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INSILICO DESIGN ON NOVEL 1-(2-METHYL)-1,3-DIOXALAN-2YL)PIPERAZINE DERIVATIVES AS ANTI-ALZHIEMER AGENTS TARGETING AchE COMPLEXED WITH E2020 ALONG WITH ADME STUDIES

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ABSTRACT: In this study, novel 1-(2-methyl)-1, 3-dioxalan-2yl)piperazine derivatives were designed. Designed derivative compounds against 1EVE molecular docking simulation was carried out with Mcule and Insilco ADME Prediction Procedures. The results of docking study revealed that the binding profile for designed derivative compounds M4, M5, M6, M7, and K6 was found significant interactions with Donepezil with catalytic active site (CAS) of 1EVE. The predicted ADME properties revealed that all compounds fulfil drug-like criteria and could be considered as good candidate for drug development. All the designed compound derivatives have Standard Drug (Donepezil) like ADME properties.

Index Terms -1-(2-methyl)-1, 3-dioxalan-2yl)piperazine derivatives, 1EVE, Mcule, Insilco ADME Prediction, molecular docking, catalytic active site (CAS).

I. INTRODUCTION

Docking is an attempt to find the best matching between two molecules. Docking is a method which predicts the preferred orientation of one ligand when bound in an active site to form a stable complex. Lock and key finding the correct relative orientation of the "key" which will open up the "lock". On the surface of the lock is the key hole in the direction to turn the key after it is inserted. The protein can be thought of the "lock" and the ligand can be thought of as a "key". To achieve an optimized conformation for both receptor and ligand and the relative orientation between protein and ligand such that the free energy of the overall system is minimized. Successful docking methods search high dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings.

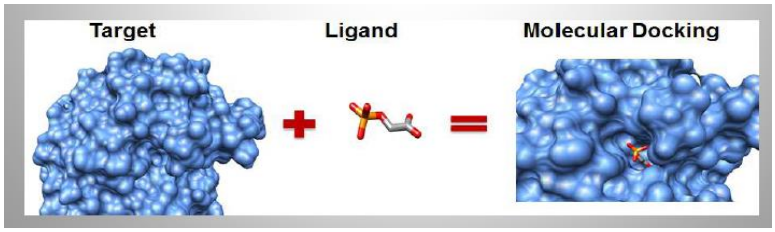


Figure 1

E2020 (Figure 2) is a member of a large family of N-benzylpiperidine-based AChE inhibitors that were developed, synthesized and evaluated by the Eisai Company in Japan, on the basis of QSAR studies, prior to elucidation of the three-dimensional (3D) structure of Torpedo californica AChE (TcAChE).[13] It was shown to significantly enhance performance in animal models of cholinergic hypofunction and to have high affinity for AChE **(Figure 3)**, binding to both electric eel and mouse AChE in the nanomolar range.

Classification: SERINE HYDROLASE, Organism: Tetronarce californica, Resolution: 2.50 Å, Chains: A, Sequence Length: 543, PDB entry: 1EVE.

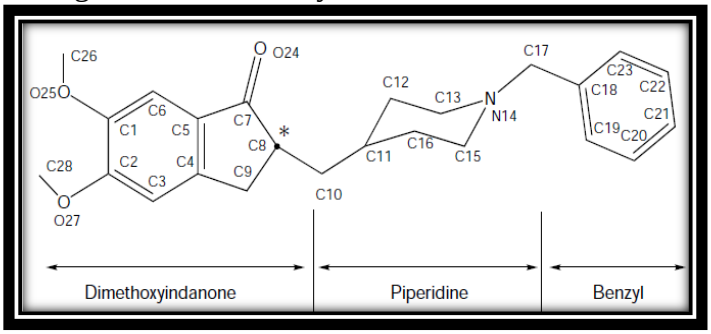


Figure 2

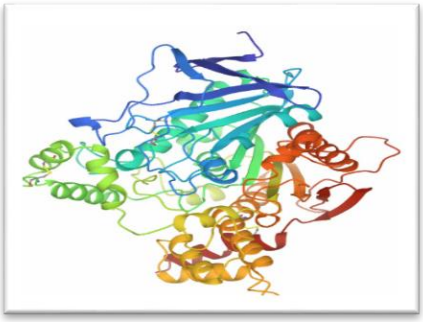


Figure 3

Alzheimer's disease, discovered by Dr. Alois Alzheimer in 1907, is described as a degenerative disease of the central nervous system (CNS) characterized especially by premature senile mental deterioration. AD patient's exhibit marked decline in cognitive ability and severe behavioral abnormalities such as irritability, anxiety, depression, disorientation, and restlessness. AD is a progressive disease, i.e., the onset of the disease may show mild symptoms but these symptoms will sooner or later become more and more severe until the patient loses his or her capacity to handle normal daily activities. While AD is commonly regarded as a senile disease, the symptoms can also manifest in presenile individuals.

Piperazine (Figure 4) was used early in the 20th century for the treatment of gout. Giround discovered the anthelmintic activity of piperazine, synthesized by Cloez in 1853, fortuitously in 1942. The same effect was observed by Biosmare in 1948 and conformed by Bayared in 1949.[1] Piperazine is a six member cyclic secondary diamine with the nitrogen in the 1, 4 - position. It can also be called diethelenediamine for convenience its molecular formula can be written $C_4H_{10}N_2$. Piperazines and substituted piperazines are important pharmacophores that can be found in many marketed drugs, such as the Merck HIV protease inhibitor Crixivan[3], and drugs under development. Piperazinyl-linked ciprofloxacin dimers reported as potent antibacterial agents against resistant strains, a novel class of mixed D2/D4 receptor antagonists, dual calcium antagonist, and potential antipsychoticagents.[4]

