TANG [HUMANITAS MEDICINE]

Review

Biologically active compounds from natural and marine natural organisms with antituberculosis, antimalarial, leishmaniasis, trypanosomiasis, anthelmintic, antibacterial, antifungal, antiprotozoal, and antiviral activities

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ABSTRACT

The biologically active compounds derived from different natural organisms such as animals, plants, and microorganisms like algae, fungi, bacteria and merine organisms. These natural compounds possess diverse biological activities like anthelmintic, antibacterial, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral activities. These biological active compounds were acted by variety of molecular targets and thus may potentially contribute to several pharmacological classes. The synthesis of natural products and their analogues provides effect of structural modifications on the parent compounds which may be useful in the discovery of potential new drug molecules with different biological activities. Natural organisms have developed complex chemical defense systems by repelling or killing predators, such as insects, microorganisms, animals etc. These defense systems have the ability to produce large numbers of diverse compounds which can be used as new drugs. Thus, research on natural products for novel therapeutic agents with broad spectrum activities and will continue to provide important new drug molecules.

Keywords antituberculosis, antimalarial, leishmaniasis, trypanosomiasis, anthelmintic

Natural products as drug escorts

There is a need for new drugs in order to treat of various infectious diseases. Increasing levels of drug resistance to current drugs encourage the development of new and novel drugs with new mechanisms of action are prime importance. Natural products or their derivatives have played an important role in the treatment of a various infections (Butler, 2005; Potterat and Hamburger, 2006). Natural products are source of medicines and they continue to play an important role in the discovery of novel drug molecules (Buss and Waigh, 1995). Drugs derived from natural resources have been obtained from different sources including plants, animals, microorganisms, and marine organisms (Mayer et al., 2007; Chin et al., 2006; Cragg et al., 2005). However, natural product yields only small quantities of the desired compound, especially those obtained from marine sources. Therefore synthetic routes towards capable natural products have become a necessary to obtaining the compounds of interest in sufficient quantities for their therapeutic uses (Paterson and Anderson, 2005). Synthesis of natural products and analogues may allow for the enhancement of desirable properties like bioactivity, toxic selectivity and solubility (Newman and Cragg, 2007).

Diseases in need of novel therapeutics

Tuberculosis

Tuberculosis (TB) is a highly infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*) and remains today a leading cause of poverty, human suffering and death (Schluger, 2005; Smith, 2003). TB is responsible for the deaths of nearly two million people per year, with approximately one third of the global population infected with the latent form of the disease. While TB in humans is primarily due to infection with *Mtb*, several other species of the *Mtb* complex, namely *M. bovis*, *M. africanum*, *M. microti* and *M. canettii* may also cause the disease (Somoskovi et al., 2007; Tiruviluamala and Reichman, 2002). Two additional species have been suggested as belonging to the *M. tuberculosis* complex: *M. caprae* and *M. pinnipedii*. *M. tuberculosis* is a Gram-positive, nonmotile rod-shaped bacterium. These rod-shaped bacilli measure is 1 - 4 μm in length and 0.3 - 0.6 μm in diameter. *Mtb* is slow growing with a generation time of 12 - 20 h. Mycobacteria possess a unique cell wall of high lipid content, which includes mycolic acids and other glycolipids (Boulahbal and Heifets, 2006). This unique cell wall is to be responsible for certain features of mycobacteria, including low cell wall permeability and pathogenicity (Rezwan et al., 2007).

It is the low permeability of the mycobacterial cell wall which plays a significant role in the antibiotic resistance of *Mtb* (Rezwan et al., 2007). TB usually affects the lungs (pulmonary TB) of an infected person, but it can also affect other areas of the body including kidneys, bones, joints and lymph nodes (extrapulmonary TB). TB is an airborne disease that spreads like common cold, with the circulation of *Mtb*-containing aerosols into the air by coughing, sneezing, talking or spitting of a person with infectious TB. Inhalation of small number of these TB bacilli by a person will result in their infection with the disease. Once the *Mtb* containing aerosols enter the pulmonary alveoli, a healthy immune system will respond by "walling-off" the TB bacilli, resulting in their protection with a thick waxy coat that allows the TB bacilli to lay dormant for

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years (latent TB) (Tsai et al., 2006). A person infected with latent TB will exhibit none of the obvious symptoms of TB, which include a fever, fatigue, weight loss, a persistent cough and sputum production which will contain blood at an advanced stage of the disease. While a person with latent TB is not infectious, they may develop the active form of the disease if their immune system is compromised. A number of factors have led to the reduction in successful treatment of the disease. These include a lengthy (6 - 9 months) multi-drug treatment program, the misuse of which can lead to the development of MDR-TB or XDR-TB and the co-infection of TB with the human immunodeficiency virus (HIV) (Copp and Pearce, 2007).

This interaction with HIV, TB has become the leading cause of death among people infected with HIV, while infection with HIV has become the most significant risk factor for a person with latent TB developing the active form of the disease. The chemotherapy of TB was first introduced in 1946, with the antibiotic streptomycin used in 1955 a multi-drug treatment regimen had been developed for the treatment of TB in combination of streptomycin, *p*-aminosalicylic acid and INH. The current chemotherapy of infectious TB involves an initial two month treatment regimen with either: SM, INH, RIF and PZA; or INH, RIF, PZA, and EMB (first-line drugs). This is followed by treatment with isoniazid and rifampin over a 4-7 month period. Current chemotherapy of latent TB involves treatment with isoniazid for 6 - 9 months in order to prevent the development of the active form of the disease (Janin, 2007). Treatment with multiple drug regimens over an extended period of time is necessary in order to minimize the emergence of MDR-TB. The long period of treatment is also necessary for the persistence of *Mtb* in the host during infection (Cho et al., 2007; Liu and Ren, 2006). Patient non-compliance, often due to the lengthy treatment period, has led to an increase in drug resistance. The MDR-TB is a tubercule bacilli resistant to at least INH and RIF (two most potent anti-TB drugs) (Janin, 2007).

Treatment of MDR-TB requires up to two years of treatment with second-line anti-TB drugs (cycloserine and ethionamide which have more side effects and are more expensive than the first-line drugs. The development of XDR-TB can then occur when second-line drugs are misused. XDR-TB is that is resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin, in addition to INH and RIF resistance (MDR-TB) (Fig. 1) (WHO, 2007; Tierney and Nardell, 2007). The WHO have executes a directly observed therapy short course (DOTS) program in an attempt to overcome the problem of patient non-compliance (Liu and Ren, 2006). However, this strategy is difficult to carry out in areas most at risk due to the lack of resources and infrastructure required to ensure adequate monitoring of drug administration (Opsenica et al., 2003; Liu and Ren, 2006). Therefore an urgent need is to develop new anti-TB drugs with greater potency and shorter duration of treatment. This should result in better patient compliance, which in turn should reduce the development of MDR-TB and XDR-TB. Novel anti-TB drugs are also needed to treat the current strains of MDRTB and XDRTB.

Tropical diseases

Malaria

Malaria, which is caused by multiplication of the protozoan parasite *Plasmodium falciparum* in erythrocytes, is a major health problem in many southern countries (Breman, 2001). More than 400 million disease cases with over 1.5 million fatalities are the annual toll of *P. falciparum* infections. The development of resistance to the standard antimalarial drug chloroquine (CQ), which had been the affordable and effective antimalarial mainstay for 50 years, has severe health implications for countries in malaria endemic regions. In a recent genetic study of the malaria parasite, it is found that this species is unexpectedly diverse; another study points to the multiple independent origins of mutations in one parasite gene that confer resistance to a widely used drug such as CQ. The results show that, in principle, *P. falciparum* could rapidly develop resistance to multiple drugs, additionally justifying further search for new drugs. The antimalarial properties of artemisinin and of other peroxides such as 1,2,4,5-tetraoxacycloalkanes against CQ-resistant strains opened a new approach to fighting malaria (Mendis et al., 2001). Malaria is one of the most common infectious diseases in tropical and subtropical countries, including parts of the Americas, Asia, and Africa. Each year, it affects nearly 400 - 900 million people and causes approximately one to three million deaths annually. Human malaria is caused by *P. falciparum, P. malariae, P. ovale,* and *P. vivax,* however, *P. falciparum* is the most prevalent for the disease and it is responsible for about 80% of infections and 90% of deaths. The first effective treatment against the *P. falciparum* parasite was the bark of cinchona tree, which contains quinine, a quinoline alkaloid. A number of medicines have been developed to treat malaria with chloroquine and its derivatives 3 as the mainstay therapy. In recent years, *P. falciparum* has become increasingly resistant to conventional antimalarial drugs, and the search for new antimalarial compounds by combining natural sources and synthetic approaches is still underway (Gessler et al., 1994; Iwasa et al., 1999; Lim et al., 2007; Theerachayanan et al., 2007; Tran et al., 2003). Malaria continues to be a growing health problem of global concern, mostly among children, malaria puts a heavy economic burden on the developing countries by exhausting health system resources and by associated loss of economic activity. Only a limited number of chemotherapeutic agents for the treatment of malaria is available, and the growing problem of drug resistance makes adequate treatment of malaria increasingly difficult (WHO, 1998). In the absence of a functional, safe and widely-available malarial vaccine, efforts to develop new antimalarial drugs are profoundly important. Since the majority of the existing antimalarial chemotherapeutic agents are based on natural products (Ekthawatchai et al., 1999), biological chemodiversity continues to play an important role in the search that would lead to antimalarial drugs. Therefore, it is necessary to search for new compounds as back-up antimalarials. As a part of our continuous search for novel bioactive compounds from plant source, plants in the genus Diospyros are the rich sources of biologically-active metabolites (Gu et al., 2004; Theerachayanan et al., 2007).

