



Design, synthesis, and antibiofilm activity of 2-arylimino-3-aryl-thiazolidine-4-ones

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ABSTRACT

A series of novel 2-arylimino-3-aryl-thiazolidine-4-ones was designed, synthesized and tested for in vitro antibiofilm activity against *Staphylococcus epidermidis*. Among them tested, some compounds with carboxylic acid groups showed good antibiofilm activity. The antibiofilm concentration of **1x** was 6.25 μM. The structure–activity relationships revealed that incorporation of 2-phenylfuran moiety could greatly enhance antibiofilm activity of thiazolidine-4-one.

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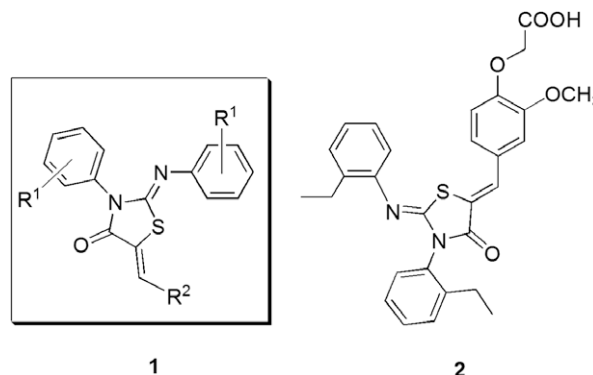
Bacterial infections are now known to predominately exist in a biofilm growth state that confers both enhanced virulence and defensive properties to the bacterium.¹ Bacteria that reside within the biofilm state also are inherently more resistant to many antibiotics and biocides that would often lead to their eradication.^{2,3} Given the breadth of biofilm mediated infections, there is a significant need for new and potent antibiofilm modulators.

Recently, several compounds had been documented which had moderate biofilm inhibitory activities against RP62A,⁴ a strain of the *Staphylococcus epidermidis*. It was also shown that these compounds elicited their effects through inhibition of the YycG histidine kinase, which was an important two-component system (TCS) control protein. All these inhibitors from a variety of structural classes included benzamides, furans, pyrimidinones, and thiazolidiones. Among these inhibitors, a typical compound **2**, which had a thiazolidione core substituted by aromatic ring, showed potent antibiofilm activity, displayed low cytotoxicity on mammalian cells and was not hemolytic. The biofilm inhibitory activity of **2** was even better than that of vancomycin, one of the antibiotics usually used in multidrug-resistant staphylococci associated infections. In this Letter, we presented our further research results on this related compound class, thiazolidione, exemplified by the general structure **1**. (Fig. 1).

According to the interaction model which had been studied by Qin et al.⁴ a four-point pharmacophore could be figured out for describing the binding of the inhibitors: each inhibitor had two hydrogen bond acceptors, hydrogen bonding to Asn503 and

Lys542; the hydrophobic moieties of the inhibitors fit into the two hydrophobic cavities. In our research, a series of 2-arylimino-3-aryl-thiazolidine-4-ones (Table 1) with hydroxyl groups, ester functional and carboxylic acid groups were designed and synthesized to expect their good hydrogen bonding capacity. Moreover, from the literature survey it was revealed that some derivatives of thiazolo[2,3-*b*]dihydropyrimidinone possessing 2-phenylfuran moiety were reported to be potent antibacterial and antifungal activities.⁵ Based on these observations, 2-phenylfuran moiety was introduced into thiazolidione core structure (**11–o** and **1u–x**).

A simple one-pot reaction consisting of aniline or substituted aniline, carbon disulfide, water, and triethanolamine catalysed by Lac Sulfur,⁶ gave 1,3-diarylthiourea (**3–7**) in good yield. Formation



1

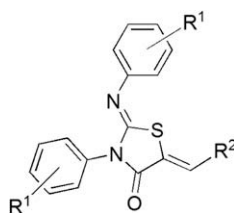
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Figure 1. Thiazolidione core structure.

