Recent Developments of Some Natural Products Against Mycobacterium Tuberculosis Infection

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Abstract: An increasing incidence of deaths due to tuberculosis (TB) and the known drawbacks of the current existing drugs including the emergence of multi drug-resistant (MDR) and extensive drug resistance (XDR) TB strains have led to a renewed interest in the discovery of new anti-TB agents. The recent researches focused on natural products have shown a useful way to obtain a potentially rich source of antiinfective drug candidates. For over 50 years, natural products have served us well on combating infectious microorganisms. The microbial and plant secondary metabolites have helped to increase our life span, reduced pain and suffering, and development of new medicine. This review covers the some naturally occurring compounds with anti-TB activities.

Keywords: Natural products, Antimycobacterial activity, Biodiversity, Biologically active compounds.

1 Introduction

Tuberculosis (TB) is a contagious-infectious disease caused by Mycobacterium species particularly M. tuberculosis (Mtb), which is an aerobic pathogenic bacterium and infection usually in the lungs. Modern TB is commonly associated with Mtb and M. bovis. The non pathogenic mycobacteria are including M. smegmatis, M. aurum. The M. avium and M. intracellulare, which cause bird TB and are associated with human diseases in advanced countries. TB is caused by inhalation of the bacillus from an infectious patient, then causing destruction of the lung. About one-third of the world population is infected with Mtb, which will more sensitive to those who are also infected with human immunodeficiency virus (HIV).

Although a BCG vaccine and chemotherapy against TB were available. Over the past decade, the area of TB therapy has undergone a basic change in emphasis for drug therapy. The increase of TB coinciding with the AIDS epidemic has resulted in additional drug-resistant isolates of Mtb. The risk of developing TB among AIDS patients is over 100 times higher than among normal individuals. Resistance to the current anti-TB therapy is another threatening problem. Multi-drug-resistant (MDR) strains of Mtb. The resurgence of DR-TB has generated a renewal of interest in a strategic search for prototype leads. The natural source emerges as a good candidate for new anti-TB agents with chemically diverse structures (Bueno et al., 2011). The advances in the therapy of TB have given way to worried over the evolution of drug resistance based on the genetically fixed mutations of Mtb. Most drugs used anti-TB possessing different mechanisms and able to cause different adverse effects on human. Therefore, it is urgentneed to search for new, low-toxic drugs superior to the currently used anti-TB drugs.

The main concern is the agents possessing activity against DR-TB strains. These MDR-TB strains are defined as Mtb strains showing resistance simultaneously against INH and RIF (Bastian and Portaels. 2003). TB with a different DR-TB involves Mtb strains displaying mono- or polyresistance not including associated resistance against INH and RIF (Bastian and Portaels. 2003). The Mtb strains may be sensitive (inhibited by first line drugs) or resistant (not inhibited by INH). The review includes the introduction and natural compounds with anti-TB activities.

2 The Importance of Natural Products as Drugs

Most collections of natural products start as extracts of fresh or dried material prepared by using various solvents. The extracts are complex mixtures of perhaps several hundred different compounds (Harvey. 2007). Different compounds derived from animals, plants and microbes have been used to treat human disease since the dawn of medicine. Natural products, semi-synthetic natural product
analogenes or synthetic compounds based on natural-product were in clinical trials and exploration of the bioactivity of natural products continues to provide novel chemical scaffolds for further drug inventions (Koehn and Carter 2005; Chin et al., 2006). Various reasons have been put forward to explain the success of natural products in drug discovery: their high chemical diversity, the effects of evolutionary pressure to create biologically active molecules, the structural similarity of protein targets across many species, and so on (Butler. 2005). Because natural products are a proven template for the development of new scaffolds of drugs (Chin et al., 2006), they have received considerable attention as potential anti-TB agents (Pauli et al., 2005).

Anti-TB active compounds have been found among many skeleton types, mainly from plants, but also from other organisms such as fungi and marine organisms (Copp and Pearce. 2007).

3 Natural Products with Anti-TB Activity

Biodiversity is changing life forms and apparently in the genetic diversity of populations, species, ecosystems and landscapes (Lopez et al., 2001; Bueno-Sanchez et al., 2009). The need for new anti-TB drugs is an urgency, natural products is an important alternative for provide new chemical agents for drug development. The vast majority of natural compounds have been tested for biological activity as novel sources of potentially biodiverse compounds. There are novel biodiversity becoming available for screening, and have been great advances in the identifying natural products. Broad biodiversity are promising for the discovery of drugs from natural sources (Coy et al., 2009; Ospina et al., 2007; Rodriguez et al., 2006). Naturally occurring compounds and extracts from plants, microorganisms and marine organisms have indicated that inhibitory activity against Mtb. Many compounds have been provided interest in phytochemical biodiversity. These compounds are adversely affecting TB survival mechanisms in humans, or have been derived from medicinal plants (Okunade et al., 2004).

4 Plants

Plant-based drugs have been used worldwide for the treatment of various diseases. Plant species still serves as a rich source of many biologically active compounds, as very few plant species have been investigated for their medicinal properties (Heinrich and Gibbons. 2001). Thus, there isan interest in phytomedicine and many medicinal plants are being screened for pharmacological activities (Gautam et al., 2007). There have to be investigate ethnobotanical antibacterials to discover new drugs. Before the advent of antibiotic therapy, plants were widely used as a source of antiseptic materials, fresh plants producing volatile natural products with antibacterial activity (Gibbons. 2008). Examples of the such species include Allium sativum (Family-Liliaceae) (Jain. 1998), Borrichia frutescens (Asteraceae) (Cantrell et al., 1996), Ferula communis (Umbelliferae) (Appendino et al., 2004), Heracleum maximum (Umbelliferae) (Newton et al., 2000), Karwinskia humboldtiana (Rhamnaceae) (Newton et al., 2000), Leucas volkensii (Labiatae) (Rajab et al., 1998), Moneses uniflora (Eriaceae) (Newton et al., 2000), Oplopanax horridus (Araliaceae) (Newton et al., 2000), Salvia multicaulis(Labiatae) (Ulubelen et al., 1997), Strobilanthis cusia (Acanthaceae) (Mitscher and Baker. 1998), Senna silvestris (Leguminosae) (Graham et al., 2003), Sommera sabiceoides (Rubiaceae) (Graham et al., 2003), Nectandra hihua (Lauraceae) (Graham et al., 2003), Senna obliqua (Fam. Leguminosae) (Graham et al., 2003), Heisteria accuminata (Olacaceae) (Graham et al., 2003), Zanthoxylum sprucei (Rutaceae) (Graham et al., 2003), Lantan a hispida (Verbenaceae) (Jimenez-Arellanes et al., 2007) Citrus aurantifolia (Rutaceae) (Camacho-Corona et al., 2008), Citrus sinensis (Rutaceae) and Olea europaea (Oleaceae) (Camacho-Corona et al., 2008). The compounds have been isolated which have anti-TB activities, for example (E)- and (Z)-phytol and phytanol which were isolated from Leucas volkensii (Rajab et al., 1998), pentacyclic triterpenoids from Lantan a hispida (Jimenez-Arellanes et al., 2007). Other compounds with anti-TB activity from plants are diterpenes as mulinane isolated from Azorella madreporica Clos (Wachter et al., 1998) and calanolide A (Xu et al, 2004). Tryptanthrinis an alkaloid from the Chinese herb Strobilanthes cusia. Tryptanthrin and its analogs are potent against MDR-TB strains, are non toxic (Mitscher and Baker. 1998). Furthermore, three molecules could be regarded as promising compounds for anti-TB agents from plants: the diterpene 12-methyl-5-dehydroacetylhorminone, isolated from Indigofera longercamomosa (Fabaceae) (Thangadurai et al., 2002), the (24R)-isomer of the triterpene Saringosterol, obtained from Lessonia nigrescens (Lessoniaceae) (Wächter et al., 2001), and the difenilalkyl ether ketone Engelhardione, isolated from Engelhardia roxburghiana (Juglandaceae) (Lin et al., 2005), which were found to inhibit Mtb H37Rv with excellent MIC values of 0.38, 0.13, and 0.21 mg/L, respectively.

