Supporting Information

Tracing the architecture of Caffeic acid phenethyl ester cocrystals: Studies on crystal structure, solubility and bioavailability implications

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SI1. Coformers screened for cocrystallization with CAPE (1:1).

No.	Coformer	Melting point (°C)	Solvent (60% w/v)	Observations	Inference
1	Caffeine (CAF)	235-238	Ethanol	i) DSC thermogram showed melting endotherm at 113.48°C. ii) PXRD showed distinct peak at 2θ value 3.5.	Formation of CAPE:CAF cocrystal was evident (however diffraction quality single crystal was not produced)
2	Nicotinamide (NIC)	130-131	Ethanol	i) DSC thermogram showed melting endotherm at 106.67°C. ii) PXRD showed distinct peak at 2θ value 4.6.	Formation of CAPE:NIC cocrystal was evident Also diffraction quality single crystal was produced.
3.	Isonicotinamide (INIC)	155-157	Ethanol	i) DSC thermogram showed melting endotherm at 107.98 °C. ii) PXRD showed distinct peak at 2θ value 4.6.	Formation of CAPE:CAF cocrystal was evident. (however diffraction quality single crystal was not produced)
4.	Gallic acid	257-258	Ethanol	DSC thermogram showed endotherm peaks at 113.8, 117.14 and 275.6 °C.	No cocrystal was produced.

No.	Coformer	Melting point (°C)	Solvent (60% w/v)	Observations	Inference
			Methanol	DSC thermogram showed sharp endotherm peaks at 127.88 °C and degradation above 225 °C	No cocrystal was produced.
			Acetone	DSC thermogram showed sharp endotherm peak 128.23°C	No cocrystal was produced.
			Ethyl acetate	DSC thermogram showed sharp endotherm peak 128.23°C	No cocrystal was produced.
5.	p-Coumaric acid	210-212	Ethanol	DSC thermogram showed endotherm peak at 126.84 °C and degradation above 190 °C.	No cocrystal was produced.
	p-Coumaric acid		Methanol	DSC thermogram showed endotherm peak at 125.45 °C and degradation above 190 °C.	No cocrystal was produced.
	p-Coumaric acid		Acetone	DSC thermogram showed endotherm peak at 126.50 °C and degradation above 194 °C.	No cocrystal was produced.
	p-Coumaric acid		Ethyl acetate	DSC thermogram showed endotherm peak at 125.80 °C and degradation above 195 °C.	No cocrystal was produced.

No.	Coformer	Melting point (°C)	Solvent (60% w/v)	Observations	Inference
6.	Curcumin	182-184	Ethanol	DSC thermogram showed endotherm peak at 122.47 °C.	No cocrystal was produced.
			Methanol	DSC thermogram showed endotherm peak at 122.47 °C.	No cocrystal was produced.
			Ethyl acetate	DSC thermogram showed endotherm peak at 122.47 °C.	No cocrystal was produced.
7.	Isoniazid	171-172	Ethanol	DSC thermogram showed endotherm peak at 101.47 °C.	No cocrystal was produced.
8.	Theophylline	273-274	Ethanol	DSC thermogram showed endotherm peak at 117.30 °C.	No cocrystal was produced.
9.	Urea	132-134	Ethanol	DSC thermogram showed endotherm peak at 99.95 and 133.14 °C.	No cocrystal was produced.
10.	Ibuprofen	75-76	Ethanol	DSC thermogram showed endotherm peak at 74 and 121.69 °C.	No cocrystal was produced.

SI2. Details of HPLC method for CAPE analysis

Waters e-2695 HPLC system integrated with a PDA 2998 detector, Empower 3 software and Waters symmetry C18 column (4.6 × 250 mm, 5 µm) maintained at 25 + 0.5 ℃ was used. Elution was carried out using mobile phase methanol: acetonitrile (50: 50 v/v) in an isocratic method at a flow rate of 1 mL/min.[1] CAPE detection was done at 246 nm. Each experiment was performed in triplicates.

