Design and modeling studies on isoindole derivatives as a novel non-classical Anti bacterial agents

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Citation

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Abstract

Isoindole antibacterial agents are currently used for treatment of various bacterial infections. The isoindoles are compounds of intense interest because of their inhibitory effect on Histidinol dehydrogenase enzyme. The invention provides histidinol dehydrogenase polypeptides and DNA (RNA) encoding histidinol dehydrogenase polypeptides and methods for producing such polypeptides by recombinant techniques. Also provided are methods for utilizing histidinol dehydrogenase polypeptides to screen for antibacterial compounds.
Histidinol dehydrogenase (HDH) is one of the enzymes involved in the L-histidine biosynthesis pathway. HDH is a dimer that contains one Zn^{2+} ion in each identical subunit. In this study, we designed isoindole agents as a novel histidinol dehydrogenase inhibitor .Then predicted possible binding conformation of our agents, which is experimentally not known, using a computational modeling method. Conformations of the designed compounds were optimized through semi-empirical method followed by PM3 calculation by the program HYPERCHEM. Among all energy minima conformers, the global minimum was selected and the QSAR properties was obtained. Then the crystal of L-histidinol dehydrogenase was obtained from the Protein Data Bank(PDB) server. Finally Docking calculations were carried out using Auto-Dock program. The good interaction of our isoindole derivatives showed that they can be as possible anti bacterial agents.

INTRODUCTION

The emergence of multidrug-resistant bacteria has challenged researchers to develop novel therapies for the prevention and treatment of infectious diseases. Traditional antibiotics exert strong selective pressure for resistance development, since they target bacterial processes essential for the growth of the organism. Alternative approaches have involved the modulation of virulence factors, elements that contribute to infection in vivo but are not essential for growth of the organism in vitro. Most attempts along this path have targeted individual virulence factors, such as pili or toxins, but these approaches have suffered from a limited spectrum of activity. The targeting of regulatory mechanisms that could affect multiple virulence factors simultaneously may offer an alternative approach.

Toward this end, the L-histidinol dehydrogenase inhibitors represent a novel target for this unique therapeutic approach.

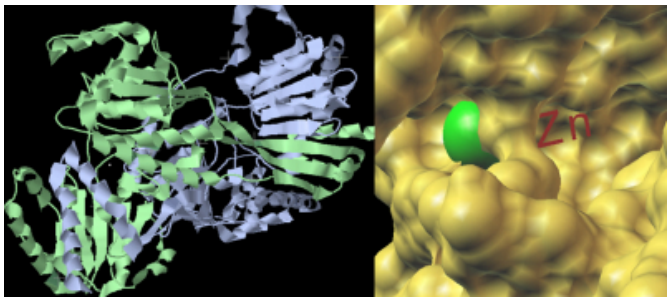
Recent researches have shown that another amino acid biosynthetic enzyme, the histidinol dehydrogenase (HDH; EC 1.1.1.23), encoded by the gene hisD in many bacteria , is essential for intramacrophagic replication, providing a novel target for the development of antibacterial agents (1). L-HDH is a homodimeric zinc metalloenzyme that catalyzes the last two steps in L-histidine biosynthesis, and it is found in microorganisms such as bacteria and fungi and in plants but not in mammals (2). Ten years ago, Dancer et al. reported that HDH is a suitable target for the development of potential herbicides (3). The approach developed by this group was to prepare HDH inhibitors which target the lipophilic binding pocket adjoining the active site of the enzyme.

In this research we designed isoindoel compounds as a novel L-HDH inhibitors and showed their efficiency by modeling studies and docking that at first the structure of desired compounds were build by using HYPERCHEM program. Conformations of the designed compounds were optimized through semi-empirical method followed by PM3 calculation by using the HYPERCHEM software. Among all energy minima conformers, the global minimum was selected. The crystal structure of L-type histidinol dehydrogenase(Figure 1) was obtained from the Protein Data Bank (PDB) server (PDB entry: 1kar). Then Docking calculations were carried out using AutoDock program

(Ver4) program.

Figure 1

Figure 1: The structure of L-HDDH obtained from PDB server(1kar).



METHOD AND MATERIALS

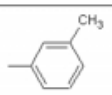
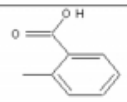
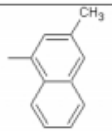
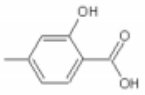
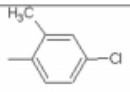
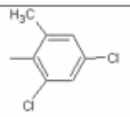
A)MOLECULAR MODELING

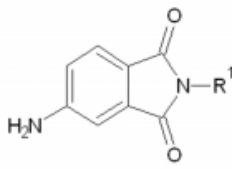
The chemical structures of isoindoles (table.1) were constructed using Hyperchem software (version 7, Hypercube Inc.) .Semi-empirical molecular orbital calculations (PM3) of the structure were performed using the Hyperchem program and the among all energy minima conformers, the global minimum of compounds were consider in docking calculations. And also,

Superimposition main pharmacophore of recognized L-HDH compounds and our potent compound was performed.

