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Synthesis of a hybrid analog of the acetylcholinesterase inhibitors huperzine A and huperzine B

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Abstract—The synthesis of a new hybrid analog of the acetylcholinesterase (AChE) inhibitors huperzine A and B is reported. An intramolecular reductive dicarbonyl coupling was used as a key reaction for constructing the tetracyclic ring system.

Huperzine A (**1**, HA) is a potent, reversible inhibitor of acetylcholinesterase (AChE), the key brain enzyme responsible for the rapid degradation of the neurotransmitter acetylcholine.[1] Because numerous studies have pointed to the existence of a cholinergic deficit in patients suffering from neurodegenerative diseases of the Alzheimer's type, considerable credence has been given to the use of AChE inhibitors in the amelioration of the Alzheimer's symptomatology.[2] In this regard, the long duration of action of huperzine A coupled with its potency, selectivity, and lack of side effects encouraged us and others to explore the structure–activity relationships of this alkaloid.[3] To date, we have been able to identify several analogs of HA that have an activity better than or comparable to that of HA.[4] Huperzine B (**2**, HB), a congener of HA, shows a lower AChE inhibitory potency.[5]

Interestingly, HB exhibits a higher therapeutic index due to its longer duration of action in comparison with HA.[6] However, due to its reduced potency, few biological studies have been reported on this alkaloid.[7] In our efforts to further explore the SAR of these naturally occurring AChE inhibitors, we believed that it would be of interest to examine an analog bearing structural features of both alkaloids, i.e. a hybrid version of HA and HB, namely structure **3** (Fig. 1).

A molecular modeling study of this hybrid analog in complex with AChE revealed that in comparison to the HA complex,[8] the cation-π interaction between the ammonium group and Trp 84 and Phe 330 is altered only slightly by the presence of the ring methylene groups. Additionally, the ring methylenes can engage in hydrophobic interactions with the same residues. Moreover, the hybrid analog **3** is capable of restoring the hydrogen bond interaction with the main chain carbonyl group of His 440 that is present in HA but lacking in HB. From this preliminary modeling study, it appeared that the hybrid structure **3** might show a

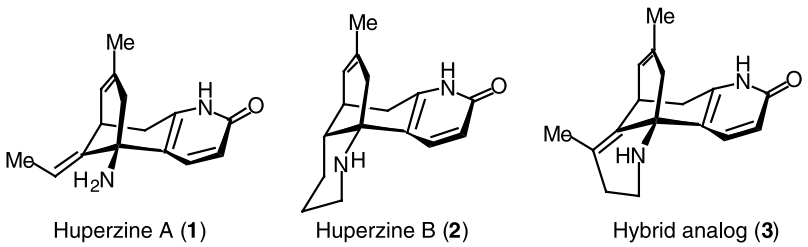

Figure 1. Structures of huperzine A, huperzine B and the hybrid analog.

