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REVIEW ARTICLE

# Recent Advances in the Discovery of GSK-3 Inhibitors from Synthetic Origin in the Treatment of Neurological Disorders

Supriyo Saha[1,*], Dilipkumar Pal[2] and Satish B. Nimse[3]

[1]*School of Pharmaceutical Sciences & Technology, Sardar Bhagwan Singh University, Dehradun-248161, Uttarakhand, India;* [2]*Department of Pharmaceutical Sciences, Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, C.G., 495 009, India;* [3]*Department of Chemistry, Hallym University, Kangwon-do, Chuncheon, 200 702, South Korea*

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**Abstract:** ***Background*:** Glycogen synthase kinase 3 (GSK-3) is a serine/threonine kinase enzyme that controls neuronal functions such as neurite outgrowth, synapse formation, neurotransmission, and neurogenesis. The enzyme has two subunits as GSK-3α and GSK-3β. 4ACC, 1Q3D, 3AFG, 1UV5, and 1Q5K are the important GSK-3 receptors isolated from Homo sapiens and Mus musculus. This enzyme mainly phosphorylates Tau protein with the increased amount in neuronal fibres together with beta-amyloid plaques that cause neuronal diseases like Alzheimer's, Parkinson's and many more.

***Objective*:** We investigated the developments of various synthetic GSK-3 inhibitors responsible for the prevention and treatment of neurological disorders, like Alzheimer's disease, bipolar disorders, acting as antidepressants, neuroprotective, *etc*.

***Results and Conclusion*:** It has been observed that structures of the GSK-3 inhibitors are comprised of benzopyridine, benzothiazole, pyrazole, pyrazine, dioxolo-benzoxazine, oxadiazole, and benzimidazole in the skeletal with cyclopropyl amide, phenyl carbamothioate, 3-[(propan-2-yl)oxy]propan-1-amine in the side chain. The molecules were evaluated against the effectivity of GSK-3, human adenosine kinase, cyclin-dependent kinase, and phosphodiesterase-4 along with tail suspension test forced swim test, percent neuronal survival and other cognitive behaviours. The observations confirmed the remarkable effects of the synthesized molecules to conquer Alzheimer, Parkinson's depression, psychosis and other forms of neurological disorders.

**Keywords:** GSK-3, Receptors, Alzheimer, Parkinson, Tau protein, Neuroprotective, Depression.

## 1. INTRODUCTION

Neurology is a study of neurons. In the body of an average person, approximately 90 billion neurons always function in a synchronized manner. A small mistake in this synchronization process turns a person into a measuring unit such as DALys (disability-adjusted life years). Recent statistics of the National Institute of Mental Health (NIMH) say that near about 5.1% of total DALys in the United States are observed with neurological disorders [https://www.nimh.nih.gov/health/statistics/personality-disorders.shtml accessed on 16.05.2020]. In the United States, almost one person out of five suffers from neurological disorders that means approximately 46.6 million people suffer from the same, amongst them the maximum number of patients are females whose ages vary between ages (18-25) years [1, 2]. According to NIMH, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, eating disorders, depression, obsessive-compulsive disorder (OCD), Alzheimer, Parkinson's, depression, post-traumatic stress disorder (PTSD), schizophrenia and suicidal tendencies are most prevailing disorders [3, 4]. So, for conquering these devastating life and society-threatening disorders, targeting glycogen synthase kinase-3 enzyme may be one of the key weapons in this regard. So now the question is, why glycogen synthase kinase-3? In 1980, glycogen synthase kinase-3 (GSK-3) first came in the limelight. The principal activity of the enzyme is to facilitate the formation of glycogen from glucose *via* uridine diphosphate glucose molecule [5, 6]. This kinase is a serine/threonine amino acid-based enzyme found abundantly in cells. There are two types of GSK-3 enzymes, such as GSK-3α and GSK-3β. The enzyme activates the downstream process of neurons *via* phosphorylation of certain residues such as serine21 (for alpha) and serine 9 (for beta) types [7]. This downstream business inhibits the energy-dependent catalytic activity [8, 9]. GSK-3α enzyme regulates the production of beta-amyloid plaques

*Address correspondence to this author at the School of Pharmaceutical Sciences & Technology, Sardar Bhagwan Singh University, Dehradun-248161, Uttarakhand, India; Tel: (+91) 7895424583;
E-mails: supriyo9@gmail.commailto; drdilip71@gmail.com

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*via* Wingless and Int-1/ phosphatidylinositol-3 pathways. Whereas GSK-$3_\beta$ works *via* a similar mechanism to modulate stress because of inflammation related to endoplasmic reticulum and mitochondrial abnormalities [10, 11]. Neurological disorders like Parkinson's, Alzheimer's, mood swings, and other cognitive behavior-related disorders are associated with these abnormalities [12, 13]. In this manuscript, we have tried to establish the connection between GSK-3 and different neurological disorders, discussed different receptors associated with GSK-3 enzyme, and finally emphasized different synthetic GSK-3 inhibitors to conquer different neurological disorders.

## 2. GSK-3 AND MAJOR NEUROLOGICAL DISORDERS

### 2.1. GSK-3 and Alzheimer Disease

Glycogen synthase kinase-3 shows hyper phosphorylation of tau protein with the increasing number of amyloid-beta plaques and other inflammatory responses followed by activation of microglial cells developing neurotoxic inflammation along with reducing the concentration of acetylcholine; these factors cumulatively cause Alzheimer's disease [14, 15].

### 2.2. GSK-3 and Parkinson Disease

Different stress-related factors, such as mitochondrial abnormalities and endoplasmic reticulum stress, are directly associated with hyper phosphorylation of tau protein. In this process, alpha-synuclein takes part in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mediated neurotoxicity. This neurotoxic behavior navigates towards Parkinson's disease [16, 17].

### 2.3. GSK-3 and Depression

Phosphorylation and dephosphorylation of GSK-$3_\beta$ are linked with expressions of 5HT1A and 5HT2, respectively. This imbalance leads to depression [18].

### 2.4. GSK-3 and Schizophrenia

Schizophrenia directly linked with dopamine $D_2$ receptor in striatum leads to the transformation of GSK-$3_\beta$ from inactive to active form *via* phosphorylation of serine9 residue. In the prefrontal cortex, the decreased amount of dopamine $D_1$ leads to the transformation of GSK-$3_\beta$ active into inactive. These transformations are linked with schizophrenia [18].

### 2.5. GSK-3 and Bipolar Disorder

Direct inhibition of GSK-3 kinase increases the modulation of mitochondria function and activity of $Na^+K^+$-ATPase enzyme through the activation of brain-derived neurotrophic factor and cyclic adenosine monophosphate response element-binding pathway. So the inhibition of GSK-3 causes lowering of intracellular calcium ion concentration and produces reactive oxygen species leads to bipolar disorder [19].

## 3. RECEPTORS LINKED WITH GLYCOGEN SYNTHASE KINASE

### 3.1. 1I09

1I09 is the primary receptor structure isolated in this category. Scientists isolated the receptor from *Homo sapiens* with baculovirus as an expressing system. It has two chains A with 420 amino acids on each chain [20].

### 3.2. 4ACC

4ACC is a GSK-3β enzyme receptor complexed with 3-amino-6-(4-{[2-(dimethylamino)ethyl]sulfamoyl}phenyl)-n-pyridin-3-ylpyrazine-2-carboxamide (7YG) as a ligand and dimethylsulfoxide. The researcher isolated the receptor from *Homo sapiens* with *Trichoplusia ni* expressing system. Two chains of the receptor comprise 385 amino acids in both chains with 266 molecules of water in the chain: A and 244 molecules of water in the chain: B. Inside the receptor, the ligand molecule is linked with LYS 85, ASP 133 ARG 141 using hydrogen bonding and with TYR 134 using pi-pi stacking interaction as well as VAL 135, LEU 188, ILE 62, ALA 83, LEU 132, CYS 199, VAL 70, ASP 200 and PHE 67 are present as surrounding residues. 4ACM CDK receptor is another partner of the ligand molecule. As per the pharmacophore data of 7YG, the ligand molecule is observed with three aromatic, four hydrophobic, three hydrogen bond donor and seven hydrogen bond acceptor centres. Swiss PDB viewer shows that the total energy of the receptor is (-) 32298.932 KJ/mol [21].

### 3.3. 4ACD

4ACD is a GSK-3β enzyme receptor complexed with 3-amino-6-{4-[(4-methyl piperazine-1-yl) sulfonyl] phenyl}-n-pyridin-3-yl pyrazine-2-carboxamide (GR9) as a ligand. Researchers isolated the receptor from *Homo sapiens* with *Trichoplusia ni* expressing system. It has two identical chains with 465 amino acids. Inside the receptor, the ligand molecule is linked with ASP 133 and LYS 85 using hydrogen bonding and with TYR 134 using pi-pi stacking interaction where VAL 135, THR 138, ARG 141, PRO 136, LEU 188, VAL 70, GLU 137, LYS 60 and CYS 199 are present as surrounding residues. As per the pharmacophore data of GR9, the ligand molecule is composed of three aromatic, four hydrophobic, two hydrogen bond donor and seven hydrogen bond acceptor centres. Swiss PDB viewer shows that total energy of the receptor is (-) 32230.959 KJ/mol [21].

### 3.4. 4ACH

4ACH is a GSK-3β enzyme receptor complexed with 3-amino-n-(3-methoxy propyl)-6-{4-[(4-methyl piperazine-1-yl)sulfonyl]phenyl}pyrazine-2-carboxamide (KDI) as a ligand. Scientists isolated the receptor from *Homo sapiens* with *Trichoplusia ni* as an expressing system. It had two chains with 465 amino acids. Inside the receptor, the ligand molecule is connected with ASP 133 and ARG 141 using hydrogen bonding and with TYR 134 using pi-pi stacking interaction and VAL 135, ILE 62, LEU 188, THR 138, VAL 70,

GLU 137 and CYS 199 are situated as surrounding residues. As per the pharmacophore data of KDI, the ligand molecule is observed with two aromatic, five hydrophobic, two hydrogen bond donor and seven hydrogen bond acceptor centres. Swiss PDB viewer panel displays that the total energy of the receptor is (-) 32492.746 KJ/mol [21].

### 3.5. 4AFJ

4AFJ is a GSK-3β enzyme receptor complexed with 5-(4-methoxyphenyl)-n-(pyridin-4-ylmethyl)-1,3-oxazole-4-carboxamide (SJJ) as a ligand. Bioinformatics expert separate the receptor from *Homo sapiens* with *Spodoptera frugiperda* as an expression system. It has two chains with 367 amino acids. Inside the receptor, the ligand molecule is linked with ARG 200, ARG 223, SER 215 and ILE 217 using hydrogen bonding. As per the pharmacophore data of SJJ, the ligand molecule comprises three aromatic, four hydrophobic, one hydrogen bond donor and four hydrogen bond acceptor centres. Swiss PDB viewer data shows that the total energy of the receptor is (-) 33298.492 KJ/mol [22].

### 3.6. 5F95

5F95 is a GSK-3β enzyme receptor complexed with 2-[(-cyclopropylcarbonyl)amino]-N-(4-phenylpyridin-3-yl)pyridine-4-carboxamide (3UP) as ligand. Researchers isolated the receptor from *Homo sapiens* with baculovirus as an expression system. It has two identical chains with 350 amino acids. Inside the receptor, the ligand molecule is linked with LYS 85 and VAL 135 using hydrogen bonding and with TYR 134 using pi-pi stacking interaction where GLN 185, ILE 62, PRO136, LEU 188, ALA 83 and ASP 200 are present as surrounding residues. As per the pharmacophore data of 3UP, the ligand molecule is observed with three aromatic, four hydrophobic, two hydrogen bond donors and four hydrogen bond acceptor centres. Swiss PDB viewer results exhibit that the total energy of the receptor is (+) 12245042.00 KJ/mol [23].

### 3.7. 1Q5K

1Q5K is a GSK-3β enzyme receptor complexed with N-(4-methoxybenzyl)-n'-(5-nitro-1,3-thiazol-2-yl)urea (TMU) as a ligand. Researchers procured the receptor from *Homo sapiens* with *Trichoplusia ni* as an expression system. It has two chains with 414 amino acids. Inside the receptor, the ligand molecule is linked with VAL 135 using hydrogen bonding, with TYR 134 using pi-pi stacking interaction and sigma interactions with ILE 62 and ARG 141 as well as PRO136, LEU 188, VAL 70 and ALA 83 that are present as surrounding residues. As per the pharmacophore data of TMU, the ligand molecule comprised of two aromatic, three hydrophobic, two hydrogen bond donors and five hydrogen bond acceptor centres. Swiss PDB viewer data reflect that the total energy of the receptor is (-) 30251.215 KJ/mol [24].

### 3.8. 1Q3D

1Q3D is a GSK-3β enzyme receptor complexed with staurosporine (STU) as a ligand. Researchers identified the receptor from *Homo sapiens* with *Spodoptera frugiperda* as an expressing system. It has two chains with 424 amino acids. Inside the receptor, the ligand molecule is linked with VAL 135 using hydrogen bonding, with TYR 134 and VAL 70 using pi-pi stacking interaction as well as LEU 188, ILE 62, GLY 63, ASN 186, ALA 83, CYS 199, ASP 133 and LEU 132 that are present as surrounding residues. As per the pharmacophore data of STU, ligand molecule is observed with three aromatic, two positive ions, six hydrophobic, two hydrogen bond donors and four hydrogen bond acceptor centres. Swiss PDB viewer results show that the total energy of the receptor is (-) 28359.221 KJ/mol [25].

### 3.9. 3F88

3F88 is a GSK-3β enzyme receptor complexed with 5-[1-(4-methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazole-2(3H)-thione (3HT) and 3-methylbenzonitrile (2HT) as ligand. Scientists procured the receptor from *Homo sapiens* with *Spodoptera frugiperda* as an expressing system. It had two chains of 349 amino acids. Inside the receptor, the ligand molecule is linked with VAL 135 using hydrogen bonding and VAL 70, ILE 62, LEU 188, CYS 199, VAL 70, THR 138, LEU 132 and ASP 200 were present as surrounding residues. As per the pharmacophore data of 3HT, the complexed ligand molecule is noticed with four aromatic, one positive ion, six hydrophobic, two hydrogen bond donor and two hydrogen bond acceptor centres. Swiss PDB viewer data exhibits that the total energy of the receptor is (-) 24870.152 KJ/mol [26].

