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Anti-infective Activity of Selected Trifluoromethyl-substituted *N*-Arylcinnamamides

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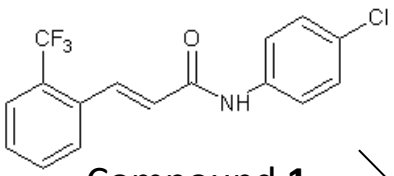
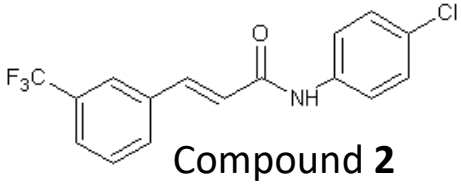
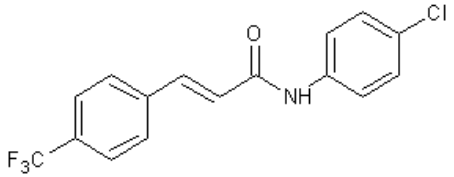
Graphical Abstract



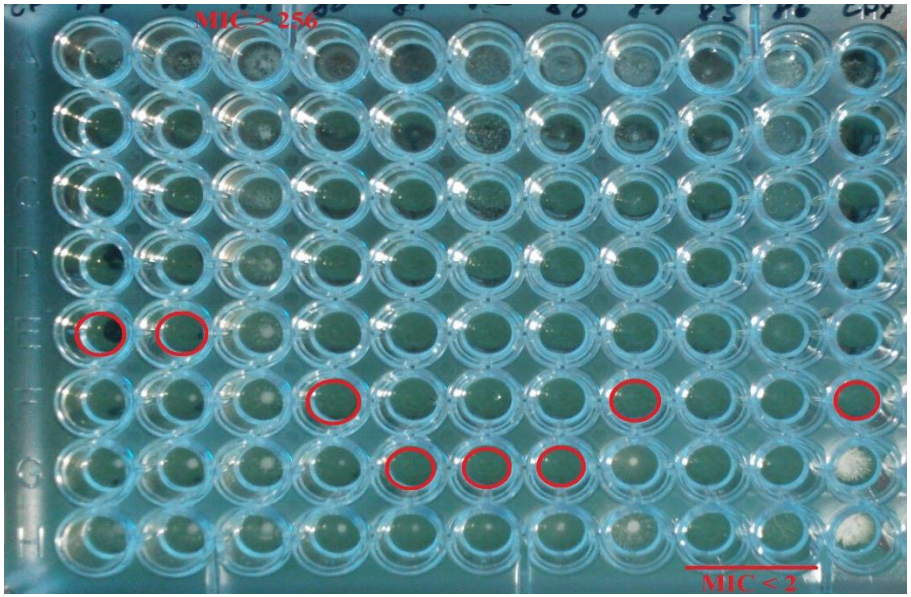
Compound **1**



Compound **2**



Compound **3**



Abstract:

The adaptation of microorganisms to antibiotics is common in all strains. This development of antibiotic resistance is significantly accelerated by the excessive use of antibiotics. One way to fight this severe problem is the research and development of new potentially antimicrobial agents.

Three series of newly synthesized trifluoromethyl-substituted *N*-arylcinnamamides were tested for their anti-infective activity. These series differ in the position of the trifluoromethyl substituent on the phenyl core of the cinnamic acid. All compounds were tested against *Staphylococcus aureus* and its methicillin-resistant forms, *Enterococcus faecalis*, and *Mycobacterium smegmatis*. The activity was determined by the microdilution method for the assessment of minimum inhibitory concentration. For this contribution, one chlorine-substituted compound at position 4 of the anilide ring from each group was selected for activity comparison. The influence of the position of trifluoromethyl is discussed.

