5.0 BIGUANIDES

Millions of individuals worldwide are suffering from diabetes mellitus which is a serious health problem. The World Health Organization (WHO) predicts that, a total of 300 million people will have diabetes mellitus by the year 2025. The guanidine containing compound group plays a very important role in biochemistry as well as managing diabetes mellitus.

Metformin is a second-generation biguanide compound 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 as well as reversing hepatomegaly and steatosis.

Metformin is the first drug of choice for treating type 2 diabetes especially in obese and overweight people as well as those with normal kidney function. Metformin is the drug of choice for treating polycystic ovary syndrome. Metformin also helps to increase HDL (High density lipoprotein) cholesterol in some patients, lower LDL (Low density lipoprotein) cholesterol and triglyceride levels.
thus helps to protect the cardiovascular complications of diabetics \(^{(190)}\) and it is in addition to glibenclamide on the WHO model list of essential anti-diabetic medicines \(^{(191)}\). Metformin reduces the basal plasma insulin concentration by improving insulin sensitivity as a result of decreasing endogenous and exogenous insulin requirements \(^{(189)}\).

The molecular structure of metformin gives it the necessary characteristics such as high guanidine polar unit and strong basicity for molecular imprinting \(^{(186)}\). Metformin (N,N-dimethylbiguanide) is also characterised by the non-polar nature of the methyl (CH\(_3\)) side chain. The two imine groups in the cis position acts as chelating agents enabling metformin to form highly coloured chelate complexes with platinium(II), copper(II), cobalt(II) and nickel(II) \(^{(192)}\).

Understanding and having the knowledge of interactions between molecules in their packing state have potentially lead to its application in designing new compounds with desired physical and chemical properties. The perfect configuration of molecules in a crystal, systematically enables highly predictable chemical and physical properties to be made which therefore give good reason for hard work at crystal engineering \(^{(1)}\). With respect to solid form design of Active Pharmaceutical Ingredients (API), systematically studying of interactions in molecular variants of metformin using Figure 5.2 as the primary molecular unit, might potentially be utilised to generate novel compounds with specific chemical and physical pharmacological properties. For this, understanding of crystal packing in particular packing motifs of the functional groups of metformin is desirable. Figure 5.1 shows the structure of metformin.
Figure 5.1 The Molecular structure of Metformin

\[ \text{H}_2\text{N} \text{N} \text{H} \text{N} \text{N} \text{CH}_3 \]

Figure 5.2 Schematic diagram of Primary molecular unit

\[ \text{H}_2\text{N} \text{N} \text{H} \text{O} \text{NH}_2 \]

Figure 5.3 Matrix of Structural Variants of the Primary Molecular Unit Studied

\[ \begin{align*}
\text{B I} & : \text{H}_2\text{N} \text{N} \text{H} \text{N} \text{N} \text{CH}_3 \\
\text{B II} & : \text{H}_2\text{N} \text{N} \text{H} \text{NH}_2 \\
\text{B III} & : \text{H}_2\text{N} \text{N} \text{H} \text{O} \text{NH}_2
\end{align*} \]

To systematically investigate potential packing motifs in this system, study of structural variants of metformin (Figure 5.3) is expected to lead to the understanding of dominate packing motifs available to these systems.

The molecular variants of the primary molecular unit (Figure 5.2) are shown in Figure 5.3. These structures are small units, exhibit restricted rotation and there is evidence of bond delocalisation within the structure \(^{(193)}\). Their rigid nature enables them bind specifically with molecular targets.
In the group of variants to be studied, there is systematic variation of hydrogen bond donor/acceptor units (e.g., N-H and O interchange in structures, that is, BII / BIII as shown in Figure 5.3) and N-akyl variants that potentially switch off the hydrogen donor/acceptor behaviour of primary amines (e.g., BI and BII as shown in Figure 5.3).

