WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Drug Discovery and QSAR Studies of Thiazole Derivatives

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A B S T R A C T

This article delves into the role of thiazole derivatives in modern drug discovery using computational tools such as QSAR, molecular docking, and ADME prediction platforms. Thiazole, a five-membered heterocyclic compound, exhibits diverse pharmacological activities and forms the backbone of several therapeutics. The study integrates synthetic methodologies, physicochemical profiling, and computational techniques to demonstrate the potential of thiazole derivatives, particularly Dasatinib, in therapeutic applications

Keywords: Thiazole.,QSAR studies

INTRODUCTION

Thiazole is a five-membered azole heterocyclic organic compound containing a ring of 3 carbon atoms, a nitrogen and a sulphur. Thiazole and its derivatives have wide industrial application in pharmacy,liquid crystals, and polymers. Thiazoles have several biological activities such as antioxidant, antitumor, anticonvulsant, anti-hyperlipidemic and anti-inflammatory.computer-aided drug design (CADD) is a unique area in drug discovery arena which apply the concept of molecular modelling to study the interaction between drugs and their target protein. Qsar is a molecular modeling technique widely used to correlate physicochemical properties of compounds and their experimentally determined activities .while molecular docking is used to study the possible orientation of the target protein to the ligand when they bind to one another to form complex.The interaction between the receptor and the ligands was studied using molecular docking.

DRUG-Drug is the substance or a molecule that is used for the prevention, diagnosis, cure ,mitigation and treatment or alleviation of its symptoms of certain diseases or abnormal conditions in man and animals.These are that change or modify a persons mental or physical condition.It gives a therapeutic effect to the patients by inhibiting or inducing the function of a biomolecule.

DRUG DISCOVERY-Drug discovery is the process through which potential new therapeutic entities are identified, using a combination of computational, experimental, translational, and clinical models . Despite advances in biotechnology and understanding of biological systems, drug discovery is still a lengthy, costly, difficult, and inefficient process with a high attrition rate of new therapeutic discovery. Drug design is the inventive process of finding new medications based on the knowledge of a biological target. In the most basic sense, drug design involves the design of molecules that are complementary in shape and charge to the molecular target with which they interact and bind.In addition to small molecules, biopharmaceuticals and especially therapeutic antibodies are an increasingly important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also gained great advances . Drug development and discovery includes preclinical research on cell-based and animal models and clinical trials on humans, and finally move forward to the step of obtaining regulatory approval in order to market the drug.

Figure1: stages of drug discovery

- Target identification – identification of new targets associated with a disease such as proteins that can be inhibited or upregulated. Identify a biological target (like a protein, enzyme, or receptor) involved in a disease.
- Hit identification – experimental and computational screening of hundreds of thousands to millions of compounds using high throughput assays to test activity against the target in vitro. Cell-based assays also assess the toxicity of these hit compounds.
- Hit-to-lead development – systematic synthetic alterations are made to the hit compounds to improve potency and confer more "drug like" properties by establishing Structure Activity Relationships (SAR). This process typically involves hundreds of compounds.
- Lead optimisation and candidate selection – Compounds are further synthetically modified and progressed to preclinical assessment, usually in both healthy and diseased animal experiments. Compounds with the best pharmacological profiles, safety, and effectiveness are prioritised.
- Phase I clinical trials – the drug candidates are administered to 20-80 healthy human volunteers. The subjects are monitored closely to look for any toxicity issues or safety concerns.
- Phase II clinical trials –This trial is primarily to assess the effectiveness of the drug in treating the disease, but safety profiles and side effects are also monitored.
- Phase III clinical trials – drug candidates are administered to thousands of volunteer patients to demonstrate safety and compare efficacy against existing treatments on a larger population, typically 300 to 3,000 volunteers.
- Approval and Phase IV monitoring –Phase IV involves continuous monitoring of any safety issues and effectiveness once the drug is administered through the healthcare system.

