Journal Academica

A. Merzoug et al., H. Muhammed
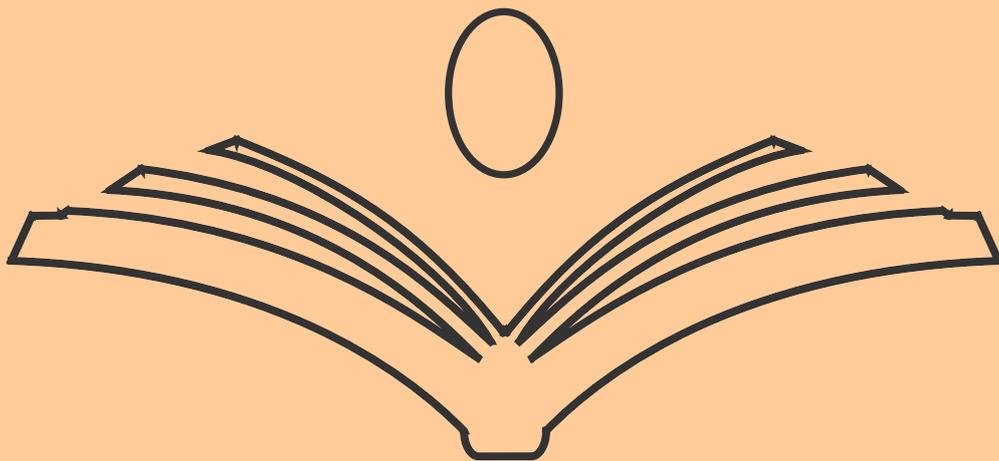
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Full Length Research Paper

Theoretical Study of the Interactions Involved in the Inhibition of Staphylococcus aureus Peptide Deformylase by GSK1322322 Derivatives

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ABSTRACT

One of the methods commonly used in pharmacochemistry is the molecular docking, it consists in predicting and in reproducing the protein ligand interactions. The molecular docking program, Surflex, was developed to assist in the development of molecules with therapeutic activity. With the RMSD values lower than 2 Å and the coefficient of correlation close to 1, the performances of Surflex software's were clearly proven.
It had been used to study the inhibition of Staphylococcus aureus peptide deformylase, an essential enzyme in a variety of pathogenic bacteria, by GSK1322322 derivatives, with the aim of discovering new antibiotic. The evaluation of the affinity of these molecules resulted in those presenting the best inhibitive effect. Compound 14, N-[(2R)-3-[2-[2-chloro-6-[(3R,4R)3-(dimethylamino)-4-methylpyrrolidin-1-yl] -5-fluoro-pyrimidin-4yl] hydrazinyl]-2-(cyclopentylmethyl)-3-oxopropyl]-N-hydroxyformamide, showed the highest affinity value, being 11.49. Docking results show that the proposed compound may aid the development of more potent inhibitors of peptide deformylase.

1. INTRODUCTION

Antibacterial resistance to hospital-acquired G positive bacterial pathogens including methicillin-resistant *Staph. aureus* (MRSA) and vancomycin-resistant *Staph. aureus* (VRSA) had been increasing at an alarming rate. Therefore, there is an urgent need to identify essential enzyme systems in the bacteria and develop potent molecules to inhibit them. Peptide deformylase (PDF) catalyzes the removal of the N-terminal formyl group from newly synthesized polypeptides and was essential in a variety of pathogenic bacteria but was not required for cytoplasmic protein synthesis in eukaryotes. It was an attractive target for the discovery of novel antibiotics (Yuan *et al.*, 2001). Many PDF inhibitors had been reported in recent years, some of which showed excellent antibacterial activity *in vitro* and in animal models. Amongst these inhibitors, NVPPDF-713 (Fritsche *et al.*, 2005) and BB-83698 (Lofland *et al.*, 2004) are currently in phase I clinical trials for the treatment of respiratory tract

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infections, although they were not further developed. GSK1322322 (Fig. 1), a novel PDF inhibitor of the hydrazide class, showed good safety and pharmacokinetic properties in a phase I clinical trial and promising proof of concept results in a phase IIa study (http://www.clinicaltrials.gov).

GSK1322322 is currently being developed for the oral and intravenous treatment of acute bacterial skin structure infections and hospitalized patients with community-acquired pneumonia (O'Dwyer K *et al.*, 2013).
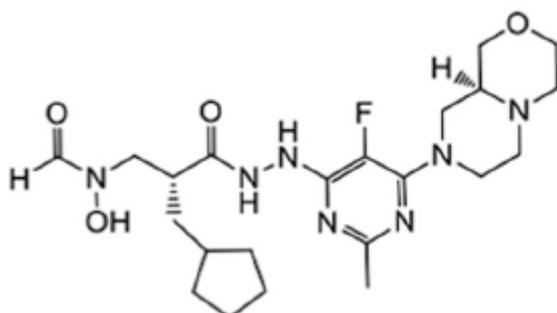

Figure 1: Chemical structure of GSK1322322
GSK1322322:N-[(2R)-3-[2-[6-[(9aS)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-5-fluoro-2-methylpyrimidin-4-yl]hydrazinyl]-2-(cyclopentylmethyl)-3-oxopropyl]-N-hydroxyformamide

Molecular docking was a widely used computational tool for the study of molecular recognition. This new approach aimed to simulate and predict the affinity of a very large number of ligands for the active site of a given therapeutic target, which was considerably easier to implement, cheaper, and faster than the use of experimental methods. Initiated in the beginning of 1980, this approach had developed to become an essential tool for bioactive molecules' research today (Chikhi and Bensegueni, 2010 and Merzoug *et al.,* 2013).

