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PAPER

Covalent assistance to supramolecular synthesis: modifying the drug functionality of the antituberculosis API isoniazid *in situ* during co-crystallization with GRAS and API compounds†

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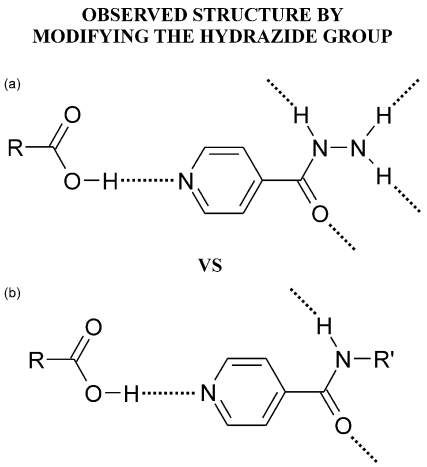
The anti-tuberculosis molecule isonicotinic acid hydrazide (isoniazid) is a promising molecule in the supramolecular synthesis of multi-component molecular complexes and also allows for its biological activity to be improved and modified by a simple covalent reaction. The low temperature crystal structures of both isoniazid (**1**) and the related *N*′-(propan-2-ylidene)isonicotinohydrazide molecule (**2**), the latter known to be a more effective agent against *Mycobacterium tuberculosis*, are reported. In addition, these two molecules were then co-crystallized with the same three Generally Regarded As Safe (GRAS) molecules, succinic acid, 4-hydroxybenzoic acid and 2-hydroxybenzoic acid, to produce the following pharmaceutical co-crystals: (isonicotinic acid hydrazide)$_2$·(succinic acid) **3**, (*N*′-(propan-2-ylidene)isonicotinohydrazide)$_2$·(succinic acid) **4**, (isonicotinic acid hydrazide)·(4-hydroxybenzoic acid) **6**, (*N*′-(propan-2-ylidene)isonicotinohydrazide)·(4-hydroxybenzoic acid) **7**, (isonicotinic acid hydrazide)·(2-hydroxybenzoic acid) **8**, and (*N*′-(propan-2-ylidene)isonicotinohydrazide)·(2-hydroxybenzoic acid) **9**. In addition, a co-crystal using 2-butanone as a modifier is also reported, (*N*′-(butan-2-ylidene)isonicotinohydrazide)$_2$·(succinic acid) **5**. Drug–drug co-crystals were also made with the anti-HIV compound 2-chloro-4-nitrobenzoic acid: (isonicotinic acid hydrazide)·(2-chloro-4-nitrobenzoic acid) **10**, and (*N*′-(propan-2-ylidene)isonicotinohydrazide)·(2-chloro-4-nitrobenzoic acid) **11**. All the co-crystals use the carboxylic acid···pyridine hydrogen bond to connect the GRAS or drug molecule to the pyridine ring. In general, the co-crystals with the modified isoniazid feature the *C*(4) homosynthon, and those with the original isoniazid a variety of homo- and heterosynthons. By comparing the melting points of the co-crystals that use isoniazid and those that use the modified isoniazid, a reduction in melting point is observed.

Introduction

The active pharmaceutical ingredient (API) isonicotinic acid hydrazide (isoniazid) has received renewed interest from the crystal engineering community due to its robust interactions with carboxylic acid containing molecules, as well as with other APIs. Co-crystals formed with Generally Regarded As Safe (GRAS) molecules have been especially successful, and hence it makes isoniazid an ideal molecule to do studies in the rapidly expanding field of pharmaceutical co-crystals.[1] Additionally, isoniazid is not only an ideal supramolecular reagent that forms co-crystals with



Scheme 1 Observed structures before (a) and after (b) modification of the hydrazide group.

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† Electronic supplementary information (ESI) available: PXRD patterns for **2–11** and DSC traces for all compounds, as well as cif files for all compounds. CCDC reference numbers 847197 (**1**), 847198 (**2**), 746445 (**3**), 847200 (**4**), 847201 (**5**), 746449 (**6**) and 847203–847207 (**7–11**, respectively). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ce06310c

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a number of co-crystal formers, but also allows for its hydrogen bonding functionality to be *modified*.[2] By adding a ketone to the crystallization solution, the hydrazide functional group on the isoniazid reacts in a condensation reaction with the ketone, and the two amine H atoms from the N atom are replaced by an inert hydrogen bonding hydrocarbon substituent. As only the amide group is now left intact, the hydrogen bonding interactions become simpler and involve chains of N–H···O hydrogen bonds to connect the isoniazid molecules together. The modification does not end there. If suitably large ketones are used, for example sterically bulky phenyl groups, the remaining amide H atom of the amide group can be prevented from approaching acceptor atoms, including the O atom of the amide, thus *masking* the amide H atom from any further intermolecular interactions. The modifying and masking fall under the concept of the covalent assistance to supramolecular synthesis purview recently introduced into crystal engineering (Scheme 1).[3]

The reaction of isoniazid with ketones has been used previously to modify, or improve, the efficacy of the molecule on a biological level. The efficacy against bacteria has especially been studied using a large number of ketones.[4] For example, the use of 2-propanone shows an increase in activity against

Table 1 Crystallographic data for **1–5** and **6–11**

	1	**2**	**3**[a]	**4**	**5**
Empirical formula	$C_6H_7N_3O$	$C_9H_{11}N_3O$	$C_8H_{10}N_3O_3$	$C_{11}H_{14}N_3O_3$	$C_{12}H_{16}N_3O_3$
Molecular weight	137.15	177.21	196.19	236.25	250.28
Crystal size/mm	0.48 × 0.25 × 0.16	0.40 × 0.40 × 0.40	0.44 × 0.42 × 0.40	0.65 × 0.20 × 0.10	0.50 × 0.20 × 0.08
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	*Pccn*	$P2_1/n$	$P2_1/c$	$P2_1/c$
T/K	173	173	173	173	173
a/Å	3.7828(1)	12.9790(5)	6.9976(4)	18.0455(3)	5.0602(3)
b/Å	11.2948(4)	17.6437(3)	19.5601(10)	8.2643(3)	31.8299(17)
c/Å	14.6870(6)	7.9695(2)	7.1495(5)	7.7750(6)	8.0552(5)
α/°	90	90	90	90	90
β/°	90	90	114.892(8)	94.445(2)	98.780(3)
γ/°	90	90	90	90	90
V/Å^3	628.25(4)	1825.00(9)	887.67(9)	1156.02(10)	1282.21(13)
Z	4	8	4	4	4
$\rho_{(calc)}$/g cm^{-3}	1.450	1.290	1.468	1.357	1.296
μ/mm^{-1}	0.105	0.719		0.101	0.095
F(000)	288	752		500	532
Scan range (*θ*)/°	2.27 to 27.99	4.23 to 67.51		2.26 to 28.00	2.56 to 28.00
Total reflections	5027	10 141		20 671	20 982
Unique reflections [*R*(int)]	916 [0.0298]	1642 [0.0448]		2782 [0.0288]	3092 [0.0438]
No. data with $I \geq 2\sigma(I)$	876	1408		2491	2520
Parameters	100	123		162	198
*R*1 [$I > 2\sigma(I)$]	0.0299	0.0435		0.0497	0.0559
w*R*2 (all data)	0.0805	0.1243		0.1421	0.1564
CCDC no.	847197	847198	746445	847200	847201

	6[a]	**7**	**8**	**9**	**10**	**11**
Empirical formula	$C_{13}H_{13}N_3O_4$	$C_{16}H_{13}N_3O_4$	$C_{13}H_{13}N_3O_4$	$C_{16}H_{17}N_3O_4$	$C_{13}H_{11}ClN_4O_5$	$C_{64}H_{60}Cl_4N_{16}O_{20}$
Molecular weight	275.26	315.33	275.26	315.33	338.71	1515.08
Crystal size/mm	0.40 × 0.40 × 0.40	0.35 × 0.25 × 0.10	0.50 × 0.08 × 0.05	0.55 × 0.46 × 0.44	0.32 × 0.26 × 0.15	0.55 × 0.45 × 0.35
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1$
T/K	173	173	173	173	173	173
a/Å	12.9083(5)	11.0130(4)	11.2793(5)	7.3504(4)	9.1538(3)	6.8490(2)
b/Å	4.9898(1)	13.1213(4)	3.7452(2)	29.8032(16)	11.0592(4)	38.7853(12)
c/Å	20.3294(9)	11.9425(4)	29.8282(15)	7.6524(4)	15.0521(5)	12.7324(4)
α/°	90	90	90	90	89.085(2)	90
β/°	91.850(4)	114.128(2)	93.567(4)	112.787(3)	72.649(2)	98.265(2)
γ/°	90	90	90	90	89.906(2)	90
V/Å^3	1308.73(8)	1574.98(9)	1257.60(11)	1545.54(14)	1454.25(9)	3347.11(18)
Z	4	4	4	4	4	2
$\rho_{(calc)}$/g cm^{-3}	1.397	1.330	1.454	1.355	1.547	1.503
μ/mm^{-1}		0.097	0.110	0.099	0.296	0.266
F(000)		664	576	664	696	1568
Scan range (*θ*)/°		2.12 to 27.99	1.37 to 27.99	2.73 to 27.99	1.42 to 28.00	1.93 to 28.00
Total reflections		24 789	8409	16 272	16 205	42 752
Unique reflections [*R*(int)]		3813 [0.0279]	2987 [0.0403]	3721 [0.0257]	6699 [0.0306]	14216 [0.0298]
No. data with $I \geq 2\sigma(I)$		3153	2208	3278	4861	13 432
Parameters		219	196	219	439	949
*R*1 [$I > 2\sigma(I)$]		0.0384	0.0443	0.0419	0.0697	0.0490
w*R*2 (all data)		0.1125	0.1130	0.1120	0.2086	0.1189
CCDC no.	746449	847203	847204	847205	847206	847207

[a] Taken from ref. 1.

