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Molecular Docking and Pharmacological Investigations of Rivastigmine-Fluoxetine and Coumarin–Tacrine hybrids against Acetyl Choline Esterase

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Abstract:
The present AChE inhibitors have been successful in the treatment of Alzheimer's Diseases however suffers serious side effects. Therefore in this view, the present study was sought to identify compounds with appreciable pharmacological profile targeting AChE. Analogue of Rivastigmine and Fluoxetine hybrid synthesized by Toda *et al*, 2003 (dataset1), and Coumarin–Tacrine hybrids synthesized by Qi Sun *et al* (dataset2) formed the test compounds for the present pharmacological evaluation. p-cholorophenyl substituted Rivastigmine and Fluoxetine hybrid compound (26d) from dataset 1 and –OCH_3 substitute Coumarin–Tacrine hybrids (1h) from dataset 2 demonstrated superior pharmacological profile. 26 d showed superior pharmacological profile comparison to the entire compounds in either dataset owing to its better electrostatic interactions and hydrogen bonding patterns. In order to identify still better compound with pharmacological profile than 26 d and 1h, virtual screening was performed. The best docked compound (PubCId: PubCid: 68874404) showed better affinity than its parent 26 d, however showed poor ADME profile and AMES toxicity. CHEMBL2391475 (PubCid: 71699632) similar to 1h had reduced affinity in comparison to its parent compound 1h. From, our extensive analysis involving binding affinity analysis, ADMET properties predictions and pharmacophoric mappings, we report p-cholorophenyl substituted rivastigmine and fluoxetine hybrid (26d) to be a potential candidate for AcHE inhibition which in addition can overcome narrow therapeutic window of present AChE inhibitors in clinical treatment of Alzheimer's disease.

Key Words: Rivastigmine-Fluoxetine hybrids; Coumarin–Tacrine hybrids, Molecular docking, pharmacological profiling, Virtual screening.

Abbreviations: AD: Alzheimer's Disease; **AChE**: Acetyl Choline Estarase; **OPLS:** Optimized Potentials for Liquid Simulations; **PDB:** Protein Data Bank.

Background:
Alzheimer's disease (AD) is one of the most common neurodegenerative disorders that constitutes about two thirds of cases of overall dementias **[1, 2, 3].** It is characterized by progressive and irreversible degeneration of neurons in the cortex and hippocampus **[3],** Alzheimer's disease is clinically

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reported with impairment in memory, decision making, orientation to physical surroundings and language.

Cholinergic hypothesis of the pathogenesis now shows dysregulation of cholinergic system forms the major pathological feature of AD **[4].** Biopsies of the cerebral cortex has shown that these cholinergic neurons which provide extensive innervations in the cerebral cortex selectively degenerate which affects the cognitive functions, especially memory **[5].** With the immense role of cholinergic system in AD, several pharmacological strategies have been aimed at correcting the cognitive deficits by manipulating cholinergic neurotransmission. The most powerful strategy developed was development of Acetyl Choline Esterase (ChEI) inhibitors that selectively blocks Acetyl Choline Esterase (AChE)- an enzyme which is involved in termination of synaptic transmission by hydrolysis of acetyl choline and finally making it unavailable for neural transmission in coxtex which otherwise is manifested as cognitive dysfunction observed in AD. Since the introduction of the first cholinesterase inhibitor in 1997, most clinicians would consider treatment by the cholinergic drugs like donepezil, galantamine and rivastigmine that forms first line pharmacotherapy for mild to moderate Alzheimer's disease **[6, 7].**

Various clinical trials of inhibitors have shown that, on the whole their effects were modest however were associated with frequent adverse reactions and lack of the drug's substrate specificity **[8].** In addition, some drugs like donepezil delays the disease worsening but nevertheless offers acute symptoms like headache, constipation, confusion and dizziness. In some patients, the regular dose of donepezil, galantamine and rivastigmine have been positively associated with acute insomnia and anorexia **[9].** Considering the side effects of the present compounds, the treatment strategy of AD thus shifted to ethnopharmacological approach which promises high activity bestowed with minimal side effects. In traditional practices of medicine, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases such as Alzheimer's disease (AD). There are numerous drugs available in Western medicine that have been directly isolated from plants, or are derived from templates of compounds from plant sources.

