WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 5, 2158-2177. Research Article ISSN 2277– 7105

INSILICO IDENTIFICATION OF NEWER POTENTIAL *GLYCOGEN SYNTHASE KINASE 3β* INHIBITORS FOR TREATMENT OF ALZHEIMER DISEASE

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Article Received on
20 March 2022,

Revised on 10 April 2022,
Accepted on 30 April 2022

DOI: 10.20959/wjpr20225-23980

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ABSTRACT

Alzheimer's disease is a progressive neurologic disorder that causes the brain to shrink (atrophy) and brain cells to die. Alzheimer's disease is the most common cause of dementia — a continuous decline in thinking, behavioural and social skills that affects a person's ability to function independently**. Aim**: This prompted us to design newer *GSK-3β* inhibitor as efficient therapeutic drugs for the treatment of Alzheimer's Disease. **Materials and Methods:** Based on the common pharmacophoric features for the inhibition of *GSK-3β* inhibitors, a series of leads were designed using computational methods. A virtual library consisting of newly designed 70 molecules as GSK-3β inhibitors was constructed. Based on these facts, a virtual library has been generated with 70 newly designed ligands containing imidazole, benzimidazole, aminothiazole, oaxzole, thaiazole, benzimidazole heterocyclic nucleus as *GSK-3β* inhibitors(70). The binding mechanism of newly designed ligands with target enzymes *GSK-3β* inhibitors was studied using a *Autodock tools 1.5.6*. **Conclusion:** The designed compounds were subjected and filtered by applying ADMET properties. The newly designed ligands GSK-3 I_{14}, GSK-3 I_{30}, GSK-3 I_{34}, GSK-3 I_{41}, GSK-3 I_{45}, GSK-3 I_{47}, GSK-3 I_{52}, GSK-3 I_{56}, GSK-3 I_{60}, GSK-3 I_{66}, GSK-3 I_{67}, GSK-3 I_{69} were found to be highly active hits.

KEYWORDS: Alzheimer's disease, *GSK-3β*, ADMET properties, docking studies.

INTRODUCTION

Alzheimer’s disease is a progressive neurological disease of the brain leading to the irreversible loss of neurons and the loss of intellectual abilities, including memory and

reasoning, which become severe enough to impede social or occupational functioning. Alzheimer's disease is also known as simply Alzheimer's, and Senile Dementia of the Alzheimer Type (SDAT). Patients with Alzheimer's have a deficiency in the levels of some vital brain chemicals which are involved with the transmission of messages in the brain – neurotransmitters. Alzheimer's is also a terminal disease – it is incurable and causes death. Aloysius Alzheimer was a German neuropathologist and psychiatrist. He is credited with identifying the first published case of "presenile dementia" in 1906, which Kraepelin later identified as Alzheimer's disease – naming it after his colleague. Alzheimer's disease accounts for 50 to 80 percent of dementia case1.

The main aim of the study is to identify a novel, safe and effective newer drugs for the treatment of Alzheimer's disease with good predicted capability to inhibit the *Glycogen synthase kinase 3*(*GSK-3β*) using Computational drug designing methods.

MATERIALS AND METHODS

Selection of Target

Protein Data Bank (PDB) is a crystallographic database for three dimensional structural data of large biological molecules, such as proteins, Nucleic acid and Complex assemblies. The targets creating the greatest enthusiasm currently for the treatment of Alzheimer's disease include *GSK-3β* inhibitors, Nicotinic receptor agonism, GABA receptor agonism and antagonism, Serotonergic modulation, Histamine H3 receptor antagonism, Phosphodiesterase inhibition. GSK-3 is emerging as a prominent drug target in the CNS.

The most exciting of the possibilities of GSK3 lies within the treatment of Alzheimer's disease where abnormal increases in GSK3 levels and activity have been associated with neuronal death, paired helical filament tau formation and neurite retraction as well as a decline in cognitive performance. Abnormal activity of GSK3 is also implicated in stroke. GSK-3 phosphorylates tau protein, the principal component of neurofibrillary tangles, inhibition of GSK-3beta offers a new approach to reduce the formation of both amyloid plaques and neurofibrillary tangles, two pathological hallmarks of Alzheimer's disease.

Ultimately human trials will help to understand the potential risks and benefits of these novel approaches across several diseases.

Some of the recent and efficient PDB file receptors for the treatment of Alzheimer's Disease with low resolution were selected and further evaluated by its resolution value (R value), optimized crystal ligand and interaction details. Some of the selected receptors listed below from which the highlighted best PDB target was selected for present study.

In the present review, we summarize the properties of GSK3 and discuss the potential for such a therapy in Alzheimer's disease.

Table No. 1: List of PDB for GSK-3β target for Alzheimer's Disease.

S.NO	CODE	RESOLUTION (A^O)	S.NO	CODE	RESOLUTION (A^O)
1	5T31	2.85	9	5OY4	3.2
2	5KPM	2.69	10	4E7W	3.3
3	**6Y9S**	**2.03**	11	6Y9R	2.08
4	5KPK	2.4	12	7B6F	2.05
5	5KPL	2.6	13	1H8F	2.8
6	5HLP	2.45	14	1J1C	2.1
7	3E3P	2	15	1J1B	1.8
8	5HLN	3.1	16	1Q5K	1.94

The active amino acid binding sites for the selected PDB*(*6Y9S) of *GSK-3β* target was identified by reviewing the journals.

Table no. 2: Active amino acid site of GSK-3β target.

Receptor	PDB code	Active amino acid binding sites
GSK-3B beta	3BEA	Tyr 323 (A), Gln 280 (A), Gln 295 (A), Leu 359 (A), Arg 344 (A), Asn 361 (A), Cys 335 (A), Phe 340 (A), Phe 360 (A), Trp 301 (A), Leu 321 (A), Leu 273 (A), Glu 366 (A), Ala 243 (A), Ala 298 (A), Gly 244 (A), Ser 318 (A), His 381 (A), His 299 (A), Pro 346 (A), Val 348 (A), Gly 244 (A), Ile 256 (A)

Pharmacophoric identification

A Pharmacophore is defined as a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecules biological activity. Hence all these chemical features were used as 3D structural query to screen the chemical database for retrieving new potent *GSK-3β* inhibitors.

Database screening

Scaffold hopping, or chemo type switching is a technology that modifies the chemical scaffold of a bioactive compound retaining the activity and key interaction points, or the interacting molecular fragments of the parent compound.

Virtual library: When the efficient journals and research articles were reviewed, compounds containing chemical features like hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), aromatic ring features were found to be effective agents as *Glycogen Synthase Kinase 3* ***(GSK-3β)*** inhibitor. A virtual scaffold library consisting of newly designed 70 molecules has *GSK-3β* inhibitors has been constructed.

Lead optimisation

1. Drug likeness screening: Drug likeness is qualitative concept used in drug design for how druglike substances is to be an effective drug Dug likeness properties was performed for all the newly designed *GSK-3β* inhibitors by using different online *softwares* like Lipinski's rule of five, *Osiris* online software, *Molinspiration* software and the results were tabulated.

2. Docking studies: All the designed ligands were subjected to docking studies using *Autodocktools 1.5.6* software and the results were discussed below. *Autodock tools1.5.6* is a molecular modeling simulation, especially effective for protein ligand docking.

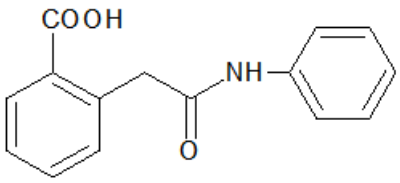
RESULTS AND DISCUSSION

In the search of new and potent *GSK-3β* inhibitors as antiepileptic agents, a virtual scaffold library of 70 molecules was constructed using chemsketch by reviewing efficient articles and journals and based on features such as HBA, HBD and Aromatic ring Pharmacophoric features.

