Molecular Docking of Mycosporine-Like Amino Acid Analogs in Neuroreceptors – $GABA_A$, $GABA_B$, DRD1, 5-HT3, and nAChR as Potential Drug Candidate for Neuropharmacology

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***Abstract*—The objective of this study is to identify and assess the Mycosporine-like Amino Acid (MAA) analogs binding properties with GABA Type A Receptor-Associated Protein (GABARAP), Dopamine Receptor D1 (DRD1), $GABA_B$, 5-Hydroxytryptamine Type 3 (5-HT3) and Nicotinic Acetylcholine Receptor (nAChR) through molecular docking using Accelrys® Discovery Studio 2.5 as potential drug candidate for neuropharmacology. The microwave promoted synthesized MAA-analogs adapted from the work of Andreguetti *et al.* and the protein receptors gathered through RCSB Protein Data Bank were prepared, defined, and simulated using a molecular docking software implemented with docking algorithms and receptor-ligand interactions protocols to calculate the binding and entropic energies of the docked ligand unto protein receptors. The MAA-cyst and other MAA-analogs were found to be compatible, favorable, thermodynamically spontaneous, and novel ligand as candidate drugs for the receptor, GABARAP based on the calculated binding and entropic energy values. Competitions and specificity have been observed when same analogs were docked unto a receptor having a specific ligand based on the magnitudes of the negative binding energy values. With the use of molecular docking software, the screening and discovery of potential drug candidate for various neuropharmacological disorders have become faster, easier, and relatively low-cost since not everything can be proved experimentally as traditional experimental methods for drug discovery takes a long time.**

***Index Terms*—GABARAP, $GABA_B$, DOPA1, 5-HT3, nAChR, molecular docking, mycosporine-like amino acid, neuroreceptors**

I. Introduction

Neurochemistry focuses on the chemical process and behavior of the nervous system involving neurotransmitters and psychopharmaceuticals, neuropeptides, or gastro-transmitters that affects the nerves. Neuropharmacology studies the activity of drugs in the nervous system [1]. Drugs have long been used to improve health and extend lives. The practice of drug delivery has changed dramatically in the last few decades and even greater changes are anticipated in the near future [2]. Development of new drug molecule is expensive and time consuming. Improving safety efficacy ratio of "old" drugs has been attempted using different methods such as individualizing drug therapy, dose titration, and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and targeted delivery are other very attractive methods and have been pursued vigorously [3].

Molecular modeling and molecular docking has been a primary tool in computer-assisted (structure-based) drug design. The aim of candidate drug-protein, ligand-receptor docking is to predict the predominant binding mode of a ligand with a protein of known 3D structure. Also through these methods of research, pharmacodynamics data such as binding energies, affinity, and selectivity can be calculated. It is necessary to understand binding properties in developing new potential molecules specifically in neurological disorders [4].

Psychiatric disorders, such as schizophrenia, bipolar disorder, and major depression, are paid more and more attention by human due to their upward tendency in modern society. Acetylcholine, dopamine, gamma-Aminobutyric acid (GABA), and serotonin are neurotransmitters of the cys-loop family. GABA's natural function is to reduce the activity of the neurons to which it binds. Some researchers believe that one of the purposes that GABA serves is to control the fear or anxiety experienced when neurons are overexcited. Dopamine is a vital neurotransmitter in the brain. It plays a role in several functions in the brain including movement, memory, pleasurable reward, behavior and cognition, attention, inhibition of prolactin production, sleep, mood, and learning. Excess and deficiency of this vital chemical is the cause of several disease conditions. Parkinson's disease and drug addiction are some of the examples of problems associated with abnormal dopamine levels.

