Original Article

Role of Derivatives Ciprofloxacin on Chronic Myeloid Leukemia: In Silico Approach

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Abstract

Introduction: chronic myeloid leukemia is one of the major diseases, which cause death worldwide. Tyrosine kinase is responsible for uncontrolled cell growth and block its function. Its inhibition is a promising route to control the out of control grow of cells. The purpose of our study involves docking of human Abl kinase with seven ciprofloxacin derivatives and the comparison of results free energy binding with positive control (Imatinib).

Methods: the present study aims to examine the interactions between human Abl kinase(2HYY) domain retrieved from protein data bank and seven ciprofloxacin derivatives in comparison with imatinib as a reference. The analysis was performed using Autodock vina Implicated in the PyRx 0.8 tool.

Results: docking revealed that, according to their free binding energy imatinib still have the lowest binding energy followed by CHOCP and MPCP. In silico ADMET predictions revealed that except DMOCP all other compounds had toxic effects.

Conclusion: these compounds may not serve as a potential inhibitor due to their high free energy binding and their toxicity in comparison with imatinib.

Keywords: ciprofloxacin, molecular docking, CML, Imatinib, Autodock vina.

I- INTRODUCTION

Chronic myeloid leukemia (CML) is one of the blood diseases grouped together under the name of "myeloproliferative syndromes". It's characterized by an increase in the production of white blood cells in the bone marrow. Some of these blood cells are aberrant, they are immature cells, which means they are not fully mature when they enter the bloodstream. With an estimated incidence of 1-2 cases per 100,000 individuals. It represents for around 15% of newly diagnosed leukemia in adults[1]. It's expected that around 9000 new CML cases will be identified in the united states in 2017, with approximately 1000 individuals dying from CML. Since the launch of imatinib in 2000, the yearly death rate in CML has fallen from 10%-20% to 1%-2%[1]. The prevalence of CML in united states has climbed from an estimated 25-30 000 cases in 2000 to an expected 80-100 000 in 2017 and will reach a peak of around 180 000 cases by 2030[2]. The fusion of the Abelson murine Leukemia (ABL1) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22 is fundamental to the pathophysiology of CML, the chimeric BCR-ABL fusion gene is responsible for the production of the oncoprotein tyrosine kinase Bcr-Abl which has an uncontrolled activity that deregulate cell proliferation, decreases leukemic cell adhesion to the bone marrow stroma and protects leukemic cells from normal programmed cell death(apoptosis). CML develops when abnormal pluripotent progenitor stem cell initiates excessive production of all cells of the myeloid lineage, primarily in the bone marrow but also in in extramedullary sites (spleen, liver). Although granulocytes production predominates, the malignant clone includes the red blood cells, megakaryocytes, monocytes, and even a proportion of B and T lymphocytes. Normal stem cells are inhibited and may emerge after the suppression of the leukemic clone of chronic myeloid leukemia by treatment.

Medicine repositioning is the process of discovering new uses for an authorized or experimental drug that are not related to its original indication. Fluoroquinolones have lately been reclassified from antibiotics to anti-cancer drugs[3]–[5]. Several studies have shown the interest of some ciprofloxacin derivatives in the treatment of leukemia[6]–[8] by different mechanisms. Our

study involves docking of human Abl kinase domain(PDB :2HYY)[9] with seven ciprofloxacin derivatives(4-TCMP, 4-MPCP, 4-PECP, 4-PMCP, 4-MBCP,4-DMOCP,4-CHOCP) (Figure 1), and comparison of these results with docking results of imatinib which is a known inhibitor of tyrosine kinase.