SI3. Details of in vivo pharmacokinetic study

The experiment protocol (CPCSEA/40/12), was approved by Institutional Animal Ethical Committee (IAEC) constituted as per guidelines of the Committee for Purpose of Control and Supervision of Experiments on Animals Government of India. The animals were housed under standard conditions of temperature (24 ± 1 °C), relative humidity (55 ± 10%) and 12 hrs light/dark cycles during said period. Animals had free access to standard pellet diet, filtered water ad libitum and were acclimatized for a period of one week prior to study. The animals were starved overnight prior to the study. Vegetable oil was used as gavage vehicle as all the crystal forms were found insoluble in it. The blood samples were mixed thoroughly with di-sodium EDTA to prevent clotting and centrifuged at 10,000 rpm for 15 min at 4 ℃. The separated plasma was transferred to pre-labeled tubes containing sodium fluoride (0.25%) and acetate buffer (0.1M) to ensure the integrity of CAPE during storage at -80 ℃ till analysis.[2,3]

Quantification of CAPE in Rat plasma

Standard solutions of CAPE and internal standard (IS), Taxifolin were prepared by dissolving each 10 mg in methanol 10 ml. The working standard solutions were prepared by diluting the stock solutions with mobile phase and spiked into the blank plasma to produce plasma

standards. The plasma samples were analysed for CAPE content by HPLC as per reported method with minor modifications. Briefly, 200 µl of each plasma sample was mixed with 100 µl of IS (100 µg/ml) and extracted with 600 µl of ethyl acetate by vortexing for 15 min. The collected supernatant phase from both extractions was dried under nitrogen flow at room temperature. The dried residues each were reconstituted with 200 µl acetonitrile, filtered through 0.45µm nylon syringe and subjected to HPLC analysis for determination of CAPE content using Waters e-2695 system integrated with a PDA 2998 detector, Empower 3 software and Waters symmetry C18 column (4.6 × 250 mm, 5 µm) maintained at 25 ± 0.5 °C throughout study. Elution was carried out with flow rate of 0.5 mL/min at ambient temperature. The solvents comprised acetonitrile (solvent A) and water (solvent B) both with 0.5% formic acid mixed using linear gradient system: initial 85% B, 25% B in 3 min, 10% B in 10 min, 0 % B in 15 min followed by isocratic 85% B held constant till 45 min. Detection was performed between 200 to 400 nm and chromatograms were extracted at 328 nm. The concentration range of the standard curve was 2 to 20 ng/mL of CAPE.

Data analysis

Pharmacokinetic parameters were calculated for the set of data by two compartment analysis using WinNonLin version 4.0 (Pharsight, Mountain View, CA,).

SI4. Differential Scanning Calorimetry (DCS), Heat-Cool-Heat study for CAPE-NIC, CAPE-INIC and CAPE-CAF co-crystals**.**

