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Supporting Information

Hydrogen- and halogen bond synergy in the self-assembly of 3,5-Dihalo-tyrosines: structural and theoretical insights

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1 Methods

1.1 Single-crystal X-ray Diffraction

Data collection of **1a** was performed at the XRD1 X-ray diffraction beamline of the Elettra Synchrotron, Trieste (Italy)[1S]. The crystals were dipped in NHV oil (Jena Bioscience, Jena, Germany) and mounted on the goniometer head with kapton loops (MiTeGen, Ithaca, USA). Complete datasets were collected at 100 K (nitrogen stream supplied through an Oxford Cryostream 700) through the rotating crystal method. Data were acquired using a monochromatic wavelength of 0.700 Å on a Pilatus 2M hybrid-pixel area detector (DECTRIS Ltd., Baden-Daettwil, Switzerland). Radiation damage has been detected during data collections. The diffraction data were indexed, integrated and scaled using XDS.[2S] The structures were solved by the dual space algorithm implemented in the SHELXT code.[3S] Fourier analysis and refinement were performed by the full-matrix least-squares methods based on F^2 implemented in SHELXL (version 2018/3).[4S] The Coot program was used for modeling.[5S] Anisotropic thermal motion refinement have been used for all atoms. Hydrogen atoms were included at calculated positions with isotropic $U_{factors} = 1.2 \cdot U_{eq}$ or $U_{factors} = 1.5 \cdot U_{eq}$ for methyl, hydroxyl and protonated amino groups (U_{eq} being the equivalent isotropic thermal factor of the bonded non hydrogen atom). Geometric restrains (DFIX, DANG) have been used for solvent molecules. **1a** molecules are packed in a chiral monoclinic unit cell, with water molecules filling voids. Despite radiation damage effects hamper accurate location and refinement of hydrogens in electron density difference maps, hints about water molecules orientations are present and solvent hydrogens have been therefore included in the model. Polar groups are involved in several hydrogen bonds and ionic bridges keeps aminoacid backbones evenly aligned along unit cell *a* axis (Table S2). Refined Flack parameter[6S] confirms the expected amino acid C⍰ S-configuration. Pictures were prepared using CCDC Mercury software. [7S] Essential crystal and refinement data are reported below (Table S1).

Data collection of **1b** was performed with a Bruker Kappa Apex II diffractometer equipped with a sealed tube detector and CCD, using Mo-Kα radiation (α = 0.71073 Å). Data collection was performed at 100 K. The diffraction data was indexed, integrated and scaled using SAINT.[8S] The structures were solved by SHELXS [9S] and refinements were performed from least squares to full matrix on F^2 using the SHELXL program.[4S] Anisotropic thermal motion refinement have been used for all atoms. Hydrogen atoms were included at calculated positions, including also solvent hydrogens. Geometric restrains (DFIX, DANG) have been used for solvent molecules. Pictures were prepared using CCDC Mercury software.[7S] Essential crystal and refinement data are reported below (Table S3).

1.1.1 Tables crystal structure 1a

Table S1. Crystallographic data and refinement details for compound 1a

	1a
CCDC Number	1996230
Chemical Formula	$C_9H_{13}Br_2NO_5$
Formula weight	375.02 g/mol
Temperature	100(2) K
Wavelength	0.700 Å
Crystal system	Monoclinic
Space Group	$P\ 2_1$
Unit cell dimensions	a = 5.692(1) Å b = 10.588(2) Å c = 10.925(2) Å α = 90° β = 93.14(3)° γ = 90°
Volume	657.4(2) $Å^3$
Z	2
Density (calculated)	1.894 $g \cdot cm^{-3}$
Absorption coefficient	5.951 mm^{-1}
F(000)	368
Crystal size	0.10·0.08·0.08 mm^3
Crystal habit	Transparent thin needles
Theta range for data collection	1.8° to 30.0°
Index ranges	$-7 \leq h \leq 7$, $-15 \leq k \leq 15$, $-15 \leq l \leq 15$
Reflections collected	7037
Independent reflections	3669, 3643 data with I>2□(I)
Data multiplicity (max resltn)	3.34 (3.23)
I/□(I) (max resltn)	22.84 (20.86)
R_{merge} (max resltn)	0.0657 (0.0662)
Data completeness (max resltn)	96.8% (96.1%)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3669 / 8 / 169
Goodness-of-fit on F^2	1.138
Δ/σ_{max}	0.000
Final R indices [I>2□(I)]	R_1 = 0.0445, wR_2 = 0.1096
R indices (all data)	R_1 = 0.0446, wR_2 = 0.1097
Flack x parameter	-0.010(10)
Largest diff. peak and hole	0.927 and -1.866 $eÅ^{-3}$
R.M.S. deviation from mean	0.257 $eÅ^{-3}$

