X-ray Crystallographic Study for Weak interactive forces playing in Unit Crystals of Natural Flavonoids: An Overview

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Abstract

Weak interactive forces play an important role to form unit crystals of chemical components. So, it is felt pertinent to look into this phenomenon in naturally occurring chemical entities. Since flavonoids are one of the main groups of natural products of biological importance, it is important to find the role of these forces in natural flavonoids.
But X-ray crystallographic study is not common for natural flavonoids. Hence, detailed X-ray crystallographic analysis obtained from the different studies on some flavonoid molecules reported from 2005 to 2017 is being considered. An analysis of hydrogen bond, C-H…O, C-H…π and π–π interactions observed in the reported structures indicate that such weak interactive forces play a dessisive role in assembling the molecules into an organized supramolecular structure. This review cites 58 references.

Key words
Crystal, flavonoid, hydrogen bond, C-H…π interaction, π–π interaction, supramolecule.

1. Introduction

Flavonoids constitute one of the main groups of naturally occurring compounds, which occur widely throughout the plant kingdom. Apart from their physiological roles in the plants, flavonoids are important components of the human diet, although they are not considered as nutrients [1]. These naturally occurring flavonoids, a major class of natural *O*-heterocycles are of much importance due their biological activities as well as pharmaceutical applications [2-3]. Many of these natural flavonoids are being used as drugs. Thus it attracts the interest of a large variety of physical and biological scientists. Investigations of the physical and chemical properties of natural flavonoids are very important in order to determine the relationship between the structure, properties and performance, and to search new derivatives with improved properties [4-5]. So, crystallographic study of these natural flavonoids is important in the sence that they may indicate the chemical stability, solubility and chemical reactivity which are useful in predicting the possible biological activities [6].
Thus the crystal structure determination of these compounds assumes importance in view of the fact that any structural changes observed in the conformation of these molecules, due to different substituents or any other factors, can lead to the better understanding of their biological activities. Again, intermolecular weak interaction plays an important role in controlling the crystal packing and recognition of aromatic compounds as an auxiliary stabilizing force, and in some cases as the driving factor directing the chemical reaction [7]
Further, weak interactions play a decisive role in assembling the molecules into an organized supramolecular structure. In presence or absence of classical hydrogen bonds , other weak interactions such as C-H…O, C-H…π and π–π play a crucial role in determining the three-dimensional structure [8-23]. It was clear that the chemical and physical properties of the crystalline solids are dependent on the arrangement of the molecules in the crystal lattice [24]. Various fields that are known from supramolecular chemistry include molecular self-assembly, molecular recognition, host-guest chemistry, interlocked molecular architectures, and dynamic covalent chemistry [25]
Hence, the understanding and utilization of weak interactions in natural flavonoid is of fundamental importance for the further development of supramolecular chemistry and prediction of crystal structures. X-ray crystallographic analysis of the natural flavonoids reported during 2005 to 2017 is discussed in this review. This resume covers 58 references.

2. Weak interactions

In order to obtain detailed information about the molecular structure of the natural flavonoids in the solid state, X-ray crystallographic investigation is very helpful. Hydrogen bonds play an important role in stabilizing flavonoid molecule. Beside this, it has also been observed that weak interactive forces play a vital role in

assembling the molecules into an organized structure and in determining the three-dimensional structure of molecular crystals. The noncovalent interactions which have been exploited in this crystallographic study are hydrogen bonding, C-H...O interaction, C-H…π interaction , π…π, dipole interactions, etc. These weak interactions are:

2.1 Hydrogen bonding: A hygrogen bond is an attractive, directional interaction with a significant role in stabilizing the molecular structure. Hydrogen bonding is now usually pointed out as a packing motif [23]. It is clearly no longer necessary to justify the relevance of this inta- and intermolecular hydrogen bonding in crystal structure of flavonoid molecule. The intramolecular hydrogen bond affects the intramolecular conformation of the molecule. Many structures simply cannot be rationalized unless hydrogen bond is actively invoked [26]. It is also recognized that it is becoming increasingly evident that the specificity, directionality, and predictability of intermolecular hydrogen bonds can be utilized to assemble supramolecular structures of, at the very least, controlled dimensionality [27].

2.2 C–H...O interaction: Assembly of any molecule may be caused not only with strong hydrogen bonds but with weak C-H…O interactions [10]. This is because of electrostatic and long-range character of all hydrogen bonds. So, in absence of hydrogen bonds, weak C–H…O bonds determine the crystal packing of natural molecule [28]. In this case, the length of C…O is an important factor. This length span the range 3.00-4.00 Å, and this sets a reasonable upper limit for a C–H….O interaction. It may be pointed out that many longer C–H…O (3.50<d<4.00 Å) could be significant when linear but while evaluating individual bonds, greatest weight is given to those bonds where short contacts (2.00<distance<2.30Å) are accompanied by linear geometries (150^0<angle<180^0) [10].

2.3 C–H…π interaction: C–H…π interaction is a non-covalent forces similar to hydrogen bonding. This interaction is very important in determining the three-dimensional structure of molecules. In a stacked arrangement, the T-shaped conformation forms the C–H…π interaction [29-31].

2.4 π–π interaction: π–π interaction can play important role in controlling the assembly of molecules. This type of interaction occur when there is face-to-face arrangement of the π-containing rings[23]. A near face-to-face alignment of the rings is extremely rare. The usual π interaction is an offset or slipped stacking which means the rings are parallel displaced. The distance of the π–π planes is an important criterion to suggest the stacking. Strong interactions are around 3.3 Å and weaker interaction lie above 3.6 Å with 3.8 Å being approximately the maximum contact for which π–π interactions are accepted [23]. It can also be noted that the order of stability in the π–π interaction of two π-systems is π -deficient- π -deficient> π -deficient- π -rich> π -rich- π rich [32-33].

3. Chemical structure of Flavonoids : Flavonoids refer to a class of secondary metabolites of plant which contains mainly an aryl sunstituted benzo-γ-pyrone carbon skeleton. Based on their chemical structures, all the compounds are broadly classified into more groups namely simple Flavans, Flavone and Flavonols, Flavanones, Isoflavone and coumarins. In the mentioned period, some natural flavonoids with X-ray crystallographic study have been reported. Chemical structures of the reported flavonoids are shown in **Fig. 1.** Among the reported flavonoids, Compound **1** is simple Coumarin, compounds **2**, **3** and **5** are furano-coumarins, compound **4** is pyrano-coumarin, compound **6-10** and compound **14-16** are flavones and compounds **11-13** are flavanones.

