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Synthesis of linear and cyclic guazatine derivatives endowed with antibacterial activity

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ABSTRACT

Antibiotic resistance has reached alarming levels in many clinically-relevant human pathogens, and there is an increasing clinical need for new antibiotics active on drug-resistant Gram-negative pathogens who rapidly evolve towards pandrug resistance phenotypes. Here, we report on two related classes of guanidinic compounds endowed with antibacterial activity. The two best compounds (**9a** and **13d**) exhibited the most potent antibacterial activity with MIC values ranging 0.12–8 μg/ml with most tested pathogens, including both Gram-positive and Gram-negative bacteria. Interestingly, MIC values were not affected (1–8 μg/ml) when measured using recent clinical isolates with various antibiotic resistance determinants. The results reported herein identify guazatine derivatives as an interesting starting point for the optimization of a potentially novel class of antibacterial agents.

The treatment of bacterial infections caused by multi-drug, extensively-drug or even pan-drug resistant strains is becoming challenging for health care practitioners. The prevalence of drug-resistant isolates has reached alarming levels in many significant human pathogens, among both Gram-negative and Gram-positive pathogens. These are often referred to as 'ESKAPE' organisms, which include *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.[1–5] This term emphasizes that these organisms have the potential to escape most of the available antibacterial therapies. It has been reported that, in U.S.A. hospitals, more people currently die of methicillin-resistant *S. aureus* than of HIV/AIDS and tuberculosis combined.[6–9] Moreover, pandrug-resistant strains are frequently reported emerging in clinically-relevant Gram-negative pathogens, such as *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*, and may represent a dramatic pace forward the return to the pre-antibiotic era.[5,10–12]

Due to both the lack of investment in antibiotic R&D and the increased spread of resistant strains, the therapeutic options are diminishing and might be limited, in some cases, to suboptimal drugs, such as colistin, often burdened by a significant toxicity and severe side effects. As illustrated by the growing concern expressed by many public health agencies and authorities, the need for new therapies and drugs active against resistant strains should be urgently addressed to eventually overcome severe consequences for global Human Health.

Our research group has been involved for years into in-depth studies on linear and cyclic derivatives of guazatine, some of which showed broad-spectrum antifungal properties.[13–18] The potential antibacterial properties of a series of such compounds was evaluated with a panel of different bacteria, including both type strains and clinical isolates (showing various antibiotic susceptibility profile), allowing the identification of some active molecules. A quite large number of compounds bearing guanidine moieties have been reported in the literature as broadly active agents against microbial pathogens, in particular against parasitic fungi.[14,15,19–24] The antibacterial activity of such compounds was not, at our best knowledge, previously evaluated. In this work, compounds from two series were tested on 13 different bacterial species, including some ESKAPE organisms.

Described compounds (Table 1) can be divided in two classes of guazatine derivatives, linear (Scaffold A) and cyclic (Scaffold B). Although the syntheses of these compounds involved some

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common steps, they differs remarkably due to the different reactivity of the intermediates.

The guanylating agents used for each synthesis have been obtained through Mitsunobu reaction between the desired alcohol and the di-Boc-pyrazole-1-carboximidamide (Scheme 1).[25] Compounds **9a–d** and **12a–e** have been described elsewhere.[14,22,24]

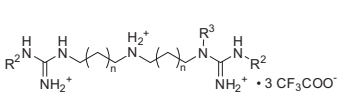
Linear compounds **5a–c** have been obtained following the straightforward protocol described in Scheme 2. Starting material bis(hexamethylene)triamine was subsequently guanylated with the appropriate guanylating agent furnishing, after Boc cleavage, the desired derivatives **5a–c**.

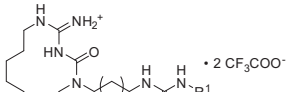
The synthesis of compounds **9a–h**, bearing longer alkyl chains, is reported in Scheme 3 starting from the common intermediates **6a–c** already described in a previous work.[14,21,24]

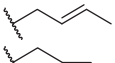
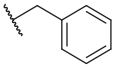
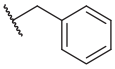
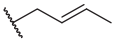
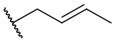
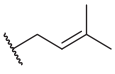
After Cbz deprotection the primary amines **7a–c** were guanylated and Boc-deprotected leading to the desired diguanidines **9a–h**.

