Electronic Supplementary Information

Mechanochemical preparation of molecular and ionic co-crystals of the hormone melatonin

O. Shemchuk,[a] V. André,[b] M. T. Duarte,[b,*] D. Braga[a], F. Grepioni[a,*]

[a]*Molecular Crystal Engineering Laboratory, Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via F. Selmi 2, 40126 Bologna, Italy, E-mail: fabrizia.grepioni@unibo.it*

[b]*Centro de Química Estrutural, Instituto Superior Técnico, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal. E-mail: teresa.duarte@tecnico.ulisboa.pt*

Contents **page**

ESI - 1: DSC and TGA measurements 2

ESI - 2: Calculated and Experimental XRPD Patterns 6

ESI - 3 : Rietveld refinements 8

ESI - 4: Tables of tested coformers 9

ESI - 5: Relevant hydrogen bonds 11

ESI - 1: DSC and TGA measurements

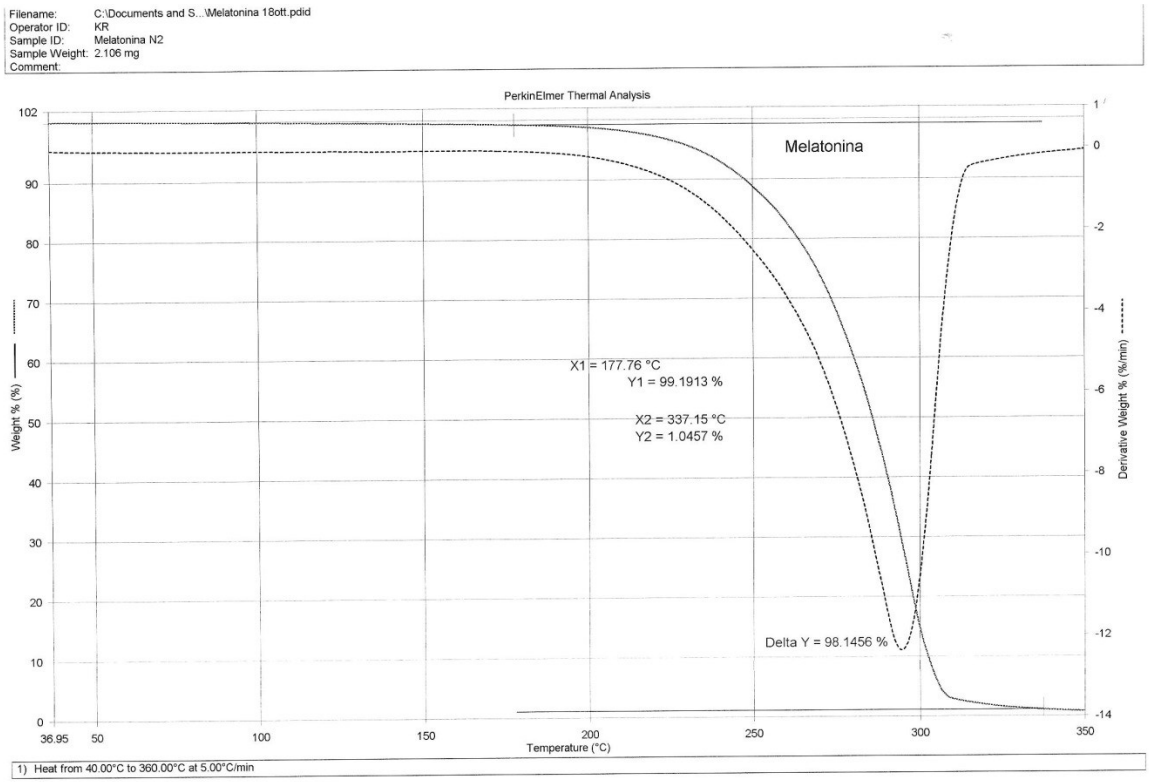

Figure ESI - 1. TGA trace of melatonin.

