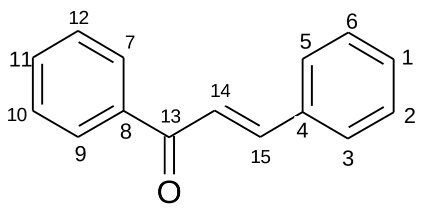
Structural studies of organic crystals of pharmaceutical relevance. Correlation of crystal structure analysis with recognised non-bonded structural motifs in the organic solid state

3.0 CHALCONES

Chalcones are natural products found in various plant species [(122)] with the general formular Ar-CH=CH-CO-Ar. The two aromatic rings in chalcones are joined by an α, β-unsaturated carbonyl system (Figure 3.1).

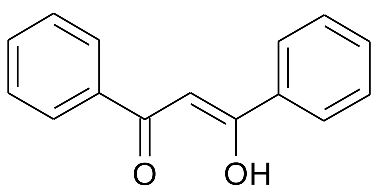
Each features –CH=CH-CO- and it is this unit that dominates the activity of these compounds. The delocalised nature of this unit gives the compound non-linear optical properties [(9)]. Chalcones belongs to an important group of natural compounds with diverse biological activities [(123)].

Figure 3.1 The Structure of Chalcones showing the numbering scheme adopted



(9)

Figure 3.2 The Structure of Hydroxylated Chalcone



(128)

They are open chain flavonoids [(125)] with very good crystallizability [(8)].

Chalcones are also very important intermediates during the synthesis of many pharmaceuticals such as flavonoids and occur in the hydroxylated form as indicated in Figure 3.2 [128, 129, 130, 127]. Chalcones are generally synthesized with the Claisen-Schmidt condensation between appropriately substituted acetophenone and benzaldehyde units. The reaction is catalysed by both base and acid under homogenous conditions [128].

Chalcones have a wide range of biological activities [132, 119] and some potential uses are anti-bacterial [133], anti-inflammatory [134, 135, 168], antimalarial [137], antiprotozoal [138], immunodulatory [139], inhibition of nitric oxide [140], tyronase inhibition [141], cytotoxic [142] and their anticancer activities [143, 144, 145, 146, 147] like antimutagenic and antimitotic.

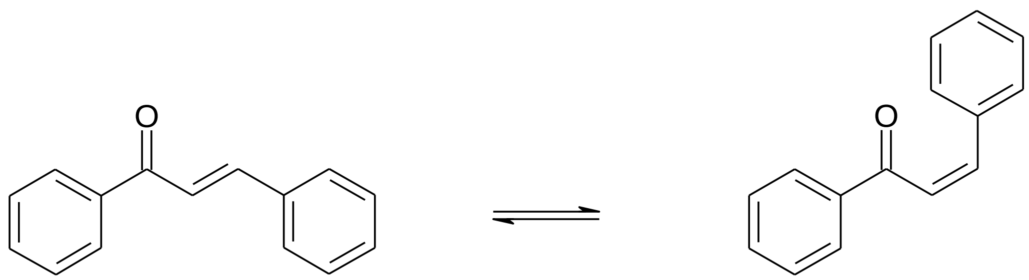
Other activities exhibited by chalcones are antiulcerative and hepatoprotective activities [148]. They can also be used as depigmenting agents [149, 150]. Those chalcones having hydroxyl groups bonded to carbon atom at position 2 are known to be very effective against infections caused by strains of methicillin-resistant *Staphylococcus aureus* [151].

Chalcones have antiviral (including anti-HIV), gastro protective, analgesic properties but this depends on the character and position of substituents on their aromatic ring. [152]. Their ability to exhibit intermolecular interactions during the formation of complexes with biomacromolecules depends on the electronic distribution around the molecule [148].

Their anticancer activity is due to their ability to inhibit angiogenesis [153], induction of mitochondria uncoupling and membrane collapse [154], interference with p53-MDM2 interaction [155, 156] and the disruption of the cell cycle [157, 158, 159, 12, 13 and 162].

The reactive enone moiety is responsible for the antimitotic activity of the chalcones. This enone activity tends to interact with the thiol residue which occurs at the colchicine binding site on tubulin causing the inhibition of tubulin polymerisation and also the disruption of mitosis [163, 113, 12, 13].

Figure 3.3 Diagram showing both the E and Z forms of Chalcones



E-form *Z*-form

Studies have shown that in solution, the double bond between C(14)-C(15) as indicated in Figure 3.1, becomes susceptible to photoisomerism resulting in a mixture of Z and E isomers. The rate of the isomerisation and the equilibrium ratio depends on a number of functions including the aromatic ring substituents and the solvent. The E and the Z forms can profoundly influence the activity of species.

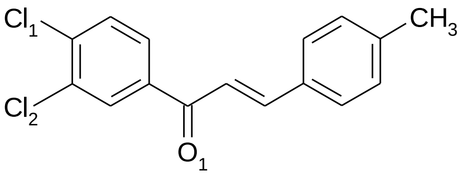
While E and Z mixtures exist in solution, the E-form invariably results on crystallization. A search of the Cambridge Structural Data Base (CSD) using the chalcone backbone (Figure 3.1) as the search structure yielded in excess of 900 hits. Of these hits, 201 were based purely on the backbone (without metal complexes, phenyl substituents and cyclic systems). It was observed that only 8 out of the 201 chalcone structures were in the Z-conformation.

It is commonly held that re-crystallisation of an E, Z-mixture in solution will yield only the E-isomer in the solid state. The degree of isomerisation is strongly influenced by the chelating and the electron donating properties of the aromatic ring substituents especially when the substitution is at position “9” (as shown in Figure 3.1) for specific compounds [(165)].

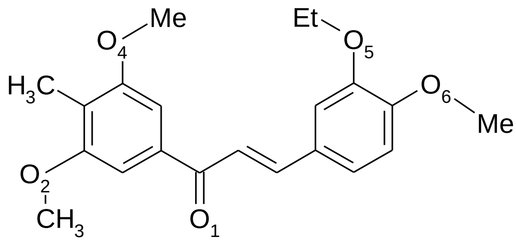
Therefore a systematical studying of the crystal packing in these systems will be informative and may potentially lead to an understanding of control of E-, Z-isomerisation in these systems and more consistency in their efficacy as Active Pharmaceutical Ingredients.

The availability of a set of closely related compounds in the crystal form (Figure 3.4) facilitated this study. The compounds were synthesized by Dr Phil Perry and Prof. T. C. Venkins as part of a wide program screening these compounds as antitumor agents.

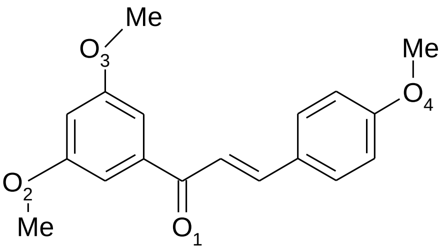
Figure 3.4 Studied Chalcones



C I

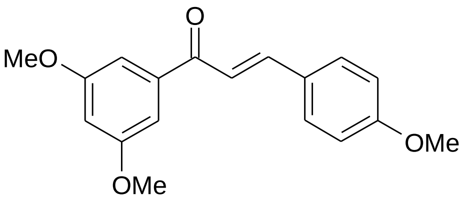


C II

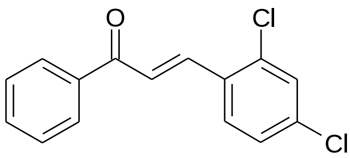


C III

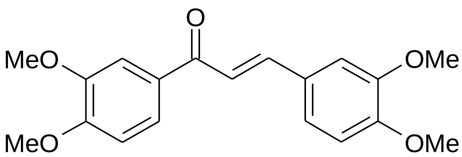
Figure 3.5 Chalones with simple crystal structures determined with Cambridge Structural Database (CSD) refcodes



CICMEH [166]



KERCUG [168]



CICSEN [167]

For reference, a subset of the chalcones hits from the Cambridge Structure Database with their reference codes (refcodes) were identified (Figure 3.5). Shea-Lin Ng *et al*

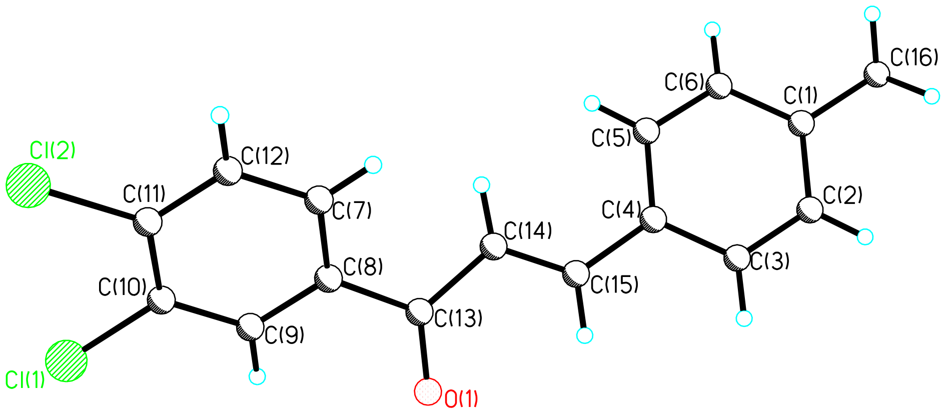
(CICMEH) [166], Phukan M *et al* (KERCUG) [168] and Teh *et al* (CICSEN) [167] were identified from the Cambridge Structural Database (ConQuest version 1.11). These were chosen for their close similarity with the compounds studied.

Details of how the chalcone crystals were analysed by *X*-ray crystallography and their structure solution refinement have been reported in Chapter 2 of this study. This section provides a general description of the crystals as well as wider discussions on intermolecular bonding and packing behaviour of the compounds.

3.1 Description of Selected Crystals

3.1.1 Compound C I

Figure 3.6 The *X*-ray Structure of C I showing the numbering scheme adopted



The structural analysis confirmed the proposed formulation of the material. C I crystallises in space group of $P2_1/c$ confirmed by successful refinement. The asymmetric unit comprises a single molecule of (E)-1- (3,4-Dichloro-phenyl)-3-p-tolyl-propenone (C I). The structure of the compound is shown in Figure 3.6 with the numbering scheme adopted.

C I comprises two phenyl rings linked by an enone unit and the structure shows phenyl ring adjacent to the carbonyl of the enone is 3,4-disubstituted with chlorine. Selected bond lengths and angles are given in Tables 3.3 and 3.4.

The relatively short carbon-carbon distance between C(14) and C(15) alongside the relatively long C(13)-C(14) distances respectively 1.326(3) Å and 1.469(3) Å, is consistent with a localised double bond in the enone unit in this structure.

The localised π-bonding is further exemplified by the short C(13)=O distance (168). Structure shows C1 adopts the (E)-configuration in the solid state. This is very similar to other chalcones in particular KERCUG (168). The only difference between the studied structure and that of KERCUG's is the presence of hydrogen atom between the two chlorine atoms in KERCUG structure.

The structure is twisted by a torsion angle 12.04(3)° at the C(13)-C(14) single bond. Little Bond delocalisation is therefore apparent in the enone unit. This twisting is replicated in KERCUG, where the two molecules in the asymmetric unit show comparable torsions of 14.6° and 10.1° (168).

