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A 1:1 cocrystal of baicalein with nicotinamide

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Cocrystallization of baicalein with nicotinamide yields a 1:1 cocrystal [systematic name: pyridine-3-carboxamide–5,6,7-trihydroxy-2-phenyl-4*H*-chromen-4-one (1/1)], $C_6H_6N_2O\cdot C_{15}H_{10}O_5$. The asymmetric unit contains one baicalein and one nicotinamide molecule, both in neutral forms. Molecules in the cocrystal form column motifs stabilized by an array of intermolecular hydrogen bonds.

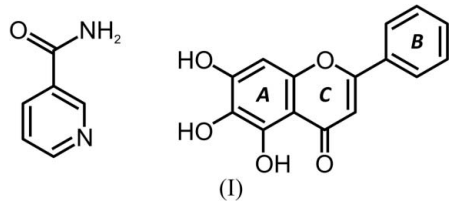
Comment

Flavones, members of the flavonoid family, are low molecular weight plant polyphenolic compounds with a wide range of biological activities (Verma & Pratap, 2010). Baicalein (5,6,7-trihydroxyflavone) is one of the main bioactive compounds found in roots of the traditional Chinese herb *Scutellaria baicalensis* (Olennikov *et al.*, 2010). It has been shown to inhibit iron-induced lipid peroxidation (Perez *et al.*, 2009) and induce apoptosis in HIV-infected cells *in vitro* (Ono *et al.*, 1989), and research into its anticancer (Miocinovic *et al.*, 2005), antioxidant (Shao *et al.*, 2002) and anti-inflammatory (Chou *et al.*, 2003) properties has shown good results.

By virtue of the fact that flavonoids (including baicalein) have low solubility in water and therefore low bioavailability (Zhang *et al.*, 2005, 2007), the discovery and identification of new solid forms of them is highly desirable. A convenient way of modifying the physicochemical properties and pharmacokinetic parameters of active compounds of pharmaceutical interest (active pharmaceutical ingredients, APIs) is cocrystallization with a substance generally regarded as safe (GRAS) (Schultheiss & Newman, 2009, and references therein). This gives rise to novel supramolecular complexes which generally exhibit enhanced solubility and dissolution rates compared with their constituent components. Recently, the structures of quercetin cocrystals with caffeine (MeOH solvate; Smith *et al.*, 2011), isonicotinamide (Smith *et al.*, 2011) and theobromine [dihydrate; Cambridge Structural Database (CSD; Allen, 2002) refcode MUPPOD (Clarke *et al.*, 2010)] have been determined, and their solubility and oral bioavailability have been shown to be improved over that of quercetin (Smith *et al.*, 2011).

Nicotinamide (NA) belongs to the vitamin B group (vitamin B3) and is classified as a GRAS substance. Therefore, this molecule is widely used in the cocrystallization of carboxylic acid functionalized APIs (Berry *et al.*, 2008). Recently, two cocrystals of orcinol (3,5-dihydroxytoluene) with NA were reported (CSD refcodes EWAQEZ and EWAQAV; Mukherjee *et al.*, 2011), showing that NA can be successfully applied to the cocrystallization of hydroxy-functionalized APIs.

Herein, the 1:1 cocrystal of baicalein with nicotinamide, (I), is reported. The asymmetric unit of (I) comprises one baicalein and one nicotinamide molecule, both in their neutral forms (Fig. 1).



(I)

It is common among flavones that two rings of the phenylbenzopyran entity, referred to as *A*/*C* (benzopyran), are conjugated and coplanar, while the third one, *B* (phenyl), is usually out of this plane. In (I), the mean planes defined by the *A*/*C* and *B* rings of baicalein are inclined to each other with a dihedral angle of 20.0 (2)°. This is higher than the values of 8.6 and 9.7° determined for baicalein crystals grown from, respectively, a methanol–water mixture (CSD refcode RAMGOB; Rossi *et al.*, 2001) and ethyl acetate (CSD refcode RAMGOB01; Hibbs *et al.*, 2003). Typically, the cocrystallization of flavonoids leads to a change in the angle between the *A*/*C* and *B* ring planes. This can be illustrated by comparing the values of these angles in quercetin–caffeine methanol solvate (Smith *et al.*, 2011) and quercetin–isonicotinamide (Smith *et al.*, 2011) cocrystals (0.2 and 24.0°, respectively) with the values of 8.1 and 22.0°, respectively, for quercetin dihydrate (CSD refcode FEFBEX01; Jin *et al.*, 1990) and quercetin pyridine solvate (CSD refcode NIXLUC; O'Mahony *et al.*, 2006).

