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NOVEL SUBSTITUTED 2'- PROP-1-EN-2-YL)- 1', 2', 3', 4'- TETRAHYDRO-[1, 1'- BIPHENYL]- 2, 6- DIOL COMPOUNDS AS ADENOSINE A2A RECEPTOR ANTAGONISTS: INDUCED-FIT MOLECULAR DOCKING STUDIES AND PHARMACOKINETIC PREDICTIONS

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ABSTRACT: Adenosine release is more apparent after seizures or *in-vitro* seizure-like activity and tissue adenosine level increases quickly after seizure commencement. These adenosine increases linked to seizures are reflections in composing a response mechanism that controls seizure intensity and duration. Much evidence from animal studies suggests that this impact is mediated by the adenosine receptor (AR), just as it is with neurotransmission in general. Efforts to produce centrally acting treatments and reduce peripheral side effects, especially cardiac adverse effects, have long been prioritized in drug development. New study is targeting highly precise areas of the A_2R might be a step forward in direct A_2R-based anti-seizure therapy. Despite significant attempts to introduce innovative tactics for the treatment of various kinds of epilepsy, this illness continues to be a serious problem across the globe. Taking inspiration from the facts above and recognizing the growing need for anti-epileptic compounds with improved pharmacodynamics and pharmacokinetic profiles in the worldwide market. The present *in-silico* research involves studying the anti-convulsant (anti-epileptic) potentials of some substituted 2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol molecules (A1 to A16) by exploring the adenosine A_{2A} receptor ($A_{2A}R$) [PDB ID: 4EIY] inhibition through induced-fit molecular docking approach, employing Schrodinger Maestro v.12.8 software. By directing medicinal chemists toward exploring novel compounds, this *in-silico* study opened the way for novel anti-epileptic drug development by identifying novel $A_{2A}R$ inhibitors, which play an essential function in managing convulsions. These solutions to synthetic compounds' never-ending search for superior anti-convulsant activity would open new avenues.

INTRODUCTION: Epilepsy is a common neurological condition that affects around 50 million individuals worldwide.

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Epilepsy affects 3-14 individuals per 1000 people in children and 5-19 people per 1000 people in adults, making it one of the most frequent brain illnesses.

It's a chronic central nervous system illness characterized by recurrent seizure episodes caused by various factors. Seizures are becoming better recognized as co-morbidity with other prevalent illnesses in adults and children, such as Alzheimer's disease and autism [1].

Nootropics are the compounds used to enhance the capacity of work and performance of the brain the drugs. The researchers revealed the anti-epileptic activity of the nootropics compounds belonging to γ-aminobutyric acid (GABA) derivative, piracetam analog like rolziracetam, oxiracetam, etiracetam and nefiracetam [2]. Anticonvulsant activity of carbazole and its derivatives was dertermined [3].

Adenosine release is more apparent after seizures or *in vitro* seizure-like activity and tissue adenosine level increases quickly after seizure commencement. These adenosine increases linked to seizures are reflections in composing a response mechanism that controls seizure intensity and duration. Much evidence from animal studies suggests that this impact is mediated by the adenosine receptor (AR), just as it is with neurotransmission in general. In several forms of experimental seizures and epilepsies, systemic infusion of AR-selective agonists reduces seizures and convulsions. AR activation also enhances the effectiveness of traditional AEDs. Anti-convulsant effects are also shown when A_1Rs are activated in specific brain areas. Elevating excitability or restricting inhibition in brain slices and cultures may elicit seizure-like or epileptiform electrical patterns (oscillatory field potentials, repetitive bursts of action potentials, *etc.*). As predicted, adenosine release is high during this sort of epileptiform activity, and it is auto-inhibitory through A_1Rs [4].

Because of their evident effects on neuronal activity, high affinity, and extensive distribution, A_1Rs has long been linked to anti-seizure effects. They are concentrated in seizure-prone locations and impact continuing transmission (neocortex and hippocampus). On the other hand, other adenosine receptors might play a role and provide therapeutic targets for epilepsy. Because A_{2A}Rs are excitatory in most brain areas, antagonists of A_{2A}Rs are more likely to exhibit anti-seizure properties. When opposed to A_1Rs, A_{2A}Rs have a much more limited anatomical distribution. As a result, it's not unexpected that it's not implicated in convulsions in many studies, and one research found that A_{2A}R regulation of convulsions was limited to the basal ganglia. Pharmacological data from *in-vivo* and *in-vitro* research indicates that A2ARs are pro-convulsant and pro-seizure, while some studies offer anti-convulsant or anatomically specific effects. Some of these effects were detected in areas with a handful of receptors, despite of valence, which might indicate non-specificity of drug dosage or concentration. At the same time, A_{2A}Rs may have functional functions even if expressed at very low levels.

