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Brazilian phytochemical diversity: bioorganic compounds produced by secondary metabolism as a source of new scientific development, varied industrial applications and to enhance human health and the quality of life*

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Abstract: Brazil is one of the few megadiversity countries in the world but investigations of its flora has revealed only a little of the present phytochemical diversity. The new molecules discovered have substantial scientific, economic and social interest, and may contribute to the development of related disciplines, besides presenting potential industrial applications for the improvement of the health and the quality of life.

INTRODUCTION

Chemistry is a central, useful and creative science, assuming in many aspects the characteristics of an interdisciplinary science, which supplies the essential means and the fundamental language for the correct understanding of other scientific disciplines [1].

Life is in fact based on chemistry. Birth, growth, reproduction, aging, diseases and death depend on chemical transformations executed by the primary and secondary metabolisms of living organisms.

The biosynthetic pathways (shikimic acid, polyketide and terpenoid) involve a relatively small number of bioreactions known to organic chemists: alkylation reactions (nucleophilic substitutions and electrophilic additions), Wagner–Meerwein rearrangements, Aldol and Claisen reactions, Schiff base formation and Mannich reaction, transamination, carboxylation and decarboxylation, oxidation (including Baeyer–Villiger) and reduction reactions, phenolic oxidative coupling and glycosylation reactions [2,3].

Biochemistry investigates the primary metabolism which produces substances thoroughly distributed in the living organisms, e.g. amino acids, proteins, lipids, carbohydrates and nucleic acids.

In Brazil, chemistry of the secondary metabolism is studied by organic chemists, frequently recognized as natural products chemists. The substances produced by the secondary metabolism, e.g. simple benzoic acids, cinnamic acids, coumarins, phenylpropenes, lignans, neolignans, flavonoids, flavolignans, xanthones, alkaloids, anthraquinones, diarylheptanoids and terpenoids are often characteristic of biological groups, such as a family or genus.

SECONDARY METABOLISM AND SCIENTIFIC DEVELOPMENT

Natural product chemistry as defined today involves mainly studies on biosynthesis, isolation, structure determination and investigation on biological properties of secondary metabolites [2,3]. Some of the

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topics investigated by natural product chemists are plant selection and collection, isolation techniques, structure determination, biological evolution, chemical ecology, chemical evolution, biochemical systematics (chemotaxonomy), semisynthesis, dereplication and biosynthesis. Thus, the knowledge of natural product chemistry leads to results, including the discovery of several new organic substances, which are of importance to other disciplines. (a) Botany: utilization of the chemical and biosynthetic knowledge for studying chemical systematics and evolution, as an aid in botanical classification for building modern systems of classification; (b) Ecology: studies on structural variation of secondary metabolites in space (ecogeographical phytochemistry) could convey to the discovery of adaptation mechanisms and coevolution of organisms in their ecosystem and to the knowledge of defense, pollination and dispersion strategies of plant species; (c) Pharmacology: chemical diversity of natural products represent an endless source of potential new leads for drugs and the pharmacological investigation of phytomedicines (ethnopharmacology) is accelerating the development of screening techniques; (d) Biotechnology: phytochemical analysis furnish the background for the selection of plant specimens for micropropagation and for monitoring secondary metabolites produced by cell cultures; (e) and Organic Chemistry: secondary metabolites represent challenges for the discovery of new reagents and synthetic methodologies seeking the preparation of useful products such as insecticides, fungicides, herbicides, human and veterinary medicines and food additives; they also represent the starting material to test reagents and reactions as well new templates for biomimetic synthesis.

The microbial transformations of natural and synthetic substances offer new horizons for structural modifications aiming to several objectives, from introduction of functional groups to molecular rearrangements.

Inorganic elements also carry out important functions in biological systems, contributing for the reception and transport of atmospheric gases, storage of energy, electron transport, osmotic balance, mechanism of activation of the cellular membranes, conformational stability of biomolecules and as reaction centers of enzymes.

Indeed, the study of the vital organic processes (animal and vegetal) needs contributions from diverse disciplines: biology, biochemistry, natural product chemistry, biophysics, physiology, genetic, etc. These joint efforts are specially important for biotechnology, an area of extremely active industrial research, specially in the search of new medicines or in the improvement of existing ones (pharmaceutical industries) and for development of agriculture and animal production. Thus, the interaction of disciplines is essential.

