

Cocrystals of Spironolactone and Griseofulvin Based on an *in Silico* Screening Method

Tudor Grecu,^a Rafel Prohens,^{b,c} James F. McCabe,^a Elliot J. Carrington,^d James S. Wright,^d Lee Brammer,^d and Christopher A. Hunter*^e

^a AstraZeneca, Silk Road Business Park, Macclesfield, Cheshire SK10 2NA, UK.

^b Unitat de Polimorfisme i Calorimetria, Centres Científics i Tecnològics, Universitat de Barcelona, Baldiri Reixac 10, 08028 Barcelona, Spain.

^c CIRCE Crystal Engineering, Isaac Newton, s/n. ParcBit, 07121 Palma de Mallorca, Spain.

^d Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK.

^e Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK.

Email: herchelsmith.orgchem@ch.cam.ac.uk.

List of all 310 CCFs virtually screened:

resorcinol, sulfamic acid, 3,4-dihydroxybenzoic acid, etidronic acid, allocitric acid, propyl gallate, t-butyl hydroquinone, isocitric acid, fumaric acid, tartaric acid, citric acid, 4-hydroxybenzoic acid, 3-hydroxybenzoic acid, malic acid, erythroic acid, D-glucuronic acid, 2,4-dihydroxybenzoic acid, gentisic acid, octyl gallate, 4-vinylphenol, sucralose, 3,3'-thiodipropionic acid, succinic acid, ascorbic acid, L-tyrosine, 2,3-dihydroxybenzoic acid, maltose, thymol, 2-phenyl phenol, sucrose, adipic acid, L-glutamic acid, hydroquinone monoethyl ether, o-cresol, L-rhamnose, aconitic acid, inositol, 4-(1,1-dimethylethyl) phenol, 2,5-xyleneol, indole, p-cresol, folic acid, glucono delta-lactone, taurocholic acid, 3,4-xyleneol, salicylic acid, skatole, 4-hydroxymethyl-2,6-di-t-butyl phenol, 4-aminobenzoic acid, 2-t-butyl-4-hydroxyanisole, oxalic acid, 3-aminobenzoic acid, taurine, 4-ethyl phenol, urea, phenol, D-isoascorbic acid, α -D-glucopyranose, 2,6-di-t-butyl-4-methylphenol, 4-hydroxybenzyl alcohol, pyridoxine, ethyl-4-hydroxybenzoate, cholic acid, 2,6-xyleneol, L-arabinose, heptyl 4-hydroxybenzoate, D-ribose, methionine, propyl 4-hydroxybenzoate, lactose, 10-undecenoic acid, saccharin, glycocholic acid, butyl 4-hydroxybenzoate, aspartic acid, methyl 4-hydroxybenzoate, 2,5-dihydroxy-1,4-dithiane, mannitol, phenethyl salicylate, 3-hydroxy-4-methoxyphenylacetic acid, L-asparagine, phenylalanine, citronellol, neotame, phenyl salicylate, cyclohexanecarboxylic acid, vanillin, α -ketobutyric acid, stearic acid, palmitic acid, lauric acid, undecanoic acid, myristic acid, 3-methyl-2-oxobutanoic acid, 2,5-dimethyl-2,5-dihydroxy-1,4-dithiane, phenylacetic acid, 3-phenyl-2-propenyl- β -D-glucopyranoside, hydrocinnamic acid, 3-phenylpropionic acid, 4-(4-hydroxyphenyl)-2-butanone, vanillyl alcohol, L-tryptophan, (E)-N-(4-hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide, myristyl alcohol, L-iso-leucine, xylitol, levulinic acid, 3-hydroxy-2-oxopropionic acid, 2-methoxy-4-vinylphenol, aspartame, 2-methyl-4-phenyl-2-butanol, biotin, isoborneol, 2-Hydroxy-4-methylbenzaldehyde, cyclohexanecarboxylic acid, L-glutamine, 2,6-dimethoxyphenol, benzoic acid, fenchyl alcohol, cysteine, α,α -dimethylphenethyl alcohol, nicotinic acid, 2-hydroxypiperitone, menthol, borneol, 5-oxodecanoic acid, 5-oxododecanoic acid, 4-isopropylbenzyl alcohol, 5-oxooctanoic acid, azodicarbonamide, methyl phenylacetate, 2-hydroxy-5-methylacetophenone, 3-methylcrotonic acid, 2-methoxybenzoic acid, 3-ethoxy-4-hydroxybenzaldehyde, α -terpineol, 4-methoxybenzoic acid, retinol, 2-methyl-2-pentenoic acid, L-histidine, glycolic acid, trans-2-methyl-2-butenic acid, propenyl guaethol, L-leucine, trans-2-hexenoic acid, stearyl alcohol, carnitine, benzoin, 1,5,5,9-tetramethyl-13-oxatricyclo[8.3.0.0]tridecane, nicotinamide, 2-hydroxy-4-methoxybenzaldehyde, L-hydroxyproline, guaiacol, cinnamic acid, sorbic acid, L-serine, D-sorbitol, 4-thujanol, levulose, 2,5-dihydroxyacetophenone, triothioacetone, phenoxyacetic acid, ethyl