Bond lengths and angles in the phenyl units are remarkable (160). The non-coplanar conformation illustrated by the two benzene rings agrees with a similar structure studied by Phukan *et al* (168). The relatively bond length of 1.726(2) Å and 1.727(2)

Å. for C(10)-Cl(1) and C(11)-Cl(2) respectively, is consistent with a C-Cl bond [160].

The conjugation resulting from the overlapping of the 3p-orbital of chlorine and the 2p-orbital of the aromatic carbon adds to the π-conjugated aromatic system [169]. This results in the chlorine atoms impacting a positive resonance effect on the system [170]. The ortho and meta substituted chloride ions might therefore increase the therapeutic effectiveness of the chalcone by causing an increase in electron delocalisation.

This is because the therapeutic effectiveness of chalcones depends on the degree of delocalised electron system [171] and this electron delocalisation possibly has an effect on the enone unit.

Figure 3.7 The packing diagram of C I viewed down the *a*-axis

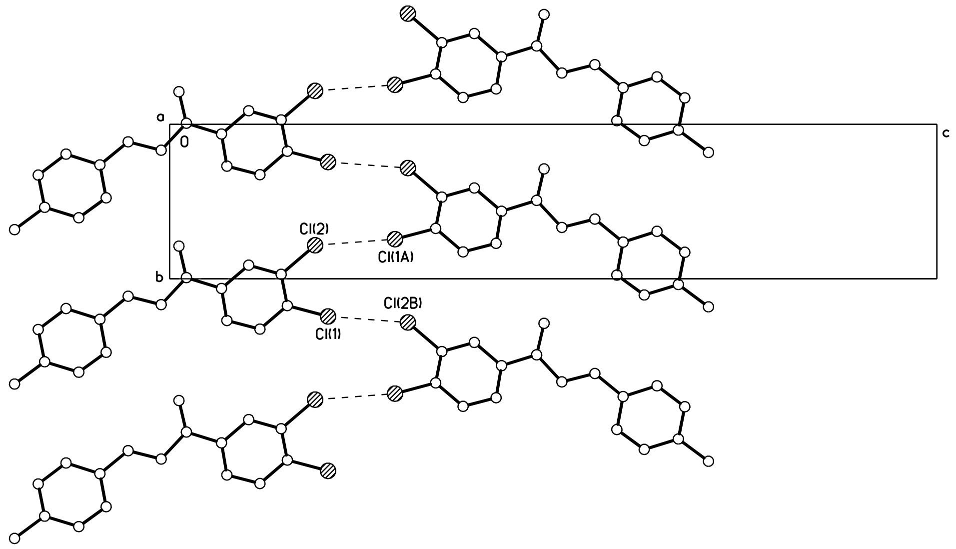


Figure 3.7 shows a view of the crystal packing of C I showing chains linked through Cl…Cl interactions between molecules related by the 2_1-screw axis.

Figure 3.7 also indicates a view down the *a*-axis of the unit cell showing the 1D chain propagating parallel to the *b*-axis[Cl(1a): –*x*, ½+*y*, ½-*z*; Cl(2b): –*x*, -½+*y*, ½-*z*]

Figure 3.8 A view down the *b*-axis showing the alternating stacking of chains in the crystal.

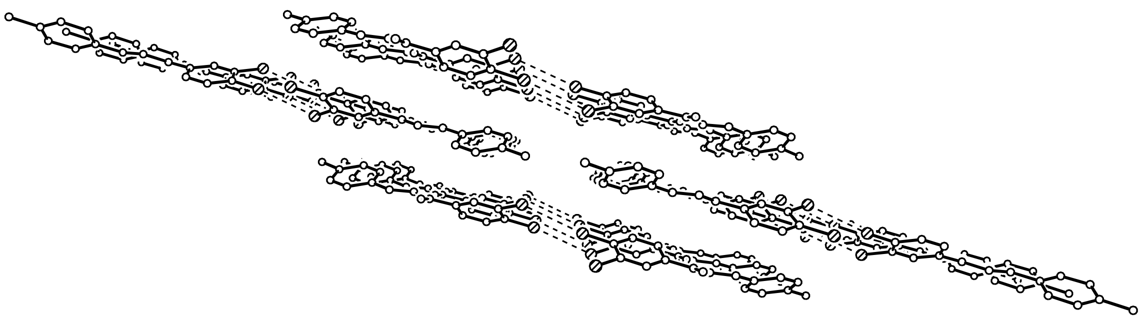


Figure 3.8 shows a perspective view down the *b*-axis showing the alternating stacking of chains in the crystal.

Figure 3.9 Crystal packing diagram of C I viewed down the *a*-axis

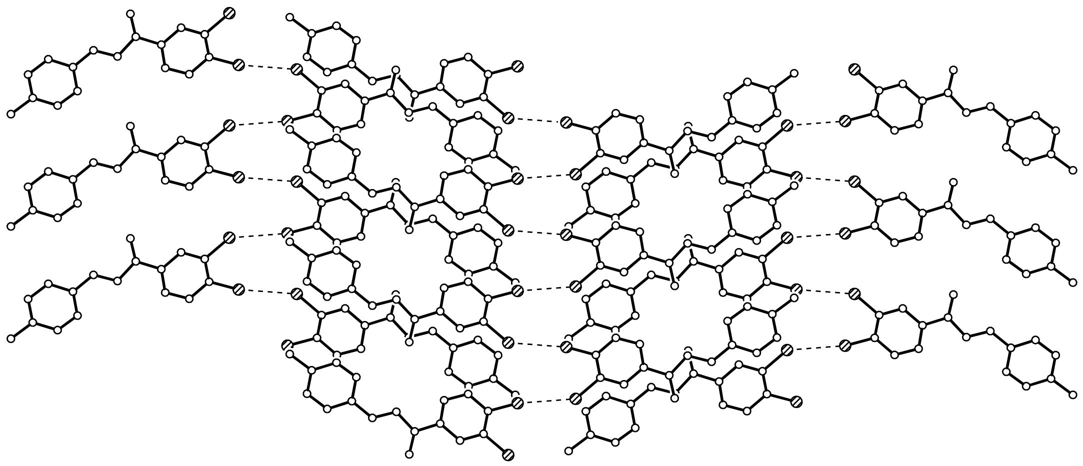


Figure 3.10 A unit cell of C I showing long-range pseudo-herringbone aromatic interactions between molecules viewed down the *c*-axis

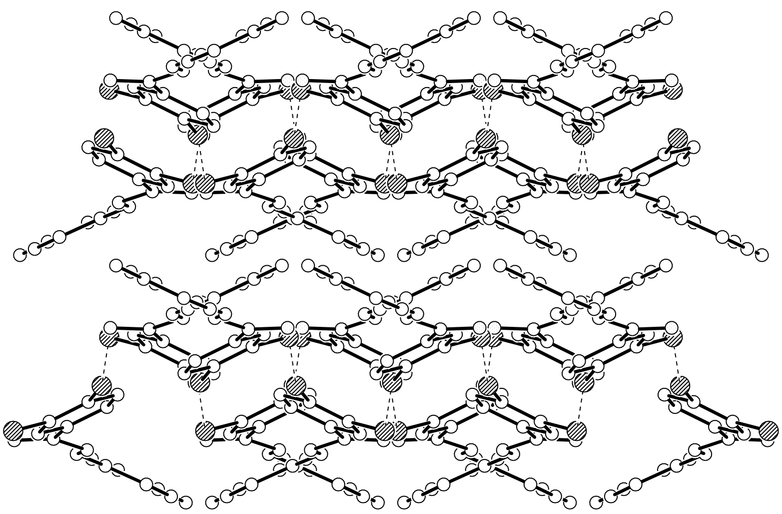


Figure 3.9 shows the crystal packing of C I viewed down the *a*-axis and a view down the *c*-axis (Figure 3.10) of the unit cell showing the long-range pseudo-herringbone aromatic interactions between molecules.

Figure 3.11 A schematic view of the chlorine-chlorine interaction involved during stacking of C I

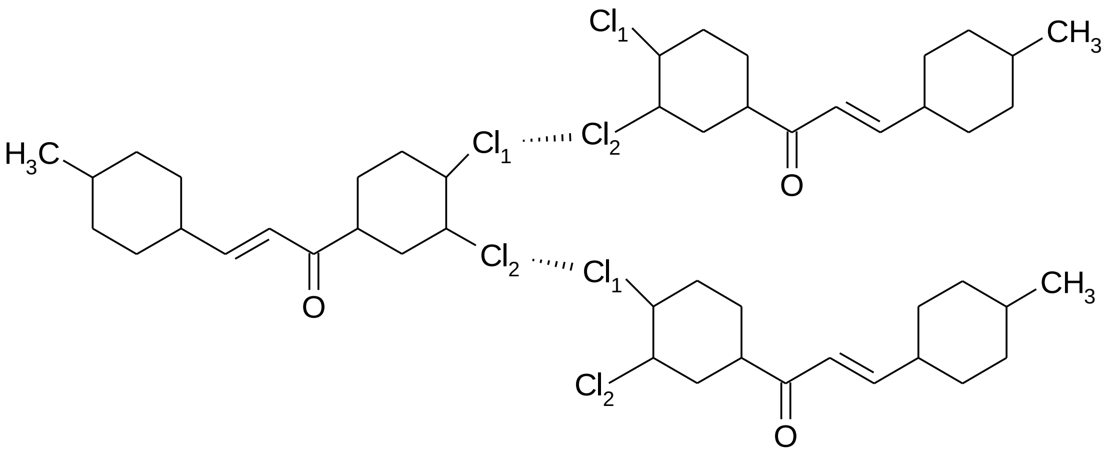


Figure 3.12 Schematic representation of the geometry of the Cl……Cl intermolecular interaction in C I

