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

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Abstract—Novel antibacterials agents, 2-(1*H*-indol-3-yl)tetrahydroquinolines, were prepared using hetero Diels–Alder chemistry and found to be effective in vitro against methicillin-resistant *Staphylococcus aureus* (MRSA). A structure–activity relationship (SAR) study was conducted to determine the important features of this series and to increase the potency of these compounds. Compounds were prepared that had minimum inhibitory concentrations (MIC's) < 1.0 μg/mL against MRSA, but had no activity versus vancomycin-resistant *Enterococcus* (VRE).

We recently published on a group of novel antibacterial agents effective versus resistant strains of Gram-positive bacteria.[1] The 2-(1*H*-indol-3-yl)quinolines were shown to be effective in vitro versus methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide intermediate-resistant *S. aureus* (GISA) and in some cases vancomycin-resistant *Enterococcus* (VRE). These compounds also exhibited promising in vivo activity and have displayed an interesting mechanism of action profile.[2] During the course of our study, a new series of substituted 2-(1*H*-indol-3-yl)tetrahydroquinolines was prepared and found to also possess antibacterial activity. We now wish to report on the activity of these novel compounds as well as discuss some of the unique structure–activity relationships (SARs) associated with this series.

One of the concerns with the original 2-(1*H*-indol-3-yl)quinolines was their high logP values leading to poor solubility and high protein binding in plasma. It was envisioned that reducing the core ring from a quinoline to a tetrahydroquinoline, and thereby introducing a more basic nitrogen, could lower the logP (compound **15**, calcd LogP = 3.56; compound **39** calcd LogP = 4.19) of these compounds and lead to more soluble compounds with lower protein binding.

The 2-(1*H*-indol-3-yl)tetrahydroquinolines were readily accessible utilizing hetero Diels–Alder chemistry developed by Kobayashi.[3] Treatment of 4-chloroaniline, *N*-Boc-5-bromoindol-3-yl carboxaldehyde and dihydrofuran with ytterbium triflate in acetonitrile in the presence of molecular sieves at ambient temperature afforded the protected tetrahydroquinolines **1** and **2** in good yield as a 2:1 mixture of diastereomers (Scheme 1).[4] Removal of the Boc protecting group from the indole proved to be problematic due to the instability of the ring system to acidic conditions. Instead, the trimethylsilylethylcarbamate (Teoc) protected *cis*- and *trans*-diastereomers, **3** and **4**, were prepared. The Teoc protecting groups were readily removed with tetrabutylammonium fluoride to give the *cis*- and *trans*-2-(1*H*-indol-3-yl)tetrahydroquinolines, **5** and **6**, in good yield, respectively.[5] The relative stereochemistry of all of the compounds was assigned by comparison of the ^{1}H NMR and ^{13}C NMR spectra with compounds **5** and **6**.[6] The C-4 proton was very different in chemical shift and coupling constant for the *cis*- and *trans*-isomers (*cis*-**5** δ 5.16 ppm, $J = 8.1$ Hz, *trans*-**6** δ 4.51 ppm, $J = 4.8$ Hz). In the case of 3-substituted anilines, two regioisomers were obtained from the reaction. Both the 5-chloro and 7-chlorotetrahydroquinolines were isolated from the reaction of 3-chloroaniline with the 7-chloro product being the major. The regioisomers and diastereomers were separated by flash chromatography and the relative stereochemistry and regiochemistry of the *cis*-diastereomer **9** was confirmed by X-ray crystallography (Fig. 1).[7]