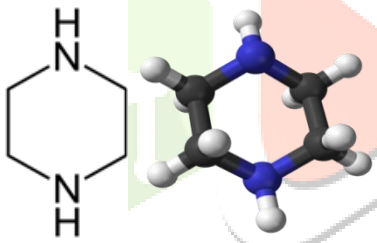


Figure 4

Dioxolane (Figure 5) is a heterocyclic acetal with the chemical formula $(CH_2)_2O_2CH_2$. It is related to tetrahydrofuran by interchange of one oxygen for a CH_2 group. The corresponding saturated 6-membered C_4O_2 rings are called dioxanes. The isomeric 1,2-dioxolane (where in the two oxygen centers are adjacent) is peroxide. 1,3-Dioxolane is used as a solvent and as a comonomer in polyacetals.[5] The perfluorinated bis(dioxolane) has been used as a I9F NMR imaging agent for tumors. The long-chain dioxolane inhibits leukotriene-B4 production in tumor cells and is an inhibitor of 5-lipoxygenase.[6] Benzodioxole-2,2-dicarboxylates and the corresponding dimethyl esters are effective anti-obesity agents. Spiro dioxolanes and oxathiolanes have been patented for the treatment of Alzheimer's disease.[7] The benzodioxole-2-thione has been used for the treatment of liver disease. A variety of simple benzodioxole-2-carboxylic acid derivatives have been examined in detail as diuretic and uricosuric agents. Dioxolane sulfamates are useful as anticonvulsants.[8] The different possible enantiomers and diastereomers of the dioxolane, oxathiolane, and its S-oxides have been separated and evaluated for their cholinergic agonist activity.[9] The bicyclic dioxolane has central nervous system (CNS) activity.[10] A series of 2-benzofuryl-4-aminomethyl-l,3-dioxolanes affect the cardiovascular system and offer protection against fibrillation, arrhythmia, and angina. The methylenedioxyphenyl pyrrolidinone inhibits blood platelet aggregation.[11]

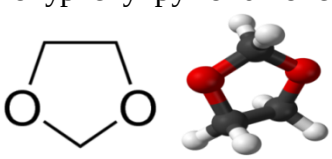


Figure 5

II. METHODOLOGY

1. MOLECULAR DOCKING PROCEDURE

STEP 1: GET TO THE TOOL (Figure 6)

https://mcule.com/apps/1-click-docking/

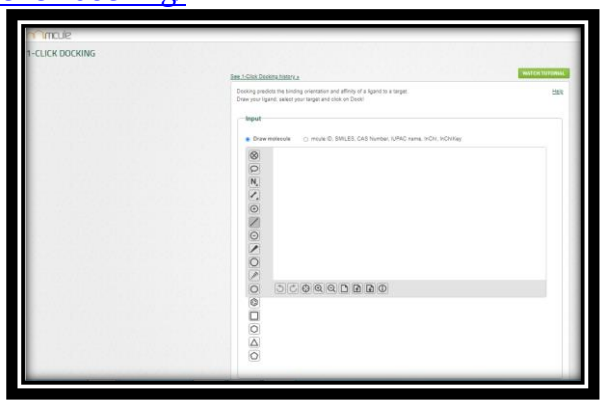


Figure 6

STEP 2: DRAW THE LIGAND (Figure 7-12)