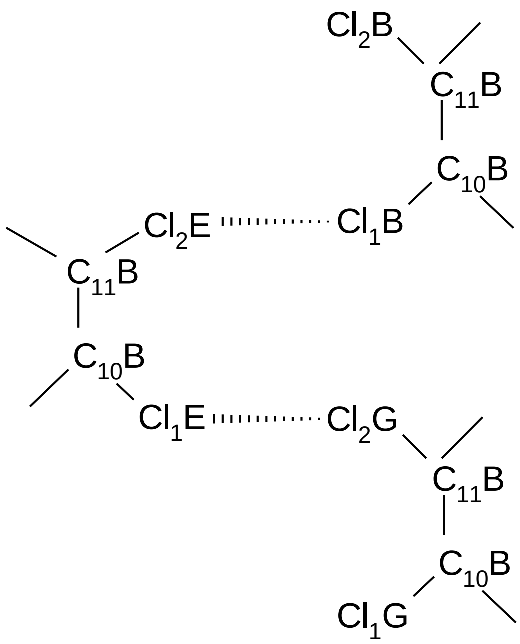


Figure 3.13 The packing diagram of KERCUG's structure viewed down the *a*-axis

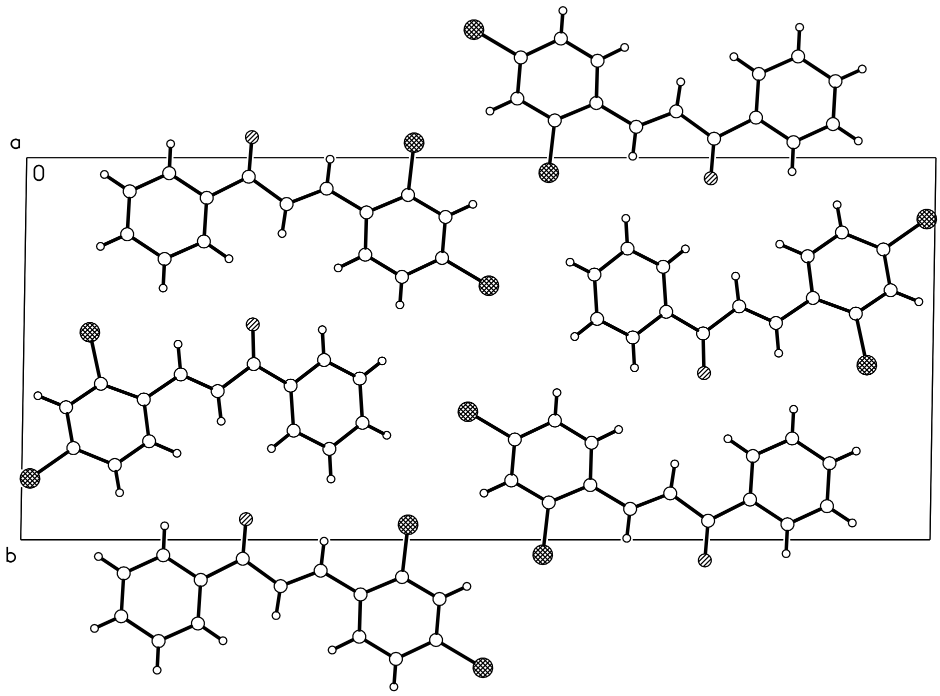
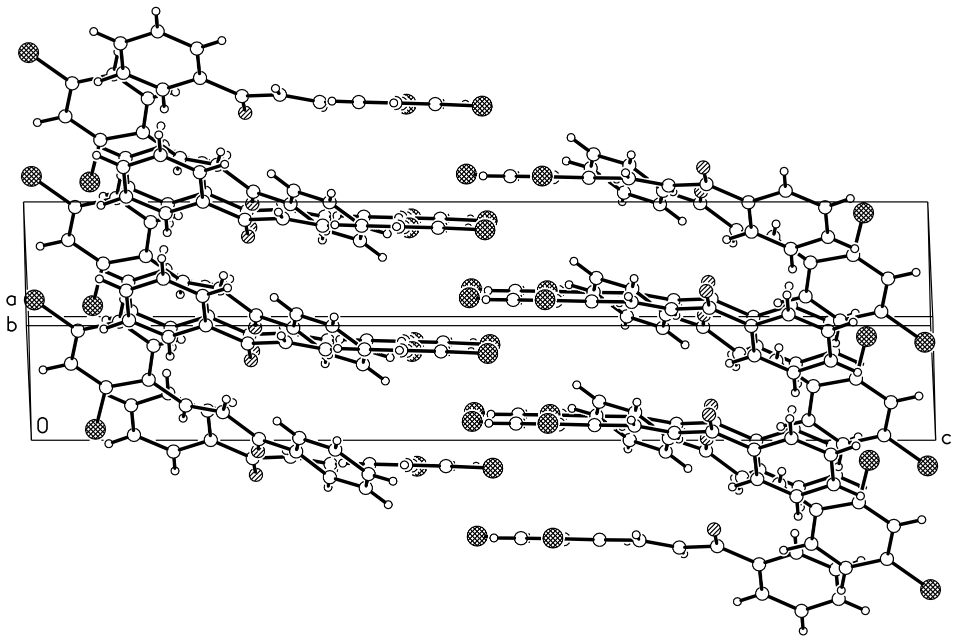


Figure 3.14 A unit cell of KERCUG's structure showing aromatic interactions between molecules viewed down the *a,b*-axis



C I consists of a molecular network of (E)-1- (3,4-Dichloro-phenyl)-3-p-tolyl-propenone and an extensive network of Cl ….Cl intermolecular links resulting in the formation of infinite zig-zag one-dimensional chains. The crystal packing of compound I is stabilised by Cl…….Cl intermolecular interactions.

Much work have been done on Cl…..Cl interactions and Awwadi F. F., *et al* (175) summarised using “ab” initio calculations and histogram distribution by concluding that the halogen-halogen interactions are directional and occurs as a result of attractive forces except F…..F interactions.

Figures 3.7, 3.8 and 3.9 shows the molecules of C I aligned edge-to-egde in zig-zag chains exhibiting alternate stacking of the crystal during packing with extensive network of intermolecular chloride-chloride interactions involving adjacent C-Cl bonds related by two-fold screw axis with a glide along b-axis. The molecules also exhibit long-range pseudo-herringbone aromatic interactions between molecules as shown in Figure 3.9.

There is the possibility of a C-Cl……Cl-C weak intermolecular interactions existing in compound I, because one of the chlorine atoms might behave like an incipient nucleophile and the other as an incipient electrophile (172).

Another school of thought argues that, for Cl……Cl interactions to exist, there should be reduced repulsion between the chlorine atoms and thus make the Cl….Cl contact closer in certain directions (173).

The ortho and meta substituted chlorine atoms participate in lateral interactions linking the molecules of C I together. The closest distance between Cl(2R) and Cl(1B) is 3.505 Å, that between Cl(1R) and Cl(2C) is 3.505 Å and that between Cl(1B) and Cl(2C) is 3.546 Å.

The contact distance between the chlorine atoms as shown in Figure 3.12 indicates a strong possibility of an interaction between these chlorine atoms during packing. This is because the contact distances are approximately the same and not more than the sum of the van der Waals radii for chlorine since the van der Waals radius for chlorine is 1.75 Å. [150, 8].

The bond angle of 167.1° between C(11)R-Cl(2R)-Cl(1B) as shown in Figure 3.10 satisfy the interaction angle maximum rule for Cl…….Cl interactions since the chlorines are attached to an sp2 hybridised carbon atom in an aromatic ring.

The Cl…..Cl interaction angle for C1(1R)-Cl(2R)-Cl(1B) which is "θ_1"should be $150° < \theta_1 < 180°$ for chlorine atoms attached to sp2 or sp3 hybridised aromatic or aliphatic carbon atoms. [232, 313]. This Cl….Cl contact distance of 3.505 Å and θ_1 being between 150° and 180° is consistent with the known geometry parameters preferred for Cl….Cl intermolecular interactions. Since both the chlorine contact distances and angles satisfy the school of thought for Cl…..Cl interactions to exist, it can therefore be concluded that, a strong possibility of a genuine non-bonded Cl……Cl intermolecular interaction exists in compound I during packing.

This Cl……Cl interaction is not replicated in KERCUG's structure.

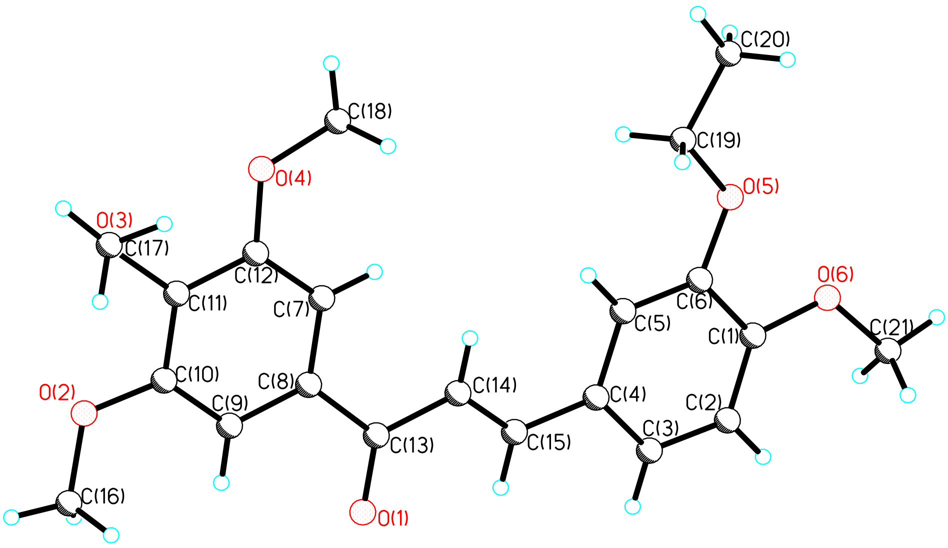
It might be due to KERCUG's structure having a hydrogen atom between the two adjacent chlorine atoms. The E-isomer conformation of chalcones is ideal for their effective stacking, but the presence of hydrogen atom between the adjacent chlorine atoms in KERCUG's structure affected the usual stacking conformation as shown by C I (Figure 3.8). They rather assumed an interwoven conformation as shown in Figure 3.14.

Therefore the crystal packing of compound I consist of molecules related by 2_1-screw axis as well as glide related molecules that are linked by interactions involving intermolecular chloride-chloride bonds along the b-axis as indicated in Figures 3.8 and 3.9. This intermolecular C–Cl….Cl-C egde-to-edge interactions scheme results in the formation noncentrosymmetric trimers. These trimers form layers which are then stacked together with the help of the Cl…..Cl interactions and these layers are propagated along [001] as indicated in Figure 3.8 in the packing state.

These chlorine-chlorine interactions might be a contributing factor for stabilising the stack conformation of compound I during packing. There is complete overlap of the component species of compound I with each other during the stack formation as indicated in Figure 3.7. According to Suezawa et al., 2001 [(126)], molecules closely related to Figure 3.6 are paired through a C-H… π interactions [(9)].

3.1.2. Compound C II

Figure 3.15 The *X*-ray Structure of C II showing the numbering scheme adopted



The successful refinement of the data collected for C II after structurally analysing the molecule, confirmed the proposed C II with space group P $\bar{1}$. This molecule crystallises with ethoxy and methoxy aromatic substituents.

The structural analysis confirmed the proposed formulation of the material. The structure of the compound is shown in Figure 3.15 with the numbering scheme adopted.

C II is a conjugated system with delocalised π-electron clouds. C II is made up of two aromatic rings and an enone fragment as shown in Figure 3.15. This asymmetric unit consists also of water molecules.

The aromatic ring adjacent to the carbonyl has 3,4,5-trisubstituted methoxy whilst the other phenyl ring has 4-monosubstituted methoxy and a 5-monosubstituted ethoxy. The (E)-3-(3-Ethoxy-4-methoxy-phenyl)-1-(3,4,5,-trimethoxy-phenyl)-propenone molecules have normal geometrical parameters.

Bond lengths of 1.326(3) Å and 1.251(2) Å establish long carbon-carbon distance and short carbon-oxygen distance respectively. These bond lengths establishing double bonds are consistent with a C=C and C=O units respectively.

The adoption of the (E)-configuration by the C II is usually preferred by chalcones in the solid state [(165)]. C II is closely related to other chalcones in particular CICSEN [(167)]. C II is twisted by torsion angle 7.39(3)° at the C(13) – C(14) single bond. Little bond delocalisation occurs in the enone unit. This twisting is simulated in CICSEN [(167)] whereby the asymmetric unit has torsion of 0.5°.

