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# Pharmaceuticals from the Sea – Past, Present, Future and Red Sea as an Example

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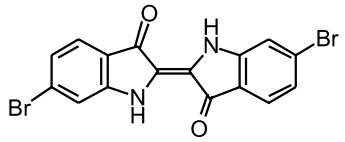
ABSTRACT. A general review on biological activities of marine natural products is presented in connection with the Saudi-French Research Programme on Marine Natural Products from the Red Sea. Due to the huge biodiversity for marine organisms from the Saudi Red Sea, researches were focused on sponges. Several preliminary promising results are presented for anti-malaria, cytotoxicity against KB cells and anti HIV-1 activities.

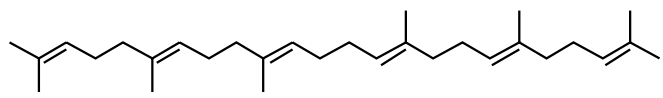
## Introduction

### *Past*

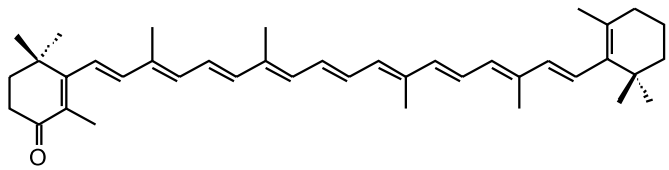
One can consider that the story of Marine Natural Products Chemistry began in 1907 by Friedlander in Germany with the first works on Tyrian Purple, the famous red dye used by Romans, but known since 1600 BC and discovered in the ancient city of Tyre from marine gastropods, mainly from *Murex brandalis*. Then, in 1916, Tsujimoto from Japan, discovered squalene, the metabolic precursor of triterpenes, methylsterols and steroids, in the oil of the shark *Centrophorus uyata*. Finally, in 1933, Lederer, from France, discovered Echinenone, the yellow-orange pigment from *Paracentrotus lividus* gonads (a sea urchin).




**Tyrian Purple**
*Murex brandalis*
Friedlander (1907)

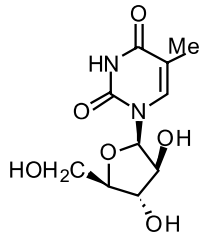


**Squalene**
*Centrophorus uyata*
Tsujimoto (1916)

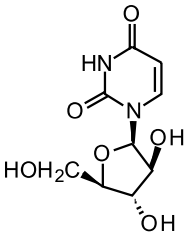



**Echinenone**
*Paracentrotus lividus*
Lederer (1933)

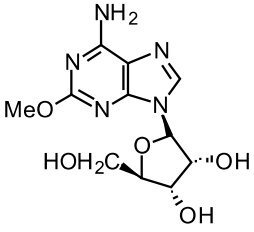
From a pharmacological point of view it is generally assumed that the very beginning of Marine Natural Products story was in the 50's with the initial works of Bergmann (USA) on the sponge *Cryptotethya crypta* from the Caribbean Sea. This sponge contained many free nucleosides and nucleoside analogues with an arabinose replacing the usual ribose moiety. Two of them, spongothymidine and spongouridine were shown to display strong antitumoral and antiviral activities.



**Spongothymidine (ara-T)**
*Cryptotethya crypta*
Bergmann (1950)

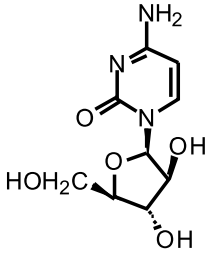


**Spongouridine (ara-U)**
*Cryptotethya crypta*
Bergmann (1955)

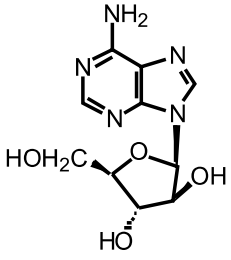


**Spongosine**
*Cryptotethya crypta*
Bergmann (1956)

This led to the very important notion of «chemical model» using the discovery that living organisms can synthesize nucleoside analogs able to interfer with «normal» nucleosides during DNA biosynthesis. Consequently, chemists synthesize new arabinose containing nucleosides with potent antitumoral and antiviral properties, two of them: arabinosylcytosine (ara-C) and arabinosyladenine (ara-A) are now available on the market as antivirals.



