

Pyrrrolizidine Alkaloids and Diterpenes from *Villasenorina orcuttii*

Amira Arciniegas,^a Ana L. Pérez-Castorena,^{*a} Karina González,^a
Marisol Reyes-Lezama,^b José Luis Villaseñor^c and Alfonso Romo de Vivar^a

^aInstituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior,
Ciudad Universitaria, Coyoacán 04510, D. F., México

^bCentro Conjunto de Investigación en Química Sustentable, Universidad Autónoma del
Estado de México-Universidad Nacional Autónoma de México (UAEM-UNAM),
Carretera Toluca-Atlaquilco, km 14.5, Toluca 50200, Estado de México, México

^cInstituto de Biología, Universidad Nacional Autónoma de México, Circuito Exterior,
Ciudad Universitaria, Coyoacán 04510, D. F., México

O estudo químico da *Villasenorina orcuttii*, a única espécie do gênero *Villasenorina*, levou ao isolamento de três diterpenos acíclicos, dois deles descritos pela primeira vez. Dois alcaloides pirrolizidínicos, flososenina e floridanina, entre outros compostos já conhecidos, também foram isolados. A configuração absoluta da floridanina foi determinada por análise de raios X usando dispersão anômala com radiação Cu K α , e seus dados de ressonância magnética nuclear (RMN) de ¹H e de ¹³C foram corrigidos.

The chemical study of *Villasenorina orcuttii*, the only species of the genus *Villasenorina*, afforded three acyclic diterpenes, two of them described for the first time. Two pyrrrolizidine alkaloids, flososenine and floridanine, among other known compounds were also isolated. The absolute configuration of floridanine was determined by X-ray analysis using anomalous dispersion with Cu K α radiation, and its ¹H and ¹³C nuclear magnetic resonance (NMR) data were corrected.

Keywords: *Villasenorina orcuttii*, diterpenes, pyrrrolizidine alkaloids, absolute configuration

Introduction

Villasenorina orcuttii, the only species of the genus *Villasenorina* (Asteraceae, Senecioneae), is a shrub that grows in the rainforest of Chiapas, Oaxaca and Southern Veracruz (Mexico) at 100 to 2000 m of elevation.¹ *Villasenorina orcuttii* (formerly *Senecio orcuttii*) was initially included into the genus *Telanthophora*, which together with the genus *Pittocaulon* is constituted by species segregated from the traditional section Terminales Greenm. of the genus *Senecio* s.l.² Further studies evidenced the differences between *Senecio* (*Telanthophora orcuttii*) and other species of *Senecio*, *Thelanthophora* or *Pittocaulon* and placed it into his own genus: *Villasenorina*.¹ To the best of our knowledge, there is no chemical work on the genus *Villasenorina*. Previous studies on its related genera, *Telanthophora*, *Senecio* and *Pittocaulon*, described

the presence, in the three of them, of sesquiterpene derivatives mainly of eremophilane and/or oplopane types, while pyrrrolizidine alkaloids (PAs) have been found only in species of *Senecio* and *Pittocaulon*.³ As continuation of our survey on Senecioneae, it is reported the isolation of three acyclic diterpenes from *Villasenorina orcuttii*: phytane-1,2,3-triol (**1**), previously obtained as a synthetic product,^{4,5} and compounds **2** and **3** which are described for the first time, two PAs: flososenine (**4**)⁶⁻⁸ and floridanine (**5**),^{6,9} together with methyl ferulate (**6**),¹⁰ pterolactame (**7**),¹¹ tyramine (**8**)¹² and β -sitosteryl glucoside (Figure 1). Additionally, the absolute configuration of floridanine (**5**) was determined by X-ray analysis and its ¹H and ¹³C nuclear magnetic resonance (NMR) data were corrected.

Results and Discussion

Compound **2** was obtained as colorless oil. Its IR spectrum indicated the presence of hydroxyl (3455 cm⁻¹) and carbonyl

*e-mail: alperezc@unam.mx

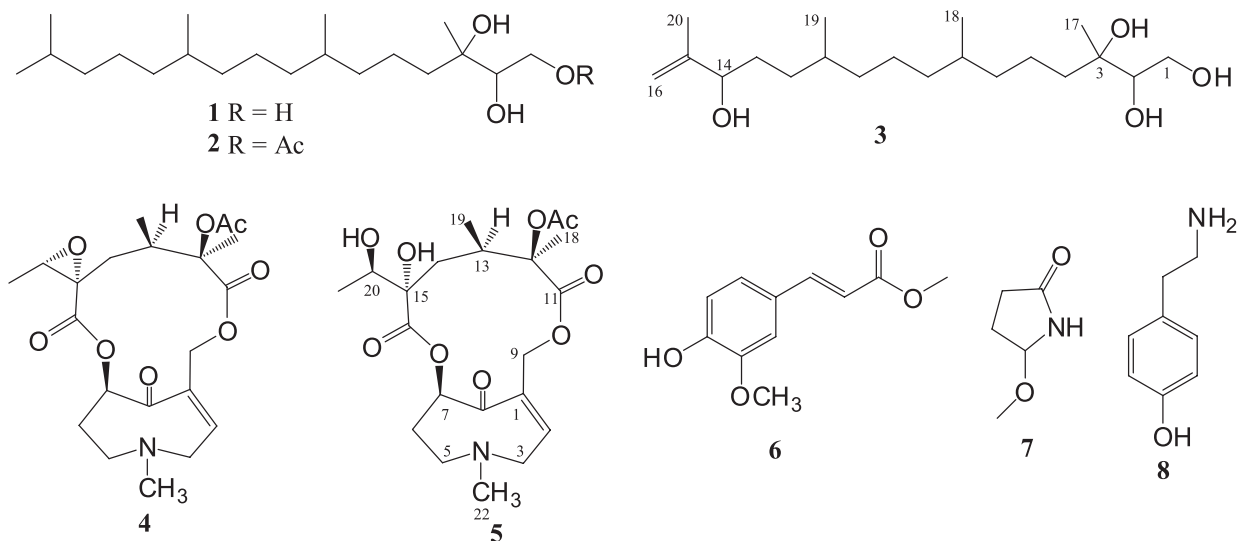


Figure 1. Chemical structures of compounds 1-8.

groups (1742 cm^{-1}). The molecular formula $\text{C}_{22}\text{H}_{44}\text{O}_4$ was determined by high-resolution electrospray ionization mass spectrometry (HRESIMS). The ^{13}C NMR analysis of **2** indicated the presence of three oxygenated carbon atoms and a carbonyl function, besides the signals of three methines, nine methylenes and five methyl groups. The ^1H NMR spectrum exhibited four secondary (δ_{H} 0.84-0.88), a tertiary (δ_{H} 1.23) and an acetyl (δ_{H} 2.12) methyl groups; an oxygenated methylene (δ_{H} 4.32, dd, J 11.6, 2.8 Hz; 4.09, dd, J 11.6, 8.4 Hz) and an oxygenated methine (δ_{H} 3.69, dd, J 8.4, 2.8 Hz). 2D NMR spectroscopy allowed the identification of a 3,7,11,15-tetramethylhexadecane skeleton with a vicinal terminal triol, one of them acetylated, indicating that compound **2** was the 1-*O*-acetyl derivative of the compound **1**, as confirmed by the isolation of **2** by the selective acetylation of the compound **1**.¹³

Compound **3**, isolated as colorless oil, showed the molecular formula $\text{C}_{20}\text{H}_{40}\text{O}_4$ (HRESIMS). The NMR spectra were similar to that one from compound **1** with the additional signals of a disubstituted double bond and a hydroxymethine. The long-range (HMBC) ^1H - ^{13}C NMR correlation experiment allowed to locate these groups at C-15 and C-14, respectively. As in compound **1**, three vicinal hydroxyl groups at C-1, C-2 and C-3 were observed, therefore, the structure of **3** was elucidated as 3,7,11,15-tetramethyl-15-hexadecene-1,2,3,14-tetraol.

The alkaloid **5** was isolated as colorless prisms, mp 199-200 °C. The molecular formula $\text{C}_{21}\text{H}_{31}\text{NO}_9$ was determined by HRFABMS. The EIMS spectrum showed a molecular ion at m/z 441 and the otonecine-type PAs diagnostic fragment ions⁶ at m/z 168 [$\text{C}_9\text{H}_{14}\text{NO}_2$]⁺, 149 [$\text{C}_9\text{H}_{11}\text{NO}$]⁺, 122 [$\text{C}_7\text{H}_8\text{NO}$]⁺ and 110 [$\text{C}_6\text{H}_8\text{NO}$]⁺. The presence of the signals of a α,β -unsaturated ketone carbonyl

at δ_{C} 186.9 and of three ester carbonyl at δ_{C} 174.6, 171.2 and 169.9 in the ^{13}C NMR spectrum suggested an acetylated macrocyclic diester of otonecine. The proton NMR spectrum of this alkaloid was similar to that of the floridanine,⁹ the main difference was the signal of H-20 assigned by the HMBC and COSY correlations at δ_{H} 3.72 (q, J 6.5 Hz), which was reported for the floridanine at δ_{H} 3.03 m. The positions of the signals of H-13 at δ_{H} 1.47 m, and of H₂-14 at δ_{H} 1.69 (d, J 14.0 Hz) and δ_{H} 1.53 (dd, J 14.0, 10.0 Hz) were also different from the reported for these same protons (H-13 at δ_{H} 1.89 m and H₂-14 at δ_{H} 2.35 m) in the floridanine. These discrepancies could be due to different positions of the acetoxy group in **5** and in the floridanine.⁹ In order to clarify these structural differences, an X-ray diffraction experiment (Figure 2) was performed establishing that compound **5** had indeed the structure reported for the floridanine.

