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Antibacterial and Antifungal Activity of Selected Styrylquinoline Derivatives

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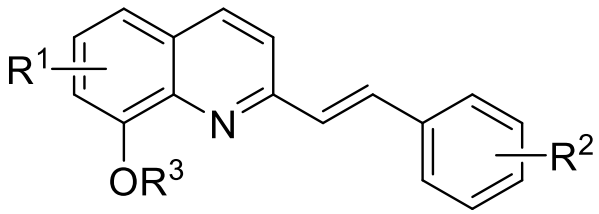
Graphical Abstract



Library (11 compounds)

R^1 = H, 5,7-Cl

R^2 = 2-NO_2, 3-NO_2, 4-NO_2, 2,4-NO_2

R^3 = H, $COCH_3$

Optimal:

R^1 = 5,7-Cl; R^2 = 2,4-NO_2; R^3 = H MIC = 9-78 μM (*S. aureus*, MRSA isolates)

R^1 = H; R^2 = 2-NO_2; R^3 = $COCH_3$ MIC = 12-47 μM (*C. albicans*, *C. krusei*, *C. parapsilosis*)

Abstract:
Although bacterial resistance is commonly known, this problem is not related only to the domain of bacteria. The occurrence of resistant mutants of fungi is also observed. Another problem with some known antifungal drugs is only topical application due to their toxicity or limited bioavailability. Thus, this situation refers to the urgency to design and discover not only antibacterial but also antifungal drugs.
Styrylquinoline derivatives structurally related to dichloroquinoline (e.g., chloroxine) are potential antimicrobial compounds. These derivatives were studied by Cieslik *et al*. recently. Some of these structures expressed antifungal activity comparable with or higher than that of the standard fluconazole. Antibacterial effect, especially against *Staphylococcus* strains, was observed as well. Based on these results, new structures were synthesized and evaluated with respect to their activity, which is presented in this work. New compounds were tested against *Candida* strains for their antifungal effect and against *Staphylococcus* and *Enteroccocus* strains for their antibacterial activity. Antibacterial effects were tested also against methicillin-resistant staphylococci and vancomycin-resistant enterococci.

Keywords: antibacterial activity; antifungal activity; styrylquinoline; *Candida*; *Staphylococcus*

Introduction

Antibacterial resistance is a serious problem which threaten the health of everyone in the world. Infections caused by resistant bacteria occurred formerly only in hospitals and are known as nosocomial infections. These infections are still really dangerous for immunocompromised patients (e.g. AIDS, transplantation, anticancer chemotherapy). Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci belong to the group of the most common causes of nosocomial infections. On the other hand, infections caused by resistant bacterial strains have become more frequent in community nowadays. Thus, the urgency of the problem is increasing[1].

Human fungal infections generally receive less attention than viral or bacterial diseases; however, mortality from invasive fungal infections is very high, often exceeding 50%[2]. *Candida* sp. is one of the most frequent causes of mycoses[2]. Fungi have adapted for commonly used antifungal drugs as well. The development of resistance, high toxicity and limited bioavailability cause a serious problem to find a suitable drug for treatment.

1. Jampilek, J. Design and Discovery of New Antibacterial Agents: Advances, Perspectives, Challenges. *Curr. Med. Chem.* **2018**, *25*, in press, doi: 10.2174/0929867324666170918122633.
2. Jampilek, J. How can we bolster the antifungal drug discovery pipeline? *Future Med. Chem.* **2016**, *8*, 1393-1397.

Styrylquinoline derivatives

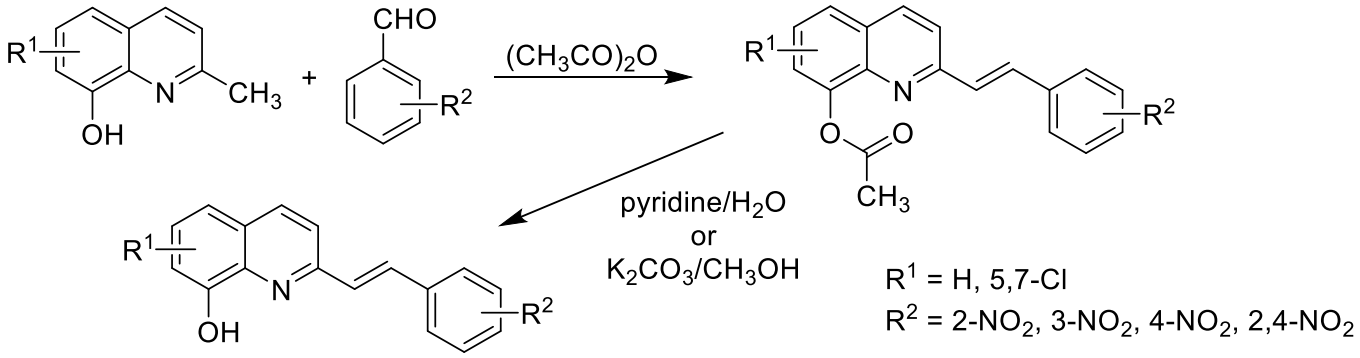
Quinoline moiety seems to be really useful for the design and synthesis of novel antimicrobial agents[3–5]. Researchers supposed that an aromatic quinoline moiety is important for antifungal activity, since its change for quinazoline or 2,4-dioxo-quinoline led to a decrease of activity or complete inactivation[4–6].

