EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 7
54-66
Year: 2016

RESEARCH OF NEW INHIBITORS OF *STAPHYLOCOCCUS AUREUS* METHIONINE AMINOPEPTIDASE BY COMPUTER SIMULATION

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Article Received on 08/05/2016 **Article Revised on 28/05/2016** **Article Accepted on 19/06/2016**

ABSTRACT

In the biomedical field, specifically in the search for new drugs for infectious diseases, molecular docking is a method of prediction potential interactions of complexes of small molecules into protein binding sites. Surflex is the one of molecular docking programs used to develop *in silico* of new inhibitors most powerful of enzymes. This software has been used to study the inhibition of the 1QXY, a methionine aminopeptidase belonging to *Staphylococcus aureus*, by various compounds. With a good percentage of the RMSD values (86%) lower than 2 Å and a correlation coefficient close to 1(r = 0.81), the performance of the program Surflex are indisputable. In our work, the affinities of 36 complexes 1QXY-inhibitors from the PDB have been tested. Among these inhibitors, the compound U16, has given by simulation with Surflex the best affinity of interaction (6.83 M^{-1}). Subsequently, we realized a molecular docking of a collection of 123 similar of the compound U16 from the PubChem. As a result of this screening, the compound CID_44370946 has a higher affinity (8.17 M^{-1}); we allowed proposing as new potential inhibitor of *Staphylococcus aureus* methionine aminopéptidase. The study of the pharmacokinetic properties of these similar shows that it fits perfectly in the margin of the criteria imposed by the rule of *Lipinski*. Finally to conclude our work we have proposed similar CID_44370946 as new potential inhibitor of *Staphylococcus aureus* methionine aminopeptidase.

KEYWORDS: Molecular Docking, Surflex, RMSD, the correlation coefficient, methionine aminopeptidase, *Staphylococcus aureus*.

INTRODUCTION

Bacterial resistance to antibiotics remains today a major problem of public health; the situation appears particularly worrying in the hospital environment.[1, 2] Among the most implicated microorganisms in these infections is *Staphylococcus aureus.*[3] S. aureus is at once a commensal germ and a major pathogen of humans, involved in 1 to 5% of infections in the community and up to 30% of infections acquired in hospitals. The treatment of S. aureus infections is more and more difficult due to the high prevalence of multi-resistant strains to antibiotics.[4]

A thematic used to treat antibiotic resistance problem is to find new therapies against a threat of more and more resistant to drugs against infections with *S. aureus*. In this context, the methionine aminopeptidase (MetAP.EC 3.4.11.18) has become an attractive target for the development of antimicrobial therapy because it is essential to bacterial survival. The MetAP is metalloprotein that catalyzes the removal of the initiator N-terminal methionine of nascent proteins, an essential step in the maturation of the proteins. MetAP is a ubiquitous enzyme in all prokaryotes and eukaryotes.[5, 6] In this title, the study of molecular interactions between the MetAP and the new inhibitors is based on the use of new molecular modeling approaches grouped together under the name of molecular docking. The molecular docking is the name given to the Molecular simulations in which different approaches are combined to study the modes of interaction between two molecules. In most cases, it is a macromolecular receptor most often a protein (target) and a small molecule (ligand).[7]

The purpose of this study is

- To test, in a first time, the reliability of the Surflex program used in this study to examine protein-ligand interactions;
- In a second time, we studied the inhibition of the methionine aminopeptidase of *S. aureus* by

computer simulation methods in order to propose *in silico* new inhibitors more powerful.
- Finally, study the biological properties ADME of the newly proposed compound.

1. MATERIALS AND METHODS 2.1.Computer

We used two powerful microcomputers (Toshiba) with a memory of 4 GB and 2 GB respectively and a processor 2.40 and 2.10 Ghz I Intel Core i3. All software used are installed under the operating system Windows 7, 32 bits version 2009.

2.2.The PDB" Protein Data Bank"

The PDB[8] is a world bank of data of three dimensional structures of biological macromolecules, mainly of proteins and nucleic acids. These structures are primarily determined by two methods: The crystallography to X-rays and the NMR. The consultation of the structures is free and can be done via the internet. His email address

is: **http://www. rcsb.org/pdb.**

2.3. Preparation of molecules for Molecular docking

The protein-ligand complex is downloaded in the *.pdb* format from the data bank by introducing its code.

ID. We have eliminated all the molecules in required of the structure of protein (the water molecules, metal ions, the different ligands of molecules, the information of cristallographies); whereas the structure of the ligand is downloaded directly in the format *.sdf*. The Surflex software requires the format *.mol2*. Therefore the two molecules (protein, ligand) are processed in the format *.mol2* via Open Babel program.

2.4.Programs used 2.4.1. Surflex

Surflex (1.3, 2005) is fast calculation software of docking for small molecules in the active site of proteins with a good accuracy.

The use of molecular docking passes through three stage.[9]
- The search for a way to define the active site either from a ligand, either from the receptor without ligand.
- A pseudo-molecule called "protomol" which will serve as a target for different ligands.
- Docking of one or several ligands.

2.4.2. Viewerlite

Viewerlite is a free tool for viewing, which allows a 3D view of a structure of biological molecule. We have used this program for the visualization of different interactions formed between the active site of MetAP and these inhibitors.

2.4.3. Open Babel

The free software OpenBabel is a system primarily used in applications of chemo-informatics for converting chemical structures files. We have used this program to convert the *.pdb* format of the protein and. *sdf* format of the ligand in *.mol2* format and also to add hydrogen atoms to the structure of the protein and the ligand.

2.5. Evaluation of Programs

2.5.1. The RMSD (root mean square deviation)

It is the ability of a program to reproduce the experimental binding modes of a ligand. For this, a ligand in its structure obtained by X-ray crystallography is docked in its site of binding and then the binding mode docked is compared with that obtained experimentally and a RMSD between the two is calculated. A good RMSD is that less than or equal to 2 Å. The current standard for evaluating the performance of a docking program is to do a test from several hundreds of complex protein-ligands crystallized.[10, 11]

2.5.2. Correlation coefficient

The Pearson correlation coefficient is used to evaluate the intensity and the direction of the linear relationship between two sets of data from the sampling of two variables metric. The values of the coefficient of correlation located between -1 and 1.[12] To study the correlation between the score obtained by the molecular docking and biological activity (IC50), we have used the various inhibitors of methionine aminopeptidase (MetAP), these inhibitors known across the PDB. In total, 23 molecules of *Staphylococcus aureus*[13] have been tested.

