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IN SILICO STUDY OF VANILLIN SCHIFF BASES AS PROTO ONCOGENE TYROSINE KINASE INHIBITORS OF CHRONIC MYELOID LEUKEMIA

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Abstract

*In this work the selected compound of vanillin based Schiff bases **(VSB1-VSB8)** was studied for their inhibition potential against enzymes of chronic myeloid leukemia which are proto-oncogene tyrosine kinase protein ABL1 (ABL1) (PDB ID: 3CS9) enzyme through molecular docking. The selected compounds show strong interaction with the target protein. The tested compounds show comparable binding energies with dasatinib, higher than imatinib and lower than nilotinib. The tested compounds are excellent prospects for the development of innovative treatment due to their strong binding energies, which point to their capacity to successfully modify the activity of chronic myeloid leukemia enzymes.*

INTRODUCTION

Chronic myeloid leukemia (CML) is a form of cancer that affects blood forming cells found in bone marrow [1, 2]. The cells that can develop into red, white or platelet forming blood cells are known as blood forming cells. Each of these cells performs a distinct role in the body. For example, white blood cells guard the body from infections like viruses and bacteria, while red blood cells deliver oxygen throughout the body. Platelets enable blood to coagulate [3, 4]. A particular kind of white blood cells grows out of control in a person with CML. The term "blasts" refers to these aberrant, immature white blood cells. More blasts produce an excess of them in the bone marrow pushing out other blood cell [5, 6]. In comparison to other forms of leukemia CML advances more slowly. Its distinction from acute leukemia is this, which causes it to be a chronic leukemia [7-9]. CML can however, occasionally grow more hostile. Through the bloodstream it can potentially spread to other areas of the body. BCR-ABL1 positive chronic myeloid leukemia (CML) is categorized as a myeloproliferative neoplasm mostly consisting of proliferating granulocytes and it has been found that the Philadelphia chromosome/translocation t(9;22)(q34;q11). Both the bone marrow and peripheral blood are impacted by CML [10-13]. Three

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categories of CML assist predict prognosis. Physicians refer to these groups as phases rather than stages. The phases are primarily determined by the quantity of immature white blood cells or blasts present in the bone marrow or blood [5]. Although several expert groups have proposed somewhat varied cutoffs to determine the phases a common system proposed by the WHO (World Health Organization)) is described below. It is possible that some physicians disagree with or do not use these cutoff criteria for the various phases. Make sure you ask your doctor to clearly clarify the phase of your CML if you have any queries about it [5, 14-17]. Chronic phase, Less than 10% of patients in the chronic period usually have blasts in their bone marrow or blood tests. The majority of these patients respond well to traditional therapy and typically exhibit very minimal symptoms if any. The majority of individuals are diagnosed in the chronic phase [5, 17-20]. Accelerated phase, If any of the following applies to the patient they are deemed to be in an accelerated phase. 1. There are at least 15% but less than 30% blasts in the blood samples. 2. Basophils make up 20% or more of the blood. 3. At least 30% of the blood is composed of promyelocytes and blasts together. 4. Extremely low platelet counts (below than 1,000/mm^3) unrelated to therapy 5. The Philadelphia chromosome containing leukemia cells have new chromosome alterations Individuals experiencing an accelerated phase of CML may exhibit symptoms like fever, anorexia and weight loss. Treatment for CML in the accelerated phase is less effective than for CML in the chronic phase [5, 15, 18]. Blast phase (also called acute phase or blast crisis), In patients in this phase 20% or more blasts are present in bone marrow and/or blood tests. The bone marrow exhibits large clusters of blasts. The bone marrow is not the only organ or tissue where the blast cells have spread. Weight loss, low appetite and fever are common in these people. At this point acute leukemia and CML behave quite similarly [5, 15]

Tyrosine kinase an abnormal enzyme produced by the Philadelphia chromosome is the cause of the abnormal growth pattern and elevated white blood cell production in CML [21, 22]. White blood cell proliferation is facilitated by an enzyme known as a fusion protein which is abnormally activated. This genetic alteration results from random harm that happens to an individual after birth. The 3 sequences from the ABL1 (Abelson) gene fuse with the 5 segment of the BCR (breakpoint cluster region) gene sequences to generate the Philadelphia chromosome (BCR-ABL fusion gene) [23, 24]. Due to its constitutively active tyrosine kinase activity, which feeds into many pro-growth and survival signaling pathways BCR/ABL is largely thought to be required for the development and maintenance of CML [25, 26]. Tyrosine kinase inhibitor (TKI) therapy the tyrosine kinase enzyme, which causes stem cells to proliferate into more white blood cells (blasts) than the body requires is blocked by this medication. Tyrosine kinase inhibitors such as imatinib, mesylate, dasatinib, nilotinib, Ponatinib, bosutinib and asciminib are used to treat CML. But still potent medication for tyrosine kinase inhibition is big challenge for the modern world. Schiff bases due to their versatile bioactive nature gain the attention of the scientist. In this study were check the inhibition potential of vanillin Schiff bases against proto-oncogene tyrosine kinase of chronic myeloid leukemia