5 Marine Natural Products

The oceans are a unique resource that provides diverse natural products such as sponges, tunicates, bryozoans, mollusks, marine bacteria and cyanobacteria. As infectious diseases develop resistance to existing drugs, the marine compounds provides novel leads against fungal, parasitic, bacterial, and viral diseases. There are a small numbers of investigations at marine products as potential leadsagainst Mtb (Donia et al.,2003). The alkaloid (+)-8-hydroxymanzamine A was isolated from a sponge
Pachyphellina sp and Petrosiidae genus (Ichiba et al., 1994). This alkaloid exhibits potent anti-TB activity against Mtb H37Rv (Yousaf et al., 2004). Ircinol A is a manzamine-type alkaloid obtained from Indo-Pacific sponges; this compound is useful for assessment in vivo against Mtb, it shows low cytotoxicity. The manzamine A inhibits Mtb H37Rv (Yousaf et al., 2004). Other compound axisonitrile-3 which is a cyanoesquiterpene isolated from the sponge Acanthella kletbra shows potent anti-TB activity (Konig et al., 2000). Pseudopteroxazole, a benzoaxazole diterpene alkaloid isolated from the West Indian gorgonian Psuedopterogorgia elisabethae, induces 97% growth inhibition for Mtb H37Rv without considerable toxic effects (Rodriguez et al., 1999). The hexane extract of the West Indian gorgonian was isolated ergorogiaene, a serrulatane-based diterpene (also known as biflorane), and induced 96% growth inhibition for MtbH37Rv (Rodriguez et al., 2001). Litosterol is a C-19 hydroxysteroid isolated from an Okinawan soft coral Litophyton viridis. It inhibited 90% of the growth of Mt (Iguchi et al., 1989). Puupehenone induced 99% inhibition of Mtb H37Rv growth. The puupehenones are shikimate-sesquiterpene derived metabolites isolated from sponges of the order Verongida and Dictyoceratida (Capon et al., 1998).

6 Insects

The prokaryotic and eukaryotic organisms have developed hundreds of different cytolytic peptides and proteins during their evolution in different phyla of the plant (Broekaert et al., 1995) and animal kingdom (Andreu and Rivas, 1998). Many cytolytic peptides are specific antimicrobially acting peptides that are part of the innate immune system of invertebrates and vertebrates. They serve as primary defense weapons against invading prokaryotic and eukaryotic microorganisms (Andreu and Rivas, 1998). Arachnid (spiders and scorpions) venoms contain toxic peptides with a large range of molecular masses, but spider venoms apparently possess a much higher diversity of ion channel and other cell receptor antagonists than scorpion venoms (Kuhn- Nentwog, 2003).

Gene-encoded antimicrobially acting peptides show great variety in amino acid sequence, structure and target specificity. Many of them are cationic, amphipathic peptides and show a higher specificity to prokaryotic than to eukaryotic cells (Corzo and Escoubas, 2003). The main site of antimicrobial activity is the plasma membrane of bacteria and parasitic protozoans. The unstructured antimicrobial peptides are electrically attracted to negatively charged groups of the cell surface, where they adopt an α-helical conformation and accumulate on the membrane. This can causes formation of transient pores, membrane perturbation and cell lysis (Matsuzaki, 1999). These kinds of compounds could be promising new anti-TB drugs. Some of them, like cecropin and melittin, isolated from different insects, posses anti-TB activity (Giangaspero et al., 2001; Zerbini et al., 2006).

7 Microorganisms

Microorganisms are rich sources of drugs, including antibiotics, immunosuppressants and the lipid-lowering statins. These drugs are produced from a very small range of the world’s microbial diversity. Approximately 6000 bacterial species have been named and estimates of 1.5 million species of fungi and 1.5 million species of algae and prokaryote might have to be revised upwards (Harvey, 2000). Streptomycin and penicillin is a antibiotic (a fungal product). It was the first effective therapeutic for TB (Davies, 2007). Selman Waksman was isolation and screening of soil bacteria in the search for bioactive small molecules, especially potential antibiotics, was validated by the discovery of streptomycin (Tripathi et al., 2005). A variety of bacterial genera have been shown to produce aminoglycoside–aminocyclitol antibiotics. These include Streptomyces, Micromonospora, Bacillus, and so on. Compounds originating from Streptomyces are named “-mycins” (e.g., tobramycin) while others are “-mics” (gentamicin), “-osins,” “-asins,” or “-acin.” Other aminoglycoside used for TB therapy are kanamicine, amikacine and capreomycin. Important drugs for TB treatment are rifamycins (RMP) which are a group of semisynthetic antibiotics of rifamycin B, isolated from Streptomyces mediartian (Davies, 2007). Other compound from microorganisms is thioclayactomycin (2E,5E)- 2,4,6-trimethyl-3-hydroxy-2,5,7-octatriene-4-hiolide] which is a unique thioclayactone antibiotic isolated initially from a soil Nocardia sp. exhibiting anti-TB activity by inhibiting mycolic acid biosynthesis (Tripathi et al., 2005).

8 Alkynes and Heterocyclic Compounds

The metabolite of several strains of the endophytic fungus of the genus Phomopsis, 3-nitropropionic acid (1), actively inhibited growth of MtbH37Ra (MIC 0.4 μg/mL). Although the high neurotoxicity of this compound was a hindrance to its use as a pharmaceutical, it could be used as a model for the synthesis of new inhibitors of isocitratelyase, an enzyme essential to the catabolism of fatty acids and virulence of Mtb [Chomcheon, et al., 2005]. Linoleic acid (2) that inhibits growth of M. phlei (MIC 2 μg/mL) is extracted from the plant Humulus lupulus. An example of polyacetylene compounds is 3S,8R stereoisomer (3) isolated from Anethum graveolens and having MIC 2-4 μg/mL when tested on a group of fast growing mycobacteria (M. fortuitum ATCC 6841, M smegmatis ATCC 14468, M. phlei ATCC 11758, M. aurum Pasteur Institute 104482, and M. abscessus ATCC 19977; for ethambutol, MIC 0.5-4 μg/mL) [Stavri, and Gibbons. 2005]. However, cytotoxicity of this class of polyacetylene compounds can lower the interest in their biological activity [Bernart, et al., 1996]. Compounds (4a) and (4b), synthetic analogs of the natural antibiotic thioclayactomycin, inhibit growth of Mtb with MIC 1-16 μg/mL, including DR strains

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The components of the plant Cinnamomum kotoense led to the isolation of a number of compounds, of which lincomolide B (5) with MIC 2.8 μg/mL had the highest anti-Tb activity [Chen, et al., 2005]. Micromolide (6), which is a γ-lactone derivative of oleic acid, isolated from the stem bark of Micromelum hirsutum and has MIC 1.5 μg/mL against Mtb H37Rv. Further evaluation on a more virulent strain of Mtb Erdman gave MIC 5.6 μg/mL [Ma, et al., 2005]. 2-Substituted furans (7a,b) and (8a,b) isolated from the roots of Polyalthia evecta possess activity against Mtb (MIC 3.1 and 6.25 μg/mL, respectively) [Kanokmedhakul, et al., 2006]. The synthesized natural compound pamamyacin-607 (9) inhibits growth of M. bovis BCG, M. smegmatis and Mtb (MIC 0.5-4.7 μg/mL). It does not show cross resistance to INH and Rif [Lefevre, et al., 2004].