In various studies, mice with genetic inactivation of A_{2A}Rs are seizure-resistant, indicating a pro-convulsant receptor function [5]. Though central expression of other adenosine receptors is minimal, pharmacological evidence for actions of the adenosine A_3 receptor (A_3R) has been described in a few investigations, with inconsistent findings. A_3R activation induces seizure-like activity in hippocampal slices, although studies assessing convulsions and utilizing systemic injection showed that this receptor had an anti-convulsant effect. As a result, A_3R effects may be region-specific. There is almost little information on the role of A_{2B}Rs in seizures, which are likewise expressed at a low level in the brain [6]. The high-affinity A_1 and A_{2B} receptors in the brain are assumed to be important for physiology, but the low-affinity A_{2B} receptors and low-density A_3 receptors may be crucial in pathological circumstances. In the dopamine-rich areas of the brain, adenosine A_2A receptors are concentrated in GABAergic medium-sized spiny neurons.

Many additional organs in the sympathetic and parasympathetic systems carry the protein expressed in adenosine A_{2A}, including endothelial cells, blood vessels, smooth muscle cells, lymphoid cells, and numerous neurons. As a result, the distribution of adenosine A_{2A} in the basal ganglia is not constrained to medium spiny neurons. It enhances the amount of adenylyl cyclase and upholds the directive of cAMP production. This receptor is critical for providing the medium for coronary artery vasodilation, which encourages the formation of new blood vessels and protects tissues from indirect inflammatory damage. The A_{2A}'s function in the brain involves modulating activity in the basal ganglia's indirect route. Because it co-localizes and is physically associated with various unrelated G-protein-coupled receptors, the A_2A has complex activities [7]. Efforts to produce centrally acting treatments and reduce peripheral side effects, especially cardiac adverse effects, have

long been prioritized in drug development. According to a new study, targeting highly precise areas of the A_2R might be a step forward in direct A_2R-based anti-seizure therapy. Despite significant attempts to introduce innovative tactics for treating various kinds of epilepsy, this illness continues to be a serious problem across the globe. Taking inspiration from the facts above and recognizing the growing need for anti-epileptic compounds with improved pharmacodynamics and pharmacokinetic profiles in the worldwide market [8].

The present *in-silico* research involves studying the anti-convulsant (anti-epileptic) potentials of some substituted2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol molecules(A1 to A16) by exploring the adenosine A_{2A} receptor ($A_{2A}R$) [Protein Data Bank ID: 4EIY, the Crystal structure of the chimeric protein of $A_{2A}R$-BRIL in complex with ZM241385 at 1.8A resolution] inhibition through induced-fit molecular docking approach, employing Schrodinger Maestro v.12.8 software. The obtained docking score (in Kcal/mol) is reported, and the results are interpreted accordingly.

MATERIALS AND METHODS:

Sketching of Ligands: The structures were first developed in the 2Dfile using Chemdraw® Ultra 8.0 software as a ".cdx" format, then converted to ".sdf" format [9].

Ligand Preparation: Small compounds were prepared for molecular docking investigations using the LigPrep module. The module also determines the ligands' lowest energy conformation. It turned a two-dimensional structure into a three-dimensional one. These structures with the lowest energy were utilized for molecular docking or Qikprop analysis. The LigPrep module used stereochemistry, protonation states, ring conformations, and tautomers to generate numerous output structures for each input structure. The number of structures created varied based on the ligands being processed; however, the number of structures that needed to be modified for the output was consistent. The key variables that influenced the number of structures are the stereochemistry, ionization nature, and tautomeric character of the input ligands. Four potential conformers were formed in the stereoisomerism: *cis*, *trans*, *R*, and *S*. In ionization, various structures were produced by altering the pH (from 2.0 to 7.0). At the same time, the algorithm created all of the potential tautomeric structures [10].

Protein Preparation: The quality of docking findings is often influenced by the protein structure. As a result, choosing a receptor structure based on resolution is highly advised. Atypical protein structure file (4EIY) with heavy atoms, fluids, co-factors, and metal ions was acquired from the PDB. The tautomeric states and ionization states were commonly ascribed during protein structure construction. In addition, the covalent bonds between metal ions and proteins were accurately assigned, as were multiple bonds and formal charges. The direction of the water molecules was taken into account when producing the protein files. During the preparation, steric clashes and hydrogen bond conflicts were also resolved. The charge cutoff was set at 0.25 and the Van der Waals scale factor was set to 1.0. On each ligand, induced-fit docking (IFD) was performed, and the best-docked posture with the lowest score was verified [11].

Grid Generation: Grid Generation is used to indicate where the ligands should bind to the receptor. The grid is generated by taking into consideration the shape of the binding site. The grid may be determined if the crystal structure is known based on the ligand location. The precise binding site [126 A° × 126 A° × 126 A° (x, y, and z, respectively)] was discovered via a literature review. The grid points were spaced 0.375 degrees apart [12].

