Quantitative Insights into Energy Contribution of Weak Intermolecular Interactions in Angular Furanocoumarin Derivatives

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Abstract: Crystal packing of seven derivatives of angular furanocoumarin derivatives obtained from CSD search is presented in the form of systematic analysis of interaction energies between neighbouring molecular pairs in the crystal rather than in terms of interaction between atoms in neighbouring molecules. Lattice energy of all the compounds and intermolecular energies of neighbouring molecular pairs partitioned into coulombic, polarization, dispersion and repulsion contributions are calculated by PIXEL-semiclassical density sums (SCDS) method. It has been found that aromatic ring stacking ($\pi\ldots\pi$) contribute more to the cohesive energy of the crystals. Weak intermolecular C-H…O and C-H… π hydrogen bonds also make significant contributions towards the stabilization of the structure.

Keywords: Furanocoumarin, PIXEL, Hydrogen bonding, Intermolecular interactions, Lattice energy

Introduction

Furanocoumarins are an important class of tricyclic aromatic compounds consisting of a fused structure of coumarin and furan nucleus. Among furanocoumarin derivatives, psoralen and xanthotoxin are most abundant linear furanocoumarin where as the angular type is mostly represented by angelicin and sphondin. Furanocoumarin derivatives are of interest because of their high photobiological activity[1-3]. Both linear and angular furanocoumarins exhibit interesting pharmacological activity, but angular structure reduces the undesirable side effects[4] such as genotoxicity[5] and skin cancer[6] as observed in case of linear furanocoumarin. Therefore, angular furanocoumarins have been paid considerable attention. The occurrence of different kinds of intermolecular interactions in crystal structures will result in different chemical and biological activities which is quite beneficial to pharmaceutical industries[7]. Strong intermolecular interactions such as N-H…O/N and O-H…O/N are well understood and are found to play a vital role in crystal packing.[8] In the last few decades, the main focus is to exploit the role of weak intermolecular interactions such as C–H···O/N[9,10], C–H···X(halogen atom)[11,12], C–H···π,[13] π···π,[14] and lp···π[15] interactions present in the crystal structure. Quantitative evaluation of these interactions is required to have

better understanding of the contribution of these interactions towards crystal packing. In this regard, CSD search has been carried out and have identified a series of seven structures belonging to angular furanocoumarin derivatives. The lattice energy of the identified structures has been calculated theoretically by PIXEL approach[16]. The theoretical calculation of the lattice energy of a crystal provides a better idea about the nature of crystal packing which corresponds to the experimentally calculated sublimation energy of the compound[17]. Molecular pairs were extracted from the crystal packing (after PIXEL calculation) and the nature and energy of the intermolecular interactions associated with the extracted molecular pairs was determined. A representative illustration of the coumarin moiety indicating the atomic numbering scheme used for the present work is shown in Figure 1. The chemical name, molecular code, chemical structure for each structure is presented in Table 1 and its precise crystallographic data in Table 2.
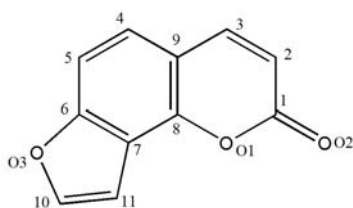

Figure 1. Chemical structure of the furanocoumarin moiety and the numbering scheme used
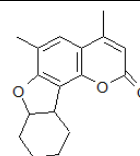
Table 1. Chemical name, coding scheme and Chemical structure of the compounds

| Chemical Name	Code	Chemical structure
Furo(2,3-h) coumarin[18] (Angelicin)	C-1	
8,9-Dihydro-8-(1-methyl ethenyl)-2*H*-furo [2,3-h] -1- benzopyran-2-one[19] (Angelomalin)	C-2	
Syn-5,6-dimethoxy-2*H*-furo(2,3-h)-1-benzopyran-2-one[20]	C-3	
5-Acetoxy-6-(1,1-dimethyl-2-propenyl)-2*H*-furo(2,3-h)(1) benzopyran-2-one[21]	C-4	
3-Phenyl-2*H*-furo(2,3-h)-1-benzopyran-2-one[22]	C-5	

Contd...

| 4,6-Dimethyltetrahydro benzoangelicin[23] | C-6 | |
| 3-Methylbutanoic acid (8S,9R)-8,9-dihydro-8-(1-hydroxy-1-methylethyl)-2-oxo-2*H*-furo [2,3-h]-1-benzopyran-9-yl ester[24] (Vaginidin) | C-7 | |
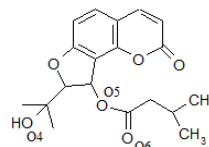
Table 2. Precise crystallographic data of angular furanocoumarin derivatives

Data	C-1	C-2	C-3	C-4	C-5	C-6	C-7
Formula	$C_{11}H_6O_3$	$C_{14}H_{12}O_3$	$C_{13}H_{10}O_5$	$C_{18}H_{16}O_5$	$C_{17}H_{10}O_3$	$C_{17}H_{16}O_3$	$C_{19}H_{22}O_6$
Mol. Weight	186.17	228.24	246.22	312.33	262.27	270.33	346.38
Crystal system	Orthorhombic	orthorhombic	Monoclinic	monoclinic	rhombohedral	tetragonal	orthorhombic
Space group	P n a 2_1	$P2_1\,2_1\,2_1$	P 2_1/n	P 2_1/n	R -3	P 42/n	$P2_1\,2_1\,2_1$
a(Å)	11.527(9)	5.210(1)	90690(10)	9.238(1)	41.021(10)	21.006(5)	9.781(1)
b(Å)	18.97(2)	10.407(1)	13.4984(5)	10.959(1)	41.021(10)	21.006(5)	17.328(6)
c(Å)	3.781(5)	20.478(2)	20.9360(9)	15.168(1)	3.888(2)	6.055(3)	21.633(2)
α(°)	90	90	90	90	90	90	90.0(10)
β(°)	90	90	91.733(2)	90.64(1)	90	90	90.0(10)
γ(°)	90	90	90	90	120	90	90.0(10)
R	0.057	0.037	0.0557	0.045	0.034	0.0662	0.078

Theoretical calculations

The lattice energies of all the compounds have been calculated by PIXEL using the coulomb-London-Pauli (CLP) model of intermolecular coulombic, polarization, dispersion and repulsion energies[16]. For this purpose H atoms were moved to their neutron value. Two output files are generated after the end of the calculation. The first (.pri file) consists of the total lattice energies partitioned into their coulombic, polarization, dispersion and repulsion contributions (Table 3). The second (mlc file) consists of a molecule–molecule interaction energy along with the symmetry elements which relate to the molecules. The interaction energy of selected molecular pairs (from the .mlc file), extracted from the crystal packing along with the involved intermolecular interactions are listed in Table 4, with the total energies being partitioned into their coulombic, polarization, dispersion and repulsion contributions. The molecular pairs are arranged in decreasing order of their stabilizing energies. The geometrical restrictions placed on the intermolecular H-bonds present in the selected molecular pairs are the sum of the Vander Waals radii + 0.4Å and the directionality is greater than 110°.

