

Article

Halogens On, H-Bonds Off—Insights into Structure Control of Dihalogenated Imidazole Derivatives

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Abstract

Halogen bonds play an important role in the targeted generation of solid-state structures, with polyhalogenated compounds enabling the simultaneous formation of various interactions. In this manuscript, we investigate the interactions of dihalogenated compounds in the solid state. Unlike investigated in previous studies, the introduction of protective groups in these compounds prevents the formation of dominant hydrogen bonds. The structures of diiodo imidazole derivatives are compared with the analogous dibromo compounds. A total of four different protective groups (two benzylic and two oxycarbonyl protective groups) are introduced and the respective compounds are characterized by X-ray crystallography. The significance of the protective groups for the solid-state structure can be distinguished on the basis of the additional donor atoms and functional groups. It can be seen that the iodo compounds in particular are capable of forming halogen bonds and that additional structural motifs can be generated by suitable protective groups.

Keywords: halogen bonding; crystal engineering; σ -hole interactions



Academic Editor: Jane S. Murray

Received: 31 October 2025

Revised: 14 November 2025

Accepted: 15 November 2025

Published: 20 November 2025

Citation: Mensing, L.; Layh, M.; Hebenbrock, M. Halogens On, H-Bonds Off—Insights into Structure Control of Dihalogenated Imidazole Derivatives. *Crystals* **2025**, *15*, 1000. <https://doi.org/10.3390/cryst15111000>

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1. Introduction

Over the past few decades, halogen bonding has gained substantial interest due to a wide range of applications in supramolecular chemistry [1], crystal engineering [2,3], (organo)catalysis [4] and medicinal chemistry [5]. Probably the first halogen-bonded complex was synthesized in 1814 by J. J. Colin [6], who synthesized an $I_2 \cdots NH_3$ adduct that was characterized about 50 years later by F. Guthrie [7]. Foundational insights into halogen bonding were supported by the theoretical work of R. S. Mulliken [8], who introduced the general concept of donor–acceptor (charge-transfer) interactions between molecules, and by O. Hassel [9], whose X-ray crystallographic studies provided early experimental evidence for interactions between halogen atoms and electron donors. However, the term ‘halogen bonding’ was coined in 1978 by Dumas et al. [10,11]

In general, halogen bonding is a non-covalent bond and is defined as an interaction between a halogen atom as an electron acceptor and a Lewis base, such as nitrogen, oxygen or sulfur as an electron donor. The typical halogen atoms involved are iodine, bromine, or chlorine. The halogen bond is a result of the anisotropic electron density on the halogen atom, called the σ -hole, in which the Lewis base is able to donate electrons and thus form a relatively strong non-covalent interaction. This interaction leads to typical features such as a near-linear angle ($\angle C-X \cdots Donor$: $\sim 180^\circ$) and the sum of the van der Waals radii of donor and acceptor exceeding the interatomic distance. Other arrangements and geometries are also possible, depending on the nature of donor and acceptor. The strength depends

on the halogen atoms involved with $F < Cl < Br < I$, due to their different polarizability. Variation of electron donor and acceptor can be used for targeted structural control in crystal engineering [12,13].

Imidazole derivatives play a crucial role in many biological systems such as hemoglobin, nucleic acid bases (purines) and the neurotransmitter histamine but are also important in areas such as supramolecular ligand chemistry [14–16]. Due to the relevance of imidazole derivatives, including halogen-substituted imidazole derivatives, and the ability of their nitrogen atoms to function as electron donors, many studies have focused on (halogen-)substituted imidazole derivatives in various research areas. In medicinal chemistry, polyhalogenated imidazole nucleosides were evaluated as antiviral drugs [17]. Furthermore, polyhalogenated benzimidazole nucleosides were also investigated as antiviral agents and were active against the HCMV virus [18]. Even in anticancer therapies, polyhalogenated benzimidazoles were investigated [19]. In different materials studies the influence of the direct substitution of the heterocycle at position C2, but also the influence of the halogen-substitution on the backbone of an imidazole derivative, regarding their potential as corrosion inhibitors, have been studied [20,21]. Furthermore, halogenated imidazole linkers are considered as ligands in metal–organic frameworks (MOFs), a field recently awarded the Nobel Prize hereby emphasizing the importance of MOFs. Halogenated imidazole derivatives are capable of enhancing the stiffness of MOFs [22], introducing a permanent dipole, and facilitating responses to electric fields [23] as well as increasing gas-uptake properties [24].

With a focus on supramolecular structures of halogen-containing imidazole derivatives, various studies were undertaken. Portilla et al. investigated the influence of halogen atoms and hydrogen bonds in the crystal structures of 1,2,4-trisubstituted imidazoles with haloaryl groups based on the presence of imidazole derivatives with haloaryl groups in several commercial antifungals [25,26]. Furthermore, Macías, Portilla et al. have investigated compounds with either two fluorine or two chlorine atoms on N-substituted 4-arylimidazoles or with only one chlorine atom, but with an unprotected N atom. Structural differences in the solid state could be attributed to different chain orientations, which are stabilized by different hydrogen bonds and halogen...halogen interactions [27].

Furthermore, the direct halogen-substitution of imidazole derivatives was also investigated in the context of supramolecular chemistry. The di- and tri-halogen-substitution of imidazole with Cl, Br, and I, and the intermolecular interactions showed that $NH\cdots N$ interactions are the main structural feature. Chains are formed, but the molecules are also stabilized by halogen...halogen bonds, and these interactions can have a major impact on structural control [28]. In addition, the influence of substituents (in this case, a benzyl protective group) on the N1 atom of the imidazole derivative was analyzed. The protection prevents the formation of $NH\cdots N$ bonds. The imidazole derivatives were monoiodinated at C2 (imidazole and benzimidazole) or C4 (imidazole). It was concluded that the C2 derivatives are capable of forming halogen bonds [28].

Beyond imidazole derivatives the literature on supramolecular chemistry shows that the balance between hydrogen bonding and halogen bonding can be adjusted and influenced by substituents and parameters during the crystallization process. Competition between both types of interactions has been reported, with evidence suggesting a direct relationship between molecular architecture and the ratio between both interactions in different cocrystals [29]. Stoichiometric control can transform a given assembly from one dominated by hydrogen bonding ($C-H\cdots O$ 'tapes') to one dominated by halogen bonding with short $I\cdots O$ contacts, despite the two-component systems being otherwise identical, thereby highlighting direct switching between both types [30]. Similarly, solvent polarity influences competitive co-crystallization: less polar solvents favor hydrogen bonding

products, whereas more polar solvents favor halogen bonding networks. In addition to the polarity of the solvent, the relative strengths of the donors and the crystallization pathways influence the ratio of hydrogen bonds to halogen bonds [31]. Trimorphic co-crystals further demonstrate the orthogonality of halogen and hydrogen bonded synthons [32]. Systematic surveys with bifunctional donors/acceptors reveal hierarchies in which geometry and electrostatics (MEP) determine which bonding type becomes the primary synthon [33,34]. In related systems, iodine frequently engages in X-N/O contacts and can even capture acceptor sites that are usually involved in NH...N hydrogen bonds. This demonstrates the ability of halogen bonding to alter packing arrangement [35]. Multifunctional donors demonstrate that hydrogen and halogen bonding can coexist or exclude each other, depending on donor geometry. These precedents justify strategies that attenuate hydrogen bonding donors and enhance halogen bonding (e.g., the use of heavier halogens or tailored conditions) when targeting structural control in halogenated imidazoles [36]. Related oxime systems show halogen bonding at O/N sites and illustrate the influence of halogen substitution on the number of hydrogen bonds [37].

In this paper, we have investigated the influence of dihalogenation of imidazoles in their C4 and C5 positions with either bromine or iodine with a focus on halogen bond formation. Furthermore, we have protected the N1 position with various protecting groups to create different electronic and steric environments, which may be essential for further considerations in supramolecular chemistry using halogen bonding as a key to structural control. In total, eight different compounds were synthesized and characterized by X-ray crystallography.

2. Materials and Methods

2.1. General Aspects

All chemicals used in this study were of p.a. grade and were obtained from ABCR (Karlsruhe, Germany), Acros Organics (Geel, Belgium), Alfa Aesar (Ward Hill, MA, USA), AppliChem (Darmstadt, Germany), BLDpharm (Shanghai, China), Carl Roth (Karlsruhe, Germany), Fisher Scientific (Waltham, MA, USA), Fluorochem (Glossop, UK), Merck (Darmstadt, Germany) Sigma-Aldrich (Burlington, MA, USA), TCI (Tokyo, Japan) or VWR (Radnor, PA, USA) and used, if not stated otherwise, without further purification.

