

*To my parents, whose  
unwavering support and love  
have been my guiding light*

## DECLARATION

I, **Kaushik Sarkar**, hereby declare that the work presented in this thesis entitled “**An Approach of Computer Aided Drug Design Tools for In Silico Pharmaceutical Drug Design and Development**” is an authentic record of research work done by me under the supervision of Dr. Rajesh Kumar Das, Assistant Professor, Department of Chemistry, University of North Bengal, Darjeeling, West Bengal, India.

The research work in this thesis has not been submitted elsewhere earlier, for the award of any other degree, diploma and fellowship to this or any other University/Institute.

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ENLIGHTENMENT TO PERFECTION

## CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled "*An Approach of Computer Aided Drug Design Tools for In Silico Pharmaceutical Drug Design and Development*" submitted by **Mr. Kaushik Sarkar**, who got his name registered for the award of Ph.D. in Chemistry degree of the University of North Bengal is absolutely based upon his own work under the supervision of me and that neither his thesis nor any part of the thesis has been submitted for any degree/diploma or any other academic award anywhere before.

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KAUSHIK SARKAR

## Preface

The work presented in this thesis is spread over a span of four and a half years. In this work, several *in silico* techniques were employed to study the potential leads against various targets such as aurora kinase, hepatitis C virus, COVID-19, monkeypox virus, adenovirus, histone lysine methyl transferase (HKMT), and ghrelin O-acyltransferase (GOAT).

Computer-aided drug design (CADD) has been extensively explored for facilitating lead discovery and optimization with advantages in terms of both high speed and low cost that finally increase the probability of success in the drug development process. A variety of *in silico* methods have evolved in CADD that have two major application areas, i.e., ligand-based drug design (LBDD) and structure-based drug design (SBDD). In the present study, we have employed both structure-based (molecular docking) and ligand-based (QSAR) drug design techniques, as together they become a powerful tool to study potential ligands for one or more targets. Further, several other *in silico* techniques were employed, and the major part of the work deals with the design of new inhibitors (drug design), repurposing techniques, and the development of predictive and statistically robust QSAR model for the design of new inhibitors. The use of drug repurposing techniques has become a game-changer in this field. It has the potential to completely transform the pharmaceutical industry by providing an innovative and efficient method of determining new therapeutic uses for already-approved drugs.

On the other hand, the QSAR technique also plays a vital role in lead optimization step in any drug discovery program, which is significantly utilized to save time, money, and, more importantly, animal sacrifice. The basic steps involved in developing predictive QSAR models comprise dataset collection, data curation, descriptor calculation, data pre-treatment of calculated descriptors, model development employing various chemometric techniques, model validation, and applicability domain determination. In this thesis, the QSAR technique was proficiently utilized to understand the structural features that are favourable for the activity as well as to attain desirable selectivity. Further, the developed QSAR model provided valuable information to design new molecules with improved activity, and it is also utilized for predicting the activity of a query or newly designed molecule.

The work has been presented in this thesis under the following sections:

- Chapter I :** Introduction
- Chapter II :** Methodology
- Chapter IIIA :** Screening of drug efficacy of rosmarinic acid derivatives as aurora kinase inhibitors by computer-aided drug design method
- Chapter IIIB :** Virtual Screening of telaprevir and danoprevir derivatives for hepatitis C virus NS3/4A protease inhibitors
- Chapter IVA :** Preliminary identification of hamamelitannin and rosmarinic acid as COVID-19 inhibitors based on molecular docking

- Chapter IVB :** Molecular docking, ADME and toxicity study of some chemical and natural plant based drugs against COVID-19 main protease
- Chapter IVC :** Repurposing of existing pharmaceutical drugs against monkeypox virus: an *in silico* study
- Chapter IVD :** Computational insights into pediatric adenovirus inhibitors: *in silico* strategies for drug repurposing
- Chapter VA :** QSAR study of benzofuran and indole derivatives to predict new compounds as histone lysine methyl transferase inhibitors
- Chapter VB :** Discovery of new oxadiazolo pyridine derivatives as potent ghrelin O-acyltransferase inhibitors using molecular modeling techniques

