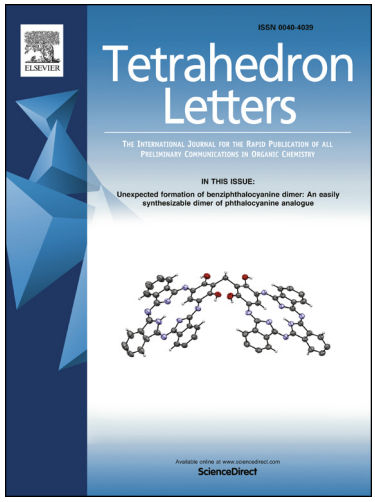

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Eutypellazines N–S, new thiodiketopiperazines from a deep sea sediment derived fungus *Eutypella* sp. with anti-VRE activities

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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.

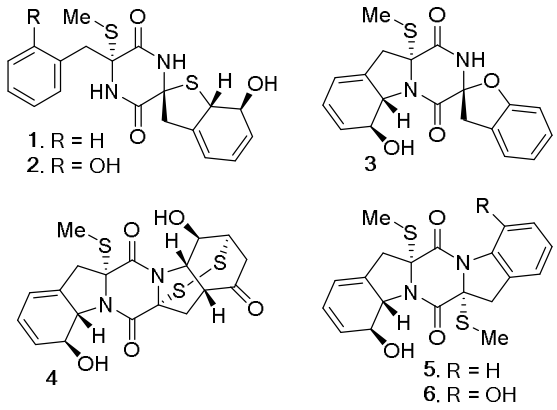


Fig 1. Structures of new thiodiketopiperazines

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

Table 1. ^{1}H NMR data of **1**-**6** in DMSO-d_6

position	1	2	3	4	5	6
3	2.98, d (13.2)	3.18, d (14.6)	2.96, d (15.6)	3.03, m	3.00, d (16.0)	3.04, d (16.0)
	3.51, d (13.2)	3.43, d (14.6)	3.09, d (15.6)		3.19, d (16.0)	3.18, d (16.0)
5	7.22, d (8.0)	7.05, d (7.5)	5.98, d (4.0)	5.97, d (4.0)	5.99, d (4.0)	6.01, d (4.0)
6	7.26, t (8.0)	6.72, t (7.5)	5.89, dd (4.0,9.8)	5.90, dd (4.0,9.8)	5.91, dd (4.0,9.8)	5.93, dd (4.0, 9.8)
7	7.26 t (8.0)	7.06, t (7.5)	5.62, d (9.8)	5.62, d (9.8)	5.65, d (9.8)	5.81, d (9.8)
8	7.26, t (8.0)	6.81, d (7.5)	4.66, dd (1.5,13.8)	4.55, brd (13.6)	5.01, brd (13.6)	4.99, brd (13.6)
9	7.22, d (8.0)		4.81, d (13.8)	4.67, d (13.6)	4.95, d (13.6)	4.95, d (13.6)
3’	2.54, d (17.1)	2.72, d (17.2)	3.31, d (16.7)	2.55, d (12.8)	3.56, d (17.0)	3.49, d (16.8)
	2.90, d (17.1)	3.16, d (17.2)	3.97, d (16.7)	2.83, dd (8.9,12.8)	3.69, d (17.0)	3.66, d (16.8)
4’				3.14, dd (7.8,8.9)		
5’	5.64, d (4.0)	5.71, d (4.0)	7.27, d (7.4)		7.35, d (7.8)	6.86, d (7.8)
6’	5.81, dd (4.0, 10.0)	5.83, dd (4.0, 9.9)	6.93, t (7.4)	2.48, d (18.9)	7.23, t (7.8)	7.19, t (7.8)
				3.10, dd (6.2,18.9)		
7’	5.64, d (10.0)	5.65, d (9.9)	7.16, t (7.4)	3.76, d (6.2)	7.34, t (7.8)	6.94, d (7.8)
8’	4.41, dd (5.9, 15.2)	4.44, dd (5.8, 15.2)	6.82, d (7.4)	4.51, d (13.0)	8.05, d (7.8)	
9’	4.20, d (15.2)	4.19, d (15.2)		4.50, d (13.0)		
SMe-2	2.27, s	2.25, s	2.24, s	2.16, s	2.36, s	2.34, s
SMe-2’					2.31, s	2.28, s
OH-8		5.37, d (5.8)	5.32, d (1.5)	5.48, br	5.48, br	5.34, br
OH-8’	5.35, d (5.9)	9.80, br		6.12, br		10.02, s
NH-1	9.06, s	9.16, s				
NH-1’	9.00, s	8.42, s	9.77, s			