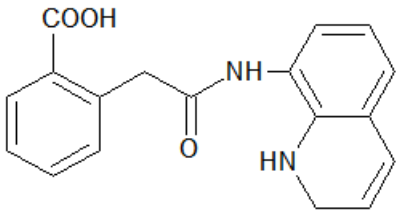
Table no. 3: Pharmacophoric features used in construction of library of GSK-3β inhibitors.

HBD	HBA	Aromatic ring
Imidazole, Benzimidazole, Aminothiazole, PhenolicOH, COOH, CH2OH, CHOH, Ether, Carbonyl, Pyridine, Nitro, Amide, Imines, Nitriles, Oxazole, Thiazole, Sulfoxide, Aniline, Alkyl amines, Hydrazine.	C=O of aliphatic and aromatic amides, C=O of aromatic ketones.	Aromatic and Heteroaromatic compounds

Virtual library of *GSK-3β* inhibitors



GSK-3B I_1



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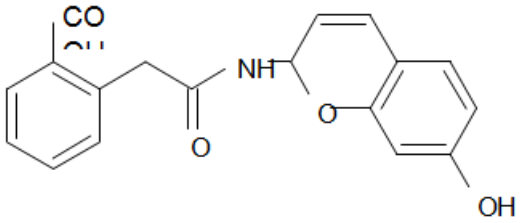

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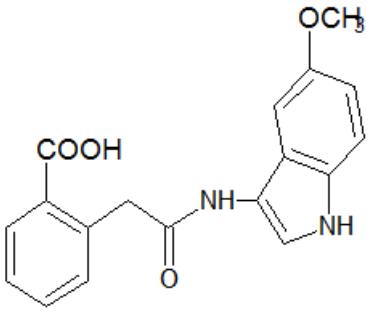

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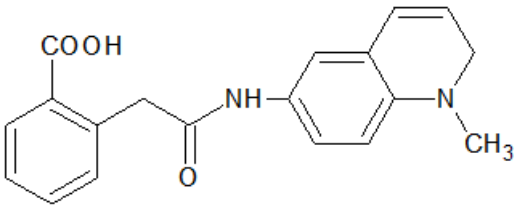

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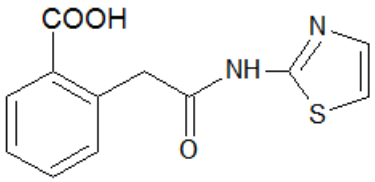

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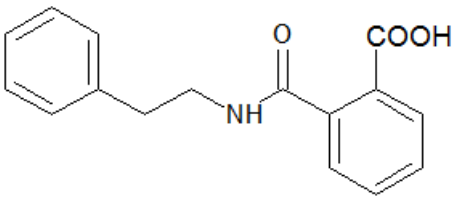

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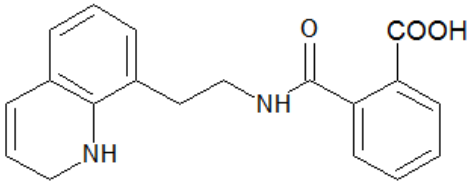

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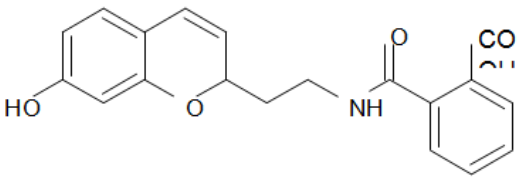

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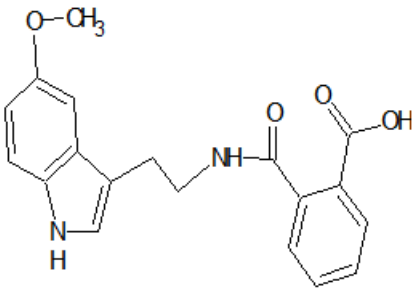

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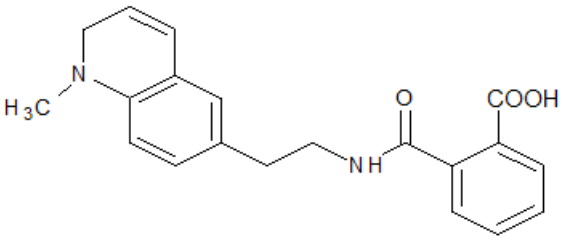

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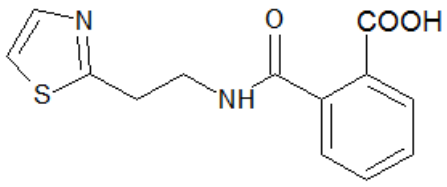

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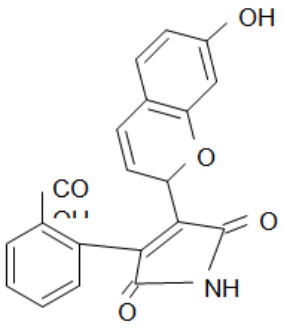

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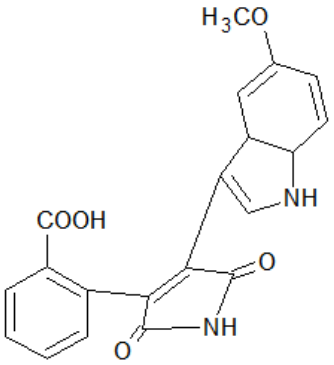

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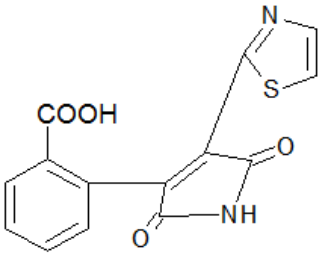

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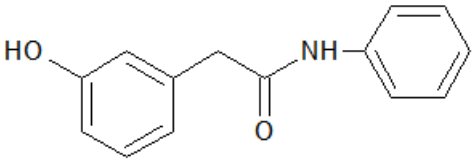

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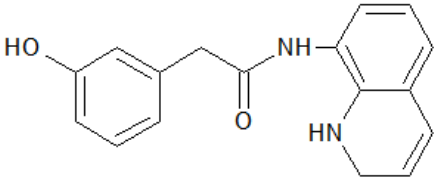

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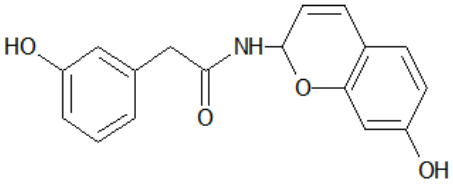

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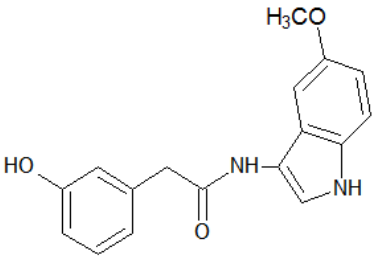

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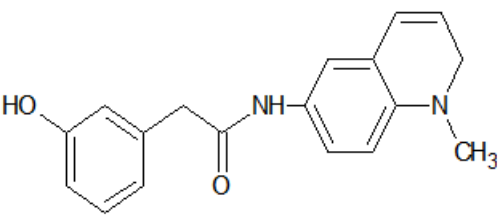

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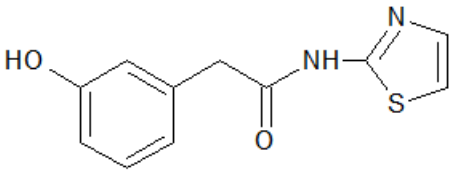

