

Review

New compounds of natural resources in 2008

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Natural products have been the most productive source of new compounds. Hundreds of new compounds are in development. Some of them have pharmaceutical activities, particularly as anti-cancer and anti-infective agents. Until October, there are 1913 new compounds separated from natural sources in 2008. The compounds have covered a wide range of species, including alkaloids, flavones, terpenoids and so on. It is hoped that more efficient and effective compounds of natural resources will be found in the further discovery process.

Key words: New compounds, natural resources, alkaloids, flavones, terpenoids.

INTRODUCTION

Natural resources have been the deviation of most new organic compounds. This is widely accepted in all ages. More than 80% of drug substances were natural products or inspired by a natural compound (Sneader, 1996). The separation, identification and structure determination of substances has been facilitated by continual development of chromatographic and spectroscopic methods of analysis. Accordingly, the number of compounds isolated is increasing rapidly. The total number of compounds isolated in this year is up to 1913, including alkaloids, flavones, phenylpropa-noids, steroids, terpenoids and other species. Terpenoid is the major part of all these products, the number of which is 750. Alkaloids and flavonoids also make up a large percentage.

Most of the substances are extracted from land plants. There are two other directions, which investigators take to enhancing chemo diversity. One is to seek plants from unusual regions of the world; the second is to examine previously poorly studied sources. Meanwhile certain special compounds are found from marine organisms and microbial metabolites, for example macrolides and poly-peptides from marine sponge. In the microbial area, the main sources are fungi and terrestrial antinomycetes.

A lot of natural products have biological activities, for example, cytotoxicity, antifungal or antibacterial activities.

Plant natural products with anticancer and antimalarial novel compounds with strong efficiency are being well investigated biologically and afforded clinical trials. There will be many promising drug candidates in the current development that are of natural origin.

SPECIES OF NEW COMPOUNDS

Alkaloids

Alkaloids comprise one of the major groups of plant constituents. Several of alkaloids were in clinical use, including reserpine (the first tranquilliser) and the dimeric indole alkaloids vinblastine and vincristine (anticancer agents). In this year, there are 136 new alkaloids isolated from natural resources.

Two new alkaloids, uncaric acid A (Figure 1) and hirsutaside A (Figure 2) were isolated from *Uncaria hirsute* (Xin et al., 2008). Three new Lycopodium alkaloids, lycoparins A-C, have been isolated from the club moss *Lycopodium casuarinoides*. Lycoparins C exhibited an inhibitory activity against acetylcholinesterase, while lycoparins A and B did not show activity (Hirasawa, et al., 2008).

Two new oxindole alkaloids, rankiniridine (Figure 3) and humanteniridine (Figure 4), having a nitrogen-carbon linkage between a humantenine-type monoterpenoid indole alkaloid and a monoterpene unit with an iridoid skeleton, were isolated from *Gelsemium rankinii* and *Gelsemium elegans* (Zhang et al., 2008).

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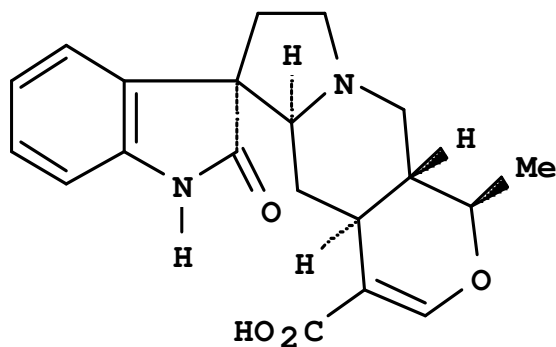


Figure 1. Uncaric acid A.

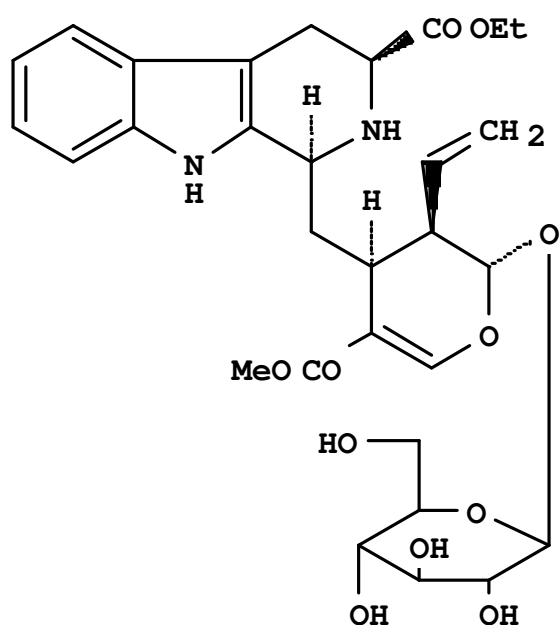


Figure 2. Hirsutaside A.

