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DECLARATION

I hereby declare that the thesis entitled “X-RAY CRYSTALLOGRAPHIC, MOLECULAR DOCKING AND DYNAMICS STUDIES OF SOME BIOLOGICALLY SIGNIFICANT ORGANIC COMPOUNDS” submitted to the University of Madras for the award of the degree of Doctor of Philosophy is the original and independent work carried out by me in the Department of Physics, RKM Vivekananda College (Autonomous), Mylapore, Chennai, during the period 2010–2017 under the supervision of Dr. K. Sethusankar, Associate Professor and Head, Department of Physics, RKM Vivekananda College (Autonomous), Mylapore, Chennai and that the thesis has not formed previously the basis for the award of any other degree, diploma, associateship, fellowship or any other similar titles.

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PREFACE

This thesis entitled "X-RAY CRYSTALLOGRAPHIC, MOLECULAR DOCKING AND DYNAMICS STUDIES OF SOME BIOLOGICALLY SIGNIFICANT ORGANIC COMPOUNDS" is a report of the research work carried out by the candidate during the period 2010-2017 under the guidance of Dr. K. Sethusankar, Associate Professor and Head, Department of Physics, RKM Vivekananda College (Autonomous), Mylapore, Chennai -600004.

Being non-destructive in nature and having wavelengths similar to molecular dimensions, X-rays are ideally suited probes for exploring the geometrical arrangement of three-dimensional arrays of molecules in crystals. The diffraction pattern obtained from X-ray scattering by crystals can be processed by mathematical algorithms to provide a molecular structure with unambiguous atomic details including atomic positions, conformational features and the symmetries involved in generating the entire crystalline substance. As there is an intimate relation between structure and function of molecular systems the precise molecular structures obtained from X-ray crystallography can be used to derive functional information of chemical and biological systems at the molecular level.

This thesis reports the results from single crystal X-ray crystallographic structural investigations, molecular docking and molecular dynamics studies of some biologically significant organic compounds. The thesis contains seven chapters and has been organized into two parts.
Part I comprising five chapters describes the X-ray crystallographic structural studies of some isoxazole, acrylate, indole, hydrazine carbothioamide and carbazole derivatives. The intensity data for all the compounds reported in this thesis were collected using Bruker axs SMART and KAPPA APEXII area-detector diffractometer.

Chapter I describes the crystal structure determination and analysis of two isoxazole derivatives. The two isoxazole derivatives crystallize in monoclinic crystal system with the space group of P2₁/c. The five membered isoxazole rings in the two compounds adopt an envelope confirmation and the six membered pyran rings in the two compounds display sofa and half-chair conformations. The crystal packing is seen to be stabilized by C—H···π interactions in these compounds.

Chapter II elucidates the crystal structure determination and analysis of two acrylate derivatives. The methyl acrylate units in both the compounds are found to be essentially planar. In the two derivatives the double bond between the carbon atoms C9 and C12 is a trans in nature. The difference between the C—O bond lengths of the methyl acrylate group in both compounds indicate the presence of resonance structures. The crystal packing is seen to be stabilized by C—H···O and C—H···π interactions in these compounds.

Chapter III deals with the crystallographic studies of three indole derivatives. In the three derivatives the indole bicyclic ring system is not
strictly planar. The five membered pyrrolidine and furan rings are found to adopt envelope and twisted confirmations, respectively. In the indole moiety, the fusion of the smaller pyrrole ring to the six membered benzene ring causes a strain which is taken up by angular distortions. The crystal packing is essentially stabilized by O—H···O, N—H···O and C—H···O interactions in all the three derivatives.

Chapter IV details the crystallographic studies of four hydrazine carbothioamide derivatives. The thiourea group in the four derivatives is found to be essentially planar. The cyclohexane in CTA I and the pyran ring in CTA3 are found to exhibit chair and screw boat confirmations, respectively. The crystal packing in the four derivatives involves N—H···S, O—H···S, N—H···O, C—H···Cl, C—H···O and C—H···π interactions.

