COMPARATIVE ANALYSIS OF ADME PROPERTIES OF THE FDA APPROVED CHRONIC MYELOGENOUS LEUKEMIA DRUGS AND ITS TARGET PREDICTION

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Abstract: Chronic myelogenous leukemia (CML) is a very rare type of cancer of the bone marrow. CML generally affects older people and infrequently occurs in young adults. Approximately 15% of all leukemia are CML. Major risk factors of CML are being older, being male, and being exposed to radiation. The pace of research on the treatment of CML is rapid, and multiple drugs have been approved in the past decade. All the approved drugs work very well and the survival rates are unceasingly measured with the newer medications.

Methodology – A comprehensive study was performed by utilizing various Bioinformatics web tools. The list of FDA Approved CML drugs were retrieved from the National Cancer Institute: Comprehensive Cancer Information website. The canonical smiles of each drug were retrieved from PubChem and Swiss ADME an online software that was used to analyze the pharmacokinetic properties of each drug candidate. Further Swiss Target Prediction tool was used to predict the most probable targets of the drug.

Result – Our study succeeded in identifying the best drug candidate among the FDA-approved CML drugs by comparatively analyzing the pharmacokinetic properties of each of the CML drugs.

Index Terms **- Chronic myelogenous leukemia, PubChem, Swiss ADME, Swiss Target Prediction, pharmacokinetic properties.**

I. INTRODUCTION

Chronic myelogenous leukemia also called chronic granulocytic leukemia or chronic myeloid leukemia is a clonal myeloproliferative condition that develops when a single pluripotent hematopoietic stem cell gains the Philadelphia chromosome.[1] According to the GLOBACAN 2020 statistics, the global incidence of leukemia is approximately 4.7 lakhs the mortality rate is 3.2 lakhs and the 5-year prevalence rate is said to be around 13 lakhs. 15% of all leukemia are chronic myelogenous leukemia. CML was first recognized in 1845 and since then it is said to exhibit a constant chromosomal abnormality in the leukemic cells. It was first identified by Nowell and Hungerford in 1960 and was named as Philadelphia (Ph) chromosome.[2] Almost 95% of patients affected with CML are said to contain the Philadelphia chromosome. In CML, a part of chromosome 9 detaches and binds to chromosome 22, and forms the Philadelphia chromosome. The Philadelphia chromosome consists of 2 major genes called the BCR gene and ABL gene, which combine and form a single gene called BCR-ABL. BCR-ABL a chimeric oncogene is responsible for the transformation of the hematopoietic cell lines. BCR-ABL gene is only found in the blood-forming cells, and not in any other organ. The BCR-ABL gene triggers the myeloid cells to produce enzymes like tyrosine kinase enzyme, which are abnormally activated. These activated enzymes are called fusion proteins and these fusion proteins are responsible for the uncontrollable growth of white blood cells.[3][4]

CML has the capability of expanding into lymphoid or myeloid lineages and can also involve in the myeloid, erythroid, B-lymphoid, monocytic, megakaryocytic, and rarely in lymphoid lineages. But the main expansion occurs in the granulocyte of the myeloid lineage in the bone marrow.[5]

Based on the number of blast cells in the bone marrow and the blood and the severity of the symptoms CML can be majorly classified into three phases: chronic phase accelerated phase and blast phase.[6] The chronic phase is a stable initial phase where there are less than 10% of peripheral blood blasts in the bone marrow and the blood. It is the earliest phase and can be easily treated.[7][8] The accelerated phase is where there are 10-19% blasts of WBCs in the nucleated and peripheral bone marrow cells. There is determined thrombocytopenia or thrombocytosis and the patients do not respond to the treatment due to the spleen size increasing WBC count. It is also called the transitional phase where cancer progresses aggressively.[9] The last phase is the blast phase/crisis. In this phase, the blasts cells are greater or equal to 20% of WBCs in the nucleated and peripheral bone marrow cells. There is a development of extramedullary blast proliferation and a large cluster of blasts can be observed on bone marrow biopsy. This phase is the most aggressive and severe and can be life-threatening.[10]

A maximum number of patients with CML are asymptomatic and are diagnosed accidentally while testing their blood or doing a complete blood count for other illnesses. Symptoms of the chronic phase include splenomegaly, anemia, thrombocytopenia, thrombocytosis, basophilia, and gastrointestinal ulcers. Symptoms of the accelerated and blast phase include bone pain, joint pain, infections, headaches, fever, and lymphadenopathy.[11] The patients receive treatment based on the phase they are diagnosed. Commonly administered treatments include Tyrosine kinase inhibitor, [12] high dose and low dose chemotherapy along with donor stem cell transplant, BRM-interferon, and splenectomy.[13] CML is the most common type of leukemia in adults, various advancements novel treatment strategies have helped patients with good prognoses. However, diagnosing patients affected with CML might be challenging due to cryptic translocations and asymptomatic conditions.[14] Hence coordinating amongst interprofessional teams which involve, pharmacists, nurses, specialists, and primary care providers can result in a successful diagnosis, treatment, and care for patients affected with CML.

II. MATERIALS AND METHODS

Data and Sources of Data

The list of FDA Approved CML drugs were retrieved from the National Cancer Institute (https://www.cancer.gov/) website. This website is part of the National Health Organization and is a leading institution that conducts cancer research and education with a powerful motive to help people live longer with a healthier lifestyle. This website provides a comprehensive list of all the FDA-approved cancer drugs for different types of cancer and cancer-related conditions. A total of FDA Approved CML drugs were retrieved which includes:

Bosulif, Busulfan, Cyclophosphamide, Cytarabine, Dasatinib, Dexamethasone, Gleevec (Imatinib Mesylate), Hydrea (Hydroxyurea), Iclusig (Ponatinib Hydrochloride), Nilotinib, and Omacetaxine Mepesuccinate.