Mycosporine-like Amino Acids (MAAs) have been shown to be highly resistant against abiotic stressors that include ultraviolet radiation (UVR), temperature, pH, and various solvents [5]. MAAs are thought to be the strongest UVA-absorbing compounds in nature [6] and

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other researches [7], [8], indicated that MAAs are natural antioxidants and increased therapeutic effectiveness. Analogs for MAAs have been studied and characterized using green technology, ultrasound, and microwave-promoted synthesis [9]. Incorporated amino acids included arginine, glutamic acid, histidine, norleucine, serine, tyrosine, tryptophan, *p*-nitro-phenylalanine, and the dipeptide carnosine.

The objective of this study is to identify and assess the MAA-analogs binding properties with GABA Type A Receptor-Associated Protein (GABARAP), Dopamine Receptor D1 (DRD1), $GABA_B$, 5-Hydroxytryptamine Type 3 (5-HT3) and Nicotinic Acetylcholine Receptors (nAChR) through molecular docking using Accelrys® Discovery Studio 2.5 as potential drug candidate for neuropharmacology.

II. Materials and Methods

A. Ligands

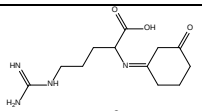
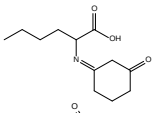
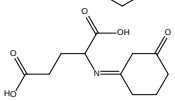
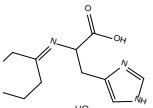
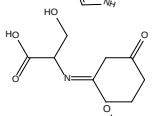
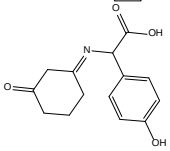
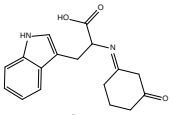
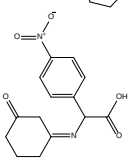
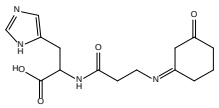
Mycosporine-like Amino Acid (MAA) analogs were selected as ligands since there were no other studies that have been done on synthetic MAAs. Table I summarized the nine (9) synthesized and published MAA-analogs by Andreguetti *et al.* (2013) [9] using microwave promoted synthesis.

Also, a ligand of MAA-cys that is not characterized was tested in molecular docking in order to compare whether a sulfur group greatly affects the MAA-analogs thermodynamically.

B. Receptor

The data that was compatible for the chosen protein receptors (GABARAP; 3D32), (DRD1), ($GABA_B$), (5-HT3; 2YMD), and (nAChR; 4UXU) was gathered through Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (*www.rcsb.org*).

TABLE I. Mycosporine-Like Amino Acid (MAA) Analogs

No.	IUPAC Name	Amino Acid Chain	Molar Mass (*g/mol*)	Chemical Formula	Chemical Structure
1	5-guanidino-2-(3-oxocyclo hexylideneamino)pentanoic acid	Arg	268.31	$C_{12}H_{20}N_4O_3$	
2	2-(3-oxocyclohexylideneamino) hexanoic acid	Nle	225.28	$C_{12}H_{19}NO_3$	
3	2-(3-oxocyclohexylideneamino) pentanedioic acid	Glu	241.24	$C_{11}H_{15}NO_5$	
4	3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	His	249.27	$C_{12}H_{15}N_3O_3$	
5	3-hydroxy-2-(3-oxocyclo hexylideneamino)propanoic acid	Ser	199.20	$C_9H_{13}NO_4$	
6	2-(4-hydroxyphenyl)-2-(3-oxocyclohexylideneamino) acetic acid	Try	275.30	$C_{15}H_{17}NO_4$	
7	3-(1*H*-indol-3-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	Trp	298.34	$C_{17}H_{18}N_2O_3$	
8	2-(4-nitrophenyl)-2-(3-oxocyclohexylideneamino) acetic acid	*p*-N-Phe	290.27	$C_{14}H_{14}N_2O_5$	
9	(*S*,*E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylideneamino) propanamido)propanoic acid	*β*-Ala-L-His	320.34	$C_{15}H_{20}N_4O_4$	

C. Protein and Ligand Preparation

From the Protein Data Bank (PDB), the protein must be cleaned from different conformations, incomplete residues, and water molecules; modify all the hydrogen atoms; and correct all connectivities, bond orders, and atom-order in amino acids. The proteins were selected to be cleaned under the "General Process Protocol" and consequently "Run / Prepare Protein" and "Prepare Ligands" were commanded.