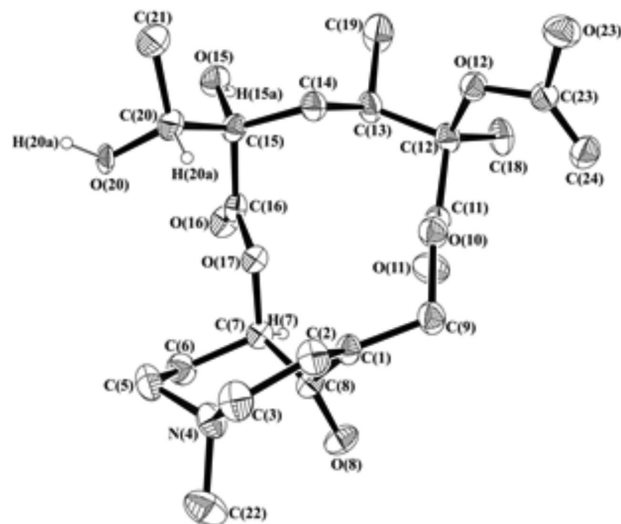


Figure 2. ORTEP representation of **5**.

Consequently, the ^1H and ^{13}C NMR data (obtained by means of 2D NMR spectroscopy) should correct those from the literature.⁹ The absolute stereochemistry of the floridanine (**5**) (*7R*, *12R*, *13R*, *15S* and *20R*) was determined by the anomalous dispersion method with Cu K_α radiation, used in the X-ray experiment, which afforded an absolute structure parameter of 0.08 (4).

Conclusions

The presence of pyrrolidizine alkaloids is in agreement with the chemistry of many genera of the tribe Senecioneae, but the absence of sesquiterpenes as well as the presence of acyclic diterpenes establish a clear chemotaxonomic difference between *Villasenoria* and its related genera *Telanthophora*, *Senecio* and *Pittocaulon* and support its position in a new genus.

Experimental

General experimental procedures

Melting points were determined on a Fisher-Jones melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 343 polarimeter. Circular dichroism was obtained on a Jasco J-720 spectropolarimeter. UV and IR spectra were recorded on a spectrophotometer Shimadzu UV 16U and a Bruker Tensor 27 spectrometer, respectively. 1D and 2D NMR spectra were obtained on a Bruker Avance III 400 MHz or on a Varian-Unity Inova 500 MHz spectrometer with tetramethylsilane (TMS) as internal standard. Electron ionization mass spectrometry (EIMS) analyses were determined on a Bruker Daltonics Analysis 3.2 mass spectrometer. HRESIMS analyses were performed on a Bruker MicrOTOF II mass spectrometer with a mass resolution of 16.500 FWHM (full width at half maximum), mass interval 50-20.000 m/z and speed of 40 Hz. Fast atom bombardment mass spectrometry (FABMS) analyses were obtained on a JEOL JMS-SX102A mass spectrometer operated with an acceleration voltage of 10 kV, and the samples were desorbed from a nitrobenzyl alcohol matrix using 6 kV xenon atoms. HRFABMS analyses were performed at a 10,000 resolution using electric field scans and polyethylene glycol ions (Fluka 200 and 300) as the reference material. Column chromatography was carried out under vacuum on silica gel G-60 (Merck, Darmstadt, Germany). Analytical thin layer chromatography (TLC) was carried out on silica gel 60-G F_{254} or RP-18W/UV₂₅₄ (Macherey-Nagel, Germany) and preparative TLC on silica gel G-200 F_{254} , layer thickness of 2.0 mm, or RP-18W/UV₂₅₄, layer thickness of 1.0 mm.

Plant material

Villasenoria orcuttii (Greenm.) B. L. Clark was collected in San Miguel Soyaltepec, Tuxtepec, Oaxaca, México, in January 2009. A voucher specimen was deposited at the Herbarium del Instituto de Biología, UNAM, México (MEXU 1256447).

Extraction and isolation

Dried and ground aerial parts (276 g) and roots (116 g) of *V. orcuttii* were separately and successively extracted with hexane and methanol. Solvents were removed under reduced pressure to obtain the respective extracts. The methanolic extracts were partitioned with EtOAc- H_2O . The aqueous extracts, which gave positive test with the Dragendorff alkaloid reagent, were treated with $\text{Zn/aq.H}_2\text{SO}_4$ ¹⁴ to give the alkaloidal residues. The hexanic extract of roots (820 mg) was fractionated by vacuum column chromatography (VCC) using hexane-EtOAc mixtures in increasing gradient of polarity. Fractions eluted with hexane-EtOAc 19:1 (65 mg) were purified by flash column chromatography (FCC) (hexane-acetone 19:1) to obtain compound **2** (25 mg). Fractions eluted with hexane-EtOAc 9:1 afforded phytane-1,2,3-triol^{4,5} (**1**, colorless oil, 361 mg). The hexanic extract of aerial parts (2.9 g) was submitted to VCC using hexane-acetone mixtures as gradient elution system to afford fractions A-C eluted with hexane-acetone 49:1, 19:1 and 9:1 mixtures, respectively. Fraction A (268 mg) was purified by FCC eluted with CH_2Cl_2 to obtain a mixture of β -sitosterol-stigmasterol (38 mg). Fractions B (150 mg) produced by FCC eluted with hexane-acetone 19:1 compound **2** (24 mg). Fraction C (550 mg) by two successive FCC eluted with hexane-acetone 9:1 and CH_2Cl_2 , respectively, afforded 250 mg of compound **1**. The ethyl acetate extract of the aerial parts (3.0 g) was purified by VCC eluting with hexane-EtOAc mixtures in gradient of increasing polarity to afford compound **1** (15 mg) from the hexane-EtOAc 9:1 mixtures, and from fractions eluted with hexane-EtOAc 4:1, a mixture (45 mg) which by preparative TLC (hexane-acetone 4:1) produced methyl ferulate¹⁰ (**6**, white needles, mp 66-67 °C, 10 mg). The ethyl acetate extract of roots (1.5 g) purified by the same way as extract of aerial parts afforded 20 mg of **1**, from the hexane-EtOAc 9:1 mixtures, and from fractions eluted with hexane-EtOAc 7:3, a mixture (95 mg) which was purified by RPTLC (reversed-phase TLC) (MeOH- H_2O 3:2 \times 4) followed of FCC (hexane-acetone 7:3) to produce compound **3** (25 mg). The alkaloidal extract of roots (480 mg) was purified by VCC (CH_2Cl_2 -MeOH in increasing gradient of polarity) to

afford, from CH₂Cl₂-MeOH 98:2 mixtures, pterolactame¹¹ (**7**, colorless needles, mp 55-56 °C, 32 mg) and tyramine¹² (**8**, white crystals, mp 160-162 °C, 98 mg), fraction E from CH₂Cl₂-MeOH 95:5, and fraction F from CH₂Cl₂-MeOH 9:1 eluates. Fraction E (65 mg) was submitted to FCC (CH₂Cl₂-MeOH 95:5) followed by a preparative TLC (CH₂Cl₂-MeOH-NH₄OH 95:4.9:0.1 × 2) to afford florosenine⁶⁻⁸ (**4**, mp 99-101 °C, [α]_D²⁵ + 30.5, *c* 0.2, CHCl₃, 5 mg). Fraction F (102 mg) afforded after two successive FCC (CH₂Cl₂-MeOH 9:1) and a preparative TLC (CH₂Cl₂-MeOH-NH₄OH 95:4.9:0.1 × 3) floridanine (**5**, 12 mg).^{6,9} The alkaloidal extract of aerial parts (450 mg) was worked up as described for the root alkaloidal extract to afford **4** (3.5 mg), **5** (10 mg), **7** (17 mg) and **8** (35 mg).

Selective acetylation of phytane-1,2,3-triol (**1**)

Compound **1** (0.28 mmol), acetylchloride (0.28 mmol) and *i*Pr₂EtN (0.56 mmol) in CH₂Cl₂ (2 mL) were stirred at -70 °C for 3 h and then 1 h at room temperature.¹³ The reaction mixture was washed with HCl (5%) and NaHCO₃ to obtain 87 mg of a mixture which was purified by FCC (hexane-acetone 85:15) to obtain 35 mg (34 %) of compound **2**.

