Supramolecular Synthons in Bumetanide Cocrystals and Ternary Products

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Section S1: PXRD comparison of cocrystal with that of the starting components.

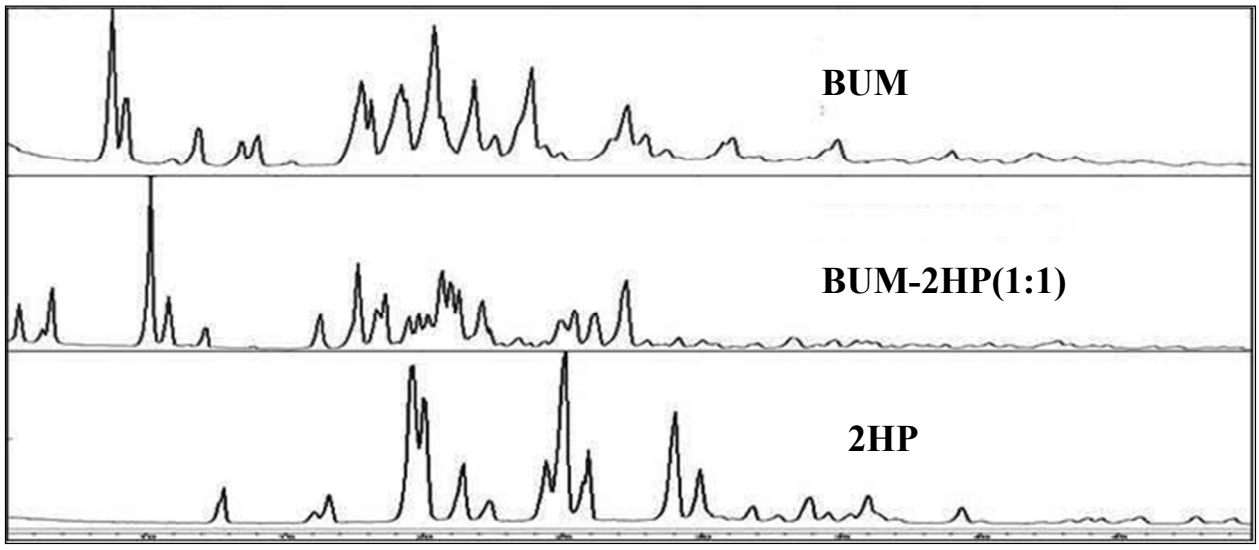


Figure S1: PXRD comparison of BUM−2HP (1:1) cocrystal.

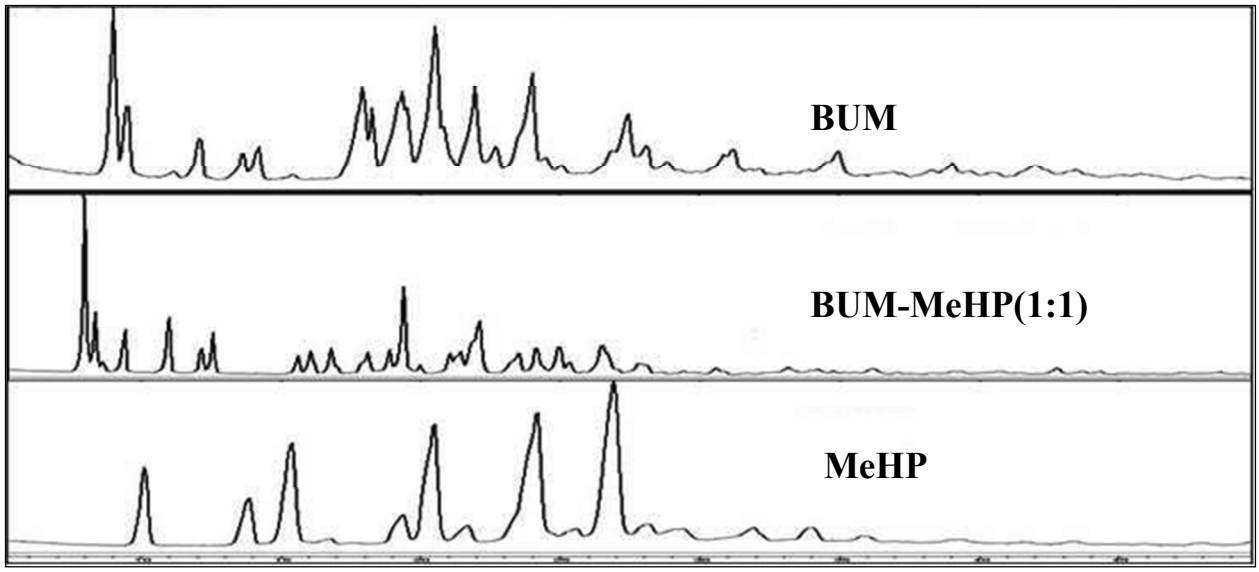


Figure S2: PXRD comparison of BUM−MeHP (1:1) cocrystal.

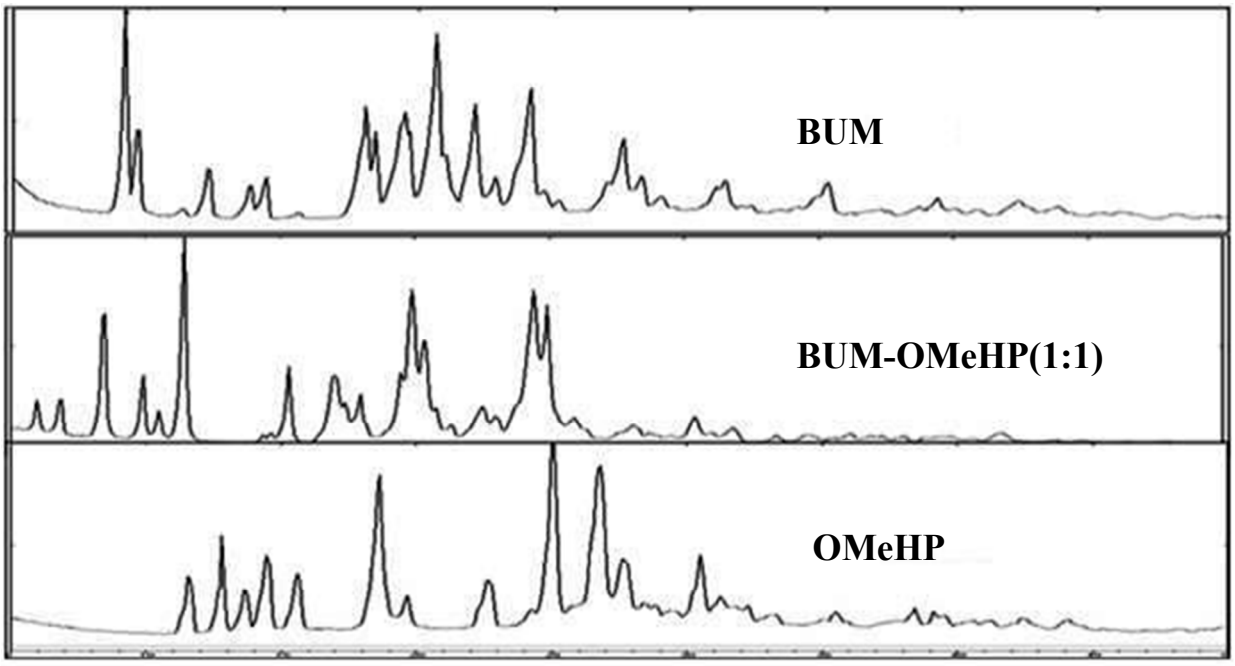


Figure S3: PXRD comparison of BUM−OMeHP (1:1) cocrystal.

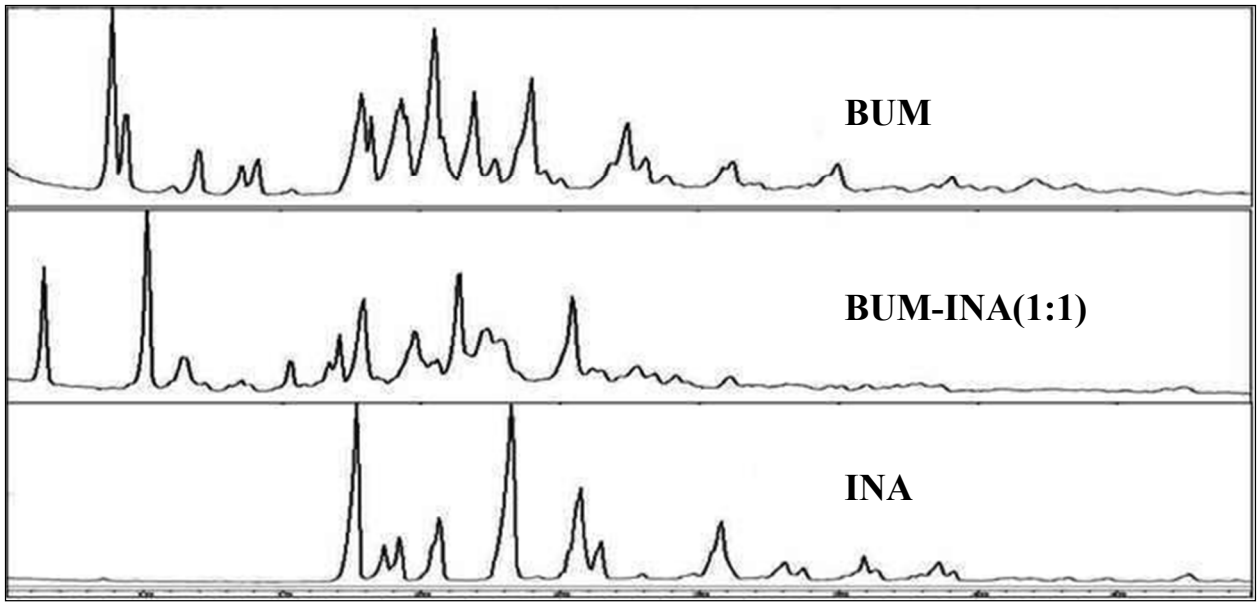


Figure S4: PXRD comparison of BUM−INA (1:1) cocrystal.

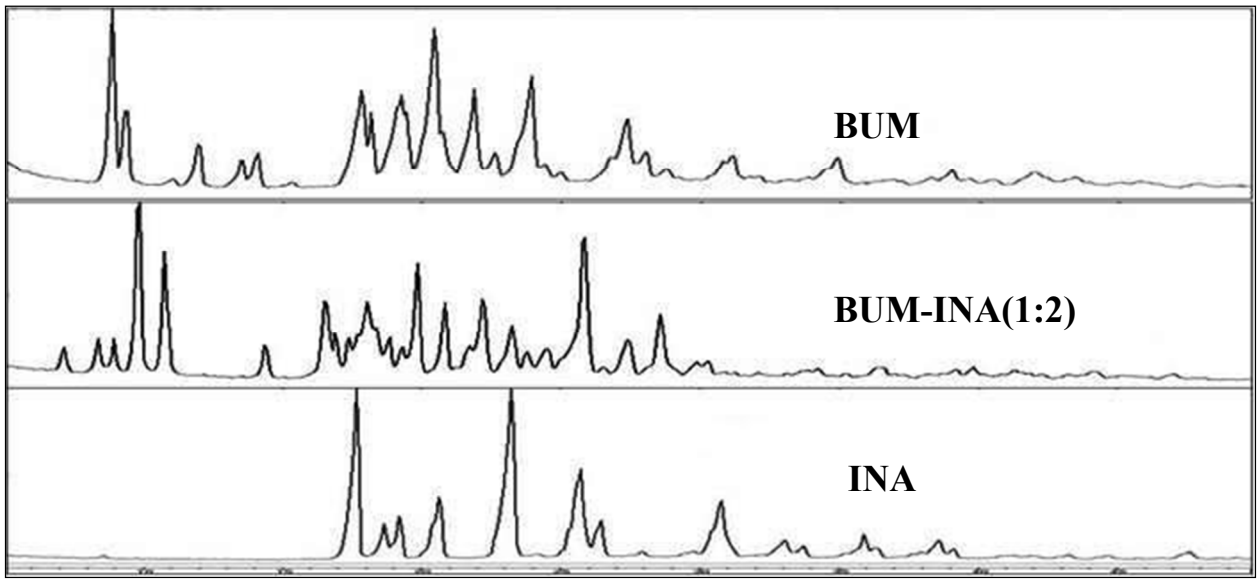


Figure S5: PXRD comparison of BUM−INA (1:2) cocrystal.

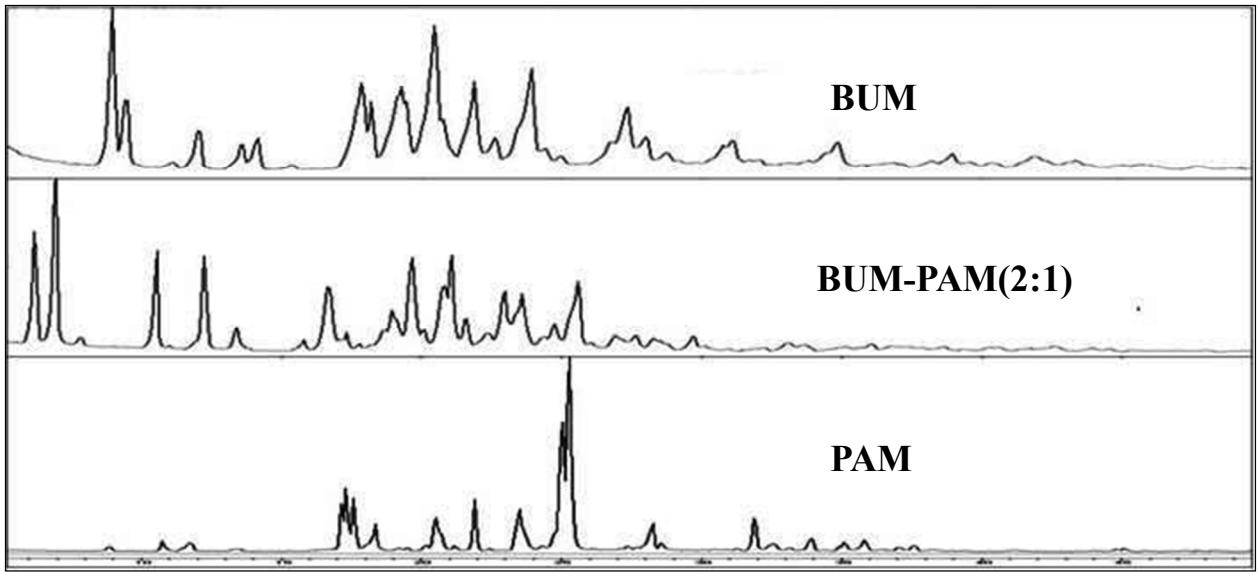


Figure S6: PXRD comparison of BUM−PAM (2:1) cocrystal.

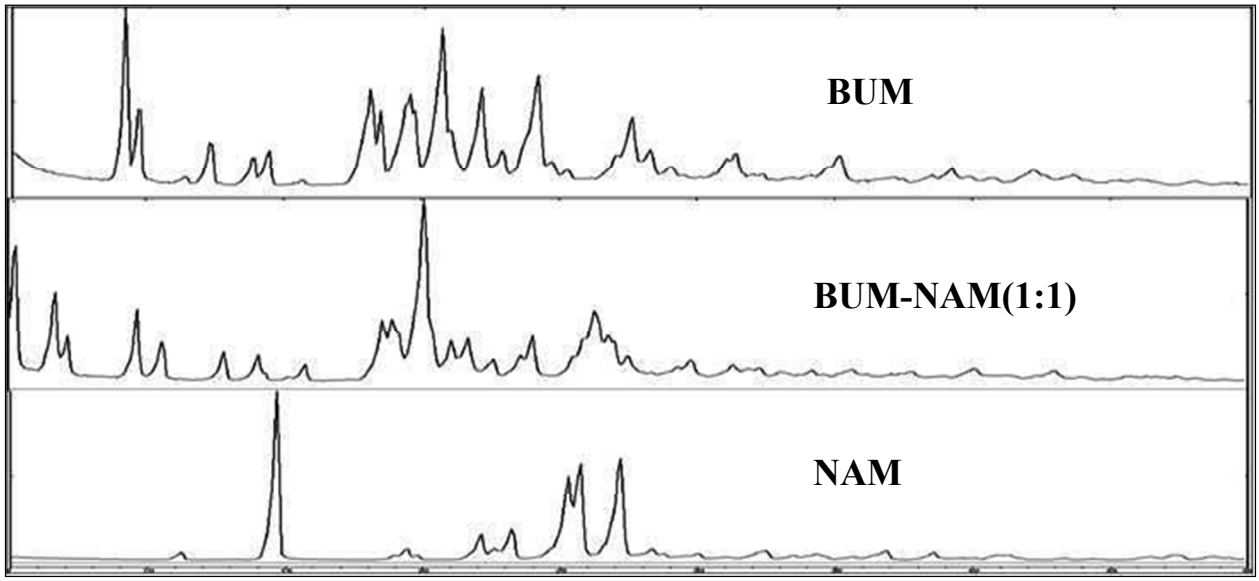


Figure S7: PXRD comparison of BUM−NAM (1:1) cocrystal.

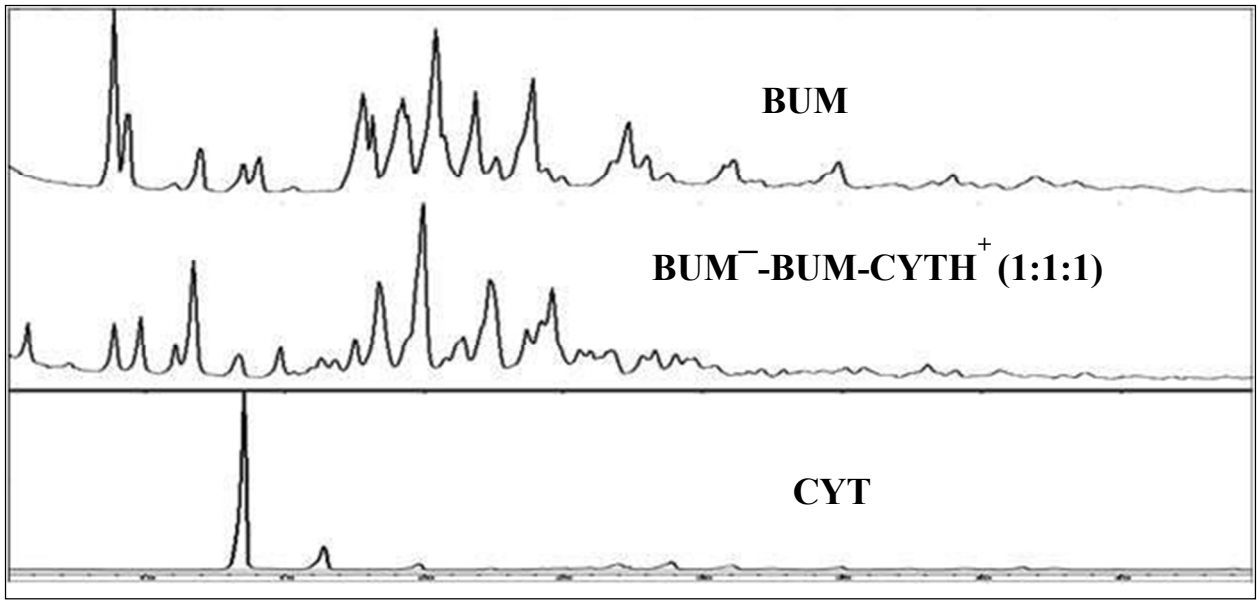


Figure S8: PXRD comparison of BUM^{-}−BUM−$CYTH^{+}$(1:1:1) cocrystal salt.

