Research Article

Crystal structural studies of ethyl-5-(4-chlorophenylsulfonyl)-4-hydroxy-2, 6-dip-tolyl-1, 2, 5, 6-tetrahydropyridine-3-carboxylate and diethyl 4-hydroxy-2-(4-nitrophenyl)-5-(phenylsulfonyl)-6-(phenylsulfonylmethyl)cyclohexa-3,6-diene-1,3-dicarboxylate

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Abstract

The crystal structures of *trans,trans*-Ethyl-5-(4-chlorophenylsulfonyl)-4-hydroxy-2,6-dip-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate **(Ia)** and *cis*-Diethyl 4-hydroxy-2-(4-nitrophenyl)-5-(phenylsulfonyl)-6-(phenylsulfonylmethyl)cyclohexa-3,6-diene-1,3-dicarboxylate **(Ib)** were elucidated by single crystal X ray diffraction. Compound **(Ia)** $C_{28}H_{28}Cl\ NO_5S$, crystallizes in the monoclinic system, space group P $2_1/c$, with a = 9.4530(7) Å, b = 25.366 (2) Å, c = 11.4353(8) Å, β = 103.092(7)°, V = 2670 (3) Å^3 and Z = 4. The compound **(Ib)**, $C_{31}H_{29}N_1O_{11}S_2$, crystallizes in the monoclinic system, space group P $2_1/c$, with a = 21.179(4) Å, b = 8.4998(16) Å, c = 17.347(3) Å, β = 102.563(3)°, V = 3048.0(10) Å^3 and Z = 4. The central piperidine ring of compound **(Ia)** adopts the sofa conformation and the central cyclohexadiene ring of compound **(Ib)** adopts the boat conformation. Details of the compounds preparation, crystal structures and hydrogen bonding interactions of the compounds are discussed.

Introduction

The 2,6-disubstituted-1,2,5,6-tetrahydropyridine skeleton is present in only a few natural products (Angle *et al.* 1995, Wang *et al.* 1992). Aspertin A and B, isolated from *Andrachne aspera*, a small perennial undershrub, is commonly found in the arid, stony and sandy regions of Pakistan (Ahmad *et al.* 2002, Nasir *et al.* 1972). Medicinally, this plant is used to improve eyesight and to treat eye sores (Satiyanati *et al.* 1976, Hoppe *et al.* 1975). (+)-Cannabisativine is an unusual macrocyclic spermidine alkaloid containing a *trans*-2,6-disubstituted-1,2,5,6-tetrahydropyridine ring, which was isolated from the roots and leaves of the common marijuana plant *Cannabis sativa L* (Lotter *et al.* 1975). Another member of this class of alkaloids, (-)-palustrine (Karrer *et al.* 1948), a toxic component of the horsetail plant *Equisetum paluster L.*, found in the meadows of Europe, has been isolated as it has a sedum alkaloid called (-)-sedacrine (Bates *et al.* 2002). Tetrahydropyridine derivatives are useful against several metabolic disorders and human ailments and are involved in the monoamine oxidase-based mechanism related to Parkinson's disease (Beeler *et al.* 2003, Deskus *et al.* 2007). They also act as inhibitors of farnesyl transferase (Gwaltney *et al.* 2003) and dihydroorate dehydrogenase (Kamei *et al.* 2005).

Cyclohexa-1,4-diene derivatives have attracted considerable attention due to their wide range of applications, besides serving as building blocks for the synthesis of natural products such as (±)-vibralactone (Zhou *et al.* 2008), DL-*proto*-quercitol and DL-*gala*-quercitol (Salamci *et al.* 1997), DL-*gala*-aminoquercitol (Kurbanoglu *et al.* 2010), scyphostatin (Fujioka *et al.* 2002), (+)-/(–)-cryptocaryones (Fujioka *et al.* 2010) and (–)-myriocin (Inai *et al.* 2008).

The core Cyclohexane unit is either prepared from natural sources or entirely via synthetic routes. Its derivatives are known to have several medical uses. They provide anticonvulsant, antimalarial, anti-inflammatory and cardiovascular effects (Aridoss *et al.* 2011, Eddington *et al.* 2000). Some of them also have fungicidal and antitumor activities (Li & Strobel, 2001). The pharmacological effects of potential new drugs depend entirely on the stereochemistry and ring conformations of the compounds. Taking these aspects

into consideration, and in order to obtain detailed information on the molecular structure in the solid state, an X-ray study of the title compounds (**Ia)** and (**Ib)** was carried out.