Analysis of Pharmacokinetic Properties

The absorption, distribution, metabolism, and excretion properties of each of the drugs were comparatively analyzed using the Swiss ADME webtool. The canonical SMILES of each drug was retrieved from PubChem (http://www.swissadme.ch/) a public repository webpage that contains free and accessible chemical information. The retrieved canonical SMILES were inputted into the Swiss ADME (http://www.swissadme.ch/) webtool, and the ADME parameters were tabulated. Comparative analysis of the tabulated data was performed to evaluate the drugs. The different pharmacokinetic parameters used in the study include:

1) **Molecular Weight (MW):** Molecular weight is the sum of the atomic masses of the atoms that make up the molecule. The molecular weight of a drug can be used to create various microstructures with explicit transport properties.

2) **Water Solubility (ESOL):** A drug's solubility in water is a significant parameter used for determining a drug's bioavailability. A positive ESOL value specifies a high solubility of the drug and a negative ESOL value specifies a low solubility of the drug.

3) **H-bond Donor and H-bond acceptor:** Hydrogen bonds play an important role in determining the ligand-binding site and are an important parameter to be considered during drug design.

4) **Number of Rotatable Bonds:** The number of rotatable bonds in a drug is a significant parameter to determine the drug's bioavailability. The drug with greater rotatable bonds will have the highest bioavailability.

5) **Number of Aromatic Heavy Atoms:** Aromatic rings are extensively used for developing several new drug candidates. Drugs having less than 3 aromatic rings are considered to be desirable.

6) **Log$P$ (iLog$P$):** The Log$P$ value determines the permeability of the drug in the target tissue and guides in selecting the correct drug delivery system to the targeted site. Log$P$ is a constituent of Lipinski's rule of 5 which signifies the lipophilicity of a drug. A positive Log$P$ value signifies an increased affinity towards the lipid phase, a negative Log$P$ value signifies an increased affinity for the aqueous phase, and the Log$P$ value zero signifies that there is an equal partition between the aqueous and lipid phase.

7) **Lipinski rule of 5:** The Lipinski rule of 5, developed by Lipinski and his co-workers is a guide to access the success rate of the drug that complies with two or more of the 4 Lipinski rules. The 4 Lipinski rules are 1. The molecular weight of the drug must be less than 500 Daltons, 2. The H-bond acceptors of a drug must be less than 10, 3. The H-bond donors of a drug must be less than 5 and the Log$P$ value of a drug should be less than 5.

8) **Lipophilicity (XLOGP3):** Lipophilicity is the ability of a drug to permeate the lipid cell membrane and reach the target site. The drug with greater lipophilicity will have a greater absorption rate.

9) **Synthetic Accessibility:** It is a measure of the degree of difficulty for synthesizing a drug. The drug with a score of 1 is said to be easily synthesized and the drug with a score of 10 is said to be difficult to synthesize.

10) **GI Absorption:** Drug absorption is mainly by passive diffusion. The small intestine in the GI tract is the place where most of the drug is absorbed. For the maximum bioavailability of the drug, a balance of hydrophilicity and lipophilicity of the drug is preferred. Lipophilicity, drug polarity, and the molecular size of the drug are the three factors that affect drug permeability.

11) **Blood-Brain Barrier:** This parameter indicates the ability of the drug to cross the blood-brain barrier, which is a selective semipermeable membrane that prevents solutes from entering the central nervous system. Only small molecules with a molecular weight of fewer than 400 Daltons pass through the BBB. The majority of the drugs permeate through the BBB via a transmembrane diffusion mechanism.

Estimation of Probable Macromolecular Targets

After the comparative analysis of the 11, FDA Approved CML drugs, the 2 most effective drugs that satisfy most of the ADME parameters were selected and the target prediction for both the drugs was performed using the Swiss Target Prediction webtool. Swiss Target Prediction web tool is used for the estimation of the most probable macromolecular targets of the drugs. The canonical SMILES of the two drugs were inputted into the Swiss Target Prediction webtool and the results were tabulated. The properties of the webtool include:

1) **Target:** The target parameter has a target score of 0 to 1, and the highest possible value is achieved if the drug is known to the target ligand. This score is used to determine the desired or highest probability ranking.

2) **Common Name:** Common name is an abbreviation for the target.

3) **Target Class:** The target class column signifies the most specific/precise target class for the drug.

4) **Probability:** The green colored bar is the probability that the protein is the target of the interrogated molecule, which is considered bioactive. A value of 1 signifies that the actual query molecule is known to be active.

III. RESULTS
The different physiological properties procured for each drug candidate are plotted into a bar graph and are subjected to comparative analysis.
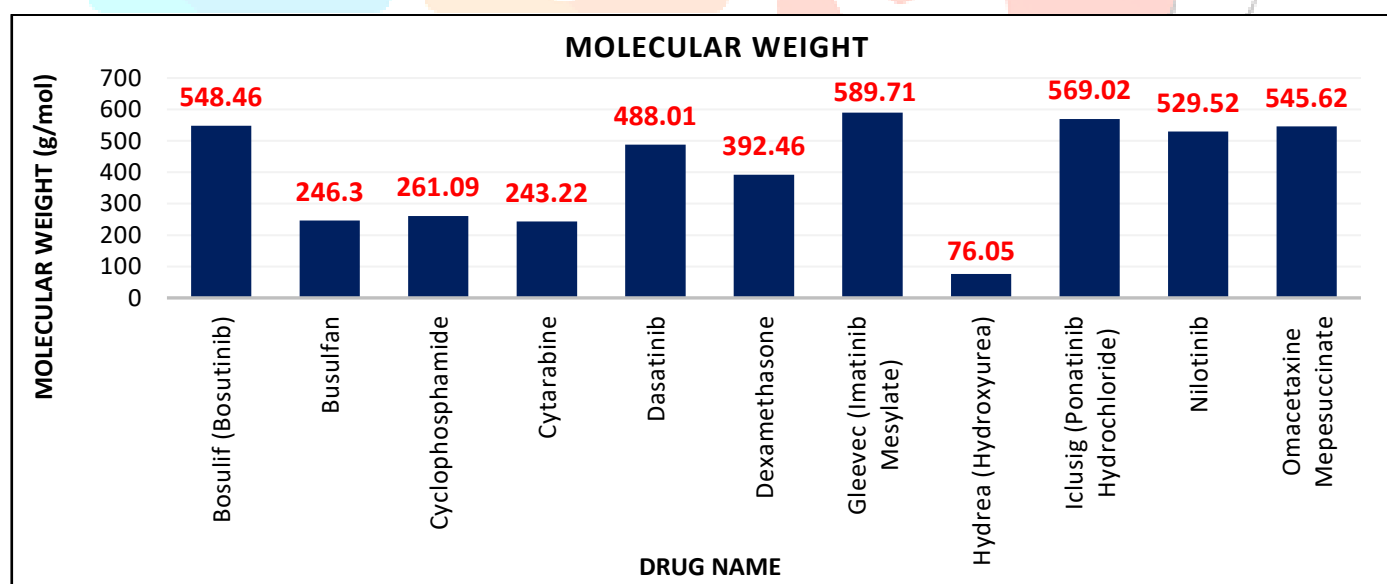