$R_1 = \Sigma \, ||Fo|-|Fc|| \, / \, \Sigma \, |Fo|$, $wR_2 = \{\Sigma \, [w(Fo^2 - Fc^2)^2] \, / \, \Sigma \, [w(Fo^2)^2]\}^{½}$

Table S2. Geometrical parameters of Hydrogen bonds found in 1a

D-H···A	d(D-H) (Å)	d(H···A) (Å)	d(D···A) (Å)	<(DHA) (°)
N_1-H0A_1...OXT_1#1	0.91	1.84	2.737(6)	168.1
N_1-H0B_1...O_2#2	0.91	2.05	2.886(7)	152.5
N_1-H0C_1...O_3#3	0.91	1.84	2.720(6)	161.2
CD1_1-HD1_1...Br2_1#4	0.95	2.97	3.902(5)	168.9
OH_1-HH_1...Br2_1	0.84	2.57	3.110(4)	123.3
OH_1-HH_1...OXT_1#5	0.84	2.00	2.632(6)	131.5
O_2-H1_2...OH_1	0.870(7)	2.032(14)	2.897(6)	173(8)
O_2-H2_2...O_1#6	0.871(7)	1.87(4)	2.721(6)	164(12)
O_3-H1_3...O_2#2	0.870(7)	2.175(16)	2.804(7)	128.9(17)
O_3-H2_3...O_1	0.870(7)	1.845(12)	2.711(6)	173(5)

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y,z ; #2 x+1,y,z+1 ; #3 -x+1,y+1/2,-z+2 ;
#4 -x+1,y+1/2,-z+1 ; #5 -x,y-1/2,-z+1 ; #6 x,y,z-1

1.1.2 Tables crystal structure 1b

Table S3. Crystallographic data and refinement details for compound 1b

Identification code	2128970
Empirical formula	$C_9H_{11}NO_4Cl_2$
Formula weight	268.09
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.3436(2)
b/Å	7.4422(2)
c/Å	20.8254(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1138.16(6)
Z	4
ρ_{calc}g/cm^3	1.565
μ/mm^{-1}	0.568
F(000)	552.0
Crystal size/mm^3	0.15 × 0.1 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.828 to 62.064
Index ranges	-10 ≤ h ≤ 10, -5 ≤ k ≤ 10, -28 ≤ l ≤ 30
Reflections collected	8858
Independent reflections	3618 [R_{int} = 0.0187, R_{sigma} = 0.0217]
Data/restraints/parameters	3618/3/152
Goodness-of-fit on F^2	1.078
Final R indexes [I>=2σ (I)]	R_1 = 0.0181, wR_2 = 0.0505
Final R indexes [all data]	R_1 = 0.0186, wR_2 = 0.0508
Largest diff. peak/hole / e Å^{-3}	0.28/-0.20
Flack parameter	-0.027(12)

Table S4. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for 1b. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor

Atom	*x*	*y*	*z*	U(eq)
OW	6426.9(17)	3452.7(15)	4588.6(7)	31.0(3)
Cl1	6459.2(4)	4832.1(4)	2339.8(2)	14.44(7)
Cl2	7937.2(5)	-1606.0(4)	1284.9(2)	17.07(7)
O3	6637.8(13)	2254.0(12)	1313.5(4)	13.51(17)
O1	8733.2(14)	-3614.3(13)	4805.0(5)	16.14(18)
O2	8418.2(14)	-799.9(13)	5178.6(4)	15.86(18)
C5	7734.7(17)	2010.2(17)	3017.8(6)	11.4(2)
N1	5905.1(13)	-136.9(14)	4234.6(5)	10.39(18)
C2	7458.9(16)	-1392.8(16)	4113.4(5)	9.8(2)
C3	8970.8(16)	-440.2(17)	3733.3(6)	12.4(2)
C4	8363.3(16)	247.3(17)	3086.4(5)	11.0(2)
C6	7183.0(17)	2624.9(15)	2419.3(6)	10.6(2)
C7	7218.1(16)	1544.8(17)	1871.0(5)	10.34(19)
C9	8416.9(17)	-855.7(16)	2545.8(6)	11.7(2)
C8	7857.6(17)	-213.3(16)	1951.3(5)	11.4(2)
C1	8253.8(16)	-2000.5(16)	4758.5(5)	10.5(2)

