chemistry

MDPI

Assessment of Computational Tools for Predicting Supramolecular Synthons

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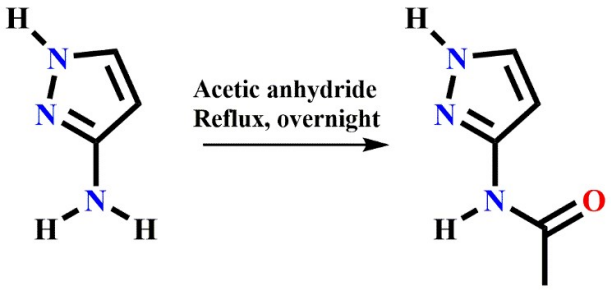
Contents:

Experimental section

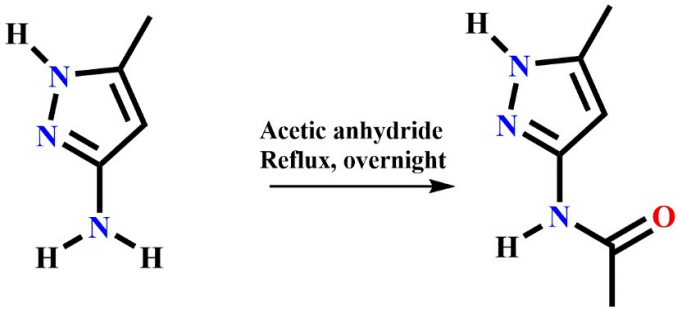
2-Amino-pyrazole, 2-amino-5-methyl-pyrazole, acetic anhydride, propionic anhydride and benzoyl chloride were purchased from Aldrich and utilized without further purification. Synthetic procedures and characterization of all molecules are provided in the Supporting Information (SI). Melting points were measured using Fisher-Johns melting point apparatus. ^{1}H NMR data were collected on a Varian Unity plus 400 MHz spectrophotometer in DMSO.

1.1 Synthesis of 3-acetamido-pyrazole, P1



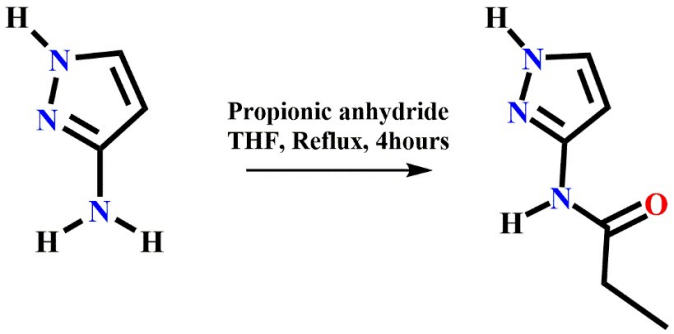
^{1}H-pyrazol-3-amine (0.486 g, 5.85 mmol) was dissolved in 50 mL of distilled water. $NaHCO_3$ (1.465 g, 17.4 mmol) was slowly added. Acetic anhydride (5ml) was then added dropwise and the resulting suspension was heated at reflux overnight. Then, the mixture was allowed to cool to room temperature and the solid obtained was filtered off and characterized as the title compound. After concentration of the filtrate, a second precipitate was obtained and also characterized as the title compound. 66% yield, m.p 218-220°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.23 (br s, 1H), 10.42 (br s, 1H), 7.54 (br s, 1H), 6.44 (br s, 1H), 1.97 (s, 3H).

1.2 Synthesis of 3-acetamido-5-methyl-pyrazole, P2



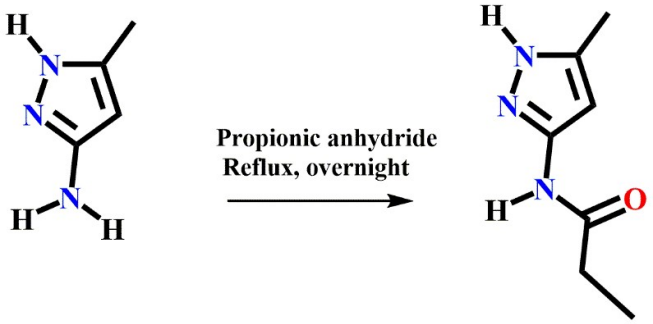
^{1}H-pyrazol-5-methyl-3-amine (2.25 g, 2.30mmol) was dissolved in 20 mL of distilled water. $NaHCO_3$ (5.8 g, 6.9 mmol) was slowly added. Acetic anhydride (8ml) was then added dropwise and the resulting suspension was heated at reflux overnight. Then, the mixture was allowed to cool down to room temperature and the solid obtained was filtered off and characterized as the title compound. 74 % yield, m.p. 215-218°C, ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.89 (s, 1H), 10.16 (s, 1H), 6.22 (s, 1H), 2.16 (s, 3H), 1.94 (s, 3H).

1.3 Synthesis of 3-propamido-pyrazole, P3



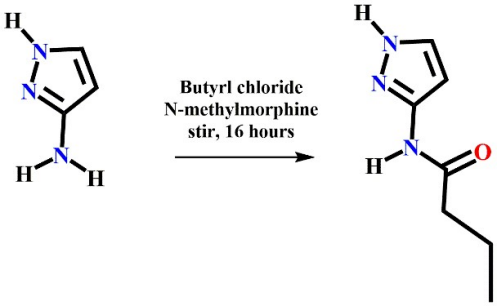
3-amino-^{1}H-pyrazole (0.486 g, 5.85 mmol) was dissolved in 10ml tetrahydrofuran in a 50ml round bottomed flask. 1 to 1.3 equivalence of propionic anhydride was added to the mixture and the resulting mixture was refluxed at 60-65 °C for 4 hours, monitored with TLC and after completion the excess solvent was removed by rotatory evaporation. The product was recrystallized from methanol to obtain the white solid as the pure product. Yield: 85%; mp 189-190˚C, ^{1}H NMR (δH; DMSO, 400MHz): ^{1}H NMR (δH; 400 MHz, DMSO-d_6): 12.26 (s, 1H), 10.29 (d, 1H), 7.56 (d, 1H), 6.48 (d,1H), 2.26 (q, 2H), 1.04 (t, 3H).

1.4 Synthesis of 3-propamido-5-methyl-pyrazole, P4



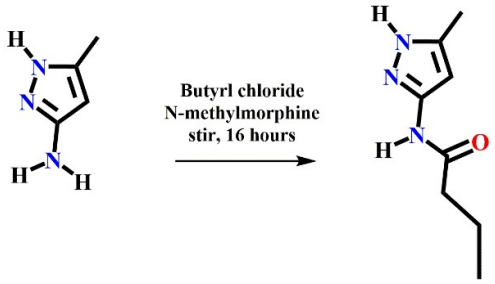
^{1}H-pyrazol-5-methyl-3-amine (2.25 g, 2.30mmol) was dissolved in 20 mL of distilled water. $NaHCO_3$ (5.8 g, 6.9 mmol) was slowly added. Propionic anhydride (10ml) was then added dropwise and the resulting suspension was heated at reflux overnight. Then, the mixture was allowed to cool down to room temperature and the solid obtained was filtered off and characterized as the title compound. 74 % yield, m.p. 189-190˚C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.92 (s, 1H), 10.15 (s, 1H), 6.25 (s, 1H), 2.26 (s, 3H), 2.17 (q, 2H), 1.03 (s, 3H).

1.5 Synthesis of 3-butyramido pyrazole, P5



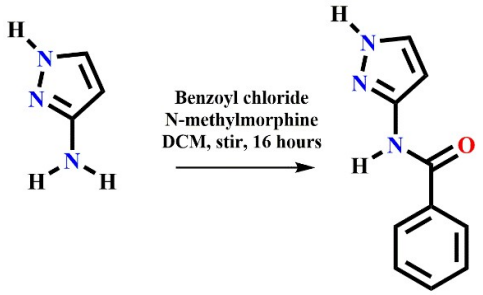
3-Aminopyrazole (0.499 g, 6.00 mmol) was dissolved in 30 mL of dichloromethane, 1.6 mL N-methylmorpholine (14.6 mmol), and 1.49 mL butyryl chloride (14.0 mmol). After stirring for 16 hours, the mixture sodium hydroxide was added dropwise, followed by 10 mL of tetrahydrofuran. The mixture was allowed to sit for 15 minutes before being concentrated again and suspended in water. The tan precipitate was filtered, air dried, and finally recrystallized in methanol to yield white crystals. 66% yield, m.p. 130-141°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.24 (1H), 10.26 (1H), 7.55 (1H), 6.48 (1H), 2.24 (2H), 1.56 (2H), 0.88 (3H).was concentrated, and the residue was dissolved in 30 mL methanol. Then, 7 mL of 2.5M

1.6 Synthesis of 3-butyramido 5-methyl pyrazole, P6



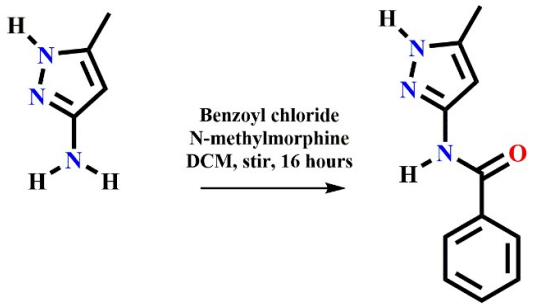
3-Amino-5-methylpyrazole (0.583 g, 6.00 mmol) was dissolved in 30 mL of dichloromethane, 1.6 mL N-methylmorpholine (14.6 mmol), and 1.49 mL butyryl chloride (14.0 mmol). After stirring for 16 hours, the mixture was concentrated, and the residue was dissolved in 30 mL methanol. Then, 7 mL of 2.5M sodium hydroxide was added dropwise, followed by 10 mL of tetrahydrofuran. The mixture was allowed to sit for 15 minutes before being concentrated again and suspended in water. The tan precipitate was filtered, air dried, and finally recrystallized in methanol to yield white crystals. ~70% yield, m.p. 184-189°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.90 (1H), 10.12 (1H), 6.25 (1H), 2.22 (2H), 2.17 (3H), 1.56 (2H), 0.87 (3H).

