editorial

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Marine natural products as sources of novel scaffolds: achievement and concern

From past to present, drug discovery has been tightly coupled with natural products. Not only were traditional medicines composed of natural agents, but also a large proportion (~50%) of modern drugs have been either directly or indirectly derived from them [1]. Although the pharmaceutical industry turned to combinatorial chemistry and high throughput screening in the 1990s, natural products have yet again attracted the attention of drug hunters in recent years [2], because they have proven to be a more promising source of drugs than combinatorially synthesized chemicals [1,3,4].

The natural product-based drug discovery depends largely on the continuous supply of novel natural agents, especially those with novel scaffolds [5]. Since natural building blocks and biosynthetic strategies are rather limited [6], natural products are highly redundant. Therefore, although the unexplored natural product universe is still ample [6], it is not an easy task to find novel agents from nature. To address this challenge, some new techniques, such as liquid–solid and liquid–liquid isolation techniques and multi-step chromatographic operations, were adopted in this quest [7]. In addition, untapped biological resources, such as marine organisms and extremophiles, were paid more and more attention, because they were considered to be promising sources of novel natural products [8,9].

Novel scaffolds derived from marine natural products

In this analysis, Dictionary of Natural Products (DNP, version 17:2) and Dictionary of Marine Natural Products (DMNP, 2007.6) are used as the starting data sources, which contain 218,168 and 34,556 natural agents, respectively. Organic compounds with explicit structures and appropriate weights (>70 Da and <2000 Da) were extracted from both datasets. As a result, 194,707 agents were obtained from DNP and 31,772 from DMNP. Through comparing the compound list in DNP and DMNP, it was found that 31,618 agents have the same CRC (or C&H) number. Therefore, these compounds were regarded as marine agents contained in DNP and the remaining 163,089 agents are considered as terrestrial agents. Molecular scaffolds, which are defined as the contiguous ring systems plus chains that link them, were generated with Murcko method [10]. The scaffold identification was performed with 'Generate Fragments' component in pipeline pilot student edition (PPSE v6.1.5), during which

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.09.002

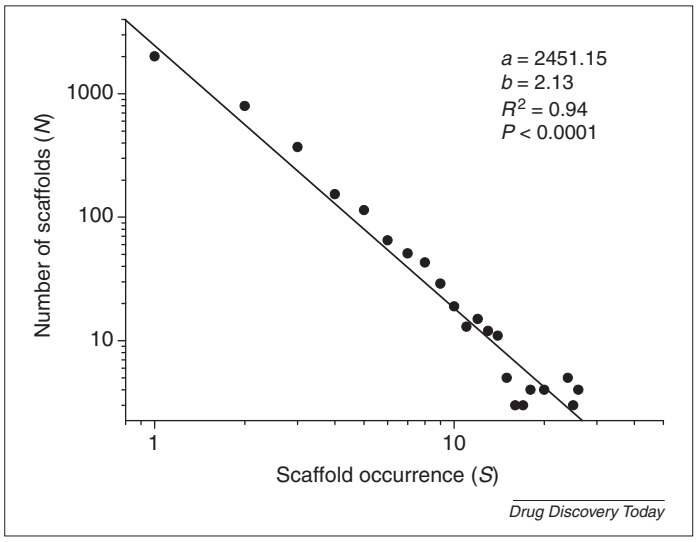

FIGURE 1

Power-law behavior of novel scaffolds in marine agent space. The number of scaffolds (*N*) decays with the increase of their occurrence in agent space (*S*) and follows the equation $N = aS^{-b}$.

the extra-cyclic double bonds and linker double bonds were removed.

The scaffold analysis revealed that the 163,089 terrestrial natural products and 31,772 marine natural agents use 25,289 and 5276 scaffolds, respectively. A structural comparison of the scaffolds revealed that 3747 (71.02%) marine scaffolds were exclusively used by 9391 marine agents. Thus, a large percent of marine scaffolds are novel. So, it can be concluded that marine natural products are promising sources of novel scaffolds, although the novel marine scaffolds cover a relatively small part (29.56%) of the marine natural product universe.

