Multicomponent ternary cocrystals of the sulfonamide group with pyridine-amides and lactams

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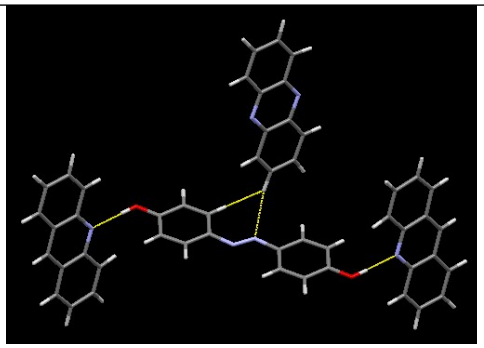
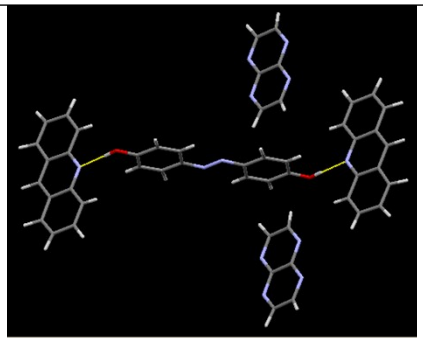
Electronic Supplementary Information†

Table S1 Refcodes of ternary cocrystals extracted from the CSD November 2014, May 2015 update (68 hits).

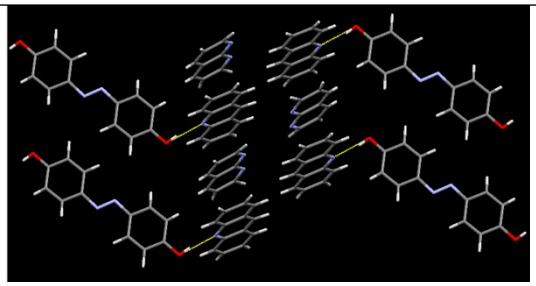
AJAKIF	BIZTIP	BUDZUV	BUFBIP	BUFQAU	ESAXIF	ENAZOI	ENAZOI01
ENEBII	ESAXIF	FIDKIN	FIJCUW	GIKROJ	KOSMUA	LENBAI	LENBEM
LENBIQ	LENBOW	LENBUC	LODMUO	LODNAV	PILLED	PILLIH	PILLON
POKFAX	QAHNAO	UBUHUW	QUQCUB	QUQCUB02	QUQPUN	SASBEU	SASBIY
TOJCEB	UBUHIK	UBUHUW	UBUJAE	UBUJEI	UBUJOS	UBUJUY	UBUKOT
UBUKEJ	UBUKUZ	VEWQAP	VILSAL	XABPOG	XAQPOV	XAQPUB	XOSSIH
YEDKAU	UTAGIG	KAVFET	BICQEL	BICQAH	BEYZEM	MEFZEM	FOTCUO
FOTDAV	FOTDID	FOTDEZ	FOTDOJ	FOTDUP	FOTFIF	FOTFOL	FORFUR
ROPKEO	ROPKAK	ROPKIS	ROPKOY				



4,4'-bis-hydroxyazobenzene:Acridine:Phenazine (1:2:2)



4,4'-bis-hydroxyazobenzene:Acridine:QNX (1:2:2)



4,4'-bis-hydroxyazobenzene:Acridine:QN (1:2:2)

Figure S1 Crystal structures of 3 ternary cocrystals published in ref. 1 (not yet archived in the CSD).

Table S2 Crystallographic parameters of binary and ternary cocrystals. and the solvent system used to obtain the single crystals.

	SMBA–VLM (1:1)	SMBA–CPR (1:2)	SMBA–NAM (1:2)	SMBA–INA (1:1)	SMBA–PAM (1:1)
Empirical Formula	$C_7H_7NO_4S$, C_5H_9NO	$C_7H_7NO_4S$, $2(C_6H_{11}NO)$	$C_7H_7NO_4S$, $2(C_6H_6N_2O)$	$(C_7H_7NO_4S)$, $(C_6H_6N_2O)$	$C_7H_7NO_4S$, $C_6H_6N_2O$
Formula weight	300.33	427.51	445.45	323.33	323.33
Crystal system	Triclinic	Orthorhombic	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	$P2_12_12_1$	*P*-1	*C*2/*c*	$P2_1/n$
T (K)	298	298	298	298	298
a (Å)	8.2121(5)	7.0964(5)	5.0179(5)	31.237(4)	10.2113(10)
b (Å)	9.3439(6)	16.230(2)	11.3168(17)	5.1056(6)	8.0850(6)
c (Å)	10.6539(8)	19.1256(15)	18.156(2)	20.362(2)	17.663(2)
α (°)	112.237(7)	90	95.966(12)	90	90
β (°)	106.40(6)	90	90.050(9)	124.55(2)	92.03(9)
γ (°)	95.743(5)	90	95.469(10)	90	90
V (Å^3)	705.92(8)	2202.8(4)	1020.7(2)	2674.6(7)	1457.3(2)
D_{calcd} (g cm^{-3})	1.413	1.289	1.449	1.606	1.474
μ (mm^{-1})	2.245	1.642	0.207	0.272	0.250
θ range	2.24 to 72.00	3.51 to 60.58	2.34 to 26.37	2.43 to 27.29	2.84 to 26.36
Z	2	4	2	8	4
R_1 [$I > 2\sigma(I)$]	0.055	0.0872	0.0548	0.0438	0.0530
wR_2 (all)	0.1543	0.2387	0.1269	0.1198	0.1190
Goodness of fit	1.059	0.932	1.040	1.056	1.005
X–Ray diffractometer	Oxford	Oxford	Oxford	Bruker	Oxford
Crystallization solvent(s)	EtOAc, THF	EtOAc, THF	EtOAc, THF	EtOAc+THF (1:1)	EtOAc, THF
CCDC No.	1414177	1414163	1414170	1414167	1414175

