**Table S1.** Hydrogen bond geometry in crystal structures **1-6**.[a]

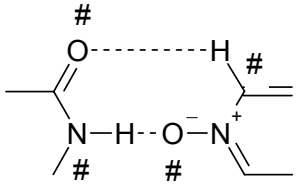
| Compound | Interaction | *d* /(Å) | *D* /(Å) | $\theta$/(°) |
|---|---|---|---|---|
| **1** | N2–H2A···O1(*syn*)[b] | 1.89 | 2.883(5) | 168.4 |
| | C1–H1···O2 | 2.25 | 3.272(6) | 156.8 |
| | N2–H2B···O1(*anti*)[b] | 1.95 | 2.927(5) | 161.9 |
| | C2–H2···O1 | 2.28 | 3.349(6) | 167.0 |
| | C5–H5···O2 | 2.27 | 3.035(6) | 125.5 |
| **2** | N2–H2A···O1(*syn*) | 1.93 | 2.915(2) | 164.9 |
| | C5–H5···O2 | 2.43 | 3.286(2) | 134.5 |
| | N2–H2B···O1(*anti*) | 1.88 | 2.852(2) | 159.8 |
| | C1–H1···O1 | 2.31 | 3.356(2) | 161.1 |
| | C4–H4···O2 | 2.47 | 3.175(2) | 121.3 |
| **3** | N2–H2A···O2(*syn*) | 1.95 | 2.956(2) | 173.2 |
| | N2–H2B···O1(*anti*, intra) | 1.73 | 2.594(2) | 141.2 |
| | C4–H4···O2 | 2.35 | 3.199(3) | 133.7 |
| | C3–H3···O1 | 2.28 | 3.365(3) | 174.2 |
| | C5–H5···O1 | 2.31 | 3.379(3) | 169.7 |
| **4** | N2–H2A···O4(*syn*) | 1.93 | 2.921(3) | 168.3 |
| | C9–H9···O2 | 2.28 | 3.334(3) | 162.8 |
| | N6–H6A···O1(*syn*) | 1.91 | 2.907(3) | 168.2 |
| | C4–H4···O3 | 2.28 | 3.339(3) | 164.0 |
| | N2–H2B···O4(*anti*) | 2.14 | 2.916(3) | 132.2 |
| | N6–H6B···O1(*anti*) | 2.27 | 2.921(3) | 121.3 |
| | N2–H2B···N3(*anti*, intra) | 2.24 | 2.729(3) | 107.9 |
| | N6–H6B···N5(*anti*, intra) | 2.16 | 2.725(3) | 113.8 |
| | C3–H3···O3 | 2.25 | 3.300(4) | 161.4 |
| | C8–H8···O2 | 2.20 | 3.237(3) | 159.3 |
| **5•(BPNO)$_{0.5}$** | N2–H2···O1 | 1.78 | 2.782(2) | 173.3 |
| | C13–H13···O3 | 2.28 | 3.271(2) | 151.0 |
| | N3–H3···O1 | 1.81 | 2.785(2) | 162.5 |
| | C10–H10···O3 | 2.43 | 3.330(2) | 139.6 |
| | C6–H6C···O3 | 2.49 | 3.484(2) | 151.5 |
| | C9–H9···O4 | 2.43 | 3.358(3) | 142.8 |
| | C17–H17···O1 | 2.18 | 3.201(2) | 155.9 |
| **6•BPNO•H$_2$O** | N3–H3···O6 | 1.73 | 2.743(2) | 178.5 |
| | C8–H8···O3 | 2.67 | 3.643(2) | 149.2 |
| | O6–H6A···O1 | 1.72 | 2.690(2) | 169.3 |
| | O6–H6B···O1 | 1.74 | 2.721(2) | 173.4 |
| | N4–H4···O2 | 1.76 | 2.749(2) | 164.7 |
| | C1–H1···O3 | 2.23 | 3.171(2) | 143.8 |
| | C2–H2···O6 | 2.32 | 3.253(3) | 143.1 |
| | C9–H9···O2 | 2.13 | 3.190(3) | 163.7 |

[a] N–H, O–H and C–H distances are neutron normalized to 1.009, 0.983 and 1.083 respectively.
[b] *Syn* and *anti* refer to primary amide N–H donors.