Methodology

Important enzymes of chronic myeloid leukemia is selected for the present study to test the synthesized vanillin Schiff bases (**VSB1-VSB8)** for their inhibition potential against the selected enzyme (proto oncogene tyrosine kinase protein ABL1 (ABL1). Three standard drugs were also tested for comparison (Imatinib, Dasatinib, Nilotinib) against target enzyme (shown in **Figure 1**). The binding interaction mechanism of synthesized vanillin based Schiff bases was tested for competitive and non-competitive inhibition of the mark enzyme of chronic myeloid leukemia (proto-oncogene tyrosine kinase protein ABL1 (ABL1), by using molecular docking protocol. The crystal structure of the enzyme was obtained from a protein database. Protein was prepared by using AutoDock MGL tools and optimizing by removing water, heteroatoms, and cofactors for simplicity of calculations. The best docking conformer with the lowest binding energy will be selected for further investigation. Protein ligand interactions images and the docking poses of vanillin based Schiff bases against target enzymes were visualized by Autodock Vina, PyMol, and Discovery Studio Visualization [88].

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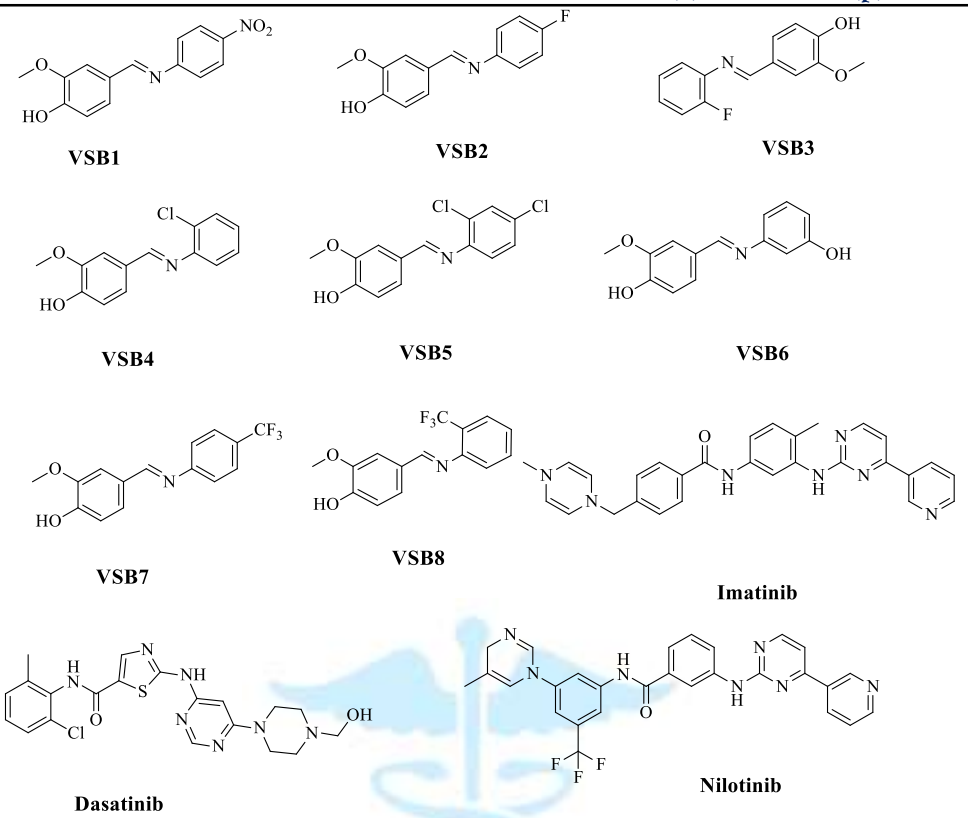


Figure 1. Structure formulae of vanillin based Schiff bases (VSB1-VSB8) and standards (Imatinib, Dasatinib, Nilotinib)

3. Results and Discussion

The interaction of these molecules was examined using molecular docking to explain the potential interaction between vanillin based Schiff bases **(VSB1-VSB8) and the** target enzyme of the chronic myeloid leukemia binding space. The resultant stable conformations were immediately loaded. All the examined compounds proved to be effective inhibitors and displayed high affinity for the target chronic myeloid leukemia proteins. The results indicate that most compounds have strong interactions with the active amino acid residues of the target chronic myeloid leukemia protein. Among the tested compounds the most potent compounds were selected for discussion (VSB1, VSB2, VSB6 and VSB8) on the basis of comparable binding energy with standard drugs.

