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RESEARCH ARTICLE

Virtual Screening and Molecular Docking Analysis Of Novel Manzamine-A Derivatives As Antimalarial Agent

Harshitha M [1 *], Siddaling Kamble [2], Hemanth S [3]

[1] *Student, Department of pharmaceutical analysis, Bharathi College of pharmacy, Mandya, Karnataka, India*
[2] *Student, Department of pharmaceutical chemistry, Faculty of pharmacy M.S. Ramaiah university of applied sciences,* Bengaluru*, Karnataka, India.*
[3] *Associate Professor, Department of pharmaceutical chemistry, Ikon Pharmacy College, Bidadi, Karnataka, India.*

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Abstract: Modern drug design, virtual screening and molecular docking commonly used to understand drug receptor interactions. For docking test against 1GNG, Glycogen synthase kinase-3 beta (GSK3) complex with FRAT tide peptide, manzamine-A analogues were used for current work. The manzamine alkaloids are absolutely one of the most fascinating marine natural products. The representative manzamine alkaloids, manzamines A–C, were isolated from a marine sponge Haliclona species collected of Cape Manzamo, Okinawa, Japan. The manzamine alkaloids are a unique class of alkaloids possessing a characteristic heterocyclic system, and exhibit a diverse range of bioactivities including cytotoxicity, antimicrobial activity, antimalarial activity, antiviral and anti-inflammatory activities, insecticidal activity and proteasome inhibitory activity. The studies' primary goal is to dock the chosen Manzamine analogues on to the protein 1 GNG and compare the result to those of manzamine A as a standard drug. PyRx, and discovery studio visualizer (DSV) application were used to carry out the virtual screening and molecular docking analysis. All 40 Manzamine A analogue compounds scores were discovered to range between -9.4 to -11.7kcal/mol at the protein active site compound 12,28-oxamanzamine A interact with amino acids such as Isoleucine (ILE A 376), Aspartic acid (ASP A 341), Arginine (ARG A 344), Glutamic acid (GLU B 333), Alanine (ALA B 336) and Proline (PRO A 346 & PRO A 380). The manzamine A derivatives have been discovered to exhibit antimalarial activities.
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Keywords: Glycogen synthase kinase-3beta; Manzamine A; Haliclona species; PyRx; Discovery studio visualizer

1. Introduction

The recent studies on manzamine alkaloids which are absolutely one of the most fascinating marine natural products. In 1986, the first manzamine alkaloid, manzamine A (1), was isolated by Higa, Jeffords, and coworkers from the marine sponge Haliclona sp. collected off Cape Manzamo, Okinawa, Japan [2, 3]

Marine invertebrates have been recognized as an important source of pharmacologically unique bioactive natural products. Apart from human medicines, the research involving marine natural products in the last three decades has also generated significant discoveries that are now utilized routinely as pharmacological tools with unique cellular targets [4, 5]. Some of them have become indispensable tools in biochemical research and played significant roles in the recent advancements of life sciences. In our search for bioactive compounds against infectious and neurological diseases, we have focused on marine alkaloids isolated from sponges and in particular the manzamine alkaloids [6] Manzamine A and 8-hydroxymanzamine-A exhibited potent in vitro and in vivo antimalarial activity against Plasmodium berghei. More than 90% inhibition of asexual erythrocytic stages of plasmodium berghei was observed after a single intraperitoneal injection of manzamine A and 8- hydroxymanzamine-A into infected mice. Survival time of infected mice was also increased to more than ten days with single doses of manzamine A (50 mM/kg) and 8-hydroxymanzamine-A (100 mM/kg), when compared with standard drugs artemisinin and CQ (4 and 6 days, respectively, at 100 mM/kg) [7]. manzamines are characterized by a unique 5-, 6-, 6-, 8-, 13-membered heterocyclic ring system coupled to a β-carboline moiety. The first representative of this class, manzamine A (1), was isolated from the marine sponge Haliclona species. collected near Manzamo Island by Higa and co-workers in 1986 and its structure including absolute configuration was established by X-ray diffraction. In recent years, the manzamines have been regarded as an interesting group of marine alkaloids with extraordinary biological activities, and as a result the molecules have received considerable attention for their chemistry and pharmacology [8]. In 1987, Higa's group reported isolation and structure of two Q5 new alkaloids, manzamine B and C from the genus Halicona[9]. In subsequent studies, manzamine D was isolated as a minor component from different marine sponges[10]. In 1988 isolation, structure and antimalarial activity of two new manzamine alkaloids, manzamine E and F, from Okinawan Xestospongia sp[11]. They exhibited moderate antimalarial activity against D6 and W2 strains of P. falciparum. 8-Hydroxymanzamine-A Q5 was isolated from a sponge,

* Corresponding author: Harshitha M

Pachypellzna sp., in 1994 and its structure was confirmed by preparing 8-methoxymanzmine-A [12]. 8-Hydroxymanzamine-A exhibited potent antimalarial activity against D6 and W2 strains of Plasmodium falciparum [13].

