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Dual-Site Binding of Bivalent 4-Aminopyridine- and 4-Aminoquinoline-Based AChE Inhibitors: Contribution of the Hydrophobic Alkylene Tether to Monomer and Dimer Affinities

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Abstract—Three series of 4-aminopyridine-and 4-aminoquinoline based symmetrical bivalent acetylcholinesterase (AChE) inhibitors were prepared and compared to previously synthesized dimers of 9-amino-1,2,3,4-tetrahydroacridine (tacrine). In each case significant, tether length-dependent increases in AChE inhibition potency and selectivity (up to 3000-fold) were observed relative to the corresponding monomer, indicating dual-site binding of these inhibitors to AChE. Assay of the corresponding alkylated *monomers* revealed that the alkylene tether played at least two complementary roles in the dimer series. In addition to reducing the entropy loss that occurs on binding both monomeric units of the dimer, the alkylene tether can also significantly improve potency through hydrophobic effects.

Introduction

One important strategy to improve drug potency and selectivity depends upon the use of bivalent ligands and the existence of neighboring recognition sites on the target of interest. Bivalent ligands which demonstrate dual-site binding include dimeric opioid ligands,[1] dimeric tetrapeptide enkephalins,[2] bis-indolecarboxamide 5-HT_{1D} receptor ligands,[3] dequalinium analogue small conductance Ca^{2+}-activated K^+ channel blockers,[4] heterodimeric FKBP ligands,[5] and *bis*-quaternary ammonium acetylcholinesterase (AChE) inhibitors such as decamethonium[6] and BW284c51[7] (Fig. 1). It is generally assumed that the primary role of the tether in a bivalent drug is to reduce the entropy loss that would occur upon binding two independent monomeric units. This reduction in entropy loss can provide remarkable affinity enhancement.[8,9]

Recently, the bivalent ligand strategy was applied to the development of blood-brain barrier penetrable AChE-targeted therapeutic agents. Dimerization of 9-amino-1,2,3,4-tetrahydroacridine (tacrine, **1**) to tacrine dimers **3f–i** resulted in dramatic increases in AChE inhibition potency and AChE/butyrylcholinesterase (BChE) selectivity (Fig. 2).[10] The synthesis and evaluation of these dimers was predicated on computational studies which indicated weak affinity of **1** to the AChE peripheral site (Trp^{279}, Tyr^{70}, Phe^{290}) located near the mouth of the active site gorge.[11] Subsequent preparation and evaluation of short-tether homologues **3a–e** confirmed that heptamethylene-linked tacrine dimer **3f** possessed optimum AChE inhibition potency and selectivity (Table 1, entry 7). Inhibition potency decreased dramatically for tethers less than 5 methylene units (**3d**, Table 1, entry 5), thus confirming the role of dual-site binding in enhancing the potency of bivalent ligands **3d–i**.[12]

Given the general importance of bivalent ligands in drug design, we considered that additional investigations on the scope and characteristics of dual-site binding in AChE were justified. The wealth of available AChE structural information[13–15] makes this enzyme an ideal candidate for further study. Therefore, three additional homologous series of dimeric inhibitors were prepared and assayed, each of which was based on monomers bearing a close structural resemblance to **1**. The aim of these studies was to address the following

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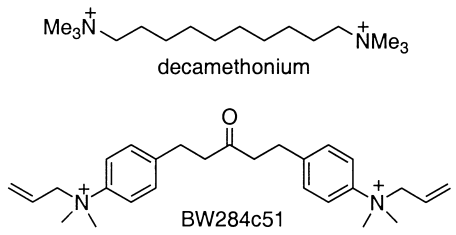


Figure 1. *bis*-Quaternary AChE inhibitors.

questions. Will compounds structurally related to **1** also show dramatic increases in AChE potency and selectivity upon dimerization? How will changes in monomer structure affect the potency of the corresponding dimers? How does the tether contribute to binding affinity? It is expected that the information gained from these studies will prove relevant to the design of bivalent ligands for other biological targets.

Bivalent Inhibitor Design and Synthesis

In designing new bivalent AChE inhibitors we focused on dimers of 4-aminoquinaldine **4**, 4-aminoquinoline **7**, and 4-aminopyridine **10**, thus retaining the core 4-aminopyridine unit of **1** (Fig. 2). Our reasoning for this selection is twofold. Firstly, analysis of the **1**–*Torpedo* AChE X-ray crystal structure reveals that the central 4-aminopyridine ring of **1** is stacked against Trp^{84} and Phe^{330} in putative cation–pi interactions, and that the two nitrogens of this ring are involved in hydrogen-bonding interactions.[14] Secondly, recent studies have shown that chemical modifications which reduce the basicity of **1** generally reduce AChE inhibition potency.[16,17] The high basicity of **1** (pK_a of conjugate acid: 9.8)[17] indicates >99% conversion to the protonated form at physiological pH; the resultant charge thus likely improves mimicry of acetylcholine. 4-Aminoquinaldine dimers **6i**,**k** and 4-aminoquinoline dimers **9i**,**k** have been evaluated previously for K^+ channel blocker activity.[18] 4-Aminopyridine dimers **12** have also been evaluated as antimicrobial agents (**12i**)[19] and as polyamine modulators of NMDA receptor function (**12b**–**c**).[20] However, to the best of our knowledge, none of these classes of dimers have been investigated as AChE inhibitors.

