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Supramolecular hydrogen-bonding patterns of co-crystals containing the active pharmaceutical ingredient (API) phloroglucinol and *N*-heterocyclesAleksandar Cvetkovski,^a Valerio Bertolasi^b and Valeria Ferretti^{b*}

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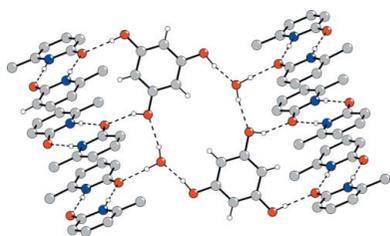
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Keywords: pharmaceutical co-crystals; hydrogen bonding; phloroglucinol; crystal packing.**CCDC references:** 1468136; 1468137; 1468138; 1468139; 1468140**Supporting information:** this article has supporting information at journals.iucr.org/b^aFaculty of Medical Sciences, University Goce Delcev, Krste Misirkov bb, 2000 PO 201, Štip The Former Yugoslav Republic of Macedonia, and ^bDepartment of Chemical and Pharmaceutical Sciences, University of Ferrara, via Fossato di Mortara 17-27, I-44121 Ferrara, Italy. *Correspondence e-mail: frt@unife.it

The active pharmaceutical ingredient phloroglucinol (PHL) has been taken as an illustrative molecule to explore the intermolecular interactions which can be established with other molecular entities to build PHL pharmaceutical co-crystals. The crystal structures of five newly synthesized co-crystals are reported, where PHL is crystallized with *N*-heterocycles, namely 2-hydroxy-6-methylpyridine (1), 2,4-dimethyl-6-hydroxypyrimidine (2), 4-phenylpyridine (3), 2-hydroxypyridine (4) and 2,3,5,6-tetramethylpyrazine (5). The structural characteristics of these co-crystals, as far as the hydrogen-bonding networks and the crystalline architectures are concerned, are strongly dependent on the chemical features of the coformer molecules, as well as on their size and shape. A detailed analysis of the intermolecular interactions established in all the PHL co-crystals of known structures has allowed the recognition of some regularities in the packing modes that can be useful in the design of new supramolecular adducts forming predictable structural motifs.

1. Introduction

In the last few years, the design and synthesis of co-crystals containing active pharmaceutical ingredients (APIs) has become the new frontier of crystal engineering (Steed, 2013; Brittain, 2012*a,b*, 2013; Blagden *et al.*, 2008; Shan & Zaworotko, 2008; Sekhon, 2009) due to the great opportunity to modify the physico-chemical properties of solid forms of drugs. Actually, in pharmaceutical co-crystals two or more components (out of which at least one is an API) are assembled through intermolecular interactions which are different from those found in the crystals of the pure components; consequently, these new crystalline forms exhibit specific physical properties, such as dissolution rate, bioavailability, physical stability *etc.* depending on the chemical nature of the co-crystal former, retaining at the same time the unaltered chemical structure of the APIs (Jones *et al.*, 2006). Currently, several APIs are known to improve their solubility profile and bioavailability when co-crystallized with appropriate cofomers (Brittain, 2012*a*; Childs *et al.*, 2013); this approach seems to be promising for the development of new pharmaceutical preparation, even if, as we have recently shown (Ferretti *et al.*, 2015), co-crystals may induce completely unpredictable effects on biological systems. The ultimate goal of the pharmaceutical co-crystal design is the enhancement of the drug performance without either altering its pharmacological behaviour or showing undesired effects, producing at the same time new solid forms having features useful for patent eligibility (Trask, 2007).



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Table 1
Experimental details.

Experiments were carried out at 295 K with Mo $K\alpha$ radiation using a Nonius Kappa CCD. H atoms were treated by a mixture of independent and constrained refinement.

	(1)	(2)	(3)	(4)	(5)
Crystal data					
Chemical formula	$C_6H_6O_3 \cdot 3C_6H_7NO \cdot H_2O$	$C_6H_6O_3 \cdot 3C_6H_8N_2O$	$C_6H_6O_3 \cdot 2C_{11}H_9N$	$C_6H_6O_3 \cdot 2C_5H_5NO$	$2C_6H_6O_3 \cdot 3C_8H_{12}N_2$
M_r	471.50	498.54	436.49	316.31	660.80
Crystal system, space group	Monoclinic, $P2_1/c$	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$	Monoclinic, $P2_1/c$
a, b, c (Å)	12.2625 (5), 14.1634 (7), 15.4250 (9)	7.7212 (2), 12.4488 (2), 14.2673 (3)	18.4503 (4), 7.3939 (2), 18.7699 (5)	7.7275 (3), 19.828 (1), 11.3080 (6)	15.6225 (4), 13.5010 (3), 17.2314 (5)
α, β, γ (°)	90, 113.8431 (16), 90	112.608 (1), 95.561 (1), 93.541 (1)	90, 114.924 (1), 90	90, 117.679 (2), 90	90, 90.235 (1), 90
V (Å ³)	2450.4 (2)	1252.65 (5)	2322.1 (1)	1534.3 (1)	3634.4 (2)
Z	4	2	4	4	4
μ (mm ⁻¹)	0.01	0.01	0.08	0.10	0.08
Crystal size (mm)	0.28 × 0.14 × 0.10	0.35 × 0.17 × 0.11	0.35 × 0.26 × 0.09	0.28 × 0.20 × 0.11	0.24 × 0.20 × 0.17
Data collection					
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	8382, 4321, 1632	9568, 5979, 4293	10 162, 5582, 2961	4785, 2693, 1170	14 448, 7827, 3828
R_{int}	0.126	0.023	0.049	0.079	0.052
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.595	0.661	0.661	0.595	0.639
Refinement					
$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.096, 0.325, 1.03	0.061, 0.222, 1.00	0.058, 0.195, 0.95	0.059, 0.191, 1.05	0.071, 0.226, 1.06
No. of reflections	4321	5979	5582	2693	7827
No. of parameters	316	373	394	232	481
No. of restraints	2	0	0	3	0
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.69, -0.29	0.32, -0.37	0.16, -0.20	0.27, -0.29	0.24, -0.25

Up to now the most effective co-crystal research (besides the in-depth understanding of structure-property relationships) relies on an efficient preparation of the desired co-crystals, which in turn requires an understanding and exploitation of the intermolecular interactions which may occur between the API and other co-crystal formers to give robust supramolecular synthons. Since hydrogen bonding is undoubtedly the most important among the intermolecular interactions, because it is highly directional and its energy can be modulated by the chemical environment, the design of a pharmaceutical co-crystal is based on the identification of specific hydrogen-bond donor and acceptor groups in APIs in order to choose a 'complementary interacting' molecule that can act as an efficient co-former.