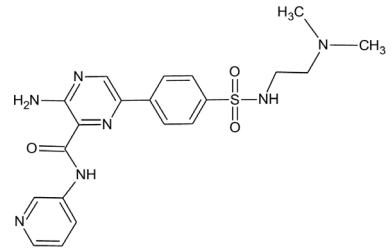
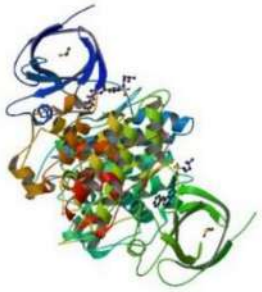
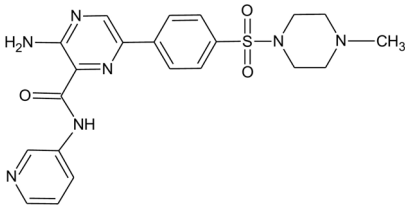
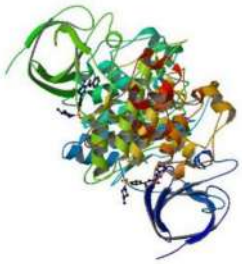
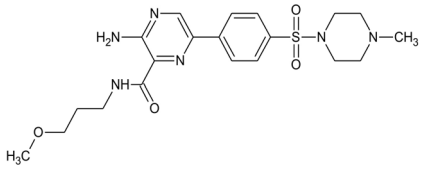
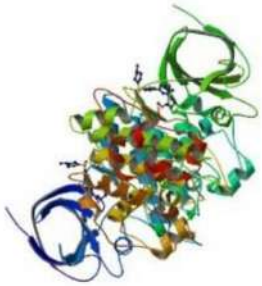
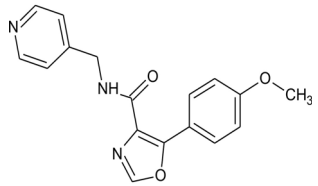
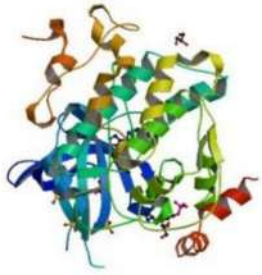
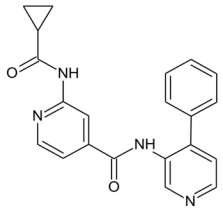
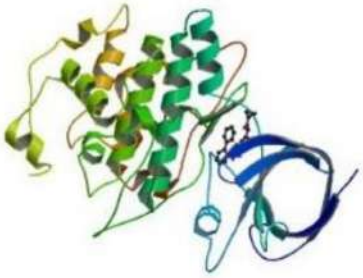
### 3.10. 1UV5

1UV5 is a GSK-3β enzyme receptor complexed with 6-bromoindirubin-3'-oxime (BRW) as a ligand. Researchers screened the receptor from *Homo sapiens* with *Spodoptera frugiperda* as an expression system. It has one chain of 350 amino acids. Inside the receptor, the ligand molecule is linked with ASP 133 and VAL 135 using hydrogen bonding, with TYR 134 using pi-pi interaction as well as VAL 70, ILE 62, LEU 188, CYS 199, THR 138, PRO 136 and ASP 200 are existed as surrounding residues. As per the pharmacophore data of BRW, the ligand is composed of two aromatic, three hydrophobic, three hydrogen bond donor and three hydrogen bond acceptor centres. Swiss PDB viewer show that the total energy of the receptor is (-) 8447.035 KJ/mol [27].

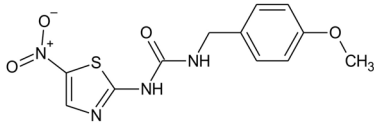
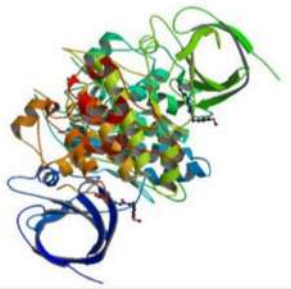
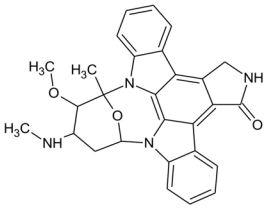
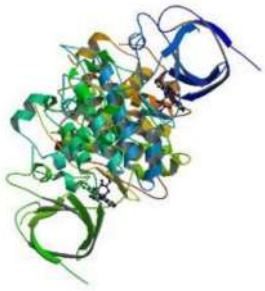
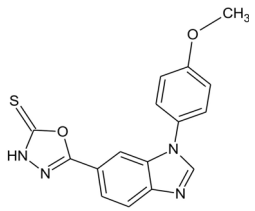
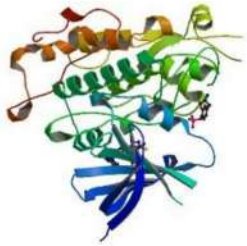
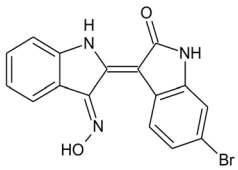
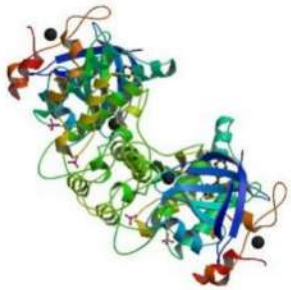
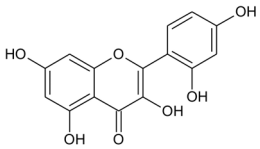
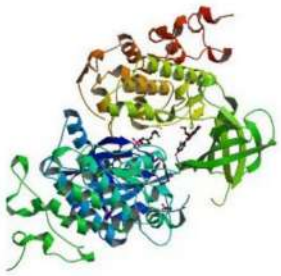
### 3.11. 6AE3

6AE3 is a GSK-3β enzyme receptor complexed with 2-[2,4-bis(oxadixyl)phenyl]-3,5,7-tris(oxidanyl)chromen-4-one (MRI) as ligand. Experts segregated the receptor from *Mus musculus* with *Spodoptera frugiperda* as an expressing system. It has four chains of 420 amino acids. Inside the receptor, the ligand molecule is linked with ASP 133, VAL 135, ASN 64 and GLY 262 using hydrogen bonding, with VAL 70 using pi-pi interaction as well as VAL 110, GLY 63, LEU 188, CYS 199, THR 138, TYR 134 and ASP 200 are present as surrounding residues. As per the pharmacophore data of MRI, the ligand is composed of two aroma-

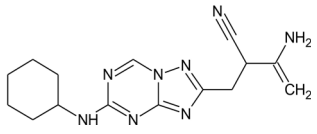
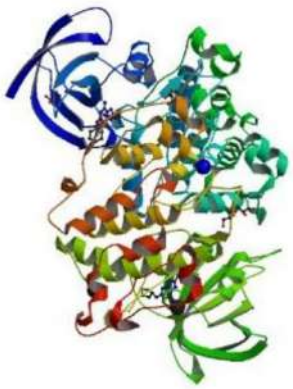
**Table 1. Details of Receptors associated with Glycogen Synthase Kinase-3 enzyme.**

| S. No. | Name of the Receptor | Ligand | Diagram of the Receptor |
|---|---|---|---|
| 1. | 4ACC |  3-amino-6-(4-{[2-dimethylamino)ethyl]sulfamoyl} phenyl)-n-pyridin-3-ylpyrazine-2-carboxamide |  |
| 2. | 4ACD |  3-amino-6-{4-[(4-methylpiperazin-1-yl) sulfonyl]-phenyl}-N-pyridin-3-yl pyrazine-2-carboxamide |  |
| 3. | 4ACH |  3-amino-n-(3-methoxypropyl)-6-{4-[(4-methyl piperazin-1-yl) sulfonyl] phenyl} pyrazine- 2-carboxamide |  |
| 4. | 4AFJ |  5-(4-methoxyphenyl)-n-(pyridin-4-ylmethyl)-1,3-Oxazole-4-carboxamide |  |
| 5. | 5F95 |  2-[(cyclopropylcarbonyl)amino]-N-(4-phenylpyridin-3- yl) pyridine -4-carboxamide |  |

**(Table 1) contd….**

| S. No. | Name of the Receptor | Ligand | Diagram of the Receptor |
|---|---|---|---|
| 6. | 1Q5K |  N-(4-methoxybenzyl)-n'-(5-nitro-1,3-thiazol-2-yl)urea |  |
| 7. | 1Q3D |  Staurosporine |  |
| 8. | 3F88 |  5-[1-(4-methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazole-2(3H)-thione |  |
| 9. | 1UV5 |  6-Bromoindirubin-3'-Oxime |  |
| 10. | 6AE3 |  2-[2,4-bis(oxidanyl)phenyl]-3,5,7-tris(oxidanyl)chromen-4-one |  |

**(Table 1) contd….**

| S. No. | Name of the Receptor | Ligand | Diagram of the Receptor |
|---|---|---|---|
| 11. | 6H0U |  (2{R})-3-[7-azanyl-5-(cyclohexylamino)- [1, 2, 4]triazolo[1,5-a] [1, 3, 5]triazin-2-yl]-2-cyano-propanamide |  |

The structures of the co-crystallized ligand molecules, along with the diagram of receptors, are mentioned in Table **1**.

tic, two hydrophobic, six hydrogen bond donor, one positive ion and seven hydrogen bond acceptor centres. Swiss PDB viewer demonstrate that the total energy of the receptor is (+) 466866.625 KJ/mol [28].

### 3.12. 6H0U

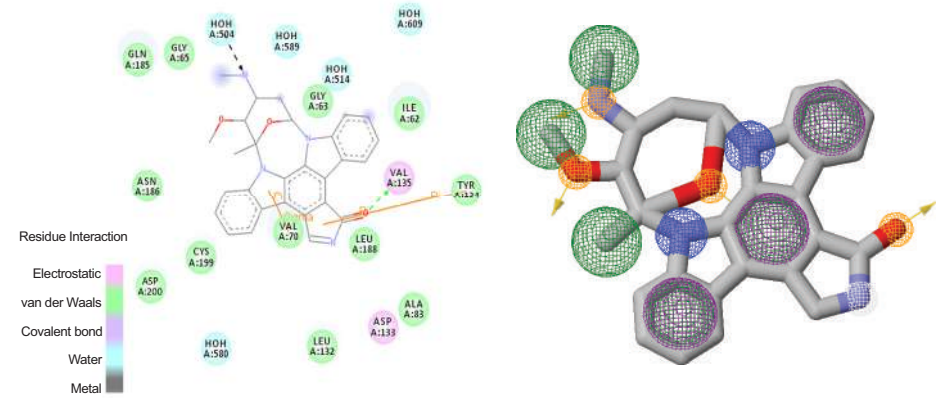
6H0U is a GSK-3β enzyme receptor complexed with (2{R})-3-[7-azanyl-5-(cyclohexylamino)- [1, 2, 4]triazolo[1,5-a] [1, 3, 5]triazin-2-yl]-2-cyano-propanamide (FKB) as ligand. Researchers screened the receptor from Homo *sapiens* with *Trichoplusia ni* as an expression system. It has two chains of 420 amino acids. Inside the receptor, the ligand molecule is connected with ASP 133, LYS 85 and ASP 200 using hydrogen bonding, with LEU 188 using sigma interaction as well as VAL 110, CYS 199, THR 138, TYR 134, PRO 136, ARG 141, VAL 135 and ILE 62 that are present as surrounding residues. As per the pharmacophore data of FKB, ligand molecule is observed with two aromatic, three hydrophobic, four hydrogen bond donors, one positive ion and five hydrogen bond acceptor centres. Swiss PDB viewer data demonstrate that the total energy of the receptor is (-) 31142.046 KJ/mol [29].

After overlapping all individual co-crystallized ligands, a common pharmacophore developed in which two common features are observed such as: two aromatic centers with 4-angstrom distance and two hydrogen bond acceptor centers with 7.7 angstrom distance [30-32] along with one terminal hydrogen bond acceptor and nearest aromatic center present within 3.0 angstrom and another pair is present within 1.3 angstrom distance (Fig. **1**) [33].

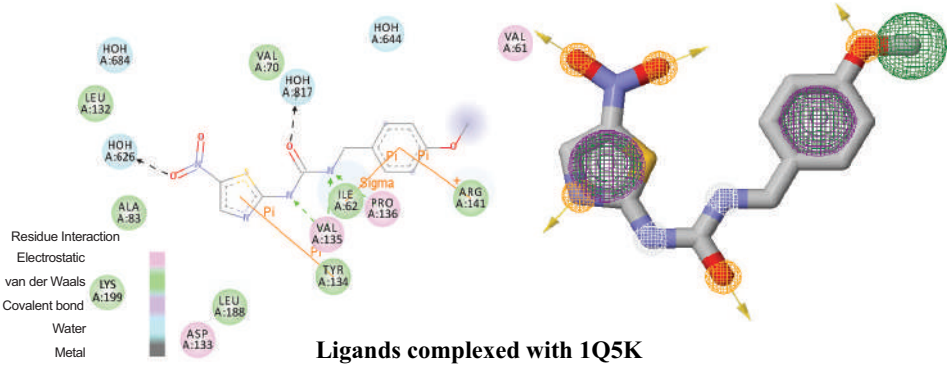
## 4. GSK-3 INHIBITORS IN THE TREATMENT OF NEUROLOGICAL DISORDERS

### 4.1. Aminopyridine Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

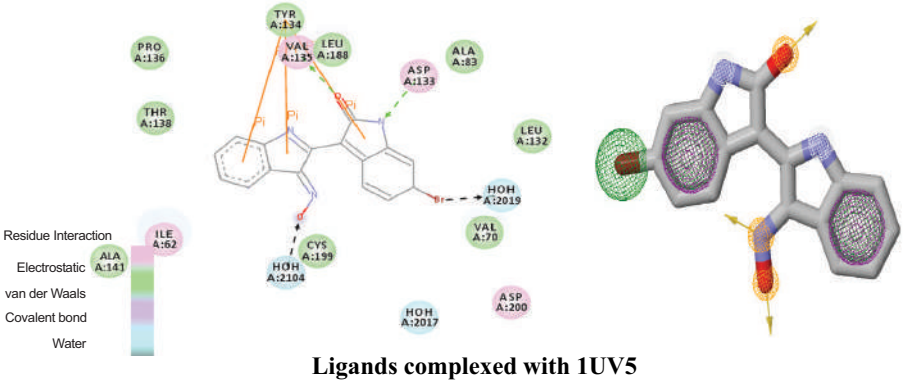
Two new sets of 2-aminopyridine derivatives are developed. Amongst them, one set of molecules as N-(2-aminopyridin-3-yl)-2-[(cyclopropanecarbonyl)amino]pyridine-4-carboxamide derivatives are produced upon reaction between 3-amino-2-butoxycarbonyl amino pyridine, hydrazine hydrate, and ferric chloride followed by 2-(cyclopropane carboxamide) isonicotinic acid and finally reacts with acetyl chloride in the presence of ethyl alcohol; whereas another set of molecules are synthesized upon reaction between 2-amino-4-O-[tert-butyl(dimethyl)silyl] pyridine, cyclopropane carboxylic acid, dimethyl aminopyridine, tetrabutylammonium fluoride, and sodium borohydride to develop N-(4-{(E)-[(2-aminopyridin-3-yl)imino]methyl}pyridin-2-yl)cyclopropanecarboxamide derivatives. Then these substances are chemically characterized by $^{1}$HNMR, Mass spectroscopy, and elemental analysis and biologically characterized by GSK-3β inhibitory, free radical scavenging, cell toxicity activity using SHSY5Y (human neuroblastoma), and PC12 (pheochromocytoma) cell models. Estimation of neuronal protection induced by cuprous ion-amyloid beta plaque neuronal toxicity and amyloid beta-induced tau protein hyperphosphorylation are also conducted. The outcomes show that the highest GSK-3β inhibitory activity, radical scavenging activity and protection of neurons against plaque formation are observed with pyridine-4-yl linked N-(4-{(E)-[(2-aminopyridin-3-yl) imino]methyl}pyridin-2-yl)cyclopropane carboxamide with 38 nM of inhibitory concentration whereas phenyl linked N-(4-{(E)-[(2-aminopyridin-3-yl)imino]methyl}pyridin-2-yl)cyclopropanecarboxamide shows maximum cell toxic behavior. It states that phenyl or pyridine-4-yl linked N-(4-{(E)-[(2-aminopyridin-3-yl)imino]methyl}pyridin-2-yl)cyclopropanecarboxamide (**1**) observed with greater activity against hyperphosphorylation of tau protein. Molecular docking studies data using 5F95 for GSK-3β receptor reveal that the aforementioned molecules show proper binding within the receptor. These data collectively suggest that these derivatives effectively worked against neurodegenerative diseases like Alzheimer's [34].