1.7 Synthesis of 3-benzamido-pyrazole, P7



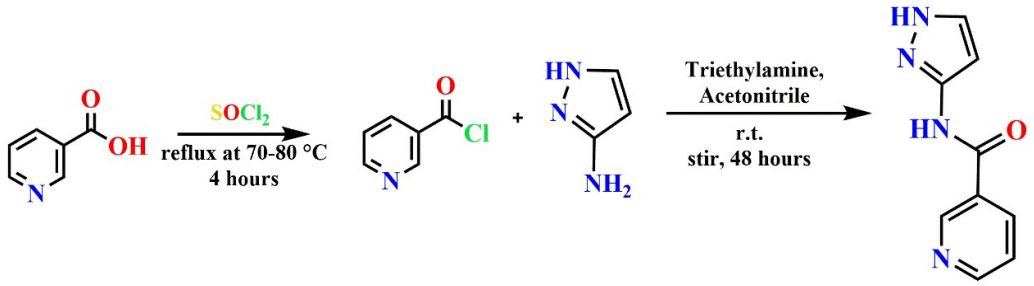
To a solution of 2.49 g of 3-amino-^{1}H-pyrazole in 150ml of dichloromethane, 8ml of n-methylmorpholine and 8ml of benzoyl chloride were added at room temperature. After 16 hours of stirring, the mixture was concentrated, and the residue was dissolved in 150ml of methanol. An amount of 3.5 g of sodium hydroxide in 35ml of water was added dropwise and 100ml of THF was added to obtain homogenous solution. After 15 minutes under stirring, the solution was filtered to get rid of the solid and the solution was concentrated and the solid obtained was poured into water. The precipitate obtained was filtered and air-dried to obtain the pure product in 86% yield, m.p. 162-164 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.47 (s, 1H), 10.83 (s, 1H), 8.00 (s, 1H), 7.66 (s, 3H), 7.50 (q, 2H), 6.63(s, 1H).

1.8 Synthesis of 3-benzamido-5-methyl-pyrazole, P8



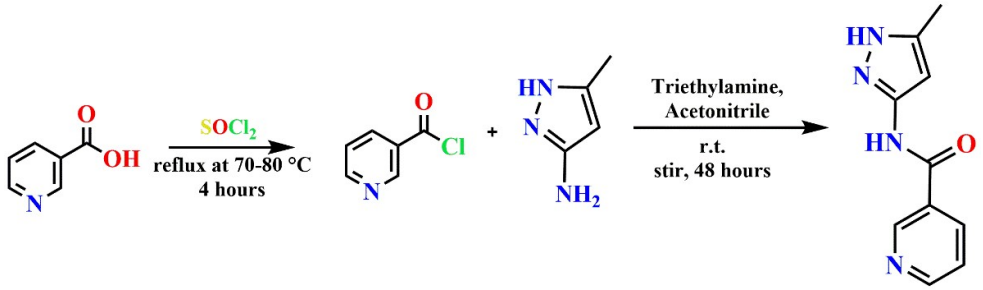
To a solution of 2.49 g of 3-amino-5methyl-pyrazole in 150ml of dichloromethane, 8ml of n-methylmorpholine and 8ml of benzoyl chloride were successfully added at room temperature. After 16 hours of stirring, the mixture was concentrated, and the residue was dissolved in 150ml of methanol. An amount of 3.5 g of sodium hydroxide in 35ml of water was added dropwise and 100ml of THF was added to obtain homogenous solution. After 15 minutes under stirring, the solution was filtered to get rid of the solid and the solution was concentrated and the solid obtained was poured into the water. The precipitate obtained was filtered and air-dried to obtain the pure product in 89% yield, m.p. 216-217 ˚C, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.12 (s, 1H), 10.67 (s, 1H), 7.98 (s, 1H), 7.53 (s, 3H), 7.48 (q, 2H), 6.40(s, 1H).

1.9 Synthesis of 3-pyridyl-pyrazole, P9



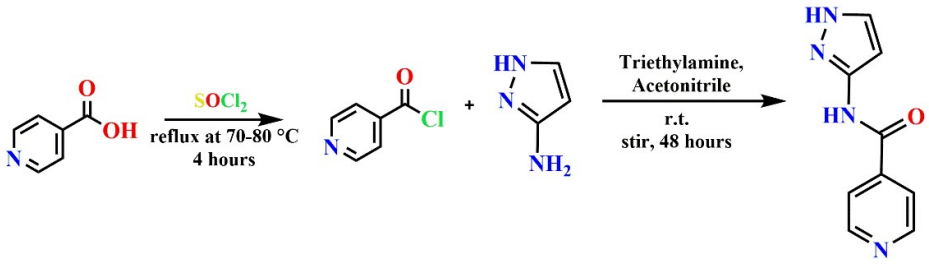
3-amino-1H-pyrazole (12mmol, 0.99g) was dissolved in 30 ml of acetonitrile. The resulting solution was treated with nicotinoyl chloride (12mmol, 1.70g) and triethylamine (2.0ml). The mixture was stirred at room temperature for 48 hours and monitored via TLC every 6 hours. Once, the reaction was completed, the organic phase was separated by filtration, washed with water and dried in air to get the white solid product. 84% yield, m.p. 226-227°C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 12.52 (s, 1H), 11.10 (s, 1H), 9.13 (s, 1H), 8.73 (s, 3H), 8.32 (s, 1H), 7.69(s, 1H), 7.53 (s,1H) and 6.66 (s, 1H).

1.10Synthesis of 3-pyridyl-5-methyl-pyrazole, P10



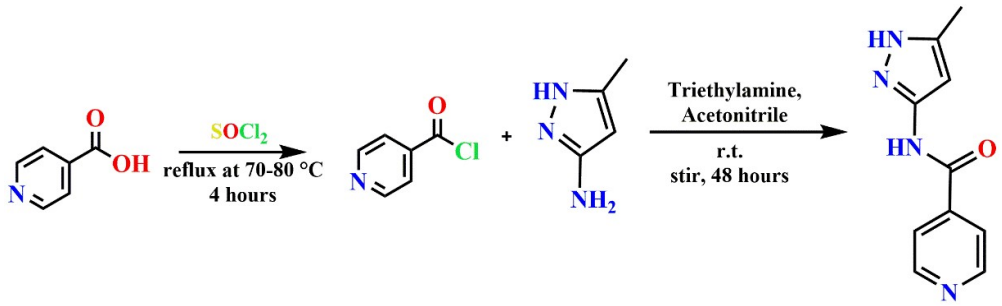
3-Amino-5-methyl-pyrazole (12mmol, 1.69g) was dissolved in 20 ml of acetonitrile. The resulting solution was treated with nicotinoyl chloride (12mmol, 1.70g) and triethylamine (1.6ml). The mixture was stirred at room temperature for 48 hours. The mixture was stirred at room temperature for 48 hours and monitored via TLC every 6 hours. Once, the reaction was completed, the organic phase was separated by filtration, washed with water and dried in air to get the yellow solid product in 85% yield, m.p. 205-207°C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 12.18 (s, 1H), 10.96 (s, 1H), 9.11 (s, 1H), 8.72 (s, 1H), 8.30(s, 1H), 7.52(s, 1H), 6.41 (s, 1H) and 2.23 (s, 3H).

1.11Synthesis of 4-pyridyl-pyrazole, P11



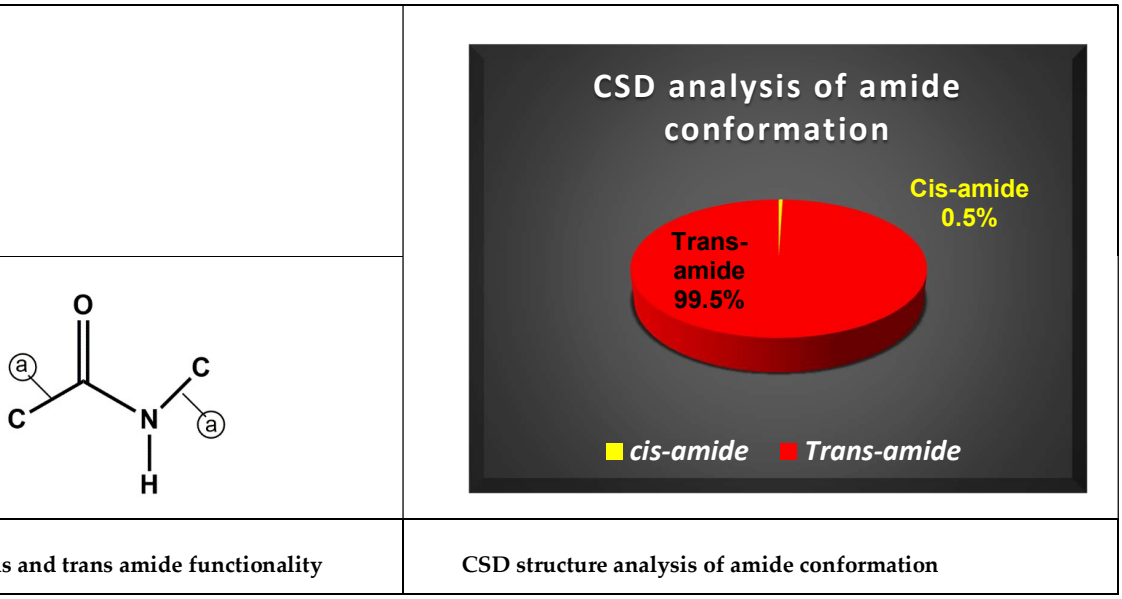
4-Amino-1H-pyrazole (12mmol, 0.99g) was dissolved in 20 ml of acetonitrile. The resulting solution was treated with nicotinoyl chloride (12mmol, 1.70g) and triethylamine (1.6ml). The mixture was stirred at room temperature for 48 hours. The mixture was stirred at room temperature for 48 hours and monitored via TLC every 6 hours. Once, the reaction was completed, the organic phase was separated by filtration, washed with water and dried in air to get the yellow solid product. 91% yield, m.p. 236-237°C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 12.55 (s, 1H), 11.17 (s, 1H), 8.74 (s, 1H), 7.89 (s, 1H), 7.69 (s, 1H), 6.65(s, 1H).