3.1. Interaction of VSB1 with ABL1: The selected compound **(VSB1)** shows good inhibition against the ABL1 enzyme with a high docking score of -12.20 kcal/mol (shown in **Table 1)** and an inhibition constant of 1.15 nM. The compound shows interaction with ASP-381, MET-290, GLN-300, LYS-294 and ILE-293 residues of the ABL1 enzyme. The compound **(VSB1)** was able to dock deeply within the pocket region of the ABL1 enzyme. Among these hydrogen bonds participating in the interaction via the ASP-381 (NH...O), ASP-381 (O...HO), GLN-300 (NH...O), LYS-294 (NH...O) (given in **Figure 2)** the bond distances are 1.9 Å, 2.2 Å, 1.8 Å and 2.5 Å respectively (shown in **Table 2**). **SB1** also exhibits hydrophobic, weak Vander Waal interaction and pi-pi interaction with MET-290 (O...ON), MET-290 (O...N), ILE-293 (O...N) , ILE-293 (O...ON) amino acids of the ABL1 enzyme with bond distances of 3.0 Å, 3.3 Å, 2.8 Å and 2.7 Å, respectively. The interaction mode/pose of compound SB1 with the above-mentioned ABL1 enzyme 3D structure are illustrated in **Figure 2**.

3.2. Interaction of VSB2 with ABL1: Interaction study of ABL1 with compound **VSB2** has a docking score of -9.09 kcal/mol (shown in **Table 1)** and inhibition constant is 219.04 nM with residue GLU-286 and LYS-271 respectively. Among these interacting compound **VSB2** forms hydrogen

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bonding with residues of GLU-286 (O...HO) and LYS-271 (NH...O) with bond distances of 2.2 Å and 1.9 Å (shown in **Table 2**), respectively. Beside these hydrogen bonds in the active site, **VSB2** also exhibits hydrophobic and weak Vander Waal interactions with the ABL1 enzyme, as represented in **Figure 3.** The interaction mode/pose of compound **(VSB2)** with above mention ABL1 enzyme 3D structure are illustrated in
Figure 3.

3.3. Interaction of VSB6 with ABL1: The compound **(VSB6)** was selected for its inhibition potential against the ABL1 enzyme with a docking score of -10.22 kcal/mol (shown in **Table 1**) and an inhibition constant of 32.19 nM. The interaction of compound **(VSB6)** with residues of the ABL1 enzyme is PHE-382 and MET-318. Among these interacting compounds **(VSB6)** forms hydrogen bonding with residues PHE-382 (O...HO), MET-318 (NH...O), MET-318 (NH...OH) and MET-318 (O...HO) with bond distances of 2.0 Å, 1.8 Å, 2.7 Å and 2.2 Å (shown in **Table 2),** respectively. Beside these hydrogen bonds in the active site, **VSB6** also exhibits hydrophobic and weak Vander Waal interactions with the ABL1 enzyme, as represented in **Figure 4**. The binding pose of compound **(VSB6)** with above mention ABL1 enzyme 3D structure are illustrated in **Figure 4**.

3.4. Interaction of VSB8 with ABL1: Interaction study of ABL1 with compound **VSB8** has a docking score of -10.36 kcal/mol (shown in **Table 1**) and inhibition constant is 25.25 nM with residues of MET-318 and THR-315 respectively. Among these interacting compound **VSB8** forms hydrogen bonding with residues of MET-318 (NH...O) and MET-318 (O...HO) with bond distances of 1.9 Å and 2.2 Å (shown in **Table 2**) respectively. Beside these hydrogen bonds in the active site, **VSB8** also exhibits hydrophobic, weak Vander Waal interaction and pi-pi interaction with the THR-315(N...O) amino acid of the ABL1 enzyme with a bond distance of 3.1 Å, as represented in **Figure 5**.