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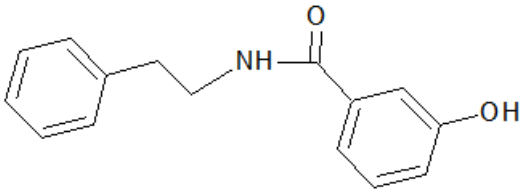

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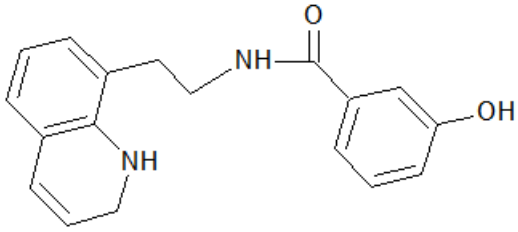

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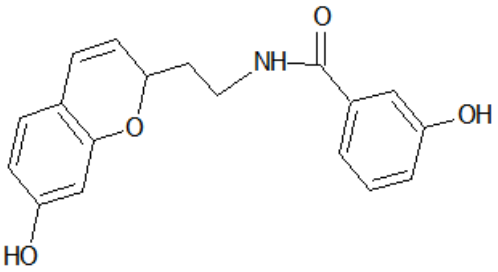

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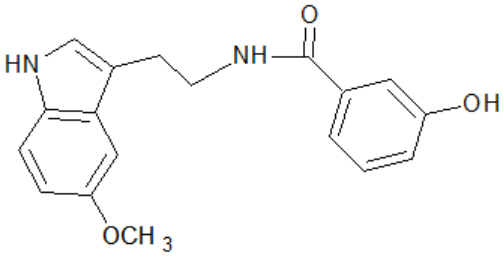

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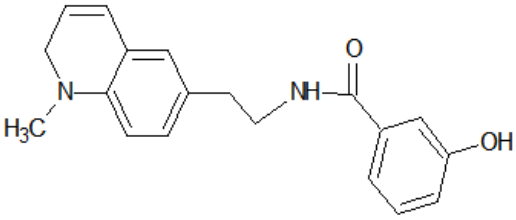

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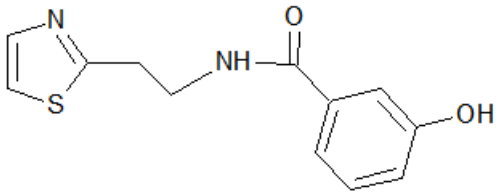

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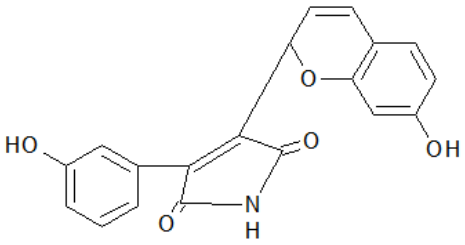

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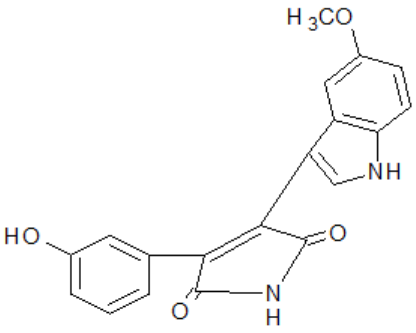

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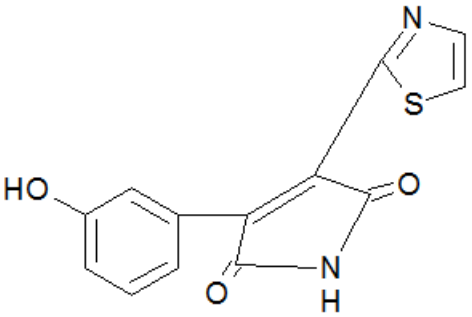

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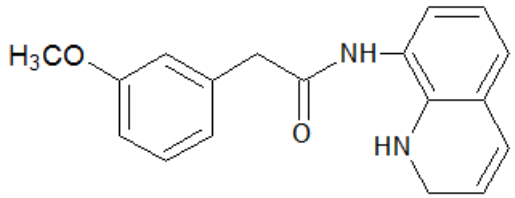

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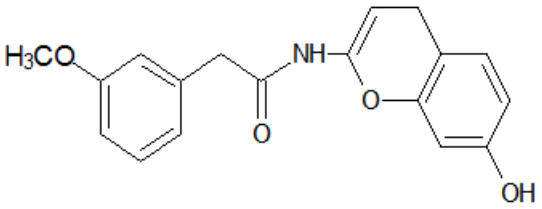

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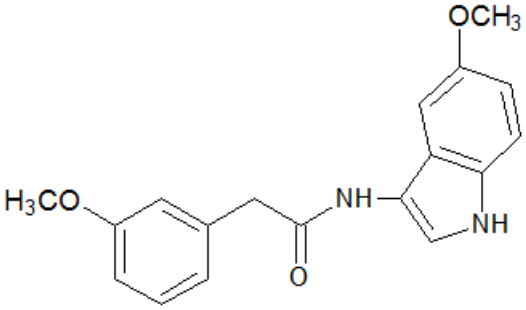

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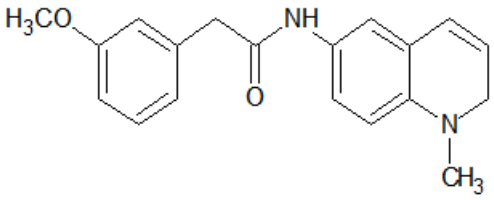

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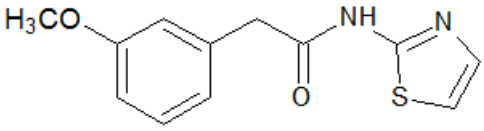

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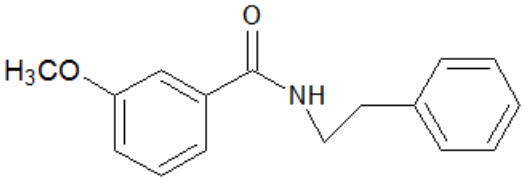

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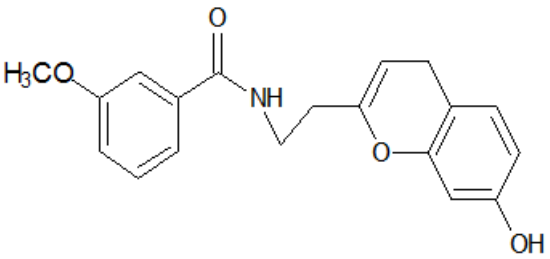

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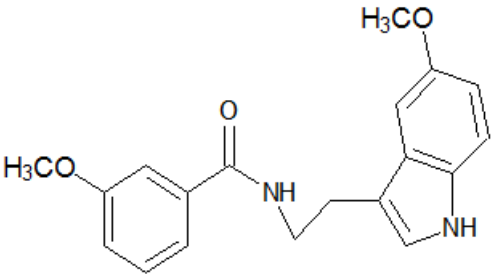

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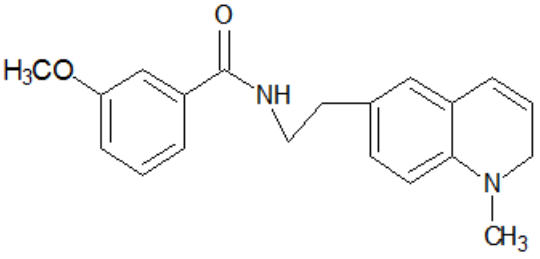