The two aromatic rings are out of plane with respect to the C(13)-C(14)-C(15)-O(1) enone unit. This is indicated by torsion angles of 1.21(3)° and 0.61(3)° for C(1) to C(6) and C(7) to C(12) respectively. The other two methoxy groups and the ethoxy group C(11)-C(10)-O(2)-C(16), C(11)-C(12)-O(4)-C(18) and C(6)-O(5)-C(19)-C(20) attached to the benzene rings are oriented diagonally with torsion angles of -174.24(2)°, -174.01(2)° and -179.53(1)° respectively.

Figure 3.16 The crystal packing diagram of C II viewed down the *a*-axis

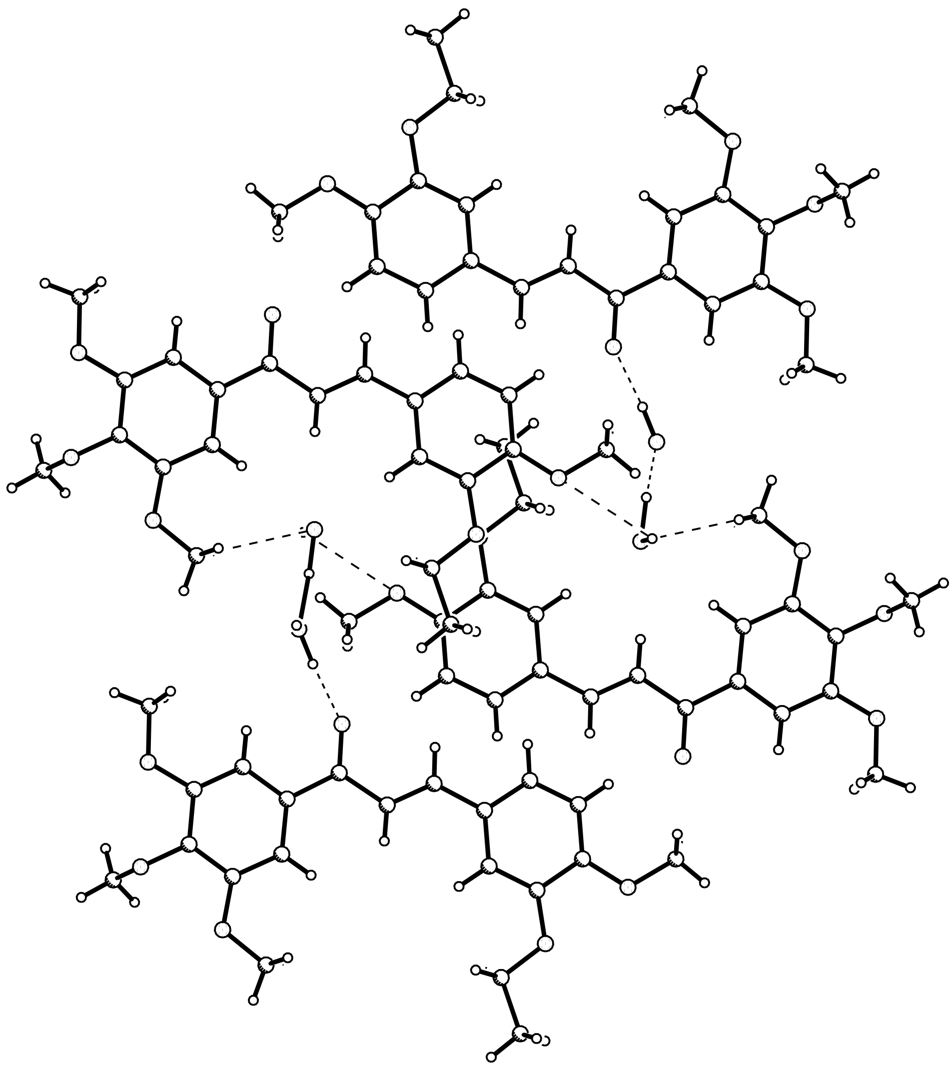


Figure 3.16 indicates a view of the crystal packing of C II showing chains linked through C-H…O, O-H…..O-H and C=O……..H interactions between molecules related by an inversion centre at the origin.

Figure 3.16 also indicates a view down the *a*-axis of the unit cell showing the 1D chain propagating parallel to the *b*-axis.[H(5), H(14), H(7), H(18) and H(1SA) have symmetry code of [–*x*, -*y*, -*z*]

Figure 3.17 A view down the *b*-axis showing stacking of chains in the crystal.

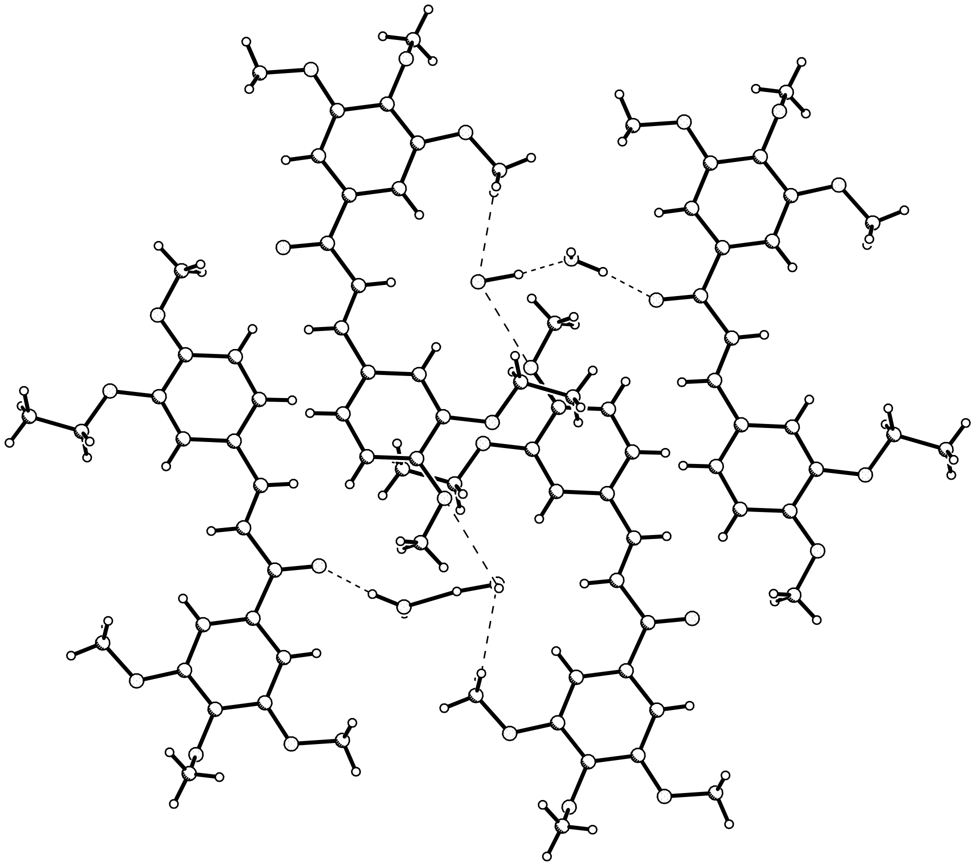


Figure 3.17 shows a perspective view down the *a*-axis showing stacking of chains in the crystal.

Figure 3.18 A unit cell of Compound C II showing aromatic stacking interactions between molecules viewed down the *b*-axis

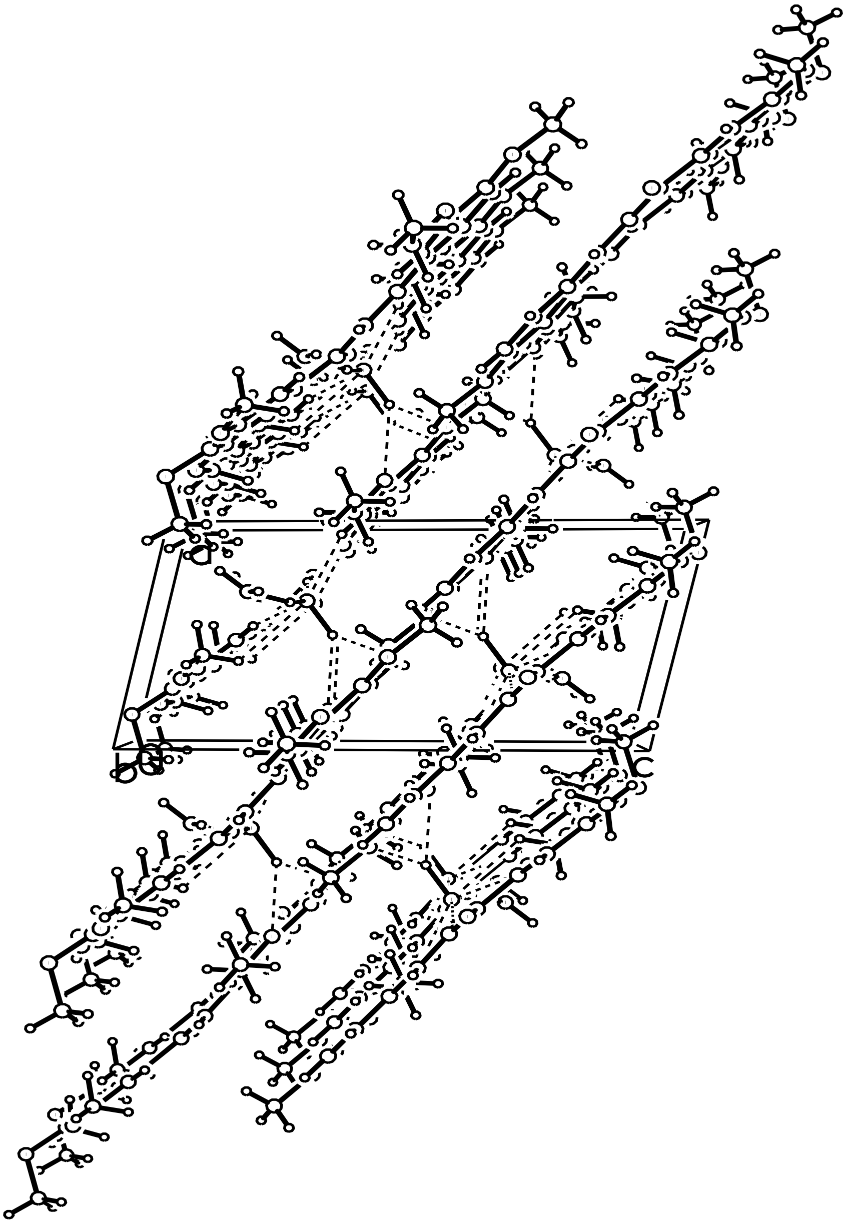


Figure 3.17 shows the sheet structure of C II viewed down the *c*-axis and a view down the *a*-axis (Figure 3.18) of the unit cell showing the aromatic stacking interactions between molecules.

