# Supplementary information

## Intermolecular interactions, Regioselectivity, and Biological Activity of L-ascorbic Acid, Nicotinic Acid and their Cocrystal

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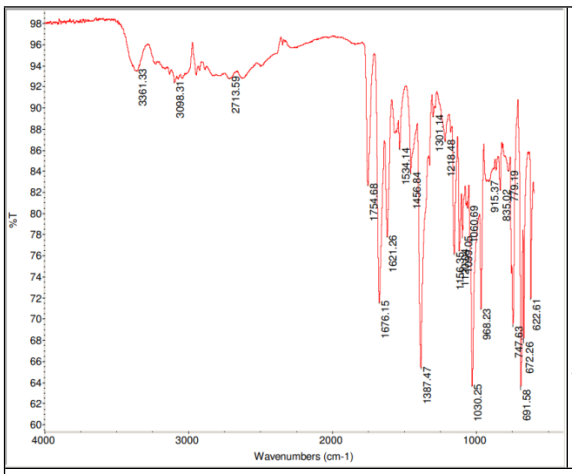
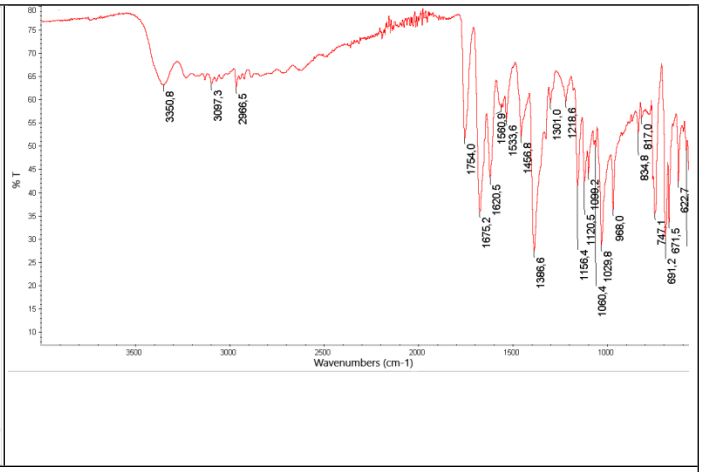
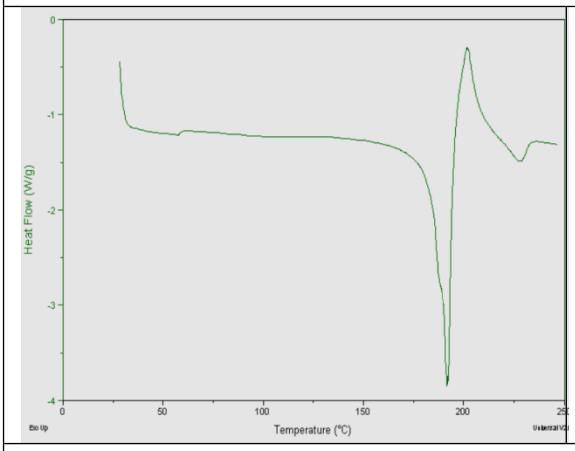
**Table S1** Preparation method and characteristics (DSC, powder X-ray diffraction and IR spectroscopy) of L-Asc · Nic co-crystal prepared by different methods

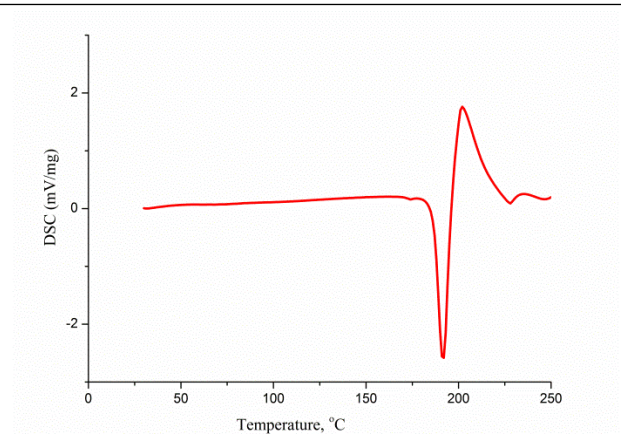
| **L-Asc · Nic** (RUWFAR (CSD 5.40)) [16] | **L-Asc · Nic** [This work] |
|---|---|
| L-Ascorbic acid, 88.1 mg (0.500 mmol), and nicotinic acid, 61.6 mg (0.500 mmol), were dissolved in 6 mL of MeOH and heated until a clear solution was obtained. The solution was slowly evaporated at room temperature and colorless crystals were harvested after two days. | Samples of L-AscNic cocrystals were obtained according to the procedure described in Ref.[16] |



