Celecoxib cocrystal polymorphs with cyclic amides: synthons of a sulfonamide drug with carboxamide coformers†

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Electronic Supplementary Information†

Table S1 Number of hits archived in the CSD on sulfonamides.

CSD version 5.34 May 2013 update	Number of primary and secondary sulfonamides	Number of sulfonamides cocrystals	Number of sulfonamides cocrystals with carboxamide	Number of sulfonamide-carboxylic acid heterosynthon (in single molecule)
Total No. hits in	953	27	3	1

Table S2 Crystallographic parameters of the Celecoxib cocrystals.

	CEL–PYR (1:1)	CEL–VLM-I (1:1)	CEL–VLM-II (1:1)	CEL–VLM-III (1:1)	CEL–CPR (1:1)	CEL–AZL (1:1)
Empirical Formula	$C_{17}H_{14}F_3N_3O_2S.C_4H_7NO$	$C_{17}H_{14}F_3N_3O_2S.C_5H_9NO$	$2(C_{17}H_{14}F_3N_3O_2S).2(C_5H_9NO)$	$C_{17}H_{14}F_3N_3O_2S.C_5H_9NO$	$C_{17}H_{14}F_3N_3O_2S.C_6H_{11}NO$	$C_{17}H_{14}F_3N_3O_2S.C_7H_{13}NO$
Formula weight	466.49	480.51	480.51	480.51	494.54	508.57
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P\bar{1}$	$P2_1/c$	$P2_1/n$	$P2_1$	$P2_1/c$
T (K)	298(2)	298(2)	298(2)	298(2)	298(2)	298(2)
a (Å)	11.0368(5)	8.7346(6)	22.591(2)	14.8501(18)	11.7189(11)	8.0409(5)
b (Å)	8.6083(4)	11.2689(10)	8.6211(8)	8.4190(11)	8.7409(6)	27.2426(18)
c (Å)	12.0762(6)	12.2391(9)	23.814(2)	17.761(2)	12.0503(10)	11.7927(8)
α (°)	90.0	81.622(7)	90.0	90.0	90.0	90.0
β (°)	109.049(5)	87.560(6)	102.163(1)	93.901(2)	103.353(10)	105.806(7)
γ (°)	90.0	73.363(7)	90.0	90.0	90.0	90.0
V (Å^3)	1084.51(9)	1141.94	4533.9(7)	2215.4(5)	1200.99	2485.6(3)
D_{calcd} (g cm^{-3})	1.429	1.384	1.408	1.441	1.368	1.359
μ (mm^{-1})	0.206	0.198	0.199	0.204	0.190	0.186
θ range	2.9578 to 26.3148	2.9516 to 28.8810	2.36 to 273.8	2.30 to 23.04	2.76 to 26.30	2.85 to 26.31
Z/Z[1]	2/1	2/1	8/2	4/1	2/1	4/1
Range h	-13 to +13	-10 to +10	-26 to +26	-18 to +18	-8 to +13	-10 to +5
Range k	-3 to 10	-14 to +13	-10 to +10	-13 to +13	-6 to +10	-33 to +31
Range l	-15 to 12	-12 to +15	-28 to +28	-10 to +10	-14 to +12	-14 to +14

Reflections collected	4337	8078	41174	23019	4400	4244
Total reflections	2656	4662	7737	3832	2941	3115
Observed reflections	2351	2382	6018	4532	2685	2455
R_1 [$I >$ 2 $\sigma(I)$]	0.0435	0.0577	0.0618	0.0545	0.0544	0.0759
wR_2 (all)	0.1109	0.1374	0.1882	0.1881	0.1559	0.2280
Goodness-of-fit	1.037	0.953	1.024	1.234	1.017	1.032
Diffract meter	Oxford CCD	Oxford CCD	Smart Bruker	Smart Bruker	Oxford CCD	Oxford CCD

Table S3 Hydrogen bonding distances/ angles.

Crystal form	Interaction	H···A /Å	D···A /Å	∠D–H···A /º	Symmetry code
CEL–PYR	N3–H3A···O3	2.05	2.908(1)	158	–[a]
	N3–H3B···O3	2.14	2.911(1)	150	1-x,1/2+y,-z
	N4–H4A···O2	2.30	3.093(9)	153	1-x,-1/2+y,-z
	C16–H16···O2	2.57	2.928(1)	103	Intramolecular
	C19–H19B···O1	2.29	3.160(1)	158	1-x,1/2+y,-z
CEL–VLM-I (1:1)	N3–H3A···O1	2.11	2.942(4)	161	x,y,-1+z
	C12–H12···O5	2.68	3.483(4)	145	1-x,2-y,-z
	N4–H4A···O5	2.23	3.037(4)	131	x,y,1+z
	N4–H4A···O1	1.87	2.813(4)	160	1-x,2-y,-z
	C12–H12···N1	2.66	3.579(6)	169	X,y,-2+z
CEL–VLM-II (1:1)	N3–H3A···O5	1.95	2.803(4)	164	x,1/2-y,1/2+z
	N3H3B···O1	2.11	2.934(4)	169	x,1/2-y,1/2+z
	N6–H6A···O6	1.90	2.763(4)	175	x,3/2-y,-1/2+z
	N6–H6B···O4	2.17	2.913(4)	148	x,3/2-y,-1/2+z
	N7–H7A···O5	2.05	2.889(4)	163	1-x,1-y,-z
	N8–H8A···O6	2.12	2.937(4)	172	-x,1-y,1-z
	C14–H14···O1	2.48	2.864(4)	105	–[a]
	C19–H19···O4	2.56	3.453(3)	162	x,1/2-y,-1/2+z
	C33–H33···O3	2.49	2.878(4)	105	–[a]
CEL–VLM-III (1:1)	N3–H3A···O3	2.10	2.905(5)	170	–[a]
	N3–H3B···O2	2.31	3.145(5)	162	1/2-x,1/2+y,5/2-z
	N4–H4A···O3	2.07	2.954(5)	177	-x,1-y,2-z
	C16–H16···O1	2.50	2.887(4)	105	Intramolecular
CEL–CPR (1:1)	N3–H3A···O2	2.56	2.918(8)	101	1-x,1/2+y,-z
	N3–H3A···O3	1.97	2.873(1)	151	1-x,1/2+y,1-z
	N3–H3B···O3	2.26	3.022(5)	165	x,1+y,-1+z
	N3–H3B···O2	2.57	2.918(8)	109	1-x,1/2+y,-z
	N4–H4A···O1	2.12	2.942(5)	160	x,y,1+z

	C16–H16···O1	2.58	2.935(1)	103	Intramolecular
	C19–H19B···O2	2.60	3.354(2)	135	x,y,1+z
CEL–AZL (1:1)	N3–H3A···O2	2.13	2.979(5)	147	2-x,-y,-z
	N3–H3B···O3	2.07	2.826(5)	158	1+x,y,z
	N4–H4A···O3	2.16	2.998(6)	164	1-x,-y,1-z
	C14–H14···O1	2.59	2.945(5)	103	Intramolecular

Table S4 IR stretching frequency of the CEL cocrystals.

API/cocrystal	–C=O (Carboxamide/cocrystal), (cm^{-1})	–S=O (Sulfonamide symmetric, asymmetric) (cm^{-1})	$–NH_2$ sulfonamide (cm^{-1})
CEL	---	1164.7, 1347.7	3339.5,3233.0
CEL–VLM-I	1632.4/1662.2	1162.8, 1344.9	3323.6, 3226.4
CEL–VLM-II	1632.4/1652.4	1162.3, 1340.4	3428.0
CEL–VLM-III	1632.4/1642.8	1340.0	3450.7
CEL–CPR	1636.0/1643.2	1169.7, 1340.3	3328.0

Table S5 Melting point of CEL cocrystals.

S.NO	API/ cocrystal	M.P of coformer/API °C	M.P of cocrystal °C
1	CEL	163	---
3	CEL–VLM-I	38-40	106-108
4	CEL–VLM-II	38-40	108-111
5	CEL–VLM-III	38-40	71-74
6	CEL–CPR	69	110-111

Table S6 ss-NMR chemical shift (ppm) of CEL cocrystals.

	CEL	CEL–VLM-I	CEL–VLM-II	CEL–VLM- III	CEL–CPR
CH_3, CH_2	19.12	19.14, 22.16, 28.42, 30.93.	20.5, 22.18, 28.52, 31.22, 41.92.	20.33, 21.35, 28.30, 31.94, 41.25.	20.58, 30.98, 43.95.
CF_3	102.40	106.88	102.45, 107.644, 110.9	107.52, 110.95	106.35,
Aromatic region	123.09	119.62	120.43	122.74	120.58
	124.17	124.86	123.38	126.14	123.05
	126.25	126.81	126.35	127.27	125.84
	129.25	129.35	128.08, 129.2	130.15	128.39
	131.17	131.65	131.62	139.98	129.27
	141.29	139.34	139.45	142.65	138.73
	142.35	141.77	141.76	143.85	141.64
	144.85	144.59	143.78		143.45, 145.43
–C=O		175.43	173.16, 175.51	174.10	180.87

Table S7 Cocrystal polymorph sets retrieved from the CSD and updated to May 2013, ver. 5.34, as well as recent publications checked manually. For a recently published survey statistics, see *Cryst. Growth Des.*, 2010, **10** 2229–2238 by R. B. H. Tan et al.