Extra Precision Docking: The IFD was generated using the structure-based drug design approach, which entails producing accurate geometry ligands to dock with the prescribed structure of a biological target. The free-state ligands are docked into the rigid state receptor's active site, enzyme, tube, and other components, leading to a projected binding mode and assessing the fit's strength. The attachment of a low-molecular-weight ligand to a macromolecular protein has its relevance in receptor-based computational approaches because the best-suited connection with low energy values and probable steric conflicts is determined. The extra-precision (XP) docking mode is a

sophisticated sampling methodology that eliminates false-positive findings from docking studies and improves the connection between excellent poses and scores. The system will produce various positions and determine the best ligand poses in terms of energy by utilizing the custom scoring mechanism. This is based on the notion that only active chemicals will contact the protein properly. The XP sampling approach is based on a modified growth plan and an anchor. Typically, a docked ligand's anchor pieces (such as rings) are picked, and the molecule is grown bond by bond from these anchor sites. Then, minimizations and scoring are carried out depending on the scoring penalties. The crossover rate was set to 0.8, and the mutation rate was set at 0.02. The maximum number of energy assessments allowed was 500000, the maximum number of generations allowed was 1000 and the maximum number of top people that automatically survived was one. A 0.2 step size was used for translations, a 5.0° step size for quaternions and a 5.0° step size for torsions. The cluster tolerance was set to 0.5, the external grid energy was set to 1000.0, the maximum binding energy was set to 0.0, the maximum number of retries was set to 10000, and 10 runs were conducted. Based on the Glide score acquired from the docking experiments, the optimum postures were chosen.

Glide Score: The optimal position may be chosen based on the Glide score or Gscore after molecular docking. The algorithm identifies favorable hydrophobic, hydrogen-bonding, and metal-ligation interactions while penalizing steric conflicts when calculating G-score. Normally G score is calculated using the following equation:

Gscore = 0.05*vdW + 0.15*Coul + Lipo + H-bond + Metal + Rewards + RotB + Site

Pharmacokinetic Predictions: The QikProp module was used to find the critical PK parameters that influence processes such as toxicity, absorption, metabolism, distribution, and elimination (ADMET). Studies on the following factors were conducted as part of the computer-assisted pharmaceutically relevant characteristics prediction based on physical descriptors: Molecular weight of the compound; Compound as Donor - Hydrogen Bonds; Number of Rotatable Bonds; Lipinski Rule of 5 Violations; Compound as Acceptor - Hydrogen Bond; QP log P for Octanol/Water; QP Log K has Serum Protein Binding and % Oral human absorption in GIT.

Bioavailability Studies: The online tool Swiss ADME was made used to perform a pharmacokinetics prediction study, namely ADME, bioavailability, and ligand drug-likeness. Based on many physicochemical properties, the bioavailability radar was made used to envisage the oral bioavailability. The parametric ranges are mentioned as following: POLAR = polarity as 20Å² < TPSA (topological polar surface area) < 130Å²; INSATU = in saturation or saturation as per fraction of carbons in the sp^3 hybridization 0.3 < Fraction Csp3 < 1; FLEX = flexibility as per rotatable bonds 0 < Number of rotatable bonds < 9; INSOLU = insoluble in water by log S scale 0 < Logs (ESOL) < 6; SIZE = size as molecular weight 150gm/mol < MV < 500gm/mol; and LIPO = lipophilicity as -0.7 < XLOGP3 < +5.0.

Absorption and Distribution Profile: In the Swiss ADME online tool, the absorption and distribution profile, such as blood-brain barrier (BBB) permeation and passive human gastrointestinal absorption (HIA), as well as permeability glycoprotein (P-gp) in the form of substrate or non-substrate was detected positive (PGP+) or negative (PGP-) in the Brain or Intestinal Estimate D permeation method (BOILED-Egg) model inside the tool system.

RESULTS AND DISCUSSION:

Molecular Docking Study: The current bioinformatics study revealed that the substituted 2'-(prop – 1 – en - 2-yl)-1', 2', 3', 4'-tetrahydro-[1,1'-biphenyl]-2,6-diolmolecules had affinity for the A2aAR in the terms: A16 (GScore: -8.97Kcal/mol) > A4 (GScore: -7.199Kcal/mol) > A6 (GScore: 7.143Kcal/mol) > A5 (GScore: -7.139 Kcal/mol) > A10 (GScore: -7.076 Kcal/mol) > A9 (GScore: -7.075Kcal/mol) > A2 (GScore: -6.884Kcal/mol) > A15 (GScore: -6.763 Kcal/mol) > A14 (GScore: -6.761Kcal/mol) > A8 (GScore: -6.538 Kcal/mol) > A7 (GScore:-6.532Kcal/mol) > A13 (GScore: -6.257 Kcal/mol) > A12 (GScore: -6.254 Kcal/mol) > A11 (GScore: -6.251 Kcal/mol) > A3 (GScore:-6.166Kcal/mol) > A1 (GScore: -6.029Kcal/mol). The compound A16 have been

identified as top inhibitor as evidenced from the Gscore of -8.97Kcal/mol **Table 1.** All the molecules have demonstrated hydrogen bonding interaction by selectively interacting with the amino acid residues PHE168 (compounds A10, A9, A8, A7, A6, A5, A4 and A2), GLU169 (compounds A13, A12, A11, and A3), ILE66 (compounds A15 and A14) and TYR271 (compound A16) *via* –OH (hydroxyl) group of the molecule. In contrast to them, molecule A1 only expressed interaction with both amino acid residues PHE168 and GLU169 through two hydroxyl moieties.