Recently our research group reported the synthesis and evaluation of the anti-mycobacterial activities of (i) 4-(2,4-dichlorophenyl)-5-phenylpyrrolo (spiro[2.2"]acenaphthene-1"-one) spiro[3.2']-6'-(2,4-dichlorophenylmethylidene)cyclohexanone (Ranjith Kumar *et al.* 2009) (ii) spiro[5.2"]acenaphthene-1"-onespiro[6.2']-6'-(2,dichlorophenylmethylidene) cyclohexanone-7-(2,4-dichlorophenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole (Ranjith Kumar *et al.* 2009) and (iii) 4H-pyrano[3,2-c] pyridine derivatives (Ranjith Kumar *et al.* 2007). In the course of finding new compounds that could be useful for the chemotherapy of tuberculosis, we identified the compounds (**Ia)** and (**Ib).** In order to establish the structure-function relationships, we have carried out X-ray diffraction experiments in order to obtain detailed information on the molecular structure in the solid phase. We also performed an NMR study on these compounds in the liquid state.

Experimental

For the preparation of compound **(Ia)** , a mixture of ethyl 4-(4-chlorophenylsulfonyl)-3-oxobutanoate (1 mmol), freshly distilled p-methylbenzaldehyde (2 mmol) and ammonium acetate (2 mmol) in ethanol (10 ml) was warmed at 60^0C for 5 min. The reaction mixture was then kept at room temperature. After 3 days, the separated solid was filtered and purified by flash chromatography (4:1 petroleum ether- ethyl acetate) affording a colorless solid. (Yield: 81%; Melting-point: 155-156°C).

For the preparation of compound **(Ib)**, a mixture of ethyl 3-oxo-4-(phenylsulfonyl)butanoate (2 mmol), 4-nitrobenzaldehyde (1mmol) and ammonium acetate (0.25 mmol) in ethanol (10 ml) was warmed at 60°C for 5 min. The reaction mixture was then kept at room temperature. After 3 days, the separated solid was filtered and purified by flash chromatography (4:1 petroleum ether-ethyl acetate) affording a colorless solid. (Yield: 78% melting-point: 152-153°C).

Structure Determination and Refinement

Single crystal X-ray intensity data for compound **(Ia)** and compound **(Ib)** were collected using a Bruker SMART APEX CCD diffractometer with Mo Kα radiation (λ=0.71073Å) at room temperature (293 K). The data reduction was performed with SAINT (Bruker 2001). An absorption correction was made using the ω-scan method. The structure of both compounds were solved using the direct method SHELXS97 (Sheldrick 1990) and all the non-hydrogen atoms were refined anisotropically by full matrix least-squares, based on the F^2 taking all the unique reflections using SHELXL97 (Sheldrick 2008). Molecular graphics were drawn using PLATON (Spek 2003). The hydrogen atoms were placed in calculated positions and included in the refinement using the riding model with C—H = 0.93–0.98, O—H = 0.82 Å and *U*iso = 1.2*U*eq(C,) for CH, CH_2 groups and *U*iso = 1.5*U*eq(C) for CH_3 and OH groups. The crystal data, experimental conditions and structure refinement parameters for the compounds **(Ia)** and **(Ib)** are presented in Tables 1 and 2. The molecular structures of the compounds **(Ia)** and **(Ib)** showing the atom numbering scheme using ORTEP 3 (Farrugia 1997) are shown in Figure 1.

Table 1. The crystal data, experimental conditions and structure refinement parameters of compound **(Ia)**.

Empirical formula	**$C_{28}H_{28}ClNO_5S$**
Formula weight	526.02
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	P 2_1/c, monoclinic
Unit cell dimensions	a = 9.4530(7) Å, α = 90° b = 25.366(2) Å, β = 103.092(7)° c = 11.4353(8), γ = 90°
Volume	2670.7(3)Å ^{3}
Z, Calculated density	4, 1.308 mg/m^3
Absorption coefficient	0.259 mm^{-1}
F(000)	1104
Crystal size	0.19x0.16x0.14mm^3
Theta range for data collection	2 .7 to 26.00 deg
Limiting indices	-11<=h<=11,-31,=k<=31 -14<=l<=14
Reflections collected / unique	52339 / 5245[R(int) = 0.0539]
Completeness to theta	99.9%
Absorption correction	ω-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5245 / 0 / 330
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma (I)]	R_1 = 0.0654, wR_2 = 0.1795
R indices (all data)	R_1 = 0.0884, wR_2 = 0.2018
Largest diff. peak and hole	0.810 and -0.674 e Å $^{-3}$

Table 2. The crystal data, experimental conditions and structure refinement parameters of compound **(Ib)**.