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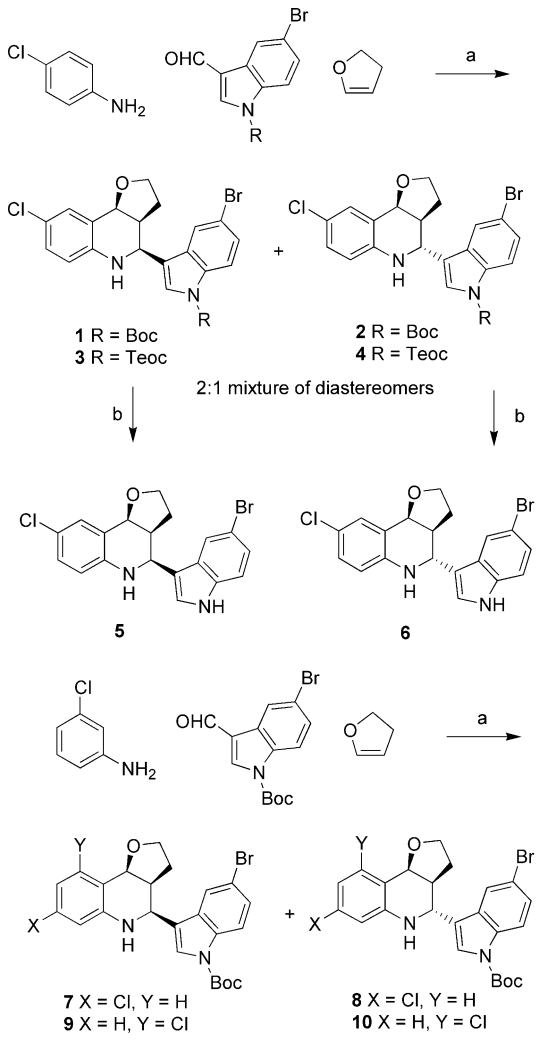


Scheme 1. (a) $Yb(OTf)_3$, 4 Å molecular sieves, MeCN, rt, 24 h (75%); (b) TBAF, THF, rt, 12 h (80%).

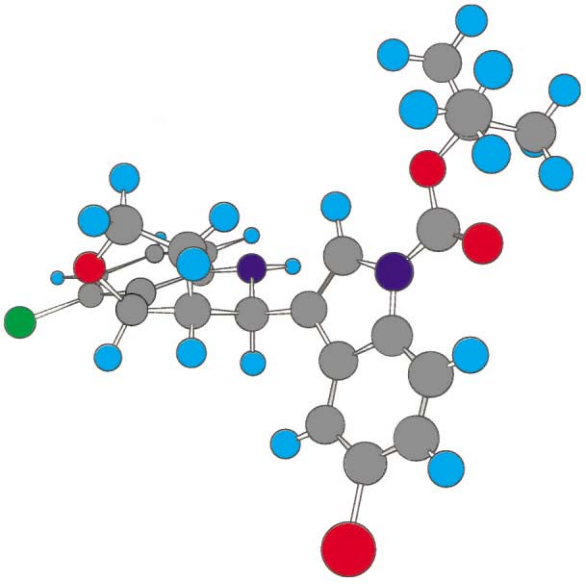
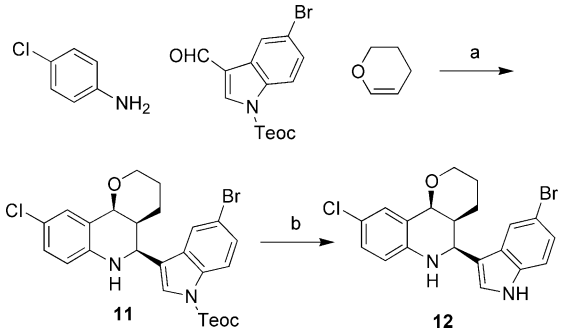


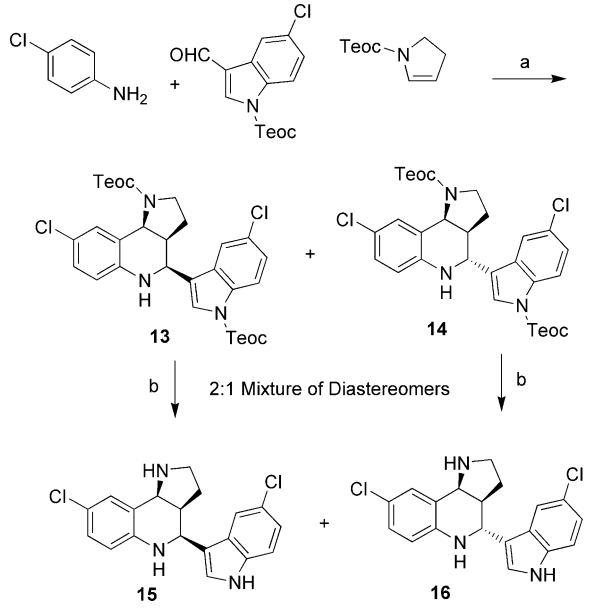
Figure 1. Chem 3D drawing of the X-ray crystal structure of compound **9** showing the all *cis* stereochemistry on the tetrahydroquinoline ring.

