5.1 Introduction

Chemical crystallographers have studied molecular complexes and molecular compounds for over a century.¹ There is a resurgence of interest in multi-component solid-state assemblies² under the banner of a new name, cocrystal, in which two or more compounds coexist through hydrogen bonds or non-covalent interactions. An advantage of cocrystals is that existing properties of solids can be manipulated by altering hydrogen bonding motifs and introducing hydrophilic/hydrophobic groups in the second component. These are more attractive in pharmaceutical industry³ as several problems encountered with Active Pharmaceutical Ingredients (APIs), in terms of their solubility, dissolution rates, and stability which can be surmounted without the need to make or break covalent bonds of the drug molecule.

The synthon approach⁴ provides rational strategies for the construction of binary/ternary cocrystals in supramolecular synthesis, crystal engineering,² and pharmaceutical solids.³ This approach mainly relies on the strong hydrogen bonds between the molecules as a principle means to control molecular self assembly during crystallization. Identification of such robust synthons is now possible from a statistical analysis of the Cambridge Structural Database.⁵ A hierarchy of supramolecular synthons was established by Allen et. al.⁶ by calculating the probability of occurrence of 75 common non-covalent ring motifs constructed from O–H···O, O–H···N, N–H···O and N–H···N hydrogen bonds. In general, recognition between unlike functional groups or heterosynthon (acid–pyridine, acid–amide) has greater probability⁷ of formation than between identical groups or homosynthon (acid–acid and amide–amide) because of greater enthalpic advantage of hydrogen bonds between unlike functional groups. Acid–pyridine heterosynthon is the most popular and frequently occurring hydrogen bond motif in the CSD, and has an occurrence probability of over 90%.⁸a compared to <50% frequency for other strong hydrogen bond synthons, such as acid–acid, amide–amide, and acid–amide (Scheme 1).⁸b

Nangia,²h,2e,2f,7a Aakeröy,²a,2h,2i,7b Jones,²d,13a,16b,22 and Zaworotko²g,3b,3c,3d,8b have
extensively utilized acid–pyridine and acid–amide synthons to construct various binary/ternary/quaternary cocrystals.

Scheme 1. Strong hydrogen bond homosynthons and heterosynthons with their occurrence probability indicated. Amide–N-oxide frequency is estimated from this chapter results.

5.2 Design of novel amide–pyridine-N-oxide heterosynthon

Unlike acid–pyridine heterosynthon, carboxamide and pyridine groups do not generally aggregate via amide–pyridine heterosynthon because the amide N–H donor is not as strong compared to acid O–H, accordingly N–H···N interaction is weaker than N–H···O hydrogen bond of the amide dimer. This is reflected in the low incidence of amide–pyridine synthon (only 4 %) in CSD structures containing primary amide and pyridine functionalities. Our research group addressed this problem in finding a complementary functional group as pyridine-N-oxide for the amide and designed a novel amide–pyridine-N-oxide heterosynthon by exploiting the better acceptor strength of anionic oxygen. Pyridine-N-oxide (N’–O’) is a stronger acceptor than pyridyl N because of its anionic character. For example, pK\textsubscript{HB} values of pyridine N, amide O and N-oxide O’ are 1.86, 1.96 and 2.70 (increasing basicity) and, moreover, electrostatic surface potential (ESP) charges at the electronegative atoms (e.g. isonicotinamide: N –43.7, O –47.4 kcal mol\textsuperscript{−1}; isonicotinamide N-oxide: O’ –53.3, O –43.1 kcal mol\textsuperscript{−1}) parallel the same trend. In terms of energy, the amide–pyridine-N-oxide two-point heterosynthon of N–H···O’ and C–H···O hydrogen bonds has an enthalpic advantage, ΔE\textsubscript{HB}, of ~3.0 kcal mol\textsuperscript{−1} is more stable than the constituent amide–amide and pyridine-N-oxide homosynthons of N–H···O and C–H···O’ H bonds (Scheme 2). The “amide–pyridine-N-oxide” heterosynthon is
sustained by syn(amide)N–H···O(oxide) hydrogen bond and auxiliary (N-oxide)C–H···O(amide) interaction, is also referred as “amide–N-oxide” synthon in this chapter.

\[ \begin{align*}
\text{amide–amide} & \quad \text{pyridine N-oxide} \\
\text{homosynthon} & \quad \text{homosynthon} \\
\end{align*} \]

\[ \begin{align*}
1. & \quad -13.11 & \quad -9.63 & \quad \Delta E_{\text{synNH}} = -0.50 & \quad -11.62 \\
2. & \quad -12.29 & \quad -9.88 & \quad \Delta E_{\text{synNH}} = 0.39 & \quad -10.94 \\
3. & \quad -11.77 & \quad -9.00 & \quad E_{\text{synNH}} = -0.15 & \quad -10.46 \\
\end{align*} \]

\[ \begin{align*}
1 = \text{acetamide and pyridine N-oxide} \\
2 = \text{isonicotinamide N-oxide} \\
3 = \text{N-methylacetamide and pyridine N-oxide} \\
\end{align*} \]

Scheme 2. Hydrogen bond synthon energy of amide–N-oxide heterosynthon calculated in Spartan 04 (HF/6-31G**) for 1 and 2, Gaussian 03 (HF/6-31G+g(d,p) for 3. The net stabilization in heterosynthon compared to homosynthons, \( \Delta E_{\text{HB}} \), is \( \sim 3 \text{ kcal mol}^{-1} \).

5.3 Evaluating the robustness of amide–pyridine-N-oxide heterosynthon

Previous results from our group\(^{9a,b}\) deal with four crystal structures containing the amide and N-oxide moiety in the same molecule: isonicotinamide-N-oxide, nicotinamide-N-oxide, pyrazinamide-N-oxide, picolinamide-N-oxide. Also three multi-component cocrystals bipyridine-N,N'-dioxide–phenobarbital, bipyridine-N,N'-dioxide–barbituric acid, and picoline-N-oxide–saccharin were studied. The amide–N-oxide synthon is present in all these crystal structures except picolinamide-N-oxide which contains amide dimer synthon in the crystal structure. From these preliminary results we concluded that there is a competition between amide–N-oxide heterosynthon and amide–amide homosynthon. It is difficult to assess the robustness of amide–N-oxide synthon because the synthon is novel and there are very few crystal structures in the CSD with amide and N-oxide functional moieties. In this present chapter, 13 additional cocrystals of carboxamide APIs and pyridine-N-oxide partners (Table 1) are discussed to find out amide–N-oxide synthon probability occurrence, and reasons for its absence in crystal structures. Finally the scope of amide–N-oxide heterosynthon in pharmaceutical solids\(^3\)
is discussed. The amide–N-oxide heterosynthon is represented as a single and two point motifs as shown in scheme 3.

Scheme 3. Amide–N-oxide heterosynthon as a two point and single point synths.

Table 1. Carboxamide APIs and pyridine-N-oxide partners used in cocrystals preparation.