Empirical formula	**$C_{31}H_{29}N_1O_{11}S_2$,**
Formula weight	655.67
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	P 2_1/c, monoclinic
Unit cell dimensions	a = 21.179(4) Å, α = 90° b = 8.4998(16) Å, β = 102.563(3)° c = 17.347 (3) Å, γ = 90°
Volume	3048.0(10) $Å^3$
Z, Calculated density	4, 1.429 mg/m^3
Absorption coefficient	0.238 mm^{-1}
F(000)	1368
Crystal size	0.17x0.14x0.11mm^3
Theta range for data collection	0.99 to 26.00 deg
Limiting indices	-26<=h<26,-10<=k<10, -21<=l<=21
Reflections collected / unique	27594 / 5975[R_{int} = 0.0455]
Completeness to theta	99.7%
Absorption correction	ω-scan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5975 / 0 / 409
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma (I)]	R_1 = 0.0667, wR_2 = 0.1828
R indices (all data)	R_1 = 0.0921, wR_2 = 0.2038
Largest diff. peak and hole	0.476 and -0.307 $eÅ^{-3}$

Results and Discussion

In compound (**Ia**), $C_{28}H_{28}Cl\ N\ O_5\ S$, the piperidinone ring adopts the sofa conformation as indicated by the puckering parameters Q = 0.4558 Å, θ = 52.91 (13)° and Φ = 5.8170° (Cremer & Pople 1975). In the central ring, the nitrogen N1 atom is deviating by -0.619(3) Å from the least-squares plane defined by the atoms (C2/C3/C4/C5/C6). The methoxy phenyl rings are equatorially oriented at dihedral angles of 83.11(1)° and 65.70(1)° with respect to the best (C2/C3/C4/C5/C6) plane in the central piperidone ring . The dihedral angle between the two [(C21—C27) and (C61—C67)] methoxy phenyl rings is 53.09(1)°. The ethoxycarbonyl group at C5 is nearly perpendicular to the methyl phenyl ring at C6, forming a dihedral angle of 79.94(2)°.

The sum of the bond angles around the N1 [346.91(4)°] atom of the tetrahydropyridine ring in the molecule is consistent with the sp^2hybridization.

Figure 2 shows a partial packing view of the compound (**Ia**) down to a-axis. An intra molecular O---H…O and inter molecular N---H…O hydrogen bonds are found.

An intermolecular C---H…π interaction C23–H23…Cg1 (-1+x, y, z) is found (Cg1 is the centroid of C31-C36 ring). There are no π-π interactions. Table 3 lists the inter- and intra- molecular hydrogen bonding. The N---H…O hydrogen bonds generate a graph set motif $C_1^1(7)$ (Bernstein *et al.* 1995) that is shown in Figure 3.

In the compound (**Ib**), $C_{31}H_{29}N_1O_{11}S_2$, the central cyclohexadiene ring adopts the boat conformation, as indicated by the puckering parameters Q = 0.181(4) Å, θ = 81.4 (13)° and Φ = 229.7(12)° (Cremer & Pople