Dimers **6f**–**i** and **9e**–**i**,**k** were prepared as the bis-hydrochloride salts in good to excellent yields (81–97%) by refluxing the corresponding diamine with 4-chloroquinaldine **13** or 4-chloroquinoline **14**, respectively

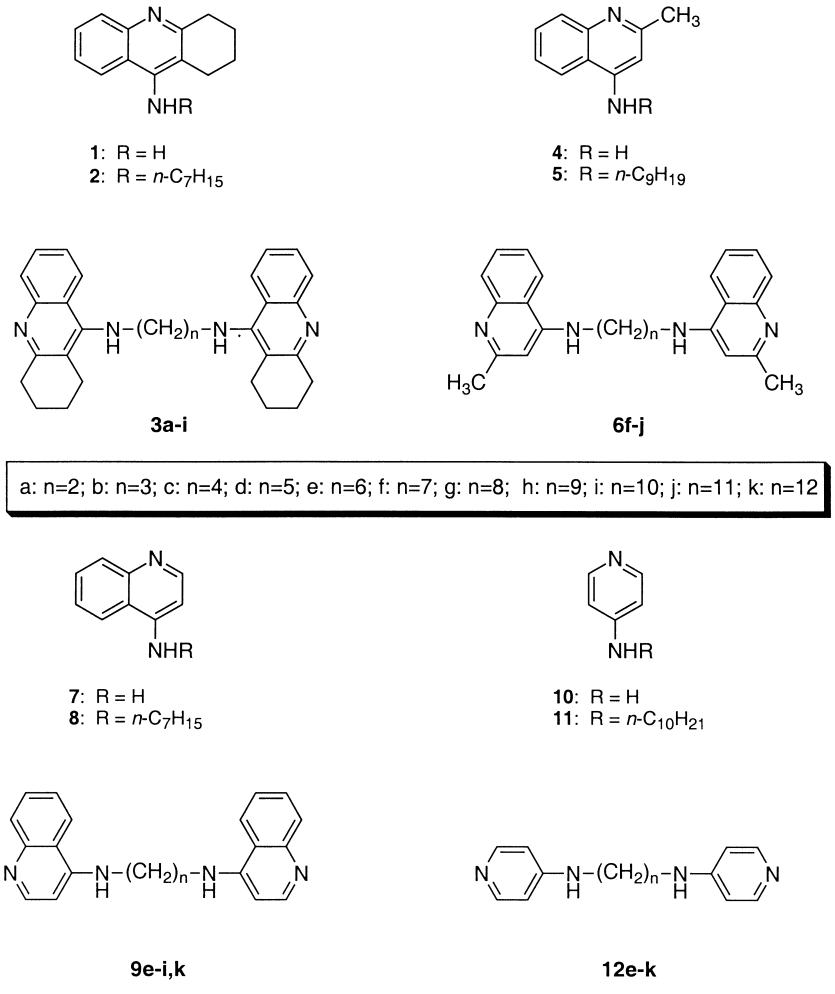


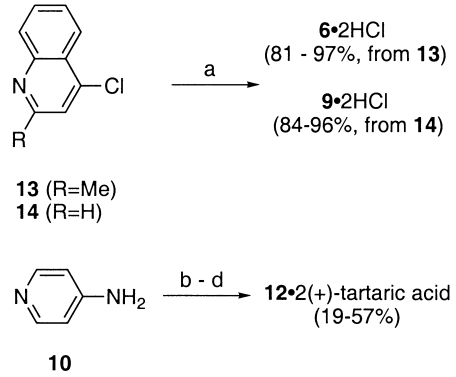
Figure 2. Structures of monomers, alkylated monomers and dimers.

Table 1. Chlorinesterase inhibition by tacrine **1** and tacrine dimers **3a–i**[a]

Entry	Drug	AChE IC_{50} (nM)[b]	BChE IC_{50} (nM)[c]	Selectivity for AChE[d]
1	**1**	223 ± 11	92 ± 2	0.4
2	**3a**	711 ± 25	102 ± 4	0.14
3	**3b**	254 ± 55	152 ± 17	0.60
4	**3c**	157 ± 23	252 ± 9	1.60
5	**3d**	28 ± 5	329 ± 21	11.7
6	**3e**	3.8 ± 0.4	119 ± 6	31.6
7	**3f**	1.5 ± 0.3	149 ± 23	99.4
8	**3g**	7.8 ± 0.9	105 ± 13	13.5
9	**3h**	31 ± 3	155 ± 25	4.9
10	**3i**	40 ± 6	167 ± 12	4.2

[a] Data from ref 12.
[b] Assay performed using rat cortex homogenate, in the presence of ethopropazine as a specific BChE inhibitor.
[c] Assay performed using rat serum, in the presence of BW284c51 as a specific AChE inhibitor.
[d] Selectivity for AChE is defined as IC_{50}(BChE)/IC_{50}(AChE).

