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Int. J. Drug Dev. & Res.
| April - June 2014 | Vol. 6 | Issue 2 | ISSN 0975-9344 |
www.ijddr.in

Role of Natural Products in Drug Discovery Process

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Abstract:
Natural products and their related moieties have historically been incredible as a source of therapeutic agents. In last 5-10 years, research into natural products in the pharmaceutical industry has reduced, owing to issues such as the lack of compatibility of traditional natural-product extract libraries with high-throughput screening. It has long been recognized that natural-product structures have the characteristics of high chemical diversity, biochemical specificity and other molecular properties that make them favourable as lead structures for drug discovery, and which serve to differentiate them from libraries of synthetic and combinatorial compounds. Recent advances in genomics and structural biology during the past decades are painting a clearer picture of the diversity of proteins targeted by natural-product molecules. Besides these, current lead generation strategies have led to a renewed interest in natural products in drug discovery.

Keywords: Drug discovery, Natural products, Sources of natural products.

Introduction

There is need of drug discovery process due to prevalence of many diseases without suitable medical products available. Among the various pharmaceutical industrial processes used for drug discovery, the Research and Development process is one of the pioneer processes. In fact, tens of thousands of compounds must be examined before enabling registration of a new drug in order to reach the market (Figure 1). This low productivity process is long and very expensive. In order to save the therapeutic innovation, following three key technologies have been introduced:

A) High Throughput Screening (HTS): HTS enables thousands of biological experiments per day by using one robot in a Standardized way

B) Genomics: Genomics and Proteomics are to bring thousands of new targets from the knowledge of human genome and functional proteome.

C) Combinatorial Chemistry: CombiChem allows the build-up of very large libraries, in a standardized format, with little problem of re-supply, and the possibility of patenting [1].

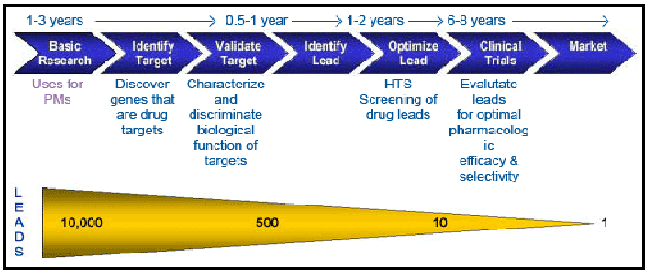

Figure 1: Drug discovery process

Identifying the active ingredient from traditional remedies, serendipity, de novo, isosteric replacement, reversal of group, biotechnology, natural products etc are the various bases for drug discovery process. Natural products (secondary metabolites) have been more successful source of potential drug leads. The term natural products is often used synonymously with secondary metabolite. It is a chemical compound

or substance produced by a living organism found in nature that usually has a pharmacological or bio activity to be used in drug discovery process. Natural product has been investigated and utilized to alleviate disease since early human history. In early 1900's before synthetic era 80% of all medicines were obtained from plant source [2-3]. Indian medicinal system has a long history and one of the oldest organized systems of medicine. It make use of natural product such as plant, terrestrial and marine animal, microorganism derived preparation to cure the dreadful disease [4-5]. Before advent of high throughput screening (HTS) and post genomic era, a huge amount of drug substance were purely natural product or were inspired by the molecule derived from natural sources. An analysis into the sources of new drug from 1981 to 2007 reveals that almost half of the drug approved since 1994 were based on natural product. [2,6-7].Natural products have always played a major role in human therapy and represent a huge reservoir of bioactive chemical diversity and help to understand the cellular pathways that are essential component of drug discovery process. The future of natural products drug discovery will be more holistic modern therapeutic skills in a complementary manner so that maximum benefits can be accrued to the patients and the community [8-10].

SLUMPED OF NATURAL PRODUCTS

Despite the success of the natural products approach in drug discovery process, in recent years it has slumped particularly within pharmaceutical industry due to some factors. These factors include:-

- Incompatibility of crude extract with high throughput assay procedures
- Lack of reproducible results
- High cost of collection of natural product sample
- Presence of artefacts in some extract
- Long resupply time for active extracts
- Difficulty in isolating active compound from extract
- Problems with large scale supply if a drug emerges from natural sources
- Slow growth and sparsely distribution of the species
- Difficulty of complying with Rio Treaty on Biodiversity
- Diversion of resources to combinatorial chemical approaches to drug iscovery
- Despite of all these slumped of natural products in pharmaceuticals, still natural products play a vital role in drug discovery process [11-15].

HISTORICAL OVERVIEW OF NATURAL PRODUCTS

Throughout the ages, humans relied on natural products. Natural products have earliest records from 2900-2600 BC documenting the uses of approximately 1000 plants derived substances such as the oil of Cedrus species (cedar), *Commiphora myrrha* (myrrh), *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (liquorice) and *Papaver somniferum* (poppy)[16] .In addition to plants around 120 minerals were listed including Arsenic sulphide, Sulphur, Lime, Potassium permanganate and even rock salt. The first Egyptian record is 'Ebers papyrus' dating from 1500 BC, document about 850 drugs such as Aloe vera (aloe), *Boswellia carteri* (frankincense) and oil of *Ricinus communis* (castor)[17]. At the same time the Chinese 'Materia medica' was documented dating from 1100 BC [18-19] (Wu Shi Er

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Bing Fang with 52 prescriptions). Likewise, documentation of the Indian ayurvedic system dates from before 1000 BC with charaka and samhitas having 341 and 516 drugs respectively[20-21]. Further the Greeks and Romans with Hippocrates (father of medicine) ~ 460 to 377 BC cover use of natural products which includes Extract of poppy, Henbane, Mandrake, Juniper and Saffron[22]. Dioscorids (100 AD) compiled De Materia medica, which described the dosage and efficacy of about 600 plants derived medicines and laid the foundation of pharmacology in Europe[23]. In 5 to 12 century the Arabs published their work in 'Canon medicinae' influenced by work of Ibn-Al-Baiter[24].

Natural products chemistry actually began with the work of Serturner who first isolated Morphine from opium poppy (*Papaver somniferum*) in 1803 [25]. Subsequent conversion into heroin was reported by Wright in 1874 [26]. In 1817 Emetine was isolated from Ipecacuanha [27] .Further other alkaloids such as Strychnine (*Strychnos nux vomica*)[28], Quinine (*Cinchona officinalis*)[28], Colchinne (*Colchicum autumnale*)[29], Atropine (*Atropa belladonna*)[30] ,Papaverine (*Papaver somniferum*)[31] etc were isolated. No historical perspective of natural products derived drugs would be complete without discussion of Aspirin (acetyl salicylic acid). Mac lagan in 1876 introduced the salicin from extract of *Salix* or *Spiraea ulmaria*[32]. Bergmann reported first antiviral agent Spongouridine and Spongothymidine from sponge[33].The first antibiotic derived from natural products is the serendipitous discovery of Penicillin from *Penicillium notatum* (fungus) by Alexander Fleming in 1928[34-36].

TYPES OF SOURCES FOR NATURAL PRODUCTS FOR DRUG DISCOVERY

Despite the rise of combinatorial chemistry as an integral part of lead discovery process, natural products still play a major role as starting material for drug discovery. Drug product have been obtained from various sources which include plants, animal, marine and microbial metabolites.

1. PLANT SOURCES

Plants have been the part of traditional medicine systems, which have been used for thousands of years in our county[37-39] .These plant based systems continue to play an essential role in health care, and it has been estimated by the World Health Organization (WHO) that approximately 80 % of the world's inhabitants rely mainly on traditional medicines for their primary health care[40] .Plant products also play an important role in the health care systems of the remaining 20 % of the population, mainly residing in developed countries and at least 119 chemical substances, derived from 90 plant species, can be considered as important drugs currently in use in one or more countries. Of these 119 drugs, 74 % were discovered as a result of chemical studies directed at the isolation of the active substances from plants used in traditional medicine[40] .Some examples are:

(a)ANTI-INFLAMATORY AGENTS

Inflammation is known to be one of the important causes responsible for many diseases[41] .Natural products used for inflammation includes Withanolides **(1)** from *Withania somnifera*. They are found to be active in arthritis and are potent inhibitor of angiogenesis, inflammation and oxidative stress. Inhibition of NFkB and NFkB regulated gene expression is primarily responsible for their anti arthritis action[42]. Another prominent

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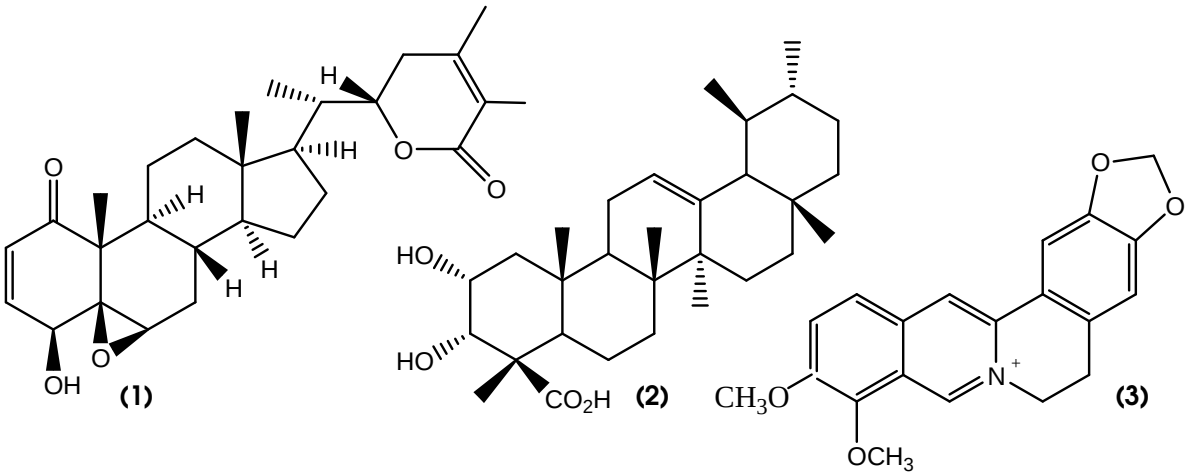
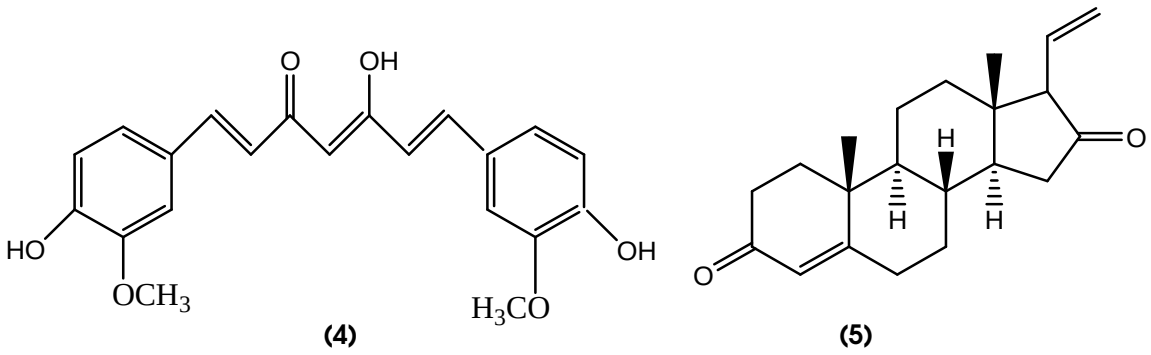
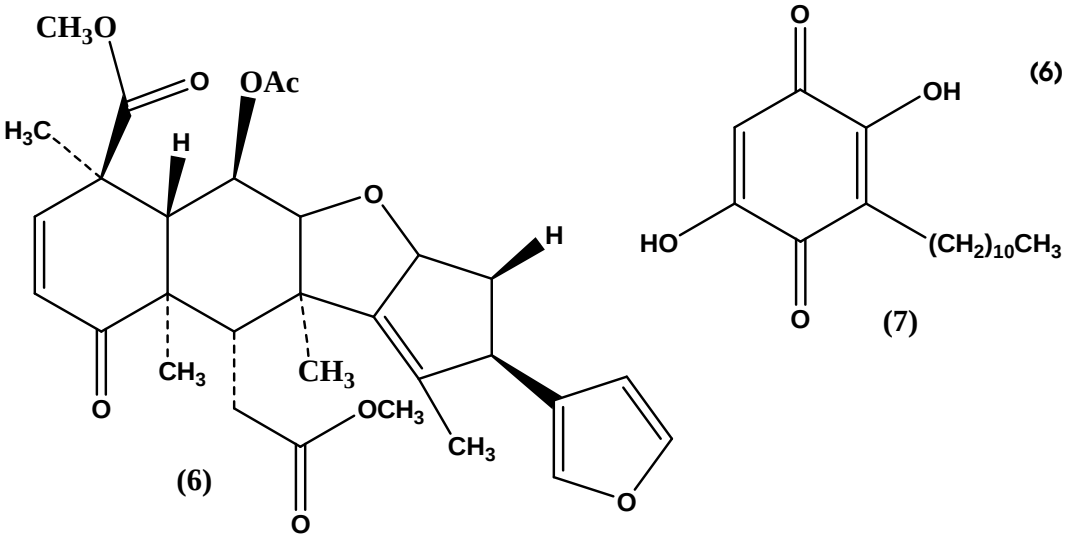
example is Salai guggal (Boswellia serrata)**(2)** which was investigated at IIM, JAMMU and also show anti arthritis action[43]. Alkaloid, berberine**(3)** from *Berberis aristata* also have anti inflammatory action by inhibition of NFkB , COX2, TNFa , IL-Iβ, IL-6[44]. Another prominent example is Curcumin**(4)** from Turmeric *Curcuma longa* , reported in 1971 to be an effective anti-inflammatory agent at CDRI LUCKNOW, show broad spectrum activity on inflammation[45-46]. Another substance is Guggulsterone**(5)** from *Commiphora mukul* (guggul)[47]. Nimbidin**(6)** from neem (*Azadirachta indica*) [48] and *Embel***(7)** a constituent of Vidang (*Embelia ribes*) also show anti-inflammatory action[49].