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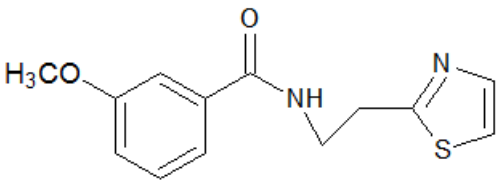

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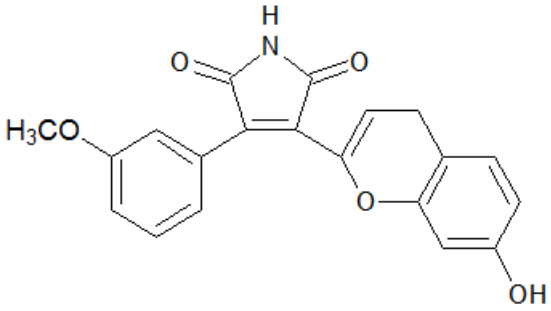
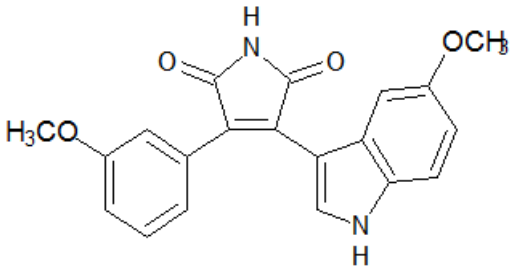
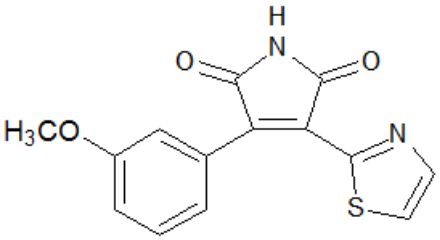


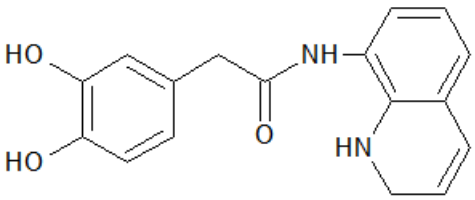
GSK-3B I_{41}



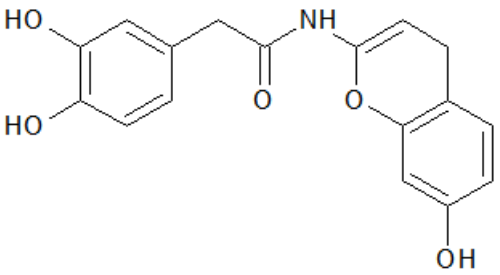
GSK-3B I_{42}



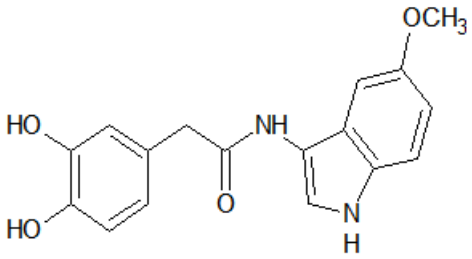
GSK-3B I_{43}



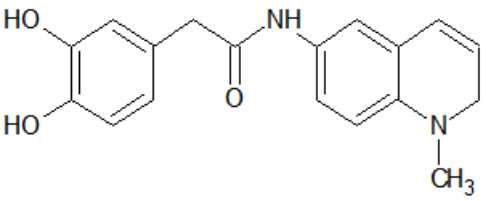
GSK-3B I_{44}



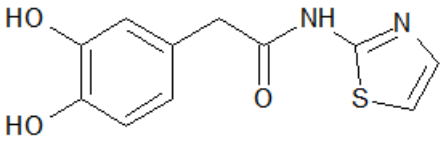
GSK-3B I_{45}



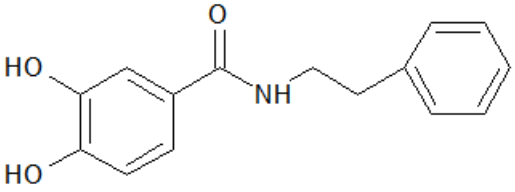
GSK-3B I_{46}



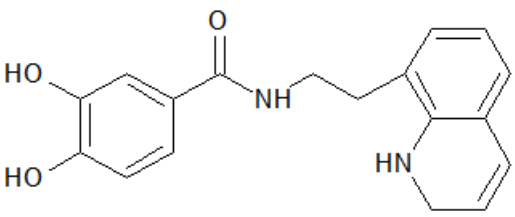
GSK-3B I_{47}



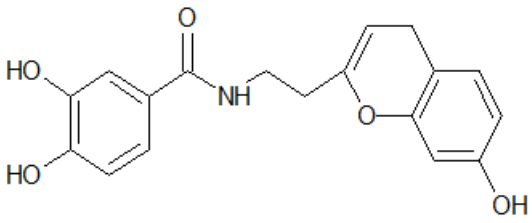
GSK-3B I_{48}



GSK-3B I_{49}



GSK-3B I_{50}



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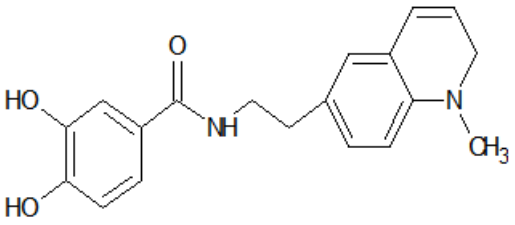
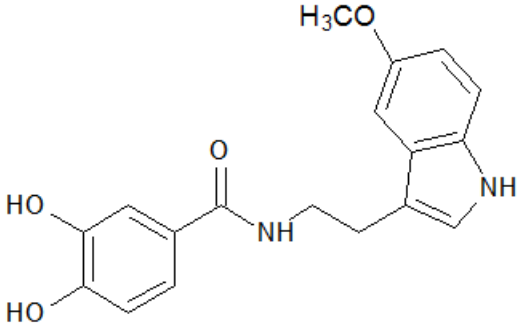
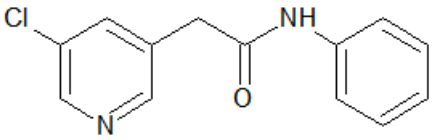


