Co-crystal engineering of phthalic acid derivatives with nitrogen-containing heterocyclic active pharmaceutical ingredients

by

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Declaration

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I declare that the above thesis is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

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Abstract

Fifteen heterocyclic active pharmaceutical ingredients were co-crystallized with phthalic acid derivatives, resulting in three series of co-crystals. Niacinamide, modified isoniazid (isoniazid modified with benzaldehyde), isoniazid, isonicotinamide niazid and benzhydrazide were co-crystallized with isophthalic acid, phthalic acid, terephthalic acid, 3-nitrophthalic acid, 5-aminoisophthalic acid, 5-nitroisophthalic acid, nitroterephthalic acid and diphenic acid. The three resulting series consisted of niacinamide, modified isoniazid and other *N*-heterocyclic API's, each being co-crystallized with phthalic acid derivative co-formers. One of the phthalic acid derivatives – nitroterephthalic acid – was crystallized and the structure was published.

The crystals formed were characterized by single crystal X-ray diffraction and their structures solved using Shelx. The structures were investigated, and their hydrogen bonding patterns as well as abnormalities were examined and discussed.

Acknowledgements

I would firstly like to thank God, for everything.

I would also like to thank my supervisor Dr M.G Smith for his time, continuous supervision, and important feedback. He has made this submission possible and provided me with valuable knowledge that I could not be more grateful for. I would not have been able to complete my dissertation without his guidance and abundant support.

A thank you to my family, who has been there for me throughout my studies, offering encouragement and support. It is truly appreciated.

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API – Active Pharmaceutical Ingredient

CCDC - Cambridge Crystallographic Data Centre

CIF – Crystallographic Information File

CIP – Cahn-Ingold-Prelog

CSD – Cambridge Structural Database

DMSO – Dimethylsulfoxide

DSC - Differential Scanning Calorimetry

FTIR - Fourier Transform Infrared Spectroscopy

GRAS – Generally Regarded as Safe

HSPM - Hot Stage Polarized Microscopy

INH- Isoniazid

QCT - Quercetin

SC-XRD - Single-crystal X-ray Diffraction

SEM - Scanning Electron Microscope

TB – Tuberculosis

TGA - ThermogravimetricAnalysis

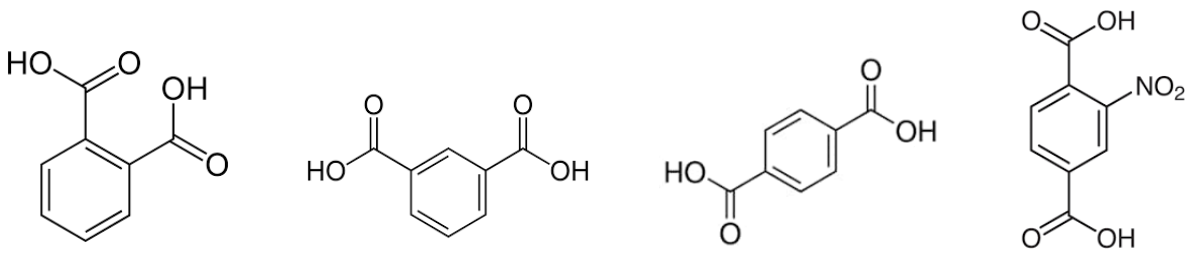
XRD – X-ray diffraction

Chapter 1 - Introductions and aims

1.1. General introduction

Co-crystal engineering of several heterocyclic active pharmaceutical ingredients (API's), with phthalic acid and phthalic acid derivative co-formers will be explored in this study. Phthalic acids are a type of dicarboxylic acid -containing two carboxyl groups and sometimes a nitro or amine group, shown in Figure 1.1, which may be involved in hydrogen bonding to the API's used. Co-crystals open new pathways in drug discovery and enhancement, as factors such as solubility, efficacy, dissolution, and bioavailability may be enhanced and or manipulated. Certain dicarboxylic acids can be difficult to dissolve, depending on the solvent used, and therefore difficult to co-crystallize with APIs, leading to a need for more research in this field. Slow evaporation, mechanochemistry and other methods were used to assemble the APIs with the co-formers (phthalic acid derivatives), leading to a matrix of co-crystals. Different solvents, conditions and techniques were used to form these supramolecular heterosynthons via hydrogen bonding or other non-covalent intermolecular bonding. Characterization was done using single crystal X-ray diffraction (SC-XRD).

An understanding of the behaviour of functional groups is essential for the design of novel co-crystals (X. Wang et al., 2018). Making use of the robust carboxylic acid – pyridine hydrogen bond in that exists between heterocyclic molecules containing a nitrogen atom and carboxylic acids, give rise to persistent supramolecular heterosynthons to establish "novel multi-component molecular solids" (X. Wang et al., 2018).



(a) (b) (c) (d)

Figure 1. 1 Structures of several phthalic acid derivatives (a) phthalic acid, (b) isophthalic acid, (c) terephthalic acid and (d) nitroterephthalic acid

1.1.2 Background

A crystal or crystalline form indicates that the unit cells, which are the structural units, repeat regularly and indefinitely in three dimensions in space (Vippagunta et al., 2001), these translational vectors named *a*, *b*, and c with angles alpha (α), beta (β) and gamma (γ), determine the shape and orientation of a unit cell. This repeating unit cell also has a volume, *V*, that holds the molecule and atoms needed for the making of a crystal (Vippagunta et al., 2001).

A unit cell (Figure 1.2) is the smallest repeating unit of a crystal structure and can be thought of as the "building block" of a crystal structure.

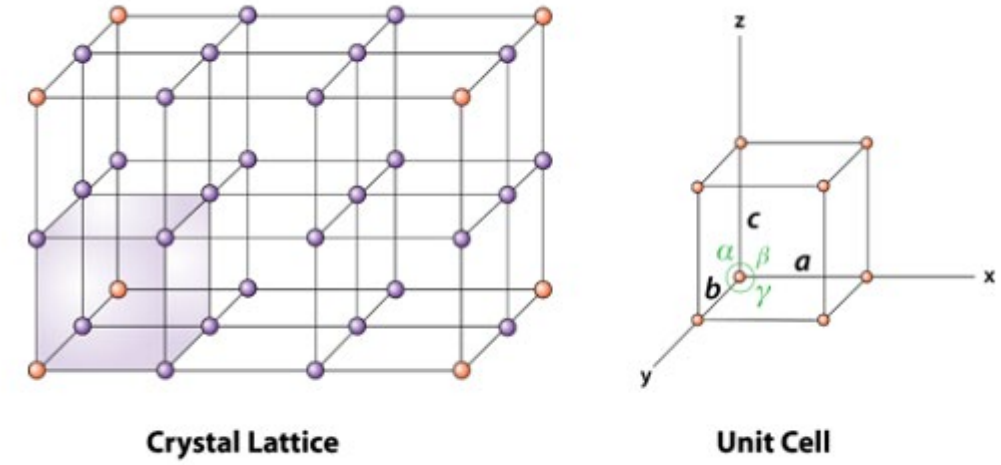


Figure 1. 2 Crystal lattice and unit cell structure (taken directly from https://semesters.in/types-of-unit-cell/ (07/10/2022))

The most common forms of crystalline structures used in drug substances are salts, solvates and polymorphs, but in this study, we will be focusing on co-crystals. A crystalline form made up of two or more components with a certain stoichiometry is known as a co-crystal (Wood et al., 2014). These structures have several requirements being:

1. All constituents are organic species.
2. None of the constituents may be charged – or this would be known as a salt.
3. The constituents may not be water- this would be classified as a hydrate.
4. The co-former should not be a solvent – as this would be classified as a solvate.
5. A directional interaction between the constituents must be present (Wood et al., 2014).

Co-crystals and solvates differ in the physical state of their isolated pure components, solvates have one component in a liquid state at room temperature whereas if both components are solid at room temperature, then the product is known as a co-crystal (Almarsson & Zaworotko, 2004).

Hydrates contain a water molecule and salts contain charged species (Aakeröy et al., 2018). The classification of organic multi-component solids can be seen in Figure 1.3.

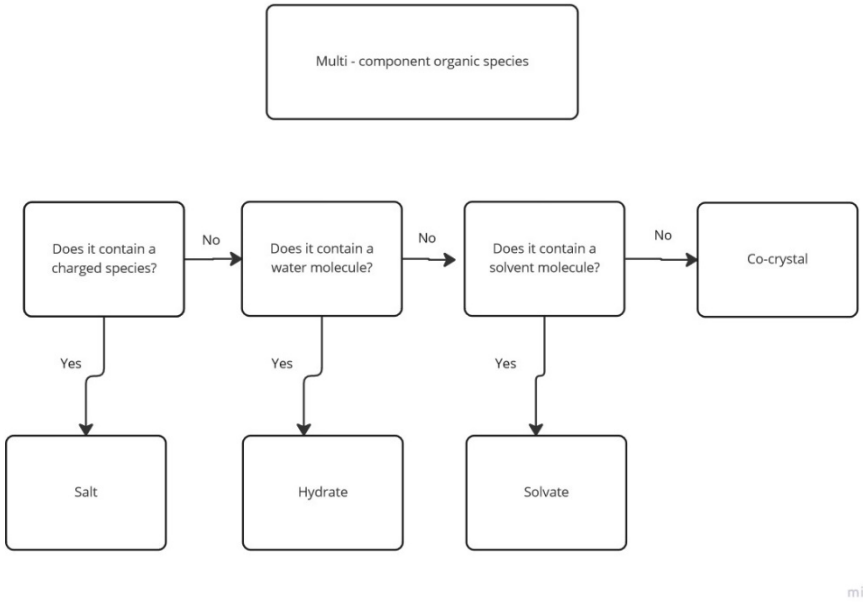


Figure 1. 3 Classification of organic multi-component solids (Aakeröy et al., 2018)

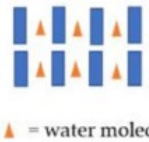
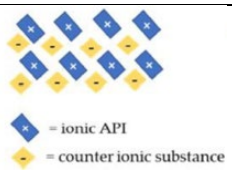
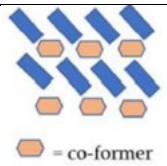
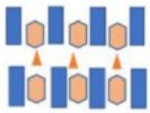
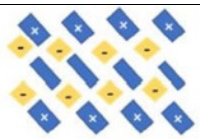
Co-crystals have different physiochemical properties to that of the starting materials because the co-crystal will have a different crystal structure (Karimi-Jafari et al., 2018).

The formation of a co-crystal results in the development of a completely new crystal structure, and the co-crystal may possess a different and new set of physical properties which may make them more desirable for pharmaceutical purposes (Karimi-Jafari et al., 2018); (Wood et al., 2014).

In drug design, co-crystallization has become very attractive as co-crystals may be used to "fine tune" bioavailability, solubility, dissolution, and other physiochemical properties (Kuminek et al., 2016) . Due to the different physiochemical properties of a co-crystal to that of the starting materials, they have gained attention in the pharmaceutical industry, when one of the starting materials is an active pharmaceutical ingredient (API). So pharmaceutical co-crystals can lead to a path of many new opportunities for drug development as well as drug delivery (Vishweshwar et al., 2006). For many years salts have been used in the pharmaceutical industry due to their improved solubility, but the

proton transfer that occurs in salts is not always desirable, whereas co-crystals combat this issue (Johan, Wouters, 2011).Table 1.1 demonstrates the differences between co-crystals and other solid forms.

Table 1. 1 Images indicating the differences between co-crystals and other solid forms (adapted from Nugrahani and Jessica, 2021)

			
Amorphous solid	Polymorphous solid	Hydrate	Solvate
			
Salt	Co-crystal	Co-crystal hydrate	Salt co-crystal

Pharmaceutical co-crystals are a relatively new and represent an unexplored but vast class of compounds(Vishweshwar et al., 2006), where a pharmaceutical co-crystal is defined as having an active pharmaceutical ingredient (API) and a benign molecule as the co-former (Kuminek et al., 2016). The co-former molecule is normally a non-toxic molecule or a substance that is on the 'Generally regarded as safe' (GRAS) list. The co-former may also be another API (Kuminek et al., 2016). Pharmaceutical co-crystals may be logically designed using crystal engineering, which opens new pathways/doors to the enhanced properties of pharmaceutical materials (Almarsson & Zaworotko, 2004).

1.1.3 Crystal Engineering:

The conception of crystal engineering was brought about in 1955 and was defined by Desiraju as "*the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties*" (G. Desiraju, 1989). Now crystal engineering has become a domain for supramolecular synthesis of new compounds.

One of the biggest problems in this field is the fact that crystal structures cannot easily be predicted from the starting materials. The way the functional group behaves in a molecule during the

crystallization process depends on the character and positions of all the functional groups in the molecule (G. R. Desiraju, 2013). An important aspect that developed in crystal engineering was proposed by Zaworotko and Almarsson which ties crystal engineering to the pharmaceutical world (Almarsson & Zaworotko, 2004). It was suggested that an API may be able to form a binary co-crystal, for example, a pharmaceutical co-crystal, by interacting it with another molecule, the co-former, on a supramolecular basis.

So, with regards to crystal engineering and the pharmaceutical industry – crystal engineering opens a new chapter in terms of the development of a new class of API's, which we now call pharmaceutical co-crystals (Fleischman et al., 2003a). Pharmaceutical co-crystals are very capable of having much more functionality in the pharmaceutical world than solvates, as co-crystal co-formers are less likely to evaporate from solid dosage configuration and therefore phase separation is unlikely (Almarsson & Zaworotko, 2004).

1.1.3.1 The Delta pKa (ΔpKa) regarding co-crystals

The pKa rule used for the prediction of co-crystals between acids and bases (Cruz-Cabeza, 2012) can be stated as follows: multi-component crystals having acid and base components with $\Delta pKa > 4$ normally leads to salts being formed, whereas $\Delta pKa < -1$ normally leads to co-crystals forming. ΔpKa with a value between -1 and 4 may lead to either a salt or co-crystal (Cruz-Cabeza et al., 2022).

This rule assists in predicting and the controlling of the assembly of a multi-component co-crystal (Lemmerer et al., 2015). This is because in co-crystals, the hydrogen bonding interactions contain longer intermolecular distances than that of hydrogen bonds in salts (G. R. Desiraju, 2002; Jeffrey, 1997).

A study by Bhogala *et al* reported that for co-crystals and salts of carboxylic acids and pyridine, the negative pKa differences between co-crystallizing acid and base pairs will normally result in the formation of co-crystals, but not molecular salts (Bhogala et al., 2005).

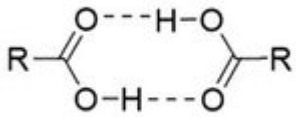
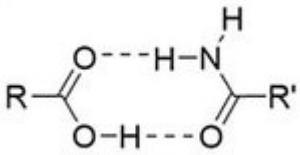
1.1.4 Bonding in co-crystals

A co-crystal is formed by merging an API with a suitable co-former which will form a supramolecular synthon (Nugrahani & Jessica, 2021). Components of a co-crystal construct themselves via non-covalent bonding, which may be via hydrogen bonds, van der Waals interactions, ionic bonds, π-π bonds (Sekhon BS, n.d.), and halogen bonds (Pedireddi et al., 1994).

“Supramolecular synthons are structural units within supermolecules that can be formed or disassembled by known or conceivable synthetic operations involving intermolecular interactions” (G. R. Desiraju et al., 1995). Supramolecular synthesis is when one molecule is bonded to another through intermolecular forces which are non-covalent.

Synthons are the way in which functional groups are bonded - which can be described as the way supramolecular synthesis takes place. Synthons set the process which will connect the molecular and supramolecular structure (Reddy et al., 1996). A homosynthon is where the intermolecular forces are between two of the same functional groups, meaning homosynthons contain identical functional groups whereas a heterosynthon has the intermolecular forces between two different functional groups and the heterosynthons contain two different functional groups (Reddy et al., 1996). Examples of homosynthons and heterosynthons can be seen in Table 1.2.

Table 1. 2 Examples of synthons based on hydrogen bonds (Hutchins, 2018)

Homosynthon	Heterosynthon
	

Supramolecular synthons are important in in the making of co-crystals as these small structural units have all the information with regards to how the molecules will construct themselves into a supermolecule (Reddy et al., 1996), below is a comparison of supramolecular synthesis versus covalent synthesis (Table 1.3).

Table 1. 3 Supramolecular versus covalent synthesis adapted from Aakeröy et al., 2018

Supramolecular synthesis	**Covalent synthesis**
The supramolecular assembly of molecules	Individual molecule
Synthon reliability	Quantitative yield
Structure-function	Structure- function
Customized performance	Customized performance

Halogen bonds are also found in co-crystal synthesis and resemble hydrogen bonds. Halogen bonds are similar to hydrogen bonds in the manner of directionality as well as strength (Aakeröy et al., 2007).

Three types of halogen bonds exist, namely;

1. A 'normal' halogen bond between electronegative atoms (nitrogen, oxygen) and the electron deficient halogen atom.
2. Type I halogen- halogen bonds where van der Waals interactions exist.
3. Type II halogen- halogen bonds which occur between electron rich and electron deficient sites on a halogen atom – London dispersion bonds.

(Metrangolo & Resnati, 2001; Pedireddi et al., n.d.)

1.1.5 Strategy for developing co-crystals

There is a need for a thorough understanding of supramolecular heterosynthons in the development of pharmaceutical co-crystals (Almarsson & Zaworotko, 2004). Crystal structures essentially can't really be predicted (Almarsson & Zaworotko, 2004), but what is predictable is the interactions that may occur prior to crystallization as certain intramolecular bonds are formed preferentially over others and therefore a "model" may be made of the outcome.

To predict if a co-crystal is possible, the following steps are important; 1) to observe if the molecular components will undergo co-crystallization; 2) observing and finding the primary intermolecular interactions; 3) looking at the general packing arrangement of the resulting co-crystal (Trask, 2007). Identification of the primary intermolecular interactions with regard to hydrogen bonding, the Cahn-Ingold-Prelog (CIP) rules are applied to groups attached to a carbon atom and when CIP rules cannot be directly applied, the highest priority rules will be tabulated in Table 1.4 (Etter et al., 1977):

Table 1. 4 Assigning hydrogen bond priorities adapted from (Margaret Etter et al., 1977)

1	Primary amides	The *cis* hydrogen takes the higher priority, compared to the *trans* hydrogen
2	Primary amines	The highest priority is given to the hydrogen atom on the highest priority side
3	Carboxylic acids	Higher priority is given to the hydrogen atom with *cis* geometry compared to the hydrogen atom with *trans* geometry.
4	Hydrogen atoms	Hydrogen atoms within an intermolecular hydrogen bond have higher priority over a hydrogen atom within an intramolecular hydrogen bond
5	Identical hydrogen atoms	With two identical hydrogens, the Cahn-Ingold-Prelog priorities of acceptor atoms in the hydrogen bonds are used to establish the priorities
6	Identical acceptor and donor atoms in two hydrogen bonds	The lone pair of electrons containing the highest priority will be on the highest priority side of a molecule (electron lone pairs are treated as acceptors) Acceptor atoms which hydrogen bond to a single hydrogen atom have lower priority than bifurcated bonds. Hydrogen atoms within a shorter hydrogen bond takes priority over hydrogen atoms within a longer hydrogen bond

In a study by Aakeröy *et al,* it was found that there was quite an improvement in the hydrogen bond synthesis of carboxylic acid---N-heterocycle co-crystals by increasing the partial negative charge of a hydrogen bond acceptor. This was done by using electron donating substituents (Aakeröy et al., 2006). In the study by Aakeröy *et al*, two ditopic symmetric ligands were synthesized: 1,4-bis[(pyrazol-1-yl)methyl]benzene and 1,4-bis[(3,5-dimethylpyrazol-1-yl)methyl]benzene. Each compound was combined in a 2:1 acid – ligand ratio with 30 different carboxylic acids, these combinations were dissolved in ethanol and then slow evaporation was used to evaporate to dryness. Infrared spectroscopy was used to characterize all solids that were formed to learn if co-crystals resulted. Co-crystal formation was indicated by 2 broad bands at around 2500cm^{-1} ad 1900 cm^{-1}, which is characteristic of an O – H ⋯N (acid⋯N – heterocycle) hydrogen bond interaction.

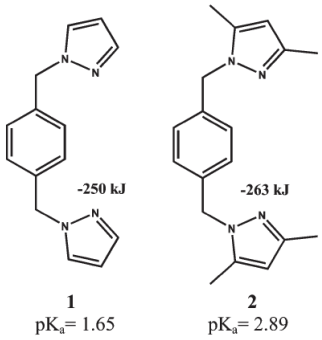


Figure 1. 4 1,4-bis[(pyrazol-1-yl)methyl]benzene (1) and 1,4-bis[(3,5-dimethylpyrazol-1-yl)methyl]benzene (2) (Aakeröy et al., 2006)

The covalent differences that distinguish 1,4-bis[(pyrazol-1-yl)methyl]benzene (Figure 1.5 (1)) from 1,4-bis[(3,5-dimethylpyrazol-1-yl)methyl]benzene (Figure 1.5 (2)) have enlarged the magnitude of the negative electrostatic potential on the nitrogen atom in 1,4-bis[(3,5-dimethylpyrazol-1-yl)methyl]benzene, this is displayed in the basicity (more likely to accept hydrogen bonds) of 1,4-bis[(3,5-dimethylpyrazol-1-yl)methyl]benzene in Figure 1.5. They concluded that with the more negative nitrogen acceptor atom, the probability of co-crystallization occurring improved (Aakeröy et al., 2006).

In light of this study, the effect of different heterocyclic compounds on co-crystallization with dicarboxylic acids will be investigated. Furthermore, in the development of co-crystal synthesis stability and thermodynamic factors should be considered. A co-crystal can be expected to form if the packing arrangements of the two molecules together are more thermodynamically stable than the original two molecules used to synthesize the co-crystal. Algorithms can then be developed to predict certain co-crystal structures as well as the thermodynamic stability of single and multi-component systems, which may be able to assist with screening for co-crystals. This is done by showing which arrangements of the involved molecules are thermodynamically likely (Karamertzanis et al., 2009).

1.1.6 Functional groups

Active pharmaceutical ingredients normally have some sort of functional group/s that will interact with other molecules. This presence of functional groups provides the means for biological activity and the potential to interact in more than one intermolecular interaction with a co-crystal former, solvent molecule or even itself which will lead to co-crystals, solvates or polymorphs respectively (Fleischman et al., 2003a).

Supramolecular synthons formed by certain functional groups, such as acid---acid, acid---amide, acid---pyridine, amide---amide, and so on are extremely important in the formation of intermolecular hydrogen bonds in the synthesis of co-crystals(An et al., 2017) also molecules that can form two hydrogen bonds have a higher probability of forming co-crystals (Nugrahani & Jessica, 2021) and are called bifurcated hydrogen bonds. One of the most frequently formed robust heterosynthon is the carboxylic acid with pyridine (Kastelic et al., 2010)

Pharmaceutical drugs normally have more than one hydrogen bonding site (donor and acceptor bonding sites), which gives rise to flexibility in the synthons and other functional groups that can be used for co-crystals. Pharmaceutical drugs with sites like this can normally form different types of hydrogen bonds. Different types of hydrogen bonds can be formed from the same functional group, and this is dependent on the donor or acceptor molecule that is used (Hutchins, 2018).

1.1.7 Stoichiometry and dimensionality

Most pharmaceutical co-crystals have a 1:1 stoichiometry in the unit cell, for example benzoic acid with isoniazid (Figure 1.6), however when using dicarboxylic acids as a co-former this would often force a 2:1 stoichiometry between the API and the co-former due to the dicarboxylic acid having two identical synthons. Therefore, when designing co-crystals of API's with dicarboxylic acid co-formers it would be prudent to use both 1:1 and 2:1 stoichiometric ratios.

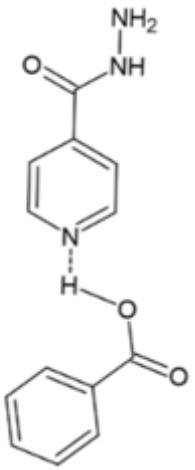


Figure 1. 5 INH:Bz(COOH) 1:1 co-crystal

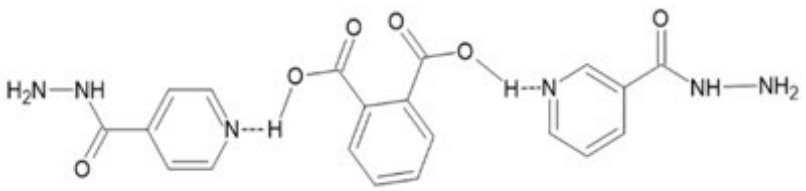


Figure 1. 6 INH:Bz(COOH)2 2:1 co-crystal

The differing number of synthons in the molecules may lead to different dimensionalities in the crystal structure, the simplest of these, where only one synthon is present forms a 0-dimensional (0D) dimer, these dimers are normally held together in the crystal structure through π-π stacking. Molecules held together by two synthons typically result in 1 dimensional (1D) ribbons and those with more than two synthons may result in 2 dimensional (2D) planes or 3 dimensional (3D) networks, depending on the geometries of the molecules (Burrows, 2003).

1.1.8 Heterocyclic active pharmaceuticals that contain a pyridine ring

1.1.8.1 Background of nitrogen containing heterocyclic API's

Heterocyclic active pharmaceutical ingredients containing a nitrogen atom that were used in this study and are listed in Table 1.5.

The APIs we are using form part of pyridinecarboxamide group. Most of these molecules contain a pyridine ring joined to an amide group or have a nitrogen / amide group present in their structure.

Isoniazid and pyrazinamide are used in the treatment of Tuberculosis (TB), niacinamide (vitamin B3) is used in many healthcare regimes.

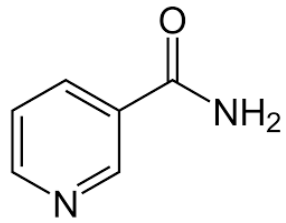
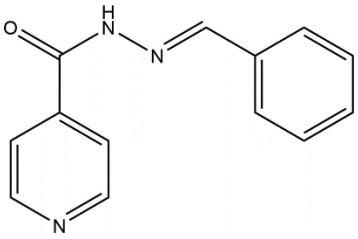
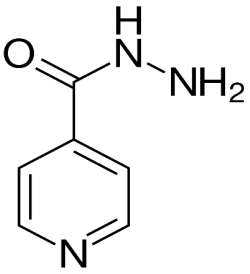
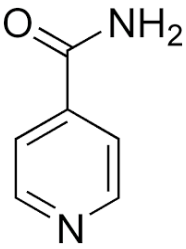
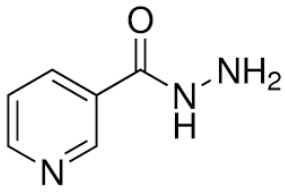
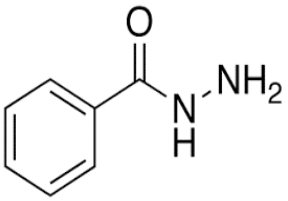
Carboxylic acid -aromatic nitrogen, hydroxyl aromatic nitrogen or acid- amide are popular and widely used heterosynthons the designing of co-crystals (Bis et al., 2007; Leiserowitz et al., 1977; Moragues-Bartolome et al., 2012; Papaefstathiou & MacGillivray, 2001)

We expect hydrogen bonding to occur through the COOH $\cdots N_{pyr}$ heterosynthon, as this is one of the key elements in co-crystal design (Kastelic et al., 2010) as well as what is known as a 'robust heterosynthon'.

Because we know that carboxylic acids readily form a robust heterosynthon with a nitrogen acceptor atom in a pyridine ring we have chosen to perform this study with a series of APIs with a pyridine ring as a skeleton in the structure, as well as derivatives of these.

The Heterocyclic pharmaceuticals that were chosen are listed in Table 1.5 below:

Table 1. 5 The N- heterocyclic pharmaceuticals used in this study

			
Niacinamide	Modified isoniazid	Isoniazid	Isonicotinamide
			
Nicotinic acid hydrazide (niazid)	Benzhydrazide		

1.1.8.2 Niacinamide

Niacinamide, also known as nicotinamide, is the amide form as well as physiologically active form of niacin (vitamin B3) (Fricker et al., 2018). Nicotinamide is a water-soluble essential nutrient regarding cell growth and maintenance (Maiese & Chong, 2003). While the deficiency of niacinamide results in the cause of pellagra (Procter & Gamble, 2002), niacinamide is now used for many skin issues and has been studied for its dermatological therapeutic benefits. With adequate bioavailability, niacinamide has been shown to have antimicrobial, vasoactive, antipruritic, and skin lightening effects as well as reduction in UV radiation-induced skin damage (Wohlrab & Kreft, 2014).

Niacinamide is a necessary component of the oxidoreduction co-enzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) (Procter & Gamble, 2002).

These co-enzymes are essential for maintaining redox homeostasis and regulating cellular metabolism and other biological events (Xiao et al., 2018). In cosmetics, niacinamide is regarded as safe and well tolerated (Wohlrab & Kreft, 2014).

While niacinamide is usually co-crystallized with API's, we have co-crystallized niacinamide with certain phthalic acid derivatives in this research.

1.1.8.3.Isoniazid

Isoniazid (INH) is one of the frontline drugs used in the treatment of Tuberculosis (TB) (Grobelny et al., 2011), one of the oldest infectious diseases in known history (Ngilirabanga et al., 2020). Due to modification of the API's properties using the supramolecular synthon approach, co-crystallization of isoniazid and other API's has gained a lot of attention (Grobelny et al., 2011).

INH has been widely used in co-crystallization because of its strong interactions with carboxylic acids – to generate pharmaceutical co-crystals (Lemmerer et al., 2010b). INH contains hydrazide and pyridine functional groups (Kamalakaran, 2018), the oxygen and nitrogen on the hydrazide groups are good hydrogen bond acceptor atoms and the nitrogen from the pyridine functional group is a great hydrogen bond acceptor (Swapna et al., 2014) .

Being an aldehyde, benzaldehyde is very reactive and therefore readily bonds covalently to isoniazid to form a Schiff base. Isoniazid is modified covalently with benzaldehyde by means of an acid catalysed condensation reaction. Firstly, nucleophilic attack of the carbonyl carbon occurs by the amine nitrogen, forming an unstable carbinolamine moiety, which is then followed by acid catalysed dehydration to form the imine (Xavier & Srividhya, 2014). The mechanism is displayed in Figure 1.8.

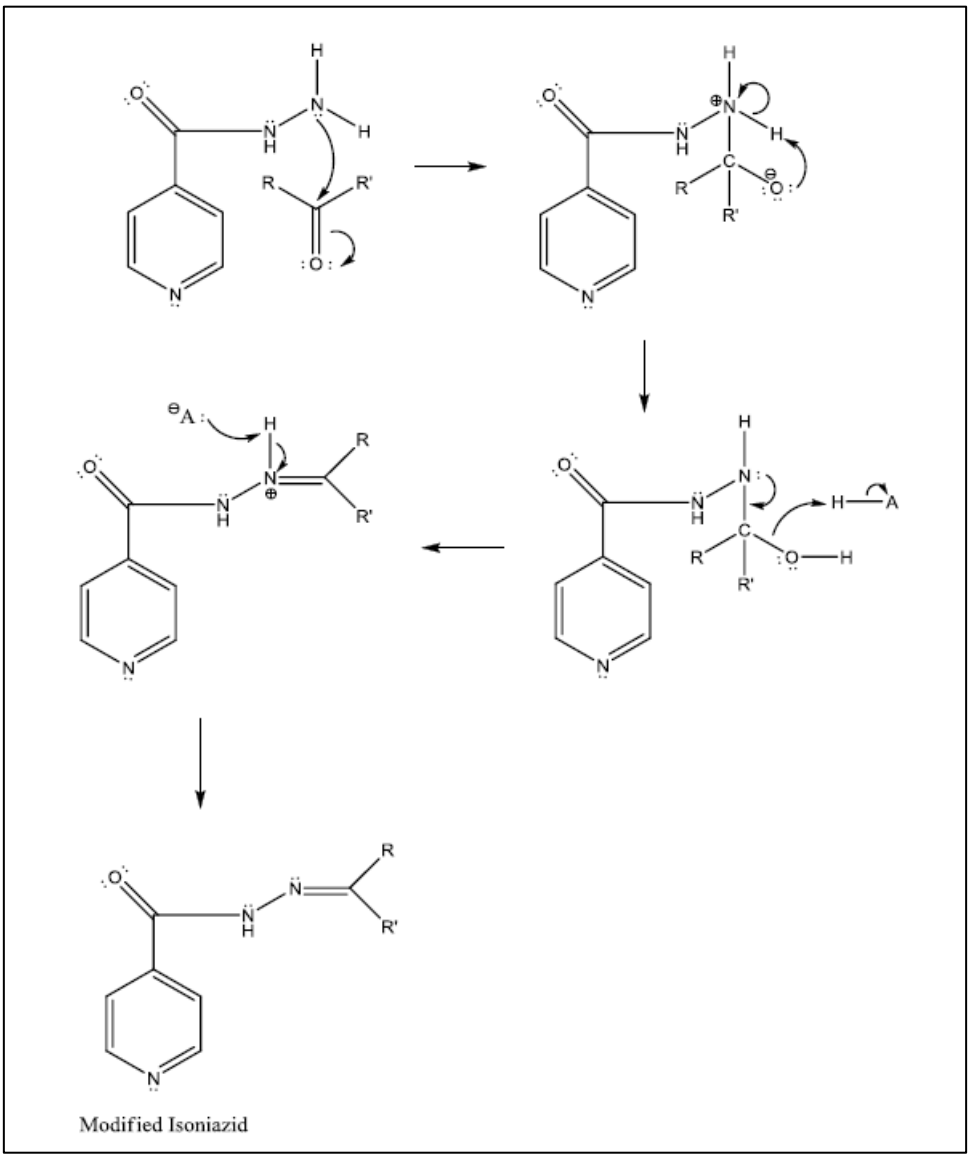


Figure 1. 7 Mechanism of covalent modification of isoniazid with benzaldehyde adapted from Xavier & Srividhya (2014)

1.1.8.4. Other Nitrogen heterocyclic API's

Similar structures to that of niacinamide and isoniazid were investigated to understand if there are general trends in hydrogen bonding and crystal packing.

Isonicotinamide is an isomer of niacinamide, differing in the position of the pyridine nitrogen. Isonicotinamide, like niacinamide, is thought to be very useful in co-crystallization because the pyridine nitrogen easily acts as an acceptor for hydrogen bonds, especially when paired with good hydrogen bond donors, such as carboxylic acids and alcohols (Báthori et al., 2011).

Niazid, or nicotinic hydrazide differs from isoniazid by the position of the pyridine nitrogen. Studies have claimed that nicotinic hydrazide derivatives possess antimicrobial, antimycobacterial, antitumour, anti-inflammatory, antiviral and antimalarial activities (Narang et al., 2012). Compared to

the other API's in this study, benzhydrazide or benzohydrazide differs in that there is no pyridine nitrogen in the ring. Benzhydrazide and its derivatives have become popular due to their biological properties, such as anti-bacterial, anti-fungal, anti-cancer and anti-tubercular activity (Kumari et al., 2018).

1.1.9 Dicarboxylic acids as functional groups

Organic acids that accommodate two functional carboxylic acid groups are known as dicarboxylic acids (Figure 1.9). They are involved in the production of many industrial materials but are also involved in the synthesis of APIs and additives (Parmar, 2014).

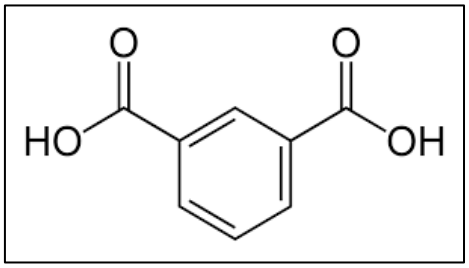


Figure 1. 8 Isophthalic acid – an example of a dicarboxylic acid

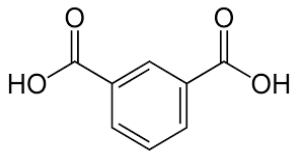
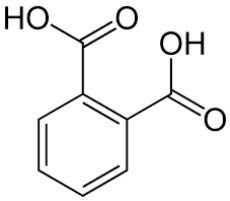
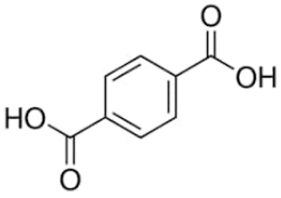
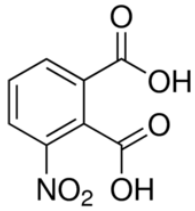
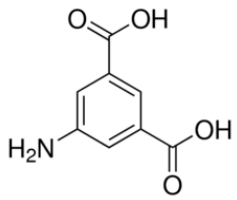
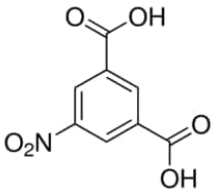
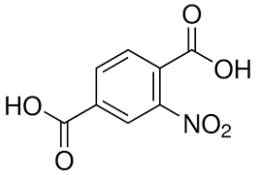
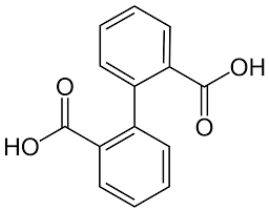
Dicarboxylic acids are used as co-crystal co-formers as the carboxyl groups (-COOH) are strong hydrogen bond donors as well as weak acceptors (Kastelic et al., 2010).

The selection of co-formers, based on the complementarity of their functional groups, size and form is one of the fundamental principles in co-crystal design (Cinčić et al., 2008; G. R. Desiraju, 2013; Moragues-Bartolome et al., 2012).

