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Towards *ab initio* screening of co-crystal formation through lattice energy calculations and crystal structure prediction of nicotinamide, isonicotinamide, picolinamide and paracetamol multi-component crystals

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Electronic Supplementary Information

DFT-D calculations

The optimisations of all the crystal structures and the minimisations of their lattice energies were performed using the GRACE software package, version 1.6.[1] This software calculates DFT energies using VASP 4.6[2,3] and implements a correction for the van der Waals energy.[4] Projector augmented wave (PAW) potentials and the PW91 exchange-correlation functional with the Vosko, Wilk, and Nusair interpolation formula were used for DFT calculations. The plane-wave cut-off energy was set at 520 eV. The *k*-point spacing in the Brillouin zone was approximately 0.7 $Å^{-1}$. The wave function convergence level was 0.5×10^{-6} kcal·mol^{-1} per atom. The van der Waals correction is expressed as a pair-wise sum over all atoms.[4] The C_6 coefficients of the van der Waals correction have been parameterised using experimental dipole oscillator strength distribution data. Minimisations were complete when the change in lattice energy was no more than 0.25×10^{-3} kcal·mol^{-1} per atom, atomic displacements were no more than 3×10^{-3} Å, and maximum atomic forces were no more than 0.7 kcal·$Å^{-1}$·mol^{-1} per atom.

Comparisons of the calculated and the experimental relative stabilities of co-former polymorphs

The calculated relative stabilities of the polymorphs of nicotinamide, fumaric acid, adipic acid, heptadecanoic acid, rac-ibuprofen, DL-mandelic acid and 3-hydroxybenzoic acid are consistent with experiment. The *P*2/*n* polymorph of nicotinamide was confirmed to be metastable by Differential Scanning Calorimetry (DSC) and variable temperature powder *X*-ray diffraction.[5] The *α* polymorph of fumaric acid was prepared by slow evaporation of an

ethanol solution,[6] whilst its β polymorph was prepared in a sublimation process at 403 K at reduced pressure.[7] For adipic acid, form I is the stable phase above 136 K and it transforms into form II below 136 K.[8] An additional form III was prepared by solvent evaporation at room temperature, but its structure was determined at 100 K.[9] The DFT-D results suggest (see Table S1) that form III is the most stable form, followed by forms II and I. A phase transition of heptadecanoic acid from form B to form C at 331 K was determined by DSC and powder *X*-ray diffraction, prior to melting at 333 K.[10] Form II of rac-ibuprofen[11] and the monoclinic polymorph of DL-mandelic acid[12] were reported as metastable phases. The monoclinic polymorph of 3-hydroxybenzoic acid was concluded to be the more stable form via a series of solubility tests and studies of heat capacities at different temperatures.[13]

The β polymorphs of alkanedicarboxylic acids are the stable forms at room temperature, followed by phase transitions to α forms at high temperatures.[14] However, the DFT-D results suggest that the α forms are more stable. The atomic coordinates for the α form of glutaric acid are not known and only its unit cell parameters are available, hence it could not be considered in this study.[15] Experimentally, at 56 K the β form of malonic acid transforms into the γ form, which has two independent molecules in the asymmetric unit.[16] However, the DFT-D optimised γ form becomes a $Z' = 1$ structure and converges to the same minimum as the optimised β form. For isonicotinamide, the order of polymorph stability from DSC results is form I > Iso3 > form II.[5] The DFT-D results suggest a stability order of form II > form I > Iso3. For carbamazepine, the order of polymorph stability from DSC results is form III > form I > form IV > form II.[17] In agreement with experiment, the DFT-D results indicate that form III is the most stable phase, whilst form II is the least stable. The calculated stability order for forms I and IV, however, is not in agreement with the DSC data, although the energy difference between these two forms is only 0.04 kcal·mol^{-1}. For 3,5-dinitrobenzoic acid, the relative stabilities of its polymorphs have not been reported.

Table S1: DFT-D lattice energies of the pure co-formers in nicotinamide, isonicotinamide and picolinamide co-crystals and salts reported in the CSD version 5.32. The most stable polymorph of each compound is given in bold.