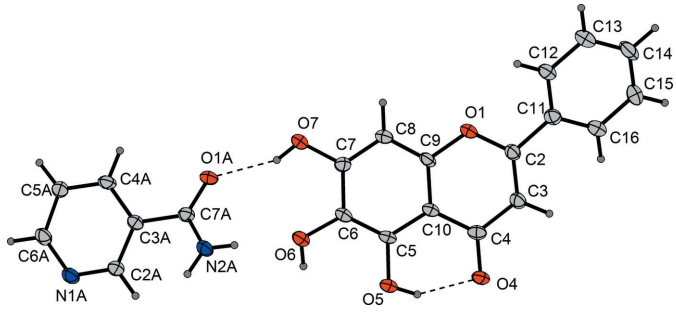


Figure 1
The molecular complex of (I), showing the atom-numbering scheme and the symmetry-independent hydrogen bonds (dashed lines). Displacement ellipsoids are drawn at the 50% probability level.

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The overall geometry of baicalein and NA in (I) is similar to that determined for the parent components. A twist of the amide group of NA relative to its pyridine ring plane is reflected in the value of the O1*A*—C7*A*—C3*A*—C4*A* torsion angle [−28.2 (5)°, Table 1] and reveals a similar conformation to that of the pure nicotinamide crystal (CSD refcode NICOAM01; Miwa *et al.*, 1999).

The supramolecular arrangement in flavonoid cocrystals depends on the number of hydroxy substituents on the flavonoid backbone, as well as on the crystallization conditions (Timmons *et al.*, 2008). Quercetin, hesperetin and apigenin exhibit hydroxy substitution on both benzopyran and phenyl rings, which facilitates the formation of O—H···O and N—H···O hydrogen-bonded two- or three-dimensional structures. Accordingly, quercetin cocrystals with caffeine (MeOH solvate; Smith *et al.*, 2011), isonicotinamide (Smith *et al.*, 2011), theobromine (dihydrate; CSD refcode MUPPOD; Clarke *et al.*, 2010) and triethylenediamine (CSD refcode COLHIV; Timmons *et al.*, 2008) reveal two-dimensional hydrogen-bonded networks, and a three-dimensional network has been observed in the quercetin–isonicotinic acid zwitterion hydrate cocrystal (CSD refcode RUWHUN; Kavuru *et al.*, 2010). Similarly, the hesperetin–isonicotinamide cocrystal (Kavuru, 2008) comprises molecules arranged into a two-dimensional sheet, while hesperetin–nicotinic acid zwitterion cocrystals (CSD refcodes RUWHEX and RUWHIB; Kavuru *et al.*, 2010) and the apigein triethyelenediamine cocrystal (Timmons *et al.*, 2008) reveal the formation of one-dimensional extended structures.

Baicalein contains a trihydroxy-substituted benzopyran ring, therefore having three potential hydrogen-bond donor atoms (O5, O6 and O7). In the crystal structure of (I), hydroxy atom O5 of each baicalein molecule acts as an H-atom donor in an intramolecular O5—H5···O4 hydrogen bond, which is common to all 5-hydroxyflavone derivatives known so far. The remaining atoms O6 and O7 act as H-atom donors in intermolecular interactions (Table 2). Each baicalein molecule is also joined to two adjacent inversion-related nicotinamide molecules, leaving no possibility for further extension into a two-dimensional structure. Similarly, 3,6-dihydroxyflavone possesses two potential hydrogen-bond donor atoms on the benzopyran ring (O3 and O6), facilitating the formation of one-dimensional helices or ribbons with a bidentate cocrystal former (CSD refcodes COLHAN and COLHIV, respectively; Timmons *et al.*, 2008).

