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# IN SILICO INVESTIGATION OF THIAZOLE DERIVATIVES: UNVEILING ANTICANCER POTENTIAL THROUGH MOLECULAR DOCKING

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## ABSTRACT

Cancer continues to be a major global health challenge, driving the need for innovative therapeutic strategies. Thiazole derivatives have garnered significant attention due to their versatile pharmacological properties, including anticancer potential. In this study, we conducted an insilico investigation to evaluate the anticancer activity of thiazole derivatives using molecular docking and pharmacokinetic profiling. A series of thiazole-based compounds were docked against key cancer-related targets. The docking results revealed strong binding affinities. Structural insights from the Protein Data Bank (PDB) highlighted the precise binding modes of these derivatives within the active sites of the target proteins. Furthermore, SwissADME was employed to assess the drug-likeness and pharmacokinetic properties of the compounds. The top-performing derivatives exhibited favorable ADME profiles, including high gastrointestinal absorption, low toxicity, and compliance with Lipinski's rule of five. These findings underscore the potential of thiazole derivatives, as promising anticancer agents. This study provides a robust computational framework for identifying and optimizing thiazole-based compounds, offering a foundation for further experimental validation and drug development.

**KEYWORDS:** Thiazole derivatives, anticancer agents, molecular docking, SwissDock, SwissADME, PDB, insilico screening.

## INTRODUCTION

### MEDICINAL CHEMISTRY

In medicinal chemistry, the chemist attempts to design and synthesize a medicine or a pharmaceutical agent which will benefit humanity. Such as compound could also be called a "drug".

In Latin word – Medicina

Meaning - art of healing.

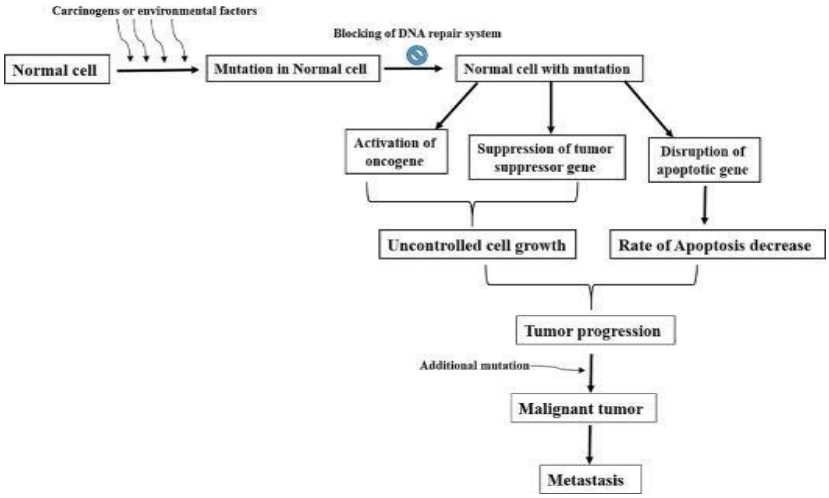
**It involves**

- Synthesis
- Structure activity relationships (SAR)
- Receptor interaction
- ADME (Absorption, Distribution, Metabolism and Excretion)

### CANCER

Cancer, the uncontrolled growth of cells, is a major cause of death throughout the world. In 2007, it killed ~7,900,000 people worldwide, a value that represents ~13% of total deaths. In the U.S., the number of deaths caused by cancer is second only to that from cardiovascular disease. While great strides have been made in the treatment of cancer over the past 50 years, it continues to be a major health concern and, therefore, extensive efforts have been devoted to searching for new therapeutic approaches.

### MECHANISM OF ACTION

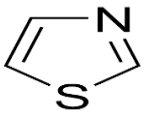


**SYMPTOMS**

Some general signs and symptoms associated with, but not specific to, cancer, include:

- ✓ Fatigue.
- ✓ Weight changes, including unintended loss or gain.
- ✓ Skin changes, such as yellowing, darkening or redness of the skin, sores that won't heal, or changes to existing moles.
- ✓ Difficulty swallowing.
- ✓ Hoarseness
- ✓ Unexplained bleeding or bruising.

**THIAZOLE**




- ➢ Thiazole or 1,3-thiazole is a 5 membered heterocyclic compound that contains both sulfur and nitrogen.
- ➢ The term "thiazole" also refers to a large family of derivatives.
- ➢ Thiazole itself is a pale yellow liquid with a pyridine like odor.
- ➢ The thiazole ring is notable as a component of the vitamin thiamine ($B_1$).

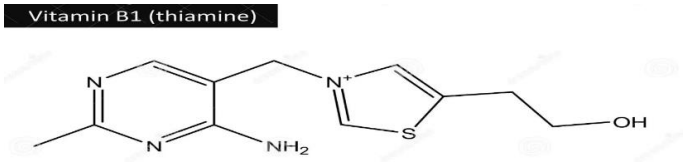
**IUPAC name:** 1, 3 Thiazole.

**PROPERTIES**

- Molecular formula – $C_3H_3NS$
- Molar mass – 85.12 $mol^{-1}$
- Boiling point -116 to 118c
- Acidity -2.5.