Therefore, In the view of above, the present study focuses computer based pharmacological profiling, evaluation and identification high affinity plant compounds from the dataset of rivastigmine and fluoxetine hybrid compound synthesized by N. Toda *et al* and colleagues **[10]** and coumarin–tacrine hybrids synthesized and evaluated by Qi Sun *et al*. **[11].**

Methodology:

Selection of compound dataset

The first dataset includes rivastigmine and fluoxetine hybrid compound synthesized by N. Toda *et al* **[10] Table1 (see supplementary material).** The second dataset involved Coumarin–Tacrine hybrids synthesized and evaluated by Qi Sun *et al*. **[11] Table 2 (see supplementary mater).**

Preparation of protein and compounds

The crystal structure of AChE receptor was retrieved from Protein Data Bank (PDB) with PDB ID: 1ACJ **[12] (Figure 2).** The X-Ray diffraction structure of AChE receptor had a resolution of 2.80 Å and R value of 0.195. Unit cell parameters were as Length [Å] a = 113.70, b = 113.70, c = 138.10, Angles [°] α = 90.00, β = 90.00, γ = 120.00. The structure was downloaded in pdb format and was further prepared for docking process. The protein was prepared using the PrepWiz module of Schrodinger suite. In the preparation procedure, the protein was first preprocessed by assigning the bond orders and hydrogens, creating zero order bonds to metals and adding disulphide bonds. The missing side chains and loops were filled using Prime Module of Schrodinger. Further all the water molecules were deleted beyond 5 Å from hetero groups. Once the protein structure was preprocessed, H bonds were assigned which was followed by energy minimization by OPLS 2005 force field **[13].** The final structure obtained was saved in.pdb format for further studies. All the ligands were optimized through OPLS 2005 force field algorithm embedded in the LigPrep module of Schrödinger suite, 2013 (Schrodinger. LLC, New York, NY) **[14].** The ionizations of the ligand were retained at the original state and were further desalted. The structures thus optimized were saved in sdf format for docking procedures.

Structure Similarity search

The compound with superior pharmacological profile amongst the two datasets was further used as query molecule in pursuit to identify still better druglike compound than any molecules mentioned in the dataset. Similarity search was supervised by Binary Finger Print Based Tanimoto similarity equation to retrieve compounds with similarity threshold of 95 % against NCBI's Pubchem compound database **[15].**

Molecular docking of compounds

Molecular docking program- Molegro Virtual Docker (MVD) which incorporates highly efficient PLP (Piece wise Linear potential) and MolDock scoring function provided a flexible docking platform **[16, 17].** All the ligands were docked at the active site of AChE. Docking parameters were set to 0.20Å as grid resolution, maximum iteration of 1500 and maximum population size of 50. Energy minimization and hydrogen bonds were optimized after the docking. Simplex evolution was set at maximum steps of 300 with neighborhood distance factor of 1. Binding affinity and interactions of ligands with protein were evaluated on the basis of the internal ES (Internal electrostatic Interaction), internal hydrogen bond interactions and sp2-sp2 torsions. Post dock energy of the ligand-receptor complex was minimized using Nelder Mead Simplex Minimization (using non-grid force field and H bond directionality) **[18].** On the basis of rerank score best interacting compound was selected from each dataset.

Bioactivity and ADMET profiling of compounds.

