Ab initio crystal structure determination of two chain functionalized pyrroles from synchrotron X-ray powder diffraction data

Iván da Silva,[1,2,a)] Sara López-Tosco,[3] David Tejedor,[3] Fernando García-Tellado,[3] and Javier González-Platas[4]

[1]*SpLine Spanish CRG Beamline at the ESRF 6, Rue Jules Horowitz, BP 220, 38043 Grenoble Cedex 09, France*
[2]*Instituto de Ciencia de Materiales de Madrid-ICMM/CSIC, Cantoblanco, Madrid 28049, Spain*
[3]*Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas, Avda. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain*
[4]*Servicio de Difracción de Rayos X, Departamento de Física Fundamental II, Universidad de La Laguna, Avda. Astrofísico Francisco Sánchez 2, 38206 La Laguna, Tenerife, Spain*

(Received 5 March 2012; accepted 19 April 2012)

The crystal structure of two chain functionalized pyrroles, methyl 1-benzyl-5-(1-(4-chlorobenzoyloxy)-2-methoxy-2-oxoethyl)-4-(4-chlorophenyl)-1H-pyrrole-2-carboxylate and methyl 1-benzyl-4-(biphenyl-4-yl)-5-(1-(4-biphenylcarbonyloxy)-2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate, which are both important active candidates as antitumoral agents, have been obtained *ab initio* from synchrotron X-ray powder diffraction data. Both compounds crystallize in the monoclinic system (space group $P2_1/c$), with $a = 20.2544(3)$ Å, $b = 6.80442(9)$ Å, $c = 21.1981(3)$ Å, $\beta = 111.6388(9)°$ and $a = 29.7747(6)$ Å, $b = 6.27495(14)$ Å, $c = 18.8525(3)$ Å, $\beta = 107.053(2)°$, respectively. These structures were determined using a direct space approach, by means of Monte Carlo technique, followed by Rietveld refinement.
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Key words: pyrroles, structure solving, powder diffraction

I. INTRODUCTION

Chain functionalized pyrroles constitute a structural motif of particular interest in synthetic and medicinal chemistry, as it is the foundation of important medicines, natural products and synthetic materials (Jones, 1992; Lehr, 1997; Le Quesne *et al.*, 1999; Boger and Hong, 2001; Johnson *et al.*, 2002; Fürstner, 2003; Walsh *et al.*, 2006; Pfefferkorn *et al.*, 2007). In particular, tetrasubstituted pyrroles 5 can be considered as hybrid scaffolds (Mehta and Singh, 2002; Tietze *et al.*, 2003) comprising a structurally privileged pyrrole ring and a naturally occurring α-hydroxy acid motif (Abell and Nabbs, 2001; Martyn *et al.*, 2003; Baran *et al.*, 2005; Gabriele *et al.*, 2006; Alcaide *et al.*, 2008). The hybrid features five points of diversity (two chemo-differentiated ester groups, two chemo-differentiated *R* groups and one N-*R*1 group) and two differentiated points for complexity generation: one on the ring (sp2-linking point; C4-H) and the other on the chain (sp3-linking point; CH(OCO*R*)*Z*]. These molecules are ideal candidates for our wide research program aimed at developing new anti-tumoral agents (Padrón *et al.*, 2005; Leon *et al.*, 2010).

This paper reports the structure solution of the two organic compounds methyl 1-benzyl-5-(1-(4-chlorobenzoyloxy)-2-methoxy-2-oxoethyl)-4-(4-chlorophenyl)-1H-pyrrole-2-carboxylate (denoted **5EA**) and methyl 1-benzyl-4-(biphenyl-4-yl)-5-(1-(4-biphenylcarbonyloxy)-2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate (denoted **5CA**). As no suitable single crystals were obtained for single crystal X-ray analysis, both structures were solved by synchrotron X-ray powder diffraction analysis. The corresponding structures were determined by means of the Monte Carlo method and refined using the Rietveld method. The X-ray powder diffraction method, thanks to the recent experimental and software algorithms advances, shows to be a very promising technique when dealing with interesting pharmaceutical compounds, since many of them can only be obtained as powder samples, rather than single crystals (David *et al.*, 1998; Dinnebier *et al.*, 2000; Harris and Cheung, 2004).

