Morphotropism and "Quasi-isostructurality" in the three high Z' concomitant polymorphs of Efinaconazole

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Electronic Supplementary Information

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1. EXPERIMENTAL METHODS

1.1 Single X-ray crystallographic analysis

Single crystal X-ray diffraction (SCXRD) intensity data of the different crystal forms of Efinaconazole were collected using a D8 Venture system equipped with a multilayer monochromator and a Mo microfocus (λ = 0.71073 Å). Frames were integrated with the Bruker SAINT software package using a SAINT algorithm. Data were corrected for absorption effects using the multi-scan method (SADABS).1 The structures were solved and refined using the Bruker SHELXTL Software Package, a computer program for automatic solution of crystal structures and refined by full-matrix least-squares method with ShelXle Version 4.8.0, a Qt graphical user interface for SHELXL computer program.2

1.2 Powder X-ray Diffraction Analysis

Powder X-ray diffraction (PXRD) patterns were obtained on a PANalytical X'Pert PRO MPD diffractometer in transmission configuration using Cu Kα1+2 radiation (λ = 1.5406 Å) with a focusing elliptic mirror and a PIXcel detector working at a maximum detector's active length of 3.347º. Configuration of convergent beam with a focalizing mirror and a transmission geometry with flat sample sandwiched between low absorbing films measuring from 2 to 40º in 2θ, with a step size of 0.026º and a total measuring time of 30 minutes to 2 hours at room temperature (298 K).

2.- CRYSTAL DATA AND STRUCTURE REFINEMENT

2.1 Efinaconazole Form I (mo_023VB48_0m_a): 1996492

Table S1. Crystal data and structure refinement for mo_023VB48_0m_a.

Identification code	mo_023VB48_0m_a	
Empirical formula	C18 H22 F2 N4 O	
Formula weight	348.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.6848(7) Å	α= 90°.
	b = 13.5498(9) Å	β= 95.085(2)°.
	c = 34.163(2) Å	γ = 90°.
Volume	5387.7(6) Å^3	
Z	12	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	2208	
Crystal size	0.581 x 0.132 x 0.118 mm^3	
Theta range for data collection	2.031 to 26.457°.	
Index ranges	-14<=h<=12, -16<=k<=16, -42<=l<=42	
Reflections collected	107134	
Independent reflections	22107 [R(int) = 0.0730]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.6527	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	22107 / 1 / 1339	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0572, wR2 = 0.1224	
R indices (all data)	R1 = 0.0868, wR2 = 0.1335	
Absolute structure parameter	-0.1(2)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.334 and -0.332 e.Å^{-3}	

Table S2. Hydrogens bonds for mo_023VB48_0m_a.

Donor --- H....Acceptor [ARU]	D - H	H...A	D...A	D - H...A
O1A --H1A ..N3B [2-x,1/2+y,1-z]	0.84	2.00	2.8125(2)	163
O1F --H1F ..N3D [-1+x,y,z]	0.84	2.03	2.8412(2)	162
O1B --H1OB ..N3A [1-x,-1/2+y,1-z]	0.84	2.00	2.8232(2)	168
O1C --H1OC ..N3E [1+x,y,z]	0.85	1.99	2.8160(2)	162
O1D --H1OD ..N3F [x,y,z]	0.86	2.00	2.8386(2)	165
O1E --H1OE ..N3C [x,y,z]	0.81	2.04	2.8133(2)	159

2.2 Efinaconazole Form II (mo_023UB227_0ma_aa): 1996493

Table S3. Crystal data and structure refinement for mo_023UB227_0ma_aa.

Identification code	mo_023UB227_0ma_aa	
Empirical formula	C18 H22 F2 N4 O	
Formula weight	348.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 22.680(5) Å	α= 90°.
	b = 11.686(3) Å	β= 90°.
	c = 13.560(3) Å	γ = 90°.
Volume	3594.0(15) $Å^3$	
Z	8	
Density (calculated)	1.288 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	1472	
Crystal size	0.444 x 0.180 x 0.048 mm^3	
Theta range for data collection	2.341 to 26.461°.	
Index ranges	-28<=h<=28, -13<=k<=13, -16<=l<=16	
Reflections collected	11846	
Independent reflections	6078 [R(int) = 0.0868]	
Completeness to theta = 26.461°	87.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.5500	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6078 / 0 / 454	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1289	
R indices (all data)	R1 = 0.1051, wR2 = 0.1432	
Absolute structure parameter	0.0(3)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.245 and -0.255 e.$Å^{-3}$	

Table S4. Hydrogen bonds for mo_023UB227_0ma_aa.

Donor --- H....Acceptor	[ARU]	D - H	H...A	D...A	D - H...A
O1B --H1OB ..N4B	[4545.02]	0.84	2.02	2.8407(7)	164
O1A --H1OA ..N4A	[4556.01]	0.84	2.16	2.8145(7)	135

2.3 Efinaconazole Form III (mo_023UB226_0ma_aa): 1996494

Table S5. Crystal data and structure refinement for mo_023UB226_0ma_aa.