Dicarboxylic acids used as co-formers may also lead to multicomponent co-crystals, which might also provide better drug performance than single component co-crystals.

Phthalic acid derivatives that are structurally related acids are used in this study and are listed in the table below (Table 1.6).

Table 1. 6 Phthalic acid derivatives used in this study

			
Isophthalic acid	Phthalic acid	Terephthalic acid	3-Nitrophthalic acid
IUPAC: benzene-1,3-dicarboxylic acid	IUPAC: benzene-1,2-dicarboxylic acid	IUPAC: benzene-1,4-dicarboxylic acid	IUPAC: 3-nitrophthalic acid
			
5-Aminoisophthalic acid	5-Nitroisophthalic acid	Nitroterephthalic acid	Diphenic acid
IUPAC: 5-aminobenzene-1,3-dicarboxylic acid	IUPAC: 5-nitrobenzene-1,3-dicarboxylic acid	IUPAC: 2-nitroterephthalic acid	IUPAC: 2,2'-biphenyldicarboxylic acid

Isophthalic acid, an aromatic dicarboxylic acid, has remarkable chemical, thermal and radiation resistance(Jafari et al., 2023) and has a number of industrial uses, such as a main constituent of polyethylene terephthalate (PET) co-polymer (Isophthalic Acid - Chemical Economics Handbook (CEH) | S&P Global, 2023).

Phthalic acid, also known as 1,2-benzenedicarboxylic acid is of importance in the industrial world and is formed as a secondary product in the production of phthalic anhydride (Lorz et al., 2007).

Terephthalic acid (containing two carboxyl groups at the 1,4 position) is mainly used in the development of saturated polyesters (Luttrell & Hester, 2016). Terephthalic acid is also useful when preparing co-ordination polymers (Hasanova et al., 2023).

3-Nitrophthalic acid is a dicarboxylic acid (containing a nitro group) which crystallizes in the $P2_1/n$ monoclinic space group and can be found naturally in fruit extract, carom seed essential oil and a number of other sources (Kahkesh & Zargar, 2023). It is a building block in supramolecular chemistry (Z. Li et al., 2024) and known for having non-linear optical as well as its high stability and good thermal stability (Ramesh et al., 2023).

5-aminoisophthalic acid, a dicarboxylic acid with an amino group and is used a lot in the metal organic frameworks of co-ordination chemistry (H. N. Wang et al., 2011), but is also used in co-crystal engineering (Mcguire et al., 2016). 5-aminoisophthalic acid can react with a number of aldehydes to form Schiff bases, due to the amino group, by removing water molecules (L. J. Zhang et al., 2019).

5-nitroisophthalic acid contains carboxylic functional groups which can act as hydrogen bond donors as well as acceptors (Hiendrawan et al., 2016), as well as a nitro group, which can act as a hydrogen bond acceptor. 5-nitroisophthalic acid has exceptional chemical and thermal stability (Chen et al., 2010) which makes it a very nice compound in co-ordination chemistry and in crystal engineering.

Nitroterephthalic acid contains two carboxyl groups, one in the *para* position, and a nitro group in the *ortho* position of the benzene ring (Bourletidis How et al., 2023). Nitroterephthalic acid has not been utilized a lot in the crystal engineering world, and it would be interesting to see what else can be done with this molecule.

Diphenic acid, also known as dibenzoic acid or 2,2'-benzoic acid, is not a phthalic acid derivative but is a dicarboxylic acid, containing a carboxylic acid group on each of the benzene rings, diphenic acid also exhibits atropisomerism (an isomerism that occurs when a single bond cannot rotate because of steric hindrance, caused by a bulky group being present) (Yurdakul et al., 2022). Diphenic acid is used in co-ordination chemistry to form various co-ordination polymers (Malaestean et al., 2009).

1.2. Aims and objectives:

The aim of this study was to develop co-crystal design strategies and to understand co-crystal structures of nitrogen-containing heterocyclic active pharmaceutical ingredients with certain phthalic acid derivatives as their co-formers.

The specific objectives of the study were;

- Preparation of a series of niacinamide (nicotinamide) co-crystals with phthalic acid derivative co-formers as well as to investigate their structures.
- Preparation of a series of isoniazid and modified isoniazid co-crystals with phthalic acid derivative co-formers as well as to investigate their structures.
- Preparation and investigation of other nitrogen-containing heterocyclic API's with phthalic acid derivatives and to obtain an understanding of their crystal structures.

The Cambridge Structural Database (version 5.4.3) 2021 (Groom et al., 2016), will be referred to the CSD throughout the dissertation.

This dissertation is presented with a short literature review, chapter2, highlighting some of the work that has been done with the API's and co-formers used in this study, followed by the experimental techniques used in chapter 3. The results from the experimental work are discussed in chapter 4, followed by the conclusion of the dissertation in chapter 5.

Chapter 2 - Literature review

2.1. Background

Discovered in 1844 when Wöhler co-crystallized quinhydrone from 1,4-benzoquinone and hydroquinone (G. R. Desiraju, 2013), co-crystals have been with us for a while and continue to be of interest due to their pharmaceutical properties and their use in other industries.

A co-crystal is recognized as a pharmaceutical co-crystal, if the following requirements are met; at minimum, one of the co-formers is regarded as an API and the other is pharmaceutically acceptable (Duggirala et al., 2016) or on the GRAS list. Most pharmaceutical co-crystals fall into the category of molecular co-crystals. Molecular co-crystals normally contain two or more different and neutral co-formers in a stoichiometric ratio which are normally held together by hydrogen bonds or halogen bonds (Coates et al., 1998).

2.2. Active pharmaceutical co-crystals

Active pharmaceutical ingredients with a crystalline/ crystal structure have preference in the pharmaceutical industry for the following reasons (Almarsson & Zaworotko, 2004):

1. Physico- chemical stability that the crystal structure gives.
2. Improved purity.
3. Ease of isolation.

When co-crystallization occurs between an API and a GRAS compound, the pharmacological activity of the API is not affected but the physical properties of the drug can be improved (Sekhon BS, n.d.). Pharmaceutical co-crystals have the ability to improve certain physiochemical properties of pharmaceutical drugs, such as bioavailability, solubility, permeability, stability, tabletability and melting point to name a few (Chaudhari et al., 2018). Due to the composition and arrangement of molecules in a crystal lattice directly affecting the crystal properties means that manipulation of the co-former can open the doorway to a wide range of co-crystals with different physiochemical properties as well as the desired physiochemical properties (Kumar et al., 2018).

Altering the melting point of certain API's can be manipulated by co-crystallizing the API with a co-former. In a study by Zhang *et al* 2017, carbamazepine (CBZ) was co-crystallized with nicotinamide (NIC) and saccharin (SAC) as co-formers. They were dissolved in a mixture of ethanol and water.

Differential scanning calorimetry (DSC) was used to measure the melting point (MP) of the starting material and it was found that the MP for CBZ in ethanol and water was 195ºC and for NIC in the same solvent was 132ºC. The melting point of the co-crystal of CBZ and NIC was determined by DSC to be 162ºC, which was between the MPs of the pure CBZ and NIC (H. Zhang et al., 2017).

Bioavailability is the rate and degree that a pure drug/compound gets absorbed into the systemic circulation (Chaudhari et al., 2018). Bioavailability and solubility are related in certain ways. Studies have demonstrated that co-crystals with API's may increase the bioavailability in BCS class II compounds- low solubility/ high permeability and BCS class III compounds – low permeability (Nugrahani & Jessica, 2021). Co-crystals are very stable because of their crystalline structure (Babu & Nangia, 2011).

Normally salt formulation is used to enhance the solubility of a pharmaceutical drug, but at most times this method proves unsuccessful with molecules that don't have a functional group that is ionizable or that have sensitive moieties that are easily decomposed or are not acidic/ basic enough to allow for salt formation (Babu & Nangia, 2011).

Because of their crystalline structure, co-crystals are stable and have huge solubility advantages over the crystalline drug form (Chaudhari et al., 2018).

Nechipadadappu *et al* synthesized two co-crystals of the anti-inflammatory drug flufenamic acid (FFA) with 4-nitrobenzoic acid (CNB) and ethenzamide (ETZ) using the solvent evaporation method and solvent drop-assisted grinding method. These co-crystals were characterized by several spectroscopic methods and single crystal x-ray diffraction was used to solve the crystal structures. In the FFA-CNB co-crystal a strong supramolecular acid-acid homosynthon was noted while in the FFA-ETZ was formed by means of a strong supramolecular acid-amide heterosynthon. The solubility study in Milipore water showed that FFA's solubility was increased by twice as much in the form of the FFA-CNB co-crystal, however there was no change in the solubility of FFA in the FFA-ETZ co-crystal.

In a solution of 0.1N HCl (pH 1) there was 5 times increase in the solubility of FFA in the FFA-NCB and FFA-ETZ co-crystals. (Nechipadappu et al., 2017)

In a study by Babu and Nangia (2011), it was found that around 60-70% of pharmaceutical drugs fall into the biopharmaceutics classification system (BCS) Class II –low solubility/ high permeability and BCS Class IV – low solubility/ low permeability (Babu & Nangia, 2011), the biopharmaceutics classification system of drugs is shown in Figure 2.1. This causes issues with several attributes including solubility, dissolution, stability, therapeutic efficacy and many more (Chaudhari et al., 2018).

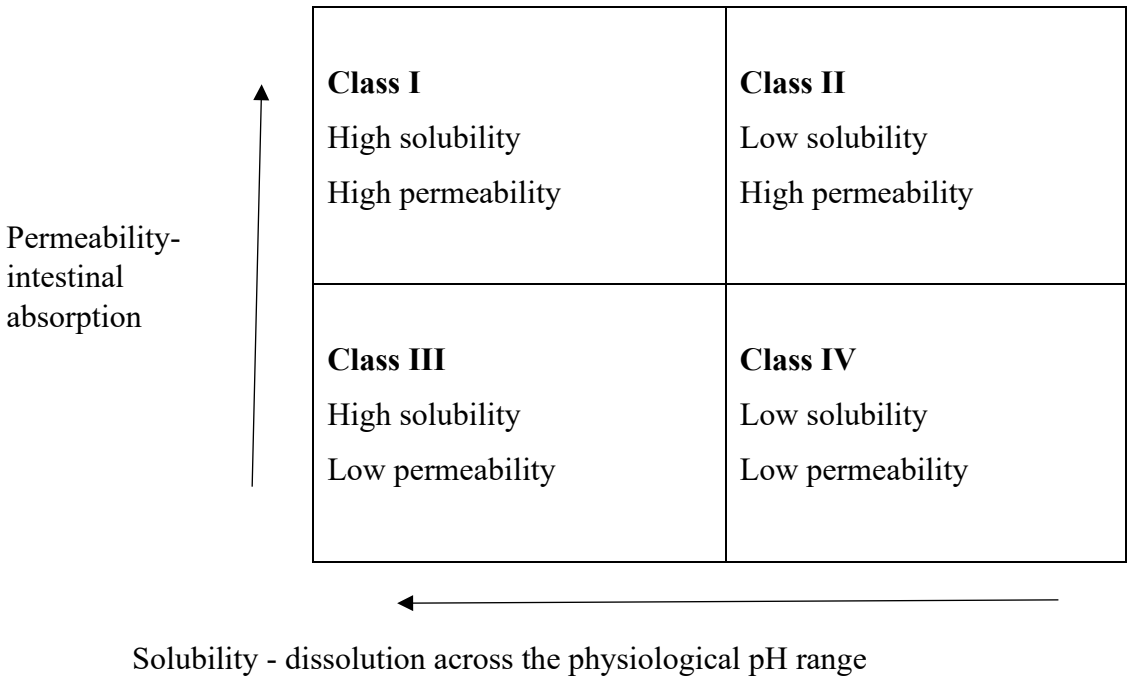


Figure 2. 1 Biopharmaceutics Classification system of drugs according to oral administration and intestinal absorption parameters (Babu and Nangia, 2011)

2.2.1. Niacinamide and its co-crystals

Niacinamide is normally used as a co-former, although in this study it was used as an API.

In a study by Berry *et al (*2008), niacinamide was co-crystallized with a number of active pharmaceutical ingredients; fenbufen, salicyclic acid, ibuprofen (racemic mixture and *S*-enantiomer), ketoprofen (R/S), paracetamol, flurbiprofen (R/S) and piracetam. From this study, three new co-crystal systems were identified, namely, ibuprofen (R/S and S) and salicylic acid (Berry et al., 2008).

Aceclofenac – a drug used for pain and inflammation with osteoarthritis and rheumatoid arthritis, has been co-crystallized with niacinamide. These co-crystals were prepared neat grinding and solution crystallization methods (Sodanapalli & Nair, n.d.).

Huang *et al* did a study in which they co-crystallized niacinamide with phloretin- a compound found in certain fruits naturally (Aitipamula et al., 2022). Phloretin has antioxidative and anti-inflammatory effects (Behzad et al., 2017), but due to its low bioavailability and substandard aqueous solubility (B. Li et al., 2011), phloretin's clinical application is limited. In the study by Huang *et al* (2019), co-crystals of phloretin · niacinamide and phloretin · isonicotinamide were prepared in a 1:1 molar ratio. Both of these co-crystals displayed an enhancement in the dissolution properties of phloretin when compared to pure phloretin, exhibiting the advantages of co-crystallization in drug manipulation

(Huang et al., 2019). The chemical structures of each starting material in this study can be seen in Figure 2.2.

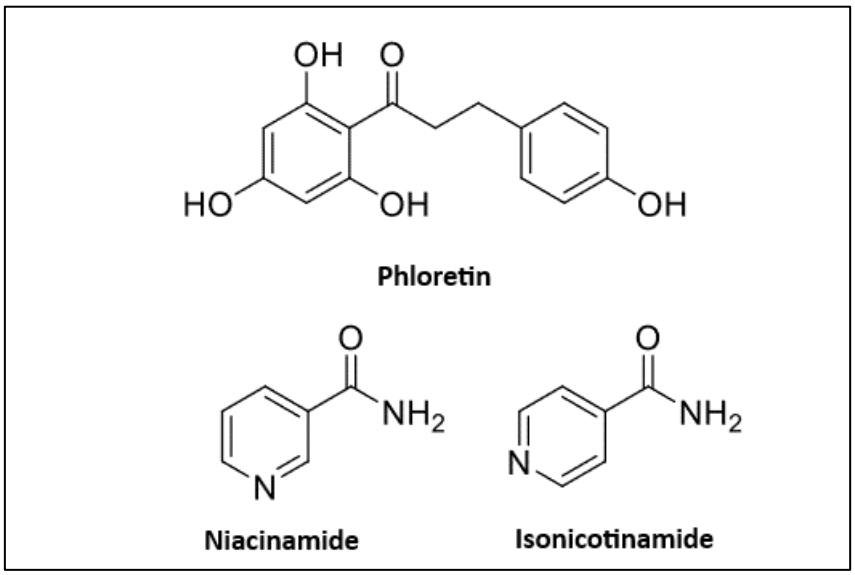


Figure 2. 2 Chemical structures of phloretin, niacinamide and isonicotinamide adapted from Huang et al., 2019

The non-steroidal anti-inflammatory drug, ibuprofen was co-crystallized with niacinamide in a study by Soares *et al* in order to quantify the ibuprofen · niacinamide co-crystal, as quantification is beneficial for the determination of the yield of the co-crystallization reaction as well as the purity of the final product acquired. Results of mid-infrared (ATR-FTIR), X-ray diffraction (XRD), Raman spectroscopy and differential scanning calorimetry (DSC) were evaluated for the quantification of the co-crystal (and its co-formers) so a calibration model could be made (to evaluate the purity of the co-crystal). Raman spectroscopy had the best result, with XRD having good results for the quantification of the co-formers, but only reasonable results for the co-crystal itself. DSC and ATR-FTIR were not efficient for quantification of the mixture (Soares & Carneiro, 2014).

Niacinamide and isonicotinamide were co-crystallized with various nitrogen heterocycle – containing aromatic dicarboxylic acids in a study by Das *et al* 2011. The dicarboxylic acids used were 3,5-pyrazole dicarboxylic acid, quinolinic acid and dipicolinic acid where the niacinamide- 3,5-pyrazole dicarboxylic acid co-crystal (in a 1:1 ratio) is held together by acid-pyridine and acid – amide supramolecular heterosynthons, what is interesting that the amide-amide common supramolecular homosynthon is not present (Das & Baruah, 2011). There is a fairly uncommon four hydrogen bonded heterosynthon which can be seen in Figure 2.3.

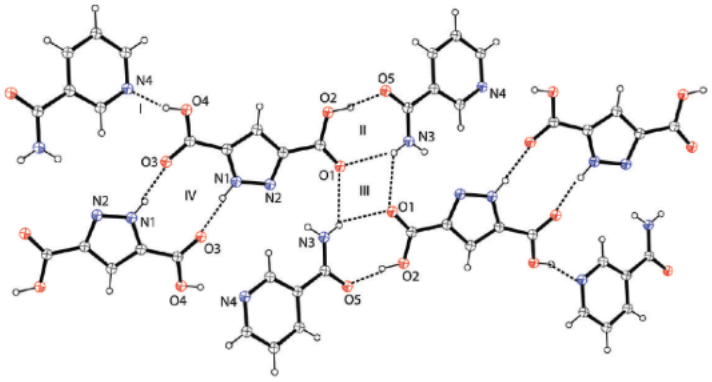


Figure 2. 3 The four different synthons present in the niacinamide- 3,5-pyrazole dicarboxylic acid, adapted from Das & Baruah, (2011).

The isonicotinamide - 3,5-pyrazole dicarboxylic acid co-crystal (in a 2:1 ratio), forms four different heterosynthons with the two isonicotinamide molecules, shown in Figure 2.4.

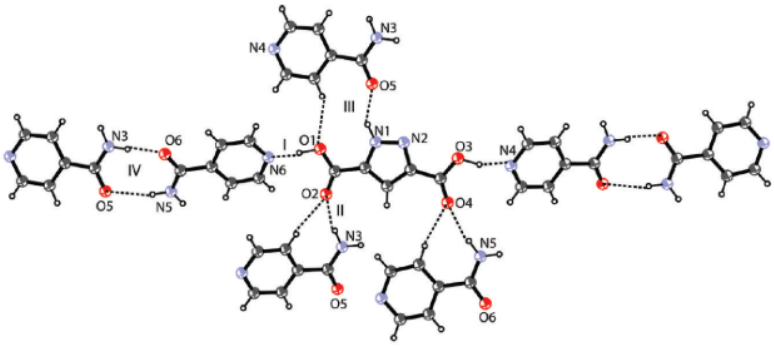


Figure 2. 4 The four different heterosynthons of the isonicotinamide - 3,5-pyrazole dicarboxylic acid co-crystal adapted from Das and Baruah, (2011)

The niacinamide – dipicolinic acid co-crystal displayed a water bridge assembly, but the isonicotinamide – dipicolinic co-crystal formed a six-component assembly via the isolated solvent water molecules that are between the molecules. Salts formed with the niacinamide and quinolinic acid and isonicotinamide and quinolinic acid (Das & Baruah, 2011). The structures of the starting materials are seen in Figure 2.5.

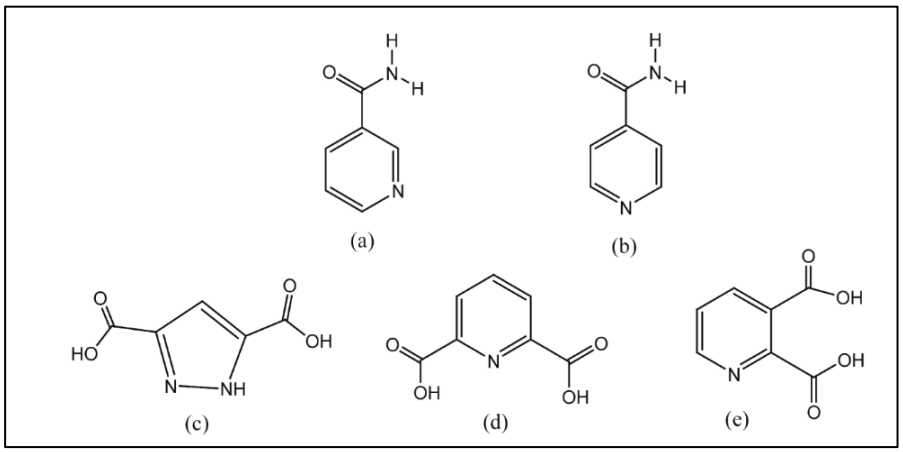


Figure 2. 5 Structures of (a) niacinamide (b) isonicotinamide (c) 3,5-pyrazole dicarboxylic acid (d) dipicolinic acid (e) quinolinic acid. Adapted from Das and Baruah, (2011)

2.2.2. Isoniazid and *N'*-benzylidenepyridine-4-carbohydrazide (modified isoniazid) co-crystals

Isoniazid is most frequently co-crystallized with carboxylic acids (86% of 110 multi-component crystals of INH) according to a search done on the CSD by Batisai (2020). A lot of research has gone into the co-crystallization of isoniazid with other GRAS compounds, because although INH has remarkable physiochemical and efficacy properties (Liu et al., 2020), it is causes hepatotoxicity (Dye, 2006) which is a serious health issue. In a study by Liu *et al*, INH was co-crystallized with quercetin (QCT) – a hepatoprotective nutraceutical. QCT has a poor water solubility while INH is considered as a soluble drug, so the strategy of this study was to combine the two via co-crystallization and increase the bioavailability of QCT, which will significantly increase the hepatoprotective properties of QCT, which would reduce the hepatotoxicity of INH. It was found that through co-crystallization the dissolution rate of QCT increased. A hepatotoxicity study of INH in rats displayed that the effects of serious hepatotoxicity was almost eliminated (Liu et al., 2020). The structures of INH and QCT from the above study are displayed in Figure 2.6.

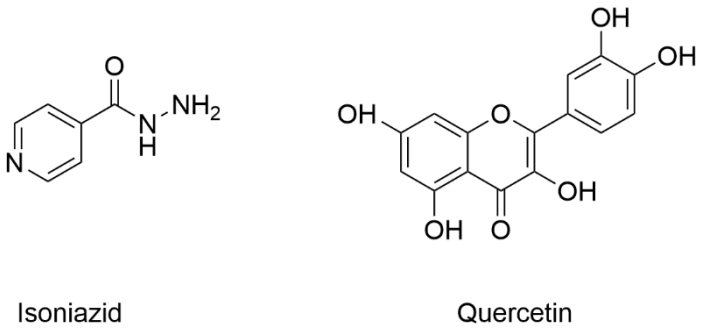


Figure 2. 6 The chemical structures of isoniazid (INH) and quercetin (QCT) adapted from Liu et al., (2020)

Isoniazid was reacted with benzoic acid, sebacic acid, suberic acid and cinnamic acid to form co-crystals via solvent evaporation and liquid assisted grinding in a study by Sarcevica *et al* (2013). A crystal structure study shows the existence of a pyridine – carboxylic acid synthon in the co-crystals analyzed. There is hydrogen bonding of the hydrazide moiety of INH via N–H···O and N–H···N, leading to different supramolecular synthons. A comparison of the INH-dicarboxylic acid (in a 2:1 ratio) displays a decrease in the melting point with an increase in the length of the dicarboxylic acid, also it was found that the solubility of the co-crystals formed increases with the increasing solubility of the dicarboxylic acid (Sarcevica et al., 2013). The structures of the starting materials are shown in Figure 2.7.

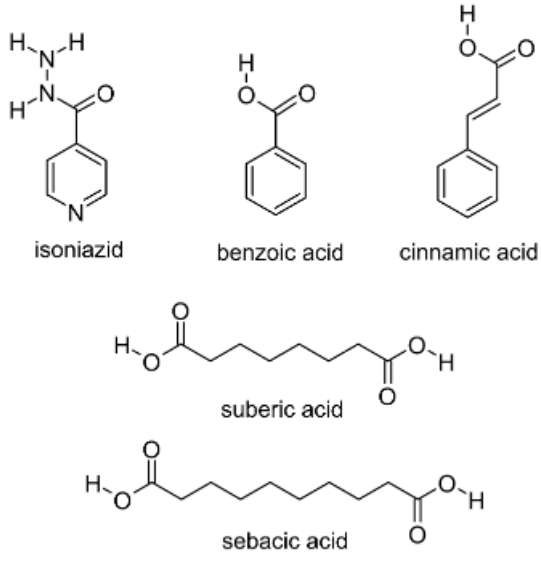


Figure 2. 7 Structures of the starting materials used in the above study, adapted from Sarcevica et al., (2013)

Dragostin *et al* (2019) synthesized new isoniazid (modified isoniazid) derivatives in a study titled "*New isoniazid derivatives with improved pharmaco-toxicological profile: Obtaining, characterization and biological evaluation*". INH was reacted with benzaldehyde, 2-nitrobenzaldehyde and 4-bromo-benzaldehyde in a 1:1 molar ratio via condensation reactions which lead to the new hydrazones of INH shown in Figure 2.8 (where INH-a is modified with benzaldehyde, INH-b is modified with 2-nitrobenzaldehyde, and INH-c is modified with 4-bromo-benzaldehyde). It was found that these compounds exhibit an improved pharmaco-toxicological profile, when compared to isoniazid (Dragostin et al., 2019).

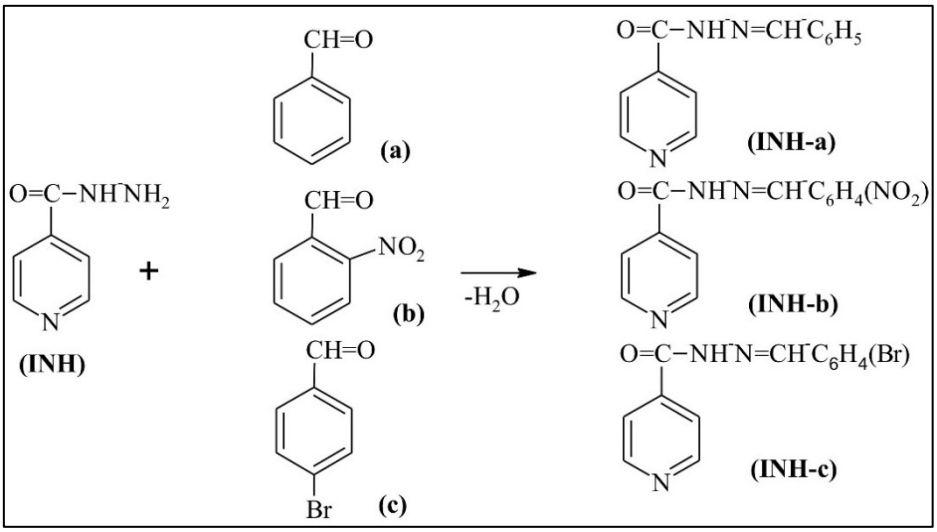


Figure 2. 8 The general reaction for obtaining the three modified benzaldehyde molecules adapted from Dragostin et al., (2019)

An unforeseen co-crystal of modified INH was formed in a study by Setshedi *et al* (2023). The aim was to modify INH with benzaldehyde and crystallize the product. Instead, the excess benzaldehyde spontaneously autoxidized to form benzoic acid and then the carbohydrazide group co-crystallized with the benzoic acid to form *N'*-[(2-methylphenyl)methylidene]pyridine-4-carbohydrazide–benzoic acid (Setshedi et al., 2023). The process in which this occurred is displayed in Figure 2.9.

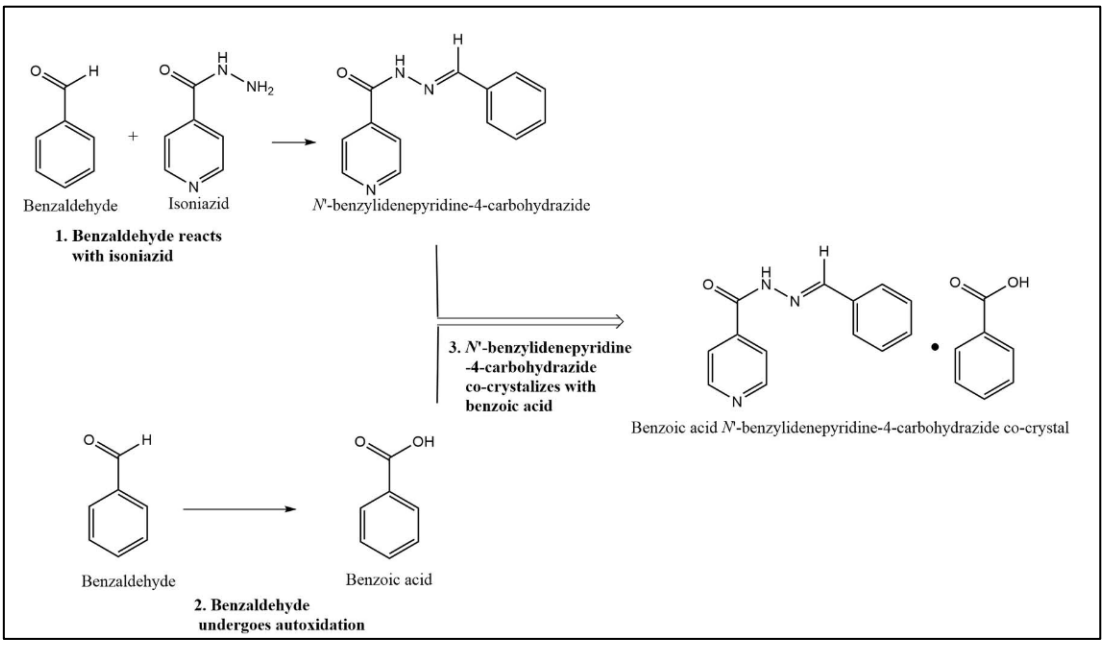


Figure 2. 9 Modification of INH with benzaldehyde, autoxidation and co-crystallization (Setshedi et al., 2023).

2.2.3 Co-crystals of nitrogen-containing heterocyclic API's

Isonicotinamide has been co-crystallized with many carboxylic acids, making use of the robust carboxylic acid···pyridine hydrogen bond (Báthori et al., 2011). Lemmerer and Fernandes (2012), co-crystallized isonicotinamide with cyclopropanecarboxylic acid, cyclobutanecarboxylic acid, and cyclopentanecarboxylic acid, all of which were liquid carboxylic acids, and cyclohexanecarboxylic acid, a solid carboxylic acid (Lemmerer & Fernandes, 2012).

In a study by Wisudyaningsih *et al* (2019), isonicotinamide was co-crystallized with QCT as well. QCT was co-crystallized with isonicotinamide using solvent evaporation methods resulting in QCT·isonicotinamide co-crystals. In the study it was found that the QCT·isonicotinamide co-crystal increased its in vitro dissolution rate (Wisudyaningsih et al., 2019).

Tothadi and Desiraju (2012) displayed Etter's generalization (the best hydrogen bond acceptor partners with the best donor) (Etter, 1990) in the co-crystallization of isonicotinamide with 3,5-dinitrobenzoic acid – where an unusual N-H···N hydrogen bond pattern was displayed (Tothadi & Desiraju, 2012). They reported, from a CSD search, that in 1:1 co-crystals of isonicotinamide with monocarboxylic acids, hydrogen bonding takes place preferably between the pyridine nitrogen and the carboxyl group. In Figure 2.10, synthon I illustrates the concept of Etter's generalization, that the best hydrogen donor bonds with the best acceptor, which in turn leaves the amide groups to hydrogen bond to each other as shown as synthon II in Figure 2.10. Synthon II correlates to the second-best acceptor partnering with

the second-best donor. Synthon III is formed when hydrogen bonding takes place between the pyridine nitrogen and the C=O of the amide moiety. However, when co-crystallization of the above staring materials is dissolved in tetrahydrofuran, synthon II is not directly formed and instead an unusual N-H···N hydrogen is formed by the amide NH_2 and the pyridine nitrogen, which gives synthon IV, displayed in Figure 2.10 (Tothadi & Desiraju, 2012).

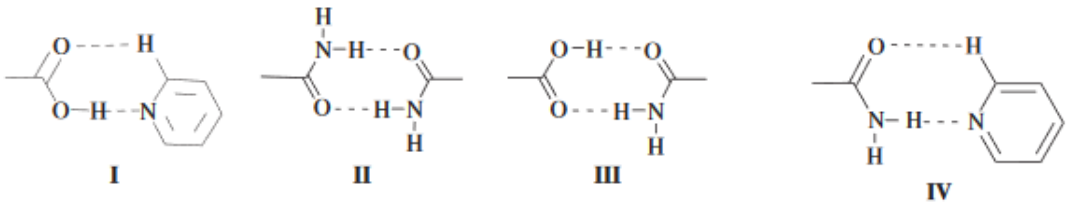


Figure 2. 10 Synthons formed in the study by Tothadi and Desiraju (2012),

There has been very little work done with benzhydrazide so far. Benzhydrazide is also known as benzohydrazide. In 1992, Kallel *et al* published a synthesized crystal of benzhydrazide by reacting benzoyl chloride with hydrazine (Kallel & Amor, 1992). Benzhydrazide crystallizes in the monoclinic $P2_1/c$ space group. (Svoboda & Fuess, 1992). (*E*)-4-hydroxy-*N'*-(3-methoxy-benzylidene)benzohydrazide (a derivative of benzhydrazide) was synthesized and crystallized in a study by Chantrapromma *et al* (2016), to study its α-glucosidase inhibitory activity.

Niazid or nicotinic acid hydrazide was crystallized by Priebe *et al* (2008) from the reaction of ethyl nicotinate with hydrazine hydrate in methanol, which crystallizes in the orthorhombic, $P2_12_12_1$ space group (Priebe et al., 2008). A study by Lemmerer *et al* (2010) used two types of supramolecular synthesis to produce a niazid – adipic acid co-crystals, one being "conventional supramolecular synthesis" – where no covalent reactions occur and "covalent assisted supramolecular synthesis" – in which one of the supramolecular molecules go through an intended covalent reaction with the second molecule as can be seen in Figure 2.11. Figure 2.11 also displays the conventional supramolecular synthesis produces 2D flat sheet structures, whereas the covalent assisted supramolecular synthesis creates 1D ribbons (Lemmerer et al., 2010a).

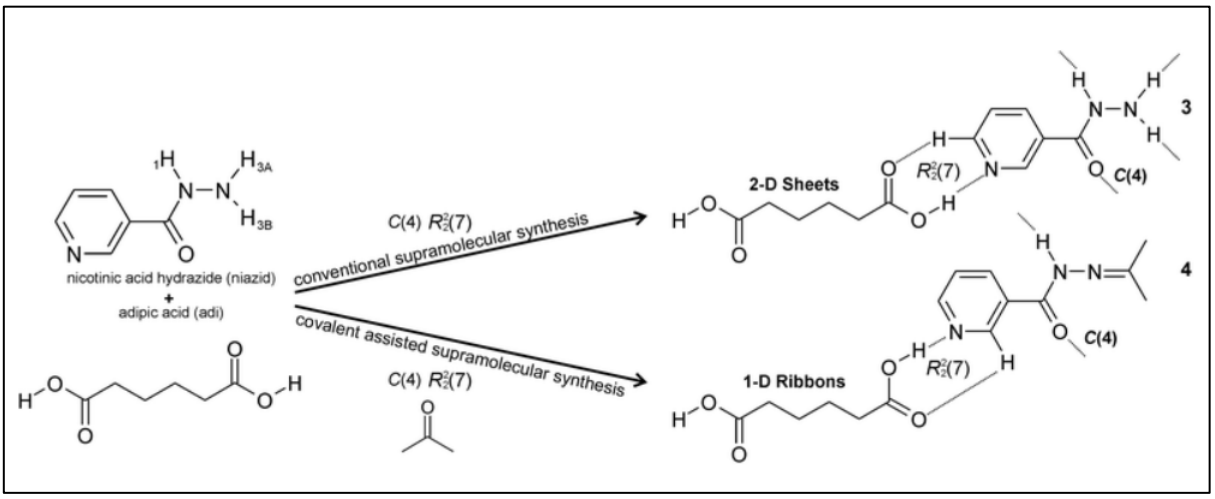


Figure 2. 11 Two types of supramolecular synthesis between niazid and adipic acid taken from Lemmerer et al., (2010a)

2.3. Co-formers used in this study

Moragues-Bartolome *et al* (2012) studied synthon preferences in the co-crystals of cis-carboxamides with carboxylic acids, using a number of database analyses, theoretical calculations and co-crystallization techniques. The *cis*- carboxamides were classified into three groups: primary amides, cyclic amides and cyclic imides. It was found that primary amides, for the most part, form heterosynthons with carboxylic acids while cyclic imides hardly form co-crystals with carboxylic acids and these types of co-crystals are very rare. Whereas with cyclic amides the amide-amide homodimer is maintained, and the carboxylic acid groups interact with the homodimer through side interactions, which results in an acid-(amide—amide)-acid structure in 66% of cases (Moragues-Bartolome et al., 2012).

Isophthalic acid was crystallized in a study by Alcala *et al* (1972) to determine if isophthalic acid has hydrogen intermolecular bonding between the carboxyl groups as compared to a series of 12 other benzenecarboxylic acids, which isophthalic acid did. Isophthalic crystallizes in a monoclinic $P2_1/c$ space group with four molecules per a unit cell (Alcala et al., 1972).

In a study that looked at the mechanical behaviour of pharmaceutical co-crystals by Bag *et al* (2021), isoniazid was co-crystallized with phthalic acid and isophthalic acid using the slow evaporation method. It was found that isoniazid co-crystallizes with isophthalic acid in 3D interlocked packing which made the co-crystal have the same brittle properties as isoniazid had originally. Whereas co-crystallization of isoniazid with phthalic acid resulted in an increase of plasticity (due to a 2D layer structure) of the co-crystal (Bag et al, 2021), this can be seen in Figure 2.12.

