Novel Pharmaceutical Co-crystals of Gefitinib: Synthesis, Dissolution, Cell Studies, and Theoretical studies

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Contents

Figure S11 – UV spectra of co-crystals in 1N HCL (pH 3.0) solution

Figure S12. PXRD spectra of cocrystal powders (a) GCA, (b) GSA.H_2O, and (c) GRes.H_2O before dissolution experiment (red) and after powder dissolution experiment (black).

Figure S13. powder dissolution rates of of Gefitinib and its cocrystals as a plot of cumulative amount of geftinib released from the powders ug/ml and mg/ml.

Figure S14. ^{1}H NMR spectrum of GCA, Cinnamic acid and Gefitinib

Figure S15. ^{1}H NMR spectrum of GRes.H_2O, Resorcinol, and Gefitinib

Figure S16. ^{1}H NMR spectrum of GSA.H_2O, sorbic acid and and Gefitinib

Table 1S – Interaction energies of GEF cocrystals (kJ/mol)

Table 2S - AA-CLP Calculation for GEF cocrystals (kJ/mol)

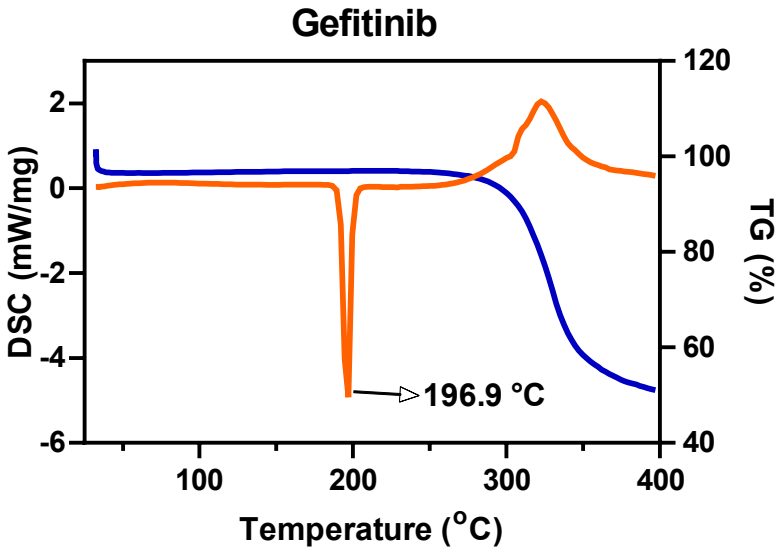