II. EXPERIMENTAL

A. Spectroscopic study

The structural identity, which is shown in Figure 1, of the studied compounds was determined spectroscopically (^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry). The details of this study, as well as information on the synthesis procedure of the compounds, can be found elsewhere (Tejedor *et al.*, 2009).

B. X-ray diffraction

High resolution powder diffraction (HRPD) patterns were collected at SpLine beamline (BM25A) of the Spanish CRG at the European Synchrotron Radiation Facility (ESRF, Grenoble) using a fixed wavelength of 1.0323(1) Å, at room temperature. The powder samples were loaded inside 0.3-mm-diameter borosilicate glass capillaries, which were rotated during exposure, to reduce the effect of possible preferential orientations. Diffraction pattern recording for each compound was carried out in a 2θ-step scan mode with a step of 0.015°, counting 24 and 9 s of acquisition time per step, for **5EA** and **5CA**, respectively. The incoming beam was monitored to normalise the resulting data to the decay of the primary beam, while the diffracted beam was collected

a)Author to whom correspondence should be addressed. Electronic mail: dasilvag@esrf.fr

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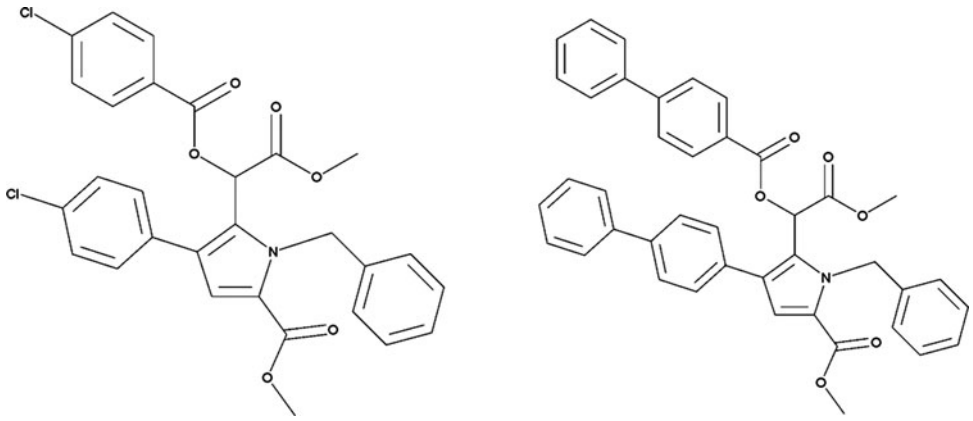


Figure 1. Structural fragments of **5EA** (a) and **5CA** (b) compounds.

using a scintillation point detector. Data were collected in the range of 1–72° 2θ for both compounds.

III. STRUCTURE DETERMINATION AND RIETVELD REFINEMENT

For **5EA** and **5CA** diffraction patterns, angular positions of the first 20 reflections (up to about 15 13° 2θ, respectively) were determined using the peak search algorithm implemented in *WinPLOTR* program (Roisnel and Rodriguez-Carvajal, 2001). These positions were used to index both patterns using *DicVOL06* program (Boultif and Louër, 2004) into the monoclinic system, yielding cells with figures of merit (De Wolff, 1968) of $M(20) = 21.6$ and 23.0, for compounds **5EA** and **5CA**, respectively. For space group determination, *EXPO2004* program (Altomare *et al.*, 2004) was used, using the statistical algorithm implemented to determine the most probable extinction group (Altomare *et al.*, 2005). In this case, the found extinction group with the highest probability was $P2_1/c$, for both crystal cells, which was confirmed by visual inspection of systematic absences.

Structures of **5EA** and **5CA** compounds were solved, by means of Monte Carlo calculations, using the parallel tempering algorithm implemented in *FOX* program (Favre-Nicolin and Cerný, 2002). Templates of the structural fragments were previously built using the software package *ChemBio Office* (version 11.0), which were introduced in *FOX* program. During the calculations, the observed and calculated intensities were compared only in the 2θ range from 1 to 25° and the molecules could translate and rotate randomly; different torsion angles could also change and the aromatic rings were treated as rigid fragments. After 15 million trials, the agreement factors were $R_{wp} = 0.055$, $GoF = 17.078$ and $R_{wp} = 0.1018$, $GoF = 14.323$.

