

# Structure-based drug designing for N-methyl-D-aspartate receptor: Link between neurodegenerative disease and glioblastoma

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## ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease followed by various other disorders such as Parkinson's disease, amyloid lateral sclerosis, Huntington's, and glioblastoma. The target that has been a key focus in this study is N-methyl-D-aspartate (NMDA) receptor that is responsible for the transmission, integration, and plasticity of excitatory signals needed for the proper functioning of the central nervous system. NMDA is also responsible for the Ca<sup>2+</sup> influx. Any damage to the NMDA receptor will lead to neuronal cell death which, in turn, leads to AD. Damage to the receptor also affects Ca<sup>2+</sup> influx by developing a lead molecule that can partially bind to the receptor and when it is damaged can prevent neural death. An alkaloid compound called moupinamide (N-transferuloyltyramine) which was determined as a lead molecule was further optimized utilizing various *in silico* methods. Using moupinamide as the basic framework, initial and secondary drug designing is done and then it is followed by docking studies, absorption, distribution, metabolism, and excretion analysis, and molecular simulations. In this study, it was observed that optimized lead molecule high modulus polyethylene could be a potential lead molecule as it showed a great potential.

## 1. INTRODUCTION

"Neurodegenerative diseases" is a broad term for a range of conditions that primarily affect the neurons in the human brain [1]. The World Health Organization anticipates that by 2050 a staggering 30 million people will be affected by Alzheimer's disease (AD), Parkinson's disease, glioblastoma (GBM), and many others. The increase in these neurodegenerative diseases leads to a toll on human populations. It is reported that it mainly affects the citizens of the United States of America, Europe, and Southeast Asia [2]. Since AD and GBM are some of the leading neurodegenerative diseases, a common link was tried to establish between the two. It was found that damage to the N-methyl-D-aspartate (NMDA) receptor can cause both AD and GBM.

NMDA is a glutamate receptor and that is one of the main excitant neurotransmitters in a mammalian brain. NMDA is also responsible for the Ca<sup>2+</sup> influx which plays an important role in various secondary signaling pathways [3]. It also plays an important role in maintaining the synaptic plasticity of the nerves and also for the cellular processes that are directly responsible for memory and learning [4,5]. When there is damage to the glutamate receptor, it leads to plaque formation that leads to AD [6]. Due to the damage, there is excessive

activation of the glutamate receptors that lead to the proliferation of the GBM cells [7]. NMDA plays a key role in both AD and GBM to prevent excessive damage to a partial inhibitor. A lot of research has been done on NMDA. By determining the active site pockets, memantine was developed and is commercially available as a partial antagonist that binds on NMDA and preventing the progression of the neurodegenerative diseases [8]. However, there were a few adverse effects due to which a more efficient antagonist is designed.

This study is continuation research based on an unpublished work that showed the effectiveness of moupinamide on partial inhibiting the NMDA receptor. In the previous study, we had performed *in silico* analysis to identify therapeutic interactions between 324 bioactive compounds and AD targets. Through drug screening, docking, ADMET, and molecular simulations, we were able to determine that moupinamide had the best bioactive interaction. Hence, using it as a basic framework, a more effective partial inhibitor is designed using structure-based computer-aided drug design (SBCADD). SBCADD was successful in developing anticancer drugs like Vibsanin B [9], so this method can be used to design a lead molecule for AD and GBM.

The main aim to be achieved through this study is the development and design of a potential lead molecule that can partially bind on to NMDA. Using moupinamide as the base framework, the initial modifications and secondary modifications are done using sketching tools such as MarvinSketch. All the designed configurations are screened against all the drug likeliness rules which then followed by ADMET analysis. Once the

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ADMET analysis is done, then the configurations are docked in the active sites of NMDA. The results that were obtained from the study showed that the designed molecule could be a potential lead molecule in partially inhibiting NMDA, which, in turn, can be used to treat both AD and GBM.

## 2. MATERIALS AND METHODS

### 2.1. Molecular Target and Active Site Determination

The NMDA receptor is the target that is responsible and acts as a link for both AD and GBM. The structure of the molecular target is retrieved from Protein Databank (PDB) [10-12]. The PDB-ID retrieved for NMDA that is used is 5EWM. It has a preexisting clinical trial ligand called EVT-101 that shows the active site pocket. The attached ligand is removed and the active sites are determined and visualized using Discovery Studio [13-19]. By uploading the PDB retrieved structure onto the Discovery Studio, the amino acid interaction and the active site can be shown, and the binding pocket can be determined.