C-2 (δ_C 66.6), a carbonyl carbon C-1 (δ_C 164.9), and the aromatic carbons. A thiomethyl group was deduced to position at C-2 according to the HMBC correlation between SMe (δ_H 2.27, s) and C-2. In regard to the remaining partial structure, a tetrahydrobenzothiophene motif (rings C and D) was established by the spin system which connected the partial backbone from the olefinic proton H-5’ (δ_H 5.64, d, J = 4.0 Hz) to H-9’ (δ_H 4.20, d, J = 15.2 Hz), in addition to the HMBC correlations from H_2-3’ (δ_H 2.54, 2.91) to C-4’ (δ_C 141.6), C-5’ (δ_C 116.7), and C-9’ (δ_C 58.1). The COSY relationship between H-8’ (δ_H 4.41, dd, J = 15.2, 5.9 Hz) and a D_2O exchangeable proton at δ_H 5.35 (d, J = 5.9 Hz) located an OH group at C-8’ (δ_C 74.0). Additional HMBC correlation between H-9’ and C-2’ (δ_C 70.1), in association with the correlations from H_2-3’ to C-1’ (δ_C 168.3) and C-2’ and from NH-1 (δ_H 9.06) to C-2’ and C-3’, clarified the tetrahydrobenzothiophene motif to be positioned at C-2’ in a spirocyclic form. The large coupling constant between H-8’ and H-9’ (15.3 Hz) agreed both protons in a *trans* orientation, while this was supported by the NOE interaction between OH-8’ and H-9’. The NOE correlations between Ha-3’ (δ_H 2.91) and H-3 (δ_H 2.98) conducted the same face of the methylene groups CH_2-3 and CH_2-3’, thus assigned the *spiro* orientation of the hydrothiophene ring (Fig. 2). Based on the ECD rules for thiodiketopiperazine-type alkaloids,[15,16] the sign of Cotton effect at 270 nm for the $n_S \rightarrow \pi_{C=O}$ transition plays a dominant role to assign the configuration of C-2/C-2’ chiral centers. The negative Cotton effect at 270 nm in **1** reflected C-2 chiral center (Fig. 3), indicating 2*R* configuration.[15] In association with the NOE data, the absolute configurations of remaining stereogenic centers were assumed to be 2’*R*, 8*S*, and 9*S*.