INDUSTRIAL APPLICATIONS—HUMAN HEALTH—QUALITY OF LIFE

The potential of phytochemical diversity for industrial applications was clearly revealed by a recent symposium [4] and a review article [5].

Some citations regarding the biological activity of secondary metabolites, published in the *Journal of Natural Products* and *Phytochemistry*, were reviewed in a recent article, including biological assay systems and types of active compounds (Table 1) [6].

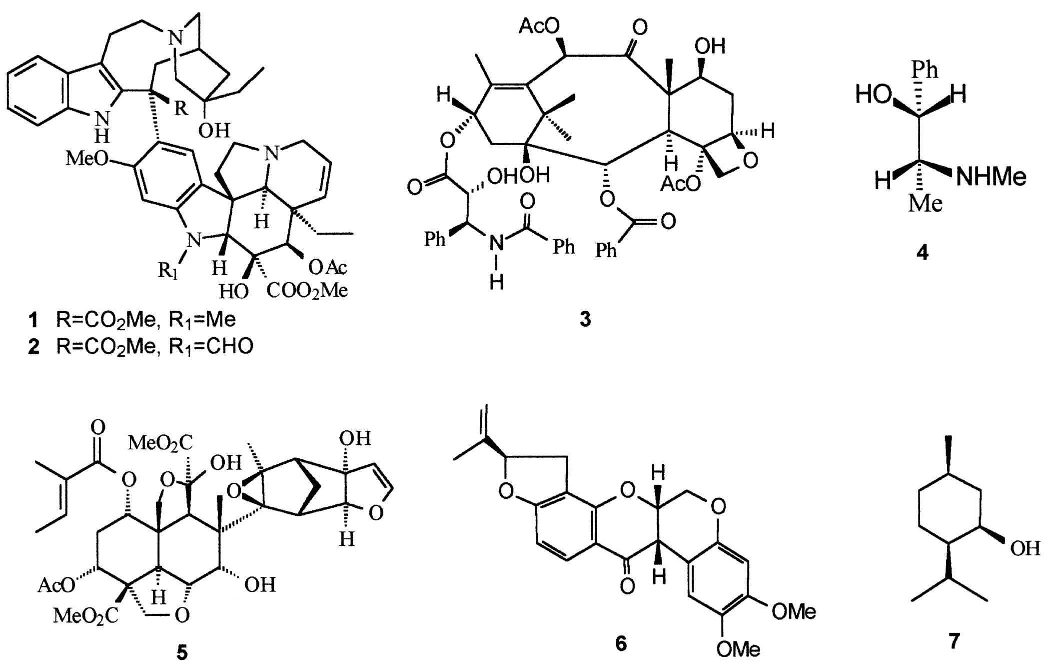
The presence of valuable chemicals in living organisms stimulates the interest of industries in the fields of pharmaceuticals (as drugs sources, e.g. **1–4**), agrochemicals (for the supply of natural fungicides and insecticides, e.g. **5** and **6**), nutrition (for the obtainment of natural substances used for flavoring and coloring foods, e.g. **7** and **8**) and cosmetics (natural fragrances, e.g. **9–11**). Pharmaceutical companies are introducing allopathic medicines at a steadily increasing cost, but in Europe and the USA the demand of natural remedies and cosmetics (Phytopharmaceuticals) is increasing (Schemes 1 and 2). There are 119 allopathic drugs derived from plants with defined structures, which are used universally and only extracted from about 90 species of higher plants.

The sales of the anti-leukemia drugs vimblastine (**1**) and vincristine (**2**), isolated from *Catharantus roseus*, a now pantropical plant originating from Madagascar, reach annual figures of US$200m [7]. Azadirachtin (**5**) is a limonoid commercially extracted from *Azadirachta indica* seeds for use as an agricultural pesticide [3].