SMBA–2HP Form I (1:1)	SMBA–2HP Form II (1:1)	SMBA–2HP Form III (1:1)	SMBA–MeHP (1:2)	SMBA–OMeHP (1:2)	SMBA–NAM–2HP (1:1:1)
C_7H_7NO4S, C_5H_5NO	C_7H_7NO4 S, C_5H_5NO	$C_7H_7NO_4S$, C_5H_5NO	C_7H_7NO4S, $2(C_6H_7NO)$	$C_7H_7NO_4S$, $2(C_6H_7NO_2)$	$C_7H_7NO_4S$, $C_6H_6N_2O$, C_5H_5NO
296.30	296.30	296.30	419.45	451.45	418.42
Monoclinic	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
$P2_1/c$	P-1	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_1/c$
298	298	298	298	298	298
14.990(4)	5.3090(3)	8.464(3)	7.3848(8)	6.95437(16)	19.7594(7)
11.3156(3)	10.5807(8)	9.721(3)	31.150(3)	12.7192(3)	5.25798(10)
7.90(2)	12.1499(10)	16.137(5)	8.9746(9)	23.9115(5)	20.2747(7)
90	76.377(7)	90	90	90	90
95.96(11)	89.18(6)	100.00	90.67	92.73	117.92
90	77.195(6)	90	90	90	90
1333(3)	646.28(8)	1307.6(7)	2064.3(4)	2112.66(8)	1861.18(12)
1.476	1.523	1.505	1.350	1.419	1.493
2.377	2.452	0.269	0.197	1.826	1.959
2.22 to 65.08	2.25 to 67.08	2.44 to 27.32	2.36 to 25.94	5.05 to 71.99	4.31 to 71.64
4	2	4	4	4	4
0.0597	0.0493	0.0502	0.0442	0.0410	0.0406
0.1880	0.1410	0.1438	0.1236	0.1148	0.1202
1.067	1.029	1.081	1.057	1.070	1.056
Oxford	Oxford	Bruker	Bruker	Oxford	Oxford
EtOAc, THF	EtOAc, THF	EtOAc, THF	EtOAc, THF	EtOAc, THF	EtOAc, THF
1414164	1414165	1414166	1414169	1414174	1414171

SMBA–INA–2HP (1:1:1)	SMBA–NAM–MeHP (1:1:1)	SMBA–NAM–OMeHP (2:1:2)	SMBA–PAM–MeHP (1:1:1)
$C_7H_7NO_4S$, $C_6H_6N_2O$, C_5H_5NO	$C_7H_7NO_4$ S, $C_6H_6N_2$ O, C_6H_7NO	$2(C_7H_7NO_4$ S), $C_6H_6N_2$ O, $2(C_6H_7NO_2)$	$C_7H_7NO_4S$, $C_6H_6N_2O$, C_6H_7NO
418.42	432.45	774.77	432.46
Monoclinic	Monoclinic	Monoclinic	Monoclinic
$P2_1/c$	$P2_1/c$	$C2/c$	$P2_1/n$
298	298	298	298
20.4140(14)	8.2357(8)	13.2514(3)	11.5333(3)
6.5885(4)	26.102(3)	7.05170(19)	7.91065(17)
14.7470(9)	9.2781(9)	38.1412(9)	22.4905(7)
90	90	90	90
101.67	98.28	91.96	100.021(3)

90	90	90	90
1942.4(2)	1973.7(3)	3562.02(15)	2020.65(9)
1.431	1.455	1.445	1.422
1.877	0.210	2.002	1.823
4.37 to 71.57	2.35 to 25.95	4.13 to 71.53	3.54 to 67.080
4	4	4	4
0.0596	0.055	0.0320	0.0647
0.2053	0.12	0.0857	0.1582
1.112	1.204	1.081	1.125
Oxford	Bruker	Oxford	Oxford
EtOAc, THF	EtOAc, THF	EtOAc, THF	EtOAc, THF
1414168	1414172	1414173	1414176

Crystal structure description of binary cocrystals:

The crystal structure of binary cocrystals are discussed first, followed by the ternary cocrystals.

Binary systems of SMBA with pyridine carboxamide coformers:

SMBA–NAM (1:2): Binary cocrystal of SMBA–NAM was crystallized in the triclinic system under *P*-1 space group and contains two molecules of NAM and one molecule of SMBA in the asymmetric unit. Both the NAM molecules form amide homodimers (Figure S2a). One homodimer of NAM is further connected to pyridine N of a neighbor NAM via N–H···N hydrogen bond and by acid–pyridine heterosynthon to the carboxylic acid of SMBA. Inversion related SMBA molecules form heterodimer between sulfonamide and carboxylic acid groups. The sulfonamide functional group forms catemer chain along the *a*-axis via N–H···O hydrogen bonds (Figure S2b).

SMBA–INA (1:1): Crystal structure of SMBA–INA was solved in the monoclinic *C*2/*c* crystals system. Homodimers of INA form acid-amide heterosynthon with anti N–H amide and C=O of the acid groups. The O–H of carboxylic acid forms acid-pyridine heterosynthon with INA pyridine N atom. The SMBA molecules form dimers via sulfonamide and carboxylic acid groups (N–H···O, Figure S2c,d), and furthermore the sulfonamides extended through catemer chains (H–N···S=O) along the 2_1 screw axis.

SMBA–PAM (1:1): SMBA–PAM single crystal was mounted on the diffractometer and the structure was solved in monoclinic crystal of $P2_1/c$ space group. SMBA being a para-substituted bifunctional molecule (sulfonamide, carboxylic acid), our idea was to get the sulfonamide-carboxamide heterosynthon $R_2^2(8)R_4^2(8)R_2^2(8)$ motifs, but what was observed is the acid-amide synthon. The pyridine N of PAM is not available for H bonding (due to intramolecular H bonding with an NH donor and also sterically shielded) (Figure S2e). The acid–amide synthon interacts with the anti N–H of PAM in a three point synthon. The sulfonamide group forms a catemer chain along the *b*-axis (Figure S2f). The PAM molecules are inserted between the sulfonamides catemer chains to give a ladder like motif.