Figure 5.4  Simple crystal structures of B I determined with Cambridge Structural Database (CSD) refcodes

For reference, a subset of BI hits from the Cambridge Structure Database (ConQuest version 1.11) with their reference codes (refcodes) were identified (Figure 5.4). These were chosen for their close similarity with the primary molecular unit. (Figure 5.2). Preponderance of ionic and hydrated forms of the primary molecular unit as shown in Figure 5.2 clearly indicate that, such polar systems may well intervene in motif formation and hence these systems will be considered alongside the true polymorphic form.
5.1 Description of Packing Motifs

5.1.1 Closely related structures of BI

This subsection discusses the packing motifs of some structures of the subset of closely related structures of B I (Figure 5.3) hits from the Cambridge Structure Database (Conquest 1.11).

Figure 5.5 Diagram of C VIII [IS_Chemstep_Om (3-diaminomethyl-1,1-dimethyl-urea)] Structure

Details of how C VIII (Figure 5.5) was analysed by X-ray crystallography and the structure solution refinement have been reported in Chapter 2 of this study.

Figure 5.6 The X-ray structure of C VIII
Structural analysis confirmed the proposed formulation of the material. C VIII crystallises in space group of P2₁/c confirmed by successful refinement of molecule. The structure of the compound is shown in Figure 5.5 and Figure 5.6 with the numbering scheme adopted. C VIII is a conjugated system with delocalised π-electron clouds.

The molecule of C VIII is made up conjugated chain of nitrogen and carbon atoms as well as a carbon-oxygen double bond as shown in Figure 5.6. This asymmetric unit consists also of counter anions (Cl⁻) and a water molecule. The cation in this compound is 3-diaminomethyl-1,1-dimethyl-urea. The cation (3-diaminomethyl-1,1-dimethyl-urea) has normal geometrical parameters.

Single bonds linking the carbon and nitrogen atoms is confirmed by bond lengths of 1.463(4) Å between N(1) and C(1), C(2) and N(1) is 1.461(4) Å, and N(2) and C(3) is 1.421(4) Å which is consistent with the known preferred bond lengths for carbon-nitrogen bonds. There is electron delocalisation along N(4)-C(4) and C(4)-N(3) bonds. The relatively short C(3)-O(1) bond distance of 1.218(3) Å is consistent with a double bonded C=O unit (136).

The slightly twisting nature of the crystal is confirmed again by bond angles of 113.8(3)° for bond angle N(2)-C(3)-N(1), that for O(1)-C(3)-N(1) is 124.5(3)° and the bond angle for O(1)-C(3)-N(2) is 121.7(3)°. The bond angles between N(3)-C(4)-N(2) is 115.8(3)°, that between N(4)-C(4)-N(2) is 123.1(3)° and the angle for N(4)-C(4)-N(3) is 121.1(3)° (185), further confirming the lack of planarity in the structure.
Figure 5.7 Interactions during stacking of Compound C VIII viewed down the 
b-axis

Figure 5.7 shows a view of the crystal packing of C VIII showing chains linked 
through H……Cl and H……O interactions between molecules related by the 21-
screw axis. Figure 5.7 also indicates a view down the b-axis of the unit cell showing 
the 1D chain

Figure 5.8 A view down the a-axis of Compound C VIII showing crystal 
packing of compound VIII
Figure 5.9  A unit cell of Compound C VIII showing intermolecular aromatic interactions between molecules viewed down the c-axis

Figure 5.8 shows the crystal packing of C VIII viewed down the b-axis and a view down the c-axis (Figure 5.9) of the unit cell showing the non-bonded intermolecular aromatic interactions between molecules of C VIII.

Figure 5.10  A schematic view of the hydrogen bonding interaction involved during stacking of C VIII
Table 5.1 Hydrogen-bonding geometry for C VIII

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N4-H(3N)....O1W</td>
<td>1.027</td>
<td>1.837</td>
<td>174.77</td>
<td>2.862</td>
<td>O1W</td>
<td>[-x+1, -y+1, -z+1]</td>
</tr>
<tr>
<td>N3-H(1N).....Cl1</td>
<td>0.975</td>
<td>2.338</td>
<td>167.50</td>
<td>3.297</td>
<td>Cl1</td>
<td>[-x+1/2, y-1/2, -z+3/2]</td>
</tr>
<tr>
<td>N3-H(2N).....Cl1</td>
<td>0.831</td>
<td>2.413</td>
<td>163.97</td>
<td>3.220</td>
<td>Cl1</td>
<td></td>
</tr>
<tr>
<td>O1W-H(1OW)....Cl1</td>
<td>0.663</td>
<td>2.536</td>
<td>157.81</td>
<td>3.160</td>
<td>Cl1</td>
<td>[x-1/2, -y+3/2, z-1/2]</td>
</tr>
<tr>
<td>N4-H(4N).....O1</td>
<td>0.834</td>
<td>2.008</td>
<td>134.67</td>
<td>2.661</td>
<td>O1</td>
<td></td>
</tr>
<tr>
<td>N4-H(4N).....O1</td>
<td>0.834</td>
<td>2.335</td>
<td>133.27</td>
<td>2.969</td>
<td>O1</td>
<td>[-x+2, -y+1, -z+1]</td>
</tr>
</tbody>
</table>

