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IN SILICO DEVELOPMENT OF NEW ANTI MALARIALS WITH MOLECULAR DOCKING AS INHIBITOR OF *PV-DHFR*

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INTRODUCTION-GOALS

The process of discovering new drugs is long and very expensive. As a result, private investments have neglected tropical diseases and malaria, which mainly affect people in poor countries, which justifies the use of molecular modeling techniques and Virtual screening which have proved to be an effective strategy for the discovery and development of drug leads

Malaria remains a major cause of public health problems in about 95 countries, mainly in the tropical zone of the world. It is estimated that this parasitic disease still affects more than 216 million people, and accounted for 445,000 deaths in 2016.

In Algeria, the species most closely met is *Plasmodium vivax* and the majority of cases are imported from countries in tropical Africa.

The increasing prevalence of multidrug-resistant malaria has significantly reduced the effectiveness of current drugs. Thus, the DHFR enzyme has proven reliable and the best target for designing new antimalarial drugs.

In this work, we focus on the inhibition of the DHFR enzyme derived from P. vivax, by the search for new inhibitory molecules of the enzyme Pv-DHFR using virtual screening of the PubChem database. basing on similarity with a series of 31 starting molecules known to inhibit this enzyme; as well as the use of the molecular doking of the analogues towards the active site of the Pv-DHFR will enable us to highlight the most powerful and selective inhibitors vis-à-vis the enzyme studied.

Finally, the application of Lipinski's rule called "the rule of 5" will allow us to verify the bioavailability of identified inhibitors.

MATERIAL AND METHODS

- HP-Z320 Tower Computing Station, Laboratory of Therapeutic Chemistry
- Docking Program: MVD Molegro.
- Databases: the 3D PDB structure of the *Pv-DHFR* chosen 2BL9 (Resolution 1.9A °) was downloaded from Protein Data Bank. The IC50 value of its reference ligand is very low (180 nmol).
- similar molecules from the 32 structures chosen for our study were downloaded from Pub Chem Data Base.
- Preparation and correction software: Swiss Pdb Viewer, Maestro LigPrep and OpenBabel.
- To validate the score function and the search algorithm, the chosen parameters are: Score Function: Score moldock [Grid], Algorithm: Moldock Optimizer, Number of run = 10, Population size = 50, Iterations = 2000
- The RMSD = 0.8 obtained allows the validation of these parameters (figure).

RESULTS AND DISCUSSION

Table N°1 Smiles, and IC_{50} from the starting chemo-library.

SMILES	IC50 µM	SMILES	IC50 µM
Pyrimethamine CCC1=C(C(=NC(=N1)N)N)C2=CC=C(C=C2)Cl	0.1 *Pf*	Oc1ccc(cc1)/C=N/c2nc3ccccc3s2	0.051
Chloroquine CCN(CC)CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl	0.03	O=N(=O)c3ccccc3/C=N/c1nc2ccccc2s1	0.0531
Proguanil CC(C)N=C(N)/N=C(\N)/NC1=CC=C(C=C1)Cl	7.4	Brc1ccc(cc1)/C=N/c2nc3ccccc3s2	0.0455
Cycloguanil CC1(N=C(N=C(N1C2=CC=C(C=C2)Cl)N)N)C	0.038	COc1cccc(c1)C(=O)NCCc2ccc(cc2)CNc3cc4c(cc3)nc(N)nc4N	39.6nm
CCCCCCc1nc(N)nc(N)c1c2ccccc2	0.06	Clc1ccc(cc1)/C=N/c2nc3ccccc3s2	0.0415
Nc3nc(N)c(c1ccccc1)c(CCCc2ccccc2)n3	0.21	NC2N=C(N)N=C(CC)C2OCCCOc1ccccc1CCC(=O)O	0.5
COC(=O)CCCc1nc(N)nc(N)c1c2ccccc2	0.39	O=N(=O)c1cccc(c1)/C=N/c2nc3ccccc3s2	0.0312
Nc3nc(N)c(c1cccc(Cl)c1)c(CCCc2ccccc2)n3	0.67	Sc1nnc(o1)c3ccc(/N=C/c2ccc(Cl)cc2)cc3	0.30
COc3ccc(CCCc1nc(N)nc(N)c1c2cccc(Cl)c2)cc3	0.41	Nc2nc(CCOCCCOc1ccccc1)c(c(N)n2)c3ccc(Cl)c3	4.6nm
COC(=O)CCCc1nc(N)nc(N)c1c2cccc(Cl)c2	0.79	Clc1ccc(cc1Cl)N2C(N)=NC(N)=NC2C	19nm
CCc1nc(N)nc(N)c1OCCCOc2ccnc3ccccc23	0.0040	Sc2nnc(c1ccc(N)cc1)n2N	0.96
CCc1nc(N)nc(N)c1OCCCOc2ccnc3ccc(Cl)cc23	0.0032	Sc1nnc(o1)c2ccc(N)cc2	0.81
O=C(NCCc3ccc(CNc1cc2c(N)nc(N)nc2cc1)cc3)c4cccs4	84.1nm	Clc1ccc(cc1)/C=N/c2ccc(cc2)c4nnc(S)n4/N=C/c3ccc(Cl)cc3	0.23

Figure N°1 The chain A (2BL9) with the two ligands (Discovery Studio)

