Supplementary Material (ESI) for CrystEngComm

Electronic Supplementary Information (ESI)†

Novel form V of Tolbutamide and a high *Z*' crystal structure of form III

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Experimental section

Tolbutamide (TBM) was purchased from Sigma-Aldrich and *p*-phenylenediboronic acid and *p*-nitrophenol from Alfa-Aesar, and *p*-nitrobenzoic acid from S. D. Fine Chemicals. MeOH and EtOH solvents are of analytical purity.

Crystallization details for this work

Form III: A 1:1 molar ratios of tolbutamide and the appropriate coformer (*p*-phenylenediboronic acid, *p*-nitrophenol or *p*-nitrobenzoic acid) were grinded in a mortar-pestle for 30 min and crystallized from absolute EtOH in separate experiments. The product was Tolbutamide form III high *Z*' crystal structure with the first and second two coformers, and form IV crystallized in the third case.

Form V: 0.5 ml of conc. HNO_3 was added to 10 ml of MeOH and cooled to –20 °C for 30 min. 30 mg of tolbutamide was dissolved in 10 ml of MeOH in a separate flask and cooled to –20°C. 1 mL of the acidified MeOH was added to the cooled tolbutamide solution and left for undisturbed crystallization at room temperature. Crystals of form V appeared after 2 days.

Crystallization details for the reported crystal structures

The reported crystal structures were collected at 153 K.

According to K. Kimura, F. Hiryama and K. Uekama, *J. Pharm. Sci.*, 1999, **88**, 385 the following conditions were used to obtain the four polymorphs.

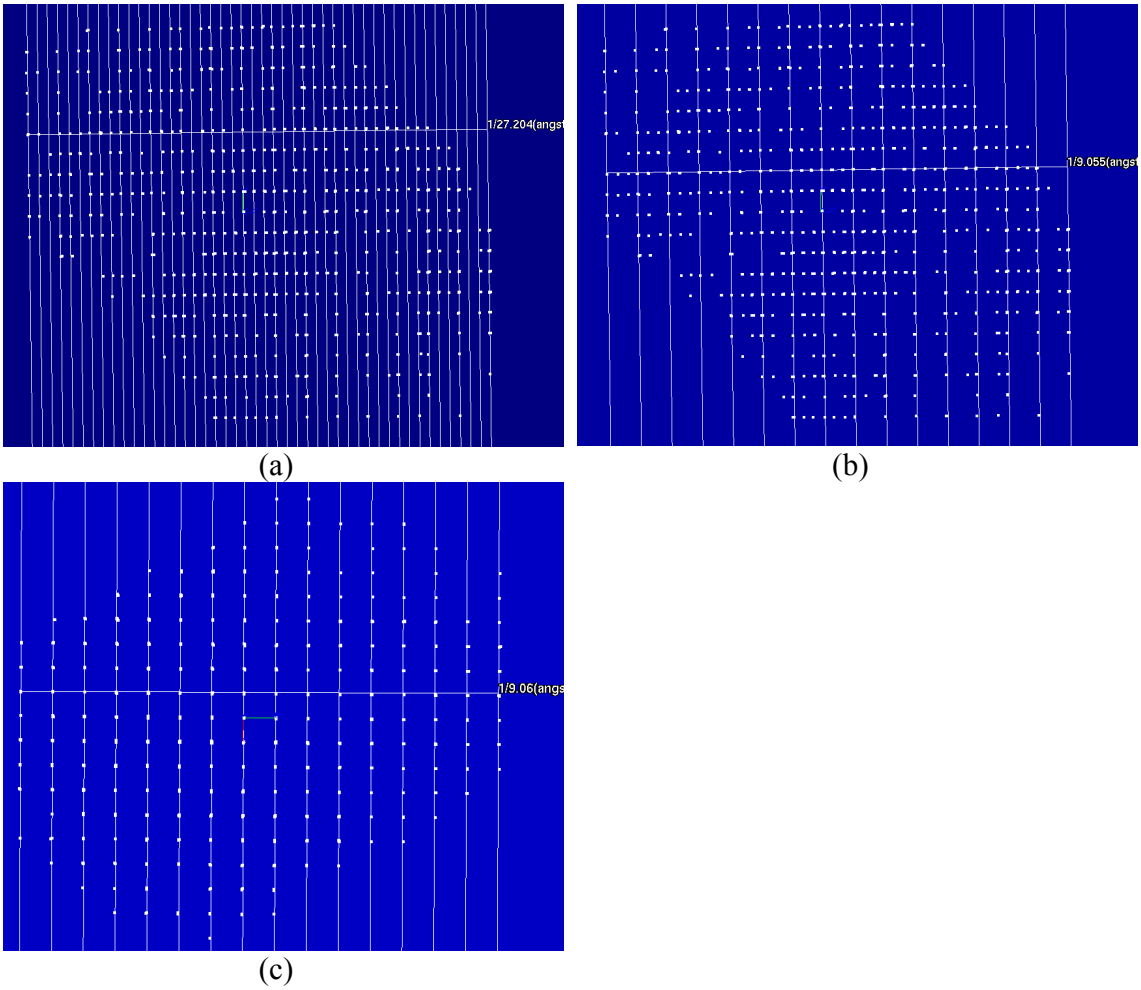
Form I was prepared by dissolving Tolbutamide (5 g) in benzene (10 mL) at 70 °C, and then hexane (5 mL) was slowly added. The resulting solution was allowed to stand at room temperature.

