Supplementary information

Invariant and variable intermolecular interactions in functionalized malonic acid half-ester derivatives: X-ray, Hirshfeld surfaces and PIXEL energy analyses

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1. General Experimental Conditions

Materials

All commercial reagents and solvents were used without further purification. All the chemicals were purchased from commercial sources. All the solvents were used as purchased. Analytical thin layer chromatography [silica gel] plates, were purchased form Merck and used as such, the spots were located by UV (254 nm & 356 nm) and iodine. Compounds already known in the literature or commercially available suitable reference is mentioned.

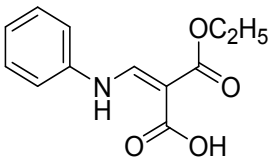
Characterization

All melting points were uncorrected and measured in Guna melting point apparatus. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 pre coated plate. Visualization was accomplished by irradiation with a UV lamp and staining with I_2 on silica gel. Column chromatography was performed using Silica Gel 60-120 Å. ^{1}H and ^{13}C–NMR spectra were obtained using a Bruker 400 MHz NMR spectrometer using tetramethyl silane (TMS) as the internal standard. Unless otherwise mentioned all proton NMR spectra were recorded on 400 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m), broad singlet (brs)], coupling constants [Hz]). All the Carbon NMR spectra were recorded on (100 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm with the respective solvent resonance as the internal standard. All NMR spectra were acquired at ambient temperature.

2. General experimental procedure for the synthesis of malonic acid half ester derivatives MHE-1-5

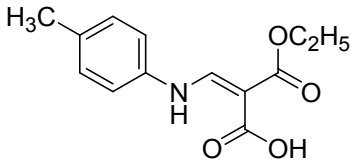
Malonic acid half ester derivatives (MHE-1–5) were prepared by $BF_3.OEt_2$ mediated hydrolysis of germinal diesters using reported method (Scheme **1)**.[1] To a solution of 2-[(arylamino)-methylene]-malonic acid diethyl ester[2] (1.0 equiv.) in $CHCl_3$ (3x w/v) $BF_3.OEt_2$ (1.0 equiv.) was added and stirred at 298 K. Completion of the reaction was determined by TLC, followed by which the reaction mixture was quenched with water (1x w/v) and extracted with chloroform (3x 10 mL). The combined organic layer was dried (anhyd. Na_2SO_4) and evaporated in rotary evaporator under vacuum. The crude product obtained was passed through a short silica gel column using a suitable eluent to get corresponding product.

2.1. Preparation of 2-phenylaminomethylene-malonic acid monoethyl ester (MHE-1)



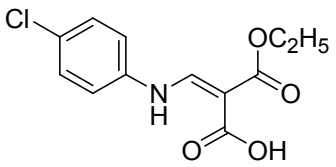
The reaction was carried out as mentioned in the general procedure[1] using 2-phenylaminomethylene-malonic acid diethyl ester[2] (1.0 g, 3.8 mmol) $BF_3.OEt_2$ (960 µL, 3.8 mmol) in chloroform (5 mL). Conditions: room temperature, 30 min. The compound MHE-**1** (0.82 g, 92%) was obtained as a white solid. The spectral data for the product obtained was comparable with the data already reported in the literature.[1] mp: 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.30 (t, *J* = 6.8 Hz, 3H), 4.27 (q, *J*= 14.0 and *J* = 7.2 Hz, 2H), 7.11-7.19 (m, 3H), 7.32-7.36 (m, 2H), 8.43 (d, *J* = 14.0 Hz, 1H), 11.62 (d, *J* = 12.8 Hz, 1H), 12.92 (brs, 1H).

2.2. Preparation of 2-(*p*-tolylamino-methylene)-malonic acid monoethyl ester(MHE-2)



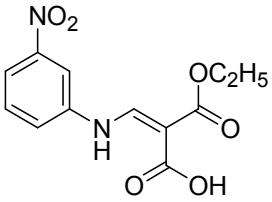
The reaction was carried out as mentioned in the general procedure[1] using 2-(*p*-tolylamino-methylene)-malonic acid diethyl ester[2] (1.0g, 3.6 mmol), $BF_3.OEt_2$ (910 µL, 3.6 mmol) in chloroform (5 mL). Conditions: room temperature, 20 min. The compound MHE-**2** (0.80 g, 90%) was obtained as a white solid. The spectral data for the product obtained was comparable with the data already reported in the literature.[1] mp: 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.2 Hz, 3H), 2.33 (s, 3H), 4.32 (q, *J* = 14.4 and *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 8.44 (d, *J* = 13.6 Hz, 1H), 11.62 (d, *J* = 13.2 Hz, 1H), 13.0 (brs, 1H).

2.3. Preparation of 2-[(4-Chloro-phenylamino)-methylene]-malonic acid monoethyl ester (MHE-3)



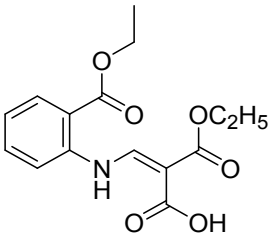
The reaction was carried out as mentioned in the general procedure[1] using 2-[(4-chloro-phenylamino)-methylene]-malonic acid diethyl ester[2] (1.0 g, 3.2 mmol) and $BF_3.OEt_2$ (850 µL, 3.2 mmol) in chloroform (5 mL). Conditions: room temperature, 2.0 h. The compound MHE-**3** (0.72 g, 81 %) was obtained as a white solid. The spectral data for the product obtained was comparable with the data already reported in the literature. [1] mp: 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.36 (t, *J* = 7.2 Hz, 3H), 4.33 (q, *J* = 14.4 and *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 8.42 (d, *J* = 13.6 Hz, 1H), 11.68 (d, *J* = 13.2 Hz, 1H), 12.97 (brs, 1H).

2.4. Preparation of 2-[(3-Nitro-phenylamino)-methylene]-malonic acid monoethyl ester (MHE-4)



The reaction was carried out as mentioned in the general procedure[1] using 2-[(3-nitro-phenylamino)-methylene]-malonic acid diethyl ester[2] (1.0 g, 3.2 mmol) and $BF_3.OEt_2$ (820 µL, 3.2 mmol) in chloroform (5 mL). Conditions: room temperature, 2.20 h. The compound MHE-**4** (0.76 g, 85 %) was obtained as a yellow solid. The spectral data for the product obtained was comparable with the data already reported in the literature.[1] mp: 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.40 (t, *J* = 6.8 Hz, 3H), 4.39 (q, *J* = 14.0 and *J* = 6.8 Hz, 2H), 7.49-7.52 (m, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 8.05-8.09 (m, 2H), 8.53 (d, *J* = 13.2 Hz, 1H), 11.91 (d, *J* = 13.2 Hz, 1H), 12.99 (brs, 1H).

