Synthesis of Conformationally Restricted Analogs of ABT-418, Isoxazolo[5,4-*g*] indolizines and Isoxazolo[4,5-*a*]quinolizines for the Nicotinic Acetylcholine Receptor Ligands

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Received August 11, 1998

Alzheimers Disease (AD) is a neurodegenerative disorder that is the most common cause of dementia or mental deterioration among the elderly.[1] Recently, substantial reduction in nicotinic cholinergic receptors has been reported in the brains associated with cognition function of AD patients.[2] Accordingly, cholinergic channel activators may be therapeutically useful in ameliorating the cognitive decline.[3] Neuronal nicotinic acetylcholine receptors (nAChRs) are widely distributed throughout the central and peripheral nervous systems. (*S*)-Nicotine, the classical but nonselective nAChR agonist, has been shown to improve significantly the impairment in memory and cognition function.[4] However, nicotine is not suitable for therapeutical use due to its undesirable side-effects including abuse potential and actions on the cardiovascular and gastrointestinal system.[5] As a consequence, much efforts have been devoted to the synthesis of nicotine analogs to furnish a selective nAChR ligand which has the positive effect of nicotine without the compound's harmful side effects for the development of AD drug.[3,6]

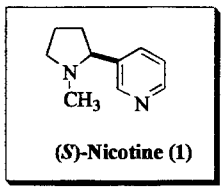
The use of conformationally restricted molecules as a means to better understand or improve the activity of the parent molecule is a common theme in medicinal chemistry.[7] Along these lines, conformationally restricted nicotine analogs, **2**,[8] **3**,[9] and **4**[10] have been synthesized and some of them showed interesting pharmacological properties. (±)-Pyrido[3,4-*b*]homotrophane (PHT, **3**) exhibited equal or surpassing bioactivity than than that of conformationally free parent nornicotine. SIB-1926 (**4**) possesses lower affinity than nicotine for $\alpha 4\beta 2$ nAChRs subtype, but showed greater efficacy than nicotine in striatal dopamine release and activation of $\beta 4$ nAChRs.

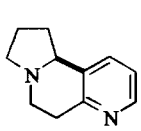
Recently, Garvey *et al.* have reported the synthesis of ABT-418 (**5**) in which a substituted isoxazole ring has been incorporated as a bioisosteric replacement for pyridine ring found in (*S*)-nicotine.[11] This compound was shown to be potent and selective neuronal nAChR ligand with cognition enhancing properties and is in Phase II trials for the symptomatic treatment of AD. While there have been many reports on the synthesis of pyrrolidine-modified analogs of **5**,[12] the synthesis of conformationally restricted analogs has been lacking.

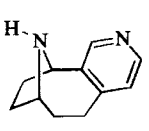
With this in mind, we wished to investigate whether the conformationally restricted analogs of **5** would interact with the nAChR binding site favorably or not. Our approach to examining these rigidifications was to tether isoxazole ring to pyrrolidine ring in **5** by inserting a methylene carbon as shown in Figure 2. Herein, we wish to report the synthesis and biological evaluation of racemic isoxazolo[5,4-*g*]indolizine **6** and isoxazolo[4,5-*a*]quinolizine **7** as conformationally restricted ABT-418 analogs for designing a selective nAChR ligand. In order to examine the effect of ring size on the interaction with nAChR, the synthesis of isoxazolo[4,5-*a*] quinolizine **7** was also included in this work.

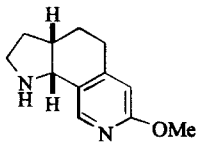
We envisioned that the target compounds can be readily prepared using isoxazole ring as a π-nucleophile through *N*-acyliminium ion strategy[14,15] The synthesis of racemic isoxazolo[5,4-*g*]indolizine **6** and isoxazolo[4,5-*a*]quinolizine **7** was accomplished as illustrated in Scheme 1. Mitsunobu coupling of succinimide **8** (*n*=1) or glutarimide **9** (*n*=2) with the isoxazolyl alcohol **10**[13] afforded *N*-alkylated imides **11** or **12**, respectively. Reduction of imide **11** or **12** with $NaBH_4$ in the presence of 1 M of H_2SO_4 in ethanol gave ethoxypyrrolidone **13** or **14**, respectively. Treatment of **13** or **14** with absolute formic acid produced the cyclized products **15** or **16** in 95% and 79% yields, respectively under the condition of reflux *via* *N*-acyliminium ion cyclization.[14] Compounds **15** or **16** were readily reduced either by BH_3·THF complex or $LiAlH_4$ to provide the final product **6** or **7** in good yields, respectively.