Refinements of the structures found by *FOX* program were carried out by the Rietveld method (Rietveld, 1969), using *FullProf* program (Rodriguez-Carvajal, 2001) in the 2θ range from 1 to 50° for both diffraction patterns, as the diffracted signal-to-noise ratios were very low for both patterns at 2θ angles above 50°. Atomic coordinates of all atoms were included in the refinement but, in order to ensure the convergence of the process, phenyl rings were treated as rigid bodies and restraints on the other bond lengths and angles were introduced, thus limiting the number of free parameters. The values for the bond lengths and angles were taken from similar molecules and molecular fragments in the CCDC database (codes: QOQGAF, BOPSEE11, ABEFOD, ACERAC and ADAGUI) and the mean-square deviations of assigned values were 0.02 Å and 1°, respectively. An overall isotropic temperature factor was introduced for each structure refinement. The peak function used for fitting the experimental data was the Thompson–Cox–Hastings Pseudo–Voigt (Thompson *et al.*, 1987), which can take into account the experimental resolution and the broadening due to size and strain effects, often present in

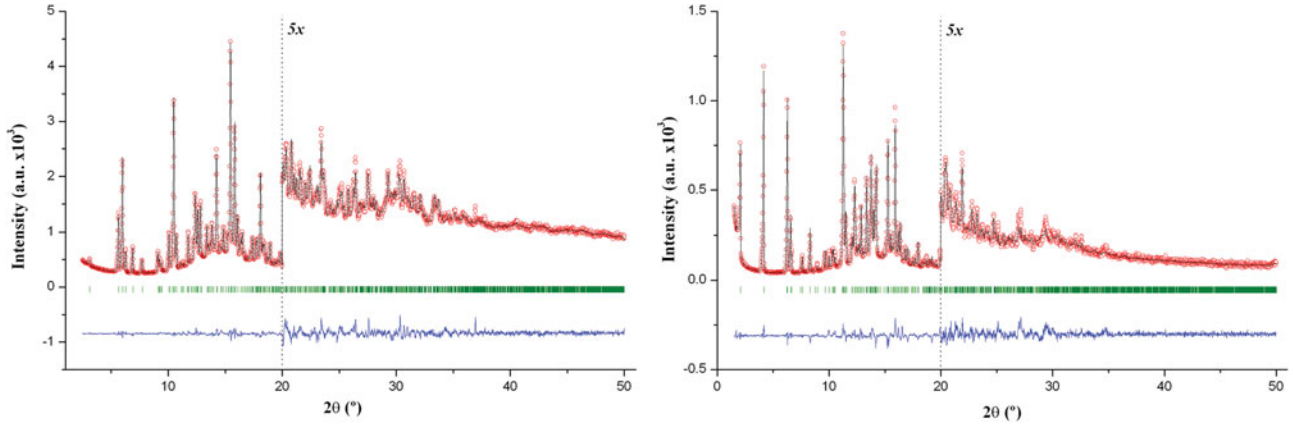


Figure 2. Final Rietveld refinement plots for **5EA** (a) and **5CA** (b), showing the experimental (red circles), calculated (black line) and difference profiles (blue line); green tick marks indicate reflection positions. From dotted vertical line: intensity scale 5-times multiplied for clarity.

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TABLE I. Crystallographic data and Rietveld refinement summary for compounds **5EA** and **5CA**.

	5EA	5CA
Formula	$C_{29}H_{23}Cl_2NO_6$	$C_{41}H_{33}NO_6$
Formula weight (g mol^{-1})	552.40	635.68
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Temperature (K)	298	298
a (Å)	20.2544(3)	29.7747(6)
b (Å)	6.80442(9)	6.27495(14)
c (Å)	21.1981(3)	18.8525(3)
β (°)	111.6388(9)	107.053(2)
Volume (Å^3)	2715.61(6)	3367.44(12)
Z	4	4
ρ (g cm^{-3})	1.351	1.254
Radiation type	Synchrotron	Synchrotron
Diffractometer	SpLine (BM25A) at the ESRF, Grenoble	SpLine (BM25A) at the ESRF, Grenoble
Data collection mode	Transmission	Transmission
Wavelength (Å)	1.0323(1)	1.0323(1)
Specimen mounting	Borosilicate glass capillary	Borosilicate glass capillary
Refinement method	Rietveld Refinement	Rietveld Refinement
R_p (%)	2.3	5.4
R_{wp} (%)	3.0	7.2
R_F (%)	3.06	10.7
R_B (%)	3.76	7.14
GoF	1.9	2.1
Profile function	Thompson–Cox–Hasting Pseudo–Voigt	Thompson–Cox–Hasting Pseudo–Voigt
No. of profile data steps	3333	3259
No. of contributing reflections	4610	5804
No. of bond length restraints	29	28
No. of bond angle restraints	40	45