Form II was prepared by storing Form IV at 60 °C, 75% RH for 10 min.

Form III was prepared by dissolving TBM (5 g) in ethanol (10 mL) at 60 °C, slowly adding warm water, and allowing the resulting solution to stand at room temperature.

Form IV was prepared by the spray-drying method. TBM was dissolved in the mixed solvent ethanol/dichloromethane (1.2:1 v/v, 150 mL) and subjected to spray-drying.

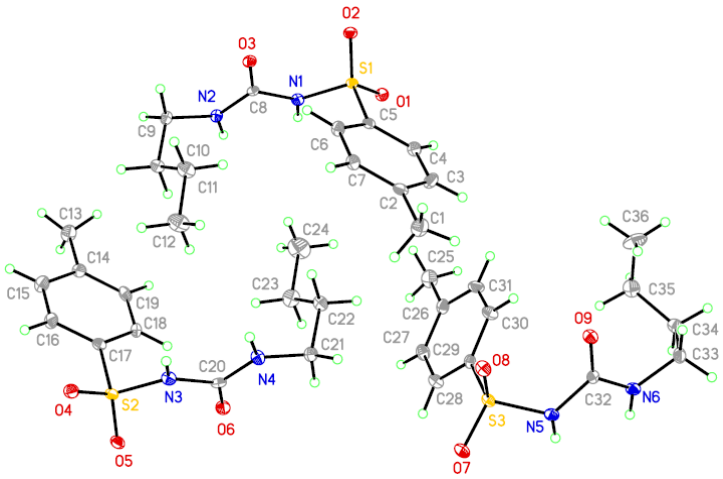
The experimental details reported in a recent paper by S. Thirunahari, S. Aitipamula, P. S. Chow and R. B. H. Tani in *J. Pharm. Sci.*, 2010, **99**, 2975 are given below.
Form I of TBM was prepared by dissolving TBM (3 g) in 6 mL of acetonitrile at 60 °C and naturally cooled to room temperature.
Form II was prepared by dissolving 1.2 g of TBM in 10 g of acetonitrile in a 20 mL vial at room temperature followed by the slow addition of 5 mL of water using a pipette into the unagitated solution.
Form III was prepared by preparing a saturated solution of TBM in ethanol at room temperature and then water was slowly added into the unagitated solution using a pipette till spontaneous nucleation of Form III crystals occurred.
Form IV was crystallized by dissolving 0.5 g of TBM in 10 mL of acetonitrile, filtered and then transferred to a 20 mL conical flask. The mouth of the flask was covered with aluminum foil (a few holes were made in the foil) and left at ambient temperature for slow evaporation of the solvent.