4. Natural Flavonoids Reported with X-ray crystallographic study:

Natural flavonoids reported with X-ray crystallographic study during this time are considered for the discussion of weak interactive forces acting in the unit crystals of the molecule. The name, natural source along with references are given in the **Table-1**

Table-1: List of the reported flavonoids

Sl. No	Name of the compound (Structure No)	Natural Source	Ref
1	*R*-(+)-marmin (7-[(6,7-dihydroxy-3,7-dimethyl-2-octenyl)-oxy]-2H-1-benzopyran-2-one (**1**)	*Aegle marmelos* Correa	34
2	*S*-(+)-Marmesin 3-dihydro-2-(1-hydroxy-1-methylethyl) 7H-furo[3,2-g][1]-benzo-pyran-7 -one (**2**)	*Aegle marmelos*	**35**
3	Heratomol benzoate (6-Benzoyloxy-2H-furo[2,3h]-1-benzopyran-2-one) (**3**)	*Heracleum thomsoni*	36
4	Selinidin 9,10-dihydro-8,8-dimethyl-2-oxo-2H,8H-benzo[1,2-b:3,4-b']-dipyran-9-yl-2-methyl-2-butenoate (**4**)	*Selinum vaginatum* (*Umbelliferae*	37
5	2-hydroxymethyl-5-hydroxy-10,11-dihydro-11(S)-(1-hydroxy-1 methylethyl)-2H-furo[2,3-g]-4H-1-benzopyran-4-one (**5**)	*Angelica archangelica* Linn	38
6	7-Hydroxy-2',6'-dimethoxyflavone (**6**)	*Avicennia officinalis* L	39
7	5, 7-Dihydroxy-2',3', 4'-trimethoxy-flavone (**7**)	*Hedyotis diffusa*	39
8	Pomiferin (**8**)	*Maclura pomifera* Balf	40
9	5-hydroxy-6,7,4′-trimethoxyflavone(**9**)	*Limnophila rugosa.*	41
10	5-hydroxy-3,7,4′-trimethoxyflavone (**10**)	*Limnophila rugosa.*	41
11	rac-8-formyl-5,7-dihydroxyflavanone (**11**),	*Eugenia rigida* DC. (Myrtaceae)	42
12	7-hydroxy-5-methoxy-6-methyl flavanone (**12**)	*Eugenia rigida* DC. (Myrtaceae)	42
13	7,3',4'-trihydroxy-8-methoxyflavanone (**13**)	*Coreopsis lanceolata* L	43
14	3′-methoxy-8-C-(1,1-dimethyl-2-propen-1-yl)-kaempferol (**14**)	*Platanus acerifolia*	44
15	Quercitrin (**15**)	*Morus alba*	45
16	Morusin hydroperoxide (**16**)	*Morus alba*	45

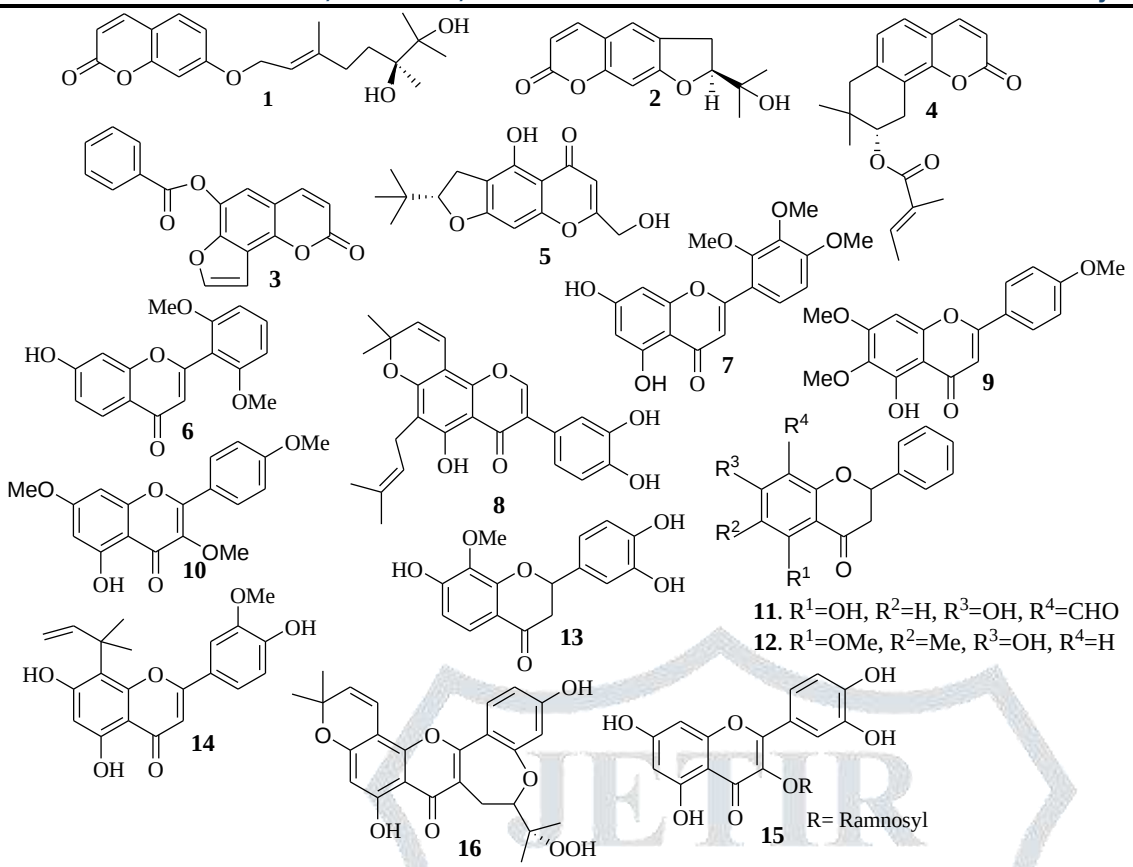
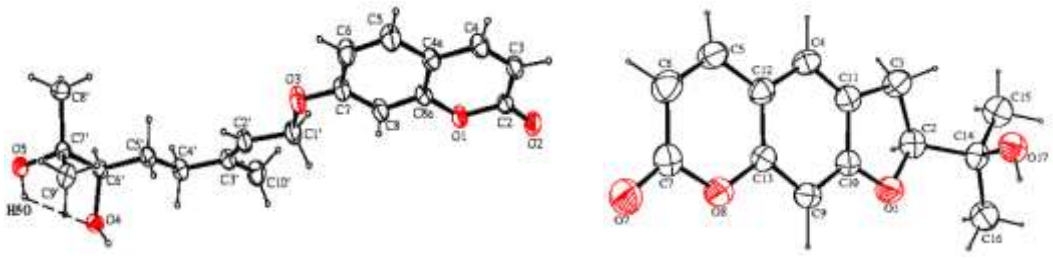