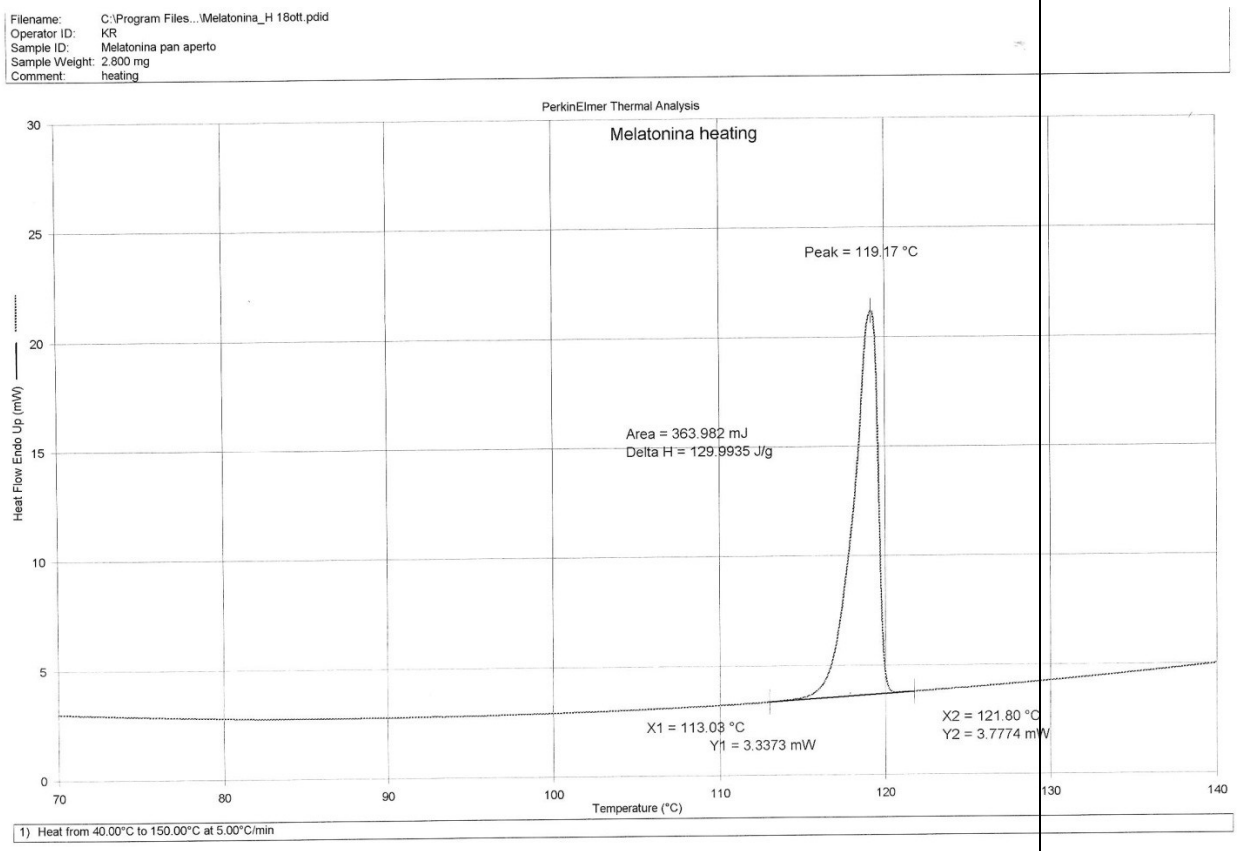

Figure ESI - 2. DSC trace of melatonin.

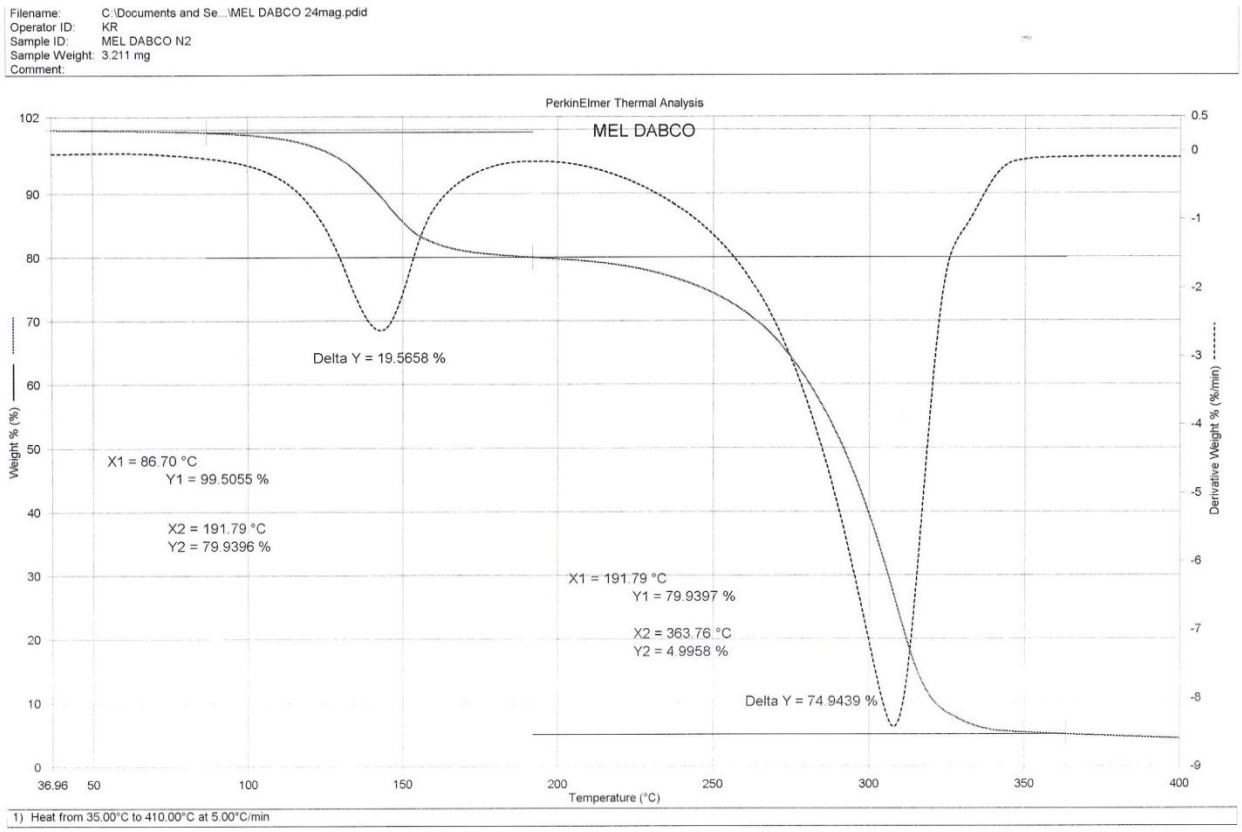

Figure ESI - 3. TGA trace of mel_2·DABCO.