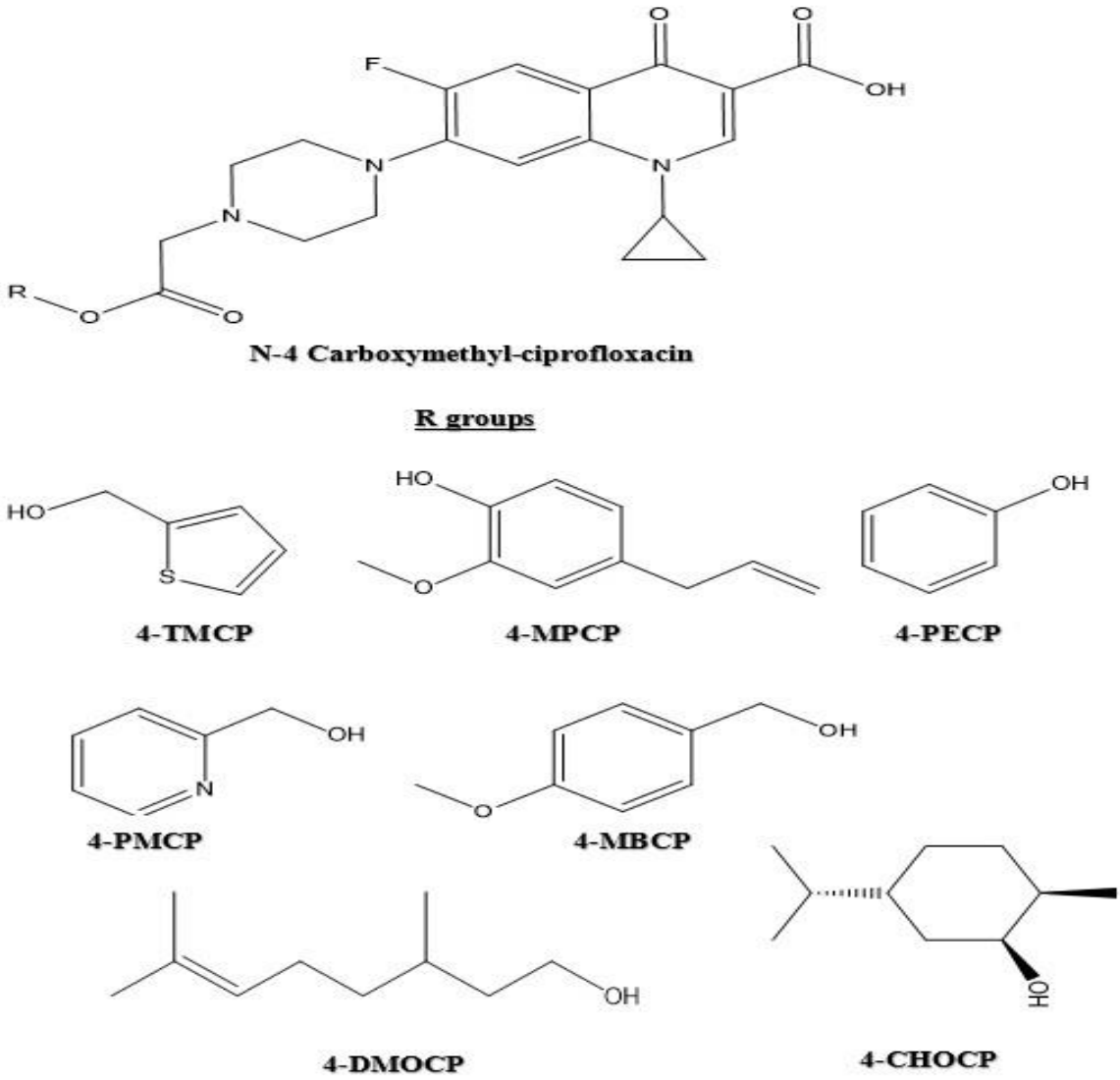

Figure 1: The seven derives from ciprofloxacin

II- Material and methods

1-Protein preparation

Three-dimensional protein structure of human Abl kinase domain obtained from protein data bank(PDB ID :2HYY) under the criteria of resolution 2.40 Å[9]. The protein includes four chains (A, B, C, D). The obtained structure also combined with water molecules and imatinib (STI571), manual procedure was done to remove water molecules and cofactors on swiss-pdbviewer.

2-Ligand preparation

Structures derived from ciprofloxacin were drawn by Chemdraw v. Ultra 12 software followed by energy minimization by using MM2 force field method in the same software. These processes are required prior to the import of ligands for the docking phase. The structures of different ligands including the control imatinib.

3-Molecular docking

In order to identify new potent inhibitors of tyrosine kinase, docking simulation was done and calculation of binding energies was performed using AutoDock VINA[10]. Firstly, the grid box with the following dimensions was set to cover the active site of the crystal structure with the following dimension in Å: center (X=10, Y=4.5, Z=20), dimension (X=86, Y=84, Z=82) with exhaustiveness of 8. Finally, analysis of the finding was performed using discovery studio[11].

