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Supporting Information for Transforming Liquid Nicotine into a Stable Solid Through Crystallization with Orotic Acid

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Supporting Information

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Crystallographic Information

Structural Data Deposition

Deposition number 2161823 contains the supplementary crystallographic data for this paper. This data is provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

(S)-Nicotinium Orotate Hemihydrate Crystals & Crystal Structure

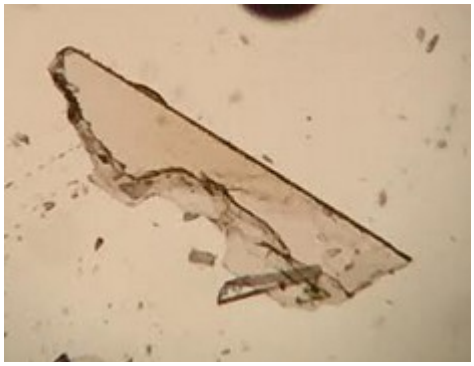

Figure S1: A crystal of orthorhombic $P222_1$ (S)-nicotinium orotate hemihydrate.

Figure S2: orthorhomb nicotinium

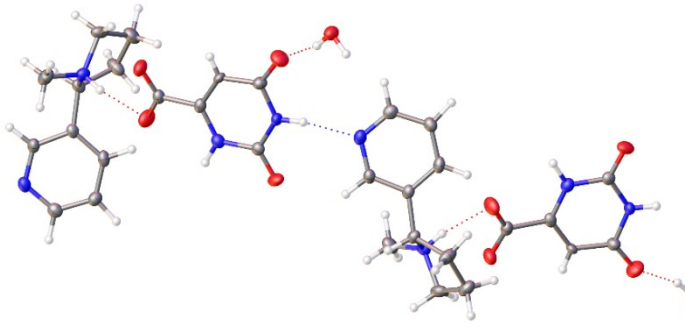

Figure S3: Diagram of orthorhombic $P222_1$ (S)-nicotinium orotate hemih bonds that are present between the acid coformer and the nicotine. Ato nitrogen (blue), carbon (grey), hydrogen (white). Hydrogen bond interac and blue dashed lines.

Table S1: Crystallographic information for nicotinium orotate hemihydrate.

Identification code	**Nicotinium_Orotate_Hemihydrate**
Empirical formula	$C_{30}H_{38}N_8O_9$
Formula weight	654.68
Temperature/K	90.0
Crystal system	orthorhombic
Space group	$P222_1$
a/Å	6.9489(7)
b/Å	9.7256(10)
c/Å	23.026(2)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1556.1(3)
Z	2
ρ_{calc}g/cm^3	1.397
μ/mm^{-1}	0.105
F(000)	692.0
Crystal size/mm^3	0.14 × 0.08 × 0.02
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.538 to 55.164
Index ranges	-9 ≤ h ≤ 9, -12 ≤ k ≤ 12, -30 ≤ l ≤ 29
Reflections collected	27746
Independent reflections	3616 [R_{int} = 0.0524, R_{sigma} = 0.0299]
Data/restraints/parameters	3616/0/231
Goodness-of-fit on F^2	1.157
Final R indexes [I>=2σ (I)]	R_1 = 0.0497, wR_2 = 0.1075
Final R indexes [all data]	R_1 = 0.0530, wR_2 = 0.1088
Largest diff. peak/hole / e Å^{-3}	0.24/-0.21

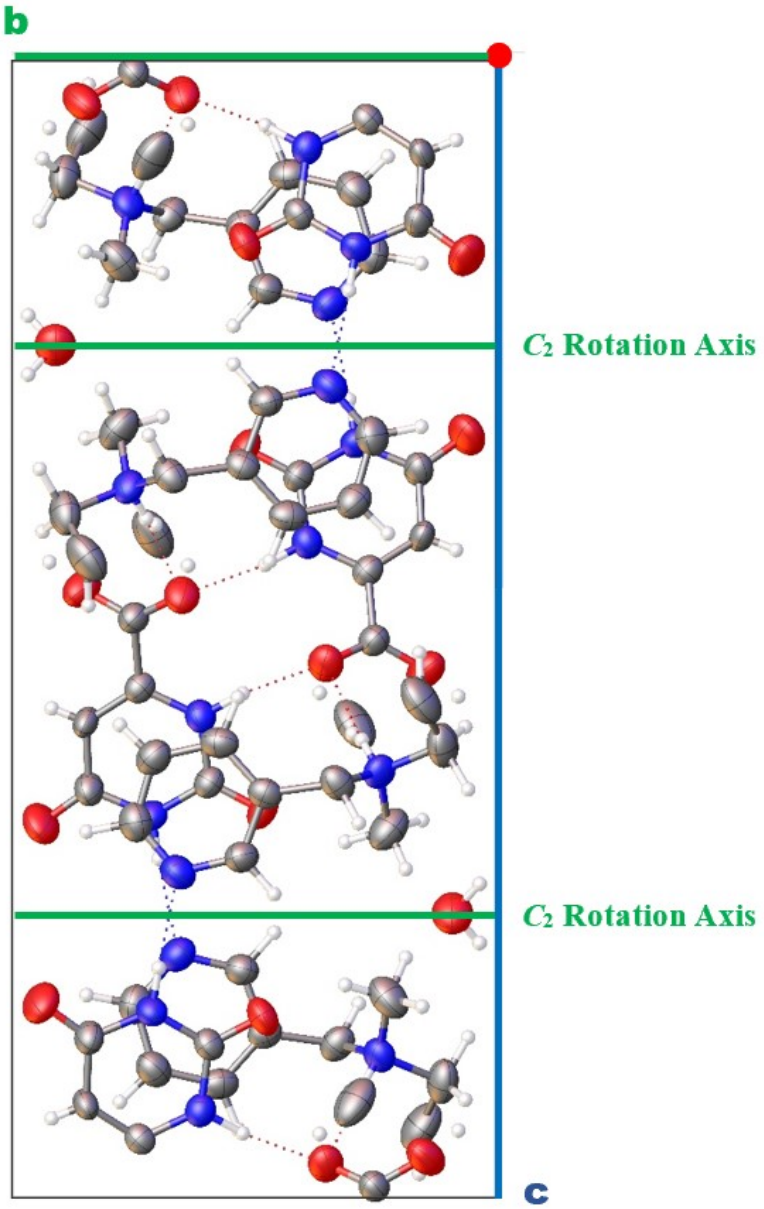

Figure S4: Diagram of unit cell view down the *a* – axis of **Salt 5**, showing the *bc* plane with water on special positions due to the C_2 rotation axes going through the oxygen molecule of each water. Atom colors: oxygen (red), nitrogen (blue), carbon (grey), hydrogen (white). Hydrogen bond interactions highlighted in red and blue dashed lines.