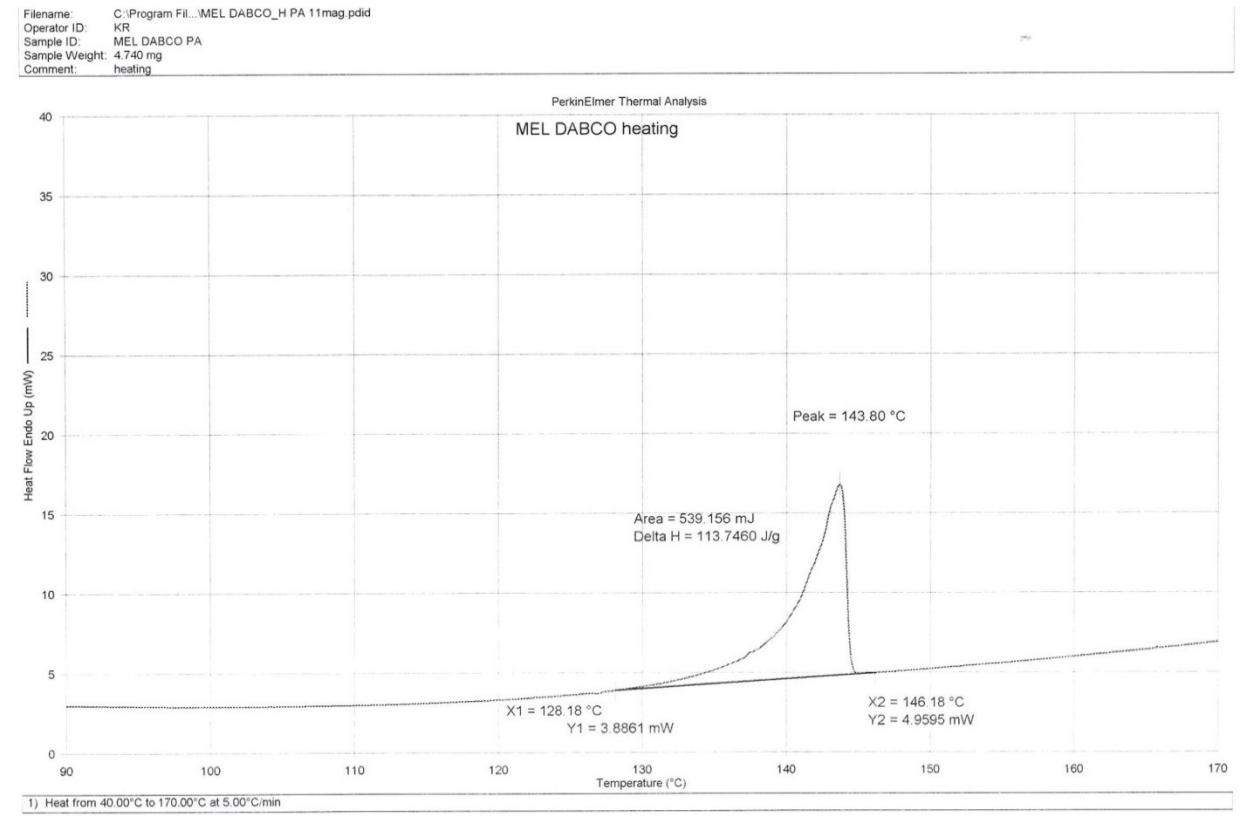

Figure ESI - 4. DSC trace of mel_2·DABCO.

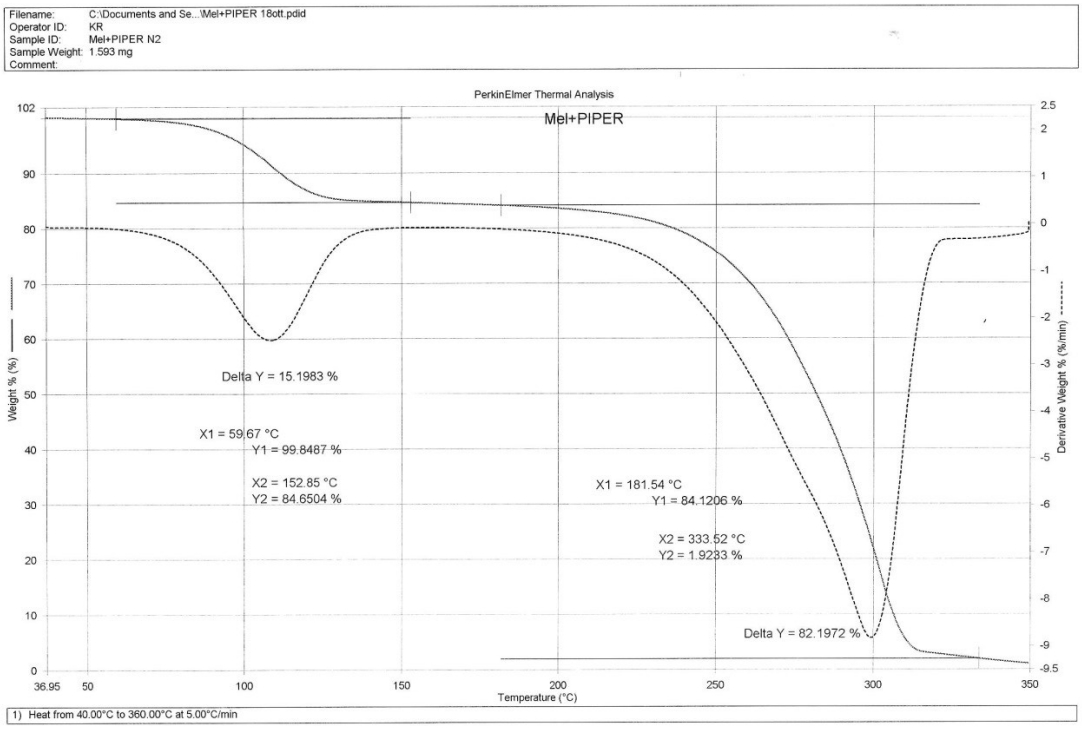

Figure ESI - 5. TGA trace of $mel_2 \cdot pip$.

