

**COMPUTER-AIDED LEAD MOLECULE  
IDENTIFICATION: SOME CASE STUDIES FOR  
MALARIA & NEURODEGENERATIVE  
DISEASES**

**ASHUTOSH SHANDILYA**



**DEPARTMENT OF CHEMISTRY  
INDIAN INSTITUTE OF TECHNOLOGY DELHI  
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**Computer-aided lead molecule identification:  
Some case studies for Malaria &  
Neurodegenerative Diseases**

by

**Ashutosh Shandilya**

**Department of Chemistry**

submitted

in fulfillment of the requirements of the degree of Doctor of Philosophy  
to the



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## *Certificate*

This is to certify that the thesis entitled, “**Computer-aided lead molecule identification: Some case studies for Malaria and Neurodegenerative Diseases**”, being submitted by **Mr. Ashutosh Shandilya** to the Indian Institute of Technology, Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bonafide research work carried out by him. Ashutosh Shandilya has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

Prof. B. Jayaram  
Department of Chemistry  
Indian Institute of Technology  
Delhi  
INDIA

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**Ashutosh Shandilya**

# *Abstract*

This thesis focuses on identification of potential lead molecules against Malaria and neurodegenerative diseases providing atomic level computational insights on the mode of action of these molecules. A few novel potential lead molecules have been identified against malarial and neurodegenerative disease targets using computational approach. These designed molecules were further assayed experimentally and found to be in good conformity with computational predictions.

The thesis is divided into seven chapters. Chapter 1 discusses the current status of computer-aided drug design in general and its role in drug discovery process. A brief overview of the current state of research on malaria and neurodegenerative diseases has been reported as well.

Chapter 2 is devoted to identifying a plausible mechanism of action artemisinin, a widely used antimalarial, via exhaustive computational approaches. This chapter also includes a justification and modeling of the target enzyme and elucidates atomistic level interaction between ligand and target enzyme. Chapter 3 and Chapter 4 presents identification of some novel hit molecules against phosphoethanolamine N-methyl transferase enzyme (*PfPMT*). A *de novo* drug design strategy is adopted to target *PfPMT*. Designed molecules were synthesized and assayed against malarial cell lines in collaboration. Further *PfPMT* enzymes were expressed and purified. Isothermal titration calorimetry assays were carried out to understand the binding kinetics of ligands and protein. Cell based studies (schizont maturation inhibition assay) were carried to identify best inhibitors against

malaria. These molecules showed low nanomolar activities against malarial cell lines.

Chapter 5 focuses on identification of novel molecules against Alzheimer's disease. Calcium-calmodulin dependent kinase IV (CAMK4) enzyme was targeted for the treatment of Alzheimer's disease. Binding of curcumin and pyrimidine based derivatives were identified as good binders, and their modes of binding were also elucidated. Acetyl cholinesterase (ACh) is a widely known target for the structure based drug designing because of its direct association with Alzheimer's disease. A few triazine hybrid molecules were designed using computational approaches. Experimentally, they were found to be show good activity against Ach in low nanomolar range.

Chapter 6 discusses a detailed theoretical account that is substantiated with some new experimental investigations on the molecular origins of the differential affinities of iminocyclitols with various glycosidases. These newly designed compounds show interesting selectivity towards the target enzymes. One of the designed molecules is shown to be a stabilizer of  $\alpha$ -galactosidase enzyme indicative of its chaperon activity. Finally in chapter 7, a summary and some perspectives emerging from the thesis work are discussed.

## सारांश

यह शोधकार्य संगणकीय अन्तर्दृष्टि द्वारा आणविक पारस्परिक क्रिया को समझकर मलेरिया एवं न्यूरो डिजेनेरेटिव रोगों के संभावित दवाओं के पहचान पर केंद्रित है. संगणकीय दृष्टिकोण को ध्यान में रखकर मलेरिया एवं न्यूरो डिजेनेरेटिव रोगों के विरुद्ध कुछ नवीन एवं महत्वपूर्ण यौगिकों का डिजाइन किया गया है. इन नवीन डिजाइन यौगिकों को प्रयोगात्मक रूप से भी परखा गया और इनका संगणकीय पूर्वानुमान के साथ अच्छा अनुरूप पाया गया.