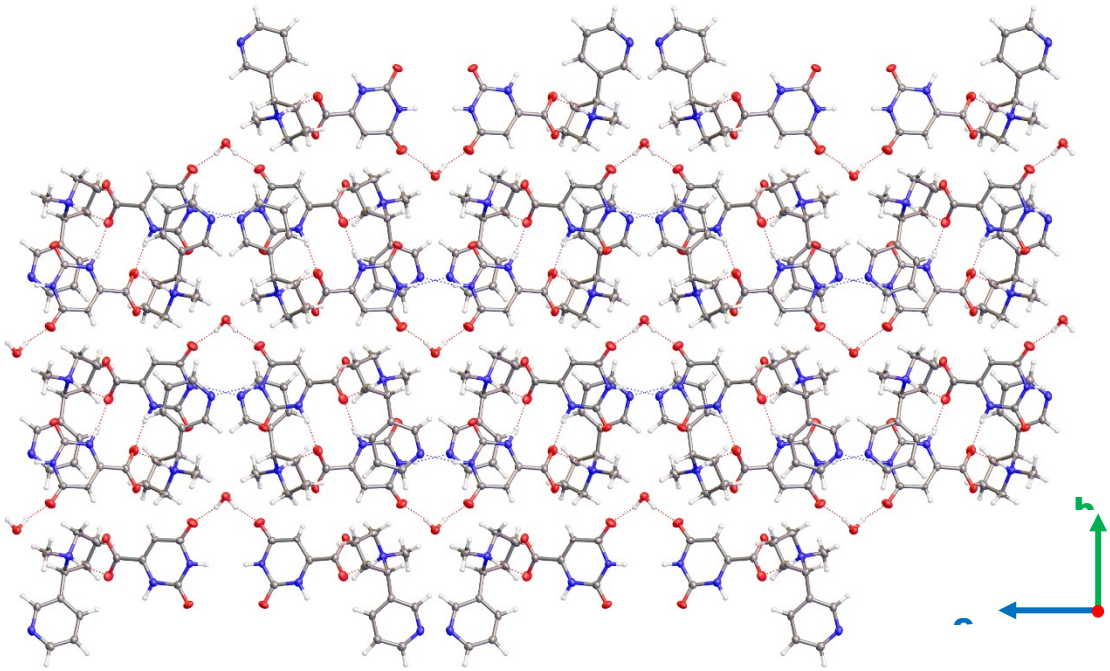

Figure S5: View down crystallographic *a* – axis of nicotinium orotate hemihydrate with *b* and *c* normal to the plane. Atom colors: oxygen (red), nitrogen (blue), carbon (grey), hydrogen (white). Hydrogen bond interactions highlighted in red and blue dashed lines.

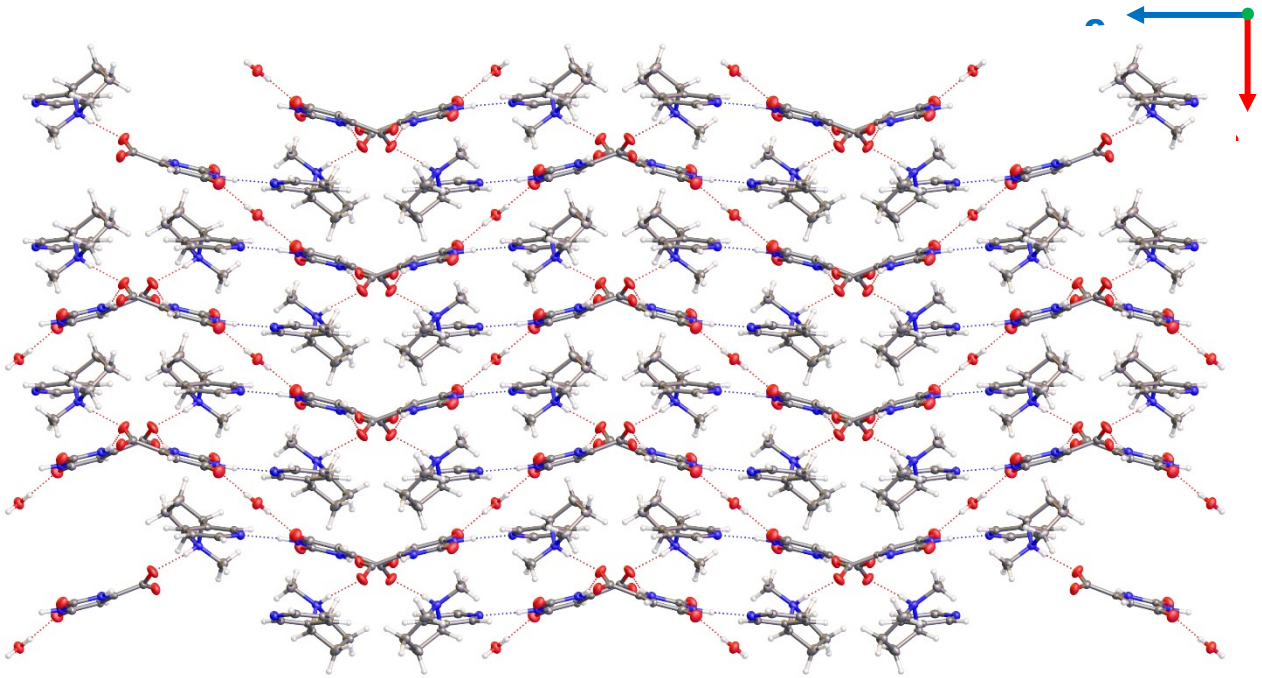

Figure S6: View down crystallographic *b* – axis of nicotinium orotate hemihydrate with *a* and *c* normal to the plane. Atom colors: oxygen (red), nitrogen (blue), carbon (grey), hydrogen (white). Hydrogen bond interactions highlighted in red and blue dashed lines.