The purpose of this study was firstly to test the ability of molecular docking software Surflex1.3 (BioPharmics, 2005),

used in this study to examine the protein-ligand interactions.

Secondly, to study the inhibition of *Staph. aureus* PDF by the method of molecular docking. We were interested to determine the mode of interaction during the binding of the GSK1322322 to the enzyme and then use this program to search for a new inhibitor of PDF through similar of GSK1322322. The compound that had the greatest affinity was the one that presents the best activity and subsequently a better inhibition.

2. MATERIALS AND METHODS

2.1 Evaluation of Docking Program
2.1.1 The RMSD (Root Mean Square Deviation)
The best value of mean RMSD between the placing of the ligand calculated by the software and the conformation in the experimental complex was the smallest possible. A prediction of a binding mode was considered successful if the RMSD was below 2.0 Å (Gabb, 1997). The current standard for evaluating the performance of a docking program was to make a test from hundreds of crystallized protein-ligand complexes (Kellenberger *et al.,* 2005, Kramer *et al.,* 1999). Surflex 1.3 was performed on 111 complexes available from PDB and the RMSD determination. The predicted RMSD was acceptable if the value did not exceed 2 Å.

2.1.2 The Correlation Coefficient (R)
The correlation coefficient (R) indicated the degree of linear relationship between two data sets with values between -1 and 1. If there was no linear relationship between the two sets of data, the coefficient correlation was very close to zero: In that case we considered the two variables not being correlated (Fox, 1999). To study the correlation between the score obtained by the molecular docking and the biological activity

(IC50), we used different inhibitors of PDF already described in literature. Availability of their IC50 values was among the criteria for selection of these molecules used to test the reliability of Surflex program using the correlation coefficient. A total of 23 molecules were tested.

2.2 The Structure of the *Stapy. aureus* Peptide deformylase

In this study, The X-ray structure of the enzyme (*Staph. aureus* PDF) was retrieved from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb), the largest archive of structural data of biological macromolecules such as proteins and nucleic acids.

The PDB ID of this enzyme is 3U7K. It is a zinc metalloenzyme composed of 163 residues of amino-acids.
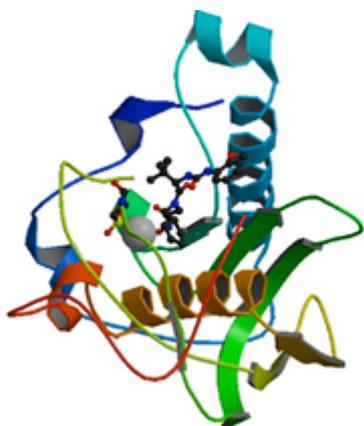
Figure 2: Crystal structures of the *Staphy. aureus* peptide deformylase

2.3 Preparation of Molecules

The protein-ligand complex was downloaded from the PDB by inserting its code ID into the pdb-format.

Surflex requires *mol2*-format. The two molecules of the complex (enzyme-ligand) were separated and transformed into the *mol2*-format with the freeware program OpenBabel.

For the docking study, derivatives of GSK1322322 were downloaded in the *sdf*-format from Pub Chem compounds

(http://www.ncbi.nlm.nih.gov), a database of chemical molecules, and eventually transformed into the *mol2*-format.

2.4 Surflex1.3

Surflex1.3 is one of the most successful docking programs. It is widely used and able to dock ligands in an environment consisting of amino acids with good precision (Jain, 2007). It is based on three major parts:

- Identification of binding pocket (protomol) with the command: Sufrlex-dock proto ligand.mol2 protéine.mol2 pl
- Ligand Docking: Surflex-dock dock lignad.mol2 pl-protomol.mol2 protein.mol2
- Result Treatment

2.5 Lipinski rule

Each drug must comply with several basic criteria, such as low cost of production, being soluble, stable, but must also conform to the schedules associated with its pharmacological properties of absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox) (Miteva *et al.*, 2006), which is based on the rule of five made by Christopher Lipinski (Lipinski *et al.*, 2001).

The "rule of 5" states that poor absorption or permeation is more likely if:

- more than 5 H-bond donors
- MWT is over 50
- Log P is over 5
- more than 10 H-bond acceptors

3. RESULTS AND DISCUSSION

3.1 The ability of molecular docking software Surflex

Program performance had been evaluated on 111 crystallized protein-ligand complexes available in the PDB. The docked binding mode was compared with the experimental binding mode and a root-mean-square distance (RMSD) between the two was calculated by Surflex; a prediction of a binding mode was considered successful if the RMSD was below 2.0 Å (Gabb, 1997).