यह शोधकार्य सात अध्याय में बटा हुआ है. पहला अध्याय सामान्य रूप से संगणकीय सहायता प्राप्त दवा के डिजाइन की स्थिति और दवा के खोज में इसकी भूमिका के चर्चा करता है. इसके साथ-साथ मलेरिया एवं डिजेनेरेटिव रोगों पर अनुसन्धान की वर्तमान स्थिति का भी संक्षिप्त अवलोकन किया गया है. अध्याय २ मलेरिया के लिए व्यापक रूप से उपयोग में आने वाली दवा आर्टीमिसिनिन के संभावित कार्रवाई की विधि के आंकलन में समर्पित है. यह अध्याय लक्षित एंजाइम एवं आर्टीमिसिनिन के बीच आणविक पारस्परिक क्रिया को भी स्पष्ट करता है.

अध्याय ३ एवं ४ में डि-नोवो ड्रग डिजाइन नीति के तहत, एन-मिथाइल ट्रांसफ़ेरेज़ (*PfPMT*) एंजाइम के विरुद्ध कुछ नवीन यौगिकों को डिजाइन किया गया है. तत्पश्चात इन डिजाइन्ड यौगिकों को संश्लेषित कर मलेरिया कोशिका परत पर परीक्षण किया गया. लिगेंड एवं एंजाइम के बाध्यकारी कैनेटीक्स का आंकलन करने के लिए समतापी कैलोरीमेट्री अनुमापन भी किया गया. इन डिजाइन यौगिकों में से कुछ यौगिक मलेरिया कोशिका एवं लक्षित एंजाइम के विरुद्ध नैनो-मोलर स्तर तक की बाध्यता दिखाई.

अध्याय ५ अल्जाइमर रोग के विरुद्ध कुछ नवीन यौगिकों के पहचान पर केंद्रित है. अल्जाइमर रोग के उपचार हेतु *CAMK4* एंजाइम को लक्षित किया गया. इसके लिए करक्यूमिन एवं पिरिमिडीन आधारित व्युत्पन्न यौगिकों को अच्छे बाइंडर के रूप में पहचान की गयी एवं उसके बाध्यकारी तंत्र को भी स्पष्ट किया गया. अल्जाइमर रोग के लिए एसिटील कोलिन्स्टरेज (ACh) एक व्यापक रूप से ज्ञात लक्षित एंजाइम है. इस रोग के उपचार हेतु सगणकीय दृष्टिकोण से कुछ नवीन त्रिज़िन (Triazine) संकरण आधारित नवीन यौगिक का डिज़ाइन किया गया. प्रयोगात्मक रूप में भी ACh के खिलाफ़ इन यौगिक ने नैनो-मोलर श्रेणी में बाध्यता दिखाई.

अध्याय ६ इमिनोसिक्लिटॉल्स (Iminocyclitols) की विभिन्न ग्लाइकोसिडेज के साथ विस्तृत सैद्धांतिक चर्चा करता है. यहाँ नवीन डिज़ाइन किये गए यौगिक लक्षित एंजाइम के प्रति दिलचस्प चयनात्मकता दिखते हैं. डिज़ाइन किये गए यौगिकों में से एक यौगिक अल्फा-गलैक्टोसिडेज ( $\alpha$ -galactosidase) स्थिरकारी के रूप में इंगित होता है. अंततः अध्याय ७ इस शोधकार्य से उभर कर आये कुछ दृष्टिकोण एवं सारांश पर केंद्रित है.