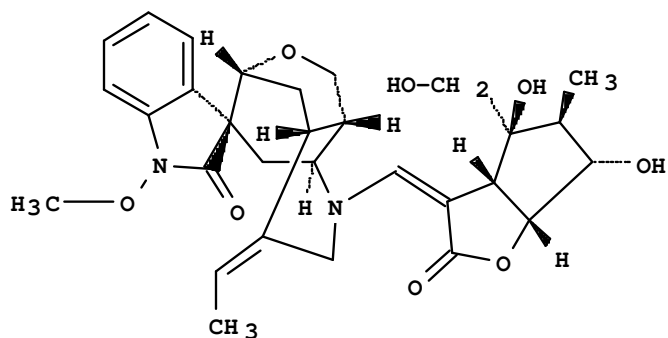


Figure 3. Rankiniridine.

Flavonoids

The fact that flavonoids are ubiquitous in natural systems

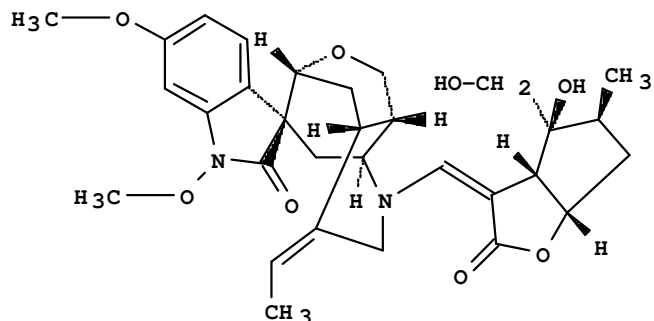


Figure 4. Humanteniridine.

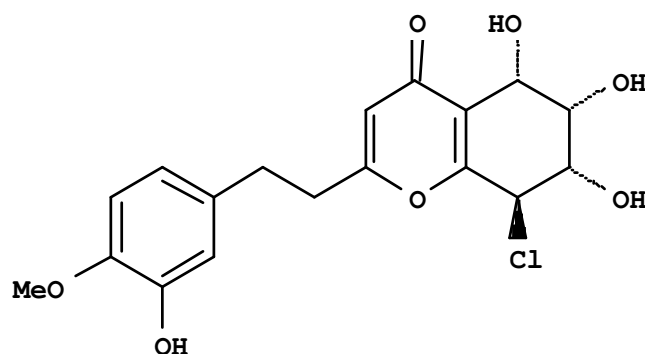


Figure 5. 8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one.

has led to wide-ranging investigations concerning the biological activity of new compounds. It can be divided into subgroups including anthocyanidins, flavonols, flavones, flavanols, flavanones, chalcones, dihydrochalcones and dihydroflavonols. It has been known for some time that flavonoids are often superb anti-oxidants, scavenging potentially hazardous free radicals in animal systems. The number of flavonoids substances found this year is 149.

8-chloro-5,6,7-trihydroxy-2-(3-hydroxy-4-methoxyphenethyl)-5,6,7,8-tetrahydro-4H-chromen-4-one (Figure 5) was isolated from the Chinese eaglewood [*Aquilaria sinensis* (Lour.) Gilg]. This compound showed cytotoxicity against human gastric cancer cell line (SGC-7901) *in vitro* by MTT method with the IC₅₀ value of 14.6 µg/mL (Liu et al., 2008).

High-throughput screening of a plant and marine invertebrate extract library to find natural products that inhibit the malarial parasite enzyme target hemoglobinase II led to the isolation of two new active prenylated chalcones, bipinnatones A and B (Figure 6), from aerial parts of the Queensland shrub *Boronia bipinnata*. Bipinnatones A and B inhibited hemoglobinase II with IC₅₀ values of 64 and 52 µM (Carroll et al., 2008).

A new cytotoxic acylated apigenin glucoside (apigenin-7-O-(6"-butyryl-β-glucopyranoside)) (Figure 7) was isolated from the methanolic extract of the leaves of *Phyllanthus emblica* L. (Euphorbiaceae) together with the

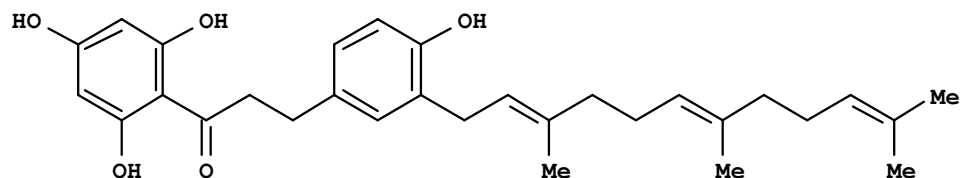


Figure 6. Bipinnatones A.