### 2.2. Lead Molecule Retrieval, Docking of the Lead Molecule, and Overlay Similarity

Moupinamide is the molecule that is used as the basic framework for the designing of an effective lead molecule (unpublished work). This structure is retrieved in the form of SDF files from PubChem [20]. This structure is then docked with the molecular target NMDA and the binding affinity obtained is used as the standard reference for the further modified structures. This is done using PyRx (Autodock Vina) which is virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets [21,22]. Once the docking between moupinamide and NMDA is done, it is then followed by overlay similarity. This is done using the Discovery Studio. Hence, moupinamide is checked for structural similarity with an existing clinical trial molecule which in this case is EVT-101. If moupinamide shows a good overlay score that is above 50%, then it can be considered as a potential molecule.

### 2.3. Initial Ligand Modifications Using Moupinamide Framework

Using moupinamide as the basic framework for modification, different lead molecules are designed. This is done using MarvinSketch [23]. The designed lead molecules are then subjected to various *in silico* methods for analysis. The initial ligand modifications are done mainly to fit perfectly into the active site pocket.

### 2.4. *In silico* Analysis of the Initial Ligand Modifications

#### 2.4.1. Drug screening

Using DruLiTo which is an open-source virtual filter, the drug-likeness properties of the molecules are determined [19]. The designed lead molecules were subjected to screening against various filters. If the molecules satisfy and pass through each of the filters, then it moves onto the next stage of the process. The filters against which the molecules were screened are Lipinski's rule of five, Veber filter, and blood-brain barrier (BBB) likeness. The molecule must pass through each of the filters, but BBB likeness is the most important filter out of the three. Since AD and GBM are neurological diseases, the molecule needs to pass through the BBB. Hence, BBB likeness helped to narrow the number of lead molecules.

#### 2.4.2. Docking

This is done using PyRx (Autodock Vina). First, the protein targets are prepared using Autodock tools, and then, it is later introduced

into PyRx [21]. Then, all the modified lead molecules are added. The energy of all the lead molecules is minimized. Once the energy of the molecules is minimized, then they are docked. The results provide the binding affinity in the form of binding energy which will show the extent of binding and the best type of configuration that would be able to bind with the target. The binding affinity of NMDA and the initially modified ligands should be more than the standard binding affinity so that it can be qualified to undergo absorption, distribution, metabolism, and excretion (ADME) analysis.

#### 2.4.3. ADME analysis

ADME is known as "absorption, distribution, metabolism, and excretion." These four criteria influence the drug levels and kinetics of drug exposure to the tissues and hence influence the pharmacological activity of the drug concerning the NMDA receptor. Pre-ADMET is a web-based application for predicting ADMET data and building drug-like library means of *in silico* method [24]. The main criteria that must be fulfilled are shown -in Table 1. If the designed molecules pass the parameters, then the best initial framework of the ligand modification is taken.

### 2.5. Secondary Ligand Modifications of Initial Ligand

Using the best initial ligand modification, further alterations are done and these modified structures are called secondary ligand modifications. These secondary ligand modifications are done to increase the stability so that there is a better efficiency when the lead molecule binds to the NMDA receptor. These structures are again modified and developed utilizing using MarvinSketch. These structures then further undergo the same *in silico* analysis as that of the initial modifications.

### 2.6. *In silico* Analysis of Secondary Ligand Modification

#### 2.6.1. Drug screening

Using DruLiTo each of the secondary ligands that were designed is screened against three parameters that are Lipinski's rule of five, Veber rule, and BBB rule. The molecule must pass through each of the filters, but BBB likeness is the most important filter out of the three. All the molecules that pass through the drug screening can be then docked against the molecular target of AD.

#### 2.6.2. Docking

This is done using PyRx (Autodock Vina). Like the initial modifications are docked, even the secondary modifications are docked with the NMDA receptor. The binding affinity that is obtained should be higher than the binding affinity of the NMDA receptor and that of the initial modifications. The lead molecules that have a higher value than that of the standard will be further analyzed for its ADME properties.

#### 2.6.3. ADME analysis

PreADMET is used to determine the ADME parameters and to check if the secondary modifications satisfy these parameters. The best candidate can be then further considered for preclinical analysis.

**Table 1:** Parameters of ADME.

Parameters	Drug candidate values
Caco-2 cell permeability	<70
Human intestinal absorption	<70%
Blood-brain barrier	<0.1
Plasma protein binding	<90%

ADME: Absorption, distribution, metabolism, and excretion

### 3. RESULTS

#### 3.1. Active Sites of NMDA

The active inhibition sites for NMDA were identified, visualized, and analyzed using Discovery Studio. The PDB Id of 5EWM was retrieved for the structure of the target and was used to identify and visualize the active sites. The two-dimensional diagram of the bound inhibitor was used for identifying the bound amino acid residues in the active site which would help us to bind our designed drug to fit into the active site pocket. The active site amino acids for the protein targets are shown in Table 2.

