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bis-Pyridinium cyclophanes: Novel ligands with high affinity for the blood–brain barrier choline transporter

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ABSTRACT

A series of *bis*-pyridinium cyclophane analogs designed as conformationally restricted *bis*-quaternary ammonium compounds were evaluated for their affinity for the blood–brain barrier (BBB) choline transporter. All the cyclophanes investigated exhibited high affinity compared to choline. Of these compounds, *N*, *N*′-(1,10-decanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium diiodide (**5c**) and *N*,*N*′-(1,9-nonanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium dibromide (**5b**) exhibited highest affinity with K_i values of 0.8 μM and 1.4 μM, respectively, and constitute some of the most potent BBB choline transporter ligands reported.

The blood–brain barrier (BBB) is comprised of brain capillary endothelial cells connected by tight cell membrane junctions that circumferentially surround the cell margin, and thus, form a continuous cell membrane, which is essentially impermeable to hydrophilic compounds.[1,2] In this respect, the BBB restricts over 98% of all potential neurotherapeutic molecules from entering the central nervous system (CNS).[1] Thus, the ability to design compounds which readily penetrate the BBB would be beneficial in pharmacotherapies for many neurological disorders.[2,3] Despite this general brain bioavailability issue, it is surprising that research efforts focused on solving this problem are lacking. A potential solution is the utilization of endogenous transporter proteins located at the BBB, the function of which is to shuttle polar nutrients and other endogenous molecules into the CNS from the periphery.[1,3] Such active transport brain vector mechanisms for drug delivery may offer new treatment strategies for neurological pathologies and diseases.[3] This approach has been successfully employed in early studies on the active transport of polar molecules such as 2-amino-3-(3,4-dihydroxyphenyl)2-methylpropanoic acid (α-methyl DOPA) and the chemotherapeutic agent (±)-2-amino-7-*bis*-[(2-chloroethyl)amino]1,2,3,4-tetrahydro-2-naphthoic acid (D,L-NAM), into the CNS from the periphery via the large neutral amino-acid transporter.[4,5]

The choline transporter at the BBB has been suggested as a brain drug delivery vector for quaternary ammonium compounds targeting the CNS.[2,3] The BBB choline transporter efficiently delivers the highly polar and positively charged choline molecule from the periphery to the CNS. Choline is a precursor of the neurotransmitter acetylcholine and other essential constituents of cell membranes, such as phosphatidylcholine and sphingomyelin.[1] The carrier-mediated transport of choline has been demonstrated in vivo and in vitro to primarily account for total brain uptake of choline.[2a,3] The BBB choline transporter has an anionic binding area that accommodates positively charged quaternary ammonium moieties as well as simple cations, such as tetramethylammonium ion.[3] Thus, the BBB choline transporter could be a portal for the delivery of pharmacologically relevant concentrations of positively charged compounds, which normally exhibit restricted permeation by passive diffusion across the BBB. In this respect, the BBB choline transporter has been shown to be responsible for the intracellular transport of the quaternary ammonium ellipticines that are cytotoxic to isolated human brain tumor cells,[6] and a nitrogen mustard alkylating agent in lymphoblasts.[7]

In our continuing effort to develop potent and selective antagonists of nicotinic acetylcholine receptors (nAChRs) as smoking cessation agents,[8,9] we have identified a number of quaternary ammonium compounds, such as *N*-*n*-octylnicotinium iodide (NONI, Fig. 1)[10], *N*,*N*′-(1,12-dodecandiyl)-*bis*-pyridinium dibromide (bPiDDB),[11a–d] and 1,3,5-tri-{5-[1-(3-picolinium)]-pent-1-yn-1-yl}benzene tribromide (tPy3PiB) as potential clinical candidates.[12] Given the high polarity and hydrophilicity of such quaternary ammonium compounds, the potential of NONI, bPiDDB and tPy3-PiB to penetrate the BBB by passive diffusion is low. However,