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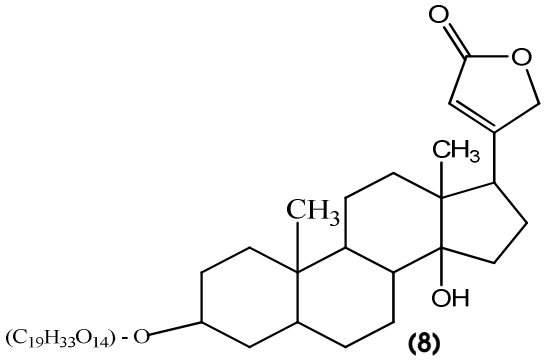
(b)CARDIO-VASCULAR AGENTS

Cardiac glycosides or cardenolides are commonly used. They are steroidal in nature with a lactone group. They inhibit the membrane bond Na-K ATPase pump resulting in depletion of intracellular K and increase in serum K which result in decrease electrical conductivity through a decrease in heart rate and increase cardiac output[50].

Yellow oleander plant (*Thevetia neriifolia*) have thevitin**(8)** A, B and peruvoside**(9)** which are potent cardiac glycoside[51]. Rauwolfia serpentine contain reserpine**(10)** ,was first tested in INDIA for anti-hypertensive activity. It inhibits action by inhibiting mono amine oxidase(MAO)[52]. The *Terminalia arjuna* bark has been used for treatment of angina. Arjunolic acid**(11)** is main constituent to exhibit this action[53]. The Coleus spp have also been reported in materia medica for treatment of heart disease[54]. Digoxin **(12)** obtained from *Digitalis purpurea* is most widely used cardenolides[55]. Another most important example is Quinidine**(13)** from *Cinchona officinalis* use as antiarrythmic agent[56].



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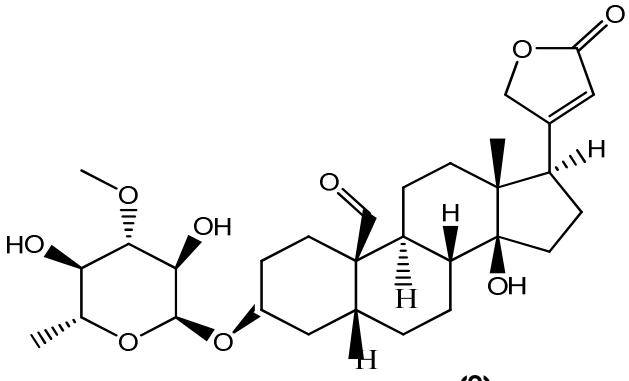

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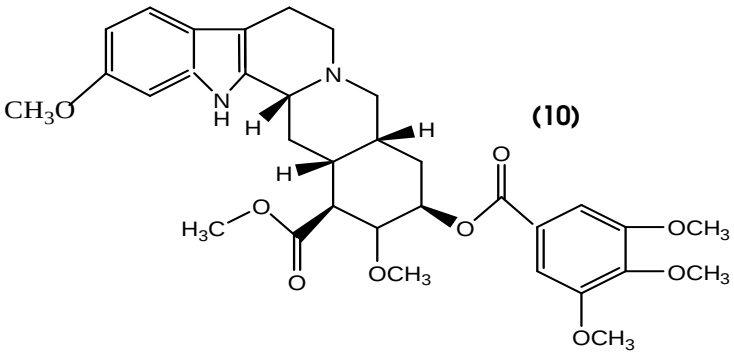

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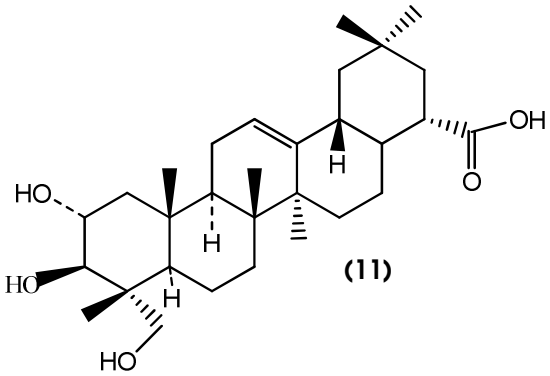

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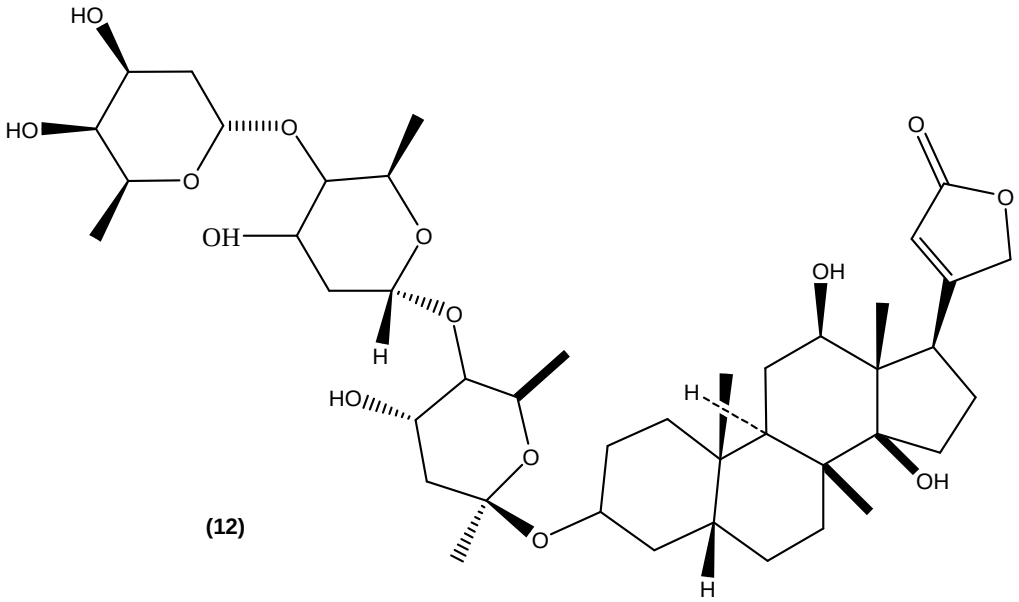

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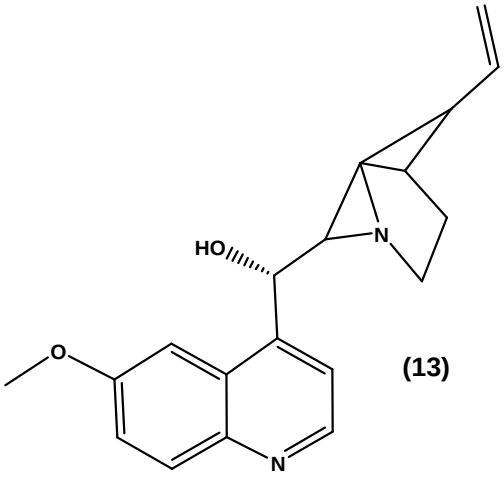

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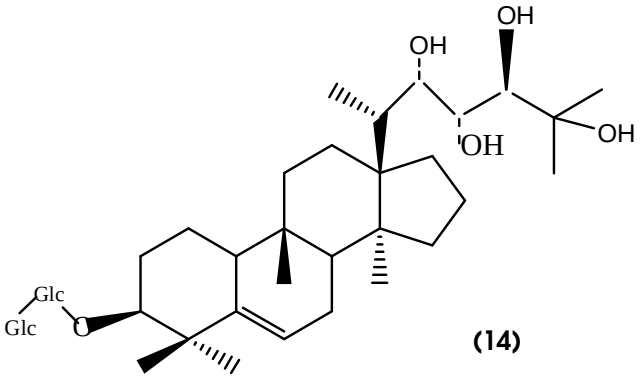
(c)ANTI DIABETIC AGENTS

India is a 'Diabetic capital of world' several remedies are used for their treatment. Most common example is Charantin **(14)** a steroidal saponin have an insulin like activity[57]. *Sylvestre Gymnema* (gurmar) from which gymnemic acid**(15)** is obtain known to show hypoglycaemic activity[58] .Futher *Momordica charantia* commonly known as Karela have momordicoside**(16)** which is used for diabetes[57]. Andrographolide**(17)** a di terpenoid lactone from *Andro graphis Paniculata* has been found to exhibit significant hypoglycaemic activity[59]. *Syzygium jambolanium* have anthocyanins**(18)** which are responsible for antidiabetic action[60]. Liquiritigenin**(19)** extracted from *Pterocarpus marsupium* also another important example[61]. *Trigonella foneum–graecum* commonly known as fenugreek, shows potent anti diabetic action[62].



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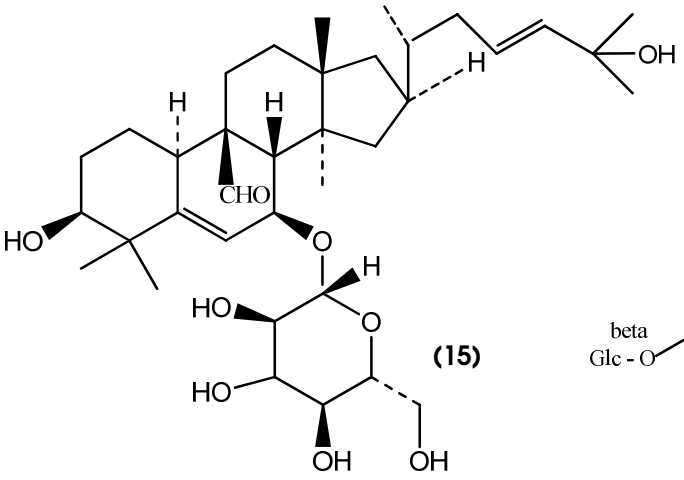

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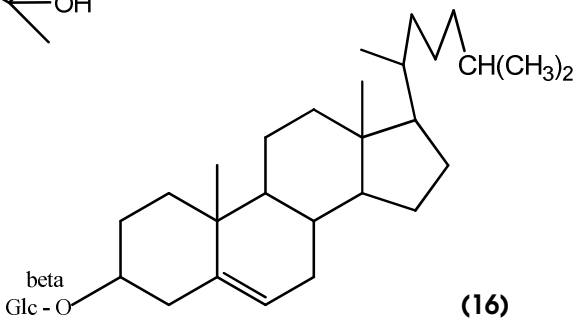

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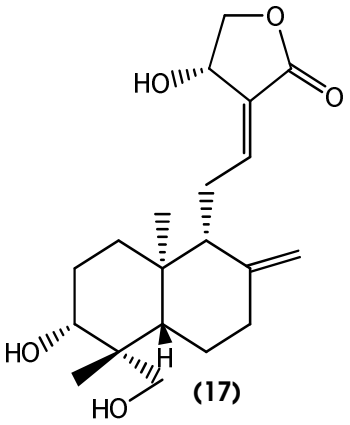

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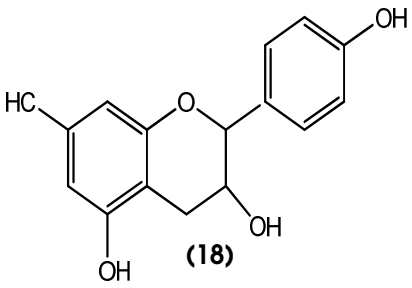