#### 3.2. Moupinamide Docking and Overlay Similarity

Using PyRx – Autodock Vina, a standard docking value was obtained between moupinamide and NMDA which was used as a base score for the further design of the lead molecule. The binding activity obtained is -9.4 and the overlay structural similarity with EVT-101 is 72%. This shows that moupinamide can be considered as a potential lead molecule for further drug design (unpublished research).

#### 3.3. Initial Ligand Modifications of Moupinamide

The initial modifications were designed using MarvinSketch. By altering the R groups that were present in the basic framework of moupinamide, 13 modifications were developed. These 13 modifications are depicted in Figure 1 and the changes are listed in Table 3. This is done mainly to fill the active site pocket effectively.

#### 3.4. *In silico* Analysis of the Initial Ligand Modifications

##### 3.4.1. Drug screening

The 13 modifications are subjected to drug screening. This was performed using DruLiTo (Drug Likeness Tool). The main parameters used for screening were Lipinski's rule, Veber filter, and BBB likeness rule. Screening in Lipinski's rules was performed based on the molecular weight, LogP value, hydrogen bond donors, and hydrogen bond acceptors. Screening in the Veber filter was performed using several rotatable bonds and polar surface area. Screening in BBB likeness rule was performed based on molecular weight, number of hydrogen bonds, and no acid groups. Twelve of the modifications passed all the drug screening filters however M 12 failed to pass the BBB filter [Table 4].

##### 3.4.2. Docking results

Docking between each of the initial lead modifications and the NMDA active site pocket is performed utilizing using PyRx. The lead modifications should bind perfectly with the active sites. If the docked modification has binding energy higher than -9.4, then it is selected to undergo ADME analysis. M 6, M 7, M 8, M 9, M 10, M 11, and M 13 had got a higher docking score than -9.4. The docking scores of M 6, M 7, M 8, M 9, M 10, M 11, and M 13 had the following values -10.3, -9.4, -9.7, -10.4, -11.1, -11.6, and -10.3, respectively [Table 4].

##### 3.4.3. ADME analysis

The screened ligand modifications from the initial docking were then tested for ADME. The ADME analysis was performed separately for each modification. The main parameters for ADME analysis are human colon adenocarcinoma (CaCO<sub>2</sub>) cell permeability, Madin-Darby canine kidney cell permeability, human intestinal absorption, BBB, and plasma protein binding [24]. If the configuration fulfills

**Table 2:** Active sites of NMDA.

Protein name	PDB ID	Ligand	Amino acid residues
NMDA	5EWM	EVT-101	Ala 75, Ile 133, Tyr 109, Phe 113, Thr 110, Ile 111, Ile 82, Pro 78, Pro 177, Phe 114, Gln 110, Asp 113, Asp 136, Met 134, Ala 135

NMDA: N-methyl-D-aspartate

**Table 3:** List of all initially modified ligands.

Ligand	Change from the moupinamide structure	Molecular formula
M 1	The nitro group is replaced by a methyl group.	C <sub>19</sub> H <sub>20</sub> O <sub>4</sub>
M 2	The nitro group is replaced by an oxygen group.	C <sub>18</sub> H <sub>18</sub> O <sub>5</sub>
M 3	Removing the double bond oxygen	C <sub>18</sub> H <sub>21</sub> NO <sub>3</sub>
M 4	Removing the aromatic group with a single hydroxyl group	C <sub>12</sub> H <sub>15</sub> NO <sub>3</sub>
M 5	Removing the aromatic group with a single hydroxyl group and methoxy group	C <sub>11</sub> H <sub>12</sub> NO <sub>2</sub>
M 6	Removing the nitro group and replacing with the pyrrole group	C <sub>20</sub> H <sub>19</sub> NO <sub>4</sub>
M 7	Removing the nitro group and replacing with the cyclohexane group	C <sub>24</sub> H <sub>28</sub> O <sub>4</sub>
M 8	Removing the nitro group and replacing with the benzene group	C <sub>24</sub> H <sub>24</sub> O <sub>4</sub>
M 9	Remove the hydroxyl group attached to the benzene group and now add a cyclopentane and attach a hydroxyl group	C <sub>21</sub> H <sub>23</sub> NO <sub>4</sub>
M 10	In the 9 <sup>th</sup> configuration, the nitro group is replaced with the pyrrole group	C <sub>23</sub> H <sub>23</sub> NO <sub>3</sub>
M 11	In the 9 <sup>th</sup> configuration, the double bond oxygen is replaced by a benzene ring.	C <sub>25</sub> H <sub>24</sub> O <sub>3</sub>
M 12	In the 11 <sup>th</sup> configuration remove the hydroxyl group present with the aromatic ring with methoxy group and add a cyclopentane with a hydroxyl group	C <sub>26</sub> H <sub>27</sub> NO <sub>3</sub>
M 13	Similar to configuration 9, instead of the cyclopentane a benzene ring is attached.	C <sub>22</sub> H <sub>21</sub> NO <sub>4</sub>