TABLE 1: DOCKING SCORES (IN DECREASING ORDER) OF SOME SUBSTITUTED 2'-(PROP-1-EN-2-YL)-1',2',3',4'-TETRAHYDRO-[1,1'-BIPHENYL]-2,6-DIOLMOLECULES

Ligand	Structure and IUPAC nomenclature	Gscore (Kcal/mol)	Amino Acid Residues	Hydrogen Bonds
A16		-8.97	TYR271	1
A4	(1'*S*,2'*R*)-4-(cyclohexylmethyl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-7.199	PHE168	1
A6	(1'*R*,2'*R*)-5'-methyl-4-(pentyloxy)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-7.143	PHE168	1
A5	(1'*S*,2'*R*)-4-(cyclopentyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-7.139	PHE168	1
A10	(1'*S*,2'*R*)-4-(cyclopentyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-7.076	PHE168	1
	(1'*R*,2'*R*)-4-(sec-butoxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-			

	biphenyl]-2,6-diol			
A9		-7.075	PHE168	1
A2	(1'*S*,2'*R*)-4-(sec-butoxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.884	PHE168	1
A15	(1'*R*,2'*R*)-4-butoxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.763	ILE66	1
A14	(1'*S*,2'*R*)-4-(cyclopentylmethyl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.761	ILE66	1
A8	(1'*R*,2'*R*)-4-(cyclopentylmethyl)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.538	PHE168	1
A7	(1'*R*,2'*R*)-4-(cyclohexyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.532	PHE168	1
	(1'*S*,2'*R*)-4-(cyclohexyloxy)-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol			

A13		-6.257	GLU169	1
A12	(1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.254	GLU169	1
A11	(1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.251	GLU169	1
A3	(1'*S*,2'*R*)-5'-methyl-4-pentyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.166	GLU169	1
A1	(1'*S*,2'*R*)-5'-methyl-4-(pentyloxy)-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol	-6.029	PHE168, GLU169	2
	(1'*S*,2'*R*)-4-butoxy-5'-methyl-2'-(prop-1-en-2-yl)-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2,6-diol			

The π-π interaction of aromatic rings present in compounds A3, A14 and A15 with the amino acid residues PHE168 and TYR271, respectively have been observed **Fig. 1.**

Hydrophobic interaction due to non-polar residue interaction at the active site of the biological target, as well as electrostatic forces, water-mediated hydrogen bonding, Van der Waals forces and hydrophobic interaction due to non-polar residue interaction at the active site of the biological target, all interact with the ligands to provide stability to the receptor-ligand complex **Fig. 2.**

As a result, the docking experiments have broadened the possibilities of opening new avenues for new classes of anti-convulsant drugs. When the structure-predicted inhibitory activity was studied, 4 key points have been observed:

(i) The only points of interactions were hydroxyl components situated in 2 and 6 positions from the pharmacophore.

(ii) The substitutions of various components like cyclopentyl, cyclohexyl, sec-butoxy, *etc*. have no prominent contribution in the

interaction with the receptor *via* hydrogen bonding; however, they played dominant roles in exhibiting electrostatic forces, Van der Waals forces, and hydrophobic interaction.

(iii) The methyl, prop-1-en-2-yl, *etc*., the part did not play an imperative role in mediating hydrogen bonding interaction. However, they played dominant roles in mediating Van der Waals forces.

(iv) Stereochemistry has a minor influence on the activity. The isomeric forms demonstrated nearly alike results.