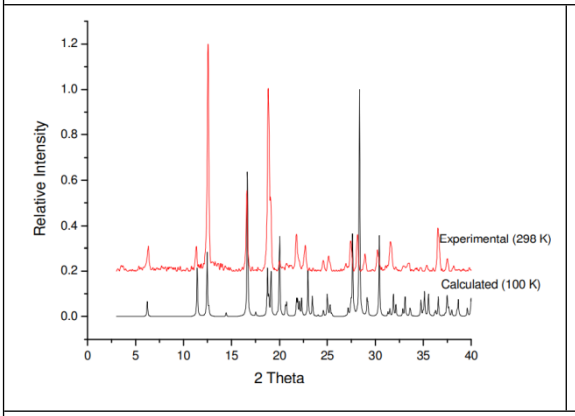



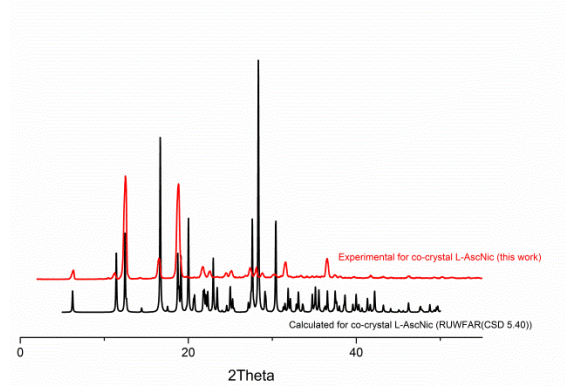

**IR***




**DSC****




**PXRD*****

*The FT-IR spectra of the powder samples were recorded on the Nicolet 6700 Fisher Thermo Scientific Instrument using the ATR FTIR in the range of 4000-400 $cm^{-1}$.

**The differential scanning calorimetry (DSC) measurements were performed to compare the thermal behaviour of co-crystals. We used the NETZSCH STA 449F1 STA449F1A-0237-M instrument in the temperature range of 30-600° C at a heating rate of 10 K/min in an argon atmosphere.

***X-ray powder diffraction (XRPD) patterns were measured using the STOE-MP diffractometer with Cu anode (Kα1, λ = 1.5406 Å, bent Ge (111) monochromator) and the Dectris Mythen 1K detector; data collected in transmission mode with 0.015-degree steps, data collection time was 2 seconds per step.

**Table S2** Hydrogen-bond parameters of pristine L-Asc structure (COFKOA (CSD)),[24] Nic crystal structure (NICOAC02 (CSD)),[25] L-AscNic cocrystal structure (RUWFAR (CSD))[14]

