Table S1. Tacrine – based hybrids with various biological activities, published in 2006 - 2022.

	Tacrin-like moiety	Second moiety	AChE/BChHE, IC_{50}	Biological action	Ref
	Tacrine – Melatonine hybrids				
1 - 13	Tacrine 6-Cl-THA	Melatonin	Human AChE/BChE 0.008 / 7.8 nM (**7**)	Antioxidant activity	[39]
1 - 23	Tacrine 6-Cl-THA	Melatonin	Human AChE/BChE 0.008 / 7.8 nM (**7**) 0.725 / 175 nM (**3**) 0.7 / 250 nM (**6**)	Inhibition of Aβ self-aggregation Neuroprotection from Aβ and damage caused by mitochondrial free radicals – incuced oxidative stress	[40]
24 - 31	Tacrine 7-MEOTA	Melatonin + Ferulic acid	AChE from electric eel, BChE from equine serum 3.62 / 1.25 nM (**28**) 8.37 / 2.91 nM (**26**) Human AChE/ BuChE 1290 / 234 nM (**26**)	Antioxidant activity Neuroprotection	[41]
	Another acrine hybrids with antioxidant activity				
32 - 48	Tacrine 6-Cl-THA	8-Hydroxyquinoline	AChE from bovine, BChE from horse serum 20 / 5 nM (**35**) 75 / 2 nM (**40**) 85 / 6.5 nM (**45**) Human AChE/BChE 5.5 / 20 nM (**35**)	Inhibition of Aβ aggregation, antioxidant activity, metal-chelating properties	[42]
49 - 66	Tacrine	Substituted benzene or pyridine moieties	AChE from electric eel, BChE from equine serum 4.55 / 3.41 nM (**58**)	Antioxidant activity Antiaggregation properties	[43, 44]
67 - 94	Tacrine 6-Cl-THA	4-oxo-4H-chromene	AChE from bovine, BChE from horse serum 75 / 0.18 nM (**70**) 0.035 / 5.0 nM (**88**) 0.775 / 0.038 nM (**74**) Human AChE/BChE 0.035 / 5.0 nM (**88**)	Antioxidant activity Human BACE-1 inhibition	[45]
95 - 100	Tacrine 6-Cl-THA	Caffeic acid	AChE from electric eel, BChE from horse serum 0.3 / 29.5 μM (**99**)	Antioxidant activity Antiaggregation properties Neuroprotection Metal- chelating properties	[46]
101	Tacrine	Silibinin	AChE from electric eel, BChE from equine serum 53.9 / 49.7 nM (**101**)	Low hepatotoxicity	[47, 48]
102 - 110	Tacrine	Ebselen	AChE from electric eel, BChE from equine serum 6.32 / 4.37 nM (**106**) 2.55 / 2.80 nM (**110**)	Antioxidant activity	[49]

111 - 127	Tacrine	b-Carbolines (pyrido[3,4 -b]indole)	AChE from electric eel, BChE from equine serum 21.6 / 39.8 nM (**122**) Human AChE 63.2 ± 2.5 nM (**122**)	Antioxidant activity Metal chelating properties Neuroprotection Antiaggregation properties	[50]
128 - 148	Tacrine 6-Cl-THA 7-MEOTA	Trolox	Human AChE/BChE 0.08 / 0.54 μM (**148**)	Antioxidant activity	[51]
149 - 153	Tacrine	N,N-dimethylated flavonoids	AChE from electric eel, BChE from equine serum 59.61 / 46.16 nM (**152**) 94.56 / 24.67 nM (**153**)	Antioxidant activity Antiaggregation properties Neuroprotection	[52]
154 - 156	Tacrine	Hydroxybenzoyl-pyridone	AChE from electric eel 0.57±0.05 μm (**156**)	Antioxidant activity Metal-chelating properties	[53]
