Supporting information for:

Utilizing crystal structures for predicting impact of mechanical and surface properties on particle fracture

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Introduction

From the Gaussian DFT energy calculation described in the Materials and Methods section, the total interaction energy (E(tot)) has been broken down into its separate terms: Classical (E(c)), Dispersive (E(dis)) and Exchange (E(ex)) components as described in Table S1. The classical term corresponds to the sum of nucleus-nucleus repulsion, electron-nucleus attraction, electron-electron Coulomb repulsion, and kinetic energy. The dispersive term is calculated using Grimme's DFT-D3 approach employing the Becke-Johnson damping. The final exchange term is a functional dependent mix of Hartree-Fock- and DFT exchange corresponding to interaction between electrons with the same spin. This is a similar approach to how the interaction energy is deconvoluted in for example CrystalExplorer. Symmetry operations in Table S1 were taken from the experimental crystal structures and are thus determined by the space group of those crystals. These symmetry operations describe the relation how to construct a specific dimer pair calculated using CrysIn.

Table S1. Intermolecular interaction energies calculated using CrystIn tool. The total energy ($E_{(tot)}$), classical ($E_{(c)}$), dispersive ($E_{(dis)}$) and exchange ($E_{(ex)}$) components are listed.

Crystal	Symmetry.operation	$E_{(c)}$ [kcal/mol]	$E_{(dis)}$ [kcal/mol]	$E_{(ex)}$ [kcal/mol]	$E_{(tot)}$ [kcal/mol]
Paracetamol form I	1/2-x,1/2+y,1/2-z	-3.3	-1.4	2.2	-1.6
	1/2-x,1/2+y,-1/2-z	-4.1	-3.9	0.0	-6.3
	1/2-x,-1/2+y,1/2-z	-3.3	-1.4	2.2	-1.6
	1/2-x,-1/2+y,-1/2-z	-4.1	-3.9	0.0	-6.3
	-1/2-x,1/2+y,-1/2-z	-1.7	-1.3	1.2	-1.1
	-1/2-x,-1/2+y,-1/2-z	-1.7	-1.3	1.2	-1.1
	-x,-y,-z	-4.8	-3.9	0.1	-6.3
	-x,-1-y,-z	**-12.2**	**-12.6**	**4.0**	**-14.1**

Crystal	Symmetry.operation	$E_{(c)}$ [kcal/mol]	$E_{(dis)}$ [kcal/mol]	$E_{(ex)}$ [kcal/mol]	$E_{(tot)}$ [kcal/mol]
	1-x,-1-y,-z	-6.7	-3.5	2.9	-6.3
	1/2+x,-1/2-y,1/2+z	-0.3	-4.8	-4.6	-9.5
	1/2+x,-1/2-y,-1/2+z	**1.7**	**-3.1**	**-8.3**	**-11.1**
	-1/2+x,-1/2-y,1/2+z	**1.7**	**-3.1**	**-8.3**	**-11.1**
	-1/2+x,-1/2-y,-1/2+z	-0.3	-4.8	-4.6	-9.5
AZD5423	-1+x,y,z	99.7	-0.3	-88.8	6.2
	-x,1/2+y,-z	90.9	-4.8	-83.8	-0.3
	-x,1/2+y,1-z	100.3	0.2	-88.3	7.3
	-x,-1/2+y,-z	90.9	-4.8	-83.8	-0.3
	1-x,1/2+y,-z	100.1	0.0	-88.4	7.0
	1-x,1/2+y,1-z	100.3	0.2	-88.3	7.3
	1-x,-1/2+y,-z	100.1	0.0	-88.4	7.0
	1+x,y,z	-3.6	-25.0	-14.2	-31.4
	-1+x,y,z	23.3	0.1	-20.4	1.5
	1-x,1/2+y,-z	13.9	-4.6	-14.5	-4.4
	1-x,1/2+y,1-z	23.3	0.1	-20.2	1.7
	1-x,-1/2+y,-z	17.9	-3.7	-17.8	-2.4
	2-x,1/2+y,-z	23.2	0.1	-20.2	1.6
	1+x,y,z	47.1	-3.4	-43.5	-0.6
	-1+x,y,z	50.0	0.0	-44.0	3.7
	-x,1/2+y,1-z	50.1	0.0	-44.1	3.6
	-x,-1/2+y,1-z	43.1	-3.0	-39.5	-0.3
	1-x,1/2+y,1-z	50.1	0.1	-44.1	3.6
	1-x,-1/2+y,-z	46.7	-1.8	-43.2	0.2
	1-x,-1/2+y,1-z	50.1	0.0	-44.3	3.5
	1+x,y,z	18.4	-8.3	-21.6	-7.1
	1-x,1/2+y,1-z	26.8	0.0	-23.9	2.0
	1-x,-1/2+y,-z	19.7	-3.1	-19.0	-1.7
	1-x,-1/2+y,1-z	22.9	-2.1	-22.8	-1.8
	2-x,-1/2+y,-z	26.9	-0.1	-24.1	1.9
	1+x,y,z	-54.3	-0.5	47.3	-5.2
	-1+x,y,z	-54.3	-0.5	47.3	-5.2
	1-x,1/2+y,1-z	-53.8	0.0	47.9	-4.1
	2-x,1/2+y,-z	-54.1	-0.3	48.2	-4.1
	-x,1/2+y,-z	-3.8	-0.3	3.2	-1.2
	-x,1/2+y,1-z	-3.5	0.1	3.7	-0.4
	-x,-1/2+y,-z	-3.8	-0.3	3.2	-1.1
	1-x,1/2+y,-z	-8.9	-3.7	6.1	-4.4
	1-x,1/2+y,1-z	-3.5	0.1	3.7	-0.3
	1-x,-1/2+y,-z	-13.0	-4.6	9.4	-6.4
	1+x,y,z	-26.9	-0.1	23.9	-2.1
	-1+x,y,z	-29.9	-3.6	24.5	-6.4
	-x,1/2+y,1-z	-26.9	-0.1	23.9	-2.1
	-x,-1/2+y,1-z	-27.4	-0.2	24.3	-2.2
	1-x,1/2+y,1-z	-26.9	-0.1	24.0	-2.0
	1-x,-1/2+y,-z	-33.0	-3.2	27.9	-5.9
	1-x,-1/2+y,1-z	-30.4	-1.9	25.1	-5.4
	1+x,y,z	-54.8	-3.4	46.0	-7.9
	1-x,1/2+y,1-z	-50.2	-0.2	44.1	-3.7
	1-x,-1/2+y,-z	**-50.6**	**-0.4**	**44.4**	**-3.9**
	1-x,-1/2+y,1-z	-56.7	-3.2	48.4	-7.6
	2-x,-1/2+y,-z	-54.8	-2.3	45.6	-8.2
	1+x,y,z	-0.6	-0.5	-0.5	-1.1
	-1+x,y,z	-0.6	-0.5	-0.5	-1.1
	-x,1/2+y,1-z	**-9.4**	**-5.3**	**4.3**	**-8.2**
	-x,-1/2+y,1-z	**-9.4**	**-5.3**	**4.3**	**-8.2**
	1-x,1/2+y,1-z	-0.5	-0.3	0.4	-0.1
	1-x,-1/2+y,-z	-0.1	0.0	0.1	-0.1
	1-x,-1/2+y,1-z	-0.5	-0.3	0.4	-0.1
	-1+x,y,z	9.6	-3.4	-14.3	-7.2
	-x,1/2+y,-z	12.1	-0.1	-14.6	-3.0
	-x,1/2+y,1-z	5.6	-3.1	-10.3	-6.8
	-x,-1/2+y,-z	12.6	0.0	-15.0	-3.0
	1-x,1/2+y,-z	9.2	-1.9	-14.1	-6.4
	1-x,1/2+y,1-z	12.7	-0.1	-15.1	-3.0
	1-x,-1/2+y,-z	12.6	0.0	-14.9	-2.9
	1+x,y,z	-29.9	-3.6	24.5	-6.4
	-1+x,y,z	-26.9	-0.1	23.9	-2.1
	1-x,1/2+y,-z	-33.0	-3.2	27.9	-5.9
	1-x,1/2+y,1-z	-30.4	-1.9	25.1	-5.4
	1-x,-1/2+y,-z	-26.9	-0.1	23.9	-2.1
	2-x,1/2+y,-z	-26.8	-0.1	23.6	-2.3
	1-x,1/2+y,1-z	-32.9	-4.6	26.3	-7.4