An intermolecular O7—H7···O1*A* hydrogen bond forms a baicalein–NA heterodimer (Figs. 1 and 2*a*, and Table 2), in which the planes defined by the *A*/*C* rings of baicalein and the N1*A*/C6*A* atoms of NA are inclined to each other at a dihedral angle of 27.3 (2)°. The heterodimers are further extended along the *a* direction into ribbons through N2*A*—H2*A*2···O1*A*^{ii} hydrogen bonds (Fig. 2*a*). Two inversion-related ribbons are assembled into a one-dimensional column in the *a* direction by means of O6—H6···N1*A*^{i} hydrogen bonds (Fig. 2*b*). C4*A*—H4*A*···O4^{iii} interactions join adjacent columns into sheets parallel to (001) (all symmetry codes as in Table 2). Other possible N—H···O and C—H···O contacts with angles significantly below 140° are regarded as structurally insignificant (Wood *et al.*, 2009).

It should be noted here that the O—H···N$_{ar}$ interaction is one of the most competitive heterosynthons (Bis *et al.*, 2007) and has also been observed in quercetin–isonicotinamide (Smith *et al.*, 2011), hesperetin–isonicotinamide (Kavuru, 2008) and quercetin–caffeine methanol solvate (Smith *et al.*,

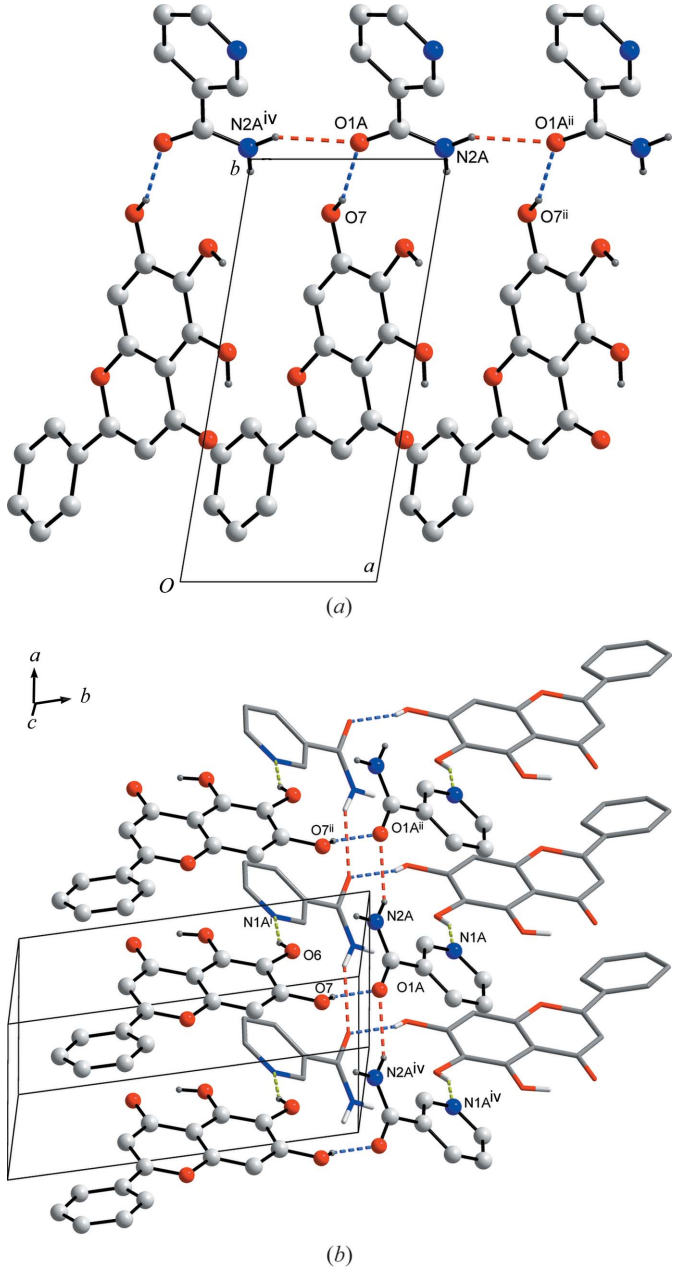

Figure 2
A packing diagram for (I), showing (*a*) ribbons of (I) along the *a* axis and (*b*) the inter-ribbon hydrogen-bond network resulting in the column motif along the *a* axis. (In the electronic version of the journal, hydrogen bonds between molecules forming the heteromolecular dimer are indicated by blue dashed lines, and red and green dashed lines, respectively, represent hydrogen bonds involved in forming the ribbon and column motifs.) Some H atoms and intramolecular hydrogen bonds have been omitted for clarity. [Symmetry codes: (i) $-x+2, -y+2, -z+1$; (ii) $x+1, y, z$; (iv) $x-1, y, z$.]

2011) cocrystals, as well as in the cocrystal of orcinol (3,5-dihydroxytoluene) with nicotinamide (CSD refcodes EWAQEZ and EWAQAV; Mukherjee *et al.*, 2011).

In summary, this report provides an insight into the previously unexplored field of baicalein cocrystallization and is a further example of the successful application of nicotinamide as a coocrystal former for hydroxy-substituted molecules. The crystal structure of (I) comprises one-dimensional ribbons, which are assembled into columns and held together by weak intermolecular C—H···O interactions. In contrast with the quercetin, hesperetin and apigenin cocrystals known so far, the crystal structure of (I) does not exhibit homomolecular hydrogen-bonded dimers.

