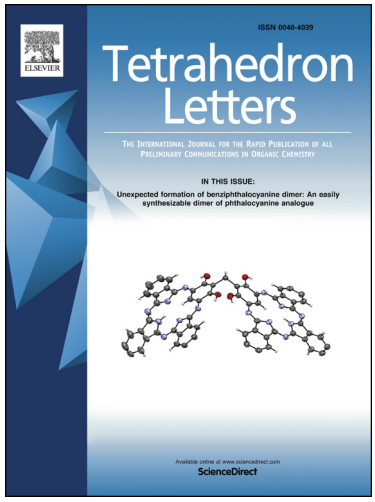

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Eutypellazines N–S, new thiodiketopiperazines from a deep sea sediment derived fungus *Eutypella* sp. with anti-VRE activities

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ABSTRACT

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Chemical investigation of a deep sea sediment derived fungus *Eutypella* sp. MCCC 3A00281 resulted in the isolation of six new thiodiketopiperazine alkaloids, namely eutypellazines N-S (**1**-**6**). Their structures were elucidated on the basis of the extensive NMR and mass spectroscopic analysis, including the ECD data for the determination of absolute configuration. The structures of eutypellazines N-P (**1**-**3**) were characteristic of unique spirocyclic skeletons, while eutypellazines N-O bearing a spirocyclic tetrahydrobenzothiophene motif were found from wide type fungus for the first time. The biogenetic generation of the spirocyclic skeletons was postulated. Compounds **3**-**5** exhibited inhibitory effects against vancomycin-resistant enterococci (VRE), suggesting that they may be the potential inhibitors toward drug resistant pathogenic bacteria after the structural modification.

Naturally occurring thiodiketopiperazine alkaloids (TDKPs) are a class of fungal secondary metabolites with diverse scaffolds,[1-5] of which the spirocyclic TDKPs are rarely found from nature. Spirocyclic TDKPs featuring a sulfur/oxygen- and nitrogen-bound *spiro* ring were firstly recognized as minor cryptic products using differential analysis of 2D NMR spectroscopy from *Aspergillus fumigatus*,[6] and lately were isolated as shunt products (terrespirodiones A-B) from the gene-deletion strains of *Aspergillus terreus*.[7] Spirobrocazines A-C are the additional samples with 2,3-dihydrobenzofuran ring located at C-2 in *spiro* form from *Penicillium brocae*,[8] whereas penicisulfuranols A-F bearing sulfur atoms on both α and β positions of diketopiperazine with a rare 1,2-oxazadecaline core were isolated from the fungus *P. janthinellum*.[9] These typical fungal metabolites were supposed to be derived from a serial specific gene clusters that are responsible for the biosynthesis. Nonribosomal peptide synthetase (NRPS) pathway is involved in the synthesis of DKP scaffold, while *S*-transferase plays a role for the formation of the transannular disulfide bridge or thiomethyl group. An array of interesting biological activities, such as the immunosuppressive properties,[10] anticancer,[11] inhibition of viral RNA polymerase[12] and antifungal activity,[13] encouraged chemists to discover additional derivatives with structural novelty and chemodiversity from nature or through the synthesis process. In our continuing search for new bioactive metabolites from deep sea sediments derived fungi, the EtOAc extract of the fungus *Eutypella* sp. MCCC 3A00281, which was isolated from South Atlantic Ocean deep-sea sediments at a depth of 5610 m (GPS 27.90 W, 6.43 S), exhibited a profile of thiodiketopiperazine-based derivatives as detected by the HPLC in association with ESIMS/MS and NMR data. Chromatographic separation of the EtOAc extract resulted in the isolation of three new spirocyclic thiodiketopiperazines (**1**-**3**) and three new pentacyclic thiodiketopiperazines (**4**-**6**) (Fig. 1), along with six known analogues.

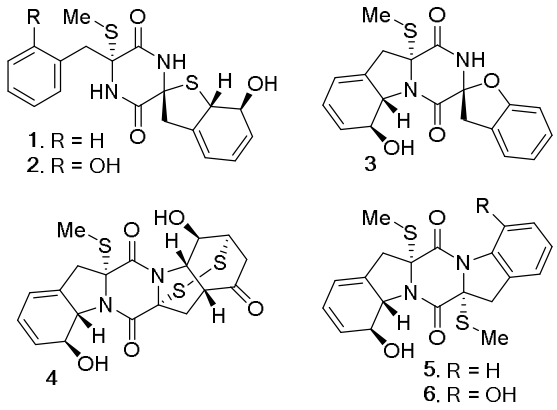

Fig 1. Structures of new thiodiketopiperazines

The molecular formula ($C_{19}H_{20}N_2O_3S_2$) of eutypellazine N (**1**) was determined on the basis of the HRESIMS ion peak at *m/z* 387.0835 [M - H]$^-$ and NMR data. The ^{1}H and ^{13}C NMR data of **1** featured a thiodiketopiperazine-type alkaloid, and were comparable to those of the coexisted phomazine B.[14] The 2D NMR data established the partial structure of a diketopiperazine nucleus, in which phenylalanine unit was recognized by the aromatic spin system in the COSY spectrum assigning to a mono-substituted phenyl ring, and the HMBC correlations of the methylene protons H_2-3 (δ_H 2.98, 3.51) to a quaternary carbon