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Supplementary information

For the manuscript

Extending the halogen-bond supramolecular synthon concept to 1,3,4-oxadiazole derivatives

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Materials and methods.

Commercially available reagent grade chemicals were used as received without further purification. Compounds were characterized by FT-IR (Nicolet, Magna 550, KBr pellets), NMR (Bruker Avance 400, 400 MHz for ^{1}H and 100.6 MHz for ^{13}C) were obtained in $CDCl_3$, the solvents were used as internal standards, operating temperature was 28°C, and the amount of sample used was not weighed neither the volume of solvent was measured. Melting points (°C degrees, Olimpus BX51 microscope plus a Linkam T95-PE temperature controlled stage equipped with an Olympus U-TV0.5XC-3 polarizer) are uncorrected. Chemical shifts for NMR spectra (□) are quoted in ppm. Infrared values (ν) are quoted in reciprocal centimeters (cm^{-1}). Elemental Analyses (C, N and H) for complexes were obtained in a FISON EA 1108.

1. Synthetic details.

Synthesis of the 4-[5-(4-alkoxylphenyl)-1,3,4-oxadiazol-2-yl]pyridine

General method: The corresponding diacylhidrazines[1] were dissolved in $POCl_3$ (18 ml); the mixtures were heated at 130°C overnight, and then cooled to room temperature. Excess $POCl_3$ was removed at reduced pressure and the remaining mixtures poured into water. The products were filtered off and crystallized from ethanol to give white solids.

4-[5-(4-hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine

Yield 70%. FTIR =2942, 2867 (Csp3-H); 1607 (C=C), 1256 (C-O). ^{1}H NMR = 8.83 (d, 2H), 8.07 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 3.8 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 4.04 (t, J = 6.4 Hz, 2H), 1.37 (m, 8H), 0.92 (t, 3H). ^{13}C NMR = 165.69, 162.59, 162.41, 151.00, 131.37, 129.11, 120.38, 115.66, 115.28, 68.52, 31.69, 29.22, 25.81, 22.73, 14.16.

4-[5-(4-heptyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine

Yield 81%. FTIR =2937, 2868 (Csp^3-H); 1609 (C=C); 1258 (C-O). ^{1}H NMR = 8.82 (d, J = 5.3 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 5.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 4.04 (t, J = 6.5 Hz, 2H), 1.83 – 1.26 (m, 10H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR = 165.56, 162.45, 162.22, 150.75, 131.29, 128.96, 120.28, 115.46, 115.13, 68.37, 31.87, 29.52, 29.25, 25.99, 22.67, 14.1.

4-[5-(4-octyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine

Yield 86%. FTIR =2926, 2858 (Csp^3-H); 1608 (C=C); 1258 (C-O). ^{1}H NMR = 8.82 (d, 2H), 8.07 (d, 2H), 7.98 (d, 2H), 7.03 (d, J = 8.4 Hz, 2H), 4.04 (t, J = 6.5 Hz, 2H), 1.87 – 1.28 (m, 12H), 0.90 (t, J = 6.8 Hz, 3H). ^{13}C NMR = 165.76, 162.51, 162.31, 150.92, 131.41, 128.31, 120.49, 115.41, 115.23, 68.41, 31.79, 29.56, 29.31, 29.23, 25.61, 22.52, 14.19.

4-[5-(4-nonyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine

Yield 79%. FTIR =2923, 2855 (Csp^3-H); 1607 (C=C), 1255 (C-O). ^{1}H NMR = 8.83 (d, J = 4.8 Hz, 2H), 8.10 – 8.03 (d, 2H), 7.98 (d, J = 5.9 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.06 – 4.01 (t, 2H), 1.86 – 1.77 (m, 2H), 1.52 – 1.41 (m, 2H), 1.39 – 1.25 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR = 165.68, 162.56, 162.34, 150.87, 131.40, 129.08, 120.40, 115.58, 115.25, 68.49, 31.99, 29.64, 29.49, 29.37, 29.23, 26.11, 22.79, 14.24.

4-[5-(4-decyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine

Yield 94%. FTIR =2920, 2856 (Csp^3-H); 1609 (C=C), 1258 (C-O).^{1}H NMR = 8.88 (d, 2H), 8.88 (d, 2H), 8.12 (d, 2H), 8.09 (d, 2H), 7.04 (d, J = 7.1 Hz, 2H), 4.04 (t, 2H), 1.82 (m, 2H), 1.28 (m, 14H), 0.88 (t, 3H). ^{13}C NMR = 166.13, 162.82, 162.14, 151.25, 131.60, 129.26, 121.23, 115.60, 115.38, 68.57, 32.04, 29.70, 29.57, 29.46, 29.25, 29.09, 25.46, 22.83, 14.25.