D. Defining the Receptor

From the "Define and Edit Binding Site" Tool, these proteins were defined as the receptor and binding sites were identified based on the available cavity on GABARAP. There were eight (8) binding sites found in GABARAP and nine (9) for DRD1. While $GABA_B$, 5-HT3, and nAChR used the binding site of the active complex or unique ligands that were already attached on the protein.

E. Simulation

A force field was applied on both receptor and ligand molecules in order for molecular simulations to run. The default force field of the Accelrys® Discovery Studio 2.5 software was "Chemistry at HARvard Molecular mechanics (CHARMm)" that was found under Tools > Simulation. CHARMm performs well over a broad range of calculations and simulations, including calculation of geometries, interaction and conformation energies, local minima, barriers to rotation, time-dependent dynamic behavior, and free energy [10]. CHARMm is designed to give good results for a wide variety of modeled systems, from isolated small molecules to solvated complexes of large biological macromolecules. However, it does not have adequate coverage for organometallic complexes [11].

F. Docking Protocol

The Dock Ligands (CDOCKER) protocol is an implementation of the CDOCKER algorithm [12]. It allows running a refinement docking of any number of ligands with a single protein receptor. CDOCKER is a grid-based (GRID 1) molecular docking method that employs CHARMm. The receptor is held rigid while the ligands are allowed to flex during the refinement. For pre-docked ligands, prior knowledge of the binding site is not required. It is possible, however, to specify the ligand placement in the active site using a binding site sphere. Random ligand conformations are generated from the initial ligand structure through high temperature molecular dynamics, followed by random rotations. The random conformations are refined by grid-based simulated annealing and a final grid-based or full force field minimization.

G. Binding Energy Calculation

From the gathered docked ligands, the binding energy was calculated using the formula shown in (1) through Receptor-Ligand Interactions Protocol.

$$E_{Binding} = E_{Complex} - E_{Ligand} - E_{Receptor} \quad (1)$$

III. Results and Discussion

A. Molecular Docking

Molecular docking is commonly used to predict the binding orientation of a ligand or drug candidate to its target protein or receptor. Protein receptors, GABARAP and DRD1 containing eight (8) and nine (9) active binding sites, respectively were treated and prepared under command protocols of Accelrys® Discovery Studio 2.5. On the other hand, $GABA_B$, 5-HT3, and nAChR used files from RCSB with its active complex and utilized the same site for docking the MAAs. Fig. 1 and Fig. 2 shows the active sites in GABARAP and DRD1 (in defined spheres), and the binding site of the active complex / unique ligands originally attached in $GABA_B$, 5-HT3, and nAChR, respectively.

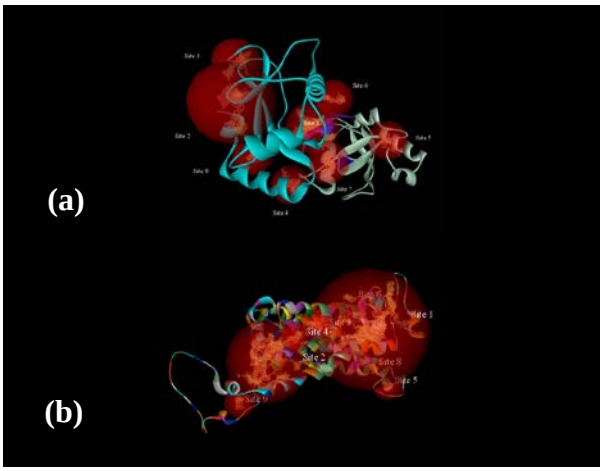


Figure 1. Active Sites (Defined Spheres) of (a) GABA Type A Receptor –Associated Protein (GABARAP) and (b) Dopamine Receptor D1 (DRD1).

