Diphenyltin(IV) complexes of the 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-olates: Synthesis and multinuclear NMR, $^{119}\text{Sn}$ Mössbauer, electrospray ionization MS, X-ray characterization and assessment of in vitro cytotoxicity

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Abstract

A series of cis-bis{5-[(E)-2-(aryl)-1-diazenyl]quinolinolato}diphenyltin(IV) complexes have been synthesized and characterized by $^1$H, $^{13}$C, $^{119}$Sn NMR, ESI-MS, IR and $^{119m}$Sn Mössbauer spectroscopic techniques in combination with elemental analysis. The structures of a ligand L$_1$H (i.e., 5-[(E)-2-(4-ethoxyphenyl)-1-diazenyl]quinolin-8-ol) and three diphenyltin(IV) complexes, viz., $\text{Ph}_2\text{Sn}(\text{L}_1\text{H})_2$ (1), $\text{Ph}_2\text{Sn}(\text{L}_4\text{H})_2$ (4) and $\text{Ph}_2\text{Sn}(\text{L}_5\text{H})_2$ (5) ($\text{L} = 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ol$: aryl = phenyl – (L$_1$H); 4'-methylphenyl – (L$_4$H) and 4'-bromophenyl – (L$_5$H)) were determined by single crystal X-ray diffraction. In general, the complexes were found to adopt a distorted cis-octahedral arrangement around the tin atom. These complexes retain their solid-state structure in non-coordinating solvent as evidenced by $^{119}$Sn NMR spectroscopic results. The in vitro cytotoxicity of 1 is reported and compared with $\text{Ph}_2\text{Sn}(\text{Ox})_2$ (Ox = deprotonated quinolin-8-ol) against seven well characterized human tumor cell lines.

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Keywords: 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ol; Diphenyltin(IV) complexes; NMR; ESI-MS; $^{119m}$Sn Mössbauer; Cytotoxicity; Crystal structures

1. Introduction

Functionally substituted 5-azoxines, hereafter 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ol, are long known as analytical reagents for qualitative detection of metal ions [1–3]. This class of azo-dyes forms complexes in solution with a wide variety of metals [3] and later these reagents have attracted the attention of several workers in recent years. Consequently, some of the earlier publications have dealt with the coordinating behavior of such reagents towards organotin [4–6], transition metals [7], mixed organotin-transition metals [7], mercury [8] and uranium [9]. Among the organotin(IV) compounds, bis{5-[(E)-2-(phenyl)-1-diazenyl]-8-quinolinolato}diphenyltin(IV), $[\text{Ph}_2\text{Sn}(\text{L}_1\text{H})_2]$ has been studied by IR, UV–Vis, $^1$H NMR [5] and $^{119}$Sn Mössbauer [4] spectroscopic techniques to indicate the
mode of coordination. The diverging results reported may reflect the different experimental conditions associated with each method. However, the closeness of the Mössbauer parameters for \([\text{Ph}_2\text{Sn}(\text{L}_2)]\) and bis(8-quinolinato)diphenyltin(IV) suggests that they have the same structure. To resolve these issues, firstly the X-ray structure of \([\text{Ph}_2\text{Sn}(\text{Ox})_2]\) has been determined. The X-ray results indicate a distorted cis-octahedral geometry where two phenyl ligands are cis to one another and trans to the nitrogen atoms of the oxinate ligands [11]. A systematic approach was then followed to study the diphényltin(IV) complexes of 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ol ligand system (Fig. 1). Further, organotin compound \([\text{Ph}_2\text{Sn(Ox)}_2]\) has been reported to possess cytotoxic properties [12] and, for this reason the cytotoxicity tests of a representative compound was performed along with \([\text{Ph}_2\text{Sn(Ox)}_2]\).

2. Experimental

2.1. Materials

\([\text{Ph}_3\text{SnCl}]\) (Fluka AG), \([\text{Ph}_2\text{SnCl}_2]\) (Aldrich), Oxine (Merck) and the substituted anilines (reagent grade) were used without further purification. The solvents used in the reactions were of AR grade and dried using standard procedures. Benzene was distilled from sodium benzophenone ketyl.

2.2. Physical measurements

Carbon, hydrogen and nitrogen analyses were performed with a Perkin–Elmer 2400 series II instrument. IR spectra in the range 400–4000 cm\(^{-1}\) were obtained on a BOMEM DA-8 FT-IR spectrophotometer with samples investigated as KBr discs. The two-dimensional experiments for the ligands were performed on a Bruker Avance 500 spectrometer equipped with a triple \((^{1}H/^13C/broad\ band)\) 5 mm inverse probe operating at 500.13 and 125.76 MHz, respectively. For the organotin compounds, the \(^{1}H\), \(^{13}C\) and \(^{119}Sn\) NMR spectra were recorded on a Bruker Avance 500 spectrometer and measured at 500.13, 125.76 and 186.18 MHz, respectively. The \(^{1}H\), \(^{13}C\) and \(^{119}Sn\) chemical shifts were referred to \(\text{Me}_2\text{Si}\) set at 0.00 ppm, CDC\(_3\) set at 77.0 ppm and Me\(_4\text{Sn}\) set at 0.00 ppm, respectively. Positive-ion and negative-ion electrospray ionization (ESI) mass spectra of unsolvated compounds were measured on an ion trap analyzer Esquire 3000 (Bruker Daltonics, Bremen, Germany) in the mass range \(m/z\) 50–1500. The samples were dissolved in acetonitrile and analyzed by direct infusion at the flow rate 5 \(\mu\)l/min. The selected precursor ions were further analyzed by MS/MS analyses under the following conditions: the isolation width \(m/z = 8\), the collision amplitude in the range 0.8–1.0 V depending on the precursor ion stability, the ion source temperature 300 °C, the tuning parameter compound stability 100%, the flow rate and the pressure of nitrogen 4 l/min and 10 psi, respectively [13,14]. Mössbauer spectra were recorded on solid samples at liquid nitrogen temperature by using a conventional constant acceleration spectrometer, coupled with a multichannel analyser (a.e.n., Ponteranica (BG), Italy) equipped with a cryostat Cryo (RIAL, Parma, Italy). A Ca\(^{119}SnO_3\) Mössbauer source, 10 mCi (from Ritverc, St. Petersburg, Russia) moving at room temperature with constant acceleration in a triangular waveform was used. The velocity calibration was made using a \(^{57}Co\) Mössbauer source, 10 mCi, and an iron foil as absorber (from Ritverc, St. Petersburg, Russia).