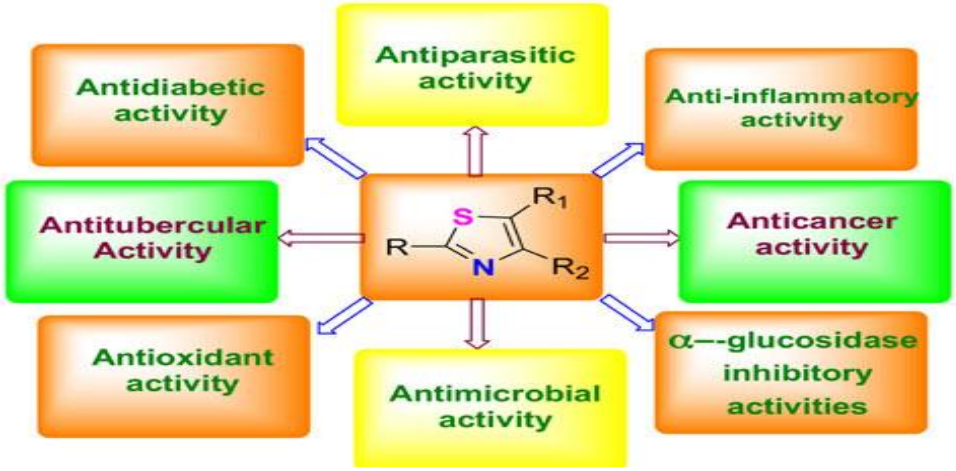
DRUG DESIGN

Drug design is the process of designing new chemicalmolecules that can interact specifically with a biological target (such as a protein or enzyme) involved in a disease, with the goal of developing an effective and safe therapeutic agent.It includes;

LIGAND-BASED DRUG DESIGN- Ligand based drug design refers to drug discovery efforts in the absence of any target structures and in the presence of chemical structures known to modulate the target drug.Most popular approaches for ligand based drug design are the QSAR method and pharmacophoremodelling.QSAR is a computational method to identify the correlation betweenthe chemical structureof a series of compounds and a particular chemical or biological process.Also known direct drug design.

STRUCTURE-BASED DRUG DESIGN- Structure based drug design proceeds through multiple cycles leading an optimized drug candidateto clinical trials.SBDD uses computational chemistry tools in which the structure of a protein is used as the basic to identify or design new chemical compound that could bind to the target resulting in the inhibition of the target protein .SBDD uses the 3D shape and structure of the protein as the basis for designing new drugs. Structures determined by NMR spectroscopy ,X-ray crystallography, and homology modelling. Also known as reverse pharmacology.

INTRODUCTION OF THIAZOLE



Figur 3 : Activities of Thiazole.

- Thiazole is a heterocyclic organic compound that has a five-membered molecular ring structure with molecular formula C3H3NS. It possesses both an electron-donating group (-S-) and an electron-accepting group (C=N).
- Thiazole is aromatic on the basis of delocalization of a lone pair of electrons from the sulphur atom completing the desirable 6 π electrons to fulfil Huckel's rule.
- The thiazole ring is present in many natural and synthetic products with a broad range of biological activities for example, thiazole containing vitamin B1 (thiamine) helps in the normal functioning of the nervous system by its role in the synthesis of acetylcholine.
- Diverse modifications of the thiazole ring at various positions led to a variety of novel compounds with wide spectrum of pharmacological activities such as antioxidant, antibacterial, antifungal, antitubercular, diuretic, anti-inflammatory and anticancer activities
- Tiazofurin and dasatinib (antineoplastic agents) , ritonavir (anti-HIV drug) , ravuconazole (antifungal agent) , nitazoxanide (antiparasitic agent) , fanetizole, meloxicam and fentiazac (anti-inflammatory agents) , nizatidine (antiulcer agent), and thiamethoxam (insecticide) are some examples of thiazole bearing products .