Crystal	Symmetry.operation	$E_{(c)}$ [kcal/mol]	$E_{(dis)}$ [kcal/mol]	$E_{(ex)}$ [kcal/mol]	$E_{(tot)}$ [kcal/mol]
	1-x,-1/2+y,-z	-23.4	-0.1	20.3	-1.6
	1-x,-1/2+y,1-z	-28.7	-4.1	22.6	-5.8
	2-x,-1/2+y,-z	-23.3	-0.1	20.3	-1.6
	1+x,y,z	-47.3	-0.8	39.9	-4.5
	1-x,-1/2+y,-z	-46.6	-0.2	40.5	-3.2
	2-x,-1/2+y,-z	-46.8	-0.2	40.6	-3.3
	-x,1/2+y,-z	-23.4	-0.1	20.3	-1.7
	-x,1/2+y,1-z	-23.8	-0.4	20.5	-1.9
	-x,-1/2+y,-z	-23.3	-0.1	20.3	-1.6
	1-x,1/2+y,-z	-30.4	-3.2	25.2	-5.4
	1-x,1/2+y,1-z	-27.2	-2.2	21.3	-5.4
	1-x,-1/2+y,-z	-23.4	-0.2	20.2	-1.7
	1+x,y,z	-50.2	-0.2	44.1	-3.8
	-1+x,y,z	-54.8	-3.4	46.0	-7.9
	1-x,1/2+y,-z	**-50.6**	**-0.4**	**44.4**	**-3.9**
	1-x,1/2+y,1-z	-56.6	-3.2	48.4	-7.6
	1-x,-1/2+y,-z	-50.2	-0.2	44.1	-3.7
	2-x,1/2+y,-z	-54.8	-2.3	45.6	-8.2
	1+x,y,z	-23.4	-0.2	20.1	-1.8
	-x,1/2+y,1-z	-23.6	-0.5	19.8	-2.4
	-x,-1/2+y,1-z	-23.7	-0.5	19.9	-2.4
	1-x,1/2+y,1-z	-28.7	-4.1	22.6	-5.8
	1-x,-1/2+y,-z	-23.3	-0.1	20.3	-1.6
	1-x,-1/2+y,1-z	-32.9	-4.6	26.3	-7.4
Terbutaline sulfate	x,-1+y,z	118.1	0.0	0.1	118.1
	1-x,1-y,-z	203.5	-0.3	1.1	204.5
	1-x,1-y,1-z	160.5	-0.1	0.3	160.8
	2-x,1-y,-z	117.9	0.0	0.2	118.1
	2-x,1-y,1-z	143.9	0.0	0.5	144.4
	x,y,1+z	-185.6	-0.1	79.7	-104.4
	x,1+y,z	-190.0	0.0	93.9	-94.1
	x,-1+y,z	-183.4	0.0	77.6	-104.4
	1-x,1-y,1-z	-196.0	-4.2	36.7	-162.6
	1-x,2-y,1-z	-192.7	0.0	96.9	-93.7
	2-x,1-y,-z	-188.0	0.0	89.2	-97.0
	2-x,1-y,1-z	-180.3	-0.8	57.8	-121.5
	2-x,2-y,1-z	-193.1	-0.1	93.8	-97.3
	x,y,-1+z	-170.7	-0.1	77.1	-92.0
	x,1+y,z	-158.6	-0.4	46.0	-111.9
	1+x,y,z	-172.3	-0.1	78.3	-92.2
	-1+x,y,z	-160.7	0.0	61.5	-98.2
	1-x,1-y,-z	-213.3	-5.8	21.9	-195.2
	1-x,1-y,1-z	-161.1	0.0	62.2	-97.8
	1-x,2-y,-z	-166.7	0.0	71.1	-94.3
	1-x,2-y,1-z	-167.2	0.0	72.7	-93.2
	2-x,1-y,-z	-189.8	-3.4	65.9	-126.0
	2-x,1-y,1-z	-167.7	0.0	73.4	-92.9
	2-x,2-y,-z	-173.8	0.0	82.2	-89.8
	2-x,2-y,1-z	-168.6	0.0	74.4	-92.8
	x,y,1+z	23.8	0.0	0.5	24.4
	x,1+y,z	23.6	-3.0	3.0	25.3
	x,-1+y,z	23.6	-3.0	3.0	25.3
	1-x,1-y,1-z	23.8	-13.0	4.4	20.0
	1-x,2-y,1-z	23.9	-0.2	-1.8	22.1
	2-x,1-y,-z	19.1	0.0	0.5	19.7
	2-x,1-y,1-z	37.8	-7.0	8.1	43.5
	2-x,2-y,1-z	20.9	-1.8	1.4	21.5
	x,-1+y,z	-190.0	0.0	93.9	-94.1
	1-x,1-y,-z	-182.0	0.0	79.6	-100.9
	1-x,1-y,1-z	-196.0	-4.2	36.7	-162.6
	2-x,1-y,-z	-188.0	0.0	89.2	-97.0
	2-x,1-y,1-z	-180.3	-0.8	57.8	-121.5
	x,y,-1+z	25.2	-8.6	6.7	28.8
	x,1+y,z	34.6	-1.1	2.9	37.3
	1+x,y,z	26.1	-0.1	-0.9	25.1
	-1+x,y,z	25.1	-0.1	1.2	26.3
	1-x,1-y,-z	37.8	-0.5	2.2	40.0
	1-x,1-y,1-z	38.6	-2.1	3.3	41.3
	1-x,2-y,-z	23.0	0.0	-0.3	22.6
	1-x,2-y,1-z	24.1	-1.8	1.4	24.6
	2-x,1-y,-z	30.3	-1.2	1.3	31.5
	2-x,1-y,1-z	35.3	-1.5	1.5	36.6
	2-x,2-y,-z	22.2	-0.1	-0.5	21.7

