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Biological Evaluation of New Largazole Analogues: Alteration of Macrocyclic Scaffold with Click Chemistry

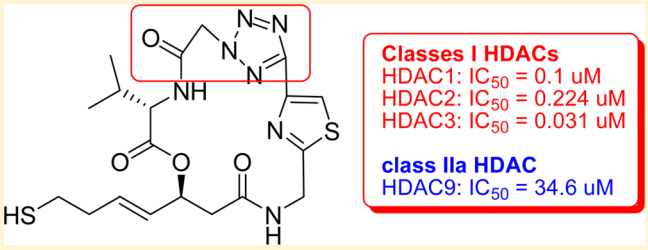
Xianlin Li,[†] Zhenchao Tu,[†] Hua Li,[†] Chunping Liu,[†] Zheng Li,[‡] Qiao Sun,[†] Yiwu Yao,[†] Jinsong Liu,[†] and Sheng Jiang*[,†]

[†]Laboratory of Regenerative Biology, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, 510530, China

[‡]The Methodist Hospital Research Institute, Houston, Texas, 77030, United States

Supporting Information

ABSTRACT: We report the design, synthesis, and biological evaluation of a new series of largazole analogues in which a 4-methylthiazoline moiety was replaced with a triazole and tetrazole ring, respectively. Compound **7** bearing a tetrazole ring was identified to show much better selectivity for HDAC1 over HDAC9 than largazole (10-fold). This work could serve as a foundation for further exploration of selective HDAC inhibitors using a largazole molecular scaffold.



KEYWORDS: *HDAC inhibitor, peptides, macrocycles, largazole, click chemistry*

Histone deacetylases (HDACs) are a family of enzymes that catalyze the deacetylation of lysine side chains in chromatin, and thereby, these enzymes are involved in a wide range of biological processes such as cell differentiation, proliferation, angiogenesis, and apoptosis.[1−4] Up to now, 18 members of the human HDAC family have been identified, which are divided into four distinct classes on the basis of their size, number of catalytic active sites, subcellular localization, and sequence homology to yeast counterparts.[5−7] Class I HDACs (1−3 and 8), class IIa HDACs (4, 5, 7, and 9), class IIb HDACs (6 and 10), and class IV HDACs (11) are Zn^{2+}-dependent proteases, while class III HDACs (sirtuins 1−7) are NAD^{+}-dependent Sir2-like deacetylases.[7] Among them, class I HDAC isoforms have been intensively studied due to their important role in tumorigenesis and development. It is highly expressed in various cancers, including gastric cancer, pancreatic cancer, colorectal cancer, prostate cancer, and hepatocellular carcinoma[8−11] but not resting endothelial cells and normal organs. Therefore, selective targeting class I HDACs by directly inhibiting its function has recently become a major area of research in cancer chemotherapy.[12−16]

Thus far, over 12 HDACis are currently in clinical trials against different cancers,[17,18] and two of them, SAHA (Figure 1)[19] and romidepsin (FK228) (Figure 1),[20] have been approved by the U.S. Food and Drug Administration (FDA) for cutaneous T-cell lymphoma (CTCL). In most cases, the reported HDAC inhibitors consist of three distinct structural motifs: the Zn(II) binding moiety, a spacer moiety, and a recognition cap group. It should be noted that the cap region is a key factor in current HDACi design because topological differences are observed in the corresponding "cap" regions of HDAC isozymes.

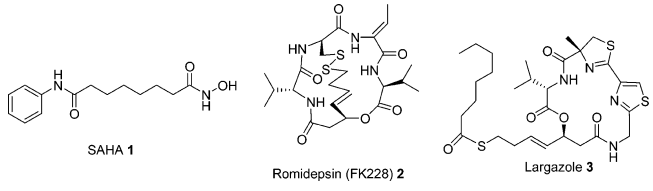


Figure 1. Structures of SAHA, romidepsin (FK228), and largazole.

Largazole **3** is a natural macrocyclic depsipeptide reported by Luesch and co-workers in 2008, which show promising HDAC1 inhibitory activity and selectivity.[21] These excellent properties of largazole have attracted significant attention and make it a becoming lead molecule for further structural optimization in pursuit of molecules of higher potency or selectivity. Recently, several research groups have completed total synthesis and structure−activity relationship (SAR) studies of largazole.[22−37] Among them, only two groups focused mostly on the alteration or elimination of the methyl group of 4-methylthiazoline moiety.[35,36] On the basis of their results, we envisioned that the 4-methylthiazoline moiety is not essential for the potency of largazole, and modification of it is tolerable. By analyzing molecular modeling of the largazole complex with HDAC1 structure, we revealed that the 4-methylthiazoline residue has hydrophobic interactions with the side chains of Phe 150 of the HDAC1, and these interactions may be crucial for HDAC class/isoform selectivity of largazole (Figure 2). Click chemistry has been widely applied in organic