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<tr>
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<td>18T</td>
<td>TMZ•BPNO (1:0.5)</td>
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<tr>
<td>13</td>
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<td>18M</td>
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<td></td>
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5.3.1 Structural description of 13 cocrystals

Barbituric acid / quinoxaline-N,N'-dioxide (8): This 1:1 cocrystal crystallized in monoclinic space group P2₁/n. Barbituric acid, BA, molecules are connected by a centro-
symmetric amide dimer (N3−H3···O3: 1.93 Å, 2.935(1) Å, 176º). Quinoxaline-N,N'-dioxide, QUINO, molecules form a helix along the b-axis via C5−H5···O1 interaction (2.28 Å, 3.091(2) Å, 130º). There is a single point amide–N-oxide synthon, N4−H4···O2 hydrogen bond (1.93 Å, 2.757(1) Å, 174º) in this crystal structure which connects QUINO C−H···O helices and amide dimers of BA molecules as shown in figure 1.

**Figure 1.** Amide dimer homosynthon between barbituric acid molecules and the single point amide–N-oxide (N−H···O – hydrogen bond) with quinoxaline-N,N'-dioxide in cocrystal 8.

**Barbituric acid / 4-methylpyridine-N-oxide (9):** This 1:2 cocrystal crystallized in triclinic space group P ̅T. 4-methylpyridine-N-oxide, PICNO, molecules flank on either side of each BA molecule sustained by amide–N-oxide synthons (N1−H1···O4: 1.75 Å, 2.746(2) Å, 171º; N2−H2···O5: 1.80 Å, 2.797(2) Å, 171º). A second symmetry-independent PICNO molecule forms dimers via C5−H5···O5 (2.14 Å, 3.222(2) Å, 174º) and C11−H11···O4 (2.24 Å, 3.312(2) Å, 170º) interactions. These motifs repeat in the crystal structure to generate 2D sheet structure as shown in figure 2.

**Figure 2.** The amide–N-oxide heterosynthon connects BA and PICNO molecules in cocrystal 9 and the assembly of molecules in a 2D sheet like structure.
Barbituric acid / pyrazine-$N,N'$-dioxide (10): This 1:0.5 cocrystal crystallized in monoclinic space group $P2_1/n$. PYZNO molecule resides at the inversion center. The BA molecules extend into 1D zigzag tape through a centro-symmetric amide dimer N1–H1···O1 hydrogen bond (1.80 Å, 2.798(2) Å, 172º). PYZNO participates in amide–$N$-oxide synthon with amide group on the other side of BA molecule (N2–H2···O4: 1.78 Å, 2.785(2) Å, 172º; C6–H6···O2: 2.45 Å, 3.437(3) Å, 151º) as shown in figure 3a.

Saccharin / 4,4'-bipyridine-$N,N'$-dioxide (11): This 1:0.5 cocrystal crystallized in monoclinic space group $P2_1/n$. A strong N2–H1···O1 hydrogen bond (1.68 Å, 2.663(2) Å, 163º) connects constituent molecules in the cocrystal. The N-oxide acceptor is involved in bifurcated C4–H4···O1 interaction (2.06 Å, 3.136(2) Å, 170º) with an aromatic C–H donor to generate helices along the $b$-axis as shown in figure 3b.

Figure 3. Pyrazine-$N,N'$-dioxide molecules connect tapes of barbituric acid on either side via amide–$N$-oxide heterosynthon in cocrystal 10. (b) A helix via amide–$N$-oxide N–H···O– and C–H···O hydrogen bonds between saccharin and 4,4'-bipyridine-$N,N'$-dioxide molecules in cocrystal 11 (viewed down the $b$-axis).

Diethyl barbituric acid (Barbital) / Pyridine-$N$-oxide (12): It crystallized in monoclinic space group $P2_1/c$ with one molecule each of ethyl barbital, EBA, and pyridine-$N$-oxide, PYNO, in the asymmetric unit. Amide–$N$-oxide heterosynthon (N2–H2···O1, 2.821(1) Å, 173º; C1–H1···O2, 3.356(1) Å, 148º, figure 4a) and hydrogen bonding of PYNO with the second amide N–H donor of EBA (N3–H3···O1, 2.867(1) Å, 172º) produce a helical assembly along the $b$-axis.
Barbital / 4-Methylpyridine-N-oxide (13): The cocrystal crystallized in monoclinic space group $P2_1/c$ with 1:2 stoichiometries of EBA and PICNO. Four PICNO molecules accept N–H···O $^-$ bonds from two EBA molecules (N1–H1···O8: 1.75 Å, 2.742(3) Å, 167°; N2–H2···O7: 1.74 Å, 2.735(3) Å, 170°; N3–H3···O6: 1.74 Å, 2.733(3) Å, 166°; N4–H4···O5: 1.74 Å, 2.743(3) Å, 172°, figure 4b). Picoline-N-oxide molecules extend into a tape through C–H···O interactions along the $a$-axis and extend into sheets in the $ab$-plane which intercalate barbital molecules through N–H···O $^-$ hydrogen bonds.

![Figure 4](image1.png)

Figure 4. (a) Amide–N-oxide heterosynthon between barbital and pyridine-N-oxide molecules in cocrystal 12. (b) N–H···O $^-$ hydrogen bond between barbital and N-oxide molecules. There are two such symmetry-independent clusters in cocrystal 13 shown in different colors (yellow and blue).

![Figure 5](image2.png)

Figure 5. (a) 1D tape of amide dimer homosynthon and O–H···O $^-$ hydrogen bond in cocrystal 14. (b) 1D tape of amide dimer homosynthon and water interrupted hydroxyl to N-oxide hydrogen bonds in cocrystal 15.
4-Hydroxybenzamide / 4,4’-bipyridine-\(N,N’\)-dioxide (14): This cocrystal was synthesized to study the influence of a competing hydroxyl group on the amide group during self-assembly. The cocrystal structure is in triclinic space group \(P\overline{1}\) and contains one 4-hydroxybenzamide and half bipyridine-dioxide molecules in the asymmetric unit. Now the amide group assembles via dimer homosynthon (\(N1–H1A···O1: 1.88 \text{ Å, } 2.892(3) \text{ Å, } 179°\)) whereas \(N\)-oxide forms hydrogen bonds with the hydroxyl group (\(O2–H2···O3: 1.65 \text{ Å, } 2.627(3) \text{ Å, } 173°\)) as shown in figure 5a. The \(N\)-oxide also accepts bifurcated hydrogen bond from amide \textit{anti} \(N–H\) donor (\(N1–H1B···O3: 2.07 \text{ Å, } 3.024(3) \text{ Å, } 158°\)).

4-Hydroxybenzamide / pyrazine-\(N,N’\)-dioxide hydrate (15): It crystallized in triclinic space group \(P\overline{1}\) with one HBAm, half PYZNO and one water molecule in the asymmetric unit. The O3 of water interrupts the hydroxyl to \(N\)-oxide hydrogen bond (\(O4–H4A···O3: 1.85 \text{ Å, } 2.822(3) \text{ Å, } 169°\); \(O2–H2···O4: 1.69 \text{ Å, } 2.666 \text{ Å, } 174°\), figure 5b). Amide dimer homosynthon (\(N1–H1A···O1: 1.91 \text{ Å, } 2.911(3) \text{ Å, } 171°\)) and \textit{anti} \(N–H\) donating to \(N\)-oxide (\(N1–H1B···O3: 2.01 \text{ Å, } 2.988(3) \text{ Å, } 162°\)) complete the strong hydrogen bond network in the ternary cocrystal.