The molecule of C VIII as shown in Figures 5.7, 5.8 and 5.9 exhibits stack packing with extensive network of hydrogen bonds. The crystal packing of C VIII is governed by an extensive three dimensional network of hydrogen bonding and Cl-O interactions. The crystal packing of C VIII consists of glide related molecules that are related by two-fold screw axis. These molecules are linked by non-bonded interactions involving intermolecular hydrogen bonding between the hydrogen atoms of the cations, water molecules and chloride anions as shown in Figure 5.8. The water molecules, cations (3-diaminomethyl-1,1-dimethyl-urea) and the Cl\textsuperscript{-} anions are linked together in the ratio 2:3:3 respectively.

The two cations (3-diaminomethyl-1,1-dimethyl-urea) are linked head-to-head by hydrogen bond interactions. Apart from the head-to-head hydrogen bond interactions, there exist intermolecular hydrogen bonding interactions laterally between the hydrogen atoms of the cations and water molecules and chloride anions. Water molecules play an important role by holding the chloride anions together as well as the cations as shown in Figure 5.8. Three types of hydrogen bonding are involved in this crystal packing. The water of hydration (hydrogen bond donor) is
symmetrically bonded to the chloride anions (hydrogen bond acceptor) with hydrogen acceptor distance (H…..A) of 2.536 Å of O(1W)-H(1OW)....Cl(1) with symmetry code [x-1/2, -y+3/2, z-1/2] as indicated in Table 5.1. The contact distance between the hydrogen atom and the chlorine atom as shown in Figure 5.8 indicates a strong possibility of an interaction between these atoms during packing. This is because the contact distances as indicated in Table 5.1 are approximately not more than the sum of their van der Waals radii which is 2.95 Å. (174, 175).

The N-H………O interaction has the hydrogen atom being the hydrogen bond donor whilst the oxygen atom is the hydrogen bond acceptor. This interaction has a hydrogen bond acceptor distance of 1.837 Å which is also less than the sum of their van der waals radii of 2.72 Å. (174, 175). Therefore it can be concluded that there is a strong possibility of genuine non-bonded hydrogen bond N-H……O interactions. The two hydrogen bond interactions involving N(4)-H(3N)....O(1W) and N(4)-H(4N)….O(1) have bond angles of 174.77° and 134.67° respectively as indicated in Table 5.1. The possibility of the hydrogen bond interaction N(4)-H(3N).....O(1W) being almost linear can not be ruled out as indicated in Table 5.1.

Another three laterally occuring hydrogen bond interaction linking the cations together involves N-H (hydrogen bond donor) and chlorine anion (hydrogen bond acceptor). The N(3)-H(1N).....Cl(1)( symmetry code of [ -x+1/2, y-1/2, -z+3/2 ]) , N(3)-H(2N).....Cl(1) and O(1W)-H(1OW)....Cl(1) (symmetry code of [ x-1/2, -y+3/2, z-1/2 ]) have bond angle of 167.50°, 163.97° and 157.81° respectively. Their respective hydrogen bond acceptor distances are 2.338 Å, 2.413 Å and 2.536 Å as shown in Table 5.1 are consistent with known preferred acceptor distance since
they are less than the sum of their van der waals raduii which is 2.95 Å. \(^{(174, 175)}\). These intermolecular head-to-head and lateral hydrogen bond interactions scheme result in the formation centrosymmetric dimers. These centrosymmetric dimers form layers which are then stacked together with the help of the water molecules and the chlorine anions. The layers are propagated along [001] as indicated in Figure 5.8 in the packing state. There is the possibility of face to face π-π interaction being exhibited by this crystal structure during its packing. There is complete overlap of the component species of C VIII with each other during the stack formation.

