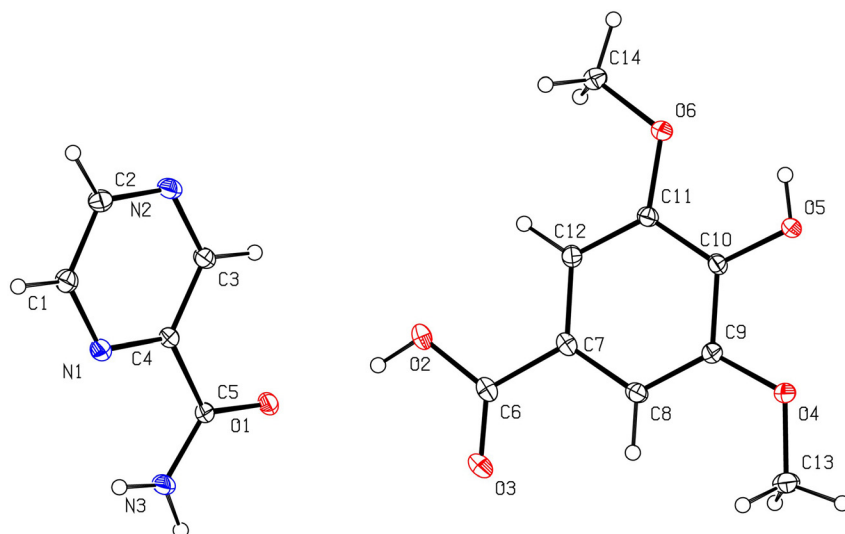


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# The crystal structure of the cocrystal 4-hydroxy-3,5-dimethoxybenzoic acid–pyrazine-2-carboxamide(1/1), $C_{14}H_{15}N_3O_6$



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## Abstract

$C_{14}H_{15}N_3O_6$ , monoclinic,  $C2/c$  (no. 15),  $a = 30.1620(13)$  Å,  $b = 3.8559(2)$  Å,  $c = 27.3897(13)$  Å,  $\beta = 117.610(4)^\circ$ ,  $V = 2822.7(3)$  Å<sup>3</sup>,  $Z = 8$ ,  $R_{gt}(F) = 0.0332$ ,  $wR_{ref}(F^2) = 0.0904$ ,  $T = 170$  K.

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The molecular structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

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**Table 1:** Data collection and handling.

|                                                                            |                                                    |
|----------------------------------------------------------------------------|----------------------------------------------------|
| Crystal:                                                                   | Colourless block                                   |
| Size:                                                                      | $0.48 \times 0.32 \times 0.25$ mm                  |
| Wavelength:                                                                | MoK $\alpha$ radiation (0.71073 Å)                 |
| $\mu$ :                                                                    | $0.12 \text{ mm}^{-1}$                             |
| Diffractometer, scan mode:                                                 | Bruker D8 Venture, $\varphi$ and $\omega$          |
| $\theta_{\text{max}}$ , completeness:                                      | $27.1^\circ$ , >99%                                |
| $N(hkl)_{\text{measured}}$ , $N(hkl)_{\text{unique}}$ , $R_{\text{int}}$ : | 26886, 3108, 0.023                                 |
| Criterion for $I_{\text{obs}}$ , $N(hkl)_{\text{gt}}$ :                    | $I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$ , 2917 |
| $N(\text{param})_{\text{refined}}$ :                                       | 212                                                |
| Programs:                                                                  | Bruker [1], Olex2 [2], SHELX [3, 4]                |

## Source of material

The mixture of pyrazinamide and syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid) with a molar ratio of 1:1 was dissolved in ethyl acetate, and the resulting mixed solution was stirred at a constant temperature water bath at 50 °C to obtain a clear solution. The solution was filtered and placed in a sample vial, covered with membrane which was punctured. The filtrate was slowly evaporated at room temperature to obtain crystals of the title compound after seven days.

## Experimental details

Absorption corrections were applied by using multi-scan program [1]. Using Olex2 [2], the structure was solved with