Table S5. Anisotropic Displacement Parameters (Å^2×10^3) for 1b. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
OW	21.6(5)	14.4(5)	56.9(8)	-12.8(5)	-0.7(6)	1.2(5)
Cl1	18.47(13)	9.87(12)	14.97(13)	-0.17(10)	-0.56(10)	2.63(10)
Cl2	26.77(15)	14.02(13)	10.40(12)	-1.92(10)	-1.77(11)	7.00(11)
O3	19.8(4)	13.1(4)	7.6(3)	1.2(3)	-1.4(3)	4.5(3)
O1	22.3(5)	10.6(4)	15.6(4)	1.5(3)	-6.6(4)	2.6(3)
O2	24.7(5)	14.3(4)	8.6(4)	-1.2(3)	-2.0(4)	-1.4(4)
C5	11.8(5)	13.4(5)	9.2(4)	0.3(4)	0.7(4)	-0.6(4)
N1	11.1(4)	10.1(4)	9.9(4)	0.8(4)	0.5(3)	0.1(3)
C2	12.0(5)	9.5(5)	7.8(4)	0.6(4)	-0.9(4)	1.0(4)
C3	11.0(5)	17.5(6)	8.7(5)	3.4(4)	0.1(4)	0.8(4)
C4	10.2(5)	14.1(5)	8.6(4)	2.1(4)	0.9(4)	1.0(4)
C6	11.0(5)	9.1(5)	11.6(5)	0.7(4)	0.8(4)	0.6(4)
C7	11.1(5)	11.6(5)	8.3(4)	2.0(4)	0.6(4)	0.6(4)
C9	12.4(5)	12.1(5)	10.5(5)	1.9(4)	1.1(4)	2.2(4)
C8	14.0(5)	11.8(5)	8.5(4)	-0.1(4)	0.6(4)	2.2(4)
C1	11.4(5)	11.4(5)	8.6(5)	2.1(4)	-0.9(4)	-1.6(4)

Table S6. Bond Lengths for 1b

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C6	1.7345(12)	C2	C3	1.5369(17)
Cl2	C8	1.7331(12)	C2	C1	1.5330(16)
O3	C7	1.3448(13)	C3	C4	1.5085(16)
O1	C1	1.2553(15)	C4	C9	1.3940(17)
O2	C1	1.2564(14)	C6	C7	1.3967(17)
C5	C4	1.3981(17)	C7	C8	1.4002(17)
C5	C6	1.3880(16)	C9	C8	1.3891(16)
N1	C2	1.4964(15)			

Table S7. Bond Angles for 1b

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	C5	C4	119.83(11)	O3	C7	C6	118.31(11)
N1	C2	C3	110.46(9)	O3	C7	C8	125.19(11)
N1	C2	C1	109.08(9)	C6	C7	C8	116.51(10)
C1	C2	C3	108.20(9)	C8	C9	C4	120.59(11)
C4	C3	C2	113.75(9)	C7	C8	Cl2	118.32(9)
C5	C4	C3	120.48(11)	C9	C8	Cl2	119.86(9)
C9	C4	C5	118.64(11)	C9	C8	C7	121.82(11)
C9	C4	C3	120.88(11)	O1	C1	O2	126.85(11)
C5	C6	Cl1	119.17(9)	O1	C1	C2	117.17(10)
C5	C6	C7	122.62(11)	O2	C1	C2	115.91(10)
C7	C6	Cl1	118.20(9)				

Table S8. Hydrogen Bonds for 1b

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
OW	HW1	O1[1]	0.874(6)	1.943(9)	2.7993(15)	166(2)
OW	HW2	O2[2]	0.871(6)	2.020(10)	2.8580(15)	160.9(19)
O3	H9	Cl2	0.84	2.52	3.0277(10)	119.5
O3	H9	O2[3]	0.84	1.83	2.5998(13)	151.7
N1	H7	O1[4]	0.91	1.81	2.7218(13)	176.5
N1	H6	Cl1[5]	0.91	2.81	3.7100(10)	169.2
N1	H8	OW	0.91	1.92	2.7977(15)	160.6
C3	H3	Cl2[6]	0.99	2.91	3.6469(13)	132.4
C9	H5	Cl1[7]	0.95	2.95	3.5426(13)	122.1

