Electronic Supplementary Material (ESI) for CrystEngComm.

Halogen bonding in 5-iodo-1-arylpyrazoles investigated in the solid state and predicted by solution ^{13}C-NMR spectroscopy

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Contents

1. General

Melting points were measured using a Boetius hot plate microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300BB instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. The spectra were recorded in $CDCl_3$ (for the experiments in pyridine-d_5, DMSO-d_6, benzene-d_6) at 298K and the chemical shifts are relative to TMS used as the internal standard. Elemental analysis was performed on a Costech Instruments EAS 32 apparatus and the results were in agreement with the calculated values. All starting materials and solvents were purchased from common commercial suppliers and were used without further purification.

2. Synthesis and structural characterization of 5-iodopyrazoles 1-3

General procedure for obtaining the 5-iodo-1-phenylpyrazoles 1-3

A mixture of 10 mmol 4-iodosydnone and 12 mmol of dimethyl acetylenedicarboxylate was refluxed in 15 mL toluene for 10 hrs. The 1-arylpyrazoles were isolated from the reaction mixture by evaporation of toluene followed by crystallization from different solvents.

Dimethyl 1-(2-isopropylphenyl)-5-iodopyrazole-3,4-dicarboxylate (**1**). Colourless crystals from 2-propanol with mp 156-158 ^{o}C. Anal. Calcd. for $C_{16}H_{17}IN_2O_4$: C 44.88; H 4.00; N 6.54; Found: C 45.17, H 4.32, N 6.76; Yield 82%.^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.15, 1.20 (2d, 6H, *J* = 6.8 Hz, Me); 2.42 (sept, 1H, *J* = 6.8 Hz, CH); 3.93, 3.94 (2MeO); 7.16-7.18 (m, 1H, H-3'); 7.29-7.36 (m, 1H, H-5') 7.45-7.54 (m, 2H, H-4', H-6'); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.0, 24.2 (2Me); 28.3 (CH); 52.4, 52.7 (2MeO); 91.6 (C-5); 120.6 (C-4); 126.4, 126.8, 128.4, 131.1 (C-3', C-4', C-5', C-6'); 137.3, 146.4 (C-1', C-2'); 145.0 (C-3); 161.3, 162.3 (2COO);

Dimethyl 1-(3-methoxyphenyl)-5-iodopyrazole-3,4-dicarboxylate (**2**).[1] Colourless crystals with mp 107-109 ^{o}C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.85 (OMe); 3.93, 3.95 (2**Me**); 7.00-7.06 (m, 3H, H-2', H-4', H-6'); 7.41 (t, *J* = 8.2 Hz, 1H, H-6'); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 52.4, 52.7, 52.9 (3**Me**O); 88.6 (C-5); 112.5, 116.7, 119.4, 129.4 (C-2',C-4', C-5', C-6'); 140.5 (C-1'); 121.7, 145.1 (C3, C-4); 160.0 (C-3'); 161.3, 162.3 (2COO).

Dimethyl 1-(3-chloro-2-methylphenyl)-5-iodopyrazole-3,4-dicarboxylate (**3**). Colourless crystals from ethanol with mp 77-78^{o}C. Anal. Calcd. for $C_{14}H_{12}ClIN_2O_4$: C 38.69, H 2.78, N 6.45; Found: C 39.03, H 3.11, N 6.69. Yield 77%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.18 (Me); 4.08, 4.10 (2**Me**); 7.31-7.33 (m, 1H, H-4'); 7.41-7.46 (m, 1H, H-5'); 7.69-7.72 (m, 1H, H-6'); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.4 (Me); 52.5, 52.9 (COOMe); 91.1 (C-5); 126.9, 127.2, 131.6 (C-4', C-5', C-6'); 135.1, 135.8, 139.6 (C-1', C-2', C-3'); 121.1, 145.4 (C-3, C-4); 161.3, 162.2 (2COO);

3. X-ray crystallography

X-ray crystallography. X-ray diffraction measurements for **1**-**3** were carried out with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated MoKα radiation. Single crystals were positioned at 40 mm from the detector and 167, 721 and 519 frames were measured each for 3, 7 and 7 s over 1° scan width for **1**, **2** and **3**, respectively. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction.[2] The structures were solved by direct methods using Olex2[3] and refined by full-matrix least-squares on F^2 with SHELXL-97[4] using an anisotropic model for non-hydrogen atoms. All H atoms were introduced in idealised positions (d_{CH} = 0.96 Å) using the riding model with their isotropic displacement parameters fixed at 120% of their riding atom. The molecular plots were obtained using the Olex2 program. The crystallographic data and refinement details are quoted in Tables 3S, while bond lengths and angles are summarised in Table 3S. CCDC - 1939542 (**1**), CCDC - 1939541 (**2**), CCDC - 1939543 (**3**) contain the supplementary crystallographic data for this contribution. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.ca.ac.uk).

Table 1S. Bond lengths (Å) and angles for **1**, **2** and **3**.

Compound 1			
Bond lengths (Å)			
I1-C10	2.059(4)	C1-C6	1.374(7)
O1-C13	1.172(6)	C2-C3	1.390(7)
O2-C13	1.290(6)	C3-C4	1.367(8)
O2-C14	1.454(6)	C4-C5	1.363(8)
O3-C15	1.179(6)	C5-C6	1.399(7)
O4-C15	1.313(6)	C6-C7	1.519(7)
O4-C16	1.436(6)	C7-C8	1.523(9)
N1-N2	1.358(5)	C7-C9	1.509(9)
N1-C1	1.438(6)	C10-C11	1.376(6)
N1-C10	1.358(5)	C11-C12	1.407(6)
N2-C12	1.324(5)	C11-C13	1.485(6)
C1-C2	1.381(7)	C12-C15	1.480(6)
Bond angles (°)			
C13-O2-C14	116.9(5)	C9-C7-C6	112.7(6)
C15-O4-C16	116.7(4)	C9-C7-C8	111.3(6)
N2-N1-C1	119.4(3)	N1-C10-I1	122.2(3)

