PREFACE

Single crystal x-ray diffraction is the most common experimental method of obtaining a detailed picture of a large molecule that allows resolution of individual atoms. It is performed by analyzing the diffraction of x-rays from an ordered array of many identical molecules. Many molecular substances, including proteins, polymers, and others solidify into crystals under the proper conditions. When solidifying into the crystalline state, these individual molecules typically adapt one of only a few possible orientations. A crystal is a three dimensional array of these molecules that are held together by Vander Waals, non-covalent bonding. The smallest representative unit of crystals is referred to as the unit cell. Understanding the unit cell of these arrays simplifies the understanding of a crystal as a whole. This is the basis of crystallography.

Crystal structure analysis has gained its importance during the last few decades due to its intense application in the field of material science and medicine particularly in the drug industry. The characterization of materials which are biologically interesting is important and hence the technique of single crystal X-ray diffractometry has gained prominence. The three dimensional structure of the materials will help in formulating structure property/function correlation which in turn will enable to modify materials to suit any requirement. The knowledge of stereochemistry of the molecules is also derived from single crystal X-ray diffraction studies. The double-helical structure of DNA, the planarity of peptide bond, the triple helical structure of collagen, the globular conformation of enzymes and antibodies—all owe their discoveries to X-ray diffraction studies. Practically all the drugs known today are the result of either accidental discoveries or from trial and error process. The X-ray studies thus play an important role in the design of appropriate drugs. Crystallographic studies on the structure, symmetry and conformation of some organic molecules of wide interest form the basis of this thesis.

Pharmaceutical chemistry is the chemistry of drugs, medicinal and pharmaceutical products. It is defined as any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient. The achievement of modern medicine is demonstrated
in the successful eradication and control of many deadly diseases. In the past few decades, pharmaceutical chemistry is widely explored in finding and developing organic compounds that are now available in pharmaceutical formulation for the treatment of diseases and often for the maintenance of better quality of human health. In recent decades, more and more synthetic organic and inorganic compounds are used as drugs.

Many organic compounds having pharmaceutical importance exhibit polymorphism. Polymorphism, the ability of a substance to exist in several different crystal forms or modifications, is a frequently observed phenomenon in molecular compounds. If a solid substance includes a solvent during crystallization, this structure is known as a pseudopolymorph, and in case of, e.g., water such crystal forms are generally called hydrates. The polymorphic modifications of a compound are chemically identical but usually differ in their physical and chemical properties, such as density, vibrational spectra, and diffraction patterns.

Co-crystals are a crystalline material composed of different species held together by non-covalent forces and are typically differentiated from a salt by the lack of proton transfer. Co-crystals offer the framework to modify the physical properties of the compounds involved without changing the molecular structure. Pharmaceutical co-crystals have become increasingly important materials because of their potential to improve physical and chemical stability of the compounds involved, decrease hygroscopicity of the crystalline material, increase kinetic or thermodynamic solubility of the compounds or modify dissolution rates for a compound.

Many organic picrates are of most interest to study because of the presence of hydrogen bonding interactions present. It is really worth-while to study the picrates of organic compounds and also some intermediates which have pharmaceutical importance.

X-ray studies thus play an important role in the design of appropriate drugs. Crystallographic studies on the structure, symmetry and conformation of some organic molecules of wide interest form the basis of this thesis.
Cyclobenzaprine is a muscle relaxant medication used to relieve skeletal muscle spasms and associated pain in acute musculoskeletal conditions. It is the well-studied drug for this application and it also has been used off-label for fibromyalgia treatment. Cyclobenzaprine has been considered structurally related to the first-generation tricyclic antidepressants.

After sustaining an injury, muscle spasms may occur to stabilize the affected body part and prevent further damage. They also generate pain. Cyclobenzaprine is FDA-approved to treat such muscle spasm associated with acute, painful musculoskeletal conditions. It decreases pain in the first two weeks. In view of the importance of cyclobenzaprine, the present work reports the crystal structure studies of cyclobenzaprine hydrochloride and its salicylate salt.

Flupentixol is a typical antipsychotic drug of the thioxanthene class. In addition to pure drug preparations, it is also available as deanxit, a combination product containing both melitracen and flupentixol. Flupentixol's main use is as a long-acting injection given two or three times weekly to individuals with schizophrenia who have poor compliance with medication and suffer frequent relapses of illness. In view of the importance of flupentixol, we report on the crystal structure of flupentixol fumarate and its dihydrochloride salt.

Opipramol is an antidepressant and anxiolytic typically used in the treatment of generalized anxiety disorder (Moller et al., 2001). Opipramol is a tricyclic compound with no reuptake-inhibiting properties. However, it has pronounced D2-, 5-HT2-, and H1-blocking potential and high affinity to sigma receptors (sigma-1 and sigma-2). Opipramol acts as a high affinity sigma receptor agonist. Opipramol has no reuptake-inhibiting properties. Crystal structure studies of opipramol and its fumarate salt have been reported.

Oxomemazine is an antihistamine and anticholinergic of the phenothiazine chemical class used for the treatment of cough. It competitively binds to histamine (H1) receptors, resulting in inhibition of the pharmacological effects of histamines. It also has some sedative, anticholinergic and antiserotoninergic effects.
Melitracen is a tricyclic antidepressant (TCA) for the treatment of depression and anxiety. Its hydrochloride derivative has actions and effects similar to amitriptyline and is administered orally in the treatment of depression. It is a bipolar thymoleptic with activating properties in low dose, is usually coadministered with flupentixol in order to decrease the side effects. Melitracen belongs to the class of non-selective monoamine reuptake inhibitors and is used in the management of depression.

