

## **Biodiversity conservation and drug discovery in Suriname. Explorations in nature's combinatorial library\***

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*Abstract:* The preservation of tropical rain forests is an important goal both for the intrinsic value of their cultural and biological diversity and for the well-being of the forest peoples who make these forests their home. In addition, tropical forests are potential sources of new pharmaceutical products which can only be found by chemical prospecting in nature's genetically encoded combinatorial library. A collaborative program to discover potential pharmaceuticals in the rain forest of Suriname is described as part of an effort to integrate biodiversity conservation and drug discovery with economic development. Progress on this project will be reported, including results obtained on the isolation of bioactive diterpenoids, quinones, alkaloids, and polyketides, and the benefits of this general approach to biodiversity and drug discovery will be discussed.

### **INTRODUCTION**

The natural products approach to drug discovery has been and continues to be a productive enterprise, as attested to by several recent reviews [1–3]. For this approach to remain effective in the new millennium, access to a diverse source of crude extracts must continue to be available. The greatest source of biological diversity (and thus of chemical diversity) in the plant world is found in the tropical rain forests of the world. As one example, Brazil is believed to be home to some 50 000 plant species, with as many as 20 000 of them being endemic; this amounts to approximately one-sixth of the world's total [4]. Regrettably, this biodiversity is rapidly being lost; Brazil's Cerrado, for example, has been reduced to about 20% of its original primary vegetation [4]. If these trends continue, much of the world's plant biodiversity will be irreversibly lost over the next 50 or so years, with negative consequences not only to drug discovery but also to the animals and human beings who depend on tropical rain forests for their existence.

### **SURINAME ICBG PROGRAM**

Beginning in the late 1980s, it was realized that plant and marine collections around the world would require much more effort than in the past, due largely to the understanding that host countries needed to reap some dividends from the use of their biodiversity. It was also recognized that conservation and economic development efforts really needed to go hand in hand with drug discovery work. A consortium of U.S. government agencies thus agreed to collaborate in the establishment of International Cooperative Biodiversity Groups (ICBGs), and five such groups were funded in 1993 after a careful

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evaluation of competing proposals. The Suriname ICBG was one of those funded, and it began work in the Fall of 1993.

The Suriname ICBG was established as a partnership between Virginia Polytechnic Institute and State University (VPISU) as the lead organization and Missouri Botanical Garden, Conservation International, Bristol-Myers Squibb Pharmaceutical Research Institute, and Bedrijf Geneesmiddelen Voorziening Suriname (the Suriname Drug Company). Its goals were to integrate the process of drug discovery from Surinamese plants with biodiversity conservation and economic development for the overall benefit of the people of Suriname and for the health benefit of the people of the United States. The program has been reviewed in detail elsewhere [5–7].

## **SURINAME**

Suriname is a relatively small country in size and also in population. It has approximately 400 000 inhabitants in an area of 166 000 km<sup>2</sup>, giving it one of the lowest population densities of any tropical country in the world. Most of the population resides along a narrow coastal strip, and the interior is largely uninhabited and covered with undisturbed Neotropical Amazonian forest. Suriname has one of the highest percentages of undisturbed rain forest of any tropical country [8].

The forest peoples of Suriname comprise two distinct ethnic groups, consisting of the native Amerindians and the so-called bushnegroes, who represent the only intact communities descended from runaway slaves remaining in the New World. This unique culture makes Suriname a fascinating place to work from an ethnobotanical point of view.

## **LEGAL AND BENEFIT-SHARING ASPECTS OF THE WORK**

The Rio Convention on Biodiversity stipulates that access to a country's genetic resources is under the control of the government of the country, and this eminently reasonable stipulation meant that the ICBG needed to obtain approval from the central government in Paramaribo for its plant collection work. However, out in the forest the local Granman, or tribal chieftain, has the authority to determine access to plants in the area under his control, and so the ICBG needed to obtain his approval also. Negotiations were initiated with the Granman of the Saramaka tribe, and resulted in the signing of an agreement between him and the ICBG (represented by Conservation International). This agreement included provisions for benefit-sharing with the Saramaka and other tribes through the establishment of a trust fund known as the Forest Peoples' Fund. Initial contributions to this fund came from payments from Bristol-Myers Squibb, and more recently from both Bristol-Myers Squibb and Dow Agrosociences, who joined the ICBG in 1998. A benefit-sharing agreement was also negotiated between the partners to assure payment of appropriate royalties to Suriname in the event of a drug being developed from a Suriname plant collection.

## **PLANT COLLECTION**

Plant collection in Suriname was originally carried out both by Missouri Botanical Garden and by Conservation International, with the former collecting on a botanical basis and the latter collecting on an ethnobotanical basis. Over 2900 plant samples have been collected from over 1000 species, and some 260 plant samples have been recollected for detailed evaluation.