Crystal	Symmetry.operation	$E_{(c)}$ [kcal/mol]	$E_{(dis)}$ [kcal/mol]	$E_{(ex)}$ [kcal/mol]	$E_{(tot)}$ [kcal/mol]
	2-x,2-y,1-z	**20.3**	**-6.6**	**3.2**	**18.5**
	x,y,-1+z	24.2	-0.1	0.0	24.2
	x,1+y,z	27.7	-0.1	0.8	28.5
	1+x,y,z	27.6	-3.9	2.5	28.9
	-1+x,y,z	27.6	-3.9	2.5	28.9
	1-x,1-y,-z	45.6	-5.3	8.6	52.7
	1-x,1-y,1-z	22.5	0.0	0.6	23.1
	1-x,2-y,-z	36.6	-1.8	3.2	39.4
	1-x,2-y,1-z	24.4	0.0	0.8	25.2
	2-x,1-y,-z	24.3	-6.7	0.9	20.3
	2-x,1-y,1-z	22.3	0.0	-0.1	22.2
	2-x,2-y,-z	**20.5**	**-7.8**	**6.1**	**21.5**
	2-x,2-y,1-z	26.8	-0.1	-0.1	26.6
	x,-1+y,z	-158.6	-0.4	46.0	-111.9
	1-x,1-y,-z	-213.3	-5.8	21.9	-195.2
	1-x,1-y,1-z	-161.1	0.0	62.2	-97.8
	2-x,1-y,-z	-189.8	-3.4	65.9	-126.0
	2-x,1-y,1-z	-167.7	0.0	73.4	-92.9
	x,y,1+z	25.2	-8.6	6.7	28.8
	x,1+y,z	19.6	0.0	-0.5	19.1
	x,-1+y,z	34.6	-1.1	2.9	37.3
	1-x,1-y,1-z	38.6	-2.1	3.3	41.3
	1-x,2-y,1-z	24.1	-1.8	1.4	24.6
	2-x,1-y,-z	30.3	-1.2	1.3	31.5
	2-x,1-y,1-z	35.3	-1.5	1.5	36.6
	2-x,2-y,1-z	**20.3**	**-6.6**	**3.2**	**18.5**
AZD4721	x,y,1+z	-4.4	-4.8	2.0	-4.4
	x,y,-1+z	-4.4	-4.8	2.0	-4.4
	1+x,y,z	-25.6	-23.8	4.9	-33.7
	1+x,y,1+z	**-11.3**	**-8.1**	**-3.8**	**-22.4**
	-1+x,y,z	-25.6	-23.8	4.9	-33.7
	-1+x,y,-1+z	**-11.3**	**-8.1**	**-3.8**	**-22.4**
	2+x,y,1+z	-4.5	-1.3	1.7	-3.7
	-2+x,y,-1+z	-4.5	-1.3	1.7	-3.7
	-x,1/2+y,-z	-5.2	-1.4	4.2	-1.9
	-x,-1/2+y,-z	-5.2	-1.4	4.2	-1.9
	1-x,1/2+y,-z	**-10.5**	**-9.9**	**4.8**	**-10.1**
	1-x,1/2+y,1-z	-4.9	-2.3	2.3	-3.7
	1-x,-1/2+y,-z	**-10.5**	**-9.9**	**4.8**	**-10.1**
	1-x,-1/2+y,1-z	-4.9	-2.3	2.3	-3.7
	2-x,1/2+y,-z	-6.6	-6.6	1.7	-8.1
	2-x,1/2+y,1-z	-3.2	-1.6	1.7	-1.6

To determine along which Miller plane in the crystal the weakest interactions occur we visually determine what dimer interactions are contributing to the interactions spanning over those Miller planes.