**Figure 5.11 Diagram of JAMRIY Structure**

![JAMRIY Diagram](image)

**Figure 5.12 A view down the ac-axis showing intermolecular hydrogen bond interactions in JAMRIY structure**
JAMRIY (Figure 5.11) has extensive intermolecular non-bonded hydrogen bonding linking the cations and anions together in the packing state (figures 5.12 and 5.13). This molecule is stabilised by N-H…Cl and N-H…N intermolecular hydrogen bonds. These intermolecular hydrogen bonds involves the hydrogen bond donor atom (N-H) of the cation and the hydrogen bond acceptor atom (Cl) of the anion or (N-C) of another cation. The chlorine anion is involved in five hydrogen bonds. The chlorine atom is sandwiched between layers of molecules along the b-axis. No intramolecular hydrogen bond of the type N-H…N exists resulting in good hypoglycaemic activity of the biguanide compounds \(^{(194)}\).
Figure 5.14 Diagram of PAJBUY Structure

![Diagram of PAJBUY Structure](image)

Figure 5.15 A view down the ab-axis showing intermolecular hydrogen bond interactions in PAJBUY structure

![View down the ab-axis showing intermolecular hydrogen bond interactions in PAJBUY structure](image)
Figure 5.16 The packing diagram of PAJBUY structure viewed along the $b$-axis

Both the intermolecular and intramolecular hydrogen bonds stabilize the crystal structure PAJBUY (Figure 5.14) as shown in Figures 5.15 and 5.16. Here the formation of hydrogen bonds exists between the biguanidium groups and the sulphate or oxalate anions as well as with water molecules. Some of the nitrogen atoms form strong double hydrogen bonds either with the carboxylate group of oxalate anion or with the sulphate groups. The N-H atoms interacts with the anions.

It can be deduced that the N-alkyl substitutents disturbed the interactions between the atoms as well as the packing configuration of these closely related structures of structure B I. There is less interactions between the molecules and their counter ions.
5.1.2 Closely related structures of BII

This subsection discusses the packing motifs of some structures of the subset of closely related structures of B II (Figures 5.3 and 5.17) hits from the Cambridge Structure Database (Conquest 1.11).

**Figure 5.17 Diagram of B II**

![Diagram of B II](image)

For reference, a subset of BII hits from the Cambridge Structure Database (ConQuest version 1.11) with their reference codes (refcodes) were identified (Figure 5.18). These were chosen for their close similarity with the primary molecular unit (Figure 5.2).
Figure 5.18 Simple crystal structures of B II determined with Cambridge Structural Database (CSD) refcodes

BDUDSM10

BGUHCL

BIGUAN

BDUBAS

BDUEN01

BGUDUSM10

BDUHCL

BIGUAN

Figure 5.19 Diagram of BDUDSM10 Structure
Figure 5.20  A view down the $ab$-axis showing intermolecular hydrogen bond interactions in BGDUSM10 structure

Figure 5.21  The packing diagram of BGDUSM10 structure viewed along the $a$-axis

Figures 5.19, 5.20 and 5.21 shows the BGDUSM10 structure and the extensive intermolecular non-bonded hydrogen bond interactions in the packing state. Two main types of hydrogen bonding occur in this structure. The hydrogen bonding interaction involves hydrogen bond donor atom (N-H) from the cation and the
hydrogen bond acceptor atom (O-S) from the anion forming a N-H…..O-S linkage. The water molecule also forms a hydrogen bond by interacting with the anion to form O-H……O-S hydrogen bond. This linkage involves a hydrogen bond donor atom (O-H) from the water molecule interacting with the hydrogen bond acceptor atom (O-S) of the anion. This compound is roughly planar as a result of intramolecular hydrogen bonding and delocalisation of π-electron density throughout the molecule \(^{196}\).

