## Supporting Information to the paper entitled

# Chemoselective recognition with phosphonate cavitands: the ephedrine over pseudoephedrine case.

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**Figure S1.** <sup>31</sup>P NMR (200MHz, MeOD, 25°C) of the **Tiiii**-drug complexes in MeOD: **Tiiii** before (red spectrum) and after addition of pseudoephedrine (green spectrum) and ephedrine (blue spectrum) hydrochlorides.



**Figure S2.** <sup>1</sup>H NMR (200MHz, 25°C) of the **Tiiii**@ephedrine hydrochloride complex in MeOD: **Tiiii** before (blue spectrum) and after addition of ephedrine hydrochloride (green spectrum) and pure ephedrine hydrochloride (red spectrum).



**Figure S3.** <sup>1</sup>H NMR (200MHz, 25°C) of the **Tiiii**@pseudoephedrine hydrochloride complex in MeOD: **Tiiii** before (blue spectrum) and after addition of pseudoephedrine hydrochloride (green spectrum) and pure pseudoephedrine hydrochloride (red spectrum).



**Figure S4.** <sup>1</sup>H NMR (200MHz, MeOD, 25°C) comparison of the **Tiiii**@ephedrine hydrochloride (blue spectrum) and **Tiiii**@pseudoephedrine hydrochloride (red spectrum) complexes.



**Figure S5.** <sup>1</sup>H NMR (400MHz, MeOD, -20°C) of the competitive titrations. a) **Tiiii** before (red spectrum), after addition of 1.eq. of pseudoephedrine (green spectrum) and 1.eq. of ephedrine (blue spectrum) hydrochlorides; b) **Tiiii** before (red spectrum), after addition of 1.eq. of ephedrine (green spectrum) and 1.eq. of pseudoephedrine (blue spectrum) hydrochlorides.



**Figure S6.** <sup>1</sup>H NMR (400MHz, MeOD, 25°C) of the filtered crystals obtained with different (-)-ephedrine:(+)-pseudoephedrine:**Tiiii** ratio compared with the **Tiiii**@( $\pm$ )-ephedrine hydrochloride complex.

#### Structural determination of the host-guest complexes

Crystal data and experimental details for data collection and structure refinement are reported in Tables S1 and S2.

The crystal structures of compounds Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@ephedrine hydrochloride•7H<sub>2</sub>O•CH<sub>3</sub>OH (1, racemic guest), Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@pseudoephedrine hydrochloride•6H<sub>3</sub>OH (2, racemic guest), Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@ephedrine hydrochloride•3H<sub>2</sub>O•3CH<sub>3</sub>OH (3, enantiopure guest), Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>. Ph]@pseudoephedrine hydrochloride•4H<sub>2</sub>O (4, enantiopure guest), Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@ephedrine hydrochloride•7H<sub>2</sub>O•CH<sub>3</sub>OH (5, enantiopure guest), Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@ephedrine hydrochloride $\bullet$ 2H<sub>2</sub>O $\bullet$ 2CH<sub>3</sub>OH (6, enantiopure guest) and Tiiii[C<sub>3</sub>H<sub>7</sub>, CH<sub>3</sub>, Ph]@ephedrine hydrochloride $\bullet$ 4H<sub>2</sub>O $\bullet$ CH<sub>3</sub>OH (7, enantiopure guest) were determined by X-ray diffraction methods. Intensity data and cell parameters were recorded at 190(2) K on a Bruker APEX II equipped with a CCD area detector and a graphite monochromator (MoK $\alpha$  radiation  $\lambda = 0.71073$  Å). The raw frame data were processed using SAINT and SADABS to yield the reflection data file<sup>1</sup>.

The structures were solved by Direct Methods using the SIR97 program<sup>2</sup> and refined on  $F_0^2$  by full-matrix least-squares procedures, using the SHELXL-97 program<sup>3</sup> in the WinGX suite v.1.80.05<sup>4</sup>.

All non-hydrogen atoms were refined with anisotropic atomic displacements except in case of disorder or for some of the lattice solvent molecules. The hydrogen atoms were included in the refinement at idealized geometry (C-H 0.95 Å) and refined "riding" on the corresponding

<sup>&</sup>lt;sup>1</sup> SADABS Bruker AXS; Madison, Wisconsin, USA 2004; SAINT, Software Users Guide, Version 6.0; Bruker Analytical X-ray Systems, Madison, WI 1999. G. M. Sheldrick, SADABS v2.03: Area-Detector Absorption Correction. University of Göttingen, Germany 1999.

<sup>&</sup>lt;sup>2</sup> A. Altomare et al. J. Appl. Cryst. 1999, 32, 115-119.