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Mycobacterium tuberculosis. 2-Propanone is the most convenient ketone to modify the hydrogen bonding functionality with as it can also function as a crystallization solvent, but it has a limited masking reach due to its sterically small methyl groups.

In this report, we ask the question: How are the structures and hydrogen bonding patterns of pharmaceutical isoniazid co-crystals altered in response to the modification of its hydrogen bonding functionality and the introduction of different co-crystal formers?

Experimental

All reagents were purchased from commercial sources and used without further purification. All solvents are of AP-grade.

Isonicotinic acid hydrazide, 1

Crystals of isoniazid were grown by slow evaporation of a methanol solution. Colourless needles were obtained after three days.

N′-(Propan-2-ylidene)isonicotinohydrazide, 2

0.200 g of isonicotinic acid hydrazide (1.46 mmol) was dissolved in 2 ml acetone and kept below the boiling point of acetone for 2 hours. Needles of the product were obtained upon cooling to room temperature.

(Isonicotinic acid hydrazide)$_2$·(succinic acid), 3

See ref. 1.

(*N′*-(Propan-2-ylidene)isonicotinohydrazide)$_2$·(succinic acid), 4

0.200 g of isonicotinic acid hydrazide (1.46 mmol) and 0.086 g of succinic acid (0.73 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (4 ml) and acetone (1 ml), refluxed in a closed vial for six hours, and left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.

(*N′*-(Butan-2-ylidene)isonicotinohydrazide)$_2$·(succinic acid), 5

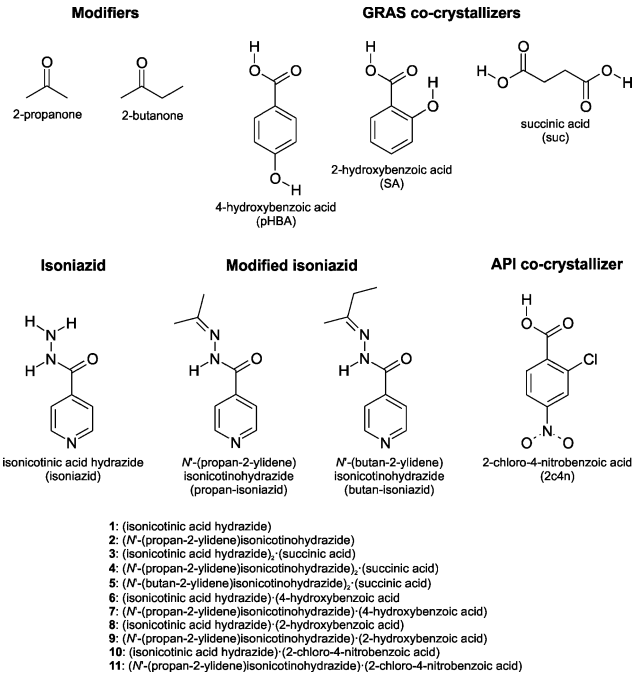
0.100 g of isonicotinic acid hydrazide (0.730 mmol) and 0.043 g of succinic acid (0.36 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (4 ml) and 4 drops of 2-butanone, refluxed in a closed vial for six hours, and left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.

(Isonicotinic acid hydrazide)·(4-hydroxybenzoic acid), 6

See ref. 1.

(*N′*-(Propan-2-ylidene)isonicotinohydrazide)·(4-hydroxybenzoic acid), 7

0.100 g of isonicotinic acid hydrazide (0.730 mmol) and 0.100 g of 4-hydroxybenzoic acid (0.73 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (4 ml) and acetone (4 ml), refluxed in a closed vial for six hours, and left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.



Scheme 2 Diagrams of the molecules used to modify the isoniazid drug molecule, as well as the co-crystal and drug formers used to prepare co-crystals **3–11**.

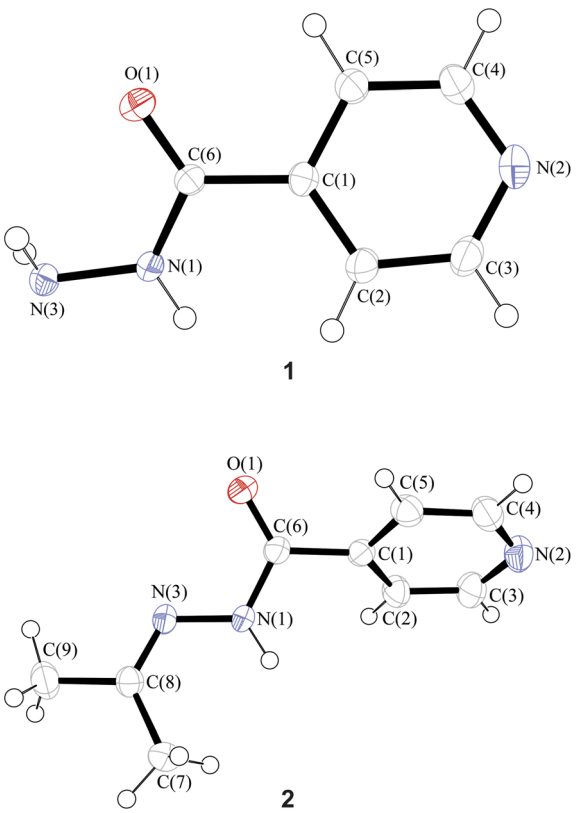


Fig. 1 The contents of the asymmetric unit for original (**1**) and modified (**2**) isoniazid, showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.

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(Isonicotinic acid hydrazide)·(2-hydroxybenzoic acid), 8

0.100 g of isonicotinic acid hydrazide (0.730 mmol) and 0.100 g of 2-hydroxybenzoic acid (0.73 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (3 ml) and left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.

(*N*′-(Propan-2-ylidene)isonicotinohydrazide)·(2-hydroxybenzoic acid), 9

0.200 g of isonicotinic acid hydrazide (1.46 mmol) and 0.200 g of 2-hydroxybenzoic acid (1.46 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (3 ml) and acetone (3 ml), refluxed in a closed vial for six hours, and left to stand at

Table 2 Geometrical parameters for hydrogen bonds in compounds **1–11**

D–H···A	*d*(D–H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	∠(D–H···A)/°	Symmetry transformations
1					
N(1)–H(1)···N(3)	0.90(2)	2.05(2)	2.919(2)	163(2)	$x - 1/2, -y + 3/2, -z + 1$
N(3)–H(3A)···N(2)	0.92(2)	2.14(2)	3.046(2)	172(2)	$-x + 1/2, -y + 1, z - 1/2$
N(3)–H(3B)···N(2)	0.89(2)	2.58(2)	3.157(2)	123	$-x + 3/2, -y + 1, z - 1/2$
2					
N(1)–H(1)···O(1)	0.88(2)	2.19(2)	3.000(2)	153(2)	$-x + 1/2, y, z + 1/2$
3					
N(1)–H(1)···N(3)	0.87(2)	2.15(2)	2.937(2)	151(1)	$-x + 1, -y + 1, -z + 1$
N(3)–H(3A)···O(1)	0.89(2)	2.24(2)	3.006(2)	145(1)	$-x + 2, -y + 1, -z + 1$
N(3)–H(3B)···O(2)	0.91(2)	2.26(2)	3.084(2)	151(1)	$-x + 3/2, y + 1/2, -z + 3/2$
O(2)–H(2)···N(2)	0.98(2)	1.65(2)	2.617(1)	172(2)	—
C(3)–H(3)···O(3)	0.93	2.71	3.334(2)	125	—
4					
N(1)–H(1)···O(1)	0.89(2)	2.30(2)	3.1805(19)	169(2)	$x, -y + 1/2, z - 1/2$
O(2)–H(2)···N(2)	0.89(3)	1.84(3)	2.7244(19)	173(3)	—
5					
N(1)–H(1)···O(1)	0.89(2)	2.25(2)	3.127(2)	168(2)	$x - 1, y, z$
O(2A)–H(2A)···N(2)	0.84	1.82	2.643(5)	165	—
O(2B)–H(2B)···N(2)	0.84	1.90	2.732(5)	171	—
6					
N(1)–H(1)···O(1)	0.875(2)	1.98(2)	2.849(1)	172(1)	$x, y - 1, z$
N(3)–H(3A)···O(3)	0.932(2	2.04(2)	2.948(2)	164(1)	$-x + 1, -y + 1, -z + 1$
N(3)–H(3B)···O(4)	0.925(2)	2.24(2)	3.126(2)	160(1)	$x - 1, -y + 3/2, z - 1/2$
O(2)–H(2)···N(2)	0.97(2)	1.72(2)	2.682(2)	171(2)	—
O(4)–H(4)···N(3)	0.876(2)	1.88(2)	2.754(1)	172(2)	$x + 1, -y + 1/2, z + 1/2$
O(4)–H(4)···N(1)	0.876(2)	2.68(2)	3.412(1)	142(1)	$x + 1, -y + 1/2, z + 1/2$
7					
N(1)–H(1)···O(4)	0.85(2)	2.66(2)	3.274(1)	131(1)	$-x + 1/2, y + 1/2, -z + 1/2$
O(2)–H(2)···N(2)	0.94(2)	1.74(2)	2.676(1)	174(2)	—
O(4)–H(4)···O(1)	0.89(2)	1.77(2)	2.624(1)	161(2)	$x - 3/2, -y + 1/2, z - 1/2$
C(4)–H(4A)···O(3)	0.95	2.61	3.278(1)	128	—
8					
N(1)–H(1)···O(4)	0.91(2)	2.05(2)	2.961(2)	173(2)	$-x + 1, -y, -z + 1$
N(3)–H(3A)···N(3)	0.90(2)	2.87(2)	3.745(2)	166(2)	$x, y + 1, z$
N(3)–H(3B)···O(1)	0.92(2)	2.16(2)	3.023(2)	156(2)	$-x + 3/2, y - 1/2, -z + 3/2$
O(2)–H(2)···N(2)	0.94(2)	1.65(2)	2.589(2)	172(2)	—
O(4)–H(4)···O(3)	0.92(2)	1.67(2)	2.556(2)	159(2)	—
9					
N(1)–H(1)···O(1)	0.90(2)	2.03(2)	2.933(1)	175(2)	$x + 1/2, -y + 1/2, z + 1/2$
O(2)–H(2)···N(2)	0.89(2)	1.80(2)	2.687(1)	174(2)	—
O(4)–H(4)···O(3)	0.89(2)	1.79(2)	2.610(1)	151(2)	—
C(4)–H(4A)···O(3)	0.95	2.49	3.200(2)	131	—
10					
N(3A)–H(3A)···O(5B)	0.79(4)	3.03(4)	3.807(3)	168(3)	$-x + 2, -y + 1, -z$
N(3A)–H(3B)···O(1A)	0.87(4)	2.11(4)	2.946(3)	161(3)	$-x + 1, -y, -z + 1$
N(1B)–H(1B)···N(3A)	0.85(4)	2.11(4)	2.911(3)	157(3)	
N(3B)–H(3C)···O(1B)	0.77(4)	2.29(4)	3.050(3)	168(4)	$-x, -y + 1, -z + 1$
N(3B)–H(3D)···O(5A)	0.83(4)	2.53(4)	3.287(3)	152(3)	$-x - 1, -y, -z + 2$
O(2A)–H(2A)···N(2A)	0.92(4)	1.69(4)	2.602(3)	171(4)	
O(2B)–H(2B)···N(2B)	0.73(4)	1.92(4)	2.642(3)	167(4)	
11					
N(1A)–H(1A)···O(1B)	0.89(4)	2.31(4)	3.151(4)	156(4)	—
N(2B)–H(2B)···O(2B)	0.88	1.86	2.718(4)	166	—
C(4B)–H(4B)···O(3B)	0.95	2.64	3.161(4)	115	—
N(1B)–H(1B)···O(1C)	0.88(4)	2.11(4)	2.979(3)	168(4)	—
N(1C)–H(1C)···O(1D)	0.87(4)	2.30(4)	3.135(4)	160(4)	—
N(1D)–H(1D)···O(1A)	0.95(4)	2.28(4)	3.145(4)	150(4)	$x - 2, y, z + 1$
O(2A)–H(2A)···N(2A)	1.08(4)	1.52(4)	2.585(3)	166(4)	—
O(2C)–H(2C)···N(2C)	0.86(5)	1.74(5)	2.605(3)	173(4)	—
O(2D)–H(2D)···N(2D)	0.91(5)	1.72(5)	2.632(4)	171(4)	—