Some styrylquinoline derivatives were tested by Cieslik *et al*. This study found that the presence of the hydroxyl moiety in position $C_{(8)}$ of the quinoline ring B significantly increased the antibacterial activity. Subsequent substitution by chlorine in positions $C_{(5)}$ and $C_{(7)}$ was very beneficial as well[7].

3. Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Silva, L.; Kralova, K. Quinaldine derivatives: Preparation and biological activity. *Med. Chem.* **2005**, *1*, 591-599.
4. Musiol, R.; Jampilek, J.; Nycz, J.E.; Peško, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O,Mahony, J.; Coffey, A.; Mrozek, A.; Polanski, J. Investigating the Activity Spectrum for Ring-Substituted 8-Hydroxyquinolines. *Molecules* **2010**, *15*, 288-304.
5. Jampilek, J.; Musiol, R.; Finster, J.; Pesko, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O,Mahony, J.; Coffey, A.; Dohnal, J.; Polanski, J. Investigating biological activity spectrum for novel styrylquinazoline analogues. *Molecules* **2009**, *14*, 4246-4265.
6. Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. Antifungal properties of new series of quinoline derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 3592–3598.
7. Cieslik, W.; Musiol, R.; Nycz, J.; Jampilek, J.; Vejsova, M.; Wolff, M.; Machura, B.; Polanski, J. Contribution to investigation of antimicrobial activity of styrylquinolines. *Bioorg. Med. Chem.* **2012**, *20*, 6960-6968.

Styrylquinoline derivatives – Synthesis

Synthesis of the discussed styrylquinoline derivatives is illustrated in Scheme 1 and described by Musiol et al. [6,8,9]



Scheme 1. Synthesis of ring-substituted styrylquinolines.

6. Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz Maniecka, K.; Oleksyn, B.; Polanski, J. Antifungal properties of new series of quinoline derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 3592–3598.
8. Musiol, R.; Podeszwa, B.; Finster, J.; Niedbala, H.; Polanski, J. An efficient microwave-assisted synthesis of structurally diverse styrylquinolines. *Chem. Mon.* **2006**, *137*, 1211–1217.
9. Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. Investigating biological activity spectrum for novel quinoline analogues. *Bioorg. Med. Chem.* **2007**, *15*, 1280–1288.

Experimental – Method

The series of styrylquinoline derivatives were tested for antimicrobial activity against three MRSA isolates, three VRE isolates and against *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 as reference and quality control strains. The antifungal activity was evaluated against *Candida albicans* CCM 8261*, C. krusei* CCM 8271 and *C. parapsilosis* CCM 8260. Ciprofloxacin and amphotericin B were used as reference antibacterial agents. MICs were determined by the microdilution method. The tested compounds were diluted in microtiter plate to final concentrations from 256 µg/mL to 2 µg/mL for bacteria and from 128 µg/mL to 1 µg/mL for *Candida*. Plates were incubated at 37 °C for 24 and 48 hours. The MIC was defined as the lowest concentration of the compound, at which no visible bacterial growth was observed. At least 3 independent measurements were made within the test, and the results were averaged.