Table 1**. Binding energies in (kcal/mol) and inhibition constant of compounds VSB1-VSB8 and (Imatinib, Dasatinib, Nilotinib) with ABL1**

Compounds	Binding Energy (kcal/mol)	Inhibition Constant (nM)
VBS1	-12.20	121.82
VBS 2	-10.0	213.67
VBS 3	-9.42	262.39
VBS 4	-9.86	205.27
VBS 5	-8.36	333.61
VBS 6	-10.22	189.95
VBS7	-9.65	252.21
VBS8	-10.36	126.20
Imatinib	-7.34	293.26
Nilotinib	-14.68	92.10
Dasatinib	-10.23	192.22

Table 2. Residues involved in interactions and their distances of selected compounds with ABL1

Compounds	Interacting amino acids	Types of interactions	Distances(Å)
VSB1	ASP-381, GLN-300, LYS-294	H-Bonding,	1.9, 2.2, 1.8, 2.5
	MET-290, ILE-293, ILE-293	π-π interaction	3.0, 3.3, 2.8, 2.7
VSB2	GLU-286, LYS-271	H-Bonding	2.2, 1.9
	MET-290, ILE-293, ILE-293	π-π interaction	3.2, 3.7, 3.62
VSB6	PHE-382, MET-318	H-Bonding	2.0, 1.8, 2.7, 2.2
	LYS-271, PHE-182, TYR-253,	π-π interaction	3.2, 3.7, 3.5, 4.2

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	VAL-256		
VSB8	MET-318	H-Bonding	1.9, 2.2
	VAL-278, ala-180, ALA-269	π-π interaction	3.7, 3.2

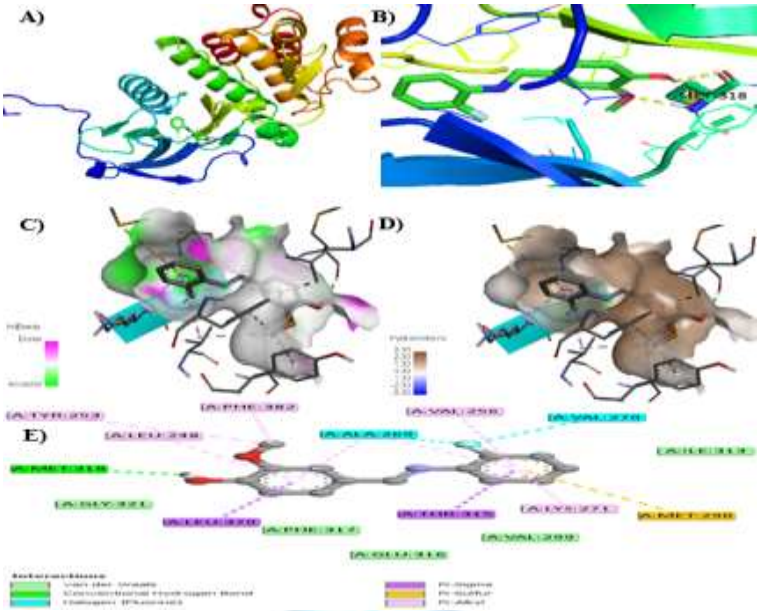


Figure 2. 3D Structure of VSB1 with ABL1 (A), 3D-interactions (B), Hydrogen bonding interaction (C), Hydrophobic interaction (D) and 2D interaction (E).

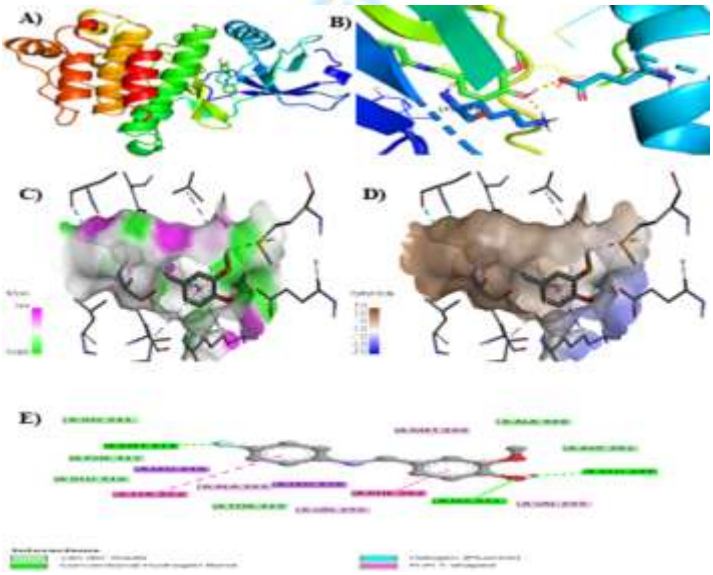


Figure 3. 3D Structure of VSB2 with ABL1 (A), 3D-interactions (B), Hydrogen bonding interaction (C), Hydrophobic interaction (D) and 2D interaction (E).