each of these parameters, then it will be considered as the main framework. Out of the seven modifications that had passed docking, only M 9 fulfilled the ADME parameters, the main parameter being the BBB. The values are shown in Table 5.

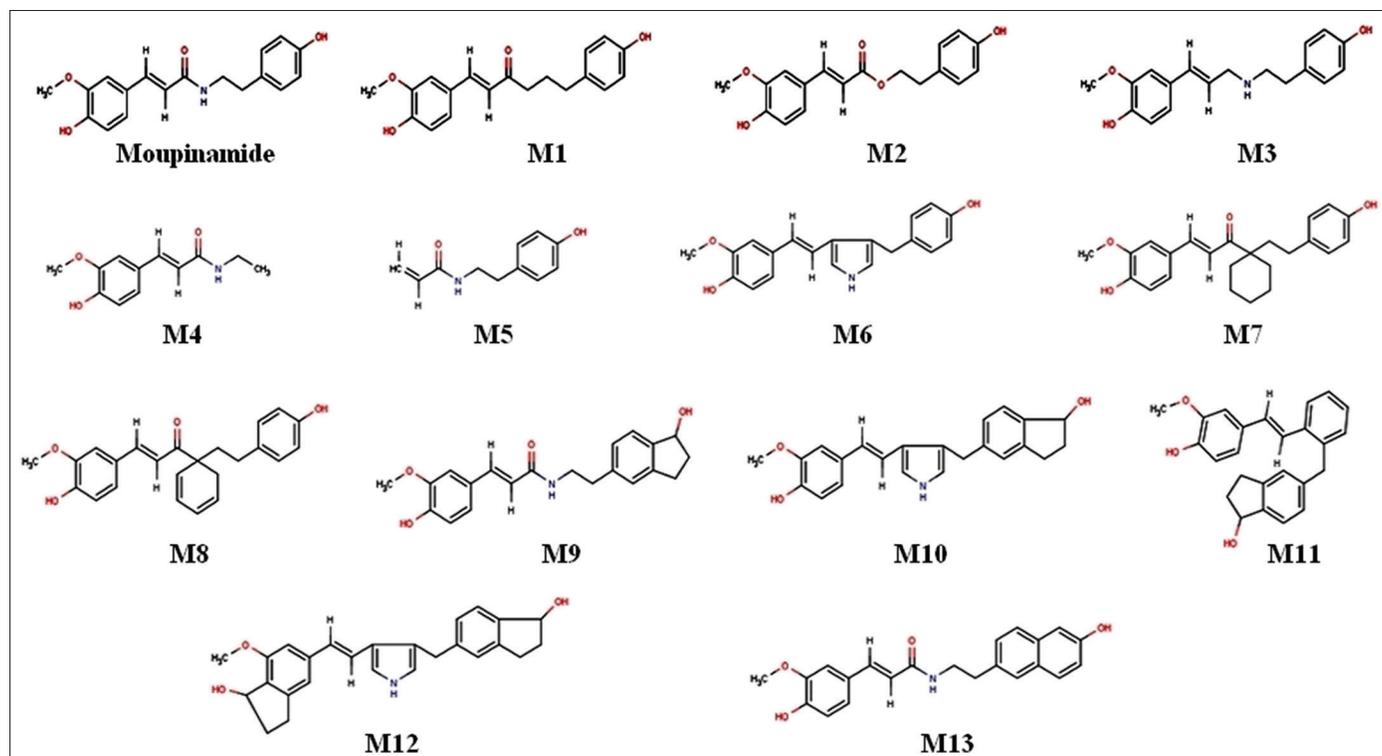
#### 3.5. Secondary Ligand Modifications Using M 9

The secondary ligand modifications were developed using M 9 as the framework. These structures were also developed using MarvinSketch. Again, by altering the R-groups and by stabilizing the hydrophobic and hydrophilic interactions, a better structure was developed. There are nine secondary modifications are depicted in Figure 2 and the changes are listed in Table 6.

