

## Evolution of toxic properties of Anti Alzheimer's Drugs through Lipinski's rule of five

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### ABSTRACT

To evaluate the toxic properties of Anti-Alzheimer's drugs, such as Galantamine hydrobromide, Physostigmine, Rivastigmine, Eptastigmine, Memantine, Xanomeline, Huperzine A and E2020 (Aricep<sup>TM</sup>) through Lipinski rule of Five. The Bioactivity properties and Drug-likeness of the above mentioned selective Drugs were calculated using Molinspiration and Molsoft tools and their toxic properties were determined by employing the Osiris server. Interestingly, after application of Lipinski's rule of five, our results revealed that all these selected drugs have fully satisfied the Lipinski's rule of five and thus were recommended as safe drugs for effective treatment of AD. In view of this, it has been suggested that consumption of these Anti-Alzheimer's drugs by children to improve their cognitive skills, may initially exert positive effects on their performing capabilities, but in long run, might cause irreparable damage in the brain which in turn will lead to deficits in cognitive functions of children.

**Keywords:** Anti-Alzheimer's drugs, Lipinski's rule of five, Molinspiration and Osiris softwares.

### INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by neuropsychological, neuropsychiatric and neurologic manifestations. This disease was first described by German Psychiatrist and Neuropathologist, Alois Alzheimer in 1906 and was named after him<sup>1</sup>. To treat Alzheimer's disease a number of pharmaceutical companies such as Food and Drug administration (FDA), the European Medicines Agency (EMA) and National Institute for clinical excellence etc., have been making clinical trials on Alzheimer's disease to design new drugs. The entire drug discovery process takes an average of 12 to 15 years to complete and to bring out a drug into market. In the broadest sense, moderately lipophilic drugs cross the Blood Brain Barrier by passive diffusion and the hydrogen bonding properties of drugs can significantly influence their Central Nervous System uptake profiles. Size, ionization properties and molecular flexibility are other factors observed to influence the transport of an organic compound across the Blood Brain Barrier (BBB)<sup>2</sup>.

Optimizing the chemical structure of lead candidates with respect to the ADME processes has become an integral part of the drug discovery paradigm<sup>3</sup>. An important ADME characteristic is simply the solubility of the drug, as only the amount of drug in solution is available for intestinal absorption and blood distribution<sup>4</sup>. The initial analyses of ADME properties, e.g. anesthetic agents in the late nineteenth century, focused on the partition coefficient (LogP) between water and oil, basically the lipophilicity of the compound. This has served as one of the fundamental principles for drug discovery and design<sup>5</sup>. Similarly, PSA (Polar Surface Area) has been used as a predictor for BBB penetration by many investigators<sup>6,7</sup>. In general, drugs aimed at the CNS tend to have lower Polar Surface Areas than<sup>8,9,10</sup> other therapeutics with PSA for CNS penetration estimated at 60–70 Å<sup>2</sup> through 90 Å<sup>2</sup>.

The foregone literature gives substantial information that the drugs meant for treatment of Neurological diseases should invariably satisfy the various criteria under Lipinski Rule of 5 for their effective therapeutical applications. Lipinski's rule of five is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski based on the observation that most of the drugs are relatively small and lipophilic molecules.

**"Rule of 5" Properties:** It is set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5"<sup>11</sup>. The rule states, that most "drug-like" molecules have  $\log P \leq 5$ , molecular weight  $\leq 500$ , number of hydrogen bond acceptors  $\leq 10$ , and number of hydrogen bond donors  $\leq 5$ . Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5", because the border values are 5, 500, 2\*5, and 5.

All the above data presented a clear picture about the latest challenging trends in the discovery of novel drugs for treating the Alzheimer's disease. In the present study, an attempt has been made to test whether the currently available drugs such as Galantamine hydrobromide, Physostigmine, Rivastigmine, Eptastigmine, Memantine, Xanomeline, Huperzine A and E2020 (Aricep<sup>TM</sup>), which are **potent Acetylcholinesterase inhibitors**, recommended for treatment of Alzheimer's disease follow Lipinski rule of Five or not by adopting the appropriate software's Viz. Molinspiration and Osiris server.

## MATERIALS AND METHODS

In the present study, the Bioactivity properties and Drug-likeness of the above mentioned selected Drugs were calculated using Molinspiration, Molsoft tools and their toxic properties were determined by employing the Osiris server.