| L-Asc crystal structure (COFKOA (CSD))[24] | | Nic crystal structure (NICOAC02 (CSD))[25] | | L-Asc·Nic cocrystal structure (RUWFAR (CSD))[14] | |
|---|---|---|---|---|---|
| hydrogen bond | D—H (Å)/H···A (Å)/ /D···A (Å)/D—H···A (°) | hydrogen bond | D—H (Å)/H···A (Å)/ /D···A (Å)/D—H···A (°) | hydrogen bond | D—H (Å)/H···A (Å)/ /D···A (Å)/D—H···A (°) |
| O(4a) – H····O(2a) | 0.820/1.929/2.681/151.9 | O(1) – H····N | 0.847/1.843/2.660/161.8 | $C(10)_{Nic}$– H····$O(5)_{Asc}$ | 0.949/2.377/3.042/126.8 |
| O(4b) – H····O(2b) | 0.820/1.908/2.667/153.3 | C(2) – H····O(2) | 0.939/2.550/3.236/130.2 | $O(5)_{Asc}$ – H ····$O(6)_{Asc}$ | 0.840/1.874/2.701/167.9 |
| O(3a) – H····O(5a) | 0.820/1.832/2.648/172.7 | C(4) – H····O(2) | 0.990/2.608/3.317/128.6 | $O(6)_{Asc}$ – H····$O(4)_{Asc}$ | 0.840/1.916/2.746/169.1 |
| O(5b) – H····O(3b) | 0.820/2.010/2.798/142.4 | C(6) – H····O(2) | 0.980/2.576/3.247/125.7 | $O(3)_{Asc}$ – H····$O(7)_{Nic}$ | 0.841/1.786/2.593/160.1 |
| O(3b) – H····O(6a) | 0.819/1.812/2.609/163.8 | | | $O(4)_{Asc}$ – H····$O(8)_{Nic}$ | 0.840/1.705/2.479/152.2 |
| O(6b) – H····O(3a) | 0.820/2.206/2.944/149.9 | | | $C(11)_{Nic}$– H····$O(2)_{Asc}$ | 0.950/2.282/3.139/149.7 |
| O(6a) – H····O(5b) | 0.819/1.978/2.782/166.8 | | | $N_{Nic}$ – H····$O(2)_{Asc}$ | 0.879/2.416/2.979/122.1 |
| C(6b) – H ····O(1a) | 0.969/2.684/3.466/138.0 | | | $N_{Nic}$ – H····$O(7)_{Nic}$ | 0.879/2.188/2.959/146.1 |
| O(5a) – H····O(6b) | 0.819/1.921/2.714/162.5 | | | | |
| C(6a) – H ···· O(4b) | 0.969/2.601/3.513/156.7 | | | | |
| C(6a) – H ···· O(1b) | 0.970/2.605/3.327/131.4 | | | | |
| C(6b) – H ····O(4a) | 0.970/2.515/3.393/150.4 | | | | |

**Table S3** Total effective charge of the L-ascorbic molecule in the structures of L-ascorbic acid (1) and its cocrystals (2–11)[6]

| | | Total effective charge of L-ascorbic (e) | | | |
|---|---|---|---|---|---|
| Coformer | CSD refcode | Mulliken | Voronoi | Hirshfeld | Reference |
| 5-(1,2-Dihydroxyethyl)-3,4-dihydroxy-furan-2(*H*)-one, **1** | COFKOA | *0.00 −0.00* | *0.02 −0.01* | *0.03 −0.03* | McMonagle & Probert (2019) |
| | COFKOA01 | 0.05 −0.05 | 0.01 −0.01 | 0.03 −0.03 | |
| | COFKOA02 | 0.04 −0.04 | 0.01 −0.01 | 0.01 −0.01 | |
| | LASCAC12 | 0.06 −0.06 | 0.09 −0.09 | 0.12 −0.12 | Milanesio *et al.* (1997) |
| | LASCAC14 | 0.01 −0.01 | 0.06 −0.06 | 0.08 −0.08 | Guzei (2009) |
| | LASCAC15 | 0.03 −0.03 | 0.07 −0.07 | 0.11 −0.11 | Fronczek (2016) |
| 4-(Pyridin-4-yl)pyridinium, **2** | POHNUY | −0.04 | 0.01 | 0.04 | Sylvester *et al.* (2019) |
| | | −0.04 | −0.03 | −0.03 | |
| Nicotinamide, **3** | OXOHEQ | 0.02 | 0.09 | 0.13 | Wang *et al.* (2016*a*) |
| | | −0.05 | 0.00 | −0.03 | |
| Nicotinamide (three molecules in the asymmetric unit) | OXOHIU | 0.01 | 0.04 | 0.01 | |
| Isonicotinamide, **4** | OXOGUF | 0 | −0.19 | 0 | |
| Bis(isonicotinamide) | OXOHAM[d] | −0.02 | −0.08 | −0.11 | |
| | | 0.15 | −0.26 | −0.03 | |
| 3-Bromopyridin-4(1*H*)-one, **5** | ULUZUY[c] | 0.03 | 0.09 | 0.14 | Wang *et al.* (2016*b*) |
| Betaine, **6** | RUWFEV | 0.67 | 0.03 | 0.04 | Kavuru *et al.* (2010) |
| Nicotinic acid, **7** | RUWFAR[b] | −0.012 | −0.01 | −0.03 | |
| Sarcosine, **8** | RUWDUJ[b] | 0.01 | 0.01 | 0.02 | |
| Isoquinoline-1-carboxylic acid, **9** | ERAVAU | −0.07 | −0.18 | −0.25 | Goher *et al.* (2003) |
| L-Serine, **10** | SERASC10[e] | 0.01 | 0.08 | 0.17 | Sudhakar *et al.* (1980) |
| Picolinic acid, **11** | – | −0.04 −0.03 | −0.17 −0.16 | −0.24 −0.24 | This work |

