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P2047

Exploring the Three-Dimensional Structures and Activity Relationships of *N*-Methyl and *N*-Desmethyl Analogues of Cyclodepsipeptide Destruxin E

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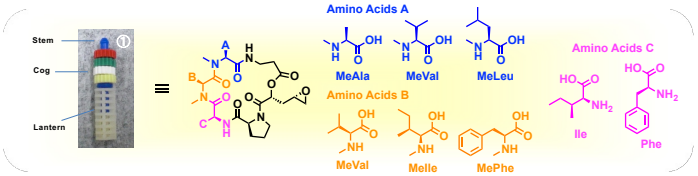
I. Introduction

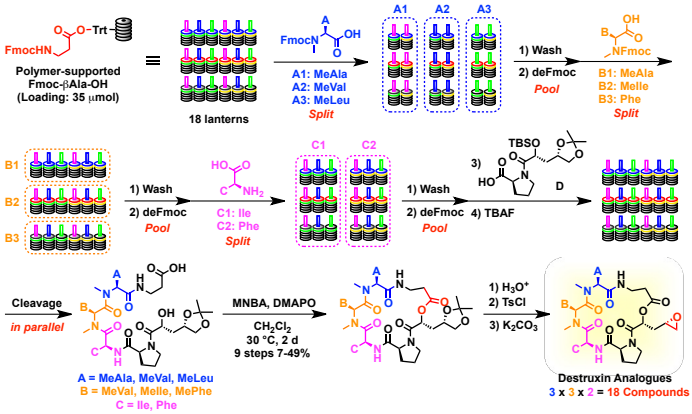
Destruxin E Inhibits bone resorption by inducing morphological changes without affecting the viability of osteoclasts, indicating destruxin E would be a novel anti-resorptive agent for osteoporosis therapy.

Destruxin E was isolated from *Metarhidium anisopliae* in 1989 based on insecticidal activity along with other derivatives [Phytochemistry, **1981**, *20*, 715–723.]. It inhibits V-ATPase at the IC_{50} value of 0.40 μM, which is the most potent among destruxin derivatives [*Chem. Biodivers.* **2005**, *2*, 123–130]. According to the Nakagawa group, destruxins have shown to inhibit osteoclast bone resorption activity. Destruxin E reversibly induce morphological changes in osteoclast-like multinucleated cells (OCLs) at concentrations lower than those exhibiting the V-ATPase inhibitory activity [*Bone*, **2003**, 33, 443]. We investigated the total synthesis of destruxin E and its analogs, as well as their biological activity, to elucidate structure-activity relationships (SAR) for morphological changes in OCLs.

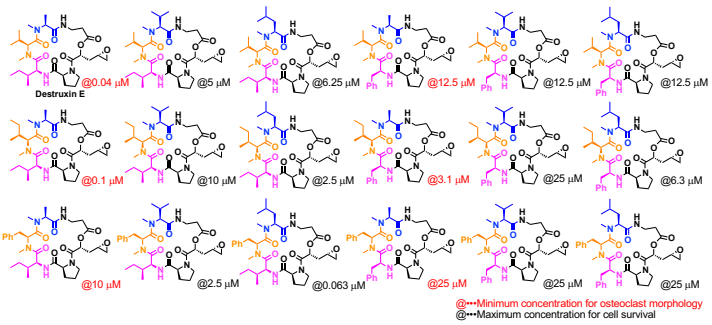
II. Results and Discussion

Combinatorial Synthesis of Side Chain-Modified Destruxin E Analogues



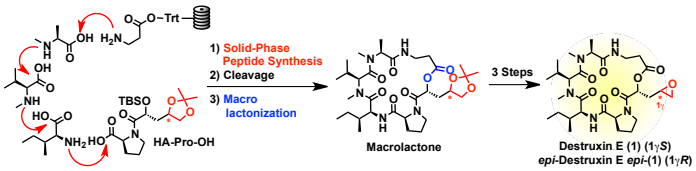


Biological Evaluation of Side Chain-Modified Destruxin E Analogues



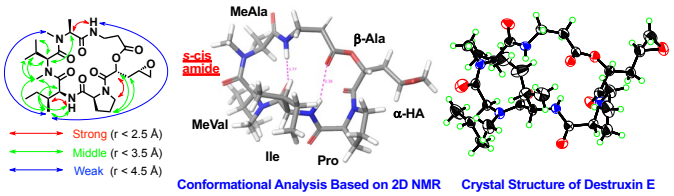
Yoshida, M.; Ishida, Y.; Adachi, K.; Murase, H.; Nakagawa,H.; Doi, T. *Chem. Eur. J.* 2015, *21*, 18417–18430.

Solid-Phase Total Synthesis of Destruxin E



Our laboratory has achieved the first total synthesis of destruxin E and determined the absolute stereochemistry. They have also shown that the stereochemistry of the side chain epoxide is important for V-ATPase inhibitory activity [*Org. Lett.* **2010**, 12, 3792].

Conformational Analysis of Destruxin E

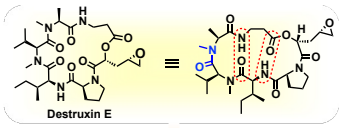


- Calculating program : Macromodel 9.9
- Conformational search method : Monte Carlo based-torsional sampling
- Constraints : 21 distances based on NOESY analysis in $CDCl_3$
- Force field (OPLS2005), Solvent for calculation ($CHCl_3$), Iteration : 50000

- Conditions: from hexane-benzene

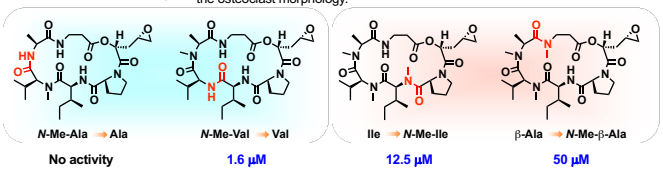
The conformational analysis by using the NMR experiments can be utilized to expect the tertiary structure of destruxin analogues.

Design and Synthesis of *N*-Methylated or Desmethylated Destruxin E Analogues



The *cis*-amide between *N*-Me-Ala and *N*-Me-Val and two intramolecular hydrogen bonds could play crucial roles for maintaining the conformation to induce osteoclast morphology.

Synthesis and biological evaluation of the following analogues would lead us to understand the role of *cis*-amide and intramolecular hydrogen bond in the osteoclast morphology.

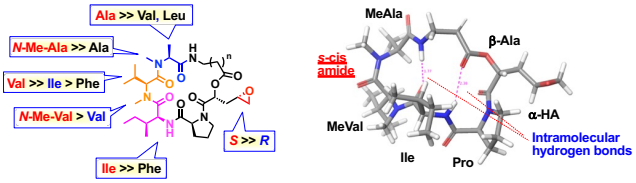


The *cis*-amide between *N*-Me-Ala and *N*-Me-Val is required to induce osteoclast morphology.

Intramolecular hydrogen bonds are important for potent biological activity.

Sato, H.; Murase, H.; Ishida, Y.; Sugiyama, H.; Uekusa, H.; Nakagawa, H.; Yoshida, M.; Doi, T. *Bioorg. Med. Chem.* 2024, *108*, 117777.

III. Summary



☆ (*S*)-Epoxide, 19-membered ring, and N-MeAla are important.
☆ *S-cis* amide bond and two intramolecular hydrogen bonds are important.

Yoshida, M.; Nakagawa, H.; Doi, T. *J. Antibiot.* 2022, *75*, 420—431.

IV. Acknowledgement

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