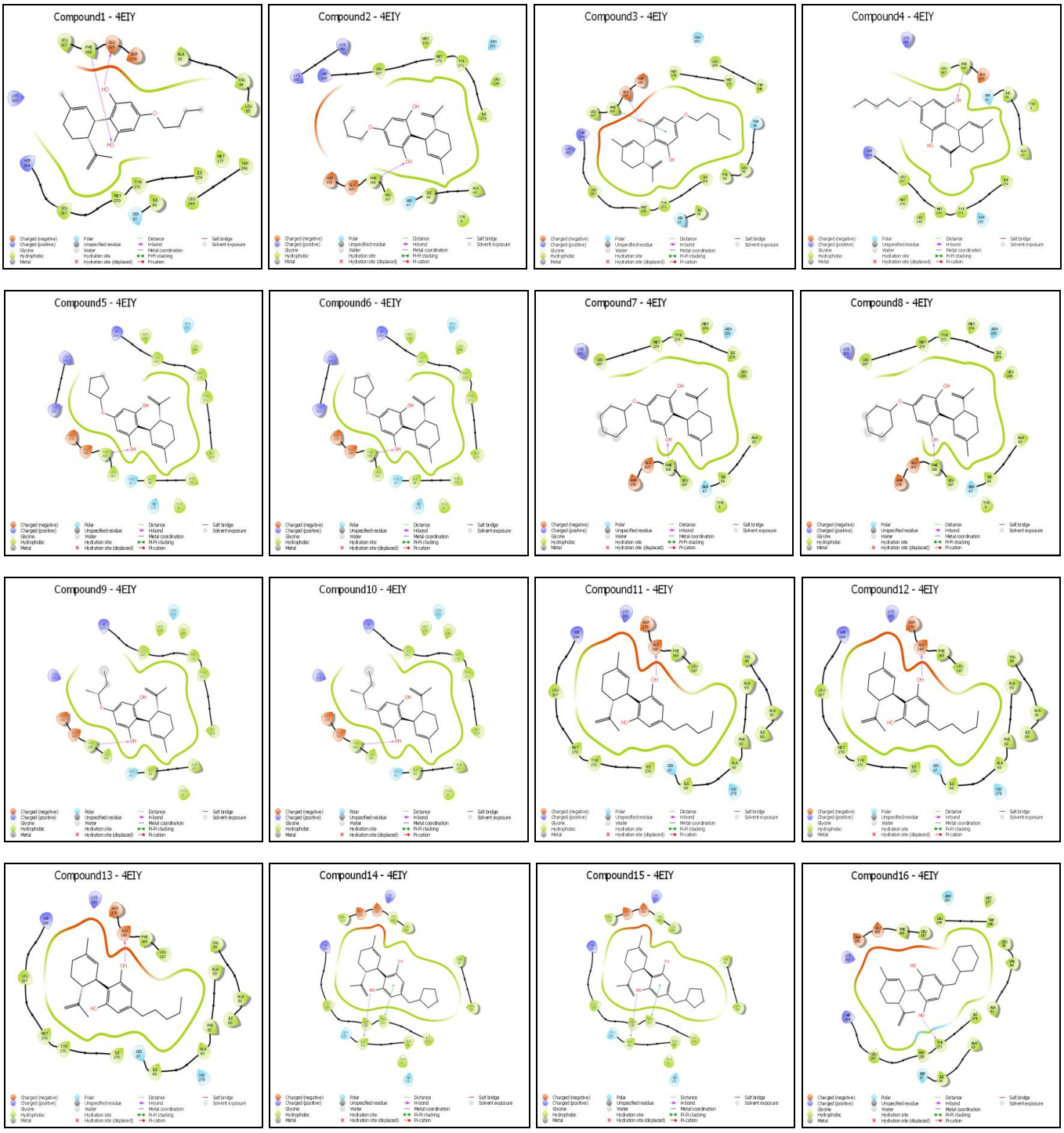

FIG. 1: 2D-INTERACTION DIAGRAMS OF SOME SUBSTITUTED 2'-(PROP-1-EN-2-YL)-1',2',3',4'-TETRAHYDRO-[1,1'-BIPHENYL]-2,6-DIOL MOLECULES

