



ROLE OF INTERMOLECULAR INTERACTIONS IN LINEAR FURANOCOUMARIN DERIVATIVES

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Keywords: furanocoumarin, lattice energy, intermolecular interactions, PIXEL.

Energy calculations have been performed on a series of ten molecules of linear furanocoumarin derivatives to obtain the total stabilization energy i.e. lattice energy of the crystal and also the energy of neighbouring molecular pairs participating in the stabilization of the crystal. The total stabilization energy (lattice energy) lies in the range -16 to -40 kcal mol⁻¹. Analysis of the energetics of the neighbouring molecular pairs in these structures shows the presence of different intermolecular interactions participating in the crystal packing. In addition to the significance of coulombic nature of bifurcated C-H...O hydrogen bonds, the stabilizing role of $\pi \dots \pi$ stacking interactions has been realized in these structures. A careful observation of energetics of different molecular pairs involving C-H...O hydrogen bond reveals that motifs involving C(sp²)-H...O hydrogen bonds are more stabilized than those of C(sp³)-H...O.

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Introduction

Furanocoumarins are an important class of heterocyclic compounds consisting of a furan ring fused with the coumarin nucleus. They can be grouped into the linear and angular type depending on symmetric or asymmetric loading of the furan ring with the coumarin nucleus. The most abundant linear furanocoumarins are psolaren, xanthotoxin, bergapten and isopimpinellin. Pharmacological studies have indicated that linear furanocoumarins such as isoimperatorin, notopterol and bergapten possess anti-inflammatory, analgesic, anti-cancer and anti-coagulant activities.¹ Furanocoumarins have received much attention on account of their ability to perform cycloaddition reactions with DNA during irradiation with UV light,²⁻⁶ a property that has given rise to wide-ranging photo chemotherapeutic applications.⁷

The different activities (chemical and biological) may be due to the presence of different types of interactions prevailing in the crystal structure. The role of strong intermolecular interactions such as N-H...O/N and O-H...O/N is well understood^{8,9} in addition to weak C-H... π ¹⁰⁻¹² and $\pi \dots \pi$ interactions.

The recent focus is to investigate the role of weak intermolecular interactions and its influence on crystal packing. In addition to the description of the crystal packing in terms of the presence of different intermolecular interactions, based purely on the concept of geometry (distance-angle criteria), it is also very important to analyze the intermolecular interaction energies of different non-covalent interactions in the solid state in order to obtain more detailed insight into the crystal packing.¹³⁻¹⁶ In this regard, a series of ten structures belonging to linear furanocoumarin derivatives have been taken into account and their lattice energies have been calculated theoretically. All the molecular pairs involved in the crystal packing were

extracted, the nature and energies associated with the intermolecular interactions associated with these molecular pairs were analyzed to explore the role of these interactions in the stabilization of the crystal lattice. A representative illustration of the linear furanocoumarin moiety indicating the atomic numbering scheme used in the present work is shown in Figure 1. The chemical name, molecular code and chemical structure of linear furanocoumarin derivatives are presented in Table 1 and their precise crystallographic details in Table 2a and 2b.

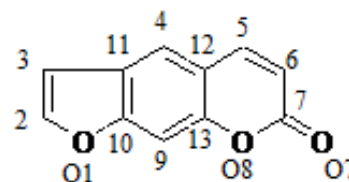


Figure 1. Linear furanocoumarin moiety indicating the numbering scheme.

Computation of interaction energies

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.²⁷⁻²⁹ For this purpose H atoms were moved to their neutron value. The total lattice energies partitioned into their Coulombic, polarization, dispersion and repulsion contributions for all the molecules are presented in Table 3. The interaction energies of the molecular pairs (partitioned into different components) extracted from the .mlc file, generated after the completion of calculation, along with the involved intermolecular interactions are listed in Table 4. 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 van der Waals radii + 0.4Å and the directionality is greater than 110°. Molecular motifs and packing diagrams were generated using Mercury software.³⁰

Table 1. Chemical name, coding scheme and chemical structure of linear furanocoumarin derivatives.

Chemical name	Code	Structure
Furo[3,2-g]benzopyran-7-one ¹⁷	M-1	
8-Methoxyfuro[3,2-g]benzopyran-7-one ¹⁸	M-2	
9-(1,1-Dimethyl-2-propenyl)-4-hydroxy-7H-furo[3,2-g]benzo-pyran-7-one ¹⁹	M-3	
4-((3,3-Dimethyl oxiranyl)methoxy)-7H-furo[3,2-g]benzopyran-7-one ²⁰	M-4	
4-((2,4,4-Trimethyl-1-cyclohexen-1-yl)methoxy)-7H-furo[3,2-g]benzopyran-7-one ²¹	M-5	
5,8-Dimethoxyfuro[3,2-g]benzopyran-7-one ²²	M-6	
2,3-Dihydro-2-(1-hydroxy-1-methyl ethyl)-7H-furo[3,2-g][1]benzo pyran-7-one ²³	M-7	
9-(3-Methylbut-2-enyloxyfuran-2-yl)-7H-furo[3,2-g]benzopyran-7-one ²⁴	M-8	
2,3-Dihydro-2-(1-hydroxy-1-methyl ethyl)-9-methoxy-7H-furo[3,2-g][1]benzo pyran-7-one ²⁵	M-9	
4-(((2E)-5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)oxy)-7H-furo[3,2-g][1]benzo pyran-7-one ²⁶	M-10	

Results and discussion

Furo[3,2-g]benzopyran-7-one (M-1)

The principal stabilizing molecular pairs extracted from crystal packing along with their interaction energies are presented in Figure 2. The molecules are packed with the involvement of C(sp²)-H4...O8 hydrogen bonds along a-axis. This interacting pair has a contribution of -4.44 kcal mol⁻¹ towards the stabilization of the crystal packing. The chains thus formed are then interconnected via weak C(sp²)-H2...O7 (motif 4, *I.E.* = -3.2 kcal mol⁻¹) and C(sp²)-H6...O1 (motif 5, *I.E.* = -0.95 kcal mol⁻¹) hydrogen bonds generating a molecular sheet in the ab plane (Figure 3a). The packing in the crystal also displays the formation of molecular chains via motif 2 along b-axis. These chains are then stacked via π ... π stacking (motif 3, *I.E.* = -4.23 kcal mol⁻¹, 90% contribution to stabilization from dispersion component) forming layers down the bc plane (Figure 3b). Furthermore, additional stabilization of -4.21 kcal mol⁻¹ was found to be imparted by motif 3 showing the presence of weak C-H...O (involving H5, H4 and H3 with O7, O8 and O1 respectively) along with C-H... π (involving H3 with C9 and C10) hydrogen bonds.

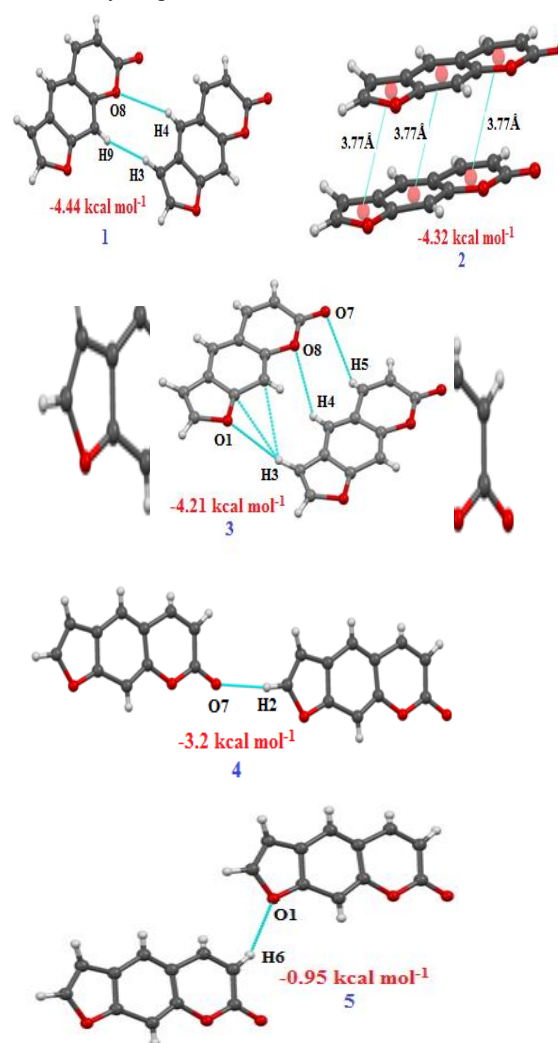
**Figure 2.** Molecular pairs (1-5) along with their interaction energies in M-1.

Table 2a. Precise crystal data for linear furanocoumarin derivatives

Data	M-1	M-2	M-3	M-4	M-5	M-6	M-7
Formula	C ₁₁ H ₆ O ₃	C ₁₂ H ₈ O ₄	C ₁₆ H ₁₄ O ₄	C ₁₆ H ₁₄ O ₅	C ₂₁ H ₂₂ O ₄	C ₁₃ H ₁₀ O ₅	C ₁₄ H ₁₄ O ₄
Formula weight, g mol ⁻¹	186.16	216.19	270.29	286.29	338.4	246.21	246.25
Crystal system	Triclinic	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P1	Pna2 ₁	C2/c	P1	P2 ₁ /n	P2 ₁ /c	P2 ₁
<i>a</i> (Å)	5.926(8)	12.911(6)	8.976(3)	8.485(1)		16.9357(5)	5.7210(10)
<i>b</i> (Å)	9.56(2)	15.804(8)	16.621(2)	11.054(2)	6.732(2)	4.3669(10)	13.8100(10)
<i>c</i> (Å)	3.777(6)	4.882(5)	17.818(2)	7.868(1)	24.375(4)	16.2558(4)	7.8640(10)
α (°)	86.1(2)	90	90	103.31(1)	12.027(3) 90	90	90
β (°)	91.6(2)	90	90	94.97(1)	115.10(2) 90	117.218(10)	100.390(10)
γ (°)	100.8(2)	90	95.79(2) 90	105.88(1)		90	90
<i>Z</i>	1	4	8	2	4	4	2
<i>R</i>	0.095	0.083	0.050	0.048	0.051	0.044	0.0523