In our results we noticed that the program Surflex reproduced the experimental data well. Indeed, 83% of RMSD values were less than 2Å. The RMSD values were consistent with the results of Kellenberger *et al.,* (2004), showing that with any program the docking was successful when the RMSD was less than 2 Å. This was also consistent with the results obtained by Chikhi and Bensegueni, (2008), Teniou (2012), and Boucherit *et al*., (2014), who have shown that the docking program Surflex produces reasonable binding modes.

3.2 The Correlation Coefficient

Ligand code	Affinity (M^{-1})	log IC50	IC50 (nM)	References
SB7	4.90	2.204	E.coli PDF (160)	(Smith et al, 2003)
SB7	3.85	2.602	S. pneumoniae PDF (400)	(Smith et al, 2003)
SB9	4.16	3.342	S. pneumoniae PDF (2200)	(Smith et al, 2003)
Actinonin	3.61	3.4	human mitochondria PDF (2700)	(Escobar-Alvarez et al, 2009)
NVC	11.86	1.114	M. tuberculosis PDF (13)	(Pichota et al, 2008)
CHEBI :221511	6.5	1.995	E.coli PDF (99)	(Apfel et al, 2000)
VRC-3375	9.07	0.602	Staph. aureus (4)	(Chen et al, 2004)
CHEBI :221578	5.64	2.079	E.coli PDF (120)	(Apfel et al, 2000)
CHEBI :221385	7.75	1.361	E.coli PDF (23)	(Apfel et al, 2000)
CHEBI :221680	8.24	1.204	E.coli PDF (16)	(Apfel et al, 2000)
CHEBI :221679	6.29	1.041	E.coli PDF (11)	(Apfel et al, 2000)
CHEBI :183077	6.96	1.991	E.coli PDF (98)	(Apfel et al, 2001)
CHEBI :182677	6.18	2.491	E.coli PDF (310)	(Apfel et al, 2001)
CHEBI :183038	3.35	3.301	E.coli PDF (2000)	(Apfel et al, 2001)
CHEBI :220703	6.40	1.934	E.coli PDF (86)	(Apfel et al, 2000)
CHEBI :220856	6.13	1.973	E.coli PDF (94)	(Apfel et al, 2000)
CHEBI :221471	5.96	2.000	E.coli PDF (100)	(Apfel et al, 2000)
CHEBI :181951	3.85	2.880	E.coli PDF (760)	(Apfel et al, 2001)
CHEBI :182927	3.65	1.838	E.coli PDF (69)	(Apfel et al, 2001)
CHEBI :182317	2.02	2.113	E.coli PDF (130)	(Apfel et al, 2001)
CHEBI :182884	1.25	2.770	E.coli PDF (590)	(Apfel et al, 2001)
CHEBI :182677	6.18	2.491	E.coli PDF (310)	(Apfel et al, 2001)
SB-485345	4.98	2.204	E.coli PDF (160)	(Smith et al, 2003)
CHEBI :221711	4.56	2.204	E.coli PDF (160)	(Apfel et al, 2000)