PXRD patterns of three component crystalline materials. Starting materials and binary combinations are compared with three-component crystalline material. 1H NMR of these ternary systems given in Section S7.

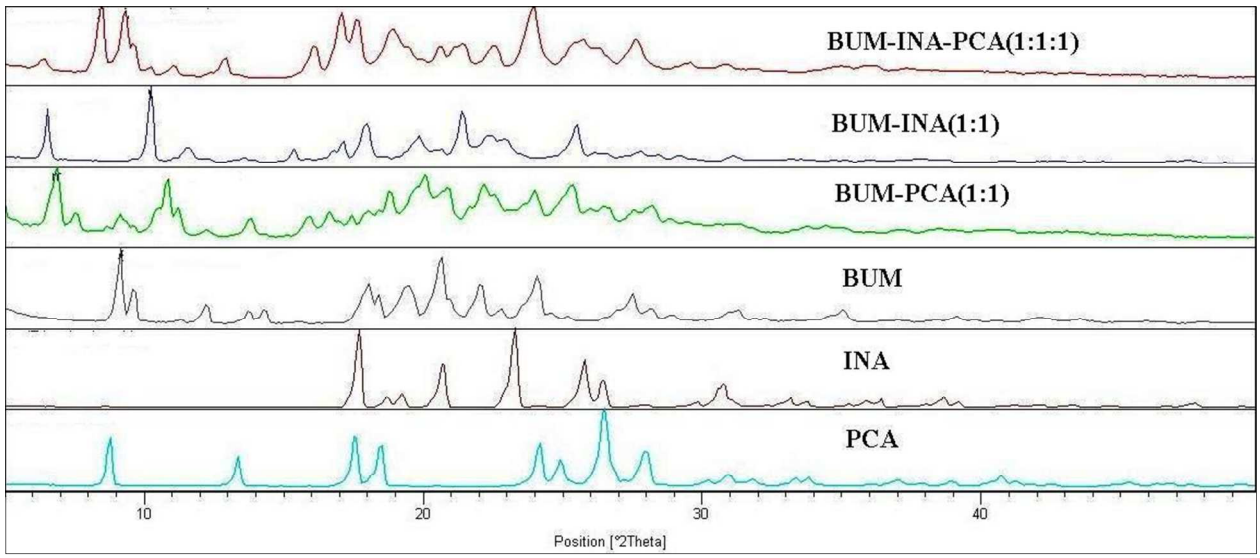


Figure S9: PXRD comparison of BUM−INA−PCA (1:1:1) cocrystal.

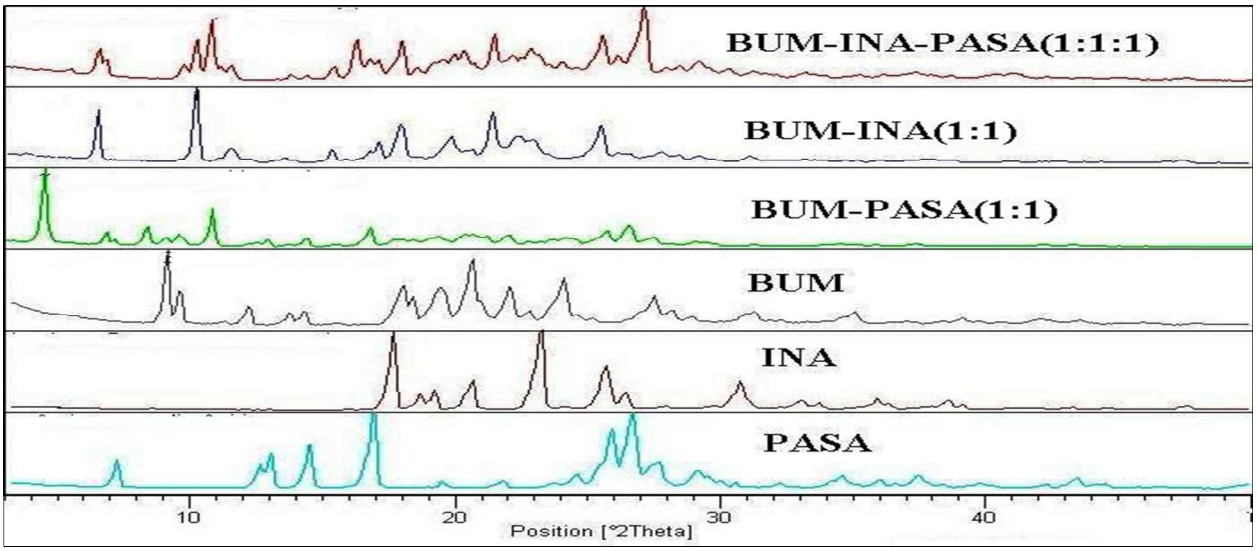


Figure S10: PXRD comparison of BUM−INA−PASA (1:1:1) cocrystal.

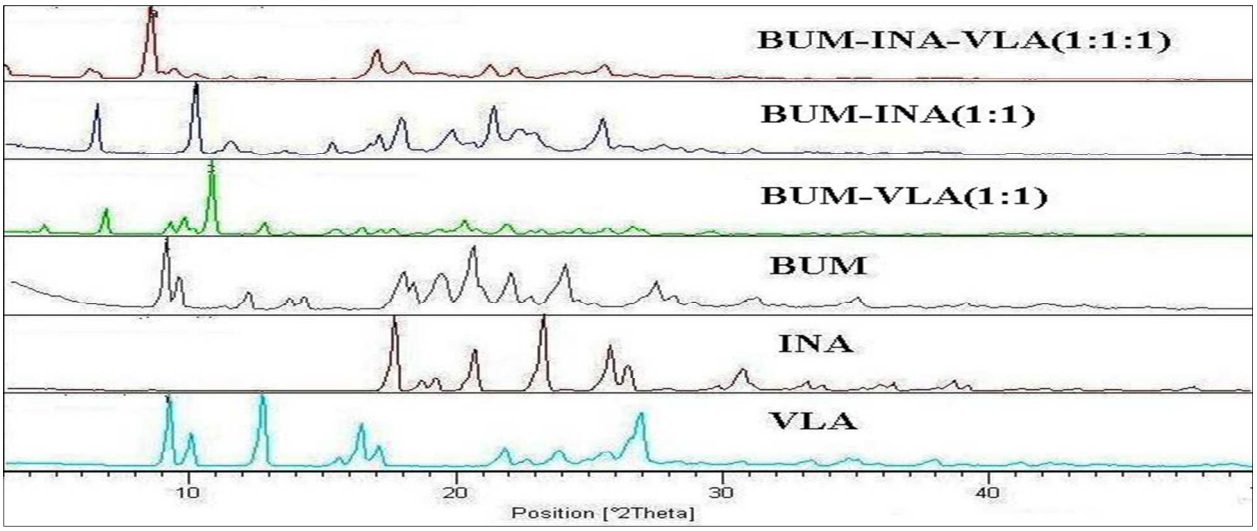


Figure S11: PXRD comparison of BUM−INA−VLA (1:1:1) cocrystal.

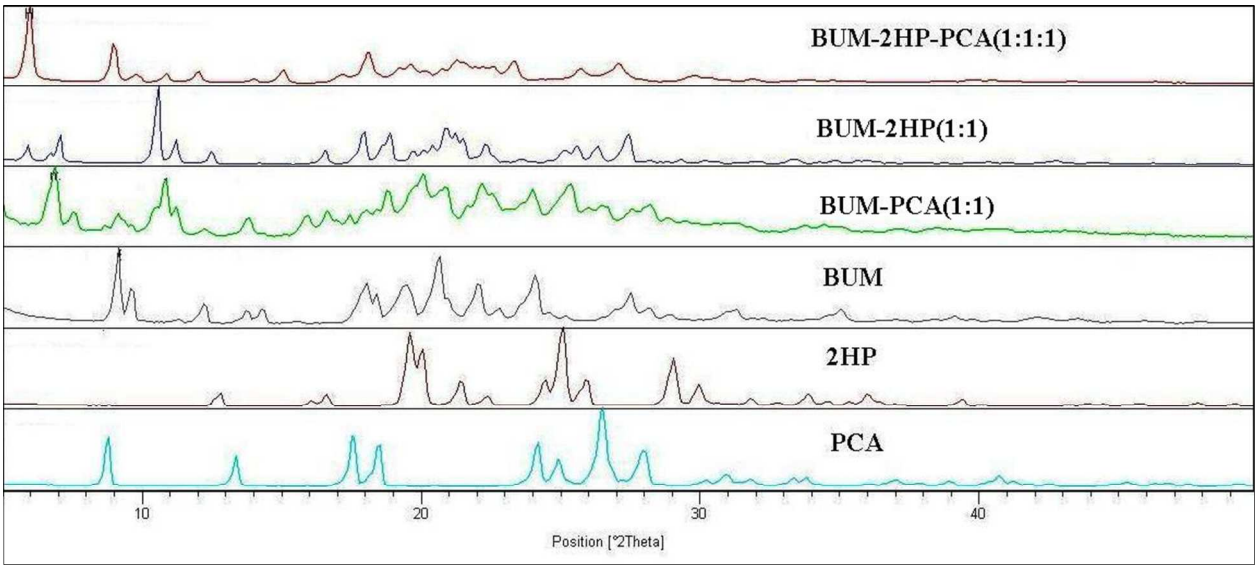


Figure S12: PXRD comparison of BUM−2HP−PCA (1:1:1) cocrystal.

Section 2: PXRD Overlay of experimental powder pattern with the calculated line profile from the X-ray crystal structure

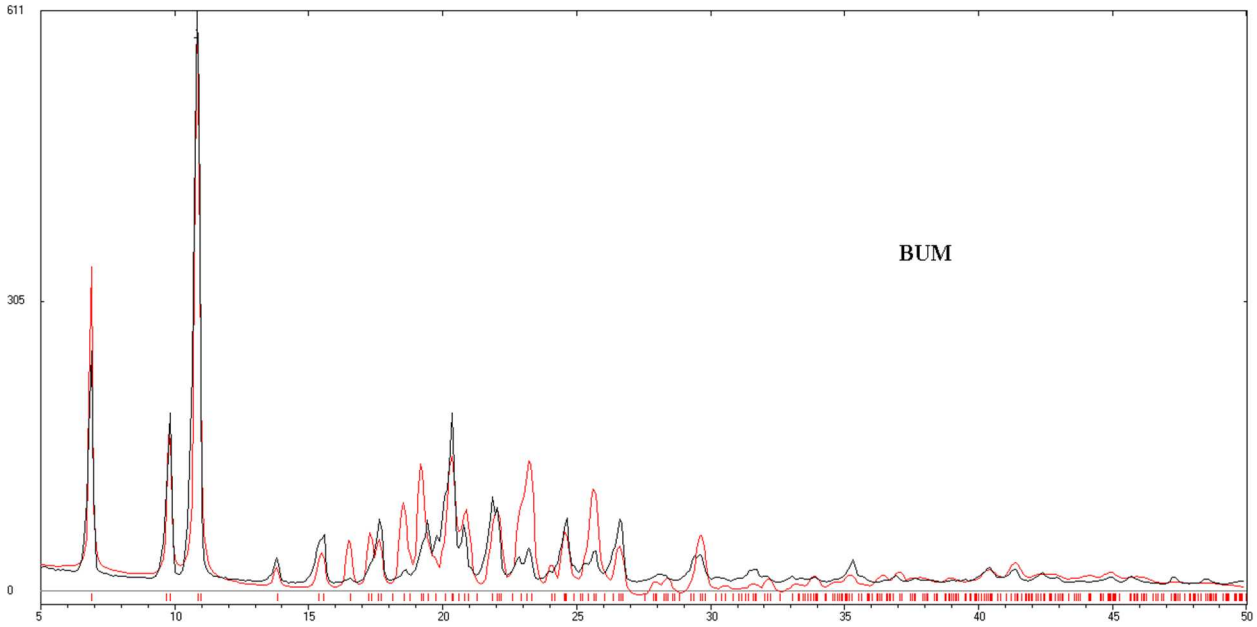


Figure S13: Overlay of BUM powder pattern with calculated the line pattern.

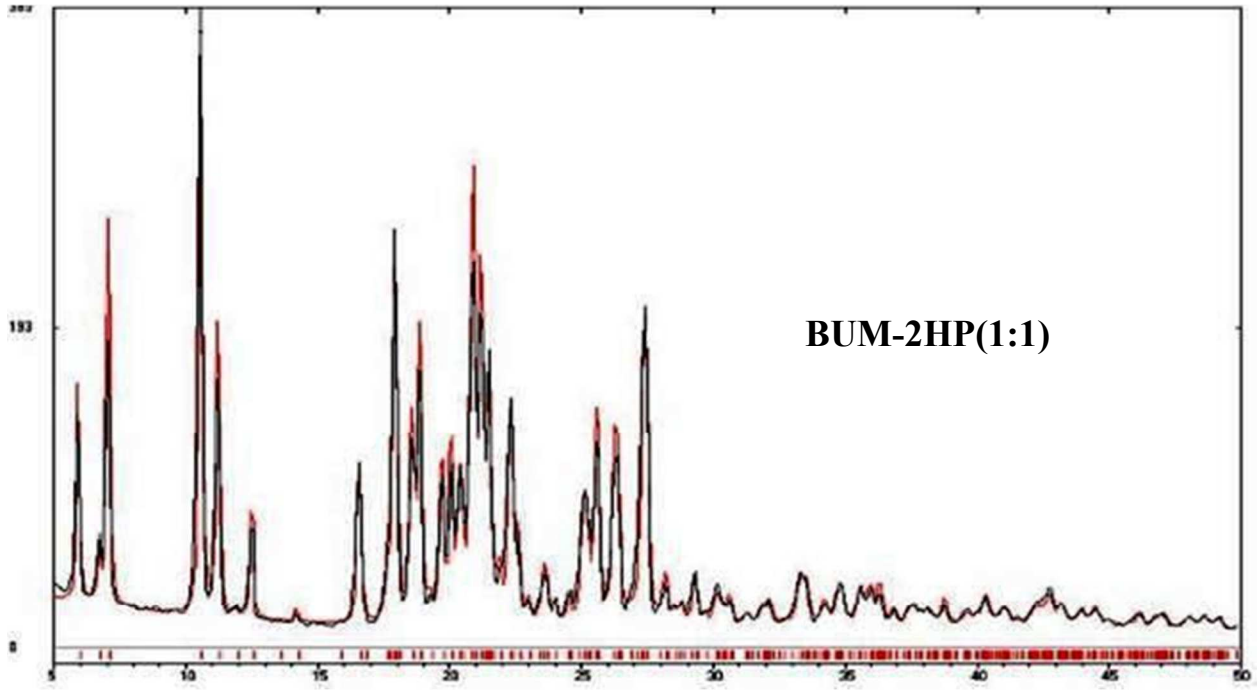


Figure S14: Overlay of BUM−2HP (1:1) cocrystal of powder pattern with the calculated line pattern.

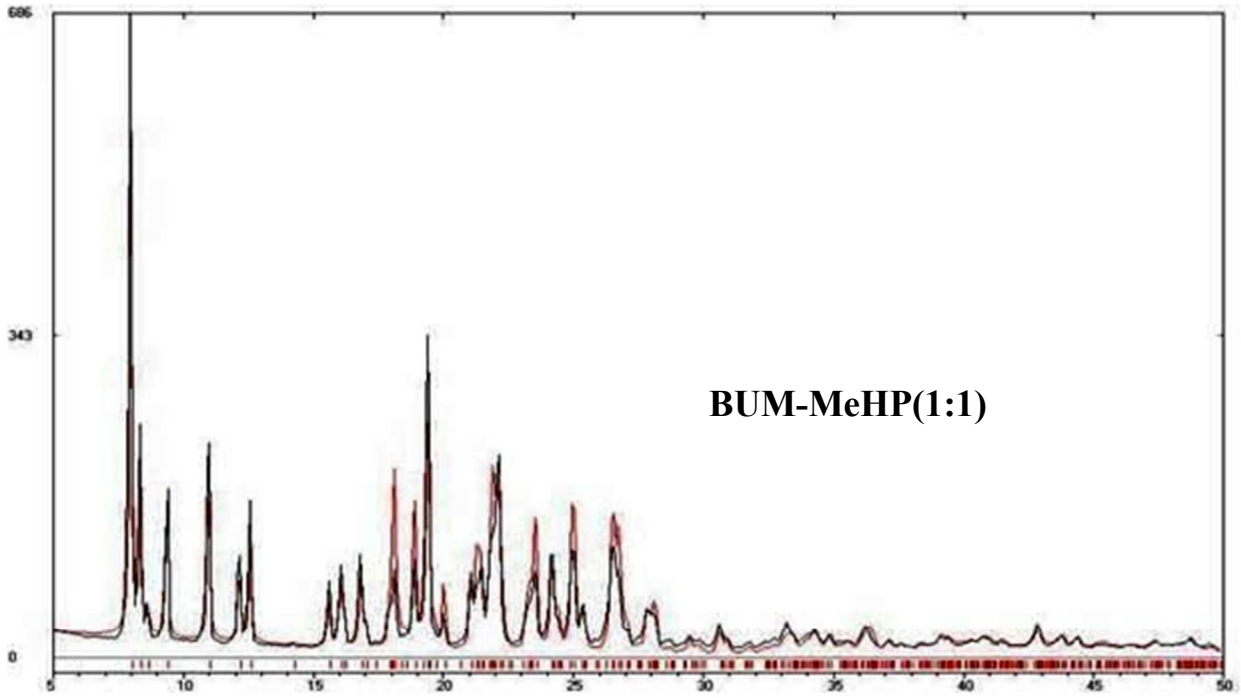


Figure S15: Overlay of BUM−MeHP (1:1) cocrystal powder pattern with the calculated line pattern.