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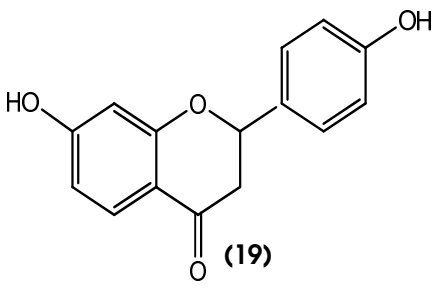

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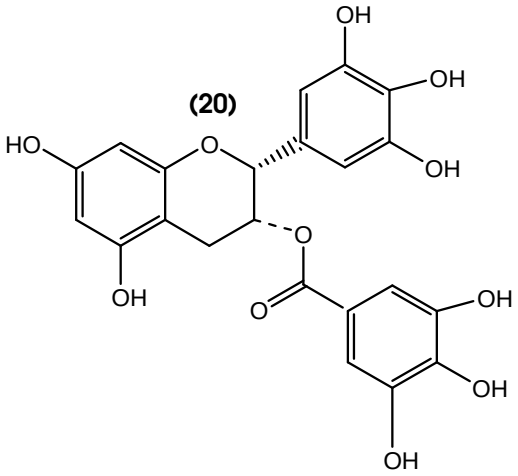
(d)ANTI OBESITY AGENTS

There are many natural products that have been used for anti obesity agent. Tea polyphenolics like 3-o-gallate **(20)** show a potent lipase inhibitor activity[63]. 3-Methylethergangalin and 5-hydroxy-7-(4'hydroxy-3'-methoxyphenyl)-1- phenyl-3-heptanone isolated from *Alpinia officinarum* have shown significant lipase inhibitory action [64-65]. *Garcinia cambogia* have hydroxycitric acid **(21)** which is used as an antiobestiy agent[66]. Guggulipid, a fraction of *Commiphora mukul* resin and has been developed at CDRI LUCKNOW, and have guggulsterone **(22)** act as hyperlipidameic agent[67-69].



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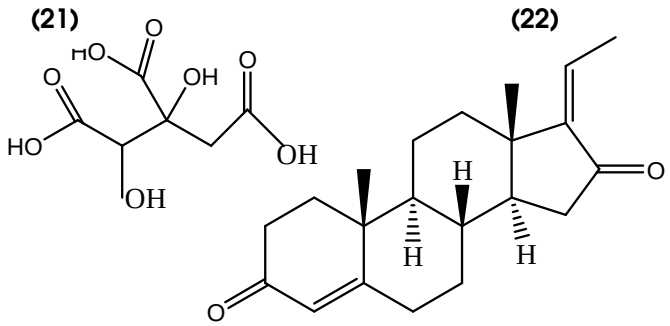
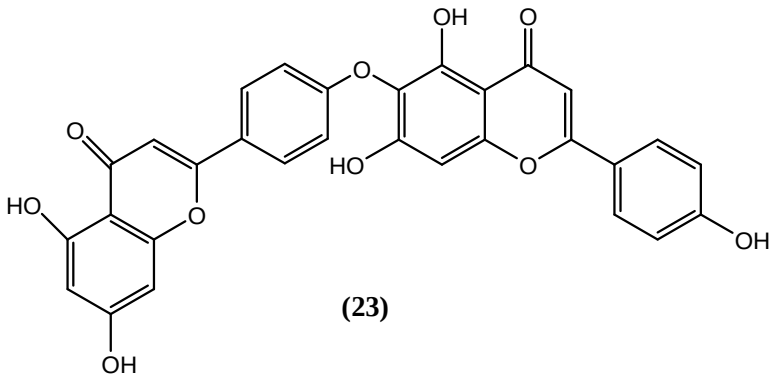


(21) **(22)**

(e)ANTI MALARIAL AGENTS

A number of medicinal plants have been used traditionally in the treatment of malaria. Several biflavonoids from Selaginella Bryopteris which includes amentoflavone **(23)** have been investigated for their anti-protozoal activity in vitro against K strain of P*lasmodium falciparum*[70]. Neem which have nimbolides **(24)** Is used as an antimalarial agent[71]. Naphthylisoquinoline alkaloids isolated from leaves of *Anastrocladus heyneanus* particularly anastrocladidine, ancistrocladidine**(25)** ancistrocladinium B **(26)** and ancistrotanzanine **(27)** have been shown to exhibit significant anti plasmodial activity[72]. Arteether **(28)** derived from artemisinin , was first isolated from the plant *Artemisia annua* was approved as antimalarial drugs[73]. Quinine from *Cinchona officinalis***(29)** is a potent antimalarial agent[74].



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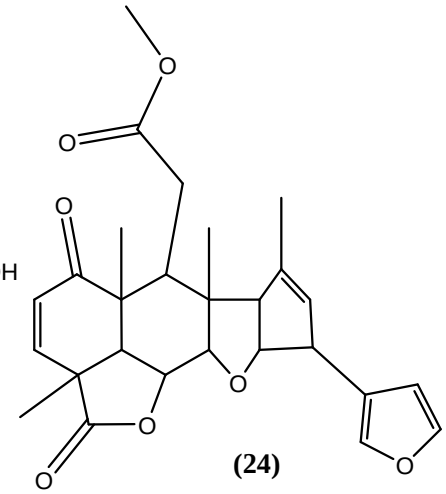

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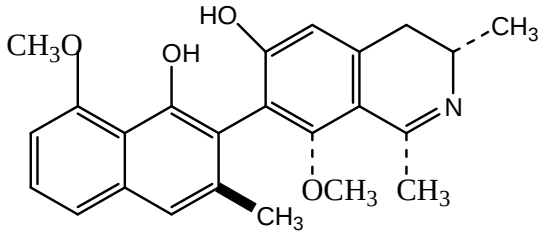

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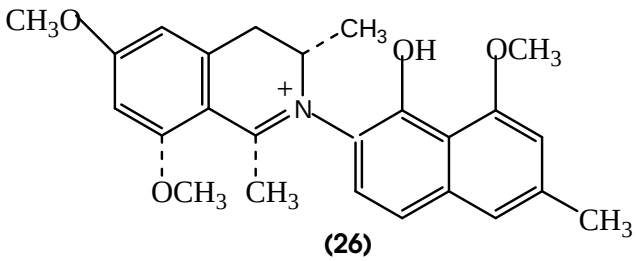

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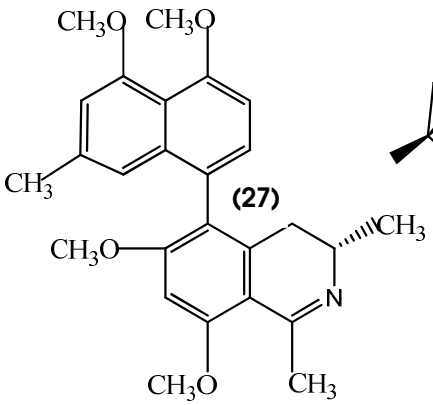

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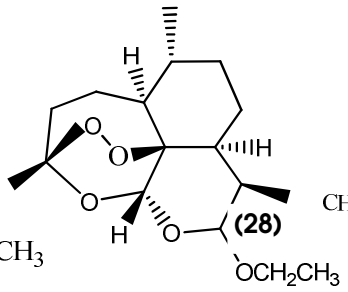

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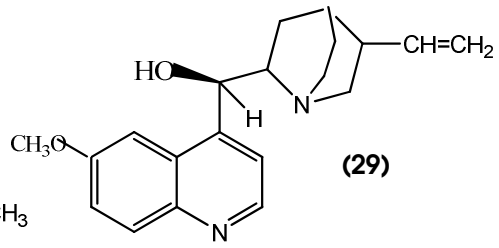

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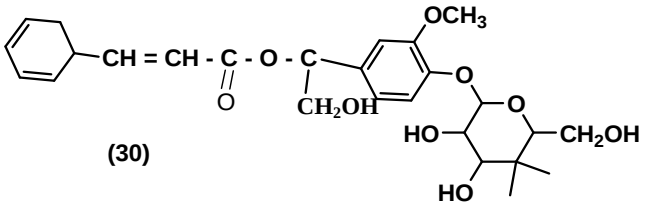
(f) IMMUNOMODULATORS

An immune modulator is defined as a biological or non-biological substance that directly influences a specific immune function or modifies one or more components of immune regulatory network to achieve an indirect effect on a specific immune function [75-76]. Many plant derived natural products have been found as an immunomodulator. The immuno-suppressant property of 5, 20_(R)-Dihydroxy-6_, 7_-epoxy-1-oxo-(5_)-with α-2, 24-dienolide from *Withania somnifera* and the steroidal alkaloid solasodine from *Solanum nigrum,* are used as immunomodulators[77]. *Picrorrhiza kurroa* was another example, the active constituent is known kutkin (**30**) and is a mixture of: Kutkoside and Picroside[78] .The polysaccharides isolated from *Arnica Montana* was revealed in carbon-clearance test and in stimulation of macrophages to excrete tumor necrosis factor[79] .The immuno-modulatory activity of *Piper betle* leaves, *Zingiber aramatica* rhizome, *Allium sativum* and *Andrographis paniculata* was displayed by their stimulation of humoral immune response by the "microtitration hematoglutinin test"[80] .The potent anti-phlogistic and anti-allergic activity of the flavonoid Wedelolactone **(31)** from *Eclipta alba* and *Wedelia calendulaceae* was found to be due to its 5-lipoxygenase inhibitory activity, suggesting that it acts by free oxygen radical scavenger mechanism[81] . Further *Calendula officinalis* have various terpenoids example copalol **(32)**, and the Martricaria recutita derived secondary metabolites which includes isobutyl angelate **(33),** β farnesene **(34)** and chamazulene **(35)** responsible for this activity[82-83]. *Echinacea purpurea*, Panax ginseng , *Serrenoa serrulata* , *Tinospora cordifolia* , *Aspaparagus racemomus* are also used as an immunomodulators[84-86] .Studies have also accounted for the tonic properties of plants like *A.indica, Holarrhena antidysenterica, Aconitum heterohyllum, Tylophora asthmatica, Ocimum gratissimum* and *Tinospora cordifolia,* in stimulation of lymphocytic and phagocytic function and inhibition of humoral components of the immune system, thus act as a good immunomodulators[87-89]



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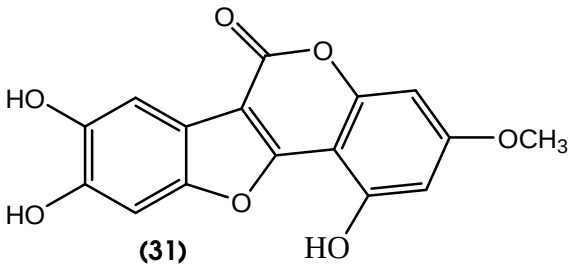

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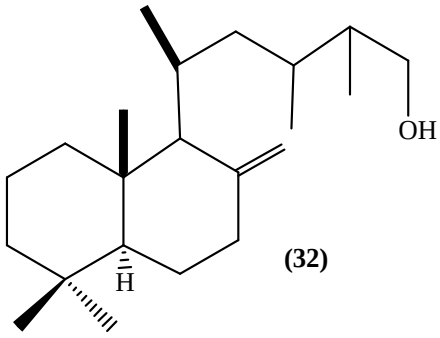

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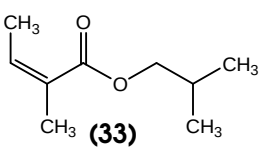

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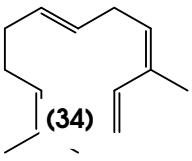

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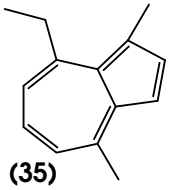

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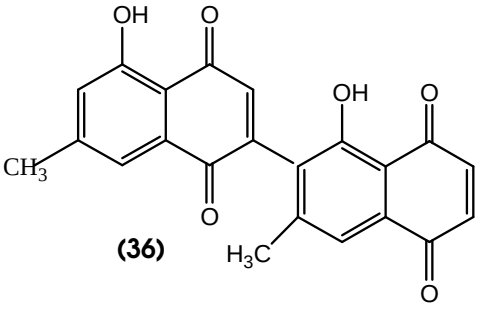
(g)ANTI LESHMANIAL AGENTS

A large number of molecule belonging to various class of natural products have been isolated which include Diospyrin**(36).** It has been isolated from Diospyros spp. And found to have very

potent antileishmanial activity against *Leishmania donavani*[90-91] .Plumbagin (**37)** from Plumbago spp. is perhaps the most potent agent[92]. Berberine **(38)** from *Berberis aristata* is another prominent example[93]. Piperine **(39)** which is found from Piper species used against promastigotis of *L. Donavani* with activity comparable to pentamidine[94]. Amarogentin **(40)** isolated from *Swertia chirata* has been found to inhibit L.donovani topoisomerase I[95]. Besides these compounds, Picroliv a standardized mixture of iridoid glycosides prepared from the root and rhizome extract of *Picrorrhiza Kurroa* shows a significant anti leshmanial activity and used in combination therapy of Kala azar fever with Na stibogluconate .It is reported to enhance the efficacy of the anti leishmanial drug and also to reduce its side effects[96-97].