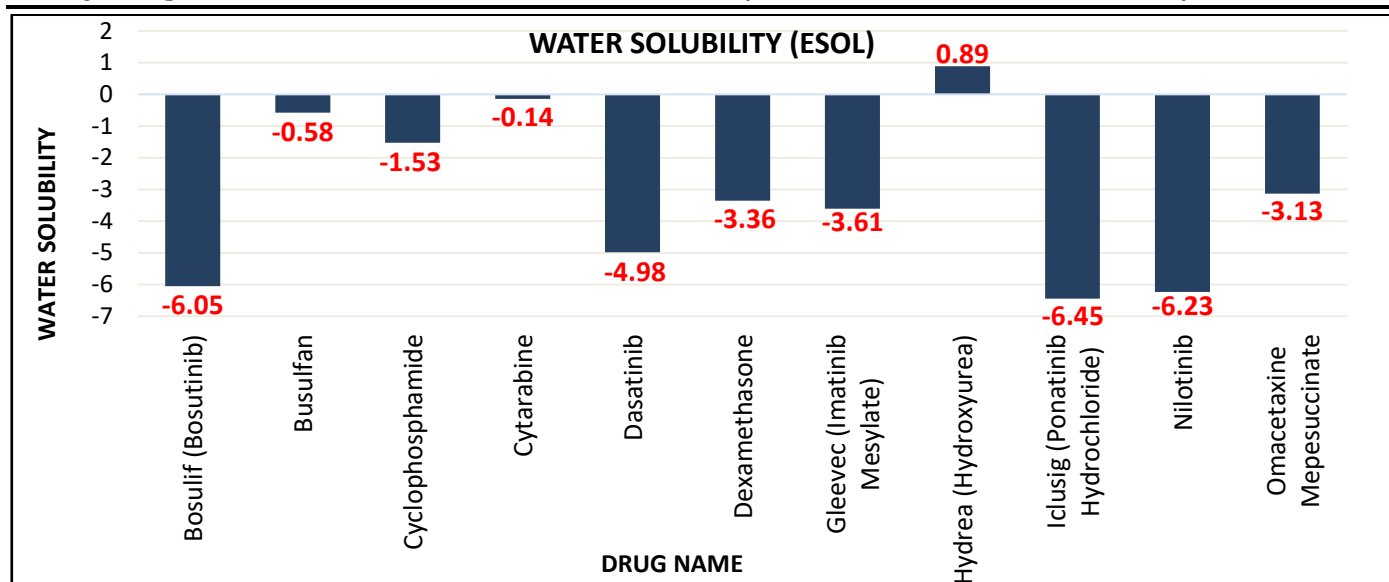**Figure 1:** Bar graph depicting the Molecular weights of the query drugs

Figure 2: Bar graph depicting the Water Solubility values of the query drugs.
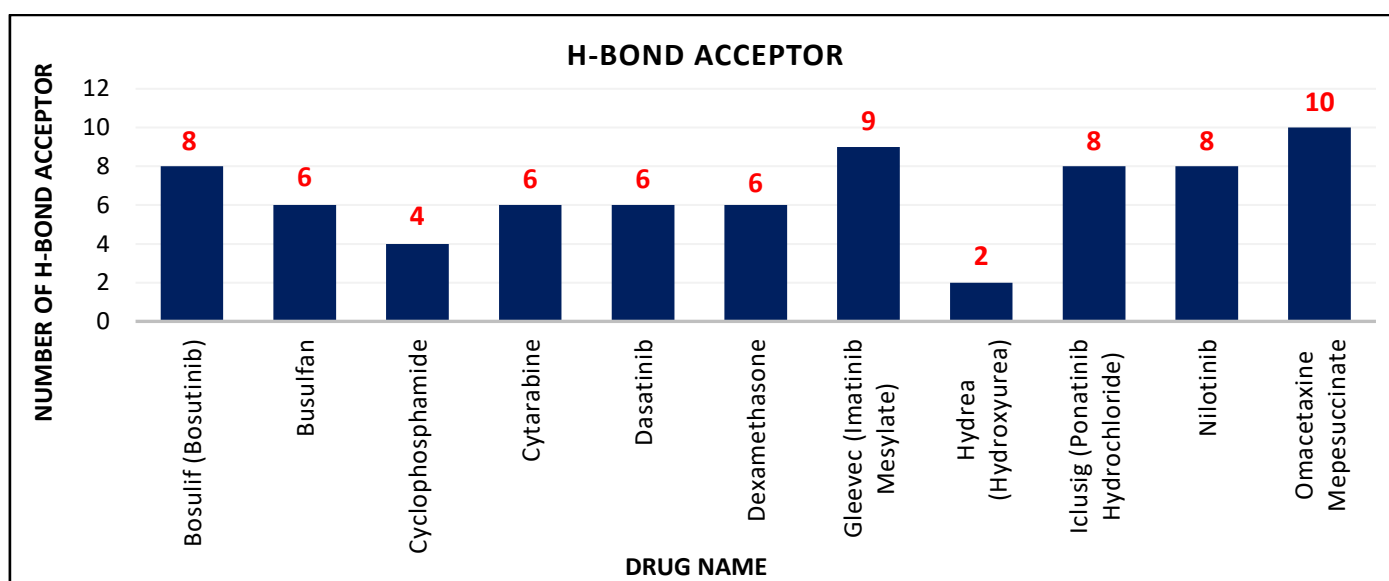