(Scheme 1). Due to the unavailability of 1,11-diaminoundecane, dimer **6j** was prepared by deprotonation of **4** with *n*-BuLi in THF, followed by alkylation with 1,11-dibromoundecane. 4-Aminopyridine dimers **12e–k** were prepared by a modification of the two step acylation-reduction method previously developed for **12i** (Scheme 1).[19] We found that the acylation reaction was remarkably slow at THF reflux, and that yields were greatly improved by increasing the reaction time from 30 min to 4 h (yields 75–100%). Reduction provided the desired dimers in acceptable yields (39–99%); these were converted to the *bis*-(+)-tartaric acid salts for improved handling, in overall yields of 19–57%. To serve as additional controls, monomers bearing an alkyl chain of the same length as the tether in the optimum dimers (**2**, **5**, **8**, **11**, vide infra) were prepared by refluxing the appropriate 4-halopyridine derivative (9-chloro-1,2,3,4-tetrahydroacridine, **13**, **14** or 4-bromopyridine) with the requisite primary amine in 1-pentanol. All compounds were recrystallized from methanol–water before assay and gave satisfactory elemental analyses (Table 2).



Scheme 1. Syntheses of bivalent inhibitors: (a) 0.5 equiv $NH_2(CH_2)_n$-NH_2, 1-pentanol, reflux 14–18 h; (b) 0.5 equiv $ClC(O)(CH_2)_{n-2}C(O)Cl$, 2 equiv Et_3N, THF, reflux, 4 h; (c) 6 equiv $LiAlH_4$, THF, reflux, 4 h; (d) 2 equiv (+)-tartaric acid, methanol.

Structure–Activity Results and Discussion

Assays for rat AChE and BChE inhibition potency were carried out by the Ellman method[21] with some minor modifications, as previously described.[12] Tacrine **1** and tacrine dimer **3f** were used as controls and their cholinesterase IC_{50} values were within error of the previous determinations. AChE inhibition potencies of the monomers **1**, **4**, **7** and **10** span a greater than 2000-fold range (Table 1, entry 1; Table 3, entries 2, 9, 17). Dimerization of the three new monomers resulted in significant, tether length-dependent increases in AChE inhibition potency and selectivity. As was seen in the tacrine dimer series,[12] AChE potency and selectivity are concurrently optimized at a specific tether length, consistent with simultaneous binding to the catalytic and peripheral sites of AChE. In the 4-aminoquinaldine series a 9-methylene tether is required to optimize both AChE potency and selectivity; **6h** is nearly 300-times more potent than the corresponding monomer **4** (Table 3, entries 5 and 2). In the 4-aminoquinoline series a tether length of 7 methylenes optimizes both AChE potency and selectivity; **9f** is nearly 600 times more potent than the corresponding monomer **7** (Table 3, entries 11 and 9). Smaller but significant increases in selectivity for AChE are also seen in these two series.

The least potent monomer **10** most dramatically illustrates the power of the dual-site binding strategy. 4-Aminopyridine (**10**) is not known as an AChE inhibitor in the literature, and in our assay it exhibited no AChE inhibition whatsoever at concentrations up to 0.5 mM, which allows extrapolation of IC_{50} > 500,000 nM (Table 3,

Table 2. Physical properties of drugs tested

Drug[a]	Yield (%)	Formula	Mp (°C)
2	79	$C_{20}H_{28}N_2 \cdot HCl$	159.8–161.5
5	90	$C_{19}H_{28}N_2 \cdot 1.05HCl \cdot 0.5H_2O$[b]	82.3–84
6f	81	$C_{27}H_{32}N_4 \cdot 2HCl \cdot 0.5H_2O$	269.8–271.4
6g	94	$C_{28}H_{34}N_4 \cdot 2HCl \cdot 2.1H_2O$	278.8–279.7
6h	93	$C_{29}H_{36}N_4 \cdot 2HCl \cdot 4H_2O$	178.8–179.7
6i	97	$C_{30}H_{38}N_4 \cdot 2HCl \cdot 2H_2O$	164.2–165.7
6j	23	$C_{31}H_{40}N_4 \cdot 2HCl \cdot H_2O$	159.5–161.1
8	77	$C_{16}H_{22}N_2 \cdot HCl$	186.1–187.9
9e	96	$C_{24}H_{26}N_4 \cdot 2HCl \cdot 2H_2O$	288–290
9f	91	$C_{25}H_{28}N_4 \cdot 2HCl$	280–282.8
9g	88	$C_{26}H_{30}N_4 \cdot 2HCl \cdot 0.5H_2O$	283.5–288.6
9h	90	$C_{27}H_{32}N_4 \cdot 2HCl$	261.1–262.4
9i	87	$C_{28}H_{34}N_4 \cdot 2HCl$	229–232.9
9k	84	$C_{30}H_{38}N_4 \cdot 2HCl \cdot 0.3H_2O$	251.3–252.1
11	86	$C_{15}H_{26}N_2 \cdot 1.05HCl$[b]	106.4–108
12e	20[c]	$C_{16}H_{22}N_4 \cdot 2(+)$-tartaric acid$\cdot 3.5H_2O$	58.1–59.2
12f	33[c]	$C_{17}H_{24}N_4 \cdot 2(+)$-tartaric acid$\cdot 1.5H_2O$	86.3–86.8
12g	28[c]	$C_{18}H_{26}N_4 \cdot 2(+)$-tartaric acid$\cdot 2.5H_2O$	73.3–75.8
12h	22[c]	$C_{19}H_{28}N_4 \cdot 2(+)$-tartaric acid$\cdot 2.4H_2O$	58.8–59.6
12i	19[c]	$C_{20}H_{30}N_4 \cdot 2(+)$-tartaric acid$\cdot 2.4H_2O$	56.0–56.3
12j	57[c]	$C_{21}H_{32}N_4 \cdot 2(+)$-tartaric acid$\cdot 2.5H_2O$	69.2–69.7
12k	47[c]	$C_{22}H_{34}N_4 \cdot 2(+)$-tartaric acid$\cdot 2.5H_2O$	59.8–60.9

