Electronic Supporting Information

Pyridine N-Oxides as Coformers in the Development of Drug Cocrystals

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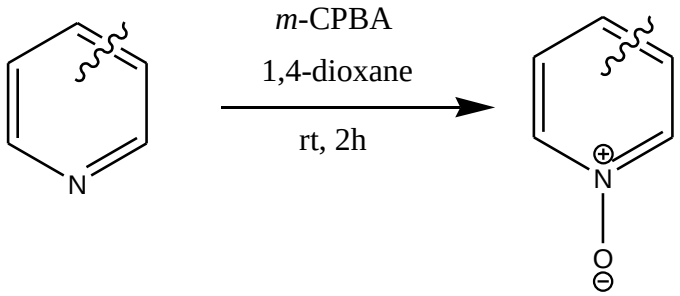
Table E1: Aqueous solubility of drugs

Drug	Solubility (mg/mL)	Reference	Cocrystal	Solubility (mg/mL)
PROP	0.157	1	C1	2.57
PABA	4.7	2	C2	10.70
FERU	0.78	3	C3	4.49
SULF	0.37	3	C4	11.00

*Solubility values for the parent API's is considered from literature

1. K. I. Momot, P. W. Kuchel, B. E. Chapman, P. Deo, and D. Whittaker, *Langmuir* 2003, **19**, 2088–2095.
2. B. Saikia, P. Bora, R. Khatioda, and B. Sarma, *Cryst. Growth Des.* 2015, **15**, 5593–5603.
3. D. S. Wishart, C. Knox, A. C. Guo, S. Shrivastava, M. Hassanali, P. Stothard, Z. Chang, and J. Woolsey, *Nucleic Acids Res.* 2006, **34,** 668–672.

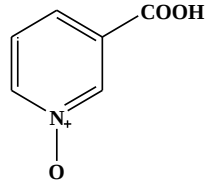
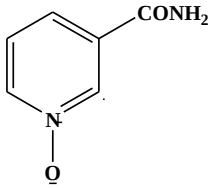
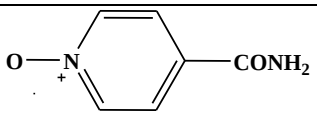
Scheme 1: Synthesis of pyridine *N*-oxides

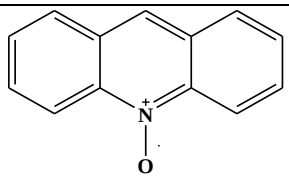
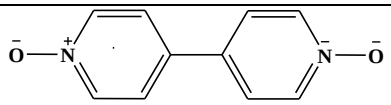
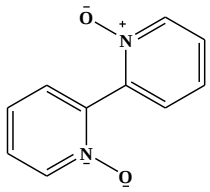


Procedure: Absolute amount of the substrate was added to about 5-7 mL of 1,4-dioxane and stir for 5 minutes at ambient condition. Stoichiometry amount of *m*-CPBA was added to the stirred solution. The homogeneous mixture was left stirring for about 20 minutes to 2 hours and monitored by TLC for completion. The precipitate was filtered, washed with cold dioxane and dried for further characterization. Results are summarized below in Table E2. Apart from dioxane the reaction was also carried out in water, acetonitrile, chloroform and methanol. Few other peracids v*iz*. H_2O_2, $K_2S_2O_7$ etc. were also introduced in the synthesis of pyridine *N*-oxides in search of suitable peracid for the listed *N*-heterocycles (Figure E1 & Table E3). FT-IR, ^{1}H- ^{13}C-NMR spectra of products are available in Figure E2.

Table E2: Synthesis of pyridine *N*-oxides and Characterization

Entry	Products	Reaction Time	Characterization

		(min)	
1	 Nicotinic acid-*N*-oxide	20	Yield % = 65; FT-IR (KBr, cm^{-1}): 464, 1273, 1484, 1576, 1716, 3079; 1H-NMR (400MHz, DMSO-D_6): δ (ppm) =7.50 (*t*, 1 H, *J* = 6.8 Hz), 7.72 (*d*, 1 H, *J* = 8.8 Hz), 8.38 (*d*, 1 H, *J* = 7.2 Hz), 8.43 (*s*, 1 H); 13C-NMR (DMSO-D6): δ (ppm) = 126.1, 127.2, 131.1, 139.4, 142.6, 165.0; Elemental analysis: Calculated: C, 51.56; H, 3.48; N, 10.10; O, 34.86; Experimental: C, 51.80; H, 3.62; N, 10.07; O, 34.50
2	 Nicotinamide-*N*-oxide	20	Yield % = 70; FT-IR (KBr, cm^{-1}): 498, 814, 884, 930, 1686, 3136; 1H-NMR (400MHz, D_2O): δ (ppm) =7.46 (*t*, 1H, *J* = 7.6 Hz), 7.68 (*d*, 1H, *J* = 8.4 Hz), 8.30 (*d*, 1H, *J* = 6.8 Hz), 8.54 (*s*, 1H); 13C-NMR (D_2O): δ (ppm) = 127.3, 130.7, 133.4, 138.5, 141.4, 167.3; Elemental analysis: Calculated, C, 52.15; H, 4.40; N, 20.36; O, 23.09; Experimental C, 52.17; H, 4.38; N, 20.28; O, 23.17
3	 Isonicotinamide-*N*-oxide	20	Yield % = 72; FT-IR (KBr, cm^{-1}): 464, 1395, 1495, 1685, 3157, 3349; 1H-NMR (400MHz, D_2O): δ (ppm) = 7.79 (d, 1H, *J* = 7.6 Hz), 8.26 (d, 1H, *J* = 6.8 Hz); 13C-NMR (D_2O): δ (ppm) = 125.6, 134.2, 138.6, 178.1; Elemental analysis: Calculated C, 52.15; H, 4.40; N, 20.36; O, 23.09; Experimental C, 52.17; H, 4.38; N, 20.28; O, 23.1

4	 Acridine-*N*-oxide	20	Yield % = 25; FT-IR (KBr, cm^{-1}): 750, 1304, 1417, 1575, 3073; ^{1}H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.53 (*t*, 1H, *J* = 7.6 Hz), 7.78 (*t*, 1H, *J* = 7.2 Hz) , 8.00 (*d*, 1H, *J* = 8.4 Hz), 8.24 (*d*, 1H, *J* = 8.8 Hz), 8.78 (*s*, 1H); ^{13}C-NMR (D_2O): δ (ppm) = 118.0, 120.1, 126.1, 128.8, 131.5, 141.7; Elemental analysis: Calculated, C, 80.20; H, 4.64; N, 7.00; O, 8.16; Experimental C, 79.98; H, 4.65; N, 7.17; O, 8.20
5	 4,4'-Bipyridine-*N*,*N*-dioxide	20	Yield % = 92; FT-IR (KBr, cm^{-1}): 834, 1240, 1320, 1468, 3063; 1H NMR (400MHz, D_2O): δ (ppm) = 7.85 (*d*, 1H, *J* = 7.6 Hz), 8.26 (*d*, 1H, *J*= 7.6 Hz); 13C-NMR (D_2O): δ (ppm) = 123, 132, 139; Elemental analysis: Calculated, C, 63.80; H, 4.36; N, 14.86; O, 16.98.; Experimental C, 63.82; H, 4.28; N, 14.89; O, 17.00
6	 2,2'-Bipyridine-*N*,*N*-dioxide	20	Yield % = 70; FT-IR (KBr, cm^{-1}): 768, 1146, 1250, 1428, 1660, 3039; 1H-NMR (400 MHz, DMSO-D_6): δ (ppm) = 7.61 (*t*, 2H), 7.70 (*d*, 1H, *J* = 8.4 Hz), 8.33 (*d*, 1H, *J* = 7.2 Hz); 13C-NMR (DMSO-D_6): δ (ppm) = 128.4, 128.8, 131.5, 139.6, 141.7; Elemental analysis: Calculated C, 63.80; H, 4.36; N, 14.86; O, 16.98.; Experimental C, 63.82; H, 4.28; N, 14.89; O, 17.00

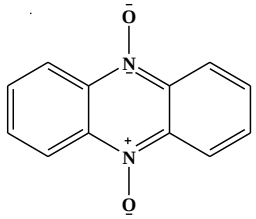
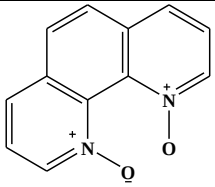
7	 Phenazine-*N*,*N*-dioxide	20	Yield % = 85; FT-IR (KBr, cm^{-1}): 766, 1092,1272, 1353; 1H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.85 (*t*, 2H, *J* = 3.6 Hz), 8.77 (*d*, 2H, *J* = 3.2 Hz); 13C-NMR ($CDCl_3$): δ (ppm) = 120.2, 131.3, 136.1; Elemental analysis: Calculated, C, 67.89; H, 3.35; N, 13.75; O, 15.01; Experimental- C, 67.92; H, 3.80; N, 13.20; O, 15.08
8	 1,10-Phenanthroline-*N*,*N*-dioxide	120	Yield % = 82; FT-IR (KBr, cm^{-1}): 898, 1263, 1486, 1574, 3076; 1H-NMR (400MHz, $CDCl_3$): δ (ppm) = 7.40 (*t*, 1H, *J* = 8 Hz), 7.58 (*d*, 1H, *J* = 8 Hz), 7.99 (*d*, 1H, *J* = 7.6 Hz, 8.08 (*s*, 1H); 13C-NMR ($CDCl_3$): δ (ppm) = 128.1, 129.3, 130.4, 132.6, 132.8, 134.0; Elemental analysis: Calculated, C, 67.89; H, 3.35; N, 13.75; O, 15.01; Experimental C, 67.92; H, 3.80; N, 13.20; O, 15.08

Table E3: Solvent screening for the synthesis of pyridine *N*-oxides

Entry	**% Isolated yield***				
	CH_3CN	$CHCl_3$	DCM	1,4-Dioxane	H_2O
1	Trace	Trace	Trace	65	Trace
2	Trace	Trace	Trace	70	Trace
3	Trace	Trace	Trace	72	Trace
4	Trace	Trace	Trace	25	Trace
5	20	60	52	92	Trace
6	15	50	44	70	Trace
7	Trace	Trace	Trace	85	Trace

8	Trace	Trace	Trace	82	Trace

* Nil to trace amount isolation of products could be because of the low or insoluble property of the starting materials in that solvent.