NMR spectra were recorded on AVANCE NEO 400 (Bruker Biospin, Ettlingen, Germany) and AVANCE NEO 500 (Bruker Biospin, Ettlingen, Germany) NMR spectrometers. Chemical shifts are reported as δ , parts per million (ppm), and referenced to internal solvent residues. Coupling constants J are stated in Hertz (Hz). The following abbreviations were used for spin multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet). High-resolution ESI-MS spectra were recorded on an Impact II VIP QTOF ESI-MS (Bruker).

Elemental analysis was performed on a vario EL III CHNS (Elementar Analysensysteme GmbH, Langenselbold, Germany).

2.2. Synthetic Procedures

The synthesis procedures and the associated analytical data can be found in the SI. Some of the procedures are taken from the literature or serve to compare the analytical data obtained with that of known compounds [38–42].

2.3. X-Ray

Intensity data were collected using monochromated MoK α radiation on a Bruker D8 Venture diffractometer with a Photon III detector using either APEX5 or APEX6 software suite [43–45]. The collection method involved ω scans. Data reduction was performed

using the program *SAINT* [44]. The crystal structures were solved by Intrinsic Phasing using *SHELXT* [46]. Non-hydrogen atoms were first refined isotropically, followed by anisotropic refinement by full-matrix least-squares calculation based on F^2 using *SHELXL* [47]. H atoms were positioned geometrically and allowed to ride on their respective parent atoms. The co-crystallized solvent molecules in compounds **3d** (*n*-pentane) and **4d** (THF) were treated as a diffuse contribution to the overall scattering without specific atom positions by *SQUEEZE/PLATON* [48]. Crystallization attempts of **3d** from other solvents resulted in the same structure with voids for co-crystallized solvents (CCDC 2499425 with co-crystallized diethylether, not further discussed). The structure of compound **3c** is disordered over two positions with a ratio of 70:30. The same crystal structure with a disordered molecule was also obtained from various other solvents (methanol, ethanol, diethyl ether, THF, toluene, ethyl acetate, *n*-hexane) and under different crystallization conditions. Further details of the crystal structure determinations are available from the Cambridge Crystallographic Data Center on quoting the depository number CCDC 2499326–2499331, 2499334–2499335 and 2499425. Table 1 with the crystallographic details were created using WinGX [49,50].

Table 1. Crystallographic data of compounds **3a–4d**.

	Cmpd 3a	Cmpd 3b	Cmpd 3c	Cmpd 3d	Cmpd 4a	Cmpd 4b	Cmpd 4c	Cmpd 4d
CCDC	2499326	2499330	2499331	2499327	2499329	2499334	2499328	2499335
Empirical formula	C ₈ H ₁₀ Br ₂ N ₂ O ₂	C ₁₁ H ₁₀ Br ₂ N ₂ O	C ₁₀ H ₈ Br ₂ N ₂	C ₁₁ H ₈ Br ₂ N ₂ O ₂	C ₈ H ₁₀ I ₂ N ₂ O ₂	C ₁₁ H ₁₀ I ₂ N ₂ O	C ₁₀ H ₈ I ₂ N ₂	C ₁₁ H ₈ I ₂ N ₂ O ₂
Formula weight	326.00	346.03	316.00	360.01	419.98	440.01	409.98	453.99
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Trigonal	Orthorhombic	Orthorhombic	Monoclinic	Trigonal
Space group	<i>Pnma</i>	<i>P2₁2₁2₁</i>	<i>P2₁2₁2₁</i>	<i>R</i> -3	<i>Pbca</i>	<i>Pbca</i>	<i>P2₁</i>	<i>R</i> -3
<i>a</i> , Å	7.2871(2)	4.82760(10)	6.64120(10)	28.4883(3)	13.8801(2)	14.1428(8)	11.5334(17)	29.2203(6)
<i>b</i> , Å	6.7709(2)	10.0063(3)	12.3670(3)	28.4883(3)	11.0928(2)	8.4991(5)	14.1707(19)	29.2203(6)
<i>c</i> , Å	21.5274(5)	24.5484(6)	12.6667(3)	8.38630(10)	15.9440(2)	21.0899(12)	14.215(3)	8.5898(3)
α , deg.	90	90	90	90	90	90	90	90
β , deg.	90	90	90	90	90	90	92.286(6)	90
γ , deg.	90	90	90	120	90	90	90	120
<i>V</i> , Å ³	1062.17(5)	1185.85(5)	1040.34(4)	5894.32(14)	2454.88(6)	2535.0(3)	2321.5(7)	6351.6(3)
<i>Z</i>	4	4	4	18	8	8	8	18
ρ_{calc} , g cm ^{−3}	2.039	1.938	2.018	1.826	2.273	2.306	2.346	2.136
$\mu(\text{MoK}\alpha)$, mm ^{−1}	7.608	6.815	7.751	6.180	5.104	4.943	5.383	4.448
Crystal size, mm ³	0.19 × 0.17 × 0.06	0.19 × 0.13 × 0.08	0.22 × 0.17 × 0.07	0.29 × 0.17 × 0.12	0.19 × 0.18 × 0.13	0.21 × 0.07 × 0.05	0.13 × 0.07 × 0.04	0.56 × 0.05 × 0.05
Temperature (K)	100(2)	100(2)	100(2)	100(2)	100(2)	123(2)	145(2)	145(2)
θ range, deg	2.951–30.117	2.198–30.044	2.302–30.090	2.477–30.105	2.555–34.669	2.409–27.488	1.767–30.048	2.504–27.500
hkl range, deg	−10:10, −9:9, −30:30	−6:6, −14:14, −34:34	−9:9, −17:17, −17:17	−40:40, −40:40, −11:11	−22:22, −17:17, −25:25	−18:18, −11:11, −27:27	−16:15, −19:19, −20:19	−37:37, −37:37, −11:11
Total/unique data/ <i>R</i> _{int}	18227/1687/0.0248	19884/3466/0.0463	18798/3053/0.0300	35924/3854/0.0298	141626/4969/0.0423	22199/2906/0.0342	7011/7011/0.0201	30218/3229/0.0276
Data/restraints/parameters	1687/0/84	3466/0/146	3053/475/200	3854/0/154	4969/0/130	2906/0/146	7011/1/505	3229/0/154
<i>R</i> ₁ / <i>wR</i> ₂ [<i>I</i> > 2σ(<i>I</i>)]	0.0123/0.0311	0.0237/0.0556	0.0134/0.0315	0.0150/0.0359	0.0187/0.0486	0.0312/0.0854	0.0434/0.1065	0.0129/0.0314
<i>R</i> ₁ / <i>wR</i> ₂ [all data]	0.0129/0.0314	0.0261/0.0564	0.0140/0.0317	0.0166/0.0363	0.0240/0.0506	0.0339/0.0868	0.0446/0.1073	0.0135/0.0316

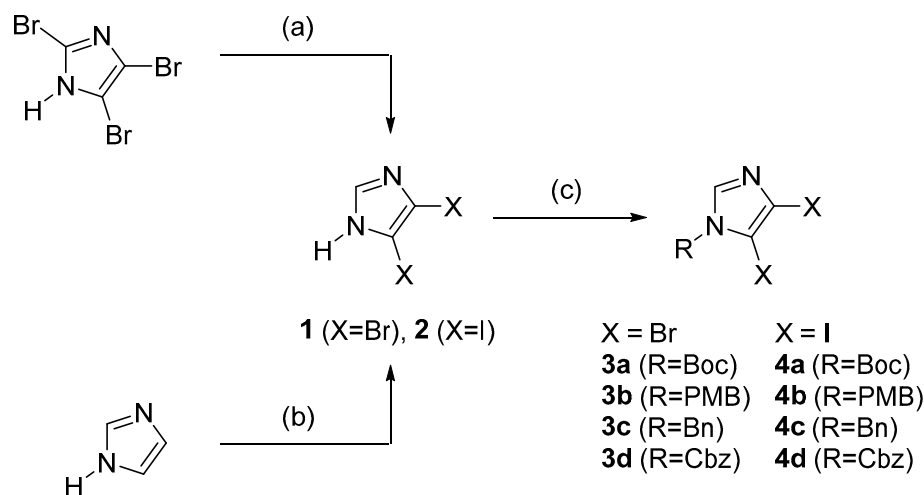
Table 1. Cont.

	Cmpd 3a	Cmpd 3b	Cmpd 3c	Cmpd 3d	Cmpd 4a	Cmpd 4b	Cmpd 4c	Cmpd 4d
Flack parameter	na	0.004(6)	0.003(5)	na	na	na	0.12(5)	na
S	1.122	1.031	1.047	1.074	1.096	1.249	1.133	1.100
Min./max. res. dens., $e\text{\AA}^{-3}$	0.464/−0.299	0.945/−0.423	0.211/−0.231	0.463/−0.385	0.596/−1.351	1.070/−1.046	2.498/−1.233	0.561/−0.568

3. Results

3.1. Synthesis of Halogenated and Protected Imidazole Derivatives

The synthesis of the halogenated imidazole derivatives was carried out either starting from imidazole or from the commercially available, tribromo derivative (Scheme 1). The dibromo derivative was prepared by dehalogenation of 2,4,5-tribromoimidazole. The dehalogenation reaction was carried out with ethylmagnesium bromide and yielded the dibromo derivative **1** in good yield. For the iodo derivatives, imidazole was reacted with iodine and iodide under basic conditions, resulting in the diiodo species **2**.