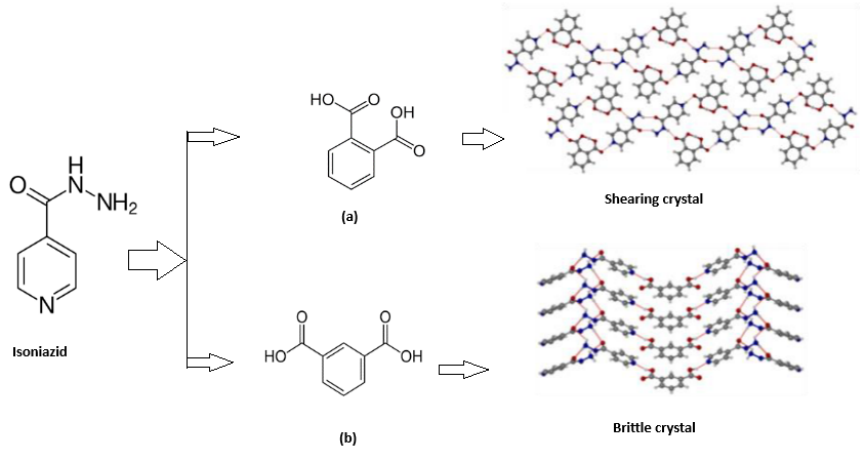


Figure 2. 12 Schematic diagram of INH co-crystallized with (a) phthalic acid and (b) isophthalic acid, adapted from Bag et al, (2021).

A search of co-crystals of isophthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with corresponding literature references and CSD reference codes, are listed in table 2.1.

Table 2. 1 Co-formers used to prepare co-crystals of isophthalic acid on the Cambridge Structural Database (version 5.4.3 - 2021) with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2021	Isoniazid	BAJXAP	(Bag, 2021b)
2011	phenanthridine	AXUGOQ	(Orola et al., 2011)
2009	1,2-bis(4-pyridyl)ethane	COZYUM	(Weyna et al., n.d.)
2010	1,4-diazabicyclo[2.2.2]octane	CUWZAW	(Marivel et al., n.d.)
2019	benzoylmetronidazole	DOGCEK	(Turner et al., 2019a)
2003	N,N'-bis(2-Pyridyl)-1,3-diaminobenzene	GABYUE	(Bensemann et al., n.d.)
2015	bis(1-(4-(1H-imidazol-1-yl)phenyl)-1H-imidazol-3-ium) 1,1'-(1,4-phenylene)bis(1H-imidazole), bis(3-carboxybenzoate)	HUTYIG	(Meng et al., 2015)
2015	2,6-bis(pyridin-4-ylmethylene)cyclohexanone	AXIMAX	(Li et al., 2015)
2015	2-((dimethylamino)methyl)-1,5-bis(pyridin-4-yl)penta-1,4-dien-3-one	AXIMEB	(Li et al., 2015)
2019	2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl benzoate	DOGCEK	(Turner et al., 2019b)
2003	N,N'-bis(2-Pyridyl)-1,3-diaminobenzene	GABYUE	(Bensemann et al., 2003a)
2004	pyridine solvate	IYUPEX	(Dale et al., n.d.)
2005	1,3-bis(4-Pyridyl)propane	JAWVOT	(Balakrishna R Bhogala et al., 2005)
2018	bis(4,4'-(azulene-1,3-diyl)dipyridine)	JIKTUV	(Ion et al., 2018)
2005	1,4-bis((Imidazol-1-yl)methyl)benzene	LATLIC	(Aakeröy et al., 2005a)
2005	bis(4-methylpyridine)	LAWBER	(Jin et al., n.d.)
2014	4,4'-bipyridine	LOYRIC	(Khan et al., 2015)

2001	Hexamethylenetetraamine	MIPVOW	(Li et al., 2001)
2005	2,5-bis(pyrid-3-yl)-1,3,4-oxadiazole	NANQAV	(Du et al., 2005a)
2005	2,5-bis(pyrid-4-yl)-1,3,4-oxadiazole	NANQEZ	(Du et al., 2005a)
2012	bis(4,6-dimethoxypyrimidin-2-amine)	NEBXOJ	(Ebenezer and Muthiah, 2012)
2007	bis(N-((4-Pyridyl)methyl)acetamide)	NEWSEO	(Aakeröy et al., n.d.)
2009	4-amino-3,5-bis(pyridin-4-yl)-1,2,4-triazole	NUGZEVO1	(Du et al., 2009a)
1998	1,3-bis((2-Aminopyrid-6-yl)ethynyl)benzene	NUHMEI	(Bielawski et al., 1998)
2007	3,6-bis(2-pyrazinyl)-1,4-dihydro-1,2,4,5-tetrazine	PESROV01	(Fu et al., 2007)
2010	Caffeine	PUPGUD	(Mahapatra et al., 2010)
2008	4-(5-(4-pyridyl)-1,3,4-oxadiazol-2-yl)pyridine N-oxide	RIYXUT	(Hou et al., 2008)
2007	bis(2-Amino-4-methyl-6-phenylpyrimidine)	SIYCEJ	(Goswami et al., 2007)
2013	5-(4-(1H-imidazol-1-yl)phenyl)pyrimidine	TENSIQ	(Dai et al., 2013)
2013	5-(pyridin-4-yl)pyrimidine	TENSOW	(Dai et al., 2013)
2013	2,4-Diamino-6-phenyl-1,3,5-triazine	TEZNET	(Delori et al., n.d.)
2003	Benzimidazole	VARJAA	(Trivedi et al., n.d.)
2008	Di-4-pyridyl sulfide	VOHWUL	(Qin et al., 2008)
2002	4,4'-Bipyridyl	XUNGIW	(N Shan et al., 2002)
2011	1,2-bis(4-pyridyl)ethene	YAHJIC	(Liu and Li, 2011)
2015	1,1'-butane-1,4-diylbis-1H-imidazole	YUMQOO	(Jin et al., 2015)
2022	4,6-dimethoxy-N^1,N^3-bis(pyridin-4-yl)benzene-1,3-dicarboxamide	VAPPEL	(Xing et al., 2022)

Although phthalic acid has little use in the industrial industry, it may prove to be very useful in the pharmaceutical industry. Phthalic acid was shown to increase the solubility of telmisartan (non-peptide angiotensin II antagonist), which is used in the treatment of arterial hypertension (Kundu et al., 2018). Phthalic acid was co-crystallized with telmisartan using the solution crystallization method and the reaction crystallization method, these co-crystals were shown to have an 11-fold and 22-fold increase in solubility when compared to the solubility of just telmisartan (Kundu et al., 2018).

Phthalic acid has also been co-crystallized with etoricoxib (used to treat a number of arthritis issues); the co-crystal was made using the slow evaporation method. The asymmetric unit of this crystal structure has one molecule of phthalic acid and one molecule of etoricoxib, which indicates that hydrogen bonds play an important role in maintaining the crystal structure (Ma et al., 2023).

A search of co-crystals of phthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.2.

Table 2. 2 Co-formers used in the preparation of phthalic acid found on the Cambridge Structural Database (version 5.4.3), with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2021	2-(cyclohexanecarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one	DAJZIB	(Liu et al., 2021)
2001	bis(trans-cinnamamide)	EBOSIX	(Ohba et al., 2001)
2016	2-Methylpyridinium 2-carboxybenzoate hijikis	EMUMIK	(Sivakumar et al., 2016)
2011	4-chloro-6-methylpyrimidin-2-amine	EXEZAJ	(Ebenezer et al., 2011)
2019	N,N-dimethylurea	GUZVEF	(Saunders et al., 2019)
2018	pyrazin-2-amine	JIHQUP	(Tamil Elakkiya et al., 2018)
2019	1,10a,12a-trimethyl-1,2,3,3a,3b,4,5,5a,6,7,10,10a,10b,11,12,12a-hexadecahydrocyclopenta[5,6]naphtho[1,2-f]indazol-1-ol	JIWJIL	(Wang et al., 2019)
2009	1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione	LUKXUL	(Bán et al., 2009)
2005	2,5-bis(pyrid-3-yl)-1,3,4-oxadiazole	NANPOI	(Du et al., 2005a)
2005	2,5-bis(pyrid-4-yl)-1,3,4-oxadiazole	NANPUO	(Du et al., 2005a)
2006	4-dimethylamino-azobenzene-2-carboxylic acid	NEKDOX	(Benedict et al., 2006)
2007	4,6-dimethylpyrimidin-2-amine	NIFCAH	(Li et al., 2007)
1997	Urea	NUHYIY	(Smith et al., 1997)
2011	1,2-bis(4-Pyridyl)ethane	ONAQIE	(Ebenezer and Muthiah, 2011)
2001	4,4'-bipyridine	SUXVOW	
2001	4,4'-dipyridylacetylene	SUXVUC	
2007	2-Amino-4,6-dimethoxypyrimidine	TIPFII	(Thanigaimani et al., 2007)
2018	pyrazine	VAXVUN01	(Dutkiewicz et al., 2018)
2020	bis(N-{2-[1-(3-ethoxy-4-methoxyphenyl)-2-(methanesulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide)	WUZLIP	(Jirát et al., 2020)
2012	pyridinium-2-olate	XAYYAZ	(Yu, 2012)
2014	tetramethylpyrazine	XOGFIK	(Wang et al., 2014a)
1995	2-Aminopyrimidine	ZAJHOH	(Byriel et al., 1995)

Terephthalic acid has been co-crystallized with a few API's, such as Isoniazid (isonicotinic acid hydrazide) – an anti-tuberculosis drug. Solvent assisted grinding and slow evaporation were used to prepare the terephthalic acid · isonicotinic acid hydrazide co-crystal (Lemmerer et al., 2011). Terephthalic acid was also co-crystallized with another API that is normally used in conjunction with isoniazid – pyrazinamide, which is a bacteriostatic drug. According to the co-former solubility rule, the solubility of the pyrazinamide · terephthalic acid decreased when compared to just pyrazinamide (Lozano et al., 2023).

The anti-fungal drug itraconazol, was successfully co-crystallized with terephthalic acid in a study by Machado *et al* (2020). The co-crystal was obtained from slow solvent evaporation, liquid assisted grinding, and ball milling with 2:1 stoichiometry and displayed stability in aqueous conditions

(Machado Cruz et al., n.d.). The scanning electron micrographs of itraconazole, itraconazole-terephthalic acid co-crystals from ball milling and itraconazole-terephthalic acid co-crystals produced via slow solvent evaporation are displayed in Figure 2.13.

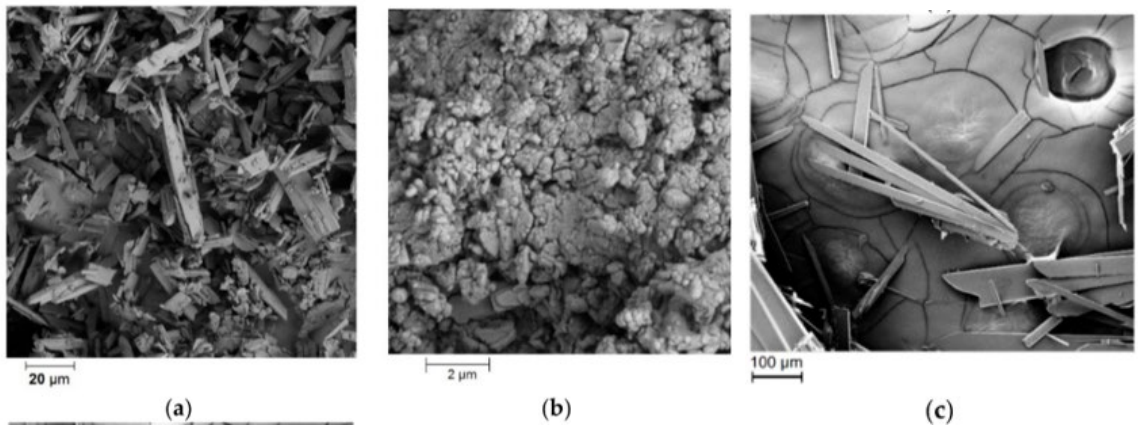


Figure 2. 13 The scanning electron micrographs of (a) crystals of itraconazole, (b) itraconazole-terephthalic acid co-crystals produced by ball milling and (c) itraconazole-terephthalic acid co-crystals produced by slow solvent evaporation, adapted from Cruz et al., (2020)

A search of co-crystals of terephthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.3.

Table 2. 3 Co-formers used in the preparation of co-crystals of terephthalic acid found on the Cambridge Structural Database (version 5.4.3), with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2012	bis(6-Bromo-1,3-benzothiazol-2-amine)	BASYUR	(Jin et al., 2012)
2005	N,N'-bis(Pyridin-4-ylmethyl)succinamide	CASNOA	(Oliver et al., 2005)
2009	4,4'-methylenebis(3,5-dimethyl-1H-pyrazole)	CUMRAE	(Basu et al., 2009)
2007	1,8-bis(4-Pyridyl)naphthalene	DIFPUE	(Mei et al., 2007)
2013	4-amino-5-fluoropyrimidin-2(1H)-one	DILTUP	(Da Silva et al., 2013)
2012	bis(4-[(E)-2-(Pyridin-2-yl)ethenyl]pyridine)	EFAWUF	(Castro-Montes et al., 2012)
2004	N,N-dimethylformamide solvate	EVOVUG	(Dale and Elsegood, 2004)
2010	bis(2,6-bis(Benzimidazol-2-yl)pyridine)	FAFNAD	(Xiao et al., 2010)
2012	4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide	FAKJUY	(Tumanov et al., 2011)
2004	Acridine	GAHFIF	(Mei and Wolf, 2004)
2006	1-(4-(4-oxopyridin-1(4H)-yl)phenyl)pyridin-4(1H)-one	GEHTUJ	(Li et al., 2006)
2019	4,4'-diazenediyldipyridine	HOWXAV	(Ding et al., 2019)
2019	4,4'-(ethane-1,2-diyl)dipyridine	HOWZIF	(Ding et al., 2019)
2019	4,4'-(ethene-1,2-diyl)dipyridine	HOXBOO	(Ding et al., 2019)
2004	pyridine	IYUNOF	(Dale et al., 2004)
2005	1,3-bis(4-pyridyl)propane	KATBAJ	(Dai et al., 2005)
2007	2,6-bis((Imidazol-1-yl)methyl)-4-methylphenol	KIDNOB	(Wang et al., 2007)
2009	N,N-dimethylacetamide	MUBNED	(Guo et al., 2009)
2005	2,5-bis(pyrid-3-yl)-1,3,4-oxadiazole	NANQID	(Du et al., 2005b)
2005	2,5-bis(pyrid-4-yl)-1,3,4-oxadiazole	NANQOJ	(Du et al., 2005b)
2007	bis(2-Amino-4,6-dimethylpyrimidine)	NIQNIL	(Devi and Muthiah, 2007)
2011	2-(pyridin-4-yl)-1H-benzimidazole	OMESOP	(Xia et al., 2011)
2011	bis(isonicotinic acid hydrazide)	ORAWIO	(Lemmerer et al., 2011b)
2004	bis((benzoylmethylene)triphenylphosphorane)	PAJSOJ	(Spencer et al., 2004)
2012	4,4'-Bipyridine	PAVXAN	(Koteswara Rao et al., 2012)
2012	4-(1H-pyrazol-3-yl)pyridine	PAXPEL	(Tan et al., 2012)
2009	2,2'-(1,4-Phenylene)bis-4,5-dihydro-1H-imidazole benzene	PUGGAA	(Shang et al., 2009)
2009	1,4-bis(Imidazol-1-yl)benzene	QOLSAM	(Shang et al., 2009)
2008	10,11,12,13-tetrahydrodipyrido[3,2-a:2',3'-c]phenazine	ROFCAR	(Liu et al., 2008)
2008	bis(2-Amino-4,6-diphenylpyrimidine)	SIYCIN	(Goswami et al., 2008)
2008	(2,2'-dimethyl-1,1'-(butane-1,4-diyl)-bis(benzimidazole))	SIYWAZ	(Jiang and Dong, 2008)
1999	2-Aminopyrimidine	SUVJEY	(Goswami et al., 1999)
2013	bis(2,4-Diamino-6-phenyl-1,3,5-triazine)	TEZMOC	(Delori et al., 2013)
2019	4,7-bis[2-(pyridin-4-yl)ethenyl]-2,1,3-benzothiadiazole	TORTAY	(Patel et al., 2019)
2020	itraconazole	UCEBUD	(Cruz et al., 2020b)
2016	bis(1-methylpyrrolidin-2-one)	UNECIB	(Geranmayeh et al., 2016)
2019	2-[2-(pyridin-4-yl)ethenyl]-1H-benzimidazole	WOLTOJ	(Garai and Biradha, 2019)
2013	1-Phenyl-3-(quinolin-5-yl)urea	WONZEG	(Kalita and Baruah, 2013)
2002	4,7-phenanthroline	WUKREZ	(Shan et al., 2002)
2012	bis(Pyridin-4(1H)-one)	XAQZIA	(Staun and Oliver, 2012)
2011	N,N'-bis(Pyridin-3-yl)terephthalamide	YAHNOM	(Lu et al., 2011)
2022	1,1'-[1,4-phenylenebis(methylene)]bis(1H-imidazole)	NENWEM	(Kumar et al., 2022)
2022	bis(pyridine-4-carbonitrile)	WEQHIN	(Sharma et al., 2022)

Three different co-crystals of pyrazinamide with 3-nitrophthalic acid were prepared in various stoichiometric ratios (1:1, 1:2, and 2:1 – pyrazinamide:3-nitrophthalic acid) by Liang *et al* (2023) and characterized by XRD, powder XRD, DSC and FTIR spectrophotometry. By analysing the hydrogen bonding patterns and studying the hygroscopicity and solubility of the three co-crystals it was found that there was a connection between the properties of the co-crystals and the internal arrangement of the molecules where the 1:2 co-crystal displayed the greatest stability as well as the best application potential. The co-crystals formed had better anti-hygroscopicity and dissolution properties, compared to just pyrazinamide (Liang et al., 2023). The preparation of pyrazinmaide – 3-nitrophthalic acid in various stoichiometric ratios is shown in Figure 2.14.

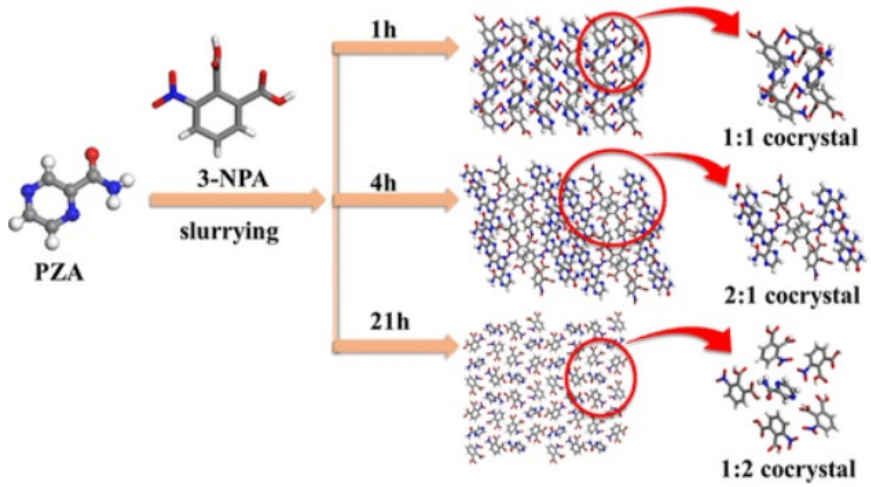


Figure 2. 14 Preparation of pyrazinamide – 3-nitrophthalic acid in various stoichiometric ratios – from Liang et al., (2023).

Mekala *et al* (2016) synthesized a benzimidazolium – 3-nitrophthalate salt to study the effect of various isomers of the structure. Benzimidazolium – 3-nitrophthalate was compared with benzimidazolium 2-nitroterephthalate, where the positions of the carboxyl groups differ. The above salt was grown using slow evporation methods and then characterized by XRD. 3-nitrophthalic acid was the proton donor and benzimidazolium acts as the proton acceptor and they were connected via strong N-H···O hydrogen bonds.

Even though the structures of 3-nitrophthalate and 2-nitroterephthalate salts with benzimidazolium are very much alike, because the positions of the carboxyl groups on the benzene rings differ, benzimidazolium – 3-nitrophthalate contains undulating sheets where as benzimidazolium 2-nitroterephthalate contains flat anti-parallel sheets (Mekala et al., 2016), as seen in Figure 2.15.

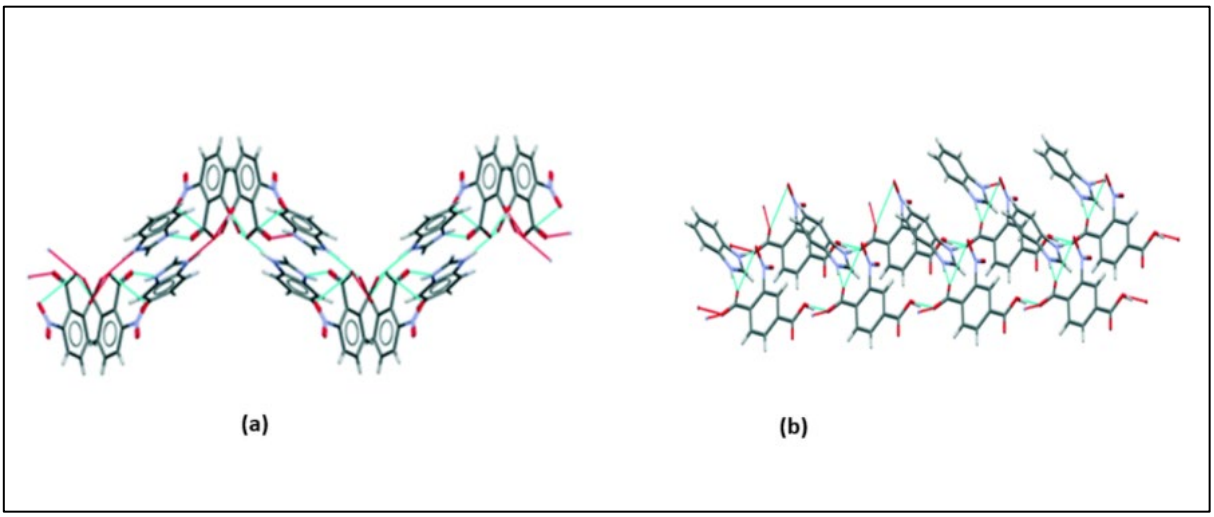


Figure 2. 15 (a) undulating sheet in benzimidazolium 3-nitrophthalate (b) plane formed by 2-nitroterephthalate ions with the benzimidazolium with the anti-parallel layer on top adapted from Mekala et al., (2016)

A search of co-crystals of 3-nitrophthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.4:

Table 2. 4 Co-formers used in the preparation of co-crystals of 3-nitrophthalic acid found on the Cambridge Structural Database (version 5.4.3), with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2022	carbamoylpyridin-1-ium 2-carboxy-6-nitrobenzoate	WASCOM	(Wen et al., 2022)
2017	4,4'-bipyridine	GAXKUO	(Amani et al., 2017)
2016	N-benzyl-9H-purin-6-amine monohydrate	ICUFIY	(Wang et al., 2016)
2016	4-(dimethylamino)benzaldehyde	SUZCOH	(Jin et al., 2016)
2014	tetramethylpyrazine dihydrate	XOGFEG	(Wang et al., 2014b)
2018	2,3-dimethylpyrazine	ZEYNAV	(Wang et al., 2018b)
2019	pyrimidin-2-amine	ZOMDAJ	(Singaravelan et al., 2019)

In a study by Fujii *et al* (2015), 5-aminoisophthalic acid crystals were found to exhibit a reversible colour change when exposed to solvent vapours (vapochromism) – this mechanism takes place via pseudo-polymorphic transformations regarding the hemihydrate (pale pink) crystals and the anhydrous (yellow) crystals. When the hemihydrate crystal is exposed to methanol, acetonitrile or ethanol it transformed into a novel anhydrous crystal. The anhydrous crystal changed back into the hemihydrate crystal when exposed to water vapour. This is because in in the hemihydrate crystal, 5-aminoisophthalic acid is in zwitterionic form, whereas the anhydrous crystal is in non-ionic form (Fujii et al., 2011). The colour changes can be seen in Figure 2.16 below.

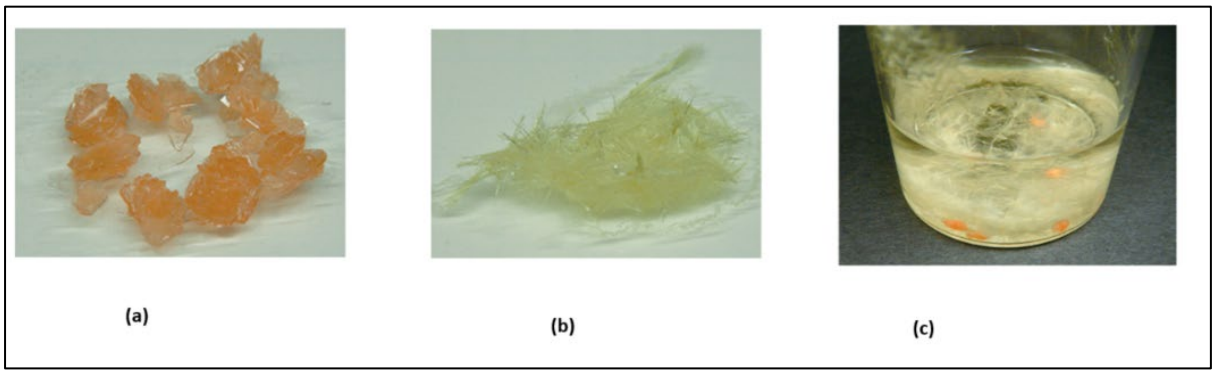


Figure 2. 16 Crystals of 5-aminoisophthalic acid (a) in hemihydrate form and (b) in anhydrous form which were simultaneously acquired from the same solution (c) adapted from Fujii et al., (2011)

A search of co-crystals of 5-aminoisophthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.5:

Table 2. 5 Co-formers used in the preparation of coo-crystals of 5-aminoisophthalic acid found on the Cambridge Structural Database (version 5.4.3 - 2021) ,with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2014	4,4'-ethane-1,2-diyldipyridine	EBALEB	(Lush and Shen, 2014)
2015	2,2',2''-((3,8,13-trimethoxy-10,15-dihydro-5H-tribenzo[a,d,g][9]annulene-2,7,12-triyl)tris(oxymethylene))tris(1-methyl-1H-imidazole) monohydrate	IWAFAQ	(Song et al., 2015)
2005	1,4-bis((Benzimidazol-1-yl)methyl)benzene	LATMAV	(Aakeröy et al., 2005)
2009	4-amino-3,5-bis(pyridin-4-yl)-1,2,4-triazole	NUGZOF	(Du et al., 2009)
2016	4-(2-(pyridin-4-yl)vinyl)pyridine	OKIGOG	(McGuire et al., 2016)
2019	1,3,7-trimethyl-3,7-dihydro-1H-purine-2,6-dione	POVXAC	(Singh et al., 2019)
2009	4,4'-bipyridine	VUQVUZ	("Search Results - Access Structures," n.d.)
2012	quinazolin-4(3H)-one	WEFKID	(Nath and Baruah, 2012)
2012	isoquinoline	WEFKOJ	(Nath and Baruah, 2012)

5-nitroisophthalic acid was co-crystallized in a 1:1 ratio with paracetamol in a study by Hiendrawan *et al* (2016) for the purpose of improved tabletability. The co-crystal was synthesized by slow evaporation techniques and then characterized by powder XRD, DSC, TGA (thermogravimetry analysis), FTIR, HSPM (hot stage polarized microscopy) and SEM. The paracetamol- 5-nitroisophthalic acid was found to have better tabletability compared to that of paracetamol alone. This study displayed how co-crystallization can enhance the mechanical properties of paracetamol (Hiendrawan et al., 2016).

5-nitroisophthalic acid has also been used as a co-former with carbamazepine (Fleischman et al., 2003b), dapsone (G. Smith & Wermuth, 2013) levetiracetam and etiracetam (levetiracetam's racemic equivalent) (George et al., 2014).

A search of co-crystals of 5-nitroisophthalic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.6:

Table 2. 6 Co-formers used in the preparation of co-crystals of 5-nitroisophthalic acid found on the Cambridge Structural Database (version 5.4.3), with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2013	4,4'-sulfonyldianiline	BIQNEW	(Smith and Wermuth, 2013)
2011	1,4-dihydroquinoxaline-2,3-dione	EVAFIR	(Wang, 2011)
2006	N-(3-Pyridyl)acetamide	KEFCII	(Aakeröy et al., 2006)
2020	1,4,7,10,13,16-hexaoxacyclooctadecane	KOTFUX	(Balakrishnan et al., 2020)
2020	N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide	OYUWUD	(Buol et al., 2020)
2003	Carbamazepine	UNIBEY	(Fleischman et al., 2003)
2001	18-crown-6 dihydrate	XIVMOE	(Balakrishnan et al., 2020)

Nitroterephthalic acid was co-crystallized with 4-dimethylaminopyridine in a study by Wu *et al* (2021), where 4-dimethylaminopyridine was reacted with eight organic acids where all eight compounds crystallize as salts. 4-dimethylaminopyridine – nitroterephthalate creates a 2D sheet (Wu et al., 2021), as shown in Figure 2.17.

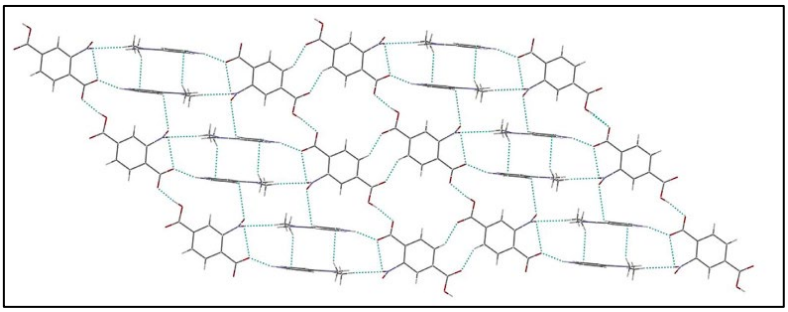


Figure 2. 17 4-dimethylaminopyridine – nitroterephthalate 2D sheet structure, adapted from Wu et al., (2021)

One reported co-crystal of nitroterephthalic acid is found on the CSD (version 5.4.3 - 2021) with correlating literature references and CSD reference code is listed in table 2.7 below.

Table 2. 7 Co-former used in the preparation of the co-crystal of nitroterephthalic acid found on the Cambridge Structural Database (version 5.4.3), with corresponding literature reference and CSD reference code

Year	Co-former	CSD reference code	Reference
2019	4-dimethylaminopyridine	IJOCIW	(Rodríguez-Cuamatzi et al., 2007)

Diphenic acid was co-crystallized with an antibacterial drug, ofloxacin (1:1 ratio) by Suresh *et al* (2020), using mechanochemical synthesis which formed a co-crystal salt. The product was characterized using single crystal XRD, powder XRD DSC and FTIR. Solubility and dissolution rate were enhanced by the ofloxacin – diphenic acid salt, when compared to the ofloxacin alone (Suresh et al., 2020).

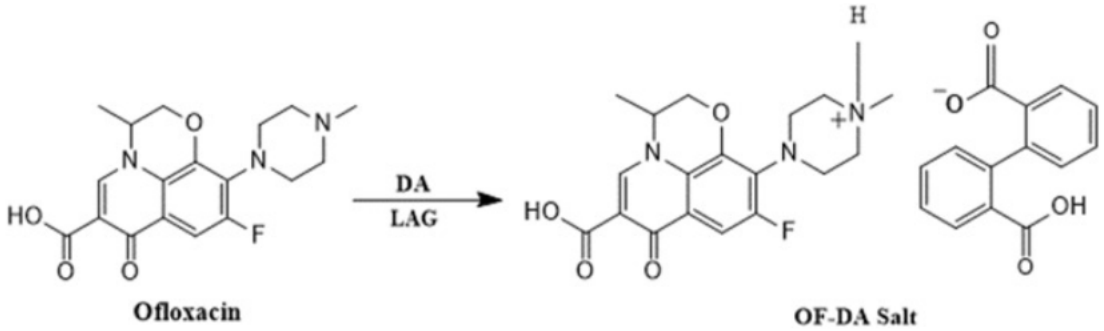


Figure 2. 18 Schematic representation of the preparation of ofloxacin – diphenic acid (OF-DA) salt, adapted from Suresh et al., (2020).

A search of co-crystals of diphenic acid with similarities to those prepared in this study was done using the CSD (version 5.4.3 -2021). The co-formers that have co-crystallized with isophthalic acid, together with correlating literature references and CSD reference codes, are listed in table 2.8:

Table 2. 8 Co-formers used in the preparation of co-crystals of diphenic acid found on the Cambridge Structural Database (version 5.4.3-2021), with corresponding literature references and CSD reference codes

Year	Co-former	CSD reference code	Reference
2014	4,4'-bipyridine	BOMGUH	(Buol et al., 2020)
2005	bis(5-chloro-2-pyridone) clathrate	FEWSEG	(Fleischman et al., 2003)
2009	bis(2(1H)-pyridinone)	FOTYET	(Telzhensky and Kaftory, 2009)
2009	bis(4-methyl-2(1H)-pyridinone)	FOTYIX	(Telzhensky and Kaftory, 2009)
2009	bis(6-methyl-2(1H)-pyridinone)	FOTYOD	(Telzhensky and Kaftory, 2009)
2003	N,N'-bis(2-Pyridyl)-1,4-diaminobenzene	GACBES	(Bensemann et al., 2003b)
2001	phenazine	GURVOE	(Shaameri and Jones, 2001)
2022	6-methylpyridine-3-carboxamide	LEBVIB	(Zhang et al., 2022)

Chapter 3 - Experimental

3.1 Synthesis

Synthesis was carried out by first weighing stoichiometric amounts of the starting material into polytop vials (5ml and 10ml), once weighed, solvents were chosen and added to each sample in different volumes (depending on the solubility of the starting materials). A stirrer bar was added to the polytop vials and then heated until all materials had dissolved as can be seen in Figure 3.1.

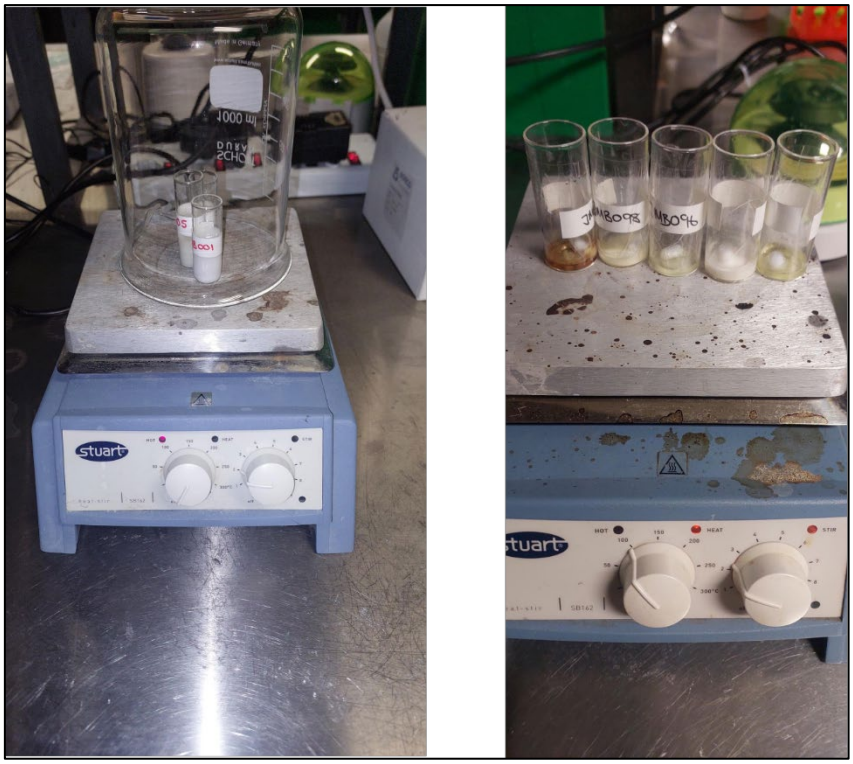


Figure 3. 1 Setup of hotplate and polytop vials for dissolving the starting materials

3.2 Crystallization

Each of the starting materials were crystallized via slow solvent evaporation methods for screening purposes of the co-crystals. This aided in identifying if any of the crystals formed were just starting materials. Then most of the co-crystals in this study were grown using slow solvent evaporation (Figure 3.2.). When no co-crystals were formed via slow solvent evaporation, other methods such as grinding, and sublimation were used to try and achieve co-crystallization (Figure 3.3).

