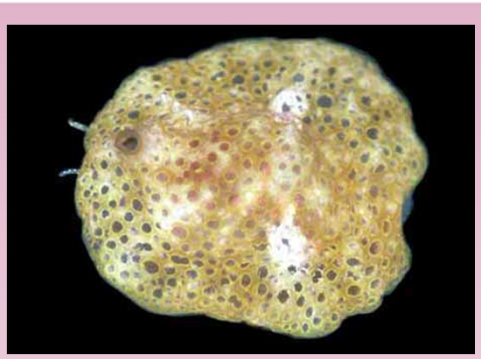
Drug Discovery Program in Marine Natural Product Lamellarin



http://rfbolland.com/okislugs/lame_spp.html

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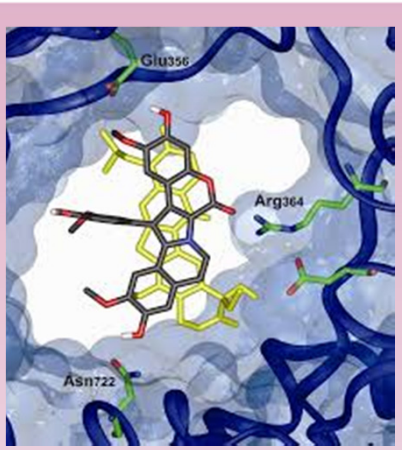
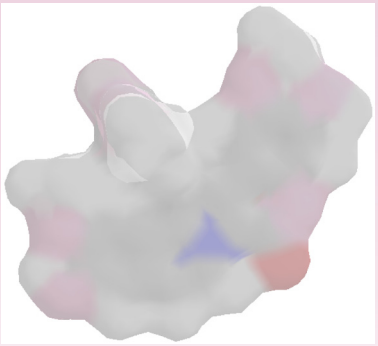
Lamellarins

Lamellarins are a group of marine natural products isolated from mollusks, ascidians, and sponges. Over 50 lamellarins have been isolated from natural sources. Previous studies have shown that lamellarins not only were cytotoxic at nanomolar level but also exhibited multidrug-resistance reversal (MDR) against some cancer cells. Moreover, some lamellarins were found to inhibit HIV-1 integrase, a novel and useful drug target for developing new drug candidates for AIDS patients with drug resistance against conventional drugs. Thus, various research groups worldwide have been involved with different aspects of drug discovery research on lamellarins including the range of other interesting biological activities and the mode(s) of their action.

Because of their low natural abundance, devising some efficient total synthetic routes for lamellarins has been an important alternative to provide lamellarins in sufficient quantity for further studies. These synthetic approaches are pivotal not only for the preparation of naturally-occurring lamellarins but also that of unnatural lamellarin derivatives. In addition, the latter could be designed to streamline or incorporate other structural requirements for the desirable pharmacological/toxicological profiles.



Alvarez, M. *et al. Anticancer Agents Med. Chem.* **2008**, *8*, 746-760.



Medicinal Chemistry of Lamellarins

Based on some organic synthesis concepts, novel and efficient synthetic routes for lamellarins have been successfully developed. Green chemistry principles have been considered and employed during the total synthesis of these compounds and their derivatives to make their preparation more environmentally friendly. This includes (1) the use of microwave as an alternative source of energy to reduce the reaction time and (2) the use of solid-supported reagents to reduce the amount of toxic chemical wastes from the reactions. Following their synthesis, the compounds were evaluated against a panel of cancer cell lines as well as normal cells to establish the structure-activity relationships (SARs).

Prospect & Outlook of Lamellarins

Research articles on lamellarins from our research group have been continuously published in international peer-reviewed journals with high impact factors, attracting attention from other research groups in the same field worldwide.

The outlook of lamellarins still lies in the development of highly efficient synthesis with fewer chemically complicated steps. Moreover, sufficiently large quantity of lamellarin derivatives could facilitate the more detailed studies of selective cytotoxicity against cancer cells over normal cells. In addition, new derivatives will be further designed to improve some of the physicochemical properties of naturally-occurring lamellarins such as low aqueous solubility. While remaining as a challenge, a strategy involving the development of a unified synthetic route for structurally diverse analogs will be implemented with the use of a common intermediate.