Compound **2**

Colorless oil; [α]_D²⁵ + 5.0 (*c* 0.11, CHCl₃); IR (CHCl₃) ν_{\max} /cm⁻¹ 3455, 1742; ¹H NMR (400 MHz, CDCl₃) δ 4.32 (dd, 1H, *J* 11.6, 2.8 Hz, H1a), 4.09 (dd, 1H, *J* 11.6, 8.4 Hz, H1b), 3.69 (dd, 1H, *J* 8.4, 2.8 Hz, H2), 1.06-1.32 (m, 21H, H4 to H15), 2.12 (s, 3H, CH₃CO), 1.23 (s, 3H, H17), 0.84-0.88 (m, 12H, H16, H18, H19, H20); ¹³C NMR (100 MHz, CDCl₃) δ 171.4 (CH₃CO), 75.7 (C2), 73.6 (C3), 65.9 (C1), 39.4, 37.7, 37.6, 37.4, 37.3, 37.2, 24.8, 24.5, 20.7 (C4 to C6, C8 to C10, C12 to C14), 32.8, 32.7, 27.7 (C15, C11, C7), 23.5 (C17), 22.7, 22.6, 19.7, 18.6 (C16 and C18 to C20), 20.9 (CH₃CO); HRESIMS *m/z* 395.3146 [M + Na]⁺ (C₂₂H₄₄NaO₄ requires 395.3132).

Compound **3**

Colorless oil; [α]_D²⁵ + 11.0 (*c* 0.21, CHCl₃); IR (CHCl₃) ν_{\max} /cm⁻¹ 3433, 1603, 1460; ¹H NMR (500 MHz, CDCl₃) δ 4.93 (br quint, 1H, *J* 1.0 Hz, H16a), 4.84 (br quint, 1H, *J* 1.5 Hz, H16b), 4.03 (br dd, 1H, *J* 11.0, 6.0 Hz, H14), 3.78 (d, 2H, *J* 5.0 Hz, H1), 3.49 (br t, 1H, *J* 5.0 Hz, H2), 1.72 (s, 3H, H20), 1.23 (s, 3H, H17), 1.05-1.60 (m, 18H, H4 to H13), 0.86* (d, 3H, *J* 6.5 Hz, H18), 0.87* (d, 3H, *J* 6.5 Hz, H19), *interchangeable signals; ¹³C NMR (125 MHz, CDCl₃) δ 147.5 (C15), 111.2 (C16), 76.5 (C14), 76.1 (C2), 74.7 (C3), 63.9 (C1), 38.4, 37.5, 37.2, 37.1, 32.3, 24.3, 24.2, 20.9 (C4 to C6, C8 to C10, C12, C13), 32.7, 32.5 (C11, C7), 23.7 (C17), 20.9 (C18 and C19) 17.5

(C20); HRESIMS *m/z* 367.2832 [M + Na]⁺ (C₂₀H₄₀NaO₄ requires 367.2819).

Floridanine (**5**)

Colorless prism from hexane-EtOAc, mp 199-200 °C; [α]_D²⁵ + 68.0 (*c* 0.10, CHCl₃); IR (CHCl₃) ν_{\max} /cm⁻¹ 3691, 3518, 1735, 1602; CD (*c* 4.5 × 10⁻⁵ mol L⁻¹, EtOH) Δε_{209 nm} + 18.6; ¹H NMR (500 MHz, CDCl₃) δ 6.09 (br t, 1H, *J* 2.0 Hz, H2), 5.15 (d, 1H, *J* 11.0 Hz, H9a), 4.98 (t, 1H, *J* 2.5 Hz, H7), 4.44 (br d, 1H, *J* 11.0 Hz, H9b), 3.72 (q, 1H, *J* 6.5 Hz, H20), 3.46 (br d, 1H, *J* 17.5 Hz, H3a), 3.32 (br d, 1H, *J* 17.5 Hz, H3b), 2.90 (m, 1H, H5a), 2.85 (m, 1H, H5b), 2.60 (dddd, 1H, *J* 14.0, 12.0, 7.5, 2.5 Hz, H6a), 2.31 (br t, 1H, *J* 14.0 Hz, H6b), 2.08 (s, 6H, H22, CH₃CO), 1.69 (d, 1H, *J* 14.0 Hz, H14a), 1.64 (s, 3H, H18), 1.53 (dd, 1H, *J* 14.0, 10.0 Hz, H14b), 1.47 (m, 1H, H13), 1.24 (d, 3H, *J* 6.5 Hz, H21), 1.19 (d, 3H, *J* 6.5 Hz, H19); ¹³C NMR (125 MHz, CDCl₃) δ 186.9 (C8), 174.6 (C16), 171.2 (C11), 169.9 (CH₃CO), 136.8 (C2), 133.9 (C1), 83.9 (C12), 81.9 (C15), 79.1 (C7), 72.7 (C20), 64.2 (C9), 59.5 (C3), 53.7 (C5), 40.3 (C22), 39.7 (C13), 36.3 (C6), 35.8 (C14), 21.6 (C18), 21.4 (CH₃CO), 17.1 (C21), 14.6 (C19); EIMS *m/z* 441 [M]⁺ (30), 397 [C₂₀H₃₁NO₇]⁺ (30), 354 [C₁₈H₂₈NO₆]⁺ (90), 168 [C₉H₁₄NO₂]⁺ (100), 149 [C₉H₁₁NO]⁺ (65), 122 [C₇H₈NO]⁺ (50), 110 [C₆H₈NO]⁺ (48); HRFABMS *m/z* 442.2080 [M + H]⁺ (C₂₁H₃₂NO₉ requires 442.2077).

Crystal data of **5**

C₂₁H₃₁NO₉·0.8 (CH₂Cl₂), MW = 509.43, *T* = 100(2) K, λ = 1.54178 Å, orthorhombic, space group P2(1)2(1)2(1). Unit cell dimensions *a* = 8.6486(2) Å, *b* = 12.2669(2) Å, *c* = 24.8567(5) Å, α = 90°, β = 90°, γ = 90°, *V* = 2637.08(9) Å³, *Z* = 4, density (calculated) = 1.283 Mg m⁻³, absorption coefficient = 2.257 mm⁻¹, *F*(000) = 1078, crystal size: 0.29 × 0.18 × 0.16 mm³, theta range for data collection: 4.02 to 66.74°, index ranges: -10 ≤ *h* ≤ 10, -14 ≤ *k* ≤ 14, -29 ≤ *l* ≤ 29, reflections collected: 37883, independent reflections: 4661 [R(int) = 0.0217], completeness to theta = 66.74° 99.6%, absorption correction = semi-empirical from equivalents, max. and min. transmission = 0.7141 and 0.5636, refinement method = full-matrix least-squares on *F*², data / restraints / parameters 4661 / 664 / 532, goodness-of-fit on *F*² = 1.057, final *R* indices [I > 2σ(I)], *R*₁ = 0.0495, *wR*₂ = 0.1466, *R* indices (all data), *R*₁ = 0.0505, *wR*₂ = 0.1486; absolute structure parameter = 0.08(4); largest diffraction peak and hole = 0.569 and -0.195 e Å⁻³, respectively; single crystals of **5** were mounted at 100 K on nylon loops and the data were collected on a Bruker APEX DUO diffractometer equipped with an Apex II CCD detector using Incoatec IμS with multilayer optic, Cu K_α radiation. Frames were

collected by omega scans and integrated using SAINT software package. Semi-empirical absorption correction (SADABS) was applied. The structure was solved by direct methods (SHELXS programs), and refined by the full-matrix least-squares on F^2 with SHELXL-97¹⁵ using the SHELXLE GUI.¹⁶ All non-hydrogen atoms were refined anisotropically. The disordered was refined using the following geometry and U_{ij} restraints and constraints implemented in the SHELXL-97 program: SIMU, DELU, SAME and DFIX. Crystallographic data for the structure of **5** were deposited in the Cambridge Crystallographic Data Center (deposition No. CCDC 930369).

Supplementary Information

¹H and ¹³C NMR spectra of compounds **1** and **4**, ¹H and ¹³C NMR and 2D NMR experiments of compounds **2**, **3** and **5**, HRESIMS of compounds **2** and **3**, and crystal refinement data of **5** are available free of charge at <http://jbc.sqb.org.br> as PDF file.

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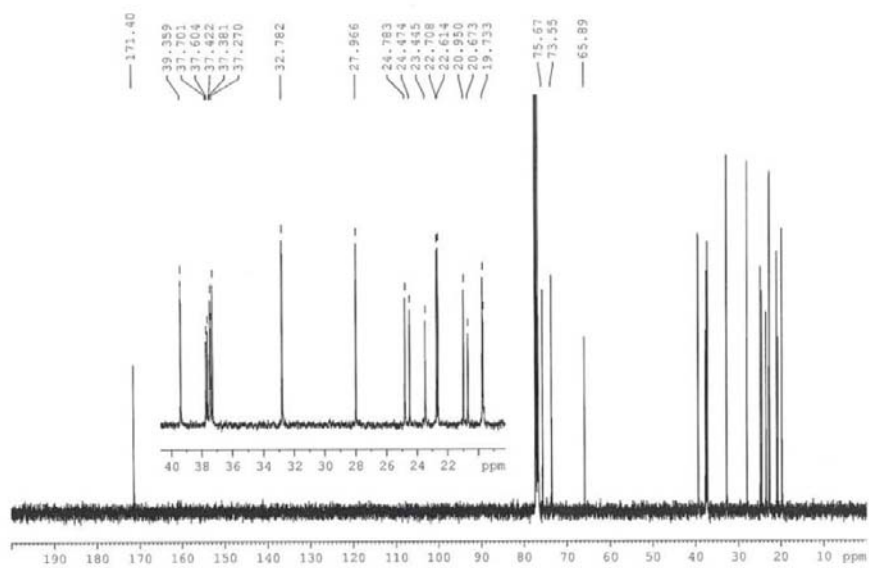


Figure S4. ^{13}C NMR (125 MHz, CDCl_3) spectrum of compound **2**.