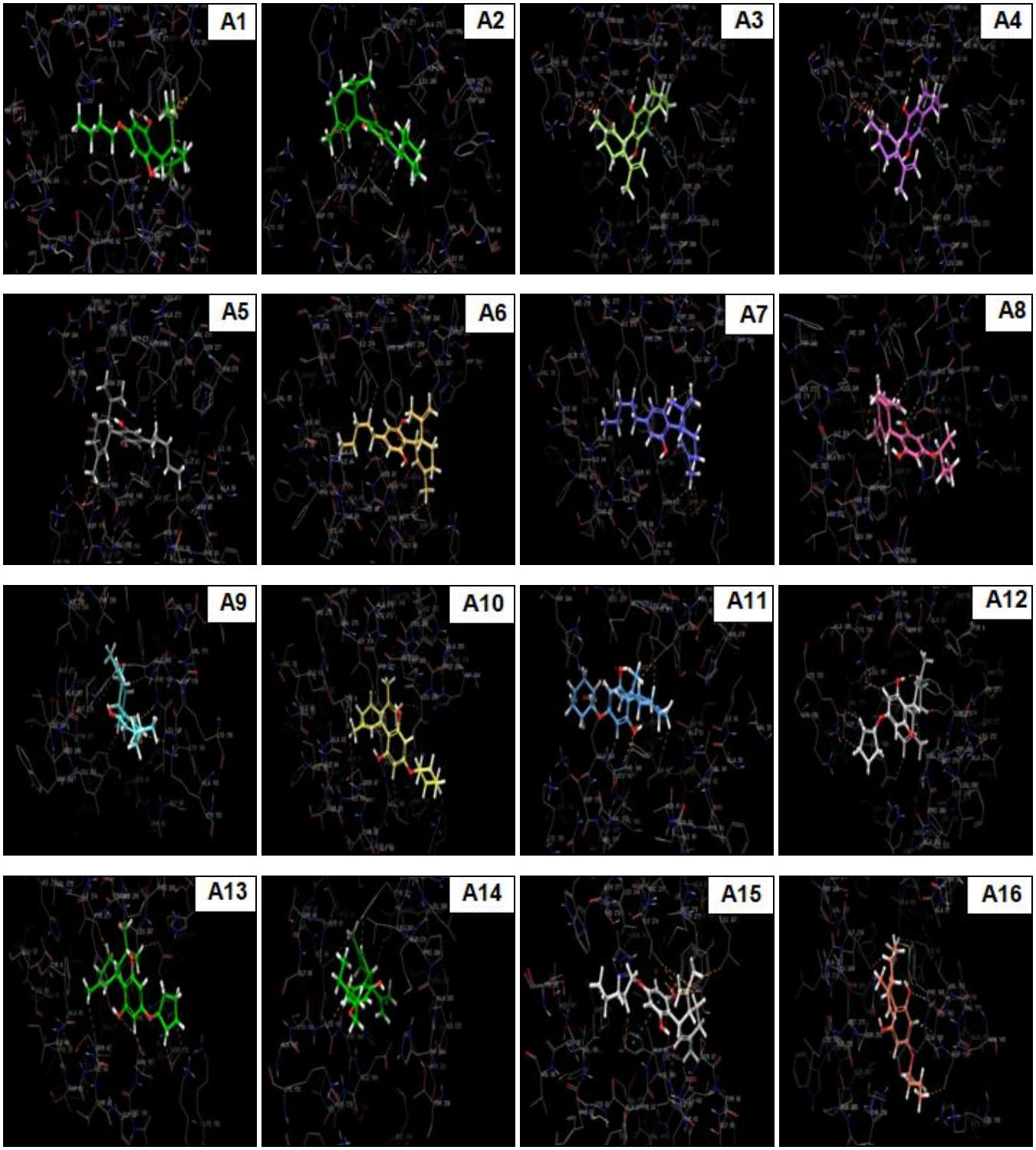

FIG. 2: 3D POSES OF SOME SUBSTITUTED 2'-(PROP-1-EN-2-YL)-1',2',3',4'-TETRAHYDRO-[1,1'-BIPHENYL]-2,6-DIOLMOLECULES

Pharmacokinetic Predictions: The observed levels of the top three candidates (A16, A4, and A6) were within the required limits based on the projected pharmacokinetic characteristics.

The projected oral absorption was significant (100%) and may be linked to oral bioavailability (OB), an important criterion in drug development **Table 2**. Higher OB is often related to reducing the dosage, and lowering the risk of adverse effects and toxicity.

On the other hand, poor OB causes a lot of variation in the mediation of pharmacological responses.

TABLE 2: PHARMACOKINETIC PROFILE OF TOP 3 MOST ACTIVE COMPOUNDS

Parameters	A16	A4	A6
Molecular weight	340.50	330.46	328.45
No. of Rotatable Bonds	4	7	4
Compound as Donor – Hydrogen Bonds	2	2	2
Compound as Acceptor– Hydrogen Bond	2	3	3
Lipinski Rule of 5 Violations	0	0	0
QP Log K Serum Protein Binding	0.779	0.934	1.313
QP log P for Octanol/Water	4.013	4.179	3.754
% Oral human absorption in GIT	100	100	100

All of the compounds had log P values in the range of 3.75 to 4.17, indicating superior CNS activity due to improved blood-brain barrier penetration (BBB). The expected lipophilicity profile was less than 5, confirming Lipinski's universal rule of five. High lipophilicity causes several issues, including limited water solubility, significantly high affinity for metabolizing enzymes, and serum protein binding, among others. Similarly, all compounds followed the "Lipinski's rule of five," lipophilicity less than 5, the molecular weight of less than 500, optimized Donor – Hydrogen Bonds of maximum 5 and Hydrogen Bonds of maximum 5, which signifies its optimized pharmacological potentials.

A significantly high human intestinal absorption was perceived from the fact that the values of molecular weight <500 in the case of all the molecules directly influence OB. The serum protein binding was quite substantial in the case of compounds having a value greater than 0.5, represented adequate binding, and will serve as a depot. In contrast, the compound has lower values, less than 0.5, and the majority of the drug will be in circulation. An optimized binding with the serum protein is reasonably needed to express the time-bound activity and exhibit better access to the target site.