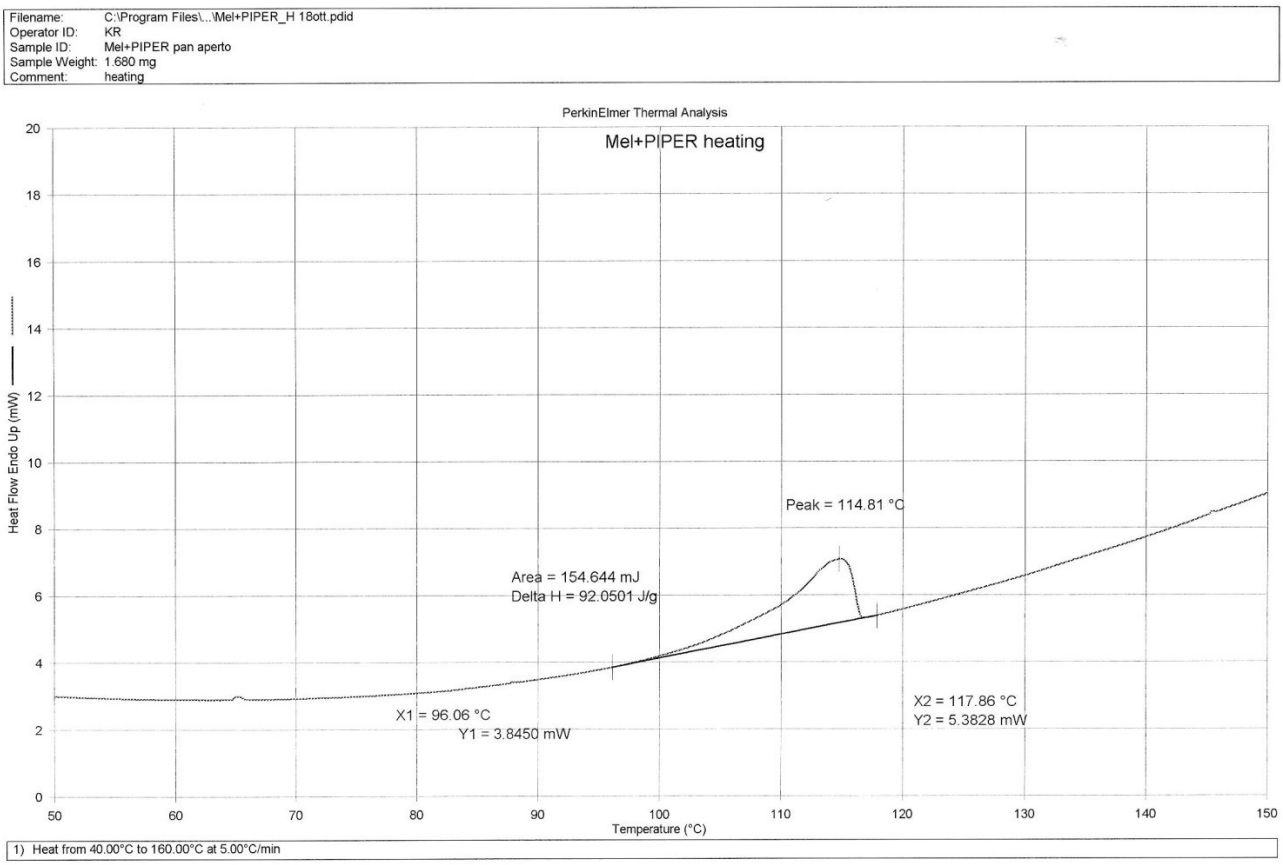

Figure ESI - 6. DSC trace of mel_2·pip.

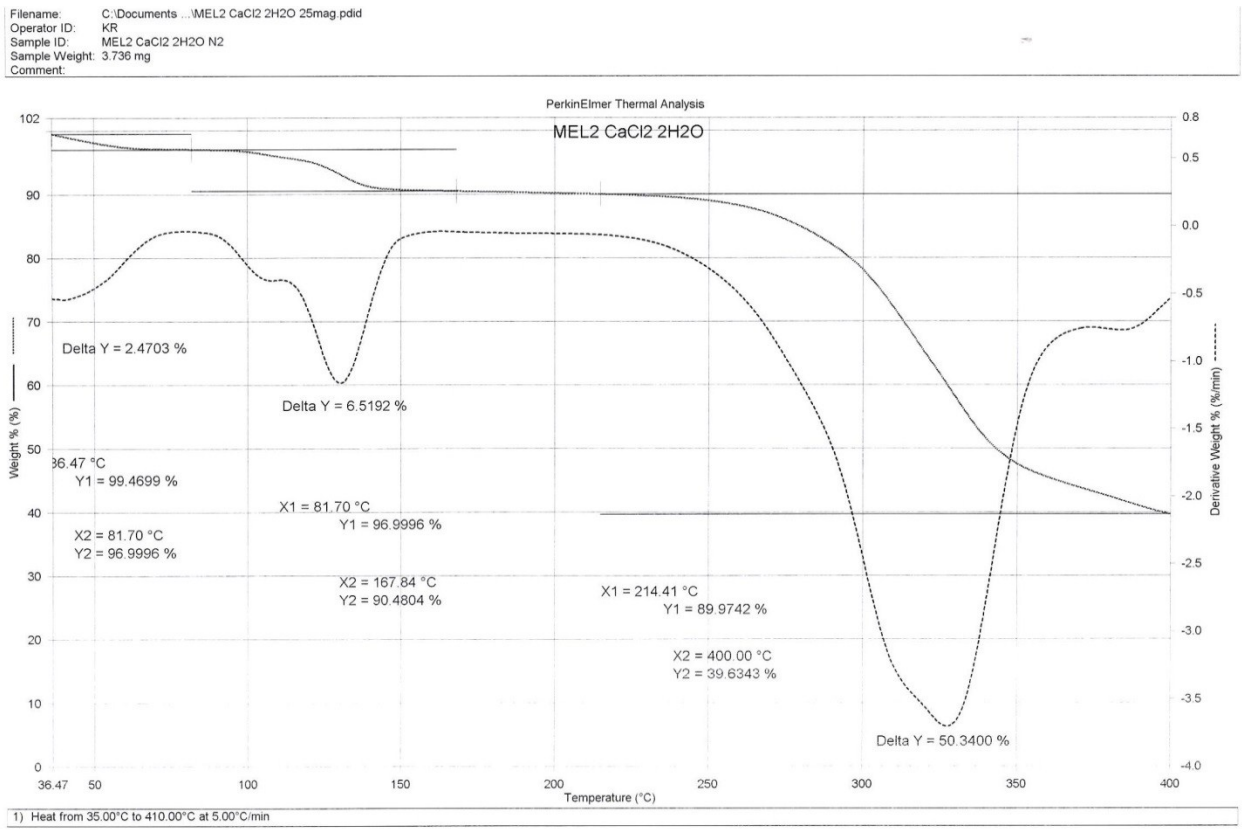

Figure ESI - 7. TGA trace of $mel_2{\cdot}CaCl_2{\cdot}2H_2O$.