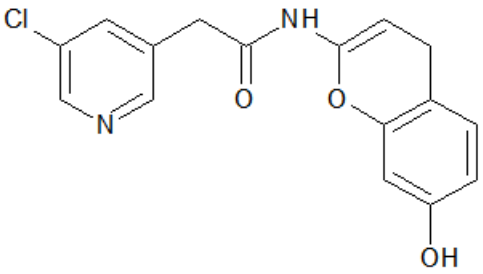
GSK-3B I_{52}



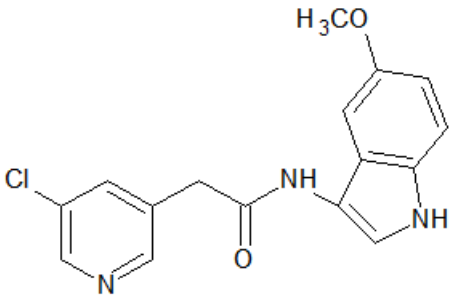
GSK-3B I_{53}



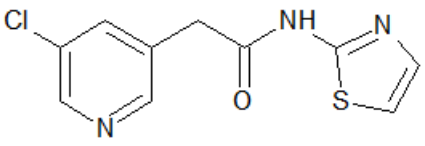
GSK-3B I_{54}



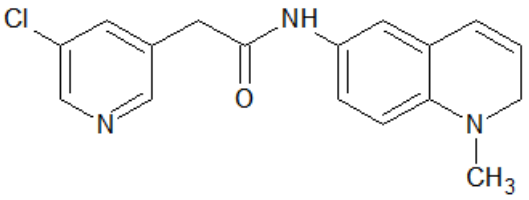
GSK-3B I_{55}



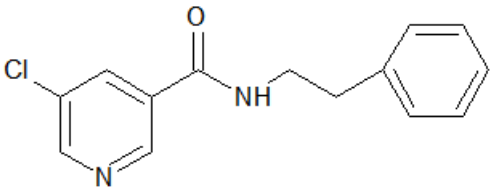
GSK-3B I_{56}



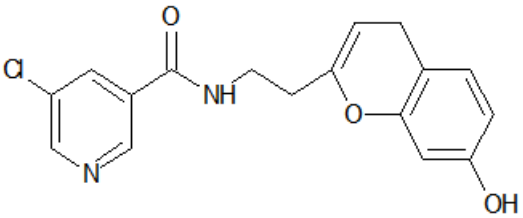
GSK-3B I_{57}



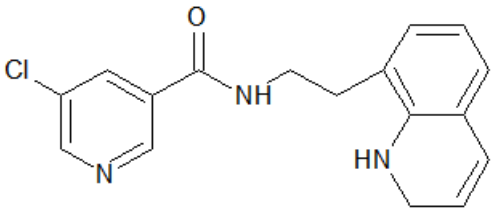
GSK-3B I_{58}



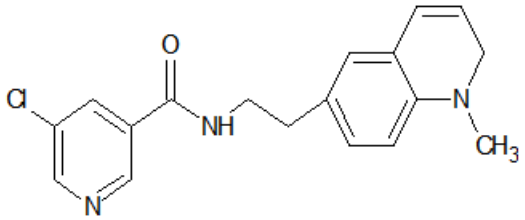
GSK-3B I_{59}



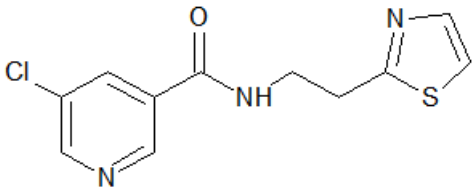
GSK-3B I_{60}



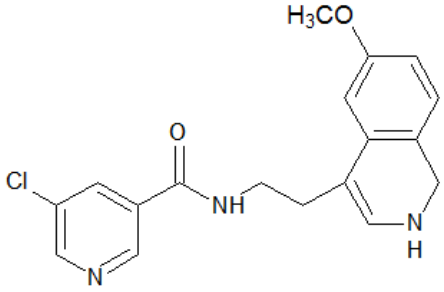
GSK-3B I_{61}



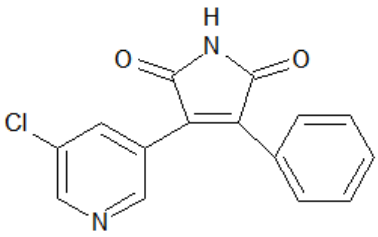
GSK-3B I_{62}



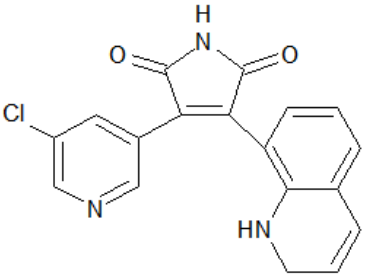
GSK-3B I_{63}



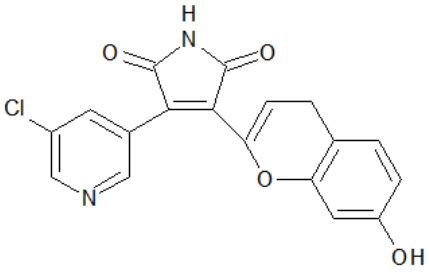
GSK-3B I_{64}



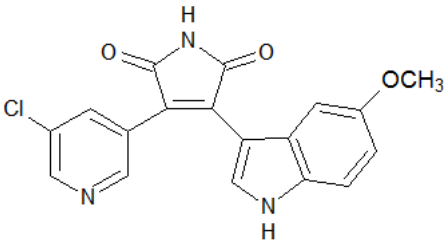
GSK-3B I_{65}



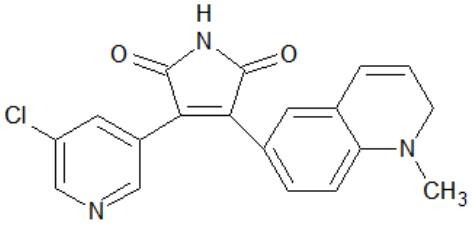
GSK-3B I_{66}



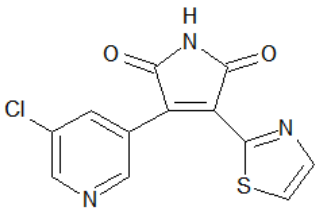
GSK-3B I_{67}



GSK-3B I_{68}



GSK-3B I_{69}



GSK-3B I_{70}

Drug likeness screening

The newly designed ligands were subjected to molecular docking, ADMET properties, Lipinski rule of five, toxicity prediction. Through this, the newly generated ligands are filtered and refined that constitutes optimization of leads.

Table no. 4: Lipinski's rule of five for the GSK-3β inhibitors.

COMPOUND	LOG P	TPSA	MOL WT	nON	nOHNH	nrotb	nViolation
GSK-3B I_1	2.44	66.40	255.27	4	2	4	0
GSK-3B I_2	2.61	78.42	308.34	5	3	4	0
GSK-3B I_3	2.26	95.86	325.32	6	3	4	0
GSK-3B I_4	2.63	91.42	324.34	6	3	5	0
GSK-3B I_5	2.88	69.64	322.36	5	2	4	0
GSK-3B I_6	1.50	79.29	262.29	5	2	4	0
GSK-3B I_7	2.46	66.40	269.30	4	2	5	0
GSK-3B I_8	1.69	78.42	322.36	5	3	5	0
GSK-3B I_9	2.08	95.86	339.35	6	3	5	0
GSK-3B I_{10}	2.64	91.42	338.36	6	3	6	0
GSK-3B I_{11}	2.90	69.64	336.39	5	2	5	0
GSK-3B I_{12}	1.12	79.29	276.32	5	2	5	0
GSK-3B I_{13}	2.39	116.9	363.32	7	3	3	0
GSK-3B I_{14}	0.68	108.9	364.36	7	3	4	0
GSK-3B I_{15}	1.74	100.2	300.30	6	2	3	0
GSK-3B I_{16}	2.42	49.33	227.26	3	2	3	0
GSK-3B I_{17}	2.59	61.35	280.33	4	3	3	0
GSK-3B I_{18}	2.23	78.79	297.31	5	3	3	0
GSK-3B I_{19}	2.60	74.35	296.33	5	3	4	0
GSK-3B I_{20}	2.85	52.56	294.35	4	2	3	0
GSK-3B I_{21}	1.47	62.22	234.28	4	2	3	0
GSK-3B I_{22}	2.43	49.33	241.29	3	2	4	0
GSK-3B I_{23}	1.67	61.35	294.35	4	3	4	0
GSK-3B I_{24}	2.06	78.79	311.34	5	3	4	0
GSK-3B I_{25}	2.62	74.35	310.35	5	3	5	0
GSK-3B I_{26}	2.87	52.56	308.38	4	2	4	0
GSK-3B I_{27}	1.09	62.22	248.31	4	2	4	0
GSK-3B I_{28}	2.36	99.62	335.31	6	3	2	0
GSK-3B I_{29}	2.85	95.19	334.33	6	3	3	0
GSK-3B I_{30}	1.72	83.05	272.29	5	2	2	0
GSK-3B I_{31}	3.12	50.36	294.35	4	2	4	0
GSK-3B I_{32}	2.77	67.79	311.34	5	2	4	0
GSK-3B I_{33}	3.14	63.36	310.35	5	2	5	0
GSK-3B I_{34}	3.39	41.57	308.38	4	1	4	0
GSK-3B I_{35}	2.01	51.22	248.31	4	1	4	0
GSK-3B I_{36}	2.97	38.33	255.32	3	1	5	0
GSK-3B I_{37}	2.59	67.79	325.36	5	2	5	0

