Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary information

Collected XRPD patterns for HAL, APZ and QTP are shown in the figure S1, and DSC measurements using different heating rates for HAL, APZ and QTP are presented in figure S2.

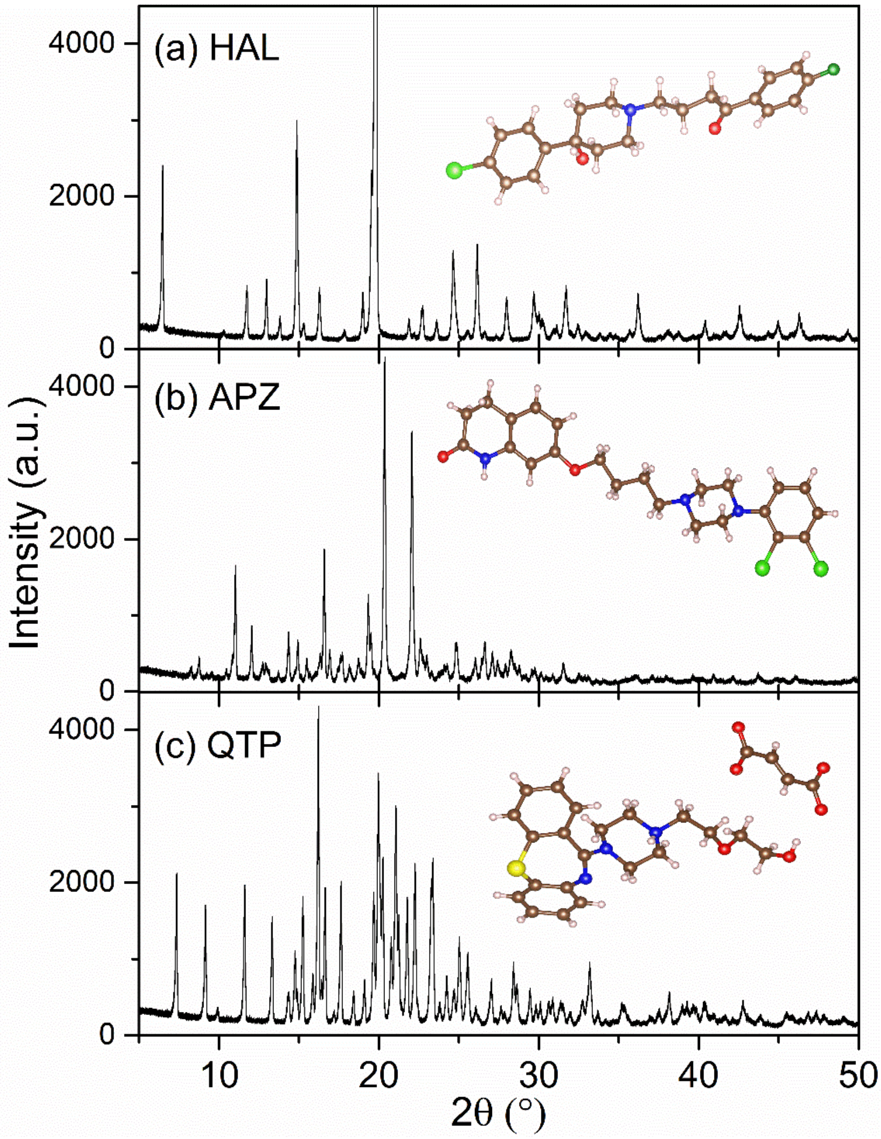

Figure S1 XRPD pattern (a) HAL, (b)APZ and (c) QTP using λ=1,5418 Å.