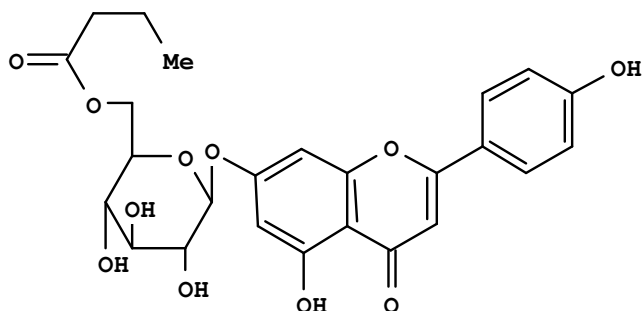


Figure 7. Apigenin-7-O-(6''-butyryl-β-glucopyranoside).

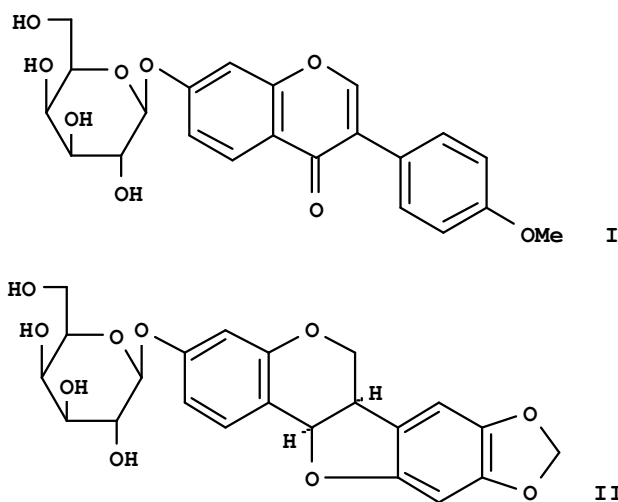


Figure 8. Formononetin-7-O-β-D-galactopyranoside (I) and Inermin-3-O-β-D-galactopyranoside (II).

known compounds: gallic acid, Me gallate, 1,2,3,4,6-penta-O-galloylglucose and luteolin-4'-O-neohesperidoside. Their structures were elucidated on the basis of spectroscopic studies (El-Desouky et al., 2008).

Two new isoflavonoid glycosides formononetin-7-O-β-D-galactopyranoside (Figure 8 I) and inermin-3-O-β-D-galactopyranoside (Figure 8 II) were isolated from *Trifolium pratense* L. roots (Drenin et al., 2008).

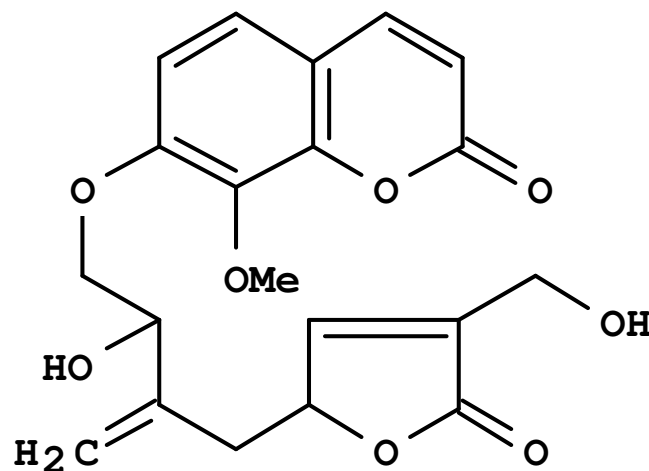


Figure 9. Anisucumarin A.

Phenylpropanoids

Phenylpropanoids are a class of plant-derived organic compounds that are biosynthesized from the amino acid phenylalanine. They have a wide variety of functions, including defense against herbivores, microbial attack or other sources of injury, as structural components of cell walls and pigment. The common types of phenylpropanoids are coumarins, lignans and lignins. The total number of new phenylpropanoid yielded is 112 in 2008.

Two new monoterpenoid coumarins: anisucumarin A and B (Figure 9), a pair of epimers, were isolated from *Clausena anisum-olens* (Wang et al., 2008).

Santolinol (Figure 10), a new lignan, has been isolated from the chloroform fraction of *Salvia santolinifolia* and assigned the structure on the basis of spectral studies including 2D NMR. In addition, three bifuranolignans namely didemethylpinoresinol 2, (+)-fraxiresinol 3 and (+)-1-hydroxysyringaresinol 4 have also been isolated for the first time from this species. All these compounds showed potent inhibitory potential against the enzyme lipoxygenase (Mehmood et al., 2008).