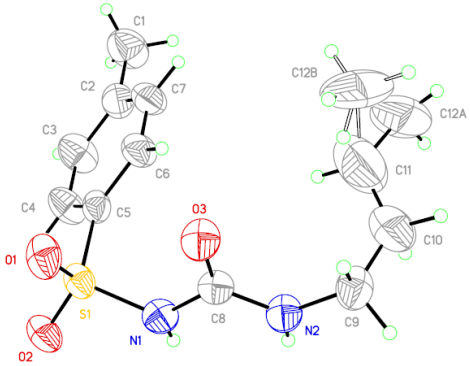
(a) (b)

(c)

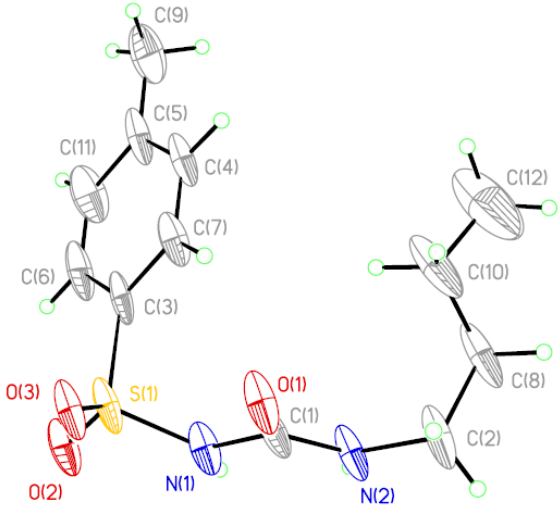
Figure S1 (a) Reflections of 100K data viewed in RLATT software, (b) if we consider only the reflections that are lying on the vertical lines we can obtain cell dimensions with *b* axis = 9.0488(16) Å, but this solution results in a comparatively bad structure. (c) Reflections at room temperature data viewed in RLATT software, from where it is not possible to obtain a cell with *b* axis of ~27 Å.



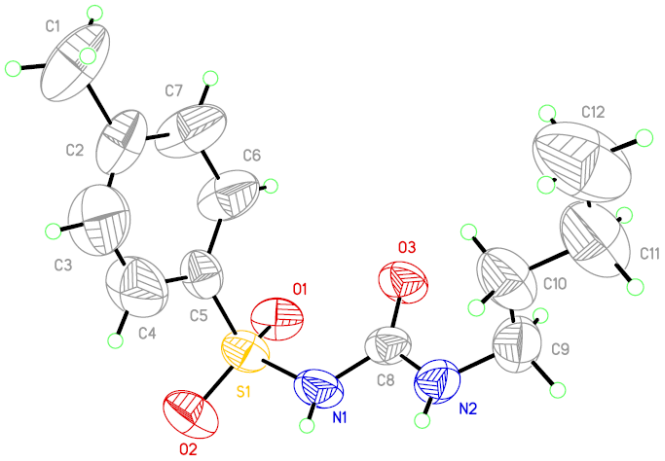
(a)



(b)

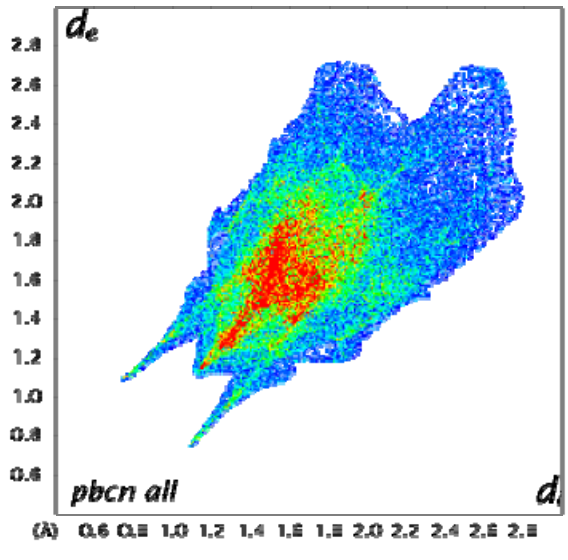
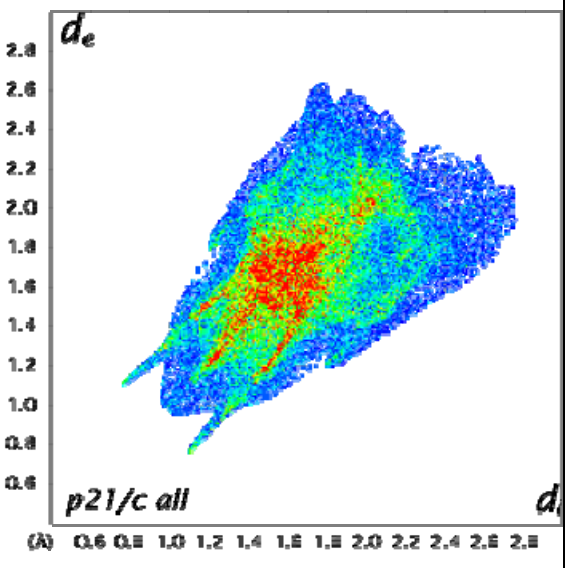