157 - 191	Tacrine	Phenolic acids Ligustrazine	AChE from electric eel, BChE from equine serum 3.9 / 24.3 nM (**165**) 2.6 / 28.6 nM (**175**) Human AChE/BChE 65.2 / 48.8 nM (**165**)	Antioxidant activity Antiaggregation properties Neuroprotection Low hepatotoxicity	[54, 55]
192 - 210	Tacrine 6-Cl-THA	Antioxidant CR- 6	Human AChE/BChE 0.44 / 17.4 nM (**207**) 0.12 / 13.4 nM (**208**) 0.27 /18.3 nM (**209**)	Antioxidant activity Antiaggregation properties Neuroprotection	[56]
211 - 240	Tacrine	Chalkone	BChE from equine serum 0.372 / 5.328 μM (**225**) 0.801 μM/- (**226**) 0.327 μM /- (**216**)	Neuroprotection	[57]
241 - 249	Huprine Y	Capsaicin	Human AChE/BChE 0.77 / 30.6 nM (**243**) 1.06 / 7.3 nM (**249**)	BACE-1 inhibition Antioxidant activity	[58]
Tacrine - Ferulic acid hybrids					
250 - 254	Tacrine	Ferulic acid	AChE from electric eel, BChE from equine serum 7.6 / 5.9 nM (**252**) 4.4 / 6.7 nM (**253**)	Antioxidant activity	[59, 60]
255	Tacrine	Ferulic acid	-	Antiaggregation properties Antioxidant activity	[61]
256 - 276	Tacrine	Ferulic acid + NO-donors	AChE from electric eel, BChE from equine serum 10.9 / 17.1 nM (**262**)	Vascular relaxation (NO - donating properties)	[62]
277 - 281	Tacrine	Ferulic acid	52.7 / 215.4 nM (**279**) 61.7 / 109.6 nM (**280**)	Neuroprotection Metal-chelating properties	[63]
282 - 294	Tacrine	Ferulic acid	AChE from electric eel, BChE from horse serum 49.5 / 69.4 nM (**285**) 37.0 / 101.4 nM (**288**)	Antiaggregation properties	[64]
Tacrine hybrids with NO-donating molecules					

295 - 309	Tacrine	NO-donating groups	AChE from electric eel, BChE from equine serum 28.2 / 13.5 nM (**295**) 5.6 / 9.9 nM (**303**) 226.0 / 7.3 nM (**308**)	Vessel relaxant activity Hepatoprotective effects	[65]
310 - 317	Tacrine	NO-donating groups	AChE from electric eel, BChE from equine serum 9.1 / 7.3 nM (**310**) 7.7 / 17.0 nM (**314**)	-	[66]
Tacrine – phenotiazine hybrids					
318 - 320	Tacrine	Phenothiazine	AChE from rat brain homogenate 89 nM / - (**318**)	Reduce P-Tau accumulation Binding with Aβ fibrils	[67]
321 - 356	Tacrine 6-Cl-THA 7-MEOTA	Phenothiazine	Human AChE/BChE 2040 / 15 nM (**321**) 8 / 190 nM (**332**)	Inhibition of Self-Induced $A\beta_{1-42}$ Aggregation Inhibition of τ(306−336) peptide aggregation	[68]
Tacrine – benzotiazole/benzofuran hybrids					
357 - 364	Tacrine	Benzotiazole Benzofurane	AChE from electric eel, BChE from equine serum 0.017 / 0.122 μM (**359**)	Antiaggegating properties	[69, 70]
365 - 369	Tacrine	Benzotiazole	AChE from electric eel 0.34 / - μM (**365**)	Antiaggegating properties (**366**) *Ex vivo* imrovement cell viability in cells treated with $A\beta_{42}$ peptide (**368, 369**)	[70]
370 - 395	Tacrine	Benzofuran	Human AChE/BChE 0.86 / 2.18 nM (**386**)	Antiaggegating properties Inhibition of hBACE-1 activity	[71]
