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Crystal Engineering of Novel Cocrystals of a Triazole Drug with 1,4-Dicarboxylic Acids

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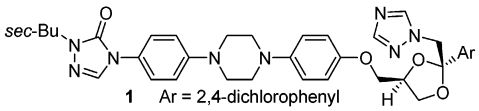
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Crystal engineering of pharmaceutical solids represents a fertile, emerging area of research.[1,2] The impetus for discovery of diverse crystal forms of drugs stems from the critical need to balance stability, bioavailability, and other performance characteristics, and also to provide valuable intellectual property protection. In the case of poorly water-soluble drugs, the dissolution rate and oral absorption of the compound can be strongly influenced by the physical state of the drug.[3] Current strategies to deal with inadequate solubility, dissolution rate, and absorption of neutral crystal forms include salt formation,[4] physical stabilization of amorphous solids,[5] complexation,[6−8] or encapsulation of organic solutions.[9] The use of a crystalline solid is nearly always the best approach for limiting physical and chemical instability of a marketed drug.[5] In addition to stability and bioavailability, crystal form characteristics such as morphology and moisture sorption can impact pharmaceutical development. The challenges of pharmaceutical research and development provide a unique opportunity to showcase the power and utility of crystal engineering to solve real-world problems.[10]

Itraconazole (**1**) is an example of an extremely water-insoluble antifungal drug that is marketed in the amorphous form (Sporanox capsule) to achieve the required oral bioavailability (Table 1).[11] Co-administration of acidic beverages with Sporanox capsules is required to achieve maximum absorption of the weak base.[12] Although the use of an acid addition salt would seem to be a logical strategy for improving the absorption properties of **1**, a survey of the patent literature failed to reveal specific reports of crystalline salts of **1**. Solution chemistry suggests that a pK_a difference of two units between acid and base is needed to form a salt that is stable in water.[13] Given the pK_a value of 3.7 for the piperazine of **1**, conventional wisdom would limit a salt screen to those strong acids having dissociation constants below 1.7. However, recent examples[1,2] illustrate that crystalline phases can be engineered by combining molecules[14] selected to match hydrogen-bond donors with acceptors and by considering structural complementarities. In short, it is becoming clear that supramolecular synthesis[15] can be applied to active pharmaceutical ingredients in the same way that it has been applied in model compounds.[16] These systems, referred to as cocrystals, could be extended to include organic acid and base combinations with pK_a differences that are inconsistent with salt formation in water. On the basis of these premises, a high-throughput (HT) crystallization screen was conducted to search for salts and cocrystals of **1** with a large number of pharmaceutically acceptable acids, which were chosen to provide a wide range of dissociation constants, shapes, sizes, and heterosynthons.

We report here the discovery of stable cocrystals consisting of hydrogen-bonded trimers of two molecules of **1** and one molecule of a 1,4-dicarboxylic acid resulting from a HT crystallization screen for **1**. The crystal structure of one congener (Figure 1) reveals an unanticipated and specific interaction between the triazole of **1** and the diacid in the solid state, which suggests a new heterosynthon for cocrystallizing triazole-containing compounds into binary (and potentially higher order) phases.[17]

Table 1. Cocrystal Forms of *cis*-Itraconazole (**1**)



1 Ar = 2,4-dichlorophenyl

$[\mathbf{1}]_2X$	X	$[\mathbf{1}]_2X$	X
2a	fumaric acid	**2d**	L-tartaric acid
2b	succinic acid	**2e**	D-tartaric acid
2c	L-malic acid	**2f**	DL-tartaric acid

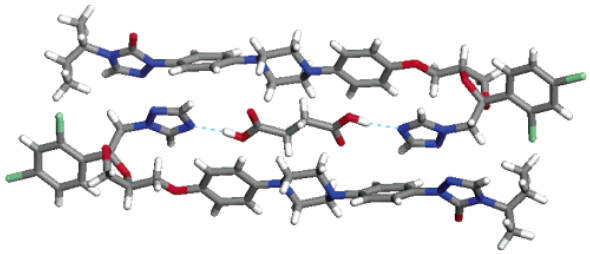


Figure 1. Trimer unit of **2b** from the single-crystal X-ray structure.

