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Biodiversity conservation and drug discovery: Can they be combined? The Suriname and Madagascar experiences

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Abstract

The approach to new drugs through natural products has proved to be the single most successful strategy for the discovery of new drugs, but in recent years its use has been deemphasized by many pharmaceutical companies in favor of approaches based on combinatorial chemistry and genomics, among others.

Drug discovery from natural sources requires continued access to plant, marine, and microbial biomass, and so the preservation of tropical rainforests is an important part of our drug discovery program. Sadly, many of the tropical forests of the world are under severe environmental pressure, and deforestation is a serious problem in most tropical countries. One way to combat this loss is to demonstrate their value as potential sources of new pharmaceutical or agrochemical products.

As part of an effort to integrate biodiversity conservation and drug discovery with economic development, we initiated an International Cooperative biodiversity Group (ICBG) to discover potential pharmaceuticals from the plant biodiversity of Suriname and Madagascar. The Group, established with funding from agencies of the United States government, involved participants from the USA, Suriname, and Madagascar. The basic approach was to search for bioactive plants in the Suriname and Malagasy flora, and to isolate their bioactive constituents by the best available methods, but the work included capacity building as well as research. Progress on this project will be reported, drawing on results obtained from the isolation of bioactive natural products from Suriname and Madagascar. The benefits of this general approach to biodiversity and drug discovery will also be discussed.

Keywords

Suriname; Madagascar; biodiversity conservation; bioactive compounds; alkaloids; cardenolides; terpenoids; marine metabolites

Introduction

Humans have depended on nature for their basic needs, including medicines, since the beginning of civilization. Today, natural products are responsible for over one-third of the approved drugs on the market, with 39% of the total drugs approved between 1983 and 1994 in 33 different disease areas being natural products or compounds derived from natural products (Cragg et al., 1997). Of the 1184 new chemical entities for all diseases worldwide approved

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between January 1981 and June 2006, 28% were natural products or derived from natural products, while 24% were synthesized using natural product scaffolds (Newman & Cragg, 2007). The use of natural products and natural product scaffolds to produce compounds with therapeutic potential has been described recently (Newman, 2008).

Plants have formed the basis of traditional medicine systems that have been in existence for thousands of years (Cragg & Newman, 2001). The plant-based systems continue to play an essential role in health care, and it has been estimated by the World Health Organization that approximately 80% of the world's inhabitants rely predominantly on traditional medicines for their primary health care. Plant products also play an important role in the health care system of the remaining 20% of the population, who mainly reside in developed countries (Cragg & Newman, 2005a). Of 119 drugs derived from 90 plants, 74% were discovered as a result of chemical studies directed at the isolation of the active substances from plants used in traditional medicine (Cragg & Newman, 2005b).

In 1805, morphine was crystallized from opium (*Papaver somniferum* L., Papaveraceae). Since then, many drugs have been developed from compounds obtained from plants (Figure 1). For example, the anti-malarial drugs quinine and artemisinin were isolated from the bark of the South American cinchona tree *Cinchona officinalis* L. (Rubiaceae) and the Chinese herb *Artemisia annua* L. (Asteraceae), respectively. The cardenolide digitoxin was obtained from the leaves of foxglove, *Digitalis purpurea* L. (Scrophulariaceae), a biennial herb that is widely distributed throughout Europe and common in England. The antihypertensive indole alkaloid drug reserpine, was isolated from the dried root of Indian snakeroot, *Rauvolfia serpentina* (L.) Benth. ex Kurz (Apocynaceae). Physostigmine, which is used for memory enhancement, was obtained from the west African plant *Physostigma venenosum* Balf. f. (Fabaceae). The Pacific Yew *Taxus brevifolia* Nutt. (Taxaceae), native to the Pacific Northwest of North America, and the Canada Yew *Taxus canadensis* Marshall are the sources of paclitaxel, a chemotherapeutic drug used in breast and lung cancer treatment. Despite its potent bioactivity, natural products such as paclitaxel could never be prepared by standard "medicinal chemistry" approaches to drug discovery, even including the newer methods of combinatorial chemistry (Kingston et al., 2000).

Well over 50% of the estimated 250,000 plant species found on earth come from tropical forests, which cover less than 7% of the earth's land surface. The majority of these tropical plants have not been studied for their chemical and biological properties. Unfortunately, tropical forests have been disappearing rapidly, and they have been reduced from about 16% of the earth's land surface in 1950 to a mere 7% today (Kingston, 2002). The loss of tropical rainforests results in a catastrophic reduction of biodiversity.