Bioavailability Profile: The oral bioavailability forecasted through the bioavailability radar showed desired INSATU = in saturation as per Csp^3 as 0.57, FLEX as per the number of rotatable bond 4, INSOLU LogS (ESOL) as -6.34 (soluble), SIZE as molecular weight (gm/mol) of 340.50 g/mol, POLAR as TPSA (Å²) 40.46 and LIPO as XLOGP3 value of 7.10 for compound A16 **Fig. 3.**

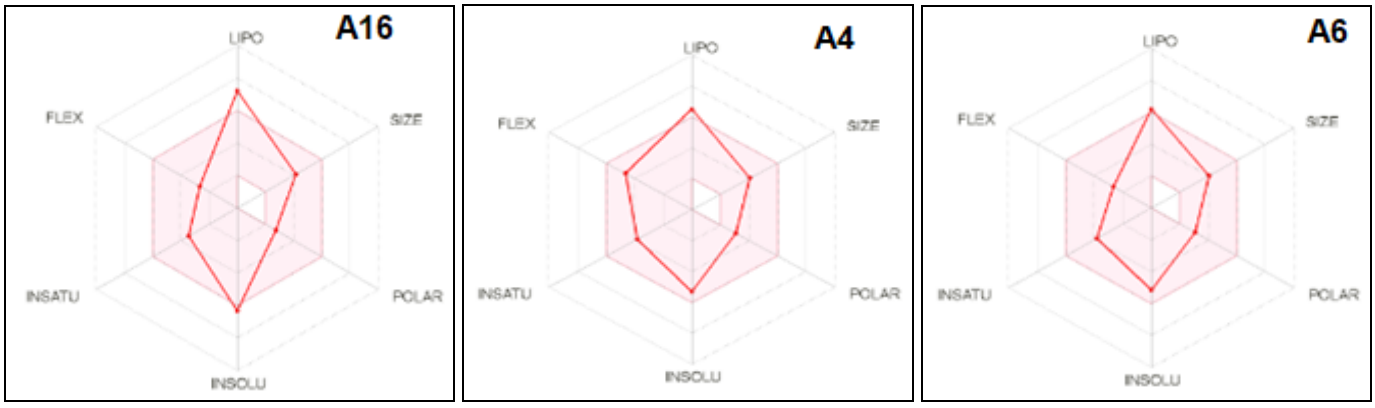

FIG. 3: BIOAVAILABILITY RADAR PLOT FOR MOST ACTIVE COMPOUNDS

For compound A4, the bioavailability radar for oral bioavailability prediction demonstrated necessary INSATU = in saturation as per Csp^3 as 0.52, FLEX as per the number of rotable bond 7, INSOLU LogS (ESOL) as -5.30 (soluble), SIZE as molecular weight (gm/mol) of 330.46 g/mol, POLAR as TPSA (Å²) 49.69,\ and LIPO as XLOGP3 value of 5.86. The oral bioavailability forecasted through the bioavailability radar for compound A6 showed required INSATU = in saturation as per Csp^3 as 0.52, FLEX as per the number of rotatable bond 4, INSOLU LogS (ESOL) as -5.16 (soluble), SIZE as molecular weight (gm/mol) of 328.45 g/mol, POLAR as TPSA (Å²) 49.69 and LIPO as XLOGP3 value of 5.34. It can be concluded that all the essential parameters lie within the prescribed limit for all the 3 molecules and the predicted bioavailability was found to be sufficiently high.

Absorption, Distribution and Metabolism Profile: Compound A16 has a higher prevalence of GIT absorption (high penetration potential) than BBB crossing potential in the BOILED-Egg model **Fig. 4**, but the other two compounds (A4 and A6) had superior BBB penetration than GIT absorption. In the predicted model, the compounds were also discovered to be PGP negative as non-substrate. Interestingly, the BOILED-Egg model has previously been offered as an accurate predictive model that aids in calculating small molecule lipophilicity and polarity. According to the bioavailability radar and BOILED-Egg representation, these chemical compounds may be viable drug candidates.

