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SYNTHESIS AND IN VITRO ACETYLCHOLINESTERASE INHIBITORY ACTIVITY OF SOME 1-SUBSTITUTED ANALOGUES OF VELNACRINE

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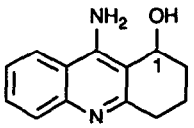
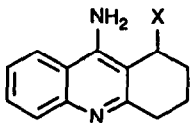
Abstract: A number of analogues of 9-amino-1,2,3,4-tetrahydro-1-acridinol (velnacrine), with 1-position substituents other than hydroxy, were prepared and evaluated for *in vitro* acetylcholinesterase inhibition.

We recently reported the synthesis of a series of 9-amino-1,2,3,4-tetrahydro-1-acridinols.[1] These compounds were acetylcholinesterase inhibitors and were active in a dementia paradigm in mice, reversing the impairment of 24-h memory induced by scopolamine. Based on these data (and data from an nbM lesion model), one of these compounds (velnacrine maleate, **1**) was chosen for clinical trials in Alzheimer's disease. Clinical trials with **1** in Alzheimer's patients have been highly encouraging.[2] We now wish to report on the synthesis and acetylcholinesterase inhibition of a number of analogues of **1** where X is a substituent other than hydroxy, compounds **2-7** shown below.



1, (maleate)



2-7

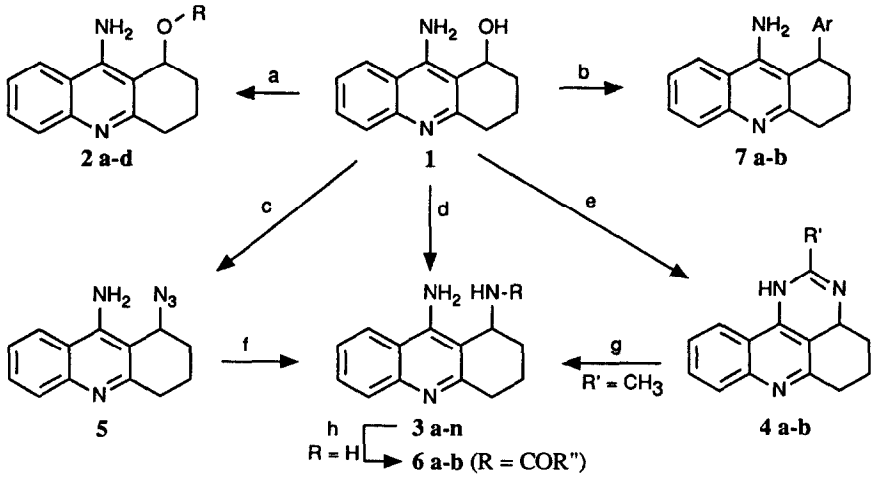
The synthesis of compounds **2-7** is outlined in scheme I. All of these compounds were synthesized by acid-catalyzed substitution of the benzylic carbinol at the 1-position of **1**, conditions that were suggested by the ease of racemization of **1** under acidic conditions.[1] For example, the synthesis of ethers **2a-d** was accomplished through an acid catalyzed dehydration, in which **1** was suspended in the appropriate alcohol and treated with a freshly prepared ethereal solution of HCl.[3]

Amines **3c-n** were synthesized in a similar manner by the treatment of **1** with an excess of para-toluene sulfonic acid monohydrate and the appropriate amine in refluxing toluene (xylenes in the case of **3e**) with azeotropic removal of water. Initial attempts to prepare the primary amine (**3a**) focused on the Ritter reaction of **1** using acetonitrile as a nucleophile and $5\%H_2SO_4/CF_3CO_2H$ as the medium to prepare an acetamide derivative which could then be hydrolyzed to the primary amine. The product isolated from this reaction, however, was compound **4a**, a novel pyrimidino[4,5,6-k,l]acridine resulting from the intramolecular ring closure of the intermediate iminium ion.[4] A similar result was obtained with benzonitrile, giving **4b**. In an attempt at using **4a** to synthesize **3a**, we envisioned reducing **4a** to **3a** using an appropriate reducing agent. In practice however, the compound derived from the reduction of **4a** using lithium aluminum hydride was the ethyl amine (**3b**).[5]