Compound name	Molecular formula	CSD reference code[a]	Polymorph type	E_{DFT-D}[b] (kcal·mol^{-1})	RMSD[c] (Å)
nicotinamide	**$C_6H_6N_2O_1$**	**NICOAM01**	***P*2$_1$/*c***	**-2333.09**	**0.071**
		NICOAM04	*P*2/*n*	(+0.25)	0.072
isonicotimaide	**$C_6H_6N_2O_1$**	**EHOWIH02**	**Form II**	**-2332.96**	**0.037**
		EHOWIH01	Form I	(+0.32)	0.044
		EHOWIH03	Iso3	(+0.38)	0.035
picolinamide	**$C_6H_6N_2O_1$**	**PICAMD**	**-**	**-2333.78**	**0.048**
oxalic acid	**$C_2H_2O_4$**	**OXALAC04**	**beta**	**-1245.35**	**0.039**
		OXALAC06	alpha	(+0.74)	0.047
malonic acid	**$C_3D_4O_4$**	**MALNAC03**	**alpha**	**-1639.61**	**0.059**
		MALNAC09	beta	(+0.44)	0.080
		MALNAC08	gamma	(+0.45)	0.155
fumaric acid	**$C_4H_4O_4$**	**FUMAAC**	**alpha**	**-1835.99**	**0.129**
		FUMAAC01	beta	(+0.02)	0.045
succinic acid	**$C_4H_6O_4$**	**SUCACB07**	**alpha**	**-2029.31**	**0.050**
		SUCACB03	beta	(+0.09)	0.034
tartaric acid	**$C_4H_6O_6$**	**ZZZDUI01**	**(racemic)**	**-2337.92**	**0.069**
		TARTAL04	(+)-enantiomer	(+1.69)	0.199
glutaric acid	**$C_5H_8O_4$**	**GLURAC04**	**beta**	**-2413.33**	**0.100**
adipic acid	**$C_6H_{10}O_4$**	**ADIPAC12**	**Form III**	**-2799.70**	**0.058**
		ADIPAC05	Form II	(+0.52)	0.126
		ADIPAC04	Form I	(+0.68)	0.032
pimelic acid	**$C_7H_{12}O_4$**	**PIMELA05**	**alpha**	**-3183.80**	**0.065**
		PIMELA06	beta	(+0.02)	0.062
suberic acid	**$C_8H_{14}O_4$**	**SUBRAC01**	-	**-3569.14**	**0.029**
azelaic acid	**$C_9H_{16}O_4$**	**AZELAC10**[d]	**alpha**	**-3954.28**	**0.066**
		AZELAC03	beta	(+0.05)	0.060
sebacic acid	**$C_{10}H_{18}O_4$**	**SEBAAC03**	-	**-4339.22**	**0.069**
thiodiglycolic acid	**$C_4H_6O_4S_1$**	**TGLYCL01**	-	**-2113.04**	**0.050**
acetic acid	**$C_2H_4O_2$**	**ACETAC07**	**low pressure**	**-1102.56**	**0.063**
		ACETAC09	high pressure	(+0.05)	0.130
trifluoroacetic acid	**$C_2H_1F_3O_2$**	**TFACET**	**-**	**-1117.30**	**0.050**
monochloroacetic acid	**$C_2H_3Cl_1O_2$**	**CLACET02**	**beta**	**-1066.29**	**0.063**
		CLACET01	alpha	(+0.09)	0.079
propionic acid	**$C_3H_6O_2$**	**PRONAC**	**low pressure**	**-1487.02**	**0.079**
		PRONAC02	high pressure	(+0.25)	0.082
dodecanoic acid	**$C_{12}H_{24}O_2$**	**LAURAC**[d]	**Form A1**	**-4953.01**	**0.126**
		LAURAC04	Form C	(+0.17)	0.090
		LAURAC01[d]	Super A	(+0.17)	0.117
n-hexadecanoic acid	**$C_{16}H_{32}O_2$**	**YEFWEM**	**Form C**	**-6493.86**	**0.150**
heptadecanoic acid	**$C_{17}H_{34}O_2$**	**DARWAU**[d]	**Form B**	**-6878.82**	**0.089**
		DARWAU01	Form C	(+0.29)	0.173
octadecanoic acid	**$C_{18}H_{36}O_2$**	**STARAC06**	**orthorhombic B**	**-7264.88**	**0.156**
		STARAC02[d]	monoclinic B	(+0.01)	0.066
		STARAC07	orthorhombic E	(+0.09)	0.083
		STARAC05	monoclinic E	(+0.10)	0.081
		STARAC01[d]	monoclinic C	(+0.97)	0.265
ibuprofen	**$C_{13}H_{18}O_2$**	**IBPRAC**	**Form I (racemic)**	**-4627.93**	**0.051**
		JEKNOC11	(S-enantiomer)	(+0.97)	0.073