2.5. 2-[(2-Ethoxycarbonyl-phenylamino)-methylene]-malonic acid monoethyl ester (MHE-5)



The reaction was carried out as mentioned in the general procedure1 using 2-[(2-ethoxycarbonyl-phenylamino)-methylene]-malonic acid diethyl ester[2] (1.0 g, 2.8 mmol) and $BF_3.OEt_2$ (750 µL, 2.8 mmol) in chloroform (5 mL). Conditions: room temperature, 1.30 h. The compound MHE-**5** (0.75 g, 81 %) was obtained as a white solid. The spectral data for the product obtained was comparable with the data already reported in the literature.[1] mp: 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ:1.36-1.43 (m, 6H), 4.35 (q, *J* = 14.4 and *J* = 7.2 Hz, 2H), 4.50 (q, *J* = 14.0 and *J* = 7.2 Hz, 2H), 7.22-7.24 (m, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.58-7.62 (m, 1H), 8.11 (dd, *J* = 7.6 and 1.2 Hz, 1H), 8.59 (d, *J* = 13.6 Hz, 1H), 12.83 (brs, 1H), 13.25 (d, *J* = 13.2 Hz, 1H).

3. Structural superimposition study

The structural superimposition is carried out to identify the conformational changes on the molecular structure upon different substitutions. The common atoms (N1/C7/C8/C9/O2/O1/C10/O3/O4/C11/C12) in MHE-1–5 are used for structural superimposition (Fig.2). The root mean square deviation (rmsd) between MHE-1 and MHE-2 involving common atoms is 0.033 Å and the corresponding value being 0.042, 0.051, 0.067 Å for, MHE-1/MHE-3, MHE-1/MHE-4 and MHE-1/MHE-5 pair, respectively. The structural superimposition diagrams indicate that the phenyl ring adopts different orientations in MHE-4–5 structures when compared with their parent compound MHE-1. It is also evident from two torsion angles C7–N1–C1–C2 and C7–N1–C1–C6 listed in Table S1.

The structural superimposition is also carried out for the above mentioned molecular pair derived from gas phase DFT calculation. We observed similar rmsd values for the optimized molecular pairs. Briefly, in structures MHE-1–3, the orientation of the phenyl ring is nearly the same. In MHE-4 and MHE-5, the departure is higher (above 20°) when compared to MHE-1–3. Again, in MHE-5, the phenyl ring is rotated in the opposite direction as compared to MHE-4. In all the optimized structures (Fig S2–3), the trend of the phenyl ring orientation is the same when compared with crystal structures. However, the values are deviated by 10–20° from the X–ray crystal structure geometry. This might be a consequence of crystal packing effect. The dihedral angle between the phenyl ring (C1–C6) and acid group (C1/N1/C7/C8/C9/O1/O2) and ester group (C1/N1/C7/C8/C10/O4/C11/C12) are listed in Table S2. It is also evident from two torsion angles C7–N1–C1–C2 and C7–N1–C1–C6 listed in Table S1 In MHE-4, the mean plane of the phenyl ring and the nitro group makes a dihedral angle of 15.34(13)°.

Table S1. Selected torsion angles observed in X–ray and DFT calculation (in parenthesis)

Atom	Compound				
	MHE-1	MHE-2	MHE-3	MHE-4	MHE-5
C7–N1–C1–C2	147.45(11) (161.9)	146.47(18) (167.4)	150.46(14) (166.3)	176.09(18) (165.5)	–179.91(14) (–156.7)
C7–N1–C1–C6	–32.44(16) (–18.9)	–33.3(3) (–13.3)	–30.0(2) (–14.4)	–3.5(3) (–15.2)	2.4(2) (23.8)

Table S2. Selected dihedral angles between various mean planes in crystal structures

Mean planes formed by atoms	Structure (Dihedral angle, °)				
	MHE-1	MHE-2	MHE-3	MHE-4	MHE-5
C1-C6 and C1N1C7C8C9O1O2	34.29(4)	34.05(6)	30.74(5)	5.50(8)	10.0(9)
C1-C6 and C1N1C7C8C10O4C11C12	34.12(3)	36.00(5)	31.06(5)	2.90(6)	10.20(6)
C1N1C7C8C9O1O2 and C1N1C7C8C10O4C11C12	2.92(7)	2.08(4)	0.38(3)	2.92(7)	2.31(5)
C1-C6 and C3N2O5O6				15.34(13)	

Table S3. Geometrical parameters for π… π stacking interactions in MHE-1–5.

Structures	centroid…centroid	Distance (Å)	Alpha (°)	Beta (°)	Gamma (°)	Cg(I)_Perp (Å)	Cg(J)_Perp (Å)	Slippage (Å)
MHE-1	Cg(I)…Cg(J)^{i}	4.280	0	31.36	31.36	3.6553(5)	3.6553(5)	2.227
MHE-2	Cg(I)…Cg(J)^{ii}	4.514	0	33.06	33.06	-3.7831(9)	-3.7831(9)	2.463
MHE-3	Cg(I)…Cg(J)^{iii}	4.341	0	30.53	30.53	-3.7393(6)	-3.7393(6)	2.205
MHE-4	Cg(I)…Cg(J)^{iv}	3.604	0	9.41	9.41	3.5558(9)	3.5557(9)	0.589
MHE-5	Cg(I)…Cg(J)^{v}	4.568	0	41.44	41.44	3.4242(8)	3.4242(8)	3.024

Symmetry (i)-x, 1-y, -z+2; (ii) 1-x, 1-y, -z+2; (iii) 1-x, 1-y, -z+2; (iv) 1-x, -y, 1-z; (v) –x+2, -y, -z+2

Cg(I) = Phenyl ring centre-of-gravity

Cg(J) = symmetry-related phenyl ring centre-of-gravity

Alpha = Dihedral Angle between Planes I and J (°)

Beta = Angle Cg-->Cg* or Cg-->Me vector and normal to plane I (°)

Gamma = Angle Cg(I)-->Cg(J) vector and normal to plane J (°)

Cg(I)-Cg(J) = Distance between ring Centroids (Å)

CgI_Perp = Perpendicular distance of Cg1 on ring Cg1J (Å)

CgJ_Perp = Perpendicular distance of Cg(J) on ring I (Å)

Slippage = Distance between Cg(I) and Perpendicular Projection of Cg(J) on Ring I (Å).