**Figure 5.22 Diagram of BGUHCL Structure**

![BGUHCL Structure](image)

**Figure 5.23 A view down the a-axis showing intermolecular hydrogen bond interactions in BGUHCL structure**

![Intermolecular Hydrogen Bond Interactions](image)
The BGUHCL (Figure 5.22) shows extensive intermolecular hydrogen bonding in the packing state as indicated in Figure 5.23 and 5.24. The non-bonded intermolecular hydrogen bonding in the structural unit in Figure 5.23 comprise mainly of N-H…Cl hydrogen bonds.

These interactions involve the hydrogen bond donor atoms (N-H) of the cation and the hydrogen bond acceptor counter anion (Cl). All the hydrogen atoms in the molecule are involved in close contact with Cl except one hydrogen atom (H) \(^{(197)}\).

**Figure 5.25 Diagram of BIGUAN Structure**

![BIGUAN Structure](image-url)
Figure 5.26  A view down the b-axis showing intermolecular hydrogen bond interactions in BIGUAN structure

Figure 5.27  The packing diagram of BIGUAN structure viewed along the b-axis

Biguanide is the name of the compound studied with reference code BIGUAN. Extensive intermolecular hydrogen bonding in this molecule involves N-H………N interaction. The molecules are linked head-to-head by two bifurcated hydrogen bonds and laterally by two hydrogen bonds. The hydrogen bond interaction involves hydrogen bond donor atom (N-H) of one molecule and hydrogen bond acceptor
atom (N) of another molecule. The intermolecular hydrogen bond interactions the molecules in chains parallel to (001). This molecule also has strong intramolecular hydrogen bonding resulting in constraining the roughly planar conformation \(^{(198)}\).

**Figure 5.28 Diagram of RAWBAS Structure**

![Diagram of RAWBAS Structure](image)

**Figure 5.29 A view down the \(a\)-axis showing intermolecular hydrogen bond interactions in RAWBAS structure**
Figure 5.30 The packing diagram of RAWBAS structure viewed along the $b$-axis

RAWBAS (Figure 5.28) has extensive non-bonded intermolecular hydrogen bonding interactions during packing as shown in Figures 5.29 and 5.30. The intermolecular hydrogen bonding links the cations and anions together in the packing state. The intermolecular hydrogen bonding linkage is of the form N-H……O-N and N-H……N=C. The N-H……O-N interaction involves the hydrogen bond donor atom (N-H) of the cation and the hydrogen bond acceptor atom (O-N) of the anion. With respect to the N-H……N=C interaction, the hydrogen bond donor atom (N-H) of one cation links to the hydrogen bond acceptor atom (N=C) of another cation. It can be noted also that every oxygen atom accepts at least one hydrogen bond (199).
Figure 5.31 Diagram of RAWBEW01 Structure

\[ \begin{align*}
\text{H}_2\text{N} & \quad \text{NH} \quad \text{HN} \\
\text{NH}_2^+ & \quad \text{NH}_2^+ \\
\text{O}_2\text{N} & \quad \text{NO}_2^- \\
\end{align*} \]

RAWBEW01

Figure 5.32 A view down the \textit{ab}-axis showing intermolecular hydrogen bond interactions in RAWBEW01 structure

Figure 5.33 The packing diagram of RAWBEW01 structure viewed along the \textit{cb}-axis
RAWBEW01\(^{(216)}\) as shown as Figure 5.31 has extensive intermolecular non-bonded hydrogen bond interactions during packing (Figures 5.32 and 5.33). A large proportion of the hydrogen atoms of the cations form hydrogen bonds by interacting with the oxygen atoms of the anions. The hydrogen bonding during packing is of the form N-H…..O-N and N-H…..N-N interactions.

This intermolecular interactions involves hydrogen bond donor atom (N-H) of the cation and the hydrogen bond acceptor atom (O-N) or (N-N) of the anion. The intermolecular hydrogen bonding interactions during packing of this structure results from electrostatic cation-anion interactions. Significant bond conjugation occurs in the dinitramide anion and the N-C bonds in the cations (Figure 5.49)\(^{(200)}\).

These closely related structures of Structure B II confirmed the potential formation of dimers when the molecules interact directly with each other. Also, the rigid nature of the structure is not disturbed during packing of the molecules.

### 5.1.3 Closely related structures of BIII

This subsection discusses the packing motifs of some structures of the subset of closely related structures of B III (Figures 5.3 and 5.34) hits from the Cambridge Structure Database (Conquest 1.11).