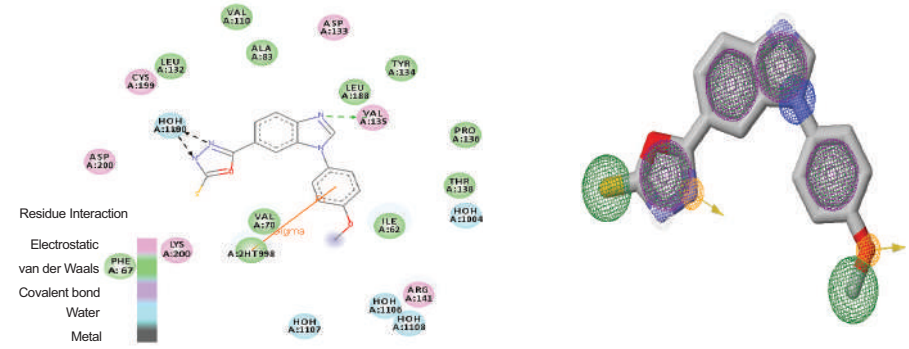

**Ligands complexed with 1Q3D**




**Ligands complexed with 1Q5K**

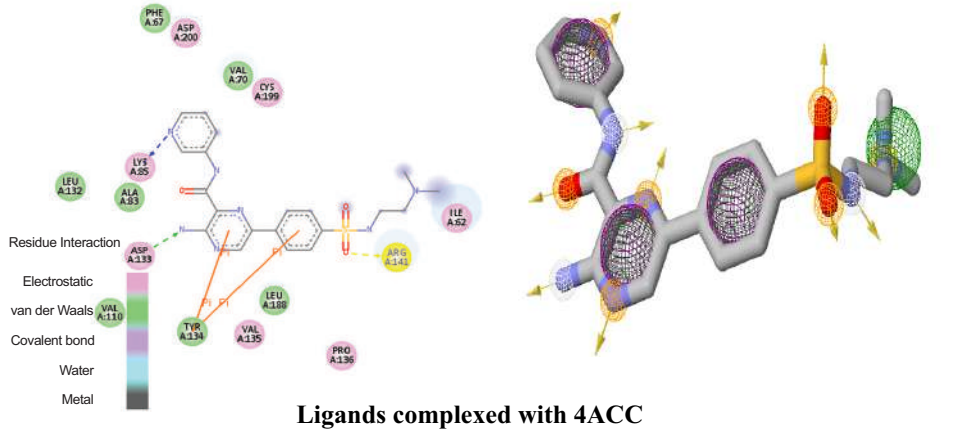



**Ligands complexed with 1UV5**

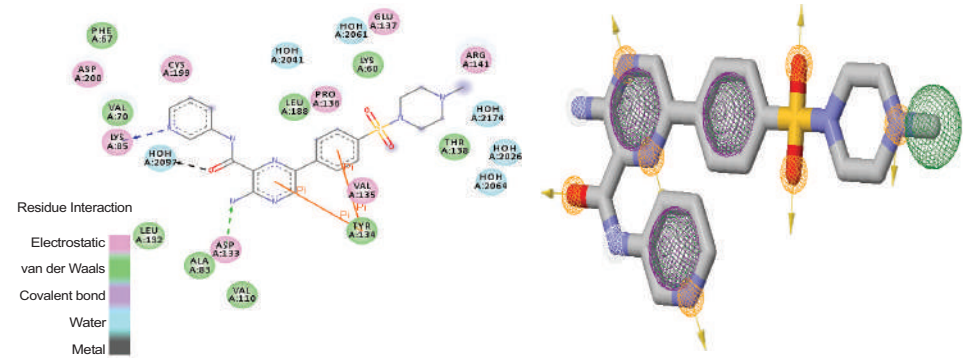



**Ligands complexed with 3F88**

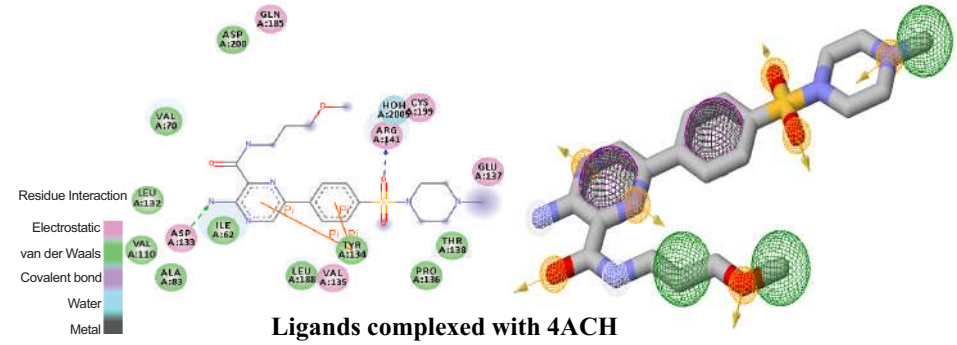
**Fig. (1).** contd...



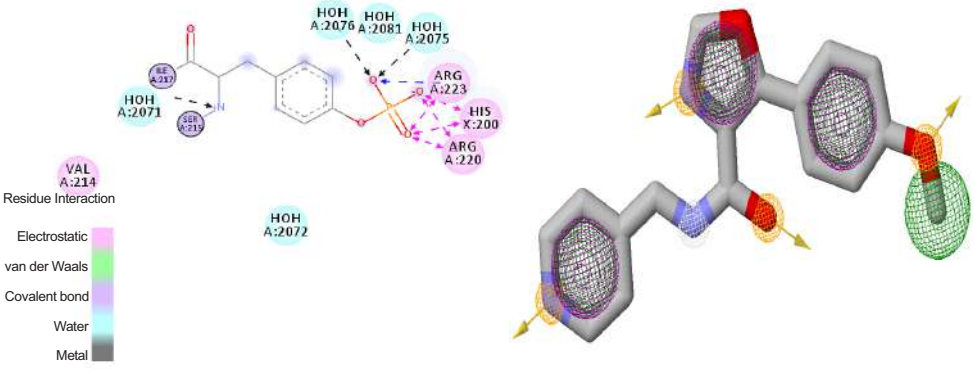

**Ligands complexed with 4ACC**




**Ligands complexed with 4ACD**

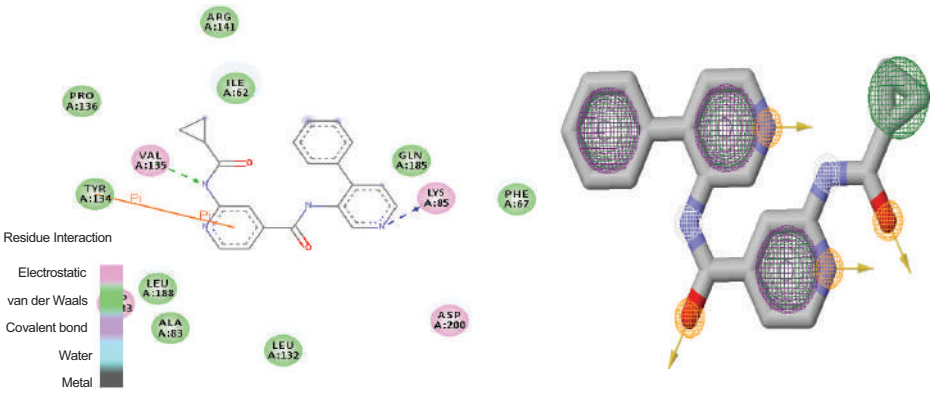



**Ligands complexed with 4ACH**

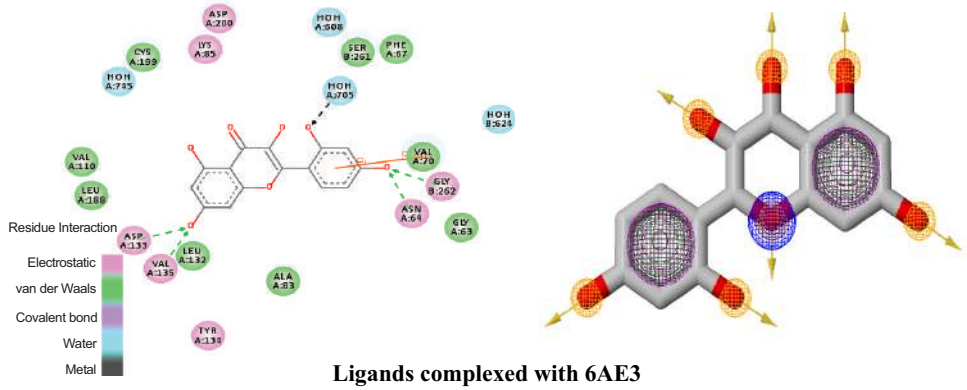



**Ligands complexed with 4AFJ**

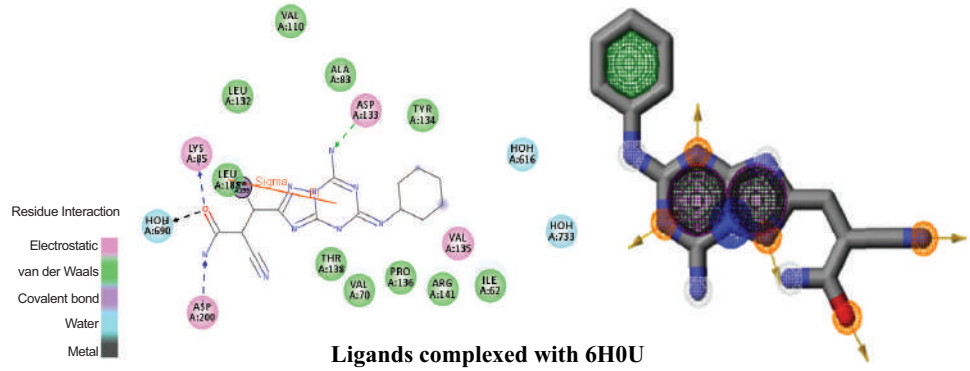
**Fig. (1).** contd...



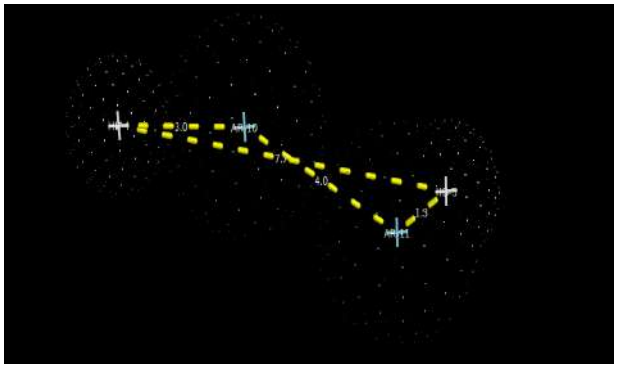

**Ligands complexed with 5F95**




**Ligands complexed with 6AE3**




**Ligands complexed with 6H0U**



General Pharmacophore of all co-crystallized structures

**Fig. (1).** Pharmacophore and structural features of all co-crystallized ligands observed within the receptors. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 4.2. Indirubin-3′-monoxime as GSK-3β Inhibitor with Neuroprotective Activity

An experiment suggests that indirubin-3′-monoxime is significantly effective against neuronal inflammation. The structure of indirubin-3′-monoxime is composed of a nitroso group linked with a bi-indole molecule. Here the experiment is designed using animals fed with a mixture of high-fat diet and indirubin-3′-monoxime (**2**). Then, the area of dark neurons and the area of the amyloid spot in the cortex and hippocampus are evaluated, followed by quantifying the amounts of glial fibrillary acidic protein and macrosialin (CD68); both are related to immunohistology staining of the cortex for reactive glial cells linked with brain injury. The experimental animals are evaluated against the GSK-3β enzyme and nuclear factor kappa beta transmitter present in cortex and hippocampus. The outcomes show that the number of dark neurons, amyloid spots, glial fibrillary acidic protein, and macrosialin in both cortex and hippocampus are highly minimized with indirubin-3′-monoxime treatment. Also, it has been observed that the inactivation of the GSK-3β enzyme and lowering of nuclear factor kappa beta transmitter in both the cortex and hippocampus are prominent with indirubin-3′-monoxime. These data indicate the importance of indirubin-3′-monoxime for the protection of neurons [35].

### 4.3. VP 2.51 as GSK-3β Inhibitor with Antidepressant Activity

A group of scientists note that VP 2.51 [N-(5-acetyl-1,3-thiazol-2-yl)-N'-(4-methoxyphenyl) urea] (**3**) is an effective antidepressant when it is tested against adult neurogenesis of the hippocampus. The experiment is designed to evaluate the behavioral test using the tail suspension method, elevated maze test and locomotor activity test. Expression of BrdU+, pH3+, and DCX+/Calret+ cells and expression of pGSK-3β, GSK-3β, GSK-3α and and estimation of beta--catenin in the hippocampus are also utilized as evaluation parameters. Antidepressant activity is tested using Morris' water maze, escape latency and swimming ability methods. The outcomes show that total $BrdU^{+}$, $pH3^{+}$, and DCX+/Calret+ cells expressions elevate with the molecule. Again, time to open/close arms, time spent in the center and locomotor activities (horizontal activity, vertical activity, resting time, movement times, along with escape latency) get improved with this treatment. Also, it is observed that GSK-3β is more effectively inhibited by VP 2.51 than that of GSK-3α. These data confirm that VP2.51 selectively inhibits GSK-3β through the protection against neuronal cell proliferation [36].

### 4.4. Pyridinyl Pyrazine Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

A group of researchers develop a series of pyridinyl pyrazine derivatives as GSK-3β inhibitors having anti-Alzheimer activity. The molecules are synthesized from bromobenzene sulfonyl chloride. Afterward it reacts with tetrahydrofuran, dioxane, organolithium reagents, 1,1′- Bis (diphenyl phosphino) ferrocene] dichloro palladium (II) to develop a series of pyridinyl pyrazine derivatives. Another series of molecules are synthesized upon reaction within tert-butyl (4-formylpyridin-3-yl)carbamate, pyrrolidine, dimethylammonium hydrochloride, trifluro acetic acid, dichloromethane, 3-aminopyridine, methyl 3-amino-6-bromo-2-pyrazinecarboxylate, 1,8-diazabicyclo[5.4.0]undec-7-ene, 3-amino-6-bromopyrazine-2-carboxylic acid or methyl 2-amino-5-bromo-pyridine-3-carboxylate, 1-hydroxybenzotriazole, O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate, diisopropylethylamine, methyl cyanide, methyl-2-amino-5-bromobenzoate, 3-aminopyridine, N,N′-diisopropylcarbodiimide and N-methyl morpholine-N-oxide. The next series of molecules are developed upon reaction between para bromo benzoic, sulfonyl chloride, 1-methylpiperazine, organolithium and 1,1′-bis (diphenyl phosphino) ferrocene] dichloro palladium (II). The fifth series of molecules are synthesized upon reaction between 5-[4-(4-methylpiperazine-1-sulfonyl) phenyl] -2-amine-3- N-(pyridin-2-yl)- pyrazin carboxamide, sodium nitrite, phosphorous oxychloride, tetrakis(triphenylphosphine) palladium (0) in presence of dimethylformamide. The sixth series of the molecules are synthesized upon reaction between 4-methylpiperizinylsulfonyl phenyl boronic acid, methyl 3-amino-6-bromo-2-pyrazinecarboxylate and 2-methoxyaniline in the presence of dimethylformamide. The final series of molecules are synthesized upon reaction between 3-amino-6-bromopyrazine-2-carboxylic acid, 3-methoxyaniline, triethylamine, 2-methoxyethylamine, 3-methoxypropylamine, and [4-[(4-methyl-1-piperazinyl) sulfonyl] phenyl] boronic acid in the presence of dimethylformamide, tetrahydrofuran and water as solvents. Then the molecules are biologically evaluated by selective inhibition of GSK-3β enzyme through inhibition, selectivity towards cyclin-dependent kinase-2 enzyme, and permeation ability study for Caco-2 (Homo sapiens colon colorectal) cell lines followed by inhibition of phosphorylation of tau protein. The outcomes show that maximum GSK-3β inhibitory activity is observed with 3-amino-6-phenylpyrazine-2-carboxamide, substituted with 4-piperazine sulfonyl and 4-[(pyrrolidine-1-yl) methyl] pyridine at 6-phenyl position with 0.22 nM inhibitory concentration. Maximum inhibition by the cyclin-dependent kinase-2 enzyme is found with 4-piperazine sulfonyl and 1,2,4-thiadiazole at the 6-phenyl position through 43 nM inhibitory concentration. Maximum tau protein inhibitory effects are shown by 3-amino-6-phenyl-N-(pyridine-3-yl) pyrazine-2-carboxamide molecule through methyl, hydrogen and 4-piperazine sulfonyl (**4**) replacements possessing 5 nM inhibitory concentration. Molecular docking studies data containing 4ACC, 4ACD, 4ACG, and 4ACH for GSK-3β receptor reveal that the aforementioned molecule show proper binding within the receptor (Fig. **2**). These data confirm the importance of synthesized pyridinyl pyrazine molecules as GSK-3β and tau phosphorylation inhibitors with greater efficacy against Alzheimer's disease [21].