# Content

<i>Certificate</i> .....	i
<i>Acknowledgements</i> .....	ii
<i>Abstract</i> .....	iii
<i>List of Figure</i> .....	xi
<i>List of Figure</i> .....	xvii
<b>Chapter 1 Introduction</b>	<b>1-33</b>
<b>I Computer aided drug design</b>	<b>2-16</b>
1.1 Current CADD approaches	4
1.1.1 Ligand based drug design (LBDD): An indirect approach	5
1.1.2 Structure based drug design (SBDD): A direct approach	9
1.1.3 Virtual Screening	11
1.1.4 Computational Docking and scoring	12
1.1.5 Molecular dynamics simulations	15
<b>II. Malaria</b>	
1.2.1 Overview	17
1.2.2 Life cycle of Malaria	17
1.2.3 Malaria Chemotherapeutics	19
1.3 Conclusion	22
<b>III Neurodegenerative Diseases</b>	
1.4 Overview of neurodegenerative disorders	24
1.5 Scope of the Thesis	26
1.6 References	27

<b>Chapter 2</b>	<b>A plausible mechanism for the antimalarial activity of artemisinin</b>	<b>34-68</b>
2.1	Introduction	35
2.1.1	Current status of mechanism of action of artemisinin	35
2.1.2	Modeling of <i>PfATP6</i>	38
2.2	Methods	47
2.2.1	Density functional theory (DFT) calculations	47
2.2.2	Docking	48
2.2.3	Scoring	49
2.2.4	Molecular Dynamics simulations	50
2.3	Results & Discussion	52
2.4	Conclusion	63
2.5	References	64
<b>Chapter 3</b>	<b>Design and synthesis of Triazine based antimalarials</b>	<b>69-88</b>
3.1	Introduction	70
3.2	Methods	73
3.2.1	Docking, scoring and molecular dynamics simulations	73
3.2.2	General Procedure for the Synthesis of Triazine	73
3.2.3	Parasite growth inhibition assay	74
3.2.4	Cytotoxicity activity measurement	75
3.3	Results and Discussion	75
3.3.1	New molecule design based on molecular docking	75
3.3.2	Molecular dynamics simulations	80
3.3.3	Synthesis	83
3.3.4	Parasite inhibition assay of newly synthesized triazine derivatives	83
3.4	Conclusion	85
3.5	References	86

<b>Chapter 4</b>	<b>Designing low nanomolar range inhibitors for Phosphoethanolamine methyl transferase</b>	<b>89-108</b>
4.1	Introduction	90
4.2	Methods	92
4.2.1	Docking and scoring	92
4.2.2	Molecular dynamics simulations	92
4.2.3	<i>In vitro</i> Cultivation of <i>P. falciparum</i> Asexual Stages	92
4.2.4	Assessment of Antimalarial activity	93
4.2.5	IC <sub>50</sub> Calculation and Data Analysis	93
4.2.6	Protein purification & Expression	94
4.2.7.	Isothermal Titration Calorimetry	95
4.3	Results and Discussion	97
4.3.1	Designing of molecules	97
4.3.2	Enzyme Kinetics and Isothermal Titration Calorimetry	104
4.3.3	Parasite growth inhibition assay	106
4.4	Conclusion	106
4.5	References	107
<b>Chapter 5</b>	<b>The Inhibitory effects of triazine and curcumin scaffolds on CAMK4 and AChE targets involved in neurodegenerative disorders</b>	<b>109-135</b>
5.1	Introduction	110
5.1.1	Calcium-calmodulin dependent kinase IV as potential target	110
5.1.2	Acetyl cholinesterase as a therapeutic target	112
5.2	Results & Discussion	114
5.2.1	Curcumin binding to CAMK 4	114

5.2.2	Modeling and Docking	114
5.2.3	Molecular dynamics simulations	115
5.2.4	Conformational changes in the curcumin-bound CAMK4 complex	118
5.2.5	Designing of molecule containing pyrimidine scaffold against CAMK4	120
5.2.6	Design of cyanopyridine-triazine hybrids against Acetylcholinesterase	122
5.2.7	Design of triazolopyrimidine scaffold against Acetylcholinesterase	126
5.3	Conclusion	130
5.4	References	131
<b>Chapter 6</b>	<b>Computational Studies on Iminocyclitol Derivatives</b>	<b>136-157</b>
6.1	Introduction	137
6.2	Methods	139
6.2.1	General procedure for enzyme assay	139
6.2.2	Computational studies	140
6.3	Results	142
6.3.1	Binding studies	142
6.3.2	Structural and dynamic basis for the binding affinity and selectivity	143
6.4	Discussion	152
6.5	Conclusions	154
6.6	References	155
<b>Chapter 7</b>	<b>Summary &amp; Perspectives</b>	<b>158-161</b>
7.1	Summary	159
7.2	Future work	161
	<i>Bio-data</i>	162