Scheme 1. Synthesis of the dihalogenated imidazole derivatives and introduction of the protective groups. (a): 1.0 eq. 2,4,5-tribromoimidazole, 2.0 eq. ethylmagnesium bromide in Et₂O, THF, 3 h, 50 °C; (b): 1.0 eq. imidazole, 2.0 eq. iodine, 3.0 eq. KI, 3.0 eq. NaOH, water, 18 h, rt; (c): (R = Boc) 1.0 eq. **1** or **2**, 1.1 eq. NaH, 1.1 eq. di-*tert*-butyl dicarbonate, THF, 18 h, rt; (R = PMB) 1.0 eq. **1** or **2**, 1.1 eq. NaH, 1.1 eq. 4-methoxybenzyl chloride, THF, 18 h, rt; (R = Bn) 1.0 eq. **1** or **2**, 1.1 eq. NaH, 1.1 eq. benzyl bromide, THF, 18 h, rt; (R = Cbz) 1.0 eq. **1** or **2**, 1.1 eq. NaH, 1.1 eq. benzyl chloroformate, THF, 18 h, rt.

The protective groups were introduced by deprotonation of the respective imidazole derivative with sodium hydride and subsequent reaction with di-*tert*-butyl dicarbonate, 4-methoxybenzyl chloride, benzyl bromide, or benzyl chloroformate. The protected compounds were obtained in moderate to good yields of 41% to 91%.

3.2. Molecular Structures of the Dihalogenated Derivatives

All compounds were obtained as single crystals and examined using X-ray crystallography. Despite the different protective groups, there are common structural features in the molecular structures within a halogen. The dibromo derivatives are characterized by bond lengths between 1.853(1) Å and 1.864(3) Å of the two carbon-bromine bonds. Although the bond lengths of these C–Br bonds vary slightly in each derivative, they are within the range of typical carbon-bromine bond lengths (1.875(11) Å, [51]). In particular, there are no significant deviations in bond lengths compared to related compounds such as functionalized monobromo and dibromo imidazoles [52–54]. The only striking feature is that unfunctionalized dibromo imidazoles have significantly shorter C–Br bonds [28]. Other intermolecular structural features of **3a**, **3b**, and **3d** are unexceptional. However, despite several attempts to crystallize compound **3c** from different solvents and under different crystallization conditions, only a disordered structure over two positions with a ratio of 70:30 could be obtained.

The molecular structures of the analogous iodo imidazole derivatives (Figure 1, compounds **3**, Figure S9, are similar) also exhibit similar structural features. The bond lengths of the two carbon-iodine bonds for compounds **4a**, **4b**, and **4d** range from 2.062(2) Å and 2.080(2) Å. As with the bromo derivatives, the differences in bond lengths between the two C–I bonds in each structure are negligible. The values are within the range of typical C_{Ar} –I bond lengths [51]. They also do not differ from functionalized monoiodoimidazoles and protonated diiodoimidazoles. However, the bond lengths are also significantly longer here than in unfunctionalized diiodoimidazoles. The structure of compound **4c** differs due to the presence of four molecules in its asymmetric unit, compared to one in the others. Here, the bond lengths are significantly more widely distributed, with very long C–I bond lengths (2.107(1) Å) to short bond lengths corresponding to those of the unfunctionalized diiodoimidazoles (2.023(1) Å).

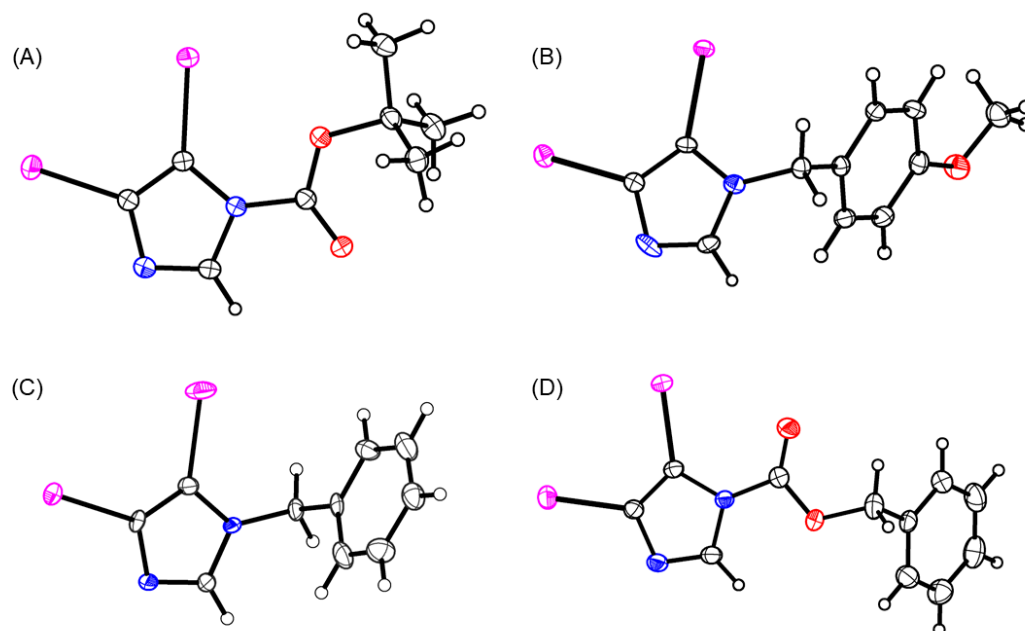


Figure 1. (A) Molecular structure of compound **4a**. (B) Molecular structure of compound **4b**. (C) An exemplary molecular structure of compound **4c** of the four molecules from the asymmetric unit. (D) Molecular structure of compound **4d** (Displacement ellipsoids are shown at the 50% level, hydrogen atoms at an arbitrary radius of 0.135 Å. Color coding: H: ○, C: ⊕, N: ●, O: ●, I: ●).

3.3. Supramolecular Features of the Dihalogenated Derivatives

While other studies on the structures of halogenated imidazole derivatives have primarily identified hydrogen bonds formed by the N–H bond of the imidazoles as the main structural elements, these interactions are not possible in the present compounds due to the protective group. Possible halogen bonds that occur should be identified and discussed on the basis of the distance criterion (smaller than the sum of the van der Waals radii [55] of the atoms involved). The distances 3.40 Å (N⋯Br), 3.37 Å (O⋯Br) and 3.70 Å (Br⋯Br) are used as a basis for the bromo compounds and 3.53 Å (N⋯I), 3.50 Å (O⋯I) and 3.96 Å (I⋯I) for the iodo compounds. In addition, the alignments of the atoms involved with each other are discussed and the formation of a halogen bond is assessed. Selected structural features of the connections are presented and discussed below.

The supramolecular structure of the Boc-protected bromine derivative **3a** features short distances between the nitrogen and the bromine atoms (Figure 2). The distance between the two atoms (3.242(1) Å) is shorter than the sum of the van der Waals radii of the atoms involved. Although the alignment of the two molecules is coplanar, the C–N⋯Br angles differ significantly from 120° (90.63(9)° and 165.2(1)°). For the interaction of an

sp^2 -hybridized nitrogen atom, however, this would be expected for efficient interaction of the free electron pair. This interaction continues in one plane, which is supported by an interaction of the carbonyl oxygen atom of the protective group with a methyl group of the *tert*-butyl unit, forming a strand of co-directional imidazole units. The second bromine atom is not directly involved in any interaction with a specific atom but interacts with the methyl groups above and below the antiparallel strands. The distance between the antiparallel strands is 3.39 Å, which indicates possible π - π interactions between the only slightly offset, stacked aromatic rings. In addition, the strands interact with neighboring strands via van der Waals interactions between the methyl groups.