1.12Synthesis of 4-pyridyl-5-methyl-pyrazole, P12



3-Amino-5-methyl-pyrazole (12mmol, 1.69g) was dissolved in 20 ml of acetonitrile. The resulting solution was treated with isonicotinoyl chloride (12mmol, 1.70g) and triethylamine (1.6ml). The mixture was stirred at room temperature for 48 hours. The mixture was stirred at room temperature for 48 hours and monitored via TLC every 6 hours. Once, the reaction was completed, the organic phase was separated by filtration, washed with water and dried in air to get the yellow solid product in 94%yield, m.p. 241-242°C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ ppm: 11.31 (s, 1H), 10.13(s, 1H), 9.10 (s, 1H), 8.72 (s, 1H), 8.30(s, 1H), 7.83(s, 1H), 6.96 (s, 1H), 5.51 (s, 1H) and 1.32 (s, 3H).

2 Molecular conformation analysis of P1-P12



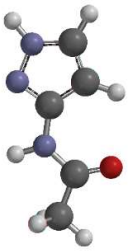
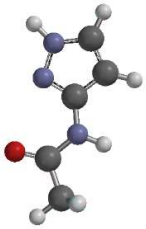
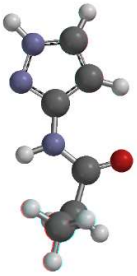
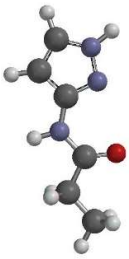
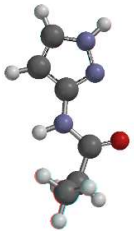
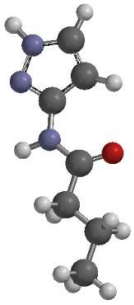
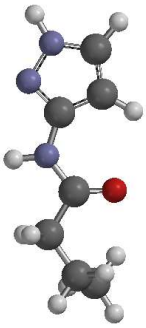
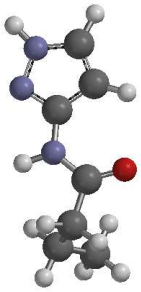
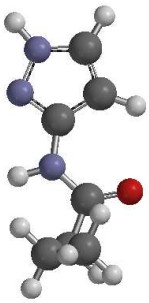
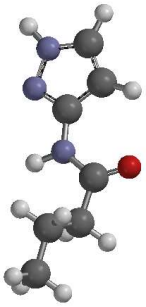
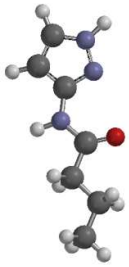
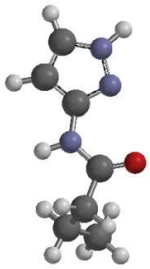
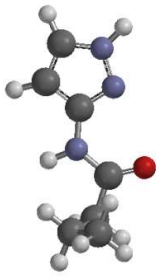
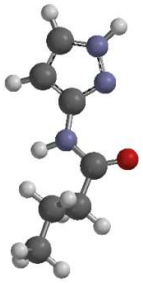
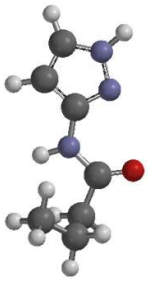
(a)cis and trans amide functionality	CSD structure analysis of amide conformation

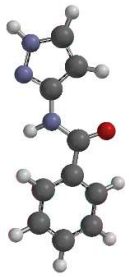
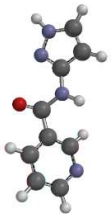
Figure S1. (**a**) *Cis* and *trans* amide functionality (both bonds are acyclic representing using symbol @) used to perform the torsion angle search. (**b**) Pie chart indicating number of structures with torsions for *cis* (yellow, ~32 structures, 0.5%) and *trans* (red, ~6303 Structures, 99.5%) conformations.

A CSD database search was performed to determine whether the molecules with amide functionality occur as *trans* conformation or *cis* conformation. A total of 6335 structures was obtained and approximately 30 (0.5%) of these structures have the *cis*-amide conformation and about 6300 structures (99%) have *trans*-amide conformation, Figure S1. Therefore, we determined the relative energy of all conformations with respect to most stable conformation with the restriction that all have a *trans*-configuration of the amide group (as suggested by the CSD analysis). Geometry optimization was performed on each conformation of **P1-P12** and the most stable conformation is given a value of 0 kJ/mol; all other conformations energies are presented relative to this, Table S1.

Table S1. Energies of each *trans* amide conformation relative to most stable *trans* conformation is shown below in kJ/mol. The conformations with duplicate energies were ignored. Note: methyl-based target molecule conformations are not shown here.

	Conformation 1	Conformation 2	Conformation 3	Conformation 4	Conformation 5

P1					
ΔE (P1)	**0**	**+50**			
ΔE (P2)	**0**	**+49**			
P3					
ΔE (P3)	**0**	**0**	**+50**	**+50**	
ΔE (P4)	**0**	**+4**	**+50**	**+53**	
P5					
ΔE (P5)	**0**	**0**	**+2**	**+2**	**+3**
ΔE (P6)	**0**	**0**	**+2**	**+3**	**+5**
P5					
ΔE (P5)	**+50**	**+51**	**+52**	**+53**	**+54**
ΔE (P6)	**+50**	**+50**	**+52**	**+53**	**+55**

P7					
ΔE (P7)	**0**	**+52**			
ΔE (P8)	**0**	**+51**			
P9/P10					
ΔE (P9)	**0**	**+4**	**+51**	**+55**	
ΔE (P10)	**0**	**+4**	**+51**	**+54**	
P11					
ΔE (P11)	**0**	**+52**			
ΔE (P12)	**0**	**+51**			

3 Molecular electrostatic potential (MEPs) calculations

Molecular electrostatic potential surfaces (MEPS) of **P1–P12** were generated with DFT B3LYP level of theory using 6-311++G** basis set in vacuum. All calculations were carried out using Spartan'08 software. All molecules were geometry optimized with the maxima and minima in the electrostatic potential surface (0.002 e/au isosurface) determined using positive point charge in the vacuum as a probe. The numbers indicate the interaction energy (kJ/mol) between the positive point probe and the surface of the molecule at that particular point. The Etter'r rule based on electrostatic potentials was used to determine the best donor-best acceptor interaction.

4 Hydrogen-bond energies (HBE) for synthon predictions

The synthon predictions for pure compounds **P1-P12** was made by calculating interaction energies to determine which of the three postulated synthons is most likely to appear in the crystal structures of the pure compounds. The hydrogen-bond parameters, α (hydrogen-bond donor) and β (hydrogen-bond acceptor) is determined using maxima and minima on the MEPS respectively (Equation S1 and S2), and the free energy of interaction is given by the product, $-\alpha\,\beta$[1]. The

$$\alpha = 0.0000162\ MEPmax^2 + 0.00962 MEP_{max} \quad \text{(Equation S1)}$$

$$\beta = 0.000146\ MEPmin^2 - 0.00930 MEP_{min} \quad \text{(Equation S2)}$$

$$E = -\sum_{ij} \alpha_i \beta_j \quad \text{(Equation S3)}$$

Table S2. Hydrogen-bond energies (in kJ/mol) for each individual synthon for molecules **P1**-**P12**. Synthon A and C are dimeric synthons; therefore, energies are presented for pairs of molecules.

	Synthon A		Synthon B	Synthon C		Synthon D	Synthon E	Synthon F
	Monomeric	Dimeric	Monomeric	Monomeric	Dimeric	Monomeric		
P1	-15.86	-31.71	-26.53	-12.37	-24.73	-20.69		
P2	-16.57	-33.14	-25.95	-13.27	-26.55	-20.79		
P3	-15.98	-31.95	-25.43	-12.35	-24.70	-19.66		
P4	-17.12	-34.25	-25.01	-13.44	-26.88	-19.63		
P5	-16.24	-32.49	-25.79	-12.57	-25.14	-19.96		
P6	-16.94	-33.88	-25.01	-13.38	-26.76	-19.75		
P7	-15.67	-31.35	-24.91	-11.21	-22.42	-17.81		
P8	-16.57	-33.14	-24.39	-11.99	-23.99	-17.65		
P9	-13.55	-27.10	-21.68	-10.78	-21.56	-17.24	-22.31	-17.75
P10	-14.83	-29.66	-19.38	-11.04	-22.07	-14.42	-22.82	-16.98
P11	-12.89	-25.78	-19.22	-10.25	-20.50	-15.29	-20.64	-16.41
P12	-13.79	-27.58	-19.41	-10.98	-21.96	-15.45	-20.80	-16.56

Table S3. Hydrogen-bond energies (in kJ/mol) for each combination synthon for molecules **P1**-**P12**.