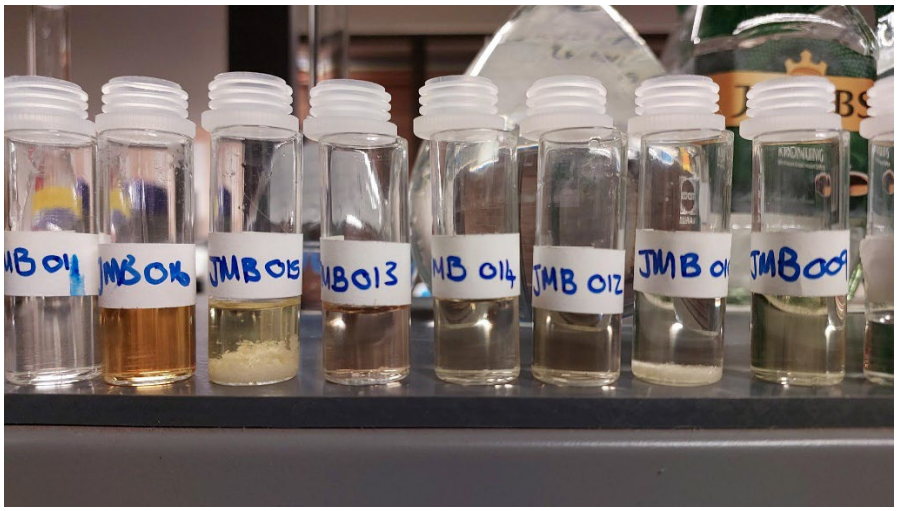


Figure 3. 2 Image of slow solvent evaporation in polytop vials

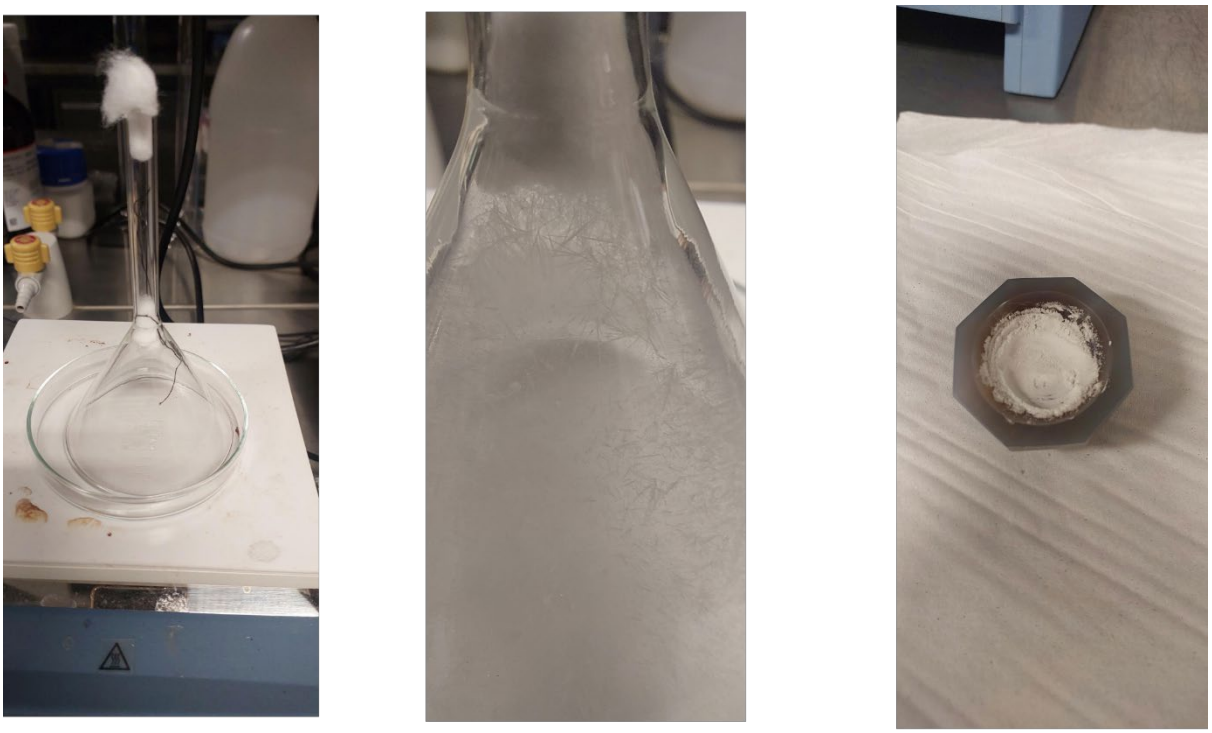


Figure 3. 3 (a) Sublimation apparatus setup to attempt co-crystallization (b) Crystals formed through sublimation (c) Agate mortar with starting material, used for grinding

Sublimation was one of the methods used for crystallization when slow solvent evaporation did not produce any crystallized products. A glass Petri dish was placed on a hot plate with the starting material in it, then a glass funnel was placed on the Petri dish, covering the starting materials. Cotton wool was used to seal the exit point of the funnel. Crystals were achieved but were starting materials.

Grinding the starting materials together was performed when no crystals formed using the slow solvent evaporation method. This was done by grinding stoichiometric amounts of starting materials together with an agate pestle and mortar. The ground up products were then dissolved in solution, heated and stirred and left to evaporate slowly over time at room temperature.

Certain materials were hard to co-crystallize, for instance niacinamide with phthalic acid, 3-nitrophthalic acid and diphenic acid. Niacinamide and phthalic acid would always form a wax like substance.

Table 3.1 below demonstrates the different temperatures, methods and solvents used to try and achieve co-crystallization between niacinamide and phthalic acid. The same methods were used with other API's and phthalic acid derivatives where no co-crystals were formed.

As seen in table 3.1, a variety of solvents and methods were used to try and achieve co-crystallization. The same methods in table 3.1 were used with a number of other phthalic acid derivatives and API's used in this study when co-crystallization could not be achieved. Many of these co-crystals were not achieved, but this will lead to other methods being used in the future to achieve co-crystallization.

Table 3. 1 An example of co-crystals that were attempted, but not formed, and the conditions used – for niacinamide and phthalic acid.

Starting materials	Sample number	Method	Solvents	Temp	Conditions	Results
Niacinamide Phthalic acid	JMB002	Slow evaporation	Methanol	80 °C	Room temperature	Wax
	JMB002b	Slow evaporation	Deionized water	80 °C	Room temperature	Wax
	JMB018	Slow evaporation	Acetonitrile Methanol	80 °C	Room temperature	Wax
	SJMB001	Filtered (0.45µm syringe filter) Slow evaporation	80% methanol DMSO	80 °C	Room temperature	In solution – no crystal
	SJMB002	Melt starting materials at 150 °C. Add solvent. Filter Slow evaporation	80% methanol	150 °C	Room temperature	Wax
	SJMB005	Liquid assisted grinding of starting materials. Slow evaporation	80% methanol	25 °C	Room temperature	Wax
	SJMB007	Liquid assisted grinding of starting materials. Slow evaporation	80% methanol	25 °C	Room temperature	Tiny crystals formed
	JMB074	Slow evaporation Wax formed – redissolved in methanol	Acetic acid Methanol Isopropanol Water	150 °C	Room temperature Bigger polytope used (20ml)	Wax
	JMB075	Slow evaporation Wax formed – redissolved in methanol	Chloroform Acetone Acetonitrile	150 °C	Room temperature Bigger polytope used (20ml)	Tiny clusters of wax
	JMB076	Slow evaporation Wax formed – redissolved in methanol	Petroleum ether Methanol	150 °C		Solid mass
	JMB079	Slow evaporation	Water Acetonitrile	150 °C	Boiled for 10 minutes	Oil / gel
	JMB 082	Grinding starting materials Sublimation (200 °C	-	200 °C	Grinding and sublimation	
	JMB090	Niacinamide was dissolved in water. Phthalic acid was dissolved in ethanol and slowly dropped onto the water phase. Slow evaporation	Water Ethanol	50 °C	Room temperature	Wax
	JMB108	Niacinamide was dissolved in water. Phthalic acid was dissolved in isopropanol and slowly dropped onto the water phase. Slow evaporation	Water isopropanol	25 °C	Room temperature	Wax

Co-crystals that were formed are reported and summarised in the Table 3.2, Table 3.3 and Table 3.4, with the conditions they were co-crystallized with.

Niacinamide Series

Table 3. 2 Co-crystals of niacinamide with phthalic acid derivatives formed and their conditions.

Co-crystal	Sample number	Methods	Solvent	Temperature	Conditions	CCDC Reference
Niacinamide with isophthalic acid	JMB001	Slow solvent evaporation Stirred over night	Methanol DMSO	50 ºC	Room temperature	2268462
Niacinamide with terephthalic acid	JMB019	Slow solvent evaporation	Methanol DMSO	70 ºC	Room temperature	2333680
Niacinamide with 3-nitrophthalic acid	JMB078	Slow solvent evaporation The bottom of the polytope vial was scratched with a diamond pen	Chloroform Acetone Acetonitrile DMSO Methanol Deionized water	90 ºC	Cold room +/- 8 ºC	2333743
Niacinamide with 5-aminoisophthalic acid	JMB021	Slow solvent evaporation	Methanol DMSO	70 ºC	Room temperature	2308247
Niacinamide with 5-nitroisophthalic acid	JMB006	Slow solvent evaporation	Methanol	50 ºC	Room temperature	2331002
Niacinamide with nitroterephthalic acid	JMB007	Slow solvent evaporation	Methanol	50 ºC	Room temperature	2334496

Modified isoniazid series

Table 3. 3 Co-crystals of modified isoniazid with phthalic acid derivatives formed and their conditions.

Co-crystal	Sample number	Methods	Solvent	Temperature	Conditions	CCDC Reference
Modified INH with isophthalic acid	MB016	Slow solvent evaporation	Benzaldehyde DMSO	70 ºC	Room temperature	2240478
Modified INH with phthalic acid	JMB086	Slow solvent evaporation. The bottom of the polytope vial was scratched with a diamond pen	Benzaldehyde DMSO	100ºC	Room temperature	2333282
Modified INH with terephthalic acid	MB017	Slow solvent evaporation	Benzaldehyde DMSO	70ºC	Room temperature	2240437
Modified INH with 3- nitrophthalic acid	MB018	Slow solvent evaporation	Benzaldehyde DMSO	70 ºC	Room temperature	2240472

Similar heterocyclic nitrogen containing API co-crystals formed

Table 3. 4 Co-crystals of similar heterocyclic nitrogen containing API's with phthalic acid derivatives formed and their conditions.

Co-crystal	Sample number	Methods	Solvent	Temperature	Conditions	CCDC Reference
INH with Isophthalic acid	MB002	Slow solvent evaporation	Methanol DMSO	70 °C	Room temperature	BAJXAP
INH with Diphenic acid	MB013	Slow solvent evaporation – crystals formed were re-dissolved in methanol	Methanol	70 °C	Room temperature	2204808
Isonicotinamide with terephthalic acid	JMB036	Slow solvent evaporation	Methanol DMSO	50°C - 100 °C	Room temperature	2312436
Isonicotinamide with diphenic acid	JMB041	Slow solvent evaporation	Methanol	50°C	Room temperature	2333254
Benzhydrazide with 5-aminoisophthalic acid	JMB046	Slow solvent evaporation	Methanol	100 °C	Room temperature	2307503
Niazid with nitroterephthalic acid	JMB056	Slow solvent evaporation	Methanol	100°C	Room temperature	2333029

3.3 Structure determination

3.3.1 Instrumentation

The crystal structures were collected on a Bruker D8 Venture Photon II diffractometer, using a molybdenum source with a wavelength of 0.71073Å. All data sets were collected at a temperature of 173K using an Oxford CRYOSTREAM 700. The reduction of data was done using *SAINT+* V6.02.6 software and empirical absorption corrections were done using *SADABS* version 2012/1 (Bruker 2012).

3.3.2 Structure solution and refinement

As a general rule for structure solution, all C-bound hydrogen atoms were located in the difference map which were positioned geometrically and were then allowed to ride on their respective parent atoms with thermal displacement parameters 1.2 times of the parent C atom when refined.

In general, all N-bound and O-bound H atoms involved in hydrogen bonding interactions were also restrained to their parent atoms using the riding model approximation applicable to their corresponding geometries. For the published nitroterephthalic acid structure, all N-bound and O-bound H atoms involved in hydrogen bonding interactions were allowed to refine freely.

3.3.3 Software utilized

A combination of WinGX (Farrugia, 1999) and Olex2 (Dolomanov *et al.,*2009) were used for solving and refining the crystals structures using SHELXT (Sheldrick., 2015) and SHELXL (Sheldrick., 2015) as both programs were extremely useful when used together.

WinGX was used to name the atoms as its interface made labelling atoms easier when compared to Olex2. Olex2 was mainly used to refine the structure, fix the cell content errors, assign atom types and fix syntax errors. WinGX was used to create the cif files as well as the cif tables. Both programs were used to solve other errors.

Ortep (Farrugia, 2012) was used to generate the Ortep diagrams of asymmetric units and then Coral Draw was used to create the .tif images or the asymmetric units.

Mercury (Macrae *et al*., 2006) was used to generate images of packing and any other unusual features of the co-crystal.

Chapter 4 – Results and discussion

4.1 Summary of results

This chapter contains a description and discussion of the 15 novel co-crystals achieved in this research project, as well as the previously unreported crystal structure of one of the starting materials, nitroterephthalic acid.

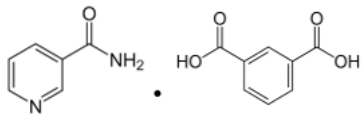
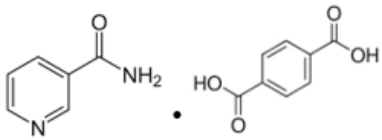
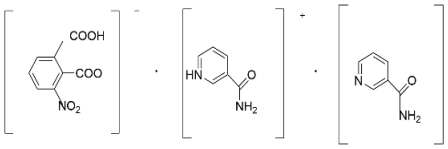
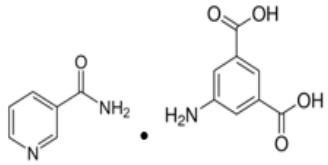
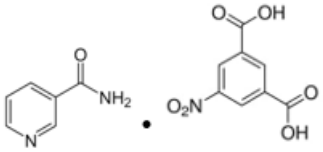
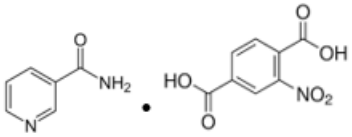
The 15 novel co-crystals form three series – with the first series containing six niacinamide (nicotinamide) co-crystals. The second is a series of four modified isoniazid co-crystals where benzaldehyde was used as the modifier. The third series contains six other *N*-heterocyclic API co-crystals, with similar structures to the niacinamide and isoniazid API's. All of the co-crystals used phthalic acid and its derivatives as co-formers.

Finally, a previously unreported crystal structure of one of the starting materials (nitroterephthalic acid) is reported. This structure was published in *Zeitschrift für Kristallography - new crystal structures* (Bourletidis *et. al.*, 2023) and is included in Appendix 1.

A graphical summary of the co-crystals and salts synthesized, solved and refined in this study are listed in Table 4.1, Table 4.2, Table 4.3 and Table 4.4 respectively.

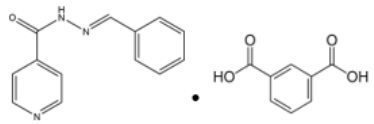
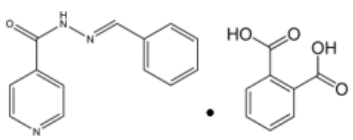
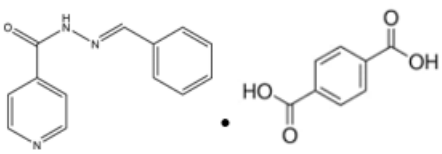
Series 1: Co-crystals/salts of niacinamide with phthalic acid derivatives

Table 4. 1 Co-crystals of niacinamide with phthalic acid derivatives

		
Sample no: JMB001 CCDC: 2268462	Sample no: JMB019 CCDC: 2333680	Sample no: JMB078 CCDC: 2333743
		
Sample no: JMB021 CCDC: 2308247	Sample no: JMB006 CCDC: 2331002	Sample no: JMB007 CCDC: 2334496

Series 2:Co-crystals of modified isoniazid (benzaldehyde modifier) with phthalic acid derivatives

Table 4. 2 Co-crystals of modified isoniazid (benzaldehyde modifier) with phthalic acid derivatives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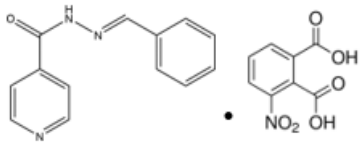
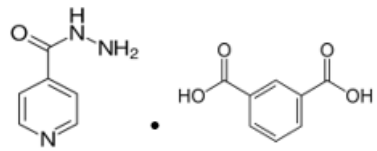
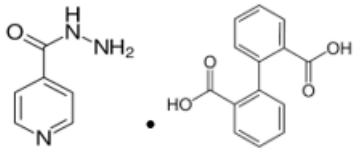
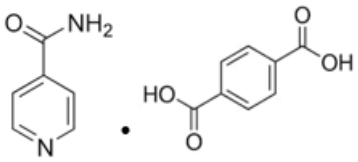
		
Sample no: MB018 CCDC: 2240472		

Series 3: Co-crystals of other nitrogen containing heterocyclic API's with phthalic acid derivatives

Table 4. 3 Co-crystals of other nitrogen containing heterocyclic API's with phthalic acid derivatives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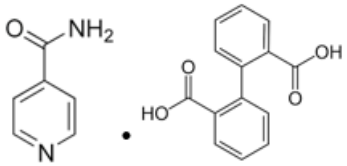
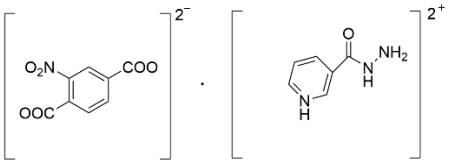
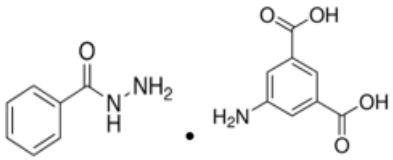
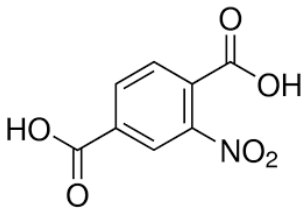
		
Sample no: JMB041 CCDC: 2333254	Sample no: JMB056 CCDC: 2333029	Sample no: JMB046 CCDC: 2307503

The crystal structure of nitroterephthalic acid

Table 4. 4 The structure of nitroterephthalic acid


Sample no: Nitroterephthalic acid CCDC: 2264065/ GOCFEN

4.2. Co-crystals of niacinamide with phthalic acid derivatives

A description and discussion of niacinamide with phthalic acid derivatives co-crystals achieved in Series 1 follows in this section. Below is the crystallographic data for series 1, summarized in Table 4.5.

Table 4. 5 Crystallographic data for series 1 (Niacinamide).

	JMB001	**JMB019**	**JMB078**
Formula	$(C_8H_6O_4) \cdot (C_6H_6N_2O)$	$(C_8H_6O_4) \cdot (C_6H_6N_2O)$	$(C_8H_4NO_6^-) \cdot (C_6H_7N_2O^+) \cdot (C_6H_6N_2O)$
M_r	288.26	288.26	455.39
Temperature/K	173(2)	173(2)	173(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal size/mm^3	0.351 x 0.226 x 0.154	0.499 x 0.222 x 0.098	0.322 x 0.199 x 0.147
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	*P 21/n*	P -1	P *21/c*
Description	Plate	Plate	Prism
Colour	Colourless	Colourless	Colourless
a/Å	7.0611(5)	7.6984(6)	7.0229(11)
b/Å	14.3670(10)	7.7440(6)	7.4067(13)
c/Å	12.4406(10)	24.1205(19)	36.674(6)
α/°	90	92.803(4)	90
β/°	96.152(4)	96.217(4)	91.199(5)
γ/°	90	118.237(3)	90
V/Å^3	1254.79(16)	1251.15(17)	1907.2(5)
Z	4	4	4
ρ (calcd)/Mg m^{-3}	1.526	1.530	1.586
μ/mm^{-1}	0.118	0.118	0.126
F(000)	600	600	944
Θ Range for data/° collection/°	2.173 to 27.998	1.710 to 26.000	2.222 to 26.341
Reflections collected	37225	36292	50777
No. of unique data [R(int)]	3018 [0.1244]	4915 [0.0788]	3685 [0.0432]
Final R($I > 2\sigma(I)$)	0.0435	0.1144	0.0370
Final wR_2 (all data)	0.1040	0.2890	0.0832
CCDC deposition number	2268462	2333680	2333743

	JMB021	**JMB006**	**JMB007**
Formula	$(C_8H_7NO_4)\cdot(C_6H_6N_2O)$	$(C_8H_5NO_6)\cdot(C_6H_6N_2O)$	$(C_8H_5NO_6)\cdot(C_6H_6N_2O)$
M_r	303.27	333.26	333.26
Temperature/K	293(2)	173(2)	293(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal size/mm^3	0.322 x 0.201 x 0.161	0.283 x 0.181 x 0.134	0.279 x 0.193 x 0.129
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	P *21/n*	$Pna2_1$	Ccc2
Description	Block	Block	Plate
Colour	Orange	White	White
a/Å	8.4540(3)	9.9107(14)	22.6720(17)
b/Å	14.2514(5)	27.944(4)	17.1287(15)
c/Å	10.8292(4)	5.1446(7)	7.2476(7)
α/°	90	90	90
β/°	90.721(2)	90	90
γ/°	90	90	90
V/$Å^3$	1304.61(8)	1424.8(3)	2814.5(4)
Z	4	4	8
ρ (calcd)/Mg m^{-3}	1.544	1.554	1.573
μ/mm^{-1}	0.120	0.128	0.129
F(000)	632	688	1376
Θ Range for data/° collection/°	2.362 to 32.069	2.180 to 28.000	1.490 to 27.999
Reflections collected	37621	22520	58226
No. of unique data [R(int)]	4555 [0.0567]	3438 [0.1664]	3317 [0.2755]
Final R($I > 2\sigma(I)$)	0.0557	0.0656	0.0957
Final wR_2 (all data)	0.1452	0.1115	0.1660
CCDC deposition number	2308247	2331002	2334496

4.2.1. Niacinamide with isophthalic acid (JMB001)

IUPAC NAME: benzene-1,3-dicarboxylic acid pyridine-3-carboxamide

Chemical formula: $C_8H_6O_4 \cdot C_6H_6N_2O$

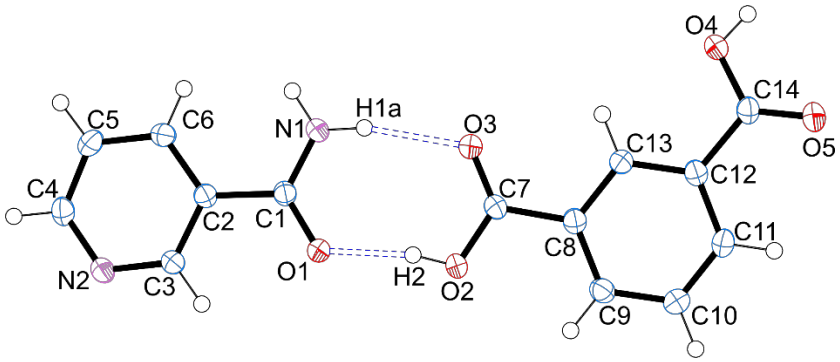


Figure 4. 1 Asymmetric unit of co-crystal niacinamide · isophthalic acid– JMB001

The asymmetric unit of niacinamide · isophthalic acid (Figure 1.4), contains one molecule of niacinamide and one molecule of isophthalic acid, which crystallizes in the monoclinic $P2_1/n$ space group. The amide moiety of niacinamide is bonded via two O1···H2-O2 and N1-H1a···O3 hydrogen bonds to form a $R_2^2(8)$ ring, using graph set notation (Bernstein et al., 1995).

With regards to the packing, each niacinamide molecule is bonded to three isophthalic molecules via hydrogen bonding, one via N2···H4a-O4, the other via N1-H1b···O5 and the last as in the asymmetric unit above as seen in Figure 4.2.

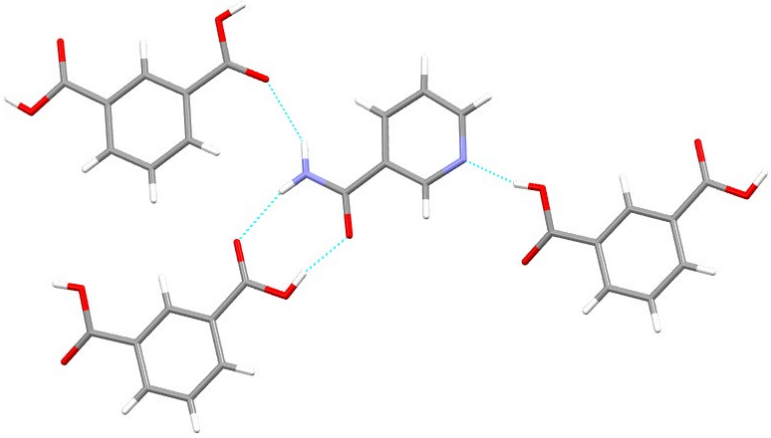


Figure 4. 2 Image of one niacinamide molecule hydrogen bonded to three isophthalic acid molecules.

Table 4. 6 Hydrogen bonds for JMB001 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4A)...O(2)#1	0.95	2.65	3.3241(19)	128.0
C(5)-H(5)...O(1)#1	0.95	2.40	3.2704(19)	152.3
N(1)-H(1A)...O(3)	0.88	2.01	2.8788(17)	166.9
N(1)-H(1B)...O(5)#2	0.88	2.20	3.0065(17)	151.8
O(2)-H(2)...O(1)	0.84	1.75	2.5794(15)	167.9
O(4)-H(4)...N(2)#3	0.84	1.82	2.6441(16)	164.8

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+3/2,z-1/2 #2 x-1/2,-y+1/2,z-1/2

#3 x,y-1,z

4.2.2 Niacinamide with terephthalic acid (JMB019)

IUPAC NAME: benzene-1,4-dicarboxylic acid pyridine-3-carboxamide

Chemical formula: $C_8H_6O_4 \cdot C_6H_6N_2O$

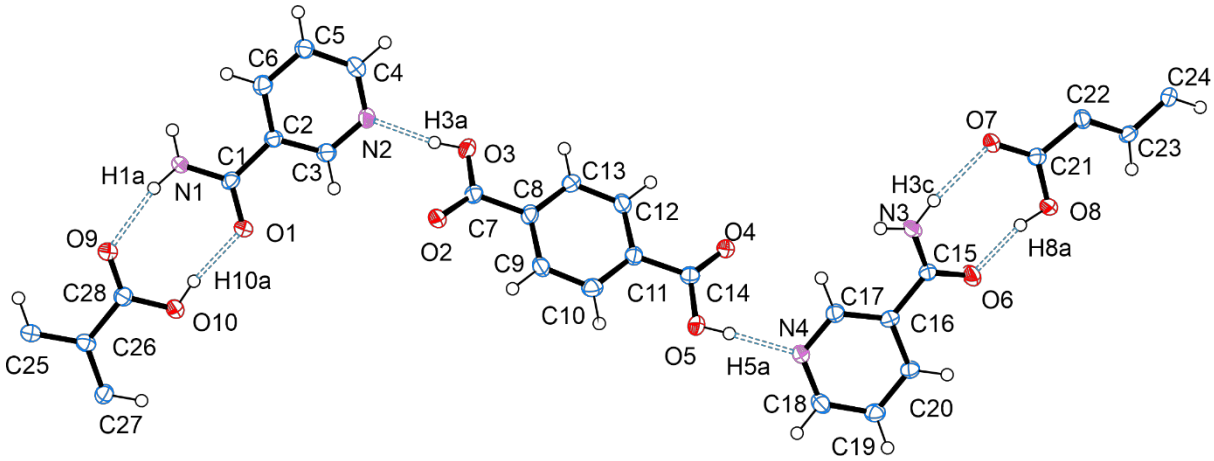


Figure 4. 3 Asymmetric unit of co-crystal niacinamide · terephthalic acid – JMB019

The asymmetric unit of niacinamide · terephthalic acid contains two molecules of niacinamide, one complete molecule of terephthalic acid and two ½ terephthalic acid molecules as shown in Figure 4.3.

The other half of terephthalic acid shown in the asymmetric unit was generated by symmetry. JMB019 crystallizes in the triclinic $P\bar{1}$ space group. There is hydrogen bonding between the amide group of niacinamide, namely O1···H10a-O10 and H1a-N1···O9, as well as O7···H3c-N3 and O6···H8a-O8, forming a $R_2^2(8)$ ring, using graph set notation (Bernstein et al., 1995). There is also hydrogen bonding between the pyridine nitrogen and the carboxyl group; N2···H3A-O3 and N4···H5a-O5 with a $D_1^1(2)$ intermolecular structure.

Each niacinamide is bonded to three terephthalic acid molecules via hydrogen bonding, via O1···H10a-O10 and H1a-N1···O9, as well as O7···H3c-N3 and O6···H8a-O8 and N1-H1B···O7 as seen in Figure 4.4 below. The crystal packing down the *b* axis is shown in Figure 4.5 below.

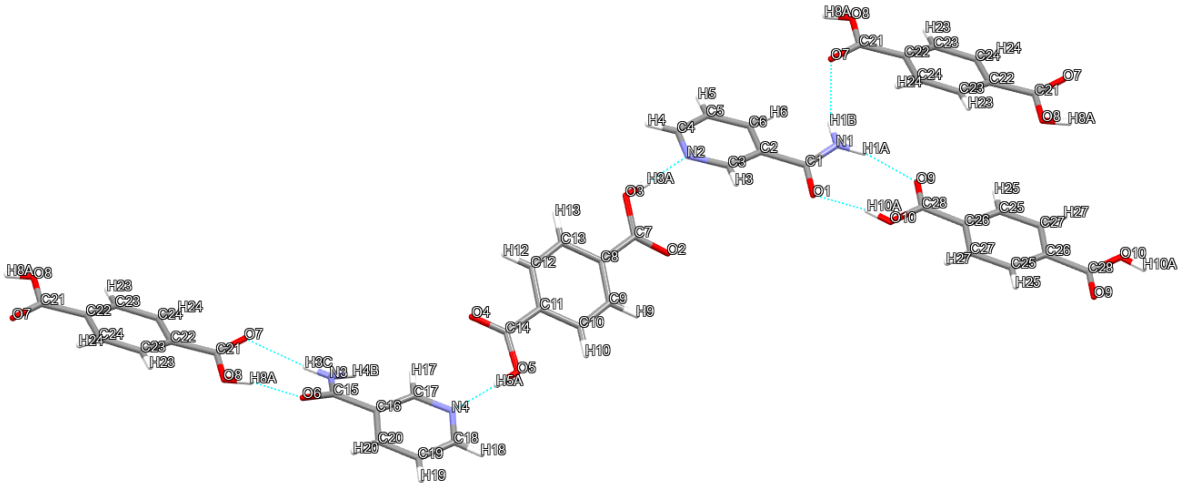


Figure 4. 4 Image showing one molecule of niacinamide hydrogen bonded to three terephthalic acid molecules.

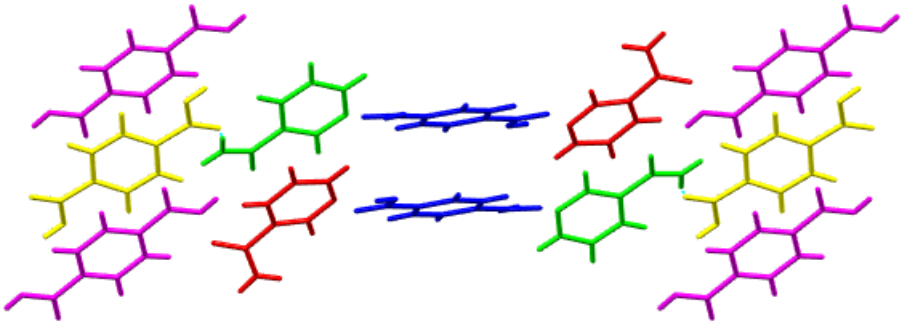


Figure 4. 5 Crystal packing of JMB019 down the *b* axis

Table 4. 7 Hydrogen bonds JMB019 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(2)...O(4)#3	0.95	2.61	3.359(7)	136.0
C(4)-H(3)...O(4)#4	0.95	2.45	3.231(7)	139.3
N(1)-H(1A)...O(9)	0.88	1.95	2.815(7)	166.3
N(1)-H(1B)...O(7)#4	0.88	2.19	3.025(6)	157.7
O(3)-H(6A)...N(2)	0.84	1.80	2.628(6)	166.3
O(5)-H(9A)...N(4)	0.84	1.88	2.716(6)	172.8
C(17)-H(13)...O(2)#5	0.95	2.58	3.210(7)	124.0
C(17)-H(13)...O(4)	0.95	2.60	3.232(7)	123.8
C(18)-H(14)...O(2)#6	0.95	2.30	3.146(7)	147.7
C(19)-H(15)...O(1)#6	0.95	2.61	3.402(7)	141.5
N(3)-H(12B)...O(7)	0.88	2.11	2.952(6)	159.2
N(3)-H(12A)...O(2)#5	0.88	2.22	3.070(6)	162.0
O(8)-H(17A)...O(6)	0.84	1.76	2.581(6)	166.6
O(10)-H(20A)...O(1)	0.84	1.83	2.658(6)	169.5
C(3)-H(2)...O(4)#3	0.95	2.61	3.359(7)	136.0
C(4)-H(3)...O(4)#4	0.95	2.45	3.231(7)	139.3
N(1)-H(1A)...O(9)	0.88	1.95	2.815(7)	166.3
N(1)-H(1B)...O(7)#4	0.88	2.19	3.025(6)	157.7
O(3)-H(6A)...N(2)	0.84	1.80	2.628(6)	166.3
O(5)-H(9A)...N(4)	0.84	1.88	2.716(6)	172.8
C(17)-H(13)...O(2)#5	0.95	2.58	3.210(7)	124.0
C(17)-H(13)...O(4)	0.95	2.60	3.232(7)	123.8
C(18)-H(14)...O(2)#6	0.95	2.30	3.146(7)	147.7
C(19)-H(15)...O(1)#6	0.95	2.61	3.402(7)	141.5
N(3)-H(12B)...O(7)	0.88	2.11	2.952(6)	159.2
N(3)-H(12A)...O(2)#5	0.88	2.22	3.070(6)	162.0
O(8)-H(17A)...O(6)	0.84	1.76	2.581(6)	166.6
O(10)-H(20A)...O(1)	0.84	1.83	2.658(6)	169.5

Symmetry transformations used to generate equivalent atoms:

#1 -x+3,-y+1,-z #2 -x,-y+1,-z+2 #3 -x+1,-y+1,-z+1

#4 -x+2,-y+2,-z+1 #5 -x+2,-y+1,-z+1 #6 -x+1,-y,-z+1

4.2.3 Niacinamide with 3-nitrophthalic acid (JMB078)

IUPAC NAME: pyridine-3-carboxamide 3-carbamoylpyridin-1-ium 3-nitrobenzene-1,2-dicarboxylate

Chemical formula: $C_8H_4NO_6^- \cdot C_6H_7N_2O^+ \cdot C_6H_6N_2O$

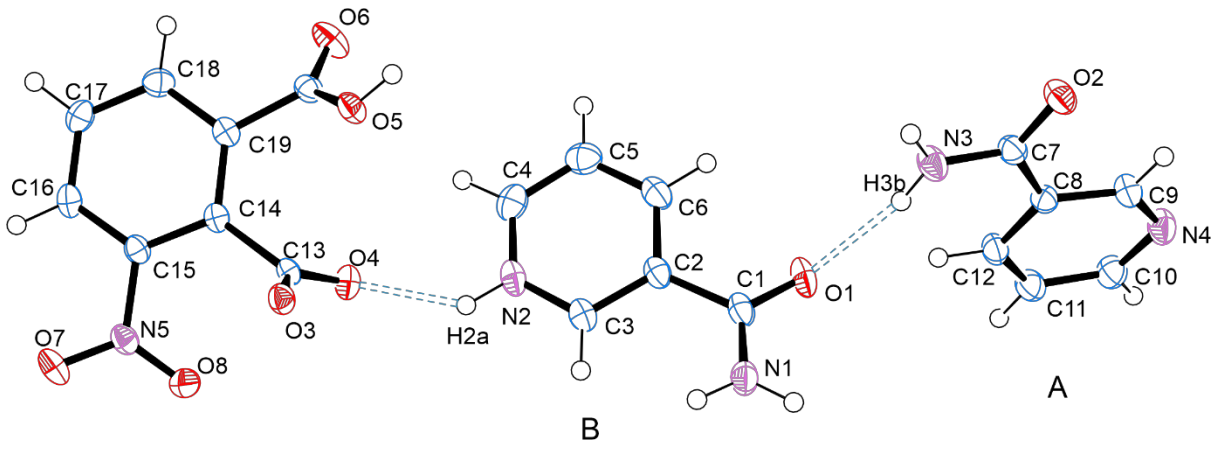
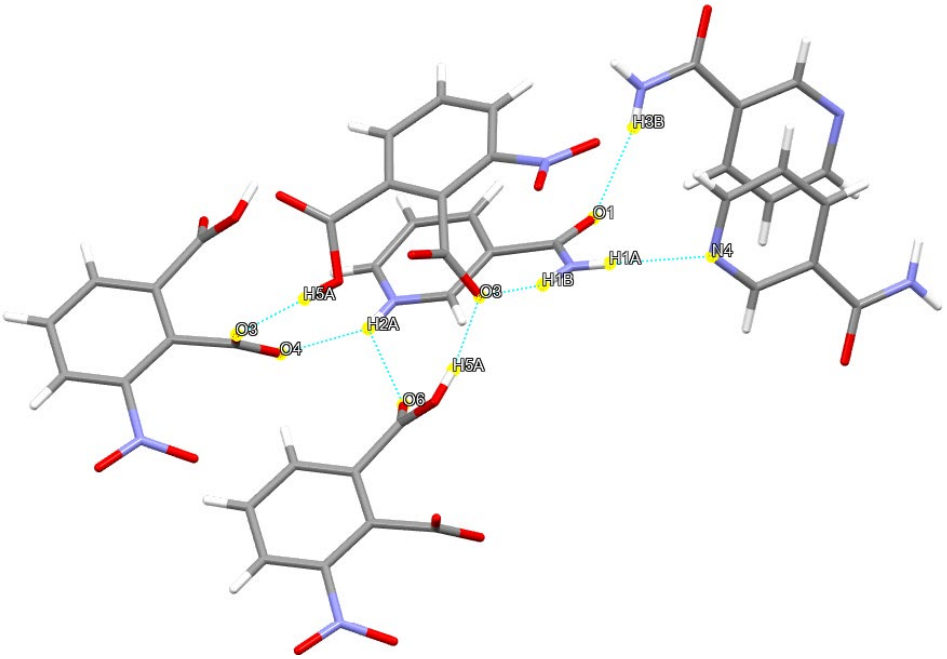


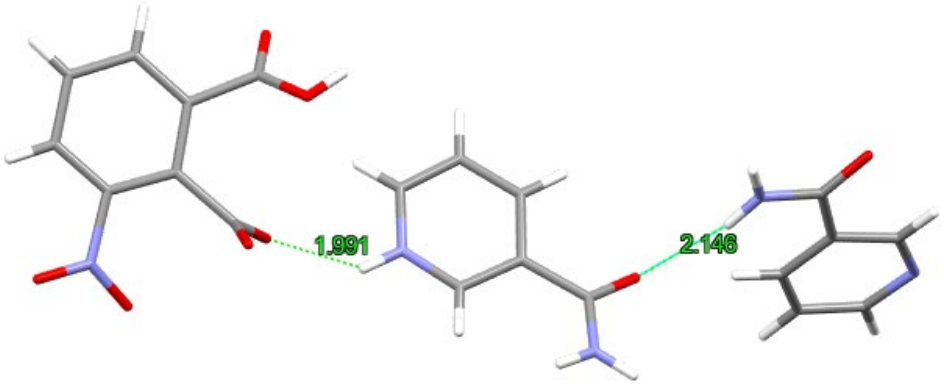
Figure 4. 6 Asymmetric unit of co-crystal salt niacinamide · 3-nitrophthalic acid – JMB078

In the asymmetric unit of niacinamide · 3-nitrophthalic acid (Figure 4.6) there is one niacinamide molecule (A), one protonated niacinamide molecule (B) and one 3-nitrophthalic acid molecule, which crystallizes in the monoclinic $P2_1/c$ space group. In the 3-nitrophthalic acid molecule, one carboxyl group is protonated and one is deprotonated. The justification for this structure is presented later in this section. The amide moiety of one of the niacinamide molecules (A) is bonded to the protonated niacinamide molecule (B) through a single O1···H3b-N3 hydrogen bond. The protonated niacinamide molecule (B) is bonded to 3-nitrophthalic acid through a single O4···H2a-N2 hydrogen bond giving rise to a $D_1^1(2)$ intermolecular structure.