Numerous pharmaceutical intermediates are available in literature. The present chapter reports the crystal and molecular structure studies of some of the important pharmaceutical intermediates. 1-(5,5-Dioxido-10H-phenothiazin-10-yl)ethanone is used in the synthesis of oxomemazine, an antihistamine and anticholinergic drug of the phenothiazine chemical class used for the treatment of coughs. 1-(4-Chloro-2-nitrophenethyl)-2-bromobenzene is an intermediate in the synthesis of 10,11-dihydro-5H-dibenzo[b,f]azepine derivatives. It has also been used successfully in the preparation of a number of biologically active compounds and drugs; e.g. the antidepressants imipramine, chloripramine are among the most commonly known. Methyl 2-(4-hydroxybenzoyl)benzoate is a starting material for the synthesis of pitofenone, which is an antispasmodic. 2,2-Diphenylacetamide is used to synthesize various biologically active and pharmaceutical compounds viz., loperamide, darifenacin, fenpiverine, etc. 2,2-Diphenyl-4-(piperidin-1-yl)-butanamide is an intermediate used in the synthesis of biologically and pharmaceutically active compounds viz., losartan, valsartan, candesartan, etc. 9-[3-(Dimethylamino)propyl]-2-trifluoromethyl-9H-thioxanthen-9-ol is a flupenthixol impurity, where in flupenthixol is a typical antipsychotic drug of the thioxanthene class. 3-(5-Hydroxy-5H-dibenzo[a,d]cyclohepten-5-yl)propyl]dimethylammonium 3-carboxyprop-2-enoate is used for the preparation of cyclobenzaprine. 3,3-Dimethylisobenzofuran-1(3H)-one is used to synthesize 10,10-dimethylanthrone. It is one of the intermediate for melitracenium chloride. Isobenzofuran-1(3H)-ones represent an important class of natural products that possess significant biological properties. 3-Chloro-N-(4 methoxyphenyl)propanamide is an intermediate in various organic preparations. Lansoprazole sulphide is an intermediate for the preparation of lansoprazole.
Lansoprazole and its analogs have been reported to have an independent gastroprotective action and selective activity against helicobacter pylori.

Cinnarizine is an antihistamine which is mainly used for the control of nausea and vomiting due to motion sickness. Cinnarizine could be also viewed as a nootropic drug because of its vasorelaxating abilities (due to calcium channel blockage), which happen mostly in brain. Enrofloxacin is a fluoroquinolone antibiotic and is a synthetic chemotherapeutic agent from the class of the fluoroquinolone carboxylic acid derivatives. It has antibacterial activity against a broad spectrum of Gram-negative and Gram-positive bacteria. Coxibs are the traditional non-steroidal anti-inflammatory drugs that counter the positive effects of aspirin in preventing blood clots. Like any other COX-2 selective inhibitor, etoricoxib selectively inhibits isoform 2 of the enzyme cyclo-oxigenase (COX-2). Levocetirizine (as levocetirizine dihydrochloride) is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine. Lomefloxacin hydrochloride is a fluoroquinolone antibiotic, used to treat bacterial infections including bronchitis and urinary tract infections. It is also used to prevent urinary tract infections prior to surgery. It is of great importance to study the crystal structures of picrates of drug molecules, because of various hydrogen bonding interactions that are possible in the solid state. In this connection, the present chapter describes the synthesis, crystal and molecular structure studies of levocetirizinium dipicrate, etoricoxibium picrate, enrofloxacinium picrate, cinnarizinium dipicrate and lomefloxacinium picrate.

In this context, the present work aims at the synthesis and crystal structure studies of some organic compounds which have pharmaceutical importance. In the present work, the crystal and molecular structure studies of twenty four compounds have been reported, out of which ten compounds are synthesized and fourteen compounds are gift samples.

The work embodied in this thesis entitled “Crystal and Molecular Structure Studies of some Pharmaceutical Compounds, Pharmaceutical Intermediates and Organic Picrates” comprises of four chapters.
Chapter I is divided into two sections. Section 1.1 gives an introduction to single crystal x-ray diffraction. Detailed aspects of single crystal X-ray diffraction is given in this chapter. In the present work, interest is focussed on (a) the preparation of most of the organic compounds, (b) crystal data and other relevant parameters regarding data collection, data reduction, structure solution and refinement, (c) atomic co-ordinates of the non-hydrogen atoms with their equivalent displacement parameters, (d) anisotropic parameters, (e) bond lengths and bond angles involving non-hydrogen atoms (f) atomic co-ordinates of the hydrogen atoms, (g) bond lengths and bond angles involving hydrogen atoms, (h) torsion angles, (j) hydrogen bonded interactions, (k) ORTEP of the molecules and (l) packing of the molecules along the crystallographic axes. The structures of all the molecules were solved by direct methods and a discussion based on the above points from (a) to (l) is made individually for all the seventeen compounds. To understand the conformation and packing features of the above compounds, the crystal structure determinations are carried out.