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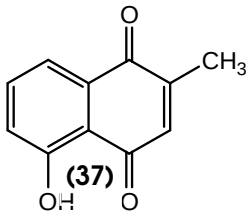

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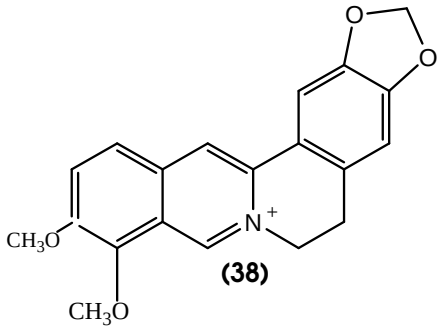

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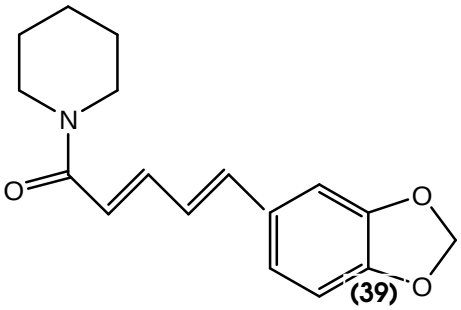

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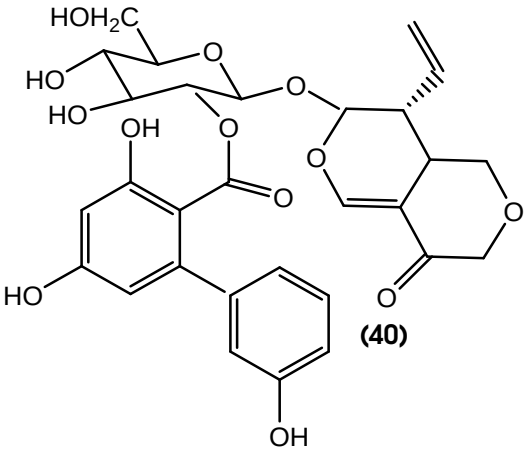

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(h)ANTI VIRAL AGENTS

Several natural products have been used as anti viral drug which include alkaloids, phenolids and terpenoids. Theasinensin **(41)** a phenolic compound found in Tea (*thea sinensis*) has been shown to exhibit a good antiviral activity[98]. The common phytosterols ursolic acid **(42)** and oleanolic acid **(43)** found in many plants also used as anti HIV agent[99] .Gallic acid **(44)** chebulagic acid **(45)** and other galloyl glucose **(46)** isolated from Terminalia Chebula have been reported to show a promising HIV integrase inhibitory activity[100] .Termilignan **(47)**, Thannilignan 7-hydroxy-3′,4′-(methylene dioxy)-flavones and anolignan B isolated from fruit rinds of *Terminalia belerica* have been reported as anti HIV agent[101-102].

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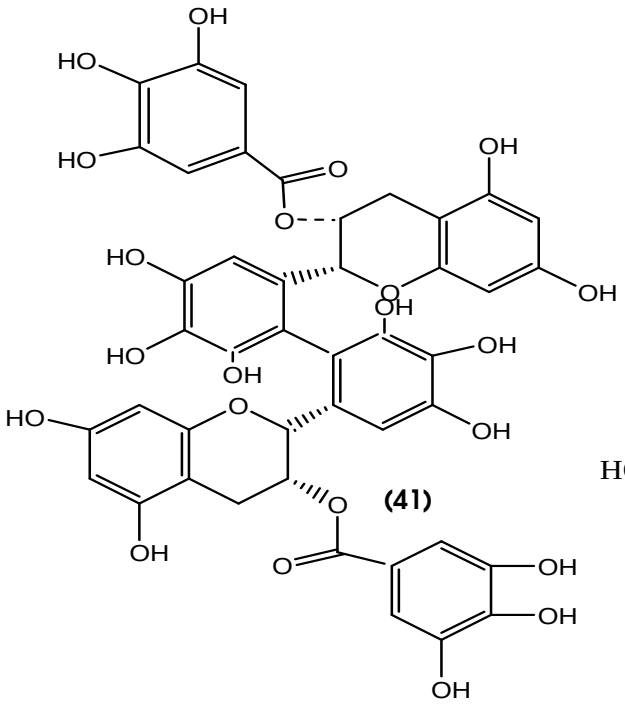

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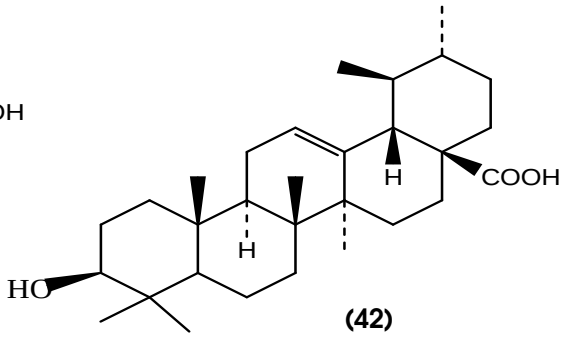

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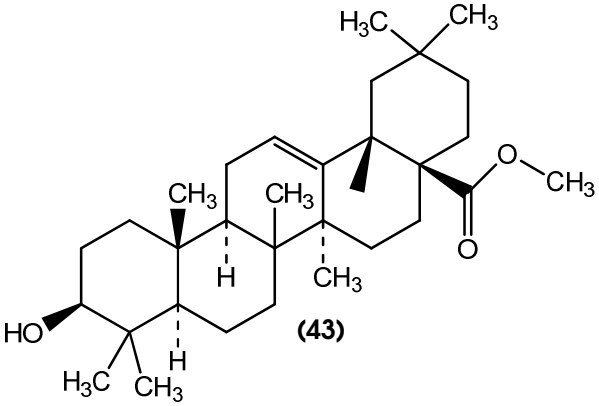

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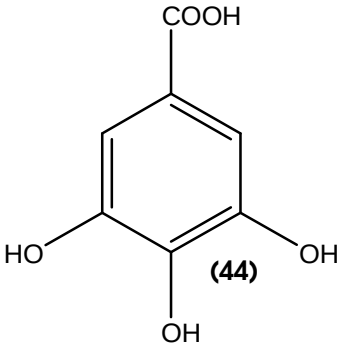

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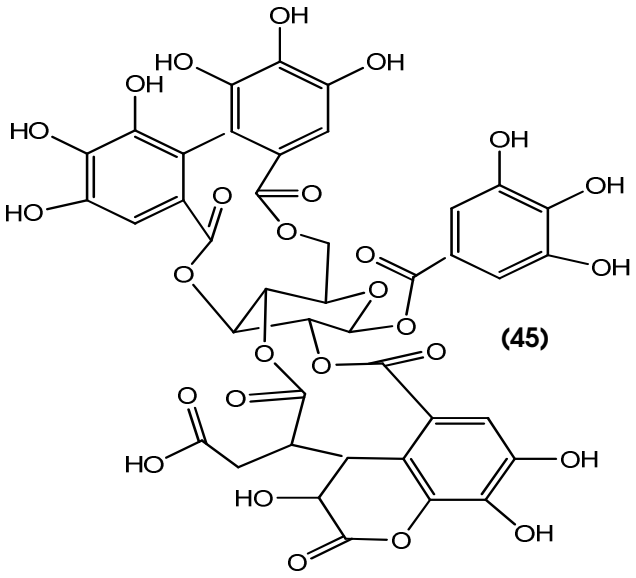

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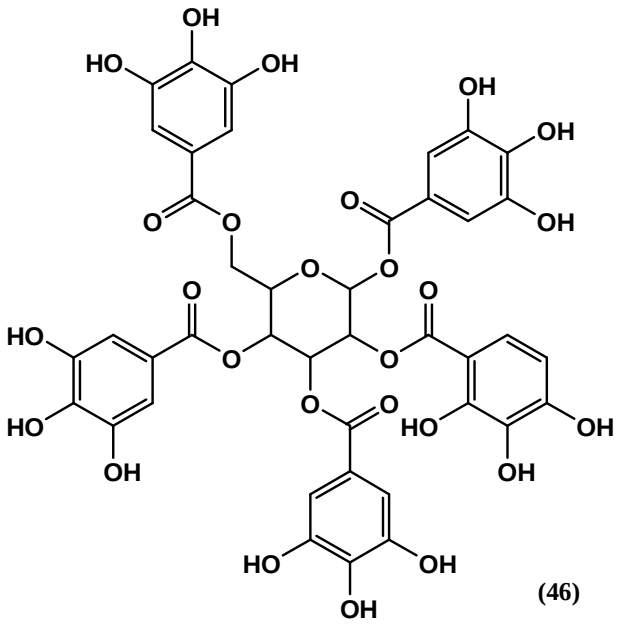

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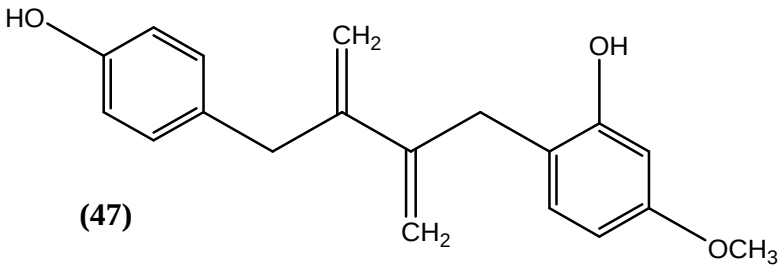

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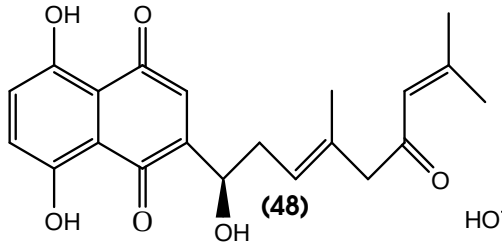
(h)ANTI NEOPLASTIC AGENT

There are few example of natural products which have been used as antineoplastic agent. Arnebin **(48)** a napthoquinone found in a *Arnebia nobeles* have been found to be active against walker carcinoma in rats[103]. A diterpenoid precalyone isolated from Roylea calyana also found useful against lymphoid leukaemia[104]. The other example include Tagitinin F **(49)** a germacranolide isolated from *Tithonia tagitiflorahas* has been also found to be active against lymphocytic leukaemia[105]. Flavoperidol**(50)** a semi synthetic flavonoid derived from (CDK) inhibitor to be tested in clinical trials[106-107] .Combretastatins**(51)** found in species of Combretacea family have reported used in cancer[108] .*Podophyllum emodii* has been used in skin cancers and warts. Podophyllotoxin**(52) ,** a lignan isolated from this plant has been used for anti cancer activity[109]. A flavanol glycoside, Stephdidoside**(53)** from *Stephrosia Candida* has found active against epidermoid carcinoma of nasopharynx[110]. Echitamine chloride**(54)** an alkaloid from *Alstonia Scholaris,* has reported to show a dose dependent regression of fibrosarcoma[111]. Tylophorine**(55)** an alkaloid isolated from *Tylophora indica* reported to show anti tumor action[112]. Parthenin**(56)** isolated from *Parthenium hysterophorus* has been reported to show cytotoxic activity in human leucocyte chromosome[113-114] .The Madagascar periwinkle, *Catharanthu roseus have* anticancerous alkaloids vincristine **(57a)**and vinblastine **(57b)**[115]**.** Another

example is The Pacific yew tree, *Taxus brevifolia* was discovered to possess excellent anticancer properties due to the presence of paclitaxel **(58)**[116]. The important plants with their biological activities are shown in Table 1.