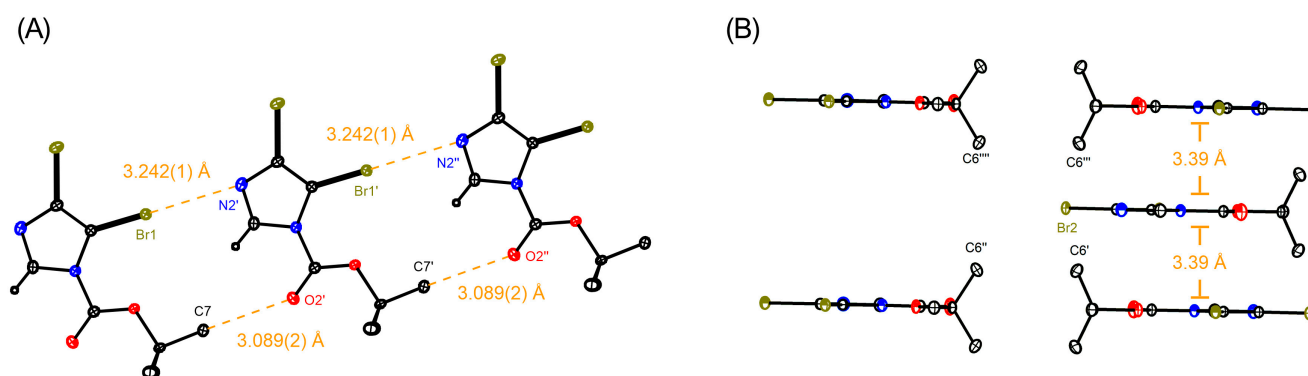


Figure 2. (A) Partial packing diagram of compound **3a** with highlighted Br...N interactions and interactions of a methyl group with an oxygen atom of the Boc protecting group (symmetry code: ' 1 + x, y, z; '' 2 + x, y, z). (B) Partial packing diagram of compound **3a** with close contacts between the methyl groups and a bromine substituent, as well as between the methyl groups of the protective groups (symmetry codes: ' 1 − x, 1/2 + y, 1 − z; '' 1/2 − x, 1/2 + y, 1/2 + z; ''' 1 − x, 1 − y, 1 − z; '''' 1/2 − x, 1 − y, 1/2 + z). (Displacement ellipsoids are shown at the 50% level, hydrogen atoms except for the imidazole protons (arbitrary radius of 0.135 Å) are omitted for clarity. Selected distances are shown in orange. Color coding: H: ○, C: ⊕, N: ●, O: ●, Br: ●).

The structure of the analogous iodo derivative **4a** exhibits similar features to the bromine derivative **3a** (Figure 3). In addition to a short distance between the iodine atom and a neighboring nitrogen atom, the compound also features close contacts (3.141(1) Å) between the iodine atom and an adjacent oxygen atom, which is smaller than the sum of the van der Waals radii. The carbon-iodine bond is also oriented towards the oxygen atom ($\angle C-I\cdots O$ 156.81(6)°). The halogen bond formed between the nitrogen and the iodine atom is similar to the interaction of the bromine derivative **3a** described above, but the bond is now almost directly aligned with the free electron pair of the nitrogen atom ($\angle C-N-I$ 124.0(1)° and 125.7(1)°). The distance between the nitrogen atom and the iodine atom is 2.890(2) Å and therefore significantly shorter than the sum of the van der Waals radii and falling within the typical range of corresponding halogen bonds [56]. In addition to these two short contacts, the molecules interact via hydrogen bonds (Figure 3B), with a geometry and bond length that indicates moderately strong hydrogen bonds (hydrogen bond geometry (C5-H5...O2') d(D-H): 0.95 Å, d(H...A): 2.38 Å, $\angle DHA$: 153.4°, d(D...A): 3.257(2) Å, A: O2' −x + 1, −y + 1, −z + 1) [57].

The structure of the PMB-protected derivative **3b** exhibits additional structural features compared to **3a** (Figure 4). On the one hand, there are short bromine...oxygen contacts (3.087(2) Å), which are significantly shorter than the sum of the van der Waals radii and the C-Br bond is aligned in an almost linear fashion with the oxygen atom ($\angle C-Br\cdots O$ 165.6(1)°). The distance is however larger than in strong halogen bonds (2.98 Å [58]). On the other hand, the bromine atom of the other C-Br bond has a short contact to the proton of a C-H bond of a neighboring imidazole (2.92 Å) in an almost linear arrangement. It is

only slightly offset and aligned with the imidazole ring of another molecule at a distance of 3.37 Å from the plane of the imidazole ring (Figure 4B). The iodo PMB compound **4b** is structurally similar to compound **4a** and also has short iodine...nitrogen contacts in which the nitrogen atom is perfectly aligned for interaction with the iodine atom (distance (I...N): 2.818(4) Å, $\angle\text{C-I}\cdots\text{N}$: 177.8(2)°). The optimal interaction with the free electron pair of the nitrogen atom is also evident from the orientation of the C–I bond relative to the sp²-hybridized nitrogen atom (120.0(3)° and 134.8(3)°). Similar to the bromo derivative **3a**, one C–I bond is also aligned with a neighboring aromatic phenyl ring (Figure 4C), with a distance of 3.59 Å between the iodine atom and the aromatic ring. A similar structural motif was also found for monoiodo imidazole [59–61]. Due to the mutual interaction, the two imidazoles stack slightly offset from each other, with a distance of 3.70 Å between the two imidazole ring planes.

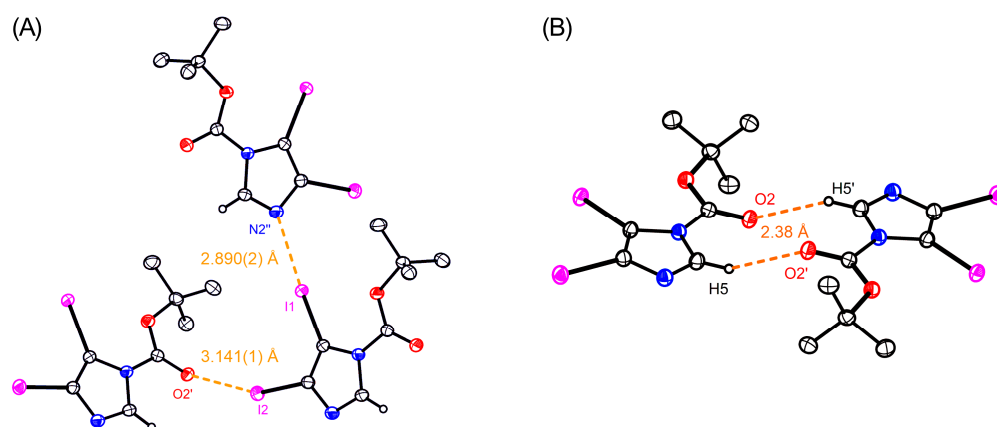


Figure 3. (A) Partial packing diagram of compound **4a** with highlighted I...N and I...O interactions (symmetry code: ' $x, 3/2 - y, -1/2 + z$ '; " $-1/2 + x, y, 1/2 - z$). (B) Partial packing diagram of compound **4a** with highlighted hydrogen bonds between the imidazole proton and the carbonyl oxygen of a protective group (symmetry code: ' $1 - x, 1 - y, 1 - z$). (Displacement ellipsoids are shown at the 50% level, hydrogen atoms except for the imidazole protons (arbitrary radius of 0.135 Å) are omitted for clarity. Selected distances are shown in orange. Color coding: H: $\circ$, C: $\oplus$, N: $\bullet$, O: $\bullet$, I: $\bullet$).

The most interesting structure is probably that of the two CBZ-protected compounds **3d** and **4d**, both of which crystallize in the trigonal space group R-3. In both compounds, the co-crystallized solvent is arranged in channels that run through the crystal (Figure 5). While the unit cell of compound **3d** contains three pentane molecules, the unit cell of compound **4d** contains three THF molecules. The structure of both molecules is very similar, indicating intrinsic interactions between the common molecular parts. The electron density of the solvent molecules is completely distributed across the channels, so that the molecules were treated as diffuse electron density. In the case of the bromo species **3d**, a cavity with a volume of 226 Å³ has formed, and in the case of the iodo species **4d**, a cavity with a volume of 252 Å³. Since the two structures differ only slightly, crystallize in the same space group with similar cell parameters, and are similarly packed, these two structures can be described as isotypic.

Both supramolecular structures feature interactions between the halogens and the nitrogen atoms of the imidazole unit with distances (I...N: 2.936(2) Å (**4d**), Br...N: 2.921(1) Å (**3d**)) smaller than the sum of the van der Waals radii indicating an attractive interaction (Figure S10A). The orientation of the C–X bond is almost linear with respect to the nitrogen atom ($\angle\text{C-I}\cdots\text{N}$: 169.48(7)° (**4d**), $\angle\text{C-Br}\cdots\text{N}$: 171.03(4)° (**3d**)). The imidazole moiety is also perfectly aligned with the halogen atom with respect to the free electron pair of the nitrogen atom ($\angle\text{C-N}\cdots\text{X}$, I: 124.1(1)° and 116.1(1)° (**4d**); Br: 112.51(9)° and 121.88(8)° (**3d**)). Additional molecular contacts are formed by intermolecular interactions between

two carbonyl groups of adjacent molecules. The molecules of **4d** (Figure S10B) arrange themselves in such a way that the C $\cdots$ O distance is 2.905(2) Å (**3d**: 2.803(1) Å) and the C = O double bond points at a slight angle to the carbonyl carbon ($\angle$ C = O $\cdots$ C, **4d**: 133.1(1)°, **3d**: 136.08(8)°). In addition, phenyl and imidazole rings are stacked on top of each other (distance, **4d**: 3.45 Å, **3d**: 3.42 Å) in such way that π - π interactions can be formed due to the planar (angle between the planes, **4d**: 5°, **3d**: 4°) slightly offset arrangement of the aromatic rings [62].