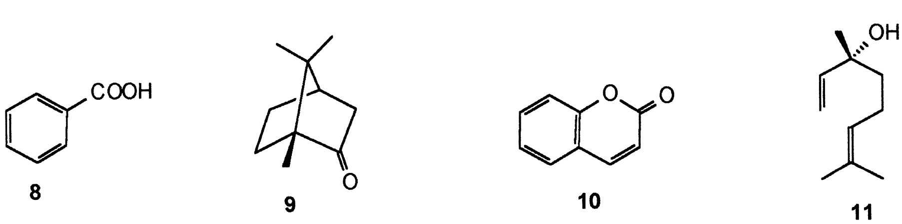
From the top 150 proprietary drugs, based on the number of prescriptions in the USA, 57% had, in

Table 1 Some selected examples of biological activities and type of active compounds described in a recent review [6]

Biological activity	Type of active natural product
Acaricidal	Chromenes
Adenylate cyclase inhibition	Manoyl oxide derivatives
Anti-dust mite	Lanostane triterpenes
Anti-*Encephalomyocarditis*	Flavonoids
Antifungal	Prenyllated isoflavones and flavanones, xanthones, rosmarinic acid
Antihypertensive	7-Oxo-10α-cucurbitadienol
Antiinflammatory	Naphthalene-isoquinoline alkaloids
Antimalarial	Abietane diterpenes
Antimicrobial	Anthraquinones, sesquiterpenes, diterpenes, isoflavans
Antioxidant	Depsides, xanthones
DNA repair in yeast inhibition	Oxo-aporphine alkaloids
Hypolipidemic	Phenolic diarylheptanoids
Insecticidal	Chromenes, furanocoumarins
Leishmanicidal	Flavans, aporphine alkaloids
Oral anti-microbial	Isoflavonoids



Scheme 1



Scheme 2

some way, its origins in biological diversity, including animals, plants, fungi, bacteria, and marine organisms. This offers compelling evidence of the contemporary importance of natural products as pharmaceuticals [8].

BRAZILIAN PHYTOCHEMICAL BIODIVERSITY

In a recent issue of *Ciência e Cultura Journal of the Brazilian Association for the Advancement of Science*, some natural products chemistry research in Brazil was summarized in a series of papers (Table 2) [9–26], reviews [27,28], along with books [29,30] and a phytochemical survey [31].

Table 2 Some natural products chemistry research in Brazil summarized in a series of papers [9–26]

Title	Ref.
Looking at the origins	9
Natural products research in Brazil	10
Marine natural products in Brazil. Part 1. Isolation and structure determination	11
Pyrrolizidine alkaloids: A word of caution	12
The official use of medicinal plants in public health	13
Chemical constituents from Myristicaceae	14
Plants as hypoglycemic agents	15
Saponin from maté (Ilex paraguariensis) and other South American Ilex species: Ten years research on Ilex saponins	16
From a medicinal plant to a pharmaceutical dosage form. A (still) long way for the Brazilian medicinal plants	17
Analogues and prodrugs, permanent useful alternatives to improve the effectiveness of natural anti-cancer compounds: Enhanced activity of slightly soluble salts of olivacine in L_{1210} leukemia	18
Merging ethnopharmacology with chemotaxonomy: An approach to unveil bioactive natural products. The case of Psychotria akaloids as potential analgesics	19
Botanical, chemical and pharmacological investigation on Cissampelos species from Paraiba (Brazil)	20
Brazilian medicinal plants: A rich source of immunomodulatory substances	21
Ethnopharmacology and sustainable development of new plant-derived drugs	22
Living pharmacies	23
New hybrid lines of the anti-malarial species Artemisia annua L. guarantee its growth in Brazil	24
Analgesic and anti-inflammatory screenings of two Brazilian medicinal plants: A positive and a false-positive result	25
The plants of the genus Phyllanthus as a potential source of new drugs	26

It is estimated that there are over two million different species of plants, animals and microorganisms throughout the Brazilian territory. The genetic diversity of plants in Brazil comprises about 55 000 identified species of a total estimated between 350 000 and 500 000. Approximately two-thirds of these species are found in the tropics and about 75% of the Brazilian species are located in two main forest formations: Tropical Atlantic Rainforest and Amazon Forest. Only 8% of the identified plant species were studied to evaluate phytotherapeutic activity of natural products and only 1100 species of plants were extensively studied for medicinal properties [7].