Carbamazepine / quinoxaline-\(N,N’\)-dioxide (16): This 1:1 cocrystal crystallized in the triclinic space group \(P\overline{1}\). A centrosymmetric amide dimer is formed between inversion related CBZ molecules using \textit{syn} \(N–H\) donor (\(N1–H1A···O1: 1.90 \text{ Å, } 2.910(3) \text{ Å, } 174°\)). CBZ \textit{anti} \(N–H\) donates to an \(N\)-oxide of QUINO (\(N1–H1B···O3: 2.02 \text{ Å, } 2.899(3) \text{ Å, } 145°\)). Adjacent CBZ dimers are connected by QUINO molecules (Figure 6a). There is a C–H···O dimer (\(C16–H16···O3: 2.45 \text{ Å, } 3.235(3) \text{ Å, } 129°\)) between inversion-related \(N\)-oxide molecules which fill the voids between amide dimers in the structure. The second \(N\)-oxide moiety is also involved in C–H···O dimer (\(C19–H19···O4: 2.46 \text{ Å, } 3.309(3) \text{ Å, } 135°\)) to connect layers of CBZ dimers.

Carbamazepine and pyrazine-\(N,N’\)-dioxide, 17: It crystallized in monoclinic space group \(P2\_1/c\) with one CBZ and half PYZNO molecule in the asymmetric unit. Similar to cocrystal 16, there is amide dimer homosynthon between CBZ molecules (\(N1–H1A···O1: 1.97 \text{ Å, } 2.940(7) \text{ Å, } 160°\)) and \textit{anti} amide \(N–H\) bonds to \(N\)-oxide of PYZNO.
in cocrystal (Figure 6b; N1–H1B···O3: 2.10 Å, 3.034(7) Å, 152°). There is a helix along the c-axis via N1–H1A···O1, N1–H1B···O3 and C–H···O hydrogen bonds. This cocrystal is isostructural to CBZ–benzoquinone cocrystal in the CSD. Both benzoquinone and pyrazine-N,N′-dioxide have similar molecular size and position of hydrogen bonding acceptor groups, therefore these crystal structures could be referred to as supramolecular equivalents, or functional group exchange leading to similar crystal packing.

Figure 6. (a) Amide dimers of CBZ are connected by anti N–H···O– hydrogen bonds of quinoxaline-dioxide and C–H···O dimers in cocrystal 16. (b) Hydrogen bonded dimers of CBZ are connected by anti N–H···O– hydrogen bond of pyrazine-dioxide in cocrystal 17.

Temozolomide and Bipyridine N,N′-dioxide (18T): Co-crystallization of a 2:1 molar ratio of temozolomide (TMZ) and BPNO from CH₃CN/EtOH afforded a 1:0.5 TMZ•BPNO crystalline adduct (cocrystal 18T in the triclinic space group P ̅1). The amide syn N–H interacts with the carbonyl of tetrazine via N1–H1A···O2 (2.10 Å, 3.085(2) Å, 164.4°) and the anti N–H is bonded to imidazole N acceptor (N1–H1B···N2: 2.10 Å, 2.996(2) Å, 145.8°). With assistance from C4–H4···O2 interaction (2.33 Å, 3.398(2) Å, 166.4°) a 1D tape of TMZ dimers runs along [001]. Such TMZ tapes are sandwiched between ribbons of BPNO molecules to make a 2D sheet in the (210) plane as shown in figure 7. Surprisingly, neither the amide N–H···O dimer synthon nor the amide–pyridine-N-oxide heterosynthon is present in this crystal structures. The absence of these commonly observed synthons suggested that there could be another polymorph.

Temozolomide and Bipyridine N,N′-dioxide (18M): This 2:1 cocrystal crystallized from DMSO with two molecules of TMZ and one molecule of BPNO in monoclinic space group P2₁/c (18M). The amide syn NH donors of crystallographically different TMZ molecules (shown as capped-stick and ball-and-stick models in figure 8) form
hydrogen bond with N-oxide of BPNO via N–H···O– hydrogen bonds (N1–H1A···O6: 1.81 Å, 2.826(1) Å, 177º; N7–H7A···O5: 1.84 Å, 2.851(2) Å, 172º). However, the anti N–H of one TMZ molecule makes no intermolecular contact whereas it is long for the second molecule (N1–H1B···O6: 2.47 Å, 3.375(1) Å, 147.7º). Other weak interactions (C14–H14···O1: 2.06 Å, 3.129(1) Å, 168.5º; C19–H19···O1: 2.31 Å, 3.396(1) Å, 173.8º) complete crystal packing.

**Temozolomide and Bipyridine N,N'-dioxide (19):** This 1:1 cocrystal of TMZ and BPNO cocrystal was obtained from DMF in the chiral space group $P2_12_12_1$. BPNO forms a linear 1D ribbon of C–H···O dimers (C12–H12···O3: 2.17 Å, 3.240(7) Å, 167.8 º; C7–H7···O4: 2.11 Å, 3.195(7) Å, 173.5 º). A TMZ molecule is bonded to one of the N-oxides from amide syn NH bond (N1–H1A···O3: 1.86 Å, 2.857(6) Å, 167.2 º). The crystal structure has alternating tapes of TMZ and BPNO molecules in a 2D sheet (Figure 9). Here too the amide anti N–H has no intermolecular contact. A likely reason for co-crystallization in multiple compositions of 1:0.5, 2:1 and 1:1 is the presence of different N/O acceptor groups in temozolomide.

### 5.3.2 Synthon trends

Zaworotko$^{3d}$ classified hydrogen bonding changes in going from single component to cocrystal structure into two categories. The first type is when the cocrystal former acts only as a spacer but the original homosynthon is retained. Cocrystals 14 to 17 having amide–amide dimer homosynthon fall into this category 1 structures. On the other hand, when there is substantial change in hydrogen bonding because of cocrystal former functional groups, e.g. acid or amide dimer homosynthon changing to acid–pyridine, amide–acid or amide–N-oxide heterosynthon, then the structure belongs to category 2. All other cocrystals with amide–N-oxide motif belong to this category 2. Cocrystal 18T without amide dimer or amide–N-oxide also placed in this category as there is a substantial change in hydrogen bonding because of BPNO cocrystal former. The second category structures are more likely to result in significant differences in the solid state property for API cocrystals since there are significant structural differences in going from homo- to heterosynthon.
Figure 7. N–H⋅⋅⋅O and N–H⋅⋅⋅N hydrogen bonds between TMZ molecules and C–H⋅⋅⋅O interaction with BPNO in cocrystal 18T (1:0.5). Usually formed amide dimer homosynthon or amide–N-oxide heterosynthon are absent in this crystal structure.

Figure 8. Amide–N-oxide hydrogen bonds in TMZ•BPNO cocrystal 18M (2:1). Symmetry-independent TMZ molecules are shown as capped-stick and ball-and-stick models. One anti N–H⋅⋅⋅O bond is long (2.47 Å) and the other anti NH donor has no intermolecular contact.