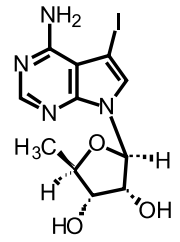
**Arabinosylcytosine (ara-C)**
Cytarabine, Aracytine, Cytarbel, Alexan®, Udicil®



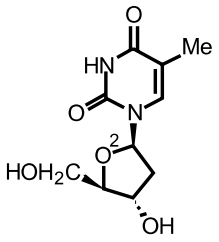
**Arabinosyladenine (ara-A)**
Vidarabine, Vira-A, Vidarabine Thilo®

In 1984, ara-A was discovered in another marine invertebrate, the Cnidaria *Eunicella cavolini.*

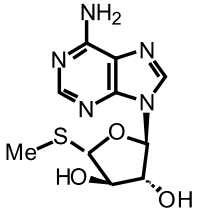
Since Bergmann's pioneering works many other unusual nucleosides and nucleoside analogs were isolated from a variety of marine organisms, invertebrates and algae as well, as shown below (Avasthi & Bhakuni, 1993).



**5-iodo-5'-deoxytubercidine**
from *Hypnea valentiae*
Rhodophyceae (red alga)
Kazlauskas *et al.,* 1983



**2'-deoxyuridine**
from *Acanthaster planci*
Echinoderm (starfish)
Kamori *et al.,* 1980

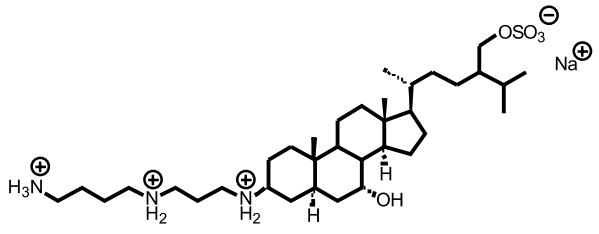


**Xylofuranosyl analog of MTA (methylthioadenosine)**
from *Doris verrucosa*
Mollusca (nudibranch)
Cimino *et al.,* 1986

All these examples have been choosen to show that any kind of chemicals and any kind of biological activity can be found in any phyla of marine organism but which are the best? and how to choose a living organism under the sea with a good probability to find an interesting biological activity? Actually, this problem is difficult to solve because very little is known about ethnocultural knowledge concerning marine organisms contrary to traditional pharmacopeia with terrestrial plants. However, some clues can help the scientific diver to select potentially bioactive organisms. Two criteria should be kept in mind. Firstly, it is important to choose sessile organisms that are devoid of mechanical protection such as shells or spines because all attached animals are necessarily protected against predators by some chemicals that act as strong deterrent or repellent. The second criteria can be deduced from the first one: the «best» attached organisms are those

that are completely devoid of epibiosis because this means that the organism is internally protected against infection by microorganisms. So, a marine organism alga or invertebrate, that appears completely clean underwater is very likely to contain a set of bioactive chemicals.

According to both criteria (attached and devoid of epibiosis) four phyla could be considered as especially interesting. Porifera (Sponges), Tunicates (Sea-squirts) and Bryozoans are always attached and most of Cnidaria are sessile with only a few of them being pelagic. Two other phyla, Echinoderms and Mollusca are known to contain bioactive metabolites but usually very toxic. Both are benthic (some few Mollusca are pelagic) and can move only slowly. These are only main points to collect the most promising invertebrates and several bioactive compounds have been isolated from fish such as squalamine, a very potent antibiotic and antitumoral amino-steroid from the shark *Squalus acanthias*.




**Squalamine**
*Squalus acanthias*
Moore *et al.,* 1993

### *Present*

It is usually admitted that Marine Natural Products (MaNaPro) chemistry began in 1973 with the publication of Paul J. Scheuer's famous book *Chemistry of Marine Natural Products*, Academic Press. Since that date a huge number of publications appeared on the chemistry and the biological activities for thousands of compounds isolated from almost all marine phyla including microorganisms, algae, invertebrates, vertebrates, ... etc. Since 1975 an International Symposium on Marine Natural Products is organized every 3 years all over the world. The Tables 1and 2 just give an idea of the considerable progress of MaNaPro chemistry and biochemistry for the last 30 years.

