Supporting information

Exploring and Characterization for Novel Cocrystals Hydrate Consisting of Captopril; Amino Acid-Derived Drug

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Table S1 The list of CCFs used for screening and the states of samples obtained by screening; crystalline (C), liquid (L), amorphous (A).

Cocrystal Former	Sample state
(+)-Camphoric acid	C
L-Tartaric acid	C
Maleic acid	C
Adipic acid	L/A
Glycolic acid	L/A
Benzoic acid	L/A
Fumaric acid	C
Malonic acid	L/A
2-Oxoglutaric acid	L/A
2,5-Dihydroxybenzoic acid	C
L-Pyroglutamic acid	L/A
Oxalic acid	C
4-Hydroxybenzoic acid	C
1-Hydroxy-2-naphthoic acid	L/A
Glutaric acid	C
Succinic acid	C
Salicylic acid	C
L-Malic acid	L/A
Hippuric acid	L/A
Citric acid	L/A
trans-Cinnamic Acid	C
Decanoic Acid	L/A
Carminic Acid	L/A
Myristic Acid	L/A
Ursodeoxycholic Acid	C
L-Phenylalanine	C
L-Proline	C
L-Serine	C
L-Threonine	C
L-Tryptophan	C
L-Tyrosine	C
L-Valine	L/A
L-Glutamine	C
L-Lysine	L/A
L-Asparagine	C
L-Alanine	C
L-Arginine	L/A
L-Aspartic acid	C
L-Cysteine	L/A
L-Glutamic acid	C
Glycine	C
L-Histidine	C
L-Isoleucine	C
L-Leucine	L/A
L-Methionine	C
Creatinine	C
Saccharin	L/A
Taurine	C
Nicotinamide	C
Urea	L/A
Betaine Anhydrous	C
Sarcosine	L/A
Isonicotinamide	C
N-methylglucamine	L/A
Lactamide	L/A
Benzamide	C
Glycolamide	C
Tromethamine	C
N-acetylglycine	C
Thiabendazole	C
Azodicarbonamide	L/A
Allantoin	C
N-acetyl-DL-tryptophan	L/A
Phenacetin	C
Diisopropanolamine	L/A
L-Theanine	C

Cocrystal Former	Sample state
Thiabendazole	C
Azodicarbonamide	L/A
Allantoin	C
N-acetyl-DL-tryptophan	L/A
Phenacetin	C
Diisopropanolamine	L/A
L-Theanine	C
3-Ethoxy-4-hydroxybenzaldehyde	L/A
(+)-Camphor	L/A
Xylitol	L/A
D-Xylose	L/A
D-Sorbitol	L/A
Thymol	L/A
Hydropuinone	L/A
pyrogallol	L/A
Lactose	L/A
Sucrose	L/A
Inositol	L/A
D-Mannitol	L/A
D-Maltose	L/A
Ethylmaltol	L/A
D-Glucono-1,5-lactone	C
Sucralose	L/A
Gallic Acid Propyl Ester	L/A
Riboflavin	L/A
meso-Erythritol	L/A
Maltol	L/A
Neotame	L/A
Sorbic Acid	L/A
Isophthalic acid	L/A
Phthalic acid	L/A
Nicotinic acid	C
Mucic Acid	L/A
Stearic acid	L/A
2-Naphthalenesulfonic acid Monohydrate	C
(+)-10-Camphorsulfonic acid	L/A
1-Naphthalenesulfonic acid	L/A
N-acetylglycine	C
Cholic acid	C
D-Araboascorbic Acid	L/A
L-Ascorbic acid	L/A
2-Aminobenzoic Acid	C
Orotic acid	L/A
4-Aminobenzoic acid	C
Sebacic acid	L/A
D-Glucuronic acid	L/A
DL-Mandelic acid	C
Piperonal	L/A
Folic Acid Hydrate	L/A
1,1,1-Trichloro-2-methyl-2-propanol Hemihydrate	L/A
Dehydroacetic Acid	L/A
Isobutyl 4-Hydroxybenzoate	L/A
Phenol Red	L/A
(-)-Borneol	L/A
Phenyl Salicylate	L/A
3-tert-Butyl-4-hydroxyanisole	L/A
Biotin	L/A