2.6. Choice of a crystallographic structure

We chose a code of good quality of the enzyme MetAP of *S.aureus*; 1QXY.

The characteristics of this enzyme are presented in the table1 below.

Table1: Main characteristics of code 1QXY.

Code	Resolution (Å)	R factor	Classification	Number of chain	Number of AA by chain	Number of atoms by chain
1QXY	1.04	0.144	3.4.11.18	1	251	1910

2.7.Inhibition of 1QXY by Surflex 2.7.1. The choice of 1QXY

Three dimensional structures for methionine aminopeptidase of *S.auerus* are available on the PDB, identified by codes: 1QXY, 1QXW, 1QXZ. The 1QXY structure (see fig. 1) has been chosen for our study, because it constitutes a compromise between good resolution and presence of co-crystallized inhibitor.

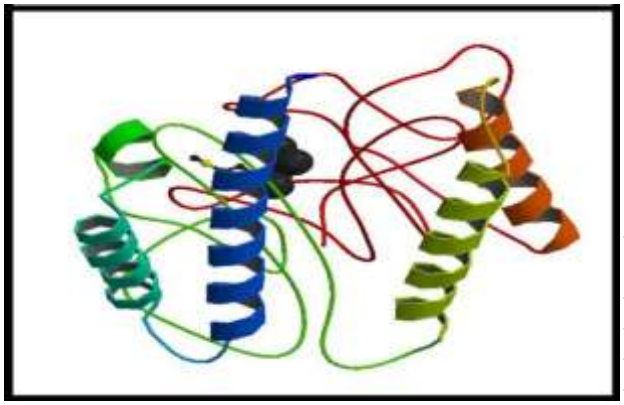


Fig. 1: Structure of 1QXY.

2.7.2. Rule of *Lipinski*

Each potential drug must comply with several basic criteria, such as its low cost of production, be soluble, stable, but must also comply with the scales associated with its pharmacological properties of absorption, distribution, metabolism, excretion and toxicity.

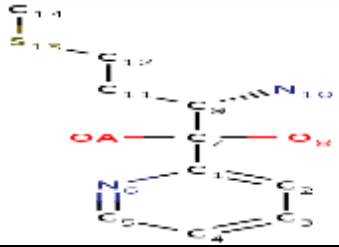
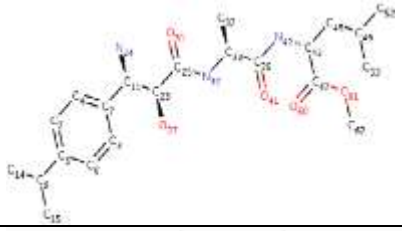
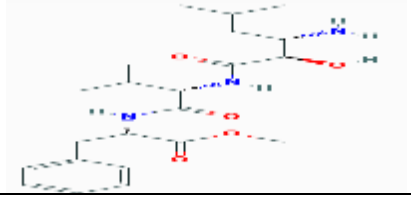
This method is essentially based on the Rule of 5 of *Lipinski.*[14, 15] In addition, Veber[16] has introduced two additional criteria to what is today commonly called "the rule of 5". The polar surface area (PSA) of compound must be less than 140° ² and the number of rotatable bonds must be less than 15.

- A molecular weight maximum should not be higher than 500 daltons (Da).
- A coefficient of partition (logP) ≤ 5.
- A number of donors of hydrogen bonds ≤ 5.
- A number of acceptors of hydrogen bonds ≤ 10.

2.7.3. Inhibition of the 1QXY by various inhibitors

We have selected the three compounds that act on the MetAP of *S.aureus*. The structures of the ligands studied are represented in the table 2 below.

Table2: Structure of ligands studied.

N°	Compound	Ligands Code	Name
1		M2C	(2S)-2-AMINO-4-(METHYLSULFANYL)-1-PYRIDIN-2-YLBUTANE-1,1-DIOL
2		U16	METHYL N-[(2S,3R)-3-AMINO-2-HYDROXY-3-(4-ISOPROPYLPHENYL)PROPANOYL]-D-ALANYL-D-LEUCINATE
3		CID_44370946	METHYL (2S)-2-[[(2S)-2-[[(2R,3S)-3-AMINO-2-HYDROXY-5-METHYLHEXANOYL]AMINO]-3-METHYLBUTANOYL]AMINO]-3-PHENYLPROPANOATE

3. RESULTS AND DISCUSSIONS

The work realized here articulates in two parts. The first part deals with the performance of the program used. The second part describes the study of interactions involved in the inhibition of the MetAP of *Staphylococcus aureus* by various molecules available in the PDB.

3.1.Tests of reliability of the docking program.

The performance of program of docking Surflex is judged by three criteria.

- The root mean square deviation (RMSD);
- Visual analysis;
- The correlation coefficient (r).

3.1.1. The RMSD

- In our case, the reliability test of the Surflex program by the RMSD has been carried out on 127 protein-ligand complexes derived randomly from the PDB. In the following figure, the results are given in percent (%), at two intervals of RMSD represented by different colors for the Surflex program.

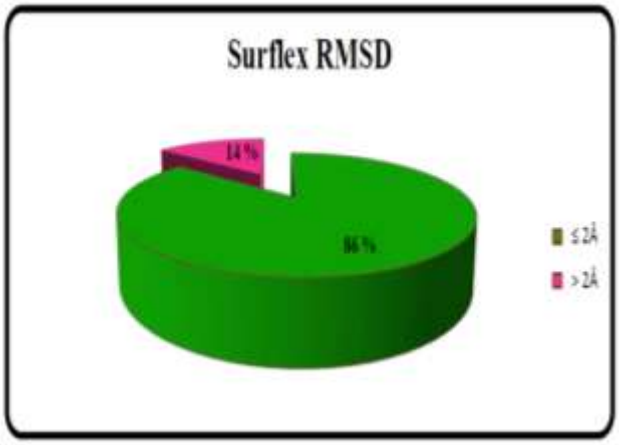


Fig. 2: Results in percentage of the RMSD test at two intervals.