From a supramolecular perspective, phloroglucinol (1,3,5-trihydroxybenzene, PHL) is a particularly attractive drug since it is rigid, *i.e.* it does not present torsional flexibility, and has three OH groups that can act as hydrogen-bonding donors and acceptors; from a chemical point of view it can be classified as a weak acid (pK_a value: 8.45). PHL is normally used as an antispasmodic agent; it is commercialized in tablets and has the appearance of a white solid soluble in water (solubility: 10.6 g L⁻¹), in alcohols and ethers. In addition, phloroglucinol and its derivatives exhibit a wide range of effects, such as anti-inflammatory, cytotoxicity (Barwell *et al.*, 1989), anti-thrombotic and profibrinolytic activities (Bae, 2011). Preclinical studies have proposed the role of phloroglucinol against the aging process and oxidative stress increasing cell viability and inhibiting lipid peroxidation (Kang, Lee, Chae *et al.*, 2006;

Kang, Zhang *et al.*, 2010; So & Cho, 2014). Finally, PHL and its derivatives are included in compositions used as anticancer (Kim *et al.*, 2015), antidepressant, antimicrobial agents and so on (Singh *et al.*, 2009).

A survey of the literature has shown that many phloroglucinol co-crystals have been obtained, the majority having an aromatic base as the co-former; in all the structures the PHL-OH groups interact preferably as hydrogen-bond donors towards a basic nitrogen, forming the hydroxyl...pyridine supramolecular heterosynthon which recently has been shown to have a very high frequency of occurrence in crystals containing hydroxyl and pyridine moieties (Bis *et al.*, 2007). As part of our continuing interest in understanding the structural features of the co-crystallization process (Bertolasi, Gilli *et al.*, 2001; Bertolasi, Pretto *et al.*, 2002), we decided to synthesize phloroglucinol co-crystals containing *N*-heterocycles as co-formers, *i.e.* pyridine/pyrimidine/pyrazine derivatives. The choice of these molecules is also justified from the fact that the *N*-heterocyclic skeleton is the basis of many essential pharmaceuticals and of many physiologically active natural products. As an example, many pyrimidine and pyrazine derivatives are found in pharmaceuticals acting against a large variety of diseases (Selvam *et al.*, 2012; Singh & Chouhan, 2014; Kao *et al.*, 2013; Wu *et al.*, 2013).

The solid-state methodology chosen to prepare the co-crystals was the slow solvent evaporation of PHL/co-former solutions, with the aim of obtaining suitable samples for single-crystal X-ray diffraction experiments. In this article five new molecular co-crystals are reported, where PHL is co-crystal-

lized with 2-hydroxy-6-methylpyridine (giving co-crystal 1), 2,4-dimethyl-6-hydroxypyrimidine (giving co-crystal 2), 4-phenylpyridine (giving co-crystal 3), 2-hydroxypyridine (giving co-crystal 4) and 2,3,5,6-tetramethylpyrazine (giving co-crystal 5). Their structural and packing features have been analysed and compared with those of all PHL-co-crystals found in the literature, with the aim of assessing the most recurrent supramolecular synthons, useful information for the design of new co-crystals having predictable structural motifs.

2. Experimental

2.1. Synthesis of co-crystals

Phloroglucinol and the other co-crystal formers were purchased from Sigma-Aldrich[®], and used without further purification. All chemicals were of analytical or chromatographic grade.

An equimolar quantity of PHL and co-crystal formers was dissolved in the minimum quantity of ethanol and left for slow evaporation at room temperature. Colourless crystals were observed after a few days.

2.2. X-ray crystallography

Single-crystal diffraction data for the five co-crystals (1)–(5) were collected on a Nonius Kappa diffractometer equipped with a CCD detector with graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$). Intensities were corrected for Lorentz and polarization effects. The structures were solved by direct methods with the *SIR97* suite of programs (Altomare *et al.*, 1999) and refinement were performed on F^2 by full-matrix least-squares methods with all non-H atoms anisotropic with *SHELXL2014/7* (Sheldrick, 2015). The data diffraction collected for compound (1) conveyed the poor quality of the crystals, and this is reflected by the R_{int} and refinement R -factors; the structure was however solved and refined without problems, then allowing the analysis of the intermolecular interactions and packing features. In (1) the H atoms were included on calculated positions, riding on their carrier atoms, apart from those belonging to the water molecule, located in a difference Fourier map and refined isotropically with restrained O–H distances. In (2) and (5) all H atoms except those of the methyl groups, included on calculated positions, were found in the difference-Fourier map and refined isotro-