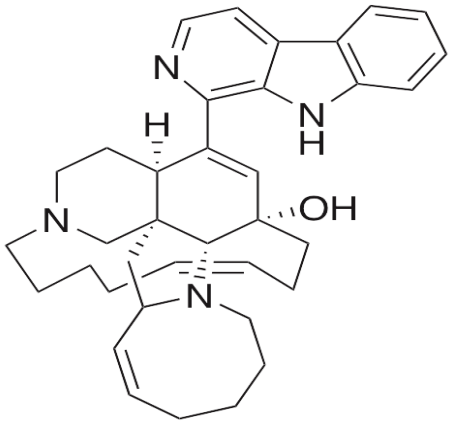

Figure 1 Structure of Manzamine A

2. Material and methods

2.1. Protein Data Bank

The Protein Data Bank (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. (See also crystallographic database). The data, typically obtained by X-ray crystallography or NMR spectroscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations (RCSB). The PDB is overseen by an organization called the Worldwide Protein Data Bank [18]

2.2. PyRx: PyRx is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. PyRx enables Medicinal Chemists to run Virtual Screening from any platform and helps users in every step of this process - from data preparation to job submission and analysis of the results[19]

2.3. Preparation of protein: Load the PDB file of protein glycogen synthase kinase -3β In the Discovery studio client structure displayed in a 3D window is the crystal structure of the ligand-binding domine of 1GNG protein with a bond ligand and 528 crystallographic waters. 528 water molecules are removed from the Hierarchy view. Protein is cleaned and hydrogen atoms are now added to the structure. Binding site of ligand is predicted from current pose and attached ligand has been removed save the file in the PDB format [20]

2.4. Obtaining ligand spatial data: The ligand molecules namely manzamine a (pub chem id - 6509753) and its 40 derivatives were identified as potential hits from PubChem database, their spatial co-ordinates were obtained as a spatial data file in SDF format[21]

2.5 Bio via discovery studio visualizer: Discovery studio is a suite of software for simulating small molecules and macromolecule systems. It is developed and distributed by Dassault systems BIOVIA. The BIOVIA Discovery studio visualizer is a free, feature rich molecular modelling application for viewing, sharing and analyzing protein and small molecules data [22]

3. Results and discussion

A computational ligand-protein docking approach was used to analyze structural complex of the 1GNG (protein) with manzamine A and its derivatives like 12,28-oxamanzamine A, 12,13-dehydromanzamine A, 6-cyclohexamidomanzamine-A, 10,11,15,16,32,33-hexahydro-8-hydromanzamine A, 6-nitromanzamine A, 32,33-dihydromanzamine A, 9-N-methylmanzamine A, 6-acetamidomanzamine A, 6-hydroxymanzamine A, 15,16,32,33-Tetrahydromanzamine A (LIGANDS) (Results are shown in Table 1) Finally docking was carried out by PyRx , Auto Dock Vina option based on scoring function. The energy of interaction of manzamine A and its derivatives with 1GNG is assigned "grid point" At each step of the simulation, the energy of interaction of ligand and protein was evaluated using atomic affinity potentials computed on a grid the remaining parameters were set as default.Article Subheadings as well as Article sub-sub headings formatting can be used as in material and methods section. The docking simulation techniques was used with manzamine A derivatives and glycogen synthase kinase -3β as the protein target and it was done with PyRx software. Two criteria were used to select the best docked protein: ligand binding position and fitness function

score comparison. A docking score that predicts pharmacological activity reflects the binding energy required to build a connection between the ligand and the receptor. It also aids in the strengthening of ligand receptor connection.The best binding affinity Kcal/mol were predicted for manzamine A are 12,28-oxamanzamine A(-11.7Kcal/mol), 12,13-dehydromanzamine A(-11.6Kcal/mol), 6-Cyclohexaamidomanzamine A(-11.4Kcal/mol), 10,11,15,16,32,33-hexahydro-8-hydromanzamine A(-11.3Kcal/mol), 6-Nitromanzamine A(-11.0Kcal/mol), 32,33-Dihydromanzamine A(-11.0Kcal/mol), 9-N-methylmanzamine A(-10.9Kcal/mol), 6-acetamidomanzamine A(-10.8Kcal/mol), 6-Hydroxymanzamine A(-10.8Kcal/mol), 15,16,32,33-Tetrahydromanzamine A. The results are shown in Tables 2 and Figures 1, 2.

