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Structure–activity relationship of indoloquinoline analogs anti-MRSA

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ABSTRACT

Indolo[3,2-*b*]quinoline analogs (**3a**–**3s**), 4-(acridin-9-ylamino) phenol hydrochloride (**4**), benzofuro[3,2-*b*]quinoline (**3t**), indeno[1,2-*b*]quinolines (**3u** and **3v**) have been synthesized. Those compounds were found to exhibit anti-bacterial activity towards Methicillin-resistant *Staphylococcus aureus* (anti-MRSA activity). Structure–activity relationship studies were conducted that indoloquinoline ring, benzofuro-quinoline ring and 4-aminophenol group are essential structure for anti-MRSA activity.

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Vancomycin that it was introduced in the 1960s by Eli Lilly, has been used in the treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) in clinical in the 1980s.¹ But because of the presence of Vancomycin-resistant *Staphylococcus aureus* in 2002,² the development of novel and potent anti-MRSA agents has become an urgent medical need.

There are a lots of Letter about compounds with quinonic skeletons that have wide ranging pharmaceutical activities, for example antitumor,^{3,4} antibacterical^{5,6} activities have been reported. In our laboratory, Yamato et al.⁷ studied antitumor activity of fused quinoline analogs based on the acridine and found that compound **1** has remarkably potent antitumor activity with dose of 6.25 mg/kg, T/C% 300 against Leukemia P388 in vivo. So, we think compound 1 (Fig. 1) including the novel skeleton of indologuinoline⁸⁻¹⁰ and its analogs might have antibacterical activity and measured compound 1's activity of anti-MRSA against OM481 and OM584,¹¹ which were clinical isolated from Okayama University hospital Japan. The result showed no activity towards MRSA. However we measured anti-MRSA activities of the analogs of compound 1 and found that compound 2 (Fig. 1) which was prepared in the study of 1, exhibited anti-MRSA activity with a minimum inhibitory concentration (MIC) of 8 µg/mL (OM481) and 16 µg/mL (OM584). So, based on the indologuinoline skeleton of the lead compound 2, a series of indologuinoline analogs, including indolo[3,2-b]quinoline analogs, 4-(acridin-9-ylamino)phenol hydrochloride, benzofuro[3,2-b]

* Corresponding author. E-mail address: take@pharm.okayama-u.ac.jp (Y. Takeuchi). quinoline, and indeno[1,2-*b*]quinoline compounds were synthesized. And their anti-MRSA activity against OM481 and OM584 strains of *S. aureus* were evaluated.

In order to understand the structure–activity relationship of indoloquinoline analogs, indoloquinoline analogs (**3a–3m** and **3s**) with kinds of substitution groups at different positions of the 11-*N*-phenyl ring, (**3o–3q**) with different kinds of substitution groups at C-7, **3n** and **3r** with *N*-methyl group were synthesized. Also, 4-(acridin-9-ylamino)phenol hydrochloride (**4**) was synthesized to ascertain the effect of number of ring. And benzofuro-quinoline (**3t**) and indenoquinoline (**3u** and **3v**) were synthesized to estimate the effect of kinds of ring.

Indolo[3,2-*b*]quinoline analogs (**3a**–**3n**) were synthesized by using a modification of the method of Gorlitzer and Weber,¹² as shown in Scheme 1. As starting materials, anthranilic acid was converted to 2-(2-chloroacetamido)benzoic acid (**5**) by reaction with chloroacetyl chloride at reflux in toluene. The amination of **5** with corresponding aniline (**6a**–**6e**) afforded corresponding 2-(2-phenylamino)acetamido benzoic acids (**7a**–**7e**). Cyclization of **7a**–**7e** by heating with boron trifluoride-diethyl ether (BF₃·OEt₂) gave the corresponding indolo[3,2-*b*]quinolones (**8a**–**8e**), which were converted to chlorides (**9a**–**9e**) by treatment with phosphorus oxychloride (POCl₃). The amination of (**9a**–**9e**) with corresponding aniline gave final products **3a–3r** (Scheme 1). And, the acetylation of **3d** by treatment with acetic anhydride gave final product **3s** (Scheme 1).