Table 2b. Precise crystal data for linear furanocoumarin derivatives

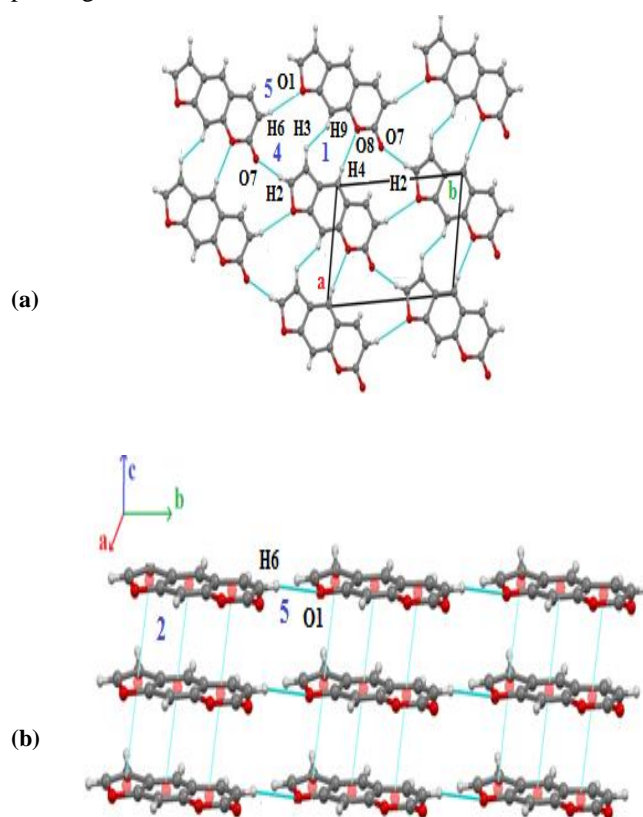
Data	M-8	M-9	M-10
Formula	C ₁₆ H ₁₄ O ₄	C ₁₅ H ₁₆ O ₅	C ₂₁ H ₂₂ O ₅
Formula Weight	270.27	276.28	354.39
Crystal System	Triclinic	Orthorhombic	Triclinic
Space group	P $\bar{1}$	P2 ₁ 2 ₁ 2 ₁	P $\bar{1}$
<i>a</i> (Å)	11.1150(10)	7.9166(9)	6.4317(10)
<i>b</i> (Å)	11.8240(10)	9.7410(10)	8.0912(16)
<i>c</i> (Å)	11.9290(10)	17.435(3)	17.206(3)
α (°)	64.90	90	91.802(15)
β (°)	83.53	90	94.240(13)
γ (°)	89.25	90	97.473(15)
<i>Z</i>	4	4	2
<i>R</i>	0.043	0.031	0.043

Table 3. Lattice energy (in kcal mol⁻¹) of compounds (M1 –M10)

Molecule	<i>E</i> _{Cou}	<i>E</i> _{Pol}	<i>E</i> _{Disp}	<i>E</i> _{Rep}	<i>E</i> _{Tot}
M-1	-4.25	-3.13	-23.94	14.98	-16.34
M-2	-8.60	-3.80	-24.90	14.31	-22.96
M-3	-12.71	-7.22	-32.50	23.68	-28.72
M-4	-15.12	-6.12	-36.01	26.72	-30.54
M-5	-11.70	-4.42	-39.81	26.05	-29.94
M-6	-14.24	-4.68	-33.58	23.97	-28.53
M-7	-18.92	-7.93	-30.31	26.69	-30.49
M-8	-13.02	-4.66	-30.06	18.97	-28.80
M-9	-19.95	-7.64	-32.31	23.82	-36.08
M-10	-18.70	-7.60	-49.68	35.30	-40.70

8-Methoxyfuro[3,2-g]benzo pyran-7-one (M-2)

The key structural motifs providing maximum contribution towards stabilization are shown in Figure 4. The most stabilized molecular pair in the crystal structure formed via $\pi \dots \pi$ molecular stacking, has a contribution of -5.81 kcal mol⁻¹ (motif 1) to the stabilization of the crystal packing.

**Figure 3.** Packing of the molecules in M-1 depicting (a) formation of molecular sheet in the *ab* plane (b) molecular chains stacked via $\pi \dots \pi$ interaction down the *bc* plane.

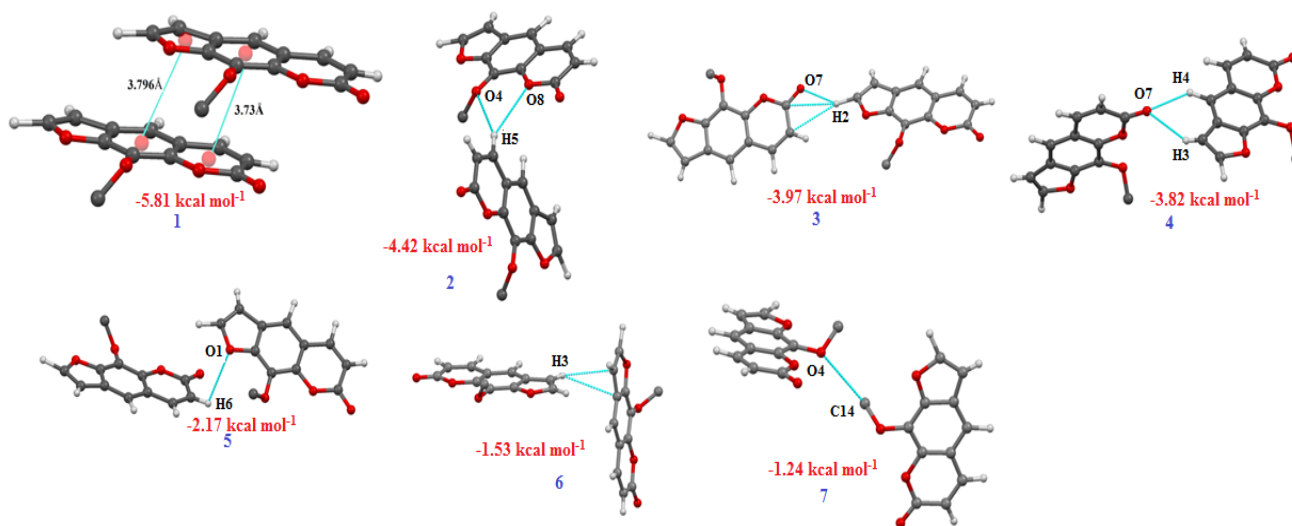


Figure 4. Molecular pairs (1-7) along with their interaction energies in M-2.

Table 4. Interaction energies ($I.E.$) (kcal mol^{-1}) 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
M-1								
1	6.938	-2.13	-1.03	-3.32	2.03	-4.44	-1+x,y,-1+z	C4-H4...O8, C3-H3...H9-C9
2	3.777	-0.07	-0.93	-10.37	7.07	-4.32	x,y,-1+z	$\pi \dots \pi$
3	5.926	-1.07	-0.72	-4.64	2.25	-4.21	-1+x,y,z	C5-H5...O7, C4-H4...O8, C3-H3...O1, C3-H3... π
4	11.100	-3.51	-1.07	-1.50	2.89	-3.20	1+x,1+y,1+z	C2-H2...O7
5	9.560	-0.24	-0.24	-1.53	0.59	-0.95	x,-1+y,z	C6-H6...O1
M-2								
1	4.882	-0.50	-0.72	-8.22	3.63	-5.81	x,y,-1+z	$\pi \dots \pi$
2	7.077	-1.53	-0.72	-3.18	1.00	-4.42	1/2+x,1/2-y,z	C5-H5...O4, C5-H5...O8
3	10.773	-3.77	-1.05	-1.72	2.56	-3.97	1/2-x,-1/2-y,-3/2+z	C2-H2...O7, C2-H2... π (C6,C7)
4	8.597	-2.94	-1.03	-1.88	2.05	-3.82	-1/2+x,1/2-y,-1+z	C3-H3...O7 C4-H4...O7
5	8.270	-0.31	-0.24	-2.19	0.57	-2.17	1/2-x,1/2+y, 1/2+z	C6-H6...O1
6	8.516	-0.09	-0.45	-2.75	1.57	-1.53	-x,-y, 1/2+z	C3-H3... π (C3, C11)
7	8.533	-0.22	-0.26	-1.96	1.29	-1.24	1-x,-y,-1/2+z	C14...O4

M-3								
1	4.191	0.02	-2.17	-14.43	8.79	-7.81	-x,y,1.5-z	C17-17...O7, C17-H17... π , stacking
2	8.978	-5.99	-3.94	-5.80	9.67	-6.09	1/2-x,1/2+y, 1.5-z	C3-H3...O7, O4-H4O...O7, O4-H4O...O8, C18-18b...O4
3	6.362	-1.72	-0.45	-7.02	4.15	-5.02	1/2-x,1/2-y,1-z	C16-H16c... π
4	9.569	-2.67	-0.78	-3.82	2.89	-4.39	1/2+x,1/2-y,1/2+z	C6-H6...O1, C2-H2...O7,H...H
5	9.445	-1.65	-0.47	-2.65	1.38	-3.39	-1/2+x, 1/2+y, z	C(sp ²)-H3... H16b-C(sp ³)
6	8.756	-0.86	-0.24	-2.98	0.86	-3.25	-1/2-x,1/2-y,1-z	C(sp ³)-H15b...C2(sp ²)
7	10.085	-0.81	-0.33	-3.34	2.03	-2.46	-x,-y,1-z	C(sp ³)- H15a ...C18
8	6.768	-2.48	-0.764	-5.28	1.64	-1.91	1-x,y,1.5-z	C=O...O=C, C16-16b...O7, stacking
9	10.643	-0.52	-0.335	-2.17	1.17	-1.88	-x,1-y,1-z	H...H
10	9.445	-0.41	-1.70	-1.50	0.41	-1.67		C18-H18a...O4
M-4								
1	4.783	-6.91	-1.53	-14.82	10.97	-12.31	-x,-y,2-z	π ... π , C14-14b...O8
2	7.386	-5.68	-1.98	-12.04	8.48	-11.23	1-x,1-y, 2-z	C17-H17c... π , C18-H18a... π , C18-H18c...O5, C14-H14a...O5
3	7.385	-3.39	-1.82	-7.36	5.30	-7.29	-x,-y,1-z	C15-H15...O7, C17-H17a...O7, C5-H5... π
4	8.485	-1.82	-0.86	-5.83	3.20	-5.30	-1+x,y,z	C17-H17b... π , C18-H18b... π , C14-14b...O8, C15-H15... π (C1)
5	10.818	-4.21	-1.96	-3.01	4.42	-4.78	-1-x,-y,2-z	C9-H9...O7
6	7.868	-2.55	-1.12	-5.06	4.16	-4.59	x,y,-1+z	C5-H5...O1, C2-H2...O5
7	11.710	-1.07	-0.86	-1.88	1.50	-2.32	-1-x,-y,1-z	C6-H6...O7
8	9.751	-0.50	-0.24	-1.91	0.28	-1.36	1-x,1-y,3-z	C2-H2...H18c -C18
9	12.061	0.12	-0.09	-1.29	0.41	-0.84	-1+x,y, 1+z	C17-H17b...O1
M-5								
1	5.685	-7.82	-2.84	-18.07	14.79	-13.95	1-x,1-y, 1-z	π ... π , C14-14b...O8, C21-21a...O7