		IBPRAC04	Form II (racemic)	(+2.95)	0.495
mandelic acid	**$C_8H_8O_3$**	**DLMAND03**	**orthorhombic (racemic)**	**-2855.46**	**0.244**
		DLMAND02	monoclinic (racemic)	(+1.48)	0.068
		FEGHAA	(S-enantiomer)	(+1.75)	0.082
3-indolylacetic acid	**$C_{10}H_9N_1O_2$**	**INACET04**	-	**-3405.48**	**0.046**
citric acid	**$C_6H_8O_7$**	**CITRAC11**	-	**-3103.01**	**0.091**
clofibric acid	**$C_{10}H_{11}Cl_1O_3$**	**BEFVAJ**[d]	-	**-3584.42**	**0.066**
cinnamic acid	**$C_9H_8O_2$**	**CINMAC07**	**alpha**	**-2900.24**	**0.029**
		CINMAC06	beta	(+0.12)	0.279
3,4-dimethoxy-cinnamic acid	**$C_{11}H_{12}O_4$**	**CEMJOT02**	-	**-3965.30**	**0.066**
ferulic acid	**$C_{10}H_{10}O_4$**	**GASVOL**	-	**-3595.70**	**0.073**
2-phenylpropionic acid	**$C_9H_{10}O_2$**	**GOGPEY**	**(R-enantiomer)**	**-3084.47**	**0.040**
2-phenylbutyric acid	**$C_{10}H_{12}O_2$**	**ROLFII**	**(racemic)**	**-3469.30**	**0.051**
diclofenac	**$C_{14}H_{11}Cl_2N_1O_2$**	**SIKLIH07**	***C*2/*c***	**-4519.74**	**0.060**
		SIKLIH08	$P2_1/c$	(+0.35)	0.101
		SIKLIH04[e]	*Pcan*	(+1.54)	0.687
benzoic acid	**$C_7H_6O_2$**	**BENZAC01**	**-**	**-2317.15**	**0.063**
4-fluorobenzoic acid	**$C_7H_5F_1O_2$**	**PFBZAD01**	-	**-2325.03**	**0.070**
2-hydroxybenzoic acid	**$C_7H_6O_3$**	**SALIAC16**	-	**-2481.73**	**0.026**
3-hydroxybenzoic acid	**$C_7H_6O_3$**	**BIDLOP**[f]	**monoclinic**	**-2480.47**	**0.042**
		BIDLOP01[d]	orthorhombic	(+0.28)	0.053
4-hydroxybenzoic acid	**$C_7H_6O_3$**	**JOZZIH**[g]	-	**-2481.36**	**0.186**
3-methylbenzoic acid	**$C_8H_8O_2$**	**ZZZKWI01**[g]	-	**-2705.00**	**0.048**
4-methylbenzoic acid	**$C_8H_8O_2$**	**PTOLIC**[d]		**-2705.58**	**0.079**
3-nitrobenzoic acid	**$C_7H_5N_1O_4$**	**MNBZAC**	**Form I**	**-2678.38**	**0.051**
		MNBZAC01[d]	Form II	(+0.48)	0.090
4-nitrobenzoic acid	**$C_7H_5N_1O_4$**	**NBZOAC04**	***A*2/*a***	**-2679.46**	**0.045**
		NBZOAC02	$P2_1/c$	(+0.39)	0.073
3,5-dinitrobenzoic acid	**$C_7H_4N_2O_6$**	**CUKCAM10**	***A*2/*a***	**-3034.96**	**0.044**
		CUKCAM01	$P2_1/c$	(+0.49)	0.069
3-(*N*,*N*-dimethyl-amino)-benzoic acid	**$C_9H_{11}N_1O_2$**	**TACGUZ**[d]	-	**-3360.47**	**0.081**
4-(*N*,*N*-dimethyl-amino)-benzoic acid	**$C_9H_{11}N_1O_2$**	**PDABZA01**	**Form I**	**-3363.91**	**0.068**
		PDABZA03[g]	Form III	(+0.50)	0.069
		PDABZA02	Form II	(+0.87)	0.073
2-chloro-4-nitro-benzoic acid	**$C_7H_4Cl_1N_1O_4$**	**VOLZEC**	**Form I**	**-2640.68**	**0.130**
		VOLZEC01	Form II	(+0.11)	0.075
niflumic acid	**$C_{13}H_9F_3N_2O_3$**	**NIFLUM10**[d]	**-**	**-4515.08**	**0.065**
flufenamic acid	**$C_{14}H_{10}F_3N_1O_2$**	**FPAMCA**	**Form III**	**-4618.15**	**0.088**
		FPAMCA11	Form I	(+0.62)	0.111
tolfenamic acid	**$C_{14}H_{12}Cl_1N_1O_2$**	**KAXXAI**	**Form II**	**-4559.62**	**0.072**
		KAXXAI01	Form I	(+1.12)	0.058
		KAXXAI02	Form III	(+1.25)	0.100
		KAXXAI03	Form IV	(+1.25)	0.054
		KAXXAI04[g]	Form V	(+2.61)	0.063

