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Potent In Vitro Methicillin-Resistant *Staphylococcus aureus* Activity of 2-(1*H*-Indol-3-yl)quinoline Derivatives

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Abstract—A novel structural class of antibacterials, 2-(1*H*-indol-3-yl)quinolines, effective against methicillin-resistant *Staphylococcus aureus* (MRSA), was discovered from a combinatorial library. A structure–activity relationship (SAR) study was conducted to determine the pharmacophore and increase the potency of these compounds. Compounds were prepared that had minimum inhibitory concentrations (MICs) $<1.0\,\mu g/mL$ against MRSA and retained activity against two strains of glycopeptide intermediate-resistant *S. aureus* (GISA).

Resistant bacterial infections are a serious threat to community health.[1] The frequency of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has been increasing for the last decade and has developed into a problem throughout the world. Vancomycin is the agent of choice and is the last line of defense for MRSA infections. Recent reports of clinical isolates of *S. aureus* resistant to the glycopeptide antibiotics has further elevated the medical community's concern.[2] Consequently, new classes of antibacterial agents, preferably bactericidal compounds with novel mechanisms of action, are needed. We now report the synthesis and potent in vitro MRSA activity of 2-(1*H*-indol-3-yl)quinoline derivatives. In addition, these agents are effective against glycopeptide intermediate-resistant *S. aureus* (GISA) strains.

A combinatorial library of 2-(1*H*-indol-3-yl)quinolines was prepared by utilizing solid-phase heterocyclic *N*-oxide chemistry.[3] The synthesis of **2** is a representative example illustrated in Scheme 1.[4] Initially, 1,2-diaminoethane was attached to Wang resin, followed by the coupling of quinoline-4-carboxylic acid and oxidation with *m*-CPBA to give resin **1**.[5] The resin was then allowed to sequentially react with benzoyl chloride and 5-bromoindole. Finally, treatment of this resin with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM) yielded **2**.[6]

Initial Kirby–Bauer screening of the library, containing three compounds per well, against a panel of microorganisms (MRSA, vancomycin-resistant *Enterococcus faecium* (VRE), *Escherichia coli*, *Pseudomonas aeruginosa*, and *Saccharomyces cerevisiae*) identified a subclass of 2-(5-bromo-1*H*-indol-3-yl)quinoline derivatives with significant zones of inhibition (>15 mm) versus MRSA and VRE.[7] Upon deconvolution, compound **2** proved to be the most potent with activity against the two Gram-positive organisms, MRSA (MIC = 12.5 μg/mL) and VRE (MIC = 25 μg/mL).[8] None of the compounds within this structural class was effective against Gram-negative bacteria in vitro. Next, a series of derivatives was prepared in order to increase potency and to evaluate the structure–activity relationship (SAR) of this novel class of antibacterial agents.

To assess the SAR of this structure class most effectively, a more flexible synthetic strategy employing the Doebner reaction was implemented.[9] The synthesis of **6** is a representative example illustrated in Scheme 2. 2-(Indol-3-yl)quinoline-4-carboxilic acid **5** was prepared in moderate yield by allowing 3-chloroaniline (**3**) to stir with 1-*tert*-butoxycarbonyl-5-bromoindole-3-carboxaldehyde (**4**) in the presence of pyruvic acid at 85 °C for 1 h.[10] The product was attached to a resin bound diamine utilizing standard amide coupling conditions. Finally, the resin was treated with 50% TFA in DCM to give **6**. The compounds utilized for the SAR study were prepared by one of these two general methods. Additional derivatives were prepared by functional group manipulation of the substituent at the quinoline C-4 position.

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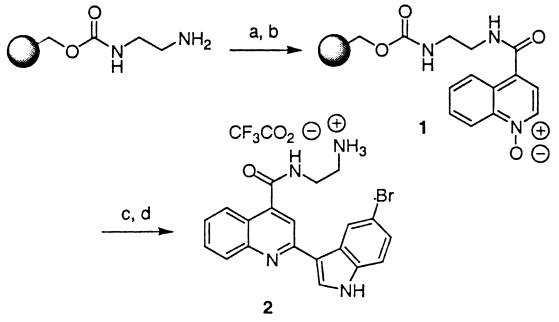
The lead molecule was divided into three distinct regions: (i) the quinoline C-4 substituent; (ii) the quinoline portion; and (iii) the 5-bromoindole region.