Results and Discussion

Furo(2,3-h) coumarin (C-1)

All the molecular pairs (1-6) extracted from the crystal packing are shown in the Figure 2. The most stabilizing molecular pair shows the presence of $C(sp^2)$-H…O hydrogen bonding involving H10 with O2 and H11 with O1, having an interaction energy of -6.21 kcal mol^{-1} (Figure 2, motif 1) with 45% contribution to stabilization from coulombic component.
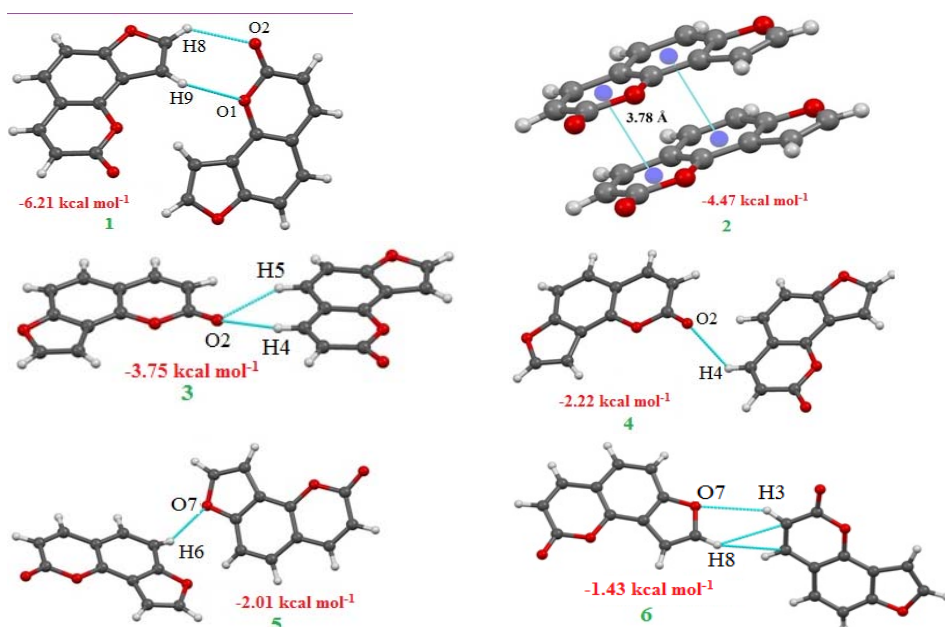
Figure 2. Molecular pairs (1-6) along with their interaction energies in C-1

Table 3. Lattice energy from CLP (in kcal mol^{-1})

Molecule	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
C-1	-8.60	-3.11	-24.66	15.46	-20.93
C-2	-9.39	-3.87	-30.59	18.06	-25.81
C-3	-11.12	-4.30	-30.21	18.59	-27.10
C-4	-9.82	-3.66	-33.43	17.99	-28.92
C-5	-8.77	-4.01	-34.5	19.41	-27.91
C-6	-10.01	-4.56	-35.32	22.9	-26.98
C-7	-14.98	-6.02	-34.29	22.37	-32.91

Table 4. PIXEL interaction energies (I.E.) (kcal/mol) between molecular pairs related by a symmetry operation and the associated intermolecular interactions in the crystal

Motif	Centroid Distance (Å)	E_{Coul}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}	Symmetry	Important interactions
				C-1				
1	6.296	-4.11	-1.34	-3.73	2.96	-6.21	1-x,1-y,-1/2+z	C10-H10…O2 C11-H11…O1
2	3.781	-0.35	-0.86	-10.15	6.9	-4.47	x,y,-1+z	π…π
3	8.945	-2.77	-0.98	-2.08	2.05	-3.75	-1/2+x,1/2-y,-1+z	C3-H3…O2 C4-H4…O2
4	8.107	-0.55	-0.59	-2.34	1.26	-2.22	1/2+x,1/2-y,z	C3-H3…O2
5	8.063	-0.50	-0.28	-2.36	1.15	-2.01	-x,1-y,-1/2+z	C5-H5…O3
6	9.734	-0.16	-0.24	-1.69	0.67	-1.43	1/2-x,1/2+y,-1/2+z	C2-H2…O3 C10-H10…π (C3, C4)
				C-2				
1	5.210	-1.67	-1.17	-9.11	5.74	-6.21	-1+x,y,z	Molecular stacking, C11-H11b…O3, C14-14c…C13, H11b…H10

Contd...

							Symmetry	Interactions
	5.831	-1.48	-0.96	-5.16	2.63	-4.99	-1/2+x, 1/2-y,2-z	C11-H11b…O1, C11-H11b…O2
3	7.380	-0.88	-0.52	-4.58	2.53	-3.46	1-x,-1/2+ y, 3/2-z	C2-H2…π, C3-H3… π, C14-H14a…π
4	8.148	-1.60	-0.91	-4.49	3.58	-3.39	-x,-1/2+y, 3/2-z	C4-H4…O3, H5…H14a
5	11.638	-1.31	-0.38	-1.94	0.91	-2.72	-1+x,-1+y , z	C13- H13a…O2
6	9.396	-1.67	-0.55	-1.09	1.24	-2.08	3/2+x,1/2-y,2-z	C13- H13b…O2
7	12.095	-0.09	-0.12	-1.84	0.78	-1.24	-1/2+x,-1/2-y,2-z	C13 -H13a…C13
8	10.407	-.09	-.09	-1.46	0.64	-1.00	x,-1+y,z	C14-H14b…π(C2, C3)
C-3								
1	8.007	-7.72	-2.31	-5.21	4.71	-10.56	1-x,-y,1-z	C10-H10…O2, C11-H11…O1, C11-H11…O2
2	3.907	-1.86	-1.84	-14.31	9.75	-8.27	1+x,y,z	π…π, C12-H12c…O4 C13-H13c…O5
3	8.023	-2.10	-0.74	-4.09	2.17	-4.71	-x,1-y,1-z	C2-H2…O4, H3…H3
4	8.422	-1.15	-0.62	-4.56	2.34	-3.99	1-x,1-y,1-z	C3-H3…π(C2,C3), H2…H3
5	10.594	-1.86	-0.50	-1.67	1.6	-2.44	1/2+x,1/2-y,1/2+z	C13-H13c…O2, C13-H13a…O2
6	11.844	-1.46	-0.38	-0.74	0.67	-1.91	-3/2+x,1/2 -y,-1/2+z	C13-H13a…O2
7	9.905	-0.0	-0.52	-2.56	1.60	-1.48	-1/2-x,-1/2+y,1/2-z	C12-H12a…C13, C10-H10…C13, H…H
C-4								
1	5.314	-5.81	-2.41	-15.65	11.64	-12.24	1-x,1-y,1-z	Molecular stacking, C11-H11…O5, C13-H13b…O1
2	5.666	-2.41	-1.19	-10.39	4.73	-9.27	-x,1-y,1-z	Molecular stacking, C14-H14b…O2, C15-H15…O2
3	9.140	-1.74	-0.66	-5.31	2.32	-5.37	1-x,2-y,1-z	C16-H16a…O5
4	9.274	-0.57	-0.74	-5.54	3.13	-3.70	-1/2+x, 3/2-y,1/2 +z	C18-H18b…O3, H…H
5	9.349	-0.67	-0.50	-5.02	2.77	-3.44	-x,2-y,1-z	C15-H15…C18, H15…H18c
6	10.959	-1.41	-0.55	-2.25	1.19	-3.01	x,1+y,z	C18-H18a…O2, C11-H11…C16
7	12.280	-2.15	-0.48	-0.98	0.86	-2.78	-1/2+x, 1/2-y,1/2 +z	C10-H10…O2
8	9.176	-0.28	-0.19	-3.68	1.86	-2.29	1/2-x,1/2+y,1/2-z	C14-H14a…π C14-H14b…π
C-5								
1	8.047	-6.95	-2.13	-5.40	4.80	-9.68	2/3-x,1/3-y,-2/3-z	C10-H10…O2 C11-H11…O1
2	3.888	-0.55	-1.22	-15.11	9.15	-7.74	x,y,-1+z	π...π

Contd...