[a] All compounds were recrystallized from methanol–water. NMR (^1H, ^{13}C) and mass spectral data were consitent with the assigned structure; elemental analyses (C, H, N) were consistent (±0.4%) with the assigned formula.
[b] Formulation also supported by chlorine analysis.
[c] Overall yield for the three-step acylation/reduction/salt formation sequence.

Table 3. Cholinesterase inhibition by monomers, dimers and alkylated monomers

Entry	Drug	Rat brain AChE IC_{50} (nM)[a]	Rat serum BChE IC_{50} (nM)[b]	Selectivity for AChE[c]
Tacrine series				
1	**2**	454 ± 53	340 ± 70	0.75
4-Aminoquinaldine series				
2	**4**	15,700 ± 1530	105,000 ± 10,300	6.7
3	**6f**	148 ± 46	2940 ± 490	20
4	**6g**	161 ± 29	1780 ± 437	11
5	**6h**	54.1 ± 2.0	2130 ± 137	39
6	**6i**	143 ± 15	2980 ± 274	21
7	**6j**	312 ± 24	4380 ± 465	14
8	**5**	3330 ± 222	10,800 ± 165	3.2
4-Aminoquinoline series				
9	**7**	50,700 ± 5350	255,000 ± 26,300	5.0
10	**9e**	215 ± 21	2730 ± 231	13
11	**9f**	87.8 ± 6.1	1800 ± 192	20
12	**9g**	94.3 ± 12.2	1060 ± 115	11
13	**9h**	124 ± 9	1570 ± 48	13
14	**9i**	483 ± 65	2150 ± 124	4.5
15	**9k**	786 ± 169	2920 ± 383	3.7
16	**8**	5950 ± 697	33,800 ± 1739	5.7
4-Aminopyridine series				
17	**10**	> 500,000[d]	> 500,000[d]	nd[e]
18	**12e**	7850 ± 1590	20,000 ± 760	2.6
19	**12f**	809 ± 62	10,700 ± 576	13
20	**12g**	908 ± 178	9220 ± 1401	10
21	**12h**	364 ± 30	7940 ± 188	22
22	**12i**	152 ± 30	14,300 ± 994	94
23	**12j**	244 ± 34	11,900 ± 567	49
24	**12k**	403 ± 39	14,400 ± 590	36
25	**11**	1570 ± 215	28,200 ± 4410	18.0

[a] Assay performed using rat cortex homogenate, in the presence of ethopropazine as a specific BChE inhibitor.
[b] Assay performed using rat serum, in the presence of BW284c51 as a specific AChE inhibitor.
[c] Selectivity for AChE is defined as IC_{50} (BChE)/IC_{50}(AChE).
[d] No inhibition detected at the highest drug concentration tested (0.5 mM).
[e] Cannot be determined because the actual AChE and BChE IC_{50} values are unknown.

entry 17). Remarkably, however, 4-aminopyridine dimers **12** are reasonably potent AChE inhibitors. Again, potency and selectivity are simultaneously optimized at a specific tether length, which in this case is 10 methylene units. The optimum dimer **12i** (AChE $IC_{50} = 152 \pm 30$ nM) is at least 3000 times more potent than the corresponding monomer, and is even more potent than tacrine **1** (Table 3, entries 22 and 17; Table 1, entry 1). Review of the IC_{50} values for shorter tether lengths (**12e**–**h**, 6–9 methylene units) demonstrates that AChE potency decreases dramatically for tether lengths less than 7 methylenes (**12f**, Table 3, entry 19). This observation is consistent with the proposal that dual-site binding contributes to the enhanced potency of **12i** relative to **10**.

As might be expected, the rank order potency of the optimum dimers (**3f** > **6h** > **9f** > **12i**) exactly parallels that of the corresponding monomers (**1** > **4** > **7** > **10**). Interestingly, however, the potency versus free monomer is *inversely* correlated to monomer potency (Table 4, column 3). The lowest affinity monomer **10** enjoys a greater than 3000-fold potency enhancement upon dimerization to **12i**; the highest affinity monomer **1** exhibits only a 149-fold potency increase upon dimerization to **3f** (Table 4). Because the potency versus free monomer also correlates with decreasing hydrophobicity of the monomer, we suspected that the hydrophobic nature of the alkylene tether might be playing a role. Therefore, alkylated monomers bearing an alkyl chain of the same length as the tether of the corresponding optimum dimers were screened (**2**, **5**, **8** and **11**, Fig. 2; Table 3, entries 1, 8, 16, 25). In the tacrine series, the tether itself appears to make no contribution to the binding affinity of dimer **3f**, as **2** is less potent than **1** (potency versus free monomer = 0.49, Table 4, column 5). However, in the 4-aminoquinaldine and 4-aminoquinoline series, the tether makes a small contribution to binding affinity, with the alkylated monomers **5** and **8** being 4.7- and 8.5-fold more potent than the corresponding free monomers **4** and **7**, respectively (Table 4, column 5). A dramatic effect is seen in the 4-aminopyridine series, where alkylated monomer **11** is at least 320-fold more potent than **10** itself (Table 4, column 5). Thus in the