#### 3.6. *In silico* Analysis of Secondary Ligand Modifications

##### 3.6.1. Drug screening

The nine secondary ligand modifications are subjected to drug screening. Six secondary configurations passed through the drug



**Figure 1:** Initial ligand modifications are done using MarvinSketch, 13 structures were developed based on modifications.

**Table 4:** Drug screening and docking results.

Modification	Lipinski's rule of five	Veber rule	BBB rule	Docked value
M 1	Passed	Passed	Passed	-9
M 2	Passed	Passed	Passed	-9.1
M 3	Passed	Passed	Passed	-8.7
M 4	Passed	Passed	Passed	-7.6
M 5	Passed	Passed	Passed	-7.9
M 6	Passed	Passed	Passed	-10.3
M 7	Passed	Passed	Passed	-9.4
M 8	Passed	Passed	Passed	-9.7
M 9	Passed	Passed	Passed	-10.4
M 10	Passed	Passed	Passed	-11.1
M 11	Passed	Passed	Passed	-11.6
M 12	Passed	Passed	Failed	-11.5
M 13	Passed	Passed	Passed	-10.3

screening clearing Lipinski's rule, Veber rule, and BBB rule. M 9.4 did not obey the Lipinski's rule of five, hence could not clear the drug screening. Furthermore, M 9.5 and M 9.8 did not clear the BBB rule, hence, it also could not clear the drug screening [Table 7].

### 3.6.2. Docking results

Since the docking score of M 9 ligand and that of NMDA was -10.4, the secondary conformations had to cross this barrier of -10.4. The six secondary ligands were docked and only three ligands M 9.1, M 9.3, and M 9.6 had a higher value than the initial ligand. Their values were -10.7, -10.6, and -10.7, respectively [Table 7].

**Table 5:** ADME results of M 9.

ID	M 9
BBB	1.30574
Buffer_solubility_mg_L	164.504
Caco2	21.8689
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Non
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	91.344649
Madin-Darby canine kidney	8.76984
Pgp_inhibition	Non
Plasma_Protein_Binding	84.986751
Pure_water_solubility_mg_L	33.0832
Skin_Permability	-3.49666
SKlogD_value	3.14429
SKlogP_value	3.14429
SKlogS_buffer	-3.33211
SKlogS_pure	-4.02868

ADME: Absorption, distribution, metabolism, and excretion

### 3.6.3. ADME analysis

These three ligands that are M 9.1, M 9.3, and M 9.6 are subjected to ADME analysis. It was, however, found that only M 9.1 passed all the parameters necessary for ADME analysis hence making it the best possible candidate that can be used as a partial inhibitor for the NMDA receptor [Table 8].