396 - 401	Tacrine 6-Cl-THA	Benzotiazole	AChE from electric eel 0.06 μM (**397**)	Antiaggegating properties Neuroprotective effects	[72]
402 - 413	Tacrine 6-Cl-THA	Benzofuran	AChE from Electric eel 0.12 μM (**404**) 0.13 μM (**408**) 0.13 μM (**412**)	Antiaggegating properties Neuroprotection	[73]
414 - 438	Tacrine 6-Cl-THA 7-MEOTA	Benzotiazole	Human AChE/BChE 1727 / 8 nM (**422**) 4 / 799 nM (**428**) 55 / 41 nM (**429**) 18 / 4657 nM (**436**)	Antiaggregation properties Low hepatotoxicity	[74]
Tacrine hybrids with NSAIDS					
439 - 443	Tacrine	Flurbiprofen	AChE from electric eel, BChE from equine serum 19.3 / 3.7 nM (**442**) 34.5 / 2.1 nM (**443**)	Inhibition of of amyloid-b formation	[75]
444 - 455	Tacrine	Flurbiprofen + NO-donors	AChE from electric eel, BChE from equine serum 4309.5 / 7.6 nM (**447**) 1456.4 / 3.9 nM (**455**)	Vasorelaxation effect	[76]
456 - 463	Tacrine	Flurbiprofen + NO-donors	AChE from electric eel, BChE from equine serum	Inhibition of of amyloid-b formation Vascular relaxation	[77]

			9.1 / 2.5 nM (**456**) 12.5 / 1.0 nM (**460**)		
464 - 471	Tacrine	Indometacine	AChE from electric eel, BChE from equine serum 62 / 30 nM (**467**) 99 / 6 nM (**469**) 10 / 57 nM (**471**)	Antioxidant activity Low hepatotoxicity	[78]
472 - 475	Tacrine	Ibuprofen	AChE from electric eel 47.25 nM / - (**475**) 39.16 nM (**475**, in the presence of H_2O_2)	Neuron-protective effects in the presence of H_2O_2. H_2O_2 – responsible drug release Inhibiting of proinflammatory cytokines (TNF-α and IL- 1β) Regulating apoptosis related proteins (Bax, Bcl-2 and cleaved caspase- 3)	[79]
Tacrine-Hupyridone hybrids					
476	Tacrine	Hupyridone	AChE from rat serum, BChE rat cortex homogenate 8.8 / 81.5 nM (**476**)	Low hepatotoxicity	[80 - 82]
Tacrine – Donepezil hybrids					
477 - 486	Tacrine 6-Cl-THA	Donepezil	AChE/AChE/BChE Bovine/human/human 0.09 / 0.27 / 66.3 nM (**480**)	Antiaggregating properties	[83, 84]
Tacrine-TPPU hybrids					
487 - 490	6-Cl-THA Huprine	TPPU, a epoxide hydrolase inhibitor	Human AChE/BChE 12.9 / 179 nM (**489**)	-	[85]
Tacrine - Huprine hybrids					
491 - 502	Tacrine	Huprine	Human AChE/BChE 0.89/24.6 nM (**491**) 0.42/44.2 nM (**493**) 0.74/75.2 nM (**497**) 0.31/51.3 nM (**499**)	Antiaggregating properties	[86]
Tacrine - Bifendate hybrids					
503 – 507	Tacrine	Bifendate	AChE from electric eel BChE from equine serum 615.51 / 4.02 nM (**504**) 27.32 / 8.63 nM (**506**) hAChE/hBChE (for 100 nM) 73.25 / 3.1% (**504**) 60.44 / 69.67% (**506**)	Antiaggreating properties Low hepatotoxicity	[87]
Tacrine hybrids with HDAC inhibitors					
508- 535	Tacrine 6-Cl-THA	Hydroxamates, HDAC inhibitors	AChE from electric eel, BChE from equine serum 13.00 / 0.58 nM (**512**) 0.12 / 361 nM (**517**) 0.26 / 140.06 nM (**535**)	Antioxidant activity Metal – chelating properties Inhibition ob Aβ aggregation Dissolving of pre-formed Aβ aggregates	[88]