The figure 2 shows that 86% of RMSD values are less than or equal to 2 Å and that only 14 % of results are higher than 2 Å. In accordance with the work of Boucherit H et *al* (2014)[17], Teniou S. (2012)[18] and Vieth et *al* (1997).[19] This result is also comparable to that reported by Chikhi A and Bensegueni A (2008)[20] and Gabb et *al* (1997)[21], which shows that any program of docking is successful when the RMSD is less than 2 Å. This is also consistent with the results obtained by Zaheer-ul-Haq et *al* (2010)[22], where six docking programs have been used: FRED, GOLD, MOE, AutoDock, FlexX and Surflex for a comparative study. The calculation of the RMSD shows that the best results were obtained by Surflex and GOLD.

3.1.2. Visual analysis by MSViewer

The visual analysis allows you to visualize the results described by the numerical value of RMSD. For the three complexes MetAP-inhibitor chosen, the visual analysis by Surflex shows that the models of the inhibitors simulated by the software (colored in pink) are correctly positioned in the active site of the methionine aminopeptidase. They have, in each time, of spatial conformations very close or even superimposable to those determined experimentally by crystallography that is found in the PDB (colored green). The results are represented in the table3 and fig. 3.

Table 3: RMSD values of the 3 complex MetAP studied.

PDB Code	Ligands Code	RMSD (Å)
1QXY	M2C	1.169
1XNZ	FCD	0.164
2GG9	U16	0.11

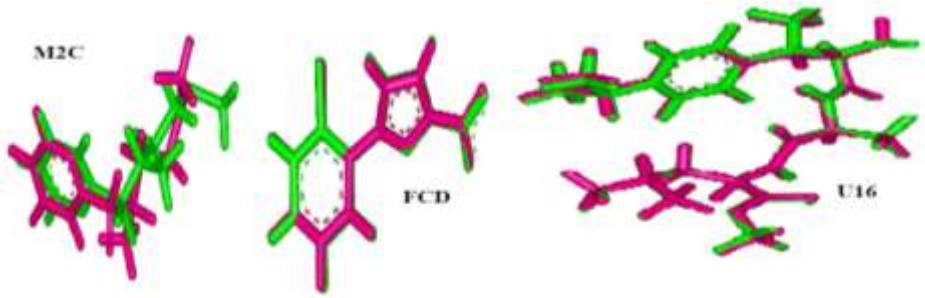


Fig. 3: Superposition of the ligand given by X-ray (colored green) and by molecular docking (colored in pink) with Surflex.

3.1.3. The linear correlation coefficient (r)

The correlation coefficient indicates the degree of linear relationship between the affinity obtained by molecular docking with surflex and IC_{50} determined experimentally. In this study, inhibitors of the MetAP from the PDB have been examined. In total, 23 complex (MetAP-inhibitors) have been tested by the Surflex software. The results of docking of inhibitors studied as well as their IC_{50} values are represented in the table 4.

Table 4: Results of the analysis by linear regression on the inhibitors of the MetAP.

N	Code	IC_{50} (µM)	Log IC_{50}	Affinity (M^{-1})
1	1QXY	16	1.20	4.28
2	1QXZ	19	1.27	4.04
3	1XNZ	0.24	-0.61	1.83
4	2BB7	2.14	-0.33	2.27
5	2EVM	0.69	-0.16	2.27
6	2EVO	0.067	-1.17	2.40
7	2GG2	0.25	-0.60	2.42
8	2GG3	0.58	-0.23	2.19
9	2GG5	0.25	-0.60	2.58

10	2GG7	1.75	0.24	2.71
11	2GG8	25	1.39	4.98
12	2GGB	12	1.07	5.14
13	2P9A	1.16	0.06	2.42
14	2P99	1.16	0.06	2.69
15	2Q93	0.55	-0.25	3.48
16	2Q94	0.36	-0.44	2.22
17	2Q95	1.56	0.19	3.03
18	2Q96	1.22	0.08	3.95
19	3IU8	0.58	-0.23	3.06
20	3PKB	0.26	-0.58	2.89
21	3PKC	0.96	-0.01	2.91
22	3PKD	0.76	-0.011	3.67
23	3PKE	250	-2.39	4.15

The linear regression analysis yielded the correlation curve next (see fig. 4).

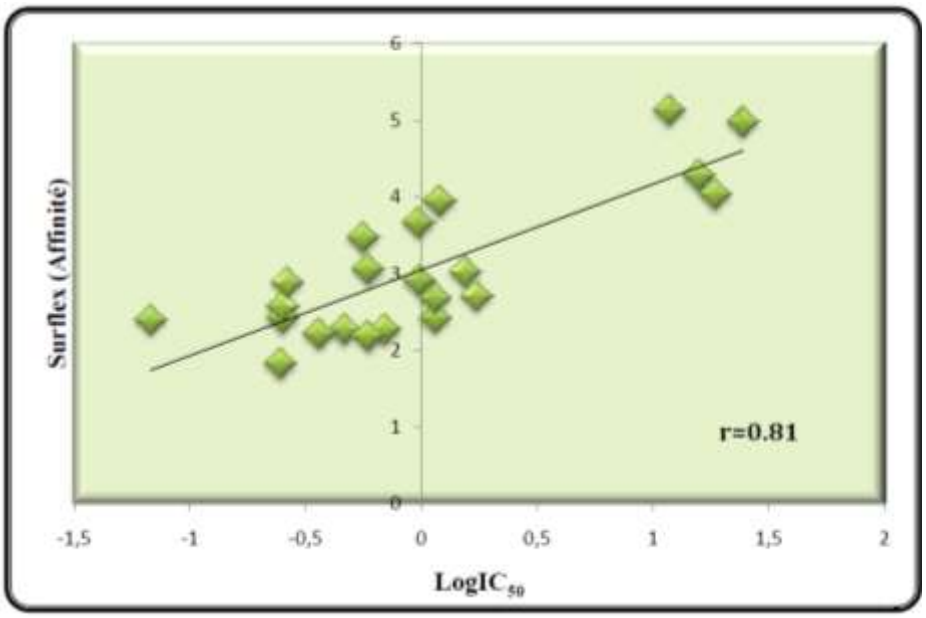


Fig. 4: correlation between the biological activity (LogIC$_{50}$) inhibitors of the MetAP and their affinities data by Surflex.