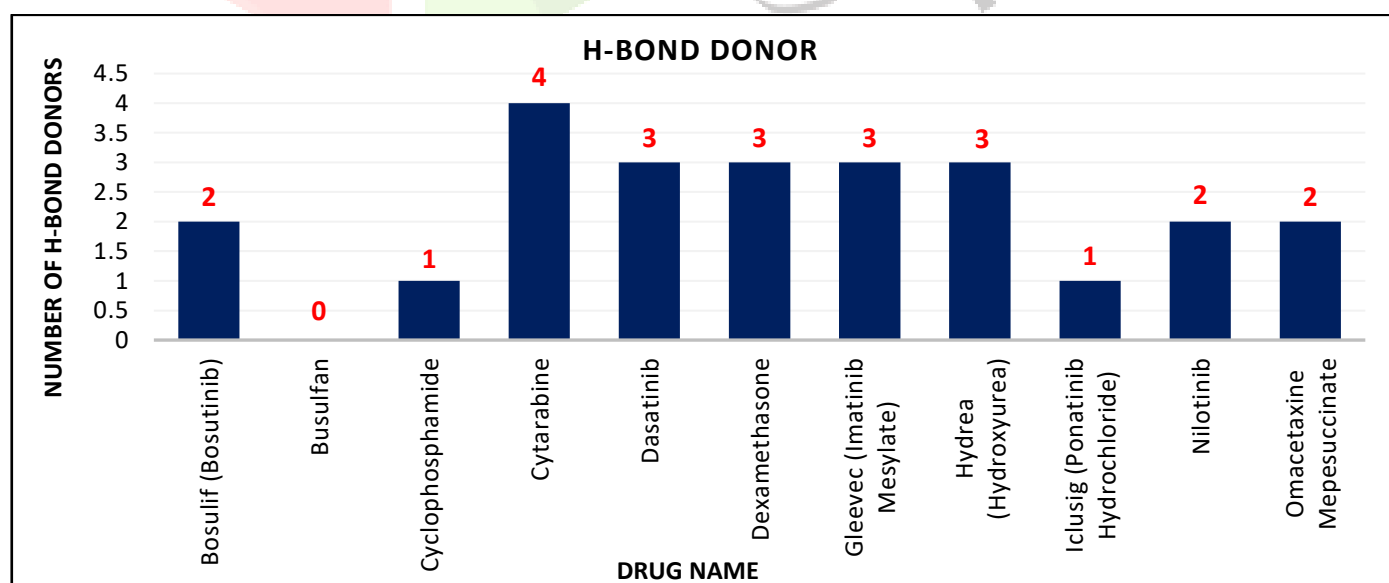**Figure 3:** Bar graph depicting the number of H-Bond acceptors of the query drugs.

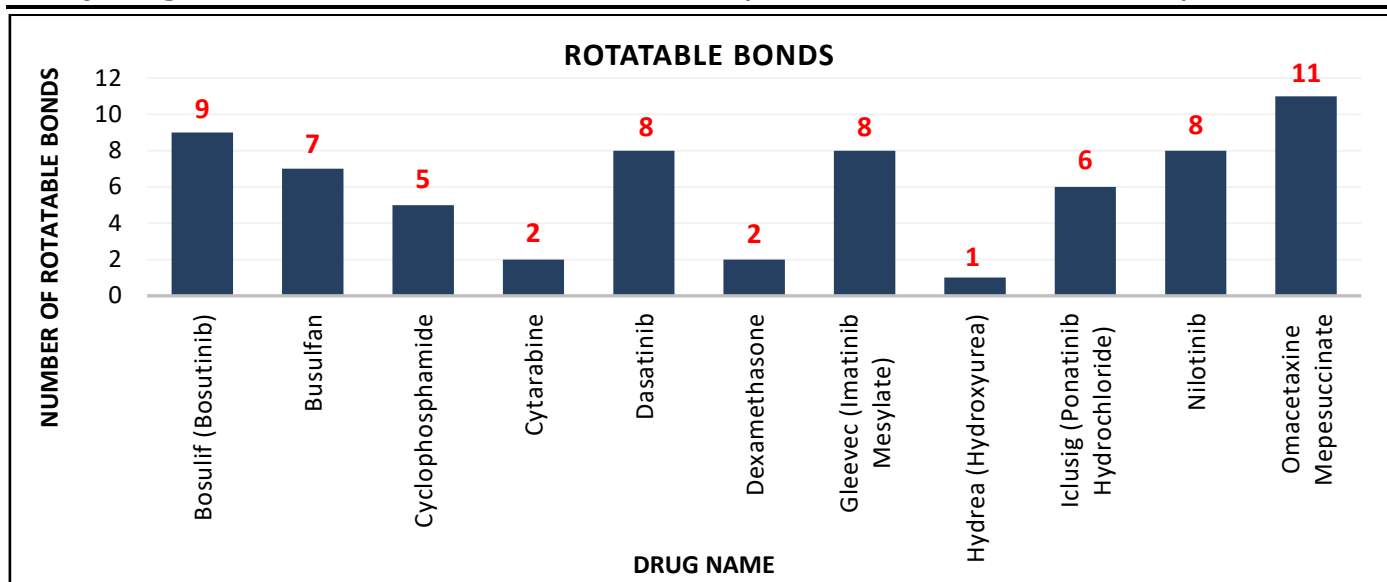**Figure 4:** Bar graph depicting the number of H-bond donors of the query drugs.

