Preface

Sulfonamides are among the first drugs selected (together with ampicillin and gentamycin) as chemotherapeutic agents in bacterial infections by E. coli in human. Sulfonamide is an antibacterial consist of synthetic organic compounds capable of inhibiting the growth of bacteria that require PABA (para-amino benzoic acid) which is structurally similar to sulfanilamide. Among the vast families of sulfonamides being currently investigated, N-substituted sulfonamides are one of the outstanding groups because of their broad biological spectrum. It is well documented that toxicological and pharmacological properties are enhanced when sulfonamides are administered in the form of their metal complexes. The coordination chemistry of sulfonamides has undergone noticeable development in recent years due to the interesting properties of these substances.

This thesis entitled **"X-ray crystallographic investigations, quantum chemical calculations, Hirshfeld surface analysis and molecular docking studies of significant sulfonamide derivatives"** presents systematic studies on significant sulfonamide derivatives including polymorphs and metallic complexes using CHN analysis, FTIR, ^{1}H NMR, ^{13}C NMR, UV-Visible, electrical conductivity, TG, DTG, and single crystal X-ray diffraction technique. X-ray crystallographic data are supported by theoretical data, workout by computational theoretical MO calculation using Schrodinger programme. The 3D Hirshfeld surface analysis and 2D fingerprint analysis are performed to study the nature of the interactions and their quantitative contributions towards the crystal packing. Quantum lattice energy are calculated for Sulfamonomethoxine (SMM), polymorph of sulfamonomethoxine (SMM-I) and Phthalylsulfacetamide (PHSCA). To correlate the structure function relationship, the synthesized metal complexes are tested for their biological response by Broth dilution method. Out of these complexes the polymorphs of sulfonamides have been subjected to molecular docking studies.

Among several transition metals, **Silver** has the most outstanding properties with antimicrobial activity because of its higher toxicity to microorganisms and lower toxicity to mammalian cells. The use of silver (I) coordination compound as building block for the construction of dimeric, polymeric or supramolecular structures has been recognized as significant area of research.

Silver is effective against a broad range of gram negative and gram positive bacteria, fungi and yeast.

Silver complexes of different sulfonamide derivatives have been prepared by the condensation reaction of metal salts with different sulfonamides; sulfaphenazole, sulfachloropyridazine and sulfadiazine.

Polymorphism is the ability of a material to exist in more than one crystalline form. Polymorph is sufficient to reveal the packing and molecular conformational difference between the two polymorphic forms due to the potential impact of solvents and impurities on the relative nucleation and growth kinetic of different forms. Polymorphism may have a considerable influence on solid-state properties that may be modify biopharmaceutical and technological behavior of drug. Polymorphs are different crystalline forms of a drug that may have different physicochemical properties and biological activities.

It is very essential to acquire the information of the structure of a molecule to understand the drug activity of a specific molecule. It is well established that the function of a molecule is associated with the molecular structure. A small change in the structure is accompanied by the change in its function. To modify the drug molecule in terms of its effectiveness against different bacteria, the Ag complexes have been tested for its biological response. Micro broth dilution method is used to determine the minimal inhibitory concentration (MIC) of the antimicrobial agent against gram negative *E. coli* and *Sh. Flexneri* and gram positive *S. aureus* and *B. Subtillis*. Molecular docking studies have been carried out by GLIDE utility from Schrodinger software for SMM, SMM I, PHSCA and SP III.