# *List of Figures*

Fig. 1.1	Schematic approach for ligand based drug design	6
Fig. 1.2.	Active site of Acetyl Cholinesterase bound with ligand	10
Fig. 1.3.	A prototype of virtual screening scheme	11
Fig. 1.4.	Broad classification of scoring functions	14
Fig. 1.5.	A representative equation to calculate forces on each atom of a system	14
Fig. 1.6.	A schematic view of molecular dynamics simulations	16
Fig. 1.7.	Life cycle of Malaria parasite	18
Fig. 1.8.	A few Aryl amino alcohol and 4-amino quinoline antimalarials	20
Fig. 1.9.	A few antifolates in clinical use against malaria	21
Fig. 1.10	A few artemisinin derivatives in clinical use	22
Fig. 1.11.	Factors associated with Neurodegenerative diseases	25
Fig. 2.1.	Molecular structure of Artemisinin	35
Fig. 2.2.	Trophozoite-stage of malarial parasite (blue) growing inside a red blood cell. <b>(a)</b> , artemisinin was transported to the food vacuole of the parasite (white), where it was converted into a free radical after an interaction with Fe <sup>2+</sup> -heme. <b>(b)</b> , artemisinin is transported from the red blood cell into the parasite artemisinin is activated by free iron, or another iron-dependent process, that occurs close to <i>PfATP6</i> in the endoplasmic reticulum. The activated artemisinin specifically and irreversibly binds and inhibits <i>PfATP6</i> , and inhibits parasite growth	37
Fig. 2.3.	Alignment of primary sequence of two proteins (1SU4 mammalian SERCA) and 1U5N	39
Fig. 2.4.	Superposition of crystal structure of mammalian SERCA in green and model structure of Plasmodium SERCA ( <i>PfATP6</i> ) in red	41
Fig. 2.5.	Superimposition of all 41 structures along with 1SU4 and 2C9M (open	

- conformation) shown in red and orange color respectively. Remaining mammalian SERCA structures are shown in transparent colors to avoid confusion. (b) Superimposition of all 39 closed conformation structures in one color 42
- Fig. 2.6. Overview of the structure of the  $\text{Ca}^{2+}$  bound *PfATP6*. Domains depicted are nucleotide domain (N) (orange), phosphorylation domain (red), actuator domain (blue), hinge domain (H) (yellow) and the trans membrane region including 10 helices (M1-M10) (cyan). Marked circle between M3, M5 and M7 is the ligand binding site and the circle between M2, M3 and M4 is the calcium binding site. 46
- Fig. 2.7. A flow chart of Pardock docking methodology 49
- Fig. 2.8. Initial docked pose of Artemisinin with SERCA on the left; Fe-artemisinin adduct docked to SERCA on the right 53
- Fig. 2.9. MD snapshots generated from individual trajectories after every 25ns for *PfATP6*enzyme (top row), artemisinin bound *PfATP6* (second row) and Fe-artemisinin adduct bound *PfATP6* (third row). Nucleotide binding (N) domain and the actuator (A) domains are seen to be closing in the case of Fe-artemisinin adduct bound *PfATP6* system 54
- Fig. 2.10. Artemisinin (yellow) and Fe-artemisinin (red) adduct docked to *PfATP6* at the start of the MD simulation initial coordinates (left). Fe-artemisinin adduct (red) moves towards the ligand binding site disrupting the helical region after 40ns (right) 57
- Fig. 2.11. Residues of *PfATP6* in the vicinity of  $5\text{\AA}$  after 40ns from simulation trajectories of (a) artemisinin and (b) Fe-artemisinin adduct 57
- Fig. 2.12. Inter-atomic distances of backbone atoms of VAL 221 of actuator domain and PHE 535 of nucleotide domain for (i) *PfATP6* (red), (ii)