C10-N1-N2	111.5(4)	N1-C10-C11	106.7(4)
C10-N1-C1	129.1(4)	C11-C10-I1	130.9(3)
C12-N2-N1	105.5(3)	C10-C11-C12	105.1(4)
C2-C1-N1	117.1(4)	C10-C11-C13	125.5(4)
C6-C1-N1	119.1(4)	C12-C11-C13	129.4(4)
C6-C1-C2	123.9(5)	N2-C12-C11	111.1(4)
C1-C2-C3	118.4(5)	N2-C12-C15	120.7(4)
C4-C3-C2	119.3(5)	C11-C12-C15	128.0(4)
C5-C4-C3	120.9(5)	O1-C13-O2	123.2(5)
C4-C5-C6	122.2(5)	O1-C13-C11	124.5(5)
C1-C6-C5	115.4(5)	O2-C13-C11	112.2(4)
C1-C6-C7	123.1(5)	O3-C15-O4	124.8(5)
C5-C6-C7	121.6(5)	O3-C15-C12	123.1(5)
C8-C7-C6	110.3(5)	O4-C15-C12	112.1(4)
Compound 2			
Bond lengths (Å)			
I1-C8	2.064(3)	N2-C10	1.319(5)
O1-C11	1.205(6)	C1-C2	1.375(7)
O2-C11	1.336(6)	C1-C6	1.373(6)
O2-C12	1.442(5)	C2-C3	1.391(7)
O3-C13	1.203(5)	C3-C4	1.358(7)
O4-C13	1.313(5)	C4-C5	1.381(6)
O4-C14	1.442(5)	C5-C6	1.398(5)
O5-C5	1.356(5)	C8-C9	1.406(8)
O5-C7	1.429(7)	C9-C10	1.415(7)
N1-N2	1.359(5)	C9-C11	1.466(8)
N1-C1	1.450(7)	C10-C13	1.501(5)
N1-C8	1.343(8)		
Bond angles (°)			
C11-O2-C12	116.2(4)	C1-C6-C5	118.0(4)
C13-O4-C14	116.0(3)	N1-C8-I1	122.9(4)
C5-O5-C7	118.1(4)	N1-C8-C9	107.2(3)
N2-N1-C1	118.1(4)	C9-C8-I1	129.6(5)

C8-N1-N2	112.2(4)	C8-C9-C10	103.0(4)
C8-N1-C1	129.5(4)	C8-C9-C11	123.2(5)
C10-N2-N1	104.9(4)	C10-C9-C11	133.7(5)
C2-C1-N1	118.2(5)	N2-C10-C9	112.6(4)
C6-C1-N1	118.1(4)	N2-C10-C13	115.5(4)
C6-C1-C2	123.4(5)	C9-C10-C13	131.9(4)
C1-C2-C3	116.9(4)	O1-C11-O2	124.2(6)
C4-C3-C2	121.4(5)	O1-C11-C9	123.9(5)
C3-C4-C5	120.7(4)	O2-C11-C9	112.0(4)
O5-C5-C4	116.5(4)	O3-C13-O4	124.7(4)
O5-C5-C6	124.0(4)	O3-C13-C10	121.9(4)
C4-C5-C6	119.6(4)	O4-C13-C10	113.4(3)
Compound 3			
Bond lengths (Å)			
I1-C8	2.055(6)	C13-C10	1.471(8)
Cl1-C5	1.725(7)	C10-C9	1.432(8)
O2-C11	1.340(7)	C9-C8	1.369(8)
O2-C12	1.439(7)	C9-C11	1.467(8)
O3-C13	1.218(7)	C1-C2	1.409(9)
O4-C13	1.330(7)	C1-C6	1.368(9)
O4-C14	1.442(8)	C2-C3	1.413(10)
O1-C11	1.199(7)	C6-C5	1.430(9)
N1-N2	1.367(7)	C6-C7	1.484(9)
N1-C8	1.375(8)	C4-C3	1.364(10)
N1-C1	1.425(8)	C4-C5	1.365(10)
N2-C10	1.316(7)		
Bond angles (^{o})			
C11-O2-C12	115.5(5)	C9-C8-N1	107.4(5)
C13-O4-C14	114.8(5)	O2-C11-C9	110.8(5)
N2-N1-C8	111.0(5)	O1-C11-O2	124.2(5)
N2-N1-C1	119.9(5)	O1-C11-C9	124.8(5)
C8-N1-C1	128.8(5)	C2-C1-N1	117.7(6)
C10-N2-N1	105.5(5)	C6-C1-N1	117.8(6)

O3-C13-O4	124.5(6)	C6-C1-C2	124.4(6)
O3-C13-C10	123.0(5)	C1-C2-C3	117.4(7)
O4-C13-C10	112.5(5)	C1-C6-C5	115.2(6)
N2-C10-C13	119.9(5)	C1-C6-C7	122.5(6)
N2-C10-C9	111.7(5)	C5-C6-C7	122.2(6)
C9-C10-C13	128.3(5)	C3-C4-C5	121.8(7)
C10-C9-C11	130.4(5)	C4-C3-C2	119.3(7)
C8-C9-C10	104.4(5)	C6-C5-Cl1	118.5(6)
C8-C9-C11	125.1(6)	C4-C5-Cl1	119.8(6)
N1-C8-I1	121.2(4)	C4-C5-C6	121.7(7)
C9-C8-I1	131.4(5)		