<sup>&</sup>lt;sup>3</sup> G. M. Sheldrick, *SHELXL-97.Program for Crystal Structure Refinement*. University of Göttingen, Germany **1997**, and *ActaCrystallogr*. **2008**, *A64*, 112 - 122.

<sup>&</sup>lt;sup>4</sup> L. J. Farrugia, J.Appl. Crystallogr. 1999, 32, 837-838.

parent atoms. The weighting schemes used in the last cycle of refinement were  $w = 1/[\sigma^2 F_o^2 + (0.1593P)^2 + 2.9529P]$ ,  $w = 1/[\sigma^2 F_o^2 + (0.0849P)^2 + 9.6239P]$ ,  $w = 1/[\sigma^2 F_o^2 + (0.1503P)^2]$ ,  $w = 1/[\sigma^2 F_o^2 + (0.2000P)^2]$ ,  $w = 1/[\sigma^2 F_o^2 + (0.1484P)^2]$ ,  $w = 1/[\sigma^2 F_o^2 + (0.1605P)^2]$  and  $w = 1/[\sigma^2 F_o^2 + (0.1760P)^2]$  where  $P = (F_o^2 + 2F_c^2)/3$ , for 1-7, respectively. Geometric calculations were performed with the PARST97 program<sup>5</sup>.

Crystallographic data (excluding structure factors) for the structures reported have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1034901 (1), -1034902 (2), -1034903 (3), -1034904 (4), -1034905 (5), -1034906 (6) and -1034907 (7), and can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge, CB2 IEZ, UK (fax: +44-1223-336-033; e-mail deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

<sup>&</sup>lt;sup>5</sup> M. Nardelli, J. Appl. Crystallogr. 1996, 29, 296-300.

Compound	1	2
Empirical formula	$C_{79}H_{102}CINO_{21}P_4$	$C_{84}H_{108}Cl1N_1O_{19}P_4$
Formula weight (g mol <sup>-1</sup> )	1560.95	1595.04
Temperature (K)	190(2)	190(2)
Crystal system	triclinic	Triclinic
Space group	<i>P</i> -1	<i>P</i> –1
Crystal size (mm <sup>3</sup> )	$0.14 \times 0.09 \times 0.07$	$0.13 \times 0.10 \times 0.08$
<i>a</i> (Å)	15.2564(6)	14.352(1)
<i>b</i> (Å)	16.7125(7	15.283(1)
<i>c</i> (Å)	19.1312(7)	19.944(1)
α (°)	65.429(1)	104.220(1)
β (°)	96.210(1)	95.842(1)
γ (°)	100.246(1)	90.923(1)
$V(\text{\AA}^3)$	4244.9(3)	4214.7(5
Ζ	2	2
$ ho_{ m calcd}$	1.221	1.257
$\mu$ (mm <sup>-1</sup> )	0.188	0.189
<i>F</i> (000)	1656	1696
$\theta$ for data collection (°)	1.39–27.65	1.43–26.98
Reflections collected / unique	57028/19696 [R(int) = 0.0358]	53434/18274 [R(int) = 0.0389]
Observed reflections $[F_o>4\sigma(F_o)]$	13540	13371
Completeness to theta	99.5 %	99.5
Data / restraints / parameters	19696 / 0 / 962	18274 / 6 / 945
Goodness-of-fit on $F^{2a}$	1.035	1.071
Final <i>R</i> indices $[F_0 > 4\sigma(F_0)]^b$	R1 = 0.0767, wR2 = 0.2327	R1 = 0.0799, wR2 = 0.2102
<i>R</i> indices (all data)	R1 = 0.1054, wR2 = 0.2616	R1 = 0.1033, wR2 = 0.2237
largest diff. peak and hole (e Å <sup>3</sup> )	1.662 and -0.549	1.063 and -0.680

 Table S1. Crystal data and structure refinement for complexes 1 and 2.