Scope for Future study

Concluding Remarks

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In the “**Introduction**” section, basic information is provided on the power of computer-aided drug design, its evolution, significance, and general information about aurora kinase and the hepatitis C virus. This section also comprises drug repurposing strategy, its major significance, and basic information about COVID-19, the monkeypox virus, and adenovirus. The detailed information on QSAR technique and ideas about HKMT and GOAT inhibitors is also included in this section. The detailed information related to various computational techniques and their methodologies has been provided in the section “**Methodology**”. Research works related to drug design are discussed in ‘**Chapter III**’, while studies of drug repurposing strategies have been thoroughly discussed in ‘**Chapter IV**’ section. Further, the QSAR-related works have been added in the ‘**Chapter V**’ section. Finally, ‘Concluding Remarks’ has been incorporated along with ‘References’, ‘Index’ and ‘Reprints’.

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## Abbreviations

0D QSAR	Zero-dimensional QSAR	GFA	Genetic function approximation
1D QSAR	One-dimensional QSAR	GGA	generalized gradient approximation
2D QSAR	Two-dimensional QSAR	GH	Growth hormone
3D QSAR	Three-dimensional QSAR	GHS-R1a	GH secretagogue receptor 1a
4D QSAR	Four-dimensional QSAR	GI	Gastrointestinal
5D QSAR	Five-dimensional QSAR	GOAT	Ghrelin O-acyltransferase
6D QSAR	Six-dimensional QSAR	GTO	Gaussian-type orbitals
7D QSAR	Seven-dimensional QSAR	HADV	Human Adenovirus
$\gamma$ -GTP	$\gamma$ -glutamyltransferase	HC	Hemorrhagic cystitis
ANN	artificial neural network	HCV	Hepatitis C virus
AAK1	Associated protein kinase 1	HF	Hatree-Fock
ACE-2	Angiotensin-converting enzyme 2	HIA	Human intestinal absorption
AD	Applicability domain	HMT	Histone methyltransferase
ADME	Absorption, distribution, metabolism and excretion	HKMT	Histone lysine methyltransferase
AgRP	Agouti-related peptide	HOMO	Highest occupied molecular orbital
AURK	Aurora kinase	HSCT	Hematopoietic stem cell transplantation
AR	Androgen receptor	HTRF	Homogeneous time-resolved fluorescence
BBB	Blood brain barrier	IC	Incremental construction
BRCA1	Breast cancer type 1	ICMR	Indian Council of Medical Research
BRCA2	Breast cancer type 2	INCENP	Inner centromere protein
CAP	Community-acquired pneumonia	IRF3	Interferon regulatory factor 3
CADD	Computer-aided drug design	IRES	Internal ribosome entry site
CCC	Concordance correlation coefficient	ISG	Interferon-stimulated gene
CDC	Centers for Disease Control and Prevention	JAK1	Janus kinase 1
CGenFF	CHARMM General Force Field	JAK2	Janus kinase 2
CMC	Comprehensive medicinal chemistry	KIF2A	Kinesin family member 2A
COMFA	Comparative Molecular Field Analysis	LBDD	Ligand-based drug design
COMSIA	Comparative molecular similarity indices analysis	LCAO	Linear combination of atomic orbitals
CNS	Central nervous system	LFER	Linear free energy relationship
CPC	Chromosome passenger complex	LGA	Lamarckian genetic algorithm
CSC	cancer stem cell	LMO	Leave-many-out
CSG	Coronavirus Study Group	LOF	Friedman lack-of-fit
DAA	direct-acting antiviral	LOO	Leave-one-out
DFT	Density functional theory	LUBAC	Linear ubiquitin chain assembly complex
DL	Deep learning	LUMO	Lowest unoccupied molecular orbital
DRC	Democratic Republic of Congo	MAVS	Mitochondrial antiviral signaling
EED	Embryonic ectoderm development	MBOAT	Membrane-bound O-acyltransferase
EGFR-TKI	epidermal growth factor receptor-tyrosine kinase inhibitors	MC	Monte carlo
EKC	Epidemic keratoconjunctivitis	MDDR	Molecular detection of drug resistance
ELISA	Enzyme-linked immunosorbent assay	MD	Molecular dynamics
EMA	European Medicines Agency	MDCK	Madin-Darby canine kidney
ErbB2	Epidermal growth factor receptor 2	MERS-CoV	Middle East respiratory syndrome coronavirus
ES	Epithelioid sarcoma	MHRA	Medicines and Healthcare products Regulatory Agency
EZH2	Enhancer of zeste homolog 2	MLR	Multiple linear regression
FA	Factor analysis	MM	Molecular mechanics
FDA	Food and drug administration	MM-PBSA	Molecular Mechanics Poisson-Boltzmann Surface Area
FEL	Free energy landscape		
FEP	Free energy perturbation		
GA	Genetic algorithm		
GB	Generalized-Born		

