BIOINFORMATION

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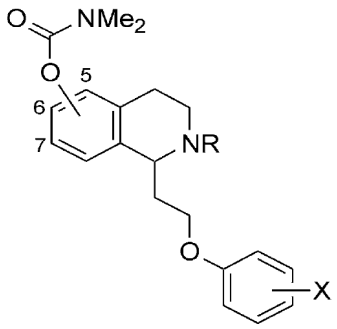
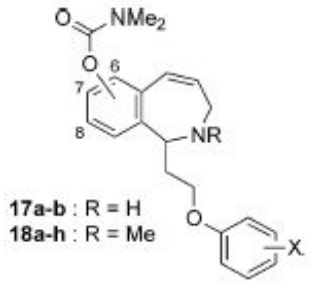
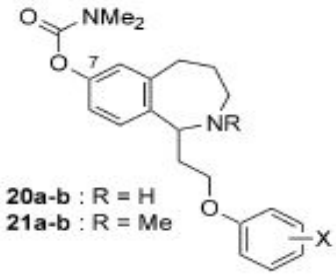
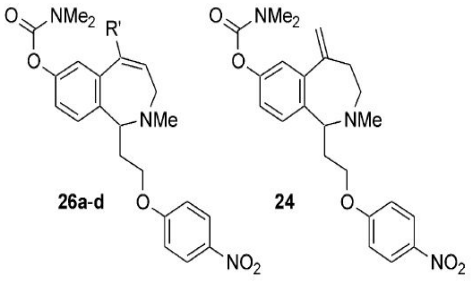
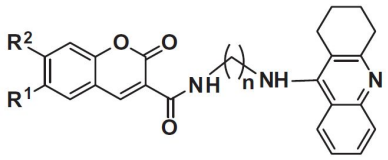
Supplementary material:

Table 1: Compounds of dataset 1 - Rivastigmine and Fluoxetine hybrids. The activity of the compounds by authors and the predicted binding affinity (rerank score) is listed.

	COMPOUNDS	Carbamate Position	IC 50 (AChE)+	R	X	Predicted affinity (Rerank Score)
	6a	6-	8	H	4-NO2	-148.143
6a-10b	6b	6-	17	H	4-Cl	-135.201
	7a	7-	101	H	4-NO2	-162.726
	7b	7-	219	H	4-Cl	-150.995
	8	5–	56	Me	4-NO2	-128.621
	9a	6-	11	Me	4-NO2	-120.178
	9b	6-	33	Me	4-Cl	-126.666
	9c	6-	16	Me	3-Me-4-NO2	-143.362
	9d	6-	11	Me	3-NO2	-127.489
	9e	6-	49	Me	4-F	-135.564
	9f	6-	34	Me	4-Br	-134.187
	9g	6-	20	Me	4-OMe	-142.828
	10a	7-	161	Me	4-NO2	-146.857
	10b	7-	265	Me	4-Cl	-133.043
	17a	7-	92	H	4-NO2	-144.747
	17b	7-	153	H	3-Me-4-Cl	-129.539
	18a	7-	66	Me	4-NO2	-155.55
	18b	7-	103	Me	3-Me-4-Cl	-147.308
17a-b : R = H	18c	7-	139	Me	4-Cl	-150.404
18a-h : R = Me	18d	7-	135	Me	4-F	-150.984
	18e	7-	285	Me	4-CF3	-151.219
	18f	6-	146	Me	3-Me-4-Cl	-151.973
	18g	8-	>1000	Me	4-NO2	-148.96
	18h	8-	>1000	Me	4-Cl	-144.191
	20a	7-	55	H	4-NO2	-136.468
	20b	7-	215	H	4-Cl	-140.733
20a-b : R = H	21a	7-	61	Me	4-NO2	-161.732
21a-b : R = Me	21b	7-	116	Me	4-Cl	-151.767
	24	-	27	-	-	-163.428
	26a	-	60	-	Me	-136.468
	26b	-	43	-	Vinyl	-157.069
	26c	-	150	-	2-Thienv	-148.58
	26d*	-	**>1000**	-	**4-Cl-Ph**	**-168.933**
						
26a-d **24**						

* Compound with highest binding affinity, + Activity tested in mouse brain.