Table S2. Calculated attachment energies for paracetamol form I, AZD5423 form B, terbutaline sulfate and AZD4721. Geometry optimization on crystal structure was done using the Compass II force field (version 1.2) and QEq charge, prior to calculation

Crystal	hkl	Multiplicity	dhkl	Eatt(Total)	% Total facet area
Paracetamol form I	**{0 1 1}**	**4**	**7.20**	**-65.57**	**47.85**
	{1 0 -1}	2	6.40	-76.64	15.89
	{0 0 2}	2	5.76	-105.15	
	{1 0 1}	2	5.67	-85.53	12.94
	{1 1 0}	4	5.59	-92.73	4.35
	{1 1 -1}	4	5.26	-82.49	9.87
	{0 1 2}	4	4.88	-91.19	
	{1 1 1}	4	4.83	-103.45	
	{0 2 0}	2	4.62	-68.84	9.11
AZD5423	**{0 0 1}**	**2**	**23.63**	**-175.91**	**47.54**
	{0 1 1}	2	14.66	-495.69	8.32
	{0-1 1}	2	14.66	-495.69	8.32
	{1 0-1}	2	9.30	-313.29	13.15
	{1 0 0}	2	9.24	-318.44	10.72
	{1 1-1}	2	8.32	-453.99	3.28
	{1-1-1}	2	8.32	-453.99	3.28
	{1 1 0}	2	8.28	-456.82	2.70
	{1-1 0}	2	8.28	-456.82	2.70
Terbutaline sulfate	{0 0 1}	2	12.55	-111.59	18.19
	{0 1 0}	**2**	**10.62**	**-88.10**	**23.43**
	{0 1 -1}	2	9.35	-91.06	18.62
	{1 0 0}	2	9.32	-119.34	11.53
	{1 0 -1}	2	8.85	-121.71	10.61
	{1 -1 0}	2	8.14	-99.66	17.34
AZD4721	**{0 2 0}**	**1**	**10.33**	**-68.52**	**17.41**
	{0-2 0}	1	10.33	-68.52	17.41
	{0 0 1}	2	9.11	-80.44	13.23
	{0 1 1}	2	8.34	-83.76	12.08
	{0-1 1}	2	8.34	-83.76	12.08
	{1 0 0}	2	5.80	-161.30	1.09
	{1 1 0}	2	5.58	-161.02	0.80
	{1-1 0}	2	5.58	-161.02	0.80
	{1 0-1}	2	5.28	-150.73	1.08
	{1 2-1}	2	4.70	-136.90	7.53
	{1-2-1}	2	4.70	-136.90	7.53
	{1 0 1}	2	4.58	-138.01	8.89

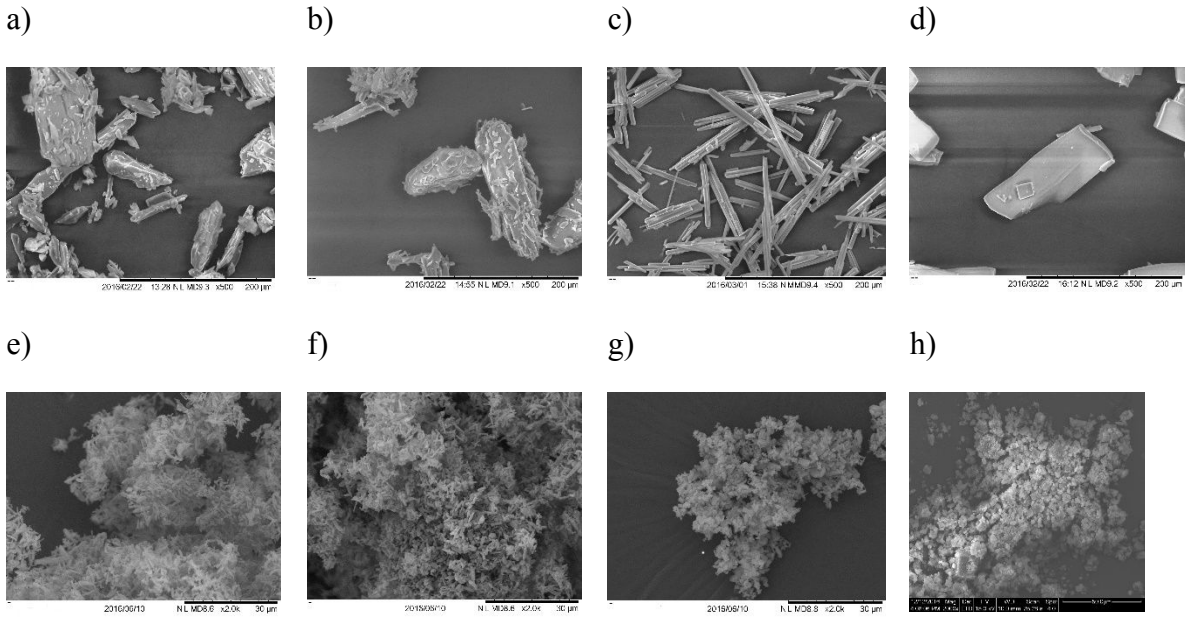
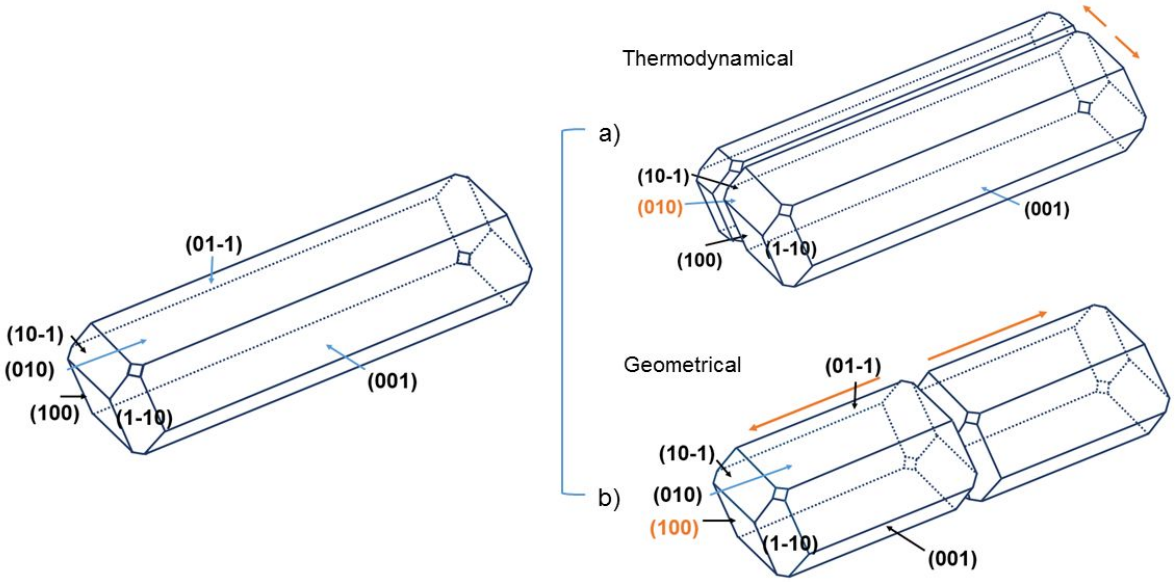