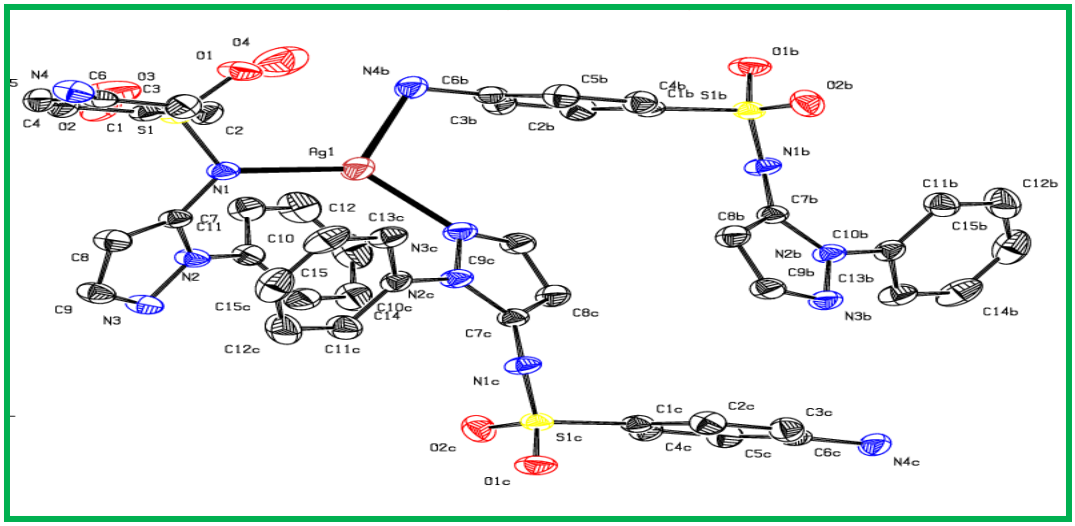
Contents of the thesis are summarized in total 10 chapters: the chapters are introduction, experimental techniques followed by seven chapters which report the systematic characterizations of the seven molecules and the last chapter is conclusion and future scope of work.

Chapter 1 presents the brief introduction of sulfonamides which is the basis of several group of drugs. It represents a class of antibiotics that have multiple clinic use. But the emergence of drug resistant strains is one of the constraints of sulfonamide therapy. For this reason the demand for new and better chemotheraputic compounds has been increased. In order to find better

compounds, metal sulfonamides have attracted much attention due to the fact that complexes showed more activity than both free ligands and the corresponding metallic salts. Due to the ability of sulfonamide derivatives to form coordination of silver complexes of the type ML_1 and ML_2, a systematic literature survey about the coordination chemistry of transition metal complexes especially silver complexes of sulfonamide is reported in this chapter. A short description of DFT studies using Jaguar module of Schrodinger software and Hirshfeld surface analysis and lattice energy calculation by PIXELC are presented and the last part of the chapter includes the importance of the antimicrobial activity and molecular docking studies in reference to X-ray structural investigations. In this context, the role of X-Ray crystallography in drug design is discussed in brief.

Chapter 2 discusses the technique used to synthesize metal complexes of sulfonamides. CHN analysis (elemental analysis), IR, ^{1}H NMR, ^{13}C NMR, UV-Visible, electrical conductivity, TG, DTG, DTA and single crystal X-ray diffraction technique are briefly discussed. The slow evaporation method, to grow the single crystals of organic molecules suitable for X-ray study is conferred in detail. Experimental techniques for collecting intensity data using CCD-4 diffractometer, structure solution and refinement are elaborated. Direct method is used to investigate the crystal structures and Broth dilution method used to investigate the biological response of the silver complexes, are discussed in detail. The software details which are used at different stages of the work are summarized at the end of this chapter.