DRUG DISCOVERY IN THIAZOLE

- The presence of thiazole ring as a part of drug structure can be determinant for its physicochemical and pharmacokinetic properties.
- More than 30 approved antibiotics contain the thiazole moiety, particularly in the form ofaminothiazole. Several of these antibiotics are being extensively used to treat infections including gram-negative pathogens.
- Several thiazole-containing anticancer drugs are being employed to treat different types of cancer. Dasatinib and dabrafenib are among the most widely used drugs to treat leukemia and melanoma, respectively.
- Ritonavir and cobicistat are examples of thiazole-containing drugs that treat human immunodeficiency virus infections.
- inflammatory properties, validating their potential use as alternative therapeutic agents. The anti-inflammatory effects of these derivatives synthetic thiazole compounds possess substantial anti-warrant further investigation and development, paving the way for new treatments that may offer effective relief from inflammation-related disorders without the adverse effects associated with conventional non-steroidal anti-inflammatory drugs (NSAIDs).

PHYSICOCHEMICAL PROPERTIES OF THIAZOLE DERIVATIVE

Table 1: properties of thiazole derivatives

S.No.	Property	Value
1	Molecular Formula	C_3H_3NS
2	Molecular Weight	85.12 g/mol
3	Physical State	Liquid

4	Storage Condition	Store in flammable materials area
5	Melting Point (M.P.)	–33 °C
6	Boiling Point (B.P.)	116 °C – 118 °C
7	Flash Point	26 °C
8	Color	Pale yellow
9	Acidity (pKa)	2.5
10	Solubility	Slightly soluble in water; soluble in ether

CHEMSKETCH

ChemSketch is a chemical structure drawing software developed by Advanced Chemistry Development, widely used in both academic and industrial settings. It allows users to create 2D and 3D molecular structures, chemical reactions, and various laboratory diagrams. ChemSketch supports the drawing of organic, inorganic, polymeric, and Markush structures with ease. One of its key features is the ability to generate IUPAC names for drawn compounds, calculate molecular formulas, and predict physicochemical properties such as molecular weight, density, and molar refractivity.

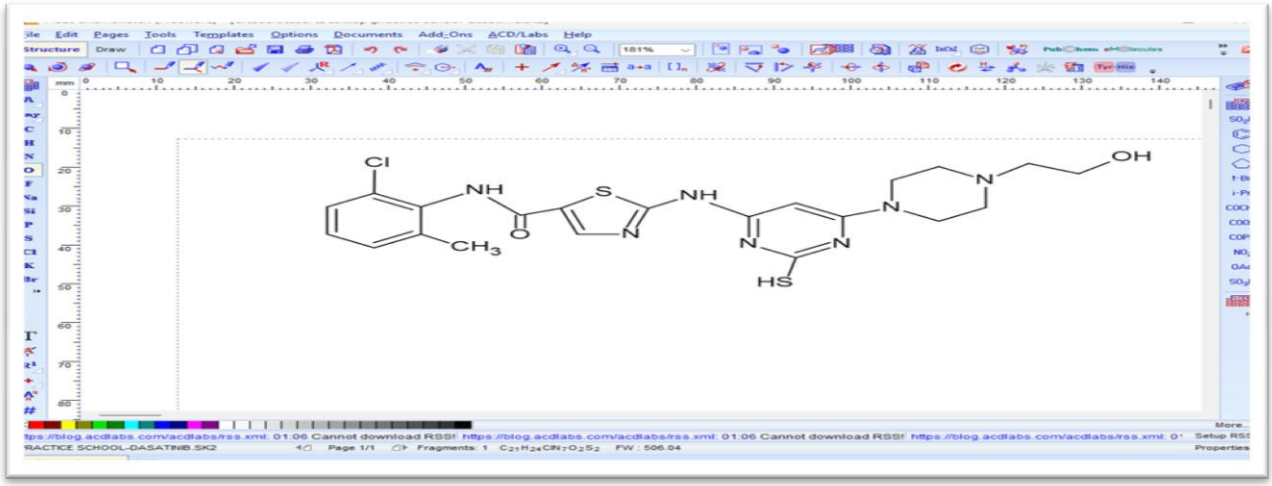


Figure 4:Dasatinib by using Chemsketch

MOLINSPIRATION

Molinspirationis an online cheminformatics tool widely used in drug discovery and molecular modeling to predict various molecular properties and assess drug-likeness. It allows users to calculate important physicochemical parameters such as molecular weight, log P (lipophilicity), topological polar surface area (TPSA), hydrogen bond donors and acceptors, and the number of rotatable bonds.