2.3. Synthesis of 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ols

2.3.1. Preparation of 5-[(E)-2-(phenyl)-1-diazenyl]quinolin-8-ol (L'\(H\))

Aniline (5.0 g, 53.7 mmol) was mixed with HCl (16 ml) and water (16 ml) and digested in a water bath for an hour. The hydrochloride was cooled to 5 °C and diazotized with ice-cold aqueous NaNO\(_2\) solution (3.7 g, 53.6 mmol, 25 ml). A cold solution of 8-hydroxyquinoline (7.78 g, 53.6 mmol), previously dissolved in 10% NaOH solution (5 g, 50 ml), was then added to the cold diazenium salt solution with vigorous stirring. A yellow colour developed almost immediately and the stirring is continued for 1 h. The reaction mixture was kept overnight in a refrigerator followed by 2 h at room temperature. The precipitate was filtered, washed several times with water to remove soluble starting materials, and then dried in air. The crude product was washed with hexane to remove any tarry materials and recrystallized from methanol to yield yellow precipitate of \(\text{L'}\(H\)\) (5.75 g, 42.9%), m.p. 182–183 °C. Anal. Calc. for \(\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}:\ C, 72.28; H, 4.45; N, 16.86\%\). Found: C, 72.35; H, 4.57; N, 16.90%. \(^{1}H\) NMR (CDCl\(_3\)); \(\delta_{H}\) 9.31 [dd, 1H, H4], 8.88 [d, 1H, H2], 8.06 [d, 1H, H6], 7.99 [d, 2H, H2' and H6'], 7.62 [m, 1H, H-3], 7.54 [m, 2H, H3' and H5'], 7.48 [m, 1H, H4'], 7.27 [d, 1H, H7] ppm. The signal for the phenol was exchanged due to presence of water in the solvent. \(^{13}C\) NMR (CDCl\(_3\)); \(\delta_{C}\) 155.4 [C8], 153.2 [C1′], 148.4 [C2], 139.9 [C5], 137.7 [C8a], 132.9 [C4], 130.6 [C4′], 129.1 [C3′ and C5′], 127.3 [C4a], 128.1 [C2′ and C6′], 122.80 [C3], 115.5 [C6], 109.9 [C-7] ppm.

The other 5-[(E)-2-(aryl)-1-diazenyl]quinolin-8-ols, viz., \(\text{L}^3\text{H}–\text{L}^6\text{H}\) were prepared analogously with appropriate anilines and their analytical and spectroscopic data are presented below.
2.3.2. Preparation of 5-[(E)-2-(methylphenyl)-1-diazenyl]quinolin-8-ol (L$^1$H)

Recrystallized from a mixture of methanol and benzene to give brown crystalline product in 69.4% yield; m.p. 184–185 °C. Anal. Calc. for C$_{16}$H$_{13}$N$_3$O: C, 72.99; H, 4.98; N, 15.96%. Found: C, 73.10; H, 4.97; N, 16.21%. $^{13}$C NMR (CDCl$_3$): $\delta_{C}$: 155.2 [C8], 151.2 [C1'], 148.4 [C2], 140.4 [C5], 137.9 [C2'], 137.7 [C8a], 133.0 [C4], 131.5 [C3'], 130.6 [C4'], 127.2 [C4a], 126.4 [C-5'], 122.8 [C3], 115.8 [C6'], 115.6 [C6], 109.9 [C7], 17.7 [CH$_3$] ppm.

2.3.3. Preparation of 5-[(E)-2-(3-methylphenyl)-1-diazenyl]quinolin-8-ol (L$^2$H)

Recrystallized from a mixture of methanol and benzene to give brown crystalline product in 64.8% yield; m.p. 159–160 °C. Anal. Calc. for C$_{16}$H$_{13}$N$_3$O: C, 72.99; H, 4.98; N, 15.96%. Found: C, 73.20; H, 5.03; N, 16.20%. $^{13}$C NMR (CDCl$_3$): $\delta_{C}$: 155.3 [C8], 153.2 [C1'], 148.4 [C2], 139.9 [C5], 138.9 [C-3'], 137.7 [C8a], 132.9 [C4], 131.4 [C4'], 128.9 [C4'], 127.2 [C4a], 123.2 [C2'], 122.7 [C3], 120.2 [C6'], 115.4 [C6], 110.0 [C7], 21.4 [CH$_3$] ppm.

2.3.4. Preparation of 5-[(E)-2-(4-methylphenyl)-1-diazenyl]quinolin-8-ol (L$^3$H)

Recrystallized from chloroform to give brick red microcrystalline product in 63% yield; m.p. 188–189 °C. Anal. Calc. for C$_{16}$H$_{13}$N$_3$O: C, 72.88; H, 4.91; N, 15.86%. Found: C, 72.88; H, 5.01; N, 15.90%. $^{13}$C NMR (CDCl$_3$): $\delta_{C}$: 155.0 [C8], 151.3 [C1'], 148.3 [C2], 148.3 [C2'], 141.1 [C4], 139.9 [C5], 137.7 [C8a], 132.9 [C4], 129.7 [C4'], 129.7 [C3], 129.7 [C6'], 115.4 [C6], 110.0 [C7], 21.5 [CH$_3$] ppm.

