Molbank **2006**, M513 http://www.mdpi.org/molbank/

Synthesis of 1-benzyl-3-chloro-4-(3,4,5-trimethoxyphenyl)azetidin-2-one

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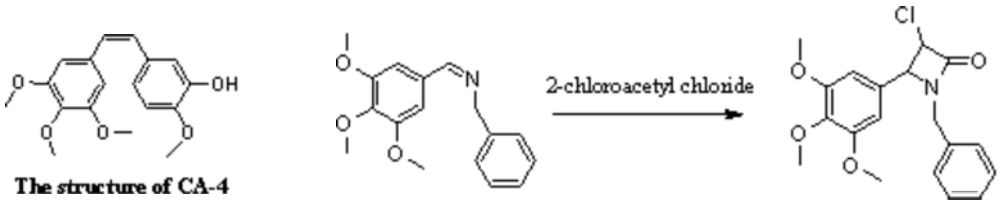
Received: 6 July 2006 / Accepted: 3 August 2006 / Published: 1 December 2006

Keywords: Combretastatin A-4, Synthesis, analogue

Abstract
Combretastatin A-4, isolated from a South African tree Combretum caffrum, is one of the most potent anti-tomour agents. In this paper, an analogue of Combretastatin A-4 was synthesized in order to improve the anti-tumour activity. Compound was characterized by IR and ^{1}HNMR.

Introduction
Cancer is the second major cause of death in the world. Although many researches about cancer all around the world, researchers still have no way to cure for most forms of human cancer. One common characteristic for all types of cancer is the requirement of a suitable blood supply. Tumor vasculature is an important and rapidly emerging target for anticancer therapy. Therefore, vasculature of tumor is nowadays intensively preclinically and clinically investigated as a new potential target for anti-tumor therapeutic strategy. [1-4]

Combretastatin A-4 (CA-4), a natural compound isolated from the bark of the South African bush willow tree *Combretum caffrum* (Combretaceae), is one of the most potent anti-vascular agents. [5] It has also been demonstrated to shut down tumor vasculature rapidly, whereas the blood flow to normal tissues was much less affected. [6-7] CA-4 has received a great deal of attention due to its relatively simple structure, high potency as cytotoxic agents and antivascular activity. A number of CA-4 analogues has been synthesized and evaluated. [6] *β*-lactam is a very useful pharmacophore existed in a lot of drugs and Banik et al. [8] reported synthesis of *β*-lactam analogues entry to novel anticancer agents. In view of these facts, a new analogue of CA-4 is synthesized in this paper. The biological evaluation of the compound would be done quickly.



The structure of CA-4

Experimental
Melting points were uncorrected and were measured with micro-melting point apparatus XT-4. IR spectra (KBr) were obtained on a Thermo Nicolet Nexus 470 FT-IR spectrometer. ^{1}H NMR spectra were determined on a Varian Mecurry 300 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Preparative separations were performed by flash chromatography on silica gel (Qingdao, 200~300mesh).

Phenyl-N-(3,4,5-trimethoxybenzylidene) methanamine (2 g, 7mmol) and triethylamine (3.9ml, 28mmol) dissolved in 50ml anhydrous DCM, and the solution was stirred in an ice-salt bath under argon

atmosphere. The mixture was stirred for a few minutes, and then a solution of 2-chloroacetyl chloride (1.7ml, 21mmol) in 20ml DCM was added dropwise, and the reaction mixture was kept in ice-salt bath stirred 24 hours. Diluted hydrochloric acid was added and stirred 5 minutes, and then washed with 3×30ml saturated $NaHCO_3$, 3×30ml saturated brine, 40×2ml water. The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual was purified by silicon-gel chromatography (25% EtOAC/petroleum ether) to afford the target compound (0.38g, 15%) as a white solid.

Melting Point: 78℃～80℃.

TLC: R_f (silica; ethyl acetate: petroleum ether, 1:2) 0.55.

IR（KBr cm^{-1}): 2996, 2944, 2841, 1694, 1637, 1580, 1462, 1417, 1230, 1020, 764.

^{1}H-NMR (300 MHz, $CDCl_3$): δ= 3.83 (s, 6H, $(OCH_3)_2$). 3.87 (s, 3H, OCH_3). 4.00 (d, H,-CHCl-). 4.33 (s, H,-CH-). 4.55 (s, H,-CH-). 4.76 (d, H,-CH-). 6.38 (s,2H, PhH). 7.15~7.35 (m,5H,PhH).

Acknowledgment
The author is grateful to Professor Xianming Hu of the State Key Laboratory of Virology, College of Pharmacy, Wuhan University for experimental advice.

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