Figure 1. Chemical structure of the reported compounds

5. Weak interactive forces playing in representative examples

Since nono-covalent weak interactions are very important for better understanding and control of major process of nature, these weak interactions in some natural flavonidsreported here, are being discussed focusing the role of these interactions in stabilising the molecular crystals. Each structure has been studied and discussed, taking the available information on the structures so far reported and published.

5.1 Hydrogen bonding in flavonoids: Hydrogen bonds are frequently responsible for stabilization of the crystal structures of natural *O*-heterocylic compounds. The presence of O-atoms in this class of compounds means that this hydrogen bond is widespread, even if not identified in many cases [10].



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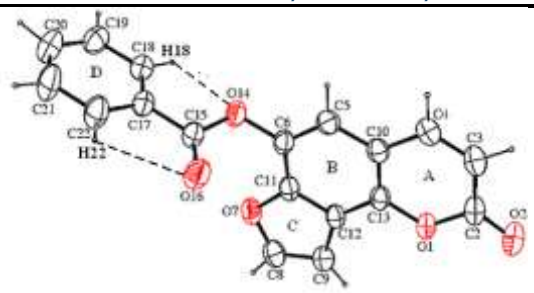

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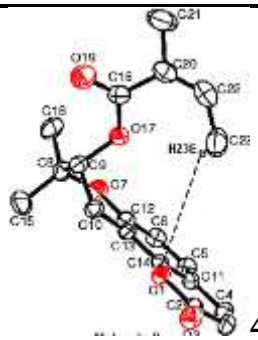

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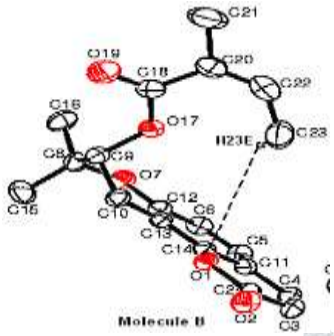

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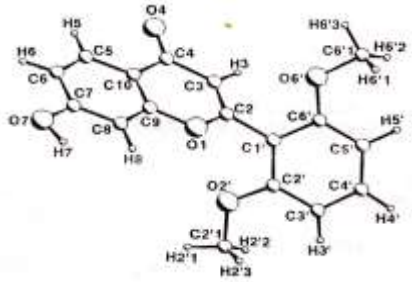

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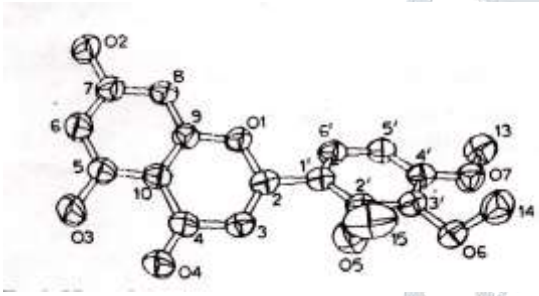

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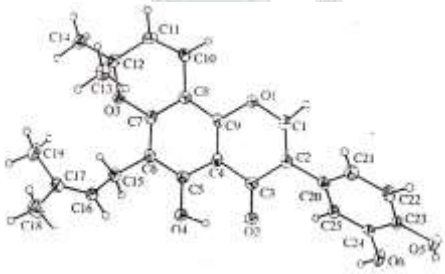

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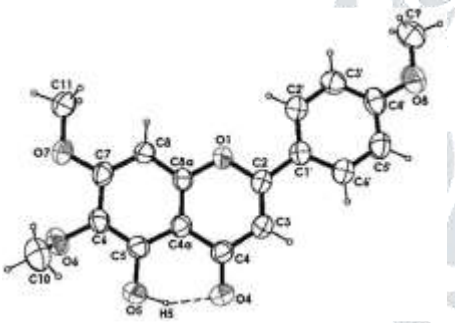

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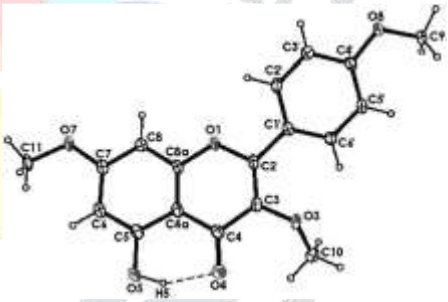

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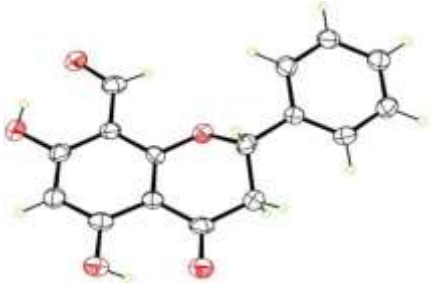

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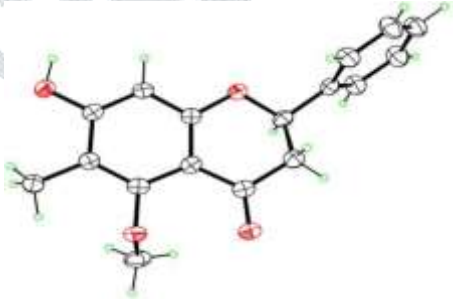