2.3.5. Preparation of 5-[(E)-2-(4-bromophenyl)-1-diazenyl]quinolin-8-ol (L$^4$H)

Recrystallized from a mixture of ethanol and benzene to give yellowish brown precipitate in 65.5% yield; m.p. 210–211 °C. Anal. Calc. for C$_{16}$H$_{13}$BrN$_3$O: C, 54.99; H, 3.07; N, 12.80%. Found: C, 55.23; H, 3.12; N, 12.86%. $^1$H NMR (DMSO-d$_6$): $\delta_{H}$: 9.34 [dd, 1H, H4], 9.04 [dd, 1H, H2], 8.05 [d, 1H, H6], 7.99 [m, 2H, H2' and H6'], 7.67 [m, 2H, H3' and H5'], 7.82 [m, 1H, H3], 7.25 [d, 1H, H7] ppm. The signal for the phenol was exchanged due to the presence of water in the solvent. $^{13}$C NMR (DMSO-d$_6$): $\delta_{C}$: 158.1 [C8], 151.5 [C1'], 149.1 [C2], 138.7 [C5], 137.9 [C8a], 132.5 [C3' and C5'], 131.9 [C4], 127.6 [C4a], 124.4 [C2' and C6'], 124.1 [C4'], 123.4 [C3], 115.2 [C6], 111.8 [C7] ppm.

2.3.6. Preparation of 5-[(E)-2-(4-ethoxyphenyl)-1-diazenyl]quinolin-8-ol (L$^5$H)

Recrystallized from chloroform to give dark brown microcrystalline product in 64.6% yield; m.p. 180–181 °C. Anal. Calc. for C$_{17}$H$_{15}$N$_3$O: C, 69.61; H, 5.15; N, 14.33%. Found: C, 69.50; H, 5.11; N, 14.52%. $^1$H NMR (CDCl$_3$): $\delta_{H}$: 9.29 [dd, 1H, H4], 8.84 [dd, 1H, H2], 8.01 [d, 1H, H6], 7.93 [m, 2H, H2' and H6'], 7.58 [m, 1H, H3], 7.23 [d, 1H, H7], 6.99 [m, 2H, H3' and H5'], 4.12 [q, 2H, OCH$_2$CH$_3$], 1.48 [t, 3H, OCH$_2$CH$_3$]. Signal for the phenol was exchanged due to the presence of water in the solvent. $^{13}$C NMR (CDCl$_3$): $\delta_{C}$: 161.2 [C1'], 154.7 [C1'], 148.4 [C2], 147.4 [C4'], 140.0 [C5], 137.7 [C8a], 132.9 [C4], 124.6 [C3' and C5'], 127.0 [C4a], 114.6 [C2' and C6'], 122.6 [C3], 114.5 [C6], 110.0 [C7], 63.6 [OCH$_2$CH$_3$], 14.8 [OCH$_2$CH$_3$].

2.4. Synthesis of the diorganotin complexes

A typical method is described below.

2.4.1. Synthesis of Ph$_2$Sn(L$^4$)$_2$ (4)

L$^4$H (1.0 g, 3.80 mmol) in hot anhydrous benzene (45 ml) was added drop-wise with continuous stirring to a hot anhydrous benzene solution (30 ml) containing Ph$_2$SnCl (1.46 g, 3.80 mmol). The reaction mixture was refluxed for 2 h, then triethylamine (0.38 ml, 3.80 mmol) was added and reflux was continued for additional 1.5 h. The reaction mixture was cooled to room temperature and filtered to remove Et$_3$N·HCl. The filtrate was collected; volatiles were removed and dried in vacuo. The residue was extracted into hexane and filtered while hot. The crude product was obtained after evaporation of the hexane. This was then recrystallized from a mixture of benzene–hexane (1:1), which upon slow evaporation afforded red crystalline product. Yield: 1.02 g (66.2%), m.p. 239–240 °C. Anal. Calc. for C$_{44}$H$_{34}$N$_6$O$_2$Sn: C, 66.27; H, 4.35; N, 10.60%. IR (cm$^{-1}$): 1248 ν(Caryl)O, 1416 ν(Caryl)O. $^1$H NMR (CDCl$_3$), 500.13 MHz) $\delta_{H}$: Ligand skeleton: 9.27 [dd, 2H, H4], 8.61 [dd, 2H, H2], 8.22 [dd, 2H, H6], 7.80 [m, 4H, H2' and H6'], 7.24 [m, 2H, H3], 7.25 [m, 4H, H3' and H5'], 7.46 [d, 2H, H7], 2.41 [s, 6H, CH$_3$]; Sn–Ph skeleton: 7.59 [m, 4H, H2*], 7.23 [m, 6H, H* and H4*] ppm. $^{13}$C NMR (CDCl$_3$), 125.76 MHz): $\delta_{C}$: 161.1 [C8], 151.4 [C1'], 143.4 [C2], 140.6 [C4'], 136.5 [C5], 135.4 [C8a], 136.1 [C4], 129.7 [C3' and C5'], Not observed, possibly overlapped by a CH signal [C4a], 122.2 [C2', C6' and C3'], 118.5 [C6], 114.5 [C7], 21.4 [CH$_3$]; Sn–Ph skeleton $^{119}$Sn $^{13}$C*, H2): 148.7 [C-1* (927)], 134.9 [C-2* (55)], 128.5 [C-4* (17)], 128.3 [C-3* (81)] ppm. $^{119}$Sn NMR (CDCl$_3$,
186.18 MHz) δSn: -385.8 ppm. 115Sn Mössbauer: δ = 0.81, Δ = 1.77, Γ₁ = 1.00, Γ₂ = 1.00 mm s⁻¹, ρ = 2.18. Positive-ion ESI mass spectra: m/z 837 [M + K⁺]; m/z 821 [M + Na⁺]; m/z 799 [M + H⁺]; m/z 721 [M – Ph⁺]; m/z 536 [M – L⁺]⁺, 100%. MS/MS of m/z 837: m/z 574 [M + K – L⁺H⁺]; m/z 536 [M – L⁺]⁺; MS/MS of m/z 799: m/z 536 [M – L⁺]⁺. MS/MS of m/z 721: m/z 645 [M – 76* + Ph⁺]; m/z 603 [M – Ph – N₂ – 90⁺]; m/z 525 [M – Ph – benzene – N₂ – 90⁺]; m/z 458 [M – L⁺H – Ph⁺]; m/z 382 [L²Sn⁺]; m/z 263 [L⁺H⁺]. MS/MS of m/z 536: m/z 458 [M – L⁺ – benzene]; m/z 444 [M – L² – toluene⁺]; m/z 417 [M – L – toluene – N₂⁺]; m/z 382 [M – L – benzene – 76⁺]. Negative-ion ESI mass spectra: m/z 262 [L²⁺], 100%.