Tactine hybrids with thio derivatives					

536 - 541	Tacrine 6-Cl-THA	Thiol group	AChE from electric eel, BChE from equine serum 7.37 / 7.04 (pIC_{50}) (**540**)	LTP enhancement Neuroprotective activity Low hepatotoxicity	[89]
542-553	Tacrine 6-Cl-THA	S-allylcysteine S-propargylcysteine	AChE from Torpedo californica 0.30 μm (**545**)	Neuroprotection	[90]
554	Tacrine	H_2S donor	-	AChE inhibition in the serum and hippocampus of AD mice Antiinflammatory activity	[91]
Tacrine hybrids with fluorescent probes					
555 - 564	6-Cl-THA	Phenylpyrano[3,2 -c]quinoline	*AChE from bovine human AChE/BChE 10.4* / 7.03 / 331 nM (**557**)	Inhibitors of $A\beta_{1-42}$ self-aggregation. BACE-1 inhibition (681)	[92]
565 - 568	6-Cl-THA	Tetrahydrobenzo[h][1,6]naphthyridine	Human AChE/BChE 0.006 / 120 nM (**565**)	Antiaggregating properties	[93]
569-591	Tacrine	Lophine	AChE from mice brain Human BChE 5.87 / 108.97 nM (**570**) n.a. / 7.10 nM (**581**)	-	[94]
Tacrine hybrids with Ca^{2+} channel blocker					
592 - 600	Tacrine	Nimodipine	*AChE from electric eel Human AChE/BChE *45 / 105/ 100000 nM (**600**)	Block of Ca^{2+} channels Neuroprotection	[95, 96]
601 - 605	Tacrine	Nimodipine	AChE from electric eel, *Human AChE 45 / 105* (**S-600**)	Ca^{2+} channel blockade Inhibition of AChE-induced $A\beta_{40}$ aggregation	[97]
606	Tacrine	Dihydropyridine	-	Reduction of phosphorylated tau levels, inhibition of the generation and release of Aβ in cells	[98]
607-618	Tacrine	Dihydropyirimidine-thiones	Human AChE/BChE 0.0373 / 1.27 μm (**617**) 5.28 / 0.372 μm (**616**)	Ca^{2+} channel blockade Weak inhibition of $A\beta_{40}$ self-aggregation	[99]
619 - 622	Tacrine 6-Cl-THA Huprine	Levetiracetam	Human AChE/BChE 3.1 / 135 nM (**±620**) 4.2 / 232 nM (**SSR-621**)	Anti-aggregating activity ($A\beta_{42}$ and tau) Reduction of AChE activity in brain (*ex vivo* test) Reduction cortical amyloid burden and neuroinflammation around Aβ plaques were significantly reduced (*ex vivo* test after therapy)	[100]
Tacrine hybrids with serotonin receptors antagonists					
623 - 628	Tacrine	1 -(phenylsulfonyl)- 4 -(piperazin- 1 -yl)- 1H-indole	AChE from electric eel, BChE from equine serum; human *AChE/**BuChE; 7.1 / 12.4 / 1.3* nm (**628**) 45.9 / 8.2 / 12.9*/ 29.7** nm (**626**)	$5HT_6$ in agonists	[101]

629-638	Tacrine	1 -(3 -(benzyloxy)- 2 -methylphenyl)piperazine 1 -benzyl- 4 -(piperazin- 1 -yl)- 1H-indole	AChE from electric eel, *human AChE, BChE from equine serum 0.005 / 0.003 / 0.024 μM (**634**)	Low hepatotoxicity Antiaggregating properties	[102]