[1]+X,1+Y,+Z; [2]-1/2+X,1/2-Y,1-Z; [3]3/2-X,-Y,-1/2+Z; [4]-1/2+X,-1/2-Y,1-Z; [5]1-X,-1/2+Y,1/2-Z; [6]2-X,1/2+Y,1/2-Z; [7]+X,-1+Y,+Z

Table S9. Torsion Angles for 1b

A	B	C	D	Angle/°	A	B	C	D	Angle/°
Cl1	C6	C7	O3	-1.96(16)	C3	C2	C1	O1	-99.25(13)
Cl1	C6	C7	C8	178.30(9)	C3	C2	C1	O2	78.16(13)
O3	C7	C8	Cl2	0.54(17)	C3	C4	C9	C8	-179.92(11)
O3	C7	C8	C9	-179.30(12)	C4	C5	C6	Cl1	-178.46(9)
C5	C4	C9	C8	0.04(18)	C4	C5	C6	C7	0.28(19)
C5	C6	C7	O3	179.29(11)	C4	C9	C8	Cl2	179.94(9)
C5	C6	C7	C8	-0.45(18)	C4	C9	C8	C7	-0.23(19)
N1	C2	C3	C4	-60.09(13)	C6	C5	C4	C3	179.90(11)
N1	C2	C1	O1	140.54(11)	C6	C5	C4	C9	-0.06(17)
N1	C2	C1	O2	-42.05(14)	C6	C7	C8	Cl2	-179.74(9)
C2	C3	C4	C5	93.10(13)	C6	C7	C8	C9	0.42(18)
C2	C3	C4	C9	-86.94(14)	C1	C2	C3	C4	-179.43(10)

Table S10. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 1b

Atom	*x*	*y*	*z*	U(eq)
HW1	7265(19)	4280(20)	4610(13)	46
HW2	5372(13)	3940(30)	4672(12)	46
H9	6718.7	1479.54	1021.45	20
H4	7685.34	2785.34	3379.79	14
H7	5176.86	-597.96	4547.36	16
H6	5248.74	2.39	3867.29	16
H8	6344.89	948.54	4362.71	16
H1	7018.69	-2462.24	3867.56	12
H3	9429.81	583.18	3990.22	15
H2	9993.94	-1288.33	3670.27	15
H5	8839.69	-2057.27	2584.16	14

1.2 X-ray Powder Diffraction

Powder X-ray diffraction data were collected on Bruker AXS D8 powder diffractometer with experimental parameters as follows: Cu-Kα radiation (λ = 1.5418 Å), scanning interval 3-40° at 2θ, step size 0.015°, exposure time 1.5 s per step.

1.3 Computational methods

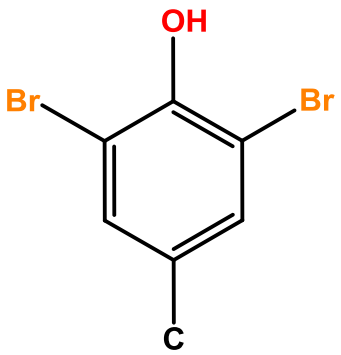
The calculations of the non-covalent interactions were carried out using the Gaussian-16 [10S] and the PBE0-D3/def2-TZVP level of theory.[11S-12S] To evaluate the interactions in the solid state, the crystallographic coordinates have been used and only the position of the H-atoms optimized. The interaction energies have been computed by calculating the difference between the energies of isolated monomers and their assembly. The interaction energies were calculated with correction for the basis set superposition error (BSSE) by using the Boys–Bernardi counterpoise technique.[13S] The Bader's "Atoms in molecules" theory (QTAIM)[14S] has been used to study the interactions discussed herein by means of the AIMAll calculation package.[15S] The molecular electrostatic potential surfaces have been computed using the Gaussian-16 software.[10S]

In order to assess the nature of interactions in terms of being attractive or repulsive and revealed them in real space, we have used NCIPLOT index, which is a method for plotting non-covalent interaction regions,[16S] based on the NCI (Non-Covalent Interactions) visualization index derived from the electronic density.[17S] The reduced density gradient (RDG), coming from the density and its first derivative, is plotted as a function of the density (mapped as isosurfaces) over the molecule of interest. The sign of the second Hessian eigenvalue times the electron density [i.e. sign(λ_2) ρ in atomic units] enables the identification of attractive/stabilizing (blue-green coloured isosurfaces) or repulsive (yellow-red coloured isosurfaces) interactions using 3D-Plots. For the plots shown in Figs. 6 and 7 the NCIplot index parameters are: RGD = 0.5; ρ cut off = 0.04 a.u.; color range: –0.04 a.u. ≤ sign(λ_2) ρ ≤ 0.04 a.u.