*Validation of chemical drugs was done by:*

- a) Random selection of different drugs used to treat Alzheimer's disease.
- b) Obtaining SMILES format for these drugs using software's.
- c) Applying 'Lipinski's rule of five' for each of these drugs.

Finally, resolving violation of the Lipinski rule.

### Software's used

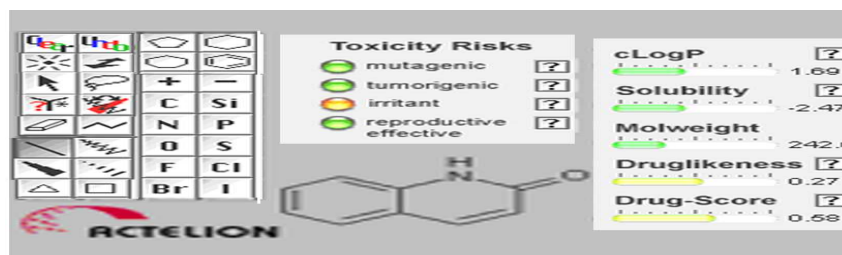
**Molinspiration tool:** Molecular properties and bioactivity of the drugs showing high affinity predicted using Molinspiration server. This server allows physico chemical properties to calculate Log P based on group contributions. The values were obtained by fitting calculated  $\log P$  with experimental  $\log P$ . PSA is good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and Blood brain barrier penetration.

**Molinspiration:** Molinspiration is an independent research organization focused on development and application of modern Cheminformatics techniques, especially in connection with the internet molinspiration offers broad range of Cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modeling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search. Our products support also fragment-based virtual screening, bioactivity prediction and data visualization. Molinspiration tools are written in Java, therefore are available practically on any computer platform.

Molinspiration supports also internet chemistry community by offering free on-line cheminformatics services for calculation of important molecular properties (for example  $\log P$ , polar surface area, number of hydrogen bond donors and acceptors), as well as prediction of bioactivity score for the most important drug targets.

**OSIRIS Soft ware:** The OSIRIS Property Explorer is a online Chemoinformatics tool. It used to predict Toxicity Risk Assessment, cLogP value, Molecular Weights, Solubility, Drug-Likeness Prediction and

Overall Drug-Likeness Score of the drug molecule. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behaviour. Drug likeliness was also calculated using OSIRIS server, which is based on a list of about 5,300 distinct substructure fragments created by 3,300 traded drugs as well as 15,000 commercially available chemicals yielding a complete list of all available fragments with associated druglikeness. The drug score combines drug-likeness, cLogP, logS, molecular weight, and toxicity risks as a total value which may be used to judge the compound's overall potential to qualify for a drug.



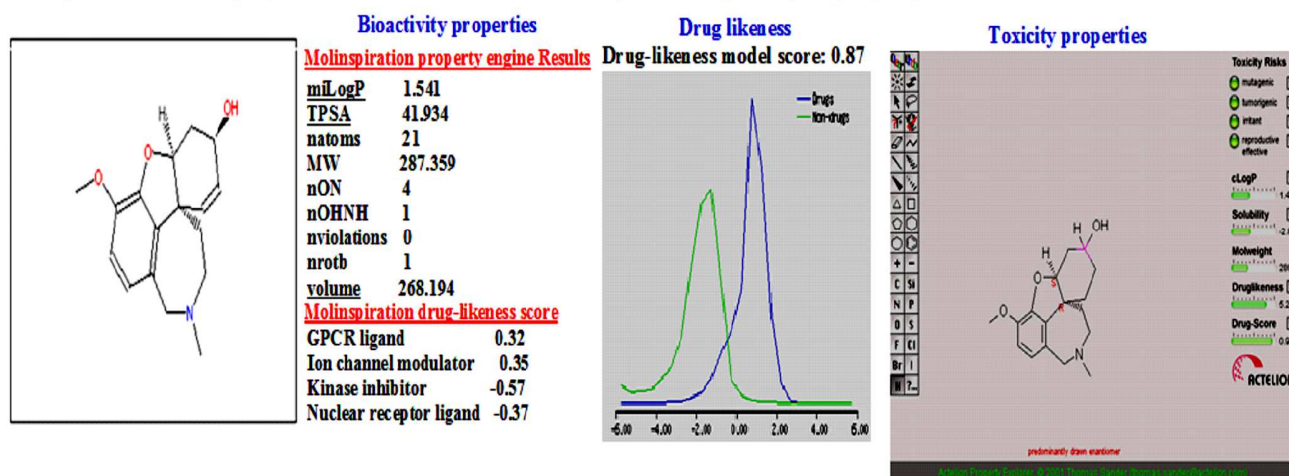
### Molsoft software:

Molsoft is a California based software company that is a primary source of new breakthrough technologies in: Molecular graphics and visualization, Molecular modeling, Docking and Virtual screening, computational biology and Cheminformatics. All molecular property predictors are calculated using fragment-based contributions. It developed an original method for splitting a molecule into a set of linear or non-linear fragments of different length and representation levels and counting the number of occurrences of each chemical pattern found. A Partial Least Squares (PLS) regression model was built and optimized for a particular property using a leave-50%-out cross-validation calculation. The method is very robust and fast (about 5K of compounds per second).

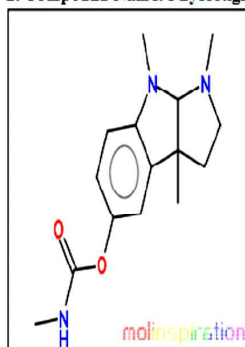
## RESULTS AND DISCUSSION

After applying the above mentioned software's for the selected Anti-Alzheimer's drugs, the following structural details were obtained.

### 1. Compound Name: Razadyne; Canonical SMILES : CN1CCC23C=CC (CC2OC4=C(C=CC (=C34) C1) OC) O.Br



2. Compound Name: Physostigmine ; Canonical SMILES: CC12CCN(C1N(C3=C2C=C(C=C3)OC(=O)NC)C)C



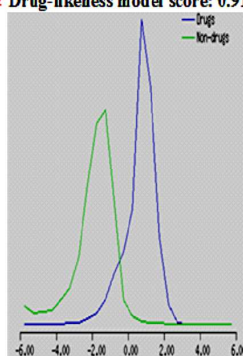
Bioactivity properties

Molinspiration property engine Results

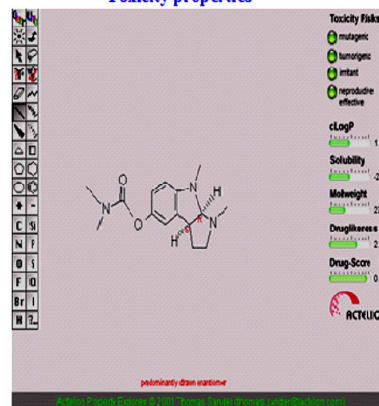
miLogP	1.94
TPSA	44.808
natoms	20
MW	275.352
nON	5
nOHNH	1
nviolations	0
nroth	2
volume	261.477
<b>Molinspiration drug-likeness score</b>	
GPCR ligand	0.18
Ion channel modulator	-0.06
Kinase inhibitor	-0.40
Nuclear receptor ligand	-0.71

Drug likeness

Drug-likeness model score: 0.91



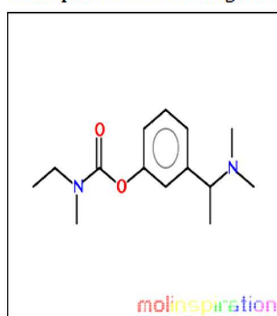
Toxicity properties



Toxicity properties panel for Physostigmine. The panel shows various toxicity risks and scores. The 'ACTELION' logo is visible at the bottom right.

<b>Toxicity Risks</b>	
mutagenic	0
tumorigenic	0
irritant	0
reproductive effective	0
<b>cLogP</b>	
Accessibility	1.94
<b>Solubility</b>	
Accessibility	-2.05
<b>Molweight</b>	
Accessibility	275.4
<b>Druglikeness</b>	
Accessibility	2.28
<b>Drug-Score</b>	
Accessibility	0.86