The other diphenylin complexes were prepared by reacting ligands, viz., L³H, L²H₁, L²H and L¹H with Ph₅SnCl by following analogous procedure. The characterization and spectroscopic data of the complexes are presented below.

2.4.2. Synthesis of [Ph₂Sn(L²⁺)₂] C₅H₅O (I)

Dark-red crystals of 1 were obtained from acetone. Yield: 0.77 g (74%), m.p. 140–141 °C. Anal. Calc. for C₄₄H₃₄N₆O₂Sn: C, 65.31; H, 3.85; N, 10.16%. Found: C, 65.34; H, 4.90; N, 11.09%. IR (cm⁻¹): 1248 ν(CarylO). 1H NMR (CDCl₃, 500.13 MHz); δH: 9.34 [dd, 2H, H₄], 8.68 [dd, 2H, H₂], 8.26 [dd, 2H, H₆], 7.91 [d, 4H, H'₂ and H'₆], 7.48 [m, 2H, H₃], 7.60 [m, 4H, H'₃ and H'₅], 7.43 [m, 2H, H₄], 7.36 [dd, 2H, H₇]. Sn–Ph skeleton: 7.48 [m, 4H, H'₂], 7.25 [m, 6H, H'₃ and H'₄] and H'₅⁺ ppm. 13C NMR (CDCl₃, 125.76 MHz); δC: 161.4 [C₈], 153.3 [C₁], 143.4 [C₂], 136.4 [C₅], 136.2 [C₈a], 135.4 [C₄], 128.6 [C₄'], 128.3 [C₃ and C₅'], 128.0 [C₄a], 122.5 [C₂ and C₆'], 122.5 [C₁₃], 118.8 [C₇]. Sn–Ph skeleton (J(tSn⁻¹, 13C, H₇): 148.7 [C–1*¹²¹⁾), 135.0 [C–2*¹²²⁾], 130.1 [C–4*¹²⁰⁾), 129.0 [C–3*¹²¹⁾ ppm. 115Sn NMR (CDCl₃, 186.18 MHz) δSn: -385.9 ppm. 119Sn Mössbauer: δ = 0.82, Δ = 1.86, Γ₁ = 0.81, Γ₂ = 0.86 mm s⁻¹, ρ = 2.27. Positive-ion ESI mass spectra of unsolvated compound: m/z 809 [M + K⁺]; m/z 793 [M + Na⁺]; m/z 693 [M – Ph⁺]; m/z 522 [M – L⁺]⁺, 100%. MS/MS of m/z 809: m/z 522 [M – L⁺]⁺; MS/MS of m/z 793: m/z 522 [M – L⁺]⁺. MS/MS of m/z 693: m/z 522 [M – L⁺]⁺. MS/MS of m/z 522: m/z 417 [M – L – benzene – N₂⁺]; m/z 368 [M – L – benzene – 76⁺]. Negative-ion ESI mass spectra: m/z 248 [L²⁺], 100%.

2.4.3. Ph₂Sn(L³⁺)₂ (2)

Red crystals of 2 were obtained from a mixture of benzene and hexane (v/v 1:1). Yield: 0.87 g (50%), mp: 194–195 °C. Anal. Calc. for C₄₄H₳₴N₆O₂Sn: C, 66.27; H, 4.30; N, 10.54%. Found: C, 66.20; H, 4.38; N, 10.6%. IR (cm⁻¹): 1251 ν(CarylO). 1H NMR (CDCl₃, 500.13 MHz) δH: 9.32 [dd, 2H, H₄], 8.63 [dd, 2H, H₂], 8.26 [dd, 2H, H₆], 7.71 [m, 4H, H'₂ and H'₆], 7.48 [m, 2H, H₃], 7.32–7.42 [m, 4H, H'₄ and H'₅]. 7.25 [d, 2H, H₇]. 2.50 [s, 6H, CH₃]. Sn–Ph skeleton: 7.60 [m, 4H, H'₂], 7.25 [m, 6H, H'₃ and H'₄] ppm. 13C NMR (CDCl₃, 125.76 MHz); δC: 161.4 [C₈], 153.5 [C₁], 143.4 [C₂], 138.9 [C₅], 136.3 [C₈a], 128.6 [C₄ and C₄'], 128.3 [C₅ and C₄a], 128.0 [C₂], 122.6 [C₁₃], 119.9 [C₆], 118.9 [C₇], 114.5 [C₇'], 21.4 [CH₃] Sn–Ph skeleton (J(tSn⁻¹, 13C, H₇): 148.8 [C–1*¹²¹⁾, 134.9 [C– 2*¹²²⁾, 131.0 [C–4*¹²⁰⁾, 128.9 [C–3*¹²¹⁾ ppm. 119Sn NMR (CDCl₃, 186.18 MHz) δSn: -386.4 ppm. 119Sn Mössbauer: δ = 0.79, Δ = 1.77, Γ₁ = 0.88, Γ₂ = 0.80 mm s⁻¹, ρ = 2.24. Positive-ion ESI mass spectra: m/z 837 [M – K⁺]; m/z 821 [M + Na⁺]; 100%; m/z 536 [M – L⁺]⁺. MS/MS of m/z 837: m/z 574 [M + K – L⁺H⁺]; m/z 536 [M – L⁺]⁺. MS/MS of m/z 821: m/z 558 [M – Na – L⁺H⁺]; m/z 536 [M – L⁺]⁺. MS/MS of m/z 799: m/z 536 [M – L⁺]⁺. MS/MS of m/z 536: m/z 458 [M – L – benzene – benzene – 76⁺]; m/z 444 [M – L – benzene – 76⁺]. Negative-ion ESI mass spectra: m/z 262 [L²⁺], 100%.