In section 1.2, an introduction to hydrogen bonding is given. Hydrogen bonds (HBs) are the most important ‘weak’ interactions encountered in solid, liquid and gas phases. They define the crystal packing of many organic and organo-metallic molecules, the 3D structure of biological macromolecules, as well as modulate the reactivity of different groups within a molecule. Hydrogen bonds (HBs) can be defined as an attractive interaction between two molecular moieties (two molecules or two parts of the same molecule) in which at least one of them contains a hydrogen atom that plays a fundamental role in the interaction. In the rank of interactions among atoms, the HB falls between chemical bonds (as covalent bonds) and nonbonding interactions such as van der Waals interactions.

A hydrogen bond is a special type of dipole-dipole bond that exists between an electronegative atom and a hydrogen atom bonded to another electronegative atom. This type of bond always involves a hydrogen atom. That explains the name. Hydrogen bonds can occur between molecules (intermolecularly), or within different parts of a single molecule (intramolecularly). The typical hydrogen bond is stronger than van der Waals forces, but weaker than covalent, ionic and metallic bonds.
Chapter II consists of nine sections. In section 2.1, describes the introduction to pharmaceutical compounds. Pharmaceutical chemistry is an area of chemistry focused on the development of new drugs and the modification of currently used drugs to prevent, cure, and relieve symptoms of disease. Modern medicine relies on a multitude of drugs that block, counteract or lesson the debilitating effects of disease-causing factors. Industry program includes inputs drawn both from the industry and academia. In the pharmaceutical industry and in the health-care delivery sector, an understanding of what constitutes pharmacologically promising entities, the optimization of their clinical effectiveness, and an understanding of their metabolism and excretion is essential for success of producing good molecular drugs. This highly flexible industry program in pharmaceutical chemistry and production allows candidates to select a curriculum focused for those interested in research, in pharmaceutical production, administration, in drug or diagnostic development, or in pharmaceutical manufacturing quality control. Pharmaceutical chemistry is the core of molecular medicine, and this program is designed to allow the candidate to learn core fundamentals as well as master individual specialties.

Section 2.2 describes the crystal and molecular structure studies of cyclobenzaprinium chloride, [systematic name: 3-(5H-dibenzo[a,d]cyclohepten-5-ylidene)-N,N-dimethylpropanaminium chloride], C_{20}H_{22}N^+·Cl^−, is two cation - anion pairs make up the asymmetric unit. The dihedral angles between the mean planes of the two fused benzene rings of the cation are 49.5° (1) and 50.9° (1). The crystal packing is stabilized by N—H···Cl hydrogen bonds and weak C—H···Cl interactions. The title compound crystallizes in a tetragonal space group I4(1)/a with a = 32.0959(7) Å; b = 32.0959(7) Å; c = 13.7578(5) Å; α = 90°; β = 90°; γ = 90°. V = 14172.6 (7) Å³; Z = 32; Dcal = 1.169 Mg/m³ at 173(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.071, wR2 = 0.198 using 8426 reflections.

In the title molecular salt [systematic name: 3-(5H-dibenzo-[a,d]cyclohepten-5-ylidene)-N,N-dimethyl-1-propanaminium 2-hydroxybenzoate], C_{20}H_{22}N^+·C_{7}H_{5}O_{3}^−, the benzene rings of the cyclobenzaprinium cation are inclined with a dihedral angle of 61.66 (7)°. An intramolecular O—H···O hydrogen bond occurs within the salicylate anion, generating an S(6) ring. In the crystal, the cation and anion are linked by an N—
H···O interaction. The title compound crystallizes in a triclinic space group \( P\text{-}I \) with a \( = 7.4700 \ (8) \ \text{Å} \); \( b = 10.8408 \ (12) \ \text{Å} \); \( c = 14.9724 \ (16) \ \text{Å} \); \( \alpha = 76.073 \ (2)° \); \( \beta = 77.357 \ (1)° \); \( \gamma = 72.574 \ (2)° \); \( V = 1108.6 \ (2) \ \text{Å}^3 \); \( Z = 2 \); \( \text{Dcal} = 1.239 \ \text{Mg/m}^3 \) at 296 (2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.048 \), \( wR_2 = 0.134 \); using 6461 reflections. These are described in section 2.3.

In section 2.4, the title salt \{Flupentixol, [systematic name: 2-[4-[3-[(EZ)-2-(trifluoromethyl)-9H-thioxanthen-9-ylidene) propyl]piperazin-1-yl]ethanol}, \( \text{C}_{23}\text{H}_{27}\text{F}_3\text{N}_2\text{OS}^+ \), \( 2\text{C}_4\text{H}_3\text{O}_4^- \), a non-merohedral twin [ratio of the twin components = 0.402 (1):0.598 (1)], the – \( \text{CF}_3 \) group is disordered over two sets of sites with occupancy factors in the ratio 0.873 (2):0.127 (2). The dihedral angle between the two outer aromatic rings of the 9H-thioxanthene unit, whose thiopyran ring has a screw-boat conformation, is 33.01 (9). The diprotonated piperazine ring adopts a chair conformation. In the crystal, intermolecular O–H···O, N–H···O and C–H···O hydrogen bonds between neighboring molecules form zigzag chains along a axis and contribute to the stabilization of the packing. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R = 0.0552 \) and \( wR_2 = 0.1550 \) using 11625 reflections. The title compound crystallizes in a triclinic space group \( P\text{-}T \) with \( a = 6.4175 \ (2) \ \text{Å} \); \( b = 9.6185 \ (4) \ \text{Å} \); \( c = 25.5771 \ (10) \ \text{Å} \); \( \alpha = 96.377 \ (4)° \); \( \beta = 96.295 \ (3)° \); \( \gamma = 92.774 \ (3)° \); \( V = 1556.63 \ (10) \ \text{Å}^3 \); \( Z = 2 \); \( \text{Dcal} = 1.422 \ \text{Mg/m}^3 \) at 295 (2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0622 \), \( wR_2 = 0.1617 \); using 11625 reflections.