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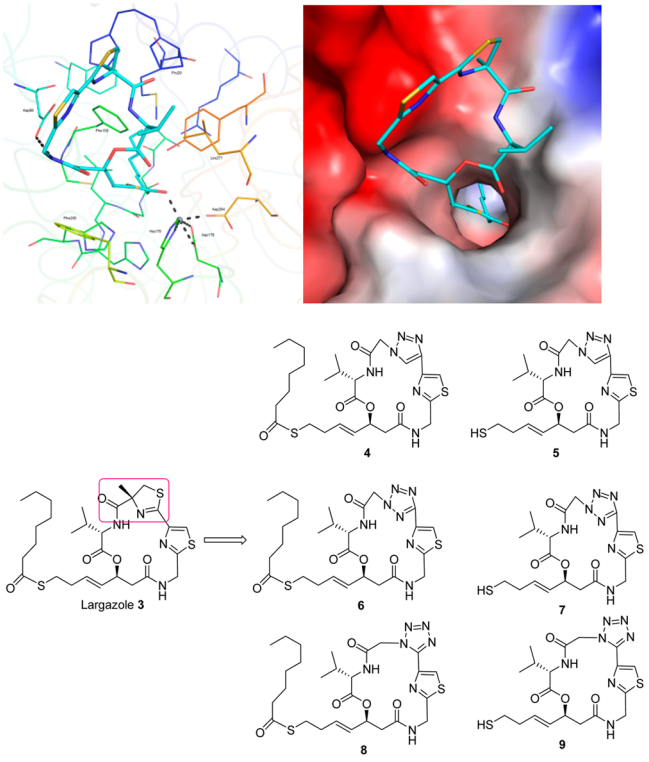
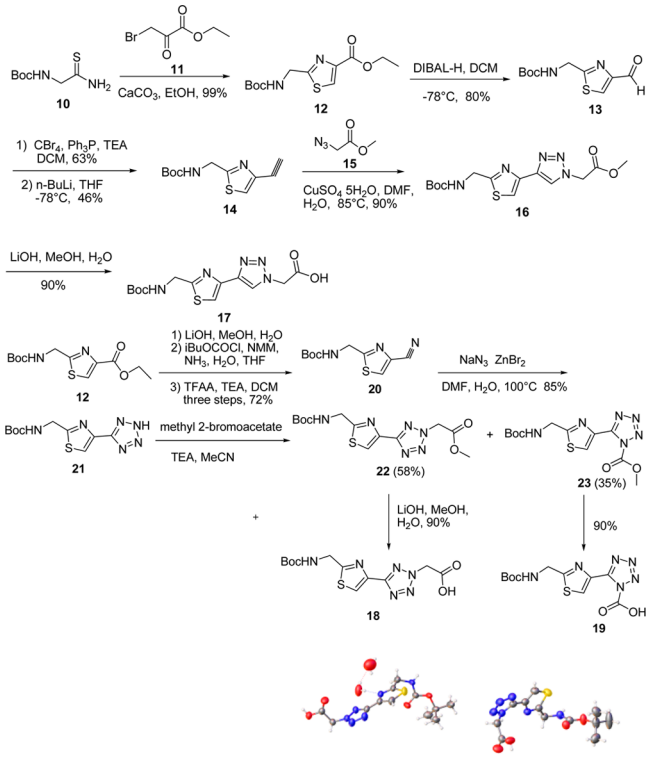


Figure 2. Plausible binding mode of largazole to HDAC1 and designed analogues.

synthesis and drug discovery since Sharpless developed it for synthesis of triazole moiety in 2001.[38−44] We envisioned that replacing the 4-methylthiazoline moiety of largazole with a more hydrophobic ring, such as a triazole or tetrazole group, would improve $\pi-\pi$ stacking interactions and could increase selectivity for HDAC1 over other isoforms. Herein, we report our efforts to modify the structural scaffold of largazole through click chemistry with the goal of further defining and expanding structure−activity relationships within the family of macrocyclic HDACis.