octadecanoate, N-ethyl-2,2-diisopropylbutanamide, ethylpalmitate, N-(2-(3,4-dimethoxyphenyl)ethyl)-3,4-dimethoxycinnamic-acidamide, lactic acid, sorbose, nootkatone, eugenyl isovalerate, phenethyl anthranilate, L-proline, L-threonine, retinyl acetate, eugenyl benzoate, 1,2,5,6-tetrahydrocuminic acid, guaiacyl phenylacetate, 2,3,5,6-tetramethylpyrazine, 4-hydroxy-3,5-dimethoxybenzaldehyde, camphor, phenethyl octanoate, 2-methoxybenzoic acid, allyl anthranilate, 4-aminobenzaldehyde, paradol, xylose, isoeugenyl acetate, phenethyl phenylacetate, 4-hydroxy-2,5-dimethyl-3-furanone, glycerine, zingerone, furaneol, isoeugenyl benzyl ether, 4-tolyl phenylacetate, tyramine, 4-dimethoxybenzene, isoeugenyl ethyl ether, β -naphthyl ethyl ether, DL-alanine, L-arginine, β -naphthyl isobutyl ether, cubebol, 2,6-dimethoxyphenol, methyl anthranilate, ocimene, trans-anethole, threobromine, 4-hydroxy-5-methyl-3-furanone, isoeugenyl methyl ether, sclareolide, 4-tolyl acetate, 5-ethyl-3-hydroxy-4-methyl-2-furanone, 2,6-dimethylpyrazine, ω -pentadecalactone, methyl phenylacetate, β -naphthyl methyl ether, piperitone, 5-methylquinoxaline, 4,5-dimethyl-3-hydroxy-2,5-dihydrofuran-2-one, methyl-2-pyrrolyl-ketone, 2-propionyl pyrrole, isobutyl N-methylantranilate, phenethyl cinnamate, cinnamyl cinnamate, L-methyl lactate, benzylcinnamate, DL-valine, 4-methyl biphenyl, diphenyl ether, benzophenone, riboflavin, Llysine, 1,3-diphenyl-2-propanone, biphenyl, methyl cinnamate, 2,6,6-trimethylcyclohex-2-ene-1,4-dione, 1,3-diphenyl-2-propanone, acetamide, diphenyl ether, benzyl disulfide, piperine, butyramide, 3,4-dimethoxybenzaldehyde, camphene, 4-methylacetophenone, 2-tridecanone, cis-2-hexenal, maltol propionate, benzoyl peroxide, glyceryl tribenzoate, maltol, caffeine, 4-phenyl-3-buten-2-one, 3,5-dimethyl-1,2-cyclopentadione, guaiacyl acetate, isoquinoline, caprolactam, 1,4-dithiane, methylcyclopentenolone, 2-thienyl disulfide, 2-naphthalenethiol, ethyl maltol, 3,4-dimethyl-1,2-cyclopentadione, methyl- β -naphthyl-ketone, benzyl cinnamate, 2-acetyl-2-thiazoline, 3,5-dimethyl-1,2-cyclopentadione, 2-oxo-3-phenylpropionic acid, 4-methoxyacetophenone, methyl anisate, octadecylamine, acetanisole, pyrazine, 2-mercaptoanisole, methyl nicotinate, 4,5-dimethylthiazole, acetylpyrazine, dihydroxyacetone, N-(1,1-Dimethyl-2-hydroxyethyl)-2,2-diethylbutanamide, 4-(2-furyl)-3-buten-2-one, 2-methyl-1,4-naphthoquinone, 3,4-dimethyl-1,2-cyclopentadione, vanillin acetate, 4-methylcinnamaldehyde, 2-methylcinnamaldehyde, piperazine, methyl isothiocyanate, 4-methoxycinnamaldehyde, 6-methylcoumarin, 2-methoxybenzaldehyde, maltitol, 2-furyl methyl ketone, phthalide, 2-decylfuran, glucose pentaacetate, piperonal, succinamide, α -ketoglutaric acid, 4-coumaric acid, γ -tocopherol, lactitol, ethyl gallate, 2-butenic acid, divanillin, furfuryl 2-methyl-3-furyl disulfide, γ -glutamylvalyl-glycine, L-alanyl-L-glutamine, 4-Allyl-2-(5-allyl-2-hydroxyphenyl)phenol.