2	5.717	-13.95	-1.79	-17.47	13.47	-12.31	-x,1-y,1-z	$\pi \dots \pi$, C14-14a...O8
3	9.500	-1.41	-1.36	-10.37	7.07	-6.09	1/2+x,1/2-y, 1/2+z	C-H... π , H...H
4	11.013	-1.94	-0.76	-1.55	1.72	-2.53	-1+x,y,-1+z	C2-H2...O7
5	13.155	-0.33	-0.07	-1.65	0.31	-1.74	1/2-x,1/2+ y, 1/2-z	C22-H22c...O1
6	14.112	-1.004	-0.41	-0.91	0.57	-1.74	1/2-x,1/2+ y, 1.5-z	C22-H22a...O7
7	6.732	0.91	-0.29	-2.91	1.15	-1.15	-1+x,y,z	H...H
M-6								
1	4.367	-2.68	-1.93	-14.77	11.47	-7.91	x,1+y,z	$\pi \dots \pi$, C15-H15c...O8, C15-H15c...O5, C14-H14c...O4
2	8.156	-3.96	-1.22	-4.71	3.82	-6.07	x,-1.5-y,-1/2+z	C3-H3...O7, C14-14c...O7, C14-14a...C7
3	9.004	-2.48	-0.69	-2.24	2.17	-3.25	-x,-1-y,-z	C15-H15b...O5
4	8.898	-0.78	-0.62	-4.21	2.61	-3.01	1-x,-2-y,1-z	C14-H14b...O4, H...H
5	8.926	-2.10	-0.79	-1.41	1.48	-2.79	x,-1/2-y,-1/2+z	C14-H14a...O7
6	9.327	-1.46	-0.24	-2.19	1.15	-2.75	-x,-2-y,-z	CH ₃ ...CH ₃
7	8.779	-1.27	-0.43	-2.05	1.17	-2.58	1-x,1/2+y, 1/2-z	C6-H6... π
8	8.72	-1.50	-0.52	-1.98	1.46	-2.56	-x,1/2+y, 1/2-z	C2-H2...O1
M-7								
1	8.030	-9.63	-3.75	-5.11	9.77	-8.72	1-x,-0.5+y, -z	C6-H6...O1, O4-H4O...O7
2	5.721	-0.91	-1.46	-9.42	6.14	-5.64	-1+x,y,z	C2-H2... π
3	7.864	-1.46	-0.96	-3.37	1.84	-3.94	x,y,-1+z	C4-H4...O7, H...H
4	10.526	-2.25	-0.74	-8.46	1.15	-3.77	1+x,y,-1+z	C3-H3a...O7
5	8.601	-2.74	-0.96	-3.01	3.39	-3.35	1-x,-0.5+y, -1-z	C4-H4...O4 C5-H5...O4
6	7.964	-1.43	-0.36	-2.89	2.01	-2.68	2-x,-0.5+y, -z	C16-H6b... π , C16-H6c...O7, C16-H6c... π
7	9.442	0.14	-0.59	-3.56	2.41	-1.63	2-x, 0.5+y, -1-z	H4...H16b H4...H15c

M-8								
1 A...B	7.415	-5.9	-1.88	-7.76	5.95	-9.58	x,1+y,z	C4'-H4'...O7 C5'-H5'...O7 C5'-H5'...O8 C6-H6'...O4 C17-H17b... O7'
2 A...A	5.697	-4.34	-1.09	-11.78	8.65	-8.60	1-x,2-y,-z	π ... π
3 B...B	5.228	-2.48	-1.41	-10.39	5.81	-8.48	-x,1-y,-z	π ... π
4 A...B	8.625	-4.54	-1.43	-4.75	4.04	-6.69	x,y,z	C5-H5...O7' C5-H5...O8' C6-H6...O4'
5 A...B	8.119	-1.74	-0.64	-4.78	2.13	-5.04	-1+x,-1+y,z	C3'-H3'...O1 C3'-H3'...O4 C15-H15... π
6 A...A	7.858	-0.88	-0.35	-6.214	2.72	-4.76	1-x,2-y,1-z	C17-H17C... C2 C14-H4a... C15
7 A...B	6.425	-0.76	-0.50	-6.72	3.25	-4.73	-x,1-y,1-z	C17'-H17a'... π C18'-H18a'... π
8 A...B	8.707	-2.13	-0.74	-4.32	2.61	-4.58	-1+x,y,z	C3-H3...O4'
9 A...B	9.103	-1.15	-0.67	-4.32	2.72	-3.42	-x,1-y,-z	C5-H5... π
10 B...B	8.027	-0.76	-0.41	-3.06	1.34	-2.92	-x,1-y,1-z	H...H
11 A...A	11.115	-3.29	-1.17	-1.74	3.32	-2.91	1+x,y,z	C2-H2...O7
12 B...B	11.115	-2.53	-0.97	-1.69	2.63	-2.58	1+x,y,z	C2-H2'...O7'
M-9								
1	9.502	-8.60	-3.01	-5.02	7.24	-9.37	1/2-x,1-y, -1/2+z	O5-H5o...O7, C15-H15a...O8, C15-H15a...O4
2	6.391	-2.96	-1.05	-6.12	3.56	-6.57	-1/2+x,1/2-y, 1-z	Molecular stacking, C2-H2...O7
3	7.917	-4.21	-1.74	-5.99	5.83	-6.14	-1+x,y,z	C6-H6...O4, C5-H5...O1, C4-H4...O5
4	6.721	-0.81	-0.64	-7.07	3.77	-4.78	-x,-1/2+y, 1/2-z	C16-H16a... π , C4-H4... C15, H15b...H3b
5	10.135	-1.69	-0.69	-2.01	0.84	-3.58	-1/2-x,1-y, -1/2+z	C3-H3b...O7, H6...H15b
6	8.994	-2.01	-0.48	-1.98	1.05	-3.42	-1/2+x,3/2-y, 1-z	C-17-H17b...O7
7	9.769	-0.88	-0.50	-3.12	1.55	-2.94	1-x,-1/2+y, 1/2-z	CH ₃ ...CH ₃ - moeity

M-10								
1	5.617	-12.76	-4.2	-17.85	16.08	-18.73	1-x,2-y,1-z	O5-H5O...O8, O5-H5O...O7, C22-H22a...O7, C22-H22b...O7, stacking
2	7.079	-4.25	-2.72	-8.84	6.83	-8.98	2-x,2-y,1-z	C19-H19...O7, C17-H17a...O7, H...H
3	9.537	-4.11	-1.24	-11.59	9.08	-7.86	1-x,3-y,1-z	π ... π
4	10.971	-3.65	-1.81	-5.78	6.02	-5.21	-1+x,1+y,z	C2-H2...O5, C2-H2...C20
5	6.432	-0.26	-0.78	-9.7	5.04	-5.18	-1+x,y,z	Stacking, H...H
6	8.091	-1.48	-1.05	-5.87	3.60	-4.78	x,-1+y,z	C14-H14a...O5, C-H...C
7	15.871	-1.31	-0.59	-7.19	4.56	-4.54	2-x,1-y,-z	C-H...C
8	12.987	-2.5	-0.62	-3.34	2.65	-3.82	-x,3-y,1-z	C9-H9...O1

Adjacent stacks are then interconnected via weak C2-H2...O7 and C2-H2... π (motif 3, *I.E.* = -3.97 kcal mol⁻¹, the major contribution being the coulombic energy) and C6-H6...O1 (motif 5, *I.E.* = -2.17 kcal mol⁻¹) forming layers in the *bc* plane (Figure 5). The second most stabilized pair involves the interaction of bifurcated donor atom H5 with O4 and O8, contributing -4.42 kcal mol⁻¹ towards the stabilization. Additional stabilization to the structure comes from motif 4 which shows the presence of bifurcated acceptor C-H...O interaction (involving O7 with H4 and H3) having stabilizing energy of -3.82 kcal mol⁻¹. Motif 6 (-1.53 kcal mol⁻¹) and 7(-1.24 kcal mol⁻¹) also provide small but significant contribution towards crystal stability.

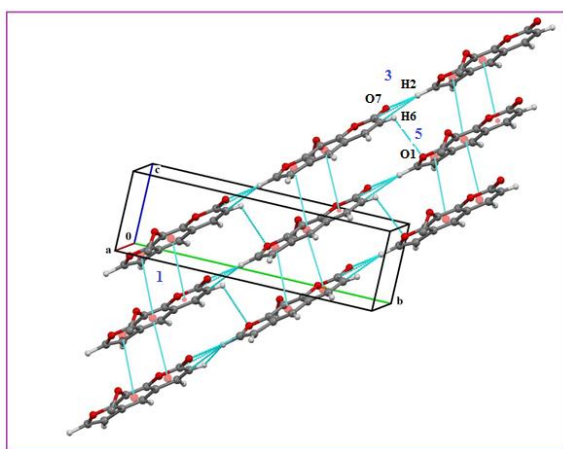


Figure 5. Packing of the molecules in M-2 showing the stacking of parallel molecular chains down the *bc* plane.

9-(1,1-Dimethyl-2-propenyl)4-hydroxy-7H-furo[3,2-g]benzopyran-7-one (M-3)

The important molecular motifs (1-10) along with their interaction energies are shown in Figure 6. The most stabilized molecular pair consists of C-H... π interaction along with C-C stacking (involving C4 of benzene ring of both the molecules) with C...C distance being 3.384Å and hence resulting in a total interaction energy of -7.81 kcal mol⁻¹.

The combined nature of the interaction is mainly dispersive in nature (85% contribution to total stabilization from dispersion component).