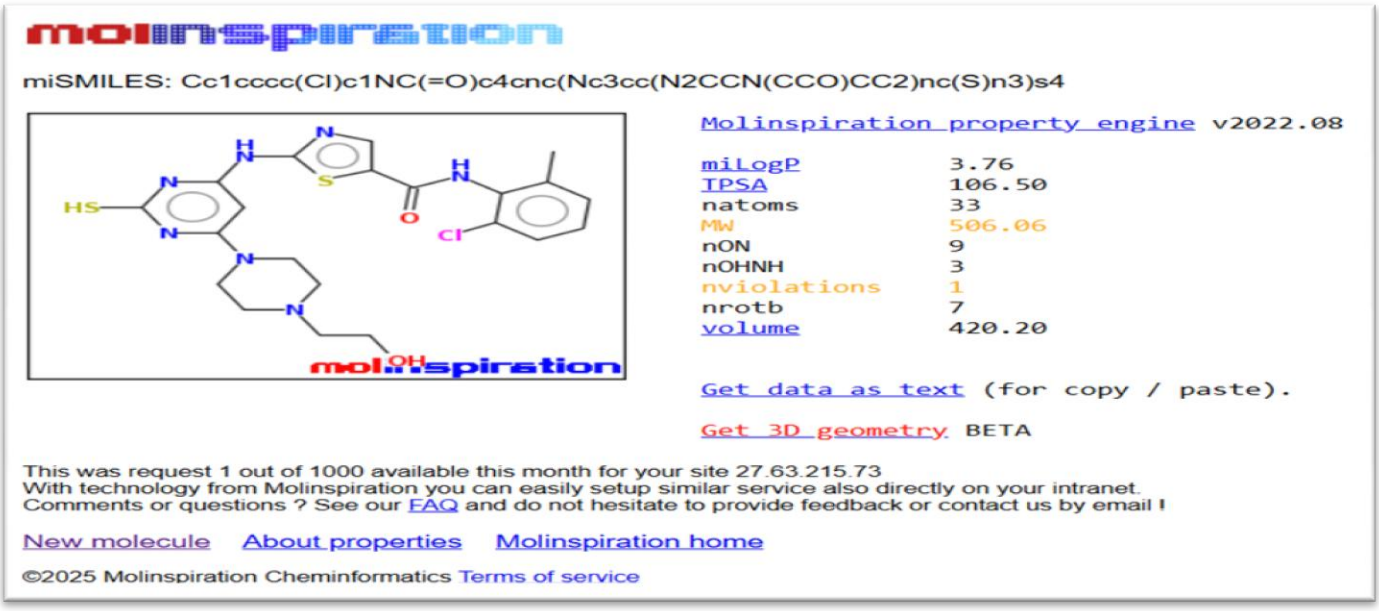


Figure 5 :Dasatinib by using Molinspiration

SWISS ADME PREDICTOR

SwissADME is a free and widely used online tool developed by the Swiss Institute of Bioinformatics (SIB) that allows researchers to evaluate the pharmacokinetics, drug-likeness, and medicinal chemistry friendliness of small molecules. It provides key insights into a compound's absorption, distribution, metabolism, and excretion (ADME) properties using SMILES or molecular structure as input.