Figure S5. COSY spectrum of compound **2**.

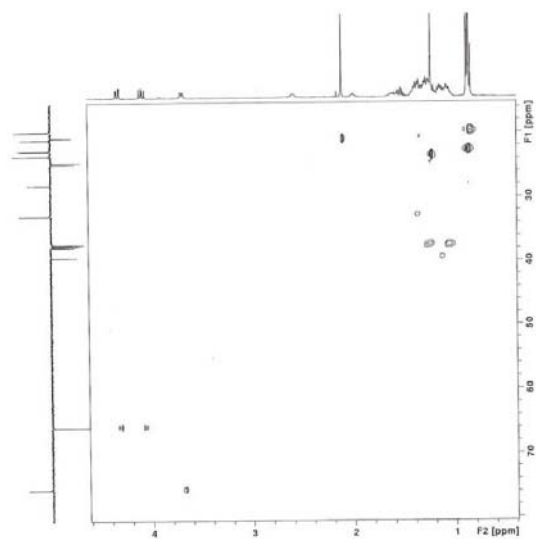


Figure S6. HSQC spectrum of compound 2.

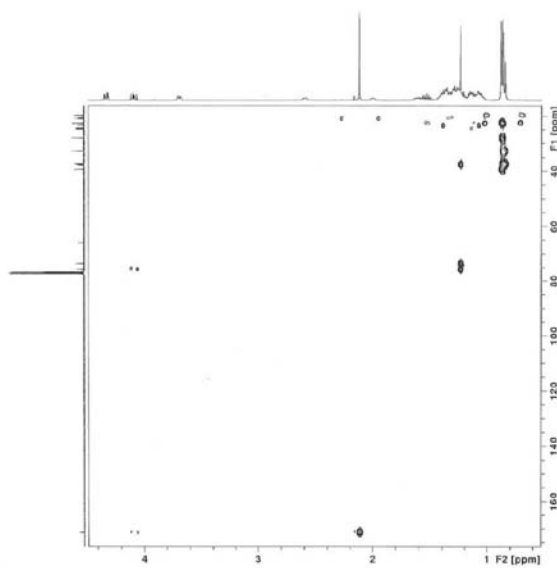


Figure S7. HMBC spectrum of compound 2.

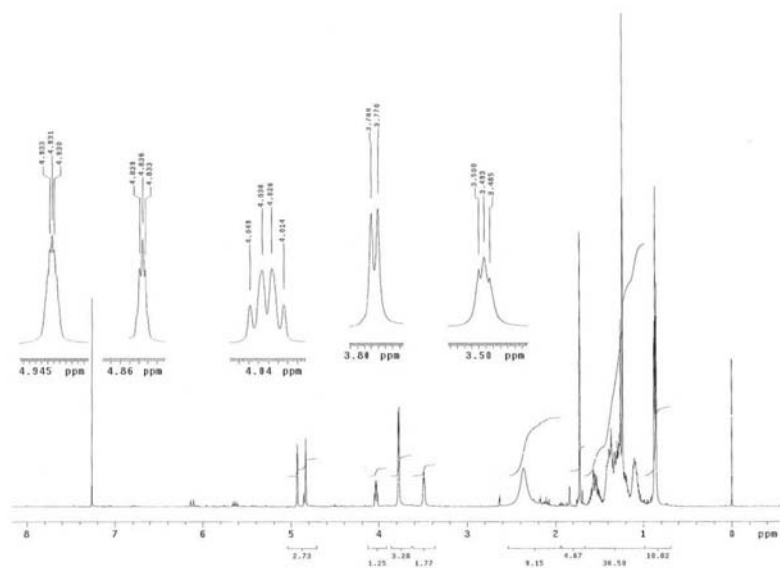


Figure S8. ^1H NMR (500 MHz, CDCl_3) spectrum of compound 3.

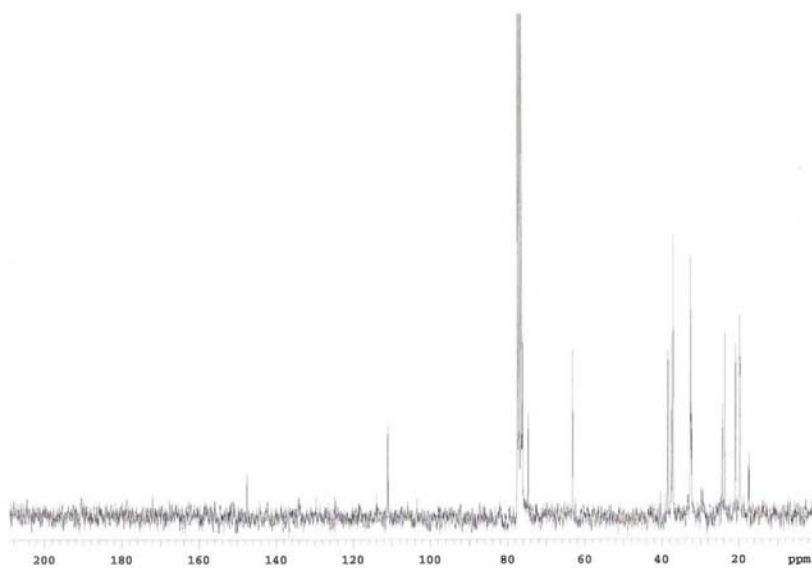


Figure S9. ^{13}C NMR (125 MHz, CDCl_3) spectrum of compound 3.

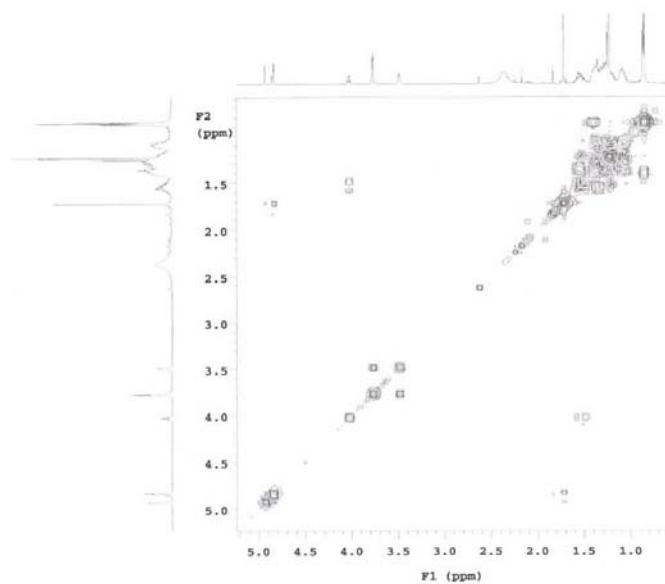


Figure S10. COSY spectrum of compound 3.

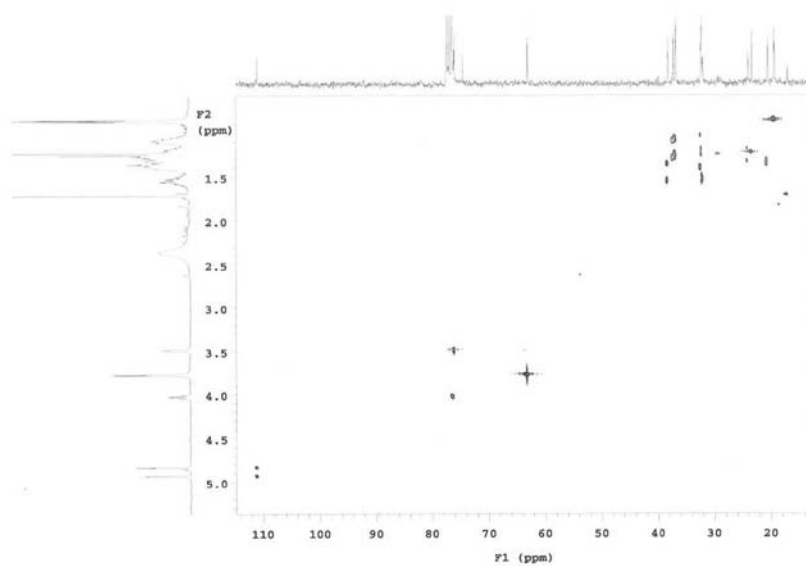


Figure S11. HSQC spectrum of compound 3.

