1.0 INTRODUCTION

One of the most important emerging frontiers in medicinal chemistry is solid state organic chemistry. Understanding solid state structures potentially leads to cogent engineering of the physical properties of organic compounds. The introduction of design into solids is often grouped under the term crystal engineering and understanding the forces involved during crystal packing is fundamental in this area (1). Pharmaceutical solids tend to exist in different physical forms (2). Issues about pharmaceutical systems are mainly concerned with the active ingredient’s physico-chemical stability and bioavailability. Pharmaceutical systems often exhibit crystal structures that have extensive hydrogen bonding, conformation flexibility and complex molecular geometry (3).

Over 70% of pharmaceutical materials involve crystallisation at some stage in their production. An opportunity to manipulate the solid form is highly advantageous (4). The drug’s solid form affects its solubility and dissolution rate, in turn controlling the bioavailability of the formulated drug. Therefore it can be said that the properties of the solid state of a pharmaceutical product can greatly affect the effectiveness, formulation, storage, suitability and stability of a formulated pharmaceutical product (5). Systematic approaches to crystal engineering are still in their infancy (1). This programme relates to an approach to crystal engineering that relies on the identification and exploitation of intermolecular interactions operating in reproducible and consistent sets recently described as structural motifs and synthons in supramolecular chemistry.
Crystal engineering involves the understanding and exploitation of intermolecular interactions involving hydrogen bonds and coordination complexation during packing. This then results in the design and synthesis of solid state molecular structures with desired physical and chemical properties. Crystal engineering involves the use of a supramolecular synthon and the secondary building unit. A synthon can be said to be a repetitive small unit that captures the importance of a crystal structure. Such an approach has gained substantial interest as a basis for predicting and designing organic crystal structures \(^{(1)}\).

1.1 **Aim and Objectives**

The main aim of this study is to investigate the non-bonded interactions in pharmaceutical solids that govern the physical pharmaceutics performance of such materials and through the use of structural techniques and correlation of these results with crystal structural database to establish the presence of physical motifs in selected systems.

To achieve such an aim, the following objectives were set.

- Structural motifs were identified by the use of single crystal and crystal packing analysis on diverse range of pharma-relevant materials. Selected systems include xanthines, cryptolepines, chalcones and biguanides
- Validating selected systems using functional group and molecular analysis and correlating them to the Structural Database
- Exploitation of selected systems using synthetic analogues
- Crystallization studies on the selected systems.
1.2 Justification of Study

The solid-state properties of a drug such as polymorphism, solvate and salt formation affect the drug’s formulation, production as well as its storage therefore having an impact on the drug’s efficacy \(^5\).

These solid-state properties affect the stability of drugs formulated as well \(^7\). Crystalline solids being more stable than amorphous solids, are said to be ideal to be used for drug manufacturing since important physico-chemical parameters of drug effectiveness such as solubility or dissolution and bioavailability profile are determined by the solid-state form of the drug \(^5\). The two most important contributors to poor bioavailability of manufactured drugs are solubility and chemical stability which are controlled by the solid-state properties of the drug. Differences in the physical properties of drugs results from differences in the lattice energies of their respective solid-state structures. Therefore the lattice energy of the solid-state structures has direct impact on the solubility and dissolution rates of manufactured drugs. Compounds with adequate solubility in the intestinal and gastric fluids are said to be bioavailable \(^7\).

This study is therefore directed at solid-state forms of pharmaceutical solids to investigate the non-bonded interactions that significantly influence lattice energy affecting the efficacy of drugs. Solid-state forms of selected systems including cryptolepines (Figure II), biguanides-metformin and its derivatives (Figure III) and xanthines (Figure V) were selected for this study based on the rigidity of their structures, physico-chemical properties and their wide range of therapeutic efficacy.
Chalcones (Figure I) were also selected due to their physico-chemical properties, semi-rigid structure and their effectiveness as antibacterial, anti-inflammatory, anti-parasitic and antimitotic drugs.

![Figure I (Chalcone)](image1)

![Figure II (Cryptolepine)](image2)

![Figure III (Metformin)](image3)

![Figure IV (Xanthine)](image4)

Chalcones (as indicated in Figure 1) have very good crystallisability and have the –CH=CH-CO- unit as the most active unit of this class of compound. They are α, β-unsaturated ketones and they prefer to react with thiols rather than amino and hydroxyl groups. This type of reaction preference by chalcones is advantageous over other alkylating agents. This is because, chalcones do not react with nucleic acids and therefore problems associated with mutagenicity and carcinogenity are eliminated.
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Chalcones exhibit intramolecular charge transfer in the excited state resulting in the formation of a significant dipole through both electron donor-acceptor units that interact with each other through the conjugated chain. They have been subjected to many theoretical and experimental investigations, as a result of their numerous pharmaceutical applications. With their potential bioactive profile, they have become compounds of increasing attraction to researchers (11).

The enone moiety which is the reactive part of the compound is responsible for the antimitotic activity of the chalcones (12, 13). The wide biological activity of chalcones is related to the electron distribution around the molecule as well as their ability to exhibit intermolecular interactions during the formation of complexes with biomacromolecules (148).

Therefore there is the need to investigate the effect of substituents, C-H…O inter and intramolecular hydrogen bond interactions, π-π interaction within stacks, and chloride-chloride interactions on the enone unit and correlating this effect to their biological activity. Knowledge about potential non-bonded interactions available to the enone unit of the solid-state of the drug may provide a basis for prediction of the efficacy of a chalcone drug.

Cryptolepine (as shown as Figure II) has the basic tetracycline structure known as quindoline (21, 170). The active form of Cryptolepine is the salt form and this has a methyl substituent on the quaternary nitrogen of the aromatic ring “B” of the quindoline structure (19, 20, 21, 22, 23, 170).
Changes in electron density around the quartenary nitrogen might affect the activity of cryptoclepines since their therapeutic effectiveness depends on the quaternary nitrogen (184). This study focusing on the salt forms of cryptoclepine was done to understand the effect of electron density distribution on the quaternary nitrogen atom of this polyaromatic compound. Understanding the effect on the how the electron density around the quartenary nitrogen atom is affected by changes in the aromatic system, intra and intermolecular hydrogen bond interactions and substituent may have considerable importance in order to predict the therapeutic effectiveness of cryptoclepines.

Biguanides and its derivatives with Figure III as their backbone structure were studied due to the wide range of their effective pharmacological properties, understanding its crystal packing, bond angles and lengths (compared to similar structures from the Cambridge Structural Data Base) as well as how each component contributes to their extended hydrogen bonding system. Metformin is a second-generation biguanide compound (15) which is widely used as an oral anti-hyperglycaemic agent clinically for treating type II diabetes mellitus (non-insulin dependent) for more than 40 years. Metformin hinder hepatic gluconeogenesis but causes an increase in glucose uptake and increasing peripheral insulin sensitivity. One of the advantages of treating diabetes mellitus (type II) with metformin is that, metformin does not cause hypoglycaemia when used alone. Metformin can be used to reduce the formation of advance glycation end products, reloading the deficient levels of glutathione in diabetes mellitus patients, improving the antioxidant defence of diabetic patients, inhibiting the development of adenocarcinomas and pancreatic carcinogenesis in hamsters (16) as well as reversing hepathomegaly and steatosis (17).
Xanthines (Figure IV) have extensive uses in medicine. The packing nature and the hydrogen bonds that come into play during crystal packing are studied to understand how hydrogen bonding plays a role in determining the solubility of medicines.