Table 4. AChE potencies of optimum dimers and alkylated monomers relative to free monomers[a]

Optimum dimer	AChE IC_{50} (nM)	Potency versus free monomer	Alkylated monomer	Potency versus free monomer
3f	1.5 ± 0.3	149	**2**	0.49
6h	54.1 ± 2.0	290	**5**	4.7
9f	87.8 ± 6.1	577	**8**	8.5
12i	152 ± 30	< 3290[b]	**11**	< 320[b]

[a] Selectivity for AChE is defined as IC_{50} (BChE)/IC_{50} (AChE).
[b] Estimate based on a lower bound for the IC_{50} of **10** (Table 3).

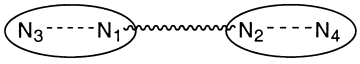
4-aminopyridine series **12** the tether provides not only the expected entropy-driven potency enhancement (as evidenced by the tether length dependence of the potency enhancement, cf. Table 3, entries 18–22), but also significantly increases the affinity of the monomer.

Why does appendage of an alkyl chain result in a significant potency increase for 4-aminopyridine **10**, and a slight potency decrease for tacrine **1**? We propose that two factors are involved. Firstly, binding of a charged ligand to a hydrophobic host requires payment of a substantial 'desolvation penalty', and appendage of hydrophobic C_7–C_{10} alkyl chains to monomers **1**, **4**, **7**, **10** should decrease the magnitude of this penalty. Dougherty's studies of the binding of protonated and quaternary amines to ethenoanthracene hosts have shed considerable light on the competition of aqueous solvation and cation–pi interaction.[22] Protonated amines typically bind very weakly to ethenoanthracene hosts, because their substantial desolvation penalty overwhelms the enthalpic benefit of cation–pi interaction. However, as the amine becomes more hydrophobic (through quaternization), the desolvation penalty is reduced, and cation–pi interaction provides impressive affinities for the ethenoanthracene host. We suggest that a similar phenomenon relates binding affinities of free and alkylated monomers to the hydrophobic active site cleft of AChE. The competing hypothesis, that attractive van der Waals interactions exist between the chain and the active site cleft of AChE, is discounted by the following observations: (a) the decamethonium/AChE structure[14] gives no evidence for this kind of interaction, and (b) previous studies of shorter homologues of **2** (*N*-Me to *N*-*n*-pentyl) also show 1.4- to 6-fold reductions in AChE inhibitory potency relative to **1**.[23]

Second, opposing the reduction of desolvation penalty, appendage of an alkyl chain may interfere with optimal binding of the monomer to the active site of AChE. The bottom of the AChE active site is quite narrow. We have previously[12] shown that the ethylene-linked tacrine dimer **3a** is less potent than tacrine **1** itself (Table 1, entries 1 and 2), and have proposed that steric crowding is responsible for the loss of potency. The lower potency of alkylated tacrine monomer **2** relative to **1** may also be a consequence of perturbation from the optimal binding conformation or unfavorable steric interactions. However, as the monomer size decreases, the range of acceptable binding conformations in the AChE active site should increase, making it possible to alleviate unfavorable steric interactions of the tether. In the case of the smallest monomer (4-aminopyridine), therefore, the maximal benefit of reduced desolvation penalty engendered by the tether can be enjoyed.

Finally, the variability of the optimum tether length in the four series (7–10 methylenes) was unexpected and deserves comment. In the published *Torpedo* AChE/decamethonium X-ray crystal structure,[14] decamethonium is bound in a slightly curved conformation and features an N_1–N_2 distance of $\approx$12 Å; in its fully extended conformation this distance is 13.7 Å (Table 5). In its fully extended conformation BW284c51 also provides a very similar separation of the two quaternary nitrogens (14.6 Å) and thus easily achieves simultaneous binding to the catalytic and peripheral sites (Table 5). At physiological pH the remaining ligands in Table 5 will also be dications, and resonance will serve to delocalize the positive charge between the endocyclic (N_1, N_2) and exocyclic nitrogens (N_3, N_4). Thus the observed variation in optimum tether lengths may be due in part to the availability of three limiting cation–pi binding modes (N_1–N_2, N_1–N_4, N_3–N_4, cf. Table 5). For **3f** and **9f** the N_1–N_2 distances are too short (9.9 Å), and the N_1–N_4 distances (both 13.4 Å) offer a much better fit. In the cases of **6h** and **12i** however, the N_1–N_2 distances (12.4 and 13.7 Å, respectively) offer a fairly close match to that of decamethonium. Thus in each case, dual site binding is feasible. Based on the alkylated monomer data discussed above, desolvation penalty may also play a role in determining the optimum tether length, which in turn would determine which binding mode is preferred. A definitive explanation for the variation in optimum tether length will require docking and/or X-ray studies. In any event, it is clear that even when small perturbations are made to the monomeric unit of a dimeric drug, a range of tether lengths should be examined.