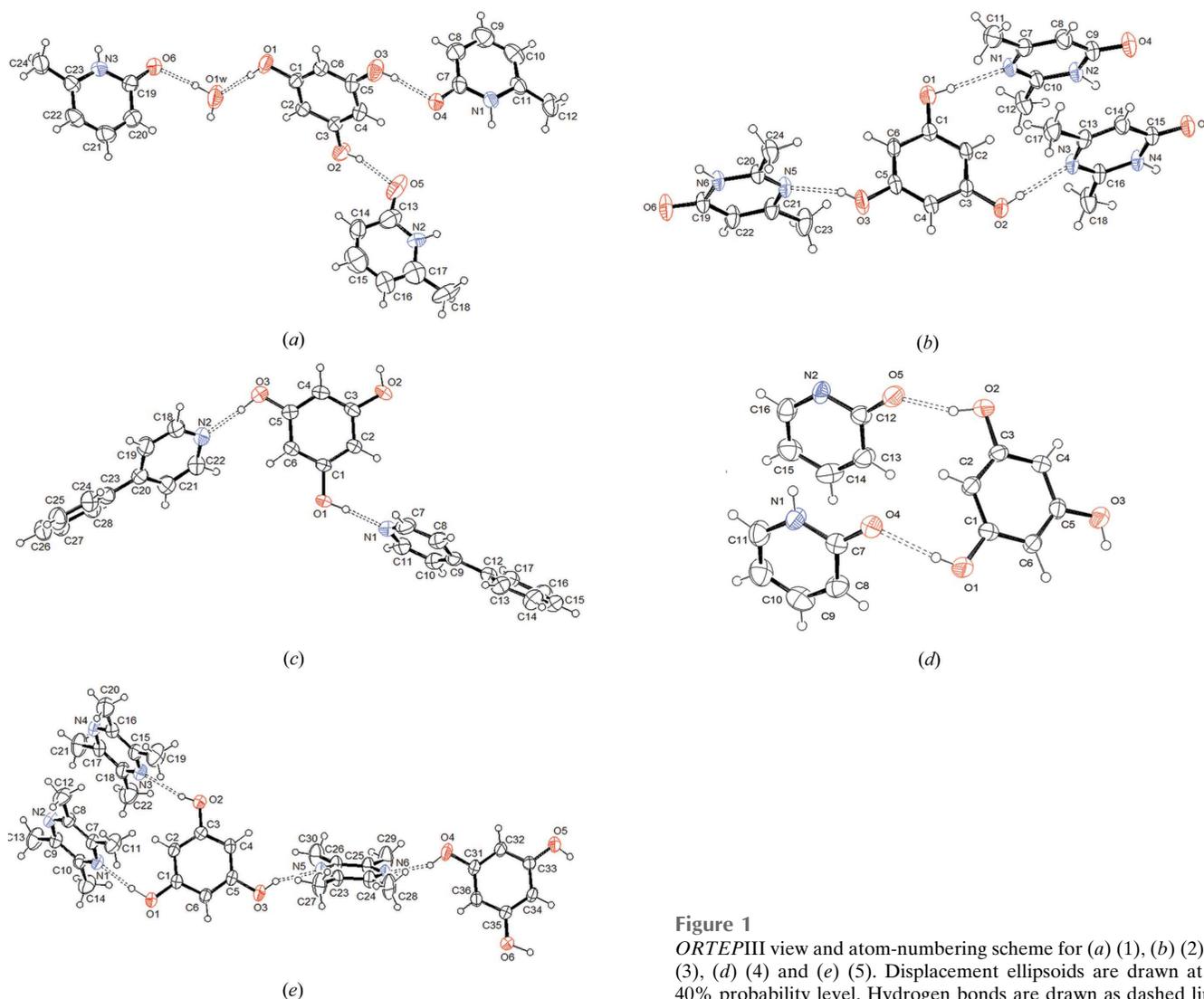


Figure 1
ORTEPIII view and atom-numbering scheme for (a) (1), (b) (2), (c) (3), (d) (4) and (e) (5). Displacement ellipsoids are drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines.

Table 2
Hydrogen-bonding parameters (Å, °).

$D-H\cdots A$	$D-H$	$D\cdots A$	$H\cdots A$	$D-H\cdots A$
Compound (1)				
O1—H···O1W	0.82	2.646 (9)	1.87	159
O2—H···O5	0.82	2.663 (7)	1.87	161
O3—H···O4	0.82	2.691 (7)	1.88	172
O1W—H···O6	0.91 (5)	2.738 (8)	1.82 (5)	173 (4)
O1W—H···O2 ⁱ	0.89 (5)	2.837 (9)	1.98 (8)	162 (7)
N2—H···O5 ⁱⁱ	0.86	2.766 (8)	1.91	175
N1—H···O6 ⁱⁱⁱ	0.86	2.784 (6)	1.93	171
N3—H···O4 ^{iv}	0.86	2.799 (6)	1.94	176
(i) $-x-1, -y-1, 1-z$; (ii) $1-x, -y, 1-z$; (iii) $x, y+1, z$; (iv) $x, y-1, z$.				
Compound (2)				
O1—H···N1	0.82 (3)	2.900 (3)	2.09 (3)	167 (3)
O2—H···N3	0.80 (3)	2.816 (3)	2.04 (3)	168 (3)
O3—H···N5	0.81 (4)	2.740 (3)	1.96 (4)	160 (3)
N2—H···O4 ⁱ	1.01 (3)	2.801 (2)	1.78 (3)	179 (3)
N4—H···O6 ⁱⁱ	0.89 (3)	2.762 (2)	1.87 (3)	177 (3)
N6—H···O5 ⁱⁱⁱ	0.96 (2)	2.824 (2)	1.87 (2)	173 (2)
C2—H···N1	0.94 (3)	3.289 (3)	2.56 (3)	134 (3)
C24—H···O3 ^{iv}	0.96	3.357 (4)	2.54	143
C4—H···O5 ^v	0.95 (4)	3.573 (3)	2.64 (4)	166 (3)
(i) $-x, 2-y, 1-z$; (ii) $x-1, y+1, z+1$; (iii) $x+1, y-1, z-1$; (iv) $1-x, -y, -z$; (v) $-x, 1-y, 1-z$.				
Compound (3)				
O1—H···N1	0.90 (4)	2.666 (3)	1.76 (4)	175 (4)
O3—H···N2	0.91 (4)	2.748 (3)	1.83 (4)	174 (3)
O2—H···O1 ⁱ	0.91 (4)	2.717 (2)	1.91 (4)	146 (3)
(i) $x, y-1, z$				
Compound (4)				
O1—H···O4	0.82 (4)	2.807 (5)	1.99 (4)	176 (4)
O2—H···O5	0.89 (4)	2.646 (4)	1.77 (4)	165 (4)
O3—H···O2 ⁱ	0.84 (6)	2.844 (6)	2.02 (6)	167 (5)
N1—H···O5 ⁱⁱ	0.90	2.762 (6)	1.86	176
N2—H···O4 ⁱⁱ	0.90	2.864 (6)	1.96	177
(i) $x, \frac{1}{2}-y, z+\frac{1}{2}$; (ii) $-x, -y, -z-1$.				
Compound (5)				
O1—H···N1	0.98 (5)	2.839 (3)	1.86 (5)	171 (4)
O2—H···N3	0.81 (4)	2.875 (4)	2.08 (4)	167 (4)
O3—H···N5	0.87 (5)	2.833 (3)	2.01 (5)	158 (4)
O4—H···N6	0.91 (4)	2.840 (4)	2.00 (4)	152 (3)
O5—H···N4 ⁱ	0.85 (4)	2.848 (4)	2.00 (4)	174 (4)
O6—H···N2 ⁱ	1.04 (6)	2.823 (4)	1.77 (6)	169 (5)
C6—H3···O2 ⁱⁱ	1.02 (3)	3.283 (4)	2.27 (3)	171 (3)
C32—H5···O6 ⁱⁱⁱ	0.94 (3)	3.273 (4)	2.33 (3)	173 (3)
(i) $x+1, y, z+1$; (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$; (iii) $2-x, y+\frac{1}{2}, \frac{3}{2}-z$.				

