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Novel bis-2,2,6,6-tetramethylpiperidine (bis-TMP) and bis-mecamylamine antagonists at neuronal nicotinic receptors mediating nicotine-evoked dopamine release

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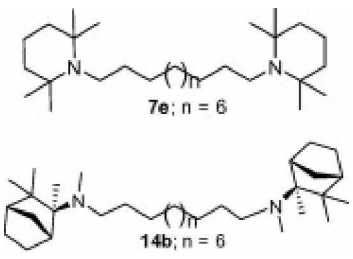
Abstract

By linking two or three mecamylamine or 2,2,6,6-tetramethylpiperidine (TMP) molecules together via a linear lipophilic bis-methylene linker or a specially designed conformationally restricted tris-linker, a series of bis- and tris-tertiary amine analogs has been synthesized and evaluated as potent antagonists at nAChRs mediating nicotine-evoked [^{3}H]dopamine release from rat striatal slices. Compounds **7e**, **14b** and **16** demonstrated high potency in decreasing nicotine-evoked [^{3}H]dopamine release (IC_{50} = 2.2, 46, and 107 nM, respectively). The preliminary structure–activity data obtained with these new analogs suggest the importance of the length of the methylene linker in the bis-analog series. Such bis-tertiary amino analogs may provide a new strategy for the design of drugable ligands that have high inhibitory potency against nAChRs mediating nicotine-evoked dopamine release in striatum, which have been suggested to be target receptors of interest in the development of potential smoking cessation therapies.

Graphical abstract

Compounds **7e** and **14b** demonstrated high potency in decreasing nicotine-evoked [^{3}H]dopamine release from rat striatal slices (IC_{50} = 2.2 and 46 nM, respectively). Such bis-tertiary amino analogs may provide a new strategy for the design of drugable ligands that have high inhibitory potency against nAChRs mediating nicotine-evoked dopamine release in striatum, which have been suggested to be target receptors of interest in the development of potential smoking cessation therapies.



Keywords: Nicotinic acetylcholine receptor; Quaternary ammonium; Dopamine release; Nicotine addiction

Article Outline

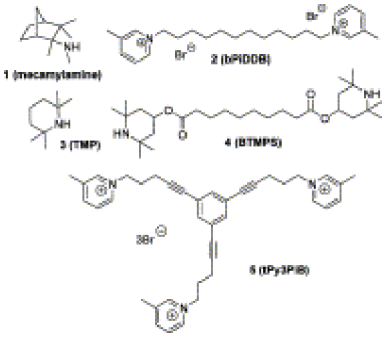


Figure 1.

Structures of mecamylamine (**1**), bPiDDB (**2**), TMP (**3**), BTMPS (**4**), and tPy3PiB (**5**).

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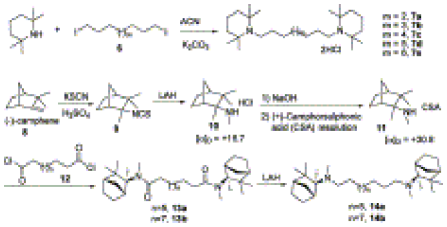

Scheme 1.

Synthesis of bis-TMP analogs **7a**–**7e**, and bis-*S*-(+)-mecamylamine analogs **14a** and **14b**.

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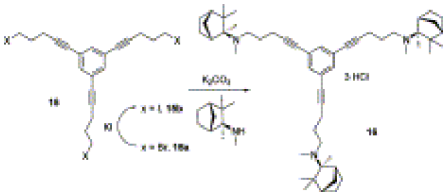

Scheme 2.

Synthesis of tris-mecamylamine analog **16**.

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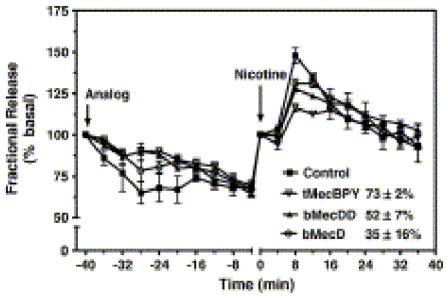

Figure 2.

S-(−)-Nicotine-evoked fractional [^{3}H]DA release from rat striatal slices superfused with 100 nM **14a** (bMecD), **14b** (bMecDD) and **16** (tMecBPY). Data are expressed as mean ± SEM fractional release as a percent of basal fractional release, that is, percent of samples prior to the addition of analog or nicotine. Control represents the amount of fractional release evoked by *S*-(−)-nicotine in the absence of analog; *n* = 3 rats/analog.

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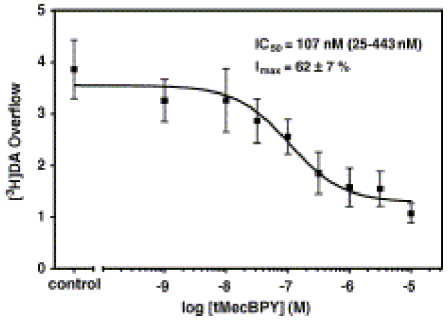

Figure 3.

Analog **16 (**tMecBPY) inhibited *S*-(−)-nicotine-evoked [^{3}H]DA overflow from rat striatal slices in a concentration-dependent manner. Control represents [^{3}H]DA overflow in response to 10 μM nicotine in the absence of analog and is expressed as a percent of tissue [^{3}H] content, mean ± S.E.M, *n* = 4 rats.

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Table 1. Inhibition of nicotine-evoked [^{3}H]DA release from superfused rat striatal slices[a]

[a] Percentage of inhibition at 100 nM are presented unless otherwise specified. Each value represents data from at least three independent experiments, each performed in duplicate.

[b] IC_{50} and I_{max} from full concentration response assays; data from 4 to 6 independent experiments.

[c] Not determined.

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