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Veiutamine. A New Alkaloid from the Fijian Sponge *Zyzzya fuliginosa*

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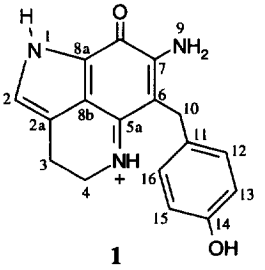
Abstract: We report the isolation and characterization of veiutamine (**1**), a new pyrroloiminoquinone derivative from the Fijian sponge *Zyzzya fuliginosa*. Veiutamine is the first pyrroloiminoquinone alkaloid bearing a C-6 *p*-oxy benzyl substituent.

Pyrroloiminoquinone derivatives have been reported from a variety of natural sources.[1-13] The sponge *Zyzzya fuliginosa* has been a rich source of pyrroloiminoquinone alkaloids; damirones A and B, discorhabdin A and makaluvamines A-F, H-M.[1,3] In our continuing investigation of *Z. fuliginosa* we have isolated a novel, cytotoxic pyrroloiminoquinone derivative, veiutamine (**1**). Veiutamine is related to the known makaluvamine D (**2**), however the unique substitution of a *p*-oxy benzyl moiety at carbon 6 clearly distinguishes it from all known pyrroloiminoquinones.[1-13]

Specimens of the sponge *Zyzzya fuliginosa* were collected in Suva Harbor, Fiji islands. The methanol extract of the freeze dried sponge was fractionated using a modified Kupchan partitioning scheme.[14] Sephadex LH20 chromatography of the chloroform soluble material yielded makaluvamines A, B, C, D (**2**), E and F, makaluvone, discorhabdin A and damirone B, as previously reported.[1] Silica gel chromatography (0.1% TFA/$CHCl_3$ to 0.1% TFA/15% MeOH/$CHCl_3$) of the aqueous methanol fraction and subsequent chromatography with Sephadex LH20 (0.1% TFA/MeOH), yielded additional quantities of makaluvamines A, C, D (**2**), and E and afforded pure veiutamine (**1**).



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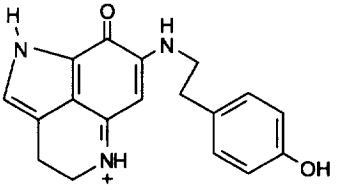

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Veiutamine (**1**) was obtained as a green TFA salt,[15] which was a brilliant purple color as a methanolic solution (7.7 mg, 0.02% dry wt). Veiutamine was found to be a potent *in vitro* cytotoxin. In a 25 cell line panel it exhibited a mean IC_{50} of 0.12 μg/mL, with some selectivity against solid tumors versus leukemia. Veiutamine (IC_{50} 0.3 μg/mL) was also shown to be 7 times more active than Makaluvamine D (**2**) (IC_{50} 2.0 μg/mL) against the human colon tumor cell line HCT 116.

^1H and ^{13}C NMR spectral data for **1** are consistent with a pyrroloiminoquinone ring system.[1-3] The ^1H and HMBC spectra also clearly indicate the presence of four nitrogen attached protons (13.04 ppm, NH1; 10.08 ppm, NH5; 8.45 and 8.55 ppm, $NH_2$9). Noticeably absent however is the diagnostic H6 singlet resonance between 5-6

ppm, suggesting substitution at C6. This is further substantiated by the absence of the corresponding methine carbon resonance, typically observed between 80-90 ppm. Instead, a quaternary carbon resonance is observed at 99.81 ppm.

A pair of *ortho*-coupled doublets, two protons each, in the aromatic region of the proton spectrum (δ 6.67, d, J = 8.5 Hz, H13, H15; 7.01, d, J = 8.5 Hz, H12, H16) and an exchangeable proton at 9.10 ppm are indicative of a *para*-substituted phenol residue, as seen in makaluvamine D (**2**).[1] This is substantiated by DEPT, HMQC, and HMBC spectral data.

HMBC correlations from aromatic H12 and H16 to C10 (27.98 ppm) and C14 (157.28 ppm) and from H10 to C6 (99.81 ppm), C11 (128.62 ppm), C7 (155.16 ppm) and C5a (159.41 ppm) identify C10 as the benzylic methylene of the *para*-substituted phenolic residue. The H10 protons are observed as a singlet in the ^{1}H NMR spectrum at 3.67 ppm. Considering the long-range correlations from H10 to carbons 5a, 6 and 7, and the absence of a second methylene resonance coupled to H10, it is evident that the phenolic substituent is a *p*-hydroxy benzyl residue attached to C6, giving structure (**1**) veiutamine.