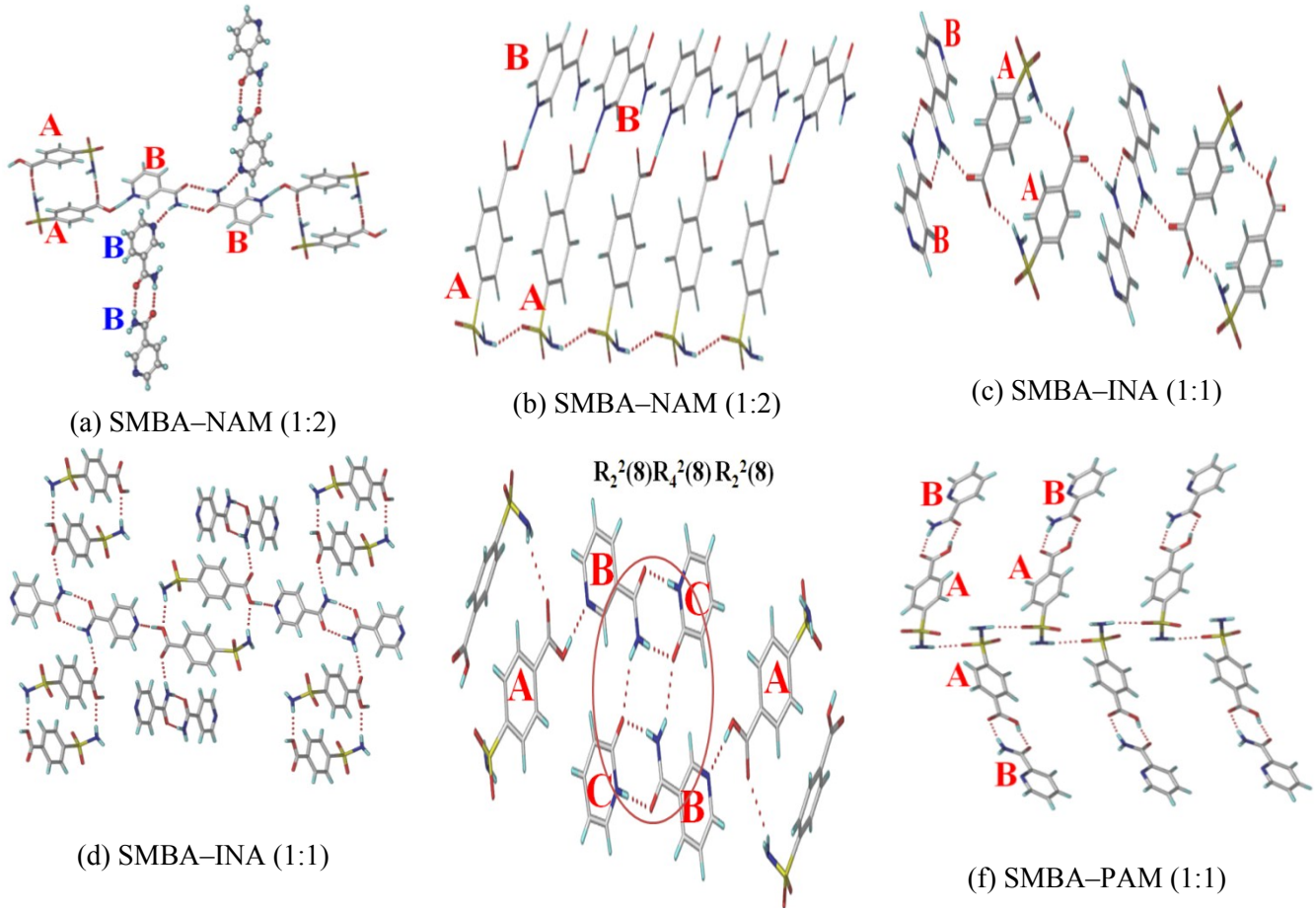
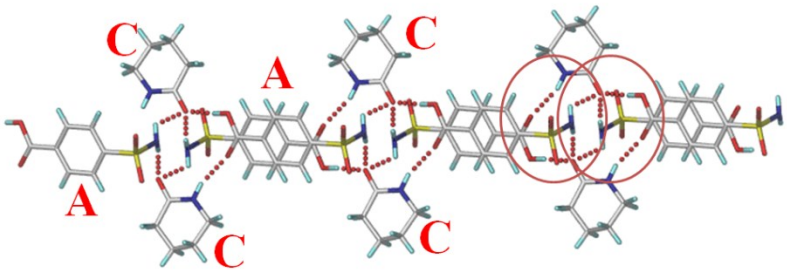


Figure S2 (a) and (b) SMBA–NAM (1:2): NAM dimers form acid-pyridine synthons on either side of SMBA dimers and these units are further connected to NAM dimers. Sulfonamide catemer chains in SMBA–NAM (1:2). (c) and (d) SMBA–INA (1:1): SMBA dimers form acid-amide, acid-pyridine synthon with INA. Acid-amide pairs are connected through N–H···O H bonds. SMBA sulfonamide dimers connected to INA dimers. (e) and (f) SMBA–PAM (1:1): Acid-amide heterosynthon followed between PAM molecules and connected to the sulfonamide N–H of SMBA. (f) Sulfonamide catemer N–H···O chain.

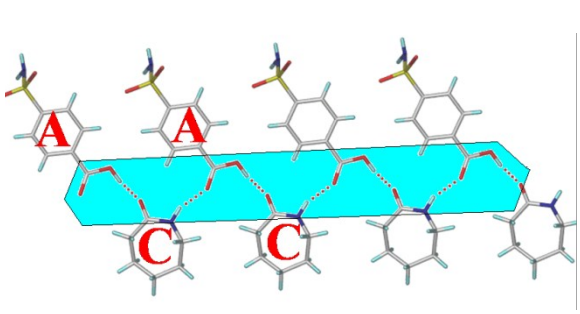
Binary systems of SMBA with aliphatic syn-amides, or lactams:

SMBA–VLM (1:1): The carboxylic acid of SMBA forms hydrogen bonds with two VLM molecules via N–H···O and O–H···O interactions. Carbonyl group of the VLM forms trifurcated hydrogen bonds with two different sulfonamide N–H and carboxylic acid O–H of SMBA (Figure S3a). All the functional groups are engaged in multiple hydrogen bonds, which results intersect rings motifs and trifurcated/ bridged synthons in this structure.

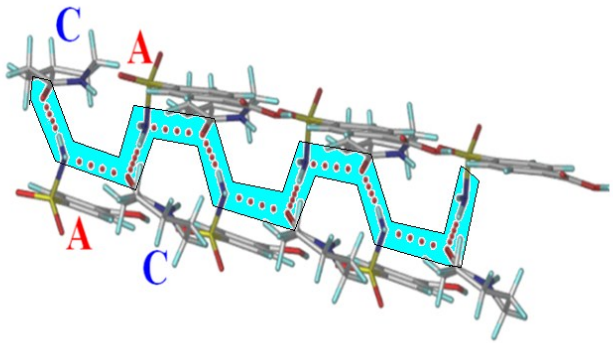
SMBA–CPR (1:2): The cocrystal SMBA–CPR crystallized in orthorhombic space group $P2_12_12_1$ with two CPR and one SMBA in the asymmetric unit. symmetry-independent CPR molecules form catemer C(4) chains of carboxylic acid groups with CPR amide, and another set of CPR also forms catemer C(4) chains, now with sulfonamide group (see ref. 2) and amide of CPR (Figure S3b,c).



(a) SMBA–VLM (1:1)



(b) SMBA–CPR (1:2)



(c) SMBA–CPR (1:2)

Figure S3 (a) The carbonyl group of VLM forms trifurcated hydrogen bonds and complex motifs in SMBA–VLM. (b) and (c) SMBA–CPR (1:2): One asymmetry-independent CPR forms acid-amide catemer chains while the second CPR forms sulfonamide-amide catemer chains along the *a*-axis.

Binary systems of SMBA with 2-hydroxypyridone (2HP) derivatives:

Cocrystal of SMBA with 2HP resulted in a trimorphic cluster designated as Form I, II and III. Their crystal structures are described below.

SMBA–2HP (1:1) Form I: Form I (crystallized in monoclinic $P2_1/c$ space group) was prepared by neat grinding and crystallization from common solvents. The C=O acceptor of 2HP forms bifurcated hydrogen bonds with carboxylic acid O–H and sulfonamide N–H donors (Figure S4a). 2HP acts as a bridge for sulfonamide and carboxylic acid functional with neighboring SMBA molecules forming a carboxylic acid–syn amide–sulfonamide motif. The other side of sulfonamide N–H forms N–H···O syn catemer chains parallel to the *c*-axis (Figure S4b). No 2HP N–H···O homodimers were observed in this structure.