Figure 3.19 A view of the intermolecular interactions involved during stacking of C II

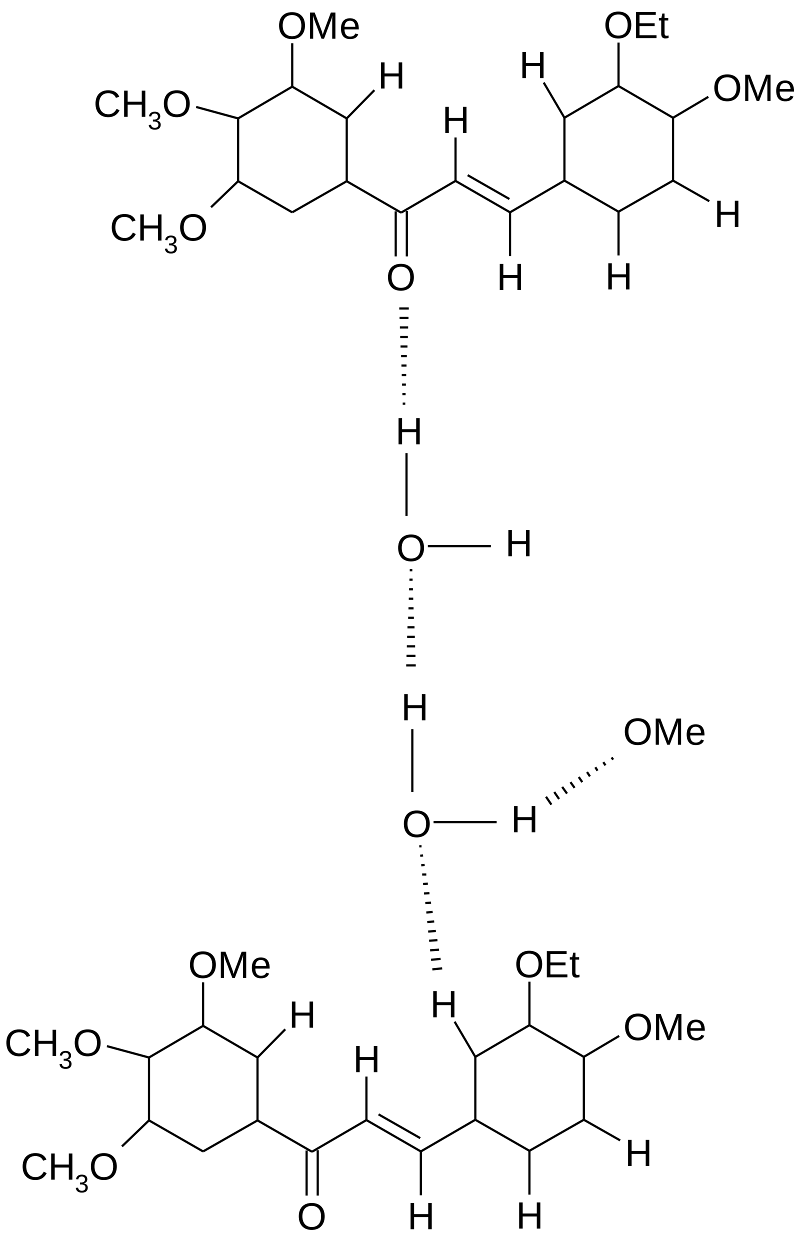


Figure 3.20 Schematic representation of the geometry of the C-H……O, O-H…..O=C and O-H….O intermolecular interactions in C II

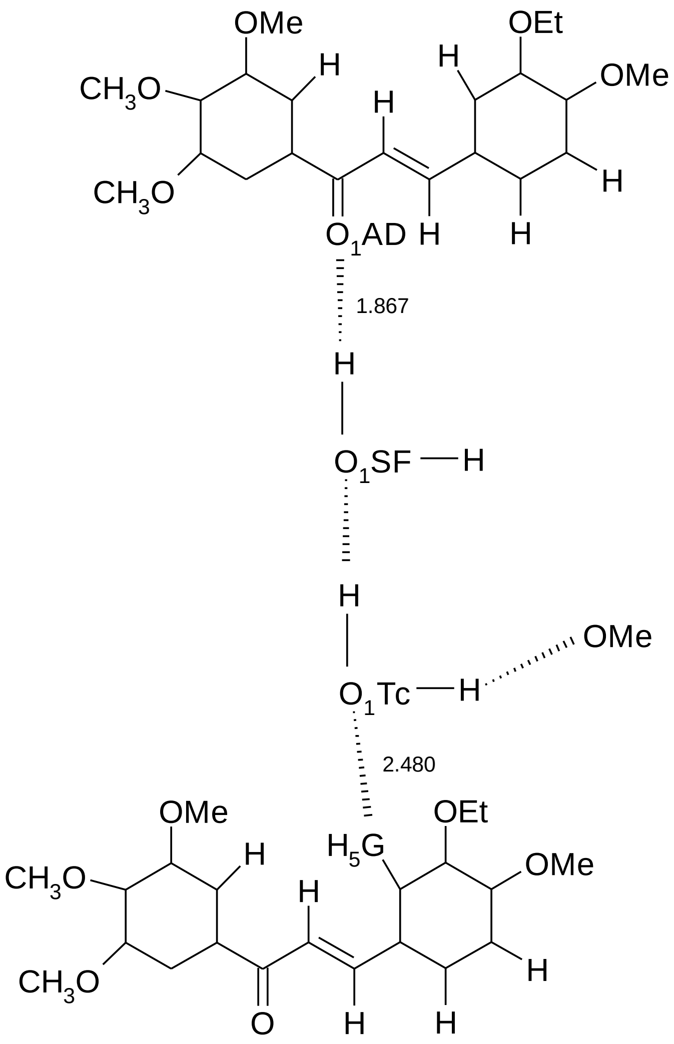


Table 3.1 Intermolecular interactions geometry for C II

D-H......A	d(D-H)	d(H..A)	<DHA	d(D..A)	A
C(5G)-H(5G)… O(1TC)	0.930	2.480	163.20	3.410	O1TC
O(1SF)-H(1SF)…O(1AD)	0.999	1.867	170.7	2.866	O1AD

Figure 3.21 The crystal packing diagram of CICSEN structure viewed down the *a*-axis

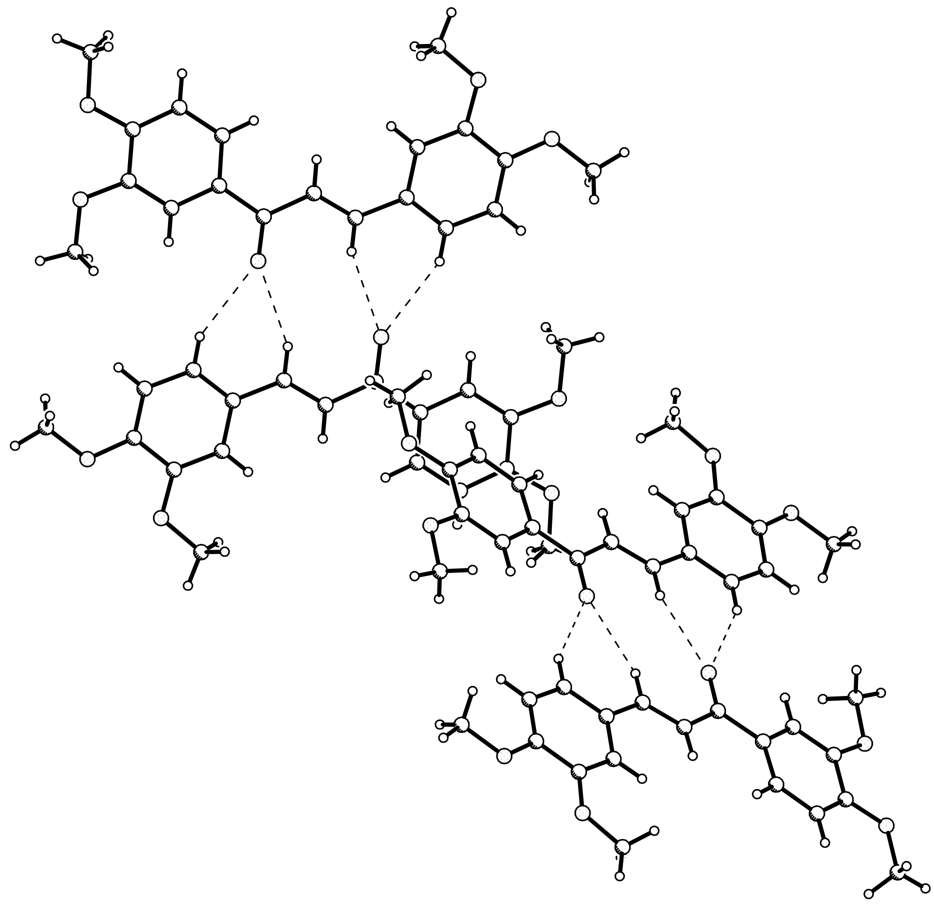
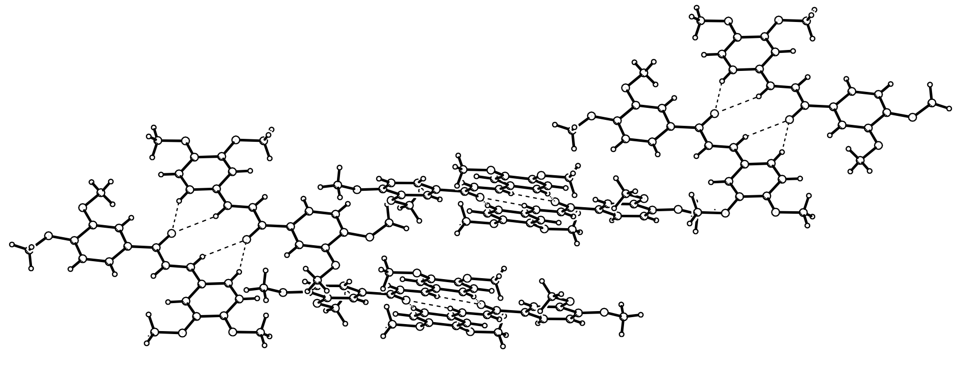


Figure 3.22 A diagram of CICSEN structure showing aromatic packing interactions between molecules viewed down the *a*-axis



Figures 3.16, 3.17, 3.18 and 3.19 show molecules of C II exhibiting stack packing with an extensive network of hydrogen bonding interactions. The crystal packing of C II is governed by a two dimensional network of hydrogen bonding.

The water molecules and (E)-3-(3-Ethoxy-4-methoxy-phenyl)-1-(3,4,5,-trimethoxy-phenyl)-propenone molecules are linked together head-to-head in the ratio 2:2 respectively.

C II consists of glide related molecules with an inversion centre at the origin that are linked by interactions involving intermolecular hydrogen bonding between the hydrogen atoms of (E)-3-(3-Ethoxy-4-methoxy-phenyl)-1-(3,4,5,-trimethoxy-phenyl)-propenone and water molecules as well as the carbonyl oxygen as indicated in Figures 3.20 and 3.21.