The protonated niacinamide molecule (B) is hydrogen bonded to two niacinamide molecules through O1···H3b-N3 and N4···H1a-N1 bonds and through O3···H1b-N1, O4···H2a-N2 and O6···H2a-N2 hydrogen bonds to three -3-nitrophthalic acid molecules, H2a forms bifurcated hydrogen bonds to O4 and O6 as can be seen in Figure 4.7



(a)



(b)

Figure 4. 7 Hydrogen bonding in co-crystal salt niacinamide · 3-nitrophthalic acid (a). Hydrogen bond lengths showing the co-crystal and salt

This structure is extremely interesting, in that in addition to the protonated/deprotonated pair of carboxyl groups mentioned previously, one of the pyridine nitrogen's is protonated while the other is not, which means that the compound is both a salt and co-crystal at the same time. Grothe *et al* (2016) refers to crystals such as these as co-crystal salts, having an $AB^{+}C^{-}$ structure (Grothe et al., 2016). When trying to solve the structure with the hydrogen H2 on O4, the checkcif file gave an A-alert for this hydrogen and a strong Q peak existed where the pyridine hydrogen currently is. However, no alert exists in the structure presented above, and the refinement improved with this modification, this is further confirmed by the bond lengths with the co-crystal having a bond length of 2.146Å and the salt

having a bond length of 1.991Å. The structure of this co-crystal salt as presented is therefore confirmed.

Table 4. 8 Hydrogen bonds for JMB078 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(16)-H(16)...O(2)#1	0.95	2.35	3.0970(16)	135.1
C(3)-H(3)...O(3)#2	0.95	2.64	3.3441(17)	131.7
C(3)-H(3)...O(6)#3	0.95	2.45	3.1324(17)	128.9
C(11)-H(11)...O(7)#4	0.95	2.55	3.3002(18)	136.6
C(10)-H(10)...O(7)#5	0.95	2.46	3.3618(18)	158.7
C(5)-H(5)...N(1)#6	0.95	2.62	3.392(2)	138.4
C(5)-H(5)...O(8)#7	0.95	2.55	3.3003(18)	135.8
N(2)-H(2A)...O(4)	0.88	1.99	2.7031(15)	137.1
N(3)-H(3A)...O(2)#8	0.88	2.12	2.9780(16)	165.9
N(3)-H(3B)...O(1)	0.88	2.15	3.0096(16)	167.0
N(1)-H(1A)...N(4)#9	0.88	2.23	3.0674(17)	159.3
N(1)-H(1B)...O(3)#2	0.88	2.12	2.9566(15)	157.5
O(5)-H(5A)...O(3)#10	0.84	1.74	2.5664(12)	169.3
C(16)-H(16)...O(2)#1	0.95	2.35	3.0970(16)	135.1
C(3)-H(3)...O(3)#2	0.95	2.64	3.3441(17)	131.7
C(3)-H(3)...O(6)#3	0.95	2.45	3.1324(17)	128.9
C(11)-H(11)...O(7)#4	0.95	2.55	3.3002(18)	136.6
C(10)-H(10)...O(7)#5	0.95	2.46	3.3618(18)	158.7
C(5)-H(5)...N(1)#6	0.95	2.62	3.392(2)	138.4
C(5)-H(5)...O(8)#7	0.95	2.55	3.3003(18)	135.8
N(2)-H(2A)...O(4)	0.88	1.99	2.7031(15)	137.1
N(3)-H(3A)...O(2)#8	0.88	2.12	2.9780(16)	165.9
N(3)-H(3B)...O(1)	0.88	2.15	3.0096(16)	167.0
N(1)-H(1A)...N(4)#9	0.88	2.23	3.0674(17)	159.3
N(1)-H(1B)...O(3)#2	0.88	2.12	2.9566(15)	157.5
O(5)-H(5A)...O(3)#10	0.84	1.74	2.5664(12)	169.3

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+3/2,z-1/2 #2 -x,y-1/2,-z+1/2 #3 x,y-1,z

#4 -x+1,y-1/2,-z+1/2 #5 x+1,-y+1/2,z+1/2 #6 x,y+1,z

#7 -x+1,y+1/2,-z+1/2 #8 -x,-y+1,-z+1 #9 -x+1,-y,-z+1

#10 -x,y+1/2,-z+1/2

4.2.4 Niacinamide with 5-aminoisophthalic acid (JMB0021)

IUPAC NAME: 5-aminobenzene-1,3-dicarboxylic acid pyridine-3-carboxamide

Chemical formula: $C_8H_7NO_4 \cdot C_6H_6N_2O$

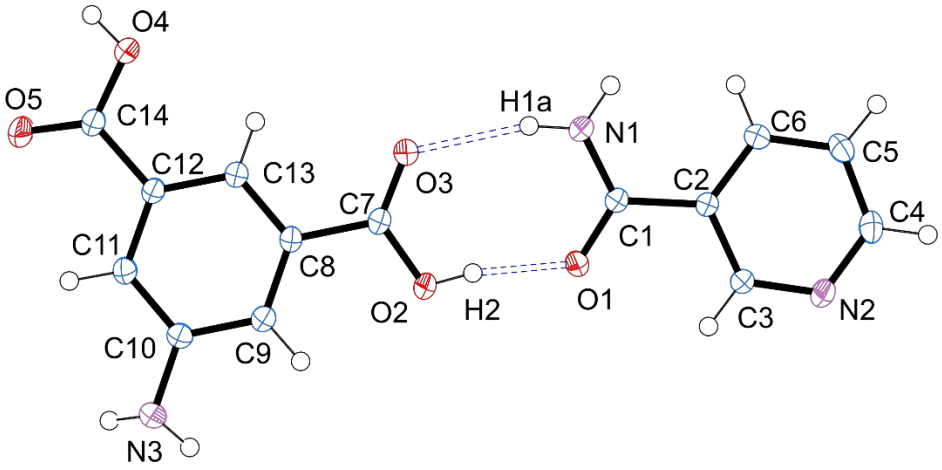


Figure 4. 8 Asymmetric unit of co-crystal niacinamide · 5-aminoisophthalic acid – JMB021

The asymmetric unit of niacinamide · 5-aminoisophthalic acid contains one molecule of niacinamide and one molecule of 5-aminoisophthalic acid (Figure 4.8), which crystallizes in the monoclinic $P2_1/n$ space group. Once again, the amide moiety of niacinamide is bonded through two O1···H2-O2 and N1-H1a···O3 hydrogen bonds to form a $R_2^2(8)$ ring.

In the packing niacinamide is bonded to three 5-aminoisophthalic acid molecules via a single N2···H4A-O4 hydrogen bond, two O3···H1A-N1 and O1···H2-O2 hydrogen bonds ($R_2^2(8)$ ring) and two O5···H1B-N1 and O3···H3D-N3 hydrogen bonds ($R_3^2(10)$ ring) as seen in Figure 4.9. The 5-aminoisophthalic acid molecule in the asymmetric unit is hydrogen bonded to 5 molecules, 3 niacinamide molecules and 2 5-aminoisophthalic acid molecules.

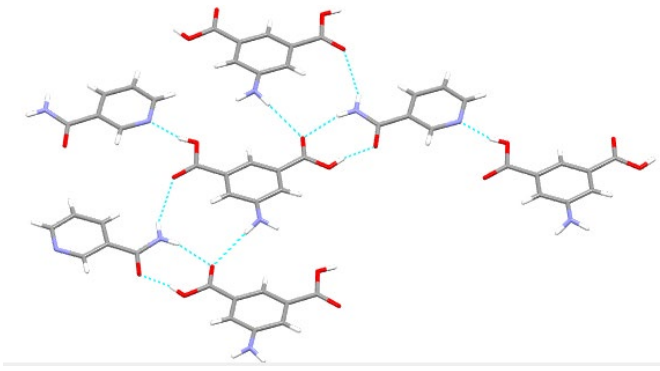


Figure 4. 9 Image showing packing regarding JMB021 down the *a* axis

Crystal packing results in alternating planes of niacinamide and 5-aminoisophthalic acid when viewed down the *b* axis, shown in Figure 4.10 below.

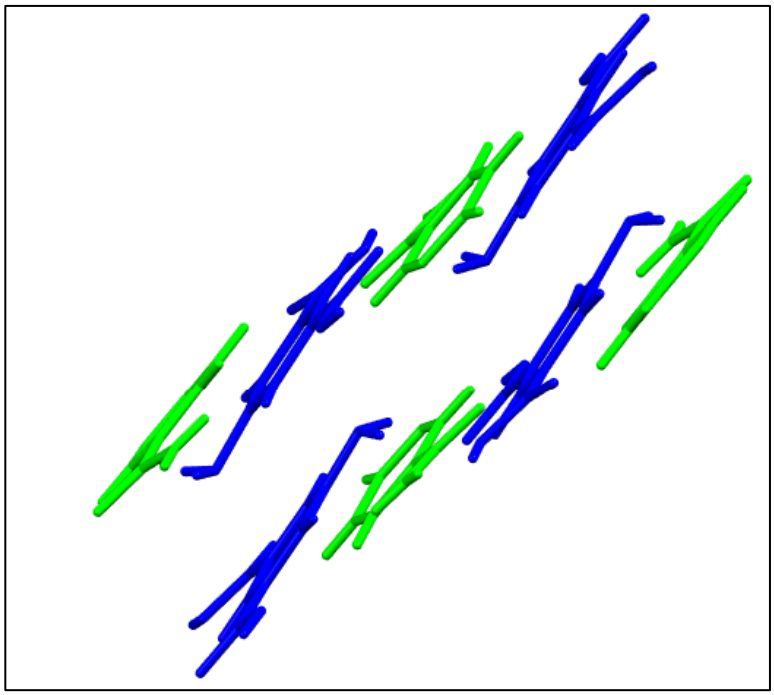


Figure 4. 10 Crystal packing of JMB021 viewed down the *b* axis

Table 4. 9 Hydrogen bonds for JMB021 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(5)-H(5)...O(1)#1	0.93	2.61	3.4313(14)	147.7
N(1)-H(1A)...O(3)	0.86	2.07	2.9090(13)	163.6
N(1)-H(1B)...O(5)#2	0.86	2.29	3.0150(14)	142.7
N(3)-H(3D)...O(3)#3	0.86	2.33	3.1604(15)	160.1
O(2)-H(2)...O(1)	0.82	1.73	2.5418(12)	167.9
O(4)-H(4A)...N(2)#4	0.82	1.86	2.6481(12)	161.2
C(5)-H(5)...O(1)#1	0.93	2.61	3.4313(14)	147.7
N(1)-H(1A)...O(3)	0.86	2.07	2.9090(13)	163.6
N(1)-H(1B)...O(5)#2	0.86	2.29	3.0150(14)	142.7
N(3)-H(3D)...O(3)#3	0.86	2.33	3.1604(15)	160.1
O(2)-H(2)...O(1)	0.82	1.73	2.5418(12)	167.9
O(4)-H(4A)...N(2)#4	0.82	1.86	2.6481(12)	161.2

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+3/2,z-1/2 #2 x+1/2,-y+1/2,z-1/2

#3 x-1/2,-y+1/2,z+1/2 #4 x,y-1,z

4.2.5 Niacinamide with 5-nitroisophthalic acid (JMB006)

IUPAC NAME: 5-nitrobenzene-1,3-dicarboxylic acid pyridine-3-carboxamide

Chemical formula: $C_8H_5NO_6 \cdot C_6H_6N_2O$

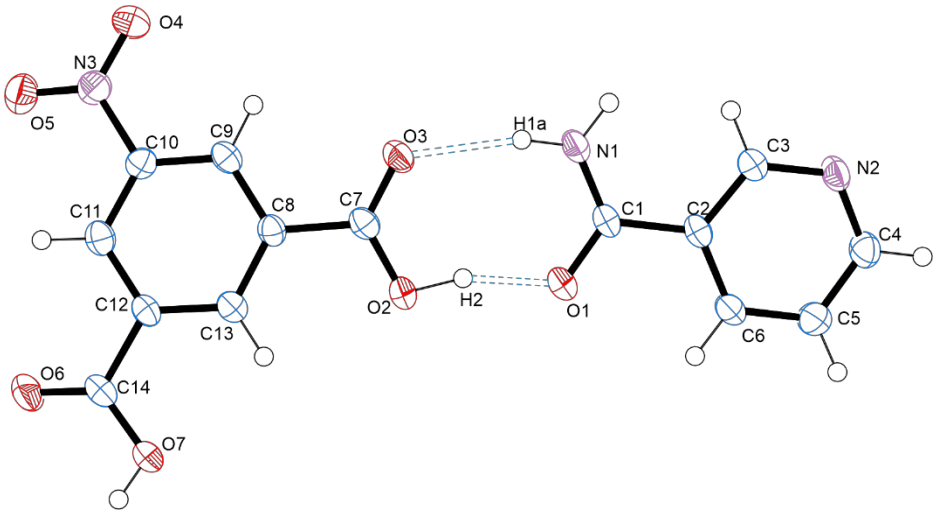


Figure 4. 11 Asymmetric unit of co-crystal niacinamide · 5-nitroisophthalic acid – JMB006

The asymmetric unit of the niacinamide · 5-nitroisophthalic acid contains one molecule of niacinamide and one molecule of 5-nitroisophthalic acid (Figure 4.11), in an orthorhombic crystal system and with a $Pna2_1$ space group. The amide group of niacinamide is bonded through two hydrogen bonds; O1···H2-O2 and N1-H1a···O3 and form a $R_2^2(8)$ ring.

In the packing, the niacinamide molecule is bonded to three 5-nitroisophthalic acid molecules and one niacinamide molecule via the following hydrogen bonds; O1···H2-O2 and N1-H1a···O3, N2···H7-O7 as well as bifurcated O4,O5···H1B-N1 hydrogen bonds. The 5-nitroisophthalic acid is bonded to three niacinamide molecules via the hydrogen bonds mentioned above. These are displayed in Figure 4.12 below.

The packing is in alternating layers of co-former and API as seen in Figure 4.13.

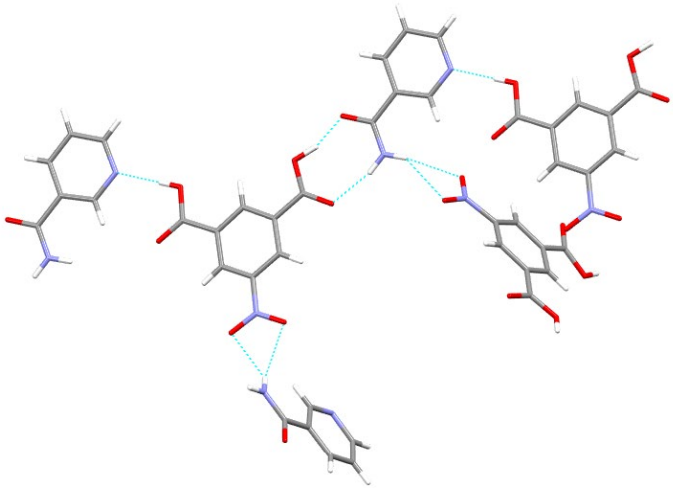


Figure 4. 12 Image of the packing of niacinamide · 5-nitroisophthalic acid

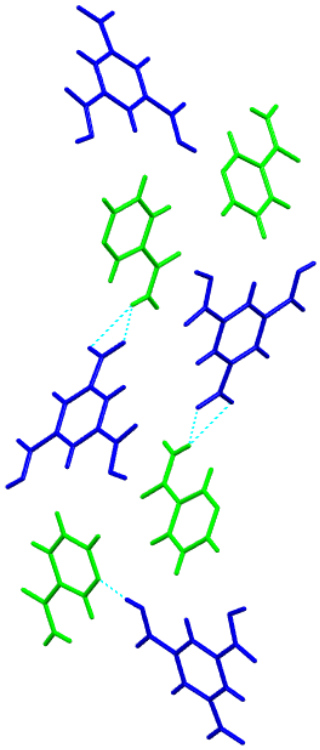


Figure 4. 13 Image of the packing of niacinamide · 5-nitroisophthalic acid down the *c* axis

Table 4. 10 Hydrogen bonds for JMB006 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(3)...O(4)#1	0.95	2.65	3.469(4)	145.0
C(3)-H(3)...O(6)#2	0.95	2.50	3.180(4)	128.1
C(4)-H(4)...O(1)#3	0.95	2.57	3.419(4)	148.9
N(1)-H(1A)...O(3)	0.88	2.01	2.867(4)	165.0
N(1)-H(1B)...O(4)#1	0.88	2.39	3.130(4)	142.4
N(1)-H(1B)...O(5)#1	0.88	2.54	3.304(4)	145.2
O(7)-H(7)...N(2)#4	0.84	1.82	2.661(4)	173.4
O(2)-H(2)...O(1)	1.03(6)	1.57(6)	2.584(3)	165(4)
C(3)-H(3)...O(4)#1	0.95	2.65	3.469(4)	145.0
C(3)-H(3)...O(6)#2	0.95	2.50	3.180(4)	128.1
C(4)-H(4)...O(1)#3	0.95	2.57	3.419(4)	148.9
N(1)-H(1A)...O(3)	0.88	2.01	2.867(4)	165.0
N(1)-H(1B)...O(4)#1	0.88	2.39	3.130(4)	142.4
N(1)-H(1B)...O(5)#1	0.88	2.54	3.304(4)	145.2
O(7)-H(7)...N(2)#4	0.84	1.82	2.661(4)	173.4
O(2)-H(2)...O(1)	1.03(6)	1.57(6)	2.584(3)	165(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,z-3/2 #2 x+1,y,z-2 #3 x+1/2,-y+3/2,z-1

#4 x-1,y,z+2

4.2.6 Niacinamide with nitroterephthalic acid (JMB007)

IUPAC NAME: 2-nitrobenzene-1,4-dicarboxylic acid pyridine-3-carboxamide

Chemical formula: $C_8H_5NO_6 \cdot C_6H_6N_2O$

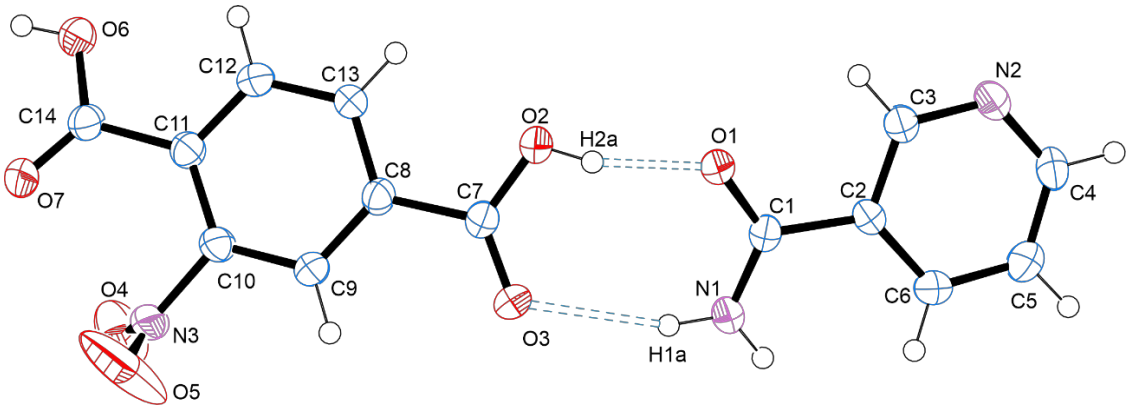


Figure 4. 14 Asymmetric unit of co-crystal niacinamide · nitroterephthalic acid– JMB007

The asymmetric unit of niacinamide · nitroterephthalic acid contains one molecule of niacinamide and one molecule of nitroterephthalic acid (Figure 4.14) and crystallizes in the orthorhombic *Ccc*2 space group. The amide moiety of niacinamide is bonded via two O1···H2a-O2 and N1-H1a···O3 hydrogen bonds to form a $R_2^2(8)$ ring, using graph set notation (Bernstein et al., 1995). The oxygens (O4 and O5) in the nitro group are disordered, resulting in elongated ellipsoids.

In the packing, each niacinamide is bonded to two terephthalic acid molecules – one as in the asymmetric unit discussed above, and the other via a single N1-H1b···O7 hydrogen bond resulting in a 3-dimensional network.

There is a rather strange short contact between adjacent nitroterephthalic acid molecules. It is possible that a H atom that is shared by the two carboxylic acid moieties in a 3-centre contact (Figure 4.15) The H atom could possibly come from the carboxylic acid O6. However, it was not possible to assign the atom unambiguously.

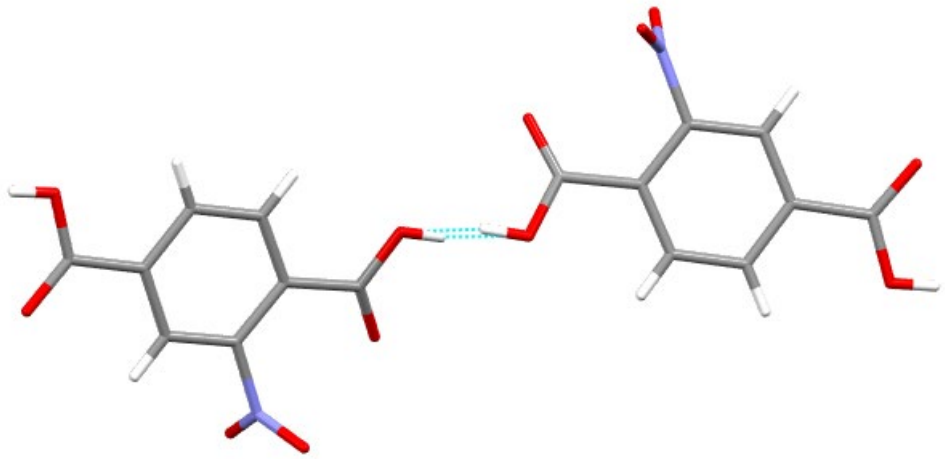


Figure 4. 15 Strange short contact between two terephthalic acid showing the shared hydrogen atom in a 3-centre contact.

When viewed down the *b* axis, the crystal packing results in alternating planes of niacinamide and nitroterephthalic acid as showed in Figure 4.16.

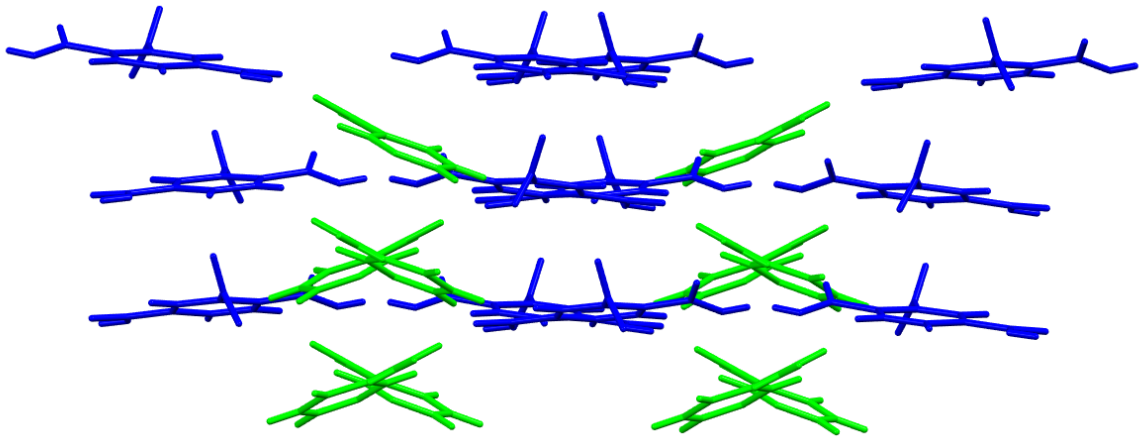


Figure 4. 16 Crystal packing of JMB007 viewed down the *b* axis

Table 4. 11 Hydrogen bonds for JMB007 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(3)...O(6)#1	0.93	2.55	3.035(7)	113.1
C(4)-H(4)...O(3)#2	0.93	2.28	3.173(6)	160.0
N(1)-H(1A)...O(3)	0.86	2.31	3.133(5)	159.1
N(1)-H(1B)...O(7)#3	0.86	2.08	2.919(5)	165.3
O(2)-H(2A)...O(1)	0.82	1.76	2.551(5)	162.8
O(6)-H(6A)...O(6)#4	0.82	1.63	2.429(7)	162.5

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,z #2 -x-1/2,y-1/2,z-1/2 #3 x-1/2,-y+1/2,z-1/2

#4 -x+1/2,-y+1/2,z

4.2.7 Key observations and discussion in the niacinamide series (Series 1)

The niacinamide series is the largest co-crystal series in this study, with six structures obtained. Five co-crystals were synthesized, as well as one co-crystal salt. Most of the crystals were either white or colourless, except for JMB021. The niacinamide ·5-aminoisophthalic acid (JMB021), produced orangish crystals, this is interesting as 5-aminoisophthalic acid crystals have the ability to partake in reversible colour change in the presence of certain solvent vapours (Fujii et al., 2011), as mentioned in the literature review (section 2.3).

All co-crystals in this series co-crystallized through amide – carboxyl heterosynthons with the exception of the co-crystal salt (JMB078), which formed a hydrogen bond via the protonated pyridine nitrogen and the carboxylate ion. In the case of JMB019, there was also hydrogen bonding from the pyridine nitrogen, in addition to the heterosynthon discussed above. It is clear that the preferred bonding pattern of niacinamide is through the amide moiety and not the pyridine nitrogen. This is in contrast to the hydrogen bonding usually found in *N*-heterocyclic compounds which is via a robust pyridine – carboxylic acid heterosynthon (Aakeröy et al., 2006). However, this does correspond to the findings of Tothadi and Desiraju (2012), discussed in section 2.2.3, where pattern III was present in all the niacinamide structures (Tothadi & Desiraju, 2012) .

In the four phthalic acid derivatives containing a nitrogen group (3-nitrophthalic acid, 5-aminoisophthalic acid, 5-nitroisophthalic acid and nitroterephthalic acid), no hydrogen bonding was observed via the amino or nitro groups, but exclusively through the carboxylic acid groups. This suggests that phthalic acid derivatives prefer bonding through the standard carboxyl moieties rather than their additional derivative groups. Replacing the amino and nitro groups with other modifiers may make an interesting future study to confirm this suggestion.

4.3 Co-crystals of modified isoniazid (benzaldehyde modifier) with dicarboxylic acids

A description and discussion of the modified isoniazid with phthalic acid derivatives co-crystals achieved in Series 2, follows in this section.

Below is the crystallographic data for series 2, summarized in table 4.6.

Table 4. 12 Crystallographic data for series 2 (Modified isoniazid)

	MB016	**JMB086**	**MB017**	**MB018**
Formula	$(C_{13}H_{11}N_3O) \cdot (C_8H_5NO_6)$	$(C_{13}H_{11}N_3O) \cdot (C_8H_6O_4)$	$2(C_{13}H_{11}N_3O) \cdot (C_8H_6O_4) \cdot 2(H_2O)$	$(C_{13}H_{11}N_3O) \cdot (C_8H_5NO_6)$
M_r	324.31	391.38	162.66	436.38
Temperature/K	173(2)	173(2)	173(2)	173(2)
Wavelength/Å	0.71073	0.71073	0.71073	0.71073
Crystal size/mm^3	0.501 x 0.272 x 0.101	0.272 x 0.134 x 0.092	0.477 x 0.214 x 0.132	0.398 x 0.253 x 0.111
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	P -1	$P2_1/c$	P -1	P -1
Description	Block	Prism	Block	Block
Colour	Colourless	Colourless	Colourless	Colourless
a/Å	6.6425(6)	6.9225(6)	6.6492(3)	8.8550(2)
b/Å	7.7369(8)	18.0454(15)	7.6769(4)	11.3201(3)
c/Å	31.673(3)	14.8384(14)	16.1295(9)	11.4225(3)
α/°	92.161(7)	90	99.269(3)	97.8730(10)
β/°	92.537(6)	102.207(4)	98.561(3)	106.2930(10)
γ/°	101.239(7)	90	100.557(3)	111.6050(10)
V/$Å^3$	1593.2(3)	1811.7(3)	785.21(7)	984.06(4)
Z	4	4	4	2
ρ (calcd)/Mg m^{-3}	1.352	1.435	1.376	1.473
μ/mm^{-1}	0.099	0.105	0.100	0.113
F(000)	676	816	340	452
Θ Range for data/° collection/°	2.578 to 26.614	1.801 to 27.997	2.603 to 27.999	1.929 to 27.999
Reflections collected	13740	75388	3954	23974
No. of unique data [R(int)]	6310 [0.1249]	4369 [0.1167]	3469 [0.0134]	4745 [0.0449]
Final $R(I > 2\sigma(I))$	0.2616	0.0756	0.0784	0.0707
Final wR_2 (all data)	0.4914	0.1554	0.1873	0.1202
CCDC deposition number	2240478	2333282	2240437	2240472

4.3.1 Isoniazid modified with benzaldehyde with isophthalic acid MB016

IUPAC NAME: 3-nitrobenzene-1,2-dicarboxylic acid N'-benzylidenepyridine-4-carbohydrazide

Chemical formula: $C_{13}H_{11}N_3O \cdot C_8H_5NO_6$

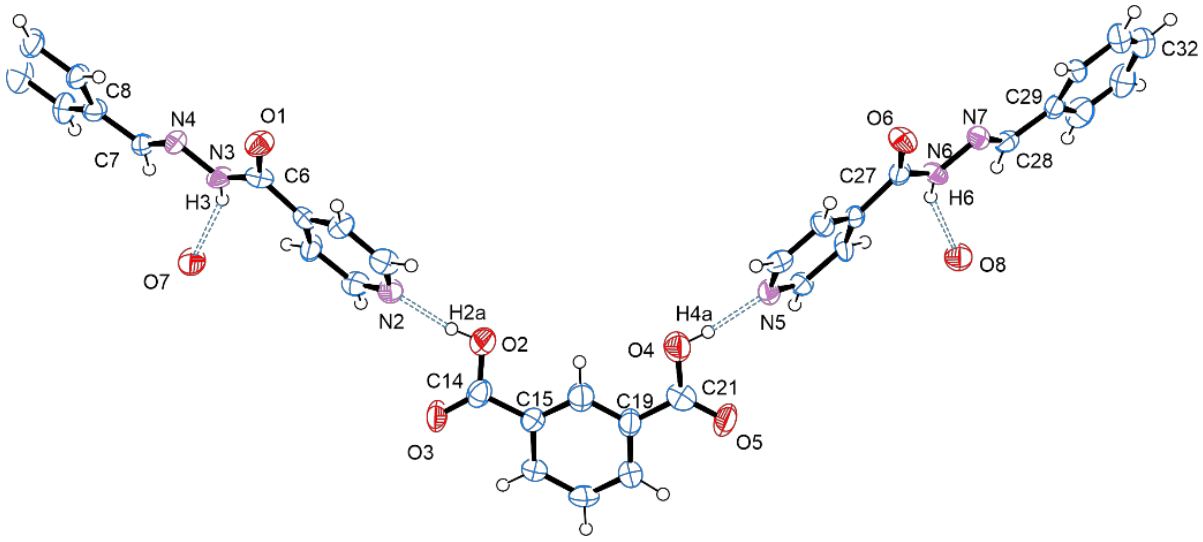
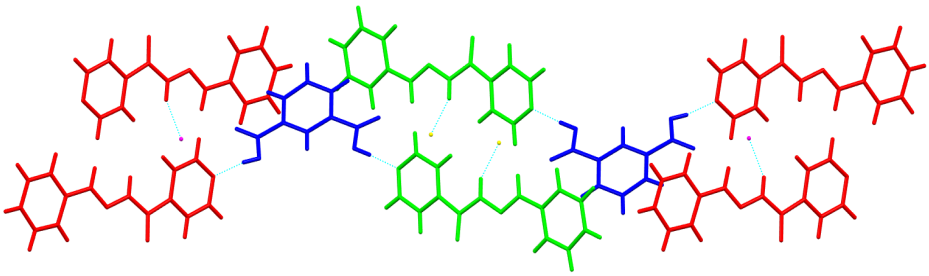


Figure 4. 17 Asymmetric unit of co-crystal hydrate of modified isoniazid · isophthalic acid– MB016

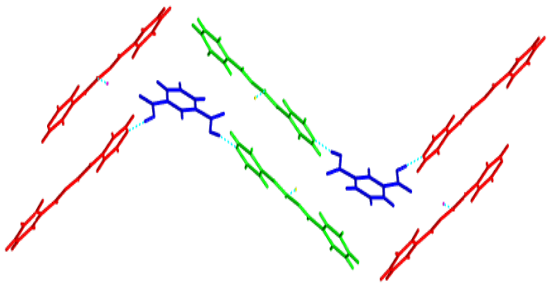
The asymmetric unit modified isoniazid · isophthalic acid contains two molecules of modified isoniazid and one molecule of isophthalic acid, there are also two oxygen atoms in the asymmetric unit, namely, O7 and O8 which belong to water molecules. However, it was not possible to determine the position of the hydrogens (Figure 4.17).

It crystallizes in the triclinic crystal system with a $P\bar{1}$ space group. The pyridine nitrogen of each modified isoniazid is bonded via single N2···H2a-O2 and N5···H4a-O4 hydrogen bonds to the carboxyl groups of isophthalic acid, with $D_2^2(11)$ graph set notation. The two oxygen atoms in the asymmetric unit are hydrogen bonded to the modified benzaldehyde via O7···H3-N3 and O8···H6-N6 hydrogen bonds with $D_1^1(2)$ graph set notation.

The packing of this unit is simply a repeating asymmetric unit, where isophthalic acid is hydrogen bonded to two modified isoniazid molecules as seen in Figure 4.18 (a) below.