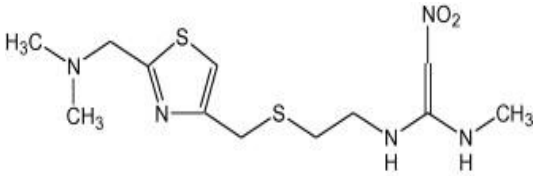
**APPLICATION**

- ➢ Thiazole molecules used as an intermediate chemical in synthetic drugs, fungicide and dyes in industries.
- ➢ A thiazole ring present naturally in the essential vitamin $B_1$ thiamine.

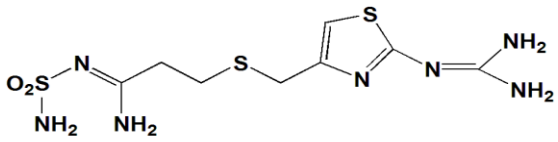



- Various derivatives of thiazole nucleus is the aim of research due to their important in various application.
- Derivatives of thiazole heteroatom used as reactant, intermediaries in the various industries like agrochemical, pharmaceutical and the pesticides industry.
- Most of the derivatives of thiazole were synthesized to achieve the industrial, biological and medicinal target by numerous research scholar and scientist in research and development laboratories.

**1) $H_2$- receptor blockers famotidine, nizatidine used in peptic ulcer.**




**Nizatidine (Anti ulcer)**

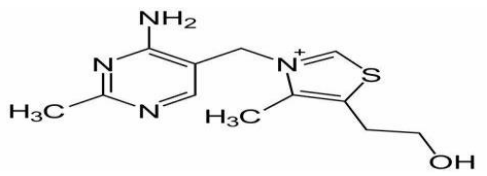



**Famotidine**

**(Anti ulcer)**

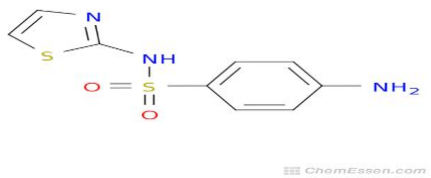
**2) Chlormethiazole used as sedative hypnotic**


**3) Vitamin $B_1$(Thiamine) used in thiamine deficiency**



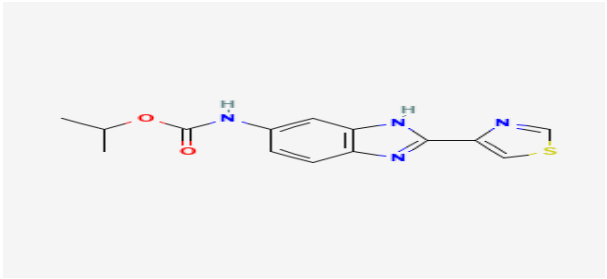

**Thiamine**

## MEDICINAL USES



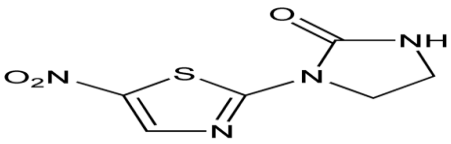
**Sulphathiazole**

**(Anti cancer)**



**Cambendazole**

**(Fungicidal)**



**Niridazole**

**(schistosomicidal)**

## MOLECULAR DOCKING

Molecular docking is a kind of computational modeling, which facilitates the prediction of preferred binding orientation of one molecule (eg. ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex.

## TYPES OF MOLECULAR DOCKING

Comprehensively utilized docking tools employ search algorithms such as

1. GENETIC ALGORITHM
2. FRAGMENT-BASEDALGORITHMS
3. MONTE CAELO ALGORITHMS

4. MOLECULAR DYNAMICS ALGORITHMS

**APPLICATION**

Molecular docking is the need of today's research. It can demonstrate the feasibility of any task, if it carried out before experimental part of any investigation. There are some areas, where molecular docking has revolutionized the findings. In particular, interaction investigations between small molecules (ligand) and protein target (may be an enzyme) may predict the activation or inhibition of enzyme. Such type of information may provide a raw material for the rational drug designing.

**AVAILABLE SOFTWARE FOR DOCKING**

Swissdock (2011)

Flex (1996)

Autodock (1990, 1998)

Slide (2002)

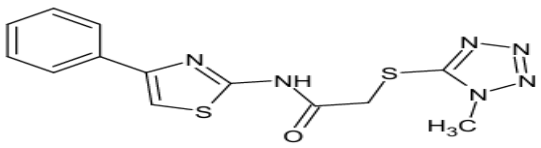
Mcdock (1999)

Sunflex (2003)

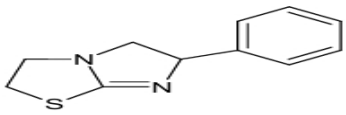
ICM (1994)

**LITERATURE REVIEW**

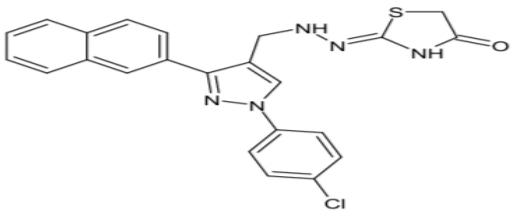
1. Asaf E. Evren et al (2018) New N-(-5 -methyl-4- phenythiazol-2-yl)-2-(substituted thio) acetamides were synthesized and studied for their anticancer activity. The tile compound were procured by reacting 2-chloro-N-(5-methyl-4- phenylthiazole-2-yl) acetamide with some mercapto derivatives.