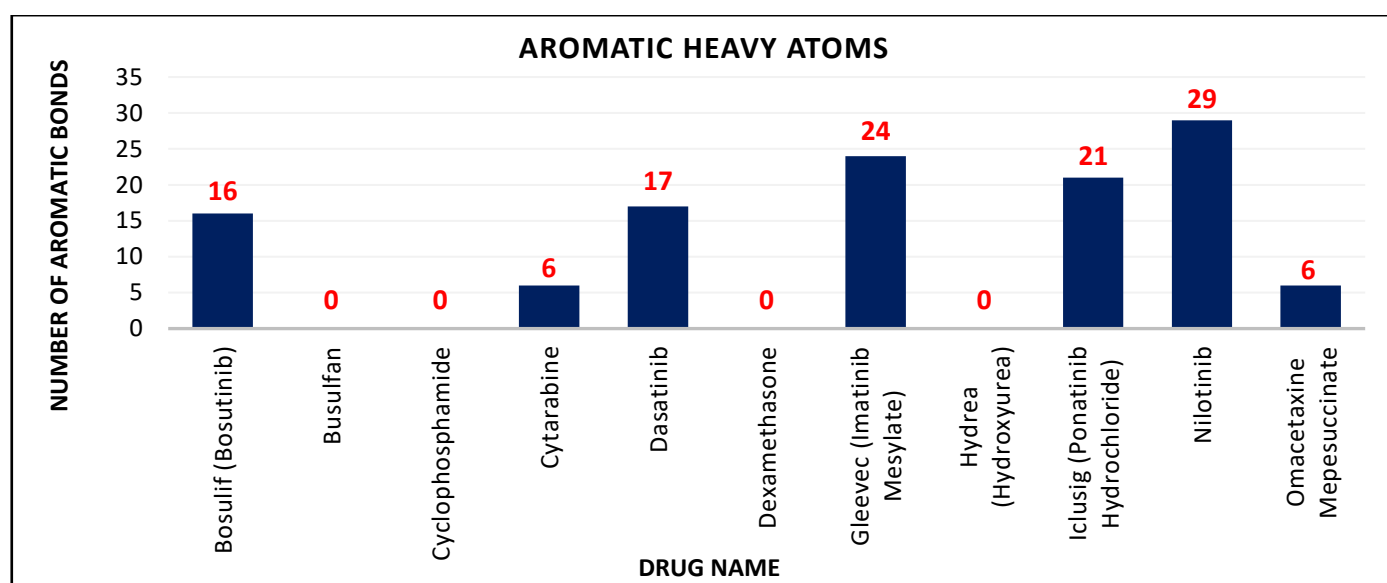**Figure 5:** Bar graph depicting the number of Rotatable bonds of the query drugs.

Figure 6: Bar graph depicting the number of Aromatic heavy atoms of the query drugs.
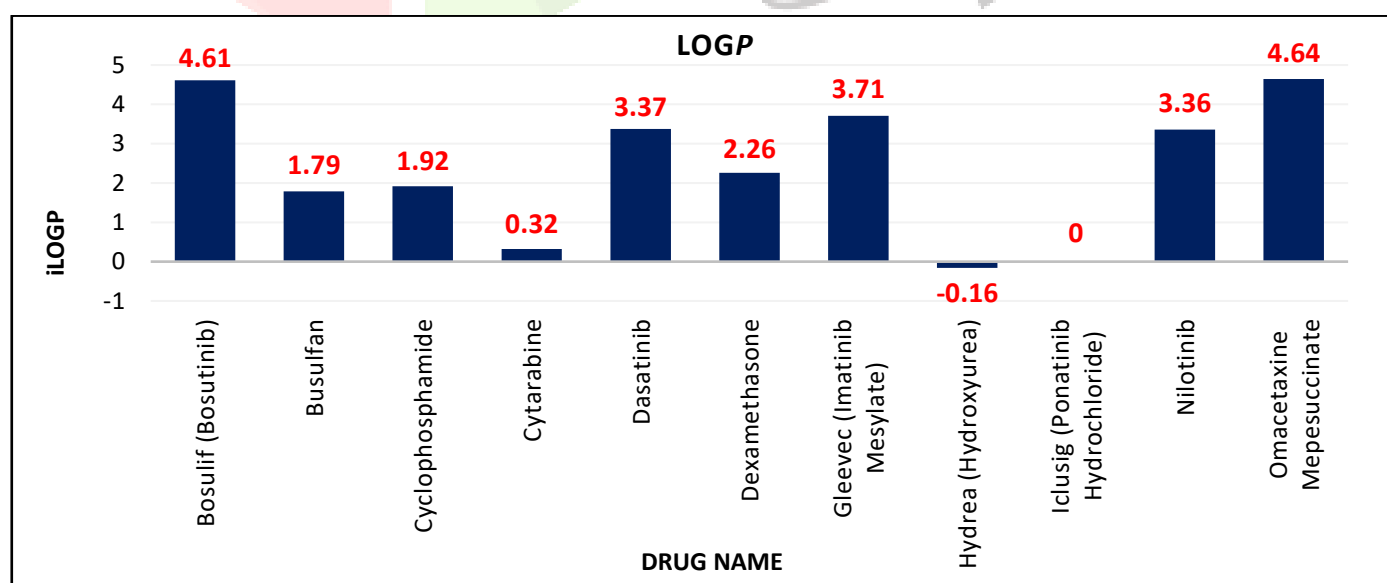

