Electronic Supplementary Information (ESI)

Novel pharmaceutical cocrystals of pelubiprofen: An approach to virtual coformer screening

Paul Kim[1], In-Seo Lee[1], Ji-Yoon Kim[1], Medard E. Mswahili[2], Young-Seob Jeong[5], Woo-Jin Yoon[3], Ho-Seop Yoon[3], Min-Jeong Lee[4,*], Guang J. Choi[1,4,*]

[1] Dept. of Medical Science, Soonchunhyang University, Asan, Chungnam 31538, South Korea;

[2] Dept. of ICT Convergence, Soonchunhyang University, Asan, Chungnam 31538, South Korea

[3] Dept. of Chemistry, Ajou University, Suwon, Gyeonggi 16499, South Korea

[4] Dept. of Pharmaceutical Engineering, Soonchunhyang University, Asan, Chungnam 31538, South Korea

[5] Dept. of Computer Engineering, Chungbuk National University, Cheongju, Chungbuk 28644, South Korea

* Corresponding authors: mj.sirius1117@gmail.com and guangchoi@sch.ac.kr

Table S1 Prediction for pelubiprofen cocrystal by Artificial neural network and ΔpKa rule.

No	Coformer	Cocrystal prediction tool					
		Data driven-based			Traditional ΔpKa rule-based		
		Labeling (0: none, 1: cocrystal)	Probability	ANN-based Rank	p*Ka*	Δp*Ka*	Δp*Ka* pred.[a] (Cocrystal: red)
1	*Caffeine*	1	0.998	1	0.7	-3.9	Cocrystal
2	*Acetamide*	1	0.988	2	0.63	-3.97	Cocrystal
3	*Isonicotinamide*[b]	1	0.982	3	3.45	-1.15	Cocrystal
4	*Nicotinamide*[b]	1	0.981	4	3.33	-1.27	Cocrystal
5	*L-tryptophan*	1	0.974	5	9.4	4.8	Salt
6	*Indoleacetic acid*	1	0.954	6	-6.13 (NH)	-10.73	Cocrystal
7	*L-prolinamide*	1	0.949	7	9.81 (NH)	5.21	Salt
8	*Oxalic acid*	1	0.913	8	1.36	-6.3	Cocrystal

9	*L-histidine*	1	0.904	9	9.44 (NH)	4.84	Salt
10	*N-phenylglycine*	1	0.881	10	5.66 (NH)	1.06	Continuum
11	*4-phenylbutyric acid*	1	0.862	11	4.81	-	-
12	*Glycolamide*	1	0.85	12	-3.4	-8	**Cocrystal**
13	*L-phenylalanine*	1	0.833	13	5.66 (NH)	1.06	Continuum
14	*Benzamide*	1	0.748	14	-0.36	-4.96	**Cocrystal**
15	*Saccharin*	1	0.683	15	1.94	-6.88	**Cocrystal**
16	*L-proline*	1	0.679	16	11.33 (NH)	6.73	Salt
17	*D-proline*	1	0.679	16	11.33 (NH)	6.73	Salt
18	*Maleic acid*	1	0.61	18	2.85	-7.79	**Cocrystal**
19	*Fumaric acid*	1	0.61	18	3.35	-8.29	**Cocrystal**
20	*L-hydroxyproline*	1	0.602	20	10.62 (NH)	6.02	Salt
21	*Isonicotinic acid*	1	0.583	21	2.35 (C=N-C)	-2.25	**Cocrystal**
22	*Glycine*	1	0.559	22	9.24 (NH)	4.64	Salt
23	*L-pyroglutamic acid*	1	0.558	23	3.61	-8.55	**Cocrystal**
24	*Mandelic acid*	1	0.539	24	3.75	-8.69	**Cocrystal**
25	*4-hydroxybenzoic acid*	1	0.532	25	4.38	-9.32	**Cocrystal**
26	*N-formylglycine*	1	0.513	26	3.56	-8.5	**Cocrystal**
27	*Sarcosine*	1	0.512	27	10.35	8.29	Salt
28	*Succinic acid*	0	0.468	28	3.55	-8.49	**Cocrystal**
29	*Nicotinic acid*	0	0.456	29	4.19 (C=N-C)	-0.41	**Cocrystal**
30	*Salicylic acid*	0	0.299	30	2.79	-7.73	**Cocrystal**
31	*Pyrrole-2-carboxylic acid*	0	0.242	31	3.62	-8.56	**Cocrystal**
32	*Citric acid*	0	0.212	32	3.05	-7.99	**Cocrystal**
33	*L-glutamic acid*	0	0.19	33	9.54 (NH)	4.94	Salt
34	*Tyrosine*	0	0.189	34	9.19 (NH)	4.59	Salt
35	*Benzoic acid*	0	0.179	35	4.08	-9.02	**Cocrystal**
36	*4-aminosalicylic acid*	0	0.164	36	2.19 (NH)	-2.41	**Cocrystal**
37	*L-isoleucine*	0	0.16	37	9.59 (NH)	4.99	Salt
38	*Glycolic acid*	0	0.11	38	3.53	-8.47	**Cocrystal**

[a] The pKa values for PF were using -4.94 as protonated base and 4.6 as acid, respectively.

[b] The co-former that formed cocrystal with PF through cocrystal screening method.