Table 1: PDF inhibitors with reported antibacterial activity and affinities values
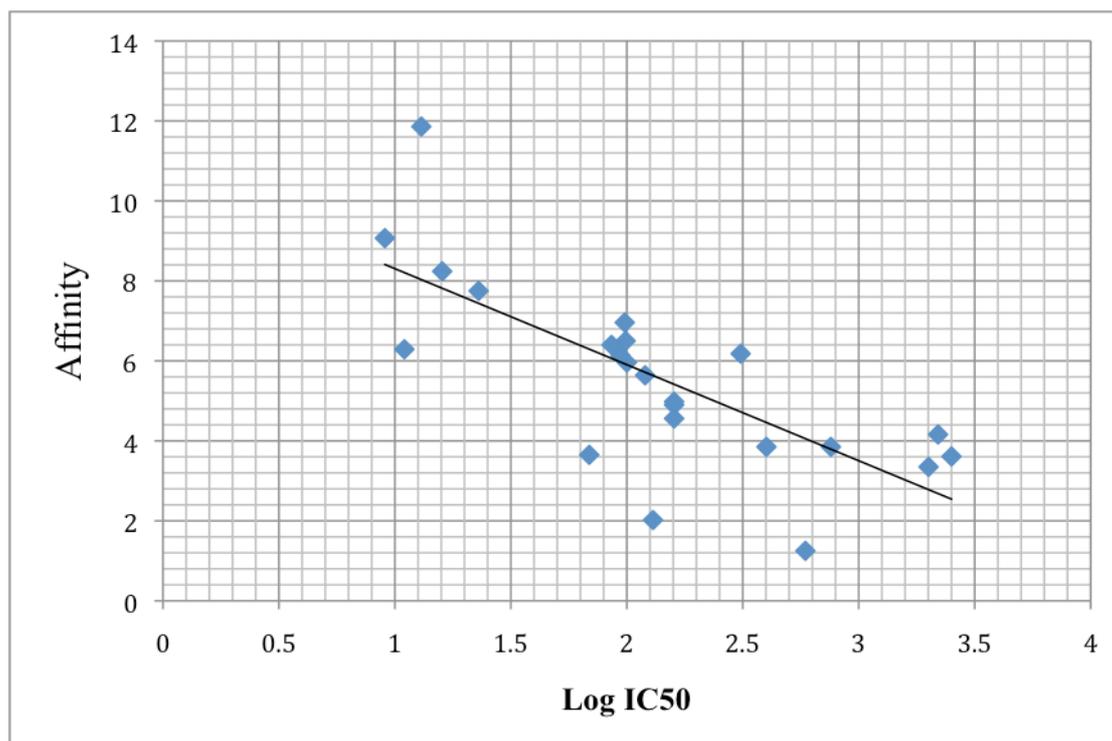
Figure 3: Correlation between biological activity (Log IC50) and affinities values of diverse complexes PDF-Inhibitors
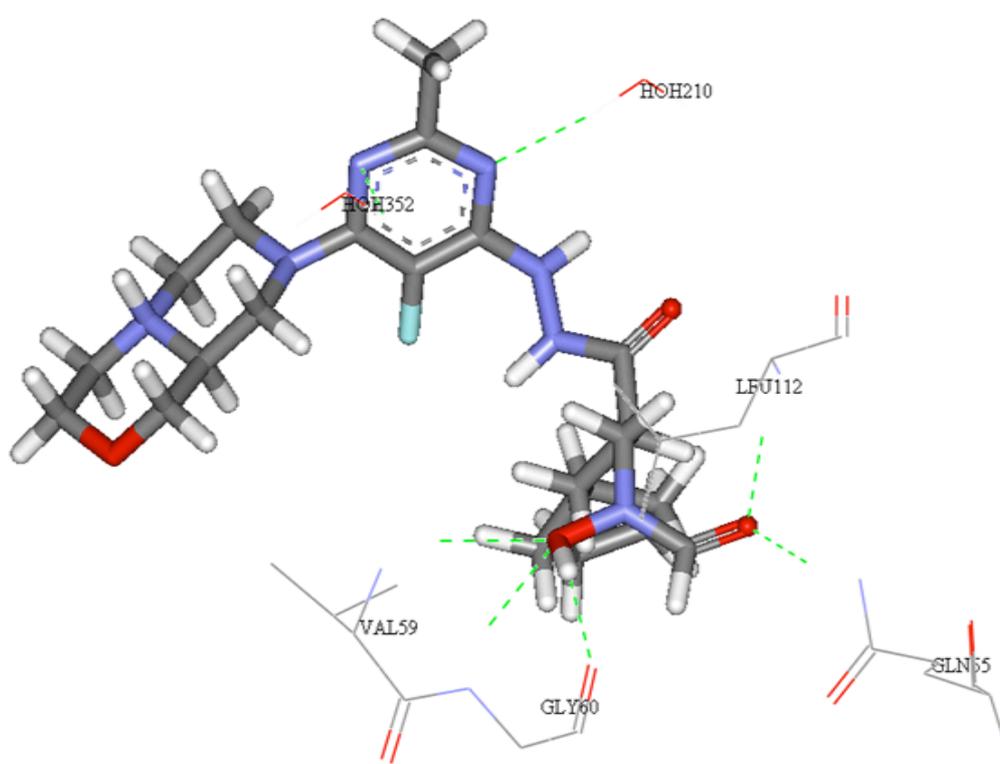

Figure 4: Docking results for compound GSK-1322322

In this study, the experimentally assessed correlation between the IC50of 23 complexes PDF-inhibitors were selected from the literature and their affinity (Table 1) was used to evaluate the ability of molecular docking software Surflex, result was gathered in the Fig. 3.

The best-docked configurations of the ligands were used to calculate affinity. The estimated affinities were plotted against the experimental inhibitory activities in Fig. 3 for all the compounds. Surflex results were in good agreement with the experimental values. A good correlation was observed with r = 0.728, which is in agreement with the results of Chikhi A and Bensegueni A., (2010), Kamel *et al.*, (2010), and Boucherit *et al.,* (2014). It demonstrated a good linear relationship and the trend could indicate that the docking program produced reasonable binding modes. It could be used to predict enzyme-inhibitors interactions.

3.3 Study of the Interactions Involved in the Inhibition of *Staph. aureus* PDF by GSK-1322322

Interesting interactions were detected between GSK-1322322 and *Staph. aureus* PDF. GSK-1322322 made several hydrogen bonds with amino acid residues of the binding pocket. In particular, the metal binding group was involved in five hydrogen bonds (Fig. 4), two by its carbonyl group with NH2 of Leu112 and lateral amine of Gln65, and three by its hydroxyl with NH2 of Val59, carbonyl and NH of Gly60 residue. The two nitrogen atoms of pyramidine ring were hydrogen bonded with HOH210 and HOH352.

The results obtained in our study were consistent with those found by other authors, e.g., O'Dwyer *et al.,* (2013) and Butler *et al.s,*(2014) who had shown that GSK1322322 was a powerful inhibitor of *Staph. aureus* peptide deformylase.