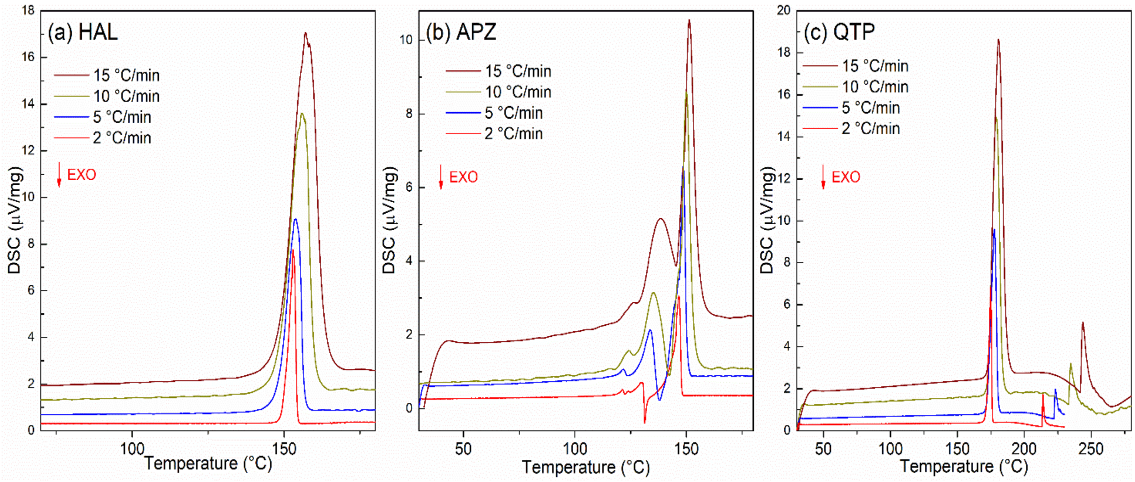

Figure S2 DSC thermograms of HAL, APZ and QTP subject to different heating rates using a new sample in each process.

To confirm the structural stability of the bioactive molecules when the sample undergoes a cyclic process, i.e. same sample submitted to consecutive heating and cooling cycles, we observe the following:

(i) the structural change observed in HAL, figure S3, is reversible;

(ii) APZ undergoes a transition to a new stable polymorphic form, figure S4;

(iii) QTP, due the evaporation of the hemifumarate salt, becomes amorphous after the first heating process, figure S5.

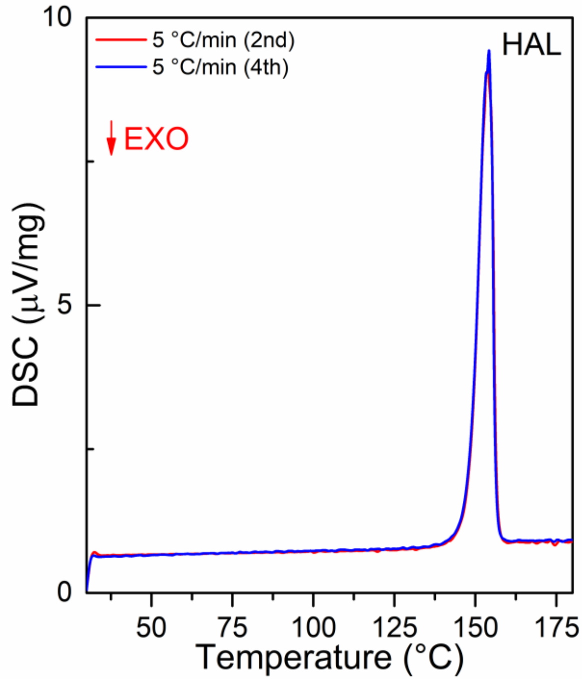

Figure S3 DSC thermograms of HAL submitted to a cycling process showing that the phase transition is reversible. Heating was followed by cooling using the same rate and the same sample in each process. The curve in red shows the result for the sample was submitted to heating for the second time, while the curve in blue shows the result the fourth cycle.