The graph shows that the value of the coefficient of correlation is greater than 0.5 ($|r| \geq 0.5$).[23] The Surflex program establishes a strong correlation (r = 0.81) between the result of docking (affinity), and the biological activity represented here by logIC$_{50}$; which is in agreement with the results of Boucherit H et *al*. (2014)[17] Mokrani E-H. (2012)[24], Chikhi A and Benseguenі A. (2010)[25] and Kamel M. M et *al*. (2010).[26]

In the light of the results of the test RMSD, visual analysis and the coefficient of the linear correlation, we can conclude that the program Surflex works correctly. So we can use it without too much risk of errors to study deeply the mechanism of inhibition of the MetAP by these inhibitors.

3.2.Study of interactions involved in the inhibition of the MetAP of *Staphylococcus aureus.*

3.2.1. Interaction 1QXY-M2C

To treat the mode of interaction of various inhibitors with the active site of the enzyme MetAP of *S. aureus* by the method of molecular docking, we have used the Surflex program which allows presenting the hydrogen bonds; these are the most important among the weak links.

The amino acids of the active site of the enzyme MetAP

Asp59, Glu60, Cys67, His76, Asn91, Asp93, Ser95, Asp104, Trn105, Trn166, His168, His175, Glu202, Gln231, Glu233.

Our approach is to study the interaction of the enzyme MetAP of *S. aureus* with the reference ligand M2C. The result is shown in fig. 5.

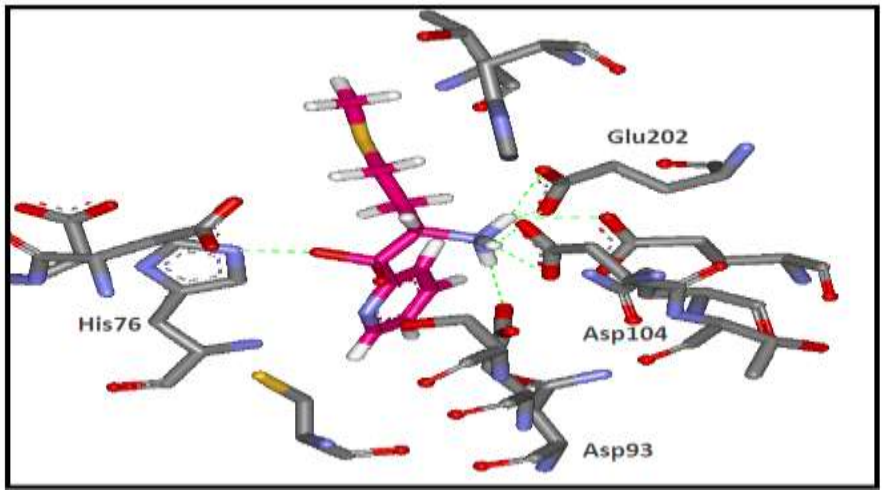


Fig. 5: docking of the inhibitor M2C in the active site of the 1QXY.

The fig. 5 shows the active site of the methionine aminopeptidase complexed with the inhibitor M2C. The inhibitor and the amino acids of the active site are represented in "stick" of different colors.

Visualization of results of the docking shows that the inhibitor M2C form with the active site of the MetAP seven hydrogen bonds with a few amino acids of the active site.

- Two hydrogen bonds are observed between the NH group of the inhibitor M2C and the carboxyl of Glu202 (H-N……. O_{E1DE2D}-C-Glu202) and (N-H…….O-C-Glu202).
- Two bridges of hydrogen are observed on the one hand between the NH group of the inhibitor and on the other hand with the carbonyl of the Residue Asp104 (N-H…….O_{D1GD2G}-C-Asp104) and (N-H…….O-C-Asp104).
- A hydrogen bond is observed between the carbonyl function of Glu233 and the NH group of the inhibitor (N-H…….O_{E2}-C_D-Glu233).
- A hydrogen bond is formed on the one hand between the NH of the inhibitor and on the other hand with the carbonyl of residue Asp93 (N-H…….O_{D1G}-C-Asp93).
- A last hydrogen bond is observed between the carbonyl of the inhibitor M2C and one of the nitrogen atoms of the cycle of His76 (C-O…….N_{E2}-His76). The following figure visualizes these interactions.

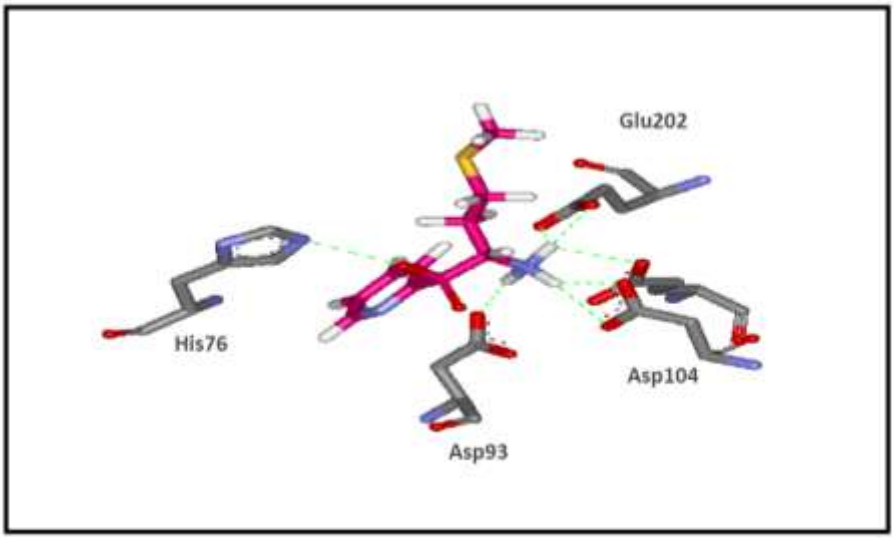


Fig. 6: Representation of the hydrogen bonds formed by the inhibitor M2C.

