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Antibacterial activity of novel benzopolycyclic amines

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ABSTRACT

Staphylococcus aureus, especially strains resistant to multiple antibiotics, is a major pathogen for humans and animals. In this paper we have synthesized and evaluated the antibacterial activity of a new series of benzopolycyclic amines. Some of them exhibited μM MIC values against *Staphylococcus aureus* and other bacteria, including methicillin-resistant *S. aureus* MRSA. Compound **8** that displayed a good selectivity index, showed to be active in eliminating bacterial cells forming a preexisting biofilm.

1. Introduction

Bacterial infection remains a serious threat to human lives because of its emerging resistance to existing antibiotics, which is an increasing public health problem. The emergence of antibiotic-resistant bacteria has increased the complexity of anti-infective therapies being administrated in hospitals becoming a major health and economic problem. Coagulase-negative staphylococci, *Staphylococcus aureus* or *Pseudomonas aeruginosa* are very often responsible for nosocomial infections. *S. aureus* is a major pathogen that causes numerous syndromes in humans and animals ranging from minor skin and wound infection to life-threatening diseases.[1] *P. aeruginosa* is a known opportunistic common pathogen that causes pneumonia, catheter-associated and urinary tract infections, and sepsis.[2] Thus, the development of new antibacterial agents against *S. aureus* or *P. aeruginosa*, especially strains resistant to multiple antibiotics, has become and urgent health issue.[3–5]

Recently, one of our groups, reported the synthesis and pharmacological evaluation of a series of novel benzopolycyclic compounds of general structures **1** and **2** with NMDA receptor antagonist activity (Fig. 1).[6–8] While performing a random screening for antibacterial activity (Table 1), we found that primary amines **2a** and **2d** displayed reasonable activity against *S. aureus* (MIC_{50} = 17 and 95 μM, respectively). This result led us to perform a deeper study on the antibacterial activity of several related compounds and to evaluate their activity against several bacterial pathogens as well as in a preformed *S. aureus* biofilm in which cells are more resistant to existing antibiotics.

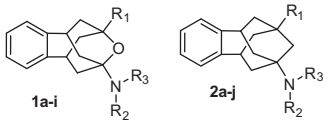

Figure 1. General structures of previously known compounds **1a–i** and **2a–j**.

We have found that either electron-withdrawing or electrodonating groups in the aromatic ring were deletorius for activity, as it was the alkylation of the amino group. Interestingly, replacement of the hydrogen atom in **2a** by a chlorine atom furnished novel compound **8**, with MIC_{50} = 36 μM against *S. aureus* and a better selectivity index than **2a** and **2d**. Compound **8** was further screened against a broader panel of pathogens, including methicillin-resistant *S. aureus MRSA*, *Staphylococcus epidermis*, *Streptococcus mutants*, *Enterococcus faecalis* and *Burkholderia cenocepacea*. The compounds were inactive against *P. aeruginosa*. Interestingly compound **8** showed to be active in eliminating cells forming a preexisting *S. aureus* biofilm.

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Table 1
Known compounds screened for anti-bacterial activity[a]

Compound	R^1	R^2	R^3	MIC_{50}
1a	H	H	H	>1000
1b	H	CH_3	$CH_2C_6H_5$	>1000
1c	H	$CH_2C_6H_5$	$CH_2C_6H_5$	>1000
1d	H	H	$CH_2C_6H_5$	>1000
1e	H	H	NH_2	>1000
1f	H	H	CH_2CCH	>1000
1g	CH_3	H	$COCH_3$	>1000
1h	CH_3	CH_3	CH_3	>1000
1i	CH_3	CH_2CH_3	CH_2CH_3	>1000
2a	H	H	H	17
2b	H	CH_3	CH_3	304
2c	OH	CH_3	CH_3	>1000
2d	F	H	H	95
2e	F	CH_3	CH_3	>1000
2f	CH_3	H	H	>1000
2g	CH_3	CH_3	CH_3	>1000
2h	CH_3	H	$CH_2C_6H_5$	>1000
2i	CH_3	CH_3	$CH_2C_6H_5$	>1000
2j	CH_3	H	CH_2CONH_2	>1000

[a] Compounds were tested against *S. aureus* and *P. aeruginosa*. None of the compounds showed activity against *P. aeruginosa*. The MIC column (μM) refers to *S. aureus* results.