4. XPac analysis

The XPac computer program[3] allows us to identify similarity and dissimilarity index 'X' between any two crystal structures, which gives us idea about how far two crystal structures deviate from perfect geometrical similarity.[4] The structural patterns common to all the crystal structure was considered as 'supramolecular construct (SC) and compared.[26]The SC may be termed as 0D similarity, 1D similarity (row of molecules match), 2D similarity (layer of molecules match) and 3D similarity (isostructural). The compound MHE-1 was used as a template for XPac analysis. Occurrence of isostructurality (3D SC) was observed between MHE-1/MHE-2, MHE-1/MHE-3 and MHE-2/MHE-3 pair of molecules. The dissimilarity index 'X' for MHE-1/MHE-2 was found to be 3.5 while for MHE-1/MHE-3 and MHE-2/MHE-3 are 3.3 and 2.4, respectively. The dissimilarity index 'X' for other pair of molecules such as MHE-1/MHE-4 (12.8), MHE-1/MHE-5 (13.9), MHE-2/MHE-4 (13.4), MHE-3/MHE-4 (11.6) and MHE-3/MHE-5 (16) was found to be higher. No similarity was detected for MHE-2/MHE-5 and MHE-4/MHE-5 pairs.

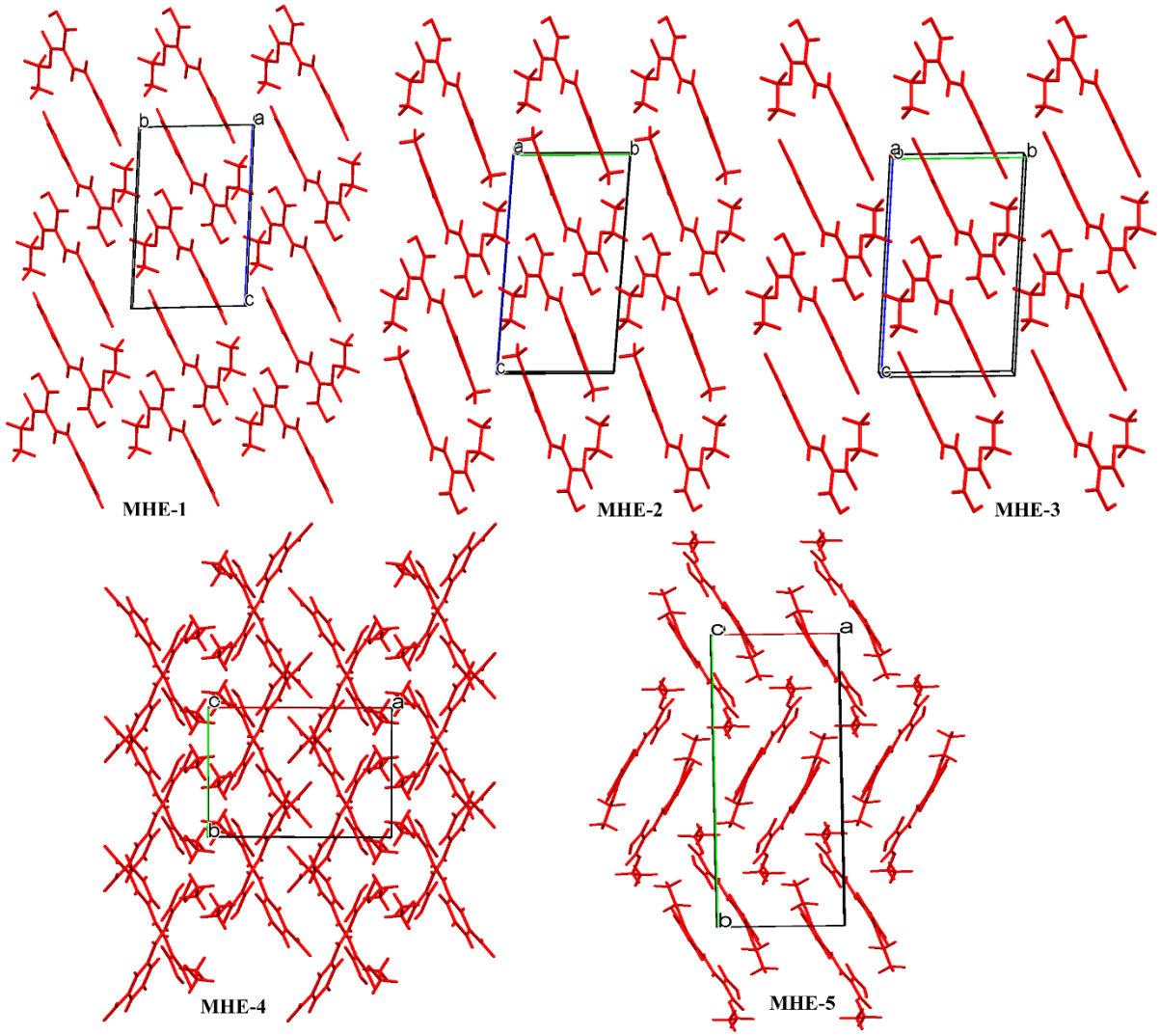


Fig. S1 The crystal packing arrangements in **MHE 1–5.**

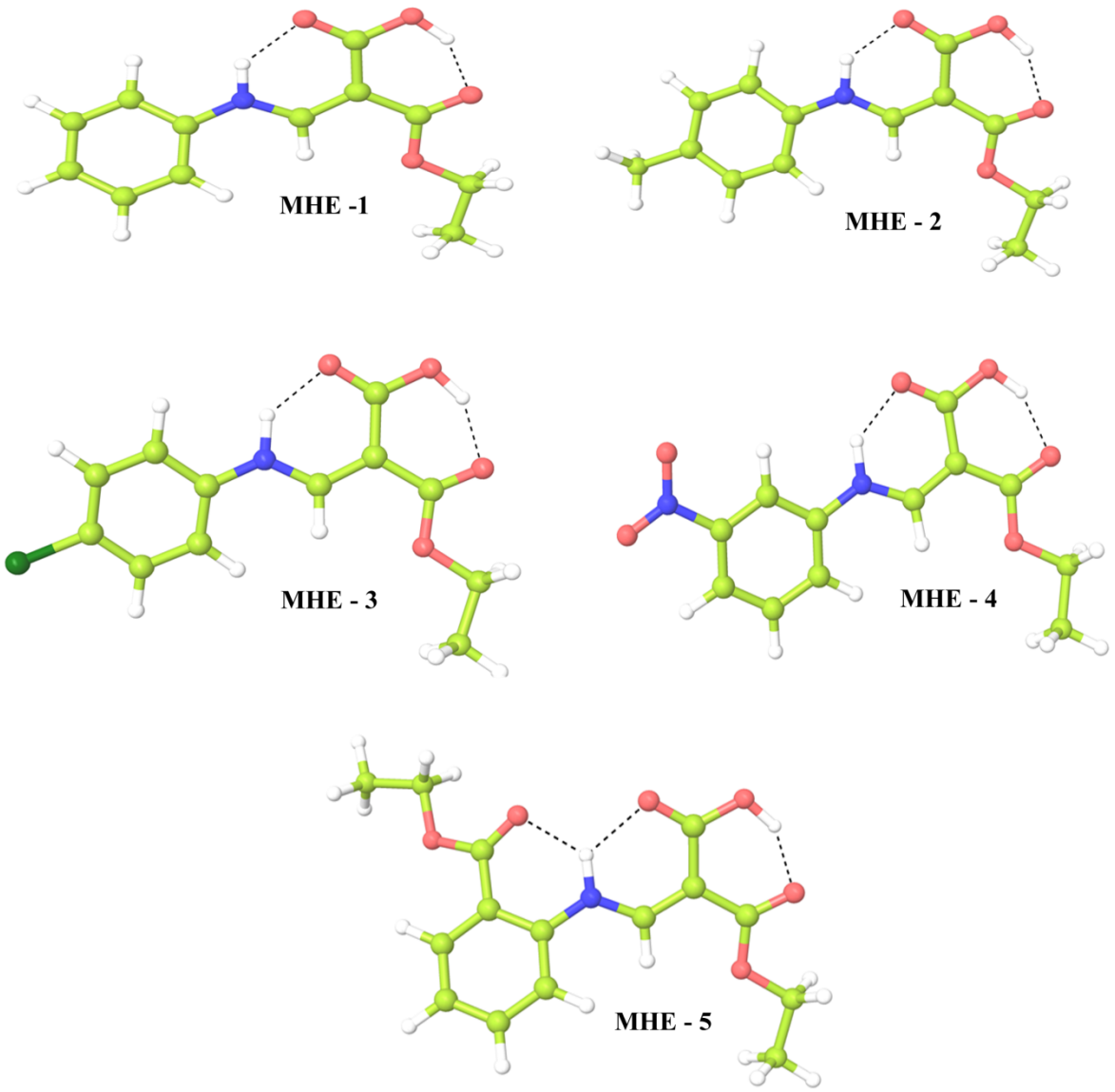


Fig. S2 A view of the optimized structures for compounds **MHE-1–5.**

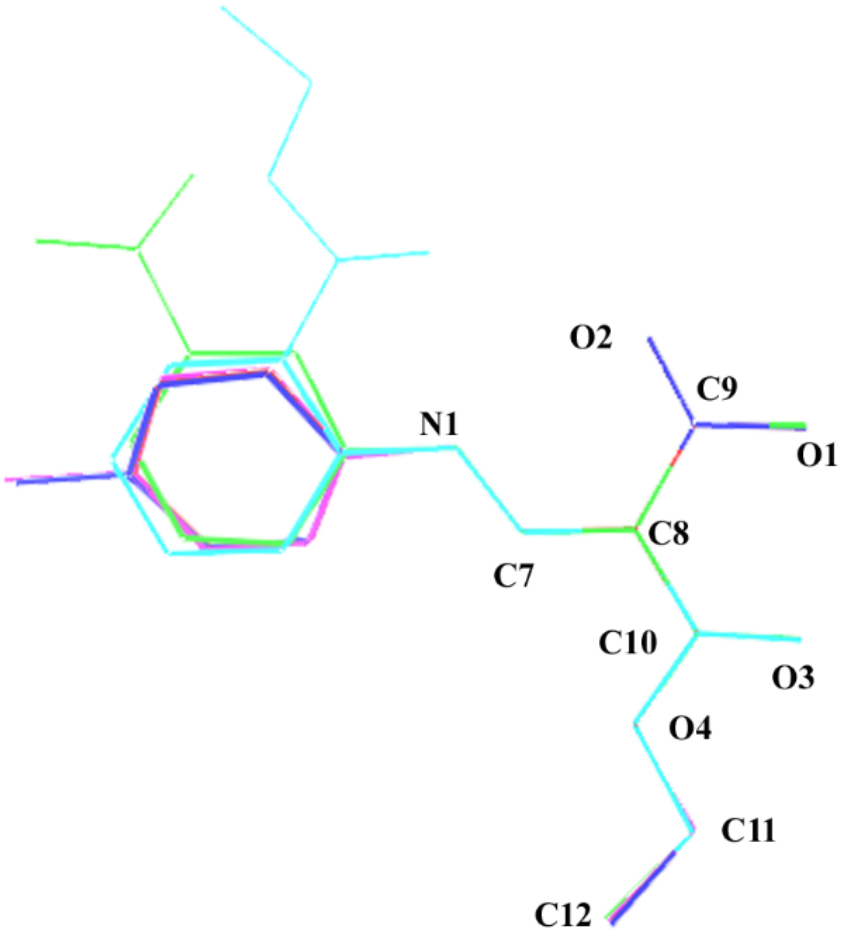


Fig. S3 Structural superimpositions of optimized structures (**MHE-1**–**5**) involving common atoms (N1/C7/C8/C9/O2/O1/C10/O3/ O4/C11/C12). The colour codes for **MHE-1** (red), **MHE-2** (blue), **MHE-3** (magenta), **MHE-4** (green) and **MHE-5** (cyan).

The rmsd between molecular pair **MHE-1/2 =0.033**

The rmsd between molecular pair **MHE-1/3 =0.019**

The rmsd between molecular pair **MHE-1/4 =0.051**

The rmsd between molecular pair **MHE-1/5 =0.067**

The rmsd between molecular pair **MHE-2/3= 0.028**

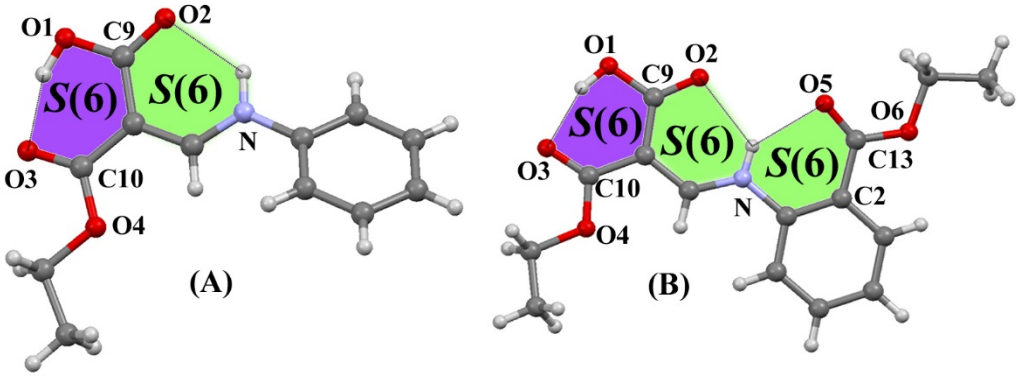


Fig. S4 Common intramolecular hydrogen bonds. (A) two fused *S*(6) ring motif and (B) three fused *S*(6) ring motif.