Figure 9. Amide–N-oxide hydrogen bonds in TMZ•BPNO cocrystal 19 (1:1). There are alternate tapes of TMZ and BPNO molecules in the 2D sheet structure. The anti NH donor makes intramolecular N–H⋅⋅⋅N interaction with imidazole N atom.
There are 35 crystal structures that contain amide and $N$-oxide moiety (13 crystal structures discussed in this chapter + 7 structures from our previous work + 15 structures from CSD$^5a$ and recent papers$^{11}$). The amide–$N$-oxide heterosynthon is present in 24 structures (70%) whereas amide dimer homosynthon occurs in 6 structures. 1 cocrystal (18T) has neither amide–$N$-oxide nor amide dimer in its crystal structure. In other 4 crystal structures, either water or solvent interrupts the formation of stronger amide–$N$-oxide heterosynthon. There are mainly three reasons for the absence of amide–$N$-oxide synthon: firstly the presence of intramolecular $N$–H···O hydrogen bond as in picolinamide-$N$-oxide. Secondly when there is a competition from a hydroxyl/water in 4-hydroxybenzamide cocrystals 14 and 15, amide dimer is favoured. Similar observation is noted in the dipolymorphic nitronyl nitroxide uracil derivative.$^{11}$ Both alpha and beta forms have strong amide–$N$-oxide synthon in their crystal structures. However, in its monohydrate crystal structure, water molecule interrupts the formation of amide–$N$-oxide synthon (Figure 10). Lastly steric factors also favour the homo-dimer as noted above in carbamazepine cocrystals 16 and 17. The steric factors promoting the amide dimer homosynthon in cocrystal 16 is verified by crystal structure prediction.

![Figure 10. Three forms of nitronyl nitroxide uracil derivative. (a) $\alpha$ form. (b) $\beta$ form. (c) Monohydrate. Both alpha and beta forms have amide–$N$-oxide synthon, whereas water interrupts the formation of this amide–$N$-oxide in monohydrate crystal structure.](image-url)
5.3.3 Crystal Structure Reproduction

As the stronger amide–N-oxide synthon is absent in cocrystals 16 and 17, a thorough screening was undertaken by varying the solvent and crystallization conditions to find out if any other strongly hydrogen bonded amide–N-oxide cocrystal exists. Experiments were unsuccessful to produce new polymorphic or different stoichiometry cocrystal. We then turned our attention to crystal structure reproduction to know reasons for amide–N-oxide synthon absence. The ab initio crystal structure prediction\textsuperscript{12} of an organic molecule is a difficult challenge but this subject generates immense interest in pharmaceutical polymorphism. The advantage of this method is that several putative structures can be generated computationally which further allow comparison of homo- and hetero-synthons, hydrogen bonding and the associated molecular packing for each predicted structure frames. The 1:1 carbamazepine–quinoxaline-N,N′-dioxide cocrystal (16) was selected for structure prediction (reproduction) test case in the observed \( P\bar{T} \) space group alone because simulation of multi-component systems\textsuperscript{13a} or single-molecule crystal structures of \( Z' > 1 \)\textsuperscript{13b} is more difficult than the single component structures (\( Z' = 1 \)) at the present time. Moreover, this simulation is only to identify whether the experimentally observed structure falls in the lowest energy ten frames of predicted structures and to see if any structures with amide–N-oxide synthon.

Crystal structures were calculated in Cerius\textsuperscript{2} program package\textsuperscript{14a} using Polymorph Predictor module and COMPASS force field. The energy range for 10 lowest frames is \(~3 \text{ kcal mol}^{-1}\), a value that is comparable to hydrogen bond energy difference, \( \Delta E_{\text{Hb}} \), between amide dimer homosynthon and amide–N-oxide heterosynthon. We therefore expected the 10 lowest energy structures to show homo- and/or hetero-synthon hydrogen bonding. As expected, among the 10 lowest energy frames in \( P\bar{T} \) space group, seven structures contain amide homo dimer and one structure with amide–N-oxide heterosynthon, and two structures without amide dimer and amide–N-oxide synthon. Structure prediction frames are listed in Table 2. Unit cell of the 3\textsuperscript{rd} lowest energy frame or frame 3 matches remarkably well (within 3\%) with the observed crystal structure in \( P\bar{T} \) space group and their energies are identical. Match of the observed crystal structure with any one of the low energy frames (typically between frames 1 to 5, \(<1 \text{ kcal mol}^{-1}\) above the global minimum) is considered to be a good result in the current day.
Table 2. Ten lowest energy crystal structure frames computed in Polymorph Predictor. The energy difference between predicted frames 1-10 is 3.02 kcal mol\(^{-1}\).

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Experimental crystal structure (16)

| Exp (min) | –57.573 | 1.45 | 10.582 | 13.100 | 6.920 | 83.21 | 72.24 | 89.50 | 906.9 |
| 1 | –57.703 | 1.46 | 10.545 | 13.744 | 6.854 | 72.95 | 72.56 | 83.85 | 905.9 |
| 2 | –55.736 | 1.46 | 8.898 | 7.1522 | 15.458 | 68.57 | 85.45 | 79.95 | 901.7 |
| 3 | –55.248 | 1.40 | 7.918 | 12.092 | 12.045 | 64.17 | 69.06 | 68.54 | 938.9 |
| 4 | –55.087 | 1.46 | 8.3682 | 7.715 | 14.452 | 79.52 | 82.01 | 83.87 | 905.4 |
| 5 | –55.079 | 1.46 | 9.448 | 13.321 | 8.2156 | 90.20 | 105.10 | 110.70 | 928.6 |
| 6 | –55.001 | 1.42 | 9.721 | 12.441 | 8.328 | 100.4 | 105.99 | 99.48 | 927.4 |
| 7 | –54.819 | 1.42 | 10.565 | 7.283 | 12.481 | 84.14 | 70.86 | 84.82 | 901.0 |
| 8 | –54.809 | 1.41 | 8.809 | 10.008 | 11.382 | 89.45 | 81.22 | 70.63 | 934.7 |

Predicted frames of cocrystal (16)

Establishing isostructurality is important when one has a large list of predicted structures and the aim is to identify predicted structure(s) that match with the experimentally observed structure. Once similar structures are identified, the matching molecular clusters are superimposed to visualize the extent of similarity between the two structures. The default size molecule cluster is 15, a central molecule plus its 14 nearest neighbours. Structures are deemed to be the same when all 15 molecules in the coordination shell match nicely. The rms deviation gives a numerical measure of similarity or identity. COSET program (COmpare, SEarch and Topology)\(^{14b}\) allows comparison of structures to identify similar crystal structures within a specified tolerance. The overlay of 15 nearest-neighbour molecules shows excellent superposition, rms deviation of 0.335, and good overlay in 2\(\theta\) and intensity of powder X-ray diffraction peaks (Figure 11). N–H···O and C–H···O hydrogen bonds between carbamazepine and quinoxaline-dioxide molecules are identical in the experimental and simulated frame 3 (Figure 5a and 12a). The 6\(^{th}\) lowest energy predicted structure i.e. frame 6, contains amide–N-oxide syn N–H···O– hydrogen bond (Figure 12b). Visualization of this structure suggests that a reason for the non-occurrence of amide–N-oxide heterosynthon in CBZ cocrystals is steric. The anti NH donor surprisingly is not hydrogen bonded to the available N-oxide acceptor in
computed 6\textsuperscript{th} frame because the dibenzazepine ring of this rigid, butterfly-shaped molecule, which overhangs just above the anti NH donor, blocks close approach of potential hydrogen bond acceptors (Figure 12b). There is however a long, bent (CBZamide)N–H···π(QUINO phenyl) interaction (3.08 Å, 124°).