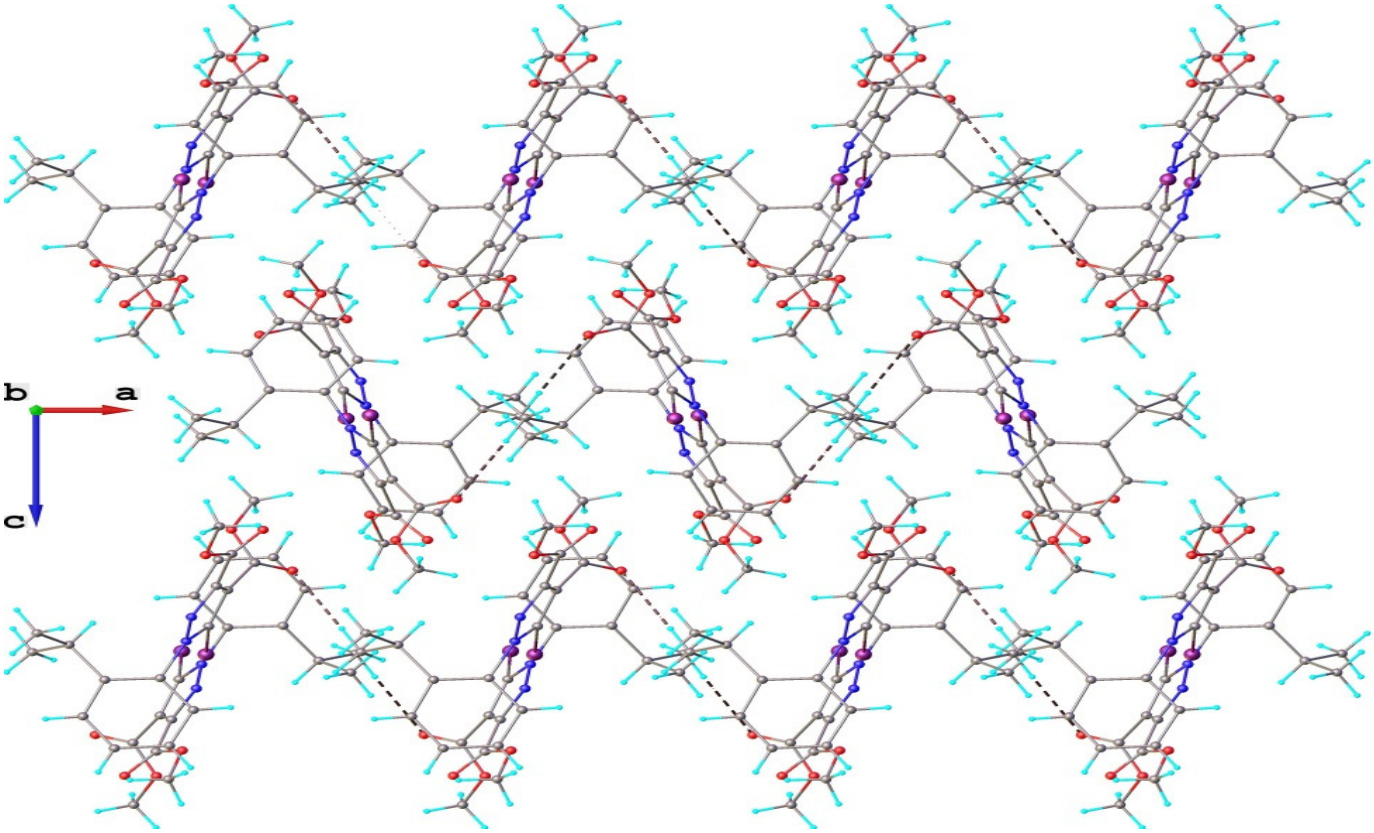


Figure 1S. Partial view of the crystal structure **1** along the b-axis.

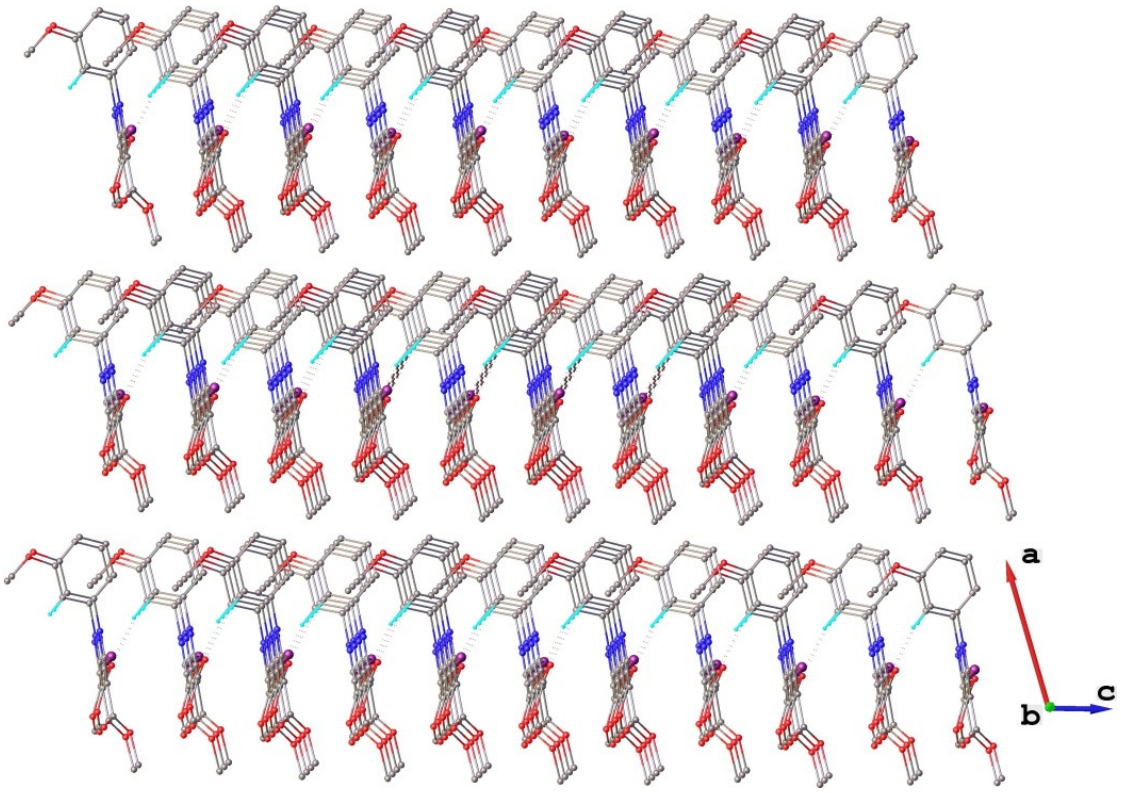


Figure 2S. Crystal packing in **2** viewed along the b-axis.