this type of organic powder samples; axial divergence asymmetry of peaks was modelled using the Finger's treatment (Finger *et al.*, 1994); 44 and 56 points were chosen regularly distributed on the experimental patterns to model the background through a linear interpolation made between two successive points. Hydrogen atoms for **5EA** and **5CA** molecules were introduced in *FullProf* at their calculated positions with *Olex2* program (Dolomanov *et al.*, 2009). During the Rietveld refinements, the position of H atoms was restrained to that of their riding atom. Owing to the possibility of deformation or rotation of both molecules, the positions of H atoms were recalculated several times during the refinement procedure before it converged.

On the final Rietveld fits, there were 79 and 86 adjustable parameters for **5EA** and **5CA**, respectively (scale factor, zero-shift, atomic coordinates, overall temperature factor, unit-cell

TABLE II. Fractional atomic coordinates and isotropic displacement parameters (Å^2) for compounds **5EA** and **5CA**.

	Atom	x	y	z	U_{iso}
5EA					
	Cl1	0.409897(5)	0.77386(2)	−0.130296(5)	0.062(1)
	Cl2	−0.024002(5)	0.66529(2)	0.188793(5)	0.062(1)
	O1	0.46103(2)	−0.28798(4)	0.17633(1)	0.062(1)
	O2	0.35619(1)	−0.38386(4)	0.17511(1)	0.062(1)
	O3	0.19723(2)	−0.01304(4)	−0.08760(1)	0.062(1)
	O4	0.11579(2)	0.00596(4)	−0.04761(1)	0.062(1)
	O5	0.18069(2)	0.25555(4)	0.04359(2)	0.062(1)
	O6	0.14591(2)	0.52545(4)	−0.01991(1)	0.062(1)
	N1	0.29788(2)	−0.05096(5)	0.09090(2)	0.062(1)
	C2	0.36772(2)	−0.10487(6)	0.11271(2)	0.062(1)
	C3	0.40180(2)	0.01302(6)	0.08083(2)	0.062(1)
	C4	0.35588(2)	0.14797(6)	0.04160(2)	0.062(1)
	C5	0.29093(2)	0.10301(6)	0.04734(2)	0.062(1)
	C6	0.24443(2)	−0.09907(6)	0.11842(2)	0.062(1)
	C7	0.24944(2)	0.00955(6)	0.17995(2)	0.062(1)
	C8	0.29090(2)	0.17648(6)	0.19895(2)	0.062(1)
	C9	0.29321(2)	0.28368(6)	0.25499(2)	0.062(1)
	C10	0.25361(2)	0.22539(6)	0.29231(2)	0.062(1)
	C11	0.21158(2)	0.05796(6)	0.27356(2)	0.062(1)
	C12	0.20976(2)	−0.04885(6)	0.21766(2)	0.062(1)
	C13	0.39330(2)	−0.26995(6)	0.15879(2)	0.062(1)