The SAR about the 4-position of the quinoline ring indicated that it was quite tolerant of modification (Table 1). For example, introduction of an amide, halogen, aminomethyl or hydroxymethyl produced compounds **6**, and **8**–**10** exhibiting potent activity (MICs $<1\,\mu g/mL$) against MRSA. Even compounds that lacked a C-4 substituent, such as compound **11**, were quite potent in vitro versus MRSA. However, a compound containing a 4-carboxylic acid substituent (**7**), was found to be inactive (MIC = 25 μg/mL).[11]

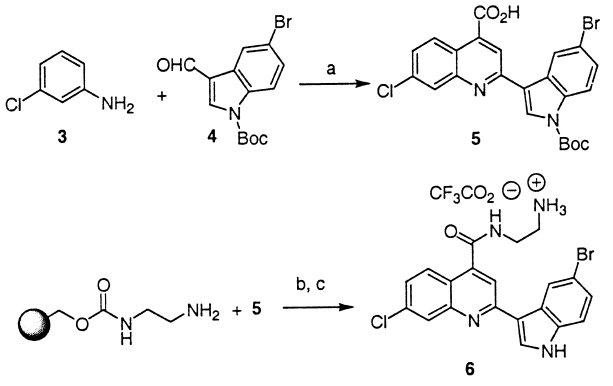
Antibacterial activity was improved by the introduction of hydrophobic substituents onto the quinoline ring (Table 2). For example, the unsubstituted lead compound **2** was found to be only moderately active (MIC = 12.5 μg/mL). However, introduction of halogens to the 5-, 6-, 7-, or 8-position of the quinoline ring produced compounds that had significantly better activity. A chlorine group at the 7-position appeared to be optimal. Compound **13**, which contained a propargyl amine in the 6-position, was prepared from the corresponding iodide utilizing a palladium mediated coupling reaction (Scheme 3), and retained reasonable antibacterial activity (MIC = 3.13 μg/mL).[12]

From the initial library, the importance of the 5-bromoindole was evident, nevertheless, a series of compounds was prepared to fully evaluate the SAR of the indole ring (Table 3). Compound **21**, which lacked the halogen substituent on the indole ring, was only moderately active (MIC = 5.00 μg/mL), whereas compounds that were substituted with a halogen (F, Cl or Br) at the indole 5- or 6-position (i.e., **23**–**26**) demonstrated potent antibacterial activity against MRSA. Interestingly, derivatives that contain the halogen at either the indole 4- or 7-position (i.e., **22** and **27**) were inactive. In addition, introduction of hydrophilic groups (i.e., CN; **30** or OH; **31**) or small ether groups (i.e., OMe; **29**) at the indole 5-position were also detrimental to antibacterial activity.

Three compounds (**6**, **9**, and **13**), were screened versus two clinical isolates of *S. aureus* (HP 5827 and HP 5836) resistant to the glycopeptide antibiotic vancomycin (Table 4). All three compounds retained good activity versus these clinically important strains, MICs = 0.39–3.13 μg/mL.

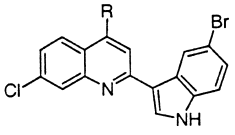


Scheme 1. (a) 4-Quinolinecarboxylic acid, PyBOP, NMM, DMAP, DMF, rt, 24 h; (b) *m*-CPBA, DCM, 24 h; (c) (i) PhC(O)Cl, DCM, rt, 10 min; (ii) 5-bromoindole, DCM, rt, 6 h; (d) TFA:DCM (1:1), rt, 1 h.



Scheme 2. (a) Pyruvic acid, acetic acid, 85 °C, 1 h; (b) PyBOP, NMM, DMF, rt, 24 h; (c) TFA:DCM (1:1), rt, 1 h.