3. Compound Name: Rivastigmine ; Canonical SMILES: CCN(C)C(=O)OC1=CC=CC(=C1)C(C)N(C)C



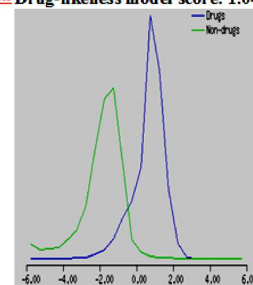
Bioactivity properties

Molinspiration property engine Results

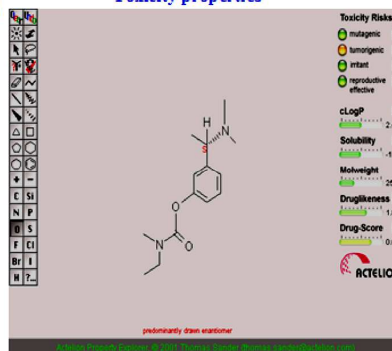
miLogP	2.276
TPSA	32.781
natoms	18
MW	250.342
nON	4
nOHNH	0
nviolations	0
nroth	5
volume	254.014
<b>Molinspiration drug-likeness score</b>	
GPCR ligand	0.07
Ion channel modulator	-0.04
Kinase inhibitor	-0.43
Nuclear receptor ligand	-0.55

Drug likeness

Drug-likeness model score: 1.04



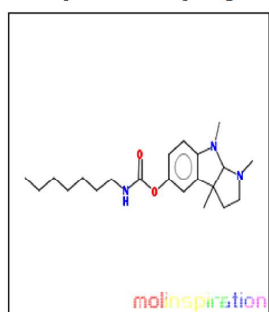
Toxicity properties



Toxicity properties panel for Rivastigmine. The panel shows various toxicity risks and scores. The 'ACTELION' logo is visible at the bottom right.

<b>Toxicity Risks</b>	
mutagenic	0
tumorigenic	0
irritant	0
reproductive effective	0
<b>cLogP</b>	
Accessibility	2.4
<b>Solubility</b>	
Accessibility	-1.62
<b>Molweight</b>	
Accessibility	250.0
<b>Druglikeness</b>	
Accessibility	1.81
<b>Drug-Score</b>	
Accessibility	0.59

4. Compound Name: Eptastigmine ; Canonical SMILES: CCCCCCNC(=O)OC1=CC=C(C=C1)N(C3C2(CCN3C)C)C



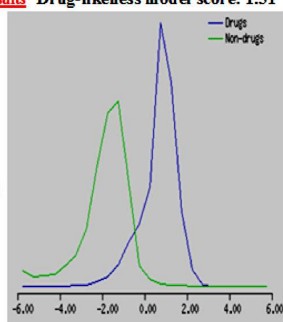
Bioactivity properties

Molinspiration property engine Results

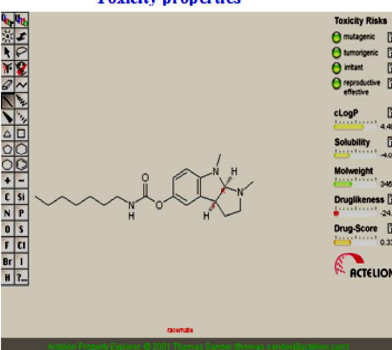
miLogP	4.894
TPSA	44.808
natoms	26
MW	359.514
nON	5
nOHNH	1
nviolations	0
nroth	8
volume	362.288
<b>Molinspiration drug-likeness score</b>	
GPCR ligand	0.18
Ion channel modulator	-0.07
Kinase inhibitor	-0.27

Drug likeness

Drug-likeness model score: 1.31



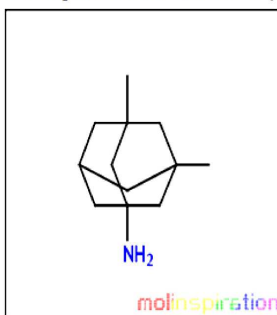
Toxicity properties



Toxicity properties panel for Eptastigmine. The panel shows various toxicity risks and scores. The 'ACTELION' logo is visible at the bottom right.