**Figure 11.** Overlay of 15 molecules of experimental carbamazepine–quinoxaline-N,N'-dioxide cocrystal (red) and simulated frame 3 (blue). (b) Overlay of PXRD pattern of experimental minimized (red) and predicted frame 3 (blue) shows excellent match.

**Figure 12.** (a) Polymorph Predictor frame 3 of CBZ•QUNIO cocrystal to show amide dimer homosynthon of syn NH groups and anti N–H···O (oxide) hydrogen bond, matches with the observed hydrogen bonding and molecular packing as shown in figure 5a. (b) Predicted frame 6 has syn amide–N-oxide hydrogen bond but the anti NH is free, offering a possible reason for the non-occurrence of amide–N-oxide heterosynthon in carbamazepine cocrystals.
5.4 Polymorphism in cocrystals

The absence of commonly observed amide dimer homosynthon and amide–N-oxide heterosynthon synthon in TMZ•BPNO cocrystal 18T (1:0.5) suggested that there could be another polymorph or a strongly hydrogen bonded cocrystal. Further experiments by changing the solvent and crystallization conditions yielded two additional TMZ•BPNO cocrystals 18M (2:1) and 19 (1:1), both of them contain amide–N-oxide synthon as anticipated. The chemical composition of 18M is same as cocrystal 18T except that previous one contains two molecules of TMZ and one molecule of BPNO and the later has one molecule of TMZ and half molecule of BPNO residing on the inversion center. These are called as polymorphs of cocrystals with different crystal packing arrangements. Polymorphism in cocrystals or multi-component crystals\textsuperscript{15} is very recent and there are only 33 cocrystal polymorph sets up to the January 2008 release of the CSD (24 structure sets have strong hydrogen bonding functional groups + 9 sets are sustained by weak C–H···O interactions or π–π stacking) when compared to 1600 polymorphic systems of single component crystals.\textsuperscript{5a}

It is difficult to infer pyridine-N-oxide cocrystal stability from melting point because of compound decomposition. The density of cocrystal 18T is higher than 18M (1.592, 1.576 g cm\textsuperscript{-3}). Lattice energy calculations place cocrystal 18T (−33.27 kcal mol\textsuperscript{-1}) substantially more stable than 18M (−30.32 kcal mol\textsuperscript{-1}) given that energy differences between polymorphs are generally small suggesting that the cocrystal 18T is more stable than 18M. Grinding\textsuperscript{16} of cocrystal 18M in a ball-mill for 1 h showed complete conversion to cocrystal 18T based on PXRD comparison (Figure 13). Further grinding of cocrystal 18T did not indicate any phase change, indicating that the stability order is consistent with density and lattice energy values. The metastable nature of cocrystal 18M may be traced to the unused amide anti N–H donor and imidazole N acceptor in intermolecular hydrogen bonding (Figure 8) reasons similar to temozolomide polymorph 2 \textsuperscript{(6b)} in chapter 4. The facile phase transition of TMZ•BPNO cocrystal 18M to 18T by grinding may therefore be understood as stabilization from more number of hydrogen bonds in the product. Although the amide–pyridine-N-oxide N–H···O hydrogen bond in structure 18T (1.81, 1.84 Å) is quite strong (more stable than amide N–H···O by ∼3 kcal mol\textsuperscript{-1}), the unutilized anti NH donor and imidazole N acceptor make the crystal structure
kinetically metastable. After grinding for 1h, hydrogen bond reorganization takes place and a single strong N−H···O− hydrogen bond in 18M is replaced by two H bonds in structure 18T, N−H···O with tetrazine C=O and N−H···N with imidazole N (Figure 14).

**Figure 13.** Powder X-ray diffraction patterns – Intensity vs. 2θ. (a) Freshly prepared cocrystal 18M (100% purity). (b) Pure cocrystal 18M ground in a mechanical ball mill for 1 h showed quantitative transformation to cocrystal 18T. (c) Further grinding for 1 h showed no change (cocrystal 18T recovered). These phase transitions indicate that cocrystal 18T is the thermodynamic phase and cocrystal 18M is a metastable polymorph. The black trace is the experimental PXRD and red lines are simulated from the X-ray crystal structure. There is a good match of observed and calculated peaks.

**Figure 14.** Hydrogen bond reorganization in TMZ•BPNO 2:1 cocrystal 18M (a) to 1:0.5 cocrystal 18T (b). Cocrystal 18M has strong amide–pyridine-N-oxide N−H···O− hydrogen bond. The unused amide anti N−H donors in cocrystal 18M (a, indicated by thin double arrows) move close to the imidazole N acceptors in cocrystal 18T (b) by 45° rotation and about half a molecular length translation. One strong N−H···O− hydrogen bond is broken and replaced by N−H···O and N−H···N bonds. Molecular rotation and translation in (a) are indicated by thick arrows.
Cocrystals 18T and 18M are also analyzed as synthon polymorphs,\textsuperscript{17} with different hydrogen boned synthons between two components in their crystal structures. Recently Vishweshwar et al. reported polymorphic cocrystals of 4-hydroxy benzoic acid / 2,3,5,6-tetramethyl pyrazine\textsuperscript{15a} with different synthons. The more stable form 2 has hierarchic synthons,\textsuperscript{10} i.e. acid–pyrazine and hydroxyl–carbonyl, whereas metastable form 1 has non-hierarchic acid–acid and hydroxyl–pyrazine synthons (Figure 15). In contrary to these results, the stable TMZ•BPNO cocrystal 18T has non-hierarchic tapes of amide N–H···O hydrogen bonds and N–H···N dimer while the metastable cocrystal 18M has hierarchic amide–pyridine-N-oxide synthon (Figure 16).

![Figure 15](image1.png)

**Figure 15.** (a) Form 1 of hydroxybenzoic acid–tetramethyl pyrazine with acid–acid and hydroxyl–pyrazine synthons. (b) Form 2 with acid–pyrazine and hydroxyl–carbonyl synthons.

![Figure 16](image2.png)

**Figure 16.** (a) Cocrystal 18T without amide dimer and amide–N-oxide synthons. (b) Polymorphic cocrystal 18M with strong amide–N-oxide heterosynthon.