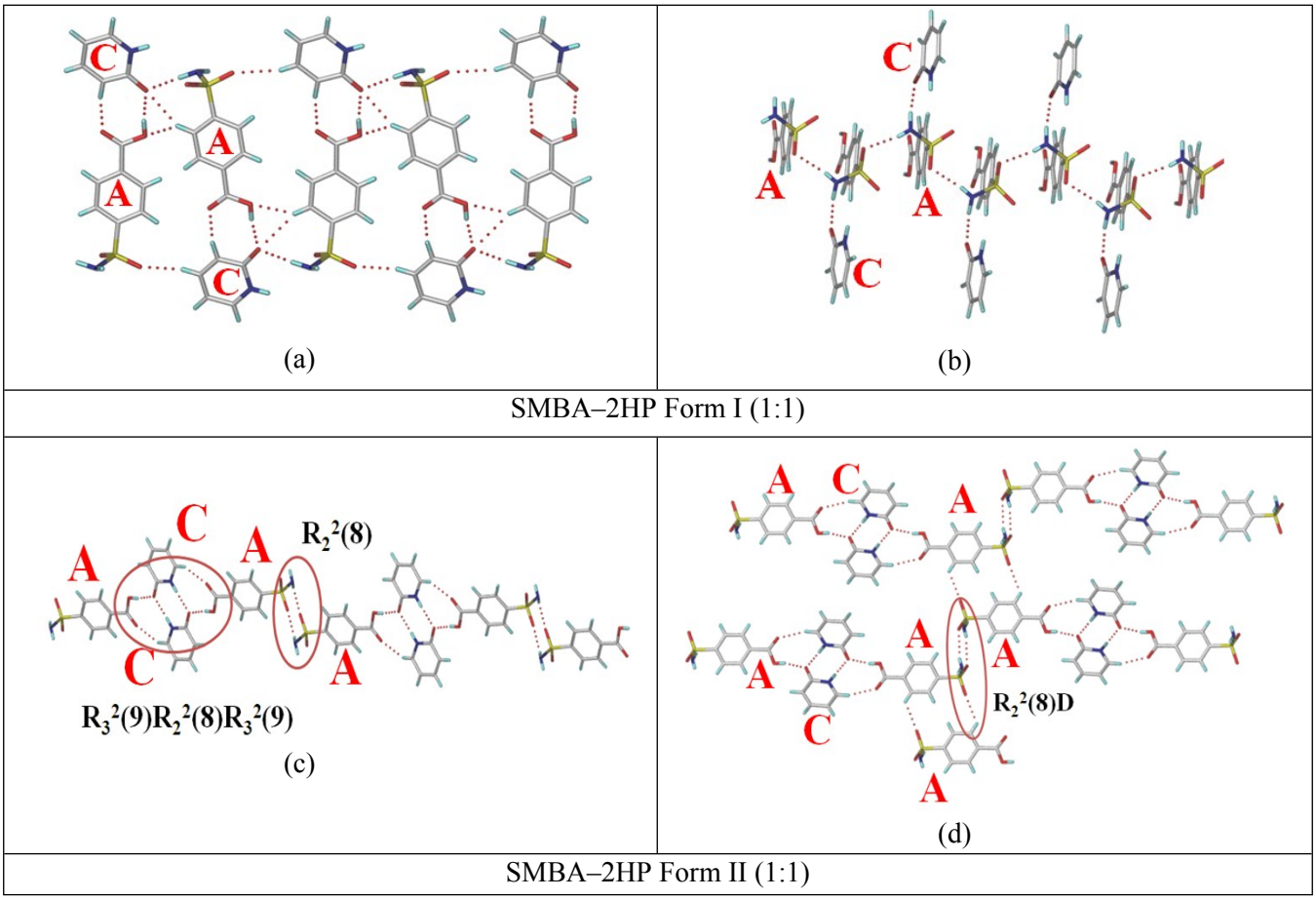
SMBA–2HP (1:1) Form II: Form II was crystallized during attempted ternary crystallization experiments of SMBA + INA + 2HP. The cocrystal was solved in triclinic *P*-1 space group. Homodimers of 2HP form the N–H···O synthon and the carbonyl groups is engaged in bifurcated H bond with the carboxylic acid O–H and further extends via auxiliary C–H···O interactions, in a $R_3^2(9)R_2^2(8)R_3^2(9)$ motif (Figure S4c). The sulfonamide groups form $R_2^2(8)$D ring dimers and further the second N–H forms H bonds with acid C=O in a $R_2^2(8)$D motif (Figure S4d).

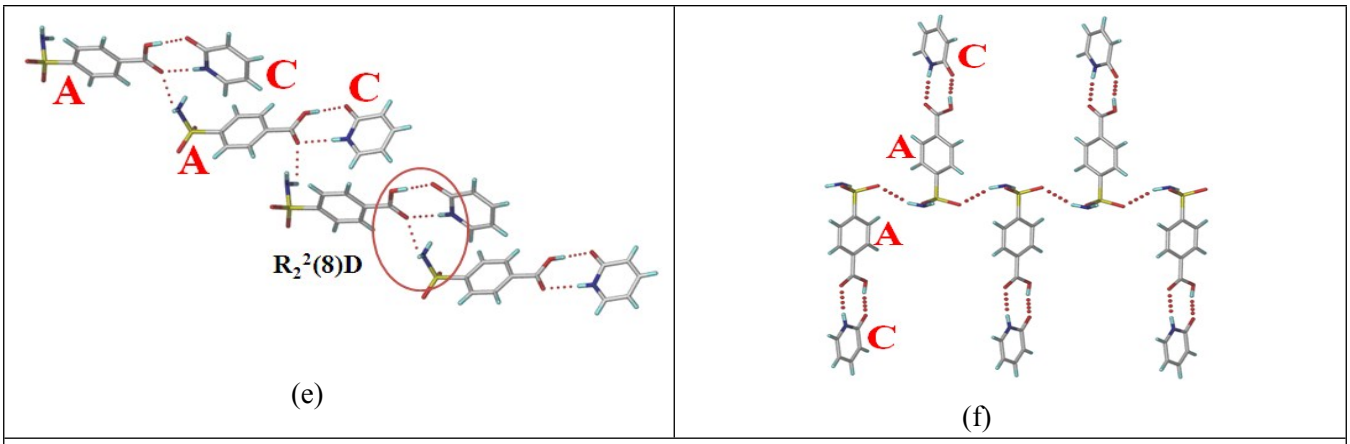
SMBA–2HP (1:1) Form III: Form III crystallized during the solution crystallization experiments performed to obtain the ternary system SMBA + PAM + 2HP. Crystal appeared on the inner walls of the conical flask. Very few crystals were observed in 2-3 batches, and this procedure was not easily reproducible, suggesting that this is a metastable polymorph. It crystallizes in the monoclinic space group $P2_1/c$. The carboxylic acid group of SMBA forms acid-amide heterodimers $R_2^2(8)$D with 2HP along the *b*-axis, which are interlinked via N–H···O bond to the sulfonamide group (Figure S4e). The sulfonamide molecules form catemer chains along the *b*-axis (Figure S4f).