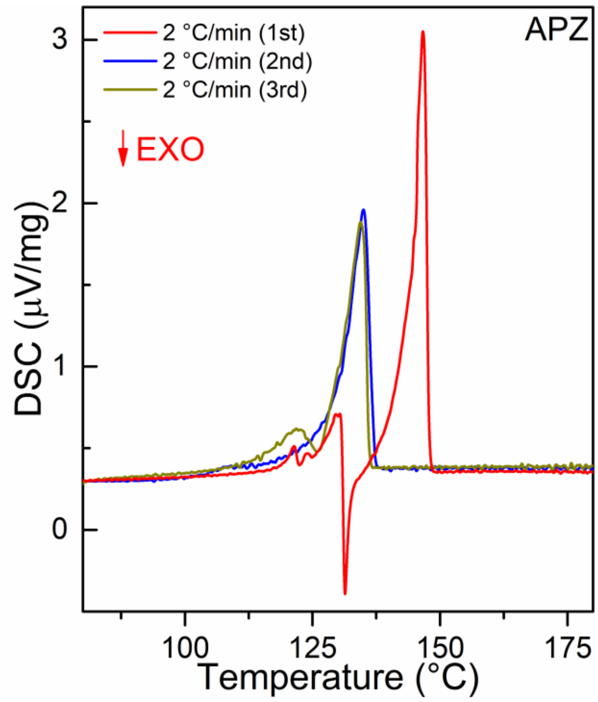

Figure S4 DSC thermograms of APZ submitted to cycling process. The different pattern collected in each cycle indicates that APZ changes the structure upon heating process. After the first process (red), new exothermic peak appears (blue), which was also observed in the third process (gray), indicating that the sample reaches a more stable polymorphic configuration.

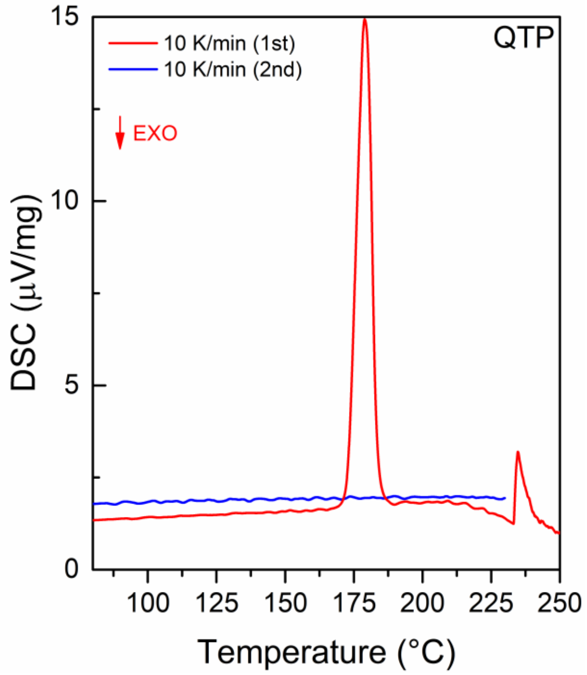

Figure S5 DSC thermograms of QTP submitted to a cycling process showing that after the first heating the molecule degrades as confirmed by the TGA-FTIR data (main text).

Figures S6 and S7 depicts the experimental and *ab initio* calculations of the Raman spectra of APZ and HAL. Calculated spectrum for the isolated molecule in the gas-phase was carried out using the Gaussian software[39].