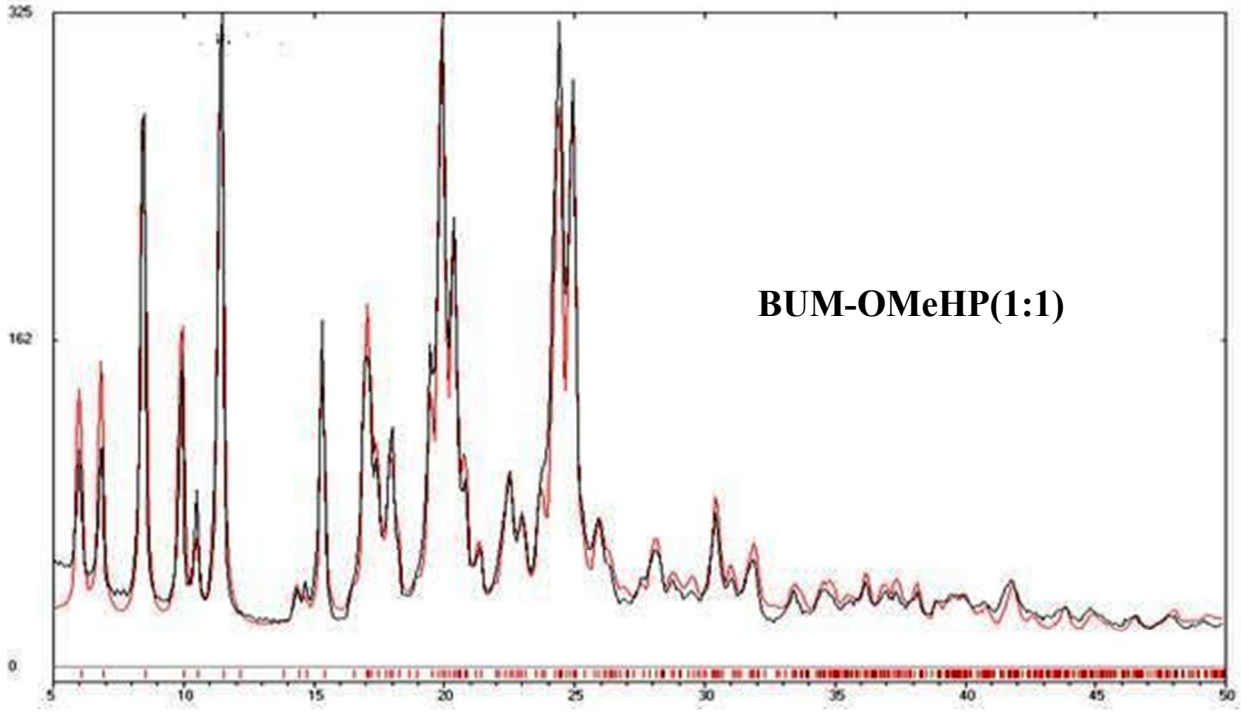


Figure S16: Overlay of BUM−OMeHP (1:1) cocrystal of powder pattern with the calculated line pattern

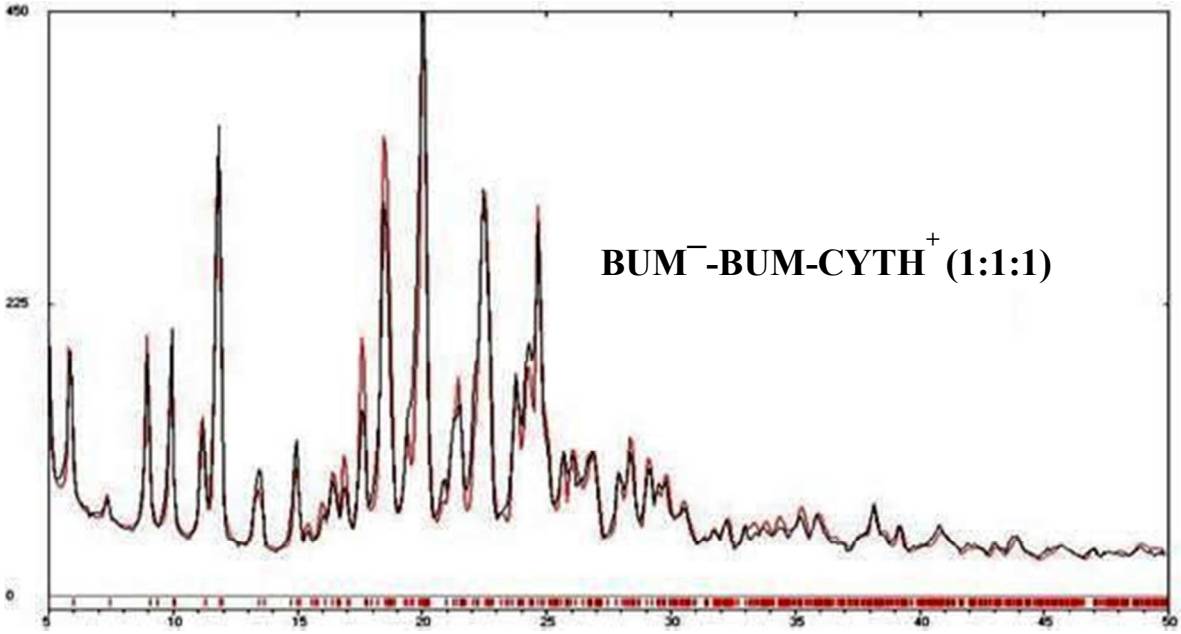


Figure S17: Overlay of BUM^{-}−BUM−$CYTH^{+}$(1:1:1) cocrystal salt powder pattern with the calculated line pattern.

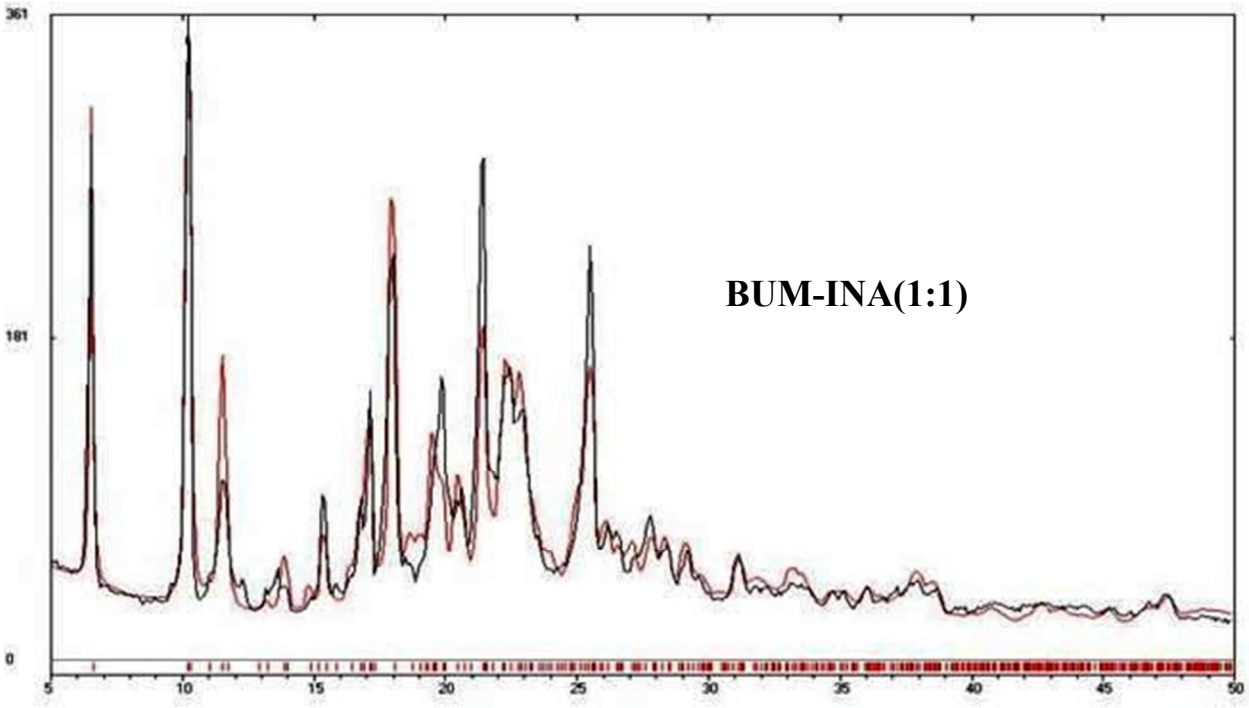


Figure S18: overlay of BUM−INA (1:1) cocrystal powder pattern with the calculated line pattern.

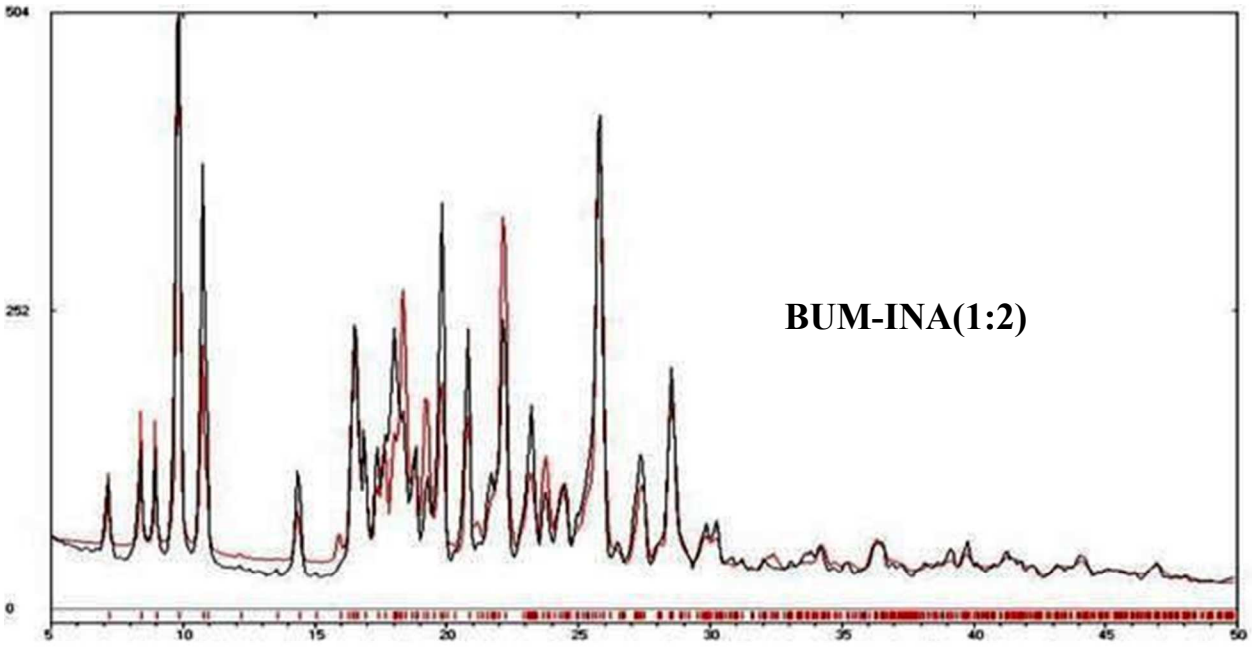


Figure S19: Overlay of BUM−INA (1:2) cocrystal powder pattern with the calculated line pattern.

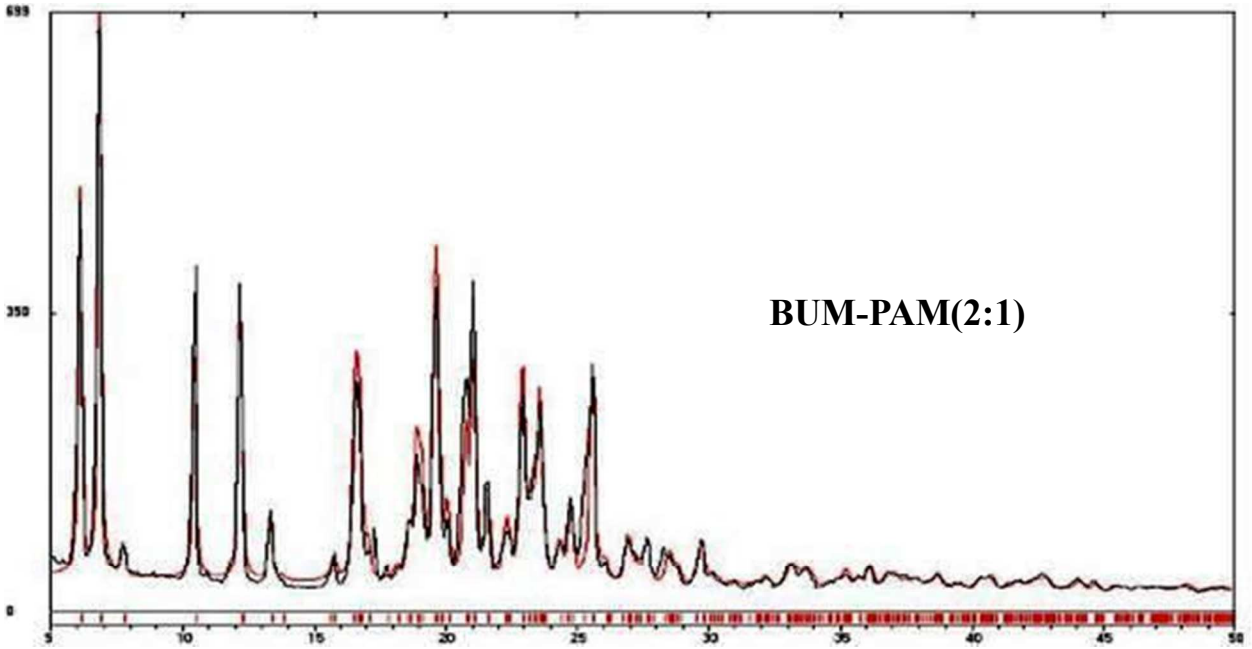


Figure S20: Overlay of BUM−PAM (2:1) cocrystal powder pattern with calculated line pattern.

Section S3 DSC of BUM and cocrystals/ salt.

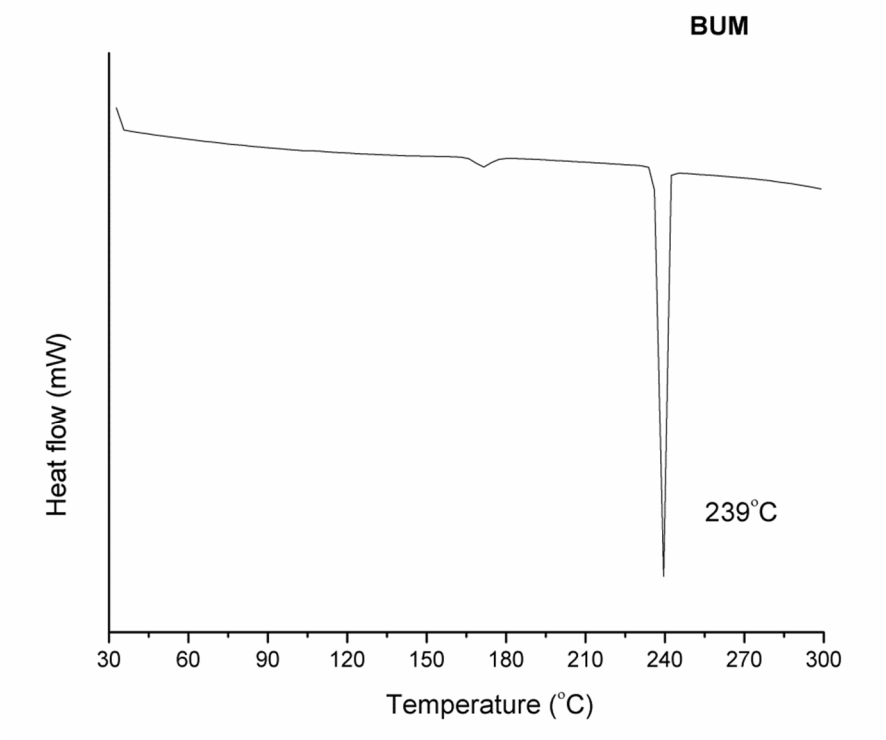


Figure S21: BUM.

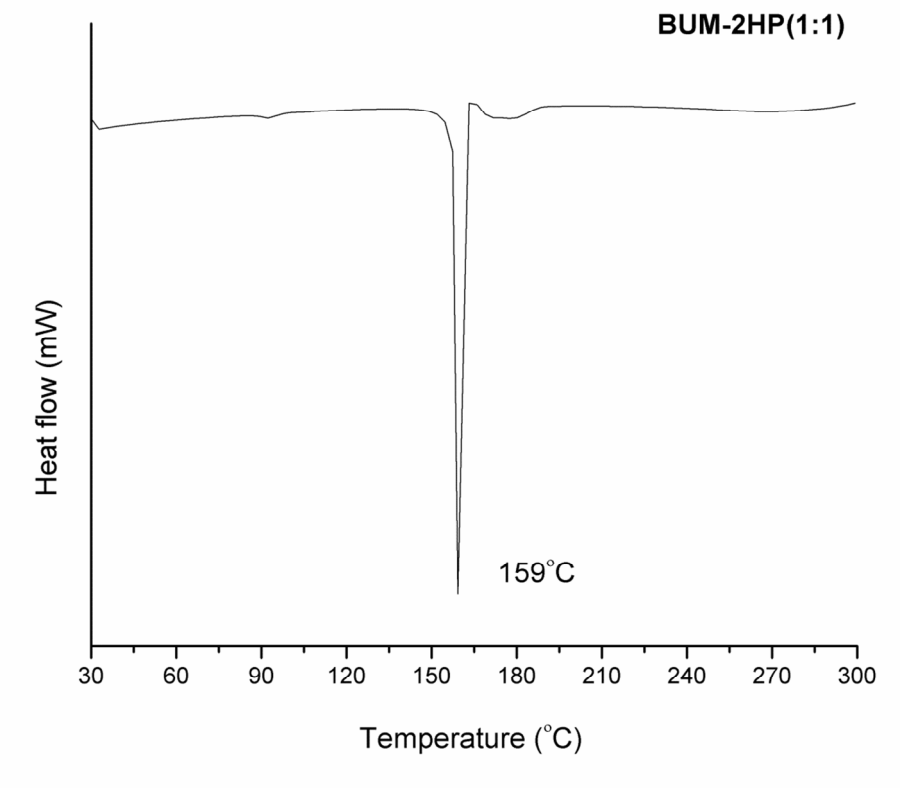


Figure S22: BUM−2HP (1:1).