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room temperature open to the atmosphere. Colourless crystals were afforded after several days.

(Isonicotinic acid hydrazide)·(2-chloro-4-nitrobenzoic acid), 10

0.200 g of isonicotinic acid hydrazide (1.46 mmol) and 0.294 g of 2-chloro-4-nitrobenzoic acid (1.46 mmol) were added into a sample vial. The solids were dissolved in hot ethanol (6 ml) and acetonitrile (5 ml), and left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.

(*N*′-(Propan-2-ylidene)isonicotinohydrazide)·(2-chloro-4-nitrobenzoic acid), 11

0.200 g of isonicotinic acid hydrazide (1.46 mmol) and 0.290 g of 2-chloro-4-nitrobenzoic acid (1.46 mmol) were added into a sample vial. The solids were dissolved in acetone (5 ml) and methanol (1 ml), and stirred for 12 hours at room temperature. The solution was left to stand at room temperature open to the atmosphere. Colourless crystals were afforded after several days.

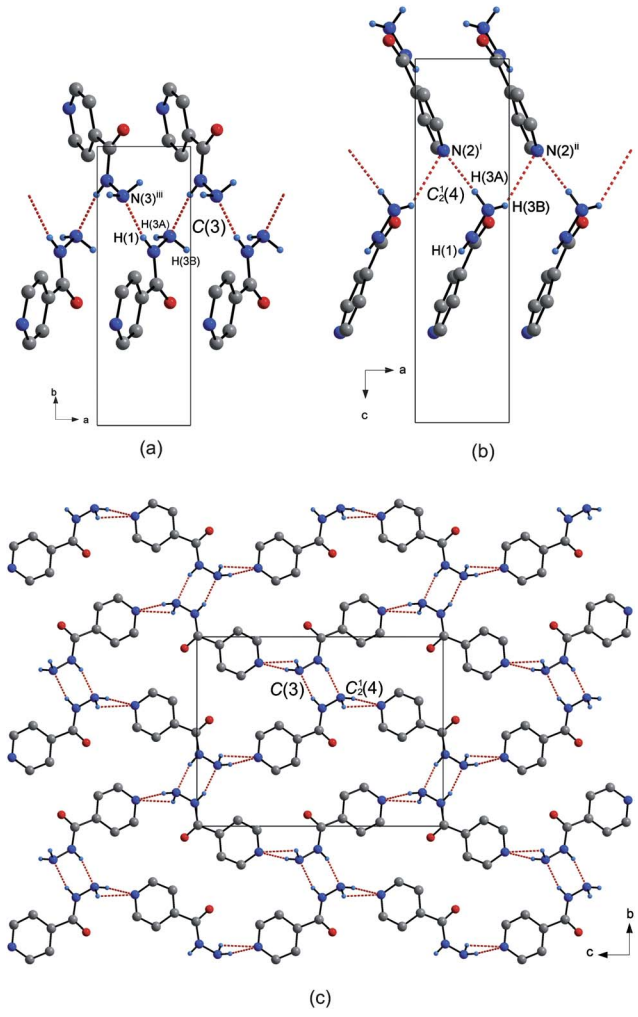

Fig. 2 Views of the homosynthon $C(3)$ chain (a) and heterosynthon $C_2^1(4)$ chain (b) in the original isoniazid molecule (**1**). (c) Packing diagram showing part of the 3-D network built up by the two chain motifs. Atoms with superscript *i*, *ii* and *iii* are at the symmetry positions [$-x + {}^1/_2$, $y + 1$, $z - {}^1/_2$], [$-x + {}^3/_2$, $-y + 1$, $z - {}^1/_2$] and [$x - {}^1/_2$, $-y + {}^3/_2$, $-z + 1$], respectively.

Single crystal X-ray diffraction. Intensity data for all compounds except **2** were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated MoKα_1 radiation (50 kV, 30 mA) at 173 K using an Oxford Cryostream 600 cooler. The collection method involved ω-scans

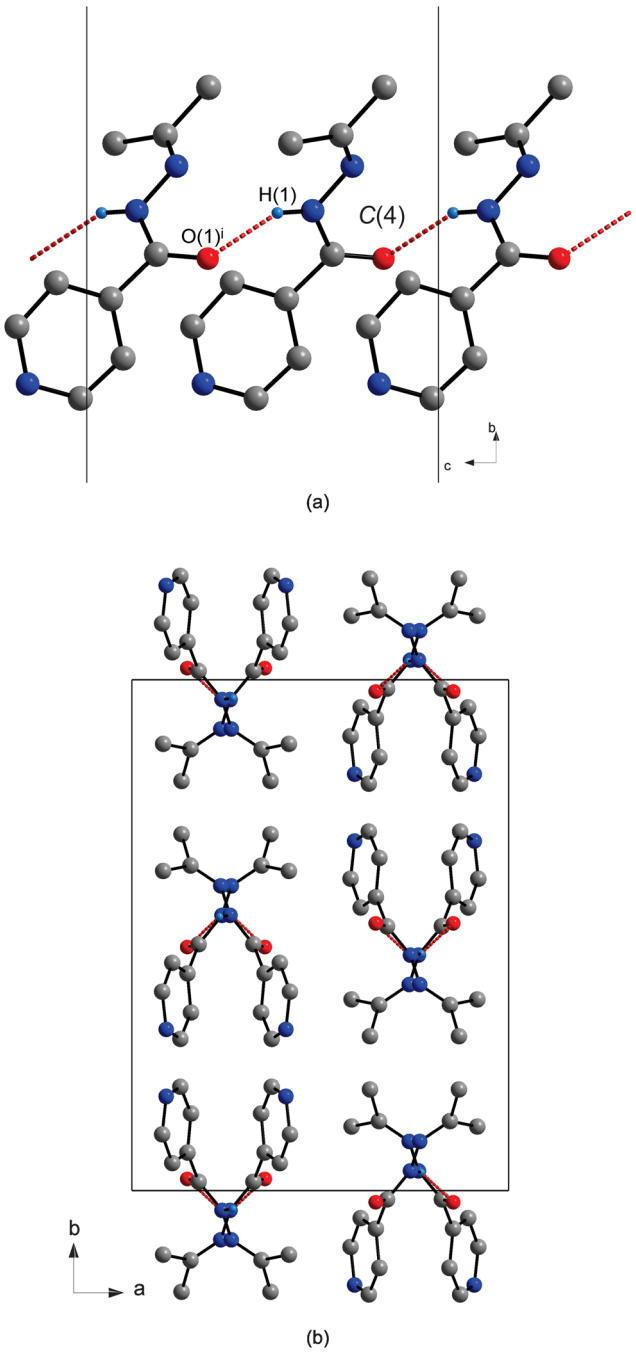

Fig. 3 (a) Detailed view of the $C(4)$ chain, which is the common homosynthon observed in modified propan-isoniazid (**2**). (b) Packing diagram showing the relative arrangement of the chains of propan-isoniazid (**2**) running along [001]. Atoms with superscript *i* are at the symmetry position [$-x + {}^1/_2$, y, $z + {}^1/_2$]

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of width 0.5°. Data reduction was carried out using the program SAINT+, version 6.02[5] and empirical absorption corrections were made using the program SADABS.[6] Single crystal diffraction data for **2** were collected in ω-scan mode on an Oxford Diffraction Gemini R Ultra diffractometer equipped with a Ruby CCD-detector with CuKα_1 (λ = 1.5418 Å, multi-layer optics) at 173 K using an Oxford Cryostream 700 cooler. Data reduction, cell refinement and empirical absorption corrections were carried out using CrysAlisPro.[7] Space group assignments were made using XPREP[5] on all compounds.