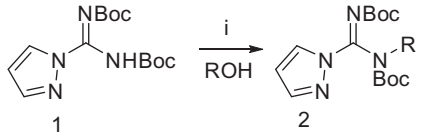
On the other hand, cyclization was obtained as reported in Scheme 4, by refluxing the common intermediate **6** in THF leading

Table 1
Structures of the synthesized compounds

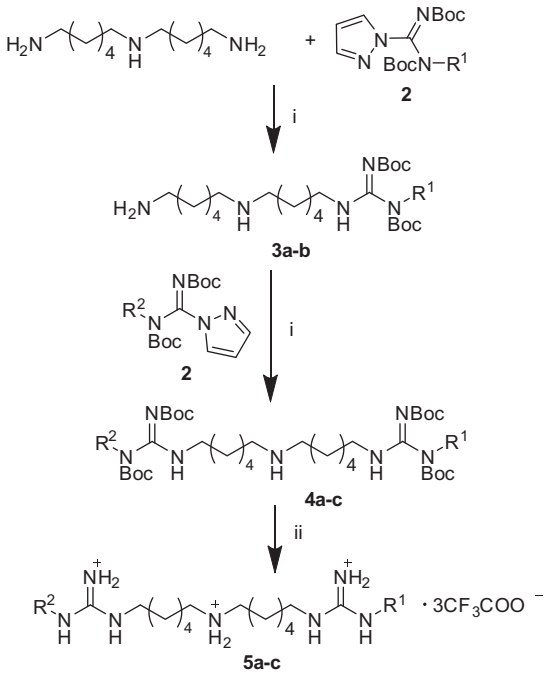




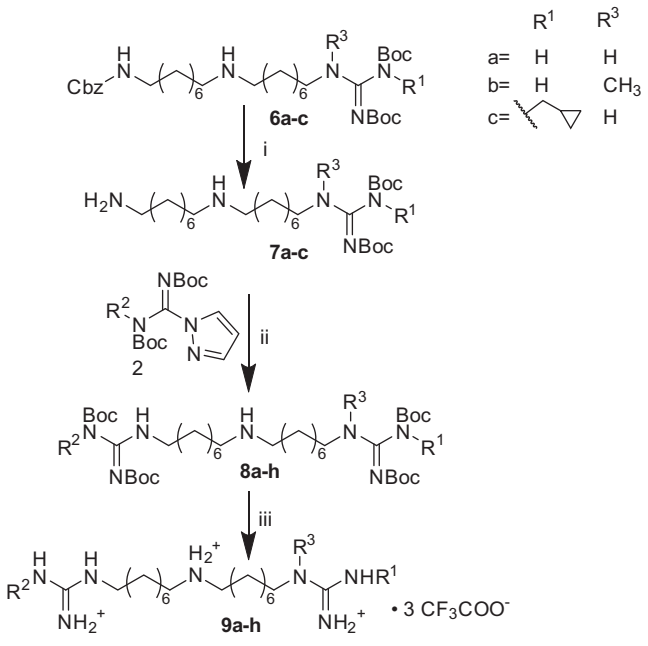
Compd	Scaffold	*n*	R^1	R^2	R^3
5a	A	4		H	H
5b	A	4			H
5c	A	4		H	H
9a[14,22]	A	6		H	H
9b[22]	A	6		H	H
9c[22]	A	6		H	H
9d[22]	A	6		H	H
9e	A	6			H
9f	A	6		H	CH_3
9g	A	6		H	CH_3
9h	A	6		H	CH_3
13a[24]	B	6		H	H
13b[14]	B	6		H	H
13c	B	6		H	H
13d[14]	B	6		H	H
13e[24]	B	6		H	H
13f	B	4		H	H
13g	B	4		H	H
13h	B	4		H	H
13i	B	4		H	H
13j	B	4		H	H



Scheme 1. Synthesis of guanylating compounds **2**. Reagent and conditions: DIAD, PPh_3, THF dry, 0 °C to reflux, 12 h.



Scheme 2. Synthesis of compounds **5a–c**. Reagents and conditions: (i) DIPEA, CH_3CN/MeOH, 50 °C, 12 h, (ii) TFA, DCM, rt, 8 h.



Scheme 3. Synthesis of linear compounds **9a–h**. Reagent and conditions: (i) H_2 Pd/C, 2-propanol, HCl, rt, 5 h; (ii) DIPEA, CH_3CN, 50 °C, 12 h, (iii) TFA, DCM, rt, 8 h.