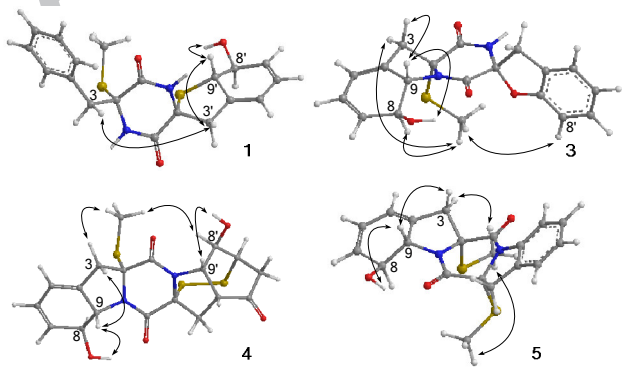


Fig 2. Key NOE correlations of **1** and **3**-**5**

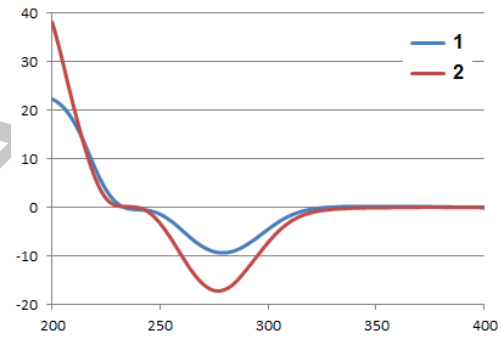


Fig 3. ECD spectra of **1**-**2**

Table 2 ^{13}C NMR data of **1**–**6** in DMSO-d_6

no	1	2	3	4	5	6
1	164.9	165.9	166.8	162.2	162.5	164.4
2	66.6	66.4	73.1	74.2	73.4	73.2
3	43.2	36.8	38.9	38.5	38.9	38.9
4	135.7	122.4	134.1	133.8	140.0	131.0
5	131.0	131.3	119.3	120.0	120.4	120.6
6	128.4	119.5	123.9	123.9	122.9	122.9
7	127.3	128.5	131.0	130.6	130.6	130.7
8	128.4	115.8	74.0	74.0	74.5	74.4
9	131.0	155.9	69.1	69.1	68.9	68.9
1’	168.3	168.0	165.9	167.5	167.6	167.0
2’	70.0	70.2	93.3	73.6	72.3	73.1
3’	45.8	45.8	39.3	47.0	39.3	39.4
4’	141.6	141.4	125.8	43.3	128.4	130.9
5’	116.6	116.7	124.9	208.3	125.2	116.5
6’	124.5	124.5	121.7	38.6	126.0	129.2
7’	132.9	132.9	128.6	45.7	128.2	118.4
8’	74.0	74.1	109.5	66.8	117.7	146.5
9’	58.1	57.9	157.2	62.4	140.0	126.6
SMe-2	13.7	13.7	14.4	14.3	14.8	15.0
SMe-2’					14.3	14.4

Eutypellazine O (**2**) has a molecular formula of $C_{19}H_{20}N_2O_4S_2$ according to the HRESIMS (*m/z* 403.0784 [M – H]$^-$, calcd for 403.0786) and NMR data, requiring an oxygen atom more than that of **1**. The NMR data of **2** were comparable to those of **1** (Tables 1 and 2), indicating the structural similarity. The distinction was attributed to the aromatic spin system, of which an ABC spin system in the COSY spectrum of **2** to replace an ABCD couplings was observed. The deshielded C-9 (δ_C 155.9) and shielded C-4 (δ_C 122.4) and C-8 (δ_C 115.8) in addition to the presence of a phenol proton at δ_H 9.70 (br) allowed the assignment of a OH group at C-9. The similar NOE interactions conducted both **1** and **2** sharing the same relative configuration. In addition, the negative Cotton effect at 270 nm (Fig. 3) and the

negative specific rotation resulted in the absolute configuration of **2** to be the same as that of **1**.

The HRESIMS data of eutypellazine P (**3**) exhibited a molecular ion peak at *m/z* 371.1063 $[M + H]^+$, which was in accordance with a molecular formula of $C_{19}H_{18}N_2O_4S$. Analyses of the 2D NMR data revealed the planer structure of **3** to be the same as that of spirobrocazine A.[8] In regard to ring A, the large coupling constant ($J_{H\text{-}8/H\text{-}9}$ = 13.7 Hz) agreed a *trans*-axial relationship of H-8 and H-9. The NOESY correlations between SMe-2 (δ_H 2.24) and H-3a (δ_H 2.96) and from H-9 (δ_H 4.81) to OH-8 (δ_H 5.32) and H-3b (δ_H 3.09) (Fig. 2) indicated the relative configurations in rings A and B to be the same those of spirobrocazine A. However, the observation of the NOE interaction between SMe-2 and H-8' (δ_H 6.82) instead of the interaction between SMe-2 and H_2-3' as observed in the NOESY of spirobrocazine A,[8] assumed **3** to be a C-2' isomer of spirobrocazine A. The positive Cotton effect (CE) at 270 nm and the negative CE at 230 nm were attributed to the exciton couplets of the chromophore interaction between the aromatic ring E and the *cisoid* diene in ring A. The signs of the Cotton effects agreed a clockwise turn of both chromophores based on the exciton chirality method (Fig. 4).[17] Thus, the stereogenic center C-2' was determined to be 2'*R* configuration. In addition, the ECD data of **3** and its enantiomer were calculated at the B31YP/6-311++G(2d, 2p) level in the gas phase using the B3LYP/6-31G(d) optimized geometries after conformational searches via the MMFF94S force field by the TDDFT-ECD method.[18,19] Comparison of the experimental ECD data of **3** with the calculated data for the model molecules (Fig. 4) in association with the NOE data indicated **3** to be in agreement with the 2*R*, 8*S* and 9*S* configurations.

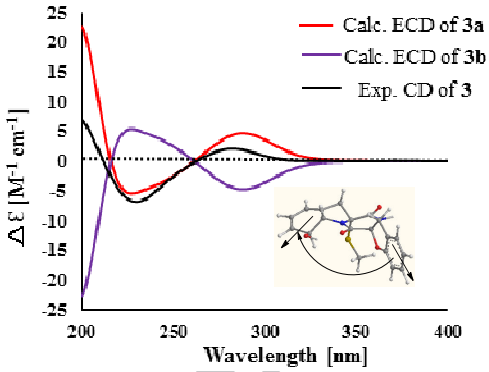


Fig 4. Comparison of the calculated ECD spectra of **3a** (2R, 8S, 9S, 2'R) and **3b** (2S, 8R, 9R, 2'S) with the experimental CD data of **3**