mefenamic acid	**$C_{15}H_{15}N_1O_2$**	**XYANAC**	**-**	**-4976.55**	**0.084**
iodine	**I_2**	**icsd_67706**	**-**	**-83.63**	**0.080**
deuterium chloride	**D_1Cl_1**	**icsd_27037**	**-**	**-148.54**	**0.069**
deuterium iodide	**D_1I_1**	**icsd_40251**	**-**	**-118.92**	**0.189**
nitric acid	**$H_1N_1O_3$**	**icsd_166941**	**high pressure**	**-677.05**	**0.147**
		icsd_166940[g]	low temperature	(+0.89)	0.294
hydrogen perchlorate	**$H_1Cl_1O_4$**	**icsd_63679**	**-**	**-597.85**	**0.077**
phosphoric acid	**$H_3P_1O_4$**	**icsd_15887**	**-**	**-1113.13**	**0.111**
formamide	**$C_1H_3N_1O_1$**	**FORMAM02**	**-**	**-838.52**	**0.057**
squaric acid	**$C_4H_2O_4$**	**KECYBU17**	**triclinic**	**-1629.38**	**0.173**
		KECYBU06	monoclinic	(+0.04)	0.028
resorcinol	**$C_6H_6O_2$**	**RESORA03**	**alpha**	**-2099.89**	**0.051**
		RESORA09	beta	(+0.45)	0.099
hydroquinone	**$C_6H_6O_2$**	**HYQUIN05**	**beta**	**-2098.62**	**0.035**
		HYQUIN06	alpha	(+0.20)	0.069
		HYQUIN	gamma	(+1.13)	0.086
fumaric acid monoethyl ester	**$C_6H_8O_4$**	**XUCQIV**	**-**	**-2590.89**	**0.040**
***p*-tetrafluoro-diiodo-benzene**	**$C_6F_4I_2$**	**ZZZAVM01**	**high temperature**	**-1666.54**	**0.060**
picric acid	**$C_6H_3N_3O_7$**	**PICRAC12**	**-**	**-3011.59**	**0.113**
chloranilic acid	**$C_6H_2Cl_2O_4$**	**CLANAC11**	**-**	**-2159.72**	**0.045**
orcinol	**$C_7H_8O_2$**	**EWAMAR**	**Form I**	**-2486.23**	**0.049**
		EWAMAR01	Form II	(+0.32)	0.109
saccharin	**$C_7H_5N_1O_3S_1$**	**SCCHRN03**	**-**	**-2651.83**	**0.039**
sulfamethazine	**$C_{12}H_{14}N_4O_2S_1$**	**SLFNMD01**	**Form I**	**-4914.68**	**0.125**
carbamazepine	**$C_{15}H_{12}N_2O_1$**	**CBMZPN01**	**Form III**	**-4732.12**	**0.066**
		CBMZPN12	Form IV	(+0.77)	0.048
		CBMZPN11	Form I	(+0.81)	0.062
		CBMZPN16	Form V	(+1.18)	0.081
		CBMZPN03[d]	Form II	(+1.66)	0.067
norfloxacin	**$C_{16}H_{18}F_1N_3O_3$**	**VETVOG**[h]	**triclinic**	**-6077.68**	**0.158**
celecoxib	**$C_{17}H_{14}F_3N_3O_2S_1$**	**DIBBUL**	**-**	**-6031.44**	**0.084**
ethyl paraben	**$C_9H_{10}O_3$**	**FEGLEI**[d]	**-**	**-3239.75**	**0.102**

[a] CSD = Cambridge Structural Database.[18] [b] $E_{DFT\text{-}D}$ is the minimised lattice energy per mole of molecule, calculated by the DFT-D method. Numbers in brackets refer to the energy differences relative to the most stable polymorph, which is given in bold face. [c] The root-mean-squared atomic displacement after optimisation, in comparison to the experimental structure, excluding hydrogen atoms. [d] Missing hydrogen atoms in the experimental structures were added manually prior to DFT-D optimisation. [e] The position of a COOH proton was edited prior to DFT-D optimisation. [f] The structure was converted from the $P112_1/c$ space group into $P2_1/c$ prior to DFT-D optimisation. [g] For structures with disordered atoms, every possible starting configuration was DFT-D optimised and the most stable results are shown. [h] The CSD contains another norfloxacin structure, VETVOG01, which was later discovered to be a sesquihydrate[19] and therefore not considered in this study.

DFT-D lattice energies and calculated stabilities of co-crystals and salts

81 co-crystals involving nicotinamide and isonicotinamide, 3 hybrid salt co-crystals of isonicotinamide, and 18 salts involving nicotinamide, isonicotinamide and picolinamide were optimised by the DFT-D method. Their lattice energies are expressed in kcal·mol^{-1} per mole of formula unit and their stabilities are calculated relative to the most stable (as determined by the DFT-D method) polymorphs of their pure component co-formers. The results are reported in Table S2.