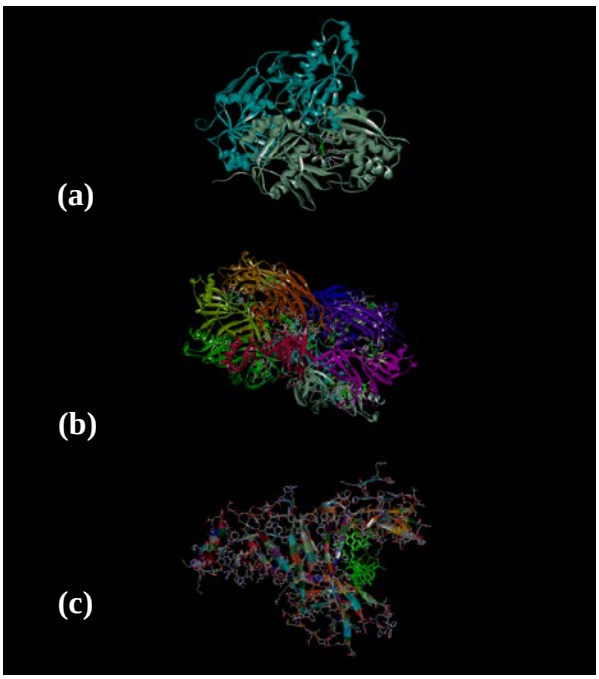


Figure 2. (a) GABAB receptor with GABA, (b) 5-Hydroxytryptamine Type 3 (5-HT3) Receptor with Serotonin, and (c) Acetylcholine Receptor with Nicotine (nAChR).

Defining the sphere in molecular docking is important since the spheres become the potential location for the ligands. Via CDOCKER, out of the eight (8) active sites of GABARAP, only on seven (7) active sites MAA-cys analog was able to dock successfully with ten (10) poses for each site.

B. GABA Type A Receptor-Associated Protein (GABARAP)

The binding energy for a given receptor-ligand interaction shows and predicts whether the docked ligand would be a spontaneous process, hence considering the ligand as a drug candidate having a sufficiently low binding energy. Presented in Table II are the average results for ten (10) poses or conformations on docking the MAA-cys in GABARAP.

TABLE II. BINDING AND ENTROPIC ENERGIES OF MAA-CYS – GABARAP INTERACTION

Active Site	Binding Energy (*kcal/mol*)	Entropic Energy (*kcal/mol*)
1	-91.855	20.370
2	-	-
3	-74.830	20.360
4	-72.574	20.373
5	-105.407	20.373
7	-81.613	20.379
8	-85.965	20.353

Table II shows that MAA-cys analog is a favorable spontaneous process thermodynamically, since binding occurs only when the Gibb's binding free energy, *dG*, is negative from sites 1, 3, 4, 5, 7, 8 based from the equation shown in (2).

$$dG = dH - TdS \quad (2)$$

The *dG* is directly related to both enthalpic – *dH*, and entropic terms – *dS*. Entropy reveals the specificity and strength of the interactions between the ligand and the receptor, and based from the data gathered, entropy values are positive (+), favoring a spontaneous process. Therefore, making MAA-cys a compatible ligand and inhibitor for GABARAP. In addition, site no. 5 is the most probable active site since it acquires a *dG* value of -105.407 *kcal/mol* shown in Fig. 3.

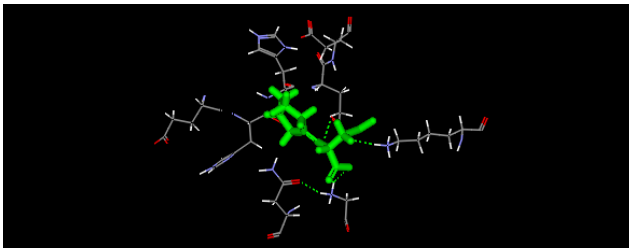


Figure 3. MAA-cys – GABARAP Interaction at Active Site No. 5.