In all cases, the structures were solved in the WinGX[8] Suite of programs by direct methods using SHELXS-97[9] and refined using full-matrix least-squares/difference Fourier techniques on F^2 using SHELXL-97.[9] All non-hydrogen atoms were refined anisotropically. Thereafter, all hydrogen atoms attached to N and O atoms were located in the difference Fourier map and their coordinates refined freely with isotropic parameters 1.5 times those of the 'heavy' atoms to which they are attached. All C–H hydrogen atoms were placed at idealized positions and refined as riding atoms with isotropic parameters 1.2 times those of the 'heavy' atoms to which they are attached.

In **5**, the positional disorder around the oxygen atoms O(2) and O(3), and the carbon atom C(12), was resolved by finding alternate positions from the difference Fourier map for the respective atoms. These atoms were then refined anisotropically with site occupancies such that the sum of the occupancies for the two alternate atom positions equalled one. The bond lengths were restrained using the SADI instruction in SHELX. Hydrogen atom positions were then calculated for the respective atoms using a riding model.

In **11**, the positional disorder around the nitrogen atom N(2b) and carbon atoms was not resolved, and the N atom refined isotropically.

Diagrams and publication material were generated using ORTEP-3,[10] PLATON[11] and DIAMOND.[12] Experimental details of the X-ray analyses are provided in Table 1.

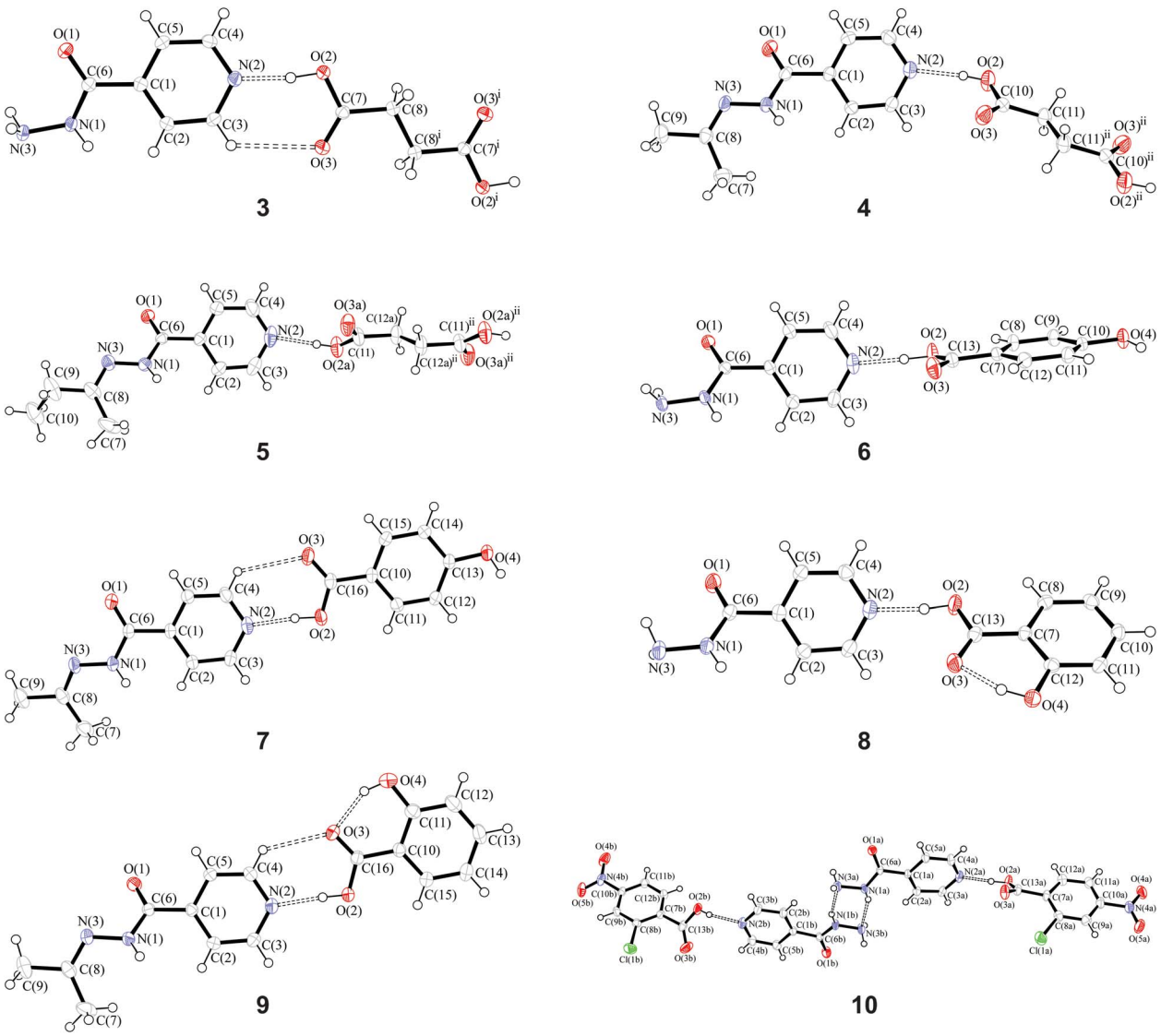

Fig. 4 The contents of the asymmetric unit for co-crystals **3–10**, showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level. Only one of the disordered components in **5** is shown. Atoms with superscript (i) and (ii) are at the symmetry positions [$-x$, $-y$, $-z+1$] and [$-x$, $-y$, $-z$] respectively.

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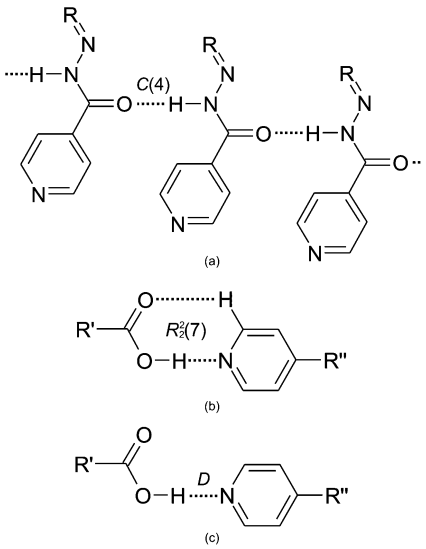
Crystallographic data for the co-crystals **3** and **6** were reported previously.[1]

Powder X-ray diffraction. Powder X-ray diffraction data for all compounds were collected at 293 K on a Bruker D2 Phaser diffractometer which employs a sealed tube Cu X-ray source ($\lambda =$ 1.5406 Å), operating at 30 kV and 10 mA, and LynxEye PSD detector in Bragg-Brentano geometry. Powder X-ray diffraction confirmed that the single crystal structures were representative of the bulk material (see the ESI†).

Differential scanning calorimetry. Differential Scanning Calorimetry (DSC) data were collected on a Mettler Toledo 822^e at a scan rate of 10 K min^{-1} in sealed aluminium pans under air. The temperature and the energy calibration was performed with pure indium (purity 99.999%, mp 156.6 °C, heat of fusion 28.45 J g^{-1}). Measurements of onset temperature and heat of fusion of the melting points of **1–11** were done in duplicate or triplicate, except for **6**. Results are summarized in Table 3, and DSC traces are given in the ESI†.



Scheme 3 The expected homosynthon for modified isoniazid in co-crystals (a), as well as the two heterosynthon variants used to co-crystallize the modified isoniazid with carboxylic acids (b and c).

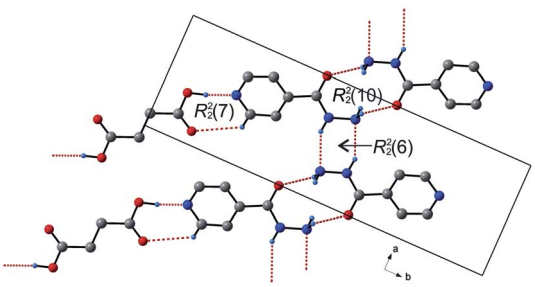


Fig. 5 Detailed view of the two homomeric synthons $R_2^2(6)$ and $R_2^2(10)$ found in isoniazid, and the heteromeric $R_2^2(7)$ hydrogen bonding of the GRAS molecule succinic acid to isoniazid in co-crystal **3**. Figure adapted from ref. 1.

Results

The compounds used to obtain the eleven crystal structures are presented in a coherent sequence in Scheme 2. The pure active pharmaceutical ingredient (API) is presented in its original (or unmodified) version, **1**. Isoniazid was reacted with acetone to prepare the modified and improved drug molecule, *N′*-(propan-2-ylidene)isonicotinohydrazide, **2**. Ethanol aided (original isoniazid) or ethanol–acetone aided (modified isoniazid) co-crystallizations were carried out with the GRAS molecules: succinic acid (suc) (**3** and **4**), 4-hydroxybenzoic acid (pHBA) (**6** and **7**) and salicylic acid (SA) (**8** and **9**). Lastly, drug–drug co-crystals were made with the anti-HIV compound 2-chloro-4-nitrobenzoic acid (2*c*4*n*) (**10** and **11**). In addition, a second modified isoniazid was made by reacting it with 2-butanone and co-crystallizing with succinic acid (**5**).