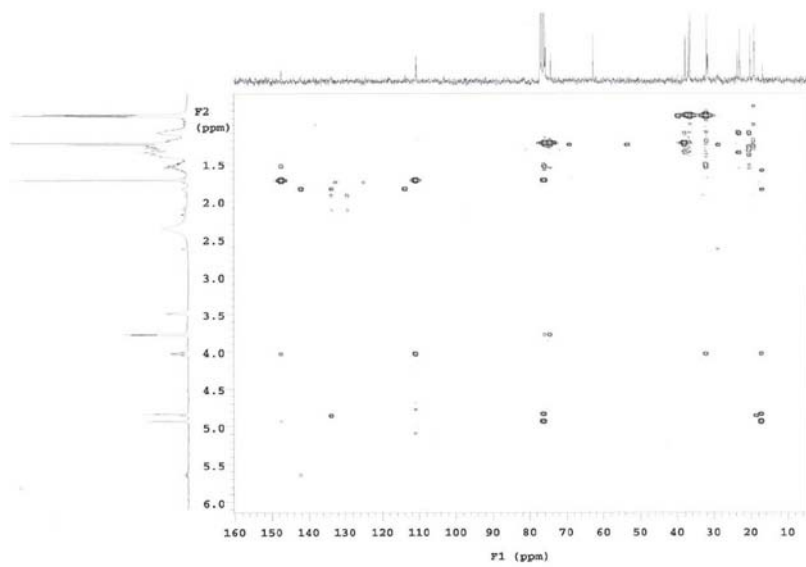


Figure S12. HMBC spectrum of compound **3**.

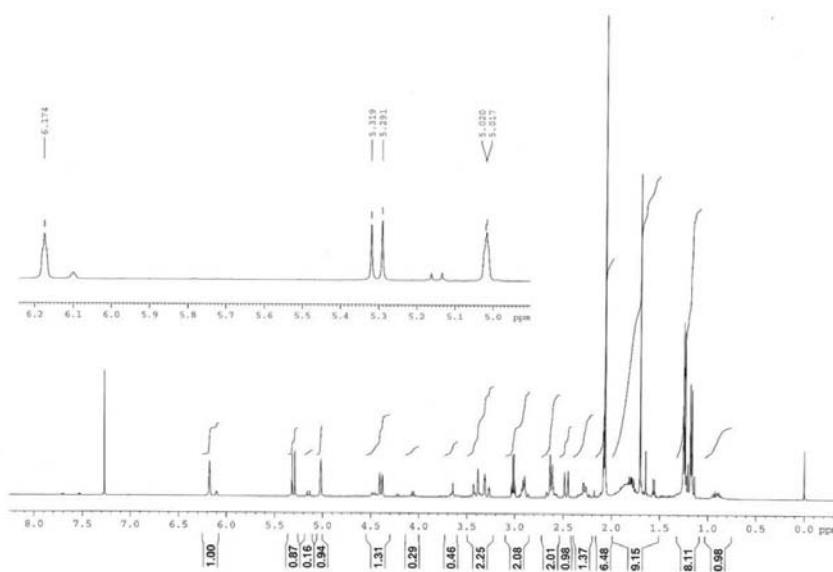


Figure S13. ^1H NMR (500 MHz, CDCl_3) spectrum of compound **4**.

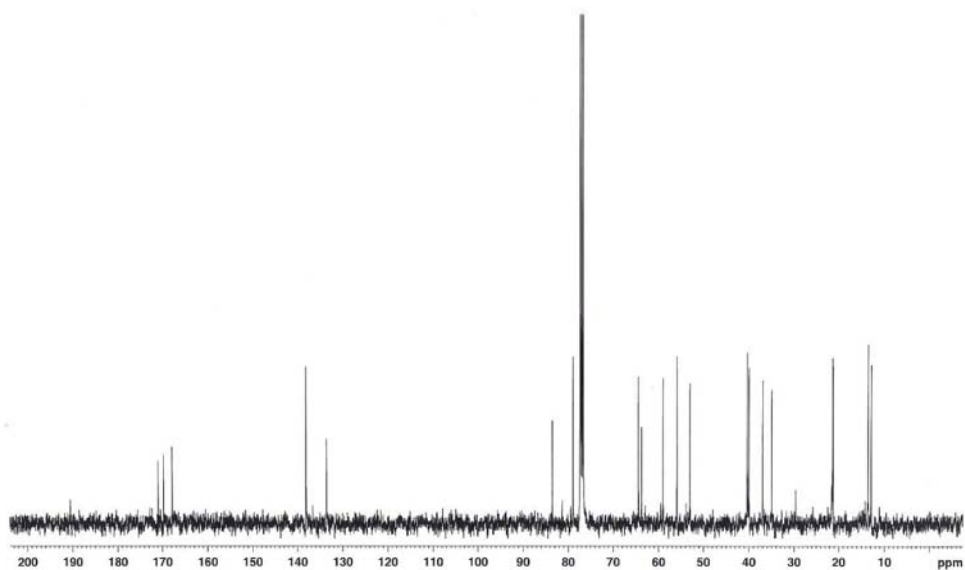


Figure S14. ^{13}C NMR (125 MHz, CDCl_3) of compound 4.

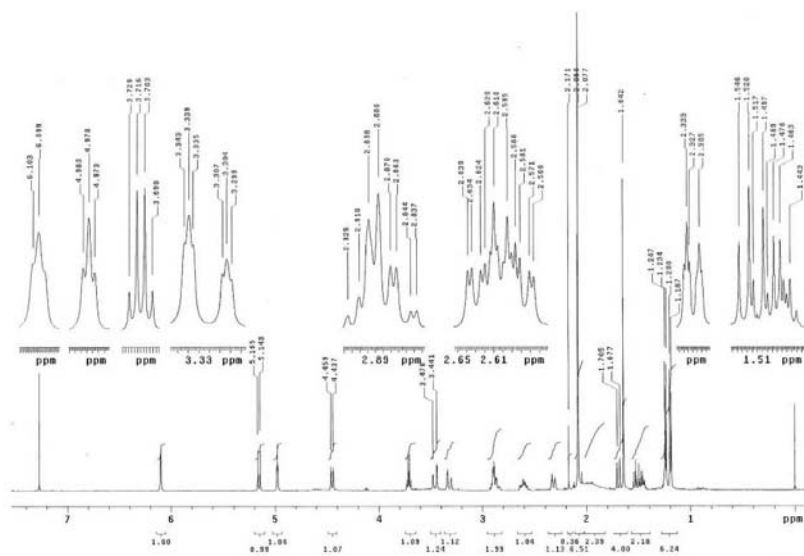


Figure S15. ^1H NMR (500 MHz, CDCl_3) spectrum of compound 5.

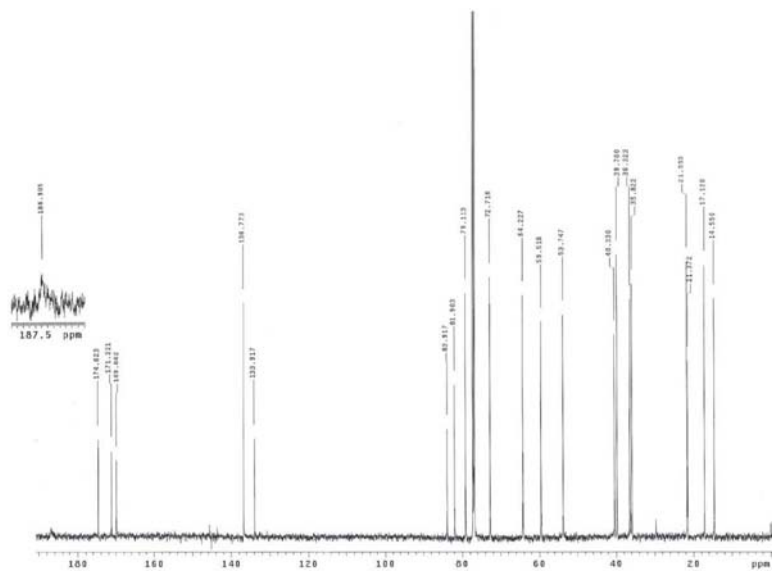


Figure S16. ^{13}C NMR (125 MHz, CDCl_3) spectrum of compound 5.

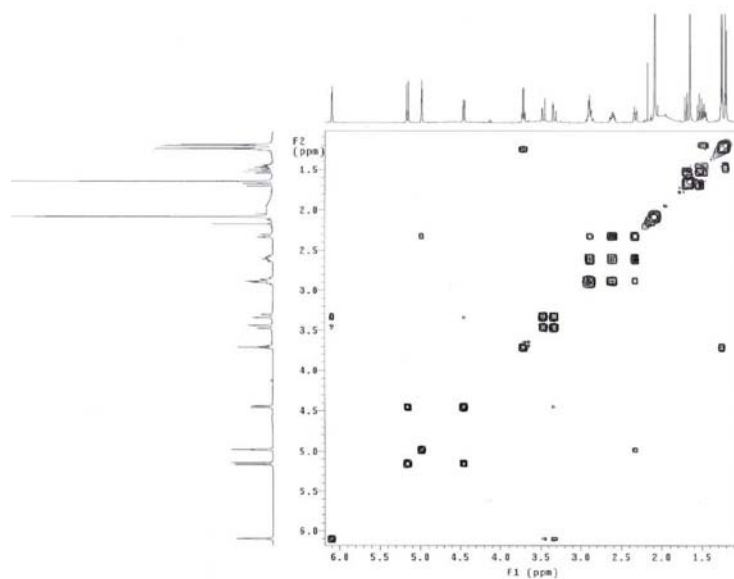


Figure S17. COSY spectrum of compound 5.