3	8.243	-1.12	-0.52	-3.99	1.43	-4.21	2/3-x,1/3-y,1/3-z	C11-H11…C11 C11…C11
4	10.217	-1.69	-0.64	-2.94	1.88	-3.39	1/3+y,2/3-x+y,- 4/3-z	C14-H14…O2 C15-H15…C16
5	9.129	-0.74	-0.59	-4.08	2.15	-3.27	2/3-x+y, 1/3-x,-2/3 +z	C3-H3…O3, C13-H13…O3, C5-H5…C4, H10…H13
6	8.848	-0.45	-0.43	-3.20	1.65	-2.44	1/3-y,-1/3 +x-y,-1/3 +z	C4-H4…O3, C4-H4…π(C5,C6)
7	9.350	-0.52	-0.31	-2.79	1.43	-2.19	1/3+y,2/3-x+y,-1/3-z	C17-H17…π (C14, C15) H15…H16
C-6								
1	6.055	-2.29	-1.65	-12.21	8.72	-7.41	x,y,-1+z	C12-H12b…O2, C15-H15a…O1, Stacking, H16a…H7c
2	6.818	-2.25	-1.26	-8.03	4.68	-6.88	1-x,1-y,-z	C16-H16b…O2, stacking
3	10.954	-3.99	-1.88	-3.56	3.89	-5.54	1-x,1-y,-1-z	C2-H2…O2, C16-H16c…O2, H2…H2
4	8.155	-2.13	-1.07	-7.19	5.42	-4.95	1/2+y,1-x,-1/2+z	C4-H4…O3, C16-H16b…π(C 10, C15)
5	8.565	-1.88	-0.72	-2.34	1.43	-3.51	y,1/2-x,1/2-z	C15-H15b…O2
6	10.481	-0.45	-0.31	-3.11	1.93	-1.93	1/2-y,x,3/2-z	C14-H14a…π(C 13)
C-7								
1 A…B	5.137	-4.56	-2.17	-14.01	8.96	-11.81	1-x,1/2+y, 3/2-z	π…π, C10-H10…O2' C10'-H10'…O2
2 A…B	9.560	-10.66	-4.18	-5.68	10.68	-9.85	x,y,z	C11-H11…O6' O4′-H40′…O4 C14′…H14a′…O4
3 A…B	5.955	-1.57	-0.72	-10.63	4.75	-8.17	1/2+x,3/2-y,2-z	C13'-H13b'…O4 C19'-H19b'…π C19…Cg1
4 A…B	9.011	-1.65	-0.72	-5.40	2.67	-5.11	-1+x,y,z	C5-H5…O3′ C14′-H14a′…π (C4′,C5′)
5 B…B	9.781	-1.98	-0.74	-3.61	1.36	-4.97	-1+x,y,z	C3′-H3′… O5′ C4′-H4′ … O5′
6 A…A	10.547	-2.19	-0.72	-4.01	2.32	-4.61	2-x,-1/2+ y,3/2-z	C5-H5…O2 C2-H2… O3 C14-H14a…π(C2, C3)
7 A…A	9.781	-1.72	-0.76	-4.46	2.48	-4.47	-1+x,y,z	C3-H3…O6
8 A…B	10.926	-2.61	-0.69	-2.15	1.09	-4.34	1+x,1+y,z	C2-H2…O2′ C2′-H2′… O2
9 A…A	10.088	-1.19	-0.79	-3.84	2.94	-2.89	1-x,-1/2+y,3/2-z	C14-H14c…O6 C13-H13b…O2

Contd...

10 B…B	10.212	-0.38	-0.33	-3.54	1.43	-2.82	-1/2+x, 3/2-y,2-z	C14′-H14b′…C5′ H13c′…H5′
11 A…B	10.119	-0.43	-0.28	-2.36	0.97	-2.10	-x,1/2+y,3/2-z	C2′-H2′… C13 C3′-H3′… C13
12 B…B	11.014	-0.12	-0.33	-1.84	1.03	-1.26	1/2+x,1/2-y,2-z	C19′-H19a′…O2′

A and B refers to two molecules in the asymmetric unit cell while 'indicate the second crystallographically independent molecule

The second most stabilized molecular pair in the crystal structure, formed via $\pi…\pi$ molecular offsets (Cg1 and Cg2 with Cg1 and Cg2 of another molecule, where Cg1 is centroid of pyrone ring and Cg2 is centroid of benzene ring, centroid to centroid distance is 3.78Å) along the crystallographic c axis, has a contribution of -4.47 kcal mol^{-1} (90% contribution to stabilization from the dispersion energy) to the stabilization of the packing. These molecular stacks are interlinked via weak $C(sp^2)$-H…O intermolecular hydrogen bonds involving bifurcated acceptor atom O2 with H3 and H4(motif 3, -3.75 kcal mol^{-1}), H3 with O2 (motif 4, -2.22 Kcal mol^{-1}) and H5 with O3 (motif 5, -2.01 kcal mol^{-1}) forming a layered arrangement down the ac plane as shown in Figure 3a. However in the bc plane, the adjacent stacks are interconnected via motif 6 (-1.43 Kcal mol^{-1}) showing the presence of $C(sp^2)$-H2…O3 and $C(sp^2)$-H10…π intermolecular contacts (Figure 3b).
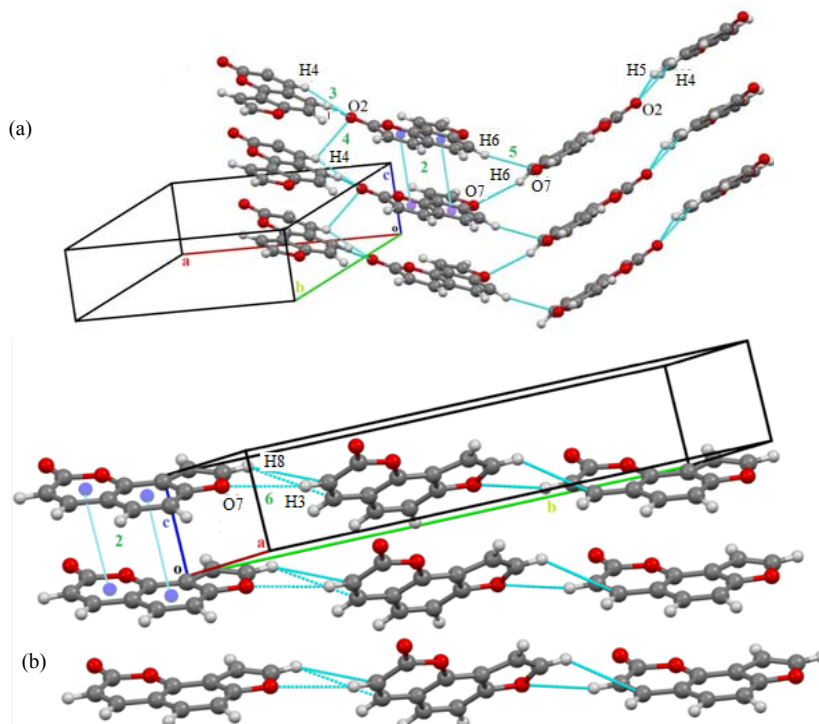

Figure 3. Packing view of the molecules depicting aromatic stacking interactions in C-1 down the (a) ac plan (b) bc plan

8,9-Dihydro-8-(1-methyl ethenyl)-2H-furo[2,3-h] -1- benzopyran-2-one (C-2)