TETRAMORPHIC COCRYSTAL SYSTEMS (3)		
LASIX:NICOTINAMIDE YASGOQ YASGOQ01 YASGOQ02 YASGOQ03	GALLICIC ACID:ACETAMIDE PEFGEO PEFGEO01 PEFGEO02 PEFGEO03	*P*-TETRA CHLORO DICYANO BENZENE :HEXA METHYL BENZENE (TBD:HMB) ADULEQ ADULEQ01 ADULEQ02 ADULEQ03 ADULEQ04
TRIMORPHIC COCRYSTAL SYSTEMS (3)		
4,4'-BIPYRIDINE:PIMELIC ACID XOLHUC XOLHUC01 XOLHUC02	ETHENZAMIDE:GENTISIC ACID QULLUF QULLUF01 QULLUF02	BARBITURIC ACID:UREA EFOZAB EFOZAB01 EFOZAB02 EFOZAB03 EFOZAB04

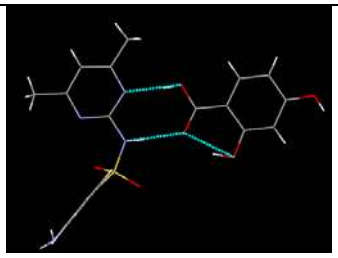
DIMORPHIC COCRYSTAL SYSTEMS (95)						
ABEKUN ABEKUN01 ABEKUN02	ABUNIU ABUNIU01	ACOYOG ACOYOG01	AJAJEA AJAJEA01	ANTCYB, ANTCYB12 ANTCYB11 ANTCYB13 ANTCYB14 ANTCYB15 ANTCYB16	ANUMEC ANUMEC01	BIVSIJ01 BIVSIJ02
COHWIF, COHWIF02, COHWIF03 COHWIF01	DOKGUG DOKGUG01	DURZAR DURZAR01	EFOZAB, EFOZAB03 EFOZAB01 EFOZAB04 EFOZAB02	ELEGUY ELEGUY01	ENAZOI ENAZOI01	EPUPUB EPUPUB01
FAHLEF01 FAHLEF02	FIHYEA FIHYEA02	HADKUT HADKUT01	IJETOG IJETOG02	IJIBEJ IJIBEJ01	KIBQOC KIBQOC01	KIHYOQ KIHYOQ01
LOFKIB LOFKIB01	MIYKOU MIYKOU01	MOXVIF MOXVIF01	MUROXA MUROXA01	NAPYMA NAPYMA01	NARSOP NARSOP01 NARSOP02	NITRIR NITRIR01
NUGZEV NUGZEV01	NUKWEW NUKWEW0 1	NUKXEX NUKXEX01	ODOBIT ODOBIT01	PTZTCQ PTZTCQ01	QUIDON QUIDON01 QUIDON02	QULLUF QULLUF01 QULLUF02
RIWWEA RIWWEA01	RURROM RURROM01	SAYMUB SAYMUB01	TAMBUE TAMBUE01	TECCAF01 TECCAF02	TEHNAW TEHNAW01	TIPWIY TIPWIY01

TUPRBN01 TUPRBN10	ULAWAF ULAWAF01 ULAWAF02	UNEZAO UNEZAO01	VAKTOS VAKTOS01	VEJXAJ VEJXAJ01	VUHFIO VUHFIO01	VUJSOJ VUJSOJ01
WATREP, WATREP01 WATREP04 WATREP02 WATREP03	WOBQEK WOBQEK01	WOTZAG WOTZAG01	WUZHOP WUZHOP01	XETZIG XETZIG01	XOLHUC XOLHUC01 XOLHUC02	YABHAM YABHAM01
ZZZGMW01 ZZZGMW02	EWAPAU EWAPAU01	EXAPID EXAPID01	UBUJIM UBUJIM01	PANQUS PANQUS01	AWIHOE02 AWIHOE03 AWIHOE04 AWIHOE05 AWIHOE06 AWIHOE07 AWIHOE08 AWIHOE09 AWIHOE10 AWIHOE11 AWIHOE12	YASGOQ YASGOQ01 YASGOQ02 YASGOQ03
CAZLAR, CAZLAR01 CAZLAR02	EXUQUJ EXUQUJ01	LOCVOO LOCVOO01	NOVSIA NOVSIA01	RIFQAY RIFQAY01 RIFQAY02 RIFQAY03	WOQBAF WOQBAF01	ZODWIY ZODWIY01
TONDUV TONDUV02	WANNUV WANNUV01	WUVKEE WUVKEE01 WUVKEE02	ISIJEA NUKYUO NUKYUO01 NUKYUO02		HOLJAU HOLJAU01 HOLJAU02 HOLJAU03 HOLJAU04 HOLJAU05 HOLJAU06 HOLJAU07	IJETEW IJETEW01
JICTUK IJETEW10	MOCCOW MOCCOW01	PIYQEU PIYQEU02	UKOSAP UKOSAP01	WATREP WATREP01 WATREP02	ACOMUC ACOMUC01	ACONIR ACONIR02
CEKKOU CEKKOU01	Temozolomide:4-OH-Benzamide[1]	Isoniazid: 4-OH Benzoic acid[2]	Isoniazid: Fumaric acid[2]	Caffeine:Theophylline[3]	Sulfacetamide: Acetamide[4]	3-OH Benzoic acid: Acridine[5]
2,4-Dihydroxybenzoic acid: Nicotinamide[5]	Malonic acid: Nicotinamide[5]	Pimelic acid: Nicotinamide[5]	Caffeine:4-Chloro-3-nitrobenzoic acid[6]			