This reaction worked remarkably well with most activated olefins examined. Interestingly, when dihydropyran was utilized in this reaction, only one product, the *cis*-isomer **11** was isolated in modest yield (Scheme 2). With Teoc protected dihydropyrrole, the reaction behaved in a similar manner to the dihydrofuran reaction with a 2:1 ratio of *cis*- to *trans*-isomers, **13** and **14**, respectively (Scheme 3). For the deprotection of these two compounds, one Teoc group came off at room temperature while the second required refluxing conditions to give the pyrrolidine products **15** and **16** in good yield.

Substitution of an alkyne group at the 6-position of the tetrahydroquinoline was accomplished via a palladium mediated coupling of 4-iodoaniline with the appropriate alkyne prior to the hetero Diels–Alder reaction. Attempts to introduce the alkyne group after cyclization from various substituted 6-iodotetrahydroquinolines via palladium mediated couplings were unsuccessful. A representative example for the preparation of the *cis*- and *trans*-piperidyl alkynes **17** and **18** is shown below (Scheme 4).



Scheme 2. (a) $Yb(OTf)_3$, 4 Å molecular sieves, MeCN, rt, 24 h (50%); (b) TBAF, THF, rt, 12 h (65%).



Scheme 3. (a) $Yb(OTf)_3$, 4 Å molecular sieves, MeCN, rt, 24 h (60%); (b) TBAF, THF, Δ, 12 h (65%).

The SARs defined around the tetrahydroquinoline series could be divided into four different aspects: (i) the substitution of the indole portion, (ii) the stereochemistry of the tetrahydroquinoline, (iii) the substitution on the tetrahydroquinoline and (iv) the ring fused to the 3,4-position of the tetrahydroquinoline.

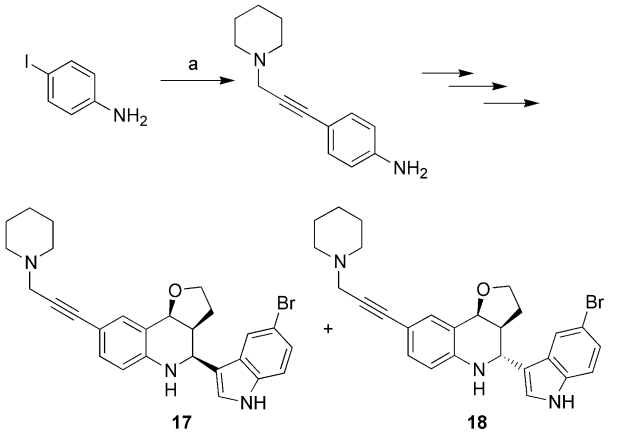
The effect on activity by the substituent on the indole ring paralleled the original 2-(1*H*-indol-3-yl)quinoline series (Table 1).[8] A halogen is required in the 5-position of the indole with 5-bromoindole being optimal.

In all but one case, the *cis*-isomer was found to be more potent than the corresponding *trans*-isomer. For example, the *cis*-isomer **5** was a full log-fold more active than its *trans*-isomer **6**.

The SARs around the substituents on the tetrahydroquinoline ring did not seem to have as dramatic an effect as the indole ring, but some trends were evident (Table 2). Substitution with a halogen at the 6-position was preferred with the 6-chloro (MIC = 0.31 μg/mL) and 6-iodo (MIC < 0.39 μg/mL) derivatives, **5** and **26**, being the most potent. The electron rich 6-OMe derivative **33** and the alkynyl derivatives, (**17**, **32** and **34**) all had measurable activities, but were less potent. The only substitution that was not tolerated was methylation of the tetrahydroquinoline nitrogen (Table 3). The *N*-methyl derivative **35** was devoid of activity.

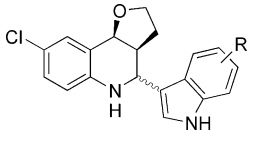
The ring fused to the 3,4-position of the tetrahydroquinoline could be modified and activity retained (Table 4). For example, the tetrahydropyran **36** was equally potent as the corresponding tetrahydrofuran **5**. However, changing the oxygen to a nitrogen, even when the nitrogen was non-basic, led to diminished activity.