Hydrogen bonding, ion-ion interaction, lipophilicity, dipole-dipole interactions and shape complimentarity tends to mediate the binding of a drug to its receptor. But the contribution of these interactions is poorly understood. Drug hydrogen bonding is directional and therefore it is considered to be very important when specificity of drug receptor binding is required \(^{(18)}\). Importantly, all the selected systems have π-systems, rigidity, are aromatic compounds and exhibit extensive hydrogen bonding interactions. The evaluation of other forces and the directional and intrinsic robustness of hydrogen bonding in crystal structures are important for drug solubility and stability studies \(^{(30)}\). The physical properties of the selected structural motifs make them ideal for crystal engineering studies.

The primary tool to be deployed in these studies will be single crystal X ray diffraction. It is therefore appropriate to introduce some of the key concepts in crystallography to support later discussions.

### 1.3 The Crystalline State

In the solid state, all crystalline material assume a regular distribution of ions or atoms in space \(^{(31)}\). A crystalline solid material is said to be perfect only when it is made up of a large number of identical molecules and these are arranged in an ordered manner and repeating in all directions \(^{(32)}\).
The unit cell is the simplest portion of a structure and shows its full symmetry which is repeated by translation. The repetition by translation of the structural unit resulting in space filling, in a three dimensional crystal can be said to be a type of symmetry occurring in all crystalline structures. The unit cell in three dimensions is established as a parallelepiped and has angles and side lengths as shown in Figure 1.1.

**Figure 1.1 A Unit cell showing angles \((\alpha, \beta, \gamma)\) and side lengths \((a, b, c)\)**

The angles \(\alpha, \beta, \gamma\) and lengths \(a, b\) and \(c\) are known as unit cell parameters.

Seven crystal classes can be observed as a result of increasing level of symmetry by introducing various relationships between the cell parameters. Table 1.1 summarises the seven crystal systems.

**Table 1.1 The Crystal Systems**

<table>
<thead>
<tr>
<th>UNIT CELL DIMENSIONS</th>
<th>CRYSTAL SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a = b = c) (\alpha = \beta = \gamma = 90^\circ)</td>
<td>Cubic</td>
</tr>
<tr>
<td>(a = b \neq c) (\alpha = \beta = \gamma = 90^\circ)</td>
<td>Tetragonal</td>
</tr>
<tr>
<td>(a \neq b \neq c) (\alpha = \beta = \gamma = 90^\circ)</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>(a \neq b \neq c) (\alpha = \gamma = 90^\circ) (\beta \neq 90^\circ)</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>(a \neq b \neq c) (\alpha \neq \beta \neq \gamma \neq 90^\circ)</td>
<td>Triclinic</td>
</tr>
<tr>
<td>(a = b \neq c) (\alpha = \beta = 90^\circ) (\gamma = 120^\circ)</td>
<td>Hexagonal</td>
</tr>
<tr>
<td>(a = b = c) (\alpha = \beta = \gamma \neq 90^\circ)</td>
<td>Trigonal/Rhombohedral</td>
</tr>
</tbody>
</table>
1.3.1 Crystal lattice

A lattice is said to be an array of equivalent points in three dimensional materials. The lattice shows the translational symmetry of the material but does not provide any information on the actual position of atoms or molecules in space \(^{(31)}\).

The infinite periodic array which contains repeated or discrete units of arranged or oriented crystals and remains exactly the same when the array is viewed from any direction is called a Bravais lattice. The Bravais lattice is a mechanism that helps in classifying the structural diversity in crystals and only indicates the underlying configuration of the crystal’s repeated units \(^{(33)}\). There are fourteen (14) distinct types Bravais lattices.

These lattices have different cell shapes with different symmetry properties \(^{(34)}\). The primitive cell does not leave voids or overlap itself when translated through all the Bravais lattice vectors but rather ends up filling all the space \(^{(33)}\). Primitive lattice is the simplest and it is usually given the symbol “P” and it has lattice points only at its eight corners. Body centred “I”, face centred “F” and “A”, “B” and “C” have additional translational symmetry within the unit cell.

The body centred lattice has lattice points at all corners as well as an additional lattice point at the cell centre with fractional coordinates of \(\frac{1}{2}, \frac{1}{2}, \frac{1}{2}\). That of the face centred lattice has lattice points at the centre of all the unit cell faces and at the corners as well. This has fractional coordinates of \(+\frac{1}{2}, \frac{1}{2}, 0\), \(+0, \frac{1}{2}, \frac{1}{2}\) and \(+\frac{1}{2}, 0, \frac{1}{2}\).

There are other face centred lattices. The face centred lattice with lattice points in just one face, as well as the placing of lattice points at the centres of faces delineated
by “a” and “b” directions and at the origin, is given by the additional translational symmetry with the symbol “C”. When the additional lattice points occur in the “bc” and “ac” planes, the face centred lattices are given the symbol “A” or “B” respectively. These lattice points do not provide information about the number of atoms or molecules in the unit. Lattice Planes (three dimension) and lattice lines (two dimension) connect the lattice points establishing the translational symmetry of the structure.

Miller indices are used to represent these lattice lines and planes. The indices \( h, k \) and \( l \) are used for a three dimensional structure. These indices can be negative, positive integers or zero \(^{(31)}\). An object is said to have symmetry if it has asymmetric units which correspond to each other across a plane as a result of rotation or reflection (or a combination) across a plane or inversion through a plane \(^{(35)}\). The development of a pattern as a result of a description of an imaginary process is called a symmetry operator. These symmetry operators tend to change the orientation or position of an object in space. Symmetry operator such as translation results in the replication of the object but at a new spatial coordinate. Rotation is a symmetry operator which involves a motion about an axis but through an angle. These symmetry elements when combined together into groups give two hundred and thirty (230) possible arrangements.

Each group is known as a Space Group \(^{(35)}\). The crystallized nature of most pharmaceutical materials makes them susceptible to polymorphism. Some of the criteria used in selecting drug polymorphs are its solid state stability, bioavailability, Gibbs free energy and solubility \(^{(36, 37)}\).
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The crystalline form and the state of solvation of the drug tend to affect the therapeutic response (38). Multiple crystalline forms (polymorphs) are developed in order to select the polymorph with the lowest energy which indicates that it is the most stable form. It is very important that the most stable crystalline form is developed because of some of the following reasons:

a) There is the need to increase the absorption of drugs by increasing their solubility so that the required therapeutic level is reached in the systemic circulation in order to elicit the positive therapeutic response.

b) When there is the need to improve upon the dissolution rate of the drug so that it takes a shorter time for the drug to reach its therapeutic level or concentration in the systemic circulation. When this happens, the drug can be used for giving very quick relief from acute symptoms.

The development of a more stable polymorph of a drug which can be the metastable or amorphous form provides a medical benefit for the patient (39). The conditions used during the crystallization process such as the temperature, addition of seeds and the solvent types used can result in different crystalline forms of a drug forming (37).

Humidity, mechanical forces such as compression, temperature changes as well as heat can be used to change one polymorphic form to the other and at times if the polymorph crystallized is unstable it changes to a more stable form (37, 40).
1.4 Non-Bonded Interactions

The shape of a molecule tends to convey a host of information to any chemist. The shape of a molecule arises as a result of a balance between various electronic-structural and steric effects. Electronic-structural and steric effects tends to have constraining effects on the intermolecular interactions, spectroscopy and reactivity \(^{(41)}\). Non bonded interactions involve repulsions or attractions that occur between atoms that are not directly linked to each other \(^{(1)}\). Some of the non-bonded interactions are van-der Waals interactions (dispersion forces), \(\pi\) stacking (\(\pi\)-stacking) and dipole-dipole interactions.