In section 2.5, the title compound \{systematic name: 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-9H-thioxanthen-9-ylidene)-propyl]piperazine-1,4-dichloride \( \text{C}_{23}\text{H}_{27}\text{F}_3\text{N}_2\text{OS}^+ \). \( 2\text{Cl}^- \), the piperazinediium ring adopts a chair conformation. The dihedral angle between the two outer aromatic rings of the 9H-thioxanthene units is 40.35 (18). The F atoms in the trifluoromethyl group are disordered over two sets of sites with occupancies of 0.803 (6) and 0.197 (6). In the crystal, molecules are connected by N–H···Cl, O–H···Cl, C–H···O and C–H···Cl hydrogen bonds, forming chains propagating along [001]. There are also C–H···π interactions present in the crystal structure.
The title compound crystallizes in a monoclinic, space group \( \text{C}_{2/c} \) with \( a = 34.1750 \ (17) \ \text{Å} \); \( b = 7.1613 \ (3) \ \text{Å} \); \( c = 22.6351 \ (11) \ \text{Å} \); \( \alpha = 90^\circ \); \( \beta = 115.307(6)^\circ \); \( \gamma = 90^\circ \); \( V = 5008.0 \ (5) \ \text{Å}^3 \); \( Z = 8 \); \( \text{Dcal} = 1.346 \ \text{Mg/m}^3 \) at 295 K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0857 \), \( wR_2 = 0.2296 \) using 5032 reflections.

In section 2.6, for the title compound \{systematic name: 2-{4-[3-(5H-dibenz-[b,f]azepin-5-yl)propyl]piperazin-1-yl}ethanol\} \( \text{C}_{23}\text{H}_{29}\text{N}_3\text{O} \), the 5H-dibenz[b,f]azepine and piperazine rings adopt boat and chair conformations, respectively, and the overall shape of the fused ring part of the molecule is a butterfly. In the crystal, O–H⋯N and C–H⋯O hydrogen bonds link the molecules into a layer parallel to the bc plane.

The title compound crystallizes in a monoclinic space group \( P \text{2}_1/c \) with \( a = 12.6215(2) \ \text{Å} \); \( b = 10.5929(2) \ \text{Å} \); \( c = 14.3629(2) \ \text{Å} \); \( \alpha = 90^\circ \); \( \beta = 90.9660(10)^\circ \); \( \gamma = 90^\circ \); \( V = 1920.02(5) \ \text{Å}^3 \); \( Z = 4 \); \( \text{Dcal} = 1.257 \ \text{Mg/m}^3 \) at 100 K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0516 \) and \( wR_2 = 0.1168 \) using 7949 reflections.

In section 2.7, for the crystal structure of the title salt \{systematic name: 4-[3-(5H-dibenz[b,f]azepin-5-yl)propyl]-1-(2-hydroxyethyl)piperazin-1-ium(2Z)-3-carboxyprop-2-enoate\}, \( \text{C}_{23}\text{H}_{30}\text{N}_3\text{O}^+\cdot\text{C}_4\text{H}_3\text{O}_4^- \), the piperazine group in the opipramol cation is protonated at only one of the N atoms. In the cation, the dihedral angle between the two benzene rings is 53.5 (6)°. An extensive array of intermolecular O–H⋯O, O–H⋯N and N–H⋯O hydrogen bonds and weak intermolecular N–H⋯O, C–H⋯O and C–H⋯π interactions dominate the crystal packing. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0405 \), and \( wR_2 = 0.0988 \) using 8285 reflections. The title compound crystallizes in a monoclinic space group \( P \text{2}_1/c \) with \( a = 8.9116(3) \ \text{Å} \); \( b = 6.7167(3) \ \text{Å} \); \( c = 20.6377(8) \ \text{Å} \); \( \alpha = 90^\circ \); \( \beta = 98.685(3)^\circ \); \( \gamma = 90^\circ \); \( V = 1221.14(8) \ \text{Å}^3 \); \( Z = 2 \); \( \text{Dcal} = 1.304 \ \text{Mg/m}^3 \) at 173(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0453 \) and \( wR_2 = 0.1017 \) using 3393 reflections. Classical hydrogen bonds found for the present structure.
In section 2.8, for the title compound [systematic name: 3-(5,5-dioxophenothiazin-10-yl)-N,N,2-trimethylpropanaminium chloride], C_{18}H_{23}N_{2}O_{2}S\text{Cl}^+, the dihedral angle between the two outer aromatic rings of the phenothiazine unit is 30.5 (2). In the crystal, the components are linked by N–H⋯Cl and C–H⋯Cl hydrogen bonds and C–H⋯π interactions. The title compound crystallizes in a triclinic space group \(P\overline{1}\) with \(a = 7.6364(7)\ \text{Å}; b = 10.4177(9)\ \text{Å}; c = 12.4732(10)\ \text{Å}; \alpha = 103.478(7)°; \beta = 90.624(7)°; \gamma = 109.852°; V = 903.21(13)\ \text{Å}^3; Z = 2; D_{\text{cal}} = 1.349 \text{ Mg/m}^3\) at 295(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \(R_1 = 0.0890, wR_2 = 0.2545\) using 3598 reflections.