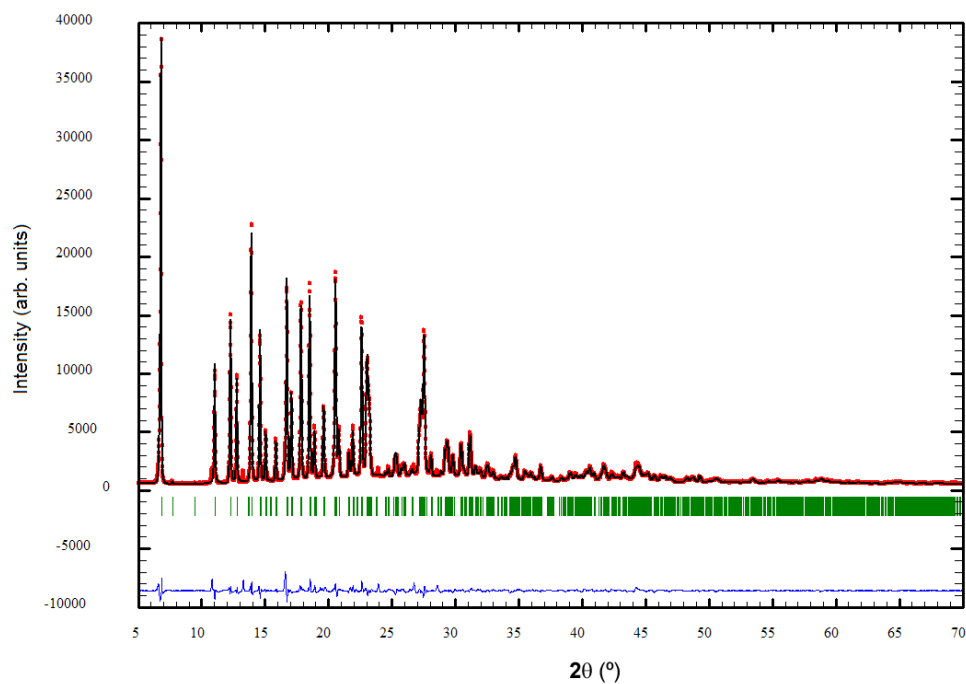


Figure S1. Results of the final Rietveld refinement of the griseofulvin-4-tert-butyl phenol cocrystal using $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). The plot shows the experimental powder XRD profile (red+marks), the calculated powder XRD profile (black solid line), and the difference profile (blue, lower line). Tick marks indicate peak positions.

