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Discovery of bisindolyl-substituted cycloalkane-anellated indoles as novel class of antibacterial agents against *S. aureus* and MRSA

Mardia Telep El-Sayed [a], Sibel Suzen [b], Nurten Altanlar [c], Knut Ohlsen [d], Andreas Hilgeroth [a,*]

[a] Institute of Pharmacy, Martin-Luther University Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle, Germany
[b] Faculty of Pharmacy, Ankara University, Tandogan, Department of Pharmaceutical Chemistry, Tandogan, 06100 Ankara, Turkey
[c] Faculty of Pharmacy, Ankara University, Tandogan, Department of Pharmaceutical Microbiology, Tandogan, 06100 Ankara, Turkey
[d] Institute of Molecular Infection Biology, Julius-Maximilian University Würzburg, 97080 Würzburg, Germany

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ABSTRACT

Antibiotic resistance is an ongoing problem in the treatment of bacterial diseases. Among the various antibacterial infections *Staphylococcus aureus* infections remain critical due to the increasing resistances, especially against the methicillin-resistant *S. aureus* (MRSA). We discovered novel antibacterial compounds with activities against both *S. aureus* and MRSA types. Structure–activity relationships (SAR) are discussed and show that the activity depends on the ring size of the anellated cycloalkane. Moreover, first substituent effects have been investigated for both the cycloalkane and the indole residues.

Bacterial resistance against antibiotics is an ongoing main problem in the therapy of bacterial infections.[1–3] Studies of resistance developments document that a discussed critical situation in the cases of *Mycobacterium tuberculosis* or *Escherichia coli* infections is persistent concerning the antibiotic resistance.[4] However, the part of resistances in the case of *E. coli* infections is very low indeed with a resistance rate of less than one per cent against novel antibiotics like tigecyclin.[4] *Staphylococcus aureus* still belongs to the most critical bacteria concerning antibiotic resistances.[5–7] In Europe 50% of the *S. aureus* isolates are methicillin-resistant *S. aureus* (MRSA) isolates depending from the investigated country.[4] However, increasing *S. aureus* resistances beside the methicillin resistance have been described against antibiotics like erythromycin, clindamycin, ciprofloxacin or moxifloxacin.[4] Glycopeptides like vancomycin or teicoplanin have been alternative antibiotics in the case of MRSA.[8,9] However, studies document increasing resistances against those alternative antibiotics. Moreover, the use of vancomycin is critical due to a limited effectiveness of the drug with a toxic drug potential.[9] Low effectiveness and increasing resistance developments have also been described for the MRSA antibiotics linezolid or quinopristin and dalfopristin from the streptogramin family.[10–12]

Bacteria develop strategies to change their genetic materials by various mechanisms.[13–16] Changes between different kinds of bacteria have also been described. Such bacteria use plasmids as mobile vehicles or bacteriophages.[17,18] The transferred genetic material encodes resistances against various antibiotics including the MRSA resistance against vancomycin with its origin in *Enterococcus* strains.[19] Thus, there is an ongoing demand to search for novel antibiotics preferably with addressing novel bacterial target structures.[3] Compounds with novel structural features may be promising for screening efforts as antibacterial agents.

Indoles are partial structures of various natural compounds isolated from marine spongs, medicinal plants or bacteria which have been reported to show antibacterial or antifungal activities.[20,21]

We have been interested to investigate the reaction of various dialdehydes with indole under mild conditions using acetic acid at room temperature. Similar reactions of an aldehyde and indole have been described under Bronsted and Lewis acidic conditions, including acetic acid.[22,23] The resulting bisindolyl-cycloalkane indoles form a novel compound class and have been discovered to show a differential activity towards various *S. aureus* types. The activity depends on the cycloalkane ring size and substituent effects of both the cycloalkane and the indole rings with interesting results for first substituted compounds. Lead structures with promising antibacterial activities against both *S. aureus* and MRSA have been identified for further drug development studies.

The reaction of indole **1** and our dialdehydes with one and two methylene groups between the functional aldehyde groups **2**

* Corresponding author. Tel.: +49 345 55 25168; fax: +49 345 55 27207.
E-mail address: andreas.hilgeroth@pharmazie.uni-halle.de (A. Hilgeroth).

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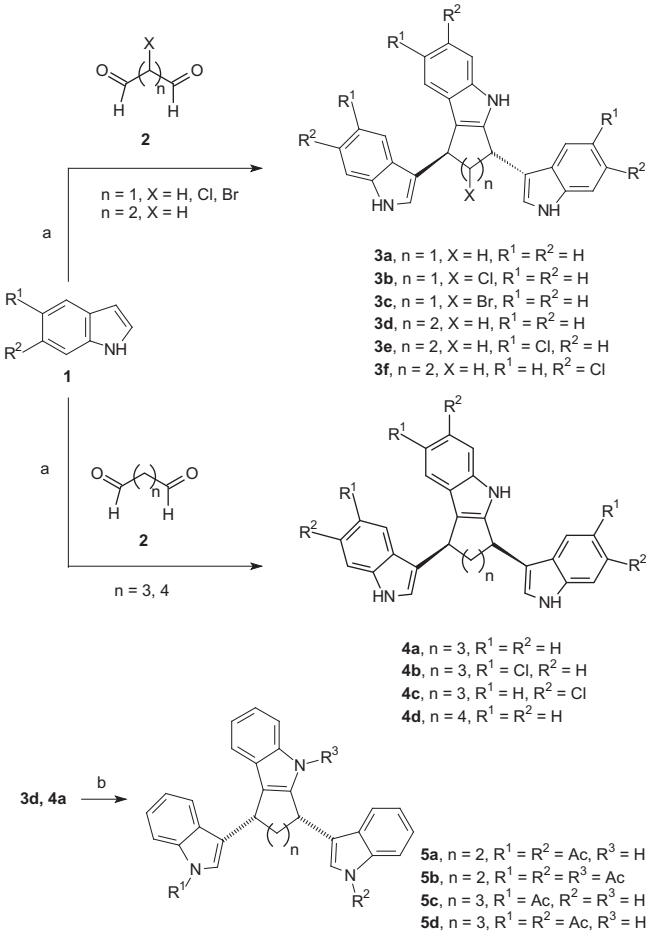
(n = 1, 2) led to the formation of bisindolyl-cycloalkane indoles **3a–f** with a *trans*-position of the indolyl residues at the cyclopentane and the cyclohexane rings, respectively (Scheme 1).[24]

