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Synthesis of (±)-Methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines

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trans-Metanicotine, a subtype ($\alpha_4\beta_2$)-selective ligand for neuronal nicotinic acetylcholine receptor, is under clinical phase for Alzheimer's disease. An efficient synthetic route for (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines, derivatives of *trans*-metanicotine, was explored. Allylation reaction of aryl aldimines with allylmagnesium bromide in THF gave (±)-methyl-(1-aryl-but-3-enyl)-amines. Protection of the amines with the Boc group and following Heck reaction of the *N*-Boc amines with 3-bromopyridine gave (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-carbamic acid *tert*-butyl esters. Deprotection of the *N*-Boc group in aqueous 1N-HCl solution gave the titled amines in good yields. Thus, *trans*-metanicotine analogues modified at the α-position of the methylamino group with aryl groups were obtained in 5 steps.

Key words: Allylation, Imine, Heck reaction, Neuronal nicotinic acetylcholine receptor, *trans*-metanicotine

INTRODUCTION

Much of the recent increase in research on nicotinic ligands has been motivated by a growing body of evidence that nicotinic cholinergic pharmacology plays a role in disorder associated with deficits of cognitive function in humans (Arneric *et al.*, 1995; Karan, 1993; Levin, 1993; Whitehouse, 1993). The importance of developing novel nicotinic ligands as potential therapeutics is emphasized by studies with nicotine itself that have demonstrated many useful CNS and cognitive effects in various disorders such as dementia (Holladay *et al.*, 1997; Williams *et al.*, 1994). However, its side effects at peripheral sites such as neuromuscular and cardiovascular limits its usefulness as a therapeutic tool (Corrigal, 1993; Khosla *et al.*, 1994; Oates *et al.*, 1988). Recent advance in molecular biology enables us to understand that nicotinic receptor exists in multiple receptor subtypes (Galzi *et al.* 1995) and among them $\alpha_4\beta_2$ subtype mediates the cognitive effects. In this regard, we have been interested in synthesis of novel nicotinic ligands that have CNS selectivity, especially to $\alpha_4\beta_2$ subtype, and may offer the potential beneficial effects of nicotine without the accompanying undesirable peripheral side effects, particularly those at neuromuscular and cardiovascular sites. Toward this end, we select *trans*-metanicotine (Fig. 1) as a lead compound to optimize since it has a great selectivity to the subtype what we are targeted (Bencherif *et al.* 1996; Lippiello *et al.*, 1996) however, it was reported to have a moderate binding affinity (Bencherif *et al.* 1996; Lippiello *et al.*, 1996) and be metabolized *in vivo* experiment as we mentioned in the previous paper (Park *et al.* 2000).

In this paper, we wish to introduce an efficient synthetic route for novel *trans*-metanicotine analogues (Fig. 1). The analogues, which have a substituent at the α-position of the methylamino group in the side chain of *trans*-metanicotine to protect molecules from metabolic fate, are designed since *trans*-metanicotine expect to be biotransformed to several metabolites *in vivo* test as we previously mentioned. We expect that the substituents would play a role to prevent the molecules from metabolic reactions by inducing steric hindrance as well as modulate biological profiles by changing electronic environment. It is well established phenomena that metabolic

trans-metanicotine

Fig. 1. Structures of *trans*-Metanicotine and (±)-Methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines

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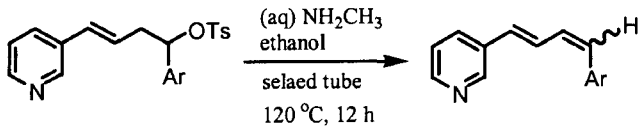
reactions of amines by momoamine oxidase is generally suppressed by introducing a substituent at the α-position of amino groups. In the previous paper, we established a concise synthetic pathway for *trans*-metanicotine analogues containing an alkyl substituent at the α-position of the amino group. The procedure, however, was not suitable for *trans*-metanicotine analogues containing an aryl substituent at the α-position of the amino group since the elimination reaction occurred instead of the substitution reaction to generate the conjugated diene compounds during the reaction between the tosylated intermediates and methylamine (Scheme 1).