The interactions of MAA-cys to GABARAP are through the amino acids: Gly1, Lys8, ASN-83, Glu-99, and Glu-102.

TABLE III. BINDING AND ENTROPIC ENERGIES OF MAA-ANALOGS IN GABARAP

MAA-analog	Active Site	Binding Energy (*kcal/mol*)	Entropic Energy (*kcal/mol*)
5-guanidino-2-(3-oxocyclohexylideneamino) pentanoic acid	2	-162.080	21.174
2-(3-oxocyclohexylideneamino) hexanoic acid	7	-120.546	20.613
2-(3-oxocyclohexylideneamino) pentanedioic acid	5	-150.887	15.725
[a1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	5	-148.726	20.7100
[b1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	5	-123.218	20.722
[c1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	5	-126.586	20.794
3-hydroxy-2-(3-oxocyclohexylideneamino) propanoic acid	7	-158.865	20.167
2-(4-hydroxyphenyl)-2-(3-oxocyclohexylideneamino) acetic acid	1	-59.047	21.126
3-(1*H*-indol-3-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	3	-96.255	21.298
[a2-]2-(4-nitrophenyl)-2-(3-oxocyclohexylideneamino) acetic acid	6	-103.278	21.273
[b2-]2-(4-nitrophenyl)-2-(3-oxocyclohexylideneamino) acetic acid	2	-123.515	21.255
[a3-](*S*,*E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	7	-227.621	21.565
[b3-](*S*,*E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	4	-171.050	21.721
[c3-](*S*,*E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	4	-199.343	21.655

Docking other MAA-analogs also showed possible ligand-receptor interaction with GABARAP. After preparing the ligands, some acquired 2 to 3 conformations: (S,E)-3-(1H-imidazol-5-yl)-2-(3-((3-oxocyclohexylidene)amino)propanamido)propanoic acid, (1H-imidazol-4-yl)-2-((3-oxocyclohexylidene) amino) propanoic acid, and 2-(4-nitrophenyl)-2-((3-oxocyclohexylidene) amino) acetic acid having a total of fourteen (14) ligands rather than the nine (9) initially proposed. Table III summarized the calculated binding and entropic energies for the different compatible MAA-analogs with its corresponding active site.

From the above data, the first conformation of (*S*,*E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino) propanamido) propanoic acid at active site no. 7 is the most potential ligand-receptor binding, even when compared to MAA-cys.

Epilepsy is the major neurodegenerative disease due to imbalance in excitatory and inhibitory type of

neurotransmitters. Some medications can be taken daily in order to prevent seizures completely or just reduce the frequency of their occurrence, and that is through targeting GABARAP. The docked MAA-analogs on different sites of GABARAP showed negative binding energies hence making it a great candidate drug.

C. Dopamine Receptor D1 (DRD1)

The MAA-analogs only docked on active sites no. 1, 3, 4, and 5 of the dopamine receptor D1. Incongruously, MAA-cys did not docked on any active sites of DRD1. Table IV summarized the binding and entropic energies for active site no. 1 of DRD1 for the different MAA-analogs.