3.4 Docking GSK-1322322 derivatives

The last part of this work was devoted to modeling with the aim of the identification of new and more effective inhibitors of the PDF. We had taken compound GSK-1322322 as starting structure for the development of new potent inhibitors. The docking by Surflex of the GSK-1322322 and its similar had given the following results presented in Table 2. In most cases, the affinity of the GSK-1322322 derivatives was increased. Of the 40 inhibitors tested, the similar N° 14 (Fig. 5) forms the most stable complex protein-ligand, and had the best inhibitory effect with an affinity value of 11.49 M^{-1}.

Table 2: Affinities between Staph. aureus PDF and GSK-1322322 derivatives

N	Compound	Affinity (M-1)	N	Compound	Affinity (M-1)
1	GSK-1322322	8.39	21	CID 58000700	9.38
2	CID 58000537	9.03	22	D 58000653	8.02
3	CID 58000743	10.22	23	D 58000631	6.86
4	CID 58000629	9.74	24	D 58000601	7.96
5	CID 58000610	7.91	25	D 58000782	9.03
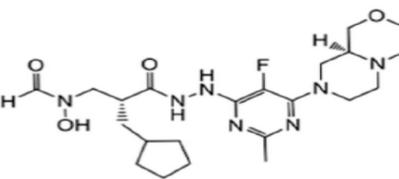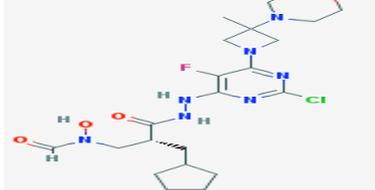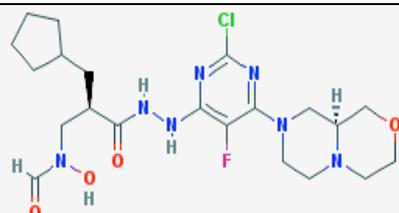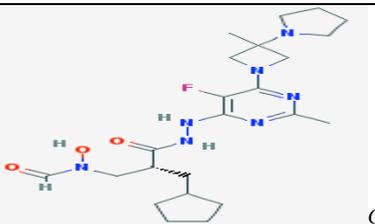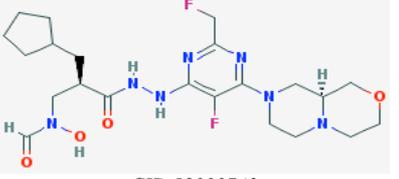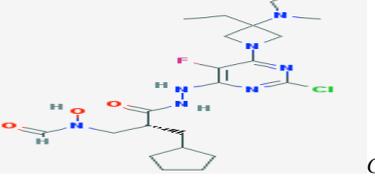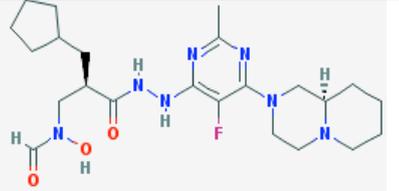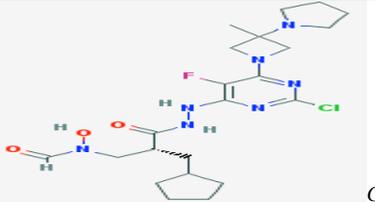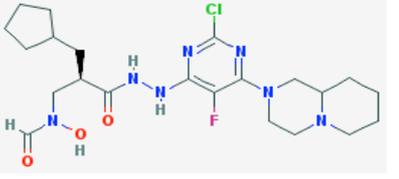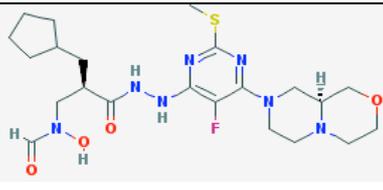
6	CID 58000721	7.46	26	D 66936306	10.00
7	CID 58000668	6.54	27	D 58000603	5.68
8	CID 58000679	8.41	28	D 58000576	9.94
9	CID 58000519	7.48	29	CID 58000573	10.29
10	CID 58000612	8.16	30	CID 58000566	10.44
11	CID 58000569	9.02	31	D 58000526	8.74