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Table 1
Anti-bacteria and antibiofilm activities of 2-arylimino-3-aryl-thiazolidine-4-ones



Compound	R ¹	R ²	<i>S. epidermidis</i> RP62A MIC ^a (μM)	<i>S. epidermidis</i> RP62A MBC ^b (μM)	Antibiofilm concentration ^c (μM)
1a	H	4-N(CH ₃) ₂ -Ph-	>200 ^d	>200	>200
1b	H	3-OCH ₃ -4-OH-Ph-	>200	>200	>200
1c	2-CH ₃	4-OH-Ph-	>200	>200	>200
1d	2-CH ₃	3-OCH ₃ -4-OH-Ph-	>200	>200	>200
1e	2-CH ₂ CH ₃	4-OH-Ph-	>200	>200	>200
1f	2-CH ₂ CH ₃	3-OH-Ph-	>200	>200	>200
1g	H	3-OCH ₃ -4-OCH ₂ COOCH ₃ -Ph-	>200	>200	>200
1h	2-CH ₃	4-OCH ₂ COOCH ₃ -Ph-	>200	>200	>200
1i	2-CH ₃	3-OCH ₃ -4-OCH ₂ COOCH ₃ -Ph-	>200	>200	>200
1j	2-CH ₂ CH ₃	4-OCH ₂ COOCH ₃ -Ph-	>200	>200	>200
1k	2-CH ₂ CH ₃	3-OCH ₂ COOCH ₃ -Ph-	>200	>200	>200
1l	2-CH ₃	H ₃ COOC 	>200	>200	>200
1m	2-CH ₂ CH ₃	H ₃ COOC 	>200	>200	>200
1n	4-CH ₃	H ₃ COOC 	>200	>200	>200
1o	4-OCH ₃	H ₃ COOC 	>200	>200	>200
1p	H	3-OCH ₃ -4-OCH ₂ COOH-Ph-	>200	>200	>200
1q	2-CH ₃	4-OCH ₂ COOH-Ph-	>200	>200	>200
1r	2-CH ₃	3-OCH ₃ -4-OCH ₂ COOH-Ph-	>200	>200	>200
1s	2-CH ₂ CH ₃	4-OCH ₂ COOH-Ph-	50	100	100
1t	2-CH ₂ CH ₃	3-OCH ₂ COOH-Ph-	50	100	100
1u	2-CH ₃	HOOC 	12.5	25	25
1v	2-CH ₂ CH ₃	HOOC 	12.5	25	25
1w	4-CH ₃	HOOC 	6.25	25	12.5
1x	4-OCH ₃	HOOC 	6.25	25	6.25
2	2-CH ₂ CH ₃	3-OCH ₃ -4-OCH ₂ COOH-Ph-	50	100	100

^a MIC assays for the antibacterial activities of the compounds were performed according to the broth microdilution (in tubes) method of the Clinical and Laboratory Standards Institute (CLSI) of America.¹⁴

^b MBC of the compounds was obtained by subculturing 100 μl from each negative (no visible bacterial growth) tube from the MIC assay, onto substance-free Mueller–Hinton agar plates. The plates were incubated at 37 °C for 24 h, and the MBC was defined as the lowest concentration of compounds which produced subcultures growing no more than five colonies on each plate.

^c In the antibiofilm concentration experiment, overnight culture of *S. epidermidis* strain RP62A was diluted 1:10 in TSB (OD₆₀₀ = 0.6–0.8), then was diluted 1:200 in MH. The bacterial suspension was inoculated into the wells of sterile 96-well polystyrene microtiter plates (Falcon) incubated at 37 °C for 6 h. The plates with young biofilm were washed gently four times with sterile PBS before adding fresh TSB containing the various concentration compounds, and incubated at 37 °C for 16 h.

^d The initiate dilution was 200 μM.

of thiazolidiones (**8–12**) from the five disubstituted symmetrical thioureas was accomplished in EtOH with chloroacetic acid and NaOAc⁷ (Scheme 1). The 3-(5-formylfuran-2-yl)benzoic acid **13**⁸

was obtained according to the known method, then an esterification of **13** with methanol in the presence of sulfuric acid gave the **14**⁹ (Scheme 2).

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