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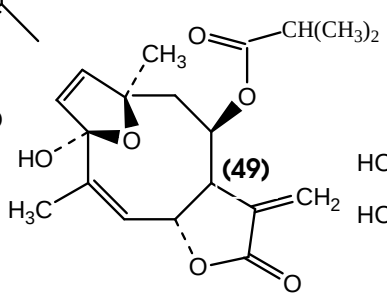

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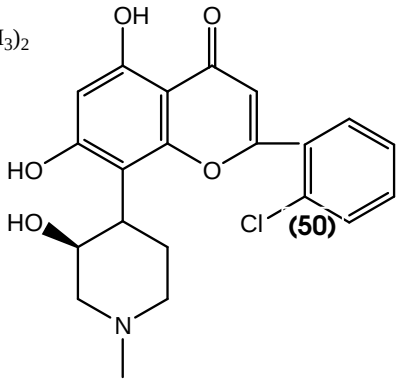

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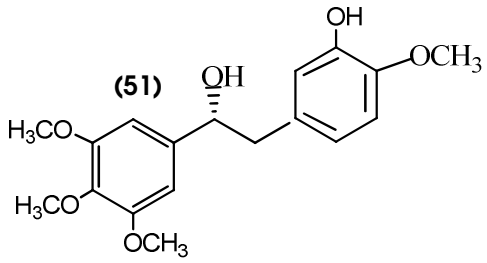

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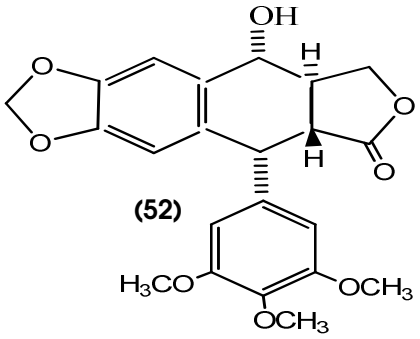

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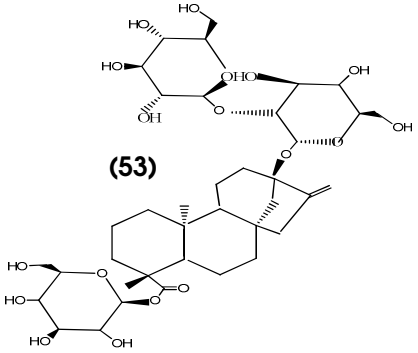

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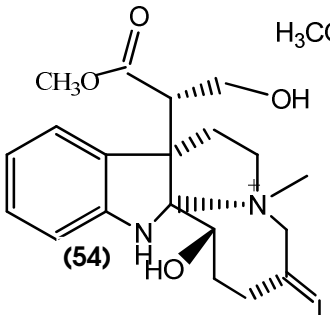

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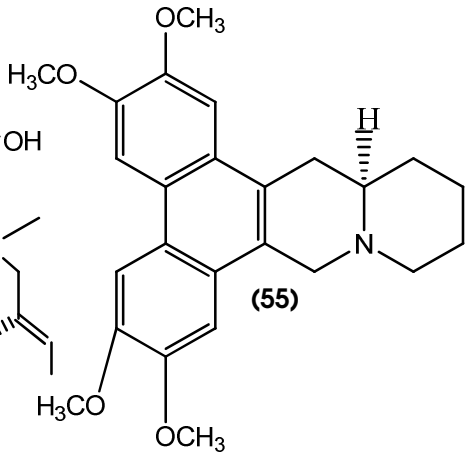

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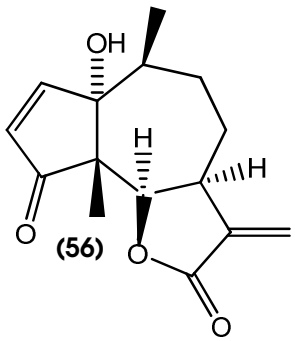

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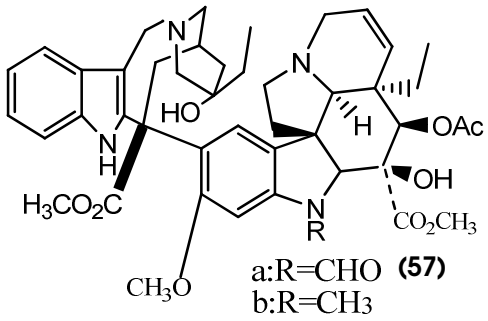

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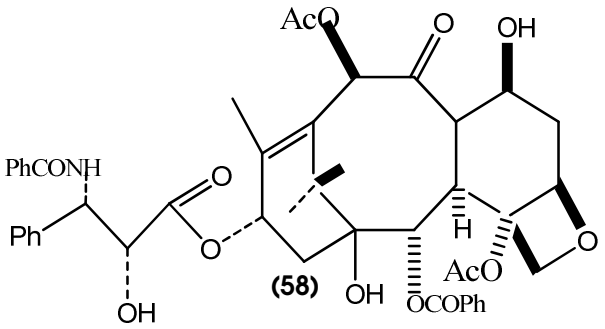

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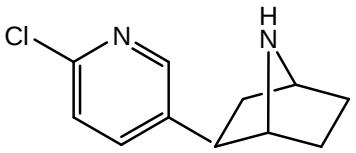
Table 1: Plants as a source of natural products and their biological activities

Source	Chemical constituents	Biological action	Marketed/traditional formulation
Achyranthes aspera	Achyranthine	Diuretic	Cystone
Adhatoda vasica	Vasicine	Bronchodilator	Diakof , Koflet
Aegle marmelos	Aegelin, Marmelosin	In bowel disease	Diarex
Aloe vera	Aloin	Demulcent	Clarina
Antethum graveolens	Anethole	Carminative	Bonnisan
Areca catechu	Tannins	Antiobesity	Koflet, Bioslim
Argyreia nervosa	Alkaloids	Aphrodisiac	Confido
Artemisia annua	Artemisinin	Antimalarial	Suteether
Asparagus adscendens	Asparanin, Sarasapogenin	Fertility enhancer	Spermon

2. ANIMAL SOURCES

Animal have also been a source of some drugs. The skin of an Ecuadorian poison frog is a source of Epibatidine**(59),** which is ten time more potent then morphine[117]. Cure of several diseases have been done by venoms and toxins of several animals. Teprotide from the extract of Brazilian viper, has led to the development of cilazapril**(60)** and captopril**(61),** which are effective anti hypertensive drugs[118].



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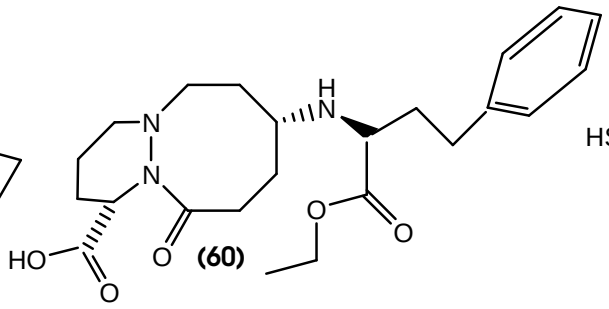

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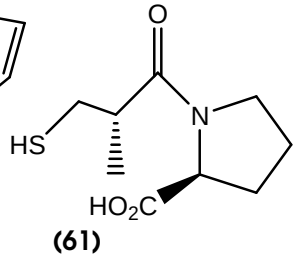

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3. MICROBIAL SOURCES

Microbe as the source novel bioactive agents come under investigation since from the serendipitous discovery of penicillin **(62)** from the filamentous fungus *Penicillium notatum* discovered by Fleming in 1929 and got the Nobel prize in 1945[119-120]. After publication of the first clinical data on penicillin G between 1942–1944, there was a worldwide efforts to discover new antibiotics from microorganisms[121]. Tetracycline **(63)** is another antibiotic which is obtained from *Streptomyces aureofaciens* used in UTI , achne and in several dental infections[122] .Choramphenicol **(64**) obtain from *Streptomyces venezuelae*[123] is another prominent example which is used in typhoid, cholera and in brain abscesses .Further the discovery of novel antibiotic structural classes was done that include the isolation of the antibiotics imipenem**(65)** norcardicin (**66**), and aztreonam (**67**)[124].Further

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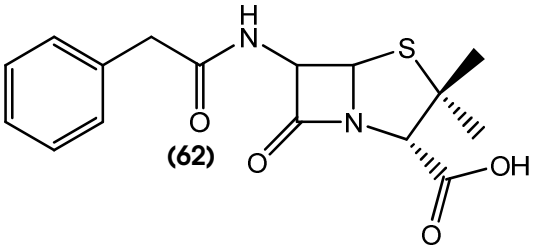
the macro fungi such as polypores are a large group of wood-rotting fungi of the phylum Basidiomycota (basidomycetes) and Ascomycota, which are a major source of pharmacologically active substances. Polypore fungi have shown strong antimicrobial compounds also have antiviral, cytotoxic, antineoplastic, cardiovascular, anti-inflammatory, immune-stimulating agent[125].

In 1953, Edmund Kornfeld first isolated vancomycin (**68**) a glycopeptide antibiotic produced in cultures of *Amycolatopsis orientalis* which is active against a wide range of gram-positive organisms such as *Staphylococci* and *Streptococci* and against gram-negative bacteria, mycobacteria and fungi[126]. The macrolide erythromycin (**69**) from *Saccharopolyspora erythraea* is an antibacterial drug. It has broad spectrum activities against gram-positive *cocci* and *bacilli* and is used for respiratory tract infections[127]. Betulinic acid (**70**), a triterpenoid obtained from the bark of *Betula pubescens* was identified as a weak inhibitor of HIV[128]. Bevirimat (PA-457) (**71**), extracted from a Chinese herb *Syzygium claviflorum* is used to inhibit the final step of the HIV Gag protein processing[129]. Ganoderic acid β (**72**), isolated from the fruiting bodies and spores of *Ganoderma lucidum*, displayed significant anti-HIV-1 protease activity[130]. Amrubicin hydrochloride (**73**), related to the anthracycline, doxorubicin (**74**) (Adriamycin®),was isolated from the fungus *Streptomyces peucetius*. is used to treat acute leukaemia, soft tissue and bone sarcomas, lung cancer, thyroid cancer and both Hodgkins and non-Hodgkins lymphomas[127] .Torreyanic acid (**75**) was isolated from an endophyte from the endangered tree, *Torreya taxifolia* and was tested in several cancer cell lines[131]. The salinosporamide A (**76**), has been isolated from actinomycete genus named *Salinospora* has been cultured using appropriate selective isolation techniques, and a very potent cytotoxin and proteasome inhibitor[132]. Ambuic acid (**77**) is an antifungal agent, which has been recently isolated from of *Pestalotiopsis microspora*[133].



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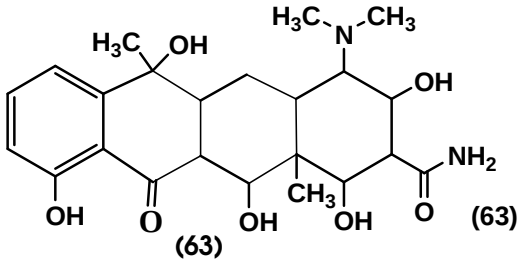

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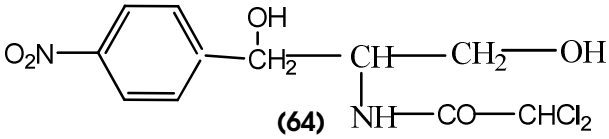

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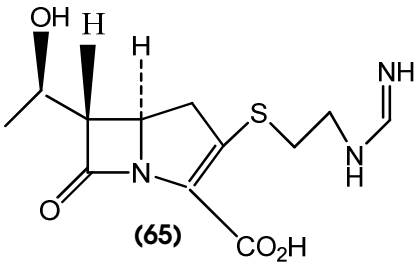

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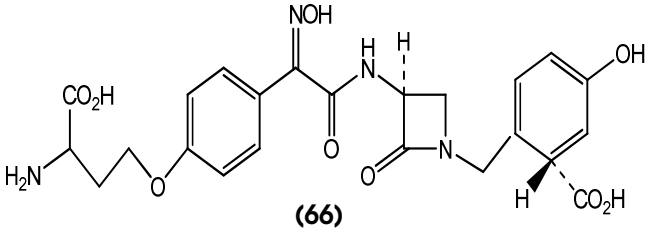

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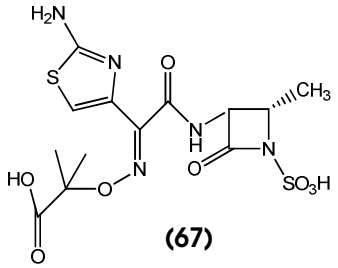