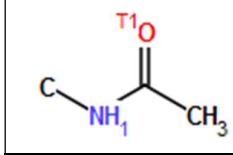
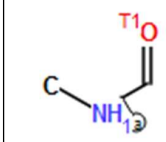
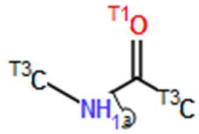
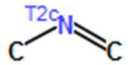
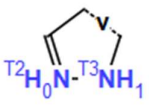
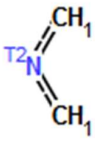
	Synthon (A+F)	Synthon (A+D)	Synthon (C+E)	Synthon C+B	Synthon (D+E)	Synthon (B+F)
	Dimeric	Dimeric	Dimeric	Dimeric		
P1	N/A	-52.40	N/A	-51.26	N/A	N/A
P2	N/A	-53.93	N/A	-52.50	N/A	N/A
P3	N/A	-51.61	N/A	-50.13	N/A	N/A
P4	N/A	-53.88	N/A	-51.89	N/A	N/A
P5	N/A	-52.44	N/A	-50.93	N/A	N/A
P6	N/A	-53.63	N/A	-51.77	N/A	N/A
P7	N/A	-49.16	N/A	-47.32	N/A	N/A
P8	N/A	-50.80	N/A	-48.38	N/A	N/A
AVG	N/A	-52.23	N/A	-50.52	N/A	N/A
S.Dev	N/A	1.67	N/A	1.81	N/A	N/A
P9	-44.85	-44.34	-43.87	-43.23	-39.55	-39.42

P10	-46.64	-44.08	-44.89	-41.45	-37.24	-36.36
P11	-42.19	-41.07	-41.14	-39.73	-35.93	-35.64
P12	-44.14	-43.03	-42.76	-41.36	-36.25	-35.97
AVG	-44.46	-43.13	-43.17	-41.44	-37.24	-36.85
S.Dev	1.84	1.49	1.61	1.43	1.64	1.74

5 Hydrogen-bond propensities (HBP) for synthon predictions

To complement the electrostatic-based calculations, we used hydrogen-bond propensity calculations (CSD Version 5.38 and Mercury 3.9) to predict the synthons in the pure compounds **P1-P12**. Each compound was sketched and auto-edited, a careful selection of functional groups (Table 2.3) and training dataset (350-500) was made and the propensities were calculated with an ROC curve higher than 0.831 ("excellent discrimination"). The propensity was used to determine the most likely synthon in these molecules.

Table S4. Functional groups used to determine the hydrogen-bond propensities for the **P1-P12** target molecules. The labels in the figures can be explained as follows: Tn = atom makes n bonds, c = atom is cyclic, ⑥ = bond is acyclic, and Hn = n bonded hydrogen atoms.

					
P1/P2	**P3/P4/P5/P6**	**P7-P12**	**P1-P12**	**P1-P12**	**P9-P12**

The propensities calculations consider all possible interactions between two donors (pyrazole NH and amide NH) and two acceptors (pyrazole N and C=O) resulting in four propensity numbers for **P1**-**P8**. In molecules with an additional acceptor group **P9**-**P12**, six different combinations of propensities are calculated. The propensity of individual and combination synthon is presented in Table S5 and S6.

Table S5. Hydrogen-bond propensities for each individual synthon possible in molecules **P1-P12**.

	Synthon A	**Synthon B**	**Synthon C**	**Synthon D**	**Synthon E**	**Synthon F**
P1	0.65	0.69	0.49	0.54		
P2	0.63	0.76	0.39	0.55		
P3	0.68	0.75	0.48	0.57		
P4	0.69	0.73	0.51	0.56		
P5	0.61	0.69	0.45	0.54		
P6	0.62	0.73	0.44	0.56		
P7	0.57	0.51	0.38	0.32		
P8	0.51	0.49	0.34	0.32		
P9	0.48	0.48	0.27	0.27	0.69	0.47
P10	0.48	0.47	0.27	0.26	0.71	0.49
P11	0.45	0.48	0.25	0.27	0.69	0.47

P12	0.45	0.47	0.25	0.27	0.7	0.49

Table S6. Hydrogen-bond propensities for combination synthons possible in molecules **P1-P12**. Combination synthon propensities are calculated by multiplying the individual synthon propensities.

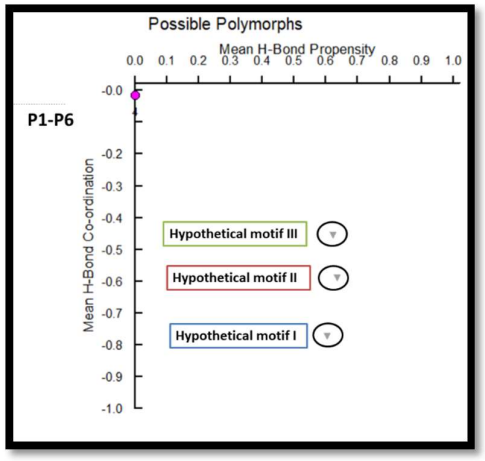
	Synthon (A+F)	**Synthon (A+D)**	**Synthon (C+E)**	**Synthon C+B**	**Synthon (D+E)**	**Synthon (B+F)**
P1	N/A	0.35	N/A	0.34	N/A	N/A
P2	N/A	0.35	N/A	0.30	N/A	N/A
P3	N/A	0.39	N/A	0.36	N/A	N/A
P4	N/A	0.39	N/A	0.37	N/A	N/A
P5	N/A	0.33	N/A	0.31	N/A	N/A
P6	N/A	0.35	N/A	0.32	N/A	N/A
P7	N/A	0.18	N/A	0.19	N/A	N/A
P8	N/A	0.16	N/A	0.17	N/A	N/A
P9	0.23	0.13	0.19	0.13	0.19	0.23
P10	0.24	0.12	0.19	0.13	0.18	0.23
P11	0.21	0.12	0.17	0.12	0.19	0.23
P12	0.22	0.12	0.18	0.12	0.19	0.23

6 Hydrogen-bond coordination (HBC)

Because of the presence of multifunctional groups on each molecule, there is chance of synthon polymorphism and synthon crossover. Each molecule was run through a polymorph assessment analysis in the propensity tool and compared to experimentally obtained structure. In order to determine whether the target molecules **P1-P12** have the chance to form synthon polymorphs, propensity-coordination analysis was performed on each molecule and the most optimal hydrogen-bond motif was obtained.

The hydrogen-bond coordination tool was used to determine the coordination of each functional group which will guide us to determine which synthon is most likely to happen. The propensity-coordination chart and the corresponding coordination for each hypothetical motif is shown in Figure S2-S5.

P1-P6

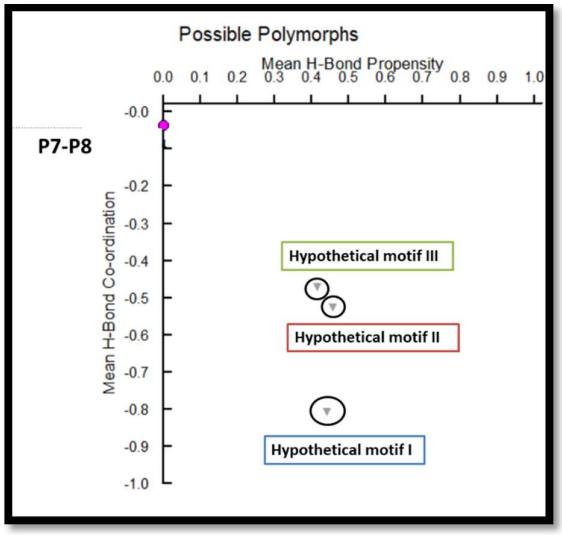


Motif #	Atom (D/A)	0	1	2	3
III	NH of pyrazole (d)	0.01	0.61	0.39	0.00
	NH of amide (d)	0.00	0.96	0.04	0.00
	N of pyrazole (a)	0.12	0.88	0.00	0.00
	O=C of amide (a)	0.02	0.74	0.23	0.01
I	NH of pyrazole (d)	0.01	0.61	0.39	0.00
	NH of amide (d)	0.00	0.96	0.04	0.00
	N of pyrazole (a)	0.12	0.88	0.00	0.00
	O=C of amide (a)	0.02	0.74	0.23	0.01
II	NH of pyrazole (d)	0.01	0.61	0.39	0.00
	NH of amide (d)	0.00	0.96	0.04	0.00
	N of pyrazole (a)	0.12	0.88	0.00	0.00
	O=C of amide (a)	0.02	0.74	0.23	0.01

(a) Propensity-coordination chart **(b) Coordination table**

Figure S2. (a)Propensity-coordination chart of **P1-P6** molecules and (b) coordination of each functional group in all predicted motifs.