artemisinin bound *PfATP6* (green) and (iii) Fe-artemisinin adduct bound *PfATP6* (blue). Area between the geometric centers of N-, H- and A-domains of *PfATP6* system (red), artemisinin-*PfATP6* system (green) and Fe-artemisinin adduct *PfATP6* system (blue) shown in right panel. Areas are calculated from triangles formed by the geometric centers of the three corresponding domains

58

Fig. 2.13. PCA based free energy landscape of open to closed conformational transition of (i) SERCA; (i) Ca<sup>2+</sup> bound SERCA, (ii) artemisinin bound SERCA, (iii) Fe-artemisinin adduct bound SERCA. The abscissa and ordinates correspond to the first and second principal components respectively

59

Fig. 2.14. Inter-atomic distance between Fe-artemisinin adduct and side chain of residue ASN 980

60

Fig. 2.15. Interaction network of Fe-artemisinin adduct and phosphorylation site through bonded and non-bonded network. (a) A three dimensional view; (b) A two dimensional representation of the same linkage

61

Fig. 2.16. Three additional hydrogen bonds were observed with Fe-artemisinin adduct and Ile 977, Asn 980 & Leu 263 during the simulation enabling the movement of N domain of *PfATP6* which was absent in case of artemisinin complex

62

Fig. 3.1. Schematic representation of major phosphatidylcholine (PC) biosynthesis pathways in Plasmodium falciparum-infected erythrocyte. The serine de-carboxylase-phosphoethanolamine methyltransferase (SDPM) pathway is depicted with red arrows. The cytidine diphosphate (CDP)-choline pathway is shown with brown arrows.

71

Fig. 3.2. Basic representative structure for the triazine analogue. Reaction

	mechanism showing serine-decarboxylase-phosphoethanolamine- methyltransferase (SDPM) pathway	77
	Reaction mechanism of serine- decarboxylase-phosphoethanolamine-methyltransferase (SDPM) pathway	
Fig. 3.3.	a. N-Methyl transferase docked with a triazine derivative (Molecule_10) b. Interactions of Molecule_10 with neighboring residues	79
Fig. 3.4.	Snapshot of active site with ligand molecule initial pose (left) and post simulation (right) depicting the closure of active site where ligand is trapped inside the active site	80
Fig. 3.5.	Snapshot of crystal structure bound with AdoMet (ligand) and phosphobase (left panel). Residues within 4 Å of AdoMet are shown. HIS 132 and TYR 19 are on either side of ligand and in close proximity (2.2 Å). On the right panel is a snapshot of active site residues surrounding Molecule_10 which shows HIS 132 and TYR 19 are parted away after 100ns of MD simulation	81
Fig. 3.6.	Interatomic distance variation carbon atom of Phenyl ring of HIS 122 and ring nitrogen atom of TYR 9	82
Fig. 3.7.	Interatomic distances of side chain atom of ILE 76, SER 27 and TYR 171 with ligand throughout the 225ns simulation showing these residues are coming closer to ligand during the course of simulation	82
Fig. 3.8.	Parasite growth inhibition assay. (a) Selected inhibitors from the docking analysis tested in the parasite growth inhibition assay using double dilution till 8 points (100 µM to 0.8 µM). (b) Cytotoxicity measurement for inhibitors	84
Fig. 4.1.	Snapshot of pre and post simulated structures of designed molecules bound with <i>PfPMT</i> . Initial pose of inhibitors are shown in pink color	