The molecule (E)-3-(3-Ethoxy-4-methoxy-phenyl)-1-(3,4,5,-trimethoxy-phenyl)-propenone is linked by hydrogen bonds involving two water molecules. Two types of hydrogen bonding are involved in this crystal packing. The first type of hydrogen bonding interaction involves two C-H…..O interactions (all hydrogen atoms coming from the same donor molecule) with the oxygen atom being the hydrogen bond acceptor molecule. The second type of hydrogen bond interaction occurs between the hydrogen atom of the water molecule acting as the hydrogen bond donor and carbonyl oxygen which becomes the hydrogen bond acceptor. There is also another O-H…..O-H hydrogen bond interaction where by, the O(1TC)-H acts as a donor molecule and the O(1SF)-H the acceptor molecule. The geometry of the hydrogen bonding interactions is indicated in Table 3.1.

There is a strong possibility of these hydrogen bond interactions occurring because the individual hydrogen bond distances are not more than the sum of their van der Waals radii which is 2.72 Å. Their individual hydrogen bond angles are consistent with the preferred known C-H……O hydrogen bond range of 86°-173° [1, 164]. The bond distance (d(D..A)) of 2.866 Å for the O-H.....O=C non-bonded hydrogen bond interaction is consistent with the preferred known hydrogen bond distance.

Comparatively, the crystal packing conformation of C II is very different to that of the CICSEN structure. The CICSEN structure formed centrosymmetric dimers as well as having non-bonded intermolecular bifurcated hydrogen bonds which is non-existence in the packing conformation of C II (Figures 3.22 and 3.23). This can be attributed to the presence of water molecules in addition to an extra methoxy group substituent in the studied structure.

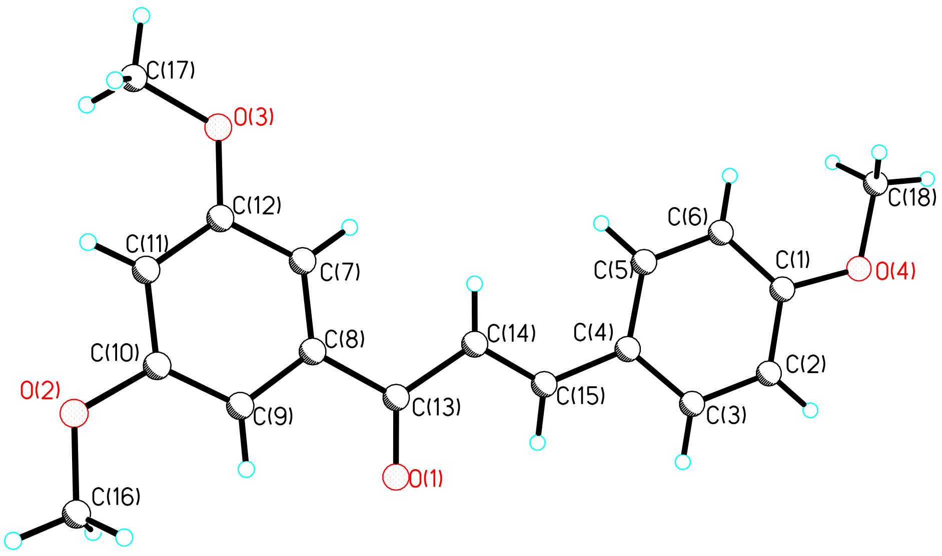
The intermolecular hydrogen bond interaction scheme in C II results in the formation noncentrosymmetric dimers. These dimers form layers which are then stacked together with the help of the two dimensional network of hydrogen bonding as well as the water molecules. These layers are propagated along [001] as indicated in Figures 3.17 and 3.18 in the packing state.

There is a possibility of intermolecular face to face stacking during packing in addition to intramolecular C-H…π interactions among the molecules [9] as indicated in Figure 3.15. According to the similar structure studied by Usman *et al* [151], there is the possibility of the existence of intramolecular C-H……O interactions.

The electron donating ethoxy and methoxy groups being attached to a π-system (aromatic ring) will increase the electron density of the system thereby causing positive resonance effect on the enone unit as well as the system. This might therefore increase the therapeutic effectiveness of the chalcone [171].

3.1.3 Compound C III

Figure 3.23 The X-ray structure of C I11



The structural analysis confirmed the proposed formulation of the material. C III crystallises in space group of $P2_1/c$ confirmed by successful refinement. The asymmetric unit is as shown in Figure 3.24 with the numbering scheme adopted.

This asymmetric molecule is a conjugated system with delocalised π-electron clouds. C III is made up of two aromatic rings linked by an enone fragment unit. The phenyl ring adjacent to the carbonyl is 4,5-disubstituted with methoxy and the other aromatic ring is 4-monosubstituted with methoxy as shown in Figure 3.24.

The relatively short carbon-oxygen distance of 1.215(7) Å between C(13)=O(1) of C III is consistent with a localised double bond in the enone unit.

C III adopts the (E)-configuration in the solid state. This (E)-configuration is consistent with the known preferred conformation of chalcones [165]. This is closely related in particular to CICMEH [166] and to other chalcones such as Allen F. H [176] and Wafo Pascal et al [149].

C III is twisted by torsion angle 1.42(1)° at the C(14)-C(15) single bond. Therefore it is apparent that little bond delocalisation occurs in the enone unit. CICMEH's structure replicates this twisting, where the asymmetric unit show torsion of 9.0°.

The bond lengths and angles in C III aromatic rings are remarkable [160].

The two aromatic rings are out of plane with respect to the C(13)-C(14)-C(15) plane. This is confirmed by torsion angles of 1.92(1)° and 0.58(1)° for C1 to C6 and C(7) to C(12) respectively. The three methoxy groups, C(6)-C(1)-O(4)-C(18), C(11)-C(12)-O(3)-C(17) and C(9)-C(10)-O(2)-C(16) are not oriented perpendicular to their attached aromatic rings and this is confirmed by torsion angles of -2.02(1)°, 0.77(1)° and -1.65(1)° respectively [149].

Figure 3.24 The packing diagram of C III viewed down the *b*-axis

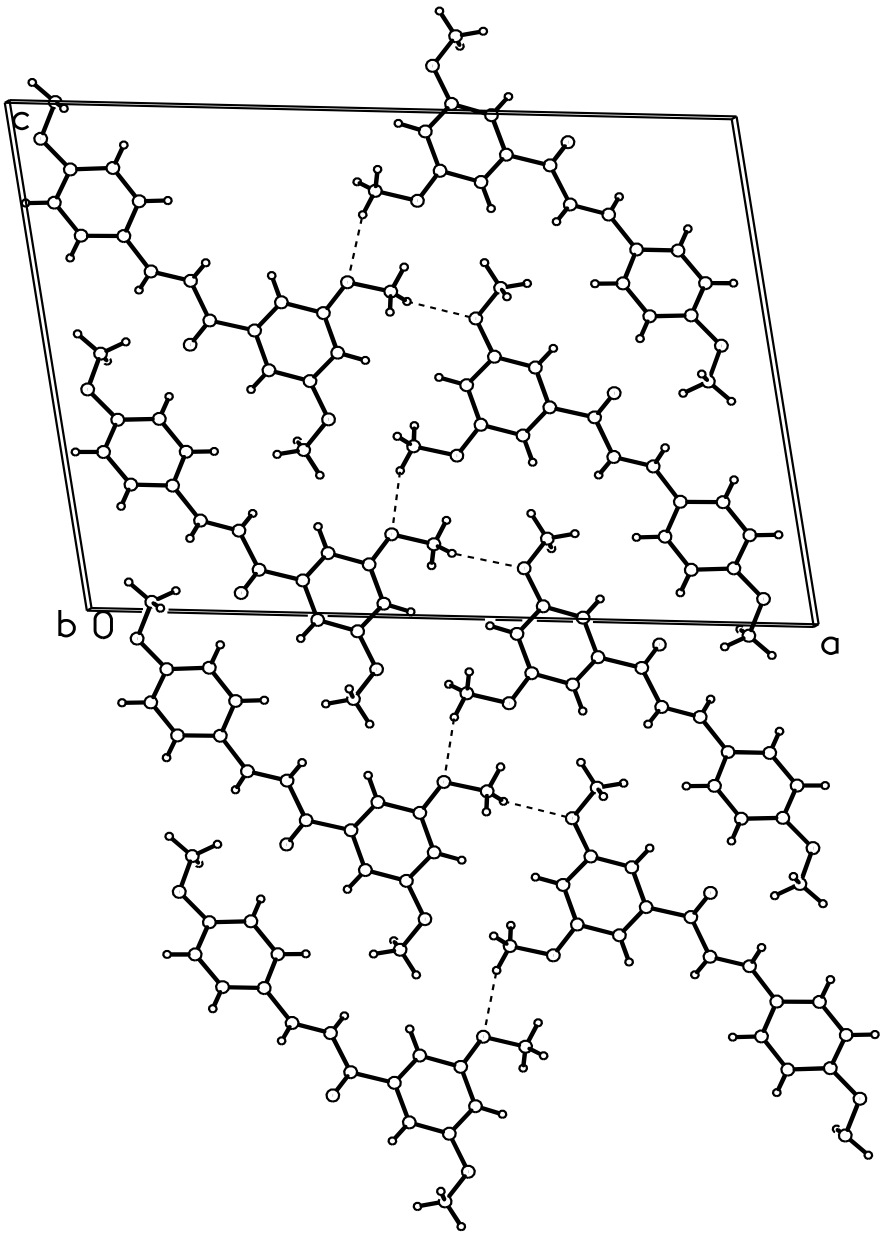


Figure 3.25 shows a view of the crystal packing of C III showing chains linked through C-H…O interactions between molecules related by the 2_1-screw axis. Figure 3.25 illustrates also a view down the *b*-axis of the unit cell showing the 1D chain propagating parallel to the *b*-axis[H(21N): *–x*, ½+*y*, ½-*z*; H(19X): +*x*, ½-*y*, ½+z]

Figure 3.25 A view down the *b*-axis showing the alternating stacking of chains in the crystal.

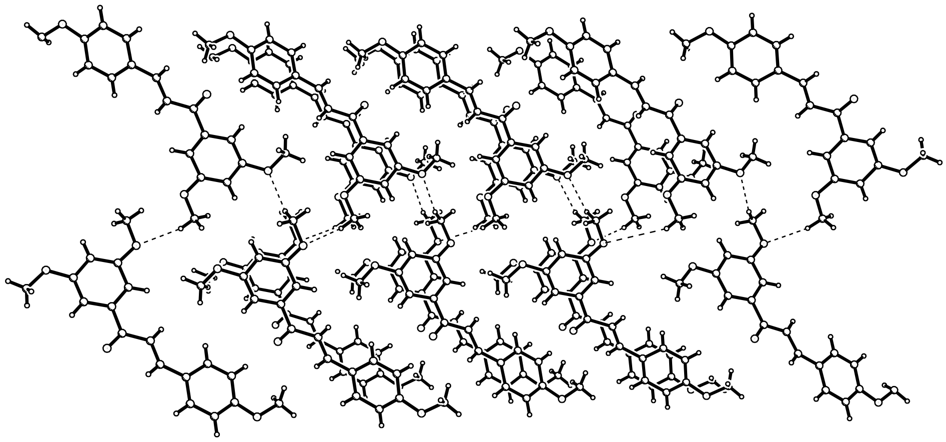


Figure 3.26 shows a perspective view down the *b*-axis showing stacking of chains in the crystal.