Experimental – Method

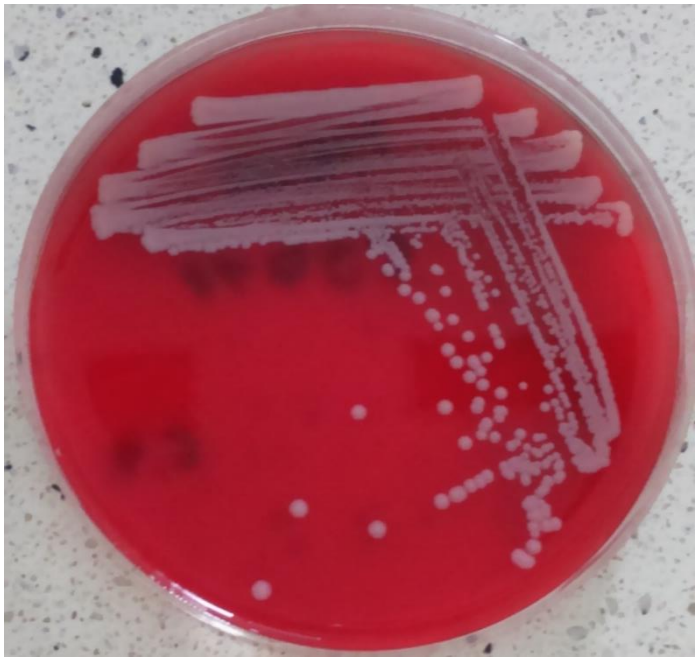


Figure 1: MRSA 63718

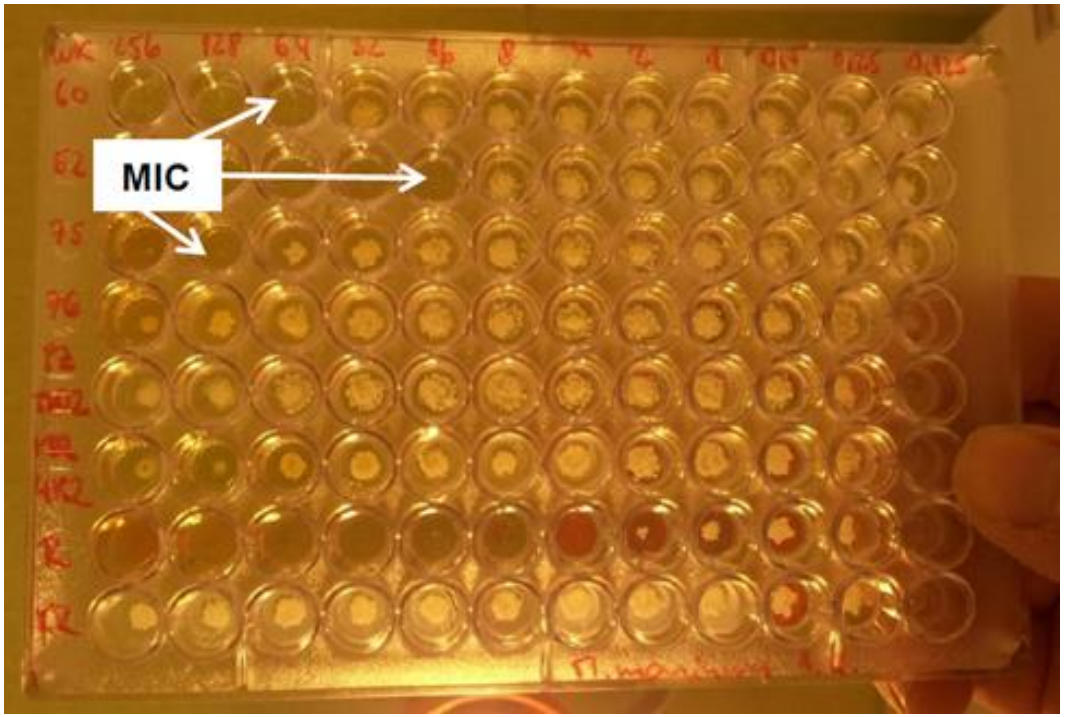
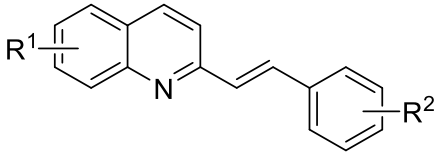


Figure 2: Microtiter plate with highlighted MIC values

Results – Antibacterial activity

Table 1. Structure of ring-substituted styrylquinolines and *in vitro* antibacterial activities (MIC [μM]) in comparison with standard ciprofloxacin (CPX).



Comp.	R^1	R^2	MIC [μM]							
			S.a.	$MRSA_1$	$MRSA_2$	$MRSA_3$	E.f.	VRE_1	VRE_2	VRE_3
1	8-OAc	2-NO_2	>765	5.98	>765	>765	>766	>766	>766	>766
2	8-OH	2-NO_2	438	>875	876	876	>876	>876	>876	>876
3	8-OAc-5,7-Cl	2-NO_2	>634	5.54	354	177	>635	>635	>635	>635
4	8-OH-5,7-Cl	2-NO_2	177	2.48	159	19.8	177	354	>709	>709
5	8-OAc-5,7-Cl	3-NO_2	317	159	317	159	>635	>635	>635	>635
6	8-OH-5,7-Cl	3-NO_2	88.6	88.6	177	177	354	354	>709	>709
7	8-OAc-5,7-Cl	4-NO_2	>634	>634	>634	635	>635	>635	>635	>635
8	8-OH-5,7-Cl	4-NO_2	354	709	709	709	354	354	354	>709
9	8-OAc	2,4-NO_2	>674	>674	>674	>674	675	675	675	>675
10	8-OAc-5,7-Cl	2,4-NO_2	286	>571	571	571	>571	>571	>571	>571
11	8-OH-5,7-Cl	2,4-NO_2	19.70	9.85	78.8	39.4	630	315	>630	630
CPX	–	–	0.75	24.1	386	48.3	3.02	3.02	3.02	193

S.a. – *Staphylococcus aureus* ATCC 29213; $MRSA_1$ – MRSA 63718; $MRSA_2$ – MRSA SA 630; $MRSA_3$ – MRSA SA 3202; E.f. – *Enterococcus faecalis* ATCC 29212; VRE_1 – VRE342B; VRE_2 – VRE368; VRE_3 – VRE725B.