Marine natural products have also attracted the attention of biologists and chemists the world over for the past five decades. This interest has led to the discovery of almost 8,500 marine natural products to date, and many of the compounds have shown very promising biological activity (Bhakuni et al., 2005) (Figure 2). The first drug directly derived from a marine source, namely ecteinascidin 743 (Yondelis®) has been granted Orphan Drug designation in Europe and the USA, and was recommended for approval by the EMEA in late July, 2007, for the treatment of soft tissue sarcomas (STS). There are also significant numbers of very interesting molecules that have come from marine sources, or have been synthesized as a result of knowledge gained from a prototypical compound, that are either in or approaching Phase II/III clinical trials in cancer, analgesia, allergy, and cognitive diseases (Newman & Cragg, 2004).

E7389 (Eribulin) is a simplified analog of halichondrin B which has been prepared by total synthesis; it is an inhibitor of tubulin assembly and is in Phase I and II clinical trials (Dabydeen

et al., 2006, Newman, 2007). Dolastatin 10, a linear peptide, from *Dolabella auricularia* Lightfoot (syn.: *Symploca* sp.) (Aplysiidae) (mollusc/cyanobacterium), strongly affected microtubule assembly and tubulin-dependent guanosine triphosphate hydrolysis. TZT-1027, which is now in clinical trial, was designed with the goal of maintaining the potent antitumor activity while reducing the toxicity of the parent compound, dolastatin 10 (Simmons et al., 2005). Bryostatin 1, a macrocyclic lactone, from *Bugula neritina* L. (Bugulidae) (bryozoan), is a potent activator of protein kinase C (PKC) (Simmons et al., 2005). Discodermolide, isolated in 1990 from the Caribbean marine sponge *Discodermia dissoluta* Schmidt (Discodermiidae), has been shown to inhibit the proliferation of human cells by arresting the cell cycle in G2- and M-phase. It hyper-stabilizes microtubules, especially prevalent during cell division, and competes with paclitaxel for microtubule binding, but with higher affinity (Klein et al., 2005). The ocean is thus also an excellent source of potential drugs.

Plant Collection and Biodiversity Conservation in Suriname and Madagascar

Background

The preceding discussion has highlighted the importance of natural products in drug discovery and development. It goes without saying that continuing natural products-based drug discovery requires access to a high degree of biodiversity, including tropical forests and reefs. Sadly, these parts of our world are under threat from deforestation, pollution, and a host of other pressures, many of them related to poverty. Drug discovery thus needs to be coupled with conservation and economic development to ensure continuing access to the necessary biodiversity for future generations. As part of an effort to integrate biodiversity conservation and drug discovery with economic development, we initiated an International Cooperative Biodiversity Group (ICBG) to discover potential pharmaceuticals from the plant biodiversity of Suriname and Madagascar. Early results from the work in Suriname have been summarized previously (Kingston et al. 1999), and this report summarizes work since then.

Why Suriname and Madagascar?

Suriname is located in the shoulder of South America, sharing borders with the Atlantic Ocean to the north, Guyana to the east, Brazil to the south, and the French Guiana to the west. Its surface area of 163,820 km² makes it one of the smaller states within the continent. Suriname has a large area of undisturbed Neotropical Amazonian forest. The interior of Suriname, with an area of approximately 150,000 square km, is largely uninhabited and covered with undisturbed Neotropical Amazonian forest, making Suriname one of the largest places anywhere for conservation of this biome (Schulz et al., 1977). Although some logging has occurred in the interior in recent years, this has so far been of limited scope, and Suriname remains a prime site for conservation efforts. It is listed as a “Group 2” country by the World Conservation Monitoring Centre, which places it in the top 50 countries in the world in richness of biodiversity, but not in the top 25 (Caldecott et al., 1994). Suriname also has a diverse flora. It is estimated to contain approximately 5,000 species of plants, and it has a higher percentage of intact, close-cover forest remaining than any other South American country (Mittermeier et al., 1990). The culture of Suriname is very different from the rest of South America, with both native Amerindian and Bushnegro populations in the interior and a blend of Creoles, Hindustanis, Javanese, Chinese, and Europeans in the coastal region. Finally, Suriname is politically stable. In contrast to some tropical countries with a rich biodiversity, Suriname has had a stable democratic government for the last several years, and recently held peaceful elections for the election of a new government.

Madagascar is perhaps the number one conservation priority in the world. It is one of the highest priority Biodiversity Hotspots (Anonymous, 1997), and one of only a handful that qualifies both as a hotspot and a mega-diversity country. The fourth largest island on Earth and the

largest oceanic island, it is about the size of France, covering 587,045 km² or 0.4% of the planet's land surface. In spite of being located only 400 km from the eastern coast of Africa, Madagascar (another piece of the supercontinent Gondwanaland) has been isolated from other land masses for more than 160 million years. Consequently, most of the plants and animals species found here evolved apart from the rest of the world and are unique to the island. The high endemism that has resulted is not just at the species level, but at the generic and family levels as well. In many respects, Madagascar is biologically a mini-continent, with levels of endemism that few other countries can match and with very high diversity in certain groups of organisms, especially given its relatively small size (Kingston, 2002). Madagascar is home to as many as 12,000 plant species, 70–80% of which are endemic. By comparison, perhaps 30,000–35,000 species occur in all of tropical Africa including the Sahel, which covers almost 35 times as much area. However, from 1950 to 1985, one half of Madagascar's forests disappeared, and in 1985 only 34% of the original forests existing in Madagascar remained. Hence, work is urgent there. As the poorest country that is both a Biodiversity Hotspot and in the top 25 countries in terms of biodiversity (Caldecott et al., 1994), and a country with a very poorly known flora, Madagascar thus was an ideal opportunity for implementation of the goals of the ICBG program.

