Supplementary material

Novel Phenothiazine/Donepezil-like Hybrids Endowed with Antioxidant Activity for a Multi-Target Approach to the Therapy of Alzheimer's Disease

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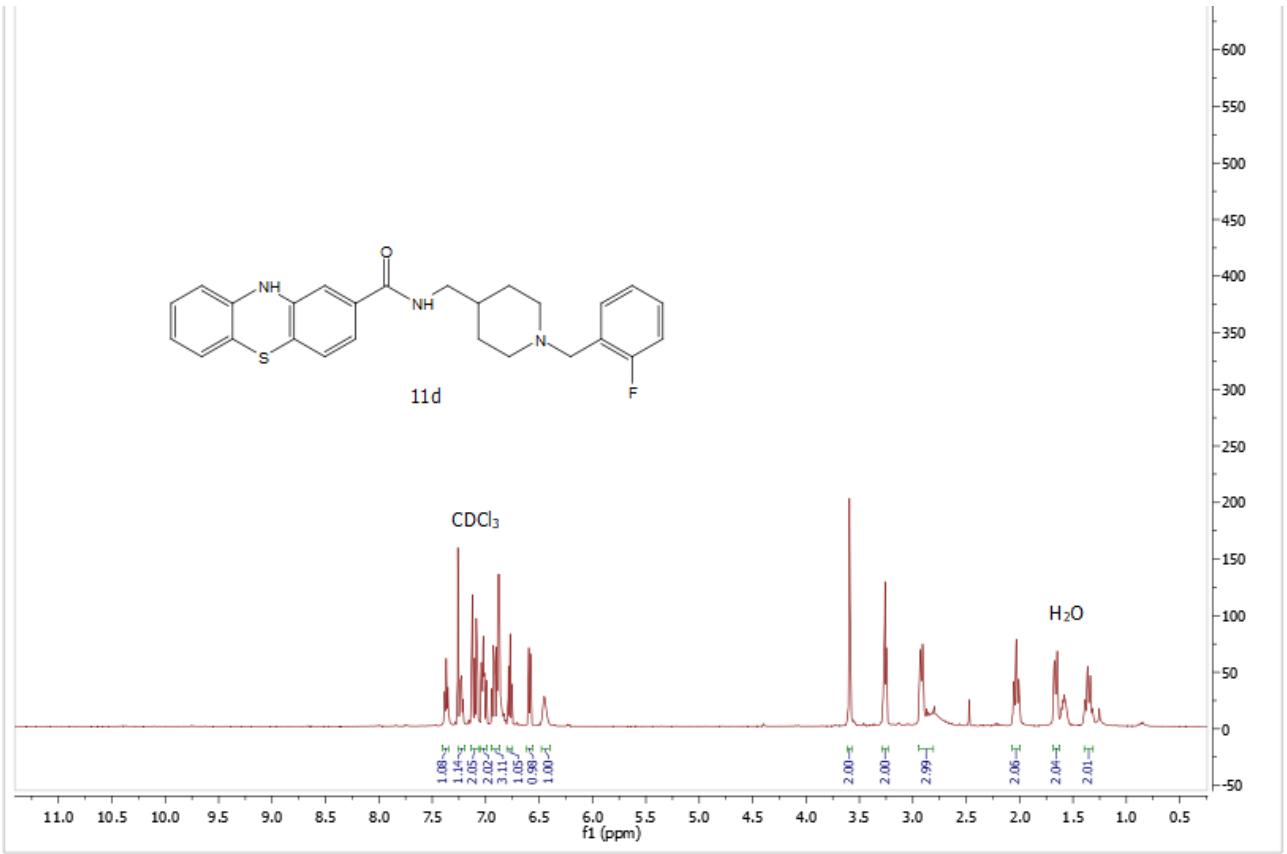
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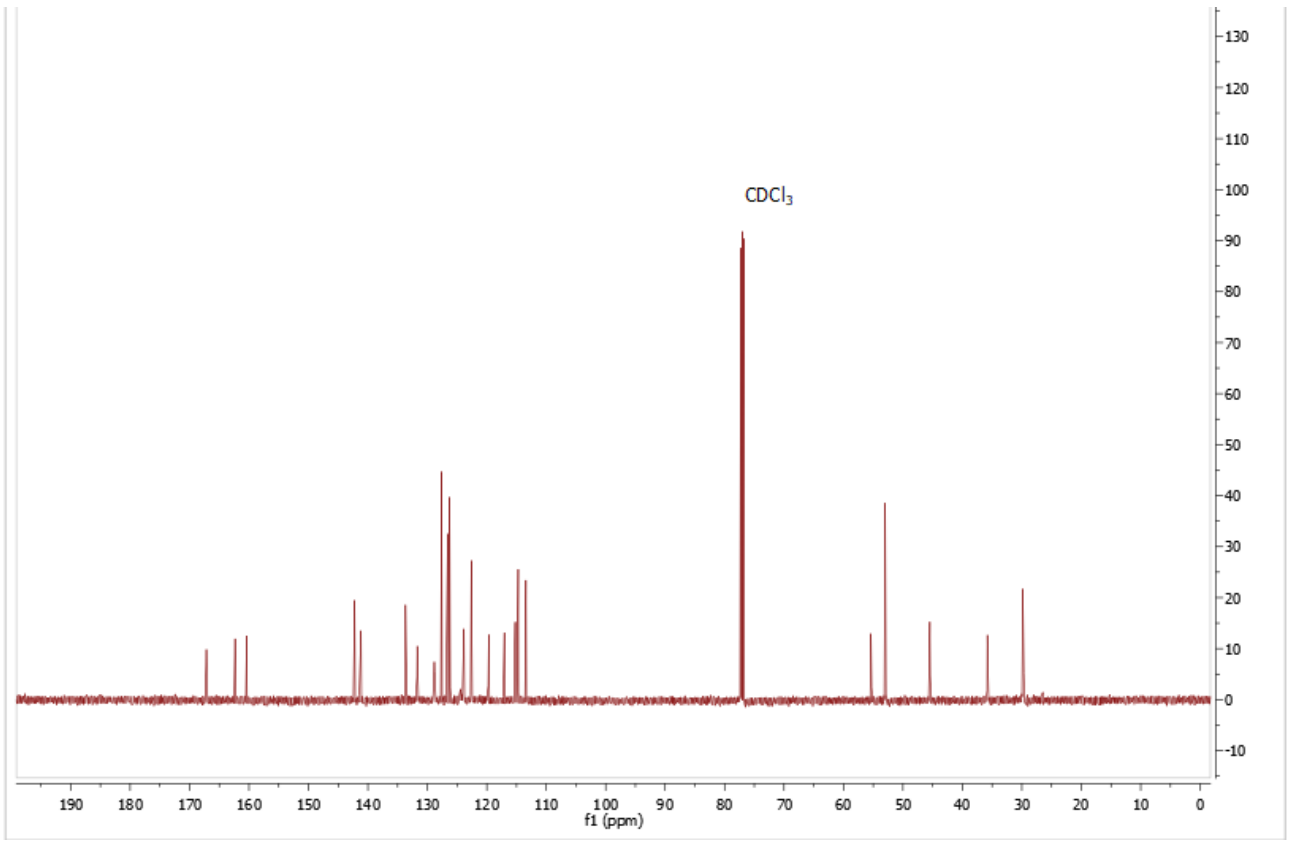
2.01