MMV	Molegro molecular viewer	RB	Retinoblastoma
MPXV	Monkeypox virus	RCSB	Research collaboratory for structural bioinformatics
MW	Molecular weight	RdRp	RNA-dependent RNA polymerase
NANBH	Non-A-non-B hepatitis	REACH	Registration, Evaluation, and Authorization of Chemicals
natoms	Number of heavy atoms	RF	Random forests
NEMO	NF- $\kappa$ B essential modulator	Rg	Radius of gyration
NIH	National Cancer Institute	RIG-I	Retinoic acid-inducible gene I
NM	Newtonian mechanics	RLR	retinoic acid-inducible gene-I-like receptor
NMR	Nuclear magnetic resonance	RMSD	Root mean square deviation
nOHNH	Number of hydrogen bond donors	RMSE	Root mean square error
nON	Number of hydrogen bond acceptors	RMSF	Root mean square fluctuation
nrotb	Number of rotatable bonds	RTI	Respiratory tract infection
NSCLC	Non-small cell lung cancer	SAM	S-adenosyl-L-methionine
NSP	Non-structural protein	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
nviolations	Number of violations	SASA	Solvent-accessible surface area
NVT	Constant number of particles, volume, and temperature	SBDD	Structure-based drug design
NPT	Constant number of particles, pressure, and temperature	SCF	Self-consistent field
OECD	Organisation for Economic Co-operation and Development	SCLC	Small cell lung cancer
OLS	Ordinary least squares	SOT	Solid organ transplantation
PCA	Principal component analysis	SPX	Smallpox
PBC	Periodic boundary condition	STAT1	Signal transducer and activator of transcription 1
PCR	Principal component regression	STO	Slater-type orbital
PDB	Protein data bank	SVM	Support vector machines
PK	Protein kinases	SVR	Sustained virologic response rate
PLS	Partial least-squares	TBK1	TANK-binding kinase 1
PME	Particle-mesh Ewald	TI	Thermodynamic integration
PMV	Python molecular viewer	TLR3	Toll-like receptor 3
PRC2	Polycomb repressive complex 2	TPSA	Topological polar surface area
PROTAC	Proteolysis-targeting chimera	ULR	Univariate linear regression
PTM	Post-translational modification	UM	uveal melanoma
QH	Quasiharmonic	UTI	Urinary tract infections
QM	Quantum mechanics	WDI	World drug index
QSAR	Quantitative structure-activity relationship	WHO	World Health Organization
QSPR	Quantitative structure-property relationship	XC	Exchange-correlation
QSTR	Quantitative structure-toxicity relationship		