Multicomponent crystals of **1** formed from polar aprotic solvents or solvent mixtures of hydrocarbons with polar aprotic solvents and required the presence of dicarboxylic acids. Polar protic solvents, including water and C_{1-3} alcohols, yielded only crystalline free base of **1**, suggesting that H-bond donating solvents interfere with cocrystal formation. Likewise, no salts or cocrystal forms of **1** were found with monoprotic carboxylic acids, such as acetic and benzoic acid. The ratio of **1** to diacid in the binary phases of **1** with fumaric acid (**2a**) and DL-tartaric acid (**2f**) was shown to be 2:1 by solution ^{1}H NMR of dissolved crystal samples. Thus, it appeared that 1 equiv of a dicarboxylic acid was tethering two drug molecules. Additional diacid−**1** combinations, selected on the basis of their similarity to fumaric and tartaric acid, containing 0.5 equiv of diacid relative to **1** yielded crystalline compounds **2b**−**2e** from THF. Compound **2b** is perhaps the most surprising of these, because succinic acid has pK_a values of 4.2 and 5.6, both of which exceed the pK_a of the conjugate acid of **1**. Maleic acid, with *Z* regiochemistry around the C=C bond, is the only 1,4-dicarboxylic acid tested that has not produced cocrystals with **1**, despite being the strongest acid (pK_{a1} of 1.9). Cocrystals could not be made with **1** and malonic, glutaric, or adipic acid. The results indicate that

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geometric fit may be more important than acid−base chemistry in directing crystallization of **1** with 1,4-dicarboxylic acids.

Hexagonal platelike crystals of **2b** were grown for single-crystal X-ray structure determination from a solution in 10/2/1 1,2-dichloroethane/ethyl acetate/1,4-dioxane. Figure 1 shows the trimeric building block from the single-crystal structure. The two molecules of **1** are oriented in antiparallel fashion to form a pocket with a triazole at either end. The extended succinic acid molecule fills the pocket, bridging the triazole groups.[18] Interestingly, interaction between the 1,4-diacid and the strongest base on **1** (piperazine) is absent in the structure of **2b**, but we cannot rule out an interaction of the α hydroxyl groups on tartaric or malic acid with the piperazine nitrogens.[19] There are no current examples of a 1,2,4-triazole-1,4-dicarboxylic acid cocrystal structure in the Cambridge Structural Database (CSD).[20] It should be noted that the crystal structure contains only two of the four stereoisomers of **1**; studies probing enantiomeric enrichment are ongoing.

Identification of multiple crystal forms of the same drug with acceptable solubility, dissolution, and stability allows for selection of the optimal form for dosage form development. To demonstrate this feature, the dissolution of the cocrystals in aqueous medium was studied to assess their potential impact on bioavailability of the drug from a solid dosage form. Figure 2 compares the dissolution profiles of **2b**−**d** into 0.1 N HCl to those of crystalline **1** (95% of all crystalline particles < 10 μm) and commercial Sporanox beads (amorphous **1**). Crystal form **2c** rivals the dissolution of the commercial product containing amorphous **1**. In general, the cocrystals behave more similarly to Sporanox than to crystalline **1**. The cocrystal forms achieve and sustain from 4- to 20-fold higher concentrations than that achieved from crystalline **1**. The practical implication is significant, because the ability to form a supersaturated solution, even transiently, can have a dramatic impact on absorption and bioavailability.[21]

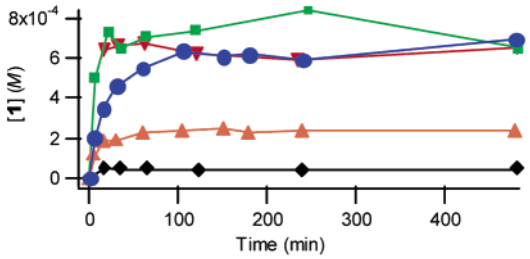


Figure 2. Dissolution profiles into 0.1 N HCl at 25 °C for Sporanox beads (■), **2c** (▼), **2d** (●), **2b** (▲), and **1** (◆).