This motif along with motif 3 (C16-H16c... π , -5.02 kcal mol⁻¹) results in the stacking of the molecules along the crystallographic *a* axis. These stacks are then interconnected via motif 2 (bifurcated O-H...O and C-H...O hydrogen bonds, -6.09 kcal mol⁻¹, with almost equal contributions from dispersion and coulombic components, Table 4), 5 (H3...H16b, -3.99 kcal mol⁻¹), 7(C15-H15a...C18, -2.46 kcal mol⁻¹), 9 (H2...H3, -1.88 kcal mol⁻¹) and 10 (C18-H18a...O4, -1.67 kcal mol⁻¹) forming layers down the *ab* plane (Figure 7a). However down the *ac* plane, similar stacks are interconnected to form layers via motif 4 (C-H...O and H...H interaction, -4.39 kcal mol⁻¹), 6 (dimeric C15-H15b...C2, -3.25 kcal mol⁻¹) and 8 (dimeric C=O...O=C along with C16-H16b...O7, -1.91 kcal mol⁻¹) (Figure 7b.)

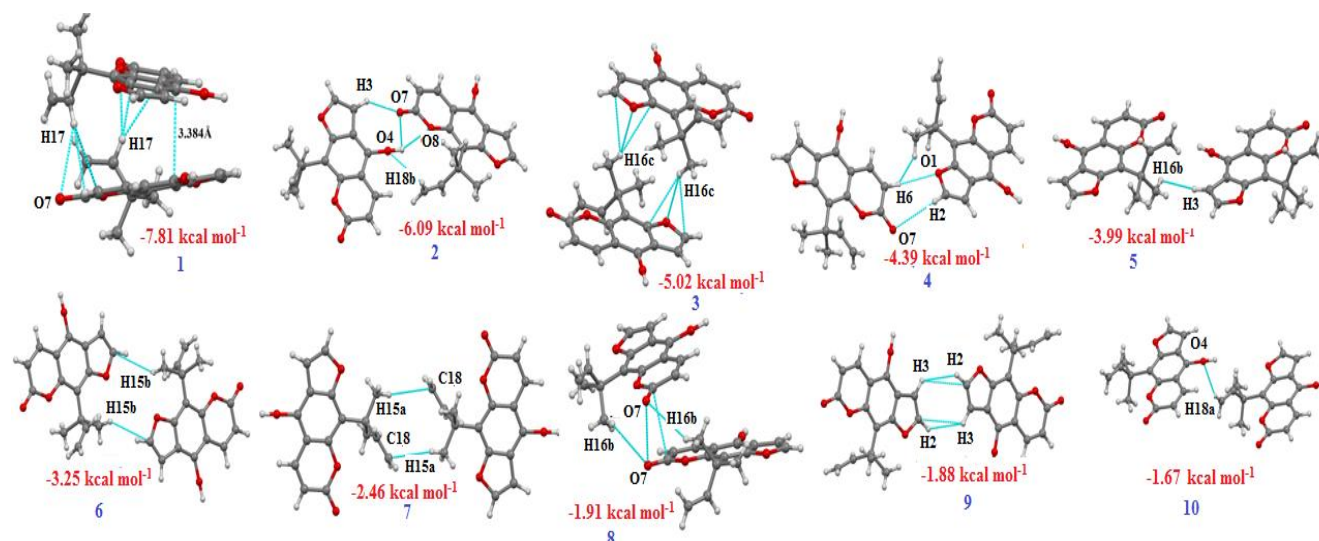


Figure 6. Molecular pairs (1-10) along with their interaction energies in **M-3**.

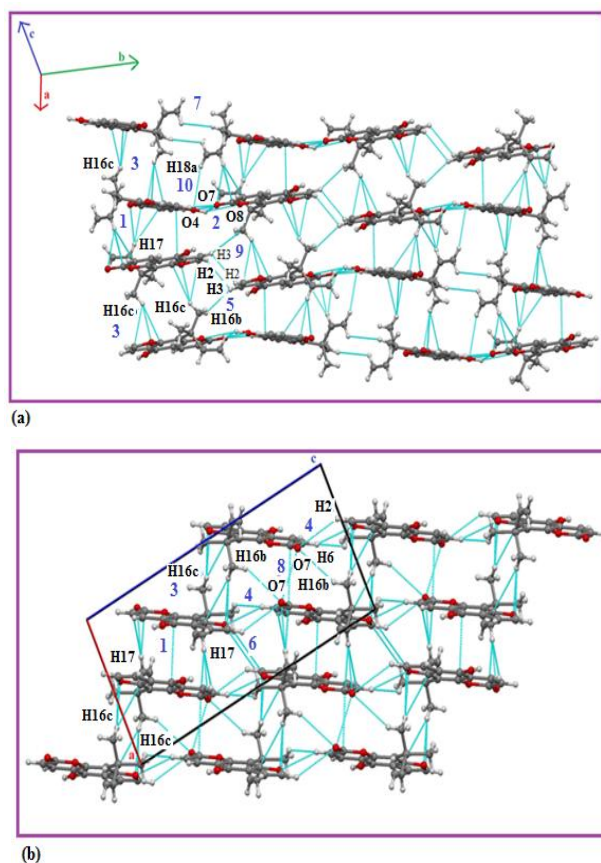


Figure 7. Packing of the molecules in **M-3** (a) *ab* plane (b) *ac* plane

4-((3,3-Dimethyloxiranyl)methoxy)-7H-furo[3,2-g]benzopyran-7-one (M-4)

The molecular pairs (1-9) extracted from the crystal packing are shown in Figure 8 along with their respective interaction energies. The most stabilized molecular pair in the crystal structure, formed via $\pi \dots \pi$ stacking along with C-

H...O (involving H14b with O8) has a contribution of -12.31 kcal mol⁻¹ (with major dispersion contribution) to the stabilization of the crystal packing. These molecular stacks are then interconnected via dimeric C-H...O involving H6 with O7 (motif 7, -2.32 kcal mol⁻¹) and H...H interaction (motif 8, -1.36 kcal mol⁻¹) (Figure 9a).

The second stabilized pair involves the presence of dimeric bifurcated C-H...O (involving H14a and H18c with O5) along with dimeric C-H... π interaction forming dimers contributing -11.23 kcal mol⁻¹ towards stabilization. The third most stabilized motif shows the presence of another bifurcated acceptor C-H...O (involving H15 and H17a with O7) and C-H... π , forming dimers related by centre of symmetry with an interaction energy of -7.29 kcal mol⁻¹ and the combined nature of the interaction is mainly dispersive in nature. These molecular dimers are then interconnected via motif 5, 8 and 9 forming sheets in the *ac* plane (Figure 9b). Motif 5 (-4.78 kcal mol⁻¹) shows the presence of dimeric C(sp²)-H9...O7 whereas motif 9 (-0.84 kcal mol⁻¹) shows the presence of C17-H17b...O1 interaction. Moreover motif 4 showing the presence of C14-H14b...O8 along with C-H... π hydrogen bonds, provide additional stabilization of -5.30 kcal mol⁻¹.

4-((2,4,4-Trimethyl-1-cyclohexen-1-yl) methoxy)-7H-furo[3,2-g]benzopyran-7-one (M-5)

The important molecular pairs (1-7) providing maximum stabilization to the crystal are shown in Figure 10. The packing of the molecules in the crystal displays the stacking of the molecules via the alternate arrangement of motif 1 and 2 along the crystallographic *a*-axis.

Both the motifs (1 and 2) shows the presence of $\pi \dots \pi$ stacking along with weak C(sp³)-H...O hydrogen bonds, contribute -13.95 and -12.31 kcal mol⁻¹ respectively towards stabilization of the crystal structure. The nature of the interaction in both the motifs is predominantly dispersive with almost 65% contribution to net stabilization.

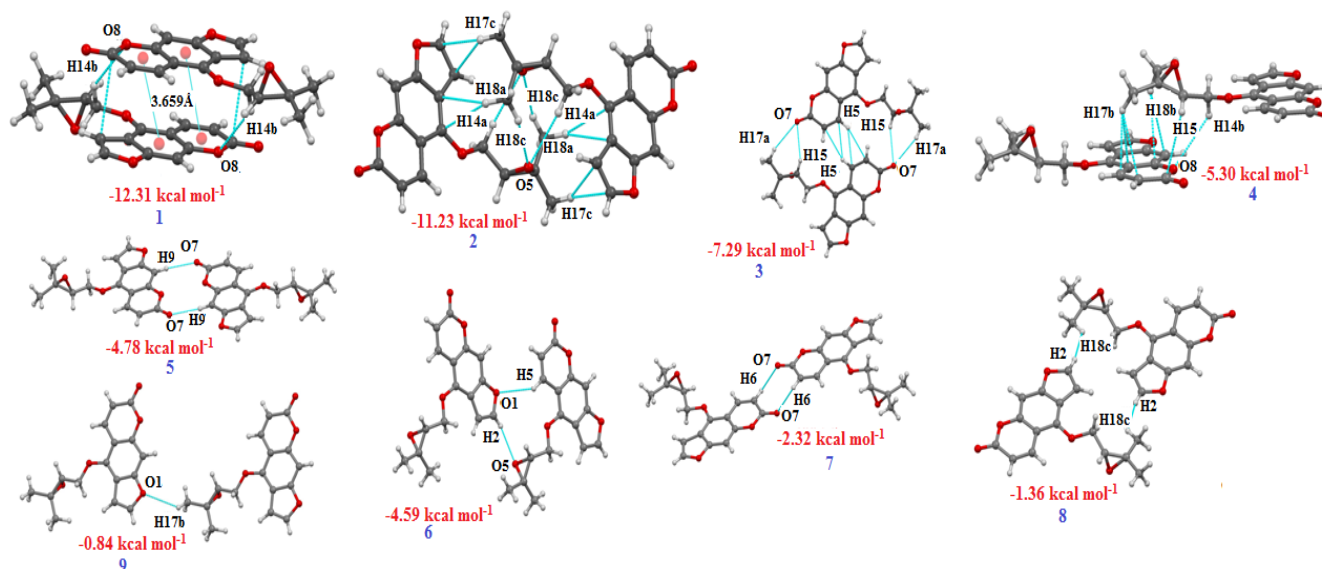


Figure 8. Molecular pairs (1-9) along with their interaction energies in **M-4**.