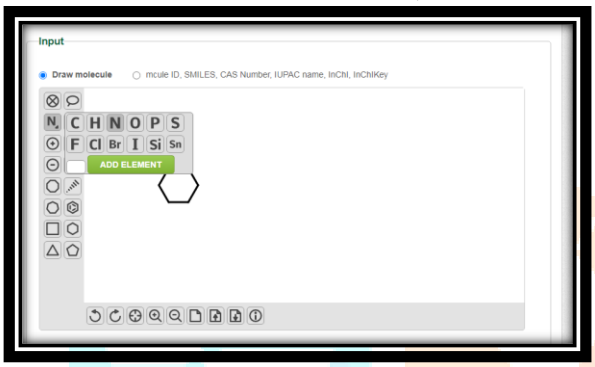


Figure 7

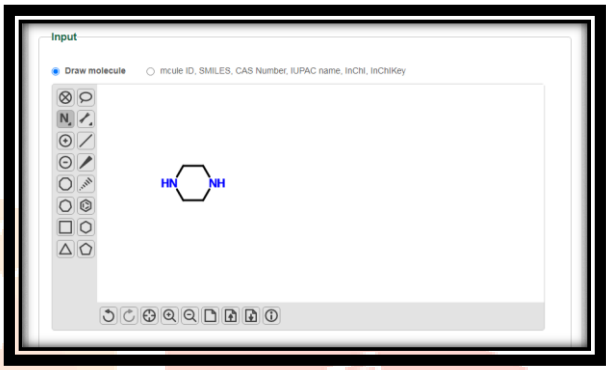


Figure 8

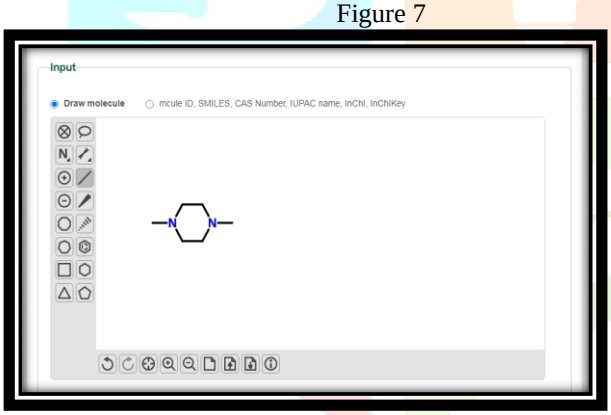


Figure 9

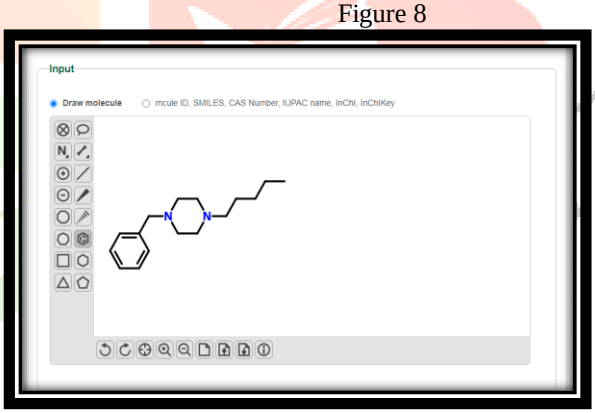


Figure 10

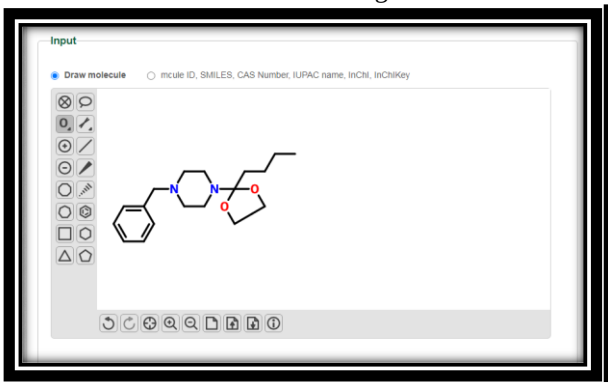


Figure 11

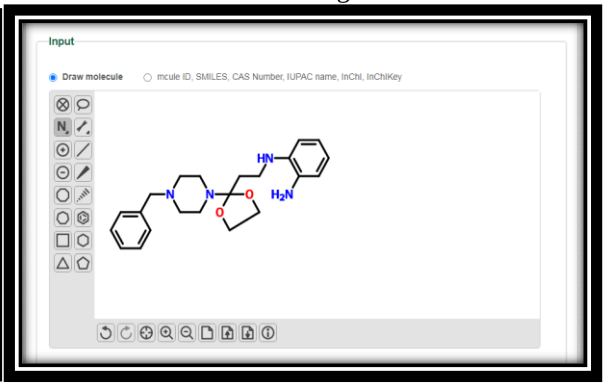


Figure 12

STEP 3: SELECT TARGET (Figure 13-15)

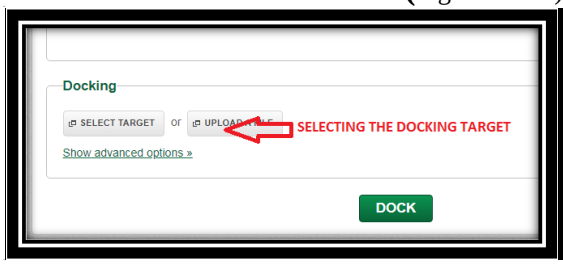


Figure 13

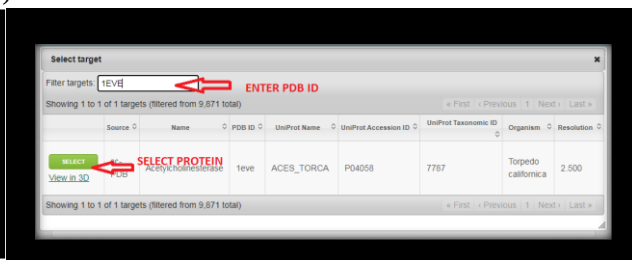


Figure 14

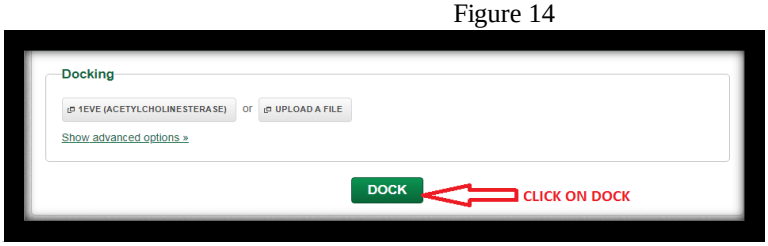


Figure 15

STEP 4: CLICK ON DOCK (Figure 16, 17)

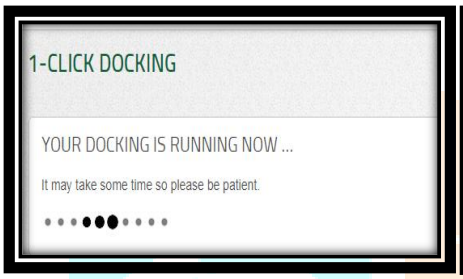


Figure 17

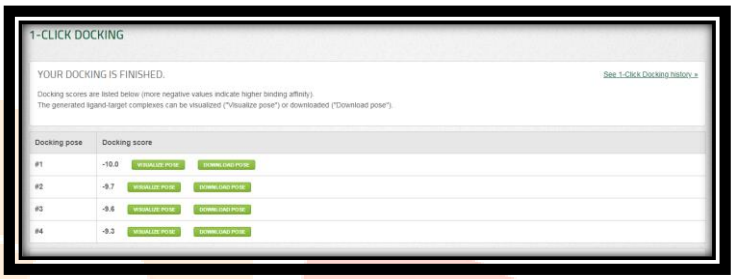


Figure 16

STEP 5: RESULT (Figure 18-20)