All the three polymorphs shows diverse in synthons, so termed as synthon polymorphs and all were attributed in multiple conditions, these cocrystal polymorphs falls under additive induced polymorph preparation.

SMBA–MeHP (1:2): Cocrystal consists of amide–amide homodimer between two asymmetric units of MeHP and sulfonamide molecules form catemer chain along the *c*-axis (Figure S4g). One asymmetric MeHP carbonyl forms bifurcated hydrogen bond with sulfonamide N–H and another carbonyl forms bifurcated H bond with carboxylic acid of SMBA. Amide homodimers reside between sulfonamide catemer chains along the *c*-axis and finally attain ladder motifs similar to few previous binary systems in this study (Figure S4h).

SMBA–OMeHP (1:2): One of the two asymmetric OMeHP molecules in SMBA–OMeHP (1:2) forms amide homodimer. Sulfonamide molecules form centrosymmetric dimer synthon between syn N–H and SO_2 groups, whereas anti N–H forms bifurcated hydrogen bonds with amide carbonyl and methoxy oxygen atom (Figure S4i). Homodimers of the sulfonamide and OMeHP are interlinked via N–H···O and C–H···O hydrogen bonding interactions leads to continuous ring motifs ($R_2^2(8)R_1^2(5)R_3^2(9)R_2^2(8)$) along the *b*-axis (Figure S4i, j). Another asymmetric OMeHP attributes acid–amide heterosynthon with COOH of SMBA.

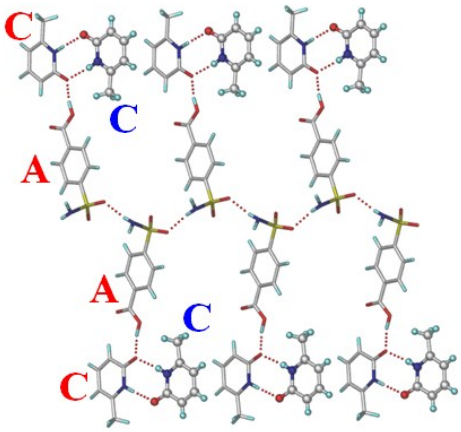




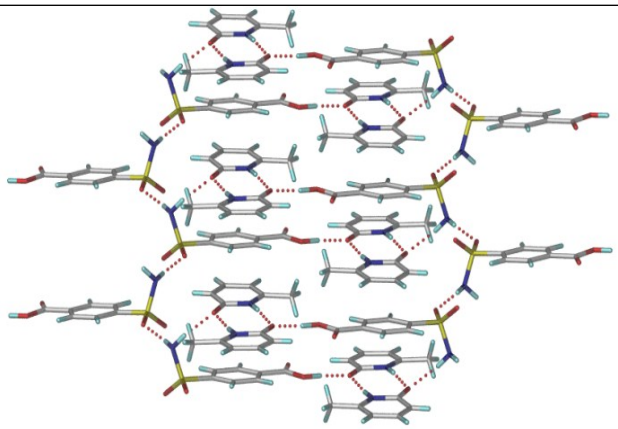
(e)

(f)

SMBA–2HP Form III (1:1)

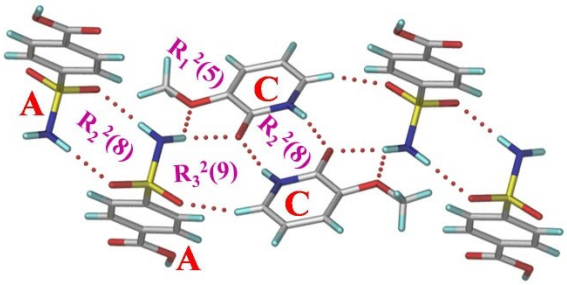


(g)

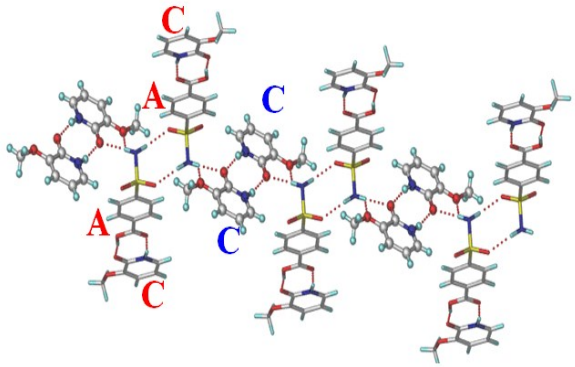


(h)

SMBA–MeHP (1:2)



(i)



(j)

SMBA–OMeHP (1:2)

Figure S4 (a) and (b) SMBA–2HP Form I (1:1): The acid-amide heterosynthon and the sulfonamide catemer chain synthons. (c) and (d) SMBA–2HP Form II (1:1): Four point synthon involving two amide and two SMBA molecules and sulfonamide N–H···O dimers. Additional C–H···O interactions results in a 2D layer structure. (e) and (f) SMBA–2HP Form III (1:1): Acid-amide heterosynthon of SMBA–2HP, which extends via N–H···O bonds with sulfonamide functional group. The sulfonamide group makes N–H···O catemer chains. (g) and (h) SMBA–MeHP (1:2): Sulfonamide catemer chains extend along the *b*-

axis and MeHP homodimers (of symmetry-independent molecules) are hydrogen bonded to the acid group of SMBA. Ladder type motifs along the *a*-axis in the crystal structure. (i) and (j) SMBA–OMeHP (1:2): N–H···O homodimers of amide and sulfonamide groups are interlinked by bifurcated N–H···O bonds.

Crystal description of ternary cocrystals:

The details of five ternary crystal structures are discussed as below.