**Figure 5.34 Diagram of B III**

![Diagram of B III](image)
Figure 5.35  Simple crystal structures of B III determined with Cambridge Structural Database (CSD) refcodes

For reference, a subset of BIII hits from the Cambridge Structure Database (ConQuest version 1.11) with their reference codes (refcodes) were identified (Figure 5.35). These were chosen for their close similarity with the primary motif.
DAWDAH as shown in Figure 5.36 and 5.37 is a Guanylurea with a space group of C2/c and have eight formula units in a unit cell.

**Figure 5.38** A schematic view of the hydrogen bonding involved during packing of DAWDAH structure
The two dimensional hydrogen bonding network in the unit cell of DAWDAH as shown in Figures 5.36, 5.37 and 5.38 is made of anions and cations loosely embedded in it. This non-bonded intermolecular hydrogen bonding interactions involves N-H (hydrogen bond donor)……O=C (hydrogen bond acceptor) and N-H (hydrogen bond donor)…..N-C (hydrogen bond acceptor) contacts.

The cations are linked head-to-head by N-H (hydrogen bond donor)……O=C (hydrogen bond acceptor) and laterally with the anions by N-H (hydrogen bond donors)…..N-C (hydrogen bond acceptor) interactions. This building up forms a loosely packed quasi two dimensional network. Therefore the molecular ions form hydrogen bonds both within a chain and with adjacent chains running parallel as well as being stacked alternately in chains. This intermolecular non-bonded hydrogen bonds results in the formation of dimers as shown in Figure 5.38. Delocalisation of the double bond occurs over the involved guanyl backbone. The anions does not distruct the head-to-head linkage of the cations\(^{(193)}\).

**Figure 5.39 Diagram of DUNHID Structure**

![Diagram of DUNHID Structure](image-url)

Figures 5.40 and 5.41 show the extensive intermolecular hydrogen bonding interactions that exist in the DUNHID structure (Figure 5.39) during packing.
Figure 5.40 A view down the $b$-axis showing intermolecular hydrogen bond interactions in DUNHID

The cations are linked together by O-H (hydrogen bond donor)…..O-P (hydrogen bond acceptor) interactions whilst the cations links to the anions by N-H (hydrogen bond acceptor)……O-P (hydrogen bond acceptor) interactions (Figure 5.40 and 5.41). The phosphate groups involved in the molecule during stacking are joined by two O-H….O bonds in chains parallel to the x-axis. Two O-H…O and three N-H….O bonds are considerably straight whilst the three other N-H…..O bonds are bent. There is constraining on the intramolecular hydrogen bond formed by N-H……O as a result of the ring formation. The packing conformation of DUNHID is made-up of chains consisting of alternate cations linked together by anions. Therefore the cation-cation direct interaction is destructed by the presence of the anions ($^{201}$).

Figure 5.41 The packing diagram of DUNHID structure viewed along the $c$-axis
Figure 5.42 Diagram of GADQAE Structure

Figure 5.43 A view down the $b$-axis showing intermolecular hydrogen bond interactions in GADQAE structure

Figure 5.44 The packing diagram of GADQAE structure viewed along the $b$-axis
GADQAE (Figure 5.42) has closely related packing arrangement as DUNHID (Figure 5.39), but it has a water molecule in addition to substituting one of the oxygen atoms in DUNHID with a methyl group. The water molecule is involved in the intermolecular interactions but the methyl group substituent is not involved in the interactions.

GADQAE in the packing state (Figures 5.43 and 5.44) exhibits three dimensional intermolecular non-bonded hydrogen bonding. The cations and anions are linked together by a bifurcated hydrogen bonding and another hydrogen bond. The bifurcated hydrogen bond involves the two hydrogen bond donor atoms (N-H) of the cations interacting with the hydrogen bond acceptor atoms (O-Pi) of the anions forming a N-H......O-Pi bond. There is another hydrogen bond interaction (N-H......O-Pi) involving one cation hydrogen bond donor atom (N-H) and a hydrogen bond acceptor atom (O-Pi) of the anion.