For the title compound [systematic name: 3-(10,10-dimethylanthracen-9-ylidene)-N,N,N-trimethylpropanaminium chloride], C_{21}H_{26}N^+·Cl^-, in section 2.9, the cyclohexane ring adopts a chair conformation. The dihedral angle between the terminal benzene rings is 40.43 (12)°. In the crystal, ions are linked through intermolecular N–H⋯Cl and C–H⋯Cl hydrogen bonds, forming supramolecular layers parallel to the bc plane. The title compound crystallizes in a monoclinic space group \(P2_1/c\) with \(a = 15.0129(18)\ \text{Å}; b = 8.8092(11)\ \text{Å}; c = 14.0135(17)\ \text{Å}; \alpha = 90°; \beta = 91.506(2)°; \gamma = 90°; V = 1852.7(4)\ \text{Å}^3; Z = 4; D_{\text{cal}} = 1.176 \text{ Mg/m}^3\) at 296(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \(R_1 = 0.0902, wR_2 = 0.2117\) using 5366 reflections.

Chapter III consists of twelve sections. In section 3.1, an introduction to pharmaceutical intermediates is described. Numerous chemical intermediates are used to prepare pharmaceutical compounds. An up-to-date survey of literature for the crystal structure studies of pharmaceutical intermediates is given in this section.

In section 3.2, for the title compound, 1-(5,5-dioxido-10H-phenothiazin-10-yl)ethanone, C_{14}H_{11}NO_{3}S, the six-membered thiazine ring fused to two benzene rings adopts a distorted boat conformation. The dihedral angle between the mean planes of the two benzene rings is 45.8 (1)°. The crystal packing is stabilized by weak intermolecular C—H⋯O interactions. The only possible significant intermolecular interaction is a C–H⋯N bond. The title compound crystallizes in a monoclinic space
group $P2_1/c$ with $a = 12.5715 (6) \text{ Å}; b = 8.7648 (4) \text{ Å}; c = 11.5828 (5) \text{ Å}; \alpha = 90^\circ; \beta = 92.142(4); \gamma = 90^\circ; V = 1275.38(10) \text{ Å}^3; Z = 4; \text{Dcal} = 1.423 \text{ Mg/m}^3 \text{ at 173 K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0362, wR2 = 0.0979 using 3700 reflections.}

In section 3.3, for the title molecule, 1-[2-(2-bromophenyl)ethyl]-4-chloro-2-nitrobenzene, $C_{14}H_{11}BrClNO_2$, the dihedral angle between the mean planes of the bromo-substituted benzene and the chloro-substituted benzene rings is 1.8 (4)$^\circ$. The nitro group is twisted by 15.8 (6)$^\circ$ from the mean plane of the benzene ring to which it is attached. The crystal packing is influenced by weak intermolecular C—H···O interactions and weak π—π stacking interactions [centroid—centroid distances = 3.903 (2), 3.596 (2) and 3.903 (2) Å]. The title compound crystallizes in a orthorhombic space group $P2_1/n$ with $a = 15.7756 (4) \text{ Å}; b = 7.3795 (2) \text{ Å}; c = 11.5236 (3) \text{ Å}; \alpha = 90^\circ; \beta = 90^\circ; \gamma = 90^\circ; V = 1341.53(6) \text{ Å}^3; Z = 4; \text{Dcal} = 1.686 \text{ Mg/m}^3 \text{ at 150 K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0306, wR2 = 0.0833 using 1901 reflections.}

In section 3.4, for the title compound, methyl 2-(4-hydroxybenzoyl)benzoate, $C_{15}H_{12}O_4$, the dihedral angle between the benzene rings is 64.0 (6)$^\circ$. In the crystal, molecules are linked by O—H···O hydrogen bonds, forming C(8) chains propagating in [101] and the packing is reinforced by weak C—H···O interactions. The title compound crystallizes in a monoclinic space group $P2_1/n$ with $a = 8.9017(12) \text{ Å}; b = 13.9940(17) \text{ Å}; c = 10.0473(12) \text{ Å}; \alpha = 90^\circ; \beta = 94.687(12)^\circ; \gamma = 90^\circ; V = 1247.4(3) \text{ Å}^3; Z = 4; \text{Dcal} = 1.364 \text{ Mg/m}^3 \text{ at 173(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0424, wR2 = 0.1104 using 3231 reflections.}

In section 3.5, for the title compound, 2,2-diphenylacetamide, $C_{14}H_{13}NO$, which has two molecules in the asymmetric unit, the dihedral angles between the mean planes of the benzene rings are 84.6 (7) and 85.0 (6)$^\circ$. N—H···O hydrogen bonds [forming R$_2^2$ (8) ring motifs] and C—H···O hydrogen bonds dominate the crystal packing, forming zigzag chains parallel to the a axis. In addition, weak intermolecular C—H···π interactions are observed. The title compound crystallizes in a monoclinic space group $P2(1)$ with $a = 5.1687(3) \text{ Å}; b = 28.5511(13) \text{ Å; c =
7.8006(4) Å; \( \alpha = 90^\circ; \beta = 7.8006(4); \gamma = 90^\circ; \) \( V = 1139.52(10) \) Å\(^3\); \( Z = 4; \) \( \text{Dcal} = 1.231 \) Mg/m\(^3\) at 200(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0370, \) \( wR_2 = 0.1051 \) using 3978 reflections.

