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GONIOTHALENOL: A NOVEL, BIOACTIVE, TETRAHYDROFURANO-2-PYRONE FROM GONIOTHALAMUS GIGANTEUS (ANNONACEAE)

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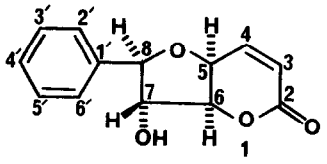
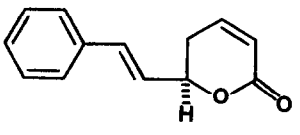
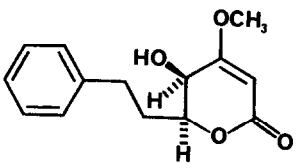
Summary: Fractionation of the stem bark of the title plant, monitoring for bioactivity with brine shrimp lethality, led to the isolation of goniothalenol (**I**). Mass, ^{1}HNMR and ^{13}CNMR spectral data helped to characterize **I** as a phenyltetrahydrofurano-2-pyrone, a novel heterocyclic ring system for natural compounds. X-Ray crystallographic analysis confirmed the structure and established the configuration for **I**.

The ethanolic extract of the stem bark (1.2 kg) of Goniothalamus giganteus Hook. fil. & Thomas (Annonaceae) was very toxic to mice during the P388 *in vivo* antileukemic screen.[2] The ethanolic residue was partitioned between water and dichloromethane, and the dichloromethane residue was partitioned between hexane and 90% aqueous methanol. A portion of the aqueous methanol residue (5.09 g, toxic at 6.25 mg/kg) was chromatographed over 600 g of silica gel 60 using a gradient of ethyl acetate in benzene. Similar 50 ml-fractions were pooled after thin-layer chromatographic (TLC) analyses (chloroform/methanol, 9:1, on silica gel), and the pools were subjected to a simple bioassay for lethality to brine shrimp (BS), Artemia salina (Leach).[3] Certain pooled fractions were among those that were significantly toxic (BS LC_{50} < 600 ug/ml); trituration of these fractions with benzene left a white residue of goniothalenol (**I**); column chromatography of the benzene washings and the following column fraction (silica gel 60, gradient of methanol in chloroform) yielded additional **I**: total 1.48 g (0.43% yield), BS LC_{50} 234 ug/ml, 9KB cytotoxicity ED_{50} 2 ug/ml, P388 toxic at 45 mg/kg and 118% T/C at 25 mg/kg. A bioactive styryl-2-pyrone, named goniothalamin (**II**), has been found previously in other species





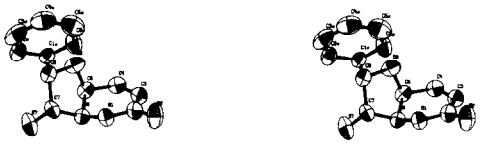


I **II** **III**

in this genus[4] and was isolated from other active chromatographic fractions. Physical and spectral parameters were recorded for **I**[5], and careful study of the ^{1}H and ^{13}CNMR spectra, analysis of chemical shifts[6] and coupling constants[7], and selective ^{1}H-^{1}H, ^{1}H-^{13}C, decoupling experiments resulted in the structural determination. A tetrahydrofurano-2-pyrone ring system is proposed; this carbon skeleton explains the observed signals at 68.1, 86.6, 83.5, and 86.0 ppm, respectively, for carbons 5-8 and for their respective proton signals at 4.64, 4.93, 4.44, and 4.73 ppm. The presence of the conjugated lactone was indicated by ^{13}CNMR signals at 161.8

(C=O), 140.5 (C_4), and 123.5 (C_3) ppm; this postulate was substantiated by the ^{1}HNMR signals at 6.22 (d, H_3) and 6.99 (dd, H_4). ^{13}CNMR signals for aromatic carbons in the region of 126-138 ppm and a multiplet for five aromatic protons at 7.38 ppm in the ^{1}HNMR suggested a phenyl ring at C_8, compatible with a biogenetic origin from styrylpyrones such as **II** and **III**.[8] In order to determine the relative configuration of all asymmetric centers, x-ray analysis of a single crystal, obtained from methanol/benzene, was performed.[9]

A search of the literature reveals that no natural furano-2-pyrones have been previously reported, although a brominated tetrahydrofurano-pyran ring system has been found in the essential oil of a marine plant.[10]



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References and Notes:

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5. Goniothalenol: mp 110°; $[\alpha]^{D}_{25}$ = +184.7° (ethanol); IR ν_{max}^{KBr} cm^{-1} 3400, 2925, 2875, 1700, 1480, 1450, 1350, 1300, 1250, 1150, 1050, 1025, 1000, 875, 810, 740, 690; CIMS m/z 233 (MH^+); EIMS m/z (%): 232 (15), 107 (25), 97 (100), 91 (18); FABMS (high resolution) m/z expt. 233.08167, calc. 233.08139 for $C_{13}H_{12}O_4$+H$^+$; ^{1}H NMR (470 MHz, $CDCl_3$) : 7.38 (5H, m, Ar-H), 6.99 (1H, dd, J = 9.9 and 5.1 Hz, H_4), 6.22 (1H, d, J = 9.9 Hz, H_3), 4.93 (1H, dd, J = 5.1 and 2.5 Hz, H_6), 4.73 (1H, d, J = 5.8 Hz, H_8), 4.64 (1H, t, J = 5.1 Hz, H_5), 4.44 (1H, dd, J = 2.5 and 5.8 Hz, H_7), 4.80 (1H, b, exch. with D_2O, 7-OH); ^{13}C NMR (200 MHz, $CDCl_3$) : 161.8 (C_2), 140.5 (C_4), 138.1 ($C_{1'}$), 128.5 ($C_{3',5'}$), 128.3 ($C_{4'}$), 126.1 ($C_{2',6'}$), 123.5 (C_3), 86.6 (C_6), 86.0 (C_8), 83.5 (C_7), 68.1 (C_5). TLC gives a reddish-brown chromophore with 30% H_2SO_4 in MeOH and heating.
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