Eutypellazine Q (**4**) has a molecular formula of $C_{19}H_{20}N_2O_5S_3$ as determined by the HRESIMS and NMR data. Analyses of the 2D NMR data established the planer structure of **4** to be a pentacyclic thiodiketopiperazine, structurally related to epicoccin I.[3] The NMR data of rings A-C in **4** were almost identical to those of the known counterpart, indicating both compounds sharing the same partial structure. The 2D NMR correlation established a perhydroindole unit for rings D and E, in which the substitution of a ketone at C-5' (δ_C 208.3) and a hydroxy group at C-8' (δ_C 66.8) was clarified by the HMBC correlation from H_2-6'and H_2-7' to C-5' and C-8. Apart from a thiomethyl group at C-2, the remaining two sulfur atoms were assumed to form a disulfide bridge on the basis of the molecular unsaturation. The presence of a quaternary carbon at C-2' (δ_C 73.6) and a methine at C-7' (δ_C 45.7), in association with the sites of molecular unsaturation, conducted a transannular disulfide bridge across C-2' and C-7'.[6] A *trans* orientation of H-8 and H-9 was deduced by the large $J_{H\text{-}8/H\text{-}9}$ value (13.0 Hz). As shown in Fig. 2, the NOE interactions established the relative configuration of **4**. The positive Cotton effects at around 270 nm was attributed to the $n_S \rightarrow \pi_{C=O}$ transition induced by the interaction of disulfide with the diketopiperazine, reflecting the 2'*R* configuration.

The HRESIMS data provided the molecular formula of eutypellazine R (**5**) to be $C_{20}H_{20}N_2O_3S_2$, requiring 12 degrees of unsaturation. The ^1H and ^{13}C NMR data were characteristic of a thiodiketopiperazine, structurally related to the coexisted phomazine B. Analyses of the 2D NMR data revealed that rings A-C of **5** was identical to that of phomazine B, whereas rings D and E were determined to be an indoline. This assignment was supported by the presence of six aromatic carbons with an ABCD spin system, in addition to the HMBC correlations from H-5' (δ_H 7.35, d, *J* = 7.8 Hz) to C-3', C-4' and C-9' and from H-8' (δ_H 8.05, d, *J* = 7.8 Hz) to C-4' and C-9'. The negative Cotton effect at 270 nm as induced by the $n_S \rightarrow \pi_{C=O}$ transition was in agreement with 2*R* and 2'*R* configurations,[15] while this was supported by the negative CE band at 230 nm for the $n_4 \rightarrow \sigma^*$ transition of the thiomethyl group. The positive CE at 250 nm was attributed to a right-hand skewed C=C-O based on the "allyic oxygen rule",[16] indicating 8*S* configuration. Thus, the remaining chiral centers were determined in association with the NOE interaction.

The structure of eutypellazine D (**6**) was determined to be a 8'-hydroxylated analogue of **5**, based on the close similarity of the NMR data with the exception of an ABC spin system of **6** to replace an ABCD spin system of **5** for the aromatic protons in ring E (Tables 1 and 2). A phenol proton at δ_H 10.02 (s, OH-8') and the HMBC correlations from OH to C-7' (δ_C 118.4), C-8' (δ_C 146.5), and C-9' (δ_C 126.2) confirmed the location of the hydroxy substitution. The similar ECD (Fig. 5) and specific rotation data revealed the absolute configurations of **6** to be the same as that of **5**.

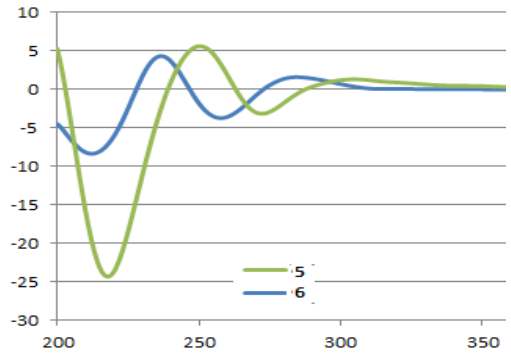


Fig 5. ECD spectra of **5** and **6**

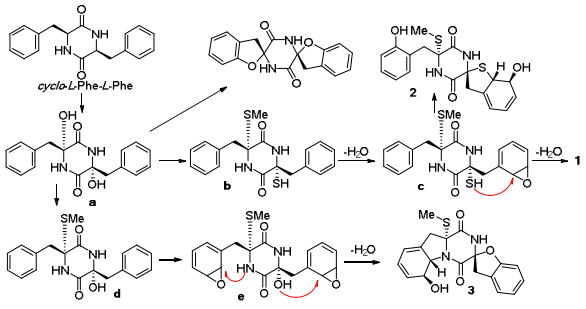
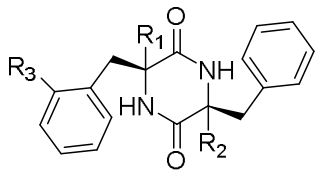