Compound	3	4
Empirical formula	$C_{159}H_{186}Cl_2N_2O_{32}P_8$	$C_{156}H_{176}Cl_2N_2O_{30}P_8$
Formula weight (g mol <sup>-1</sup> )	2955.76	2877.65
Temperature (K)	190(2)	190(2) K
Crystal system	Monoclinic	Triclinic
Space group	P21	<i>P</i> 1
Crystal size (mm <sup>3</sup> )	$0.13 \times 0.10 \times 0.09$	$0.13 \times 0.10 \times 0.09$
<i>a</i> (Å)	14.085(2)	15.316(2)
<i>b</i> (Å)	20.896(2)	16.319(2)
<i>c</i> (Å)	28.155(3)	19.612(2)
α (°)	-	66.028(2)
β (°)	98.184(2)	74.353(5)
γ (°)	-	77.507(2)
$V(Å^3)$	8202(2)	4281.2(9)
Ζ	2	1
$ ho_{ m calcd}$	1.197	1.116
$\mu (\mathrm{mm}^{-1})$	0.187	0.176
<i>F</i> (000)	3128	1520
$\theta$ for data collection (°)	1.46–24.51	1.39–24.29
Reflections collected / unique	85012/27191[R(int) = 0.1608]	43263 / 27219 [R(int) = 0.0628]
Observed reflections $[F_o > 4\sigma(F_o)]$	12246	12476
Completeness to theta	99.5	99.1
Data / restraints / parameters	27191 / 1 / 1783	27219 / 11 / 1593
Flack parameter	-0.06(13)	-0.22(14)
Goodness-of-fit on <i>F</i> <sup>2a</sup>	0.969	1.056
Final <i>R</i> indices $[F_0>4\sigma(F_0)]^b$	R1 = 0.0915, wR2 = 0.2281	R1 = 0.1210, wR2 = 0.3039
R indices (all data)	R1 = 0.1999, wR2 = 0.2928	R1 = 0.2142, wR2 = 0.3714
largest diff. peak and hole ( $e \text{ Å}^3$ )	1.111 and -0.442	0.872 and -0.437

 Table S2. Crystal data and structure refinement for complexes 3 and 4.

Compound	5	6
Empirical formula	$C_{157}H_{186}Cl_2N_2O_{34}P_8$	$C_{158}H_{180}Cl_2N_2O_{30}P_8$
Formula weight (g mol <sup>-1</sup> )	2963.74	2905.70
Temperature (K)	190(2)	190(2)
Crystal system	Monoclinic	Monoclinic
Space group	P21	<i>P</i> 2 <sub>1</sub> /c
Crystal size (mm <sup>3</sup> )	0.12 x 0.10 x 0.08	0.14 x 0.12 x 0.09
<i>a</i> (Å)	13.9589(6)	13.917(2
<i>b</i> (Å)	37.935(2)	37.798(6)
<i>c</i> (Å)	15.3453(6)	15.357(2)
eta (°)	91.459(1)	91.273(2)
$V(Å^3)$	8123.2(6)	8076(2)
Ζ	2	2
$ ho_{ m calcd}$	1.212	1.195
$\mu$ (mm <sup>-1</sup> )	0.190	0.188
<i>F</i> (000)	3136	3072
$\theta$ for data collection (°)	1.33–26.42	1.33–23.36
Reflections collected / unique	97734/32936 [R(int) = 0.0818]	76484 23455 [R(int) = 0.2625]
Observed reflections $[F_o>4\sigma(F_o)]$	20473	8538
Completeness to theta	99.0	99.8
Data / restraints / parameters	32936 / 0 / 1782	23455 / 2 / 1620
Flack parameter	0.03(7)	-0.11(19)
Goodness-of-fit on <i>F</i> <sup>2a</sup>	1.006	0.999
Final <i>R</i> indices $[F_0>4\sigma(F_0)]^b$	R1 = 0.0804, wR2 = 0.2117	R1 = 0.1144, wR2 = 0.2672
R indices (all data)	R1 = 0.1304, wR2 = 0.2463	R1 = 0.2799, wR2 = 0.3578
largest diff. peak and hole ( $e \text{ Å}^3$ )	1.231 and -0.352	0.989 and -0.406

 Table S3. Crystal data and structure refinement for complexes 5 and 6.

Compound	7
Empirical formula	$C_{157}H_{180}Cl_2N_2O_{31}P_8$
Formula weight (g mol <sup>-1</sup> )	2909.69
Temperature (K)	190(2)
Crystal system	Monoclinic
Space group	P21
Crystal size (mm <sup>3</sup> )	0.12 x 0.10 x 0.08
<i>a</i> (Å)	13.898(2)
<i>b</i> (Å)	37.849(5)
<i>c</i> (Å)	15.383(2)
$\beta$ (°)	91.633(2)
$V(Å^3)$	8088.6(19)
Ζ	2
$ ho_{ m calcd}$	1.195
$\mu$ (mm <sup>-1</sup> )	0.188
<i>F</i> (000)	3076
$\theta$ for data collection (°)	1.08–23.36
Reflections collected / unique	75584/23446[R(int) = 0.1228]
Observed reflections $[F_0 > 4\sigma(F_0)]$	13003
Completeness to theta	99.7
Data / restraints / parameters	23446 / 1 / 1733
Flack parameter	0.06(12)
Goodness-of-fit on $F^{2a}$	1.009
Final <i>R</i> indices $[F_o > 4\sigma(F_o)]^b$	R1 = 0.0933, wR2 = 0.2468
<i>R</i> indices (all data)	R1 = 0.1644, wR2 = 0.2951
largest diff. peak and hole ( $e \text{ Å}^3$ )	111 and -0.380

 Table S4. Crystal data and structure refinement for complex 7.