Marine metabolites pseudopyronines A and B (16a,b, MIC 0.78-3.125 μg/mL) inhibit the growth MtbH37Rv [Demaray, et al., 2008]. Pyrones (17, MIC 4 μg/mL) is a component of Piper sanctum that is active against Mtb [Mata, et al., 2004]. Ferulenol (18a) isolated from the Sardinian giant fennel Ferula communis is effective against M. smegmatis (MIC 0.5 μg/mL), as well as M. fortuitum, M. phlei and M. aurum (MIC 2 μg/mL). The analogs of compound, (18b-d), compound (18b) with a benzyloxy group retained its activity against Ms and M. phlei, and, to a lesser extent, against M. fortuitum and M. aurum, while the activity of (18c) and (18d) with the hydroxy and acetoxy groups is considerably lower [Schinkovitz, et al., 2003]. Ostruthin (19), the metabolite of Peucedanum

9 Phenols and Quinines

Phenylpropanoids (10) and (11), metabolites of Pimpinella sp., inhibit growth of a number of mycobacteria, including M. intracellulare, Ms, M. aurum, and M. phlei (MIC 1.25-10 μg/mL) [Tabanca, et al., 2005]. The tricyclic diphenol ether engelhardion (12) is very active against MtbH37Rv
ostruthin Koch, inhibit the growth of M. aurum (MIC 3.4 μg/mL) [Negi, et al., 2008].

Compounds (20a-h), isolated from the lichen fungus Microsphaeropsis sp., show different activities against MtbH37Ra (MIC 25, 3.12–6.25, 12.5, 1.56–3.12, 50 μg/mL, respectively), but are also characterized by cytotoxicity [Seephonkai, et al., 2002]. One of the xanthone dimers isolated from the endophytic fungus of the genus Phomopsis, phomoxanthone A (22a), is very active against MtbH37Ra (0.5 μg/mL), while its deacetylated derivative (22b) is inactive. Phomoxanthone B (22c) is less active (MIC 6.25 μg/mL). Both active compounds are cytotoxic [Isaka, et al., 2001].

10 Peptides

Four cyclic peptides, enniatins H (25a), I (25b), B (25c), and B4 (25d), which are the components of the pathogenic fungus Verticillium hemipterigenum, inhibit growth of MtbH37Ra (MIC 3.12–6.25 μg/mL) [Nilanonta, et al., 2003]. Syringomycin E (26), isolated from Pseudomonas syringae pv. Syringae, is active against Msrg (MIC 1.5 μg/mL) [Buber, et al., 2002]. The metabolite of Nocardia sp., namely, the thiazole peptide nocathiacin (27) shows activity against MtbATCC 35828, M. avium A26778, and M. avium A26640 (MIC≤0.008, 0.06, and 0.25 μg/mL, respectively). Compounds from this class show poor pharmacokinetics and solubility [Pucci, et al., 2004].
11 Alkaloids

The development of natural anti-TB drugs, these anti-TB natural products obtained from higher plant extracts. Tryptanthrin, an alkaloid from the Chinese herb Strobilanthes cusia, allowed the construction of hundreds of analogs in an attempt to optimize the activity (Lester et al., 1998). Two compounds, the known antibiotic pyrrolnitrin (28) and banegasine (29), isolated from the zoobacterium Aristabacter necator, act synergically against Msg (MIC (29) > 0.5 µg/mL, (28) 0.3 µg/mL, (28) + (29) 0.075 µg/mL) [Cain, et al., 2003]. Their analog celastramycin A (30), which is a dichloropyrrole metabolite of the Streptomyces strain, has a broad spectrum of anti-TB activity (MIC 0.05-3.1 µg/mL against Msg, M. aurum, M. vaccae, and M. fortuitum) [Pullen, et al., 2002]. The bis-1-oxaquinolizidine alkaloid (−)-araguspongine C (32), isolated from the sea sponge Xestospongia exigua, inhibits growth of Mtb H37Rv (MIC 1.9 µg/mL) [Orabi, et al., 2002]. In the series of quinolone alkaloids (33a-d), isolated from the fruits of Evodia rutaecarpa, compounds with unsaturated aliphatic chains at 2-position exhibited better anti-TB activity as compared with saturated chain compounds [Negi, et al., 2010]. Agelasine E (33a) and agelasine D (33b) were previously isolated from the sea sponge Agelas nakamura. While agelasine E is inactive, its methoxy analogs (33c-g), having different terpenoid side chains, demonstrate high activity against Mtb H37Rv (MIC 3.13, 1.56, and 3.13 µg/mL respectively).

25a R₁=R₂=R₃=R₄=i-Pr, R₅=s-Bu
25b R₁=R₂=R₃=R₅=i-Pr, R₄=s-Bu
25c R₁=R₂=R₃=R₅=i-P
25d R₁=i-Bu, R₂=R₃=R₅=i-Pr, R₄=R₅=i-Pr

26 R=NHCOCH₂CH(OH)(CH₃)₂CH₃

31a, 31b, 31c, 31d, 32
Presence of an alkoxy group at the terminal nitrogen atom is a very important factor for the anti-TB activity of these compounds. However, there is only slight difference between the activities of agelasine D (33b) and its alkoxy derivatives (33f) and (33g) [Vik, et al., 2006]. Similar analog of the compounds, 9-methyladenine (33h), has MIC of 6.25 µg/mL [Bakkestuen, et al., 2005]. The tetracyclic alkaloid cryptolepine (34a), isolated from Cryptolepis
sanguinolenta, is active against a number of fast-growing mycobacteria, including M. aurum (MIC 2 μg/mL), M. phlei (MIC 4 μg/mL), and M. fortuitum (MIC 16 μg/mL) [Gibbons, et al., 2003].

33a R=c, 33b R=d  33c R=a, R1=CH3  33d R=b, R1=CH3
33e R=c, R1=CH3  33f R=d, R1=CH3  33g R=d, R1=t-Bu

34a34b, R=H  34c R=OH
Metabolite of Allium neapolitanium (34b) displayed enhanced activity against the Msg(mc22700), when compared with that for (34c) (MIC 2-8 μg/mL). Furthermore, the activity of (34b) was greater against Msg (mc2 2700) than Msg (ATCC 14468) (MIC 16 μg/mL for (34c) and 8 μg/mL for (34b) [O’Donnell, and Gibbons. 2007]. The metabolites of the Thailand pathogenic fungus Hirsutella nivea BCC 2594 hirsutellones A- D (35a-d) inhibit growth of MtbH37Ra (MIC 0.78, 3.125, 0.78, 0.78 μg/mL, respectively). Compound (35d) exhibits moderate in vitro cytotoxicity, while other compounds are less cytotoxic [Isaka, et al., 2005]. Hirsutellone F (35e), which is a new dimer alkaloid isolated, together with known hirsutellones A, B, and C, from the seeds of the fungus Trichoderma sp. BCC 7579 shows a weaker anti-TB activity against MtbH37Ra (MIC 3.12 μg/mL) than hirsutellones A, B, and C [Isaka, et al., 2006]. The known alkaloid ecteinascidin 770 (36a) and the new one, ecteinascidin 786 (36b), both isolated from Ecteinascidia thurstoni, inhibit growth of MtbH37Ra (MIC 0.1 and 1.6 μg/mL, respectively) [Suwanborirux, et al., 2002].