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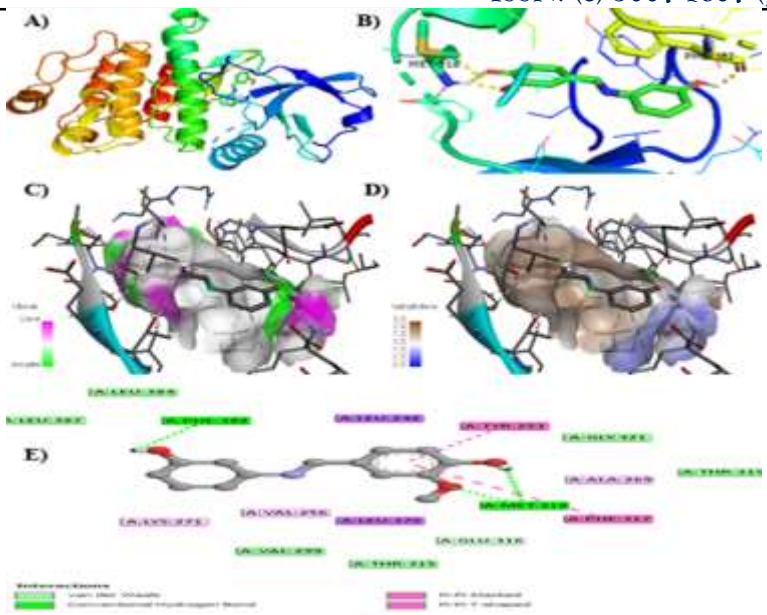


Figure 4. 3D Structure of VSB6 with ABL1 (A), 3D-interactions (B), Hydrogen bonding interaction (C), Hydrophobic interaction (D) and 2D interaction (E).

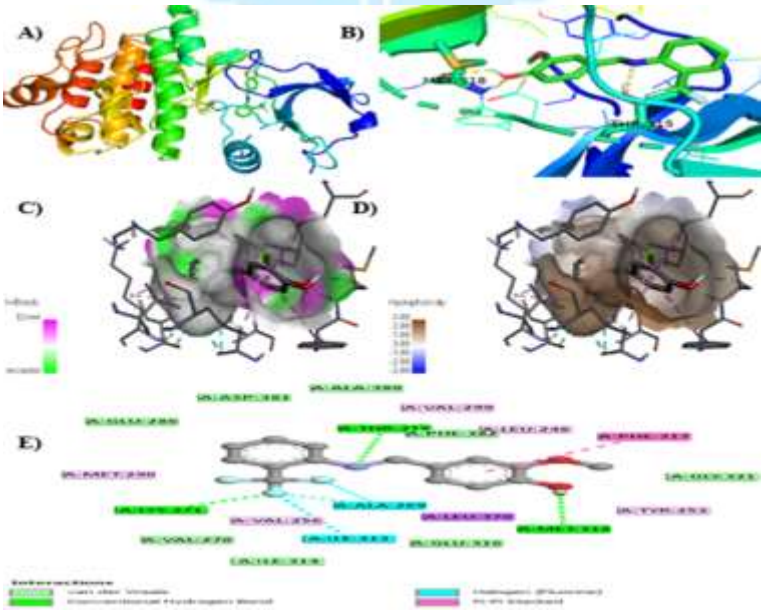


Figure 5. 3D Structure of VSB8 with ABL1 (A), 3D-interactions (B), Hydrogen bonding interaction (C), Hydrophobic interaction (D) and 2D interaction (E).

4. Conclusion

Vanillin based Schiff bases are significant in drug development, with a wide range of pharmacological effects. This is due to the ability of the Vanillin based Schiff bases molecule to bind with receptors at several sites. The selected compound of vanillin based Schiff bases **(VSB1-VSB8)** was studied for their inhibition potential against enzymes of chronic myeloid leukemia which are proto-oncogene tyrosine kinase protein ABL1 (ABL1) (PDB ID: 3CS9) enzyme. The tested compounds show comparable binding energies with dasatinib, higher than imatinib and lower than nilotinib. The tested compounds are

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excellent prospects for the development of innovative treatment due to their strong binding energies, which point to their capacity to successfully modify the activity of chronic myeloid leukemia enzymes.

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Conflict of Interest

The authors declare no conflict of interest

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