Figure S 1. SEM micrographs of a) paracetamol 1 un-micronized, b) paracetamol 2 un-micronized, c) AZD5423 un-micronized, d) AZD4721 un-micronized, e) paracetamol 1 micronized, f) paracetamol 2 micronized, g) AZD5423 micronized, and h) AZD4721 micronised (analysed with a SEM Quanta 200). A benchtop SEM (Hitachi TM3030, Hitachi High-Technologies, Japan) was used at 15 kV. The micronized samples were gold coated for 100 seconds at 20mA in argon atmosphere using a Cressington Sputter Coater 108 Auto (Cressington Scientific Instruments Ltd, UK)

AZD5423



AZD4721

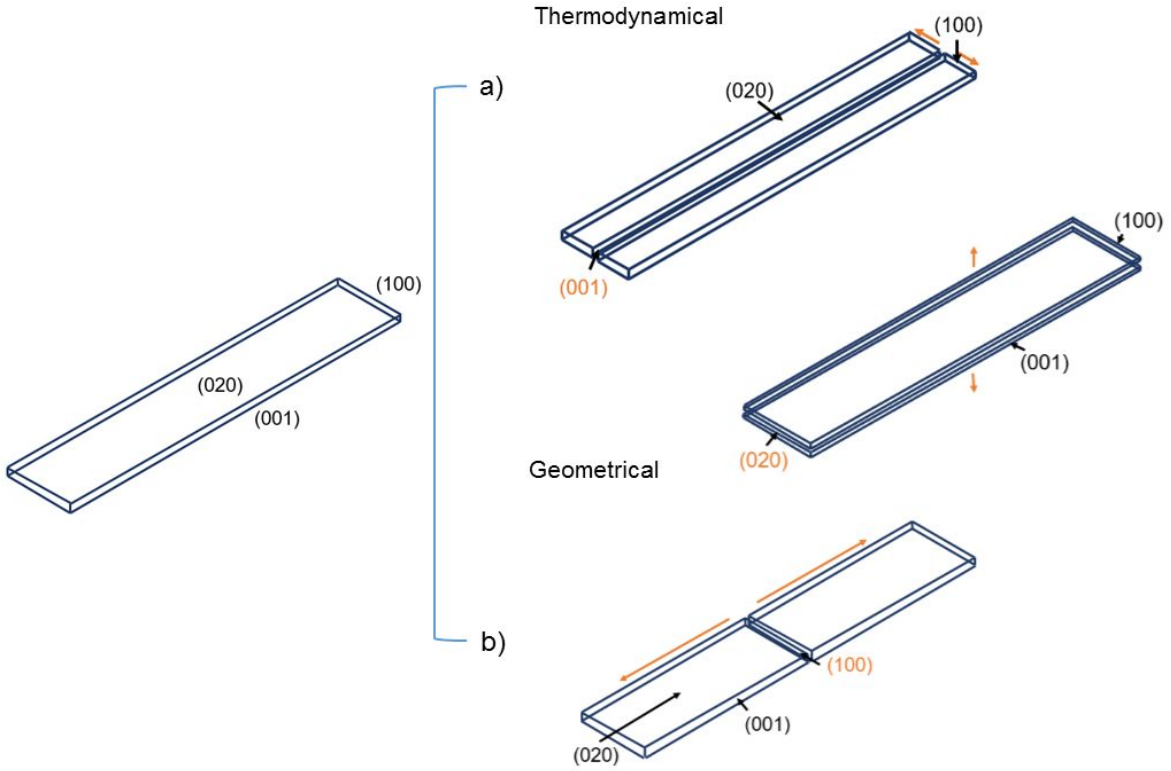


Figure S 2. Proposed fracture mechanism of a) AZD5423 and b) AZD4721 (data based on Figure S 3)

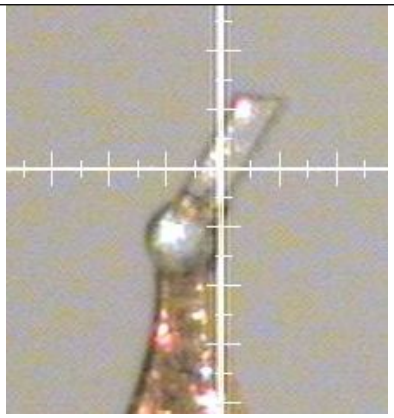
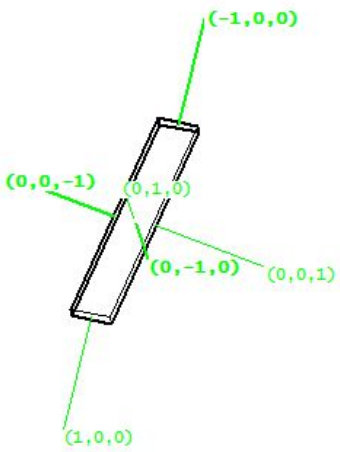
cell_length_a 5.885(10) cell_length_b 20.856(19) cell_length_c 9.30(3) cell_angle_alpha 90 cell_angle_beta 100.2(4) cell_angle_gamma 90 loop exptl_crystal_face_index_h exptl_crystal_face_index_k _exptl_crystal_face_index_l _exptl_crystal_face_perp_dist 0 1 0 0.021 0 -1 0 0.019 0 0 1 0.041 0 0 -1 0.039 1 0 0 0.221 -1 0 0 0.202		