Suriname and Madagascar ICBG consortium partners and their roles

The research consortium consists of USA-based groups from the Missouri Botanical Garden, who carry out plant collection work, Conservation International, who focus on conservation and economic development work as well as plant collection in Suriname, and Virginia Polytechnic Institute and State University (VPISU). In addition to these groups, in-country teams from Bedrijf Geneesmiddelen Voorziening Suriname (BGVS) in Suriname and Centre National d'Application et des Recherches Pharmaceutiques (CNARP) in Madagascar play key roles in coordinating the in-country work and preparing extracts for study. Finally, groups from Bristol-Myers Squibb Pharmaceutical Research Institute (BMS, 1993–2002), Eisai Research Institute (ERI, 2003–present), and Dow Agro Sciences (DAS, 1998–present) carried out screening and isolation studies on extracts of interest to them.

Plant collection in Madagascar and Suriname

In Madagascar the basic procedure was for plant collections to be made by a team from the Missouri Botanical Garden, and for these collections to be ground and extracted with an ethanol/chloroform mixture by scientists at CNARP. The dried extracts were then shipped to VPISU, where they were bioassayed using either a yeast-based screen for DNA-damaging agents or a mammalian antiproliferative assay using the A2780 human ovarian cancer cell line. The collections were all made around the Zahamena protected area, which involved a challenging hike into and out of the collecting area (Kingston, 2002).

In Suriname the process was a little different, since collections were made both by Conservation International (CI) and by Missouri Botanical Garden (MBG). The CI team collected on an ethnomedical basis, after extensive discussions with the tribal healer of the village involved. The MBG team, on the other hand, collected on a botanical basis, which led to some overlap of the collections (Kingston, 2002).

Biodiversity conservation in Madagascar and Suriname

Primary responsibility for the biodiversity conservation aspects of this work was assumed by MBG and CI. MBG had the goal of contributing to a comprehensive botanical inventory of Suriname and to preparing inventories of selected areas of Madagascar, while CI focused on strengthening the capabilities to plan and implement sustainable use policies and enhancing the value of biodiversity to local communities through benefit-sharing agreements, educational programs, and other approaches (Kingston et al., 2000). One of the many fruits of the MBG

work in Madagascar has been the publication of guides to the ferns of Zahamena, the nature reserve near the MBG collection sites during the 1998–2003 period (de Rasolohery, 2006).

Bioactive compounds of higher plants from Suriname and Madagascar rainforests and marine metabolites from Madagascar

The major biologically active components isolated from Suriname and Madagascar plants can be classified into (a) alkaloids (b) aromatic compounds (c) cardenolides (d) terpenoids (e) glycosides and (f) marine metabolites.

Alkaloids (Figure 3)

Bioassay-guided fractionation of the methanol extract of the leaves of *Eclipta alba* (L.) Hassk. (Asteraceae) yielded eight steroidal alkaloids (Abdel-Kader et al., 1998). Verazine was active with an IC_{12} value of 0.38 μ M; IC_{12} is the concentration required to inhibit the growth of a microorganism in a 12 mm diameter zone. The methanol extract of *Micropholis guyanensis* (A. DC.) Pierre (Sapotaceae) and *Genipa americana* L. (Rubiaceae) collected at Asindopo village, Suriname, yielded the known cryptolepine hydrochloride (Yang et al., 1999a). From the aerial parts of *Monnieria trifolia* L. (Rutaceae) from Suriname, ten alkaloids were purified (Cao et al., 2008). Bioassay-guided fractionation of the alkaloid portion of a CH_2Cl_2 -MeOH extract of *Tabernaemontana calcarea* Pichon (Apocynaceae) from Madagascar resulted in the isolation of fifteen alkaloids (Chaturvedula et al., 2003b). Camptothecin and 9-methoxycamptothecin were purified from a *Coffea* spp. (Rubiaceae) from Madagascar. It can be noted, however, that camptothecins have recently been shown to be produced by a fungus designated RJMEF001 isolated from *Nothapodytes foetida* (Wight) Sleumer (Icacaceae), and it is thus very possible that the true source of these alkaloids is a fungal species (Cao et al., 2006a).