	and Final pose of the inhibitor is shown in green color. Initial coordinates of residues Tyr 19 and His 132 are in close proximity (Pink color). Post simulation these two residues move away from each other simulation in presence of inhibitor	99
Fig. 4.2.	Interatomic distances between oxygen atom of tyrosin ring structure (Tyr 19) and nitrogen atom of histidine ring structure (His 132) for each of the complex	100
Fig. 4.3.	A two dimensional representation of active site residue of <i>PfPMT</i> enzyme interacting with designed molecules	102
Fig.4.4.	Interatomic distances between showing maximum occupancy of hydrogen bonds throughout the simulation run. In the topmost panel three residues Asp 61, Asp 85 and Asp 110 forming hydrogen bond with molecule M1. Second panel from the top displays hydrogen bond Ser 37, Asp 61, Asn 89 with molecule M2. Third panel from the top confirms the hydrogen between molecule M4 and Tyr 19, Ser 37, Asn 89. Last panel shows hydrogen bonds formation with side chain of Ser 37, Ser 64 and Tyr 160 and M7	103
Fig. 4.5.	Isothermal titration calorimetry of molecules M1, M2, M3, M4, M7 against <i>PfPMT</i> enzyme	105
Fig. 4.6.	A correlation plot between computational binding free energies and computational binding energies	105
Fig. 5.1.	(A) Overall structure of CAMK4 complexed with curcumin. Residues forming hydrogen-bonded interaction (green) and functionally important residues (yellow) are shown in ball and stick. Structure of curcumin is shown in light red (ball and stick). (B) Residues forming close interactions with the anionic curcumin and (C) Neutral curcumin are	

- shown in ball and stick 117
- Fig. 5.2. Interatomic distance between terminal oxygen of negatively charged curcumin and side chain oxygen atom of Asp164 is shown in red. Distance plot between terminal oxygen of curcumin and side chain of oxygen atom of Asp164 is shown in blue 118
- Fig. 5.3. Interatomic distances between carbon atom of C $\alpha$  Leu52 and carbon atom of phenyl ring of negatively charged curcumin and neutral curcumin shown in red and blue, respectively. (B) Distance plot of side chain carbon atom of Val121 and center of mass of phenyl ring of negatively charged and neutral curcumin is shown in red and blue, respectively 119
- Fig. 5.4. Interatomic distances between carbon atom of C $\alpha$  Thr200 and carbon atom of phenyl ring of negatively charged curcumin and neutral curcumin shown in red and blue, respectively. (B) Distance plot of side chain carbon atom of Asp185 and center of mass of phenyl ring of negatively charged and neutral curcumin is shown in red and blue, respectively 120
- Fig. 5.5. (a) & (b) are the docked structures of compounds **4d** and **4h**, respectively, with AChE. Tyr residues is shown in blue, Phe in yellow, His in purple, Ser in green, and Trp in magentas colors. The  $\pi$ - $\pi$  stacking between two aryl centers and H-bonding interactions are shown by red colored dashed lines 124
- Fig. 5.6. Design strategy of multifactorial anti-AD agent 126
- Fig. 5.7. Inhibitors (shown in ball and stick). The key residues are shown in stick and other residues are shown by different color such as TYR70, TYR121, TYR279 (Green), TRP84, TRP279 (Magenta), SER122,

	SER200 (Cyan), GLU199 (tint-wheat), PHE330, PHE331 (Yellow), HIS440 (Orange). Plot (A, C, E) shows interaction of inhibitor (10d, 10e, 10c) with key residue in the active site of AChE respectively. Plot (B, D, E) shows Ligplot representation of inhibitor (10d, 10e, 10c) respectively	129
Fig. 6.1.	Amino-substituted five-membered iminocyclitols	138
Fig. 6.2.	Interaction of compound <b>3</b> (left panel) and compound <b>4</b> (right panel) with active site residues of $\alpha$ -glucosidase. Circled residues are shown to be mutually exclusively interacting with particular ligand	145
Fig. 6.3.	Interaction of compound <b>3</b> (left panel) and compound <b>4</b> (right panel) with active site residues of $\beta$ -glucosidase Compound <b>4</b> forms three hydrogen bonds with GLN 19, GLU 165 and GLU 348. Compound <b>3</b> forms additional hydrogen bond with ASN 164, and van der Waals interactions with several aromatic residues in the active site apart from the GLN 19, GLU 165 and GLU 348	146
Fig. 6.4.	Interaction of compound <b>3</b> (left panel) and compound <b>4</b> (right panel) with active site residues of $\alpha$ -galactosidase. Compound <b>4</b> shows hydrogen bond linkage with LEU 142, SER 175, SER 194, Asp 229 and ASP 231 showing better fitting than compound <b>3</b> as electrostatic interactions with ASP 229, SER 175 and SER 194 are missing in case of compound <b>3</b>	146
Fig. 6.5.	Interaction of compound <b>3</b> residues (left panel) and compound <b>4</b> (right panel) with active site residues of $\beta$ -glucosidase. Compound <b>4</b> shows hydrogen bonding interactions with only two residues namely HIS 379 and GLU 525 but compound <b>3</b> forms additional hydrogen bonds with TYR 491 and few more non polar interactions with active site residues	147