Malaria is a public health problem most especially in the tropical countries where majority bear the burden of the disease (MIM, 2004). About two million children, mostly less than five years and pregnant women die from malaria related illness each year and nine out of ten cases are found in Sub-saharan Africa (WHO, 2001). Most vulnerable group in the endemic areas constitutes people in the rural environments who often had little or no access to modern medicine. This situation has been complicated further by the emergence of MDR strains of *P. falciparum* and rapid spread of vectormosquito resistance to insecticides (Coker et al., 2000, Masaba et al., 2000). Hence, there is an urgent need to find alternative therapies that are not only effective against resistant malaria but are also available and a-fordable to this vulnerable group who are not economically buoyant to afford expensive orthodox medicine

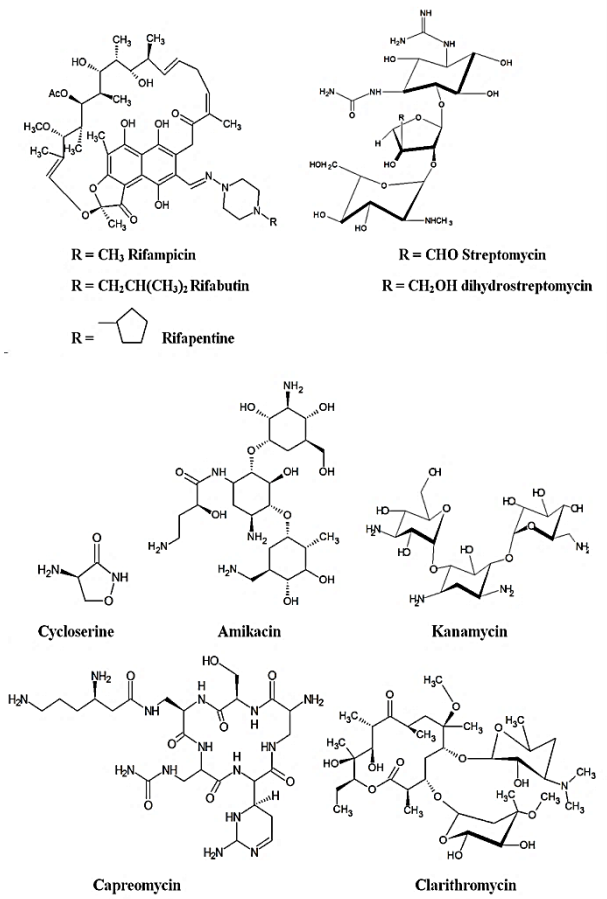

Fig. 1. Structures of some drugs for the treatment of tuberculosis.

or have no access to modern health facilities (Oyewole et al., 2008).

Malaria is a disease of enormous importance by any standard of measure and the recent emergence and rapid spread of chloroquino-resistant strains of *P. falciparum* threaten to increase the annual death toll. As a result, there is a great need for development of novel antimalarial drugs. Out of the four species of *Plasmodium* that affects humans, *P. falciparum* is the most prevalent and pathogenic. Terpens, alcaloids and oxygenated heterocycles are potentially active against malaria (Go, 2003). The Calophyllum and Garcinia species of the Clusiaceae family are a well-known source of phenolic secondary metabolites, especially xanthones. In the last few years, a huge number of prenylated and non-prenylated xanthones have been identified from thoses species. In the present study, we focused our attention on two plants native to New-Caledonia: Garcinia vieillardii, from which we first isolated antioxidant xanthones (Hay et al., 2004) and *Calophyllum caledonicum*, latex is used as a diuretic. As part of our ongoing project on the isolation of natural compounds from Clusiaceae and the assessment of their biological activity, we recently characterized from *C. caledonicum* new antifungal xanthones and chroman acids inhibiting pea seeds mitochondria (Hay et al., 2003; Morel et al., 2002). The evaluation of the antiplasmodial activity of natural xanthones isolated from both *C. caledonicum* and *Garcinia vieillardi* along with some synthetic derivatives prepared during the project dealing with the total synthesis of original natural xanthones (Hay et al., 2004; WHO, 2007).

Four species of *Plasmodium* are responsible for human

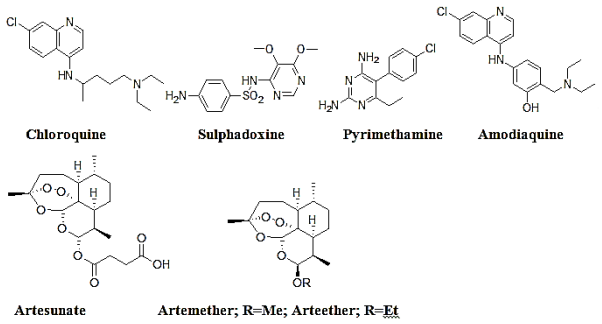

Fig. 2. Antimalarial drugs.

malaria, namely *P. falciparum*, *P. vivax*, *P. malariae* and *P.ovale*. Of these, *P. falciparum* is the most likely to progress to severe illness or death (Griffith et al., 2007). Those people living in the poorest communities worldwide are at the greatest risk of contracting malaria, with the majority of cases and deaths found in sub-Saharan Africa. Other areas also affected by the disease are Asia, Latin America, the Middle East and parts of Europe. The majority of deaths resulting from malarial infection in Africa are among young children. Every 30 seconds a child in Africa is killed by malaria and many of those children who survive a severe episode of malaria are at risk of suffering brain damage or learning impairments as a result of infection with the disease. The *Plasmodium* parasites are transmitted from person to person through the bite of an infected female *Anopheles* mosquito needing blood to nurture her eggs. Once inside the human host, the malaria parasite goes through a series of changes as part of its life-cycle. The parasite is able to evade the immune system as a result of the various stages it progresses through in the life-cycle, allowing the parasite to infect the liver and red blood cells of the host. Eventually the parasite develops into a form that can be transmitted to a mosquito when it bites the infected host. Then once inside the mosquito the parasite matures until it reaches the sexual stage, the stage at which it can again be transmitted to a human through the bite of the infected vector. The first symptoms of the disease appear 10 to 15 days after being infected and include fever, vomiting, headache and chills (WHO, 2007). If treatment is not available or the parasite is resistant to drugs used to treat the disease, then rapid progression to severe illness or death can occur (WHO, 2007).

The emergence and rapid spread of antimalarial drug resistance is a major contributing factor to the increasing rates of mortality and morbidity due to the disease (Golenser et al., 2006). The inappropriate use of antimalarial drugs such as chloroquine, sulfadoxine, pyrimethamine and amodiaquine during the past century has contributed significantly to the development of multi-drug resistance of *P. falciparum* to conventional malaria chemotherapies (WHO, 2007). More recently a class of artemisinins (including artesunate, artemether and arteether (Fig. 2), have been developed as antimalarial drugs.

These drugs possess the most potent and fast-acting antimalarial activity of all antimalarial drugs, are active against multi-drug resistant *P. falciparum* and to date no resistance to this class of compound has been reported (WHO, 2007). Currently WHO recommends artemisinin-based combination therapies (ACTs) for the treatment of drug resistant malaria (WHO, 2007). However, the increased use of ACTs in the treatment of malaria is placing greater drug pressure on the parasite which may increase the chances of the resistant parasite genotypes being selected. There are currently no alternatives to the use of artemisinins in the chemotherapy of *P.*

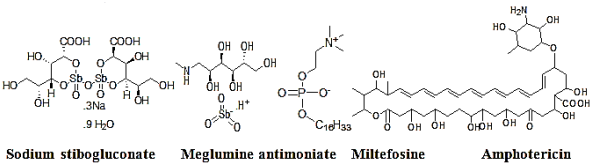

Fig. 3. Antileishmanial drugs.

falciparum malaria (WHO, 2007). There is also the issue of neurotoxicity, with the artemisinins found to be neurotoxic in *in vivo* animal model assays and *in vitro* studies with neuronal cell cultures (Haynes, 2006). However the neurotoxicity in the animal models was dependent upon the route of administration and it has not been definitively proven if these drugs cause neurotoxic side effects in humans (Haynes et al., 2006). The emergence of drug resistant malaria in combination with the lack of vector control has created a pressing need for discovery of new antimalarial drug candidates in the fight against the disease.