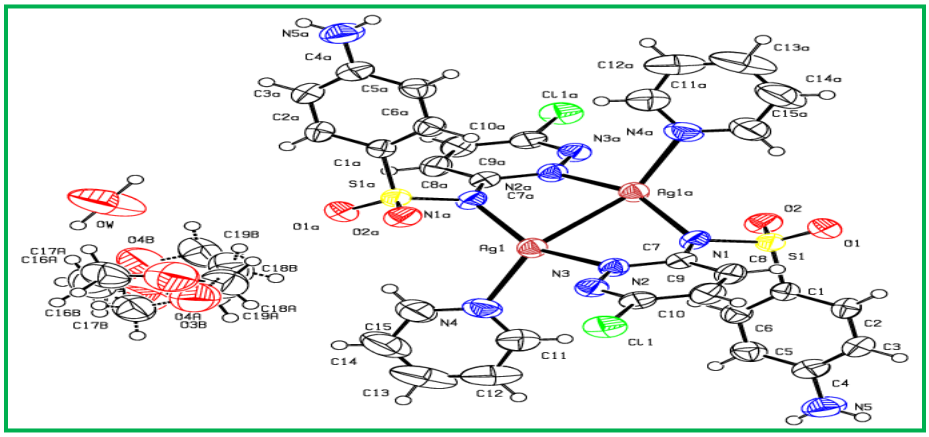
Chapter 3 presents synthesis, spectroscopic characterizations, antibacterial activities and crystal structure of silver complex of sulfaphenazole dihydrate. The title compound has been synthesized by reflux method. Red colored diamond shaped crystals of the title compound are grown from solution of pyridine. The title compound $[Ag(C_{15}H_{12}N_4O_2S)(H_2O)_2]$ crystallizes in the monoclinic space group C2/c with lattice parameters a = 28.5551(8) Å, b = 7.8294(2) Å, c = 18.6984(5) Å, β = 126.675 (1)□ and Z= 8. The structure is solved by Patterson method and refined to a final R=0.026 for 3850 reflections with I≥2σ(I). The IR, ^{1}H NMR and ^{13}C NMR spectral data suggest the binding of silver atom to the sulfonamide ligand which is in agreement with the crystal structure determination. Thermogravimetric studies shows that the final residual mass left at 950°C correspond to 50.70% for silver complex ORTEP view of the title molecule is as shown below.



X-ray analysis has revealed that the geometry of the silver atom is a distorted trigonal array. Its coordination sphere is formed by aryl amine N, sulfonamido N and pyrazoline N from three symmetry related ligand molecules. Each metal ion is chelated by N1 of a single SPZ ligand. The lattice of [AgSPZ.2H2O]n holds bidimensional sheets. In the crystal structure, the molecules are linked via N–H···O, O–H···O, π···π and C–H···π intermolecular and C–H···O intramolecular interactions. The Ag-N distances are comparable with those of other reported silver complexes. The optimized geometry, molecular orbital properties, Mulliken charge distribution of atoms and total energies of the title compound has been calculated using Density Functional Method (B3LYP). The optimized geometry has been predicted and compared with experimental data. Hirshfeld surface (HS) analysis is used as a technique to understand the nature of intermolecular interactions within crystal structure using a fingerprint plot. Ag-sulfaphenazole exhibits different antibacterial behavior against gram positive and gram negative bacteria. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. **CCDC1010579.**

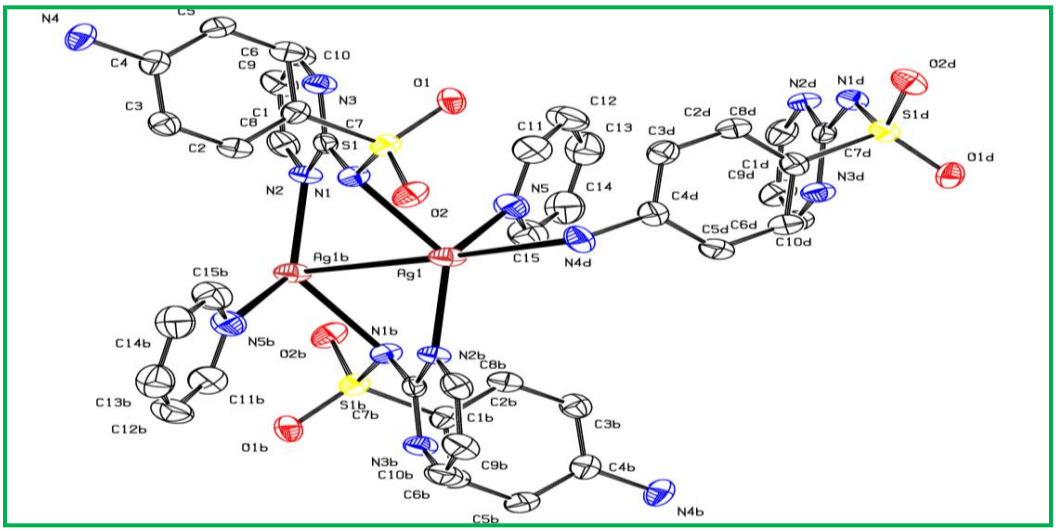
Chapter 4 reports synthesis, spectroscopic characterizations, antibacterial activities and crystal structure of silver complex of sulfachloropyridazine. Reflux method is used to synthesize the title molecule. Colorless parallelopiped crystals of the title compound are grown from the mixture of pyridine and 1,4 dioxane. The title compound crystallizes in the monoclinic space group $P2_1/n$ with lattice parameters a=15.9642(3) Å, b=8.1207(2) Å, c=17.6392(4) Å, β = 101.145(1)° and Z=4. The structure is solved by direct methods and refined to a final R=0.041 for 5165