Aromatic Compounds (Figure 4)

Several types of aromatic compounds such as quinones, phenols, coumarins, benzophenone derivatives, xanthenes, flavonoids, stilbenes, lignans, etc. have been obtained as the active constituents from Suriname and Madagascar plants. Two benzoquinones were isolated from the leaves of *Miconia lepidota* Schrank & Mart. ex DC. (Melastomataceae) collected in northern Suriname, and a limited SAR study was carried out on these compounds (Gunatilaka et al., 2001). Three alkyl phenolic compounds were isolated after chromatographic separation of the methanol extract of the dried fruits of *Protorhus thouvenotii* Lecomte (Anacardiaceae) from Madagascar (Cao et al., 2004b). Several cytotoxic coumarins and prenylated benzophenones were separated from the bark of *Ochrocarpos punctatus* H. Perrier (Clusiaceae) from Madagascar (Chaturvedula et al., 2002). Guttiferones of *Rheedia calcicola* Jum. & H. Perrier (Clusiaceae) from Madagascar showed mild activity against A2780 human ovarian cancer cell line (Cao et al., 2007a). Two xanthenes were obtained from the Madagascar plant *Terminalia calcicola* H. Perrier (Combretaceae) (Cao et al., 2007b). Rotenolone and rotenone were isolated from the methanol extract of *Mundulea chapelieri* (Baill.) R. Viguier ex Du Puy & Lab (Fabaceae), which was collected from the province of Toamasina in eastern Madagascar (Cao et al., 2004c). From the butanol-soluble portion of an extract of *Sloanea rhodantha* (Baker) Capuron var. *rhodantha* (Elaeocarpaceae) from Madagascar, seven compounds were purified, and five showed weak inhibitory activity against the drug-resistant FCM29 strain of *Plasmodium falciparum* Welch (Cao et al., 2006b). A2780 guided fractionation of an extract of the fruit of *Macaranga alnifolia* Baker (Euphorbiaceae) from Madagascar led to the isolation of four new prenylated stilbenes, schweinfurthins E-H, and the known prenylated stilbene vedelianin. Schweinfurthin E was also tested in the 60-cell human tumor cancer screen at the National Cancer Institute (NCI). The assay measure used by the NCI that most closely corresponds to the IC_{50} values for antiproliferative activity is the

GI₅₀ value, and schweinfurthin E exhibited a mean panel GI₅₀ of 0.19 μ M. All lines of the leukemia subpanel were found to be highly sensitive to schweinfurthin E, while all lines of the ovarian cancer subpanel (OVCAR-3, -4, and -8 and SK-OV-3) were somewhat resistant, with GI₅₀ values averaging 2.2 μ M. This result is somewhat surprising in view of the sensitivity of the A2780 ovarian cancer cell line to schweinfurthin E, but can be explained in part by the fact that the A2780 cell line is a drug-sensitive line (Yoder et al., 2007). A pair of lignans, didymochlaenones A and B, were isolated from a Madagascar fern *Didymochlaena truncatula* (Sw.) J. Sm. (Dryopteridaceae). The optical rotation and circular dichroism spectrum of didymochlaenone B were approximately the opposite of those of didymochlaenone A, indicating that didymochlaenone B most likely has the opposite stereochemistry to that of didymochlaenone A at the 2 and 4 positions. Although it is unusual for a plant to produce two similar compounds with opposite stereochemistry, it is not unprecedented; thus, various *Pinus* sp. (Pinaceae) produce both (+) and (–)- α -pinene, and (+) and (–)-limonene both occur in peppermint (Cao et al., 2006a).

Cardenolides (Figure 5)

Bioassay-guided fractionation of an ethanol extract obtained from the Madagascar plant *Elaeodendron* sp. (Celastraceae) led to the isolation of six cardenolides. Four compounds each with a 1,4-dioxane ring between rings A and A' showed significant antiproliferative activity against A2780 human ovarian cancer cells with IC₅₀ values of 0.019 to 0.19 μ M (Cao et al., 2007c). The ethanol extract of *Strophanthus boivinii* Baill. (Apocynaceae) from the rainforest of Madagascar afforded ten cardenolide glycosides. All compounds were tested against the A2780 human ovarian cancer cell line, and boivinide A was active with an IC₅₀ of 0.17 μ M (Karkare et al., 2007).