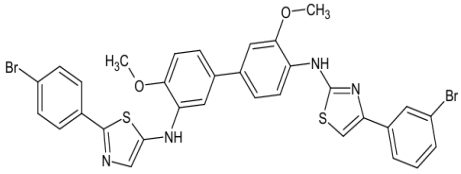

2. Ahmed R. Ali et al (2013) A series of imidazo (2,1-b) thiazoles bearing pyrazole moieties 4-6(a-c) was synthesized through the reaction of 6 -hydrazinylimidazo (2,2-b) thiazoles 3a-c with different β – di-carbonyl compounds.



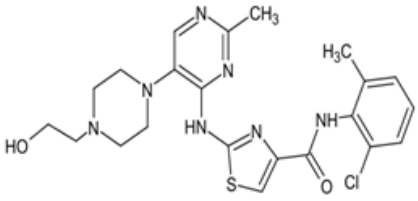
3. Hayam A. Abd EL Salamet. Al (2023) Novel series of heterocyclic compound pairing hybrids pyrazole, naphthalene and pyrazoline/thiazolidine moieties were synthesized. The carbothiamide were used as starting materials for synthesis of a variety of pyrazolylthydrazinyl - thiazole derivatives.



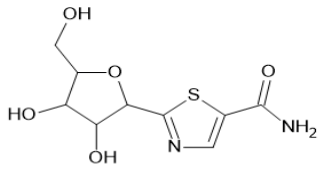
4. G. Turan – Zitouni Edip Temet (2015), synthesis and evaluation of bis-thiazide derivative as new anti-cancer agents. When new bis-thiazole derivative (1-10) were synthesized via ring closure of 1,1-(3,3'-dimethoxybiphenyl-4,4'diyl) bis(thiourea) with phenyl bromide.



5. A.R. Oliveria aval (2021) In this study synthesis, anticancer activity and mechanism of action new phthalimide –1,thiazole derivatives.

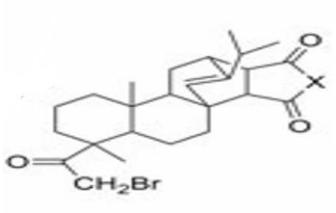


6. Anuradha, et al (2019) In this study computational studies, synthesis and biological evaluation of thiazole based molecules as anti-cancer agents.

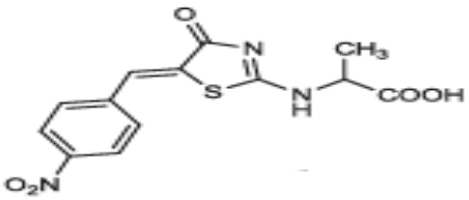



2-[3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3-thiazole-5-carboxamide

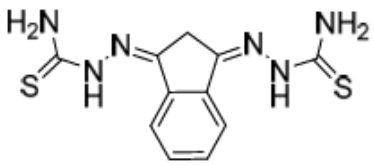
7. Rimma M. Su Hanova, Alexander N. Lobov et al (2019): Synthesis of new 1,8-thiazole derivatives of maleopimaric acid as anticancer, antibacterial and antifungal agents.(Naturalproduct research).



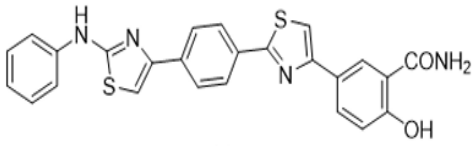

8. D.N Pansare, D.N. Shelke and D.B Shinde et al (2017) A facial systhesis and Anticancer activity of (Z)-2-( (5(4- nitrobenzxlidene) – 0x0 – 4,5 dihydrothiazole -2-yl) amino) – substituted acid (journal of hetrocyclic chemistry).



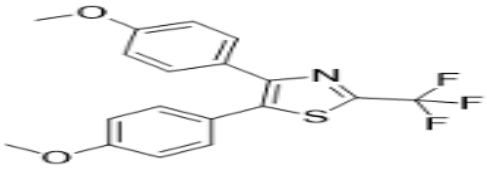

9. Ismail Althagati, Nashwa El- Metwaly and Thorava A. Farghalx et al (2019) New series of thiazole derivative, synthesis, structural Elucidation, Antimicrobial activity, molecular modeling and MOE docking.