All the compounds were screened for its drug ability by lipinksi filters. Biological activity of the ligands was predicted using Molinspiration webserver (© Molinspiration Cheminformatics 2014). The complete ADMET properties was calculated using admetSAR **[19, 20].**

Pharmacophoric Mapping

Pharmacophoric mapping which involves ligand interaction patterns, hydrogen bond interaction, hydrophobic interactions

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was evaluated using Accelrys Discovery Studio 3.5 DS Visualizer **[21].**

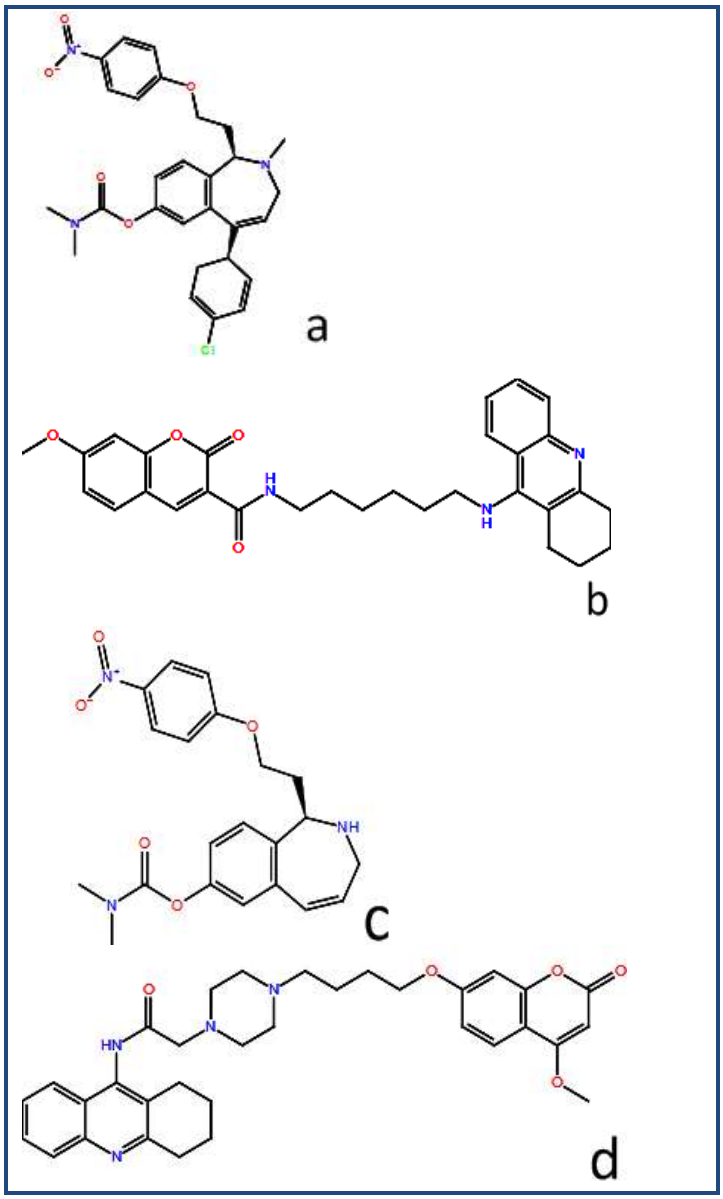

Figure 1: Structures of compounds (**a**) **26 d (dataset1)** (((1R)-5-[(1R)-4-chlorocyclohexa-2,4-dien-1-yl]-2-methyl-1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1H-2-benzazepin-7-ylN,N-dimethylcarbamate)); (**b**) **1h (dataset 2)** (7-methoxy-2-oxo-N-{6-[(1,2,3,4-tetrahydroacridin-9-yl)amino]hexyl}-2H-chromene-3-carboxamide;ethane); (**c**) **26 d similar - PubCid: 68874404** ([(1R)-1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1H-2-benzazepin-7-yl N,N-dimethylcarbamate]); (**d**) **1 h similar CHEMBL2391475 (PubCid: 71699632) (**2-(4-{4-[(4-methoxy-2-oxo-2H-chromen-7-yl)oxy]butyl}piperazin-1-yl)-N-(1,2,3,4-tetrahydroacridin-9-yl)acetamide)