COMPOUND	LOG P	TPSA	MOL WT	nON	nOHNH	nrotb	nViolation
GSK-3B I_{38}	3.15	63.36	324.38	5	2	6	0
GSK-3B I_{39}	3.41	41.57	322.41	4	1	5	0
GSK-3B I_{40}	1.63	51.22	262.33	4	1	5	0
GSK-3B I_{41}	2.90	88.63	349.34	6	2	3	0
GSK-3B I_{42}	3.38	84.19	348.36	6	2	4	0
GSK-3B I_{43}	2.25	72.06	286.31	5	1	3	0
GSK-3B I_{44}	1.29	81.58	324.38	5	4	5	0
GSK-3B I_{45}	1.77	99.02	313.31	6	4	3	0
GSK-3B I_{46}	2.13	94.58	312.32	4	6	4	0
GSK-3B I_{47}	2.39	72.79	310.35	5	3	3	0
GSK-3B I_{48}	1.01	82.45	250.28	5	3	3	0
GSK-3B I_{49}	1.97	69.55	257.29	4	3	4	0
GSK-3B I_{50}	1.20	81.58	310.35	5	4	4	0
GSK-3B I_{51}	1.59	99.02	327.34	6	4	4	0
GSK-3B I_{52}	2.40	72.79	324.38	5	3	4	0
GSK-3B I_{53}	2.15	94.58	326.35	6	4	5	0
GSK-3B I_{54}	2.51	41.99	246.70	3	1	3	0
GSK-3B I_{55}	2.32	71.45	316.74	5	2	3	0
GSK-3B I_{56}	2.69	67.02	315.76	5	2	4	0
GSK-3B I_{57}	2.95	45.23	313.79	4	1	3	0
GSK-3B I_{58}	1.56	54.88	253.71	4	1	3	0
GSK-3B I_{59}	2.52	41.99	260.72	3	1	4	0
GSK-3B I_{60}	2.15	71.45	330.77	5	2	4	0
GSK-3B I_{61}	1.75	54.02	313.79	4	2	4	0
GSK-3B I_{62}	2.96	45.23	327.81	4	1	4	0
GSK-3B I_{63}	1.19	54.88	267.74	4	1	4	0
GSK-3B I_{64}	1.91	63.25	343.81	5	2	5	0
GSK-3B I_{65}	2.92	62.83	284.70	4	1	2	0
GSK-3B I_{66}	3.09	74.85	337.77	5	2	2	0
GSK-3B I_{67}	2.62	92.29	354.75	6	2	2	0
GSK-3B I_{68}	3.10	87.85	353.76	6	2	3	0
GSK-3B I_{69}	3.36	66.06	351.79	5	1	2	0
GSK-3B I_{70}	1.97	75.72	291.72	5	1	2	0

ADMET properties

The ADMET results of the selected ligands like GSK-$3I_{14}$, GSK-$3I_{41}$, GSK-$3I_{47}$, GSK-$3I_{66}$ GSK-$3I_{67}$ were depicted in the following images.

originalSMILES O=C(O)c1ccccc1C=4C(=O)NC(=O)C=4C2=CNC3C=CC(=CC23)OC
miSMILES: O=C(O)c1ccccc1C=4C(=O)NC(=O)C=4C2=CNC3C=CC(=CC23)OC

Molinspiration property engine v2021.10

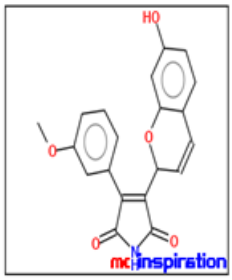
miLogP	0.68
TPSA	108.49
natoms	27
MW	364.36
nON	7
nOHNH	3
nviolations	0
nrotb	4
volume	310.16

Get data as text (for copy / paste).

Get 3D geometry BETA

GSK-3I$_{14}$

originalSMILES O=C(NC2=O)C(C3OC(C=C(O)C=C4)=C4C=C3)=C2C1=CC(OC)=CC=C1
miSMILES: O=C(NC2=O)C(C3OC(C=C(O)C=C4)=C4C=C3)=C2C1=CC(OC)=CC=C1



Molinspiration property engine v2021.10

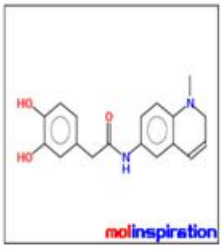
miLogP	2.90
TPSA	88.63
natoms	26
MW	349.34
nON	6
nOHNH	2
nviolations	0
nrotb	3
volume	298.35

Get data as text (for copy / paste).

Get 3D geometry BETA

GSK-3I$_{41}$

originalSMILES OC1=C(O)C=CC(CC(NC2=CC=C(N(C)CC=C3)C3=C2)=O)=C1
miSMILES: OC1=C(O)C=CC(CC(NC2=CC=C(N(C)CC=C3)C3=C2)=O)=C1



Molinspiration property engine v2021.10

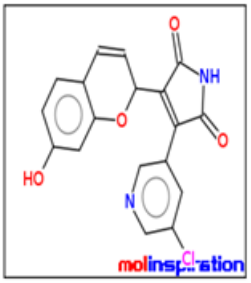
miLogP	2.39
TPSA	72.79
natoms	23
MW	310.35
nON	5
nOHNH	3
nviolations	0
nrotb	3
volume	282.40

Get data as text (for copy / paste).

Get 3D geometry BETA

GSK-3I$_{47}$

originalSMILES ClC1=CN=CC(C2=C(C3OC(C=C(O)C=C4)=C4C=C3)C(NC2=O)=O)=C1
miSMILES: ClC1=CN=CC(C2=C(C3OC(C=C(O)C=C4)=C4C=C3)C(NC2=O)=O)=C1



Molinspiration property engine v2021.1

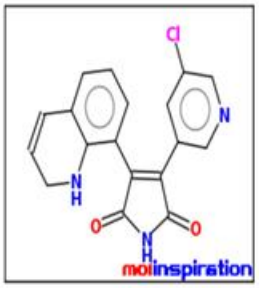
miLogP	2.62
TPSA	92.29
natoms	25
MW	354.75
nON	6
nOHNH	2
nviolations	0
nrotb	2
volume	282.18

Get data as text (for copy / paste).

Get 3D geometry BETA

GSK-3I$_{66}$

originalSMILES ClC1=CN=CC(C2=C(C3=C(NCC=C4)C4=CC=C3)C(NC2=O)=O)=C1
miSMILES: ClC1=CN=CC(C2=C(C3=C(NCC=C4)C4=CC=C3)C(NC2=O)=O)=C1



Molinspiration property engine v2021.10

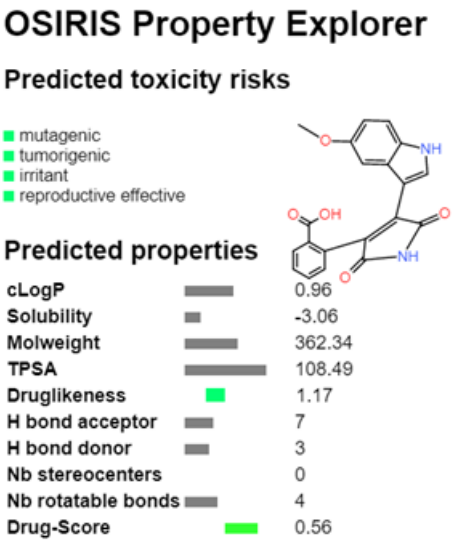
miLogP	3.09
TPSA	74.85
natoms	24
MW	337.77
nON	5
nOHNH	2
nviolations	0
nrotb	2
volume	277.56

Get data as text (for copy / paste).

