新規薬剤を志向した生理活性物質の探索

Abstract

Infectious diseases have been reported as one of the biggest causes of deaths worldwide. As the number of infectious diseases to human beings is increasing over the years, more than 3500 outbreaks are foreseen by 2020. Diseases with long histories like yellow fever, dengue, plague, and influenza still exist and serious attention should be paid to overcome these. In addition, several new infectious agents have appeared such as corona virus, henipa virus, and avian influenza virus. Numerous drug discovery programs against diseases have resulted in clinical medicines, however, there remain diseases without effective drugs or vaccines.

In our collaborative projects for new bioactive molecules, we screened extracts of marine macroorganisms and microorganisms collected around Okinawa against penicillin binding proteins (PBPs) of drug-resistant bacteria, adenovirus (AdV), and dengue virus (DeNV) in parallel to cytotoxicity. During the study, we identified new bioactive compounds: two sesterterpenoids **1-2**, three spongian diterpenoids **4-6**, a cyclic tetrapeptide **17**, a cycloheximide analog **21**, and an alkaloid leucascine (**29**). In this dissertation, we discuss their structures and bioactivity in addition to characterization of known ones.

From the sponge *Luffariella variabilis*, a furanosesterterpenoid **1** showing PBP inhibition with IC_{50} 16.8 μM and a cytotoxic bicyclic sesterterpenoid **2** with IC_{50} 1.0 μM have been found.

Three new and six known spongian diterpenoids **4-6** and **7-12** were isolated from the sponge *Hyatella* aff. *intestinalis*. Although the new compounds did not exhibit antiviral activity against AdV, spongiatriol (**9**) and isospongiatriol (7) showed antiviral activity at IC_{50} 17.0 and 52.0 μM, respectively. Spongiatriol (**9**) also showed cytotoxicity at IC_{50} 3.4 μM.

Since several marine bacterial ferments, coded MA90523, MA90524 and MA40925, showed anti-DeNV activity, they were separated to give cycloheximide (**16**), a new cycloheximide analog **21** and anisomycin (**20**). Although attempts to supply more amount of compound **21** failed, a new cyclic tetrapeptide **17** was obtained instead. Compounds **16** and **20** showed potent anti-DeNV activity at IC_{50} 0.02 and 0.03 μg/mL, respectively.

A cytotoxic pyridine alkaloid leucascine (**29**) was obtained from the sponge *Leucascus protogenes*. The sole absolute configuration of compound **29** was elucidated by comparing experimental data of chiral derivatives with calculated data of model molecules.

New cytotoxins **37-40** and **42** were isolated from the sponge *Dysidea* cf. *arenaria* and the nudibranch *Phyllidiella pustulosa* with IC_{50} 3.1, 1.9, 8.4, 3.1, and 14.2 μM, respectively.