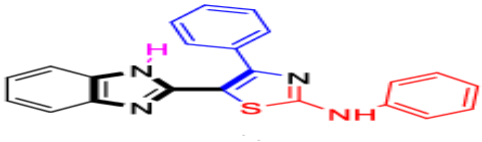

10. Rajitha Sadashiva, Damadara Narai, Jyothi Kudva et al (2017) Synthesis, structure characterization, in vitro and insilico biological evaluation of a new series of thiazole nucleus integrated with pyrazoline scattolds.



11. Mohammed F. Arshad, Aftab Alam, Abdullah Ayed Alshammari, shahamah Jomah. Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents.

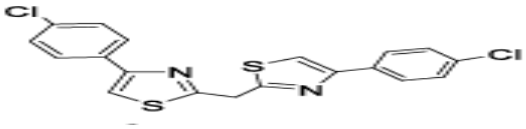


12. Vikas M. Bangade, Prakash R. Mali and Harshades M. Meshram et al (2021) synthesis of potent anticancer substituted 5- Benzimidazole-2-amino thiazole controlled by bifunctional Hydrogen bonding under microwave irradiations.

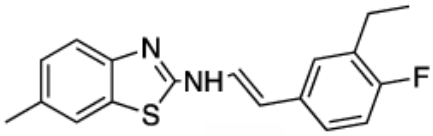


13. Sobhi M Gomba, Hyam A Abdelhady, Doaa Aassin Aboubakr h et al (2021). Thiazole based thiosemi carbazole : synthesis, cytotoxicity evaluvation and molecular docking study.

14. Aisha. Y. Hassan, Marwa. T. Sarg. Ebtehal. M. Husseiny et al (2020). synthesis, characterization and anticancer activity of some Benzo thiazole and thiazole derivatives.




15. Iswatun Hasanah Abdullah Ripain and Nurziana Ngah.et al (2021). A brief review on the thiazole derivative, synthesis methods and biological activities.




**AIM**

Aim of this project is to design and In Silico Investigation of Thiazole Derivatives: Unveiling Anticancer Potential through Molecular Docking.

**OBJECTIVE**

- To select the various scheme by different compound molecule based on the selected nucleus.
- Unfit compounds will be filtered based on the Lipinski rule.
- The elected compounds are involved in the molecular docking.

**MATERIALS AND METHODS**

**A) MOLINSPIRATION**

This software is used to draw the structure and calculate the properties.

**B) SWISSADME**

Swiss ADME software (www.swissadme.ch) from the Swiss Institute of Bioinformatics (http://www.sib.swiss) was used to estimate individual ADME behaviours of compounds from M. oleifera using a web server that shows the Submission page of Swiss ADME in Google. The list is formatted to have one input molecule per line with multiple inputs, as defined by the simplified molecular input line entry system (SMILES), with the results displayed in tables, graphs, and an excel spreadsheet for each molecule (Egan et al., 2000).

**C) SwissDock**

The structure of the target protein, as well as that of the ligand, can be automatically prepared for docking in SwissDock, a docking web server (Bitencourt-Ferreira et al.,2019). The seamless visualisation significantly aids the analysis of docking findings and their incorporation into existing research pipelines. In the UCSF Chimera molecular viewer, which can be launched directly from the web browser. A docking assay can be started in just three steps using SwissDock's web interface: users must identify a protein structure, one or more putative ligands, and docking parameters.

Users are given several sample files that can be directly imported into the form by clicking on a connection. There are also sample output files to go along with it (Grosdidier et al., 2011; Patil et al., 2021).

**D) Target selection**

The structure of a target protein can be calculated by choosing its identifier from the Protein Data Bank or uploading structure files. Users who are unfamiliar with 3D structure files can use the first choice to start a docking assay with just a PDB code. The SwissDock website has a high-quality library of 260 manually curated protein complexes that can be downloaded in the CHARMM format (Patil et al., 2021). Ligand selection: A ligand can be chosen by entering its identifier from the ZINC database or uploading structure files. Users who are unfamiliar with 3D structure files can use the former option to start a docking assay with just a ZINC accession code (AC) (Grosdidier et al., 2011). SMILES (Simplified Molecular Input Line Entry System) is a type of chemical notation that enables a consumer to describe a chemical structure in a computer-readable format. A SMILES alert will appear if the consumer puts too many bonds on an atom, for example, indicating that the arrangement is impossible (Kim et al., 2016).

**E) MOL INSPIRATION**

Mol inspiration is a database of chemical molecules and their biological assay activities. molinspiration is the world's largest repository of publicly available chemical data. Chemicals can be found using their names, molecular formulas, structures, and other identifiers (Kim et al.,2016). Find details on chemical and physical properties, biological activities, protection and toxicity, patents, and literature citations, among other things. SMILES (Simplified Molecular Input Line Entry System) is a type of chemical notation that enables a consumer to describe a chemical structure in a computer-readable format. SMILES is a versatile and easy-

to-learn notation. SMILES of all the 6 phytochemicals are taken from molinspiration. (Kim et al., 2016).