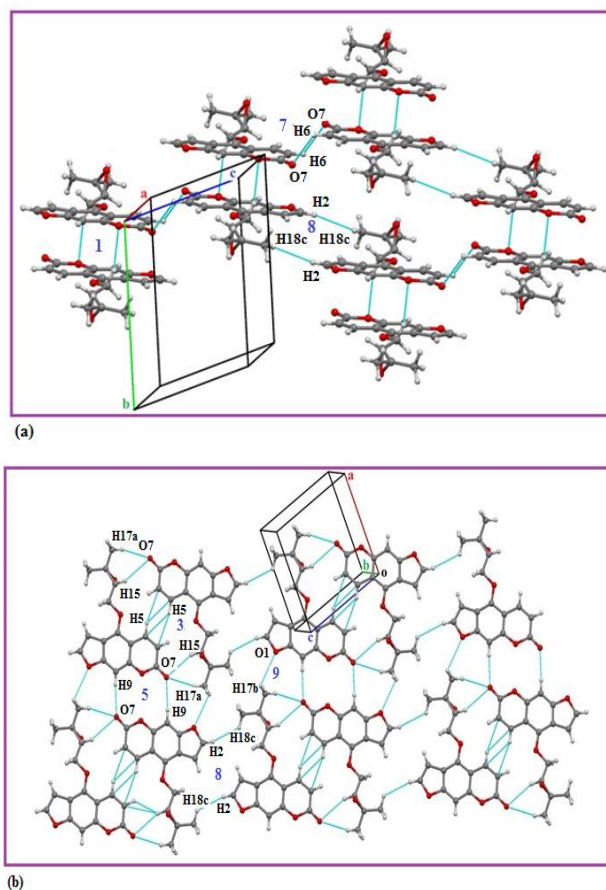


Figure 9. Packing of the molecules in **M-4** depicting (a) aromatic stacking interaction down the *bc* plane (b) molecular sheets in the *ac* plane

These stacks are then interlinked via $C(sp^2)$ -H2...O7 (motif 4, $-2.53 \text{ kcal mol}^{-1}$) hydrogen bonds along the *c* axis forming layers down the *ac* plane (Figure 11a). The packing in the crystal also involves the formation of molecular chains along the *b* axis via $C(sp^3)$ -H22c...O1 hydrogen

bond, contributing $-1.74 \text{ kcal mol}^{-1}$ (motif 5). These molecular chains are then interconnected via another $C(sp^3)$ -H22a...O7 hydrogen bonds of same stabilization energy (motif 6, $-1.74 \text{ kcal mol}^{-1}$) (Figure 11b)

5,8-Dimethoxyfuro[3,2-g]benzopyran-7-one (M-6)

The key structural motifs (1-8) providing maximum stabilization to the crystal are shown in Figure 12. The molecules in the crystal stack together via $\pi \dots \pi$ along with weak $C(sp^3)$ -H...O hydrogen bonds (motif 1, $-7.91 \text{ kcal mol}^{-1}$, 75% contribution to total stabilization from dispersion component) resulting in the formation of a molecular ladder. The weak bifurcated C-H...O involving H3 and H14c with O7 along with weak $C(sp^3)$ -H14a...C7 (motif 2, $-6.07 \text{ kcal mol}^{-1}$) and another C-H...O hydrogen bond involving H14a with O7 (motif 5, $-2.79 \text{ kcal mol}^{-1}$) connect the molecular ladder in a zig-zag manner along the *c* axis (Figure 13a). The third most stabilized molecular motif in the crystal are the molecular pairs formed via dimeric weak C-H...O hydrogen bonds (involving H15b with O5, motif 3, $-3.25 \text{ kcal mol}^{-1}$) with comparable contribution from coulombic ($-2.48 \text{ kcal mol}^{-1}$) and dispersion energy ($-2.24 \text{ kcal mol}^{-1}$). These dimeric units are then connected by weak C-H...O (involving H14b with O4) hydrogen bonds along with C-H...H-C interaction (motif 4, $-3.01 \text{ kcal mol}^{-1}$) forming chains. These chains are then stacked via motif 1 forming layers (Figure 13b). Moreover, the presence of motif 7 which involves C-H... π interactions and motif 8 showing C-H...O interaction, both having almost similar stabilization energies (-2.58 and $-2.56 \text{ kcal mol}^{-1}$) were also observed to stabilize the crystal packing.

2,3-Dihydro-2-(1-hydroxy-1-methylethyl)-7H-furo[3,2-g][1]benzopyran-7-one (M-7)

The principal stabilizing motifs (1-7) imparting maximum energy contribution to the crystal packing are presented in Figure 14.

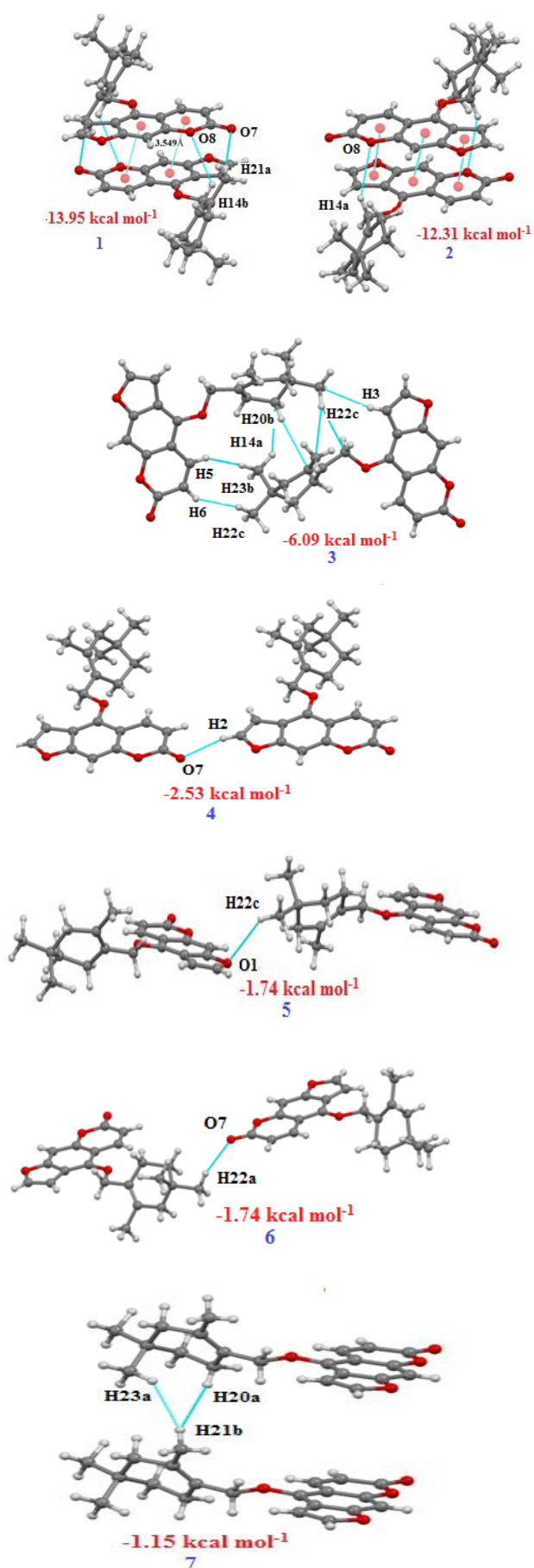
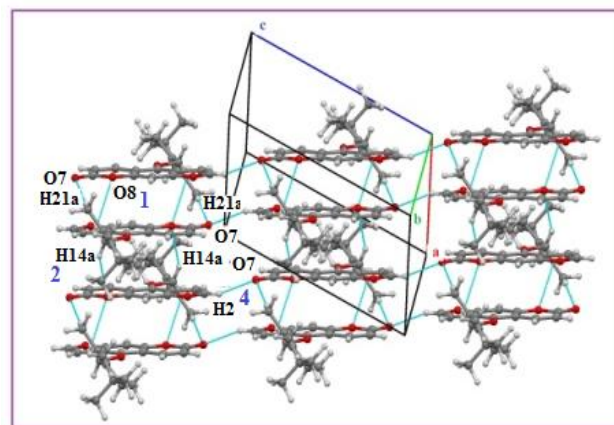
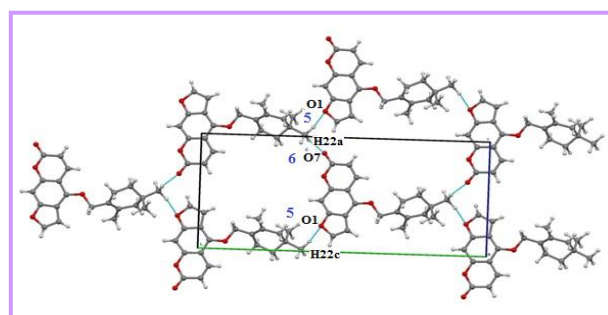


Figure 10. Molecular pairs (1-7) along with their interaction energies in **M-5**



(a)



(b)

Figure 11 Packing of the molecules in **M-5** depicting (a) stacking of molecules down the ac plane (b) molecular chains formed via C-H...O hydrogen bonds

The most stabilized molecular pair in **M-7** consist of short O4-H4O...O7 interaction along with weak C-H...O (involving H6 with O1) and hence resulting in an interaction energy of $-8.72 \text{ kcal mol}^{-1}$ (motif 1, Figure 14).

It is to be noted that the coulombic contribution towards the net interaction energy for motif 1 is $-9.63 \text{ kcal mol}^{-1}$ which is 50% of the total stabilization energy. Motif 1 along with bifurcated C-H...O involving H4, H5 with O4 (motif 5, $I.E.= -3.35 \text{ kcal mol}^{-1}$) is involved in the formation of zig-zag chains along the crystallographic *b* axis. Another weak C-H...O involving H3a with O7 (motif 4, $I.E.= -3.77 \text{ kcal mol}^{-1}$ with major contribution from dispersion) along with C-H...C and C-H...H-C (motif 7, $I.E.= -1.63 \text{ kcal mol}^{-1}$) interconnect the zig-zag chains (Figure 15).

The second most stabilized motif involves the presence of weak C-H... π interaction contributing $-5.64 \text{ kcal mol}^{-1}$ (90% contribution to net stabilization from dispersion component) towards stabilization of crystal. It has been observed that motif 3 ($-3.94 \text{ kcal mol}^{-1}$) and 6 ($-2.68 \text{ kcal mol}^{-1}$) also make significant contributions towards the stabilization of the crystal structure.