All the molecular pairs (1-8) extracted after the PIXEL calculation are represented in Figure 4 along with their interaction energies. Molecules are stacked along the crystallographic a axis

utilizing motif 1. Motif 1 is the most stabilized pair with an interaction energy of -6.21 kcal mol^{-1} in the crystal packing and consist of weak C-H…O (involving H11b with O3) and molecular stacking along with C-H…C and H…H interaction. The nature of the combined interaction is predominately dispersive in nature (75% contribution to total stabilization comes from dispersion energy). Adjacent stacks are then interlinked via motif 5 and 8 (Figure 5). Motif 5 (I.E. = -2.72 kcal mol^{-1}) involves the presence of weak C-H…O (involving H13a with O2) whereas the presence of C-H…π links the molecules in motif 8 (I.E. = -1 kcal mol^{-1}). The second most stabilized pair involves the interaction of bifurcated donor H11b with acceptor atoms O1 and O2, contributing -4.99 kcal mol^{-1} towards crystal stability. Another molecular pair shows the presence of C-H…π hydrogen bond (motif 3, Figure 4) having an interaction energy of -3.46 kcal mol^{-1}. Motif 4 (I.E.= -3.39 kcal mol^{-1}) involves the presence of C-H…O (involving H4 with O3) along with H…H interaction whereas another C-H…O interaction links the molecules in motif 6 (I.E.= -2.08kcal mol^{-1}). Furthermore, additional stabilization of −1.24 kcal mol^{-1} was also observed to be provided by motif 7.
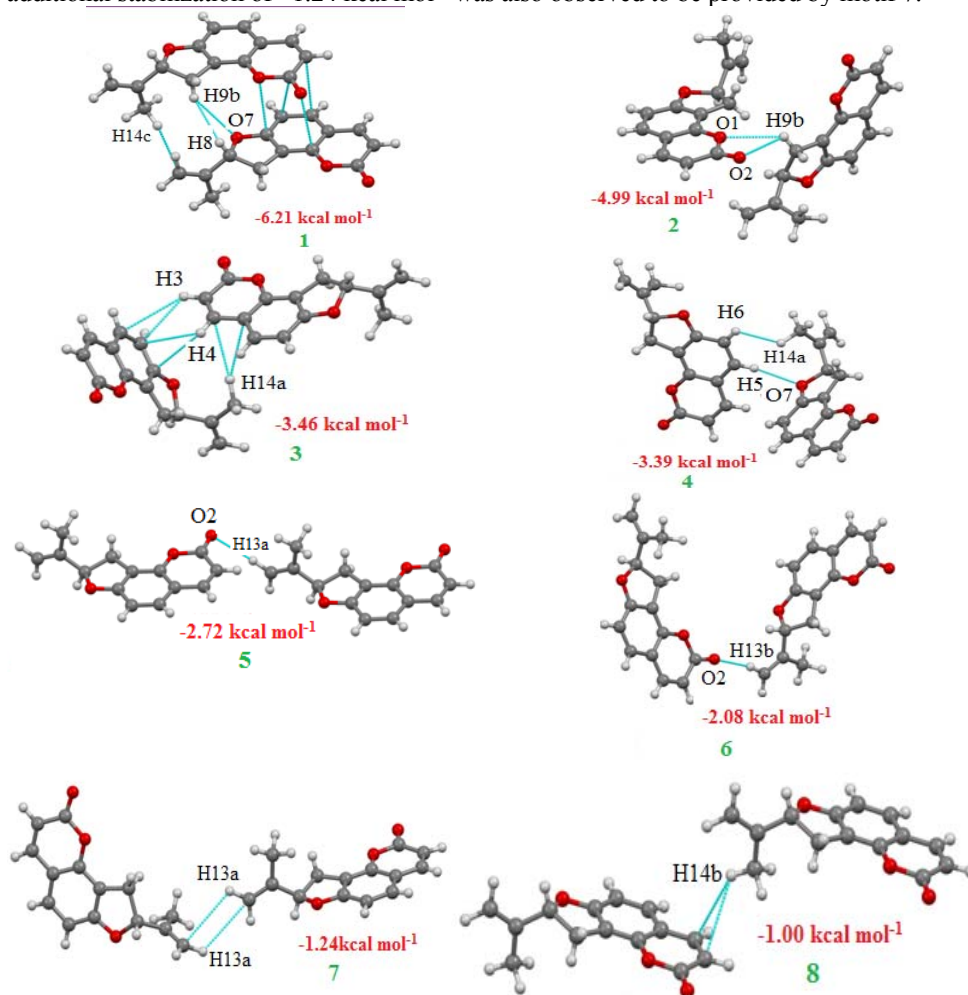

Figure 4. Molecular pairs (1-8) along with their interaction energies in C-2
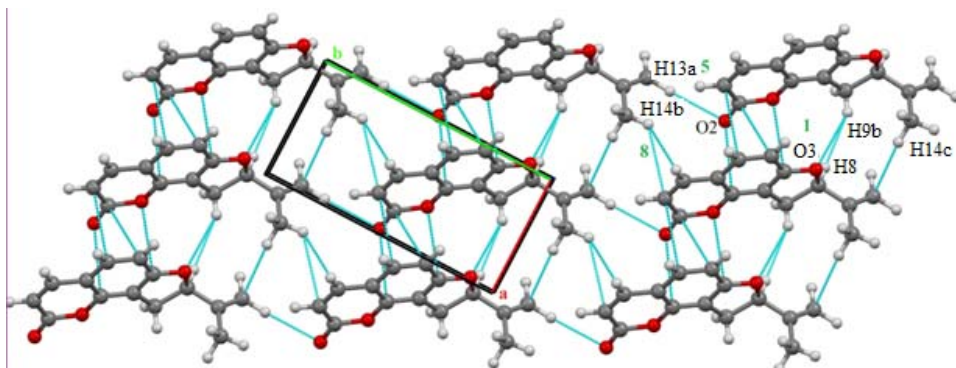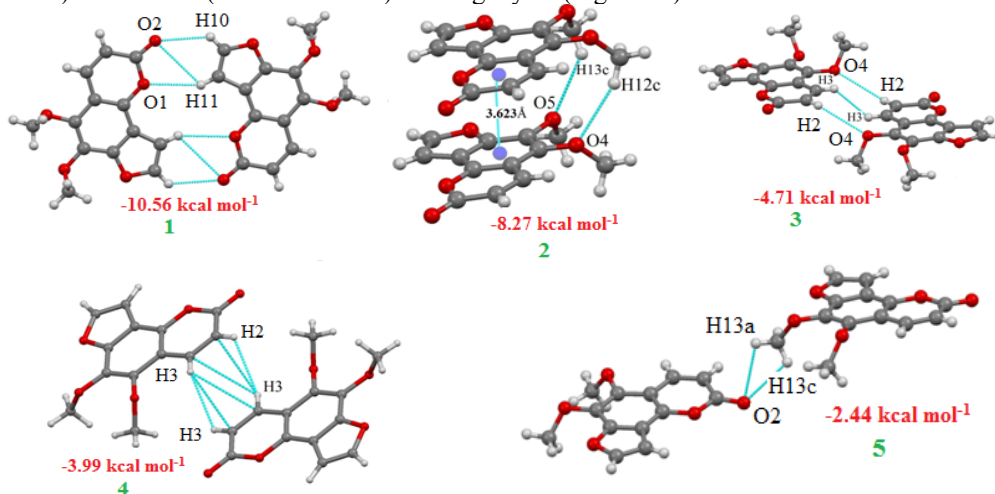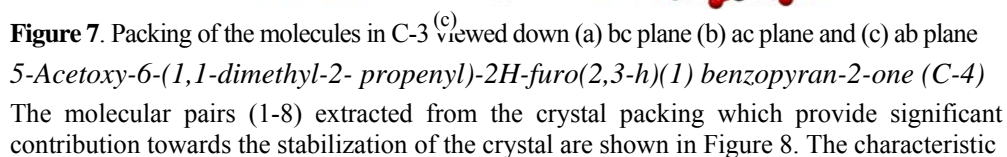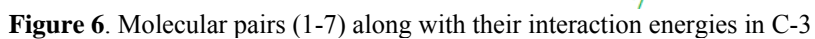
Figure 5. Packing of molecules in C-2 showing stacking of the molecules down the ab plane

Syn-5,6-dimethoxy-2H- furo(2,3-h)-1-benzopyran-2-one (C-3)