P7-P8

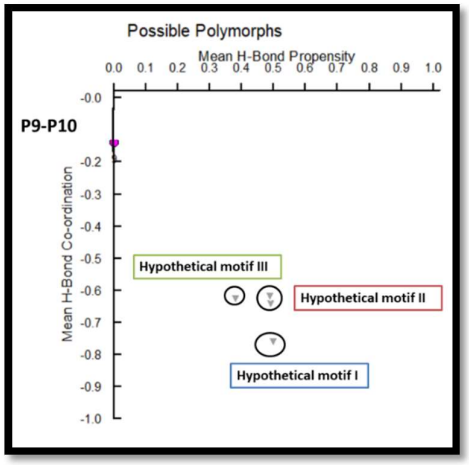


Motif #	Atom (D/A)	0	1	2	3
I	NH of pyrazole	0.01	0.72	0.27	0.00
	NH of amide	0.02	0.95	0.03	0.00
	N pyrazole	0.17	0.83	0.00	0.00
	O=C amide	0.04	0.82	0.14	0.00
III	NH of pyrazole	0.01	0.72	0.27	0.00
	NH of amide	0.02	0.95	0.03	0.00
	N pyrazole	0.17	0.83	0.00	0.00
	O=C amide	0.04	0.82	0.14	0.00
II	NH of pyrazole	0.01	0.72	0.27	0.00
	NH of amide	0.02	0.95	0.03	0.00
	N pyrazole	0.17	0.83	0.00	0.00
	O=C amide	0.04	0.82	0.14	0.00

(a) **Propensity-coordination chart** (b) **Coordination table**

Figure S3. Propensity-coordination chart of **P7-P8** molecules and the coordination of each functional group in all predicted motifs.

P9-P10

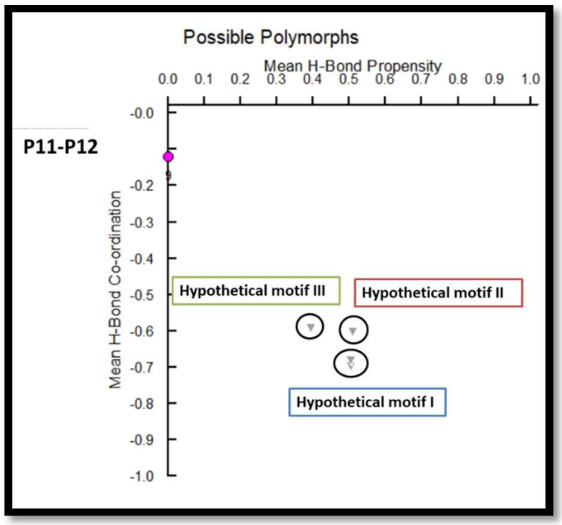


Motif #	Atom (D/A)	0	1	2	3
I	NH of pyrazole (d)	0.00	0.62	0.38	0.00
	NH of amide (d)	0.02	0.95	0.03	0.00
	N of pyridine (a)	0.11	0.81	0.08	0.00
	N pyrazole (a)	0.40	0.60	0.00	0.00
	C=O amide (a)	0.17	0.80	0.03	0.00
III	NH of pyrazole (d)	0.00	0.62	0.38	0.00
	NH of amide (d)	0.02	0.95	0.03	0.00
	N of pyridine (a)	0.11	0.81	0.08	0.00
	N pyrazole (a)	0.40	0.60	0.00	0.00
	C=O amide (a)	0.17	0.80	0.03	0.00
II	NH of pyrazole (d)	0.00	0.62	0.38	0.00
	NH of amide (d)	0.02	0.95	0.03	0.00
	N of pyridine (a)	0.11	0.81	0.08	0.00
	N pyrazole (a)	0.40	0.60	0.00	0.00
	C=O amide (a)	0.17	0.80	0.03	0.00

(a) Propensity-coordination chart **(b) Coordination table**

Figure S4. Propensity-coordination chart of **P9**-**P10** molecules and the coordination of each functional group in all predicted motifs.

P11-P12



Motif #	Atom (D/A)	0	1	2	3
I	NH of pyrazole (d)	0.01	0.83	0.16	0.00
	NH of amide (d)	0.01	0.96	0.03	0.00
	N of pyridine (a)	0.11	0.82	0.07	0.00
	N of pyrazole (a)	0.35	0.65	0.00	0.00
	C=O of amide (a)	0.19	0.78	0.03	0.00
III	NH of pyrazole (d)	0.01	0.83	0.16	0.00
	NH of amide (d)	0.01	0.96	0.03	0.00
	N of pyridine (a)	0.11	0.82	0.07	0.00
	N of pyrazole (a)	0.35	0.65	0.00	0.00
	C=O of amide (a)	0.19	0.78	0.03	0.00
II	NH of pyrazole (d)	0.01	0.83	0.16	0.00
	NH of amide (d)	0.01	0.96	0.03	0.00
	N of pyridine (a)	0.11	0.82	0.07	0.00
	N of pyrazole (a)	0.35	0.65	0.00	0.00
	C=O of amide (a)	0.19	0.78	0.03	0.00

(a) Propensity-coordination chart **(b) Coordination table**

Figure S5. Propensity-coordination chart of **P11-P12** molecules and the coordination of each functional group in all predicted motifs.

7 Crystal structures

P1-P12 were kept in a vial for slow evaporation methanol solvent in order to obtain crystals suitable for single crystal X-ray diffraction. If suitable crystals were not obtained in methanol, then different solvents were tried to grow crystals.

Table S7. Experimental details of crystals obtained in this study

	Molecules	Solvent used	Morphology	Melting point
Group 1	P1	Methanol	Block, colorless	218-220℃
	P2	Methanol	Plate, colorless	215-218℃
	P3	Methanol	Plates, colorless	189-190℃
	P4	Methanol	Block, colorless	189-190℃
	P5	Methanol	Crystals not solved	130-141℃
	P6	Methanol	Crystals not solved	184-189℃
	P7	Methanol	Block, colorless	162-163℃
	P8	Methanol	Prism, colorless	217-218℃
Group 2	P9	Methanol	Crystals not solved	227-228℃
	P10	Methanol	Block colorless	205-206℃
	P11	Methanol	Block colorless	236-237℃
	P12	Methanol	Crystals not solved	241-242℃

8 ^{1}H NMR for Target molecules

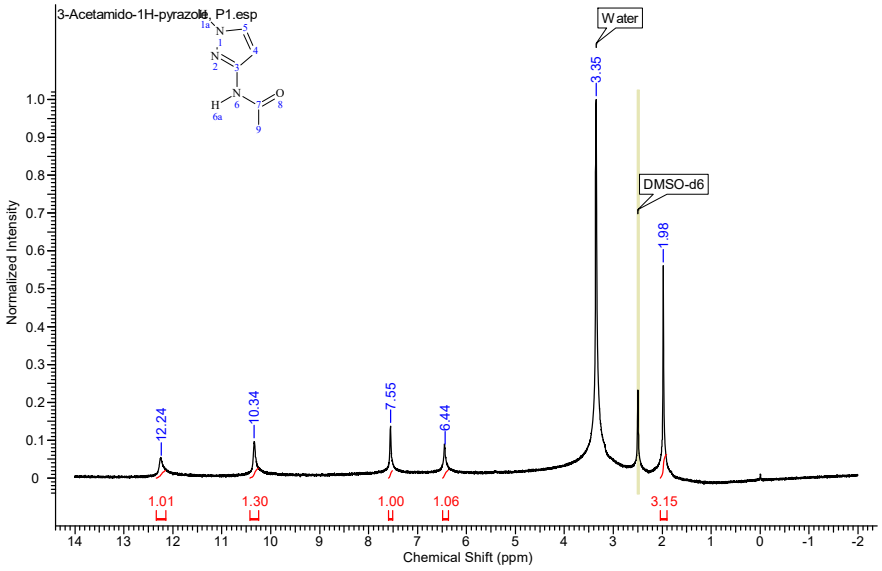


Figure S6. [1]H NMR of 3-acetamido-1H-pyrazole, **P1**.

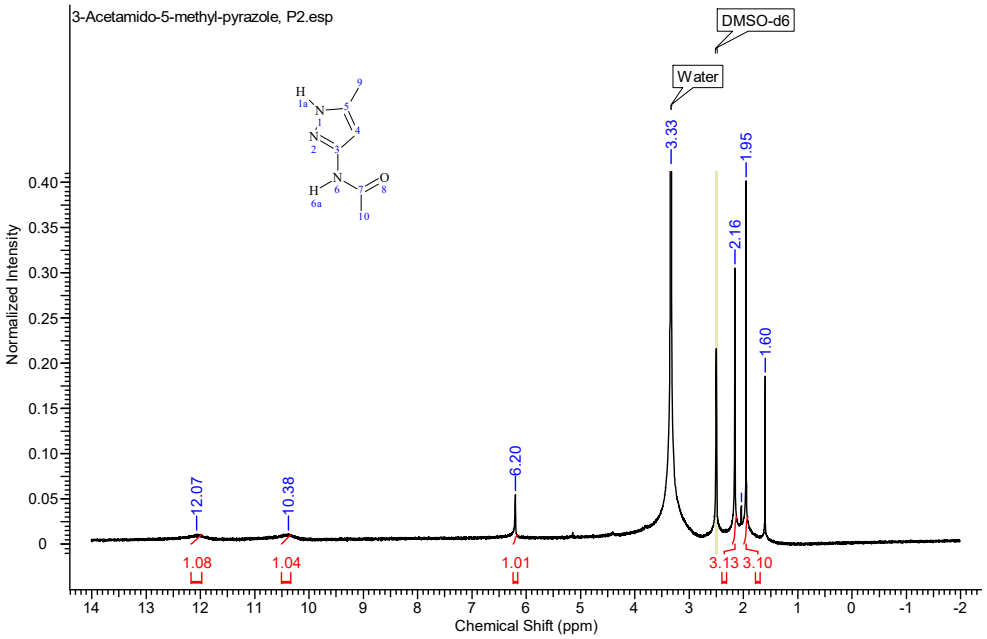


Figure S7. [1]H NMR of 3-acetamido-5methyl-1H-pyrazole, **P2**.

