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Article

Entrapped Transient Chloroform Solvates of Bilastine

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A polymorph screening has been conducted from form I and from form III, by using different combinations of solvents at several concentrations and temperatures, with variable cooling rates, under both thermodynamic and kinetic conditions. The following methodologies have been applied:

Evaporations at room temperature: the product is dissolved in the solvent. The solution is kept in opened vials at room temperature while the solvent slowly evaporates until crystallization of a solid occurs.

Crystallizations at fast cooling rate from r.t to 0ºC: the product is dissolved in the solvent at room temperature and the solution is suddenly cooled to 0ºC until precipitation of some solid.

Crystallizations at slow cooling rate from high temperature: the product is dissolved in the solvent at high temperature. The heater is switched off and the solution is let to cool down to room temperature inside the heating block.

Crystallizations at medium cooling rate from high temperature: the product is dissolved in the solvent at high temperature. The heater is switched off and the solution is let to cool down to room temperature outside the heating block.

Crystallizations at fast cooling rate from high temperature: the product is dissolved in the solvent at high temperature. The heater is switched off and the solution is let to cool down suddenly to 0ºC inside a water-ice bath.

Crystallizations by antisolvent diffusion: the product is dissolved in the solvent at room temperature and an antisolvent is let to diffuse through a needle into the solution.

Precipitations by adding antisolvent at r.t.: the product is dissolved in the solvent at room temperature and an antisolvent is added. The samples which did not precipitate are cooled to 0ºC-4ºC until precipitation of some solid occurs.

Slurries: a suspension of the product in the solvent at r.t. is stirred using sealed tubes and after some time the resulting solid is filtered and dried under vacuum.

Desolvations: different methodologies are applied in order to desolvate form S_B of BL. Keeping under vacuum at different temperatures or at 0% RH, or heating at 90ºC under inert atmosphere during different times.

The solids obtained in each experiment have been analysed by PXRD and a summary of the results obtained are shown in Tables S1 and S2.

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Table 1. Screening of BL.

	I	III	I	III
Methodology	**Chloroform**		**Anhydrous chloroform**	
1. Evap.	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$ +III	III	III
2. Cryst. r.t. to 0ºC	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
3. Cryst. high T slow rate	$S_{CHCl3\text{-}H2O}$	-	-	III
4. Cryst. high T medium rate	I+II+ $S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$	-	III
5. Cryst. high T fast rate	$S_{CHCl3\text{-}H2O}$	-	-	-
6. Antisolv. diffusion	I, $S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$, III	I, III	III
7. Precip. Antisolv.	I, III, $S_{CHCl3\text{-}H2O}$	I, III, $S_{CHCl3\text{-}H2O}$	I, II, III	I, II, III

Table 2. Slurries starting from different solid forms.

Starting Form	mg	Solvent (mL)	Time	PXRD Result
$S_{CHCl3\text{-}H2O}$	20	DMF (0.1)	30′	I
$S_{CHCl3\text{-}H2O}$	20	anhydrous DMF (0.1)	30′	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 0/100)	1 month	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 20/80)	1 month	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 40/60)	1 month	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 60/40)	1 month	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 80/20)	1 month	I
I	20	anh. $CHCl_3$/anh. DMF (0.1: 100/0)	1 month	III
I	50	anhydrous $CHCl_3$ (0.2)	30′	III
I	50	$CHCl_3$ (0.25)	1h	all dissolved
I	50	anhydrous $CHCl_3$ (0.25)	1h	all dissolved
I	7100	anhydrous $CHCl_3$ (10)	48h	III
I	170	$CHCl_3$ (1.2)	20h	$S_{CHCl3\text{-}H2O}$
III+I	540	$CHCl_3$ (3.6)	20h	$S_{CHCl3\text{-}H2O}$
III	50	anhydrous $CHCl_3$ (0.2)	30′	III + $S_{CHCl3\text{-}H2O}$
III	50	$CHCl_3$ (0.25)	1h	all dissolved
III	50	anhydrous $CHCl_3$ (0.25)	1h	all dissolved
III	50	$CHCl_3$ (0.15)	1h	III
III	50	anhydrous $CHCl_3$ (0.15)	1h	III
mixture	2000	$CHCl_3$ (12)	overnight	$S_{CHCl3\text{-}H2O}$

Desolvations

Different methodologies were applied in order to desolvate 25 mg of BL $S_{CHCl3\text{-}H2O}$:

1.- Keeping under vacuum for 3h.

PXRD result: $S_{CHCl3\text{-}H2O}$

2.- Keeping under vacuum at 50ºC for 30 minutes:

PXRD result: III

3.- Keeping under 0% relative humidity (P_2O_5 atmoshpere) for 2 days.

PXRD: $S_{CHCl3\text{-}H2O}$

4.- Heating at 90ºC for 1h under inert atmosphere (vacuum/argon).

PXRD result: Form III

5.- Slurring in heptane at 90ºC for 1h.