f1 (ppm)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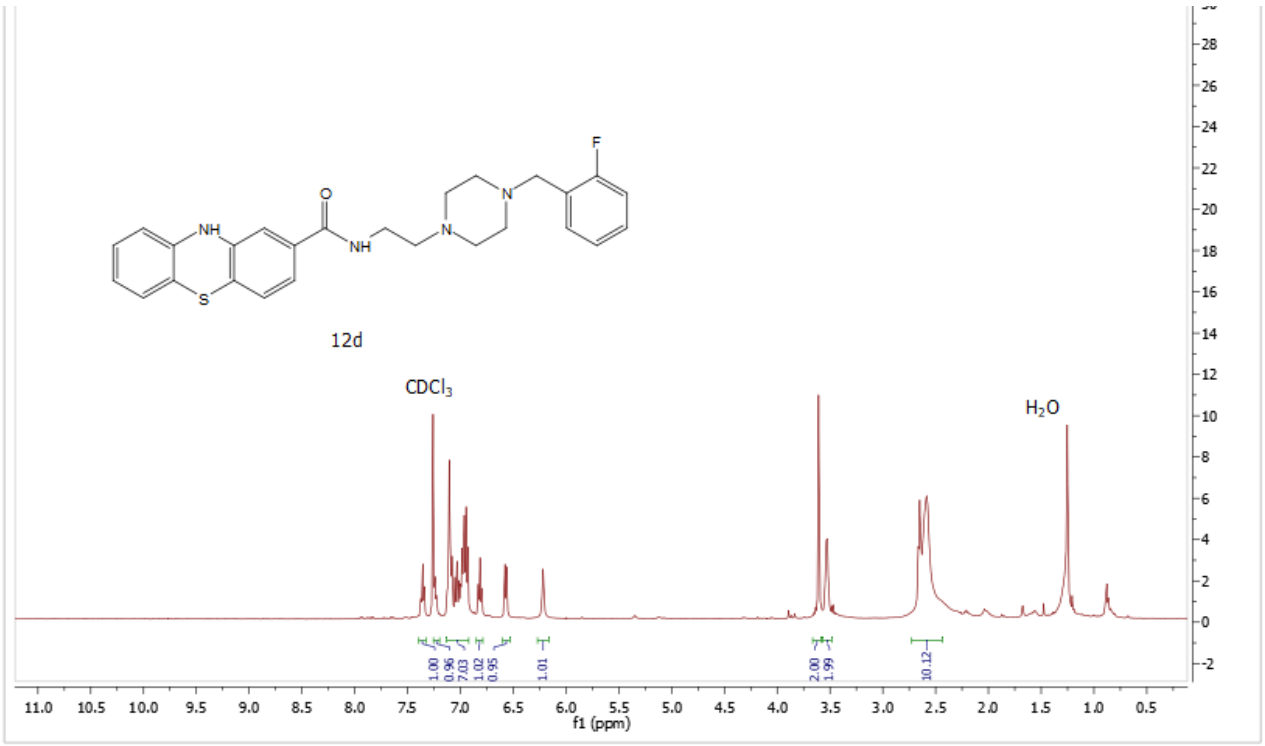
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NH
N
N
S
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2.00