Table S2: DFT-D lattice energies of nicotinamide, isonicotinamide and picolinamide co-crystals and salts, and their stabilities relative to the lattice energies of the pure co-former crystals.

CSD reference code[a]	Co-crystal composition	E_{DFT-D} [b] (kcal·mol^{-1})	ΔE[c] (kcal·mol^{-1})	RMSD[d] (Å)
CUYXUQ[e]	(citric acid)·(nicotinamide)$_2$	-7778.18	-9.00	0.106
RUYHEZ	(4-hydroxybenzoic acid)·(nicotinamide)	-4820.03	-5.59	0.041
NUKXUN	(malonic acid)·(nicotinamide)$_2$	-6311.28	-5.49	0.051
DUZPAQ	(succinic acid)·(nicotinamide)$_2$	-6700.03	-4.55	0.041
SUTTUX[e]	(2-chloro-4-nitrobenzoic acid)·(nicotinamide)	-4977.97	-4.20	0.306
NUKZOJ	(sebacic acid)·(nicotinamide)$_2$	-9009.48	-4.09	0.093
NUKYOI	(adipic acid)·(nicotinamide)$_2$	-7469.96	-4.08	0.054
XAQPUB[e]	(3,5-dinitrobenzoic acid)·(3-(*N*,*N*-dimethylamino)-benzoic acid)·(nicotinamide)	-8732.35	-3.84	0.151
XAQQIQ	(3-hydroxybenzoic acid)·(nicotinamide)	-4817.26	-3.70	0.097
NUKZEZ	(suberic acid)·(nicotinamide)$_2$	-8238.98	-3.67	0.072
NUKYEY	(glutaric acid)·(nicotinamide)	-4749.97	-3.56	0.046
EWAQAV	(orcinol)·(nicotinamide)$_4$	-11822.02	-3.45	0.067
NUKYAU	(fumaric acid)·(nicotinamide)	-4172.32	-3.24	0.067
SODDOF	(2-hydroxybenzoic acid)·(nicotinamide)	-4818.03	-3.22	0.066
NUKZAV	(suberic acid)·(nicotinamide)	-5905.06	-2.84	0.134
EXAQIE	(tolfenamic acid) ·(nicotinamide)$_2$	-9228.40	-2.61	0.206
IACNCA	(3-indolylacetic acid)·(nicotinamide)	-5740.96	-2.40	0.199
FIFLAI	(heptadecanoic acid)·(nicotinamide)	-9213.92	-2.02	0.157
NUKYUO	(pimelic acid)·(nicotinamide)	-5518.83	-1.94	0.057
EXAQOK	(mefenamic acid) ·(nicotinamide)$_2$	-9644.56	-1.84	0.155
EXAQEA	(niflumic acid) ·(nicotinamide)	-6849.78	-1.61	0.120
GOGQID	(ethyl paraben)·(nicotinamide)	-5574.44	-1.61	0.045
NUKZID	(azelaic acid)·(nicotinamide)	-6288.87	-1.50	0.492
NUKYIC	(adipic acid)·(nicotinamide)	-5134.28	-1.50	0.072
JILZOU	(mandelic acid)·(nicotinamide)	-5189.94	-1.40	0.092
JEMDIP	(N-hexadecanoic acid)·(nicotinamide)	-8828.27	-1.32	0.179
UCOTUC	(dodecanoic acid)·(nicotinamide)	-7286.09	-1.22	0.180
EXAQAW[e]	(flufenamic acid)·(nicotinamide)	-6952.45	-1.22	0.128
SODDIZ	(ibuprofen)·(nicotinamide)	-6962.08	-1.06	0.069
PEQBES	(octadecanoic acid)·(nicotinamide)	-9598.75	-0.78	0.181
UMUYOR	(isonicotinamide)·(nicotinamide)	-4666.65	-0.60	0.048
SOGLAC	(ibuprofen)·(nicotinamide)	-6961.49	-0.48	0.180
UNEZES	(carbamazepine)·(nicotinamide)	-7065.35	-0.15	0.069
VIGDAR[f]	(celecoxib)·(nicotinamide)	-8362.70	1.82	1.706
ULAWAF02	(oxalic acid)·(isonicotinamide)$_2$	-5925.54	-14.27	0.067

