Synthesis, antibacterial activity and SAR study of novel amidino 2-substituted benzimidazole derivatives

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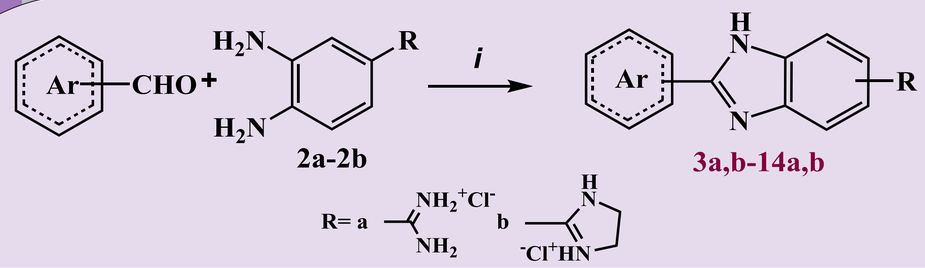
Bacterial organisms causing infectious diseases represent an increasing public health problem regardless of the current availability of numerous antimicrobial agents. *Staphylococcus aureus* represents a major Gram-positive human pathogen while *Moraxella catarrhalis* is establishing its role as an emerging respiratory Gram-negative pathogenic microorganism. A series of novel 2-substituted benzimidazole derivatives were synthesized according to the Scheme 1.



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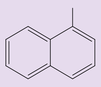
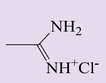
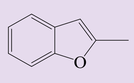
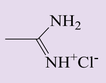
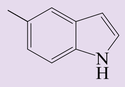
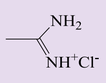
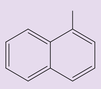
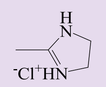
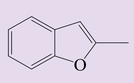
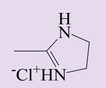
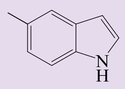
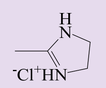
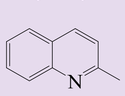
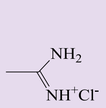
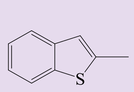
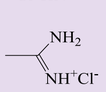
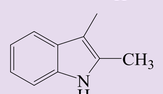
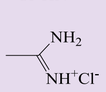
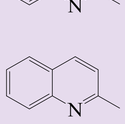
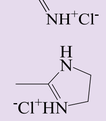
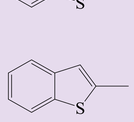
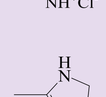
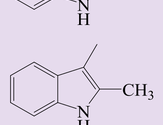
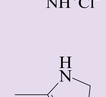
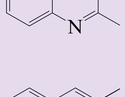
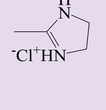
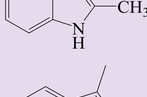
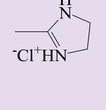
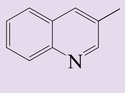
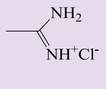
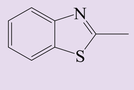
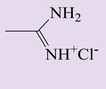
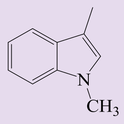
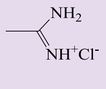
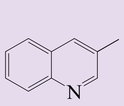
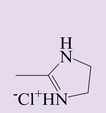
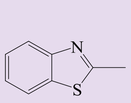
3a			7a			11a		
3b			7b			11b		
4a			8a			12a		
4b			8b			12b		
5a			9a			13a		
5b			9b			13b		
6a			10a			14a		
6b			10b			14b		

The antibacterial activity was assessed against Gram-positive and Gram-negative bacteria. The values of clogP (a partition coefficient) and $clogD_{7.5}$ (calculated distribution coefficient, pH 7.5) were determined and the lipophilic character of compounds has been found to be important parameter for the observed activity of the tested benzimidazole derivatives against *M. catarrhalis*.

Table 1. Antibacterial activity of tested compound

Cpd	cLogP/$logD_{7.5}$*	*MICs (μg/mL)*			
		S. aureus	*E. faecalis*	*E. coli*	*M. catarrhalis*
3a	3.45/1.84	64	32	128	8
3b	3.73/2.15	64	64	128	8
4a	2.7/0.95	64	32	128	8
4b	2.98/1.82	>128	64	128	16
5a	2.56/2.07	128	64	128	4
5b	2.84/1.33	32	32	64	4
6a	2.49/0.73	128	128	>128	8
6b	2.77/1.59	128	>128	>128	16
7a	2.93/1.32	64	32	128	8
7b	3.21/1.62	128	32	128	8
8a	3.4/1.79	32	16	64	2
8b	3.68/2.1	128	32	128	8
9a	3.1/1.36	128	32	8	8
9b	3.38/2.23	64	64	8	8
10a	2.38/1.89	64	64	128	2
10b	2.66/1.11	>128	32	>128	2
11a	2.55/1.03	64	64	>128	4
11b	2.83/1.39	>128	>128	>128	32
12a	2.71/2.21	64	64	>128	4
12b	2.99/1.44	64	64	>128	8
13a	2.36/1.86	16	32	128	2
13b	2.64/1.08	32	32	128	2
14a	2.22/1.73	64	>128	>128	2
14b	2.5/0.96	>128	>128	>128	2
15a	1.27/-0.47	>128	>128	128	32
16a	1.18/0.68	>128	128	64	32
16b	1.46/-0.09	128	128	64	16
Azitromicin	-	4	4	16	0.25

The specific moiety at the 2-position of the benzimidazole was extensively modified with several fused heterocyclic functional groups containing nitrogen and sulphur heteroatoms.

Figure 1. SAR of tested compound

The indolo 2-substituted benzimidazole 13a demonstrated solid activity against *S. aureus* (MICs 16 μg/mL) and *M. catarralis* (MICs 2 μg/mL). Furthermore, the SAR results obtained in this study will be applied for the further optimization of this heteroaromatic core and for the design of novel derivatives in order to improve initially observed antibacterial activity.

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