Figure 2

Table 1: Structures of the inhibitors.

Comp.	R^1	Comp.	R^2	Comp.	R^2
1		5		9	
2		6		10	
3		7			
4		8			

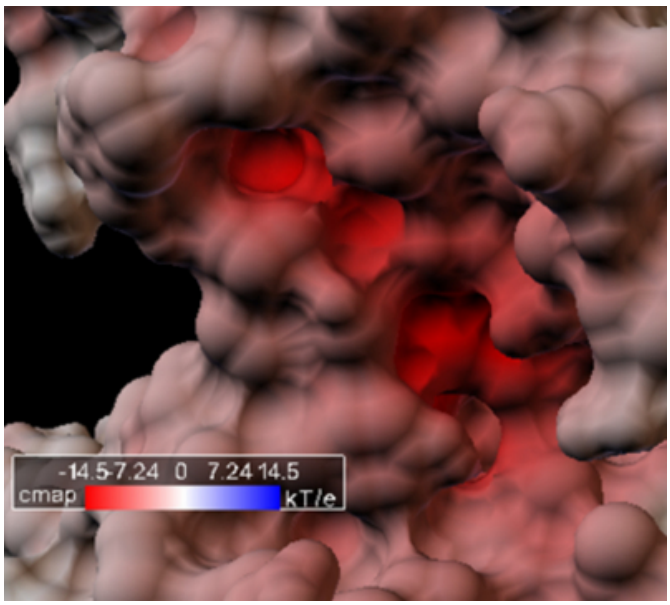


B)DOCKING STUDY

Docking studies were carried out by using the program AUTODOCK 4. This program starts with a ligand molecule in an arbitrary conformation, orientation, and position and finds favorable dockings in a protein-binding site using both simulating annealing and genetic algorithms. The program AutoDockTools (ADT), which has been released as an extension suite to the Python Molecular Viewer, was used to prepare the protein and the ligand . For the macromolecule (L-type histidinol dehydrogenase, that was generated by resorting to multi body molecular dynamics simulations, was downloading from the PDB bank server [PDB entry 1kar]), polar hydrogens were added, and then Kollman United Atom charges and atomic solvation parameters were assigned. The grid maps of docking studies were computed using the AutoGrid4 included in the Autodock4 distribution. Grid center was centered on the active site was obtained by trial and error and previous study by Cosconati et al and 60x60x60 points with grid spacing of 0.375 were calculated (Figure 2).

Figure 3

Figure 2: The active site and map of potential surface



The GA-LS method was adopted to perform the molecular docking. The parameters for GA were defined as follows: a maximum number of 250,000 energy evaluations; a maximum number of generations of 27,000; mutation and crossover rates of 0.02 and 0.8, respectively. Pseudo-Solis & Wets parameters were used for local search and 300 iterations of Solis & Wets local search were imposed. The number of docking runs was set to 50. Both Autogrid and Autodock computations were performed on Cygwin. After docking, all structures generated were assigned to clusters based on a tolerance of 1 A ° all-atom RMSD from the lowest-energy structure. Hydrogen bonding and hydrophobic interactions between docked potent agents and macromolecule were analyzed using ADT (Version 1.50).

RESULTS AND DISCUSSION

Molecular geometry of our designed compounds has been calculated by the semi-empirical method using PM3. Now, Based on obtained results from the superimposition of our compounds on main pharmacophore recognized L-HDH inhibitor that synthesized and evaluated by E. Dancer et al, We observed good overlay on main interaction zone (Figure 3).

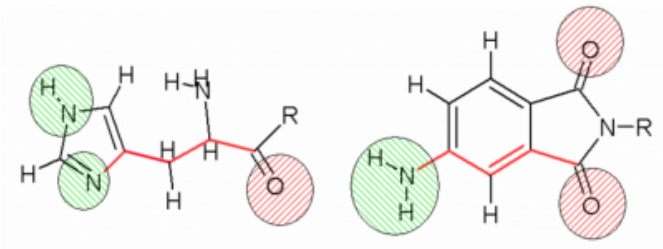
We expected potential H-bond acceptor sites formed by the carbonyl groups. We promoted two carbonyl groups in the newly designed compounds. And also, we improved Log p for better penetration by placed phenyl rings instead of imidazole ring .Of course, H-bond sites been remained by NH_2 group.

The variable substituent played main role to better connection between ligand and receptor.

In figure 2 we showed our concepts to design new lead compound.