TABLE IV. MAA-ANALOGS BINDING AND ENTROPIC ENERGIES FOR ACTIVE SITE NO. 1 OF DRD1

MAA-analog	Binding Energy (*kcal/mol*)	Entropic Energy (*kcal/mol*)
5-guanidino-2-(3-oxocyclohexylideneamino) pentanoic acid	-161.129	21.0900
2-(3-oxocyclohexylideneamino) hexanoic acid	-63.392	20.644
2-(3-oxocyclohexylideneamino) pentanedioic acid	23.849	20.704
[a1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	-163.074	20.831
[b1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	20.641	21.284
[c1-]3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	-61.599	20.754
3-hydroxy-2-(3-oxocyclohexylideneamino) propanoic acid	-53.516	20.180
2-(4-hydroxyphenyl)-2-(3-oxocyclohexylideneamino) acetic acid	-36.036	21.099
3-(1*H*-indol-3-yl)-2-(3-oxocyclohexylideneamino) propanoic acid	-93.965	21.279
[a2-]2-(4-nitrophenyl)-2-(3-oxocyclohexylideneamino) acetic acid	-102.291	21.310
[b2-]2-(4-nitrophenyl)-2-(3-oxocyclohexylideneamino) acetic acid	-70.455	20.795
[a3-](*S,E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	-170.133	21.594
[b3-](*S,E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	-143.904	21.567
[c3-](*S,E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino)propanamido) propanoic acid	-105.564	21.488

In the active site no. 1 of DRD1, 2-(3-oxocyclohexylideneamino) pentanedioic acid and the second conformation of 3-(1H-imidazol-4-yl)-2-(3-oxocyclohexylideneamino) propanoic acid are not favorable in binding to the receptor, while the most potential ligand-receptor binding is the first conformation of (S,E)-3-(1H-imidazol-5-yl)-2-(3-(3-oxocyclohexylidene amino) propanamido) propanoic acid having a binding energy of -170.133 *kcal/mol*, as shown in Fig. 4. The active site no. 3 for DRD1 was not favorable in binding to the receptor for all MAA-analogs since all binding energies acquired was greater than zero.

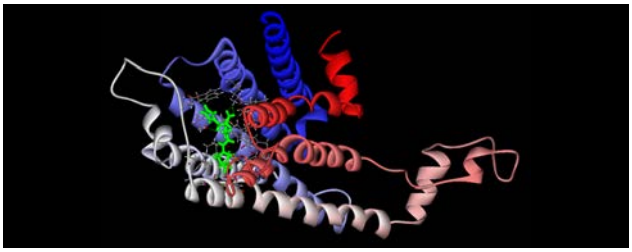


Figure 4. [a3-](*S,E*)-3-(1*H*-imidazol-5-yl)-2-(3-(3-oxocyclohexylideneamino)propanamido)propanoic acid Docked in the Active Site No. 1 of DRD1.

Dopamine plays a key role in the regulation of various physiological functions of normal brain including reward, locomotion, behavior, learning, and emotion. It is not then surprising that the dysregulation of the dopaminergic system has been linked to pathophysiology of many diseases, such as Alzheimer's disease, schizophrenia, Parkinson's disease, attention deficit hyperactivity disorder, depression, and drug addiction, leading to the clinical use of drugs that target dopamine neurotransmission in the treatment of these disorders [13].

D. 5-Hydroxytryptamine Type 3 (5-HT3)

Based from the ten (10) MAA-analogs including MAA-cys, 2-(3-oxocyclohexylideneamino)hexanoic acid in 5-HT3 obtained the lowest binding energy of -61.368 *kcal/mol* and from the ligand interaction diagram the binding occurred on the amino acids: Glu-349, His-170, Trp-65, and Trp-278 at the active binding site. Fig. 5(a) and Fig. 5(b) showed the docking, and the 2D ligand interaction of 2-(3-oxocyclohexylideneamino)hexanoic acid in 5-HT3, respectively.