2.4.5. Ph₂Sn(L⁴⁺)₂ (5)

Orange crystals of 5 were obtained from a mixture of benzene and hexane (v/v 1:1). Yield: 0.28 g (45.7%), mp: 275–276 °C. Anal. Calc. for C₄₂H₳₸Br₂N₄O₂Sn: C, 54.40; H, 3.04; N, 9.06%. Found: C, 54.28; H, 3.33; N, 8.89%. IR (cm⁻¹): 1248 ν(CarylO). 1H NMR (CDCl₃, 500.13 MHz) δH: 9.33 [dd, 2H, H₄], 8.17 [dd, 2H, H₂], 7.70 [d, 2H, H₆], 7.54 [m, 4H, H'₂ and H'₆], 7.22 [m, 4H, H'₃ and H'₅], 7.34 [dd, 2H, H₃], 7.10 [d, 2H, H₇]. Sn–Ph skeleton: 7.40 [m, 4H, H'₂], 7.22 [m, 6H, H'₃ and H'₄] ppm. 13C NMR (CDCl₃, 125.76 MHz); δC: 161.8 [C₈], 151.6
Table 1
Crystal data, data collection parameters and convergence results for L₆H, 1 · (CH₃)₂CO, 4 and 5

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<td>4</td>
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<tr>
<td>Dₓ (g cm⁻³)</td>
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<td>1.414</td>
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<td>μ (mm⁻¹)</td>
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<td>0.729</td>
<td>0.728</td>
<td>2.898</td>
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<td>Transmission factors (min, max)</td>
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<td>0.81, 0.94</td>
<td>0.76, 0.60</td>
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<tr>
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<td>Bruker SMART APEX</td>
<td>Nonius CAD4</td>
<td>Nonius CAD4</td>
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<tr>
<td>2θmax (°)</td>
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<td>28.3</td>
<td>26.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Reflections measured</td>
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<td>14289</td>
<td>12596</td>
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<tr>
<td>Independent reflections (R(int))</td>
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<td>8626</td>
<td>1887</td>
<td>2970</td>
</tr>
<tr>
<td>Independent reflections with I &gt; 2σ(I)</td>
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<td>498</td>
<td>241</td>
<td>254</td>
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<tr>
<td>Max, min Δ(ε/Å³)</td>
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<td>0.59, –0.33</td>
<td>0.84, –0.88</td>
<td>0.98, 1.02</td>
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</table>

Crystals of ligand L₆H and diphenyltin(IV) compounds 1 · (CH₃)₂CO, 4 and 5 suitable for an X-ray crystal structure determination were obtained from benzene, acetone, hexane and benzene–hexane mixture (1:1 v/v), respectively. Intensity data were collected with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å), either on Nonius CAD4 diffractometers (for L₆H, 4 and 5) or a Bruker SMART APEX (for 1). Crystal data, data collection parameters and convergence results are listed in Table 1. For the tin complexes 1 · (CH₃)₂CO, 4 and 5, empirical absorption corrections based on a multiscan approach [15] or on azimuthal scans [16] were applied to the data sets before averaging over symmetry-related reflections; no absorption correction was made for the intensity data of

Ligand numbering scheme as shown in Fig. 1 and numbering scheme for Sn–Ph skeleton as shown below:

\[ \text{Sn}^{119} \]

\[ \text{Ph}_2\text{Sn(L}_6\text{)} \] (6)

Orange crystals of 6 were obtained from a mixture of benzene and hexane (v/v 1:1). Yield: 0.33 g (45.8%), mp: 125–126 °C. Anal. Calc. for C₄₆H₃₉N₆O₄Sn: C, 64.43; H, 4.47; N, 9.80%. Found: C, 64.53; H, 4.50; N, 10.01%. IR (cm⁻¹): 1248 v(C=aryl(O)). ¹H NMR (CDCl₃, 500.13 MHz): δH: 9.24 [dd, 2H, H4], 8.60 [dd, 2H, H2], 8.17 [d, 2H, H6], 7.86 [m, 4H, H2', and H6'], 7.27 [m, 2H, H3], 7.44 [m, 2H, H7], 6.95 [m, 2H, H3' and H5'], 3.97 [q, 4H, OCH₂CH₃], 1.31 [t, 6H, OCH₂CH₃]; Sn–Ph skeleton: 7.58 [m, 4H, H₂*, 7.22 [m, 6H, H3* and H4*] ppm. ¹³C NMR (CDCl₃, 125.76 MHz); δC: 160.9 [C₄'], 160.7 [C8], 143.4 [C2], 143.3 [C1'], 136.5 [C5], 136.1 [C₄'], 135.4 [C₈a], 128.4 [C₆a], 124.3 [C’' and C’'], 122.3 [C3], 118.1 [C6], 114.7 [C’’ and C’’'], 114.4 [C7], 63.8 [OCH₂CH₃], 14.8 [OCH₂CH₃]; Sn–Ph skeleton (¹⁷²¹⁰¹¹⁹Sn, ¹³C), Hz): 148.8 [C-1*(925)], 134.9 [C-2*(55)], 128.5 [C-3*(82)] ppm. ¹¹⁹Sn NMR (CDCl₃, 186.18 MHz) δSn: –386.1 ppm. ¹¹⁹Sn Mössbauer: δ = 0.80, Δ = 1.82, Γ₁ = 0.91, Γ₂ = 0.91 mm s⁻¹, ρ = 2.27. Positive-ion ESI mass spectra: m/z 897 [M + K⁺]; m/z 881 [M + Na⁺]; m/z 566 [M + Li⁺]; m/z 351 [SnPh₃⁺]. MS/MS of m/z 881: m/z 566 [M + Li⁺]; MS/MS of m/z 566: m/z 412 [M – L₅ – 76 – benzene]⁺.