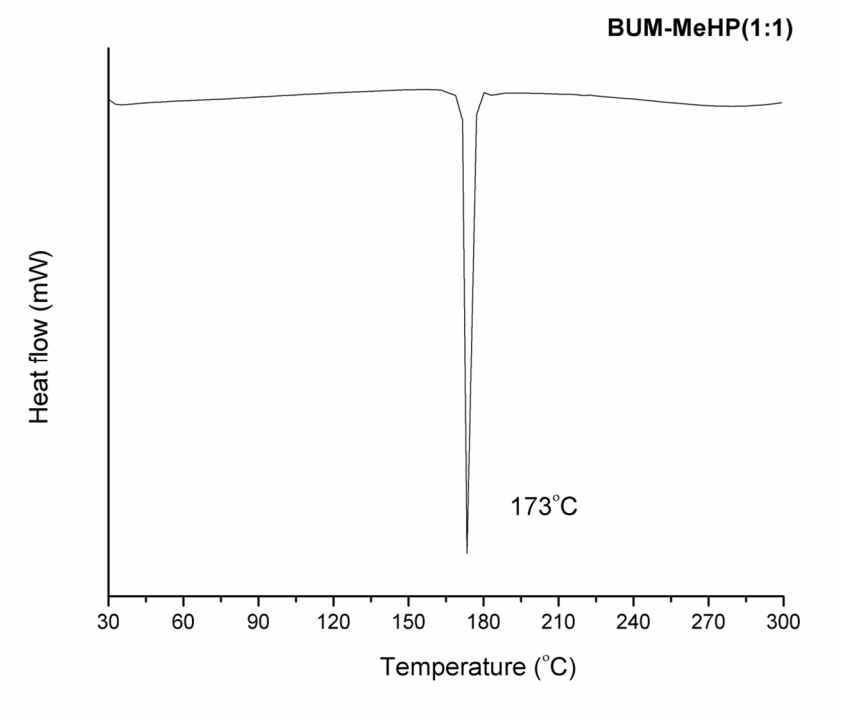


Figure S23: BUM−MeHP (1:1).

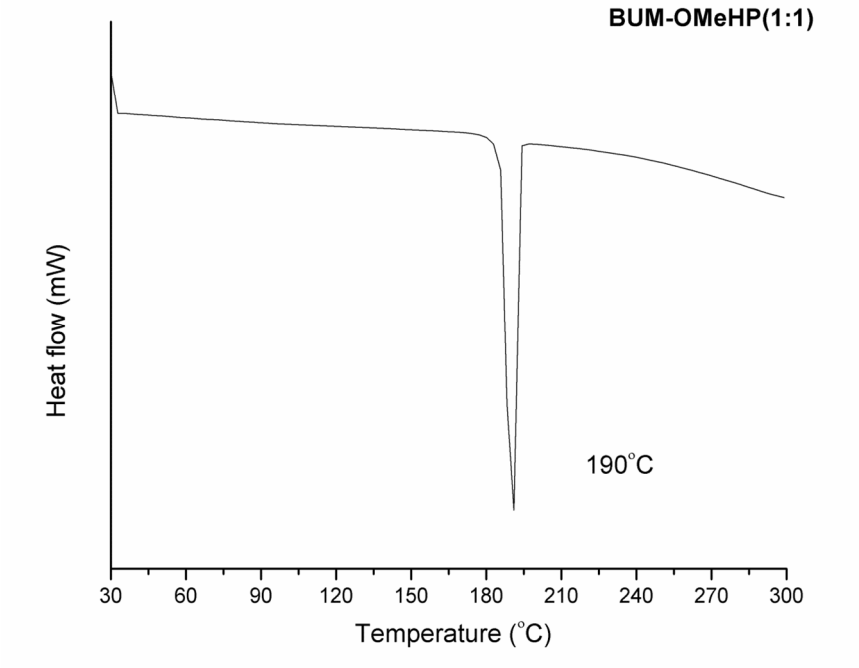


Figure S24: BUM−OMeHP (1:1).

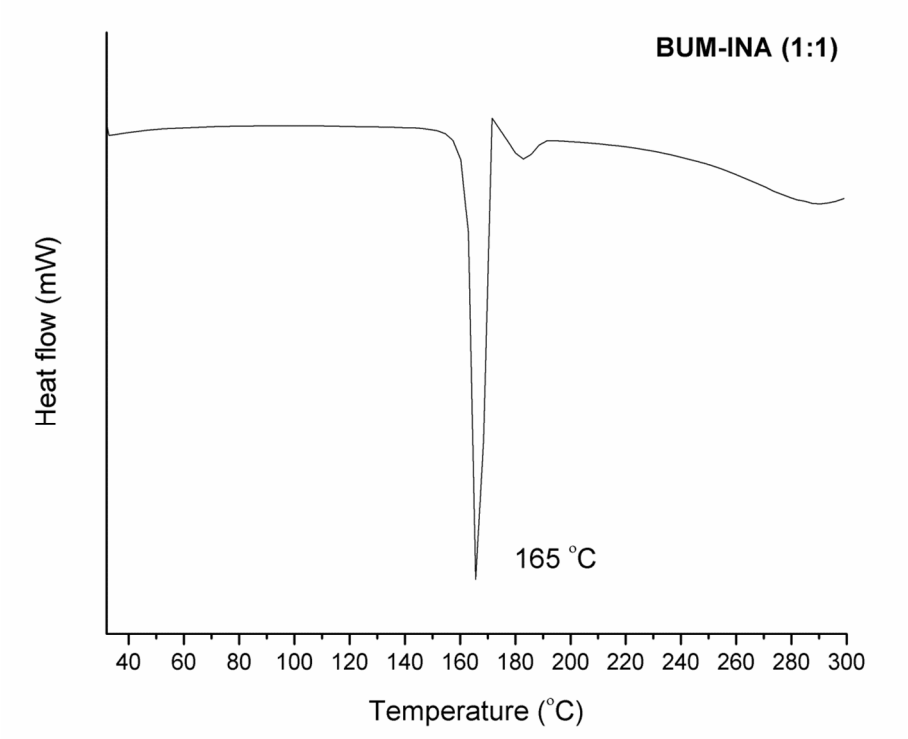


Figure S25: BUM−INA (1:1).

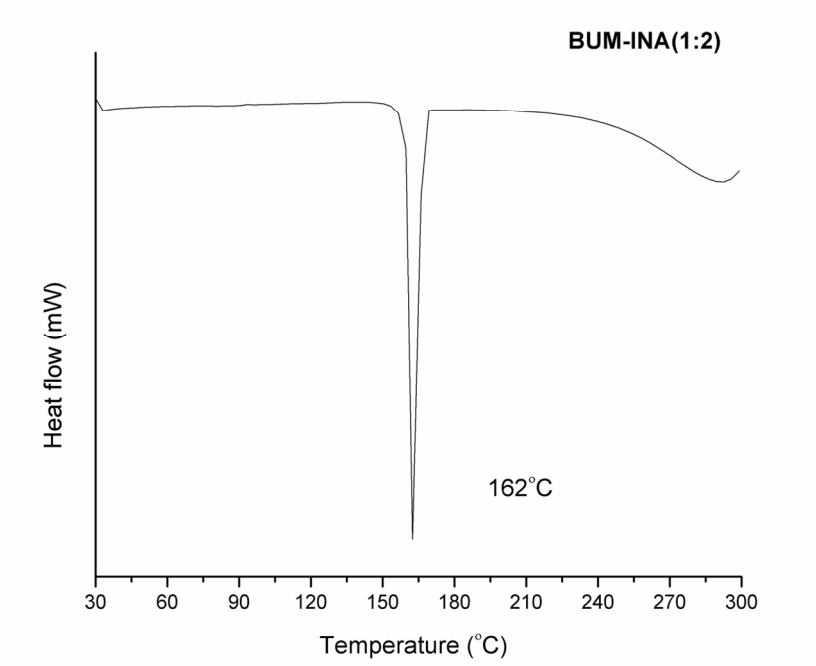


Figure S26: BUM−INA (1:2).

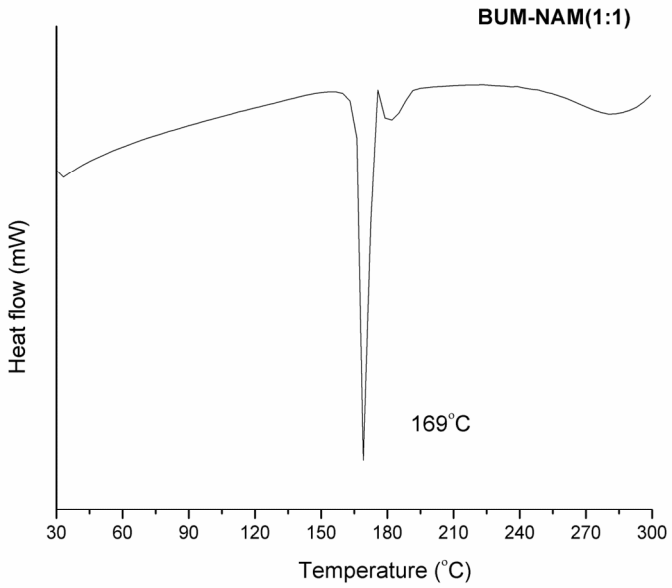


Figure S27: BUM−NAM (1:1).

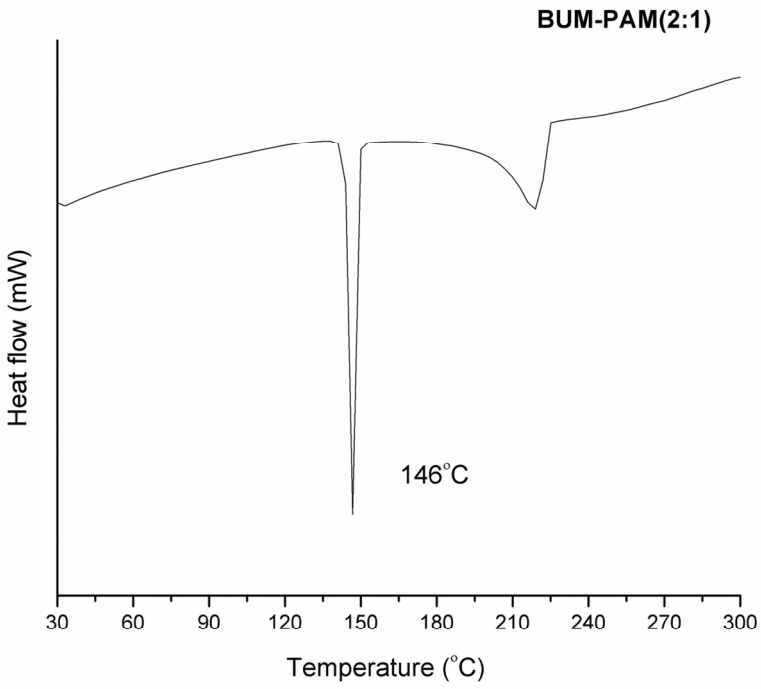


Figure S28: BUM−PAM (2:1).

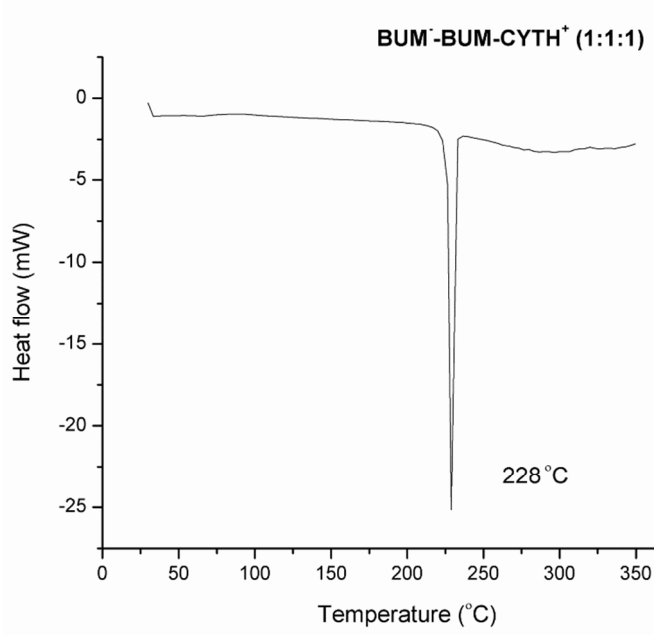


Figure S29: BUM^{-}−BUM−$CYTH^{+}$ (1:1:1).

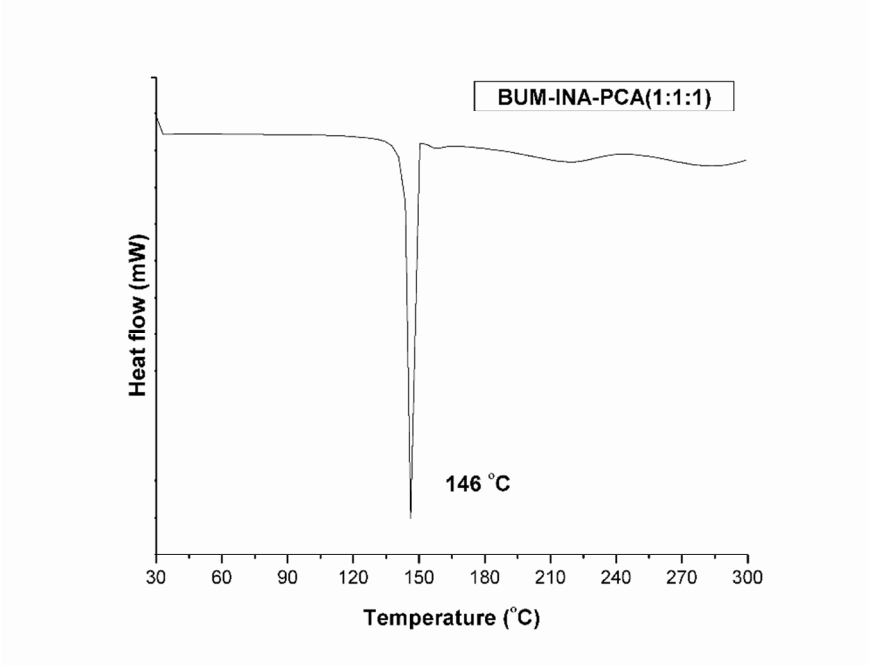


Figure S30: BUM−INA–PCA (1:1:1).

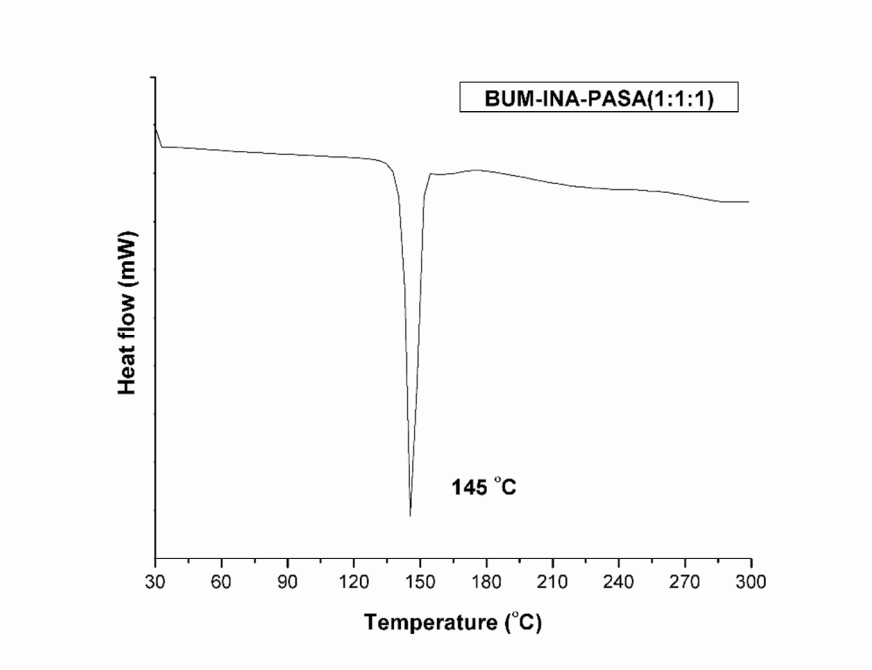


Figure S31: BUM−INA –PASA (1:1:1).

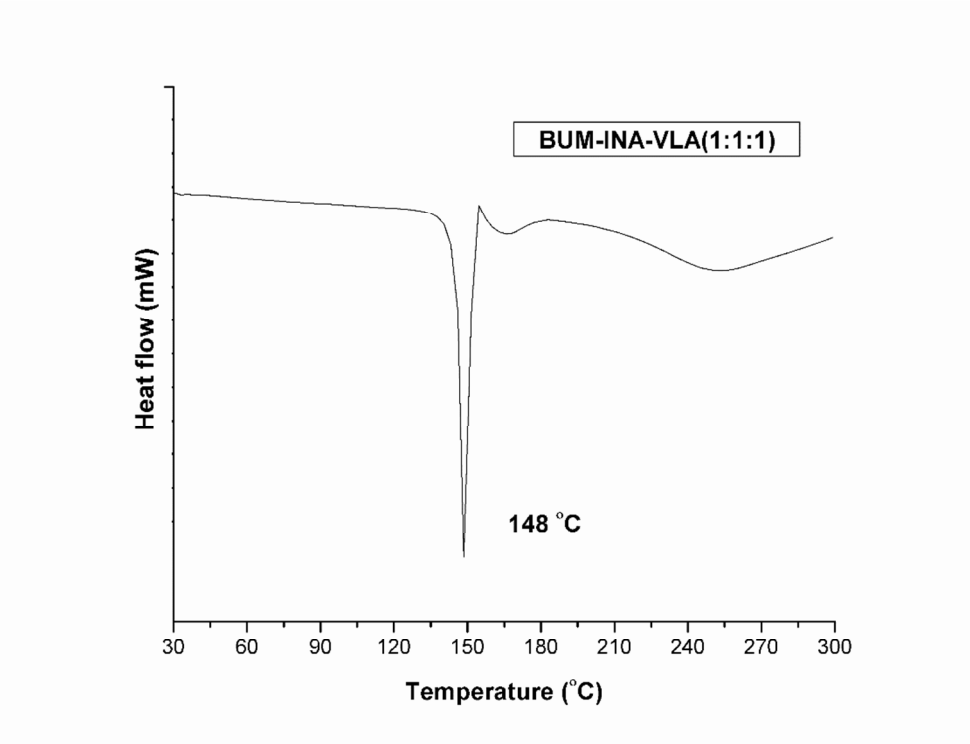


Figure S32: BUM−INA–VLA (1:1:1).