The common structural feature in TMZ polymorphs (single component) of chapter 4 and TMZ•BPNO cocrystal polymorphs (multi-component) discussed in this chapter 5 is that the metastable modification has unused hydrogen bond donors/ acceptors\textsuperscript{18} whereas all good donors and acceptors are used in hydrogen bonding in the stable form. The anti NH does not make intermolecular hydrogen bond in metastable TMZ polymorph 2 (6b) and TMZ•BPNO cocrystal 18M. The reorganization of functional groups upon grinding results in the unused atoms making new hydrogen bonds in the stable form, i.e. N–H···O in TMZ polymorph 1 (6a) and N–H···O and N–H···N bonds in cocrystal 18T. Conformational polymorphism arising out of different conformers A and B in TMZ single component polymorphs discussed in chapter 4 is not observed in cocrystal
polymorphs 18T and 18M. Both cocrystals have stable conformer $A$ and occurrence of polymorphism may be ascribed to different hydrogen bond synthons and presence of unused hydrogen bond donor/acceptors. Apart from the TMZ·BPNO polymorphic cocrystal system, two more example are chosen from 33 cocrystal polymorph sets deposited in CSD to illustrate the reasons for occurrence of polymorphism in cocrystals. N,N'-bis(4-bromophenyl) melamine and 5,5-diethylbarbituric acid (refcodes JICTUK01/10) is a dimorphic substance. Polymorphism in this cocrystal is due to changes in conformation of bromo-phenyl ring attached to melamine. One of the phenyl rings is planar and other is perpendicular to melamine ($-8.73^\circ, -87.9^\circ$) in $P2_1/n$ cocrystal as shown in figure 17a. Whereas both the phenyl rings are planar ($-9.04^\circ, -8.21^\circ$) in $P\bar{1}$ cocrystal as shown in figure 17b. Polymorphism in 1:1 cocrystal of benzoquinone/1,4-dihydroxy benzene (refcodes QUIDON/01) arise due to differences in packing. Both cocrystal polymorphs have similar linear tapes of O–H···O hydrogen bonds, however the arrangements of these tapes are different in polymorphs. Triclinic cocrystal has a parallel linear tapes connected by C–H···O H-bonds in a layered structure (Figure 18a), whereas these tapes are arranged perpendicularly to each other and extend into third dimension in the monoclinic cocrystal (Figure 18b).

![Figure 17](image1.png)

**Figure 17.** Conformational polymorphism in JICTUK01/10. (a) One of the phenyl rings is planar and other is perpendicular to melamine ($-8.73^\circ, -87.9^\circ$) in $P2_1/n$ cocrystal (b) Both the phenyl rings are planar ($-9.04^\circ, -8.21^\circ$) in $P\bar{1}$ cocrystal.

![Figure 18](image2.png)

**Figure 18.** Packing polymorphism in JICTUK01/10. (a) 1D tapes of molecules are arranged in a sheet in triclinic cocrystal. (b) 1D tapes of molecules are arranged perpendicularly to each other in the monoclinic cocrystal.
It appears that the differences in cocrystal polymorphs arise due to reasons similar to those for single component polymorphic structures, i.e. differences in conformation, hydrogen bonding, and/or molecular packing. This could mean that the not so frequent occurrence of polymorphism in cocrystals (33 sets) compared to classical polymorphism in single component crystals (1600 sets), is not due to a fundamental structural difference but for the simple reason that studies on cocrystals are very recent and the time dedicated for multi-component crystals is less when compared to single component molecules. An early notion that cocrystals are less prone to polymorphism should be reviewed in due course.

5.5 Hydration stability in cocrystals

The molecular complexes or cocrystals containing therapeutic molecules represent an emerging class of pharmaceutical materials offering the potential to optimize physical/chemical properties. These are called as pharmaceutical cocrystals formed between an Active Pharmaceutical Ingredients (API) with another pharmaceutically acceptable molecule in the solid-state. The resulting multi-component solid with a distinct physicochemical profile is designed such that it will improve properties in terms of solubility, melting point, physical stability and/or hygroscopic stability of the substance. The proof of concept with 4-methylpyridine-N-oxide in relation to controlling hydration is discussed now. Picoline-N-oxide, PICNO, is a hygroscopic compound and readily absorbs moisture from the atmosphere during storage and handling. Vacuum drying of wet PICNO at 110-120 °C showed water absorption bands in its IR spectrum after 3 h. A cocrystal of barbital and picoline-N-oxide in 1:2 ratio (13) was prepared by grinding in mortar-pestle for 15 min and the resulting crystalline solid was exposed to different relative humidity conditions (ca. 50% and then 100%). IR spectra were recorded at regular intervals (Figure 19), from a few days up to a month, to monitor the increase in intensity of H$_2$O absorption peaks. These qualitative results show that there is substantial improvement in the hydration stability of a pyridine-N-oxide by cocrystal formation. An advantage with the amide–N-oxide heterosynthon is that hydrogen bonding in the EBA·PICNO cocrystal 13 is sufficiently different from that of amide dimer of EBA and C–H···O dimer of PICNO (Figure 20), which resulted in hygroscopic stability of cocrystal 13 over simple picoline-N-oxide molecule.
Figure 19. Infrared spectra. (a) 4-Methylpyridine-N-oxide, the starting material has significant amount of moisture based on the broad OH band centered at 3500 cm$^{-1}$. (b) Barbital has peaks at 3242, 3109, 2961, 2879 cm$^{-1}$. (c) Cocrystal as prepared, peaks at 3076, 2980 and 2754 cm$^{-1}$. (d) Cocrystal in open air after 3 days, peaks at 3076, 2980 and 2739 cm$^{-1}$. (e) Cocrystal in open air after 4 weeks, peaks at 3076, 2976 and 2725 cm$^{-1}$. (f) Cocrystal in RH 100% after 1 day, the broad band indicates moisture. There is insignificant moisture uptake at 50% RH even after 1 month but the crystal hydrates in saturated water vapour environment 100% RH).
In pharmaceutical formulations certain classes of drugs pose particular problems. One such problem arises in the case of hygroscopic drugs, which tend to absorb water from the air. This is disadvantageous because moisture uptake enhances molecular mobility and can affect flow, compaction, dissolution, stability, storage, and final product during drug processing and formulation. Many examples are reported wherein the role of water was found to be very crucial in promoting the solid-state phase transitions to hydrate/metastable anhydrate or an amorphous form and sometimes disintegrating the salts to individual components or inducing drug–excipient interactions. Delavirdine methanesulfonate\textsuperscript{19} is one such example which has adversely affected in their dissolution profile when its tablets were exposed to high relative humidity conditions. It was observed that the change in moisture content in the stressed tablets was shown to cause the salt to dissociate, resulting in the free base and methanesulfonic acid, which further lead to a subsequent acid–base reaction between the methanesulfonic acid and excipient in the tablets. Norfloxacin is another unusual example, where tablet dissolution behaviour was adversely affected in lower humidities. The water molecules induce proton transfer between norfloxacin molecules in the solid state, as the anhydrate (neutral COOH) converts into norfloxacin dihydrate (ionic COO\textsuperscript{−} form) at higher relative humidity conditions.\textsuperscript{19,20} The change from a neutral crystal to an ionic crystal after

**Figure 20.** (a) C–H···O dimer of 4-methylpyridine-N-oxide. (b) Amide dimer homosynthon which is present in all four polymorphs of barbital drug. (b) Strong amide–N-oxide hydrogen bonds in EBA•PICNO cocrystal 13 (2:1).
exposure to 75% RH at room temperature resulted in a higher dissolution rate, because of ionic form (Figure 21). While proton transfer may not be considered a major change in the molecular structure, water effect on the solid-state properties is definitely significant.