(S)-Nicotinium Orotate Hemihydrate Powder X-Ray Diffraction Pattern

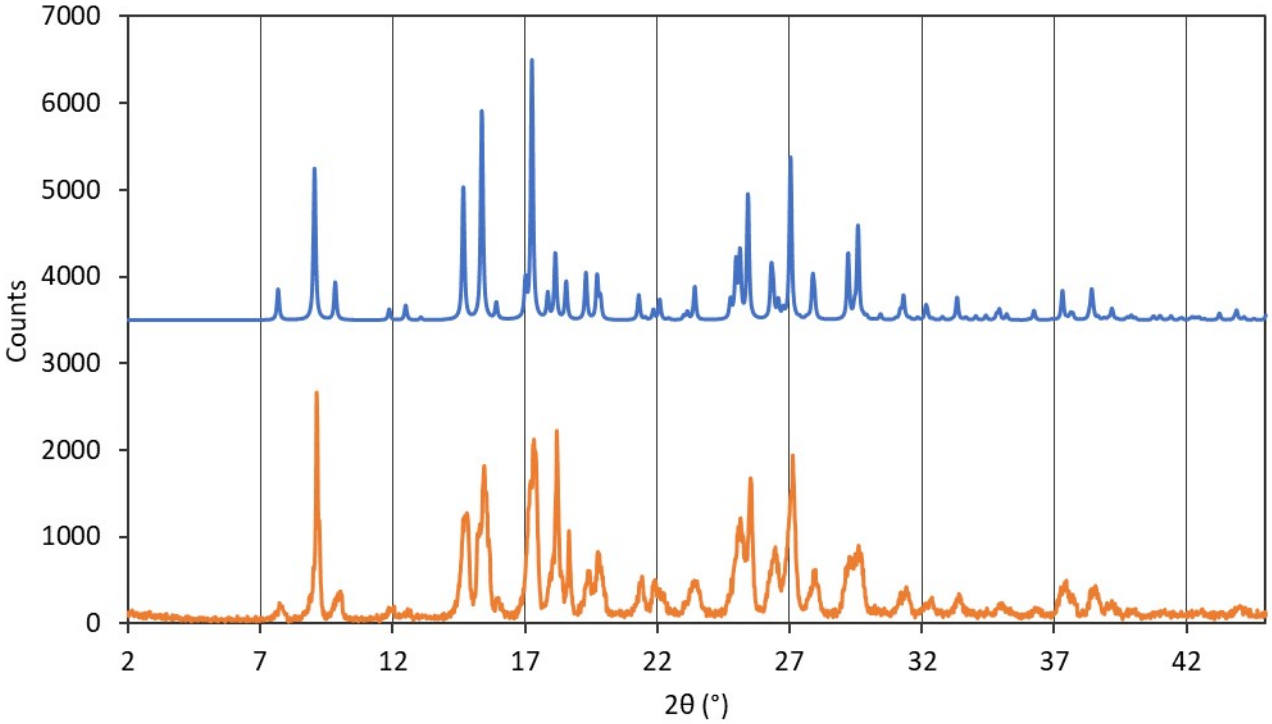

Figure S7: Powder X-ray diffractograms of (S)-nicotinium orotate hemihydrate. The simulated diffractogram (upper) was generated from single crystal x-ray diffraction data and is shown with an offset of 3,500 counts. The experimentally obtained diffractogram (lower) was collected from the bulk sample.

(S)-Nicotinium Orotate Hemihydrate Face Indexing

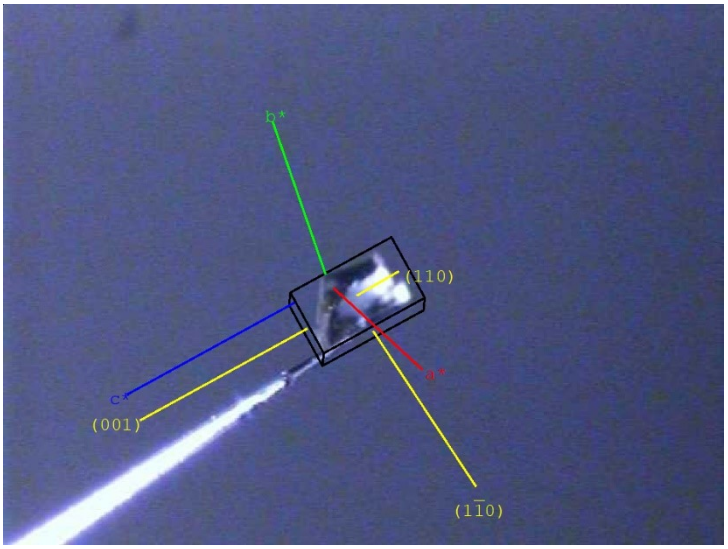

Figure S8: Image from the face indexing of a crystal of (S)-nicotinium orotate hemihydrate. The apparent diagonal surface is a fracture edge not a crystallographic face.

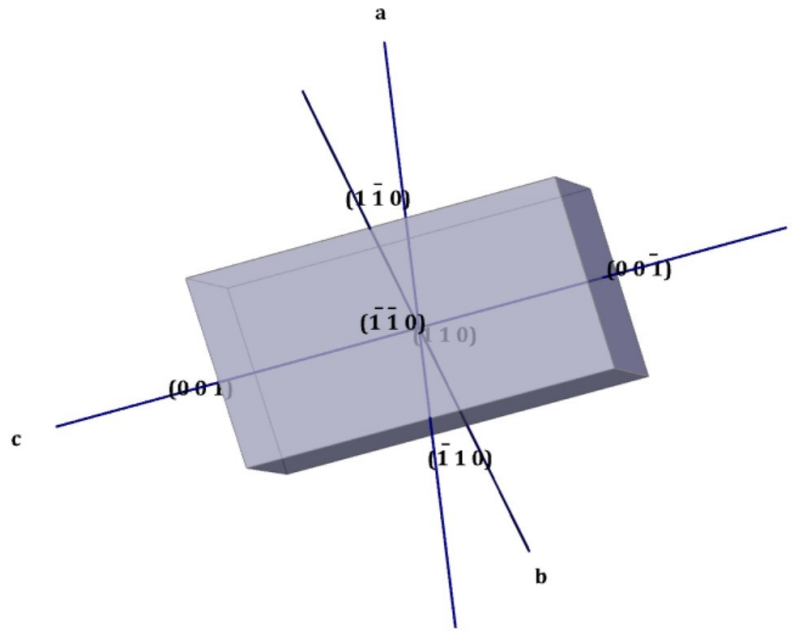

Figure S9: Image of idealized habit of (S)-nicotinium orotate hemihydrate produced using WinXMorph. Kaminsky, W. (2007). *J. Appl. Cryst*. 40, 382-385.

Table S2: Properties of previously reported nicotine salts and co-crystals, as well as the orotate salt dscribed herein.

Properties of Nicotine Solids

Salt/Co-Crystal	Molecular Formula	Photostable?	Melting Point (°C)	$\Delta H^{\circ}_{fusion}$ (J/g)	$\Delta H^{\circ}_{fusion}$ (kJ mol^{-1})	$\Delta S^{\circ}_{fusion}$ (kJ mol^{-1} K^{-1})
Nicotine-DITF	$C_{16}H_{14}F_4I_2N_2$	N/A	54	N/A	27.6	N/A
Nicotine-DOB	$C_{22}H_{14}F_8I_2N_2$	N/A	68	N/A	24.3	N/A
Nicotine-D1	$C_{42}H_{40}N_2O_2$	N/A	92	N/A	37.9	N/A
L-Malate I	$C_{14}H_{20}N_2O_5$	✓	116.4	37.71	11.20	2.875×10^{-2}
L-Malate II	$C_{14}H_{20}N_2O_5$	✓	122.2	61.91	18.35	4.641×10^{-2}
D-Malate	$C_{14}H_{20}N_2O_5$	✓	93.4	62.83	18.62	5.080×10^{-2}
DL-Malate	$C_{14}H_{20}N_2O_5$	✓	120.0	52.51	15.56	3.958×10^{-2}
Orotate	$C_{15}H_{18}N_4O_4 \cdot \frac{1}{2} H_2O$	✓	135.5	80.16	26.24	6.421×10^{-2}