One interesting aspect of the original 2-(1*H*-indol-3-yl)quinoline series was that the activity versus VRE seems to require the presence of a basic amine spaced with a linker some distance off of the 4-position of the quinoline. All of the compounds in the quinoline series,



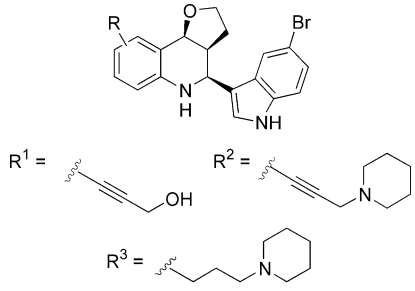
Scheme 4. (a) Propargyl bromide, piperidine, $Pd(PPh_3)_4$, CuI, 45 °C, 18 h.

Table 1. Structure–activity relationships around the indole portion and relative stereochemistry of the tetrahydroquinoline



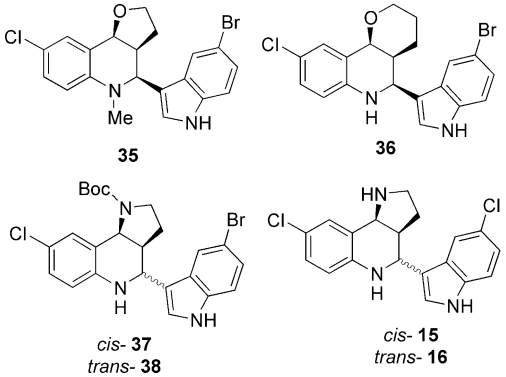
Compd	R	Isomer	MIC (μg/mL) MRSA
5	5-Br	*cis*	0.31
19	5-Cl	*cis*	0.78
20	H	*cis*	> 25
21	6-F	*cis*	6.25
22	2-Me	*cis*	> 25
6	5-Br	*trans*	3.13
23	5-Cl	*trans*	3.13
24	H	*trans*	6.25
25	6-F	*trans*	12.5

Table 2. Structure–activity relationships around the tetrahydroquinoline portion



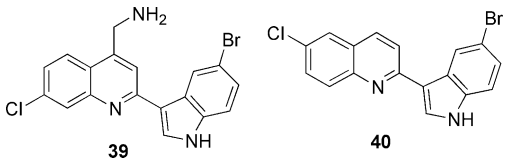
Compd	R	MIC (μg/mL) MRSA	Compd	R	MIC (μg/mL) MRSA
26	6-I	< 0.39	**30**	5,7-diCl	1.56
5	6-Cl	0.31	**31**	6,8-diCl	1.56
9	8-Cl	3.13	**32**	R^1	3.13
27	6-F	0.78	**17**	R^2	1.56
28	8-F	6.25	**33**	OMe	1.56
29	6-CF_3	0.78	**34**	R^3	12.5

Table 3. Structure–activity relationships around the ring fused to the 3,4-position of the tetrahydroquinoline



Compd	MIC (μg/mL) MRSA	Compd	MIC (μg/mL) MRSA
35	> 25	**38**	1.56
36	< 39	**15**	3.13
37	0.78	**16**	6.25

Table 4. In vitro potency versus vancomycin-resistant *Enterococcus faecium* (VRE)



39 **40**

Compd	MIC (μg/mL) MRSA	MIC (μg/mL) VRE
39	0.78	1.56
40	0.60	>25
15	3.13	>25
16	6.25	>25

lacking such an amine, were devoid of activity versus VRE (MIC's > 25 μg/mL). Only one set of distereomers in the tetrahydroquinoline series, **15** and **16**, had a basic nitrogen directly attached to the 4-position of the tetrahydroquinoline. These two compounds were also both devoid of activity versus VRE suggesting that at least a one atom spacer may be needed between the core ring and the basic nitrogen for activity versus VRE.

In conclusion, a novel structural class of 2-(1*H*-indol-3-yl)tetrahydroquinoline antibacterials with potent in vitro (<1.0 μg/mL) activity versus methicillin resistant *S. aureus* has been discovered. A SAR study revealed that the indole portion was sensitive to structural changes while the tetrahydroquinoline was tolerant to several modifications. Studies are currently underway to evaluate the in vivo efficacy of this series of compounds.