Figure E1: Bar diagram showing yield % of pyridine *N*-oxides with respect to H_2O_2, *m*-CPBA and TBHP

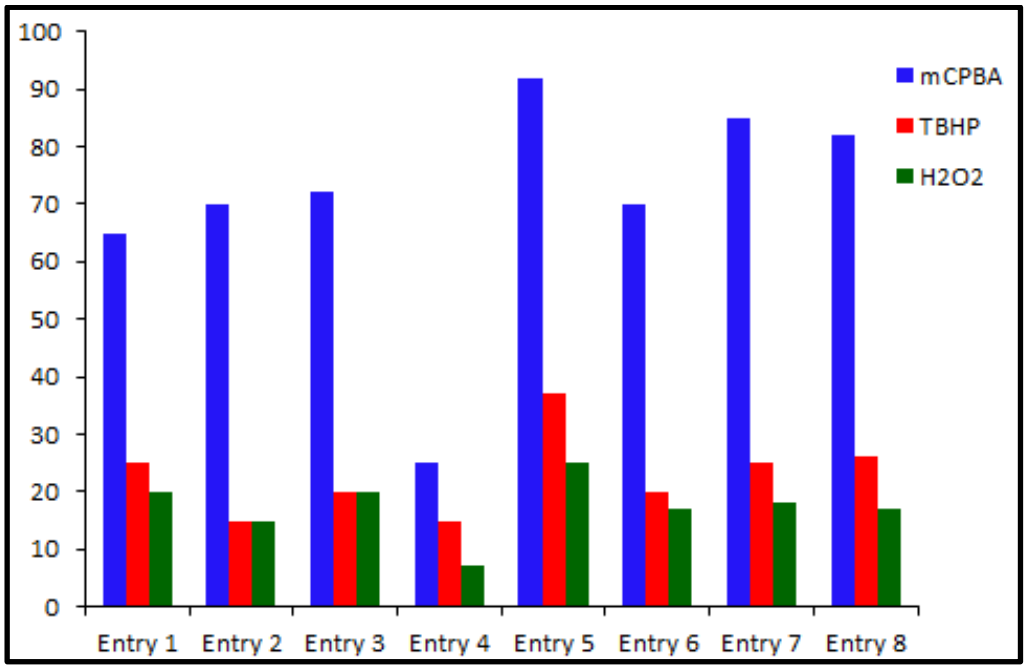
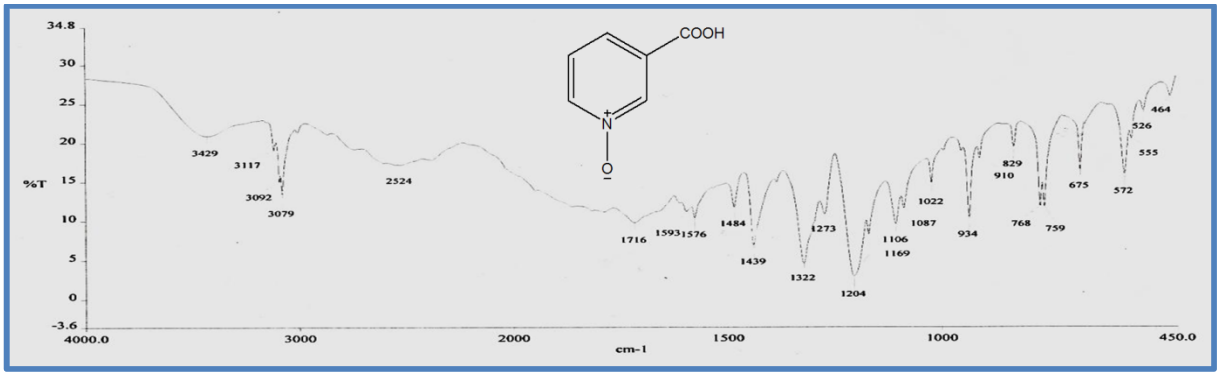
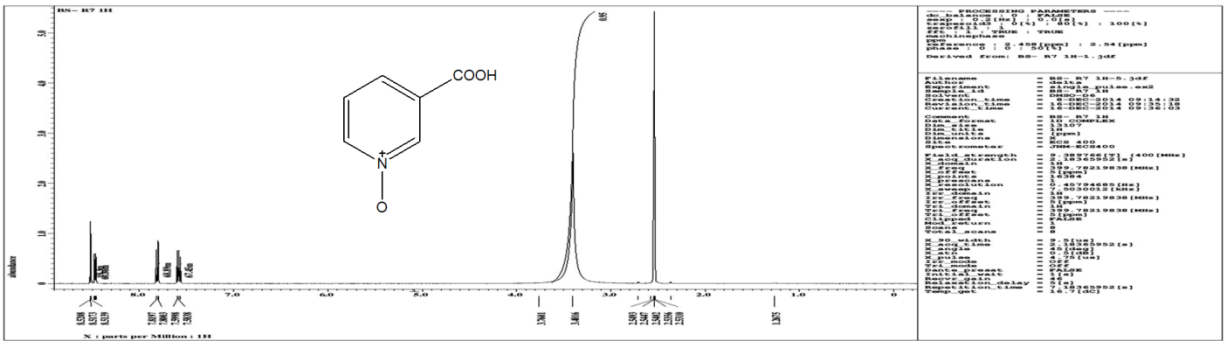


Figure E2 FT-IR and ^{1}H-, ^{13}C NMR spectra of product pyridine *N*-oxides

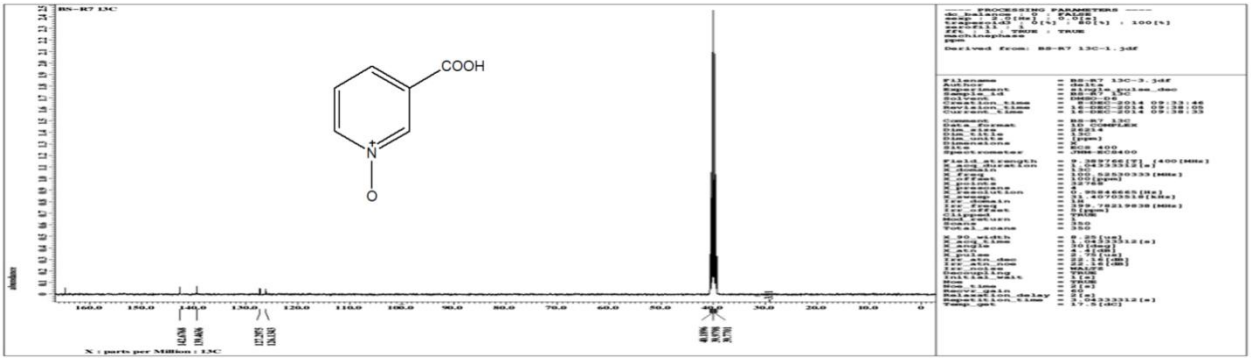
Entry 1: Nicotinic acid *N*-oxide



FT-IR

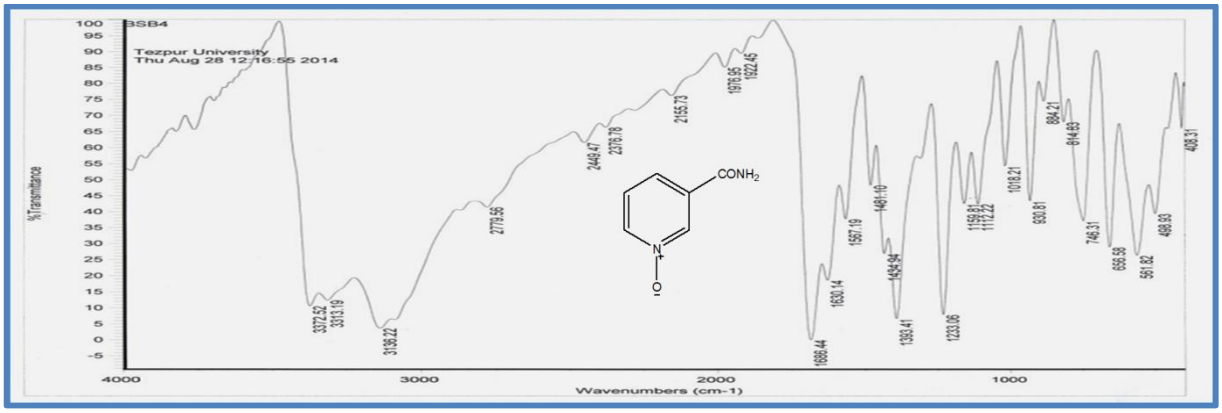


^{1}H-NMR



^{13}C-NMR

Entry 2: Nicotinamide *N*-oxide



FT-IR

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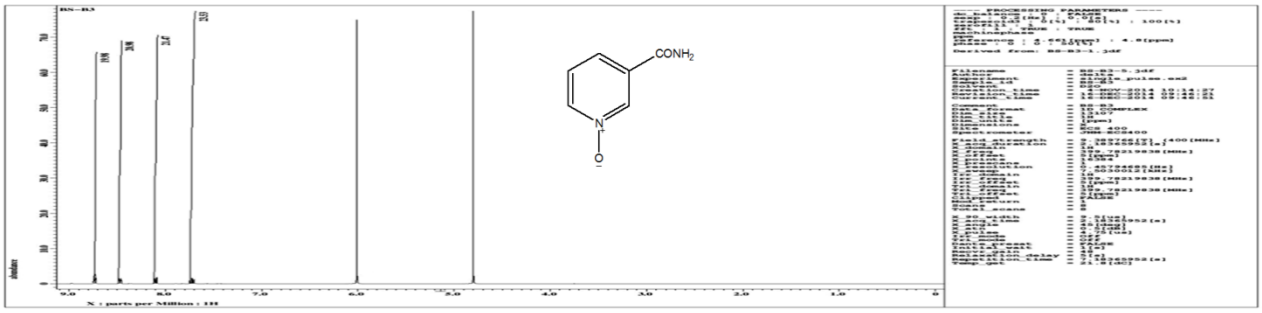
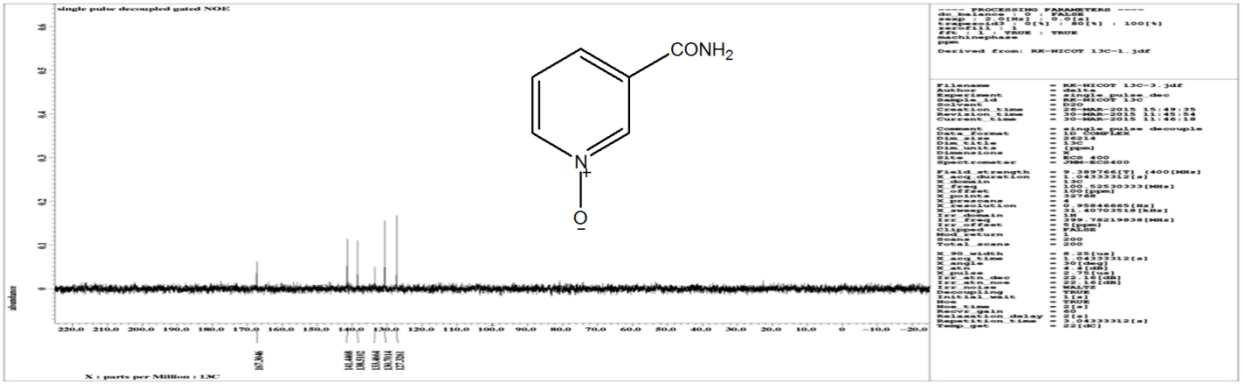
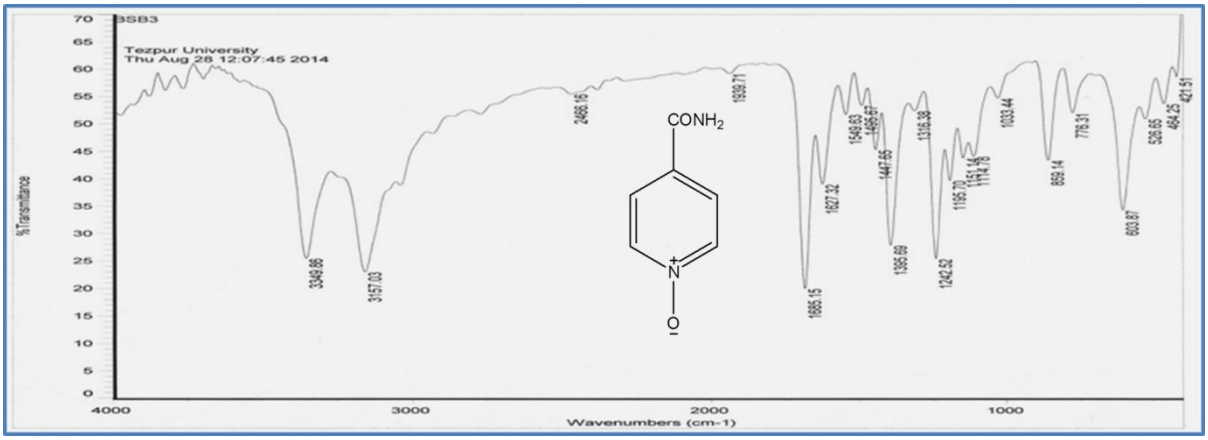


