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INHIBITION OF OXIDOSQUALENE CYCLASE BY SUBSTITUTED QUINOLIZIDINES

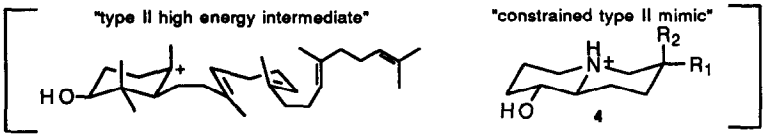
Angela L. Marquart, Gerald L. Schatzman, Norton P. Peet, William R. Moore, Edward W. Huber, Steven L. Gallion and Michael R. Angelastro*

Marion Merrell Dow Research Institute
2110 E. Galbraith Road, Cincinnati, Ohio. 45215, U.S.A.

Abstract: Substituted hydroxyquinolizidines have been synthesized as conformationally restricted analogs of the type II high energy intermediate formed during the cyclization of 2,3-oxidosqualene to lanosterol. Compounds **4a** and **4b** were found to be potent inhibitors of rat liver oxidosqualene cyclase (OSC) with K_i values of 0.51 μM and 0.11 μM, respectively.

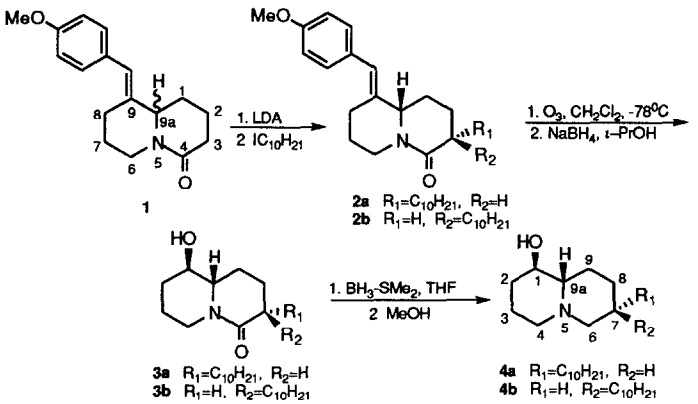
The inhibition of cholesterol biosynthesis is a potential therapeutic target for the treatment of hypercholesterolemia. Of the many possible points of intervention in the biosynthesis of cholesterol, the inhibition of HMG-CoA has attracted the major effort.[1] However, more recently the inhibition of 2,3-oxidosqualene cyclase (OSC),[2] squalene epoxidase and squalene synthase have received increasing attention. A review of the enzymatic cyclization of squalene and oxidosqualene has recently been published.[3]

The inhibition of OSC has been achieved with synthetic analogs of squalene and oxidosqualene that contain modifications to either the oxirane functionality, the backbone skeleton or the trisubstituted olefins.[3] In addition, heterocyclic compounds that contain a nitrogen atom positioned to mimic the charged center of one of the discrete high energy intermediates formed during the cyclization process have produced potent inhibition.[4] Hydroxypiperdines which mimic the second high energy intermediate (Type II) have been reported to be potent inhibitors.[5] Herein, we report the synthesis of hydroxyquinolizidines as conformationally restricted type II mimics.



Treatment of **1**[6] with LDA (THF), followed by addition to iododecane gave the easily separable diastereomers **2a** and **2b** each as an enantiomeric pair. Coupling constants and NOE data were used to established the relative stereochemistry of **2a** and **2b**[7]. Ozonolysis of **2a** (-78°C, CH_2Cl_2) and reduction of the crude product ($NaBH_4$, O°C, *i*-PrOH , CH_2Cl_2) without isolation afforded **3a**. Reduction occurred exclusively anti to the bridgehead proton. Reduction of the amide **3a** (BH_3•SMe_2, THF) and subsequent methanolysis gave the aminoalcohol **4a**.[8] The C-3 epimer **2b** was converted to **4b**[9] in a similar fashion.[10] The chair-chair conformation shown for **4** was derived from NMR data and molecular modeling. The low energy conformation was determined using the semi-empirical AM1 hamiltonian within Spartan 3.0 and confirmed with single point *ab initio* calculations.[11]

Compounds **3a, 3b, 4a** and **4b** were tested as inhibitors of purified rat liver OSC[12] in the presence of Tween 80 (0.25%). Substrate concentrations for K_i determinations were 2.5, 5, 10, 20, 30, 40 and 50 μM. All other



conditions were the same as previously described[13]. Compounds **3a** and **3b** are poor inhibitors, whereas compounds **4a** and **4b** are potent inhibitors with IC_{50} values of 0.43 μM and 0.17 μM, respectively. Kinetic studies[13] indicate that **4a** and **4b** are competitive inhibitors of OSC with K_i values of 0.51 μM and 0.11 μM, respectively. Quinolizidine **4b**, with the equatorial substituent at C-7, is structurally closer to the type II high energy intermediate than the less potent OSC inhibitor **4a**, in which the C-7 substituent is axial. Interesting to note is the potent inhibition of **4b** despite the positioning of the hydroxyl substituent at C-1 rather than the anticipated preferred position at C-2. The synthesis of additional hydroxyl substituted compounds is planned.

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7. For example, for **2b** an H-2ax to H-3 coupling constant of 11.9 Hz was used to establish H-3 as axial. NOE's between H-9a(ax) (δ 4.04,dd, J=9.7, 4.9 Hz) and H-2ax, H-6ax and H-8ax support an anti relationship between H-9a and H-3, and a chair-chair like conformation.
8. **4a**: ^{1}H NMR ($CDCl_3$) 3.30(ddd, J=11.4, 9.2, 4.3 Hz, 1H), 2.69-2.58(m, 2H), 2.15(dd, J=11.4, 3.2 Hz, 1H), 2.06-1.82(m, 3H), 1.77-1.16(m, 24H), 1.25(s, 3H), 0.89(t, J=6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) 72.15, 69.07, 59.93, 56.09, 34.05, 33.68, 31.90, 31.36, 29.79, 29.75, 29.68, 29.64, 29.34, 28.03, 27.51, 23.78, 23.10, 22.67, 14.10; HRMS for $C_{19}H_{37}NO$ calc 295.2875, found 295.2873.
9. **4b**: ^{1}H NMR ($CDCl_3$) 3.30(ddd, J=11.3 8.8, 4.6Hz, 1H), 2.84(dm, J=10.2 Hz, 1H), 2.75(dm, J=11.3 Hz, 1H), 2.17(dq, J= 12.4, 2.8 Hz, 1H), 2.11-1.98(m, 2H), 1.91-1.81(m, 1H), 1.81-1.54(m, 4H), 1.29(s, 3H), 1.36-1.11(m, 20H), 0.87(t, J=6.4 Hz, 3H); ^{13}C NMR (CDCl3) 72.76, 68.66, 62.33, 55.81, 35.90, 34.60, 33.92, 31.90, 30.92, 29.83, 29.64, 29.60, 29.33, 28.70, 26.69, 23.34, 22.67, 14.11; HRMS for $C_{19}H_{37}NO$ calc 295.2875, found 295.2863.
10. All compounds gave satisfactory ^{1}H, ^{13}C and HRMS or combustion analysis.
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