Study on the water solution fraction from the leaves of *Paulownia coreana* led to the isolation of a new phenylpropanoid glycoside, (R,S)-7-hydroxy-7-(3,4-dihydroxyphenyl)-ethyl-O-α-L-rhamnopyranosyl(1→3)-β-d-(6-O-caffeoyl)-glucopyranoside (Figure 11) (Kim et al.,

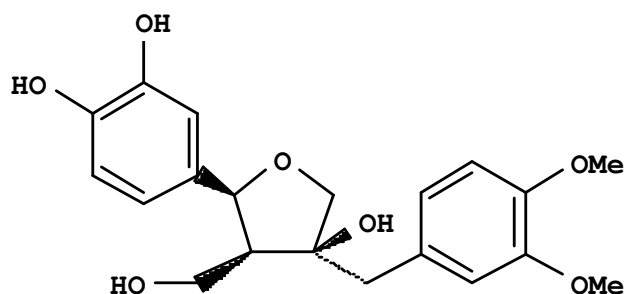


Figure 10. Santolinol.

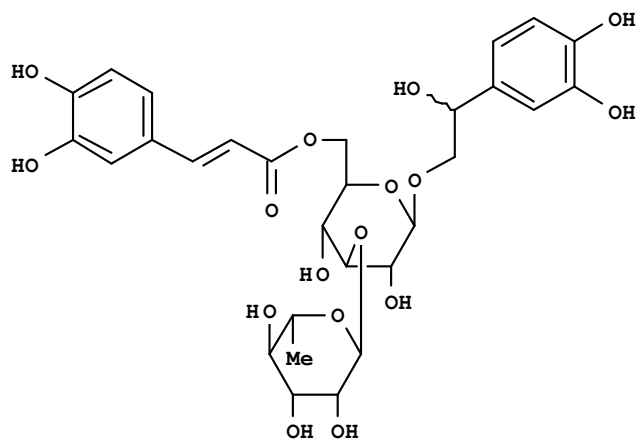


Figure 11. (R,S)-7-hydroxy-7-(3,4-dihydroxyphenyl)-ethyl-O- α -L-rhamnopyranosyl(1 \rightarrow 3)- β -D-(6-O-caffeoyl)-glucopyranoside.

2008).

Five new stilbene oligomers, laetevirenol A-E (Figure 12), were isolated from *Parthenocissus laetevirens*, together with three known stilbene oligomers. Biomimetic transformations revealed a possible biogenetic route, where stilbene trimers were enzymically synthesized for the first time. In addition, their antioxidant activities were evaluated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. The results showed that stilbene oligomers with an unusual phenanthrene moiety exhibited much stronger antioxidant activities. Thus, the photocatalyzed cyclization of stilbenes was supposed to be an antioxidant activity promoting transformation, which was hypothesized to play a role in the antioxidative defense system of the plant (He et al., 2008).

Steroids

In this year, new steroids from natural sources are as many as 104 compounds. Steroids always have a carbon skeleton with four fused rings, generally arranged in a 6-6-6-5 fashion. Steroids vary by the functional groups attached

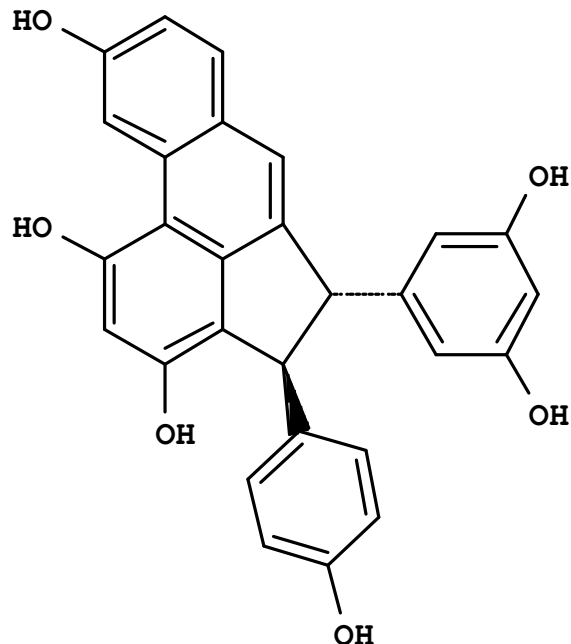


Figure 12. Laetevirenol A.

to these rings and the oxidation state of the rings. Hundreds of distinct steroids are found in plants, animals and fungi. β -sitosterol is the most common steroid found in plants. Some phytosterols have cholesterol-lowering properties (reducing cholesterol absorption in intestines) (Ostlund et al., 2003).

A new pregnane glycoside, 3-O- α -lycotetraosyl 5 β -pregna-3 β , 16 β -diol-20-one (Figure 13) was isolated from overripe tomato, the fruit of *Lycopersicon esculentum* MILL (Nohara et al., 2008).