Recent publications of polymorphic cocrystals not yet assigned REFCOD in CSD

1 P. Sanphui, N. J. Babu and Ashwini Nangia, *Cryst. Growth Des.*, 2013, **13** , 2208.

2 S. Aitipamula, A. B. H. Wong, P. S. Chow and R. B.H. Tan, *CrystEngComm*, 2013,**15**, 5877.
3 M. D. Eddleston, B. Patel, G. M. Day and W. Jones, *Cryst. Growth Des.*, DOI: 10.1021/cg401179s.
4 N. R. Goud and A. Nangia, *CrystEngComm*, 2013, **15**, 7456.
5 A. Lemmerer, D. A. Adsmond, C. Esterhuysen and J. Bernstein, *Cryst. Growth Des.*, 2013, **13**, 3935.
6 S. Ghosh, A. Mondal, M. S. R. N. Kiran, U. Ramamurty and C. M. Reddy, *Cryst. Growth Des.*, DOI: 10.1021/cg400928v.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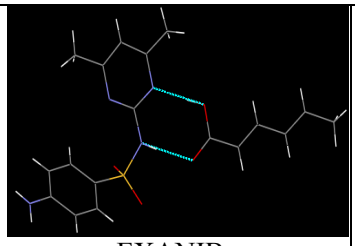
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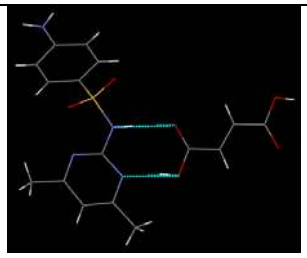
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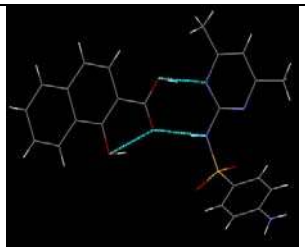
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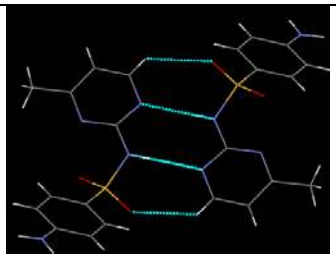
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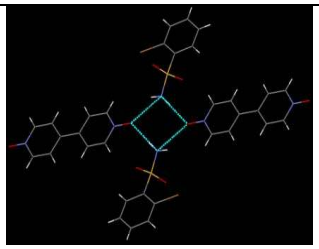
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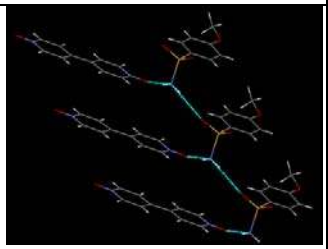
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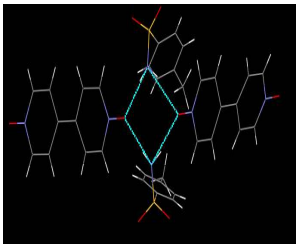
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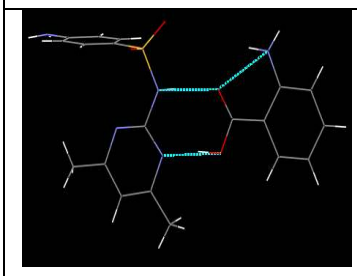
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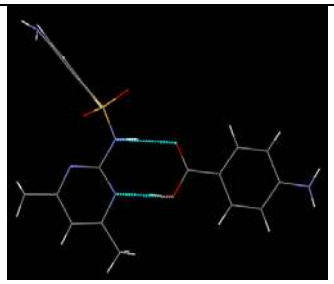
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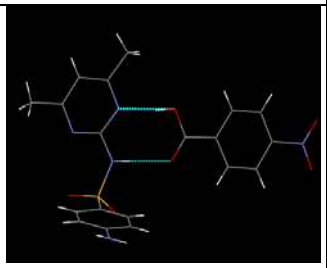
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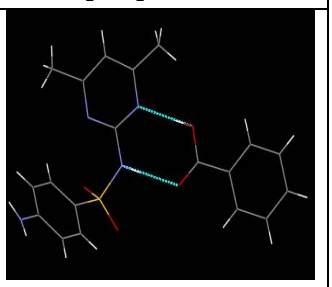
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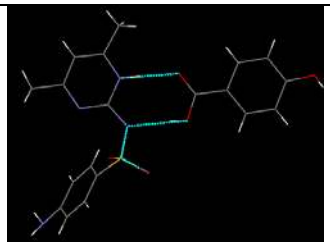
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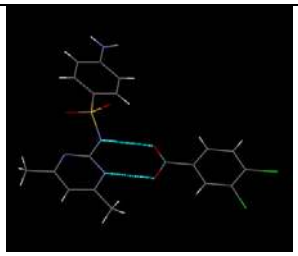
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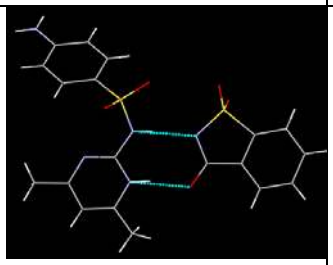
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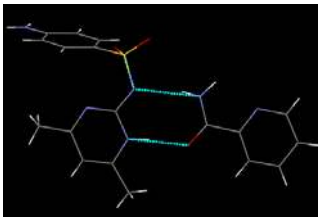
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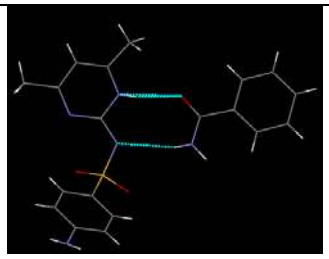

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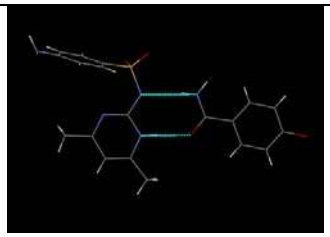

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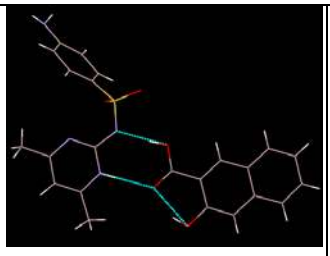

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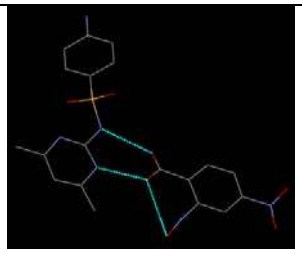
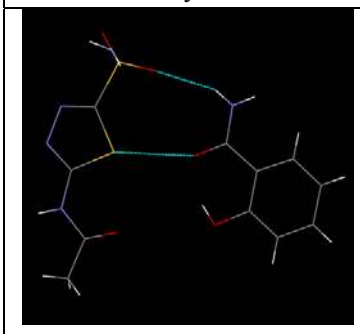


XEXCIE
2-amino-Py···COOH



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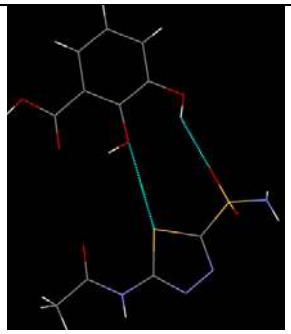

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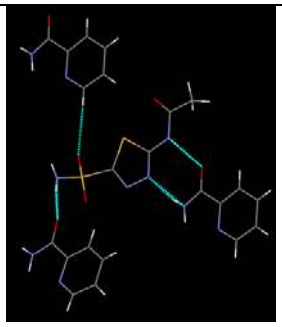

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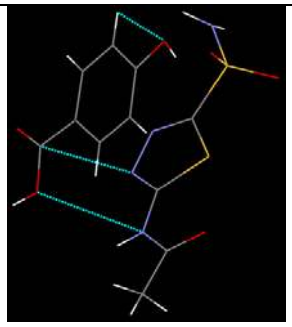
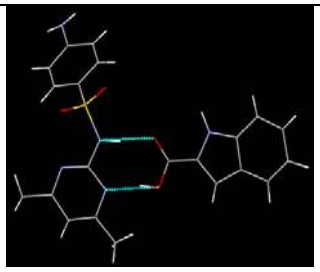


RUYGIC



XEXCAE
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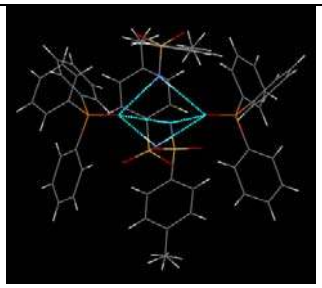
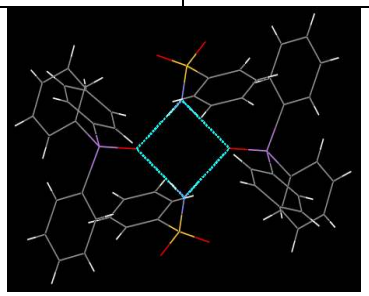
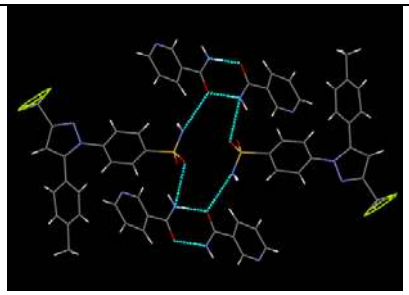


JACWEL
SO_2NH_2···P-oxide

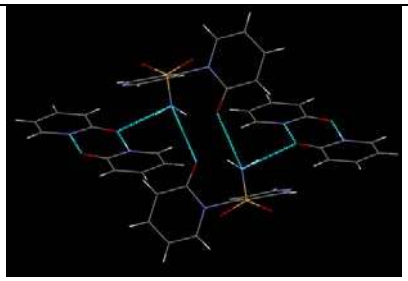


JAYCAN
SO_2NH_2···As-oxide

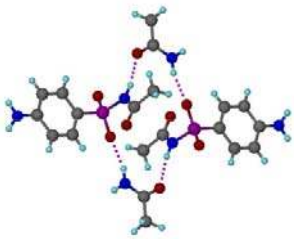
Fig. S1 CSD Refcodes search of sulfonamides cocrystals. Several molecules contain the SO_2-NH-2-NH-Py moiety and the cocrystals with carboxylic acids/ carboxamides contain the heterosynthon with the basic moiety but not the SO_2NH group.[1] Sulfonamide–N-oxide cocrystals were reported recently.[2] The common synthons are named.



VIGDAR
Celecoxib–nicotinamide

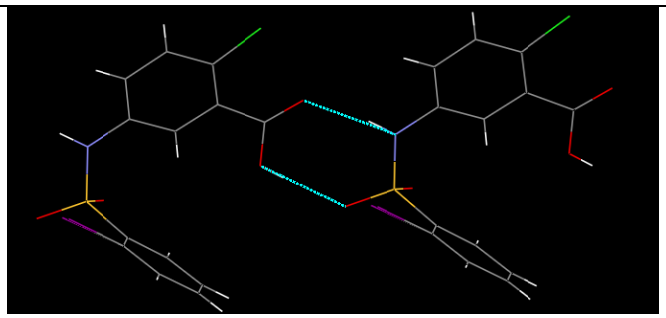


NARWAG
Sulfonamide–2-pyridone



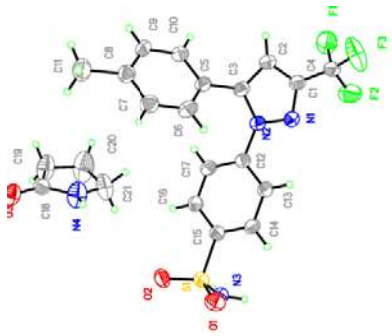
CrystEngComm, 2013, **15**, 7456.
Sulfacetamide–acetamide

Fig. S2 Sulfonamides cocrystals with pyridine and primary carboxamides, but there is no predictable motif.