<b>Toxicity Risks</b>	
mutagenic	0
tumorigenic	0
irritant	0
reproductive effective	0
<b>cLogP</b>	
Accessibility	4.89
<b>Solubility</b>	
Accessibility	-1.06
<b>Molweight</b>	
Accessibility	359.5
<b>Druglikeness</b>	
Accessibility	-24.4
<b>Drug-Score</b>	
Accessibility	0.33

5. Compound Name: Memantine ; Canonical SMILES: CC12CC3CC(C1)(CC(C3)C2)N(C)



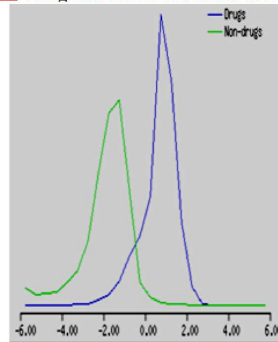
Bioactivity properties

Molinspiration property engine Results

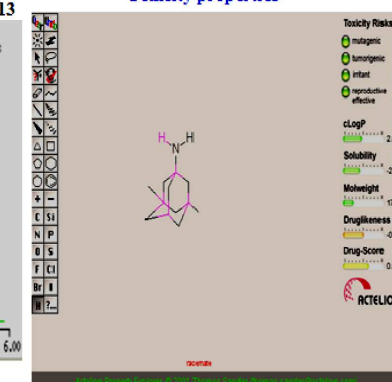
miLogP	2.771
TPSA	26.023
natoms	13
MW	179.307
nON	1
nOHNH	2
nviolations	0
nroth	0
volume	191.669
<b>Molinspiration drug-likeness score</b>	
GPCR ligand	-0.52
Ion channel modulator	-0.34
Kinase inhibitor	-1.45
Nuclear receptor ligand	-1.30

Drug likeness

Drug-likeness model score: 0.13



Toxicity properties

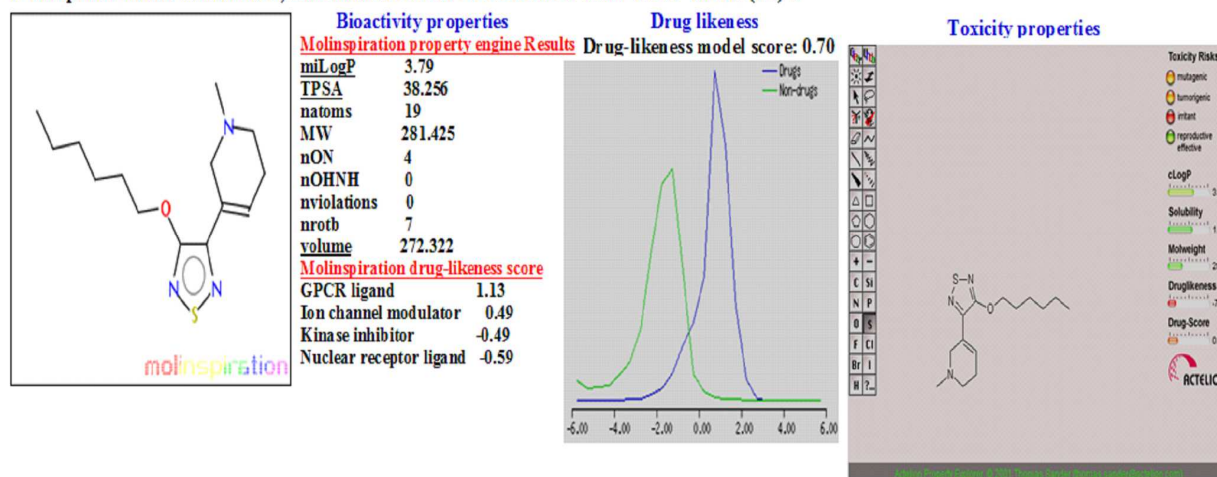


Toxicity properties panel for Memantine. The panel shows various toxicity risks and scores. The 'ACTELION' logo is visible at the bottom right.