Table S2 Cocrystal screening of PF with coformers selected by ANN

	ΔpK_a	**ANN rank**	**LAG**	**Slow eva**	**Fast eva**
Caffeine	-3.9	1	Mixture	Mixture	Viscous→caffeine
Acetamide	-3.97	2	Mixture	PF	Viscous
Isonicotinamide	-1.15	3	Cocrystal	Cocrystal	Cocrystal

Nicotinamide	-1.27	4	Mixture	Mixture	Cocrystal
Indoleacetic acid	-10.73	6	Mixture	Mixture	Mixture
Oxalic acid	-6.3	8	Mixture	Mixture	Viscous→Mixture
Glycolamide	-8	12	Mixture	Mixture	Viscous
Benzamide	-4.96	14	Mixture	Mixture	Viscous
Saccharin	-6.88	15	Mixture	Mixture	Mixture
Maleic acid	-7.79	18	Mixture	Mixture	Mixture
Fumaric acid	-8.29	18	Mixture	Mixture	Mixture
Isonicotinc acid	-8.67 or -2.25	21	Mixture	Mixture	Mixture
L-pyroglutamic acid	-8.55	23	Mixture	Mixture	Mixture
Mandelic acid	-8.69	24	Mixture	Mixture	Mixture
4-hydroxybenzoic acid	-9.32	25	Mixture	Mixture	Mixture
N-formylglycine	-8.5	26	Mixture	Mixture	Viscous→Mixture
Sarcosine	-7	27	Mixture	Mixture	Mixture

Table S3 Crystal data for pelubiprofen cocrystal

Compound reference	**PF-INA**
Chemical formula	$C_{16}H_{18}O_3 \cdot C_6H_6N_2O$
Formula mass	380.43
Crystal system	Monoclinic
a/Å	18.2765(12)
b/Å	6.1664(3)
c/Å	35.009(2)
β/°	90.6002(19)
Unit cell volume/Å^3	3945.3(4)
Temperature/K	290(1)
Space group	C2/*c*
No. of formula units per unit cell, Z	8
Radiation type	Mo Kα
Absorption coefficient, μ/mm^{-1}	0.09
θ min-max/°	3.2-26.0
No. of reflections measured	14588
No. of unique reflections	3864
R_{int}	0.044
wR_2	0.179
Final R_1 values ($F_o^2 > 2\sigma(F_o^2)$)	0.049
GOF	1.13

Min. and max. resd. Den./eÅ^{-3}	0.37, -0.26
CCDC number	2100280

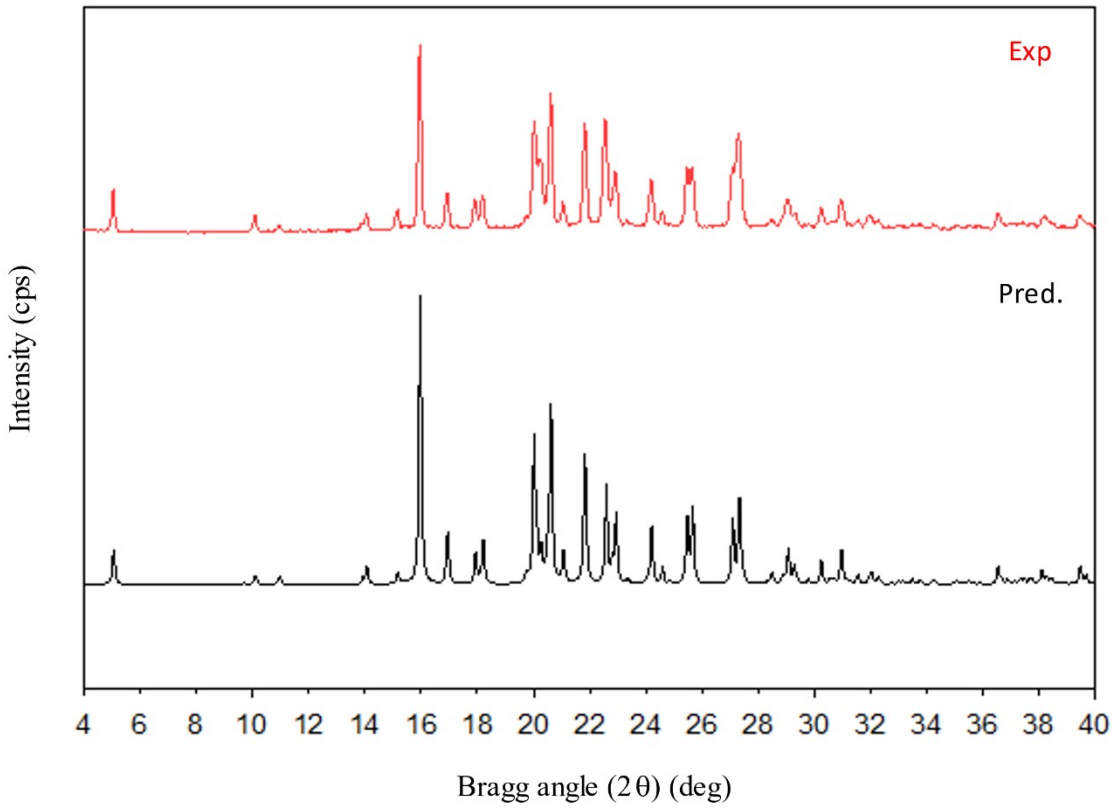

Figure S1. Experimental and calculated PXRD patterns of PF-INA pair.