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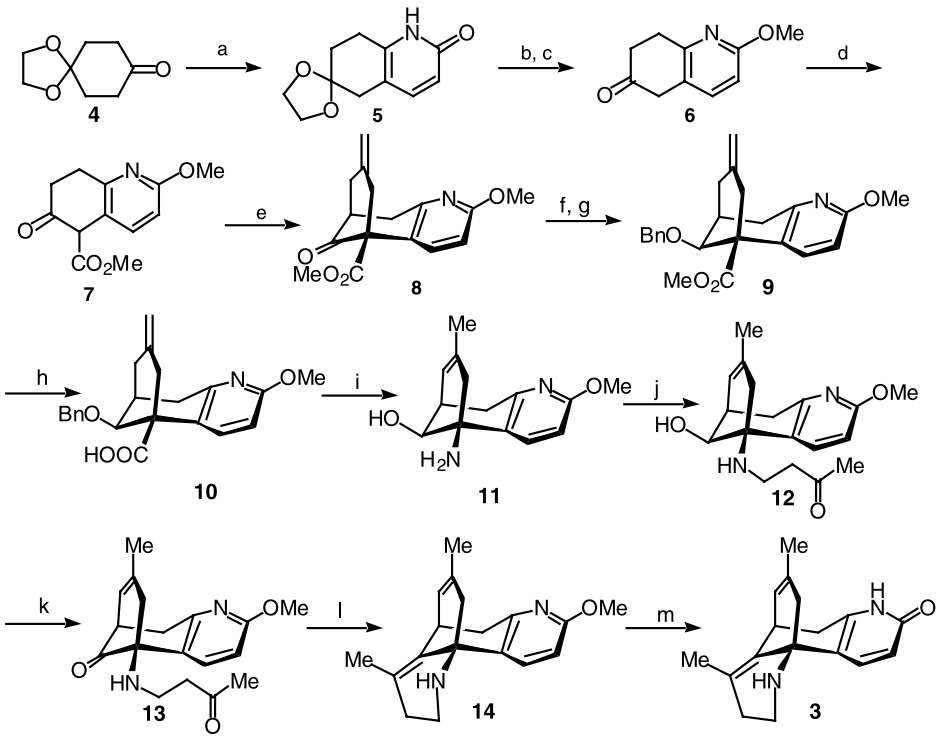
reasonably good AChE inhibitory potency, and it was therefore deemed to be a reasonable candidate for synthesis. In this paper, we describe a method for the synthesis of hybrid analog **3** that is applicable to a broader range of compounds.

The pathway that was followed to assemble the hybrid analog **3** is shown in Scheme 1. The intermediate **8** was obtained using our previously established protocol.[9] Accordingly, the commercially available ketone **4** was treated with ethyl propiolate and ammonia in methanol at 100°C in a pressure reactor for 8 h to give the fused ring pyridone **5** in 65% yield. After conversion of the pyridone to methoxypyridine by *O*-methylation employing Ag_2CO_3/MeI, the ketal was deprotected with acetone/HCl under reflux to obtain compound **6**. Reaction of ketone **6** with 2.2 equiv. of NaH and 4.0 equiv. of dimethyl carbonate yielded the β-ketoester **7** in good yield. The β-ketoester **7** was treated with 2-methylene-1,3-propanediol diacetate, DBU, and a catalytic amount of $Pd(OAc)_2/PPh_3$ to provide the annulation product **8** in 85% yield.

Attempted saponification of ester **8** to the corresponding keto acid led only to isolation of the ring-opened diacid. We therefore converted β-ketoester **8** to the protected hydroxy ester **9** in 78% yield by reduction with $NaBH_4$ in methanol at −78°C followed by benzylation. Attempted hydrolysis of compound **9** with 6N NaOH in methanol resulted only in recovery of starting material. On the other hand, the use of LiI and NaCN in DMF at reflux for 4 h afforded **10** in 70% yield. Next, the carboxylic acid was subjected to Curtius rearrangement, and the resulting intermediate isocyanate was reacted with 8N HCl at 100°C for 10 min to provide amino alcohol **11** with concomitant *O*-debenzylation and double bond isomerization in 42% yield.[10] Compound **11** was then subjected to a Michael addition reaction employing methyl vinyl ketone as an electrophile to afford the amino ketone **12** in 78% yield. Oxidation of compound **12** with PDC in CH_2Cl_2 provided the diketone **13**.[11] Intramolecular reductive coupling of diketone **12** under McMurry reaction conditions[12] using $TiCl_4/Zn$ gave the desired cyclic olefin **14** in 62% yield.[9] The final hybrid structure **3** was obtained in 84% yield from **14** by removal of the protecting group with Me_3SiI in $CHCl_3$ at reflux.[10]

In conclusion, the present work provides a convenient method for preparing structures embodying features of both HA and HB. Preliminary biological studies reveal that racemic **3** is able to inhibit AChE with a potency that is comparable to that of HB. Details of the enzymatic studies of **3** and related analogs will be reported separately.