Table S2 Crystallographic data for CPL disulfide

Empirical formula	$C_{18}H_{28}N_2O_6S_2$
Formula weight	432.55
Crystal system	monoclinic
Space group	$P2_1$ (#4)
Unit cell dimensions (◦) and (Å)	a = 6.6677(3) Å b = 11.0901(5) Å c = 14.4626(7) Å β = 91.659(7) o
Volume (Å^3)	1068.99(8) Å^3
Z	2
Density (calculated) (g/cm^3)	1.344 g/cm^3
F (000)	460.00
μ (CuKα) (cm^{-1})	25.725 cm^{-1}
T (K)	98.0±1
Crystal size (mm)	0.240×0.240×0.210 mm
Collected reflections	12272
Unique reflections	3837
R_{int}	0.0455
$R(F)$, $F>2\sigma(F)$	0.0300
$wR(F^2)$, $F>\sigma(F)$	0.0790
$R(F)$, all data	0.0309
Δ_r (min., max.) eÅ^{-3}	-0.27, 0.20

Single crystals consisting of CPL disulfide were prepared by crystallization from the CPL-LPR aqueous solution. CPL and LPR (molar ratio 1: 1) were dissolved in water. Hexane was quietly drop on the aqueous solution. The solution was maintained at 20°C until clear single crystals were precipitated. The crystallographic data of CPL disulfide have been deposited at the Cambridge Crystallographic Data Centre under the reference numbers CCDC 2190702.

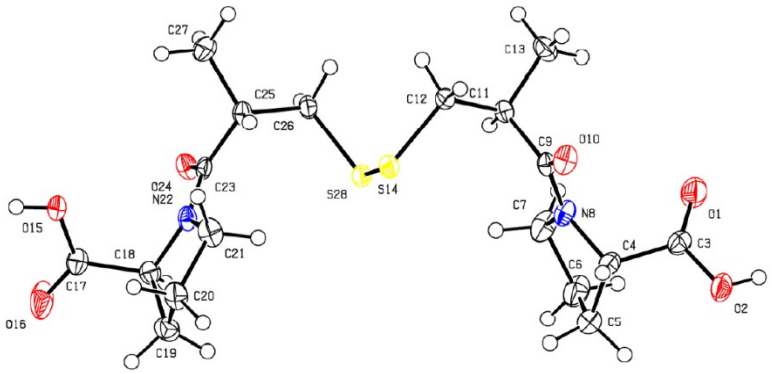

Fig. S1 ORTEP diagram of CPL disulfide with the atomic labeling.

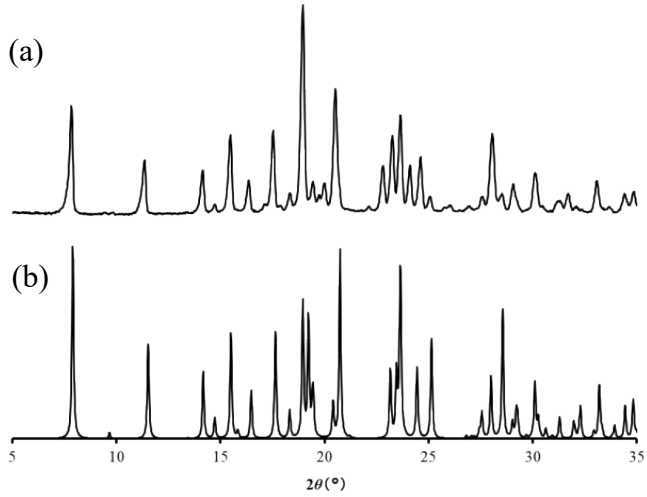

Fig. S2 PXRD diffraction patterns of (a) CPL-LPR cocrystal hydrate prepared by HM and (b) SCXRD analysis.

Comparison of Hydrogen Bond Network between CPL and CPL-LPR Cocrystal

We compared hydrogen bonds in the crystal structure of CPL and CPL-LPR cocrystal hydrates. **Figure S3** shows the crystal packing of CPL-LPR cocrystal hydrate.

In the crystal structure of CPL, only O3-H3 of the carboxy group and O8 of the amide group were hydrogen-bonded, whereas six kinds of hydrogen bonds were present in CPL-LPR cocrystal hydrate (**Table S3**).[S1]

Among these, the carboxy group O3-H3 of CPL was hydrogen bonded to the carboxylate C14-O21 of LPR.

Generally, dimers tend to form in the synthon involving the carboxylic acids of acidic compounds.[S2,S3]

The fusion enthalpy is considered to be large since the binding energies of these synthons are relatively strong.

Therefore, the CPL-LPR cocrystal hydrate had a higher melting point than the CPL crystal resulting from strong hydrogen bonds due to the formation of dimer consisting of carboxylic acids in the CPL-LPR cocrystal hydrate.