1.4 CSD Survey

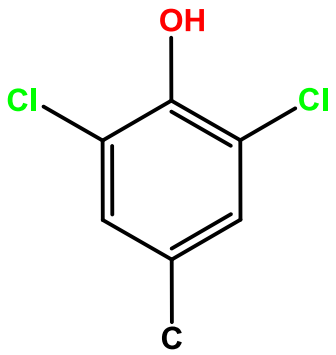
1.4.1. Refcodes of the crystal structures endowed with a 3,5-dibromo phenol group featuring a carbon atom in 4- position. In red the structures displaying a close contact involving at least one halogen and a nucleophilic atom (C, N, P, O, S, Se, F, Cl, Br, I were considered), with geometrical features typical of a halogen bond (Nu···X–C angle > 150°).

1	AFIRUE	27	FATLER
2	AGIKUY	28	FATLER01
3	AZOZOF	29	FATLER02
4	BAJYIU	30	GAPTUM
5	BAJYIU01	31	HOSGAX
6	BAJYIU02	32	JOWVIC
7	BEDSEK	33	KUPXAU
8	BEDSIO	34	OBEHUY
9	BHTPMC20	35	OBUTIQ
10	BRESTO10	36	PILYAN
11	BRESTO11	37	QATKOM
12	BZBARO	38	QECGEM
13	CAJYAQ	39	REFRUS
14	CEKNEL	40	REFRUS01
15	DACZAL	41	SEDRIE
16	DBTPFH10	42	SOVGEP
17	DBTYRM	43	SULSAV
18	DEYXOW	44	TIJVIR
19	DIWJOK	45	TINQOY
20	DLBENC	46	VORXIJ
21	ESOQAG	47	XAFNOK
22	EXEJEX	48	XIQXUR
23	EXEJIB	49	XIRTEA
24	EXEJOH	50	YIBXUF
25	EXEJUN	51	ZIXSAA
26	EXEKAU	52	NUFJUW



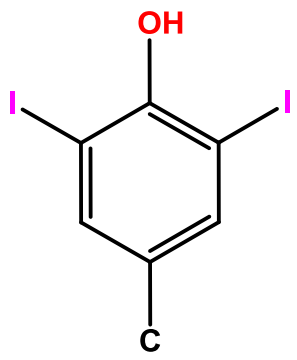
1.4.2. Refcodes of the crystal structures endowed with a 3,5-dichloro phenol group featuring a carbon atom in 4- position. In red the structures displaying a close contact involving at least one halogen and a nucleophilic atom (C, N, P, O, S, Se, F, Cl, Br, I were considered), with geometrical features typical of a halogen bond (Nu···X–C angle > 150°).

1 AHOGIN
2 CHPGLY
3 CIXPOR
4 GAKVAP
5 GOCFIQ
6 HOSMEJ
7 ITEKOH
8 KOMTOV
9 LADTUF
10 LAQTEF
11 LAQTIJ
12 LUXGAO
13 MEGMAM
14 MORKUZ
15 MURYIJ
16 NIDLIN
17 OBEHOS
18 QANKUO
19 QANKUO01
20 QUCKIJ
21 SULSEZ
22 TIJVEN
23 VAZYAZ
24 WAPFUP
25 XAZVUQ
26 XAZWAX
27 XAZWEB
28 XIPQIW
29 XIPQIW01



1.4.3. Refcodes of the crystal structures endowed with a 3,5-diiodo phenol group featuring a carbon atom in 4- position. In red the structures displaying a close contact involving at least one halogen and a nucleophilic atom (C, N, P, O, S, Se, F, Cl, Br, I were considered), with geometrical features typical of a halogen bond (Nu···X–C angle > 150°).