Table 1 Binding affinity of compounds 1 to 40

Sl.No	Compound	Compound id	Docking score
1	12,28-oxamanzamine A	11272782	-11.7
2	12,13-dehydromanzamine A	23643835	-11.6
3	6-cyclohexamidomanzamine A	44195287	-11.4
4	10,11,15,16,32,33-hexahydro-8-hydromanzamine A	44448189	-11.3
5	6-Nitromanzamine A	44195529	-11.0
6	32,33-Dihydromanzamine A	44448204	-11.0
7	9-N-methylmanzamine A	44627725	-10.9
8	6-acetamidomanzamine A	46225868	-10.8
9	6-Hydroxymanzamine A	10393120	-10.8
10	15,16,32,33-Tetrahydromanzamine A	44448187	-10.7
11	15,16,32,33-Tetrhydro-8-hydroxymanzamine A	44448188	-10.7
12	8-Isobutamidomanzamine A	46225875	-10.7
13	8-Hydroxymanzamine A	5270765	-10.7
14	Manzamine A N-oxide	5276607	-10.7
15	6-Isobutamidomanzamine A	46225874	-10.7
16	6-N-propamidomanzamine A	46225870	-10.4
17	8-acetamidomanzamine A	46225869	-10.4
18	3,4-dihydromanzamine A	10460242	-10.4
19	8-Nitromanzamine A	44627624	-10.3
20	9-N-methyl-8-methoxymanzamine A	23643639	-10.3
21	6-N-Hexamidomanzamine A	46225880	-10.2
22	8-N-Hexamidomanzamine A	46225881	-10.2
23	6-N-Octamidomanzamine A	46225882	-10.2
24	8-N-Propamidomanzamine A	46225871	-10.2
25	8-N-Octamidomanzamine A	46225883	-10.0
26	8-Cyclohexamidomanzamine A	46225893	-10.0
27	6-N-butamidomanzamine A	46225872	-10.0
28	9-N-propylmanzamine A	44627835	-10.0
29	6-N-pentamidomanzamine A	46225876	-9.9
30	8-N-butamidomanzamine A	46225872	-9.9
31	9-N-Isopentylmanzamine A	44627937	-9.9
32	9-N-Isobutylmanzamine A	44627837	-9.8
33	9-N-neopentylmanzamine A	44627938	-9.8
34	32,33-dihydro-31-hydroxymanzamine A	44566805	-9.8
35	8-methoxymanzamine A	44568096	-9.7
36	8-N-Pentamidomanzamine A	46225877	-9.7
37	9-N-butylmanzamine A	44627837	-9.7
38	6-Methoxymanzamine A	44626476	-9.6
39	9-N-Methylmanzamine A	44568054	-9.4
40	9-N-ethylmanzamine A	44627834	-10.4

Table 2: Top 10 compound docking score and interacting amino acid

Sl.no	Ligand	Interacting amino acids
1	12,28-Oxamanzamine A	Isoleucine, Aspartic acid, Arginine, Glutamic acid, Alanine, Proline,
2	12,13-Dehydromanzamine-A	Leucine, Isoleucine, Proline, Alanine, Glutamic acid
3	6-Cyclohexamidomanzamine A	Aspartic acid, Alanine, Isoleucine, Leucine, Glutamic acid
4	10,11,15,16,32,33-Hexahydro-8-hydromanzamine A	Arginine, Aspartic acid, Glutamic acid, Lysine, Serine,
5	6-Nitromanzamine A	Arginine, Aspartic acid, Isoleucine, Glutamic acid, Leucine
6	32,33-Dihydromanzamine A	Isoleucine, Proline, Leucine, Glutamic acid, Aspartic acid,
7	9-N-Methylmanzamine A	Aspartic acid
8	6-Acetamidomanzamine A	Leucine, Proline, Isoleucine, Alanine
9	6-Hydroxymanzamine A	Glutamic acid, Aspartic acid, Arginine, Lysine
10	15,16,32,33-Tetrahydromanzamine A	Alanine, Glutamic acid