TABLE 1. Marine natural products – state of the art since 1970.

| Phyla | Publications | Identified molecules |
|---|---|---|
| Bryozoans | 229 | 140 |
| Chlorophyceae | 320 | 211 |
| Tunicates | 858 | 629 |
| Echinoderms | 612 | 775 |
| Mollusca | 1,138 | 901 |
| Phaeophyceae | 1,185 | 1,025 |
| Rhodophyceae | 1,034 | 1,119 |
| Cnidaria | 1,536 | 2,010 |
| **Total** | **6,912** | **6,810** |
| **Porifera (Sponges)** | **2,272** | **3,812** |

From MarinLit Database, V. 10.7, September 1999.

It appears from Table 1 that sponges represent about one third of the total publications and more than the half of all new molecules ever found in marine organisms.

TABLE 2. Sponge chemistry – state of the art since 1970.

| Period | Publications | Identified molecules |
|---|---|---|
| 1970 - 1974 | 65 | 105 |
| 1975 - 1979 | 165 | 226 |
| 1980 - 1984 | 207 | 328 |
| 1985 - 1989 | 451 | 704 |
| 1990 - 1994 | 775 | 1,384 |
| 1995 - 1998 | 609 | 1,065 |
| **Total** | **2,272** | **3,812** |

From MarinLit Database, V. 10.7, September 1999.

It appears from Table 2 that since 1990, several compounds were isolated from a sponge every couple of days! So, the question is: Why Sponges are so interesting?

First of all the position of Porifera among other animal phyla shows that sponges, the simplest animals, are exactly situated between true unicellular organisms such as archeobacteria, bacteria, microalgae, protozoa, and the true pluricellular metazoa. This special position of Porifera on the phylogenetic tree (Fig. 1) makes difficult an unambiguous definition for a sponge. Without differentiated tissues and organs, and with totipotent amoeboid cells able of undergoing any kind of differentiation, Sponges belong to the subkingdom of Parazoa (Bergquist, 1978; Margulis & Schwartz, 1982).

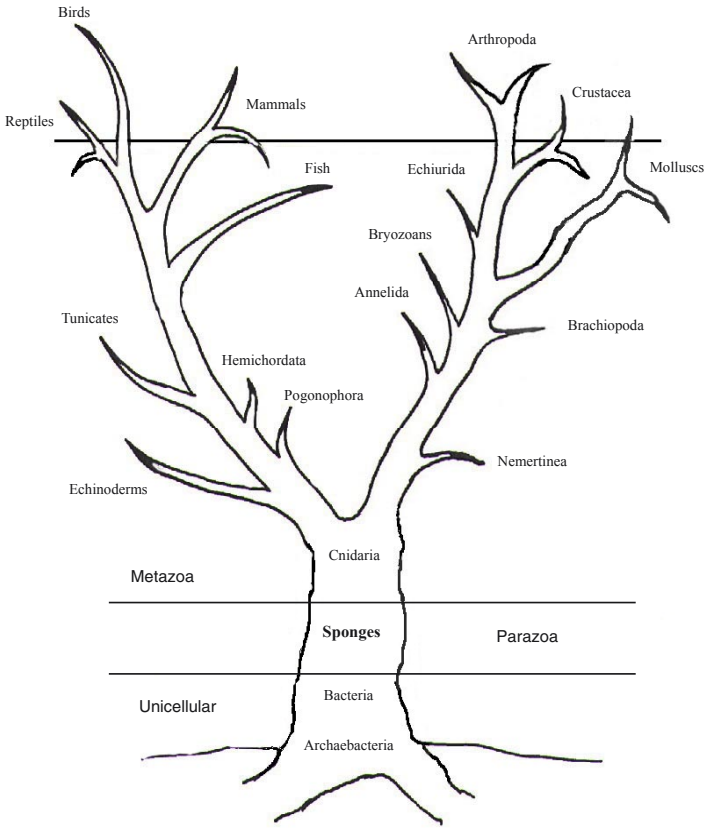



FIG. 1. Position of sponges among other phyla.

From an ecological point of view sponges are always sessile, most of them are living on rocks or stones but some species have been observed on plant roots, especially in mangroves. Being attached and, for most of them despite their siliceous or calcareous spicules, sponges are chemically protected against predators. Furthermore, those devoid of any epibiosis are also protected against microorganisms such as bacteria. These chemical weapons can be elaborated by the sponge itself or can originate from endosymbiotic microorganisms. So, what sponges really synthesize?