^{1}H-NMR

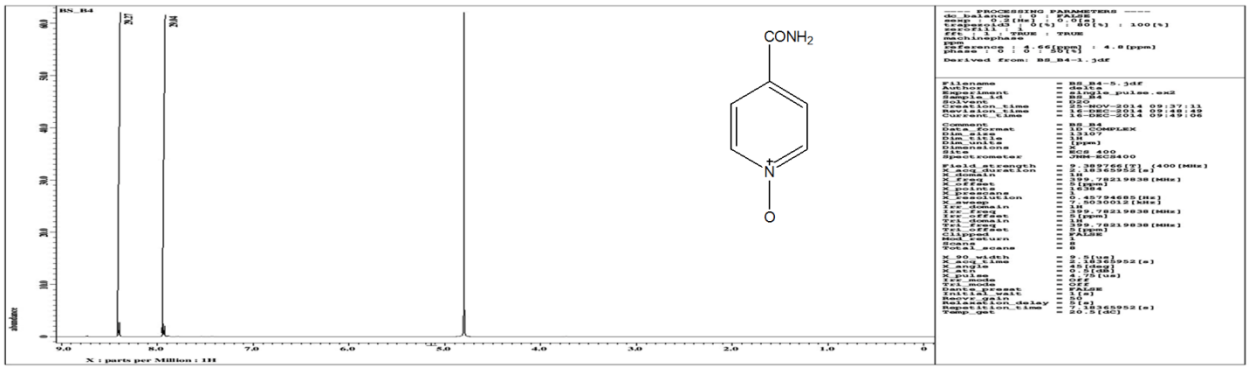


^{13}C-NMR

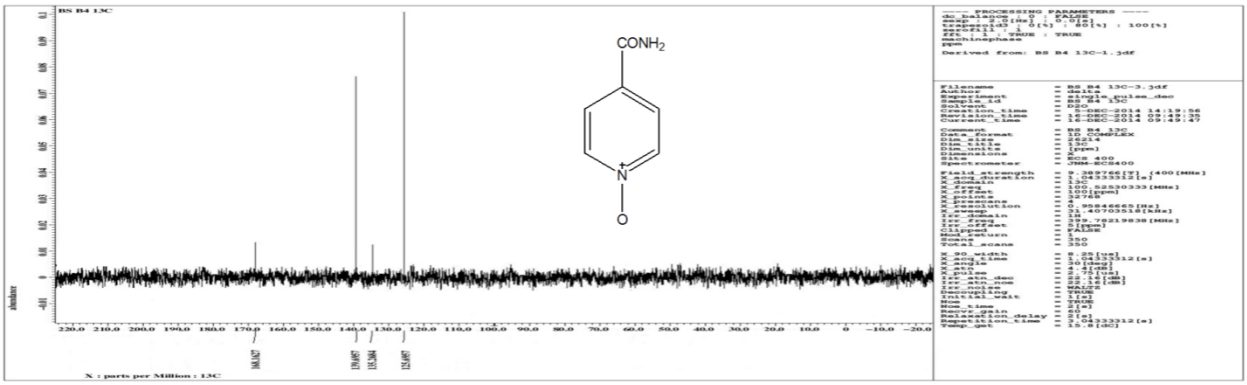
Entry 3: Isonicotinamide *N*-oxide



FT-IR

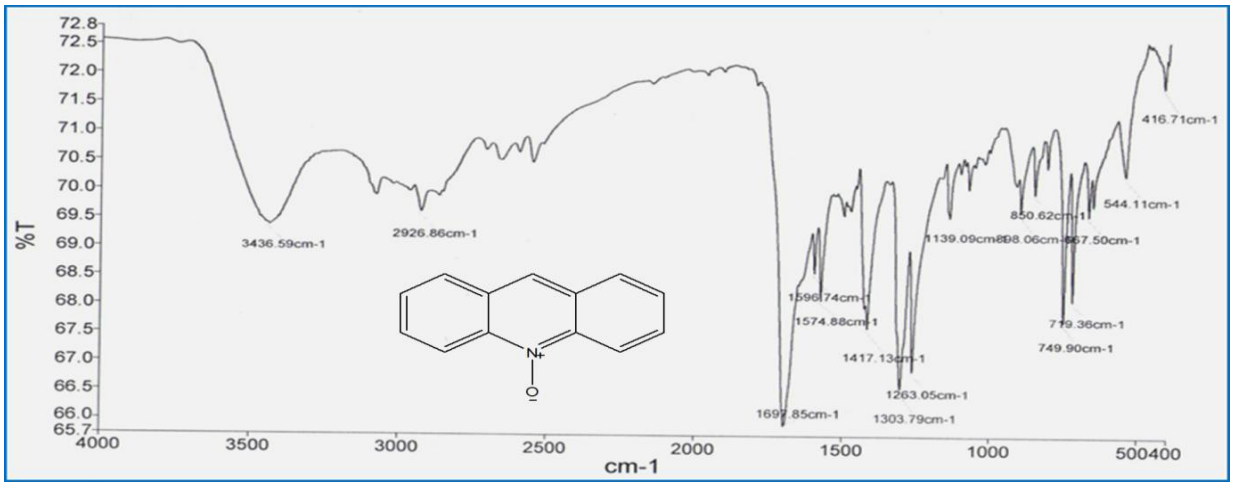


^{1}H-NMR



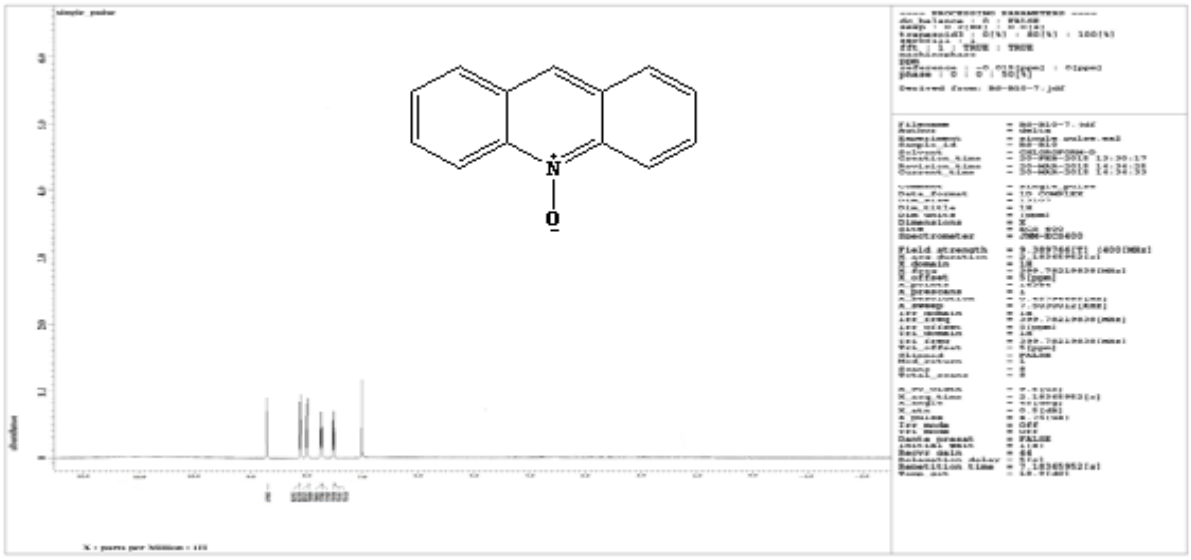
^{13}C-NMR

Entry 4: Acridine N-oxide

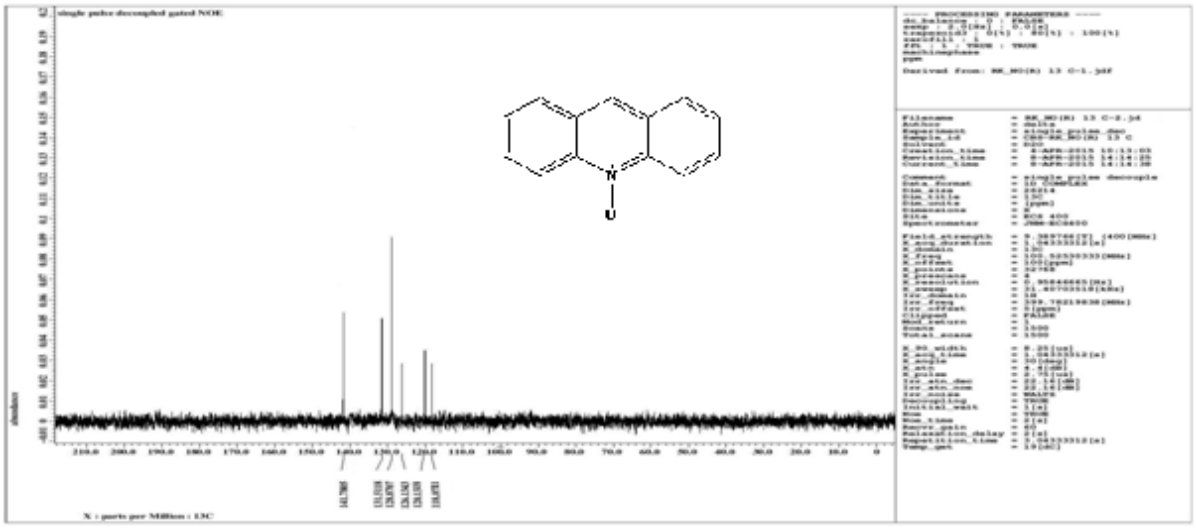


FT-IR

Electronic Supporting Information

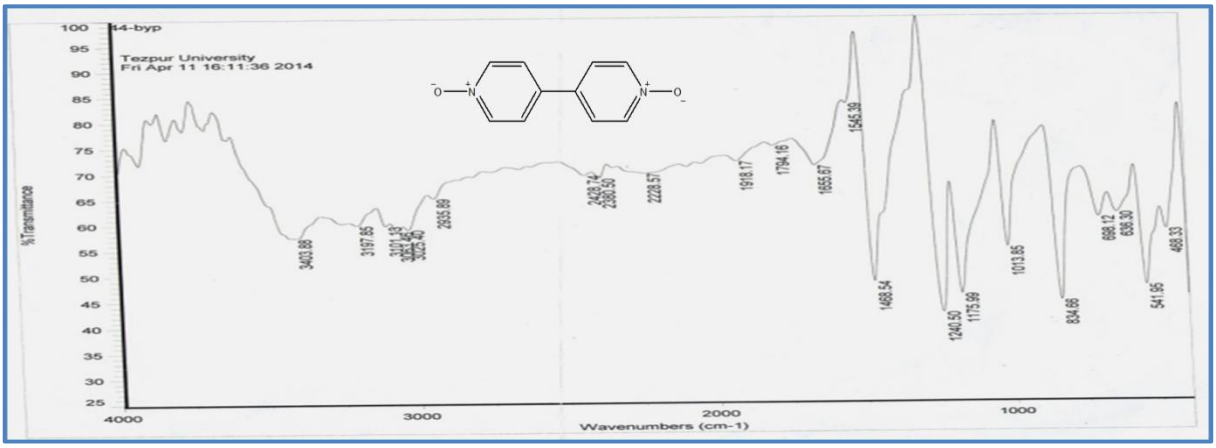