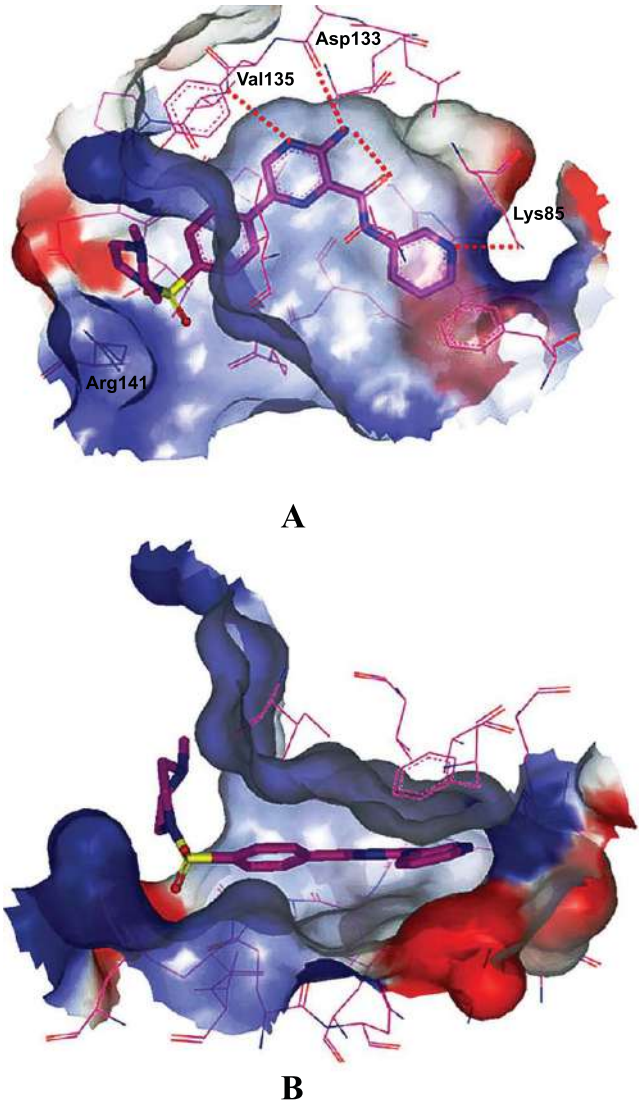



**Fig. (2).** X-ray crystal structure of GSK-3 inhibitor in the GSK3β ATP site. (**A**) Top view; (**B**) side view. Resolution 2.6 Å. Figures are prepared using VIDA 4.0.3 from Open Eye Scientific Software, 9 Bisbee Court, Suite D, Santa Fe, NM 87508. [Copyright permission granted by Berg @ 2012 from American Chemical Society]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 4.5. Benzoxazine and Indole Derivatives as GSK-3β Inhibitor with Neuroprotective Activity

Scientists develop a series of benzoxazine and indole derivatives as GSK-3β inhibitors. The benzoxazine derivatives are developed by reaction between substituted 2-aminophenol and substituted methyl bromoacetate in the presence of potassium carbonate, cesium carbonate, benzoyl chloride, and dimethylformamide. The indole derivatives are obtained by the reaction within indole-2,3-dione, sodium hydride, p-tolylmagnesium bromide, 2,6-lutidine in the presence of dry tetrahydrofuran. Later, the synthesized molecules are evaluated through human adenosine kinase and glycogen synthase kinase-3beta enzymes. The outcomes reveal that benzoxazine having naphthyl and 4-flurophenyl or phenyl sulfonyl substitutions and indole having naphthyl and methyl substitutions (**5**) are endowed with greater inhibition characteristics against human adenosine kinase (concentration 13.6 μM, 40 μM and 57.4 μM, respectively) and glycogen synthase kinase-3beta (concentration 5.4 μM, 4.1 μM and 10 μM, respectively). Molecular docking studies data involving 1BX4 for human adenosine kinase and 1HF8 for GSK-3β receptors reveal that the aforementioned molecule exhibits proper binding within the receptor. These data confirm the selective molecular activity against human adenosine kinase and glycogen synthase kinase-3 beta enzymes which are correlated with neuronal protection [37].

### 4.6. 6-Amino-4-(Pyrimidine-4-yl)pyridone as GSK-3β Inhibitor with Neuroprotective Activity

Scientists develop a series of molecules having 6-Amino-4-(pyrimidine-4-yl) pyridine derivatives as glycogen synthase kinase-3beta enzyme inhibitors. The molecules are synthesized upon reaction within 2,6-dihydroxypyridine-4-carboxylic acid, phosphorous oxychloride, tetramethylammonium hydrochloride, methyl formate, potassium carbonate, dimethyl formamidine, and substituted amine. The sixth position of the structure is further substituted with heteroaromatic ring structures to afford the final structure. These structures are biologically evaluated through GSK-3β cell-free enzyme inhibition, GSK-3β whole-cell enzyme inhibition, human liver microsome incubation assay and central multiparameter optimization score. The outcomes reveal that three structures with parent molecule 1-methyl-4-(pyrimidine-4-yl) pyridin-2(1H)-one and substitution at a 6th position with 2-(2-methoxyphenyl) ethan-1-amine, 4-phenylpiperidin-4-ol, and 2-(2-methoxyphenyl) morpholine, respectively (**6**) are characterized with greater inhibition at the concentration of 17.4nM, 8.5 NM and 6.1 nM concentrations, respectively. These data confirm the importance of the molecules as a neuroprotective agent [38].

### 4.7. 5-Aryl-4-carboxamide-1,3-oxazoles as GSK-3β Inhibitor with Neuronal Activity

A group of researchers develop 5-Aryl-4-carboxamide-1,3-oxazole derivatives as glycogen synthase kinase-3 beta enzyme inhibitors with neuronal activity. The molecules are prepared when substituted benzoic acid, sulfonyl chloride, ethyl isocyanoacetate, and hexafluorophosphate azabenzotriazole tetramethyl uranium react with each other. Molecular series are divided into three categories such as substituted 5-phenyl-1,3-oxazole-4-carbonyl, substituted 5-phenyl-N-[(pyridin-4-yl) methyl]-1,3-oxazole-4-carboxamide and substituted 5-(3-chloro-4-methoxyphenyl)-N-methyl-1,3-oxazole-4-carboxamide. The molecules are evaluated against the glycogen synthase kinase-3beta enzyme. The outcomes show that 5-(3-chloro-4-methoxyphenyl)-N-[(2-methyl pyridine-4-yl) methyl]-1,3-oxazole-4-carboxamide (7) exhibit good inhibitory effect as that of the enzyme with acceptable pharmacokinetic parameters. Molecu-

lar docking studies data using 1Q5K receptor reveal that the aforementioned molecule displays good binding within the receptor voxel. This information collectively indicates the importance of the derivative(s) of it with immense neuronal protectivity [22].

### 4.8. 6BIO and 6BIOder as GSK-3β Inhibitor with Tat Induced Neurotoxicity

Scientists discover the Tat protein-induced neuroprotective effects of 6BIO and 6BIoder, the novel glycogen synthase kinase- 3 beta inhibitors. Dactinomycin, 6BIO, quinine ethyl carbonate, indirubin-3′-oxime, and epirubicin hydrochloride are evaluated against Tat dependent transcriptase enzyme. Amongst them, 6BIO (8) is observed to produce 62 percent inhibition with 1μM concentration. Another set of experiments involve studies such as determining relative luciferase activity and percent cell viable activity, which are performed at 0.025, 0.05, 0.1, and 1.0 μM concentration against TZM-bl cell lines. Reverse transcription activity against phytohemagglutinin and interleukin-2 activated peripheral blood mononuclear cells are performed for a timeline of (1-2) week. Percent apoptosis activity against peripheral blood mononuclear cells is also determined using (0.1, 0.5, and 1.0) μM concentration range. The outcomes show that relative luciferase and percent cell viable activities decrease with a concentration gradient. Reverse transcription decreases and the percentage of apoptosis increases with the concentration gradient. Also, it is also observed that U87MG (human primary glioblastoma cell line) is inhibited by 6BIO and the aforementioned molecule also inhibits CDK5 (cyclin-dependent kinase)/p35, CDK2/cyclin A, and CDK1/cyclin B complexes. These data confirm the importance of 6BIO against Tat protein-induced neuronal toxicity [39].

### 4.9. Pyrimidin-4-one-1,2,3-Triazole Derivatives as GSK-3β Inhibitor with Anti-Depressant Activity

A group of researchers discover that pyrimidin-4-one-1,2,3-triazole is evaluated as an inhibitor of glycogen synthase kinase-3beta with antidepression activity. Molecules are synthesized upon reaction between ethyl 3-oxo-3-phenylpropanoate and N-methylthiourea in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene, propargyl bromide and substituted azide. The biological activities against glycogen synthase kinase-3beta and *in vitro* antidepression activity using tail suspension test and forced swim test are performed. The outcomes reveal that compound 2-({[1-(3,4-dimethylphenyl)-1H-1,2,3-triazol-4-yl] methyl}sulfanyl)-3-methyl-6-phenylpyrimidin-4(3H)-one (9) has a greater inhibitory effect against glycogen synthase kinase at the concentration of 82 nM. Good behavioral activity is noticed here with tail suspension and forced swim tests. Molecular docking studies data using 1Q3D receptor show that the aforementioned molecule is displayed with a maximum dock score of (-) 7.10 with glide energy (-) 49.94. This data clearly states the importance of the molecule as an antidepressant agent [40].

### 4.10. Benzimidazole Based Thiadiazole and Carbohydrazide Derivatives as GSK-3β Inhibitor with Anti-Depressant Activity

Here scientists report the antidepression activity of benzimidazole-based thiadiazole and carbohydrazide derivatives by measuring the inhibition against glycogen synthase kinase-3 beta enzyme. The synthesis of these molecules is started from 2-methyl benzimidazole. Further 2-methyl benzimidazole reacts with ethyl bromoacetate, hydrazine hydrate and substituted aliphatic acid to generate benzimidazole linked carbohydrazide derivatives. Benzimidazole-linked thiadiazole derivatives are developed by reactions between 2-methyl benzimidazole, ethyl bromoacetate, hydrazine hydrate and substituted aliphatic thiocyanate in the presence of concentrated sulfuric acid. The molecules are biologically assessed against glycogen synthase kinase-3beta enzyme and their antidepression activity is tested using tail suspension and forced swim tests. The outcomes furnish that molecule 3-(1H-indol-3-yl)-N'-[1-(2-methyl-1H-benzimidazol-1-yl) ethenyl]-2,3-dioxopropanehydrazide (**10**) is discerned with maximum inhibition properties against the enzyme (inhibitory concentration: 92nM) with the least immobility time in tail suspension test (less than 100 seconds) and forced swim test (less than 50 seconds). Molecular docking studies data using the 1Q3D receptor reveal that the aforementioned molecule shows a maximum dock score of (-) 7.69. So, these factors show the maximum antidepression activity noted with benzimidazole based carbohydrazide derivative [41] through above model(s).

### 4.11. Triazolotriazine-Based Dual GSK-3β/CK-1δ Ligand with Neuroprotective Activity

In this manuscript, scientists develop new triazolotriazine derivatives (12-15) and evaluated their effects against glycogen synthase kinase-3beta and casein kinase-1delta enzymes. It is observed that molecule 12 shows maximum activity against both the enzymes with inhibitory concentration values of 0.17μM and 0.68μM, respectively. Further it makes out that compound 12 [(2Z)-3-[7-amino-5-(cyclohexylamine) [1, 2, 4] triazolo[1,5-a] [1, 3, 5]triazin-2-yl]-2-cyanoprop-2-enamide] (**22**) reverses the cell toxicity behavior of 6-hydroxydopamine in P-Ser9-GSK3β beta-Catenin (Figs. **3** and **4**). Findings show that the synthesized molecule beholds as a gsk-3beta inhibitor along with protection against neuronal membrane toxicity [29].