- Fig. 6.6. Interatomic distances between compounds **3** and **4** with active site residues of the four enzymes forming hydrogen bonds/contacts: In each panel, lower graph depicts interatomic distances between compound **3** and the neighboring residues and the upper graph those of compound **4**. 148
- Fig. 6.7. A representative energy minimized docked structure of propyl derivative **5** complexed with  $\beta$ -galactosidase (top left) forming hydrogen bonds with functionally important amino acid in the active site, butyl derivative **6** due to presence of hydrophobic chain shows mostly non polar interactions with the side chain residues in the active site of  $\alpha$ -glucosidase (top right panel). Isopropyl derivative **7** docked in the active site cavity of  $\alpha$ -glucosidase interacting with side chain residues (bottom left), benzyl derivative **8** shows at least three hydrogen bonds and some non-polar interactions with active site residues of  $\beta$ -galactosidase 151
- Fig. 6.8. Model of mutated structure (pink) active site superimposed on the wild type structure (cyan) of  $\alpha$ -galactosidase. (b) MD simulated protein ligand complex (pink) superimposed on the wild type structure (cyan) shows restoration of the structure in the active site 154

# *List of Tables*

Table 1.1	List of commonly used software suites for drug design	3
Table 1.2	Ligand based drug designing strategy	5
Table 1.3.	Molecular docking tools with their search algorithm and source	13
Table 2.1	Comparative root mean square deviations (RMSD) of the three dimensional structures of Ca <sup>2+</sup> -ATPase representatives and their transport intermediates	43
Table 2.2.	Partial charges on each atom of artemisinin, deoxyartemisinin and heme-artemisinin adduct	48
Table 2.3.	Molecular dynamics simulations protocol	52
Table 2.4.	Average binding free energies of the aforementioned complexes computed from the MD trajectories	55
Table 3.1.	Computational and experimental binding affinities of 14 synthesized compounds tested against <i>P. falciparum</i> cell lines	78
Table 4.1.	Computationally predicted binding affinities and experimentally observed IC <sub>50</sub> values of designed molecules	98
Table 4.2.	Binding affinity of designed molecules against <i>PfPMT</i> enzyme estimated by ITC method	104
Table 5.1.	Average binding energy for anionic and neutral form of curcumin bound with CAMK4	118
Table 5.2.	Computationally predicted binding affinities of curcumin along with designed molecules and their <i>in vitro</i> IC <sub>50</sub> against CAMK4	121
Table 5.3	Computed binding energies and their <i>in vitro</i> IC <sub>50</sub> of a few molecules designed and synthesized against AChE	125
Table 6.1.	Energy of compounds ( <b>3-8</b> ) with different protonation states	142
Table 6.2.	Results of computational and experimental studies on the inhibition of	

	glycosidases with compounds <b>1-4</b>	144
Table 6.3.	Difference in surface area ( $\text{\AA}^2$ ) of active site of protein bound with compounds <b>3</b> and <b>4</b>	149
Table 6.4.	Results of computational and experimental studies on the inhibition of glycosidases with compounds ( <b>5 – 8</b> )	150