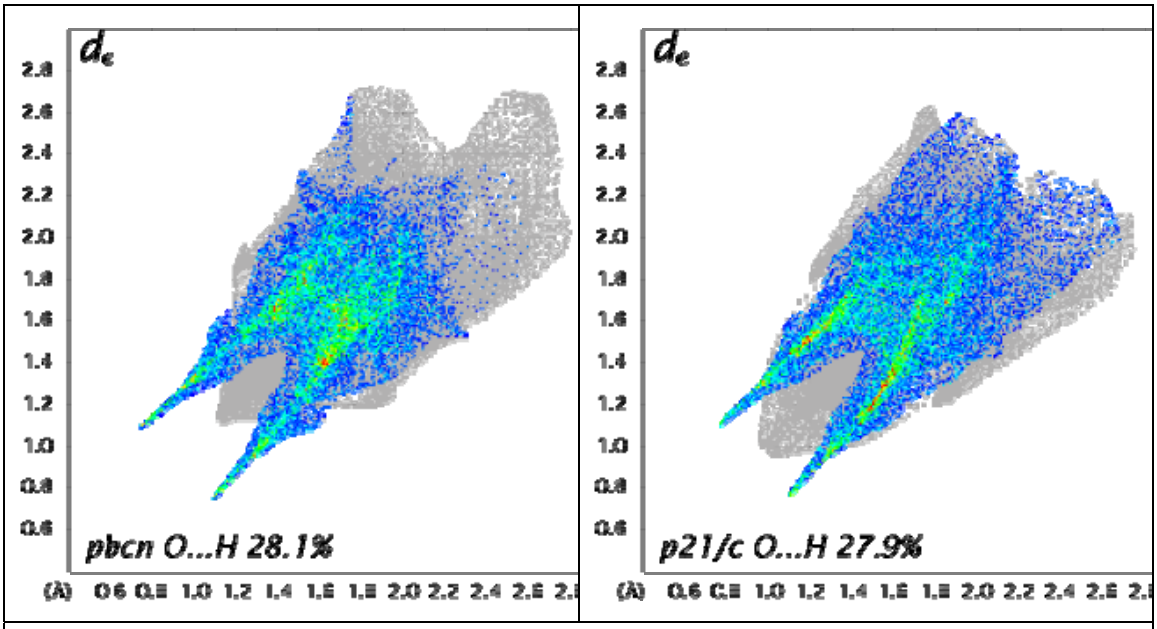
(c)



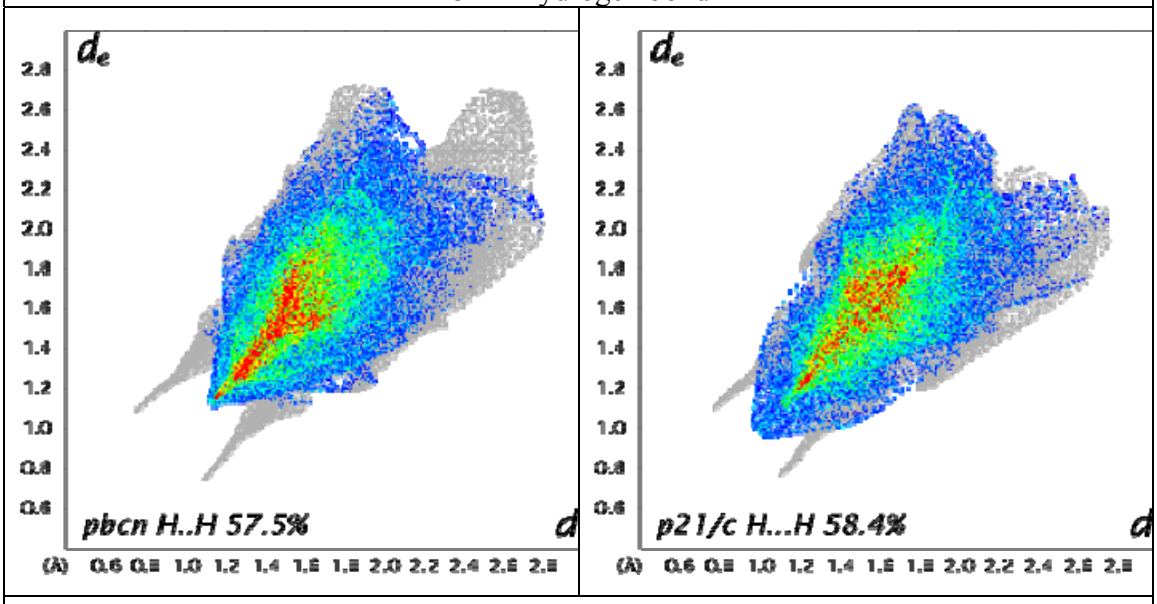
(d)