The distances and angles within the eleven compounds reported are generally as expected.[13] Seeing that the hydrogen

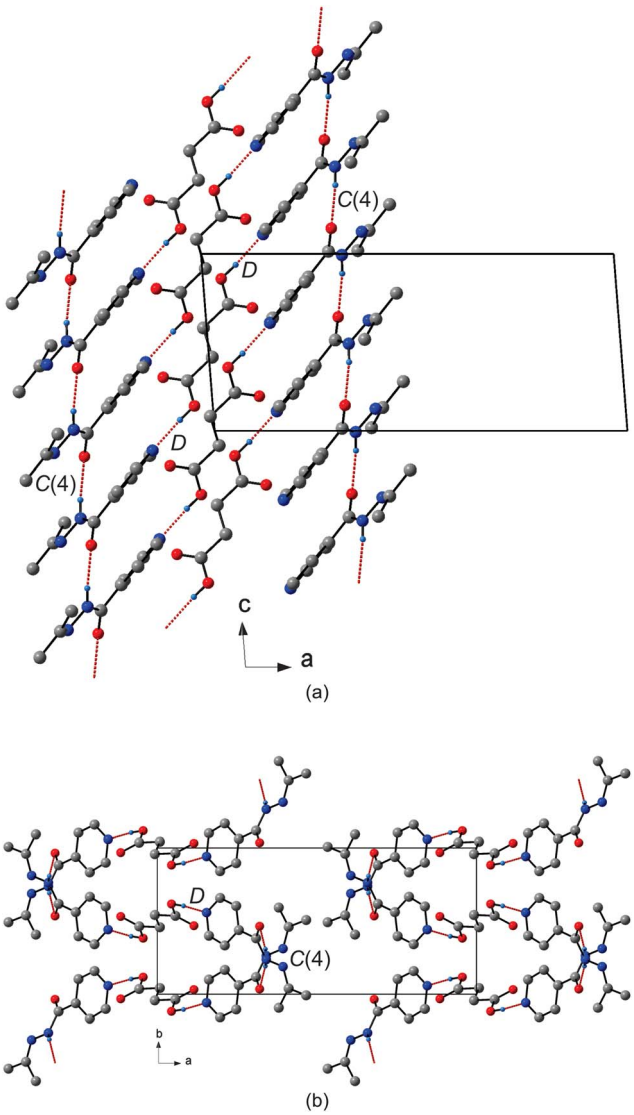


Fig. 6 (a) The sandwich-like packing of the GRAS molecule succinic acid bordered by propan-isoniazid in **4**. (b) The relative packing of the 2-D sandwiched layers.

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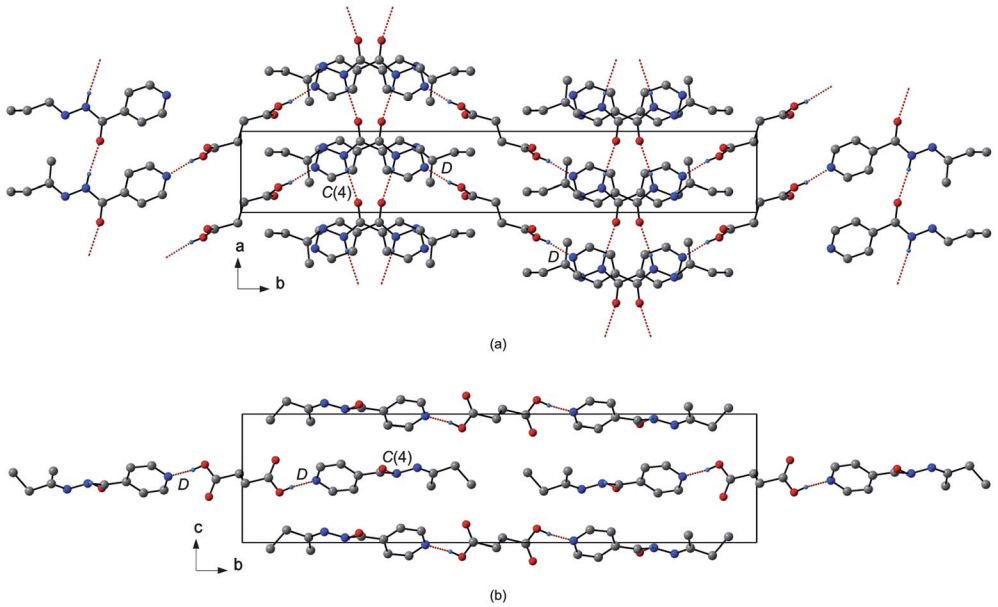

Fig. 7 (a) View of the hydrogen bonding interactions from the succinic acid to the butan-isoniazid molecules in co-crystal **5**, using the same synthons as seen in **4**. Here, ribbons are formed instead of 2-D layers. (b) The packing of adjacent ribbons.

bonded interactions are central to this study, the hydrogen atoms on the isoniazid and its modified derivatives are all labelled consistently in order to make comparisons of the eleven structures easier. H(1) is the hydrogen atom bonded to the amide group, and is the hydrogen atom always present. The two hydrogen atoms on the NH_2 of the hydrazide are labelled H(3A) and H(3B). If there are multiple molecules in the asymmetric unit (ASU), then the letters A, B, *etc.* are added after H(1), and similarly, A and B, C and D, *etc.* after H(3). The H atoms on the carboxylic acid functional groups are labelled consistently H(2) and on the phenol H(4), and if there are multiple molecules in the ASU, appended again using letters.

Crystal structures of isoniazid and modified isoniazid

The crystal structure of isoniazid (**1**) has been reported in the literature previously by Jensen in 1954,[14] and by Bhat *et al.* in 1974.[15] The temperature of the crystal structure determinations was room temperature, respectively INICAC and INICAC01 in the Cambridge Structural Database (CSD),[16] and to provide for consistent comparison throughout all 11 structures, redetermined in this study at 173 K. The unit cell and conformation of the molecule are the same as before, and the atomic labelling scheme and displacement ellipsoids of the isoniazid molecule in the asymmetric unit (ASU) are shown in Fig. 1a.

The crystal structure of isoniazid (**1**) consists of a 3-D network built up by three strong N–H···N hydrogen bonds (see Table 2). The amide H(1) hydrogen bonds to N(3) to form a $C(3)$[17] hydrogen bonded chain down the *a*-axis (Fig. 2a). The two hydrazide H atoms H(3A) and H(3B) form a $C_2^1(4)$ chain by hydrogen bonding both to the pyridine N atom N(2), also running down the *a*-axis (Fig. 2b). By virtue of these hydrogen bonding interactions having acceptor atoms on both ends of the isoniazid molecule, a 3-D network is built up (Fig. 2c). Note that the oxygen atom of the amide group is not used in any strong hydrogen bonding interactions.

The crystal structure of the modified isoniazid, *N′*-(propan-2-ylidene)isonicotinohydrazide (**2**), hereafter shortened to propan-isoniazid, shows a substantial change in hydrogen bonding pattern and packing. The removal of the two hydrazide H atoms, replaced now by the propylidene group, removes two thirds of the hydrogen bonding functionality of the original isoniazid

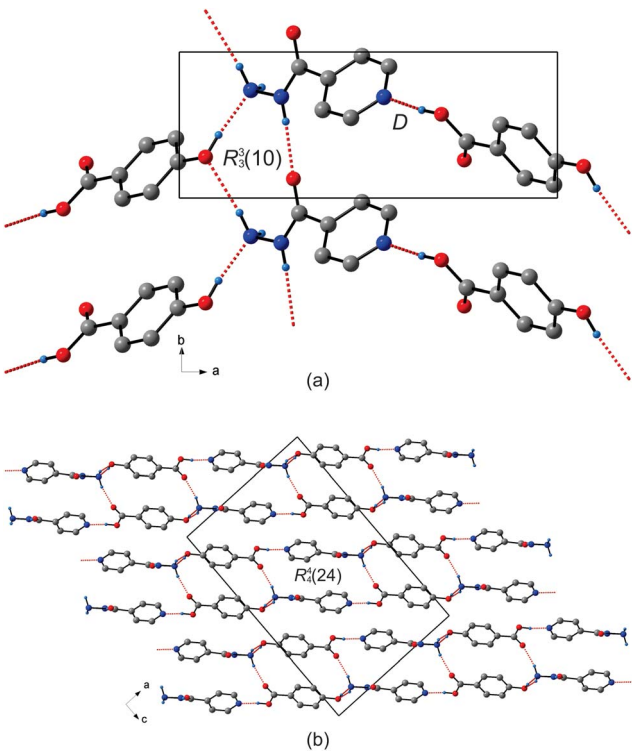

Fig. 8 (a) The heteromeric and homomeric synthons connecting the isoniazid and pHBA molecules to each other in **6**. (b) The 2-D layer formed by the combination of all the hydrogen bonding interactions. Figure adapted from ref. 1.