Figure 3.26 Crystal packing diagram of C III showing herringbone arrangement viewed down the *b*-axis

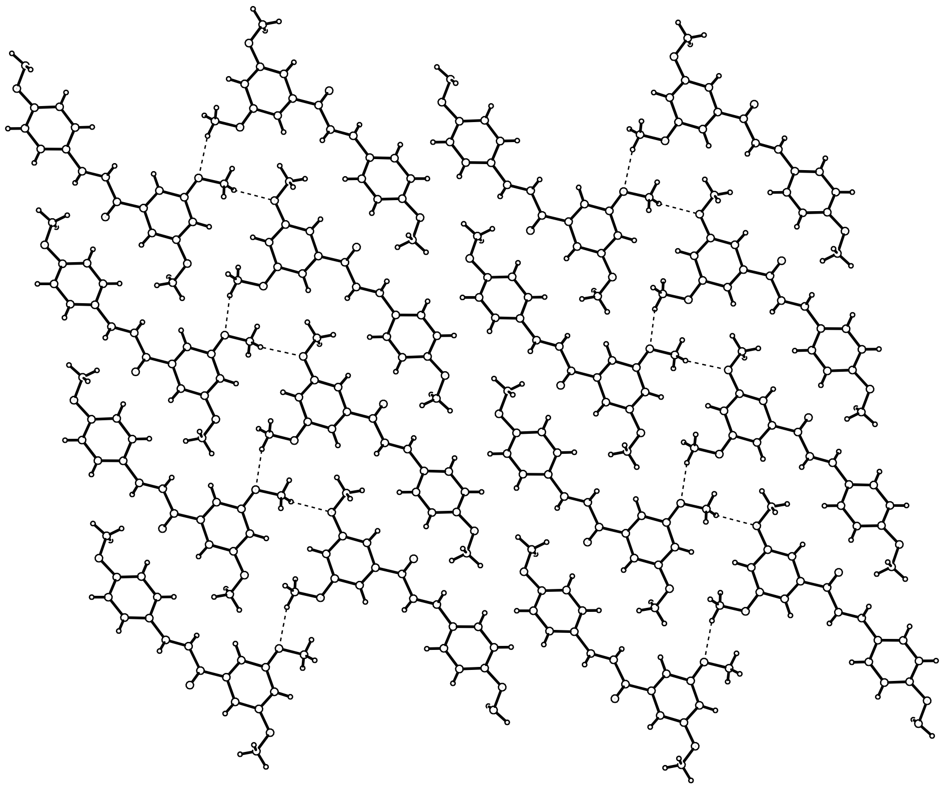


Figure 3.27 A unit cell of Compound C III showing herringbone aromatic interactions between molecules viewed down the *a*-axis

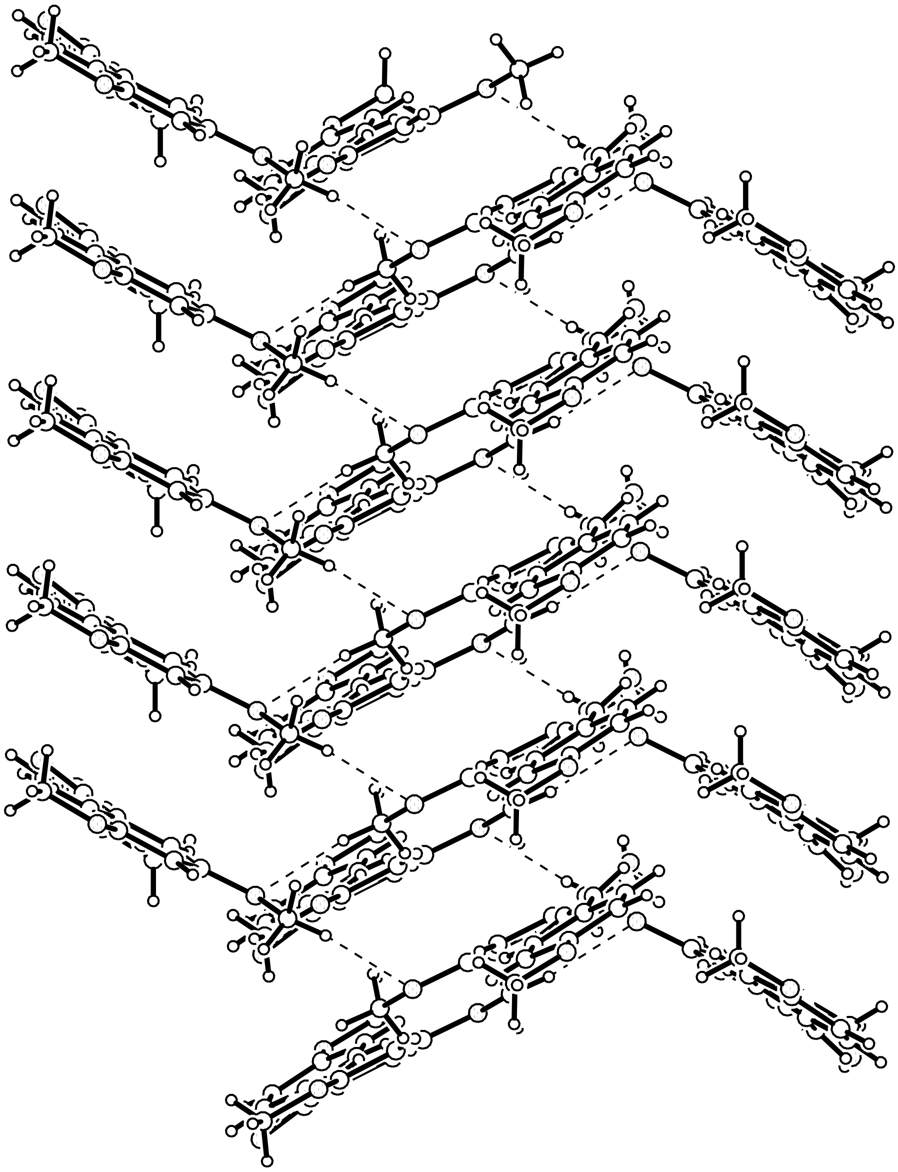


Figure 3.27 shows the herringbone arrangement of C III viewed down the *b*-axis and a view down the *a*-axis (Figure 3.28) of the unit cell showing herringbone aromatic stacking interactions between molecules.

Figure 3.28 A view of the non-bonded hydrogen interaction involved during packing of C III

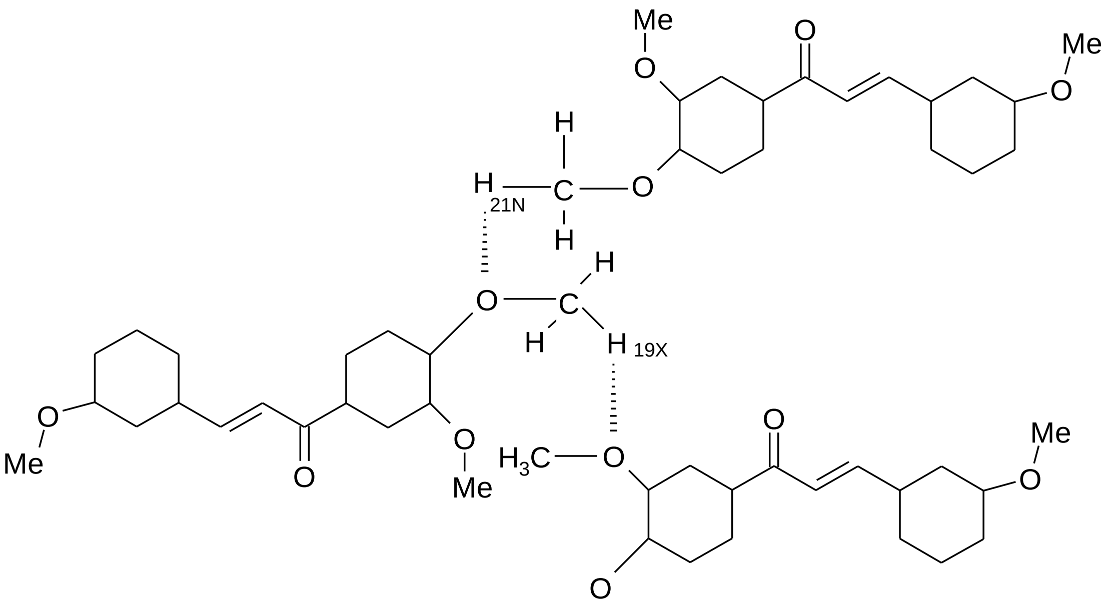


Figure 3.29 Schematic representation of the geometry of the C-H……O intermolecular interaction in compound III

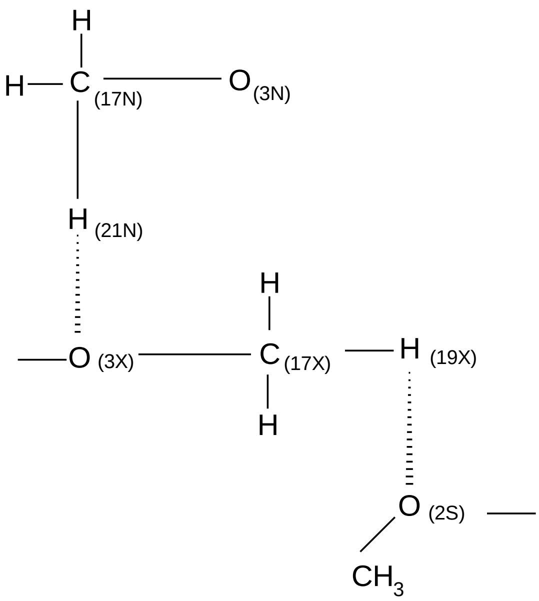


Table 3.2 Non-bonded hydrogen interaction geometry for compound III

D-H......A	d(D-H)	d(H..A)	<DHA	d(D..A)	A
C(17N)-H(21N)…O(3X)	0.960	2.579	166.50	3.539	O3X
C(17X)-H(19X)… O(2S)	0.960	2.682	159.00	3.642	O2S

Figure 3.30 The crystal packing diagram of CICMEH structure viewed down the *a*-axis