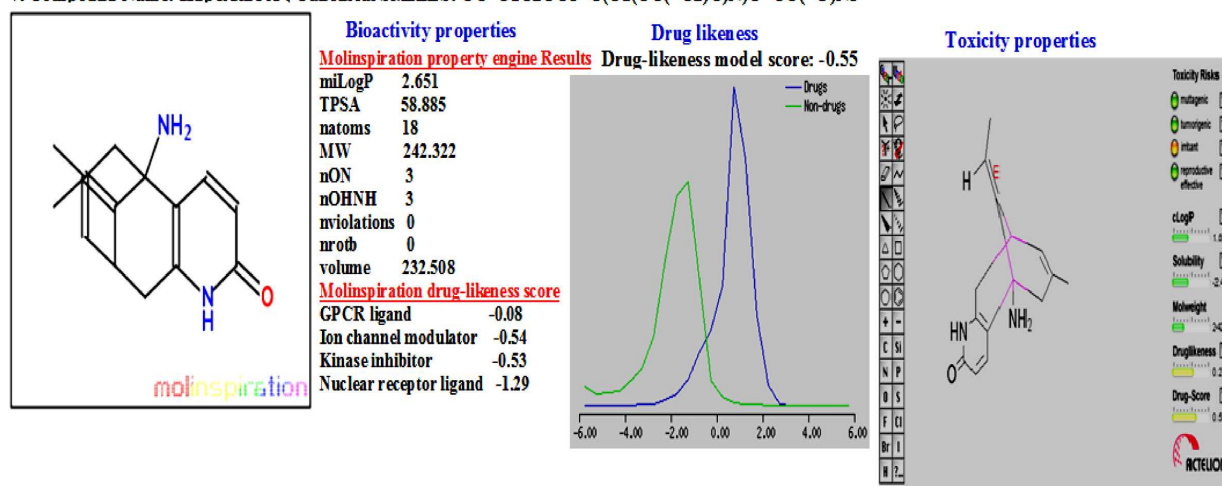
<b>Toxicity Risks</b>	
mutagenic	0
tumorigenic	0
irritant	0
reproductive effective	0
<b>cLogP</b>	
Accessibility	2.02
<b>Solubility</b>	
Accessibility	-2.94
<b>Molweight</b>	
Accessibility	179.0
<b>Druglikeness</b>	
Accessibility	0.8
<b>Drug-Score</b>	
Accessibility	0.6



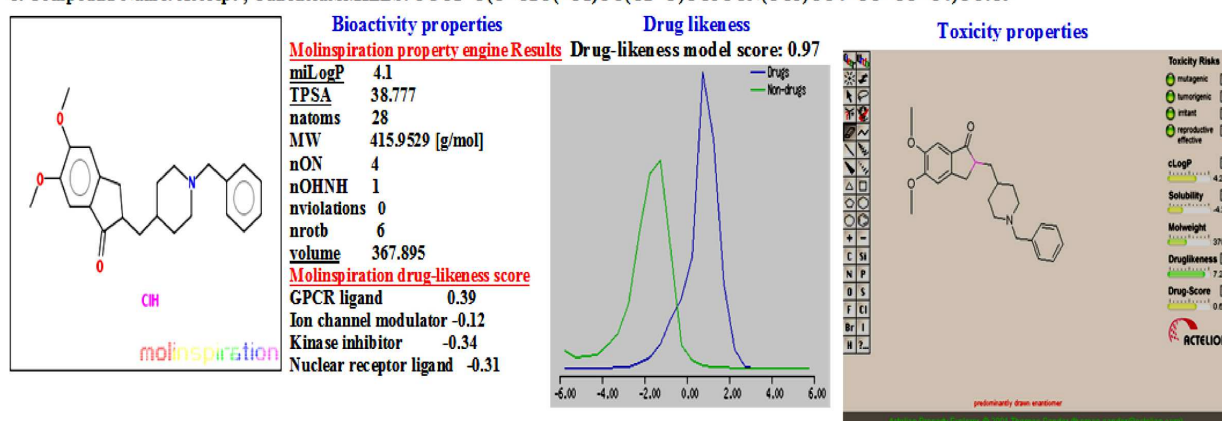
## 6. Compound Name: Xanomeline ; Canonical SMILES: CCCCCOC1=NS=C1C2=CCCN (C2) C



## 7. Compound Name: Huperzine A ; Canonical SMILES: CC=C1C2CC3=C(C1(CC(=C2)C)N)C=CC(=O)N3



## 8. Compound Name: Aricept ; Canonical SMILES: COC1=C(C=C2C(=C1)CC(C2=O)CC3CCN(CC3)CC4=CC=CC=C4)OC.C1



From the data (Table-1), it was observed that among the eight drugs selected, Eptastigmine has high milog P value (4.894) followed by E2020 (Aricept<sup>TM</sup>) (4.1), Xanomeline (3.79), Memantine (2.771), Huperzine A (2.651), Rivastigmine (2.276), Physostigmine (1.94), and Galantamine hydrobromide (1.541). An orally active anti-Alzheimer's drug needs not only sufficient metabolic stability to maintain integrity in the intestine and liver but also should across the BBB. At the molecular level, the BBB is not homogenous but consists of a number of partially overlapping zones contained in a highly anisotropic lipid layer<sup>12</sup>. The conformational mobility of the lipid chains is relatively low at or near the water (blood)/ lipid interface and interface at the center of the bilayer. In addition, the hydrophilic/lipophilic