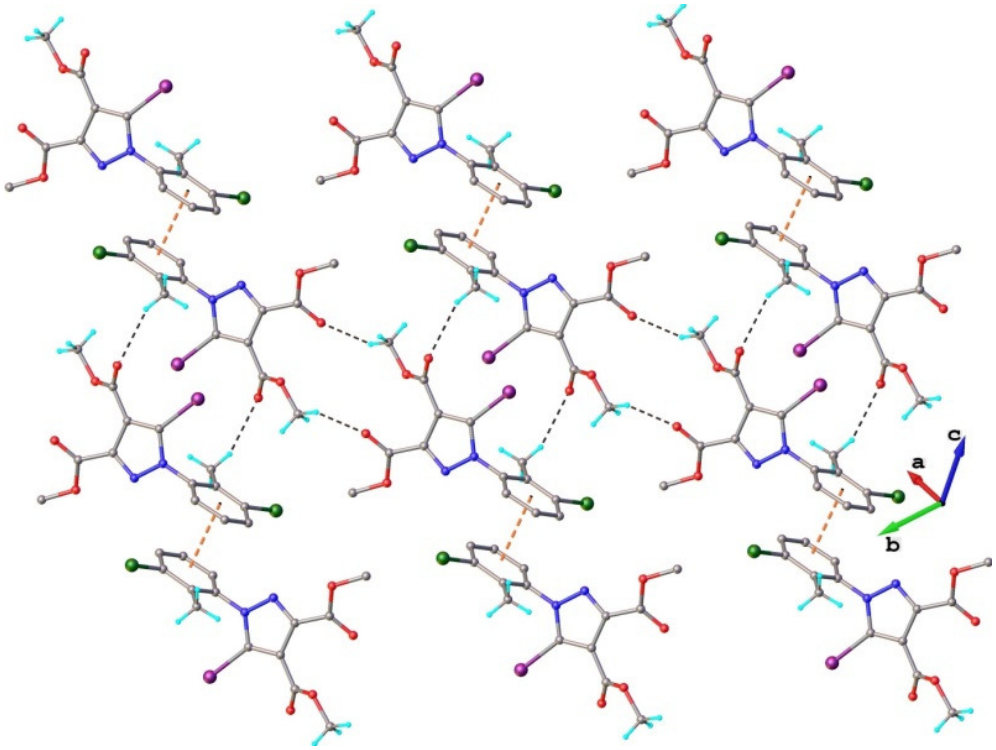
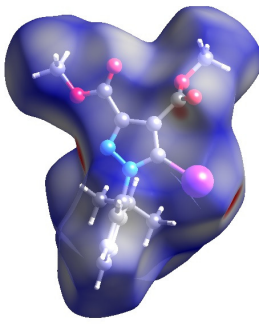
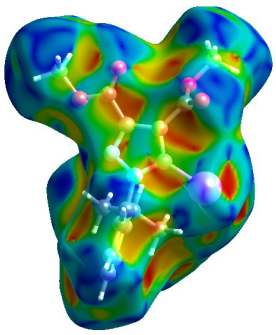
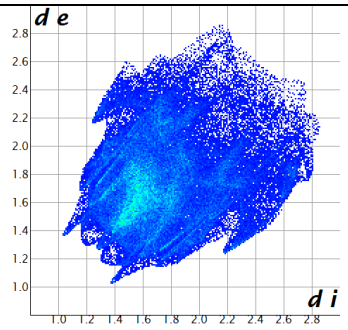
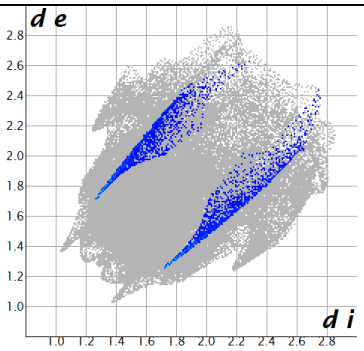
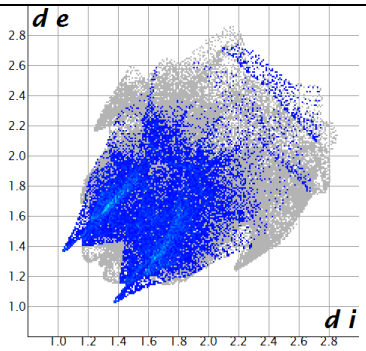
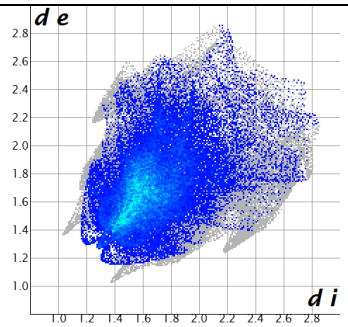
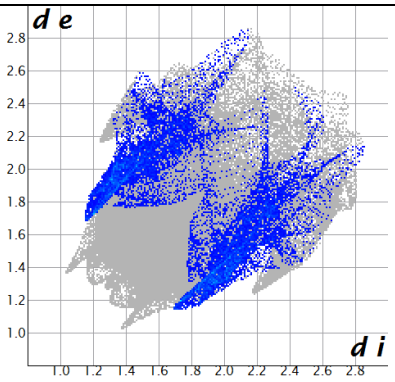
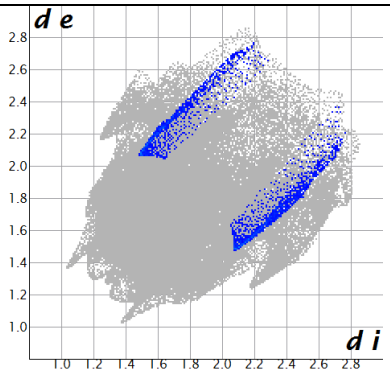
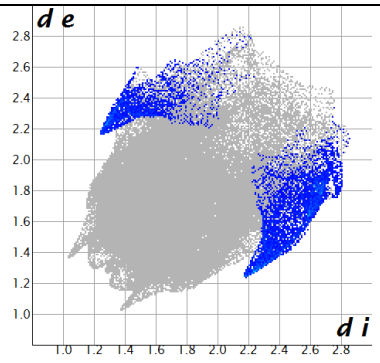
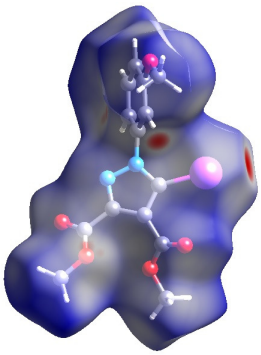
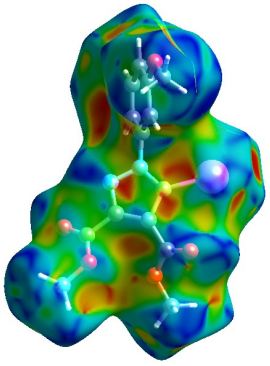
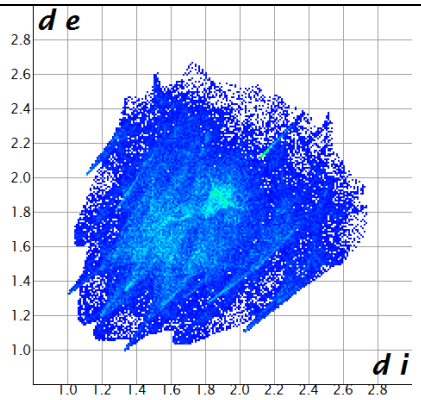
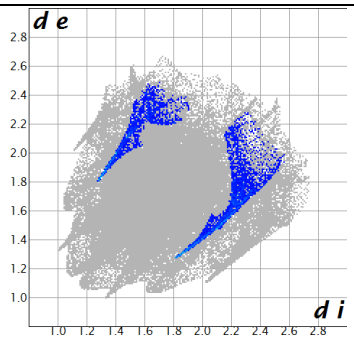
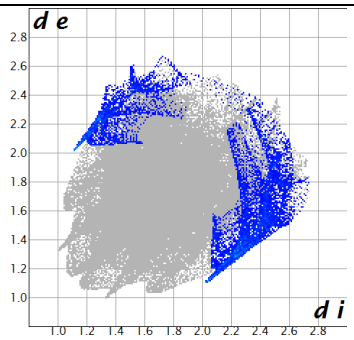
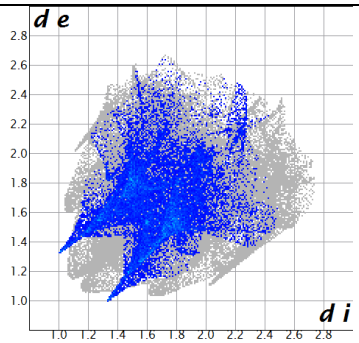
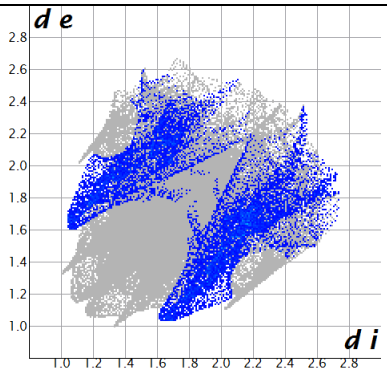
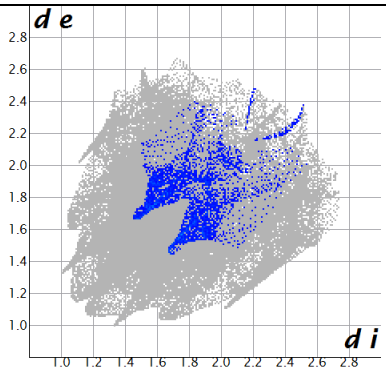
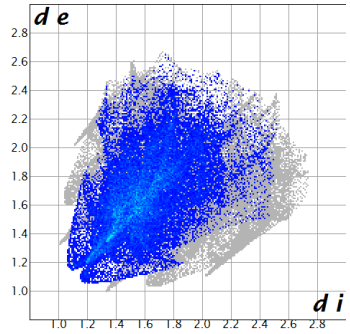


Figure 3S. 2D supramolecular network in the crystal structure of **3**. The CH---O hydrogen bonds and the centroid-to-centroid distances are shown in black and orange dashed lines, respectively.