Manzamine alkaloids isolated from sea sponges are promising from the viewpoint of their anti-TB activity. Manzamines A (37a), E (37c), and F (37d) and their hydroxyl derivatives 6-hydroxymanzamine E (37e) and (+)-8-hydroxymanzamine A (37b) show activity against MtbH37Rv (MIC 1.5, 3.8, 2.6, 0.4, and 0.9 μg/mL, respectively) [Rao, et al., 2006]. Manadomanzamines A (38a) and B (38b) inhibit growth of MtbH37Rv (MIC 1.9 and 1.5 μg/mL, respectively) [Peng, et al., 2003].
Terpenes: Compound (39), isolated from Indigofera longeracemosa, is active against Mtb (MIC 0.38 μg/mL) [Woldemichael, et al., 2003]. Diterpenes (40) and (41) from Calceolaria pinnifolia [Woldemichael, et al., 2004], the structurally related lecherol A, isolated from Sapium haematospermum (MIC 4 μg/mL) [Woldemichael, et al., 2004], and metabolite of Melica volkensii 6-isolated from Sapium haematospermum (MIC 4 μg/mL) [Woldemichael, et al., 2004], and metabolite of Melica volkensii 6-hydroxycyclacolate (42) have the same value of MIC against MtbH MtbH37Rv. Ugandensial (43, from Warbugia ugandensis) inhibit growth of M. aurum and M. phlei at this value of MIC [Negi, et al., 2010]. The diterpenes diaporteines A (44a) and B (44b) were isolated from the fungus Diaporthe sp. Compound (44b) has anti-TB activity against MtbH37Ra (MIC 200 μg/mL) [Trivedi, et al., 2003]. The presence of a carbonyl group is important for the anti-TB activity. A metabolite of the African tree Combretum imberbe, traditionally used in folk medicine is imberbic acid (45), which shows activity against M. fortuitum (MIC 1.56 μg/mL) [Katerere, et al., 2003]. The chemical modifications of the parent structure of curcumin (at the C-3 position to cinnamate-based esters) resulted in an 4-fold increase in anti-TB activity (46a), MIC 3.13 μg/mL for MtbH37Ra, for curcumin MIC 12.5 μg/mL) [Trivedi, et al., 2008]. Triterpene (47), isolated from Elateriospermum tapos, is active against Mtb H37Ra (MIC 3.13 μg/mL, for INH and kanamycin sulfate MIC 0.05 & 1.25 μg/mL, respectively) [de Souza, et al., 2009]. Aegicerin (48a) and protoprimulagenin A (48b) were isolated from Aegiceras sp., Embelia Schimperi, and the Peruvian plant Clavija procera. Aegicerin (48a) was tested on 37 different strains of TB (MIC 1.6-3.1 μg/mL against one strain of H37Rv, 21 sensitive clinical strains, two clinical isolates resistant to INH, and 13 MDR clinical strains). The inactivity of protoprimulagenin A (48b) (MIC 200 μg/mL) demonstrates that as in the case of (44a) and (44b), the presence of a carbonyl group is critical for the anti-TB activity. An oleane type triterpene shows uniformly high activity against a wide range of both sensitive and resistant strains. Regrettably, for many MDR strains, its excellent anti-TB activity (for comparison, MIC is 4-32 μg/mL for INH and 2-16 μg/mL for RIF) has not yet been effected [Rojas, et al., 2006].

Scalarane derivatives: A series of heteronemin-related anti-TB scalaranes, both from natural products and from chemical derivatization. Based on the activity profile, three main regions; i.e., the substituted groups hovering over C-19/C-18 and furan moiety, the functionalities in the vicinity of C-16 and the right-hand side of ring D, and the substituted groups on C-12, were speculated as the areas influencing the anti-TB activity of the scalaranes. The results suggested the promising possibility for the further investigation toward the modes of actions and/or target sites of the compounds (Jaisamut et al., 2009.). Tetracarbocyclic sesterterpenes of the scalarane family are rare natural products found exclusively in marine invertebrates, distributing mainly among the Dyctioceratid sponges, especially those of the genera Hyrtios [Crews, et al., 1986; Doi, et al., 1993; Kobayashi, et al., 1994; Ryu, et al., 1996; Ledroit, et al., 2004], Hyatella [Karuso, et al., 1989; Hernández-Guerrero, et al., 2006; Somerville, et al., 2006], Phyllospongia [Rao, et al., 1991; Li, et al., 2007], Sennespongia [Rho, et al., 2004], and Spongia [Nam, et al., 2006; Fontana, et al., 1999]. Of particular interest among the scalaranes in this report is heteronemin (55). The compound was first isolated from the sponge Heteronema erecta [Kazlauskas, et al., 1976; Kashman, and Rudi, 1977], and later along with its several sesterterpene analogs from various sponge species. Heteronemin was reported to be biologically active in, cytotoxicity, protein function.
inhibition, and anti-TB activity [Sayed, et al., 2000]. Specifically for the latter, 55 was first reported active against Mtb H37Rv with a MIC of 6.25 μg/ml and an IC50 of 1.3 μg/ml. Despite the promising anti-TB activity, 55 and its related scalarane congeners have never been investigated extensively for the further application with regard to their biological activities. This is attributed to the cytotoxicity of 55 itself, of which the IC50s were reported to be at least 10-fold more potent than that of its anti-TB activity. For examples, in our previous report [Wonganuchitmeta, et al., 2004], 55 was found to be cytotoxic with the IC50s in a range of 0.2–0.5 μM against a panel of cancer cell lines (MCF-7, HeLa, HT-29, and KB). It has been suggested, however, that certain chemical derivatization and/or microorganism-assisted structural transformation may improve the anti-TB activity and lower the cytotoxicity of the compounds [Sayed, et al., 2000]. Recently, we reported the isolation of a series of scalarane-type sesterterpenes from the Thai sponge Brachiaster sp. The isolated sesterterpenes included 55 (as a major component), heteronemin acetate (56), 12-deacetyl-12-epi-19-deoxysscalarin (57), 12-epi-19-deoxysscalarin (58), and 12-deacetoxysscalarin acetate (59) [Wonganuchitmeta, et al., 2004]. The biological activities of the isolated compounds were assessed to show the anti-TB activity with the MICs in a range of 100–102 μM. The results indicated that slight changes in certain functionalities exert considerable influences on the potency of the anti-TB activities, as well as on the selectivity between the anti-TB. The biologically active scalaranes, the oxygenated functionalities in the vicinity of the furan moiety of the scalaranes, i.e., the functional groups surrounding C-19 and C-20, may contribute to the biological activities, especially related to the chemotherapeutic uses.

**A minor scalarane derivative:** Along with the isolation of 55 from the Thai sponge Hyrtios sp., a minor scalarane derivative (60) was isolated from the hexane extract. The structure 60 compound, designated as 12-epideacetyl-19α-acetoxy-20α-methoxyscalaran, was a new member of the tetracarbocyclic sesterterpenes, possessing an attached dihydrofuran moiety with two acid-labile acetal carbons (Jaisamut et al., 2009).

**Derivatizations of the scalaranes:** Similar to several previous reports, we were able to obtain 55 as a major component from the sponge Hyrtios sp. in a very good yield (isolated yield 1.6 g from 101 g of freeze-dried sponge). The scalaranes obtained here included 12-OXOHeteronemin (61); 12-deacetyl-12-epi-20-deoxoscalarin (62); scalarafuran (63); 16-deacetoxy-15,16-dehydroscalarmaron (64); 12-deacetyl-12-episcopaladial (65); 12-deacetyl-12,18-diepiscleraladial (66); 12-deacetyl-12-oxoscalaradial (67); and 12-episcopalradial (68). Referred to as INH, RIF, and kanamycin; MICs 0.02, 0.04, and 2.58 μM, respectively. Referred to as passive transporter; IC50 0.45 μM. Cell viability >80% at the highest concentration of 5 μg/ml (Jaisamut et al., 2009). Naturally, our first attempts for the structural modification were to remove the acetate functionalities, both from C-16 and from C-19. To our surprise and disappointment, 55 was too labile to most standard transformations for such acetate removal. In addition, in most attempts, the degradation of 55 proceeded so destructively that neither starting materials nor any possible side products were recoverable. The reaction generally proceeded cleanly and swiftly within less than 5 min. Prolonged exposure to such acidic medium, as expected, led to the epimerization at C-18, yielding 66 [Gavagnini, et al., 2004] in a trace amount. With both 55 and 65 in hand, the two compounds were conveniently used for a series of simple transformations in a paralleled manner. Chromate oxidation at 12-OH yielded the o xo derivatives 7 [Kazlauskas, et al., 1976 and 67 [Gavagnini, et al., 2004], and acetylation on the same hydroxyl group did the 12-acetate derivatives 56 and 68 [Crews, et al., 1986], respectively. It is noteworthy to mention here that, whereas the above transformations progressed smoothly with reasonable yields, O-methylations onto C-12 of both 55 and 65 were too slow. This presumably resulted from the steric hindrance surrounding C-12, providing an environment similar to that of a neopentyl system. On the other hand, with LAH reduction, 55 again, was too labile, whereas 65 did proceed sluggishly under reflux [Kuenhe, et al., 1988], and instead of the expected triol, a recylized tetrahydrofuranol [Fontana, et al., 1999] was obtained only in a low yield. Manipulation of 55 toward the furan functionality was carried out simply via pyrolytic cleavage. Brief exposure of 55 to a non-oxidative pyrolytic condition resulted in rapid decomposition, and three major products, 63 [Kazlauskas, et al., 1976], 64 [Kazlauskas, et al., 1976], and 66, were isolated.