![Figure 21. Hydration induced proton transfer in norfloxacin forms. Norfloxacin anhydrous neutral form was converted to ionic dihydrate form at 75% RH conditions.](image)

Hygroscopicity is therefore a challenging problem for certain drugs. Such compounds must be handled in controlled humidity environments during manufacture and the final product must be packaged in individual moisture resistant blisters in order to prevent changes or degradation of the product. An alternative to deal with hygroscopic solids is by choosing a non-hygroscopic crystalline form of an API. It could be a different polymorph, solvate, salt or cocrystal which is resistant to hydration at ambient RH conditions. Recent patent highlights that a pharmaceutical composition comprising of propylene glycol solvate of an API (celecoxib sodium propylene glycol solvate) has a decreased hygroscopicity and increased aqueous solubility when compared to pure API (celecoxib sodium salt). Caffeine and theophylline drugs are other examples that get converted to hydrates at 98% RH, while their cocrystals with oxalic acid are stable at 98% RH for 7 weeks. Co-crystallization or non-covalent modification of API is therefore an emerging alternative method to modify physical and chemical properties, especially for neutral drug molecules, has a potential utility in pharmaceutical formulation. Several amorphous, crystalline, hygroscopic, or poorly soluble drugs can be made more soluble, more stable, and less hygroscopic by co-crystallization with a suitable cocrystal former which satisfy otherwise free hydrogen bond donors/acceptors sites in the drug molecule.

The cocrystals of APIs discussed in this chapter do not classify as pharmaceutical cocrystals because of the N-oxides are not under GRAS (generally regarded as safe) list of chemicals. However, it is known in the literature that the oxidation of pyridine
nitrogen to $N$-oxide often enhances drug-like behaviour to give molecules with good oral bioavailability, pharmacokinetic properties, solubility, and metabolic stability. Affinity at the target receptor or binding site may also increase because of stronger hydrogen bonding with the drug molecule. Further, $N$-oxide is a common route for phase 1 metabolism of drugs containing pyridine moiety and these metabolites often contribute to drug action. Many new $N$-oxide drug molecules (anti HIV, anti-viral and anti-bacterial drugs)\textsuperscript{24} are popular targets for medicinal chemists. A phosphodiesterase-IV-inhibitor of $N$-oxide active pharmaceutical ingredient\textsuperscript{25} is a highly hygroscopic molecule known to exhibit eight forms of anhydrate/hydrates and undergo variety of phase transformations on changing relative humidity conditions. The stronger hydrogen bond acceptor strength of $N$-oxide in these molecules could be exploited to make predictable cocrystals with amide type cocrystal formers to optimize their physical properties. Cocrystals of antitumour drug temozolomide with GRAS carboxylic acid or carboxamide molecules are synthesized to improve hydrolytic stability of TMZ is discussed in the next chapter 6.

5.6 Conclusions

A novel carboxamide–pyridine-$N$-oxide heterosynthon sustained by $\text{syn}(\text{amide})N$–$H$···$O$–(oxide) hydrogen bond and auxiliary $(N$-oxide)$C$–$H$···$O$(amide) interaction was designed by exploiting the better acceptor strength of the anionic oxygen. Synthon robustness was evaluated in 35 crystal structures that contain amide and pyridine-$N$-oxide functional groups. Amide–pyridine-$N$-oxide heterosynthon competes with amide dimer homosynthon. 24 structures have amide–pyridine-$N$-oxide, 6 structures with amide–amide dimer, and remaining structures are devoid of both amide dimer and amide–$N$-oxide synthons. Amide dimer synthon is present in three situations: presence of an intramolecular $N$–$H$···$O$ hydrogen bond as in picolinamide-$N$-oxide, competition from another strong hydroxyl (–OH) group in cocrystal 14 and 15, and lastly steric factors imposed by dibenzazepine group of CBZ in cocrystals 16 and 17 as confirmed from crystal structure prediction on CBZ•QUINO (1:1) cocrystal 16 in Cerius\textsuperscript{2}.

Temozolomide forms three different stoichiometry cocrystals $18T$, $18M$ and $19$ (1:0.5, 2:1 and 1:1) with 4,4'-bipyridine-$N,N'$-dioxide. Structures $18T$ and $18M$ exhibit synthon polymorphism in cocrystals. The stable cocrystal $18T$ has neither amide–$N$-oxide nor
amide dimer synthon whereas metastable cocrystal 18M contains strong amide–N-oxide heterosynthon. More interestingly, this strongly hydrogen bonded cocrystal 18M converts to cocrystal 18T with moderate hydrogen bonds upon grinding for one hour. The metastable nature of cocrystal 18M is ascribed to unused hydrogen bond donors/acceptors in the crystal structure which are completely utilized in the stable polymorphic cocrystal 18T. Apart from generating diverse supramolecular structures, cocrystals offer the potential to modify physical and chemical properties of substances. 4-picoline-N-oxide deliquesces within a day; while its 2:1 picoline-N-oxide and ethyl barbituric acid cocrystal (13) assembled by amide–N-oxide heterosynthon does not absorb moisture at 50% relative humidity (RH) levels up to four weeks. Cocrystal 13 has better resistance to hydration as the hydrogen bonding in crystal structure is completely different from that of individual components.

5.7 Experimental Section

Crystal Structure Prediction (CSP): Lattice energy minimization of experimental structures was carried out using version 4.8 of Cerius² molecular modeling environment running on Silicon Graphics workstations. COMPASS force field was applied. The minimized structure was used as a model for running a rigid polymorph prediction using polymorph predictor (PP) module. Structures were generated keeping the molecular conformation rigid. Conformational variations were expected to be minimal for these rigid molecules except torsions in the azepine-amide portion of CBZ. Structure clustering, energy computations and ranking in increasing lattice energy were performed next. COSET program was used for PP analysis and RMSD calculations on experimental and predicted structures.

Hydration stability: The Lancaster catalogue indicates that picoline-N-oxide is hygroscopic and should be tightly sealed. When 0.5-1.0 gm of the compound was left in an open petri dish for one day the solid deliquesces completely. The relative humidity was ca. 50% (in the range 45-55%) under ambient conditions of Hyderabad climate during the experiment period of December 2006 (temperature range 25-35 °C). We performed a qualitative experiment to assess the gross differences in hydration nature of 4-picoline-N-oxide compared to its cocrystal with barbital wherein the N-oxide moiety is
engaged in strong bonding with an amide partner. The solid was placed in a petri dish exposed to ambient humidity conditions (ca. 50% RH) for the specified time and IR spectra were recorded to monitor water absorption peaks. In the second experiment, the solid was placed in 100 mL beaker, which was kept in a closed jar containing distilled water to expose the sample to 100% relative humidity conditions for a specified time and IR spectra were recorded.