pically. In (3) all the H atoms were found in the difference Fourier map and refined isotropically; in (4) the H atoms of the phloroglucinol molecule were found in the difference Fourier map and refined isotropically, while the others were included on calculated positions. All calculations were performed using *SHELXL97* (Sheldrick, 2015) implemented in the *WinGX* system of programs (Farrugia, 1999). Experimental details are given in Table 1. Tables S1–S5 of bond distances and angles for compounds (1)–(5), respectively, are given in the supporting information.

2.3. CSD search

The crystallographic data of the published phloroglucinol co-crystals were retrieved from the October 2014 release of

the Cambridge Structural Database (Groom *et al.*, 2016). Only the structures exhibiting no crystallographic disorder have been considered.

3. Description of the structures

ORTEP views of the five co-crystals are shown in Figs. 1(a)–(e). The hydrogen-bonding geometrical parameters are given in Table 2.

3.1. Crystal structure of PHL–2-hydroxy-6-methylpyridine (1)

The structural determination shows the presence of a PHL–coformer–water (1:3:1) co-crystal, the hydroxypyridine molecule being in its pyridone form. The electronic effect of substituents bonded at position 6 of the 2-hydroxypyridine derivatives is inductive in character and strongly influences the position of the tautomeric equilibrium, possibly affecting the relative acidity of the O–H group with respect to the N–H group. A consequence of this is that with substituents such as chloro- or methoxy groups the pyridines are mainly in the aromatic form, while 2-hydroxy-6-methylpyridine is always in the pyridone form (Forlani *et al.*, 2002). In the crystal the pyridone moieties form dimeric units by $R_2^2(8)$ supramolecular homosynthons (ring *A* in Fig. 2a) through N–H···O hydrogen-bonding interactions; each phloroglucinol molecule links two of these dimers forming bifurcated O–H···O interactions with the carbonyl O atoms, the last hydroxyl group being involved in an O–H···O hydrogen bond with water. The water molecule, in turn, donates two bonds with its two H atoms acting as both hydrogen-bonding donors and acceptors to give the $R_4^4(16)$ ring *B* shown in Fig. 2(a).

3.2. Crystal structure of PHL–2,4-dimethyl-6-hydroxypyrimidine (2)

The asymmetric unit of (2) is made of PHL and the coformer in its ketonic form in a 1:3 ratio. The pyrimidone moieties are linked in dimers by N–H···O interactions forming the usual $R_2^2(8)$ ring; at variance with (1), in this case a second N atom on each pyrimidone ring is free to accept a O–H···N hydrogen bond from phloroglucinol, in such a way that three dimers are put together by a unique PHL molecule. The resulting characteristic pattern is shown in Fig. 2(b).

3.3. Crystal structure of PHL–4-phenylpyridine (3)

In (3) the ratio of PHL–coformer (4-phenylpyridine) is 1:2. The structural motifs made by O–H···N/O hydrogen bonds are quite simple: each PHL interacts with two pyridine derivatives *via* O–H···N bonds of $D_1^1(2)$ type and with two adjacent phloroglucinol molecules forming O–H···O $C_1^1(6)$ chains, which run parallel to the *c* direction and are separated by layers of 4-phenylpyridine derivatives (Fig. 2c).

3.4. Crystal structure of PHL–2-hydroxypyridine (4)

The asymmetric unit of (4) is composed of PHL and 2-hydroxypyridine in the ratio 1:2. Even in this case, the pyri-

done tautomer is present and the cofomer molecules are linked in dimers by $\text{N}-\text{H}\cdots\text{O}$ interactions forming $R_2^2(8)$ rings. Two dimers are connected to one PHL molecule [$D_1^1(2)$ motif] which in turn uses its third OH group to form $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds with adjacent drug molecules [$C_1^1(6)$ motif]. The final packing is made of parallel zigzag ribbons running along the b direction (Fig. 2*d*).

3.5. Crystal structure of PHL–2,3,5,6-tetramethylpyrazine (5)

The stoichiometry for co-crystal (5) is PHL–pyrazine (2:3). The three pyrazine moieties are crystallographically different since one of them simply bridges two drug molecules through its N atoms located at the opposite site of the molecule, while the others are both linked to the same phloroglucinol molecules, as shown in Fig. 1(e). These four molecules form a $R_4^4(22)$ ring (Fig. 2*e*).

4. Hydrogen-bonding analysis

As discussed in the previous paragraph, the three OH groups of the phloroglucinol molecule are all involved in hydrogen bonds acting always as donors (only sometimes as acceptors).