The water molecule takes part in the interactions by hydrogen bonding to the oxygen atom of the anion. This hydrogen bonding involves the hydrogen bond donor atom (O-H) of the water molecule and the hydrogen bond acceptor atom (O-Pi) of the anion forming a O-H......O-Pi bond. The intermolecular Pi-O(1)...H(3A)-N hydrogen bonds strongly links the cations in chains resulting in the formation of a head-to-tail linkage. Strong intramolecular N-H...O hydrogen bonding also results in the closer of the six membered ring.(Figures 5.43 and 5.44). The hydrogen donor atoms (N-H) and the hydrogen bond acceptor atom (C=O) only interacts with the anions and therefore there is no direct linkage between the cations.
The water molecules only interact with the anion and does not come into contact with the cation\(^{(202)}\).

**Figure 5.45 Diagram of EKIBAB Structure**

![Diagram of EKIBAB Structure](image)

**Figure 5.46 A view down the c-axis showing intermolecular hydrogen bond interactions in EKIBAB structure**

![A view down the c-axis showing intermolecular hydrogen bond interactions in EKIBAB structure](image)

**Figure 5.47 The packing diagram of EKIBAB structure viewed along the b-axis**

![The packing diagram of EKIBAB structure viewed along the b-axis](image)
The EKIBAB structure exhibits extensive hydrogen bonding in the packing state (Figures 5.46 and 5.47). Two dimensional intermolecular hydrogen bonding links the cations and the anions together in the packing state. The hydrogen bonding linkage involves hydrogen bond donor atom (H) of the cations interacting with hydrogen bond acceptors atom (O) of the anions to form a N-H.....O-Se hydrogen bond. These interactions results in the formation of dimers. There is the existence of a non-linear intramolecular hydrogen bond (N₃-H₅...O₄).

Pseudo-π-π-stacking interactions exist between adjacent guanylurea moieties. This results in the coherence of the layers. Van der waals forces tend to control the bonding between the double sheets which stack normal to (011). Significant delocalization of electrons occurs over the non H-atom skeleton as indicated in Figure 5.21. The rigid structure of the cation is not affected by the presence of the anion linking the cations together. The hydrogen bond donor atom (N-H) interacts with the anions and the hydrogen bond acceptor atom (C=O) of another close contact cation (203).

**Figure 5.48 Diagram of KAGLUA Structure**

![Diagram of KAGLUA Structure](image)
Figure 5.49  A view down the $a$-axis showing intermolecular hydrogen bond interactions in KAGLUA structure

Figure 5.50  The packing diagram of KAGLUA structure viewed along the $c$-axis

Figures 5.49 and 5.50 show extensive intermolecular non-bonded hydrogen bonding existing in this structure (1-Carbamoylguanidinium).
Non-bonded intermolecular two dimensional hydrogen bonding involves the hydrogen atom (donor atom) of the cations bonding to chloride ion hydrogen bond acceptor of the anion like N-H......Cl. Bifurcated hydrogen bonding links the cations to the anions.

There is also intermolecular hydrogen bonding in the form of O-H......O. The O-H (hydrogen bond donor) of the anion links with the O=C (hydrogen bond acceptor) of the cation. There is also pseudo-\(\pi-\pi\) –stacking interactions involving pairs of 1-carbamoylguanidinium which are parallel to each other. The hydrogen bond donor atom (N-H) and acceptor atom (C=O) interacts only with anions in the packing state. There is therefore no direct contact between the cations\(^{204}\).

**Figure 5.51 Diagram of TAKZOV Structure**

![Diagram of TAKZOV Structure](image)

The packing conformation of the TAKZOV (Figures 5.52 and 5.53) structure is closely related to the packing arrangement exhibited by KAGLUA in Figures 5.49 and 5.50. The only difference is the substitution of Co atom with Mn\(^{2-}\) atom.
Figure 5.52  A view down the c-axis showing intermolecular hydrogen bond interactions in TAKZOV structure