3.2.2. Interaction 1QXY-inhibitors

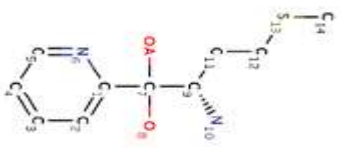
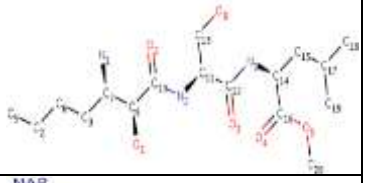
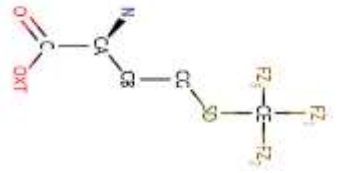
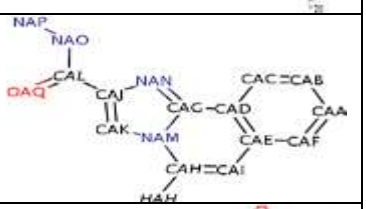
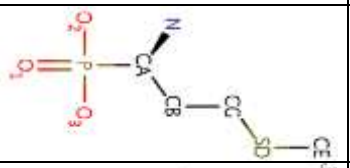
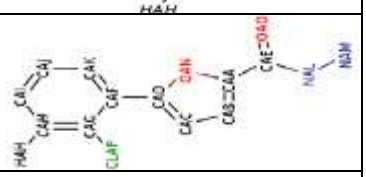
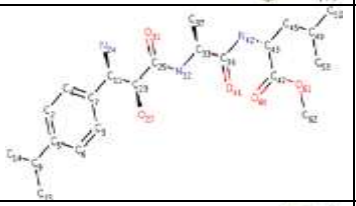
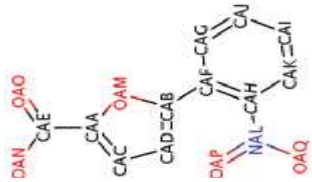
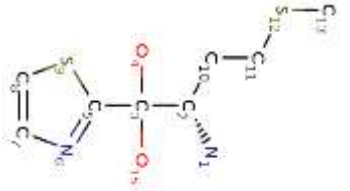
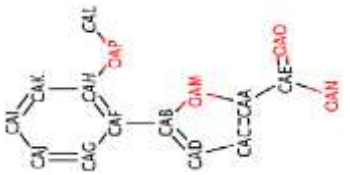
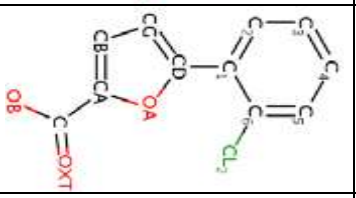
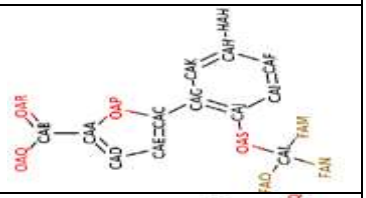
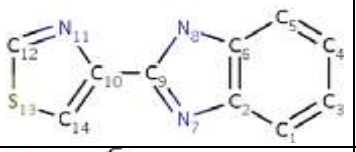
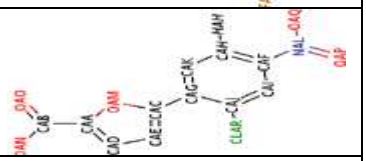
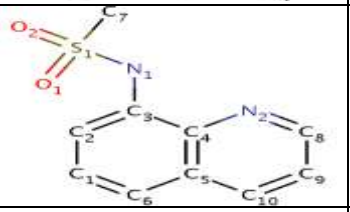
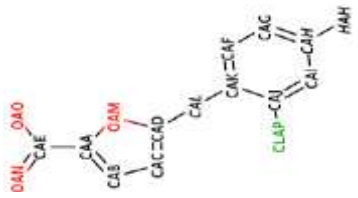
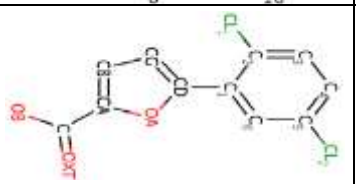
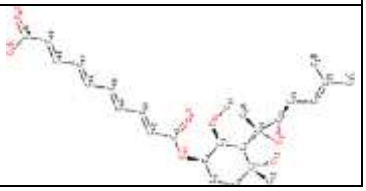
The docking of 36 molecules derived from the PDB is performed on the crystallographic structure 1QXY. We have compared the result of docking of these inhibitors (affinity) with the ligand of reference and propose the best inhibitor of the enzyme MetAP.