The Hirshfeld surface analysis (Figure 6) also shows the high similarity of the two structures. The fingerprint plots (generated with the CrystalExplorer 21 [63] software) for the reciprocal interactions for carbon and hydrogen are shown as examples. It is evident that a large part of the interactions takes place via van der Waals interactions (cf. H $\cdots$ H plot). The pattern is strongly reminiscent of the interaction of alkanes with characteristic short interactions ($d_e = d_i \approx 1.2$ Å). It can also be seen that the disordered solvent was treated as a uniform electron density, resulting in very long interactions via the channel formed. The typical wing-like pattern of the reciprocal C $\cdots$ H interactions indicates the presence of C-H $\cdots$ π interactions, such as those formed in aromatic systems arranged orthogonal to each other [64,65]. The presence of π - π stacking interactions is illustrated by the plot of reciprocal C $\cdots$ C interactions which shows a strong signal reflecting the typical distance of 3.6 Å ($d_e = d_i \approx 1.8$ Å) [62]. A proportional overview of all selected interactions in the totality of intermolecular contacts shows that the differences between compounds **3d** and **4d** are also negligible in terms of the individual proportions.

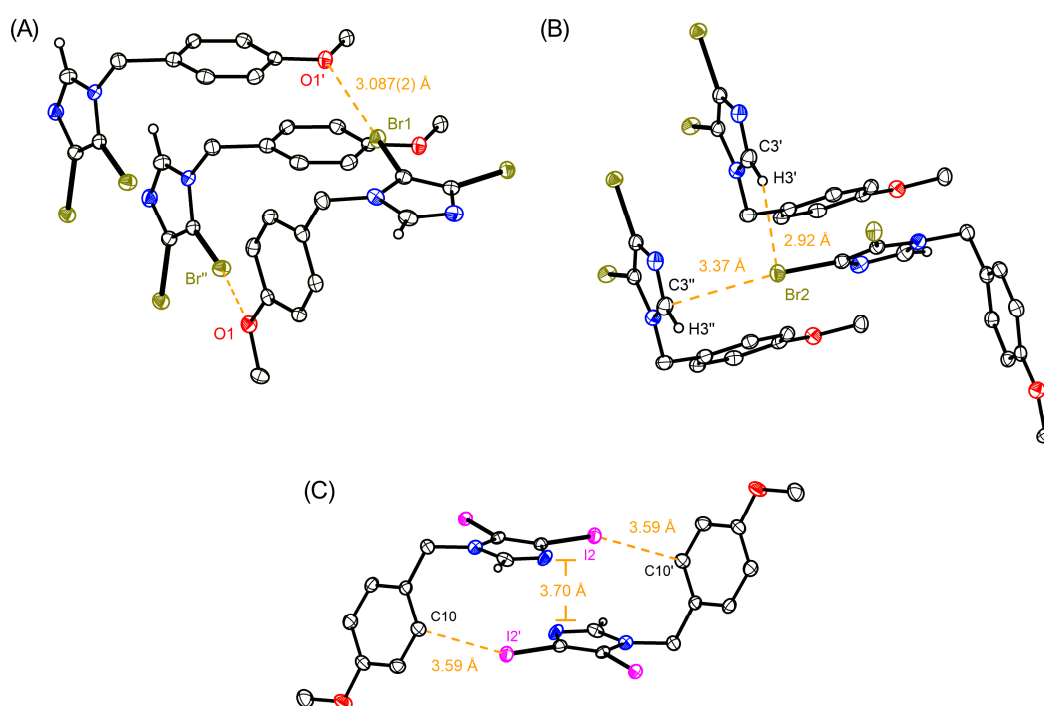


Figure 4. (A) Partial packing diagram of compound **3b** with highlighted Br $\cdots$ O interaction (symmetry code: $' -\frac{1}{2} + x, 3/2 - y, 1 - z; '' \frac{1}{2} + x, 3/2 - y, 1 - z$). (B) Partial packing diagram of compound **3b** with close contacts of an imidazole proton and a bromine substituent, as well as interaction of a bromine substituent with a neighboring aromatic (symmetry codes: $' -x, \frac{1}{2} + y, 3/2 - z; '' 1 - x, \frac{1}{2} + y, 3/2 - z$). (C) Partial packing diagram of compound **4b** with highlighted interaction of the iodine atoms with neighboring aromatic atoms (symmetry code: $' 1 - x, 1 - y, 1 - z$). (Displacement ellipsoids are shown at the 50% level, hydrogen atoms except for the imidazole protons (arbitrary radius of 0.135 Å) are omitted for clarity. Selected distances are shown in orange. Color coding: H: $\circ$, C: $\bullet$, N: $\bullet$, O: $\bullet$, Br: $\bullet$, I: $\bullet$).

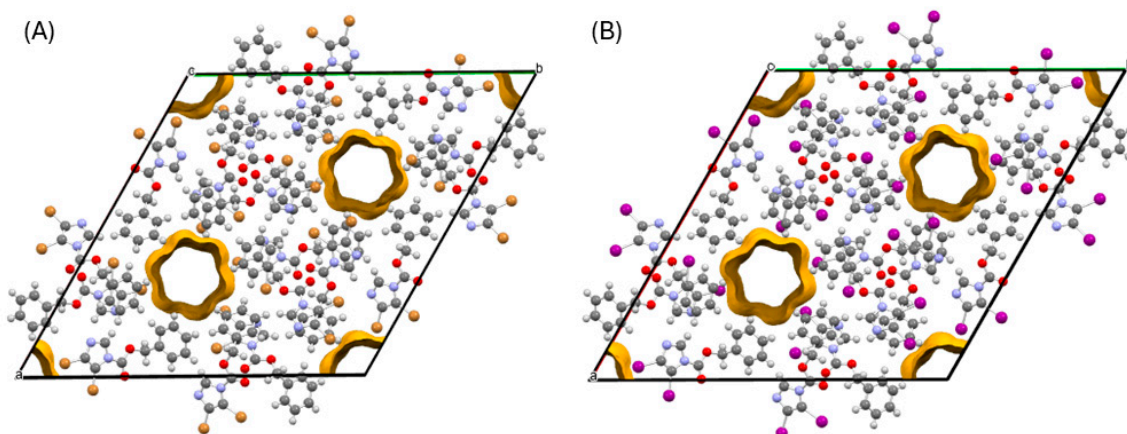


Figure 5. (A) Packing diagram of compound **3d** viewed along the c-axis. (B) Packing diagram of compound **4d** viewed along the c-axis. (The molecules are shown in stick model. The channels formed by the disordered solvent are outlined in yellow. Color coding: H: $\circ$, C: $\bullet$, N: $\bullet$, O: $\bullet$, Br: $\bullet$, I: $\bullet$).