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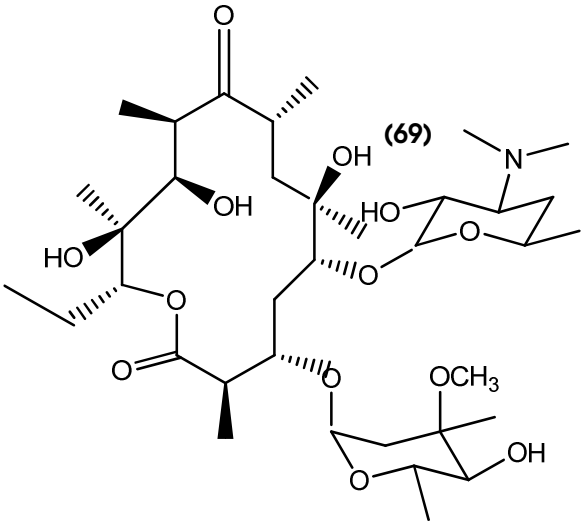

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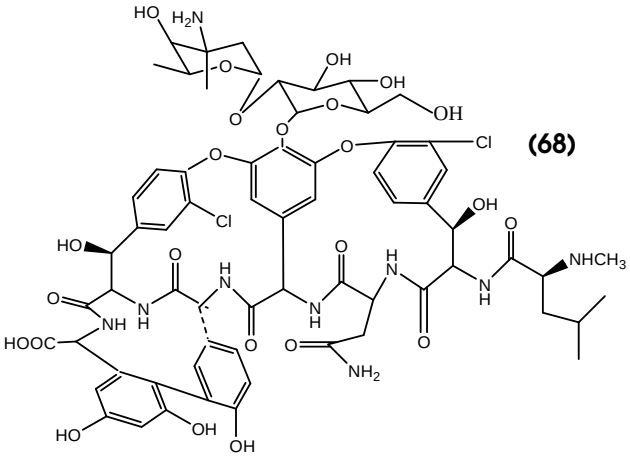

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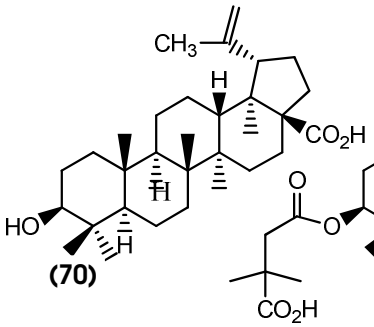

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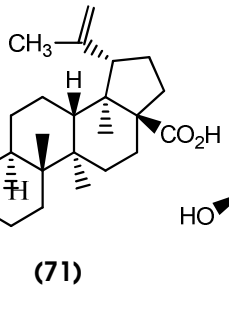

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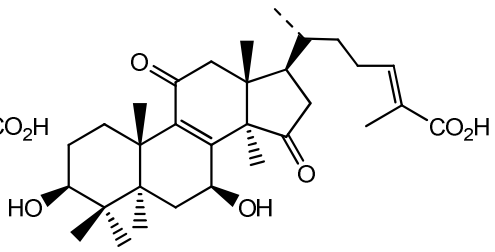

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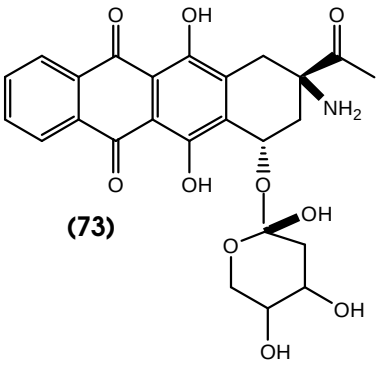

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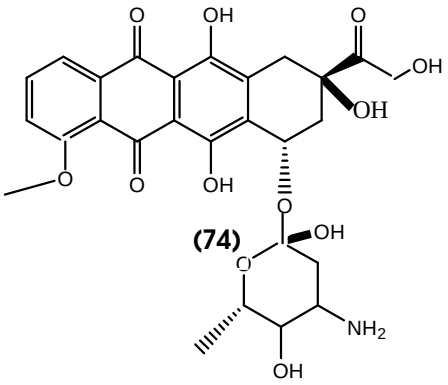

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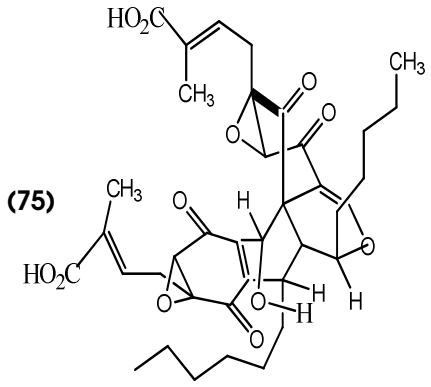

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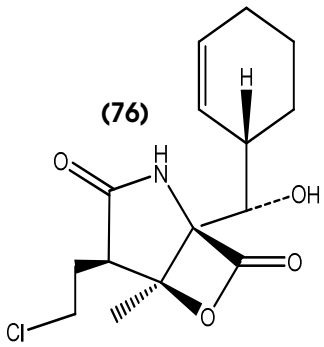

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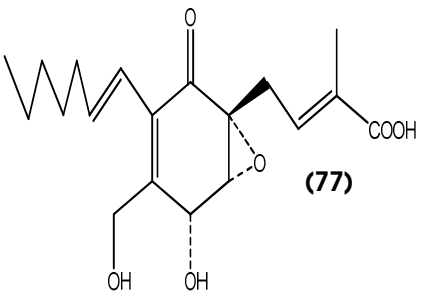

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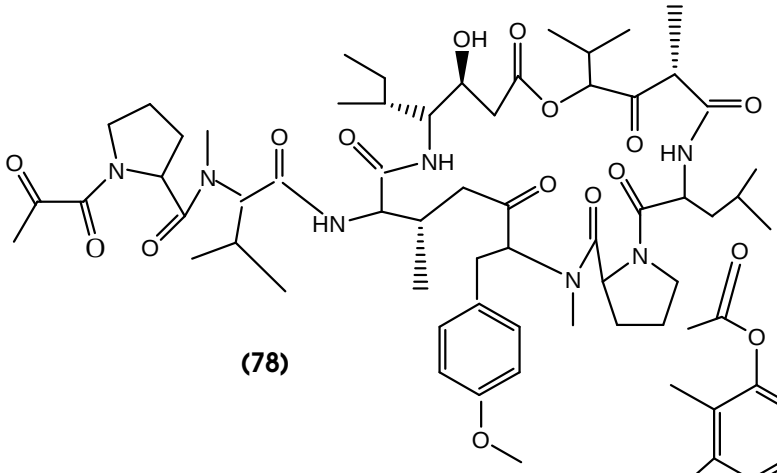
4. MARINE SOURCES

70% of planet earth's surface is covered by ocean, pharmaceutical companies began to realize that the ocean would possess unique biodiversity and may be a possible source for potential drug candidate[134] .These progressive advancements in the past 40 years of exploration of the marine environment have resulted in the isolation of thousands of structurally unique bioactive marine natural products. Some examples include, Ziconotide (Prialt®, Elan Corporation) a peptide first discovered in a tropical cone snail, which was approved for the treatment of pain. Plitidepsin**(78)**(Aplidin®,PharmaMa), a depsipeptide was isolated from the Mediterranean Tunicat *Aplidium albicans*[135-136] . Plitidepsin is effective in treating various cancers, including melanoma, small cell and non-small cell lung, bladder as well as non-Hodgkin lymphoma and acute lymphoblastic leukemia[137]. Ecteinascidin 743**(79)** (ET743; Yondelis™) was isolated from the ascidian Ecteinascidia turbinate and used as an anticancer agent[138]. Spisulosine **(80),** isolated from the marine clam *Spisula* polynyma, exhibited substantial selective activity against tumor cells compared to normal cells[139]. Cryptophycin **(81)** recognize cancerous tumor cells, even those of "solid tumors" such as those in brain, colon, ovarian, prostate, pancreas, lung and breast cancers and it can destroy the cells of multi-drug resistant (MDR) tumors[140].



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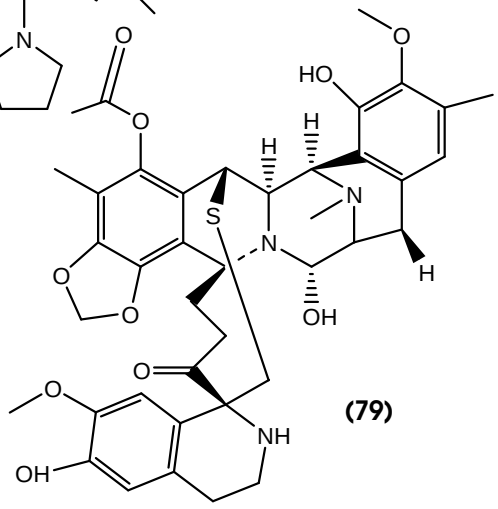

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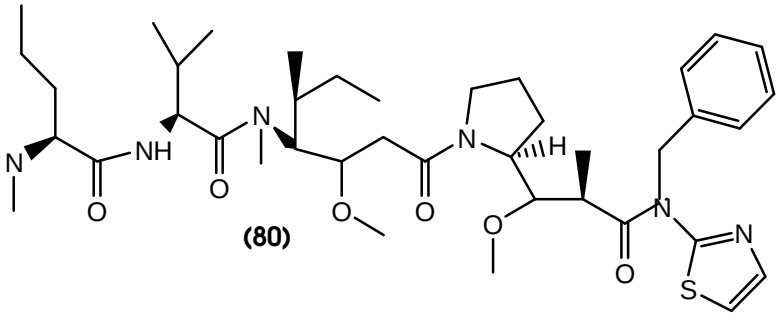

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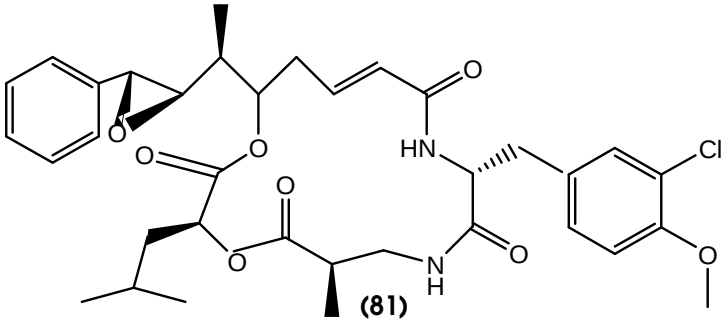
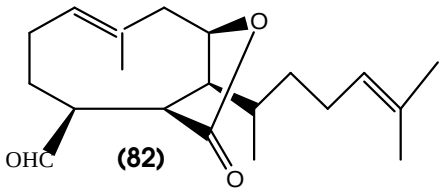
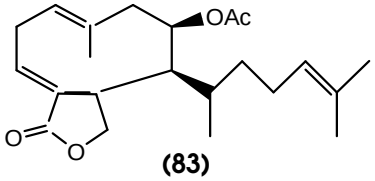
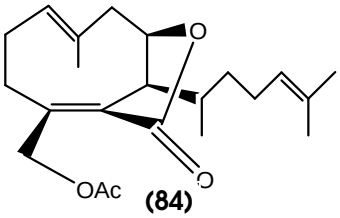
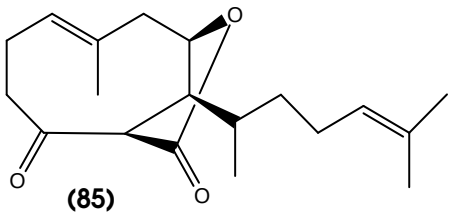


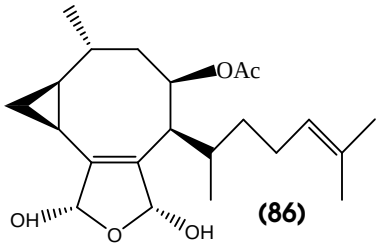
Natural Products from Marine Algae: Green, brown and red algae have been intensively assessed for their antibacterial and antifungal activities. The brown algae, *Dictyota dichotoma* afforded diterpenes, , dictyolides A **(82),** 4-acetoxydictylolactone **(83)** dictyolides B**(84)** and nordictyolide **(85)** which display antitumor activities[141] . Another example is crenuladial **(86)**, isolated from the brown alge. *Dilophus ligatus* which displayed antimicrobial activity against *Staphylcoccus aureus, Micrococcus luteus and Aeromonas hydrophyla*[142].



