Supplementary Information

An Expedient Synthesis of Tacrine-Squaric Hybrids as Potent, Selective and Dual-Binding Cholinesterase Inhibitors

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Table S1. Ensemble docking of the reference ligands and the squarico-tacrine derivatives for the four AChE conformations and single docking against the BuChE

| Compound | Conformation \(^{a}\) | AChE GlideScore / (kcal mol\(^{-1}\)) | BuChE GlideScore\(^{b}\) / (kcal mol\(^{-1}\)) |
|----------|-----------------|---------------------------------|------------------------|
| 3a       | 1ZGC            | −13.6                           | −9.1                   |
| 3b       | 2CKM            | −13.7                           | −7.7                   |
| 3c       | 2CKM            | −13.6                           | −8.0                   |
| 4a       | 2CKM            | −13.4                           | −7.6                   |
| 4b       | 2CKM            | −13.7                           | −7.7                   |
| 4c       | 1ZGC            | −13.1                           | −7.9                   |

\(^{a}\)Docking result against the AChE conformation with the lowest Glide Score in the ensemble docking experiment; \(^{b}\) docking result for the BuChE enzyme (PDB code 5K5E). AChE: acetylcholinesterase; BuChE: butyrylcholinesterase.

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Figure S1. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3a.

Figure S2. $^{13}$C NMR (APT) spectrum (101 MHz, CDCl$_3$) of compound 3a.
Figure S3. 2D COSY NMR of compound 3a.

Figure S4. 2D HSQC NMR of compound 3a.
Figure S5. Expansion (about 1.0 to 4.0 ppm of $^1$H and 10.0 to 50.0 ppm of $^{13}$C) of 2D HSQC NMR of compound 3a.

Figure S6. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3b.
Figure S7. $^{13}$C NMR (APT) spectrum (101 MHz, CDCl$_3$) of compound 3b.

Figure S8. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 3c.
Figure S9. $^{13}$C NMR (APT) spectrum (101 MHz, CDCl$_3$) of compound 3c.

Figure S10. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$) of compound 4a.
Figure S11. $^{13}$C NMR (APT) spectrum (101 MHz, DMSO-$d_6$) of compound 4a.

Figure S12. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$) of compound 4b.
Figure S13. $^{13}$C NMR (APT) spectrum (101 MHz, DMSO-$d_6$) of compound 4b.

Figure S14. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$) of compound 4c.
Figure S15. $^{13}$C NMR (APT) spectrum (101 MHz, DMSO-$d_6$) of compound 4c.