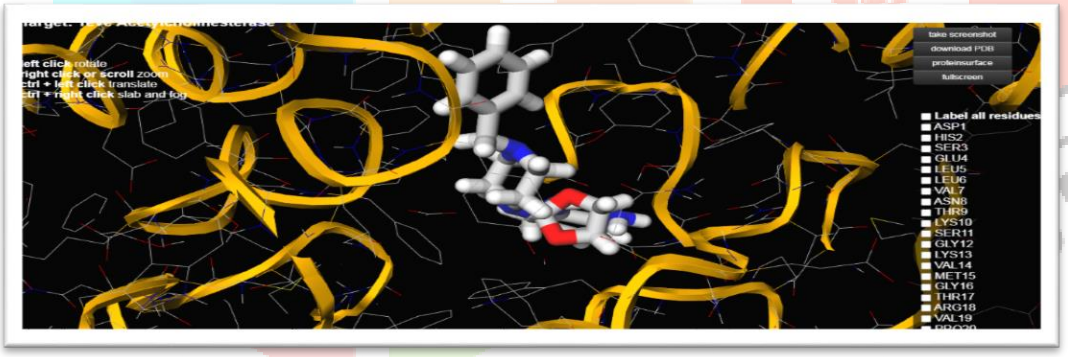


Figure 18

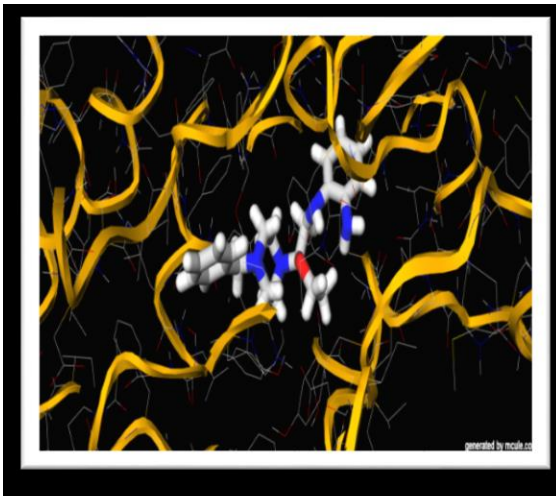


Figure 19

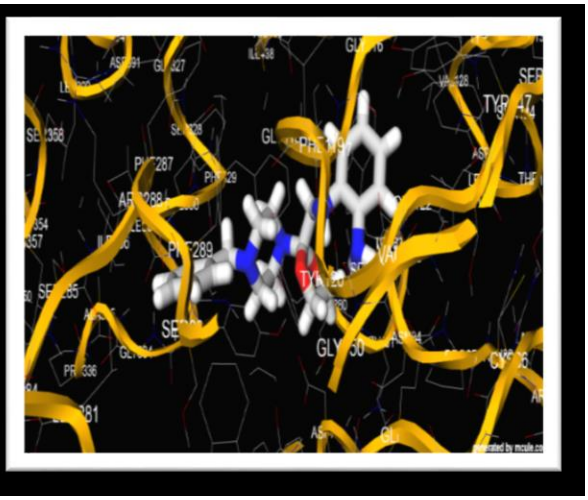


Figure 20

2. ADME PREDICTION PROCEDURE

STEP 1: GET TO THE TOOL (Figure 21)

http://www.swissadme.ch/

STEP 2: RESULT (Figure 22)

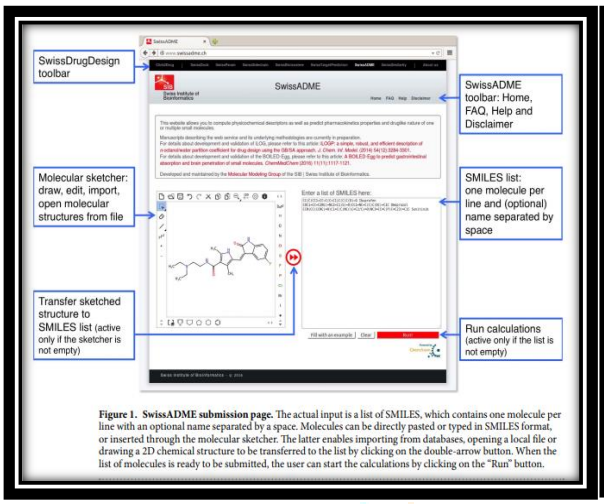


Figure 21

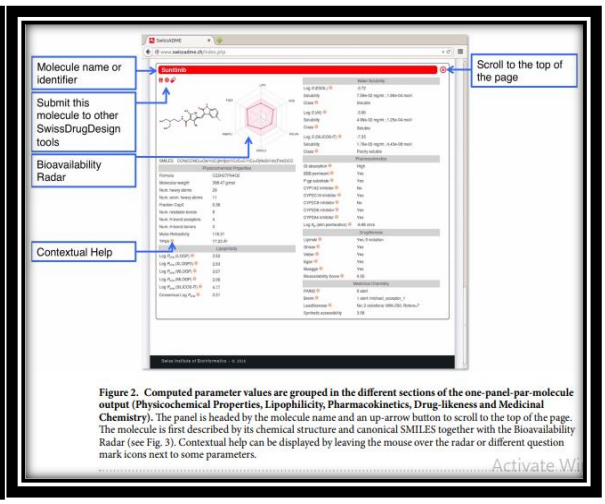


Figure 22

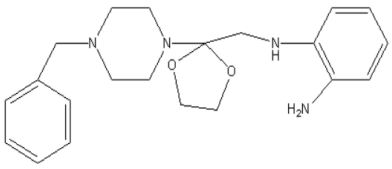
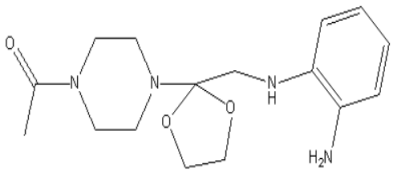
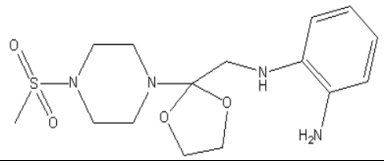
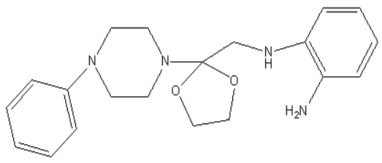
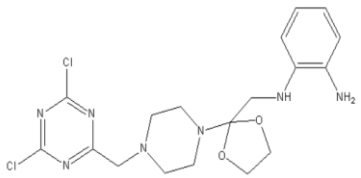
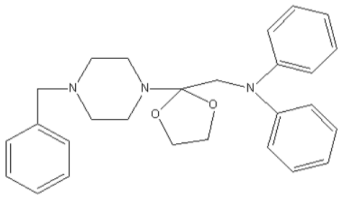
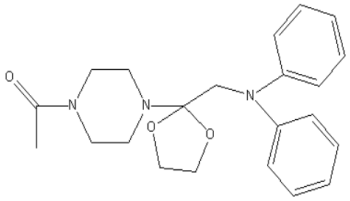
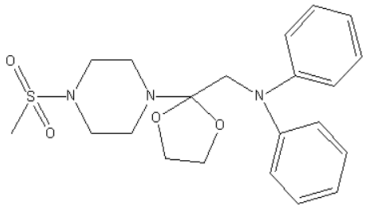
RESULTS AND DISCUSSION

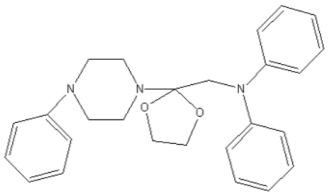
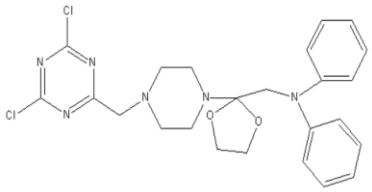
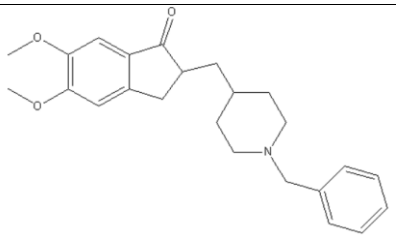
Docking studies:

The designed Novel Acetyl cholinesterase, Piperazine, 1, 3-Dioxolane derivative compounds were carried out E2020 by Mcule 1 Click Docking method.