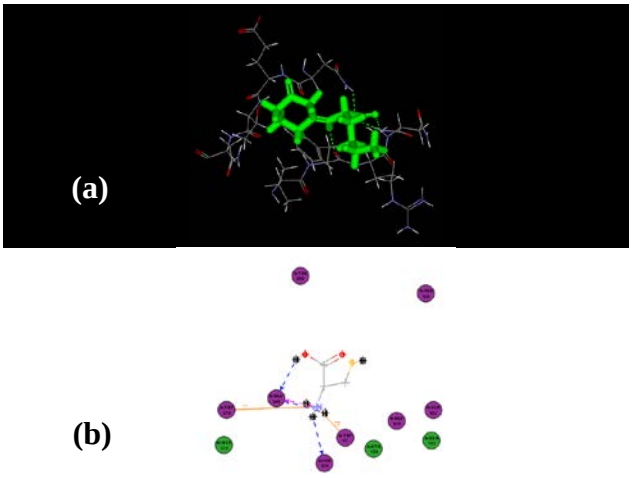


Figure 5. (a) Molecular Docking and (b) 2D Ligand Interaction of 2-(3-oxocyclohexylideneamino)hexanoic acid in 5-HT3.

E. Nicotinic Acetylcholine Receptor (nAChR)

As shown in Fig. 6(a), amongst the 10 MAA-analogs, the first conformation of 3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino)propanoic acid obtained the lowest binding energy of -92.861 *kcal/mol*, while the actual binding energy for the ligand complex was -105.486 *kcal/ mol*. These results suggest that if MAA-analogs would be the best candidate for nAChR, the concentration should be higher in order compensate for the needed binding energy. The bond formed in O of the hydroxyl with Thr-58 and Gln-61, Leu-57 in the amino group, and Leu-52 to one of the ketones tells us that there is ligand to protein interaction as shown in Fig. 6(b).

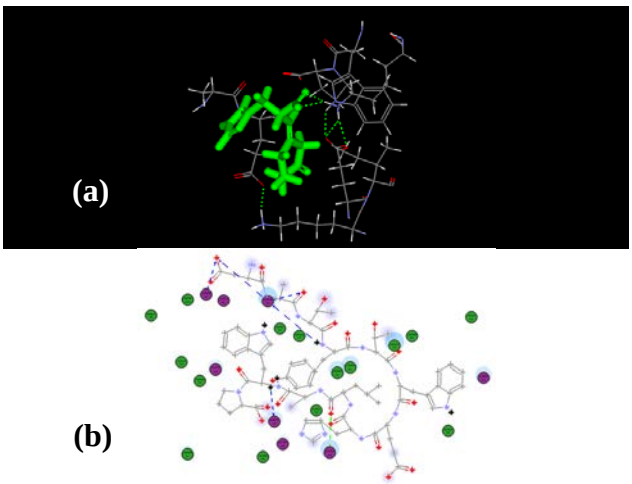


Figure 6. (a) Molecular Docking and (b) 2D Ligand Interaction of 3-(1*H*-imidazol-4-yl)-2-(3-oxocyclohexylideneamino)propanoic acid in nAChR.

IV. Conclusion

With the use of molecular docking software, Accelrys® Discovery Studio 2.5, the screening and discovery of potential drug candidate for various neuropharmacological disorders have become faster, easier, and relatively low-cost since not everything can be proved experimentally as traditional experimental methods for drug discovery takes a long time.

The MAA-cyst analog has been proven to be compatible and novel ligand as candidate drugs for the receptor, GABA Type A Receptor-Associated Protein (GABARAP) in its seven (7) active sites. The calculation results of the binding (–) and entropic (+) energy values suggest that docking of MAA-cys unto GABARAP is a favorable and spontaneous process thermodynamically. Other MAA-analogs were also tested and found out to be compatible to the said receptor with a broad variation of ligands like benzodiazepines that help reduces the transmission of neural message which acts as antidepressants and anticonvulsants. However, docking of the MAA-cys to dopamine receptor D1 (DRD1) was not successful and were only capable of docking to four (4) active sites out of nine (9) found. This concludes that the receptor, DRD1 is more specific than GABARAP for ligands. Competitions have been observed when same analogs were docked unto a receptor having a specific ligand based on the magnitudes of the negative binding energy values, still not all of the MAA-analogs docked successfully for 5-HT3 and nAChR.

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