Experimental

Baicalein was obtained from Sino-Future Bio-Tech Co. Ltd, nicotinamide was obtained from Sigma–Aldrich and both were used without further purification. Baicalein (0.025 g, 0.181 mmol) was dissolved in a close-to-saturated solution of nicotinamide in ethyl acetate (10 ml). Slow evaporation of the resulting solution yielded amorphous material and crystals of (I), which were separated manually and used for X-ray analysis.

Crystal data

$C_6H_6N_2·C_{15}H_{10}O_5$
M_r = 392.36
Triclinic, $P\overline{1}$
a = 5.248 (2) Å
b = 11.422 (3) Å
c = 14.952 (4) Å
α = 84.38 (3)°
β = 82.29 (3)°
γ = 79.83 (3)°
V = 871.7 (5) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.11 mm^{-1}
T = 100 K
0.48 × 0.07 × 0.04 mm

Data collection

Kuma KM-4-CCD κ-geometry diffractometer with a Sapphire2 CCD area detector
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2009)
T_{min} = 0.739, T_{max} = 1.000
11110 measured reflections
3432 independent reflections
2076 reflections with $I > 2\sigma(I)$
R_{int} = 0.065

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.181
S = 1.08
3432 reflections
265 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Selected torsion angles (°).

O1—C2—C11—C12	20.0 (4)	C4*A*—C3*A*—C7*A*—O1*A*	−28.2 (5)
C3—C2—C11—C16	21.4 (5)	C2*A*—C3*A*—C7*A*—N2*A*	−30.7 (5)

All H atoms were found in difference Fourier maps, but in the final refinement cycles they were repositioned in their calculated positions and refined using a riding model, with C—H = 0.95 Å, N—H = 0.88 Å and O—H = 0.84 Å, and with U_{iso}(H) = 1.2U_{eq}(C,N) or 1.5U_{eq}(O).

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2009); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2009); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg, 2005); software used to prepare material for publication: *SHELXL97*.

Table 2
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O5—H5···O4	0.84	1.81	2.563 (3)	148
O6—H6···N1*A*^{i}	0.84	1.91	2.694 (4)	155
O7—H7···O1*A*	0.84	1.94	2.720 (3)	154
N2*A*—H2*A*2···O1*A*^{ii}	0.88	2.23	2.996 (4)	145
C4*A*—H4*A*···O4^{iii}	0.95	2.32	3.200 (4)	154

Symmetry codes: (i) $-x+2, -y+2, -z+1$; (ii) $x+1, y, z$; (iii) $x-1, y+1, z$.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG3251). Services for accessing these data are described at the back of the journal.

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