(a)



(b)

Figure 4. 18 (a) The packing of MB016; (b) The packing of MB016 viewed along *a* axis

Table 4. 13 Hydrogen bonds for MB016 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(28)-H(28)...O(8)	0.95	2.44	3.216(12)	138.3
C(7)-H(7)...O(7)	0.95	2.55	3.290(11)	135.2
C(5)-H(5)...O(3)#1	0.95	2.50	3.303(13)	142.5
C(2)-H(2)...O(7)	0.95	2.50	3.307(12)	142.2
C(26)-H(26)...O(5)#1	0.95	2.50	3.313(13)	143.2
C(23)-H(23)...O(8)	0.95	2.55	3.345(11)	141.4
N(3)-H(3)...O(7)	0.88	2.05	2.839(10)	149.2
N(6)-H(6)...O(8)	0.88	2.08	2.880(10)	151.4
O(2)-H(2A)...N(2)	0.84	1.77	2.599(11)	169.7
O(4)-H(4A)...N(5)	0.84	1.79	2.618(11)	170.1
C(2)-H(2)...O(7)	0.95	2.50	3.307(12)	142.2
C(5)-H(5)...O(3)#1	0.95	2.50	3.303(13)	142.5
C(7)-H(7)...O(7)	0.95	2.55	3.290(11)	135.2
C(23)-H(23)...O(8)	0.95	2.55	3.345(11)	141.4
C(26)-H(26)...O(5)#1	0.95	2.50	3.313(13)	143.2
C(28)-H(28)...O(8)	0.95	2.44	3.216(12)	138.3
N(3)-H(3)...O(7)	0.88	2.05	2.839(10)	149.2
N(6)-H(6)...O(8)	0.88	2.08	2.880(10)	151.4
O(2)-H(2A)...N(2)	0.84	1.77	2.599(11)	169.7
O(4)-H(4A)...N(5)	0.84	1.79	2.618(11)	170.1

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z

4.3.2 Isoniazid modified with benzaldehyde with phthalic acid JMB086

IUPAC NAME: 3 benzene-1,2-dicarboxylic acid N'-benzylidenepyridine-4-carbohydrazide

Chemical formula: $C_{13}H_{11}N_3O \cdot C_8H_6O_4$

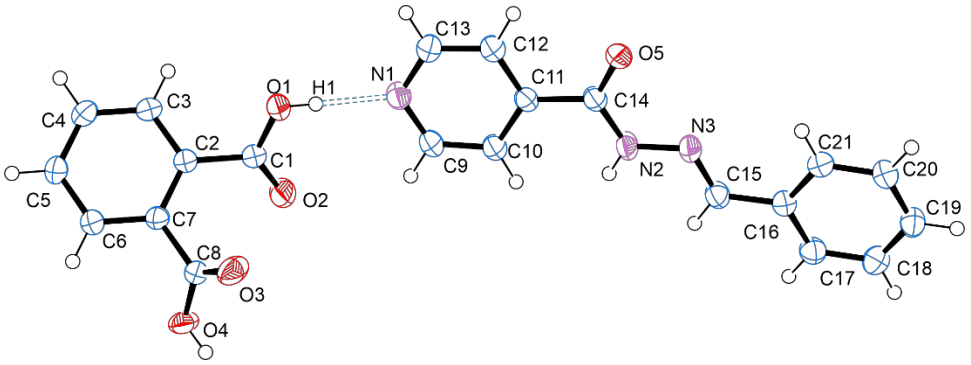


Figure 4. 19 (a) Asymmetric unit of co-crystal of modified isoniazid · phthalic acid– JMB086

The asymmetric unit of modified isoniazid · phthalic acid contains one molecule of modified isoniazid and one molecule of phthalic acid, crystallized in the monoclinic crystal system with space group $P2_1/c$. The pyridine nitrogen of the modified isoniazid is bonded to phthalic acid through a single N1···H1-O1 hydrogen bond with $D_1^1(2)$ graph set notation.

Each modified isoniazid molecule is bonded to three phthalic acid molecules through N1···H1-O1, O3···H2-N2 and O5···H4-O4 hydrogen bonds. Phthalic acid is bonded to three modified isoniazid molecules via the same bonds and can be seen in the Figure 4.20 below.

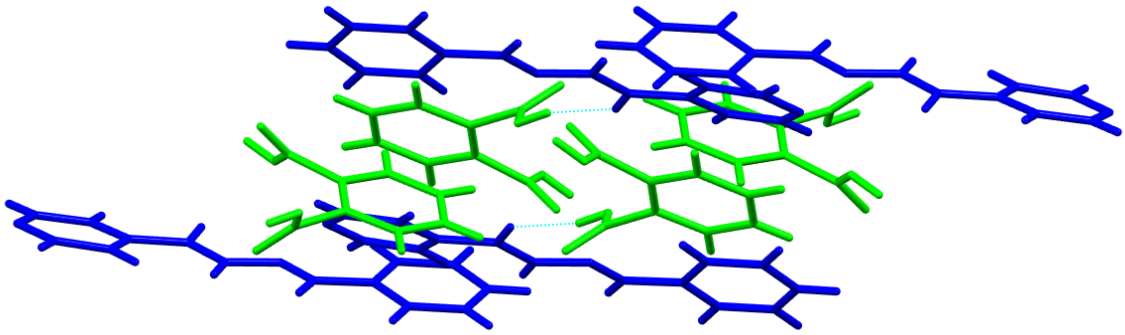


Figure 4. 20 The packing of JMB086 along the *b* axis

Table 4. 14 Hydrogen bonds for JMB086 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2)...O(3)#1	0.88	2.53	3.229(2)	136.8
O(1)-H(1)...N(1)	0.84	1.81	2.640(2)	167.3
O(4)-H(4)...N(3)#2	0.84	2.58	3.060(2)	117.7
O(4)-H(4)...O(5)#2	0.84	1.81	2.6276(18)	165.1

Symmetry transformations used to generate equivalent atoms:

#1 x-1,-y+1/2,z-1/2 #2 -x+1,y-1/2,-z+3/2

4.3.3 Isoniazid modified with benzaldehyde with terephthalic acid MB017

IUPAC NAME: benzene-1,4-dicarboxylic acid N'-benzylidenepyridine-4-carbohydrazide hydrate

Chemical formula: $2(C_{13}H_{11}N_3O) \cdot C_8H_6O_4 \cdot 2(H_2O)$

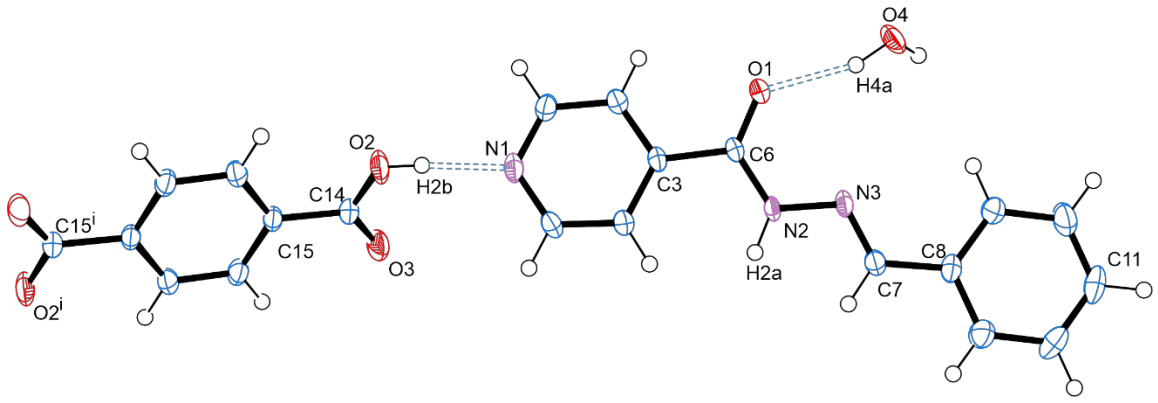


Figure 4. 21 Asymmetric unit of co-crystal of modified isoniazid · terephthalic acid– MB017

In the asymmetric unit of MB017, there is one molecule of modified isoniazid, 1/2 molecule of terephthalic acid and one water molecule (Figure 4.21), which crystallizes in the triclinic crystal system and space group $P\bar{1}$. The pyridine nitrogen of the modified isoniazid is hydrogen bonded to terephthalic acid through a N1···H2a-O2 bond and to the water molecule though an O1···H4a-O4 hydrogen bond, both with $D_1^1(2)$ graph set notation.

Each modified isoniazid is hydrogen bonded to one terephthalic acid molecule through N1···H2a-O2, and two water molecules through O1···H4a-O4 and O4···H2a-N2 hydrogen bonds. Each water molecule is hydrogen bonded to two modified isoniazid molecule and one terephthalic acid molecule as shown in the Figure 4.22 below.

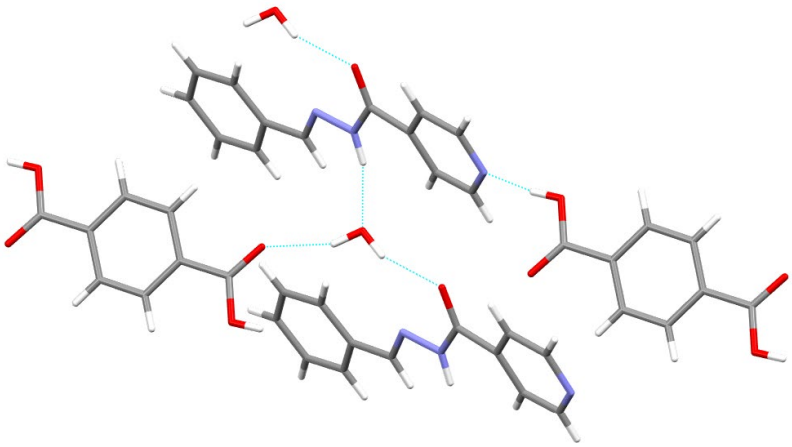


Figure 4. 22 Hydrogen bonding in MB017 down the *b* axis

Table 4. 15 Hydrogen bonds for MB017 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2A)...N(1)	0.84	1.78	2.596(2)	164.4
C(7)-H(7)...O(4)#2	0.95	2.48	3.228(3)	135.8
C(1)-H(1)...O(3)#3	0.95	2.47	3.266(3)	141.5
C(4)-H(4)...O(4)#2	0.95	2.53	3.318(3)	140.8

Symmetry transformations used to generate equivalent atoms:

#1 -x+3,-y+1,-z+2 #2 x+1,y,z #3 x-1,y,z

4.3.4 Isoniazid modified with benzaldehyde with 3-nitrophthalic acid MB018

IUPAC NAME: 3-nitrobenzene-1,2-dicarboxylic acid N'-benzylidenepyridine-4-carbohydrazide

Chemical formula: $C_{13}H_{11}N_3O \cdot C_8H_5NO_6$

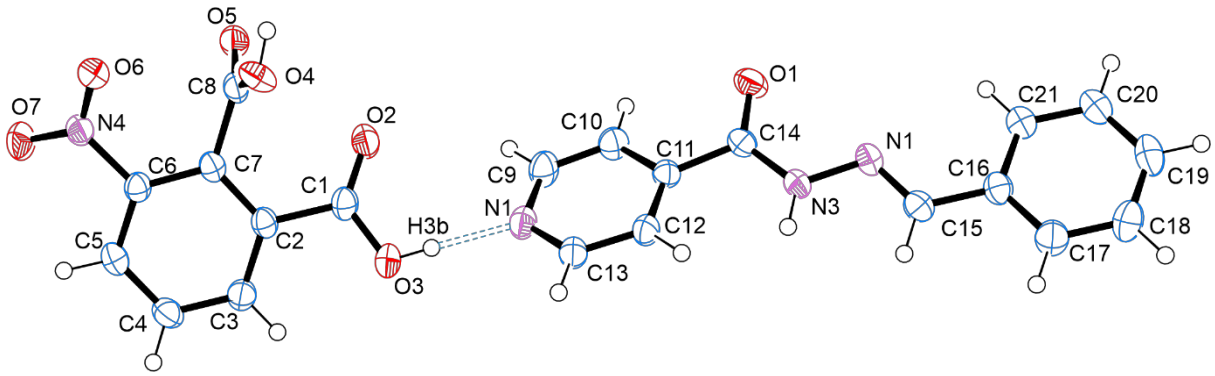


Figure 4. 23 Asymmetric unit of co-crystal of modified isoniazid · 3-nitrophthalic acid– MB018

As seen in Figure 4.23, the asymmetric unit of modified isoniazid · 3-nitrophthalic acid contains one molecule of modified isoniazid and one molecule of 3-nitrophthalic acid, crystallized in a triclinic $P\bar{1}$ space group. Bonding through a single N1···H3b-O3 hydrogen bond is observed between the two molecules as seen in Figure 4.23, above. This forms a $D_1^1(2)$ intermolecular structure.

With regard to packing, each modified isoniazid molecule is bonded to three 3-nitrophthalic acid molecules via N1···H3b-O3, O5···H3-N3 and O1···H4a-O4 hydrogen bonds, forming a $R_4^4(28)$ ring as seen in Figure 4.24. This ring results in tubular spaces between molecules along the *b* axis.

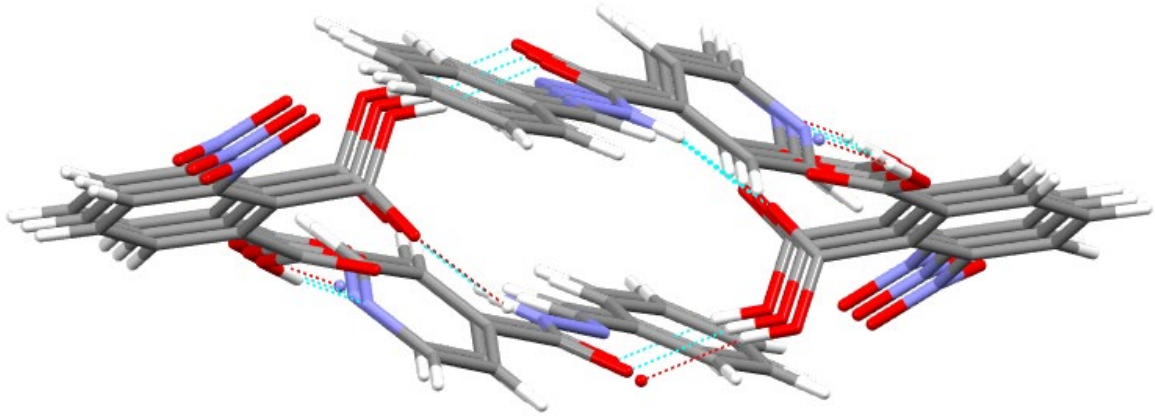


Figure 4. 24 The packing diagram down the *b* axis of MB018, displaying the $\boldsymbol{R_4^4(28)}$ ring.

Table 4. 16 Hydrogen bonds for MB018 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(5)-H(5)...O(1)#1	0.95	2.62	3.298(2)	128.4
O(3)-H(3B)...N`	0.84	1.74	2.5805(18)	174.2
O(4)-H(4A)...O(1)#2	0.84	1.78	2.6009(16)	165.4
C(15)-H(15)...O(5)#3	0.95	2.61	3.3820(19)	139.0
C(12)-H(12)...O(5)#3	0.95	2.27	3.1658(19)	157.8
C(13)-H(13)...O(7)#3	0.95	2.53	3.415(2)	154.9
N(3)-H(3)...O(5)#3	0.88	2.03	2.8840(17)	164.4

Symmetry transformations used to generate equivalent atoms:

#1 x,y+1,z+1 #2 -x+1,-y+1,-z+1 #3 x,y-1,z

4.3.5 Key observations and discussion in the modified isoniazid series (Series 2)

Four co-crystals were obtained in this series, with three of the four structures having a triclinic crystal system and $P\bar{1}$ space group, with transparent block shaped crystals. JMB086 (modified benzaldehyde with phthalic acid) was the only co-crystal in the series that had a monoclinic crystal system in the $P2_1/c$ space group, with prism shaped crystals. This crystal was special as it was the only phthalic acid co-crystal, and many attempts were made to co-crystallize phthalic acid to an API.

Benzaldehyde, being an aldehyde, is very reactive and therefore readily bonds covalently to isoniazid to form a Schiff base. The reaction of isoniazid and benzaldehyde could be performed at room temperature using a simple magnetic stirrer. Where it was necessary to heat the sample, this was only to ensure that the solids were completely dissolved.

Crystallization was difficult as benzaldehyde has a slow evaporation rate and therefore obtaining a crystal sometimes took weeks. To speed up evaporation, samples were left in a warm laboratory which had no air-conditioning (+- 27°C) – which also gave the lab a pleasant smell. In order to aid crystallization, the polytop vials were scratched with a diamond pen.

There are other crystals from this series which are still in the process of crystallization but have not crystallized at the time of writing this dissertation, due to the slow evaporation of the benzaldehyde. However, these will still be characterized at a later stage.

Two of the four modified isoniazid crystals resulted in hydrates. The water molecules in these two structures did not originate from the solvent, but as by-product of the reaction and is formed from the aldehyde oxygen of the original benzaldehyde and the two hydrogen atoms from the terminal amine group of the isoniazid. For this reason, INH which is modified by aldehydes or ketones usually produce a hydrate.

All four structures were bonded through the expected robust pyridine - carboxylic acid heterosynthon usually found in isoniazid (Lemmerer *et al*.,2010b).

Phthalic acid has been extremely hard to co-crystallize with the other API's, this is supported by the fact that there are few reported structures of these in the literature compared to isophthalic acid and terephthalic acid. This is probably because of the steric effects of four oxygen atoms being clustered into a small space (see Figure 4.25). In order for the hydrogen bond to form the orientation of the phthalic acid must be favourable.

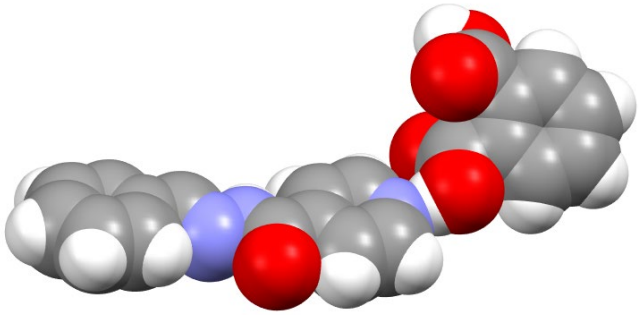


Figure 4. 25 Spacefill diagram of JMB086 demonstrating the steric effects of four oxygen atoms on phthalic acid being clustered into a small space

4.4. Co-crystals of other nitrogen containing heterocyclic API's with phthalic acid derivatives

A description and discussion of the other *N*- heterocyclic API's with phthalic acid derivatives co-crystals achieved in Series 3, follows in this section.

Below is the crystallographic data for series 3, summarized in table 4.7.

Table 4. 17 Crystallographic data for series 3 (Other N-heterocyclic API's)

	MB002	**MB013**	**JMB036**
Formula	$(C_8H_6O_4) \cdot 2(C_6H_7N_3O)$	$C_{14}H_{10}O_4 \cdot C_6H_7N_3O$	$(C_8H_6O_4) \cdot 2(C_6H_6N_2O)$
M_r	219.20	379.36	410.38
Temperature/K	293(2)	173(2)	173(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal size/mm^3	0.277 x 0.172 x 0.136	0.259 x 0.312 x 0.157	0.234 x 0.227 x 0.158
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	*Pmn*2_1	*P*2_1/c	*C*2/c
Description	Block	Block	Block
Colour	Colourless	Yellow	Colourless
a/Å	42.117(2)	12.6104(3)	20.8371(8)
b/Å	6.2110(3)	9.9700(3)	5.2243(2)
c/Å	3.7536(2)	15.8763(4)	19.1062(7)
α/°	90	90	90
β/°	90	109.5170(10)	118.8350(10)
γ/°	90	90	90
V/$Å^3$	981.90(9)	1881.37(9)	1822.01(12)
Z	4	4	4
ρ (calcd)/Mg m^{-3}	1.483	1.339	1.496
μ/mm^{-1}	0.113	0.098	0.113
F(000)	456	792	856
Θ Range for data/° collection/°	0.967 to 27.990	1.713 to 27.999	2.231 to 27.998
Reflections collected	4090	46099	70443
No. of unique data [R(int)]	1766 [0.0638]	4537 [0.0327]	2191 [0.0716]
Final R($I > 2\sigma(I)$)	0.0767	0.0547	0.0414
Final wR_2 (all data)	0.1866	0.1084	0.1151
CCDC deposition number	868958	2204808	2312436

	JMB041	JMB056	JMB046
Formula	$(C_{14}H_{10}O_4) \cdot 2(C_6H_6N_2O)$	$(C_6H_9N_3O^{2+}) \cdot (C_8H_3NO_6^{2-})$	$(C_8H_7NO_4) \cdot (C_7H_8N_2O)$
M_r	486.47	347.27	317.30
Temperature/K	173(2)	173(2)	173(2)
Wavelength/Å	0.71073	0.71073	0.71073
Crystal size/mm^3	0.440 x 0.081 x 0.041	0.206 x 0.192 x 0.078	0.382 x 0.235 x 0.132
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P2_1/n$
Description	Needle	Block	Block
Colour	Colourless	Colourless	Yellow
a/Å	8.3730(14)	15.1110(6)	18.3690(6)
b/Å	15.638(3)	6.7515(3)	3.80100(10)
c/Å	19.409(3)	15.0503(7)	21.5232(7)
α/°	70.671(9)	90	90
β/°	80.412(10)	106.311(2)	108.8670(10)
γ/°	89.998(9)	90	90
V/$Å^3$	2360.5(7)	1473.66(11)	1422.02(8)
Z	4	4	4
ρ (calcd)/Mg m^{-3}	1.369	1.565	1.482
μ/mm^{-1}	0.099	0.129	0.113
F(000)	1016	716	664
Θ Range for data/° collection/°	1.382 to 25.999	1.404 to 27.997	1.769 to 28.000
Reflections collected	72841	71194	64283
No. of unique data [R(int)]	9281 [0.2225]	3549 [0.1370]	3402 [0.0519]
Final R($I > 2\sigma(I)$)	0.1737	0.0766	0.0416
Final wR_2 (all data)	0.3029	0.1921	0.1344
CCDC deposition number	2333254	2333029	2307503

4.4.1. Isoniazid with isophthalic acid MB002

IUPAC NAME: benzene-1,3-dicarboxylic acid pyridine-4-carbohydrazide

Chemical formula: $C_8H_6O_4 \cdot 2(C_6H_7N_3O)$

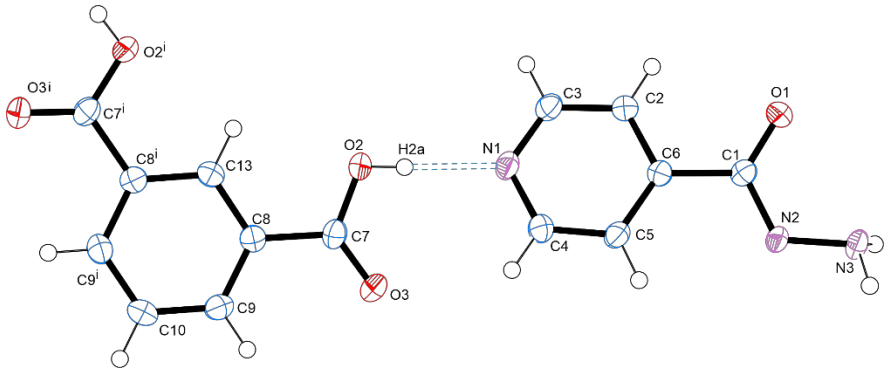


Figure 4. 26 Asymmetric unit of co-crystal of isoniazid · isophthalic acid– MB002

The structure of MB002 has been submitted to the CSD (Bag, 2021) in 2021 and discussed in the literature review, however it was resynthesized and refined for this project as a reference point. This is the only structure in this dissertation that is not novel.

The asymmetric unit of isoniazid · isophthalic acid includes one molecule of isoniazid and ½ a molecule of isophthalic acid, the other half of the isophthalic acid molecule shown in Figure 4.25 was generated by symmetry. Crystallizing in the orthorhombic $Pmn2_1$ space group, the pyridine nitrogen is hydrogen bonded via a N1···H2a-O2, forming a $D_1^1(2)$ intermolecular structure.

Each isophthalic acid molecule in the packing, is hydrogen bonded to two isoniazid molecules via a N1···H2a-O2 bond (forming a $D_2^2(11)$ intermolecular structure) as shown in Figure 4.26. each isoniazid molecule is bonded to four other isoniazid molecules through N2···H3A-N3 hydrogen bond and O1···H3B-N3 bonds as displayed in Figure 4.27. Figure 4.28 displays the four hydrogen bonds from 1 isoniazid molecule to four other isoniazid molecules and packing along the *b* axis can be seen in Figure 4.29.

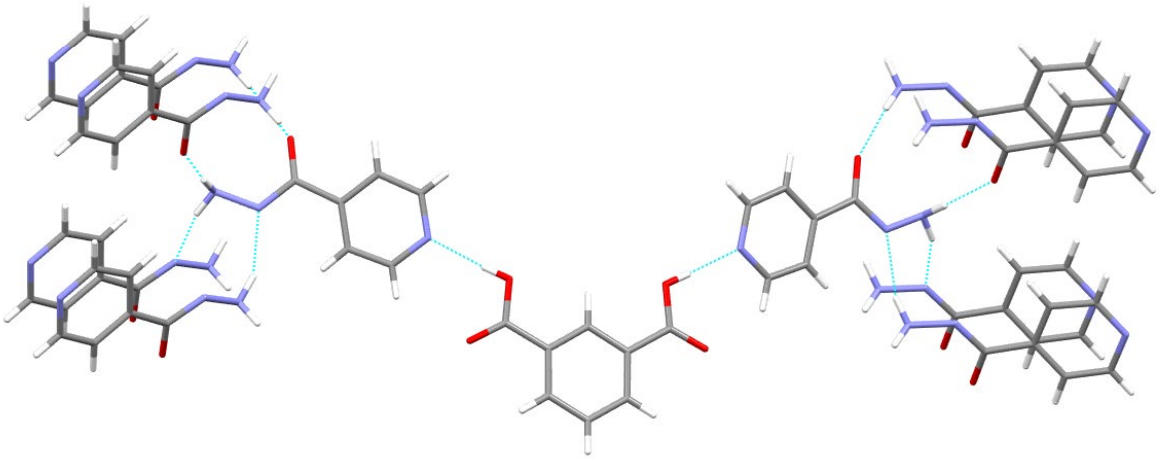


Figure 4. 27 Packing of co-crystal of isoniazid · isophthalic acid

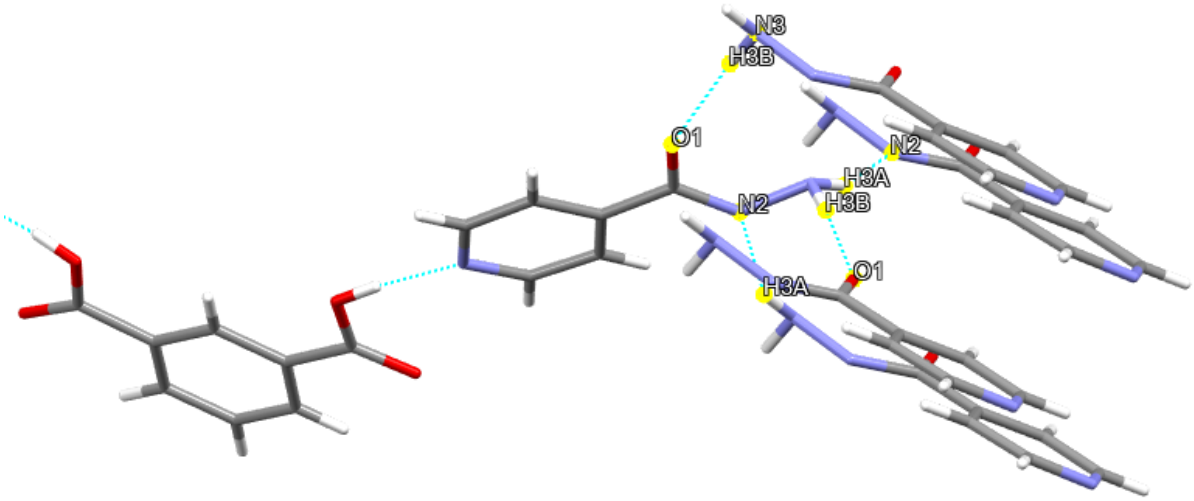


Figure 4. 28 Image displaying the four hydrogen bonds from one isoniazid molecule to four other isoniazid molecules.

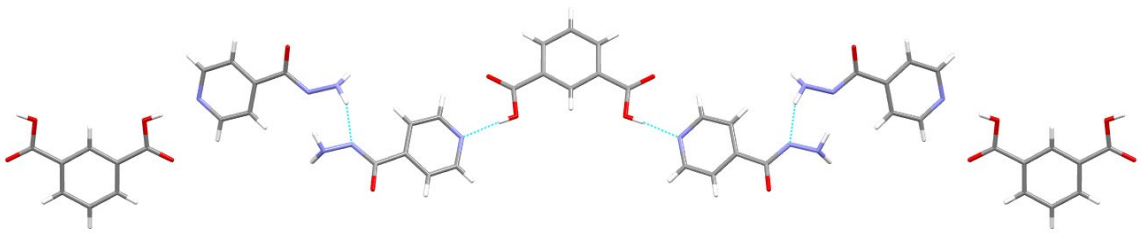


Figure 4. 29 Packing of isoniazid · isophthalic acid down the *b* axis

Table 4. 18 Hydrogen bonds for MB002 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2A)...O(1)#2	0.86	2.26	2.975(5)	140.3
N(2)-H(2B)...N(1)#3	0.86	2.41	2.935(5)	119.9
N(1)-H(1A)...N(2)#4	0.86	2.15	2.935(5)	152.2
C(1)-H(1)...O(2)#5	0.93	2.58	3.217(6)	126.1
C(5)-H(5)...O(2)#6	0.93	2.61	3.272(6)	128.2

Symmetry transformations used to generate equivalent atoms:

#1 -x,y,z #2 -x+1/2,-y,z+1/2 #3 -x+1/2,-y+1,z+1/2

#4 -x+1/2,-y+1,z-1/2 #5 x,y-1,z #6 x,y,z-1

4.4.2. Isoniazid with diphenic acid - MB013

IUPAC NAME: [1,1'-biphenyl]-2,2'-dicarboxylic acid pyridine-4-carbohydrazide

Chemical formula: $C_{14}H_{10}O_4 \cdot C_6H_7N_3O$

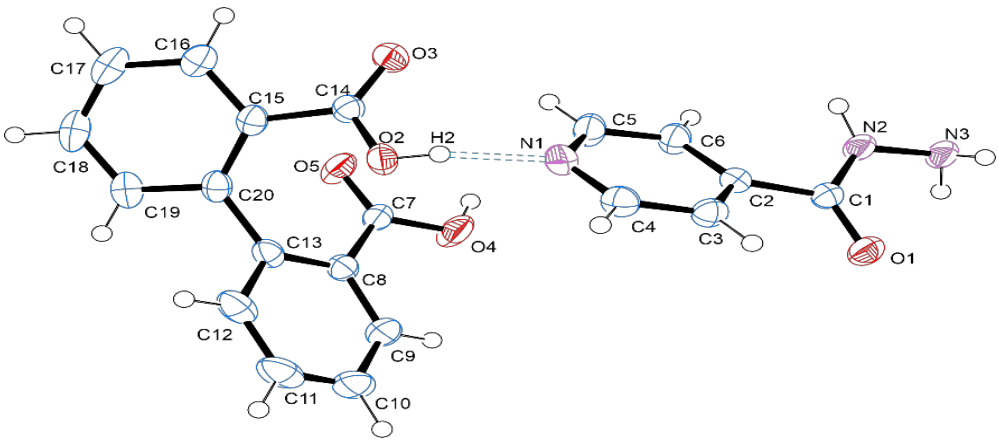


Figure 4. 30 Asymmetric unit of co-crystal of isoniazid · diphenic acid – MB013

In this asymmetric unit there is one molecule of isoniazid and one molecule of the bulky diphenic acid (Figure 4.30), these crystallize in the monoclinic $P2_1/c$ space group. The hydroxyl hydrogen from one of the carboxyl groups on diphenic acid hydrogen bonds to the pyridine nitrogen of the isoniazid through N1···H2-O2 forming a $D_1^1(2)$ intermolecular structure.

In diphenic acid, the two aromatic rings are separated by a single bond, allowing rotation around that single bond. In the crystal structure one plane is offset from the other by an angle of 30.96°, this allows the two carboxylic acid moieties to lie in positions almost parallel to each other (Figure 4.31).

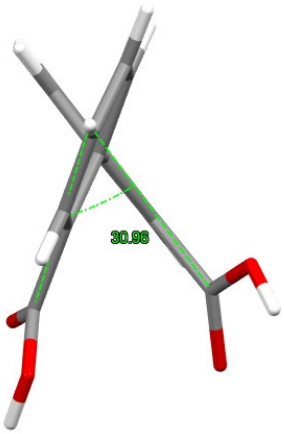


Figure 4. 31 The bond angle between the two carboxylic acid groups

Each isoniazid molecule is bonded to three diphenic acid molecules through the following hydrogen bonds; N1···H2-O2, O3···H3B-N3 and can be seen in Figure 4.32.

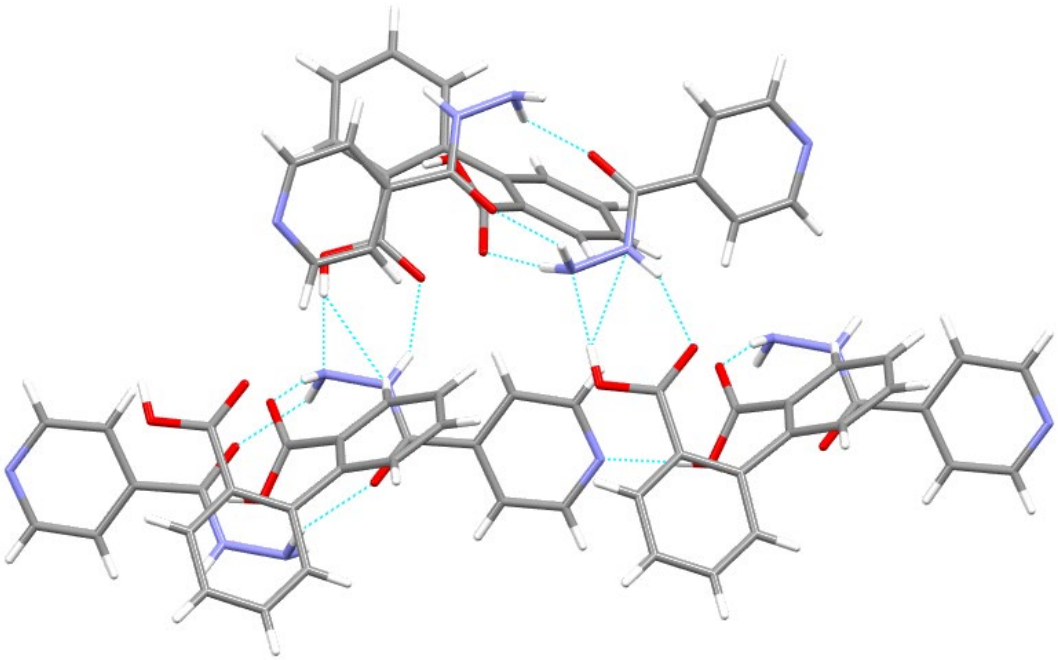


Figure 4. 32 The packing of MB013

Table 4. 19 Hydrogen bonds for MB013 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(2)-H(2)...N(1)	0.84	1.79	2.6164(15)	166.3
O(4)-H(4)...N(2)#1	0.84	2.54	3.2697(16)	145.5
O(4)-H(4)...N(3)#1	0.84	1.84	2.6761(16)	177.4
N(3)-H(3A)...O(1)#2	0.88	2.07	2.8613(16)	148.4
N(3)-H(3B)...O(3)#3	0.88	2.14	3.0114(17)	171.3
C(6)-H(6)...O(3)#4	0.95	2.41	3.3113(17)	158.3
C(4)-H(4A)...O(5)#5	0.95	2.39	3.2227(17)	145.6
C(5)-H(5)...O(3)	0.95	2.61	3.2794(17)	127.4
C(4)-H(4A)...O(5)#5	0.95	2.39	3.2227(17)	145.6
C(5)-H(5)...O(3)	0.95	2.61	3.2794(17)	127.4
C(6)-H(6)...O(3)#4	0.95	2.41	3.3113(17)	158.3
N(3)-H(3A)...O(1)#2	0.88	2.07	2.8613(16)	148.4
N(3)-H(3B)...O(3)#3	0.88	2.14	3.0114(17)	171.3
O(2)-H(2)...N(1)	0.84	1.79	2.6164(15)	166.3
O(4)-H(4)...N(2)#1	0.84	2.54	3.2697(16)	145.5
O(4)-H(4)...N(3)#1	0.84	1.84	2.6761(16)	177.4
N(2)-H(2A)...O(5)#4	0.876(19)	2.000(18)	2.8115(15)	153.6(16)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1/2 #2 -x+2,-y,-z+1 #3 x,y-1,z

#4 -x+2,y-1/2,-z+1/2 #5 x,-y+3/2,z+1/2

4.4.3 Isonicotinamide with terephthalic acid (JMB036)

IUPAC NAME: benzene-1,4-dicarboxylic acid pyridine-4-carboxamide

Chemical formula: $C_8H_6O_4 \cdot 2(C_6H_6N_2O)$

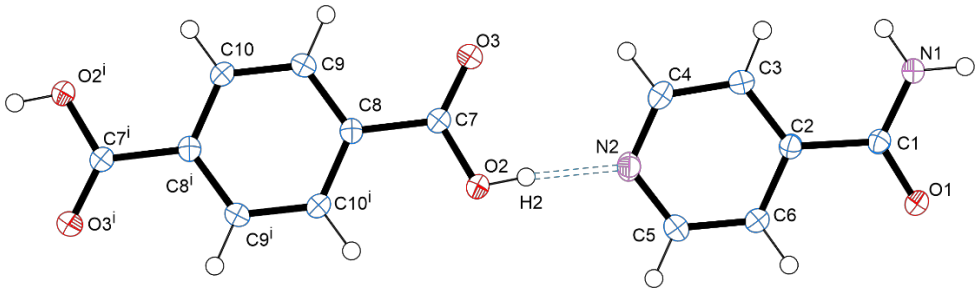


Figure 4. 33 Asymmetric unit of co-crystal of isonicotinamide · terephthalic acid – JMB036

The asymmetric unit of isonicotinamide · terephthalic acid contains one molecule of isonicotinamide and a ½ molecule of terephthalic acid (Figure 4.33), and crystallizes in the monoclinic *C*2/c space group. There is a discrete, $D_1^1(2)$ hydrogen bond, formed between the pyridine nitrogen and the hydrogen of the carboxyl group through N2···H2-O2.