The principal packing motifs (1-8) along with their respective interaction energies are shown in Figure 6. In this compound, the maximum stabilization comes from weak $C(sp^2)$-H…O interactions, involving bifurcated donor H11 with O1 and O2 and H10 with bifurcated acceptor O2, generating dimers in the crystallographic bc plane acting across the centre of symmetry. The energy stabilization of this dimer is -10.56 Kcal mol^{-1} as obtained from energy calculation performed using PIXEL. One striking feature of this dimer is that the share of coloumbic component in the total stabilization is 50%. These dimers are then interconnected via motif 4 ($C(sp^2)$-H3…π, I.E. = -3.99 kcal mol^{-1}) and motif 5 (weak C-H…O hydrogen bonds involving H13a and H13c with O2 being the acceptor atom, I.E. = -2.44 kcal mol^{-1}) forming sheets in the bc plane (Figure 7a). The second most stabilized molecular pair in the crystal formed via π…π stacking interaction along with weak C-H…O interaction (involving H12c with O4 and H13c with O5) has a contribution of -8.27 kcal mol^{-1} (with major dispersion contribution) to the stabilization of the crystal packing. Adjacent stacks are connected via weak C-H…O hydrogen bonds (motif 5 and motif 6 with stabilization energies being -2.44 and -1.91 Kcal mol^{-1}) in the ac plane (Figure 7b). However in the ab plane, molecular stacks formed by motif 2 are connected via motif 3 (dimeric $C(sp^2)$-H2…O4 along with H3…H3 interaction, I.E. = -4.71 kcal mol^{-1}) motif 4 (-3.99 kcal mol^{-1}) and motif 7 (-1.48 kcal mol^{-1}) forming layers (Figure 7c).

Figure 6. Molecular pairs (1-7) along with their interaction energies in C-3

(a)

(b)

(c)

Figure 7. Packing of the molecules in C-3 viewed down (a) bc plane (b) ac plane and (c) ab plane

5-Acetoxy-6-(1,1-dimethyl-2- propenyl)-2H-furo(2,3-h)(1) benzopyran-2-one (C-4)

The molecular pairs (1-8) extracted from the crystal packing which provide significant contribution towards the stabilization of the crystal are shown in Figure 8. The characteristic

packing feature in this molecule consist of molecular stacking along with weak C-H…O hydrogen bonds. The key packing motifs(1,2) in this structure shows the presence of molecular stacking along with weak C-H…O hydrogen bonds involving H11, H13b with O5 and O1(motif 1, interaction energy(I.E) being -12.24 kcal mol^{-1}) and bifurcated acceptor atom O2 with H14b and H15 (motif 2, I.E = -9.27 kcal mol^{-1}). The combined nature of the interaction in these two pairs is dispersive in nature with 65% (motif 1) and 75% (motif 2) of contribution from dispersion component. These two structural motifs (1,2) are stacked alternatively along the crystallographic a axis. Adjacent stacks are then interconnected via motif 3(dimeric C-H…O), 5 and 6 having energies -5.37, -3.44 and -3.01 kcal mol^{-1} respectively (Figure. 9b). The packing in the crystal also displays the formation of molecular chain via C(sp^3)-H18a…O2 along with C(sp^2)-H11-C16 (motif 6, I.E = -3.01 Kcal mol^{-1}) along b- axis. The molecular chains are then interlinked by more stabilized motif 4 (C(sp^3)-H18b…O3 along with H…H interaction, I.E. = -3.7 Kcal mol^{-1}) and motif 7 (C(sp^2)-H10…O2, I.E. = -2.78 Kcal mol^{-1}, 60% contribution from coulombic component) forming sheets in the bc plane (Figure. 9a). However, it is observed that motif 8 showing C-H…π also provides additional stabilization of -2.29 kcalmol^{-1}.
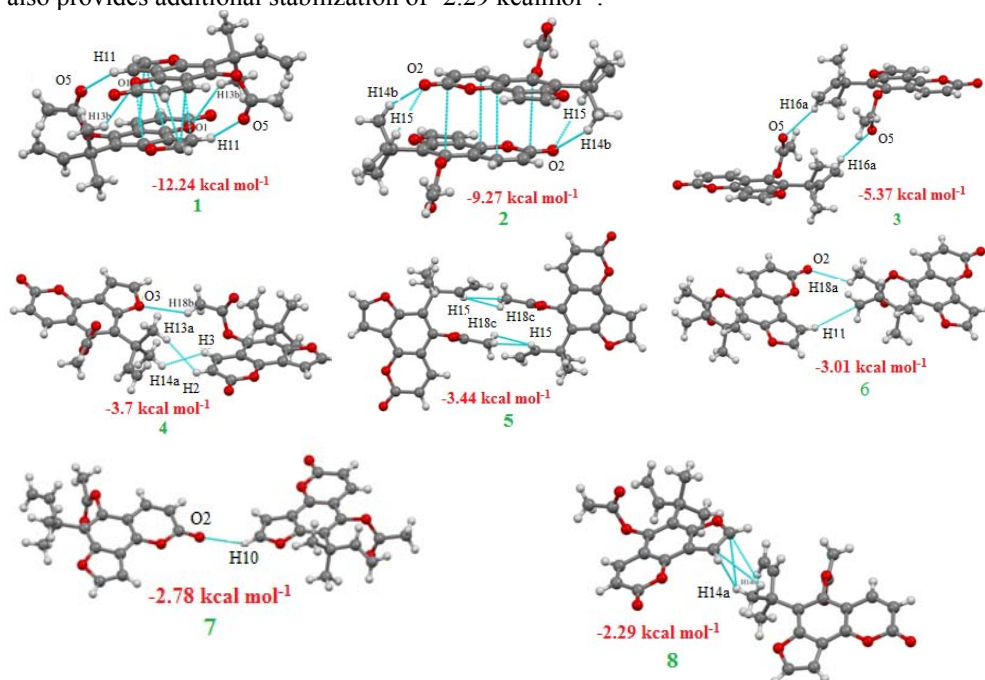

Figure 8. Molecular pairs (1-8) along with their interaction energies in C-4

3-Phenyl-2H-furo(2,3-h)-1- benzopyran-2-one (C-5)

The important packing motifs (1-7) extracted from crystal packing along with their stabilization energies are shown in Figure 10. The molecules are packed with the involvement of weak dimeric C(sp^2)-H…O interaction involving H11, H10 with O1 and O2 (motif 1, I.E. = -9.68 Kcal mol^{-1}, about 50% contribution from coulombic component) and H3, H13 with bifurcated acceptor atom O3 along with C-H…π interaction (motif 5, I.E. = -3.27 Kcal mol^{-1}), forming molecular zig-zag chains along the crystallographic b axis. The zig-zag chains thus formed are interconnected via motif 2, 3 and 6 (Figure 11).