2.5. X-ray crystallography

The crystals of ligand L₆H and diphenyltin(IV) compounds 1 · (CH₃)₂CO, 4 and 5 suitable for an X-ray crystal structure determination were obtained from benzene, acetone, hexane and benzene–hexane mixture (1:1 v/v), respectively. Intensity data were collected with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å), either on Nonius CAD4 diffractometers (for L₆H, 4 and 5) or a Bruker SMART APEX (for 1). Crystal data, data collection parameters and convergence results are listed in Table 1. For the tin complexes 1 · (CH₃)₂CO, 4 and 5, empirical absorption corrections based on a multiscan approach [15] or on azimuthal scans [16] were applied to the data sets before averaging over symmetry-related reflections; no absorption correction was made for the intensity data of
ligand L\textsuperscript{6}H. The structures were solved by direct methods with the help of the SHELXS-97 program [17] and refined on reflection intensities \( F^2 \) using the SHELX-97 program [18]. In the final least-squares refinements, all non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms were placed in idealized positions and included as riding on the corresponding atoms. Further details on the structures are available as supplementary material in CIF format, see below.

2.6. Biological tests

The in vitro cytotoxicity test of compound \( 1 \) and Ph\textsubscript{2}Sn(Ox)\textsubscript{2} were performed using the SRB test for the estimation of cell viability. The cell lines WIDR (colon cancer), M19 MEL (melanoma), A498 (renal cancer), IGROV (ovarian cancer) and H226 (non-small cell lung cancer) belong to the currently used anticancer screening panel of the National Cancer Institute, USA [19]. The MCF7 (breast cancer) cell line is estrogen receptor (ER)\+/progesterone receptor (Pgr)\+ and the cell line EVSA-T (breast cancer) is (ER)\-/(Pgr)\- . Prior to the experiments, a mycoplasma test was carried out on all cell lines and found to be negative. All cell lines were maintained in a continuous logarithmic culture in RPMI 1640 medium and found to be negative. All cell lines were maintained in a continuous logarithmic culture in RPMI 1640 medium with Hepes and phenol red. The medium was supplemented with 10% FCS, penicillin 100 U/ml, and streptomycin 100 \( \mu \)g/ml. The cell lines were mildly trypsinized for passage and for use in the experiments. RPMI and FCS were obtained from Life technologies (Paisley, Scotland). SRB, DMSO, Penicillin and streptomycin were obtained from Sigma (St. Louis MO, USA), TCA and acetic acid from Baker BV (Deventer, NL) and PBS from NPBI BV (Emmer-Compascuum, NL).

The test compounds \( 1 \) and Ph\textsubscript{2}Sn(Ox)\textsubscript{2}, and reference compounds were dissolved to a concentration of 250000 ng/ml in full medium, by 20-fold dilution of a stock solution which contained 1 mg of compound 1/200 \( \mu \)l. Compound \( 1 \) and Ph\textsubscript{2}Sn(Ox)\textsubscript{2} were dissolved in absolute ethanol. Cytotoxicity was estimated by the microculture sulfurhexadimethine B (SRB) test [20].

2.6.1. Experimental protocol and cytotoxicity tests

The experiment was started on day 0. On day 0, 150 \( \mu \)l of trypsinized tumor cells (1500–2000 cells/well) were plated in 96-wells flat-bottomed microtiter plates (falcon 3072, BD). The plates were pre-incubated for 48 h at 37\(^\circ\)C, 8.5% CO\textsubscript{2} to allow the cells to adhere. On day 2, a 3-fold dilution sequence of ten steps was made in full medium, starting with the 250000 ng/ml stock solution. Every dilution was used in quadruplicate by adding 50 \( \mu \)l to a column of four wells. This results in a highest concentration of 62500 ng/ml being present in column 12. Column 2 was used for the blank. To column 1, PBS was added to diminish interfering evaporation. On day 7, washing the plate twice with PBS terminated the incubation. Subsequently, the cells were fixed with 10% trichloroacetic acid in PBS and placed at 4\(^\circ\)C for an hour. After five washings with tap water, the cells were stained for at least 15 min with 0.4% SRB dissolved in 1% acetic acid. After staining, the cells were washed with 1% acetic acid to remove the unbound stain. The plates were air-dried and the bound stain was dissolved in 150 \( \mu \)l (10 mM) tris–base. The absorbance was read at 540 nm using an automated microplate reader (Labsystems Multiskan MS). Data were used for construction of concentration–response curves and the determination of \( ID_{50} \) values by use of Deltasoft 3 software.

3. Results and discussion

3.1. Syntheses

The diphenyltin(IV) complexes of the 5-[(E)-2-(aryl)-1-diazeny]quinolin-8-ol ligand (LH) could be prepared by reacting stoichiometric amounts of Ph\textsubscript{2}SnCl\textsubscript{2} and LH in a suitable solvent under conditions described by Blake et al. [21] and Ghuge et al. [4]. These reactions proceeded smoothly but resulted into a complex mixture in both the cases that could be separated with great difficulty. In view of this, an effort have been made to develop a new synthetic strategy via disproportionation dearylation reaction (reaction (1)) which proved to be convenient for synthesizing cis-Chis-[5-[(E)-2-(aryl)-1-diazeny]-8-quinolinolato]diphenyltin(IV) compounds. The complexes could be isolated by fractional crystallization with high purity in moderate yield. The work-up detail and characterization data for the complexes is described in Section 2.4.

\[
\begin{align*}
2\text{LH} + 2\text{Ph}_2\text{SnCl} + 2\text{Et}_3\text{N} &\rightarrow \text{Ph}_2\text{Sn}(\text{L})_2 + \text{Ph}_4\text{Sn} + 2\text{Et}_3\text{N} \cdot \text{HCl} \\
(\text{conditions: reflux, 3-4 h, Et}_3\text{N})
\end{align*}
\]

(1)

The complexes are crystalline in nature, stable in air but slowly lose the solvent of crystallization and become amorphous. These amorphous solids retain their chemical composition and properties as evidenced by spectroscopic results. The complexes are soluble in all common organic solvents.