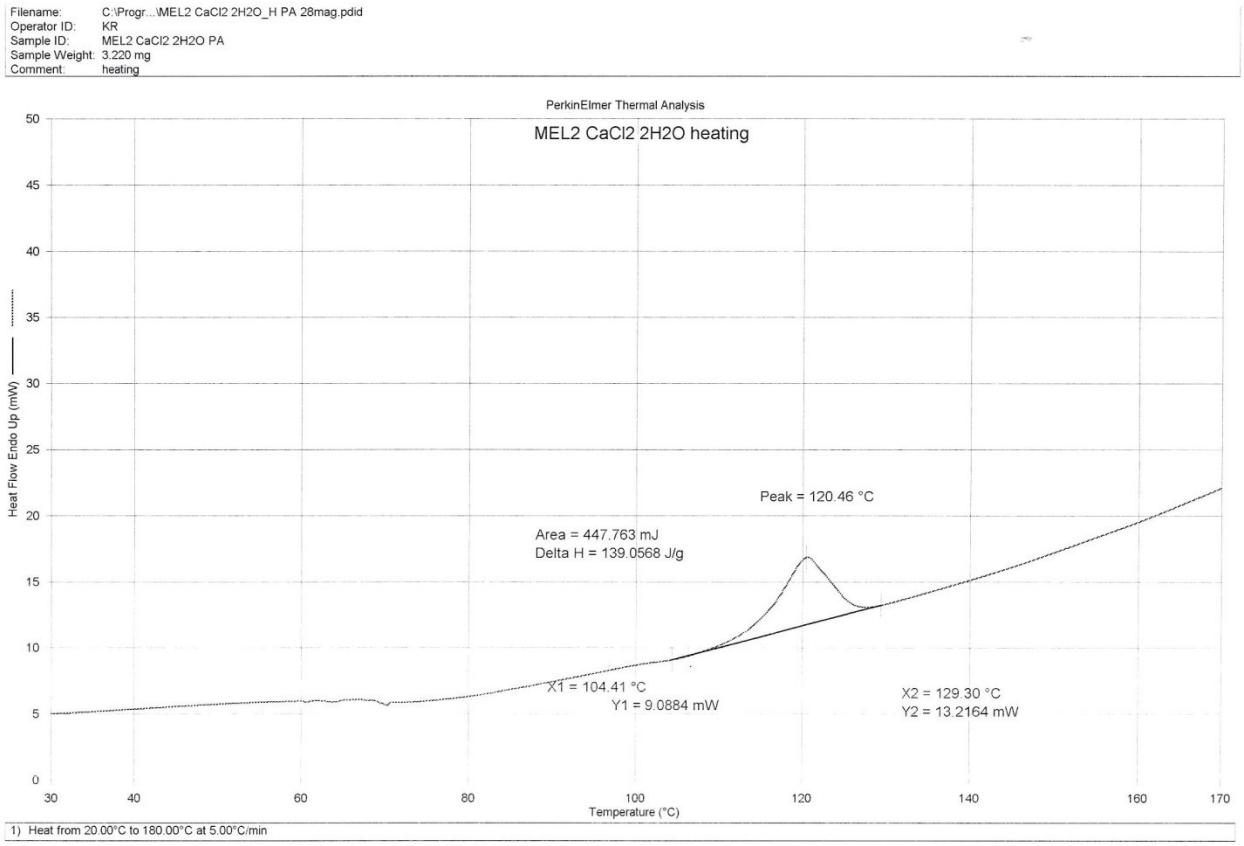

Figure ESI - 8. DSC trace of $mel_2{\cdot}CaCl_2{\cdot}2H_2O$.

ESI – 2: XRPD: comparison between reagents and products

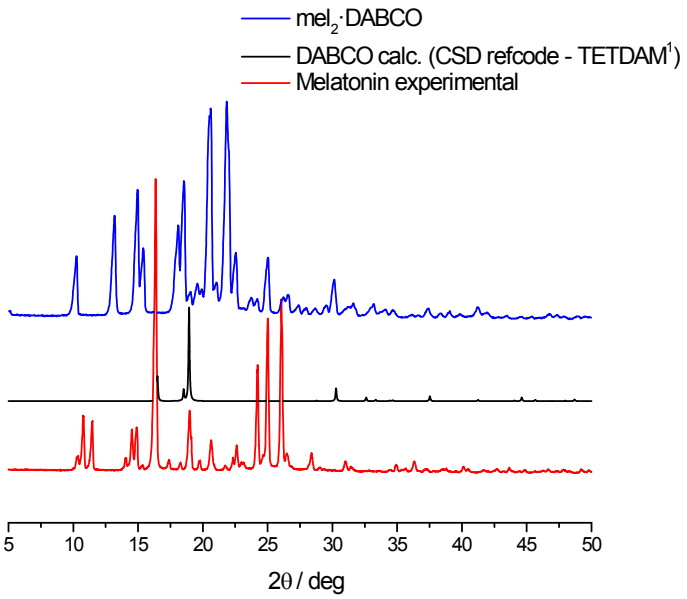

Figure ESI - 9. XRPD comparison between mel_2·DABCO and starting materials. (Ref. 1: T. Wada, E. Kishida, Y. Tomiie, H. Suga, S. Seki and I. Nitta, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 1317-1318.)

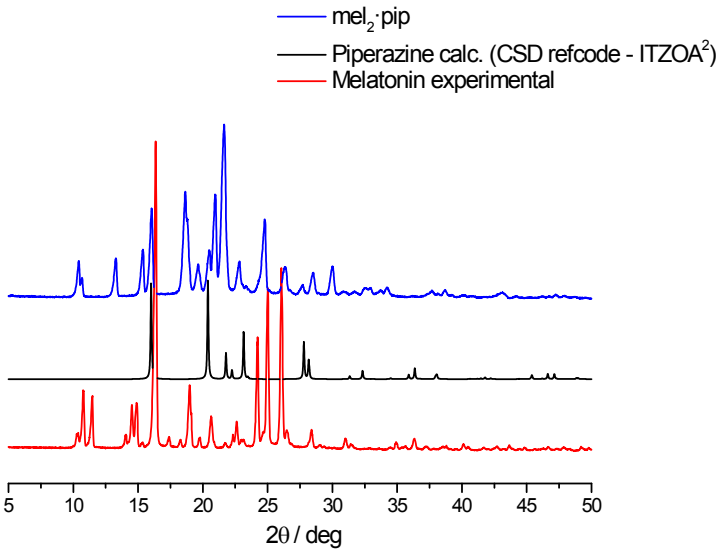

Figure ESI - 10. XRPD comparison between mel_2·pip and starting materials. (Ref. 2: A. Parkin, I. D. H. Oswald and S. Parsons, *Acta Crystallographica Section B Structural Science*, 2004, **60**, 219-227.)

