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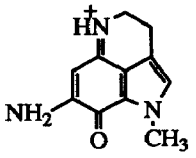
Convenient Syntheses of Pyrroloiminoquinone and its Lexitropsin-linked Derivative

Huiying Wang, Naim H. Al-Said and J. William Lown*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

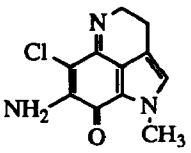
Abstract: The syntheses of 1-4, pyrroloiminoquinone chromophore and its lexitropsin carrier linked derivative designed to improved cellular uptake are described.

Marine natural products have received increasing attention as a source of new and useful anticancer drugs. Recently, a series of publications described a new class of highly cytotoxic pyrroloiminoquinones based on a pyrrolo[4,3,2-de]-quinoline skelecton: makaluvamines, isolated from the Fijian Sponges of the Genus *Zyzzya*,[1] batzellines and isobatzellines, isolated from the Caribbean sponge *Batzella sp.*,[2] damirones, isolated from Pacific sponge *Damiria sp.*,[3] discorhabdins, isolated from New Zealand sponges of the genus *Latrunculia*.[4] The makaluvamines are related structurally to other cytotoxic marine metabolites, that exhibit potent in vitro cytotoxicity toward the human colon tumor cell-line HCT 116, show differential toxicity toward

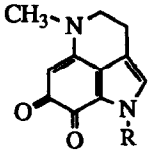


Makaluvamine A

Batzelline C



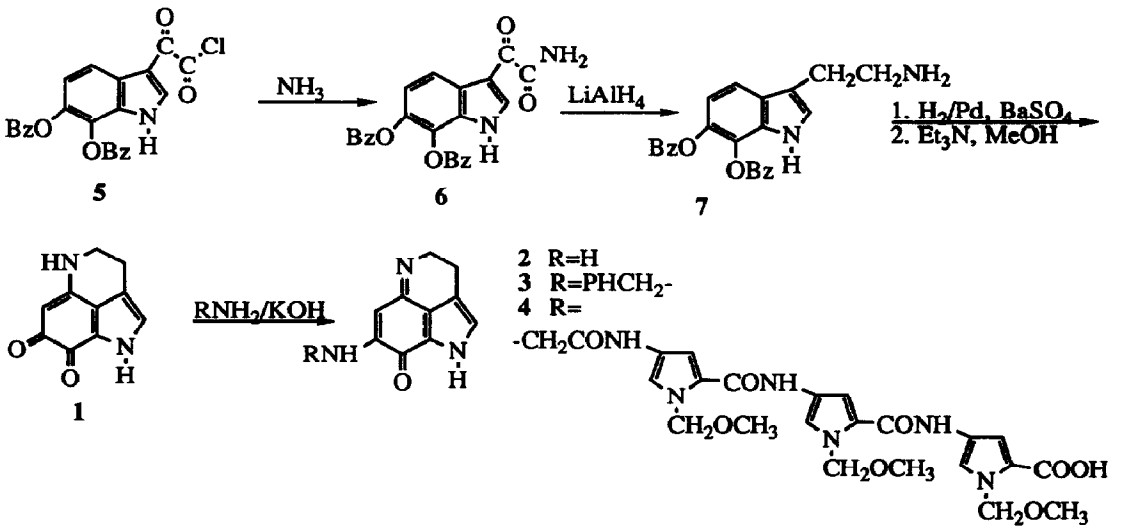
Isobatzelline C



Damirone A R=CH_3
Damirone B R=H

the topoisomerase II sensitive CHO cell line xrs-6, and inhibit topoisomerase II in vitro. This activity may be mediated by intercalation into DNA and/or single-strand breakage.[1,5] Makaluvamine A exhibits in vivo antitumor activity against the human ovarian carcinoma Ovcar3 implanted in athymic mice.[1] In view of its growing importance we report a convenient synthetic route to the pyrroloiminoquinone pharmacophore and of its conjugation to a lexitropsin designed to increase its cellular uptake.[6]

Several studies have been reported on the synthesis of damirones[7] and batzelline C and isobatzelline C.[8] We reported herein a simplified synthesis of pyrrolo[4,3,2-de]-quinoline-7,8-dione **1**, 7-amino-pyrrolo[4,3,2-de]-quinoline-8-one **2** and its derivatives **3-4**. The synthesis started from the known compound 6,7-dibenzyloxyindolyl-3-glyoxylic acid chloride **5**,[9] which was converted to amide **6** by reaction with ammonia in ethyl ether in 70% yield. After reduction with $LiAlH_4$ in THF to yield amine **7** in 60% yield, the benzyl protecting groups were removed by hydrogenolysis. The resulting dihydroxyindole derivative was not stable enough for purification, it underwent oxidative cyclization readily in methanol and triethylamine under air to provide pyrroloiminoquinone chromophore **1**.[10] Coupling of chromophore **1** with RNH_2 was achieved in methanol in the presence of KOH to give, after separation with Sephadex LH-20-100 using water as eluent, the pure compounds **2-4** in 40-50% yield.[10]



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10. For **1**: ^{1}H-NMR(DMSO-d6): δ 12.45(brs, 1H, -NH), 8.53(s, 1H, -NH), 7.09(s, 1H, C_2-H), 5.03(s, 1H, C_6-H), 3.48(t, J=6.8Hz, 2H, C_4-H), 2.72(t, J=6.8Hz, 2H, C_3-H). FT-IR(MeOH cast): 3112, 2920, 1674, 1602, 1537, 1439, 1333, 1292, 1220 cm^{-1}. HRMS m/e 188.0567, $C_{10}H_8N_2O_2$, requires: 188.0585; **2**: ^{1}H-NMR(CD_3OD): δ 6.97(s, 1H, C2-H), 5.23(s, 1H, C_6-H), 3.62(t, J=6.8Hz, 2H, C_4-H), 2.84(t, J=6.8Hz, 2H, C_3-H). HRMS m/e 187.0737, $C_{10}H_9N_3O$, requires: 187.0746; **3**: ^{1}H-NMR(CD_3OD): δ 7.36-7.28(m, 5H, Ar-H), 7.09(s, 1H, C_2-H), 5.49(s, 1H, C_6-H), 4.56(s, 2H, CH_2), 3.82(t, J=6.8Hz, 2H, C_4-H), 2.90(t, J=6.8Hz, 2H, C_3-H). FT-IR(MeOH cast): 3112, 2920, 1674, 1602, 1537, 1439, 1333, 1292, 1220 cm^{-1}. HRMS m/e 275.1056, $C_{17}H_{13}N_3O$, requires: 275.1058; **4**: ^{1}H-NMR(CD_3OD): δ 7.42(d, J=1.5Hz, 1H), 7.36(s, 1H), 7.34(s, 1H), 6.92-6.82(m, 3H), 6.79(d, J=1.5Hz, 1H), 5.57(s, 6H, CH_2), 5.22(s, 1H, C_6-H), 3.65(brs, 2H, CH_2), 3.52(t, J=6.8Hz, 2H, C_4-H), 3.16(s, 9H, CH_3), 2.72(t, J=6.8Hz, 2H, C_3-H).

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