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A 1:1 pharmaceutical cocrystal of myricetin in combination with uncommon piracetam conformer: X-ray single crystal analysis and mechanochemical synthesis

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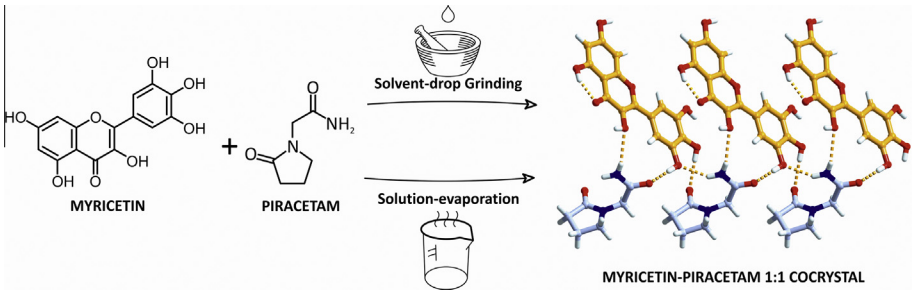
HIGHLIGHTS

- A 1:1 myricetin-cocrystal was grown from solution and obtained *via* solvent-drop grinding.
- Piracetam adopts an uncommon conformation, encountered in its coordination compounds.
- Molecules form a 3D hydrogen-bonded network.
- Hirshfeld surface analysis reveals presence of stabilizing C···C and H···C contacts.
- Cocrystalline phase is stable up to 200 °C.

GRAPHICAL ABSTRACT



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ABSTRACT

Combination of two Active Pharmaceutical Ingredients, myricetin and piracetam, yields a 1:1 cocrystal characterized by X-ray single-crystal and powder diffraction, Raman spectroscopy, ^{1}H NMR, thermal analysis (DSC and TG-DTA) methods. Constituents of the cocrystalline phase were also investigated in terms of Hirshfeld surfaces. Compounds in their neutral forms cocrystallize in the $Pna2_1$ space group of orthorhombic system. Notably, piracetam adopts an uncommon conformation, not encountered in its cocrystals previously described. In the crystal lattice, a three-dimensional hydrogen-bonded network is observed, including formation of a 2D molecular scaffolding motif. A scale-up procedure is readily available with use of solvent-drop grinding method, in which application of a variety of common solvents leads to formation of the cocrystal, as confirmed by XRPD and Raman spectroscopy.

1. Introduction

Cocrystallization as a method of obtaining new forms of Active Pharmaceutical Ingredients (APIs) with improved physicochemical properties (e.g., solubility, stability, and melting point) has gained much attention in recent years and is a promising alternative to so far employed preparation of salts, hydrates, solvates and other forms [1]. Cocrystal design for a specific API is based on evaluating possible heteromolecular synthons, which are reliable hydrogen bonding motifs sustaining crystal structures. So far few pharmaceutical cocrystals of flavonoids have been reported, with the most promising results obtained for quercetin, cocrystallization of which leads to compounds with improved solubility and bioavailability [2].

Myricetin (3,3′,4′,5,5′,7-hexahydroxyflavone, Scheme 1) is one of the main flavonoid constituents in grapes, red wine, onions and berries, and is encountered in many other fruits, vegetables,

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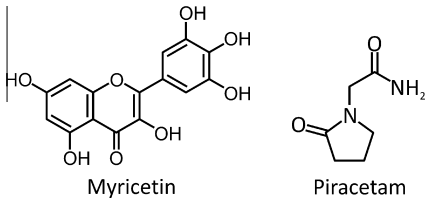

Scheme 1.

and food of plant origin [3]. The compound is considered an Active Pharmaceutical Ingredient (API), with scientific interest attributed to anti-oxidant, antitumor, and anti-inflammatory properties [4]. Myricetin possess multiple hydroxyl substituents, therefore a coformer with a reliable hydrogen bond acceptor potential has to be selected for cocrystallization. Resulting selection of piracetam (2-oxo-1-pyrrolidinyl-acetamide, Scheme 1) is related to its acid/base neutrality and presence of hydrogen-bonding acceptor sites. Piracetam is a nootropic drug, used to treat memory and balance problems under a marketed name Nootropil [5], showing efficiency also in stroke treatment [6] and reducing alcohol-withdrawal symptoms [7]. Unlike myricetin, crystal structure of which remains undetermined, five polymorphic forms and a hydrate of piracetam are known [8]. A search of the Cambridge Structural Database [9] (ver. 5.34) reveals that 9 cocrystals of piracetam have been reported so far, including cocrystals with gentisic [10] and p-hydroxybenzoic [10] acids, L-tartaric [11], citric [11] and mandelic [11] acids as well as 4-hydroxybenzoic [12] acid and hydroquinone [13].