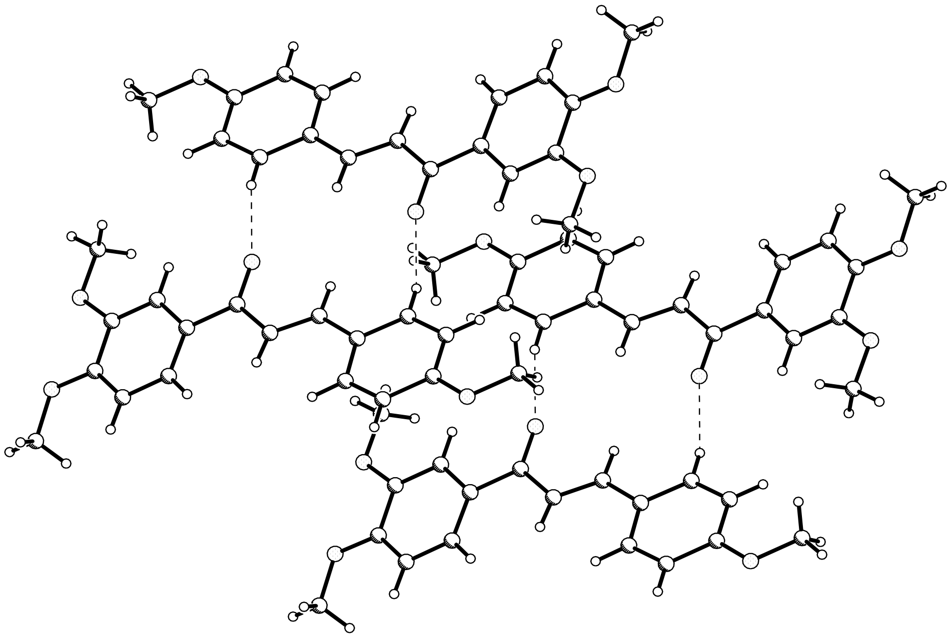
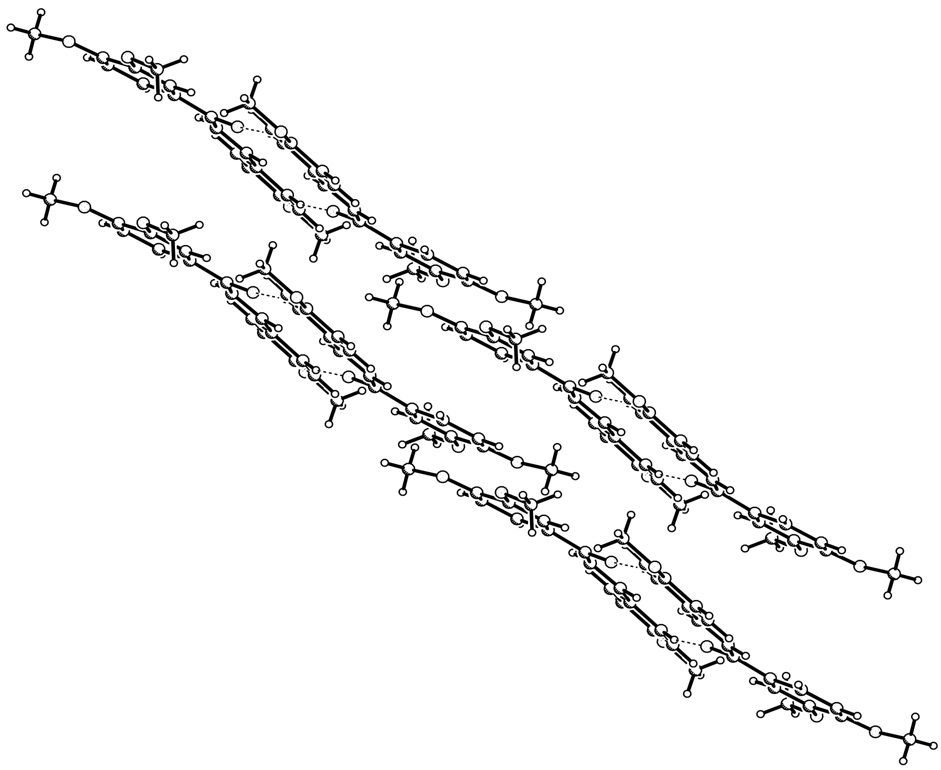


Figure 3.31 A diagram of CICMEH structure showing aromatic packing interactions between molecules viewed down the *c*-axis



Figures 3.25, 3.26, 3.27 and 3.28 show the molecules of C III exhibiting herringbone aromatic interactions during packing with extensive network of non-bonded hydrogen interactions. C III molecules (1-(3, 5-dimethoxy-cyclohexyl)-3-(4-methoxy-cyclohexyl)-Propan-1-one) are linked together by intermolecular C-H…..O interactions. The crystal packing of C III is governed by a two dimensional network of non-bonded hydrogen intearctions. The crystal packing of C III comprises glide related molecules that are linked by interactions involving intermolecular C-H…..O hydrogen bonding as indicated in Figure 3.27. Figure 3.25, 3.26 and 3.27 illustrates a two-one screw axis parallel to the y-axis with a centre of inversion on the y-axis.

The intermolecular hydrogen interactions occuring between the donor hydrogen atom of the methoxy substituent of (E)- 1-(3, 5-dimethoxy-cyclohexyl)-3-(4-methoxy-cyclohexyl)-Propan-1-one which symmetrically interacts with the oxygen atom of the methoxy substituent of another (E)- 1-(3, 5-dimethoxy-cyclohexyl)-3-(4-methoxy-cyclohexyl)-Propan-1-one which is the hydrogen bond acceptor.

The molecule (E)- 1-(3, 5-dimethoxy-cyclohexyl)-3-(4-methoxy-cyclohexyl)-Propan-1-one is linked edge-to-edge by intermolecular hydrogen interactions involving C-H…….O-CH_3 (methoxy substituents) propagated in a zig-zag conformation. Only one type of hydrogen bonding interaction is involved in this crystal packing. The geometry of the non-bonded hydrogen interactions is indicated in Table 3.2.

There is a strong possibility of these intermolecular hydrogen bonding interactions occurring because the individual hydrogen bonding distances as shown in Table 3.2, are not more than the sum of their van der Waals radii which is 2.72 Å.

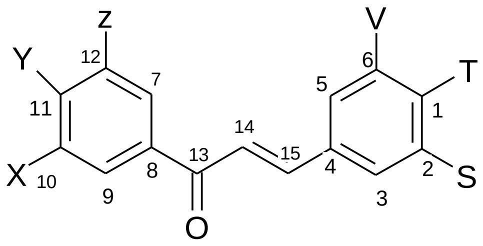
Their individual hydrogen interaction angles as shown in Table 3.2 is consistent with the preferred known C-H……O hydrogen bond range of 86°-173° [1, 164]. Therefore it can be concluded that there is a strong possibility of intermolecular hydrogen C-H…….O interactions occurring in the stacking conformation of C III. This is because the contact distance between the interacting atoms are not more than the sum of their van der Waals radii and their bond angles and distances are consistent with preferred known bond distances and angles.

With respect to the closely related molecules of CICMEH's structure, they form centrosymmetric dimers involving C-H…….O interactions. These C-H……O interactions does not involved the adjacent substituted methoxy groups as in C III. (Figures 3.31 and 3.32). The difference in the stacking conformation is probably due to the presence of a hydrogen atom between the two substituted adjacent methoxy groups in C III. (Figure 3.24).

These hydrogen bonding interactions scheme results in the formation of noncentrosymmetric trimers. These trimers form layers which are then stacked edge-to-edge together with the help of the two dimensional network of hydrogen bonding interactions. These layers are propagated along [001] as indicated in Figures 3.26, 3.27 and 3.28 in the packing state. There is also C-H…π interactions [9] and π - π interactions between molecules as illustrated by Figure 3.22.

There is the possibility of the methoxy groups increasing the therapeutic effectiveness of the chalcone because of their positive resonance effect on the π-system (171).

The figure below shows the numbering scheme adopted with the corresponding substituents (same as Figure 3.1)



S = H, C_2H_5O
T = H, C_2H_5O, CH_3O
V = CH_3O, H , C_2H_5O
X = Cl_1, CH_3O, H
Y = Cl_2, CH_3O, H
Z = H, CH_3O

(9)

In order to illustrate the effect of a substituent on the bond length of the C=O bond as well as on the bond angles and length of the carbon atoms with the substituents, a table of selected bond lengths and angles for the four chalcone structures were compared in Tables 3.3 and 3.4 respectively.

Table 3.3 Selected bond lengths (Å) **Page 113**

Compound	C(13)-O(1)	C(1)-S	C(2)-Z	C(6)-T	C(10)-X	C(11)-Y	C(12)-V	C(8)-C(13)	C(13)-C(14)	C(14)-C(15)	C(15)-C(4)
I	1.225(3)	1.503(3)	0.930(H)	0.930(H)	1.726(2)	1.727(2)	0.930(H)	1.495(3)	1.469(3)	1.327(3)	1.462(3)
II	1.251(2)	1.374(2)	0.930(H)	1.389(2)	1.374(3)	1.385(2)	1.388(2)	1.498(3)	1.481(3)	1.326(3)	1.467(3)
III	1.215(7)	1.373(6)	0.930(H)	0.930(H)	1.382(6)	0.930(H)	1.365(6)	1.496(8)	1.477(8)	1.338(7)	1.465(7)

Table 3.4 Selected bond Angles (°)

Compound	C(8)-C(13)-O(1)	O(1)-C(13)-C(14)	C(14)-C(15)-C(4)
I	119.6(7)	121.7(7)	129.2(6)
II	120.05(19)	120.51(19)	127.45(19)
III	119.36(19)	122.23(19)	127.9(2)

Considering the carbon-oxygen [(C=O) carbonyl] bond length, Table 3.3 indicates Compound (II) has the longest bond length of 1.251(2)Å when the three chalcones were compared with each other. This is followed by compound (I) with bond length of 1. 225(3) Å and finally compound (III) with the shortest bond length of 1.215(7) Å for the carbonyl functional group.

Potential little delocalisation of electrons occurs along the O(1)-C(13)-C(14)-C(15) and this is evidenced by changes in the carbon-carbon double bond length as indicated in Table 3.3. The electron delocalisation along O(1)-C(13)-C(14)-C(15) is a possibility because, as the bond length of C(13)=O(1) increases, the bond length of C(14)=C(15) decreases. The compound with the longest bond length for C(14)=C(15) (carbon-carbon double bond) is compound III with a bond length of 1.338(7) Å, followed by compounds I and II with lengths of 1.327(3) Å and 1.326(3) Å respectively as shown in Table 3.3.

It will be noted from the study that the E-isomer being the most thermodynamically stable form of chalcones, is very important for the stacking conformation of chalcones.

It will be noted that the non-bonded intermolecular interactions existing between compounds I, II and III are different. Compound I illustrated Cl……Cl interactions with long-range pseudo-herringbone aromatic interactions whilst compound II exhibited C-H…..O, O………O and H-O……O=C non-bonded intermolecular hydrogen interactions with stack packing.

Compound III showed non-bonded intermolecular hydrogen interactions between adjacent substituted methoxy groups of adjacent molecules. These C-H…..O interactions in compound III resulted in the compound exhibiting herringbone conformation during stacking. The non-bonded intermolecular interactions between compounds I and III are closely related just that the aromatic substuents involved are different.

There is a strong possibility that, the non-bonded intermolecular interactions in compounds I, II and III played a very important role in stabilizing the stacking conformation in addition to determining the packing conformation of these compounds.

Comparatively the closely related structures of KERCUG, CICSEN and CICMEH showed differences in hydrogen bond interactions in addition to their stacking conformation. These dissimilar intermolecular hydrogen bond interactions and packing conformation is probably due the position of the substituents as well as the external environment of the compound.

With respect to the bond angles, it will be noted from Table 3.4 that, there is no significant difference between the bond angles of C I, C II and C III. There is the possibility after comparing the four compounds that, the number and closeness of the methoxy and ethoxy substituents (electron donating) a chalcone has, the bond length of the enone unit will be affected as shown in Table 3.3.