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References and Notes:

1. Radisky, D.C.; Radisky, E.S.; Barrows, L.R.; Copp, B.R.; Kramer, R.A.; and Ireland, C.M. *J. Am. Chem. Soc.* **1993**, *115*, 1632-1638.
2. Carney, J.R.; Scheuer, P.J.; Kelly-Borges, M. *Tetrahedron* **1993**, *49*, 8483-8486.
3. Schmidt, E.W.; Harper, M.K.; Faulkner, D.J. *J. Nat. Prod.* **1995**, *58*, 1861-1867.
4. Kobayashi, J.; Cheng, J.-f.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hiratia, Y.; Sasaki, T.; Lu, H.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4939-4949.
5. Cheng, J.-f.; Ohizumi, Y.; Wälchli, M.R.; Nakamura, H.; Hiratia, Y.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1988**, *53*, 4621-4624.
6. Kobayashi, J.; Cheng, J.-f.; Yamamura, S.; Ishibashi, M. *Tetrahedron Lett.* **1991**, *32*, 1227-1228.
7. Sakemi, S.; Sun, H.H.; Jefford, C.W.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *30*, 2517-2520.
8. Sun, H.H.; Sakemi, S.; Burres, N.; McCarthy, P. *J. Org. Chem.* **1990**, *55*, 4964-4966.
9. Copp, B.R.; Ireland, C.M.; Barrows, L.R. *J. Org. Chem.* **1991**, *56*, 4596-4597.
10. Stierle, D.B.; Faulkner, D.J. *J. Nat. Prod.* **1991**, *54*, 1131-1133.
11. Perry, N.B.; Blunt, J.W.; McCombs, J.D.; Munro, M.H.G. *J. Org. Chem.* **1986**, *51*, 5476-5478.
12. Perry, N.B.; Blunt, J.W.; Munro, M.H.G. *Tetrahedron* **1988**, *44*, 1727-1734.
13. Perry, N.B.; Blunt, J.W.; Munro, M.H.G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127-4128.
14. Kupchan, S.M.; Britton, R.W.; Ziegler, M.F.; Siegel, C.W. *J. Org. Chem.* **1973**, *38*, 178-179.
15. HRFABMS, MH^+ 294.12427, $C_{17}H_{16}N_3O_2$ requires 294.12425 (Δmmu -0.0133); UV (MeOH) λ_{max} 246, 344, 550; UV (MeOH/KOH) λ_{max} 228, 330, 470; FTIR (TFA salt) υ_{max} 3416, 1675, 1609, 1549, 1514, 1439, 1409, 1334, 1199, 1138, 1023, 988, 798 cm^{-1}; ^{1}H NMR (TFA salt, 500 MHz, DMSO-d_6) δ 2.84 (t, J = 7.5 Hz, $H_2$3), 3.67 (s, $H_2$10), 3.77 (dt, J = 2.5, 7.5 Hz, $H_2$4), 6.67 (d, J = 8.5 Hz, H13, H15), 7.01 (d, J = 8.5 Hz, H12, H16), 7.29 (d, J = 2.5 Hz, H2), 8.45 (s, NH9), 8.55 (s, NH9), 10.08 (s, NH5), 13.04 (s, NH1); ^{1}H NMR (TFA salt, 500 MHz, MeOH-d_4) δ 2.94 (t, J = 7.5 Hz, $H_2$3), 3.71 (s, $H_2$10), 3.84 (t, J = 7.5 Hz, $H_2$4), 6.72, (d, J = 8.5 Hz, H13, H15), 7.05 (d, J = 8.5 Hz, H12, H16), 7.13 (s, H2); ^{13}C NMR (TFA salt, 125 MHz, MeOH-d_4) δ 19.51 (C3), 27.98 (C10), 44.76 (C4), 99.81 (C6), 116.56 (C13, C15), 120.63 (C2a), 123.98 (C8b), 125.36 (C8a), 126.98 (C2), 128.62 (C11), 129.71 (C12, C16), 155.16 (C7), 157.28 (C14), 159.41 (C5a), 168.92 (C8).

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