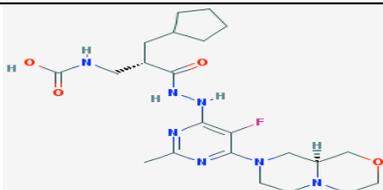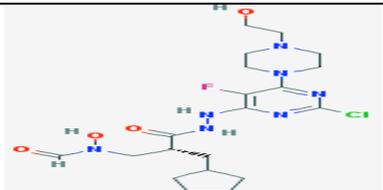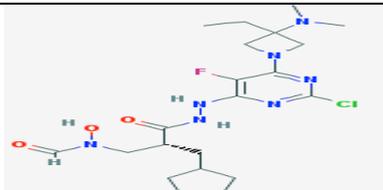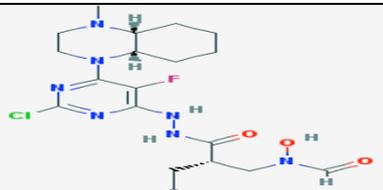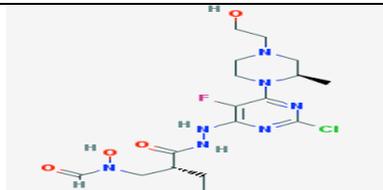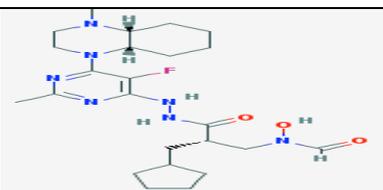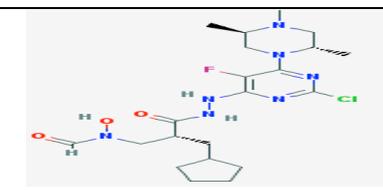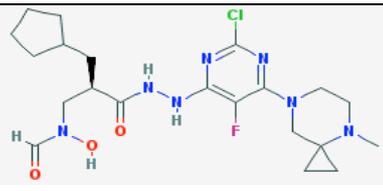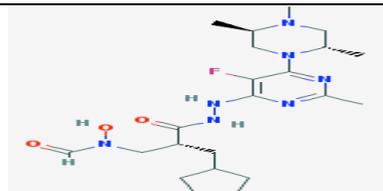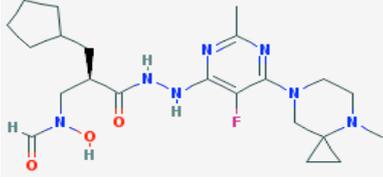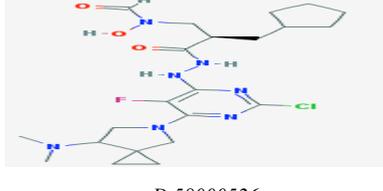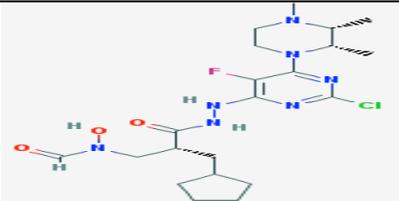
12	CID 58000735	7.41	32	CID 58000738	7.60
13	CID 58000639	9.15	33	D 58000687	7.90
14	**CID 58000550**	**11.49**	34	CID 77201119	10.12
15	CID 58000749	9.26	35	CID 66936126	9.05
16	CID 58000582	5.89	36	ID 58000778	8.72
17	ID 58000643	8.68	37	D 58000645	8.87
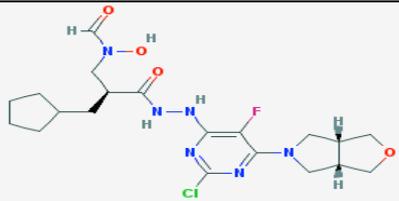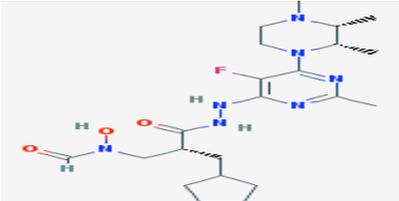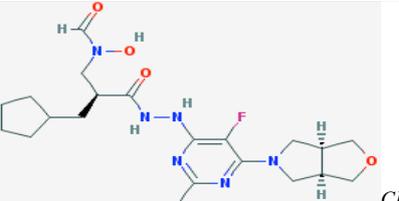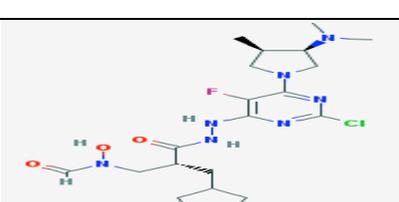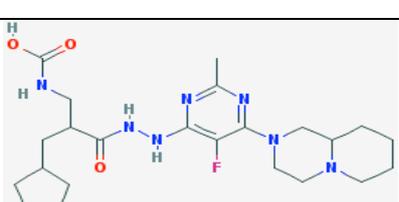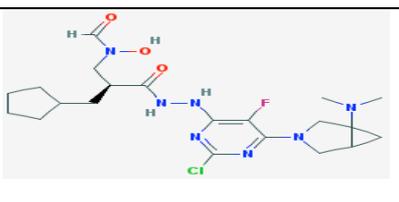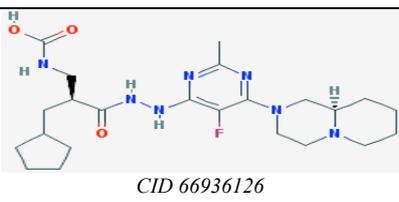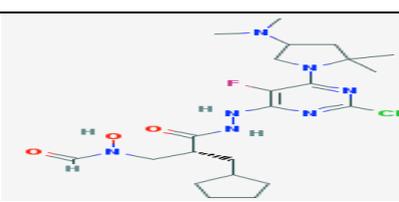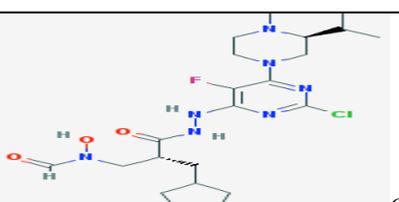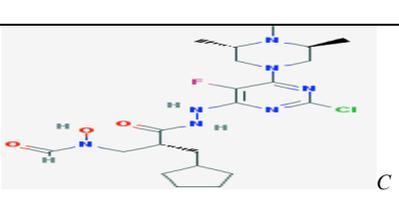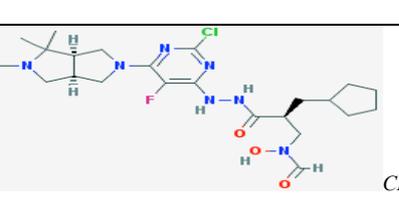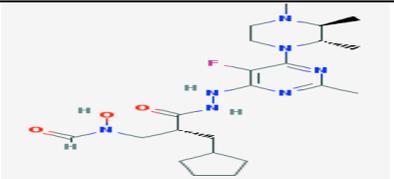
18	CID 58000531	8.63	38	D 58000767	9.83
19	CID 66936767	10.87	39	CID 58000711	6.29
20	CID 58000783	10.32	40	ID 58000762	8.53
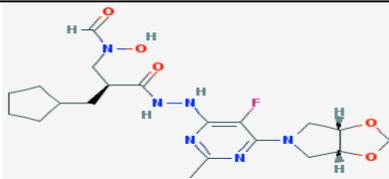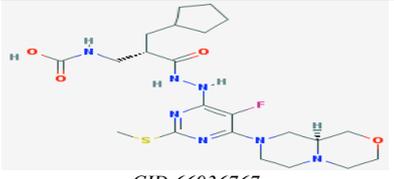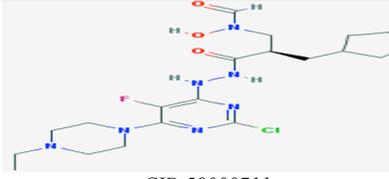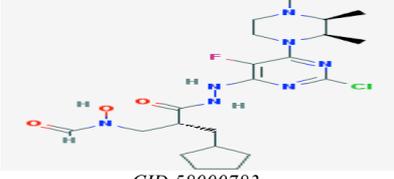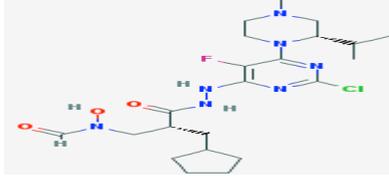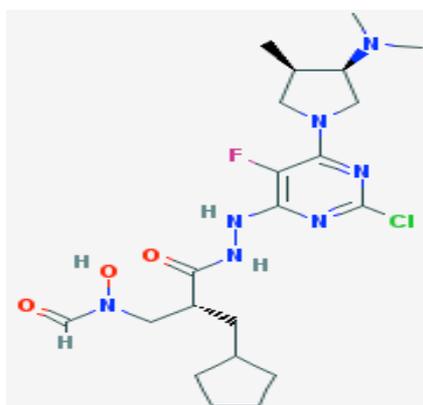
Figure 5: Chemical structure of Compound 14