RESULTS AND DISCUSSIONS

(±)-Methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines were synthesized as shown in Scheme 2. Reactions of aryl aldehydes and 40% aqueous methylamine produced aldimines **1a-e** (Boulos, J., Schulman, J., 1998) in moderate to good yields (74-94%). Allylation of aldimines **1a-e** with allylmagnesium bromide in anhydrous THF gave (±)-methyl-(1-phenyl-but-3-enyl)-amines **2a-e** in excellent yields (Yamamoto, Y., Asao, N., 1993). Protection of the amine moiety of (±)-methyl-(1-phenyl-but-3-enyl)-amines **2a-e** with Boc group gave (±)-methyl-(1-aryl-but-3-enyl)-carbamic acid *tert*-butyl esters **3a-e**. Palladium metal-catalyzed C-C coupling reaction of 3-bromopyridine and intermediates **3a-e** in Heck reaction conditions (Frank *et al.*, 1978) afforded crude (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-carbamic acid *tert*-butyl esters. After purification of products with silica gel short column, deprotection reactions of the compounds using aqueous 3N-HCl solution gave (±)-methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines **4a-e** in 5 steps. This synthetic route is suitable for synthesis of *trans*-metanicotine analogues modified at the α-position of the methylamino group with an aryl group which couldn't be generated by the previous synthetic route that we established (Park *et al.* 2000).



Scheme 1. Elimination reaction from tosylated intermediates and methylamine

MATERIALS AND METHODS

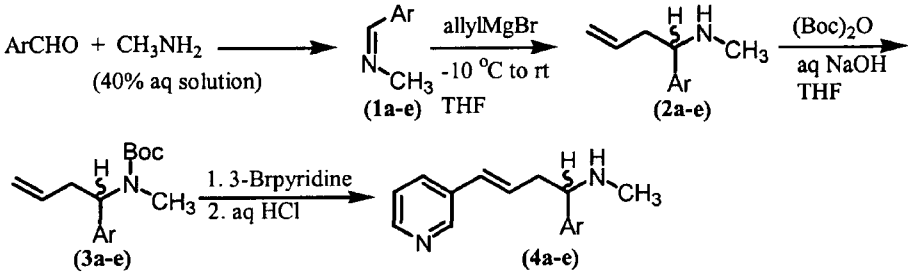
Materials

All starting materials were obtained from commercial suppliers, and used without further purification. All solvents used for reaction were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. ^{1}H-NMR spectra were recorded on a Varian Gemini 2000 instrument (200 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet) and dd (doublet of doublets). ^{13}C-NMR spectra were recorded on a Varian Gemini 2000 instrument (50 MHz) spectrometer, fully decoupled and chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane as an internal standard. Analytical thin-layer chromatography (TLC) was performed using commercial glass plate with silica gel 60F 254 purchased from Merck. Chromatographic purification was carried out by flash chromatography using Kieselgel 60 (230~400 mesh, Merck).

Synthetic procedures

Experimental conditions for the synthesis of aldimines (1a-e)

To a stirred solution of 40% methylamine in water (1.7 equiv) was added aldehydes (1 equiv) slowly in ice-bath. After 2 h, the reaction mixture was extracted with methylene chloride and washed with brine. Organic layer was separated and dried over KOH pellet. After removal of solid, evaporation of the filtrate under reduced pressure gave the titled compounds as pale yellowish syrup. The product was used to the next reaction without further



Scheme 2. Synthetic pathway for (±)-Methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines

purification.

Benzaldimine (1a)

94%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 3.52 (3H, s, N-CH_3), 7.40 (1H, s, aromatic ring H), 7.41, 7.43 (2H, d, *J*= 4Hz, aromatic ring H), 7.67-7.72 (2H, m, aromatic ring H), 8.30 (1H, s, aldehyde H).