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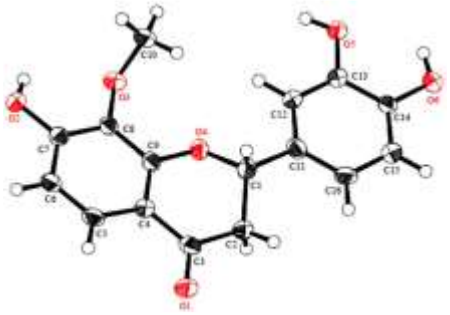

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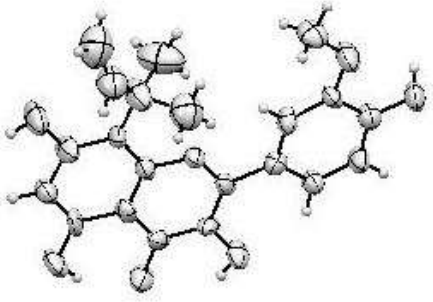

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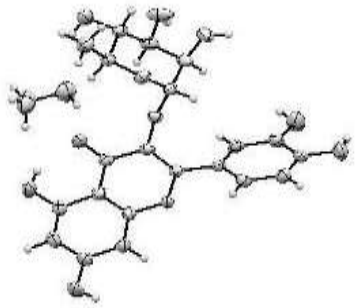

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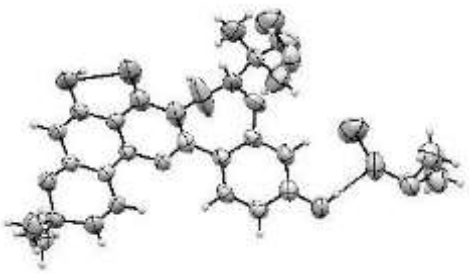

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Fig. 2 Thermal ellipsoid plot of the reported compounds. H -atoms are shown as small spheres of arbitrary radii. The broken line shows the O-H…O intramolecular hydrogen bond.

In compound (**1**) there is a short intramolecular contact between the H atom of the O5 hydroxyl group and oxygen atom O-4. This leads to the formation of a pseudo-five-membered ring comprising atoms O-4, C-6', C-7', O-5 and OH-5 at the end of the side chain (**Fig. *2***). Hydroxy atom O-5 acts as a donor in forming the continuous chain of classical hydrogen bonds. An ORTEP view of the compound (**1**) indicating atomic numbering scheme [46] is shown in **Fig.2**. The dihedral angle between the pyrone and benzene rings of this compound (**1**) is only 1.38(4)^o, confirming the perfect planarity of the benzopyran moiety. This planarity of the benzopyran moiety confirms the aromatic character of this system. The constituent atoms (C1', C2', C3', C4', C5', C6', C7', O5) of the side chain at C7 are coplanar as expected from the double bond between C2' and C3'. The greatest torsion angle deviation from 0 or ±180^o is seen for C4'-C5'-C6'-C7' [-173.0(1)^o][38]

Gupta and Goswami [38] reported that the dihedral angle between the pyrone and benzene rings of the marmesin (**2**) is 0.3(1)^o. This low value of dihedral angle confirms the perfect planarity of the coumarin moiety. The furan ring has a 2α–envelope conformation with a phase angle of pseudorotation Δ = 25.47^o and maximum angle of torsion ϕ_μ =17.84^o [47]. The asymmetry parameter ΔC_s(C2) which gives the distortion from ideal mirror symmetry bisecting the C10-C11 bond is 1.99 [48]. The dihedral angle between the planes of furan ring and benzopyran moiety is 3.2(1)^o. This supramolecular structure of marmesin (**2**) is dictated by two intermolecular hydrogen bonds. The stronger of these two hydrogen bonds (O17-H17O…O7) gives rise to a chain running parallel to the [010] direction. The chains are linked into sheets by the second hydrogen bond (C5-H5…O17). So, in this compound (**2**), hydrogen bonds play an important role in determining its supramolecular chemistry (***Fig. 2***).

In the compound (**3**) the rings of the furocoumarin moiety are coplanar. The phenyl ring (D) bonded to C15 is rotated by 88.5(1)^o with respect to the furocoumarin fragment. Here also, this geometry of the compound is governed by hydrogen bonds playing in the crystal. The above orientation is stabilized by two weak intramolecular C-H…O hydrogen bonds (C18…O14 = 2.729(3) Å and C22…O16 = 2.857(3) Å) as described by Gupta and Goswami [38]. A general view of the Heratomol benzoate (**3**) indicating atom numbering scheme is shown in ***Fig. 2***.

Crystallographic studies on angelicain (**5**), revealed there are two crystallographically independent molecules, A and B, in the asymmetric unit (***Fig. 4***). In both the molecules, the benzopyran moietis are coplanar [highest displacement, 0.030(3)Å for atom C3A and 0.040(2)Å for C5B] and this is typical for 255 structures with the benzopyran moiety found in the Cambridge Structural Database [49].

In both the molecules, A and B, of the compound (**5**) the hydroxyl group at C5 has a *gauche* arrangement with respect to the H5-O5-C5-C4 torsion angle, giving rise to a strong intramolecular contact between the H atom of the O5 hydroxyl group and carbonyl atom O4. This leads to the formation of a pseudo-six-membered ring comprising atoms O4, C4, C4a, C5, O5 and H5 (***Fig. 4***). Intermolecular O16-H16…O9 links molecules A and B into dimers. Intermolecular O16-H16…O9 hydrogen bonds play a key role in compound (**5**) to link its molecules A and B into dimers. These dimers are connected by O9-H9…O16 hydrogen bonds to form infinite double chains in a stepwise fashion along the diagonal of the unit cell [38].

Hydrogen bonds are frequently responsible for the stabilization of the crystals of hydroxyflavone. When a hydroxyl group is at C-5 position, an intramolecular hydrogen bond is formed with the neighbouring carbonyl oxygen atom. Other hydroxyl functionalities, if present in the molecule, can form intermolecular hydrogen bonds [50]. Sometimes they form intermolecular hydrogen bonds with solvent molecule, such as water [51]. In compound (**6**), there are intra and inter molecular hydrogen bonds. An intermolecular hydrogen bond O7-H7…O4 exists between the hydroxyl and carbonyl group and forms the polymer chain [52].