Five new steroids, griffinisterones A-E (Figure 14), were isolated from the octocoral *Dendronephthya griffini*. The structures of these compounds were elucidated by extensive spectroscopic anal. Griffinisterones C and D were found to significantly inhibit the accumulation of the pro-inflammatory iNOS protein of the LPS-stimulated RAW264.7 macrophage cells (Chao et al., 2008).

Two new steroid glycosides: distolasteroside D6 (Figure 15) and distolasteroside D7, were isolated along with the previously known distolasterosides D1, D2, and D3 and echinasteroside C from the Far Eastern starfish *Distolasterias nipon*. Like neurotrophins, distolasterosides D1, D2, and D3 were shown to induce neuroblast differentiation in a mouse neuroblastoma C1300 cell culture (Kicha et al., 2008).

Terpenoids

The terpenoids are a large and diverse class of naturally-occurring organic chemicals, derived from five-carbon isoprene units assembled in thousands of ways. They play

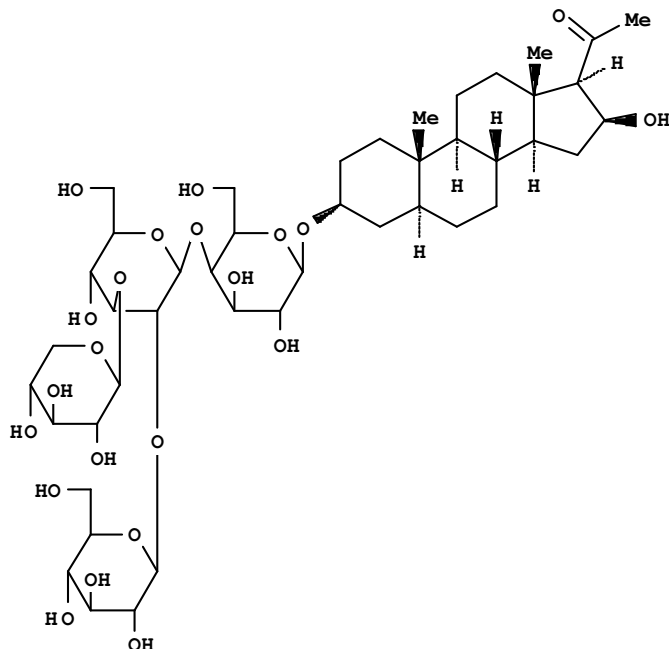


Figure 13. 3-O- α -lycotetraosyl-5 β -pregna-3 β , 16 β -diol-20-one.

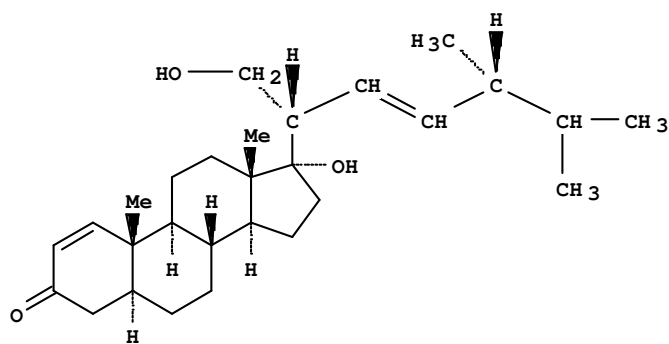


Figure 14. Griffinsteroles A.

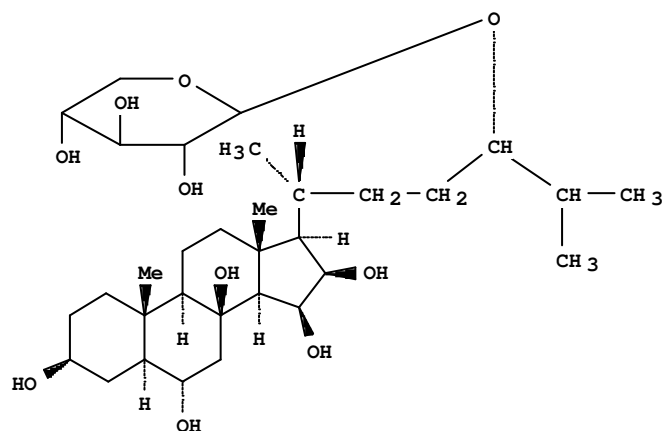


Figure 15. Distolasteroside D6.

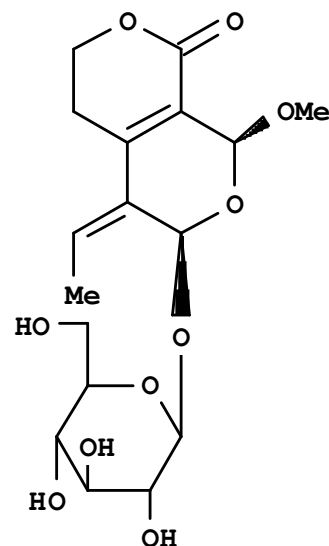


Figure 16. Swertiajaposides C.

an important role in traditional herbal remedies and under investigation for antibacterial, antineoplastic and other pharmaceutical functions. The terpenoids can be classified according to the number of isoprene units: monoterpenoids (2 isoprene units), sesquiterpenoids (3 isoprene units), diterpenoids (4 isoprene units), sesterterpenoids (5 isoprene units), triterpenoids (6 isoprene units) and so on. The terpenoids take a large part of new natural products, the number of which is 750.