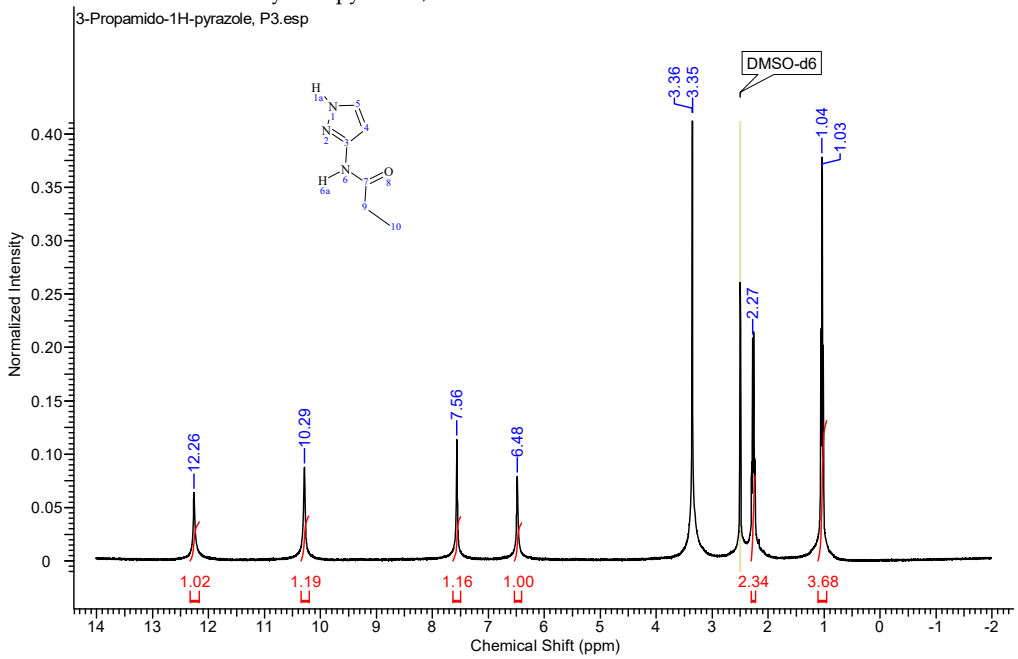


Figure S8. [1]H NMR of 3-propamido-1H-pyrazole, **P3**.

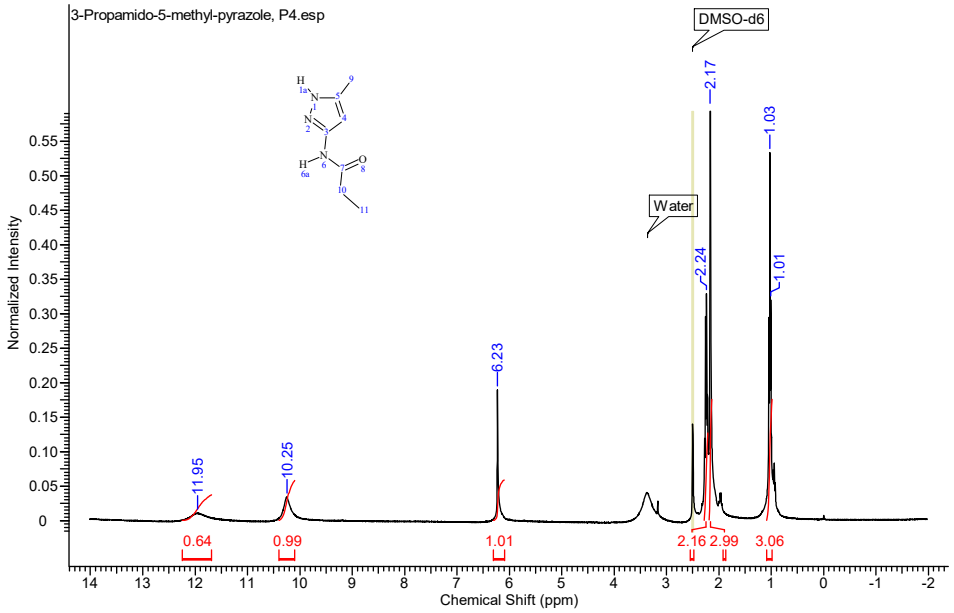


Figure S9. ^{1}H NMR of 3-propamido-5methyl-1H-pyrazole, **P4**.

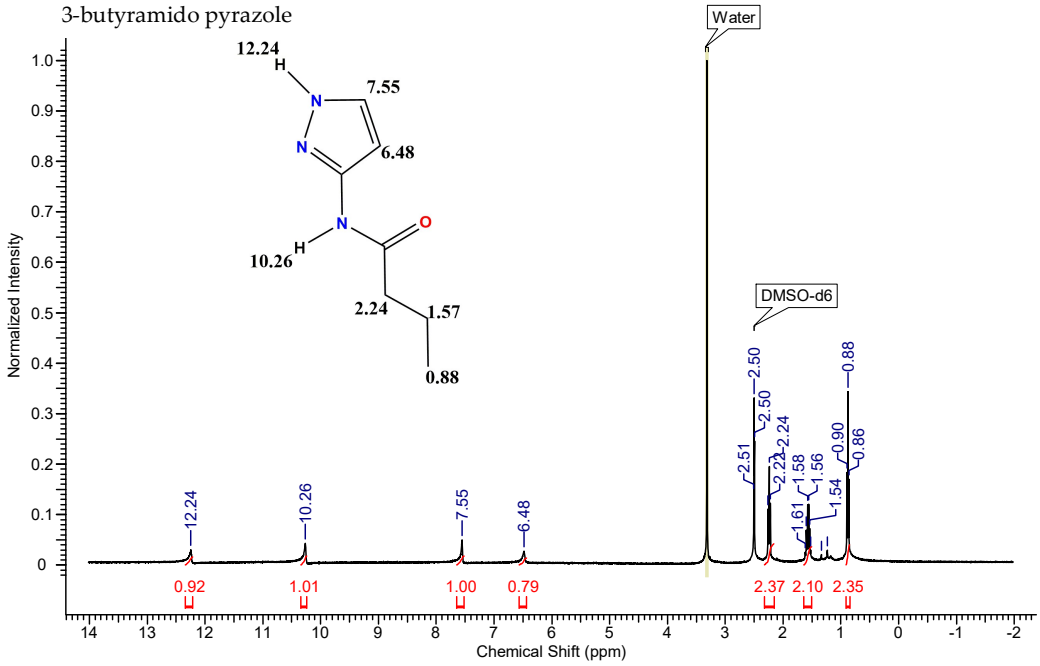


Figure S10. 1H NMR spectrum of 3-butyramido pyrazole, **P5**.

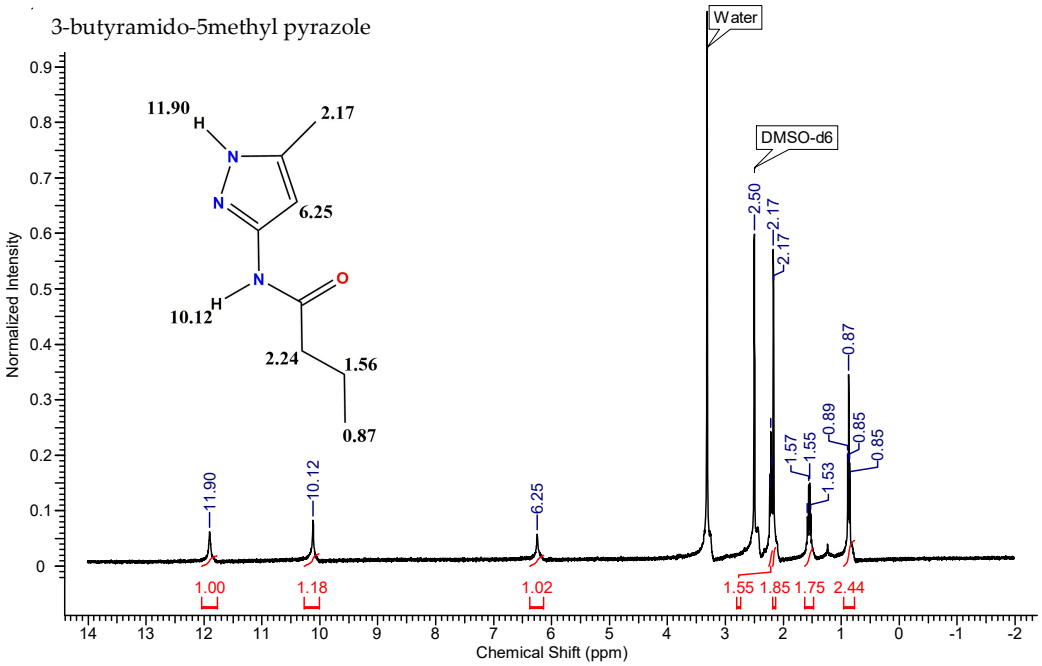


Figure S11. NMR spectrum of 3-butyramido 5-methyl pyrazole, **P6**.