Table 2: Compounds of dataset 2 - derivatives of Coumarin-Tacrine hybrids. The activity of the compounds by authors and the predicted binding affinity (rerank score) is listed.



Compound name	R1	R2	n	Ki for AChE (nM)+	Predicted affinity (Rerank Score)
1a	H	H	5	34.4	-115.72
1b	H	OCH3	5	44.3	-149.84
1c	OCH3	H	5	39.4	-100.44
1d	CH3	H	5	35.8	-120.7
1e	OCH3	OCH3	5	70	-163.39
1f	OCF3	H	5	76.1	-102.47
1g	H	H	6	16.7	-142.47
1h*	**H**	**OCH3**	**6**	**30.9**	**-166.33**
1i	OCH3	H	6	24.3	-99.524
1j	CH3	H	6	30.1	-144.96
1k	OCH3	OCH3	6	56.1	-145.48
1l	OCF3	H	6	59.6	-135.25
1m	H	H	7	42.2	-100.94
1n	H	OCH3	7	55.2	-80.694
1o	OCH3	H	7	50.7	-145.73
1p	CH3	H	7	66.1	-128.94
1q	OCH3	OCH3	7	91.1	-139.79
1r	OCF3	H	7	78.2	-139.11

* compound with highest binding affinity
+In vitro assessment of AChE activity (procedures as described by Yang *et al.*1961 & Ellman *et al.* 1961)

Table 3: Binding energy profile of parent compounds and its respective similar against AChE.

	26 D	1h	26 D similar PubCid: 68874404	1H similar CHEMBL2391475 (PubCid: 71699632)
Total Energy (Rerank Score)	-168.933	-166.33	-172.543	-151.81
External Ligand interactions	-180.626	-194.201	-195.367	-182.921
Protein - Ligand interactions	-180.626	-194.201	-195.367	-182.921
Steric (by PLP)	-138.054	-157.996	-157.787	-153.367
Steric (by LJ12-6)	-35.426	-35.311	-34.671	-27.574
Hydrogen bonds	-4.301	-0.894	-2.91	-1.98
Electrostatic (short range)	-2.035	0	0	0
Electrostatic (long range)	-0.81	0	0	0
Internal Ligand interactions	11.693	27.872	22.825	31.111
Torsional strain	2.121	9.76	1.88	9.729
Torsional strain (sp2-sp2)	0	0	0	0
Hydrogen bonds	0	0	0	0
Steric (by PLP)	1.899	3.557	4.076	4.136
Steric (by LJ12-6)		14.555	16.868	17.245
Electrostatic	7.673	0	0	0

Table 4: Bioactivity prediction of Parent and similar compounds against various drug targets

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
26d	0.15	-0.12	-0.36	-0.11	-0.17	1.25*
1H	-0.07	-0.30	-0.20	-0.30	-0.08	0.18
26 D similar PubCid: 68874404	0.11	0.06	-0.24	-0.18	-0.05	-0.03
1H similar -CHEMBL2391475 (PubCid: 71699632)	-0.11	-0.51	-0.35	-0.43	-0.13	-0.08

* Compound 26d from dataset showing activity highest enzyme inhibition and least activity against other drug targets testifying its target specificity against enzymes (in the present case AChE)