Leishmaniasis

Leishmaniasis is a devastating disease caused by infection with kinetoplastid parasites of the genus *Leishmania*. Globally 350 million people in 88 countries on five continents (Africa, Asia, Europe, North America and South America) are at risk of infection with the disease, with a yearly incidence of two million cases (Luque-Ortega and Rivas, 2007; Salem and Werbovetz, 2006). There are twenty *Leishmania* species that are pathogenic for humans, which are transmitted through the bite of female phlebotomine sandflies (Lukes et al., 2007). There are three main forms of the disease namely visceral leishmaniasis (VL or kala-azar), cutaneous leishmaniasis (CL) and mucocutaneous leishmaniasis (MCL). VL infection is the most severe form of the disease and if left untreated is fatal. It is estimated that 500,000 people are affected by this disease annually, with 90% of cases occurring in Bangladesh, India, Nepal, Sudan and Brazil (Rijal et al., 2007). Members of the *L. donovani* complex are the causative agents of VL, where the parasites reside in the liver, spleen and bone marrow and are classified into four species: *L. archibaldi*, *L. chagasi*, *L. donovani* and *L. infantum*. Infection with the cutaneous form of the disease typically results in the development of chronic, self-healing skin ulcers at the site of the sandfly bites 36. It is estimated that 1.5 million people are affected by CL annually, with 90% of cases occurring in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria (Lukes et al., 2007).

CL is not a fatal disease but can result in mutilation, disfiguration or disability when the skin lesions are multiple. A range of *Leishmania* parasites have been found to cause CL. In the Old World, the disease is caused by several species including *L. major*, *L. tropica* and *L aethiopica*, while CL in the New World is primarily caused by members of the *L. vianna* subgenus (including *L. v. panamensis* and *L. v. braziliensis*) and members of the *L. mexicana* complex (including *L. m. amazonensis* and *L. m. mexicana*) (Akilov et al., 2007; Soto and Berman, 2006). Infection with the mucocutaneous form of the disease typically results in lesions in the mucous tissues of

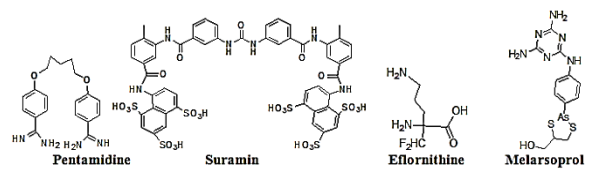

Fig. 4. Drugs used to treat chagas disease.

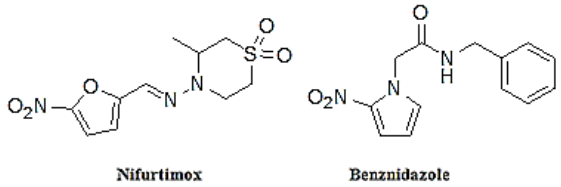

Fig. 5. Drugs used to treat sleeping sickness.

the nose, mouth, throat cavities and surrounding tissues (Salem and Werbovetz, 2006). While infection with MCL is not life threatening, the lesions often result in massive tissue destruction and disfiguration which can cause significant social prejudice. The number of people suffering from leishmaniasis has increased over the last decade and of particular concern is the emergence of *Leishmania*/HIV coinfection, where *Leishmania* acts as an opportunistic parasite. Cases of *Leishmania*/HIV coinfection have been reported in 35 countries, with the majority of the cases in southwestern Europe. The visceral form of the disease is most frequently associated with HIV and in the recent past 70% of adult cases of acute VL have been coupled with HIV infection and up to 9% of AIDS (acquired immune deficiency syndrome) sufferers develop opportunistic VL (Donaghy et al., 2007). Chemotherapy is the only means of treatment of leishmaniasis, with the pentavalent antimonials sodium stibogluconate and meglumine antimonate first-line drugs having been used to treat the disease for over 50 years (Fig. 3). There are however a variety of drawbacks to using these drugs to treat leishmaniasis including increasing incidence of drug resistant parasites, long duration of treatment by injection in hospital, and toxic side effects. Amphotericin B is a secondary treatment and has become a first choice drug in north-west India where increasing resistance to antimonials has been observed, however the drug exhibits renal toxicity. More recently new agents have been found to exhibit better efficacy against Indian VL. One such example is liposomal amphotericin B, which requires fewer injections and is well tolerated. Another example is the orally active agent miltefosine. However, liposomal amphotericin B is expensive making it unaffordable in developing nations, while miltefosine is possibly teratogenic and so should be used under strict observation and to avoid the development of drug resistance should be utilized in combination (Boelaert et al., 2002). There is therefore a great need for new drugs to treat leishmaniasis.

Trypanosomiasis

Human trypanosomiasis is yet another vector-borne tropical disease that is in need of novel therapeutics. The disease is caused by parasitic protozoan trypanosomes of the genus *Trypanosoma* (African Trypanosomiasis, 2007). There are two forms of human trypanosomiasis, namely African trypanosomiasis (sleeping sickness) and American trypanosomaisis (Chagas disease) (Fig. 4).

African trypanosomiasis (Sleeping sickness)

Sleeping sickness is transmitted to humans through the bite of an infected tsetse fly, with 60 million people at risk and tens of thousands killed every year as a result of infection with the disease (Willert et al., 2007). There are two forms of African trypanosomiasis depending on the parasite involved. These are *Trypanosoma brucei rhodesiense* found in Eastern and Southern Africa, and *T. b. gambiense* found in Western and Central Africa. The *Trypanosoma* parasites are injected in the saliva of the tsetse fly (male and female) into the host upon being bitten. Initially the trypanosomes multiply in the

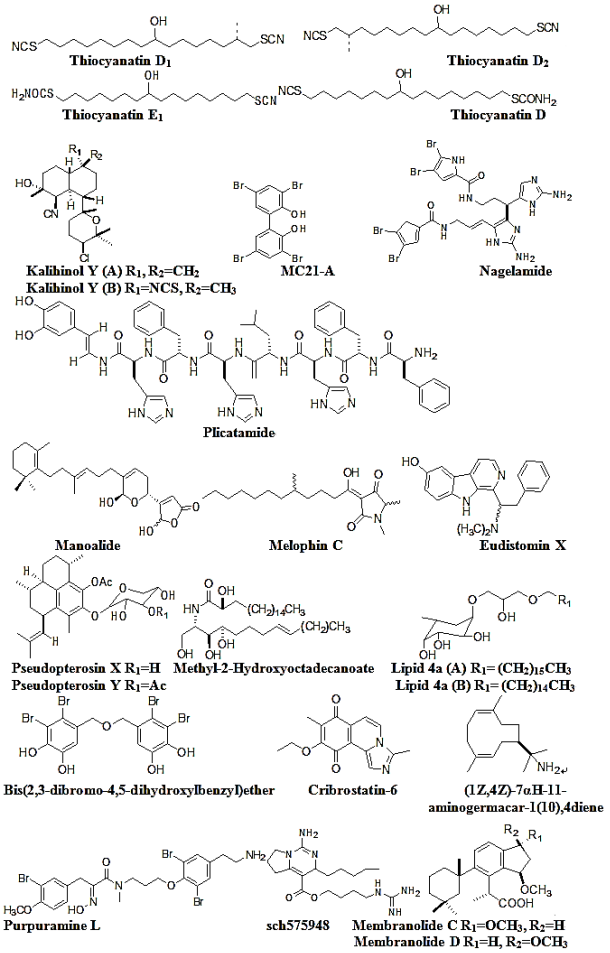

Fig. 6a. Anthelminthic and antibacterial compounds.