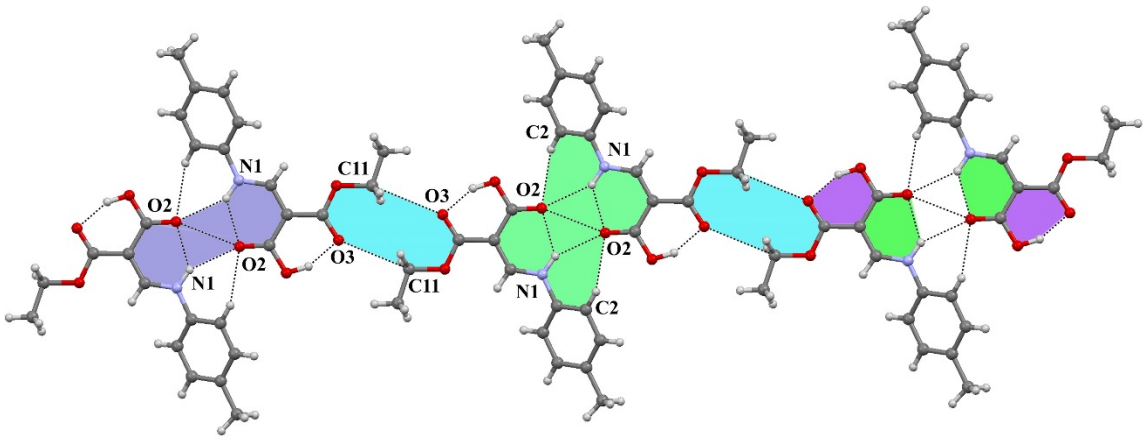


Fig. S5 Part of the crystal structure displaying various intermolecular interactions led to the formation of molecular ribbon in **MHE-2**

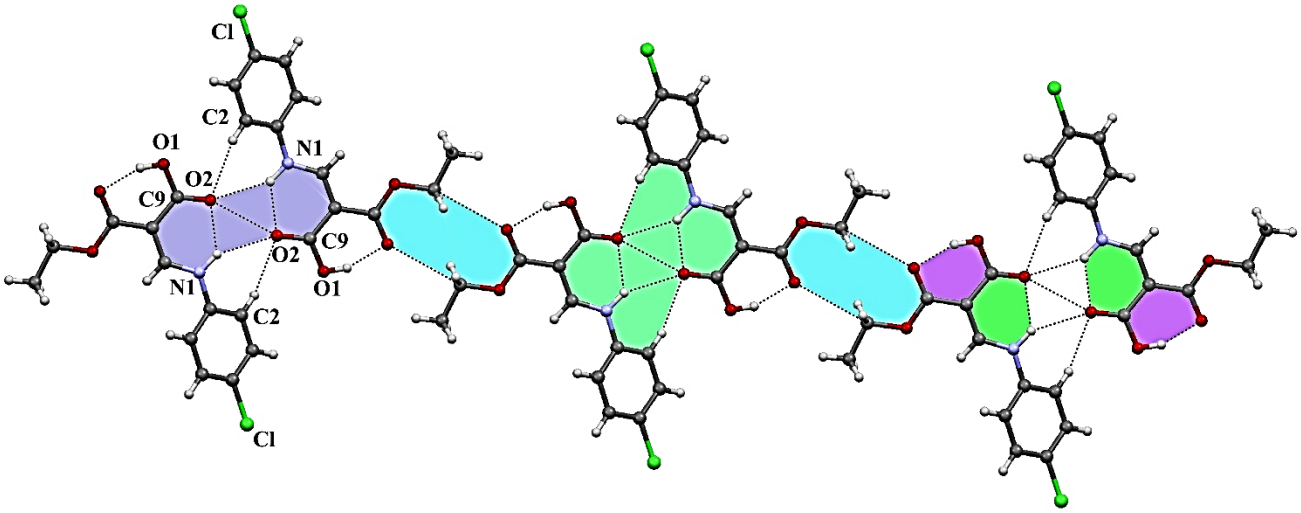


Fig. S6 Part of the crystal structure displaying various intermolecular interactions led to the formation of molecular ribbon in **MHE-3**

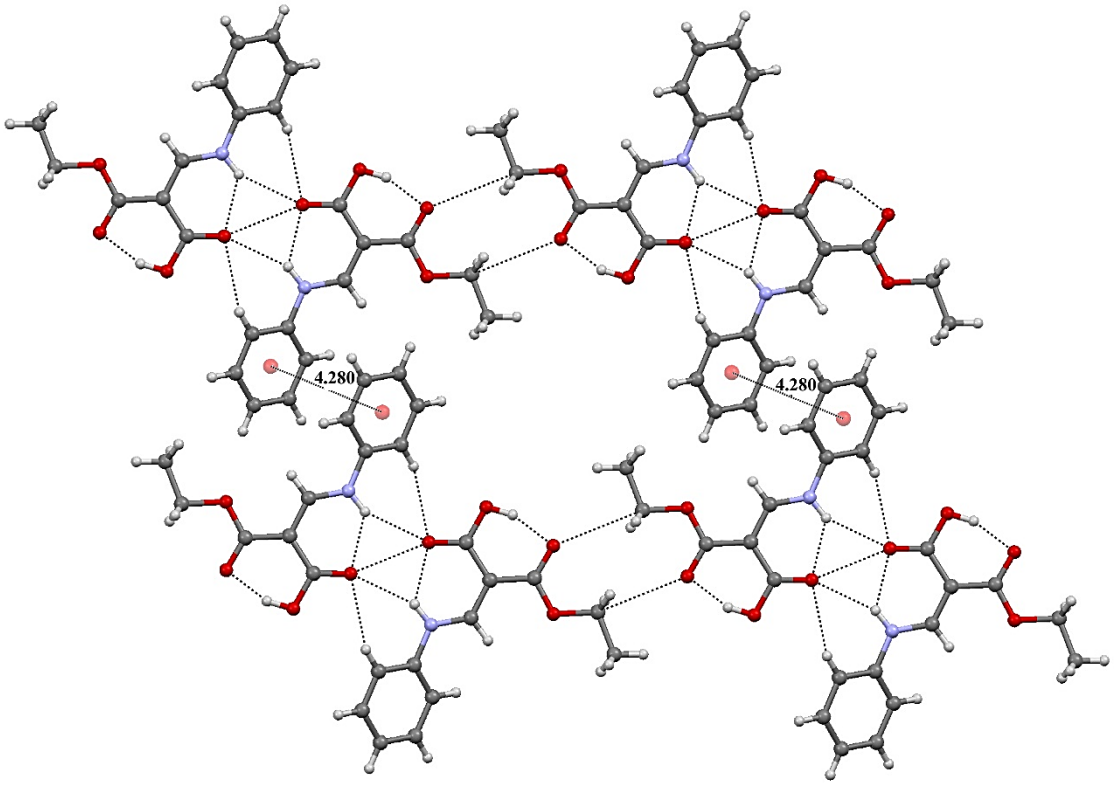


Fig. S7 Adjacent layers of molecular ribbons are interlinked by weak π…π stacking interactions **MHE-1**