### 4.12. VP 1.15 as GSK-3β and Phosphodiesterase Inhibitor with Antipsychotic and Cognitive Enhancer

In this experiment, a newly developed glycogen synthase kinase-3beta and phosphodiesterase inhibitor, VP 1.15 (chemically known as (5Z)-N-(2-hydroxyethyl)-2,3-diphenyl-1,2,4-thiadiazol-5(2H)-iminium) (**11**) are appraised with the enhancement of cognitive behavior and psychosis tendency. Here, C57BL/6J mice are taken and behavioral activities such as motor activities were tested at the dose level of 3.0 mg/kg and 7.5 mg/kg of the molecule. Another group of animals, initially induced with acute schizophrenia using

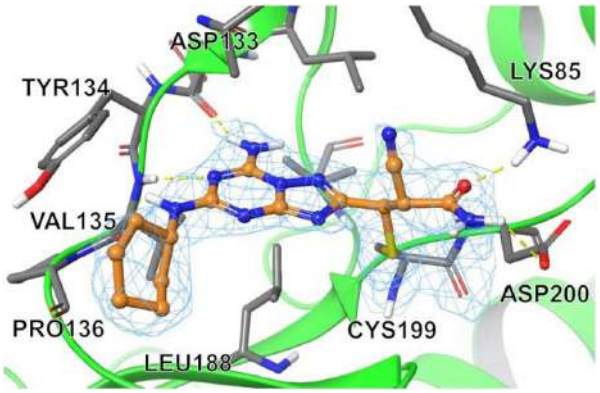



**Fig. (3).** X-Ray structure of GSK-3 inhibitor is covalently bound in the ATP binding pocket of GSK-3β at a resolution of 2.3 Å (PDB code: 6H0U). The electron density is attributed to GSK-3 inhibitor is depicted as a cyan mesh map (σ level: 1.0); protein secondary structure is depicted as a green cartoon, while residues forming the binding pocket are highlighted as grey sticks; inhibitor is represented as a ball-and-stick model. [Copyright permission is granted by Redenti @ 2019 from Wiley-VCH]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

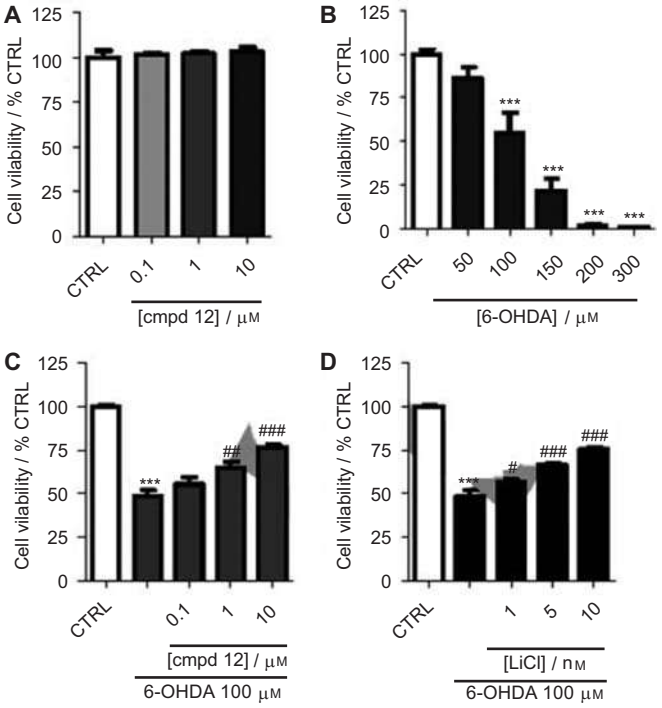



**Fig. (4). A**) GSK-3 inhibitor do not affect PC12 cell viability. **B**) Dose dependency of 6-OHDA toxicity in PC12 cells. **C-D**) PC12 cells are pretreated with an increased concentration of 12 or LiCl and then with 6-OHDA. Data represent mean ± s.e.m. (n=3). ***p<0.001 *vs* CTRL, #p<0.1, ##p<0.01, ###p<0.001 *vs* 6-OHDA. One-way ANOVA followed by Newman-Keuls test. [Copyright permission is granted by Redenti @ 2019 from Wiley-VCH].

a combination of amphetamine (5mg/kg) and MK-801 (0.3 mg/kg) (also known as dizocilpine, a potent antagonist of N-methyl-D-aspartate receptor) is undergone by evaluation of prepulse inhibition using (3 mg/kg) dose of VP 1.15 . Latent inhibition and puzzle box experiments are performed with the molecule or in combination with amphetamine towards spatial object recognition, Y maze type cognitive behavioral test and fear conditioning test. The end result reveals that near about 5000 cm distance is traveled by the animals in an hour and maximum prepulse inhibition is observed with the molecule proportional with the increment in noise (decibel). Conditioned suppression behavior data show maximum observation from VP 1.15 under pre-exposure to 4 CS-US (Conditioned Stimuli-Unconditioned stimuli) with a greater number of alterations. These data clearly state the effects of VP 1.15 on the improvement of psychotic and cognitive behavior [42].

### 4.13. Oxadiazole Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

Here researchers develop a different series of oxadiazole derivatives with the purpose of glycogen synthase kinase-3-beta inhibition. The first series of oxadiazole derivatives (4a-c) are developed by the reactions within heteroaromatic acid, sulfonyl chloride, hydrazine hydrate and triethylamine in the presence of alcohol. The second series of oxadiazole-linked biphenyl molecules (8a-h,9a-f,10a-f) are developed by the reactions between bromobenzene, toluene, arylboronic acid, and oxadizoles (4a-c) in the presence of sodium hydroxide and dimethylformamide. The third series of phenyl oxadiazoles (15-18a-d) molecules are developed by the reactions between para-substituted benzoic acid, sulfonyl chloride, hydrazine hydrate and triethylamine in the presence of alcohol and dimethylformamide. Fourth series of N'-[(Z)-phenylmethylidene]pyridine-4-carbohydrazide derivatives (20a-d) are produced by reactions between pyridine-4--carbohydrazide and aldehyde in the presence of alcohol. The fifth series of pyridine-linked oxadiazole derivatives (26a-d) are created by the reactions between 2-aminopyridine-4-carboxylic acid, sulfonyl chloride, hydrazine hydrate, benzyl halide and triethylamine in the presence of alcohol and dimethylformamide. The sixth series of benzothiazole linked oxadiazole derivatives (34,35) are developed by the reactions within pyridine-4-carboxylic acid, acetic acid, potassium thiocyanate, acetic anhydride, benzyl halide, sodium hydroxide and triethylamine in presence of alcohol and dimethylformamide. The final series of dibenzo [b,d] furan linked oxadiazole derivatives (40,41) are formulated by the reactions between 4-hydroxy methyl benzoate, bromine, dichloromethane, hydrazine hydrate, triethylamine, and benzoyl halide in the presence of dimethylformamide and alcohol. The molecules are judged against glycogen synthase kinase-3(alpha/beta), cyclin-dependent kinase focused on p35 cells, casein kinase-1, aurora kinase-A and protein kinase C alpha type. Molecular docking studies are performed against the 3F88 protein. Furthermore, the effect of 9e and 26d (selected as per previous experimental data) on wild-type zebrafish embryo is revealed . The outcomes show that 9e and

26d are the most active molecules against GSK-3α with inhibitory concentrations (0.005 and 0.002) μM, GSK-3β with (0.014 and 0.017) μM inhibitory concentrations. It is also observed with undersized bent tail at 30 μM concentration against zebrafish along with promising docking interactions. These data clearly denote that N-[4-(5-{[(2'-cyano[1,1'-biphenyl]-4-yl)methyl]sulfanyl}-1,3,4-oxadiazol-2-yl)pyridin-2-yl]acetamide (26d) and 4'-({[5-(2H-1,3-benzodioxol-5-yl)-1,3,4-oxadiazol-2-yl]sulfanyl}methyl)-4-methoxy [1,1'-biphenyl]-2-carbonitrile (9e) (**12**) are active against neurological disorders especially Alzheimer's disease [43].

### 4.14. 1 Aryl-3-Benzylurea Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

Scientists develop 1-Aryl-3-Benzylurea derivatives using coupling and microwave reactions. The derivatives are synthesized by the reactions within substituted bromo N-benzyl-N'-pyridin-2-yl urea, palladium, substituted boronic acid, sodium ethoxide in the presence of ethanol using Suzuki coupling reaction (32-62). Another set of molecules (63-66) are modified by the reactions within substituted cyano N-benzyl-N'-pyridin-2-ylurea or N-benzyl-N'-(6--cyano-1,3-benzothiazol-2-yl) urea, sodium azide, ammonium chloride in the presence of dimethylformamide at 100˚C temperature. The synthesized molecules are estimated with percent glycogen synthase kinase-3β inhibitory activity and results show that N-[(4-methoxyphenyl) methyl]-N'-[5-(1H-tetrazol-5-yl)-1,3-benzothiazol-2-yl] urea (66) is endowed with greater activity (inhibitory concentration 140 nM). The molecule shows proper binding interaction within the receptor 1Q5K (**13**). These data confirm the importance of benzyl urea derivatives as glycogen synthase kinase inhibitors associated with anti-Alzheimer's activity [44].

### 4.15. Acylaminopyridine Derivatives with Pyrrolopyridinone Core as GSK-3β Inhibitor with Neuronal Activity

Here a group of researchers develop four different series of acylaminopyridines such as thiazolylpyridines (1-7), fused phenylpyridines (8-16) pyridylpyridines (17-21), and heterocyclic pyridines (22-26) followed by the assessment of glycogen synthase kinase-3-beta enzyme inhibition. The thiazolylpyridine derivatives are formed by the reactions between 2-amino-4-cyano pyridine and cyclopropane-carbonyl chloride. The fused phenyl pyridine derivatives are synthesized by the reactions between boron coupled N-[4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl) pyridin-2-yl]cyclopropanecarboxamide and 2-amino-6-bromo-3,4-dihydronaphthalen-1(2H)-one. Here the synthesis of pyridylpyridine derivatives is initiated by the reactions between 5-bromo-pyridine-2-carboxylic acid and boron coupled N-[4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl) pyridin-2-yl]cyclopropanecarboxamide and the final heterocyclic pyridine derivatives are developed by the reactions between 1-(5-hydroxy-1-methyl-1H-pyrazol-3-yl)ethan-1-one, phosphorous oxybromide and methylcyanide. Biological activity confirms that maximum activity is observed with 2-{2-[(cyclopropane carbonyl) amino] pyridin-4-yl}-4-(cyclopropyl methoxy)-1,3-thiazole-5--carboxamide (**14**) with inhibitory concentration of 0.29 nM. These data confirm that thiazolyl pyridines are the most active molecule against glycogen synthase kinase enzyme [45].

### 4.16. Benzimidazole Linked 1,3-Oxadiazole Derivatives as GSK-3β Inhibitor with Anti-Depressant Activity

Here a group of researchers develop a series of benzimidazole linked 1,3-oxadiazole derivatives (7a-s) with glycogen synthase kinase-3beta enzyme inhibition property and anti-depression activity. Molecules are developed by the reactions between benzene-1,2-diamine, trifluoroacetic acid, acetone, potassium carbonate, bromoacetic acid, and substituted diamine in the presence of alcohol and dimethylformamide. Then synthesized molecules are biologically evaluated against glycogen synthase kinase-3beta enzyme with staurosporine as a reference compound. Antidepression activity is performed with 7a, 7d, 7i, 7r using tail suspension and forced swim tests taking fluoxetine as standard. The conclusion reveals that (**15**) N-phenyl-2-[(5-{[2-(trifluoromethyl)-1H-benzimidazol-1-yl] methyl}-1,3,4-oxadiazol-2-yl) sulfanyl] acetamide (7a) show maximum inhibition against glycogen synthase kinase-3beta enzyme (at 0.13 μM of inhibitory concentration). With the same concentration, it exhibits the lowest time for immobility in the tail suspension test (less than 150 seconds) and forced swim test (less than 80 seconds). Molecular docking studies against the 3F88 receptor reveals that the aforementioned molecule shows a maximum dock score of (-) 8.70. So, these factors indicate the antidepressant property of benzimidazole-linked oxadiazole derivative through inhibition of GSK-3β [46].

### 4.17. 3-Indolyl-4-Indazolylmaleimides as GSK-3β Inhibitor with Antiparkinsonian Activity

In this article, a group of scientists create a series of 3-indolyl-4-indazolylmaleimide derivatives (5-35) by the reactions within substituted indole, alkyl halide, sodium hydride, ethanediol dichloride and tertiary potassium butanol in the presence of dimethylformamide and tetrahydrofuran. Then the molecules are assessed with glycogen synthase kinase-3-beta inhibition. Outcomes exhibit that 3-(5-fluoro-1H-indol-3-yl)-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione (18) and 3-(5-bromo-1-methyl-1H-indol-3-yl)-4-(1H-indol-3-yl)- 1H-pyrrole-2,5-dione (22) are observed with better kinase inhibitory activity with 0.0114 μM and 0.0035 μM with $K_i$ values 7.6 nM and 2.3nM, respectively. Molecular docking study data of these molecules against the 1Q3D receptor show good interactions within the receptor voxel. After treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and synthesized molecule (18 and 22), cytological changes in the midbrain region are also noticed (Fig. **5**). The outcomes reveal that PHF-1, total tau, alpha-synuclein and glycogen synthase kinase-3beta enzyme are noticed with minimized expression. Molecule 18 show maximum cell viability by tetrazolium 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay process **(24)**. These data confirm the noticeable activity of the molecule against Parkinson's disease [47].

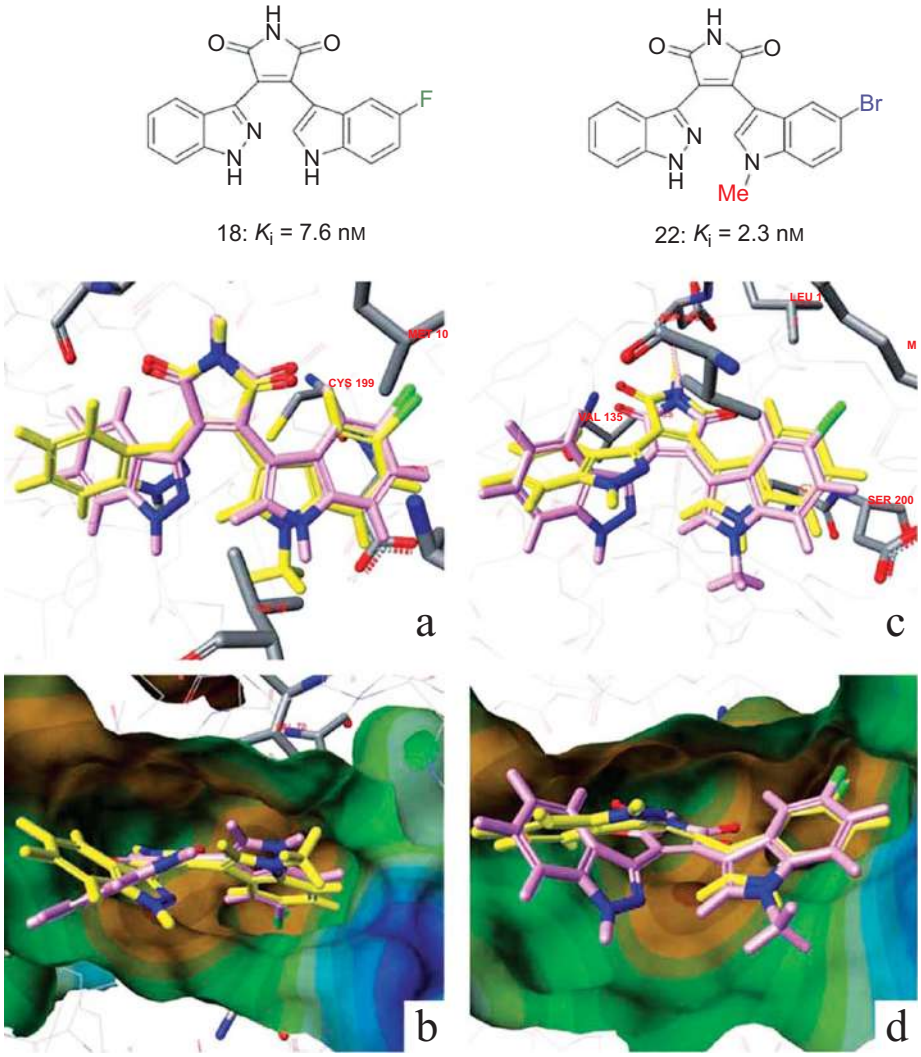



**Fig. (5).** Docking pose of the inhibitors to the ATP-binding site of GSK-3beta. [Copyright permission is granted by Kozikowski @ 2006 from Wiley-VCH Verlag GmbH& Co. KGaA, Weinheim]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 4.18. Novel Pyrazolo-pyridine Carboxamide as GSK-3β Inhibitor with Anti-Alzheimer Activity

A group of researchers study the anti-Alzheimer's activity of the novel 6-Methyl-N-[3-[[3-(1-methylethoxy) propyl] carbamoyl]-1H pyrazol-4-yl] pyridine-3-carboxamide (**16**) against GSK-3β enzyme. The molecule is administered in C57BL/6Njcl mice for cold water stress examination. Also, the effect of the molecule on tau phosphorylation and aggregated tau in JNPL3 mice brain by assessing the percent control of ratio between phosphorylated tau protein and total tau protein in specialized markers such as AT8, AT180, AT270, pThr205, pSer262, pSer396, pSer422 is studied. Again, measuring the band intensity of total tau, the value of pThr205, HT7 is also evaluated. The effect of the molecule on insoluble/aggregated tau protein in mouse brain with the assessment of band intensity of total tau, pThr205, HT7 is evaluated. The outcomes reveal that after the administration of molecule (10 mg/kg dose) on mice, the concentration in plasma, hippocampus, cerebral cortex, and cerebellum get decreased exponentially and amongst all the enzymes, only glycogen synthase kinase and cyclin-dependent kinase enzymes are markedly inhibited. Also, the cold-water stress-induced tau phosphorylation data suggest that with an increase in molecular concentration, the band intensity of phosphorylated and total tau protein ratio is decreased. A similar type of marker lowering data is seen with AT8, AT180, AT270, pThr205, pSer262, pSer396, pSer422. Here the bands intensity of total tau, pThr205, HT7 is also lowered. It is found that the aforementioned molecule significantly minimizes the phosphorylation of tau protein which clearly states the anti-Alzheimer activity of this novel molecule [48].