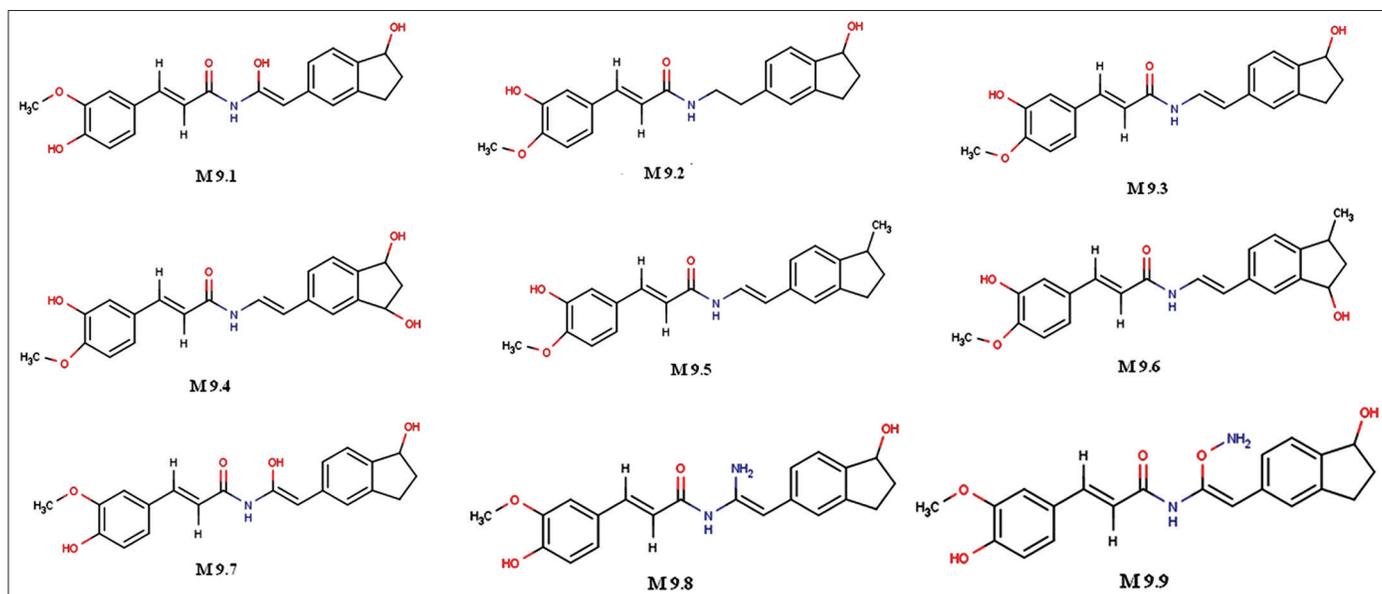


Figure 2: M9 is taken as the skeletal structure to design nine secondary structures.

Table 6: List of secondary ligand modifications.

Modifications	Changes from M 9 structure	Molecular formula
M 9.1	Add a double bond to the original framework	$C_{21}H_{21}NO_4$
M 9.2	Alter the ortho-carbons	$C_{21}H_{23}NO_4$
M 9.3	Combine both the double bond and the ortho groups	$C_{21}H_{21}NO_4$
M 9.4	Add a hydroxyl group to cyclopentane	$C_{21}H_{21}NO_5$
M 9.5	Replace hydroxyl group with a methyl group in cyclopentane	$C_{22}H_{23}NO_3$
M 9.6	Add a methyl group in place of the existing hydroxyl group and add a hydroxyl opposite to methyl	$C_{22}H_{23}NO_4$
M 9.7	Add hydroxyl group to M 9.1 near the double bond	$C_{21}H_{21}NO_5$
M 9.8	Add an amine group to M 9.1 near the double bond	$C_{21}H_{22}N_2O_4$
M 9.9	Add an oxy-amine group to M 9.1 near the double bond	$C_{21}H_{22}N_2O_5$

Table 7: Drug screening and docking results.

Modification	Lipinski's rule of five	Veber rule	BBB rule	Docked value
M 9.1	Passed	Passed	Passed	-10.7
M 9.2	Passed	Passed	Passed	-9.8
M 9.3	Passed	Passed	Passed	-10.6
M 9.4	Failed	Passed	Passed	-10.4
M 9.5	Passed	Passed	Failed	-11.5
M 9.6	Passed	Passed	Passed	-10.7
M 9.7	Passed	Passed	Passed	-9.2
M 9.8	Passed	Passed	Failed	-10.6
M 9.9	Passed	Passed	Passed	-10.4

Table 8: Description of the structure after ADME analysis.