Figure S1 – TG-DSC curve of Gefitinib pure

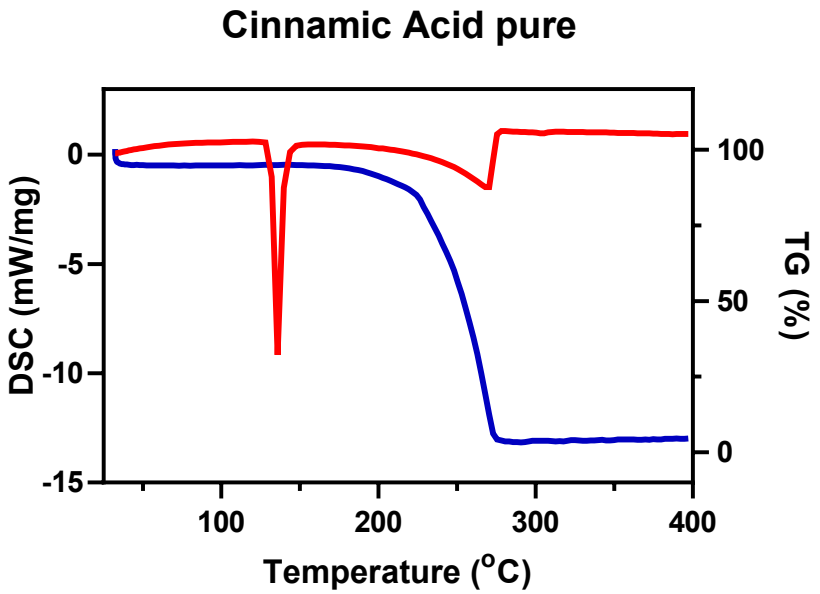


Figure S2 – TG-DSC curve of Cinnamic Acid pure

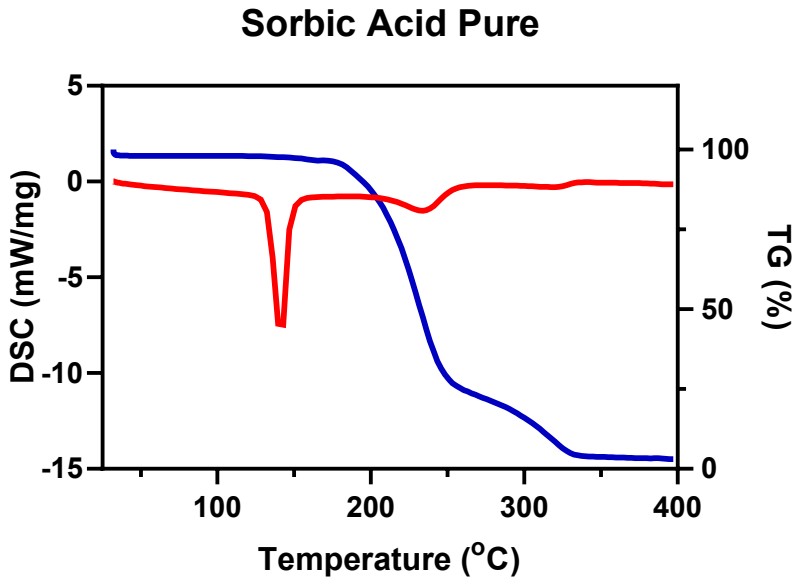


Figure S3 – TG-DSC curve of Sorbic Acid pure

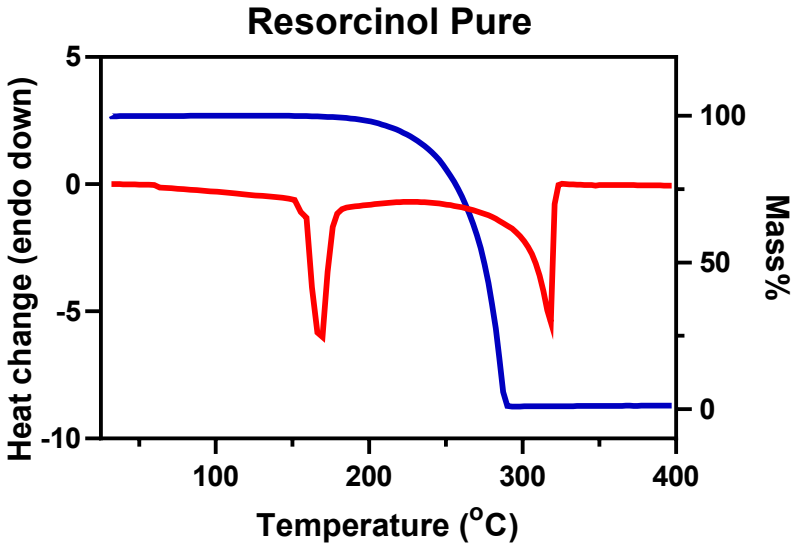


Figure S4 – TG-DSC curve of Resorcinol pure

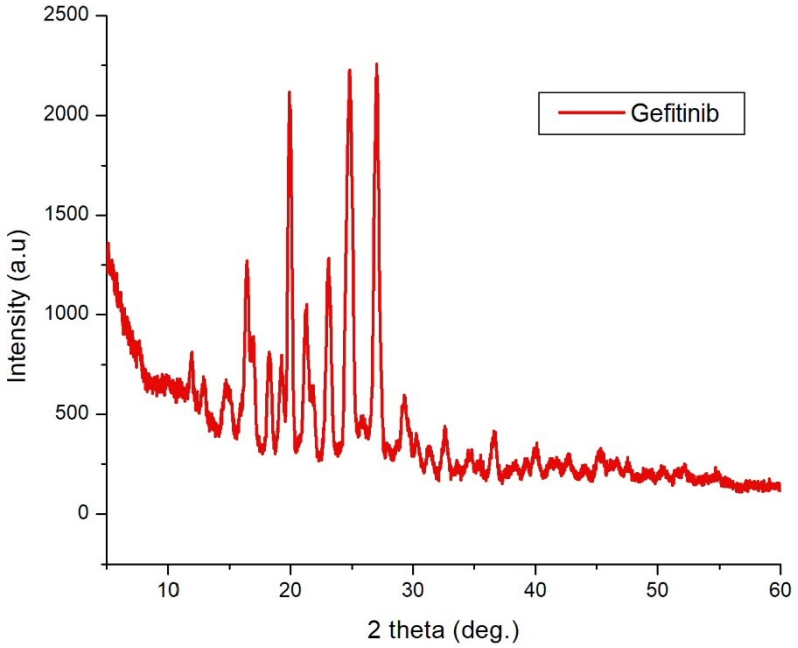


Figure S5. PXRD curve of GEF

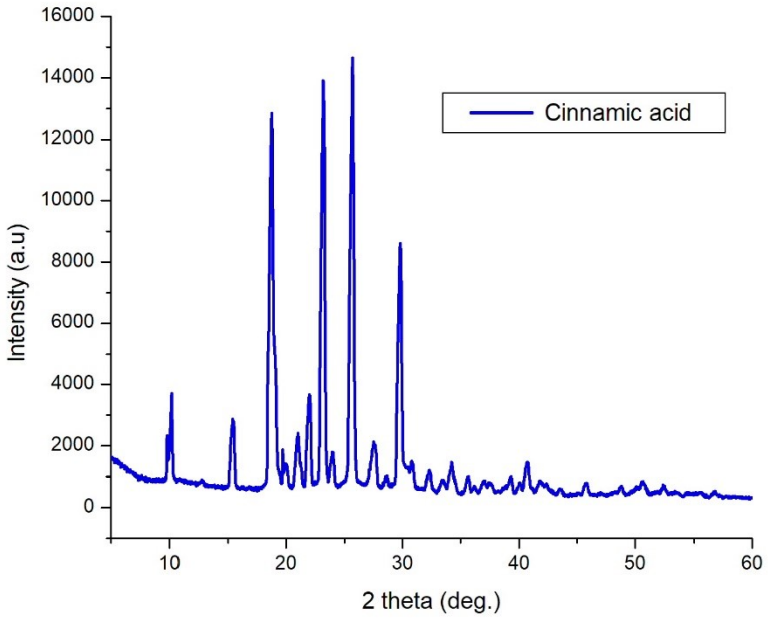


Figure S6. PXRD curve of CA

