New Crystal Forms for Biologically Active Compounds. Part 2: Anastrozole as N-Substituted 1,2,4-Triazole in Halogen Bonding and Lp-π Interactions with 1,4-Diiodotetrafluorobenzene

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Abstract: For an active pharmaceutical ingredient, it is important to stabilize its specific crystal polymorph. If the potential interconversion of various polymorphs is not carefully controlled, it may lead to deterioration of the drug’s physicochemical profile and, ultimately, its therapeutic efficacy. The desired polymorph stabilization can be achieved via co-crystallization with appropriate crystallophoric excipients. In this work, we identified an opportunity for co-crystallization of anastrozole (ASZ), a well-known aromatase inhibitor useful in second-line therapy of estrogen-dependent breast cancer, with a classical XB donor, 1,2,4,5-tetrafluoro-3,6-diiodobenzene (1,4-FIB). In the X-ray structures of ASZ·1.5 (1,4-FIB) co-crystal, different non-covalent interactions involving hydrogen and halogen atoms were detected and studied by quantum chemical calculations and QTAIM analysis at the ωB97XD/DZP-DKH level of theory.

Keywords: anastrozole; non-covalent interactions; halogen bonding; lp-π interactions; DFT; QTAIM

1. Introduction

The generation of a new salt form is a proven way to modify the physical and chemical properties of an active pharmaceutical ingredient (API) [1]. To be able to give rise to a new salt form, however, the API in question should be ionizable. For non-ionizable APIs, co-crystallization with a crystallophoric excipient (non-API component of the solid drug form) has become an alternative, proven way of accessing a broad range of solid forms and thus modifying various physicochemical properties and increasing API’s stability [2–4]. An overwhelming majority of API co-crystals reported today are based on hydrogen bonding as the principal means of constructing the crystalline form. However, halogen bonds have emerged as an equally promising basis for designing new co-crystalline API forms [5–12]. However, despite the emergence of this intriguing supramolecular interaction, halogen-bonded API co-crystals remain relatively scarce. This may have to do with the limited range of pharmaceutically acceptable excipients containing polarized halogen atoms [13]. In continuation of our efforts to identify new crystalline forms for APIs that would be stabilized by halogen bonding [14,15], we turned our attention to screening of crystallization conditions for the title compound, anastrozole (IUPAC name 2,2′-(5-(1H-1,2,4-triazol-1-yl)methyl)-1,3-phenylene)bis(2-methylpropanenitrile), abbreviated as ASZ), which is an aromatase inhibitor useful in second-line therapy of estrogen-dependent breast cancer [16–18].
We choose this API as a potential recipient of XB due to its 1,2,4-triazole moiety, containing at least two nucleophilic $N_{sp^2}$ atoms as potential XB acceptor centers. One of them is a hydrogen bond [19] (HB) acceptor in the crystal structure of ASZ itself (Figure 1) [20].

![Figure 1. Structure of anastrozole with assigned hydrogen bond donor (red) and hydrogen bond acceptor centers (blue) found in its crystal structure (SATHOL) [20].](image)

Previously, we successfully cocrystallized another API, nevirapine, with classic XB donor, 1,2,4,5-tetrafluoro-3,6-diiodobenzene (also known as 1,4-diiodotetrafluorobenzene, 1,4-FIB). Noticeably, 1,4-FIB has already been employed in the co-crystal formation for a number of biologically active compounds including nicotine [21], pyrazinamide, lidocaine, and pentoxifylline [22]. It should be noted, however, that in these studies (as well as in present work), 1,4-FIB is employed as an exploratory co-crystallization partner. For its use as an excipient for the design of solid drug forms, a further clinical investigation will be required. In this work, we found ASZ can also be cococrystallized with 1,4-FIB from their solution in MeOH, forming the 2:3 adduct. Herein, we present the results of combined single-crystal XRD experimental and theoretical studies of the adduct and noncovalent interactions found in it.

2. Materials and Methods

2.1. Materials

Anastrozole, 1,2,4,5-tetrafluoro-3,6-diiodobenzene, and MeOH were obtained from a commercial source and used as received.