**Table 2:** Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å<sup>2</sup>).

| Atom | x           | y          | z           | <i>U</i> <sub>iso</sub> */ <i>U</i> <sub>eq</sub> |
|------|-------------|------------|-------------|---------------------------------------------------|
| O1   | 0.56662 (3) | 0.0655 (2) | 0.54435 (3) | 0.02445 (18)                                      |
| N1   | 0.60173 (3) | 0.5166 (2) | 0.45423 (4) | 0.0218 (2)                                        |
| N2   | 0.69684 (3) | 0.3579 (3) | 0.53927 (4) | 0.0249 (2)                                        |
| N3   | 0.51929 (3) | 0.2810 (3) | 0.45875 (4) | 0.0259 (2)                                        |
| H3A  | 0.491294    | 0.205486   | 0.457612    | 0.031*                                            |
| H3B  | 0.518530    | 0.394685   | 0.430512    | 0.031*                                            |
| C1   | 0.64322 (4) | 0.6002 (3) | 0.45116 (4) | 0.0242 (2)                                        |
| H1   | 0.640595    | 0.720280   | 0.419648    | 0.029*                                            |
| C2   | 0.69032 (4) | 0.5150 (3) | 0.49321 (4) | 0.0245 (2)                                        |
| H2A  | 0.718939    | 0.571263   | 0.488832    | 0.029*                                            |
| C3   | 0.65518 (4) | 0.2764 (3) | 0.54266 (4) | 0.0222 (2)                                        |
| H3   | 0.657912    | 0.166425   | 0.574972    | 0.027*                                            |
| C4   | 0.60813 (3) | 0.3495 (3) | 0.49992 (4) | 0.0184 (2)                                        |
| C5   | 0.56231 (4) | 0.2240 (3) | 0.50270 (4) | 0.0193 (2)                                        |
| O2   | 0.61489 (3) | 0.2606 (3) | 0.65175 (3) | 0.0328 (2)                                        |
| H2   | 0.595774    | 0.212153   | 0.618624    | 0.049*                                            |
| O3   | 0.54274 (3) | 0.4049 (3) | 0.65135 (3) | 0.0338 (2)                                        |
| O4   | 0.60475 (3) | 0.8957 (2) | 0.84733 (3) | 0.02575 (19)                                      |
| O5   | 0.70135 (3) | 0.8013 (2) | 0.89552 (3) | 0.02545 (19)                                      |
| H5   | 0.732144    | 0.780853   | 0.905804    | 0.038*                                            |
| O6   | 0.74877 (3) | 0.4689 (2) | 0.84692 (3) | 0.02410 (18)                                      |
| C6   | 0.58786 (4) | 0.3805 (3) | 0.67547 (4) | 0.0231 (2)                                        |
| C7   | 0.61908 (4) | 0.4811 (3) | 0.73399 (4) | 0.0203 (2)                                        |
| C8   | 0.59544 (4) | 0.6379 (3) | 0.76150 (4) | 0.0206 (2)                                        |
| H8   | 0.560301    | 0.674983   | 0.743037    | 0.025*                                            |
| C9   | 0.62340 (4) | 0.7399 (3) | 0.81596 (4) | 0.0195 (2)                                        |
| C10  | 0.67530 (4) | 0.6872 (3) | 0.84306 (4) | 0.0191 (2)                                        |
| C11  | 0.69814 (4) | 0.5182 (3) | 0.81547 (4) | 0.0188 (2)                                        |
| C12  | 0.67039 (4) | 0.4186 (3) | 0.76080 (4) | 0.0200 (2)                                        |
| H12  | 0.686214    | 0.309061   | 0.741916    | 0.024*                                            |
| C13  | 0.55209 (4) | 0.9394 (3) | 0.82403 (5) | 0.0292 (3)                                        |
| H13A | 0.540312    | 1.083520   | 0.790878    | 0.044*                                            |
| H13B | 0.543925    | 1.052702   | 0.850882    | 0.044*                                            |
| H13C | 0.535728    | 0.712219   | 0.814259    | 0.044*                                            |
| C14  | 0.77398 (4) | 0.2809 (3) | 0.82252 (4) | 0.0242 (2)                                        |
| H14A | 0.771375    | 0.407308   | 0.790254    | 0.036*                                            |
| H14B | 0.758633    | 0.051426   | 0.811122    | 0.036*                                            |
| H14C | 0.809313    | 0.254247   | 0.849353    | 0.036*                                            |

the ShelXT [3] structure solution program using Intrinsic Phasing and refined with the ShelXL [4] refinement package. The H atoms were fixed, fixed *U*<sub>iso</sub> were set to 1.2 times of all C(H) groups and N(H,H) groups; 1.5 times of C(H,H,H) groups and O(H) groups.

## Comment

Pyrazinamide (PZA) belongs to nicotinamide analogs. Because of its good antibacterial activity and strong bactericidal effect, it is widely used in the treatment of tuberculosis in clinical practice. However, due to its low water solubility

and low bioavailability, its oral absorption effect is severely inhibited. In recent years, drug co-crystal technology, as an emerging technology, enhances the efficacy of drugs by improving the solubility and permeability of drugs [5]. Compared with other crystal engineering techniques, drug co-crystals have unique advantages in reviving older small-molecule drugs. Cocrystals of pyrazinamide were obtained with 2,4-dihydroxybenzoic acid (CCDC: 1554966, NEFFEM), 2,3-dihydroxybenzoic acid (CCDC: 1554791, NEFGIR), 2,6-dihydroxybenzoic acid (CCDC: 1554970, NEFGEN) [6], pyrogallol (CCDC: 904232, HEDRAL), temozolomide (CCDC: 926521, KIJSER) [7], fumaric acid (CCDC: 849830, LATTIL), succinic acid (CCDC: 849831, LATTOR) [8] and so on.

The is one 4-hydroxy-3,5-dimethoxybenzoic acid molecule and one pyrazine-2-carboxamide molecule in the asymmetric unit (see the figure). In the unit cell of the title crystal, the main forces include the p-p stacking between the pyrazine ring and the benzene ring, and the formation of intermolecular hydrogen bonds between the amide group on pyrazinamide and the carboxyl group on syringic acid. The O1 atom on the amide group of the pyrazinamide molecule is a hydrogen bond acceptor, and the H2 atom on the carboxyl group (O2–H2) of syringic acid is a hydrogen bond donor, forming an intermolecular hydrogen bond [O2–H2–O1; *d*(O2–O1) = 2.7145(10) Å]. The N2 atom on the pyrazine ring is a hydrogen bond acceptor, and the H5 atom on the hydroxyl group (O5–H5) of the syringic acid molecule acts as a hydrogen bond donor, forming an intermolecular hydrogen bond [O5–H5–N2; *d*(O5–N2) = 2.7538(11) Å]. Amides on pyrazinamide molecules form intramolecular hydrogen bonds [O1–H3A–N3; *d*(O1–N3) = 2.8814(12) Å].

The structure of the pure 4-hydroxy-3,5-dimethoxybenzoic acid has been reported [9]. It has also been shown that cocrystals of this acid with pyridine-3-carboxamide can be obtained [9].

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