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PHYSICAL PARAMETERS FOR BRAIN UPTAKE: OPTIMIZING LOG *P*, LOG *D* AND pK_a OF THA

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Abstract: Two positions on the acetylcholinesterase (AChE) inhibitor, 9-amino-1,2,3,4-tetrahydroacridine (THA), have been identified which can be modified to vary log *P*, log *D* and pK_a values. Most importantly, these changes can be carried out without altering its AChE activity.

The acetylcholinesterase (AChE) inhibitor 9-amino-1,2,3,4-tetrahydroacridine (THA) has been reported to produce improvements in patients suffering from senile dementia of the Alzheimer's type (SDAT).[1] The clinical activity observed with THA has provided an impetus to develop superior analogs with a view to improving its clinical efficacy.[2]

THA differs from other AChE inhibitors in achieving high ratio of brain to plasma concentrations; remarkably, following i.p. administration to mice, the brain to plasma ratio for THA is 10.[3] THA has interesting physical properties relative to other AChE inhibitors since both its pK_a (9.8) and log *P* (2.8) are high.[4,5] The higher pK_a is due to the presence of a 4-amino-pyridine group. Because of this high pK_a, only 0.4% of THA is present as the uncharged form in plasma (pH 7.4). Since it is the latter form that presumably crosses the blood-brain barrier (BBB), it can be argued that brain uptake of THA could be improved by increasing the availability of the neutral species. The small amount of unprotonated THA leads to a very low log *D* (0.41 at pH 7.5).[6] Log *D* is defined as the ratio of the concentration of compound in the lipid phase (*n*-octanol) to the concentration of all species in the aqueous phase at a given pH. Using the technique of Clarke,[5] no partitioning of the hydrochloride salt into *n*-octanol was observed at pH 7.5; thus log *D* is a measure of the partitioning of neutral molecules at pH 7.5.

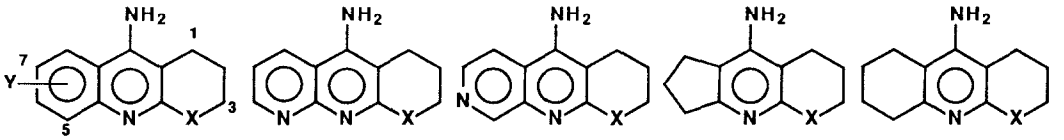
Another parameter important in considering brain uptake of drugs is the log *P* of the uncharged species. Current theories agree that compounds with a log *P* around 2.5-3.0 would cross the BBB readily;[4] the log *P* of 2.8 of THA is in the optimal range for brain uptake. From this analysis, we hypothesized that brain uptake of THA could be improved by increasing its log *D*. In order to maintain its therapeutic effect this change would have to be accomplished without compromising THA's AChE inhibitory activity.

We report the identification of positions on THA that permit the manipulation of its physical properties without altering AChE inhibitory activity. In addition, compounds with log *P*, log *D*, and pK_a values in a range predicted to maximize brain uptake have been identified.

Of the various possibilities considered for increasing log *D* of THA, the strategy of replacing the C-4 methylene group by an oxygen atom is appealing. The effect of this change on pk_a, (hence log *D*) and log P was not predictable. Thus to investigate the overall effect of replacement of C-4 methylene by an oxygen atom on pk_a,

(hence log *D*) and log P, we synthesized two series of compounds: one consisting of THA analogs **1-5** (**X** = CH_2), and the other consisting of the same analogs containing an oxygen atom in the C-4 position (**X** = O). A comparison of their log *P*, pK_a and AChE inhibitory activity was made.

The compounds were prepared by a titanium(IV) chloride-promoted condensation of readily available ortho-aminonitriles with the appropriate carbonyl components at room temperature. This unprecedented procedure was especially suited for the synthesis of the formerly unknown 2,3-dihydropyrano[2,3-b]pyridine compounds exemplified by structures **1b**, **1d**, **1f**, **1h**, **1j**, **1l**, **2b**, **3b**, **4b** and **5b**.[7,8] Their IC_{50}'s for inhibition of brain AChE and pK_a's are shown in Table 1.[9] Two trends are clearly evident. First, replacement of the C-4 methylene by an electron withdrawing oxygen produced a series of compounds with pK_a values 2-3 log units lower than those of the corresponding carbon-containing compounds. Second, the oxygen analogs, with the exception of compounds **2** and **3**, were only 2-3 times less active than the carbon analogs. These findings are consistent with inhibition of AChE by the charged species that is present in both series.[10]



1 **2** **3** **4** **5**

Table 1: Comparison of pK_a and AChE inhibition of THA analogs **1-5**

Compd. No.	X	Y	pK_a	IC_{50} (nM)[9] [AChE inh.]	Compd. No.	X	Y	pK_a	IC_{50} (nM)[9] [AChE inh.]
1a (THA)	CH_2	H	9.8	143 ± 40 (16)	**2a**	CH_2	-	8.8	429 ± 147 (9)
1b	O	H	7.8	266 ± 91 (10)	**2b**	O	-	6.4	6262±1255 (6)
1c	CH_2	8-F	9.1	78 ± 30 (5)	**3a**	CH_2	-	7.3	2600 ± 690 (3)
1d	O	8-F	6.9	335 ± 150 (5)	**3b**	O	-	5.6	42±3 μM (3)
1e	CH_2	7-Cl	-	3680 ± 1740 (5)	**4a**	CH_2	-	10.2	658 ± 295 (4)
1f	O	7-Cl	-	9810 ± 3020 (5)	**4b**	O	-	7.8	1120 ± 657 (5)
1g	CH_2	8-Cl	9.3	39 ± 15 (7)	**5a**	CH_2	-	11.0	360 ± 69 (3)
1h	O	8-Cl	6.6	313 ± 220 (5)	**5b**	O	-	7.8	455 ± 259 (7)
1i	CH_2	8-OMe	10.4	615 ± 159 (5)					
1j	O	8-OMe	8.11	606 ± 111 (4)					