2.2. X-ray Structure Determination

Crystal of ASZ·1.5(1,4-FIB) was investigated on an Xcalibur, Eos diffractometer at 100 K (monochromated MoKα radiation with $\lambda = 0.71073$ Å). The structure was solved by the direct methods (SHELX program [23]) in the OLEX2 program package [24]. The carbon-bound H atom positions were calculated and included in the refinement in the ‘riding’ model approximation. $U_{iso}(H)$ were set to 1.5$U_{eq}(C)$ (for CH$_3$ groups) or 1.2$U_{eq}(C)$ (for CH$_2$ and CH groups). The C–H bond lengths are 0.98 Å for CH$_3$ groups, 0.99 Å for CH$_2$ groups, and 0.95 Å for CH groups. Empirical absorption correction was applied in the CrysAlisPro [25] program. For crystallographic data and refinement parameters see Supplementary material (Table S3). Supplementary crystallographic data was deposited at Cambridge Crystallographic Data Centre (CCDC 1960975) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
2.3. Powder X-ray Diffraction Experiments

The X-ray diffraction of powder samples was measured at room temperature on a D8 Discover high-resolution diffractometer using monochromated CuKα (λ = 1.54184 Å) radiation.

2.4. Computational Details

The single point calculations based on the experimental X-ray geometry of (ASZ)$_3$(1,4-FIB)$_4$ have been carried out at the DFT level of theory using the dispersion-corrected hybrid functional ωB97XD [26] with the help of the Gaussian-09 [27] program package. The Douglas–Kroll–Hess 2nd order scalar relativistic calculations requested relativistic core Hamiltonian were carried out using the DZP-DKH basis sets [28–31] for all atoms. The topological analysis of the electron density distribution with the help of the atoms in molecules (QTAIM) method developed by Bader [32] has been performed by using the Multiwfn program [33]. The Cartesian atomic coordinates of a model supramolecular cluster are presented in Supporting Information, Table S4.

3. Results and Discussion

3.1. Halogen Bonding in ASZ·1.5(1,4-FIB)

Slow evaporation of a MeOH solution of ASZ with 1,4-FIB taken in a 1:1 ratio leads to the formation on single crystals of ASZ·1.5(1,4-FIB) suitable for the X-ray diffraction experiment. It is notable that we also tried to synthesize the ASZ·1.5(1,4-FIB) pure phase both by mechanical grinding of 2:3 ASZ + 1,4-FIB mixture with MeOH additions during the process or by crystallization of the same 2:3 mixture from methanol with the following grinding of obtained crystalline material. Powder X-ray diffraction experiments for both cases show that ASZ·1.5(1,4-FIB) coexists with some other unidentified phases (see Figures S3 and S4 in SI). For details on the powder x-ray diffraction experiments see also Section 2.3.

According to the single-crystal XRD data, the cocrystallization of ASZ with 1,4-FIB does not lead to any relevant changes, considering the 3σ criterion, in covalent bond lengths of ASZ [20] and 1,4-FIB [34].

As expected, the C–I···N contacts were found in ASZ·1.5(1,4-FIB) (Figure 2), which can be interpreted as halogen bonding [35]. In accordance with their geometrical parameters (Table 1), the theoretically estimated energies of these contacts are 4.6–5.3 kcal/mol (I3S···N2) and 4.8–6.0 kcal/mol (I1S···N3), which is comparable with a lower limit for strength of “moderate” hydrogen bonding according to Jeffrey’s classification (“strong”: 40–15 kcal/mol; “moderate”: 15–4 kcal/mol; “weak”: <4 kcal/mol) [36]. For 1,4-FIB, the molecular electrostatic potential calculations were reported [37–39], which confirm the σ-hole electrophilicity [40,41] of iodine atoms in this molecule.

| C–I···X | d(I···X), Å | R_{IX} | \angle(C–I···X),° |
|---------|-------------|--------|------------------|
| C8S–I3S···N2 | 2.913 (6) | 0.83 | 175.3 (2) |
| C1S–I1S···N3 | 2.883 (7) | 0.82 | 169.3 (2) |
| C4S–I2S···F6S | 3.390 (5) | 0.98 | 149.97 (19) |
| C4S–I2S···I3S | 3.8529 (8) | 0.97 | 157.68 (18) |
| 3.53 (I···N) | | | |
| Comparison | 3.45 (I···F) | 1.00 | 180 |
| 3.96 (I···I) | | | |

a Comparison is the vdW radii sum [42] for distances and classic XB angle. b R_{IX} = d(I···X)/(R_{vdW}(I) + R_{vdW}(X)).
Previously, the C–I···N XBs including 1,2,4-triazole moiety was mentioned only in two metal-organic frameworks (FALNEN [43] and UMOTOG [44]) and one free 4H-1,2,4-triazole (FARCIN01 [45]). We analyzed all the structures containing the C–I···N XBs with 1,2,4-triazoles in CCDC and found 9 more structures [44,46–52]. It is notable that in all corresponding works, these interactions were not even mentioned. The I···N distances are in the range of 2.839 (4)–3.378 (3) Å, and the ∠(C–I···N) angles vary from 157.18 (17) to 177.57 (8)° (for details see Table S1 in supplementary materials). In ASZ·1.5 (1,4-FIB), both distances (2.883 (7) and 2.913 (6) Å) are shorter than in most previously published structures, which can be explained by the electron-withdrawing I substituent in 1,4-FIB. Noticeably, the C–Cl···N [53–55] and C–Br···N [45,53,56–58] XBs including 1,2,4-triazole moiety are also mentioned in the literature.