Compound 14: *N-[(2R)-3-[2-[2-chloro-6-[(3R,4R)-3-(dimethylamino)-4-methylpyrrolidin-1-yl]-5-fluoropyrimidin-4-yl]hydrazinyl]-2-(cyclopentylmethyl)-3-oxopropyl]-N-hydroxyformamide*
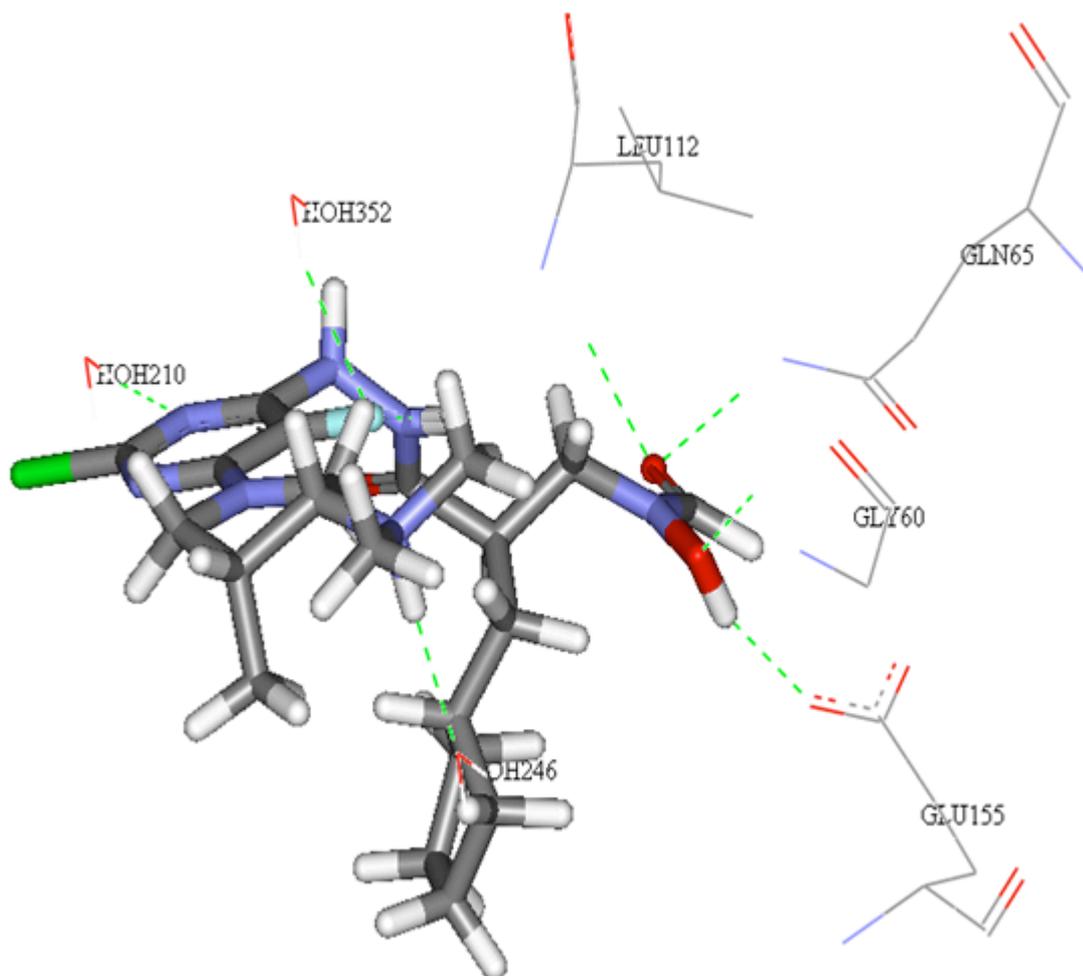
Figure 6: Binding modes of compound 14 with the active site of *Staph. aureus* PDF