**F) PDB**

The Protein Data Bank (PDB) is a three-dimensional structural data database for large biological molecules including proteins and nucleic acids (Burley et al.,2017). The data, which is usually obtained by X-ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy, and submitted by biologists and biochemists from all over the world, is freely accessible on the Internet through the websites of its member organisations (PDBe, PDBj, RCSB, and BMRB). The Worldwide Protein Data Bank, or wwPDB, is the entity in charge of the PDB. The PDB is crucial in structural biology fields including structural genomics. Scientists are now required to apply their structure data to the PDB by most major scientific journals and some funding agencies. Protein structures deposited in the PDB are used by many other databases. SCOP and CATH, for example, define protein structures, while PDBsum visualises PDB entries using data from other sources, such as Gene Ontology. The 3D structures of all the compounds are taken from Protein Data Bank (Berman et al., 2007).

**Method**

**A) MOLINSPIRATION**

The canonical SMILE identities of the phytochemicals chosen under study were retrieved from molinspiration.

**B) SWISSADME**

The structural and chemical characteristics of the selected compounds as a drug were demonstrated using SwissADME.

**C) PDB**

The enzymes such as, cancer protein p53 (8OXG), were chosen from protein data bank (PDB).

**D) SwissDock**

Each phytochemical was docked with every enzyme to study the bonding capacity and other characteristics of the bonding using SwissDock.

## PLAN OF WORK

Identify the various compound from the articles.

ADME analysis of the compounds by computational process.

Determination of drug-likeness property of the compounds.

Selected compounds for molecular for docking analysis.

Finalize the top hit compounds from the selected compounds.

## RESULT

**Table 1: General properties of the selected compound molecules.**

| Sr. No. | Compound No. | Molecular Formula | Molecular weight (g/mol or Da) |
|---|---|---|---|
| 1. | Compound 1 | C20H21N3O3S2 | 415.53g/mol |
| 2. | Compound 2 | C23H19N3O2S | 401.48g/mol |
| 3. | Compound 3 | C26H19CIFN5OS | 503.98g/mol |
| 4. | Compound 4 | C21H17N3O4S | 407.44g/mol |
| 5. | Compound 5 | C16H12CIN3O2S | 345.80g/mol |
| 6. | Compound 6 | C19H19N5O3S2 | 429.52g/mol |
| 7. | Compound 7 | C18H14F3N3O2S | 393.38g/mol |
| 8. | Compound 8 | C20H21N3O3S2 | 415.53g/mol |
| 9. | Compound 9 | C19H15N5O3 | 361.42g/mol |
| 10. | Compound 10 | C16H11CIN2OS | 314.79g/mol |
| 11. | Compound 11 | C29H36N2O3S | 492.67g/mol |
| 12. | Compound 12 | C20H16N4O2S | 376.43g/mol |
| 13. | Compound 13 | C19H15N7O2S | 405.43g/mol |
| 14. | Compound 14 | C26H19CI2N5O2S | 536.43g/mol |
| 15. | Compound 15 | C16H17CIN8S | 388.88g/mol |

From the compound molecule out of 15 compounds selected in the various scheme only 6 compounds were chosen for the insilico drug designing for the potent drug candidate for cancer. The (table 1) describes the molecular formula, smiles and the molecular weight less than 500 Da which is a key feature that can be referred to compound molecule drug similarity and therefore selected compounds under present study are in the range of required properties and can be considered as ideal drug characteristics.

**Table 2: Physicochemical properties of the selected compound molecules.**

| Sr. No | Small Molecule | Num. heavy atoms | Num. arom. heavy atoms | Fraction Csp3 | Num. Rotatable bonds | Num. H Bond acceptors | Num. H- bond donors | Molar refractivity | TPSA ($^0A^2$) |
|---|---|---|---|---|---|---|---|---|---|
| 1. | Compound 2 | 29 | 21 | 0.17 | 4 | 4 | 1 | 118.50 | 95.73$A^2$ |
| 2. | Compound 5 | 23 | 17 | 0.00 | 4 | 4 | 3 | 94.08 | 105.98$A^2$ |
| 3. | Compound 7 | 27 | 17 | 0.11 | 6 | 7 | 2 | 98.54 | 98.98$A^2$ |
| 4. | Compound 9 | 26 | 17 | 0.05 | 4 | 4 | 1 | 111.91 | 98.19$A^2$ |
| 5. | Compound 13 | 29 | 12 | 0.05 | 5 | 6 | 2 | 125.38 | 136.18$A^2$ |
| 6. | Compound 15 | 26 | 17 | 0.25 | 4 | 5 | 3 | 111.25 | 133.12$A^2$ |

The (Table 2) this section compiles simple molecular and physical parameters such as molecular weight (MW), molecular refractivity (MR), count of heavy atoms and aromatic heavy atoms, flexibility of rotatable bonds , number of hydrogen bond acceptors and number of hydrogen bond donors, fraction of carbon sp3 hybridization and polar surface area (PSA). The PSA is determined using a fragmental technique known as topological polar surface area (TPSA) between 20 and 130 Å2 with polar atoms sulphur and phosphorus. This has shown to be a valuable descriptor in many models and rules for fast estimating some ADME qualities, particularly biological barrier crossing properties like absorption and brain access (Daina et al., 2017).

