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Relevance of Marine sources in the Bioactive Natural Products

Relevancia de las fuentes marinas en los productos naturales bioactivos

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Resumen:

Los productos naturales derivados de las fuentes marinas son significativos en los metabolitos secundarios biológicamente activos. Los organismos marinos parecen ser una fuente propicia para prometer productos del futuro naturalmente activos debido a la notable diversidad de compuestos químicos que se aislaron. Comúnmente, los productos naturales son estructuras complejas de compuestos que describen la orientación exacta de la tierra. Debido a la diversidad química y las actividades biológicas del bencimidazol y el anillo de pirrol que contienen productos naturales contra muchas enfermedades, tienen un papel importante en la investigación del campo farmacéutico.

Palabras Clave: bencimidazol; pirrol; organismos marinos.

Abstract:

Natural products derived from the marine sources are significant in biologically active secondary metabolites. Marine organisms appear to be auspicious source for promising naturally active products of the future due to the remarkable diversity of chemical compounds that were isolated. Commonly the natural products are complex structure of compounds which describes exact orientation of the earth. Because of the chemical diversity and biological activities of benzimidazole and pyrrole ring contained natural products against many diseases, they have an important role in the research of pharmaceutical field.

Keywords: benzimidazole; pyrrole; marine organisms; Spongothymidine.

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1. Introduction:

The marine environment is an extraordinary treasure of different kind of bioactive natural products, pertains morphological and biological features which are not available generally in terrestrial natural products (Sawangwong et al, 2004). In the world, 70% of earth was occupied by oceans and almost 75% of diverse plants and animal species lives in oceans (Mayer et al, 2010). The 34 phyla of life out of the 36 are represented in oceans whereas only 17 phyla of life representing the terrestrial environment (Schwartz et al, 1998). In a recent review regarding the source of new natural products, 63% of the new drugs are classified as naturally derived modified natural product or synthetic compound with a natural product as pharmacophore (Grothaus et al, 2009). The below graphics (figure 1) contains the detail representation of total number of new compounds isolated from different marine source from 2001-2010, is described (Mahbub et al, 2014).

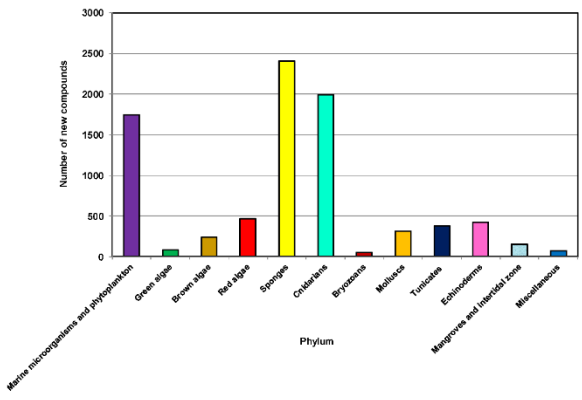

Figure 1. Total number of new compounds isolated from different types of marine sources 2001–2010.

According to the report the living organisms were started living in the oceans over 3500 million years ago. Marine organisms such as sponges, fishes, shells, sea slugs, soft corals, mollusca, tunicates, echinoderms, nudibranchs, sea hares, opisthobranches, bryozoans, prawns, and marine microorganisms are sources of bioactive compounds (Vieira et al, 2014). The long process of formation of the marine natural products has caused in finest level of communications with biological macromolecules and its target. The development of marine organisms with the appropriate mechanisms due to its sustain in an extreme temperature, pressure, variable of salinity and in addition to overcoming the effects of mutations, viral pathogens, bacteria. The oceans appear to be superior than to the terrestrial ecosystem with regards to evolutions and biodiversity (Jimeno et al, 2004).