**Marine-Derived Antimycobacterium Compounds:** In an attempt to characterize structural classes that could serve as lead anti-TB agents, structurally diverse marine-derived natural and semisynthetic compounds were examined for in vitro activity against Mtb.

Some compounds including steroids, scalarin sesquiterpenoids, tetra bromospiericyclohexadienylisoxazolines, quinone-methide and peptide have been identified as antituberculosis agents (El Sayed, et al., 2000). There are only two reports of in vitro anti-TB activity from marine origin. Masetolide A (55) and viscosin (56) are cyclic depsipeptides isolated from cultures of two Pseudomonas species isolated from a marine alga and tube worm, respectively (Gerard, et al., 1997). When tested against Mtb, masetolide A and viscosin displayed MIC values of 5–10 and 10–20 mg/mL, respectively. When tested against M. avium intracellulare, masetolide A (55) and viscosin (56) had MICs of 2.5–5 and 5–10 mg/mL, respectively (Gerard, et al., 1997). Pseudopteroxazole (57) and seco-pseudopteroxazole (58) are new benzoxazole diterpene alkaloids isolated from the West Indian gorgonian Pseudopterogorgia elisabethae (Rodriguez, et al, 1999). Both compounds induced 97 and 66%, respectively, growth inhibition for Mtb H37Rv at a concentration of 12.5 mg/mL without significant cytotoxicity (Rodriguez, et al, 1999).
These reports illustrate the significance of marine-derived secondary metabolites, as a possible unexplored resource for new anti-TB leads.

**Discussion:** Chemically diverse marine-derived secondary metabolites were tested against Mtb H37Rv. These compounds show promising anti-TB activity in the range of 70–99% inhibition of this OI pathogen. Kahalalides A (59) and F (60) are two known polypeptides isolated from the sacoglossan mollusk Elysia rufescens (Hamann, and Scheuer, 1993; Hamann, et al, 1996). Kahalalide A inhibited 83% of the growth of Mtb H37Rv at 12 mg/mL. Compounds massetolide A and viscosin showed significant activity against Mtb. Litosterol (61), naphthalsterols B (62), and C (63) are known C19-hydroxysteroids reisolated by our group from a Red Sea Nephthea sp. (Iguchi, et al, 1989; Liu, et al, 1992). Compounds 61 and 63 inhibited 90 and 96% of the growth of Mtb H37Rv, with MICs of 3.13 and 12.5 mg/mL, respectively. The poor solubility of litosterol and naphthalsterols B in the aqueous tissue culture media obscured accurate IC50 and cytotoxicity determinations. Unlike 61 and 63, naphthalsterol B (62) inhibited only 69% of growth of Mtb H37Rv, which indicates that C-7 hydroxylation reduces the activity. When this C-7 hydroxyl is blocked by an acetate, as in 63, or completely absent, as in 61, the activity is significantly improved. This is the first report of anti-TB activity of this class of compounds. Compounds 61 and 63 are also good candidates for further investigation since they show minimal toxicity.

Puupehenone (64), 15-cyanopuuphenone (65), puuphedione (67), 15-oxopuuphenol (68), 15α-methylpuuphenol (69), 15α-cyanopuuphenol (70), compounds 66, and 71-7517-21 are natural sesquiterpene-shikimate derived metabolites or semisynthetic derivatives of puupehenone, which is isolated from sponges of the orders Verongida and Dictyoceratida.20–22 Puupehenone (64), 15-cyanopuuphenone (65), and 15α-cyanopuuphenol (70) induced 99, 90, and 96% inhibition of Mtb H37Rv growth, respectively. Puupehenone shows an MIC of 12.5 mg/mL and an IC50 of 2.0 mg/mL. Clearly, the quinone-methide system in ring D of puupehenone is essential for activity as illustrated by both compounds 64 and 65. Compounds with substitution or addition of cyano functionality at position C-15 retain activity and show reduced toxicity. On the other hand the 15-oxo- or methyl derivatives were shown to be inactive. Heteronemin (76) is a scalarin-type sesterterpene previously isolated from the sponge Heteronema erecta and recently isolated by our group from a Red Sea sponge.23 Heteronemin displayed a 99% inhibition of Mtb H37Rv with an MIC of 6.25 mg/mL and IC50 of 1.3 mg/mL. This is the first report of anti-TB activity for the scalarin-type sesterterpene class of compounds. The high cytotoxicity of these compounds prohibited further testing; however, microbial and/or chemical modifications of these compounds may produce less toxic and more active derivatives. Aerothionins are a group of brominated spirocyclohexadienylisoxazolines isolated from Verongid sponges (Moody, et al, 1972; Kerman, et al, 1990; Acosta, et al, 1992; Gao, et al, 1999). Both 11-hydroxyaerothionin (77) and 11-oxo-12 epihydroxyaerothionin (78) induced 70 and 60% inhibition, respectively, of Mtb growth while 11-oxoaerothionin (79) induced no inhibition at all. This suggests that hydroxylation at positions 11 or 12 is essential for the activity of these compounds. Despite the moderate activity, of 77 and 78, their low cytotoxicity and common occurrence in Verongid sponges suggest that they could be possible leads if additional chemical or microbial hydroxylation is accomplished. This report and the recent report of anti-TB activity of pseudopteroxazole suggests that further evaluation of other related isoxazoline and oxazole derivatives could also afford improved activity.
46a $R=\text{OCOCH}_3$, 46b $R=\text{OH}$
47 48a $R_1+R_2=\text{O}$
48b $R_1=\text{H}$, $R_2=\text{OH}$

49a $R=\text{24R}$, 49b $R=\text{24S}$

50 saturated, 51 unsaturated

53a $R_1=\text{CO(CH}_2_{16}\text{CH}_3, R_2=\text{CH}_3$,
53d $R=\text{CH}_3$

53b $R_1=\text{H}$, $R_2=\text{CH}_3$

53e $R_1=\text{H}$, $R_2=\text{C}_2\text{H}_5$

54a $R=\text{CH}_3$

Massetolde A (55): $R=\text{CH}_3$
Viscosin (56): $R=\text{H}$
Pseudopteroxazole (57)