The classical descriptor for Lipophilicity (Table 3) is the partition coefficient between n octanol and water (log Po/w). Due to the vital importance of this physicochemical property for pharmacokinetics drug development, it has its own area in SwissADME. Many computer approaches for estimating log Po/w have been devised, with varying results on various chemical sets. Multiple predictors are commonly used to pick the best accurate approaches for a chemical series or to achieve consensus estimation. To improve prediction accuracy using consensus log Po/w, the models behind the predictors should be as diverse as possible. In this regard, SwissADME provides access to five freely available predictive models: XLOGP3, an atomistic method with corrective factors and a knowledge-based library; WLOGP, our own implementation of a purely atomistic method based on Wildman and Crippen's fragmental system; MLOGP, an archetype of topological method based on a linear relationship with 13 molecular descriptors implemented; and SILICOS-IT, a hybrid method based on 27 fragments and 7 topological descriptor (http://silicos-it.be.s3-website-eu-west 1.amazonaws.com/software/filter-it/1.0.2/filter-it.html, accessed June 2016); and finally iLOGP, our in-house physics-based method relying on free energies of solvation in noctanol and water calculated by the Generalized-Born and solvent accessible surface area (GB/SA) model. iLOGP was benchmarked on two drug or drug-like external sets and performed

equally as or better than octanol and water calculated by the Generalized-Born and solvent accessible surface area (GB/SA) model. iLOGP was benchmarked on two drug or drug-like external sets and performed equally as or better than six well-established predictors (Mahanthesh et al., 2020). Consensus Log P value is highest (3.47) for compound 2 and lowest (1.99) for compound 13. Such high lipophilic nature of compound 2 is suggestive of its enhanced efficacy as a transdermal drug. compound would not show much effect as an oral drug as its ability to cross cell membrane is significantly low.

**Table 3: Lipophilicity properties of the selected compound molecules.**

| Sr. No. | Small Molecule | iLOGP | XLOGP3 | WLOGP | MLOGP | SILICOSIT | Consenusus Log *P* o/w |
|---|---|---|---|---|---|---|---|
| 1. | Compound 2 | 3.47 | 5.77 | 5.05 | 2.80 | 6.54 | 4.73 |
| 2. | Compound 5 | 2.49 | 4.48 | 4.13 | 2.23 | 4.39 | 3.54 |
| 3. | Compound 7 | 2.84 | 5.06 | 5.95 | 2.81 | 5.35 | 4.40 |
| 4. | Compound 9 | 2.76 | 4.27 | 3.05 | 2.02 | 4.42 | 3.30 |
| 5. | Compound 13 | 1.94 | 4.37 | 1.20 | 1.24 | 3.02 | 2.35 |
| 6. | Compound 15 | 3.00 | 2.96 | 1.63 | 0.98 | 2.19 | 2.15 |

**Table 4: Water Solubility of the selected compounds.**

| Sr. no. | Selected molecule | ESOL | | | | ALI | | | | SILICOS-IT | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LOG S (ESOL) | Solubility | | class | Log S (ESO L) | Solubility | | Class | Log S (ESO L) | Solubility | | Class |
| | | | Mg/ml | Mol/L | | | mg/m L | mol/ L | | | mg/m L | mol/ L | |
| 1. | Compound 2 | -6.24 | 2.33e-04mg/ml | 5.81e-07mol/l | Moderately soluble | -7.55 | 1.3e-05mg/ml | 2.82e-08mol/l | Moderately soluble | -8.72 | 7.72e-07mg/ml | 1.92e-09mol/l | Moderately soluble |
| 2. | Compound 5 | -5.09 | 2.82e-03mg/ml | 8.14e-06mol/l | Moderately soluble | -6.43 | 1.30e-04mg/ml | 3.75e-07mol/l | Moderately soluble | -5.90 | 4.32e-04mg/ml | 1.25e-06mol/l | Moderately soluble |
| 3. | Compound 7 | -5.54 | 1.14e-03mg/ml | 2.91e-06mol/l | Moderately soluble | -6.80 | 6.28e-05mg/ml | 1.60e-07mol/l | Moderately soluble | -6.84 | 5.69e-05mg/ml | 1.45e-07mol/l | Moderately soluble |
| 4. | Compound 9 | -4.99 | 3.69e-03mg/ml | 1.02e-05mol/l | Moderately soluble | -6.04 | 3.26e-04mg/ml | 9.03e-07mol/l | Moderately soluble | -6.84 | 5.20e-05mg/ml | 1.44e-07mol/l | Moderately soluble |
| 5. | Compound 13 | -5.08 | 3.35e-03mg/ml | 8.26e-06mol/l | Moderately soluble | -6.95 | 4.59e-05mg/ml | 1.13e-07mol/l | Moderately soluble | -6.34 | 1.85e-04mg/ml | 4.56e-07mol/l | Moderately soluble |
| 6. | Compound 15 | -4.34 | 1.80e-02mg/ml | 4.62e-05mol/l | Moderately soluble | -5.42 | 1.48e-03mg/ml | 3.82e-06mol/l | Moderately soluble | -5.95 | 4.37e-04mg/ml | 1.12e-06mol/l | Moderately soluble |