PXRD result: I+II+maybe III

Experiments to grow single crystals:

Table 3. Cool crystallizations.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	10	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
	anhydrous chloroform	26	$S_{CHCl3\text{-}H2O}$	S_{CHCl3}
III	chloroform	6	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
	anhydrous chloroform	26	$S_{CHCl3\text{-}H2O}$	S_{CHCl3}

Table 4. Crystallizations by MEK diffusion.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	11	I	-
	anhydrous chloroform	20	I	-
III	chloroform	7	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
	anhydrous chloroform	1	III	-

Table 5. Crystallizations by acetone diffusion.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	11	I	-
III	chloroform	7	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
	anhydrous chloroform	1	III	-

Table 6. Crystallizations by pentane diffusion.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	10	$S_{CHCl3\text{-}H2O}$	-
	anhydrous chloroform	20	III	-
III	chloroform	7	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
	anhydrous chloroform	1	III	-

Table 7. Crystallizations by Et_2O diffusion.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	11	I	-
	anhydrous chloroform	20	III	-
III	chloroform	7	III + $S_{CHCl3\text{-}H2O}$	-
	chloroform	2	III	-
	anhydrous chloroform	1	III	S_{CHCl3}
	anhydrous chloroform	2	III + I	-

Table 8. Crystallizations by DIE diffusion.

Starting Form	Solvent	Time (days)	PXRD Result	Single Crystal Result
I	chloroform	11	I	-
	anhydrous chloroform	20	III	-
III	chloroform	6	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
	anhydrous chloroform	1	III	-

Table 9. Crystallizations and evaporations from $CHCl_3$.

	Form I (40 mg)	Form III (60 mg)	
Conditions	**PXRD**	**PXRD**	**Single crystal**
open to air	I	III+II	-
septum with thin needle	III+II+$S_{CHCl3\text{-}H2O}$	mixture	-
septum with thick needle	II	mixture	-
parafilm covered	mixture	$S_{CHCl3\text{-}H2O}$ +II	
+ 0.5 mL pentane and 5ºC	-	-	poorly diffracting crystals
5ºC	-	-	poorly diffracting crystals

Table 10. Crystallizations from anhydrous $CHCl_3$ at 5ºC.

Conditions	PXRD Result	Single Crystal Result
closed tube	III+ $S_{CHCl3\text{-}H2O}$	-
closed tube	$CHCl_3$ evaporated	-
closed tube	$S_{CHCl3\text{-}H2O}$	S_{CHCl3}

Table 11. Crystallizations from $CHCl_3$ at 5ºC.

Starting Form	mg	$CHCl_3$ (mL)	PXRD Result	Single Crystal Result
I	460	3.2	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$
III	330	2.3	$S_{CHCl3\text{-}H2O}$	$S_{3CHCl3\text{-}H2O}$

Stability

Stability of $S_{CHCl3\text{-}H2O}$ at different relative humidities:

Form $S_{CHCl3\text{-}H2O}$ (20 mg) was placed at r.t. in desiccators over P_2O_5 (RH 0%) and saturated salt solutions providing specific RH. Phase transformations were identified using PXRD.

Table 12. Stability under different RH conditions.

RH (%)	PXRD results	
	10 days	1 month
P_2O_5 (0%)	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
LiCl (11%)	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
$MgCl_2$ (33%)	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
K_2CO_3 (43%)	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
NaBr (57%)	$S_{CHCl3\text{-}H2O}$	III
NaCl (75%)	$S_{CHCl3\text{-}H2O}$	III

Stability of different forms under $CHCl_3$ atmospheres:

20 mg of different forms of BL were placed in recipients under different $CHCl_3$ atmospheres from 0% to 100% $CHCl_3$ (0/100 – 100/0) using $CHCl_3$/DMF solutions (v/v).

Table 13. Stability under different $CHCl_3$ atmospheres.

$CHCl_3$/DMF	Starting Form	6 Days	12 Days	1 Month
0/100	I	I	I	

0/100	III	III	III	
0/100	$S_{CHCl3\text{-}H2O}$	II + I trace	II + I trace	
20/80	I	-	I	
20/80	III	-	III	
20/80	$S_{CHCl3\text{-}H2O}$	-	I	
40/60	I	-	I	
40/60	III	-	III	
40/60	$S_{CHCl3\text{-}H2O}$	-	I	
60/40	I	-	I	I
60/40	III	-	III	I + III
60/40	$S_{CHCl3\text{-}H2O}$	-	$S_{CHCl3\text{-}H2O}$	
80/20	I	-	I	I
80/20	III	-	III	I + III
80/20	$S_{CHCl3\text{-}H2O}$	-	$S_{CHCl3\text{-}H2O}$	
100/0	I	-	$S_{CHCl3\text{-}H2O}$ +I	$S_{CHCl3\text{-}H2O}$
100/0	III	-	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$
100/0	$S_{CHCl3\text{-}H2O}$	-	$S_{CHCl3\text{-}H2O}$	$S_{CHCl3\text{-}H2O}$

Relative stability data among anhydrous forms II and III:

Table 14. Thermodynamic relative stability.

Starting Form	Time	PXRD Result
II + III	1 h.	I
II + III	10 min.	II↓ + III
II↓ + III	10 min.	II↓ + III + I

Table 15. Crystal data of forms I, $S_{3CHCl3\text{-}H2O}$ and S_{CHCl3}.