4-Drug-likeness prediction

The molinspiration properties explorer use a balance of various molecular properties and structure features that determine whether a molecular is similar to known drugs. The method implemented uses sophisticated Bayesians statistics to make a comparison, the structures of representative ligands that are active on a specific target with the structures of inactive molecules. Properties analyzed are TPSA, Log P, molecular weight and Lipinski's rules (https://www.molinspiration. com/cgi-bin/properties).

5-ADMET Prediction

ADMET characteristics of a substance deal with its absorption, distribution, metabolism, excretion and toxicity and through human body. ADMET constitutes the pharmacokinetic profile of drugs, is very important in assessing its pharmacodynamic activity. There are numerous online and offline software programs available today, to assist us in forecasting the behavior of candidate for medication. In this study, we have used the admetSAR prediction tool (http://lmmd.ecust.edu.cn:8000).

III-Results and discussion

Binding energy. Autodock vina generated 9 different conformations for each ligand which are classified according to their binding affinity (Kcal/mol). The ligands displayed the free energy of binding -7.2 to 10.1 Kcal/mol (Figure2). As shown in figure 2, all selected ligands have binding energy lower than imatinib (-10.1). Eslami et al. showed that 4-DMOCP was more active and can be a good candidate for treatment of chronic myeloid leukemia[12]. In our study CHOCP and MPCP displayed the lowest energy of -9 Kcal/mol. The binding energy of the control imatinib was much lower than CHOCP and MPCP as shown in figures 3.

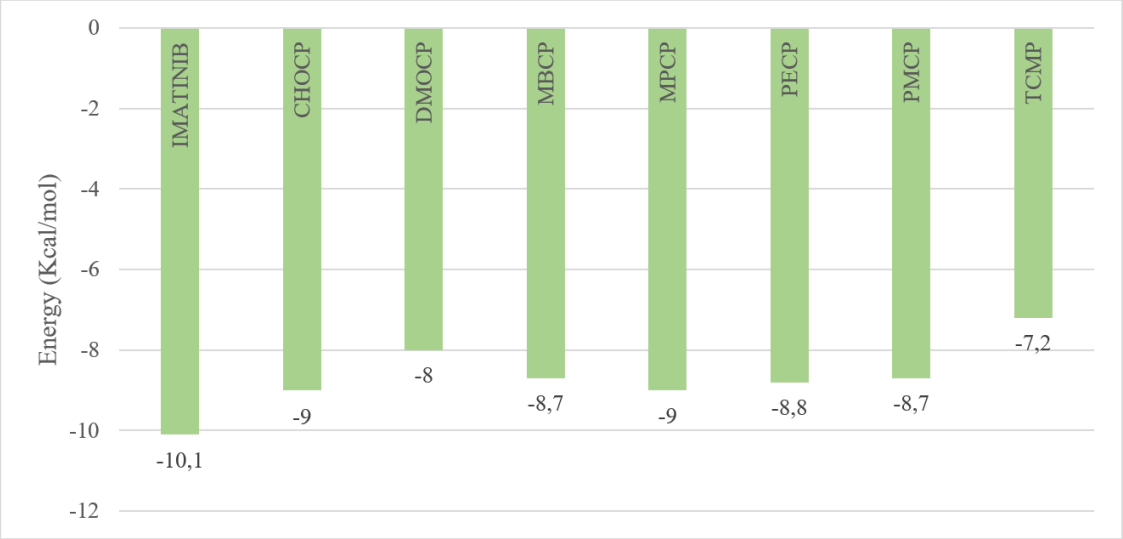

Figure 2: Binding free energy of the seven compounds and Imatinib drugs.