1 SUKZAC
2 BELYOJ
3 CACSUX
4 DITYRE
5 DITYRE01
6 DITYRS
7 DITYRS01
8 DITYRS02
9 DUKZIS
10 DUKZIS10
11 FESTUV
12 GAPVAU
13 GAPVIC
14 ROFJUT
15 SATJOM
16 TUJSUM
17 WALVOU
18 XAZWIF
19 XAZWIF01
20 ZELCOL
21 ZELCOL01
22 JUTBUY



2 Figures

2.1 Crystal structure **1a**

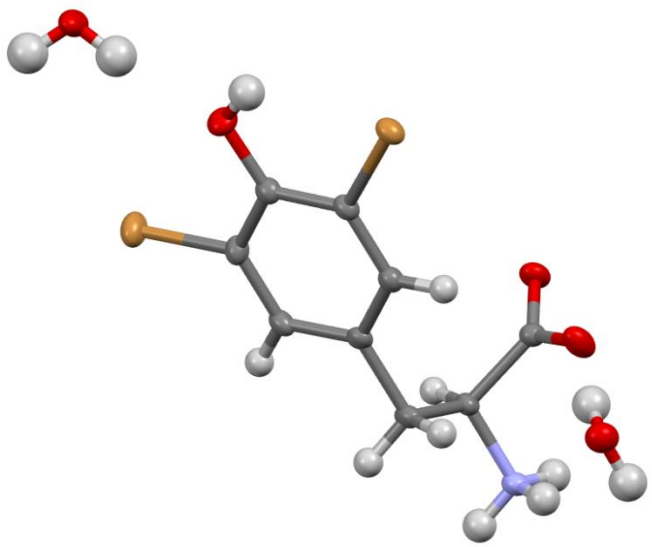


Figure S1. Ellipsoids representation of **1a** molecular structure. Color code: Carbon, grey, Nitrogen, violet, Oxygen, red, Bromine, orange, Hydrogen, whitish.

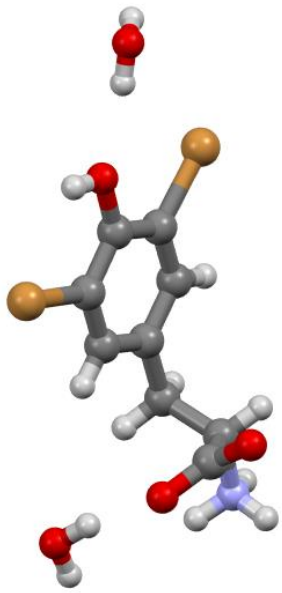


Figure S2. Ball and stick representation of **1a** Asymmetric unit, view along axis *a*. Carbon, grey, Nitrogen, violet, Oxygen, red, Bromine, orange, Hydrogen, whitish.

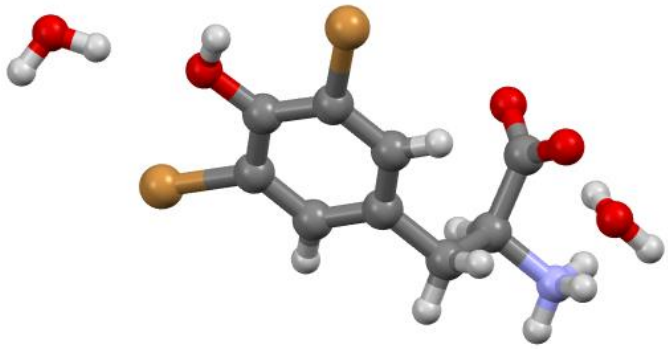


Figure S3. Ball and stick representation of **1a** Asymmetric unit, view along axis *b*. Carbon, grey, Nitrogen, violet, Oxygen, red, Bromine, orange, Hydrogen, whitish.

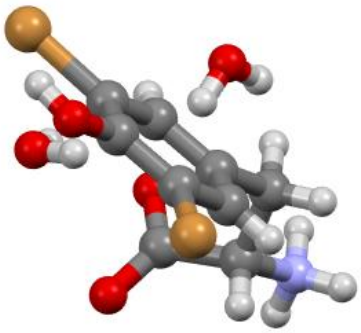


Figure S4. Ball and stick representation of **1a** Asymmetric unit, view along axis *c*. Carbon, grey, Nitrogen, violet, Oxygen, red, Bromine, orange, Hydrogen, whitish.

2.2 Crystal structure **1b**

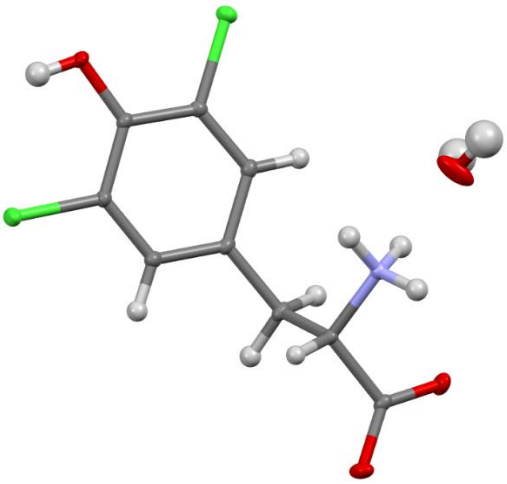


Figure S5. Ellipsoids representation of **1b** molecular structure. Color code: Carbon, grey, Nitrogen, violet, Oxygen, red, Chlorine, greed, Hydrogen, whitish.