To study in detail the binding mode and mechanism of action between designed compounds and E2020 molecular docking was performed. The docking results reveal that the inhibitors well fit into the active site pocket of E2020. Docking scores were displayed in **Table 1**

Table 1: Characterization of Designed Derivative Compounds

Comp. code	Structures	Mol. Formula	Mol. Weight (g/mole)	IUPAC name
A1		$C_{21}H_{28}N_4O_2$	368.47	N1-((2-(4-benzylpiperazin-1-yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2-diamine
A2		$C_{16}H_{24}N_4O_3$	320.39	1-(4-(2-((2-aminophenylamino) methyl)-1,3-dioxolan-2-yl) piperazin-1-yl)ethanone
A3		$C_{15}H_{24}N_4O_4S$	356.44	[[amino-(1-Phenylethoxyamino) methylidene]N-cyclohexylsulfamate
A4		$C_{20}H_{26}N_4O_2$	354.45	N1-((2-(4-phenylpiperazin-1-yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2-diamine
A5		$C_{18}H_{23}CL_2N_7O_2$	440.33	N1-((2-(4-((4,6-dichloro-1,3,5-triazin-2-yl) methyl) piperazin-1-yl)-1,3-dioxolan-2-yl) methyl) benzene-1,2-diamine
B1		$C_{27}H_{31}N_3O_2$	429.55	N-((2-(4-benzylpiperazin-1-yl)-1,3-dioxolan-2-yl) methyl)-N-phenylbenzenamine
B2		$C_{22}H_{27}N_3O_3$	381.47	1-(4-(2-((diphenylamino)methyl)-1,3-dioxolan-2-yl) piperazin-1-yl)ethanone
B3		$C_{21}H_{27}N_3O_4S$	417.52	(2R)-1-methylsulfonyl-?N-[(1R)-1-[3-(pyridine-2-ylmethoxy)phenyl]ethyl]piperidine-2-carboxamide

B4		$C_{26}H_{29}N_3O_2$	415.53	N-phenyl-N-((2-(4-phenylpiperazin-1-yl)-1,3-dioxolan-2-yl) methyl) benzenamine
B5		$C_{24}H_{26}Cl_2N_6O_2$	501.41	N-((2-(4-((4,6-dichloro-1,3,5-triazin-2-yl) methyl) piperazin-1-yl)-1,3-dioxolan-2-yl) methyl)-N-phenylbenzenamine
Std		$C_{24}H_{29}NO_3$	379.49	2-((1-benzylpiperidin-4-yl) methyl)-2,3-dihydro-5,6-dimethoxyinden-1-one

Computational analysis of Designed Derivative Compounds

A total 10 designed Piperazine derivative compounds were carried out Molecular Docking studies with 1EVE Protein.

It was observed that the most potent 1EVE inhibitor in our designed derivative compounds B2, B3, B4 and B5 displayed significant interactions in the CAS binding sites of the enzyme to provide maximal inhibitory profile as similar to Donepezil Standard drug. The position of compounds B2, B3, B4 and B5 with respect to the key residues in the binding sites were shown in**.**

The results of 10 designed derivative compounds with 1EVE were obtained as Molecular docking Studies were mentioned in**.**

Table 2: Molecular docking results representing docking sores

S.NO	CODE	DOCKING SCORE (1)	DOCKING SCORE (2)	DOCKING SCORE (3)	AVERAGE
1.	A1	-9.0	-8.8	-8.7	-8.83
2.	A2	-9.1	-9.0	-9.0	-9.03
3.	A3	-9.6	-8.4	-7.7	-8.56
4.	A4	-10.1	-9.5	-9.4	-9.6
5.	A5	-10.0	-9.8	-9.6	-9.8
6.	B1	-9.8	-9.7	-9.4	-9.63
7.	B2	-10.4	-10.3	-9.7	-10.13
8.	B3	-10.4	-10.4	-9.9	-10.23
9.	B4	-10.6	-10.3	-10.1	-10.33
10.	B5	-11.5	-10.6	-10.2	-10.76
11.	Std	-10.5	-10.1	-9.9	-10.16

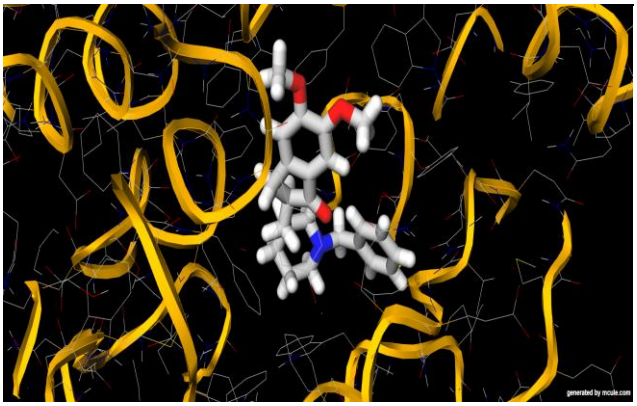
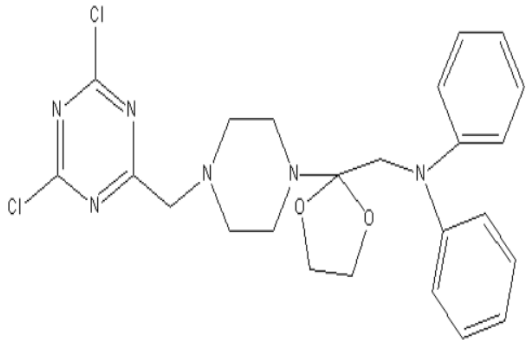



FIGURE 23: Binding interaction of Standard (Donepezil) with 1EVE

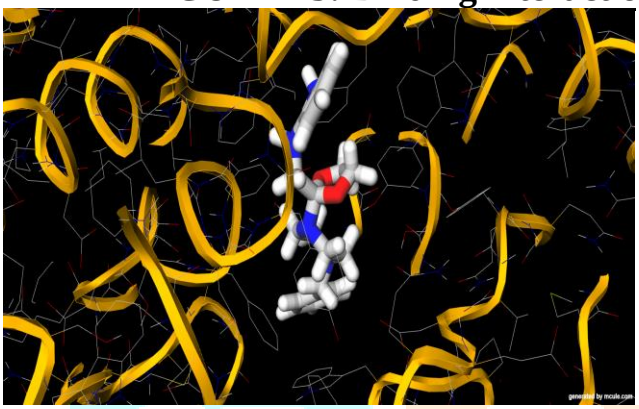
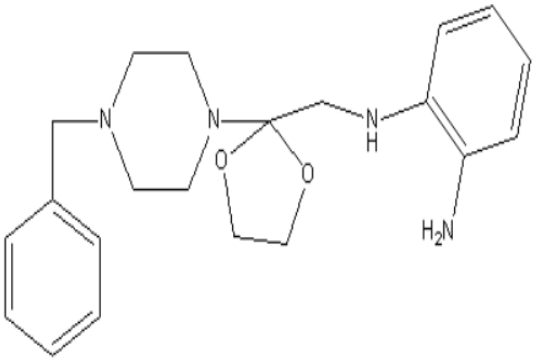