ULAWAF	(oxalic acid)·(isonicotinamide)$_2$	-5924.92	-13.65	0.061
ULAWEJ	(malonic acid)·(isonicotinamide)$_2$	-6315.42	-9.89	0.128
LUNNOX	(fumaric acid)·(isonicotinamide)$_2$	-6508.80	-6.89	0.041
ULAWUZ	(adipic acid)·(isonicotinamide)$_2$	-7472.13	-6.51	0.031
LUNNAJ	(monochloroacetic acid)·(isonicotinamide)	-3405.39	-6.14	0.048
LUNPEP	(thiodiglycolic acid)·(isonicotinamide)$_2$	-6785.05	-6.09	0.057
LUNNUD01	(succinic acid)·(isonicotinamide)$_2$	-6701.06	-5.83	0.029
XAQPOV	(3,5-dinitrobenzoic acid)·(3,4-dimethoxycinnamic acid)·(isonicotinamide)	-9338.57	-5.35	0.103
BUFBIP	(3,5-dinitrobenzoic acid)·(4-(*N*,*N*-(dimethyl-amino)-benzoic acid)·(isonicotinamide)	-8737.14	-5.31	0.126
YIPCIK	(*p*-tetrafluoro-diiodobenzene)·(isonicotinamide)$_2$	-6337.65	-5.19	0.126
AJAKEB	(4-nitrobenzoic acid)·(isonicotinamide)	-5017.56	-5.14	0.047
LUNMEM	(3-hydroxybenzoic acid)·(isonicotinamide)	-4818.27	-4.84	0.061
ASAXOH	(3-nitrobenzoic acid)·(isonicotinamide)	-5015.89	-4.55	0.038
ULAWOT	(glutaric acid)·(isonicotinamide)$_2$	-7083.73	-4.48	0.059
MOVTOH	(benzoic acid)$_2$·(isonicotinamide)	-6971.71	-4.45	0.085
VAKTUX	(resorcinol)·(isonicotinamide)$_2$	-6769.99	-4.17	0.071
BUFQAU	(3,5-dinitrobenzoic acid)·(ferulic acid)·(isonicotinamide)	-8967.68	-4.07	0.133
BUDZUV	(3,5-dinitrobenzoic acid)·(3-methylbenzoic acid)·(isonicotinamide)	-8076.97	-4.05	0.094
VAKVIN	(hydroquinone)·(isonicotinamide)$_2$	-6768.55	-4.01	0.081
AJAKIF	(3,5-dinitrobenzoic acid)·(4-methylbenzoic acid)·(isonicotinamide)	-8077.43	-3.93	0.080
VETVUM	(norfloxacin)·(chloroform)·(isonicotinamide)	-8871.59	-3.74	0.098
BUDWEC	(benzoic acid)·(isonicotinamide)	-4653.67	-3.55	0.057
VAKTOR	(4-hydroxybenzoic acid)·(isonicotinamide)	-4817.79	-3.48	0.401
ASAXUN	(4-fluorobenzoic acid)·(isonicotinamide)	-4661.18	-3.19	0.061
ISIJIE	(suberic acid)·(isonicotinamide)	-5905.04	-2.94	0.039
HANBOO	(propionic acid)$_2$·(isonicotinamide)	-5309.93	-2.93	0.114
ISIJEA	(pimelic acid)·(isonicotinamide)	-5519.66	-2.89	0.092
JAWWAG	(acetic acid)·(isonicotinamide)	-3438.40	-2.88	0.061
ROLFOO[f]	(2-phenylpropionic acid)·(isonicotinamide)	-5420.26	-2.84	0.119
EWAQID	(orcinol)·(isonicotinamide)$_2$	-7154.87	-2.71	0.069
LUNMAI	(cinnamic acid)·(isonicotinamide)	-5235.85	-2.65	0.049
ULAXEK	(adipic acid)·(isonicotinamide)	-5135.18	-2.52	0.049
ISIJAW	(azelaic acid)·(isonicotinamide)	-6289.75	-2.52	0.086
ROLFUU	(2-phenylbutyric acid)·(isonicotinamide)	-5804.63	-2.37	0.035
ULAXAG	(glutaric acid)·(isonicotinamide)	-4748.58	-2.29	0.080
XAQQEM	(2-hydroxybenzoic acid)·(isonicotinamide)	-4816.73	-2.04	0.089
RONDAA	(2-phenylpropionic acid)·(isonicotinamide)	-5419.32	-1.89	0.050
LUNPAL	(mandelic acid)·(isonicotinamide)	-5190.16	-1.75	0.067
LUNNEN	(fumaric acid monoethyl ester)·(isonicotinamide)	-4925.59	-1.74	0.082
UMUYUX	(clofibric acid)·(isonicotinamide)	-5919.10	-1.73	0.061
YIPCEG	(iodine)·(isonicotinamide)	-2418.18	-1.60	0.041
UMUZAE	(diclofenac)·(isonicotinamide)	-6854.21	-1.51	0.088
RONDEE	(2-phenylbutyric acid)·(isonicotinamide)	-5803.47	-1.20	0.044
LUNMIQ	(3-(*N*,*N*-dimethylamino)benzoic acid)·(isonicotinamide)	-5694.27	-0.84	0.071
GAVHER	(formamide)·(isonicotinamide)	-3172.08	-0.60	0.067
LOFKIB	(carbamazepine)·(isonicotinamide)	-7064.75	0.32	0.041
LOFKIB01	(carbamazepine)·(isonicotinamide)	-7064.41	0.67	0.136
EXAPEZ	(sulfamethazine)·(picolinamide)	-7252.06	-3.60	0.102