UV Degradation Studies Spectra

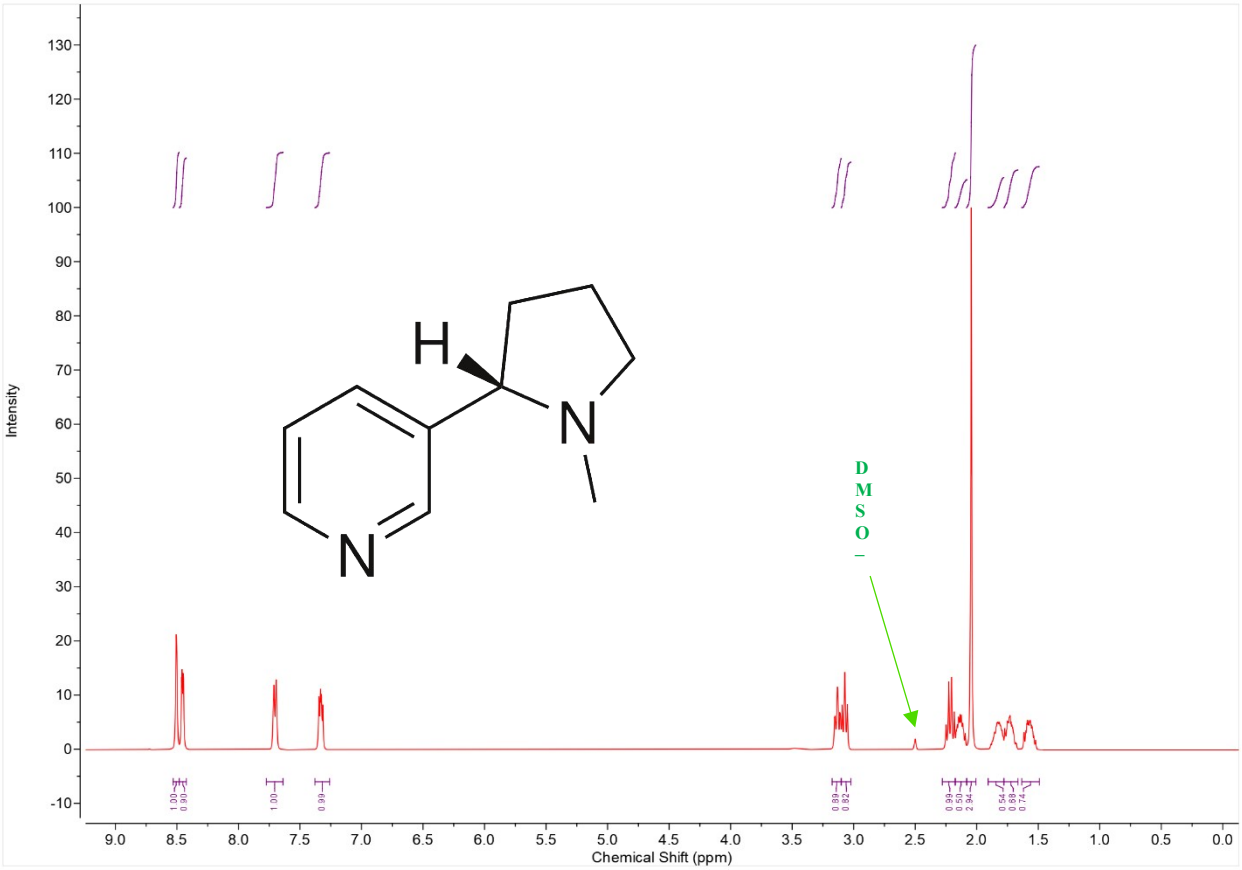

Figure S10: ^{1}H-NMR spectrum for (S)-nicotine from the bottle.

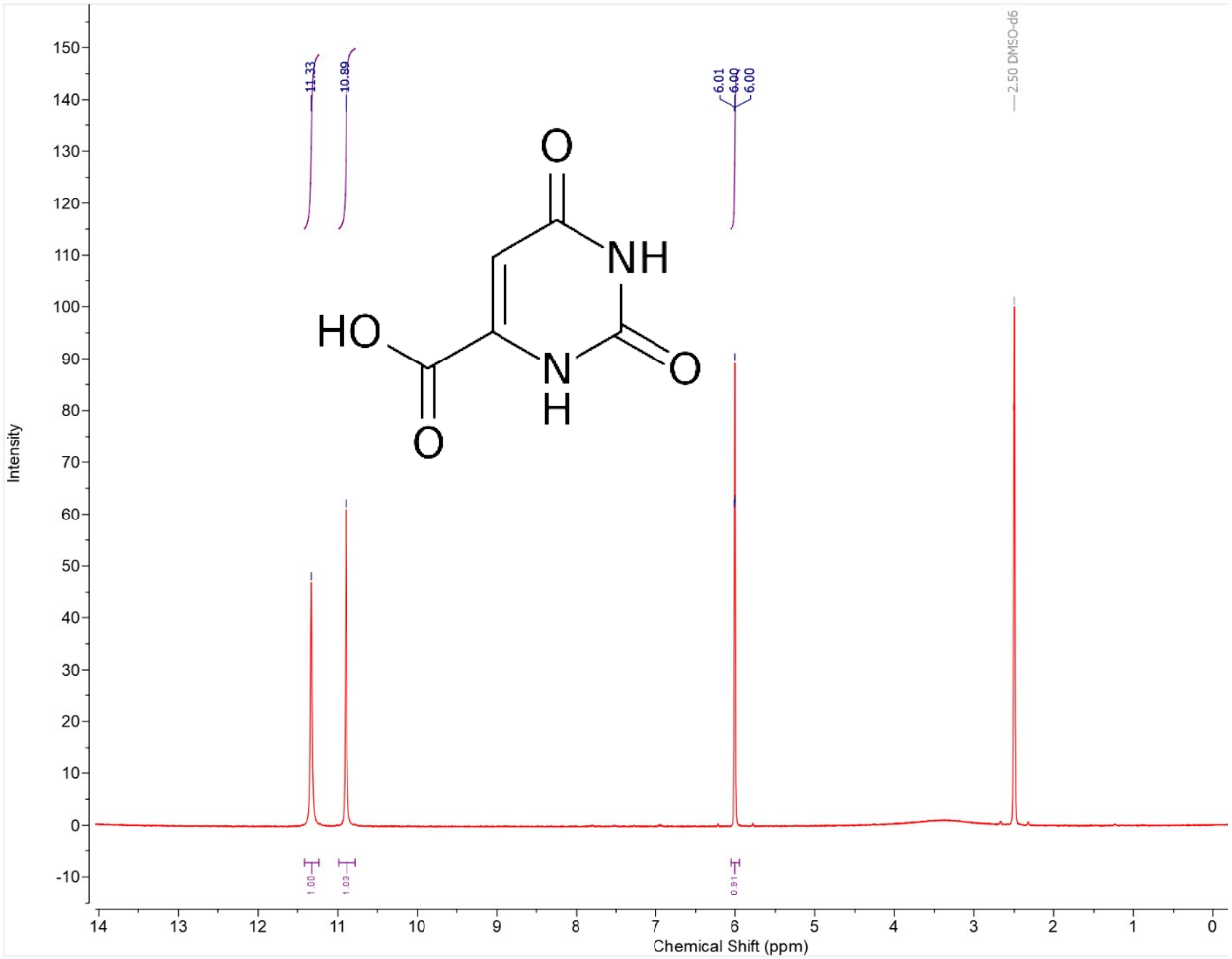

Figure S11: ^{1}H-NMR spectrum for orotic acid from the bottle.