Figure 5.53  The packing diagram of TAKZOV structure viewed along the a-axis
Extensive hydrogen bonding network exist in this compound. Three dimensional non-bonded intermolecular hydrogen bonding links the cations and anions together. The intermolecular interaction between the cations and anions involves the hydrogen bond donor atom (N-H) of the cation and the hydrogen bond acceptor atom (O-H, Cl- Mn$^{2+}$) of the anion forming a N-H……O-H and N-H……Cl-Mn$^{2+}$ interaction. There is also a lateral linkage between the cations and the anions through interaction between hydrogen bond donor atom (O-H) of the anion and the hydrogen bond acceptor atom (O=C) of the cation forming a O-H……O=C bond. This compound has a flattened trans-octahedral coordination made up of two oxygen molecules from water and four chloride ions. The hydrogen bond donor atom (N-H) and acceptor atom (C=O) of the cation interacts with corresponding atoms of the anions. There is no contact directly between the cations.$^{205}$

**Figure 5.54 Diagram of MECSOD Structure**

MECSOD as shown in Figures 5.54, 5.55 and 5.56 has three dimensional hydrogen bonding. There are two bifurcated non-bonded intermolecular hydrogen bonds. The cations and anions are linked together by N-H……Cl-Zn and N-H……O=C interactions.
Figure 5.55  A view down the \( ac \)-axis showing intermolecular hydrogen bond interactions in MECSOD structure

![Diagram showing intermolecular hydrogen bonds in MECSOD structure.]

Figure 5.56  The packing diagram of MECSOD structure viewed along the \( a \)-axis

![Diagram showing packing of MECSOD structure.]

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These hydrogen bond linkage involves hydrogen bond donor (N-H) and hydrogen bond acceptors (O=C) and (Cl-Zn). All the seven hydrogen atoms in the structure (cation) are involved in the intermolecular hydrogen bonding. Hydrogen bonding plays an important role in stabilising the structure. Therefore there is an intermolecular template-to-template linkage as well as intramolecular N$_1$-H$_3$…O$_5$ interaction. There is no direct contact between the cations and the rigid structure of the cation is not affected in the packing state$^{(206)}$.

**Figure 5.57 Diagram of JODZOR Structure**

![Diagram of JODZOR Structure](image)

**Figure 5.58 A view down the c-axis showing intermolecular hydrogen bond interactions in JODZOR structure**
Three dimensional intermolecular non-bonded hydrogen bonding exists in the packing state of the JODZOR structure. Two independent guanylurea chains as indicated in Figure 5.57, 5.58 and 5.59 are linked head-to-tail by hydrogen bonds and also laterally being hydrogen bonded to $\text{Cl}^-$ anions and water molecules.

The hydrogen bond donor atoms (N-H) of the cations interacts with the hydrogen bond acceptor atoms (O-H), ($\text{O}=$C) and cations ($\text{Cl}^-$). The hydrogen bond interactions that occur are N-H.....O-H, N-H.....O= C and N-H......Cl. These interactions are mainly responsible for stabilising the compound in the packing state.

There is a $\pi$-electron delocalisation and this contributes to a strong intramolecular N(3)-H...O(1) hydrogen bonding. The free water molecule in this compound is directly involved in the interactions and plays an important role in the linkage of the cations to the anion ($\text{Cl}^-$) when compared to the bound water molecule of KAGLUA and TAKZOV which does not take part directly in linking the cations to the anions (207).
The closely related structures of structure B III maintained their rigid structure even in the packing state irrespective of the presence of an anion. Non-bonded intermolecular hydrogen bonding interactions can be said to play an important role in all the functional units studied by being involved intramolecularly as well as intermolecularly during packing of the molecules. These non-bonded hydrogen bonds, considering the structures studied, can be said to play a very important role mostly by determining and stabilising the conformation of the crystal packing of compounds.

Almost all the studied structure irrespective of their counter ions exhibited N-H….O or N-H……Cl non-bonded intra or intermolecular interactions during packing. The counter ions in all the compounds studied were responsible for the different packing conformation exhibited by the compounds. The molecules also maintained their rigid structure in the packing state irrespective of the presence of a counter ion or not. Their ability to maintain their original structure makes them suitable candidates as API’s because there is the possibility of them binding with specific molecular targets.

The free water molecules directly interact with both the cations and anions and therefore play an important role in the packing state of the compound. There is the possibility of potential formation of dimers when the molecules of these structures interact directly with each other. Blocking the hydrogen bond donor atoms with methyl substituents potentially has an effect on the packing of the molecules. This is because fewer interactions occur between the cations, anions, cation and anion.