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A NOVEL CONDENSED TROPONE-ISOQUINOLINE ALKALOID, PAREITROPONE, FROM *CISSAMPELOS PAREIRA*

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Abstract: A novel condensed tropone-isoquinoline alkaloid, named pareitropone, showing potent cytotoxic activity, has been isolated from the roots of *Cissampelos pareira*.

During our survey of novel antileukemic compounds from South American medicinal plants,[1] a novel condensed tropone and isoquinoline alkaloid, named pareitropone, for which the general term "tropoisoquinoline" is proposed, has been isolated from the roots of *Cissampelos pareira* (Menispermaceae). In the present communication, a full account of structural elucidation and potent cytotoxic activity of pareitropone with highly condensed aromatic heterocyclic nuclei are described.

The methanolic extract showing antileukemic activity against p-388 cells was partitioned between methylene chloride and water. The methylene chloride soluble fraction was further separated by silica gel column chromatography and reversed phase HPLC,[2] conducted in conjunction with a bioassay against p-388 cells, to give a novel tropoisoquinoline alkaloid, pareitropone (0.0004%), which is positive to Dragendorff reagent.

Pareitropone (**1**),[3] reddish-brown needles, mp 97 - 99°C, possessed the molecular formula, $C_{18}H_{13}NO_3$, according to HR EI-MS spectrum (291.0905). In the ^1H NMR spectrum,[3] two methoxy protons (δ 4.06 and 4.19), an aromatic singlet proton (δ 7.14) and two each coupled aromatic protons (δ 7.53 and 8.71) assignable to H-1 and 16 on isoquinoline skeleton were observed. In addition, cross conjugated α,β-unsaturated group bearing signals (δ 7.19 and 8.25; δ 7.21 and 8.17), both α-protons of which were long range coupled each other at the value of 2.8 Hz, were considered to be based on tropone skeleton. In the ^{13}C NMR spectrum,[3] eight quaternary carbons resonated around aromatic region (δ 119.86, 125.15, 129.53, 141.41, 142.33, 151.60, 157.59 and 158.96) and

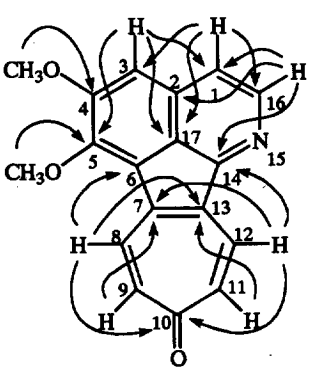

Fig. 1 Structure of pareitropone (**1**); Arrows show HMBC correlations.

carbonyl signals (δ 188.09) were observed in addition to carbon signals corresponding to the above protons in PFG-HSQC spectrum.[4] The structural relationship between the isoquinoline and the tropone skeletons and the position of two methoxyl groups were secured by ^{1}H-^{13}C long range correlation in PFG-HMBC spectrum,[5] shown in Fig. 1. From the foregoing evidence, the structure of **1** was determined to be the novel tropoisoquinoline alkaloid.

Pareitropone (**1**) with a tropone moiety showed highly potent cytotoxicity (IC_{50} 0.8 ng/ml) against cultured p-388 cells more than several tropoloisoquinoline alkaloids with a tropolone moiety, such as pareirubrine A and B,[6] imerubrine[7,8] and grandirubrine[7,9] (IC_{50} 0.33, 0.17, 1.20 and 0.18 μg/ml, respectively, against p-388 cells). Extreme increment of activity was also shown in the case of colchicide with a tropone moiety, which lacks the 10-methoxy group of colchicine with a tropolone moiety.[10]

Further pharmacological evaluations of pareitropone, which showed highly promising activity more than tropoloisoquinoline alkaloids, and the derived tropoisoquinoline alkaloids are in progress.

References and Notes

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2. The solvent system of silica gel column chromatography is CH_2Cl_2 - MeOH, and that of reversed phase HPLC is 100% MeOH and CH_3CN-MeOH-Sodium Phosphate Buffer (pH 3.5) = 2 : 2 : 1.
3. HR EI MS of **1** m/z: 291 (M^+, Calcd for $C_{18}H_{13}NO_3$ 291.0895, Found 291.0905). ^{1}H-NMR data of **1** ($CDCl_3$, 400MHz): 4.06 (3H, s, 4-OMe), 4.19 (3H, s, 5-OMe), 7.14 (1H, s, H-3), 7.19 (1H, dd, 2.8, 12.0, H-9), 7.21 (1H, dd, 2.8, 12.0, H-11), 7.53 (1H, d, 5.5, H-1), 8.17 (1H, d, 12.0, H-12), 8.25 (1H, d, 12.0, H-8), and 8.71 (1H, d, 5.5, H-16). ^{13}C-NMR data ($CDCl_3$, 100MHz): 56.59 (q, 4-OMe), 62.16 (q, 5-OMe), 107.52 (d, C-3), 118.78 (d, C-1), 119.86 (s, C-17), 125.15 (s, C-6), 129.53 (s, C-2), 130.34 (d, C-12), 133.19 (d, C-8), 140.81 (d, C-11), 141.37 (d, C-9), 141.41 (s, C-13), 142.33 (s, C-7), 146.75 (d, C-16), 151.60 (s, C-5), 157.59 (s, C-14), 158.96 (s, C-4), and 188.09 (s, C-10). λ_{MeOH} nm (ε): 213 (21000), 240 (17700), 270 (11200, sh), 342 (15500) and 400 (4600). ν_{CHCl_3} cm^{-1}: 2950, 1605, 1590, 1490, 1475 and 1285.
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