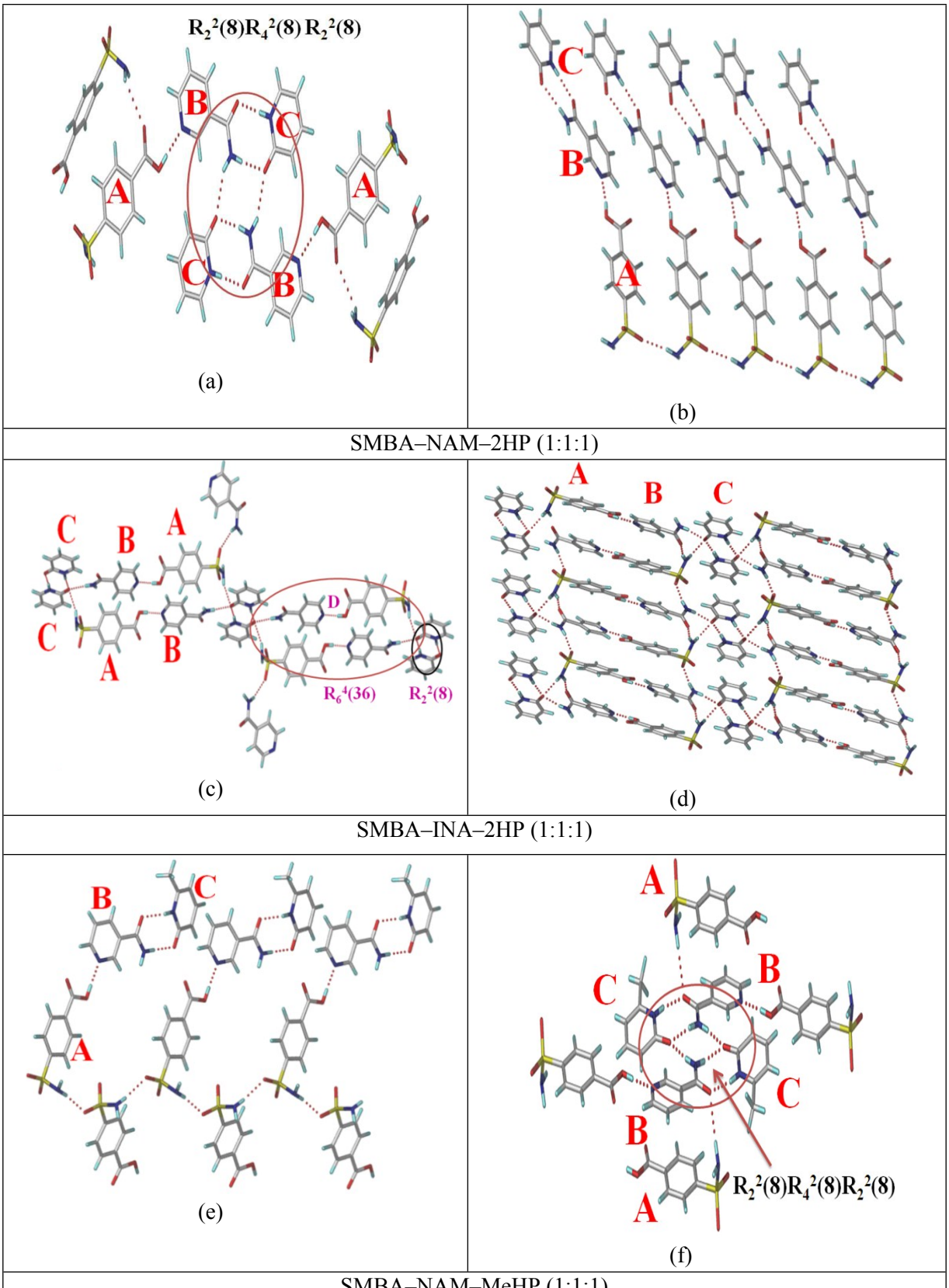
SMBA–NAM–2HP (1:1:1): The crystal structure contains pyridine carboxamide–syn amide heterodimer between NAM and 2HP (Figure S5a). Two heterodimers are interlinked via N–H···O hydrogen bonds via tetramer ring $R_2^2(8)R_4^2(8)R_2^2(8)$ motifs. The carboxylic acid of SMBA forms the acid–pyridine heterosynthon with NAM and sulfonamides form 1D catemer chains along the *b*-axis. The second sulfonamide N–H forms N–H···O hydrogen bond with the C=O of acid moiety. These interactions lead to a ladder type structure (Figure S5b), which is similar to SMBA–NAM (1:2, Figure S2b). The N–H···O heterodimer NAM–2HP is favored over NAM homodimer and acid···amide synthon with 2HP is replaced by the stronger acid···pyridine heterosynthon in this ternary structure.

SMBA–INA–2HP (1:1:1): The tricomponent system (ground material in stoichiometric ratio) crystallized in the monoclinic space group $P2_1/c$. 2HP forms amide homodimer and carbonyl group interacts with INA–NH_2 and sulfonamide NH_2 via trifurcated hydrogen bonds (Figure S5c). The carboxylic acid group of SMBA forms acid–pyridine synthon with INA pyridine N acceptor. Inversion related units of SMBA, INA and 2HP form large ring of $R_6^4(36)R_2^2(8)$D motif, which are stacked through sulfonamide catemer chains along the *c*-axis (Figure S5d). Such successive ladder motifs are joined by 2HP homodimers through N–H···O hydrogen bonds to result in ABCABC type patterns.

SMBA–NAM–MeHP (1:1:1): The ternary cluster favored amide heterodimer between NAM and MeHP compared to the homosynthons of NAM/MeHP and the carboxylic acid of SMBA forms acid-pyridine heterosynthon with NAM (Figure S5e). Sulfonamide catemer chains run along the *c*-axis. Inversion related NAM–MeHP heterodimers form discrete hydrogen bonds with the anti N–H of NAM to the C=O of MeHP via $R_2^2(8)R_4^2(8)R_2^2(8)$ motif. These units are further extended by acid–pyridine heterosynthon with the sulfonamide NH_2 hydrogen bonded to NAM carbonyl group (Figure S5f).

SMBA–PAM–MeHP (1:1:1): The crystal structure was solved in monoclinic space group $P2_1/c$. The dimer of MeHP forms discreet synthon with carboxylic acid O–H of SMBA (Figure S5g). Discrete chains of sulfonamide, PAM and carboxylic acid form inversion related ring of $R_4^4(26)$ motif, which are connected to PAM via N–H···O hydrogen bonds. Four SMBA and four PAM molecules form large ring motifs (Figure S5h).

SMBA–NAM–OMeHP (2:1:2): The presence of multiple molecules in the asymmetric units favors more diverse synthons in this ternary cocrystal. Two symmetry-independent OMeHP molecules (drawn with different bond types) form homodimer synthons and reside between the sulfonamide groups of symmetry independent SMBA molecules gave $R_1^2(5)R_2^2(8)R_1^2(5)$ motifs (Figure S5i). The SMBA engages in acid-pyridine and acid-amide heterosynthons to different NAM molecules (Figure S5j).


