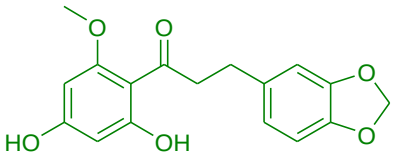
ABSTRACT

Multipronged Search for Pharmacologically Active Compounds: Amazonian Plants, Chalcones, Benzothienopyrimidines and β-Allenyl Esters

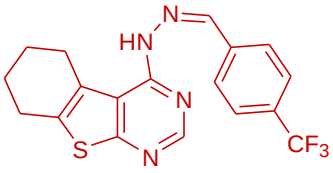
José C. Aponte

Wednesday, December 9th 2009
Chemistry Department, Room LL16, 11:00 am

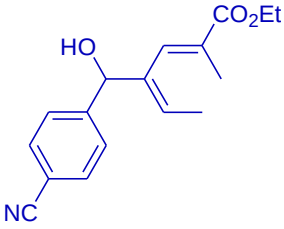
The need to find and develop better, cheaper drugs against cancer and infectious diseases cannot be denied. The use of nature as source of inspiration for chemical diversity and the screening of synthetic libraries are our principal tools in order to find molecules with high activity and high selectivity. Herein, we will present a multipronged approach that involved Peruvian medicinal plants and three different series of synthetic compounds: chalcones, benzothienopyrimidines and (2*E*,4*E*)-4-carbinol alkadienoate



Dihydrochalcone



Benzothienopyrimidine



(2*E*, 4*E*)-4-carbinol Alkadienoate

Plant-based cancer therapies used in traditional medicine are more often than not viewed with skepticism because cancer is likely to be poorly defined in terms of folklore and traditional medicine. Nevertheless, it is significant that over 60% of currently used anticancer agents are derived in one way or another from natural sources. Today, almost 80% of people in developing countries still rely on traditional folk medicine as their primary source of medicinal care. During the past years we have been working on eight different Peruvian medicinal plants, isolating and characterizing their main cytotoxic metabolites and testing them against infectious diseases when possible.

The economical, facile and rapid synthesis of chalcones and benzothienopyrimidines make them attractive as potential drug candidates to fight some of the so-called neglected diseases that affect the populations of many countries in the Third World, chiefly among them, leishmaniasis, Chagas disease and tuberculosis. Chalcones or 1,3-diaryl-2-propen-1-ones, are prominent secondary metabolites precursors of flavonoids and isoflavonoids in plants. Benzothienopyrimidines were chosen after a phenotypic screening of small molecule libraries by high throughput cell imaging. We synthesized series of the natural product analogs and benzothienopyrimidines to explore their pharmacological profile.

Akynylenolates (α-alkynyl enolates) can generate highly functionalized building blocks under mild conditions. The aldol reaction of β-allenoate using a commercial THF solution of tetrabutylammonium fluoride (TBAF) yielded polyfunctionalized (2*E*, 4*E*)-4-carbinol alkadienoate—a valuable building block—in highly regio- and stereoselective fashion. In contrast to metal-mediated reactions, the selectivity of this simple base-promoted reaction is dictated by the fact that it is under thermodynamic control.