Figure S 3 Single crystal x-ray of AZD4721

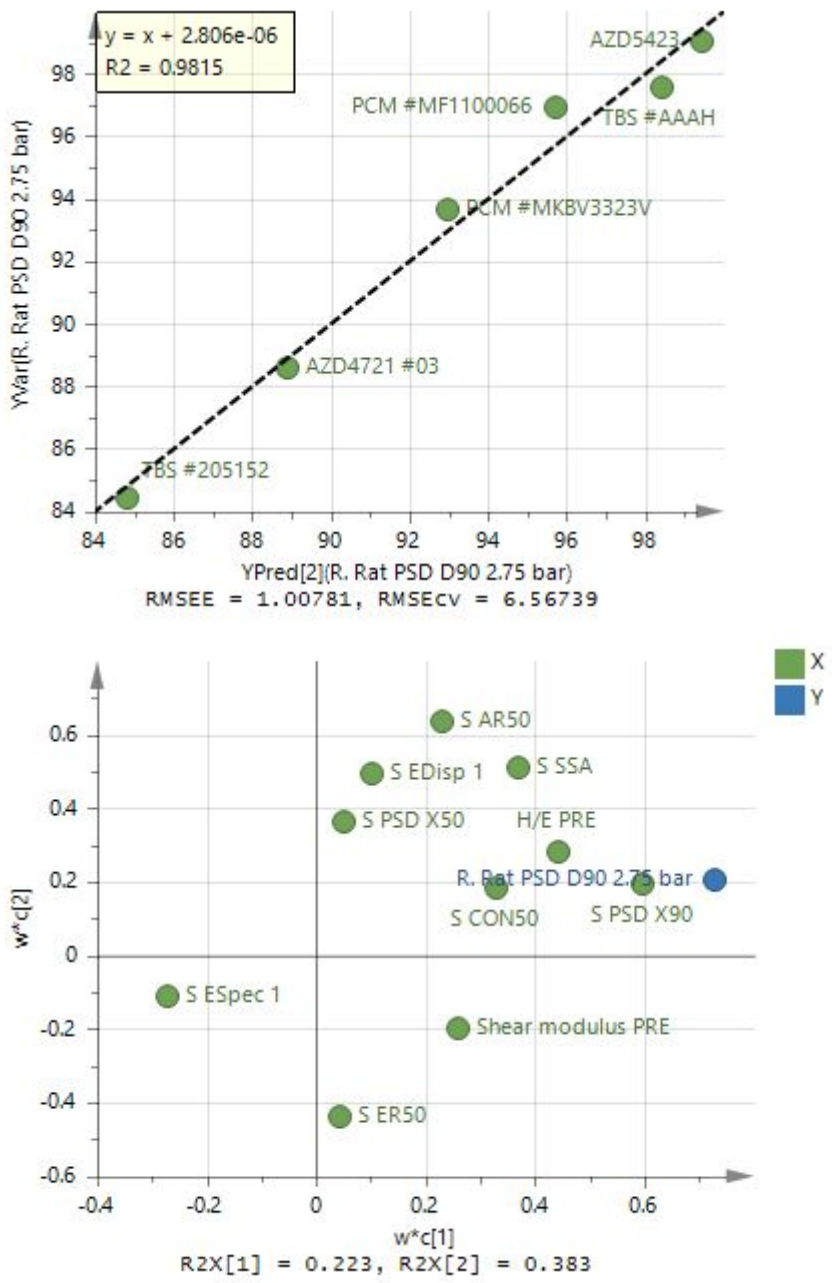
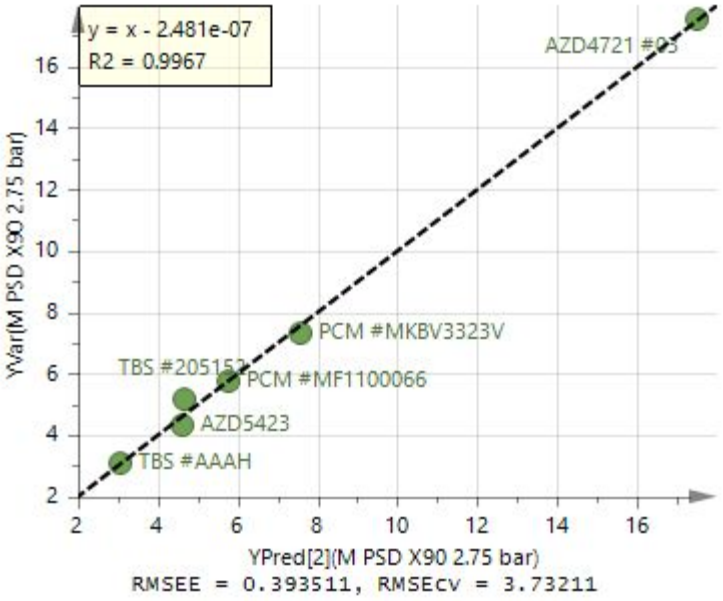
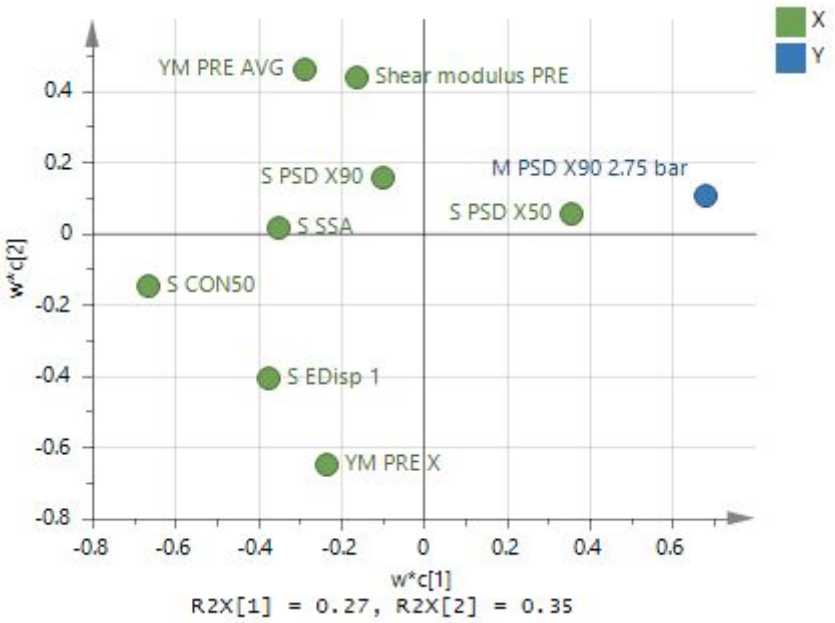