In section 3.6, for the title compound, 2,2-diphenyl-4-(piperidin-1-yl)-butanamide, \( \text{C}_{21}\text{H}_{26}\text{N}_2\text{O}, \) the dihedral angle between the mean planes of the two benzene rings is 81.1 (9)°. The piperidine ring is in a chair conformation. The crystal packing is stabilized by N—H•••N and N—H•••O hydrogen bonds and weak intermolecular C—H•••O interactions. The title compound crystallizes in a orthorhombic space group \( P\text{ca}_2_1\) with \( a = 18.1070 \) (12) Å; \( b = 10.3025 \) (9) Å; \( c = 10.3025 \) (9) Å; \( \alpha = 90^\circ; \beta = 90^\circ; \gamma = 90^\circ; \) \( V = 1793.7 \) (2) Å\(^3\); \( Z = 4; \) \( \text{Dcal} = 1.194 \) Mg/m\(^3\) at 173(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0355, \) \( wR_2 = 0.0987 \) using 4817 reflections.

In section 3.7, for the title compound, 2-(4-methylphenyl)benzonitrile, \( \text{C}_{14}\text{H}_{11}\text{N}, \) the dihedral angle between the mean planes of the two benzene rings is 44.6 (7)°. The crystal packing is stabilized by weak intermolecular \( \pi–\pi \) stacking interactions, the centroid–centroid distances being 3.8172 (12) and 3.9349 (12) Å. The title compound crystallizes in a orthorhombic space group \( P2_1(1)2_1(1)2_1(1) \) with \( a = 7.6726(4) \) Å; \( b = 11.4037(5) \) Å; \( c = 12.2426(5) \) Å; \( \alpha = 90^\circ; \beta = 90^\circ; \gamma = 90^\circ; \) \( V = 1071.18(9) \) Å\(^3\); \( Z = 4; \) \( \text{Dcal} = 1.198 \) Mg/m\(^3\) at 200(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0403, \) \( wR_2 = 0.0996 \) using 1546 reflections.

For the title compound, 9-[3-(dimethylamino)propyl]-2-trifluoromethyl-9H-thioxanthen-9-ol, \( \text{C}_{19}\text{H}_{20}\text{F}_3\text{NOS}, \) the dihedral angle between the mean planes of the two benzene rings attached to the thioxanthene ring is 41.8 (7)°; the latter has a slightly distorted boat conformation. The F atoms are disordered over three sets of sites \( \text{[occupancy ratio} = 0.564 \) (10): 0.287 (10):0.148 (5)] and the methyl groups are disordered over two sets of sites \( \text{[occupancy ratio} = 0.72 \) (4):0.28 (4)]. The crystal packing is stabilized by O—H•••N and C—H•••S hydrogen bonds and weak C—H•••Cg
interactions. The title compound crystallizes in a monoclinic space group \( P2(1)/n \) with 
\[ a = 7.6183(3) \ \text{Å}; \ b = 13.9605(4) \ \text{Å}; \ c = 17.4172(7) \ \text{Å}; \ \alpha = 90^\circ; \ \beta = 101.053(4)^\circ; \ \gamma = 90^\circ; \ V = 1818.05(11) \ \text{Å}^3; \ Z = 4; \ \text{Dcal} = 1.342 \ \text{Mg/m}^3 \text{ at 170(2) K.} \text{The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0539, wR2 = 0.1159 using 4697 reflections. These are described in section 3.8.}

In section 3.9, in the cation of the title salt, 3-(5-Hydroxy-5H-dibenzo[a,d]cyclohepten-5-yl)propyl]dimethylammonium 3-carboxyprop-2-enoate, \( \text{C}_{20}\text{H}_{24}\text{N}_{0.5}\text{C}_{4}\text{H}_{3}\text{O}_{4}^- \), the N-atom in the dimethylammonium group is protonated. The dihedral angle between the mean planes of the two six-membered rings fused to the cyclohepten-5-yl ring is 54.4 (1). An intramolecular O–H···O hydrogen bond occurs in the anion. The crystal packing is stabilized by intermolecular O–H···O and N–H···(O,O) hydrogen bonds and weak C–H···O interactions, forming a two-dimensional network. The title compound crystallizes in a monoclinic space group \( P2(1) \) with 
\[ a = 9.2115(2) \ \text{Å}; \ b = 11.5840(2) \ \text{Å}; \ c = 10.4640(2) \ \text{Å}; \ \alpha = 90^\circ; \ \beta = 101.591(2)^\circ; \ \gamma = 90^\circ; \ V = 1093.80(4) \ \text{Å}^3; \ Z = 2; \ \text{Dcal} = 1.243 \ \text{Mg/m}^3 \text{ at 173(2) K.} \text{The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0344, wR2 = 0.0925 using 5190 reflections.}