The synthesis of the primary amine (**3a**) was accomplished through the intermediacy of azide **5**,

prepared by the reaction of **1** with diphenylphosphoryl azide under Mitsunobu conditions.[6] Catalytic reduction of **5** then gave **3a** cleanly. Two acyl derivatives of **3a** (**6a and 6b**) were synthesized by the selective acylation of **3a** at the 1-position using an acid chloride and triethylamine in tetrahydrofuran.[7]

As further extension of this chemistry, **1** could serve as an electrophile in a Friedel-Crafts alkylation of electron rich aromatic substrates (using the same conditions as the Ritter approach) giving **7a** and **7b**.



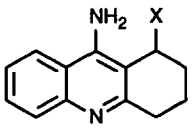
Scheme I

Reagents and conditions: (a) ROH, HCl/Et_2O; (b) ArH, 5% H_2SO_4/CF_3CO_2H; (c) $C_2H_5O_2CN{=}NCO_2C_2H_5$, $(C_6H_5)P$, $(C_6H_5O)_2P(O)N_3$, THF, 65°C; (d) R_1R_2NH, TsOH, toluene (xylenes for **3e**), reflux; (e) R'CN, 5% H_2SO_4/CF_3CO_2H; (f) 10% Pd/C, H_2, 50 psi, EtOH; (g) $LiAlH_4$, THF, reflux; (h) R"COCl, Et_3N, THF.

Compounds **2-7** were evaluated for their ability to inhibit acetylcholinesterase *in vitro* as described previously.[1b] As can be seen in table I, substitution of the hydroxyl group in **1** with an alkyl ether was well tolerated. Activity increased with increasing chain length up to the propyl ether (**2c**) and the butyl ether (**2d**) was about equipotent with **1**. Substitution of the 1-position of **1** with alkyl amines was less well tolerated with each substitution less potent than the corresponding ether (**3a-3d**). The benzyl and phenethyl derivatives (**3e-3g**) were slightly more potent than the butylamine (**3d**) but not as potent as the propyl amine (**3e**). The 1-pyrrolamine (**3h**) was equipotent with **3a**. The pyrrolidino (**3i**) and the larger piperidino (**3j**) derivatives were slightly less active than **1**, but substitution at the 4-position of the piperidine with a phenyl group (**3k**) or replacement of the carbon in the 4-position of the piperidine with a substituted nitrogen (**3l, 3m**) or with oxygen (**3n**) dramatically reduced esterase activity. Acylating the primary amine (**3a**) to give the amides **6a** and **6b** decreased activity by about an order of magnitude relative to **3a**. The azide precursor of **3a** (**5**) showed no loss of activity.

In a previous publication from our group,[8] it was reported that fusion of a pyrazolo ring to the alicyclic ring of **1** gave compounds with reduced activity. In the present investigation, the fused pyrimidino derivatives (**4a** and **4b**) gave similar results. On the other hand, the arylated derivatives **7a** and **7b** had activity equal to or better than **1**.