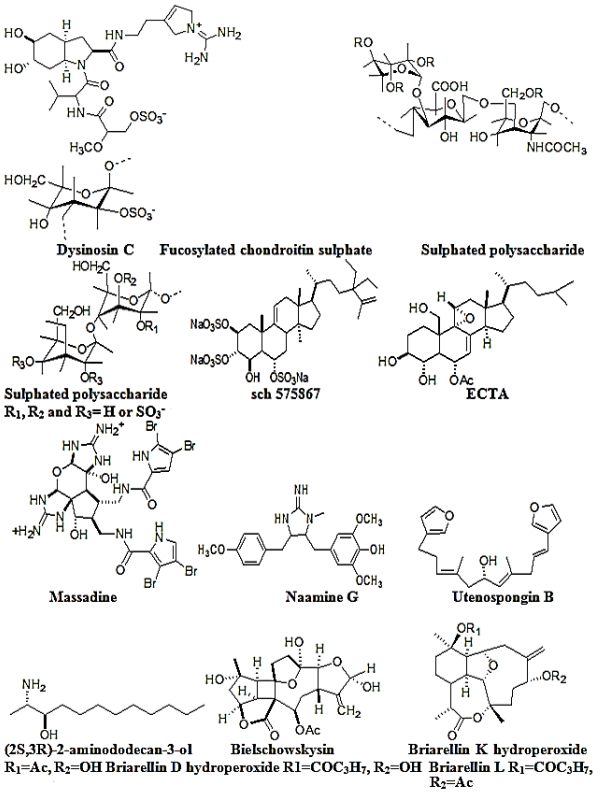

Fig. 6b. Anthelminthic and antibacterial compounds.

subcutaneous tissues, the bloodstream and the lymphatic system. After a period of time the *Trypanosoma* parasites cross the blood-brain barrier to invade the central nervous system (CNS). Symptoms from the first stage of sleeping sickness (haemolymphatic phase) include irregular fever, headaches, progressive apathy, enlarged lymph glands and spleen, joint pain, swollen tissues and anemia.

The second stage (neurological phase) begins once the parasite has crossed the blood-brain barrier with symptoms including confusion, increased apathy, sensory disturbances, poor coordination, and sleep abnormalities (African Trypanosomiasis, 2007; Salem and Werbovetz, 2006). Without treatment the disease progresses to the final stage resulting in seizures, drowsiness, coma and death. Infection with *T. b. rhodesiense* accounts for less than 10% of the reported cases of sleeping sickness, with this subspecies causing acute infection and symptoms develop after only a few weeks or months. Progression of the disease is rapid with the parasite invading the CNS. Infection with *T. b. gambiense* accounts for over 90% of the reported cases of African trypanosomiasis, with this subspecies causing a chronic form of the disease where a person can be infected for months or years without any symptoms developing. However, once symptoms have developed the disease is likely to have progressed to an advanced stage where the CNS is affected. Many wild and domestic animals can develop trypanosomiasis, with the subspecies *T. b. brucei* the cause of animal trypanosomiasis in cattle (Salem and Werbovetz, 2006; African Trypanosomiasis, 2007). Animals can also host the human pathogenic parasites, in particular *T. b. rhodesiense*. Animals therefore play a significant part in the spread of the disease by acting as reservoir hosts. This disease is also lethal to animals and the infection of cattle is particularly damaging to economic growth in affected rural areas (African Trypanosomiasis, 2007).

Treatment of sleeping sickness depends on the stage of the disease. Pentamidine is used to treat the first stage of *T. b. gambiense* infection (Fig. 5), while suramin isused in the treatment of the first stage of *T. b. rhodesiense* infection. The drugs used to treat the first stage of the disease are less toxic, more effective and more easily administered. However, in order to successfully treat the second stage of the disease the drugs need to be able to cross the blood-brain barrier (BBB). Melarsoprol is used to treat both forms of sleeping sickness in the second stage, while eflornithine is only effective against second stage *T. b. gambiense*. These second phase drugs are more difficult to administer and they are relatively toxic (African Trypanosomiasis, 2007). There is also the problem of developing resistance to melarsoprol, which has increased to 30% in areas of central Africa (Salem and Werbovetz, 2006). Therefore there is a pressing need to develop new therapeutic agents for the treatment of sleeping sickness with greater potency and less toxicity.

American trypanosomiasis (Chagas disease)

American trypanosomiasis, a disease caused by the parasite *T. cruzi*, is widespread throughout Latin America with the prevalence of human infection estimated at 16-18 million cases and 21,000 deaths per year due to the disease. Approximately 120 million people (25% of inhabitants of Latin America) are at risk of contracting the disease. Transmission of Chagas disease occurs through the blood-feeding of "Assassin" bugs (subfamily of *Triatomina*e), blood transfusion, organ transplantation and transplacentally. The "Assassin" bugs are typically located in poor quality housing, usually in rural areas. They surface during the night to take a blood meal from the

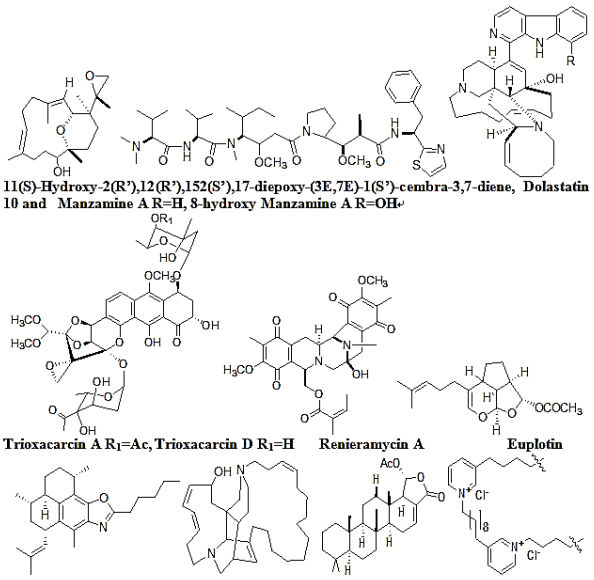

Fig. 6c. Anthelminthic and antibacterial compounds.

inhabitants, during which the infective parasite (*T. cruzi*) is released into the insect's faeces. *T. cruzi* then enters the host through the wound produced by the insect's bite or through anintact mucous membrane, for example the conjunctiva. This usually results from the host unknowingly rubbing the infected faeces into the bite wound, the mouth or the eye (Salem and Werbovetz, 2006). American trypanosomiasis is a zoonotic disease that affects a variety of mammals including dogs, cats, bats and rodents, which serve as reservoir hosts (Salem and Werbovetz, 2006). The initial stage of Chagas disease is an acute phase during the first few weeks or months of infection and is typically symptomless. However, a small number of patients exhibit symptoms which include tiredness, fever, enlarged liver or spleen, and swollen lymph glands. The most well recognised symptom of the acute phase of Chagas disease is the swelling of the eyelid, either due to the bite wound being close to the eye or because infected faces were rubbed into the eye. On occasion, infants and young children die as a result of severe inflammation or infection of the heart muscle or the brain. If left untreated the acute phase will develop into the chronic phase of the disease. Approximately 30% of people with Chagas disease are at risk of developing fatal cardiac and intestinal complications, which can take decades to develop during the chronic phase (Chagas Disease Fact Sheet, 2007). Possible cardiac complications include an enlarged heart, heart failure, altered heart rate or rhythm and cardiac arrest. Intestinal complications can include the development of irreversible lesions of the gastrointestinal tract, and enlarged oesophagus or colon (Chagas Disease Fact Sheet. 2007; Salem and Werbovetz, 2006).

The main treatment of Chagas disease involves chemotherapy with the nitroheterocyclic drugs, nifurtimox and benznidazole. These drugs are most effective in treating acute phase or short term (up to a few years) chronic phase of the disease. However, they exhibit very low potency against long term chronic phase Chagas disease. Treatment with these drugs also results in several serious side effects including vomiting, anorexia, allergic skin disorders and peripheral polyneuropathy (Salem and Werbovetz, 2006). As a result new drugs for the treatment of Chagas disease are required possessing greater potency and less toxicity.

Anthelminthic and antibacterial compounds (Fig. 6)

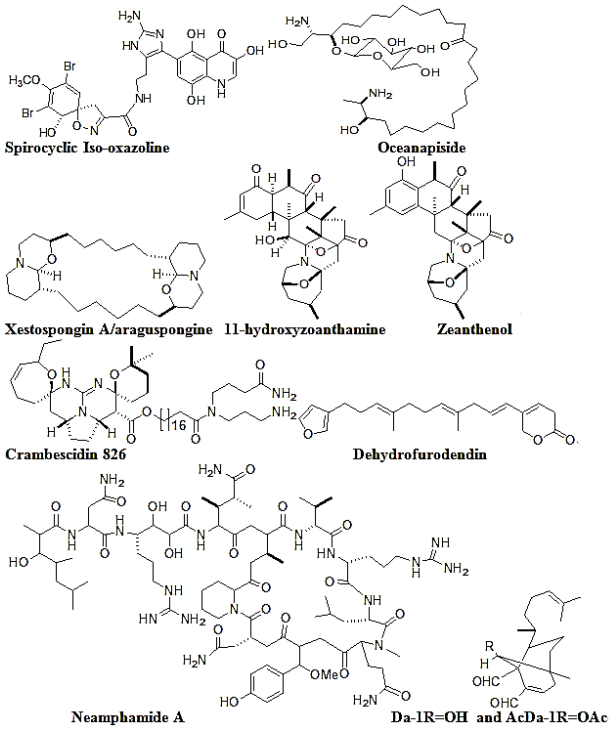

Fig. 6d. Anthelminthic and antibacterial compounds.