1.4.1 Dipole-Dipole Interactions

As a result of the fluctuations existing in their electron clouds, polar molecules tend to have permanent charges. The interaction of these permanent charges gives rise to dipole-dipole interactions. Dipole-dipole interactions are weaker when compared to ion-ion interactions in ionic solids because the polar molecules tend to have partial charges. The strength of the dipole-dipole interactions for a diatomic molecule is directly related to difference in their electronegativity \(^{(106, 107)}\).

1.4.2 Dispersion forces

These are forces that exist between non-polar molecules. The distortion of the electron cloud of a neighbouring molecule by the dipole moment on one molecule causes a dipole moment on that molecule. This two dipole moments by interacting with each other cause an attracting force between each other resulting in the formation of London forces. Factors that turn to affect the effectiveness of the London forces are the polarizability of the molecules and how easy it is to distort the electron clouds of the molecules \(^{(106, 107)}\).
1.4.3 π-π Stacking

The stacked arrangement often adopted by aromatic molecules due to interatomic interactions is referred to as stacking or π-π interaction. The consecutive base pairs in DNA are a common example of a stacked system. Proteins exhibit stacking conformation involving the overlapping of two relatively non-polar rings \(^{(97)}\).

This aromatic interaction (or π-π interaction) is a noncovalent interaction that occurs between organic aromatic moieties. These interactions results from the intermolecular overlapping of σ-orbitals in π-conjugated systems. The strength of these interactions increases as the number of π-electrons increases. These π-π interactions act strongly on flat polycyclic aromatic hydrocarbons as a result of many delocalized π-electrons in these systems \(^{(98)}\).

1.5 Hydrogen Bonds

The attraction between molecules or atoms that results in the formation of chemical compounds containing two or more atoms is known as a chemical bond. A chemical bond is therefore an attraction which is caused by the electromagnetic force between electrons and nuclei, either between opposing charges or resulted from a dipole attraction.

A chemical bond can be said to be a hydrogen bond depending on the bond’s physical and geometric properties \(^{(42)}\). A hydrogen bond is the attractive intra or intermolecular interaction that occurs between one or more other electronegative atoms like nitrogen, oxygen or fluorine, groups of atoms or molecules with a hydrogen atom. The hydrogen bond involves the covalent bonding of the hydrogen atom to another electronegative atom to create the bond \(^{(106)}\).
Figure 1.2  Diagram of hydrogen Bonds

\[ \text{A-H..B} \quad \text{A-H..B}_1 \]

\[ \text{A-H..B} \quad \text{A-H..B}_2 \]

The illustration of the hydrogen bond as indicated in Figure 1.2, involves the bond lengths of A……B and H……B, the planarity involving AHBX and the bond angles of AHB and HBX.

It can however be generalized that all O…..H bond distances measuring up to 3.6 Å qualify to be called hydrogen bonds\(^{(1)}\).

Figure 1.3  Diagram showing the geometry of a hydrogen bond.

As shown Figure 1.3 that a typical distance between 2.8 and 3.2 Å exists for N……O distance and an angle larger than 150° exists for the angle N-H……O is usually between 100 and 180° \(^{(43)}\). A hydrogen bond is said to occur when a hydrogen atoms lies between two atoms which are strong electronegatively and small in size with lone pair of electrons. An example of such atoms are “F”(flourine), “N”(nitrogen) and “O”(oxygen) \(^{(6)}\). The non-linearity of hydrogen bonds is attributed to the different molecular packing requirements. There is also the case whereby a single hydrogen atom tends to take part in two hydrogen bonds and this type of hydrogen bonding is indicated in Figure 1.2 as A-H……B\(_1\)-X and …..B\(_2\)-X, is said to be bifurcated\(^{(1)}\).
The bonding of a hydrogen atom to strong electronegative atoms results from a dipole-dipole interaction force and it is said to be an electrostatic phenomenon. \(^{(6)}\).

Hydrogen bonding occurs between donor atoms like O-H or N-H and acceptor atoms O-C, O-H and N. Hydrogen bonding is said to be partially covalent in nature because they come about as a result of a balance of attractive and repulsive forces between the partial charges on the atoms involved in the hydrogen bond formation.

The difference in electron affinity of atoms of molecules, results in partial charges being created on these molecular atoms. Hydrogen atoms tends to loose electrons to be partially positively charged whilst other atoms like oxygen and nitrogen atoms gain these electron to be partially negative charged. The interaction of these two partial charges results in hydrogen bond formation \(^{(44)}\). Hydrogen bond is a very strong bond with bond energy about 5 to 30 kJ/mole and tends to dominate all other types of intermolecular interactions and survives even sometimes in the vapour state. This type of bond also introduces water soluble properties to compounds \(^{(6)}\). Hydrogen bonding is said to be either intramolecular when it occurs within different parts of a single molecule or intermolecular when it occurs between molecules \(^{(45, 46)}\).

The N-H or O-H hydrogen bond directionality mostly points to the lone pair of electrons of the acceptor atom which is sp\(^2\) or sp\(^3\) hybridised oxygen atom. This aspect of the hydrogen bonding has been studied by a lot of researchers and they all concur to the directionality of hydrogen bonds being towards sp\(^2\) or sp\(^3\) hydridised oxygen atom \(^{(1)}\).
Hydrogen bonds tend to form zero, one and two dimensional networks. Zero hydrogen bonded zero networks occur when the hydrogen bond results in the formation of a closed loop like in a carboxylic acid dimer as indicated as Figure 1.4

**Figure 1.4 Diagram showing Hydrogen Bonded Zero Network (Closed Loop)**

Here the conformation of the hydrogen bonding is not dependant on the nature of the substituent “R” and allows the compound to have a centrosymmetric space group (47).

In the case of one dimensional hydrogen bonded network, two or more molecules which form the zero dimensional conformation exist as an array of molecules with the related translation of successive molecules as occurs in secondary amides. One dimensional hydrogen bonded network is shown in Figure 1.5.

**Figure 1.5 Diagram indicating One Dimensional Hydrogen Bonded Conformation**

(105)
With respect to the one dimensional hydrogen bonded network, the conformation depends on the shape and size of the substituent. This type of arrangements only occurs in acids with small substituent groups\(^{(48)}\). Two dimensional hydrogen bonded network is as shown in Figure 1.6. Molecules with two dimensional networks do not pack efficiently.

**Figure 1.6  Diagram illustrating two dimensional hydrogen bonded network**

It has been noted that, the more the dimensional hydrogen bonded network, more the molecules deviate from close packing in favour of hydrogen bonding\(^{(49)}\). Hydrogen bonding is an important aspect of our lives on earth such as our dependence on water. Hydrogen bonding is responsible for stabilising and holding the three dimensional structures of the DNA helical structure (such as RNA structures) and the protein structure (such as β-sheets, α-helices of peptide and protein secondary structures as well as the tertiary structures of proteins) together. Hydrogen bonding comes into play during the distribution of drugs in a biological system, having some effects on membrane transport and being involved in ligand (such as drugs)-protein (such as enzymes and drug receptors) complex formation resulting in a therapeutic effect\(^{(43)}\).
Hydrogen bonding can therefore be said to be a partial covalent dipole-dipole interaction. Hydrogen bonding is strong, directional, has shorter interatomic radii when compared to those of van der Waals and uses a limited number of interactive atoms. It should be noted that, the pressure, bond strength and the temperature determines the length of the hydrogen bond \(^{(107)}\).