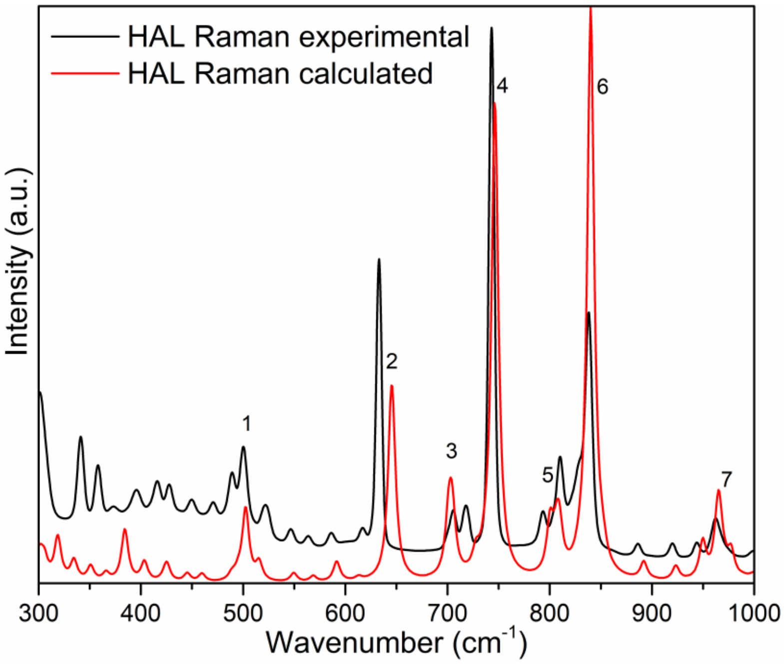

Figure S6 Experimental and calculated Raman spectra of APZ. The calculated spectrum of the gas phase was obtained using the atomic coordinates from the published crystal structure.

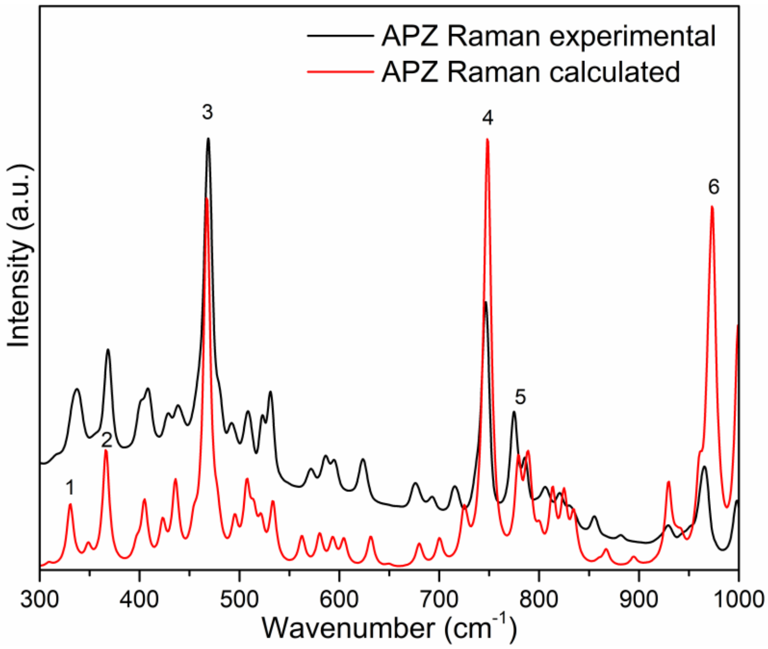

Figure S7 Experimental and calculated Raman spectra of APZ. The calculated spectra of the gas phase was obtained using the atomic coordinates from the published crystal structure.

INS spectrum of HAL and APZ calculated from the normal modes using aCLIMAX[31] are given in figure S8. Comparison of the calculations for the isolated molecules vibrations, figures S9, with that of the crystal showing an overall good agreement.