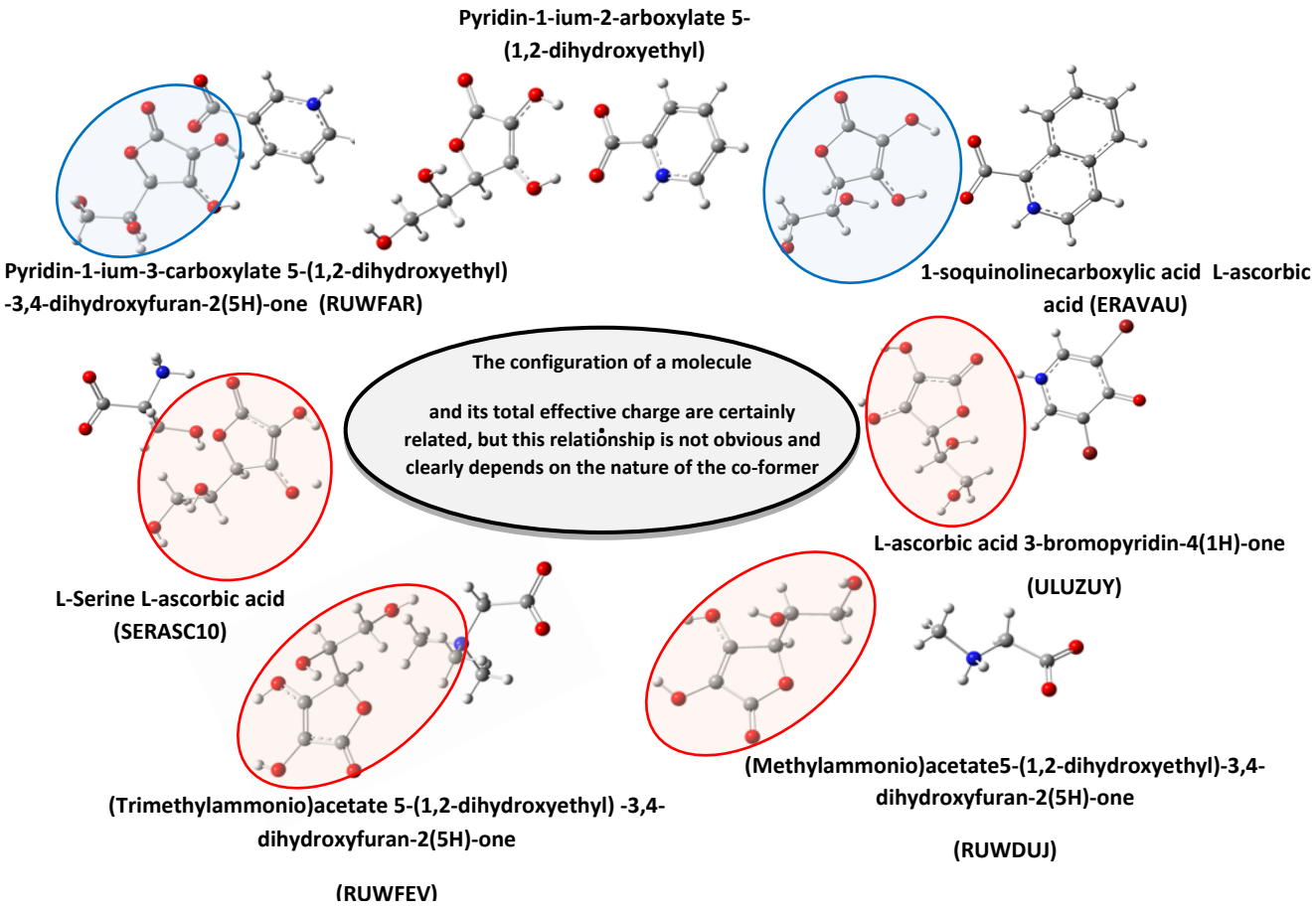



**Figure S1** Structures of binary co-crystals containing the L-Asc molecule in a chelating configuration indicating the sign of the total effective charge of the molecule (Table S3).

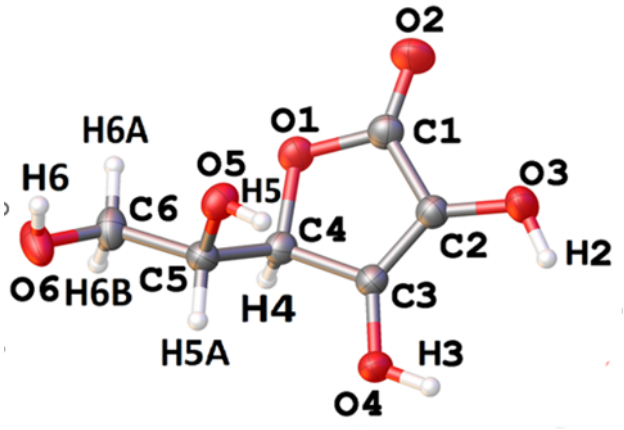



**Figure S2** Structure of the L-Asc molecule showing the atom-numbering schemes[6]

**Table S4** The calculated descriptor values (MultiWFN) for all atoms of the conformer molecule 'a' (COFKOA(CSD)), the atom-numbering scheme at Figure S2

| Atom index | $f^+$ | $f^-$ | $f^0$ | $f^2$ |
|---|---|---|---|---|
| O1 | 0.02636 | 0.06853 | 0.04744 | -0.04217 |
| O2 | 0.06802 | 0.19974 | 0.13388 | -0.13173 |

| | | | | |
|---|---|---|---|---|
| O3 | 0.05570 | 0.06016 | 0.05793 | -0.00445 |