Table 5. Calculated N–N distances for bivalent AChE inhibitors[a]



Inhibitor	N_1–N_2 Distance (Å)	N_1–N_4 Distance (Å)	N_3–N_4 Distance (Å)
Decamethonium	13.7	na	na
BW284c51	14.6	na	na
3f	9.9	**13.4**	16.2
6h	**12.4**	16.3	20.1
9f	9.9	**13.4**	16.2
12i	**13.7**	17.5	21.6

[a] Distances measured in the fully extended conformation, using PC Spartan Plus.

Conclusion

4-Aminopyridine- and 4-aminoquinoline based monomers whose inhibition potencies span a 2000-fold range were dimerized in order to study dual-site binding to AChE. In all cases significant tether length-dependent potency and selectivity enhancements (up to 3000-fold) were seen, relative to the corresponding monomers, indicating simultaneous binding to the catalytic and peripheral sites of AChE. Assay of alkylated *monomers* in each series revealed that the alkylene tether can play at least two complementary roles in the dimers. For large hydrophobic monomers like tacrine, the tether increases potency by reducing entropy loss on binding. For the smaller, less hydrophobic monomers 4-aminoquinaldine, 4-aminoquinoline, and 4-aminopyridine, the tether increases potency both by reducing entropy loss on binding, and by reducing the desolvation penalty of the monomer. This latter effect can be quite significant. In the case of the smallest and least hydrophobic

monomer 4-aminopyridine, appendage of a *n*-decyl chain to the exocyclic nitrogen increases AChE inhibitory potency at least 320-fold.

Experimental

9-Amino-1,2,3,4-tetrahydroacridine (**1**) was obtained from Sigma as the HCl salt. 4-Aminoquinaldine (**4**) and 4-aminopyridine (**10**) were obtained from Aldrich and converted to their hydrochloride and (+)-tartaric acid salts, respectively. 4-Aminoquinoline (**7**)[24] and 9-chloro-1,2,3,4-tetrahydroacridine[12] were prepared according to the literature methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical ionization (CI) mass spectra were acquired using CH_4 as the reagent gas. Melting points were determined with an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analysis was performed by the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (Shanghai, PRC). Optical rotations were measured on a Perkin–Elmer 241 Polarimeter.

Representative syntheses of dimers

***N,N′*-di-4-Quinaldinyl-1,9-diaminononane *bis*-hydrochloride (6h·2HCl).** 4-Chloroquinaldine (518 mg, 2.92 mmol), 1,9-diaminononane (231 mg, 1.46 mmol), and 1-pentanol (10 mL) were combined in a 25 mL round bottom flask equipped with magnetic stirring bar and condenser, and heated under reflux for 14 h. The solid product was collected by suction filtration, washed with toluene, recrystallized from 10% MeOH–H_2O, and dried in vacuo to provide **6h**·2HCl (693 mg, 93%). ^{1}H NMR (D_2O): δ 1.41 (br, 10H), 1.69 (t, J = 6.5 Hz, 4H), 2.41 (s, 6H), 3.30 (t, J = 7.1 Hz, 4H), 6.22 (s, 2H), 7.15 (d, J = 8.40 Hz, 2H), 7.34 (t, J = 7.8 Hz, 2H), 7.55 (t, J = 7.8 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H); ^{13}C NMR (CD_3OD): δ 25.11, 28.99, 30.19, 31.21, 31.40, 44.80, 99.96, 119.50, 122.90, 125.88, 127.95, 131.58, 148.52, 153.87, 160.49; MS ($CI^+(CH_4)$): 441 (freebase + H); mp: 178.8–179.7°C. Anal. calcd for $C_{29}H_{36}N_4$·2HCl·4H_2O: C, 59.48; H, 7.92; N, 9.57. Found: C, 59.75; H, 7.66; N, 9.74.

***N,N′*-di-4-Quinaldinyl-1,11-diaminoundecane *bis*-hydrochloride (6j·2HCl).** A 50 mL round bottom flask equipped with magnetic stirring bar was charged with 4-aminoquinaldine (995 mg, 6.30 mmol), dry THF (15 mL), purged with N_2, and cooled to −78°C. *n*-BuLi (3.3 mL, 1.89 M, 6.3 mmol) was added via syringe; after 30 min at −78°C the solution was warmed to room temperature and stirred for an additional 30 min. After cooling to −78°C once again, 1,11-dibromododecane (988 mg, 3.14 mmol) was added. After 30 min the cooling bath was removed and the reaction stirred at room temperature overnight. The reaction was quenched by addition of satd $NaHCO_3$ (5 mL) and extracted with EtOAc (2×30 mL). The combined organic layers was washed with H_2O (30 mL) and brine (20 mL), dried ($MgSO_4$), filtered and stripped. Column chromatography on silica gel (900:100:7 CH_2Cl_2:MeOH:concd NH_4OH) provided pure free base. The corresponding *bis*-hydrochloride salt was prepared with HCl(g) in MeOH, affording 342 mg (23%) of **6j**·2HCl as a white solid. ^{1}H NMR (D_2O): δ 1.20–1.36 (br, 14H), 1.69 (quintet, J = 7.1 Hz, 4H), 2.60 (s, 6H), 3.46 (t, J = 7.0 Hz, 4H), 6.51 (s, 2H), 7.58 (t, J = 7.7 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.81 (t, J = 7.6 Hz, 2H), 8.13 (d, J = 8.4 Hz, 2H); ^{13}C NMR (CD_3OD): δ 21.24, 28.19, 29.35, 30.50, 30.62, 30.68, 45.00, 99.60, 117.40, 120.99, 123.73, 128.33, 135.27, 139.54, 155.57, 157.28; MS ($CI^+(NH_3)$): calcd for $C_{31}H_{41}N_4$: 469. Found: 469; mp: 159.5–161.1°C. Anal. calcd for $C_{31}H_4N_4$·2HCl·2H_2O: C, 64.46; H, 8.03; N, 9.70. Found: C, 64.11; H, 7.93; N, 10.09; N, 10.09.