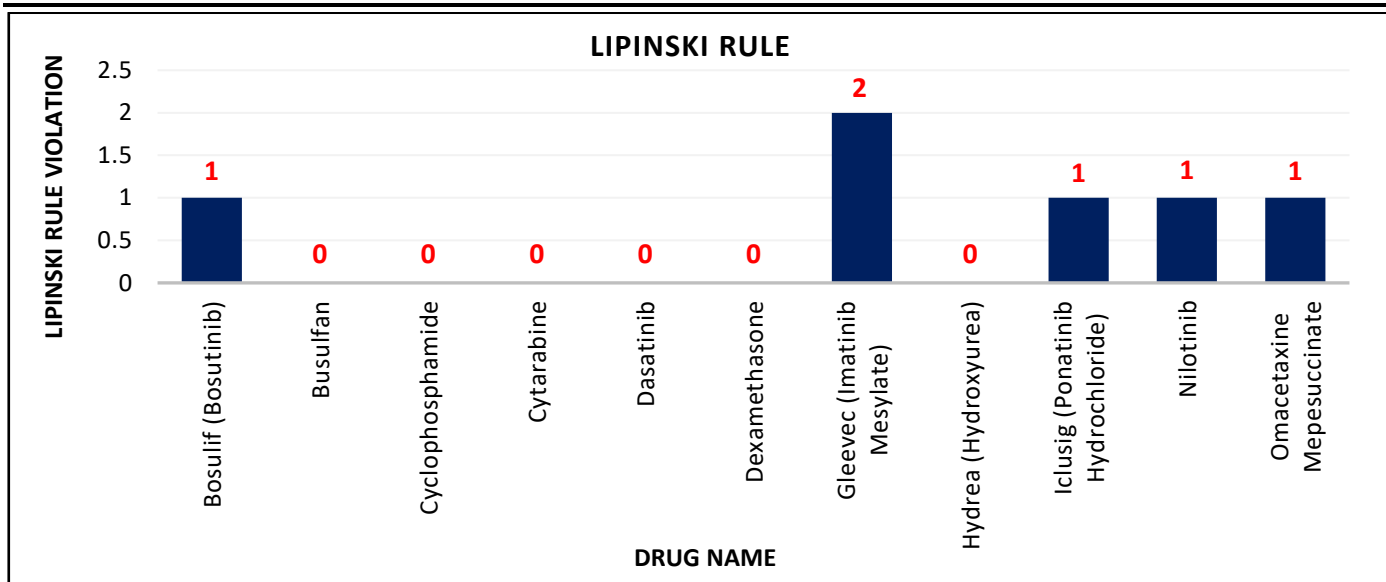**Figure 7:** Bar graph depicting the Log P values of the query drugs.

Figure 8: Bar graph depicting the number of Lipinski violations exhibited by the query drugs.
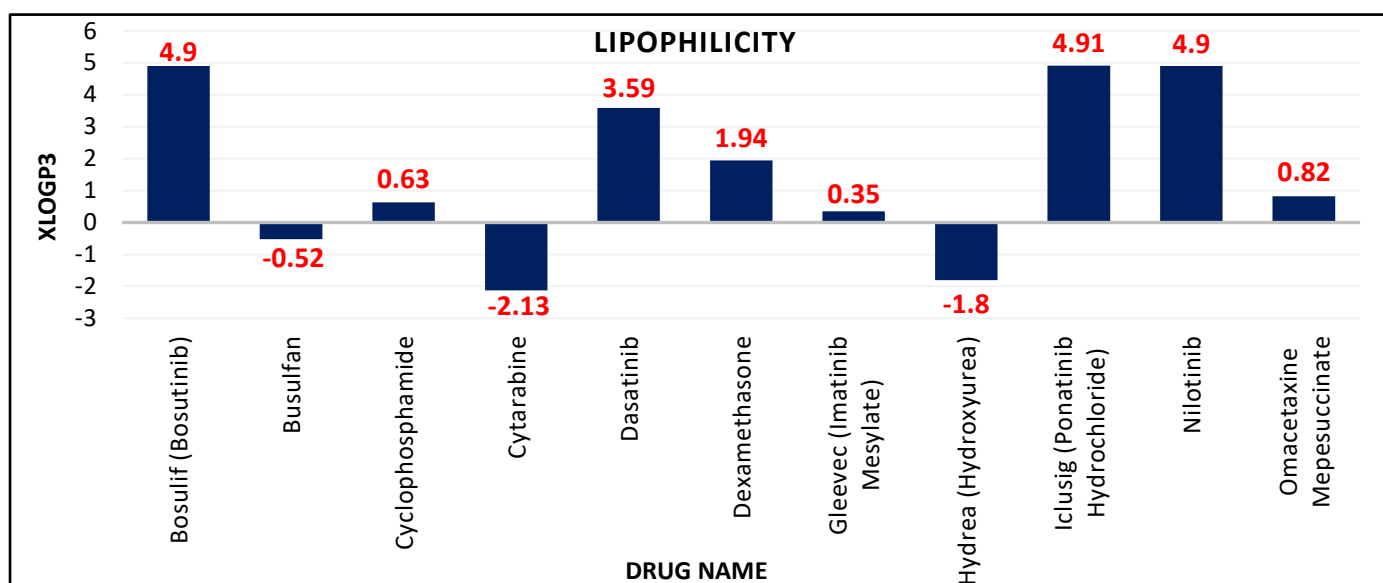

Figure 9: Bar graph depicting the Lipophilicity values of the query drugs.
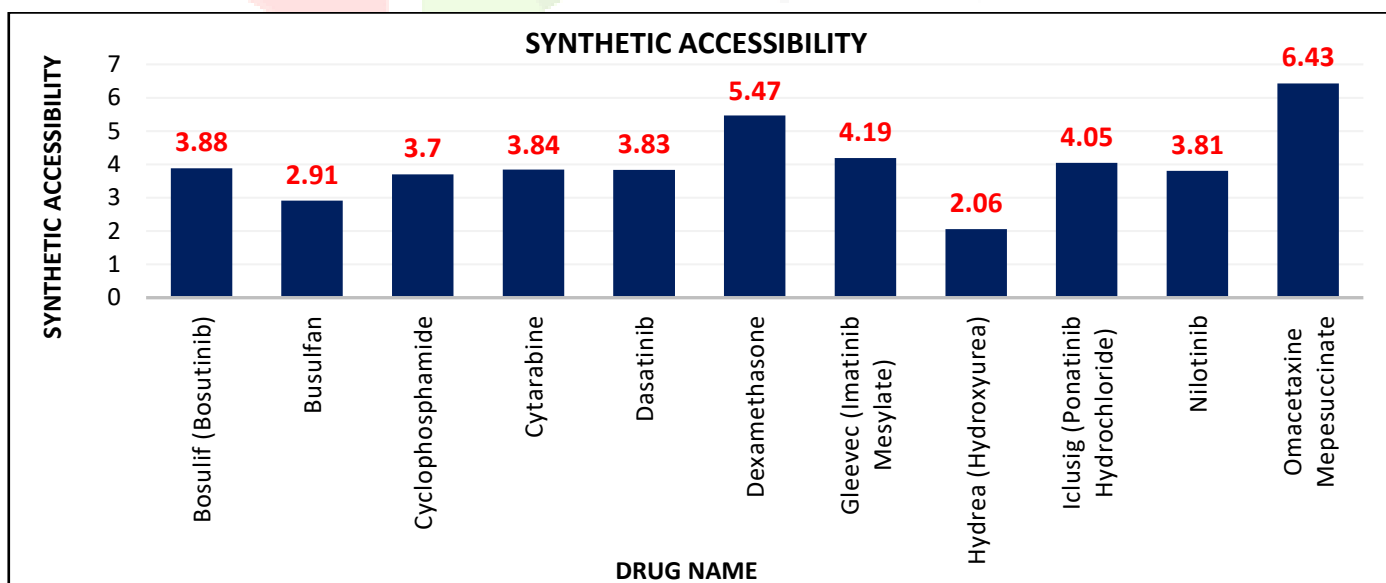