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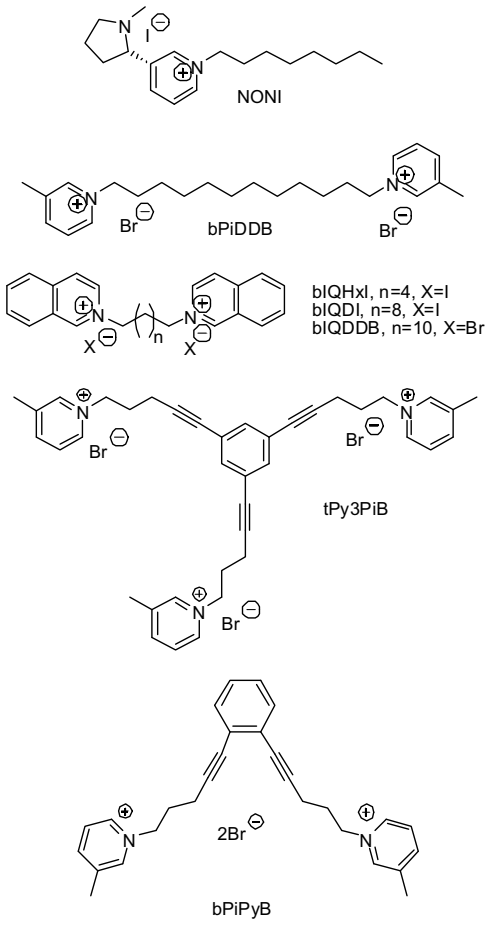

Figure 1. Structure of some *mono*-, *bis*- and *tris*-quaternary ammonium compounds which act as potent nAChR antagonists.

NONI, bPiDDB and tPy3PiB all have good affinity for the BBB choline transporter with K_i values of 49 μM, 36 μM and 60 μM, respectively; these values are comparable to that of choline ($K_m \approx 45$ μM). It is important to note that NONI and bPiDDB have both been shown to enter the brain through active transport via the BBB choline transporter.[11b,13] This current study evaluates the affinity of some novel, conformationally restricted *bis*-quaternary ammonium cyclophane analogs for the BBB choline transporter as drug delivery vectors for incorporating into the molecular design of quaternary ammonium drug candidates that target therapeutically relevant sites in the CNS.

Apart from bPiDDB, our initial studies have also identified a series of additional *bis*-quaternary ammonium analogs with good affinity for the BBB choline transporter.[14] Structurally, these analogs are composed of two quaternary ammonium head groups linked through an *n*-alkyl linker of different carbon chain lengths. Due to the flexibility of the linker, these *bis*-quaternary ammonium analogs can adopt a large number of conformations. Based upon COMFA modeling, a specific conformation of these *bis*-quaternary ammonium analogs was suggested to be favorable for binding to the BBB choline transporter.[13] In this current study, we have synthesized a series of novel conformationally restricted *bis*-quaternary ammonium analogs and have determined their affinity for the BBB choline transporter. The information obtained from this study may have utility in the design of a new generation of pharmacologically active *bis*-quaternary ammonium molecules possessing good brain bioavailability.

The *bis*-pyridinium cyclophane compounds designed for this study were synthesized as illustrated in Figure 2. The dipyridino compound **3** is novel, and was prepared through Sonagashira coupling of 3-bromopyridine (**1**) with 1,9-decadiyne (**2**) in pyrrolidine in the presence of *bis*-(triphenylphosphine)palladium(II) chloride and cuprous iodide as catalyst. The conversion of **3** to the desired *bis*-pyridinium cyclophanes **5a–5d** was carried out in acetonitrile at reflux. After initial quaternization of the dipyridine intermediate **3** at one of the pyridine *N*-atoms, the second quaternization can occur via either intramolecular quaternization (cyclization), or via intermolecular quaternization with another molecule of **3**. We found that the desired cyclization product **5** was best obtained utilizing the appropriate diiodo precursor **4** under high dilution conditions (<5 mM), which suppressed the formation of by-products arising from intermolecular reactions. However, under these high dilution conditions, the reaction was extremely slow, and even after 7 days, the reaction did not reach completion. As expected, the reaction rate was even slower when the dibromides **4b** ($n = 7$) and **4d** ($n = 9$) were utilized to prepare **5b** and **5d**. The presence of polymeric by-products is also problematic in the purification of the cyclophane products, and necessitates costly and time-consuming reverse-phase preparative HPLC purification. It was also observed that the shorter the length of the dihaloalkane **4**, the more difficult was the intramolecular cyclization reaction. The general procedure for the preparation of compounds **5a**–**5d** are provided below.[15] Compounds **5a–5d** were obtained in good purity and were all fully characterized by ^{1}H and ^{13}C NMR, and mass spectroscopic analysis.