639 - 668	Tacrine	Vilazodone	AChE from rat cortex, BChE from rat serum 3.319 / 15.79 μm (**643**)	Low hepatotoxicity Low cardiotoxocity 5 -HT1A agonist 5 -HT reuptake inhibitor	[103]
Tacrine hybrids with modulator of muscarinic receptors					
669 - 674	Tacrine 6-Cl-THA	Gallamine	*AChE from electric eel Human AChE/BChE 0.467*/ 7.61/ 1.50 nM (**669**) 28.9*/ 23.2 / 2.40 nM (**673**)	Allosteric M2 receptor modulation	[104]
675 - 690	Tacrine	Xanomeline	AChE from electric eel, BChE from equine serum 8.18 / 8.29 (pIC_{50}) (**687**) 8.21 / 8.23 (pIC50) (**690**)	Enhanced M1 allosteric affinity	[105]
691 - 711	Tacrine 6-Cl-THA 7-MEOTA	Benzylquinolone carboxylic acid (BQCA)	Human AChE/BChE 1.5 / 49.3 μM (**696**) 0.13 / 0.67 μM (**699**) 42 / 372 nM (**706**)	Muscarinic receptors antagonists	[106]
712 - 717	Tacrine	Xanomeline	AChE from electric eel pIC_{50} = 9.55 (**715**)	-	[107]
Tacrine hybrids with cannabinoid CB1 receptor antagonists					
718 - 721	Tacrine	Cannabinoid CB1 receptor antagonists	Human AChE pIC_{50} = 6.5 (**720**)	CB1 receptor antagonists	[108]
Tacrine hybrids with modulator of NMDA receptors					
722 - 728	7 -MEOTA	Adamantylamine	Human AChE/BChE 0.47 / 0.11 μM (**725**)	-	[109]
729 - 732	6-Cl-THA	Benzohomoadamantane	Human AChE/BChE 0.3 / 0.5 nM (**731**)	NMDA inhibition	[110]
Tacrine hybrids with modulator of opioid receptors					
733 - 747	Tacrine 6-Cl-THA	Tianeptine	AChE from rat brain homogenate Human BChE 6.79 / 52.44 nM (**736**) 156.19 / 3.59 nM (**737**)	Reduction of the *in vitro* basal secretion of S100B	[111]
Tacrine hybrids with MAO inhubitors					
748 - 760	Tacrine 6-Cl-THA	Selegiline	AChE from electric eel, BChE from equine serum 22.6 / 9.37 nM (**754**)	MAO-A, MAO-B inhibition	[112]
761 - 780	Tacrine	Coumarin	AChE from electric eel, BChE from equine serum 17.70 / 38.00 nM (**766**) 33.63 / 80.72 nM (**773**)	MAO-B selective inhibition Low neurotoxocity	[113]
Tacrine hybrids with natural products					

781 - 800	Tacrine	Coumarin	AChE from electric eel, BChE from equine serum 0.092 / 0.234 μM (**786**) 0.398 / 0.099 μM (**790**)	Metal-chelating ability Antiaggregating properties Low neurotoxicity,	[114]
801-805	Tacrine	Coumarin	Human AChE/BChE 0.0154 / 0.328 μM (**803**)	-	[115]
806 - 826	Tacrine	Flavonoid	AChE from electric eel, BChE from equine serum 8.4 / 35.0 nM (**825**) 10.3 / 25.8 nM (**826**)	Metal-chelating ability Antiaggregating properties Low neurotoxicity	[116]
827 - 834	Huprine Y	Rhein	Human AChE/BChE 1.07 / 950 nM (**±827**) 1.52 / 1070 nM (**±828**)	Antiaggregating propertiesd BACE-1 inhibition Prevent the loss of synaptic proteins in hippocampal slices (*ex vivo*)	[117]
835 - 837	Tacrine	Carbazole	AChE from electric eel; human BChE 0.48 / 52.14 μM (**835**)	Neuroprotection from ROS-or Aβ-induced toxicity	[118]