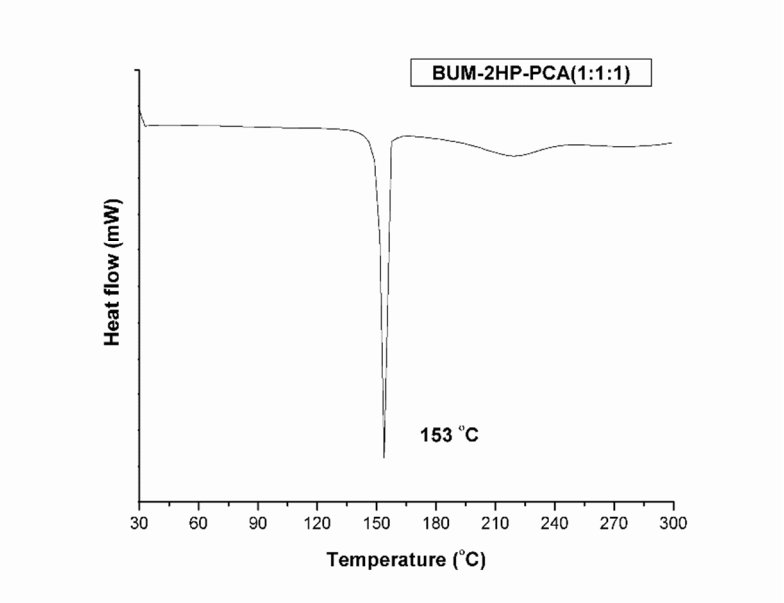


Figure S33: BUM–2HP–PCA (1:1:1).

Section S4: FT−IR spectra of BUM cocrystals.

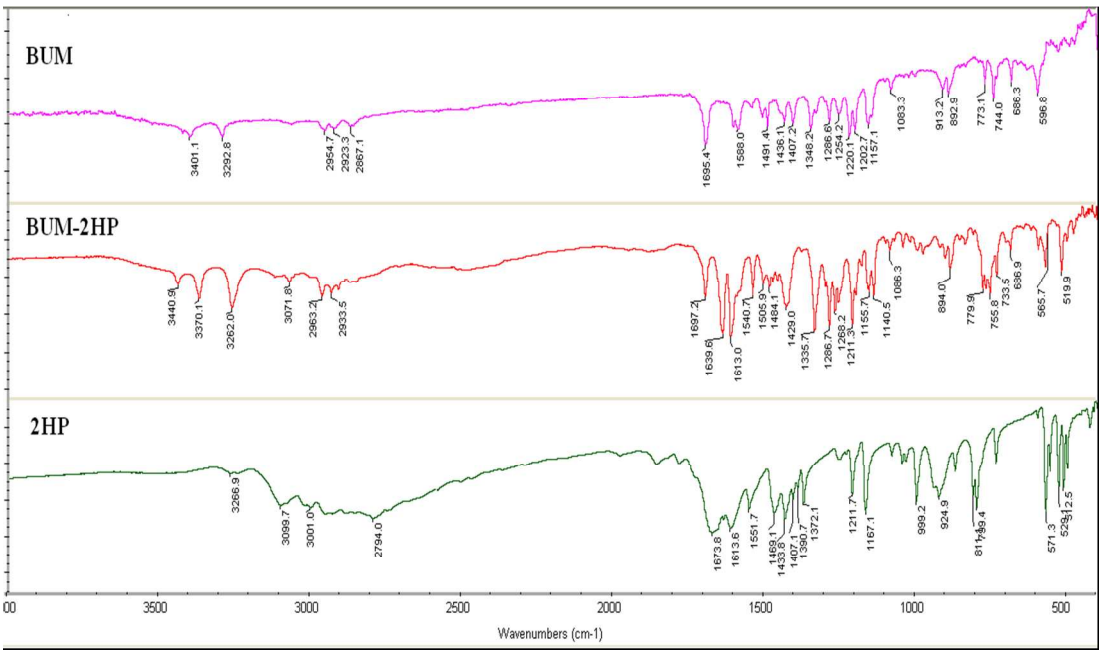


Figure S34: IR comparison of BUM−2HP (1:1) cocrystal.

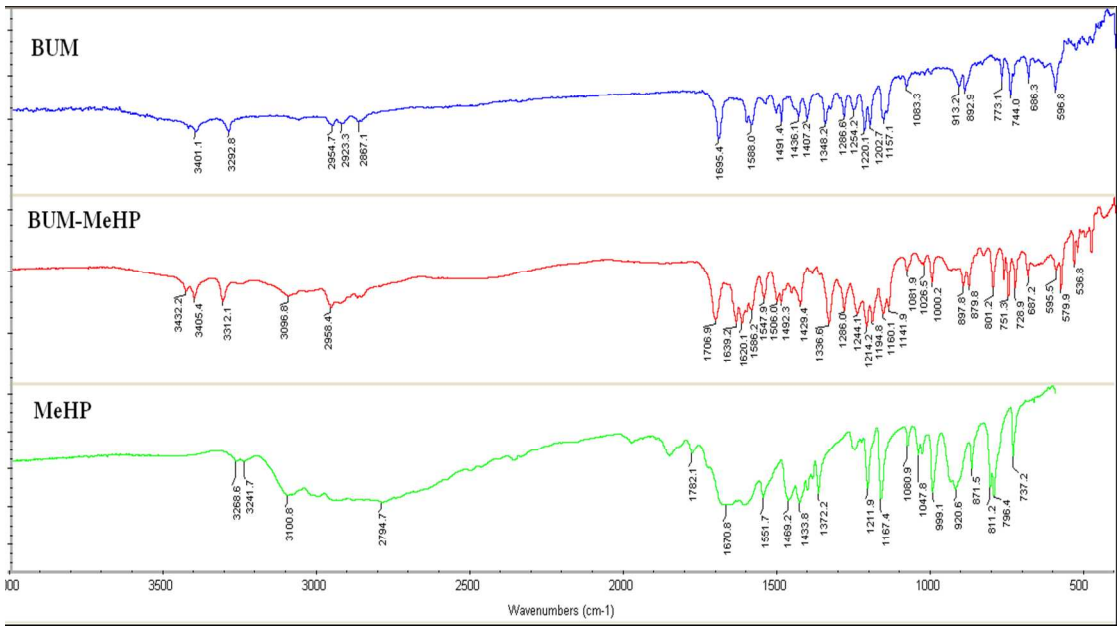


Figure S35: IR comparison of BUM–MeHP (1:1) cocrystal.

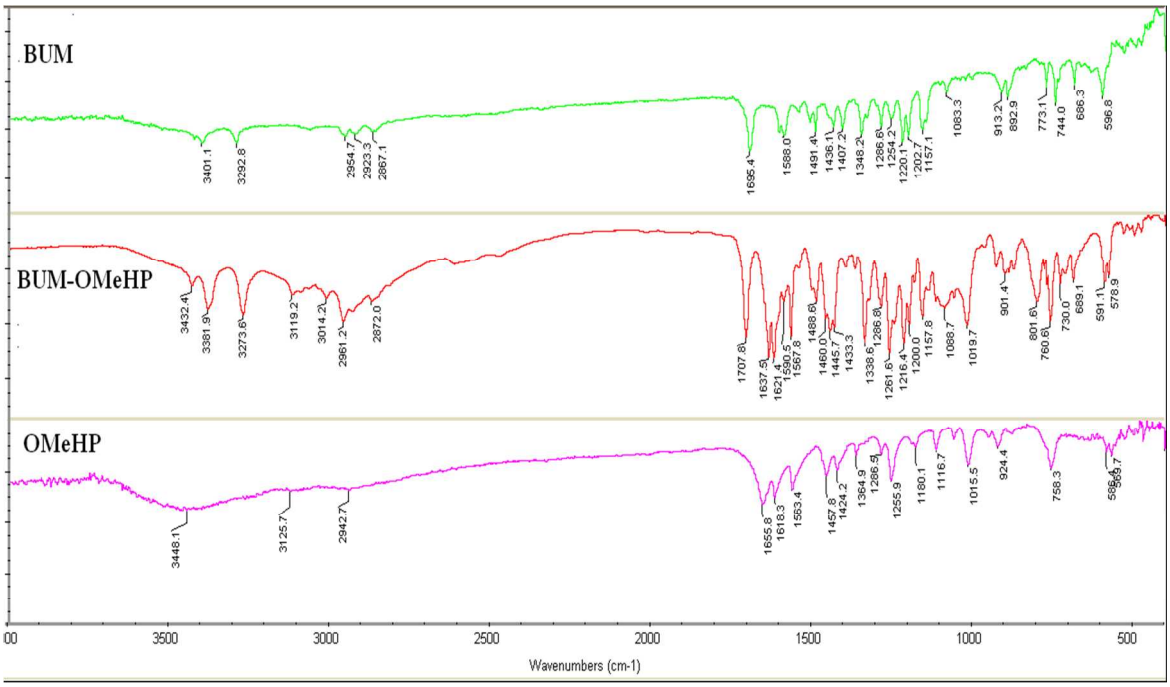


Figure S36: IR comparison of BUM−OMeHP (1:1) cocrystal.

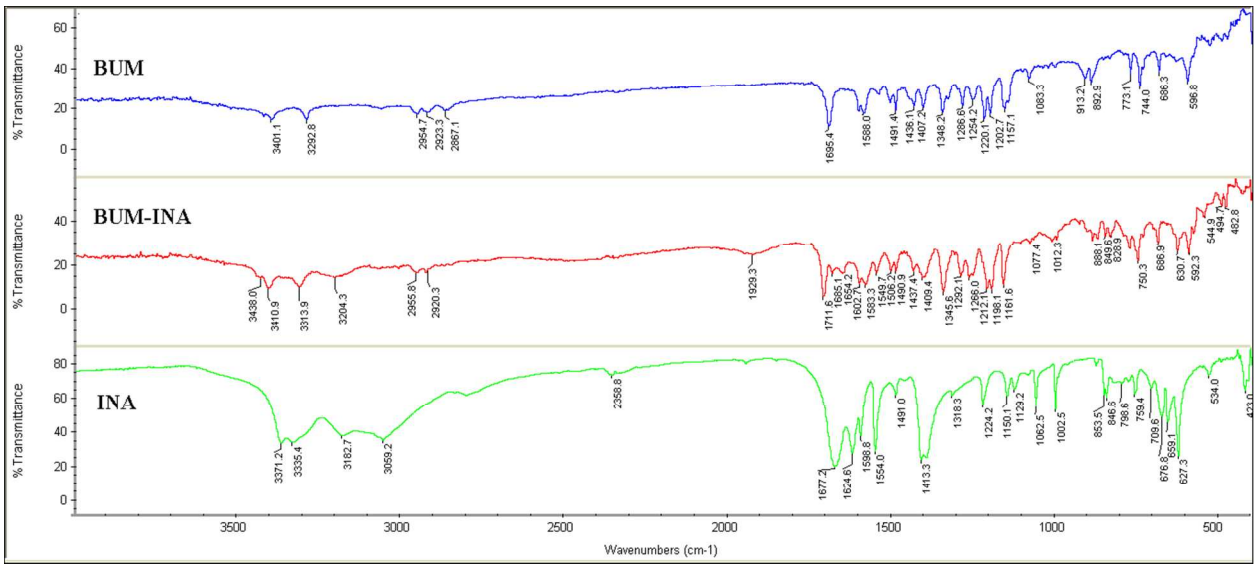


Figure S37: IR comparison of BUM−INA (1:1) Form-I cocrystal.

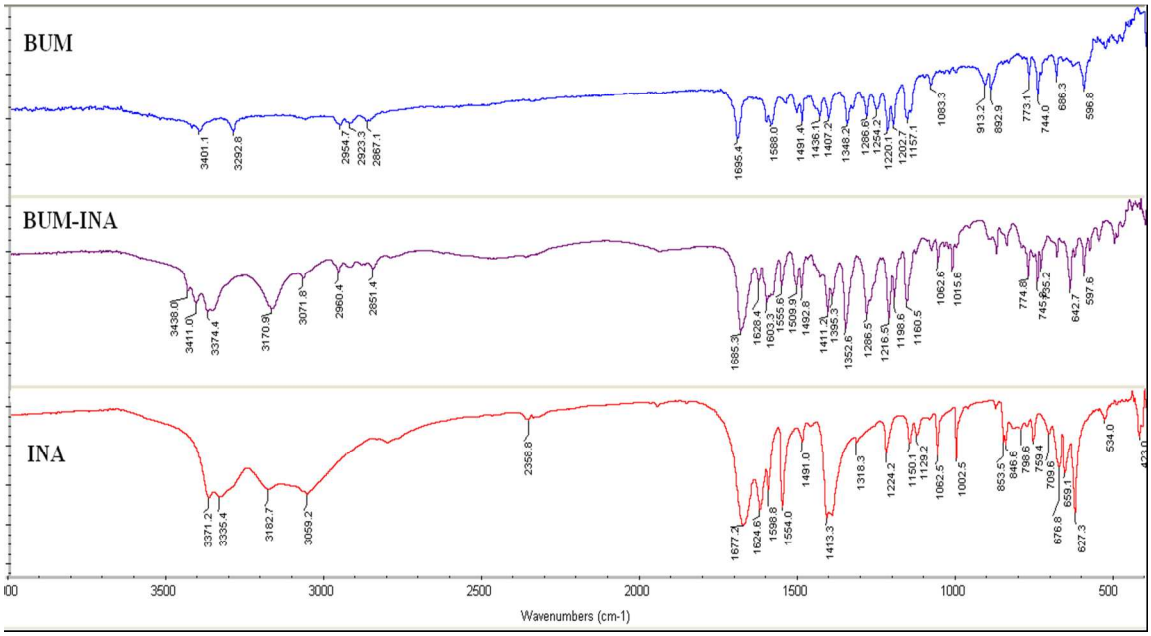


Figure S38: IR comparison of BUM−INA (1:2) cocrystal.

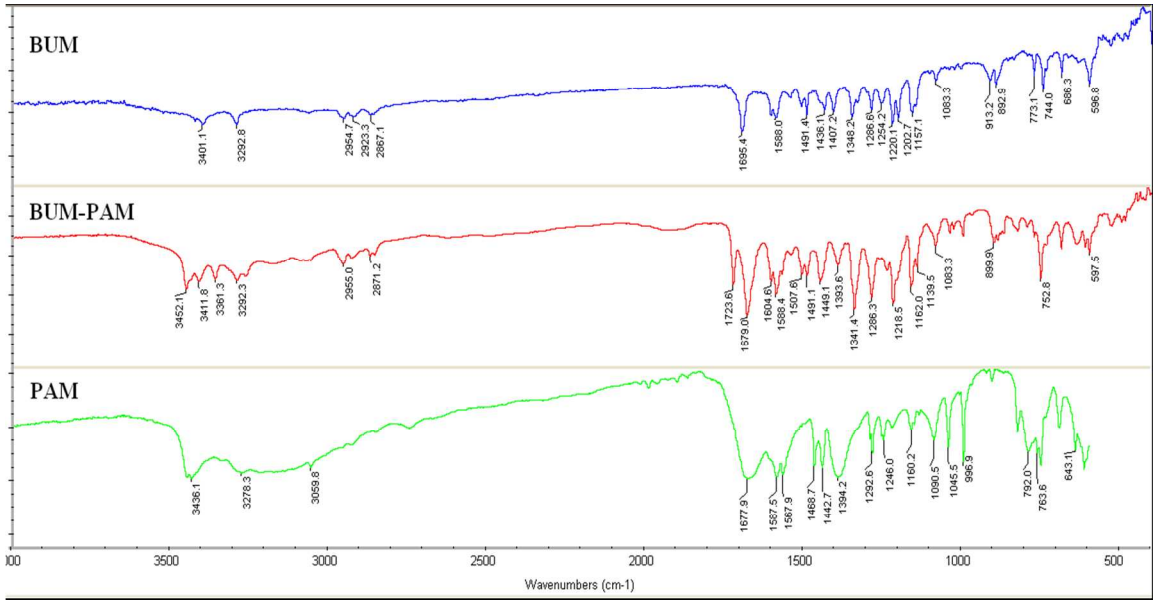


Figure S39: IR comparison of BUM−PAM (2:1) cocrystal.

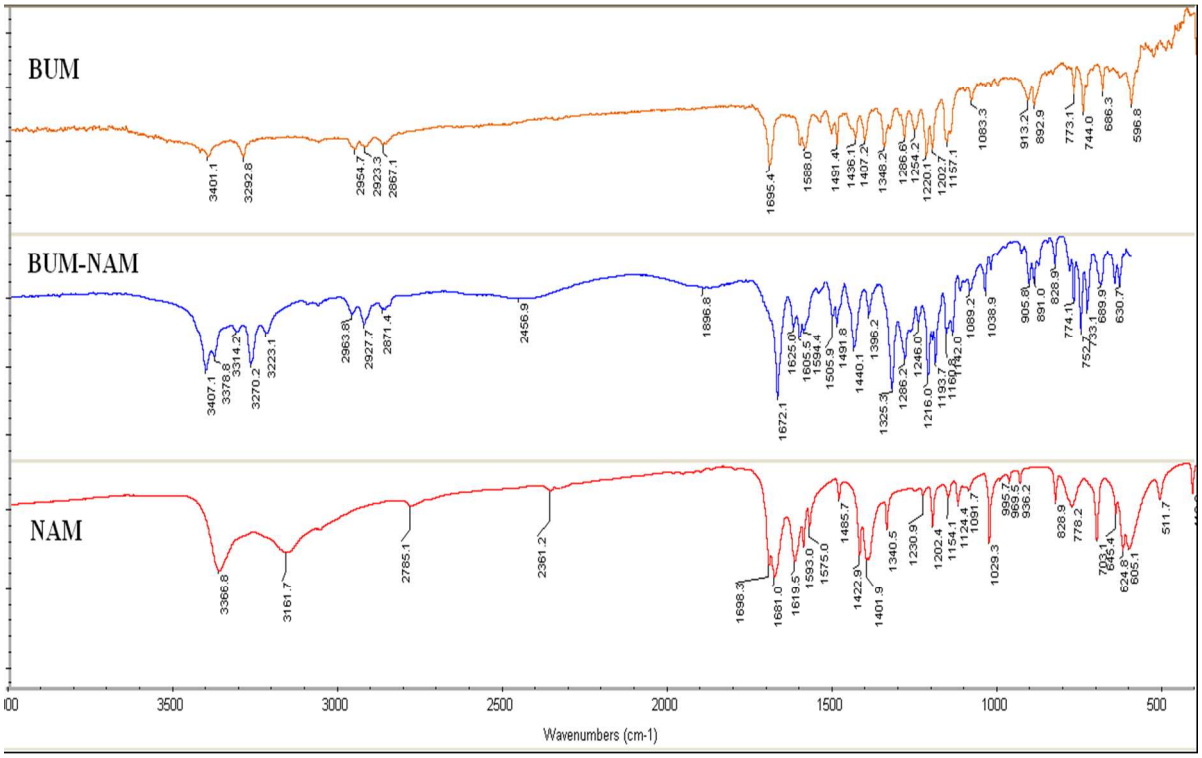


Figure S40: IR comparison of BUM−NAM (1:1) cocrystal.