One study contributed to the search of novel anthelmintic marine natural products. The novel acyclic lipids thiocyanatins, were isolated from the Australian sponge Oceanapia sp. (Capon et al., 2004) and were shown to be nematocidal (LD99 = 3.1 – 8.3 µg/ml) to the commercial livestock parasite Haemonchus contortus. Although the mechanism of action of these compounds remains undetermined, the investigators noted that both the 2°-alcohol, SCN functionalities and chain length influenced the nematocidal activity.

In view of the fact that resistance to current antibiotics remains a significant challenge for pathogenic bacterial infections, studies contributed to the search for novel antibacterial marine natural products (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005). Four studies reported on the mechanism of action of novel marine antibacterial agents. A series of kalihinols, diterpenes isolated from the Philippine marine sponge Acanthella cavernosa, as potential bacterial folate biosynthesis inhibitors. The investigators reported that the pyranyl-type kalihinols Y and X, although potent antibacterials (MIC = 1.56 µg/ml), were however less selective inhibitors of bacterial folate biosynthesis than the furanyl type kalihinols, with the "C-10 position important for potency" (Bugni et al., 2004). A bactericidal compound named MC21-A, a 3,3′,5,5′-tetrabromo-2,2′-biphenyldiol, from the new marine bacterium Pseudoalteromonas phenolica sp. nov. MC21-A was bactericidal (MIC = 1 - 2 µg/mL) against 10 clinical isolates of methicillin-resistant *S. aureus*, and displayed comparable bioactivity to vancomycin (MIC = 0.25 - 2 µg/ml). The mechanism of action of MC21-A involved permeabilizing bacterial cell membranes, and thus "might be a useful compound" because of a mode of action that differs from vancomycin (Isnansetyo and Kamei, 2003).

A new dimeric bromopyrrole alkaloid, nagelamide G was isolated from the Okinawan marine sponge Agelas sp. (Endo et al., 2004). Nagelamide G exhibited antibacterial activity against *M. luteus*, *B. subtilis* and *E. coli*, but weakly inhibited

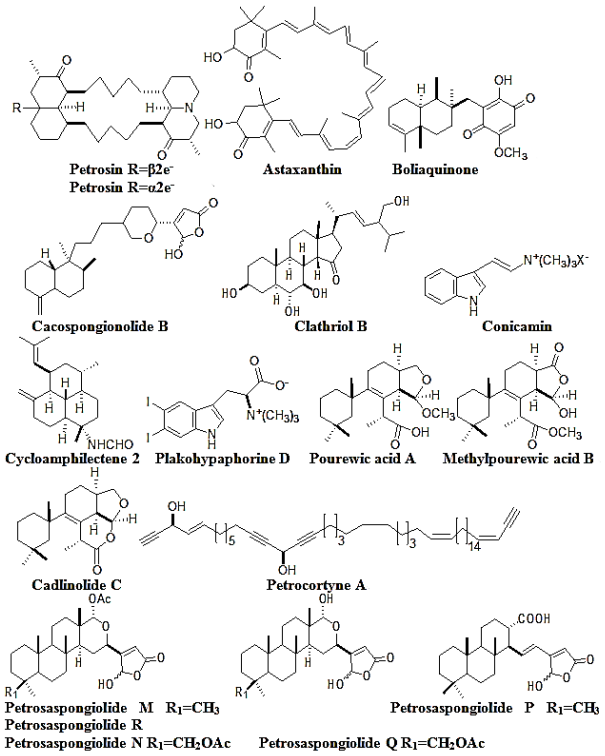

Fig. 6e. Anthelminthic and antibacterial compounds.

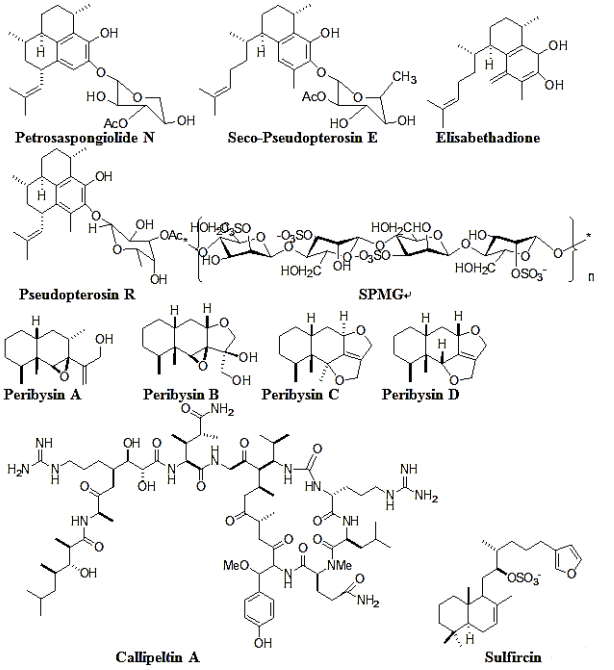

Fig. 6f. Anthelminthic and antibacterial compounds.

protein phosphatase 2 A (IC_{50} = 13 μM), thus suggesting that this enzyme may not be the main molecular target responsible for the antibacterial activity of this compound. A new antimicrobial octapeptide plicatamide from the hemocytes of the marine tunicate *Styela plicata*, In a detailed mechanistic study these investigators discovered that despite its small size, the octapeptide plicatamide proved to be a potent, rapidly acting and broad spectrum antimicrobial. The fact that both wild type and methicilin-resistant S. aureus responded to plicatamide with a massive and rapid potassium efflux is "consistent with an antimicrobial mechanism that targets their cell membrane". Nevertheless, these studies highlight the fact that novel antibiotics are present in marine bacteria, tunicates, sea hares, soft corals, algae, sponges, worms, and fish (Tincu et al., 2003).

Two papers reported on antibacterial activity in compounds isolated from marine sponges: the isolation of several manoalide derivatives from a Luffariella sp. sponge collected in Palau, which was active against *S. aureus* at 5 – 10 μg/disk. The presence of an OH group at the C-25 position (hemiacetal moiety) is important for antibacterial activity (Namikoshi et al., 2004). Thirteen tetramic acids isolated from the marine sponge *Melophlus sarassinorum*. Interestingly, only melophlin C showed pronounced antibacterial activity against B. subtilis and S. aureus (Wang et al., 2003a). Antimicrobial compounds isolated from marine tunicates: the β-carboline eudistomin X, isolated from the *Micronesian ascidian Eudistoma s*p. was active against *B. subtilis*, *S. aureus* and *E. coli* (Schupp et al., 2003). An antimicrobial peptide isolated from sea hares: 33 amino acid antimicrobial peptide dolabellanin B2 from the sea hare *Dolabella auricularia*. One hundred percent inhibition of growth of *B. subtilis*, *H. influenza* and *Vibrio vulnificus* was reported with 2.5 - 5 μg/mL dolabellanin B2 (Iijima et al., 2003). Antimicrobial peptides isolated from marine soft corals: two new diterpenes, pseudopterosin X and Y from the soft coral Pseudopterogorgia elisabethae which showed antibacterial activity against Gram-positive bacteria *Streptococcus pyogenes*, *S. aureus*, and *Enterococcus faecalis*, while being inactive against Gram-negative bacteria (Ata et al., 2004).