Table 5: ADMET profiles of parent compound and its respective similar

	26D		1h		26 D similar PubCid: 68874404		1H similar CHEMBL2391475 (PubCid: 71699632)	
Model	**Result**	**Probability**	**Result**	**Probability**	**Result**	**Probability**	**Result**	**Probability**
Absorption								
Blood-Brain Barrier	BBB+	0.746	BBB-	0.605	BBB+	0.909	BBB+	0.842
Human Intestinal Absorption	HIA+	0.993	HIA+	0.855	HIA+	0.991	HIA+	0.834
Caco-2 Permeability	Caco2-	0.561	Caco2-	0.651	Caco2-	0.575	Caco2-	0.537
P-glycoprotein Substrate	Substrate	0.837	Substrate	0.679	Substrate	0.792	Substrate	0.809
P-glycoprotein Inhibitor	Inhibitor	0.891	Non-inhibitor	0.647	Inhibitor	0.753	Inhibitor	0.782
Distribution & Metabolism								
CYP450 2C9 Substrate	Non-substrate	0.807	Non-substrate	0.828	Non-substrate	0.799	Non-substrate	0.836
CYP450 3A4 Substrate	Substrate	0.798	Substrate	0.555	Substrate	0.695	Substrate	0.657
CYP450 1A2 Inhibitor	Non-inhibitor	0.654	Inhibitor	0.572	Non-inhibitor	0.555	Non-inhibitor	0.771
CYP450 2D6 Inhibitor	Non-inhibitor	0.810	Non-inhibitor	0.785	Non-inhibitor	0.809	Non-inhibitor	0.578
CYP450 3A4 Inhibitor	Inhibitor	0.667	Inhibitor	0.763	Inhibitor	0.811	Inhibitor	0.705
Excretion & Toxicity								
Human Ether-a-go-go-Related Gene Inhibition	Inhibitor	0.6113	Inhibitor	0.6655	Inhibitor	0.7666	Inhibitor	0.8209
AMES Toxicity	Non-AMES toxic	0.532	Non AMES toxic	0.572	AMES toxic*	0.964	Non AMES toxic	0.700
Carcinogens	Non-carcinogens	0.686	Non-carcinogens	0.930	Non-carcinogens	0.762	Non-carcinogens	0.945
Honey Bee Toxicity	Low HBT	0.664	Low HBT	0.805	Low HBT	0.599	Low HBT	0.837
Acute Oral Toxicity	III	0.596	III	0.675	III	0.5766	III	0.708

* Compound PubCid: 68874404 similar to 26d demonstrating AMES toxicity, with high probability value therefore can be excluded from further pharmacological investigation

Table 6: Interaction profile of compounds in the binding pocket of AChE

Compounds	Van der Waals Contacts (n)	Electrostatic Contacts (n)	H Bonds (n)	σ /π-π interactions (n)
26d	17 Ile 287, Ser 81, Tyr 331, Tyr 334, Phe 330, Phe 331, Trp 279, Phe 290, Tyr 70, Val 71, Gly 119, Trp 432, Leu 333, Ile 439, Met 436, Ser	12 Phe 288, Arg 289, Gly 80, Trp 84, Asn 85, Tyr 121, Asp 72, Ser 122, Tyr 442, His 440, Gly 441, Glu 199	3 Arg 289, Phe 288, Phe 288	1 Phe 331

	200, Tyr 130			
1h	16 Trp 279, Glu 73, Gln 74, Phe 290, His 440, Phe 330, Ser 200, Ser 81, Gly 441, Trp 432, Ile 439, Gly 80, Tyr 442, Met 436, Glu 199, Asn 85	6 Tyr 70, Tyr 221, Asp 72, Tyr 334, Trp 84, Phe 288	1 Tyr 121	2 Phe 330, Trp 84
26 D similar PubCid: 68874404	13 Met 436, Ile 439, Phe 331, Gly 441, Glu 199, Ile 444, Gly 118, Trp 279, Tyr 70, Tyr 334, Trp 432, Tyr 116, Leu 127	12 Tyr 442, His 440, Ser 200, Tyr 130, Gly 117, Ser 124, Gly 123, Ser 122, Asn 85, Asp 72, Tyr 121, Ser 81	1 Phe 331	2 Trp84, Phe 330
1H similar CHEMBL2391475 (PubCid: 71699632)	11 Gly 118, Trp 279, Phe 330, Tyr 334, Phe 331, Tyr 70, Asn 85, Gly 80, Tyr 442, Glu 199, Glu 278	4 Ser 291, Arg 289, Ser 286, His 440	0	2 Trp 84, Phe 331

n=number of contacts