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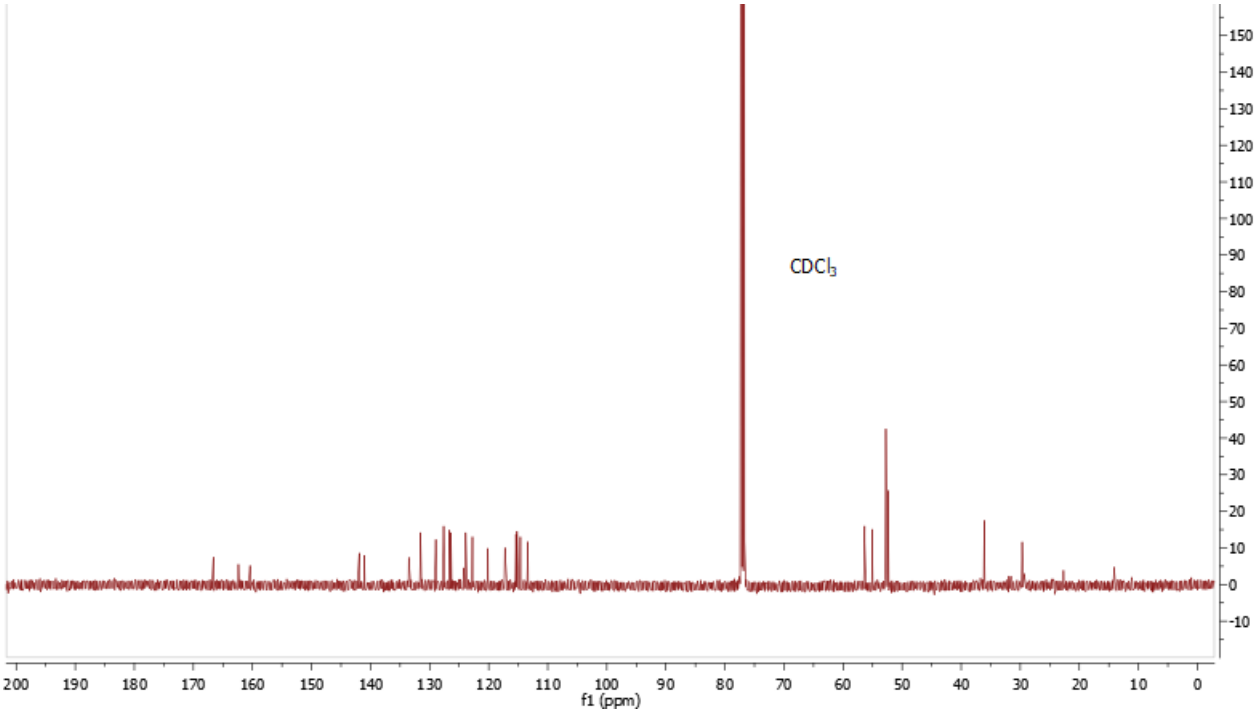
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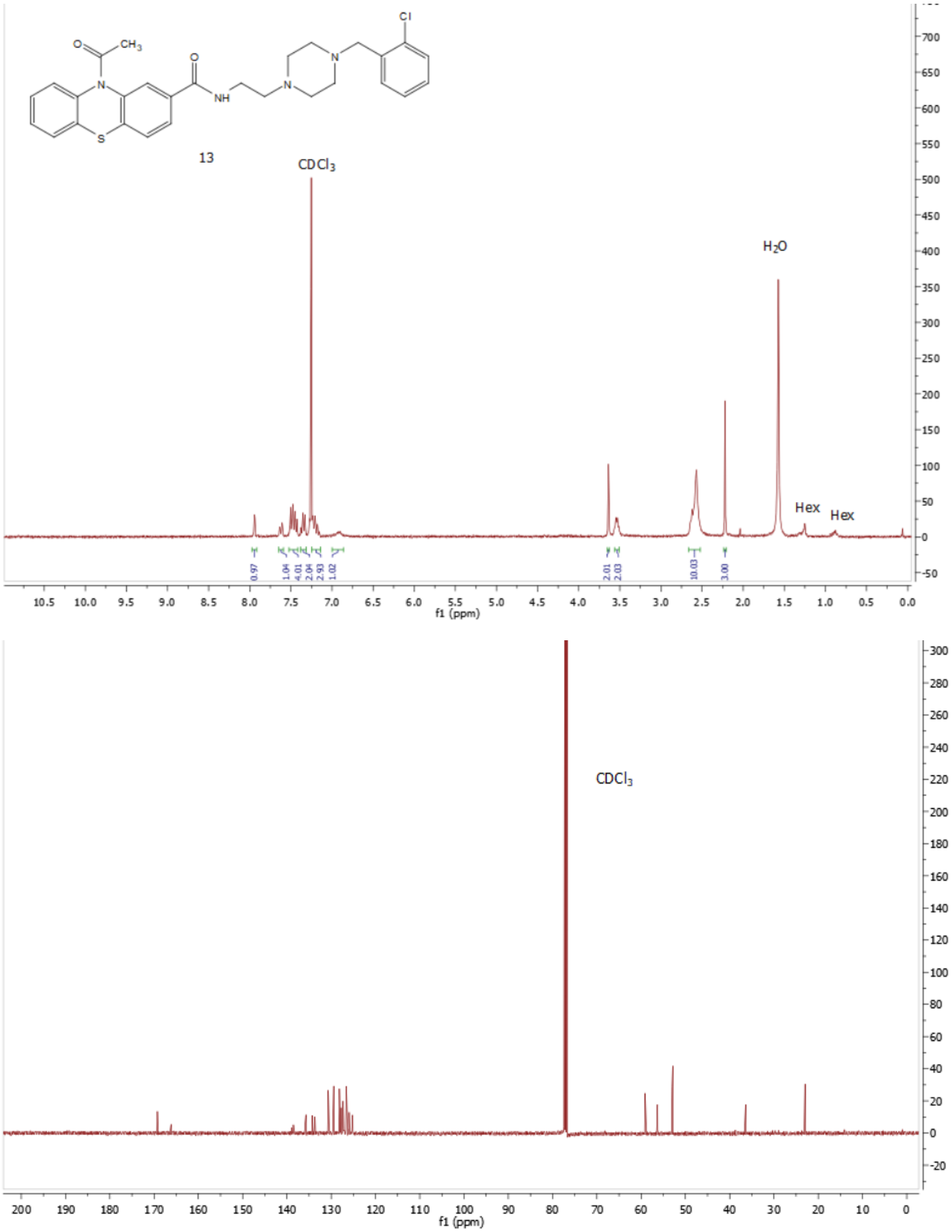