4-[5-(4-nonyloxyphenyl)-1,3,4-thiadiazol-2-yl]pyridine

A solution of the corresponding N'-4-noniloxybenzoylpyridine-4-carbohydrazide (7.4 mmol) in Lawesson's reagent (9 mmol) and toluene (50 mL) was refluxed for 24 h and then cooled to room temperature. The toluene was removed at reduced pressure and the residue was poured into ethanol. The product was filtered off and purified by chromatographic column (hexane/Ethyl acetate 4:1) and recrystallised from ethanol. Yields (51%)

FTIR (disco KBr) [cm^{-1}] =2922, 2855 (Csp^3-H); 1604 (C=C), 1254 (C-O). ^{1}H RMN: ($CDCl_3$, TMS, 400 MHz): δ ppm = 8.77 (d, J = 5.6 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 4.9, 2H), 7.00 (d, J = 8.8Hz, 2H), 4.03 (t, 2H), 1.92 – 1.16 (m, 14H), 0.89 (t, 3H). ^{13}C RMN: (CDCl3, TMS, 101 MHz):δ ppm = 169.5, 164.8, 162.1, 150.9, 137.4, 129.8, 122.2, 121.5, 115.3, 68.5, 32.0, 29.6, 29.5, 29.3, 29.2, 26.1, 22.8, 14.2.

Complexes preparation (1 – 6)

The halogen-bonded complexes were obtained by co-crystallization of the donor and acceptor mixed in 3:1 stoichiometric ratio with appropriate solvents followed by slow evaporation to yield single crystals.

Complexes **1-5** were obtained either from dioxane or from a THF/ETOH 1:2 mixture, whereas complex **6** were only obtained from a THF/ETOH 1:2 mixture.

Complex 1 for $C_{25}H_{21}F_3I_3N_3O_2$

Calcd(%). C: 36.04, N: 5.04, H: 2.54. Found(%). C: 36.25, N: 4.89, H: 2.63.

Complex 2 for $C_{26}H_{23}F_3I_3N_3O_2$

Calcd(%). C: 36.86, N: 4.96, H: 2.74. Found (%). C: 36.75, N: 4.75,H: 2.83.

Complex 3 for $C_{27}H_{25}F_3I_3N_3O_2$

Calcd(%). C: 37.65, N: 4.88, H: 2.93. Found (%). C: 37.78, N: 4.71,H: 2.99.

Complex 4 for $C_{28}H_{27}F_3I_3N_3O_2$

Calcd(%). C: 38.42, N: 4.80,H: 3.11. Found (%).C: 38.51, N: 4.69,H: 3.22.

Complex 5 for $C_{29}H_{29}F_3I_3N_3O_2$

Calcd(%). C: 39.17, N: 4.73,H: 3.29. Found (%). C: 39.25, N: 4.59, H: 3.33.

Complex 6 for $C_{50}H_{54}F_3I_3N_6O_2S_2$

Calcd(%). C: 47.18, N: 6.60,H: 4.28. Found (%). C: 47.26, N: 6.57,H: 4.35.

Thermal Data

Phase Transition Temperature, °C				**Dioxane**	**THF/ETOH 1:2**
Complex	**n**	**Ligand**	**Complex**	**Yield(mg)****	**Yield(mg)****
1	6	Cr 125.1 I	134.2 -138.5	83% (27.13)	75%(24.52)
2	7	Cr 134.9 I	117.0 -119.2	78%(25.93)	81%(26.92)
3	8	Cr 106.5 I	121.4 -122.8	85%(28.72)	73%(24.67)
4	9	Cr 104.4 I	142.4 - 142.9	81%(27.81)	77%(26.44)
5	10	Cr 97.2 I	143.5 - 144.1	68%(23.72)	61%(21.28)
6	9*			--	88%(30.77)

(*) Thiadiazole

(**) Based on 1,3,5-triodotrifluorobenzene.