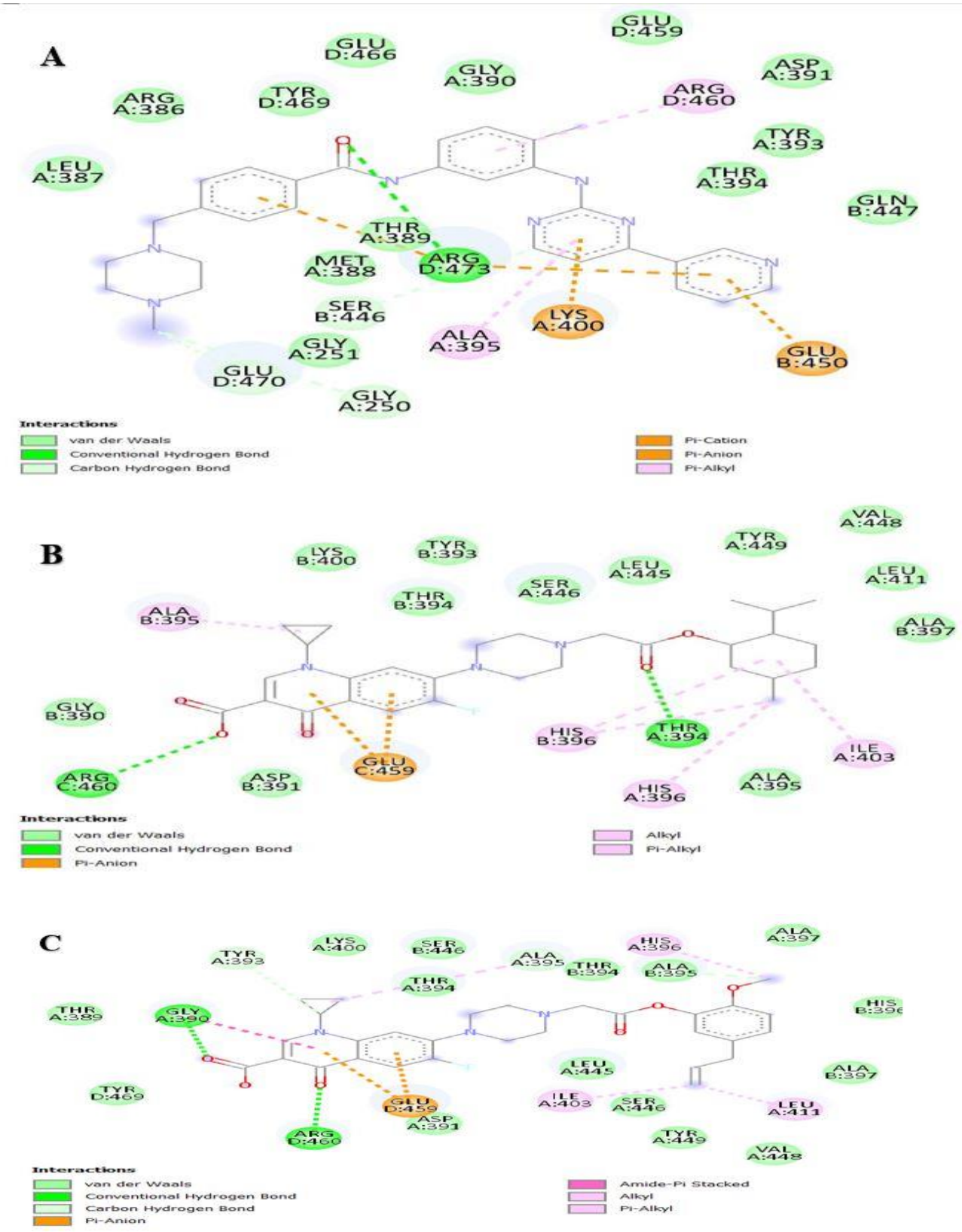

Figure 3: Molecular docking of imatinib(A), CHOCP(B), MPCP(C)

Prediction of drug likeness. A good drug candidate is well absorbed and distributed throughout the organism for appropriate metabolism and action. Failure of drugs during clinical trials due to adverse effects caused by toxicity is costly and harmful to the drug development process. In sillico drug likeness presents a plethora of possibilities that aid in the discovery of new targets and lead to compounds with predicted biological activity. Table 1 illustrate the drug-like properties of test compounds predicted by Molispiration free web tools for cheminformatics community. The Molinspiration tool measure the LogP (Octanol-water partition coefficient). Which measures the hydrophilicity of the compounds, higher log P indicate lower hydrophilicity. A lower molecular weight would increase absorption rate, most drugs are kept al the lowest possible molecular weight. TPSA or topological polar surface area[13], denotes the surface of polar atoms in a compound. Increase TPSA is linked to decreased membrane permeability, and compounds with higher TPSA were better substrates for p-glycoprotein (liable for drug efflux from the cell). When comparing the compounds, lower TPSA was found to be more favorable for drug-like properties. A compound with good CNS penetration also was predicted to have lower TPSA value[14]. Lipinski rules of five developed using a set of simple molecular descriptors[15]. According to the rule, most "drug-like" molecule must have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, number of hydrogen bond donors ≤ 5. Molecules that violate one of these rules may have bioavailability issues[16]. The analysis of the seven ligands showed that the compounds with good affinity (CHOCP, MPCP) violate Lipinski rules. PECP (-8.8 Kcal/mol) was found to be most conforming to these properties used to predict drug-likeness (Table I).