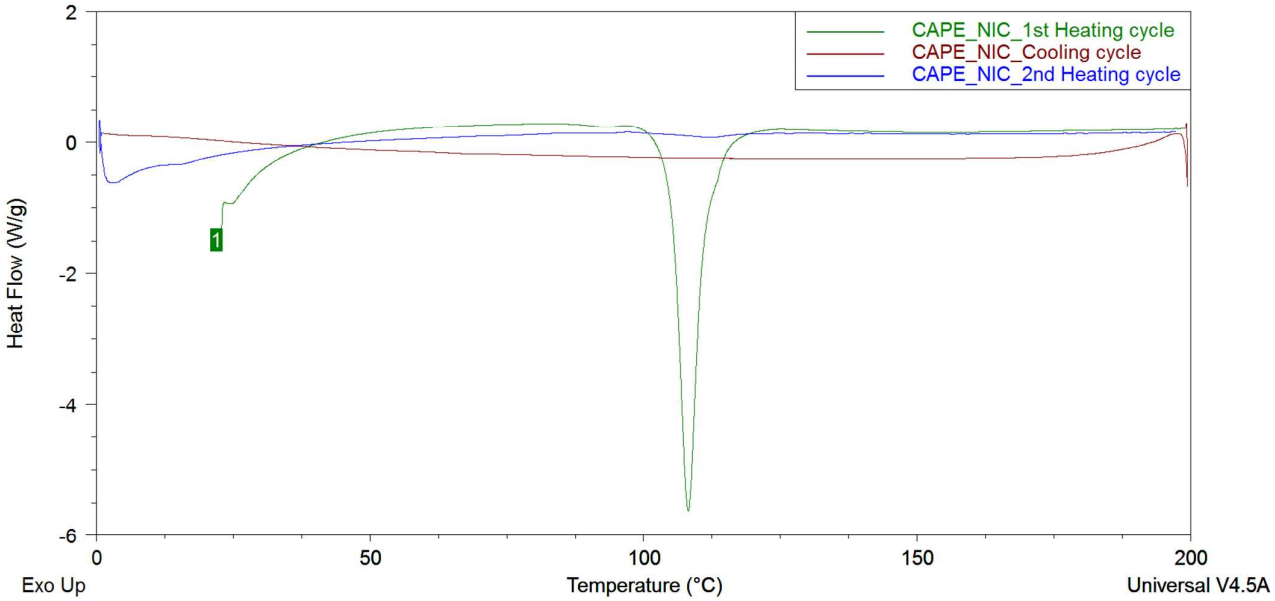

Figure SI4.A. DSC thermogram of CAPE-NIC co-crystal, Heat-Cool-Heat cycle.

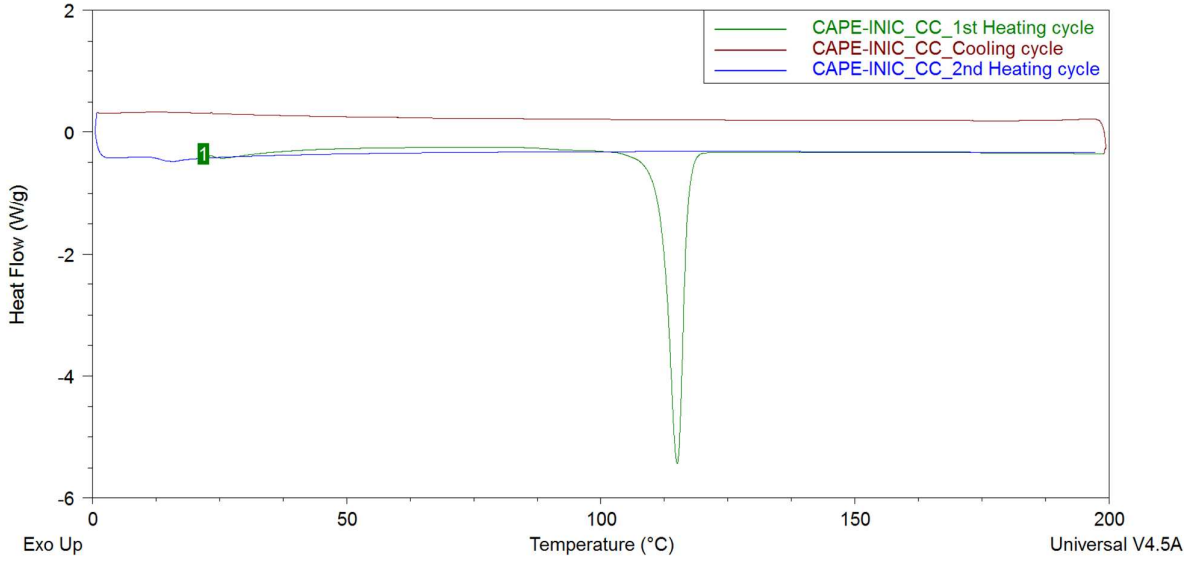

Figure SI4.B. DSC thermogram of CAPE-INIC co-crystal, Heat-Cool-Heat cycle.