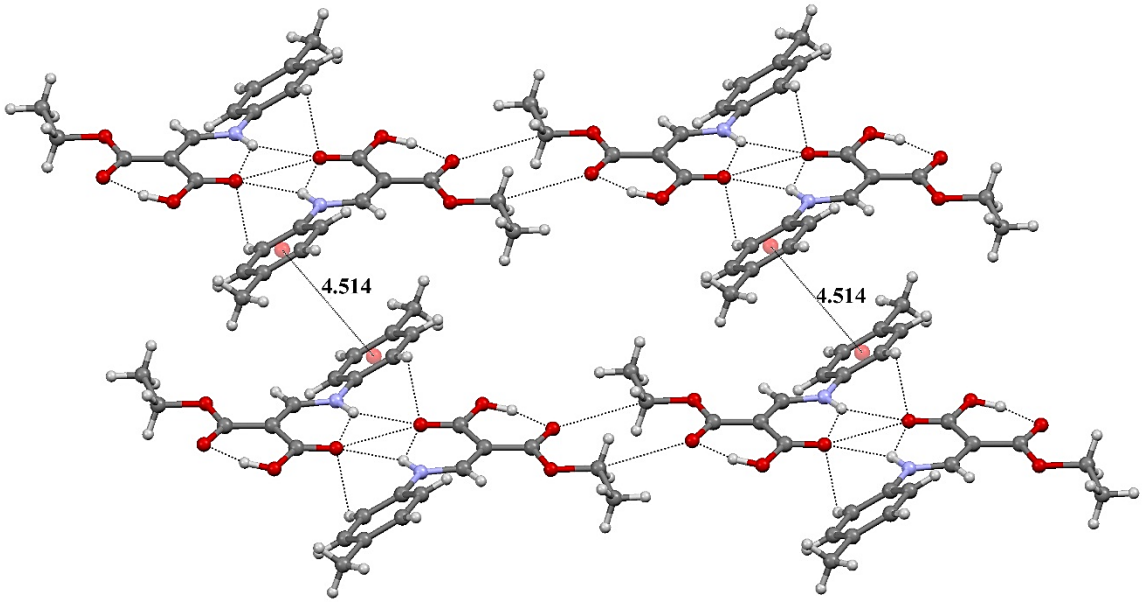


Fig. S8 Adjacent layers of molecular ribbons are interlinked by weak π…π stacking interactions **MHE-2**

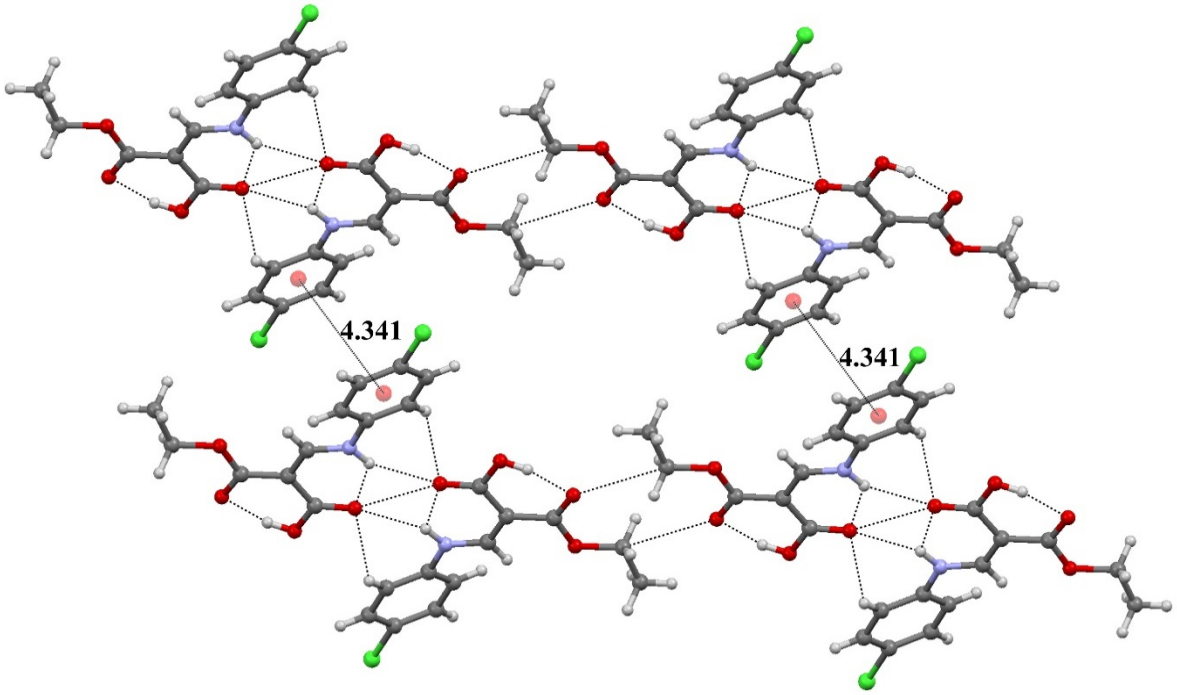


Fig. S9 Adjacent layers of molecular ribbons are interlinked by weak π…π stacking interactions **MHE-3**