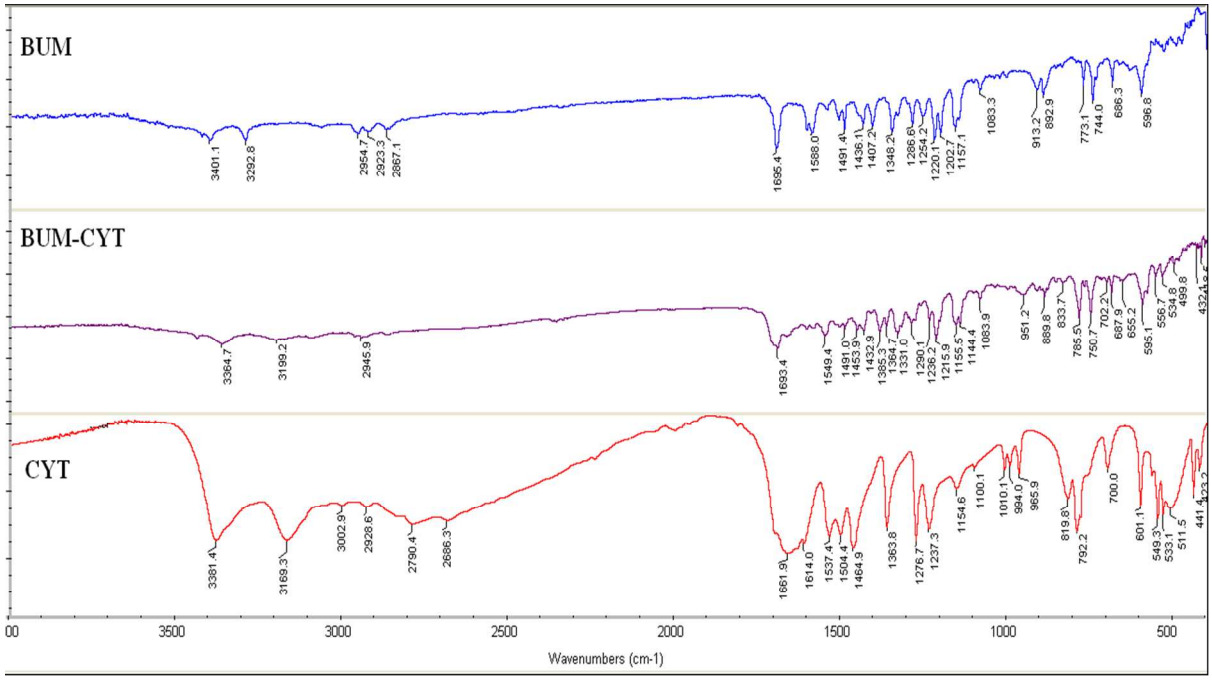


Figure S41: IR comparison of BUM^{-}−BUM−$CYTH^{+}$(1:1:1) cocrystal salt.

IR Comparison of Ternary cocrystals

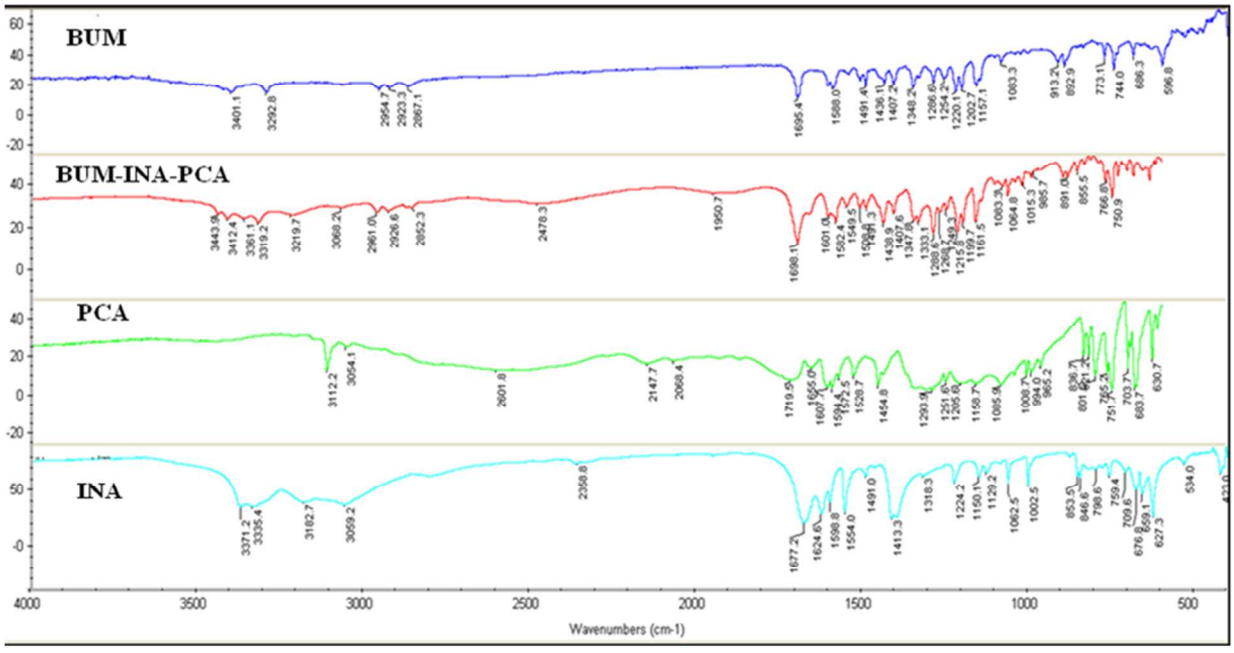


Figure S42: IR comparison of BUM−INA−PCA (1:1:1) cocrystal.

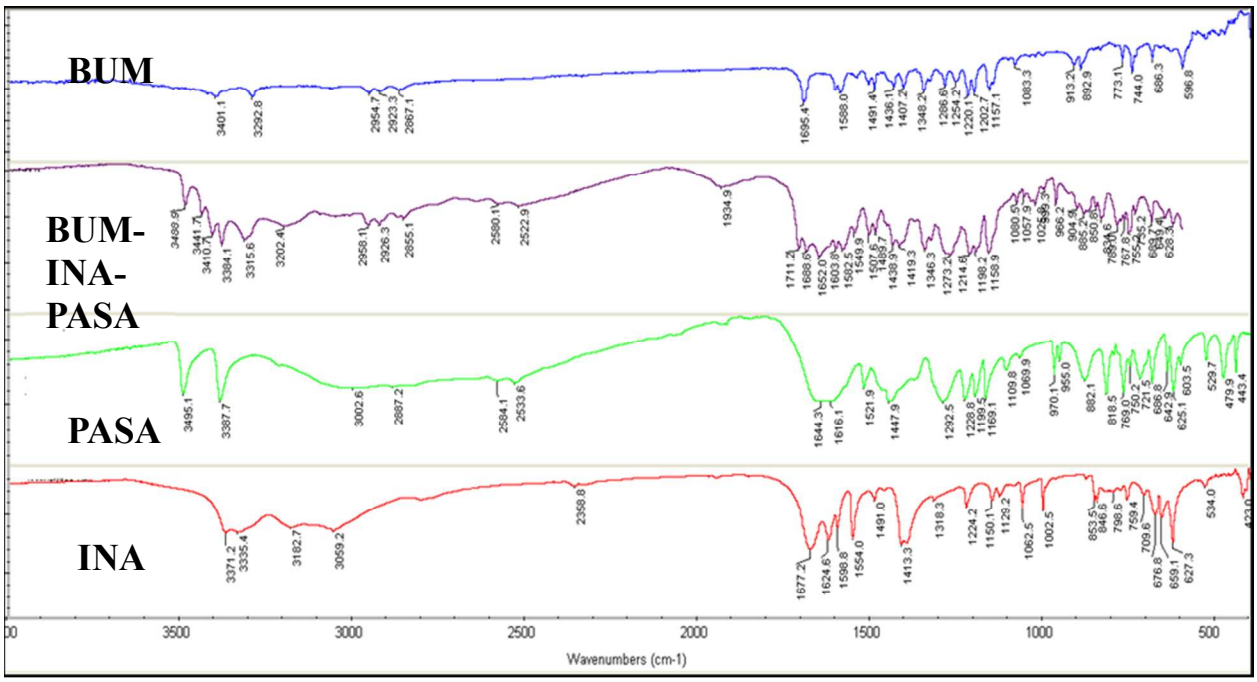


Figure S43: IR comparison of BUM−INA−PASA (1:1:1) cocrystal.

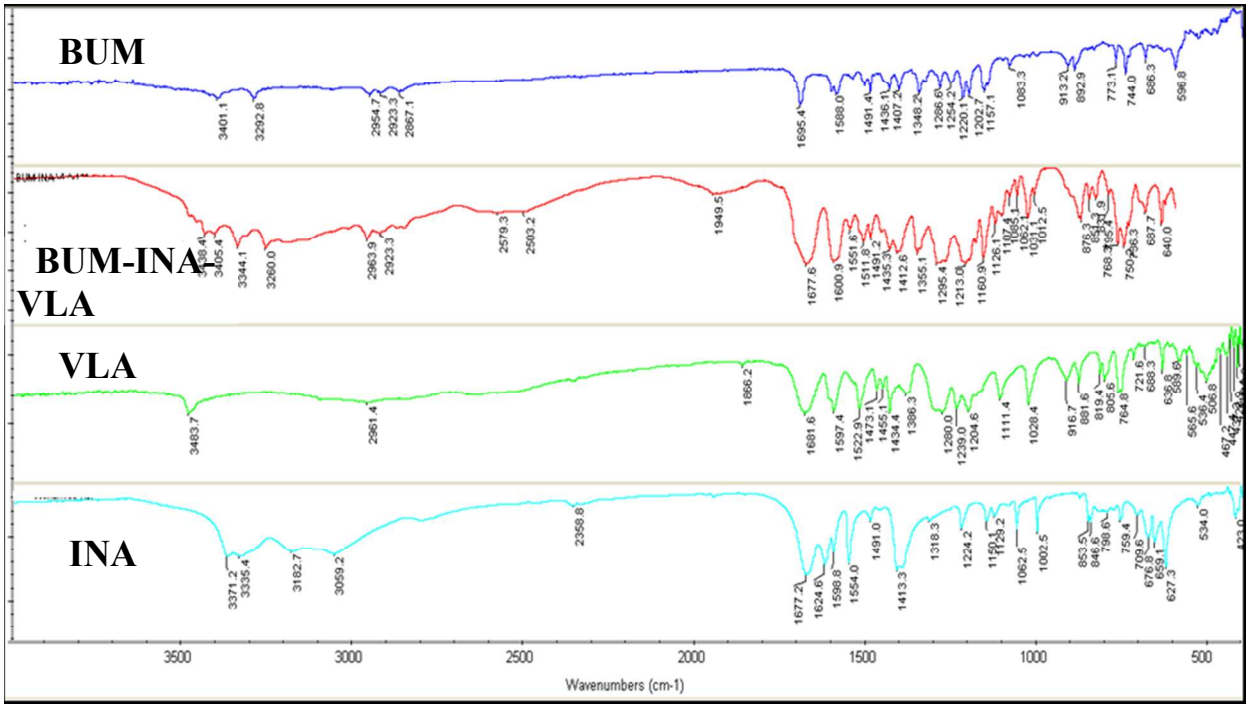


Figure S44: IR comparison of BUM−INA−VLA (1:1:1) cocrystal.

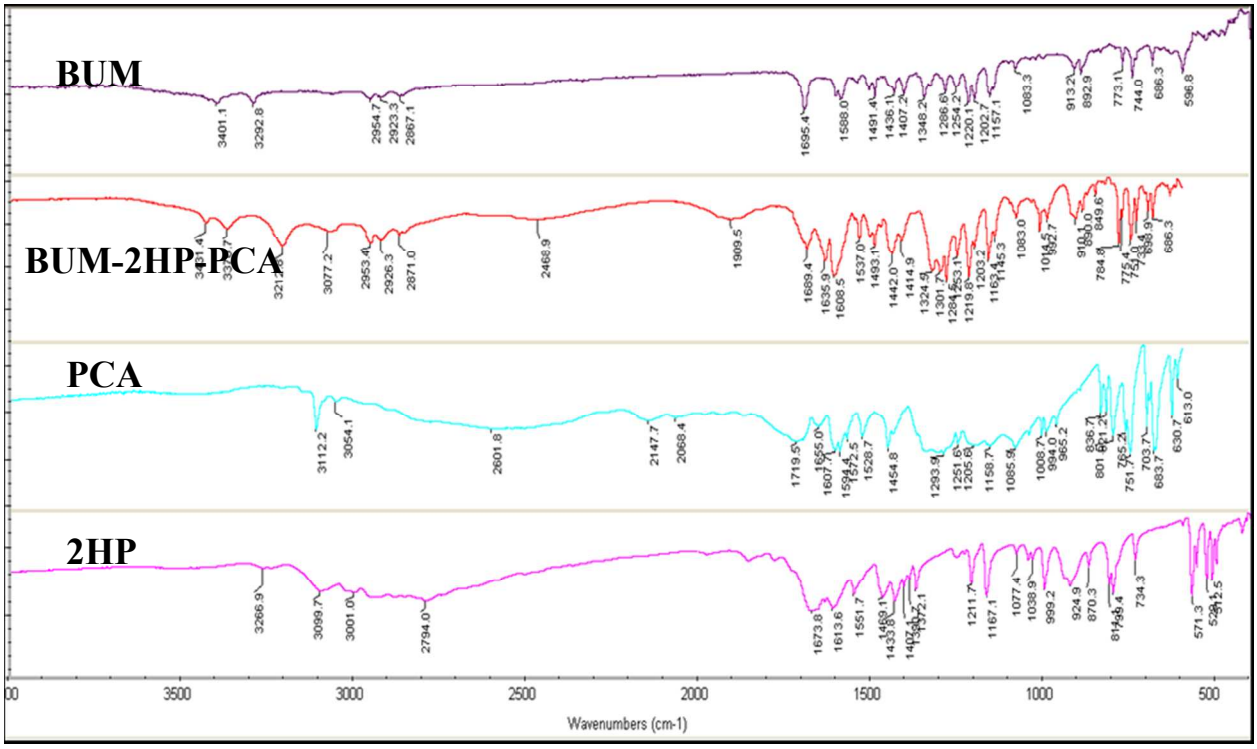
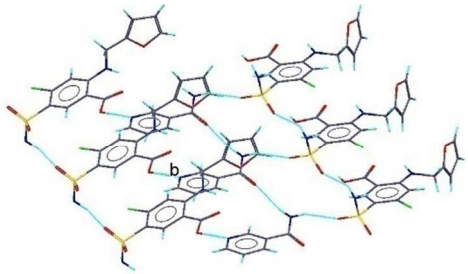


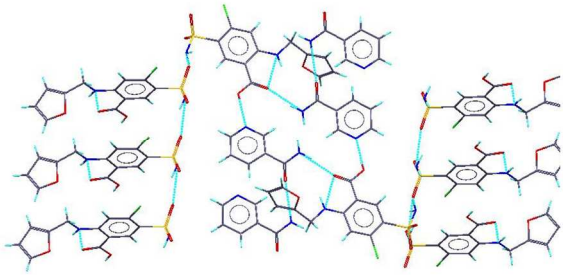
Figure S45: IR comparison of BUM−2HP−PCA (1:1:1) cocrystal.

Section S5: Synthons present in reported SMBA, Furosemide cocrystals[1-5] to compare with those present in BUM crystal structures.

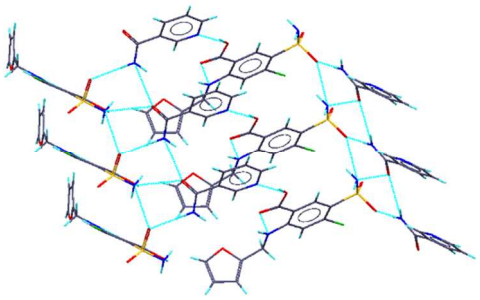
Figure S46: Furosemide−nicotinamide



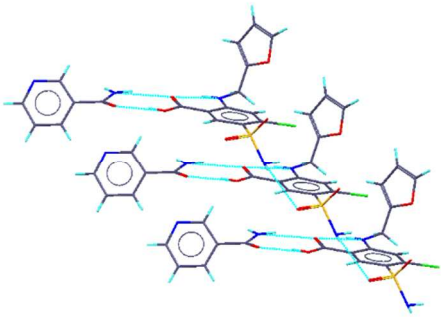
Form I (YASGOQ)



Form II (YASGOQ01)

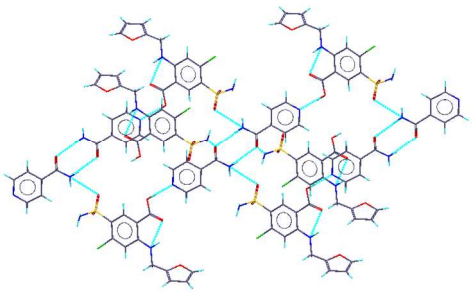


Form III (YASGOQ02)

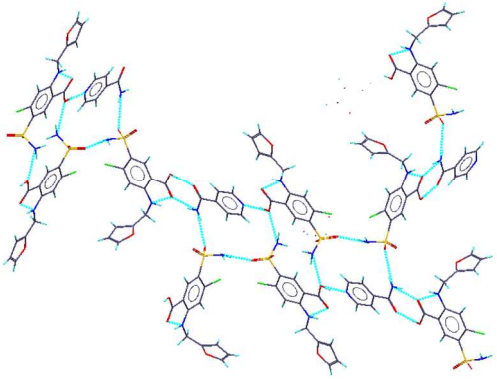


Form IV (YASGOQ03)

Figure S47: Furosemide−isonicotinamide

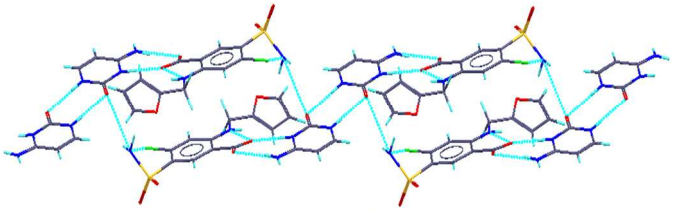


(LOFLID)