pseudopteroxazole (58)
Kahalalide A (59)
Table 1. *In vitro* inhibitory activity against *Mtb* H37Rv.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>% inhibition 12.5µg/mL</th>
<th>Structural class</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litosterol (61)</td>
<td>90</td>
<td>Steroid</td>
<td>Iguchi, et al, 1989</td>
</tr>
<tr>
<td>Nephalersterol-C (63)</td>
<td>96</td>
<td>Steroid</td>
<td>Liu, et al, 1992</td>
</tr>
<tr>
<td>Puupehenone (64)</td>
<td>99</td>
<td>Shikimate-sesquiterpene</td>
<td>Hamann, et al, 1993</td>
</tr>
<tr>
<td>Puupehedione (67)</td>
<td>0</td>
<td>Shikimate-sesquiterpene</td>
<td>Hamann, et al, 1993</td>
</tr>
<tr>
<td>Heteronemin (76)</td>
<td>99</td>
<td>Sesterterpene</td>
<td>Kazlauskas, et al, 1976</td>
</tr>
<tr>
<td>11-Hydroxyaerothionin (77)</td>
<td>70</td>
<td>Tetrabromo isxazoline</td>
<td>Moody, et al, 1972</td>
</tr>
<tr>
<td>12-epi-11-oxo-12-hydroxyaerothionin (78)</td>
<td>60</td>
<td>Tetrabromo isxazoline</td>
<td>Kernan, et al, 1990</td>
</tr>
<tr>
<td>11-Oxoaerothionin (79)</td>
<td>0</td>
<td>Tetrabromo isxazoline</td>
<td>Acosta, et al, 1992</td>
</tr>
<tr>
<td>Chemical Name</td>
<td>R₁</td>
<td>R₂</td>
<td>R₃</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Litosterol (61)</td>
<td>H</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>Nephalsterol-B (62)</td>
<td>OH</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>Nephalsterol-C (63)</td>
<td>OAc</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>Pupehenone (64)</td>
<td>H</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>15-Cyanopupehenone (65)</td>
<td>CN</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>20-O-Acetylpupehenone (66)</td>
<td>H</td>
<td>OAc</td>
<td></td>
</tr>
<tr>
<td>15-Oxopupehenol (67)</td>
<td>=O</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15a-Methylpupehenol (68)</td>
<td>α-Me</td>
<td>OH</td>
<td>OH</td>
</tr>
<tr>
<td>15a-cyanopupehenol (69)</td>
<td>α-CN</td>
<td>OH</td>
<td>OH</td>
</tr>
<tr>
<td>15a,19,20-Tri-O-acetylpupehenol (70)</td>
<td>OAc</td>
<td>OAc</td>
<td>OAc</td>
</tr>
<tr>
<td>15a-Methyl-19,20-di-O-acetylpupehenol (71)</td>
<td>α-Me</td>
<td>OAc</td>
<td>OAc</td>
</tr>
<tr>
<td>15a-Cyano-19,20-di-O-acetylpupehenol (72)</td>
<td>α-CN</td>
<td>OAc</td>
<td>OAc</td>
</tr>
<tr>
<td>15a-Nitromethyl-19,20-di-O-acetylpupehenol (73)</td>
<td>α-CH₃NO₂</td>
<td>OAc</td>
<td>OAc</td>
</tr>
<tr>
<td>15a-(1-Nitroethyl)-19,20-di-O-acetylpupehenol (74)</td>
<td>α-CH(CH₃)NO₂</td>
<td>OAc</td>
<td>OAc</td>
</tr>
</tbody>
</table>

Pupehedione (67)  
Heteronemin (75)
Recent Developments of Some Natural...  © 2017 NSP Natural Sciences Publishing Co.

Figure Marine compounds with anti-TB activity Ten marine compounds were reported as anti-TB agents, a considerable increase (Mayer et al., 2009). Isolated Plakortide P (82) and bioactive oxapolycyclic diterpene bipinnapterolide B (83) from the Colombian gorgonian coral Pseudopterogorgia bipinnata (Ospina et al. (2007) which weakly inhibited growth of Mtb H37Rv (66% inhibition at 128μg/mL). (Zhang et al. (2008) identified two new dimeric naphtha-γ-pyrone 8′-O-demethylnigerone (84) and 8′-O-demethylisonigerone (85) from the marine derived fungus Aspergillus carbonarius which showed weak anti-TB activity against Mtb (H37Rv, MIC=43 and 21.5μM, respectively). Interestingly, the presence of conjugated C=C–C=O bonds in the pyrane ring appeared to be crucial for antifungal activity. As a result of a continued investigation of the Caribbean sea whip Pseudopterogorgia elisabethae, Wei et al. (2007a) reported that the novel tricarbocyclic norditerpenes caribenols A (86) and B (87) weakly inhibited Mtb (H37Rv, MIC=128 and 63 μg/mL, respectively). Furthermore, Wei et al. (2007b) discovered two novel ring B abeo-sterols parguesterols A (88) and B (89) in the Caribbean sponge Svenzea zeai, which inhibited Mtb (H37Rv, MIC=7.8 and 11.2μg/mL, respectively). Hopefully future information on the selectivity index of
these two compounds will provide additional information to support the notion that they might “constitute important lead structures for the development of novel TB drugs due to their strong activity, specificity, and low toxicity”. (Berrue et al. (2007) noted that several bioactive polyketides, 24-norisoplicol acid A (90), dinorspicoic acid A (91), and nospicoic acid A (92) from the Caribbean sponge Plakortis zyggompha also inhibited Mtb (H37Rv, MIC99=50μg/mL). Although all of these studies demonstrate that marine terpenes and polyketides constitute potentially novel anti-TB leads. Calanolide A 109 was also found to have activity against all Mtb strains tested, including some which are resistant to standard anti-TB drugs. This property is unique amongst antiviral agents and may allow more efficient treatment of patients infected with both HIV and tuberculosis. The related coumarins calanolide B (costatolide), dihydrocalanolide B and oxocalanolide are also under preclinical development (Mayer et al., 2011).
Recent Developments of Some Natural ...
Table 2. Natural products with antitubercular activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Plant Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E)- and (Z)-phytol and phytanol (97)</td>
<td>Leucas volkensii</td>
</tr>
<tr>
<td>Oleanolic acid (95)</td>
<td>Lantana hispida</td>
</tr>
<tr>
<td>Mulinane (96)</td>
<td>Azorella madreporica Clos</td>
</tr>
<tr>
<td>Calanolide A (94)</td>
<td>Calophyllum lanigerum</td>
</tr>
<tr>
<td>Tryptanthrin (93)</td>
<td>Strobilanthes cusia</td>
</tr>
<tr>
<td>12-methyl-5-dehydroacetylhorminone (98)</td>
<td>Indigofera longeracemosa</td>
</tr>
<tr>
<td>(24R)-Saringosterol (100)</td>
<td>Lessonia nigrescens</td>
</tr>
<tr>
<td>Engelhardione (99)</td>
<td>Engelhardia roxburghiana</td>
</tr>
<tr>
<td><strong>Marine organisms</strong></td>
<td></td>
</tr>
<tr>
<td>(+)-8-hydroxymanzamine A (106)</td>
<td>Pachypellina sp</td>
</tr>
<tr>
<td>Ircinol A (108)</td>
<td>Indo-Pacific sponges</td>
</tr>
<tr>
<td>Manzamine A (107)</td>
<td>Indo-Pacific sponges</td>
</tr>
<tr>
<td>Axisonitrile-3 (101)</td>
<td>Acanthella kethla</td>
</tr>
<tr>
<td>Pseudopteroxazole (105)</td>
<td>Pseudopterogorgia elisabethae</td>
</tr>
<tr>
<td>Erogorgiaeene (102)</td>
<td>Pseudopterogorgia elisabethae</td>
</tr>
<tr>
<td>Litosterol (103)</td>
<td>Litophyton viridis</td>
</tr>
<tr>
<td>Puupehenone (104)</td>
<td>Hyrtios sp</td>
</tr>
</tbody>
</table>
Seven compounds (111, 112–117) were showed anti-TB activity. A diterpene alkaloid homopseudopteroxazole (112), isolated from the Caribbean sea plume P. elisabethae (Rodríguez and Rodriguez, 2003), inhibited growth of Mtb H37Rv (MIC=12.5 μg/mL). A manzamine alkaloid (Rao et al. 2003), (+)-8-hydroxymanzamine A (111) was very potent against Mtb (H37Rv, MIC=0.91 μg/mL), comparing favorably with rifampin (MIC=0.5μg/mL). A alkaloid ingenamine G (113) demonstrated activity against Mtb H37Rv at 8 μg/mL (De Oliveira et al. 2004). A new scalarane-type bioactive sesterterpene, 12-deacetoxyscalarin 19-acetate (54), which was purified from the Thai sponge Brachiaster sp. (Wonganuchitmeta et al., 2004), inhibited growth of a nonvirulent strain of Mtb by 50% at MIC=4 μM, comparing favorably with kanamycin sulfate (MIC=3.5–8.5 μM). As a result of identify marine natural products that inhibit the mycothiol-S-conjugate amidase, a mycobacterial detoxification enzyme (Nicholas et al. 2003), reported several activecompounds: a mixture of 1,3 pyridinium polymers (115) isolated from the marine sponge Amphimedon sp., IC50=0.1 μM; an Oceanapiside sp.-derived bromotyrosine compound (116), IC50=3 μM; and the glycosphingolipid oceanapiside (117), IC50=10 μM Oceanapiside, was observed to be a “simple non-competitive inhibitor” of the mycothiol-S-conjugate amidase enzyme (Mayer, et al., 2005).