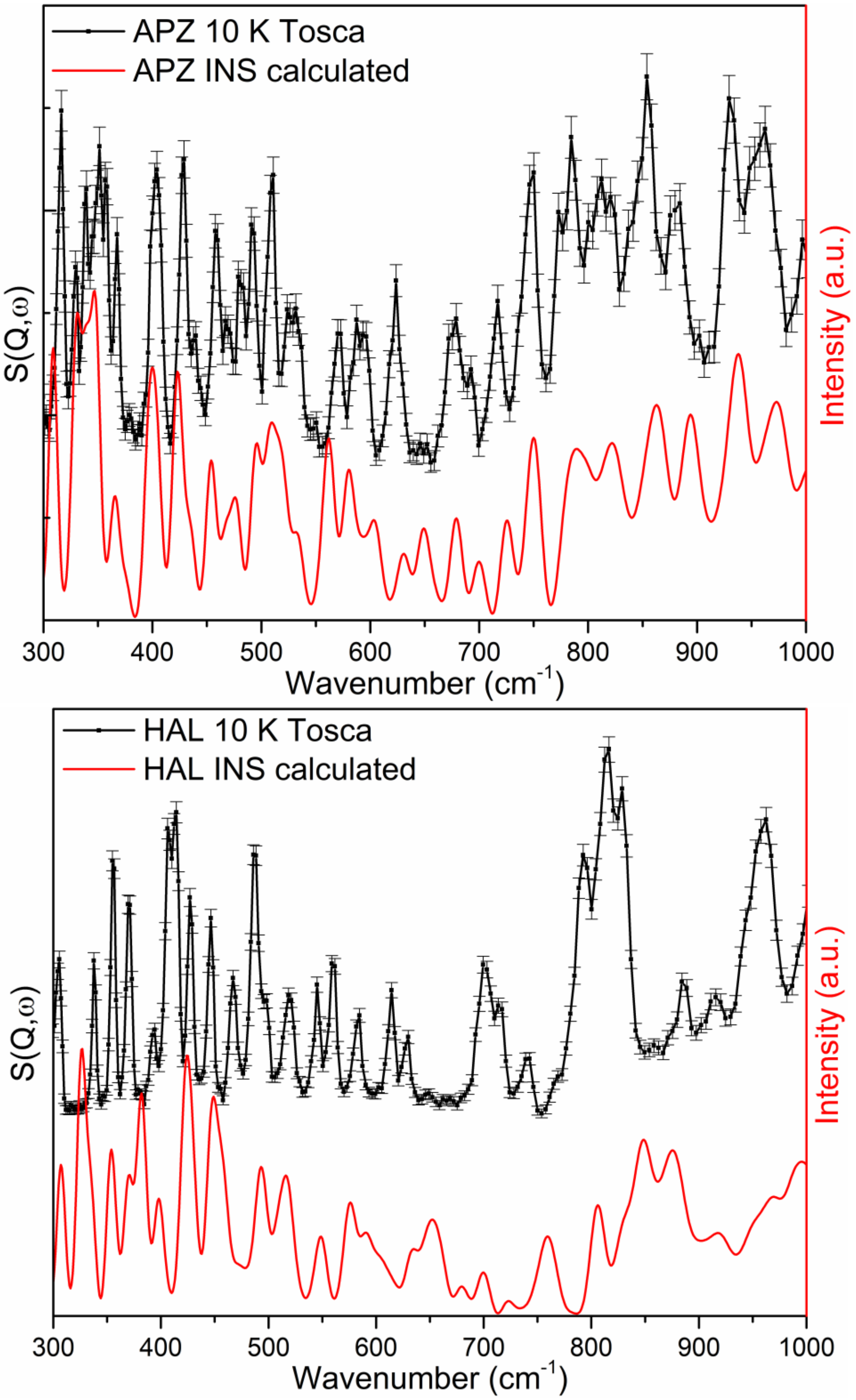

Figure S8 Experimental and calculated INS spectra for APZ and HAL at high frequencies. Calculated spectra using Gaussian were computed using the atomic coordinates from the published crystal structures. The results are plotted in different y-axis for better visualization.