Figure 4

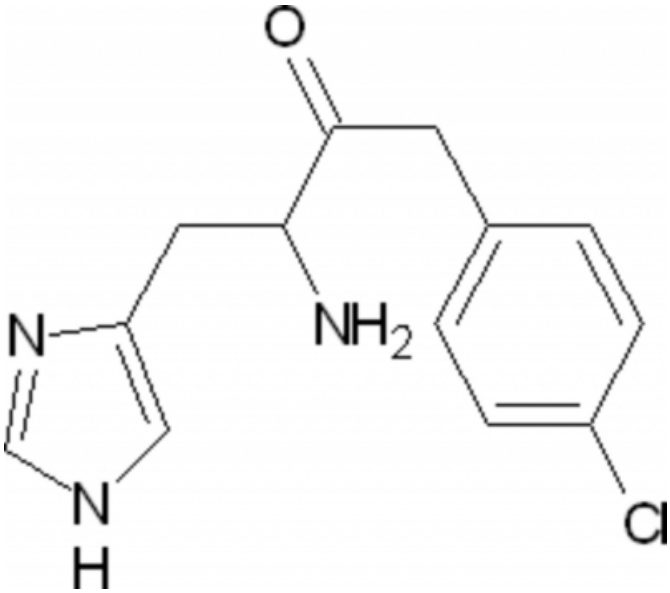
Figure 3. a) Recognized HDH-inhibitor b) Designed compounds Red and green circles show H-bond sites and Red line present relatively same distance between main pharmacophores



Now, Flexible docking of all data sets used for the computational study was carried out on the active site of L - HDH.To comparison we docked HDH-inhibitor (Figure 4) that the results and interactions shown in table 2 and Figure 5,6.

Figure 5

Figure 4: The structure of HDH inhibitors.



The predicted binding energies and inhibitory constant of these inhibitors into the active site are listed in Table 2.

Figure 6

Table 2: Docking results by using AutoDock 4 software.

Comp.	Binding energy [1]	Ki [2]	Comp.	Binding energy [1]	Ki [2]
1	-6.21	28	7	-6.95	7.5
2	-6.72	11	8	-7.89	1.2
3	-6.69	13	9	-6.38	20
4	-7.04	6.5	10	-6.13	31
5	-5.5	176	HDH-inhibitor	-6.6	18
6	-6	44			

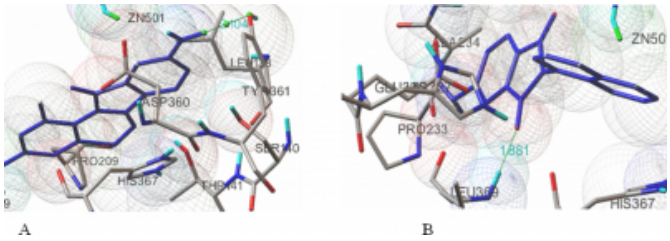
1) The predicted binding energy (kcal/mol)
2) The predicted inhibitory constant (micromolar)

The orientation of the most potent isoindole compounds (Comp.8 and Comp4) , in the active site of L-HDH was examined by a docking experiment (Figure 5).(4) This molecular modeling shows the NH_2 substituent forms a hydrogen bonding interaction with the O of TYR361(distance=2.104) in Comp8.

The carbonyl group of indole ring forms hydrogen bond with the H of LEU369 (distance=1.881) in Comp4.

Figure 7

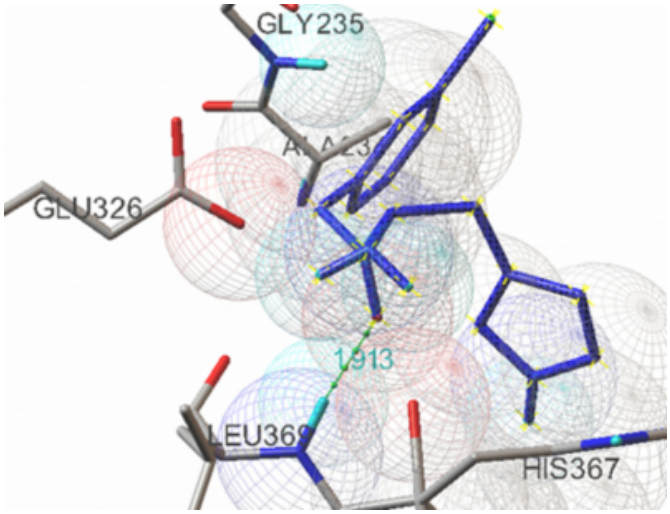
Figure 5: Docked structures of Comp8(a), Comp4 (b) in Model of L-HDH. Our agents are displayed as Blue sticks, and Hydrogen bonds are represented with dashed green lines.(Docking study by using ADT program and HDH model obtained from PDB server)



And also, the interaction of HDH-inhibitor showed in below figure. The molecular modeling shows the carbonyl substituent forms a hydrogen bonding interaction with the H of LEU369(distance=1.913) in HDH-inhibitor that it is approved our design concepts.

Figure 8

Figure 6: Docked structures of HDH-inhibitors in Model of HDH. Agent is displayed as blue sticks, and Hydrogen bonds are represented with dashed green lines.(Docking study by using ADT program and HDH model obtained from PDB server)



By consideration obtained results and these observations we can expect our compounds could be as novel L-HDH inhibitors.

CONCLUSION

In conclusion, in the present work we have proven that these compounds are theoretically active against bacteria by inhibiting the L-histidinol dehydrogenase. Our suggest that HDH a suitable target for novel compounds which represent valuable candidates for the potential development of an alternative, non-classical antibacterial therapy, notably against strains resistant to conventional antibiotic treatments.

References

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4. Docking studies were performed using Autodock softwareVersion 4.0.

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