### 4.19. Newer Generation 7,7-dimethyl-2,4,6,7,8,9-hexahydro-5H-pyrazolo[3,4-b]quinolin-5-one Derivative as GSK-3β Inhibitor with Mood-Stabilizing Activity

Here scientists produce a series of pyrazolo-quinoline-5-one derivatives as glycogen synthase kinase-3beta enzyme inhibitors with the special purpose of developing a

newer generation of mood stabilizers. In this approach, the molecules are formed by microwave reaction between substituted 4-amino pyrazole, 5,5-dimethyl cyclohexane-1,3-dione, and aromatic aldehyde/ketone in the presence of triethylamine and ethanol; followed by inhibition of glycogen synthase kinase-3alpha/beta enzymes. The end-result reveals that BRD4963, BRD3937, BRD1172, BRD1652, and BRD0209 possess greater inhibition of the enzyme. Amongst them, BRD1652 and BRD0209 are observed with a maximum inhibition of glycogen synthase kinase-3beta enzyme with an inhibitory concentration of 0.004 and 0.005 μM, respectively. Western blot analysis data on DU145 cells show that after 0.5h and 24h, phosphor beta-catenin, T-beta catenin, t-CRMP2 are prominently increased. The amphetamine-induced hyperactivity behavioral data of BRD1652 (**17**) seems like a sign curve where the travelled distance is lowered with an increase in concentration from 1mg/kg to 10 mg/kg dose. These data confirm BRD1652 as an inhibitor of glycogen synthase kinase enzyme with mood-stabilizing property [49].

### 4.20. 3-([1, 2, 4] Triazolo [4,3-a]pyridin-3-yl)-4-(indol-3-yl)-maleimides as GSK-3β Inhibitor with Neuroprotective Activity

A group of researchers develop a series of 3-([1, 2, 4] triazolo [4,3-a] pyridin-3-yl)-4-(indol-3-yl)-maleimides as glycogen synthase kinase-3beta inhibitors along with neuronal protection properties. The molecules ($7_{a-p}$) are synthesized by reactions between 2-([1, 2, 4]triazolo[4,3-a]pyridin-3-yl)acetamide and methyl (1H-indol-3-yl)(oxo)acetate (**18**) in the presence of tertiary butyl alcohol and its potassium salt. The molecules are evaluated through inhibition of glycogen synthase kinase-3beta enzyme and the data suggest that $7_b$, $7_c$, $7_d$, $7_e$, $7_f$, $7_g$, $7_h$, $7_l$, $7_m$, and $7_n$ have greater activity against glutamate-induced neurotoxicity in cerebellar granule neuronal cell of rat. Molecular docking studies data confirm the good interaction of the molecules with 1Q3D receptor along with tyrosine, isoleucine, aspartic acid, glycine, and valine which are present as surrounding residues. Oxygen-glucose deprivation data show that molecule 7f possesses higher cell viability with minimization of percent ischemic area of the brain. The neuronal toxicity data confirm that 3-(5-chloro-1-methyl-2,3-dihydro-1H-indol-3-yl)-4-([1, 2, 4] triazolo[4,3-a]pyridin-3-yl)-1H-pyrrole -2,5-dione ($7_f$) is the most promising molecule with neuronal protective property [50].

### 4.21. Benzo[e]isoindole-1,3-dione Derivatives as GSK-3β Inhibitor with Neuroprotective Activity

In this article, researchers modulate a series of benzo[e]isoindole-1,3-dione derivatives ($2_{a-v}$, $8_a$ and $8_b$) using 5-ethyl-7,8-dimethoxy-1H Pyrrolo[3,4-c] isoquinoline-1,3 (2H)-dione as scaffold by the reactions between methyl 4-methyl-2-phenylpenta-2,3-dienoate, 4-nitrobenzonitrile, dichloromethane and ammonia in presence of methanol and tetrahydrofuran ($2_{a-v}$). Other two molecules ($8_a$ and $8_b$) are developed by the reactions within 2-amino-4,5-dimethoxybenzoic acid, isoamyl nitrite, trichloroacetic acid, cumylamine and lithium hydroxide in presence of alcohol, tetrahydrofuran and dimethylformamide. The molecules are evaluated by percent glycogen synthase kinase activity. The outcomes show that $8_a$ (7,8-dimethoxy-5-methyl-1H-benzo[e]isoindole-1,3(2H)-dione), $8_b$ (5-ethyl-7,8-dimethoxy-1H-benzo[e]isoindole-1,3(2H)-dione) and $2_u$ (methyl 4-iso-butyl- 5-methyl-1,3-dioxo-2,3-dihydro-1H-benzo[e]isoindole-6-carboxylate) are highly effective against kinase activity having inhibitory concentration 0.270 μM, 0.092 μM and 0.486 μM, respectively. Among them, $8_a$ is also effective against cyclin dependent kinase-2 and 4 enzymes (Figs. **6** and **7**). Molecular docking studies against 1UV5 receptor display a perfect docking interaction between molecules with surrounding amino acids. The zebrafish embryo assay shows that molecule $8_a$ is observed with more or less similar activity as that of lithium chloride after three days of incubation with the activation of wingless and Int-1-catenin signaling pathway. This information confirms the neuroprotective effect of 7,8-dimethoxy-5-methyl-1H-benzo[e]isoindole-1,3(2H)--dione with promising glycogen synthase kinase-3beta enzyme inhibition activity [51].

### 4.22. Benzo[e]isoindole-1,3-dione Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

In this article, researchers develop a series of Benzo[e]isoindole-1,3-dione derivatives (8a-i) as GSK-3β inhibitors with the activation of the wingless and Int-1 / beta-catenin pathway for the positive response towards Alzheimer's disease. Molecules are synthesized from the reactions involving tert-butyl piperidine-4-yl carbamate, substituted sulfonyl chloride, di-tert-butyl pyro carbonate, triethylamine, and trifluoroacetic acid in the presence of dichloromethane and tetrahydrofuran. Molecules are biologically evaluated for inhibition of glycogen synthase kinase-3beta and cyclin-dependent Kinase 2 followed by relative luciferase activity and molecular docking studies against the 1UV5 receptor. The outcomes show that 8c and 8g are endowed with maximum activity against GSK-3β (inhibitory concentration: 0.31 μM) and percent cyclin-dependent kinase enzymes (40.8%). Maximum relative luciferase activity data show that 8i (**19**) is the most active with a better docking pose with arginine, lysine, and aspartic acid present as surrounding residues. These data confirm the importance of these molecules to treat Alzheimer's disease [52].

### 4.23. Benzothiazepinone Derivatives as GSK-3β Inhibitor with Anti-Alzheimer Activity

In this article, a group of researchers develop a series of benzothiazepine derivatives ($6_{a-y}$) upon reaction between aryl aldehyde, pentanedioic acid, and 2-aminobenzenethiol in the presence of pyridine and piperidine ($6_{a-r}$, $6_{u-y}$). Another set of molecules ($6_s$ and $6_t$) are synthesized from 3-[(4-oxo-2-phenyl-3,4-dihydro-1,5-benzothiazepin-5(2H)-yl) methyl] benzonitrile ($6_m$) followed by inhibition of glycogen synthase kinase-3beta enzyme. The outcomes suggest that 2-benzyl-5-[(2-nitrophenyl) methyl]-2,3-dihydro-1,5-benzothi-

azepin-4(5H)-one ($6_v$) is observed with maximum kinase inhibitory effect. Amongst other kinase inhibition, $6_v$ shows maximum inhibition against tyrosine-protein kinase (Abl) (by 18.1%). The molecular docking studies against the 1PYX receptor show that $6_v$ is surrounded by arginine 209 and serine 236 within the receptor voxel. This data confirm the glycogen synthase kinase-3beta inhibitory effect of the molecule with a possible anti-Alzheimer's effect [53].

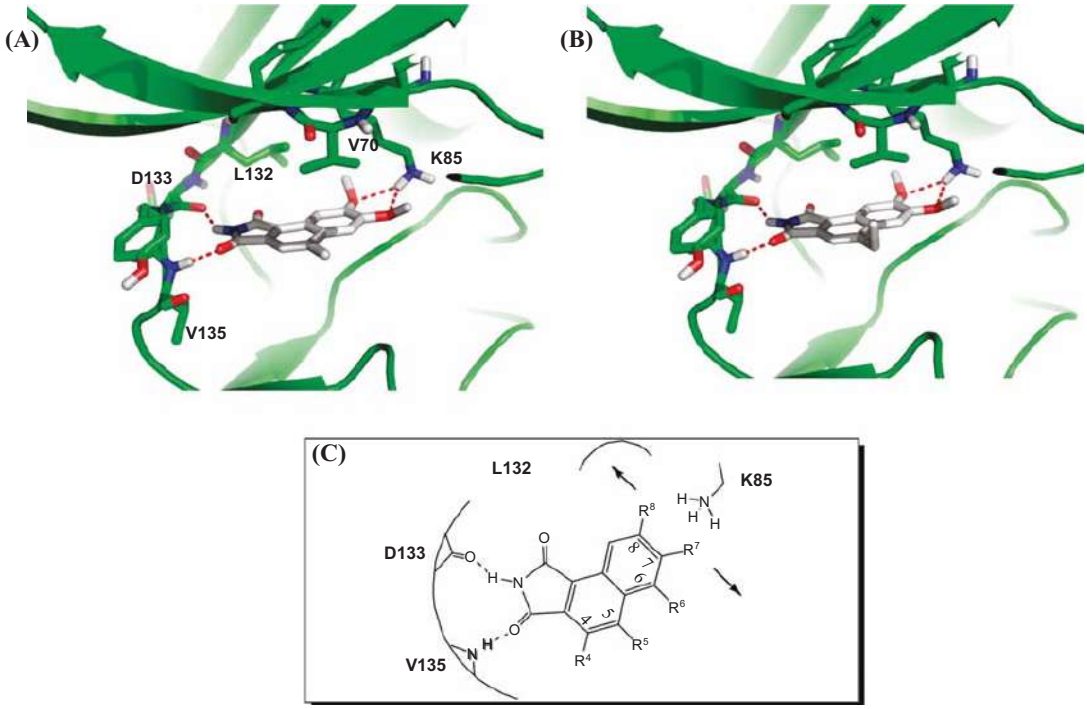



**Fig. (6).** (**A**) Docked binding modes of the inhibitors in the ATP binding site of GSK-3β. (**B**) The small molecules and the critical interacting residues of GSK-3β are represented by sticks. Hydrogen bonds are shown as red dash lines. (**C**) Schematic representation of the binding mode of the inhibitors in the ATP binding site of GSK-3β. The arrows indicate the moving directions of the substituents compared to compound 8a. [Copyright permission is granted by Zou @ 2010 from American Chemical Society]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

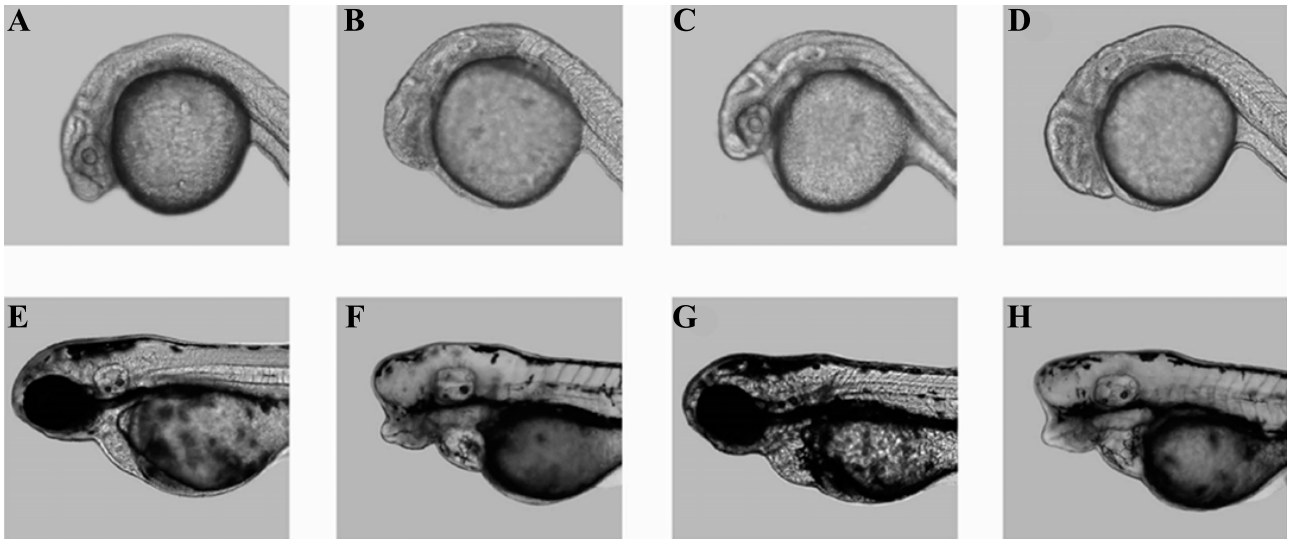



**Fig. (7).** Effects on the zebrafish embryos by LiCl and GSK-3 inhibitors. (**A**, **E**) Heads of 1 and 3 dpf control embryos. (**B**, **F**) Heads of 1 and 3 dpf embryos are treated with 0.3MLiCl. This compound causes eyeless phenotype of zebrafish embryos. (**C**, **G**) Heads of 1 and 3 dpf embryos are treated with 25mM9. This compound shows no obvious effect on zebrafish embryos. (**D**, **H**) Heads of 1 and 3 dpf embryos are treated with 25mM compound 8a. This compound causes eyeless phenotype of zebrafish embryos. [Copyright permission is granted by Zou @ 2010 from American Chemical Society].