Table 1. Physical and Biological Data for Velnacrine Analogues



Compd.	X	mp °C[a]	yield %	acetylcholinesterase inhibition IC_{50}, μM[b]
1	OH[c]	ref 1b	ref 1b	3.64 (2.82-4.69)
2a	OCH_3	192-194	60	4.74 (3.38-6.64)
2b	OC_2H_5	199-201	43	0.298 (0.208-0.428)
2c	$O(CH_2)_2CH_3$	187-190	36	0.193 (0.045-0.834)
2d	$O(CH_2)_3CH_3$	162-163	44	1.9 (0.41-8.8)
3a	NH_2[d]	187 dec	49	8.59 (6.2-11.88)
3b	NHC_2H_5[e]	164-167	38	4.79 (3.51-6.52)
3c	$NH(CH_2)_2CH_3$	175-177	55	12.5 (6.3-24.6)
3d	$NH(CH_2)_3CH_3$	164-166	67	48.8 (35.2-67.6)
3e	$NHCH_2C_6H_5$	166-168	49	20.1 (16-25.3)
3f	$NHCH_2$-3,4-$(CH_3O)_2C_6H_3$	160-162	18	38.4 (30.4-48.6)
3g	$NH(CH_2)_2C_6H_5$	120-122	61	18.6 (9.3-38.5)
3h	NH-1-C_4H_4N	185-188	27	8.16 (5.93-11.25)
3i	1-C_4H_8N	201-203	44	18 (13.1-24.8)
3j	1-$C_5H_{10}N$	215 dec	52	8.4 (6.74-10.47)
3k	4-(C_6H_5)-1-C_5H_9N	189-190	36	>100
3l	4-(CH_3)-1-$C_4H_8N_2$	200-202	31	>100
3m	4-(C_6H_5)-1-$C_4H_8N_2$[c]	205-207	25	>100
3n	4-C_4H_8NO	215-217	11	>100
4a	f	207-207.5	30	>100
4b	g	230 dec	33	>100
5	N_3	163 dec	18	11.8 (5.6-24.6)
6a	$NHCOCH_3$	190 dec[h]	22	64.9 (48.7-86.4)
6b	$NHCO(CH_2)_4CH_3$	214 dec	35	51.8 (39-68.8)
7a	2-C_4H_3S	243 dec[i]	17	0.49 (0.345-0.696)
7b	2,4-$(CH_3O)_2C_6H_3$	197-199	50	4.82 (3.59-6.46)

[a]Melting points are uncorrected; compounds analyzed for C, H and N within ±0.4% of the theoretical values and exhibited ^1H NMR and IR spectra consistent with the structures. [b]The detailed procedures for the use of rat striatal tissue in this test are described in ref. 1b. [c]Maleic acid salt. [d]Di-maleic acid salt. [e]Fumaric acid salt, hemi-hydrate. [f]**4a**: R'=CH_3 (see scheme I). [g]**4b**: R'=C_6H_5 (see scheme I). [h]Hemi-fumaric acid salt, hydrate. [i]Fumaric acid salt.

In summary then, we have prepared a number of 1-substituted analogues of 9-amino-1,2,3,4-tetrahydro-1-acridinol (**1**) through an acid-catalyzed substitution of the benzylic carbinol. These compounds were tested for *in vitro* acetylcholinesterase inhibition activity and compared to **1**. Several of these compounds, particularly the ethyl and propyl ethers, **2b** and **2c**, and the thiophene derivative, **7a**, were better acetylcholinesterase inhibitors that the parent, **1**. There has been much indirect evidence over the past several decades for an accessory, lipophilic binding site in acetylcholinesterase,[9] and the existence of additional sites for lipophilic binding has recently been confirmed in the X-ray structure of acetylcholinesterase from *Torpedo californica* electric organ.[10] While a number of the compounds in this series clearly exceed the steric restraints in the active site binding pocket (compounds **3k-3m**, for example), it may be that **2b**, **2c** and **7a** offer additional possibilities for interaction with a lipophilic binding pocket, while, at the same time, staying within steric limits. We have no explanation for the difference in activity between the alkylethers (**2b-d**) and their respective alkylamines (**3b-d**). It may be that the additional N-H bond of **3(b-d)** functions as a hydrogen bond donor, either intra- or intermolecularly, in a way that contributes to an unfavorable interaction in the binding pocket. Alternatively, it may be that the presence of a basic nitrogen changes the charge distribution of the aminoacridine ring system in a way that causes unfavorable binding interactions with the binding sites of acetylcholinesterase.

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3. The use of freshly prepared ethereal HCl helped to suppress the formation of the elimination product, 9-amino-3,4-dihydroacridine.
4. The position of the double bond as drawn for **4a** and **4b** is supported by the chemical shift of the methine proton (**5**: δ3.97; **4a**: δ4.72; **4b**: δ4.84).
5. The structure of **3b** was verified by independent synthesis: reduction of **6a** with $LiAlH_4/AlCl_3$ gave material identical in all respects to the product isolated from the reduction of **4a**.
6. Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.
7. The position of acylation was confirmed by the coupling of the amide NH to the methine proton on the acyclic ring, which went away upon D_2O exchange.
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