Molecular pair 2 involves π…π stacking, contributing -7.74 Kcal mol^{-1} towards stabilization. One striking feature of consideration is that out of the total stabilization of -16.88 kcal mol^{-1}, 90% of stabilization is imparted by dispersion component. Molecular pair 3 shows C-H…C interaction (-4.21 kcal mol^{-1}) whilst the presence of C-H…O and C-H…π hydrogen bond links the molecule in motif 6 (-2.44 Kcal mol^{-1}). Moreover, the presence of motif 4 (I.E = −3.39 kcal/mol) which involves C-H…O(involving H14 with O2) and CH···π interactions and motif 7(I.E=−2.84 kcal/mol) showing weak C-H···π hydrogen bond along with H…H interaction were also observed to stabilize the crystal packing.
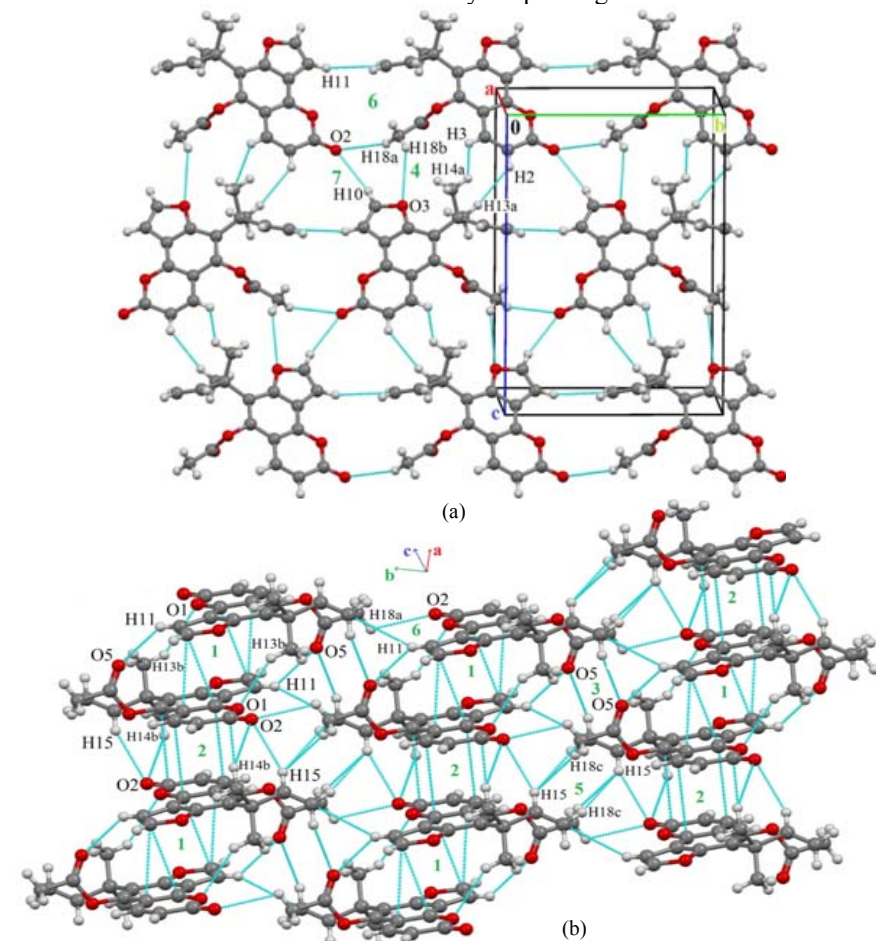

(a)

(b)

Figure 9. Packing of the molecules in C-4 viewed down (a) bc plane (b) ab plane
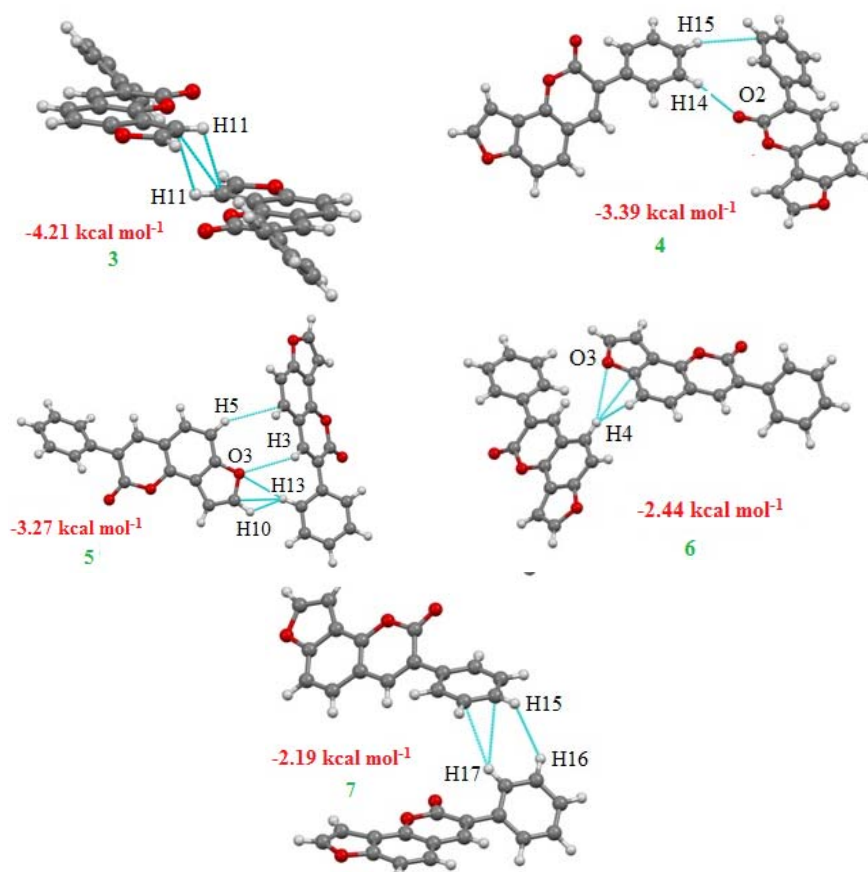
Figure 10. Molecular pairs (1-8) along with their interaction energies in C-5
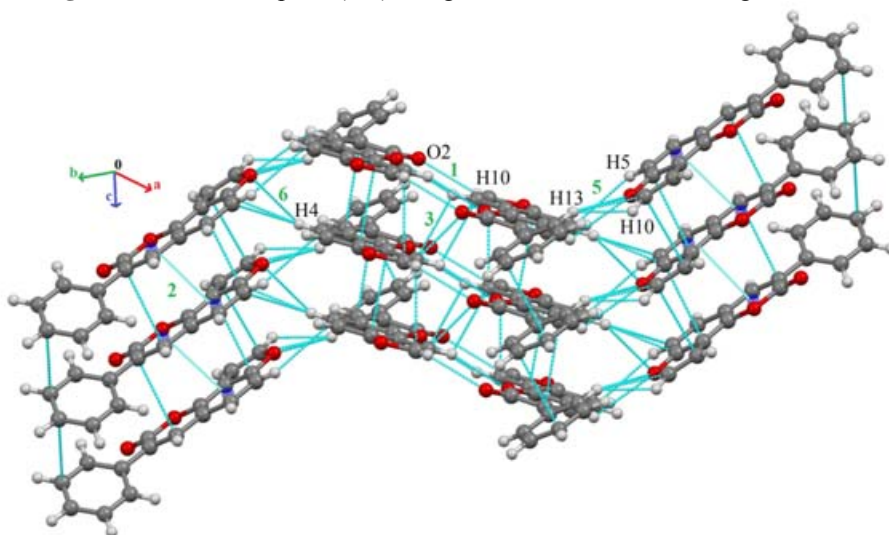

Figure 11. Crystal packing depicting zig-zag arrangement of molecules in C-5

Dimethyltetrahydro benzoangelicin (C-6)