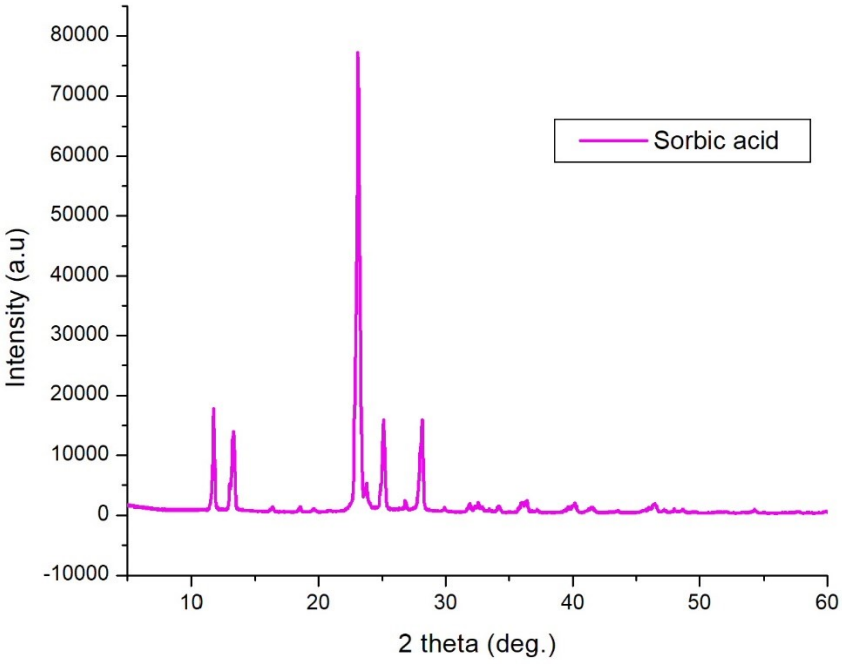


Figure S7. PXRD curve of SA

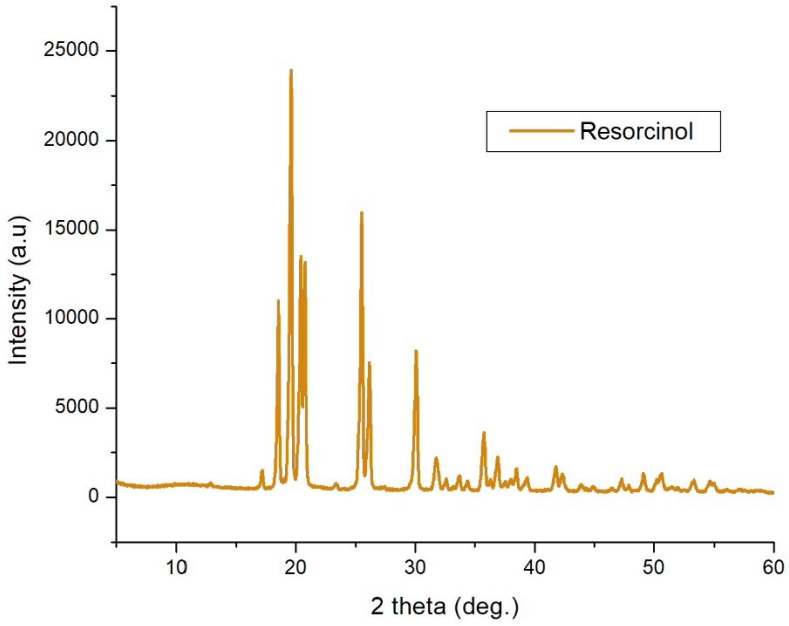


Figure S8. PXRD curve of RES

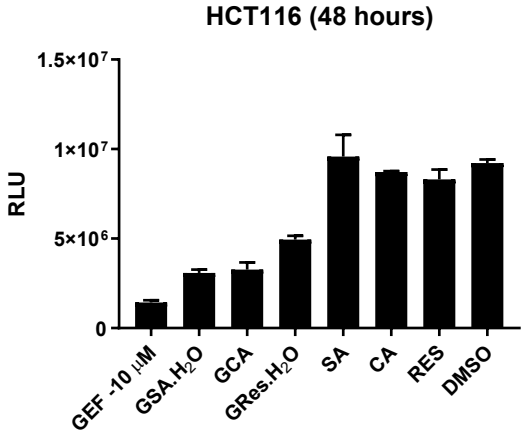


Figure S9 Anticancer activity screening on HCT116 cell line with synthesized co-crystals along with the respective controls at 10μm for 48 hrs.

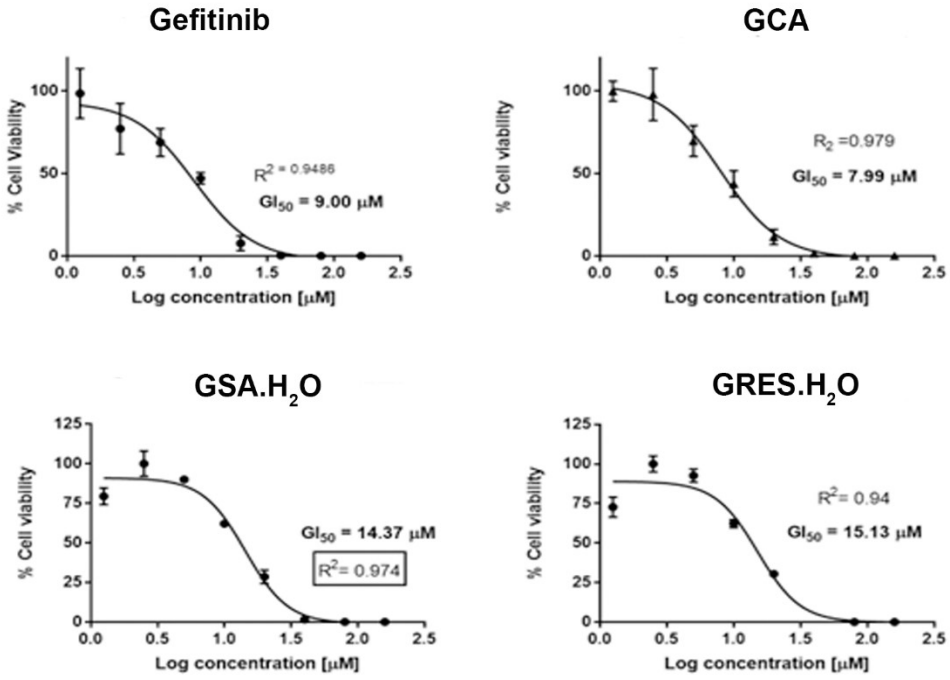


Figure S10. Dose-response curve of the synthesized co-crystals in HCT116 (48 hr) along with GI_{50} values