FIGURE 24: Binding interaction of A1 with 1EVE

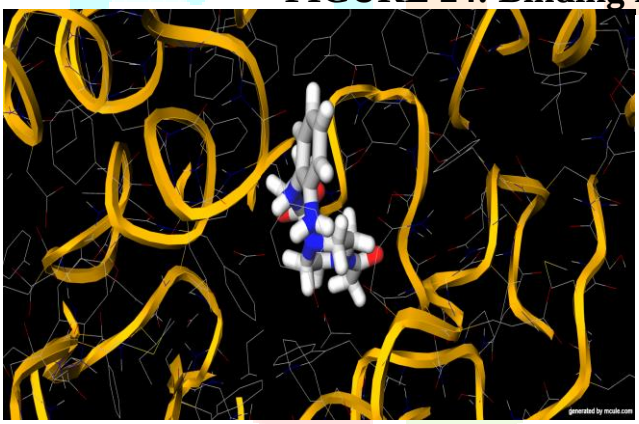
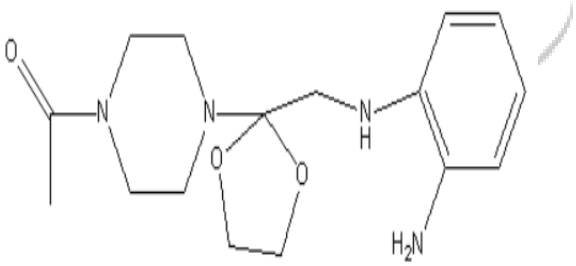



FIGURE 25: Binding interaction of A2 with 1EVE

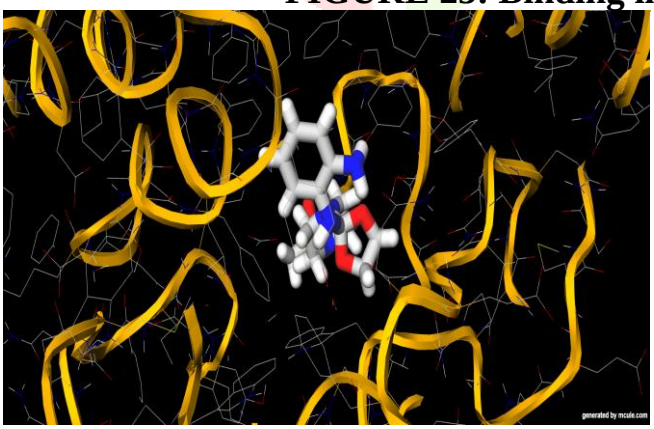
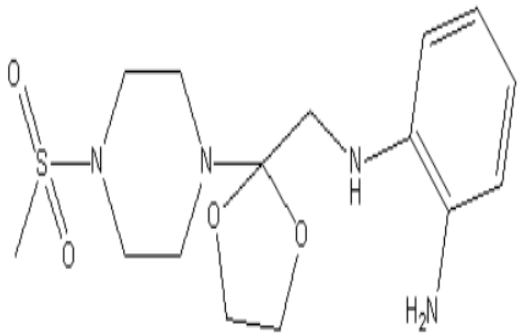
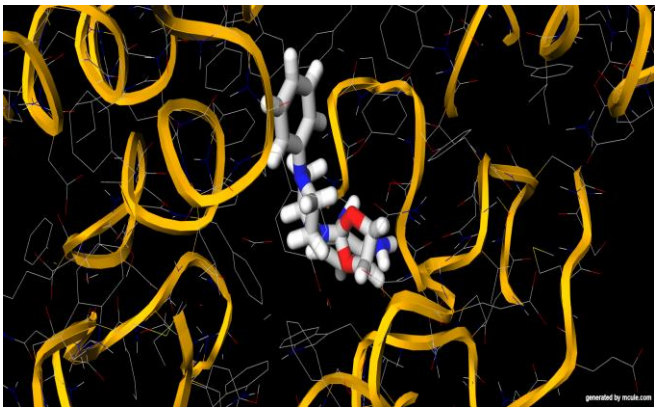



FIGURE 26: Binding interaction of A3 with 1EVE



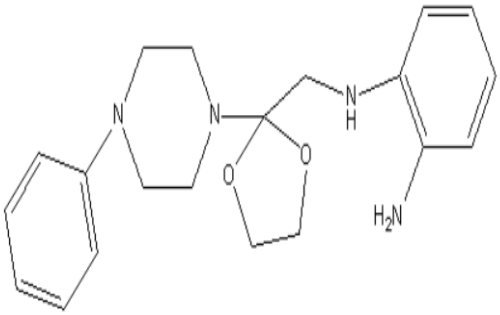
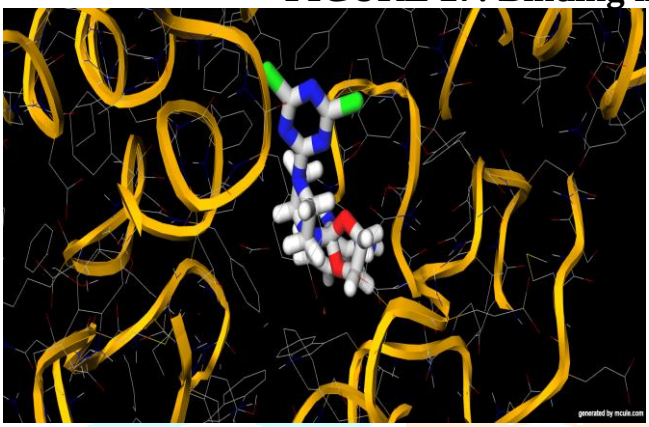