As a result of van der waals and electrostatic interactions between atoms, hydrogen bond donors like N-H tends to interact with aromatic systems such as benzene ring resulting in the formation of hydrogen bonds about half the strength of a normal hydrogen bond.

### 1.6 Structure-Activity Relationships of Selected Systems

A single crystal is the most ideal form of an organised medium. Knowledge about the intermolecular and intramolecular interactions within single crystals enables one to predict and understand interactions in complex molecules. Intermolecular forces play an important role in the absorption phenomena of a compound \(^{(1)}\).

The crystal structure of chalcones plays a very important role in its physical and pharmacological properties. Examples of some of the researches done on the structural activity relationships of chalcones are given below.

Dong et al probe the quantitative structure activity relationship of flavonoids as vasorelaxant agents using a comparative molecular field analysis. Quercetin a well known vasodilator was used as positive control and the experiment was performed on aortic rings with endothelium.
They found out that these flavonoids have high vasodilatory effects but their effects become reduced when “ally” substituents were added. They also found out that the relaxation activity of the flavonoids is directly related to the dose used (50).

Hugo et al also described the antibacterial activities of chalcones. They realised that the antibacterial properties chalcones is mainly on gram positive bacterial. They linked the antibacterial effects of chalcones to their features such as the presence of a C-4’-hydroxyl group, C-4’-oxygenated substituent and a C-3’-isoprenoid side chain. Also a C-2’-hydroxyl group is very important for the stability of the compound. Another aspect of chalcones that Hugo et al realised was the activity of the chalcones against the human pathogenic microorganisms. They concluded that this activity is correlated to the patterns of the aromatic rings of chalcones (51).

The carbon-carbon double bond in chalcones was expoxidated by Jin H et al. They did the expoxidation using urea-hydrogen peroxide under an ultrasound irradiation. This reaction method is considered to be very safe, shorter reaction time and the oxidant that was used is safe and the experiment was done under mild conditions (52).

Moni et al deduced that different physicochemical and structural requirements are necessary for chalcones to exhibit their antibacterial and antimalarial activities. The quinolinyl chalcones exhibited effective antitubercular activity whilst the pyrimidine analogues also exhibited effective antimalarial activity (53).
The solubility of the core structure of chalcones (1,3-diphenyl-2-propenone) was improved using lipidic formulations under supercritical carbon dioxide processing methods by Sampaio de sousa et al\(^{(54)}\). The methoxylated and hydroxylated chalcones have been found to be selective and potent inhibitors of the mutant \((482T)\) breast cancer resistant protein and their mode of action may not involve the ATPase inhibition. This effect was investigated by Yi Han et al\(^{(55)}\).

Xue et al deduced that cryptolepines are more active than their oxygen and carbon isosteres. These isosteres were placed at (nitrogen) N-10 atom\(^{(56)}\). Seth et al also indicated that the alkylation of the nitrogen N-5 of the teracyline structure and the \(\omega\)-cycloakylpentyl substituent also at N-5 resulted in broad spectrum inhibition of many opportunistic infections.

The tetracycline moiety of cryptolepines is however not a requirement for its antifungal activity. They also indicated that the quindoline moiety is essential for their antifungal activity\(^{(57)}\).

### 1.7 Structure Motifs

**1.7.1 Hydrogen Bonding Interactions**

Hydrogen bonding is the most frequent and most important non van der waals interaction in molecular crystals. Hydrogen bonding tends to stabilise structures of biological molecules both in solution as well as in the solid state. The crystal packing adopted by molecules is affected by the sensitivity of the chlorine-chlorine bond and carbon-chlorine bond.
Hydrogen atoms bonded covalently to carbon atoms, form short intermolecular interactions with oxygen atoms rather than to carbon or hydrogen atoms. The hydrogen atom involved in the carbon-hydrogen-oxygen bonds (C-H…O) interactions is not repelled but points towards the lone pairs of electrons of the oxygen atom. C-H…O bonds are linear, assume a planar structure wherever possible and have short bond lengths.

**Figure 1.7  Intra and intermolecular hydrogen bonding in urea derivative.**

Figure 1.7 shows the intra and intermolecular hydrogen bonding in urea derivative. They differ from the oxygen-hydrogen-oxygen (O-H…O) and nitrogen-hydrogen-oxygen (N-H…O) contacts \(^1\). The length of H…O typically is between 1.8Å to 2.0Å for hydrogen bonds in the form N-H….O and 1.6Å and 1.8Å for O-H…O bonds. It is now noted that all O…H distances that measure up to 2.15Å are bonded interactions. Closed loops that consist of hydrogen bonds are the simplest and such networks formed by these bonds are zero-dimensional. Examples can be said of cyclic dimers of racemic carboxylic acids \(^1\). Phenol structures form closed rings consisting of three to four hydrogen bonds and such ring formation is favoured energetically \(^{58,59}\).
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Figure 1.8  Diagram showing hydrogen bonding involving C-F.....H and N-O.....H in 9-nitro-7-(trifluoromethyl)dodecahydropyrido[1,2-a]benzimidazole (60).

Figure 1.8 shows the hydrogen bonding involving C-F.....H and N-O.....H viewed along the b-axis.

Hydrogen bond formation in compounds increases their boiling point. This was noted by Pauling during their investigation of hydrogen bonds and an example can be given of acetyl chloride having a higher boiling point than trifluoroacetyl chloride (1).
Arvi indicated that bonds formed as a result of hydrogen bonding tend to have an enormous effect on the physical and chemical properties of most molecules. They also control the conformation of nucleic acids and proteins. An example is the secondary structure of protein.

The shape of this secondary structure is controlled by the hydrogen bonding existing between the carbonyl oxygen of the amide moiety with the N-H bond of another. Also complementary N…H-N and =O….H-N bonds stabilize the two strands of the double helix of nucleic acids \(^{(62)}\). Further studies done by Rychlewska and Warzajtis noted that when the terminal carbonyl groups are located at only one side of the molecule, the crystals pack in a head to head or head to tail pattern. This occurs as a result of intermolecular hydrogen bonding \(^{(63)}\). Cioslowski and Mixo deduced that some planar benzenoid hydrocarbons such as chrysene, phenanthrene and benzanthracence have non-bonding repulsive hydrogen atom interactions. The distance between these hydrogen atoms is less than 2.18 Å and the hydrogen atoms are located at 1 to 4 positions \(^{(64)}\).

### 1.7.2 Carbon and hydrogen atom non-bonded interactions

Hydrogen atoms often occur at the extremities of molecules and also they turn to define the shape of the molecule. As a result of their ability to help in defining the molecular structures, correct estimation of their van der waals radius is very important.

Even though intramolecular hydrogen-hydrogen bonding distance of 1.713 (3) Å has been observed, bond distance between intermolecular hydrogen-hydrogen bond is usually between 1.1 Å and 1.2 Å.
The carbon: hydrogen ratio is greater in aromatic compounds compared to aliphatic compounds. Compounds with aromatics have greater tendency to stack in the crystal more efficiently and effectively because of the greater number of carbon-carbon interactions.