The dialdehydes with a longer alkyl chain between the aldehyde functions **2** (n = 3, 4) reacted with indole in the same way to give the bisindolyl-cycloalkane indoles **4a–d** with a *cis*-position of the indole substituents at the respective cycloheptane and cyclooctane residues. The different stereochemistry of both compounds **3** and **4** was derived from the ^{1}H NMR data with just one signal for those CH protons of the cycloalkane ring having a *trans*-positioning and the same configuration of both CH groups being either both *S* or *R*, respectively, in compounds **3**.

The *cis*-orientated alkyl CH protons of the cycloalkane ring in compounds **4** show each single signals in the ^{1}H NMR spectra due to the different CH configurations of being *S* and *R* or *R* and *S*, respectively.[25] The compound stereochemistry has been confirmed by X-ray crystal structure of the later reported trisacetylated derivative **5b**.

The suggested reaction pathway for both compound formations may have followed a classical electrophilic reaction of each aldehyde function of the dialdehyde at the electron-rich C3 atom of each indole first. Then one reacted aldehyde function underwent an electrophilic reaction with the third indole at its corresponding C3 atom and the other one reacted aldehyde function condensed with the C2 atom of that third indole to give the cycloalkane structure within a ring-closure reaction.

The *N*-acetylation reactions at room temperature followed a stepwise procedure to mono-, bis- and trisacetylated products **5a–d**, respectively, using aceting anhydride in dichloromethane and both 4-(dimethylamino)pyridine (DMPA) and triethylamine as basic auxiliaries to facilitate the addition of the electrophilic acyl residue after proton abstraction.[26]



Scheme 1. Reagents and conditions for compounds **3a–f**, **4a–d** and **5a–d**: (a) HAc, rt; (b) Ac_2, DMAP, Et_3N, CH_2Cl_2, rt.

All compounds **3–5** have been evaluated as novel antibacterial agents against different *S. aureus* variants, including *S. aureus* strain ATCC 25923, MRSA standard ATC 43300 and a clinical MRSA isolate. The minimal inhibitory concentration (MIC) for the antibacterial in vitro growth has been determined for each compound. The MIC value is defined as the lowest concentration which completely inhibits a visible bacterial growth.[27]

We started with the cycloalkane indoles **3a**, **3d**, **4a** and **4d** to investigate the influence of the increasing alkyl ring size on the antibacterial activity. The cyclopentane indole **3a** showed a residual activity against *S. aureus* with a MIC value of 50 μg/mL (Table 1). However, improved activity was found against both MRSA variants, the MRSA standard and the MRSA isolate with a MIC value of 12.5 μg/mL. Sultamicillin and ampicillin were used as standards for comparison of the MRSA activity. Both compounds were less effective than compound **3a**.

Surprisingly, the cyclohexane indole **3d** exhibited main increases in activity with a MIC value of 3.125 μg/mL against both *S. aureus* and the MRSA standard. The activity against the MRSA isolate with a MIC value of 6.25 also increased. The cycloheptane indole **4a** with a further methylene group within the cycloalkyl chain showed the same strong activity against *S. aureus* with a MIC value of 3.125 μg/mL. However, the activities against the MRSA variants were little lowered with MIC values of 6.25 μg/mL against the MRSA standard and 12.5 μg/mL against the MRSA isolate. Nevertheless, the compound was much more active against the MRSA standard than sultamicillin or ampicillin. A further elongation of the cycloalkane chain in the cyclooctane indole **4d** had no influence on the activity data with unchanged MIC values of 3.125 μg/mL against *S. aureus*, 6.25 μg/mL against the MRSA standard and, finally, 12.5 μg/mL against the MRSA isolate if compared to those MIC values obtained for the cycloheptane indole **4a**. These results show that the six-membered cycloalkane ring has the optimized size for the antibacterial activity against all *S. aureus* variants. This activity is much stronger than that which was determined for the used standard antibiotics.

We then introduced halogen substituents into the free methylene position of the cyclopentane ring of compound **3a**. This compound showed the comparably lowest activity within our novel antibacterial compound class although it was as active as the used

Table 1
Antibacterial activity data of compounds **3a–f**, **4a–d** and of the acetyl derivatives **5a–d**

	MIC values[a] [μg/mL]		
	S. aureus	MRSA standard	MRSA isolate
3a	50	12.5	12.5
3b	3.125	3.125	6.25
3c	3.125	3.125	6.25
3d	3.125	3.125	6.25
3e	3.125	6.25	12.5
3f	12.5	12.5	12.5
4a	3.125	6.25	12.5
4b	3.125	6.25	6.25
4c	3.125	6.25	12.5
4d	3.125	6.25	12.5
5a	100	100	100
5b	50	50	50
5c	25	12.5	12.5
5d	100	50	50
Sultamicillin	0.78	25	25
Ampicillin	1.56	50	50

[a] All MIC values have been determined in duplicate and were almost identical.