Compounds **6** and **7** were evaluated for their binding affinities to neuronal nAChRs by measuring the displacement of [^{3}H]cytisine, which has been shown to bind with



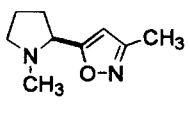

2


BHT (3)



SIB-1926 (4)

Figure 1


ABT-418 (5)

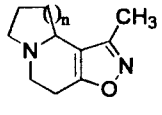
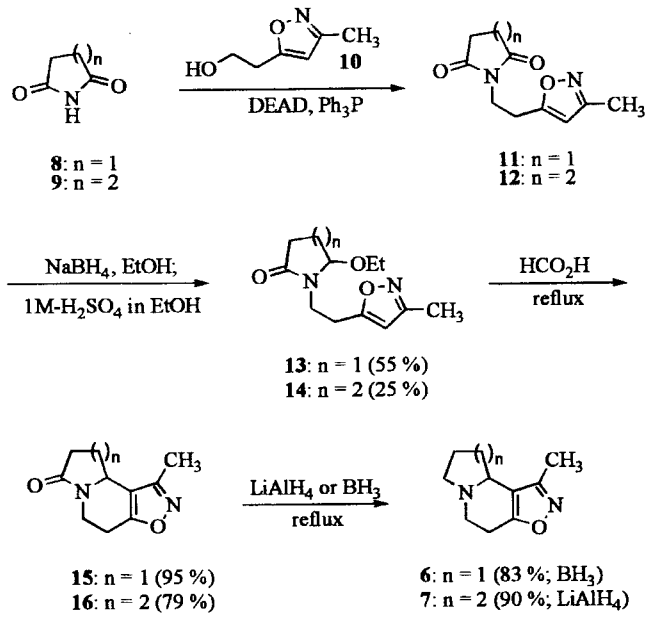

6, n=1
7, n=2

Figure 2



Scheme 1

high affinity to the $\alpha4\beta2$ nAChRs subtype, from a preparation of whole rat brain using (*S*)-nicotine as a reference.[16] Surprisingly, compounds **6** and **7** showed no noticeable binding affinities to neuronal nAChRs when tested up to 100 μM. The significant loss of binding affinity of these compounds compared to ABT-418 indicates that the bridging unit used to restrict the conformation of ABT-418 (**5**) may interact with the binding site of nAChR unfavorably, and in turn impart negative effect.

In summary, we have synthesized new isoxazolo[5,4-*g*] indolizine **6** and isoxazolo[4,5-*a*]quinolizine **7** as conformationally restricted ABT-418 analogs using *N*-acyliminium ion strategy. Further synthesis of other conformationally restricted analogs and their pharmacological evaluation will be required to design a beneficial AD drug.

Experimentals

^{1}H NMR spectra were recorded on a Gemini Varian-300 (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Gemini Varian-300 (75 MHz) spectrometer. Infrared (IR) spectra were recorded on Perkin Elmer 16F-PC FT-IR using a potassium bromide pellet. Low (EI) resolution mass spectra were determined on HP GC 5972 and HP MS 5988A system at 70 eV.

(±)-5-Ethoxy-1-[2-(3-methylisoxazol-5-yl)ethyl] pyrrolidin-2-one (13). A solution of succinimide **8** (2 g, 20 mmol), **10**[13] (2.8 g, 22 mmol) and triphenylphosphine (5.8 g, 22 mmol) in THF (50 mL) was cooled to 0 °C and treated with diethyl azodicarboxylate (3.9 g, 22 mmol) dropwise over a 5 min period. After stirring for 24 h at room temperature, the reaction mixture was concentrated, and subjected to short-column chromatography (EtOAc/hexane=1 : 1-2 : 1) to afford 1-[2-(3-methylisoxazol-5-yl)ethyl] pyrrolidine-2,5-dione (**11**) as a crude product, which was used for next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 5.94 (1H, s, isoxazole-H), 3.83 (2H, t, *J*=7.1 Hz, NCH_2), 3.04 (2H, t, *J*=7.1 Hz, CH_2-isoxazole), 2.71 (4H, s, 2x $NCOCH_2$), 2.25 (3H, s, isoxazole-CH_3): MS (EI), m/z (M^+) 208.