Solvent-drop grinding [14] as a method of mechanochemical synthesis is becoming a frequently applied screening technique for pharmaceutical cocrystals [15,16], moreover successfully employable for controlling cocrystal polymorphism [17] or even metal–organic frameworks synthesis [18]. Combination of X-ray powder diffraction (XRPD) and Raman spectroscopy as complementary techniques provides an excellent tool for cocrystal screening [19] and monitoring cocrystallization [20] in mechanochemical synthesis of cocrystals, and was recently applied to study cocrystallization of piracetam with hydroquinone [13].

As a part of our on-going research on flavonoid cocrystallization [21], a 1:1 cocrystal of myricetin and piracetam (**MyrPac**) was synthesized by both solution–evaporation and solvent-drop grinding techniques and analyzed in terms of X-ray single crystal diffraction, Hirshfeld surfaces, X-ray powder diffraction, Raman spectroscopy, thermal (TG-DTA and DSC) analysis, and ^{1}H NMR in solution.

2. Experimental

2.1. Materials

Myricetin (>98% HPLC) was obtained from Sino-Future Bio-Tech Co., Ltd., piracetam (>98% TLC) was obtained from Sigma Aldrich and both were used without further purification. Pure grade solvents were purchased from POCh S.A. and used as received.

2.2. Cocrystallization via slow evaporation

Myricetin (25 mg, 0.077 mmol) and piracetam (11 mg, 0.077 mmol) were combined in 8 mL isopropyl alcohol with stirring. Resulting solution was filtered and allowed to slowly evaporate at ambient temperature. After 13 days, dark-yellow, block-like crystals (Fig. S1) precipitated (yield 54%). The solid phase was filtered, washed with ethyl acetate, allowed to dry at ambient conditions and used for single-crystal X-ray diffraction. Same procedure was employed to obtain samples for powder diffraction, Raman spectroscopy, thermal analysis (TG-DTA and DSC) and ^{1}H NMR solution study.

2.3. Cocrystallization via solvent-drop grinding

50 mg of myricetin and a 1:1 stoichiometric amount of piracetam (22 mg) were combined along with solvent (one drop, c.a. 25 μL) in a 5 mL stainless steel grinding jar with two 7 mm stainless steel grinding balls. Samples were ground in a Narva Vibrator Mill for 30 min (3 × 10 min with 5 min cooling periods) at a rate of 50 Hz, with addition of methanol, ethanol, isopropanol, acetone, ethyl acetate, acetonitrile or chloroform. Resulting solids were dried overnight at ambient conditions and characterized using powder X-ray diffraction and Raman spectroscopy.

2.4. Raman spectroscopy

Raman spectra were collected on a MultiRAM FT-Raman spectrometer (Bruker Optik GmbH, Ettlingen, Germany). Samples were scanned in a range of 3600–50 cm^{-1} with 2 cm^{-1} resolution and using a 1064 nm laser light.

2.5. Powder diffraction analysis

X-ray powder diffraction (XRPD) analyses were carried out on a Bruker D8-Advance diffractometer equipped with a VÅNTEC-1 detector ($\lambda_{Cu\text{-}K\alpha1}$ = 1.5406 Å). The equipment was operated at 30 kV and 40 mA, and data were collected at room temperature in the range of 2θ = 3–40°.

2.6. Single-crystal X-ray diffraction analysis

Crystallographic measurement was performed on a Kuma KM4-CCD automated four-circle diffractometer with graphite monochromatized Mo $K\alpha$ radiation at 100(2) K, using an Oxford Cryosystems cooler. A room-temperature measurement (at 296(2) K) was undertaken on a Xcalibur R with Mo $K\alpha$ radiation, results of which are not discussed. Selected crystallographic data for the 100 K structure are provided in Table 1 (full data for both structures can be found in Supplementary Table S1). Data collection, cell refinement, and data reduction and analysis were carried out with CRYSALISCCD and CRYSALISRED, respectively [22]. Diffraction data have been corrected for absorption effects by multi-scan [22].

Table 1
Selected crystallographic data, data collection and structure refinement details for **MyrPac**.

	MyrPac
Formula	$C_{15}H_{10}O_8{\cdot}C_6H_{10}N_2O_2$
Formula weight (g mol^{-1})	460.39
Crystal description	Block, yellow
Crystal size (mm)	0.54 × 0.13 × 0.11
Crystal system	Orthorhombic
Space group (no.)	$Pna2_1$ (33)
a, b, c (Å)	22.886(6), 11.641(3), 7.148(2)
Z	4
Vol. (Å^3)	1904.3(9)
ρ_{calc} (g cm^{-3})	1.606
Temperature (K)	100(2)
θ Range (°)	3.19–36.88
Reflns collected/independent	30,018/6710
Observed reflns ($I > 2\sigma(I)$)	5656
R(int)	0.031
Data/parameters/restraints	6710/304/1
GoF = S_{all}	1.01
R [$F^2 > 2\sigma(F^2)$]	0.039
$wR(F^2)$	0.098
$\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	0.49/−0.23