Identification code	mo_023UB226_0ma_aa	
Empirical formula	C18 H22 F2 N4 O	
Formula weight	348.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.6651(17) Å	α= 90°.
	b = 13.535(2) Å	β= 104.745(5)°.
	c = 11.7609(16) Å	γ = 90°.
Volume	1795.7(4) Å^3	
Z	4	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	736	
Crystal size	0.185 x 0.056 x 0.040 mm^3	
Theta range for data collection	2.195 to 26.403°.	
Index ranges	-14<=h<=14, -16<=k<=16, -14<=l<=14	
Reflections collected	12037	
Independent reflections	7003 [R(int) = 0.1498]	
Completeness to theta = 25.242°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7454 and 0.5228	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7003 / 1 / 453	
Goodness-of-fit on F^2	0.969	
Final R indices [I>2sigma(I)]	R1 = 0.0580, wR2 = 0.1383	
R indices (all data)	R1 = 0.0767, wR2 = 0.1474	
Absolute structure parameter	0.2(10)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.559 and -0.425 e.Å^{-3}	

Table S6. Torsion angles [°] for mo_023ub226_0m_aa.

Donor --- H....Acceptor [ARU]	D - H	H...A	D...A	D - H...A
O2A --H2OA ..N4B [2646.02]	0.84	2.02	2.8295(4)	162
O2B --H2OB ..N4A [2756.01]	0.84	2.12	2.8265(4)	141

Table S7. H-bond N···HO distance values in all molecules in the asymmetric unit of Forms I, II and III

H-bond	Efinaconazole molecules (distance H-bond (Å))									
	F-I A	F-I B	F-I C	F-I D	F-I E	F-I F	F-II A	F-II B	F-III A	F-III B
N···HO	1.998	2.002	**1.996**	1.997	2.041	2.031	2.023	**2.157**	2.121	2.018

3.- RMSD ANALYSIS

Figure S1. Asymmetric unit of the polymorph form I

Table S8. Rmsd values between all molecules in the asymmetric unit of Forms I, II and III

Rmsd	F-I-A	F-I-B	F-I-C	F-I-D	F-I-E	F-I-F	F-II-A	F-II-B	F-III-A
F-I-B	0.0738								
F-I-C	0.0888	0.0647							
F-I-D	0.0152	0.0671	0.0865						
F-I-E	0.0807	0.0404	0.0304	0.0770					
F-I-F	0.0232	0.0593	0.0744	0.0171	0.0645				
F-II-A	0.0793	0.0457	0.0338	0.0765	0.0182	0.0644			
F-II-B	0.0229	0.0665	0.0747	0.0244	0.0673	0.0205	0.0783		
F-III-A	0.0272	0.0667	0.0881	0.0213	0.0780	0.0248	0.0665	0.0313	
F-III-B	0.0685	0.0330	0.0407	0.0631	0.0269	0.0525	0.0315	0.0638	0.0570

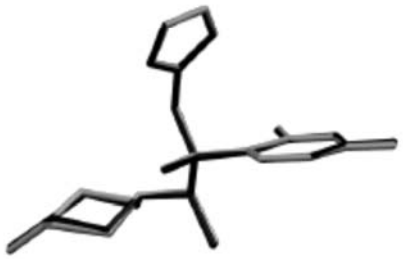

Figure S2. Molecular overlay between molecules A and C of form I

4.- HIRSHFELD ANALYSIS

4.1 Hirshfeld surfaces fingerprint plots of Form I: comparative footprint and contribution (%) of intermolecular contacts