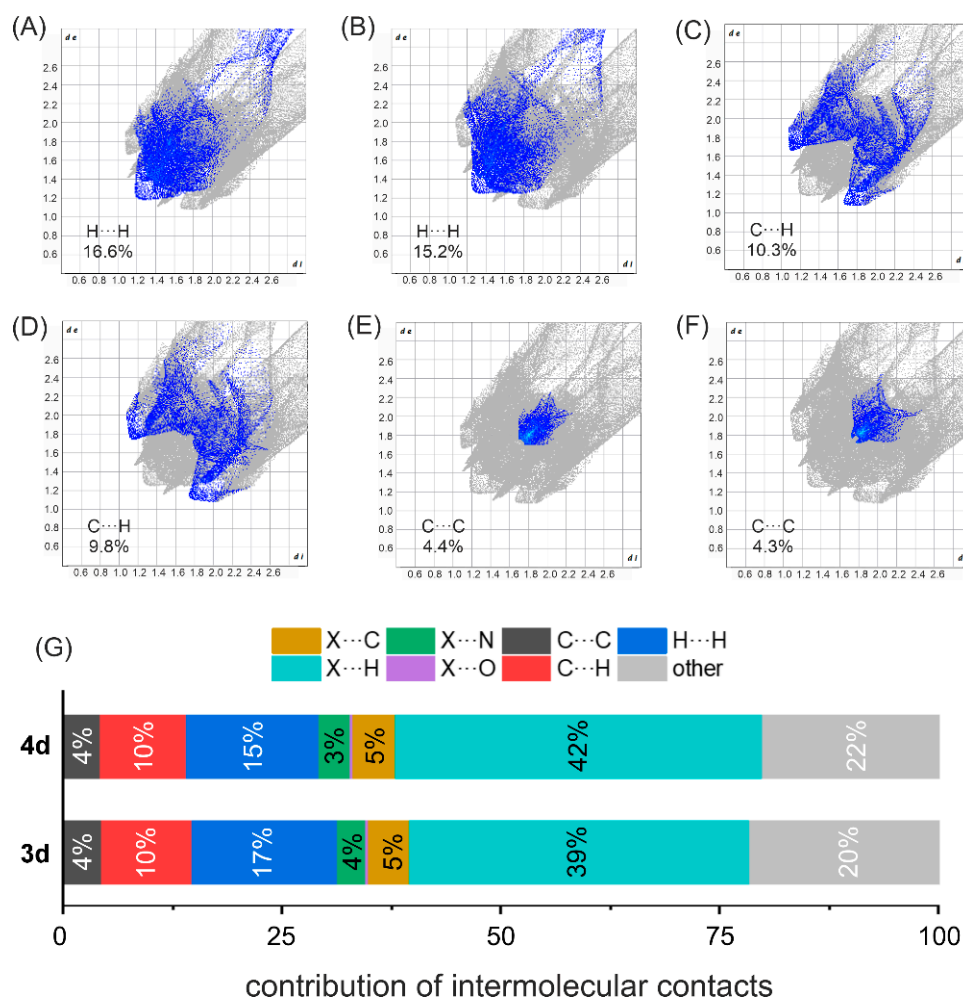


Figure 6. Fingerprint plot of the reciprocal H...H interactions of compound **4d** (A) and compound **3d** (B), fingerprint plot of the reciprocal C...H interactions of compound **4d** (C) and compound **3d** (D), fingerprint plot of the reciprocal C...C interactions of compound **4d** (E) and compound **3d** (F), and overview of the proportions (rounded to integers) of selected interactions in the total intermolecular interactions for compounds **3d** (top) and **4d** (bottom) (G) (The proportion of X...O contacts (purple) is <0.5%).

4. Discussion

Comparison of Halogen-Bonding Related Effects

The correlation between the halogen bonds and the various protective groups is determined based on the distances between potential donor–acceptor combinations. The shortest contact distance observed in all crystal structures are used as basis for a comparison (Table 2). Fundamentally, the electron density of the aromatic compound should play a significant role in the strength of the halogen bond [66,67]. Carbamate protective groups should therefore reduce the electron density in the ring whereas benzylic protective groups should not have a strong influence on the electron density. If anything, the PMB protective group should be less electron-withdrawing than the Bn protective group.

Table 2. Overview of the shortest contacts found in the respective compounds.

Compound	N...X [Å]	O...X [Å]	X...X [Å]
3a	3.242(1)	3.6241(4)	nd ^a
4a	2.890(2)	3.141(1)	nd ^a
3b	3.458(3)	3.087(2)	nd ^a
4b	2.818(4)	nd ^a	nd ^a
3c	nd ^a	na ^b	nd ^a
4c	2.96(1)	na ^b	3.866(1)
3d	2.921(1)	nd ^a	3.9404(7)
4d	2.936(1)	nd ^a	nd ^a

^a no corresponding contact found up to a distance of 4.0 Å. ^b the compound does not contain any oxygen atoms.

For contact distances up to 4.0 Å there are hardly any interactions. Among the presented examples for interactions in bromo compounds, the O...Br interaction (3.6241(4) Å) in **3a** is more likely to be a result of the stacking of corresponding molecular parts due to the orientation. The same applies to the Br...Br interaction (3.9404(7) Å) in compound **3d**. The bonds in the N...Br interaction (3.458(3) Å) of compound **3b**, which are aligned nearly orthogonal to each other, make it difficult for the atoms to interact in an optimal way. The suboptimal alignment of the free electron pair of the nitrogen atom in the N...Br interaction (3.242(1) Å) in compound **3a** is also evident in compound **3d**, although the distance is significantly shorter (2.921(1) Å). Only the Br...O interactions (3.087(2) Å) of compound **3b** indicate a real interaction and are in the range of reported Br...O interactions of various compounds [68,69]. The fact that halogen bonds play a greater role in more polarizable atoms is evident as the number of analogous halogen bonds is greater in the iodo derivatives.

More attractive interactions can be identified in the iodo compounds and are attributed to σ -hole interactions. Only the interaction of the two iodine atoms with a distance of 3.866(1) Å in compound **4c** appears to be the result of a pure packing effect, especially since the value is only slightly below the sum of the van der Waals radii [55]. In compound **4a**, an attractive I...O interaction can be identified (3.141(1) Å) and is in the range of reported I...O interactions of various compounds [67,70]. I...N interactions that indicate halogen bonds can be determined for all compounds. The observed distances increase in the order PMB < Boc < Cbz < Bn. This is however not expected from the electron-withdrawing properties and may be the result of additional interactions, which are not solely attributable to the halogens.

Although no single effect can be identified that influences halogen bonds, the set of compounds clearly shows the differences between the individual halogens in terms of

their potential to form halogen bonds and the effects of these bonds. Strong interactions with the σ -hole of the halogens can only be detected in the iodo compounds, which is also reflected in the orientation of the nitrogen atoms involved. These interactions have a strong structure-determining effect and allow for the formation of molecular networks. The fact that halogen bonds never determine a structure on their own is clearly demonstrated by the example of the isotopic compounds **3d** and **4d**, which have the same structural arrangement, so that neither the bromo nor the iodo compound exhibits optimal interaction of the nitrogen atoms with the halogen atoms.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cryst15111000/s1>. NMR data, synthetic procedures and additional figures.

Author Contributions: Conceptualization, M.H.; Formal analysis, M.L. and M.H.; Investigation, L.M. and M.H.; Data curation, L.M., M.L. and M.H.; Writing—original draft, L.M. and M.H.; Writing—review and editing, L.M., M.L. and M.H.; Visualization, M.H.; Supervision, M.H.; Project administration, M.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by University of Münster. MH would like to express his gratitude to the Fonds der Chemischen Industrie (VCI) for its financial support.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

aq.	aqueous
Boc	<i>tert</i> -butoxycarbonyl
Bn	benzyl
Cbz	benzyloxycarbonyl
Cmpd	compound
DCM	dichloromethane
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
na	not available
PMB	<i>p</i> -methoxybenzyl
sat.	saturated
THF	tetrahydrofuran

References

1. Meazza, L.; Foster, J.A.; Fücke, K.; Metrangolo, P.; Resnati, G.; Steed, J.W. Halogen-bonding-triggered supramolecular gel formation. *Nat. Chem.* **2013**, *5*, 42–47. [\[CrossRef\]](#)
2. Bulfield, D.; Engelage, E.; Mancheski, L.; Stoesser, J.; Huber, S.M. Crystal Engineering with Multipoint Halogen Bonding: Double Two-Point Donors and Acceptors at Work. *Chem. Eur. J.* **2020**, *26*, 1567–1575. [\[CrossRef\]](#)
3. Torubae, Y.V.; Shaashua, O.; Braunstein, S.; Pappo, D. Halogen Bond-Driven Ligand Displacement: Co-Crystal Lattice Versus Coordination Bonds. *Chem. Eur. J.* **2025**, *31*, e202404784. [\[CrossRef\]](#)
4. Keuper, A.C.; Fengler, K.; Ostler, F.; Danelzik, T.; Piekarski, D.G.; Garcia Mancheno, O. Fine-Tuning Substrate-Catalyst Halogen-Halogen Interactions for Boosting Enantioselectivity in Halogen-Bonding Catalysis. *Angew. Chem. Int. Ed. Engl.* **2023**, *62*, e202304781. [\[CrossRef\]](#)
5. Staron, J.; Pietrus, W.; Bugno, R.; Kurczab, R.; Satala, G.; Warszycki, D.; Lenda, T.; Wantuch, A.; Hogendorf, A.S.; Hogendorf, A.; et al. Tuning the activity of known drugs via the introduction of halogen atoms, a case study of SERT ligands—Fluoxetine and fluvoxamine. *Eur. J. Med. Chem.* **2021**, *220*, 113533. [\[CrossRef\]](#) [\[PubMed\]](#)