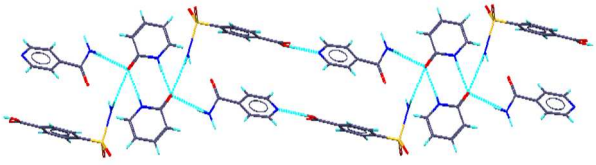
(LOFLEZ)

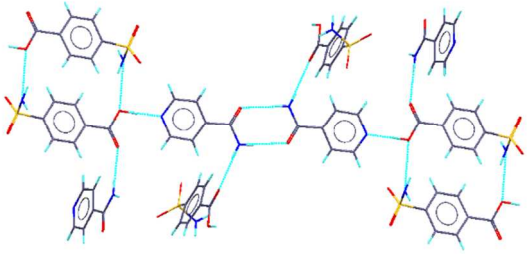
Figure S48: Furosemide−cytosine



XAVTIZ

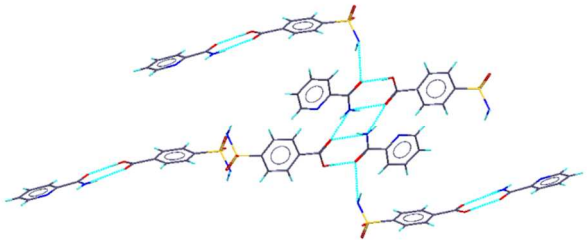
Figure S49:SMBAcocrystals



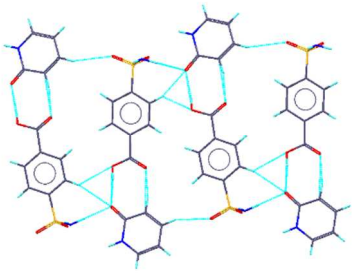


SMBA−NAM (FURWOG)

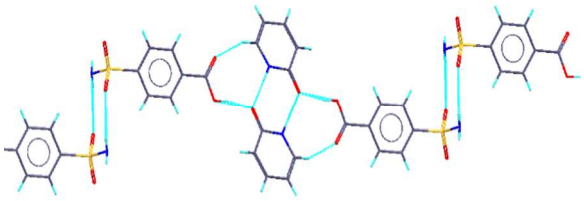
SMBA−INA (FURWOG)



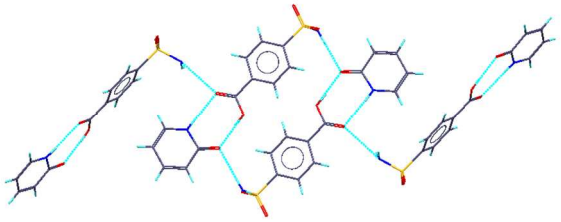
SMBA−PAM (FURYEY)



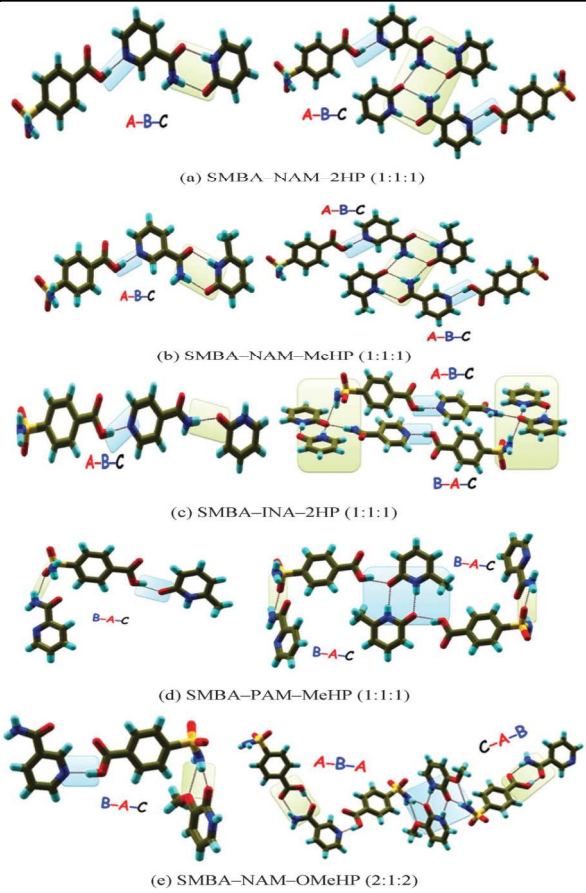
SMBA−2HP Form I, (FURWIA01)



SMBA−2HP Form II, (FURWIA02)



SMBA−2HP Form III, (FURWIA)



(FURXIB, FURXOH, FURWUM, FURXUN, FURYIC)

Section S6: Stability studies on BUM cocrystals in solvent media.

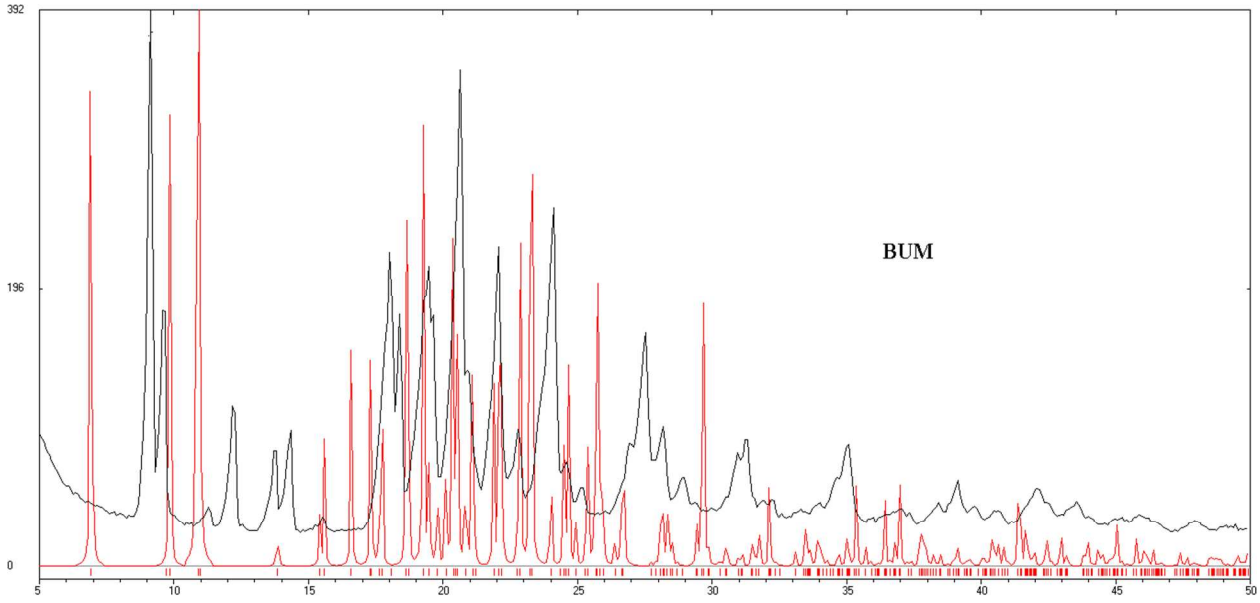


Figure S50: Overlay of calculated PXRD of BUM and experimental PXRD of commercially available BUM used in this study.

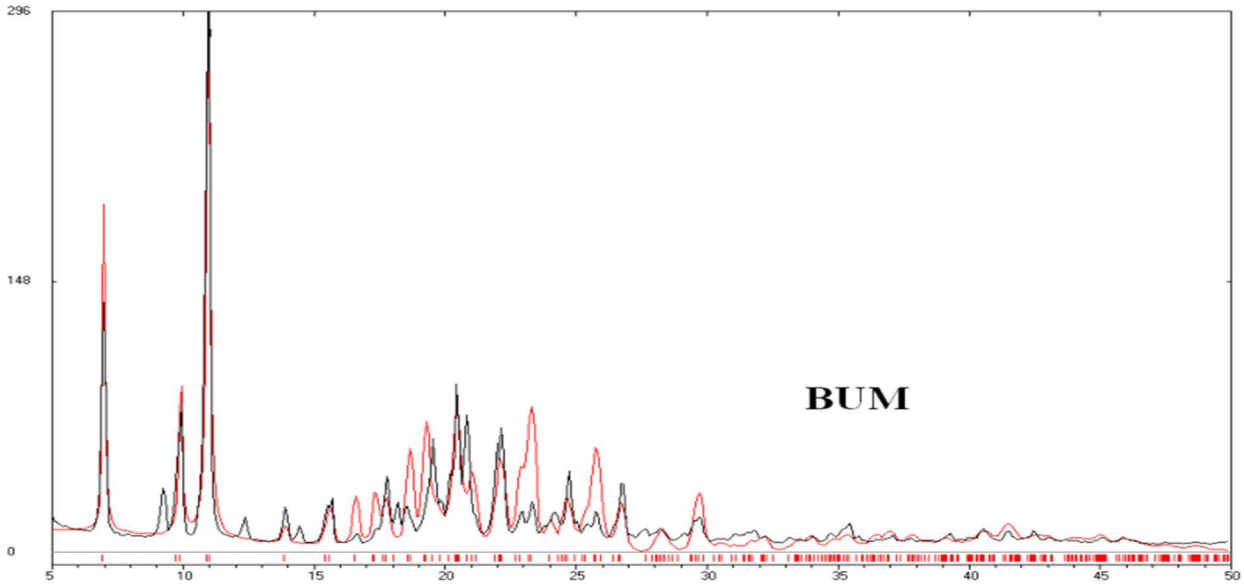


Figure S51: Overlay of calculated PXRD of BUM and experimental PXRD after 24 hours slurry experiment. There are small new peaks at 9.2 and 12.5° 2θ but otherwise the major peaks are matching. Hence the commercially available BUM form does not completely convert to the stable BUM form after 24 hour of slurry crystallization in ethyl acetate (EtOAc) solvent.

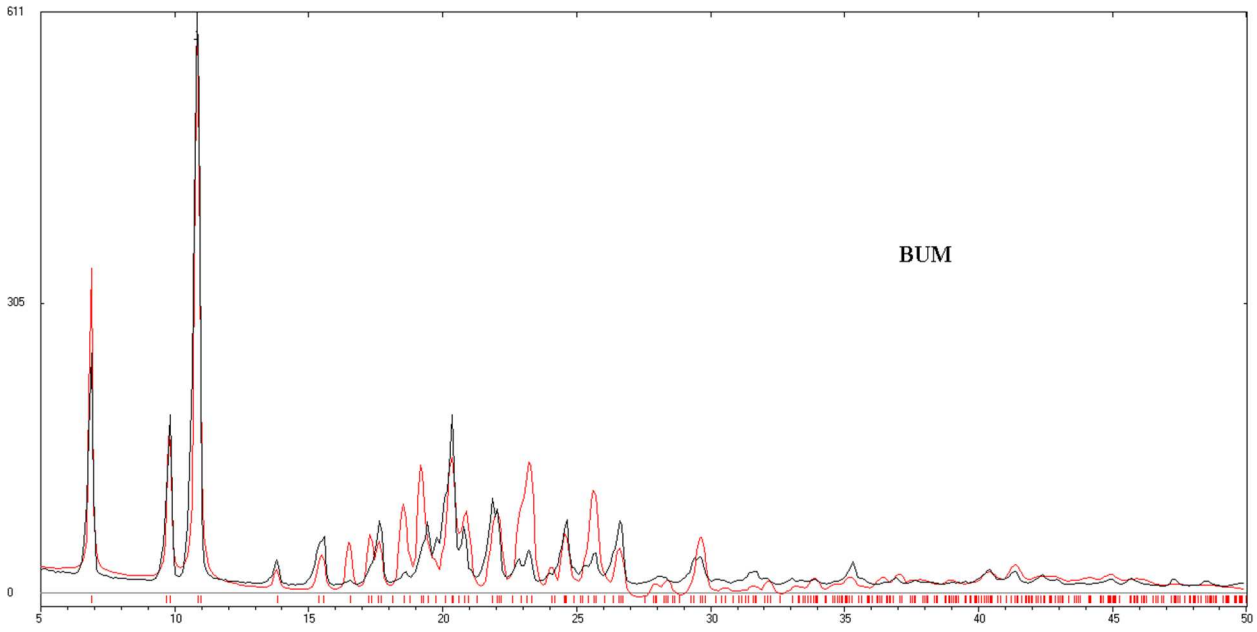


Figure S52: Overlay of calculated PXRD of BUM and experimental PXRD after 72 hours slurry experiment. Hence the commercially available BUM form converts to the stable BUM form after 72 hours slurry crystallization experiment in ethyl acetate (EtOAc) solvent.

Section S7: 1H NMR Analysis of the ternary crystalline materials.

In order to find out the exact composition in the ternary crystalline materials, NMR experiments were performed of the single components as well as ternary crystalline materialsinDMSO-D6 solvent (solvent peak at 2.50(5) ppm). In NMR spectra, the different colour dots correspond to different protons of the component molecule. Here, three different molecules are highlighted which is indication of three different molecules in the crystalline product. In NMR spectra, well separated and distinct protons of the molecules are taken into account. The area under curve is an indication of number of protons attached to that molecule in the product. In all cases the ratio present in the reaction product is the same as that used for crystallization. The stoichiometry of the ternary system is established by 1H NMR integration.

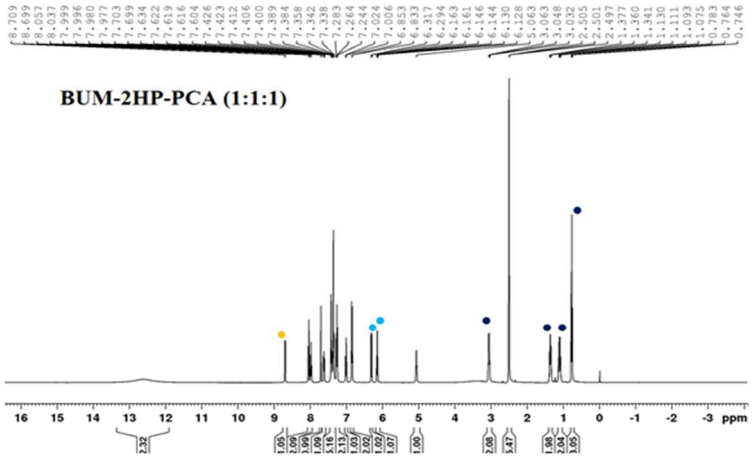


Figure S53: 1H-NMR of BUM-2HP-PCA: yellow, light blue and deep blue correspond to 2HP, PCA and BUM.

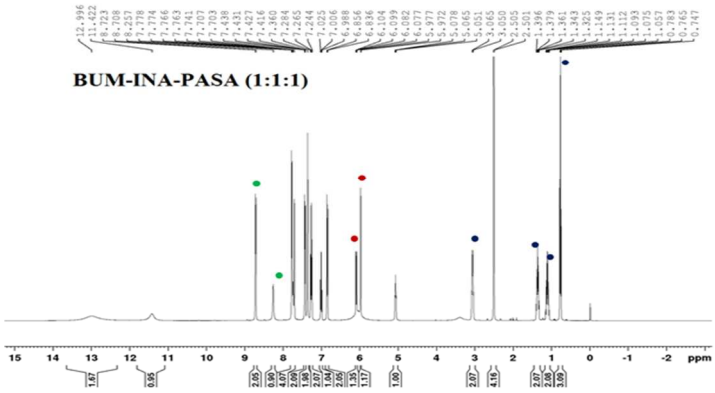


Figure S54: 1H NMR of BUM-INA PASA:green, red and dark blue correspond to INA, PASA and BUM.

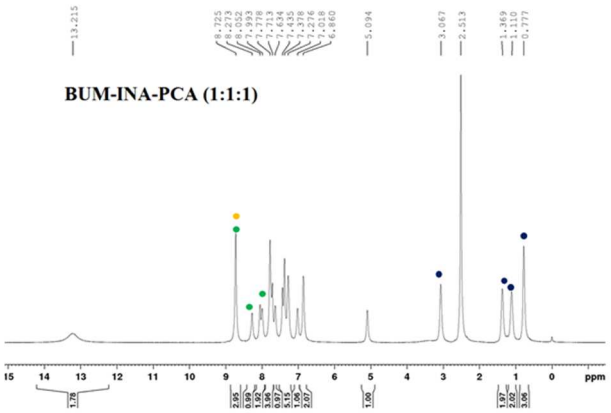


Figure S55: 1H-NMR of BUM-INA-PCA:yellow, green and dark blue correspond to PCA, INA and BUM.

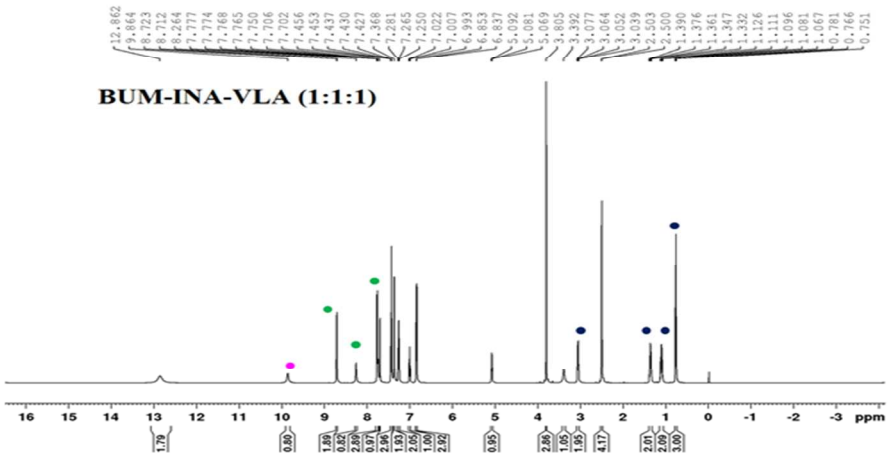


Figure S56: 1H-NMR of BUM-INA-VLA: pink,green and dark blue correspond to VAL, INA and BUM.

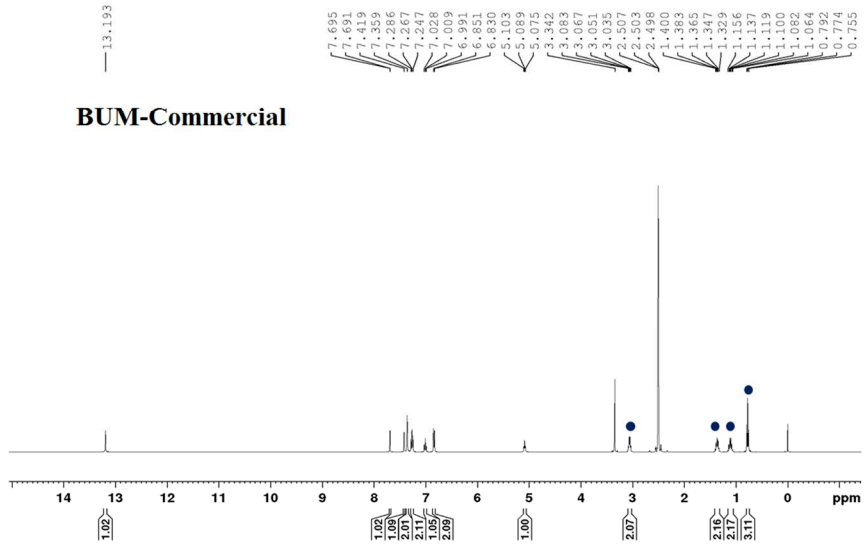


Figure S57: 1H-NMR of BUM: dark blue corresponds to alkyl group in BUM. The remaining protons are functional groups hydrogen atoms.