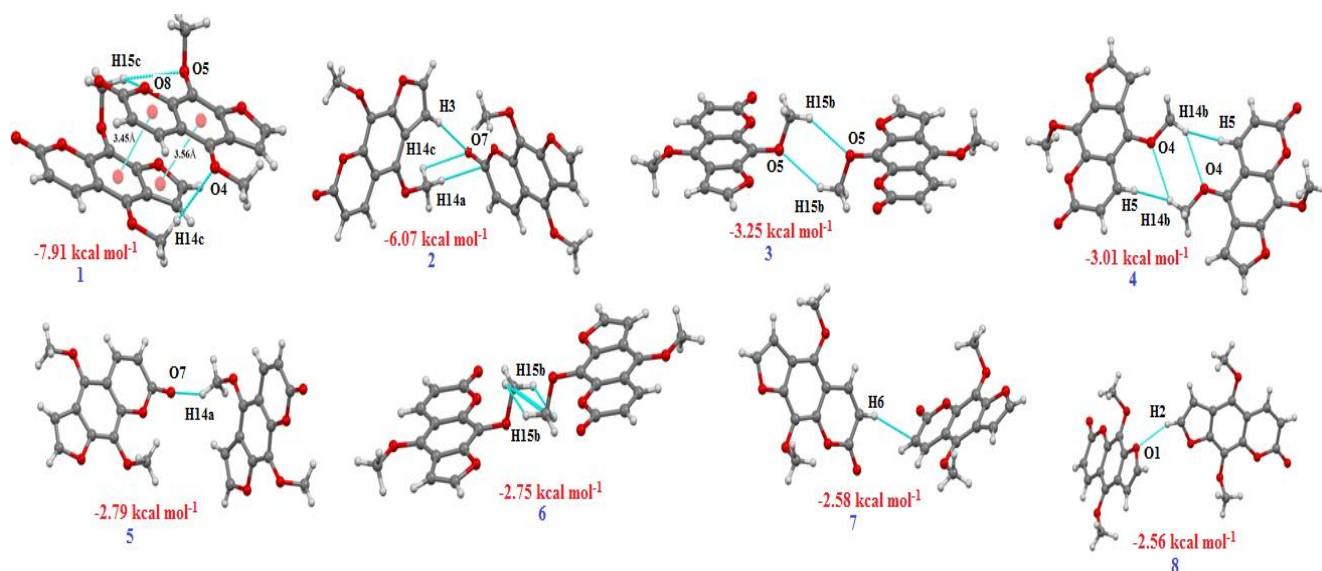


Figure 12. Molecular pairs (1-8) along with their interaction energies in M-6

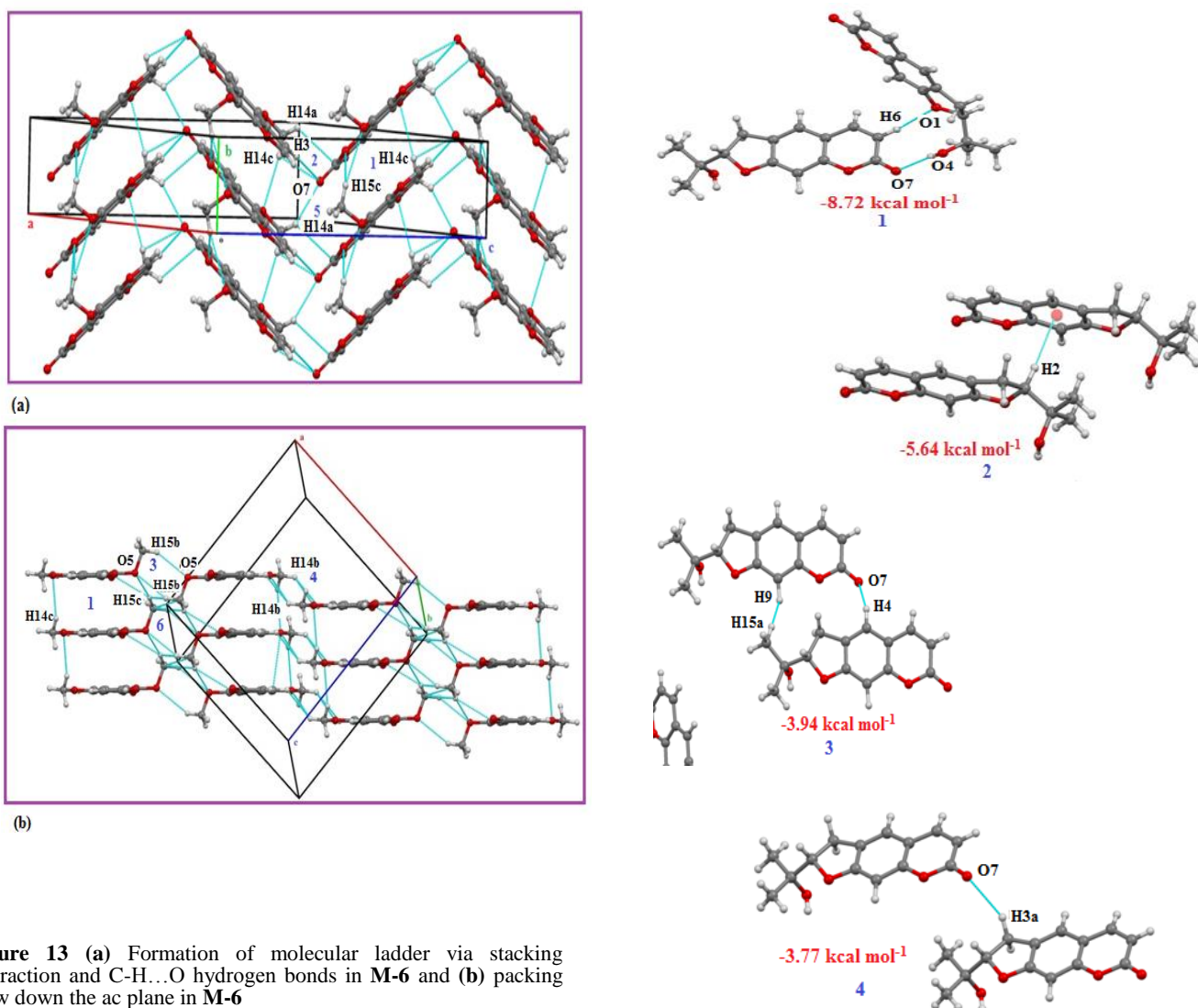


Figure 13 (a) Formation of molecular ladder via stacking interaction and C-H...O hydrogen bonds in M-6 and (b) packing view down the ac plane in M-6

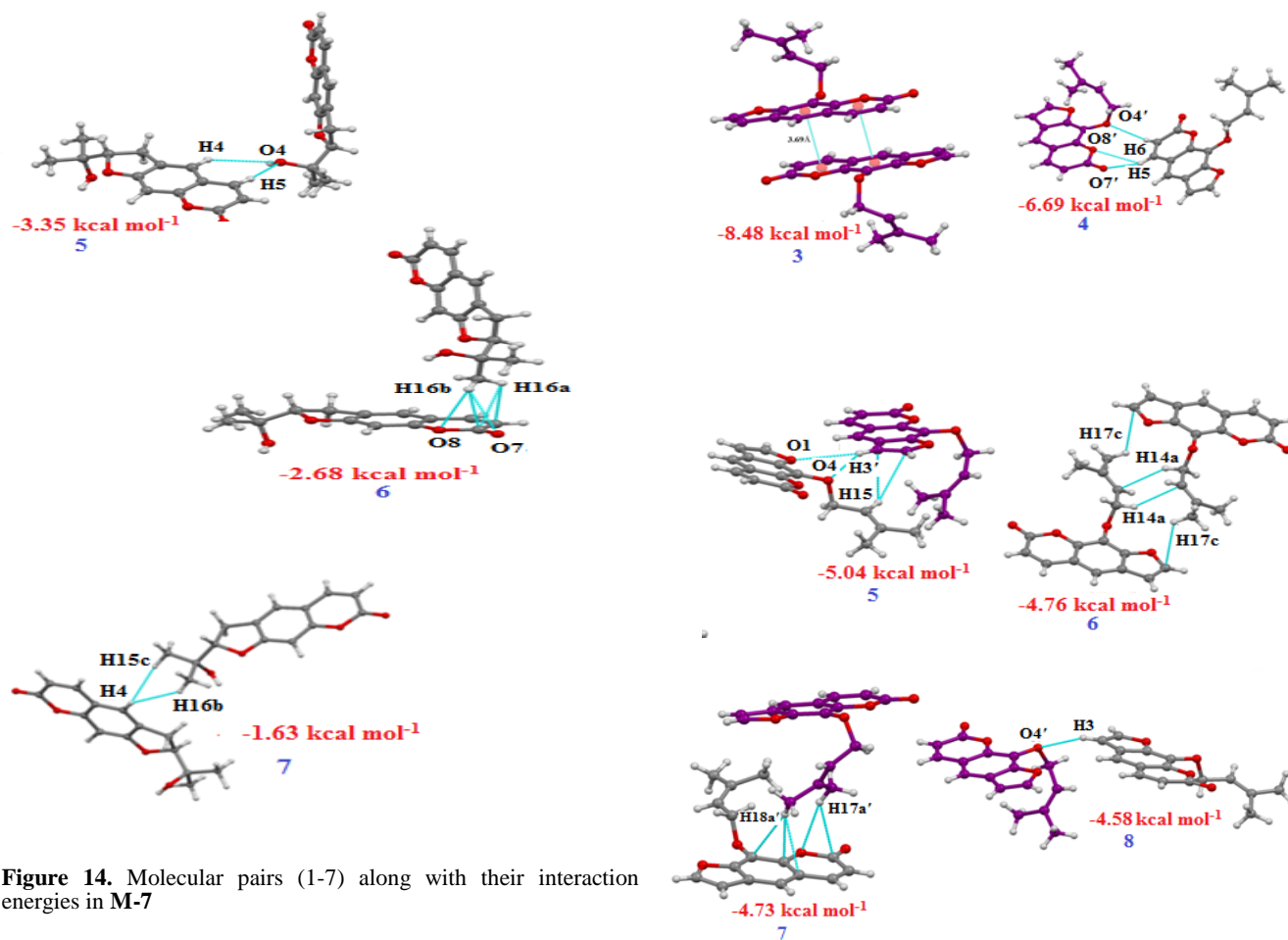


Figure 14. Molecular pairs (1-7) along with their interaction energies in M-7

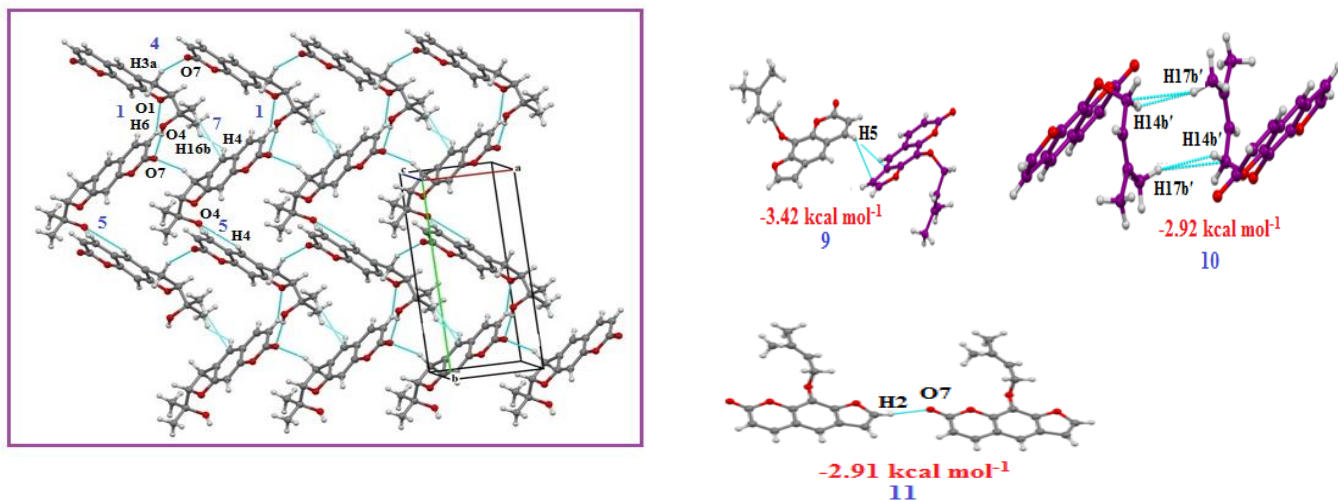


Figure 15. Formation of zig-zag chains via O-H...O and C-H...O hydrogen bonds in M-7.