Figure S1 NMR spectra of selected compounds.

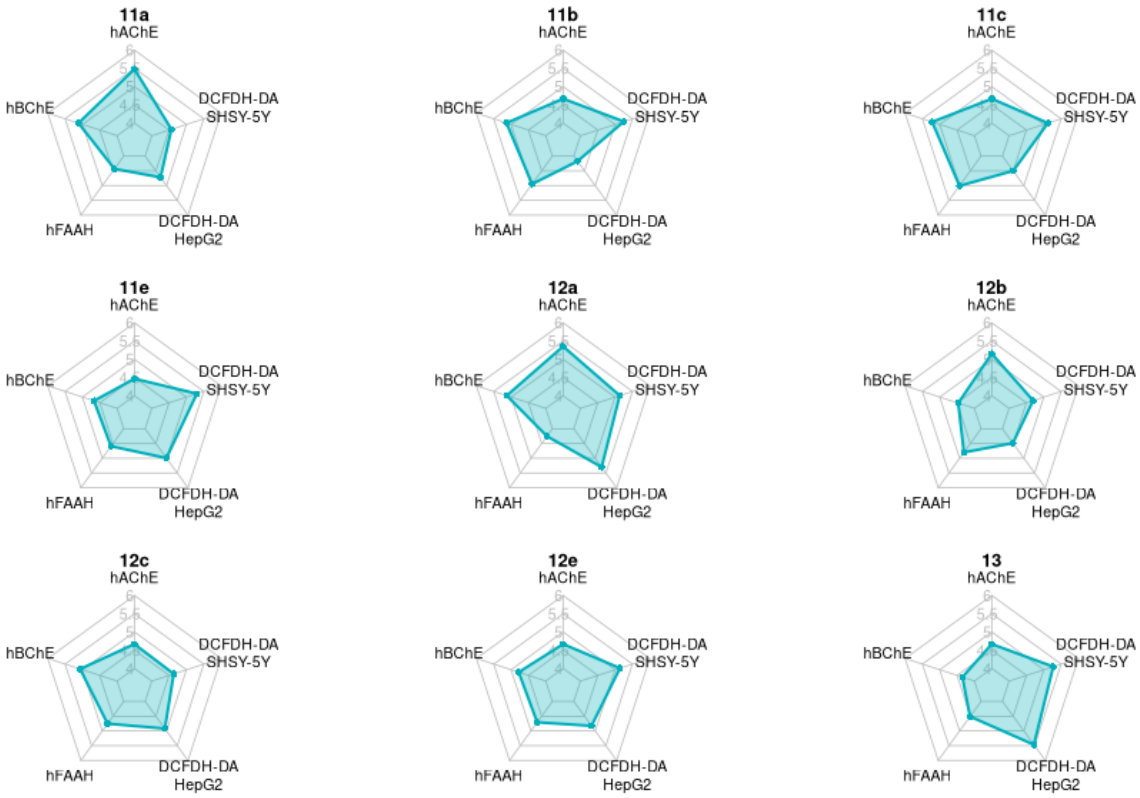

Figure S2. Summary chart representing the biological activities of compounds **11a–c**, **11e**, **12a–c**, **12e** and **13**. Data are reported as pIC_{50}. If IC_{50} was not evaluated the included data was estimated on the basis of the percentage of inhibition at 10 μM.