FIGURE 27: Binding interaction of A4 with 1EVE



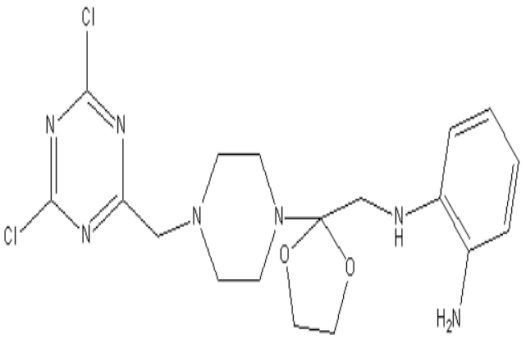
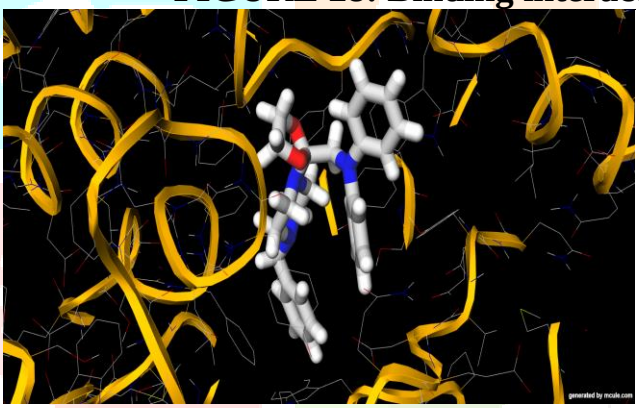


FIGURE 28: Binding interaction of A5 with 1EVE



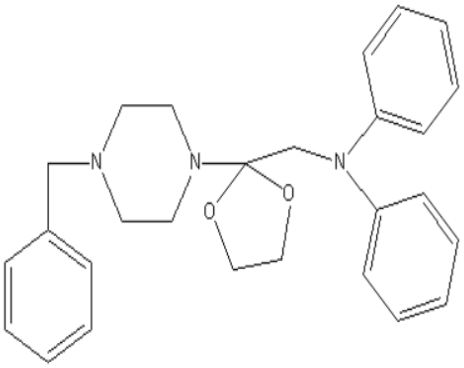
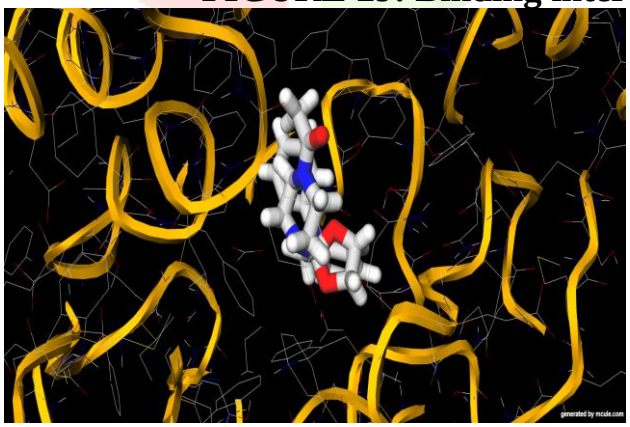


FIGURE 29: Binding interaction of B1 with 1EVE



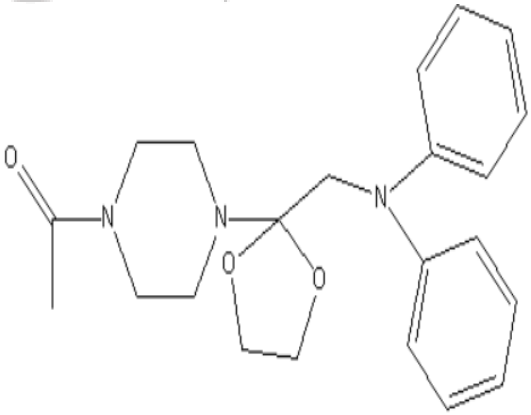


FIGURE 30: Binding interaction of B2 with 1EVE

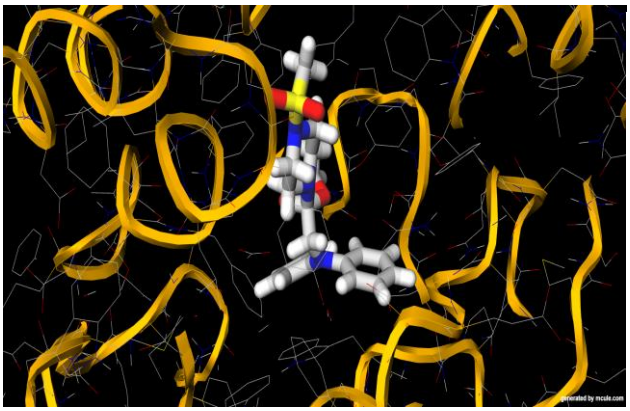
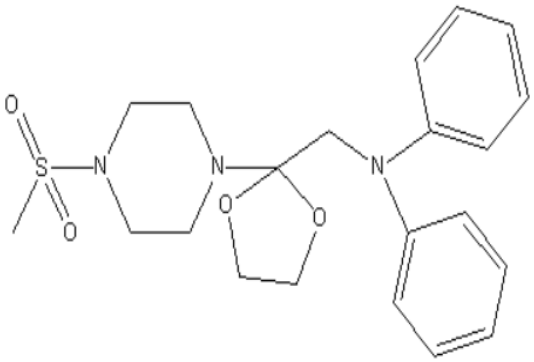



FIGURE 31: Binding interaction of B3 with 1EVE

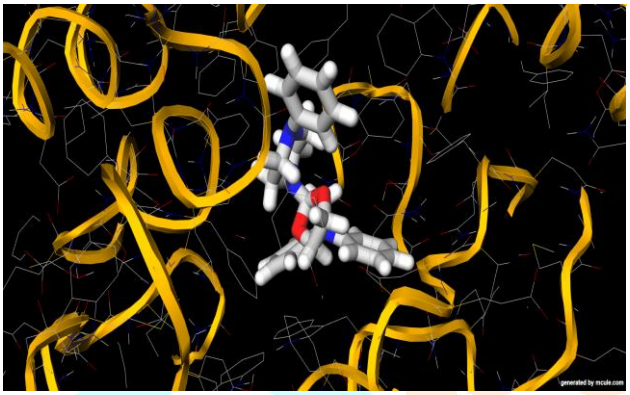
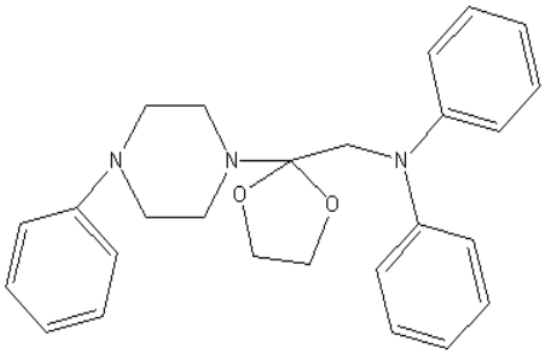