To a stirred solution of the above compound **11** in 50 mL of ethanol was added $NaBH_4$ (1.5 g, 39 mmol) in portionwise at 0 °C. The mixture was treated dropwise with an ethanolic 1 M-H_2SO_4 solution (33 mL) over 2 h. The mixture was warmed to room temperature and further stirred for 12 h. The reaction mixture was quenched by adding saturated $NaHCO_3$ solution at 0 °C. The resultant insoluble solid was filtered off through a pad of Celite 545 and the filtrate was concentrated to remove ethanol. The residue was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/hexane=2 : 1-EtOAc/MeOH= 10 : 1) to afford **13** (2.4 g, 55%; 2 steps): ^{1}H NMR ($CDCl_3$) δ 5.87 (1H, s, isoxazole-H), 4.77 (1H, dd, *J*=6.2, 1.5 Hz, NC*H*OEt), 3.62 (1H, m, NC*H*CH_2), 3.43 (1H, m, NC*H*CH_2), 3.40 (2H, q, *J*=7.0 Hz, OCH_2CH_3), 2.98 (2H, m, CH_2-isoxazole), 2.44 (1H, m, NCOC*H*), 2.24 (1H, m, NCOC*H*), 2.20 (3H, s, isoxazole-CH_3), 2.11 (1H, m, $NCOCH_2CH$), 1.94 (1H, m, $NCOCH_2CH$), 1.16 (3H, t, *J*=7.0 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 175.07, 170.10, 159.85, 102.48, 89.50, 61.86, 38.73, 28.78, 25.44, 24.95, 15.26, 11.39; MS (EI), m/z (M^+) 238.

(±)-6-Ethoxy-1-[2-(3-methylisoxazol-5-yl)ethyl] piperidin-2-one (14). Compound **12**, which was prepared from the coupling of glutarimide (**9**, 1.1 g, 9.9 mmol) with **10**, was reduced by treatment of $NaBH_4$ to afford **14** according to the procedure described above in 25% yield for two steps: **12**, ^{1}H NMR ($CDCl_3$) δ 5.90 (1H, s, isoxazole-*H*), 2.97 (2H, t, *J*=7.4 Hz, NCH_2), 2.65 (4H, t, *J*=6.6 Hz, 2x $NCOCH_2$), 2.59 (2H, t, *J*=7.4 Hz, CH_2-isoxazole), 2.25 (3H, s, isoxazole-CH_3), 1.95 (2H, t, *J*=6.6 Hz, CH_2); MS (EI), m/z (M^+) 222; 14, ^{1}H NMR ($CDCl_3$) δ 5.89 (1H, s, isoxazole-H), 4.43 (1H, m, NC*H*OEt), 3.85 (1H, m, NC*H*CH_2), 3.47 (2H, q, *J*=7.2 Hz, OCH_2CH_3), 3.46 (1H, m, NC*H*CH_2), 3.14 (1H, m, *CH*-isoxazole), 2.98 (1H, m, *CH*-isoxazole), 2.46 (1H, m, NCOC*H*), 2.28 (1H, m, NCOC*H*), 2.26 (3H, s, isoxazole-CH_3), 2.06 (2H, m, $NCOCH_2CH_2$), 1.65 (2H, m, $NCOCH_2CH_2CH_2$) 1.25 (3H, t, *J*=7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 170.36, 170.15, 159.49, 102.34, 87.24, 63.13, 44.45, 32.20, 26.80, 25.40, 15.67, 15.19, 11.17; IR (KBr) 1650 cm^{-1}; MS (EI), m/z (M^+) 252.

(±)-1-Methylisoxazolo[5,4-*g*]indolizidin-7-one (15). A solution of **13** (2.5 g, 10.4 mmol) in formic acid (5 mL) was heated at reflux for 5 h. The excess of formic acid was distilled off under reduced pressure and the residue was poured into a mixture of ethyl acetate and saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc only) to afford **15** (1.91 g, 95%): ^{1}H NMR ($CDCl_3$) δ 4.67 (1H, m, H_{9a}), 4.50 (1H, m, H_5), 2.95 (1H, m, H_5), 2.83-2.76 (2H, m, 2x H_4), 2.65-2.55 (2H, m, 2x H_8), 2.46 (1H, m, H_9), 2.29 (3H, s, CH_3), 1.80 (1H, m, H_9); ^{13}C NMR ($CDCl_3$) δ 172.92, 166.24, 155.88, 114.01, 52.31, 35.5, 31.34, 25.56, 22.90, 10.33; MS (EI), m/z (M^+) 192.