838 - 844	6-Cl-THA	Scutellarin	Human AChE/BChE 1.63 / 1210 nM (**838**) 1.9 / 174 nM (**839**)	-	[119]
845 – 852	Tacrin 6-Cl-THA 7-MEOTA	Resveratrol	Human AChE/BChE 0.8 / n.a. μM (**845**)	Antiaggreating properties Antiinflammatory activity	[120]
853 – 861	Tacrine	Carbohydrates	AChE from mice brain extract, BChE from mice blood serum 84.4 / 11.7 nM (**854**) 2.2 / 4.93 nM (**857**)	-	[121]
862 - 882	Tacrine 6-Cl-THA 7-MEOTA	Tryptophan	Human AChE/BChE 6.3 / 9.1 nM (**S-873**)	Inhibition of $A\beta_{42}$-self-aggregation	[122]
883 - 889	Tacrine	Indole	AChE from electric eel, BChE from equine serum 0.173 / 0.066 μM (**887**)	-	[123]
890 - 902	Tacrine 6-Cl-THA	Anacardic acid, cardanol, and cardol from cashew nutshell liquid	Human AChE/BChE 2.54 / 0.265 nM (**891**) 20.8 / 0.0352 nM (**890**) 17.0 / 0.177 nM (**897**)	Antiinflammatory activity Neuroprotection (**890, 891**) at 0.01 μM Low hepatotoxicity Low neurotoxicity	[124]
		Tacrine hybrids with organic scaffolds			
903 - 917	Tacrin	Trimethoxybenzene	Human AChE/BChE 5.08 / 1.38 nM (**912**) 59.00 / 0.139 nM (**916**)	-	[125]
918 - 921	Tacrine	Tiofen-based photoswitcher	AChE from electric eel, BChE from equine serum *Human AChE 4.3 / 5.9 / 49.6* nM (open) (**921**) 1.8 / 7.2 / 19.1* nM (closed) (**921**)	Inhibition of AChE-induced Aβ aggergation	[126]
922 - 939	Tacrine 6-Cl-THA 7-MEOTA	Quinone	Human AChE/BChE 1.93 / 256 nM (**926**) 0.72 / 542 nM (**930**)	Antiaggregating properties Neuroprotection from ROS-or Aβ-induced toxicity	[127]

				Low hepatotoxicity	
940 - 944	Tacrine 6-Cl-THA	Propargylamine	AChE from electric eel, BChE from equine serum 11.2 / 83.5 nM (**941**) Human AChE 9.4 ± 0.7 (**941**)	Low hepatotoxicity Low neurotoxicity	[128]
945 - 953	7-MEOTA	p-Anisidine	Human AChE/BChE 1.36 / 10.2 μm (**951**) 1.35 / 10.9 μm (**955**)	-	[129]
959 - 973	Tacrine 6-Cl-THA	Triazole	AChE from electric eel, BChE from equine serum 2.00 / 0.055 μM (**968**) 0.521 / 1.853 μM (**970**)	-	[130]
974 - 989	Tacrine	Isatine	AChE from electric eel, BChE from equine serum 57.85 / 0.11 nM (**977**) 0.42 / 0.57 nM (**984**) 0.62 / 3.52 nM (**986**)	Inhibition of self-induced $A\beta_{1-40}$ aggregation Metal-chelating properties	[131]
990 - 1039	Tacrine 6-Cl-THA 7-MEOTA	Pyrimidone	AChE from the cerebral cortex of a mouse 51.1 / - nM (**1035**)	GSK-3β inhibition Regulation of the tau protein pathway in SH-SY5Y-derived neurons Neuroprotection	[132]
1040 - 1052	Tacrine	Carbamate	Human AChE/BChE 22.15 / 16.96 nM (**1050**)	-	[133]
1053 - 1066	Tacrine	Phosphorus group	AChE from electric eel, BChE from equine serum 6.11 / 12.86 nM (**1055**)	Lower hepatotoxicity *in vitro*	[134]

Table S2. Summary of in vivo study of anti-AD properties of the hybrids.

Hybrid	Tacrin	Second moiety	Mode of injection, drug dose	*In vivo* effects	Ref.