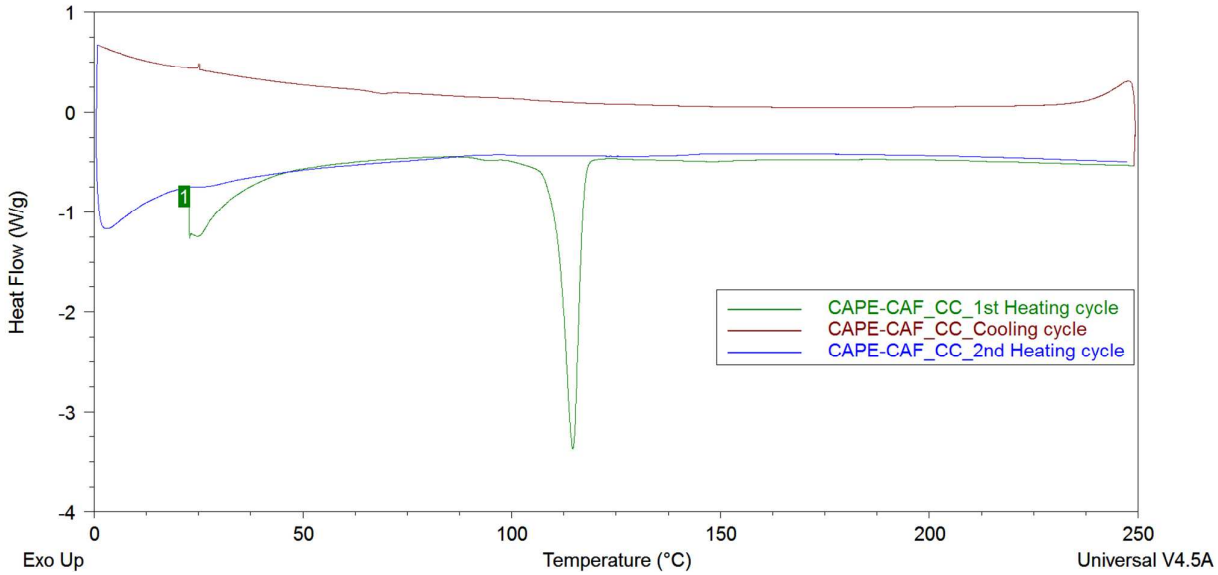

Figure SI4.C. DSC thermogram of CAPE-CAF co-crystal, Heat-Cool-Heat cycle.

SI5. Refcodes with 1,2-benzenediol and amide functional groups in the same crystal structure.

EVIJUO	FIXROV	GAZWUB	HEDRAL	HEDREP
HEDRIT	HEDROZ	HUMJII	MUPMOA	MUPNAN
MUPNUH	MUPPAP	NAXHOL	PEFGEO	PEFGEO01
PEFGEO02	PEFGEO03	PEFGIS	REBXIH	VEQTIW
ZEBXEL	ZEBXIP	ZEBXOV	ZEBXUB	ZIKNOY
ZIKPAM	ZIKPUG			

The refcodes marked in RED represent crystal structures with benzene diol and amide heterosynthon

The refcodes marked in BLUE represent crystal structures with competing homosynthons such as amide-amide, OH-OH etc

The refcodes marked in BLACK represent crystal structures with other heterosynthons such as acid-amide, amide-pyridine etc.

SI6. HPLC Chromatograms of CAPE and its cocrystals.