These chemical compounds have been developed gradually to interact with their biological specific targets to validate the subject of drug discovery (Henkel et al, 1999). The involvement of chemistry into the natural product field is mainly related to the isolation, biosynthesis and structure elucidation of new products that possess medicinal properties. Because of the chemical diversity and biological activities against diseases, they have an important role in the research of pharmaceutical field (Molinski, 2009). From earlier onwards, marine isolated natural

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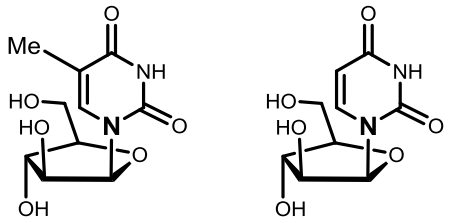
substances have been the richest source of bioactive compounds and lead chemical structures.

The marine organisms provide a health benefit. They are potential candidates for the treatment of several human diseases such as cancer, microbial infections and inflammatory processes. The high remarkable hit rates of marine products in screening for drug leads makes the marine organisms more attractive (Hamann et al, 2003). Marine natural products are generally not primary metabolites and it was not generated by biological or regular metabolic pathways. Its secondary metabolites and the function associated with the development, growth, or propagation of a species are from secondary metabolites (Stempien et al, 1957).

In the definition, a natural product is a molecule which is produced by a biological source (Henkel et al, 1998). In late 1950, *Bergmann et al* formally reported the first biologically active marine natural product (Editorial of *Nat. Chem. Biol*. 2007). In late 1970, it was established that all the marine plants and animals are genetically and biochemically unique. There are 15,000 unique natural compounds which have been described. In this sense 3000 products have been isolated from sponges (Moore et al, 2010). As examples of the unique structural architecture, it was found the unusual presence of arabino or ribo-pentosyl nucleosides in marine sponges. This shows that naturally occurring nucleosides could also contain sugars other than ribose and deoxyribose (figure 2) (Bennett, 1963).



Spongothymidine Spongouridine

Figure 2. Natural compounds contain nucleosides with arabinose.

Marine samples reveal a much higher hit rate for antitumor and antibiotic activities. The highlights of marine natural products in the pipelines of pharmaceutical products are summarized in several recent reviews (Elderfield, 1957). The exploration of marine microorganisms for biotechnological application is known. This comprises the production of bioactive compounds for pharmaceutical use, as well as the development of other valuable products, such as enzymes, nutraceuticals and cosmetics. These are good reasons to intensively study and explore marine biodiversity for new drug candidates.

2. Benzimidazole contained natural products.

Imidazole is a five-membered aromatic heterocyclic system which contains an imino group and non-adjacent nitrogen atoms at 1,3 positions. Imidazole acts as amphoteric in nature. Imidazole nucleus is found in many natural products, mainly in alkaloids. The imidazole moiety is incorporated in number of such as histidine, histamine, and biotin (figure 3) (Xie et al, 20015).

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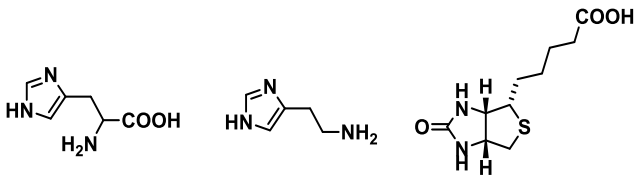

Figure 3. Imidazole contained biological molecules.

Benzimidazole is a heterocyclic aromatic system which contains a phenyl ring which is fused to the 4,5 positions of imidazole. The NH group present in benzimidazoles is relatively strongly acidic and weakly basic. Another characteristic of benzimidazoles is that they can form salts. Benzimidazoles with unsubstituted NH groups exhibit fast prototrophic tautomerism, which leads to equilibrium mixtures of asymmetrically substituted compounds (Labanauskas et al, 2000). This bicyclic benzimidazole moiety led to substances which are an important group of compounds with many medicinal, agricultural and wide variety of applications. It is one of the privileged structure in medicinal chemistry and significant pharmacophore in the drug development field. At the position of nitrogen atom or carbon atoms at the ring of benzimidazole bears the substitution products like acyl groups, alkoxy groups, and thiol groups (Sharma et al, 2008). Benzimidazole derivatives have occupied a notable place in the field of pharmacology and building blocks of many bioactive molecules. Benzimidazole moiety is a structural isostere of the indole and purine as well as other natural compounds that makes them active substances because of their interactions with biotargets. Since the presence of crucial Benzimidazole-derived alkaloids are rare in nature, and only a few examples of these natural products can be found in the literature (He et al, 1992). On the other hand, the occurrence of the imidazole skeleton in various natural sources is quite common. Benzimidazole-containing natural products were isolated from marine sponges of the *Leucetta and Clathrina* genus, also isolated 2-aminoimidazoles alkaloids (clathridine A and naamidine G, H). Some relevant interesting and potentially therapeutic biological activities are often associated with these benzimidazole contained alkaloids. Additionally, in their preparation issue they are synthetically challenging structural motifs (Faulkner, 1992).