Terpenoids – Sesquiterpenoids (Figure 6)

Bioassay-guided fractionation of the EtOAc extract of both *Allamanda cathartica* L. (Apocynaceae) and *Himatanthus fallax* (Mull. Arg.) Plumel (Apocynaceae) from Suriname using the Sc-7 yeast strain resulted in the isolation of the weakly active isoplumericin and plumericin (Abdel-Kader et al., 1997). Continuation of the chemical examination of the bioactive constituents of the wood of *Vepris punctata* (L. Verd.) Mziray (Rutaceae) from Madagascar resulted in the isolation of a new sesquiterpenoid lactone (Chaturvedula et al., 2004). The structure of this new compound was established on the basis of 1D and 2D NMR spectroscopic data interpretation and chemical modifications. All the isolated compounds from *V. punctata* were tested against the A2780 human ovarian cancer cell line; the four sesquiterpenoids showed moderate activity. Bioassay-guided fractionation of the leaf extract of *Vernonia pachyclada* Baker (Asteraceae) from Madagascar led to the isolation of three new sesquiterpene lactones, designated glaucolides K-M. The structures of the new compounds were determined using 1D and 2D NMR spectroscopy, and the structure and stereochemistry of glaucolides K were confirmed by single-crystal X-ray diffraction. Glaucolide K showed moderate activity in the A2780 human ovarian cancer cell line, with an IC₅₀ of 5.8 μ M (Williams et al., 2005).

Terpenoids – Diterpenoids (Figure 7)

The plant *Renealmia alpinia* (Rottb.) Maas (Zingiberaceae) from Suriname was selected for investigation based on its ethnomedical use as a febrifuge, but testing in the yeast Sc-7 assay gave a positive response, indicative of cytotoxic activity. Using this bioassay, the two new labdane diterpenes, 11-hydroxy-8(17), 12(*E*)-labdadien-15,-16-dial 11,15-hemiacetal and 16-oxo-8(17),12(*E*)-labdadien-15-oic acid, and the known diterpene, 8(17),12(*E*)-labdadien-15,16-dial, have been isolated. The absolute configuration of 11-hydroxy-8(17),12(*E*)-labdadien-15,-16-dial 11,15-hemiacetal and 16-oxo-8(17) was established by CD

spectroscopy and by the formation and subsequent NMR analysis of *R*-methoxyphenylacetyl esters. The hemiacetal 11-hydroxy-8(17),12(*E*)-labdadien-15,-16-dial 11,15-hemiacetal and 16-oxo-8(17) was cytotoxic to M109 cells, with an IC₅₀ value of 8.2 μM (Zhou et al., 1997; Yang et al., 1999b). Bioactivity-directed fractionation of a methanol extract of *Hymenaea courbaril* L. (Fabaceae) from Suriname afforded the three new diterpenoids (13*R*)-13-hydroxy-1(10),14-*ent*-halimadien-18-oic acid, (2*S*,13*R*)-2,13-dihydroxy-1(10),-14-*ent*-halimadien-18-oic acid, and (13*R*)-2-oxo-13-hydroxy-1(10),14-*ent*-halimadien-18-oic acid. The configurations of these compounds were determined from X-ray crystallography of (13*R*)-13-hydroxy-1(10),14-*ent*-halimadien-18-oic acid, circular dichroism of (2*S*,13*R*)-2,13-dihydroxy-1(10),-14-*ent*-halimadien-18-oic acid and (13*R*)-2-oxo-13-hydroxy-1(10),14-*ent*-halimadien-18-oic acid, in addition to spectral studies of prepared derivatives. (13*R*)-13-Hydroxy-1(10),14-*ent*-halimadien-18-oic acid exhibited weak activity toward the 1138 mutant yeast strain and the A2780 human ovarian cancer cell line (Abdel-Kader et al., 2002). Bioassay-guided fractionation of the MeOH and EtOAc fractions of extracts of two lianas (*Casimirella* sp., Icacinaceae) collected in Suriname has led to the isolation of five new diterpenoids, humirianthone, 1-hydroxy-humirianthone, 15*R*-humirianthol, patagonol, and patagonal, and the five known diterpenoids. All 10 diterpenoids showed some activity against the A2780 human ovarian cancer cell line. Humirianthol and annonalide were submitted to the NCI for testing in the 60 cell-line screen. With the exception of humirianthone, the other compounds were not isolated in sufficiently large quantities for testing. Only after humirianthol and annonalide were tested was a large enough quantity of humirianthone isolated. The total growth inhibition (TGI) values for humirianthol in the 60 cell lines ranged from >100 to 2.5 μM, and the values for annonalide were between >100 and 4.8 μM (Adou et al., 2005). These values were not sufficiently potent or selective to warrant further investigation. Bioassay-directed fractionation of an extract of the root and bark of *Podocarpus madagascariensis* Baker (Podocarpaceae) resulted in the isolation of a new totarol diterpenoid in addition to the three known cytotoxic diterpenoids 19-hydroxytotarol, totaradiol, and 4β-carboxy-19-nor-totarol (Reynolds et al., 2006). From a CH₂Cl₂/MeOH extract of the bark of *Casearia lucida* Tul (Flacourtiaceae) from Madagascar, 11 new clerodane diterpenes, namely, casearalucins A-K were isolated (Prakash et al., 2002).