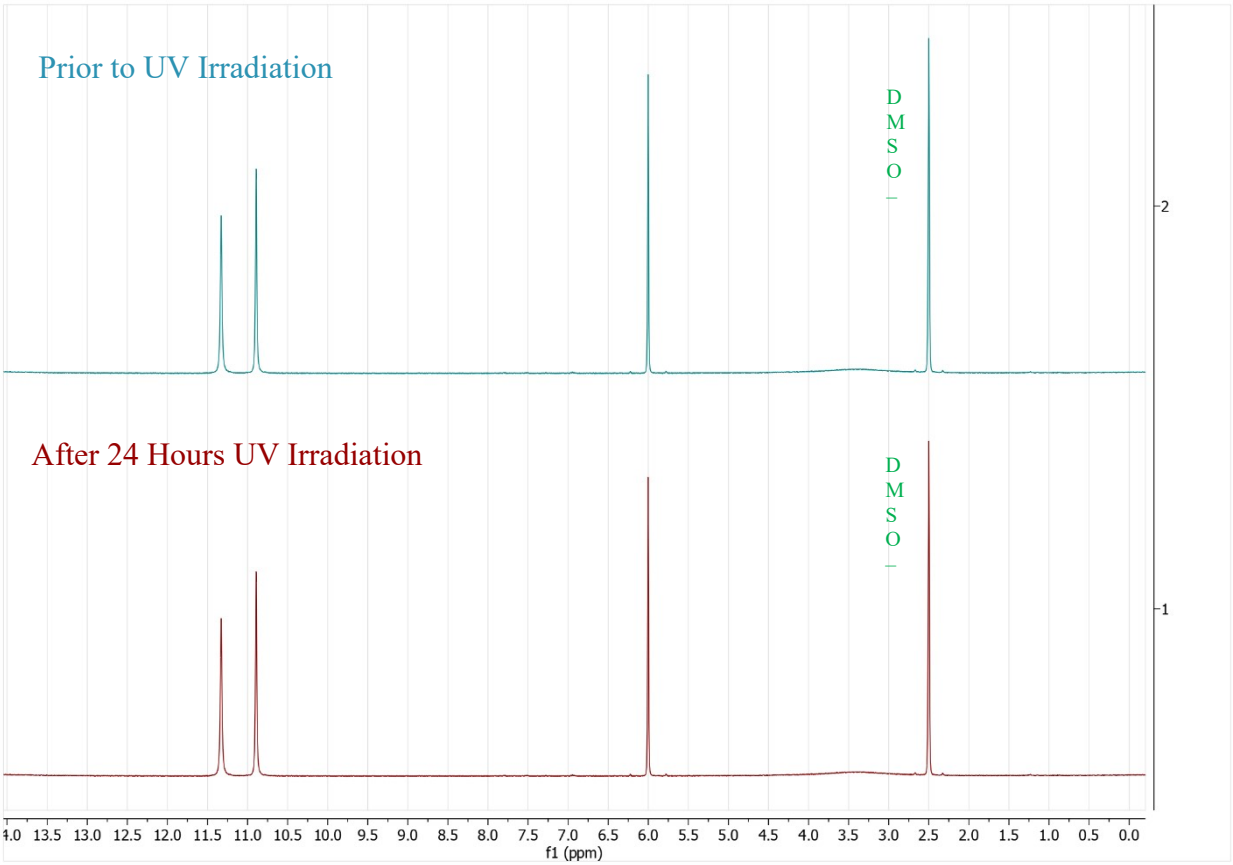

Figure S12: ^{1}H-NMR spectra of solutions of orotic acid prepared from samples in which the crystalline phase received either no UV irradiation (upper) or 24 hours of UV irradiation (lower).