Figure 1.9 Diagram showing hydrogen bonding (C-H.....O) during packing in chalcones viewed along the b-axis.

Figure 1.9 shows the hydrogen bonding (C-H.....O) in chalcones during packing viewed along the b-axis. The carbon-hydrogen interactions become optimised especially when neighbouring molecules close-pack in three dimensions. The crystal structure that is formed is known as the herringbone structure. This indicates that, molecules with monoclinic space groups and translational symmetry elements held together by intermolecular carbon-hydrogen bonds are generally non-parallel.
Hydrogen-hydrogen bond interactions are very important in compounds with low carbon-hydrogen interactions. It can also be noted that intramolecular carbon-hydrogen interactions tend to introduce steric effects within the molecule resulting in conformational changes. Crystal packing is related to the shape, size and the surface contouring of the molecule \(^{(1)}\).

Rabinovich \emph{et al} found out that the compound being studied had its two molecules occurring in the asymmetric unit and also these two molecules are related by a pseudo-b-glide which is nearly normal to the a-axis. They also indicated that the bromine atom tends to lock together the stacks formed by the molecules during packing. There are other short contacts between Br…H and C….H \(^{(66)}\). Jungk and Schmidt established that chalcones have the same intramolecular contacts occurring between the nitro-group and the ethylenic bridge \(^{(67)}\). Marx \emph{et al} also indicated 3-benzylidene-8-methoxy-6-methylchroman has its molecular structure being stabilised by weak intramolecular C-H…O interactions. C-H…O and C-H…π weak interactions tend to stabilise the crystal packing \(^{(68)}\). Teh \emph{et al} during their study of the compound 1,3-Bis(3,4-dimethoxyphenyl)prop-2-en-1-one found out that the molecules of this compound have C-H…O hydrogen bonds linking them into a centrosymmetric dimer. Also C-H…π interactions stabilises the crystal structure \(^{(69)}\).

Jasinski \emph{et al} found out that the stabilisation of the crystal of their compound depends on van der waals interactions resulting the molecules of the compound being arranged in rows in a zigzag conformation \(^{(70)}\).
Yogavel et al established that the compound 1,2,3-Trimethoxy-5,11-dihydroindolo[1,2-b]isoquinoline-5,11-dione tends to have four molecules in its asymmetric unit when it crystallizes. These molecules also exhibit four different types of \( \pi \)-stacks during packing. They also tend to have two types of packing sheets during packing with the molecules alternating between one sheet and the other. \( \pi \)-\( \pi \) and C-H…O interactions stabilizes the supramolecular structure \(^{(71)}\).

**Figure 1.10** Diagram showing intra and intermolecular hydrogen bonding in Xanthines (Theophylline)

The establishment of weak intermolecular C-H…..O interactions stabilizing the molecules of the compound being studied in the crystal state was done by Thamotham et al \(^{(72)}\). Ravishankar also indicated that the ketone group of the compound 1-(4-chlorophenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one exists in the s-cis conformation in relation to the olefinic double bond. O-H…..O hydrogen bonds links the screw-related molecules resulting in the formation of chains along the c-axis.
A three dimensional network is formed by the chains since they are interconnected by C-H….O and C-H….Cl interactions \(^{(73)}\). A closely related compound understudied by Sathiya et al also concluded having the C-H….O interactions forming rings of graph motifs \(^{(74)}\). The non-planar compound 1,3-Bis(4-chlorophenyl)prop-2-en-1-one have \(\pi-\pi\) interactions pairing the molecules of the compound.

The pairs are then connected to each other by hydrogen bonding interactions \(^{(75)}\). S.-L. Ng et al indicated that weak intermolecular C-H….\(\pi\) interactions stabilize the crystal packing of their compound with the involvement of the two aromatic rings. The molecules also stacked along the b-axis during packing \(^{(76)}\).

Teh et al established that Br…..Br short contact interactions stabilizes their compound \(^{(77)}\). C-H….O weak intra and intermolecular interactions are responsible for the stabilisation of the compound 3-benzylidene-8-methoxy-6-(prop-2-enyl)chroman-4-one during crystal packing. This was indicated by Suresh et al \(^{(78)}\). Harrison et al found out that the formation of molecular chains of their compound in the crystal structure is as a result of intermolecular C-H….O interactions \(^{(79)}\). Butcher et al also indicated that the interactions between the methoxy hydrogen atom and the ketone oxygen atom in the prop-2-ene group results in a C-H…..O hydrogen bonding. This bonding is responsible for stabilising the crystal packing of the compound \(^{(80)}\). Sunder et al established that weak intermolecular C-H……O interactions tend to stabilize the crystal packing of 16-[4-(3-chloroproproxy)-3-methoxybenzylidene]-4-androstene-3,17-dione \(^{(81)}\).
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The linkage of the molecules of the compound studied by Patil et al in the crystalline state is as a result of intermolecular C-H……O interactions. The molecular chains formed as a result of the linkage occur along the c-axis\(^{(82)}\). The conformation of the packing molecules of 16-(4-isopropylbenzylidene)androst-4-ene3,17dione is assumed to be controlled by the weak intermolecular C-H……O interactions. Thanotharan et al established this in 2004 during their studies on chalcones\(^{(83)}\).

Subbiah et al also indicated that a three dimensional network is formed as a result of the cross-linkage of intramolecular O-H……O hydrogen bonds by four intermolecular C-H……O hydrogen bonds\(^{(84)}\).

Arslan et al synthesized a new benzimidazole compound methyl-1-n-butyl-2-(3,4-dichlorophenyl)-1H-benzimidazole-5-carboxylate. C-C-C-N torsion angle of \(-39.7(3)\)° exist between the benzimidazole group and the phenyl ring. The symmetry related molecules has C-H…O interactions linking them together to form chains\(^{(85)}\).

The compound synthesized by Pei et al tends to crystallize with the mid-point of the central C-C bond. Located on an inversion center is the molecule of tetrabenzimidazolyethanediamine. O(or N)-H……O and O-H……N hydrogen bonds stabilize the crystal packing\(^{(86)}\).

Yang et al deduced that their compound forms a C(12) chain along the [010]direction as a result of their molecules being linked by C-H…..Cl hydrogen bonds\(^{(87)}\).
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The crystal structure of the compound synthesized by Özbey et al, is stabilized by hydrogen bonds (88).

Qin et al also indicated that their studied compound with the formular C$_{34}$H$_{32}$N$_{10}$.2C$_2$H$_6$O$_2$ has its crystal packing being stabilized by O-H….N and N-H……O hydrogen bonding. The main molecule of this compound occurs on an inversion center and the compound crystallizes in space group P1$^-$(89).

**Figure 1.11** Diagram of hydrogen bonding in a chalcone

Figure 1.11 is a diagram showing an intra-molecular hydrogen bond (C(2)-OH(2)...O(1) in a chalcone compound. Devia A. C et al in 1999 deduced the existence of an intramolecular hydrogen bond between the H of the OH group at position 2' and the carbonyl oxygen atom of their chalcone compound. They also deduced that this interaction has an effect on the physicochemical properties of chalcones such as their adsorptivity (90).

Baumer et al indicated that there is a ring closure of the six membered pseudo-rings in the cation as a result of the intramolecular hydrogen bond interaction between a hydrogen atom of an amino group. There is another hydrogen bond interaction between the oxygen atom of the perchlorate anion and the second hydrogen atom of the amino group (91).
Walczak et al reported the first benzimidazole derivative structure having 2-alkyl and 4-amino substituents. They also indicated that the ethylamino groups do not take part in any hydrogen bonding but the imidazole rings participate in hydrogen bonding. These hydrogen bond interactions by N-H……N interactions link the compound molecule in chains (72).