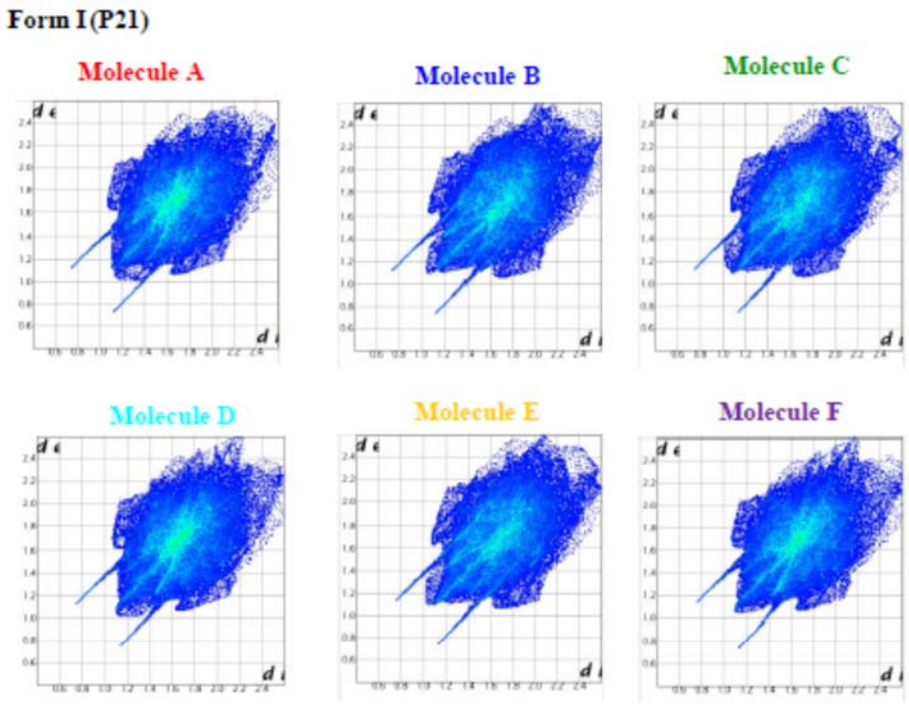

Table S9. Contribution (%) of intermolecular contacts of Form I

Form I	Molecule A	Molecule B	Molecule C	Molecule D	Molecule E	Molecule F
F-H	16.8	17.3	17.6	16.7	17.2	16.5
C-H	10.9	10.4	10.9	10.8	10.7	10.8
H-H	54.6	51.5	51.1	55.0	51.5	55.54
N-H	13.1	16.1	16.2	13.0	16.1	12.9

4.2 Hirshfeld surfaces fingerprint plots of Form II: comparative footprint

Form II (P212121)

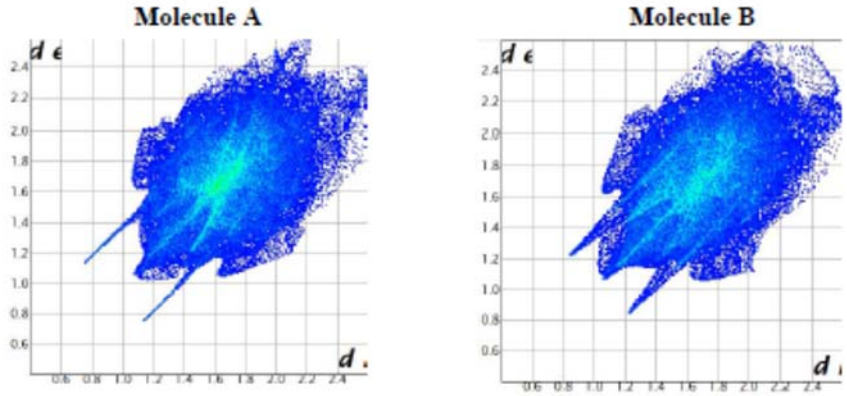

Table S10. Contribution (%) of intermolecular contacts of Form II

Form II	Molecule A	Molecule B
F-H	17.1	16.5
C-H	10.9	10.9
H-H	51.4	55.0
N-H	16.1	13.0

4.3 Hirshfeld surfaces fingerprint plots of Form III: comparative footprint

Form III (P21)

Molecule A **Molecule B**

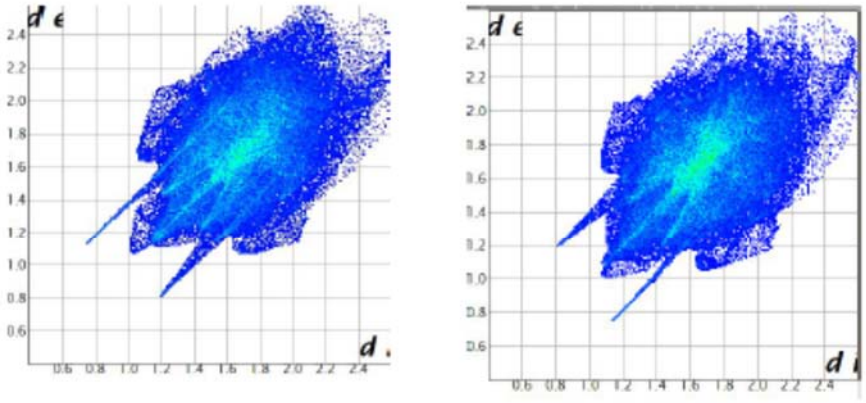

Table S11. Contribution (%) of intermolecular contacts of Form III

Form II	Molecule A	Molecule B
F-H	16.3	17.6
C-H	10.9	10.6
H-H	55.2	51.3
N-H	13.0	16.0

Table S12. Contribution (%) of intermolecular contacts of Forms I, II and III calculated through Hirshfeld surfaces fingerprint plots (average of all molecules in the asymmetric unit)

Contact	Polymorph		
	Form I	Form II	Form III
F-H	17.02	16.80	16.95
C-H	10.75	10.90	10.75
H-H	53.18	53.20	53.25
N-H	14.57	14.55	14.50

5. REFERENCES

[1] SADABS Bruker AXS; Madison, Wisconsin, USA, 2004; SAINT, Software Users Guide, Version 6.0; Bruker Analytical X-ray Systems: Madison, WI, 1999. Sheldrick, G. M. SADABS v2.03; Area-Detector Absorption Correction; University of Göttingen: Germany, 1999. Saint,Version 7.60A; Bruker AXS 2008; SADABS, V. 2008-1, 2008.

[2] G. M. A, Sheldrick, Acta Crystallogr., Sect. A:, 2008, 64, 112−122.