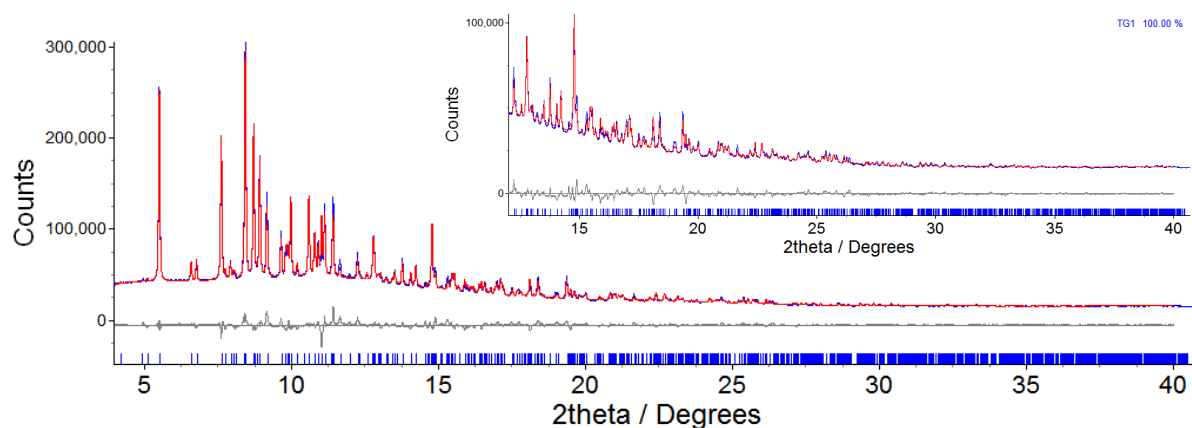


Figure S2. Results of the final Rietveld refinement of the spironolactone-phenol cocrystal using synchrotron X-ray radiation ($\lambda = 0.82665 \text{ \AA}$): observed (blue) and calculated (red) profiles and difference plot [$I_{\text{obs}} - I_{\text{calc}}$] (grey) of the Rietveld refinement (2θ range $4.0 - 40^\circ$). The blue tick marks below the patterns give the positions of the Bragg reflections.

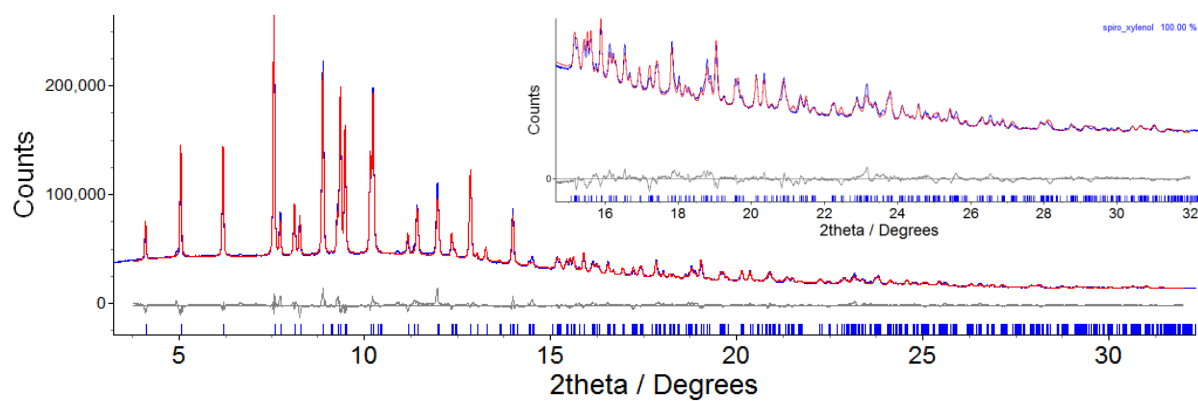


Figure S3. Results of the final Rietveld refinement of the spironolactone-phenol cocrystal using synchrotron X-ray radiation ($\lambda = 0.82665 \text{ \AA}$): observed (blue) and calculated (red) profiles and difference plot [$I_{obs} - I_{calc}$] (grey) of the Rietveld refinement (2θ range $4.0 - 32^\circ$). The blue tick marks below the patterns give the positions of the Bragg reflections.

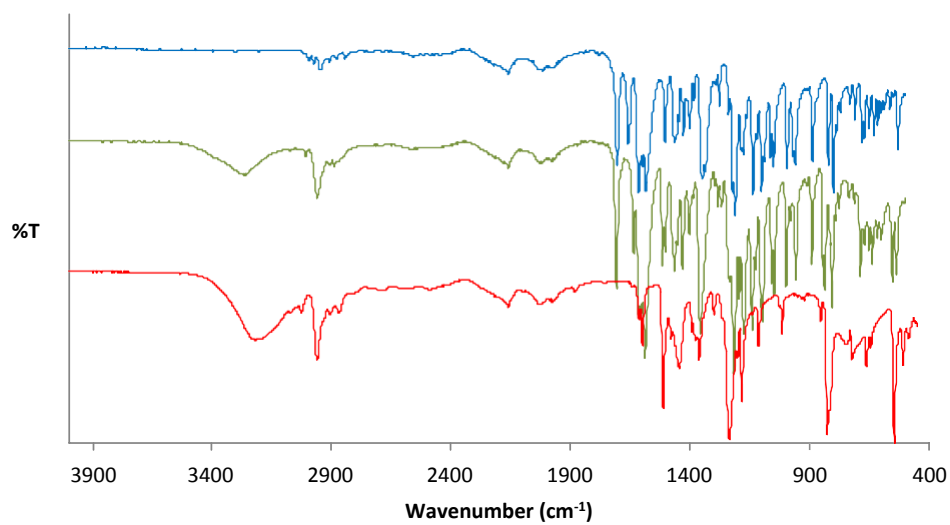


Figure S4. IR spectra of griseofulvin (blue), 4-*tert*-butyl phenol (red) and the cocrystal (green) (arbitrary vertical scale).