Figure S4. Observed vs. predicted plot of d90 reduction ratio (top) and Scatter plot showing the loading vectors of the two PLS components (below)


y = x - 2.481e-07
R2 = 0.9967
AZD4721 #03
PCM #MKBV3323V
TBS #205157
PCM #MF1100066
AZD5423
TBS #AAAH
YVar(M PSD X90 2.75 bar)
YPred[2](M PSD X90 2.75 bar)
RMSEE = 0.393511, RMSECV = 3.73211


X
Y
YM PRE AVG
Shear modulus PRE
S PSD X90
M PSD X90 2.75 bar
S PSD X50
S SSA
S CON50
S EDisp 1
YM PRE X
w*c[2]
w*c[1]
R2X[1] = 0.27, R2X[2] = 0.35

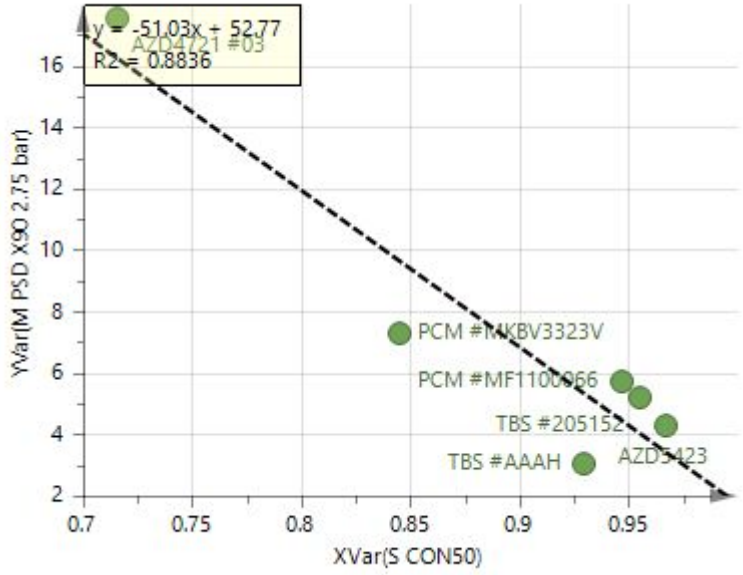


Figure S5. Observed vs. predicted plot of micronised d90 (top), Scatter plot showing the loading vectors of the two PLS components (middle) and Scatter plot convexity vs. micronised d90 (bottom)

Table S3. Summary of particle size distributions of both micronized and un-micronized sample. Un-micronized samples were analyzed with a Mastersizer 3000 instrument and the micronized samples with a Mastersizer 2000 instrument equipped with a Scirocco unit (Malvern Instruments Limited, Malvern, UK).

Material		Disp. pressure (bar)	D (0.10) - µm	D (0.50) - µm	D (0.90) - µm	D (0.90-0.10) - µm	PDI	SSA - m^2/g [a]	Reduction ratio D (0.90) -%
Paracetamol 1	un-micronized	2.00	6.91	40.30	188.00	181.09	4.49	0.24	96.95
	micronized	2.75	0.56	1.58	5.73	5.17	3.27	3.03	
Paracetamol 2	un-micronized	2.00	5.29	27.40	115.00	109.71	4.00	0.29	93.64
	micronized	2.75	0.59	1.70	7.31	6.73	3.95	3.39	
AZD5423	un-micronized	2.00	3.13	9.46	435.00	431.87	45.65	1.04	99.01
	micronized	2.75	0.55	1.66	4.29	3.74	2.25	13.94	
Terbutaline sulfate 1	un-micronized	2.00	4.38	11.00	33.30	28.92	2.63	0.56	84.44
	micronized	2.75	0.60	2.39	5.18	4.58	1.91	4.91	
Terbutaline sulfate 2	un-micronized	2.00	20.60	70.60	126.00	105.40	1.49	4.54	97.56
	micronized	2.75	0.49	1.22	3.07	2.58	2.11	11.37	
AZD4721	un-micronized	2.00	32.90	74.60	154.00	121.10	1.62	< 0.1	88.60
	micronized	2.75	0.85*	6.16	17.55	16.71	2.71	3.01	

[a] Analyzed using Tristar 3000 and 3020 (Micromeritics, US) using nitrogen as adsorptive

Table S4. Calculated surface energies using equilibrium model for paracetamol form I, AZD5423 form B, terbutaline sulfate and AZD4721. Geometry optimization on crystal structure was done using the Compass II force field (version 1.2) and QEq charge, prior to calculation