**Table S2.** IR stretching frequency (KBr, $cm^{-1}$) of the N–H group in pyridine *N*-oxides compared to starting pyridyl-amides.

| Pyridine amide | Pyridine *N*-oxide amide |
|---|---|
| Isonicotinamide 3368, 3184 | Isonicotinamide *N*-oxide **1** 3350, 3153 |
| Nicotinamide 3368, 3159 | Nicotinamide *N*-oxide **2** 3298, 3144 |
| Picolinamide 3435, 3171 | Picolinamide *N*-oxide **3** 3250, 3103 |
| Pyrazinamide 3416, 3290 | Pyrazinamide-4-*N*-oxide **4** 3381, 3194 |
| Phenobarbital 3306 | **5**•$(BPNO)_{0.5}$ 3186 |
| Barbituric acid 3182, 3096 | **6**•BPNO•$H_2O$ 3101, 3007 |

**Table S3.** Torsion angle (O–N–$O^-$–C, # atoms) in amide–*N*-oxide heterosynthon.

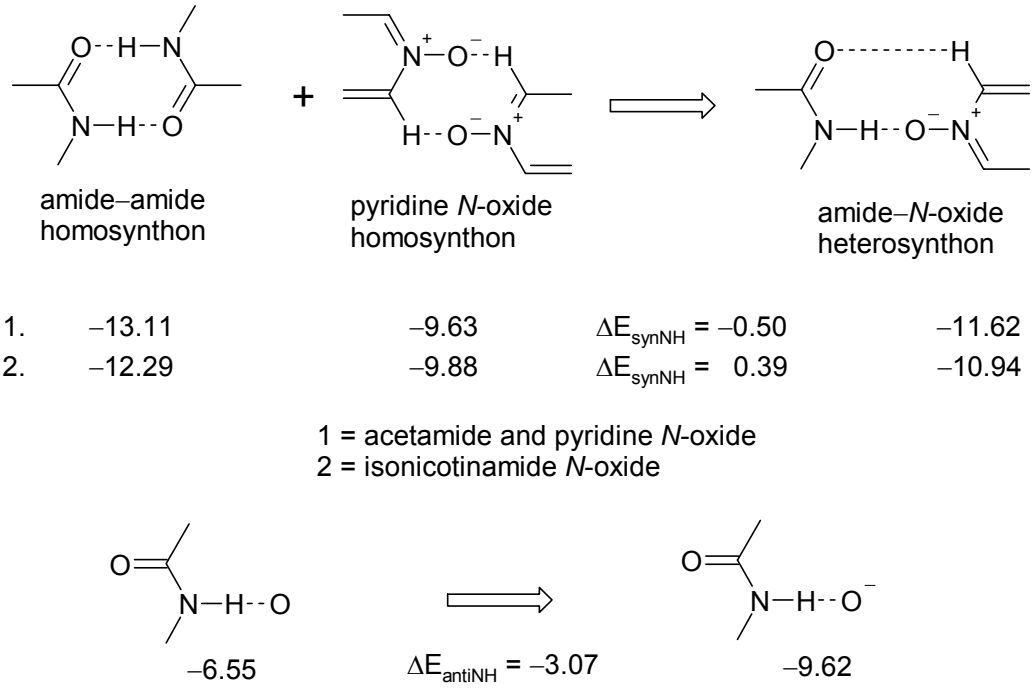


| Compound | Torsion angle (º) |
|---|---|
| Isonicotinamide *N*-oxide **1** | 12.5 |
| Nicotinamide *N*-oxide **2** | 25.1 |
| Picolinamide *N*-oxide **3** | absent |
| Pyrazinamide-4-*N*-oxide **4** | 10.1, 14.3 |
| Phenobarbital•$(BPNO)_{0.5}$ | 21.0 |
| Barbituric acid•BPNO•$H_2O$ | 40.3 |