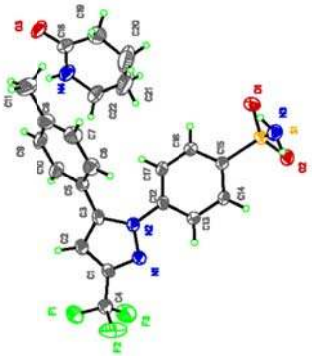


GOLJAT

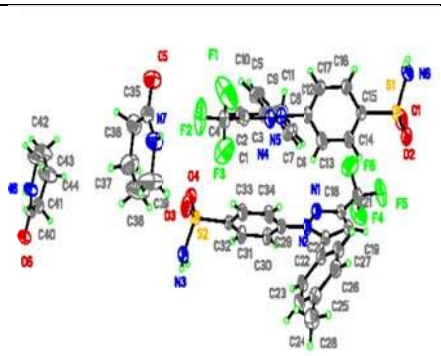
Fig. S3 Sulfonamide–carboxylic acid synthon in a single molecule structure.



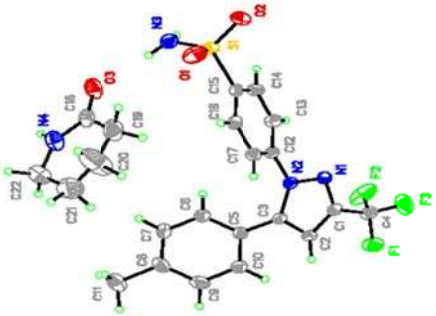
CEL–PYR (1:1)



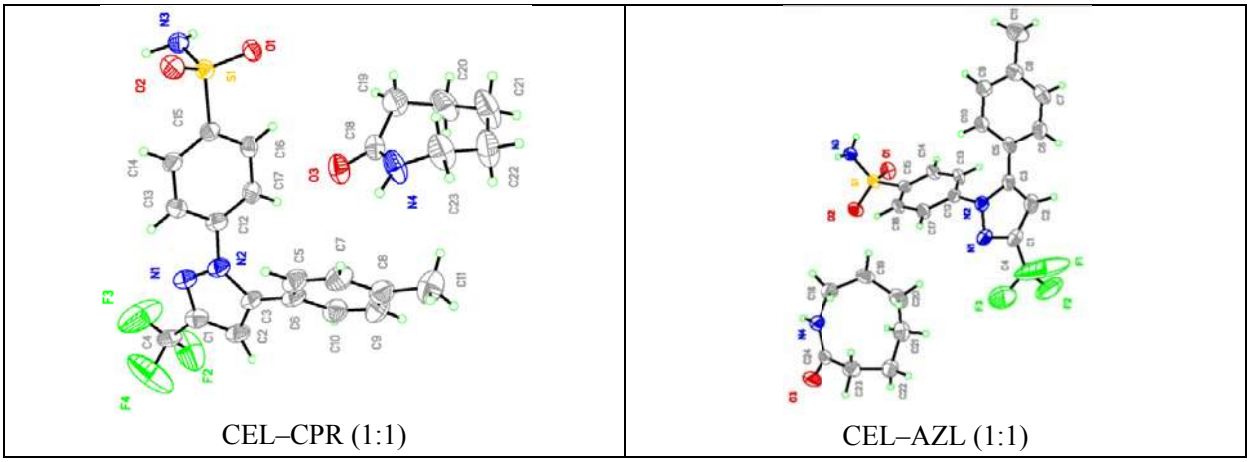
CEL–VLM-I (1:1)



CEL–VLM-II (1:1, Z' = 2)

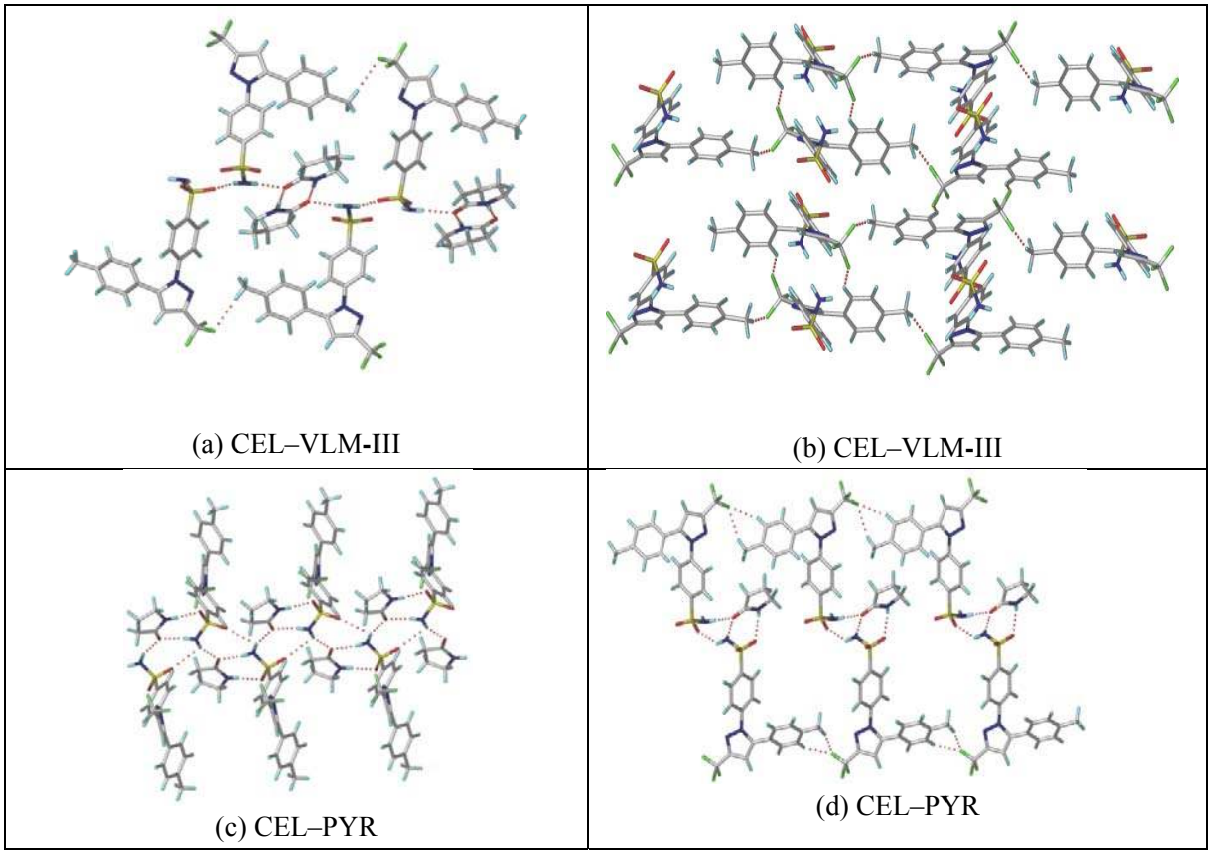


CEL–VLM-III (1:1)



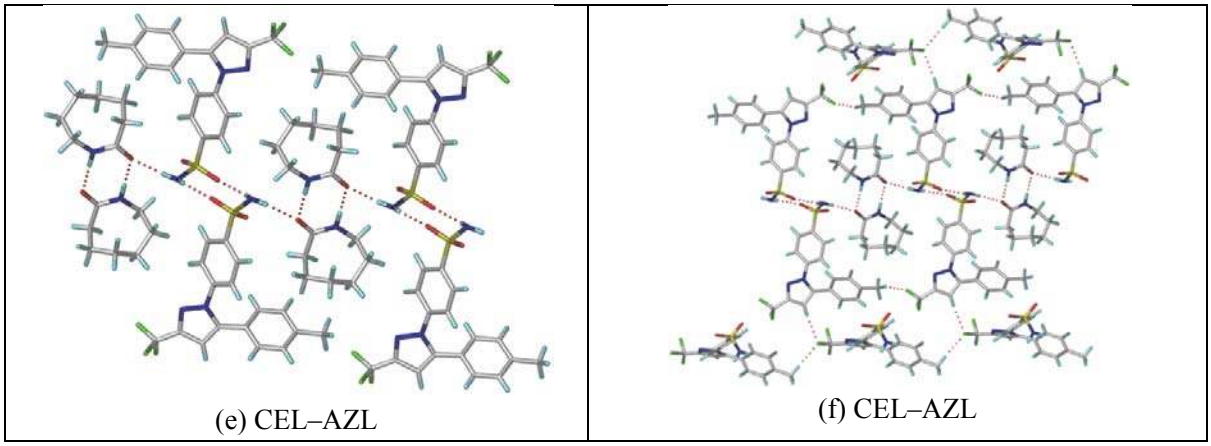
CEL–CPR (1:1) | CEL–AZL (1:1)

Fig. S4 ORTEP diagrams (heavy atoms at 35% probability) of CEL cocrystals confirm the molecular composition and stoichiometry.