Being in the C2/c space group the crystal structure has a glide plane along the c axis, resulting in the zigzag pattern shown in Figure 4.34.

The isonicotinamide molecule is bonded to another isonicotinamide molecule through O1···H1A-N1 hydrogen bonds, forming a $R_2^2(8)$ ring, and two terephthalic acid molecules via N2···H2-O2 and O3···H1B hydrogen bonds. Terephthalic acid is bonded to four isonicotinamide molecules via two O3···H1B-N1 hydrogen bonds and two N2···H2-O2 hydrogen bonds, this can be seen in Figure 4.35 below.

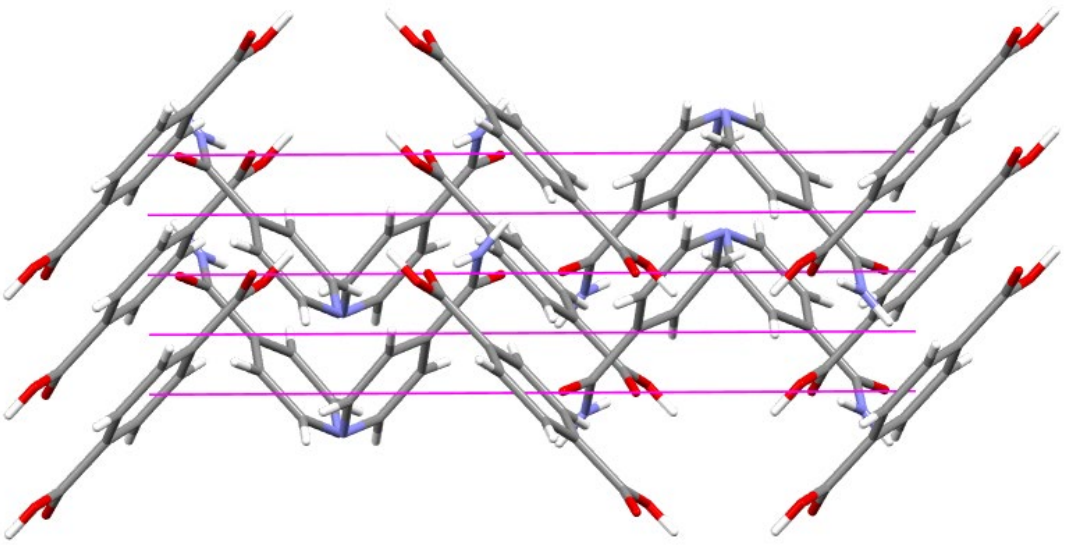


Figure 4. 34 Image showing glide planes along the *c* axis

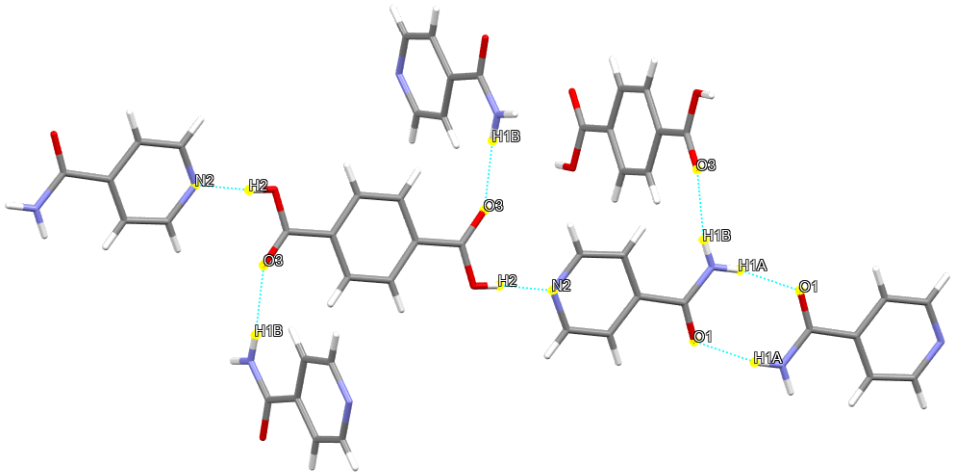


Figure 4. 35 Image showing hydrogen bonding between the isonicotinamide and terephthalic acid molecules.

Table 4. 20 Hydrogen bonds for JMB036 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(4)...O(2)#2	0.95	2.65	3.2759(14)	123.5
C(6)-H(6)...O(3)#3	0.95	2.44	3.3605(13)	163.6
N(1)-H(1A)...O(1)#4	0.899(16)	1.985(16)	2.8786(12)	172.6(13)
N(1)-H(1B)...O(3)#3	0.923(16)	2.029(16)	2.9449(12)	171.5(14)
O(2)-H(2)...N(2)#5	0.99(2)	1.61(2)	2.5951(12)	176.4(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z #2 -x+3/2,y+1/2,-z+1/2 #3 -x+1,y,-z+1/2

#4 -x+3/2,-y-1/2,-z+1 #5 x,y-1,z

4.4.4 Isonicotinamide with diphenic acid (JMB041)

IUPAC NAME: [1,1'-biphenyl]-2,2'-dicarboxylic acid pyridine-4-carboxamide

Chemical formula: $C_{14}H_{10}O_4 \cdot 2(C_6H_6N_2O)$

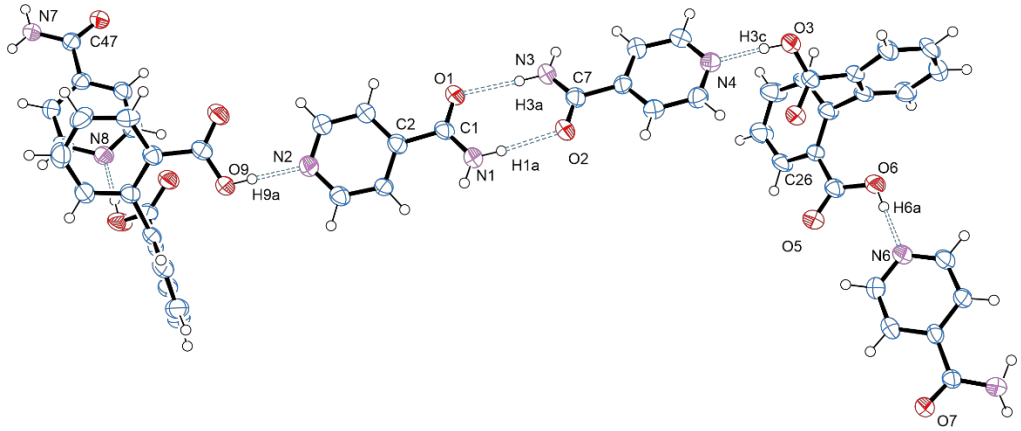


Figure 4. 36 Asymmetric unit of co-crystal of isonicotinamide · diphenic acid – JMB041

The asymmetric unit of isonicotinamide · diphenic acid is crystallized in the triclinic $P\bar{1}$space group and contains four molecules of isonicotinamide and two molecules of diphenic acid, as seen in Figure 4.36. The amide moieties of two of the isonicotinamide molecules are bonded via O2···H1a-N1 and O1···H3a-N3 hydrogen bonds forming a $R_2^2(8)$ ring. These isonicotinamide molecules are then hydrogen bonded to diphenic acid molecules, on either side, via N4···H3c-O3 and N2···H9a-O9 bonds

(forming a $D_1^1(2)$ intermolecular structure). Then both diphenic acid molecules are hydrogen bonded to additional isonicotinamide molecules via N6···H6a-O6 and N8···H11a-O11 bonds forming $D_1^1(2)$ intermolecular structure.

In the packing, each isonicotinamide is hydrogen bonded to one other niacinamide molecules and two diphenic acid molecules. Each diphenic acid molecule is hydrogen bonded to four isonicotinamide molecules. An image of the packing of isonicotinamide · diphenic acid along the *a* axis is shown below – Figure 4.37. Diagrams of JMB041 along the *a* axis, *b* axis and *c* axis, sorted by symmetry equivalence can be seen in Figure 4.38.

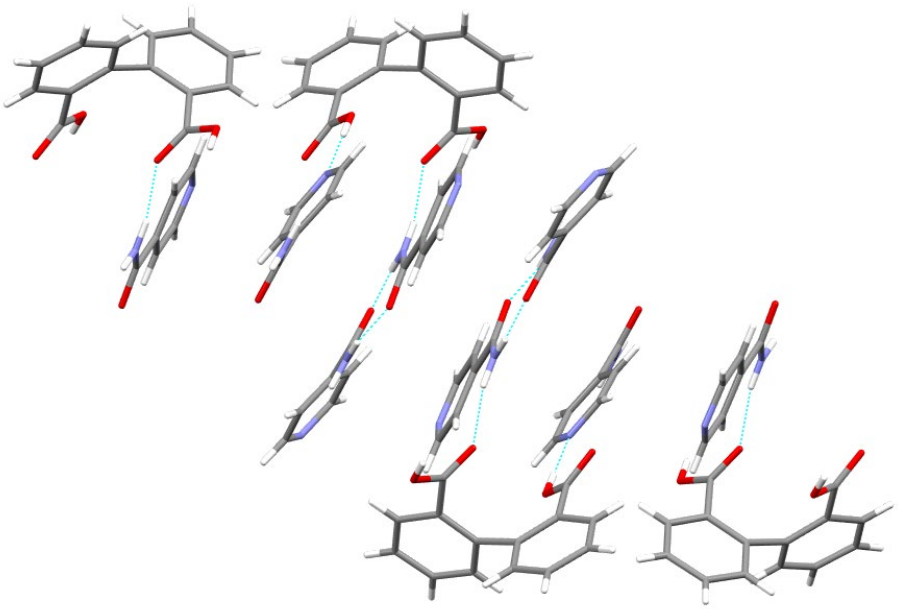


Figure 4. 37 Packing of JMB041 along down the *a* axis

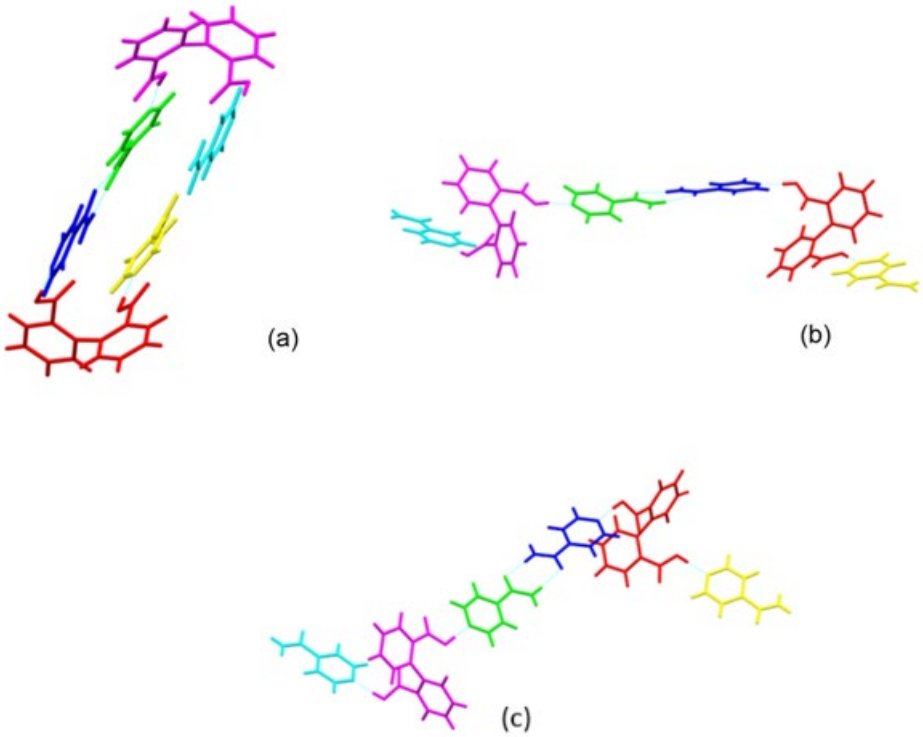


Figure 4. 38 Diagrams of JMB041 along the (a) *a* axis, (b) *b* axis and (c) *c* axis, sorted by symmetry equivalence

Table 4. 21 Hydrogen bonds for JMB041 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(2)...O(8)#1	0.95	2.66	3.350(6)	130.2
C(5)-H(4)...O(8)	0.95	2.54	3.183(6)	124.9
N(1)-H(1A)...O(2)	0.88	2.04	2.920(5)	173.0
N(1)-H(1B)...O(8)#1	0.88	2.11	2.933(6)	155.8
C(9)-H(8)...O(4)#2	0.95	2.44	3.372(6)	165.9
N(3)-H(3A)...O(1)	0.88	2.03	2.913(5)	176.3
N(3)-H(3B)...O(4)#2	0.88	2.09	2.935(5)	161.1
C(30)-H(30)...O(5)	0.95	2.54	3.176(7)	124.8
C(32)-H(32)...O(5)#1	0.95	2.62	3.325(6)	131.8
C(49)-H(49)...O(10)#2	0.95	2.46	3.388(6)	165.3
N(5)-H(5A)...O(12)#3	0.88	2.04	2.917(5)	172.1
N(5)-H(5B)...O(5)#1	0.88	2.13	2.955(5)	156.4
N(7)-H(7A)...O(7)#4	0.88	2.04	2.920(5)	175.0
N(7)-H(7B)...O(10)#2	0.88	2.09	2.934(5)	161.0
O(3)-H(3C)...N(4)	0.84	1.73	2.560(5)	171.7
O(6)-H(6A)...N(6)	0.84	1.76	2.602(5)	179.3
O(9)-H(9A)...N(2)	0.84	1.78	2.614(5)	169.2
O(11)-H(11A)...N(8)	0.84	1.71	2.550(5)	175.8

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z #2 x-1,y,z #3 x+4,y,z #4 x-4,y,z

4.4.5 Niazid with nitroterephthalic acid (JMB056)

IUPAC NAME: 2-nitroterephthalate diazaneyl-(pyridin-3-yl)methanone

Chemical formula: $C_6H_9N_3O^{2+}C_8H_3NO_6^{2-}$

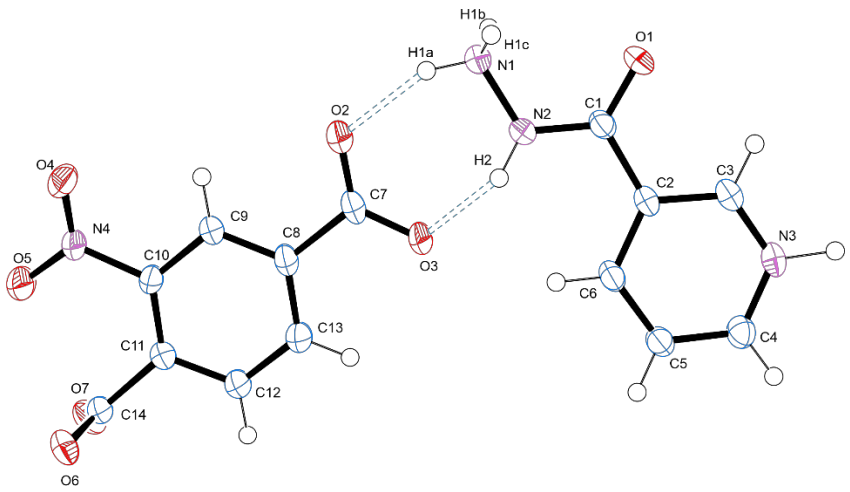


Figure 4. 39 Asymmetric unit of salt of niazid · nitroterephthalic acid – JMB056

This compound crystallizes as a salt, having a +2 charge on the niazid component and a -2 charge on the nitroterephthalate. The niazid has two extra protons, one being on N3 and the other on N1 as seen in the Ortep diagram (Figure 4.39)

The asymmetric unit niazid · nitroterephthalic acid contains one molecule of niazid and one molecule of nitroterephthalate, crystallized in a monoclinic *P*21/c space group. The hydrogen bonds form a $R_2^2(7)$ ring via O2···H1a-N1 and O3···H2-N2 hydrogen bonds. The O4 atom of the nitrate group is disordered with 2 parts, one having a 0.75 occupancy and the other having a 0.25 occupancy. The disorder is not shown in the Ortep diagram; however the disorder is solved in the structure refinement.

In the packing, each niazid molecule is bonded to three nitroterephthalic acid molecules via the following hydrogen bonds; O2···H1a-N1 and O3···H2-N2, O6···H3a-N3, O6···H1c-N1, O7···H1b-N1. The O6 oxygen atom is bifurcated, having hydrogen bonds to H3a and H1c. Each nitroterephthalic acid is bonded to three niazid molecules via the same bonds, this is displayed in the packing image below – Figure 4.40.

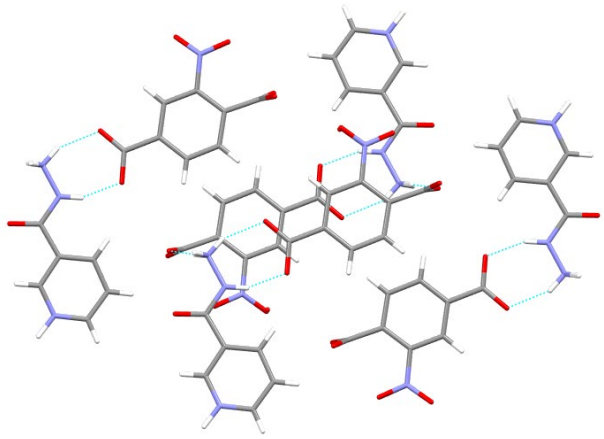


Figure 4. 40 Packing of niazid · nitroterephthalic acid co-crystal down the *b* axis

Table 4. 22 Hydrogen bonds for JMB056 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(3)-H(3)...O(5)#1	0.95	2.63	3.470(3)	148.1
C(4)-H(4)...O(4)#2	0.95	2.44	3.146(3)	130.5
C(4)-H(4)...O(5)#2	0.95	2.64	3.582(3)	173.7
C(5)-H(5)...O(1)#3	0.95	2.26	3.039(3)	139.2
C(5)-H(5)...O(6)#4	0.95	2.57	3.197(3)	123.7
N(1)-H(1A)...O(6)#5	0.88	1.83	2.712(3)	177.2
N(1)-H(1B)...O(2)	0.88	1.88	2.694(2)	152.9
N(2)-H(2)...O(3)	0.88	1.76	2.575(2)	153.6
O(7)-H(7)...N(1)#6	0.84	1.95	2.752(3)	160.4
C(3)-H(3)...O(5)#1	0.95	2.63	3.470(3)	148.1
C(4)-H(4)...O(4)#2	0.95	2.44	3.146(3)	130.5
C(4)-H(4)...O(5)#2	0.95	2.64	3.582(3)	173.7
C(5)-H(5)...O(1)#3	0.95	2.26	3.039(3)	139.2
C(5)-H(5)...O(6)#4	0.95	2.57	3.197(3)	123.7
N(1)-H(1A)...O(6)#5	0.88	1.83	2.712(3)	177.2
N(1)-H(1B)...O(2)	0.88	1.88	2.694(2)	152.9
N(2)-H(2)...O(3)	0.88	1.76	2.575(2)	153.6
O(7)-H(7)...N(1)#6	0.84	1.95	2.752(3)	160.4

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z #2 x-1,-y+3/2,z-1/2 #3 x,-y+3/2,z-1/2

#4 -x+1,y+1/2,-z+1/2 #5 -x+1,-y+1,-z+1 #6 -x+1,-y+2,-z+1

4.4.6 Benzhydrazide with 5-aminoisophthalic acid (JMB046)

IUPAC NAME: 5-aminobenzene-1,3-dicarboxylic acid benzohydrazide

Chemical formula: $C_8H_7NO_4 \cdot C_7H_8N_2O$

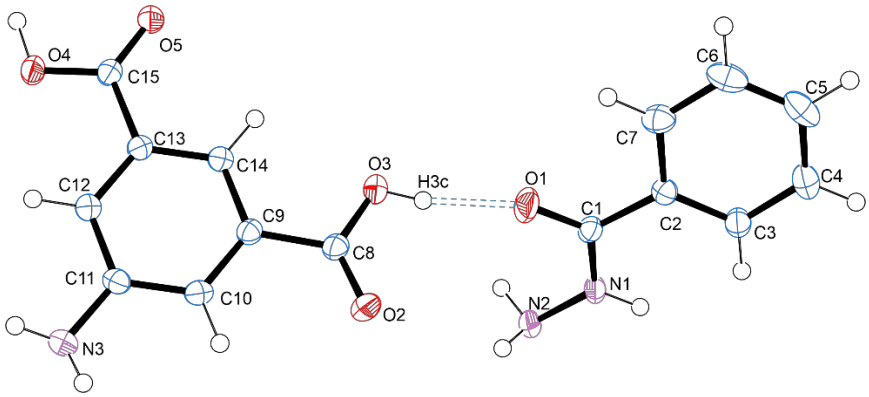


Figure 4. 41 Asymmetric unit of co-crystal of benzhydrazide · 5-aminoisophthalic acid – JMB046

The benzhydrazide · 5-aminoisophthalic acid asymmetric unit contains one molecule of benzhydrazide and one molecule of 5-aminoisophthalic acid (Figure 4.41), which crystallizes in the monoclinic $P2_1/n$ space group. There is a single hydrogen bond between the two molecules making a discrete ($D_1^1(2)$) hydrogen bond via O1···H3c-O3.

With regard to packing, each benzhydrazide molecule is hydrogen bonded to four 5-aminoisophthalic acid molecules via O1···H3c-O3, O2···H2a-N2, N3···H2b-N2, N2···H4a-O4 and O5···H1-N1 shown in Figure 4.42 below. Each nitroterephthalic acid is hydrogen bonded to four benzhydrazide molecules and two nitroterephthalic acid molecules.

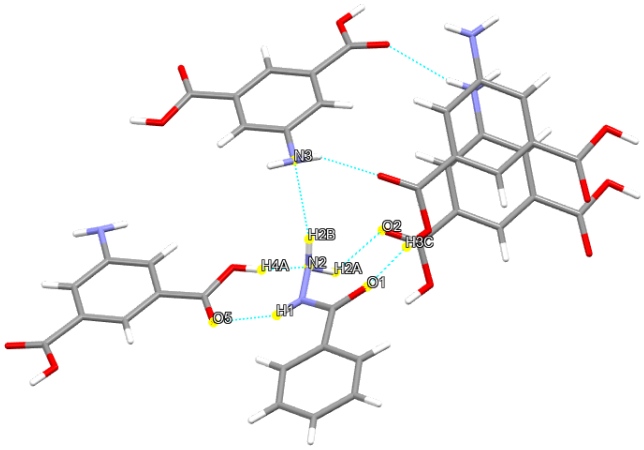


Figure 4. 42 Image showing the hydrogen bonds of benzhydrazide

Table 4. 23 Hydrogen bonds for JMB046 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3C)...O(1)	0.84	1.79	2.6148(12)	167.5
N(1)-H(1)...O(5)#1	0.88	2.13	2.8857(13)	144.1
N(3)-H(3A)...O(2)#2	0.85(2)	2.17(2)	2.9665(14)	156.2(17)
N(3)-H(3B)...O(4)#3	0.89(2)	2.25(2)	3.0552(14)	149.3(17)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+3/2,z+1/2 #2 -x+3/2,y-1/2,-z+1/2

#3 -x+1,-y,-z

4.4.7 Key observations and discussion in the *N*-heterocyclic series (Series 3)

This series contains a number of co-crystals that were co-crystallized with phthalic acid derivatives but where it was not possible to obtain more than two crystal structures in the time frame available.

There were two co-crystals that contained colour in this study, one being isoniazid with diphenic acid (MB013) which gave rise to yellow crystals. All attempts to co-crystallize diphenic acid with an API resulted in a brownish solution when dissolved. However, the other co-crystal containing diphenic acid (JMB041) has colourless crystals. Then again, the co-crystal containing 5-aminoisophthalic acid (JMB046) also gave rise to yellow crystal (a colour was often useful to determine whether or not the desired product had formed).

In this series a different dicarboxylic acid is introduced, namely, diphenic acid. Although diphenic acid is not a phthalic acid derivative, it also has two carboxyl groups close to each other, similar to phthalic acid and so, was used in order to compare the two. In co-crystallization of both INH and isonicotinamide, the standard hydrogen bonding patterns observed in the phthalic acid derivatives namely, the pyridine - carboxylic acid heterosynthon discussed previously, were found to occur. This suggests that the presence of an extra aromatic ring does not play a role in the hydrogen bonding and dicarboxylic acids with both one and two rings bond in the same way.

Isonicotinamide behaves similarly to isoniazid at the pyridine site. However, in both cases where isonicotinamide was used as an API, an amide – amide homosynthon was formed between two isonicotinamide molecules. This suggests that the amide – amide homosynthon is favoured over the amide – carboxylic acid heterosynthon found in niacinamide, despite carboxylic acid groups being

available to hydrogen bond. For future studies it may be interesting to do a comparison of amide – amide *vs* amide – carboxylic acid synthons in *N*-heterocyclic compounds.

With niazid, it was not possible to obtain a co-crystal, but a salt was obtained with a +2 charge on the niazid and a -2 charge on the nitroterephthalic acid. Since all the usual hydrogen bonding sites were protonated, it is not really possible to compare the H-bonding patterns between niazid and isoniazid in this case. It is unclear how this highly charged salt was formed as only methanol was used as a solvent and this is not normally observed in other niazid co-crystals, however it is plausible that the salt formed because water may have been present in the methanol, which would allow the formation of a salt (because of water's labile protons).

Benzhydrazide is not an *N*-heterocyclic compound, but it was used because of its structure similarity to the other compounds in this section. Interestingly, in the absence of the pyridine nitrogen, this was the only structure in this study where, in the amide group, only the oxygen atom of the amide group (and not the nitrogen of the amide group) was involved in hydrogen bonding. This strongly suggests that the presence or absence of the pyridine nitrogen plays a significant role in the hydrogen bonding patterns taking place outside of the ring via the substituents. As a future study a more thorough study of benzhydrazide hydrogen bonding patterns is warranted.

4.6 The crystal of nitroterephthalic acid

Nitroterephthalic acid was in powder form in the original container when purchased. However, with all starting materials in this study, the pure compounds were crystallized to examine the morphology as an indicator to determine whether co-crystallization had taken place in the crystallized products. While obtaining the unit cells of starting materials from the CSD, it was noticed that nitroterephthalic acid had not previously been crystallized.

Therefore, it was decided to determine the crystal structure and publish it. This was published (Z. Kristallogr. - N. Cryst. Struct. 2023; 238(5): 875–876) and a copy of the publication is included in Appendix 1.

IUPAC NAME: 2-nitroterephthalic acid

Chemical formula: $C_8H_5NO_6$

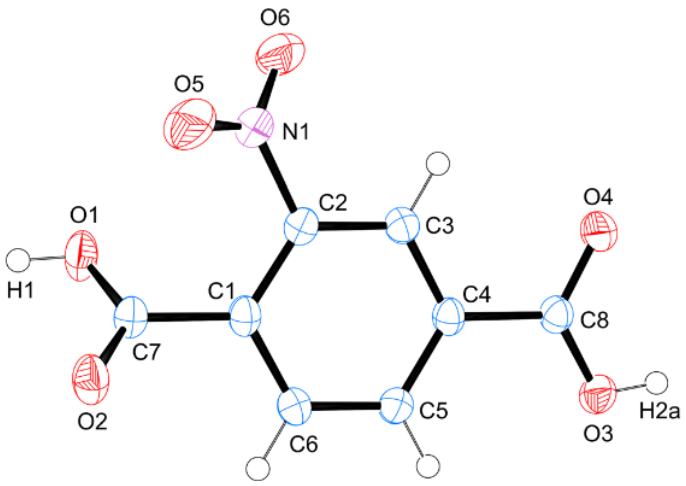


Figure 4. 43 Asymmetric unit of nitroterephthalic acid crystal

The nitroterephthalic acid asymmetric unit contains one molecule of nitroterephthalic acid and crystallizes in the monoclinic space group C2/c. There is disorder displayed on the COOH group meta to the NO_2 group, with the hydrogen equally being on either of the two oxygen atoms.

Each nitroterephthalic acid molecule is hydrogen bonded to neighbouring nitroterephthalic acid molecules through a COOH/COOH homosynthon forming 1-D chains.

Table 4. 24 Hydrogen bonds for nitroterephthalic acid [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(2A)...O(3) #1	0.84	1.84	2.667(12)	170
O(1)-H(1)...O(2) #2	0.84	1.78	2.6194(15)	172

Symmetry transformations used to generate equivalent atoms:

#1 -x+1 ,y, -z+1/2 #2 -x+1/2, -y+1/2, -z+2

Chapter 5 – Conclusion

In this study 15 novel co-crystals were successfully synthesized, and their crystal structures determined. These consisted of three series namely, niacinamide, modified isoniazid and other *N*-heterocyclic API's with phthalic acid derivative co-formers. The crystal structure of one previously determined co-crystal was also refined and the structure of 3-nitroterephthalic acid (one of the dicarboxylic acids used in this study) was published.

A series of niacinamide (nicotinamide) co-crystals with phthalic acid derivative co-formers was synthesized and their structures were investigated. Six novel co-crystals were obtained and detailed structures and hydrogen bonding patterns were discussed and compared.

Isoniazid was modified with benzaldehyde, giving rise to *N'*-benzylidenepyridine-4-carbohydrazide, which was reacted with phthalic acid derivatives. This produced four novel co-crystals which were solved and their structures investigated.

Lastly a number of other nitrogen containing heterocyclic API's, with similarities to niacinamide and isoniazid, were reacted with the phthalic acid derivatives which lead to another five novel co-crystals. These also had their structures solved and investigated for similarities.

A literature review and a comprehensive CSD search of the structures involved was conducted, and findings were presented in chapter 2.

A variety of methods for supramolecular synthesis and crystallization were used to produce the co-crystals in this study, including mechanochemistry, sublimation, slow solvent evaporation, phase - dropping, and tampering with crystallization conditions, such as differing polarity of solvents, changing ambient temperatures and modifying glassware.

Both WinGX and Olex2were used to refine and troubleshoot crystal structures and a discussion was presented where the user indicated where each of the two software was more effective.

All 17 crystal structures were refined using WinGX and Olex2. Several complex issues such as disorder were solved, and difficult placement of hydrogen atoms were resolved. Cif files were prepared for publication and all 15 novel co-crystals and the novel crystal were uploaded onto the CSD.

Ortep diagrams were generated for all crystal structures, Mercury was used to generate hydrogen bonding figures, and hydrogen bonding was investigated using Mercury. Corel Draw was used to prepare the images for publication.

These structures, their hydrogen bonding patterns, and any abnormalities were discussed and described in chapter 4.

One structure was published in an accredited peer reviewed journal.

The aims and objectives of this study were achieved, and future work will include writing up Series 1 (niacinamide) and Series 2 as two separate publications and submitting them to Acta Crystallographica Section C.

Further experimental work for series 1, 2 and 3 will include investigations of the outcomes when the amide and nitro groups of the phthalic acid derivatives are replaced with groups containing different atoms, as well as an in-depth study of the hydrogen boding patterns concerning benzhydrazide. Also by examining the co-crystallization and bonding patterns of these API's with the co-formers used in this study, may potentially result in the development of modified API's with higher efficacy and other beneficial properties.

References

Aakeröy, C. B., & Sinha, A. S. (2018). Co-crystals: Introduction and Scope. *Monographs in Supramolecular Chemistry*, *2018-January*(24), 1–32. https://doi.org/10.1039/9781788012874-00001

Aakeröy, C. B., Desper, J., & Fasulo, M. E. (2006). Improving success rate of hydrogen-bond driven synthesis of co-crystals. *CrystEngComm*, *8*(8), 586–588. https://doi.org/10.1039/b609709j

Aakeröy, C. B., Fasulo, M., Schultheiss, N., Desper, J., & Moore, C. (2007). Structural competition between hydrogen bonds and halogen bonds. *Journal of the American Chemical Society*, *129*(45), 13772–13773. https://doi.org/10.1021/JA073201C/SUPPL_FILE/JA073201CSI20070914_053617.PDF

Aitipamula, S., Shan, L. P., & Gupta, K. M. (2022). Polymorphism and distinct physicochemical properties of the phloretin–nicotinamide cocrystal. *CrystEngComm*, *24*(3), 560–570. https://doi.org/10.1039/D1CE01352A

Alcala, R., Martínez-Carrera, S., & IUCr. (1972). The crystal structure of isophthalic acid. *Urn:Issn:0567-7408*, *28*(6), 1671–1677. https://doi.org/10.1107/S0567740872004844

Almarsson, Ö., & Zaworotko, M. J. (2004). Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? In *Chemical Communications* (Issue 17, pp. 1889–1896). Royal Society of Chemistry. https://doi.org/10.1039/b402150a

An, J. H., Lim, C., Ryu, H. C., Kim, J. S., Kim, H. M., Kiyonga, A. N., Park, M., Suh, Y. G., Park, G. H., & Jung, K. (2017). Structural Characterization of Febuxostat/l-Pyroglutamic Acid Cocrystal Using Solid-State 13C-NMR and Investigational Study of Its Water Solubility. *Crystals 2017, Vol. 7, Page 365*, *7*(12), 365. https://doi.org/10.3390/CRYST7120365

Babu, N. J., & Nangia, A. (2011). Solubility advantage of amorphous drugs and pharmaceutical cocrystals. In *Crystal Growth and Design* (Vol. 11, Issue 7, pp. 2662–2679). https://doi.org/10.1021/cg200492w

Bag, P. P. (2021a). Introduction of plasticity to change mechanical behaviour of pharmaceutical crystals by co-crystallization: A solution of long standing problem in isoniazid. *Engineered Science*, *15*, 129–137. https://doi.org/10.30919/es8d1501

Báthori, N. B., Lemmerer, A., Venter, G. A., Bourne, S. A., & Caira, M. R. (2011). Pharmaceutical Co-crystals with isonicotinamide-vitamin B3, clofibric acid, and diclofenac-and two isonicotinamide hydrates. *Crystal Growth and Design*, *11*(1), 75–87. https://doi.org/10.1021/cg100670k

Batisai, E. (2020). Multicomponent crystals of anti-tuberculosis drugs: a mini-review. *RSC Advances*, *10*(61), 37134–37141. https://doi.org/10.1039/D0RA06478E

Behzad, S., Sureda, A., Barreca, D., Nabavi, S. F., Rastrelli, L., & Nabavi, S. M. (2017). Health effects of phloretin: from chemistry to medicine. *Phytochemistry Reviews*, *16*(3), 527–533. https://doi.org/10.1007/S11101-017-9500-X/FIGURES/2

Bernstein, J., Davis, R. E., Shimoni, L., & Chang, N. -L. (1995). Patterns in Hydrogen Bonding: Functionality and Graph Set Analysis in Crystals. *Angewandte Chemie International Edition in English*, *34*(15), 1555–1573. https://doi.org/10.1002/ANIE.199515551

Berry, D. J., Seaton, C. C., Clegg, W., Harrington, R. W., Coles, S. J., Horton, P. N., Hursthouse, M. B., Storey, R., Jones, W., Friščić, T., & Blagden, N. (2008). Applying hot-stage microscopy to co-crystal screening: A study of nicotinamide with seven active pharmaceutical ingredients. *Crystal Growth and Design*, *8*(5), 1697–1712. https://doi.org/10.1021/cg800035w

Bhogala, B. R., Basavoju, S., & Nangia, A. (2005). Tape and layer structures in cocrystals of some di- and tricarboxylic acids with 4,4′-bipyridines and isonicotinamide. From binary to ternary cocrystals. *CrystEngComm*, *7*(90), 551–562. https://doi.org/10.1039/B509162D

Bis, J. A., Vishweshwar, P., Weyna, D., & Zaworotko, M. J. (2007). Hierarchy of supramolecular synthons: Persistent hydroxyl···pyridine hydrogen bonds in cocrystals that contain a cyano acceptor. *Molecular Pharmaceutics*, *4*(3), 401–416. https://doi.org/10.1021/MP070012S/SUPPL_FILE/MP070012SSI20070321_042648.CIF

Bourletidis How, J. M., Lemmerer, A., & Smith, M. G. (2023). The crystal structure of nitroterephthalic acid, C8H5NO6. *Zeitschrift Fur Kristallographie - New Crystal Structures*, *238*(5), 875–876. https://doi.org/10.1515/ncrs-2023-0248

Burrows, A. D. (2003). *Crystal Engineering Using Multiple Hydrogen Bonds*. 55–96. https://doi.org/10.1007/B14137

Chaudhari, S., Nikam, S. A., Khatri, N., & Wakde, S. (2018). CO-CRYSTALS: A REVIEW. *Journal of Drug Delivery and Therapeutics*, *8*(6-s), 350–358. https://doi.org/10.22270/jddt.v8i6-s.2194

Chen, S. P., Ren, Y. X., Wang, W. T., & Gao, S. L. (2010). Nanoporous lanthanide-carboxylate frameworks based on 5-nitroisophthalic acid. *Dalton Transactions*, *39*(6), 1552–1557. https://doi.org/10.1039/B914879E

Cinčić, D., Friščić, T., & Jones, W. (2008). Isostructural Materials Achieved by Using Structurally Equivalent Donors and Acceptors in Halogen-Bonded Cocrystals. *Chemistry – A European Journal*, *14*(2), 747–753. https://doi.org/10.1002/CHEM.200701184

Coates, G. W., Dunn, A. R., Henling, L. M., Ziller, J. W., Lobkovsky, E. B., & Grubbs, R. H. (1998). Phenyl-perfluorophenyl stacking interactions: Topochemical [2+2] photodimerization and photopolymerization of olefinic compounds. *Journal of the American Chemical Society*, *120*(15), 3641–3649. https://doi.org/10.1021/JA974072A/SUPPL_FILE/JA3641A.PDF