This is probably the most important problem for the chemists who are interested in Sponge chemistry. Actually, three possibilities can be considered (Djerassi, 1981).

1 – the metabolite is really synthesized by the Sponge itself,

2 – the metabolite is produced by a host microorganism or can come from the diet,

3 – the metabolite can originate from a symbiotic association between the Sponge and a specific microorganism.

Consequently, Porifera phylum is considered as the richest for chemodiversity. All classes of chemicals have been found in Sponges including rare nitrogen- and sulfur containing groups such as isonitriles, sulfones, ... etc. Sponges belonging to Axinellidae Order often contain unusual nitrogen containing sesquiterpenes and unusual nor-A sterols. Dictyoceratida and Dendroceratida sponges (all devoid of spicules) contain high levels of terpenes, especially rare sesterterpenes (with five regularly linked isoprene units) and low levels of sterols. From a biochemical point of view, sponge metabolites displayed all kinds of biological activities, especially antitumoral, antiviral and antibacterial but also other interesting activities including antimalaria, immunomodulation, antifungal, and antifouling. Now, let us review some basic terms and data concerning biological assays.

**Biological tests for cancer – a short summary**

*in vitro* On cell cultures, determination of *cytotoxicity* with $CD_{50}$, $CC_{50}$, $LC_{50}$

*in vivo* On living animals, determination of *antitumoral* or *antineoplastic activity* with T/C value

On human beings. These are clinical tests with Phase I, II, and III. Only in that case the term *anticancer* is used.

Progress of the researches

**Definitions for used data**

$CD_{50}$, $CC_{50}$ Cytotoxic dose (in µg/mL) or cytotoxic concentration (in µM/mL) : dose or concentration that inhibits cells growth to 50% on the control growth[1]

$LC_{50}$ Lethal concentration : concentration that kills 50% of the cells

$$T/C = \frac{\text{Mean survival time of the test group}}{\text{Mean survival time of the control group}} \times 100$$

***Currently Accepted Values***

An extract is considered as active when $CD_{50} \leq 20$ µg/mL

A pure compound for which $CC_{50} \leq 10$ µg/mL can enter in *in vivo* tests

When $LC_{50} / CC_{50} > 5$ the pure compound is supposed to have no major in vivo toxicity problems

A compound is considered as interesting when T/C > 125 % (increase in life span of 25%)

When T/C ≥ 150% the compound can enter in the «clinical trial series».

***Antiviral Evaluation - A Short summary***

Similarly with cytotoxicity, $ED_{50}$, the effective dose 50 % (in µg/mL) or $EC_{50}$ the effective concentration 50% (in µM/mL) is the dose or the concentration that reduces by 50 % the virus cytopathic effect *in vitro.*

It is usually considered that an extract or a pure compound is

Active when 1 µg/mL ≤ $ED_{50}$ or $EC_{50}$ ≤ 10 µg/mL

Very active when $ED_{50}$ or $EC_{50} \leq 1$ µg/mL

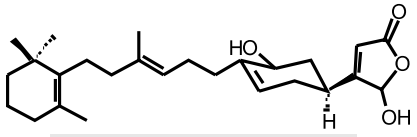
Another interesting data is the Therapeutic Index, T.I. defined as:

$$T.I. = \frac{\text{Cytotoxicity (as } CD_{50} \text{ in µg/mL)}}{\text{Activity (as } ED_{50} \text{ in µg/mL)}}$$

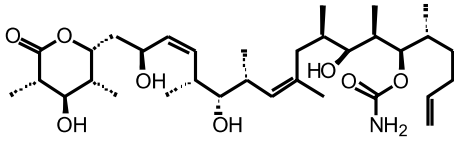
The higher $CD_{50}$ the lower cytotoxicity and the lower $ED_{50}$ the higher activity, so the higher T.I. the higher antiviral activity. Consequently, a lead compound should have both a low cyto-toxicity and a high antiviral activity[2].

For antiparasitic activities mainly for antimalaria, the similar $IC_{50}$, inhibitory concentration (or dose) 50 % is used.

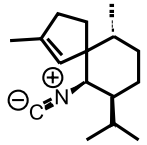
To illustrate these data the three following compounds isolated from Sponges are currently used for clinical tests.