Results & Discussion:

Table 1 (see supplementary material) shows the affinity (rerank) scores of compounds of dataset1 along with the AChE activity (IC 50) as assessed by the Toda *et al*. Similarly, the affinity scores along with activity (Ki) (predicted by Sun wt al) against AChE is shown in **Table 2 (see supplementary material)**. Evident from the docking (rerank) scores 26 d **(Figure 1a)** from dataset 1 and compound 1h **(Figure 1b)** from dataset 2 demonstrated highest binding affinity. In particular, compound 26 d a hybrid molecule with the motifs of Rivastigmine and Fluoxetine with functional modification with p-chlorophenyl showed highest affinity than compounds in either groups. From keen perusal of the structural details of 26d, it may be assumed that large substituent (R= p-chlorophenyl) may attributed to its better activity (IC50 >1000) and highest affinity (Rerank Score=-168.933).

From dataset 2, compound 1h- a Coumarin–Tacrine hybrid demonstrated highest binding affinity against AChE. However, our observations of binding affinity did not correlate with the estimated activity by authors, 1q as described by authors shows highest activity (Ki= 91.1), while adhering to our observation it is 1h which showed highest binding affinity (rerank score=**-166.33**). The discrepancies observed is an important subject for further investigation. However, taking into consideration all the compounds from dataset1 and 2, unarguably 26d (from dataset) **(Figure 2)** demonstrated highest binding affinity and in addition showed optimal *in vitro* activity.

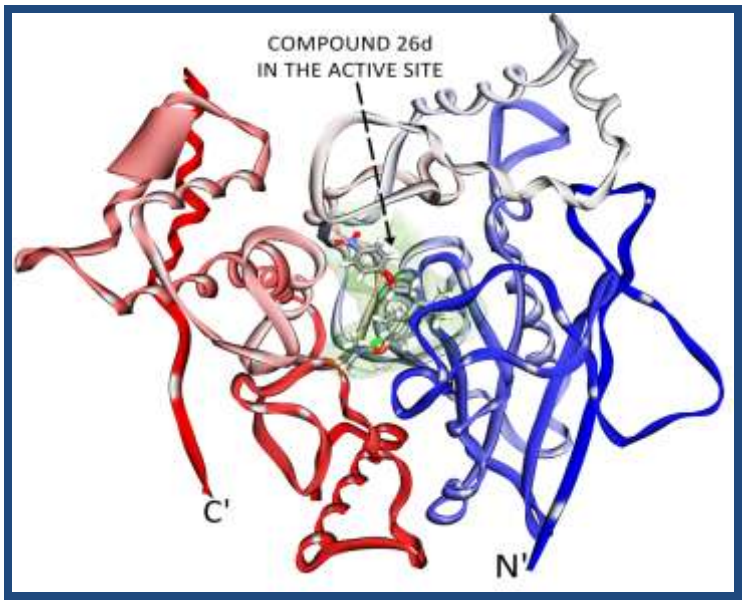

Figure 2: Compound 26 d ((1R)-5-[(1R)-4-chlorocyclohexa-2,4-dien-1-yl]-2-methyl-1-[2-(4-nitrophenoxy)ethyl]-2,3-dihydro-1H-2-benzazepin-7-ylN,N-dimethylcarbamate) (dataset1) in the binding pocket (green shade) of AChE (PDB ID: 1ACJ). Red to blue spectrum of the helix represent N to C terminal of the protein structure.

In further approach, in pursuit to identify even better molecule endowed with superior pharmacological profile than compound 26 d from dataset 1 and compound 1h from dataset 2, virtual screening was performed against Pubchem database (taking compound 61 as query). A total of 14 compounds structurally similar to compound 26d were retrieved while 18 structural similar were retrieved against its parent compound 1h. All the similar compounds those akin to 26 d and 1h retrieved hitherto were docked against AChE structure. Compound with Pubchem Id: 68874404 **(Figure 1c)** showed superior binding affinity out of all the similar 14 compounds retrieved against its parent compound 26 d, while, compound CHEMBL2391475 (PubCid: 71699632) **(Figure 1d)**

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demonstrated superior affinity among all the 18 compounds retrived with respect to its parent compound1h **Table 3 (see supplementary material)**.