101	Tacrine	Silibinin	i.p. 2 μmol/100 g	Low hepatotoxicity *in vivo* Cognitive improvement in scopolamine-injected mice, similar to that of tacrine	[47, 48]
165	Tacrine	Phenolic acids Ligustrazine	i.g. 1.27 mg/100 daily 4 weeks	Low hepatotoxicity *in vivo* After 4 weeks of intragastric administration, cognitive function and synaptic plasticity were significantly improved and Aβ plaques were decreased in the APP/PS1 mice	[55]
193, 197	6-Cl-THA	Antioxidant CR-6	i.p. 10 mg/kg/day 4 weeks	Positive tendencies in improving cognition, oxidative stress, and amyloid pathology on wild-type and APP/PS1 mice	[56]
216, 225, 226	Tacrine	Chalkone	5 mg/kg/day 1 week	*In vivo* behavior studies showed a cognitive improvement in mice pretreated with scopolamine. Recovery of scopolamine-induced glutathione depletion, in-brain malondialdehyde (MDA) level decrease	[57]

249	Huprine Y	Capsaicin	i.p. 2 mg/kg 3 times/week 4 weeks	Significant enhance of learning and memory in 10-month-old APP/PS1 mice. Decrease of the $A\beta_{42}/A\beta_{40}$ ratio in hippocampus. Improvement in basal synaptic efficacy, and significant reduction of hippocampal oxidative stress and neuroinflammation	[58]
254	Tacrine	Ferulic acid	i.p. 1.22 mg/100g	No improvement in scopolamine-injected mice (compd. amplifies scopolamine action)	[60]
255	Tacrine	Ferulic acid	i.g. 2 mg/kg/day, 20 mg/kg/day 3 weeks	Cognitive impairment, increase of ChAT activity and decreases AChE activity in Aβ icv mice	[61]
262	Tacrine	Ferulic acid + NO-donors	i.d. Behavioral. studies 1.978 μmol/100 g Hepatotoxicity study 11.86 μmol/100 g	Cognitive improvement in scopolamine-injected mice Low hepatotoxicity *in vivo*	[62]
285, 288	Tacrine	Ferulic acid	i.g. 30 mg/kg/day	Cognition improving in scopolamine-injected adult ICR mice Low hepatotoxocity *in vivo*	[64]
295, 303, 310	Tacrine	NO-donating groups	i.p. Hepatotoxicity study 5.93 μmol/ 100 g Behavioral studies 1.978 μmol/100 g	Much less hepatotoxicity compared to tacrine (**295, 303**). Cognition improving in scopolamine-injected mice	[66]
332	6-Cl-THA	Phenothiazine	i.p. 14 mg/kg	Non-toxic in doses 14 mg/kg *In vivo* CNS availability, relatively low elimination from the brain tissue	[68]
386	Tacrine	Benzofuran	Oral intake Behavioral studies 20 μmol/kg/day 10 days Hepatotoxicity equimolar to 30 mg/kg of tacrine	Low hepatotoxicity *in vivo* Cognitive improvements in ICR mice	[71]
436	6-Cl-THA	Benzotiazole	i.p. 2 mg/kg/day 4 days	Mild cognitive improvements	[74]
442, 456	Tacrine	Flurbiprofen + NO-donors	i.d. Behavioral studies 1.978 μmol/100 g Hepatotoxicity 11.86 μmol/100 g	Cognition improving activity in ICR mice Low hepatotoxicity *in vivo* (Hybrid **456** showed the lowest toxicity)	[77]
475	Tacrine	Ibuprofen	I.p. 0.9 mg/100g/day 4 weeks	Improving spatial memory of Aβ-induced AD model rats	[79]
476	Tacrine	Hupyridone	I.p. 0.36 μmol/kg 0.72 μmol/kg every third day, 28 weeks	Attenuates scopolamine-induced impairments of cognition in APP/PS1 mice. At high concentrations (10 μM) did not induce obvious hepatotoxicity	[80]