Terpenoids – Triterpenoids (Figure 8)

Bioassay-guided fractionation of the methanol extract of *Odontadenia macrantha* (Willd. ex Roem. & Schult.) Markgr. (Apocynaceae) from Suriname afforded a new limonoid, odontadenin A. Odontadenin A was found to be moderately active against A2780 with an IC₅₀ value of 3.2 μM (Chaturvedula et al., 2003a). Bioassay-guided separation of a dichloromethane fraction of *Malleastrum* sp. (Meliaceae) from Madagascar followed by silica gel column chromatography and diol HPLC afforded three new limonoids, malleastrones A–C, respectively. The novel isolates malleastrones A and B displayed antiproliferative activity against a variety of tumor cell lines (A2780, MDA-MB-435 breast cancer cells, HT-29 colon cancer cells, H522-T1 non-small cell cancer cells, and U937 histiocytic lymphoma cells) and exhibited notable IC₅₀ values ranging from 0.19–0.63 μM (Murphy et al., 2008). Five new triterpenoids, acridocarpusic acids A–E were isolated from the cytotoxic MeOH extract obtained from the leaves and flowers of *Acridocarpus vivy* Arènes (Malpighiaceae) collected in Madagascar (Cao et al., 2004a).

Triterpenoid glycosides (saponins) (Figure 9)

Bioassay-guided fractionation of a methanol extract of *Albizia subdimidiata* (Splitg.) Barneby & J.W. Grimes (Fabaceae) from Suriname using the engineered yeast strains 1138, 1140, 1353, and Sc7 of *Saccharomyces cerevisiae* Meyen ex E.C. Hansen (Saccharomycetaceae) as the bioassay tool resulted in the isolation of the two active saponins; one of these, albiziatrioside, is described for the first time. Albiziatrioside was active against these yeast strains with IC₅₀

values ranging from 32.5–37.9 μM (Abdel-Kader et al., 2001). Six saponins were purified from the MeOH extract of *Acacia tenuifolia* (L.) Willd. (Fabaceae), which was collected at Botopasi, Sipaliwini District, Suriname. The new compounds, acaciosides B and C, exhibited weak activity against the engineered yeast strains 1138, 1140, 1353, and Sc7 of *Saccharomyces cerevisiae* (Seo et al., 2002b). The MeOH extract of *Swartzia schomburgkii* Benth. (Fabaceae) from Suriname was tested active against the 1138, 1140, and 1353 assays. Eight saponins, five active and three inactive, were separated, two of which, swartziadioside and swartziatrioside were new. Five showed weak activity in our yeast bioassay, with IC_{50} values in the 0.1–1.5 millimolar range. In a test at Bristol-Myers Squibb using the M-109 cell line, three compounds showed weak activity, with IC_{50} values against the M-109 cell line in the 25–50 μM range (Abdel-Kader et al., 2000). *Polyscias amplifolia* (Baker) Harms (Araliaceae) from Madagascar gave four saponins, two of which were new oleanolic acid saponins. They were active against A2780 with IC_{50} values in the range 6.7 to 10.8 $\mu\text{g/mL}$ (Prakash et al., 2003). A novel triterpenoid saponin, pittoviridoside, which possesses an unusual 2,3,4-trisubstituted glycosidic linkage, has been isolated from *Pittosporum viridiflorum* Sims (Pittosporaceae) from Madagascar using the engineered yeast strains 1138, 1140, 1353, and Sc-7 for bioactivity-guided fractionation. Pittoviridoside showed weak activity (IC_{12} 85, 80, 140, and 100 $\mu\text{g/mL}$) against the 1138, 1140, 1353, and Sc7 strains in our yeast bioassay. In a test using the A2780 human ovarian cancer cell line, it also exhibited weak activity (IC_{50} 7.9 μM) (Seo et al., 2002a). A2780 guided fractionation of an EtOH extract obtained from the roots of the Madagasy plant *Albizia gummifera* (J.F. Gmel.) C.A. Sm. (Fabaceae) led to the isolation of three new cytotoxic oleanane-type triterpenoid saponins, gummiferaosides A–C. The structures of these new compounds were elucidated using 1D and 2D NMR experiments, including 1D TOCSY and HSQC-TOCSY, and mass spectrometry. Gummiferaosides A–C showed activity against the A2780 human ovarian cancer cell line with IC_{50} values of 0.37, 0.70, and 0.26 μM , respectively (Cao et al., 2007d).