## List of publications

**Research articles related to thesis**

1. **Sarkar, K.**, and Das, R. K. Virtual Screening of Telaprevir and Danoprevir Derivatives for Hepatitis C Virus NS3/4A Protease Inhibitors. *Letters in Drug Design & Discovery*, **2024**, 21(4), 809-822.
2. **Sarkar, K.**, Das, B., and Das, R. K. Discovery of new oxadiazolo pyridine derivatives as potent ghrelin O-acyltransferase inhibitors using molecular modeling techniques. *In Silico Pharmacology*, **2023**, 11(1), 35.
3. **Sarkar, K.**, Nandi, S. and Das, R.K. Computational insights into pediatric adenovirus inhibitors: *in silico* strategies for drug repurposing. *Journal of Biomolecular Structure and Dynamics*, **2023**, 1-14.
4. **Sarkar, K.**, Ghosh, S. and Das, R.K. QSAR study of benzofuran and indole derivatives to predict new compounds as histone lysine methyl transferase inhibitors. *European Journal of Chemistry*, **2023**, 14(2), 231-245.
5. **Sarkar, K.** and Das, R.K. Repurposing of existing pharmaceutical drugs against monkey-pox virus: an *in silico* study. *Analytical Chemistry Letters*, **2022**, 12(6), 655-670.
6. **Sarkar, K.** and Das, R.K. Molecular docking, ADME and toxicity study of some chemical and natural plant based drugs against COVID-19 main protease. *International Journal of Computational Biology and Drug Design*, **2021**, 14(1), 43-63.
7. **Sarkar, K.** and Das, R.K. Preliminary identification of hamamelitannin and rosmarinic acid as COVID-19 inhibitors based on molecular docking. *Letters in Drug Design & Discovery*, **2021**, 18(1), 67-75.
8. **Sarkar, K.**, Sarkar, S. and Das, R.K. Screening of Drug Efficacy of Rosmarinic Acid Derivatives as Aurora Kinase Inhibitors by Computer-Aided Drug Design Method. *Current Computer-Aided Drug Design*, **2021**, 17(5), 627-646.

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1. **Sarkar, K.**, Yadav, S., Alharbi, M., Aziz, T. and Das, R.K. Exploring the Potency of 6-Bromo-3-Methylquinoline Analogues as Prostaglandin F<sub>2</sub> $\alpha$  Inhibitors. *Journal of Biomolecular Structure and Dynamics*, **2024** (Accepted).

2. Reja, S., **Sarkar, K.**, Mukherjee, D., Guha, S., Ghosh, S., Saha, T., Kumar, P., Das, P., and Das, R. K. Novel bioinspired dinuclear Cu (II) 'paddle wheel' acetate complex: Catalytic and in vitro biological activity studies. *Journal of Molecular Structure*, **2024**, 1300, 137263.
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13. **Sarkar, K.** and Das, R.K. In silico study of rosmarinic acid derivatives as novel insulin fibril inhibitors. *Journal of Computational Biophysics and Chemistry*, **2021**, 20(06), 641-654.

#### **Review articles not related to thesis**

1. **Sarkar, K.** and Das, R.K. Quorum sensing inhibitor: a new strategy against pathogenic bacteria. *Adv Res Endocrinol Metab*, **2021**, 3(1): 109-113.
2. **Sarkar, K.** and Das, R.K. A review on quorum sensing inhibitors. *Int. J. Pharm. Sci*, **2019**, 5224-5233.

#### **Book chapter not related to thesis**

1. **Sarkar, K.** and Das, R.K. Impact of COVID-19 Pandemic Crisis on Economy, Education and Health System in India. *Kripa Drishti Publications*, **2020**, ISBN: 978-81-947839-5-4.

#### **Book not related to thesis**

1. **Sarkar, K.** and Das, R.K. Computational Drug Design for Beginners: Tools & Protocols. *Eliva Press*, **2021**, ISBN: 978-1636481890.

## List of Seminars, Webinars and Symposiums Presented

1. **Sarkar, K.** and Das, R.K. Drug Repurposing against Monkeypox Virus using Computational Approaches. Paper presentation in National Seminar on Frontiers in Chemistry-2023 & Bharat Ratna Prof. C.N.R. Rao Endowment Lecture. Department of Chemistry, NBU. 14<sup>th</sup> March, 2023.
2. **Sarkar, K.** and Das, R.K. Preliminary Identification of Hamamelitannin and Rosmarinic Acid as COVID-19 Inhibitors Based on Molecular Docking. Paper presentation in Two Day International Webinar on Emerging Field of Chemistry and Biomedical Research. Department of Chemistry, CBPBU. 7<sup>th</sup> August, 2020.