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Synthetic analogs of indole-containing natural products as inhibitors of sortase A and isocitrate lyase

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ABSTRACT

Guided by the inhibitory activities of indole-containing natural products against isocitrate lyase (ICL) from *Candida albicans* and sortase A (SrtA) from *Staphylococcus aureus*, a series of compounds structurally analogous to natural products were synthesized. Eight SrtA inhibitors and an ICL inhibitor having higher activities than the natural products were discovered by screening the enzyme inhibitory activities of synthesized compounds. Among the SrtA inhibitors discovered, six exhibited higher activities than *p*-hydroxymercuribenzoic acid, which suggests that these compounds have great potential as alternative antibacterial agents.

Natural products have been regarded as a major source of pharmaceutical leads and therapeutic agents.[1] They are mostly secondary metabolites obtained by the action of various enzymes, which implies that they have great potential of efficiently interacting with enzymes. Nevertheless, natural products have attracted little research interest in recent years due to the limited quantities that can be obtained from nature, lengthy and low-yielding syntheses, and non-druggable physicochemical properties.[2] To overcome these disadvantages, efforts have been made to construct chemical libraries based on natural products.[3] Compounds bearing the structural features of natural products as well as druggable properties have been synthesized and constituted into chemical libraries. In continuation of our researches on the discovery of inhibitors of enzymes related to antimicrobial activities,[4] we have built a small chemical library with indole-type natural product scaffolds and examined the enzyme inhibitory activities of the library compounds. Sortase A (SrtA) and isocitrate lyase (ICL) were selected as target enzymes since they play crucial roles in the survival or virulence of various pathogenic bacteria and fungi.[5–8]

SrtA is an enzyme that catalyzes the covalent attachment of surface proteins to the peptidoglycan cell layer in Gram-positive bacteria such as *Staphylococcus aureus*.[5] Since surface proteins promote interactions between the invading pathogen and animal tissues, thereby providing strategies for bacterial escape from the host's immune response, SrtA has been regarded as a promising target in the development of efficient antibacterial agent.[7] The development of SrtA inhibitors has been attempted by examining natural products or high-throughput screening of chemical libraries; however, efficient SrtA inhibitors have not been discovered yet.

ICL is an enzyme that transforms isocitrate into glyoxylate in the glyoxylate cycle. The glyoxylate cycle is a reaction sequence in which acetates are converted to succinates during the energy production and biosynthesis of cell constituents; this cycle enables bacteria and fungi to grow on acetate in a hostile environment inside the macrophage where glucose is not available.[6] It has been discovered that the microbial virulence of *Candida albicans* significantly decreased in the case of mutant strains lacking the ICL. However, limited examples of ICL inhibitors have been reported thus far, and they have mostly not been successful due to their low activities or high toxicities.[8]

In a previous work, we had reported the discovery of six known 5-hydroxyindole compounds (**2**–**7**) along with a novel compound 6-hydroxydihydro-β-carboline **1** from the tropical sponge *Hyrtios* sp. and examined their inhibitory activities against ICL from *C. albicans* (Fig. 1).[4a] Among them, bis-5-hydroxyindole containing glyoxy linker (**7**) showed promising activity level (IC_{50}: 29 μg/mL, 89.0 μM). Subsequently, the inhibitory activities of these compounds against SrtA from *S. aureus* were examined;[10] however, inhibitions were not observed with any of the compounds except dihydro-β-carboline **1** that exhibited moderate inhibitory activity (IC_{50}: 67 μg/mL, 290 μM) (Table 1). Consequently, compounds **1** and **7** were considered to be attractive scaffolds for the construction of our chemical library due to their promising levels of

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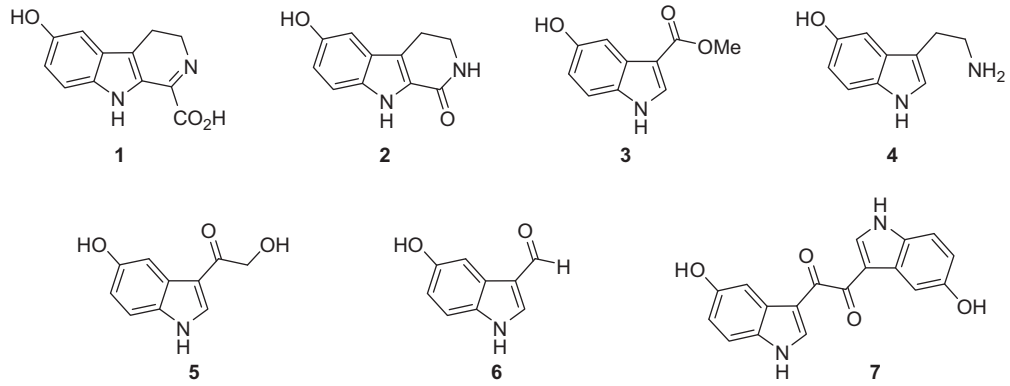


Figure 1. Compounds obtained from the tropical marine sponge *Hyrtios* sp.