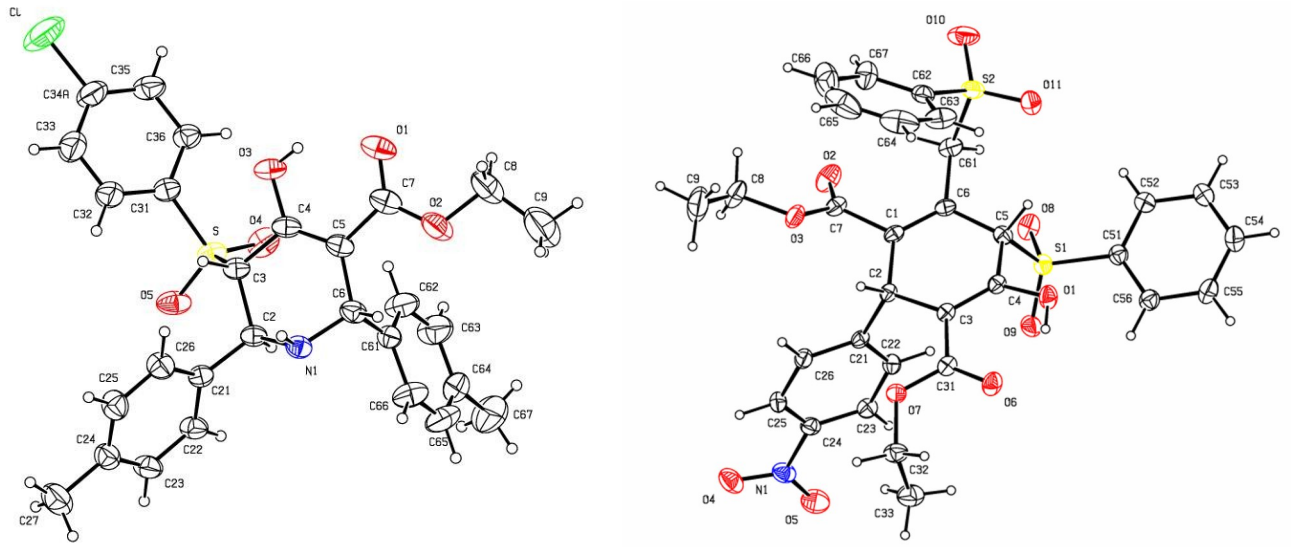

Figure 1. The molecular structure of compounds (**Ia**) (left) and **(Ib)** (right) showing the atom numbering scheme. Displacement ellipsoids are drawn at 30% probability level, using ORTEP 3. Hydrogen atoms are drawn as spheres of arbitrary size.

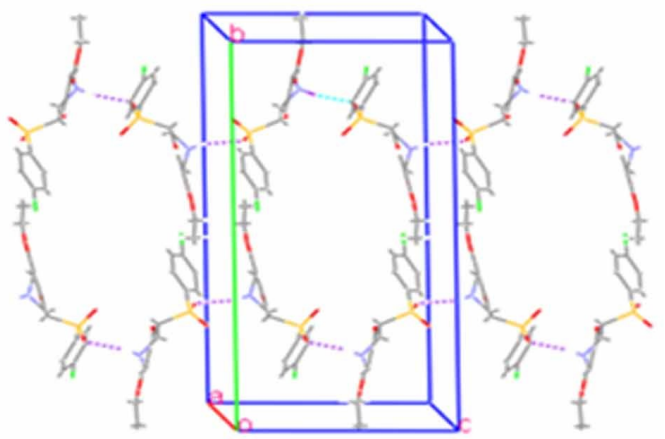

Figure 2. Partial packing diagram of the compound (**Ia)** viewed down to 'a' axis. For clarity only selected atoms are shown.

1975). In the central ring , atoms C2 and C5 are deviating by -0.117(5) Å and 0.189(5) Å, respectively, from the least-squares plane defined by the atoms C1/C3/ C4/C6. The dihedral angle between the two adjacent [(C51—C56) and (C62—C67)] phenyl sulfonyl rings is 55.1(1)°. The ethoxycarbonyl group at C1 is equatorially oriented to the C2 nitrophenyl ring making a dihedral angle of 77.73(1)°.

Table 4 lists the inter- and intra-molecular hydrogen bonding interactions. Numerous C-H…O hydrogen bonds are found to stabilize the structure. There are no π-π interactions. The crystal packing of the molecules down to the b-axis is shown in Figure 4. The C (53)-H (53)...O (2) hydrogen bond generating a graph set motif of $R_4^4(30)$ (Bernstein *et al.* 1995) is shown in Figure 5.

Spectral data

The identity of the compounds (**Ia)** and (**Ib)** has been ascertained by NMR spectral data. A detailed analysis

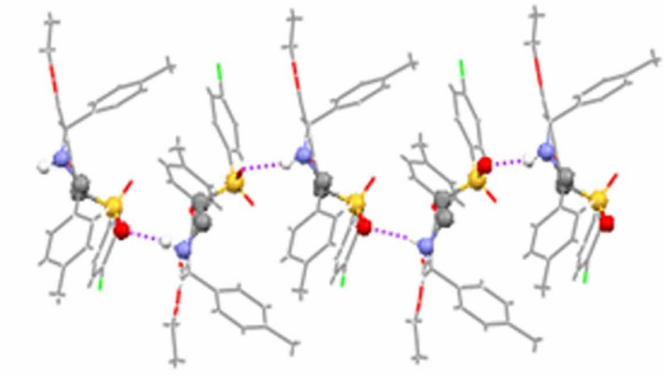

Figure 3. Linear Chain pattern $C_1^1(7)$ of compound **(Ia)** in the crystal structure.