Several sphingolipids and glycolipids from soft corals of the Andaman Islands (Indian Ocean) (Dmitrenok et al., 2003). Although the MIC were not reported, "preliminary tests for antibacterial activity of lipids" demonstrated that these compounds inhibited the growth of *E. coli*, *Pseudomonas aeruginosa*, *B. subtilis* and *B. pumilus* on solid agar. The presence of antibacterial compounds in marine algae: 5-bromophenols isolated from the marine red alga Rhodomela confervoides, the known compound bis (2,3-dibromo-4,5-dihydroxybenzyl) ether showed antibacterial activity against S. aureus (MIC = 70 μg/ml), *Staphylococcus epidermidis* and *P. aeruginosa* (MIC = 70 μg/ml) (Xu et al., 2003). Additional antibacterial marine natural products were isolated from sponges: the antibacterial activity of a novel nitrogen heterocyclic compound cribrostatin 6 isolated from the dark-blue marine Cribochalina sp. sponge. Cribrostatin 6 showed antibacterial activity against Gram-positive bacteria, and it was most active against S. pneumoniae (MIC = 0.5 μg/ml), a leading cause of infection and mortality worldwide (Pettit et al., 2004). Goud et al. reported a novel purpuramine L from the Indian marine sponge *Psammaplysilla purpurea* which was active against *S. aureus*, *B. subtilis* and *C. violaceum*. A new nitrogenous sesquiterpene germacrane was isolated from an Axinyssa n. sp. sponge that demonstrated strong antimicrobial activity against S. aureus and B. subtilis (Satitpatipan and Suwanborirux, 2004). A bicyclic guanidine alkaloid from the marine sponge *Ptilocaulis spiculifer*, contributing a new member to the crambescin A class of compounds (Yang et al., 2003c). Interestingly, 50 μg of the guanidine alkaloid was as potent as 10 μg gentamicin. Two diterpenes membranolides C and D derived from an Antarctic cactus sponge, displayed "modest yet broad spectrum" Gram-negative antibiotic activity (Ankisetty et al., 2004). Two novel antibacterial peptides were isolated from marine worms: two small 21-residue peptides arenicin-1 and-2, from the coelomocytes of the marine lugworm Arenicola marina. Both arenicins were active against Gram-positive L. monocytogenes, Gram-negative *E. coli* and

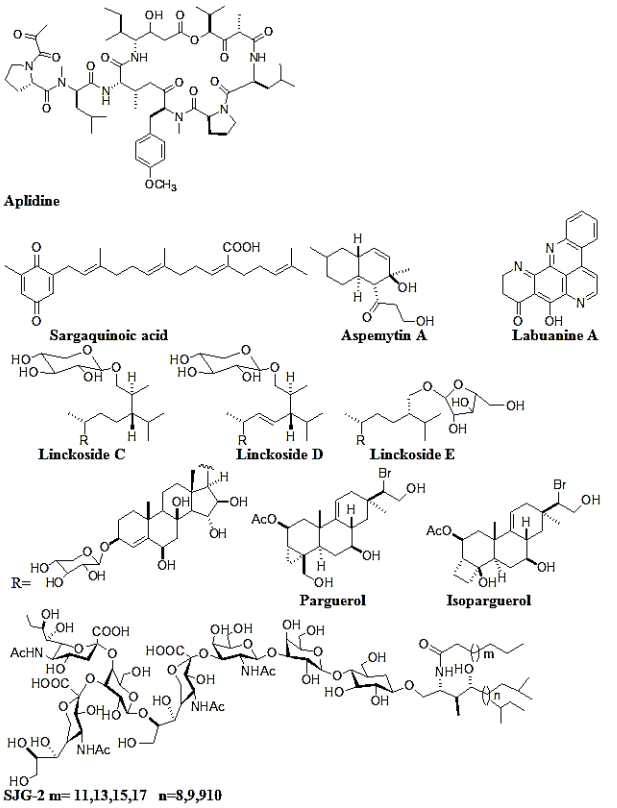

Fig. 7a. Antifungal compounds.

the fungus *C. albicans* (Ovchinnikova et al., 2004). A 51-amino acid highly basic and hydrophobic peptide perinerin from the marine clamworm *Perinereis aibuhitensis* is an organism that is extensively used as bait in fisheries and aquaculture. Perinerin, a peptide that is constitutively present in the marine worm and whose sequence appears to be novel among all know antimicrobial peptides, was active against Gram-negative and Gram-positive bacteria as well as fungi (Pan et al., 2004). Antimicrobials peptides were screening both genomic and mRNA transcripts from a number of different species of flatfish. The most active peptide coded as NRC-13 which was derived from the American plaice Hippoglossoides platessoides Frabricius, "rapidly (5 to 10 min) and efficiently (95 - 100%)" killed antibiotic-resistant *P. aeruginosa*, methicillin resistant *S. aureus* and *C. albicans* (Patrzykat et al., 2003).

Antifungal compounds (Fig. 7)

The studies reported on the antifungal properties of 6 novel marine natural products isolated from marine sponges and ascidians (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005). Several novel marine antifungals were isolated from marine sponges. A sterol sulfate isolated from a deep-water marine sponge of the family Astroscleridae, which exhibited antifungal activity against "supersensitive" Saccharomyces cerevisiae (MIC = 15 µg/ml) (Yang et al., 2003b) and reinvestigated the antifungal properties of a previously described sterol isolated from the marine sponge Dysidea arenaria (Jacob et al., 2003).

Interestingly, a reversal of fluconazole resistance from 300 to 8.5 µM when combined with 3.8 µM of the D. arenaria sterol, putatively as a result of inhibition of the MDR1-type efflux pump in multidrug-resistant *C. albicans*. With the purpose of finding more selective antifungal agents, inhibitors of the pathogenic fungus *C. albicans* geranylgeranyltransferase

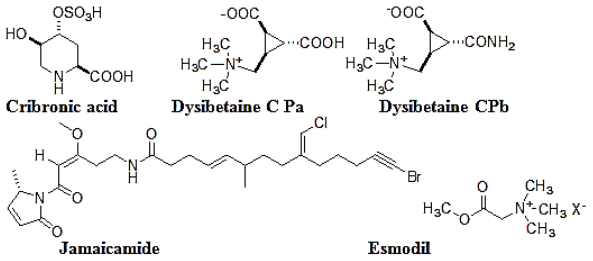

Fig. 7b. Antifungal compounds.

(GGTase), an enzyme that shares only 30% amino acid sequence homology with the human GGTase. Bioassay-guided fractionation resulted in the isolation of a novel alkaloid massadine from the marine sponge Stylissa aff. massa, which inhibited fungal GGTase (IC_{50} = 3.9 µM) (Nishimura et al., 2003). One imidazole alkaloid, naamine G was reported from the Indonesian marine sponge *Leucetta chagosensis* that exhibited strong antifungal activity against the phytopathogenic fungus Cladosporium herbarum (Hassan et al., 2004). It remains to be determined if this compound will also be effective against fungi that infect mammalian hosts.

The untenospongin B, isolated from the Moroccan marine sponge Hippospongia communis, was more potent than amphotericin B, a clinically used antifungal agent, against *Candida tropicalis* (MIC = 4 - 8 µg/ml) and *Fusarium oxysporum* (MIC = 2 - 4 µg/ml). Further studies are required to determine the toxicity of untenospongin B in vivo as well as its molecular mechanism of action. Kossuga et al., reported a new antifungal agent polyketide, (2S,3R)-2-aminododecan-3-ol, isolated from the Brazilian ascidian *Clavelina oblonga*, which was very active against C. albicans (MIC = 0.7 ± 0.05 µg/ml). Although the mechanism of action of this compound remains undetermined its bioactivity was comparable to the clinically used antifungal agents nystatin (MIC = 1 - 4 µg/ml) and ketoconazole (MIC =1 - 4 µg/ml) (Rifai et al., 2004).

Antimalarial, antiprotozoal, antituberculosis and antiplatelet compounds

The studies were reported in the area of antimalarial, antiplatelet, antiprotozoal and antituberculosis pharmacology of structurally characterized marine natural products. Ten compounds were shown to possess antimalarial activity. Moderate antimalarial activity (IC_{50} = 10 µg/ml) against *P. falciparum* was observed with bielschowskysin, a highly oxygenated hexacyclic diterpene isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* (Marrero et al., 2004), as well as the novel diterpenes of the eunicellin class, briarellins K hydroperoxide, D hydroperoxide and L, isolated from the gorgonian *Briareum polyanthes* (IC_{50} = 9, 9 and 8 µg/mL, respectively) (Ospina et al., 2003). Moderate cytotoxic activity against the *P. falciparum* W2 (chloroquine-resistant) strain by the novel cembradiene diterpenoid isolated from the Caribbean gorgonian octocoral Eunicea sp., (IC = 23, 15 and 16 µg/ml, respectively) (Wei et al., 2004). The antimalarial activity of dolastatin 10, a peptide microtubule inhibitor isolated from the sea hare *D. auricularia* which is a potent anticancer drug. Although study was described and dolastatin 10 showed potent inhibition of *P. falciparum* (IC_{50} = 0.1 nM) by affecting the schizont stage of intraerythrocytic development, which has the highest concentration of tubulin, the investigators concluded that dolastatin 10 was an "unpromising basis for further antimalarial evaluation" because of the lack of marked selectivity for parasite over mammalian cells (Fennell et al., 2003). The manzamine alkaloids as potential antimalarial