reflections with I≥2 σ (I). The solvent molecule 1,4 dioxane exhibits the positional disorder which is removed by assigning occupancy 0.54 and 0.46. The peak for the sulfonamidic (N–H) group in the free ligands at around 3138 cm^{-1} is not present in the spectra of the complex, confirming the deprotonation of the $–SO_2NH–$ moiety. The IR and NMR spectral data suggest the binding of silver atom to the sulfonamide ligand which is in agreement with the crystal structure determination. Thermogravimetric studies shows that the final residual mass left at 950°C correspond to 49% for silver complex. Figure below represents the asymmetric unit of the dimeric complex, the molecular structure thereof is viewed through the symmetry operator $-x$, $-y$, $-z+2$.



X-ray analysis has revealed that in the title molecule silver ion is surrounded by three N atoms and one Ag atom leading to a distorted tetrahedral geometry. A quiet shorter Ag...Ag separation distance of 2.836 Å compare to that in metallic silver (2.836 Å) predicts the rarest metal-metal bonding involving s or d orbitals. In the crystal structure, the molecules are linked via N–H···O and π···π intermolecular interactions. The optimized geometry, molecular orbital properties, and total energies of the title compound have been calculated using Density Functional Method (B3LYP). Comparison of the experimental geometric parameters and theoretical one indicated that all optimized bond lengths and angles are in good agreement. The 3D Hirshfeld surface analysis and 2D fingerprint analysis are performed to study the nature of the interactions and their quantitative contributions towards the crystal packing. Title compound has been evaluated for their antibacterial activity for Gram positive and Gram negative bacterial strains. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication No **CCDC 1473330**.

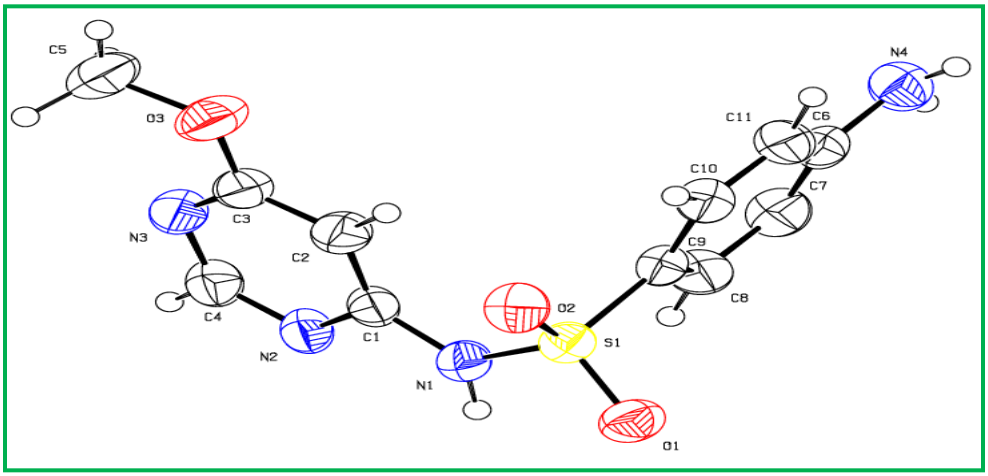
Chapter 5 reports the synthesis, spectroscopic characterizations, antibacterial activities and crystal structure of silver complex of sulfadiazine in the presence of pyridine, $[Ag_2(C_{10}H_{10}N_4O_2S)_2(C_5H_5N)_2]$. The title compound has been synthesized by chemical route and its crystal structure is determined by single crystal X-ray diffraction at room temperature. The complex crystallizes in the monoclinic space group $P2_1/c$ with lattice parameters a=8.7146(8)Å, b=11.5221(11) Å, c=16.4934(16) Å, β =96.340(2)˚ and Z=4. The structure is solved by direct method and refined to a final R=0.026 for 3576 reflections with I≥2 σ (I). The ORTEP diagram of the title molecule is as shown below.