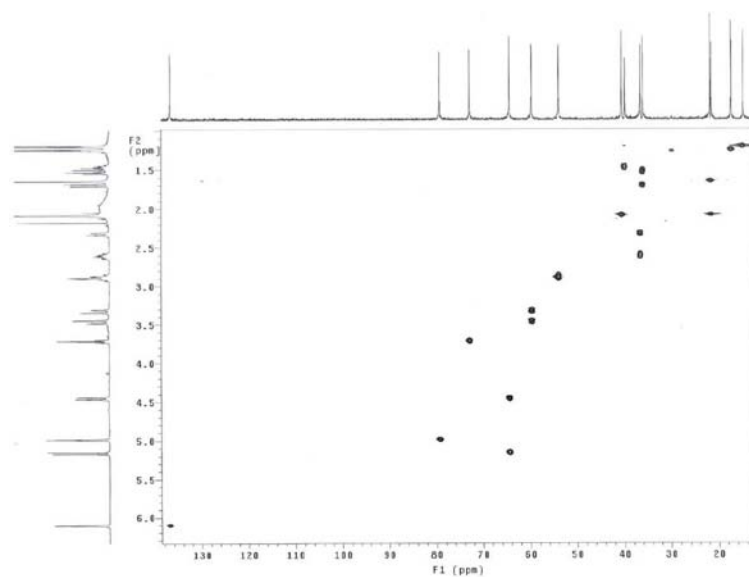


Figure S18. HSQC spectrum of compound 5.

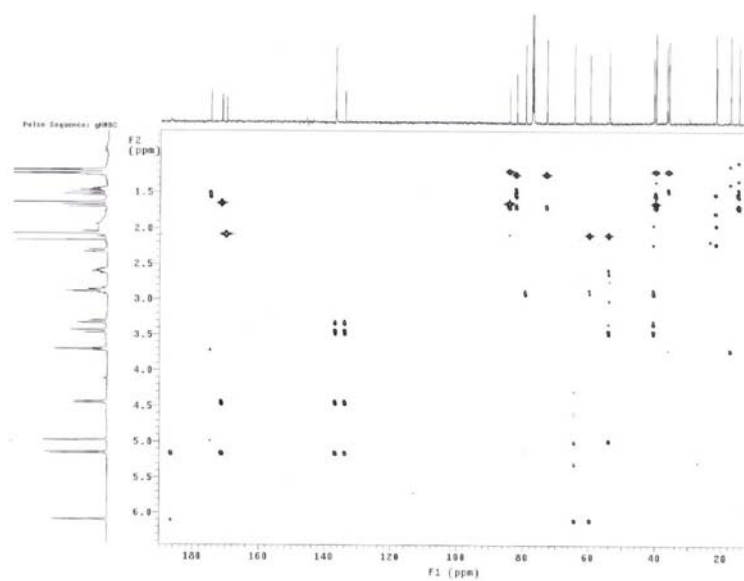


Figure S19. HMBC spectrum of compound 5.

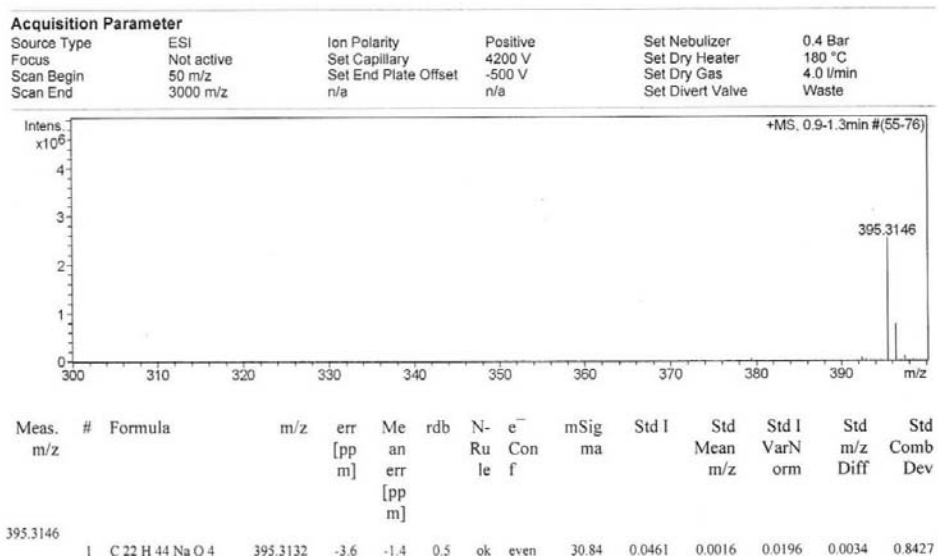


Figure S20. HRESIMS spectrum of compound 2.

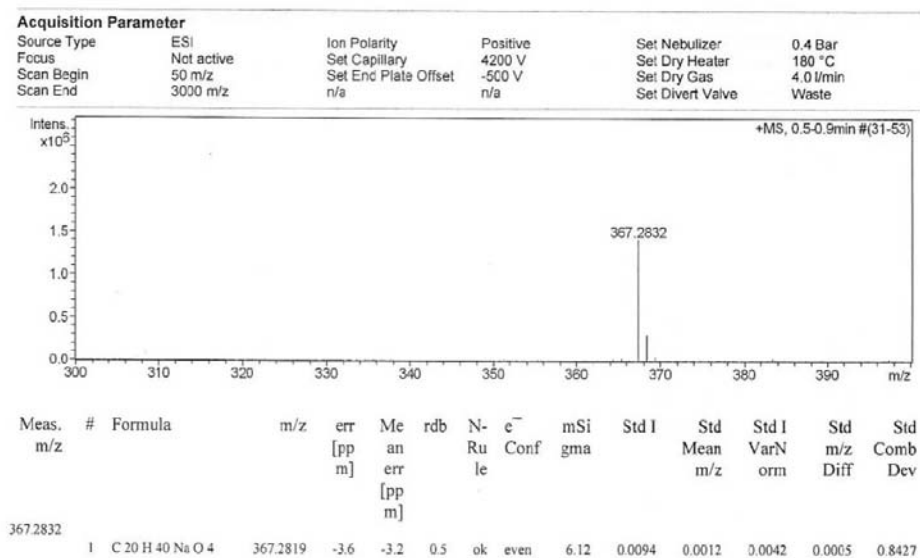


Figure S21. HRESIMS spectrum of compound 3.

Table S1. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **5**. U(eq) is defined as one third of the trace of the orthogonalized U^j tensor

	x	y	z	U(eq)		x	y	z	U(eq)
N(4)	2906(3)	8625(2)	3206(1)	68(1)	C(3A)	2053(17)	7886(15)	2857(7)	74(2)
C(22)	2548(5)	8800(3)	3776(1)	102(1)	C(5A)	4470(30)	8229(12)	3049(8)	69(3)
O(8)	2091(5)	10844(4)	3113(2)	65(1)	C(6A)	5365(18)	9261(9)	3013(6)	64(2)
O(10)	966(4)	10305(3)	1548(1)	60(1)	C(7A)	4380(20)	10031(14)	2685(7)	53(2)
O(11)	2267(4)	11793(3)	1783(1)	79(1)	C(8A)	2780(14)	10054(11)	2902(5)	50(2)
O(12)	1410(20)	10581(12)	500(4)	57(2)	C(9A)	599(9)	10734(6)	2314(3)	63(1)
O(23)	-783(7)	11425(6)	710(2)	74(1)	C(11A)	1064(10)	10658(7)	1382(3)	51(1)
C(1)	1273(8)	9560(6)	2468(3)	49(1)	C(12A)	1973(12)	11180(11)	908(5)	54(2)
C(2)	932(14)	8524(5)	2556(5)	65(2)	C(13A)	3720(14)	10870(11)	919(6)	56(2)
C(3)	1646(9)	7950(8)	2978(4)	69(2)	C(19A)	4614(13)	11338(10)	444(6)	80(3)
C(5)	4580(16)	8510(8)	3117(5)	76(2)	C(18A)	1742(11)	12419(7)	898(4)	67(2)
C(6)	5251(9)	9623(6)	3017(4)	67(2)	C(23A)	-187(19)	10800(15)	296(5)	61(2)
C(7)	4208(12)	10174(8)	2603(4)	50(1)	C(24A)	-650(20)	10063(13)	-130(5)	76(3)
C(8)	2484(8)	10110(8)	2794(3)	51(1)	C(14)	4029(3)	9589(2)	952(1)	56(1)
C(9)	308(4)	10229(4)	2094(2)	63(1)	C(15)	5507(2)	9278(2)	1264(1)	52(1)
C(11)	1829(4)	11164(3)	1448(2)	54(1)	C(16)	5548(2)	9884(1)	1799(1)	49(1)
C(12)	2343(7)	11264(7)	857(3)	55(1)	C(20)	5566(3)	8050(2)	1389(1)	62(1)
C(13)	4016(9)	10798(8)	800(3)	64(2)	C(21)	5763(5)	7361(2)	889(1)	92(1)
C(19)	4678(12)	10992(9)	245(4)	102(3)	O(15)	6816(2)	9588(2)	962(1)	70(1)
C(18)	2271(8)	12476(4)	697(3)	71(1)	O(16)	6531(2)	10524(1)	1923(1)	67(1)
C(23)	-87(10)	10776(9)	444(2)	56(1)	O(17)	4322(2)	9632(1)	2105(1)	49(1)
C(24)	-757(12)	10023(10)	41(3)	80(2)	O(20)	6823(3)	7919(1)	1753(1)	79(1)
O(8A)	2541(10)	10688(6)	3290(3)	62(2)	C(25)	457(13)	6995(12)	1163(4)	159(2)
O(10A)	1394(5)	11157(3)	1841(2)	60(1)	Cl(1)	731(5)	7016(4)	506(1)	204(2)
O(11A)	239(5)	9882(4)	1338(2)	64(1)	Cl(2)	1811(2)	6320(3)	1547(1)	162(1)
O(12A)	1400(40)	10690(20)	425(8)	58(2)	C(25A)	1290(40)	6811(15)	1350(8)	171(3)
O(23A)	-1020(12)	11431(9)	515(3)	70(2)	Cl(1A)	538(15)	7663(10)	914(6)	196(3)
C(1A)	1434(18)	9777(10)	2561(5)	53(2)	Cl(2A)	1437(11)	5457(9)	1169(5)	178(3)
C(2A)	850(20)	8786(10)	2574(8)	59(2)					