The marine sponges have been a rich and diversified source of important natural products. Kealiiquinone was isolated by Scheuer and Clardy in 1990 as a red, long needle and as a secondary metabolite of the calcareous leukonoid sponges of the genus *Leucetta* collected on the islands of Spain and Micronesia (figure 4) (Sulivan, et al, 2009).

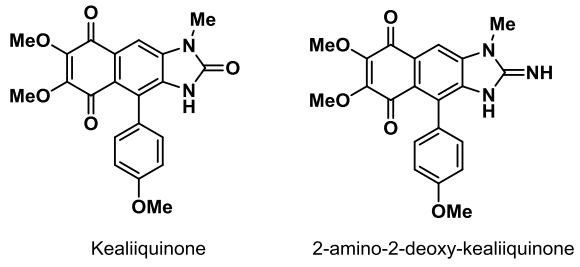

Figure 4. Benzimidazole alkaloid from *Leucetta* and *clathrina* sponge *i.e.* kealiiquinone and 2-amino 2-deoxykealiiquinone.

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This naphthoimidazole derivative is a red crystalline compound that decomposes at 300 ºC. It has a unique structure consisting of three linear fused rings. The kealiiquinone architecture consist in a 2,3 dimethoxy 1,4-napthoquinone fused to an imidazolone ring in the central axis of the molecule and 4-anisolyl substituent attached to the central ring of this tricyclic system. The above description confers a regiochemistry of great interest and a special synthetic challenge.

2-Deoxy-2-aminokealiiquinone was isolated in 1997 by Schmitz and co-workers also from a sponge *Leucetta* taken from Micronesia, its shows better biological activity (IC_{50} = 43.8µM) compared to kealiiquinone (IC_{50} = 92µM) has been reported for this alkaloid still now (Carrol et al, 1990). It was found to have moderate activity against initial toxicity assays including KB cells and HSV II virus, but no broad scale evaluation was or subsequently been performed due to small amount of natural product.

The biological activity assays for kealiiquinone and regioisomer kealiiquinone have been evaluated in *vitro* against thirty-nine human cancer cell lines (Fu et al, 1997). It was found that both kealiiquinone (IC_{50} = 92µM) and isomer of kealiiquinone possesses week biological activity, but both are cytotoxic. This means unique mode of action (Smith et al, 1997). The above highlights the great importance in this natural product and highly expressive, the synthesis of the natural product and the structural analogs in an efficient and simple way.

On the other side, Kealiinine A-C were isolated in 2004 from sponges of *Leucetta* and *Clathrina* families collected in Indonesia by Proksch and co-workers. All the alkaloids which were isolated from *Leucetta* and *Clathrina* sponge contains minimum one oxygenated benzyl group. One more interesting features of this collection of *Leucetta* alkaloid is that kealiiquinone and Kealiinine has a [2,3-*d*] naphthoimidazole moiety. Kealiinine A was obtained as a yellowish-brown powder and was found to give a 50% mortality rate in brine shrimp assay, *Artemia salina*, at a concentration of 20 µg/mL. kealiinines B and C were evaluated against breast cancer line MCF7 using MTT growth, with activity values determined as IC_{50} 28.8 and >100 µM (figure 5) (Tsuno et al, 2001).