Swamy and Ravikumar also indicated that the crystal structure of their studied compound is stabilized by C-H……π interactions. The molecules are also linked together long the c-axis by N-H….N interactions resulting in the formation of hydrogen bonds (93).

Li et al (2003) established that the dimers formed by the molecules of their compound are connected by hydrogen bond interactions of N-H……N (94).

The two compounds studied by Gdaniec et al (2003) have similar molecules. Even though there are a large number of easily available hydrogen bond acceptor sites for hydrogen bond interactions, only a hydrogen atom from the amino group participates in hydrogen bonding. A pair of N-H……N hydrogen bond interactions which seems to be nearly linear tends to assemble the molecule of the compound into discrete centrosymmetric dimers (95).

The compound as indicated by Li et al (2005), has molecules of the compound 2-(2-nitrophenyl)-1H-benzimidazole forming molecular chains along the b-axis. These molecular chains occur as a result of intermolecular N-H……N hydrogen bonding, C-H……O hydrogen bonds link these chains into a two dimensional network (96).
1.7.3 Halogen-halogen interactions

Short interactions between halogen substituents and hetero atoms such as nitrogen, sulphur and oxygen tend to occur in crystals. Intermolecular interactions usually occur between chlorine-chlorine (Cl….Cl) atoms. A partial covalent bond exists between Cl….Cl interaction which is about three percent of the full strength of a covalent bond.

**Figure 1.12 Preferred Geometrical Parameters Essential for Cl…….Cl Interaction**

![Diagram](image)

The first preferred geometry shown as (1) indicates that angles “a” and “b” should be equal and around 160° ± 10°. The second preferred geometry indicated as (2) shows that the angle “a” should be between 150°-180° and angle “b” should be around 80°.
Much research involving halogen……halogen interactions have been done. Awwadi et al \((175)\) using ab initio calculations and histograms concluded that, the maximum “θ” (angle) needed for halogen….halogen interactions to occur depends on three factors which are:

- The halogen atom involved
- The hybridisation of the carbon atom to which the halogen atom is attached
- The type of atoms bonded to this carbon atom apart from the halogen atom attached to it.

The first arrangement shown as (1) in Figure 1.12 is usually exhibited by compounds with two-fold axis, an inversion centre or a mirror plane in relation to the two chlorine atoms. The second geometry indicated as (2) is most of the time the conformation exhibited by compounds with orthorhombic and monoclinic space groups with adjacent C-Cl bonds which are related by a glide plane or a two-fold screw axis \((1, 175)\).

**Figure 1.13 Halogen-Halogen bonding in 1,4-dichlorobenzene** \(^{(1)}\)
The Cl…Cl interaction helps to stabilise the crystal structure. This Cl…Cl interaction forms a two dimensional motifs of which one is the planar sheet which is usually exhibited by triclinic structures.

The monoclinic structures tend to exhibit the linear ribbon and singly corrugated sheet conformation whilst the orthorhombic structures exhibit the doubly corrugated sheet packing conformation. Substitution on an aromatic ring with chlorine tends to produce crystal modifications resulting in short axes of around 4Å \(^{(1)}\).

### 1.7.4 Stack and Herringbone Patterns of Aromatic Molecules

Aromatic rings are said to be planar two dimensional objects which pack very well in either herringbone or stack structure motifs. The best stacking is observed when there is a close-packing of the bumps in one of the rings with those of the adjacent ring being depressed.

**Figure 1.14**  Diagram showing Stack Packing (left) and Herringbone Packing (right)
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Research has shown that adjacent phenyl rings do not orientate themselves with interplanar angles within the range of 5° to 30° so as not to lose the stacking interactions resulting in the stability. Phenyl rings can pack at steep angles within a range of 40° to 90° resulting in the formation of a herringbone pattern \(^{(1)}\).

1.8 Analytical Methods for Analysis of Solid State

A liquid will freeze at a temperature low enough to form either an amorphous or a crystalline solid. The difference between the amorphous and crystalline solid is that, in the case of the crystalline solid, all the ions, atoms or molecules lie in an orderly array whilst the opposite occurs for the amorphous solid. The amorphous solid has its atoms, molecules or ions being randomly arranged \(^{(46)}\). Spectroscopy enables the putting together of information about the molecular and solid state properties of compounds. It involves the use of a broad range of techniques such as:

- X-ray and Powder X-ray diffraction methods for characterisation of crystals or crystal structure analysis
- Solid state NMR
- Mass spectroscopy
- Raman spectroscopy
- Infra-red spectroscopy

The different vibrational spectroscopic methods mentioned are used to monitor and detect solid state transformations \(^{(24)}\). More detail is provided in the following section.
Table 1.2 illustrates the energy transitions in each region of the electromagnetic spectrum.

**Table 1.2  Table of Energy transitions in each region of the electromagnetic spectrum**

<table>
<thead>
<tr>
<th>Spectrum Region</th>
<th>Energy Transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infra-red</td>
<td>Vibrational</td>
</tr>
<tr>
<td>X-Rays</td>
<td>Bond Breaking</td>
</tr>
<tr>
<td>Ultraviolet/Visible</td>
<td>Electronic</td>
</tr>
<tr>
<td>Microwave</td>
<td>Rotational</td>
</tr>
<tr>
<td>Radiofrequencies</td>
<td>Nuclear spin (nuclear magnetic resonance), Electronic spin resonance)</td>
</tr>
</tbody>
</table>

1.8.1 Vibrational Spectroscopy

**Figure 1.15 Vibrational Energy Levels**

![Vibrational Energy Levels Diagram](image)
Figure 1.15 shows the vibrational energy levels involved in infrared and Raman spectroscopy. Most organic or inorganic compounds with covalent bonds tend to absorb various frequencies of electromagnetic radiation in the infra-red region. Vibrational spectroscopy involves infra-red spectroscopy and Raman spectroscopy. The nuclei of a molecule in the ground state are in equilibrium because there is no net force from its electrons and other nuclei. The molecule vibrates as a result of its nuclei being subjected to diverse forces during the electronic transition state. Rotational transitions in addition to the electronic transitions occur during the vibration of the molecule.

The type of transitions that is observed in the electronic spectrum of a molecule is governed by selection rules which depend on changes in total orbital angular momentum of an electron about the internuclear axis. The selection rule for vibrational transitions with respect to infra red spectroscopy, depends on the fact that change in the electric dipole moment of the molecule must take place during the course of the vibration motion. In the case of Raman spectroscopy, the selection rule for vibrational transitions depends on changes that occur with respect to the polarisability ellipsoid during vibration. Molecules are not required to have permanent electric dipole moment for this selection rule to apply, but where the molecule changes from one vibrational level without a dipole moment to a level with one. Selection rules concerned with changes in symmetry are the Laporte selection rule which concerns atoms or molecules with a centre of inversion (centrosymmetry) only.
This is because these molecules or atoms undergo transitions that is accompanied by changes in parity (that is transitions involving “g to u” and “u to g” and not “g to g” or “u to “). The other selection rule allows transitions involving “g to g” and “u to u” \(^{(36)}\).