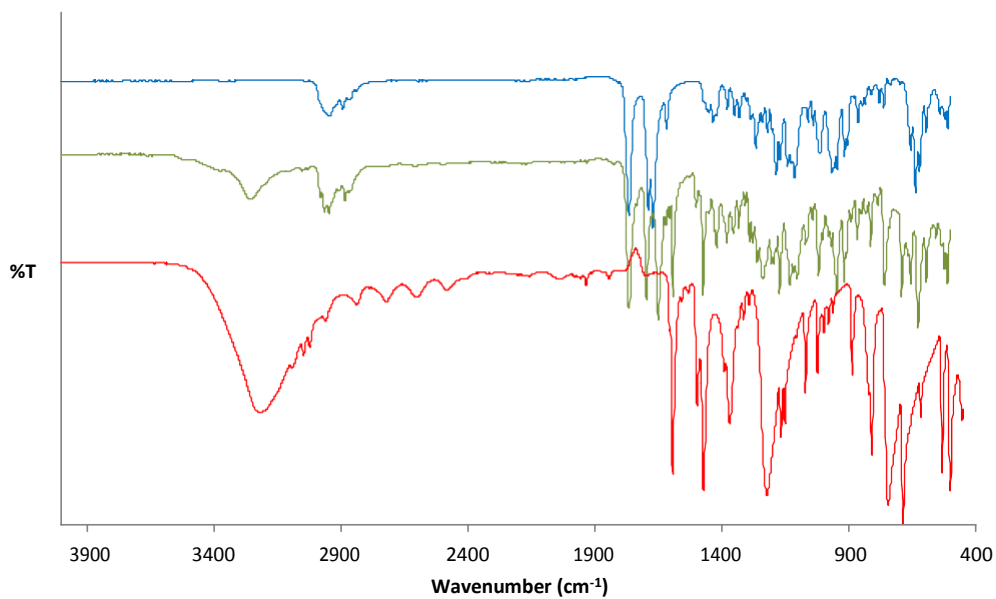


Figure S5. IR spectra of spironolactone (blue), phenol (red) and the cocrystal (green) (arbitrary vertical scale).

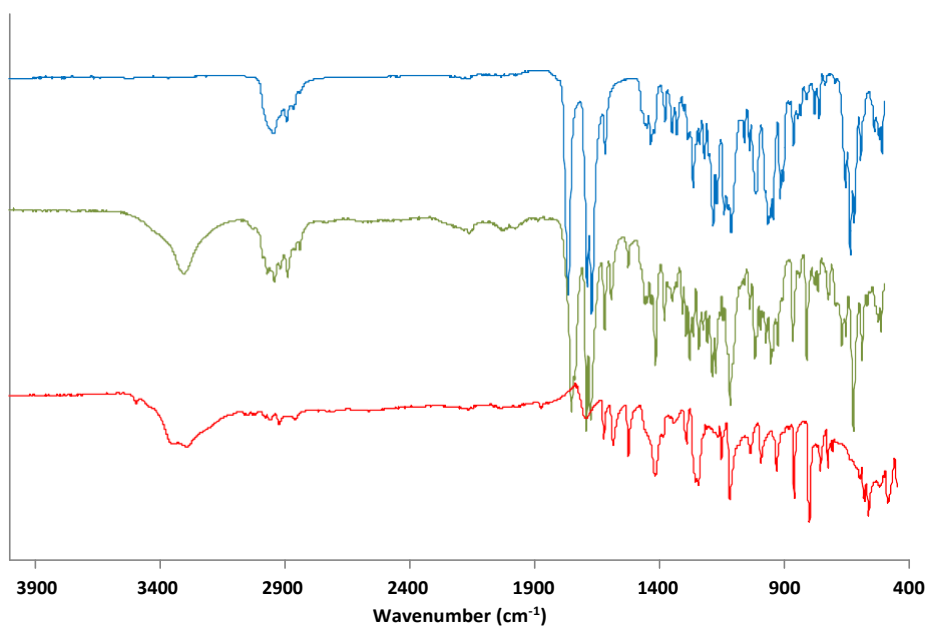


Figure S6. IR spectra of spironolactone (blue), 2,5-xyleneol (red) and the cocrystal (green) (arbitrary vertical scale).