**Hydrogen bond energy calculations in Spartan 04**

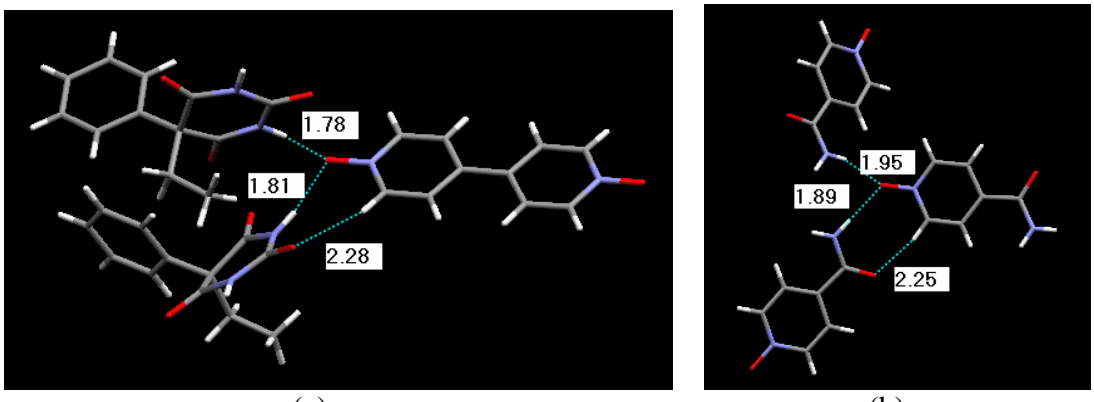
The energy of hydrogen bond synthons was calculated on model compounds acetamide, pyridine *N*-oxide and isonicotinamide *N*-oxide using the method reported by us in ref. 16.

The amide–*N*-oxide heterosynthon is stabilized by ~0.5 kcal/mol compared to homosynthons, amide and pyridine *N*-oxide dimers, when the *syn* NH of the amide group is considered (Scheme S1). In addition the *anti* NH engages in N–H···$O^-$ bond with *N*-oxide compared to N–H···O in the amide tape. The energy of a single N–H···$O^-$ is estimated as: heterosynthon = –11.62 kcal/mol = N–H···$O^-$ + C–H···O hydrogen bonds. If the $sp^2$ hybridized C–H···O interaction is ~2 kcal/mol, the N–H···$O^-$ bond = –9.62 kcal/mol. The energy of a single neutral N–H···O in amide dimer = 13.11 ÷ 2 = –6.55 kcal/mol. So the enthalpic advantage in the heterosynthon compared to competing homosynthons, designated as $\Delta E_{HB}$, is ~3.0 kcal/mol. This energy difference looks chemically reasonable because both N–H donors form stronger N–H···$O^-$ hydrogen bonds in amide *N*-oxide structures whereas pyridyl amides have neutral N–H···O/ N–H···N hydrogen bonds.




**Scheme S1.** Hydrogen bond energy calculation in model compounds.

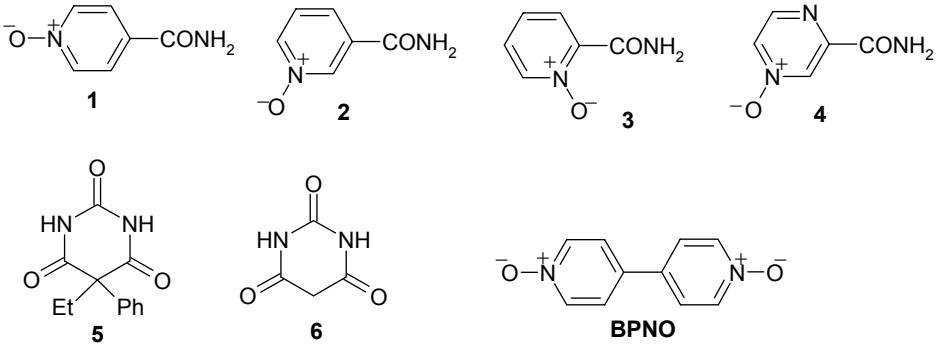
The above enthalpy calculation is also valid in the cocrystal of phenobarbital and BPNO, **5**•$(BPNO)_{0.5}$, because CONH of two different molecules H bond with a pyridine *N*-oxide moiety such that there is one amide–*N*-oxide synthon and one N–H···$O^-$ H bond. In effect, two secondary amide groups in the cocrystal play the role of *syn* and *anti* NH donors in isonicotinamide *N*-oxide **1** (Figure S1). The H bond energy calculation is similar to give $\Delta E_{HB}$ ~3 kcal/mol.




(a) (b)

**Figure S1.** (b) Portion of the crystal structure of **5**•$(BPNO)_{0.5}$ to show the bifurcated $O^-$ as part of amide–*N*-oxide synthon and N–H···$O^-$ interaction. BPNO resides on the inversion center. (b) Identical bifurcated H bond motif in isonicotinamide *N*-oxide **1**.