Insects
Cecropin (111)  
Melittin

Micro-organisms
Streptomycin, kanamycin, amikacine and capreomycin  
Rifamycins  
Thiolactomycin  
Drosophila melanogaster  
Apis mellifera  
Streptomyces spp, Micromonospora spp,  
Bacillus spp  
Streptomyces mediterrani  
Nocardia sp.
**Tryptanthrin**: Tryptanthrin and its analogs are potent against MDR-TB strains, are non toxic and give promising blood and tissue levels after oral administration to mice. The more potent of these, PA-505 and PA-510, are two orders of magnitude more potent than tryptanthrin itself and have been extensively evaluated *in vivo* but failed to cure infected mice. Tryptanthrin (118) is a potent structurally novel indolo-quinazolinone alkaloids, active against MDR-TB with a MIC of 0.5-1.0 µg/ml. But *in-vivo* data and *in-vitro* toxicity are needed before this structural prototype is applied in MDR-TB [Mitscher, and Baker. 1998; Potewar et al., 2008].

**Diterpenoids**: These compounds (fig 20) known for various medicinal value have recently been screened for anti-TB activities against *Mtb*. Many analogues have shown potent anti-TB activity and it has been established that benzooxazole moiety is not essential for the activity. All the tested compounds were derivatives possess inhibitory activity against the enzymes isolated from natural sources [Molina-Salinas et al., 2010].

**Simple carbohydrate derivatives**: The simple sugar involved in the cell wall biosynthesis, many simple monosacharide derivatives (119) exhibited activity against *Mtb* H37Rv. Few of the compounds have shown potent activity against MDR of *Mtb* strain. However, many compounds displayed toxicity in the animals [Bijev and Georgieva. 2010].

**Marine Natural products**: Kahalalides A, isolated from the Sacoglossan mollusk Elysia rufescens, inhibited the growth of *Mtb* H37Rv. Similarly, Litosterol ans nephalasterol C, the C19 hydroxy steroids, isolated from the red sea Nephtheasp; had 90 and 96 % inhibitory activity against *Mtb* H37Rv. Heteronemin a sesquiterpene isolated from a red sea sponge; displayed anti-TB activity against *Mtb* H37Rv with MIC 6.25µg/ml and IC50 1.3 µg/ml [Tripathi et al., 2005].

**Structure of tryptanthrin**

**Pseudoterpetroxazole  Seco-pseudoterpetroxazole  Ergorgiaene  7-Hydroxyergorgiaene**

**Elisapterosin B**

**Kahalalide A**

**R1=H, R2=OH; Litosterol R1=OAc, R2=OH; Nephalsterol**
Anti-TB Natural Products Isolated Following These Technologies

Among those extracts active in both the *M. smegmatis* screen and the confirmatory BACTEC screen against MTB and MAC, were the well known medicinal plants *Glycyrrhiza glabra* and *Hydrastis canadensis*. From *G. glabra* a series of flavonoids including the anti-TB agent licoisoflavone [figure 11 was isolated. It proved to be less active against *Msg* (50 mg/L) than MTB (25 mg/L). From *H. canadensis* the well known antibacterial alkaloid berberine was isolated [figure 11. It was more active in vitro against *Msg* than against MTB (25 mg/L).

An exciting result was obtained in exploring the constituents of the Chinese medicinal plant, *Strobilanthes cusia*. The active constituent turned out to be tryptanthrin. It has also been isolated from indigoferous plants, such as *Strobilanthes cusia*, *Polygonum tinctorium*, and *Isatis tinctoria*, which find folkloric use as topical fungicides, and in the cannon ball tree, *Couroupita guianensis*. Tryptanthrin and certain analogs are also prepared by directed biosynthesis using fermentation of the yeast, *Candida lipolytica*, to which a variety of synthetic tryptophane analogs were fed. Thus tryptanthrin and some of its analogs were known as antiinfectives (although not as anti-TBs). In BACTEC studies, tryptanthrin proved rather more potent against *Mtb* H37Rv (1 mg/L) and *M. avium* (4 mg/L) than against *Msg* (6 mg/L). This potency is in the same range as that of established anti-TB agents such as STR, INH and ETH. Rather more excitingly, against MDR-TB strain 10038, which was not affected by these three agents at comparatively high doses, tryptanthrin was equally active. Tryptanthrin can be proposed to be operating by a molecular mechanism different than that employed by most of the existing anti-TB agents and might be useful in cases where existing agents would fail to maintain or cure patients. The dichloromethane extracts of the above-ground biomass and roots of *Quinchamalium majus* led to the identification of six known constituents, betulinic acid (120), daucosterol (121), 5,7-dihydroxyflavone (122), oleanolic acid (123), (D)-2S-pinocembrin (124), and ursolic acid (125), for the first time in this species. Their chemical structures were determined on the basis of spectroscopic evidence and chemical transformation methods. All of these compounds along with additional 11 analogues were evaluated for their anti-TB potential against *Mtb* (Qiao Gu et al., 2004). Six compounds of previously known structures were identified as betulinic acid (120), daucosterol (121), 5,7-dihydroxyflavone (122), oleanolic acid (123), (D)-2S-pinocembrin (124), and ursolic acid (125) from the dichloromethane-soluble extract of roots of *Q. majus*. Among these constituents, the presence of 123and 125was confirmed by observation of their respective acetyl and/or methyl derivatives (123a, 123b, 125b, 125c). Six related triterpenoids, a-amyrenone (119), a-amyrenone (117), amyrone (118), amyrin (116), oleanolic acid. All of the isolates obtained from *Q. majus* along with 11 analogues were evaluated for their potential to inhibit the growth of *Mtb* and African green monkey Vero cells, respectively, according to established protocols (Collins and Franzblau, 1997; Cantrell et al., 1996). The results showed that three common triterpenes, betulinic acid (121), oleanolic acid (123) and ursolic acid (125), along with the flavanone 124exhibited significant inhibitory activity in a microplate alamar blue assay with MIC values of 62, 30, 31, and 90 μg/ml, respectively, while the other two isolates 121and 122were inactive (MIC>128 μg/ml). It was observed that a reduction of the carboxylic acid group in compounds 123and 125to the corresponding methyl group resulted in the complete loss of activity even though the 3-hydroxy group was not modified as in 126and 127or was oxidized to a ketone group as in 128and 129. In addition, the complete loss of activity as in 123b and 125b was also observed for both 123and 125if the 3-hydroxy and carboxylic acid groups were simultaneously changed to the corresponding acetate and methyl ester, respectively. However, modification of only the carboxylic acid of 123to its corresponding methyl ester (123c) retained the anti-TB activity in the same order of magnitude while the cytotoxicity against Vero cells was enhanced ca. threefold. Replacement of only the 3-hydroxy group of 123to its corresponding acetate (123a) resulted in a remarkable reduction of the anti-TB activity. In contrast to the observations with compound 123, methyl ursolate (125c) decreased the anti-TB activity twofold and enhanced the cytotoxicity somewhat when compared to 125. More interestingly, modification of the 3-hydroxy group of 125to the corresponding acetate (125a) reduced the cytotoxicity about three times while still keeping the same anti-TB activity (Wachter et al., 1999). Furthermore, plant-derived extracts often led to the isolation of common triterpenoids with only a moderate activity such as betulinic acid, oleanolic acid, ursolic acid, and their epi-isomers (Wachter et al., 1999; Caldwell et al., 2000; Cantrell et al., 2001; Gu et al., 2004; Woldemichael et al., 2004). Therefore, triterpenoids in initially active plant extracts in order to facilitate the search for novel anti-TB agents. Natural products play a major role in drug discovery, as a unique source of original structures and provide models for future drug design. In the field of anti-TB agents, the lichen dibenzofuran derived secondary metabolite: usnic acid (130) has been shown to display an interesting activity. So, for the development of a new class of anti-TB agents in order to fight resistance and shorten the duration of therapy to synthesis of natural product-like hybrids is an efficient route. A series of 3,3-dimethyl-3Hbenzofuro[3,2-f][1]benzopyran and 1,2-dihydro-3,3-dimethyl-3Hbenzofuro[3,2-f][1]benzopyran, which displayed significant activities when tested against *Mtb* H37Rv and Beijing strains, with MIC99 in the range of 1-10 μg/ml. The most active compound (130a) exhibited a MIC99 of 5 μg/ml and 1μg/ml respectively against *Mtb* H37Rv and *M. smegmatis* (Prado et al. 2006). The most active compound (131) displayed MIC 95 8 μg/ml against *Mtb* H37Rv (Prado
et al. 2007). In the next trial, the group was successful in producing molecules 132 and 133 with more potency of MIC95 in the range 0.6-2.5 μg/ml against MtbH37Rv (Alvey et al. 2008; Alvey et al. 2009). A series of pyranocoumarin derivatives, and found two compounds (134a and 134b) were bactericidal in their effect on Mtb since their MBC/MIC ratios was 2.