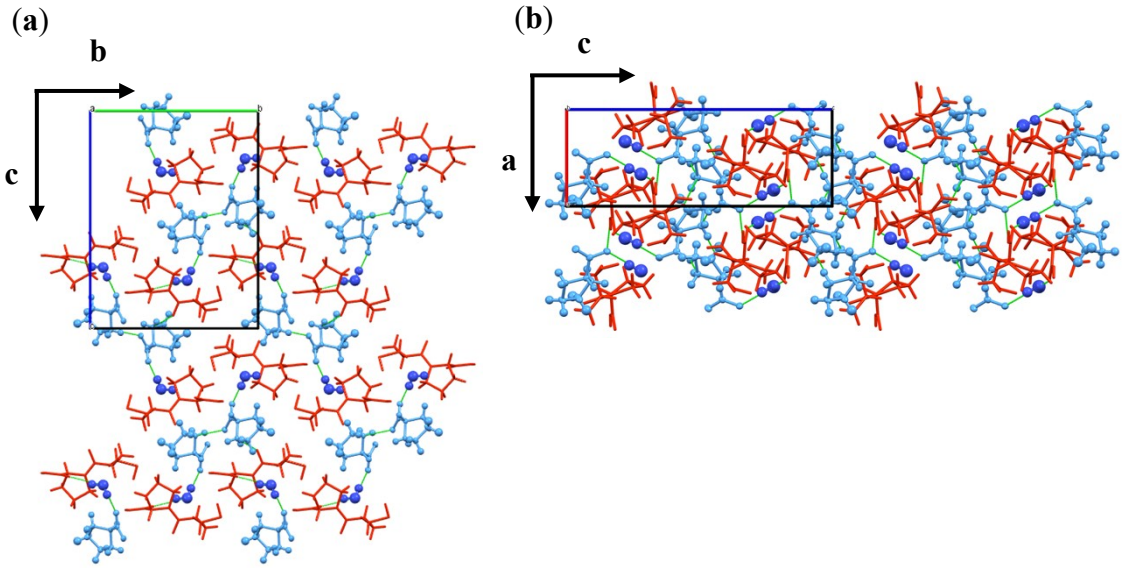

Fig. S3 Crystal structure of CPL-LPR cocrystal hydrate: (a) *a*-axis, (b) *b*-axis packing diagram

Table S3 Hydrogen bonding formed in CPL-LPR.

Donor-H	Acceptor	D-H（Å）	H…A(Å)	D…A(Å)	D-H…A(°)
O3-H3	O21	0.80(5)	1.74(5)	2.533(3)	170(5)
O22-H22A	O13[1]	0.955(9)	2.042(17)	2.973(3)	164(4)
O22-H22B	O21	0.95(3)	1.96(3)	2.912(3)	173(3)
N19-H19A	O20[2]	0.81(4)	1.94(4)	2.712(3)	157(3)
N19-H19B	O8[2]	0.89(4)	1.90(3)	2.721(3)	152(3)

Symmetry Operators：(1) -X+1,Y+1/2,-Z+1/2,(2) X+1/2-1,-Y+1/2+1,-Z+1

□S1□ Joanna Bojarska, Waldemar Maniukiewicz, Andrzej Fruzin´ ski, Lesław Sieron´ and Milan Remko, Captopril and its dimer captopril disulfide: comparative structural and conformational studies. *Acta Cryst.* **C71** (2015) 199-203.

□S2□ Liping Zhou, Stephanie Dodd, Christina Capacci-Daniel, Sudhakar Garad, Riccardo Panicucci, Vijay Sethuraman, Co-crystal formation based on structural matching. Eur. J. Pharm. Sci. 88 (2016) 191-201.

□S3□ Tapas Kumar Adalder, Ravish Sankolli and Parthasarathi Dastidar, Homo- or Heterosynthon? A Crystallographic Study on a Series of New Cocrystals Derived from Pyrazinecarboxamide and Various Carboxylic Acids Equipped with Additional Hydrogen Bonding Sites. Cryst. Growth Des. 12 (2012) 2533-2542.

Table S4 The lists of intermolecular interactions between donor and acceptor atoms in CPL (left) and CPL-LPR cocrystal hydrate (right table). This table indicated the number of intermolecular interactions affecting the physical stability was different between CPL and CPL-LPR.

Number	Atom1	Atom2
1	O3	O1
2	O1	H8
3	O2	H8
4	**O2**	**H15**
5	O2	H7
6	O3	H1
7	C6	H1
8	H11	O1
9	H11	H1
10	S1	H2

Number	Atom1	Atom2
1	O3	O21
2	O8	N19
3	O13	O22
4	O20	N19
5	O21	O22
6	H3B	O13
7	O3	H15
8	H5B	O22
9	H5B	H22B
10	H11B	O22
11	O3	C14
12	H3	O21
13	H3	C14
14	O8	H16B
15	O8	H19B
16	C1	H19B
17	C4	H17B
18	H5A	H16A
19	O13	H22A
20	C7	O22
21	H10A	O22
22	O20	H19A
23	O21	H22B