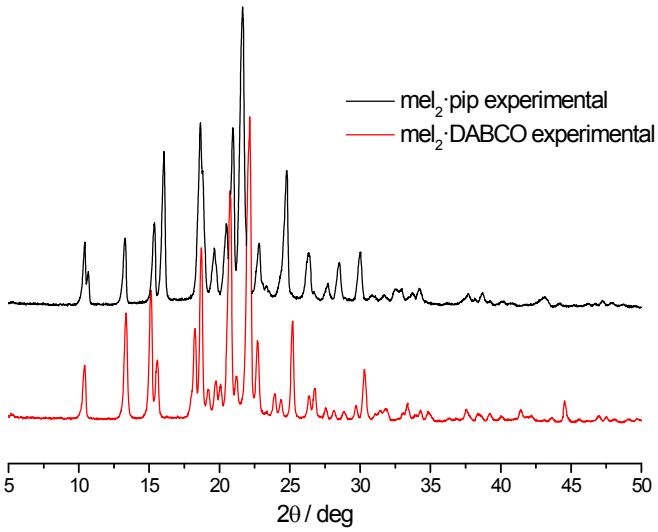

Figure ESI - 11. Comparison between the experimental XRPD pattern of mel_2·pip and mel_2·DABCO.

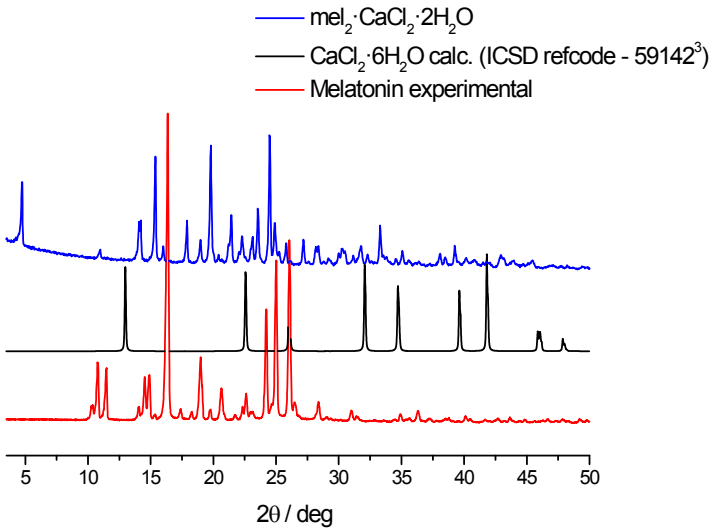

Figure ESI - 12. XRPD comparison between mel_2·$CaCl_2$·$2H_2O$ and starting materials. (Ref. 3: P. A. Agron and W. R. Busing, *Acta Crystallographica Section C Crystal Structure Communications*, 1986, **42**, 141-143.)

ESI - 3: Rietveld refinements

Experimental (blue curve), calculated (red curve), and difference (grey curve) powder patterns. Peak positions are marked in blue.

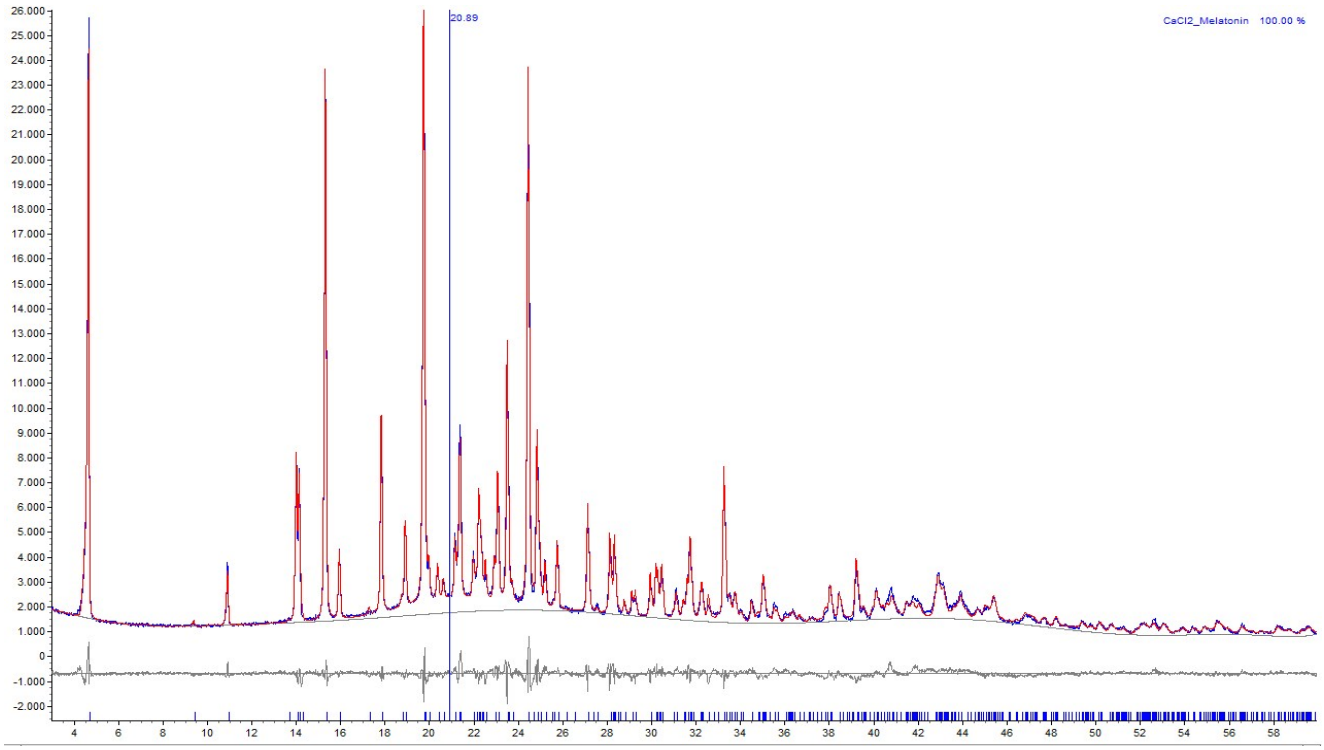

Figure ESI-13. Rietveld refinement of $mel_2 \cdot CaCl_2 \cdot 2H_2O$. R_wp=4.83, R_p=3.73, R_exp=2.17, χ^2=2.23.