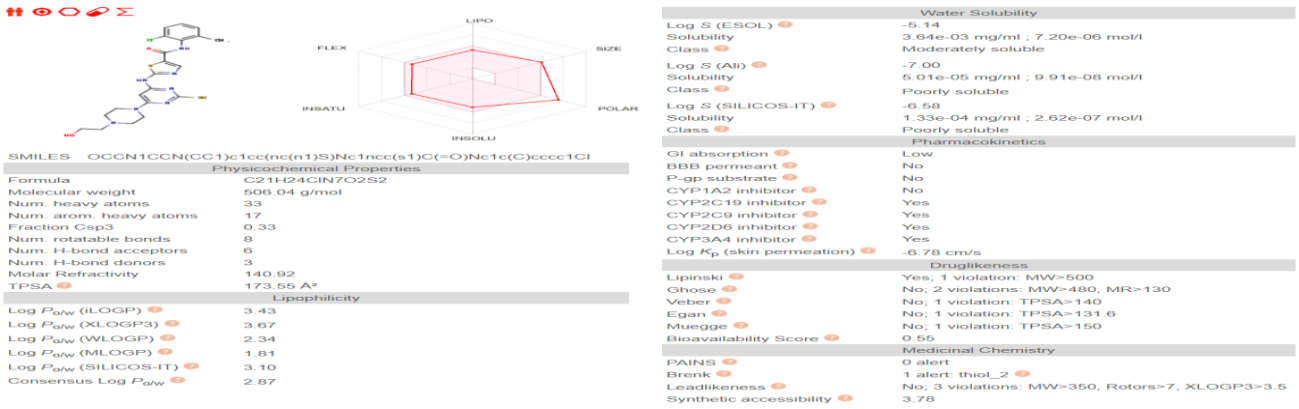


Figure 6 :Dasatinibby using swiss ADME predictor

PROTEIN DATA BANK

The Protein Data Bank (PDB) is a globally recognized repository that archives three-dimensional structural data of biological macromolecules such as proteins, nucleic acids, and complex assemblies. Established in 1971, the PDB is maintained by the Worldwide Protein Data Bank (wwPDB) consortium, which includes organizations like RCSB (USA), PDBe (Europe), PDB (Japan), and BMRB. Researchers deposit experimentally determined structures obtained through techniques like X-ray crystallography, NMR spectroscopy, andcryo-electron microscopy (cryo-EM) into the database. Each structure in the PDB is assigned a unique four-character PDB ID, which can be used to retrieve atomic-level information about the molecule, including its 3D coordinates, ligands, and binding sites.

5OWR | pdb_00005owr

Human STK10 bound to dasatinib

Szklarz, M., Muniz, J.R.C., Vollmar, M., von Delft, F., Bountra, C., Knapp, S., Edwards, A.M., Arrowsmith, C., Elkins, J.M.

To be published

Released	2017-09-13
Method	X-RAY DIFFRACTION 2.3 Å
Organisms	Homo sapiens
Macromolecule	Serine/threonine-protein kinase 10 (protein)
Unique Ligands	1N1, CA

Figure 7 :Dasatinib by using Protein data bank

SYNTHESIS OF THIAZOLE DERIVATIVES

Hantzsch thiazole synthesis-Hantzsch thiazole synthesis is one of the most reliable ways of synthesizing thiazoles. It is a condensation of α-haloaldehydes or ketones with thioureas in neutral, anhydrous solvents to form 2-aminothiazoles. For example, 2-(phenylamino)-4-methylthiazole can be obtained by the reaction of *N*-phenylthiourea with chloroacetone in anhydrous acetone and 1 hour stirring under reflux. A high percentage yield of 96% is obtained in this reaction.

Cook–Heilbron synthesis -Cook–Heilbron synthesis leads to 2,4-disubstituted 5-aminothiazole derivatives by the reaction of an α-aminonitrile and dithioacids or esters of dithioacids, carbon disulfide, carbon oxysulfide, or isothiocyanates under mild reaction conditions .

Gabriel thiazole synthesis.-cyclization reaction of acylaminocarbonyl compounds and a stoichiometric amount of phosphorus pentasulfide at 170 °C.

MOLECULAR DOCKING

- Molecular docking is a computational technique that predicts the binding affinity of ligands to receptor proteins.
- Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex .

- Knowledge of the preferred orientation is used to predict the strength of association or binding affinity between two molecules using scoring functions.
- The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play central role in signal transduction.
- The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized.
- Molecular recognition plays a key role in promoting fundamental bimolecular events such as enzyme- substrate, drug-protein and drug-nucleic acid interactions.