***p*-Tolualdimine (1b)**

94%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.38 (3H, s, -CH_3), 3.50 (1H, s, N-CH_3), 7.24, 7.27 (2H, d, *J*= 6Hz, aromatic ring H), 7.58, 7.62 (2H, d, *J*= 8Hz, aromatic ring H), 8.26 (1H, s, aldehyde H).

Anisaldimine (1c)

89%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 3.48 (3H, s, N-CH_3), 3.84 (3H, s, OCH_3), 6.90, 6.95 (2H, d, *J*= 10Hz, aromatic ring H), 7.63, 7.67 (2H, d, *J*= 8Hz, aromatic ring H), 8.22 (1H, s, aldehyde H).

4-Chlorobenzaldimine (1d)

82%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 3.52 (3H, s, N-CH_3), 7.37, 7.41 (2H, d, *J*= 8Hz, aromatic ring H), 7.63, 7.67 (2H, d, *J*= 8Hz, aromatic ring H), 8.25 (1H, s, aldehyde H).

3,4-Dichlorobenzaldimine (1e)

74%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 3.52 (3H, s, N-CH_3), 7.50-7.52 (2H, m, aromatic ring H), 7.82 (1H, s, aromatic ring H), 8.20 (1H, s, aldehyde H).

Experimental condition for the synthesis of (±)-methyl-(1-aryl-but-3-enyl)-amines (2a-e)

To a stirred solution of aldimines (**1a-e**) in anhydrous THF was added allylmagnesium bromide (1.5 equiv) slowly at -10°C for 2 h. The reaction was continued for overnight at room temperature. The reaction mixture was cooled in ice-bath and was added saturated ammonium chloride solution. The reaction mixture was stirred for 30 min and was evaporated to remove THF. Extraction with methylene chloride and the organic layer was separated and dried over KOH pellet. After removal of solid, evaporation of the filtrate under reduced pressure gave the titled compounds as pale yellowish syrup. The crude product was purified by silica gel flash coulmn chromatography.

(±)-Methyl-(1-phenyl-but-3-enyl)-amine (2a)

93%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.17 (3H, s, N-CH_3), 2.45 (2H, t, *J*= 7.4Hz, -CH_2-), 3.53 (1H, t, *J*= 13.4 Hz, -CH-N), 5.04-5.13 (2H, m, =CH_2), 5.66-5.75 (1H, m, -CH=), 7.27-7.34 (5H, m, aromatic ring H).

(±)-Methyl-(1-p-tolyl-but-3-enyl)-amine (2b)

95%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.29 (3H, s, N-CH_3), 2.34 (3H, s, -CH_3), 2.49 (2H, t, *J*= 12.8Hz, -CH_2-), 3.56 (1H, t, *J*= 14.0Hz, -CH-N), 5.02-5.12 (2H, m, =CH_2), 5.60-5.80 (1H, m, -CH=), 7.13-7.26 (4H, m, aromatic ring H).

(±)-Methyl-[1-(4-methoxyphenyl)-but-3-enyl]-amine (2c)

90%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.27 (3H, s, N-CH_3), 2.42 (2H, t, *J*= 13.8Hz, -CH_2-), 3.50 (1H, t, *J*= 13.8 Hz, -CH-N), 3.81 (3H, s, OCH_3) 5.00-5.13 (2H, m, =CH_2), 5.64-5.73 (1H, m, -CH=), 6.86, 6.90(2H, d, *J*= 8.6Hz, aromatic ring), 7.21, 7.25 (2H, m, *J*= 8.6Hz, aromatic ring H).

(±)-Methyl-[1-(4-chlorophenyl)-but-3-enyl]-amine (2d)

91%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.26 (3H, s, N-CH_3), 2.37 (2H, t, *J*= 14.4Hz, -CH_2-), 3.52 (1H, t, *J*= 13.6 Hz, -CH-N), 5.04-5.12 (2H, m, =CH_2), 5.60-5.80 (1H, m, -CH=), 7.22-7.33 (4H, m, aromatic ring H).