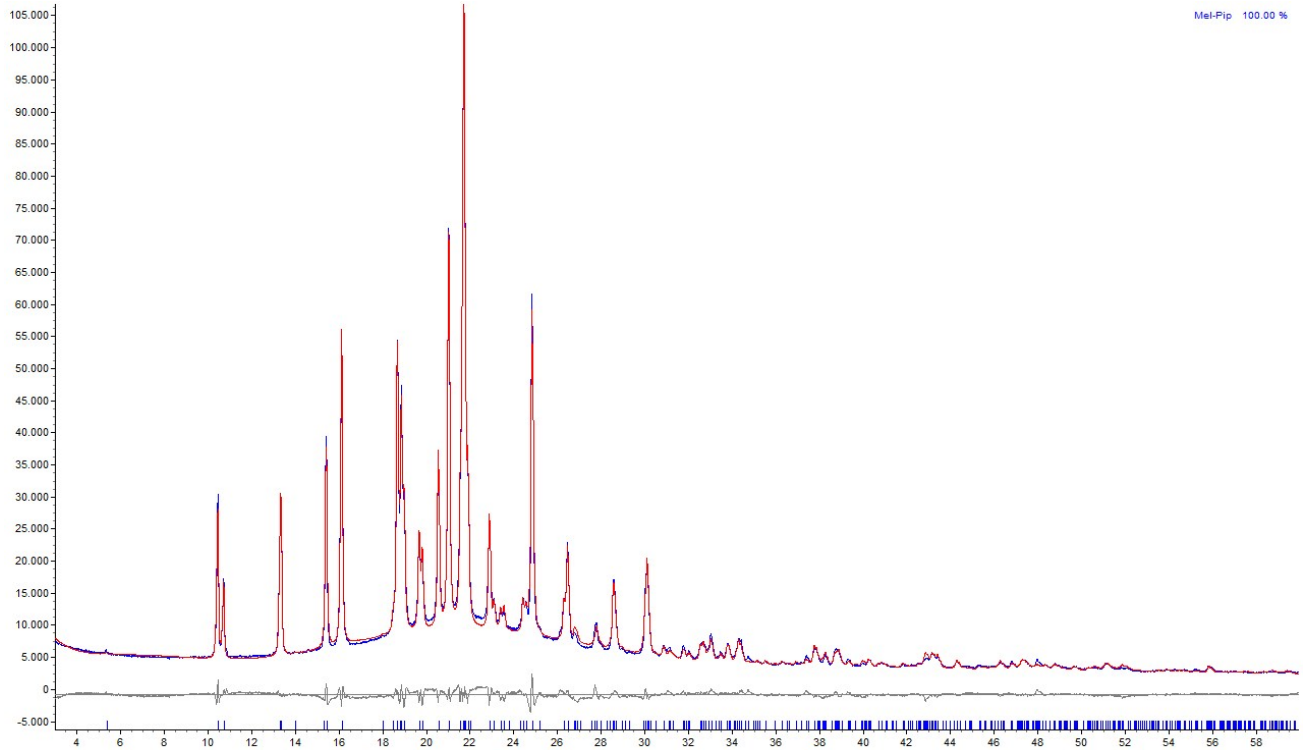

Figure ESI - 14. Rietveld refinement of $mel_2 \cdot pip$. R_wp=4.53, R_p=3.58, R_exp=1.18, χ^2=3.84.

ESI - 4: Tables of the tested co-formers.

General comments:

The ball-milling experiments were performed using two different ball millers Retsch MM400 and MM200. When co-crystallization experiments resulted into formation of a new phase (with piperazine, DABCO, and $CaCl_2$), the ball-milling experiments were repeated at least 10 times, using different stoichiometric ratios, solvents, time and frequency. The operating frequency for Retsch MM200 was from 15 to 25 Hz, and 20Hz for Retsch MM400. Neat grinding resulted in a physical mixture of starting materials. LAG was tried with acetone, methanol and ethanol and the latter gave the best results for melatonin co-crystallization with piperazine and DABCO. Consequently, EtOH was used in all the following grinding experiments. Amorphization of melatonin was never observed (not even in the unsuccessful co-crystallization experiments). In all the cases where co-crystallization was successful the grinding process led to the formation of either pure co-crystals or a physical mixture of co-crystal and starting materials. In the experimental part of this manuscript, one of the possible strategies leading to co-crystal formation is presented.

Table ESI-1a. Organic acids.

#	Co-former	Method	Result
1	Nicotinic acid	Kneading with EtOH	✘
2	Fumaric acid	Kneading with EtOH	✘
3	Isophthalic acid	Kneading with EtOH	✘
4	4-aminosalicylic acid	Kneading with EtOH	✘
5	Succinic acid 1:2	Kneading with EtOH	✘
6	Glutaric acid 1:2	Kneading with EtOH	✘
7	Ascorbic acid	Kneading with EtOH	✘
8	Barbituric acid	Kneading with EtOH	✘
9	Nalidixic acid	Kneading with EtOH	✘

Table ESI-1b. Amino acids.

#	Co-former	Method	Result
1	L-tryptophan	Kneading with EtOH	✘
2	L-Glutamic acid	Kneading with EtOH	✘
3	L-Glutamine	Kneading with EtOH	✘
4	L-Histidine	Kneading with EtOH	✘
5	L-aspartic acid	Kneading with EtOH	✘

Table ESI-2. Inorganic salts.

#	Co-former	Method	Result
1	$CaCl_2$	Kneading with EtOH Slurry in EtOH Evaporation from EtOH Slurry in water	✔ ✔ ✘ ✘

2	$MgCl_2 \cdot 6H_2O$	Kneading with EtOH Slurry in EtOH Evaporation from EtOH	✘ ✘ ✘
3	KBr	Kneading with EtOH	✘
4	NaCl	Kneading with EtOH	✘
5	$Sr(NO_3)_2$	Kneading with EtOH	✘
6	LiCl	Kneading with EtOH Slurry in EtOH Evaporation from EtOH	✘ ✘ ✘
7	$SrCl_2 \cdot 6H_2O$	Kneading with EtOH	✘
8	NaBr	Kneading with EtOH	✘
9	$ZnCl_2$	Kneading with EtOH Slurry in EtOH Evaporation from EtOH Slurry in water	✘ ✘ ✘
10	$AgNO_3$	Kneading with EtOH	✘
11	$Cu(NO_3)_2 \cdot 3H_2O$	Kneading with EtOH	✘

Table ESI-3. Phenols, ethers, quinones.

#	Co-former	Method	Result
1	Thymol	Kneading with EtOH Evaporation from EtOH	✘ ✘
2	Eugenol	Kneading Slurry in the excess of eugenol Crystallization from eugeno	✘ ✘ ✘
3	Carvacrol	Kneading Slurry in the excess of carvacrol Crystallization from carvacrol	✘ ✘ ✘
4	Dioxane	Kneading Slurry in the excess of dioxane	✘ ✘
5	Benzoquinone	Kneading with EtOH	✘

Table ESI-4. Nitrogen containing compounds.