3. Structural Characterization

Crystal Structure Determination

All the data collection of the X-ray diffraction experiment were carried out in an Agilent Supernova diffractometer with Cu radiation (= 1.5418 Å) at 293 K. Data were indexed, integrated and scaled with the CrysAlisPRO[2] programs. The crystal structures of **1**-**6** were solved by direct methods and refined with the full-matrix least-squares technique on F^2 by using the SHELXS-97 and SHELXL-97[3] programs included in the WINGX[4] software package. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were set on geometrical positions and refined with a riding model. A summary of the crystallographic data and structure refinement is given in Table S1. The final geometrical calculations and the graphical manipulation were carried out with PARST97[5] and DIAMOND[6]and MERCURY[7] programs, respectively.

CCDC numbers 1409983, 1409982, 1409981, 1409980, 1409979 and 1409978 for **1**-**6**, respectively, contain the supplementary crystallographic data for this paper. 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)1123-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table S1. Crystallographic data for complexes **1**-**6**.

	1	***2***	***3***	***4***	***5***	***6***
Formula	$C_{25}H_{21}F_3I_3N_3O_2$	$C_{52}H_{46}F_6I_6N_6O_4$	$C_{27}H_{25}F_3I_3N_3O_2$	$C_{28}H_{27}F_3I_3N_3O_2$	$C_{29}H_{29}F_3I_3N_3O_2$	$C_{50}H_{54}F_3I_3N_6O_2S_2$
FW	833.150	1694.35	861.20	875.22	889.25	1272.81
Crystal system	Triclinic	Triclinic	Triclinic	Triclinic	Triclinic	Monoclinic
Space group	*P* -1	*P* -1	*P* -1	*P* -1	*P* -1	*C*2/*c*
a(Å)	9.0898(5)	10.0662(2)	9.5563(3)	9.5328(3)	10.4878(10)	27.3644(3)
b(Å)	12.7927(8)	14.4987(3)	11.4823(3)	11.9482(3)	12.3896(11)	13.4467(1)
c(Å)	13.8531(7)	20.6364(5)	14.1520(4)	13.9164(3)	12.7932(12)	28.0955(3)
α(º)	114.273(6)	82.220(2)	99.118(2)	82.274(2)	78.982(8)	-
β(º)	98.513(5)	81.567(2)	92.177(2)	85.796(2)	82.201(8)	94.042(1)
γ(º)	100.445(5)	89.177(2)	92.289(2)	87.527(2)	81.597(8)	-
V(Å³)	1398.9(2)	2951.78(11)	1530.48(8)	1565.57(7)	1604.2(3)	10312.33(18)
Z	2	2	2	2	2	8
μ(mm⁻¹)	26.732	25.351	24.458	23.922	23.357	15.493
T(K)	293(2)	293(2)	293(2)	293(2)	293(2)	293(2)
ρ_{cal} (g cm⁻³)	1.978	1.906	1.869	1.857	1.841	1.640
λ(Å)	1.5418	1.5418	1.5418	1.5418	1.5418	1.5418
Index ranges	-11≤ *h* ≤ 10	-11 ≤ *h* ≤ 12	-11 ≤ *h* ≤ 8	-11 ≤ *h* ≤ 11	-12 ≤ *h* ≤ 12	-32 ≤ *h* ≤ 33
	-15 ≤ *k* ≤ 15	-17 ≤ *k* ≤ 17	-14 ≤ *k* ≤ 13	-14 ≤ *k* ≤ 14	-14 ≤ *k* ≤ 15	-16 ≤ *k* ≤ 12
	-15 ≤ *l* ≤ 17	-25 ≤ *l* ≤ 20	-17 ≤ *l* ≤ 17	-13 ≤ *l* ≤ 17	-15 ≤ *l* ≤ 13	-34 ≤ *l* ≤ 33
Total Reflections	12192	22644	11481	16642	14866	37841
Indep. Reflections (R_{int})	5430(0.077)	11582 (0.057)	6006 (0.0490)	6127 (0.0382)	6265(0.0960)	10289(0.0239)
Obs. reflect. [I> 2σ(I)]	4405	9443	5482	5499	4890	10289
Parameters	325	668	344	352	361	597
Goodness-of-fit	1.037	1.024	1.040	1.080	1.277	1.052
R [I> 2σ(I)]	0.0822	0.0577	0.0347	0.0560	0.1410	0.0412
R_w [I> 2σ(I)]	0.2240	0.1536	0.0879	0.1580	0.3318	0.0412
R (all data)	0.0940	0.0684	0.0374	0.0593	0.1489	0.0468
R_w (all data)	0.2568	0.1694	0.0913	0.1640	0.3535	0.1108

Table S2. F···F interactions data for complexes **1**-**5**.			
Complex	**d(F···F)/Å**	**θ_1/°**	**θ_2/°**
1	2.547(1)[a]	160.4(6)	160.4(6)
2	2.592(6)[b]	153.6(4)	154.2(4)
3	2.613(4)[c]	149.8(2)	149.8(2)
4	2.624(6)[d]	152.3(3)	152.3(3)
5	2.543(1)[e]	163.7(9)	163.7(9)
Symmetry codes: (a) –x+1,-y,-z+1; (b)-x+1,-y+1,-z+1; (c) –x,-y-1,-z+1; (d) –x+1,-y+2,-z+3; (e) –x,-y,-z.			