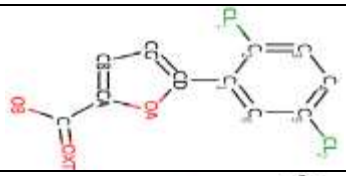
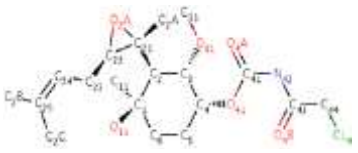
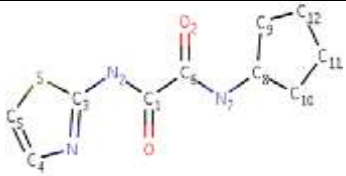
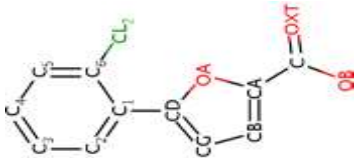
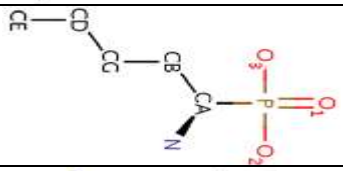
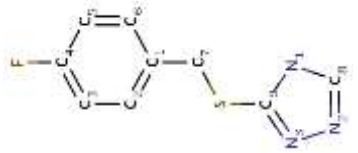
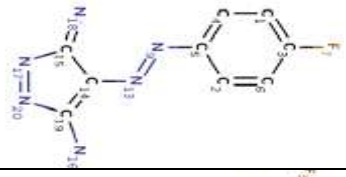
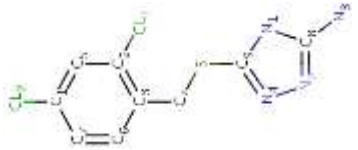
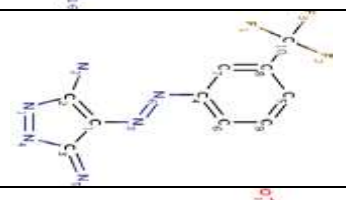
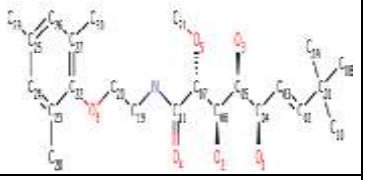
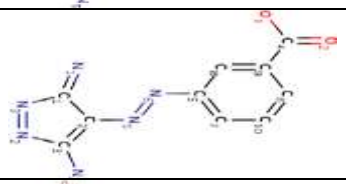
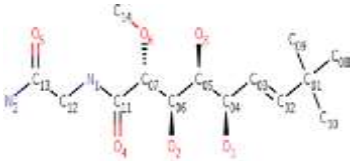
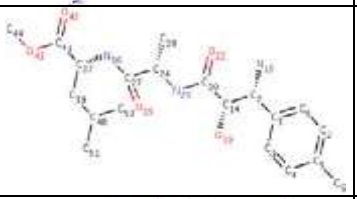
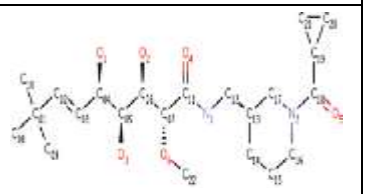
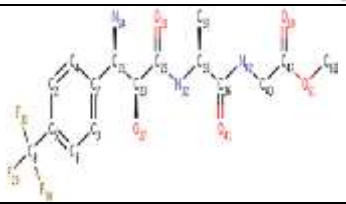
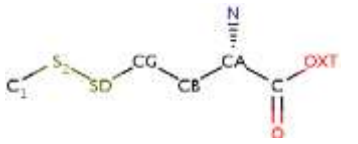
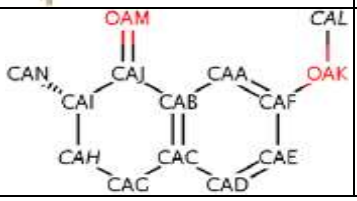
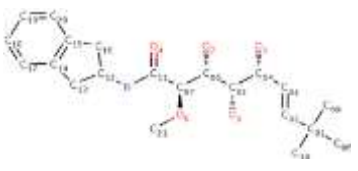
The results of docking are presented in the table 5.

The first result (affinity) is that of the reference ligand (inhibitor M2C) and the others correspond to the various

inhibitors tested. We have chosen the inhibitor M2C as a reference because it is the first proposed ligand as an inhibitor of the MetAP of *S.aureus.*

Table 5: Result of docking with the Surflex program.

N.	PDB code of the ligand	Affinity (M^{-1})	Structure	N	PDB code of the ligand	Affinity (M^{-1})	Structure
1	M2C	4.28		**19**	U17	5.00	
2	MF3	3.97		**20**	YE7	3.49	
3	MPH	5.77		**21**	YE6	3.11	
4	U16	6.83		**22**	B23	3.92	
5	M3C	3.28		**23**	B21	3.32	
6	FCD	3.13		**24**	A04	3.84	
7	TMG	3.11		**25**	A05	3.14	
8	QMS	3.64		**26**	A18	2.44	
9	FC2	3.54		**27**	FUG	2.58	

10	U19	2.58		**28**	TN4	1.81	
11	CT0	3.55		**29**	FCD	3.95	
12	NLP	4.75		**30**	T03	3.25	
13	U13	2.40		**31**	T07	3.76	
14	U12	3.47		**32**	Y02	5.35	
15	U14	3.48		**33**	Y16	5.03	
16	U15	5.73		**34**	Y08	3.15	
17	U11	5.17		**35**	SCH	6.51	
18	7NP	3.05		**36**	Y10	3.17	

Among the complex MetAP-inhibitor contained in the table 5, the compound U16 has the best result of docking (affinity = 6.83 M^{-1}), so it can be considered as the most potent inhibitor of methionine aminopeptidase of *S. aureus.*

3.2.3. Rule of *Lipinski*

Before studying the mode of interaction between the enzyme MetAP and compound selected, it was very important to complete this study by the application of the method of filtering ADME/Tox which is based on the Rule of 5.[14,15] The result is shown in the table 6.

Table 6: The criteria of the rule of Lipinski for the inhibitor studied.

N	compounds	PM	nOH,NH	nO, N	Clog P	nrotb
4	U16	421.53	4	5	1.73	11

PM: molecular weight; **nOH, NH :** number of H bonds donors; **nO, N:** number of H-bonds acceptors; **clogP:** logP or partition coefficient calculated; **nrotb:** rotable bonds.

The table 6 shows that the compound U16 studied responds perfectly to the rule of Lipinski. In accordance with the results of *Lipinski*[14,15]' this molecule is able to present a biological activity without having problems of absorption by oral route.

However, other criteria are taken into account in the selection of molecules potentially candidates (see table7).

Table7: Other Criteria.

N	compounds	Number of halogen	alkyl chains	Number of Cycles	Number of oxygen atom	Number of nitrogen atom
4	U16	0	0	1	5	3

The result of the table 7 shows that the compound U16 studied fits perfectly in the margin of these criteria. The visual analysis shows that the inhibitor U16 is well placed in the active site of the enzyme MetAP (see fig. 7). It establishes six hydrogen connections.

- Two bridges of hydrogen are observed between the NH group of the inhibitor and the carbonyl of Glu202 (N-H…….O_{E1}-C_D-Glu202) and (N-H…….O_{E2}-C_D-Glu202). - Two bridges hydrogen are stabled between the NH group of the inhibitor and the carbonyl function of Glu233 on the one hand and the carbonyl function of Asp93 on the other hand (N-H …….O_{E1}-C_D-Glu233) and (N-H…….O_{D1}-C_G-Asp93).
- A hydrogen bond is formed between the carbonyl function of Asp104 and the hydroxyl of the inhibitor (O-H……OD1-CG-Asp104).
- A hydrogen bond is formed between the NH group of the inhibitor and the carbonyl function of residue Asp104 (N-H…….O_{D2}-C_G-Asp104).

The following fig. 7 View the interactions.