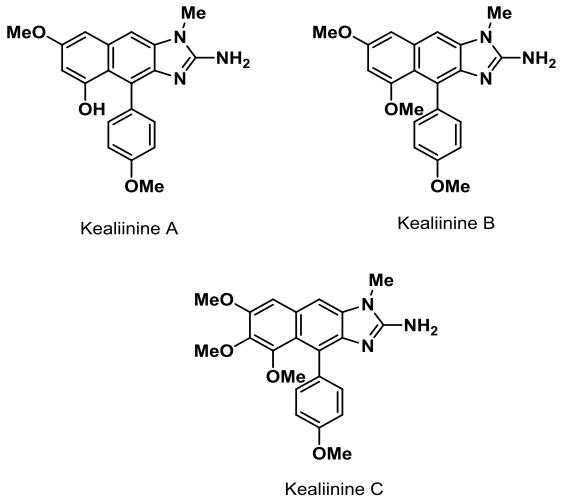

Figure 5. Benzimidazole contained marine natural products Kealiinines A-C.

It has been suggested that Kealiinine C may serve as a biosynthetic precursor to kealiiquinone and 2-amino-2-deoxy kealiiquinone, but there is no experimental evidence to support this hypothesis.

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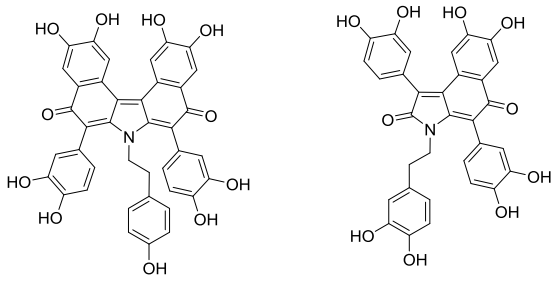
3. Pyrrole ring contained natural products.

Pyrrole is well known as a biologically imporatnt scaffold which has a immense nature of activities. The combination of different pharmacophores in a pyrrole ring system has led to the formation of more active compounds (Pai et al, 1999). Pyrrole derivatives are considered as a one of the effective source of biologically active compounds (Sundberg et al, 1996) that contains a significant set of advantageous properties and can be found in many natural products. Drugs containing a pyrrole ring system are known to have important medicinal properties such as anticancer, antibacterial, antifungal, antiprotozoal, antimalarial and many more (Rewcastle et al, 1990). Due to the diversity of these analogs in the therapeutic response profile, many researchers have been working to explore this skeleton to its maximum potential against several diseases or disorders. Many of pyrrole contained natural products have been isolated from marine organisms such as sponge, tunicates and etc (Mahbub et al, 2014). Ningalin family of natural products such as Ningalin A, B, C and D contains 3,4 diaryl-subsituted pyrrole nucleus in the core. Also, structurally closely related natural products like purpurone (Steglich et al, 2000) and lamellarin (Ruchirawat et al, 2001) class of compounds has pyrrole core in center of molecule (figure 6).

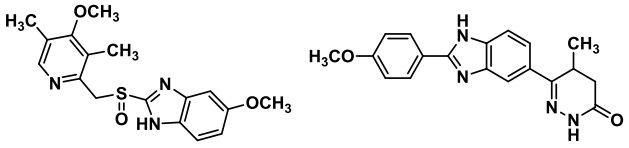


Purpurone Ningalin C

Figure 6. Natural products with pyrrole ring core.

4. Pharmacological importance of benzimidazole.

Benzimidazole is biologically vital scaffold and valuable structural motif for the development of molecules with pharmaceutical and biological interest. The synthesis of benzimidazole-based structures has resulted in various drugs that are present on the market, such as omeprazole, pimobendan, and mebendazole. Benzimidazole is a functional moiety present in the structure of vitamin B12 (figure 7) (Benett, 1963).



Omeprazol Pimobendan

Figure 7. Benzimidazole based structure of Omeprazole, and Pimobendan.

4.1. Benzimidazole as anti-cancer agents.

Cancer is a fatal disease categorized by abnormal growth of cells. Such a growth can be rapid or slow depending on the cancer type. Carbomethoxy

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benzimidazole derivatives of UK -1 assessed for cytotoxicity determination with alamar blue assays against different cancer lines, particularly MCF-7 cell lines. As relevant example the 4-carboxylate subsituted benzimidazole attached benzoxazole derivative shows cytotoxicity value IC_{50} between 70 to 100 μM (figure 8) (Kumar et al, 2002).