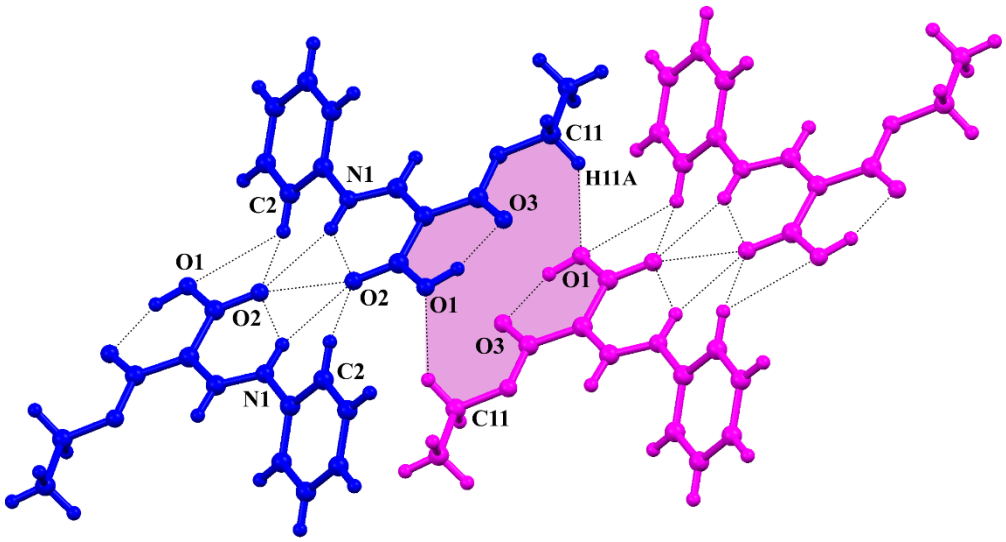


Fig. S10 Adjacent layers of molecular ribbons are interlinked by C11…C9 interactions **MHE-1-3**

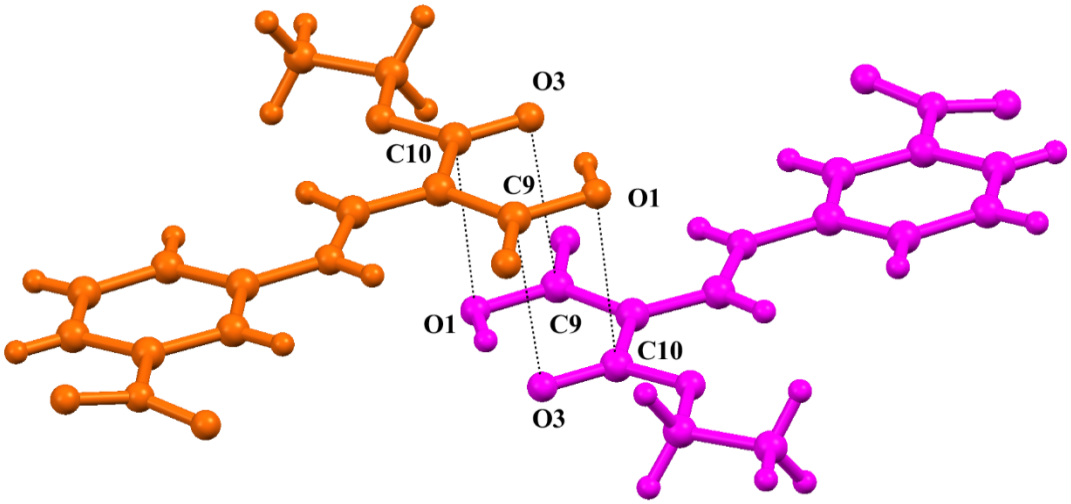


Fig. S11 Stacking between the carbonyl group (C10 and O3 atoms) of the ester moiety and carboxylic acid moiety (O1 and C9 atoms).