Specifically, the oxa analog **1b** had a pK_a of 7.78, indicating that more than 35% of the compound would be uncharged at physiological pH; this is in marked contrast to THA, for which only 0.4% would be present as the neutral species. This is consistent with the fact that the log *D*, at plasma pH, for **1b** is higher than that of THA (1.37 and 0.46 respectively). We measured brain and plasma levels for THA and the oxa analog **1b**. These data are shown in figure 1.[11] As has been previously reported, THA exhibited a ten-fold higher level in brain than in plasma.[3] In contrast, compound **1b** exhibited higher plasma than brain levels. The lower brain level observed

with **1b** does not correlate with increased log *D* but rather with a lowering of log *P*. Indeed, this was found to be the case; from table 2 it can be seen that THA has a higher log *P* (2.71) than **1b** (1.86).

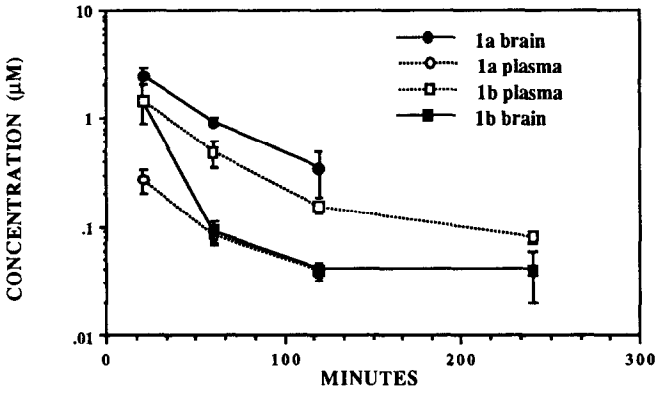


Figure 1. Brain and plasma levels for 1a (THA) and 1b in mice following 3.2 mg/kg i.p.

In short, while we succeeded in increasing the log *D* of THA by replacing the C-4 methylene with an oxygen without significantly losing *in vitro* AChE activity, we also lowered its log *P*. It would appear that the advantage gained by increasing log *D* is offset by the decrease in log *P*, the net result being that **1b** exhibits a lower brain to plasma ratio than THA. The next logical step was to keep the log *D* and pK_a the same while increasing log *P*. Our strategy to achieve this was to compensate for the hydrophilicity of the oxygen atom by substituting an alkyl group on **1b**.

Table 2: Comparision of physical properties of 8-methyl anlogs THA and **1b**.[12]

Compd. No.	X	Y	pK_a	Log *P* [5]	Log *D*	IC_{50} (nM) [9] [AChE inh.]
1a (THA)	CH_2	H	10.03 ± 0.07	2.71	0.46	143 ± 40 (16)
1k	CH_2	8-CH_3	9.98 ± 0.11	-	-	99 ± 49 (3)
1b	O	H	7.8	1.86	1.37	266 ± 91 (10)
1l	O	8-CH_3	8.06	2.28	1.63	150 ± 68 (5)

We synthesized the 8-methyl derivatives **1k** and **1l**; their pK_a, log *P*, log *D* and IC_{50} are compared in table 2. As predicted, log *P* of **1l** increased by one half log compared to **1b**; and for the oxa-analog, incorporation of a methyl group slightly increased the pK_a and raised log *D* by 0.26 log unit. Interestingly, the latter trend suggests the dominant effect of oxygen at C-4 for influencing both the pK_a and log *D*. Most important, incorporation of a C-8 methyl group had little effect on the IC_{50}s for AChE inhibition. Thus we have shown with **1l** that compounds with physical properties that might increase brain concentration can be synthesized without losing

AChE activity. For example, the log *P* of **1l** could be further increased to match that of THA by incorporating one or more carbons.

Overall, two positions on THA have been identified which can be modified to develop compounds with desirable physical parameters. A series of 4-oxa-analogs of THA was synthesized which exhibits lower pK_as and log *P*s but higher log *D*s compared to the corresponding 4-carbon containing analogs. The log *P* of these 4-oxa analogs could be improved by incorporating lipophilic groups at the 8 position. These alterations in log *P*, log *D* and pK_a could be achieved without altering the AChE activity.

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9. Human AChE purified from red blood cells was purchased from Sigma Chemical Company (St. Louis, MO). For the determination of AChE activity see Ellman, G. K.; Courtney, K. D.; Andres, V.; Featherstone, R. M. *Biochem. Pharma.* **1961**, *7*, 88.

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11. Brain and plasma levels of THA and **1b** were measured by the procedure described in reference 3.

12. Pk_a of **1k** was measured in MeOH-H_2O (1:1). Pk_a of THA in same solvent is 9.83 ± 0.16 (n =3).