In the title compound, Ag(I) ion exhibits five coordinated highly distorted pentadentate geometry, being coordinated to the sulfonamidic N1, the heterocyclic N3 and aniline N4 of two tridenate sulfadiazine ligands. The terminal N5 of a pyridine solvent complete the coordination sphere. The optimized geometric parameters of the title compound are calculated using Schrodinger software. The Hirshfeld surface and full 2-D fingerprint plots are decomposed to highlight particular atom pair close contacts which enables separation of contributions from different interaction types. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. **CCDC 1473216**.

Chapter 6 summarizes the crystal and molecular structure of sulfamonomethoxine, $(C_{11}H_{12}N_4O_3S)$. It crystallizes in monoclinic space group $P2_1/n$ with Z = 4 having unit cell parameters a= 9.1712 Å, b=6.1925 Å, c=22.0197 Å, α=90.00˚, β=99.55˚and γ=90.00˚. The final

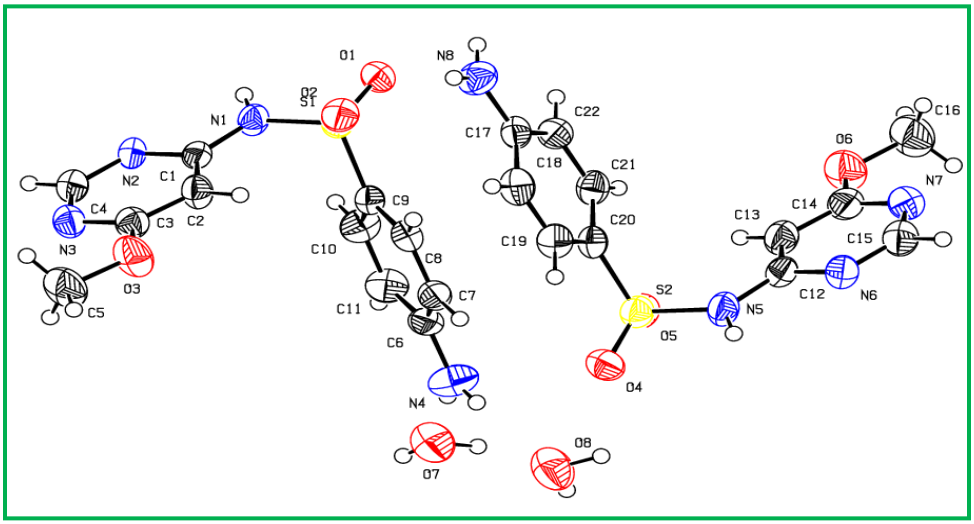
residual index R is 0.038 for the 2835 observed reflections. Sulfamonomethoxine, 4-Amino-N-(6-methoxy-4-pyrimidinyl) benzenesulfonamide, belongs to novel groups of sulfonamide family, long acting, anti-infective and antibacterial sulfonamides. Diversified C–H···O, N–H···N and S–O···π interactions result in to an extensive hydrogen bonding network involving all the donor and acceptor groups of the molecule and the weak $\pi \cdots \pi$ stacking interaction involving the centroids of the two symmetry related pyrimidine ring, Cg-Cg separation distance is 4.297(16) Å. The optimized geometric parameters of the compound are calculated using Schrodinger software. Hirshfeld surface analysis has been carried out to understand the nature of intermolecular interaction and their contribution towards the crystal packing. To establish that molecular packing revealed from the X-ray data are in most stable conformation, the energies associated with the intermolecular interactions and the nature of interactions are calculated using PIXEL by extracting only those molecular pair, involved in the crystal packing. Molecular docking studies have been carried to correlate the structure function relationship. ORTEP representation of molecular structure of the molecule with atom numbering scheme is shown below. Thermal ellipsoid atoms are drawn at 50% probability level.



The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. **CCDC 1007866**.