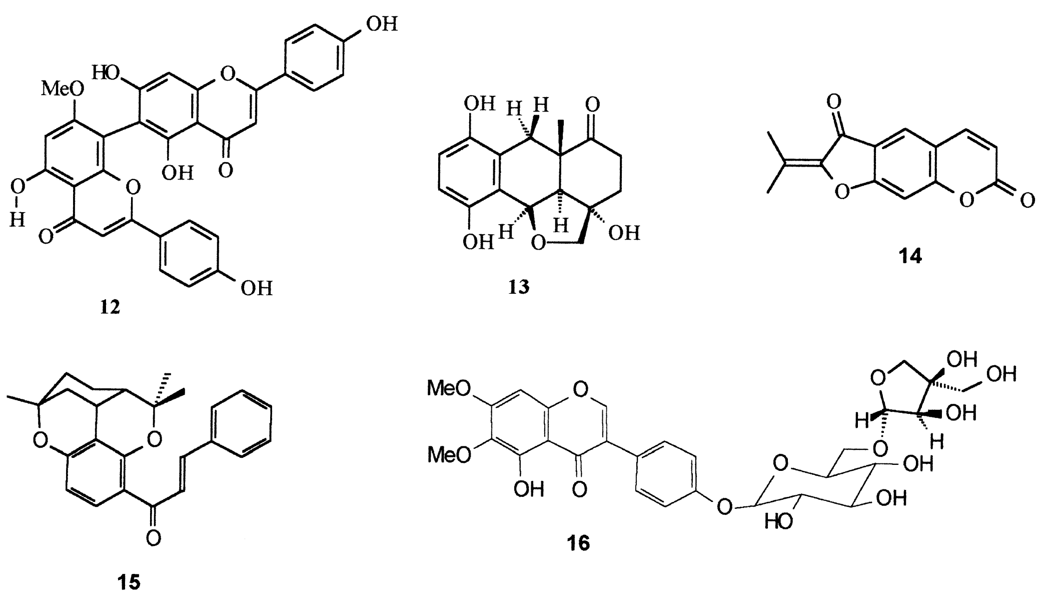
Obviously, the opportunities for identification of products with potential economic and social interest increase with the biodiversity of species, what places Brazil in a privileged situation.

The natural products chemistry research activities in Brazil are historically linked with the formation of human resources, specially at the graduate degree level (Master and Doctorate), contributing significantly to strengthen the teaching and researcher staff of several high education institutions.

Some additional examples from recent natural product chemistry research in Brazil are given. It shows the great phytochemical diversity and some of the potential applications may be also inferred from the informations on Table 1 [6].

The novel natural biflavone **12**, recently isolated from the Brazilian plant *Ouratea hexasperma*, was found to be a potent inhibitor of cellular growth, DNA and protein synthesis using Sarcoma 180 tumour cells [32].

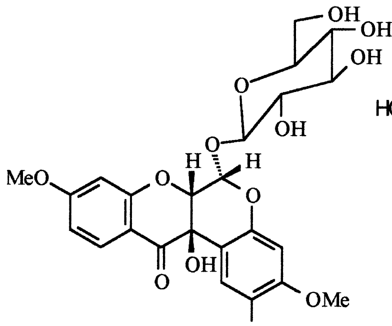
The structural diversity of natural substances isolated from Brazilian plants can be classified on the basis of basic skeletons and biogenetic origin as: benzoates (e.g. **13** isolated from *Auxemma glazioviana* [33]), xanthonoids, coumarinoids (e.g. **14** isolated from *Brosimum gaudichaudii* [34]), cinnamoyl derivatives, γ-lactones, stilbenoids, α-pyranoids, lignoids, chalconoids (e.g. **15** isolated from *Aniba rosaedora* [35]), flavanonoids, flavonoids, virolanoids, isoflavonoids (e.g. **16** isolated from *Dalbergia nigra* [36]), isoflavanonoids, pterocarpanoids, rotenoids (e.g. **17**, isolated from *Clitoria fairchildiana* [37]), isoflavanoids, flavonoid dimers (e.g. **18** isolated from *Magonia glabrata* [38], **19** and **20** isolated from *Myracrodruon urundeuva* [39], **21–23** isolated from *Ouratea hexasperma* [40]), neoflavonoids, phenylalanine alkaloids, triptophan alkaloids, alkaloid dimers (e.g. **24** and **25** isolated from *Tabernaemontana laeta* [41]), anthraquinonoids, sesquiterpenoids (e.g. **26** and **27** isolated from *Wedelia paludosa* [42]), diterpenoids (e.g. **28** isolated from *Vellozia caputadeae* [43] and **29** isolated from *Croton nepetaefolius* [44]), triterpenoids (e.g. **30** isolated from *Lophanthera lactescens* [45], **31** isolated from *Enterolobium contorstisiliquum* [46] and **32** isolated from *Centrosema bracteosum* [47]), polyketides (e.g. **33** isolated from *Rauwolfia mattfeldiana* [48]), diarylheptanoids, quassinoids (e.g. **34** and **35** isolated from *Simaba cuneata* [49]), benzophenones (e.g. **36** (tautomers **36a**, **36b** in $CHCl_3$ or benzene), 15-epiclusianone, isolated from *Rheedia gardneriana* [50–52]), steroids and miscellaneous (Schemes 3–5).