The synthesis of the key intermediates, **17**−**19**, started with a previously characterized thiazole-4-ester **12**, which was obtained from commercially available thioamide **10** using the modified Hantzsch procedure (Scheme 1).[32−37] Reduction of **12** with DIBAL-H afforded aldehyde **13** in 80% yield followed by Corey−Fuchs reaction for the synthesis of the terminal alkyne **14**. The terminal alkyne **14** reacted smoothly with azide **15** at room temperature in the presence of catalytic amount of copper sulfate and sodium ascorbate in DMF and water, giving the triazole **16** in 90% yield. The ester group of **16** was saponified with LiOH, which afforded an important intermediate **17** in high yield. Subsequent transformation of thiazole-4-ester **12** into nitrile **20** involved a three-step sequence: (i) hydrolysis of ester **12**, (ii) formation of amide from acid and ammonia, and (iii) dehydration using trifluoroacetic anhydride and base (72% yield). The click reaction of nitrile **20** with sodium azide furnished the tetrazole intermediate **21** in 100% yield in the presence of zinc bromide. Subsequent reaction of the tetrazole **21** with ethyl bromoacetate and triethyl amine generated two alkylated products. After chromatographic separation of the two alkylated products, we got the major one bearing the ethylacetate at the N-2 position of the tetrazole in 58% yield and the minor one bearing the

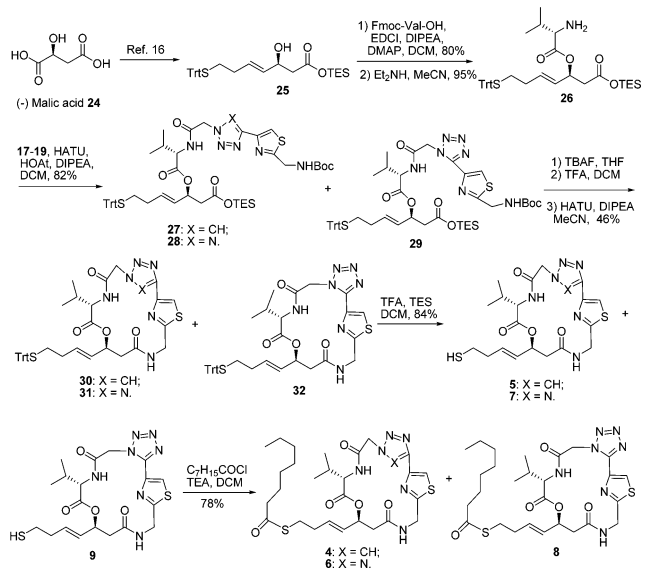
Scheme 1. Synthesis of the Key Fragments 17−19



ethylacetate at the N-1 position of the tetrazole isomer in 35% yield. Then, the two alkylated products were subjected to basic ester hydrolysis to generate the desired tetrazole acetic acids **18** and **19** in 90% yield, respectively, the structures of which were confirmed by X-ray crystallographic analysis.[45]

The synthesis of the designed analogues **4**−**9** was prepared as outlined in Scheme 2. Our synthesis started from the known enantionpure allylic alcohol **25**, which could be easily prepared from commercially available (−)-malic acid **24** using our previously reported method.[32−37] Sequential coupling with enantiomerically pure amino acid Fmoc-L-valine yielded the depsipeptide, which was further subjected to remove the Fmoc

Scheme 2. Synthesis of Lagazole's Analogues 4−9



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group to provide the amine **26**. Treatment of the amine **26** with the key intermediates **17**−**19** in different combinations in the presence of HATU and HOAt at room temperature gave the cyclization precursors **27**−**29**, respectively. The formation of the 17-membered cycloamide was achieved in a three-step sequence involving TBAF and TFA-mediated removal of the 2-(trimethylsilyl) ethanol and Boc groups, respectively, and subsequent macrolactamization with HATU/DIPEA in anhydrous CH_3CN to provide the intermediates **30**−**32** in 46% yield, respectively (three steps). Removal of the *S*-trityl protecting group was accomplished with *i*-Pr_3SiH and TFA to provide analogues **5**, **7**, and **9** in good yield, respectively. Subsequently, acylation of **5**, **7**, and **9** with octanoyl chloride under basic conditions afforded analogues **4**, **6**, and **8** in 78% yield, respectively.

After completion of the synthesis of all six largazole analogues **4**−**9**, we evaluated their biochemical activity against HDACs 1−3 and 9 using SAHA as the positive control. The results are summarized in Table 1 and showed interesting

Table 1. IC_{50} Values for HDAC1-1, HDAC2, HDAC3, and HDAC9 Inhibition (μM)[a]

	IC_{50}(μM)				selectivity
sample	HDAC1	HDAC2	HDAC3	HDAC9	HDAC1/HDAC9
largazole	0.146	1.72	0.604	8.33	0.02
4	17.6	32.1	14.0	63.2	0.3
5	2.35	3.88	0.885	32.0	0.07
6	7.42	30.8	3.99	>100	<0.04
7	0.1	0.224	0.031	34.6	0.003
8	NA	25.1	10.4	18.4	
9	1.67	3.27	0.649	16.2	0.1
SAHA	0.196	0.537	0.11	15.6	0.01

[a]SAHA was used as a positive control. Values are means of three experiments, and standard error of the IC_{50} was generally less than 10%.