With the aim of gaining deeper insight into the PHL hydrogen-bonding capability, a search of the CSD (Groom *et al.*, 2016) has been performed of all its co-crystals of known structure. Excluding disordered structures, 30 entries have been found (Santra & Biradha, 2011; Boldog *et al.*, 2004; Haberhauer *et al.*, 2004; Ung *et al.*, 1994; Biradha & Zaworotko, 1998; Gao *et al.*, 2008; Arora *et al.*, 2009; Bis *et al.*, 2007; Santra & Biradha, 2008; Sarma *et al.*, 2008; Mahapatra *et al.*, 2010; Lavender *et al.*, 1998; Shi *et al.*, 2010; Ghosh *et al.*, 2005; Coupár *et al.*, 1996; Barooah *et al.*, 2003; Vishweshwar *et al.*, 2003; Imai *et al.*, 2009; Hou *et al.*, 2010; Liu *et al.*, 2001), two of which are simple solvated PHL [solvent: dimethylsulfoxide (Polyanskaya *et al.*, 2011) and water (Thomas *et al.*, 2011)]. The complete list of CSD entries, together with information on the co-crystals' composition and donor \cdots acceptor distances of $\text{O}-\text{H}(\text{hydroxyl})\cdots X$ interactions, considering only those in which the PHL hydroxyl group acts as a donor, are reported in Table S6 of the supporting information. There are three types of acceptor atoms: nitrogen (in most cases aromatic N), oxygen (carbonylic or hydroxylic) and OW from water molecules. The donor \cdots acceptor distance distributions are shown in the two histograms of Fig. 3(a) and (b) for $\text{O}\cdots\text{N}$ and $\text{O}\cdots\text{O}$, respectively. The $\text{O}\cdots\text{N}$ distances vary in the quite

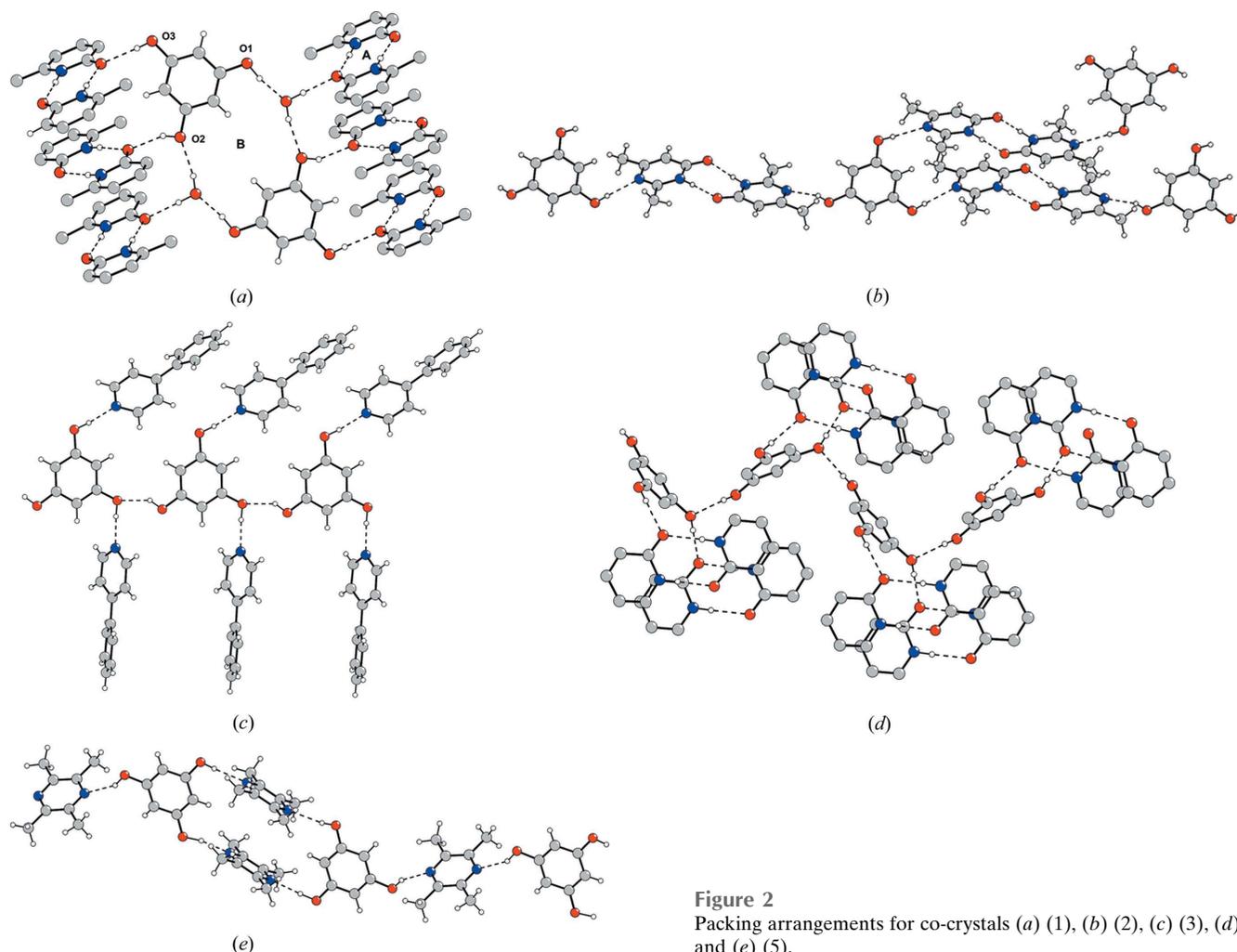


Figure 2
Packing arrangements for co-crystals (a) (1), (b) (2), (c) (3), (d) (4) and (e) (5).

Table 3

O...N distances (Å) and cofomer pK_a in phloroglucinol co-crystals with mean values in angle brackets.

CSD code	O...N distance (mean)	Cofomer pK_a	ΔpK_a	Reference
(3) ^a	<2.707>	4-Phenylpyridine: 5.5	2.95	Bansal (1999)
(5) ^a	<2.843>	Tetramethyl pyrazine: 2.88 5.62	5.62	Keyworth (1959)
HAHNOU ^b	2.741	2,2'-Bipyridine: 4.34	4.11	Martell <i>et al.</i> (2001)
HIMGAL ^c	2.741	4-Methylpyridine: 6.02	2.43	Braude & Nachod (1955)
HIMGEP ^c	<2.738>	2,4-Dimethylpyridine: 6.72	1.73	Clarke & Rothwell (1960)
HODLES ^d	<2.615>	Imidazole: 6.95	1.50	Bruice & Schmir (1958)
KIHZEH ^e	<2.766>	4-Cyanopyridine: 1.90	6.55	Gramstad (1993)
MORVEV ^f	<2.831>	Phenazine: 1.23	7.22	Albert & Phillips (1956)
MORVIZ ^f	<2.852>	Phenazine: 1.23	7.22	Albert & Phillips (1956)
MORVOF ^f	<2.663>	Acridine: 5.60	2.85	Braude & Nachod (1955)
MORVUL ^f	<2.805>	Phenazine: 1.23	7.22	Albert & Phillips (1956)
PUPGOX ^g	2.846	Caffeine: 0.61	7.84	Hodgman (1951)
PUVMIC ^h	<2.798>	2,2'-Bipyridine: 4.34	4.11	Martell <i>et al.</i> (2001)
RAWDIC01 ⁱ	<2.717>	Urotropine: 4.89	3.56	Cooney <i>et al.</i> (1986)
TEKKOI ^j	<2.741>	4,4'-Bipyridine: 4.96	3.49	Ashton <i>et al.</i> (1982)
VAKVEJ ^k	<2.775>	Nicotinamide: 3.33	5.12	Gressel & Gallelli (1968)