Keywords: anti-infective activity; *N*-arylcinnamamides; *Staphylococcus aureus*; MRSA; *Enterococcus faecalis*; *Mycobacterium smegmatis*

Introduction

- Cinnamic acids derivatives are frequently investigated and developed due to their broad spectrum of biological activity.
- Three new series of trifluoromethyl-substituted *N*-arylcinnamamides with different positions of the trifluoromethyl substituent on the phenyl core of cinnamic acid were prepared.
- The anti-infective activity of these structures was tested against reference strain *Staphylococcus aureus* ATCC 29213, three MRSA isolates, reference strain *Enterococcus faecalis* ATCC 29212 and fast growing strain of mycobacteria *Mycobacterium smegmatis* ATCC 700084.
- Antimicrobial effect was assessed by determination of minimum inhibitory concentrations (MICs).
- Microdilution method on a microtiter plate was used for simultaneous testing of multiple substances in multiple concentrations. Ciprofloxacin was used as the reference antibiotic.
- MIC was determined visually as the lowest concentration with no visible bacterial growth.

Results

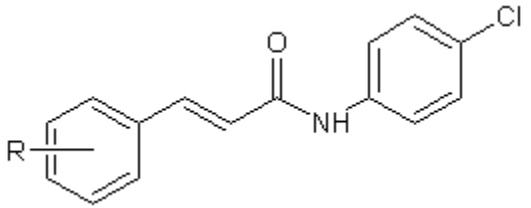


Table 1: Minimum inhibitory concentration (MIC) in µg/mL and µM; *S. aureus* – *Staphylococcus aureus*, MW – molecular weight, CIP - ciprofloxacin

Comp.	MW	R	*S. aureus* ATCC 29213		MRSA 63718		MRSA SA 630		MRSA SA 3202	
			MIC							
			µg/mL	µM	µg/mL	µM	µg/mL	µM	µg/mL	µM
1	325.71	2-CF_3	256	786	256	786	256	786	256	786
2	325.71	3-CF_3	8	24.6	4	12.3	2	6.1	>256	>786
3	325.71	4-CF_3	>256	>786	>256	>786	>256	>786	> 56	>786
CIP	331.35	–	0.25	0.75	8	24	128	386	16	48

Results

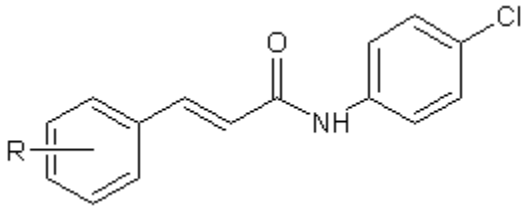


Table 2: Minimum inhibitory concentration (MIC) in µg/mL and µM; *S. aureus* – *Staphylococcus aureus* ATCC 29213, *E. faecalis* – *Enterococcus faecalis* ATCC 29212, *M. smegmatis* – *Mycobacterium smegmatis* ATCC 700084, MW – molecular weight, CIP - ciprofloxacin

Comp.	MW	R	*E. faecalis*		*M. smegmatis*	
			MIC			
			µg/mL	µM	µg/mL	µM
1	325.71	2-CF_3	256	786	64	197
2	325.71	3-CF_3	> 256	> 786	8	24.6
3	325.71	4-CF_3	> 256	> 786	> 256	> 786
CIP	331.35	–	0.5	1.5	0.125	0.38

Discussion

- (2*E*)-*N*-(4-Chlorophenyl)-3-[3-(trifluoromethyl)phenyl]prop-2-enamide (**2**) showed the highest activity against *S. aureus* and MRSA isolates. Only isolate MRSA SA 3202 was not sensitive to any structure. In this case, the *meta*-position carries the antistaphylococcal effect. The changes to the *ortho*-position and *para*-position lead to a significant reduction or total loss of activity.
- None of the tested structures was active against *E. faecalis.*
- In the case of antimycobacterial activity, the relationship between the activity and the position of substitution is very similar to that of staphylococci. Compound **2** with the trifluoromethyl moiety on the phenyl core of the cinnamic acid in *meta*-position demonstrated the highest activity against *M. smegmatis*. The change to the *ortho*-position leads to a decrease of activity, and the change to the *para*-position causes total loss.

Conclusions

- Trifluoromethyl-substituted *N*-arylcinnamamides bring interesting anti-infective activity, especially against *S. aureus,* including MRSA, and *M. smegmatis.*
- (2*E*)-*N*-(4-Chlorophenyl)-3-[3-(trifluoromethyl)phenyl]prop-2-enamide was the most active compound.
- When comparing the position of the trifluoromethyl substituent on the phenyl core of the cinnamic acid, the antistaphylococcal and antimycobacterial activities increase in the order: *para* < *ortho* < *meta*.

Acknowledgments

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