Table 3. Hydrogen bonds [Å and°].*

D-H…A	D-H	H…A	D…A	D-H…A
O(3)-H(3A)…O(1)	0.82	1.89	2.597(3)	144
N(1)-H(1)…O(5)$^{(i)}$	0.92	2.22	3.1244(3)	165
C(23)-H(23)…Cg1$^{(ii)}$	0.92	2.98	3.794(2)	147

*The symmetry transformations used to generate equivalent atoms are the following:
(i) x, 1/2-y,-1/2+z
(ii) -1+x,y,z

of the two-dimensional NMR spectra has helped assign the hydrogens and carbons of interest in these compounds. The numbering scheme for carbons and hydrogens given here for the NMR data and the crystal structure is used for convenience and is not the accepted way of numbering according to IUPAC rules.

The ^1H, ^{13}C and the 2D NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard and $CDCl_3$ as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz.

Compound (Ia)

***trans,trans*-Ethyl 5-(4-chlorophenylsulfonyl)-4-hydroxy-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (Ia)**

The $-CH_3$ protons (H-9) of the ester group appear as a triplet at 0.79 ppm with the coupling constant *J*= 6.9 Hz and the $-CH_2$ protons (H-8) appear as a multiplet between 3.62-4.02 ppm. The two singlets at 2.32 and 2.34 ppm were assigned to two methyl groups (H-27 & H-67) attached to phenyl groups. The H-2 & H-3 appears as a broad singlet at 4.35 ppm (2H) and H-6 as a singlet at 5.01 ppm. A multiplet between 7.07 – 7.26 ppm (8H), the two doublets at 7.54 ppm (2H) & at 7.94 ppm (2H) with the coupling constant *J* = 8.1 Hz

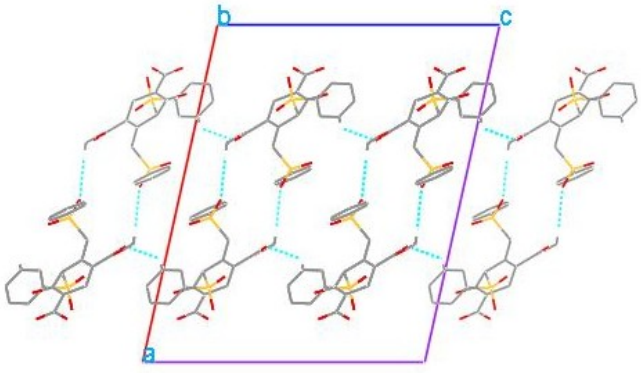

Figure 4. Partial packing diagram of the compound (**Ib)** viewed down to 'b' axis. For clarity only selected atoms are shown.

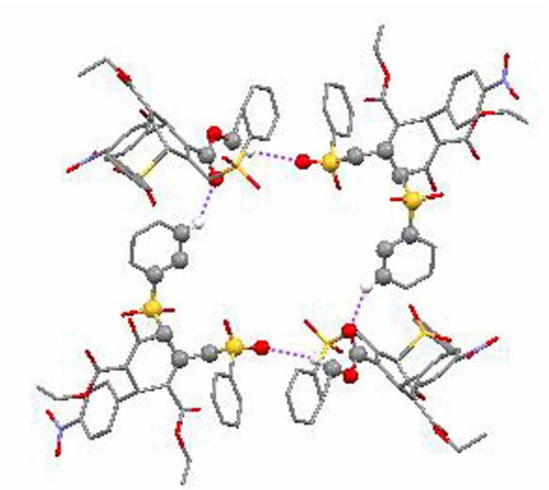

Figure 5. Ring pattern $R_4^4(30)$ formed by intermolecular H-bonds is observed in the crystal packing of compound (**Ib)**.

were due to the aromatic hydrogens. A broad singlet at 12.23 ppm was assigned due to the H-3A proton. The aliphatic methyl carbon signal appears at 13.8 ppm (C-9) and aromatic methyl carbon signals at 21.4 & 21.5 ppm.(C-27 & C-32). There are three aliphatic CH carbon signals at 53.6, 53.9 & 66.9 ppm (C-2, C-6 & C-3) and six aromatic CH carbon ones at 127.3, 128.2, 129.3, 129.8, 129.9 & 131.1 ppm. The peak at 61.2 was due to the CH2 (C-8) carbon. Quaternary carbon signals were assigned as follows: C-4 at 160.9, C-5 at 107.5 and C-7 at 171.2 ppm. Others appear at 136.2, 137.3, 137.9, 138.2, 139.9 & 141.3 ppm.