The important molecular pairs (1-6) extracted from the molecular packing are shown in Figure 12. The molecules in this structure are stacked along the crystallographic b axis utilizing weak C-H…O interaction involving H15a with O1 and H12b with O2 along with stacking interaction (C10-C1 with C…C distance being 3.42Å) and C-H…H-C interaction (motif 1). The stabilization energy of this pair is -7.41 kcal mol^{-1} as obtained from energy calculation performed using PIXEL. These molecular stacks are then linked via motif 2 (involving dimeric C(sp^3)-H16b…O2 along with stacking interaction C3…C2 with C…C distance being 3.385Å) and motif 3 (dimeric C(sp^3)-H…O hydrogen bonds involving H16c and H2 with bifurcated acceptor atom O2 along with C(sp^2)-H…H- C(sp^2) with H…H distance being 2.194Å which is less than the sum of their vander waal radii indicating the interaction between the two atoms) having energies -6.88 and -5.54 Kcal mol^{-1} respectively, forming a layered arrangement in the bc plane (Figure 13). Motif 4 involves the presence of weak C(sp^2)-H4…O3 and C(sp^3)-H16b…π hydrogen bonds and contribute -4.95 kcal mol^{-1} towards stabilization. However, additional stabilization of -3.51 and -1.93 kcal mol^{-1} was observed to be provided by motif 5(C15-H15b…O2) and 6(C14-H14a…C13) respectively.
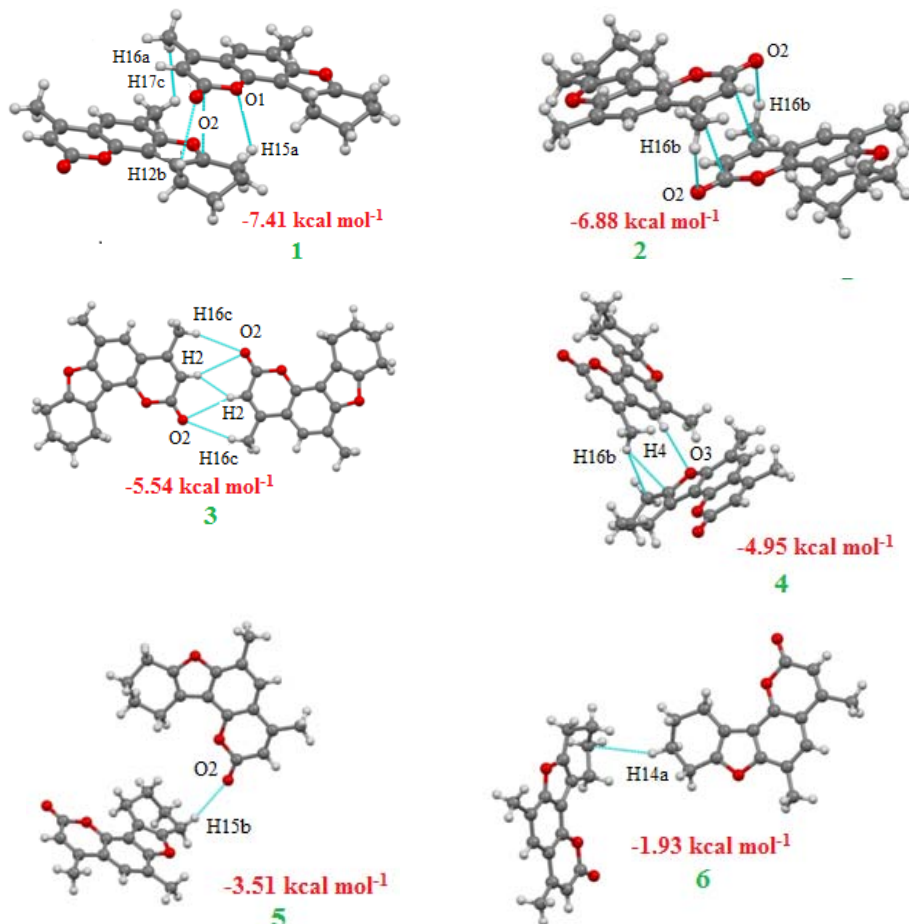

Figure 12. Molecular pairs (1-6) along with their interaction energies in C-6
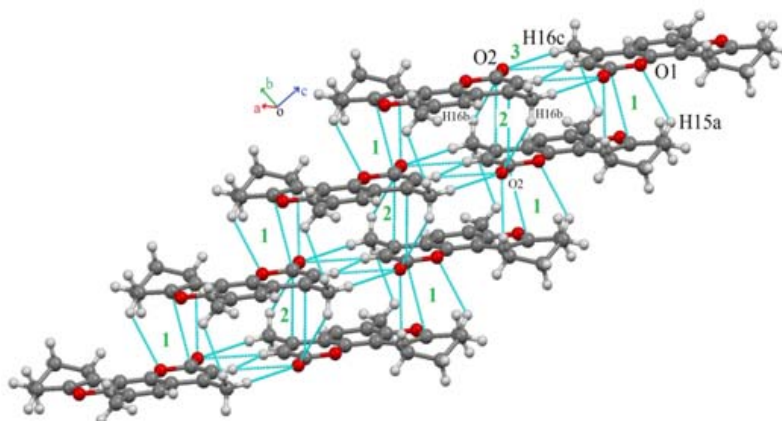
Figure 13. Packing of the molecules viewed down bc plane in C-6

3-Methylbutanoic acid (8S,9R)-8,9-dihydro-8-(1-hydroxy-1-methylethyl)-2-oxo-2H-furo[2,3-h]-1-benzopyran-9-yl ester (C-7)