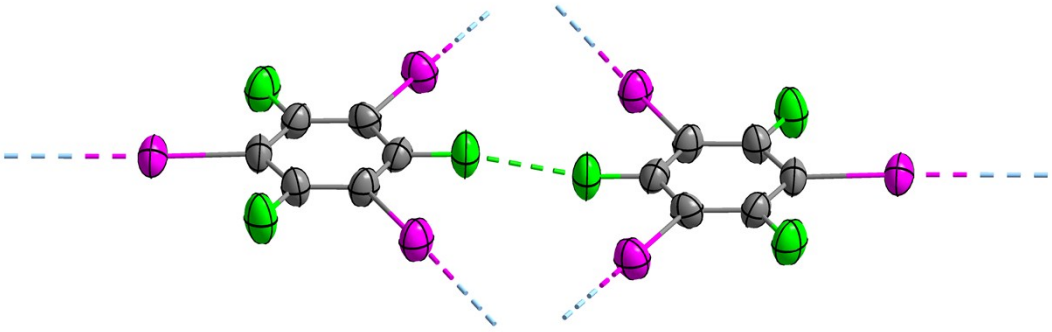

Figure S1. Type I F···F interactions.

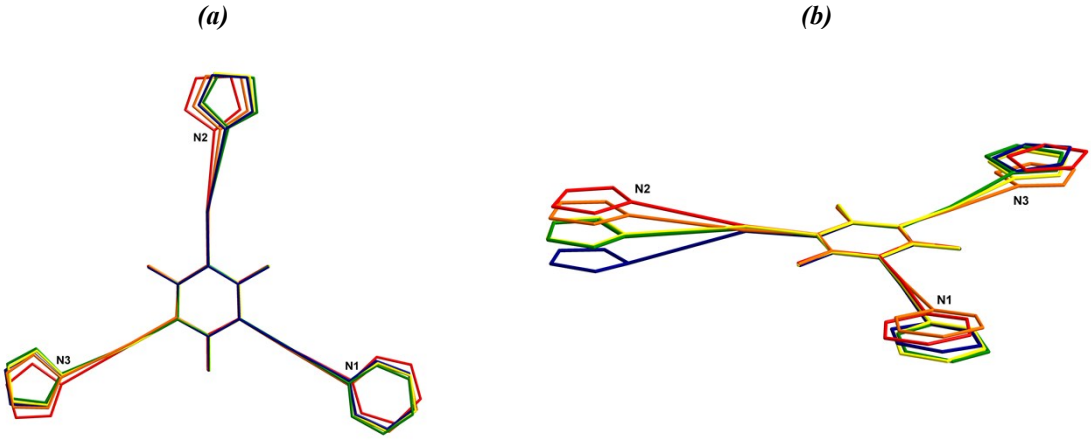

Figure S2. Compounds **1**(red), **2**(blue), **3**(green), **4**(yellow) and **5**(orange).

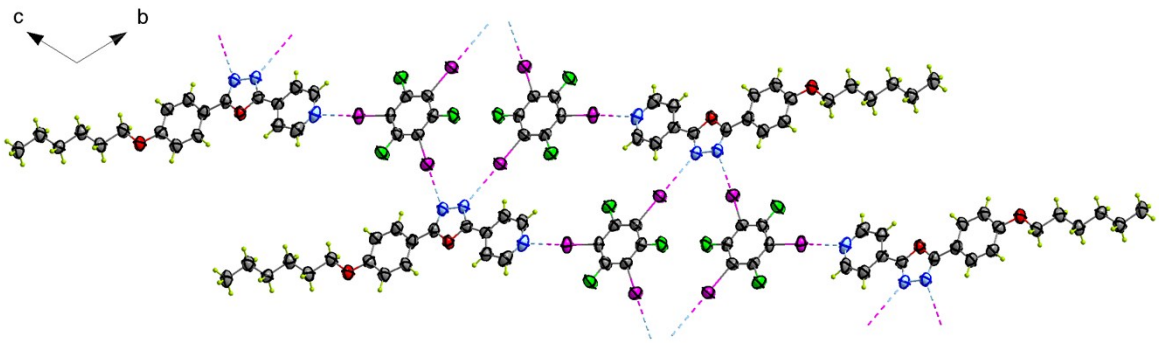

Figure S3. View of the halogen bonded chain in **1** growing perpendicular to *b*-axis.