^{1}H-NMR



^{13}C-NMR

Entry 5: Bipyridine 4,4′- *N*,*N*′-dioxide

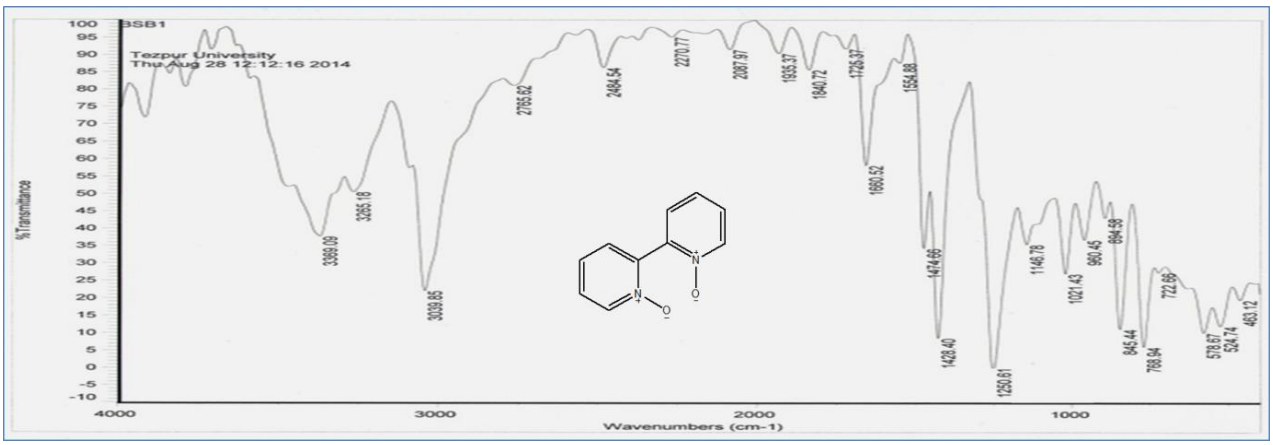


FT-IR

^{1}H-NMR

^{13}C-NMR

Entry 6: 2, 2′- Bipyridine *N*,*N*′-dioxide



FT-IR

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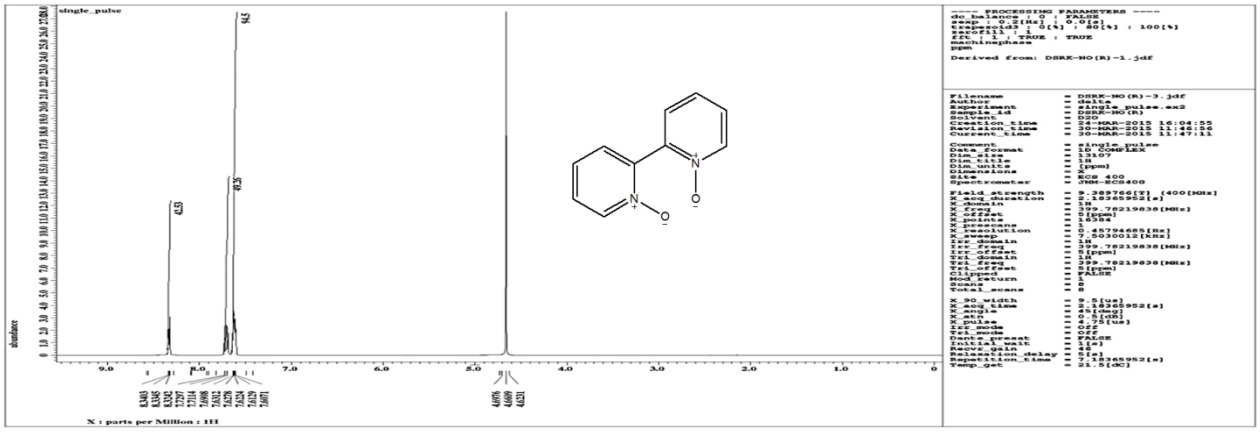
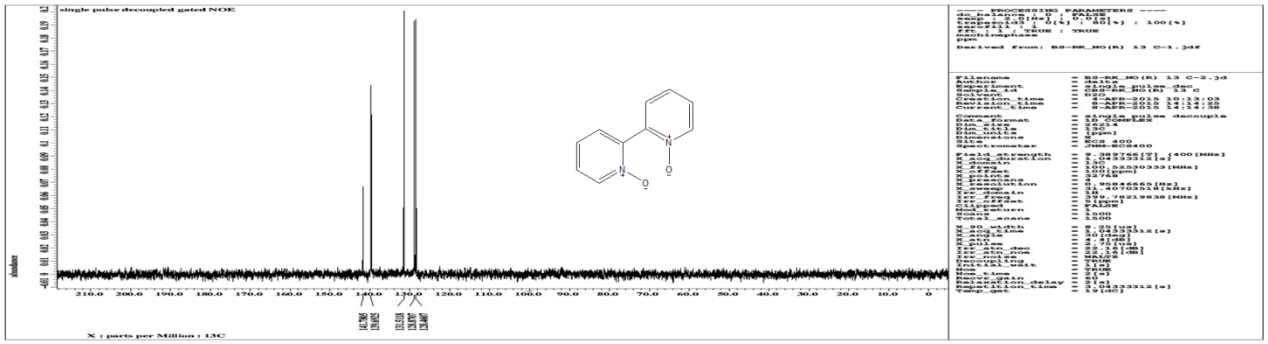
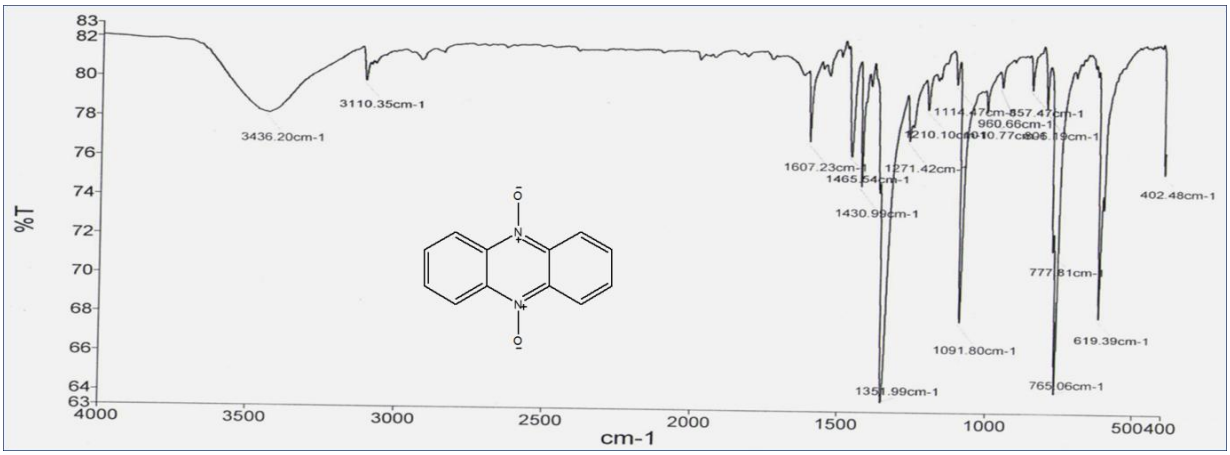