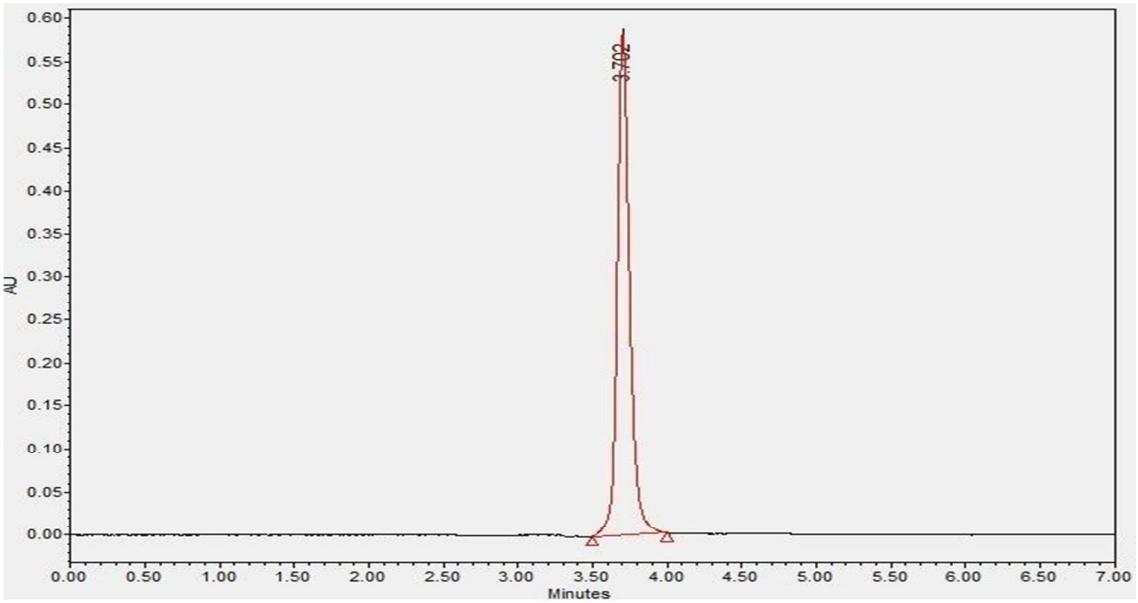

Figure SI6.A. Representative HPLC chromatogram of CAPE.