Figure S2 ORTEP diagrams at 35% probability of electron density in the ellipsoids. (a) Three symmetry independent molecules at 100 K of form III. (b) One molecule of form III with disorder in the butyl chain at 298 K. (c) 100 K data set solved using ⅓ the *b* axis = 9.04 Å. The thermal ellipsoids are elongated indicating that the electron density is not accounted for correctly in the crystal structure solution. (d) Form V crystal structure at 298 K.

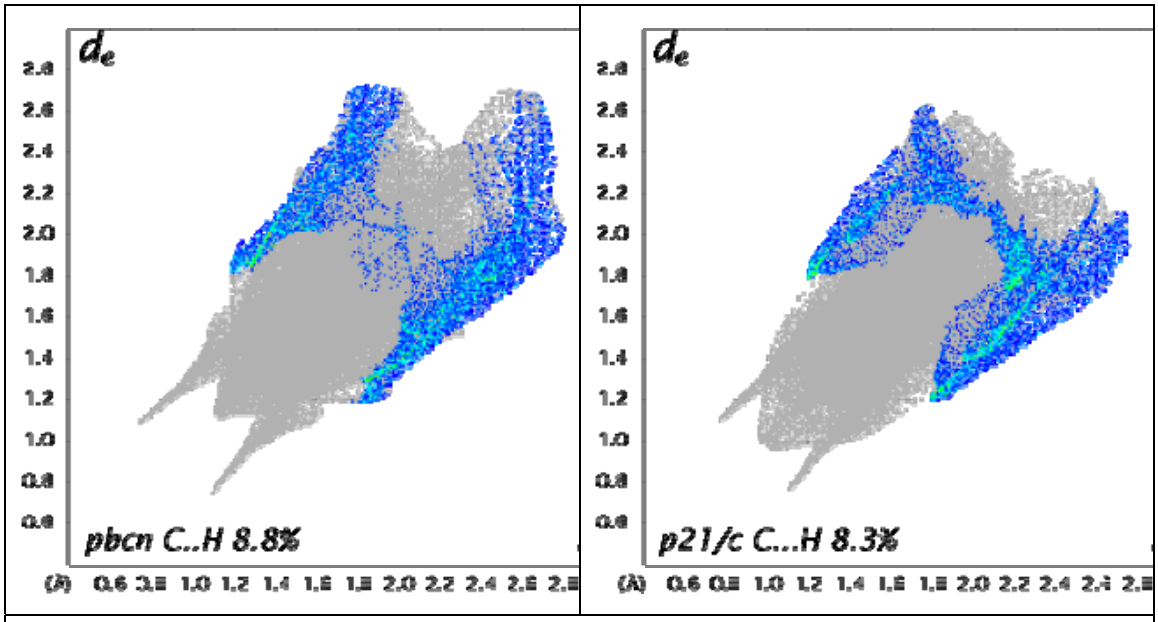
Form V	Form IV
	
For all interactions	



O···H hydrogen bond



H···H interactions



C···H interactions

Figure S3 2D fingerprint Hirshfeld plots of Tolbutamide forms V and IV show clear differences in hydrogen bonding and hydrophobic interactions regions.