### 1.8.1.1 Infra-red spectroscopy

The vibration portion of the infra-red region involves wavenumbers between 400cm\(^{-1}\) and 4000cm\(^{-1}\). The infra-red spectrum gives very important information about the structure of organic molecules. Infra-red spectrum is very important because each compound has its own unique spectrum and absorption. It helps in obtaining structural information about a molecule \(^{(102)}\).

Infra red is a reliable method used in assigning compounds to their class as well as it being very rapid and simple. Infra-red spectrum is used to also detect and measure directly the molecular vibration of compounds. Functional groups vibrate at a well defined frequency that is specific, characteristic and unique for that particular functional group.

The infra-red instrument is made up of a source of infra-red light that emits radiation throughout the instruments frequency range. This light is then broken into two beams of the same intensities and one beam is made to pass through the sample to be examined. Recombination of the two beams occurs later on resulting in the creation of an interference pattern. Absorption of energy of a particular frequency by the sample from the light emitted occurs when the sample has a frequency of vibration that falls within the frequency range of the instrument. The spectrum is made up of absorption downward peaks plotted against wavenumber \(^{(101)}\).
1.8.1.2 Raman spectroscopy

Raman spectroscopy is based on light scattering effect. When the frequency of the incident radiation does not correspond to the absorption frequency of the molecule, the photons of the incident radiation generally bounce off the molecule.

This results in a greater number of incident photons being scattered in all directions by the target molecule without a change in their energy. This effect is referred to as elastic scattering or Rayleigh scattering.

Raman scattering or inelastic scattering results when there is exchange of energy between the incident photons and the target molecule during their interaction with the target molecule. Stokes scattering is when a molecule absorbs energy during the Raman Effect. The resulting photon of lower energy then generates stokes line on the red side of the incident spectrum.

Anti-Stokes scattering results, when the molecule loses energy and the incident photons become shifted to the blue side of the spectrum generating the anti-Stokes line.

Raman spectroscopy involves instruments that use laser as their source of light. It is used for determining particular functional groups and analysing mixtures. Raman spectroscopy also deals with both vibrational and rotational transitions. In the case of the Raman spectroscopy, observed scattered light is made at right angles to the incident beam. As a result of this, the detector is placed at right angles to the monochromatic light source. Raman spectra are mostly used for identifying functional groups of compounds in the powder, gaseous, liquid and solution states as well as in the pressed pellet form.
1.8.2 X-Ray Diffraction

The accepted definitive techniques for determining the structure of solids and their molecules are X-ray and X-ray powder diffraction. Diffraction arises from the interference of waves caused by an object placed in the path of these waves. These wave interferences create a pattern of bright spots against a dark background called a diffraction pattern (46).

Figure 1.16 Schematic diagrams showing wave interferences during diffraction

When two waves as indicated in Figure 1.16 are in phase (\(\phi =0^\circ\)), then they reinforce one another giving constructive interference. When out of phase (\(\phi =90^\circ\)), they cancel one another leading to destructive interference (32, 100). X-Ray crystallography is mainly concerned with diffraction of X-rays involving the subject of Fourier transformation (99).

X-ray crystallography compared to other spectroscopic methods, gives more detailed information about the structures of materials. Crystal structure determination can be used on a wide variety of structural sizes ranging from proteins, natural and synthetic polymers to very small molecules (32).
X-Rays are scattered by the electrons in matter. The scattering of X-rays by electrons in matter provides a lot of information and this is used to determine the structure of molecules and crystals at atomic level. The distances between atoms or ions are a few Angstroms. Interference between scattered X-rays from particular electron centres results in interference maxima and minima. When a beam of energetic electrons strikes a target, electrons are ejected from one of the metal atom core orbital of the target material. One of the processes involved in X-ray crystallography is X-ray Diffraction. Diffraction experiments require X-ray of a single wavelength (monochromatic light).

Figures 1.16 and 1.17 show diffraction from points on lattice planes of a crystal as a result of X-rays scattering.

**Figure 1.17** Diagram Showing Reflection of X-Rays through points in a Lattice by Imaginary Planes

The arrow from plane A shows “reflection” from that plane.

“Reflection” from B plane is out of phase with “reflection” from planes A and C.

The “reflection” from this plane (C) is in phase with that from A.

$d$ is the perpendicular spacing between the lattice planes.
Figure 1.18  Diagram Showing Reflection of X-Rays through points in a Lattice by Imaginary Planes

$2\theta$ is the deviation from direct beam

$b$ is the angle of incidence ($90-\theta$ )

$a$ is the angle of “reflection” ($90-\theta$ )

$c$ is the path differences each of which is $d \sin \theta$

$d$ is the spacing in the crystal

Diffraction can be said to be similar to reflection from a mirror. Therefore from Figures 1.16 and 1.17, the angle of incidence is the same as the angle of reflection. Also because scattered waves from adjacent lattice planes are in phase, it establishes that, the path travelled is an integral multiple of the wavelength which is $n\lambda$. This is valid only for certain angles of scattering. Bragg then deduced the following equation:

$$n\lambda = 2d_{hkl} \sin \theta_{hkl}$$

Where $\lambda$ is the used radiation wavelength

$n$ is an integer or order of reflection

$n\lambda$ is the path difference between different scattered waves from adjacent lattice planes.

d is the perpendicular spacing between lattice planes in the crystal

$\theta$ is the X-ray beam angle of incidence \(^{34}\).
The Bragg equation allows a diffracted beam to be labelled uniquely with its three indices \((hkl)\) as well as the scattering angle which is calculated from the unit cell geometry using the value of “\(d\)”.

Every crystal when subjected to X-rays produces the following:

- A particular geometry; this geometry is produced as a result of an individual scattered X-ray beam at the detector when this beam is travelling in a definite direction from the crystal. This crystal geometry can establish the repeat distances between molecules\(^{32}\).
- Symmetry; there is a relationship between the pattern symmetry produced by the crystal and the symmetry of the unit cell of the structure.
- Intensities of the individual spots; these vary, some being very weak and others very strong.

The intensities establish the positions of the atoms because the individual atoms tend to interact with the X-rays to generate different amplitudes depending on the direction of scattering.

X-Ray absorption by solids follows the equation:

\[
\frac{I}{I_o} = e^{-\mu T}
\]

Where \(\mu\) = linear absorption coefficient

\(T\) = the path length through the solid

\(I\) = intensity of the beam after passing through the solid

\(I_o\) = intensity of the incident beam

The above equation can be used to determine the size of crystals\(^{99}\).
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The positions of the atoms relative to the planes of a particular set affect the intensity of that particular reflection \((h, k, l)\). Each of the reflections in a crystal diffraction pattern is associated with the phase \((\phi)\) and the amplitude \(|F|\) of the diffracted wave. The vector \(F_{hkl}\) arises from its amplitude \(|F|\) and relative phase \((\phi)\).