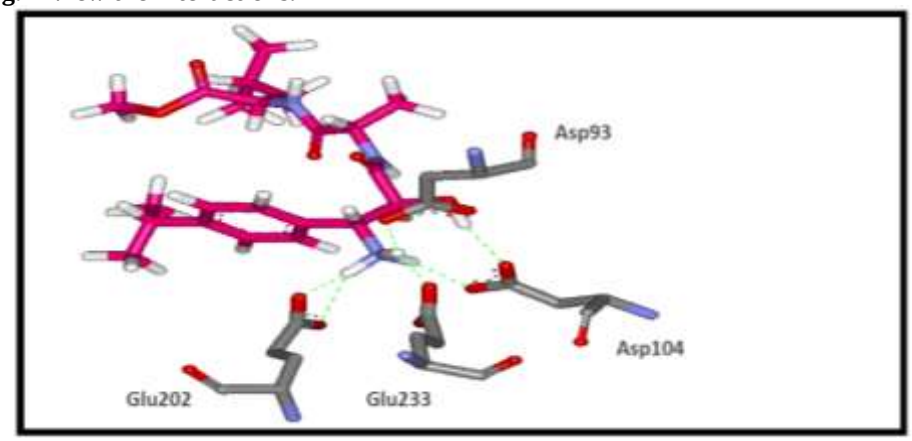


Fig. 7: Representation of the hydrogen bonds of the compound U6 in the active site of MetAP.

For this we have chosen this compound as a model in order to interpret their different interactions established between the enzyme and the inhibitor.

3.3.Proposal of new inhibitors of methionine aminopeptidase of *S. aureus*

3.3.1. Inhibition of the MetAP by the similar of the inhibitor U16

In the aim of finding new inhibitors the most powerful of the MetAP of *S. aureus*, we have made the molecular docking of a collection of 123 similar of the compound U16 with 90% similarity. These chemical compounds are downloaded from the PubChem database. The results of docking by Surflex are presented in the table 8.

Table 8: Affinity of 123 similar to the inhibitor U16.

Number	Code of the inhibitor	Affinity (M^{-1})	Number	Code of the inhibitor	Affinity (M^{-1})
1	CID_449548	-137.02	**63**	CID_59907094	-71.47
2	CID_6914645	- 43.77	**64**	CID_59907109	-76.93
3	CID_6914647	- 67.45	**65**	CID_59907129	-93.70
4	CID_6914684	-81.45	**66**	CID_60017178	-70.22
5	CID_9927170	-62.37	**67**	CID_60163070	-83.65
6	CID_10024419	-73.79	**68**	CID_66553210	-85.14
7	CID_10250032	-62.63	**69**	CID_66747105	-101.97
8	CID_10349769	-193.00	**70**	CID_66747864	-98.80
9	CID_10636385	-38.87	**71**	CID_66747877	-98.21
10	CID_10660316	-38.37	**72**	CID_67561042	-89.42
11	CID_11080827	-99.19	**73**	CID_67561249	-65.61
12	CID_11524030	-64.11	**74**	CID_68809105	-81.59
13	CID_11576841	-85.07	**75**	CID_69029540	-95.43
14	CID_11654865	-79.41	**76**	CID_70092990	-68.08
15	CID_11784202	-62.53	**77**	CID_70093444	-74.24
16	CID_12015843	-64.76	**78**	CID_70095050	-76.95
17	CID_12819558	-75.83	**79**	CID_70321927	-42.73
18	CID_12854544	-115.54	**80**	CID_70503453	-83.57
19	CID_20843162	-67.45	**81**	CID_70509898	-87.43
20	CID_12945766	-66.64	**82**	CID_70511049	-87.43
21	CID_12945768	-71.76	**83**	CID_70581568	-44.65
22	CID_12988911	-48.29	**84**	CID_70838476	-52.93
23	CID_16741223	-105.23	**85**	CID_70973469	-85.73
24	CID_20300678	-40.60	**86**	CID_70973481	-104.98
25	CID_20752346	-56.77	**87**	CID_72946549	-89.06
26	CID_20752683	-90.64	**88**	CID_73345714	-107.42
27	CID_20752685	-84.30	**89**	CID_73345715	-112.31
28	CID_20752687	-65.34	**90**	CID_73350150	-109.94
29	CID_20810579	-70.21	**91**	CID_73924373	-45.43
30	CID_20843160	-43.71	**92**	CID_73924390	-74.34
31	CID_20843161	-69.94	**93**	CID_73924463	-45.43
32	CID_20843163	-81.43	**94**	CID_73924480	-74.34
33	CID_23647795	-81.43	**95**	CID_73933787	-45.43
34	CID_23647796	-67.45	**96**	CID_73933804	-74.34
35	CID_24849974	-63.61	**97**	CID_73933877	-45.43
36	CID_24916901	-145.38	**98**	CID_73933894	-74.34
37	CID_24916902	-144.98	**99**	CID_78065659	-58.73
38	CID_44370803	-126.24	**100**	CID_88573825	-73.84
39	CID_44370809	-136.30	**101**	CID_89807932	-62.26
40	CID_44370862	-136.30	**102**	CID_89808170	-68.59
41	CID_44370882	-85.11	**103**	CID_90655733	-65.70
42	CID_44370888	-126.24	**104**	CID_90655734	-44.56
43	CID_44370929	-113.74	**105**	CID_90663501	-106.43
44	CID_44370946	8.17	**106**	CID_90675073	-45.61
45	CID_44373435	-113.55	**107**	CID_90675074	-45.61
46	CID_44373652	-110.97	**108**	CID_90675326	-59.71
47	CID_44373815	-106.39	**109**	CID_90675327	-59.71
48	CID_44515317	-74.04	**110**	CID_90888423	-79.02
49	CID_49803791	-103.61	**111**	CID_90961150	-64.27
50	CID_49861037	-123.14	**112**	CID_91129368	-85.84
51	CID_49861038	-125.07	**113**	CID_100966022	-154.77
52	CID_49861042	-125.07	**114**	CID_101052199	-62.22
53	CID_49861043	-123.14	**115**	CID_101177680	-61.71
54	CID_51356562	-66.99	**116**	CID_101398910	-133.43
55	CID_51380937	-65.00	**117**	CID_101536046	-73.08

56	CID_54071727	-86.66	**118**	CID_103262890	-46.90
57	CID_54071728	-86.66	**119**	CID_103263917	-54.19
58	CID_54131195	-68.57	**120**	CID_106112357	-38.52
59	CID_54143250	-46.68	**121**	CID_106112726	-38.06
60	CID_57511263	-40.96	**122**	CID_114145224	-38.52
61	CID_59655562	-74.80	**123**	CID_249062904	-62.62
62	CID_59906914	-54.84			

According to the results of this table, the similar N°. 44 (CID_44370946) presented a strong affinity (8.17 M^{-1}), higher than that of the inhibitor U16 (6.83M^{-1}).