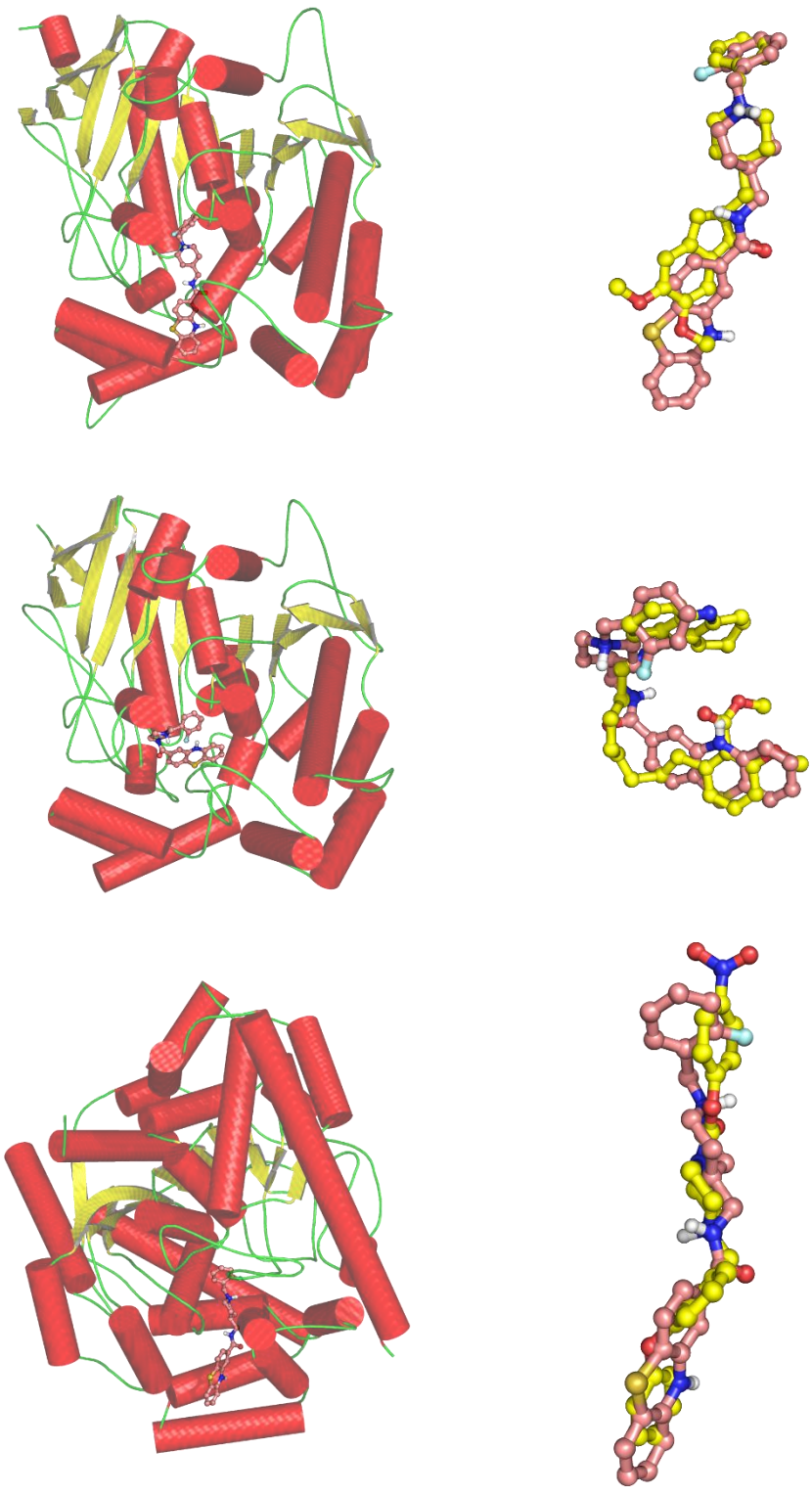

Figure S3 Overlay of the binding mode of **11d** (salmon carbons) and donepezil, TKN and JZL (yellow carbons) to AChE (top), BChE (center) and FAAH (bottom), respectively.

ADME prediction

Table S1. Physicochemical descriptors and ADME properties of tested compounds **11a-11e**, **12a-12e** and **13** calculated by QIKPROP v. 2.5.

Compound	MW[a]	clog *P*[b]	log BB[c]	P_{Caco-2}[d]	Oral Absorp.[e]	CNS act.[f]	Violations Rule of 5[g]	HBD[h]	HBA[i]	PSA[j]
11a	429.58	5.342	-0.015	552	100	+	1	2.0	5.0	53.49
11b	464.02	5.71	0.127	571	100	+	1	2.0	5.0	52.01
11c	443.61	5.58	0.008	573	100	+	1	2.0	5.0	51.72
11d	447.57	5.50	0.070	562	100	+	1	2.0	5.0	52.97
11e	459.60	5.44	-0.086	555	100	+	1	2.0	5.75	61.30
12a	444.59	4.27	0.288	135	100	+	0	2.0	7.0	59.22
12b	479.04	4.61	0.407	134	100	+	0	2.0	7.0	59.21
12c	458.62	4.49	0.288	135	100	+	0	2.0	7.0	59.02
12d	462.58	4.42	0.360	135	100	+	0	2.0	7.0	59.21
12e	474.62	4.36	0.217	135	100	+	0	2.0	7.75	67.12
13	521.08	3.91	0.230	88	100	+	1	1.0	9.50	71.81

[a](Acceptable <500); [b] Predicted octanol/water partition coefficient log *P* (acceptable range − 2.0 to 6.5); [c] Predicted BBB permeability (acceptable range − 3 to 1.2); [d] Predicted Caco-2 cell permeability in nm/s (acceptable range: < 25 is poor and > 500 is great); [e] Percentage of human oral absorption (acceptable range: < 25% is poor and > 80% is high); [f] qualitative CNS activity parameter from (--) inactive, (++) active; [g] Number of violations of Lipinski's rule of five; [h] number of hydrogen bond donors HBD; [i] number of hydrogen bond acceptors HBA; [j] polar surface area PSA.