References: (a) present work; (b) Haberhauer *et al.* (2004); (c) Biradha & Zaworotko (1998); (d) Gao *et al.* (2008); (e) Bis *et al.* (2007); (f) Sarma *et al.* (2008); (g) Mahapatra *et al.* (2010); (h) Lavender *et al.* (1998); (i) Ghosh *et al.* (2005); (j) Coupar *et al.* (1996); (k) Vishweshwar *et al.* (2003).

large range 2.59–2.95 Å, while the O...O narrower range is 2.60–2.89 Å. In a recent paper (Alvarez, 2013) the distribution of distances in the CSD between two specific atoms has been extensively analyzed and the relative histograms for diverse atomic couples extracted, distinguishing between simple van der Waals contacts and hydrogen bonds. According to these distributions, the structural parameters found in PHL co-crystals show that the O–H...N interactions listed in Table S1 can be classified as strong/medium hydrogen bonds.

On the basis of the pK_a equalization principle (Gilli *et al.*, 2009), the strongest hydrogen bonds are associated with a very low ΔpK_a value, *i.e.* the difference between donor and acceptor acidic constants. The ΔpK_a value associated with a general $D-H...A$ interaction is calculated as

$$\Delta pK_a(D-H...A) = pK_{AH}(D-H) - pK_{BH}^+(A-H^+).$$

The wide O...N distance distribution described above can then be correlated to the chemical diversity, expressed in terms of acidity constant, displayed by the cofomer molecules in PHL co-crystals. As shown in Table 3, the cofomer pK_a values range from 0.6 to 6.95. The plot of ΔpK_a versus N...O is shown in Fig. 4. Despite the many approximations used (mean value of N...O distances; pK_a value sometimes not exactly corresponding to the cofomer molecule but to similar molecular entities), a linear trend is clearly visible, indicating that this system is a good example of the validity of the pK_a equalization principle.

5. Role of water molecules in co-crystal structures

Out of 34 PHL co-crystal structures, 16 have co-crystallized solvent molecules. In 11 cases the solvent turns out to be water. As stated by Clarke *et al.* (2010), ‘*water is indeed in many ways the nemesis of crystal engineering*’ and, accordingly, even in this case the presence of co-crystallized water molecules makes it difficult to rationalize the hydrogen-bonding network. A general finding for PHL co-crystals is that the water molecules are present when the cofomers have an overabundance of hydrogen-bonding donor or acceptor groups, and a possible explanation could be the requirement of maximizing the interactions among the entities constituting the crystal. On the other hand, there is no rule about the number of water molecules in the asymmetric unit (from one to four, see Table S6) or the stoichiometric ratio among the co-crystal's components. Moreover, the water molecules could in principle compete with the PHL-OH groups for the formation of hydrogen bonds with the cofomer molecules. To explore this possibility, hydrogen-bond propensities (Galek *et al.*, 2007) were calculated using the program *Mercury* 3.5.1.

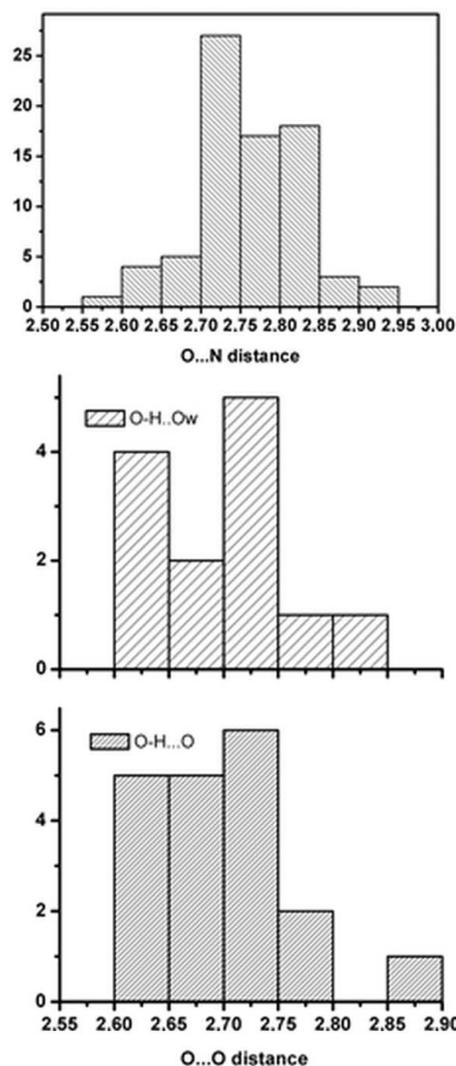


Figure 3 Histograms of donor...acceptor distances (Å) in O–H...X (X = N, O) hydrogen-bonding interactions found in phloroglucinol co-crystals.