#	Co-former	Method	Result
1	Quinoxaline	Kneading with EtOH	✘
2	Morpholine	Kneading Slurry in the excess of morpholine	✘
3	Piperazine	Kneading with EtOH Evaporation from EtOH Slurry in water	✔ ✘ ✘
4	DABCO (triethylenediamine)	Kneading with EtOH Evaporation from ethanol Slurry in water	✔ ✘ ✘
5	4,4'-bipyridine	Kneading with EtOH	✘

		Slurry in EtOH Evaporation from EtOH	
6	e-Caprolactam	Kneading with EtOH	✘
7	Caffeine anhydrous	Kneading with EtOH	✘
8	4,4'-trimethylenedipiperidine	Kneading with EtOH	✘
9	Hexamine	Kneading with EtOH Evaporation from EtOH	✘ ✘
10	Carbamazepine	Kneading with EtOH	✘
11	Pyrazine	Kneading with EtOH Slurry in EtOH	✘ ✘
12	Quinuclidine	Kneading with EtOH	✘
13	3-quinuclidinol	Kneading with EtOH	✘
14	Adenosine	Kneading with EtOH Slurry in EtOH Evaporation from water/ethanol mixtures Crystallization from melt Solvothermal crystallization in water	✘ ✘ ✘ ✘ ✘
15	Urea	Kneading with EtOH	✘
16	4-aminopyridine	Kneading with EtOH	✘

ESI-5. Relevant hydrogen bonds

Table ESI-5. Relevant hydrogen bonds in the obtained co-crystals (see Fig. ESI-15 below).

Co-crystal	Donor···Acceptor	D···A distance, Å
mel_2·DABCO	N(1)···N(3)	2.895(4)
	N(2)···O(2)	2.997(3)
mel_2·pip	N1M···O2M	2.984(6)
	N2M···N1	3.012(9)
	N1···O1M	3.33(1)
mel_2·$CaCl_2$·$2H_2O$	N2M···Cl1	3.45(1)
	Ow···Cl1	3.167(4)

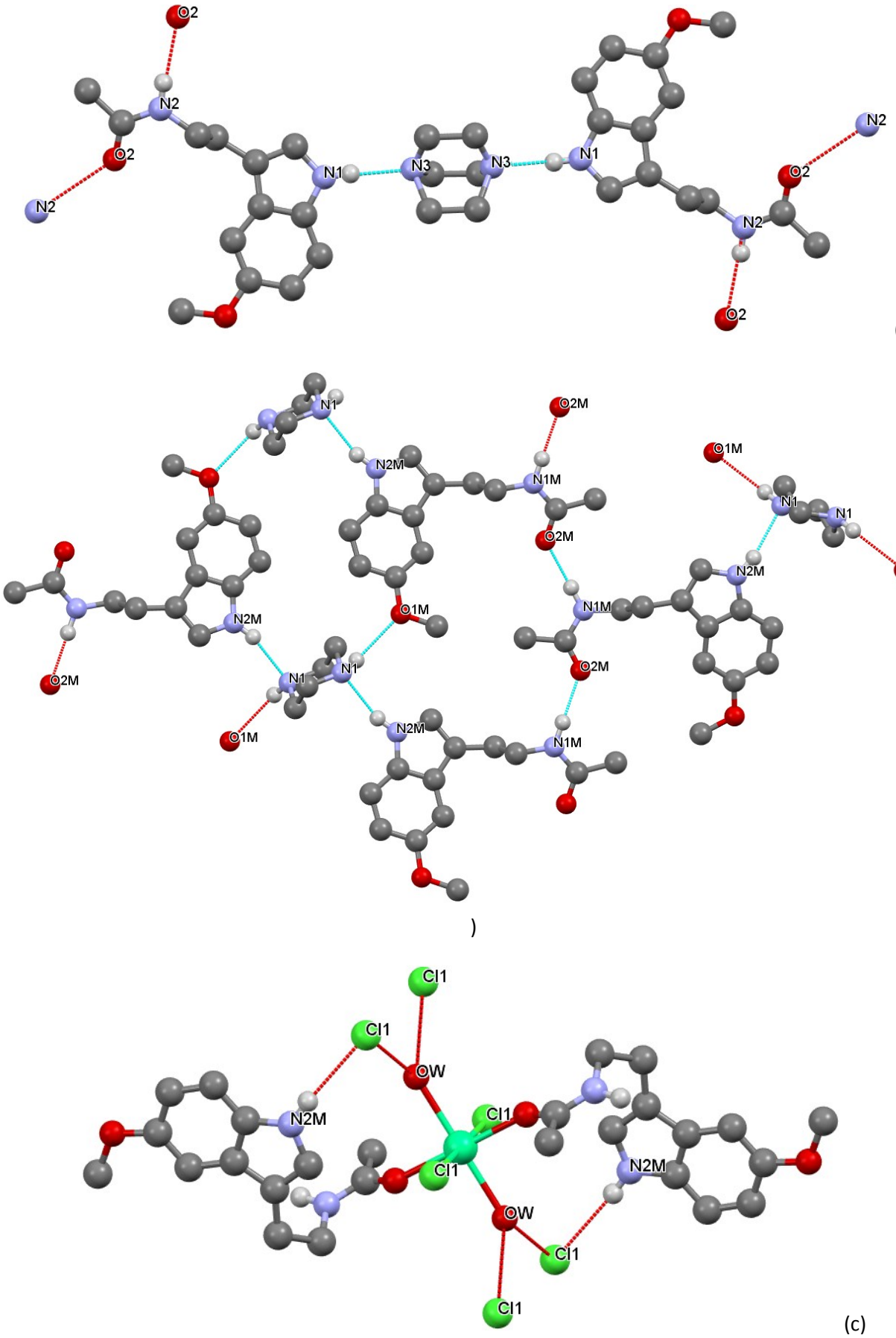

Fig. ESI-15. Relevant hydrogen bond in a) mel_2·DABCO, b) mel_2·pip, c) mel_2·$CaCl_2$·$2H_2O$. CH hydrogens are omitted for the sake of clarity.