interface at the blood/membrane boundary consists of perturbed and bound water, charged polar lipid head moieties connected to long lipid chains. As a result, a drug approaching the BBB is confronted with a thick layer that is capable of non-covalent interactions with the drug, similarly to that of receptor but with much looser steric requirements. High lipophilicity frequently leads to compounds with high rapid metabolic turnover<sup>13</sup> and low solubility and poor absorption. As lipophilicity (LogP) increases, there is an increased probability of binding to hydrophobic protein targets other than the desired one, and therefore, there is more potential for toxicity.

The biological activity of a drug was almost entirely due to their Log P and their rate of metabolism was linearly related to LogP. Furthermore, optimal activity is observed at  $\text{LogP} = 2$ <sup>14</sup>. The drugs used to treat neurological disorders have LogP value mostly between 2 to 4<sup>15</sup>. Subsequently, indicated that LogP is predominantly a measure of drug volume or surface area, plus hydrogen bond acceptor potential. Thus, both hydrogen bonding potential and drug volume contribute to permeability.

Lipophilicity was the first of the descriptors to be identified as important for CNS penetration. Kujawski<sup>16</sup> *et al.*, reasoned that highly lipophilic molecules will be partitioned into the lipid interior of membranes and will be retained there. However, ClogP correlates nicely with LogBBB with increasing lipophilicity increasing brain penetration. An analysis of small drug-like molecules suggested that for better brain permeation<sup>17</sup> and for good intestinal permeability<sup>18</sup>, the LogP values need to be greater than 0 and less than 3.

Contrary to this, the Total Polar Surface Area was for maximum in Huperzine A (58.885) followed by Eptastigmine (44.808), Physostigmine (44.808), Galantamine hydrobromide (41.934), E2020(Aricep<sup>TM</sup>) (38.777), Xanomeline (38.256), Rivastigmine (32.781), and Memantine (26.023). The Polar Surface Area (PSA) and the molecular volume components were the most important descriptors, with PSA strongly predominating (Van de Waterbeemd and Kansy, 1992). Palm *et al.*, (1999) developed a dynamic PSA approach whereby the set of available conformations were used and the contribution of each to the overall PSA was calculated using a Boltzman distribution thereby taking into account conformational flexibility. Based on their results in intestinal Caco-2 cells, drugs with a PSA of 60 Å<sup>2</sup> or less are completely absorbed, whereas those with at least 140 Å<sup>2</sup> are not. Kelder (1999) found that non-CNS drugs transported passively and transcellularly needed a PSA of 120 Å<sup>2</sup> or less, whereas the drugs can be targeted to the CNS with a PSA less than 60–70 Å<sup>2</sup>. Similar conclusions were made by van de Waterbeemd based on a study of marketed CNS and non-CNS drugs (Van de Waterbeemd *et al.*, 1998). Their cutoff for PSA cutoff for CNS penetration is 90 Å<sup>2</sup> or below and a molecular weight cutoff of 450.

Ertl has developed a topological PSA (TPSA) approach that fits these criteria<sup>19</sup>. TPSA is based on dissecting the contributions of polar groups in drugs contained in the WDI. Comparison with Clark's results demonstrated almost no difference between the two approaches. Analysis has also shown that a large PSA (Lipinski, 1997; Clark, 2000) (greater than 150–200 Å<sup>2</sup>) or rotatable bonds (Veber *et al.*, 2000) beyond 10 lead to dramatically decreased permeability and oral bioavailability.

Regarding the number of atoms, more number of atoms were presented in E2020 (Aricep<sup>TM</sup>) (28) followed by Eptastigmine (26), Galantamine hydrobromide (21), Physostigmine (20), Xanomeline (19), Huperzine A, Rivastigmine (18) and Memantine (13). Hydrogen bonding approach was later extended and developed into a pair of rather simple rules for predicting BBB penetration. Because hydrogen bonding is primarily associated with oxygen and nitrogen moieties in a molecule, then, if the sum of the nitrogen (N) and oxygen (O) atoms in the molecule is five or less, then the molecule has a high probability of entering the CNS.