It was initially thought that this dual collecting strategy would give some insight into the relative effectiveness of "botanical" vs. "ethnobotanical" collecting methods. A rigorous comparison was not possible for technical reasons, but a simple comparison using the yeast assay at VPISU as the standard assay indicated that ethnobotanical extracts gave a slightly higher "hit rate" (3.8%) than botanical extracts (2.8%); this difference is probably not statistically significant.

One area where the ethnobotanical approach did prove fruitful, however, was in the identification of antimalarial extracts. This is not surprising, since malaria can readily be identified by the shamans, and the bioassay used can be related directly to this disease. In a sample of nine extracts collected on the basis of antimalarial activity, five had  $IC_{50}$  values against the W2 clone of *Plasmodium falciparum* of 10  $\mu\text{g/mL}$  or less, and only one extract was completely inactive. This is a much higher "hit rate" than would be expected for a random collection of plant extracts, and indicates the value of the ethnobotanical approach for certain specific diseases.

## NATURAL PRODUCTS CHEMISTRY

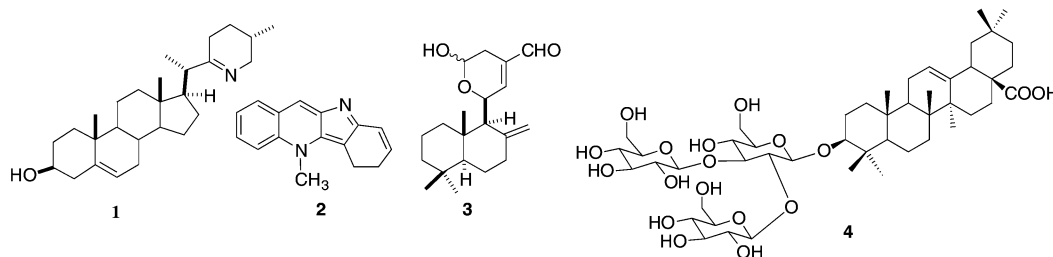
The major thrust of the work at Virginia Polytechnic Institute and State University has been the isolation and structure elucidation of compounds with potential anticancer activity. The bioassays used until recently were based on the differential growth of DNA repair-proficient and repair-deficient yeast cells [9] with an additional cell line being used for the detection of cytotoxic agents [10]. Recently, the mammalian A2780 cell line has been used to detect cytotoxic agents.

### Isolation and structure elucidation

To date we have isolated over 50 active compounds from Suriname extracts, with 23 of them being new to Nature. A selection of these compounds is described below.

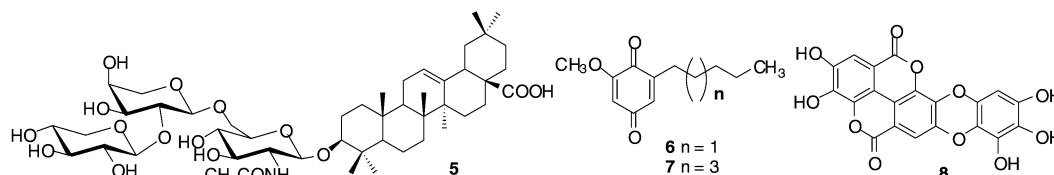
#### Alkaloids

Six new analogs of verazine (**1**) were isolated from *Solanum surinamense* (previously identified as *Eclipta alba*) [9]. The known alkaloid cryptolepine (**2**) was isolated from *Microphilis guyanensis*, and a number of analogs were prepared in an SAR study [11].



#### Terpenes

The new labdane diterpenoid **3** was isolated from *Renalmia alpinia*, and its stereochemistry was determined by a combination of CD, NOESY, and Mosher ester studies [10]. Studies of *Swartzia schomburgkii* yielded a group of six triterpenoid glycosides of which compound **4** is one example [12]. Studies of *Albizia subdimidiata* and a *Pithecellobium* sp. have also yielded several additional triterpenoid glycosides such as the aminoglycoside **5** [13].



### Polyketides

Studies of *Miconia lepidota* gave the bioactive benzoquinones **6** and **7** as the major active constituents, and an SAR study indicated that the cytotoxicity of the quinones increased to some extent with chain length of the alkyl side chain [14]. The structure of ellagic acid derivative **8** was assigned by a combination of chemical derivatization and NOE spectroscopy [15].

## BIODIVERSITY CONSERVATION

Although the work described above has yet to yield a new drug, the Suriname ICBG has already played a part in one significant conservation development. Conservation International worked closely with the government of Suriname in the establishment of the Central Suriname Nature Reserve. This reserve links three smaller protected areas in the center of Suriname into one contiguous area of over 1.6 million ha, and a part of the justification for establishing this reserve was to provide a sustainable source of biodiversity for future drug discovery.

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