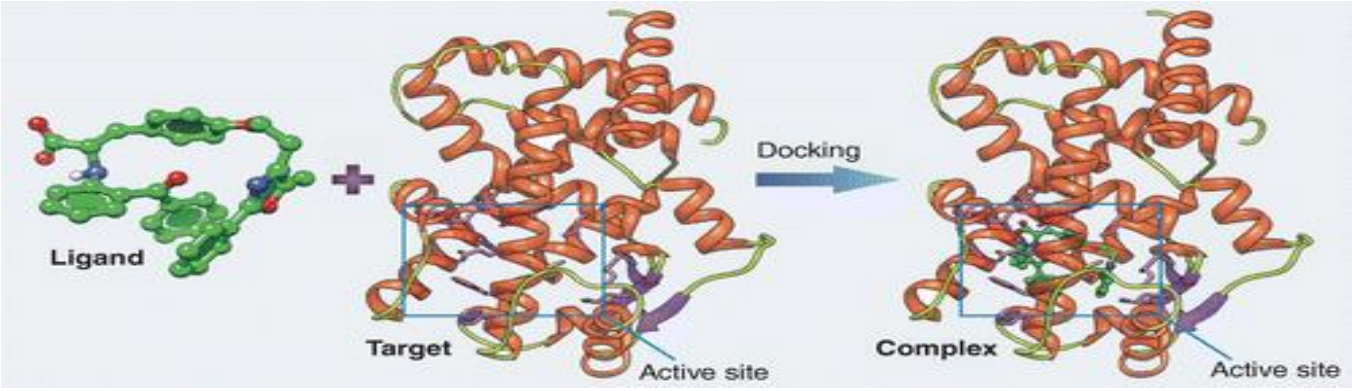


Figure 8 : molecular docking

TYPES OF MOLECULAR DOCKING

1.**Rigid docking -** Rigid docking, also known as rigid ligand docking, is a method in molecular modeling where both the receptor and ligand molecules are treated as rigid objects, meaning their shapes and bond lengths/angles do not change during the docking process. It focuses on finding the best spatial arrangement of the ligand within the receptor, considering only rotations and translations.

2.Flexible docking - Flexible docking is a molecular docking method that accounts for the flexibility of both the ligand and the protein receptor during binding simulations. It expands upon rigid docking by allowing the protein's side chains and the ligand to explore different conformations, which is crucial for accurately predicting binding interactions. This approach can lead to a more realistic prediction of binding poses and affinities compared to rigid docking.

MOLECULAR DOCKING SOFTWARES

Table 2: Molecular docking softwares

SOFTWARE	WHO MADE IT	WHAT IT DOES	SPECIAL FEATURES
DOCK	UCSF Chimera team	Fits small molecules into protein	Uses grids to check how well they fit
Auto Dock	Scripps Research Institute	Widely used, flexible or rigid docking	Uses smart algorithm (genetic) to find best fit
ArgusLab	Mark Thompson	Drug design & molecule modeling	Combines quantum + classical science
GOLD	CCDC, UK	Protein-ligand docking	Handles flexible parts, water, and metals
Mol Dock	Mol Soft	Fast docking for small molecules	Checks shape, charge, and attraction forces