6. Colin, J.J.; Gaultier de Claubry, H. Sur le combinaisons de l'iode avec les substances végétales et animales. *Ann. Chim.* **1814**, *90*, 87–100.
7. Guthrie, F. XXVIII.—On the iodide of iodammonium. *J. Chem. Soc.* **1863**, *16*, 239–244. [[CrossRef](#)]
8. Mulliken, R.S. Structures of Complexes Formed by Halogen Molecules with Aromatic and with Oxygenated Solvents1. *J. Am. Chem. Soc.* **1950**, *72*, 600–608. [[CrossRef](#)]
9. Hassel, O.; Hvorslef, J.; Vihovde, E.H.; Sörensen, N.A. The Structure of Bromine 1,4-Dioxanate. *Acta Chem. Scand.* **1954**, *8*, 873. [[CrossRef](#)]
10. Dumas, J.; Peurichard, H.; Gomel, M. CX₄··· base interaction as models of weak charge-transfer interactions: Comparison with strong charge-transfer and hydrogen-bond interactions. *J. Chem. Res.* **1978**, *2*, 54–55.
11. Bulfield, D.; Huber, S.M. Halogen Bonding in Organic Synthesis and Organocatalysis. *Chem. Eur. J.* **2016**, *22*, 14434–14450. [[CrossRef](#)] [[PubMed](#)]
12. Desiraju, G.R.; Ho, P.S.; Kloo, L.; Legon, A.C.; Marquardt, R.; Metrangolo, P.; Politzer, P.; Resnati, G.; Rissanen, K. Definition of the halogen bond (IUPAC Recommendations 2013). *Pure Appl. Chem.* **2013**, *85*, 1711–1713. [[CrossRef](#)]
13. Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. The Halogen Bond. *Chem. Rev.* **2016**, *116*, 2478–2601. [[CrossRef](#)] [[PubMed](#)]
14. Zhang, L.; Peng, X.M.; Damu, G.L.; Geng, R.X.; Zhou, C.H. Comprehensive review in current developments of imidazole-based medicinal chemistry. *Med. Res. Rev.* **2014**, *34*, 340–437. [[CrossRef](#)]
15. Scharf, P.; Müller, J. Nucleic Acids with Metal-Mediated Base Pairs and Their Applications. *ChemPlusChem* **2013**, *78*, 20–34. [[CrossRef](#)]
16. Jash, B.; Müller, J. Metal-Mediated Base Pairs: From Characterization to Application. *Chem. Eur. J.* **2017**, *23*, 17166–17178. [[CrossRef](#)]
17. Chien, T.C.; Saluja, S.S.; Drach, J.C.; Townsend, L.B. Synthesis and antiviral evaluation of polyhalogenated imidazole nucleosides: Dimensional analogues of 2,5,6-trichloro-1-(beta-D-ribofuranosyl)benzimidazole. *J. Med. Chem.* **2004**, *47*, 5743–5752. [[CrossRef](#)] [[PubMed](#)]
18. Townsend, L.B.; Devivar, R.V.; Turk, S.R.; Nassiri, M.R.; Drach, J.C. Design, synthesis, and antiviral activity of certain 2,5,6-trihalo-1-(beta-D-ribofuranosyl)benzimidazoles. *J. Med. Chem.* **1995**, *38*, 4098–4105. [[CrossRef](#)]
19. Mikula, M.; Hanusek, K.; Paziewska, A.; Dzwonek, A.; Rubel, T.; Bomszyk, K.; Ostrowski, J. Halogenated imidazole derivatives block RNA polymerase II elongation along mitogen inducible genes. *BMC Mol. Biol.* **2010**, *11*, 4. [[CrossRef](#)] [[PubMed](#)]
20. Abdulazeez, I.; Zeino, A.; Kee, C.W.; Al-Saadi, A.A.; Khaled, M.; Wong, M.W.; Al-Sunaidi, A.A. Mechanistic studies of the influence of halogen substituents on the corrosion inhibitive efficiency of selected imidazole molecules: A synergistic computational and experimental approach. *Appl. Surf. Sci.* **2019**, *471*, 494–505. [[CrossRef](#)]
21. Dadou, S.; Elyoussfi, A.; Dagdag, O.; Koudad, M.; Isaad, J.; Kim, H.; Berisha, A.; Azghay, I.; Salhi, A.; Ahari, M.H.; et al. The impact of halogen substitution on the corrosion inhibition of imidazothiazole derivatives for mild steel in corrosive media (Part A). *Colloids Surf. A* **2024**, *687*, 133451. [[CrossRef](#)]
22. Chaplais, G.; Fraux, G.; Paillaud, J.-L.; Marichal, C.; Nouali, H.; Fuchs, A.H.; Coudert, F.-X.; Patarin, J. Impacts of the Imidazolate Linker Substitution (CH₃, Cl, or Br) on the Structural and Adsorptive Properties of ZIF-8. *J. Phys. Chem. C* **2018**, *122*, 26945–26955. [[CrossRef](#)]
23. Namsani, S.; Yazaydin, A.O. Electric field induced rotation of halogenated organic linkers in isorecticular metal–organic frameworks for nanofluidic applications. *Mol. Syst. Des. Eng.* **2018**, *3*, 951–958. [[CrossRef](#)]
24. Hou, J.; Rios Gomez, M.L.; Krajnc, A.; McCaul, A.; Li, S.; Bumstead, A.M.; Sapnik, A.F.; Deng, Z.; Lin, R.; Chater, P.A.; et al. Halogenated Metal–Organic Framework Glasses and Liquids. *J. Am. Chem. Soc.* **2020**, *142*, 3880–3890. [[CrossRef](#)] [[PubMed](#)]
25. Elejalde-Cadena, N.R.; García-Olave, M.; Macías, M.A.; Portilla, J. Influence of halogen atoms and hydrogen bonds in the crystal structure of 1,2,4-trisubstituted imidazoles having haloaryl groups. *J. Mol. Struct.* **2023**, *1286*, 135662. [[CrossRef](#)]
26. Kathiravan, M.K.; Salake, A.B.; Chothe, A.S.; Dudhe, P.B.; Watode, R.P.; Mukta, M.S.; Gadhwe, S. The biology and chemistry of antifungal agents: A review. *Bioorg. Med. Chem.* **2012**, *20*, 5678–5698. [[CrossRef](#)]
27. García-Olave, M.; Elejalde-Cadena, N.R.; Portilla, J.; Macías, M.A. C H ··· X (X = F, Cl) and Cl ··· Cl halogen-mediated interactions driving the crystal packing in N-substituted 4-arylimidazoles. *J. Mol. Struct.* **2023**, *1272*, 134181. [[CrossRef](#)]
28. Andrzejewski, M.; Marciniak, J.; Rajewski, K.W.; Katrusiak, A. Halogen and Hydrogen Bond Architectures in Switchable Chains of Di- and Trihaloimidazoles. *Cryst. Growth Des.* **2015**, *15*, 1658–1665. [[CrossRef](#)]
29. Aakeröy, C.B.; Rajbanshi, A.; Desper, J.; Moore, C.; Urbina, J.F. Structural Competition between Hydrogen Bonds and Halogen Bonds. *J. Am. Chem. Soc.* **2007**, *129*, 11824–11825. [[CrossRef](#)] [[PubMed](#)]
30. Oh, T.; Aakeröy, C.B.; Sinha, A.S.; Desper, J. Switching Between Halogen and Hydrogen Bonding via Stoichiometric Variations in Co-Crystals. *CrystEngComm.* **2012**, *14*, 6110–6114. [[CrossRef](#)]
31. Robertson, C.C.; Perutz, R.N.; Brammer, L.; Hunter, C.A. Hydrogen Bonding Versus Halogen Bonding: The Solvent Decides. *Chem. Sci.* **2017**, *8*, 5392–5398. [[CrossRef](#)]