In compound (**7**), there is an intramolecular hydrogen bond between carbonyl O atom and the H atom of 5-hydroxy group, O(4)…O(3)=2.586 Å. This carbonyl O atom can form another intermolecular hydrogen bond with the 7-hydroxy group, O(2)…O(4)= 2.759(5) Å. View of the compound is given in **Fig.3** [53].

The hydroxyl group in compound (**8**) has a gauche arrangement with respect to the H4-O4-C5-C4 torsion angle, giving rise to a short intramolecular hydrogen bond [1.67 (2) Å] between the H atom of the C-5 hydroxyl and the carbonyl group. Again, in the

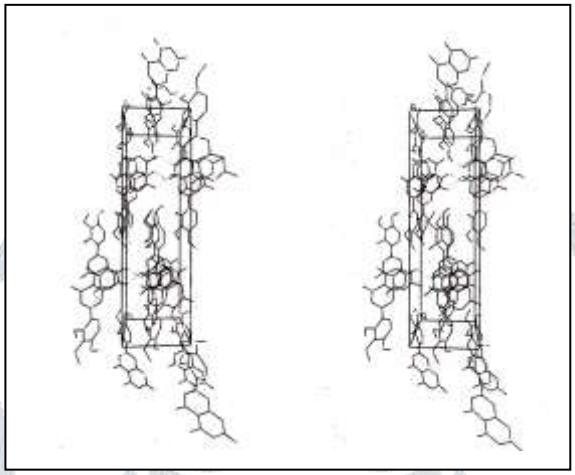


Fig. 3 Stereoscopic view of the unit cell of compound (**7**) with hydrogen bonds

crystal lattice of the compound (**8**), relatively strong intra and intermolecular O-H…O hydrogen bonds link the molecular units into a one-dimensional chain [54] (**Fig. 1 and 4**).

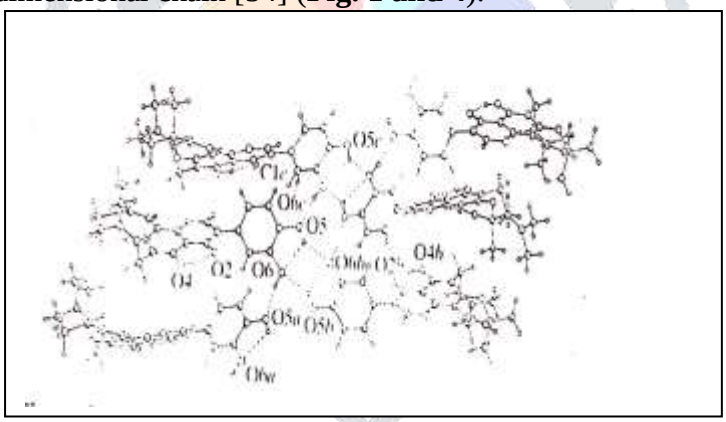


Fig. 4 Part of the structure of (**8**) showing the formation of a molecular chain of edge fused rings. Atoms with the labels a, b, c are at the symmetry positions (x, -y, 0.5+z), -x,-y, -z) and (x, -y, z-0.5) respectively.

In compound **9**, the hydroxyl group at C5 has a gauche arrangement with respect to the H5–O5–C5–C4a torsion angle, giving rise to a strong intramolecular hydrogen bond between the H atom of the O5 hydroxyl group and carbonyl atom, O4. This leads to the formation of a pseudo-six-membered ring comprising of atoms O4, C4, C4a, C5, O5 and H5. Similarly, in compound **10**, the hydroxy group, O4, has a gauche arrangement with respect to the H5–O5–C4–C4a torsion angle (1.4°), giving rise to a short [1.74(4) A] intramolecular hydrogen bonding contact between the H atom of the hydroxyl group and carbonyl atom O4 [41].

In compound **11**, both the hydroxyl group form intramolecular hydrogen bonds, HO-5 to the flavanone carbonyl (O···O 2.571(4) Å) and HO-7 to the formyl carbonyl (O···O 2.603(4) Å). The formyl group lies essentially in the plane of the flavanone aromatic ring, with a C−C−C−O torsion angle of 2.4(9)° and the stereogenic C-2 atom lies 0.61Å out of plane. The structure of compound **12** is shown in Figure 2. A disorder exists in which C-2 has the opposite configuration with 26% occupancy, which also changes the position of the phenyl substituent. The HO-5 group forms an intermolecular hydrogen bond to the flavanone carbonyl, O···O 2.715(2) Å. As in **11**, the formyl substituent lies in the plane of the aromatic A-ring [C− C−C−O torsion angle

−0.7(4)°]. Both OH groups again form intramolecular hydrogen bonds, with O···O distances of 2.540(3) and 2.595(2) Å, the longer one being to the formyl group [42]. Similar results were reported previously [55-56]. Both the hydroxyl groups at 3', 4' positions are linked with hydrogen bond. The methoxyl O is also linked with adjacent OH group by the hydrogen bond in compound **13**. C-5 OH is hydrogen bonded with nearby carbonyl moiety of the ring C of the flavonol. Likewise OH at C-4' is also linked with C-3' methoxyl group by hydrogen bond.both these bonds give the molecule extra stability [43]. There are intramolecular hydrogen bonds between O2 and O3 and between O5 and O6. These hydrogen bonds form a six-member and a five-member hydrogen-bonded rings, respectively. In the solid state, the water molecule is serving as a hydrogen bonding hub by a bifurcated donor hydrogen bond to two hydroxyl groups of the flavonol **15**. In addition, the sugar moiety, methanol and water molecules make a hydrophilic network which is stabilized by intermolecular hydrogen bonds as evidenced by the experimental X-ray crystallographic data [45]. In compound **16**, intramolecular hydrogen bond is formed between C-5 OH and carbonyl group of ring C. intermolecular hydrogen bonds are formed with the DMSO solvent molecule by C-4' OH [45].

5.2 C-H…O interactions in flavonoids:

A weak noncovalent bonding interaction, C-H**…**O interaction, is revealed in natural flavonoids leading to successful realization of the structural architechture [15].