Table S2. Bond lengths (Å) and angles (degree) for compound **5**

N(4)-C(3A)	1.456(19)	C(20)-O(20)	1.422(3)	C(2A)-C(1A)-C(8A)	120.0(13)
N(4)-C(22)	1.465(4)	C(20)-C(21)	1.514(3)	C(2A)-C(1A)-C(9A)	122.9(12)
N(4)-C(5)	1.471(14)	C(25)-Cl(1)	1.650(9)	C(8A)-C(1A)-C(9A)	115.5(9)
N(4)-C(3)	1.482(9)	C(25)-Cl(2)	1.724(10)	C(1A)-C(2A)-C(3A)	112.3(14)
N(4)-C(5A)	1.49(2)	C(25A)-Cl(1A)	1.639(14)	N(4)-C(3A)-C(2A)	98.9(12)
N(4)-C(8A)	1.911(13)	C(25A)-Cl(2A)	1.726(14)	C(6A)-C(5A)-N(4)	102.2(11)
O(8)-C(8)	1.246(9)	C(3A)-N(4)-C(22)	124.0(6)	C(5A)-C(6A)-C(7A)	105.7(12)
O(10)-C(11)	1.316(6)	C(3A)-N(4)-C(5)	110.5(7)	C(8A)-C(7A)-C(6A)	110.0(12)
O(10)-C(9)	1.474(5)	C(22)-N(4)-C(5)	111.6(5)	C(8A)-C(7A)-O(17)	108.8(12)
O(11)-C(11)	1.197(5)	C(3A)-N(4)-C(3)	18.4(6)	C(6A)-C(7A)-O(17)	109.1(14)
O(12)-C(23)	1.325(18)	C(22)-N(4)-C(3)	107.2(4)	O(8A)-C(8A)-C(1A)	116.9(11)
O(12)-C(12)	1.462(16)	C(5)-N(4)-C(3)	127.8(5)	O(8A)-C(8A)-C(7A)	116.4(11)
O(23)-C(23)	1.198(10)	C(3A)-N(4)-C(5A)	95.8(8)	C(1A)-C(8A)-C(7A)	121.2(11)
C(1)-C(2)	1.323(9)	C(22)-N(4)-C(5A)	119.5(8)	O(8A)-C(8A)-N(4)	105.9(9)
C(1)-C(8)	1.486(7)	C(5)-N(4)-C(5A)	15.4(7)	C(1A)-C(8A)-N(4)	93.5(8)
C(1)-C(9)	1.494(8)	C(3)-N(4)-C(5A)	112.6(6)	C(7A)-C(8A)-N(4)	94.2(8)
C(2)-C(3)	1.407(15)	C(3A)-N(4)-C(8A)	107.9(8)	O(10A)-C(9A)-C(1A)	112.2(7)
C(5)-C(6)	1.504(9)	C(22)-N(4)-C(8A)	103.6(5)	O(11A)-C(11A)-O(10A)	125.1(8)
C(6)-C(7)	1.527(8)	C(5)-N(4)-C(8A)	94.9(6)	O(11A)-C(11A)-C(12A)	124.1(8)
C(7)-O(17)	1.409(12)	C(3)-N(4)-C(8A)	108.7(5)	O(10A)-C(11A)-C(12A)	110.7(9)
C(7)-C(8)	1.568(11)	C(5A)-N(4)-C(8A)	104.4(8)	O(12A)-C(12A)-C(18A)	110.8(14)
C(11)-C(12)	1.539(7)	C(11)-O(10)-C(9)	116.4(4)	O(12A)-C(12A)-C(11A)	106.9(13)
C(12)-C(18)	1.540(9)	C(23)-O(12)-C(12)	119.9(12)	C(18A)-C(12A)-C(11A)	110.7(9)
C(12)-C(13)	1.562(8)	C(2)-C(1)-C(8)	120.2(7)	O(12A)-C(12A)-C(13A)	104.4(16)
C(13)-C(19)	1.514(8)	C(2)-C(1)-C(9)	120.4(6)	C(18A)-C(12A)-C(13A)	111.6(9)
C(13)-C(14)	1.530(10)	C(8)-C(1)-C(9)	118.9(6)	C(11A)-C(12A)-C(13A)	112.1(9)
C(23)-C(24)	1.481(9)	C(1)-C(2)-C(3)	120.4(9)	C(19A)-C(13A)-C(12A)	112.7(10)
O(8A)-C(8A)	1.255(15)	C(2)-C(3)-N(4)	109.2(7)	C(19A)-C(13A)-C(14)	109.0(8)
O(10A)-C(11A)	1.326(9)	N(4)-C(5)-C(6)	108.5(7)	C(12A)-C(13A)-C(14)	113.8(10)
O(10A)-C(9A)	1.459(8)	C(5)-C(6)-C(7)	106.6(7)	O(23A)-C(23A)-O(12A)	123.0(14)
O(11A)-C(11A)	1.194(12)	O(17)-C(7)-C(6)	110.0(7)	O(23A)-C(23A)-C(24A)	124.9(14)
O(12A)-C(23A)	1.42(3)	O(17)-C(7)-C(8)	108.0(7)	O(12A)-C(23A)-C(24A)	112.1(16)
O(12A)-C(12A)	1.43(3)	C(6)-C(7)-C(8)	109.6(6)	C(13)-C(14)-C(15)	111.6(4)
O(23A)-C(23A)	1.188(19)	O(8)-C(8)-C(1)	118.9(6)	C(13)-C(14)-C(13A)	14.5(5)
C(1A)-C(2A)	1.317(16)	O(8)-C(8)-C(7)	114.6(7)	C(15)-C(14)-C(13A)	114.0(5)
C(1A)-C(8A)	1.480(13)	C(1)-C(8)-C(7)	121.8(7)	O(15)-C(15)-C(16)	108.30(17)
C(1A)-C(9A)	1.509(15)	O(10)-C(9)-C(1)	113.0(4)	O(15)-C(15)-C(20)	110.19(18)
C(2A)-C(3A)	1.67(2)	O(11)-C(11)-O(10)	124.3(4)	C(16)-C(15)-C(20)	107.42(16)
C(5A)-C(6A)	1.488(13)	O(11)-C(11)-C(12)	121.4(4)	O(15)-C(15)-C(14)	109.37(16)
C(6A)-C(7A)	1.512(14)	O(10)-C(11)-C(12)	114.2(4)	C(16)-C(15)-C(14)	109.70(16)
C(7A)-C(8A)	1.48(2)	O(12)-C(12)-C(11)	111.9(7)	C(20)-C(15)-C(14)	111.78(18)
C(7A)-O(17)	1.52(2)	O(12)-C(12)-C(18)	112.0(8)	O(16)-C(16)-O(17)	124.43(19)
C(11A)-C(12A)	1.555(15)	C(11)-C(12)-C(18)	108.1(6)	O(16)-C(16)-C(15)	124.20(19)
C(12A)-C(18A)	1.534(15)	O(12)-C(12)-C(13)	104.3(10)	O(17)-C(16)-C(15)	111.35(16)
C(12A)-C(13A)	1.558(13)	C(11)-C(12)-C(13)	108.9(5)	O(20)-C(20)-C(21)	111.9(2)
C(13A)-C(19A)	1.524(14)	C(18)-C(12)-C(13)	111.6(5)	O(20)-C(20)-C(15)	105.32(19)
C(13A)-C(14)	1.596(13)	C(19)-C(13)-C(14)	112.0(7)	C(21)-C(20)-C(15)	112.5(2)
C(23A)-C(24A)	1.451(16)	C(19)-C(13)-C(12)	111.9(6)	C(16)-O(17)-C(7)	116.4(5)
C(14)-C(15)	1.543(3)	C(14)-C(13)-C(12)	109.8(6)	C(16)-O(17)-C(7A)	116.0(8)
C(15)-O(15)	1.410(3)	O(23)-C(23)-O(12)	123.7(8)	C(7)-O(17)-C(7A)	11.1(9)
C(15)-C(16)	1.524(3)	O(23)-C(23)-C(24)	126.3(8)	Cl(1)-C(25)-Cl(2)	117.3(6)
C(15)-C(20)	1.540(3)	O(12)-C(23)-C(24)	109.9(9)	Cl(1A)-C(25A)-Cl(2A)	118.1(11)
C(16)-O(16)	1.198(3)	C(11A)-O(10A)-C(9A)	115.3(6)		
C(16)-O(17)	1.342(2)	C(23A)-O(12A)-C(12A)	119(2)		