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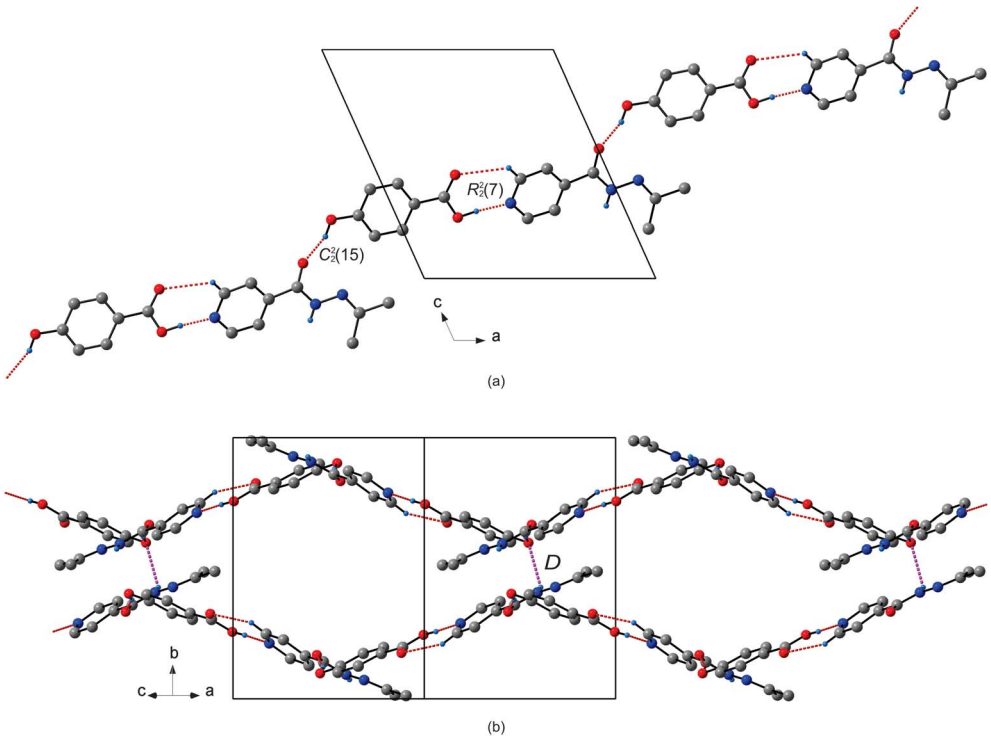

Fig. 9 (a) The $R_2^2(7)$ ring is used to connect the pHBA molecules to the propan-isoniazid molecules in **7**. The combination of the carboxylic acid⋯pyridine and phenol⋯carbonyl hydrogen bond creates a $C_2^2(15)$ chain formed by the two molecules. (b) These chains are then connected by a fairly oblique discrete hydrogen bond from the amide H(1) to the carbonyl of the acid molecule, shown in purple dashed lines.

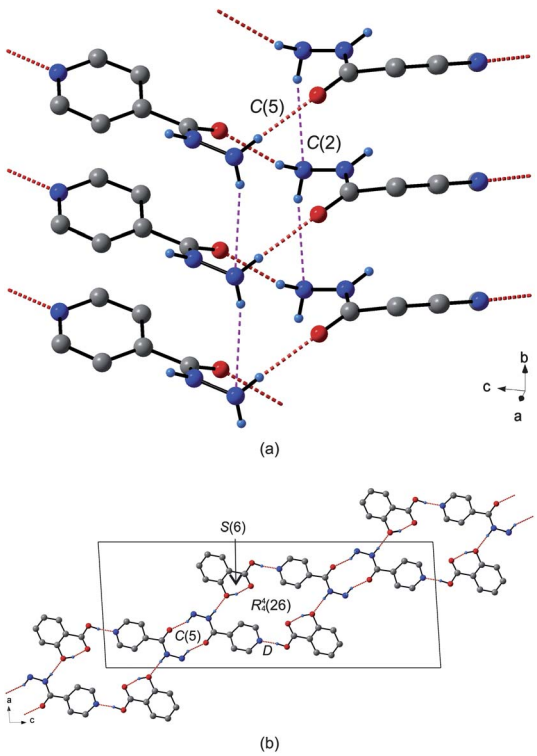

Fig. 10 (a) The two chain homosynthons used by isoniazid in co-crystal **8**. (b) Edge-on view of the 2-D layer formed.

molecule. The crystal structure of this modified isoniazid was also reported previously, again only at room temperature (RUGSIW),[18] and redetermined here at 173 K (Fig. 1b). The crystal structure consists of a 1-D network of *C*(4) chains formed by homomeric hydrogen bonding of the amide group, *i.e.* H(1) hydrogen bonds to O(1) to form chains along the *c*-axis (Fig. 3a). The packing consists of stacking of these chains in a head to tail fashion to form a checkerboard pattern (Fig. 3b).

Crystal structures of isoniazid and modified isoniazid in co-crystals with the GRAS compound succinic acid using two different modifiers, 2-propanone and 2-butanone

The crystal structure of the co-crystal (isoniazid)$_2$·(succinic acid) (**3**) has been reported previously in the literature.[1] The contents

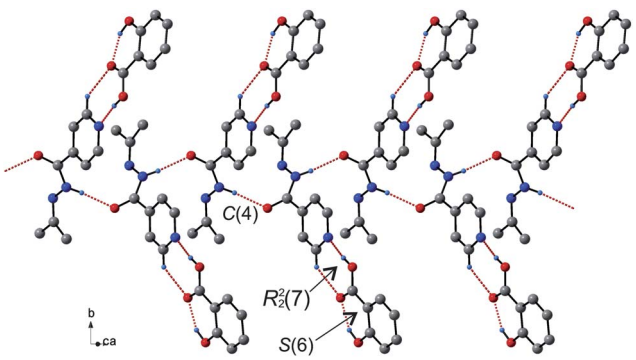

Fig. 11 The *C*(4) homosynthon and $R_2^2(7)$ heterosynthon used in co-crystal **9**.

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of the ASU, and labelled atomic numbering scheme, are shown in Fig. 4. The crystal structure of **3** is typical of the other known co-crystals and relates well to the ones reported later. In order to form co-crystals with other compounds, use is made of the robust heteromeric carboxylic acid···pyridine hydrogen bond. This hydrogen bond exists in two geometric variants. The carboxylic acid functional group can be co-planar with the pyridine ring, and then features a supporting weak C–H···O hydrogen bond to form a $R_2^2(7)$ ring. Alternatively, the two hydrogen bonding functional groups are not co-planar, resulting in a discrete *D* hydrogen bond only (Scheme 3).

Co-crystal **3** displays the $R_2^2(7)$ ring variant when forming a hydrogen bond between the GRAS molecule succinic acid and isoniazid. Adding succinic acid as a co-crystal former results in a substantial change in the hydrogen bonding pattern observed in the isoniazid co-crystal in contrast to the pure isoniazid structure (see Table 2). The amide H(1) now forms a $R_2^2(6)$ ring instead of a *C*(3) chain to N(3), and the hydrogen atoms on N(3) no longer hydrogen bond to the pyridine. Instead, H(3A) hydrogen bonds to O(1) to form a larger $R_2^2(10)$ ring, and H(3B) hydrogen bonds to the carboxylic O(2) (Fig. 5). The overall packing of co-crystal **3** consists of a 3-D network, consisting of stacked layers of the hydrogen bonded isoniazid and succinic acid.

By altering the crystallization procedure used to produce co-crystal **3**, in this case by adding 2-propanone (acetone) as the crystallization solvent, the modification of the hydrazide functional group occurs *in situ* during co-crystallization with succinic acid to produce co-crystal (propan-isoniazid)$_2$·(succinic acid) **4**, bringing further changes to the hydrogen bonding and packing. The ASU and numbering scheme of **4** are shown in Fig. 4. Just as was the case when comparing the crystal structures of isoniazid and propan-isoniazid, the hydrogen bonding interactions of the propan-isoniazid molecule adopts the *C*(4) homomeric chain and the hydrogen bond of succinic acid to the propan-isoniazid adopts the *D* variant. As such, there are only two strong hydrogen bonding interactions, resulting in a different packing arrangement (Fig. 6a). The packing consists of 2-D layers in the *bc*-plane, where the layers are formed by propan-isoniazid *C*(4) chains sandwiching the central succinic acid molecules (Fig. 6b).

For co-crystals with succinic acid, we decided to modify the isoniazid again using a different modifying group, 2-butanone, to make the structurally related co-crystal (butan-isoniazid)$_2$·(succinic acid) (**5**). This co-crystal, whose ASU is shown in Fig. 4, has the same two synthons as co-crystal **4**, *C*(4) and *D*, but has a different packing arrangement. The same sandwiches are formed, where succinic acid molecules hydrogen bond on both ends to terminating butan-isoniazid molecules, which then form ribbons through the *C*(4) chains (Fig. 7a). These ribbons extend along the *a*-axis and pack in layers next to each other, with adjacent layers offset from each other (Fig. 7b). This shows that the addition of an extra C atom on the modifying group can lead to a different packing arrangement, but nonetheless uses the same hydrogen bonding interactions.

Crystal structures of isoniazid and propan-isoniazid in co-crystals with two different GRAS compounds, 4-hydroxybenzoic acid and 2-hydroxybenzoic acid

We now illustrate the concept of making pharmaceutical co-crystals while modifying the functionality of the drug molecule using two GRAS molecules that have different hydrogen bonding groups. The previous co-crystals were made using a dicarboxylic acid molecule; here we use a single carboxylic acid functional group together with a phenol group. The modifier 2-propanone is kept constant.

The crystal structure of the co-crystal (isoniazid)·(4-hydroxybenzoic acid) (**6**) was reported previously,[1] and a labelled atomic numbering scheme of the ASU is shown in Fig. 4. The crystal structure is built up from repeating $R_3^3(10)$ rings using the amide H(1), one of the amine H(3A) atoms and the phenol H(4) atom (Fig. 8a). In fact, a *C*(4) homosynthon is present within the larger $R_3^3(10)$ synthon. On the other end of the GRAS molecule pHBA, the carboxylic acid group hydrogen bonds to the pyridine ring using the *D* variant (Fig. 8a), whereas the second amine H (3B) hydrogen bonds to the carbonyl of the acid group to form a $R_4^4(24)$ ring. Together, these hydrogen bonds form a 2-D layer in the *ac*-plane (Fig. 8b).