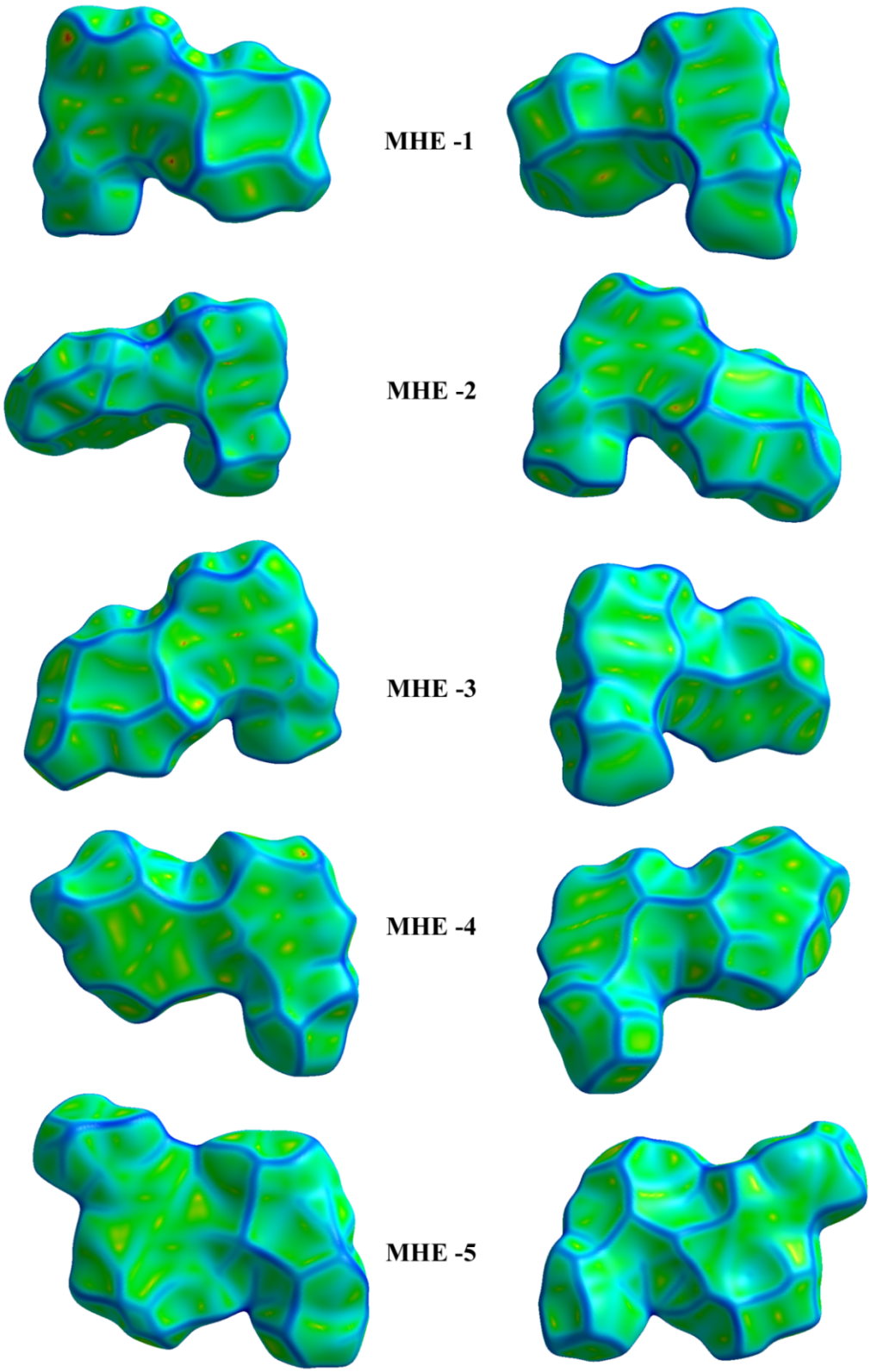


Fig. S12 Views of the Hirshfeld surfaces mapped with curvedness for **MHE-1–5.**

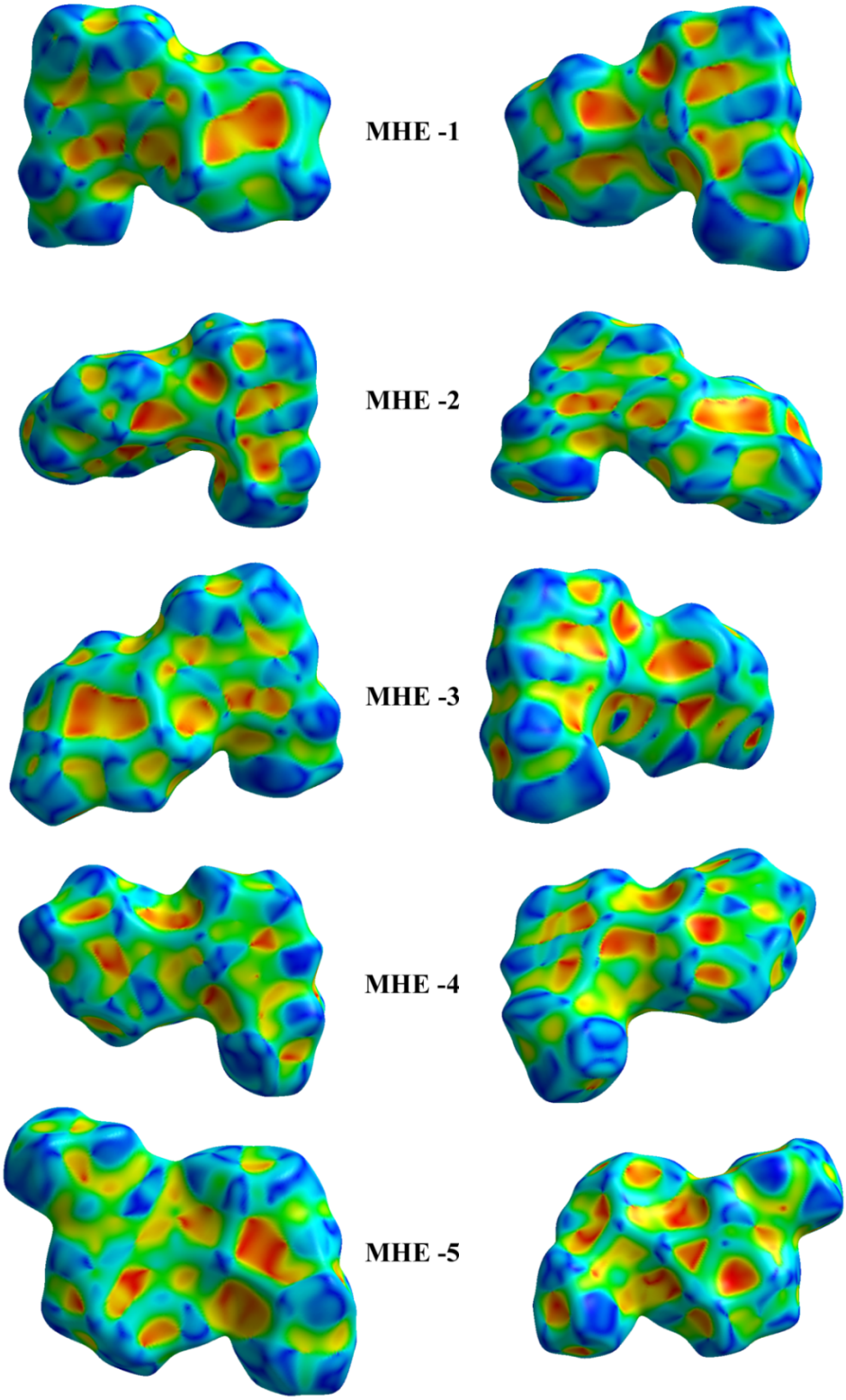


Fig. S13 Views of the Hirshfeld surfaces mapped with shape index for **MHE-1–5.**

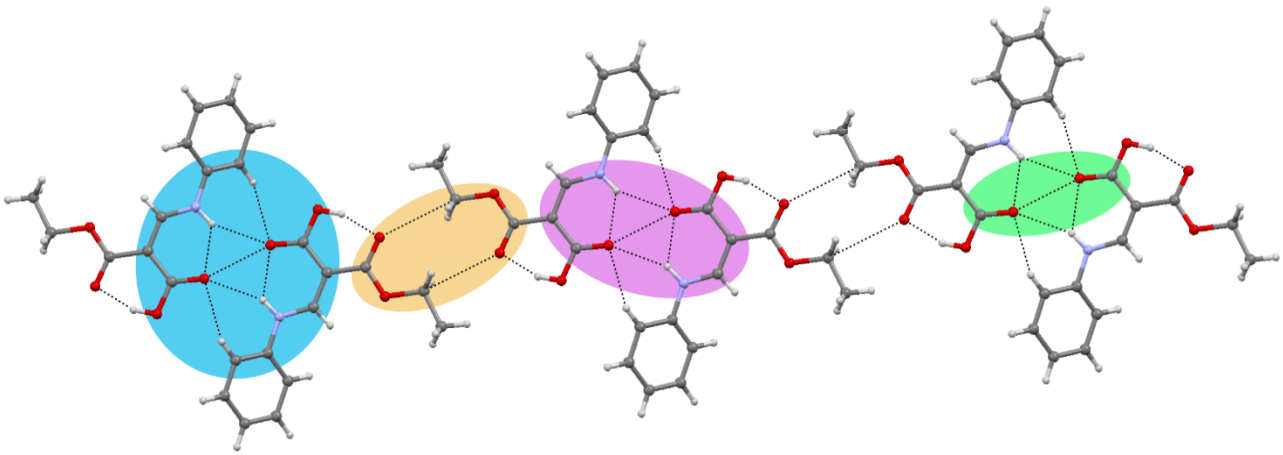


Fig. S14 Various fragments in **MHE-1**–**3** which are used for the CSD search highlighted in different colours.

5. References

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