It worthy to note that though PubCid: 68874404 showed slightly higher affinity to AChE than its parent compound 26d , however, quite apparent from predicted activity scores, **Table 4 (see supplementary material)** it shows abruptly less activity for enzyme inhibition. In addition the ADMET profiles were comparatively poor when compared to its parent compound 26d **Table 5 (see supplementary material)**. However, the important drawback of compound PubCid: 68874404 was that it was predicted to be Ames toxic. Therefore, it can be presumed that, though it has good affinity profile, however, it should not form candidate drug owing to its toxicity.

While in the case of CHEMBL2391475 the affinity score was 1.09 folds declined than its parent compound 1h **Table 3 (see supplementary material)** in addition the predicted enzyme inhibition activity was considerably lower **Table 4 (see supplementary material)**. Further ADMET profile of this compound was quite poor; therefore even this compound should not form an important candidate against AChE inhibition.

In the further perusal, our pursuit was to reveal the rationale behind superior pharmacological profile of 26 d. In terms of binding affinity, the appreciable binding can be attributed to its excellent interaction profile especially in terms of electrostatic and H-bonding interactions **Table 3 (see supplementary material)**. Apparent from the docking profile of compound 26 d energy values of descriptors of external ligand interactions contributes 14.4 folds higher stability than internal ligand interactions. Further external ligand interactions were stabilized mostly by stearic energy guided by Piece wise linear potentials while in internal ligand interactions, the torsional strain contributes for the stability of the ligand receptor interactions (and the same trend holds true for 1h of dataset 2 and similar compounds).

As show in **Table 6 (see supplementary material),** the interaction profile of 26 d was quite appreciable than compound 1h from dataset 2 and its respective similar CHEMBL2391475 (PubCid: 71699632). An obvious thing which can be noted is, although 26 d similar compound PubCid: 68874404 shows good interaction profile, nevertheless, as mentioned above suffer with poor ADME properties and AMES toxicity.

Owing to optimal affinity, high enzyme inhibition activity and non-toxicity, 26 d was further analyzed for pharmacophoric mappings. Comprehensively shown in **Figure 3**, the compound 61 demonstrates van der Waals interactions with 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 200, Tyr 130 and electrostatic interactions with Phe 288, Arg 289, Gly 80, Trp 84, Asn 85, Tyr 121, Asp 72, Ser 122, Tyr 442, His 440, Gly 441, Glu 199. The Compound is a hydrogen bond donor to Arg 289, Phe 288, Phe 288. In addition π-π interactions are observed with Phe 331.

Considering, optimal activity as experimentally predicted AChE activity (predicted by Toda *et al*) and our analysis including better binding affinity, ADMET properties interaction profiles and pharmacophoric features, we anticipate compound 26 d may form a potential candidate for AChE inhibition in clinical treatment of Alzheimer's disease.