| O4 | 0.03634 | 0.08373 | 0.06003 | -0.04739 |
| O5 | 0.01695 | 0.08213 | 0.04954 | -0.06518 |
| O6 | 0.01944 | 0.09693 | 0.05818 | -0.07750 |
| C1 | 0.09221 | 0.04636 | 0.06929 | 0.04586 |
| C2 | 0.07344 | 0.11842 | 0.09593 | -0.04498 |
| C3 | 0.10561 | 0.09712 | 0.10137 | 0.00849 |
| C4 | 0.02504 | 0.03065 | 0.02785 | -0.00561 |
| C5 | 0.02035 | 0.02695 | 0.02365 | -0.00659 |
| C6 | 0.02360 | 0.02276 | 0.02318 | 0.00083 |
| H2 | 0.06306 | 0.00940 | 0.03623 | 0.05366 |
| H3 | 0.09759 | 0.00569 | 0.05164 | 0.09191 |
| H4 | 0.05343 | 0.00873 | 0.03108 | 0.04470 |
| H5 | 0.03271 | 0.00825 | 0.02048 | 0.02446 |
| H5A | 0.03729 | 0.00866 | 0.02298 | 0.02863 |
| H6 | 0.07405 | 0.00841 | 0.04123 | 0.06564 |
| H6A | 0.04247 | 0.00791 | 0.02519 | 0.03456 |
| H6B | 0.02730 | 0.00954 | 0.01842 | 0.01776 |