Glycoresins from *Ipomoea squamosa* (Figure 10)

The pharmaceutical partner in our International Cooperative Biodiversity Group in Suriname, Bristol-Myers Squibb Pharmaceutical Research Institute, obtained an isolate (BMS-247181) from an *Ipomoea* sp. (Convolvulaceae) from Suriname that exhibited potent *in vitro* activity toward the M109 lung cancer cell line. The compound was identified as a resin glycoside, and a tentative structure was proposed, although the stereochemistry was not determined. BMS-247181 had a maximum UV absorption at 280 nm and a molecular mass of approximately 900 Daltons. A preliminary *in vivo* experiment indicated that it had a narrow therapeutic window, and work on the extract at BMS was discontinued. BMS withdrew from the Suriname ICBG in 2002, and it was subsequently decided to reinvestigate the cytotoxic constituents of *Ipomoea* sp. from Suriname, in the expectation that they might contain additional resin glycosides with potentially improved properties as compared with BMS-247181. The original extract from which BMS-24718 had been isolated was no longer available, but eight *Ipomoea* extracts were available from the National Cancer Institute and two *Ipomoea* extracts were available in-house, including one (E940631) that was a re-collection of the original plant that had furnished the extract provided to BMS. Analysis of all 10 extracts was carried out by LC-MS, using 280 nm as a monitoring wavelength and 800–1000 Da as a scanning range, and E940631 was chosen as the starting material since its LC-MS chromatogram showed peaks that had the same UV pattern and similar MW(s) to BMS-247181. E940631 had an IC_{50} value of 8.0 $\mu\text{g/mL}$ against the A2780 ovarian cancer cell line. The new glycoresins, ipomoeassins A–F, have been isolated from the leaves of *Ipomoea squamosa* Choisy. The structures were elucidated by spectroscopic analyses and chemical transformations. The absolute configurations of C-5 (ipomoeassins C–E) and C-11 (ipomoeassins A and B) were determined by their derivatives with (*R*)- and (*S*)-MPA. All the isolates were active in the A2780 human ovarian cancer cell line assay with an IC_{50} value of 0.5, 0.4, 2.9, 0.035, 3.3, and 0.036 μM ,

respectively. Interestingly, ipomoeassin D, which differs from ipomoeassin C only by an acetyl group, is almost 2 orders of magnitude more cytotoxic than ipomoeassin C, with an IC_{50} value of 35 nM. The fully acetylated derivatives of the five natural products were significantly less active than the ipomoeassins, with IC_{50} values of 15.8 and 19.1 μ M. All this suggests that relatively minor structural variations may make significant differences to activity and possibly other activities also. Ipomoeassin F exhibited potent activity against A2780 human ovarian cancer cell lines with an IC_{50} value of 0.036 μ M, which was much more active than ipomoeassin A (0.5 μ M). Here, we can see again that sometimes a slight modification of the structure will enhance the activity dramatically (Cao et al., 2005, 2007e).

Recently, a concise, flexible, and efficient total synthesis of the cytotoxic resin glycosides, ipomoeassin B and ipomoeassin E, was reported. While the analytical and spectroscopic data of the synthetic material nicely matched those of the natural products, the authors also noticed a previously unrecognized concentration dependence of its 1H NMR spectrum in C_6D_6 (Fuerstner & Nagano, 2007).

Marine metabolites (Figure 11)

The crude extract from the marine tunicate (NB0405-31, *Trididemnum* sp., Didemnidae) had an IC_{50} value of approximately 3.9 μ g/mL in the A2780 antiproliferative assay. Liquid-liquid partitioning of the crude led to a dichloromethane fraction with an IC_{50} value of 0.46 μ g/mL. Column chromatography over RP-C18 yielded two active fractions: 0.17 and 0.46 μ g/mL. These fractions were subjected to RP-C18 HPLC and resulted in the isolation of two known antiproliferative agents, bistramides A and D. Bistramide A has been reported to exhibit antiproliferative activity in the nanomolar range against a number of tumor cell lines *in vitro* (Rizvi et al., 2006), and displayed an IC_{50} value of 0.19 μ M against the A2780 cancer cell line. Previous studies have shown that this marine metabolite exerts its antiproliferative activity by binding directly to monomeric G-actin and depolymerizing filamentous F-actin, an entity essential for cellular division and motility. Further isolation of additional bioactive molecules is currently underway, including a novel bistramide (Murphy et al., 2007, 2009).

Conservation and development advances

The Suriname ICBG played a part in one significant conservation development, the establishment of the Central Suriname Nature Reserve. During the mid 1990's there was pressure on the Government of Suriname to approve logging concessions for much of central Suriname; the award of these concessions would have been devastating to the region and especially to the forest peoples who live there. The Suriname ICBG partner Conservation International worked closely with the government of Suriname to find a creative solution that would yield badly needed revenue while at the same time preserving the forest. The final outcome was the establishment of the Central Suriname Nature Reserve, which links three smaller protected areas in the center of Suriname into one contiguous area of over 1.6 million ha, and Conservation International entered into a 100-year lease of this Reserve. The lease fees provided welcome revenue to the government, and the forest was preserved for posterity; truly a win-win situation. The Suriname ICBG program provided a part of the justification for establishing this reserve, by showing the value of the forest as a sustainable source of biodiversity for future drug discovery (Kingston, 2001).