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TABLE II. Continued

	Atom	x	y	z	U_{iso}
	C14	0.49235(2)	−0.45111(6)	0.22233(2)	0.062(1)
	C15	0.36842(2)	0.31681(6)	−0.00048(2)	0.062(1)
	C16	0.33515(2)	0.49740(6)	−0.00735(2)	0.062(1)
	C17	0.34776(2)	0.64181(6)	−0.04749(2)	0.062(1)
	C18	0.39396(2)	0.60598(6)	−0.08091(2)	0.062(1)
	C19	0.42731(2)	0.42462(6)	−0.07403(2)	0.062(1)
	C20	0.41457(2)	0.28011(6)	−0.03394(2)	0.062(1)
	C21	0.22255(2)	0.19003(6)	0.00578(2)	0.062(1)
	C22	0.17149(2)	0.05523(6)	−0.04484(2)	0.062(1)
	C23	0.15345(2)	−0.15308(6)	−0.13581(2)	0.062(1)
	C24	0.14647(2)	0.43297(6)	0.02876(2)	0.062(1)
	C25	0.10740(2)	0.50807(6)	0.07107(2)	0.062(1)
	C26	0.10348(2)	0.38979(6)	0.12256(2)	0.062(1)
	C27	0.05898(2)	0.43787(6)	0.15610(2)	0.062(1)
	C28	0.01822(2)	0.60716(6)	0.13876(2)	0.062(1)
	C29	0.02250(2)	0.72687(6)	0.08773(2)	0.062(1)
	C30	0.06676(2)	0.67865(6)	0.05363(2)	0.062(1)
5CA					
	O1	0.36426(4)	1.0202(2)	0.21768(7)	0.147(2)
	O2	0.28912(4)	1.0301(2)	0.19114(6)	0.147(2)
	O3	0.28053(4)	0.6966(2)	0.51307(6)	0.147(2)
	O4	0.20872(4)	0.6467(2)	0.45133(7)	0.147(2)
	O5	0.22528(4)	0.4166(2)	0.34097(7)	0.147(2)
	O6	0.22199(4)	0.1237(2)	0.41093(6)	0.147(2)
	N1	0.28524(5)	0.7169(2)	0.30035(8)	0.147(2)
	C2	0.32519(7)	0.7820(3)	0.28212(9)	0.147(2)
	C3	0.36141(6)	0.6490(3)	0.31930(9)	0.147(2)
	C4	0.34280(6)	0.5006(3)	0.3597(1)	0.147(2)
	C5	0.29994(6)	0.5865(3)	0.36045(9)	0.147(2)
	C6	0.23620(6)	0.7641(3)	0.27137(9)	0.147(2)
	C7	0.20993(6)	0.6884(3)	0.19543(9)	0.147(2)
	C8	0.21772(6)	0.5043(3)	0.16089(9)	0.147(2)
	C9	0.18748(6)	0.4488(3)	0.09153(9)	0.147(2)
	C10	0.15035(6)	0.5751(3)	0.05724(9)	0.147(2)
	C11	0.14232(6)	0.7637(3)	0.09175(9)	0.147(2)
	C12	0.17151(6)	0.8194(3)	0.16024(9)	0.147(2)
	C13	0.32420(6)	0.9418(3)	0.22514(9)	0.147(2)
	C14	0.36372(6)	1.1502(3)	0.15412(9)	0.147(2)
	C15	0.37377(6)	0.3581(3)	0.42217(9)	0.147(2)
	C16	0.41557(6)	0.4358(3)	0.46600(9)	0.147(2)
	C17	0.44461(6)	0.3081(3)	0.52102(9)	0.147(2)
	C18	0.43114(6)	0.1016(3)	0.53087(9)	0.147(2)
	C19	0.38859(6)	0.0224(3)	0.4860(1)	0.147(2)
	C20	0.35973(6)	0.1508(3)	0.43207(9)	0.147(2)
	C21	0.45931(6)	−0.0166(3)	0.5893(1)	0.147(2)
	C22	0.50728(6)	−0.0106(3)	0.6043(1)	0.147(2)
	C23	0.53615(6)	−0.1365(3)	0.66123(9)	0.147(2)
	C24	0.51585(6)	−0.2662(3)	0.70213(9)	0.147(2)
	C25	0.46722(6)	−0.2718(3)	0.68710(9)	0.147(2)
	C26	0.43880(6)	−0.1469(3)	0.63008(9)	0.147(2)
	C27	0.26528(6)	0.5010(3)	0.39672(9)	0.147(2)
	C28	0.24910(6)	0.6357(3)	0.45216(9)	0.147(2)
	C29	0.28012(6)	0.9111(3)	0.53978(9)	0.147(2)
	C30	0.20401(6)	0.2449(3)	0.35882(9)	0.147(2)
	C31	0.15479(6)	0.1818(3)	0.31131(9)	0.147(2)
	C32	0.13175(6)	0.0085(3)	0.3307(1)	0.147(2)
	C33	0.08982(6)	−0.0640(3)	0.28369(9)	0.147(2)
	C34	0.06995(6)	0.0414(3)	0.2170(1)	0.147(2)
	C35	0.09202(6)	0.2150(3)	0.19762(9)	0.147(2)
	C36	0.13471(6)	0.2864(3)	0.24423(9)	0.147(2)
	C37	0.02493(6)	−0.0093(3)	0.1739(1)	0.147(2)
	C38	0.01381(6)	−0.2238(3)	0.15984(9)	0.147(2)
	C39	−0.02561(6)	−0.2827(3)	0.10347(9)	0.147(2)
	C40	−0.05422(6)	−0.1252(3)	0.06036(9)	0.147(2)
	C41	−0.04260(6)	0.0882(3)	0.07366(9)	0.147(2)
	C42	−0.00388(6)	0.1460(3)	0.13064(9)	0.147(2)