(±)-Methyl-[1-(3,4-dichlorophenyl)-but-3-enyl]-amine (2e)

92%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.18 (3H, s, N-CH_3), 2.34 (2H, t, *J*= 15.6Hz, -CH_2-), 3.49 (1H, t, *J*= 13.2Hz, -CH-N), 5.05-5.12 (2H, m, =CH_2), 5.60-5.80 (1H, m, -CH=), 7.13, 7.14 (1H, d, *J*= 1.80Hz, aromatic ring H), 7.38, 7.42 (2H, d, *J*= 8.2Hz, aromatic ring H).

Experimental conditions for the synthesis of (±)-methyl-(1-aryl-but-3-enyl)-carbamic acid tert-butyl ester (3a-e)

To a stirred solution of di-*tert*-butyl dicarbonate (1M/THF) and (±)-methyl-(1-aryl-but-3-enyl)-amines (**2a-e**) was added 10% aqueous NaOH solution slowly at room temperature. After 3 h, the reaction mixture was extracted with ethyl acetate and washed with brine. Organic layer was separated and dried over anhydrous magnesium sulfate. After removal of solid, evaporation of the filtrate under reduced pressure gave the titled compounds as pale yellowish syrup in quantitative yields. The product was purified by silica gel short column.

(±)-Methyl-(1-phenyl-but-3-enyl)-carbamic acid *tert*-butyl ester (3a)

~100%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.42 (9H, s, Boc group), 2.38 (3H, s, N-CH_3), 2.68 (2H, t, *J*= 8.3Hz, -CH_2-), 3.71 (1H, t, -CH-N), 5.12 (2H, m, =CH_2), 5.84 (1H, m, -CH=), 7.22 (5H, m, aromatic ring H).

(±)-Methyl-(1-*o*-tolyl-but-3-enyl)-carbamic acid *tert*-butyl ester (3b)

~100%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.48 (9H, s, Boc group), 2.53 (3H, s, CH_3), 2.56 (3H, s, N-CH_3), 2.63 (2 H, t, *J*= 8.6Hz, -CH_2-), 3.75 (1H, t, -CH-N), 5.10 (2H, m, =CH_2), 5.80 (1H, m, -CH=), 7.16 (4H, m, aromatic ring H).

(±)-Methyl-[1-(4-methoxyphenyl)-but-3-enyl]-carbamic acid *tert*-butyl ester (3c)

98%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.39 (9H, s, Boc group), 2.54 (3H, s, N-CH_3), 2.58 (2H, t, *J*= 8.5Hz, -CH_2-), 3.80 (3H, s, OCH_3), 3.71 (1H, t, -CH-N), 5.15 (2H, m, =CH_2), 5.84 (1H, m, -CH=), 7.12 (4H, m, aromatic ring H).

(±)-Methyl-[1-(4-chlorophenyl)-but-3-enyl]-carbamic acid *tert*-butyl ester (3d)

95%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.47 (9H, s, Boc group), 2.56 (3H, s, N-CH_3), 2.66 (2H, t, -CH_2-), 3.76 (1H, t, -CH-N), 5.30 (2H, m, =CH_2), 5.80 (1H, m, -CH =), 7.26 (4H, m, aromatic ring H).

(±)-Methyl-[1-(3,4-dichlorophenyl)-but-3-enyl]-carbamic acid *tert*-butyl ester (3e)

95%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 1.45 (9H, s, Boc group), 2.58 (3H, s, N-CH_3), 2.65 (2H, t, -CH_2-), 3.75 (1H, t, -CH-N), 5.12 (2H, m, =CH_2), 5.80 (1H, m, -CH =), 7.11, 7.15 (1H, d, *J*= 6.8Hz, aromatic ring H), 7.37, 7.42 (2H, d, *J*= 12Hz, aromatic ring H).

Experimental condition for the synthesis of (±)-Methyl-(1-aryl-4-pyridin-3-yl-but-3-enyl)-amines (4a-e)

Reaction mixture of compounds **3a-e**, 3-bromopyridine (1.05 equiv), palladium acetate (0.015 equiv), tri(*o*-tolyl) phosphine (0.06 equiv), triethylamine and acetonitrile was heated to reflux for overnight. The reaction mixture was extracted with dichloromethane and washed with brine. Organic layer was separated and dried over anhydrous magnesium sulfate. After removal of solid, evaporation of the filtrate under reduced pressure gave crude products. The products were used to the next reaction without further purification.