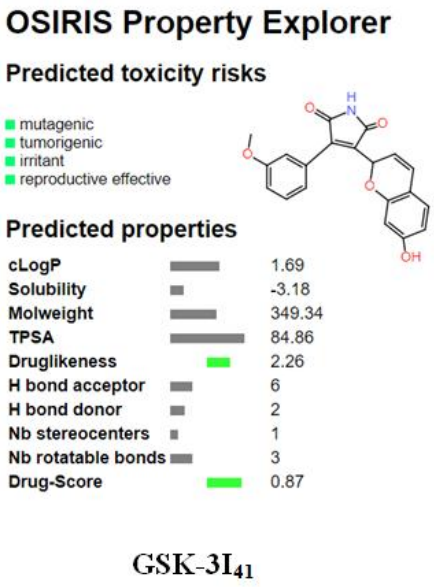
Get 3D geometry BETA

GSK-3I$_{67}$

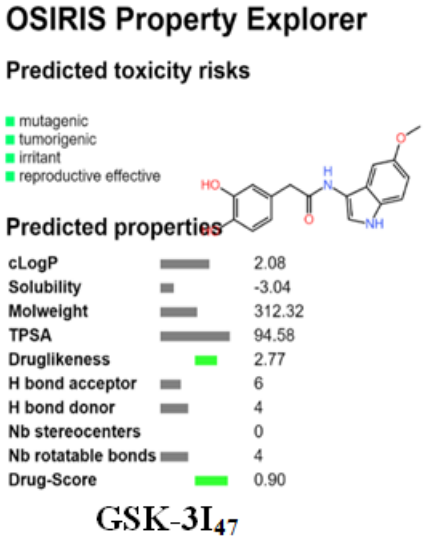
Toxicity



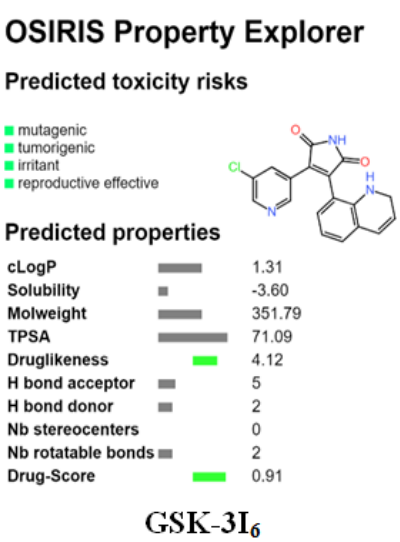
GSK-3I$_{14}$



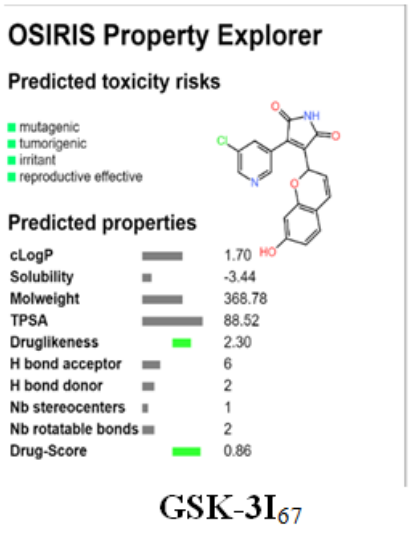
GSK-3I$_{41}$



GSK-3I$_{47}$



GSK-3I$_{6}$



GSK-3I$_{67}$

Thus all newly70 designed ligands (*GSK-3β* inhibitors) have satisfied all the above filtering method of good predictive activity with good docking scores and also drug likeness properties confirming that these molecules are accepted to be orally bioavailable.

Docking results

Docking studies: *Autodock tools1.5.6* is a molecular modeling simulation, especially effective for protein ligand docking. Based on docking scores, all the newly designed ligands were categorized as highly active, moderately active and low active hits as below.

Table no. 4: List of docking score for designed GSK-3β ligands(Autodock 1.5.6)

S.NO	LIGAND CODE	DOCKING SCORE (kcal/mol)
1	GSK-3B I_1	-6.04
2	GSK-3B I_2	-6.73
3	GSK-3B I_3	-6.57
4	GSK-3B I_4	-7.38
5	GSK-3B I_5	-6.47
6	GSK-3B I_6	-6.09
7	GSK-3B I_7	-6.01
8	GSK-3B I_8	-6.27
9	GSK-3B I_9	-7.0
10	GSK-3B I_{10}	-6.64
11	GSK-3B I_{11}	-6.12
12	GSK-3B I_{12}	-5.56
13	GSK-3B I_{13}	-6.84
14	GSK-3B I_{14}	-8.39
15	GSK-3B I_{15}	-6.4
16	GSK-3B I_{16}	-6.98
17	GSK-3B I_{17}	-6.59
18	GSK-3B I_{18}	-6.24
19	GSK-3B I_{19}	-7.38
20	GSK-3B I_{20}	-7.20
21	GSK-3B I_{21}	-6.85
22	GSK-3B I_{22}	-5.97
23	GSK-3B I_{23}	-7.1
24	GSK-3B I_{24}	-6.28
25	GSK-3B I_{25}	-6.23
26	GSK-3B I_{26}	-6.03
27	GSK-3B I_{27}	-5.82
28	GSK-3B I_{28}	--7.2
29	GSK-3B I_{29}	-7.37
30	GSK-3B I_{30}	-7.74
31	GSK-3B I_{31}	-5.01
32	GSK-3B I_{32}	-7.21
33	GSK-3B I_{33}	-6.14
34	GSK-3B I_{34}	-7.5

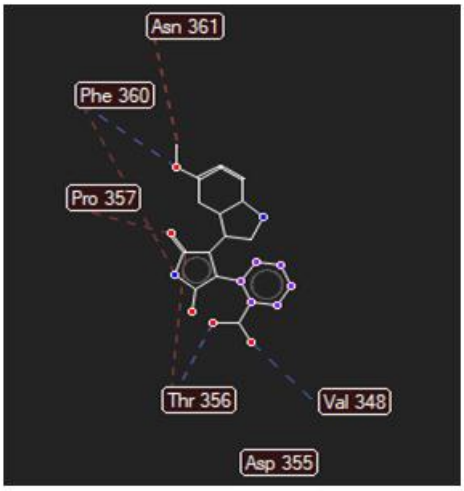
S.NO	LIGAND CODE	DOCKING SCORE (kcal/mol)
35	GSK-3B I_{35}	-6.2
36	GSK-3B I_{36}	-5.7
37	GSK-3B I_{37}	-6.9
38	GSK-3B I_{38}	-6.52
39	GSK-3B I_{39}	-5.63
40	GSK-3B I_{40}	-5.61
41	GSK-3B I_{41}	-8.25
42	GSK-3B I_{42}	-5.1
43	GSK-3B I_{43}	-7.49
44	GSK-3B I_{44}	-5.28
45	GSK-3B I_{45}	-7.93
46	GSK-3B I_{46}	-7.18
47	GSK-3B I_{47}	-8.09
48	GSK-3B I_{48}	-7.23
49	GSK-3B I_{49}	-6.41
50	GSK-3B I_{50}	-5.66
51	GSK-3B I_{51}	-7.24
52	GSK-3B I_{52}	-7.62
53	GSK-3B I_{53}	-6.46
54	GSK-3B I_{54}	-6.08
55	GSK-3B I_{55}	-5.89
56	GSK-3B I_{56}	-7.92
57	GSK-3B I_{57}	-6.61
58	GSK-3B I_{58}	-6.16
59	GSK-3B I_{59}	-5.44
60	GSK-3B I_{60}	-7.74
61	GSK-3B I_{61}	-6.55
62	GSK-3B I_{62}	-6.33
63	GSK-3B I_{63}	-6.57
64	GSK-3B I_{64}	-6.11
65	GSK-3B I_{65}	-6.53
66	GSK-3B I_{66}	-8.29
67	GSK-3B I_{67}	-8.27
68	GSK-3B I_{68}	-7.19
69	GSK-3B I_{69}	-7.83
70	GSK-3B I_{70}	-5.47