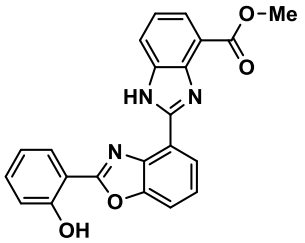

Figure 8. Biological active 4-carboxylate subsituted benzimidazole attached benzoxazole.

4.2. As antiviral agents.

Benzimidazole contained heterocyclic substituents at C-5 position and/or C-2 has been synthesized. They were functionalized with pyridine, *N*-methyl pyrrole, or imidazole and they were evaluated biologically against coxacakieviruses. The derivatives of *N*-methyl pyrrole, and imidazole subsituted benzimidazole (figure 9) shows lead molecule character against adenoviral replication (.

Figure 9. Benzimidazole contained antiviral agents *N*-methyl pyrrole, imidazole.

4.3. As anti-HIV agents.

Naphthamidines and 2-aminobenzimidazoles involved in the reaction to synthesis 5-methyl-benzoimidazole 2-diamine which is analyzed for HIV Type I integrase inhibitors, resulted a potent integrase inhibitor (figure 10).[36]

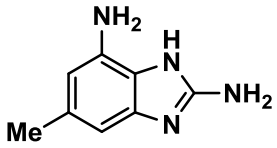

Figure 10. Anti-HIV agent 5-methyl-benzoimidazole 2-diamine.

4.4 As antitubercular activity.

Benzimidazole contained 5-bromo or 5-nitro-2-styryl derivatives were synthesized, looking for antitubercular activity against Mycobacterium tuberculosis. They displayed antitubercular activities in promising way.[37]

4.5. As anti-Alzheimer agents.

Thoroughly observed scaffold of benzimidazole and synthesized many 1-isopropyl-4-aminobenzyl-6-ether-linked benzimidazoles based on a moderately selective CDK5 inhibitor Roscovitine. Biological assay and molecular modeling showed that one of the compound in the series has oxygen linked at 8-position (CDK5/p25 IC_{50} = 13μM) with appreciable affinity for CDK5 (Xie et al, 2005).

4.6. As anti-analgesic and anti-inflammatory agents.

Achar and coworkers synthesized a series of 2-(methylamino) benzimidazole derivatives, showed potent analgesic (89% at 100 mg/kg) and anti-

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inflammatory (100% at 100 mg/kg) activities, respectively, compared with standard drug Nimesulide (100% at 50 mg/kg) (figure 11) (Michejda et al, 2010).

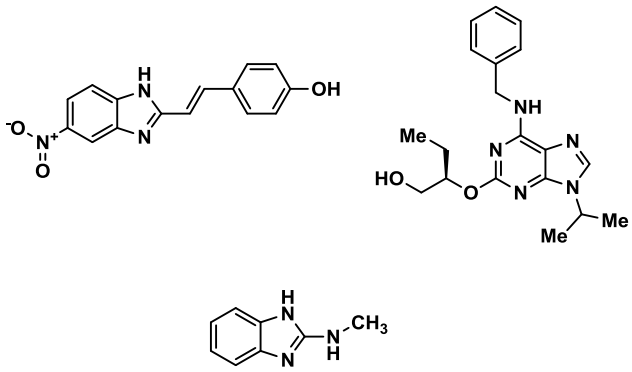

Figure 11. Biological active benzimidazole derivatives of anti-tubercular agent, anti-alzheimer agent, and anti-analgesic agent.

5. Conclusions:

Marine sponges contributed numerous amount of biologically active natural products to the medicinal field. Especially, benzimidazole alkaloids shows good biological activities against many diseases. Kealiiquinone and his family of alkaloids isolated from Lucetta sponges has good cytotoxicity against different cancer cell lines. Pyrrole ring contained alkaloids like Ningalin family of compounds isolated from tunicates in the Ningaloo reef, shows MDR resistant property against cancer cells.

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