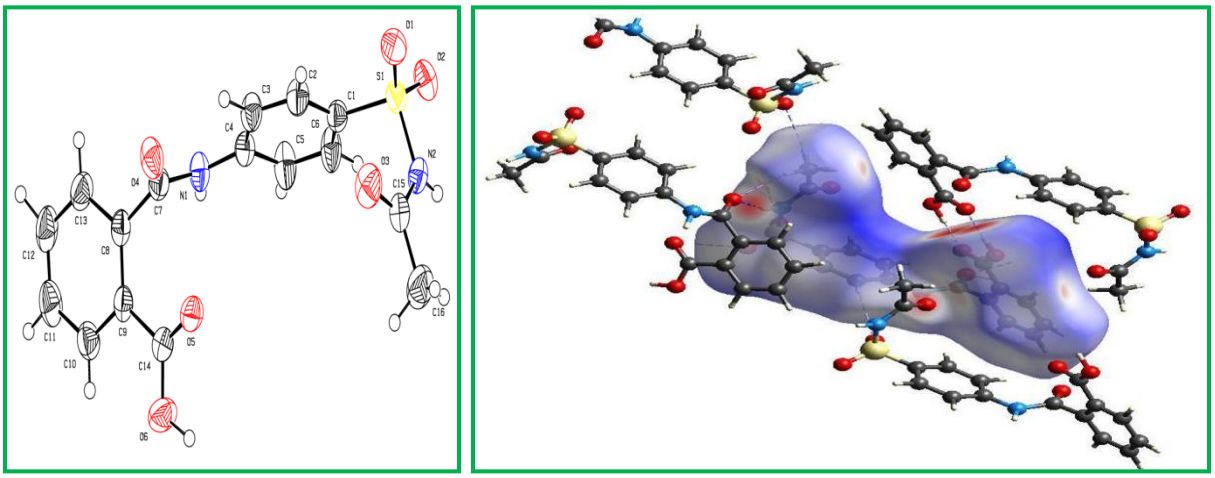
Chapter 7 discusses the crystal and molecular structure of polymorph of sulfamonomethoxine. It crystallizes in triclinic space-group having two molecules of sulfamonomethoxine monohydrate per asymmetric unit with lattice parameters a = 6.1316(3) Å, b = 9.7178(3) Å, c =

23.022 1(7) Å, α = 91.303(2)°, β = 93.832(2)° and γ = 93.7310(10)°. The structure is solved by direct method and refined to a final R= 0.054 for 6209 reflections with I≥2σ (I). In the crystal structure, the molecules are linked via N–H···N, N–H···O, C–H···O intermolecular and C–H···O intramolecular interactions. The hydrate molecules play prominent role in the packing of the Poly-I structure by hydrogen bond interactions. The structure is further stabilized by intermolecular π···π and C–H···π interactions. ORTEP view of the title molecule with 50% ellipsoid is as shown below.



Ab initio quantum chemical calculations are performed by B3LYP method, using 6-31G** basis set with the help of Schrodinger software. The computed geometrical parameters are in good agreement with the experimental data. The molecular HOMOs, LUMOs, total energy and dipole moment are calculated using B3LYP method. The Hirshfeld surface and 2-D fingerprint plots are decomposed to highlight particular atom pair close contacts which enables separation of contributions from different interaction types. To establish that molecular packing revealed from the X-ray data are in most stable conformation, the energies associated with the intermolecular interactions and the nature of interactions are calculated using PIXEL by extracting only those molecular pair, involved in the crystal packing. The different receptors are docked with sulfamonomethoxine and the energy values calculated using Schrodinger software. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication **CCDC No. 1008703**.