## Crystal data for structures 1-6




Crystal data for **1**: $C_6H_6N_2O_2$, $M$ = 138.13, orthorhombic, space group $Pna2_1$, $a$ = 13.467(3), $b$ = 11.722(3), $c$ = 3.7370(10) Å, $V$ = 589.9(3) Å$^3$, $Z$ = 4, $\rho_{cal}$ = 1.555 g cm$^{-3}$, $T$ = 100(2) K, $\mu$ = 0.120 mm$^{-1}$, *F(000)* = 288, 1988 reflections measured, 679 independent, 625 observed reflections ($I > 2\sigma_1$), 99 parameters, $R1$ = 0.0687, $wR2$ = 0.1384 (all data).

Crystal data for **2**: $C_6H_6N_2O_2$, $M$ = 138.13, monoclinic, space group $P2_1/n$, $a$ = 11.0498(16), $b$ = 3.6869(5), $c$ = 15.019(2) Å, $\beta$ = 110.064(2)°, $V$ = 574.73(14) Å$^3$, $Z$ = 4, $\rho_{cal}$ = 1.596 g cm$^{-3}$, $T$ = 100(2) K, $\mu$ = 0.123 mm$^{-1}$, *F(000)* = 288, 3173 reflections measured, 1136 independent, 1061 observed reflections ($I > 2\sigma_1$), 99 parameters, $R1$ = 0.0379, $wR2$ = 0.1028 (all data).

Crystal data for **3**: $C_6H_6N_2O_2$, $M$ = 138.13, orthorhombic, space group *Pbca*, $a$ = 12.940(3), $b$ = 7.3496(19), $c$ = 13.087(3) Å, $V$ = 1244.6(5) Å$^3$, $Z$ = 8, $\rho_{cal}$ = 1.474 g cm$^{-3}$, $T$ = 298(2) K, $\mu$ = 0.114 mm$^{-1}$, *F(000)* = 576, 3790 reflections measured, 1219 independent, 905 observed reflections ($I > 2\sigma_1$), 99 parameters, $R1$ = 0.0504, $wR2$ = 0.1405 (all data).

Crystal data for **4**: $C_5H_5N_3O_2$, $M$ = 139.12, triclinic, space group *P*-1, $a$ = 5.403(3), $b$ = 7.508(4), $c$ = 14.978(8) Å, $\alpha$ = 96.838(9), $\beta$ = 97.094(9), $\gamma$ = 102.822(9)°, $V$ = 581.1(5) Å$^3$, $Z$ = 4, $\rho_{cal}$ = 1.590 g cm$^{-3}$, $T$ = 298(2) K, $\mu$ = 0.127 mm$^{-1}$, *F(000)* = 288, 5890 reflections measured, 2323 independent, 1829 observed reflections ($I > 2\sigma_1$), 197 parameters, $R1$ = 0.0669, $wR2$ = 0.1933 (all data).

Crystal data for **5•(BPNO)$_{0.5}$**: $C_{17}H_{16}N_3O_4$, $M$ = 326.33, monoclinic, space group $P2_1/c$, $a$ = 10.3768(12), $b$ = 15.8728(18), $c$ = 9.4522(11) Å, $\beta$ = 93.165(2)°, $V$ = 1554.5(3) Å$^3$, $Z$ = 4, $\rho_{cal}$ = 1.394 g cm$^{-3}$, $T$ = 100(2) K, $\mu$ = 0.101 mm$^{-1}$, *F(000)* = 684, 7009 reflections measured, 3072 independent, 2463 observed reflections ($I > 2\sigma_1$), 226 parameters, $R1$ = 0.0458, $wR2$ = 0.1154 (all data).

Crystal data for **6•BPNO•H$_2$O**: $C_{14}H_{14}N_4O_6$, $M$ = 334.29, orthorhombic, space group *Pbca*, $a$ = 16.2210(11), $b$ = 6.5971(5), $c$ = 27.0692(19) Å, $V$ = 2896.7(4) Å$^3$, $Z$ = 8, $\rho_{cal}$ = 1.533 g cm$^{-3}$, $T$ = 100(2) K, $\mu$ = 0.122 mm$^{-1}$, *F(000)* = 1392, 17132 reflections measured, 2844 independent, 2270 observed reflections ($I > 2\sigma_1$), 233 parameters, $R1$ = 0.0510, $wR2$ = 0.1204 (all data).

Amide N–H and $H_2O$ protons were refined from the difference Fourier map. C–H hydrogens were generated geometrically and allowed to ride on their parent atom. Structures were refined by the full matrix least-squares method in SHELX. The *R*-factor is reasonable in all crystal structures.