Cruz, R. M., Boleslavská, T., Beránek, J., Tieger, E., Twamley, B., Santos-Martinez, M. J., Dammer, O., & Tajber, L. (2020). Identification and Pharmaceutical Characterization of a New Itraconazole Terephthalic Acid Cocrystal. *Pharmaceutics 2020, Vol. 12, Page 741*, *12*(8), 741. https://doi.org/10.3390/PHARMACEUTICS12080741

Cruz-Cabeza, A. J. (2012). Acid–base crystalline complexes and the p K a rule. *CrystEngComm*, *14*(20), 6362–6365. https://doi.org/10.1039/C2CE26055G

Cruz-Cabeza, A. J., Lusi, M., Wheatcroft, H. P., & Bond, A. D. (2022). The role of solvation in proton transfer reactions: implications for predicting salt/co-crystal formation using the ΔpKa rule. *Faraday Discussions*, *235*(0), 446–466. https://doi.org/10.1039/D1FD00081K

Dannenberg, J. J. (1998). An Introduction to Hydrogen Bonding By George A. Jeffrey (University of Pittsburgh). Oxford University Press: New York and Oxford. 1997. ISBN 0-19-509549-9. *Journal of the American Chemical Society*, *120*(22), 5604–5604. https://doi.org/10.1021/JA9756331

Das, B., & Baruah, J. B. (2011). Supramolecular synthons and hydrates in stabilization of multicomponent crystals of nicotinamide and isonicotinamide with N-containing aromatic dicarboxylic acids. *Crystal Growth and Design*, *11*(12), 5522–5532. https://doi.org/10.1021/CG201096C/SUPPL_FILE/CG201096C_SI_007.CIF

Desiraju, G. (1989). Crystal engineering : the design of organic solids. *Materials Science Monographs*, Volume 54

Desiraju, G. R. (2002). Hydrogen bridges in crystal engineering: Interactions without borders. *Accounts of Chemical Research*, *35*(7), 565–573. https://doi.org/10.1021/AR010054T/ASSET/IMAGES/LARGE/AR010054TF00007.JPEG

Desiraju, G. R. (2013). Crystal engineering: From molecule to crystal. In *Journal of the American Chemical Society* (Vol. 135, Issue 27, pp. 9952–9967). https://doi.org/10.1021/ja403264c

Desiraju, G. R., David, P., Curtin, Y., Lain, P., & Paul, C. (1995). Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis. *Angewandte Chemie International Edition in English*, *34*(21), 2311–2327. https://doi.org/10.1002/ANIE.199523111

Dragostin, I., Dragostin, O. M., Samal, S. K., Dash, S., Tatia, R., Dragan, M., Confederat, L., Ghiciuc, C. M., Diculencu, D., Lupușoru, C. E., & Zamfir, C. L. (2019). New isoniazid derivatives with improved pharmaco-toxicological profile: Obtaining, characterization and biological evaluation. *European Journal of Pharmaceutical Sciences*, *137*, 104974. https://doi.org/10.1016/J.EJPS.2019.104974

Duggirala, N. K., Perry, M. L., Almarsson, Ö., & Zaworotko, M. J. (2016). Pharmaceutical cocrystals: Along the path to improved medicines. *Chemical Communications*, *52*(4), 640–655. https://doi.org/10.1039/c5cc08216a

Dye, C. (2006). Global epidemiology of tuberculosis. *The Lancet*, *367*(9514), 938–940. https://doi.org/10.1016/S0140-6736(06)68384-0

Etter, M. C. (1990). Encoding and Decoding Hydrogen-Bond Patterns of Organic Compounds. *Accounts of Chemical Research*, *23*(4), 120–126. https://doi.org/10.1021/AR00172A005/ASSET/AR00172A005.FP.PNG_V03

Fleischman, S. G., Kuduva, S. S., McMahon, J. A., Moulton, B., Bailey Walsh, R. D., Rodríguez-Hornedo, N., & Zaworotko, M. J. (2003a). Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine. *Crystal Growth and Design*, *3*(6), 909–919. https://doi.org/10.1021/cg034035x

Fricker, R. A., Green, E. L., Jenkins, S. I., & Griffin, S. M. (2018). The Influence of Nicotinamide on Health and Disease in the Central Nervous System. In *International Journal of Tryptophan Research* (Vol. 11) 1-11. SAGE Publications Ltd. https://doi.org/10.1177/1178646918776658

Fujii, K., Sakon, A., Sekine, A., & Uekusa, H. (2011). Reversible color switching of an organic crystal induced by organic solvent vapors. *Crystal Growth and Design*, *11*(10), 4305–4308. https://doi.org/10.1021/CG2010437/SUPPL_FILE/CG2010437_SI_002.CIF

George, F., Tumanov, N., Norberg, B., Robeyns, K., Filinchuk, Y., Wouters, J., & Leyssens, T. (2014). Does chirality influence the tendency toward cocrystal formation? *Crystal Growth and Design*, *14*(6), 2880–2892. https://doi.org/10.1021/CG500181T/SUPPL_FILE/CG500181T_SI_002.CIF

Grobelny, P., Mukherjee, A., & Desiraju, G. R. (2011). Drug - drug co-crystals: Temperature-dependent proton mobility in the molecular complex of isoniazid with 4-aminosalicylic acid. *CrystEngComm*, *13*(13), 4358–4364. https://doi.org/10.1039/C0CE00842G

Groom, C. R., Bruno, I. J., Lightfoot, M. P., & Ward, S. C. (2016). The Cambridge structural database. *Acta Crystallographica Section B: Structural Science, Crystal Engineering and Materials*, *72*(2), 171–179. https://doi.org/10.1107/S2052520616003954

Grothe, E., Meekes, H., Vlieg, E., Ter Horst, J. H., & De Gelder, R. (2016). Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System. *Crystal Growth and Design*, *16*(6), 3237–3243. https://doi.org/10.1021/ACS.CGD.6B00200/ASSET/IMAGES/LARGE/CG-2016-002009_0008.JPEG

Hasanova, S. S., Yolchueva, E. A., Mashadi, A. Q., Muhammad, S., Ashfaq, M., Muhammed, M. E., Munawar, K. S., Tahir, M. N., Al-Sehemi, A. G., & Alarfaji, S. S. (2023). Synthesis, Characterization, Crystal Structures, and Supramolecular Assembly of Copper Complexes Derived from Nitroterephthalic Acid along with Hirshfeld Surface Analysis and Quantum Chemical Studies. *ACS Omega*, *8*(9), 8530–8540. https://doi.org/10.1021/acsomega.2c07686

Hiendrawan, S., Veriansyah, B., Widjojokusumo, E., Soewandhi, S. N., Wikarsa, S., & Tjandrawinata, R. R. (2016). Physicochemical and mechanical properties of paracetamol cocrystal with 5-nitroisophthalic acid. *International Journal of Pharmaceutics*, *497*(1–2), 106–113. https://doi.org/10.1016/J.IJPHARM.2015.12.001

Huang, S., Xu, J., Peng, Y., Guo, M., & Cai, T. (2019). *Facile Tuning of the Photoluminescence and Dissolution Properties of Phloretin through Cocrystallization*. *Crystal Growth & Design* 2019 19 (12), 6837-6844. https://doi.org/10.1021/acs.cgd.9b01111

Hutchins, K. M. (2018). Functional materials based on molecules with hydrogen-bonding ability: Applications to drug co-crystals and polymer complexes. In *Royal Society Open Science* (Vol. 5, Issue 6) 180564. Royal Society Publishing. https://doi.org/10.1098/rsos.180564

Isophthalic Acid - Chemical Economics Handbook (CEH) | S&P Global. (2023). Retrieved November 6, 2023, from https://www.spglobal.com/commodityinsights/en/ci/products/isophthalic-acid-chemical-economics-handbook.html

Jafari, P., Barzegar-Jalali, M., Hemmati, S., & Jouyban, A. (2023). Determination of the solubility profile of isophthalic acid in some aqueous solutions of betaine-based deep eutectic solvents: Study the extent of H-bonding interactions between starting materials of deep eutectic solvents in aqueous medium. *Sustainable Chemistry and Pharmacy*, *35*. https://doi.org/10.1016/j.scp.2023.101208

Johan, Wouters, Q. L. (2011). Pharmaceutical Salts and Co-crystals. *Pharmaceutical Salts and Co-Crystals*, 406. http://ebook.rsc.org/?DOI=10.1039/9781849733502

Kahkesh, H., & Zargar, B. (2023). Estimating the anti-corrosive potency of 3-nitrophthalic acid as a novel and natural organic inhibitor on corrosion monitoring of mild steel in 1 M HCl solution. *Inorganic Chemistry Communications*, *158*, 111533. https://doi.org/10.1016/J.INOCHE.2023.111533

Kallel, A., & Amor, B. H. (1992). Crystal structure of benzhydrazide, NH2NHCO(C6H5). *Zeitschrift Für Kristallographie - Crystalline Materials*, *198*(1–4), 137–138. https://doi.org/10.1524/ZKRI.1992.198.14.137

Kamalakaran, A. S. (2018). MOLECULAR ADDUCTS OF ISONIAZID: CRYSTAL STRUCTURE, ELECTRONIC PROPERTIES, AND HIRSHFELD SURFACE ANALYSIS. *Journal of Structural Chemistry*, *59*(7), 1518–1533. https://doi.org/10.1134/S002247661807003X

Karamertzanis, P. G., Kazantsev, A. V., Issa, N., Welch, G. W. A., Adjiman, C. S., Pantelides, C. C., & Price, S. L. (2009). Can the formation of pharmaceutical cocrystals be computationally predicted? 2. Crystal structure prediction. *Journal of Chemical Theory and Computation*, *5*(5), 1432–1448. https://doi.org/10.1021/ct8004326

Karimi-Jafari, M., Padrela, L., Walker, G. M., & Croker, D. M. (2018). Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. In *Crystal Growth and Design* (Vol. 18, Issue 10, pp. 6370–6387). American Chemical Society. https://doi.org/10.1021/acs.cgd.8b00933

Kastelic, J., Hodnik, Ž., Šket, P., Plavec, J., Lah, N., Leban, I., Pajk, M., Planinšek, O., & Kikelj, D. (2010). Fluconazole cocrystals with dicarboxylic acids. *Crystal Growth and Design*, *10*(11), 4943–4953. https://doi.org/10.1021/CG1010117/SUPPL_FILE/CG1010117_SI_003.PDF

Kumar, A., Kumar, S., & Nanda, A. (2018). A review about regulatory status and recent patents of pharmaceutical co-crystals. In *Advanced Pharmaceutical Bulletin* (Vol. 8, Issue 3, pp. 355–363). Tabriz University of Medical Sciences. https://doi.org/10.15171/apb.2018.042

Kumari, D., Bansal, H., & Deepa Kumari, C. (2018). Benzohydrazides: As potential bio-active agents. *543. The Pharma Innovation Journal*, *7*(8), 543–550. www.thepharmajournal.com

Kuminek, G., Cao, F., Bahia de Oliveira da Rocha, A., Gonçalves Cardoso, S., & Rodríguez-Hornedo, N. (2016). Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5. In *Advanced Drug Delivery Reviews* (Vol. 101, pp. 143–166). Elsevier B.V. https://doi.org/10.1016/j.addr.2016.04.022

Kundu, S., Kumari, N., Soni, S. R., Ranjan, S., Kumar, R., Sharon, A., & Ghosh, A. (2018). Enhanced Solubility of Telmisartan Phthalic Acid Cocrystals within the pH Range of a Systemic Absorption Site. *ACS Omega*, *3*(11), 15380–15388. https://doi.org/10.1021/acsomega.8b02144

Leiserowitz, L., Nader, F., & IUCr. (1977). The molecular packing modes and the hydrogen-bonding properties of amide:dicarboxylic acid complexes. *Urn:Issn:0567-7408*, *33*(9), 2719–2733. https://doi.org/10.1107/S0567740877009376

Lemmerer, A., Bernstein, J., & Kahlenberg, V. (2010a). Covalent assistance to supramolecular synthesis: directing the supramolecular assembly of co-crystals by in situ modification of hydrogen bonding functionality. *CrystEngComm*, *13*(1), 55–59. https://doi.org/10.1039/C0CE00347F

Lemmerer, A., Bernstein, J., & Kahlenberg, V. (2010b). One-pot covalent and supramolecular synthesis of pharmaceutical co-crystals using the API isoniazid : a potential supramolecular reagent. *CrystEngComm*, *12*(10), 2856–2864. https://doi.org/10.1039/C000473A

Lemmerer, A., Bernstein, J., & Kahlenberg, V. (2011). Hydrogen bonding patterns of the co-crystal containing the pharmaceutically active ingredient isoniazid and terephthalic acid. *Journal of Chemical Crystallography*, *41*(7), 991–997. https://doi.org/10.1007/s10870-011-0031-9

Lemmerer, A., & Fernandes, M. A. (2012). Adventures in co-crystal land: high Z′, stoichiometric variations, polymorphism and phase transitions in the co-crystals of four liquid and solid cyclic carboxylic acids with the supramolecular reagent isonicotinamide. *New Journal of Chemistry*, *36*(11), 2242–2252. https://doi.org/10.1039/C2NJ40186J

Lemmerer, A., Govindraju, S., Johnston, M., Motloung, X., & Savig, K. L. (2015). Co-crystals and molecular salts of carboxylic acid/pyridine complexes: can calculated pKa's predict proton transfer? A case study of nine complexes. *CrystEngComm*, *17*(19), 3591–3595. https://doi.org/10.1039/C5CE00102A

Li, B., Li, R., & Yan, W. (2011). Solubilities of phloretin in 12 solvents at different temperatures. *Journal of Chemical and Engineering Data*, *56*(4), 1459–1462. https://doi.org/10.1021/JE101168W/ASSET/IMAGES/LARGE/JE-2010-01168W_0001.JPEG

Li, Z., Wen, X., Jin, S., Gao, X., Xu, W., Zhen, Y., Shi, C., & Wang, D. (2024). Crystal and Molecular Structures of Three Co-crystals from 1,3-Dimethyl-3,7-dihydro-1H-purine-2,6-dione and Carboxylic Acids. *Journal of Chemical Crystallography*, *54*(1), 41–53. https://doi.org/10.1007/S10870-023-01000-3/FIGURES/6

Liang, Z., Li, X., Ji, S., Cheng, J., Jing, H., Zhang, J., & Lu, Y. (2023). Pyrazinamide-3-Nitrophthalic Acid Cocrystals: Synthesis, Transformation, and Property Evaluation. *Crystal Growth and Design*, *23*(12), 8646–8655. https://doi.org/10.1021/ACS.CGD.3C00790/ASSET/IMAGES/LARGE/CG3C00790_0014.JPEG

Liu, F., Wang, L. Y., Yu, M. C., Li, Y. T., Wu, Z. Y., & Yan, C. W. (2020). A new cocrystal of isoniazid-quercetin with hepatoprotective effect: The design, structure, and in vitro/in vivo performance evaluation. *European Journal of Pharmaceutical Sciences*, *144*, 105216. https://doi.org/10.1016/J.EJPS.2020.105216

Lorz, P. M., Towae, F. K., Enke, W., Jäckh, R., Bhargava, N., & Hillesheim, W. (2007). Phthalic Acid and Derivatives. In *Ullmann's Encyclopedia of Industrial Chemistry*. Wiley. https://doi.org/10.1002/14356007.a20_181.pub2

Lozano, J. D., Velasquez-Diaz, S., Galindo-Leon, L., Sanchez, C., Jiménez, E., & Macías, M. A. (2023). Co-crystals of pyrazinamide (PZA) with terephthalic (TPH) and trimesic (TMS) acids: Structural insights and dissolution study. *Journal of Molecular Structure*, *1273*. https://doi.org/10.1016/j.molstruc.2022.134338

Luttrell, W. E., & Hester, R. L. (2016). Terephthalic acid. In *Journal of Chemical Health and Safety* (Vol. 23, Issue 6, pp. 49–52). Elsevier Inc. https://doi.org/10.1016/j.jchas.2016.09.005

Ma, Y. H., Zhu, M. M., Zhang, C. N., Tang, X. S., Zhang, W. G., & Ma, W. J. (2023). The co-crystal structure of etoricoxib-phthalic acid (1/1), C18H15ClN2O2S·C8H6O4. *Zeitschrift Fur Kristallographie - New Crystal Structures*, *238*(4), 641–643. https://doi.org/10.1515/ncrs-2023-0129

Machado Cruz, R., Boleslavská, T., Beránek, J., Twamley, B., Santos-Martinez, M. J., Dammer, O., & Tajber, L. (n.d.). *pharmaceutics Identification and Pharmaceutical Characterization of a New Itraconazole Terephthalic Acid Cocrystal*. https://doi.org/10.3390/pharmaceutics12080741

Maiese, K., & Chong, Z. Z. (2003). Nicotinamide: Necessary nutrient emerges as a novel cytoprotectant for the brain. In *Trends in Pharmacological Sciences* (Vol. 24, Issue 5, pp. 228–232). Elsevier Ltd. https://doi.org/10.1016/S0165-6147(03)00078-6

Malaestean, I. L., Speldrich, M., Baca, S. G., Ellern, A., Schilder, H., & Kögerler, P. (2009). Diphenic Acid-Based Cobalt(II) Complexes: Trinuclear and Double-Helical Structures. *European Journal of Inorganic Chemistry*, *2009*(8), 1011–1018. https://doi.org/10.1002/EJIC.200801138

Margaret Etter, B. C., Macdonald, J. C., Bernstein, J., & Sloan, A. P. (1977). PLUTO. Program for plotting molecular and crystal structures. In *J. Appl. Cryst. 23. Submitted. KATRUSlAK, A* (Vol. 99). Paris) Colloq.

Matts, Paul & Oblong, John & Bissett, D.L.. (2002). A Review of the range of effects of niacinamide in human skin. *Int Fed Soc Cosmet Chem* Mag. 5. 285-289.

Mcguire, S. C., Travis, S. C., Tuohey, D. W., Deering, T. J., Martin, B., Cox, J. M., & Benedict, J. B. (2016). Crystal structure of the co-crystal of 5-amino-isophthalic acid and 1,2-bis(pyridin-4-yl)ethene. *Research Communications Acta Cryst*, *72*, 639–642. https://doi.org/10.1107/S2056989016005259

Mekala, R., Mani, R., Rietveld, I. B., Jagdish, P., Mathammal, R., & Jiang, H. (2016). Crystal growth and physical properties of the organic salt benzimidazolium 3-nitrophthalate. *CrystEngComm*, *18*(42), 8194–8206. https://doi.org/10.1039/C6CE01712F

Metrangolo, P., & Resnati, G. (2001). Halogen bonding: a paradigm in supramolecular chemistry. *Chemistry (Weinheim an Der Bergstrasse, Germany)*, *7*(12), 2511–2519. https://doi.org/10.1002/1521-3765(20010618)7:12<2511::aid-chem25110>3.0.co;2-t

Moragues-Bartolome, A. M., Jones, W., & Cruz-Cabeza, A. J. (2012). Synthon preferences in cocrystals of cis -carboxamides:carboxylic acids. *CrystEngComm*, *14*(7), 2552–2559. https://doi.org/10.1039/C2CE06241K

Narang, R., Narasimhan, B., Sharma, S., Sriram, D., Yogeeswari, P., De Clercq, E., Pannecouque, C., & Balzarini, J. (2012). Synthesis, antimycobacterial, antiviral, antimicrobial activities, and QSAR studies of nicotinic acid benzylidene hydrazide derivatives. *Medicinal Chemistry Research*, *21*(8), 1557–1576. https://doi.org/10.1007/S00044-011-9664-7/FIGURES/5

Nechipadappu, S. K., Tekuri, V., & Trivedi, D. R. (2017). Pharmaceutical Co-Crystal of Flufenamic Acid: Synthesis and Characterization of Two Novel Drug-Drug Co-Crystal. *Journal of Pharmaceutical Sciences*, *106*(5), 1384–1390. https://doi.org/10.1016/J.XPHS.2017.01.033

Ngilirabanga, J. B., Aucamp, M., Pires Rosa, P., & Samsodien, H. (2020). Mechanochemical Synthesis and Physicochemical Characterization of Isoniazid and Pyrazinamide Co-crystals With Glutaric Acid. *Frontiers in Chemistry*, *8*, 595908. https://doi.org/10.3389/FCHEM.2020.595908/BIBTEX

Nugrahani, I., & Jessica, M. A. (2021). Amino acids as the potential co-former for co-crystal development: A review. In *Molecules* (Vol. 26, Issue 11) 3279. MDPI AG. https://doi.org/10.3390/molecules26113279

Papaefstathiou, G. S., & MacGillivray, L. R. (2001). Discrete versus infinite molecular self-assembly: Control in crystalline hydrogen-bonded assemblies based on resorcinol. *Organic Letters*, *3*(24), 3835–3837. https://doi.org/10.1021/OL0165948/SUPPL_FILE/OL0165948_S2.CIF

Parmar, M. S. (2014). Dicarboxylic Acid. *Encyclopedia of Toxicology: Third Edition*, 76–79. https://doi.org/10.1016/B978-0-12-386454-3.01217-3

Pedireddi, V. R., Reddy, D. S., Goud, B. S., Craig, D. C., Rae, A. D., & Desiraju, G. R. (1994). The nature of halogen ⋯ halogen interactions and the crystal structure of 1,3,5,7-tetraiodoadamantane. *Journal*

of the Chemical Society, Perkin Transactions 2, *11*, 2353–2360. https://doi.org/10.1039/P29940002353

Priebe, J. P., Mello, R. S., Nome, F., & Bortoluzzi, A. J. (2008). Nicotinohydrazide. *Acta Crystallographica Section E: Structure Reports Online*, *64*(1), o302. https://doi.org/10.1107/S160053680706655X/BH2145ISUP2.HKL

Ramesh, K. S., Saravanakumar, M., Saravanan, R., Kumar, M., Chang, J. H., & Munusamy, S. (2023). Exploring the cutting-edge properties of 3-nitrophthalic acid single crystal: growth, structure, optical and quantum chemical studies. *Journal of Materials Science: Materials in Electronics*, *34*(24), 1–18. https://doi.org/10.1007/S10854-023-11113-2/TABLES/7

Sarcevica, I., Orola, L., Veidis, M. V., Podjava, A., & Belyakov, S. (2013). Crystal and molecular structure and stability of isoniazid cocrystals with selected carboxylic acids. *Crystal Growth and Design*, *13*(3), 1082–1090. https://doi.org/10.1021/CG301356H/SUPPL_FILE/CG301356H_SI_002.CIF

Sekhon, B.S. (2009). Pharmaceutical co-crystals- a review. *Ars Pharm*, 2009; 50(3): 99-117. [http://hdl.handle.net/10481/27459]

Setshedi, I. B., Lemmerer, A., & Smith, M. G. (2023). Co-crystallization of N′-benzylidenepyridine-4-carbohydrazide and benzoic acid via autoxidation of benzaldehyde. *Acta Crystallographica Section E: Crystallographic Communications*, *79*(8), 682–685. https://doi.org/10.1107/S2056989023005698/EX2072ISUP5.MOL

Shekhar Reddy, D., Ovchinnikov, Y. E., Shishkin, O. V., Struchkov, Y. T., & Desiraju, G. R. (1996). Supramolecular synthons in crystal engineering. 3. Solid state architecture and synthon robustness in some 2,3-dicyano-5,6-dichloro-1,4-dialkoxybenzenes. *Journal of the American Chemical Society*, *118*(17), 4085–4089. https://doi.org/10.1021/JA953372U/SUPPL_FILE/JA4085.PDF

Smith, G., & Wermuth, U. D. (2013). Proton-transfer and non-transfer compounds of the multi-purpose drug dapsone [4-(4-Aminophenylsulfonyl)aniline] with 3,5-dinitrosalicylic acid and 5-nitroisophthalic acid. *Journal of Chemical Crystallography*, *43*(12), 664–670. https://doi.org/10.1007/S10870-013-0470-6/FIGURES/5

Smith, M. (2018). *Crystal and Co-Crystal Engineering of Isoniazid, 4-Aminoantipyrine, Benzophenone and their Derivatives.* [PhD] [Doctoral thesis UNIVERSITY OF THE WITWATERSRAND].

Soares, F. L. F., & Carneiro, R. L. (2014). Evaluation of analytical tools and multivariate methods for quantification of co-former crystals in ibuprofen-nicotinamide co-crystals. *Journal of Pharmaceutical and Biomedical Analysis*, *89*, 166–175. https://doi.org/10.1016/J.JPBA.2013.11.005

Sodanapalli, Riyaz & Nair, Rahul & Bachala, Thanuja. (2011). Synthesis and Characterization of a Pharmaceutical Co-Crystal: (Aceclofenac: Nicotinamide). *Journal of Pharmaceutical Sciences and Research.* Vol.3(6), 1288-1293.

Svoboda, I., & Fuess, H. (1992). Crystal structure of benzhydrazide, NH2NHCO(C6H5). *Zeitschrift Fur Kristallographie - New Crystal Structures*, *198*(1–2), 137–138. https://doi.org/10.1524/ZKRI.1992.198.1-2.137/HTML

Suresh, A., Gonde, S., Mondal, K., Sahoo, J., & Chopra, D. (2020). *Improving solubility and intrinsic dissolution rate of ofloxacin API through salt formation via mechanochemical synthesis with diphenic acid*. *Journal of Molecular Structure,* Volume 1221,128806. https://doi.org/10.1016/j.molstruc.2020.128806

Swapna, B., Maddileti, D., & Nangia, A. (2014). Cocrystals of the tuberculosis drug isoniazid: Polymorphism, isostructurality, and stability. *Crystal Growth and Design*, *14*(11), 5991–6005. https://doi.org/10.1021/CG501182T/SUPPL_FILE/CG501182T_SI_007.PDF

Tothadi, S., & Desiraju, G. R. (2012). Unusual co-crystal of isonicotinamide: the structural landscape in crystal engineering. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *370*(1969), 2900–2915. https://doi.org/10.1098/RSTA.2011.0309

Trask, A. V. (2007). An overview of pharmaceutical cocrystals as intellectual property. In *Molecular Pharmaceutics* (Vol. 4, Issue 3, pp. 301–309). https://doi.org/10.1021/mp070001z

Vippagunta, S R *et al*. "Crystalline solids." *Advanced drug delivery reviews* vol. 48,1 (2001): 3-26. doi:10.1016/s0169-409x(01)00097-7

Vishweshwar, P., McMahon, J. A., Bis, J. A., & Zaworotko, M. J. (2006). Pharmaceutical co-crystals. In *Journal of Pharmaceutical Sciences* (Vol. 95, Issue 3, pp. 499–516). John Wiley and Sons Inc. https://doi.org/10.1002/jps.20578

Wang, H. N., Meng, X., Qin, C., Wang, X. L., Yang, G. S., & Su, Z. M. (2011). A series of pillar-layer metal–organic frameworks based on 5-aminoisophthalic acid and 4,4′-bipyridine. *Dalton Transactions*, *41*(3), 1047–1053. https://doi.org/10.1039/C1DT11304F

Wang, X., Zhang, K., Geng, Y., Sun, Y., Chen, F., & Wang, L. (2018). A series of cocrystals formed by 2,3-dimethylpyrazine bridging various aromatic acids through hydrogen bonds: Synthesis, structural characterization and synthon discussion. *Journal of Molecular Structure*, *1165*, 106–119. https://doi.org/10.1016/J.MOLSTRUC.2018.03.105

Wisudyaningsih, B., Setyawan, D., & Siswandono. (2019). Co-crystallization of quercetin and isonicotinamide using solvent evaporation method. *Tropical Journal of Pharmaceutical Research*, *18*(4), 672–702. https://doi.org/10.4314/tjpr.v18i4.3

Wohlrab, J., & Kreft, D. (2014). Niacinamide - Mechanisms of Action and Its Topical Use in Dermatology. *Skin Pharmacology and Physiology*, *27*(6), 311–315. https://doi.org/10.1159/000359974

Wood, P. A., Feeder, N., Furlow, M., Galek, P. T. A., Groom, C. R., & Pidcock, E. (2014). Knowledge-based approaches to co-crystal design. *CrystEngComm*, *16*(26), 5839–5848. https://doi.org/10.1039/c4ce00316k

Wu, R., Yu, Y., Guo, M., Jin, S., & Wang, D. (2021). Eight salts of 4-dimethylaminopyridine and organic acids by H-bonds and some noncovalent associations. *Journal of Molecular Structure*, *1230*, 129850. https://doi.org/10.1016/J.MOLSTRUC.2020.129850

Xavier, A., & Srividhya, N. (2014). "Synthesis and Study of Schiff base Ligands." *IOSR Journal of Applied Chemistry IOSR-JAC*, *7*(11), 6–15. www.iosrjournals.org

Xiao, W., Wang, R. S., Handy, D. E., & Loscalzo, J. (2018). NAD(H) and NADP(H) Redox Couples and Cellular Energy Metabolism. In *Antioxidants and Redox Signaling* (Vol. 28, Issue 3, pp. 251–272). Mary Ann Liebert Inc. https://doi.org/10.1089/ars.2017.7216

Yurdakul, Ö., Köse, D. A., Şahin, Z. S., & Şahin, O. (2022). New mixed ligand complexes of alkaline earth metal cations containing nicotinamide and diphenic acid. Synthesis and structural properties. *Journal of Molecular Structure*, *1270*, 133893. https://doi.org/10.1016/J.MOLSTRUC.2022.133893

Zhang, H., Zhu, Y., Qiao, N., Chen, Y., & Gao, L. (2017). Preparation and characterization of carbamazepine cocrystal in polymer solution. *Pharmaceutics*, *9*(4) 54. https://doi.org/10.3390/pharmaceutics9040054

Zhang, L. J., Qi, L., Chen, X. Y., Liu, F., Liu, L. J., Ding, W. L., Li, D. L., Yuan, G. C., Tong, J. Z., Chen, F. Y., Huang, H. J., & Wang, Y. H. (2019). Synthesis, Crystal Structure and Photophysical Properties of Two Reduced Schiff Bases Derived from 5-Aminoisophthalic Acid. *Journal of Chemical Crystallography*, *49*(4), 260–266. https://doi.org/10.1007/S10870-018-0761-Z/FIGURES/5

Appendix 1

The crystal structure of nitroterephthalic acid

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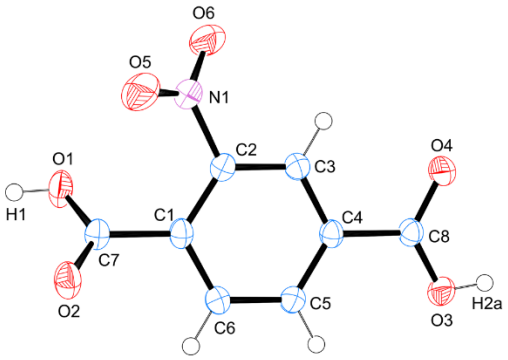
Jeraldine Maire Bourletidis How, Andreas Lemmerer and Mark G. Smith*

The crystal structure of nitroterephthalic acid, $C_8H_5NO_6$



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Abstract

$C_8H_5NO_6$, monoclinic, $C2/c$ (no.15), a = 12.8112(9) Å, b = 11.7614(8) Å, c = 11.1954(8) Å, β = 100.726(3)°, V = 1657.4(2) Å^3, Z = 8, $R_{gt}(F)$ = 0.042, $wR_{ref}(F^2)$ = 0.1247, T = 173 K.

CCDC no.: 2264065

The crystal structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

1 Source of materials

Nitroterephthalic acid was commercially sourced and was not purified further. An amount of 0.1004 g of nitroterephthalic acid (0.476 mmol) was dissolved in 3 ml of AP-grade methanol, the mixture was stirred and then heated at 50 °C in a polytop vial. The solution was left to evaporate slowly at room temperature, with the cap being left only slightly open. Colourless needles formed after seven days.

Table 1: Data collection and handling.

Crystal:	Needle, colourless
Size:	0.27 × 0.09 × 0.06 mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ:	0.15 mm^{-1}
Diffractometer, scan mode:	Bruker D8 Venture Photon, ω-scans
θ_{max}, completeness:	28°, >99 %
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	25064, 2014, 0.075
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 1657
$N(param)_{refined}$:	136
Programs:	Bruker programs [1], SHELX [2, 3], WINGX [4], PLATON [5]

2 Experimental details

C-bound hydrogen atoms were located in the difference map then positioned geometrically and were allowed to ride on their respective parent atoms with thermal displacement parameters 1.2 times of the parent C atom. The coordinates and isotropic displacement parameters of the N-bound and O-bound H atoms involved in hydrogen bonding interactions were allowed to refine freely. Diagrams and publication material were generated using ORTEP [6], WINGX [4] and PLATON [5].

3 Discussion

Nitroterephthalic acid is a derivative of terephthalic acid and is synthesized by the nitration of terephthalic acid [7]. It is used as a modifier in polyethylene terephthalate [8] as well as in the modification in polyethylene glycol [9]. Nitroterephthalic acid is also used in the preparation of many metal organic frameworks [10, 11].

Nitroterephthalic acid crystallizes in the monoclinic space group $C2/c$ and the asymmetric unit contains one molecule of nitroterephthalic acid. The COOH group

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

	x	*y*	*z*	U_{iso}*/U_{eq}
C1	0.34135 (11)	0.23098 (13)	0.73605 (12)	0.0237 (3)
C2	0.36042 (11)	0.32704 (13)	0.67086 (13)	0.0246 (3)
C3	0.39191 (11)	0.32075 (13)	0.56015 (13)	0.0249 (3)
H3	0.4032	0.3877	0.5169	0.03*
C4	0.40678 (11)	0.21368 (13)	0.51308 (12)	0.0229 (3)
C5	0.38817 (12)	0.11643 (13)	0.57525 (13)	0.0262 (3)
H5	0.3973	0.0437	0.5417	0.031*
C6	0.35597 (12)	0.12516 (13)	0.68707 (13)	0.0270 (3)
H6	0.3439	0.0582	0.73	0.032*
C7	0.30179 (11)	0.23826 (13)	0.85332 (13)	0.0248 (3)
C8	0.44830 (12)	0.20770 (13)	0.39755 (13)	0.0243 (3)
N1	0.35517 (11)	0.44047 (12)	0.72372 (13)	0.0330 (3)
O1	0.22013 (10)	0.30211 (11)	0.85094 (10)	0.0362 (3)
H1	0.2027	0.3019	0.9197	0.054*
O2	0.34512 (9)	0.18225 (11)	0.94139 (10)	0.0325 (3)
O3	0.46074 (9)	0.11143 (10)	0.35226 (9)	0.0299 (3)
H2A[a]	0.4844	0.1198	0.2877	0.045*
O4	0.46986 (11)	0.30093 (10)	0.35290 (10)	0.0392 (3)
H2B[a]	0.4926	0.289	0.2883	0.059*
O5	0.38634 (12)	0.45010 (12)	0.83345 (12)	0.0475 (4)
O6	0.32168 (14)	0.51810 (12)	0.65542 (13)	0.0522 (4)

[a]Occupancy: 0.5.

meta to the nitro position displays disorder with the hydrogen atom being found equally on either of the two oxygen atoms. In the diagram of the asymmetric unit, one of the two disordered positions has been omitted. All bond lengths in the structure are standard. Each nitroterephthalic acid molecule is hydrogen bonded to an adjacent molecule *via* a COOH···COOH homosynthon. The molecules arrange themselves in 1–D chains with alternating inversions and two-fold rotations. The centre of inversion and rotation axes are respectively found at the centre of the successive COOH···COOH homosynthons.

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References

1. Bruker. *Apex2 (version 2012.10–0), Saint (version 27B), Sadabs (version 2012/1);* Bruker AXS Inc: Madison, Wisconsin, USA, 2012.
2. Sheldrick G. M. Shelxt – integrated space-group and crystal-structure determination. *Acta Crystallogr.* 2015, *A71*, 3–8.
3. Sheldrick G. M. Crystal structure refinement with Shelxl. *Acta Crystallogr.* 2015, *C71*, 3–8.
4. Farrugia L. J. *WinGX* suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* 1999, *32*, 837–838.
5. Spek A. L. Platon. *Acta Crystallogr. D* 2009, *65*, 148–155.
6. Farrugia L. J. WinGX and ORTEP for Windows: an update. *J. Appl. Crystallogr.* 2012, *45*, 849–854.
7. Ghaemy M., Mighani H. Synthesis and identification of dinitro– and diamino– terephthalic acid. *Chin. Chem. Lett.* 2009, *20*, 800–804.
8. Bardak F. Experimental and DFT analysis of structural and spectroscopic features of nitroterephthalic acid, and computational insights into its molecular interactions with hER–α *via* molecular docking. *J. Mol. Struct.* 2019, *1175*, 458–470.
9. Zhang H., Wang Z., Liu O. Development and validation of a GC—FID method for quantitative analysis of oleic acid and related fatty acids. *J. Pharmaceut. Anal.* 2015, *5*, 223–230.
10. Lee G., Yoo D. K., Ahmed I., Lee H. J., Jhung S. H. Metal–organic frameworks composed of nitro groups: preparation and applications in adsorption and catalysis. *Chem. Eng. J.* 2023, *451*, 138538.
11. Hasanova S. S., Yolchueva E. A., Mashadi A. Q., Muhammad S., Ashfaq M., Muhammed M. E., Munawar K. S., Tahir M. N., Al-Sehemi A. G., AlarfajiSynthesis S. S. Characterization, crystal structures, and supramolecular assembly of copper complexes derived from nitroterephthalic acid along with hirshfeld surface analysis and quantum chemical studies. *ACS Omega* 2023, *8*, 8530–8540.