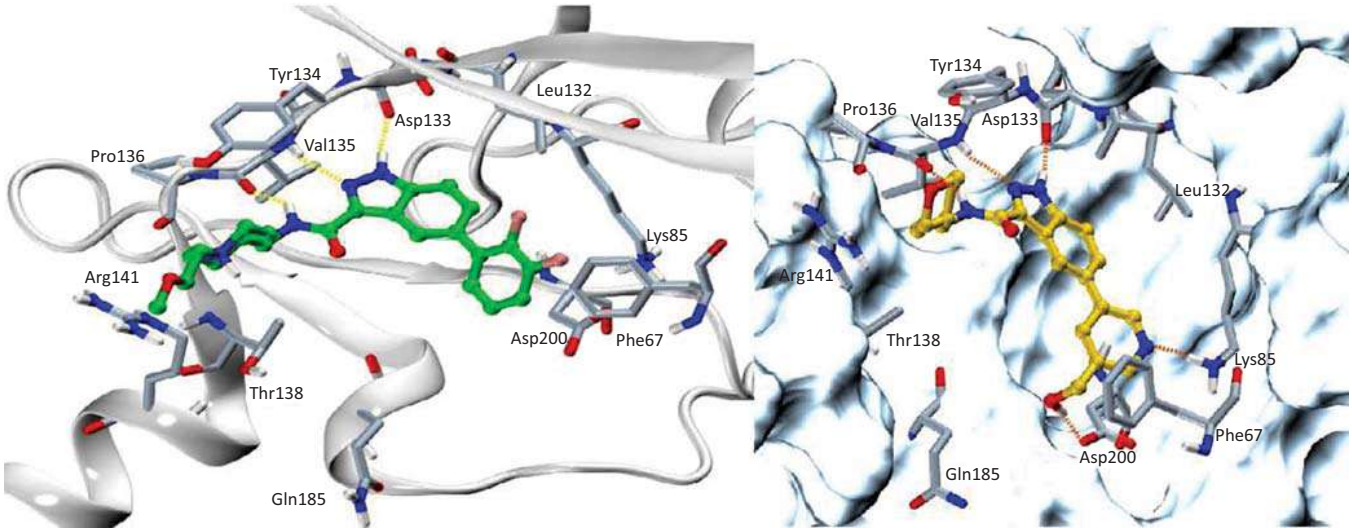



**Fig. (8).** X-ray co-crystal structure of GSK-3β kinase inhibitors (PDB ID: 6TCU). [Copyright permission is granted by Prati @ 2020 from American Chemical Society]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 4.24. 1,3,4-Oxadiazole Derivative as GSK-3β Inhibitor with Anti-Alzheimer Activity

In this manuscript, the researchers develop a series of 1,2,3-oxadiazole derivatives (20a-y) by the chemical reactions within methyl aryl ester, hydrazine hydrate, methanol, carbon disulfide, benzyl halide and trifluoroacetic acid in the presence of dimethylformamide and alcohol. The molecules are evaluated against the glycogen synthase kinase-3beta enzyme. Outcomes show that molecule (20x) (3-[({5-[1-(4-methoxyphenyl)-1H-benzimidazol-6-yl]-1,3,4-oxadiazol-2-} sulfanyl) methyl] benzonitrile) has the capacity to produce maximum inhibitory activity (inhibitory concentration 2.3nM). Further, the molecule shows significant kinase activity against cyclin-dependent kinase-1 (inhibitory concentration: 4.6μM) and protein kinase-c theta inhibitory action (inhibitory concentration: 3.5μM). These data confirm the glycogen synthase kinase inhibitory effect of the aforementioned molecule during viable treatment against Alzheimer's disease [26].

### 4.25. Indazole Derivatives as GSK-3β Inhibitor with Mood-Stabilizing Activity

In this article, a group of scientists develop a series of indazole derivatives (2-16) by using two different procedures. In step-1, molecules (2-12) are synthesized from substituted 5-bromo-1H-indazole-3-carboxamide using substituted boronic acid, [1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium(II), cesium carbonate and dioxane and using substituted boronic acid, substituted bromide, [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), cesium fluoride and dioxane for compound (11-12). Another set of molecules (13-16) is prepared from 5-bromo-N-[(oxan-4-yl) methyl]-1H-indazole-3-carboxamide using bis(pinacolato)diboron, Bis (diphenylphosphino)ferrocene] dichloropalladium (II), potassium acetate, dioxane, substituted bromide, palladium-tetrakis (triphenylphosphine) and dimethylformamide. The synthesized molecules are evaluated against glycogen synthase kinase-3beta and hERG gene. The end results exhibit that molecule 14-(5-[5-(hydroxymethyl) pyridin-3-yl]-N-[(oxan-4-yl) methyl]-1H-indazole-3-carboxamide) is attributed with greater activity towards glycogen synthase kinase (inhibitory concentration: 0.004 μM) and hERG (inhibitory concentration greater than 100 μM). The molecule shows a dose-dependent inhibition against amphetamine-injected motility test with an effective dose of 10 mg/kg compared to that of lithium chloride (50 mg/kg) (Fig. **8**). This data clearly states the importance of 5-[5-(hydroxymethyl) pyridin-3-yl]-N-[(oxan-4-yl) methyl]-1H-indazole-3-carboxamide (26) for the treatment of mood swing [54].

### 4.26. AR-A014418 as GSK-3β Inhibitor with Anti-Alzheimer Activity

In this manuscript, a group of researchers prepare a novel thiazole derivative (AR-A014418) by the interaction between 5-nitro-1,3-thiazol-2-amine and 1-(isocyanatomethyl)-4-methoxybenzene in the presence of dimethylformamide (21). The synthesized molecules are assessed against glycogen synthase kinase-3, cyclin-dependent kinase-5 and 2, AMPK (AMP-activated protein kinase), Chk (checkpoint kinase), CKII (Casein kinase-2), JNK (c-Jun N-terminal kinase), Lck (lymphocyte c-Src kinase), MAPK (mitogen-activated protein kinase) Rsk2 (ribosomal S6 kinase-2), MAPKAPK-2 (mitogen-activated protein kinase-activated protein kinase-2), MEK1(mitogen-activated protein kinase/extracellular signal-regulated kinase-1), MSK1(mitogen- and stress-activated protein kinase-1), p70 S6K (p70 ribosomal protein S6 kinase), PDK1 (3-phosphoinositide-dependent protein kinase-1), PhosK (phosphorylase kinase), PKA (protein kinase A), PKBa (protein kinase B), PKCa (protein kinase C), PRAC (p38-regulated/activated kinase),

ROCKII: (Rho-dependent protein kinase II), SAPK (stress-activated protein kinase), SGK (serum- and glucocorticoid-induced kinase), CSK (carboxyl-terminal Src kinase), cdk2 (cyclin-dependent kinase) and adenosine triphosphate. The after-effects reveal that maximum kinase activity is manifested against GSK-3 (inhibitory concentration= 104nM), phosphoryl kinase and carboxyl-terminal Src kinase with adenosine triphosphate (inhibitory concentration of 38nM). Again, engineered 3T3 fibroblast cells are treated with lithium to express tau protein and the expression is checked by western blot analysis using phosphospecific antibody on tau (p-Tau S396). After that, the synthesized molecule is assessed with inhibition of phosphorylation of tau protein. The results show that AR-A014418 significantly inhibits tau phosphorylation with 1.5nM of inhibitory concentration. This data clearly states the values and significance of this molecule against Alzheimer's disease [24].

### 4.27. 5-(3-chlorophenyl)-1,3-diphenyl-1H-1,2,4-benzotriazepine as GSK-3β Inhibitor with Antiparkinsonian Activity

In this manuscript, neurodegenerative efficacy of 5-(3-chlorophenyl)-1,3-diphenyl-1H-1,2,4-benzotriazepine (SC001) (**27**) is evaluated against 6-hydroxydopamine (as neurotoxic substance destroys dopamine neurotransmitter) induced neurons (Parkinson model) along with alsterpaullone (9-nitro-7,12-dihydro-5H-indolo[3,2-d] [1]benzazepin-6-one), VP 1.14 ((5Z)-2,3-diphenyl-N-[(pyridin-3-yl) methyl]-1,2,4-thiadiazol-5(2H)-imine), VP 1.16 (ethyl [(Z)-(2,3-diphenyl-1,2,4-thiadiazol-5(2H)-ylidene)amino] acetate), VP 3.36 (3-acetyl-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione), VP 3.35 (3-(bromoacetyl)-4-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2,5-dione), VP 3.16 (3-acetyl-4-(1H-indol-3-yl)-1H-pyrrole-2,5-dione) and VP 0.7 (N'-N'-dodecanal-yl-1-ethyl-4-hydroxy-1,2-dihydroquinoline-3-carbohydrazide-1-ethyl-4-hydroxy-1,2-dihydroquinoline-3-carbohydrazide. The consequences reveal that SC001 is found with remarkable percentage of survived neurons having minimized dose-dependent neurotoxicity. Glutamate (3 mM concentration) induced neuronal cells which are treated with SC001 (10μM) are also observed with maximum neuronal survival behavior. The number of dopaminergic neurons present in substantia nigra pars compacta have markedly elevated level of 6-hydroxydopamine and lipopolysaccharide treated SC001. Similar observations are noticed with tyrosine hydroxylase-immunoreactive neuronal cells (Fig. **9**). So, these data confirm the importance of SC001 in the management of Parkinson's disease [55].

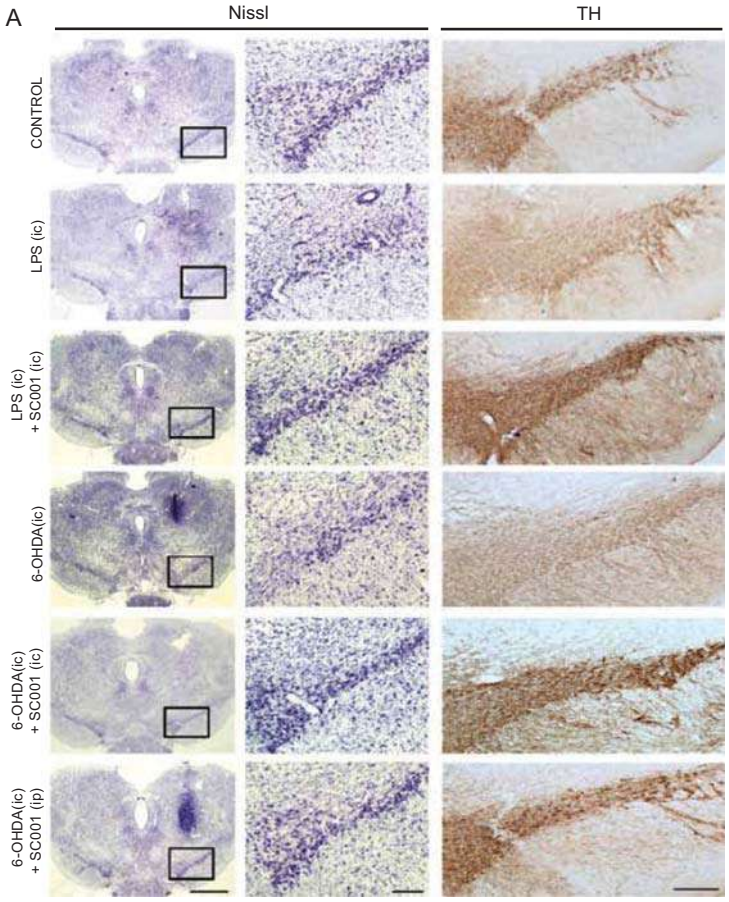



**Fig. (9).** contd...

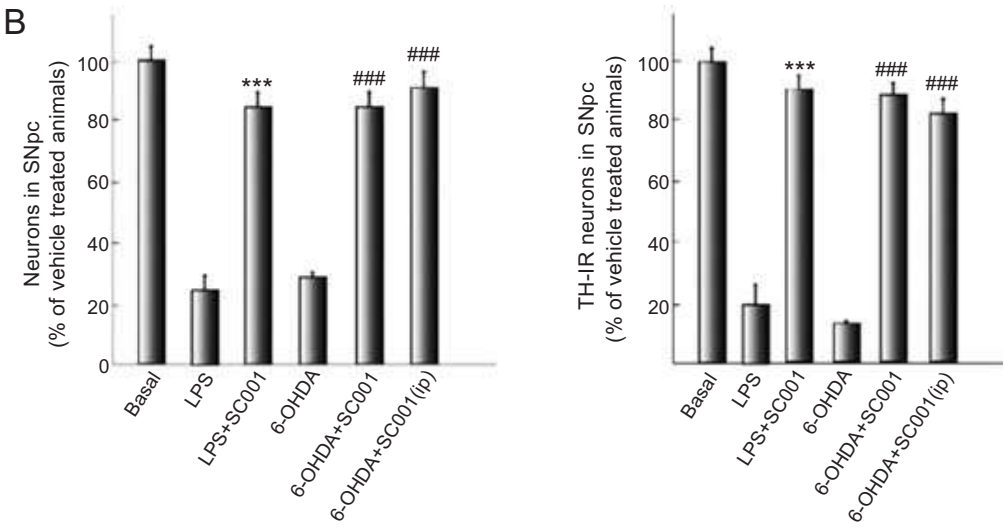



**Fig. (9).** Effect of SC001 on dopaminergic cell death *in vivo*. Rats are treated with LPS or 6-OHDA alone or in combination with the compound SC001 as is indicated in methods and shown schematically in (**A**). Brains are removed, and tissue sections are processed for Nissl stain to label neurons or tyrosine hydroxylase (TH) immunoreactivity to label dopaminergic neurons. Scale bars, 500 μm. Inset scale bars, 100 μm. (**B**) Quantification of the numbers of neurons is stained with cresol violet (Nissl stain) or TH-immunoreactive cells. Values represent the mean ± SD, expressed as a percentage of vehicle-treated animals, from three different experiments, four animals per experiment per experimental group, and five independent sections per animal. ***$p \leq 0.001$ *versus* LPS-treated animals. $^{###}p \leq 0.001$ *versus* 6-OHDA-treated animals. ic, intracerebral; ip, intraperitoneal. [Copyright permission is granted by Morales-Garcia @ 2013 from American Chemical Society]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

All the compounds and structures mentioned above are synthetic GSK-3 inhibitors which are used for the treatment of various neurological disorders as shown Fig. **10**. Finally, a common pharmacophore is developed using the twenty-seven GSK-3 ligands. The common features reflect that the pharmacophore(s) comprising two aromatic centers with 3.3 angstrom distance and one hydrogen bond acceptor center with 2.3 angstrom distance from the aromatic center (Fig. **11**) is visible within the structure(s).

## 5. DISCUSSION

In the present communication, it is observed that eleven receptors related to GSK-3 such as 1Q3D, 1Q5K, 1UV5, 3F88, 4ACC, 4ACD, 4ACH, 4AFJ, 5F95, 6AE3 and 6H0U are available in Protein Data Bank. All the surrounding residues and the directly linked amino acids present within the co-crystallized ligands are visualized through Discovery Studio Client. Amongst the interactions, hydrogen bonding, pi-pi and sigma interactions are the most common. As per the molecular dynamics simulation study of 1I09, it is confirmed that LYS 69 residue is essential for catalytic activity. But recently developed GSK-3 receptors have shown that residues like LYS LYS 85, TYR 134, VAL 135, ARG 141, and ASP 200 are also important for the catalysis process [56]. After overlapping of all the co-crystallized ligands, a common pharmacophore is generated, where two common features are observed such as (a) two aromatic centers that lie within 4 angstrom distance and (b) two hydrogen bond acceptor centers that exist within 7.7 angstrom distance. One terminal acceptor and the nearest aromatic centre are kept at a distance within 3.0 angstrom and the other pair stay within 1.3 angstrom distance. In this manuscript, total twenty-seven molecules are selected for the category of GSK-3 inhibitors which are effective against various neurological disorders like Alzheimer's, depression, beta-amyloid plaque formation, Parkinson disease, mood instability, psychosis, cognitive abnormality and neuronal toxicity. The structural features for GSK-3 inhibitors comprise aminopyridine, benzopyrole, thiazole, pyrazinyl-pyridine, morpholine, pyridinylpyrimide, oxazole, triazole, benzimidazole, thiadiazole, oxadiazole, benzthiazolyl tetrazole, pyrazole, benzothiazepine, 1,8a-dihydro [1, 2, 4]triazolo[4,3-a]pyridine and benzodiazepines heterocyclic ring systems. After a comparison between pharmacophore of co-crystallized ligands and GSK-3 inhibitors, it is noticed that two aromatic centers and one hydrogen bond acceptor center lie with a very similar distance between the centers [two aromatic centers are linked within (3.3-4.0) angstrom distance whereas one hydrogen bond acceptor center is linked with the nearest aromatic center within (3.0-3.3) angstrom distance]. So, it is confirmed that all the synthesized GSK-3 inhibitors where the co-crystallized ligands share a common feature are effective against neurological disorders.