Many aspects of drug research are considerably aided by having a soluble molecule, particularly handling and formulation. Furthermore, for oral administration discovery efforts, solubility is a key factor determining absorption (Table 4). A medicine intended for parenteral administration must also be highly soluble in water in order to deliver a sufficient amount of active component in the tiny volume of such a pharmaceutical dosage. SwissADME includes two topological approaches for predicting water soluble. The first is based on the ESOL model, whereas the second is based on Ali et al work. Both are distinct from the fundamental universal solubility equation in that they do not include the melting point parameter, which is difficult to estimate. In addition, they show a significant linear relationship between anticipated and experimental values (R2=0.69 and 0.81, respectively). SILICOS-IT created the SwissADME third predictor for solubility. This fragmental technique corrected by molecular weight has a linear correlation coefficient of R2= 0.75 (http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html, accessed June 2016). The decimal logarithm of the molar solubility in water is used to calculate all projected values (log S). Solubility in mol/l and mg/ml, as well as qualitative solubility classes, are also available from SwissADME. SwissADME estimates solubility (log S) utilizing two approaches (topological and fragmental), with a value of -10 and below deemed insoluble and a value of -4 and above regarded soluble (Diana et al., 2017).

**Table 5: Pharmacokinetic Properties of the selected compounds.**

| Sr.no. | Small Molecule | GI absorption | BBB permeant | P-gp substrate | CYP1 A2 inhibit or | CYP2 C19 inhibit or | CYP2 C9 inhibit or | CYP2 D6 inhibit or | CYP3 A4 inhibit or | Log Kp (cm/ s) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | Compound 2 | High | No | No | Yes | Yes | Yes | No | Yes | -4.65cm/s |
| 2. | Compound 5 | High | No | No | Yes | Yes | Yes | No | Yes | -5.23cm/s |
| 3. | Compound 7 | High | No | No | Yes | Yes | Yes | No | Yes | -5.11cm/s |
| 4. | Compound 9 | High | No | No | Yes | Yes | Yes | No | Yes | -5.47ccm/s |
| 5. | Compound 13 | High | No | No | No | No | Yes | No | No | -5.67cm/s |
| 6. | Compound 15 | High | No | Yes | Yes | No | Yes | No | Yes | -6.57cm/s |

Various ADME behaviours of the chemical under research are evaluated using specialised models, the predictions of which are summarised in the Pharmacokinetics part. A multiple linear regression model is one that seeks to predict the skin permeability coefficient (Kp). Kp was discovered to be linearly associated with molecular size and lipophilicity (R2=0.67) by Potts and Guy. The lower the log Kp (in cm/s), the less permeant the molecule is to the skin. Both passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation predictions are based on the readout of the BOILED-Egg model, an intuitive graphical classification model that can be viewed in the SwissADME result page by clicking the red button below the sketcher once all input molecules have been processed. Other binary classification models are offered, which rely on a small molecule's proclivity to be a substrate or inhibitor of proteins that control essential pharmacokinetic behaviours. The ability to assess active efflux through biological membranes, such as from the gastrointestinal wall to the lumen or from the brain, requires knowledge of compounds that are substrate or non-substrate of the permeability glycoprotein (P-gp, suggested as the most important member among ATP-binding cassette transporters or ABC-transporters). P-gp has a number of functions, one of which is to protect the central nervous system (CNS) from xenobiotics. P-gp is also overexpressed in some tumour cells, resulting in multidrug-resistant malignancies (Mahanthesh et al.,2020). (Table 5) The pharmacokinetics and drug similarity studies utilising SwissADME revealed that the selected compounds 2,5,7,9,13 and 15 have high GI absorptionteh selected compounds 2,5,7,13 and 15 are not BBB permeant, and none of the compounds are P-gp substrates which require a P gp for absorption in the body, all of the selected compounds under consideration can be utilised to easily target specific enzymes for their therapeutic impact without P-gp binding.

**Table 6: Drug-likeness and Bioavailability score of the selected compounds.**

| Sr. No. | Small molecules | Lipinski | Ghose | Veber | Egan | Muegge | Bioavailability score |
|---|---|---|---|---|---|---|---|
| 1. | Compound 2 | Yes; 0 violation | Yes | Yes | Yes | No;1 violation XLOGP3>5 | 0.55 |
| 2. | Compound 5 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| 3. | Compound 7 | Yes; 0 violation | No; 1 violation: WLOGP>5.6 | Yes | No; 1 violation: WLOGP>5.88 | No; 1 violation: XLOGP3>5 | 0.55 |
| 4. | Compound 9 | Yes; 0 violation | Yes | Yes | Yes | Yes | 0.55 |
| 5. | Compound 13 | Yes; 0 | Yes | Yes | No; 1 | Yes | 0.55 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | violation | | | violation: TPSA>131.6 | | |
| 6. | Compound 15 | Yes; 0 violation | Yes | Yes | No; 1 violation: TPSA>131.6 | Yes | 0.55 |