Chapter V discusses the crystal structure determination and analysis of three carbazole derivatives. The carbazole moiety in the three compounds is essentially planar. Atom S1 in the three derivatives is found to have a distorted tetrahedral configuration. The benzene ring of the phenylsulfonyl group is almost perpendicular to the carbazole moiety in compounds I and III. The crystal packing in all three compounds is stabilized by intermolecular C—H···O and C—H···π hydrogen bonds.

Part II consisting of chapters VI and VII explains the activity studies taken up for the fourteen small molecules whose structures were determined as detailed above. Molecular docking estimates the binding orientation and
affinity of possible drug candidates to specific targets and hence predicts the activity of the small molecule. Biological macromolecules such as proteins exist in a dynamic state of motion which is essential for their specific functions such as intermolecular protein-ligand binding. Molecular dynamics simulations provide a means to model the flexibility and conformational changes in proteins associated with ligand binding.

Chapter VI Results of the docking studies undertaken using Schrodinger’s GLIDE software are discussed in detail in chapter VI. The two isoxazole derivatives were individually docked with human Bromodomain4 (BET-BRD4) as target protein to examine their anti-proliferative effects. Human Factor Xa (FXa) was used as the protein target for docking with each of the two acrylate derivatives to investigate their activity as possible anticoagulant agents. Activity studies of the three indole derivatives were carried out by docking them individually with Cyclin Dependent Kinase2 (CDK2) to explore their anticancer activity. Human Carbonic anhydrase(CA) was chosen as target protein for docking studies of each of the four hydrazine carbothioamide derivatives. Human TopoisomeraseIIβ was used for docking of the three carbazole derivatives to examine their DNA intercalating activity. The binding affinity of the docked complexes were evaluated in terms Glide energy and docking scores. The hydrogen bond and hydrophobic interactions between the docked molecules and target proteins were analysed based on their Pymol and Ligplots diagrams.
Chapter VII GROMACS software was used for molecular dynamics simulation of three of the docked complexes which showed high affinity between protein and ligand. Results of the Molecular dynamics simulations of the \textit{BRD4-ISZ1}, \textit{CDK2-IND3} and \textit{CA-CTA3} docked complexes have been discussed in chapter VII. The resulting trajectory was used to analyse the stability of the complex formed using RMSD and Radius of gyration values of the complexes, to identify the hydrogen bonds formed and to estimate the binding association of the complexes.

The following research papers have been published based on this research work:

**List of Publications:**

1. 3’-Hydroxymethyl-1’-methyl-3’-nitro-4’-(o-tolyl)spiro-[indoline-3,2’-pyrrolidin]-2-one  

2. 1-Methyl-3-(naphthalen-1-yl)-3,3a,4,9b-tetrahydro-1Hchromeno[4,3-c]isoxazole-3a carbonitrile  

3. 1-Methyl-3-p-tolyl-3,3a,4,9b-tetrahydro-1H-chromeno[4,3-c]isoxazole-3a carbonitrile  

4. (Z )-Methyl 2-[(2-ethoxy-6-formylphenoxy)methyl]-3-(4-ethylphenyl)acrylate  
5. (Z)-Methyl 3-(2,4-dichlorophenyl)-2-[(2-formylphenoxy)methyl]acrylate  

6. Methyl 4’-(4-bromoanilino)-2’,5-dioxo-5H-spiro[furan-2,3’-indoline]-3-carboxylate  

7. Methyl 4-anilino-2’,5-dioxo-1’,2’-dihydro-5H-spiro[furan-2,3’-indole]-3-carboxylate  

8. *(E)*-2-[(4-chloro-2H-chromen-3-yl)methylidene]-N-cyclohexyl hydrazine carbothioamide  

9. Crystal structures of two hydrazinecarbothioamide derivatives: *(E)*-N-ethyl-2-(4-oxo-4H-chromen-3-yl)methylidene]hydrazinecarbothioamide hemihydrate and *(E)*-2-[(4-chloro-2H-chromen-3-yl)methylidene]-N-phenylhydrazine-carbothioamide  

10. Crystal structure of 3-[(E)-(2-hydroxy-3-methoxybenzylidene)amino]-1-methyl-1-Phenylthiourea  

X-RAY CRYSTALLOGRAPHIC, MOLECULAR
DOCKING AND DYNAMICS STUDIES OF SOME BIOLOGICALLY
SIGNIFICANT ORGANIC COMPOUNDS

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