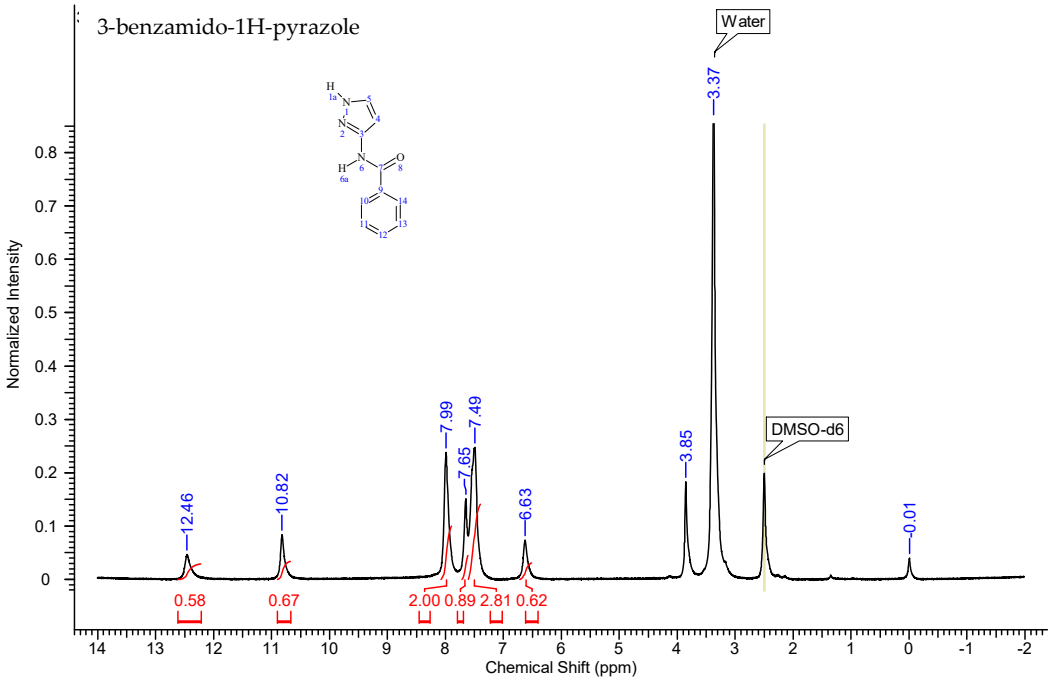


Figure S12. ^{1}H NMR of 3-benzamido-1H-pyrazole, **P7**.

3-benzamido-5methyl-1H-pyrazole

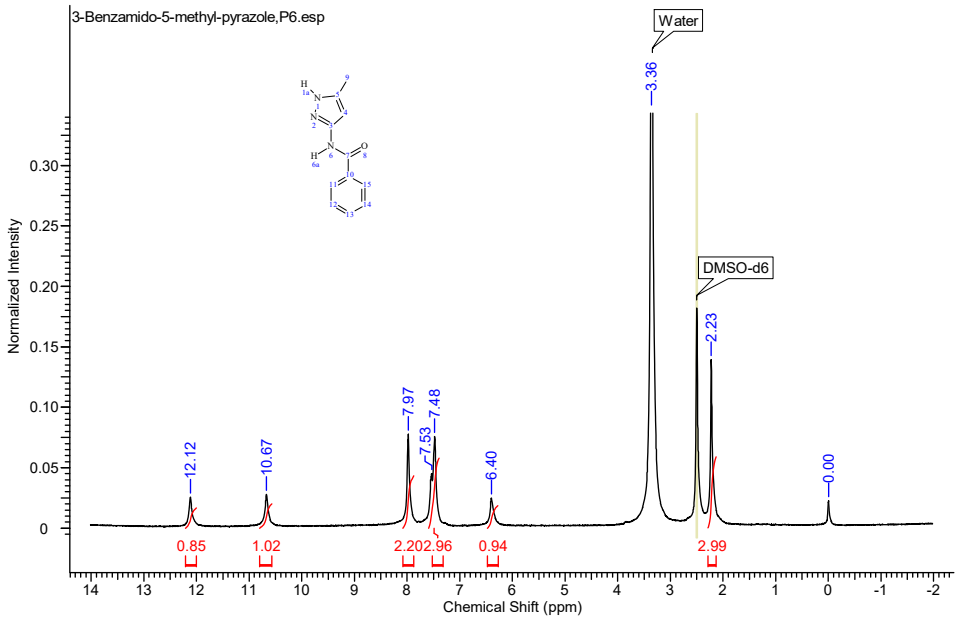


Figure S13. ^{1}H NMR of 3-benzamido-5methyl-1H-pyrazole, **P8**

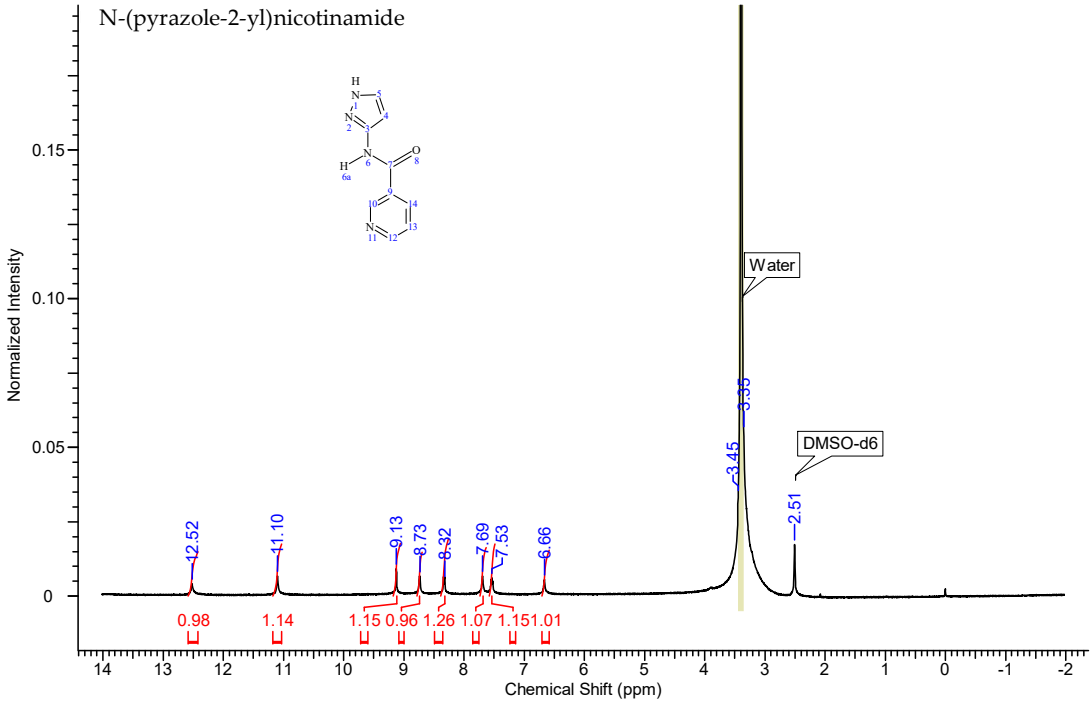


Figure S14. ^{1}H NMR of N-(pyrazole-2-yl)nicotinamide, **P9**.