Of the 3747 novel marine scaffolds, a few are prevalent in the universe of marine natural products. A large part (53.51%) of the scaffolds, however, occur only once in the universe. Therefore, the occurrence of novel scaffolds in marine agent space follows a power law (Fig. 1).

Concern over the novel scaffolds from marine natural products

Although scaffold novelty is an attractive property in drug development, other properties are also important. From a recent analysis of unique natural products that led to approved drugs in 1981–2006 [11], we found that the average *C* log *P* of natural product leads was 1.08, and most (91.7%) of the leads had a *C* log *P* of <4.5. Thus, hydrophilicity is a critical determinant of drug-likeness of natural products [11]. The hydrophobic natural agents (with *C* log $P \geq 4.5$) have low potential for drug development.

Through calculating the *C* log *P* values of the terrestrial and marine compounds by Sybyl (Version 7.0), we found that the average *C* log *P* of marine agents with novel scaffolds is 3.846 ± 0.038 and 40.3% of these agents are highly hydrophobic (with *C* log $P \geq 4.5$). The average *C* log *P* of total marine natural products is even higher (4.34 ± 0.02). In comparison, the average *C* log *P* of terrestrial agents is 2.82 ± 0.01 and 26.2% of these agents are highly hydrophobic (with *C* log $P \geq 4.5$). Thus, it seems that although marine natural products are important as a source of novel scaffolds, their drug development potential is restricted by their relatively high hydrophobicity. It is of interest to investigate why marine natural products are more hydrophobic than terrestrial counterparts.

Chemical and evolutionary explanations to the high hydrophobicity of marine agents

As known to all, the hydrophilicity of natural compounds is mainly determined by O and N atom contents. The more the O and N atoms contained in the agents, the more hydrophilic the agents. We observed that the O + N contents of marine natural products (including those with novel scaffolds) were less than that of terrestrial compounds, and the O contents of the marine natural products is especially lower. Hence, the high hydrophobicity of marine natural products can be well explained in terms of their relatively low O contents. Since ocean is more hypoxic than terrestrial environments, the low O contents in marine agents seem to result from the low oxygen availability in oceanic environments. This explanation is preliminarily supported by the fact that the products of oxygen-involved reactions are indeed more hydrophilic than the reactants. Through analyzing the aerobic metabolic network simulated by Raymond and Segrè [12], we identified 175 reactions that use oxygen explicitly, which contain 135 reactants and 153 products. The average *C* log *P* of the products (0.75 ± 0.22) is evidently lower than that of reactants (1.34 ± 0.25) ($P < 0.05$), which strongly suggests that the participation of oxygen in metabolic reactions can significantly enhance the hydrophilicity of metabolites.

Evolutionary studies have revealed that the element (*e.g.* C, N, S) composition of proteins is influenced by the environmental supply of these elements [13,14]. The present analysis indicates that the ecological imprints in organism compositions can be observed not only in macromolecules but also in small-molecule metabolites, which implies that environmental factors may be taken into consideration to help find novel and druggable natural products. To build a bridge between environmental factors and natural product properties, evolutionary biology may make positive contributions. Since evolutionary biology has provided meaningful inspirations for drug discovery [15,16], we argue that evolution, a central concept in biology, should be given enough attention by drug hunters.

Conclusion

To address the challenge in novel scaffold discovery, opening up new sources of natural product supply is a viable tactic. The present analysis reveals that a large part of scaffolds of marine natural products are novel in comparison with those of terrestrial agents. However, the high hydrophobicity of the marine compounds is a big hurdle to their further progress in drug development pipeline. The hydrophobic feature of marine agents can be explained from their low O atom contents, which can be further attributed to the low oxygen abundance in oceanic environments. This evolutionary explanation means that the hydrophobicity of marine compounds is an intrinsic property and thus is difficult to be overcome by technical advances. Therefore, despite the contributions of marine natural products in supplying novel scaffolds, the druggability of these compounds is a concern in the follow-up drug development.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2010.09.002.

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