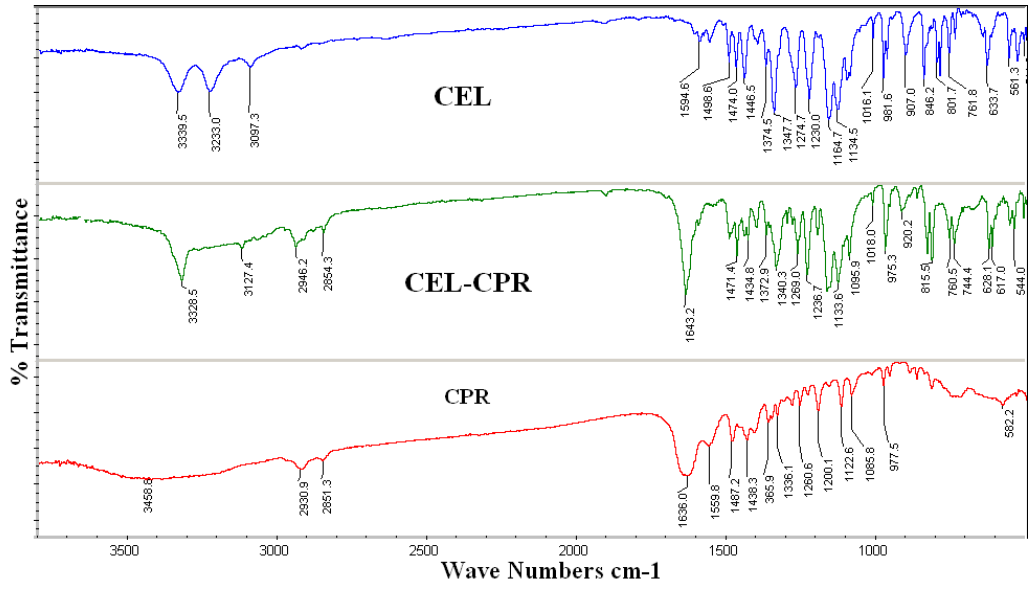
(a) CEL–VLM-III | (b) CEL–VLM-III

(c) CEL–PYR | (d) CEL–PYR

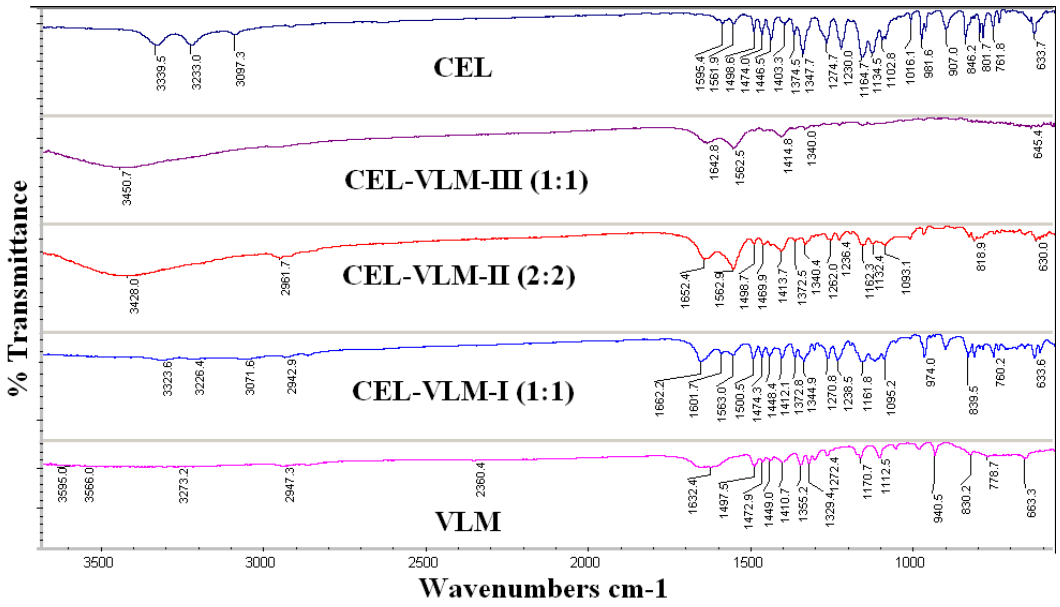


(e) CEL–AZL (f) CEL–AZL

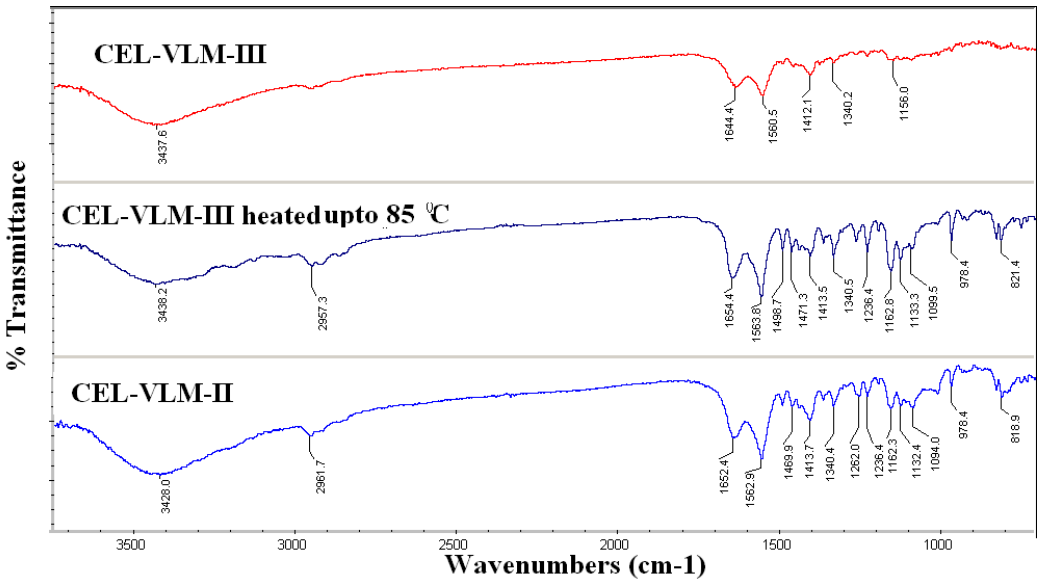
Fig. S5 (a) Crystal structure of CEL–VLM-III (1:1) is sustained by amide dimer and sulfonamide catemer synthons, along with (b) auxiliary C–H···F interactions. (c) Sulfonamide–carboxamide heterosynthon of N–H···O H-bonds in CEL–2-PYR. (d) A view of the trimer synthon of two CEL and one PYR molecules. (e) CEL and AZL dimer $R_2^2(8)$ motifs are connected by N–H···O hydrogen bonds, which extend through C–H···F interactions.



(a)

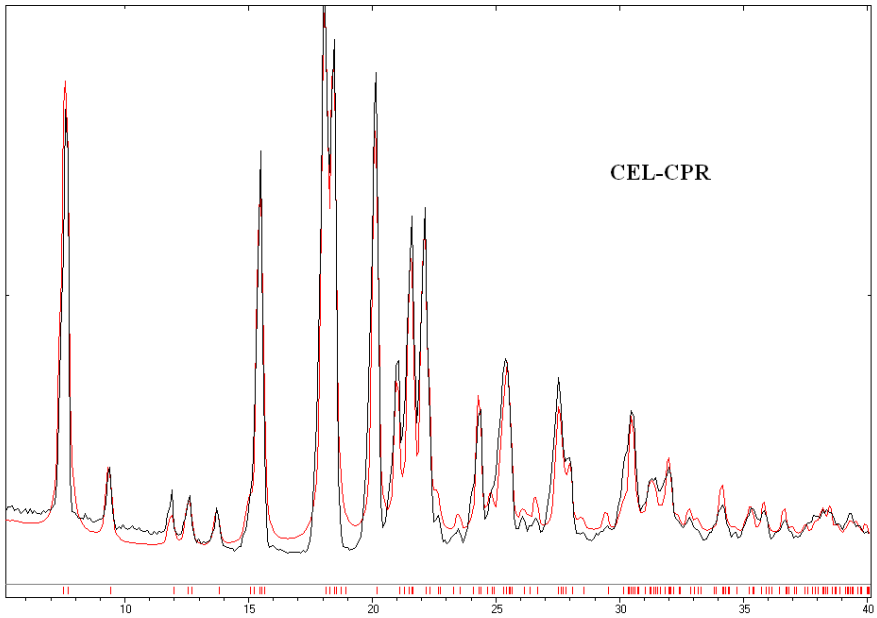


(b)