In addition to the establishment of the Nature Reserve, the Suriname ICBG program provided small but significant economic development opportunities to the forest peoples through a series of micro-loans and grants. The funds for these purposes came from upfront contributions provided by the group's commercial partners BMS and DAS, and the grants and loans were channeled through the Forest Peoples' Fund, administered by representatives of the Suriname people. Conservation International also established a training program for tribal healers, so

that the ethnomedical knowledge would be preserved from the present generation to the next one. In the communities, those participating in the project developed an increased awareness of medicinal plant knowledge. Other tangible benefits of the program include direct and indirect employment, the establishment of popular organizations and micro enterprises, and a noticeable decline in animosity between surrounding communities participating in the project. In addition, inter-country relations were improved as the Chiefs of the Saramaka and Tirio tribes of Suriname visited the King of the Naso-tribe participating in the Panama ICBG. Finally, some impressive petroglyphs were discovered in the Tirio Indigenous community of Kwamalasamutu, and plans for their protection and sustainable development have been prepared.

In Madagascar development work was again coordinated by Conservation International, with the direct assistance of MBG and CNARP. In the first phase of the program (1998–2003) the development work was focused around the Zahamena National Park, where the plant collections took place, and included projects such as construction of a simple bridge over a seasonal river, construction of grain storage buildings, and renovation and equipping of a primary school. Projects in the current phase of the program in the arid north of the country have focused on development of associations for market gardening and farming, building of watering places and wells with more than 2000 beneficiaries, reforestation, and dam construction. Funds for these projects were again provided by the upfront contributions provided by the commercial partners DAS and ERI. In addition, after extensive studies and stakeholder involvement, the beautiful Montagne des Francais was officially awarded the temporary status of a Protected Area, and the Ambodivahibe Bay area was granted temporary status as a new protected area in late 2008. Work is in progress to designate additional areas as Protected Areas.

Other benefits to Madagascar include the establishment of a laboratory at CNARP to carry out bioassays for antimalarial compounds, and training of several Malagasy scientists in botany, microbiology, and chemistry.

Conclusion

The Suriname and Madagascar ICBG programs have achieved many of their objectives. The local people in Suriname and Madagascar have benefited significantly from the ICBG program, as indicated above, and significant portions of the forest cover of both countries have been conserved for future generations to use and enjoy. Although the work described above has yet to yield a new drug, the ipomoeassins from *Ipomoea squamosa* have attracted attention from both the pharmaceutical industry and academia (Fuerstner & Nagano, 2007). *In vitro*, these compounds showed potent activity and good selectivity against various cancer cell lines, but the *in vivo* results did not yet meet the desired expectations. Continued investigation of these compounds is warranted, for past studies have proven that even slight structural modifications may help increase its *in vivo* efficacy, thus making it suitable for further development. In conclusion, it can be stated that the results and the accomplishments of the Suriname and Madagascar ICBG programs have had a significant impact on biodiversity conservation, on the cooperating institutions and the local communities in the host countries, and progress has been made in the discovery of anticancer agents from natural sources.

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Figure 1.
Examples of drugs developed from plants

Figure 2.
Examples of marine natural product drugs.

Verazine from *E. alba*
 $IC_{12} = 0.35 \mu M$ (1138)

Cryptolepine from *M. guyanensis*
 $IC_{50} = 2.6 \mu M$ (1138 yeast strain)

Alkaloid from *E. trifolia*
 $IC_{50} = 35.6 \mu M$ (A2780)

19-*epi*-voacristine from *T. calcarea*
 $IC_{50} = 10.4 \mu M$ (A2780)

Camptothecin from *Coffea* sp.
 $IC_{50} = 0.2 \mu M$ (A2780)

9-Methoxycamptothecin from *Coffea* sp.
 $IC_{50} = 0.05 \mu M$ (A2780)

Figure 3.
Alkaloids.

Figure 4.
Aromatic compounds.

Figure 5.
Cardenolides.

Figure 6.
Terpenoids – Sesquiterpenoids.

Diterpenoid from *R. alpinia*
 IC_{12} = 9.4 μ ML (Sc-7)
 IC_{50} = 8.2 μ M (M109)

Diterpenoid from *H. courbaril*
 IC_{12} = 2.9 mM (1138)
 IC_{50} > 125 μ M (A2780)

Humirianthol from *Casimirella* sp.
 IC_{50} = 3.0 μ M (A2780)

Annonalide from *Casimirella* sp.
 IC_{50} = 3.8 μ M (A2780)

Diterpenoid from *P. madagascariensis*
 IC_{50} = 5.5 ~ 6.4 μ M (A2780)

Diterpenoid from *C. lucida*
 IC_{50} = 7.3 μ M (A2780)

Figure 7.
 Terpenoids – Diterpenoids.

Figure 8.
Terpenoids – Triterpenoids.

Figure 9.
Triterpenoid glycosides (saponins).

Figure 10.
Ipomoeassins A–F

Bistramide A from *Trididemnum* sp.
 IC_{50} : 0.19 μ M (A2780)

Figure 11.
Bistramide A.