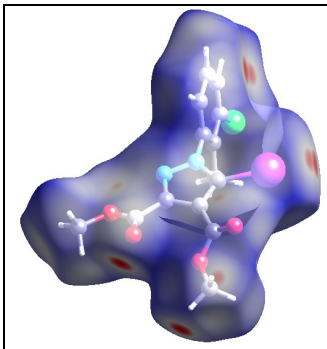
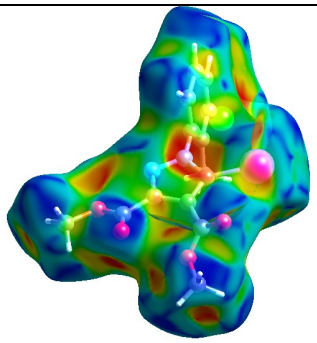
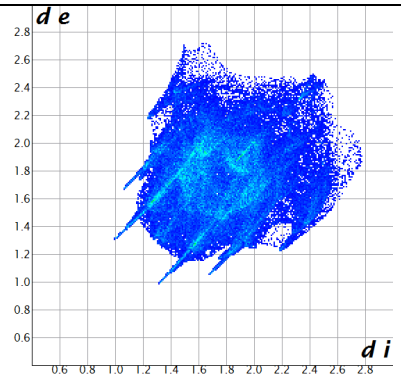
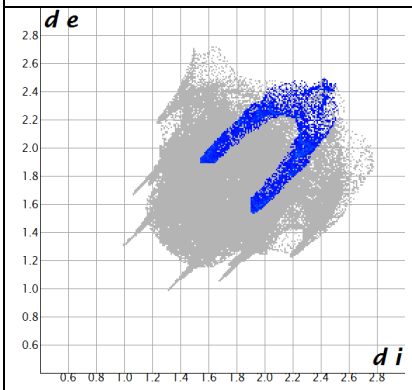
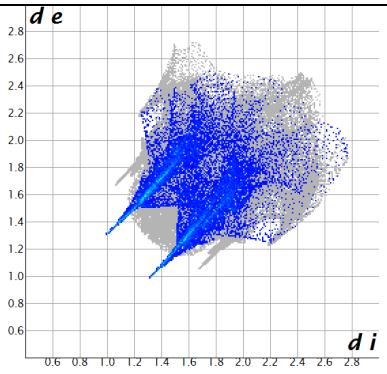
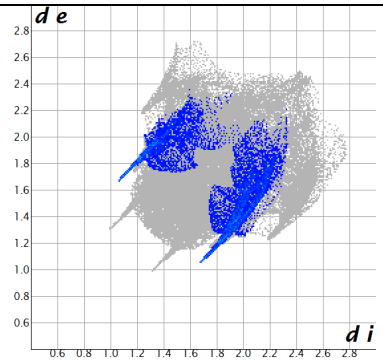
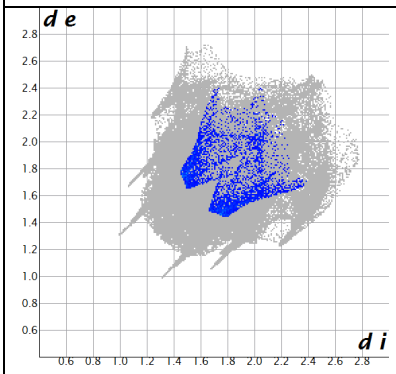
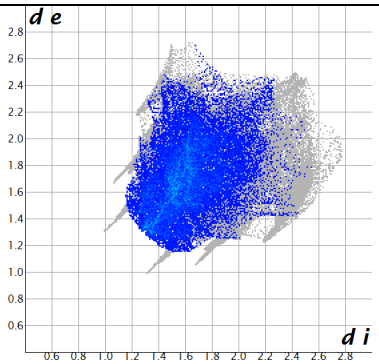
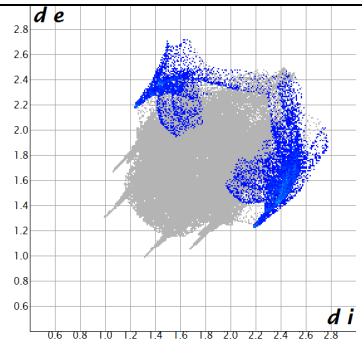
4. Hirshfeld analysis

Table 2S. Hirshfeld surface representations for compounds 1-3 depicting the most important interactions

Compound 1		
		
Hirshfeld Surface (d_{norm})	Hirshfeld Surface (Shape Index)	Fingerprint Plot
		
I···N(3.5%)	O···H (21.9%)	H···H (45.6%)
		
C···H (14.0%)	I···O (2.2%)	I···H (7.2%)
Compound 2		

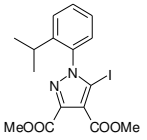
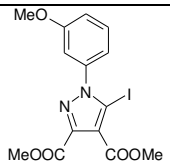
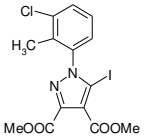
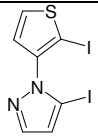
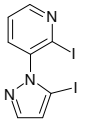
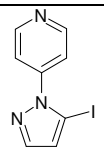
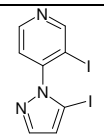
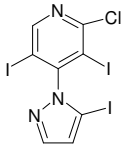
		
Hirshfeld Surface (d_{Norm})	Hirshfeld Surface (Shape Index)	Fingerprint Plot
		
I···O (4.8%)	I···H (9.2%)	O···H (20.9%)
		
C···H (12.3%)	O···C (4.2%)	H···H (35.5%)

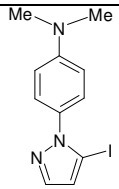
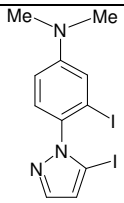
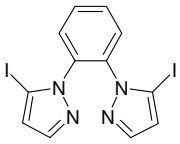
Compound 3

		
Hirshfeld Surface (d_{Norm})	Hirshfeld Surface (Shape Index)	Fingerprint Plot
		
I···C (5.0%)	O···H (19.5%)	Cl···H (10.4%)
		
O···C (4.4%)	H...H (31.1%)	I...H (9.3%)

5. The propensity of halogen bonding in highly substituted pyrazoles – comparative data

Table 3S. 1-Arylpyrazoles **1-3** and relevant examples from the literature: halogen bonding features. The table presents the types of iodine bonding in the series of compounds together with their important features such as bond length, contact length and contact angle (pyr=pyrazole; Ar=aryl)