Acknowledgements

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References and Notes

1. Hoemann, M. Z.; Kumaravel, G.; Xie, R. L.; Rossi, R. F.; Meyer, S.; Sidhu, A.; Cuny, G. D.; Hauske, J. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2675.
2. (a) Oliva, B.; Miller, K.; Caggiano, N.; Cuny, G. D.; Hoemann, M. Z.; Hauske, J. R.; Chopra, I. *Abstracts of Papers*, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Sept 17–20, 2000; American Society for Microbiology: Washington, DC, 2000, Paper # 2180. (b) Oliva, B.; Cuny, G. D.; Hoemann, M. Z.; Hauske, J. R.; Chopra, I. *Abstracts of Papers*, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, ON, Sept 17–20, 2000; American Society for Microbiology: Washington, DC, 2000, Paper # 2181.
3. (a) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423. (b) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.
4. **General procedure: *cis*-5 and *trans*-6.** To a solution of 4-chloroaniline (4.19 mmol) and *N*-Teoc-5-bromoindol-3-yl carboxaldehyde (4.19 mmol) in 20 mL of acetonitrile was added 4 Å molecular sieves (1.05 g), ytterbium triflate (0.4 mmol), and enol ether (8.37 mmol). The reaction mixture was stirred for 12 h at 20 °C. The reaction mixture was diluted with DCM (50 mL) and filtered through Celite. The filter pad was washed with DCM (100 mL) and the combined organics concentrated in vacuo. The crude solid was purified by flash chromatography (silica gel, hexanes/EtOAc 10:1) to give both the *cis*-**3** and *trans*-**4** separately in a 2:1 ratio (74% yield). To a solution of *cis*-**3** (0.91 mmol) in THF 10 mL was added 1.0 M TBAF in THF (1.1 mmol). The reaction was stirred for 1 h at 20 °C. The reaction mixture was diluted with DCM (25 mL) and washed with satd NH_4Cl (25 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The crude solid was purified by flash chromatography (silica gel, DCM/MeOH 20:1) to give *cis*-**5** (80% yield). The *trans*-**6** isomer was deprotected in an identical procedure (80% yield).
5. All compounds tested were characterized by ^{1}H NMR, ^{13}C NMR, and MS. A representative example: compound **5**. ^{1}H NMR, (DMSO), (300 MHz) δ 11.26 (s, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.21 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 7.00 (dd, J = 8.7, 2.8 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.03 (s, 1H), 5.16 (d, J = 8.1 Hz, 1H), 4.90 (d, J = 2.9 Hz, 1H), 3.60 (m, 2H), 2.83 (m, 1H), 1.98 (m, 1H), 1.43 (m, 1H), ^{13}C NMR, (DMSO), (300 MHz) δ 145.08, 134.94, 128.93, 127.46, 123.99, 123.93, 123.66, 121.12, 120.42, 116.38, 115.52, 113.57, 111.26, 74.59, 65.90, 49.06, 43.79, 25.16, MS (APCI) m/z 403 $[MH]^+$. **6**: ^{1}H NMR, (DMSO), (300 MHz) δ 11.30 (s, 1H), 7.83 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.23 (dd, J = 5.2, 2.0 Hz, 1H), 7.21 (d, J = 2.6 Hz, 1H), 7.07 (dd, J = 8.4, 2.2 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.39 (s, 1H), 4.51 (d, J = 4.8 Hz, 1H), 3.89 (m, 2H), 3.67 (q, J = 6.2 Hz, 1H), 2.56 (m, 1H), 1.97 (m, 1H) 1.61 (m, 1H), ^{13}C NMR, (DMSO), (300 MHz) δ 146.0, 136.1, 130.9, 128.8, 128.6, 126.8, 124.4, 122.5, 121.8, 119.9, 116.7, 115.0, 114.5, 111.9, 75.9, 64.9, 50.3, 41.6, 29.7, MS (APCI) m/z 403 $[MH]^+$.
6. For a description of reagents and instrumentation, see ref 1.
7. X-ray crystal structure obtained by Dr. Armstrong's group at Boston College.
8. For a description of the MIC determinations, see ref 1.