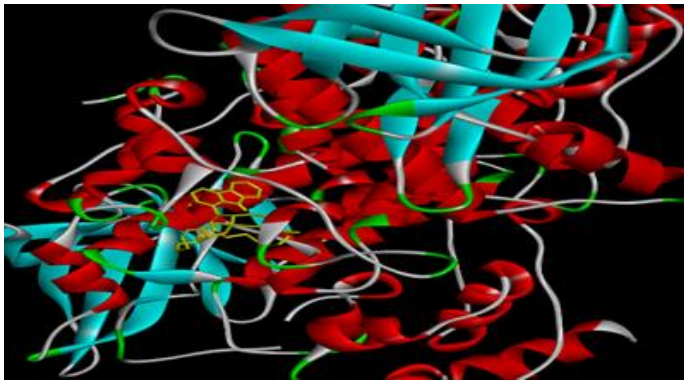

Figure 1 3D interaction of 1GNG with 12,28-oxamanzamine A

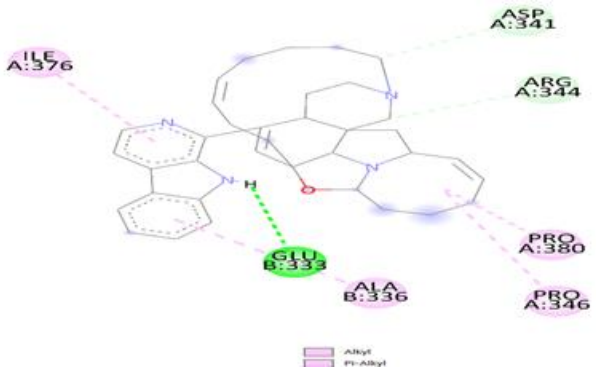

Figure 2 Interaction of amino acid with 12,28-oxamanzamine

4. Conclusion

In conclusion, our research conducted molecular docking studies on derivatives of manzamine A, specifically 12,28-oxamanzamine A, with target protein 1GNG. The results revealed that 12,28-oxamanzamine A exhibited a significant binding affinity of -11.7 kcal/mol. This potent lead molecule demonstrates promising potential as an antimalarial drug, as it forms interactions with amino acids involving alkyl, pi-alkyl, and conventional hydrogen bonds between the protein and the ligand. Notably, the interacting amino

acids include Isoleucine, Aspartic acid, Arginine, Glutamic acid, and Alanine. This compound holds the potential to serve as a robust candidate for the development of potent antimalarial inhibitors.

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Author's short biography

Harshitha M:

Harshitha M is a determined and accomplished individual, holding a Bachelor of Pharmacy (B.Pharm) degree and currently pursuing a Master of Pharmacy (M.Pharm). Her academic journey reflects a deep-rooted passion for pharmaceutical sciences, marked by her unwavering commitment to the field. With her B.Pharm background, she has already acquired a strong foundation in pharmaceutical knowledge and principles.

Siddaling Kamble:

Siddaling Kamble, a dedicated and accomplished student at the Faculty of Pharmacy, M.S. Ramaiah University of Applied Sciences, has made impressive strides in the field of pharmaceutical sciences. With a Bachelor of Pharmacy (B.Pharm) already under their belt, Siddaling is now on a remarkable academic journey, currently pursuing a Master of Pharmacy (M.Pharm) dept of pharmaceutical chemistry at RUAS , primary area of interest lies in the fascinating realm of molecular docking studies and computer-aided drug design (CADD).QSAR. Pharmacophore modeling, molecular dynamic ss

Hemanth S:

Hemanth S is an esteemed Associate Professor within the Department of Pharmaceutical Chemistry at the prestigious Ikon Pharmacy College. With a strong academic background and a wealth of professional experience, Hemanth is a guiding force in the realm of pharmaceutical education and research. His expertise spans various facets of pharmaceutical chemistry, making him an invaluable asset to both the academic institution and the field at large. As an educator and researcher, Hemanth S has demonstrated a commitment to nurturing the next generation of pharmaceutical scientists while actively contributing to cutting-edge research initiatives. His dedication and knowledge continue to inspire and shape the future of pharmaceutical chemistry.