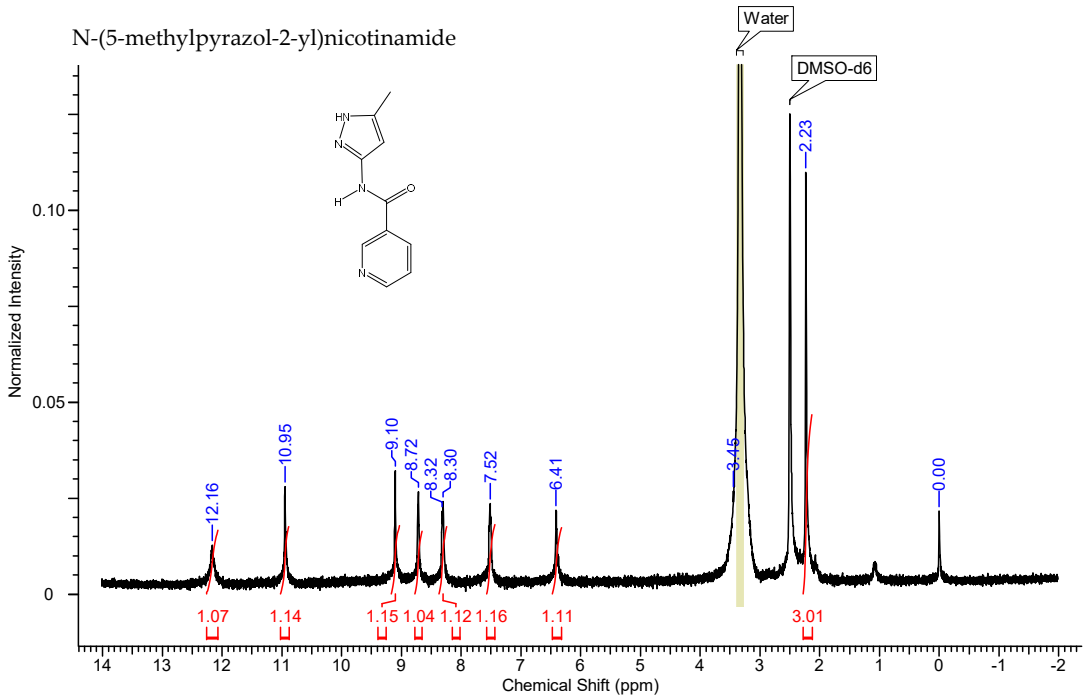


Figure S15. NMR spectrum of N-(5-methylpyrazol-2-yl)nicotinamide, **P10.**

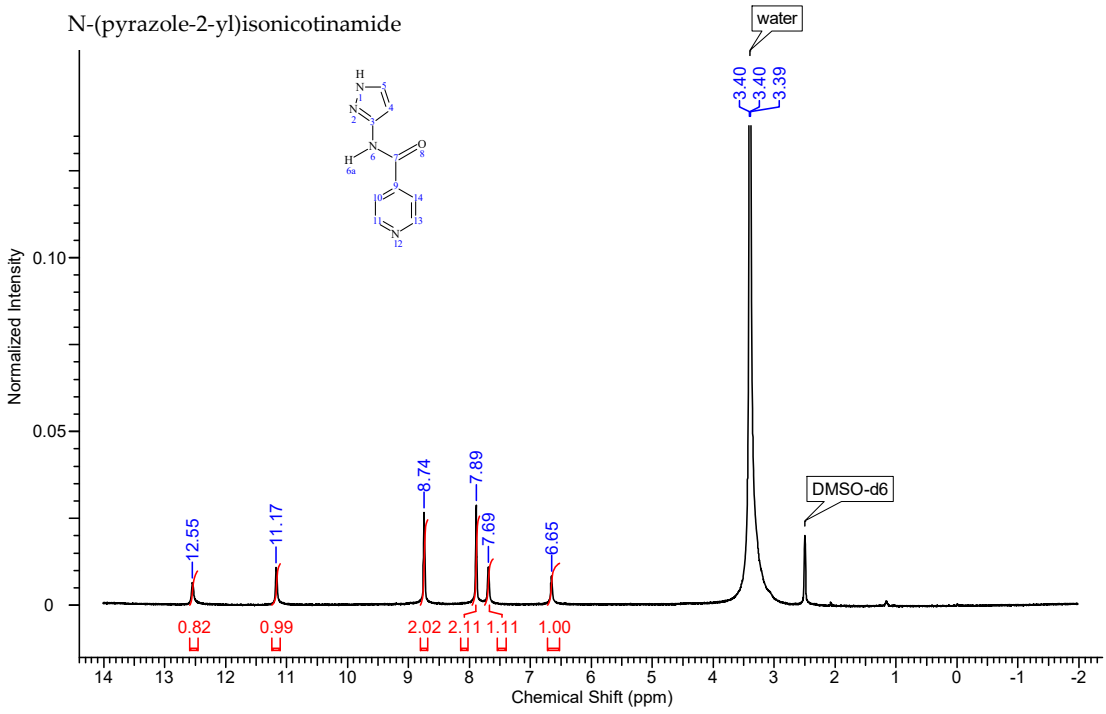


Figure S16. NMR spectrum of N-(pyrazole-2-yl)isonicotinamide, **P11.**

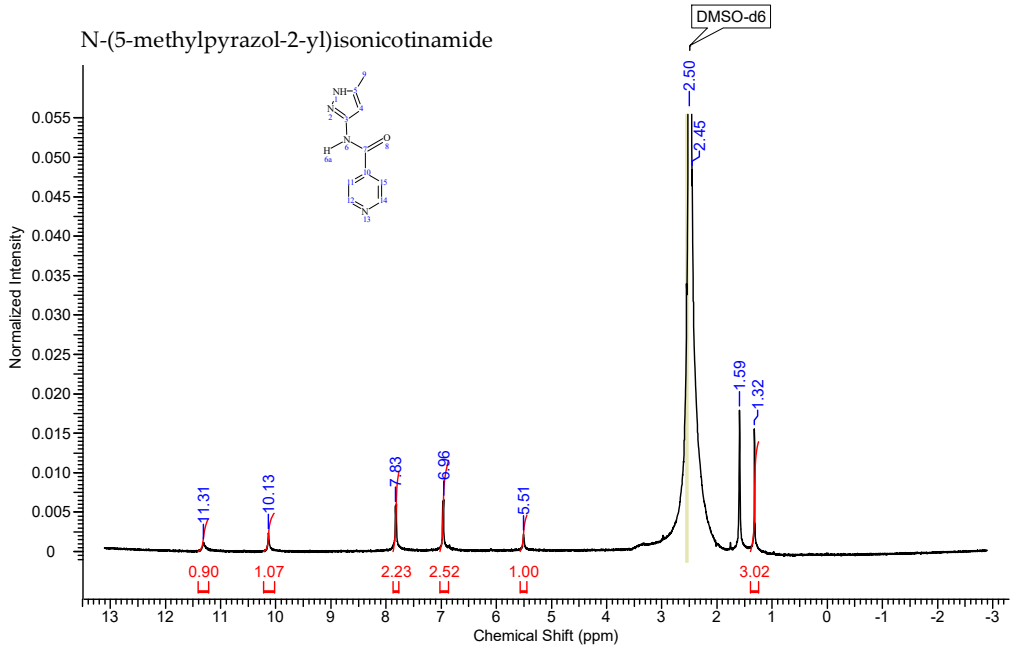


Figure S17. NMR spectrum of N-(5-methylpyrazol-2-yl)isonicotinamide, **P12.**

9 Crystallography experimental details

All datasets except those previously reported were collected on a Bruker Kappa APEX II system using MoKα radiation. Data were collected using APEX2 software[2]. Initial cell constants were found by small widely separated "matrix" runs. Data collection strategies were determined using COSMO[3]. Scan speed and scan widths were chosen based on scattering power and peak rocking curves. The unit cell constants and orientation matrix were improved by least-squares refinement of reflections thresholded from the entire dataset. Integration was performed with SAINT[4], using this improved unit cell as a starting point. Precise unit cell constants were calculated in SAINT from the final merged dataset. Lorenz and polarization corrections were applied. Multi-scan absorption corrections were performed with SADABS[5]. Data were reduced with SHELXTL[6]. The structures were solved in all cases by direct methods without incident. Except as noted, hydrogen atoms were located in idealized positions and were treated with a riding model. All non-hydrogen atoms were assigned anisotropic thermal parameters. Refinements continued to convergence, using the recommended weighting schemes. In structures P4 and P10, final structure solutions were performed using intrinsic phasing methods implemented with ShelXT and structure refinements were performed by least-squares refinements against |F|[7] followed by difference Fourier synthesis using ShelXL[8-10], implemented in Olex2 software packages [11].

CCDC 2072631-2072636 contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam. ac.uk.

9.1 Crystallographic data

Code	P1	P3	P4	P7	P10	P11
Formula moiety	$C_5H_7N_3O$	$C_6H_9N_3O$	$C_{14}H_{22}N_6O_2$	$C_{10}H_9N_3O$	$C_{10}H_{10}N_4O$	$C_9H_8N_4O$
Empirical formula	$C_5H_7N_3O$	$C_6H_9N_3O$	$C_{14}H_{22}N_6O_2$	$C_{10}H_9N_3O$	$C_{10}H_{10}N_4O$	$C_9H_8N_4O$
Molecular weight	125.14	139.16	306.37	187.20	202.22	188.19
Color, Habit	blocks, colorless	plates, colorless	Blocks, colorless	Blocks, colorless	Colorless, Plate	Blocks, Colorless
Crystal system	Monoclinic	orthorhombic	monoclinic	orthorhombic	orthorhombic	monoclinic
Space group, *Z*	P2(1)/c, 8	pbca, 16	Cc, 4	pbca, 16	Pna21, 4	C2/c, 8
***a*, Å**	15.212(4)	9.962(4)	7.570(2)	10.586(3)	21.043(11)	11.261(3)
***b*, Å**	11.424(3)	10.024(4)	21.799(6)	14.558(4)	8.832(5)	11.476(3)
***c*, Å**	7.214(2)	28.792(12)	10.659(3)	25.523(7)	5.500(3)	13.654(3)
***α*, °**	90.00	90.00	90	90.00	90.00	90
***β*, °**	102.42(2)	90.00	108.247(17)	90.00	90.00	103.67(2)
***γ*, °**	90.00	90.00	90	90.00	90.00	90
Volume, Å^3	1224.3(6)	2875.(2)	1670.5(8)	3933.4(19)	1022.2(10)	1714.5(7)
Density, g/cm^3	1.358	1.286	1.218	1.265	1.426	1.458

T, ºK	296(2)	296 (2)	130(2)	200 (2)	180.(2)	130(2)
Crystal size, min x mid x max	0.128X0.208X0.278	0.064X0.168X0.304	0.136X0.202X0.252	0.108X0.252X0.394	0.075x0.352x0.502	0.112X0.218X0.432
X-ray wavelength, Å	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
μ, mm^{-1}	0.100	0.092	0.086	0.086	0.091	0.102
Trans min / max	0.97/0.99	0.97, 0.99	0.98, 0.99	0.97/0.99	0.96/ 0.99	0.96/0.99
θ_{min}, °	2.25	2.83	1.87	2.50	1.94	2.57
θ_{max}, °	21.98	21.20	25.39	22.05	25.30	24.88
Reflections						
collected	30410	30040	1523	69812	23993	21370
independent	2263	2543	998	3486	1800	1565
observed	1384	1534	219	2093	1184	1260
R_{int}	0.1016	0.1286	0.1197	0.1294	0.4966	0.0487
Threshold expression	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)	> 2σ(I)
No. parameters	181	200	219	270	145	135
No. restraints	0	0	5	0	0	0
R_1 (observed)	0.0650	0.0580	0.1197	0.0518	0.0883	0.0381
wR_2 (all)	0.1730	0.1555	0.2232	0.1518	0.2194	0.1037
Goodness of fit (all)	1.051	1.034	1.075	1.037	0.976	1.073
ρ_{max}, ρ_{min}, e Å^{-3}	0.215,-0.241	0.641, -0.491	0.552, -0.600	0.195,-0.179	0.265,-0.341	0.226, -0.206
Completeness to 2θ limit	0.972	0.993	0.989	0.988	0.976	0.987

10 References

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