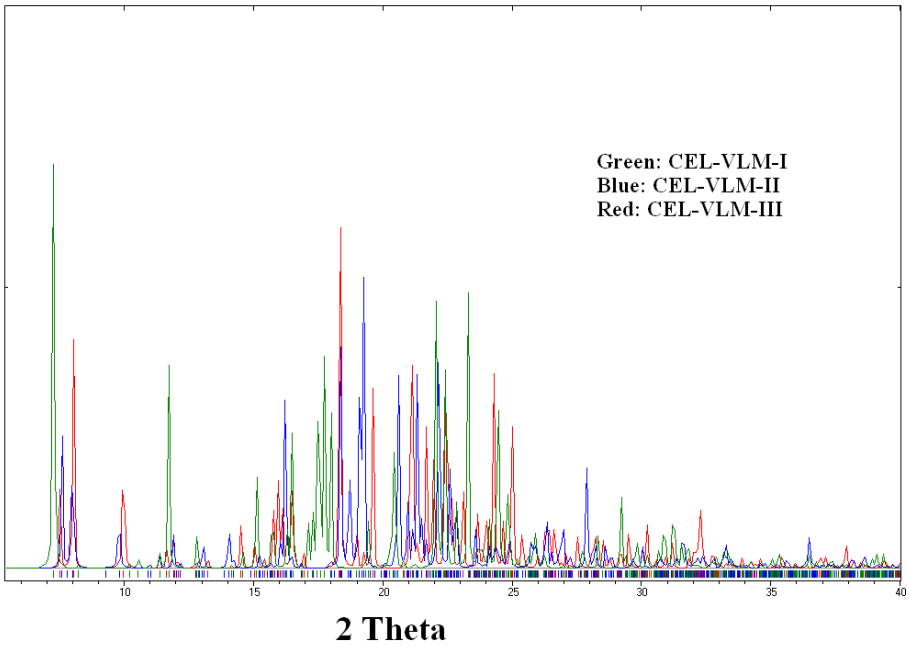


(c)

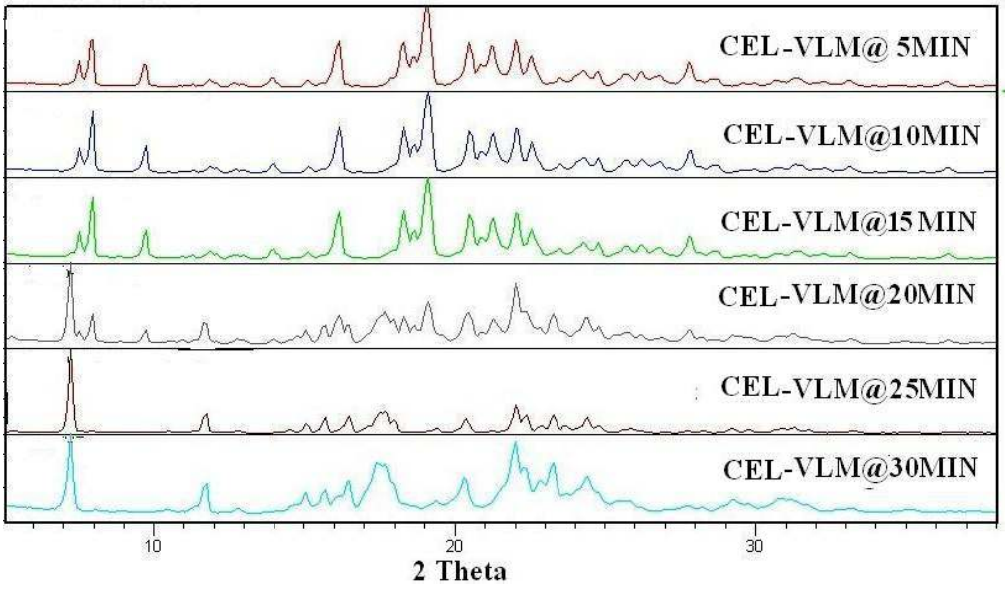
Fig. S6 FT-IR spectra. (a) CEL, CPR and grinded material in (1:1) ratio CEL–CPR; (b) CEL, VLM and trimorphic forms CEL–VLM-I, CEL–VLM-II and CEL–VLM-III; (c) Heating form III CEL–VLM up to 85 ˚C shows peak at 1654.4 cm^{-1} that is characteristic of CEL–VLM-II, to show phase transformation of form III to form II upon heating.


CEL-CPR
10
15
20
25
30
35
40
2 Theta

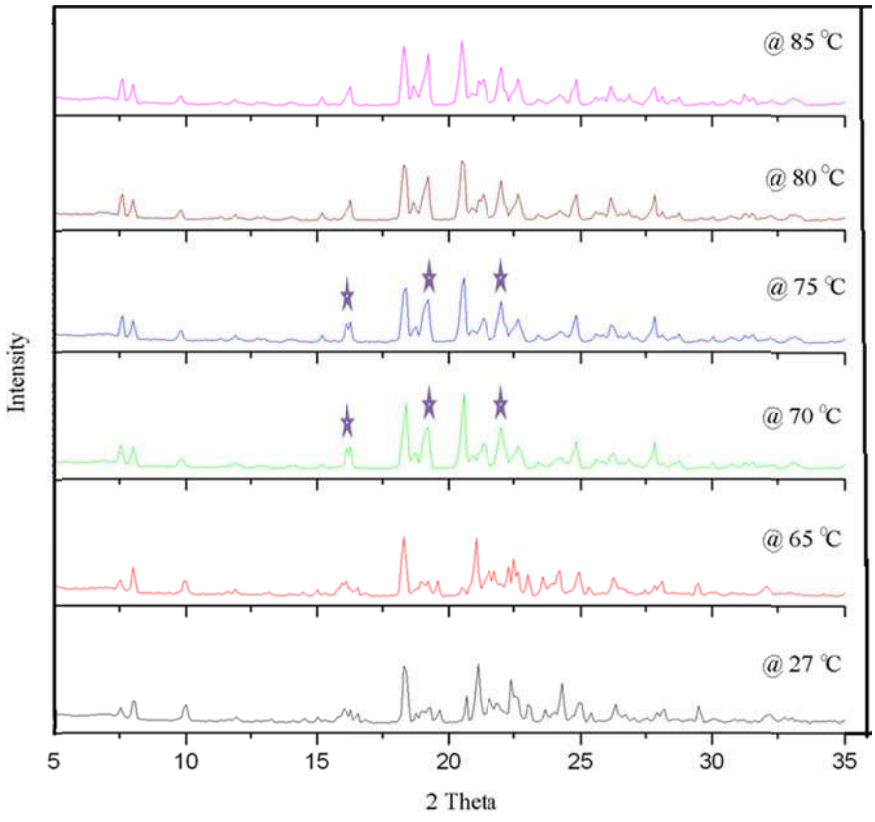
(a)


Green: CEL-VLM-I
Blue: CEL-VLM-II
Red: CEL-VLM-III
10
15
20
25
30
35
40
2 Theta

(b)



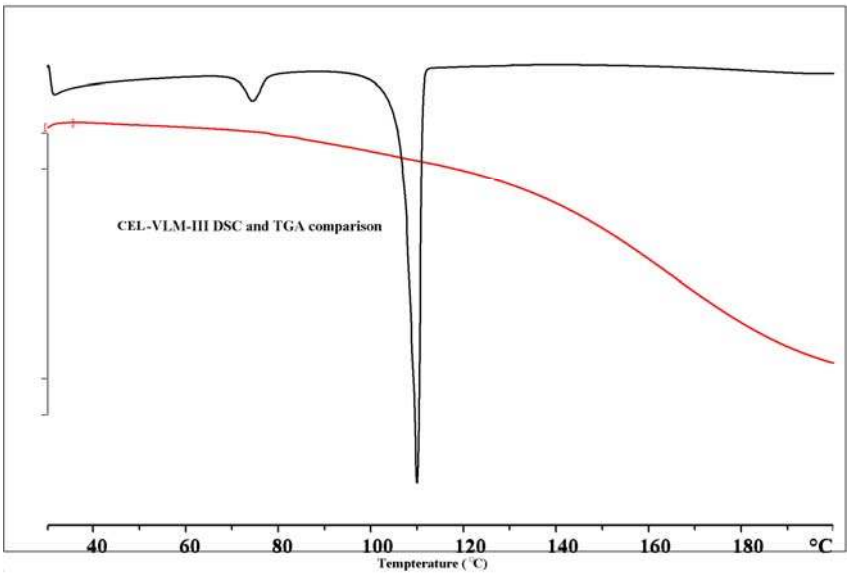
(c)