The crude products was suspended in aqueous 3N-HCl solution. The solution was stirred at room temperature for overnight. The reaction mixture was alkalized by adding 10% aqueous NaOH solution, extracted with ethyl acetate and dried over anhydrous magnesium sulfate. After removal of drying agent, evaporation of the filtrate under reduced pressure gave crude products. The crude product was purified by silica gel flash coulmn chromatography.

(±)-Methyl-(1-phenyl-4-pyridin-3-yl-but-3-enyl)-amine (4a)

45%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.31 (3H, s, N-CH_3), 2.63 (2H, t, *J*= 13.2Hz, -CH_2-), 3.66 (1H, t, *J*= 13.4Hz, -CH-N), 6.10-6.25 (1H, m, -CH=), 6.37, 6.45 (1H, d, *J*= 15.8Hz, =CH-), 7.17-7.34 (6H, m, aromatic ring H, pyridine ring H), 7.59, 7.63 (1H, d, *J*= 7.6Hz, pyridine ring H), 8.42, 8.44 (1H, d, *J*= 4.6Hz, pyridine ring H), 8.53 (1H, s, pyridine ring H).

(±)-Methyl-(1-*o*-tolyl-4-pyridin-3-yl-but-3-enyl)-amine (4b)

52%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.30 (3H, s, N-CH_3), 2.62 (2H, t, *J*= 13.6Hz, -CH_2-), 3.63 (1H, t, *J*= 13.4 Hz, -CH-N), 6.10-6.25 (1H, m, -CH=), 6.38, 6.46 (1H, d, *J*= 16.2Hz, =CH-), 7.13-7.27 (6H, m, aromatic ring H, pyridine ring H), 7.60, 7.64 (1H, d, *J*= 8.0Hz, pyridine ring H), 8.41, 8.43 (1H, d, *J*= 6.0Hz, pyridine ring H), 8.52 (1H, s, pyridine ring H).

(±)-Methyl-[1-(4-methoxyphenyl)-4-pyridin-3-yl-but-3-enyl]-amine (4c)

55%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.35 (3H, s, N-CH_3), 2.66 (2H, t, *J*= 13.6Hz, -CH_2-), 3.79 (3H, s, OCH_3), 3.61 (1H, t, *J*= 13.4Hz, -CH-N), 6.12-6.28 (1H, m, -CH=), 6.41, 6.48 (1H, d, *J*= 16Hz, =CH-), 7.16-7.29 (6H, m, aromatic ring H, pyridine ring H), 7.62, 7.66 (1H, d, *J*= 7.9Hz, pyridine ring H), 8.44, 8.46 (1H, d, *J*= 5.9Hz, pyridine ring H), 8.57 (1H, s, pyridine ring H).

(±)-Methyl-[1-(4-chlorophenyl)-4-pyridin-3-yl-but-3-enyl]-amine (4d)

35%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.29 (3H, s, N-CH_3), 2.58 (2H, t, *J*= 13.8Hz, -CH_2-), 3.64 (1H, t, *J*= 13.8 Hz, -CH-N), 6.08-6.23 (1H, m, -CH=), 6.36, 6.44 (1H, d, *J*= 16.0Hz, =CH-), 7.19-7.36 (6H, m, aromatic ring H, pyridine ring H), 7.59, 7.63 (1H, d, *J*= 7.6Hz, pyridine ring H), 8.43, 8.45 (1H, d, *J*= 4.6Hz, pyridine ring H), 8.53 (1H, s, pyridine ring H).