XOZWAL	(isonicotinamidium)·(perchlorate)	-2959.36	-28.54	0.071
LICLAL	(nicotinamidium)·(perchlorate)	-2959.35	-28.41	0.111
VUFPIV	(nicotinamidium)·(iodide)	-2476.14	-24.13	0.155
TAFBUX	(nicotinamidium)·(chloride)	-2503.01	-21.38	0.043
VAXLIP	(nicotinamidium)·(nitrate)	-3026.71	-16.58	0.085
EMINUJ	$(nicotinamidium)_2$·(squarate)	-6312.11	-16.56	0.039
DAYFEP	$(isonicotinamidium)_2$·(squarate)	-6311.40	-16.09	0.041
LACTEO	(nicotinamidium)·(dihydrogen phosphate)	-3459.23	-13.01	0.057
HILLIY	(isonicotinamidium)·(dihydrogen phosphate)	-3457.70	-11.60	0.056
LICLEP01	(nicotinamidium)·(hydrogen oxalate)	-3589.92	-11.48	0.139
YICJEA[e]	(nicotinamidium)·(trifluoroacetate)	-3461.06	-10.68	0.174
GAHJAB[g]	(isonicotinamidium)·(picrate)	-5354.86	-10.31	0.173
POVZIK	(nicotinamidium)·(hydrogen chloranilate)	-4502.87	-10.06	0.075
POVZOQ	(isonicotinamidium)·(hydrogen chloranilate)	-4502.20	-9.52	0.051
IPOZAO	(nicotinamidium)·(picrate)	-5353.51	-8.84	0.141
JAWVUZ	(isonicotinamide)·(isonicotinamidium)·(hydrogen tartarate)	-7010.96	-7.12	0.157
POVZEG	(picolinamidium)·(hydrogen chloranilate)	-4499.91	-6.42	0.036
EYIXAL	(picolinamidium)·(squarate)	-3969.42	-6.27	0.033
VEQHIJ	(isonicotinamidium)·(saccharinate)	-4989.09	-4.31	0.069

[a] CSD = Cambridge Structural Database.[18] [b] $E_{DFT\text{-}D}$ is the minimised lattice energy of a co-crystal (or a salt) calculated by the DFT-D method and is expressed in kcal per mole of formula unit which consist of two or more co-former molecules in a fixed stoichiometric ratio. [c] ΔE is the calculated energy change in forming a co-crystal or salt from the most stable polymorphs of the pure co-formers. [d] The root-mean-square atomic displacement after optimisation, in comparison to the experimental structure, excluding hydrogen atoms. [e] For structures with disordered atoms, every possible starting configuration was DFT-D optimised and the most stable result is shown. [f] Disordered atoms labelled with "?" in the CSD cif file were ignored in the DFT-D optimisation. [g] Missing hydrogen atoms in the experimental structures were added manually prior to DFT-D optimisation.

Lattice energy minimisations of 24 alternative celecoxib:nicotinamide co-crystal structures