2. Results and discussion

2.1. Synthesis

The target compounds were synthesized according to Scheme 1. Key intermediate **4** was synthesized from the known enone **3**,[9] through a Prins–Ritter transannular cyclization with chloroacetonitrile in the presence of sulfuric acid, as we have recently reported.[8] Previously, we had synthesized fluoroamine **2d** from **4** in 44% overall yield by a two-step sequence that involved cleavage of the chloroacetyl group of **4** using thiourea,[8] followed by substitution of the hydroxyl group by diethylaminosulfur trifluoride (DAST). Now, we have found that **2d** is also available in a much higher overall yield by first performing the DAST reaction to give fluoro derivative **5**, followed by cleavage of the chloroacetyl group with thiourea.

Reaction of **4** in neat thionyl chloride at reflux for 1 h followed by column chromatography furnished **6** in 56% yield. Cleavage of the chloroacetyl group of **6** led to amine **8** in 73% yield. Reductive alkylation of **8** with formaldehyde and $NaBH_3CN$ in acidic media furnished the tertiary amine **11** in 34% yield.

On the other hand, nitration of the aromatic ring of **5** with fuming nitric acid led to **7** in 86% yield. Cleavage of the chloroacetyl group led to nitroamine **9** in 82% yield. Reductive alkylation of **9** as carried out in **8** furnished the tertiary amine **10** in 86% yield. Finally, catalytic hydrogenation of **9** furnished diamine **12** in quantitative yield.

The structure of all new compounds was confirmed by elemental analysis and/or HRMS, IR, ^1H NMR and ^{13}C NMR.

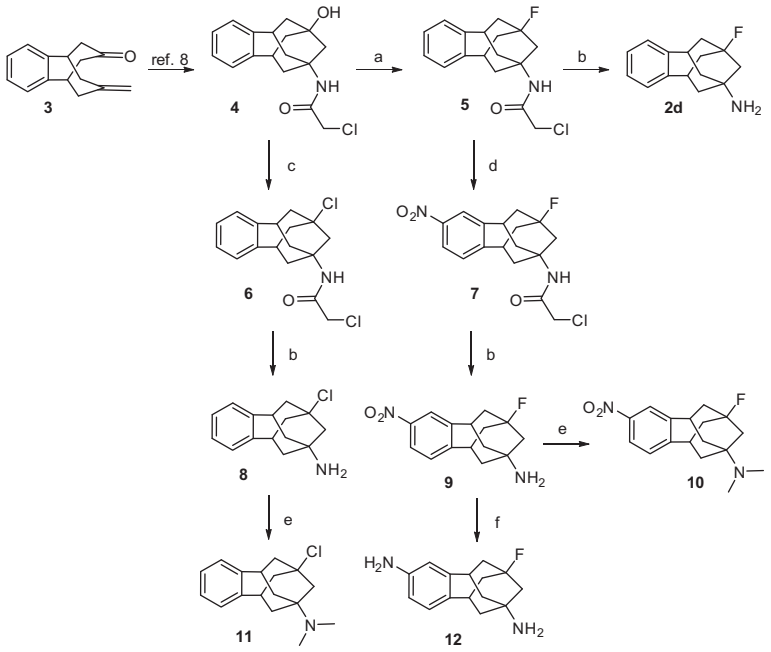
2.2. Antibacterial activity

The antibacterial activity of the different benzopolycyclic amines compounds on planktonic cells of *P. aeruginosa* and *S. aureus* were investigated by determination of MIC_{50} and MIC_{100} values

Table 2
MIC's and cytotoxicity[a]

Compound	*S. aureus* (μM)				*P. aeruginosa* (μM)			
	MIC_{50}	MIC_{100}	CC_{50}	SI	MIC_{50}	MIC_{100}	CC_{50}	SI
2a	17	>39	58.5	3.4			58.5	
2b	304	<625	44.5	0.15	<2500	5000	44.5	
2c	<10000	>10000	>100	—			>100	
2d	95	<312						
8	36	<156	363.2	10.1	1250	>1250	363.2	
9	125	<312						
10	<425	<1250						
11	<625	<1250						
12	<375	<1250						

[a] See experimental for details. MIC_{50} for ciprofloxacin are 0.3 μM and 1.2 μM against *S. aureus* and *P. aeruginosa*, respectively.



Scheme 1. Synthesis of amines **2d** and **8**–**12**. Reagents and conditions: (a) DAST, DCM, −30 °C to 5 °C, 89% yield; (b) thiourea, glacial AcOH, abs ethanol, reflux, 86% for **2d**, 73% for **8**, 82% for **9**; (c) thionyl chloride neat, reflux, 1 h, 56% yield; (d) fuming HNO_3, Ac_2O, AcOH, 0 °C to rt, overnight, 86%; (e) formaldehyde, $NaBH_3CN$, glacial AcOH, methanol, rt, 34% for **11**; 86% for **10**; (f) H_2, 10% Pd/C, methanol, 1 atm, rt, 24 h, quantitative yield.