The different structural motifs (1-12) contributing towards the crystal packing are shown in Figure 14. The molecule crystallizes with two molecules in the asymmetric unit [molecule A (carbon atom = grey colour) and B (carbon atom = violet colour)]. In this compound, there exists three types of molecular pairs A–A, A–B and B–B and energetically A–B type molecular pairs are more stable than the A–A and B–B type. The two molecules in the asymmetric unit are connected with a strong O-H…O and weak C-H…O (involving H40′ and H14a′ with bifurcated acceptor atom O4) hydrogen bonds and this pair is second most stabilized pair in the crystal, energy being -9.85 Kcal mol^{-1}, the principal stabilization of around 50% corresponding to coulombic component. The most stabilized molecular pair in the crystal structure is stacked along the crystallographic c axis via π…π stacking along with weak C-H…O hydrogen bonds and has a contribution of -11.81 kcal mol^{-1}(motif 1) to the stabilization of the crystal packing. These stacks are then interconnected via motif 2,3,4,6 and 8 as depicted in Figure 15a. Molecular pair 5 (bifurcated C-H…O , I.E. = -4.97 kcal mol^{-1}) and 7 (C3-H3…O6, I.E. = -4.47 kcalmol^{-1}) propagates along the same direction forming chains. The two different chains formed by these motifs are interconnected via more stabilized motif 3 (Fig. 15c). Motif 3 involves the presence of C…π (C19…Cg1) interaction along with C-H…O and C-H…π. The combined nature of these interactions is mainly of dispersive nature. The packing in the crystal also displays the formation of molecular chain utilizing motif 6 (-4.61 kcalmol^{-1}) which consist of weak C-H…O and C-H…π hydrogen bond. Motif 7(-4.47 kcal mol^{-1}) and 9 (C-H…O interaction involving H13b with O2 and H14c with O6, I.E. = -2.89 kcalmol^{-1}) interconnects the chains formed by motif 6 as shown in Figure 15b.
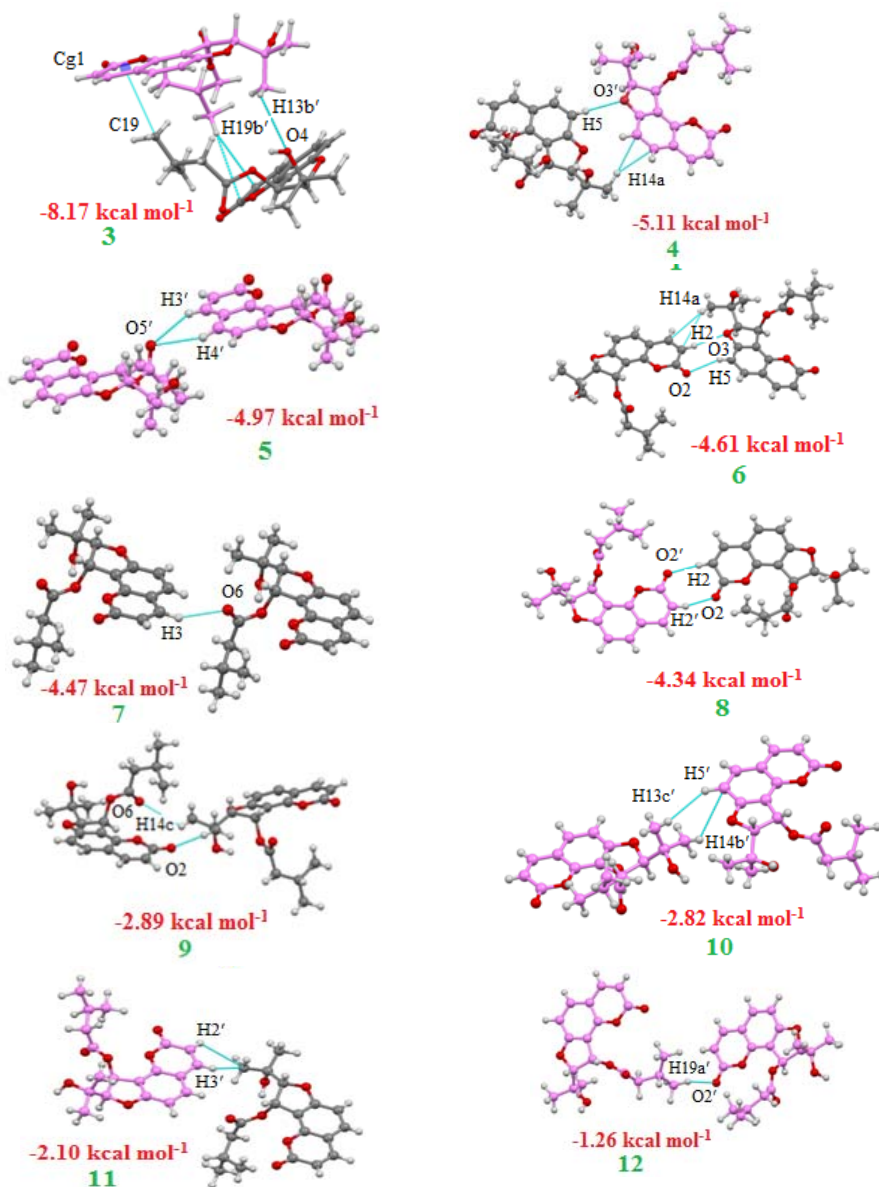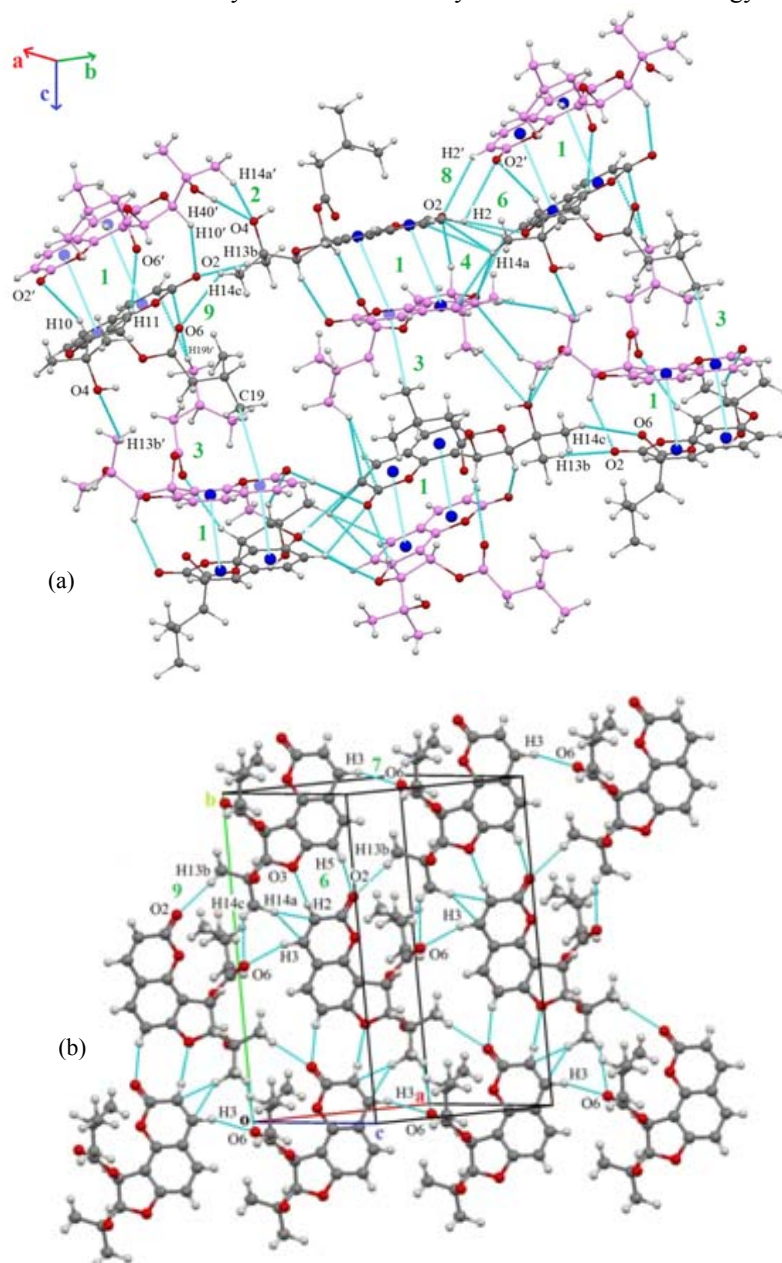
Figure 14. Molecular pairs (1-12) along with their interaction energies in C-7

A careful analysis of the different structural motifs obtained in these compounds leads to the following relevant observations:

1. The structural motifs providing maximum stabilization to the structure shows the presence of C-H…O hydrogen bonds or π…π stacking interactions.
2. The interaction energies of the motifs involving π…π stacking interactions were observed to be in range -4.5 to -11.5 kcal mol⁻¹. These molecular pairs show significantly high dispersion component when compared to related molecular pairs showing the presence of intermolecular hydrogen bonds in the crystal structure.
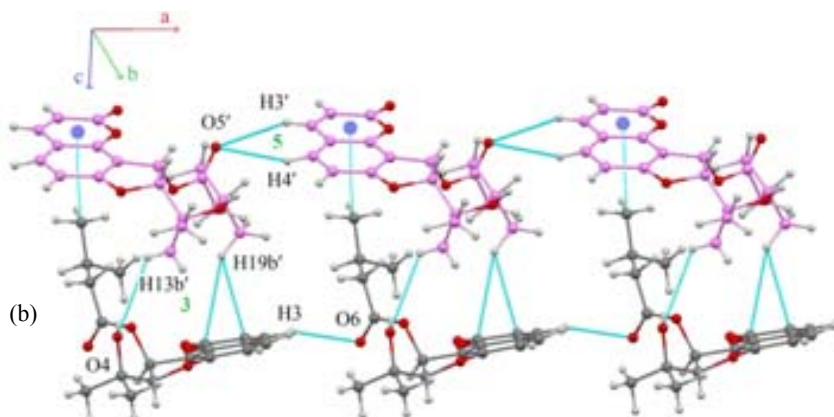
3.   The energy of the molecular pairs interacting via C-H…O hydrogen bonds lies mostly in the range -2 to -6 kcal mol^{-1} whereas those interacting via C-H…π lies in the range-1 to -4 kcal mol^{-1}.
4.   The total interaction energy *i.e* lattice energy of the compounds lie in the range -20 to - 33 kcal mol^{-1} and the main contribution to lattice energy comes from dispersion. The lattice energy is maximum in case of C-7 containing two molecules in the asymmetric unit cell. The extra stability of C-7 arises mainly from its coulombic energy.

Figure 15. Packing of the molecules in C-7 viewed down (a) bc plane (b) ab plane and (c) ac plane

Conclusion

The present work provides a quantitative evaluation of energy of formation of various molecular pairs and their contribution towards stability of the packing. Analysis of geometry and energetics associated with the molecular pairs play an important role in the field of Crystal Structure Prediction. It is basically the interaction between the neighbouring molecules rather than the interaction between the atoms of the neighbouring molecules that influence the crystal structure and are vital in analyzing the cohesive energy of the crystal. Molecular pairs obtained after PIXEL calculation shows the presence of different structural motifs and their analysis suggests that considerable stabilization to the crystal packing is imparted by weak intermolecular interactions mainly π…π, C-H…O and C-H…π.

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