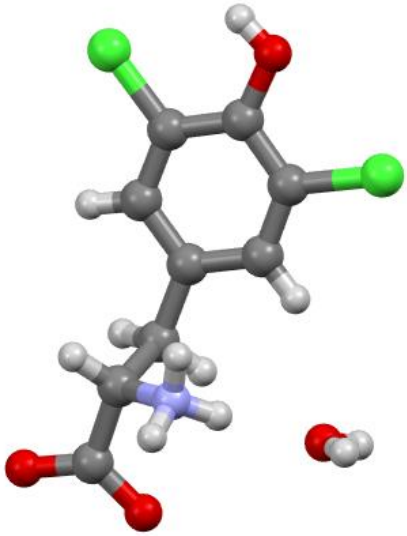


Figure S6. Ball and stick representation of **1b** Asymmetric unit, view along axis *a*. Carbon, grey, Nitrogen, violet, Oxygen, red, Chlorine, green, Hydrogen, whitish.

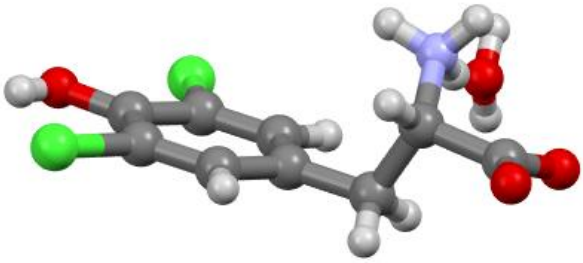


Figure S7. Ball and stick representation of **1b** Asymmetric unit, view along axis *b*. Carbon, grey, Nitrogen, violet, Oxygen, red, Chlorine, green, Hydrogen, whitish.

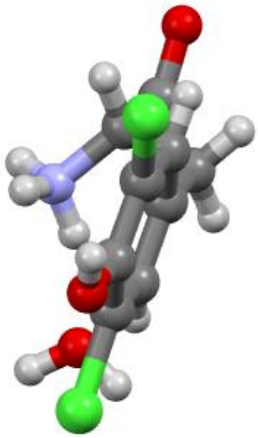


Figure S8. Ball and stick representation of **1b** Asymmetric unit, view along axis *c*. Carbon, grey, Nitrogen, violet, Oxygen, red, Chlorine, green, Hydrogen, whitish.