**Manoalide** (1980)
*Luffariella variabilis*
Anti-inflammatory : $IC_{50}$ = 0.05 µM
De Silva & Scheuer, 1980




**Discodermolide** (1990)
*Discodermia* sp.
Immunosuppresor : $IC_{50}$ = 0.20 µM
Gunasekera *et al.,* 1990




**Axisonitrile-3** (1992)
*Acanthella klethra*
Antimalarial : $IC_{50}$ = 16.5 ng/mL
Angerhofer *et al.,* 1992
Di Blasio *et al.,* 1976
Wright *et al.,* 1996

[1]The dose is used for an extract that contains several compounds; the concentration is used for a pure substance for which the molecular weight is known.
[2]A virus must be cultured inside a living cell so, a good antiviral should kill or reduce the virus replication without strong or lethal effect for the host cell.

### *Future and Red Sea as an Example*

With more than 2,000 km of coasts with large area unknown for biodiversity and for a biochemical point of view, Arabian Red Sea could be considered as the future of Marine Natural Products Chemistry and Biochemistry. Furthermore, the location of the King Abdulaziz University at Jeddah, just in the middle of the eastern Red Sea coast is ideal to perform a complete and systematic programme of research on bioactive MaNaPro.

However, several works have been published in this field since the 70's with organisms from Aqaba Gulf, mainly by researchers from Egypt and Israel. From MarinLit Data Base the first publications appeared in 1973 for Sponges (Kashman *et al*., 1973), in 1974 for Cnidaria (Bernstein *et al*., 1974), in 1985 for Molluscs (Mebs, 1985) and in 1988 for Tunicates (Rudi *et al*., 1988).

## Methods and Results

For a given sample the working chain is displayed on Figure 2.

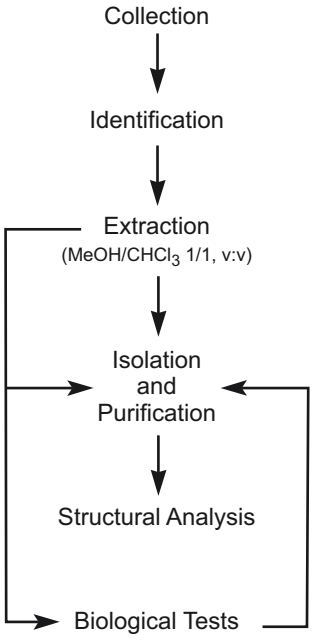



FIG. 2. The working chain.

The selection of the area as well as the collection of the samples is normally arranged and performed by Dr. Al-Sofyani. Sponges identification is performed by Dr. Jean Vacelet at Oceanological Center in Marseille-Endoume, France.

All the extractions of the secondary metabolites are carried out at marine chemistry department at Faculty of Marine Science. The biological evaluations are performed under the auspices of the French National Scientific Research Centre (CNRS) within a network called «Research Group/ Natural Products» (GDR) managed by Dr . T. Sévenet from the Institute for the Chemistry of Natural Substances, Gif/Yvette, France. These biological screenings include: Cytotoxicity on KB cells; Terminal Differentiation Induction on NSCLC-N6 cell line[3]; Antibacterial and antifungal properties (on 2 Gram > 0: *Staphylococcus aureus* and *Enterococcus hirae*; 1 Gram < 0 : *Escherichia coli* and 2 fungi strains : *Candida albicans* and *Saccharomyces cerevisiae*); Immunomodulation on rat splenocyt; Anti HIV-1[4] on infected T4 lymphocytes and performed by Pr. J.C. Chermann, INSERM, Marseille)[5]; Anti HSV[6] on infected Vero cells, and antiparasitic bioassays on Malaria (Plasmodium), Leishmania and Trypanosomia. Table 3 summarizes the initial results.

TABLE 3. Marine natural products from the Red Sea.

| Phyla | Studied species | | Printed publications | | Identified structures | |
|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % |
| **Sponges** | **48** | **51** | **98** | **58** | **166** | **55** |
| Cnidaria | 39 | 41 | 39 | 23 | 106 | 35 |
| Tunicates | 2 | 2 | 17 | 10 | 18 | 6 |
| Molluscs | 5 | 6 | 13 | 9 | 11 | 4 |
| **Total** | **94** | | **167** | | **301** | |

From MarinLit Database, V. 10.7, September 1999.