In section 3.10, for the title compound, 3,3-dimethyl-2-benzofuran-1(3H)-one, \( \text{C}_{10}\text{H}_{10}\text{O}_{2} \), all the non-H atoms except the methyl C atoms lie on a crystallographic mirror plane. In the crystal, C–H···O hydrogen bonds link the molecules into zigzag chains running parallel to [100]. Weak π–π stacking interactions between the benzene rings [centroid–centroid distance = 7.0069(5) \ \text{Å}] link the chains in the [010] direction. The title compound crystallizes in an orthorhombic space group \( P n m a \) with 
\[ a = 14.3537(9) \ \text{Å}; \ b = 7.0069(5) \ \text{Å}; \ c = 8.2605(5) \ \text{Å}; \ \alpha = 90^\circ; \ \beta = 90^\circ; \ \gamma = 90^\circ; \ V = 830.80(9) \ \text{Å}^3; \ Z = 4; \ \text{Dcal} = 1.297 \ \text{Mg/m}^3 \text{ at 123(2) K.} \text{The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R1 = 0.0591, wR2 = 0.1439 using 1840 reflections.}
The title compound, \( C_{10}H_{12}ClNO \), is a halogenated derivative of a secondary amide bearing an aromatic substituent. The \( \text{C( O)—N(H)—C_{\text{ar}}—C_{\text{ar}} \) torsion angle of \(-33.70 (18)\) rules out the presence of resonance spanning the amide as well as the aromatic system. In the crystal, classical \( \text{N—H…O} \) hydrogen bonds, as well as \( \text{C—H…O} \) contacts connect the molecules into chains propagating along the a axis. The title compound crystallizes in an orthorhombic space group \( Pbc\alpha \) with \( a = 9.6326 (3) \) Å; \( b = 8.6650 (2) \) Å; \( c = 25.7944 (8) \) Å; \( \alpha = 90^\circ; \beta = 90^\circ; \gamma = 90^\circ; \) \( V = 2152.97 (11) \) Å\(^3\); \( Z = 8; \) \( D_{\text{cal}} = 1.318 \text{ Mg/m}^3 \) at 200 K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R1 = 0.0355, \) \( wR2 = 0.0919 \) using 2668 reflections. These are described in section 3.11.

Section 3.12 describes the “ordering of the water molecule in the crystal structure of 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methylthio-1H-benzimidazole hydrate (Lansoprazole sulphide hydrate), \( C_{15}H_{14}F_3N_3O_2S \). It crystallizes in the triclinic space group \( P\bar{1} \) with two molecules in the asymmetric part of the unit cell. The molecules are almost identical; the normal probability plots show that the differences between them are of statistical nature. The crystal structure is determined mainly by the \( \text{O—H…N} \) and \( \text{N—H…O} \) hydrogen bonds; and both symmetry independent molecules create the hydrogen-bonded structures on their own. The common motif is the \( \text{C}_2^2 (6) \) chain of molecules along x (A) or y (B), but the interactions between the chains are different: chains of molecules A are joined by \( \text{O—H…N(pyridine)} \) hydrogen bonds while those of molecules B– by relatively strong \( \text{O—H…S} \) hydrogen bonds. Additionally, in both cases there are also \( \text{C—H…S}, \text{C—H…π} \) and \( \pi…\pi \) interactions between the neighbouring molecules.

Chapter IV consists of six sections. Section 4.1 describes the introduction to organic picrates. Picric acid forms crystalline picrates with various organic molecules, and such picrates are convenient for identification and qualitative analysis of the organic compounds. Picric acid forms charge transfer molecular complexes with a number of aromatic compounds such as aromatic hydrocarbons, amines etc. through electrostatic or hydrogen bonding interactions and aromatic heterocyclic compounds have been investigated. Since it is useful to understand the nature of structures of picrates of basic compounds, it is advantageous to study the interaction of drug molecules with picric acid. Now, it has become clear that the picrates of basic aromatic hydrocarbons are formed through \( \pi\)-bonding (\( \pi…\pi \) interaction), while picrates...
of aromatic heterocycles are formed through ionic and hydrogen bonding or π-π interaction. The crystal structures of a large number of picrate salts and picric acid complexes have been studied to understand the conformational features and charge transfer processes.

Section 4.2 describes the crystal structure studies of cinnarizinium di-cation of the title compound {systematic name: 1-diphenylmethyl-4-[(2E)-3-phenylprop-2-en-1-yl]piperazine-1,4-diium bis(2,4,6-trinitrophenolate)}, C_{26}H_{32}ON_{2}^{2+} 2C_{6}H_{2}N_{3}O_{7}^{-}, the piperazine group is protonated at both N atoms and adopts a slightly distorted chair conformation. Strong N—H...O hydroxy cation–anion hydrogen bonds link the dication and two anions. In the cation, the (2E)-3-phenylprop-2-en-1-yl fragment is disordered over two positions in a ratio of 0.586 (4): 0.414 (4). Two nitro groups in one anion and three in the other one demonstrate rotational disorder. The crystal packing is stabilized by weak intermolecular π–π [centroid–centroid distances = 3.844 (7), 3.677 (9), 3.825 (5), 3.634 (2) and 3.729 (7) Å], C—H...π and C—H...O interactions. The title compound, crystallizes in a monoclinic, space group P 2_1/c with a = 15.1987(2) Å; b = 10.09128(17) Å; c = 25.0724(3) Å; α = 90°; β = 95.9171(14)°; γ = 90°; V = 3824.97(10) Å^3; Z = 4; D cal = 1.436 Mg/m^3 at T = 295(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R = 0.0950 and wR2 = 0.2766 using 7319 reflections.