As previously stated, "drug-likeness" evaluates the likelihood of a molecule becoming an oral drug in terms of bioavailability. Structure or physicochemical inspections of research compounds progressed enough to be deemed oral drug candidates were used to determine drug-likeness. This concept is frequently used to filter chemical libraries in order to eliminate compounds having features that are most likely incompatible with a good pharmacokinetics profile. This SwissADME section provides access to five rule-based filters that cover a wide variety of attributes and determine if a molecule is drug-like. These filters are frequently derived from studies conducted by big pharmaceutical firms to improve the quality of their proprietary chemical collections (Mahanthesh et al.,2020). The Lipinski (Pfizer) filter was the first rule-of-five filter, and it was adapted by the Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) systems. Multiple estimations allow for consensus views or the selection of methodologies that best suit the end-needs user's in terms of chemical space or project-related demands. Any infringement of any of the rules outlined above is highlighted in the output panel. Out of the five filters Lipinski (Pfizer) filter and the Veber (GSK) filter showed Yes for all the selected compounds from different scheme. The Ghose (Amgen) filter and Muegge (Bayer) filter showed Yes for all the selected compounds.The bioavailability scores for all the above mentioned compound was 0.55.

**Table 7: Medicinal Chemistry of the selected compounds.**

| Sr. No. | Small molecule | PAINS | Brenk | Lead Likeness | Synthetic accessibility |
|---|---|---|---|---|---|
| 1. | Compound 2 | 0 alert | 1 alert: imine_1 | No; 2 violations: MW>350, XLOGP3>3.5 | 3.85 |
| 2. | Compound 5 | 0 alert | 1 alert: imine_1 | No; 1 violation: XLOGP3>3.5 | 3.02 |
| 3. | Compound 7 | 0 alert | 1 alert: imine_1 | No; 2 violations: MW>350, XLOGP3>3.55 | 3.22 |
| 4. | Compound 9 | 0 alert | 1 alert: imine_1 | No; 2 violations: MW>350, XLOGP3>3.5 | 3.67 |
| 5. | Compound 13 | 0 alert | 1 alert: imine_1 | No; 2 violations: MW>350, XLOGP3>3.5 | 4.19 |

| | | | | | |
|---|---|---|---|---|---|
| 6. | Compound 15 | 0 alert | 0 alert | No; 1 violation: MW>350 | 3.09 |

This section is designed to assist medicinal chemists in their daily drug development efforts. The detection of possibly troublesome segments is possible thanks to two complementary pattern recognition approaches. PAINS (pan assay interference chemicals, also known as frequent hitters or promiscuous compounds) are molecules with substructures that respond potently in assays regardless of the protein target. Baell et al. identified such fragments, which result in false positive biological output, by analysing six orthogonal assays and breaking down the molecules active on two or more assays into 481 recurring fragments, which are thought to lead to promiscuous chemicals. If such moieties are detected in the molecule being evaluated, SwissADME issues a warning. One of the most important components of CADD's work is assisting in the selection of the most promising virtual molecules to be synthetized and tested in biological assays or other investigations. In this selection procedure, synthetic accessibility (SA) is a crucial issue to consider. Clearly, medicinal chemists are the best at determining SA for a reasonable number of compounds. None of the selected compounds in the SwissADME interpretation have a PAINS signal. All the selected phytochemicals in SwissADME interpretation did have a Brenk signal exceptcompound 15. Out of the 6 selected compounds showed lead likeness. All the compounds of slected from various scheme expressed and followed the filtered rule invoked in the SwissADME, the violations shown by the molecules are minimal and the SwissADME interpretation did not post any PAINS alert of any of the molecules (Ranjith, D., & Viswanath, S. 2019).

**Table 8: Molecular Docking of selected compounds against Target Proteins using SwissDock.**

| Sr. No. | Selected compound | 8OXG (kcal/mol) |
|---|---|---|
| 1. | Compound 2 | - 8.462 |
| 2. | Compound 5 | - 7.133 |
| 3. | Compound 7 | - 7.180 |
| 4. | Compound 9 | - 7.689 |
| 5. | Compound 13 | - 8.016 |
| 6. | Compound 15 | - 7.072 |

Table (8) shows the molecular docking of the selected compounds such as compounds 2,5,7,9,13,15 with protein targets such as cancer protein p53 (8OXG), were chosen from protein data bank (PDB) by using SwissDock to explore their potential to be used as drugs for cancer treatment. The selected compounds 2,5,7,9,13,15 has shown greater affinity with the

selected protein targets at their catalytic sites and hence they can be taken into consideration for potential drug candidates.

## CONCLUSION

CADD has drastically reshaped research and development routes in drug candidate identification due to the rapid rise in biological and chemical information. In terms of implementation, time, and money, the use of computational techniques in the drug discovery and development process is frequently praised. In this work, a publicly available web-based application called SwissADME was used to assess the ADME qualities of selected compounds found in the different schemes and to analyze potential drug candidates for cancer treatment.

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