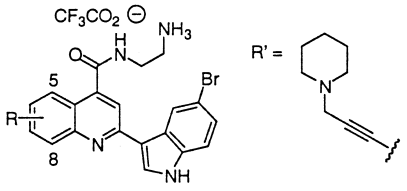
Table 1. Structure–activity relationships around the C-4 substituent



Compd	R	MIC (μg/mL) MRSA	MIC (μg/mL) VRE
6[a]	$C(O)NH(CH_2)_2NH_2$	0.78	1.56
7	CO_2H	25	25
8	Cl	< 0.39	3.13
9[a]	CH_2NH_2	0.78	1.56
10	CH_2OH	0.31	2.50
11	H	0.60	> 25

[a]TFA salt.

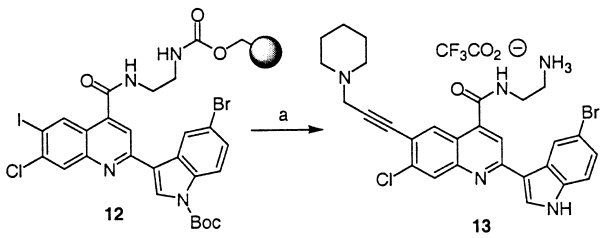
Table 2. Structure–activity relationships around the quinoline portion



Compd	R	MIC (μg/mL) MRSA	MIC (μg/mL) VRE
2	H	12.5	25
6	7-Cl	0.78	1.56
13	6-R′; 7-Cl	3.13	6.25
14	6-Cl	1.56	3.13
15	5,7-diCl	0.78	1.56
16	7,8-diCl	0.78	0.78
17	7-F	3.13	3.13
18	8-Cl	1.56	3.13
19	8-F	6.25	12.5
20	6,7-OCH_2O	12.5	ND[a]

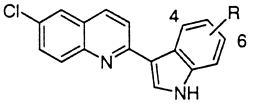
[a]ND, not determined.

In conclusion, a novel structural class of 2-(1*H*-indol-3-yl)-quinoline antibacterials with potent in vitro (< 1.0 μg/mL) activity versus Gram-positive bacteria has been discovered. Several analogues were effective against two important glycopeptide intermediate-resistant *S. aureus* (GISA) clinical isolates, however, none of the analogues were effective against Gram-negative bacteria in vitro. A SAR study revealed that the indole portion was sensitive to structural changes while the quinoline, especially at the C-4 region, was tolerant to several modifications. Studies are currently underway to evaluate the in vivo efficacy of this series of compounds.



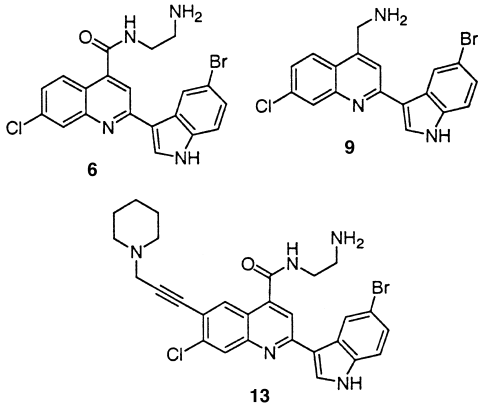
Scheme 3. (a) Propargyl bromide, piperidine, $Pd(OAc)_2$, PPh_3, CuI, THF, rt, 24 h; (b) TFA:DCM (1:1), rt, 1 h.

Table 3. Structure–activity relationships around the indole region



Compd	R	MIC (μg/mL) MRSA	MIC (μg/mL) VRE
21	H	5.00	> 25
22	4-F	> 25	> 25
23	5-F	0.78	12.5
24	5-Cl	0.78	> 25
25	5-Br	0.62	> 25
26	6-F	1.56	6.25
27	7-Cl	> 25	> 25
28	5-OBz	1.56	> 25
29	5-OMe	> 25	> 25
30	5-CN	> 25	> 25
31	5-OH	12.5	> 25

Table 4. In vitro potency versus two glycopeptide intermediate-resistant *Staphylococcus aureus* (GISA) clinical isolates



Compd[a]	MIC (μg/mL) HP-5827	MIC (μg/mL) HP-5836
6	0.78	0.39
9	0.39	0.39
13	1.56	3.13

[a]TFA salt.

Acknowledgements

The authors are grateful to Dr. Robert Smith for providing many insightful suggestions. Dr. Fredrick Tenover (United States Center for Disease Control and Prevention) kindly provided the GISA strains.