4-(Acridin-9-ylamino)phenol hydrochloride (**4**) was synthesized according to the reported method.¹³ Anthranilic acid was







Fig. 1. Structure of compounds 1, 2 and 2's anti-MRSA activity.

converted to 2-(2-phenoxyacetamido)benzoic acids $(10)^{14}$ by reaction with phenoxyacetyl chloride in aqueous sodium hydroxide. Treatment of 2-(2-phenoxyacetamido)benzoic acids with polyphosphoric acid gave benzofuro[3,2-*b*]quinolin-11(5*H*)-one (11) which was converted to 11-chlorobenzofuro[3,2-*b*]quinoline (12) by treatment with phosphorus oxychloride (POCl₃). The amination of

12 by treatment with 4-aminophenol gave the final product **3t** (Scheme 2).

Anthranilic acid and 1-indanone (**13u**) or 3-methyl-1-indanone (**13v**) by heating gave indeno[1,2-*b*]quinoline (**14u** and **14v**), which were converted to chlorides (**15u** and **15v**) by treatment with phosphorus oxychloride (POCl₃). The amination of **15u** and **15v** by treatment with 4-aminophenol gave the final products **3u**¹⁵ and **3v** (Scheme 3).

Anti-MRSA activity was measured in terms of minimum inhibitory concentrations (MICs, μ g/mL). The MRSA strains used for the evaluation of anti-MRSA activity were OM481 and OM584 that were clinical isolated from Okayama University hospital Japan as a prototype of Japanese hospital-associated MRSA strains. The assay results are summarized in Table 1.

These results indicate that tetracyclic indologuinoline compounds are critical for anti-MRSA activity against both OM481 and OM584 strains than tricyclic compound 4. The position and kinds of substitution group is important to anti-MRSA activity against both strains, especially indologuinoline analogs 3d showed apparent anti-MRSA activity towards OM481 with MIC's of 4 µg/ mL and OM584 with MIC's of 2 µg/mL. This implies that the 4'hydroxy group is important to anti-MRSA activity against both strains. The introduction of substitution groups in 7-position of indologuinoline analogs (30-3q) showed anti-MRSA activity, especially methoxy group (3p) showed apparent anti-MRSA activity towards both strains, with MIC's of 2 µg/mL each. Indenoquinoline (3u) and methylindenoquinoline (3v) showed weak anti-MRSA activity. However benzofuroquinoline $(3t)^{10}$ showed apparent anti-MRSA activity towards both strains, with MIC's of 2 µg/mL each. So the SAR indicated that the number and kinds of ring,





Scheme 2.



 Table 1

 Anti-MRSA activities of indoloquinoline analogs 3a-3v



						MIC (J	.ıg/mL)							MIC (µg/mL)	
Compd. No.	Х	\mathbb{R}^1	\mathbb{R}^2	R ³	\mathbb{R}^4	OM481	OM584	Compd. No.	Х	\mathbb{R}^1	\mathbb{R}^2	R ³	\mathbb{R}^4	OM481	OM584
2	Ν	Н	Н	2'-OMe, 4'-OH	Н	8	16	3m	N	Н	Н	4'-NO2	Н	>250	>250
3a	Ν	Н	Н	_	Н	8	4	3n	Ν	Н	Н	4'-OH	Me	>250	>250
3b ^a	Ν	Н	Н	2'-OH	Н	16	16	30	Ν	Cl	Н	4'-OH	Н	8	4
3c	Ν	Н	Н	3'-OH	Н	16	8	3p	Ν	OMe	Н	4'-OH	Н	2	2
3d	Ν	Н	Н	4'-OH	Н	4	2	3q	Ν	Me	Н	4'-OH	Н	4	2
3e	Ν	Н	Н	2'-OMe	Н	>250	>250	3r	Ν	Н	Me	4'-OH	Н	>250	8
3f	Ν	Н	Н	3'-OMe	Н	>250	>250	3s ^a	Ν	Н	Н	4'-OAc	Н	16	8
3g	Ν	Н	Н	4'-OMe	Н	16	8	3t	0	Н	—	4'-OH	Н	2	2
3h	Ν	Н	Н	2'-Cl	Н	8	4	3u	CH_2	Н	_	4'-OH	Н	>250	>250
3i	Ν	Н	Н	3'-Cl	Н	125	125	3v	CH	Н	Me	4'-OH	Н	16	4
3ј	Ν	Н	Н	4'-Cl	Н	8	4	4						>250	>250
3k	Ν	Н	Н	4'-F	Н	8	8	Vancomycin						2	1
31	Ν	Н	Н	4'-Me	Н	62.5	62.5								

Grey shade is shown in a compound having about the same activity standard compound (vancomycin). ^a Compound **3b** and **3s** are hydrochloride.

position and kinds of substitution group are effecting to anti-MRSA activity. Further structural development studies are under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.10. 058.

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