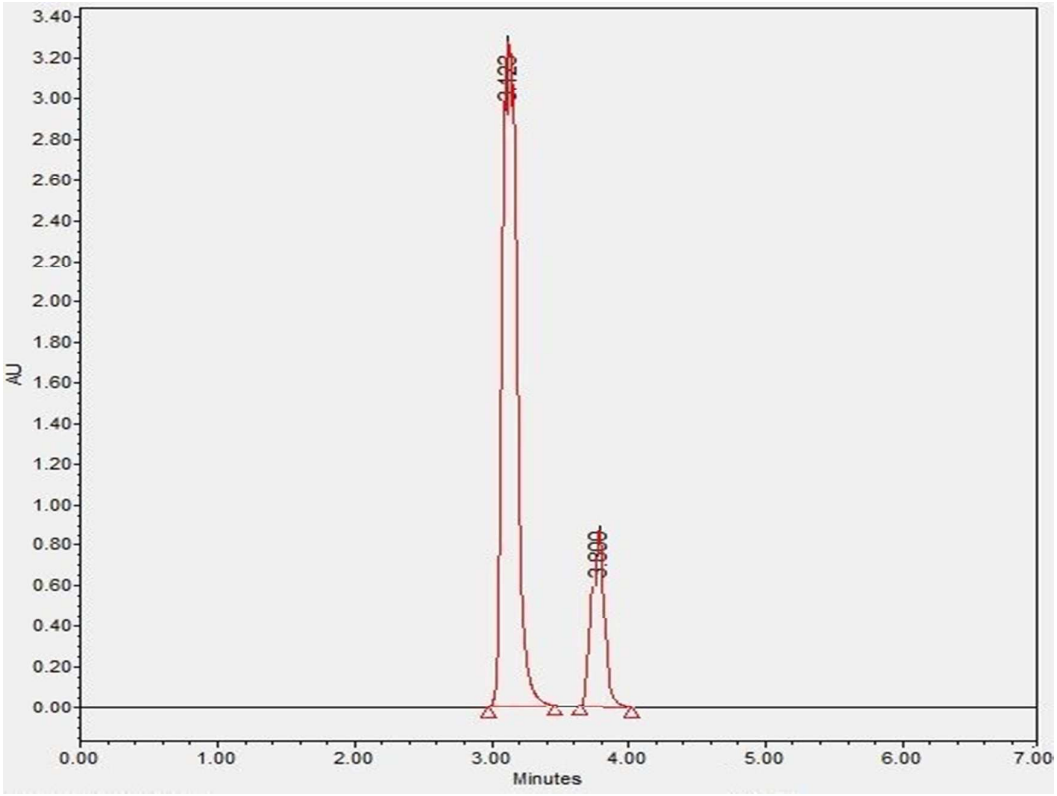

Figure SI6.B. Chromatogram for CAPE-CAF. The chromatogram depicts elution at 3.123 min for CAF and 3.80 min for CAPE.

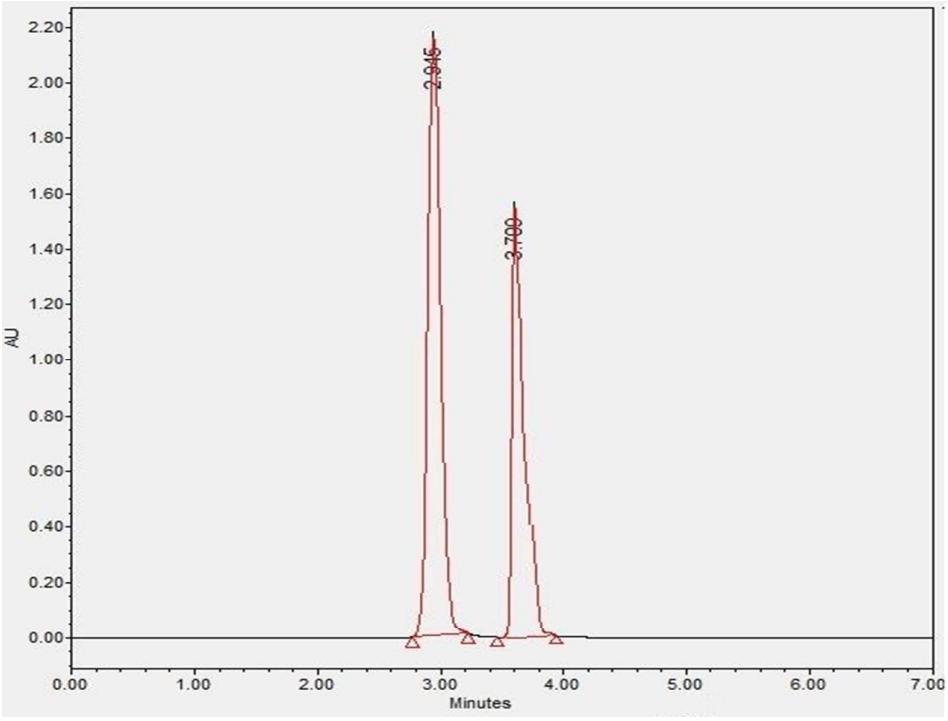

Figure SI6.C. Chromatogram for CAPE-INIC. The chromatogram depicts elution at 2.915 min for INIC and 3.70 min for CAPE.