32. Topić, F.; Rissanen, K. Cocrystal Trimorphism and Stoichiomorphism of mdppo and tfib: Orthogonality of Hydrogen- and Halogen-Bonding Motifs. *Chem. Commun.* **2019**, *55*, 8663–8666. [\[CrossRef\]](#)
33. Aakeröy, C.B.; Chopade, P.D.; Desper, J. Mapping the Supramolecular Landscape of Competing Hydrogen- and Halogen-Bond Donors in Crystal Engineering. *CrystEngComm* **2013**, *15*, 4720–4730. [\[CrossRef\]](#)
34. Aakeröy, C.B.; Spartz, C.L.; Dembowski, S.; Dwyre, S.; Desper, J. A systematic structural study of halogen bonding versus hydrogen bonding within competitive supramolecular systems. *IUCr* **2015**, *2*, 498–510. [\[CrossRef\]](#)
35. Abeyskera, A.M.; Aakeröy, C.B.; Sinha, A.S.; Desper, J. Mapping out the Relative Influence of Hydrogen and Halogen Bonds in Crystal Structures of a Family of Amide-Substituted Pyridines. *Cryst. Growth Des.* **2020**, *20*, 6078–6088. [\[CrossRef\]](#)
36. Gamekkanda, J.; Sinha, A.S.; Desper, J.; Đaković, M.; Aakeröy, C.B. Competition between hydrogen bonds and halogen bonds: A structural study. *New J. Chem.* **2018**, *42*, 10512–10520. [\[CrossRef\]](#)
37. Meier, C.; Seichter, W.; Mazik, M. Combination of Hydrogen and Halogen Bonds in the Crystal Structures of 5-Halogeno-1H-isatin-3-oximes: Involvement of the Oxime Functionality in Halogen Bonding. *Molecules* **2024**, *29*, 1174. [\[CrossRef\]](#)
38. Iddon, B.; Khan, N. Azoles. Part 5. Metal-halogen exchange reactions of polybromoimidazoles. *J. Chem. Soc. Perkin Trans. 1* **1987**, *1987*, 1445–1451. [\[CrossRef\]](#)
39. Lovely, C.; Du, H.; He, Y.; Sivappa, R. New Methods of Imidazole Functionalization—From Imidazole to Marine Alkaloids. *Synlett* **2006**, *2006*, 0965–0992. [\[CrossRef\]](#)
40. Lima, H.M.; Garcia-Barboza, B.J.; Khatibi, N.N.; Lovely, C.J. Total syntheses of isonaamine C and isonaamidine E. *Tetrahedron Lett.* **2011**, *52*, 5725–5727. [\[CrossRef\]](#)
41. Lovely, C.J.; Du, H.; Sivappa, R.; Bhandari, M.R.; He, Y.; Dias, H.V. Preparation and Diels-Alder chemistry of 4-vinylimidazoles. *J. Org. Chem.* **2007**, *72*, 3741–3749. [\[CrossRef\]](#)
42. Heller, S.T.; Sarpong, R. Chemoselective esterification and amidation of carboxylic acids with imidazole carbamates and ureas. *Org. Lett.* **2010**, *12*, 4572–4575. [\[CrossRef\]](#)
43. APEX5, Version 2023.9.2; Bruker AXS Inc.: Madison, WI, USA, 2023.
44. SAINT, Version 8.40B; Includes Xprep and SADABS, Eventuell TWINABS; Bruker AXS Inc.: Madison, WI, USA, 2001.
45. Sheldrick, G.M. SADABS; University of Göttingen: Göttingen, Germany, 1996.
46. Sheldrick, G.M. SHELXT-integrated space-group and crystal-structure determination. *Acta Crystallogr. A* **2015**, *71*, 3–8. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* **2015**, *C71*, 3–8.
48. Spek, A.L. PLATON SQUEEZE: A tool for the calculation of the disordered solvent contribution to the calculated structure factors. *Acta Crystallogr. C* **2015**, *71*, 9–18. [\[CrossRef\]](#) [\[PubMed\]](#)
49. Farrugia, L.J. WinGXandORTEP for Windows: An update. *J. Appl. Crystallogr.* **2012**, *45*, 849–854. [\[CrossRef\]](#)
50. Burnett, M.N.; Johnson, C.K. ORTEP-III Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations; Oak Ridge National Laboratory Report ORNL-6895; Oak Ridge National Laboratory: Oak Ridge, TN, USA, 1996.
51. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lengths in organic compounds. *J. Chem. Soc. Perkin Trans. 2* **1987**, *1987*, S1–S19. [\[CrossRef\]](#)
52. Noland, W.E.; Cole, K.P.; Britton, D. 4,5-Dibromo-1-methyl-1H-imidazole. *Acta Crystallogr. E* **2003**, *59*, o458–o460. [\[CrossRef\]](#)
53. Jimbo, T.; Tsuji, M.; Taniguchi, R.; Sada, K.; Kokado, K. Control of Aggregation-Induced Emission from a Tetraphenylethene Derivative Through the Components in the Co-crystal. *Cryst. Growth Des.* **2018**, *18*, 3863–3869. [\[CrossRef\]](#)
54. Hosten, E.C.; Betz, R. Crystal structure of 4-bromo-1H-imidazole, at 200 K, C₃H₃BrN₂. *Z. Kristallogr. N. Cryst. Struct.* **2015**, *230*, 27–28. [\[CrossRef\]](#)
55. Bondi, A. van der Waals Volumes and Radii. *J. Phys. Chem.* **1964**, *68*, 441–451. [\[CrossRef\]](#)
56. Troff, R.W.; Mäkelä, T.; Topić, F.; Valkonen, A.; Raatikainen, K.; Rissanen, K. Alternative Motifs for Halogen Bonding. *Eur. J. Org. Chem.* **2013**, *2013*, 1617–1637. [\[CrossRef\]](#)
57. Steiner, T. The Hydrogen Bond in the Solid State. *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76. [\[CrossRef\]](#)
58. Gamekkanda, J.; Sinha, A.; Desper, J.; Đaković, M.; Aakeröy, C. The Role of Halogen Bonding in Controlling Assembly and Organization of Cu(II)-Acac Based Coordination Complexes. *Crystals* **2017**, *7*, 226. [\[CrossRef\]](#)
59. Węclawik, M.; Gagor, A.; Piecha, A.; Jakubas, R.; Medycki, W. Synthesis, crystal structure and phase transitions of a series of imidazolium iodides. *CrystEngComm* **2013**, *15*, 5633–5640. [\[CrossRef\]](#)
60. Nwachukwu, C.I.; Bowling, N.P.; Bosch, E. C-I⋯N and C-I⋯pi halogen bonding in the structures of 1-benzylidiodimidazole derivatives. *Acta Crystallogr. C* **2017**, *73*, 2–8. [\[CrossRef\]](#)
61. Wu, Y.; Izquierdo, S.; Vidossich, P.; Lledos, A.; Shafir, A. NH-Heterocyclic Aryliodonium Salts and Their Selective Conversion into N1-Aryl-5-iodimidazoles. *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 7152–7156. [\[CrossRef\]](#)
62. Riwar, L.J.; Trapp, N.; Kuhn, B.; Diederich, F. Substituent Effects in Parallel-Displaced pi-pi Stacking Interactions: Distance Matters. *Angew. Chem. Int. Ed.* **2017**, *56*, 11252–11257. [\[CrossRef\]](#)

63. Spackman, P.R.; Turner, M.J.; McKinnon, J.J.; Wolff, S.K.; Grimwood, D.J.; Jayatilaka, D.; Spackman, M.A. CrystalExplorer: A program for Hirshfeld surface analysis, visualization and quantitative analysis of molecular crystals. *J. Appl. Crystallogr.* **2021**, *54*, 1006–1011. [[CrossRef](#)]
64. Spackman, M.A.; McKinnon, J.J. Fingerprinting intermolecular interactions in molecular crystals. *CrystEngComm* **2002**, *4*, 378–392. [[CrossRef](#)]
65. Nishio, M. The CH/ π hydrogen bond in chemistry. Conformation, supramolecules, optical resolution and interactions involving carbohydrates. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13873–13900. [[CrossRef](#)]
66. Chernysheva, M.V.; Bulatova, M.; Ding, X.; Haukka, M. Influence of Substituents in the Aromatic Ring on the Strength of Halogen Bonding in Iodobenzene Derivatives. *Cryst. Growth Des.* **2020**, *20*, 7197–7210. [[CrossRef](#)]
67. Padgett, C.W.; Dean, R.; Cobb, A.; Miller, A.; Goetz, A.; Bailey, S.; Hillis, K.; McMillen, C.; Toney, S.; Guillet, G.L.; et al. Comparison of N $\cdots$ I and N $\cdots$ O Halogen Bonds in Organoiodine Cocrystals of Heterocyclic Aromatic Diazine Mono-N-oxides. *Cryst. Growth Des.* **2024**, *24*, 2425–2438. [[CrossRef](#)] [[PubMed](#)]
68. Jones, R.H.; Knight, K.S.; Marshall, W.G.; Coles, S.J.; Horton, P.N.; Pitak, M.B. The competition between halogen bonds (Br $\cdots$ O) and C–H $\cdots$ O hydrogen bonds: The structure of the acetone–bromine complex revisited. *CrystEngComm* **2013**, *15*, 8572–8577. [[CrossRef](#)]
69. Kikkawa, S.; Takeno, M.; Nakayama, T.; Koike, D.; Saito, Y.; Tashiro, M.; Aoyama, Y.; Hikawa, H.; Azumaya, I. Effect of Br $\cdots$ O Bonding on the Chiral Assembly of Brominated Amides in the Crystalline Phase. *Cryst. Growth Des.* **2024**, *24*, 9564–9570. [[CrossRef](#)]
70. Fotović, L.; Bedeković, B.; Pičuljan, K.; Stilinović, V. Order versus Disorder in the Cocrystals of m-Halogenopyridines with m-Halogenobenzoic Acids: The Effects of the I $\cdots$ O Halogen Bond. *Cryst. Growth Des.* **2022**, *12*, 7508–7517. [[CrossRef](#)]

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