The crystal structure using the propan-isoniazid to form the co-crystal **7** has a very different packing to **6**. The co-crystal forms the $R_2^2(7)$ variant to connect the propan-isoniazid with pHBA. These two molecules are then joined *via* a hydrogen

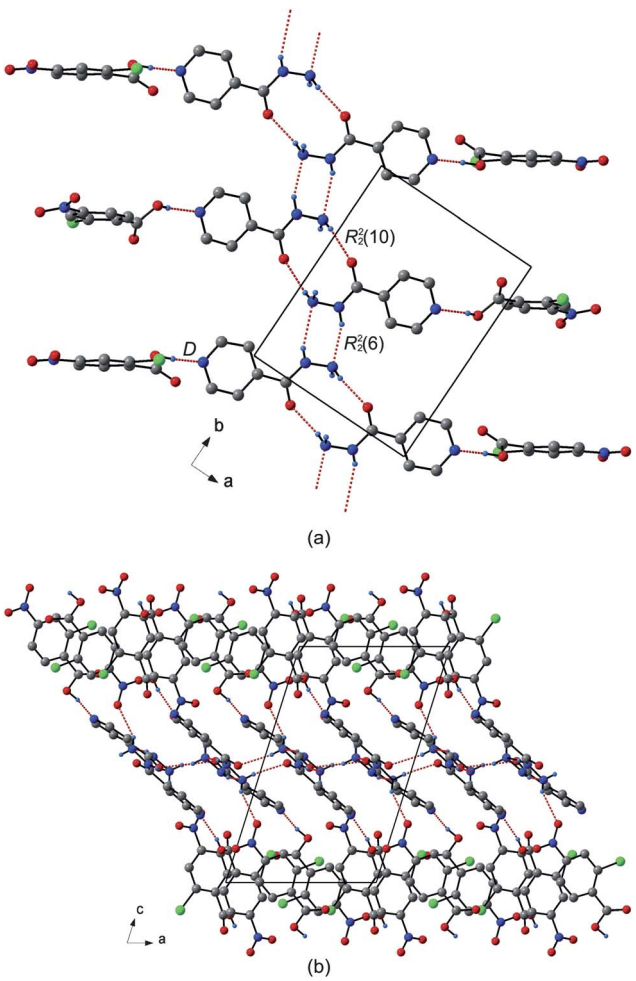

Fig. 12 (a) The alternating sequence of $R_2^2(6)$ and $R_2^2(10)$ rings found in isoniazid, and the heteromeric *D* hydrogen bonding of the 2*c*4*n* molecule to isoniazid in co-crystal **10**. The same sequence of rings is seen in co-crystal **3**. (b) Part of the repeating 3-D network.

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bond from the phenol H(4) to the carbonyl O(1) of the amide to form a $C_2^2(15)$ chain approximately along the *a*-axis (Fig. 9a). These chains are connected by a hydrogen bond from the amide H(1) to the phenol O(4) in a discrete hydrogen bond, with a very oblique angle of 131(1)°. This hydrogen bond joins the chains along the *b*-axis to form a 2-D layer in the *ac*-plane that has the width of the *b*-axis cell parameter (Fig. 9b). In other words, the *C*(4) homosynthon is not formed in this co-crystal.

The next pair of co-crystals alters the position of the phenol group relative to the carboxylic acid by using the GRAS compound 2-hydroxybenzoic acid, also known as salicylic acid (SA). The crystal structure of the co-crystal (isoniazid)·(2-hydroxybenzoic acid) (**8**) has one molecule of isoniazid and SA in the ASU, shown in Fig. 4 with their atomic numbering scheme. The isoniazid molecules are connected by two homosynthons, a *C*(5) chain from H(3B) to O(1), and a *C*(2) chain from H(3A) to N(3). These two chains run along the *b*-axis (Fig. 10a). The isoniazid molecules are connected to the SA molecule by the *D* variant of the carboxylic acid···pyridine hydrogen bond, as well as a hydrogen bond from the amide H(1) to the phenol O(4) atom. The combination of these two hydrogen bonds results in a $R_4^4(26)$ ring (excluding the *S*(6) hydrogen bond of the H(4) hydrogen bonding to O(3)). All these combine to form a 2-D layer along the *bc*-plane (Fig. 10b).

Co-crystal **9**, (propan-isoniazid)·(2-hydroxybenzoic acid), using the propan-isoniazid, shows the expected homosynthon. A *C*(4) chain formed from the remaining amide hydrogen bonding functional group forms along the [$\bar{1}$01] direction, with the SA molecule pendant to the propan-isoniazid using the $R_2^2(7)$ variant. The *S*(6) hydrogen bond is the only interaction retained compared to **8** (Fig. 11).

Crystal structures of isoniazid and propan-isoniazid in drug–drug co-crystals with 2-chloro-4-nitrobenzoic acid

We prepared co-crystals with a second drug molecule instead of a GRAS molecule. In previous studies, the potential anti-HIV drug molecule 2-chloro-4-nitrobenzoic acid (2*c*4*n*) has been co-crystallized with the GRAS molecule nicotinamide.[19] Isoniazid itself has been used in drug–drug co-crystals with other anti-tuberculosis drugs.[20] We combined 2*c*4*n* with both isoniazid (**10**) and modified isoniazid (**11**).

The crystal structure of the co-crystal (isoniazid)·(2*c*4*n*) **10** crystallizes with two molecules of isoniazid and two molecules of 2*c*4*n* in the ASU (Fig. 4), $Z' = 2$. This is in contrast to the other co-crystals **3–9** that had $Z' = 1$ each time. The two crystallographically independent moieties of the two molecules are labelled using A and B. The isoniazid molecules are connected to each other by alternating $R_2^2(6)$ and $R_2^2(10)$ rings along the [220] direction using the H atoms H(1A) and H(1B), and H(3B) and H(3C) respectively. Both 2*c*4*n* molecules hydrogen bond to the isoniazid molecules using the *D* variant to form ribbons (Fig. 12a). The remaining two H atoms on the amine group, H(3A) and H(3D), hydrogen bond to the O atoms of the nitro group on 2*c*4*n* to form a 3-D network (Fig. 12b).

The crystal structure of the co-crystal (propan-isoniazid)·(2*c*4*n*) **11** crystallizes with four molecules of propan-isoniazid and four molecules of 2*c*4*n* in the ASU (Fig. 13), giving a $Z' = 4$. This is double to what is observed for the unmodified co-crystal **10**. The four crystallographically independent moieties of each of the molecules are labelled A to D such that they hydrogen bond to each other forming ribbons. Note that the B pair of propan-isoniazid and 2*c*4*n* are a cation/anion pair, with the remaining three pairs being neutral molecules. The four isoniazid molecules

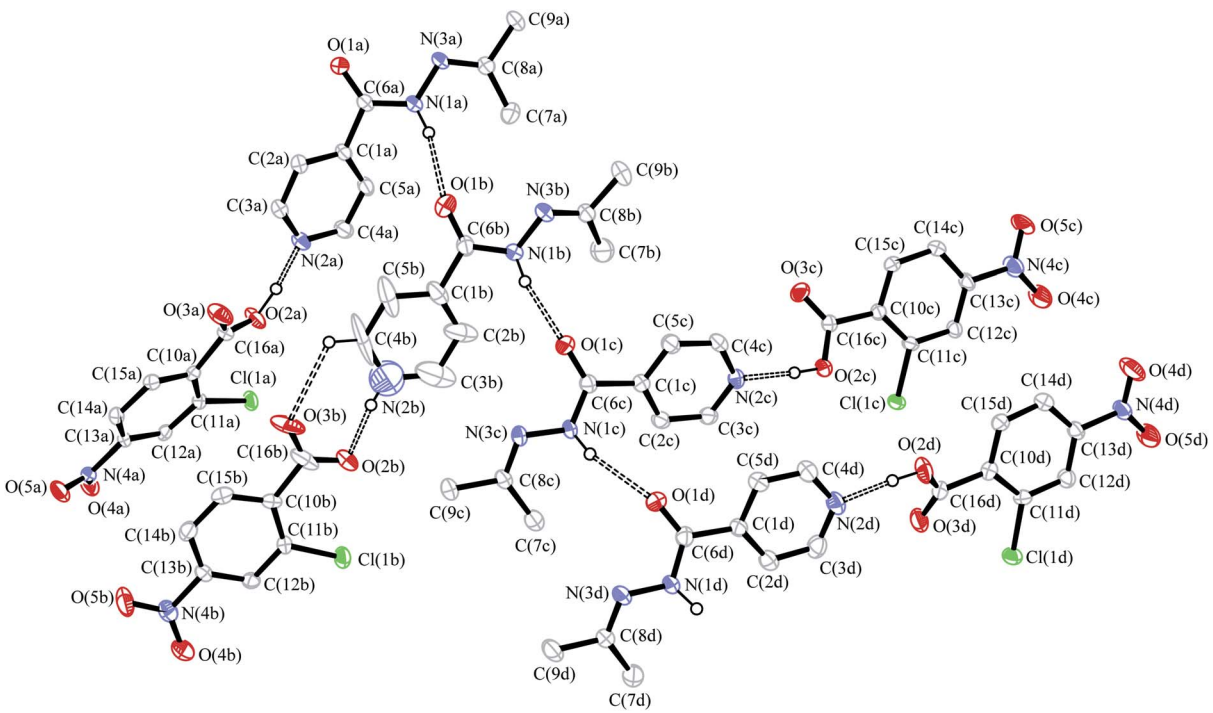

Fig. 13 The contents of the asymmetric unit for co-crystal **11**, showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.

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form a four-molecule repeating unit, where A and B molecules form a pair aligned in the same direction, followed by the C and D molecule in a pair rotated by 180° (Fig. 14a). The *C*(4) homosynthon is used to connect all the propan-isoniazid molecules. The 2*c*4*n* drug molecules hydrogen bond to the pyridine of the isoniazid to form ribbons. The hydrogen bonds seen in the A, C and D pairs are of the *D* variant. The charge-assisted hydrogen bond resulting from proton transfer from the B acid to the B propan-isoniazid can be considered to be the ionic equivalent of the neutral $R_2^2(7)$ hydrogen bond, where the H atom moves along a vector from the donor to the acceptor. These ribbons are connected by type I and II halogen bonds from the Cl atoms to the O atoms of the nitro groups to form a 3-D network (Fig. 14b).