## 6. AUTHORS' INSIGHT ON THE TOPIC

The present manuscript shows that the glycogen synthase kinase enzymes are directly related to various neurological disorders. Also, it is observed that to develop some newer generation GSK-3 inhibitors, the focus should be imposed on the disease pattern and the essential pharmacophoric features should lie within the molecule. It is noticed that hetero atoms and heterocyclic rings play an essential role in conquering diseases.

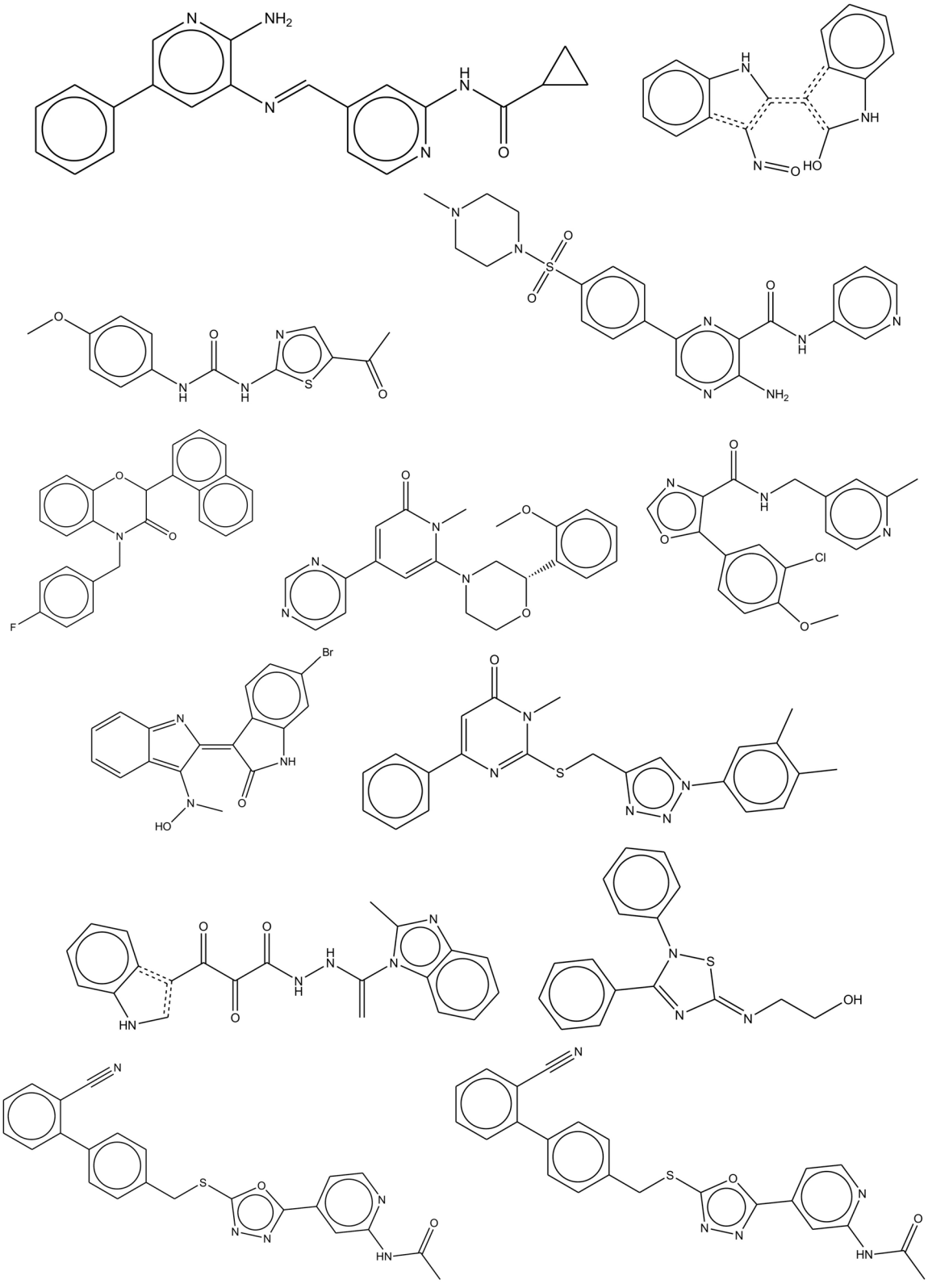


**Fig. (10).** contd...

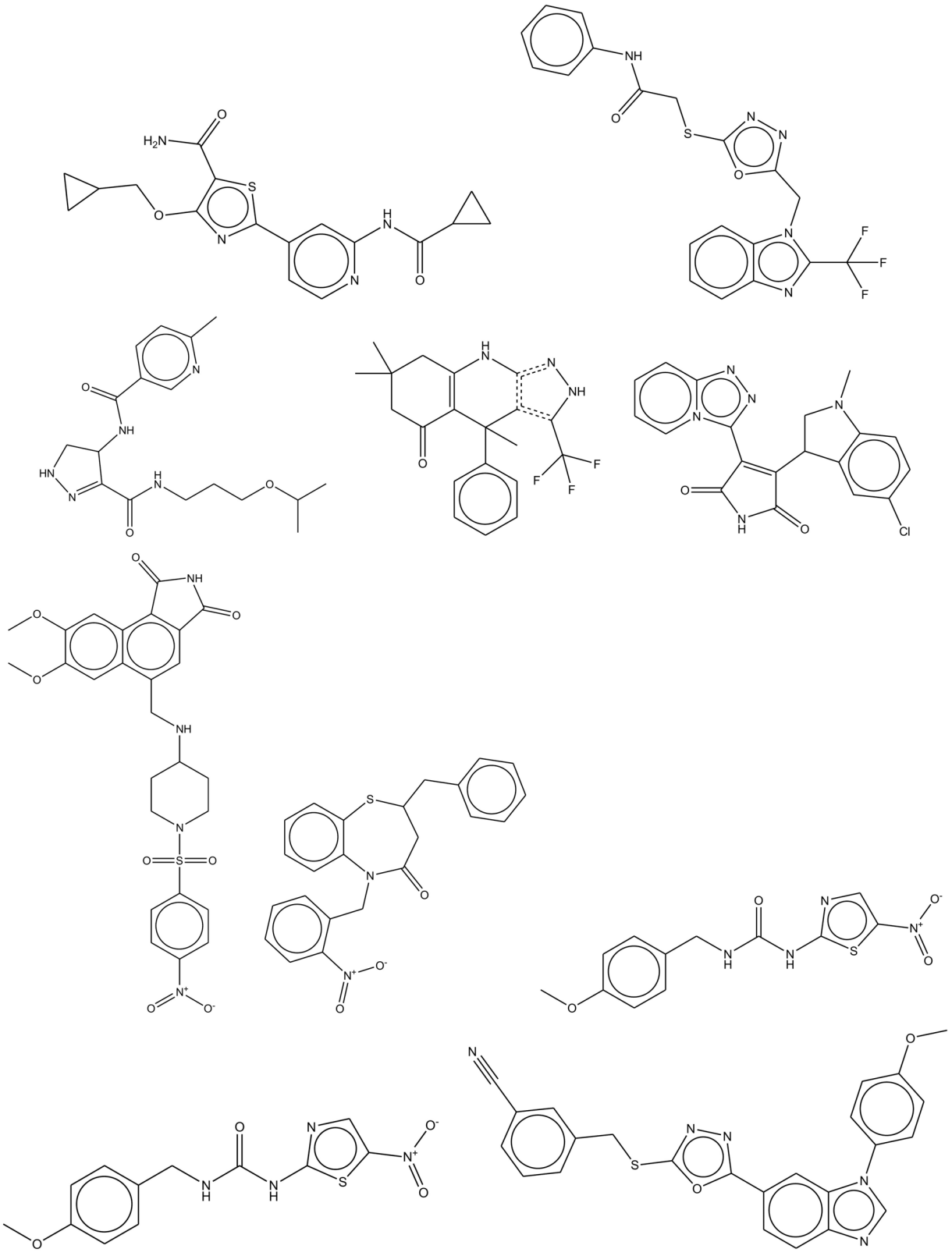


**Fig. (10).** contd...

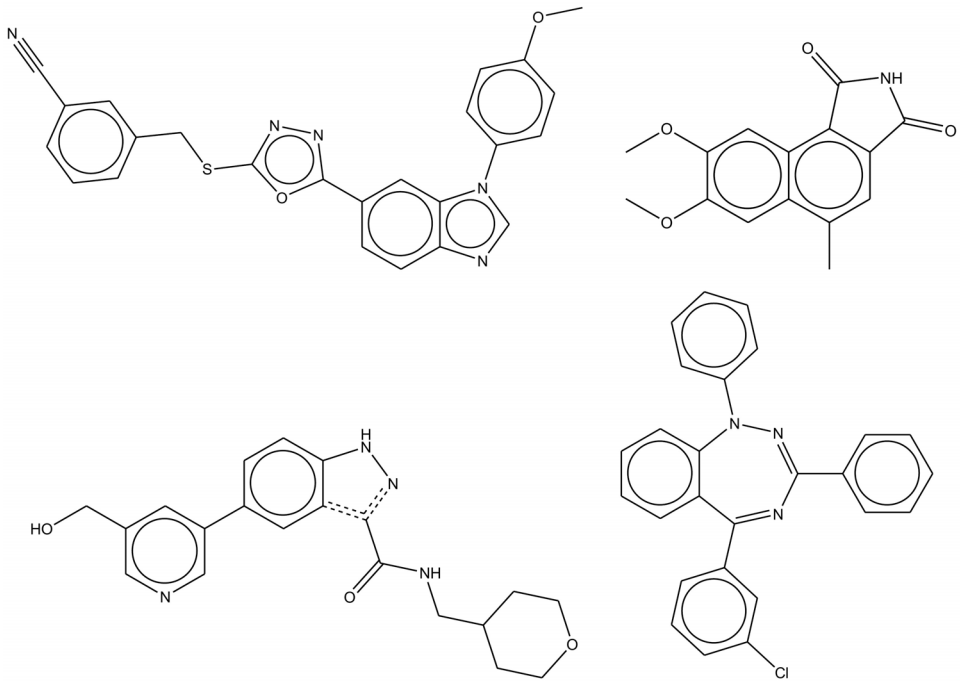



**Fig. (10).** Chemical structures of GSK-3 inhibitors used in the treatment of neurological disorders.

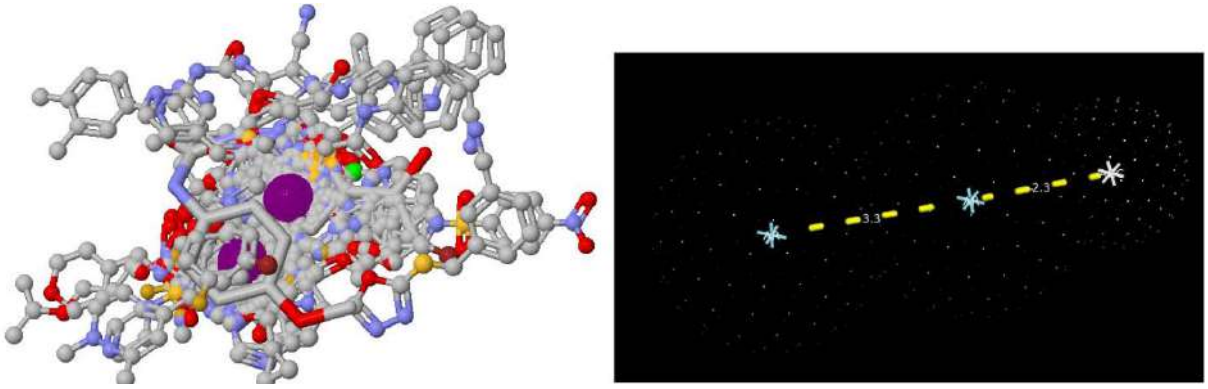



**Fig. (11).** Pharmacophore of GSK-3 inhibitors. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

## CONCLUSION AND FUTURE SCOPE

We know, worldwide depression, Alzheimer's, Parkinson's, schizophrenia disease are the most common devastating diseases. Careful observations within the fundamental facts indicate an intimate relationship between activation/inactivation of glycogen synthase kinase-3 enzyme and etiology of neurological disorders. Also, there exists a direct/indirect relationship between phosphorylation/dephosphorylation properties of the GSK-3 kinase, the balance level between 5-hydroxytryptamine (1A and 2) subtypes, expression characteristics of dopaminergic (D1 and D2) receptors, phosphorylation natures of tau protein, deposition characteristics of beta-amyloid plaques and principles of neurological disorders like Alzheimer's, Parkinson's, depression, and other mental disorders. Towards the development of various synthetic derivatives, different heterocyclic rings containing structures such as indole, pyridine, thiazole, oxadiazole, pyrazine, piperazine, imidazole and benzimidazole are most commonly used in different cases. On the same consideration, as per the structural features, it is justified and confirmatory that GSK-3 inhibitors with benzo pyridine, benzothiazole, pyrazole, pyrazine, dioxolo-benzoxazine, oxadiazole, benzimidazole, and cyclopropyl amide, phenyl carbamothioate, 3-[(propan-2-yl) oxy] propan-1-amine side chain in the core nucleus would show remarkable results against Alzheimer's, Parkinson, depression and related disorders.

They would exhibit good inhibitory profiles with glycogen synthase kinase-3, human adenosine kinase, cyclin-dependent kinase, phosphodiesterase-4, and caspase enzymes. So, if sufficient focuses are imposed on the development of newer generation synthetic GSK-3 inhibitors, it will work as a boon to society.

On the other hand, there is the availability of a lot of folkloric plants such as *Bacopa monnieri* (brahmi), *Nardostachys jatamansi* (jatamansi), *Convolvulus pluricaulis* (shankhpushpi), *Bergenia ciliata* (pashanbhed), *Picrorhiza kurroa* (kutki), *Myristica dactyloides* (javitri) and *Eclipta prostrate* (bhringraj) which are traditionally used to conquer neurological disorders. So, the bottom line is if, in future, the development would be diversified on semi-synthetic derivatives for GSK-3 inhibitors utilizing the resources of nature and scientific minds, in that case, it would be charismatic to total humanity.

## LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| 5HT | = | 5 Hydroxytrptamine |
| ADHD | = | Attention Deficit/Hyperactivity Disorder |
| ASD | = | Autism Spectrum Disorder |
| AT180 | = | Phospho-Tau (Thr231) Monoclonal Antibody |
| AT270 | = | Phospho-Tau (Thr181) Monoclonal Antibody |
| AT8 | = | Phospho-Tau (Ser202, Thr205) Monoclonal Antibody |
| BrdU | = | Bromodeoxyuridine |
| CDK5 | = | Cyclin-Dependent Kinase-5 |
| CRMP2 | = | Collapsin Response Mediator Protein 2 |
| DCX | = | Doublecortin-immunoreactive |
| DU145 | = | Human prostate cancer cell line |
| GSK-3 | = | Glycogen Synthase Kinase-3 |
| hERG | = | human ether-a-go-go related gene |
| HT7 | = | Tau monoclonal antibody |
| nM | = | Nanometer |
| OCD | = | Obsessive-compulsive disorder |
| pH3 | = | Phosphohistone H3 |
| PHF-1 | = | Phospho-epitope at Ser 396/404 |
| pSer | = | Phosphorylated serine |
| pThr | = | Phosphorylated threonine |
| PTSD | = | Post-Traumatic Stress Disorder |
| Src Kinase | = | Proto-oncogene tyrosine-protein kinase |
| μM | = | Micrometer |

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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