In the crystal structure of heratomol benzoate (**3**) two intermolecular C-H…O close contacts also exist for the system lying within the 2.5Å range as reported by Gupta and Goswami [38]. These intermolecular C-H**…**O interactions link the molecules into chains that run parallel to the b-axis .

Selinidin, 9,10-dihydro-8,8-dimethyl-2-oxo-2H,8H-benzo[1,2-b:3,4-b']-dipyr-an-9-yl-2-methyl-2-butenoate (**4**), belongs to a group of naturally occurring coumarins which have 2',2'-dimethyl-dihydropyranocoumarin as their basic skeleton. The absolute configuration of selinidin was reported to be 9(S) [57]. The crystal structure of selinidin contains two crystallographically independent molecules, A and B, in its asymmetric unit. An ORTEP view of the molecules A and B with atomic labeling (thermal ellipsoids drawn at 40% probability) is shown in **Fig. 5**.

These molecule A and B forms dimer by the π–π interactions. These dimers are connected by C-H…O interactions to form chains along the a-axis of the unit cell. The adjacent chain links are rotationally related. Further intermolecular C-H**…**O interaction are responsible to link the dimer chains to form crystal structure of selinidin. In the packing diagram it can also be seen that the 2-methylbutenoyloxy side chains lie in layers perpendicular to the c-axis [38].

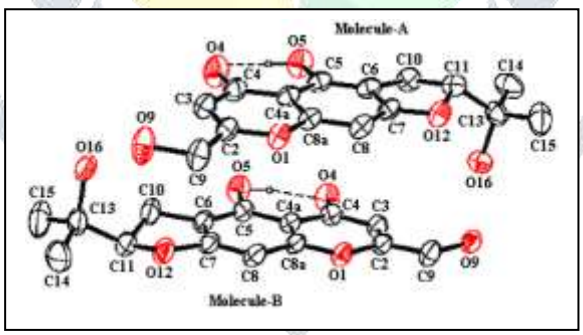
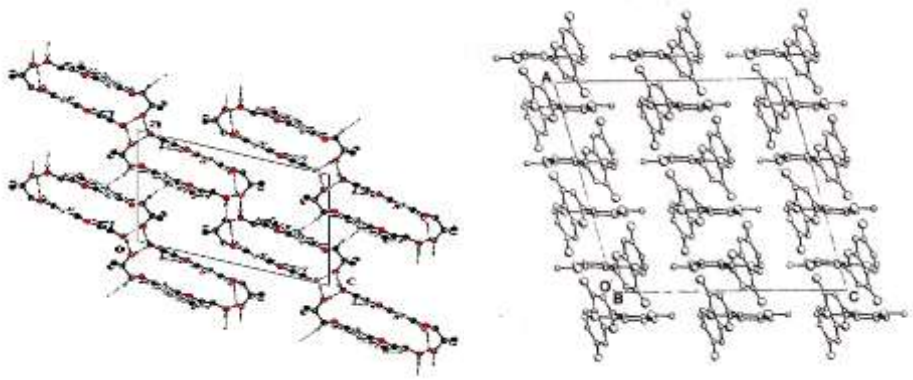


Fig. 5: ORTEP view of the two independent molecules (**4**) in the asymmetric unit, showing the atom-numbering scheme. The thin broken line shows the C- H…π intramolecular hydrogen bond. For clarity, only H atoms involved in C-H…π hydrogen bonding have been included.

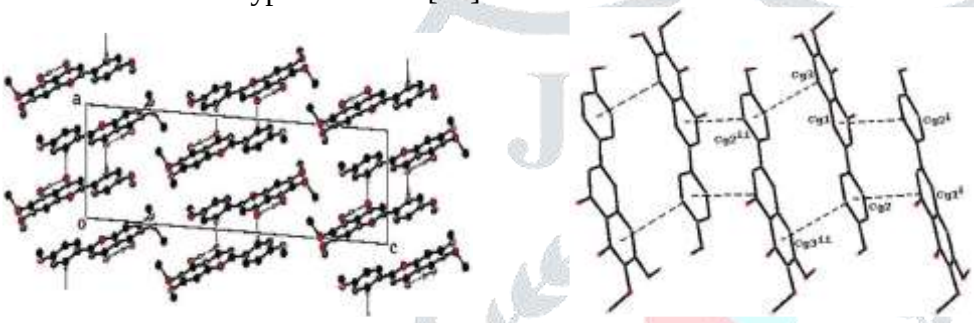
In the compound (**5**) also there are two crystallographically independent molecules A and B as described. Intermolecular O16-H16…O9 hydrogen bonds in compound (**5**) link its molecules A and B into dimers. Further, intermolecular C-H…O interaction is one of the crucial interactive forces to arrange these dimer chains to form supramolecular structure of angelicain (**5**) (**Fig. 6**)[38].



5 **6**

Fig. 6 Crystal packing of compound (**6**). and angelicain (**5**) along b-axis

In compound (**6**), there exists some C-H…O short contact. C8-H8…O4, C6'1-H6'1…O7, C6'1-H6'3…O7 these three interactions are responsible for the crystal packing (***Fig. 6***) [52]. In compound **9**, the Intermolecular C6′–H16…O4 hydrogen bond links the molecules into dimers. The dimers are arranged in a manner to form layers (**Fig**. **7**). The crystal structure of compouns **10** is stabilized by the presence of four intermolecular interactions of the type C–H…O [41].



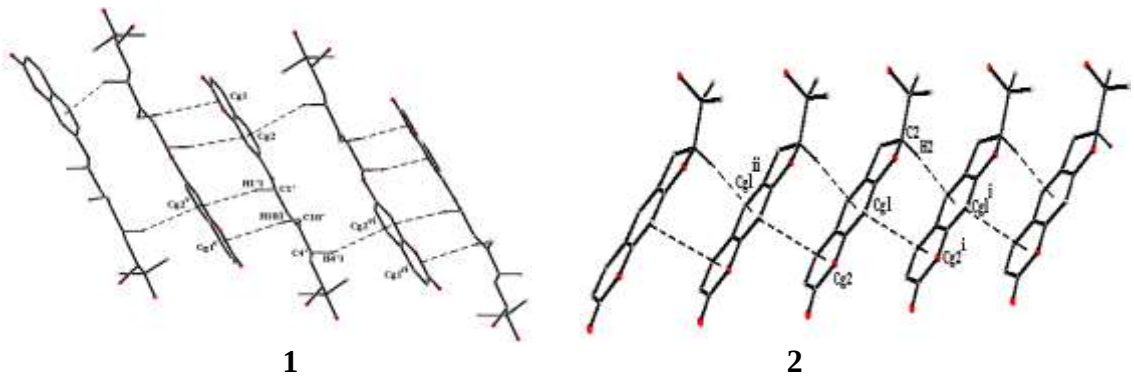
9 **10**

Fig. 7 Crystal packing of compound (**9**). and compound (**10**).