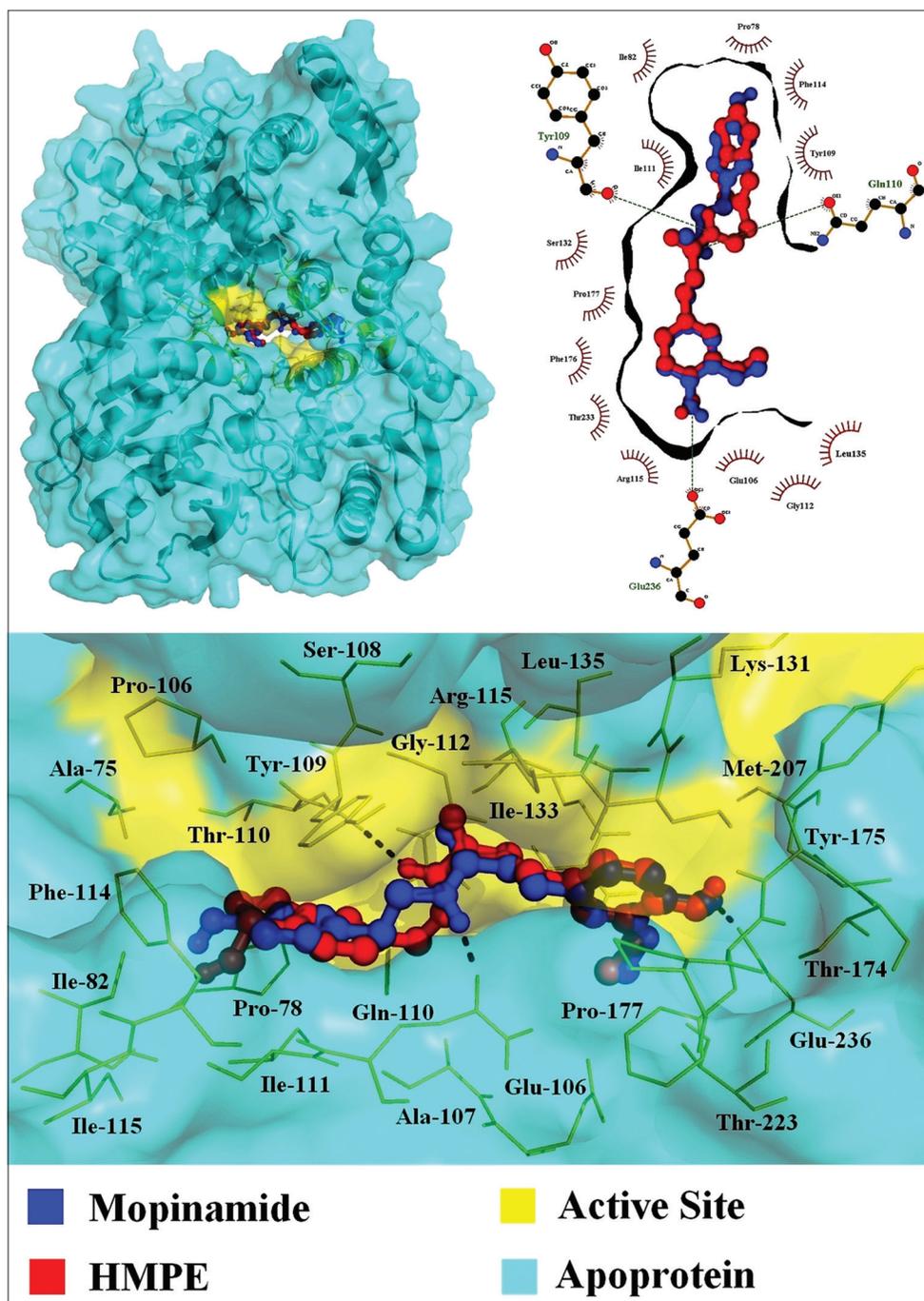
ID	M 9.1
BBB	0.890612
Buffer_solubility_mg_L	19.9537
Caco2	21.849
CYP_2C19_inhibition	Non
CYP_2C9_inhibition	Inhibitor
CYP_2D6_inhibition	Non
CYP_2D6_substrate	Non
CYP_3A4_inhibition	Non
CYP_3A4_substrate	Weakly
HIA	91.729343
Madin-Darby canine kidney	9.55018
Pgp_inhibition	Non
Plasma_Protein_Binding	84.457405
Pure_water_solubility_mg_L	4.13469
Skin_Permiability	-3.61593
SKlogD_value	3.25724
SKlogP_value	3.25724
SKlogS_buffer	-4.24578
SKlogS_pure	-4.92936

ADME: Absorption, distribution, metabolism, and excretion

The modification M 9.1 was given the name of high modulus polyethylene (HMPE). The structural similarity and its binding sites are shown in Figure 3. HMPE could be now considered as a lead molecule and further studied through pre-clinical analysis.

#### 4. DISCUSSION

AD and GBM are common forms of neurodegenerative disorders that affect a wide range of people. There is still no effective cure or therapy to treat both of the disorders. Through this study, we were able to design a molecule that could be used against both diseases. It has been



**Figure 3:** Pymol visualization of N-methyl-D-aspartate with moupinamide and high modulus polyethylene.

known that the NMDA receptor plays a key role in both the diseases, hence making it an ideal candidate for the *in silico* study.

Through a previously unpublished study, we were able to find a molecule called moupinamide that is bound to the NMDA receptor. This structure was used as a base structure to perform various structural modifications to develop 13 primary structures and nine secondary structures. These structures were then subjected to screening, docking, and ADME analysis. Through this study, we were able to develop a molecule called HMPE which has shown to have a good binding affinity with NMDA [Table 5]. It was also shown to follow all the necessities in ADME analysis. The HMPE structure also showed similar interactions with

NMDA like moupinamide, hence making it an ideal molecule to inhibit the NMDA receptor. In summary, we can conclude by saying that HMPE can be considered as lead candidate in binding with NMDA, which, in turn, could lead to treating AD and GBM.

This article imparts knowledge in application of computer aided drug design, and it contributes toward the knowledge in the process of modification of the lead molecule from the base framework of the initial lead molecule which, in turn, gives us an improved version of a known candidate, which can be used as a much efficient inhibitor for the NMDA receptor. The result obtained from this research will serve as an insight which aid in pre-clinical and further *in vivo* studies.

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## 6. CONFLICTS OF INTEREST

None declared.