GENERAL STEPS IN MOLECULAR DOCKING

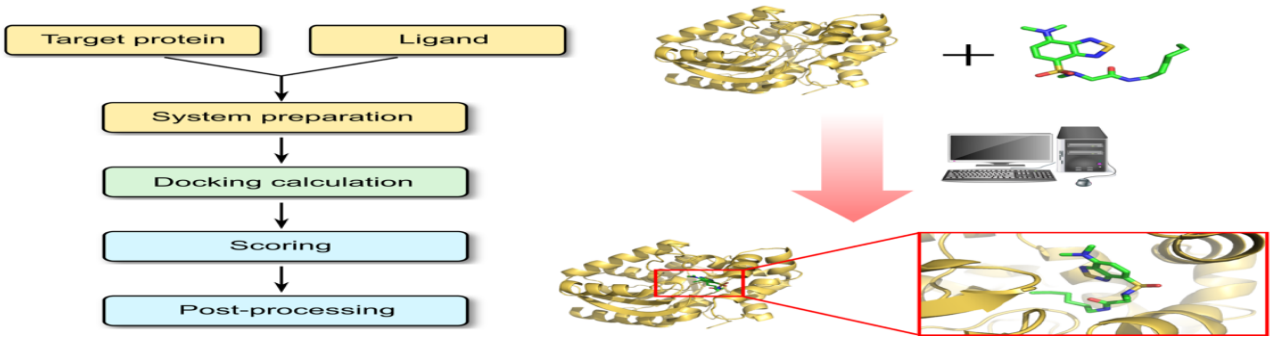


Figure 9: steps involved in molecular docking

TARGET PROTEIN DETERMINATION AND PREPARATION-The properties of the selected protein structure affect docking result. With the development of X-ray crystallography, NMR, Cryo-EM, and similar structure determination methods, the number of protein with known three-dimensional (3D) structure is rapidly increasing and they are accessible to the public in database like the protein data bank (PDB).The first step of docking is retrieving the 3D structure of the protein, preferably bound by a ligand, from the PDB. Using 3D structure with high resolution or structures bond by a high-affinity ligand is suggested.

PREPARATION OF LIGAND-By using different databases such as ZINC, Pub Chem Ligands molecule can be downloaded. It can be draw in Chemsketch tool in mol file. Then utilized LIPINSKY'S RULE OF 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failuredue to drug likeness properties for molecules.

DETERMINATION OF DOCKING TYPE-Choice of docking type to be used depends on the needs of the researcher. If docking of several molecules at the binding site of a protein at a specific pH, water, and solubility is desired, flexible docking program may be preferred. However, if many more compounds are to be scanned from database, flexible docking method may be bad option unless there is high processor and a fast computer.

SELECTION OF THE BEST DOCKING SCORING FUNCTION-The best docking scoring function is selected depending on the stability of the ligand-protein complex. It is difficult to choose a suitable scoring function that gives a correct binding pattern and the possible ligand. Scoring functions should be able to differentiate binders from nonbinders clearly. In addition to this, it should be able to discriminate between correct and incorrect binding modes of a ligand with high accuracy and in a reasonable time . Scoring functions are classified into three main categories: Empirical, force field, and knowledge-based.

DOCKING VALIDATION-Like any other technique, the docking process should also be validated. The docking results are validated by redocking of reference ligands with targets and comparing the RMSD (root mean square deviation) values, binding pose, binding affinity, and coverage of the estimated bindings with previously acquired results. If the ligand and target structures are complex, it is recommended to carry out molecular dynamics studies.

MOLECULAR DOCKING OF DASATINIB WITH SIK2

Salt-inducible kinases (SIKs) control cyclic adenosine monophosphate (cAMP)-dependent production of the anti-inflammatory cytokine interleukin-10 (IL-10) in macrophages. The three SIK isoforms reported are SIK1, SIK2 (QIK), and SIK3 (QSK). SIK2 modulates metabolic pathway, steroidogenesis, adipogenesis, adipocyte energy metabolism, fatty acid oxidation, and centrosome splitting. SIK2 overexpression has been implicated in the development of chronic inflammatory diseases, gastric cancer and acute kidney injury.