Due to the assumed marine biodiversity throughout the Arabian Red Sea coasts we consider that it is extremely important for Saudi researchers to study their inumerable marine species in connec-

[3]Non-Small Cell Lung Cancer – Nantes, 7th strain.,
[4]Human Immunodeficiency Virus (AIDS).
[5]French National Research Centre for Medicine and Health. Let us recall that Pr. Chermann was the co-discoverer of HIV-1 and he shared the Prince Faysal Award for Medicine in 1993.
[6]*Herpes simplex* Virus.

tion with international scientific institutions. In this context we present here the first results obtained by the Saudi-French Research programme on Marine Natural Products launched in 1996 between the Faculty of Marine Science (FMS), King Abdulaziz University in Jeddah and ISOMer (Institute for Substances and Organisms from the Sea, University of Nantes. Within only 4 years we have studied more than 100 species for a biological point of view (slightly more than all other countries since 1973), as summarized in Table 4.

TABLE 4. Saudi-French research programme on marine natural products.

| Year | Collected samples | | |
|---|---|---|---|
| | Sponges | Cnidaria | Tunicates |
| 1996 | 23 | 3 | – |
| 1997 | 25 | 3 | 1 |
| 1998 | 7 | 1 | 1 |
| 1999 | 35 | – | 2 |
| **Total** | **90** | **7** | **4** |

Now, we present here our first results concerning antimalaria activity (Table 5), cytotoxicity on KB cells (Table 6) and anti HIV-1 activity (Table 7).

TABLE 5. Antimalaria activity – first results.

| Species* | Extract | $IC_{50}$ (µg/mL) |
|---|---|---|
| *Acanthella carteri* | MeOH | < < 0.4 |
| *Acervochalina* sp. | MeOH / $CHCl_3$ | < 0.42 |
| *Suberea mollis* | $CHCl_3$ | < 0.42 |
| *Siphonochalina* sp. | MeOH / $CHCl_3$ | < 0.63 |
| *Suberea mollis* | MeOH | < 0.80 |
| *Acanthella carteri* | $CHCl_3$ | 0.80 |

*all studied species are Sponges.

It clearly appears from Table 5 that the methanolic extract of the Axinellidae sponge *Acanthella carteri* displays potent antimalaria activity contrary to the chloroform extract. Chemical analysis of this species are in progress to compare its secondary metabolites with those of other *Acanthella* species already known for their antimalaria activities such as *Acanthella klethra* (Angerhofer, 1992).

TABLE 6. Cytotoxicity on KB cells – first results.

| Species* | Extract | % of inhibition at | |
|---|---|---|---|
| | | 10 µg/mL | 1 µg/mL |
| *Suberea mollis* (SP) | MeOH | 100 | 83 |
| *Acanthella carteri* (SP) | MeOH / $CHCl_3$ | 100 | 77 |
| *Acervochalina* sp. | MeOH / $CHCl_3$ | 94 | 92 |
| *Suberea mollis* (SP) | $CHCl_3$ | 94 | 52 |
| *Rumphella* sp. (GO) | MeOH / $CHCl_3$ | 87 | 60 |

*SP : Sponge ; GO : Gorgonian

It clearly appears from Table 6 that the first four extracts are very active. The two first sponges are chemically studied, especially Suberea mollis and its composition along with the activity of the main secondary metabolites will be published soon.

TABLE 7. Anti HIV-1 activity – first results.

| Species* | Extract | % of inhibition at | |
|---|---|---|---|
| | | 0.05 µg/mL | 0.005 µg/mL |
| *Acervochalina* sp** | MeOH / $CHCl_3$ | 100 | 100 |
| *Siphonochalina* sp.*** | MeOH / $CHCl_3$ | 100 | active |

*all studied species are Sponges.
**still active at 0.001 µg/mL without noticeable cytotoxicity at that dose.
***slightly cytotoxic at 0.001 µg/mL.

All these first results have been obtained within four years only and are considered as extremely satisfying for all people involved in this project in Saudi Arabia and in France as well. However we must keep a cold head because all the very promising results came from *in vitro* tests and not yet from *in vivo* experiments. To have an idea of what long it takes to get a new drug from a promising molecule, Figure 3 gives the different steps to get through before a new molecule becomes a new pharmaceutical available on the market.