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## 8. REFERENCES

- Forman MS, Trojanowski JQ, Lee VM. Neurodegenerative diseases: A decade of discoveries paves the way for therapeutic breakthroughs. *Nat Med* 2004;10:1055-63.
- Slee M, Pretorius P, Ansorge O, Stacey R, Butterworth R. Parkinsonism and dementia due to gliomatosis cerebri mimicking sporadic Creutzfeldt-Jakob disease (CJD). *J Neurol Neurosurg Psychiatry* 2006;77:283-4.
- Conn PJ, Pin JP. Pharmacology and functions of metabotropic glutamate receptors. *Ann Rev Pharmacol Toxicol* 1997;37:205-37.
- Castellano C, Cestari V, Ciamei A. NMDA receptors and learning and memory processes. *Curr Drug Targets* 2001;2:273-83.
- Ciamei A, Aversano M, Cestari V, Castellano C. Effects of MK-801 and nicotine combinations on memory consolidation in CD1 mice. *Psychopharmacology* 2001;154:126-30.
- Danysz W, Parsons CG. Alzheimer's disease,  $\beta$ -amyloid, glutamate, NMDA receptors, and memantine-searching for the connections. *Br J Pharmacol* 2012;167:324-52.
- Ramaswamy P, Devi NA, Fathima KH, Nanjiah ND. Activation of NMDA receptor of glutamate influences MMP-2 activity and proliferation of glioma cells. *Neurol Sci* 2014;35:823-9.
- Olivares D, Deshpande KV, Shi Y, Lahiri KD, Greig HN, Rogers TJ, *et al.* N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. *Curr Alzheimer Res* 2012;9:746-58.
- Drummond E, Nayak S, Faustin A, Pires G, Hickman RA, Askenazi M, *et al.* Proteomic differences in amyloid plaques in rapidly progressive and sporadic Alzheimer's disease. *Actaneuropathologica* 2017;133:933-54.
- Shimmyo Y, Kihara T, Akaike A, Niidome T, Sugimoto H. Flavonols and flavones as BACE-1 inhibitors: Structure-activity relationship in cell-free, cell based and *in silico* studies reveal novel pharmacophore features. *Biochim Biophys Acta* 2008;1780:819-25.
- Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug development pipeline: Few candidates, frequent failures. *Alzheimers Res Ther* 2014;6:37.
- Mirjalili MH, Moyano E, Bonfill M, Cusido RM, Palazón J. Steroidal lactones from *Withania somnifera*, an ancient plant for novel medicine. *Molecules* 2009;14:2373-93.
- Brooks BR, Brooks CL, Mackerell AD, Nilsson L, Petrella RJ, Roux B, *et al.* CHARMM: The biomolecular simulation program. *J Comput Chem* 2009;30:1545-615.
- Eswar N, Marti-Renom MA, Webb B, Madhusudhan MS, Eramian D, Shen M, *et al.* Comparative protein structure modeling with modeller. *Curr Protoc Bioinform* 2006;15:615-30.
- Rocchia W, Alexov E, Honig B. Extending the applicability of the nonlinear poisson-boltzmann equation: Multiple dielectric constants and multivalent ions. *J Phys Chem B* 2001;105:6507-14.
- Chen R, Weng Z. ZDOCK: An initial-stage protein-docking algorithm. *Proteins* 2003;52:80-7.
- Matsuzawa N, Seto J, Dixon DA. Density functional theory predictions of second-order hyperpolarizabilities of metallocenes. *J Phys Chem A* 1997;101:9391.
- Delley B. An all-electron numerical method for solving the local density functional for polyatomic molecules. *J Chem Phys* 1990;92:508-17.
- Drug Likeness Tool; NIPER S.A.S. Nagar. Available from [http://www.niper.gov.in/pi\\_dev\\_tools/drulitoweb/drulito\\_index.html](http://www.niper.gov.in/pi_dev_tools/drulitoweb/drulito_index.html). [last accessed on 2020 Oct 01].
- Kim S, Thiessen PA, Bolton EE, Chen J, Fu G, Gindulyte A, *et al.* PubChem substance and compound databases. *Nucleic Acids Res* 2016;44:D1202-13.
- Paolini GR, Besnard J, Muresan S, Hopkins AL. Quantifying the chemical beauty of drugs. *Nat Chem* 2012;4:90-8.
- Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods Mol Biol* 2015;1263:243-50.
- Available from: <http://www.chemaxon.com>. [Last accessed on 2020 Oct 01].
- Available from: <https://www.preadmet.bmdrc.kr>. [Last accessed on 2020 Oct 01].

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