5.3 C-H…π interactions in flavonoids:

Burley and Psteko described that simple aromatic nucleus residue of some compounds prefer to associate *via* enthalpically favourable edge-to-face C-H…π interactions [58]. Natural flavonoids bears, in almost all cases, the aromatic rings. So, this C-H…π interactions becomes important in molecular packing and stacking of natural flavonoids.

In compound (**1**), the classical hydrogen bonds make a continuous chain of the molecules.Chains of molecules are packed together to form well-defined layers. Molecules within the layers are arranged in anti-parallel manner. This layer are arranged in such a manner that H(1'), H(10') and H(4') can make T-shaped interactions with the aromatic benzopyran ring. Thus, this manner is stabilized by C-H…π hydrogen bonds (**Fig. 8**). C-H…π hydrogen bonds between the side chain atoms and the coumarin nucleus precludes the approach between planar aromatic systems [38].



1 **2**

Fig.8 Molecular stacking of **1** and **2** along the b-axis showing the linking of the molecules by C-H…π interactions. Ring centroids involved in the C-H…π interactions are joined by dashed lines.

In compound (**2**), there is one C–H...π(arene) hydrogen bond with H…centroid distance of less than 3.0Å which serves to link all of the sheets into a single three-dimensional frame work. Here, the intermolecular C–H...π interaction is between the C(2)- H(2)….benzene ring of the benzopyran ring [38]

In the crystal structure of heratomol benzoate (**3**), intermolecular C-H…π interactions are observed and these interactions influence the packing of molecules in the unit cell [38]. C–H...π interaction becomes much important in compound (**4**) for the orientation of the side chain as well as the total structure. The crystal structure of selinidin (**4**) contains two crystallographically independent molecules, A and B, in its asymmetric unit. An ORTEP view of the molecules A and B with atomic labeling (thermal ellipsoids drawn at 40% probability) is shown in **Fig.5**. Comparison of the molecular dimensions of 2-methylbutenoyloxy side chain at C9 in molecules A and B has revealed considerable deviations in the bond lengths, bond angles and torsion angles. The structural variability of the side chain originates from different geometry of C-H…π interactions in molecules A and B. 2-methylbutenoyloxy side chain adopts an extended structure in molecule A [C13-C10-C9-O17= -168.7(3)º] leading to C-H…π interaction with another molecule at (x, -1 + y, z) and a folded structure in molecule B [C13-C10-C9-O17= -68.0(3)º] leading to C-H…π interaction within the same molecule
(**Fig.5**) [38]. In the compound (**5**) also there are two crystallographically independent molecules A and B as described in section 4.1 (**Fig. 1**). Intermolecular O16-H16…O9 hydrogen bonds in compound (**5**) link its molecules A and B into dimers. Further intermolecular C-H…O and C-H…π hydrogen bonds link the dimer chains to form supramolecular structure of angelicain (**5**) (**Fig. 6**) [38]. In compound (**10**), beside the stabilization by C–H…O interaction, the molecule is further stabilized by one C–H…π (arene) hydrogen bond with H…centroid distance of <2.7 A which serves to link molecules in the layers [41]. Besides, hydrogen bond, there is C-H.....π interaction (proton to centroid distance 2.958 (2) Å and C–H..... Centroid angle 116.6(3) in the crystal lattice of compound **16** [45]

5.4 π–π interaction in flavonoids:

π–π interaction can govern the self-assembly of a wide variety of natural *O*-heterocycles. They can define the molecular packing and stacking in the crytal of the compound.

The crystal structure of compound (**1**) is stabilized by hydrogen bond, C-H…O and C-H…π interactions. Classical hydrogen bonds form the chain of the molecules and these chains are packed to form layers in anti-parallel manner which is stabilized by C-H**…**π interactions. This arrangement makes possible the most common interaction, π–π contact, among aromatic nucleus of the compound [38]. In the same process as compound (**1**), in the compound (**2**), the chains are formed by hydrogen bonds and these chains are linked to form the three-dimensional framework. The three dimensional framework of marmesin (**2**) is further stabilized by π–π interactions between the pyrone and phenyl rings (**Fig. 8**). The interacting molecules are related by unit-cell translations along the short a-axis [38].

In the crystal structure of heratomol benzoate (**3**), intermolecular C-H…π and π–π interactions are observed and these interactions have influence on the packing of molecules in the unit cell. The molecules form π–stacked columns along the a-axis with a stacking distance of about 3.30Å between their planar tricyclic furanocoumarin fragments. Despite the out-of-plane rotation, the phenyl rings D are situated on the external sides of the overlapping furanocoumarin nuclei and do not hinder their strong π–stacking [38]. Crystal structure of compound (**4**) contains two crystallographically independent molecules A and B. Here, π–π interaction plays an important role in between these two crystallographically independent molecules. π-π interactions link molecules A and B into dimers (**Fig. 10**). Molecules A and B are oriented in a manner that facilitates intermolecular π-π interactions [38].