Halogen bonding was also found between 1,4-FIB molecules, represented by bifurcated C–I···(I,F) contact (Figure 3). Both distances are less than vdW sums, and both angles are around 150° (Table 1) and fall into an acceptable value for XBs. These non-covalent interactions are weak, viz. 1.3 kcal/mol in the case of I2S···F6S and 1.6 kcal/mol in the case of I2S···I3S.

A resembling feature can be found in the structure KUWRAX [59], where both I···F and I···I distances are less than the corresponding vdW sums (3.6889 (7) vs 3.96 Å and 3.409 (3) vs 3.45 Å), however, in this structure, the corresponding ∠(C–I···F) angle (125.09 (13)°) is not high enough to recognize this interaction as halogen bonding. Thus, ASZ·1.5 (1,4-FIB) demonstrates the first example of bifurcated C–I···(I,F) halogen bonding between 1,4-FIB molecules.
3.2. Lone-Pair–π Interactions in ASZ·1.5(1,4-FIB)

Besides the expected C⋯I–N halogen bonding, the C⋯I–C contacts (Table 2) were identified between ASZ and 1,4-FIB molecules in ASZ·1.5(1,4-FIB) (Figure 4). According to the \( \angle (C\cdots I–C) \) angle, which is close to 90° (Table 2), this interaction can be interpreted as lp(I)⋯π(C) interaction [60]. Their theoretically estimated strength is 1.6 kcal/mol.

![Figure 4. The lp(I)⋯π(C) interaction between ASZ and 1,4-FIB molecules in ASZ·1.5(1,4-FIB).](image)

| C⋯I–C          | \( d(C\cdots I) \), Å | \( R_{CI} \) | \( \angle (C\cdots I–C) \),° |
|----------------|------------------------|-------------|-----------------------------|
| C9⋯I1S–C1S     | 3.528 (8)              | 0.96        | 86.6 (3)                    |
| C9S⋯I2S–C4S    | 3.686 (8)              | 1.00        | 92.9 (3)                    |
| Comparison     | 3.68                   | 1.00        | 90                          |

\( ^{a} \) Comparison is the vDW radii sum [42] for distances and classic XB acceptor angle. \( ^{b} \) \( R_{CI} = \frac{d(C\cdots I)}{(R_{vdW}(I) + R_{vdW}(C))} \).

Previously, the lp(I)⋯π(C) interactions including 1,2,4-triazole moiety were discussed only for five 1,2,4-triazolium iodides [61,62], where these interactions are interionic. We analyzed the CCDC data and identified 23 more structures with the C⋯I interactions including 1,2,4-triazoles. 1,2,4-triazolium iodides [20,63–70] were also found in 15 structures. The C⋯I–M interactions [71–76] in 1,2,4-triazole-containing MOFs were detected in 6 structures. Structure XIWGOC contains the C⋯I–C interactions between neutral isolated molecules [78] identified. The C⋯I distances vary from 3.4363(2) to 3.670 (3) Å (for details see Table S2), and the C9⋯I1S distance (3.528 (8) Å) in ASZ·1.5(1,4-FIB) is within this range.

Besides, possible lp(I)⋯π(C) interaction between 1,4-FIB molecules was found (Figure 5). Although the C⋯I distance is around the vDW sum (3.686 (8) vs 3.68 Å), further theoretical calculations performed on experimentally determined atomic coordinates (see next section) confirmed the existence of the interaction and its noncovalent nature (estimated energy is 0.9–1.1 kcal/mol). Notably, the same interactions were found by us for 1,4-FIB and other iodofluorobenzenes [60,79,80].