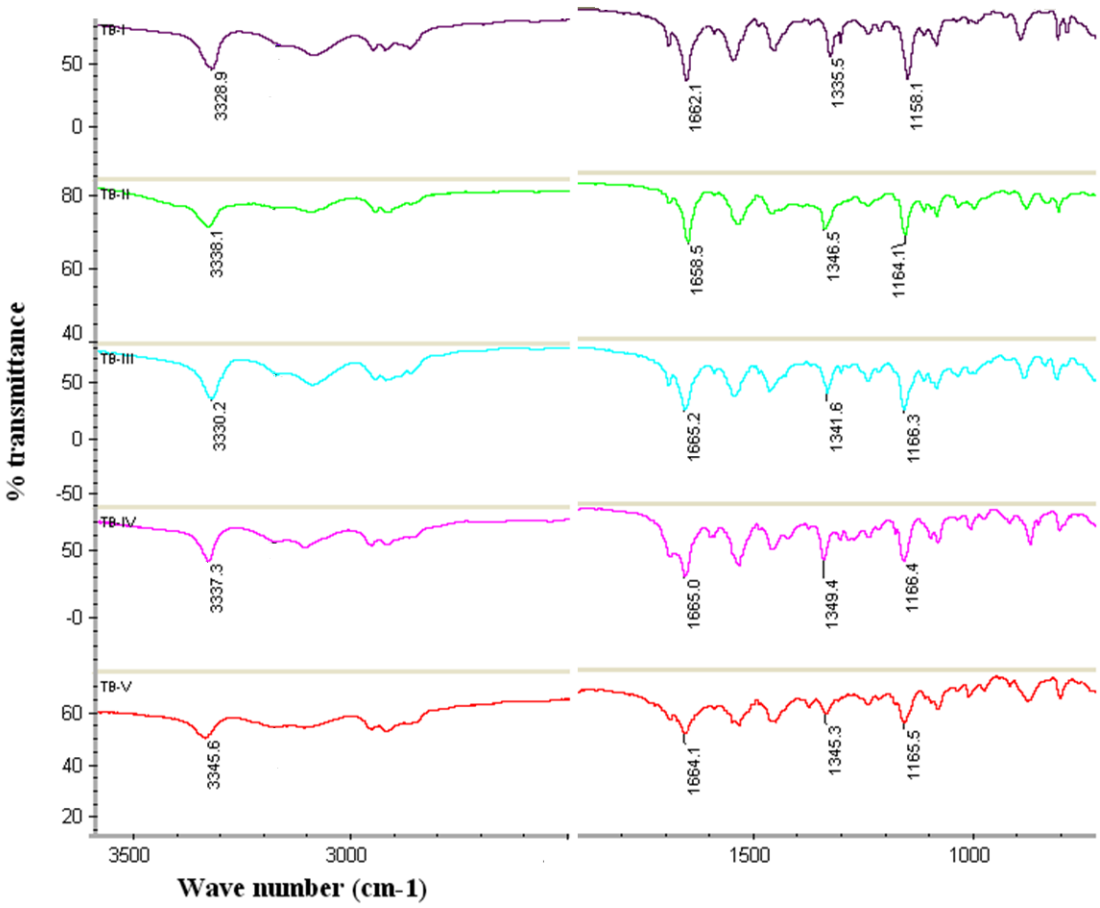
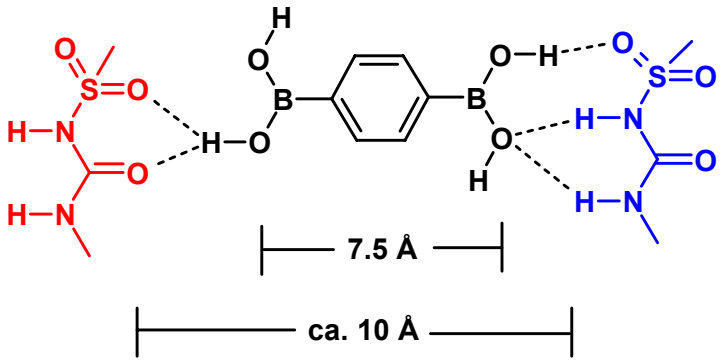
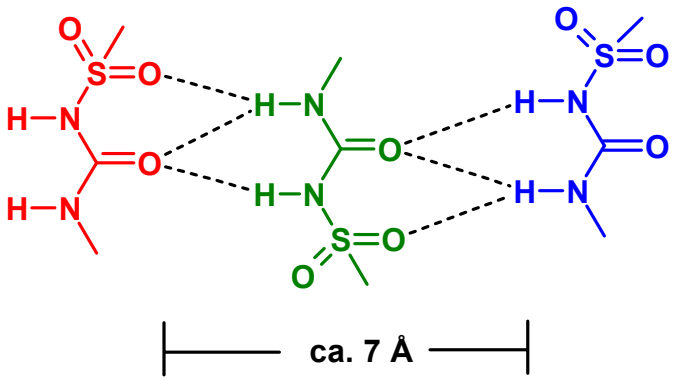


Figure S4 Comparison of FT-IR spectra of Tolbutamide new form V and reported polymorphs I-IV.