Discussion – Antibacterial activity

In general, the results of the screening with respect to the antibacterial activities (see Table 1) of novel styrylquinoline derivatives confirmed findings about structure-activity relationships of these structures from former studies.

Antistaphyloccocal activity depends on the hydroxyl moiety in position $C_{(8)}$. The activity decreases in case of its acetylation.

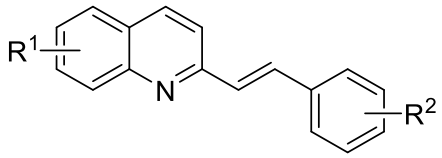
The importance of the substitution by chlorine in $C_{(5)}$ and $C_{(7)}$ positions of the quinoline scaffold was confirmed.

Structures differently substituted by NO_2 were investigated. Higher activity was observed for the monosubstitution of styryl in positions $C_{(2)}'$ and $C_{(3)}'$ than in $C_{(4)}'$. However, 5,7-dichloro-2-[(*E*)-2-(2,4-dinitrophenyl)ethenyl]quinolin-8-ol (**11**) showed high activity against all four staphylococci; thus, it seems that 2,4-NO_2 disubstitution of the styryl moiety significantly increases the activity.

The tested compounds showed only moderate activity or were completely inactive against enterococci. Nevertheless, a higher activity was observed for 5,7-dichloroquinoline-8-ol derivatives.

Results – Antifungal activity

Table 2. Structure of ring-substituted styrylquinolines and *in vitro* antifungal activities (MIC [μM]) in comparison with standard amphotericin B (AMB).



Comp.	R^1	R^2	MIC [μM]		
			C. albicans	*C. krusei*	*C. parapsilosis*
1	8-OAc	2-NO_2	12.0	23.9	47.9
2	8-OH	2-NO_2	438	219	219
3	8-OAc-5,7-Cl	2-NO_2	>317	>317	>317
4	8-OH-5,7-Cl	2-NO_2	44.3	44.3	88.6
5	8-OAc-5,7-Cl	3-NO_2	79.4	159	317
6	8-OH-5,7-Cl	3-NO_2	44.3	88.6	177
7	8-OAc-5,7-Cl	4-NO_2	>317	>317	>317
8	8-OH-5,7-Cl	4-NO_2	177	88.6	88.6
9	8-OAc	2,4-NO_2	>337	>337	>337
10	8-OAc-5,7-Cl	2,4-NO_2	>286	>286	>286
11	8-OH-5,7-Cl	2,4-NO_2	158	158	>315
AMB	–	–	4.33	8.66	4.33

C. albicans – *Candida albicans* CCM 8261; *C. krusei* – *Candida krusei* CCM 8271; *C. parapsilosis* – *Candida parapsilosis* CCM 8260.

Discussion – Antifungal activity

Chlorinated compounds showed only moderate antifungal activity against tested strains of *Candida*.

Similarly as in case of antibacterial effect, the acetylation of 5,7-dichloroquinoline-8-ol derivatives decreased antifungal activity.

2-[(*E*)-2-(2-nitrophenyl)ethenyl]quinolin-8-yl acetate (**1**) was the most potent against fungi, which is in contrast with observations and relationships for antibacterial activity.

Conclusions

New synthesized styrylquinoline derivatives were evaluated for their antibacterial and antifungal activity. Eleven of them were selected, and their results were presented in this contribution.

The highest activity was observed against the tested strains of *Staphyloccocus aureus* including its methicilin-resistant isolates. 5,7-Dichloro-2-[(*E*)-2-(2,4-dinitrophenyl)ethenyl]quinolin-8-ol (**11**) expressed higher activity against MRSA than ciprofloxacin. 5,7-Dichloroquinoline-8-ol derivatives are assumed to be promising antistaphyloccocal agents.

The tested compounds showed only moderate activity or were completely inactive against enterococci.

Only moderate activity was observed against *Candida* sp. Contrary to antibacterial structure-activity relationships, 2-[(*E*)-2-(2-nitrophenyl)ethenyl]quinolin-8-yl acetate (**1**) showed the highest activity against all 3 tested *Candida* species.

Acknowledgments

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