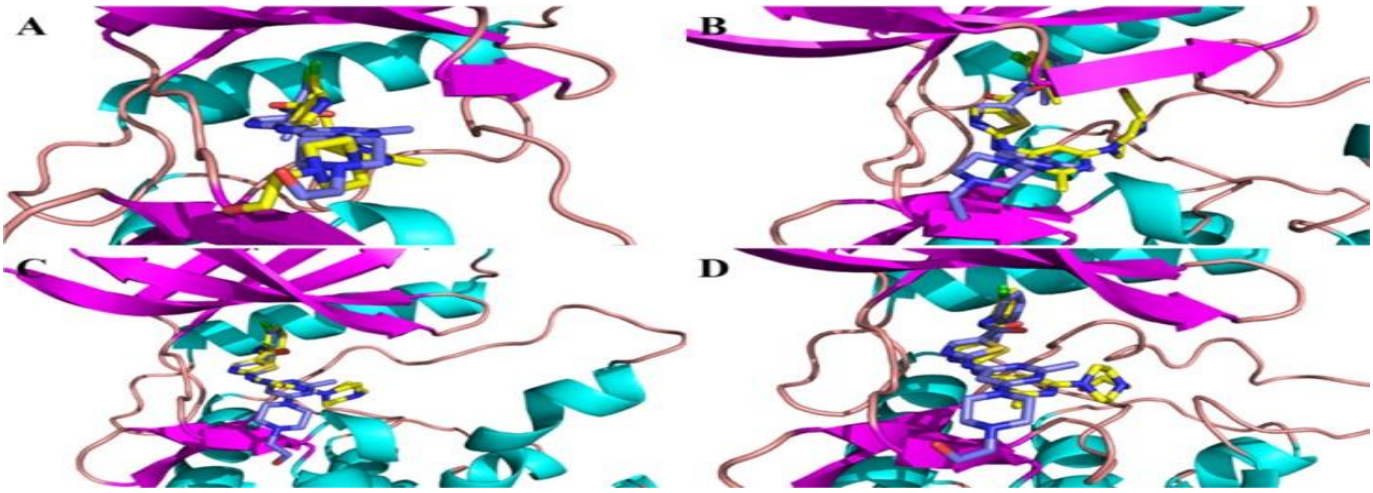


figure 10: Selected results of dasatinib docking with SIK2. (A)SIK2-I, (B) SIK2-II, (C) SIK2-III.(D)SIK2-1V.

Before performing molecular docking to construct the initial Dasatinib/SIK2 binding model, we evaluated the docking power via a "re-docking" strategy. The root-mean-square deviation (RMSD) obtained between the crystal structure and the conformer with the lowest energy (−11.92 kcal/mol) Hence, we performed molecular docking to construct the Dasatinib/SIK2 complex.A PDB survey revealed that ≥20 kinase crystal structures formed complexes with Dasatinib.All structures demonstrated nearly the same binding pattern with Dasatinib, as highly conserved binding pockets were present for all of the structures. Dasatinib could form a close binding interaction with SIK2. The ABL crystal structure was included for comparison. A relatively good overlap was observed. Therefore, the binding pockets observed in the SIK2 homology model may be suitable for consideration and the status of Dasatinib in the binding sites should be reliable. A hydrogen bond network that potentially facilitated the binding affinity was observed between Dasatinib and SIK2.

SUMMARY

The thiazole nucleus is important pharmacophore in many biologically active compounds and is found in many clinically used drug such as bleomycin, tiazofurin, ritonavir, meloxicam, nizatidine, nitazoxanide and etc. Also some new thiazole-based drugs such as ravuconazole, febuxostat, sodelglitazar and dasatinib were introduced recently. Utilizing software like ChemSketch, Molinspiration, and SwissADME, we were able to visualize molecular structures, analyze physicochemical properties, and predict ADME characteristics, all of which are crucial in assessing drug-likeness and pharmacokinetic behavior.Dasatinib, an established anticancer drug featuring a thiazole ring, was explored using ChemSketch to understand its molecular framework. Tiazofurin, another notable thiazole-based anticancer compound, was analyzed through Molinspiration and SwissADME, providing insights into its drug-like nature and potential effectiveness in biological systems.The synthetic methodologies discussed—including Hantzsch, Cook–Heilbron, Gabriel, and condensation reactions—demonstrate the versatility and efficiency in producing various thiazole derivatives with high yield and biological relevance.The project concludes that thiazole is a versatile and promising pharmacophore in the field of drug discovery.

CONCLUSION

The aim of this review is to summarize the Drug discovery and QSAR study of thiazole derivative. The most fundamental goal in drug design is to predict whether a given molecule will bind to a target and if so how strongly. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand so that the free energy of the overall system is minimized. The detailed knowledge of various synthetic strategies and biological effects would be of great help in the drug discovery and development process.Various recent new drugs developments in thiazole derivatives show better effect and less toxicity.The thiazole nucleus plays a crucial role in discovering novel medications to treat numerousdiseases.

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