Figure 5. The lp(I)⋯π(C) interaction between 1,4-FIB molecules in ASZ·1.5(1,4-FIB).
3.3. Hydrogen Bonding in ASZ·1.5(1,4-FIB)

As well as in the structure of free ASZ, cyano N atoms are involved in weak hydrogen bonding (theoretically estimated strength of appropriate contacts vary from 0.9 to 1.9 kcal/mol) (Figure 6 and Table 3). Apart from methyl H atoms, the hydrogen atom in the methylene group is also an HB donor, which was not observed in the ASZ structure previously.

![Figure 5. The lp(I)···π(C) interaction between 1,4-FIB molecules in ASZ·1.5(1,4-FIB).](image)

![Figure 6. The C–H···N HBs in ASZ·1.5(1,4-FIB).](image)

**Table 3. Parameters of the C–H···N HBs in ASZ·1.5(1,4-FIB).**

| C–H···N | \(d(H\cdot\cdot\cdotN)\) Å | \(R_{HN}\) Å | \(d(C\cdot\cdot\cdotN)\) Å | \(\angle(C–I\cdot\cdot\cdotX)\)° |
|---------|-----------------|-------------|-----------------|-----------------|
| C7–H7A···N5 | 2.484 | 0.90 | 3.441 (10) | 168.6 |
| C16–H16B···N4 | 2.733 | 0.99 | 3.62 (1) | 153.9 |

*Comparison* a

\(a\) Comparison is the vdw radii sum [42] for distances and minimal HB angle. \(b\) \(R_{HN} = d(H\cdot\cdot\cdotN)/(R_{vdW}(H) + R_{vdW}(N))\).

3.4. Theoretical Study of Different Non-covalent Interactions in ASZ·1.5(1,4-FIB)

The supramolecular structure of ASZ·1.5(1,4-FIB) is formed by various non-covalent contacts (viz. lp-π interactions, hydrogen, and halogen bonding). We performed quantum chemical calculations and QTAIM analysis [32] to study the nature and energies of these non-covalent contacts in a model supramolecular cluster (ASZ)_{3}(1,4-FIB)_{4} based on the appropriate X-ray diffraction data (Supporting Information, Table S4). This approach depends very slightly on the basis set [81,82] or method [83,84] used and it was already successfully used by us previously for similar chemical systems [14,15,79,85,86] and upon studies of different non-covalent interactions (e.g., hydrogen/chalcogen/halogen bonds, stacking interactions, metallophilic interactions) in other organic and inorganic compounds [14,15,87–92]. The results of QTAIM analysis are presented in Table 4 and visualized in Figure 7.
The distinctive features of the crystal structures obtained and characterized in detail in this work are the presence of XBs with both triazole N atoms, firstly found for anastrazole. Apart from that, the adduct structure demonstrates the lp(I)···π(triazole) attractive interactions, which may also be important for the adduct.

4. Conclusions

In combination with 1,2,4,5-tetrafluoro-3,6-diiodobenzene, a classical XB donor, we have identified a new halogen-bonded solid for anastrozole, an anticancer aromatase inhibitor drug. These findings continue to provide proof-of-principle for the productive employment of halogen bonds in the design and discovery of stable crystalline forms of important drug substances. Moreover, these results suggest that the range of potential XB donors for co-crystallization with basic nitrogen-rich molecular frameworks can potentially be expanded beyond the classical ones. The distinctive features of the crystal structures obtained and characterized in detail in this work are the presence of XBs with both triazole N atoms, firstly found for anastrazole. Apart from that, the adduct structure demonstrates the lp(I)···π(triazole) attractive interactions, which may also be important for the adduct.
formation. The findings encourage us to continue searching for yet novel opportunities to detect XBs as indispensable forces leading to the formation of a new crystal. The results of these studies will be reported in due course.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/2073-4352/10/5/371/s1, Figure S1: Structural motifs around the C–I···N XBs including 1,2,4-triazole moiety in CCDC structures; Figure S2: Structural motifs around the lp(I)···C interactions including 1,2,4-triazole moiety in CCDC structures; Figure S3: Powder X-ray diffraction data (blue line) of mixture, obtained by mechanical grinding of 2ASZ + 3(1,4-FIB) mixture with MeOH additions; Figure S4: Powder X-ray diffraction data (blue line) of mixture, obtained by grinding of crystalline material grown from 2ASZ + 3(1,4-FIB) solution in methanol; Table S1: Parameters of the C–I···N XBs including 1,2,4-triazole moiety in CCDC structures; Table S2: Parameters of the lp(I)···C interactions including 1,2,4-triazole moiety in CCDC structures; Table S3: Crystal data and structure refinement for ASZ 1.5(1,4-FIB); Table S4: Cartesian atomic coordinates of model supramolecular cluster.

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