Discussion

The co-crystals reported in this study, namely **3–11**, show that the modification of isoniazid still allows for co-crystals to be formed with carboxylic acid containing co-crystal former molecules. A previous study of the modification and masking process was carried out using a number of different ketones and keeping the co-crystal former the same, namely 3-hydroxybenzoic acid.

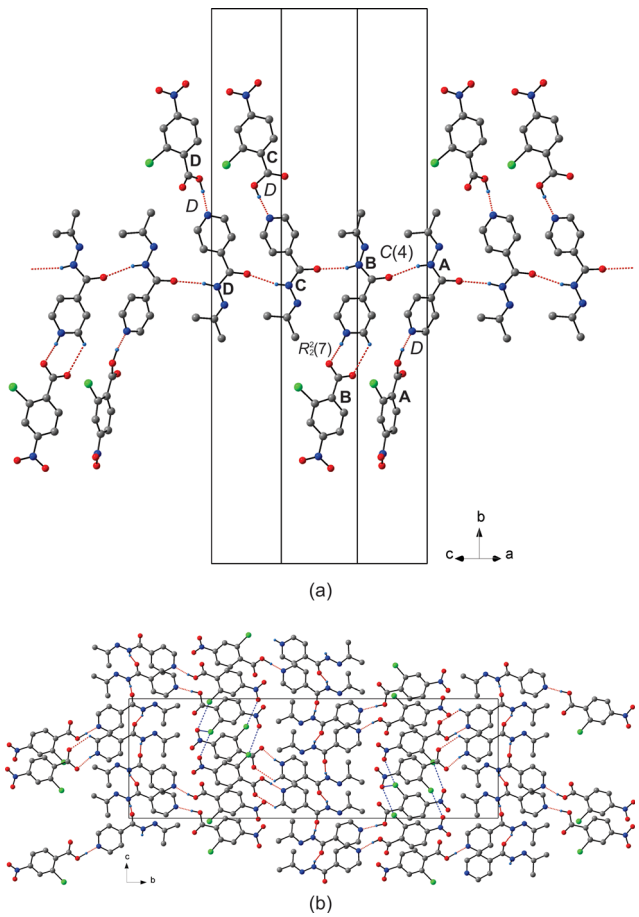

Fig. 14 (a) The *C*(4) chain formed by four crystallographically independent propan-isoniazid molecules, and the four 2*c*4*n* molecules hydrogen bonding to them, labelled (a–d). (b) View of the ribbons connected by the halogen bonding to make a 3-D network.

Here, co-crystal **4** showed that the concept works for alkyldicarboxylic acid molecules, whereas co-crystals **7**, **9** and **11** show that benzoic acid derivatives remain a good co-crystal former choice. In terms of the observed hydrogen bonding interactions, the robustness of the carboxylic acid···pyridine hydrogen bond has been illustrated again as it is the dominant heteromeric interaction to make co-crystals between isoniazid and various carboxylic acid molecules. Regardless of the type of hydrogen bond, *i.e.* the geometric variant, all nine co-crystals feature this hydrogen bond. An unexpected charged variant was observed in one of the pairs of 'molecules' in co-crystal **11**, where the B pair is in fact a cation/anion pair. This is seen in the bond distances of the COO^- moiety, which has a ratio of 1.008 for the two C–O bond lengths. The three other pairs have values of 1.063, 1.077 and 1.096, which is indicative of a neutral acid group with no proton transfer to a base molecule.[21] As to why three pairs of molecules remain neutral, and one charged, is unclear at this stage. However, it is possible that this imbalance is one of the reasons for having a $Z' = 4$ asymmetric unit, as all molecules have similar hydrogen bonding interaction. What does differ significantly however is the geometries of the four isoniazid moieties, as seen in Table 3 for the C(2)–C(1)–C(6)–N(1), N(3)–N(1)–C(6)–O(1) and C(6)–N(1)–N(3)–C(8) torsion angles. In addition, crystals of this co-crystal (**11**) were harvested from a rapid evaporation process, and hence could represent the kinetic product of the crystallization process.

In terms of the homomeric interactions between isoniazid and the modified isoniazid, some trends can be observed. Isoniazid, both in its original and modified form, seldom undergoes any heteromeric interactions when co-crystallized, and those kinds of interactions are only seen in co-crystals **6** and **7**. Pure isoniazid itself does undergo a heteromeric interaction in its unimolecular structure, a heteromeric $C_2^1(4)$ interaction; but in co-crystals, this interaction is not seen as the pyridine group is already bonding to the various carboxylic acids. More prevalent are homomeric interactions seen in all co-crystals reported here. Most common is the *C*(4) homosynthon in isoniazid, especially when in its modified form. This is expected as the amide chain formed by N–H···O hydrogen bonded interactions is very robust.[22] Even when other modifiers are used, apart from 2-propanone and 2-butanone, this homosynthon is seen.[2] Correlated with the presence of a *C*(4) homosynthon is the torsion angle of the modified group relative to the amide functional group. The absolute torsion angle C(6)–N(1)–N(3)–C(8) is close to 180° when the *C*(4) is not formed, and varies from about 148.8(3) to 166.20(14)° when *C*(4) is present (Table 3). Similar correlations are seen in the rotation of the amide group relative to the pyridine group, where the absolute torsion angle C(2)–C(1)–C(6)–N(1) varies from 18.1(2) to 37.09(17)° when the *C*(4) homosynthon is present, and is considerably more linear when *C*(4) is not present (3.3(4) to 16.7 (3)°). The *C*(3) homosynthon in pure isoniazid is not seen in any of the unmodified co-crystals; instead $R_2^2(6)$ and $R_2^2(10)$ rings are observed. These are common for isoniazid co-crystals.[1]

A part of the structural study of preparing co-crystals with both original and modified isoniazid is the effect on the melting point of the co-crystals, and how the removal of hydrogen bonding functionality in general could alter the melting points. In Table 3, the melting points of all 11 compounds discussed in this report are listed, as well as their enthalpies of fusion. The

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Table 3 Comparative features of all compounds

	1	2	3	4	5	6	7	8	9	10	11
Melting point/°C	170.4(1)	160.0(2)	139.1(1)	126.2(3)	109.3(2)	161.6	156.2(3)	145.8(1)	114.0(1)	116.3(5)	93.4(6)
Heat of fusion/kJ mol^{-1}	31.0(3)	29.9(7)	39.3(4)	31.8(8)	39.5(3)	49.5	52.8(1)	49.3(6)	41.4(2)	40.3(5)	33.4(7)
NH_2 modified	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes
Homosynthons	$C(3)$	$C(4)$	$R_2^2(6)/R_2^2(10)$	$C(4)$	$C(4)$	$C(4)$	No	$C(2)/C(5)$	$C(4)$	$R_2^2(6)/R_2^2(10)$	$C(4)$
Heterosynthons	$C_2^1(4)$	None	None	None	None	$R_4^3(10)$	$D/C_2^2(15)$	None	None	None	None
Acid···pyridine variant	—	—	$R_2^2(7)$	D	D	D	$R_2^2(7)$	D	$R_2^2(7)$	D/D	$D/R_2^2(7)^a/D/D$
Isoniazid and modified isoniazid: C(2)–C(1)–C(6)–N(1)/°	−18.1(2)	50.90(19)	−19.48(18)	31.9(2)	34.8(2)	37.09(17)	−8.66(17)	34.8(2)	36.50(16)	16.7(3) (A) 3.3(4) (B)	145.0(3) (A) −22.7(4) (B) 29.8(4) (C) 23.6(4) (D)
Isoniazid and modified isoniazid: N(3)–N(1)–C(6)–O(1)/°	−5.5(2)	5.0(2)	−8.0(2)	−5.0(2)	−9.2(2)	6.07(19)	0.91(18)	−0.6(3)	−7.21(17)	5.0(4) (A) −0.9(4) (B)	−3.3(5) (A) 8.8(5) (B) 4.8(5) (C) −4.1(5) (D)
Mod. isoniazid: C(6)–N(1)–N(3)–C(8)/°	—	−159.82(13)	—	163.26(15)	166.20(14)	—	173.21(11)	—	153.02(11)		−167.9(3) (A) −148.8(3) (B) 163.0(3) (C) 159.3(3) (D)

[a] Charged, N^+–H···O^-.

highest melting point is seen for pure isoniazid **1**, which then decreases by 10 °C for the pure modified isoniazid **2**. Does a similar trend occur in the four co-crystal pairs, namely **3–4–5**, **6–7**, **8–9** and **10–11**? The answer is yes, but the question that begets to be asked is if that can be correlated to the absence of the two H bonding donors. Since hydrogen bonding is the strongest of the intermolecular forces observed in molecular co-crystals, decreasing the number of potential hydrogen bonds in the isoniazid molecule by two thirds can be a factor, in addition to the disruptive influence of the heteromeric interactions required for co-crystallization in this study. The enthalpies of fusion show a less clear trend, with the co-crystal pairs **3–5** and **6–7** showing equal or increasing enthalpies of fusion, implying that the co-crystal using a modified isoniazid is equal or more stable than the co-crystal using the original isoniazid. The caveat is that all intermolecular interactions and their contributions to the lattice energy need to be considered, but further investigations showing a similar trend in co-crystal stability might shed light on this.

Conclusions

The nine co-crystals (seven of them new) reported in this study show that it is possible to prepare co-crystals of potential medical relevance that are prepared by reacting the active pharmaceutical ingredient with a ketone. The covalent and supramolecular reactions that occur in solution must not be in a position to interfere with each other, and this is the case for isoniazid. The pyridine group in isoniazid shows that it is an excellent attractor for carboxylic acids. Additionally, the hydrazide functional group can be easily modified, allowing for the expansion of supramolecular reactivity and physiological improvement. This work shows that if any new frontline tuberculosis drugs need to be marketed using the isoniazid backbone, and their chemical or physical properties need to be improved, co-crystallization is a viable method offering a measure of control.

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