Table S3. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **5**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^* a^* U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}		U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N(4)	74(1)	56(1)	73(1)	12(1)	-17(1)	-8(1)	C(3A)	76(5)	48(3)	97(5)	2(4)	-1(4)	-1(4)
C(22)	110(2)	121(3)	74(2)	26(2)	0(2)	-30(2)	C(5A)	76(4)	40(5)	90(5)	6(4)	-22(4)	-5(4)
O(8)	71(2)	52(2)	73(3)	-12(2)	15(2)	-3(2)	C(6A)	66(3)	49(5)	77(3)	1(4)	-18(3)	0(3)
O(10)	57(2)	64(2)	58(2)	14(1)	-2(1)	-3(1)	C(7A)	60(3)	40(4)	59(4)	-4(3)	-5(3)	-5(3)
O(11)	92(2)	77(2)	69(2)	-4(1)	-1(2)	-19(2)	C(8A)	58(3)	29(3)	64(4)	-2(3)	-5(2)	-4(3)
O(12)	53(2)	60(3)	58(3)	6(2)	4(2)	6(2)	C(9A)	64(3)	63(3)	61(3)	4(2)	5(2)	21(3)
O(23)	55(2)	85(2)	81(3)	-9(3)	-3(2)	13(2)	C(11A)	50(3)	47(3)	55(3)	6(2)	0(2)	12(2)
C(1)	38(2)	52(3)	57(2)	6(2)	-2(2)	1(2)	C(12A)	52(3)	46(3)	63(3)	9(2)	1(2)	8(3)
C(2)	66(3)	48(3)	80(3)	-6(3)	-13(2)	-5(3)	C(13A)	51(3)	44(3)	74(5)	10(3)	3(3)	0(3)
C(3)	71(4)	42(2)	94(4)	-1(2)	-5(3)	-10(3)	C(19A)	62(4)	72(5)	107(7)	35(5)	16(4)	5(4)
C(5)	81(4)	65(5)	83(3)	13(4)	-20(3)	13(4)	C(18A)	63(4)	51(3)	86(5)	15(3)	-12(4)	1(3)
C(6)	56(2)	74(4)	70(2)	0(3)	-8(2)	-2(3)	C(23A)	58(3)	64(3)	61(5)	9(4)	0(3)	0(3)
C(7)	49(3)	45(3)	57(3)	0(2)	1(2)	-7(2)	C(24A)	95(7)	79(4)	55(6)	3(4)	-14(5)	-1(4)
C(8)	50(3)	44(2)	60(3)	-3(2)	7(2)	-2(2)	C(14)	54(1)	52(1)	62(1)	6(1)	-2(1)	1(1)
C(9)	47(2)	78(2)	65(2)	20(2)	4(1)	8(2)	C(15)	44(1)	50(1)	63(1)	5(1)	6(1)	3(1)
C(11)	51(2)	53(2)	59(2)	6(1)	-1(1)	6(2)	C(16)	39(1)	39(1)	68(1)	5(1)	1(1)	2(1)
C(12)	54(3)	53(2)	59(2)	14(2)	-2(2)	0(2)	C(20)	72(1)	46(1)	68(1)	0(1)	2(1)	10(1)
C(13)	53(3)	67(3)	71(3)	23(3)	1(2)	8(2)	C(21)	129(3)	64(1)	85(2)	-16(1)	-5(2)	26(2)
C(19)	94(4)	112(6)	99(5)	52(4)	39(4)	25(4)	O(15)	53(1)	80(1)	76(1)	10(1)	19(1)	2(1)
C(18)	65(3)	56(2)	93(4)	25(2)	-9(2)	2(2)	O(16)	49(1)	61(1)	92(1)	-7(1)	4(1)	-13(1)
C(23)	51(2)	66(2)	52(3)	7(3)	1(2)	3(2)	O(17)	43(1)	44(1)	59(1)	-4(1)	2(1)	-5(1)
C(24)	74(3)	106(4)	60(4)	-6(4)	2(3)	-13(3)	O(20)	94(1)	59(1)	84(1)	2(1)	-17(1)	29(1)
O(8A)	84(4)	39(2)	64(3)	-7(2)	12(2)	-12(3)	C(25)	136(4)	225(5)	115(2)	59(4)	40(3)	54(4)
O(10A)	66(2)	55(2)	59(2)	5(2)	-3(2)	13(2)	Cl(1)	222(3)	278(4)	110(1)	15(2)	34(2)	64(3)
O(11A)	59(2)	70(2)	63(2)	10(2)	0(2)	-10(2)	Cl(2)	94(1)	219(3)	172(2)	49(2)	-1(1)	11(2)
O(12A)	56(2)	60(4)	58(4)	10(3)	3(3)	3(3)	C(25A)	140(6)	228(5)	143(5)	41(4)	40(5)	39(5)
O(23A)	61(3)	69(3)	79(5)	2(4)	-12(3)	9(3)	Cl(1A)	184(5)	231(6)	172(5)	41(5)	12(5)	47(5)
C(1A)	52(3)	49(3)	59(3)	5(2)	3(3)	2(3)	Cl(2A)	125(5)	222(5)	188(7)	40(5)	9(5)	25(6)
C(2A)	56(3)	52(4)	69(3)	-7(4)	-6(3)	-2(3)							

Table S4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for compound **5**

	x	y	z	U(eq)		x	y	z	U(eq)
H(22A)	3335	9274	3936	153	H(6AB)	5557	9564	3376	77
H(22B)	2539	8097	3963	153	H(7A)	4830	10780	2697	64
H(22C)	1530	9145	3808	153	H(9AA)	-459	10507	2212	75
H(2)	200	8165	2332	78	H(9AB)	507	11321	2586	75
H(3A)	2072	7254	2842	83	H(13A)	4169	11200	1252	67
H(3B)	877	7782	3261	83	H(19D)	4647	12134	473	120
H(5A)	4774	8033	2803	91	H(19E)	4098	11131	108	120
H(5B)	5072	8177	3437	91	H(19F)	5670	11048	445	120
H(6A)	6320	9561	2878	80	H(18D)	2220	12742	1218	100
H(6B)	5273	10051	3355	80	H(18E)	633	12585	896	100
H(7)	4520	10954	2559	60	H(18F)	2225	12722	574	100
H(9A)	-738	9905	2072	76	H(24D)	-878	9344	23	114
H(9B)	201	10973	2244	76	H(24E)	184	9998	-394	114
H(13)	4688	11191	1064	76	H(24F)	-1581	10348	-307	114
H(19A)	4079	10578	-21	153	H(14A)	3960	9143	621	68
H(19B)	5758	10752	236	153	H(14B)	3112	9424	1176	68
H(19C)	4624	11771	159	153	H(14C)	3130	9236	1127	68
H(18A)	2375	12543	306	107	H(14D)	4105	9296	582	68
H(18B)	3114	12872	873	107	H(20)	4586	7833	1574	74
H(18C)	1277	12783	810	107	H(21A)	4784	7335	691	139
H(24A)	-1115	10441	-271	120	H(21B)	6068	6620	992	139
H(24B)	-1631	9632	201	120	H(21C)	6566	7681	660	139
H(24C)	32	9499	-74	120	H(15A)	7170(40)	10208(11)	1023(13)	105
H(2A)	-148	8604	2439	71	H(20A)	7150(60)	7278(17)	1794(18)	119
H(3AA)	1492	7322	3064	88	H(25A)	-564	6659	1233	190
H(3AB)	2732	7533	2588	88	H(25B)	404	7759	1290	190
H(5AA)	4904	7735	3326	82	H(25C)	664	6850	1683	205
H(5AB)	4440	7845	2699	82	H(25D)	2339	7075	1441	205
H(6AA)	6371	9134	2834	77					

Table S5. Hydrogen bonds for compound **5** (\AA and degree)

D-H...A	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)
O(15)-H(15A)...O(23A) ^a	0.835(11)	2.51(3)	3.138(12)	133(3)
O(20)-H(20A)...O(8) ^b	0.842(11)	1.892(12)	2.734(5)	179(6)
O(20)-H(20A)...O(8A) ^b	0.842(11)	1.979(19)	2.793(7)	162(5)
O(15)-H(15A)...O(23) ^a	0.835(11)	2.44(3)	3.127(8)	140(4)

Symmetry transformations used to generate equivalent atoms: ^a $x + 1, y, z$ ^b $-x + 1, y - 1/2, -z + 1/2$.