The affinity of the above *bis*-pyridinium compounds for the BBB choline transporter was determined by evaluation of their ability to inhibit [^{3}H]-choline uptake into brain. These assays were conducted using the in situ rat brain perfusion method, as modified by Allen and Smith.[16] Inhibition coefficients (K_i, concentration of analog inhibiting 50% of [^{3}H]-choline uptake into brain) were determined using a single inhibitor concentration, as previously described.[13] K_i values were compared by ANOVA followed by Bonferroni's multiple comparisons test to determine inhibition of [^{3}H]-choline uptake.

Our previous studies have shown that the BBB choline transporter distributes the *mono*-quaternary ammonium compound NONI into the CNS.[11] NONI has previously been shown to inhibit nicotine-evoked dopamine release in rat striatal slices,[10,17] which suggested the potential for these compounds as a treatment for smoking cession and other CNS disorders. We have recently shown that more polar, di-cationic *bis*-quaternary ammonium compounds can also serve as potent ligands for dopamine-releasing neuronal nicotinic receptors.[8,9] For example, bPiDDB potently and selec-

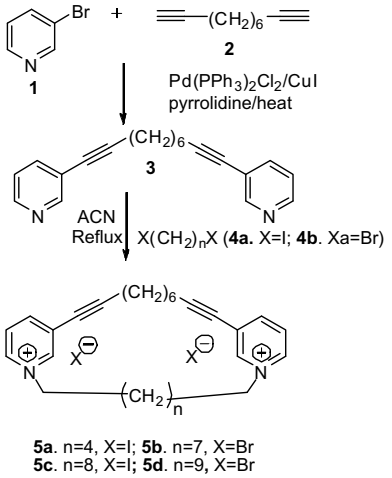

Figure 2. Synthesis of *bis*-pyridinium cyclophane compounds **5a–5d**.

tively inhibits nAChRs mediating nicotine-evoked [^{3}H]dopamine release[11a] and decreases nicotine self-administration.[11f] Moreover, bPiDDB has been shown to utilize the BBB choline transporter for ~90% of its permeation into brain.[11b] This current study was initiated to further explore this drug-transporter interaction, in order to better understand how the BBB choline transporter can serve as a vector for the delivery of other CNS-active *bis*-quaternary ammonium compounds.

In the absence of a crystal structure of the BBB choline transporter, the design of potential ligands utilizing QSAR studies with existing structural leads is a valuable method for exploring the SAR of these ligands, and for understanding the topological features of the transporter binding site. Thus, *bis*-pyridinium cyclophanes (**5a–5d**) were designed as novel *bis*-quaternary ammonium analogs with restricted conformation. All these cyclophane analogs were evaluated for their ability to interact with the BBB choline transporter and to inhibit [^{3}H]-choline uptake into rat brain. The results are summarized in Table 1.

Overall, all the *bis*-pyridinium cyclophanes synthesized (**5a–5d**) exhibited excellent affinity for the BBB choline transporter. These results suggest that, compared to *mono*-quaternary ammonium ligands such as NONI, *bis*-quaternary ammonium compounds have higher affinities for the choline transporter. This is consistent with other studies on non-cyclic *bis*-azaaromatic ammonium compounds, which also exhibit high affinities for the BBB choline transporter.[14] Compared with choline, all the *bis*-pyridinium cyclophanes in this study and *bis*-quaternary ammonium compounds from previous studies demonstrated higher or comparable affinities for the BBB choline transporter, although they lack the terminal hydroxyl group present in the choline molecule. These results may indicate that the gain in affinity for the BBB choline transporter upon addition of a second quaternary ammonium moiety is enough to compensate for the loss in affinity which results from the removal of the hydroxyl group in the choline molecule.

Moreover, this study also provides insights about the preferred conformation of *bis*-quaternary ammonium compounds for their interaction with the BBB choline transporter binding site. For an open chain *bis*-quaternary ammonium compound, it is reasonable to speculate that after one of the cationic moieties of the *bis*-quaternary ammonium ligand is anchored to the choline binding site, the second cationic moiety may then bind to another adjacent anionic binding site on the transporter, which is different from the choline binding site. Because the linker moieties in these *bis*-quaternary ammonium compounds are highly flexible, these ligands can adopt a large number of conformations when interacting with the transporter binding site. For example, in two possible extreme cases, the ligand may bind in a fully extended conformation, where the two cationic moieties are furthest apart, or in a conformation where the cationic groups are close to each other. The *bis*-pyridinium cyclophanes **5** are designed as conformationally restrained versions of non-cyclic *bis*-quaternary compounds such as bPiDDB. There are two alkyl linkers connecting the two pyridine moieties in these molecules, the linker attached to the C-3 positions of the two pyridine rings is kept constant in all the cyclophanes structures (**5a–5d**), while the second linker attached to the nitrogen atoms of the two pyridine rings are varied in length in order to mimic the different alkyl chain lengths in the non-cyclic *bis*-quaternary ammonium analogs. These structural changes restrict the conformational flexibility of the molecule and constrains the molecules into 'folded' conformations with variable distances between the two quaternary ammonium centers.