(±)-Methyl-[1-(3,4-dichlorophenyl)-4-pyridin-3-yl-but-3-enyl]-amine (4e)

58%, ^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.29 (3H, s, N-CH_3), 2.56 (2H, t, *J*= 13.4Hz, -CH_2-), 3.62 (1H, t, *J*= 13.4Hz, -CH-N), 6.11-6.23 (1H, m, -CH=), 6.38, 6.46 (1H, d, *J*= 15.8Hz, =CH-), 7.16-7.28 (2H, m, aromatic ring H) 7.36-7.47 (2H, m, aromatic ring H, pyridine ring H), 7.61, 7.65 (1H, d, *J*= 7.8Hz, pyridine ring H), 8.44, 8.46 (1H, d, *J*= 3.4Hz, pyridine ring H), 8.54 (1H, s, pyridine ring H).

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REFERENCES

Arneric, S. P., Sullivan, J. P., and Williams, M., Neuronal acetylcholine receptors: novel targets for CNS therapeutics. In Psycopharmacology: fourth generation of progress. Bloom, F. E., Kupfer, D. J. (Eds), New York; Raven press, 94-110 (1995).

Bartus, R. T., Dean, R. L. I., Beer, B., and Lippa, A. S., The cholinergic hypothesis of geriatric memory dysfunction. *Science*, 217, 408-417 (1982).

Bencherif, M., Lovette, M. E., Fowler, K. W., Arrington, S. R., Reeves, L. K., Caldwell, W. S., and Lippello, P. M., RJR-2403: A nicotinic agonist with CNS selectivity I. *In vitro* characterization. *J. Pharmcol. Exp. Ther.*, 279, 1413-1421 (1996).

Boulos, J. and Schulman, J., Synthesis of Oxazolyl- and Furanyl-substituted Imidazole Hydrochlorides and Methiodides. *J. Heterocyclic Chem.*, 35, 859-863 (1998).

Corrigal, W., Nicotine addiction: considerations in the therapeutic use of nicotine. *Med. Chem. Res.*, 2, 603-611 (1993).

Frank, W. C., Kim, Y. C., and Heck, R. F., Palladium-catalyzed vinylic substitutionreactions with heterocyclic bromides. *J. Org. Chem.*, 43, 2947-2949 (1978).

Galzi, J. L. and Changeux, J. P., Neuronal nicotinic receptors; Molecular organization and regulations. *Neuropharmacology*, 34, 563-582 (1995).

Halloday, M. W., Dart, M. J., and Lynch, J. K., Neuronal nicotinic acetylcholine receptors as targets for drug discovery. *J. Med. Chem.*, 40, 4170-4194 (1997).

Karan, L. D., Nicotine as a potential therapeutic agent: an overview and clinical perspective. *Med. Chem. Res.*, 2, 514-521 (1993).

Khosla, S., Laddu, A., Ehrenpreis, S., and Somberg, J. C., Cardiovascular effects of nicotine: relation to deterious effects of cigarette smoking. *Am. Heart J.*, 127, 1669-1672 (1994).

Levin, E. D., Nicotine involvement in cognitive function: possible therapeutic applications. *Med. Chem. Res.*, 2, 612-627 (1993).

Lippello, P. M., Bencherif, M., Caldwell, Arrington, S. R., Fowler, K. W., Lovette, M. E., and Reeves, L. K., RJR-2403: A CNS-selective nicotinic agonist with therapeutic potential. In Alzheimer's disease: From molecular biology to therapy; Becker, R., Giacobini, E., Eds.; Birkhauser; Boston (1996).

Oates, J. A., Wood, A. J. J., Benowitz, N. L., Pharmacologic aspects of cigarette smoking and nicotine addiction. *N. Engl. J. Med.*, 319, 1318-1330 (1988).

Park, H., Jang, J., and Sin, K. S., A Concise Synthetic Pathway for *trans*-Metanicotine Analogues. *Arch. Pharm. Res.*, 23, 202-205 (2000).

Whitehouse, P. J., Cholinergic therpy in dementia. *Acta Neurol. Scand. Suppl.*, 149, 42-45 (1993).

Williams, M., Sullivan, J. P., and Arneric, S. P., Neuronal nicotinic acetylcholine receptors. *Drug News & Perspectives*, 7, 205-223 (1994).

Yamamoto, Y. and Asao, N., Selective Reactions Using Allylic Metals., *Chem. Rev.*, 93, 2207-2293 (1993).