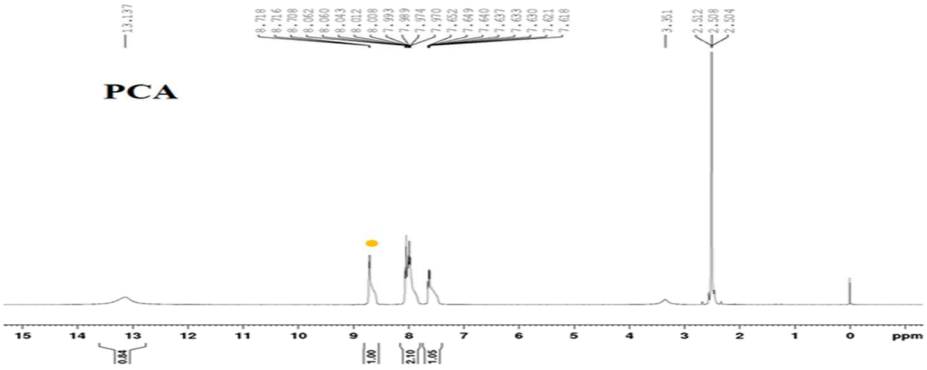


Figure S58: 1H-NMR of PCA: protons used to calculate integration are color coded.

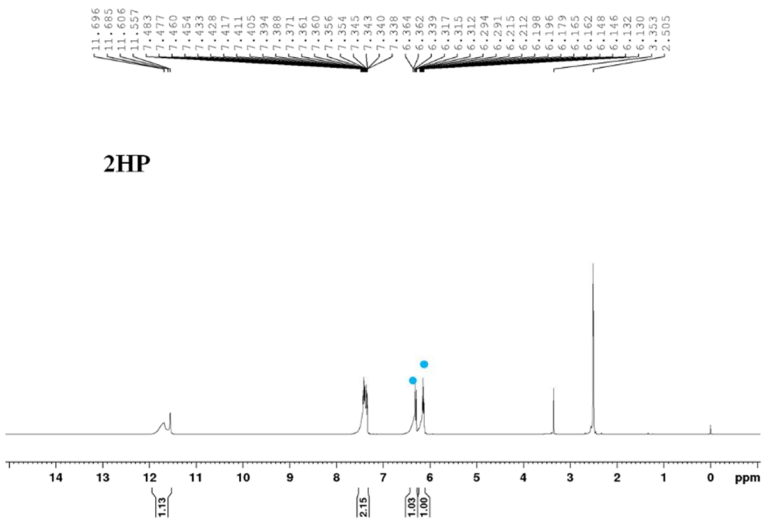


Figure S59: 1H-NMR of 2HP: protons used to calculate integration are color coded.

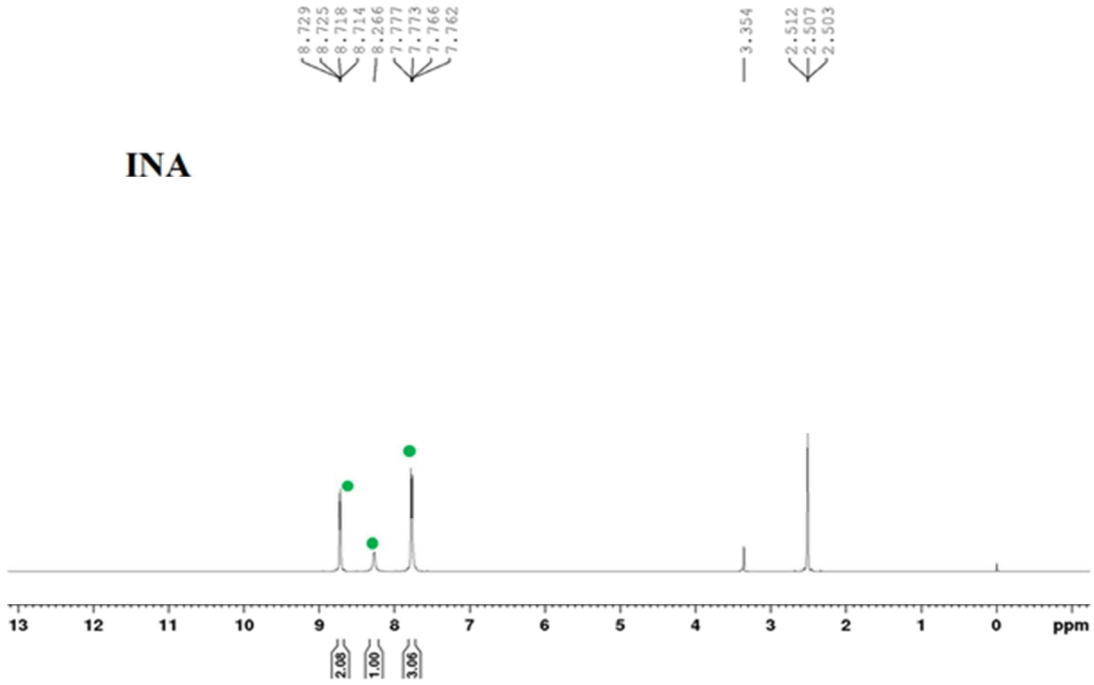
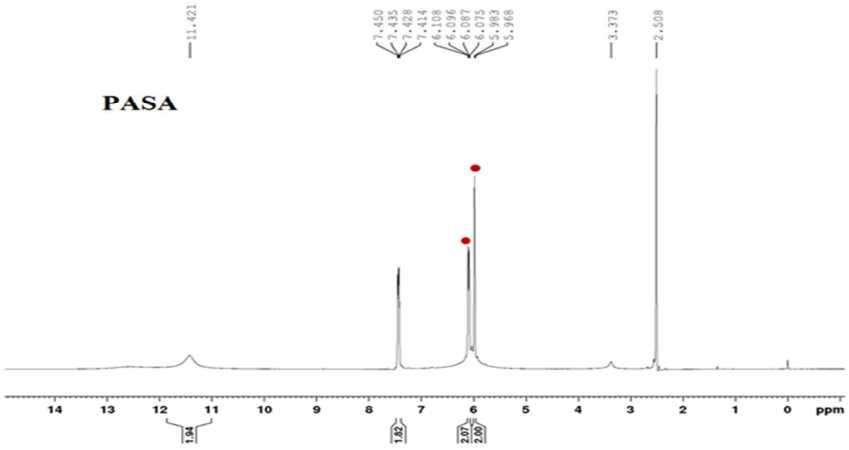


Figure S60: 1H-NMR of INA: protons used to calculate integration are color coded.



FigureS61: 1H-NMR of PASA: protons used to calculate integration are color coded.

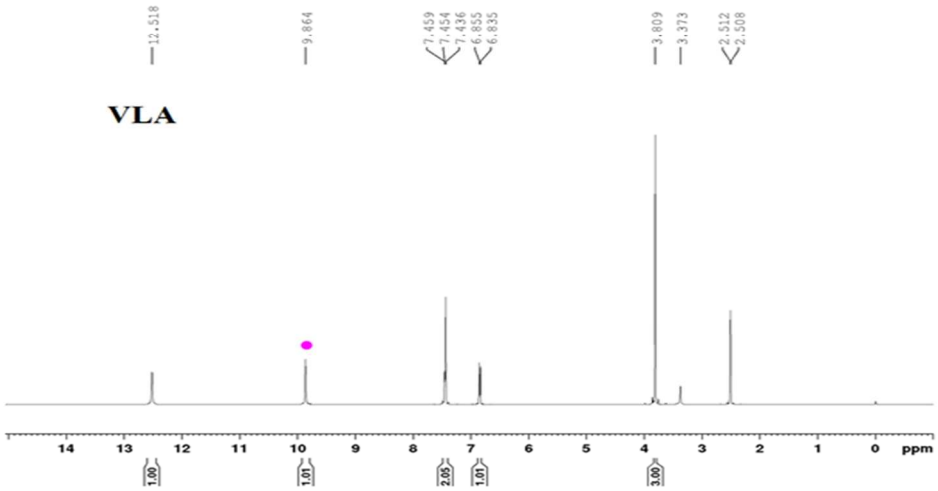


Figure S62: 1H-NMR of VLA: protons used to calculate integration are color coded.

Table S1: For supramolecular synthons analysis CSD version 5.38 and conquest 1.19 is used. First the basic functional groups are drawn and contacts (non-covalent interactions) are defined as intermolecular distance within sum of VdW+ 0.0.

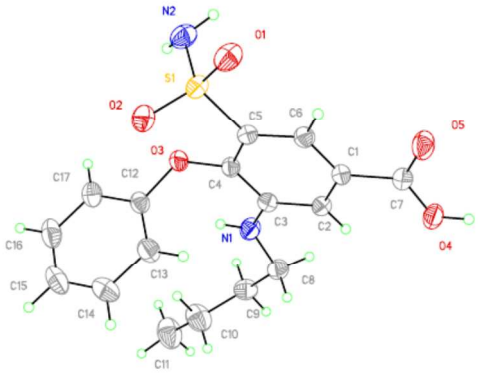
	Supramolecular synthon	No of hits
1	Acid–amide	494
2	Amide-amide	4406
3	Acid-acid	6890
4	Sulfonamide catemer	315
5	Sulfonamide dimer	99
6	Acid-pyridine	1655
8	Pyridine–Sulfonamide	33

77 Salts of Cytosine			23 neutral crystals with Cytosine
UWAMIQ	GATMOF	FICXIZ	CUVDIH
UWANAJ	GITYEN	TAZXAU	CUVDIH01
ACITEM	JAYNIG	TAZXEY	CUVDON
ACITIQ	JEJLEQ	VISVIE	CUVDON01
ACITOW	JOXBAB	WIGGAW	CUVDUT
ADALAS	KEQPEC	XICRIM	CUVDUT01

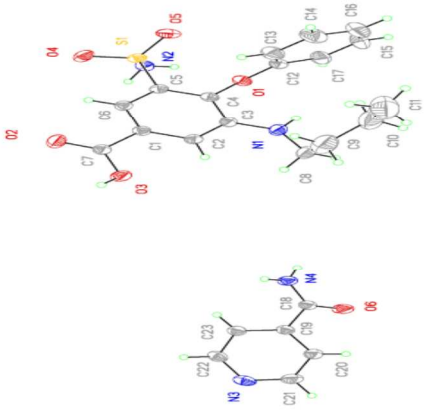
Table S2: Refcodes of Cytosine containing crystals in CSD.

CASCIJ	KEVSAG	XICROS	CYTFUR
CIRVUV	KINTOS	XOMKAN	CYTFUR01
CIRWAC	LEZHON	XOMKIV	CYTOSM
CTSGLM	LIWSIU	XOMZUW	CYTOSM02
CUKCUH	LIWSOA	YUMGOD	CYTOSM03
CUKDAO	NALFIS	ZAZGEO	CYTOSM11
CYTRES10	NALFOY	ZEGDOG	CYTOSM12
CYTSCA	NALFUE	ZEGDUM	CYTOSM13
DOTGID	NALGAL	ZEGFAU	CYTSIN
DOTGOJ	OCIRAT	ZEGFEY	CYTSIN01
DUJCAN	ODICOU	ZEYDAK	CYTSIN02
DUJCAN01	ODICOU01	ZEYDIS	OYEREQ01
DUJCAN02	OJERIE	ZEYJAQ	PUJWUO
DUZNIW	OYEREQ	ZEYJOE	QOBCER
DUZNOC	OYERIU	ZEYJUK	QOBCOB
EFUNUP	RIVCII	ZEYKAR	XOMKER
ENODIV	ROFLAZ	ZEYKEV	ZEYNOI
EPAMAK	SEGZUZ	ZEYLEW	
EPAMAK01	TAZWUN	ZEYLIA	

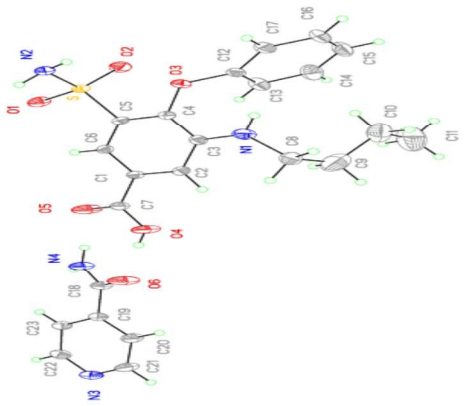
Table S3: ORTEP Diagrams of BUM and its cocrystals.



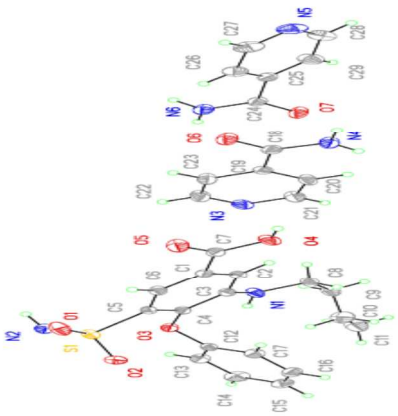
(a) BUM



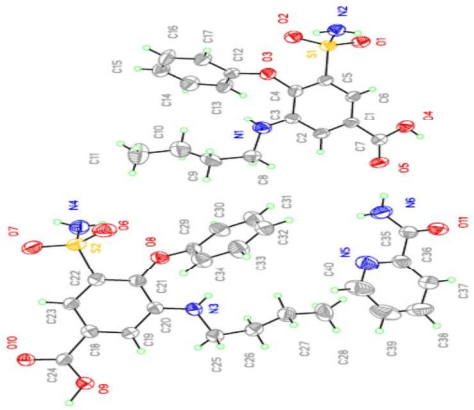
(b) BUM-INA form I (1:1)



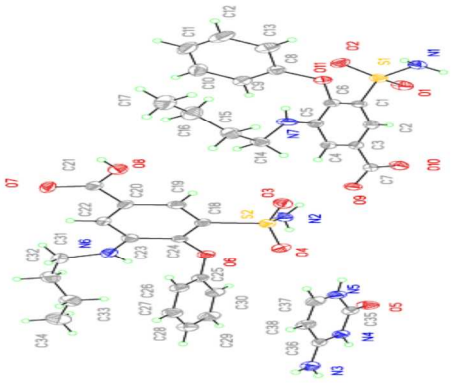
(c) BUM-INA form II (1:1)



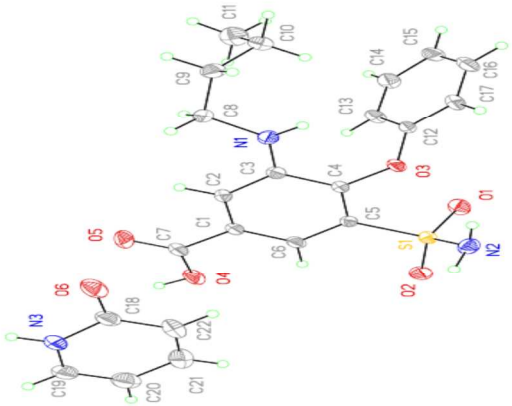
(d) BUM-INA (1:2)



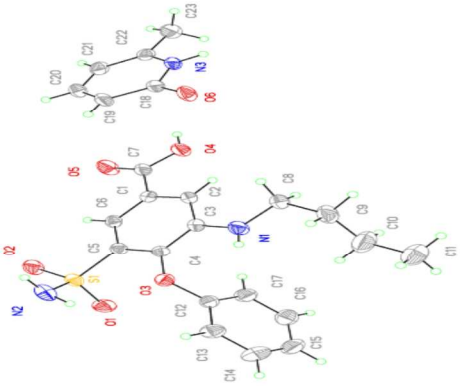
(e) BUM-PAM(2:1)



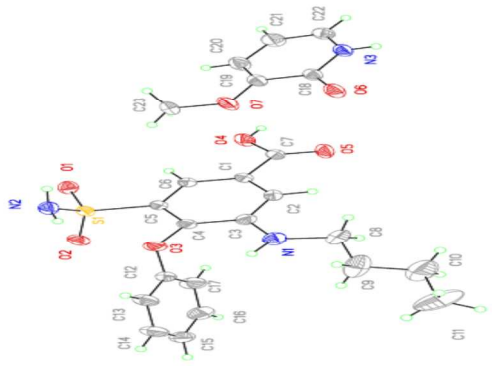
(f) BUM^{-}−BUM−$CYTH^{+}$(1:1:1)



(g) BUM-2HP(1:1)



(h) BUM-MeHP(1:1)



(i) BUM-OMeHP(1:1)

Table S4 pK_a values of coformers resulting in cocrystals /salt of BUM.[a]

Compound	pK_a/ pK_b	ΔpK_a	Cocrystal/salt
BUM	4.69	--	--
INA	3.45	1.24	1:1 and 1:2 cocrystal
NAM	3.63	1.06	1:1 cocrystal
PAM	1.17	3.52	2:1cocrystal
CYT	2.34	2.35	1:1:1 salt cocrystal

[a] p*Ka*'s were calculated using Marvin 5.10.1, 2012, ChemAxon (http://www.chemaxon.com). pK_b = pK_a (base-H^+).

References

(1) Ueto, T.; Takata, N.; Muroyama, N.; Nedu, A.; Sasaki, A.; Tanida, S.; Terada, K. *Cryst. Growth Des.* **2012**, *12*, 485−494.

(2) Harriss, B. I.; Vella−Zarb, L.; Wilson, C.; Evans, I. R. *Cryst. Growth Des*. **2014**, *14*, 783−791.

(3) Kerr, H. E.; Softley, L. K.; Suresh, K.; Nangia, A.; Hodgkinson, P.; Evans, I. R. *CrystEngComm* **2015**, *17*, 6707–6715.

(4) Goud, N. R.; Gangavaram, S.; Suresh, K.; Pal, S.; Manjunatha, S. G.; Nambiar, S.; Nangia, A.; *J. Pharm. Sci*. **2012**, *101*, 664–680.

(5) Bolla, G.; Nangia, A. *Chem. Commun.* **2015**, *51*, 15578−15581.