Four new secoiridoid glucosides, swertiajaposides C-F (Figure 16), were isolated from the whole plant of *Swertia japonica* MAKINO together with two known compounds, 8-hydroxy-10-hydrosweroside and senburiside IV (Kikuchi et al., 2008).

Five new guaiane-type sesquiterpenoids, hedyosumins A-E (Figure 17), together with five known ones, were isolated from the aerial parts of *Hedyosmum orientale*. Two known sesquiterpenoids, 10 α -hydroxy-1,5 α H-guaia-3,7(11)-dien-8 α , 12-olide and 9 α -hydroxyasterolide, were obtained as natural products for the first time. Their structures were elucidated on the basis of spectroscopic methods. 9 α -Hydroxyasterolide showed moderate activities against A-549 and HL-60 tumor cell lines with the IC₅₀ values of 3.1 and 8.8 μ M (Su et al., 2008).

A new triterpene (Figure 18) was isolated from the plant *Rhus taitensis* collected in Papua New Guinea. Tetrahydroxysqualene was isolated using bioassay-guided fractionation of the methanolic extract of *R. taitensis* leaves and twigs. The structure of tetrahydroxysqualene was elucidated on the basis of HRESIMS and 1D and 2D NMR spectra. Tetrahydroxysqualene exhibit-ed antituberculosis activity with an MIC of 10.0 μ g/mL, while showing only modest cytotoxicity (Noro et al., 2008).

Ten new highly oxygenated triterpenoids, kadcoccolactones A-J (Figure 19), and two known triterpenoids; kad-

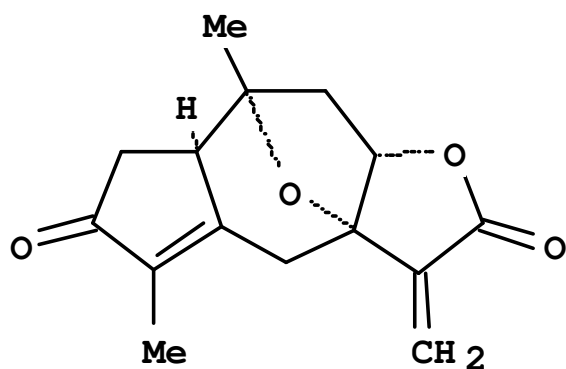


Figure 17. Hedyosumins A.

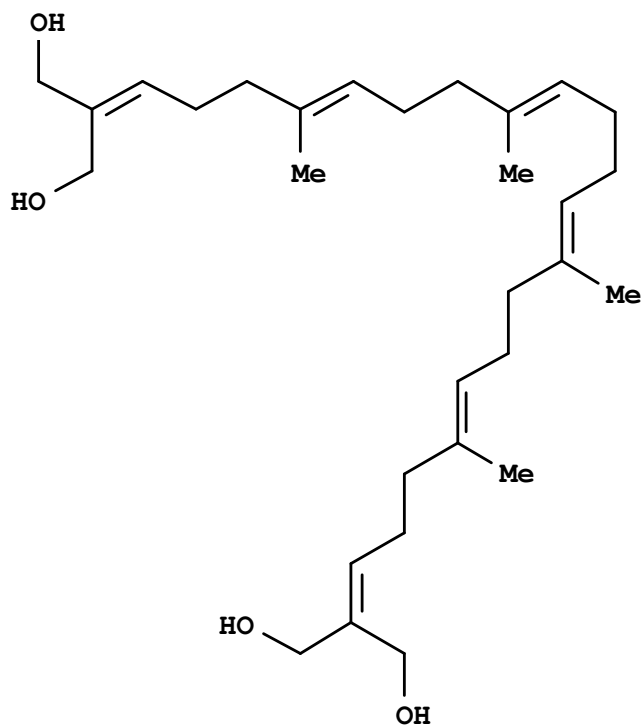


Figure 18. Tetrahydroxysqualene.