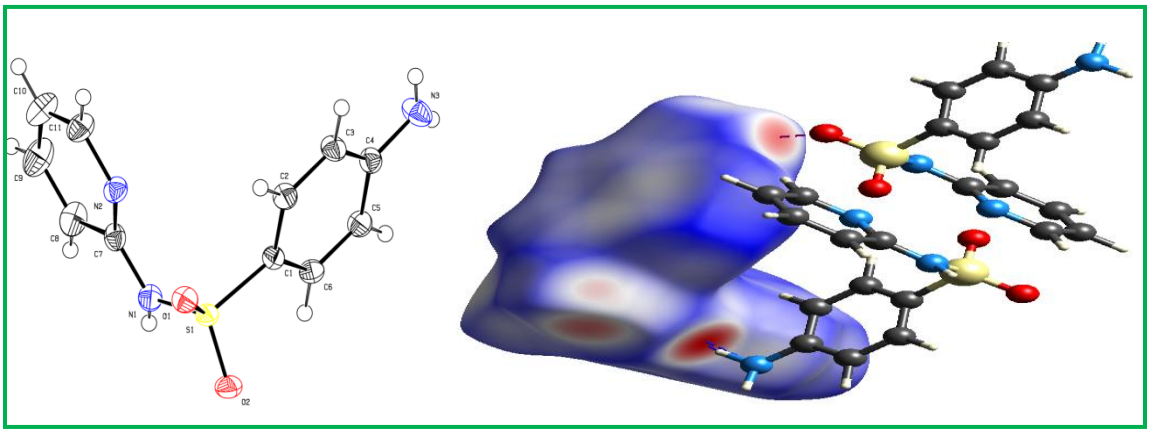
Chapter 8 presents the quantum chemical calculation, Hirshfeld surface analysis and molecular docking of Phthalyl sulfacetamide, 2-([(4-([Acetylamino] sulfonyl) phenyl) amino] carbonyl) benzoic acid. Phthalyl sulfacetamide is an antibiotic sulfonamide used as a leprostatic agent to treat urinary tract infections. The crystals of phthalyl Sulfacetamide are grown from methanol solvent to perform quantum chemical calculation, Hirshfeld surface analysis and molecular docking. The title compound crystallizes in monoclinic crystal system with $P2_1/n$ space group and Z= 4 having lattice parameter a = 7.98410(10)Å, b = 12.8208(2)Å, c = 16.6607(3)Å and β = 93.2390(10) °. The structure is solved by direct methods and refined to a final R=0.054 for 3202 reflections with I≥2 σ (I). In the crystal structure, the molecules are linked via N–H···O, C–H···O and O–H···O intermolecular interactions. The structure is further stabilized by π···π interactions. ORTEP view of the molecule is as shown below.



The optimized geometric parameters of the title compound are calculated using Schrodinger software. Hirshfeld surface (HS) analysis is used as a technique to understand the role of intermolecular interactions in stability of crystal packing. Detailed quantitative analysis of the crystal packing have been performed with calculation of the interaction energies of the extracted molecular pairs from the crystal packing using PIXELC module in Coulomb-London–Pauli (CLP) computer program package. Molecular docking is used to predict the structure of the intermolecular complex formed between two molecules. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. **CCDC 1007230**.

Chapter 9 reports the quantum chemical calculation, Hirshfeld surface analysis and molecular docking studies of third polymorph of sulfapyridine. In order to do so, the crystals of

sulfapyridine are grown from 3- picoline by slow evaporation method. The title compound, 4-amino-N-(1,2-dihydropyridin-2-ylidene) benzenesulfonamide polymorphic form (III) ($C_{11}H_{12}N_4O_3S$) crystallizes in the monoclinic space group $C2_1/c$ with lattice parameters a=12.7226(18)Å, b=11.6789(17)Å, c= 15.302(2)Å, β=93.561(2)° and Z=4. The structure is solved by direct methods and refined to a final R= 0.0475 for 2297 reflections with I≥2σ (I). In the crystal structure, the molecules are linked via N–H···N and N–H···O intermolecular and C-H···O intramolecular interactions. The structure is further stabilized by intermolecular π···π and C–H···π interactions. ORTEP view of the title molecule with 50% ellipsoid is as shown below.



Density functional theory (DFT) methods have been used to calculate all quantum chemical calculations performed using the JAGUAR module from Schrodinger software package. The different receptors are docked with title molecule to examine its biological response. Hirshfeld surface (HS) analysis is used as a technique to understand the nature of intermolecular interactions within a crystal structure using a fingerprint plot. The crystallographic data of the structure described in this chapter are deposited with the Cambridge Crystallographic Data Centre as supplementary publication **CCDC No. 1473219**.

Chapter 10 covers the conclusion drawn from the entire work and scope for the future work.