HDACs isoform selectivity. Largazole displayed good selectivity for the classes I HDACs (HDAC1, IC_{50} = 0.146 μM; HDAC2, IC_{50} = 1.72 μM; and HDAC3, IC_{50} = 0.604 μM) over the classes II HDAC (HDAC9, IC_{50} = 8.33 μM). Our assay showed that a decreased level of selectivity between HDAC1 and HDAC9 was found for compound **4** (15-fold), in which the 4-methylthiazoline moiety was replaced with a triazole ring. For its thiol analogues **5**, the selectivity between HDAC1 and HDAC9 is 3.5-fold less to that of largazole. Molecular modeling shows that the binding conformation of compound **5** with HDAC1 has a big change in comparison with largazole in Figure 3A. The triazole ring of compound **5** has van der Waals interaction with Leu271 not Phe 150. This suggests that a 4-methylthiazoline moiety is needed for more potent inhibition of HDAC1 of largazole. On the basis of this result, we assumed that the 4-methylthiazoline moiety of largazole may interact with the hydrophobic pocket in the cap of HDAC1, which could increase the selectivity between HDAC1 and HDAC9. Therefore, introducing a more aromatic residue in the 4-methylthiazoline moiety part of largazole would be able to improve van der Waals interactions. We thus designed and synthesized compound **6** with a tetrazole ring to increase the van der Waals interactions. As shown in Table 1, the inhibition of compound **6** to HDAC1 decreased slightly, but the selectivity between HDAC1 and HDAC9 is similar to that of largazole. To our delight, its free thiol **7** shows much better

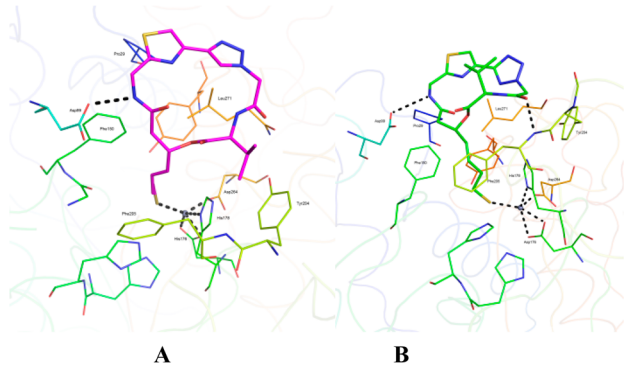

Figure 3. Plausible binding mode of compound **5** and **7** to HDAC1.

selectivity for HDAC1 over HDAC9 to that of largazole (10-fold), which may be a benefit for the future development of specific therapeutic agents. Molecular modeling reveals that the distance between the tetrazole ring and Leu271 and Tyr204 is in the range of van de Walls radius in figure 3B. Therefore, it is not surprising that the tetrazole ring may result in favorable and well-defined van der Waals interactions in comparison with the triazole ring in Figure 3A. To evaluate the position of substitute group on tetrazole ring influence activity or not, compound **8** was designed and synthesized, in which substitute group in the N1 position on the tetrazole ring. As compared to compound **6**, the resulting compound **8** has lost the inhibitory activity against HDAC1 and shows much less selectivity for HDAC1 over HDAC9. It is apparent that its corresponding thiol analogue **9** shows much less selectivity for HDAC1 over HDAC9 than other thiols **5** and **7**. Molecular modeling found that the binding conformation of compound **8** with HDAC1 has a big difference in comparison with compound **6**. Therefore, the position of substitute in the tetrazole ring plays a significant role in the selectivity for inhibition of HDAC1 over HDAC9.

In summary, a series of new largazole's analogues **4**−**9** have been designed based on the molecular modeling of the complex structure of HDAC1 with largazole. Nitrogen functionality was employed as the replacement of 4-methylthiazoline moiety of largazole under the concept of click chemistry. Biological results demonstrate that 4-methylthiazoline moiety variations of largazole have various effects to the selectivity toward HDAC1 over HDAC9. For compound **6** with a tetrazole ring (N-2 substitute), the selectivity between HDAC9 and HDAC1 is similar to that of largazole. Its free thiol **7** was identified to show higher selectivity against HDAC1 over HDAC9 by comparison with largazole. These results clearly indicate that the introduction of appropriate aromatic groups into the largazole skeleton is a useful optimizing tool for this unique class of anticancer agents. Various biological studies including inhibitory studies on different cancer cell lines, inhibitory studies on metastatic tumors in animal models, and the activities against the missing HDAC isoforms are currently in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Moleular modeling, experimental procedures, compound characterization data, and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*Tel: (86) 20-32015318. Fax: (86) 20-32015318. E-mail: jiang_sheng@gibh.ac.cn.

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Notes

The authors declare no competing financial interest.

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