Based on docking scores, all the newly 70 designed ligands were categorized as highly active, moderately active and low active hits as below.

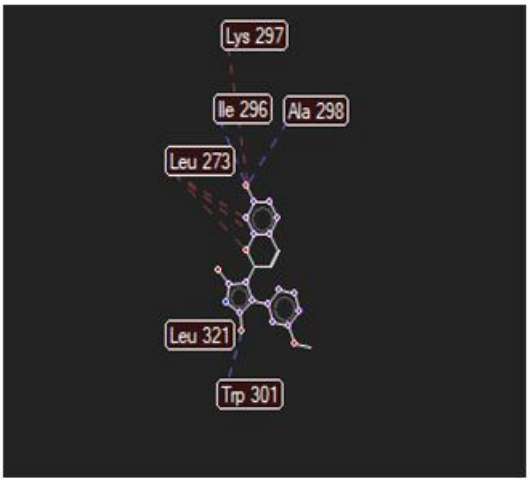
Table no. 5: Docking results of GSK-3Bβ inhibitors using Autodock Tools 1.5.6

HIGHLY ACTIVE (12)	MODERATELY ACTIVE (45)	LEAST ACTIVE (13)
GSK-3B I_{14}, GSK-3B I_{30}, GSK-3B I_{34}, GSK-3B I_{41}, GSK-3B I_{45}, GSK-3B I_{47}, GSK-3B I_{52}, GSK-3B I_{56},	GSK-3B I_1, GSK-3B I_2, GSK-3B I_3, GSK-3B I_4, GSK-3B I_5, GSK-3B I_6, GSK-3B I_7, GSK-3B I_8, GSK-3B I_9, GSK-3B I_{10}, GSK-3B	GSK-3B I_{12}, GSK-3B I_{22}, GSK-3B I_{27}, GSK-3B I_{31}, GSK-3B I_{36}, GSK-3B I_{39}, GSK-3B I_{40}, GSK-3B I_{42},

GSK-3B I_{60}, GSK-3B I_{66}, GSK-3B I_{67}, GSK-3B I_{69}	I_{11}, GSK-3B I_{13}, GSK-3B I_{15}, GSK-3B I_{16}, GSK-3B I_{17}, GSK-3B I_{18}, GSK-3B I_{19}, GSK-3B I_{20}, GSK-3B I_{21}, GSK-3B I_{23}, GSK-3B I_{24}, GSK-3B I_{25}, GSK-3B I_{26}, GSK-3B I_{28}, GSK-3B I_{29}, GSK-3B I_{32}, GSK-3B I_{33}, GSK-3B I_{35}, GSK-3B I_{37}, GSK-3B I_{38}, GSK-3B I_{43}, GSK-3B I_{46}, GSK-3B I_{48}, GSK-3B I_{49}, GSK-3B I_{51}, GSK-3B I_{53}, GSK-3B I_{54}, GSK-3B I_{57}, GSK-3B I_{58}, GSK-3B I_{61}, GSK-3B I_{62}, GSK-3B I_{63}, GSK-3B I_{64}, GSK-3B I_{65}, GSK-3B I_{68}	GSK-3B I_{44}, GSK-3B I_{50}, GSK-3B I_{55}, GSK-3B I_{59}, GSK-3B I_{70}

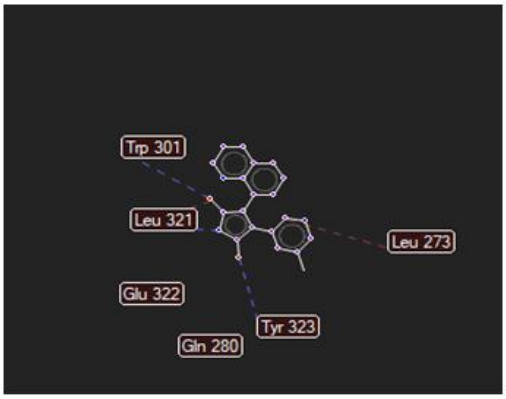


GSK-3BI$_{14}$

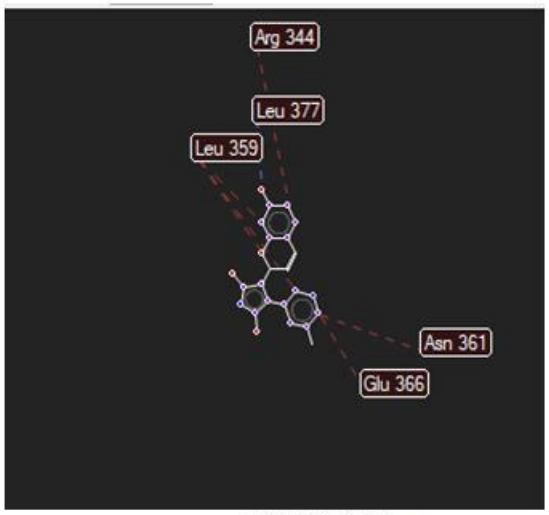


GSK-3BI$_{41}$

GSK-3BI$_{47}$



GSK-3BI$_{66}$



GSK-3BI$_{67}$

CONCLUSION

Our *Insilico* identification approach have revealed that all newly designed GSK-3Bβ inhibitors can be used for treatment of Alzheimer's disease. By reviewing the literature, the important chemical features like hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), aromatic ring which can inhibit the activity of *GSK-3β* were identified. 3D structural query of newer 70 heterocyclic ligands were screened to retrieve new potent the *GSK-3β* inhibitors Lipinski rule of five and ADMET properties screening assisted us to discard the nondrug-like compounds further move, the screened drug like compounds were identified and were further subjected to molecular docking study. Hence, we propose that the final hit compounds like GSK-3B I14, GSK-3B I30, GSK-3B I34, GSK-3B I41, GSK-3B I45, GSK-3B I47, GSK-3B I52, GSK-3B I56, GSK-3B I60, GSK-3B I66, GSK-3B I67, GSK-3B I69 as possible virtual leads to design and synthesis novel *GSK-3β* inhibitors. Active designed hits containing heterocycles like Benzimidazole, Aminothiazole, Imidazole, Pyridine, Thiazole, Oxazole will be synthesized and screened further for enzyme inhibition studies, Pharmacological evaluation studies (both *invitro* and *invivo*) in future.

ACKNOWLEDGEMENT

We consider this, as an opportunity to express our sincere thanks to The Dean, Our Principal and Our Guide, College of Pharmacy, Madras Medical College, Chennai-03.

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