489	6-Cl-THA	TPPU, an epoxide hydrolase inhibitor	Oral intake 2 mg/kg/day 4 weeks	Significant amelioration in short-term and long-term working memory of SAMP8 mice Reduction of neuroinflammation lack of neurotoxicity	[85]
506	Tacrine	Bifendate	Oral intake Behavioral studies 20 μmol/kg/day 4 days Hepatotoxicity studies i.g. 106 mg/kg	Low hepatotoxicity *in vivo* Ameliorated the cognition impairment in the scopolamine treated ICR mice (8–10 weeks old).	[87]
536, 537	Tacrine	Thiol group	i.c.v.	Enhance of the hippocampal LTP *in vivo*	[89]

541	6-Cl-THA		Synaptic plasticity study 50 μM (541) Hepatotoxicity 6 μmol/100 g (536 - 537)	Low hepatotoxicity *in vivo*	
542	Tacrine	H_2S donor	i.p. 15 mmol/kg/day 20 days	Improvment of cognitive and locomotor activity in AD mice (therapeutic effect of the lower dose was only partial) Low hepatotoxocity *in vivo*	[90]
598, 605	Tacrine 6-Cl-THA	Huprine	i.p. 10 μmol/kg	*Ex vivo* inhibition of AChE from OF1 mice	[96],[97]
619, 622	Tacrine Huprine	Levetiracetam	Inhibition of AChE i.p. 2.5 mg/kg (**619**) 5 mg/kg (**621**) Efficacy Studies i.p. 5 mg/kg/day 4 weeks	Inhibition of C57BL6J mouse brain AChE 10 min after administration A reduction of number of epileptic seizures and reduction of Aβ burden in the cortex of APP/PS1 mice (**621**) Cognitive improvement in transgenic 5-month-old APP/PS1 mice (**619, 621**).	[100]
626	Tacrine	1 - (phenylsulfonyl)- 4 -(piperazin- 1 - yl)- 1H-indole	i.p. 0.3 - 10.0 mg/kg	Cognitive improvementt in scopolamine-injected mice. Dose-dependent reduction of scolopamine-induced hyperlocomotion	[101]
643	Tacrine	Vilazodone	Oral intake 30 mg/kg	Behaviour impaimeint in scopalomine-treated mice Alleviation of the depressive symptom in tail suspension test	[103]
696	Tacrine	Xanomeline	I.p. 2 μmol/100 g	Significantly enhance scopolamine action	[106]
831	Huprine Y	Rhein	Determination of Synaptic Protein Levels i.v. 10 μM Aβ Lowering Effect i.p. 2 mg/kg 3 times per week for 4 weeks	*Ex vivo* reduction of Aβ levels of in hippocam (2-month-old C57bl6 mice) An increase of APP levels in brain of 10 - month-old APP/PS1 mice	[117]
835	Tacrine	Carbazole	i.p. 25 μmol/kg 50 μmol/kg	Improve memory deficit in mice induced by scopolamine	[118]
(S)-873	6-Cl-THA	Tryptophan	Behavioral studies i.c.v 10 nM 100 nM Toxicity study i.p. 70 mg/kg	Pro-cognitive potential in a scopolamine-induced cognitive deficit rat model (9 - 12 weeks old wistar rats)	[122]
926, 930	6-Cl-THA	Quinone	i.p. 10 μmol/kg 50 μmol/kg	*Ex vivo* dose-dependent inhibition of cholinesterase activity in telencephalon	[127]
970	Tacrine	Triazole	i.p. 5 mg/kg/day 10 mg/kg/day 20 mg/kg/day. 4 days	Memory improvement in scopolamine-induced impairment for all concentrations	[130]
1017 **1035**	Tacrine 6-Cl-THA	Pyrimidone	i.p. 15 mg/kg/day 15 days	Significant amelioration of memory and spatial behavior in Scop-injected mice (8–10 weeks old) Hybrid was **1035** slightly better than **1017**	[132]