(a)



(b)

Figure S5 A putative scheme to show a hydrogen-bonded complex between TBM and p-PDBA in solution (a) which gives way to the high Z' structure of form III (b). TBM molecules in the same orientation are hydrogen bonded on either side of p-PDBA (placed in an inversion symmetry orientation) and a third TBM molecule replaces the central linker molecule, but now with its sulfonyl group on the opposite side to give three crystallographic molecules in the unit cell of TBM form III (Z' = 3)

Table S1 Crystallographic data of form III (Z' = 3) and new polymorph V.

	Form III		Form V
Chemical formula	C12 H18 N2 O3 S	C12 H18 N2 O3 S	C12 H18 N2 O3 S
Formula weight	270.34	270.34	270.34
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/n$	$P2_1/n$	$Pbcn$
T/K	100	298	298
a/Å	11.5613(17)	11.787(5)	15.851(6)
b/Å	27.189(4)	9.043(4)	9.288(4)
c/Å	13.556(2)	13.955(6)	19.691(8)
α/°	90	90	90
β/°	102.803(2)	104.644(7)	90
γ/°	90	90	90
Z/Z'	12/3	4/1	8/1
V/Å^3	4155.2(11)	1439.2(10)	2899.2(19)
D_{calc}/g cm^{-3}	1.296	1.248	1.239
μ/mm^{-1}	0.236	0.227	0.226
Reflns collected	39777	14600	25042
Unique reflns	7363	2846	2568
Observed reflns	5713	2304	1647
$R_1[I > 2\sigma(I)]$	0.0652	0.0714	0.0784
wR_2 [all]	0.1505	0.1679	0.2086
Goodness-of-fit	0.963	1.099	1.062
Diffractometer	Bruker CCD	Bruker CCD	Bruker CCD

Table S2 Crystallographic data of reported for polymorphs I-IV are reproduced from *J. Pharm. Sci.*, 2010, 99, 2975 for ready reference.

Table 2. Summary of Crystallographic Data of TB Polymorphs

Crystal Data	Form I[La]	Form II	Form III	Form IV
Empirical formula	$C_{12}H_{18}N_2O_3S$	$C_{12}H_{18}N_2O_3S$	$C_{12}H_{18}N_2O_3S$	$C_{12}H_{18}N_2O_3S$
Formula weight	270.34	270.34	270.34	270.34
Crystal habit	Prism	Plate	Needle	Needle
Sample type	Single crystal	Single crystal	Single crystal	Powder
Crystal system	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Temperature (K)	153	153	153	298
Color	Colorless	Colorless	Colorless	White
Space group	$Pna2_1$	Pc	$P2_1/n$	$P2_1/c$
a/Å	19.626(9)	9.087(8)	11.735(2)	10.091
b/Å	7.803(4)	17.228(3)	9.042(8)	15.646
c/Å	9.058(4)	17.951(4)	13.732(3)	9.261
α/°	90	90	90	90
β/°	90	95.01(3)	103.57(3)	100.49
γ/°	90	90	90	90
V/Å^3	1387.3(11)	2799.8(10)	1416.4(5)	1438.9
Z	4	8	4	4
d_{calc}/g cm^{-3}	1.294	1.283	1.268	1.248
μ (mm^{-1})	0.236	0.234	0.231	0.227 (calculated)
Reflections collected	6197	14,332	11,123	—
Unique reflections	2118	8617	3514	—
Observed reflections	2002	8016	2669	—
$R_1[I > 2\sigma(I)]$	0.0572	0.0555	0.0976	$R_p = 3.96\%$
wR_2 [all]	0.1559	0.1434	0.2742	$R_{wp} = 5.38\%$
Goodness-of-fit	1.115	1.070	1.159	—
Diffractometer	Rigaku Saturn CCD area detector	Rigaku Saturn CCD area detector	Rigaku Saturn CCD area detector	Bruker AXS

[a]Determined in this work.