Fig 6. Biogenetic postulation of **1**-**3**

Biogenetically, ketopiperazine of cyclo-*L*-Phe-*L*-Phe was considered as the precursor to derive the structural diversity. The

dual hydroxylation was achieved by the enzymes such as AtaC to afford the intermediate **a**, whose mono-methoxylated product was isolated from the same strain. *S*-transferase mediated the introduction of thiomethyl group or SH group to C-2 or C-2' has been proved in the literature.[6,7] In the present work, the isolation of the intermediates (**7**-**12**) partially provided the evidence for the biogenetic postulation. Selective epoxidation at aromatic ring was probably undertaken by the epoxidase such as AtaF, while nucleophilic attack occurring in the intermediates of **b-e** generated **1** and **3**, respectively, Compound **2** was suggested to be derived from **1** by hydroxylation in the aromatic ring (Fig. 6).



7. $R_1 = R_2 = SMe$, $R_3 = OH$
8. $R_1 = SMe$, $R_2 = OH$, $R_3 = H$
9. $R_1 = OMe$, $R_2 = OH$, $R_3 = H$
10. $R_1 = R_2 = SMe$, $R_3 = H$
11. $R_1 = R_2 = R_3 = H$
12. $R_1 = R_2 = H$, $R_3 = OH$

Compounds **1**-**6** were tested against bacteria of *Staphylococcus aureus* ATCC 25923 and vancomycin-resistant enterococci (VRE), and **3**-**5** showed moderate inhibitory effects (Table 3), while additional tests of the compounds against diverse pathogenic bacteria are under progress.

Table 3. MIC data of compounds **1**-**6** for anti-VRE activities

	MIC (μM)	
	Staphylococcus aureus ATCC 25923	VRE
1	64	64
2	64	64
3	32	32
4	16	16
5	32	32
6	16	32
PG	0.35	
levofloxacin		1

VRE: vancomycin-resistant enterococci, PG (penicillin G) and levofloxacin were used as the positive controls.

In conclusion, present work reported three new thiodiketopiperazines with unique spirocyclic skeleton, which enriched the members of naturally occurring spirocyclic thiodiketopiperazines. The tetrahydrobenzothiophene motif based spirocyclic analogues, eutypellazines N-O (**1**-**2**), were found from wide type fungus for the first time. These spirocyclic compounds were postulated to be derived from *cyclo*-*L*-Phe-*L*-Phe through oxidation, sulfur linkage, and nucleophilic attack. The inhibitory effects of **3**-**5** against VRE suggested them to be potential leads as the anti-drug resistant pathogenic bacteria.

Acknowledgments

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Supplementary Material

NMR spectroscopic data for the new compounds (**1**–**6**), IR, and ESIMS/MS data. This material is available free of charge via the Internet at http://www.sciencedirect.com.

Graphical **Abstra**

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

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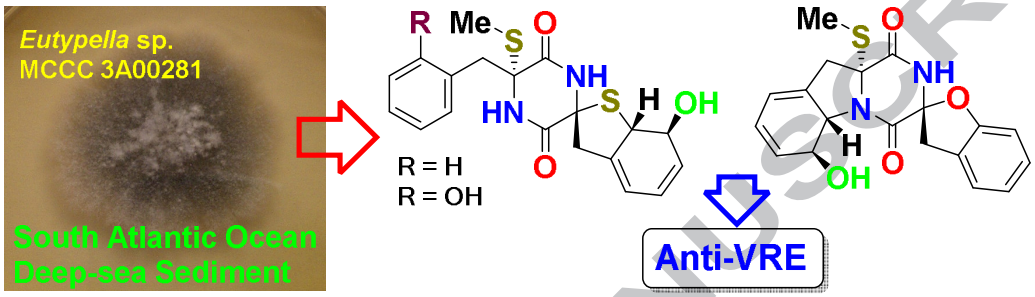

Highlight

- Eutypellazines N-S are discovered from *Eutypella* sp. as new alkaloids.
- Eutypellazines N-P with spirocyclic skeletons are rarely found from nature.
- Eutypellazines P-R inhibited vancomycin-resistant enterococci.