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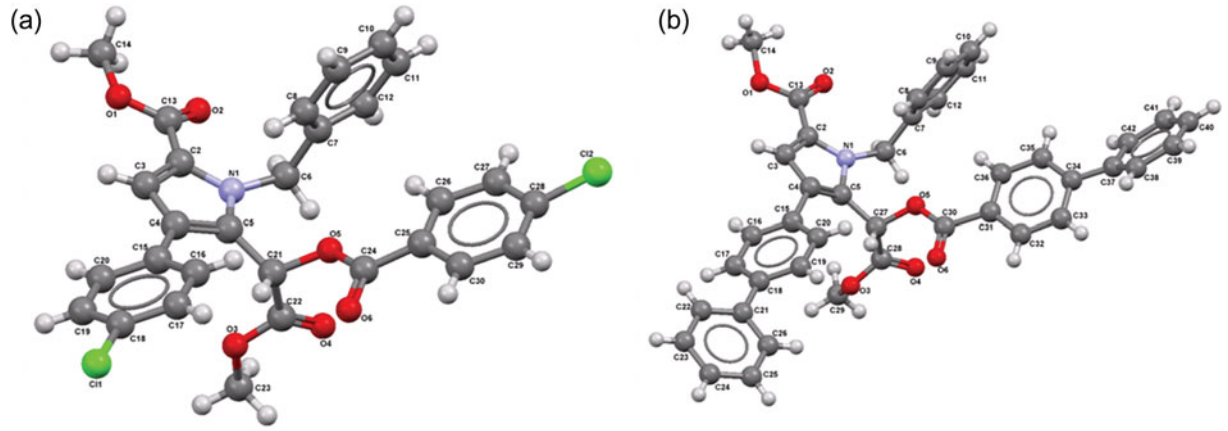


Figure 3. Molecular structures of **5EA** (a) and **5CA** (b) compounds, showing the atom-numbering scheme.

parameters and peak-shape parameters), taking into account the introduced constraints. In Figure 2, the plot of the final fits for both compounds are given. Crystallographic and refinement-related data are reported in Table I, while atomic coordinates and displacement parameters for non-H atoms are reported in Table II.

IV. DISCUSSION

The final molecular structures and crystal packings are shown in Figures 3 and 4, respectively. The structures of **5EA** and **5CA** are very similar; both molecules contain a pyrrol ring as central part, two ester groups (methyl ethanoate and methyl methanoate) and one toluene group with a torsional angle (N1-C6-C7-C8) of 15.14(6)° and 32.8(3)° respectively, being the main difference between them. However, the angle defined by the planes formed between the pyrrol ring and the benzenic ring were quite similar, 86.92(2)° for **5EA** and 85.34 (10)° for **5CA**. The main difference between **5EA** and **5CA** is the substitution in the same relative position, containing a 4-chlorobenzoic acid and a 4-biphenylcarboxylic acid, respectively. In the last case, this group has a slight torsional