(±)-1-Methylisoxazolo[4,5-*a*]quinolizidin-7-one (16). Compound **16** was prepared from **14** (570 mg, 2.3 mmol) according to the procedure described above in 79% yield: ^{1}H NMR ($CDCl_3$) δ 5.15 (1H, m, H_{10a}), 4.53 (1H, m, H_5), 2.81 (1H, m, H_5), 2.77-2.71 (2H, m, 2x H_4), 2.70-2.58

(2H, m, 2x H_8), 2.36 (1H, m, H_{10}), 1.95 (1H, m, H_{10}), 1.83 (1H, m, H_9), 1.59 (1H, m, H_8); ^{13}C NMR ($CDCl_3$) δ 169.42, 166.71, 155.90, 113.80, 52.87, 38.65, 32.27, 28.50, 23.23, 19.13, 11.38; IR (KBr) 1636 cm^{-1}; MS (EI), m/z (M^+) 206.

(±)-1-Methylisoxazolo[5,4-*g*]indolizidine (6). To a solution of **15** (200 mg, 1.04 mmol) in THF (15 mL) was dropwise added a 1 M solution of BH_3·THF complex (3.6 mL, 3.6 mmol) at room temperature. The reaction mixture was heated at reflux for 20 h. After cooling to room temperature, the reaction mixture was treated with combined solution of acetic acid and water (2 mL, 1/1) followed by addition of saturated $NaHCO_3$. The mixture was extracted with ethyl acetate three times. The combined organic layer was dried ($MgSO_4$), concentrated, and dissolved in a mixture of aqueous 30% NaOH and methanol (2/5). The reaction mixture was heated at reflux for 3 h and poured into a mixture of ethyl acetate and water. The extracted organic layer was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/MeOH=10 : 1-5 : 1) to afford **6** (153 mg, 83%): ^1H NMR ($CDCl_3$) δ 3.69 (1H, dd, J=7.1, 6.9 Hz, H_{9a}), 3.30 (1H, m, H5), 2.91-2.82 (3H, m, 2x H_4, H_7), 2.78-2.62 (2H, m, H_5, H_7), 2.25 (1H, m, H_9), 2.24 (3H, s, CH_3), 2.22-1.83 (2H, m, 2x H_8), 1.68 (1H, m, H_9), ^1H-^1H COSY experiment also confirmed above signal assignment; ^{13}C NMR ($CDCl_3$) δ 166.58, 156.54, 114.15, 56.03, 49.76, 45.54, 28.84, 23.08, 20.84, 10.40; IR (KBr) 1456 cm^{-1}; MS (EI), m/z (M^+) 178.

(±)-1-Methylisoxazolo[4,5-*a*]quinolizidine (7). To a solution of **16** (300 mg, 1.5 mmol) in 10 mL of THF was added $LiAlH_4$ (228 mg, 6.0 mmol) at 0 °C and the reaction mixture was heated at reflux for 24 h. After cooling to 0 °C, the reaction mixture was treated with Na_2SO_4·10 H_2O (*ca.* 500 mg) and further stirred for 2 h at this temperature. The insoluble solid was filtered off through a pad of Celite 545 and the filtrate was dried ($MgSO_4$), concentrated, and purified by flash column chromatography (EtOAc/MeOH=20 : 1) to afford **7** (250 mg, 90%): ^1H NMR ($CDCl_3$) δ 3.03-2.92 (4H, m, 2x H_7, H_5, H_{10a}), 2.69-2.58 (2H, m, H_5, H_4), 2.46 (1H, m, H_4), 2.26 (3H, s, CH_3), 2.15 (1H, m, H_{10}), 1.85 (1H, m, H_{10}), 1.70-1.66 (2H, m, 2x H_8), 1.46-1.15 (2H, m, 2x H_9); ^{13}C NMR ($CDCl_3$) δ 166.38, 156.38, 114.25, 58.24, 55.19, 51.93, 29.65, 25.61, 24.16, 23.78, 11.69; IR (KBr) 1460 cm^{-1}; MS (EI), m/z (M^+) 192.

Acknowledgment. This work was supported from the Korea Ministry of Science and Technology (2E-14578). We are grateful to Dr. Changbae Jin at KIST for performing binding assay experiments.

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