Scheme 3

Harpalyce brasiliana Benth. (Leguminosae-Papilionoideae) is a Brazilian North-eastern shrub, named 'raiz-de-cobra' (snake-root), popularly used for treating snake bites [53]. Two prenylated pterocarpans with anti-snake bite activity, cabenegrins A-I (**37**) and A-II (**38**), were isolated and identified from a locally well known anti-snake bite medicine named 'Específico Pessoa', [54] manufactured and sold in the Brazilian north and north-east, available to plantation workers as an oral anti-dote. The plant commonly known as 'cabeça de negro' which furnishes the extract used in the preparation of this remedy has not been identified so far, being kept as a secret by the manufacturers. There are about 10 plants with the name 'cabeça de negro' in South America. Two plants reputed as anti-snake bite medicine occur in the Ibiapaba region of North-east Brazil: *Bredemeyera floribunda* Willd (Polygalaceae), named 'pacari', and *Harpalyce brasiliana* (Leguminosae-Papilionoideae). The first one afforded the active saponin bredemeyeroside [55].

In a recent paper we report the isolation and characterization of the new isoflavone harpalycin (**39**), the flavonol quercetin (**40**), a prenylated pterocarpan (**41**) and the triterpene betulinic acid (**42**), an anti-HIV



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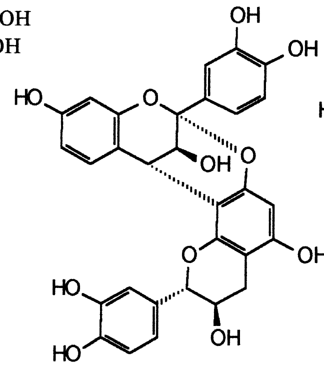

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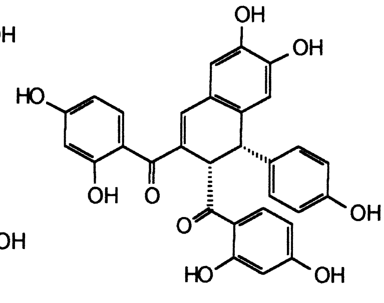

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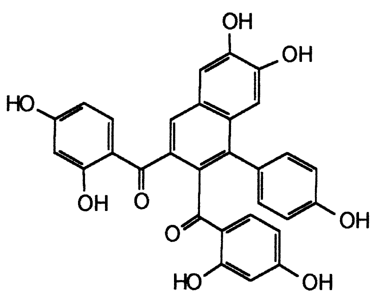

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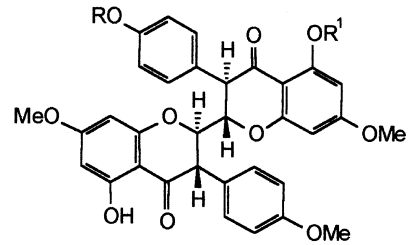
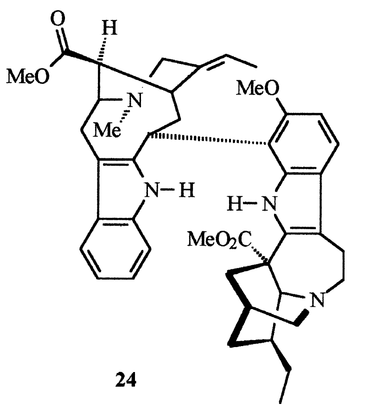