Hydrogen-bond propensity is based on a statistical model making use of the molecular information stored in the Cambridge Structural Database (CSD). The dataset for this model is made of molecules containing one or more of the functional groups present in a given target system. The existence of a hydrogen bond between potential donor and acceptor atoms is decided using distance and angle criteria. A hydrogen-bond propensity for a donor–acceptor pair is a value between 0 and 1, where 0 indicates no likelihood of a hydrogen-bond formation and 1 indicates that a hydrogen bond is always formed. In view of the PHL–co-crystal types found, the entry VAXVEI [phloroglucinol bis(isonicotinamide) dihydrate] has been chosen as a target system. It is characterized by three functional groups: water, phenyl-OH (O of ar-hydroxy), aromatic N. The obtained values of the propensity for the considered functional groups are listed in Table 4. It is interesting to note that the highest propensity value is associated with hydrogen bonds formed between water molecules and aromatic N; however, a close examination of the PHL–co-crystals reveals that in these systems the water molecules interact rarely with the aromatic N atoms, most frequently acting as H-donors towards other water molecules, OH or C=O groups [see for example the interaction lists for compound (1)]. In addition, no conserved supramolecular motif could be found in hydrated structures, therefore no classification is possible. In almost all the structures, the co-crystallized water molecules exploit the full range of their hydrogen-bonding capability, acting both as hydrogen-bond donors and acceptors. In view of this, it can be assumed that their presence could provide a considerable contribution to the crystal stability; for example, Fucke *et al.* (2013) have recently shown that the hydrogen-bonding network involving the solvent molecules in hydrated Piroxicam is one of the major stabilizing factors of the crystal structure with respect to the non-hydrated drug.

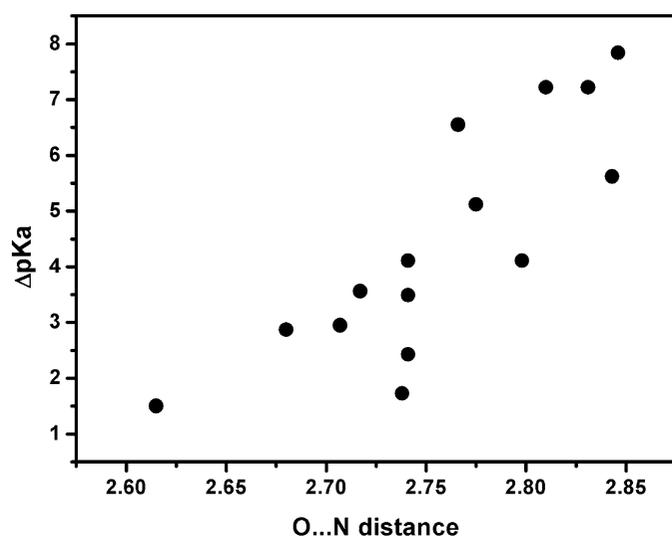


Figure 4
 ΔpK_a versus O...N distances (Å) in PHL co-crystals.

Table 4
 Predicted intermolecular hydrogen-bond propensities (applied to VAKVEI).

Donor	Acceptor	Propensity	Lower bound	Upper bound
O of water	N of aromatic_nitrogen	0.83	0.81	0.84
O of water	O of water	0.66	0.65	0.66
O of ar_hydroxy	N of aromatic_nitrogen	0.61	0.58	0.64
O of water	O of ar_hydroxy	0.41	0.38	0.43
O of ar_hydroxy	O of water	0.38	0.36	0.40
O of ar_hydroxy	O of ar_hydroxy	0.18	0.17	0.20

6. Packing comparison: non-solvated structures

Considering the number of functional groups present in the co-former molecules and other chemical characteristics such as size and shape, it is possible to distinguish different ways of packing. When the coformer molecule has only one hydrogen-bond acceptor functional group [(3), HIMGAL, HIMGEP (Biradha & Zaworotko, 1998), KIHZEH (Bis *et al.*, 2007), MORVOF (Sarma *et al.*, 2008)] the packing is determined by the relative sizes of PHL and the coformer. KIHZEH (Bis *et al.*, 2007) has been included in this group in view of the fact that the phenyl-cyano group is a poor hydrogen-bond acceptor. If the two molecules have strictly comparable molecular size, the stoichiometric PHL:coformer ratio is 1:3 and an isolated supramolecular complex is formed. An example is reported in Fig. 5(a).

Conversely, when the size of the co-former is much larger, the steric hindrance prevents the formation of the supramolecular aggregation of Fig. 5(a) and the PHL:coformer ratio changes to 1:2. In the two structures [(3), MORVOF Sarma *et al.*, 2008], representative of such a situation, the packing motif is the same. It is characterized by parallel $C_1^1(6)$ chains formed by the O–H...O bonded phloroglucinol molecule, in which two out of three OH groups are involved. The third ‘free’ hydroxyl, as well as that acting as a hydrogen-bond acceptor in the main chain, are linked through O–H...N interactions with the co-former molecules, which are organized on both sides of the chain in a perpendicular way (Figs. 2c and 5b).

Interestingly, the same crystal packing mode is found for (4) (Fig. 2d). Actually, this co-crystal can rationally be included in this last group, since the dimeric pyridine unit behaves as a unique molecule as far as the crystal packing is concerned. As a matter of fact, the cyclic amide hydrogen-bonded homodimer is a robust synthon which is highly conserved. In the CSD 445 entries containing such a molecular group have been found (organic structures only), with a mean N...O distance of 2.79 (5) Å. In six co-crystal structures, *i.e.* (5), HOPKAZ (Arora *et al.*, 2009), MORVEV, MORVUL (Sarma *et al.*, 2008), PUVMIC (Lavender *et al.*, 1998), RAWDIC01 (Ghosh *et al.*, 2005) and TEKKOJ (Coupar *et al.*, 1996), the co-crystallized molecule has two (in one case, RAWDIC01, three) hydrogen-bonding acceptor groups, located on opposite sides. The 1:3 PHL–coformer stoichiometric ratio in this case is never observed, being 1:2 or 2:3. In all cases a peculiar packing mode is recognizable, since each PHL molecule binds two co-former molecules on one side and one on the other side,

forming a zigzag ribbon motif (with alternating PHL-coformer molecule layers). In this case the size and shape of the co-crystallized molecule is irrelevant: it can be of the same size and shape as the phloroglucinol (5, Fig. 2e), it can be planar with a different size (*e.g.* TEKKOJ, Fig. 5c) or it can be different in size and shape (RAWDIC01, Fig. 5d).