**Table S5** The calculated descriptor values (MultiWFN) for all atoms of the conformer molecule 'b' (COFKOA(CSD)), the atom-numbering scheme at Figure S2

| Atom index | $f^+$ | $f^-$ | $f^0$ | $f^2$ |
|---|---|---|---|---|
| O1 | 0.02516 | 0.07035 | 0.04775 | -0.04519 |
| O2 | 0.06430 | 0.20437 | 0.13433 | -0.14008 |
| O3 | 0.03393 | 0.08514 | 0.05953 | -0.05121 |
| O4 | 0.05576 | 0.06010 | 0.05793 | -0.00434 |
| O5 | 0.01778 | 0.07308 | 0.04543 | -0.05530 |
| O6 | 0.01965 | 0.09139 | 0.05552 | -0.07174 |
| C1 | 0.08788 | 0.04831 | 0.06809 | 0.03957 |
| C2 | 0.06762 | 0.12651 | 0.09707 | -0.05890 |
| C3 | 0.10095 | 0.10034 | 0.10065 | 0.00061 |
| C4 | 0.02493 | 0.03192 | 0.02842 | -0.00699 |
| C5 | 0.02055 | 0.02700 | 0.02377 | -0.00645 |
| C6 | 0.02373 | 0.02287 | 0.02330 | 0.00086 |
| H2 | 0.06545 | 0.00962 | 0.03754 | 0.05584 |
| H3 | 0.09917 | 0.00570 | 0.05244 | 0.09347 |
| H4 | 0.04174 | 0.00953 | 0.02563 | 0.03222 |
| H5 | 0.06571 | 0.00688 | 0.03629 | 0.05883 |
| H5A | 0.03851 | 0.00446 | 0.02149 | 0.03404 |
| H6 | 0.06814 | 0.00810 | 0.03812 | 0.06003 |
| H6A | 0.04225 | 0.00967 | 0.02596 | 0.03258 |
| H6B | 0.02728 | 0.00471 | 0.01599 | 0.02257 |

**Table S6** The calculated descriptor values (MultiWFN) for all atoms of

the conformer molecule L-Asc $_{\text{L-AscNic}}$ (RUWFAR (CSD)), the atom-numbering scheme at Figure S2

| Atom index | $f^+$ | $f^-$ | $f^0$ | $f^2$ |
|---|---|---|---|---|
| O1 | 0.01669 | 0.07558 | 0.04613 | -0.05889 |
| O2 | 0.04240 | 0.23208 | 0.13724 | -0.18968 |
| O3 | 0.03511 | 0.08108 | 0.05809 | -0.04598 |
| O4 | 0.05618 | 0.05856 | 0.05737 | -0.00238 |
| O5 | 0.01954 | 0.06093 | 0.04023 | -0.04139 |
| O6 | 0.01760 | 0.08487 | 0.05124 | -0.06727 |
| C1 | 0.05862 | 0.05042 | 0.05452 | 0.00820 |
| C2 | 0.05498 | 0.12044 | 0.08771 | -0.06546 |
| C3 | 0.07677 | 0.10239 | 0.08958 | -0.02562 |
| C4 | 0.02017 | 0.02852 | 0.02434 | -0.00836 |
| C5 | 0.02407 | 0.03105 | 0.02756 | -0.00697 |
| C6 | 0.02315 | 0.02441 | 0.02378 | -0.00126 |
| H2 | 0.10111 | 0.00740 | 0.05425 | 0.09371 |
| H3 | 0.12820 | 0.00544 | 0.06682 | 0.12276 |
| H4 | 0.03795 | 0.00919 | 0.02357 | 0.02876 |
| H5 | 0.08126 | 0.00555 | 0.04340 | 0.07572 |
| H5A | 0.05530 | 0.00415 | 0.02973 | 0.05115 |
| H6 | 0.07198 | 0.00720 | 0.03959 | 0.06478 |
| H6A | 0.01902 | 0.00404 | 0.01153 | 0.01498 |
| H6B | 0.05128 | 0.00665 | 0.02897 | 0.04463 |