$R_2^2(8)R_4^2(8)R_2^2(8)$
A
B
C
(a)
(b)
SMBA–NAM–2HP (1:1:1)
D
$R_6^4(36)$
$R_2^2(8)$
(c)
(d)
SMBA–INA–2HP (1:1:1)
(e)
$R_2^2(8)R_4^2(8)R_2^2(8)$
(f)
SMBA–NAM–MeHP (1:1:1)

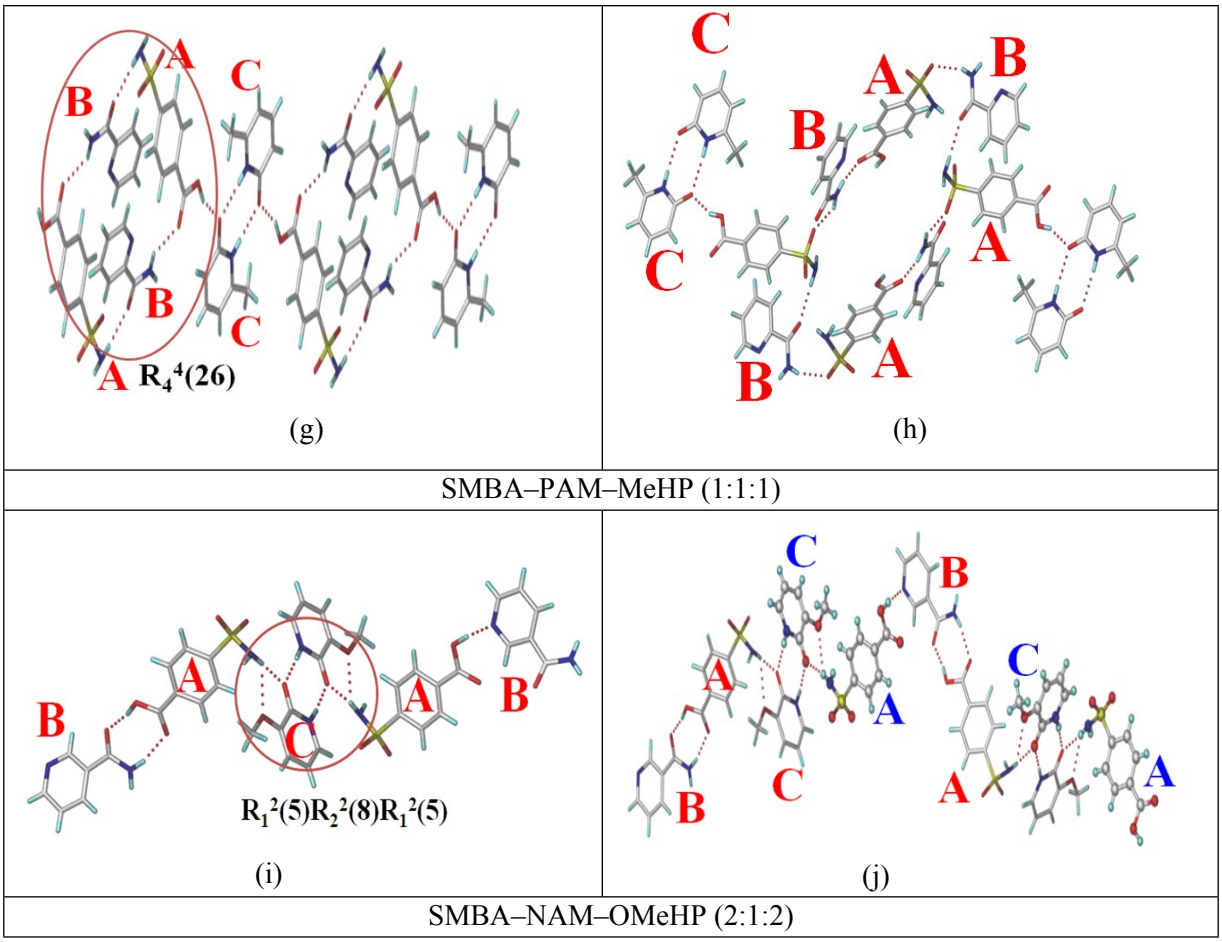


Figure S5 (a) and (b) SMBA–NAM–2HP (1:1:1): Amide heterodimer of NAM–HP and sulfonamide catemer chains. (c) and (d) SMBA–INA–2HP (1:1:1): Large ring motifs of two SMBA, two INA and two 2HP molecules via H bonds and the ladder network structure. (e) and (f) SMBA–NAM–MeHP (1:1:1): Amide heterodimer of NAM–MeHP and sulfonamide catemer chains along with the extended network of H bonds. (g) and (h) SMBA–PAM–MeHP (1:1:1): Tetramer rings of two SMBA and two PAM molecules are interlinked via MeHP dimers. (i) and (j) SMBA–NAM–OMeHP (2:1:2): Acid-pyridine and acid-amide hetersynthons and OMeHP homodimers of symmetry-independent molecules.

Experimental section:

SMBA–NAM Cocrystal (1:2) 100 mg (0.49 mmol) of SMBA and 59.78 mg (0.49 mmol) of NAM were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in solvent mixture of 5 mL of EtOAc and THF as well as individual solvents in a 25 mL conical flask at room temperature. Good quality crystals were harvested at ambient conditions after 3–4 days. The ground material composition taken was 1:1, but the product crystallized in 1:2 ratio.

SMBA–INA Cocrystal (1:1) SMBA (100 mg, 0.49 mmol) and INA (59.78 mg, 0.49 mmol) were ground well in a mortar–pestle for 20–30 min by adding 5 drops of EtOAc. The ground solid was kept for crystallization in 5 mL of EtOAc and THF mixture as well as individual solvents at room temperature. Single crystals were harvested at ambient conditions after 3–4 days.

SMBA–PAM Cocrystal (1:1) (100 mg, 0.49 mmol) of SMBA and (59.78 mg, 0.49 mmol) of PAM were ground well in mortar–pestle for 20–30 min by adding 5 drops of EtOAc. The ground material was kept

for crystallization in 5 mL solvent EtOAc and THF solvent mixture as well as separate solvents at room temperature. Single crystals were harvested at ambient condition after 3–4 days.

SMBA–VLM Cocrystal (1:1) 100 mg (0.49 mmol) of SMBA and 48.5 mg (0.49 mmol) of VLM were ground well in a mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc (solvent assisted grinding). The ground material subjected for crystallization in 5 mL of EtOAc and THF as well as individual solvents each at room temperature. Good diffractable crystals were harvested at ambient condition after 3–4 days.

SMBA–CPR Cocrystal (1:2) 100 mg (0.49 mmol) SMBA and 55.37 mg (0.49 mmol) CPR were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in 5 mL solvent mixture of EtOAc and THF as well as individual solvents in a 25 mL conical flask at room temperature. Good quality single crystals were harvested at ambient conditions after 3–4 days. The ground material composition was taken in 1:1 molar ratio but the crystallized product has 1:2 stoichiometry.

SMBA–2HP Form I Cocrystal (1:1) SMBA (100 mg, 0.49 mmol) and 2HP (46.55 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min through solvent assisted by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in 5 mL solvent mixture of EtOAc and THF as well as individual solvents at room temperature. Diffraction quality single crystals were harvested at ambient conditions after 3–4 days.

SMBA–2HP Form II Cocrystal (1:1) SMBA (100 mg, 0.49 mmol) and 2HP (46.55 mg, 0.49 mmol) and INA in equivalent molar ratio were ground well in mortar–pestle for 20–30 min by solvent assisted grinding by adding 4–7 drops of EtOAc with the intention to obtain a ternary cocrystal. The ground material was allowed for solvent evaporation crystallization in 5 ml solvent mixture of EtOAc and THF. product was kept for crystallization in EtOAc, THF to obtain diffraction quality single crystals after 3–4 days. X-ray diffraction showed it to be a new polymorphs of SMBA–2HP.