These two compounds had a MIC value of 16μg/mL (Xu et al. 2006). Translocase I (Mra Y) is one of the enzymes involved in the biosynthesis of peptidoglycan and is a possible target for developing antibiotics. In the course of screening for new antibiotics with translocase I inhibitory activity, Hotoda et al. found the capuramycin (135a), with a selective antibacterial activity against mycobacteria along with its methylated derivative, A-500359A (135b). In continuation the same group isolated A-500359E (135c) lacking the azepan-2-one moiety of capuramycin. So, in an effort to increase the potency of capuramycin skeleton, Hotoda developed the analogues of 135a, 135c and tested for their translocase I inhibitory activity and in vitro antimycobacterial activity. It was observed that the aryl analogs were found to be effective substituents for capuramycin analogues. The most active compound (135d) displayed a MIC of 6.25 μg/ml against M.smege and best potency particularly against MDR-TB (Hotoda et al. 2003).
Recent Developments of Some Natural...
Discussion And Conclusion

The bioactivity or pharmacology of structurally characterized natural products. The use a modification of chemical classification (Schmitz et al., 1993) to assign natural product structures to six major chemical classes, namely, polyketides, terpenes, peptides, alkaloids, shikimates, and sugars. Novel antibacterial, anti-TB, the preclinical pharmacology of extracts or structurally uncharacterized marine compounds, (Karabay-Yavasoglu et al., 2007) (Martins et al., 2008; Tadesse et al., 2008); strong antibiotic-producing potential in actinomycetes from sediments in Norway (Bredholt et al., 2008); antibacterial activity of deep-sea bacteria from sediments of the West Pacific Ocean (Xu et al., 2007); potent antimycobacterial activity in the green alga Enteromorpha intestinalis (Nair et al., 2007); a nonhemolytic antimicrobial lipopeptide derived from the marine bacterium Bacillus circulans (Das et al., 2008); a T-antigen binding lectin with bioactivity against a broad spectrum of Gram-positive and Gram-negative bacteria from Holothuria scabra (Gowda et al., 2008); anti-TB in long-chain fatty acids isolated from the red alga Polysiphonia virgata (Saravanakumar et al., 2008; Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005; Mayer et al., 2007, 2009). The preclinical pharmacology of structurally characterized natural compounds isolated from animals, algae, fungi and bacteria is discussed in a comprehensive manner. Anti-TB activity was reported for natural products. Sustained preclinical research with natural products demonstrating novel pharmacological activities, will probably result in the expansion of the current pharmaceutical clinical pipeline, which currently consists of natural products, analogs or derivatives targeting tuberculosis.

Further encouragement was found when tryptanthrin was found to be little affected by serum protein binding and the bacteriostatic and bacteriocidal ratio was acceptable. The structure of tryptanthrin is simple, low molecular weight and has a structure which differs from all established anti-TB agents. Preparation of several analogs demonstrated that activity was preserved throughout a significant range of structural changes. Using variants, several hundreds of analogs have been prepared and evaluated. These structures include many novel analogs and a number of these are at least 100-fold more potent than tryptanthrin itself. Analogous substitution chemistry demonstrated that a wide range of substituents in the D ring was also compatible with powerful in-vitro anti-TB activity. Some of these analogs are 100-fold more potent in-vitro than Just as with tryptanthrin itself, these analogs generally retained their activity when tested against MDR-Mtb strains. An interesting trend is noted in that the activity increases with aliphatic substitution (PA-505 (2-aza-8-(2-octyl) tryptanthrin) was selected for detailed biological evaluation. These analogs are generally approximately equally active against several sensitive strains of A4-TB and several MDR-TB strains. In the tryptanthrin series, analogs are occasionally cidal but are most commonly static. Tryptanthrin is clearly a poorer choice for in-vitro evaluation than PA-505. Despite the ultimate disappointment with the in-vitro anti-TB properties of tryptanthrin analogs, and that a wide variety of natural products structures possess potential utility for the treatment of MDR bacterial infections. The marine environment clearly holds an enormous potential for providing new leads for the development of anti-TB agents. The identification of new structural classes active against Mtb will provide undescribed mechanisms of action and better treatments for resistant strains. Much of the disease burden lies in regions possessing coastal areas rich in marine life. As a result the eventual establishment of mariculture facilities for the production of bioactive materials provides a viable alternative to total synthesis. The reasonably high yields of many sophisticated marine natural products provide an opportunity for the utilization of endemic resources to combat this devastating disease. Cultivation of marine sponges for metabolite production is continuing to make solid progress as an alternative for production of complex marine natural products that are not amenable to cost-effective, large scale synthesis. In this paper we report three new anti-TB structural classes; C-19 hydroxy steroids, scalarin sesquiterpenoids, and tetrabromo spirocyclohexa dienylisoxazolines as well as two classes related to previous reports; kahalalides (peptides), and puupehenones (quinone methide).

More than 50% of the medicines introduced in world medical practice are connected with natural compounds to some extent. It can be as native metabolites and synthetically the modified derivatives. The discovery of natural compounds with remarkable pharmacological properties and also tens other compounds of a plant and animal origin with various high biological activity allow to hope for prompt discovery of highly effective low-toxic natural compound which will be leader in struggle against a TB. Natural products are an important source of anti-TB compounds for leads of new drugs. In the past decade there has been renewed attention and interest in the use of traditional medicine globally. It is necessary to carry out activities allow to characterize and develop suitable trades in medicinal and aromatic plants, on the basis of a clear identification of the real market and thus facilitating the monitoring and control of the relevant entities. The development of the natural products represents an opportunity for the improvement of the standard of living of rural communities and for the conservation of zones rich in biodiversity (Bueno et al., 2011; McMannis. 2007). The natural products sector has interesting opportunities in international and regional markets.

There is a common interest in the discovery of new products and new uses; and this represents an opportunity for this sector.

References


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