^{1}H-NMR



^{13}C-NMR

Entry 7: Phenazine *N*,*N*′- dioxide



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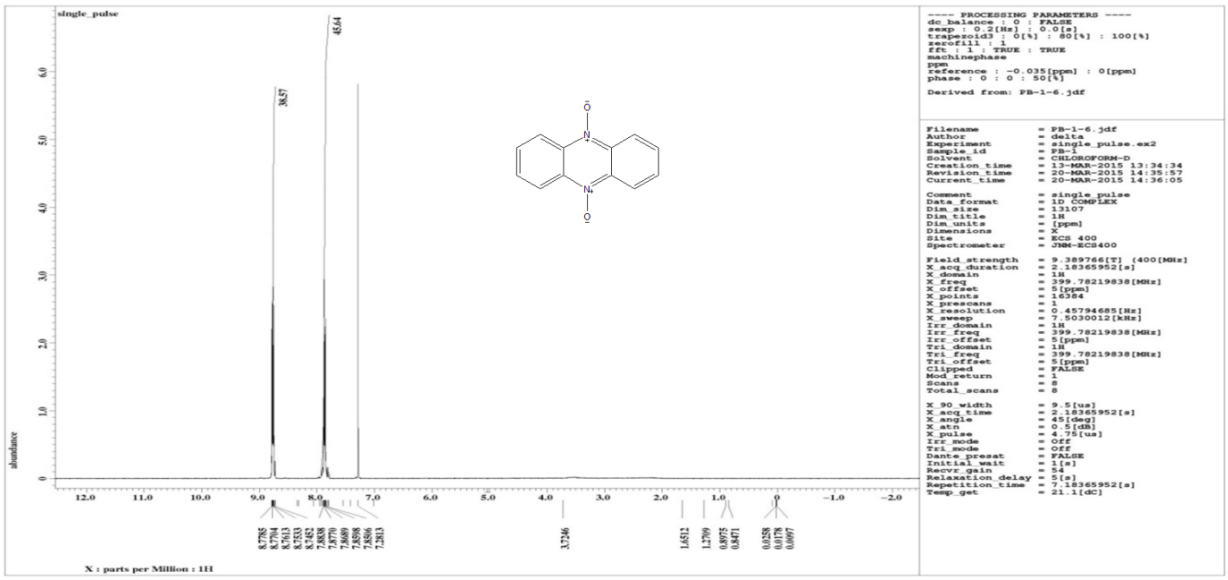
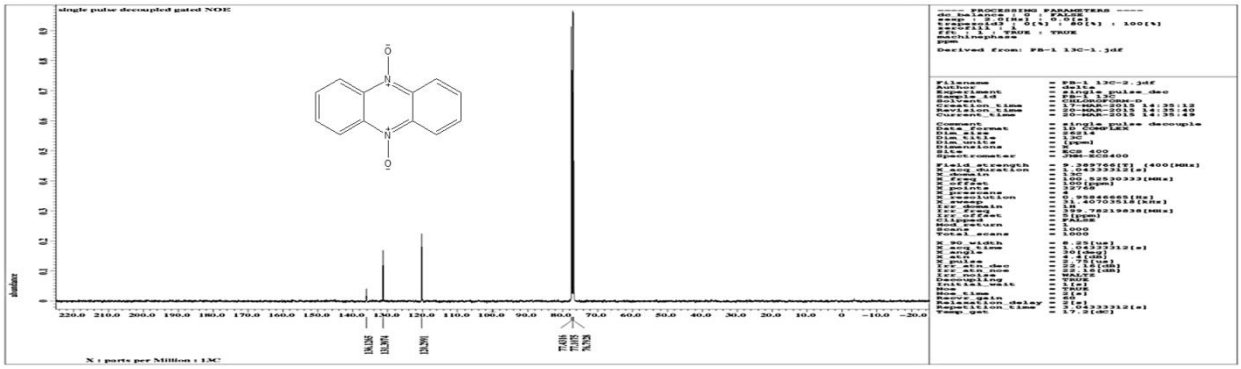
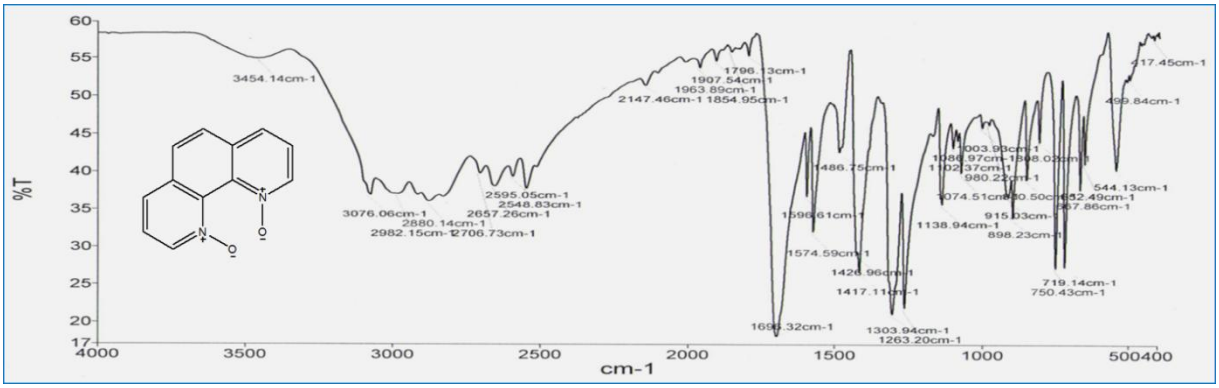


^{1}H-NMR



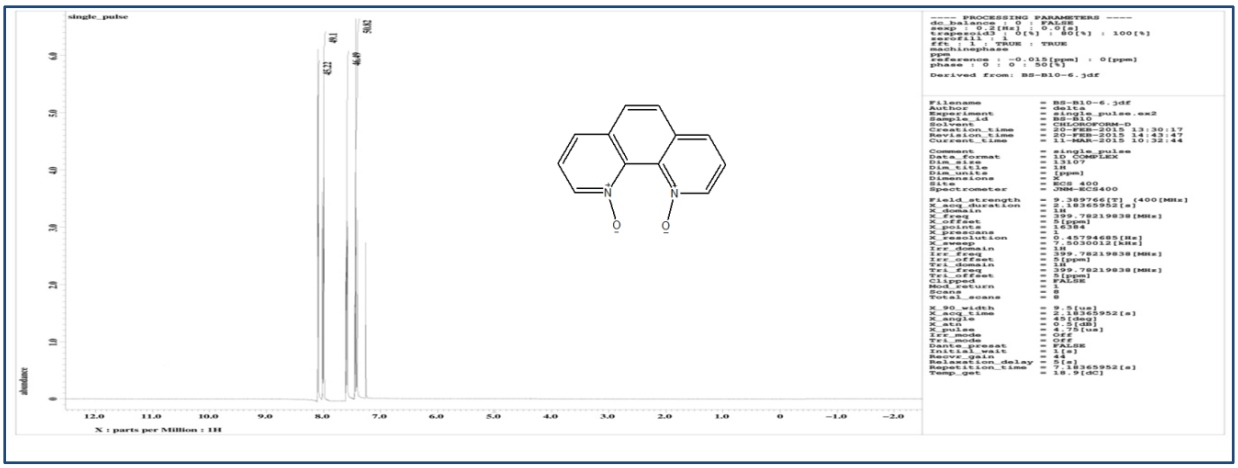
^{13}C-NMR

Entry 8: 1,10- Phenanthroline *N*,*N*′- dioxide



FT-IR

Electronic Supporting Information



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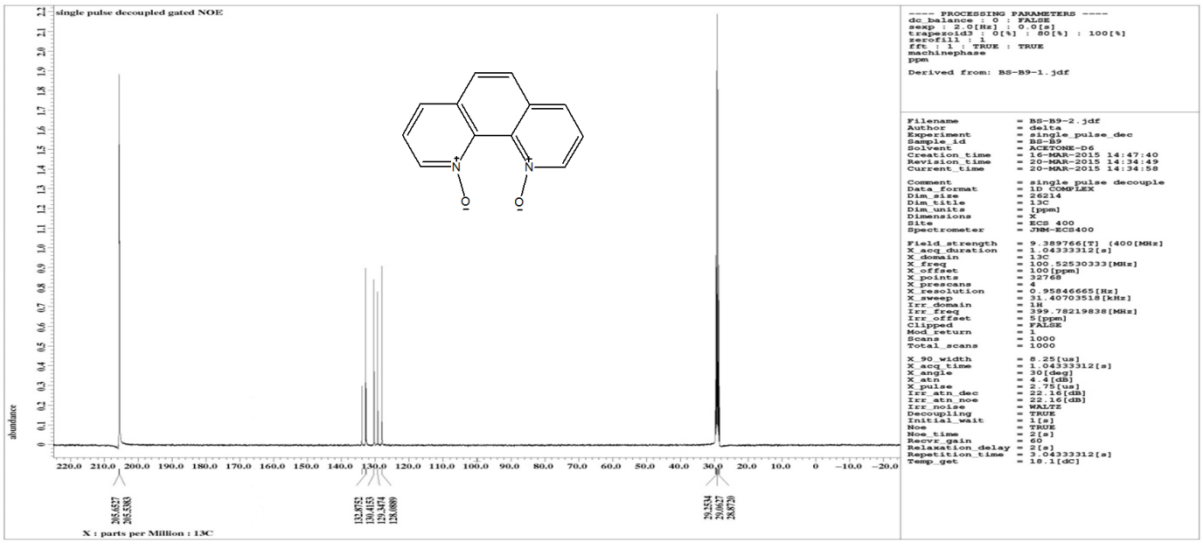


^{13}C-NMR

Table E4: Cocrystallization condition

Coformer	Drug	Coformer : Drug	Crystallizing solvent	Outcome
	PROP	1:1 and 1:2	Methanol	C1
		1:1 and 1:2	Water	IC
		1:1 and 1:2	Ethanol	C1
		1:1 and 1:2	Ethyl acetate	C1
		1:1 and 1:2	Acetonitrile	C1
		1:1 and 1:2	Dichloromethane	C1
		1:1 and 1:2	Methanol	C2