Compound Ib

Cis-Diethyl 4-hydroxy-2-(4-nitrophenyl)-5-(phenylsulfonyl)-6-[(phenylsulfonylmethyl]-3,6-cyclohexadiene -1,3-dicarboxylate

The $-CH_3$ protons (at H-33 & H-9) of the ester group appear as a triplet at 0.79 ppm (coupling constant J = 7.2 Hz) and 1.15 ppm (coupling constant *J* = 5.7 Hz), respectively. The $-CH_2$ protons of the ester group (H-32) appear as a multiplet between 3.97-4.07 ppm and as a quartet (C-8) with the coupling constant *J* = 7.2 Hz. The $-CH_2$ (H-61A & H-61B) protons undergo geminal coupling with the coupling constant *J* = 14.1 Hz and appear as doublets at 4.74 & 5.28 ppm. The protons H-2 & H-5 undergo long range coupling with the coupling constant *J* = 3.9 Hz and appear as doublets at 5.14 and 5.32 ppm, respectively. The aromatic protons signal appears as follows: a multiplet between 7.54 – 7.73 ppm (6H) and the four doublets at 7.76 (2H, *J* = 8.7 Hz), 7.83 (2H, *J* = 8.1 Hz), 7.99 (2H, *J* = 8.1 Hz) and 8.13 ppm (2H, *J* = 8.7 Hz). A broad singlet at 12.20 ppm was assigned due to the H-1 proton. The ester methyl carbon signals (C-9 & C-33) appear at 13.8 and 13.9 ppm. There are two aliphatic CH carbon signals at 44.4 (C-2) & 69.8 ppm (C-5) and

Table 4. Hydrogen bonds [Å and°].*

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(6)	0.82	1.83	2.536(4)	143
C(5)-H(5)...O(11)	0.98	2.31	3.112(5)	139
C(22)-H(22)...O(9)	0.93	2.35	3.271(5)	169
C(61)-H(61A)...O(2)	0.97	2.13	2.896(6)	135
C(61)-H(61B)...O(8)	0.97	2.24	2.962(5)	131
C(53)-H(53)...O(2)$^{(i)}$	0.93	2.52	3.208(6)	131
C(8)-H(8A)...O(10)$^{(ii)}$	0.97	2.6	3.518(7)	159

*The symmetry transformations used to generate equivalent atoms are the following:
(i) *x*, −*y*−1/2, *z*+1/2
(ii) *x*, −*y*−1/2, *z*+1/2

eight aromatic CH carbon signals at 128.1, 128.8, 129.3, 129.5, 130.6, 134.2, 134.5 & 138.3 ppm. The peak at 57.7 ppm is due to the CH_2 (C-61) carbon. The ester CH2 carbon signals appear at 61.7 (C-32) and 62.0 ppm (C-8). Quaternary carbon signals were assigned as follows: C-2 at 141.5, C-4 at 160.4, C-3 at 102.5, C-7 at 164.5 and C-31 at 170.2 ppm. Others appear at 121.9, 123.3, 140.1, 146.5 and 147.1 ppm.

Conclusion

trans,*trans*-Ethyl 5-(4-chlorophenylsulfonyl)-4-hydroxy-2,6-di-p-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate and *cis*-Diethyl 4-hydroxy-2-(4-nitrophenyl)-5-(phenylsulfonyl)-6-[(phenylsulfonylmethyl]-3,6-cyclohexadiene-1,3-dicarboxylate were synthesized. The single crystals of the compounds (**Ia**) and (**Ib)** were obtained by the slow evaporation method (solvent: 4:1 petroleum ether -ethyl acetate). The conformational features of these compounds in the solid and liquid phase were analysed by X-ray diffraction and NMR, respectively. Further studies on structure-activity relationships of these compounds are in progress in our research group.

Supplementary Material

Crystallogtaphic data (excluding structure factors) for the structures of **(Ia)** and **(Ib)** reported in this paper have been deposited with the Cambridge Crystallographic data Centre as supplementary publication no. CCDC 838483 and CCDC 860790. Copies of the data can be obtained, free of charge, on application to, CCDC, 12 Union Road, Cambridge, and CB2 1 EZ UK; Fax: 044-1223-336033; Email: deposit@ccdc.cam.uk or at: http://www.ccdc.cam.ac.uk/.

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Conflicts of Interest

There are no conflict of interests to be declared.

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