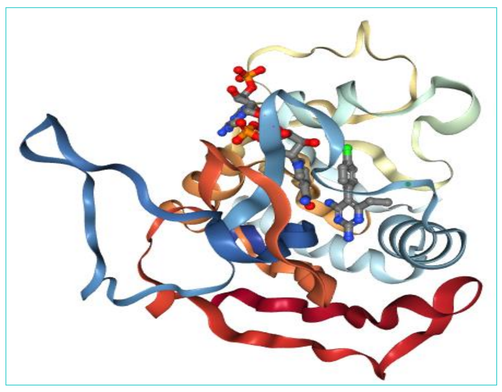


Table N°2 : the 5 best poses (hits) of all chemo-library (4125 similars)

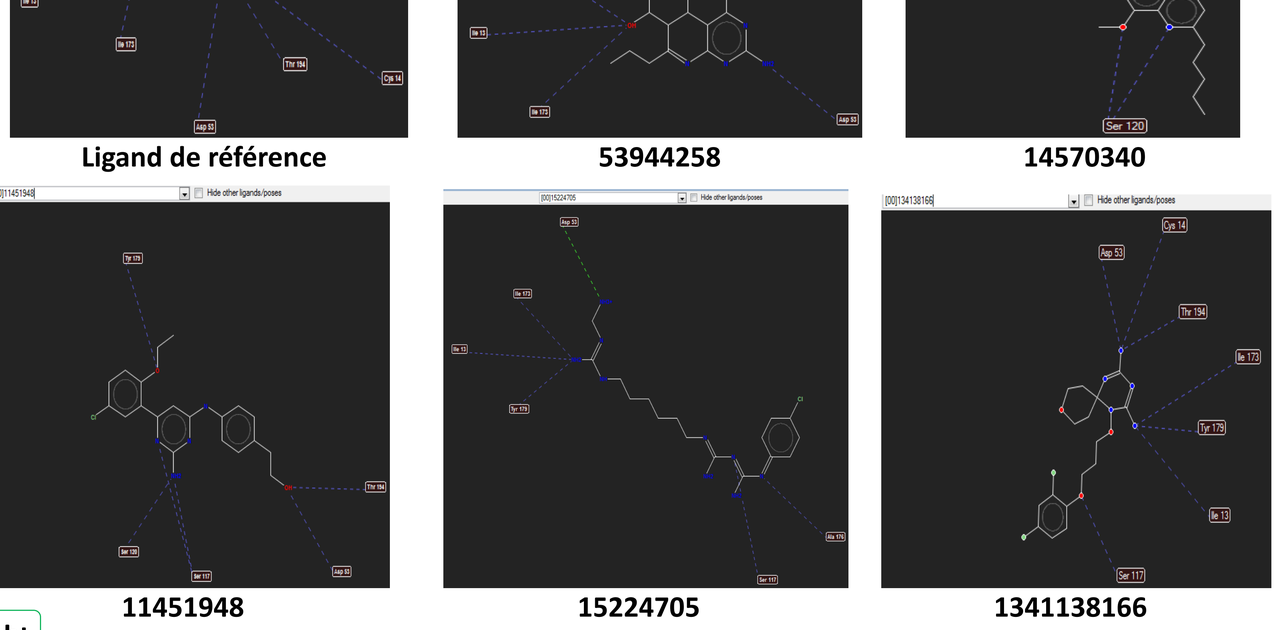
	E-Total	HBond	MW
Ligand de reference	-98.128	-3.658	248.71
53944258	-154.681	-5.59496	399.424
14570340	-142.215	-7.28282	381.471
11451948	-141.184	-5.80989	383.851
15224705	-134.28	-6.86182	379.891
134138166	-132.8	-8.09107	402.276

Table N°3 Lipinski criteria of the best inhibitors of PV-DHFR obtained after virtual screening.

	Poids moléculaire < ou =500Da	log P < ou = 5	nOHN < ou =5	nON < ou =10	Liaisons rotables < ou =10	Moldock Score
53944258	399.424	2.57	5	10	7	-154.681
14570340	381.471	4.20	4	7	8	-142.215
11451948	383.851	4.13	3	6	7	-141.184
15224705	379.891	0.44	9	9	8	-134.28
134138166	402.276	2.47	4	8	6	-132.8

- according to Palangpon.K et al, the key residues of the active sites are the following amino acids: Ile173, Ile13, Asp53, Cys14, Try173 and Thr194
- The 5 molecules of Table N2 have a MolDock score higher than that of the reference ligand
- With a MolDock score evaluating at -154.68, the compound 53944258 is presented as the best inhibitor out of this screening and which has not been described before. The visual analysis shows that this compound inhibits PV-DHFR by forming 6 hydrogen bonds in the active site, 4 of which with the key residues but with a completely different binding mode by involving the oxygen of the hydroxyl and nitro functions of the side chains. .
- Compound 14570340 is considered as the second best inhibitor out of our virtual screening with a score equal to -142.22.
- For the 5 best poses, no electrostatic bond is established.
- It can be seen from Table 3 that the compounds tested can be proposed as new inhibitors of *PV-DHFR* without causing problems of oral administration and this according to the work of Lipinski et al.

Figure N°2 : Interactions of 5 Hits with residues of the active site of the enzyme; in blue the hydrogen bonds, and in green the electrostatic interactions (Molegro).



CONCLUSION

Virtual screening of the similar 4125 allowed us to evaluate their MolDock Score and to highlight the compounds: 53944258, 14570340, 11451948, 15224705, 134138166, as potential (hits) and potent inhibitors of the *PV-DHFR* enzyme. the application of Lipinsky's Rule of 5 gives us a positive insight into the ADME properties of these 5 hits.

It will be ideal in the continuation of this study to test in vitro and / or in vivo the biological activity of the newly proposed compounds in order to validate our in silico results.

References

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