Crystal morphology and particle size are important for handling of a drug substance and for reliable manufacture of dosage forms with uniform drug content. The morphology of the cocrystals of **1** ranges from fine needles for **2a** and **2d**−**f**, to needles or rectangular plates for **2c**, and hexagonal plates for **2b**. Form **2b** is particularly easy to filter and dry to a free-flowing powder.

In conclusion, cocrystals of **1** possessing diverse physical properties have been engineered on the basis of structures identified from HT crystallization. The solubility and dissolution properties of cocrystals can be similar to those of the amorphous compound and superior to the crystalline pure phase, thus presenting opportunities to increase bioavailability even in cases where stable, crystalline salt forms cannot be found. It is clear that satisfying the geometric constraints is a criterion of cocrystal formation and must be considered when attempting to tailor crystal forms. The observation that the acid moieties in **2b** do not associate with the strongest base in **1** is inconsistent with the principle of strongest-to-strongest interactions dominating self-assembly.[22] Differences in pK_a in water may not reliably predict interactions in the solid state or the capacity for a drug and salt-former to form cocrystals. Thus, studies limited to systems that follow the generally accepted rules of matching pK_a values to ensure a strong salt pair in water are likely to overlook real opportunities for producing optimal medicines with minimal process and formulation issues.

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Supporting Information Available: Micrographs and powder X-ray diffraction patterns for **2a**−**2f** (PDF); crystallographic data from **2b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Seddon, K. R.; Zaworotko, M. *Crystal Engineering: The Design and Application of Functional Solids*; NATO-ASI Series; Kluwer: Norwell, MA, 1999; Vol. 539.
(11) Sporanox capules (made by Janssen Pharmaceutica) contain amorphous itraconazole coated on 0.4−0.5 mm diameter sucrose spheres. Other inactive ingredients include hydroxypropyl methylcellulose, poly(ethylene glycol) (PEG) 20 000, and starch.
(12) Only about 30% bioavailability of **1** is achieved from commercial Sporanox capsules under optimal conditions, while up to 55% can be absorbed from the marketed solution formulation in acidified HP-β-cyclodextrin (Physician's Desk Reference, Electronic Library, Thomson MicroMedex Inc., 2003).
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(17) $2(C_{35}H_{38}Cl_2N_8O_4)\cdot C_4H_6O_4$; $P2_1/c$; a = 30.145(4) Å, b = 5.7435(7) Å, c = 21.580(3) Å, β = 105.133(2)°; Z = 4; T = 100(2) K; GOF = 1.010; R^2 = 0.0925; wR^2 = 0.2153.
(18) The bond distances (N···O = 2.755 Å and (C═O)O−H = 0.925 Å) and the N···H−O bond angle (170.4°) are consistent with a hydrogen-bonding interaction between the 4-nitrogen of each 1,2,4-triazole and a carboxylic acid moiety. The carboxylic acid bond distances (C1B···O1B = 1.205(5) Å and C1B···O2B = 1.326(4) Å) indicate that the acid proton has not been transferred to the triazole. Furthermore, a peak consistent with intensity normally observed for protons was located from the difference map at 0.961(2) Å from O2B along the O2B···N3 vector.
(19) In the crystal structure of Figure 1, the α carbon pro-S hydrogen of succinic acid that is closest to a piperazine nitrogen is 2.65 Å, and the angle is 131°.
(20) A search of the CSD using ConQuest v. 1.5 revealed one example of intermolecular hydrogen bonding between a triazole and a carboxylic acid (REFCODE KOPSOX) and seven examples where a triazole is protonated by a carboxylic acid. There are many examples of hydrogen-bonding interactions between carboxylic acids and heterocyclic nitrogen in the CSD.
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