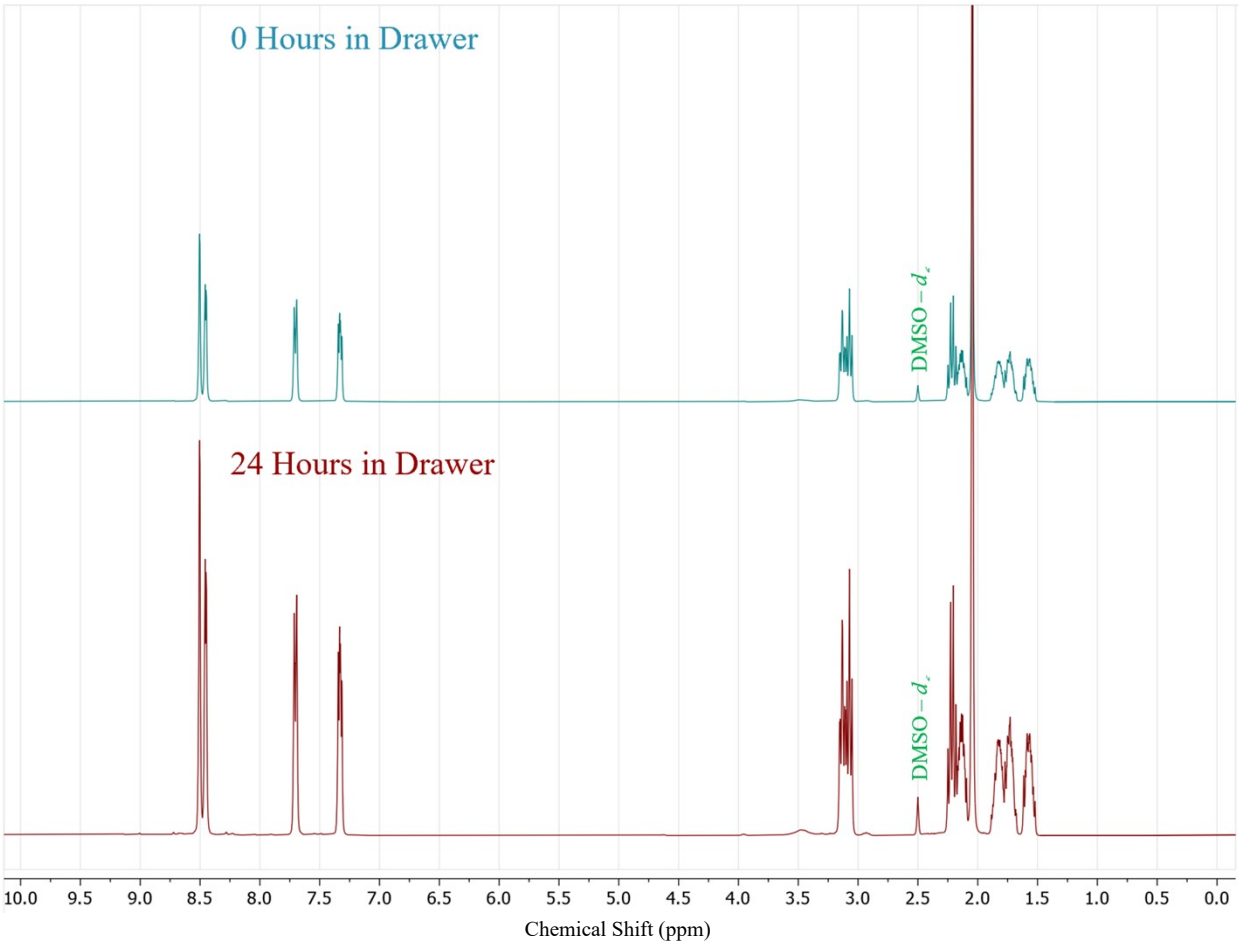

Figure S13: ^{1}H-NMR spectra of solutions of (S)-nicotine prepared from samples in which the liquid was in a vial in a dark drawer for either 0 hours (upper) or 24 hours (lower).

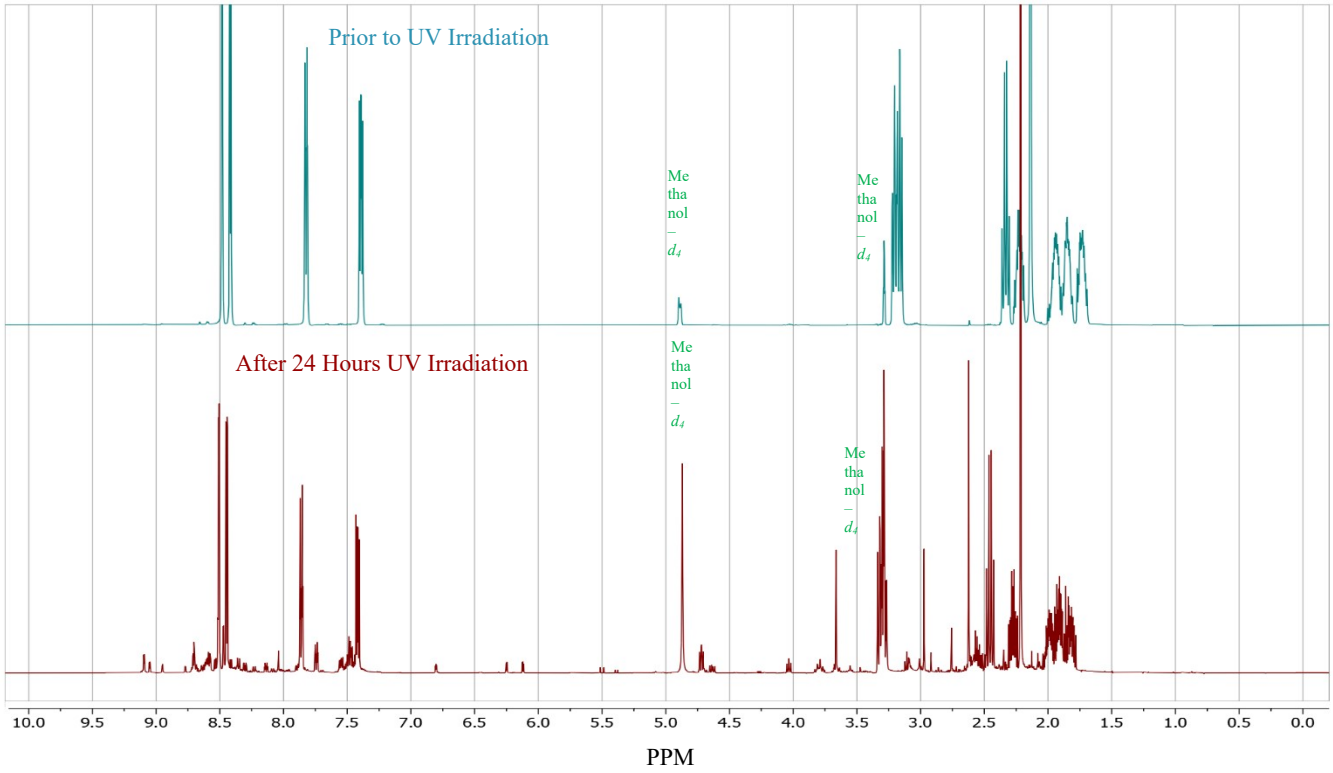

Figure S14: ^{1}H-NMR spectra of deuterated methanol solutions of liquid (S)-nicotine prepared from samples in which the liquid API received either no UV irradiation (upper) or 24 hours of UV irradiation (lower).