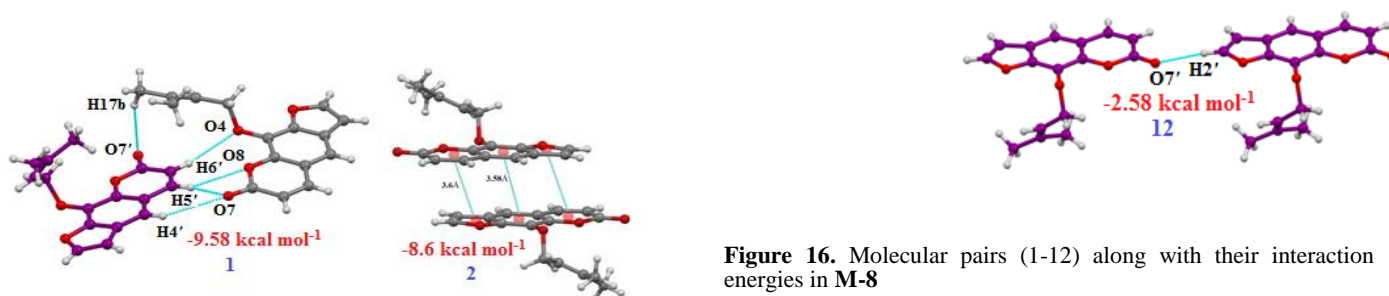


Figure 16. Molecular pairs (1-12) along with their interaction energies in M-8

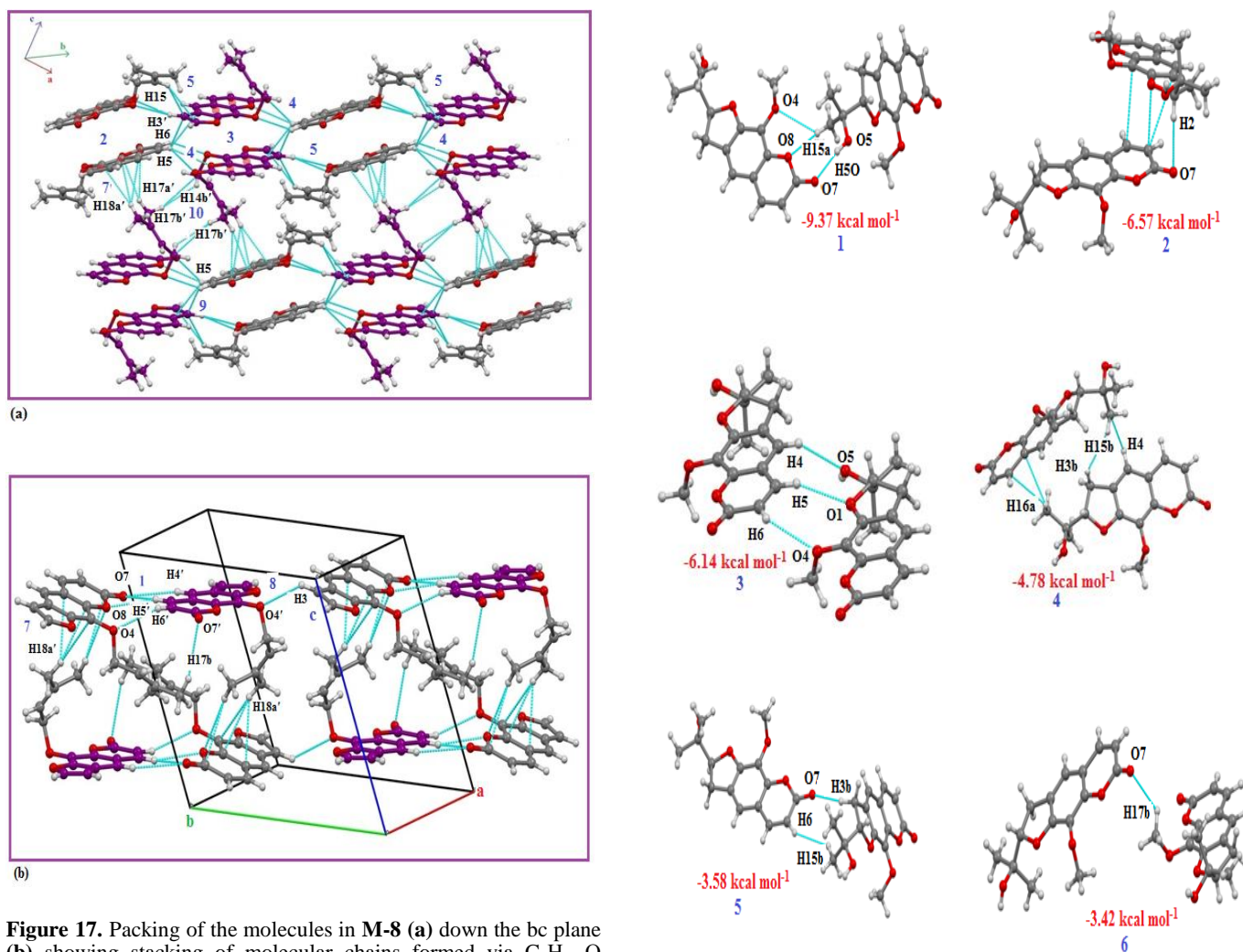


Figure 17. Packing of the molecules in **M-8** (a) down the bc plane (b) showing stacking of molecular chains formed via C-H...O hydrogen bonds

9-(3-Methylbut-2-enyloxyfuran)[3,2-g]benzopyran-2-one(**M-8**)

The important stabilizing molecular pairs (1-12) extracted from the crystal packing are presented in Figure 16. The molecule crystallizes with two molecules in the asymmetric unit [molecule A (carbon atom = grey colour) and B (carbon atom = purple colour)]. The two molecules in the asymmetric unit are interacting via weak C-H...O hydrogen bonds (involving bifurcated donor atom H5 with O7' and O8', H6 with O4') and this pair is fourth most stabilized pair in the crystal, energy being $-6.69 \text{ kcal mol}^{-1}$. This pair (motif 4) along with motif 5 (showing the presence of bifurcated donor C-H...O interaction along with C-H... π , $-5.04 \text{ kcal mol}^{-1}$) propagates along the b-axis forming chains. The chains so formed are then stacked along c axis utilizing motifs 2,3,7,9 and 10 as shown in Figure 17a.

Both the motifs 2 and 3 involves $\pi \dots \pi$ stacking and provide almost equal contributions (-8.6 and $-8.48 \text{ kcal mol}^{-1}$) towards stabilization, with maximum contribution from dispersion component. The packing in the crystal also displays the formation of molecular chains via motif 1 (the most stabilized motif showing the presence of C-H...O hydrogen bonds having stabilization energy $-9.58 \text{ kcal mol}^{-1}$) and 8 (involving C(sp²)-H3...O4', *I.E.* = $-4.58 \text{ kcal mol}^{-1}$). The chains so formed are then interconnected via motif 7 ($-4.73 \text{ kcal mol}^{-1}$) showing the presence of C-H... π interaction (Figure 17b).

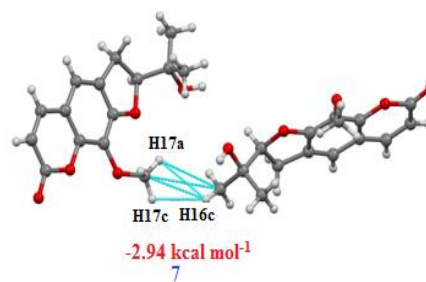
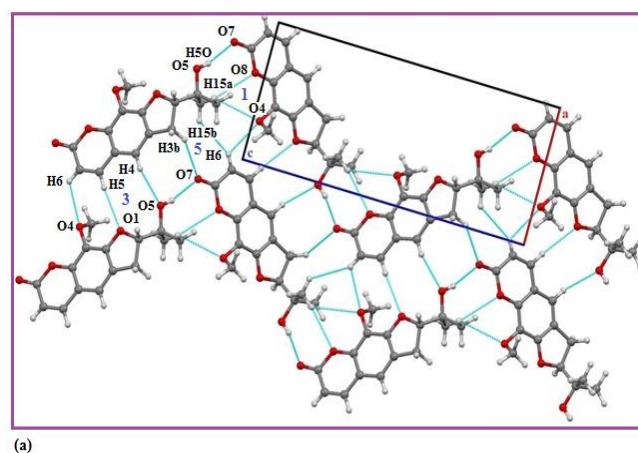


Figure 18. Molecular pairs (1-7) along with their interaction energies in **M-9**