Figure 10: Bar graph depicting the Synthetic accessibility values of the query drugs.
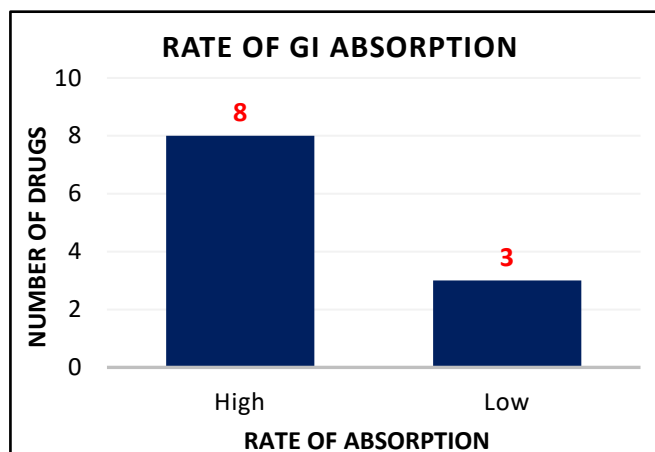
Figure 11: Bar graph depicting the number of query drugs having high/low rates of GI absorption
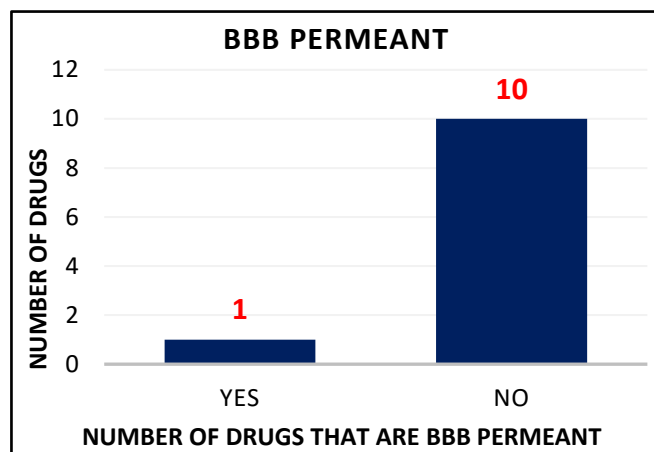

Figure 12: Bar graph depicting the number of query drugs that are BBB permeant.

Table 1: Tabular column representing the possible targets of the drug Bosulif (Bosutinib).

Target	Common Name	Target Class	Probability Score
Leucine-rich repeat serine/threonine-protein kinase 2	LRRK2	Kinase	0.931217878655
G protein-coupled receptor kinase 7	GRK7	Kinase	0.931217878655
Homeodomain-interacting protein kinase 4	HIPK4	Kinase	0.931217878655
Serine/threonine-protein kinase TAO2	TAOK2	Kinase	0.931217878655
STE20/SPS1-related proline-alanine-rich protein kinase	STK39	Kinase	0.931217878655

Table 2: Tabular column representing the possible targets of the drug Nilotinib.

Target	Common Name	Target Class	Probability Score
Phosphatidylinositol-5- phosphate 4-kinase type-2 gamma	PIP4K2C	Enzyme	0.999887246019
Tyrosine-protein kinase FYN	FYN	Kinase	0.999887246019
Macrophage colony stimulating factor receptor	CSF1R	Kinase	0.999887246019
Tyrosine-protein kinase ABL	ABL1	Kinase	0.999887246019
Serine/threonine protein kinase RAF	RAF1	Kinase	0.999887246019

IV. DISCUSSION
Analysis of pharmacokinetic properties of 11 drugs

The pharmacokinetic properties (ADME- Absorption, Distribution, Metabolism, and Excretion) properties of each drug candidate were procured through the SWISS ADME database. The data was represented graphically to evaluate each property.

Figure 1 depicts the graphical representation of the molecular weights of the 11 drugs among which Gleevec (Imatinib Mesylate) had the highest molecular weight of 589.71 g/mol, and Hydrea (Hydroxyurea) had the lowest molecular weight of 76.05 g/mol. The average value of molecular weights of all the drugs was 408.13 g/mol.

Figure 2 depicts the graphical representation of the water solubility (ESOL) of the 11 drugs among which Hydrea (Hydroxyurea) showed the highest water solubility with a positive ESOL value of 0.89, whereas the drugs Iclusig (Ponatinib Hydrochloride), Nilotinib, and Bosulif (Bosutinib) had the lowest water solubility with a negative ESOL value of -6.45, -6.23, and -6.05 respectively. The average ESOL value of all the drugs was -3.197.

Figure 3 depicts the graphical representation of the H-bond acceptors of the 11 drugs among which Omacetaxine Mepesuccinate, Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Nilotinib, Bosulif (Bosutinib) had the highest H-bond acceptor values of 10, 9, 8, 8, and 8 respectively. Hydrea (Hydroxyurea) had the lowest H-bond acceptor value of 2 and the average value of H-bond acceptors of all the drugs was 6.63.