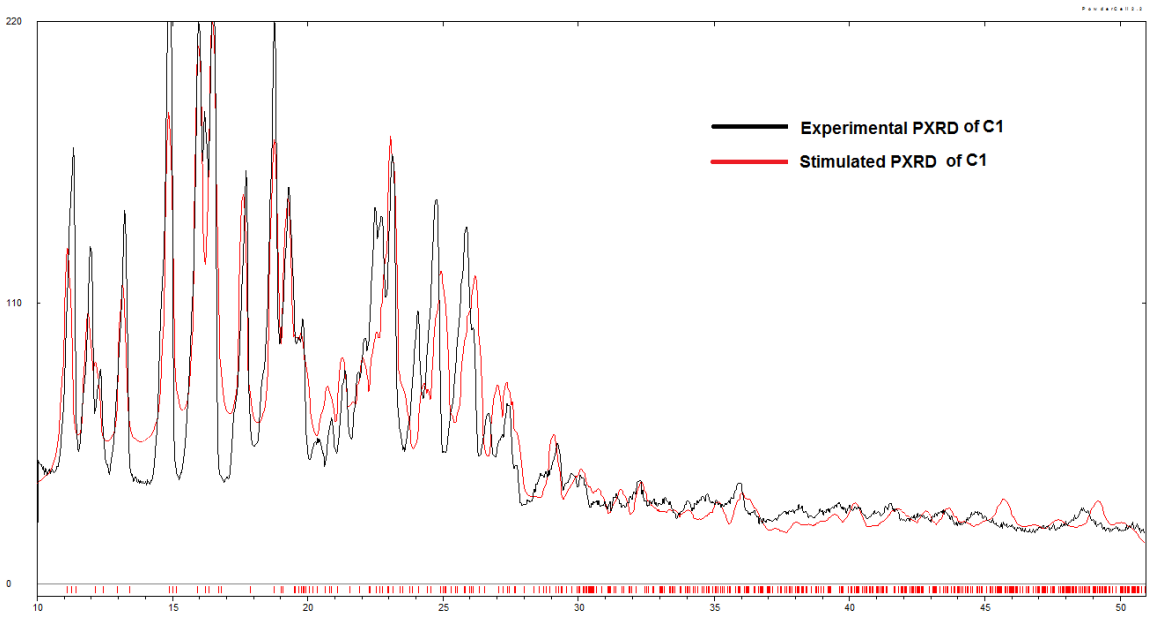
BPNO	PABA	1:1 and 1:2	Water	IC
		1:1 and 1:2	Ethanol	C2
		1:1 and 1:2	Ethyl acetate	IC
		1:1 and 1:2	Acetonitrile	C2
		1:1 and 1:2	Dichloromethane	IC
	FERU	1:1 and 1:2	Methanol	C3
		1:1 and 1:2	Water	IC
		1:1 and 1:2	Ethanol	C3
		1:1 and 1:2	Ethyl acetate	C3
		1:1 and 1:2	Acetonitrile	C3
		1:1 and 1:2	Dichloromethane	IC
	SUTH	1:1 and 1:2	Methanol	C4
		1:1 and 1:2	Water	C4
		1:1 and 1:2	Ethanol	C4
		1:1 and 1:2	Ethyl acetate	IC
		1:1 and 1:2	Acetonitrile	C4
		1:1 and 1:2	Dichloromethane	IC
∗ IC= Individual component				

Table E5: Table for literature melting points of pure drug molecules, coformer N-oxides.

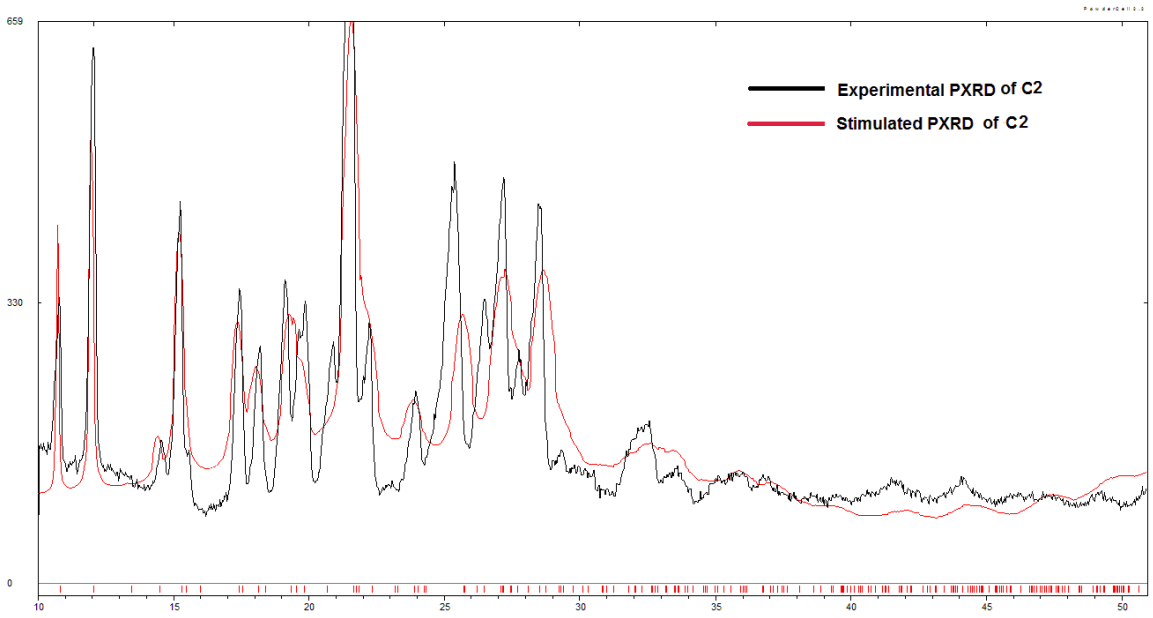
Coformer	Drug	Melting point (°C)	Cocrystal	Melting point (°C)	
				Onset	Endset
4,4'-Bipyridine-N,N'-dioxide [298–306 °C]	Propofol	17–18	C1	108.6	112.6
	p-Aminobenzoic acid	187–189	C2	248.6	257.6
	Ferulic acid	168–172	C3	184.9	198.7
	Sulfathiazole	200–202	C4	162.8	167.4

Figure E3: Reitveld refinement of experimental powder X-ray diffraction patterns of cocrystals with simulated generated from single crystal data.