BBB penetration = (N+O) = ≤ 5

Further, it was obvious that E2020 (Aricep<sup>TM</sup>) has highest molecular weight (379.5) followed by Eptastigmine (356.514), Galantamine hydrobromide (287.359), Xanomeline (281.425), Physostigmine (275.352), Rivastigmine (250.342), Huperzine A (242.322) and Memantine (179.307). Van de Waterbeemd (2002) has suggested that MW should be kept below 450 to facilitate brain penetration and

to be lower than that for oral absorption. For marketed CNS drugs, the mean value of MW is 310, compared with a mean MW of 377 for all marketed orally active drug (Leeson and Davis, 2004) regarding.

While Physostigmine, Eptastigmine have 5 nON's, Galantamine hydrobromide, Rivastigmine, Xanomeline and E2020 (Aricep<sup>TM</sup>) have 4 nON's, Huperzine A has 3 nON's, Memantine has 1 nON. Huperzine A has 3 nNHOH, Memantine has 2 nNHOH, Galantamine hydrobromide, Physostigmine and Eptastigmine had 1 nNHOH, Rivastigmine, Xanomeline and E2020 (Aricep<sup>TM</sup>) had no nNHOH.

All the QSAR equations emphasize the importance of hydrogen bonding whether through polarity, PSA, hydrogen bond donor and acceptor counts, or simply counting heteroatoms capable of hydrogen bonding. All of these measurements are correlated, for instance, (O + N) atom count is highly correlated with PSA but measures hydrogen bond acceptors. CNS penetration requires a sum of these heteroatoms of 5 or less (Österberg and Norinder, 2000). Compounds with high hydrogen bond forming potential, such as peptides with their amide groups, peptides even as small as di- or tripeptides, have minimal distribution through the BBB (Pardridge, 1998). Increasing hydrogen bonding decreases BBB penetration. It should be pointed out that there are other heteroatoms in drugs that can function as hydrogen bond acceptors (HBA) and total HBA, including (N + O) would probably give a better measure.

Similarly, the highest rotatable bonds were present in Eptastigmine (8) followed by Xanomeline (7), E2020 (Aricep<sup>TM</sup>) (6), Rivastigmine (5), Physostigmine (2), Galantamine hydrobromide (1) and Memantine, Huperzine A does not have any rotb. Apart from these, it was also observed that E2020 (Aricep<sup>TM</sup>) has high volume (367.895), followed by Eptastigmine (362.288), Xanomeline (272.322), Galantamine hydrobromide (268.194), Physostigmine (261.477), Rivastigmine (254.014), Huperzine A (232.508) and Memantine has least (191.669). Rotatable bond count is now a widely used filter following the finding that greater than ten rotatable bonds correlates with decreased rat oral bioavailability (Veber DF Johnson et al., 2000). CNS drugs have significantly fewer rotatable bonds than other drug classes. Most centrally acting compounds have rotatable bond count of five or less (Leeson and Davis, 2004).

As per the data presented in the **Table-2**, it was evident that all the eight selected drugs were free from toxic properties like mutagenic, tumorigenic, irritant nature and their effects on the reproductive system. As a corollary to this, the solubility and drug score properties for these drugs were also within the permissible optimum range. Except Eptastigmine all drugs exhibited drug likeliness.

### CONCLUSION

However, in the present study the adverse effects of Anti-Alzheimer's drug, Galantamine hydrobromide on prolonged administration in albino mice **in the absence of AD** has been focused. From our observations on the structure and the bioactivity properties of these selected drugs, it was obvious that the memory boosters available in the market on different trade names have structural similarities with the Anti-Alzheimer's drugs currently prescribed for treating the Alzheimer's patients. From these observations it has been suggested that these Anti-Alzheimer's drugs, if consumed by the children to improve their cognitive skills, may initially exert positive effects on their performing capabilities, but in long run, might cause irreparable damage to several biosynthetic pathways in the brain which in turn will affect the overall well being of children. However, further elaborate research investigations are necessary to make concrete suggestions on these aspects in future.

### ACKNOWLEDGEMENTS

B. Nirmala Kumari is thankful to UGC for awarding Rajiv Gandhi National Fellowship under which the above work was carried out.

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