**Figure S7.** Ortep view (20% probability level) of **1** with the labelling scheme. H atoms have been omitted for clarity. Water molecules O5W-O10W are disordered over two positions.



**Figure S8.** Ortep view (20% probability level) of **2** with the labelling scheme. H atoms have been omitted for clarity.



**Figure S9.** Ortep view (20% probability level) of the two independent complexes in **3** with the labelling scheme. The guest included is the enantiomer 1-(R), 2-(S). H atoms have been omitted for clarity.



**Figure S10.** Ortep view (20% probability level) of the two independent complexes in **4** with the labelling scheme. The guest included is the enantiomer 1-(S), 2-(S). H atoms have been omitted for clarity.



**Figure S11.** Ortep view (20% probability level) of the two independent complexes of **5** with the labelling scheme (crystals obtained from a solution containing a molar ratio ephedrine:pseudoehpdrine of 8:2). The guest included is the enantiomer 1-(R), 2-(S). H atoms have been omitted for clarity.



**Figure S12.** Ortep view (20% probability level) of the two independent complexes of **6** with the labelling scheme (crystals obtained from a solution containing a molar ratio ephedrine:pseudoehpdrine of 2:8). The guest included is the enantiomer 1-(R), 2-(S). H atoms have been omitted for clarity.



**Figure S13.** Ortep view (20% probability level) of the two independent complexes of **7** with the labelling scheme (crystals obtained from a solution containing a molar ratio ephedrine:pseudoehpdrine of 1:1). The guest included is the enantiomer 1-(R), 2-(S). H atoms have been omitted for clarity.

Complex 1			
Hydrogen bonds			
N1…O3C	2.787(5)	N1-H1A-O3C	155.8(3)
N1…O3D	2.834(3)	N1-H1B-O3D	161.8(2)
01…03A	2.639(4)	-	-
Cl1…O1W	3.116(5)	-	-
Cl1…O3W	3.199(4)	-	-
$C-H\cdots\pi$ interactions (	N-bonded methyl gro	oup of the guest with the aro	matic cavity)
C1…CentroidD	3.826(4)	C1-H1D-CentroidD	145.0(3)
C1…CentroidC	3.771(5)	C1-H1E-CentroidC	130.6(2)
<i>C-H… chlorine intera</i>	ctions		
C9A…Cl1	3.843(4)	C9A-H9A1-Cl1	174.9(2)
C9B…Cl1	3.865(4)	C9B-H9B2-Cl1	176.0(3)
C9C···Cl1	3.878(4)	С9С-Н9С2-С11	170.0(3)
Distance of N from the	e least-squares plane	e defined by the four O atom	s of the PO groups
N1…plane	0.085(4)		
	C	Complex 2	
Hydrogen bonds			
N1…O3C	2.832(6)	N1-H1B-O3C	157.9(9)
N1…O3D	2.816(4)	N1-H1A-O3D	159.1(9)
01…03A	2.684(4)	O1-H1-O3A	147.83(2)
Cl1…O2S	3.174(8)	-	-
Cl1…O3S	3.224(9)	-	-
Cl1…O4S	3.093(6)		
<i>C-H</i> ··· $\pi$ interactions ( <i>N</i> -bonded methyl group of the guest with the aromatic cavity)			
C1…CentroidD	3.816(4)	C1-H1D-CentroidD	158.0(4)
C1…CentroidC	3.741(5)	C1-H1E-CentroidC	130.3(2)
$C-H\cdots$ chlorine interactions			