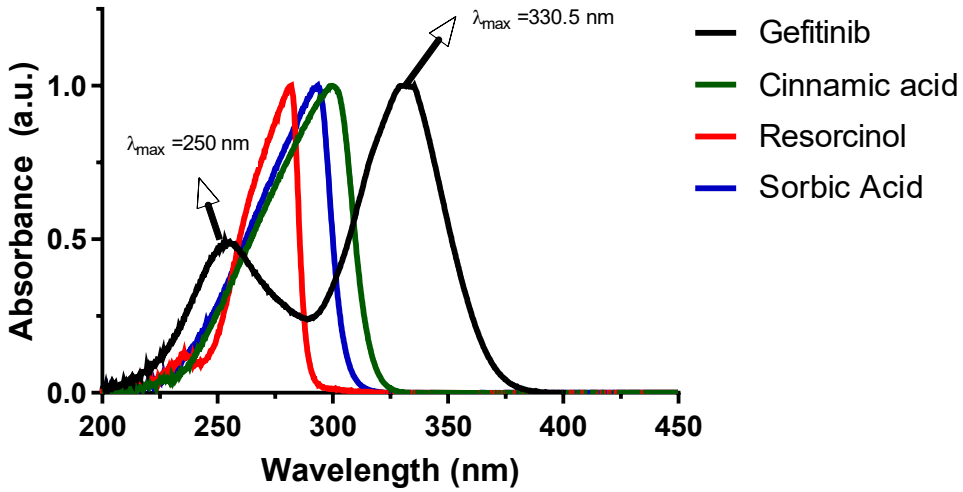
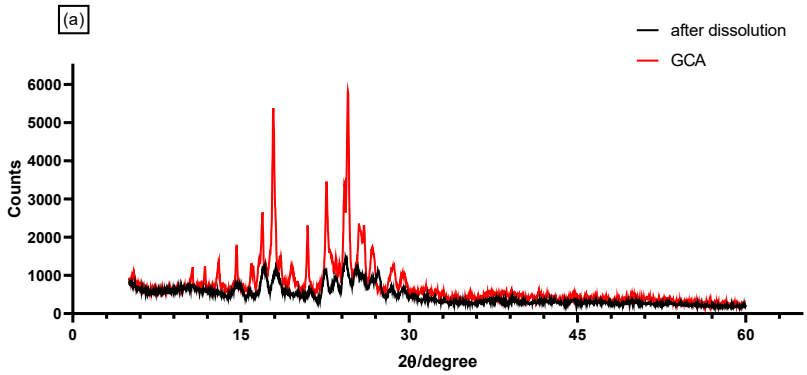


Figure S11. UV spectra of co-crystals in 1N HCL (pH 3.0) solution



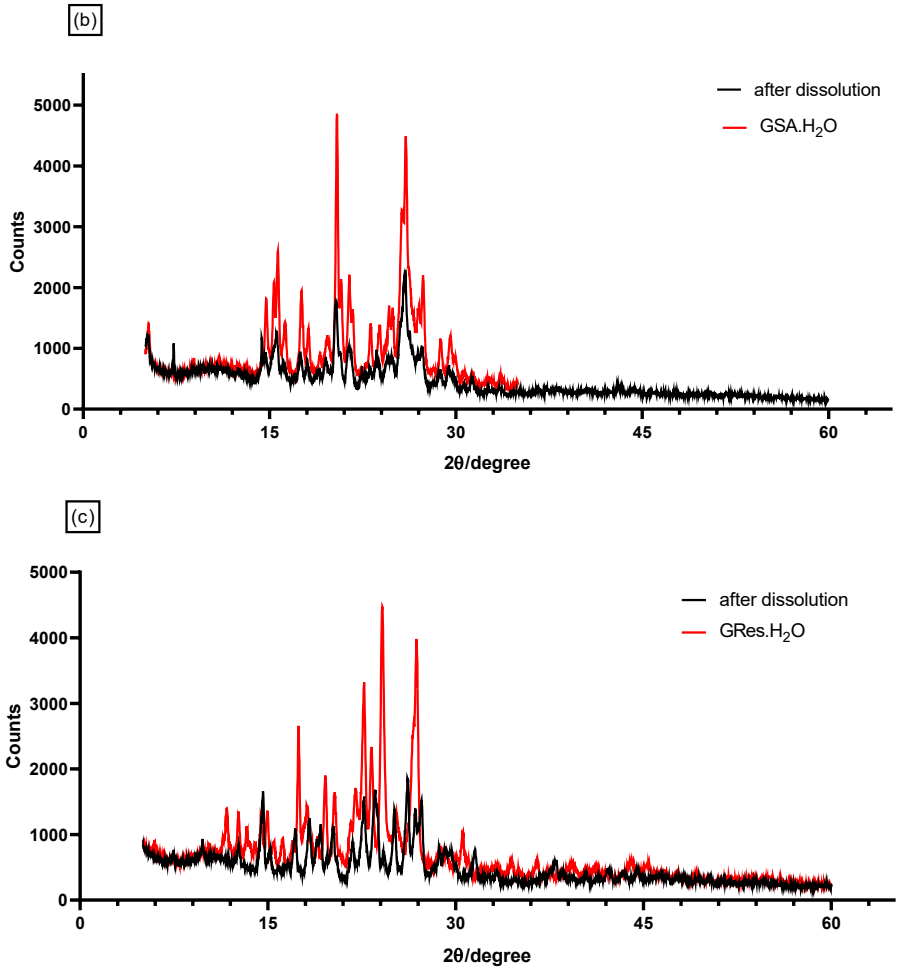


Figure S12. PXRD spectra of cocrystal powders (a) GCA, (b) GSA.H_2O, and (c) GRes.H_2O before dissolution experiment (red) and after powder dissolution experiment (black).