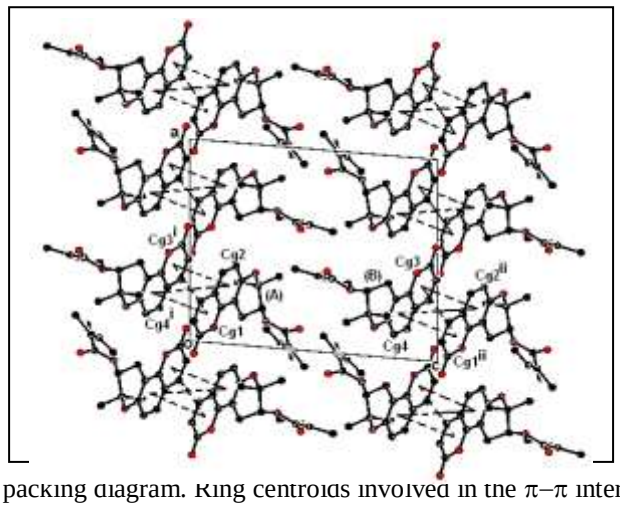
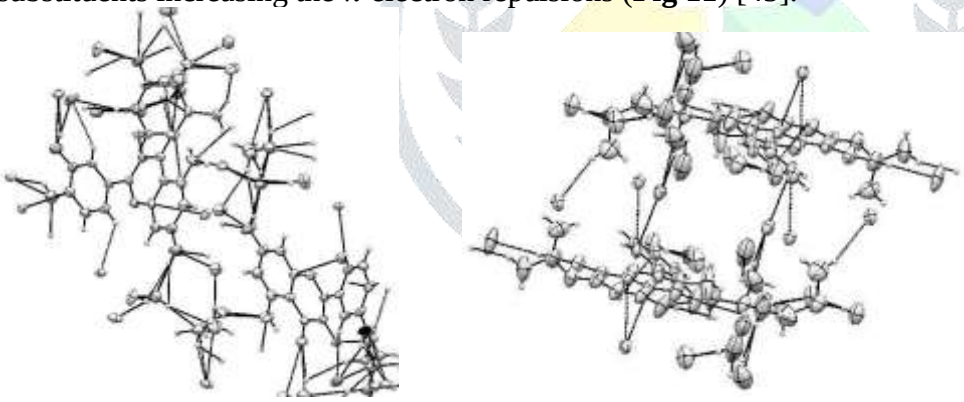


Fig. 10 A crystal packing diagram. Ring centroids involved in the π–π interactions are joined by dashed lines. Hydrogen atoms have been omitted for clarity.

Crystal structure of compound (**5**) also contains two crystallographically independent molecules A and B. Intermolecular O16-H16…O9 hydrogen bonds and π–π interactions link molecules A and B into dimers. Molecules A and B are oriented in a manner that facilitates intermolecular π–π interactions [38]. In compound (**9**), the layers are formed by C6′–H16…O4 interactive bond and within the layers, the dimmers are arranged in a parallel fashion and stabilized themselves by π–π interactions [41]. Molecule of compound (**10**) within the layer formed by C–H…O and C–H…π (arene) interactions are further stabilized by π–π interactions between pyrone and phenyl ring [41]. It is reported that flavonoids (**15**-**16**) have a tendency to be stabilized by intermolecular π□π interactions in the solid state **[**7**].** Jiang et al described the presence of π–π interaction in flavonoids **15** and **16** for the stabilization of the crystal packing. The geometries of π–π interactions in **15** and **16** are, as evidenced by X-ray crystallographic study, to adopt an offset face-to-face interaction in a ring B (π-rich)–ring C (π-deficient) contact mode with centroid-centroid distances of 3.802(4) Å and 3.741(3) Å, respectively. The distance between two centroids is in the upper range of normal π–π interactions. It is also stated that this is because of the fact that ring A and ring B are polarized by the electron donating OH substituents increasing the π-electron repulsions (**Fig 11**) [45].



15 **16**

Fig. 11 Crystal Packing of Compound **15** and **16**

6. Some analysis:

On the basis of above discussion, it is to be noted that the weak interactive forces play an important role in stabilizing the molecular framework of natural flavonoids. Weak intermolecular interactions play a decisive role in determining the three-dimensional structure of molecular crystals. Classical hydrogen bonds are by far the most important – and best known of these interactions, but in the absence of strong hydrogen-bond donors or acceptors (or sometimes in spite of their presence), other weak interactions (C-H…O, C-H…π and π–π) play a crucial part in assembling the molecules into an organized supramolecular structure. An analysis of π–π interactions reveals that near face-to-face alignment of the aromatic rings is extremely rare. The usual π–π stacking is an offset arrangement of the rings *i.e.* the rings is parallelly displaced. Such a parallelly displaced structure has a contribution from π–σ attraction, the more so with increasing offset. An analysis of the dihedral angles between the pyrone and benzene rings in flavonoidal compounds reported in this review shows the perfect planarity of the benzopyran moiety. The planarity of the benzopyran moiety confirms the aromatic character of this system. An analysis of the π–π interactions in compounds incorporating the benzopyran

moiety and having two independent molecules, say,A and B, per asymmetric unit, shows that the molecules, A and B, are connected by π–π interactions forming dimers. In 5-hydroxy-6,7,4'-trimethoxyflavone, intermolecular C6'-H16…O4 hydrogen bond links the molecules into dimers. The dimers are arranged in a manner to form layers. Within the layers, the dimers are stabilized by π-π interactions. In the molecule, the crystal structure is stabilized by the presence of C-H…O, C–H...π and π–π interactions. The short C-H…O intramolecular contact C2'-H12...O1=2.733(2) Å in 5-hydroxy-6,7,4'-trimethoxyflavone can maintain the phenyl ring nearly coplanar with the benzopyran plane. Hydrogen bonds are frequently responsible for stabilization of the crystal structures of hydroxyflavonoids. When a hydroxy group is located at C-5, an intramolecular hydrogen bond is formed with the neighbouring carbonyl oxygen atom. The length of the carbonyl bond agrees with this hydrogen bond. A continuous chain of hydrogen-bonded molecules is formed in some of flavonoids molecules with a hydrogen bond donor group (-OH) at one end and an acceptor (C=O) at the other. Ultimately, all these four weak interactions play the crucial role in the molecule of natural flavonoids.

7. Conclusion: The flavonoids have many benefits to the human health; the problem lies with their solubility and bioavailability that limits their usage. So the understanding of the molecular framework can help us to predict their chemical properties. X-ray crystallographic study is an important tool to understand the stabilization of the natural flavonoids in their molecular crystals to know their properties in better way. Crystal engineering can also be applied to these natural molecules based on the knowledge of X-ray crystallographic reports. Thus, this resume will surely enrich the ongoing research on stability, chemical and biological properties of natural flavonoids.

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