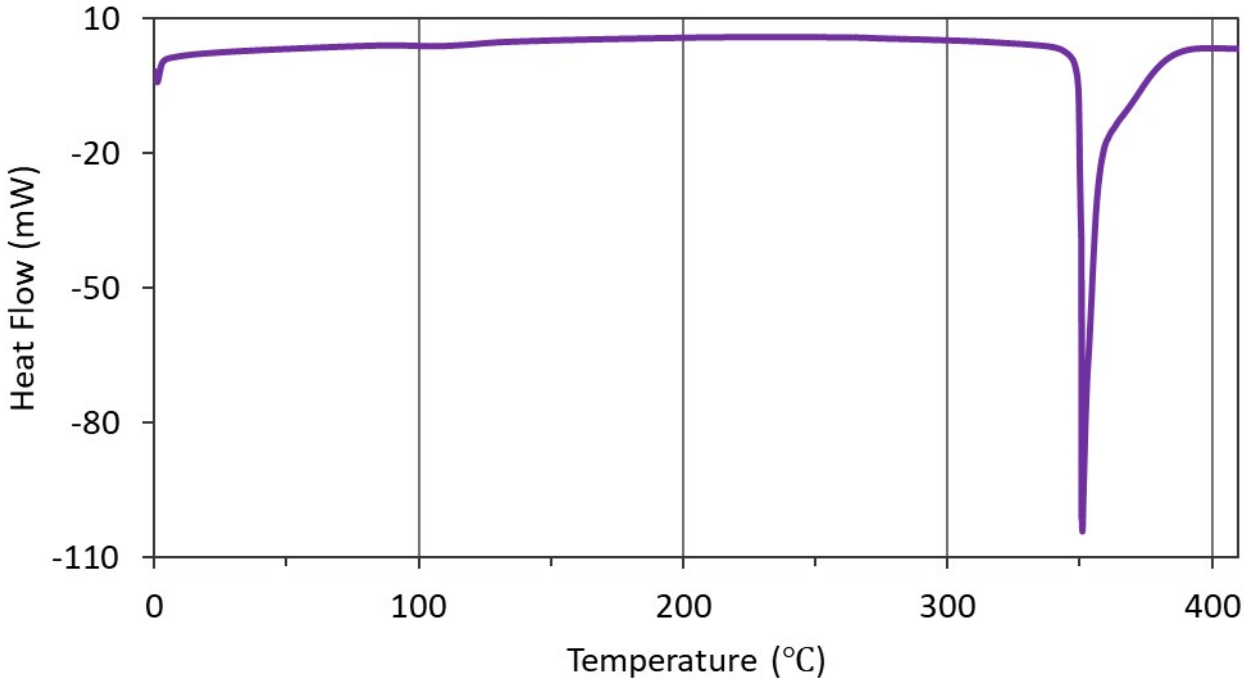

Figure S15: DSC endothermic scan showing the orotic acid melting event. The melting event peaks at 350.9 ℃.

Orotic Acid DSC Endothermic Melting Scan

Hirshfeld Surface Analysis

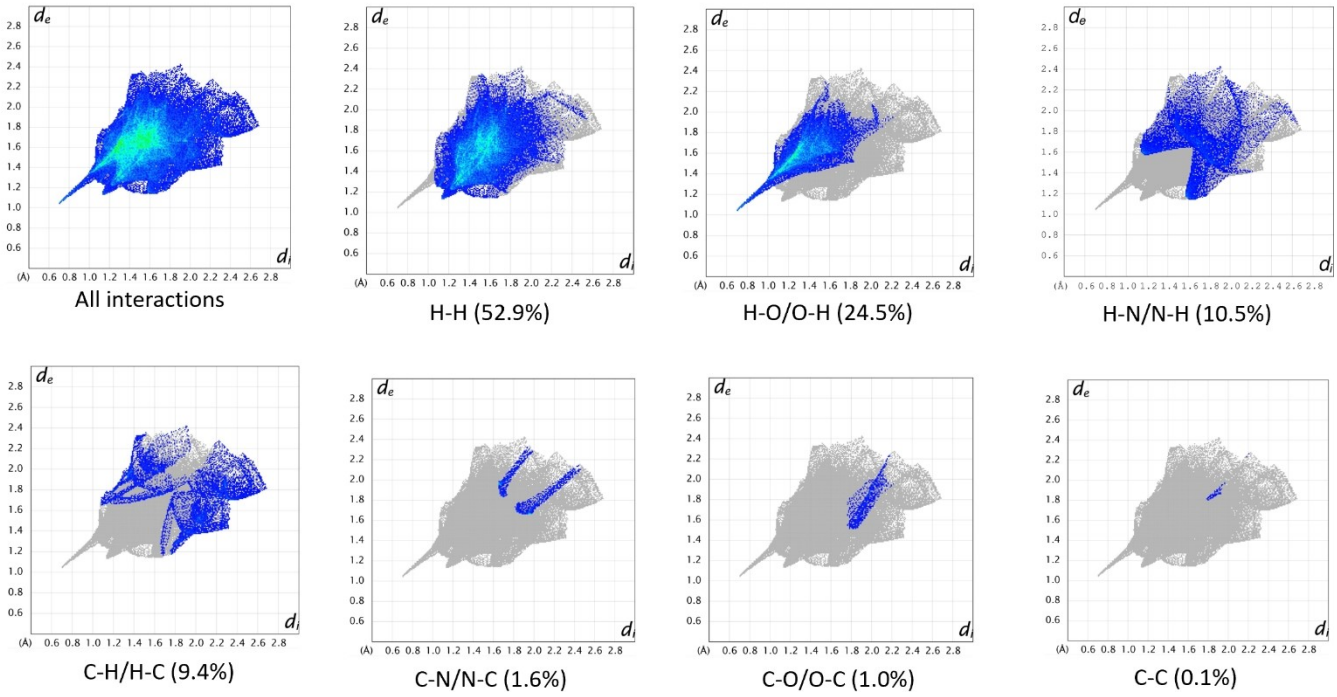

Figure S16: Hirshfeld surface fingerprint plots of the nicotinium in orthorhombic nicotinium L-malate (CCDC Refcode: QAXQOZ).

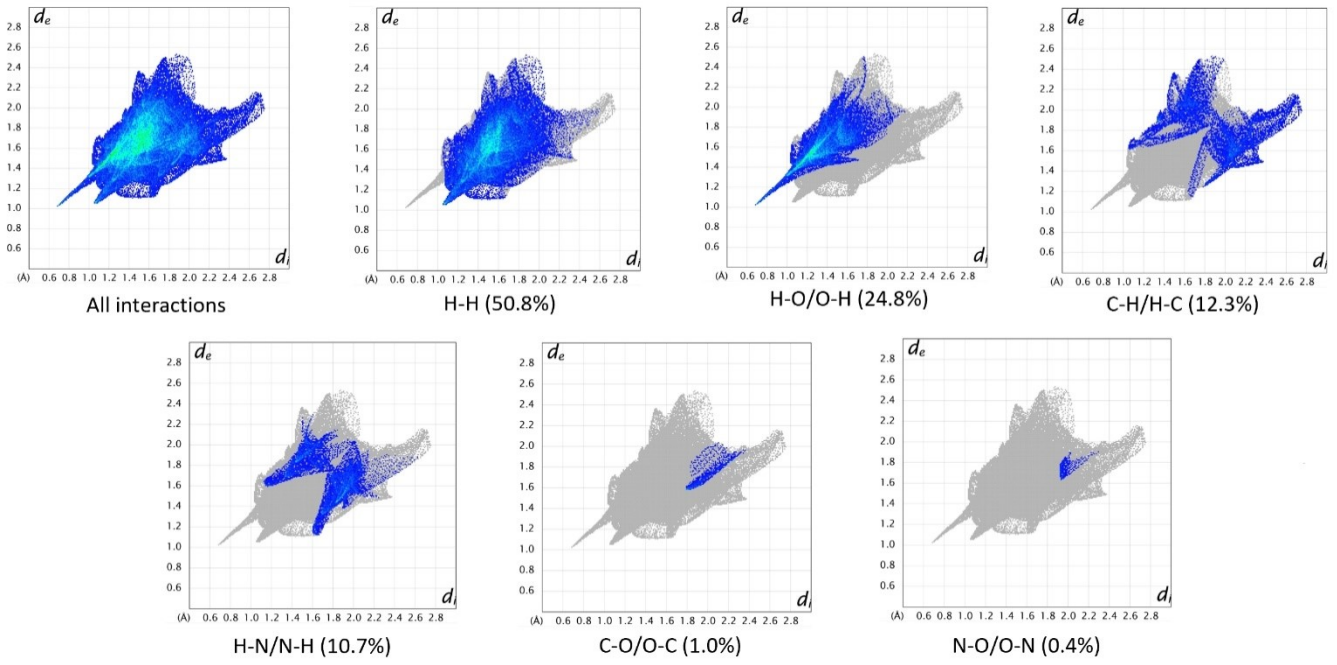

Figure S17: Hirshfeld surface fingerprint plots of the nicotinium in monoclinic nicotinium L-malate (CCDC Refcode: QAXQOZ01).