The presence of a linker unit containing two acetylene moieties conjugated with the pyridine ring was designed to further restrict molecular flexibility. Thus, the increased affinity of the *bis*-pyridinium cyclophanes **5a–5d** compared to the affinities of the corresponding non-cyclic analogs may be attributed to the conformational features in these molecules that are favored for interaction with BBB choline transporter binding site.

In this respect, the length of the linker unit connecting the quaternary ammonium centers may also play an important role in the interaction of these compounds with the BBB choline transporter binding site. As shown in Table 1, both **5b** and **5c**, which are tethered with 9 and 10-carbon linkers, respectively, at the pyridinium *N*-atom, exhibited the highest affinity ever reported for a BBB choline transporter ligand, while compounds with longer *N–N* linker units (i.e., **5d**) or shorter *N–N* linker units (i.e., **5a**) both exhibit decreased affinity. Interestingly in our previous study, the non-cyclic *bis*-analog, bIQDI, where two isoquinolinium moieties are tethered with a 10-carbon *N–N* linker, also exhibits high affinity for the BBB choline transporter compared to analogs that incorporate shorter and longer *N–N* carbon linkers into their structures (i.e., bIQHxI and bIQDDB, respectively). These results suggest that the optimum distance between the two quaternary ammonium nitrogen atoms for binding to the BBB choline transporter reflects a substrate conformation that corresponds with a 'folded' conformation of the non-cyclic *bis*-quaternary ammonium molecule The presence of two different linkers in the cyclophane analogs may also enhance the interaction of these molecules with the BBB choline transporter. All these observation suggest that the *bis*-quaternary ammonium cyclophanes can serve as a novel template in identifying potent ligands with high affinity for the BBB choline transporter. Importantly, we have recently reported that the *bis*-azaaromatic quaternary ammonium compound bPiPyB (Fig. 1), which represents a conformationally restricted, 'folded' analog of the bPiDDB molecule, has affinity for α4β2 nAChRs[19] and inhibits α4/6β4 subunit combinations of nAChRs generated from a *Xenopus* oocyte expression system.[20] Thus, the design of *bis*-quaternary ammonium nAChR antagonist molecules with conformational properties that allow facilitated transport into the CNS may be feasible.

In conclusion, a novel group of *bis*-pyridinium cyclophanes incorporating one fixed, relatively rigid linker and a second more conformationally flexible linker of varying carbon chain length has been synthesized and evaluated for affinity for the BBB choline transporter. Excellent affinity for the BBB choline transporter has been observed in these cyclophane molecules. To the best of our knowledge, **5c** and **5b** exhibit the highest affinity for the BBB choline transporter ever reported for compounds of this structural class. These results suggest that *bis*-quaternary ammonium cyclophanes may serve as a novel template for the discovery of potent, highly polar, cationic CNS agents with high affinity for the BBB choline transporter. This information also indicates that a rational incorporation of a specific structural moiety into highly hydrophilic, cationic CNS agents can confer high BBB choline transporter affinity on the molecule, affording more potential for the drug to access the CNS and achieve therapeutically relevant brain concentrations.

Table 1
Affinity of choline, NONI, *bis*-pyridinium compounds, and cyclophanes **5a–5d** for the BBB choline transporter

Compound	K_i (μM)
5a	15.2
5b	1.4
5c	0.8
5d	33.8
bIQHxI[14]	29
bIQDI[14]	9.5
3bIQDDB[14]	22
NONI[13]	49
bPiDDB[14]	36
Choline[18]	41