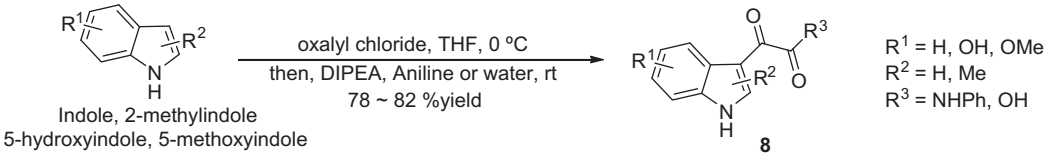
Table 1
Inhibitory activities of natural products **1**–**7** against ICL and SrtA[a]

Entry	Compound	ICL IC_{50}[b] (μg/mL, μM)	SrtA IC_{50} (μg/mL, μM)
1	**1**	87 (380)	67 (290)
2	**2**	>100	>100
3	**3**	>100	>100
4	**4**	53 (301)	>100
5	**5**	61 (318)	>100
6	**6**	40 (247)	>100
7	**7**	29 (89)	>100
8	3-NP[c]	6.0 (51)	—
9	*p*-HMB[d]	—	42 (124)

[a] Enzyme inhibitory activities were measured as described in Refs. 4,10.
[b] Previously reported data.[4a]
[c] 3-Nitropropionate, an ICL inhibitor used as a positive control.
[d] *p*-Hydroxymercuribenzoic acid, a SrtA inhibitor used as positive control.

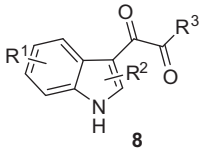
activities as well as druggable physicochemical properties.[11] In addition, easy and fast syntheses of various analogs are possible since methods for the syntheses of indoles and β-carbolines have been well studied and established.

We began our research by examining the analogs of **7**. One of the indole moieties was substituted with functionalities bearing a hydrogen bond donor (OH, NH) adjacent to the carbonyl group. Reactions between the corresponding indoles and oxalyl chloride followed by the addition of aniline or water afforded desired products (**8a**–**8h**) with high yields (78–82%) (Scheme 1).[12] Disappointingly, the synthesized analogs listed in Table 2 showed no ICL inhibitory activities; this suggests that both the indole moieties of **7** are required.[9] In the case of SrtA inhibitory activity, however, the compounds obtained from indole (**8a** and **8e**; entries 1 and 5) and 2-methylindole (**8d** and **8h**; entries 4 and 8) exhibited potent activities, while the compounds containing 5-hydroxy and 5-methoxyindole moieties exhibited no activities (entries 2, 3, 6, and 7). In particular, the SrtA inhibitory activities of compound **8d** (IC_{50}: 17 μg/mL, 61 μM) and **8e** (IC_{50}: 13 μg/mL, 60 μM) were twice as high as that of *p*-hydroxymercuribenzoic acid (*p*-HMB)[7d] (IC_{50}:



Scheme 1. Synthesis of indoleglyoxamide (**8a**–**8d**) and indoleglyoxylate (**8e** and **8f**).

Table 2
SrtA and ICL inhibitory activities of **8**[a]



Entry	Compound	R^1	R^2	R^3	ICL IC_{50}[b] (μg/mL, μM)	SrtA IC_{50}[c] (μg/mL, μM)
1	**8a**	H	H	NHPh	>100	46 (174)
2	**8b**	OH	H	NHPh	>100	>100
3	**8c**	OMe	H	NHPh	>100	>100
4	**8d**	H	Me	NHPh	>100	17 (61)
5	**8e**	H	H	OH	>100	13 (69)
6	**8f**	OH	H	OH	>100	>100
7	**8g**	OMe	H	OH	>100	>100
8	**8h**	H	Me	OH	>100	27 (133)

[a] Enzyme inhibitory activities were measured as described in Refs. 4,10.
[b] IC_{50} of 3-nitropropionate (positive control) = 6.0 μg/mL (50 μM).
[c] IC_{50} of *p*-HMB (positive control) = 42 μg/mL (142 μM).