1. Interaction energy calculations:

Interaction energies for Gefitinib co-crystal were calculated using B3LYP/6-31G(d, p) quantum level theory in Crystal Explorer package. Table 1S represents the total interaction energies of gefitinib co-formers. Where total interaction energy is sum of electrostatic, polarization, dispersion and repulsion energies with scale factors of 1.057, 0.740, 0.871 and 0.618, respectively. Electrostatic interaction plays important role in stabilization of GSA.H_2O and GCA co-crystals. In case of GRes.H_2O dispersion interactions are contributing to co-crystal stabilization. GRes.H_2O are further stabilized by total solvation energy of -10 kJ/mol with significant contribution from electrostatic energy of -5.6 kJ/mol from water molecule.

Table 1S. Interaction energies for GEF cocrystals (kJ/mol). R is the distance between molecular centers of mass (Å).

	R	$E_{electrostatic}$	$E_{polarisation}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}
GRes.H_2O	3.57	-33.4	-8.2	-46.1	53.7	-48.4
GCA	10.10	-91.9	-22.4	-14.4	130.9	-45.5
GSA.H_2O	10.29	-106.5	-34.5	-15.0	117.3	-78.7

2. CLP calculations:

we have calculated the lattice energies of Gefitinib coformers using the Coulomb−London−Pauli model (AA-CLP) proposed by Gavezzotti[1]. It allows the analysis of the intermolecular energies between a pair of molecules and their contributions towards the total lattice energy. The total lattice energy is sum of coulombic, polarization, dispersion and repulsion energies and the calculation results are summarized in Table 2S.

Table 2S. AA-CLP Calculation for GEF cocrystals (kJ/mol)

S.no		$E_{coulombic}$	$E_{polarisation}$	$E_{dispersion}$	$E_{repulsion}$	E_{total}
1	GCA	-28.6	-35.6	-165.3	67.3	-162.1
2	GSA.H_2O	-24.6	-31.2	-118.3	62.0	-112.2
3	GRes.H_2O	-31.8	-30.7	-114.5	61.7	-115.3

As shown in table, we found that GCA showed lowest total interaction energy of -162.1 kcal/mol compared to GRes.H_2O and GSA.H_2O with total interaction energies of -115.3 and -112.2 kJ/mol. H_2O. In all the GEF cocrystals dispersion energies played significant role in stabilisation of lattice energy. Our dissolution studies do not show correlation with lattice-free energy of co-crystals. Theoretically, the dissolution rates of Gefitinib in different co-crystals will not only depend on lattice-free energy but also upon the energy barrier for transition of co-crystal form to solvated form. For example, GCA co-crystal despite having highest lattice energy stabilization tend to show faster rate of dissolution probably due to low energy barrier for the transition of crystalline form to solvated form.

(a) (b)

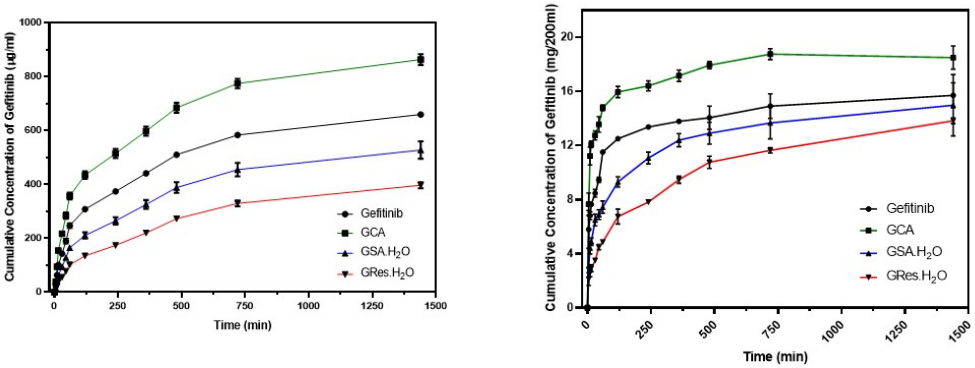


Figure S13. Powder dissolution rates of Gefitinib and its cocrystals as a plot of cumulative amount of gefitinib released from the powders ug/ml and mg/ml.