1-Arylpyrazole	Structure	Halogen bond type(s)	C-I length [Å]		XB length [Å]		C-I...A [°]		Comments
		D-I···A	C_{pyr}-I	C_{Ar}-I	I···A (Pyr)	I···A (Ar)	C-I···A (Pyr)	C-I···A (Ar)	
1		C_{pyr}-I...N_{pyr}	2.064	-	2.992	-	174.16	-	
2		C_{pyr}-I...O	2.066	-	3.096	-	174.24	-	
3		C_{pyr}-I... π_{Ar}	2.063		3.445				
ISODOK 800824		C_{pyr}-I...N_{pyr} C_{Ar}-I... π_{pyr}	2.065	2.071	3.046	3.498	164.06	168.97	
ISODUQ 800825		C_{pyr}-I...N_{pyr} C_{Ar}-I...π_{pyr}	2.086	2.112	2.970	3.591	169.38	162.31	
ISOFAY 800826		C_{pyr}-I...N_{Ar}	2.089	-	2.798	-	176.75	-	
ISOFEC 800827		C_{pyr}-I... π_{Ar} C_{Ar}-I...N_{Ar}	2.066	2.097	3.643	2.967	151.44	176.27	
ISOFIG 800828		C_{pyr}-I...N_{pyr} C_{Ar}-I... π_{pyr}	2.059	2.087	3.386	3.388	149.43	172.62	One iodine not implied in XB

ISOFOM 800829		C_{pyr}-I...N_{pyr}	2.076	-	3.130	-	168.83	-	
ISOFUS 800830		C_{pyr}-I...N_{pyr} C_{Ar}-I... π_{pyr}	2.062	2.106	3.030	3.581	166.39	157.65	
ISOGAZ 800831		C_{pyr}-I... π_{pyr}	2.067	-	3.447	-	165.24	-	

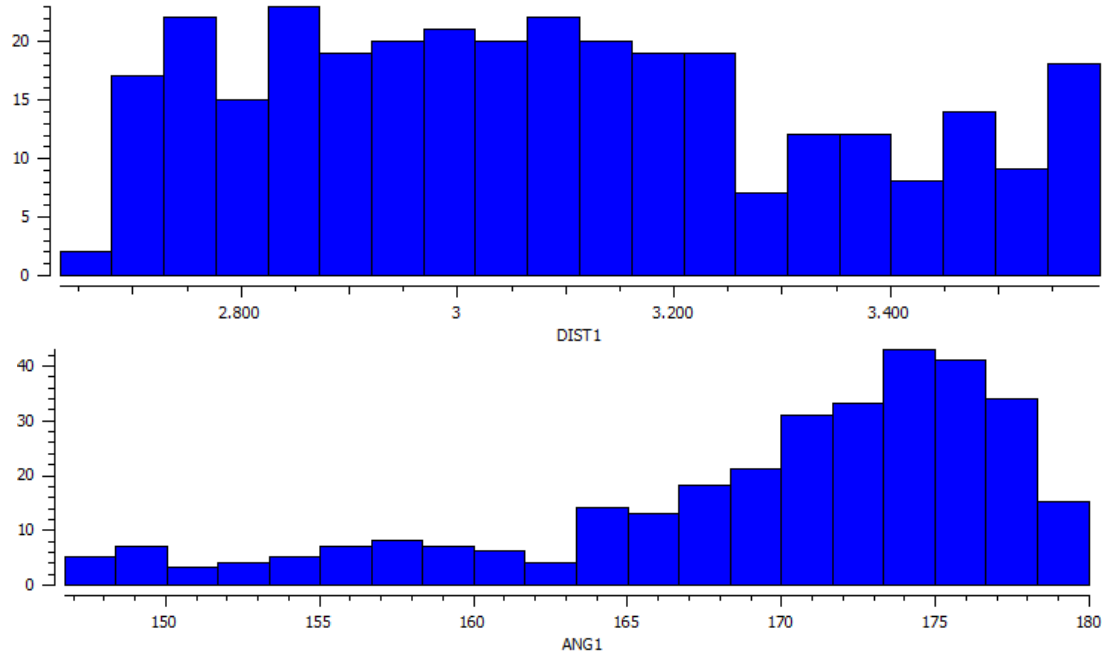


Figure 4S. Histogram representations of the C-I···N parameters in 231 examples from the CCDC database with the following restrictions: I···N distance of maximum 3.6 A and C-I···N angle between 145° and 180°