There is one cation–anion pair in the asymmetric unit of the title compound [systematic name: 4-(3-carboxy-6-fluoro-4-oxo-1,4-dihydroquinolin-7-yl)-1-ethylpiperezin -1-i um 2,4,6- trinitrophenolate], C_{19}H_{23}FN_{3}O_{3}^{+}.C_{6}H_{2}N_{3}O_{7}^{-}. This is described in section 4.3. The six-membered piperazine group in the cation adopts a slightly distorted chair conformation and contains a protonated N atom. The dihedral angles between the mean planes of the cyclopropyl and piperazine rings in the cation with the 10- atom ring system of the quinolone group are 48.1 (1) and 69.9 (5)°, respectively. The picrate anion interacts with the protonated N atom of an adjacent cation through a bifurcated N—H...O three-center hydrogen bond, forming an R_1^2 (6) ring motif. Furthermore, there is an intramolecular O—H...O hydrogen bond. The dihedral angle between the mean planes of the anion benzene and cation piperazine, quinoline and cyclopropyl rings are 61.3 (6), 31.1 (4) and 70.4 (9)°, respectively. The title compound, crystallizes in a triclinic space group P ı with a = 7.211 Å; b = 12.577 Å; c = 16.236 Å; α = 105.56°; β = 96.37°; γ = 96.22°; V = 1395.0 Å^3; Z = 2; D cal =
1.399 Mg/m³ at T = 295(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R₁ = 0.0567 and wR₂ = 0.1626 using 5443 reflections.

For the cation of the title salt (systematic name: 5-\{5-chloro-3\-[4-(methylsulfonyl) phenyl]-2-pyridyl\}-2-methylpyridinium 2,4,6-trinitrophenolate), C₁₈H₁₆ClN₂O₂S⁺·C₆H₂N₃O₇⁻, the mean planes of the two pyridine rings in the bipyridine unitare twisted by 33.9 (2)° with respect to each other is described in section 4.4. The dihedral angles between the mean planes of the sulfonyl benzene ring and the chloropyridine and methylpyridine rings are 51.2 (0)° and 49.3 (9)°, respectively. The title compound, crystallizes in a monoclinic space group P 2₁/c with a = 9.02500(10) Å; b = 12.74960(10) Å; c = 21.8011(3) Å; α = 90°; β = 98.1140(10)°; γ = 90°; V = 2483.43(5) Å³; Z = 4; D calc = 1.573 Mg/m³ at T = 123(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R = 0.0378 and wR₂ = 0.1010 using 4932 reflections.

Section 4.5 describes the two cation–dianion pairs in the asymmetric unit of the title compound, C₂₁H₂₇ClN₂O₃²⁺·2C₆H₂N₃O₇⁻ {systematic name: 1-\{2-(carboxymethoxy) ethyl\}-4-\{(R)-(4-chlorophenyl)-phenylmethyl\}piperazine-1,4 diium bis (2,4,6-trinitrophenolate)}. The piperazine group in the levocetirizinium cation is protonated at both N atoms. The acetyl end groups form R₂²(8) hydrogen-bonded motifs with adjacent cations. Each picrate end group interacts with the protonated N atom in the cation through a bifurcated N—H···O hydrogen bond, forming R₁²(6) ring motifs. Strong and weak intermolecular N—H···O and strong O—H···O hydrogen bonds, and weak π–ring and π–π stacking interactions [centroid–centroid distance = 3.7419 (14) Å] dominate the crystal packing, creating a three-dimensional supramolecular structure. The title compound, crystallizes in a monoclinic space group P2₁ with a = 11.24440(10) Å; b = 15.7720(2) Å; c = 20.6204(2) Å; α = 90°; β = 95.9980(10)°; γ = 90°; V = 3636.94(7) Å³; Z = 4; D calc = 1.547 Mg/m³ at T = 295(2) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final R₁ = 0.0441 and wR₂ = 0.1207 using 11120 reflections.
Section 4.6 describes the cation of the title compound \{systematic name: (RS)-4-(3-carboxy-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydroquinolin-7-yl)-2-methyl piperazin-1-ium 2,4,6-trinitrophenolate \}, \( \text{C}_{17}\text{H}_{20}\text{F}_{2}\text{N}_{3}\text{O}_{3}^{+}\cdot \text{C}_{6}\text{H}_{2}\text{N}_{3}\text{O}_{7}^{-} \), the piperazine ring adopts a slightly distorted chair conformation and contains a protonated N atom. An intramolecular O—H···O hydrogen bond occurs in the cation. The dihedral angles between the mean planes of the six-atom piperazine ring and the 10-atom fused ring system is 43.3 (5)°. The title compound, crystallizes in a triclinic space group \( P \overline{1} \) with \( a = 10.9314(4) \) Å; \( b = 11.6748(4) \) Å; \( c = 12.0530(4) \) Å; \( \alpha = 92.969(3) \)°; \( \beta = 115.555(3) \)°; \( \gamma = 109.852(3) \)°; \( V = 1269.14(8) \) Å³; \( Z = 2 \); \( D_{cal} = 1.519 \) Mg/m³ at \( T = 123(2) \) K. The structure was solved by direct methods and refined by full-matrix least-squares procedures to final \( R_1 = 0.0627 \) and \( wR_2 = 0.1760 \) using 5002 reflections.

The literature survey for the present work is till to-date. On the whole, the entire work presented in the thesis provides valuable information about crystal and molecular structure studies of varieties of organic molecules, which have pharmaceutical importance.

Based on the above experimental investigations, the following research papers have been published in International journals.

RESEARCH PUBLICATIONS FROM THE THESIS

1. **2-(4-Methylphenyl)benzonitrile**  

2. **1-(5,5-Dioxido-10H-phenothiazin-10-yl)ethanone**  

3. **2,2-Diphenyl-4-(piperidin-1-yl)-butanamide**  

4. **1-[2-(2-Bromophenyl)ethyl]-4-chloro-2-nitrobenzene**  