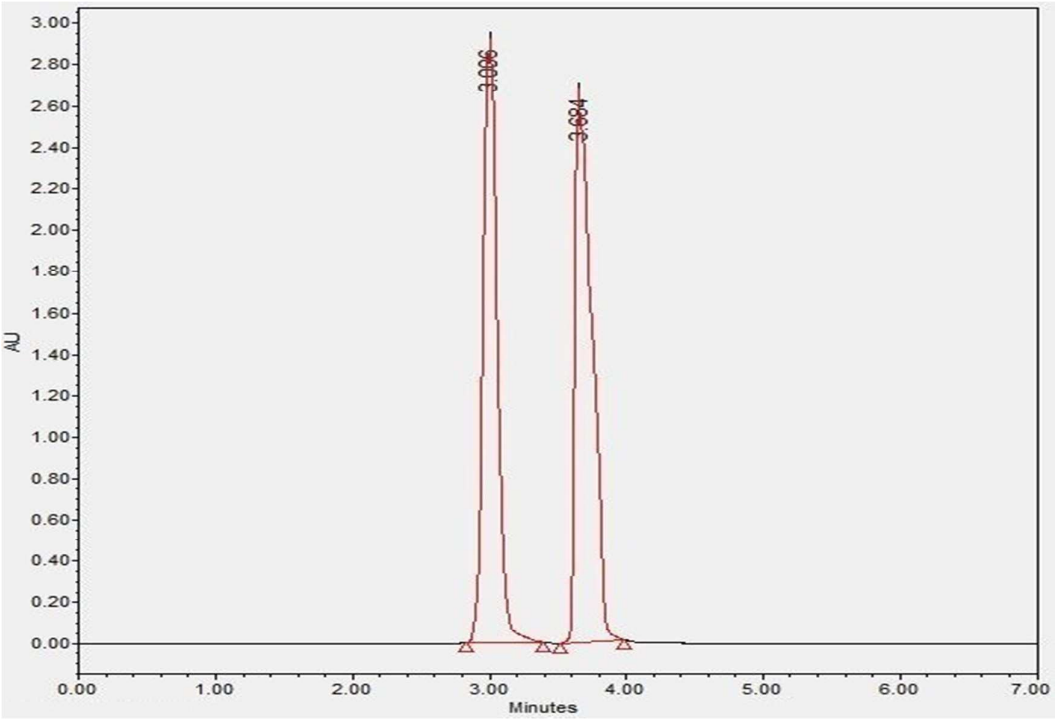

Figure SI6.D. Chromatogram for CAPE-NIC. The chromatogram depicts elution at 3.006 min for NIC and3.684 min for CAPE.

SI7. BDFH morphology crystals (calculated)

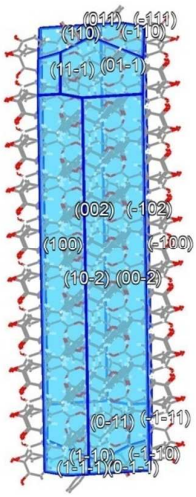

Figure SI7.A. BFDH model of CAPE-NIC showing the projected diol groups long the major (100) face. (Projected parallel to the (100) face)

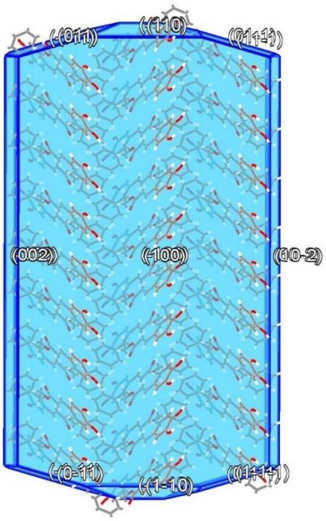

Figure SI7.B. BFDH model of CAPE-NIC showing the projected diol groups long the major (100) face. (Projected perpendicular to the (100) face)

References

1. Ceschel, G.; Maffei, P.; Sforzini, A.; Borgia, S. L.; Yasin, A.; Ronchi, C. *Fitoterapia*. **2002**, 73, S44.
2. Wang, X.; Bowman, P. D.; Kerwin, S. M.; Stavchansky, S. *Biomed Chromatogr.* **2007**, *21, 343*.
3. Celli, N.; Mariani, B.; Dragani, L. K.; Murzilli, S.; Rossi, C.; Rotilio, D. J. *Chromatogr. B.* **2004**, *810, 129.*