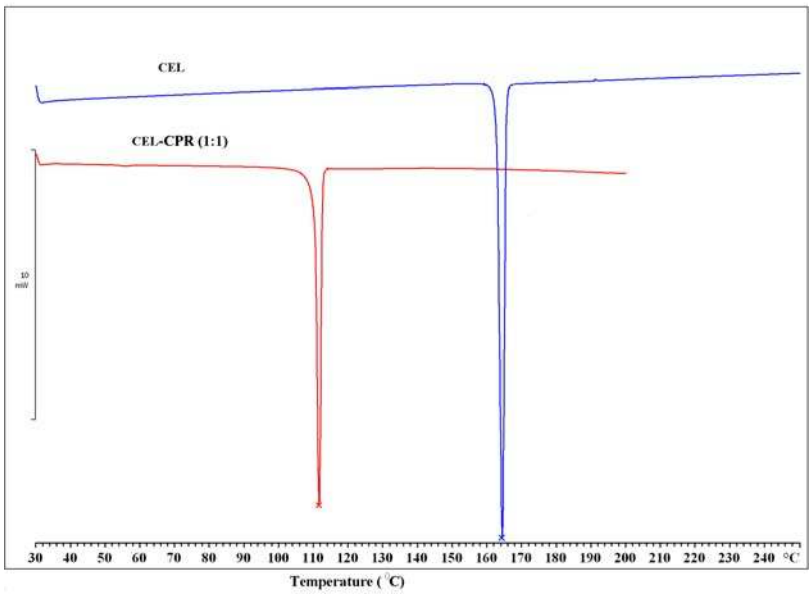
(d)

Fig. S7 (a) PXRD comparison of CEL–CPR (1:1) grinded material (black) with the calculated lines from the X-ray crystal structure (red) indicate purity of the bulk phase. (b) Calculated X-ray diffraction lines of CEL–VLM polymorphs I-III. (c) PXRD comparison of an equimolar ratio of CEL and VLM grinding experiment for different times of 5-30 min shows gradual transformation from polymorph II to I (CEL–

VLM-I is product) at room temperature. (d) VT-PXRD of CEL–VLM-III up to 85 °C showed conversion to CEL–VLM-II at 70 °C.



(a)



(b)

Fig. S8 (a) DSC and TGA of CEL–VLM-III. There is no weight loss at 70-80 ˚C which indicates a phase transformation. (b) DSC of CEL and CEL–CPR (1:1) to show the melting point of the cocrystal.

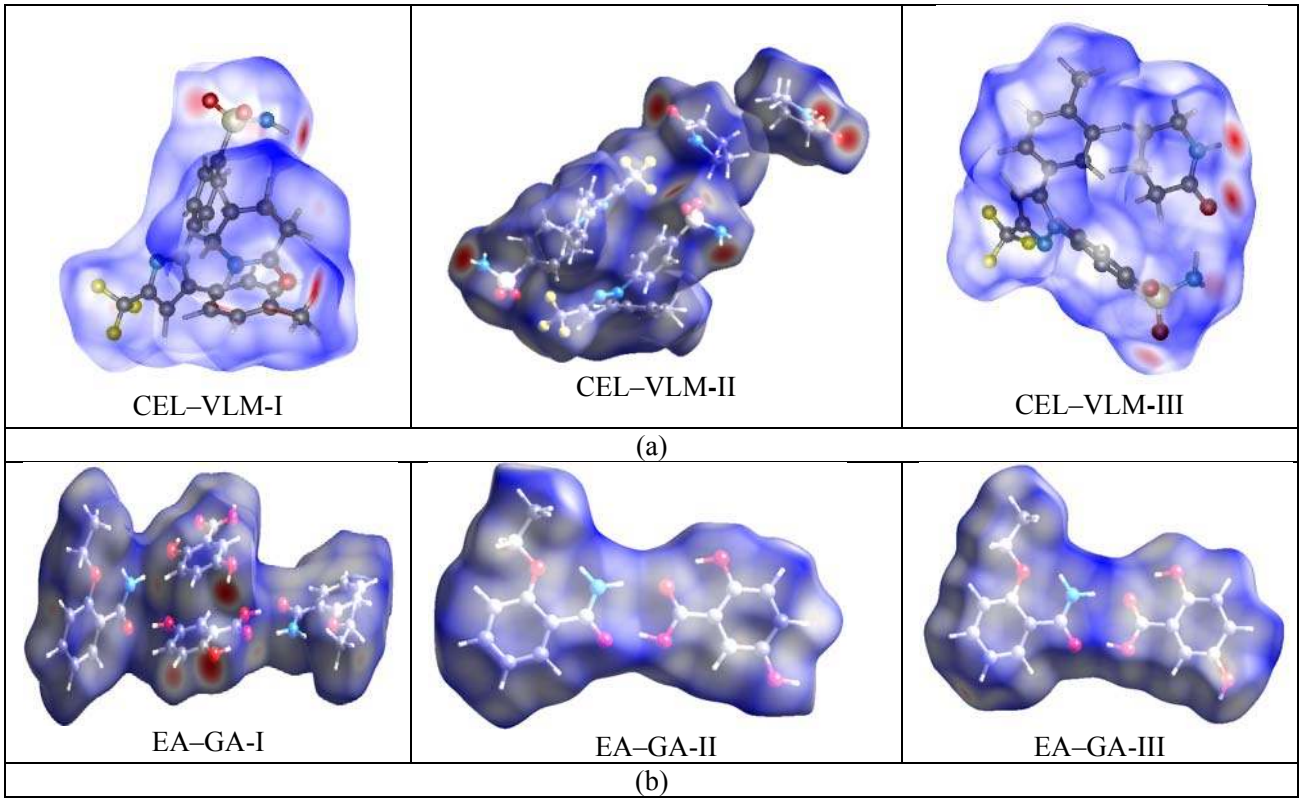
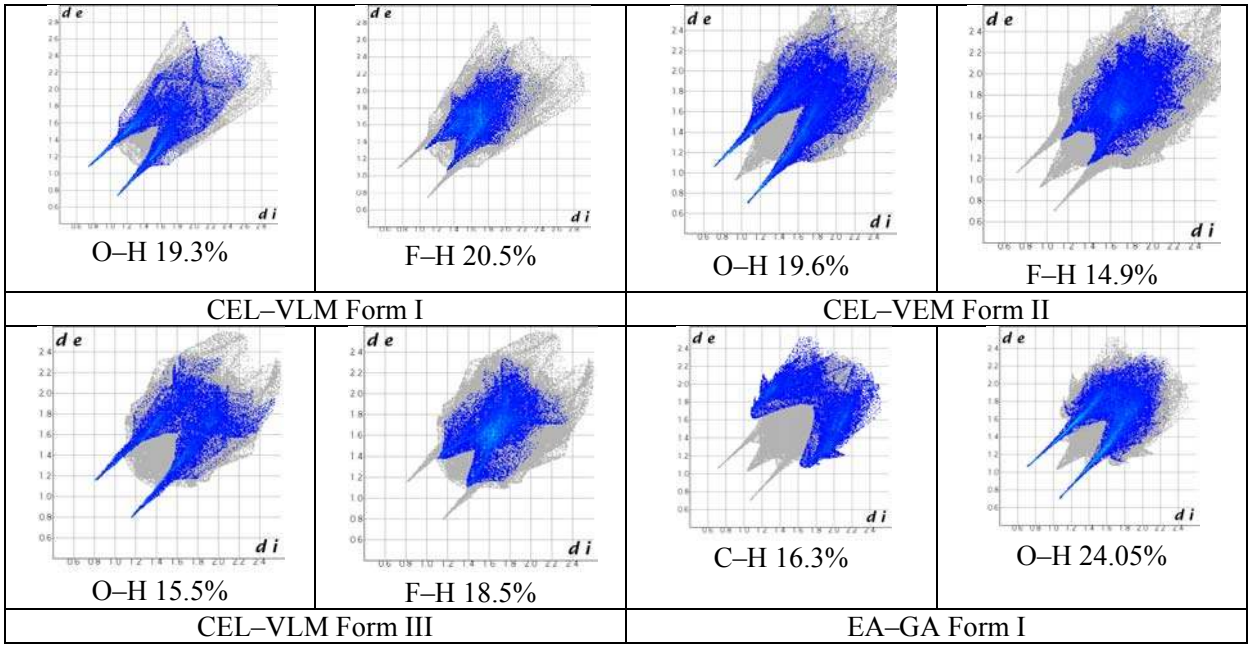


Fig. S9 Hirshfeld surface electron density maps of polymorphic cocrystals. (a) CEL–VLM-I, CEL–VLM-II, and CEL–VLM-III; (b) EA–GA-I, EA–GA-II and EA–GA-III.