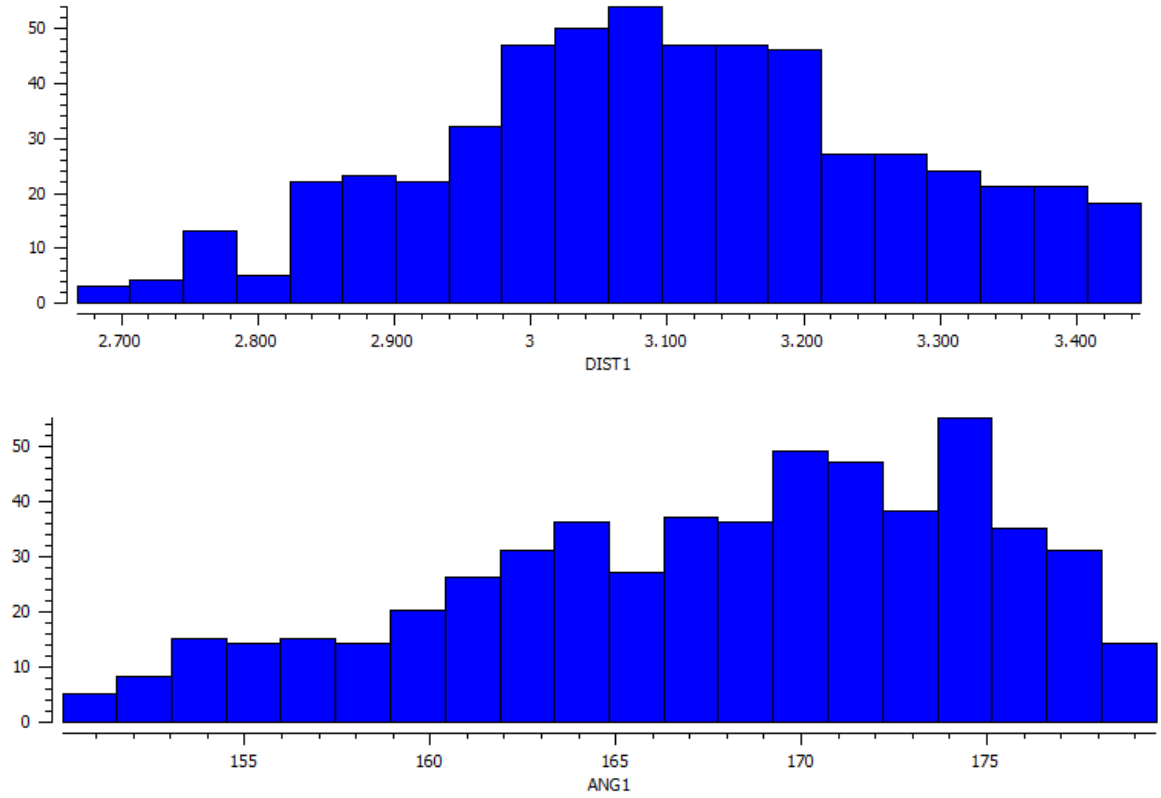
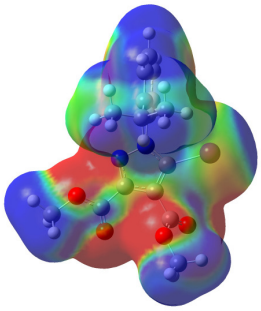
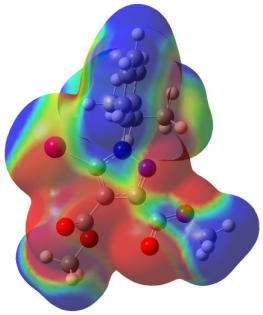
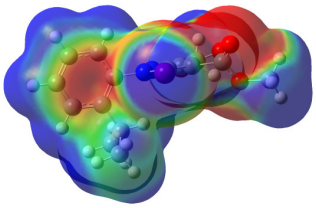
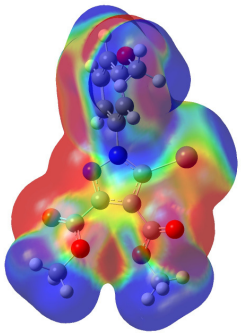
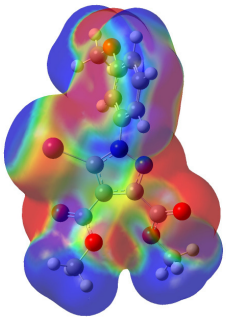
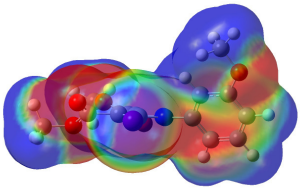
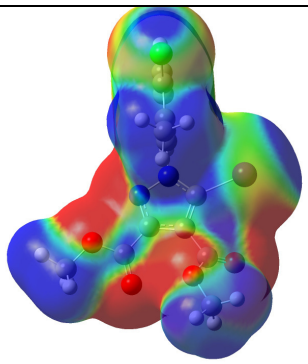
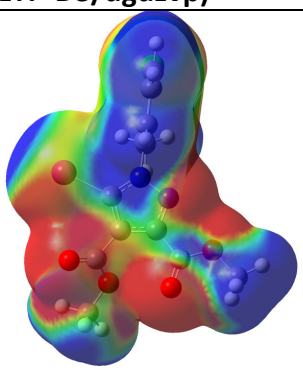
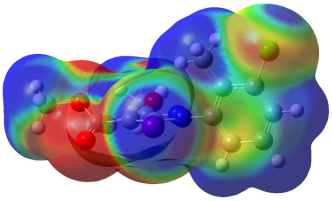
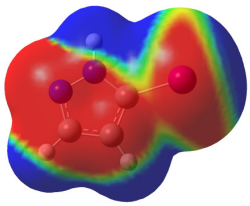
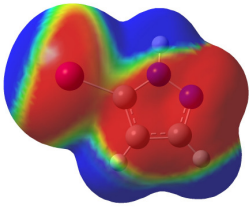
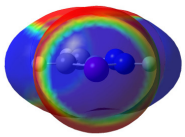


Figure 5S. Histogram representations of the C-I···O parameters in 543 examples from the CCDC database with the following restrictions: I···N distance of maximum 3.45 A and C-I···N angle between 145° and 180°

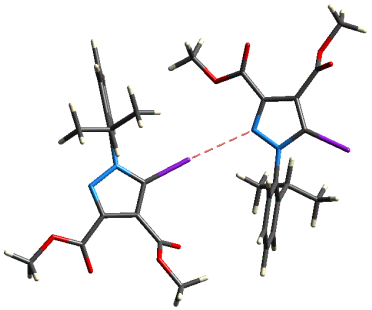
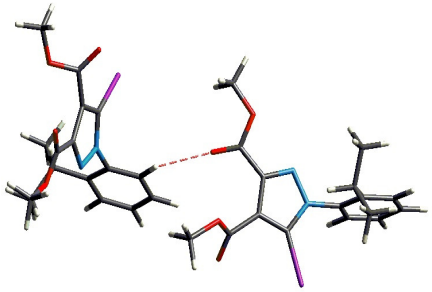
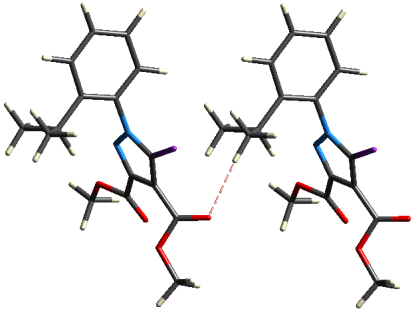
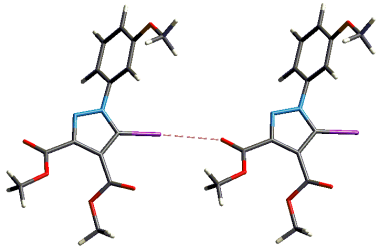
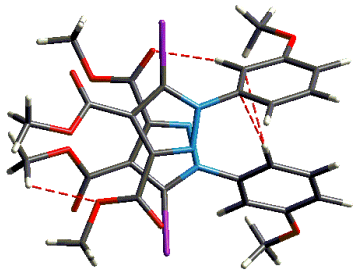
6. Quantum mechanical calculations