3.2. IR spectra

The IR spectra of the ligands, \( L^1\text{H} - L^6\text{H} \) and their diphenyltin(IV) complexes, \( 1 - 6 \) are very complex due to the presence of a large number of vibrational modes due to ring stretches, deformation, in-plane and out-of-plane ring and CH deformations, etc. However, these modes are of little value in understanding the structure and bonding of the complexes. Valuable information can, however, be obtained from the frequencies of \( \nu(\text{OH}) \) and \( \nu(\text{Ar-O}) \) modes. The \( \nu(\text{OH}) \) in \( L^1\text{H} - L^6\text{H} \) occurs at around 3380 cm\(^{-1}\) as broad band which is assigned due to the presence of intermolecular H-bonding interactions involving
the O–H ⋅⋅⋅N bonds and also has been detected in the structure determined by X-ray crystallography on the analogous system, i.e., 5-[(2-ethoxyphenyl)diazenyl]quinolin-8-ol [22] and 5-[(E)-2-(4-ethoxyphenyl)-1-diazenyl]quinolin-8-ol (L’H) (vide infra, see X-ray discussion). The ν(OH) band is found to be absent in the diphenyltin complexes, 1–6, confirming bonding through the O-atom of the ligand. A strong band at around 1235 cm⁻¹ in the ligands is found to be shifted to around 1250 cm⁻¹ in the complexes, is assigned to the ν(C(aryl)–O) (i.e., C₈–O). An upward shift of this stretching frequency is expected in the complexes because the large polarity of –O–SnR₆ bond increases the conjugative interaction of the oxygen atom with the π-ring, resulting in an increase of the C–O bond order [23]. The ν(C(=N)) vibration could not be assigned with certainty. Thus, IR spectroscopy provides only information of C₈–O–Sn linkage in the complexes.

3.3. ¹¹⁹Sn Mössbauer data

In order to resolve the structural issues (cis- or trans-structure), ¹¹⁹Sn Mössbauer spectroscopy have been performed on the complexes, 1–6 in the solid state. The Mössbauer data, i.e., isomer shift (δ), quadrupole splittings (Δ) and the line widths at half-peak height (Γ) for the diphenyltin complexes are given in Section 2.4. Generally, δ values can differentiate between a cis- or a trans-R₂SnX₄ octahedral system. The cis-complexes have lower δ values than the trans-complexes [24], however, the δ values could not be utilized for characterizing the complexes since there are no reference compounds of the type [Ph₂Sn(Ox)]₂ known having trans-R₂SnX₄ structure. On the other hand, Δ has proved useful in distinguishing between a cis- and a trans-configuration in the complexes. The Δ values in the range between 1.7–2.2 and 3.5–4.2 mm s⁻¹ have been classified for a cis- and trans-octahedral geometry, respectively [25,26]. The complexes 1–6 display a doublet nature of spectrum and Δ values are in the range 1.77–2.20 mm s⁻¹. The observed Δ values lie inside the range delimited for cis-R₂Sn octahedral geometry. The Δ values compare well with the data for [Ph₂Sn(Ox)]₂ complex (Δ = 1.70 [25]) having a cis-R₂Sn octahedral geometry [11]. Furthermore, the ratio ρ of the Δ to the δ has been found to be useful in determining the coordination number of tin [27] and in the complexes, ρ is ≥2.0, which indicate that the complexes have six-coordinate structure. Similar magnitude of δ and Δ values in all the complexes, further indicate that the complexes are isostructural. Thus, Mössbauer spectroscopic data suggest a cis-R₂Sn octahedral geometry where equatorial positions defined by two oxygen, a nitrogen and a phenyl group while axial site is occupied by a phenyl and a nitrogen atom.

3.4. ¹H, ¹³C and ¹¹⁹Sn NMR data

The ¹H and ¹³C NMR signals of L¹H–L⁶H were assigned by the use of correlated spectroscopy (COSY), heteronuclear single-quantum correlation (HSQC) and heteronuclear multiple-bond connectivities (HMBC) experiments. The conclusions drawn from the ligand assignments were then subsequently extrapolated to the complexes 1–6 owing to the data similarity. The ¹H NMR integration values were completely consistent with the formulation of the products. The ¹H and ¹³C NMR chemical shift assignment of the diphenyltin moiety is straightforward from the multiplicity pattern, resonance intensities and also by examining the ²J(¹³C–¹¹⁹Sn) coupling constants [28]. In the ¹H and ¹³C NMR spectra of the complexes, 1–6, there is only one set of NMR signals for both the phenyl groups (Sn–Ph) and for the ligands, which provides evidence for the magnetic equivalence of both the phenyls and both ligands on the NMR time scale. This indicates their relative symmetrical arrangement in the coordination sphere of the central tin atom in solution. The chemical shifts δ (¹³C) of the carbon atoms of the phenyl substituents (Sn–Ph) are not very sensitive to changes in the coordination of central tin atom. Nevertheless, the values δ (¹³C (¹₉)), which are shifted mostly by 5 ppm downfield, in comparison with those in compounds having four coordinate tin atom [29]. The value of the coupling constants ²J(¹¹⁹Sn–¹³C(Sn–Ph)) (n = 1–4) matches closely with the data for hexa-coordinated [Ph₂Sn(Ox)]₂ complex in CDCl₃ solution [30]. In order to provide further structural evidence to establish the structure of the complexes in solution, we further recorded ¹¹⁹Sn NMR spectra. The complexes 1–6, display a sharp singlet at around −386 ppm and the δ (¹¹⁹Sn) chemical shifts lie inside the range (between −125 and −515 ppm) delimited for six coordinate diorganotin compounds [31]. The δ (¹¹⁹Sn) values are comparable with the shift observed for [Ph₂Sn(Ox)]₂ complex (−397 ppm in CHCl₃ solution [30] and −394.2 in CDCl₃ [30]). Thus, ¹¹⁹Sn NMR data indicate that the complexes retain their solid state structures (see Mössbauer and X-ray discussion) in solution.