	Form I	$S_{3CHCl3\text{-}H2O}$	S_{CHCl3}
Empirical formula	C_{28} H_{37} N_3 O_3	C_{31} H_{42} Cl_9 N_3 O_4	C_{29} H_{38} Cl_3 N_3 O_3
Formula weight	463.60	839.72	582.97
Temperature	300(2) K	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	*P* $2_1/c$	*P n a* 2_1	*P* 2_1
Unit cell dimensions	a = 23.3850(10) Å b = 8.8675(4) Å c = 12.6208(5) Å β= 93.1300(10) °	a = 13.5381(5) Å b = 30.9658(11) Å c = 9.4457(4) Å β=90º	a = 17.3058(11) Å b = 9.3567(5) Å c = 20.2407(13) Å β= 114.980(2)°
Volume	2613.23(19) $Å^3$	3959.8(3) $Å^3$	2970.9(3) $Å^3$
Z	4	4	4
Density (calculated)	1.178 Mg/m^3	1.409 Mg/m^3	1.303 Mg/m^3
Absorption coefficient	0.077 mm^{-1}	0.674 mm^{-1}	0.343 mm^{-1}
F(000)	1000	1736	1232
Crystal size	0.310 x 0.197 x 0.106 mm^3	0.602 x 0.230 x 0.072 mm^3	0.418 x 0.226 x 0.108 mm^3
Theta range for data collection	2.457 to 26.411°	1.998 to 26.349°	2.443 to 26.409°
Index ranges	-28<=h<=29, -11<=k<=11, -14<=l<=15	-16<=h<=16, -33<=k<=36, -11<=l<=9	-21<=h<=21, -11<=k<=11, -25<=l<=25
Reflections collected	32444	14248	32238
Independent reflections	5355 [R(int) = 0.0409]	6272 [R(int) = 0.0295]	12095 [R(int) = 0.0664]
	99.8 %	98.2 %	99.8 %

Completeness to theta = 25.242°	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
Absorption correction	0.7454 and 0.6923	0.7454 and 0.6562	0.7454 and 0.6500
Max. and min. transmission	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Refinement method	5355 / 2 / 311	6272 / 2 / 436	12095 / 13 / 695
Data / restraints / parameters	1.029	1.055	1.020
Goodness-of-fit on F^2	R1 = 0.0579, wR2 = 0.1473	R1 = 0.0584, wR2 = 0.1491	R1 = 0.0773, wR2 = 0.1760
Final R indices [I>2sigma(I)]	R1 = 0.0828, wR2 = 0.1668	R1 = 0.0674, wR2 = 0.1576	R1 = 0.1132, wR2 = 0.1973
R indices (all data)	0.0114(13)	n/a	n/a
Extinction coefficient	0.703 and -0.436 e.Å^{-3}	1.500 and -1.001 e.Å^{-3}	1.477 and -1.067 e.Å^{-3}
Largest diff. peak and hole			
CCDC	2069948	2069945	2069946

Table 16. Crystal data and structure refinement parameters of forms III and $S_{CHCl3-H2O}$.

	Form III	**$S_{CHCl3-H2O}$**
Empirical formula	C_{28} H_{37} N_3 O_3	C_{28} H_{37} N_3 O_3 · $CHCl_3$ · 0.57 (H_2O)
Formula weight	463.60	839.72
Temperature	300 K	300 K
Wavelength	0.63493 Å	0.61927 Å
Crystal system	Monoclinic	Orthorhombic
Space group	*P* 2_1/c	*P n a* 2_1
Unit cell dimensions	a = 14.7632(7) Å	a = 10.1919(4) Å
	b = 9.9583(3) Å	b = 33.3569(12) Å
	c = 19.7925(10) Å	c = 9.3124(2) Å
	β= 112.818(3) °	β=90 °
Volume	2682.1(2) Å^3	3165.9(2) Å^3
Z	4	4
Density (calculated)	1.148 Mg/m^3	1.245
Measured 2θ range, stepsize	0.326-44.546, 0.006	0.376-43.198, 0.006-16<=h<=16,
Rietveld refinement details:		
Profile function	Pseudo-Voigt	Pseudo-Voigt
2θ range used	2.206-24-00	1.906-35.00
Number of reflections	797	1636
Data points	3633	5516
Parameters	113[a]	128[b]
Restraints	112[a]	117[b]
R_{wp}	0.024	0.023
$\chi_{Rietveld}$/ $\chi_{Pattern\text{-}Matching}$	1.642	1.440
CCDC	2069947	2069944

[a] Parameters: 34 atomic coordinates, $B_{Overall}$, scale factor, zero shift, 4 profile parameters, 4 cell parameters. Restraints: 37 bond, 52 angle and 23 to define atomic planes (2 rings and 1 -COOH).

[b] Parameters: 39 atomic coordinates, $B_{C,N,O}$, B_{Cl}, $B_{O(CHCl3)}$, scale factor, zero shift, 3 profile parameters, 3 cell parameters. Restraints: 40 bond, 54 angle and 23 to define atomic planes (2 rings and 1 -COOH).