FIGURE 32: Binding interaction of B4 with 1EVE

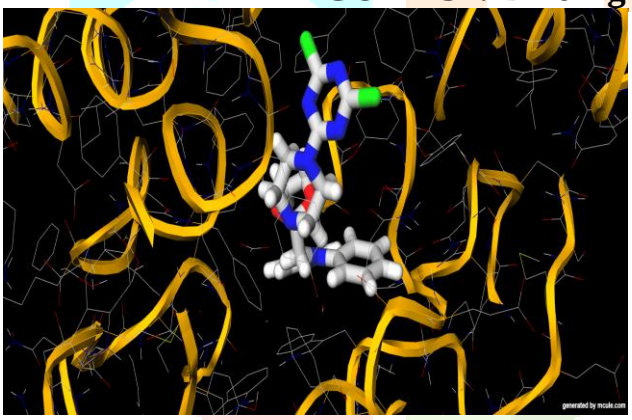
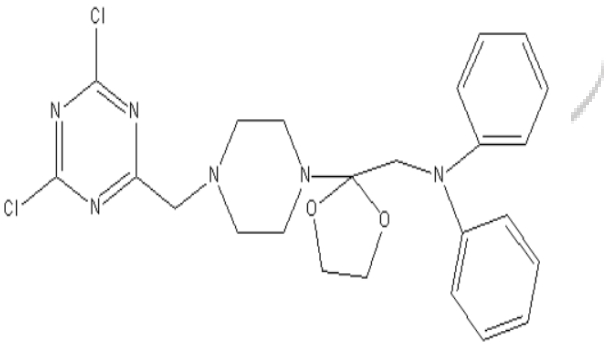



FIGURE 33: Binding interaction of B5 with 1EVE

ADME studies:

To Predict the *In-silico* ADME profile of synthesized molecules was done by using the SWISS ADME programme physically significant descriptors and pharmacologically relevant properties of these compounds were predicted.

Fundamental physiochemical features of CNS drugs are mainly related to their ability to penetrate the blood-brain barrier (BBB) and exhibit CNS activity. Our results indicated that compounds from all the two series **(A_1-A_5)** and **(B_1-B_5)** showed drug like characteristics based on Lipinski's rule of five (Mol MW<500, logP<5, donor HB<5, acceptor HB<10). All the synthesized derivative compounds were showed very low permeability for Caco-2, displayed good oral absorption, indicate their moderate binding with plasma protein and presented moderate in silico possible toxicity risks. The predicted ADMET properties revealed that all compounds fulfil drug-like criteria and could be considered as good candidate for drug development.

All the synthesized compound derivatives have Standard Drug (Donepezil) like ADMET properties. The results of *in-silico* ADME studies mentioned in.

ADME studies:

ADME properties were calculated using SWISSADME server and results were displayed in **Table 3, 4.**

Table 3: In-silico Absorption and Distribution studies of Designed Derivative Compounds

Comp. Code	ABSORPTION						
	Human Intesti_ _nal (HIA)	Aqueo_ us Solubil _ity (logS)	CaCO-2 Perme_ _ability (LogP, cm/s)	P-glycoprotein Substrate		Blood Brain Barrier Penetration (BBB)	Skin permeation
				Substrate	Inhibitor		
A1	HIGH	YES	NO	YES	NO	YES	-7.04 CM/S
A2	HIGH	YES	NO	YES	NO	NO	-8.64 CM/S
A3	HIGH	YES	NO	YES	NO	NO	-8.56 CM/S
A4	HIGH	YES	NO	YES	NO	YES	-6.75 CM/S
A5	HIGH	YES	NO	YES	NO	NO	-6.97 CM/S
B1	HIGH	NO	NO	YES	NO	YES	-5.73 CM/S
B2	HIGH	YES	NO	YES	NO	YES	-6.87 CM/S
B3	HIGH	YES	NO	YES	NO	YES	7.24 CM/S
B4	HIGH	NO	NO	YES	NO	YES	-5.43 CM/S
B5	HIGH	NO	NO	NO	NO	YES	-5.65 CM/S
DONEPEZIL	HIGH	NO	NO	YES	NO	YES	-5.58 CM/S
LIMIT	1.0000	1-7.5	4.0000	1.0000			1.0000

*=Inhibitor/Substrate

Table 4: In-Silico Metabolism Studies of Designed Derivative Compounds

Comp. Code	CYP450 Inhibitor					Lipinski
	1A2	2C9	2D6	2C19*	3A4	
A1	NO	NO	YES	NO	NO	YES 0 Violation
A2	NO	NO	NO	NO	NO	YES 0 Violation
A3	NO	NO	NO	NO	NO	YES 0 Violation
A4	NO	NO	YES	NO	NO	YES 0 Violation
A5	YES	NO	YES	NO	YES	YES 0 Violation
B1	NO	YES	YES	NO	YES	YES 0 Violation
B2	NO	NO	YES	YES	YES	YES 0 Violation
B3	NO	YES	YES	YES	YES	YES 0 Violation
B4	YES	YES	YES	NO	YES	YES 0 Violation
B5	YES	YES	YES	YES	YES	YES 0 Violation
Donepezil	NO	NO	YES	NO	YES	YES 0 Violation

*=Inhibitor/Substrate

CONCLUSION:

All the designed compound derivatives of Novel 1, 4-disubstituted Piperazine Derivative Compounds were evaluated with Physical, spectral Characterization and its computational analysis by appropriate were compared with Donepezil, Piperazine Analog standard drugs respectively.

The results of docking study revealed that the binding profile for synthesized derivative compounds B2, B3, B4, and B5 was found significant interactions with Piperazine Analogue due to interactions with CAS of 1EVE.

The predicted ADME properties revealed that all compounds fulfil drug-like criteria and could be considered as good candidate for drug development. All the synthesized compound derivatives have Standard Drug (Donepezil) like ADME properties.

The further scope of designed derivatives of Novel 1, 4-disubstituted Piperazine derivatives need to evaluation of various *in vivo* Pharmacological Studies to bring potentially active molecules.

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