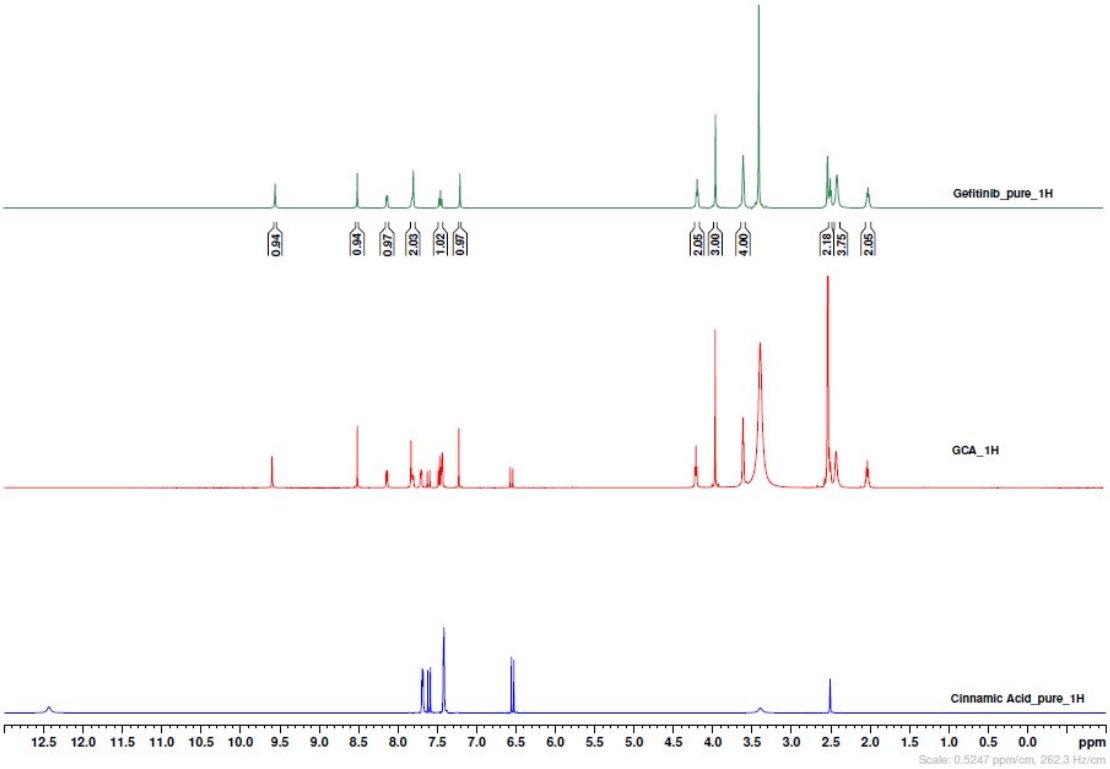


Figure S14. [1]H NMR spectrum of GCA, Cinnamic acid and Gefitinib

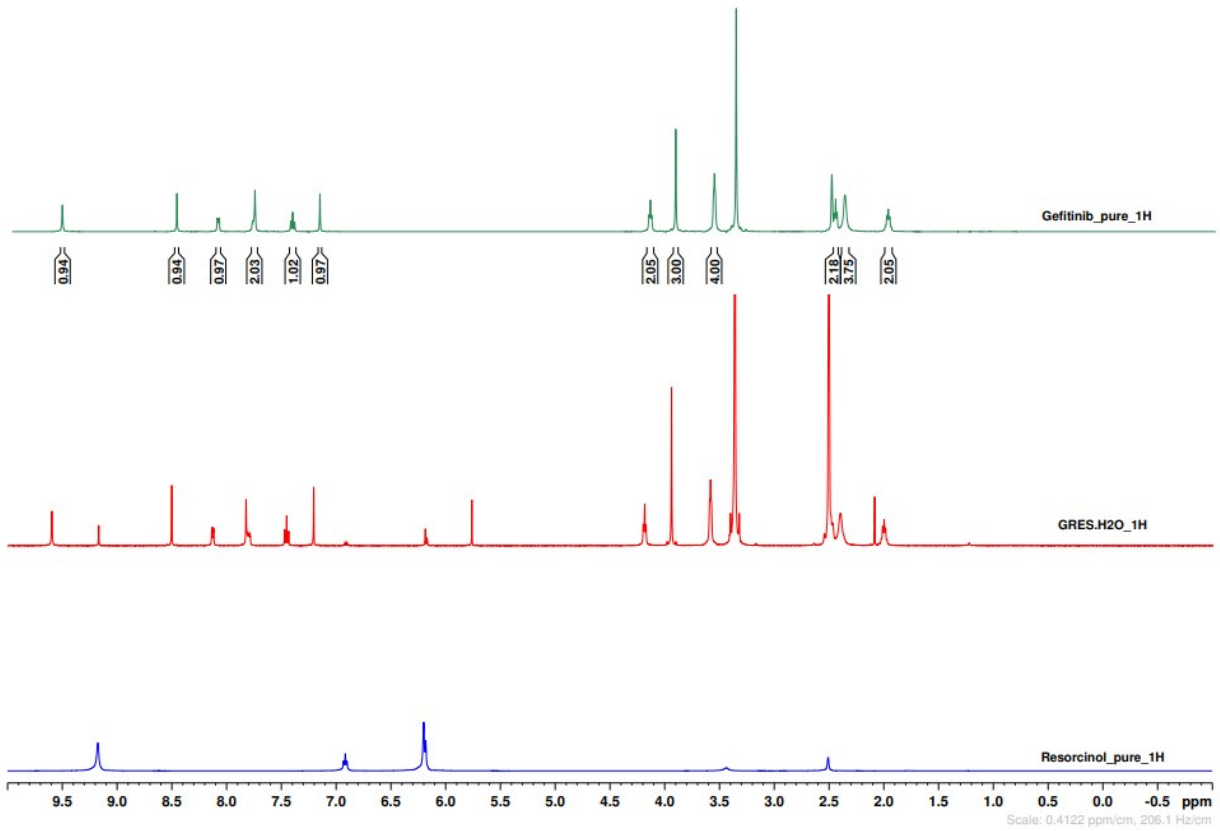


Figure S15. ^{1}H NMR spectrum of GRes.H_2O, Resorcinol, and Gefitinib