A representative binding mode of the compound 14 with the active site of *Staph. aureus* PDF is given in Fig. 6. Compound 14 binds in the binding pocket of *Staph. aureus* PDF through the formation of various distinct hydrogen bonded with selected amino acid residues.

The affinity increase might be attributed to the formation of new interactions (Fig. 6). The metal binding group formed a new hydrogen bond with the carboxyl of Glu 155, the essential residue for PDF catalytic activity, by its hydroxyl group and the flour formed an additional hydrogen bond with HOH352.

Visual analysis showed that compound 14 was stabilized by the formation of five supplementary hydrogen bonds with amino acids residues of *Staph. aureus* PDF. The first and the second were formed between the carbonyl of metal

binding group of the inhibitor and amine function of Gln 65 and Leu 112. The third was formed between carbonyl function of Gly 60 and hydroxyl of inhibitor.

The forth hydrogen bond was observed between the nitrogen atom of pyramidine ring and HOH210. Finally, the amine of dimethylamino group Glu376 formed a hydrogen bond with HOH246.

3.5 Prediction of pharmacological properties

The ADME/Tox screening of the proposed compound 14 showed that it completed all the five Lipinski parameters, which indicate the potentiality of this compound to become a drug:

1. Molecular weight = 485.98 g/mol
2. Partition coefficient log P = 3.8
3. Hydrogen bond donors = 3
4. Hydrogen bond acceptors = 9
5. Flexible bonds = 9

Compound 14 was accepted to be orally bioavailable.

4. CONCLUSION

This study showed that the Surflex program can be used to predict enzyme-inhibitors interactions. The results indicate that the Surflex program did a rational job in docking and should assist significantly in the drug discovery process.

The inhibitory activity against PDF of GSK1322322 and its derivatives were tested using molecular docking with Surflex. Among the compounds studied, compound 14 was the best inhibitor of *Staph. aureus* PDF. Its affinity was increased from 8.39 to 11.49 M^{-1}. This new compound successfully passed ADME/Tox screening.

An *in vitro* and *in vivo* experimental study will later allow the verification of the theoretical results obtained *in silico*.

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ABBREVIATIONS

E. coli*: Escherichia coli*
IC50: The half maximal inhibitory concentration
M. tuberculosis: *Mycobacterium tuberculosis*
PDB: Protein Data Bank
PDF: peptide deformylase
RMSD: Root Mean Square Deviation
Staph. aureus: *Staphylococcus aureus*
S. pneumonia: *S treptococcus pneumonia*

Full Length Reproduction

Perfect Me Perfect Unity

Hanan Muhammed Abdul-Rashid *
Toronto (Canada)

PERFECT ME PERFECT UNITY

What a marvelous touch of a feeling
That suddenly reached my heart and cling
One step I took to the great pilgrimage
Has wiped clean my distorted image
Every breath I took I wish I grasped
Till my heartbeat stopped and body collapsed
Never have I experienced a smile of true bliss
With such calmness and state of great peace
I started touching my body with disbelief
For life outside was only tears, stress and grief
I almost panicked and flee
When suddenly attention circled and gripped me
Everyone was a reflection of everyone
But with faces from different continents, still they were one
The kindness reflected, honest words uttered,
Uniform ihrams and modest clothes dressed
Were all signs of Islamic Ummah's ultimate unity
Mingled with the individuals purity
How I wish the nations were centered just in Hajj
How I wish I lived and passed with my personality I discovered in hajj
For my soul and body's core
Has proved to imbibe delight through every pore

2008

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