3.5. Mass spectrometry

The typical positive-ion ESI mass spectra of studied compounds 1–6 consist of molecular adducts with sodium and potassium ions, i.e., [M + Na]+ and [M + K]+ ions, together with the product of tin-oxygen bond cleavage [M – L]+, which is the base peak of spectra for 1, 2 and 4. In the case of 1 and 4, the product of tin-carbon cleavage is observed as well leading to the [M – Ph]+ ion. The ligand ion [L]− is formed in the negative-ion ESI-MS as a complementary species to [M – L]− observed in the positive-ion mode, but the spectra of 2, 5 and 6 are very noisy. All discussed mechanisms of the ion formation were already reported previously [13,14,32]. The molecular weight of all studied compounds can be confirmed from the information obtained from both positive-ion and negative-ion first-order spectra. Tandem mass spectra (MS/MS) provide the characteristic neutral losses, which can be correlated with particular structural features, such as neutral losses of 90
or 92 (toluene) for 2, 3 and 4, 76 or 78 (benzene) for 1 and 5, 79 (HBr) for 5, etc.

3.6. Structural results from single crystal X-ray diffraction

The molecular structures of the ligand L₆H and organotin(IV) complexes 1 (obtained as 1 · (CH₃)₂CO), 4 and 5 are depicted in Figs. 2–5 [33], respectively, while selected geometric parameters are given in Table 2.

The ligand L₆H exists as the trans-isomer. In the solid state, both intra and intermolecular H bonds occur. The intramolecular hydrogen bond between the hydroxy H and the N atom (O· · ·N = 2.755(2) Å, O–H· · ·N = 115°) can be assigned the graph set symbol S₁(5) [34], whereas the intermolecular H bond (O· · ·N = 2.865(2) Å, O–H· · ·N = 137°) corresponds to the formation of a R₂(10) ring and links neighboring molecules around inversion centres to dimers (Fig. 2). The same hydrogen bond pattern
is observed for the isomer 5-{(2-ethoxyphenyl)-1-diazenyl}-quinolin-8-ol described by Chen et al. [22].

In contrast to ligand L 6H, the organotin complexes 1Æ(CH₃)₂CO, 4, and 5 represent van der Waals crystals without remarkably short intermolecular interactions. Shortest contacts are associated with C\(\cdots\)H distances of 2.8 Å and CH\(\cdots\)O distances of 2.5 Å. No short inter-halo-gen distances occur in the bromine containing compound 5.

The organotin complexes 4 and 5 show very similar lattice parameters and share all relevant packing features; they are most probably isomorphous. In both structures, the molecules are located on 2-fold crystallographic axes. In 1Æ(CH₃)₂CO, the organotin complex and the solvent molecule are in general positions; the molecule of the former does not exhibit local C\(\text{2}\) symmetry. In the chelating ligand coordinated to tin via the atoms O1A and N1A, the 10 membered quinolino ring N1A–C9A and the phenyl moiety C10A–C15A subtend a dihedral angle of 20° whereas the corresponding groups are significantly closer to coplanarity in the other ligand (O1/N1) as well as in L\(^4\)H, 4, and 5 with dihedral angles in the range of 5–7°. Apart from these differences in conformation, all three organotin complexes show essentially the same arrangement of donor atoms found in Ph₂Sn(Ox)₂ [11]. The oxygen atoms of the two chelating ligands occupy trans positions in a strongly distorted octahedron; the nitrogen donors are situated in trans geometry with respect to the tin-coordinating phenyl C. The so-formed O–Sn–O and N–Sn–C angles range between 157° and 164°. The ipso-carbon atoms of the phenyl ligands form angles of 107.48(5)° (1), 109.6(4)° (4) and 110.0(2)° (5) at the tin atom, in good agreement with the angle reported for [Ph₂Sn(Ox)₂] (108.61 (9)°) with cis-R₂Sn octahedral geometry [11].

3.7. In vitro cytotoxicity

Ph₂SnOx₂ has shown antitumour activity in the National Cancer Institute (USA) test panel [12]. The results of the in vitro cytotoxicity test in human tumour cell lines on Ph₂SnOx₂ and compound 1 are given as ID₅₀ values in

### Table 2

| Bond Lengths (Å) and Torsion Angles (°) for L⁴H and 1, 4 and 5 |
|-----------------|-----------------|-----------------|-----------------|
| Sn–C20          | 2.1463(14), 2.1509(15) | 2.134(7)        | 2.149(4)        |
| Sn–O1           | 2.096(11), 2.0968(10)  | 2.093(5)        | 2.099(5)        |
| Sn–N1           | 2.2833(13), 2.3868(13)| 2.359(6)        | 2.345(5)        |
| O1–C1           | 1.352(2)         | 1.3240(17), 1.3185(17)| 1.326(8)        | 1.313(5)        |
| N1–C2           | 1.366(2)         | 1.3662(19), 1.3680(18)| 1.345(8)        | 1.361(5)        |
| N1–C3           | 1.312(3)         | 1.3218(19), 1.3198(19)| 1.306(8)        | 1.315(5)        |
| N2–N3           | 1.262(2)         | 1.2619(18), 1.2596(18)| 1.250(8)        | 1.253(5)        |
| C20–Sn–C20A     | 107.48(5)        | 109.64(4)       | 110.02(2)       |
| O1–Sn–N1        | 75.18(4), 73.53(4)| 73.68(19)       | 73.66(11)       |
| O1–Sn–O1A       | 157.19(4)        | 158.1(2)        | 159.04(16)      |
| C20–Sn–N1       | 159.15(5), 164.06(5)| 158.0(2)        | 157.06(14)      |
| N1–Sn–N1A       | 79.99(4)         | 73.1(3)         | 73.02(17)       |
| C7–N2–N3–C10    | –179.24(18)      | 179.56(12), 178.43(12)| –179.66(6)      | 178.8(3)        |

Fig. 5. Structure of a molecule of 5 in the crystal. The hydrogen atoms have been omitted for clarity.
Table 3, and compared with the data for some compounds that are in current clinical use as antitumour agents. The table clearly shows that Ph$_2$SnO$_2$ is more active in vitro than cisplatin against all seven human cancer cell lines. Compound 1 is less active than cisplatin. The compound tested may be used as a model for modification in order to improve cytotoxic and dissolution properties.

4. Supplementary material

CCDC Nos. 266988–266991 contain the supplementary crystallographic data for complexes L$^1$H, 5, 1 · (CH$_3$)$_2$CO and 4, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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References