Table 9: Criteria of the rule of *Lipinski* for the Compound CID_44370946.

N	compounds	PM	nOH, NH	nO, N	ClogP	nrotb
44	CID_44370946	421.5304	4	**6**	2.4	12

According to the table 9, we find that the similar CID_44370946 has a molecular weight lower than 500g/mol knowing that the Surflex program is more effective in the presence of small molecules of the ligand. The LogP of similar is less than 5, which indicates a better lipophilic character. Therefore, we little to say that similar CID_44370946 meets the rule of *Lipinski.*

3.1.2. Interaction: 1QXY- CID_44370946

The visualization of results of the docking shows that similar CID_44370946 form with the active site of the MetAP seven hydrogen interactions.

- Two bridges hydrogen are observed between the NH group of compound CID_44370946 and the two carbonyl functions of the residue Asp104(N-H…….O_{D2}-C_G-ASP104) and (N-H…….O_{D1}-C_G-Asp104).
- A hydrogen bond is formed between the hydroxyl function of CID_44370946 and the carbonyl of the residue Asp104 (H-O…….O_{D2}-C_G-Asp104). - A hydrogen bond is observed between the hydroxyl of compound CID_44370946 and one of the nitrogen atoms of the cycle of His168 (H-O…….N_{E2}-His168).
- A hydrogen bond is observed between on the one hand the NH group similar CID_44370946 and on the other hand with the carbonyl function of the Glu233 (N-H…….O_{E1}-C_D-Glu233).
- A hydrogen bridge is formed between the carbonyl of the Residue Asp93 and the NH group of compound CID_44370946 (N-H……O_{D1}-C_G-Asp93).
- The last hydrogen bridge is formed between the NH group of similar CID_44370946 and the carbonyl of Glu202 (N-H……O_{E1}-C_D-Glu202).

The hydrogen bonds are summarized in fig. 8 below.

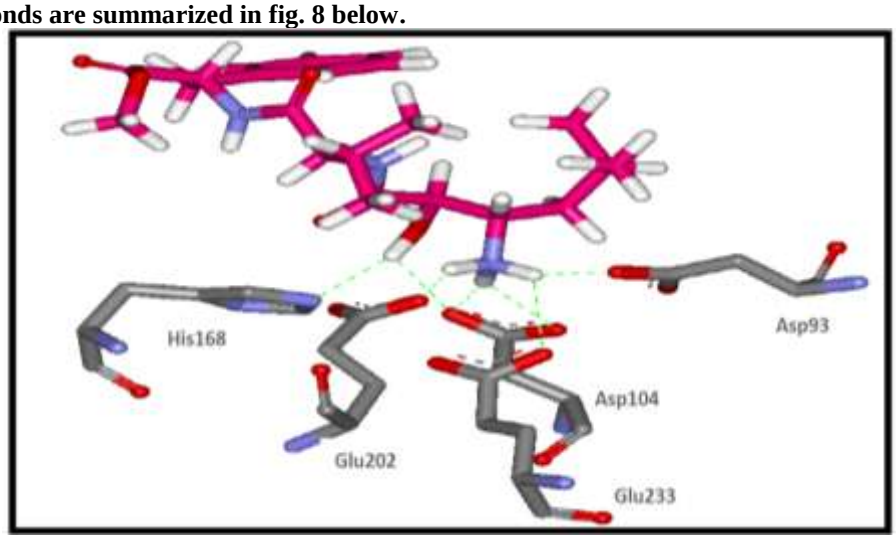


Fig. 8: Representation of the hydrogen bonds formed by the compound CID_44370946.

The inhibition of the MetAP of *Staphylococcus aurues* by the similar of inhibitor U16 has been tested by studies of molecular docking in the binding site of the enzyme MetAP.

Among the various compounds used in this study, the compound CID_44370946 not only has a better affinity (8.17 M^{1}) but also of pharmacokinetic properties more interesting. This brings us to confirm that it is a new

molecule biologically very active, which can be taken by the oral route without problems. Therefore we can propose the compound CID_44370946 as a new, more potent inhibitor of the MetAP of *Staphylococcus aurues.*

CONCLUSION

The objective of our work is to acquire skills in computer stimulation including the molecular docking by Surflex program. This program is used to simulate the protein-ligand interactions and to assist in the development of new structures more powerful use as an inhibitor of methionine aminopéptidase: promising therapeutic target for treating infections caused by *Staphylococcus aureus*. In the first part of our work we have tested the program Surflex according to three criteria: the first test is the RMSD which to compare the deviation between the simulated structure by surflex and that obtained by crystallography. Of all 127 protein-ligand complexes arbitrarily taken from the PDB, 86% have given a RMSD less than 2 Å. The second test is the visual analysis which shows a maximum overlay of the ligand calculated by surflex and the experimental conformation of the same ligand from the PDB. The last test is the correlation coefficient which to compare the experimental values of IC_{50} with their affinities obtained by the molecular docking. On 23 inhibitors of methionine aminopeptidase examined, a positive correlation is observed between the two values analyzed with r=0.81. These criteria has allowed us to provide evidence that the program Surflex is highly reliable and can be used without much risk of errors in predicting MetAP-inhibitor interactions. In the second part of this work, we have identified the best inhibitor of *S. aureus* MetAP among the 36 compounds from the PDB that we studied by Surflex. The compound U16, being the best inhibitor, it has an affinity of 6.83 M^{-1}. The third part was used in the research of new inhibitors of methionine aminopeptidase. For this, we have made a docking of a collection of 123 similar composed of the compound U16 downloaded from the PubChem. We retain the similar CID_44370946 as the best enzyme inhibitor; its affinity is greater than that of the reference ligand is 8.17 M^{-1}.

The last step of the study indicates that similar CID_44370946 meets the criteria imposed by *Lipinski*, which is essential to allow the placing on the market of a potential drug.

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