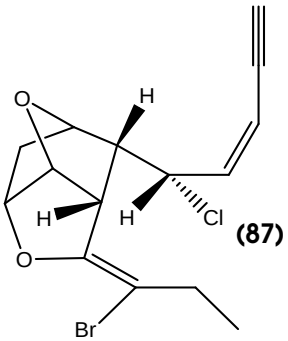


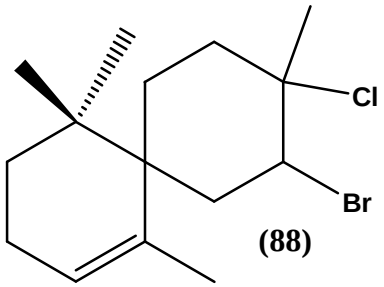






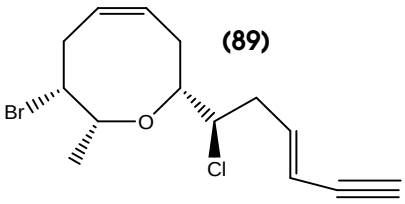
Red algae, in particular the genus Laurencia (Rhodophyta), are source of halogenated sesquiterpenes and diterpenes. Furthermore, this genus is unique in producing C15-acetogenins, for example those constituents which possess a terminal enyne such as **(87)**[143] There have been many chamigrenes **(88)** which have been isolated from the genus Laurencia[144].

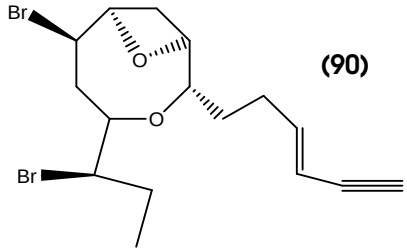




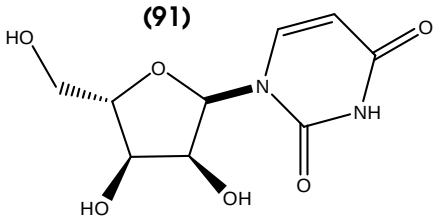
5β-dimethylcyclohexane**(89)** which are cyclic polyhalogenated monoterpenes isolated from the Chilean red alga *Plocamium cartilagineum* .These compounds show insecticidal activity against the Aster leafhopper, *Macrosteles fascifrons*[145] .Other examples include laurepinnacin , an acetylenic cyclic ether from the red alga *Laurencia pinnata* Yamada, and

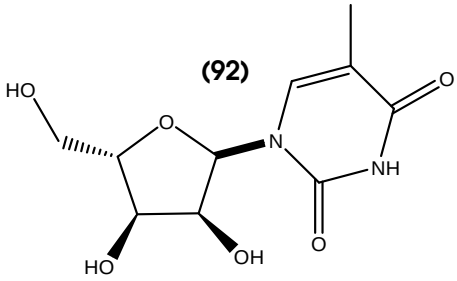
(*Z*)laureatin **(90)** from the red alga *L.* nipponica Yamada. These have all shown to display potent insecticidal activity against the mosquito larva, *C. Pipiens*[146].

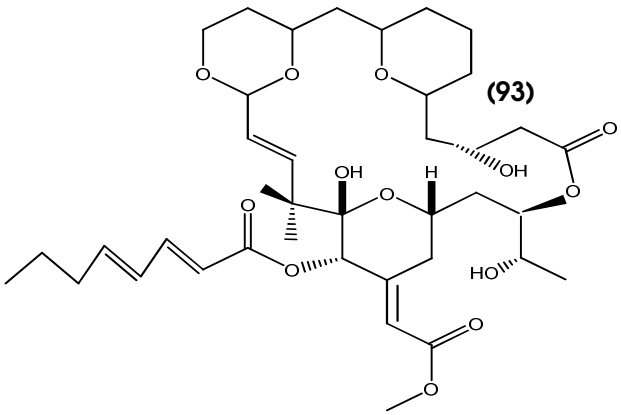


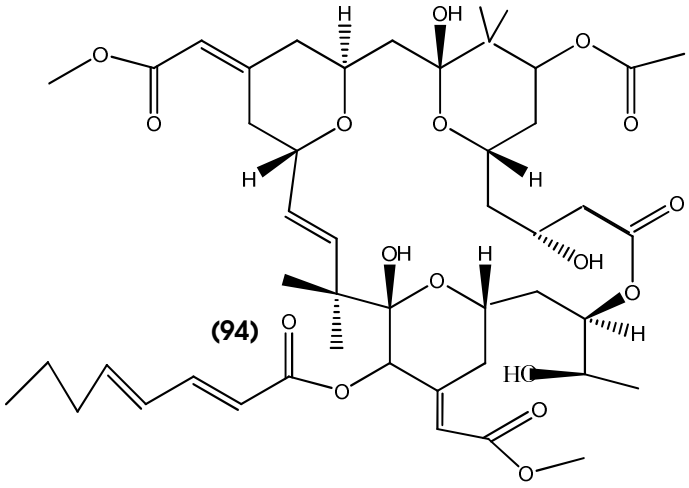


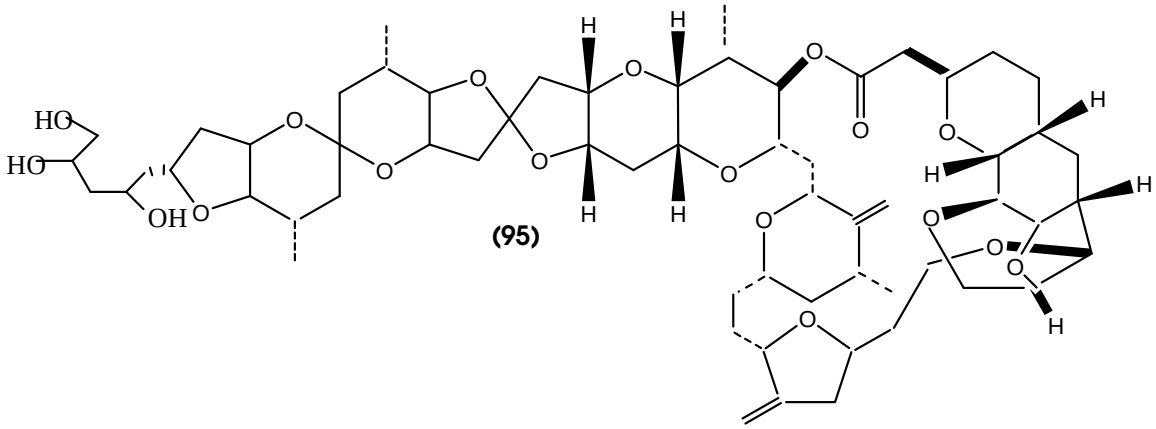
Natural Products from Marine Sponges: The first discovered biologically active compound from marine sponge source is reported on the isolation and identification of spongouridine **(91)** and spongothymidine **(92)** from the Caribbean sponge *Cryptotheca crypta* , which have antiviral activity and the synthesis of structural analogues led to the development of cytosine arabinoside (Ara-C) as a anticancer agent, together with (Ara-A) as an antiviral agent[147]. The bryologs **(93)** class of synthetic derivatives, derived from bryostatin 1 **(94)** an antineoplastic compound isolated from the bryozoan, *Bulgula neritina* used as an anti-Alzheimer's drug[148-149]. Halichondrin B **(95)** has been isolated from *Halichondria okadai sponge, used* for the treatment of breast carcinoma[150].











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DRUG DISCOVERY PROCESS FROM NATURAL PRODUCTS PRO'S AND CON'S:

The drug development from the natural resources has some pros as well as con's are as follows:

PROS

1. Natural products are very large in numbers with an excellent chemical diversity.
2. Natural products are "naturally bioactive". They come from life organisms and have been tailored to play a biological role.
3. Long term history of usage.
4. Wider public acceptance.
5. Limitations of original molecule can be overcome if the natural resources serve as starting point , as it has a bilateral promise of delivering the original isolate as a candidate or a semi-synthetic molecule development.

CONS

1. The choices to be made between crude extracts, fractions and pure compounds for the pharmacological screening are very difficult.
2. Concentration of active compounds in a fraction or in an extract is unknown.
3. Biological interferences occur between NP and enzymatic based screening tests.
4. NP are often chemically complex for medicinal chemists.
5. The access of biodiversity is considered to be complex, too expensive, with uncertain and difficult re-supply issues.
6. The convention on biodiversity recognises access of biodiversity to everybody. But in practice, it is difficult to find the right office or administrative centre which has the legal mandate to deal with these issues.
7. The rights attached to natural products are sensible and complex.
8. Difficult to patent NP.
9. Longer Derelictions and isolation steps
10. When we isolate an active product, hemi synthetic or synthetic derivatives of this compound have to be made to improve activity and to get quantitative structure activity-relationship information.
11. The drug discovery and eventual commercialization would pressurize the resource substantially and might lead to undesirable environmental concerns(151-152).

NATURAL PRODUCT DISCOVERY APPROACHES

Screening of natural product extracts is complicated due to the presence of fluorescent or insoluble compounds. Advances in detection technologies and new screening assays have

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overcome many of these challenges. Following are the approaches for drug discovery:

1. CELL-BASED ASSAYS

They are generally preferred in drug discovery because the assessment of molecular interactions occurs within the context of a living cellular environment. In addition, information about drug penetration is obtained early on. However, cell based activities are more variable and less sensitive, and may be more resource intensive due to extensive assay development time. Cell based assays can be simple growth inhibition assays measuring the effect of compounds on cellular growth. Such assays use spectrophotometric or turbidimetric method for detection of activity. Other cell-based assays that are frequently used in natural product discovery are those that measure activation of genes upstream of cellular functions like proliferation and differentiation [153-154]

2. BIOCHEMICAL ASSAYS

Biochemical assays have the advantages of providing target-specific information. One of the newer biochemical assays is a capillary electrophoresis (CE) technique used for the detection of functional activity of compounds as well as their relative binding strengths in crude extracts even in the presence of interferences. This approach uses electrophoretically mediated micro-analysis (EMMA) which incorporates laser-induced fluorescence detection for maximum detection[155-156].

3. NEWER DRUG DISCOVERY

Although bioactivity assays are most commonly employed to identify lead structures, newer screening methods are being developed which do not necessarily depend on an initial understanding of bioactivity. A virtual screening approach used in combination with HTS has proven to be effective in the search of neuraminidase (NA) inhibitors for influenza viruses A and B. The combination of virtual screening with HTS not only saves time but also money[157].

Other non-activity–based lead identification methods have utilized genetic studies of biosynthetic pathways of natural product. Trichamide**(96)** a cyclic peptide produced by a biosynthetic gene cluster in the genome of the global, bloom forming marine cyanobacterium Trichodesmium erythraeum[158]. Similarly, ECO-02301**(97)** an anti fungal secondary metabolite, was successfully discovered by a genomic approach. Another example is E-837**(98a)**,E-492**(98b)**,E-975**(98c).**Another example is aspoquinolones A-D**(99),** four prenylated quinolin-2-one alkaloids, were produced from Aspergillus nidulans HKI by the combination of genomic and analytical screening approaches[159].

The benefit of natural products is that their biological sources is most likely available and can be employed for production. With recent advances in whole genome sequencing, it is also likely that the genome of the biological source itself can be sequenced. By growing knowledge of the pathways and developments in genetics and sequencing it is become increasingly possible to manipulate these pathways to generate a new set of biologically active molecules that are similar to the parent compound. The combination of biological pathway modifications to design novel natural products engineered by rational pathways is described as combinatorial biosynthesis [160].