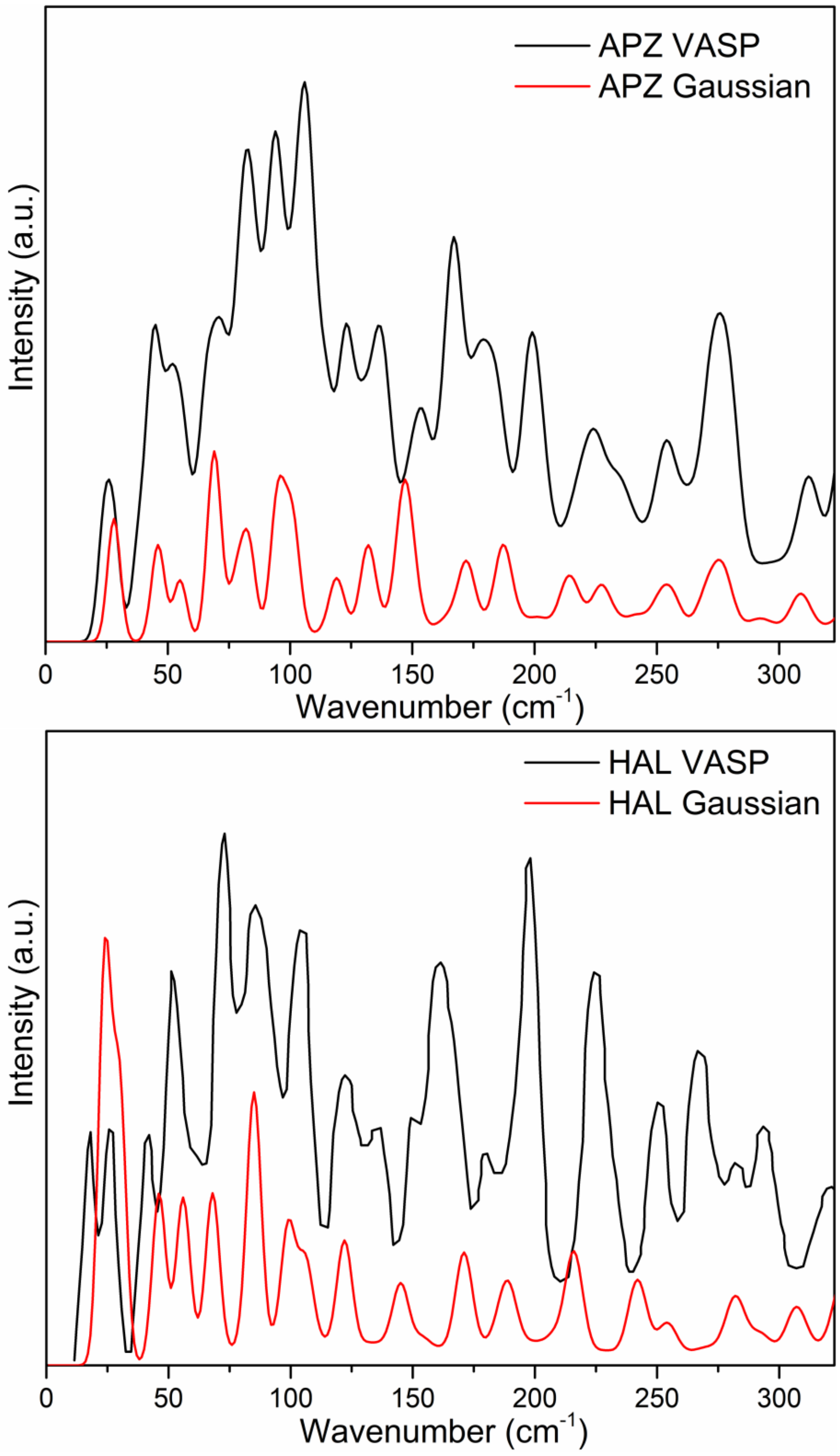

Figure S9 INS of the isolated molecule of APZ and HAL calculated using Gaussian compared to the results obtained using VASP.

Table S1. Assignment of the main vibration observed in the RS spectra calculated using Gaussian. The modes are numbered in Figures S6 and S7. The frequencies in meV are approximated values.

HAL			
Mode	Frequency (cm^{-1})	Frequency (meV)	Assignment
1	502	63	contributions from the whole molecule
2	646	80	vibrations in the fluorophenyl group 4
3	703	88	vibrations in group 3
4	746	90	vibrations in the fluorophenyl group 4
5	806	100	mixed vibrations from groups 2 and 3
6	840	105	vibrations in the hydroxyclorophenylpiperidino
7	965	120	vibrations in group 3
APZ			
1	331	40	vibrations in the dihydro-quilonine group 1
2	367	45	dominated by mixed vibrations in groups 2 and 3
3	467	60	vibrations in the diclorophenylpiperazine group 4
4	748	90	vibrations in the dihydro-quilonine group 1
5	780	95	vibrations in the dihydro-quilonine group 1
6	974	120	dominated by mixed vibrations in groups 1 and 3