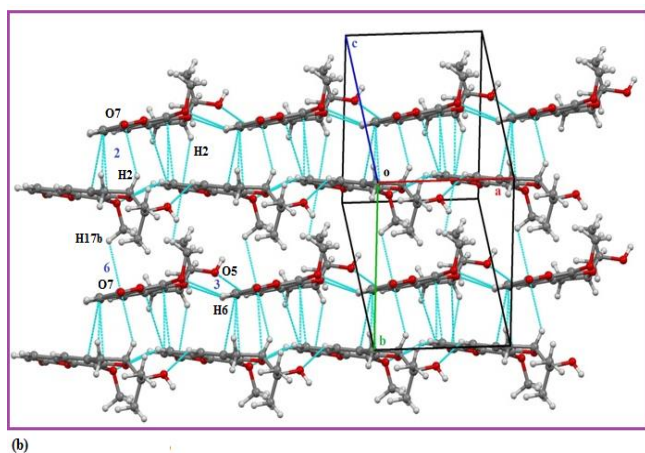


Figure 19a. Zig-zag chains formed via O-H...O and C-H...O hydrogen bonds in ac plane in **M-9** (b) packing view of the molecules down the ab plane in **M-9**

2,3-Dihydro-2-(1-hydroxy-1-methylethyl)-9-ethoxy-H-furo[3,2-g][1]benzopyran-7-one (M-9)

The important molecular motifs (1-7) extracted from the crystal packing are shown in Figure 18. The strong O5-H5O...O7 and bifurcated donor C-H...O involving H15a with O8 and O4 (motif 1, $-9.37 \text{ kcal mol}^{-1}$, the major contribution being the coulombic energy) participate in the formation of zig-zag chains along the crystallographic c axis. The zig-zag chains are then interconnected with the presence of motif 3 (C-H...O hydrogen bonds, $-6.14 \text{ kcal mol}^{-1}$) and motif 5 (C3-H3b...O7 hydrogen bond along with H6...H15b, $-3.58 \text{ kcal mol}^{-1}$) (Figure 19a). The second most stabilized pair shows the presence of molecular stacking along with C2-H2...O7 and hence contributing $-6.57 \text{ kcal mol}^{-1}$ (with major dispersion component, Table 4) towards the stabilization. These stacks are then connected via motif 3 forming layers. Two such layers are then interconnected via C17-H17b...O7 hydrogen bonds (motif 6, $-3.42 \text{ kcal mol}^{-1}$) (Figure 19b).

4-[(2E)-5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl]oxy-7H-furo[3,2-g][1]benzopyran-7-one (M-10)

The molecular pairs providing maximum stabilization to the structure extracted from the molecular packing are shown in Figure 20.

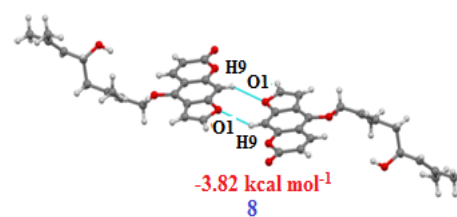
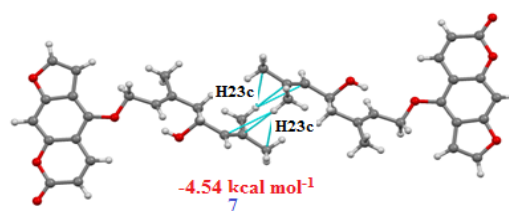
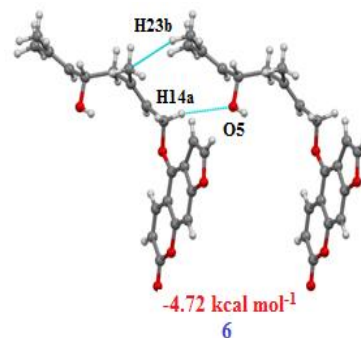
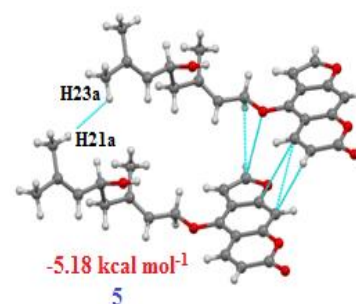
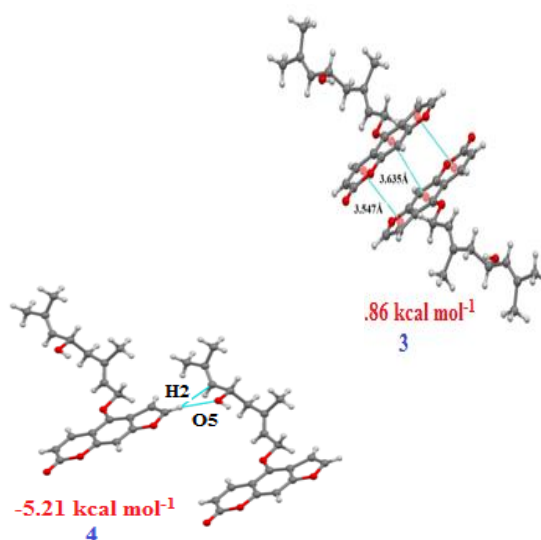
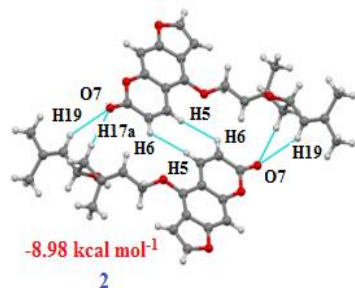
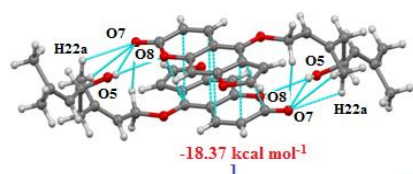
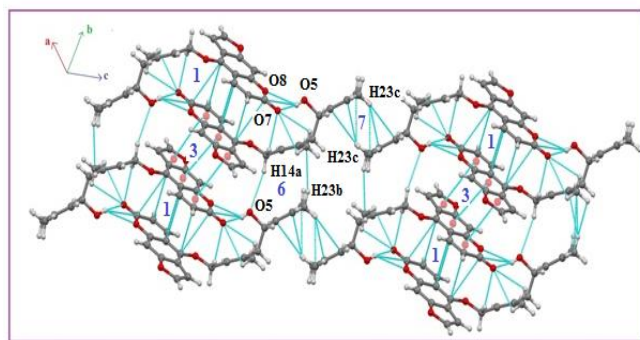
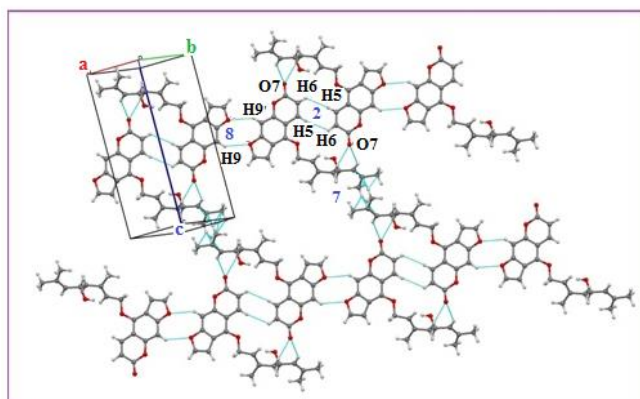


Figure 20 Molecular pairs (1-8) along with their interaction energies in **M-10**



(a)



(b)

Figure 21 Packing of the molecules in **M-10** (a) stacking of molecules down the *bc* plane (b) formation of molecular chains via C-H...O hydrogen bond

The most stabilized molecular pair 1 shows the presence of O-H...O and weak C-H...O resulting in the formation of dimer related by centre of symmetry. Along with these interactions, it also involves stacking interaction (C-C stacking) and hence resulting in a total interaction energy of $-18.73 \text{ kcal mol}^{-1}$ with significant contribution from coulombic ($-12.76 \text{ kcal mol}^{-1}$) and dispersion ($-17.85 \text{ kcal mol}^{-1}$) energies. These dimeric units are then staked along *b*-axis via motif 3 ($I.E. = -7.86 \text{ kcal mol}^{-1}$) involving $\pi\cdots\pi$ interaction. Adjacent stacks are then interconnected via motif 6 and 7 as shown in Figure 21a. Motif 6 ($-4.72 \text{ kcal mol}^{-1}$) shows the presence of weak C-H...O along with C-H...C interaction whereas $C(sp^3)\text{-H}23c\cdots C(sp^3)$ interactions binds the molecules in motif 7 ($-4.54 \text{ kcal mol}^{-1}$). The second stabilized pair showing the presence of dimeric bifurcated C-H...O hydrogen bond along with H...H interaction (motif 2, $I.E. = -8.98 \text{ kcal mol}^{-1}$) and dimeric C9-H9...O1 hydrogen bonds (motif 8, $I.E. = -3.82 \text{ kcal mol}^{-1}$) are involved in the formation of molecular chains. The chains so formed are then interconnected via motif 7 (Figure 21b).

A careful analysis of some key supramolecular motifs obtained in these compounds leads to the following relevant observations:

1. The maximum stabilization to the crystal structure comes from molecular pairs showing the presence of $\pi\cdots\pi$ stacking along with weak C-H...O hydrogen bonds with energy ranging between -7 to $-13.95 \text{ kcal mol}^{-1}$.

2. The energy of the molecular pairs interacting via $C(sp^2)\text{-H}\cdots O$ lies in the range -0.95 to $-3.77 \text{ kcal mol}^{-1}$ with average value being $-2.53 \text{ kcal mol}^{-1}$ while that of molecules interacting via $C(sp^3)\text{-H}\cdots O$ lies in the range -0.84 to $-3.42 \text{ kcal mol}^{-1}$ with average value of $-2.07 \text{ kcal mol}^{-1}$.
3. The energy of the molecular pairs interacting via bifurcated C-H...O interaction ranges between -4 to -6 kcal mol^{-1} with 45-50% contribution from coulombic component.
4. The lattice energy of the structures lies in the range -16 to $-40 \text{ kcal mol}^{-1}$.

Conclusions

Crystallographic analysis of crystal packing in the identified structures of linear furanocoumarin derivatives with inputs from PIXEL energy calculations suggest the presence of molecular pairs which are the key structural motifs beneficial for the packing of molecules. It has been observed that structural motifs involving $\pi\text{-}\pi$ stacking and bifurcated C-H...O are the most significant contributors towards stabilization of structures. Dispersion energy is the major stabilization component in case of stacking interactions. Analysis of C-H...O hydrogen bonds shows that molecular pairs involving $C(sp^2)\text{-H}\cdots O$ hydrogen bonds are more stabilized than those involving $C(sp^3)\text{-H}\cdots O$. The knowledge gained about the role of weak non bonded interactions can be utilized in various scientific disciplines including biochemistry and rational drug design, crystal engineering and molecular devices to materials science and the mechanical properties of solids.

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Received: 22.08.2015.

Accepted: 11.09.2015.