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15. General procedure for the preparation of *bis*-pyridinium cyclophanes: the key intermediate, 3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridine (**3**), was prepared by mixing 1,9-decandiyne (**2**) (2.8 g, 20.9 mmol) and 3-bromopyridine (**1**) (50 mmol) in pyrrolidine followed by the addition of $Pd(PPh_3)_2Cl_2$ (50 mg) and CuI (50 mg). The mixture was heated to 60–70 °C for 2 h. The solvent was removed in vacuum and the residue was subjected to silica gel chromatography. 3-Bromopyridine was eluted from the column with hexane and ethyl acetate (10:1); the product **3** was eluted subsequently from the column with hexane and ethyl acetate (2:1) and the solvent evaporated to afford an oil (5.1 g, 85%). ^{1}H NMR δ ppm 8.59 (d, J = 1.5 Hz, 2H), 8.43 (dd, J = 1.8 Hz, J = 5.1 Hz, 2H), 7.62 (dt, J = 1.8 Hz, J = 7.8 Hz, 2H), 7.15 (ddd, J = 0.9 Hz, J = 4.8 Hz, J = 7.8 Hz, 2H), 2.40 (t, J = 6.9 Hz, 4H), 1.59–1.63 (m, 4 H), 1.46–1.49 (m, 4H). Compound **3** and a molar equivalent of an appropriate dihaloalkane **4** were mixed in acetonitrile to afford a concentration of approximately 1 mM. The mixture was refluxed for 7 days. The solvent was removed in vacuo after cooling, and the resulting residue was taken up in water (20 mL) and diethyl ether (50 mL). The aqueous layer was extracted extensively with diethyl ether (5× 50 mL) to remove the starting materials. Removal of most of the water from the aqueous layer afforded a residue which was dissolved in methanol (10 mL). Evaporation of methanol/water under vacuum followed by drying of the resulting residue under high vacuum afforded the *bis*-pyridinium cyclophane as a solid glass.
N,*N*′-(1,6-hexanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium diiodide (**5a**). ^{1}H NMR (300 MHz, D_2O) δ ppm 8.76 (s, 2H), 8.56 (d, J = 6.0 Hz, 2H), 8.29 (d, J = 8.4 Hz, 2H), 7.81 (dd, J = 6.3 Hz, 8.1 Hz, 2H), 4.40 (t, J = 7.5 Hz, 4H), 2.39 (t, J = 6.3 Hz, 4H), 1.85–1.84 (m, 4H), 1.49–1.52 (m, 4H), 1.38–1.42 (m, 4H), 1.18–1.22 (m, 4H). MALDI-TOFMS. m/z 499 (M–I) (Calcd for $C_{26}H_{32}IN_2$+, 499.45).
N,*N*′-(1,9-Nonanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium dibromide (**5b**). ^{1}H NMR (300 MHz, D_2O), δ ppm 10.39 (s, 2H), 9.52 (d, J = 5.7 Hz, 2H), 8.18 (d, J = 7.5 Hz, 2H), 8.00 (m, 2H), 5.06 (t, J = 7.2 Hz, 4H), 2.49 (t, J = 6.3 Hz, 4H), 2.08–2.18 (br, 4H), 1.60–1.80 (br, 12H), 1.42–1.56 (br, 8H), 1.37–1.40 (br, 2H). MALDI-TOFMS. m/z 493, 495, (M–Br), (Calcd for $C_{29}H_{38}BrN_2^+$, 493.22, 495.22).
N,*N*′-(1,10-decanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium diiodide (**5c**). ^{1}H NMR (300 MHz, D_2O), δ ppm 10.11 (s, 2H), 9.37 (d, J = 6.3 Hz, 2H), 8.22 (dt, J = 7.8 Hz, J = 1.2 Hz, 2H), 8.03 (dd, J = 6.3 Hz, J = 7.8 Hz, 2H), 4.99 (t, J = 8.1 Hz, 4H), 2.49 (t, J = 6.6 Hz, 4H), 2.15–2.17 (m, 4H), 1.38–1.75 (m, 24H). MALDI-TOFMS. 555 m/z (M–I), (Calcd for $C_{30}H_{40}IN_2^+$, 555.22).
N,*N*′-(1,11-Undecanediyl)3,3′-(1,9-decadiyn-1,10-diyl)-*bis*-pyridinium dibromide (**5d**). ^{1}H NMR (300 MHz, D_2O), δ ppm 9.92 (s, 2H), 9.48 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 8.1 Hz, 2H), 8.05 (m, 2H), 5.08 (br, 4H), 2.49 (t, J = 6.3 Hz, 4H), 2.05–2.15 (br, 4H), 1.70–1.82 (br, 12H), 1.55–1.65 (br, 4H), 1.45–1.55 (br, 4H), 1.30–1.45 (m,8H). MALDI-TOFMS. m/z 521, 523 (M–Br), (Calcd for $C_{31}H_{42}BrN_2^+$, 521.25, 523.25).
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