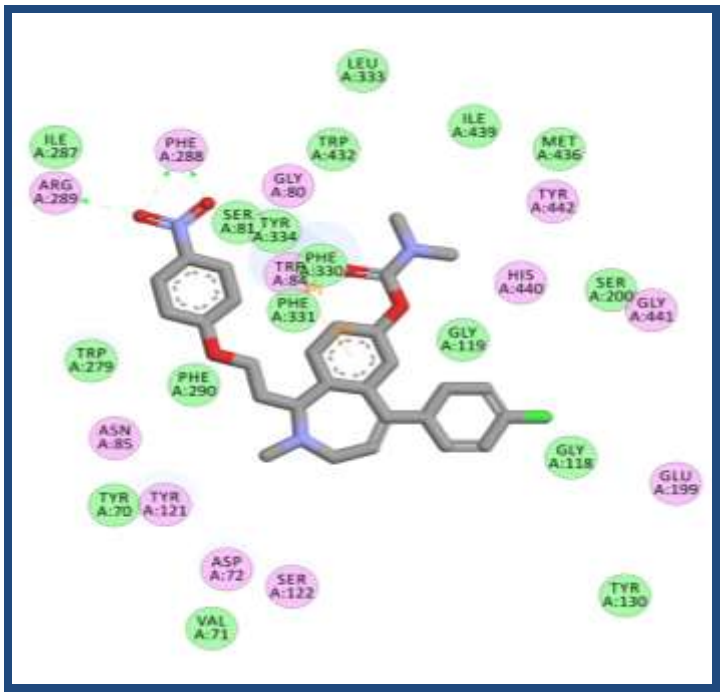

Figure 3: Interactions of compound 26 d in the active site of AChE. Residues circled in green participate in van der Waals interaction with the ligand while residues in pink forms electrostatic interactions. Hydrogen bonds are shown as green arrows between ligand and residues Arg 289, Phe 288

Conclusion:

From, our extensive analysis involving binding affinity analysis, ADMET properties predictions and pharmacophoric mappings, we anticipate p-cholorophenyl substituted rivastigmine and fluoxetine hybrid (26d) synthesized by Toda *et al*, 2003 to be a potential candidate for AChE inhibition which in addition can overcome narrow therapeutic window of present AChE inhibitors in clinical treatment of Alzheimer's disease.

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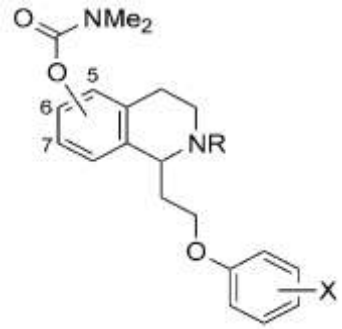
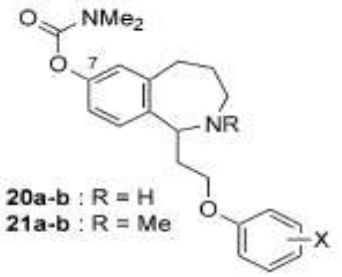
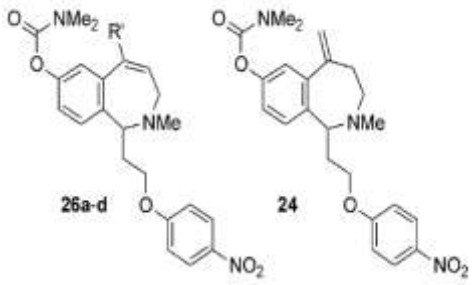
Supplementary material:

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
	18c	7-	139	Me	4-Cl	-150.404
	18d	7-	135	Me	4-F	-150.984
	18e	7-	285	Me	4-CF3	-151.219
17a-b : R = H	18f	6-	146	Me	3-Me-4-Cl	-151.973
18a-h : R = Me	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
	21a	7-	61	Me	4-NO2	-161.732
	21b	7-	116	Me	4-Cl	-151.767
20a-b : R = H						
21a-b : R = Me						
	24	-	27	-	-	-163.428
	26a	-	60	-	Me	-136.468
	26b	-	43	-	Vinyl	-157.069
	26c	-	150	-	2-Thienv	-148.58
26a-d **24**	**26d***	-	**>1000**	-	**4-Cl-Ph**	**-168.933**

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

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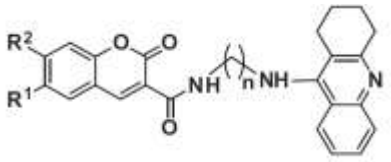
Table 2: Compounds of dataset 2 - derivatives of Coumarin-Tacrine hybrids. The activity of the compounds by authors and the predicted binding affinity (rerank score) is listed.



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

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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

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	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

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