The experimental co-crystal structure of VIGDAR[20] reports disordered fluorine atoms, which were rationalised before DFT-D optimisation. The reported crystal structure also possesses unoccupied hydrogen bonding sites and has S=O bond lengths of 1.596 and 1.405 Å. In addition, the reported C=O bond of the nicotinamide amide group is longer than its C-N bond. 24 variations of the celecoxib:nicotinamide co-crystal packing were investigated by altering the molecular conformations, including; rotation of the pyridine ring by 180° (2 conformations), rotation of the nicotinamide amide group by 180° (2 conformations), rotation of the sulfonamide group by 120° (3 conformations) and consideration of the disordered trifluoromethyl group (2 conformations) in celecoxib. All 24 (2x2x3x2) structures were optimised with the DFT-D method and converged to 12 distinct structures. Both starting conformations of the trifluoromethyl group, Pos_a and Pos_b, always led to the same optimised structure. Rotating the pyridine ring by 180°, in general, led to less stable structures, except for those with conformer_10a and conformer_10b (see Table S3), in which intermolecular hydrogen bonds were formed between the pyridine ring and the sulfonamide during the optimisations. Structures with conformer_5a and conformer_5b involve a rotation of the amide group by 180° in nicotinamide and an anti-clockwise rotation of the sulfonamide group by 120° in celecoxib (viewing along the S-C bond), which facilitates hydrogen bonding between the two molecules. These two structures converged to the most stable structure of all. Note that in both conformer_5a and conformer_5b, the nitrogen atom of the amide group of nicotinamide occupies a position which corresponds to the amide oxygen in the reported VIGDAR structure, whilst the nitrogen atom of the sulfonamide group of celecoxib occupies a position which corresponds to the sulfonyl oxygen with the longer S=O bond in the reported VIGDAR structure. Hence, based on these geometric comparisons and lattice energy considerations, we are confident that the real co-crystal structure of celecoxib and nicotinamide corresponds to the optimised structure with conformer_5a or conformer_5b, except that the trifluoromethyl group is disordered. Note that this most stable co-crystal structure is still 0.36 kcal·mol^{-1} less stable than the separate nicotinamide and celecoxib structures. This small energy difference is, at least in part, due to the stabilising effect of the disordered trifluoromethyl group, which is not taken into account in the lattice energy calculations. A cif containing the proposed celecoxib:nicotinamide co-crystal structure is provided as a separate file.

Table S3: Effect of 24 variations in molecular conformations in the celecoxib:nicotinamide 1:1 co-crystal structure on the DFT-D minimised lattice energy. The structure with conformer_1a corresponds to the structure reported in the CSD with reference code VIGDAR.[20]

Starting conformation	Fluorine atoms[a]	Pyridine ring[b]	Amide group[c]	Sulfon-amide[d]	E_{DFT-D} [e] (kcal·mol^{-1})	ΔE[f] (kcal·mol^{-1})
conformer_1a	Pos_a	+0°	+0°	+0°	-8362.70	1.82
conformer_1b	Pos_b	+0°	+0°	+0°		
conformer_2a	Pos_a	+0°	+0°	+120°	-8357.00	7.52
conformer_2b	Pos_b	+0°	+0°	+120°		
conformer_3a	Pos_a	+0°	+0°	+240°	-8353.94	10.58
conformer_3b	Pos_b	+0°	+0°	+240°		
conformer_4a	Pos_a	+0°	+180°	+0°	-8353.24	11.28
conformer_4b	Pos_b	+0°	+180°	+0°		
conformer_5a	Pos_a	+0°	+180°	+120°	-8364.16	0.36
conformer_5b	Pos_b	+0°	+180°	+120°		
conformer_6a	Pos_a	+0°	+180°	+240°	-8360.65	3.87
conformer_6b	Pos_b	+0°	+180°	+240°		
conformer_7a	Pos_a	+180°	+0°	+0°	-8358.60	5.92
conformer_7b	Pos_b	+180°	+0°	+0°		
conformer_8a	Pos_a	+180°	+0°	+120°	-8351.03	13.49
conformer_8b	Pos_b	+180°	+0°	+120°		
conformer_9a	Pos_a	+180°	+0°	+240°	-8351.09	13.43
conformer_9b	Pos_b	+180°	+0°	+240°		
conformer_10a	Pos_a	+180°	+180°	+0°	-8358.04	6.48
conformer_10b	Pos_b	+180°	+180°	+0°		
conformer_11a	Pos_a	+180°	+180°	+120°	-8361.26	3.27
conformer_11b	Pos_b	+180°	+180°	+120°		
conformer_12a	Pos_a	+180°	+180°	+240°	-8357.22	7.30
conformer_12b	Pos_b	+180°	+180°	+240°		

[a] "Pos_a" and "Pos_b" stand for the positions of the fluorine atoms without and with the label "?" in the cif file, respectively. [b] "+0°" stands for the conformation of the pyridine ring in the original structure, whilst "+180°" represents a rotation by 180°. [c] "+0°" stands for the conformation of the amide group in the original structure, whilst "+180°" represents a rotation by 180°. [d] "+0°" stands for the conformation of the sulfonamide group in the original structure, whilst "+120°" and "+240°" represent rotations by 120° and 240° respectively in an anti-clockwise direction, viewing along the S-C bond. [e] E_{DFT-D} is the minimised lattice energy of the co-crystal calculated by the DFT-D method and is expressed in kcal per mole of building blocks which consist of one nicotinamide molecule and one celecoxib molecule. [f] ΔE is the difference in lattice energy between an optimised co-crystal structure and the sum of lattice energies of nicotinamide (E_{DFT-D} of NICOAM01 in Table 1) and celecoxib (E_{DFT-D} of DIBBUL in Table 1).

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