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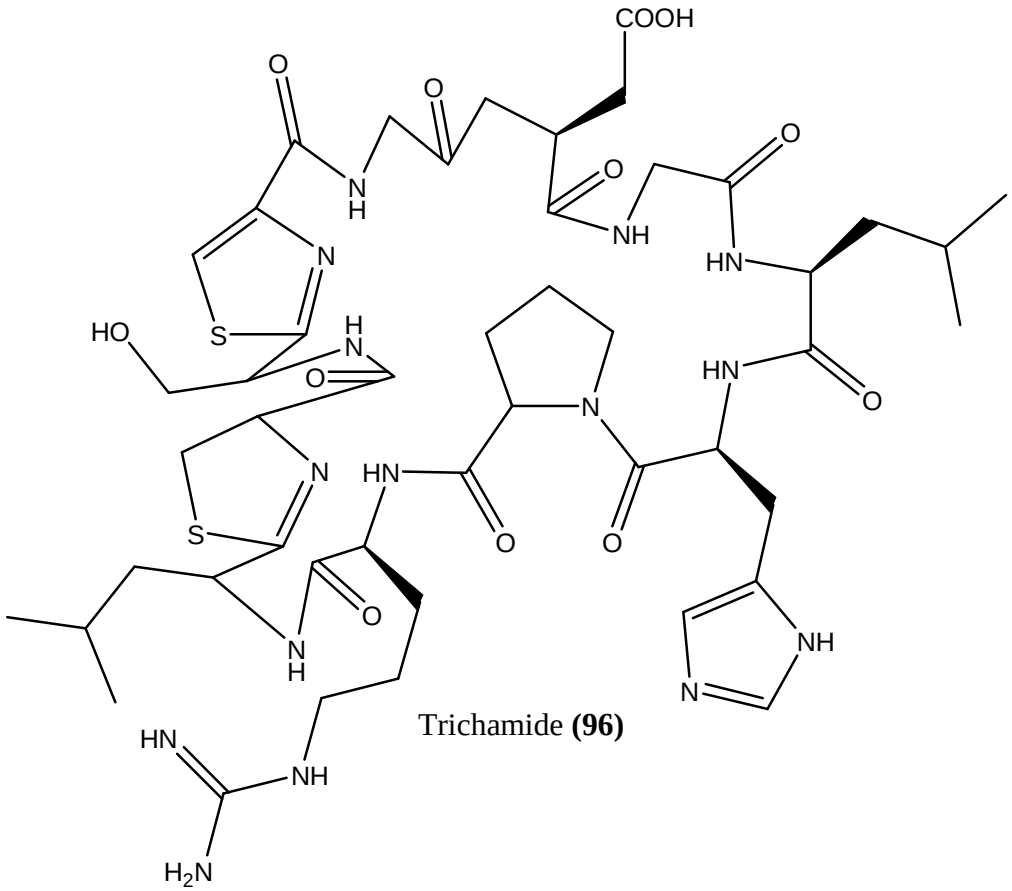
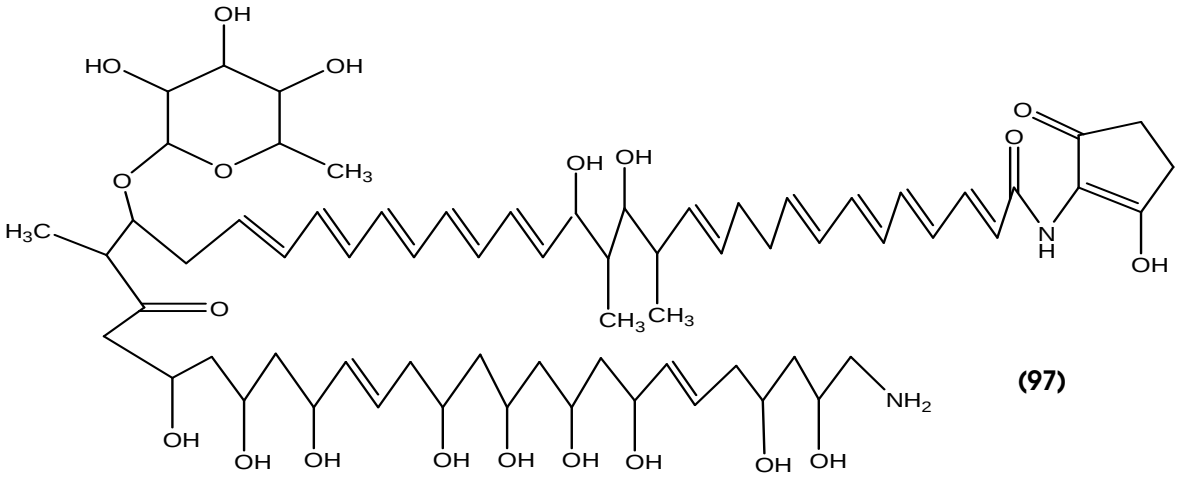


Trichamide **(96)**



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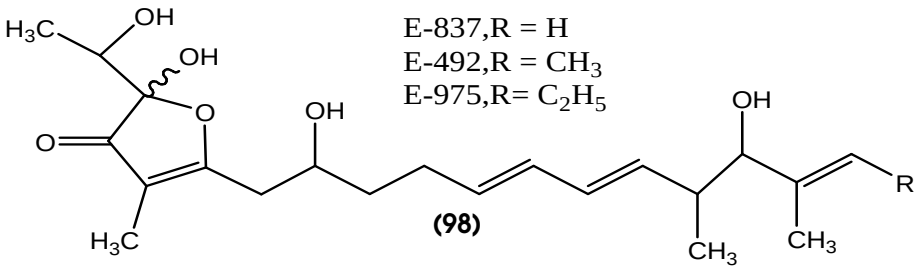
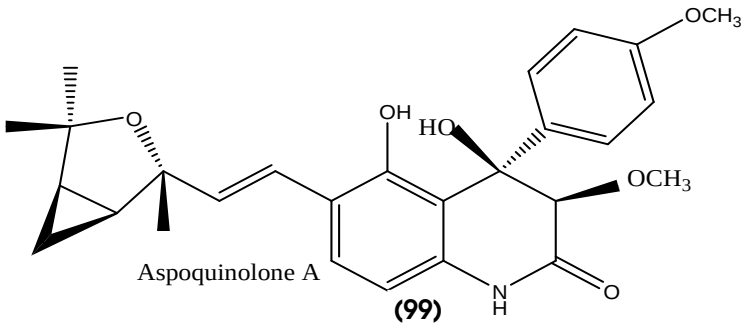


E-837,R = H
E-492,R = CH_3
E-975,R= C_2H_5

(98)



Aspoquinolone A

(99)

At present, all biochemical and cell-based assays are amenable to natural product screening with the possible exception of high content screening (HCS) method. HCS utilizes cell arraying and automated fluorescence imaging technology, and can provide spatial and temporal information in the context of structural and functional integrity of each individual cell. In vast majority of industrial natural products discovery programs, compounds with desirable characteristics (hits) are identified by bioactivity assays. Coupled with fractionation methods, purified bioactive single compounds are result.

ANALYTICAL TECHNIQUES: OVERCOMING HURDLES OF NATURAL PRODUCT DRUG DISCOVERY PROCESS

The natural product of interest must be extracted from the source, concentrated, fractionated and purified, yielding essentially a single biologically active compound, to be a potential drug lead. Historically, this process has suffered from three major hurdles. The first is to rapidly identify known compounds, a process known as "dereplication." This step has been greatly facilitated by advances in directly coupled high performance liquid chromatography-mass spectrometer (LC-MS) systems and searchable natural product computer databases. The most general of these methods known as electrospray ionization (ESI) and atmospheric pressure ionization (API), can generate the ions essential for mass spectrometric analysis for greater than 90% of analytes, ranging from amino acids to proteins and nucleic acids. Correlation of both molecular weight and UV absorption data with known compounds by database searching is normally sufficient to classify sets of compounds, and reduces the time required for dereplication to a matter of hours versus days or weeks previously[161-162].

The second major hurdle in the process is the structural determination of new molecular entities (NME) but it has been revolutionized by advances in spectroscopic techniques, particularly mass spectrometry and high resolution Nuclear Magnetic Resonance (NMR). The sensitivity is increased in these techniques and so sample can be worked up in less than a milligram to determine the structure. One of the most powerful of these techniques is Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR/MS), which is capable of measuring molecular mass with exceptional accuracy. Combining the tools of high-resolution mass spectrometry with two-dimensional NMR spectroscopy allows structure determination to be carried out on sub-milligram or milligram amounts of a compound in a matter of hours or days, rather than weeks or months. Although the determination of complex structures is technically challenging, it is no longer a major impasse in the drug discovery process. In those cases in which the biological activity profile meets criteria for potency and selectivity, preliminary SAR studies

are conducted and the process is scaled up[163-164].

The third challenge that continues to impact natural product drug discovery is the isolation and purification of the active principles from a complex matrix. While advances in separation technology, such as high performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC), and capillary electrophoresis have improved resolving power, the purification step in the process is often rate-limiting. This challenge is twofold. One must first correlate the biological signal of interest with the responsible compound(s), and then devise preparative separation methods to yield sufficient quantities of the pure material for further research. The general paradigm for bioassay-guided purification is shown in Figure 2. Progression is dependent upon how many "cycles" of fractionation and bioassay are required. In those cases when the bioassay turnaround time is lengthy, the delay can be a practical limitation. Innovative approaches have now been advanced to identify active components in mixtures by virtue of their target binding affinity. One approach is Frontal Affinity Chromatography (FAC), which has been employed to simplify the deconvolution of activities in natural product extracts. In FAC, the target is immobilized on a column and the mixture is continuously infused through the system. The compounds with the greatest affinity for the target will have the longest "breakthrough" times. Recently, NMR spectroscopy has been very effective in identifying active ligands in a natural product mixture by means of Saturation Transfer Difference (STD) approaches. Unlike synthetic compounds, supply of natural products may be initially limited, owing to sourcing limitations or the impracticality of synthesis. This "supply issue" is particularly critical for source organisms such as marine invertebrates or rare plants. However, microbial products, as well as many plant-derived agents, are amenable to culturing on a production scale. Importantly, synthetic methodologies continue to be developed for large-scale synthesis of highly complex products [165].

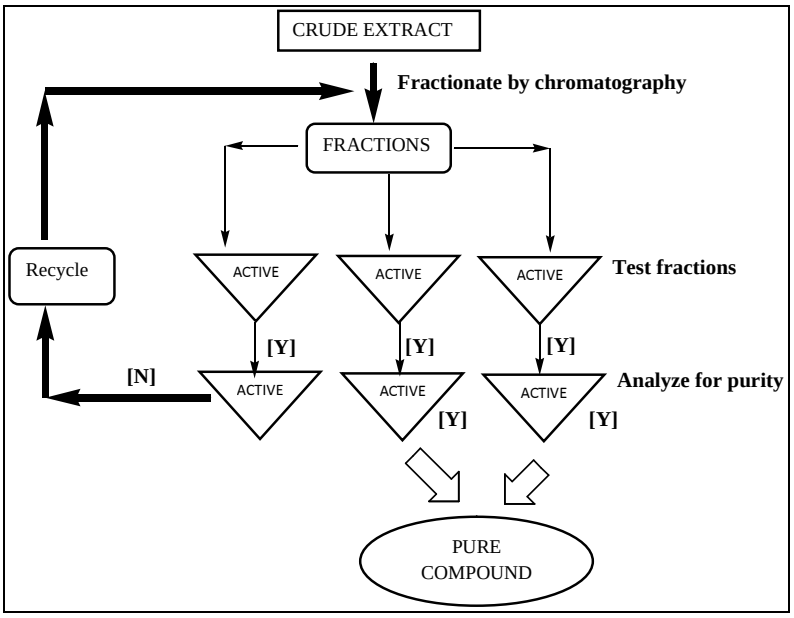


Figure 2: Paradigm for bioassay-guided purification

NEW TRENDS IN FIELD OF NATURAL PRODUCT DRUG DISCOVERY

The processes of drug discovery from natural products have been modified by some new advances:

1. The SepBox from Sepiatec Company is enabling to do Automatic isolation. This apparatus is able to prepare pure compounds from a crude extract by preparative HPLC extract by iterative HPLC.
2. NMR has moved forward with an impressive boost in sensitivity with high fields (900MHz), capillary-NMR, cryogenic probes, LC-NMR. It is possible, in theory, to screen in a NMR tube proteins ligand interactions.
3. After HPLC separation with Kiadis Company device, On-line multi pharmacological detections are today possible which allow parallel flow bioassay lines for biological activity, selectivity analyses and spectrometric data in order to obtain structural information.
4. Progress in metabolomics will soon permit to predict the chemical composition of a plant extract through the genome, transcriptome and proteome (enzymes) data [166-167].

CONCLUSIONS

Natural products as building blocks for molecular libraries, Instead of viewing natural products as a stand-alone approach distinct from combinatorial synthesis, it is now much more effective to implement strategies that combine both approaches. In various principle, it is seems the unique molecular diversity of natural products can be leveraged in the design of combinatorial libraries. The target-oriented or focused-library approach seeks to elaborate structural modifications onto an existing bioactive natural-product scaffold in analogue patterns, systematic fashion in order to ameliorate its inherent biological activity or drug-like properties. Presently, the drug discovery engine operates at an accelerated pace in comparison with the era in which natural products were pre-eminent sources of drug leads, numerous approaches have been developed to capture their intrinsic value. The essential breakthroughs in separation and structure determination technologies have lowered the hurdles inherent in screening mixtures of structurally complex molecules. The confluence of these technologies with advances in genomics, metabolic engineering and chemical synthesis offer the new method along with the technologies to explore the remarkable chemical diversity of nature's 'small molecules' in the pursuance for new drugs.

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Article History: ----------
Date of Submission: 16-09-2013
Date of Acceptance: 29-09-2013
Conflict of Interest: NIL
Source of Support: NONE