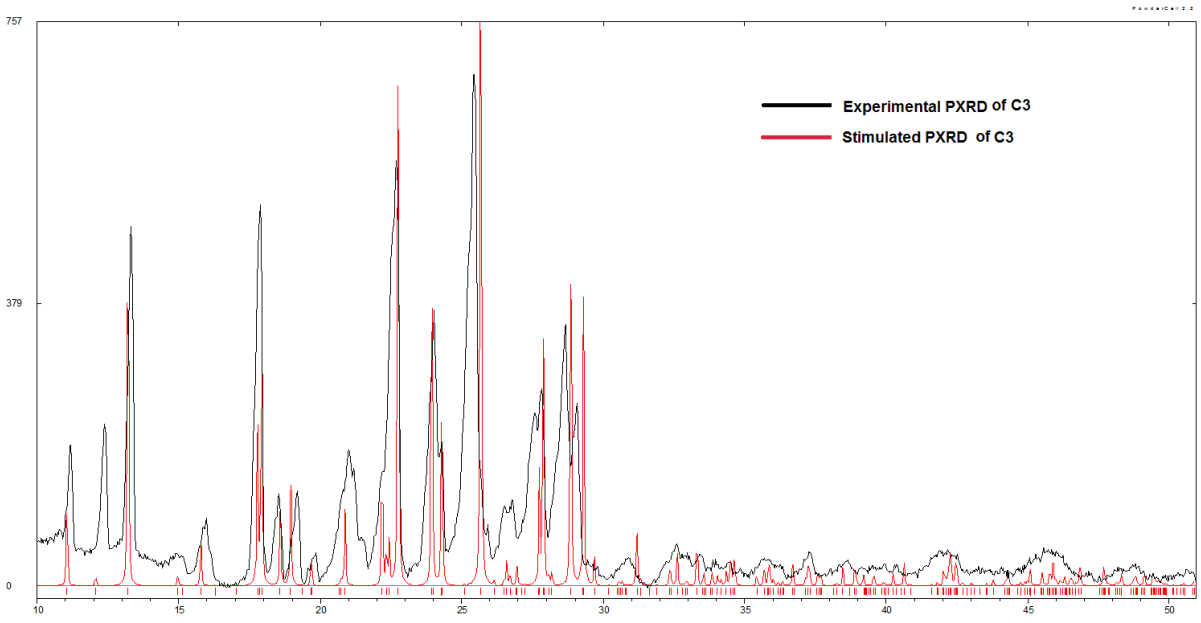
Electronic Supporting Information



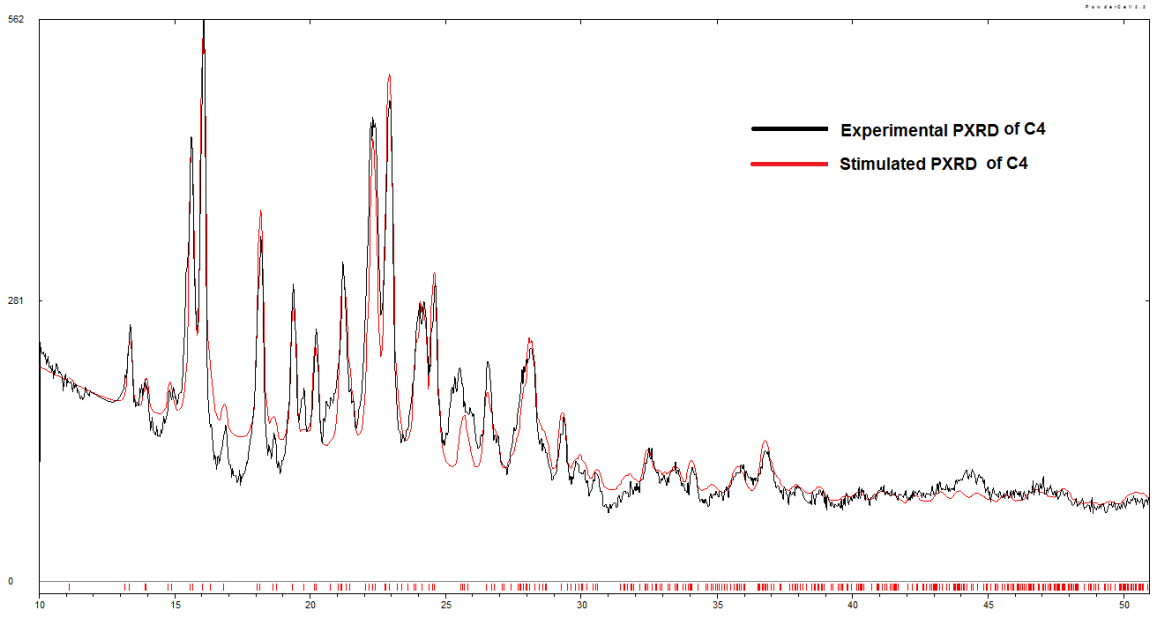
Cocrystal C1



Cocrystal C2

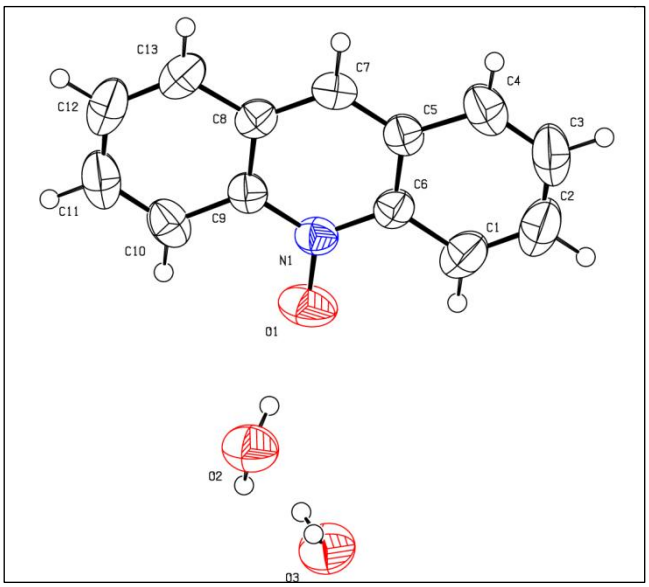


Cocrystal C3

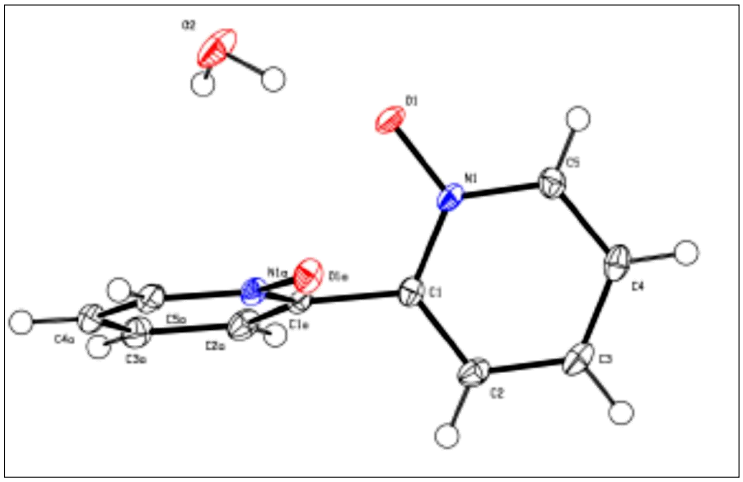


Cocrystal C4

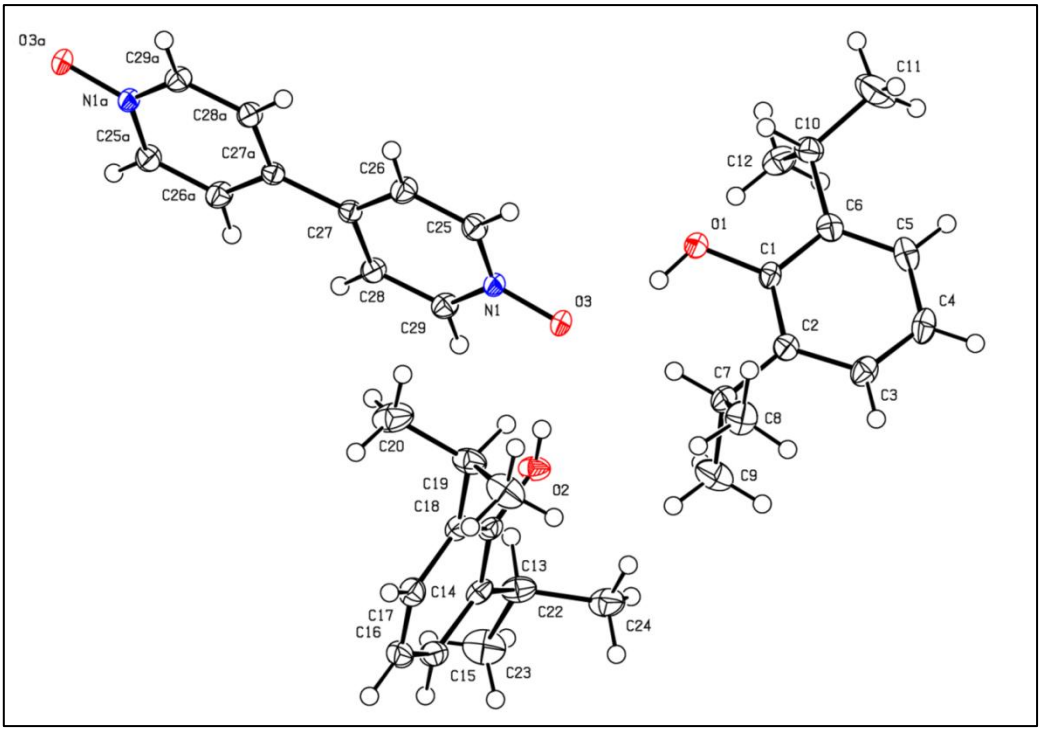
Figure E4: ORTEPs at 35% probability ellipsoid (entry **4**, **6** and cocrystals **C1** – **C4**).



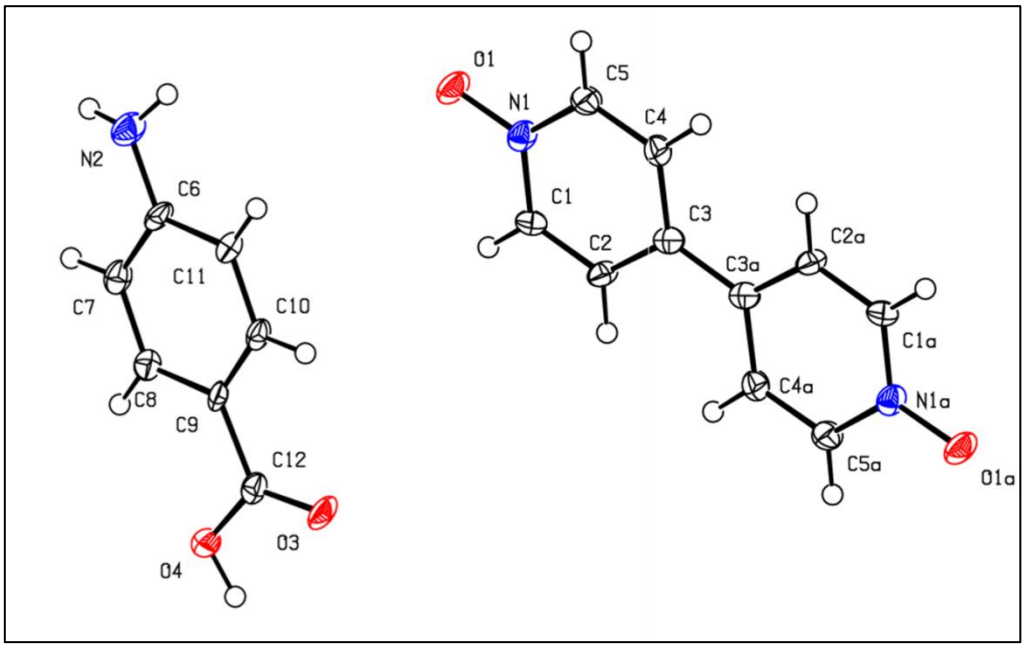
Entry 4



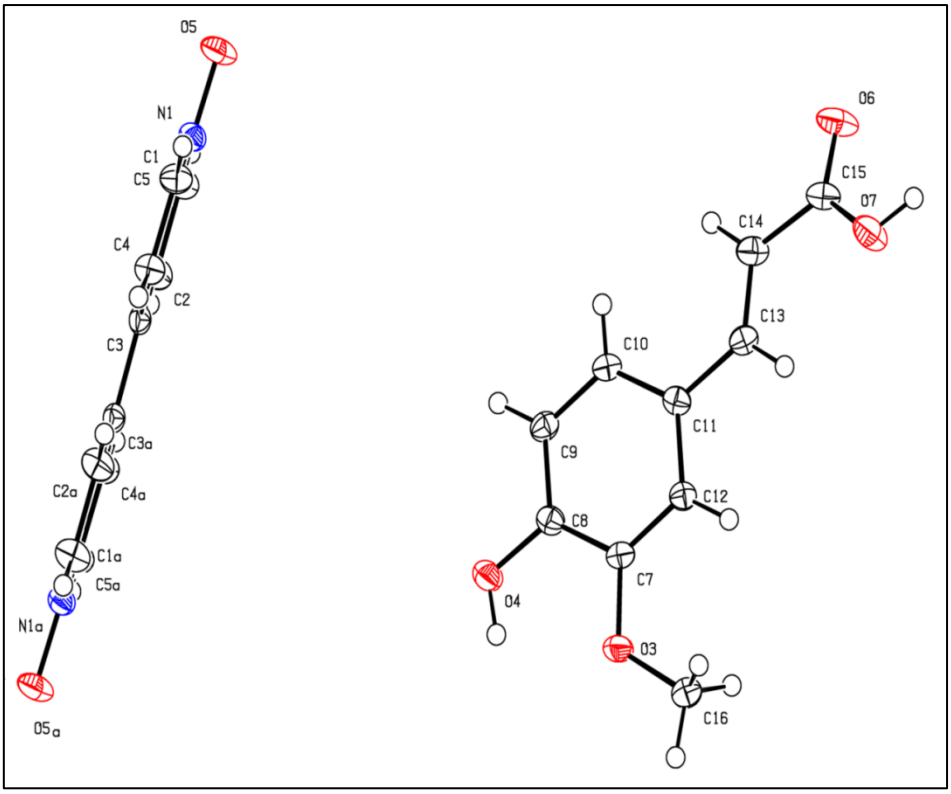
Entry 6



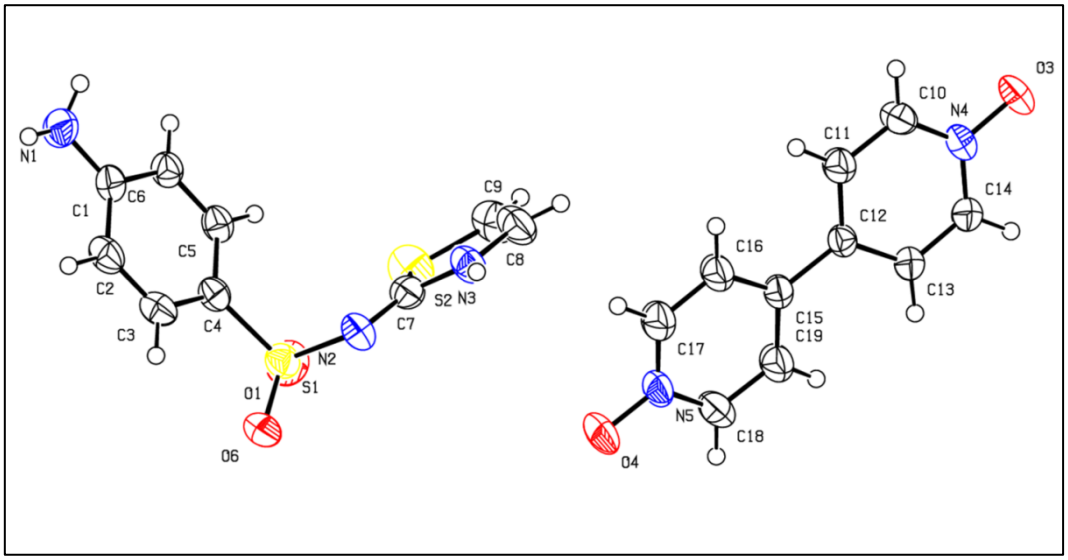
Cocrystal **C1**



Cocrystal **C2**



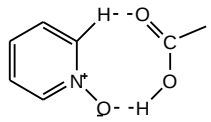
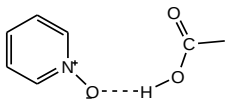
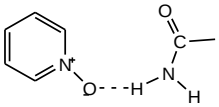
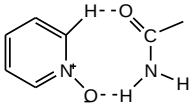
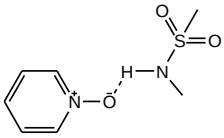
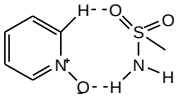
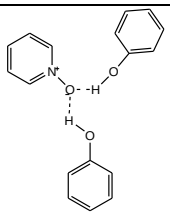
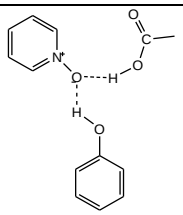
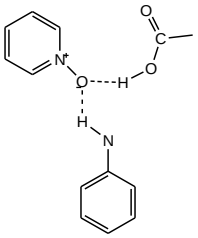
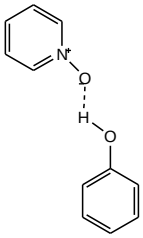
Cocrystal **C3**