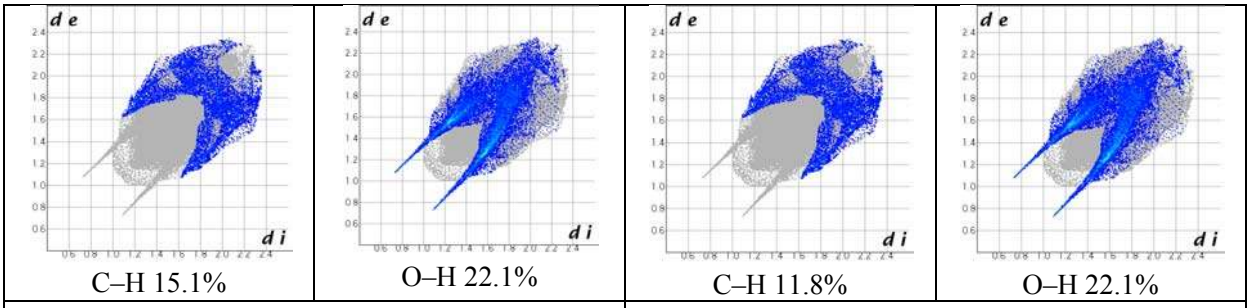


Fig. S10 Hirshfeld finger print plots of the top two (major) interactions in trimorphs. (a) O···H + F···H in CEL–VLM and O···H + C···H in EA–GA structures (see Table 1 for values).

Experimental Section

Celecoxib was purchased from Yarrow Chemicals, Mumbai, India and the coformers and solvents were purchased from Merck/Aldrich-Sigma local suppliers. All chemicals are of analytical or chromatography grade. Water filtered through a double deionized purification system (AquaDM, Bhanu, Hyderabad, India) was used in all experiments. Experimental details of cocrystal preparation are summarized below.

Table S8 Summary of experimental conditions for CEL cocrystals.

Crystal form	CEL (mg, mmol)	Coformer (mg, mmol)	Solvent added for grinding	Solvent for crystallization (v/v ratio)
CEL	100.0,	---	---	---
CEL–2PY (1:1)	100.0, 0.262	22.2, 0.262	EtOAC, THF	EtOAC, THF (1:1)
CEL–VLM-I (1:1)	100.0, 0.262	25.99, 0.262	EtOAC, THF	THF, Anisole
CEL–VLM-II (1:1)	100.0, 0.262	25.99, 0.262	EtOAC, THF	EtOAC–Cyclohexane (1:1), THF–Cyclohexane (1:1).
CEL–VLM-III (1:1)	100.0, 0.262	25.99, 0.262	EtOAC, THF	THF–Cyclohexane (1:1)
CEL–CPR (1:1)	100.0, 0.262	29.6, 0.262	EtOAC, THF	Anisole–THF (1:1)
CEL–AZL (1:1)	100.0, 0.262	33.29, 0.262	EtOAC, THF	EtOAC, Anisole–THF (1:1)

CEL–PYR (1:1) cocrystal

100 mg (0.262 mmol) of the celecoxib and 22.2 mg (0.262 mmol) PYR were ground in a mortar-pestle for 20 min by liquid assisted grinding Ethylacetate, THF as a solvent, and then kept for crystallization in 10 mL Ethyl acetate–THF solvent mixture (1:1) in v/v ratio at room temperature in 25 mL conical flask covered with Aluminum paper. Block morphology crystals appeared after solvent evaporation at ambient conditions after 3-4 days. m.p. 130-131 °C.

CEL–VLM-I (1:1) cocrystal

100 mg (0.262 mmol) celecoxib and 25.99 mg (0.262 mmol) VLM were ground in a mortar-pestle for 10 min by liquid assisted grinding Ethylacetate, THF as a solvent, and then kept for crystallization in 10 mL Ethyl acetate–THF, EtOAc–Cyclohexane solvent mixture (1:1) in v/v ratio and in Anisole (10 mL) at room temperature in 25 mL conical flask covered with Aluminum paper. Block morphology crystals appeared after solvent evaporation at ambient conditions after 3-4 days. m.p. 106-108 °C.

CEL–VLM-II (1:1) cocrystal

100 mg (0.262 mmol) celecoxib and 25.99 mg (0.262 mmol) VLM were ground in a mortar-pestle for 20 min by liquid assisted grinding Ethyl acetate, THF as a solvent, and then kept for crystallization in 10 mL Ethyl acetate–THF, EtOAc–Cyclohexane solvent mixture (1:1) in v/v ratio at room temperature in 25 mL conical flask covered with Aluminum paper. Block morphology crystals appeared after solvent evaporation at ambient conditions after 3-4 days. m.p. 108-111 °C.

CEL–VLM-III (1:1) cocrystal

100 mg (0.262 mmol) celecoxib and 25.99 mg (0.262 mmol) VLM were kept direct crystallization in different solvents like EtOAc, THF, EtOAc:Cyclohexane, THF:Cyclohexane in 1:1 v/v ratio at room temperature in 25 mL conical flask covered with aluminum foil. After 3-4 days good quality crystals were appeared. m.p 71-72 °C.

CEL–CPR (1:1) cocrystal

100 mg (0.262 mmol) celecoxib and 29.6 mg (0.262 mmol) CPR were ground in a mortar-pestle for 20 min by liquid assisted grinding Ethylacetate/THF as a solvent, and then kept for crystallization in 10 mL Ethyl acetate–THF, EtOAc–Cyclohexane, Anisole–THF solvent mixture (1:1) in v/v ratio at room temperature in 25 mL conical flask covered with Aluminum paper. Block morphology crystals appeared after solvent evaporation at ambient conditions after 3-4 days. m.p. 110-111 °C.

CEL–AZL (1:1) cocrystal

100 mg (0.262 mmol) celecoxib and 33.29 mg (0.262 mmol) AZL were ground in a mortar-pestle for 20 min by liquid assisted grinding Ethyl acetate/THF as a solvent, and then kept for crystallization in 10 mL Ethyl acetate as a solvent at room temperature in 25 mL conical flask covered with Aluminum paper. Block morphology crystals resulted after solvent evaporation at ambient conditions after 3-4 days. m.p. 108-109 °C.

Single crystal X-ray diffraction

A single crystal obtained from the crystallization solvent(s) was mounted on the goniometer of Oxford Gemini (Oxford Diffraction, Yarnton, Oxford, UK) or Bruker Smart (Bruker-AXS, Karlsruhe, Germany) X-ray diffractometer equipped with Mo-Kα radiation source (λ = 0.71073 Å). Data reduction was performed using CrysAlisPro 171.33.55 software. Crystal structures were solved and refined using Olex2-1.0 with anisotropic displacement parameters for non-H atoms. Hydrogen atoms were experimentally located through the Fourier difference electron density maps in all crystal structures. All O–H, N–H and C–H atoms were geometrically fixed using HFIX command in SHELX-TL program of Bruker-AXS. A check of the final crystallographic information file (CIF) with PLATON did not show any missed symmetry. X-Seed was used to prepare the figures and packing diagrams. Crystallographic .cif files are deposited with the CCDC Nos. 954140 – 954145.

Powder X-ray diffraction

All the new solid phases, CEL and coformers were analyzed by Powder X-ray diffraction on a Bruker AXS D8 diffractometer (Bruker-AXS, Karlsruhe, Germany). Experimental conditions: Cu-Kα radiation (λ = 1.54056 Å); 40 kV; 30 mA; scanning interval 5-50° 2θ at a scan rate of 1° min^{-1}; time per step 0.5 s.

The experimental PXRD patterns and calculated X-ray lines from the single crystal structure were compared to confirm the purity of the bulk phase of cocrystals using Powder Cell.

Thermal analysis

DSC experiments were performed on a Mettler-Toledo DSC 822e module. Samples were placed in vented aluminum sample pans for DSC. A typical sample size is 2-5 mg for DSC. The temperature range was 30-250 °C at 5K min^{-1} for DSC. Samples were purged with a stream of dry N_2 gas flowing at 80 mL min^{-1}.

Vibrational spectroscopy

Thermo-Nicoet 6700 FT-IR spectrometer (Waltham, MA, USA) was used to record IR spectra. IR spectra were recorded on samples dispersed in dry KBr pellets.

Solid-state NMR spectroscopy

The solid-state 13C NMR spectra were obtained on a Bruker Ultrashield 400 spectrometer (Bruker BioSpin, Karlsruhe, Germany) utilizing a ^{13}C resonant frequency of 100 MHz (magnetic field strength of 9.39 T). Approximately 100 mg of crystalline sample was lightly packed into a zirconium rotor with a Kel-F cap. The crosspolarization, magic angle spinning (CP-MAS) pulse sequence was used for spectral acquisition. Each sample was spun at a frequency of 5.0 ± 0.01 kHz and the magic angle setting was calibrated by the KBr method. Each data set was subjected to a 5.0 Hz line broadening factor and subsequently Fourier transformed and phase corrected to produce a frequency domain spectrum. The chemical shifts were referenced to TMS using glycine (δ glycine = 43.3 ppm) as an external secondary standard.

References

1. E. Elacqua, D. Bucar, R. F. Henry, G. G. Z. Zhang and L. R. MacGillivray, *Cryst. Growth. Des.*, 2013, **13**, 393.
2. N. R. Goud, N. J. Babu and A. Nangia, *Cryst. Growth Des.*, 2011, **11**, 1930.