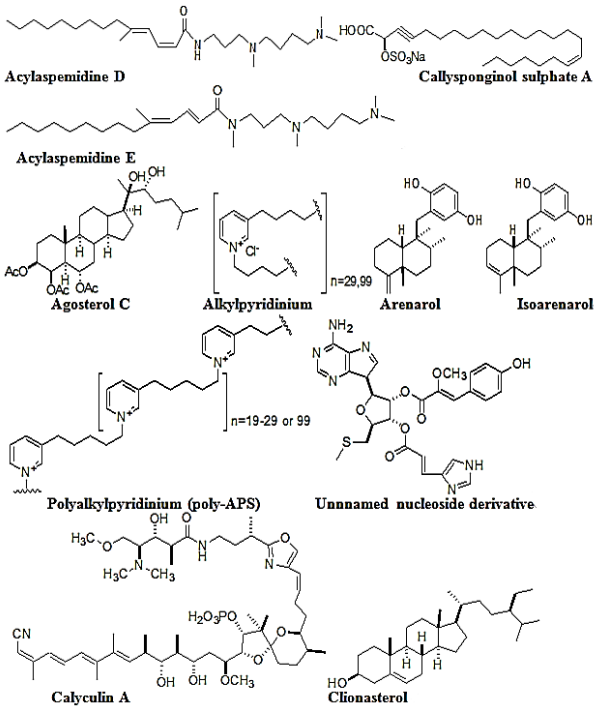

Fig.8a. Antiviral compounds.

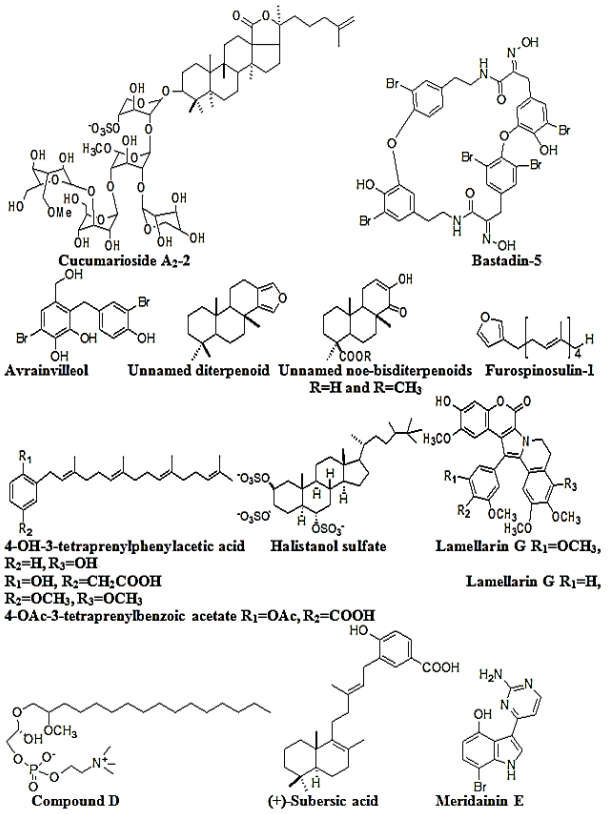

Fig. 8b. Antiviral compounds.

agents, Manzamine A was observed to be particularly active against *P. falciparum* (D6 clone, IC_{50} = 4.5 ng/ml) and *P. falciparum* (chloroquineresistant W2 clone, IC_{50} = 8.0 ng/ml), which compared well with artemisinin used as a control (IC_{50} = 10 and 6.3 ng/ml, respectively) (Rao et al., 2003). As part of an ongoing screening program for novel bioactive compounds frommarine Streptomycetes, trioxacarcins A and D isolated from the marine Streptomyces sp. isolate B8652 BCC 5149 possessed "extremely high antiplasmodial activity" against the parasite *P. falciparum* K1 and NF54 strains (IC_{50} = 1.5 - 1.6 and 2.3 - 1.7 ng/ml, respectively) whichwas much higher than the clinically used compound chloroquine (IC_{50} = 70 and 3.7 ng/ml, respectively) (Maskey et al., 2004). Three compounds were shown to possess antiprotozoal activity. The isolation of renieramycin A a compound from the Japanese sponge Neopetrosia sp. that dose-dependently inhibited recombinant Leishmania amazonensis proliferation (IC_{50} = 0.2 µg/ml) while showing cytotoxicity at "ten times higher concentration (IC_{50} = 2.2 µg/ml)" (Nakao et al., 2004a). The activity of the sesquiterpene euplotin C, isolated from the marine ciliate *Euplotes crassus* on pathogenic protozoa *Leishmania major* and *Leishmania infantum*. Because a significant leishmanicidal activity was noted against both Leishmania species (LD_{50} = 4.6 – 8.1 µg/ml), this natural product as "synergistic compound(s) for current antiprotozoon chemotherapeutics" (Savoia et al., 2004). Non-cytotoxic variant analogues of truncated defensins isolated from the Mediterranean mussel *Mytilus galloprovincialis* were antiprotozoal. Two defensin fragments, designated D and P, killed both the African trypanosome Trypanosoma brucei (ID_{50} = 4 - 12 µM), which causes sleeping sickness, and the causative agent of cutaneous leishmaniasis, namely *L. major* (ID_{50} == 12 - 45 µM), in a time and concentration-dependent manner. The mechanism may involve binding of the defensin fragments "to parasite membranes", perhaps affecting membrane fluidity (Roch et al., 2004).

Some compounds were contributed to the search for antituberculosis agents. A diterpene alkaloid homopseudopteroxazole, isolated from the Caribbean sea plume *P. elisabethae*, inhibited growth of *M. tuberculosis* H37Rv (MIC = 12.5 µg/ml) (Rodríguez and Rodríguez 2003). As part of a manzamine alkaloid, (+)-8-hydroxymanzamine A was very potent against *M. tuberculosis* (MIC = 0.91 µg/ml), comparing favorably with rifampin (MIC = 0.5 µg/ml) (Rao et al., 2003).

A alkaloid ingenamine G (53) that demonstrated activity against *M. tuberculosis* H37Rv at 8 µg/ml (De Oliveira et al., 2004). A scalarane-type bioactive sesterterpene, 12-deacetoxyscalarin 19-acetate, which was purified from the Thai sponge Brachiaster sp. (Wonganuchitmeta et al., 2004), inhibited growth of a nonvirulent strain of *M. tuberculosis* by 50% at MIC = 4 µM, comparing favorablywith kanamycin sulfate (MIC = 3.5 - 8.5 µM). As a result of marine natural products that inhibit the mycothiol-S-conjugate amidase, a mycobacterial detoxification enzyme, several active compounds: a mixture of 1,3 pyridinium polymers isolated from the marine sponge Amphimedon sp., IC_{50} = 0.1 µM; an Oceanapiside sp.-derived bromotyrosine compound, IC_{50} = 3 µM and the glycosphingolipid oceanapiside, IC_{50} = 10 µM. Oceanapiside, was observed to be a "simple non-competitive inhibitor" of the mycothiol-S-conjugate amidase enzyme (Nicholas et al., 2003). Two studies contributed to antiplatelet pharmacology of marine natural products, using a new microplate assay for Ca^{2+}-induced platelet aggregation, determined that xestospongin A, isolated from the marine sponge Xestospongia sp., inhibited both collagen- and epinephrine-induced platelet aggregation more potently than aspirin (Pimentel et al., 2003). The effects of several zoanthamine-type alkaloids isolated from the zoanthids *Zoanthus numphaeus* and *Zoanthus* sp. on the aggregation of human platelets: 11-hydroxyzoanthamine demonstrated strong inhibition of thrombin-, collagen- and arachidonic acidinduced platelet aggregation which appeared related to the hydroxyl

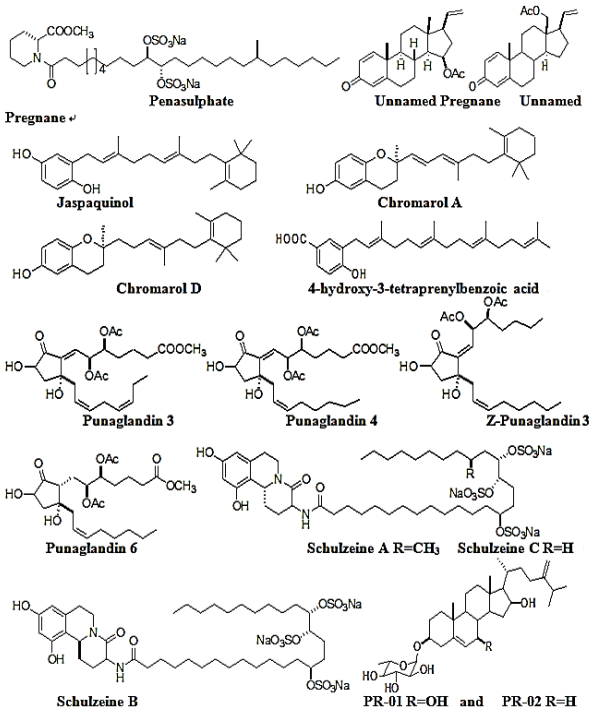

Fig. 8c. Antiviral compounds.

group at C-11; in contrast, aromatization in ring Awas probably responsible for the selectivity of zoanthenol towards collagen-induced aggregation (Villar et al., 2003).