Scheme 1. *Reagents and conditions*: (a) ethyl propiolate, NH_3/MeOH (approx. 8N), 100°C, 8 h, 65%; (b) Ag_2CO_3, MeI, $CHCl_3$, reflux, 2.5 h, 95%; (c) acetone/3N HCl (1:1), reflux, 3 h, 90%; (d) 2.2 equiv. NaH, 4.0 equiv. $(MeO)_2CO$, THF, reflux, 3.5 h, 87%; (e) $(CH_3CO_2CH_2)_2C{=}CH_2$, $Pd(OAc)_2/PPh_3$ (1:4.1), DBU, 1,4-dioxane, rt, 0.5 h, then reflux, 3.5 h, 85%; (f) $NaBH_4$, MeOH, −78°C, 0.5 h; (g) BnBr, NaH, DMF, 0°C, 5 h, 78% (2 steps); (h) LiI, NaCN, DMF, reflux, 4 h, 70%; (i) $(PhO)_2P(O)N_3$, Et_3N, toluene, reflux, 3 h, then 8N HCl, reflux, 10 min, 42%; (j) $CH_2{=}CHCOCH_3$, Et_3N, CH_2Cl_2, rt, 15 h, 78%; (k) PDC, CH_2Cl_2, rt, 5 h, 71%; (l) $TiCl_4$, Zn, pyridine, THF, reflux, 20 h, 62%; (m) Me_3SiI, $CHCl_3$, reflux, 4 h, then MeOH, reflux, 15 h, 84%.

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10. Spectral data for selected compounds: **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, 1H, *J* 9.0 Hz), 6.59 (d, 1H, *J* 9.0 Hz), 5.37–5.34 (m, 1H), 3.86 (s, 3H), 3.68 (s, 1H), 3.13 (dd, 1H, *J* 5.7, 17.7 Hz), 2.85–2.76 (m, 2H), 2.37 (d, 1H, *J* 17.1 Hz), 1.81 (d, 1H, *J* 17.1 Hz), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7, 152.0, 136.6, 133.2, 131.0, 120.9, 108.5, 73.6, 53.9, 53.3, 42.1, 38.4, 37.4, 22.8; MS (EI) *m*/*z* 246 (M^+, 48%), 231, 215, 190 (100%), 174, 162, 147, 91, 77. **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (d, 1H, *J* 8.6 Hz), 6.59 (d, 1H, *J* 8.6 Hz), 5.44–5.42 (m, 1H), 3.87 (s, 3H), 3.63 (br t, 1H, *J* 6.3 Hz), 3.06–2.93 (m, 2H), 2.90–2.78 (m, 2H), 5.59 (d, 1H, *J* 17.0 Hz), 2.02–1.93 (m, 3H), 1.73 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.49, 153.45, 136.03, 133.46, 133.07, 131.83, 125.06, 122.32, 108.25, 54.22, 53.28, 47.47, 40.45, 39.25, 34.27, 32.39, 29.69, 22.79; MS (EI) *m*/*z* 282 (M^+, 35%), 267, 227, 84, 70, 61, 43 (100%). **3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, 1H, *J* 9.3 Hz), 6.34 (d, 1H, *J* 9.3 Hz), 5.40 (d, *J* 15.4 Hz), 3.59 (br s, 1H), 3.08–2.90 (m, 3H), 2.73 (br d, 1H, *J* 17.8 Hz), 5.59 (br d, 1H, *J* 16.4 Hz), 2.20–1.95 (m, 3H), 1.71 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.81, 143.52, 139.64, 133.71, 124.27, 123.14, 117.45, 54.14, 45.21, 38.52, 35.29, 33.16, 31.12, 29.69, 22.71, 18.35; MS (EI) *m*/*z* 268 (M^+, 52%), 253 (100%), 225, 213, 197, 119, 77.
11. Oxidation using either Dess–Martin periodinane or tetra-*n*-propylammonium perruthenate resulted in complex mixtures of products.
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