**Cambridge Structural Database (CSD):** There are 35 crystal structures that contain amide and N-oxide moiety (13 crystal structures discussed in this chapter + 7 structures from our previous work + 15 structures from CSD and recent papers). The amide–N-oxide heterosynthon is present in 24 structures (cocrystals 8-13, 18M, 19, ADECIW, BAFTAH, BAQZAI, GEYWOW, JEDKUZ, MEGCUZ, MEGDAE, MEGDAE, MEGDEI, MEGDIM, MEGDUY, RBBHUM, YEQRUX, ZIVQEA, HALLUC, alpha and beta forms of nitronyl nitroxide uracil derivative) and 11 structures with out amide–N-oxide heterosynthon (cocrystals 14-17, 19, CETQUO, FAQRIY, JOCPUM, UGISUY, MEGDOS and monohydrate of nitronyl nitroxide uracil derivative). A second search was carried out in CSD for cocrystal polymorphs. All polymorphs with 3D coordinates reported, No errors, Not Polymeric, No ions were searched in Version 5.29, ConQuest 1.10, January 2008 update to give 5167 hits. Crystal structures with high disorder were excluded. There are totally 33 polymorphic sets of which 24 cocrystal sets (AJAJEA, ENAZOI, EXUQUB, HADKUT, IJETOG, JICTUK, MACCID, MUROXA, QUINOD, SAYMUB, TECCAF01, TEHNAW, WOTZAG, XETZIG, ZIGPAG, WATERP, ODOBIT, GIDLUB, PTZTCQ, UNEZAO, UNEZES, KIHYQO, ULAWAF and 4,4-dihydroxybenzophenone•1,2-bis (4-Pyridyl) ethylene) have strong hydrogen bonding groups whereas 9 sets (ABUNIU, DURZAR, IJETEW, NAPYMA, NARSOP, RIFQAY, SEOTCR, TAMBE, FAHLEF) do not have strong H-bonding groups. They contain other non-covalent intermolecular interactions and/ or π-stacking.

**Synthesis of cocrystals**

**BA·QUINO (8):** 40 mg (0.312 mmol) of barbituric acid and 50.6 mg (0.312 mmol) of quinoxaline-N,N'-dioxide [1:1] were ground in mortar/pestle for 5 minutes with 5 drops of acetonitrile and dissolved in 10 mL of acetonitrile. Slow evaporation of solvent resulted in yellow colored block like 1:1 cocrystals over a period of 2–3 days.
**BA·PICNO (9):** 50 mg (0.390 mmol) of barbituric acid and 85 mg (0.780 mmol) of 4-methylpyridine-N-oxide [1:2] were dissolved in 6-8 mL of THF and allowed to evaporate slowly over a period of 3-4 days to get needle shaped 1:2 cocrystals.

**BA·PYZNO (10):** 50 mg (0.390 mmol) of barbituric acid and 43.7 mg (0.390 mmol) of pyrazine-N,N’-dioxide [1:1] were dissolved in 3 mL of water and allowed to evaporate slowly over a period of 3-4 days to get irregular block shaped 1:0.5 cocrystals.

**SAC·BPNO (11):** 50 mg (0.272 mmol) of saccharin and 25.6 mg (0.136 mmol) of bipyridine-N,N’-dioxide [1:0.5] were ground in mortar/pestle for 5 minutes adding 5 drops of acetonitrile and later dissolved in 10-15 mL of acetonitrile. Slow evaporation of the solvent over a period of 2-3 days resulted in needle shaped 1:0.5 cocrystals.

**EBA·PYNO (12):** Cocrystal was obtained when 50 mg (0.271 mmol) of barbital and 50.3 mg (0.543 mmol) of pyridine-N-oxide [1:2] were dissolved in 5-8 mL of EtOAc and allowed to evaporate slowly over a period of 3-4 days to yield 1:1 cocrystals.

**EBA·PYNO (13):** Cocrystal was obtained when 50 mg (0.271 mmol) of barbital and 59 mg (0.543 mmol) of 4-methylpyridine-N-oxide [1:2] were dissolved in 5-8 mL of EtOAc and allowed to evaporate slowly over a period of 3-4 days to yield 1:0.5 cocrystals.

**HBAm·BPNO (14):** Cocrystal was obtained when 36.4 mg (0.265 mmol) of 4-hydroxy benzamide and 50 mg (0.265 mmol) of bipyridine-N,N’-oxide [1:1] were dissolved in 5 mL of acetone, 5 mL of methanol, and 2 mL of water and allowed to evaporate slowly in a beaker to yield colorless plate shaped 1:0.5 cocrystals after 3 to 4 days.

**HBAm·PYZNO (15):** Cocrystal was obtained when 53.7 mg (0.392 mmol) of 4-hydroxy benzamide and 40 mg (0.392 mmol) of pyrazine-N,N’-oxide [1:1] were dissolved in 5 mL water and allowed to evaporate slowly in a beaker to get 1:0.5·H2O cocrystals.

**CBZ·QUINO (16):** Cocrystal was obtained when 50 mg (0.211 mmol) of carbazamazepine and 22.4 mg (0.106 mmol) of quinoxaline-N,N’-oxide [1:0.5] were ground in mortar/pestle using acetonitrile as solvent for liquid assisted grinding. After the new binary phase material was confirmed by IR, it was dissolved in 8 mL acetonitrile and allowed to evaporate slowly to get pale yellow coloured 1:1 cocrystal after 3-4 days.

**CBZ·PYZNO (17):** Cocrystal was obtained when 80 mg (0.339 mmol) of carbazamazepine and 19 mg (0.169 mmol) of pyrazine-N,N’-oxide [1:0.5] were ground in mortar/pestle using acetonitrile as solvent for liquid assisted grinding. After the new binary phase material was confirmed by IR, it was dissolved in 5 mL DMF and allowed to evaporate slowly to get pale colourless 1:0.5 cocrystal after 3-4 days.
TMZ·BPNO (18T): 46.5 mg of TMZ (0.24 mmol) and 27.1 mg of BPNO (0.12 mmol) were dissolved in a mixture of 6 mL CH$_3$CN and 2 mL EtOH (3:1) and the solvents were allowed to evaporate slowly. Both 1:0.5 cocrystal and hydrate of TMZ appeared concomitantly after a few days.

TMZ·BPNO (18M): 46.5 mg of TMZ (0.24 mmol) and 27.1 mg of BPNO dihydrate (0.12 mmol) were dissolved in 2 mL of DMSO and allowed to evaporate in a beaker over a period of 2 weeks to get 2:1 of TMZ and BPNO stoichiometry cocrystal.

TMZ·BPNO (19): 50 mg of TMZ (0.24 mmol) and 54.2 mg of BPNO dihydrate (0.24 mmol) were dissolved in 5 mL of DMF and allowed to evaporate in a beaker over a period of 2 weeks to get 1:1 of TMZ and BPNO stoichiometry cocrystal.

5.8 References


14) (a) Polymorph Predictor and Cerius^® suite of programs are software products of Accelrys Inc., [http://www.accelrys.com](http://www.accelrys.com). (b) COSET is developed and


23) GRAS chemicals list is available at http://www.cfsan.fda.gov/~dms/eafus.html.