The vector \(F_{hkl}\), which is the structure factor, is the addition of individual waves from scattered objects contributing to a resultant diffracted wave. The structure factor is calculated using the following formular:

\[
F_{hkl} = |F| \cos \phi + i|F| \sin \phi
\]

\(F_{hkl}\), being the structure factor of the reflection with indices \(h, k, l\), the equation becomes:

\[
F_{hkl} = |F|_{hkl} \cos \phi_{hkl} + i|F|_{hkl} \sin \phi_{hkl}
\]

\[
F_{hkl} = |F|_{hkl} (\cos \phi_{hkl} + i\sin \phi_{hkl})
\]

\[
F_{hkl} = |F|_{hkl} e^{i\phi_{hkl}} \quad \text{whereby } e^{i\phi} = \cos \phi_{hkl} + i\sin \phi_{hkl} \quad (32)
\]

The interaction between the scattering phenomena and the structure of the scattering substance is established by the use of the principle of Fourier transformation \((99)\). This is because an object is said to scatter radiation of wavelength that is comparable to its own size. The mathematical relationship between the scattering pattern and the object is called Fourier Transformation whilst the scattering pattern is the Fourier transform of the object. The objects image is said to be the Fourier transform of the scattering pattern. There is a forward Fourier transform which produces a set of discrete values resulting from the integration of a continuous function where as the reverse Fourier transform creates a continuous function from a set of discrete values.
It is unfeasible to calculate the electron density directly from the diffraction pattern since the intrinsic phase shifts ($\phi_{hkl}$) of the different reflections produced by the scattered atoms are not known. In order to solve this phase problem of X-ray crystallography, the intrinsic phase shifts ($\phi_{hkl}$) are determined by Patterson and Direct Methods techniques which involve the estimation of the electron density map.

1.8.2.1 Patterson Methods
The diffracted beam tends to be the Fourier transform of the electron density but this Fourier transform requires the amplitudes and phases of all reflections. Therefore, the square of the amplitudes with all phases set equal to zero, (that is, all waves were assumed to be in phase), results in what is called Patterson synthesis or Patterson Map which looks like an electron density map.

1.8.2.2 Direct Methods
This is the method whereby approximate reflection phases are obtained from measured intensities with electron density as the Fourier transform of the diffraction pattern resulting in the structure of the crystal being determined. This method involves the selection of the most important reflections, knowing the probable relationships among their phases and analysing different possible phases to see how the probability relationships are satisfied ($^{32}$).
Figure 1.19  A Schematic Flow Chart illustrating the successive steps involved in Crystal Structure Determination

1. SELECTION OF SUITABLE CRYSTAL AND MOUNTED FOR X-RAY ANALYSIS

2. DETERMINE THE UNIT CELL GEOMETRY AS WELL AS THE PRELIMINARY SYMMETRY INFORMATION

3. THE INTENSITY DATA MUST BE DETERMINED

4. DATA REDUCTION (CORRECTIONS APPLIED TO DATA)

5. SOLVE THE STRUCTURE BY: PATTERSONS METHODS OR DIRECT METHODS OR OTHER METHODS

6. FIND ALL THE ATOMS AND POSITIONS (FOURIER AND DIFFERENCE FOURIER SYNTHESIS)

7. REFINE THE MODEL STRUCTURE

8. INTERPRET YOUR RESULTS
Chapter 1

1.8.2.3 Powder X-ray Diffraction (PXRD)

PXRD identifies crystalline solid phases, crystallinity and phase purity \(^{(145, 110)}\).

Every crystalline material has its own unique solid phase and XRD pattern which forms the basis of it being identified. The combination of a high degree of accuracy with absolute specificity makes PXRD a unique technique for identifying crystalline solid phases \(^{(113)}\).

It is very important to study the structures of pharmaceutical materials because it determines the physical properties of these materials. Materials used in pharmaceutical products go through many processes during the preparation of a pharmaceutical product. As a result of that there may be some changes in its structure. Processes like compression, granulation, drying and grinding tend to reduce particle size as well as accelerate the solubility of materials. It also changes the polymorphic form of the material and makes the material more amorphous \(^{(108)}\).

It is however limited when being used to evaluate the product quality of the drug. It can be used to identify the active ingredient in various pharmaceutical dosage forms such as tablets, capsules and suppositories. X-ray Powder diffraction (PXRD) is a non-destructive experimental method and therefore becomes the ideal choice for structural studies of materials. PXRD can be used to determine the active ingredient in a variety of dosage forms and crystalline solid phases \(^{(111, 112)}\) as well as determining the positions of atoms in crystals \(^{(113)}\).
Each crystalline material in a powder gives its unique XRD pattern independently of the other crystals in the powder\textsuperscript{(111, 112)} and this technique can be used to investigate crystalline and non-crystalline substances that may not be crystalline.

Using the shape of the reflections, information about the crystallinity and texture of materials can be determined\textsuperscript{(114, 115, 116, 117)}. The PXRD method is very advantageous because it is simple and also the analysis of the dosage form is done directly with or without minimal sample pre-treatment\textsuperscript{(118)}. Pre-treatment of samples is labour intensive and results in alterations being made in the properties of the materials under study.

PXRD also makes it possible to distinguish between the solvated and unsolvated (anhydrous) forms of drug materials since these forms tend to affect the powder flow, bioavailability and dissolution rate of the drugs. Examples are Ampicillin, Caffeine, Prednisolone and Theophylline. It is also used to identify the active ingredient in drug formulations as well as for drug identification even if the weight fraction of the compound is as small as 0.05g. Another advantage is that numerous reference diffraction patterns are readily available\textsuperscript{(145)}.

### 1.8.2.4 Databases

There are four widely used databases containing the structural information about crystal structure determinations. This is made possible by the ability to store and retrieve the numerical crystal crystallographic results in a computer. The Inorganic Crystal Structure Database (ICSD) which contains data on all structures that contain no C-C or C-H bonds.
The Cambridge Structural Database (CSD) has information on organic, organometallic and metal complexes which were determined as a result of the use of X-Ray and neutron diffraction. The Protein Data Bank (PDB) contains information on more than 300 macromolecules.

Finally is the Metals Crystallographic Data File (CRYSTMET) which has information on metallic phases that have been analysed using diffraction methods. There are other databases such as the Powder Diffraction file which reference powder patterns, has data for about 44,000 compounds and whole other databases \(^1\). The CSD is deployed throughout this work and each structure is given 6 letters identification (ID). These IDs will be used to identify structures obtained from the Database and discussed in this thesis.

The Cambridge Structural Database contains information on more than 436,436 structures. It is said to be increasing at a rate of 7,000 structures or more per year. The CSD statistics below has been released by the Cambridge Crystallographic Data Centre relating to the Database as on 1\(^{st}\) January 2008.

<table>
<thead>
<tr>
<th>Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of structures</td>
</tr>
<tr>
<td>Number of different compounds</td>
</tr>
<tr>
<td>Number of literature sources</td>
</tr>
<tr>
<td>Organic structures</td>
</tr>
<tr>
<td>Transition metal present</td>
</tr>
<tr>
<td>Li-Fr or Be-Ra present</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Main group metal present</td>
</tr>
<tr>
<td>3D Coordinates present</td>
</tr>
<tr>
<td>Error –free coordinates</td>
</tr>
<tr>
<td>Neutron studies</td>
</tr>
<tr>
<td>Powder diffraction studies</td>
</tr>
<tr>
<td>Low/High temperature studies</td>
</tr>
<tr>
<td>Absolute configuration determined</td>
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<tr>
<td>Disorder present in structure</td>
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<tr>
<td>Polymorphic structures</td>
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<tr>
<td>R-factor &lt; 0.100</td>
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<tr>
<td>R-factor &lt; 0.070</td>
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<tr>
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</tr>
<tr>
<td>R-factor &lt; 0.030</td>
</tr>
<tr>
<td>Number of atoms with 3D coordinates</td>
</tr>
</tbody>
</table>

The Cambridge Structural database is made up of three sections which is the numerical data section, the chemical connectivity section and the bibliographic section. Searches of entry can be down using either the bibliographic category or the chemical connectivity category.