***N,N′*-di-4-Quinolyl-1,7-diaminoheptane dihydrochloride (9f·2HCl).** Following the procedure described above for **6h**, 4-chloroquinoline (543 mg, 3.32 mmol) and 1,7-diaminoheptane (216 mg, 1.66 mmol) were combined to provide **9f**·2HCl (687 mg, 91%). ^{1}H NMR (CD_3OD): δ 1.51–1.54 (br, 6H), 1.82 (apparent quintet, J = 6.8 Hz, 4H), 3.59 (t, J = 7.3 Hz, 4H), 6.84 (d, J = 7.2 Hz, 2H), 7.67 (apparent t, J = 7.1 Hz, 2H), 7.83 (d, J = 7.4 Hz, 2H), 7.90 (dt, J = 1.4, 7.1 Hz, 2H), 8.36 (d, J = 7.0 Hz, 2H), 8.40 (dd, J = 0.6, 8.5 Hz, 2H); ^{13}C NMR (CD_3OD): δ 28.75, 29.88, 30.88, 45.52, 99.96, 119.15, 122.07, 124.63, 128.84, 135.51, 140.33, 144.05, 158.29; MS ($CI^+(CH_4)$): 385 (free base + H); mp: 280–282.8°C. Anal. calcd for $C_{25}H_{28}N_4$·2HCl: C, 65.64; H, 6.61; N, 12.25. Found: C, 65.46; H, 6.49; N, 12.24.

***N,N′*-di-4-Pyridyl-1,10-diaminodecane *bis*(+)-tartaric acid salt (12i·2(+)-tartaric acid).** 4-Aminopyridine (3.06 g, 32.6 mmol) was weighed into a 100 mL two-neck round bottom flask equipped with magnetic stirring bar, septum and condenser. After purging with N_2 gas, dried THF (40 mL) and triethylamine (3.27 g, 32.3 mmol) were added by syringe. Sebacoyl chloride (3.92 g, 16.4 mmol) was added by syringe and the reaction mixture was heated under reflux for 4 h, during which time yellow precipitates formed. The solvent was then removed in vacuo, the solid was washed with 10% K_2CO_3 (100 mL) and water (50 mL), and dried under vacuum to provide the diamide (4.88 g, 84%). The diamide (2.27 g, 6.15 mmol) and $LiAlH_4$ (1.40 g, 36.9 mmol) were combined in a 100 mL two-neck round bottom flask equipped with magnetic stirring bar, septum and condenser. After purging with N_2 gas, dried THF (40 mL) was added by syringe and the reaction mixture was heated under reflux for 4 h. Standard Fieser work up and recrystallization from methanol (five times to remove traces of 4-aminopyridine generated during the amide reduction step) provided **12i** (519 mg, 38%). Combination with (+)-tartaric acid (456 mg, 3.04 mmol) in methanol provided 570 mg (58%) of the desired salt after one recrystallization. ^{1}H NMR confirmed a 2:1 stoichiometry of tartaric acid and **12i**. ^{1}H NMR (DMSO-d_6): δ 1.27 (br, 12H), 1.51–1.54 (m, 4H), 3.17–3.18 (m, 4H), 4.04 (s, 4H), 6.75 (d, J = 6.1 Hz, 4H), 8.10–8.12 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 26.35, 28.02, 28.70, 28.93, 42.00, 71.83, 107.17 (br), 113.07 (br), 141.92 (br), 156.84, 174.33; MS($CI^+(NH_3)$): 327 (free base + H); mp: 56.0–56.3°C; $[\alpha]_D$ = +9.04° (25°C, c = 0.5). Anal. calcd for $C_{20}H_{30}N_4$·2(+)-tartaric acid·2.4 H_2O: C, 50.20; H, 7.04; N, 8.36. Found: C, 50.22; H, 6.54; N, 8.43.