References and Notes

1. Chu, D. T. W. *Annu. Rep. Med. Chem.* **1998**, *33*, 141.
2. Hiramatsu, K.; Hanaki, H.; Ino, T.; Yabuta, K.; Oguri, T.; Tenover, F. C. *J. Antimicrob. Chem.* **1997**, *40*, 135.
3. Hoemann, M. Z.; Melikian-Badalian, A.; Kumaravel, G.; Hauske, J. R. *Tetrahedron Lett.* **1998**, *39*, 4749.
4. See ref 3 for experimental detail.
5. All reagents and chemicals were purchased from Aldrich, Lancaster, Advanced Chemtech, Novabiochem and/or Fluka. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian 300 MHz spectrometer. Chemical shifts are reported in ppm relative to DMSO (2.53 ppm for ^{1}H and 39.52 ppm for ^{13}C). Mass spectrometry data were obtained on a Micromass Platform LC. Final compounds were purified by preparatory HPLC (C-18, MeCN:H_2O 70:30 with 0.5% TFA) and lyophilized to amorphous solids.
6. All compounds tested were characterized by ^{1}H NMR, ^{13}C NMR, and MS. A representative example, compound **6**: ^{1}H NMR (300 MHz, DMSO) δ 9.04 (s, 1H), 8.83 (bs, 1H), 8.59 (s, 1H), 8.15 (m, 3H), 7.58 (d, J = 10 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H), 3.39 (d, J = 5.4 Hz, 2H), 2.79 (t, J = 6.2 Hz, 2H); ^{13}C NMR (300 MHz, DMSO) δ 166.60, 155.96, 148.55, 142.36, 136.01, 134.29, 130.49, 127.30, 127.18, 126.05, 124.97, 124.74, 120.99, 117.19, 114.47, 113.96, 113.51, 43.16, 41.27; MS (APCI) m/z 443 $[MH]^+$.
7. The isolates used for MIC determinations were ATCC-33591 for MRSA and ATCC-51559 for VRE.
8. MICs were determined by measuring the growth of the cultured organism in a Brain–Heart Infusion (BHI) broth in a 96-well microtiter plate at 2-fold serial dilutions. The well with the lowest concentration containing no growth represents the MIC value. Vancomycin was used as a standard in all studies with an MIC = 1.56 μg/mL versus MRSA.
9. Doebner, O. *Ber.* **1883**, *16*, 2357.
10. General procedure for the Doebner reaction: Compound **5**: To a 500 mL round-bottom flask was added pyruvic acid (13.6 g, 154 mmol), 5-bromo-1-*tert*-butoxycarbonylindole-3-carboxaldehyde (25 g, 77 mmol) and 300 mL of acetic acid. The reaction mixture was heated to 85 °C for 30 min until the solid had dissolved. 3-Chloroaniline (16.3 mL, 154 mmol) was added and the reaction mixture stirred at 85 °C for 90 min until an orange precipitate had formed. The mixture was filtered hot and the solid washed with cold acetic acid until a

colorless filtrate was obtained leaving a pale-yellow solid. The solid was washed with ether and dried under vacuum to afford pure product (12.4 g, 32% yield). Compound **5**: ^{1}H NMR (300 MHz DMSO) δ 8.98 (s, 1H), 8.61 (bs, 1H), 8.55 (d, J = 9.3 Hz, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 9.5 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 1.83 (s, 9H); MS (APCI) m/z 501 $[MH]^+$.

11. Holmes, R. E. US Patent 3,870,712, 1975; *Chem. Abstr.* **1975**, *83*, 9822.

12. To a 250 mL fritted flask containing resin-bound aryl iodide (5 g, 3.5 mmol) was added palladium acetate (0.66 g, 2.8 mmol), copper(I) iodide (33 mg, 0.2 mmol), triphenylphosphine (1.1 g, 4.2 mmol), THF (200 mL), piperidine (6.9 mL, 70 mmol), and propargyl bromide (2.5 mL, 28 mmol). The flask was agitated overnight and the resin washed with THF (3×200 mL), DMF (3×200 mL), MeOH (3×200 mL), and DCM (3×200 mL). The resin was dried under vacuum to give the resin bound product.