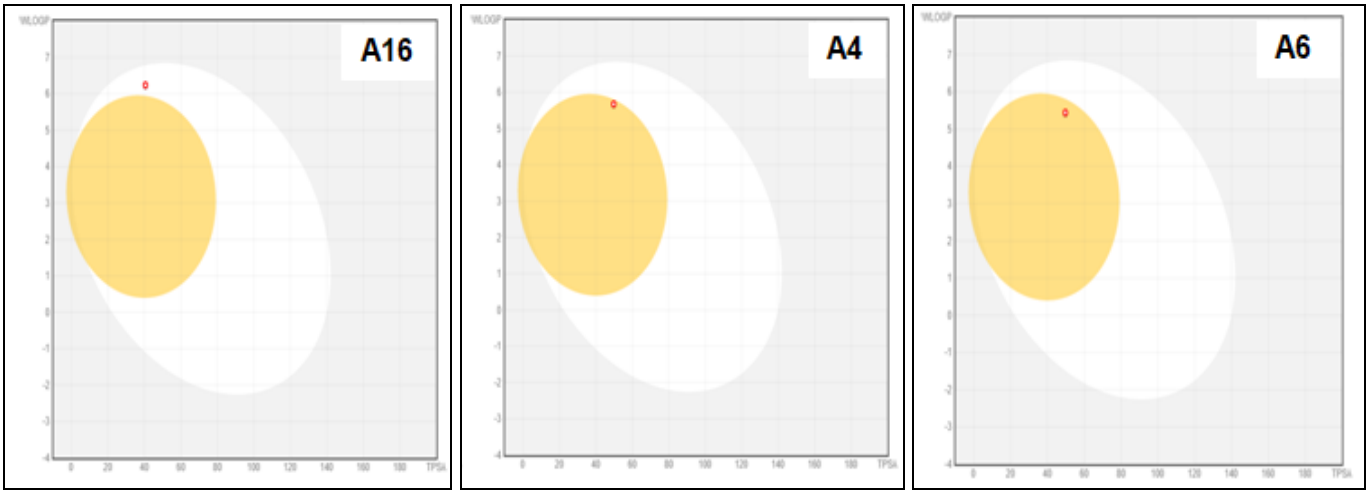

FIG. 4: BOILED-EGG MODEL FOR MOST ACTIVE COMPOUNDS

CONCLUSION: By directing medicinal chemists toward the development of new substituted 2'-(prop – 1 – en - 2-yl) -1', 2', 3', 4'-tetrahydro-[1,1'-biphenyl]-2,6-diol,this *in-silico* study opened the way for novel anti-epileptic drug development by identifying novel adenosine A_{2A} receptor inhibitors, which play an essential function in managing the convulsions.

These inhibitors demonstrated the creation of hydrogen bonds (through –OH group) as well as the presence of electrostatic forces, Van der Waals forces and hydrophobic interaction supported the stabilization of the ligand-receptor complex, which provide a path for increased penetration into the receptors' active site cavity.

The absorption, distribution, bioavailability, and characteristics concluded that the compounds had desired bioavailability and pharmacokinetics profiles. These solutions to the never-ending search for superior anti-convulsant activity in synthetic compounds would provide opportunities for academics, modern scientists, and scholars and expand pharmacotherapeutic choices.

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REFERENCES:

1. Mahapatra DK and Bharti SK: Medicinal Chemistry with Pharmaceutical Product Development. New Jersey: Apple Academic Press 2019.
2. Dhama N, Sucheta, Kumar A, Verma V and Kumar Sunil: A review on synthesis and pharmacological activities of piracetam and its derivatives. Asian J of Chemistry 2021; 34(1):1-8.https://doi.org/10.14233/ajchem.2022.23357
3. Rawat B, Sucheta, Rahi S and Arpana Rana A: Carbazole: an updated profile of biological activities. International Journal of Research in Pharmacy and Chemistry 2021; 11(3): 76-98.doi: https://dx.doi.org/10.33289
4. Tescarollo FC, Rombo DM, DeLiberto LK, Fedele DE, Alharfoush E and Tomé ÂR: Role of adenosine in epilepsy and seizures. J Caffeine Adenosine Res 2020; 10(2): 45-60.doi: 10.1089/caff.2019.0022.
5. Boison D: Adenosine and epilepsy: from therapeutic rationale to new therapeutic strategies. Neuroscientist. 2005; 11(1): 25-36.doi: 10.1177/1073858404269112.
6. Masino SA, Kawamura M and Ruskin DN: Adenosine receptors and epilepsy: current evidence and future potential. Int Rev Neurobiol 2014; 119: 233-55. doi: 10.1016/B978-0-12-801022-8.00011-8.

7. Aryati WD, Salamah NN, Syahdi RR and Yanuar A: The Role and Development of the Antagonist of Adenosine A2A in Parkinson's disease. In: Neuroprotection London Intech Open 2019.
8. Deb PK, Kokaz SF, Abed SN, Chandrasekaran B, Hourani W and Jaber AY: Pharmacology of Adenosine Receptors. In: Frontiers in Pharmacology of Neurotransmitters. Singapore Springer 2020.
9. Joseph TM and Mahapatra DK: Bacterial DNA Gyrase (Topoisomerase) Inhibitory Potentials of Heterocyclic Natural Products: Investigations through Induced-Fit Molecular Docking Approach. Research and Reviews: J Drug Design Discov 2018; 5(2): 7-9. Doi: http://pharmajournals.stmjournals.in/index.php/RRJoDDD
10. Silky S, Neerupma D and Arun G: Inhibitory Perspective of New Synthesized Compounds against Angiotensin Receptor: Schrodinger-based Induced-Fit Molecular Docking. J Pharm Res Int 2021; 33(32A): 79-87.doi: 10.9734/jpri/2021/v33i32A31718.
11. Mahapatra DK and Bharti SK: Handbook of Research on Medicinal Chemistry: Innovations and Methodologies. New Jersey: Apple Academic Press 2017.
12. Mahapatra DK and Bharti SK: Drug Design. New Delhi: Tara Publications Private Limited 2016.

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