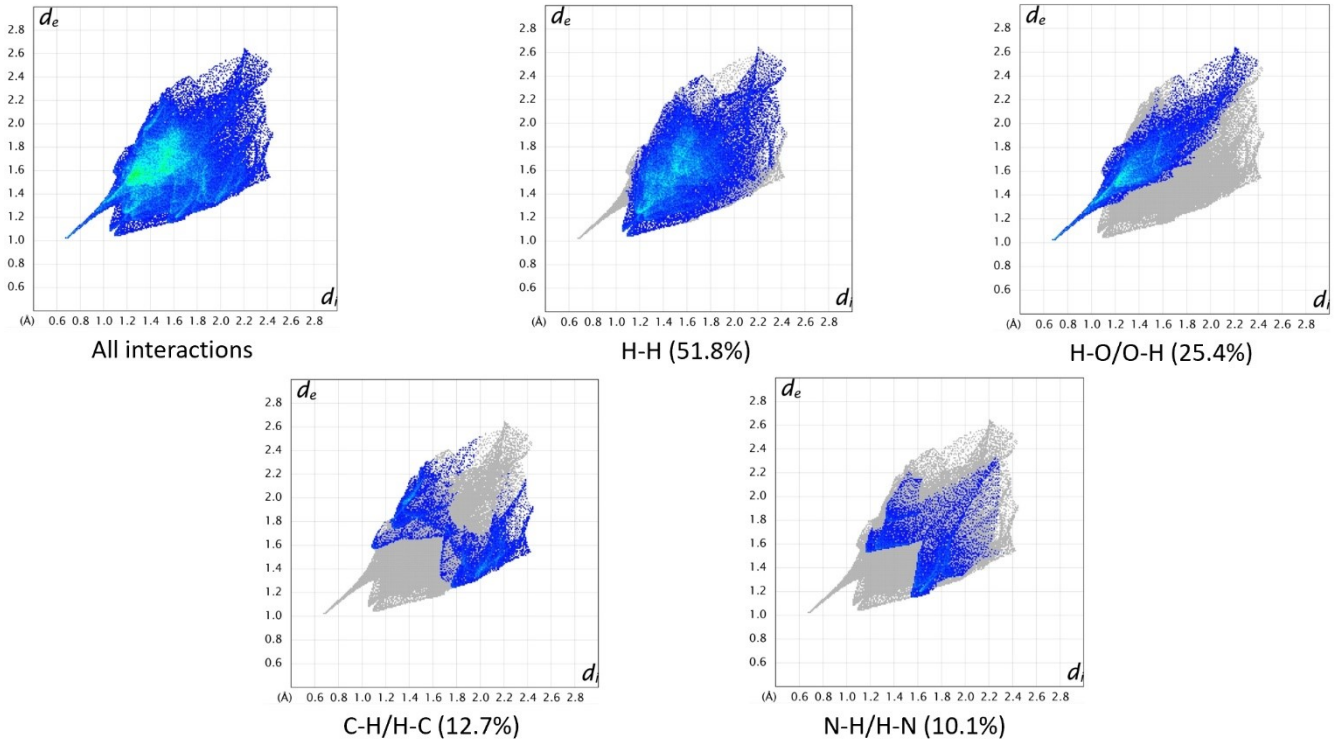

Figure S18: Hirshfeld surface fingerprint plots of the nicotinium in orthorhombic nicotinium D-malate (CCDC Refcode: QAXRAM).

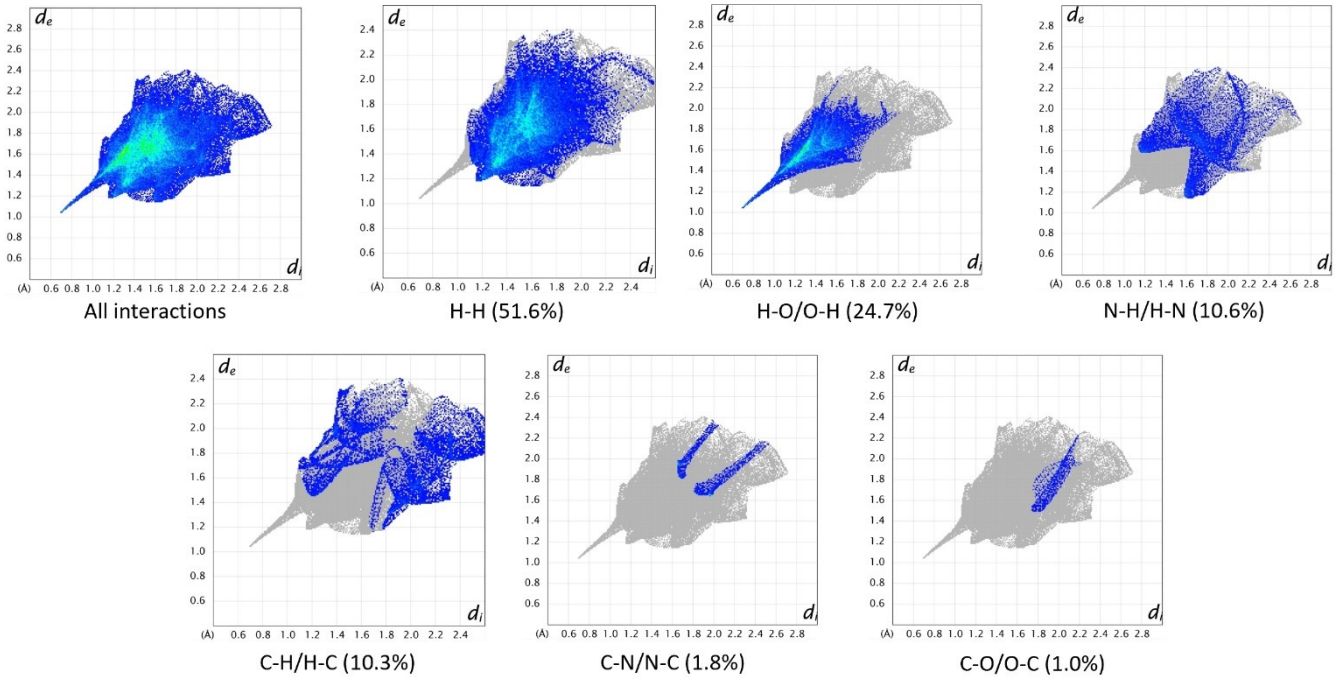

Figure S19: Hirshfeld surface fingerprint plots of the nicotinium in orthorhombic nicotinium DL-malate (CCDC Refcode: QAXQOZ02).