Antiviral compounds (Fig. 8)

Interest in the antiviral pharmacology of marine natural products remained high and was reported to possess antiviral properties against the HIV virus by targeting a number of diverse molecular targets. As a result of an effort to identify small molecules that disrupt protein–protein interactions involved in HIV-1 cellular entry, a new polycyclic guanidine alkaloid crambescidin 826 was reported from the marine sponge Monanchora sp. (Chang et al., 2003). Crambescidin 826 inhibited HIV-1 envelope-mediated fusion in vitro (IC_{50} = 1 – 3 μM), thus suggesting that this class of compounds might ultimately aid in "the rational design of small molecule HIV-1fusion inhibitors". A C22 furanoterpene designated dehydrofurodendin from a *Madagascan Lendenfeldia* sponge, that was active against HIV-1 reverse transcriptase-associated RNA- and DNA-directed DNA polymerase (IC_{50} = 3.2 – 5.6 μM) (Chill et al., 2004). As a result, a HIV-inhibitory depsiundecapeptide neamphamide A was isolated from the Papua New Guinea marine sponge *Neamphius huxleyi* (Oku et al., 2004). Neamphamide A potently inhibited the cytopathic effect of HIV-1 infection in a cell-based in vitro assay (EC_{50} = 28 nM). An extensive study on the mechanism of action of two diterpenes, Da-1 and AcDa-1, isolated from the marine alga *Dictyota menstrualis* that inhibited HIV-1 virus replication in the PM-1 cell line in vitro. Although both diterpenes did not affect viral attachment nor internalization of the virus into PM-1 cells, they inhibited the RNA-dependent DNA polymerase activity of the viral reverse transcriptase enzyme (IC_{50} = 10 and 35 μM, for Da-1 and AcDa-1, respectively) in a cell-free in vitro assay (Pereira et al., 2004). These results suggested that "inhibition of synthesis of the proviral DNA by the diterpenes" was the probable mechanism involved in HIV replication inhibition in PM-1 cells. The inhibition of HIV by two bis-quinolizidine alkaloids petrosins isolated from the Indian

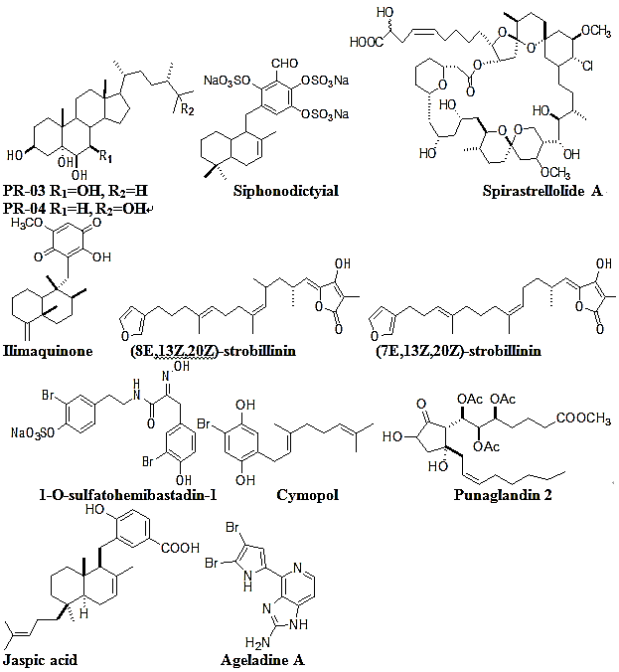

Fig. 8d. Antiviral compounds.

marine sponge *Petrosia similis*. The extensive investigation determined that both petrosins inhibited HIV-1 replication (IC_{50} = 41.3 - 86.8 μM), formation of giant cells (IC_{50} =21.2 - 36.1 μM) and recombinant reverse transcriptase in vitro (IC_{50} = 10.6 - 14.8 μM) (Goud et al., 2003a).

Marine compounds with miscellaneous mechanism of action, interestingly, and in contrast with chemical structure which was isolated from a variety of organisms, includes not only nitrogen-containing compounds (i.e. proteins, peptides), but also terpenes and polyketides. A limited number of these marine natural products, namely acylspermidine D and E, ageladine A, alkylpyridiniums, Atriolum robustum nucleoside, calyculin A, Cell-III, meridianin E, Psammocinia sp. diterpenes, punaglandins and strobilin-felixinins, both the pharmacological activity and a molecular mechanism of action have been investigated and reported.

These natural compounds affecting the cardiovascular, immune and nervous systems, as well anti-inflammatory effects (Pascual et al., 2004), antimicrobial activity in sub-Arctic marine invertebrates (Lippert et al., 2003), antifilarial activity of the red alga *Botryocladia leptopoda* (Lakshmi et al., 2004), antiviral effects of a sulfated exopolysaccharide from the marine microalga *Gyrodinium impudicum* (Yim et al., 2004) and *Sargassuum patens* (Zhu et al., 2004), a polyhydroxylated fucophlorethol isolated from the marine brown alga *Fucus vesiculosus* shown to be bactericidal towards selected Gram-positive and Gram-negative bacteria in vitro (Sandsdalen et al., 2003); and an improvement of "current cytokine-based therapies" by sulphated polysaccharides purified from the green alga Codium fragile, as well as fucoidan and carrageenan, isolated from brown and red algae, respectively (Nika et al., 2003). The bioactivities or pharmacology of natural products have been established (Mayer and Lehmann, 2000, 2002, 2004, 2005; Schmitz et al., 1993). Major chemical class namely, polyketides, terpenes, nitrogen-containing compounds or polysaccharides. These natural products are possessing anthelmintic antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral properties (Mayer and Lehmann, 2000; Mayer and

Hamann, 2002; Mayer and Hamann, 2004; Mayer and Hamann, 2005). Natural products as sources of new drugs (Newman et al., 2003), marine natural products from marine invertebrates and spongeassociated fungi (Proksch et al., 2003a,b), the biopotential of marine sponges from China oceans (Frenz et al., 2004; Laurent and Pietra, 2004; Zhang et al., 2003) antimicrobial marine: genomic screening to identify novel marine antimicrobial peptides (Patrzykat and Douglas, 2003); marine natural products as anti-infective agents (Donia and Hamann, 2003) mining marine microorganisms as a source of new antimicrobials and antifungals (Bernan et al., 2004) antimicrobial peptides from marine invertebrates (Tincu and Taylor, 2004), bioactive peptides from marine sources: pharmacological properties and isolation procedures (Aneiros and Garateix, 2004) antituberculosis, antimalarial and antifungal marine pharmacology: antimycobacterial natural products (Copp, 2003) naturally occurring peroxides from marine sponges with antimalarial and antifungal activities (Jung et al., 2003); antifungal compounds from marine organisms (Molinski, 2004) antiviral marine pharmacology: algae as a potential source of antiviral agents (Luescher-Mattli, 2003); marine natural products as lead anti-HIV agents (Gochfeld et al., 2003); anti- HIV activity from marine organisms (Tziveleka et al., 2003), proteoglycans from sponges as tools to develop new agents for AIDS and Alzheimer's disease (Fernandez-Busquets and Burger, 2003); antiviral marine natural products (Gustafson et al., 2004). Some xanthones showed moderate activity on a chloroquino-resistant strain of *P. falciparum* (Ignatuschenko et al., 1997). Moreover, the in vivo antimalarial activity of some hydroxyxanthones has been recently demonstrated (Fotie et al., 2003). The inhibitory activity of xanthones against hematin aggregation and has potential antimalarial activity (Portela et al., 2004).

CONCLUSION

The natural and marine pharmacology research continued to proceed at a very active pace, involving natural product chemists and pharmacologists. Thus, if the rate of preclinical and clinical pharmacological research continues to be sustained over time, additional marine natural products will probably become available as novel therapeutic agents to treat multiple disease categories. The natural and synthetic approaches developed here to isolate new structures, in association with the biological evaluation, is providing interesting clues in the step-by-step improvement of the biological activity

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None.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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