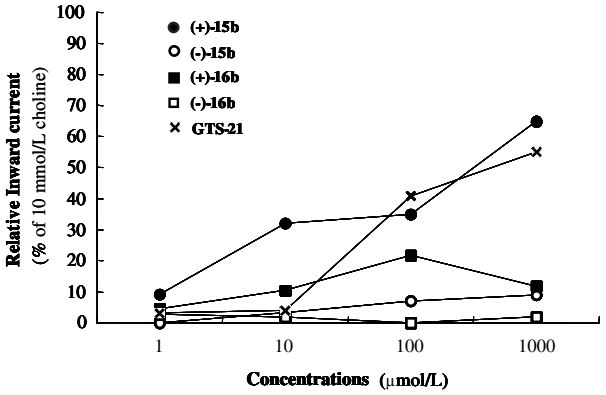



**Figure 3.** Agonistic activity of benzo[*b*]thiophene-2-yl derivatives for the α7 nicotinic receptor by electrophysiological measurements of the α7 nicotinic receptor-mediated inward current in PC12 cells.

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17. All data in the tables are the mean of two experiments.
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