2.3 Powder pattern **1a**

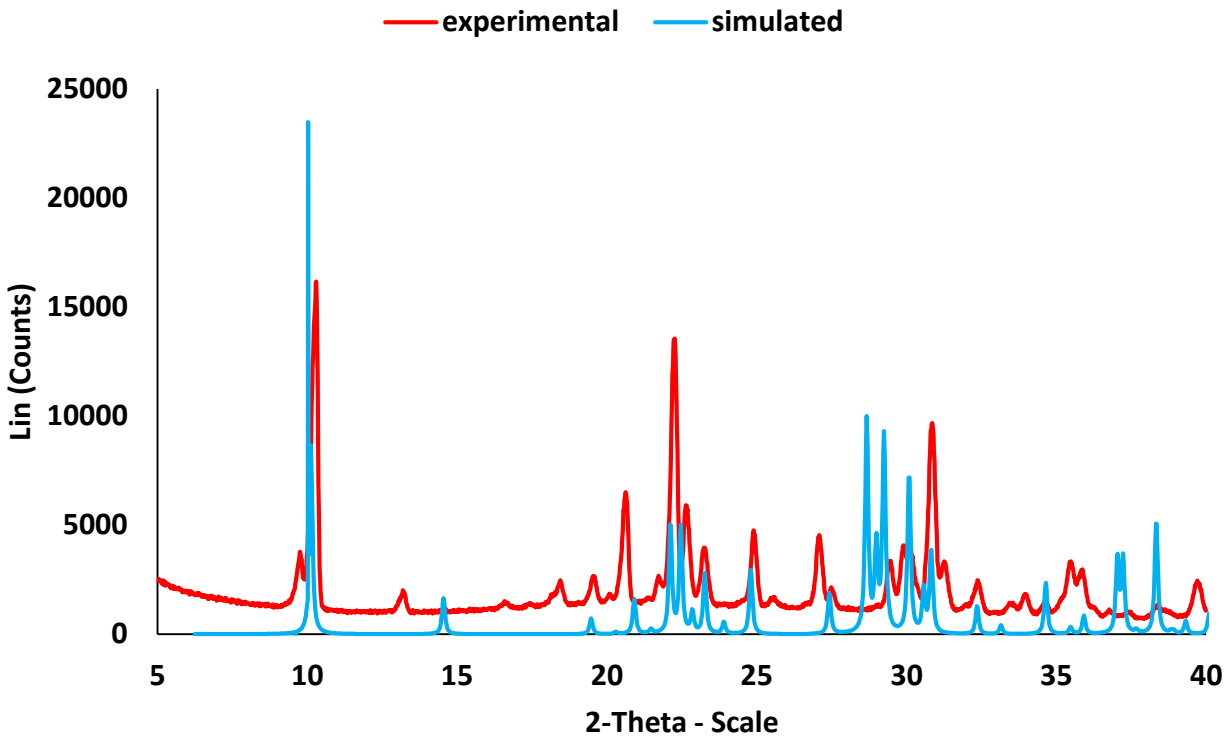


Figure S9. X-ray powder pattern of bulk commercial powders of 3,5-dibromotyrosine (red) compared with the powder pattern simulated from the crystal structure **1a** (light blue).

2.4 Powder pattern **1b**

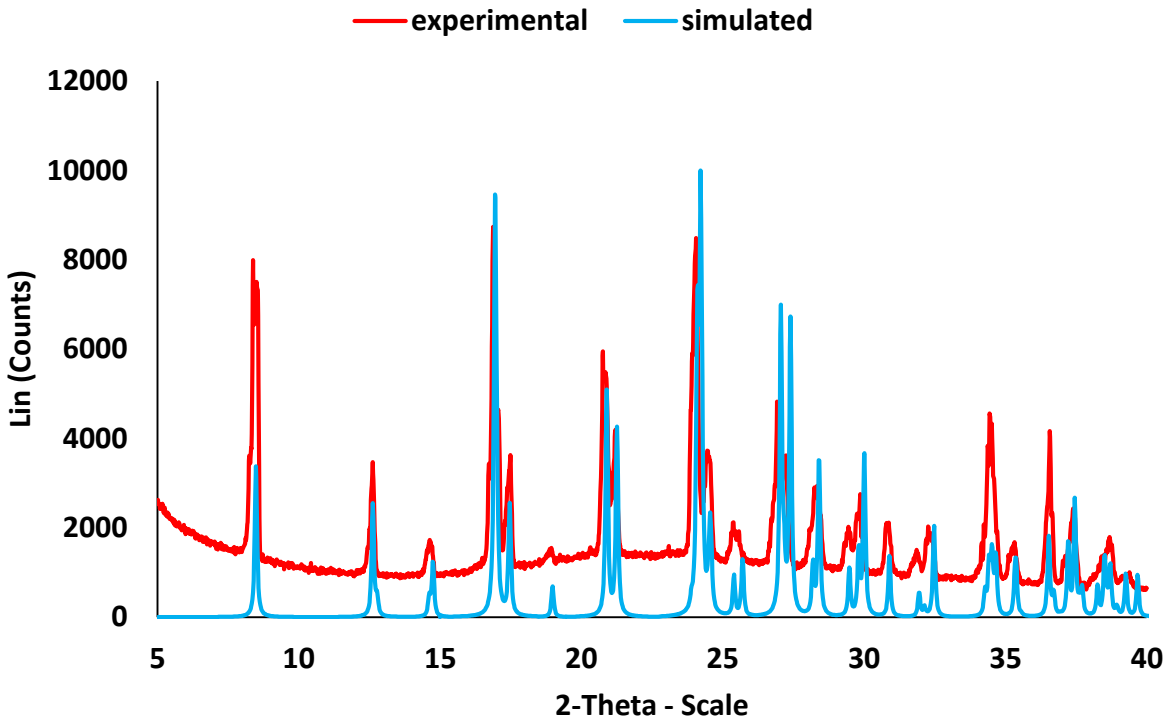


Figure S10. X-ray powder pattern of bulk commercial powders of 3,5-dichlorotyrosine (red) compared with the powder pattern simulated from the crystal structure **1a** (light blue)

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