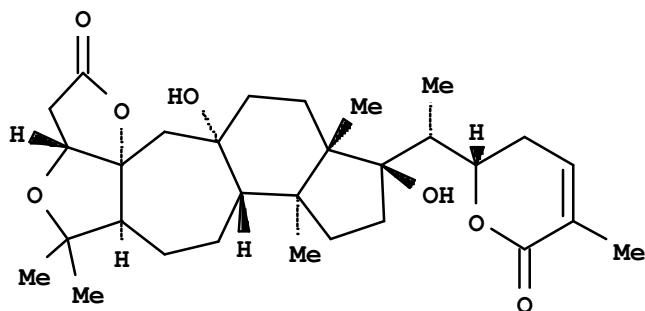


Figure 19. Kadcocclactones A.

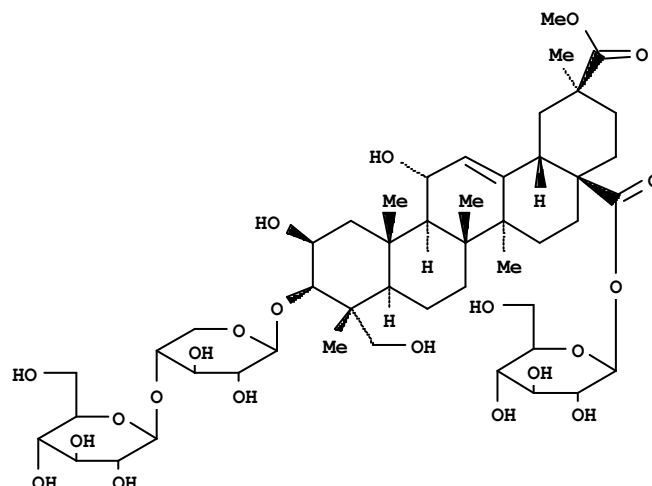


Figure 20. Phytolaccasaponins N-1.

suphilactone A and micrandilactone B were isolated from the stems of the evergreen climbing plant *Kadsura coccinea*. The structures of the new compounds were elucidated by spectroscopic evidence, with that of kadcocclactones A confirmed by single-crystal X-ray diffraction analysis (Gao et al., 2008).

Five new triterpene saponins named phytolaccasaponins N-1 (Figure 20), N-2, N-3, N-4, and N-5 were isolated from the roots of *Phytolacca americana* together with seven known triterpene saponins. The MDR-reversal activity of all these compounds was evaluated on the basis of the amount of calcein accumulated in MDR human ovarian cancer 2780 AD cells in the presence of each compound. The most effective compound was 8 (155% of control at 25 µg/mL) (Wang et al., 2008).

Others

Researchings based on natural isolations lead to other types of substances, which cover a much wider range, including glycosides, phenolic acid, fatty acid, polypeptides etc. Some of the new substances with uncomplicated structures have strongly activities. There are 332 new compounds found this year.

Ten minor new glycosidic constituents (1-10) (Figure 21), together with 10 known compounds, have been isolated from a neuroprotective fraction of an ethanolic extract of the tubers of *Gymnadenia conopsea*. The compounds isolated were evaluated for activity of *in vitro* assays for acetylcholine esterase and monoamine oxidase inhibitory activities (Zi et al., 2008).

In recent years, marine sources and microorganism metabolites are two potential areas that have obtained lots of new compounds. In 2008, the number of new chemical substances derived from these two areas is rising, up to 330. There is no doubt that marine organisms

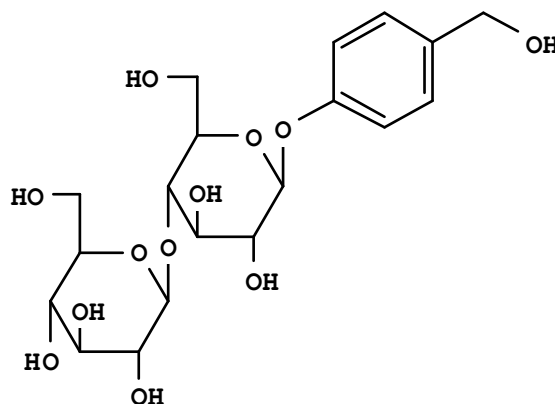


Figure 21. Compound 1.

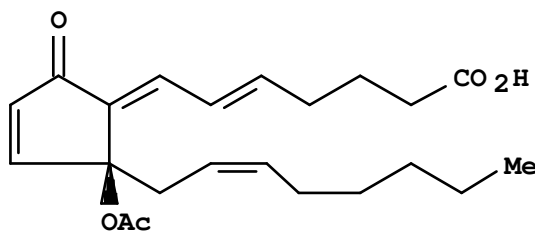


Figure 22. Claviridic acid A.

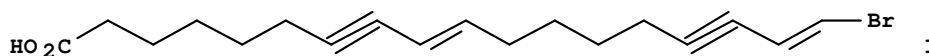


Figure 23. Compound I.

and metabolites will lead to more novel products in future.

Marine natural products

There has been a great interest in finding new compounds from marine sources. Coral, sponges and marine algae have a wealth of biologically potent chemicals with inflammatory, antiviral and anticancer activities. The usual types are long-chain fatty acids, macrolides and polypeptides.