21 R=R[1]=H

22 R=Me, R[1]=H

23 R=H, R[1]=Me



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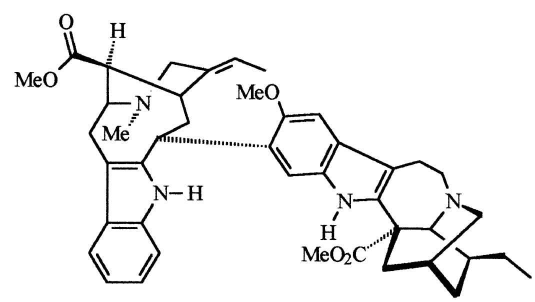

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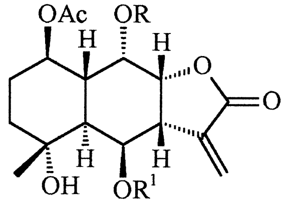
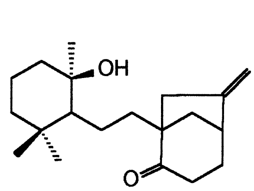


26 R=Ac, R[1]=*iso*-butyroxy

27 R=*iso*-butyroxy, R[1]=Ac



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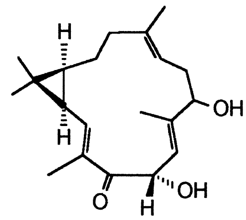

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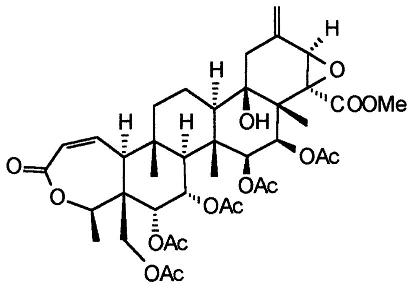
Scheme 4



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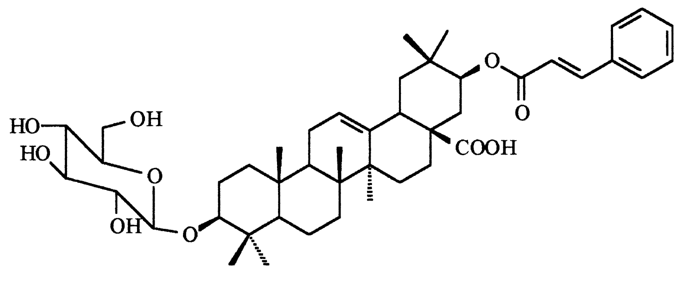

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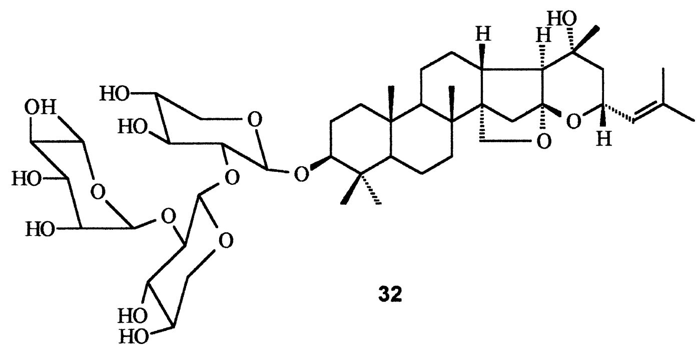

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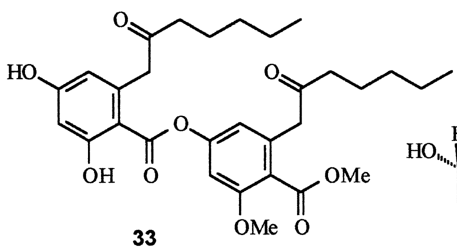