Table I: Calculation of molecular properties and bioactive score through Molinspiration

Ligand	Log P	TPSA	Molecular weight	Lipinski violation
Imatinib	3.89	86.28	493.62	0
CHOCP	3.41	92.08	527.64	1
DMOCP	3.59	90.39	529.65	1
MBCP	1.41	101.32	509.34	1
MPCP	1.27	101.32	535.57	1
PECP	0.86	92.08	465.48	0
PMCP	0.55	104.98	466.47	0
TCMP	1.25	92.08	485.54	0

admetSAR prediction. from admetSAR (version 2.0) server[17], [18], reveal that CHOCP had better human intestinal absorption (HIA) than imatinib. Greater HIA indicate that the compound may be better absorbed from the intestinal tract when administered orally. The penetration through the blood brain-barrier (BBB) was significantly higher for the imatinib. In terms of metabolism CHOCP, DMOCP, imatinib were a substrate/non inhibitor of CYP450 microsomal enzyme while PECP was given to be non-metabolized by CYP450 and an inhibitor. Inhibitor of CYP450 means that it will interfere with the biotransformation of drugs metabolized by the CYP450. The AMES toxicity test is used to assess whether a compound is mutagenic or not. All the test ligands expressed positive AMES toxicity test which implies that the ligands are mutagenic except for DMOCP and the imatinib. The carcinogenic profile also indicated that the ligands, like imatinib were non carcinogenic. The computed LD50 in the rat model was critical information obtained from the admetSAR server. When the LD50 doses are compared, the compound with the lower dose is more lethal than the ligand with the higher dose. We discovered that PECP and TCMP had nearly the same LD50 as imatinib (2.505, 2.542, 2.531 respectively). DMOCP had the lowest LD50 of 1.7160 and was the most toxic of the test ligands (Table II).

Table II: ADMET profile of the test ligands and the imatinib

Compound	HIA	BBB	CYP inhibition/substrate	AMES toxicity	Carcinogenicity	LD50 in rat
Imatinib	0.9884	0.9906	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	2.5310
CHOCP	0.9895	0.9646	Substrate/noninhibitor	Toxic	Noncarcinogenic	2.0860
DMOCP	0.9564	0.9566	Substrate/noninhibitor	Nontoxic	Noncarcinogenic	1.7160
MBCP	0.9835	0.9807	Substrate/inhibitor	Toxic	Noncarcinogenic	2.269
MPCP	0.9801	0.9690	Substrate/inhibitor	Toxic	Noncarcinogenic	2.2370
PECP	0.9800	0.9761	NonSubstrate/inhibitor	Toxic	Noncarcinogenic	2.5050
PMCP	0.9828	0.9826	NonSubstrate/inhibitor	Toxic	Noncarcinogenic	2.6860
TCMP	0.9618	0.9832	NonSubstrate/inhibitor	Toxic	Noncarcinogenic	2.5420

IV-Conclusion

After comparing and analyzing all of the parameters, our admetSAR study revealed that none of the ciprofloxacin derivatives are effective against human Abl kinase enzyme. It's admet properties were very different from imatinib which is our control. Apart from other factors, DMOCP was found to be the most toxic because of its low LD50 value. Finally, the derivatives compounds didn't prove to be outstanding base drug candidates because they are non-potent, non-selective, low oral bioavailability and toxic. In the present study, we discovered that the derivatives ciprofloxacin wasn't able to show best free binding energy than imatinib in the docking results. These ligands couldn't be used as inhibitors of human tyrosine kinase enzyme.

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