Chemical investigation of the nonpolar extract of soft coral *Clavularia viridis* resulted in isolation of five new prostanoids, designated as claviridic acids A-E (Figure 22). The isolated marine prostanoids exhibited potent inhibitory effect on PHA-induced proliferation of peripheral blood mononuclear cells (PBMC), as well as significant cytotoxic activity against human gastric cancer cells (AGS) (Lin et al., 2008).

New brominated fatty acids and new sterol esters have been isolated from an unidentified marine sponge the marine sponge (Figure 23) was tested for activities again-

st *Artemia salina* and some fungi (Taniguchi et al., collected in Papua New Guinea. A major component of 2008).

Five new cytotoxic macrolide glycosides phorbosides A-E (Figure 24), each possessing a macrolide ring appended to a rare ene-yne-trans-2-chlorocyclopropane, were isolated from the same Western Australian sponge (Phorbos sp.) that provided phorboxazoles A and B (MacMillan et al., 2008).

Secondary metabolites

Microorganisms such as bacteria and fungi have been invaluable for isolating new compounds. Some microbial metabolites have provided lead compounds in medicine field. These microorganisms produce a large variety of antimicrobial agents such as penicillin, cephalosporins and tetracyclines. There are 194 new substances obtained from this aspect this year.

A new aromatic secondary metabolite named scoparal (Figure 25) has been isolated from ethanol solution part

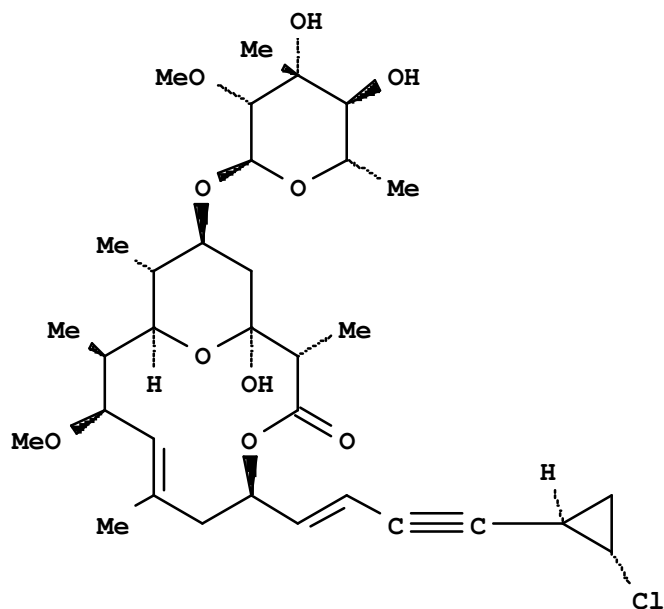


Figure 24. Phorbasides A.

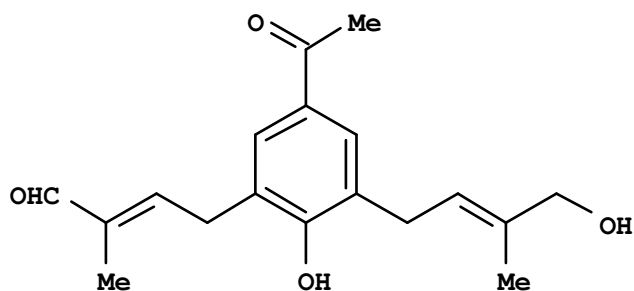


Figure 25. Scoparal.

of *Artemisia scoparia* collected from Mangora City of Pakistan. Structure of scoparal was elucidated with the aid of spectroscopic techniques including 2D NMR (Ali and Jahangir, 2008).

A new tryptophan-polyketide hybrid, codinaeopsin (Figure 26), was isolated from an endophytic fungus collected in Costa Rica. The structure of codinaeopsin, which was deduced from NMR and mass spectral data, contains an unusual heterocyclic unit linking indole and decalin fragments. Codinaeopsin is active against *Plasmodium falciparum*, the causative agent of the most lethal form of malaria (IC₅₀ = 2.3 µg/mL or 4.7µM) (Kontnik and Clardy, 2008).

Conclusions

Natural products usually are extracted from tissues of

terrestrial plants, marine organisms or microorganism fermentation broths. A crude extract from any one of these sources contains novel, structurally diverse chemical compounds. Technical drawbacks associated with natural product research have been lessened, and there are better opportunities to explore the biological activity of previously inaccessible sources of natural products (Alan, 2008). There was a number of dramatic advances in analytical techniques including TLC and GC, IR, NMR and MS that were powerful tools for separation and structure determination (Phillipson, 2007). It is sure that a great deal of new compounds will be isolated from natural system in the future investigations.

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