Table S5. Relevant intermolecular contacts (Å and °) for complexes 1-4

C9B····Cl1	3.896(3)	C9B-H9B2-Cl1	171.3(2)
C9C···Cl1	3.876(4)	C9C-H9C1-Cl1	174.2(2)
C9D····Cl1	3.878(4)	C9D-H9D2-Cl1	175.1(3)
Distance of N from t	he least-squares p	lane defined by the four O aton	is of the PO groups
N1…plane	0.358(5)		
		Complex 3	
Hydrogen bonds			
N1X···O3C	2.760(9)	N1X-H1X1-O3C	145.6(6)
N1X···O3B	2.860(9)	N1X-H1X2-O3B	156.0(6)
O1X···O3A	2.784(9)	О1Х-Н1Х…ОЗА	145.4(6)
N1Y…O3G	2.824(9)	N1Y-H1Y1-O3G	158.9(66)
№1Ү…ОЗН	2.767(8)	N1Y-H1Y2-O3H	143.6(6)
O1Y…O3F	2.682(9)	O1Y-H1Y-O3F	164.0(6)
O3S…Cl1X	3.120(9)	O3S-H3S-Cl1X	144.3(2)
O3W…Cl1X	3.158(9)	-	-
O2W…Cl1Y	3.185(9)	-	-
$C$ - $H$ ··· $\pi$ interactions	(N-bonded methy)	l group of the guest with the ar	omatic cavity)
C1X…CentroidC	3.932(8)	C1X-H1X4-CentroidC	138.4(3)
C1Y…CentroidH	3.916(7)	C1Y-H1Y4-CentroidH	132.5(2)
<i>C-H</i> ··· <i>chlorine inter</i>	ractions		
C9A…Cl1X	3.903(9)	C9A-H9A1-Cl1X	176.0(6)
C9B…Cl1X	3.900(9)	C9B-H9B2-Cl1X	171.7(6)
C9C····Cl1X	3.829(9)	С9С-Н9С1-С11Х	171.5(6)
C9F…Cl1Y	3.858(9)	C9F-H9F1-Cl1Y	176.7(6)
C9G…Cl1Y	3.828(9)	C9G-H9G2-Cl1Y	174.0(5)
C9H···Cl1Y	3.809(9)	C9H-H9H1-Cl1Y	173.0(6)
Distance of N from the least-squares plane defined by the four O atoms of the PO groups			
N1X…plane	0.031(9)	N1Y…plane	0.011(9)
		Complex 4	
Hydrogen bonds			
N1X···O3A	2.865(3)	N1X-H1X2-O3A	159.0(2)
N1X···O3B	2.841(4)	N1X-H1X1-O3B	149.7(2)

O1X···O3C	2.742(5)	O1X-H1X-O3C	175.8(2)
N1Y…O3G	2.783(4)	N1Y-H1Y1-O3C	164.5(2)
N1Y…O3H	2.797(5)	N1Y-H1Y2-O3B	160.2(2)
O1Y…O3F	2.725(6)	O1Y-H1Y-O3F	139.0(2)
O4W <sup>a</sup> Cl1X	3.0648(3)	-	-

<i>C-H</i> $\cdots$ $\pi$ <i> interactions (N-bonded methyl group of the guest with the aromatic cavity)</i>			
C1X…CentroidA	3.749(8)	C1X-H1X5-CentroidA	140.8(4)
C1X…CentroidB	3.871(8)	C1X-H1X3-CentroidB	155.0(7)
C1Y…CentroidE	3.770(6)	C1Y-H1Y4-CentroidE	131.5(2)
C1Y…CentroidH	3.900(7)	C1Y-H1Y3-CentroidH	154.6(3)
C- $H$ ··· chlorine interaction	ctions		
C9A…Cl1X	3.9028(4)	C9A-H9A1…Cl1X	176.3(7)
C9B…Cl1X	3.7859(5)	C9B-H9B1…Cl1X	168.5(6)
C9C···Cl1X	3.8305(3)	C9C-H9C2…Cl1X	175.0(6)
C9D····Cl1X	3.8682(4)	C9D-H9D2…Cl1X	176.5(6)
C9F…Cl1Y	3.8528(4)	C9F-H9F1…Cl1Y	1762.8(5)
Distance of N from the least-squares plane defined by the four O atoms of the PO groups			
N1X…plane	0.165(1)	N1Y…plane	0.423(1)
<sup>a</sup> +x,+y,+z+1			



**Figure S14.** Perspective view of the equilibrium geometry of the **Tiiii**@ephedrine complex obtained by molecular mechanics calculation using the MMFF force field implemented in Spartan06<sup>6</sup>. Ephedrine and the chloride ion have been represented in ball and stick mode. Colors are as follows: C, gray; H, white; N, blue; O, red; P, orange.

<sup>&</sup>lt;sup>6)</sup> Wavefunction Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612



**Figure S15.** Perspective view of the equilibrium geometry of the **Tiiii**@pseudoephedrine complex obtained by molecular mechanics calculation using the MMFF force field implemented in Spartan06<sup>6</sup>). Ephedrine and the chloride ion have been represented in ball and stick mode. Colors are as follows: C, gray; H, white; N, blue; O, red; P, orange.