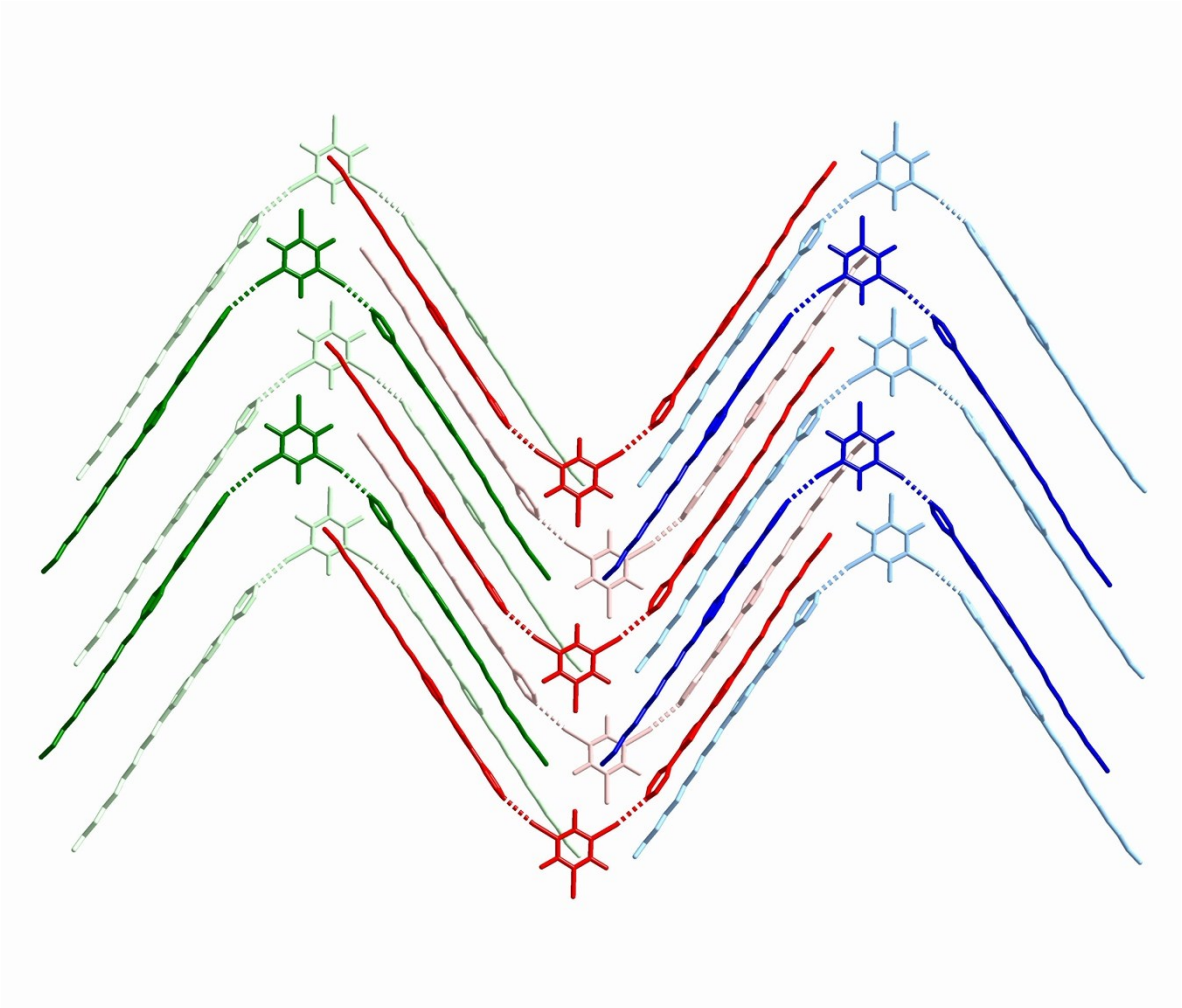

Figure S4. Crystal packing of **6**, showing two adjacent layers (above in bold, below in light colour).