Crystal	hkl	Multiplicity	dhkl	Esurf (Total)	Esurf (vdW)	Esurf (Electrostatic)	Effective surface charge	Epolar	% Total facet area
Paracetamol form I	{0 1 1}	4	7.20	0.31	0.11	0.21	0.00	0.00	13.98
	{1 0 -1}	2	6.40	0.33	0.15	0.18	0.00	0.00	2.72
	{0 0 2}	2	5.76	0.41	0.11	0.30	0.00	0.00	0.97
	{1 0 1}	2	5.67	0.32	0.10	0.22	0.00	0.00	4.06
	{1 1 0}	4	5.59	0.35	0.13	0.21	0.00	0.00	
	{1 1 -1}	4	5.26	0.29	0.12	0.18	0.00	0.00	22.31
	{0 1 2}	4	4.88	0.39	0.12	0.27	0.00	0.00	
	{1 1 1}	4	4.83	0.34	0.13	0.21	0.00	0.00	3.78
	{0 2 0}	2	4.62	0.23	0.17	0.06	0.00	0.00	18.86
	{3 5 1}	4	1.42	0.32	0.13	0.19	0.00	0.00	1.16
	{0 7 2}	4	1.29	0.26	0.15	0.11	0.00	0.00	1.74
	{4 5 -5}	4	1.16	0.30	0.11	0.19	0.00	0.00	2.47
	{3 7 0}	4	1.15	0.30	0.14	0.16	0.00	0.00	1.78
	{0 1 10}	4	1.14	0.41	0.10	0.31	0.00	0.00	4.01
	{5 1 5}	4	1.12	0.33	0.11	0.22	0.00	0.00	3.07
	{5 2 5}	4	1.10	0.33	0.11	0.22	0.00	0.00	3.37
AZD5423	{0 0 1}	2	23.63	0.49	0.13	0.36	0.02	0.00	13.72
	{2 1 -3}	2	4.29	0.38	0.15	0.23	-0.03	0.00	7.26
	{2 -1 -3}	2	4.29	0.38	0.15	0.23	0.03	0.00	7.26
	{2 1 1}	2	4.25	0.38	0.15	0.23	-0.03	0.00	6.96
	{2 -1 1}	2	4.25	0.38	0.15	0.23	0.03	0.00	6.96
	{1 -1 -2}	2	7.48	0.50	0.15	0.34	0.07	0.00	3.73
	{1 1 -2}	2	7.48	0.50	0.15	0.34	-0.07	0.00	3.73
	{2 1 -1}	2	4.58	0.37	0.14	0.23	-0.03	0.00	3.71
	{2 -1 -1}	2	4.58	0.37	0.14	0.23	0.03	0.00	3.71
	{1 -1 1}	2	7.40	0.50	0.15	0.35	0.12	0.00	1.94
	{1 1 1}	2	7.40	0.50	0.15	0.35	-0.12	0.00	1.94
	{1 0 0}	2	9.24	0.35	0.15	0.21	0.04	0.00	1.91
	{1 0 -1}	2	9.30	0.35	0.14	0.21	0.00	0.00	1.83
	{1 0 1}	2	8.05	0.39	0.15	0.24	0.02	0.00	1.79
	{2 0 -3}	2	4.41	0.37	0.14	0.23	0.00	0.00	1.76
	{1 1 -1}	2	8.32	0.48	0.14	0.34	-0.01	0.00	1.66
	{1 -1 -1}	2	8.32	0.48	0.14	0.34	0.01	0.00	1.66
	{2 -1 -2}	2	4.51	0.37	0.14	0.23	0.06	0.00	1.57
	{2 1 -2}	2	4.51	0.37	0.14	0.23	-0.06	0.00	1.57
	{1 0 -2}	2	8.16	0.40	0.15	0.26	0.09	0.00	1.56
	{1 -1 0}	2	8.28	0.48	0.16	0.32	0.07	0.00	1.40
	{1 1 0}	2	8.28	0.48	0.16	0.32	-0.07	0.00	1.40
	{1 -2 -1}	2	6.59	0.66	0.15	0.51	0.09	0.00	1.34
	{1 2 -1}	2	6.59	0.66	0.15	0.51	-0.09	0.00	1.34
	{1 0 2}	2	6.63	0.45	0.16	0.29	0.04	0.00	1.31
	{2 1 2}	2	3.94	0.42	0.16	0.26	-0.06	0.00	1.28
	{2 -1 2}	2	3.94	0.42	0.16	0.26	0.06	0.00	1.28
	{2 -1 0}	2	4.49	0.37	0.14	0.23	0.06	0.00	1.13
	{2 1 0}	2	4.49	0.37	0.14	0.23	-0.06	0.00	1.13
	{1 -2 0}	2	6.57	0.66	0.15	0.51	0.09	0.00	1.08
	{1 2 0}	2	6.57	0.66	0.15	0.51	-0.09	0.00	1.08
Terbutaline sulfate	{0 9-4}	2	1.21	0.33	0.06	0.27	0.00	0.00	2.78
	{0 1-2}	2	6.12	0.35	0.10	0.25	1.52	0.29	3.72
	{0 0 1}	2	12.55	0.37	0.09	0.28	0.82	0.74	6.77
	{1 0 1}	2	6.60	0.34	0.10	0.24	0.00	0.00	7.38
	{0 1 -1}	2	9.35	0.31	0.08	0.23	0.00	0.00	9.38
	{1 -1 0}	2	8.14	0.29	0.08	0.21	0.00	0.00	10.40
	{1 0 0}	2	9.32	0.28	0.10	0.18	1.52	1.03	11.09
	{0 1 0}	2	10.62	0.34	0.06	0.28	0.00	0.00	14.16
	{1 0 -1}	2	8.85	0.21	0.12	0.08	1.52	0.88	32.24
AZD4721	{1 0 1}	2	4.58	0.41	0.16	0.25			5.15
	{0 -2 0}	1	10.33	0.27	0.14	0.13	-0.12	0.05	9.38
	{0 2 0}	1	10.33	0.27	0.14	0.13	0.12	0.05	9.38
	{0 -1 1}	2	8.34	0.32	0.12	0.20	-0.12	0.01	11.08
	{0 1 1}	2	8.34	0.32	0.12	0.20	0.12	0.01	11.08

Table S5 Summary of mechanical property calculations (see details in description below).

Compound	Crystal ID	Hardness (FORCITE, Hill)			Young´s modulus (CASTEP)				H/E
		Bulk modulus (GPa)	Shear modulus (GPa)	Hardness (GPa) [a]	X (GPa)	Y (GPa)	Z (GPa)	Average (GPa)	
Paracetamol	HXACAN07	7.168	3.474	0.768	26.828	4.980	7.888	13.232	0.058
AZD5423		18.502	6.302	1.640 [b]	16.746	41.081	27.683	28.503 [c]	0.058
Terbutaline sulfate	ZIVKAQ	6.168	4.313	0.568	16.736	35.441	29.376	27.184	0.021
AZD4721		7.540	4.159	0.734	13.139	17.126	24.800	18.355	0.040

[a] Calculated according to equation 1

[b] Hardness calculated using an in-house force field

[c] Young´s modulus calculated using Compass II force field

Hardness was predicted using Forcite and Compass II force field (version 1.2) with QEq charge and maximum iteration was set to 500. Geometry optimization was done prior to the calculations with same settings. To calculate the hardness, the following equation was used (Equation 1):

$$H = y(k^2G)^{0.585} \quad (1),$$

where y is 0.15889 and, k is the shear modulus (G) divided by the bulk modulus (K). Equation 1 is optimized to the calculation of mechanical properties determined by Forcite Hill modulus.

Young´s modulus was predicted using CASTEP-module and geometry optimization was done prior to calculation. For DFT-D correction, the Grimme method was used with GGA and PBE functional. Maximum iteration was set to 500 instead of 100 to ensure a fully optimized molecule. Energy cut-off was set to 620 eV, and the k-point separation was set to 0.05/Å in the calculation.

Table S6. Summary of estimated lattice energies

Material	Estimated lattice energy (kJ/mol)
Paracetamol 1	-126
AZD5423	-328
Terbutaline sulfate 1	-1356
AZD4721	-251