Synthesis of alkylated monomers

***N*-*n*-Heptyl-9-amino-1,2,3,4-tetrahydroacridine hydrochloride (2·HCl).** 9-Chloro-1,2,3,4-tetrahydroacridine (500 mg, 2.30 mmol) and *n*-heptylamine (265.5 mg, 2.30 mmol) were heated under reflux in 1-pentanol (5 mL) for 14 h. Aqueous work up followed by chromatography (CH_3OH:CH_2Cl_2.concd NH_3 = 100:893:7) yielded free base **2** which was dissolved in $CHCl_3$, purged with HCl(g), and concentrated in vacuo to yield 2·HCl (541.2 mg, 79%). ^{1}H NMR (CD_3OD): δ 0.88 (t, J = 6.8 Hz, 3H), 1.27–1.46 (m, 8H), 1.85 (5-let, J = 7.3 Hz, 2H), 1.91–2.00 (m, 4H), 2.67–2.69 (m, 2H), 3.00–3.03 (m, 2H), 3.94 (t, J = 7.4 Hz, 2H), 7.57 (ddd, J = 1.6, 6.9, 8.6 Hz, 1H), 7.75–7.87 (m, 2H); 8.38 (d, J = 8.7 Hz, 1H); ^{13}C NMR (CD_3OD): δ 23.49, 24.09, 25.37, 28.18, 29.80, 30.47, 32.03, 33.34, 49.67, 113.33, 117.54, 120.59, 126.81, 127.01, 134.60, 140.27, 152.14, 158.54; MS($CI^+(NH_3)$): 297 (free base + H); mp: 159.8–161.5°C. Anal. calcd for $C_{20}H_{28}N_2$·HCl: C, 72.16; H, 8.78; N, 8.41; Cl, 10.65. Found: C, 71.85; H, 8.82; N, 8.55; Cl, 10.32.

***N*-*n*-Nonyl-4-aminoquinaldine hydrochloride (5·HCl).** 4-Chloroquinaldine (541 mg, 3.05 mmol) and nonylamine (523.6 mg, 3.66 mmol) were treated as above to provide 5·HCl (878.7 mg, 90%). ^{1}H NMR (CD_3OD): δ 0.84–0.92 (m, 3H), 1.27–1.54 (m, 13H), 1.79 (5-let, J = 7.3 Hz, 2H), 3.58 (t, J = 7.3 Hz, 2H), 6.69 s, 1Hz), 7.62 (ddd, J = 1.3, 7.0, 8.4 Hz, 1H), 7.77–7.90 (m, 2H); 8.34 (d, 1H); ^{13}C NMR (CD_3OD): δ 20.85, 24.20, 28.56, 29.68, 30.86, 30.95, 31.12, 33.50, 45.20, 99.81, 117.79, 120.99, 124.16, 128.09, 135.03, 139.45, 155.74, 157.64; MS($CI^+(NH_3)$): 285 (free base + H); mp: 82.3–83.4°C. Anal. calcd for $C_{19}H_{28}N_2$·1.05HCl·0.5 H_2O: C, 68.79; H, 9.13; N, 8.44; Cl, 11.22. Found: C, 68.80 H, 9.12; N, 8.40; Cl, 11.32.

***N*-*n*-Heptyl-4-aminoquinoline hydrochloride (8·HCl).** 4-Chloroquinoline (508 mg, 3.11 mmol) and *n*-heptylamine (429.3 mg, 3.73 mmol) were treated as above to provide 8·HCl (662.7 mg, 77%). ^{1}H NMR (CD_3OD): δ 0.88 (t, J = 6.8 Hz,3H), 1.25–1.50 (m, 8H), 1.79 (5-let, J = 7.4 Hz, 2H), 3.56 (t, J = 7.4 Hz, 2H), 6.82 (d, J = 7.1 Hz, 1Hz), 7.67 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.81–7.93 (m, 2H); 8.3–8.40 (m, 2H); ^{13}C NMR (CD_3OD): δ 24.15, 28.54, 29.70, 30.64, 33.42, 45.31, 99.64, 118.88, 121.89, 124.30, 128.50, 135.13, 140.16, 143.84, 157.91; MS($CI^+(NH_3)$): 243 (free base + H); mp: 186.1–187.9°C. Anal. calcd for $C_{16}H_{22}N_2$·HCl: C, 68.92; H, 8.31; N, 10.05; Cl, 12.72. Found: C, 68.89; H, 8.34; N, 9.99; Cl, 12.82.

***N*-*n*-Decyl-4-aminopyridine hydrochloride salt (11·HCl).** 4-Bromopyridine hydrochloride (512.6 mg, 2.64 mmol) and decylamine (827.7 mg, 5.27 mmol) were treated as above to provide 11·HCl (615.3 mg, 86%). ^{1}H NMR (CD_3OD): δ 0.83 (t, J = 6.7 Hz, 3H), 1.23–1.36 (m, 14H), 1.62 (5-let, J = 7.13 Hz, 2H), 3.24–3.28 (m, 2H), 6.82(d, J = 7.47 Hz, 1Hz), 7.92 (apparent d, J = 7.86 Hz, 1H), 8.04 (apparent d, J = 7.83 Hz, 1H); ^{13}C NMR (CD_3OD): δ 24.20, 28.43, 29.90, 30.88, 30.91, 31.14, 33.52, 44.39, 106.36, 111.73, 139.67, 142.08, 160.45 MS($CI^+(NH_3)$): 235 (free base + H); mp: 106.4–108°C. Anal. calcd for $C_{15}H_{26}N_2$·1.05HCl: C, 66.07; H, 10.00; N, 10.27; Cl, 13.65. Found: C, 66.37 H, 10.13; N, 10.16; Cl, 13.68.

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