4. Computational details

Molecular Electrostatic Potential

For the calculation of the molecular electrostatic potential each molecule was first optimized with the B3PW91 method and the 6-311G(*d,p*) basis set employing the G03 program.[8] For iodine the atom basis set reported by Glukhovstev *et al*[9] was taken from the EMSL database.

The presence of a minimum was verified by the calculation of the vibrational frequencies within the harmonic approximation for each molecule. The obtained wave function (wfn file) served as input in the WFA program[10] to calculate the maximum and minimum electrostatic potential for the relevant atoms in each molecule. In 1,3,5-trifluorotriiodobenzene the iodine atom presented a positive electrostatic potential of +29.75 kcal/mol that varied only marginally among the three atoms. The positive electrostatic potential reveals the ability of these atoms to form halogen bonds.[11]

For the 4-[5-(4-hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine (**1**) and the 4-[5-(4-nonyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine (**2**) molecule the molecular electrostatic potential on the N1 N2 and N- nitrogen atoms (for clarity on the nomenclature see the figure below) is summarized in the following table:

Table S3. Electrostatic potential in kcal/mol on relevant atoms of the respective molecule (see Figure below)

Molecule	N1	N2	N3
(**1**)	-36.48	-36.75	-37.22
(**2**)	-36.47	-36.79	-37.29

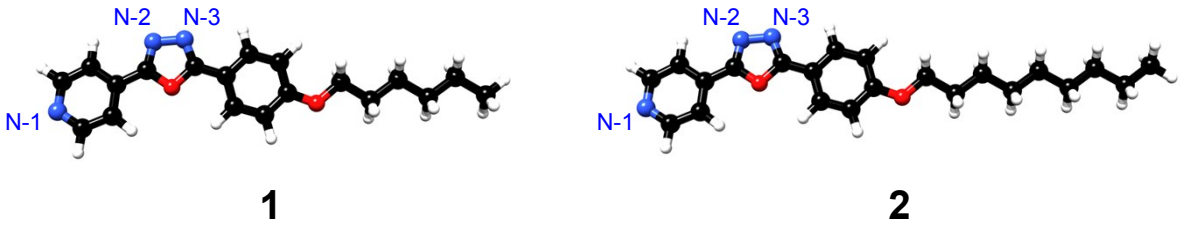

Figure S5. 4-[5-(4-hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine (1) and the 4-[5-(4-nonyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine (2) and nitrogen atom labels

In both molecules nitrogen N3 is the one with the highest negative potential. This would indicate that N3 should form the strongest halogen bond with 1,3,5-trifluorotriiodobenzene molecule. If no other molecular interactions and crystal packing effects would be present the bond between N3 and the 1,3,5-trifluorotriiodobenzene should be shortest. The X-Ray crystal structure shows that this bond is shorter in comparison to the halogen bond involving N2 but not shorter than the one to the pyridine nitrogen atom (N1). One may suggest that in the case of the pyridine nitrogen atom the overall geometry of the molecule and the possible arrangements in the crystal allow the halogen bond to be shorter than the other two.

Intermolecular interaction energies.

To estimate the interaction energy of each halogen bond in the crystal we took the atom positions of 1,3,5-trifluorotriiodobenzene and 4-[5-(4-hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine from the X-Ray structure and performed single point energy calculation with the M06-2X functional and the def2-TZVP basis set[12] in combination with the respective effective core potentials[13] as implemented in the ORCA package.[14]

Then, we selected pairs of 4-[5-(4-hexyloxyphenyl)-1,3,4-oxadiazol-2-yl]pyridine and 1,3,5-trifluorotriiodobenzene from the X-Ray structure that interact via an iodine nitrogen halogen bond involving the N1, N2 or N3 atom. The respective interaction energies for each iodine-nitrogen halogen bonded complex are given in the following table.

	N-1	N-2	N-3
Energy [kcal/mol]	6.30	4.67	5.69

If the Molecular Electrostatic Potential is the main contributor to the interaction energy one would expect the energies to be modulated by the distance between the atoms forming the halogen bond, since no geometry optimization of the pairs were performed. Indeed, the obtained energies correlate with the distance between the two halogen bonded atoms (N and I) for each complex that increases from 2.95 Å (N1), 3.11 Å (N3) to 3.26 Å (N2). Additionally, the results allow to estimate the average interaction energy for the nitrogen iodine halogen bonds as 5.55 kcal/mol.

5. References

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