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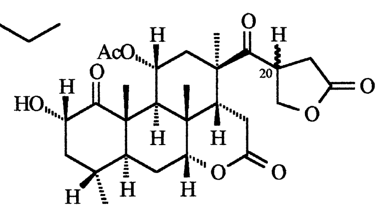
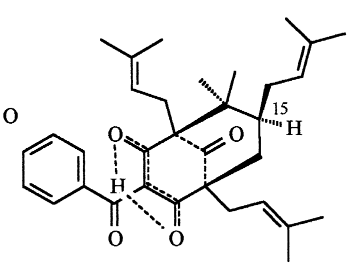


34 20(*R*)
35 20(*S*)



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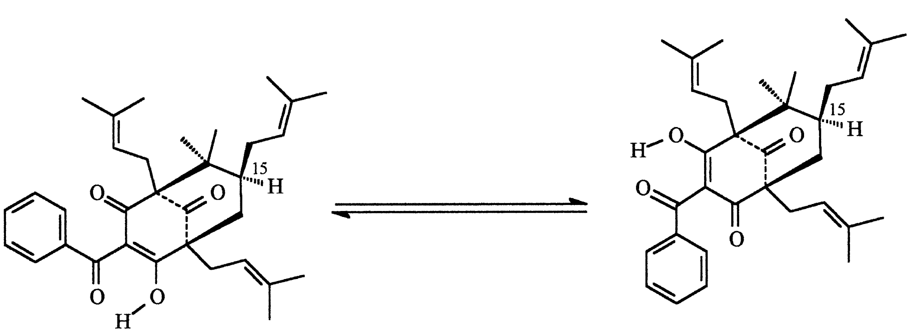
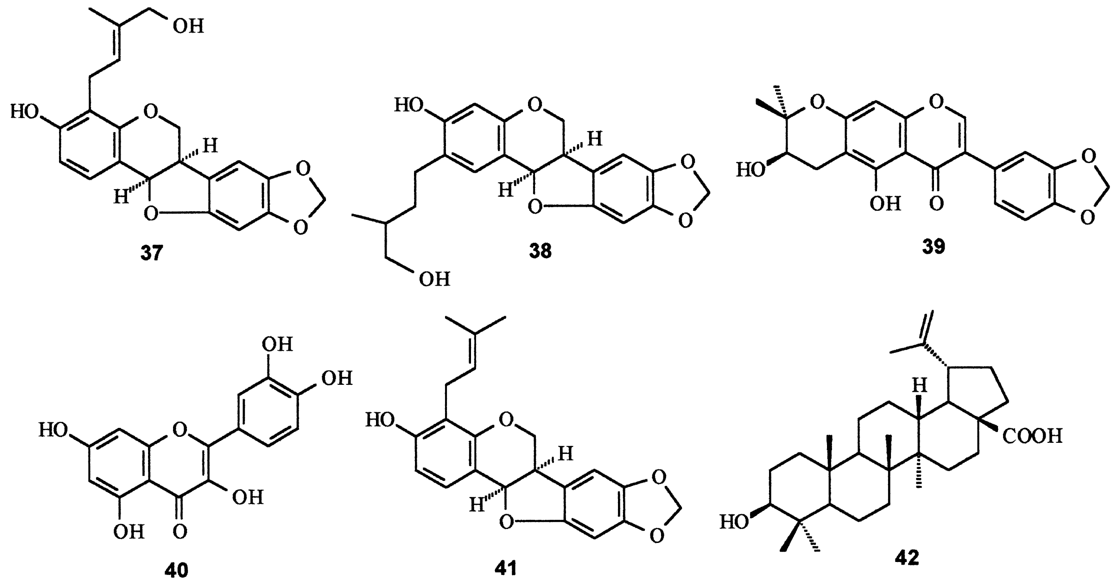


36a **36b**

Scheme 5

agent [57], from leaves and roots of a specimen of *Harpalyce brasiliana* (Scheme 6). There is one previous paper about this plant [58].

The terrestrial and marine living organisms possess largely unexplored chemical mechanisms for communication, adaptation, evolution and construction of ecological niches essential for the coexistence



Scheme 6

of individual species. Plants as living laboratories have the essential conditions for biosynthesis of numerous beneficial substances for the preservation and survival of the mankind and the machinery for bioproduction in amount and quality of compounds to alleviate diseases that continue making fatal victims (cancer, aids, malaria, etc.).

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