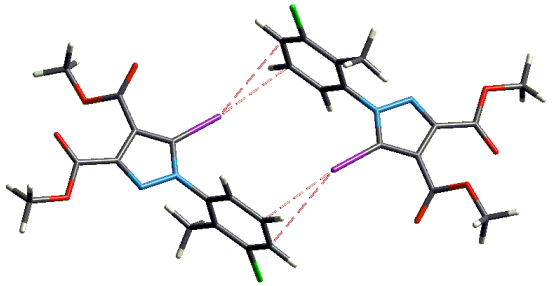
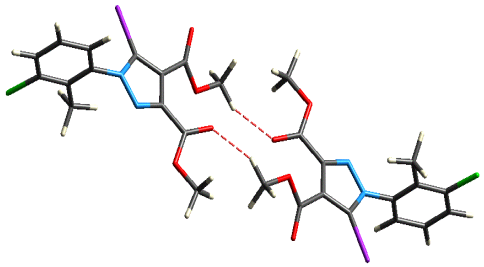
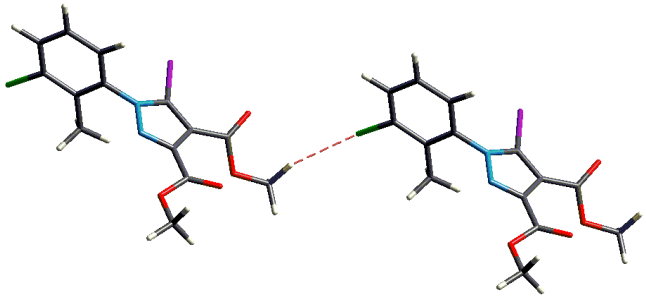
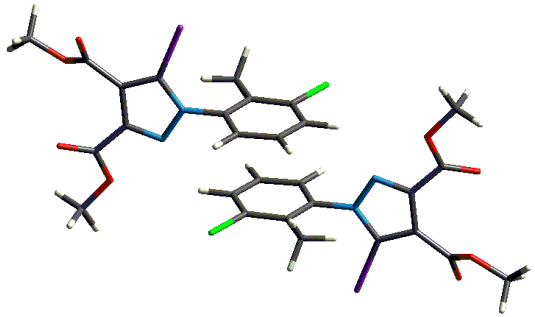
Table 4S. ESP of compounds 1-3 and 5-iodopyrazole (different side views)

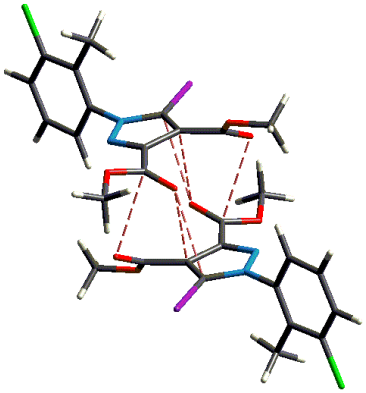
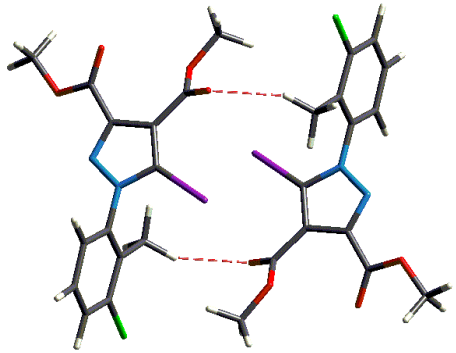
		
1 (B3LYP-D3/dgdzvp)		
		
2 (B3LYP-D3/dgdzvp)		
		
3 (B3LYP-D3/dgdzvp)		
		
5-iodo-1H-pyrazole (B3LYP-D3/dgdzvp)		

Interaction energies

Table 5S. Binding energies considered for the important interactions in compounds **1-3**

1	 **D1**	 **D4**	 **D5**
	C-I ··· N ; ΔE = -40.9 kJ/mol (-9.9 kcal/mol)	**C-H ··· O=C ; ΔE = -24.2 kJ/mol (-5.86 kcal/mol)**	**C-H ··· O=C ; ΔE = -31.6 kJ/mol (-7.65 kcal/mol)**
2	 **D2**	 **D6**	
	C-I···O ; ΔE = -23.1 kJ/mol (-5.59 kcal/mol)	**π···π; ΔE = -90.7 kJ/mol (-21.98 kcal/mol) (includes other interactions)**	

3	 **D3**	 **D7**
	C-I···π ; ΔE = -30.2 kJ/mol (-7.31 kcal/mol) (2 simultaneous interactions)	**C-H···O=C ; ΔE = -19.1 kJ/mol (4.57 kcal/mol)**
	 **D8**	 **D9**
	C-H···Cl ; ΔE = -1.97 kJ/mol (-0.48 kcal/mol)	**π···π ; ΔE = -49.5 kJ/mol (-11.99 kcal/mol) (includes other int.)**

	 **D10**	 **D11**
	C=O···π of C=O···C=O interaction; ΔE = -54.1 kJ/mol (-13.11 kcal/mol)	**C-H···O=C ; ΔE = -54.06 kJ/mol (-13.1 kcal/mol)**

7. ^{13}C-NMR solution-state experiments: data tables

Table 6S. ^{13}C NMR chemical shifts of **3** in presence of different XB acceptors as deuterated solvents or dissolved in $CDCl_3$

1-Py	**Et_3N (1 Eq)***	**Et_3N***	**Py-d_5**	**DMSO**	**DABCO***	**Base**
145.38	145.31	145.2	146.42	144.74	144.74	C-3/C-4
121.06	121.03	120.85	121.13	120.47	120.47	
91.09	**91.88**	**92.77**	**97.75**	**96.39**	**96.46**	**C-5**
135.12	135.07	134.99	135.13	134.02	134.74	C-1'/C-2'/C-3'
135.76	135.69	135.59	135.64	134.37	135.19	
139.6	139.63	139.64	140.79	139.67	139.69	
126.98	126.95	126.89	127.79	127.7	126.7	C-4'/C-5'/C-6'
127.18	127.1	127.16	127.84	128.1	126.8	
131.63	131.52	131.38	131.59	131.5	130.96	
15.35	15.31	15.24	15.28	14.9	15.06	Me
52.55	52.45	52.32	52.27	52.35	52.03	Me
52.91	52.82	52.45	52.64	52.73	52.45	Me
161.31	161.3	161.26	162.67	161.5	161.3	COO
162.17	162.17	162.15	162.97	161.92	162.35	COO

Table 7S. The chemical shifts of the carbon atoms in **3** with increasing concentration of DABCO (C_6D_6 as solvent)

-	**2:1**	**1:1**	**1:2**	**1:4**	**Mole ratio**
147.46	147.37	147.27	147.2	147.12	C-3/C-4
121.56	121.57	121.55	121.54	121.52	
91.58	**93.73**	**95.81**	**97.19**	**98.6**	**C-5**
135.88	135.92	135.94	135.96	135.97	C-1'/C-2'/C-3'
136.24	136.22	136.19	136.17	136.13	
140.81	141.03	141.2	141.36	141.5	
127.64	127.63	127.62	127.61	127.62	C-4'/ C-5'/C-6'
127.76	127.85	127.92	127.98	128.05	
131.81	131.74	131.66	131.61	131.57	
15.65	15.73	15.79	15.82	15.87	Me

52.46	52.75	52.42	52.39	52.38	Me
52.77	53.04	52.73	52.71	52.7	Me
162.64	162.79	162.9	162.99	163.05	COO
162.65	162.89	163.12	163.26	163.41	COO

References

1. F. Dumitrascu, C. Draghici, D. Dumitrescu, L. Tarko, D. Raileanu, *Liebigs Ann./Recl.* **1997**, 2613-2616.

2.CrysAlisRED, Oxford Diffraction Ltd.,Version 1.171.34.76, 2003.

3. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.,* **2009**, *42*, 339–341.

4. Sheldrick, G. M. SHELXS, *Acta Cryst.,* **2008**, *A64,* 112–122.