Figure 4 depicts the graphical representation of the H-bond donor values of 11 drugs among which Cytarabine had the highest H-bond donor value of 4 followed by Dasatinib, Dexamethasone, Gleevec (Imatinib Mesylate), and Hydrea (Hydroxyurea) with H-bond donors 3, Nilotinib, Omacetaxine Mepesuccinate, and Bosulif (Bosutinib) with H-bond donor values of 2 and Iclusig (Ponatinib Hydrochloride), and Cyclophosphamide with H-bond donor values of 1. Busulfan had the lowest H-bond donor value of 0 and the average value of H-bond donor values of all the drugs was 2.18.

Figure 5 depicts the graphical representation of the number of rotatable bonds of the 11 drugs among which Omacetaxine Mepesuccinate had the highest number of rotatable bonds of 11, followed by Bosulif (Bosutinib), Gleevec (Imatinib Mesylate), and Nilotinib with rotatable bonds of 9, 8, and 8 respectively. Hydrea (Hydroxyurea) had the lowest number of the rotatable bond of 1 and the average number of rotatable bonds of all the drugs was 6.09.

Figure 6 represents the graphical comparison of the number of aromatic heavy atoms of the 11 drugs among which Nilotinib had the highest number of aromatic heavy atoms with a value of 29, followed by Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Dasatinib, and Bosulif having rotatable bonds 24, 21, 17, and 16 respectively. Busulfan, Cyclophosphamide, and Hydrea (Hydroxyurea) had the lowest number of aromatic heavy atoms with a value of 0 and an average of 10.8.

Figure 7 depicts the graphical representation of Log P values of the 11 drugs among which Omacetaxine Mepesuccinate, Bosulif (Bosutinib), Gleevec (Imatinib Mesylate), Dasatinib, and Nilotinib had the highest Log P values of 4.64, 4.61, 3.71, 3.37, and 3.36 respectively. The drugs Hydrea (Hydroxyurea), and Iclusig (Ponatinib Hydrochloride) had the lowest Log P values of -0.16, and 0 respectively. The average Log P value of all the drugs was 2.34.

Figure 8 depicts the graphical representation of drugs violating the LIPINSKI'S Rule. Among the 11 drugs, Gleevec (Imatinib Mesylate) had 2 Lipinski violations, Iclusig (Ponatinib Hydrochloride), Nilotinib, Omacetaxine Mepesuccinate, and Bosulif (Bosutinib) had 1 Lipinski violation and the remaining drugs had no violations.

Figure 9 depicts the graphical representation of lipophilicity of the 11 drug candidates among which Iclusig (Ponatinib Hydrochloride), Bosulif (Bosutinib), and Nilotinib had the highest positive XLOGP3 values of 4.91, 4.9, and 4.9 respectively. Cytarabine had the lowest lipophilicity with a negative value of -2.13. The average lipophilicity value of all the drugs was 1.59.

Figure 10 depicts the graphical representation of synthetic accessibility of the 11 drugs among which Omacetaxine Mepesuccinate had the highest synthetic accessibility with a value of 6.43 followed by Dexamethasone (5.47), Gleevec (Imatinib Mesylate) (4.19), Iclusig (Ponatinib Hydrochloride) (4.05), Bosulif (Bosutinib) (3.88), Cytarabine (3.84), Dasatinib (3.83), and Nilotinib (3.81). The drug Busulfan had the lowest synthetic accessibility with a value of 2.91. The average synthetic accessibility of all the drugs was 4.01.

Figure 11 depicts the rate of GI absorption of the 11 drugs. Among the 11 drugs Bosulif (Bosutinib), Busulfan, Cyclophosphamide, Dasatinib, Dexamethasone, Hydrea (Hydroxyurea), Iclusig (Ponatinib Hydrochloride), Omacetaxine Mepesuccinate had high GI absorption rates, and the rest of the drugs namely Cytarabine, Gleevec (Imatinib Mesylate), and Nilotinib had low GI absorption rates.

Figure 12 depicts the graphical representation of the number of drugs that are BBB permeant. Among the 11 drugs, all the drugs except for Cyclophosphamide are not BBB permeant.

Estimation of the drug targets

After analyzing the various ADME properties of the 11 FDA-approved drugs prescribed in the treatment of CML, we were able to deduce that the drugs **Bosulif** and **Nilotinib** were the best drug candidates compared to the rest of the drugs. Further, the inhibitory targets of the drugs Bosulif and Nilotinib were obtained through the Swiss Target Prediction software. The top 5 inhibitory targets of the drug Bosulif are; LRRK2, GRK7, HIPK4, TAOK2, and STK39. The inhibitory targets fall into the category of kinases and have a probability score of 0.931217878655 as represented in *Table 1*.

The top 5 inhibitory targets of the drug Nilotinib are; PIP4K2C, FYN, CSF1R, ABL1, and RAF1. The inhibitory targets fall into the category of kinases except for PIP4K2C which belongs to the class of enzymes and has a probability score of 0.999887246019 as represented in *Table 2*.

V. CONCLUSION

Chronic myeloid leukemia abbreviated as CML is an uncommonly occurring cancer majorly affecting older people that originates in the bone marrow. It's commonly caused due to spontaneous chromosomal mutations, and CML patients have a median survival of 5 to more than 5 years as it's usually diagnosed at a later stage. With the advancement in the medical care system, CML can be controlled with certain FDA-approved drugs such as Bosulif (Bosutinib), Busulfan, Cyclophosphamide, Cytarabine, Dasatinib, Dexamethasone, Gleevec (Imatinib Mesylate), Hydrea (Hydroxyurea), Iclusig (Ponatinib Hydrochloride), Nilotinib, and Omacetaxine Mepesuccinate.

Our study aimed to choose the best drug candidate among the list of drugs approved by the FDA in treating CML. By analyzing the various ADME properties of query drugs, the study was successful in identifying the 2 best drug candidates, namely Bosulif (Bosutinib), and Nilotinib as they satisfied the majority of the properties compared to other drugs. The study also succeeded in identifying the possible target molecules of the drugs Bosulif (Bosutinib), and Nilotinib.

VI. ABBREVIATIONS

BBB - Blood Brain Barrier, GI - Gastrointestinal, FDA - Food and Drug Administration.

VII. COMPETING INTERESTS

We declare that we have no competing interests.

VIII. REFERENCES

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