## Conclusion

In conclusion the Saudi-French research programme on Marine Natural Products is very promising just four years after it was launched. Among a hundred of studied marine invertebrates at least four sponges and one gorgonian were shown to display potent antimalaria, cytotoxicity agains KB cells and anti HIV-1 activities. Furthermore, inter-

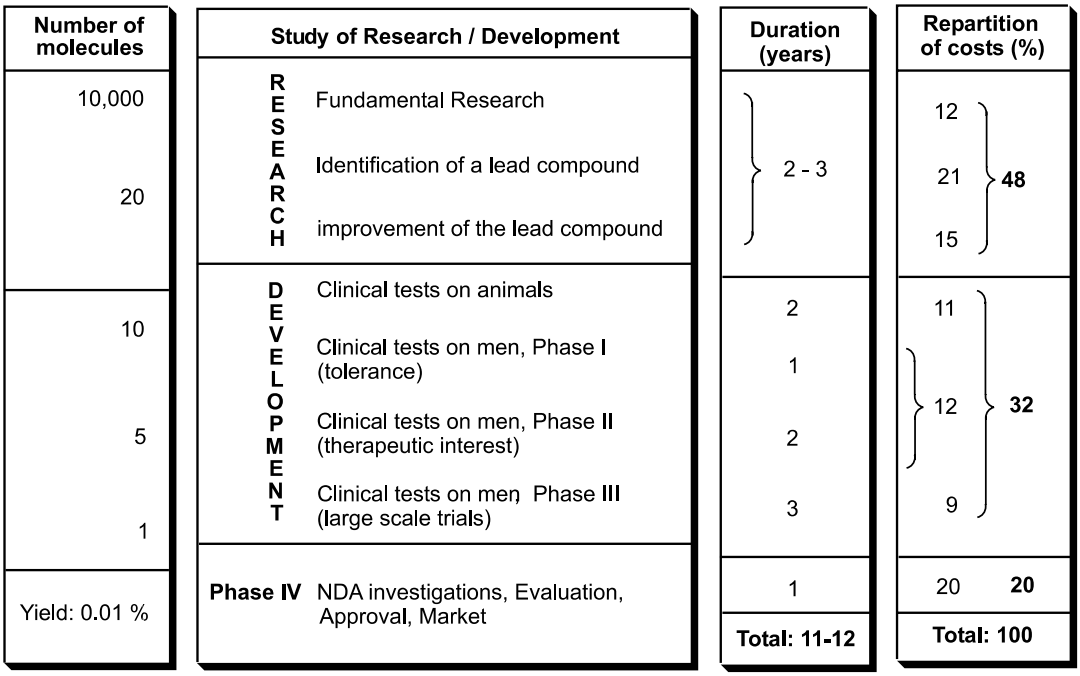



FIG. 3. The steps to get through from a lead compound to a new pharmaceutical.

esting compounds mainly in the lipid field, such as new phospholipid fatty acids have been identified and will be published soon. Despite the lack of grants for young scientist interested in MaNaPro chemistry, these first results are due to intense activity of researchers from both countries as well as a considerable marine biodiversity on the Saudi Red Sea coasts. For the future researches will focus on new marine organisms, mainly sponges, complete identification and mechanisms of action of bioactive compounds from already active fractions and continuation of extensive research of bioactivities against cancer, malaria and viral diseases.

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# الماضي والحاضر والمستقبل للعقاقير البحرية (البحر الأحمر كمثال)

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*و قسم الكيمياء البحرية ، كلية علوم البحار ، جامعة الملك عبد العزيز ، جـــدة - المملكة العربية السعودية*

*المستخلص.* تهدف الدراسة الحالية إلى اعطاء تصور عام عن الأنظمة البيولوجية لمنتجات الكائنات البحرية ونشاطاتها . مع إعطاء نبذة عن نتائج البرنامج العلمي السعودي الفرنسي المشترك في مجال المنتجات الطبيعية البحرية من البحر الأحمر والكشف عن الأنشطة البيولوجية للمركبات الطبيعية . ونظرًا للتعدد النوعي للكائنات البحرية في بيئة البحر الأحمر ، تم التركيز على الاسفنجيات البحرية ، وتشير نتائج الدراسات الأولية الحالية إلى وجود نشاط ضد الملاريا وضد سمومية خلايا KB وضد HIV-1 . ولا يزال البحث مستمرًا في فصل المركبات ومعرفة التركيب الكيميائي للمركبات الطبيعية .