Cocrystal **C4**

Table E6: Cambridge Structural Database (CSD) Analysis for N-oxide cocrystals

Search Limits: Only organic and aromatic molecules, R factor less than 10% structures, no ions, no disordered and polymeric structures.

Hydrogen Bond Synthon	Reported Structure [CSD Refcode]	Hydrogen Bond Synthon	Reported Structure [CSD Refcode]
	CUZDAC; DAQZOL; DAQZUR; EQISIH; EQISON; FAFTAH; FOVPIQ; GAQVEA GAQVEA01; HOPKIH; HUZCUA; IWERUY; LICJUD; LIZVOH LIZWUO; NIMBAM PANRIH; PICFUM; RIYXUT; ROKQAJ RUJGUJ; SOPJEM WAJVUA; WOJGUX; WOJHAE; WOJHEJ; XONCIO		EDILAI; KAVFET ; LIZVIB; PYOTCA10 ROKQEN; TAWNEL TIXLAO; VARBOG WAJWAH; WAJWEL WOJHIM; HUWHAK
	VIGGOI; VIGGUO; WOBQEK01; WOBQIO		Nil
	IWERAE; IWEREI		Nil
	LEQXAG; MOCNEY; PUYTAE; SIPSIU; SIPSOA; TIBZIO; YEXSEA; FAJZUO; RUWPEG		WAJXAI; HUWHAK
	SOJPEM; WAJWEL; HUZCUA		CIRNEY; DATQUL; DUZPEU; FAFTEL; HIDRIX; HINGUF; HOPKAZ; JUDNAX; LAPLEU; LIZVUN; LIZWAU; LIZWIC NELTIH; NILZOX

			NILZUD; QUMDIM NPOAPL; OWIYEZ PIFHAO; QUMDEZ RADHAH; RIDJOD RIDKUK; RIDLEV RIDPAV; RIDPEZ RIDQIE; SIPSEQ SUVZEO; TAZLOW TEFRUS; WAJVOU WAJVUA; WAJWAH WAJWIP; WAJWUB WIRWID; XIBGUL FAKBAX

Figure E5: Hirshfeld 2D finger print plots of the interactions present in cocrystals (C1-C4).

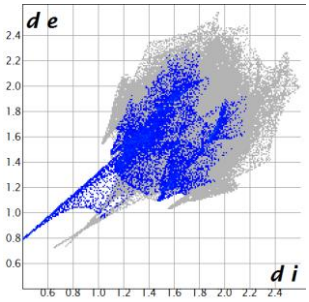
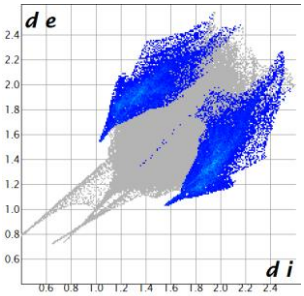
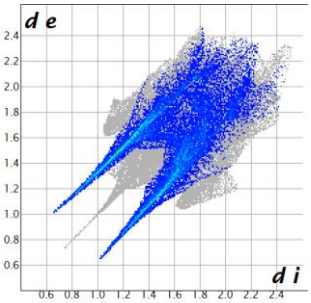
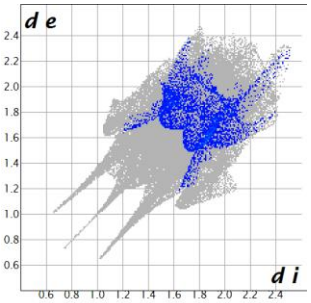
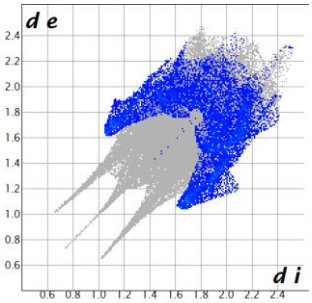
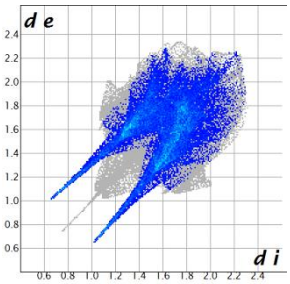
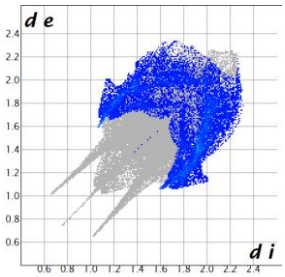
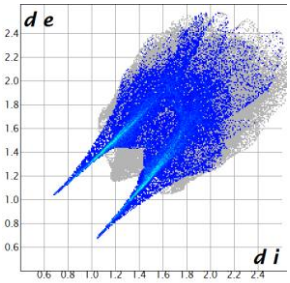
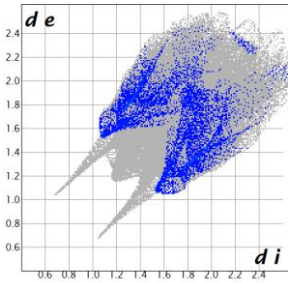
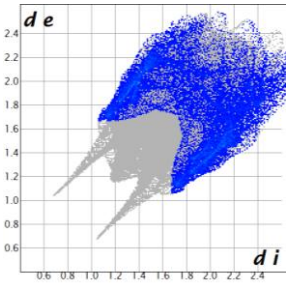
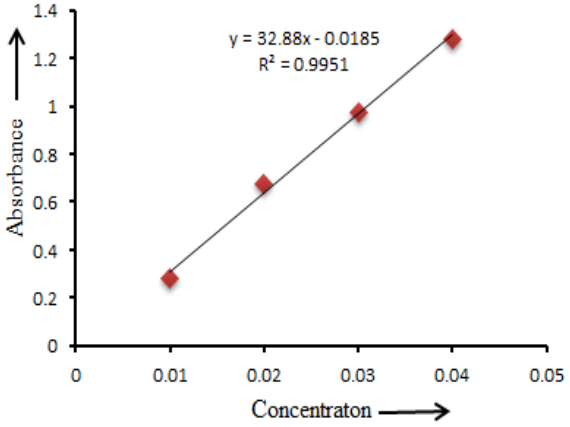
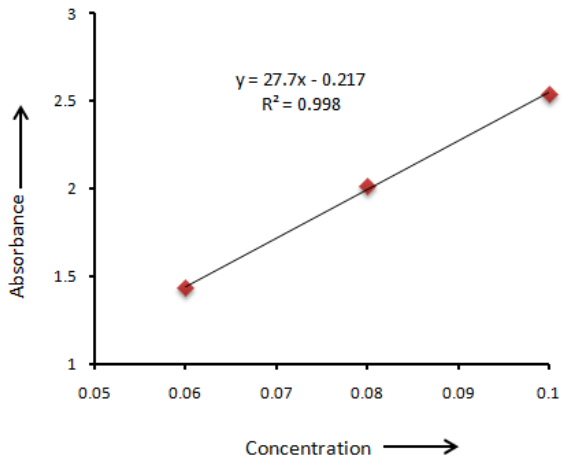
O···H interactions	N···H interactions	C···H interactions
Cocrystal C1		
	**N/ A**	
6.7 %	0.0 %	17.6 %
Cocrystal C2		
		
29.4%	4.8%	14.9%
Cocrystal C3		
	N/A	
13.5%	0.0%	17.9%
Cocrystal C4		
		
27.1%	5.9%	18.0%

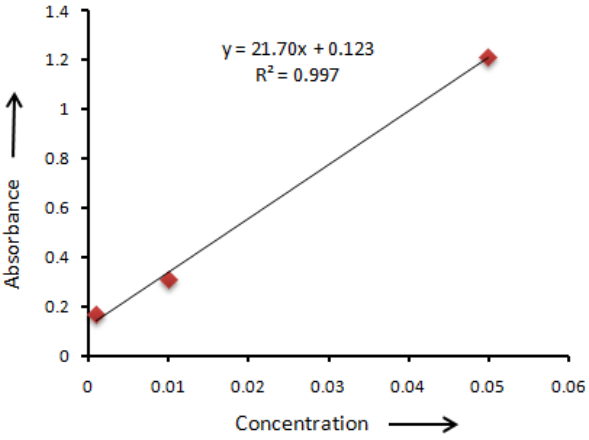
Figure E6: Calibration curves for solubility determination of the cocrystals (C1 to C4).



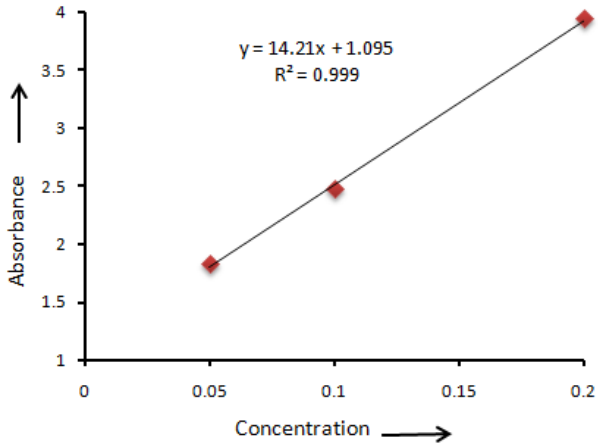
Cocrystal C1



Cocrystal C2



Cocrystal C3



Cocrystal C4