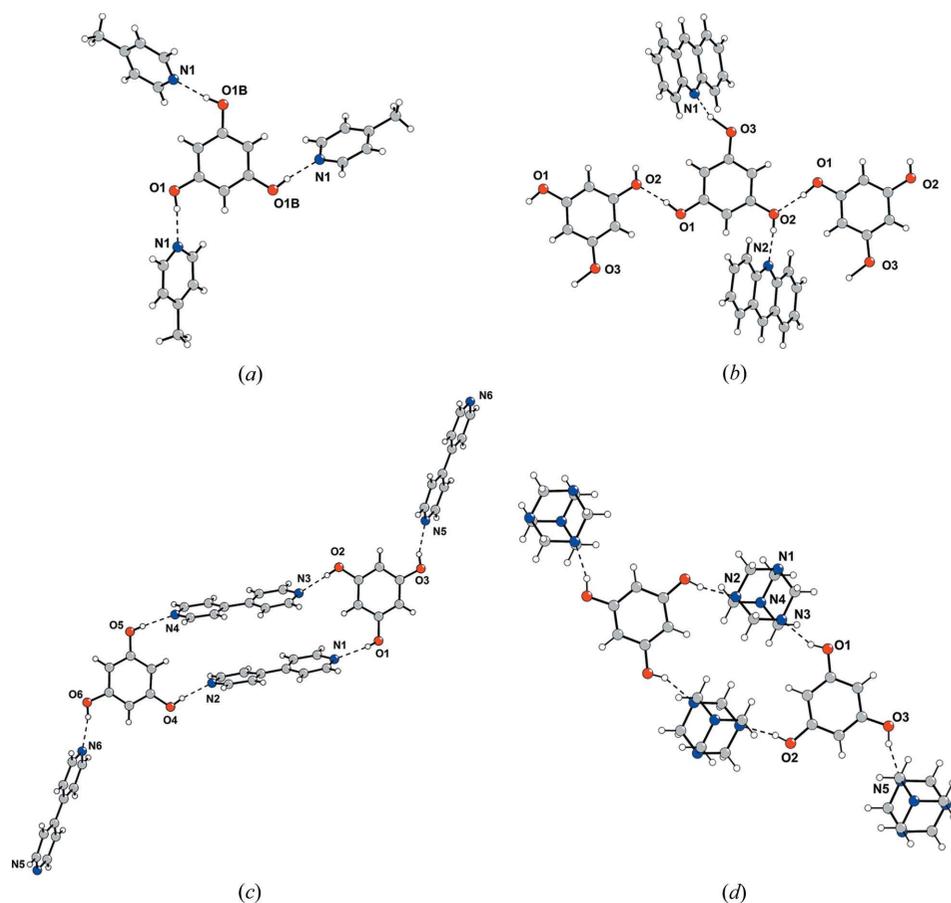


Figure 5
Hydrogen-bonding motifs in CSD entries: (a) HIMGAL (coformer: 4-methylpyridine; Biradha & Zaworotko, 1998); (b) MORVOF (coformer: acridine; Sarma *et al.*, 2008); (c) TEKKOJ (coformer: 4,4'-bipyridine; Coupar *et al.*, 1996); (d) RAWDIC01 (coformer: urotropine; Ghosh *et al.*, 2005).

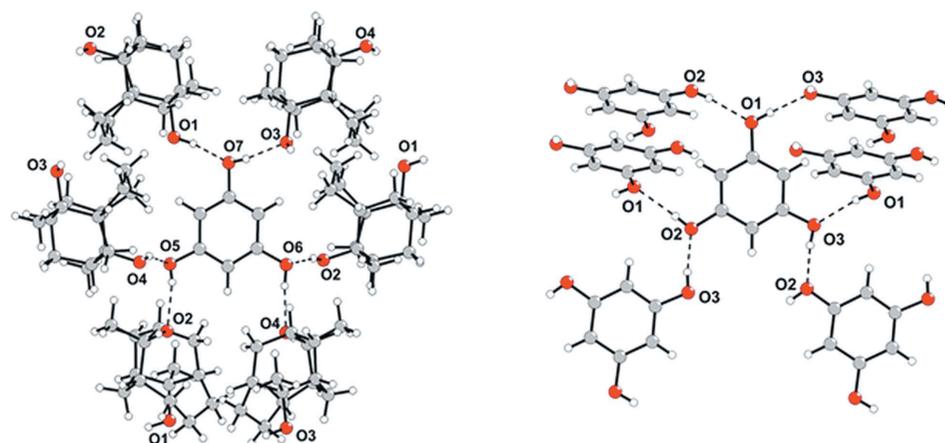


Figure 6
Hydrogen-bonding arrangement around the PHL molecule in HIBHEF (coformer: 2,8-dimethyl tricyclo-syn-2,5yn-8-diol; Ung *et al.*, 1994) and in pure phloroglucinol PHGL0L01 (Görbitz *et al.*, 2008).

Analogous to the previous case, compound (2) can be included in this group of co-crystals, considering the dimeric unit as a unique block. The packing motif just described is nicely reproduced (Fig. 2b).

Finally, when the co-former molecule has both hydrogen-bonding donor and acceptor groups [HIBHEF (Ung *et al.*, 1994), ULAZEM (Baroah *et al.*, 2003), XIBQUU (Liu *et al.*, 2001)], each OH group belonging to the drug molecule acts as both a hydrogen-bonding donor and acceptor. It is interesting to note that when the size of the coformer molecule is small enough (HIBHEF, XIBQUU), the PHL moiety is surrounded by six molecules in a way resembling what is found in the pure phloroglucinol crystal (Görbitz *et al.*, 2008; see Fig. 6)

7. Conclusions

A detailed analysis of the hydrogen-bonding intermolecular interactions and packing modes in pharmaceutical co-crystals containing the API phloroglucinol has been presented. As expected, the phenolic OH groups of the phloroglucinol molecule, which have an acidic character, readily interact with basic groups, in particular aromatic nitrogens. Moreover, these groups, which in principle can act both as a hydrogen-bonding donor or acceptor, preferentially form O—H...N interactions whose strength can be reasonably predicted on the base of the pK_a equalization principle. The packing modes of the PHL-co-crystals can be rationalized on the basis of the chemical characteristics of the co-former molecules, such as their size, shape and number of functional groups. Furthermore, it has been shown that robust supramolecular synthons, such as amide...amide hydrogen-bonded dimers, can be considered just like unique molecules as far as the description of the crystalline architecture is concerned. Finally, the packing rationalization was possible for the hydrated structures, although the

high number of interactions in which the co-crystallized water molecules participate suggest they could contribute to the overall stability of the crystal.

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