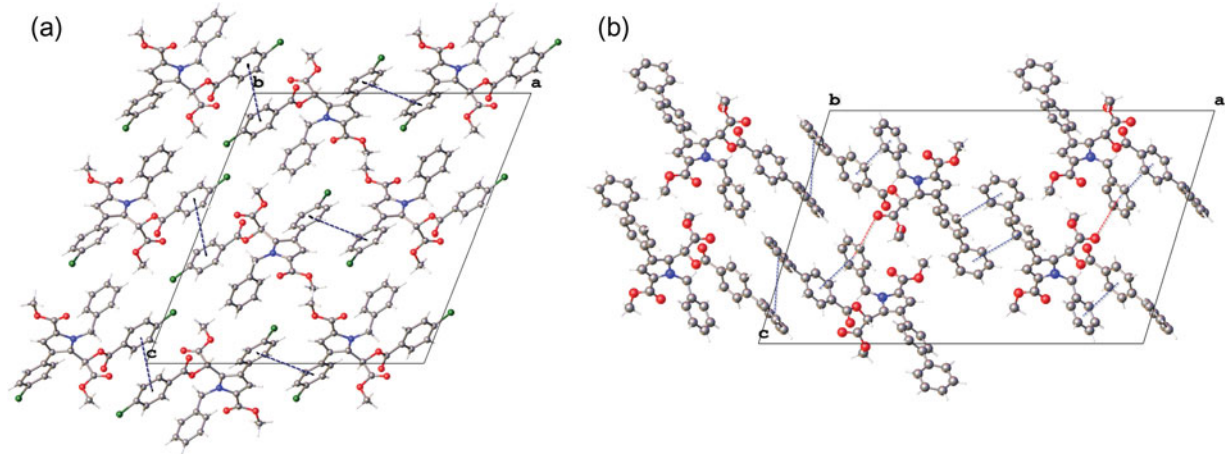


Figure 4. Crystal structures of **5EA** (a) and **5CA** (b) viewed along the *b*-axis. Intermolecular contacts are shown as dotted lines.

TABLE III. Geometry of intermolecular C-H. . .O contacts of compounds **5EA** and **5CA**.

	D–H. . .*A*	*D*–H (Å)	H. . .*A* (Å)	*D*. . .*A* (Å)	*D*–H. . .*A* (º)
5EA					
	C23–H23C. . .O6[a]	0.96	2.41	3.3348(5)	160
	C29–H29. . .O4[b]	0.93	2.35	3.1807(5)	149
	C30–H30. . .O4[c]	0.93	2.59	3.4820(5)	162
5CA					
	C23–H23. . .O1[d]	0.93	2.53	3.251(2)	134
	C29–H29A. . .O6[e]	0.96	2.10	2.866(2)	135

[a]Symmetry code: $x, y-1, z$.
[b]Symmetry code: $-x, 1-y, -z$.
[c]Symmetry code: $x, 1+y, z$.
[d]Symmetry code: $-x+1, -y+1, -z+1$.
[e]Symmetry code: $x, y+1, z$.

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angle between the rings [39.12(9)° and 36.12(9)°], being these values similar to others found in the literature for this type of group (Brown *et al.*, 1977; Busetti, 1982). No classical hydrogen bonds were found in both structures. The molecules in **5EA** are linked by weak π–π stacking interactions (*Cg*...*Cg*) with distances of 4.3081(2) Å [$Cg4...Cg4^{i}$; *Cg4* = C25–C30; symmetry code: (*i*) $-x, 1-y, -z$; perpendicular distance of 3.6660(2) Å with slippage of 2.263 Å] and 4.5049 (3) Å [$Cg3...Cg3^{ii}$; *Cg3* = C15–C20; symmetry code: (*ii*) $1-x, 1-y, -z$; perpendicular distance of 3.5655(2) Å with slippage of 2.753 Å] (see Figure 4a). Also C–H...O intermolecular contacts exists (Table III). The packing in **5CA** is stabilized by very weak π–π interactions where (*Cg*...*Cg*) distances are from 4.5631(11) Å [$Cg4...Cg3^{i}$; *Cg4* = C21–C26; *Cg3* = C15–C20; symmetry code: (*i*) $1-x, -y, 1-z$] to 4.8148(10) Å [$Cg6...Cg6^{ii}$; *Cg6* = C37–C42; symmetry code: (*ii*) $-x, -y, -z$] as significant distances. Also C–O...*Cg* (π-ring) interaction is present [3.8948(14) Å for O...*Cg*, 4.591(2) Å for C...*Cg* and 118.56(11)° for C–O...*Cg* angle] (see Figure 4b). As in **5EA** molecule, C–H...O intermolecular contacts are also present in **5CA** (Table III).

V. CONCLUSION

In this work we report the structure determination of methyl 1-benzyl-5-(1-(4-chlorobenzoyloxy)-2-methoxy-2-oxoethyl)-4-(4-chlorophenyl)-1H-pyrrole-2-carboxylate and methyl 1-benzyl-4-(biphenyl-4-yl)-5-(1-(4-biphenylcarbonyloxy)-2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate compounds from synchrotron radiation X-ray powder diffraction data applying the Monte Carlo and Rietveld methods. For both cases, the crystal packing was stabilized by very weak π–π stacking interactions, C–H...O and C–O...*Cg* (π-ring) intermolecular contacts.

CCDC 851218 and 851219 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

ACKNOWLEDGMENTS

We thank the SpLine staff for their assistance in using BM25A-SpLine beamline. The financial support from the Spanish Ministerio de Ciencia e Innovación (PI201060E013) is also acknowledged.

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