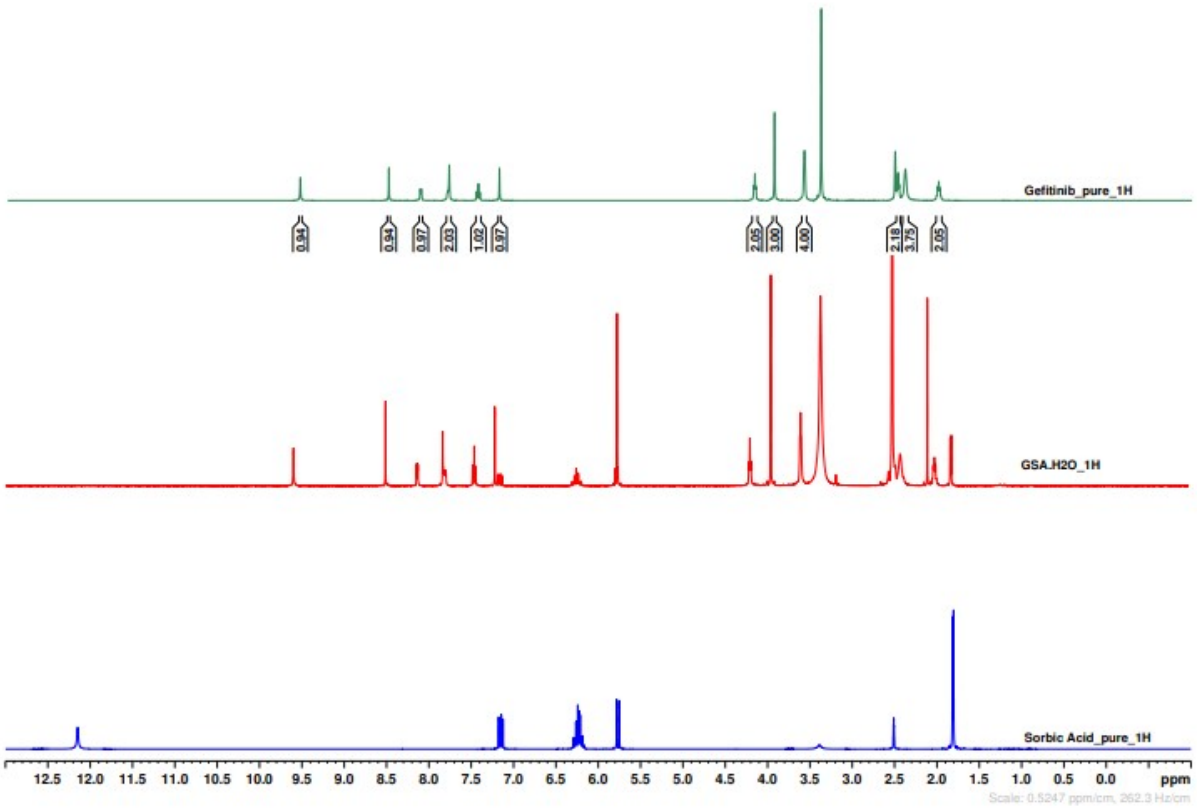


Figure S16. ^{1}H NMR spectrum of GSA.H_2O, sorbic acid and Gefitinib

1. A. Gavezzotti, *New Journal of Chemistry*, 2011, **35**, 1360-1368.