SMBA–2HP Form III Cocrystal (1:1) SMBA (100 mg, 0.49 mmol), 2HP (46.55 mg, 0.49 mmol) and PAM in equivalent molar ratio were ground well in mortar–pestle for 20–30 min through solvent assisted by adding 4–7 drops of EtOAc with the intention to obtain a ternary cocrystal. The ground material was kept for crystallization in 5 mL solvent mixture of EtOAc and THF as well as individual solvents at room temperature. Single crystals were harvested at ambient conditions after 3–4 days. X-ray diffratction showed it to be yet another polymorph designated as Form III.

SMBA–MeHP Cocrystal (1:2) SMBA (100 mg, 0.49 mmol) and MeHP (53.41 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min through solvent assisted grinding by adding 5 drops of EtOAc. Further ground material was kept for crystallization in 5 mL solvent mixture of EtOAc and THF as well as separate solvents. Good quality crystals were harvested at ambient conditions after 3–4 days. The product crystallized in 1:2 ratio.

SMBA–OMeHP Cocrystal (1:2) SMBA (100 mg, 0.49 mmol) and OMeHP (68.10 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min through solvent assisted grinding by adding 5 drops of EtOAc. The ground material was kept for crystallization in 5 mL solvent mixture of EtOAc and THF as well as separate solvents. Good quality crystals were harvested at ambient condition after 3–4 days. The ground material crystallized in 1:2 ratio.

SMBA–NAM–2HP Cocrystal (1:1:1) 100 mg (0.49 mmol) SMBA, 59.78 mg (0.49 mmol), NAM and 2HP (46.55 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in solvent mixture of 5 mL EtOAc and THF as

well as individual solvents in a 25 mL conical flask at room temperature. Good quality single crystals were harvested at ambient conditions after a week.

SMBA–INA–2HP Cocrystal (1:1:1) 100 mg (0.49 mmol) SMBA, 59.78 mg (0.49 mmol) INA and 2HP (46.55 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min by adding a few drops of EtOAc solvent. The ground material was kept for crystallization in solvent mixture of EtOAc and THF (1:1) as well as individual solvents in a 25 mL conical flask at room temperature. Good quality crystals were harvested at ambient conditions after few days.

SMBA–NAM–MeHP Cocrystal (1:1:1) 100 mg (0.49 mmol) SMBA, 59.78 mg (0.49 mmol), NAM and MeHP (53.41 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in solvent mixture of 5 mL EtOAc and THF as well as individual solvents in a 25 mL conical flask at room temperature. Good quality crystals were harvested at ambient conditions after a week.

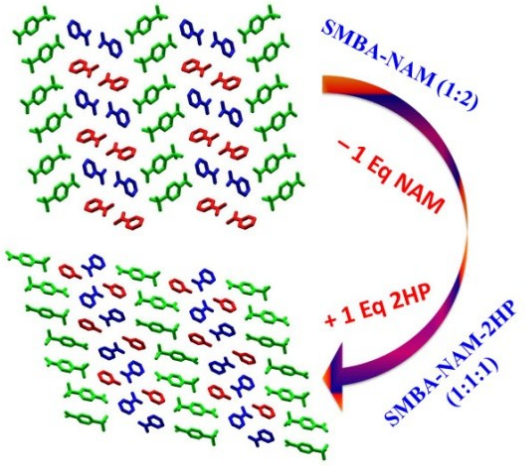
SMBA–PAM–MeHP Cocrystal (1:1:1) 100 mg (0.49 mmol) SMBA, 59.78 mg (0.49 mmol) PAM and MeHP (53.41 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in solvent mixture of 5 mL EtOAc and THF as well as individual solvents in a 25 mL conical flask at room temperature. Good quality crystals were harvested at ambient conditions after a week.

SMBA–NAM–OMeHP Cocrystal (2:1:2) 100 mg (0.49 mmol) SMBA, 59.78 mg (0.49 mmol) NAM and OMeHP (68.10 mg, 0.49 mmol) were ground well in mortar–pestle for 20–30 min by adding 4–7 drops of EtOAc. The ground material was kept for crystallization in solvent mixture of 5 mL EtOAc and THF as well as individual solvents in a 25 mL conical flask at room temperature. Good quality crystals were harvested at ambient conditions after a week.

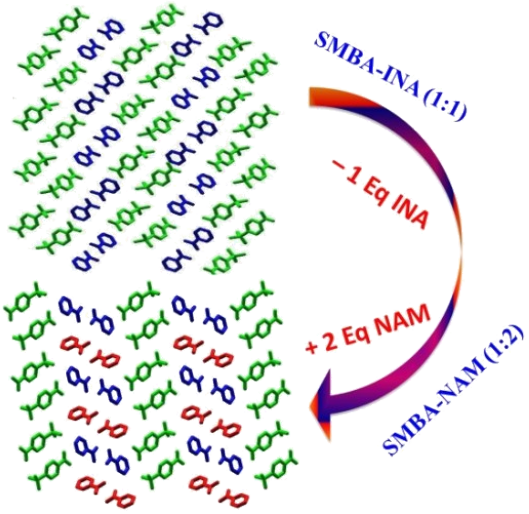
Single crystal X-ray diffraction:

A single crystal obtained from the crystallization experiment was mounted on the goniometer of Oxford Gemini (Oxford Diffraction, Yarnton, Oxford, UK), X-ray diffractometer equipped with Cu-Kα radiation source (λ = 1.54184 Å). Data reduction was performed using CrysAlisPro 171.33.55 software. Crystal structure was 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. Data was reduced by Saint Plus and further continued with 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 parameters of all the cocrystals are summarized in Table S2.

A few single crystals diffraction data were collected at 298 K on Bruker SMART APEX-1 CCD area detector system equipped with a graphite monochromator, Mo-Kα fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (40 KV, 30 mA). The frames were integrated with the Bruker SAINT software using a narrow-frame integration algorithm. Data was corrected for absorption effects using the multi-scan method (SADABS). The structure was solved and refined using the Bruker SHELX-TL software. Crystallographic cif files are deposited with the CCDC (Nos. 1414163-1414177).



(a) SMBA–NAM (1:2) binary to SMBA–NAM–2HP (1:1:1) ternary cocrystal



(b) SMBA–INA (1:1) to SMBA–NAM (1:2)

Figure S6 (a)View of the 2D packing arrangements for binary cocrystal SMBA–NAM (1:2) and the corresponding ternary SMBA–NAM–2HP (1:1:1), to show the replacement of one equivalent of NAM by the third coformer 2HP. (b) One equivalent of INA is replaced by 2 equivalents of NAM. Even though the latter is a binary system, the hydrogen bonded assembly involves three molecules in (b).

References:

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