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New Benzylidenethiazolidinediones as Antibacterial Agents

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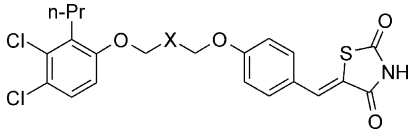
Abstract—A novel benzylidenethiazolidinedione has been discovered with antimicrobial activity. Here, we present the results of a structure–activity study on this compound with respect to its antimicrobial activity.

Wide spread resistance to many commercially available antibiotics is emerging and it is predicted that resistance to these agents will only increase.[1] There are now examples of both Gram-positive and Gram-negative infections which are resistant to all known commercial agents.[2] The discovery of novel antibacterial agents working through an unexploited mechanism of action are less likely to be compromised by pre-existing resistance mechanisms to currently used antibiotics.[3] As part of our effort to identify such new antibiotic agents,[4] we have screened our proprietary compound collection for whole cell activity against *Staphylococcus aureus*. Hits were further profiled to identify compounds with at least a Gram positive spectrum of activity (MIC values <16 μg/mL) with a mechanism of action other than general non-specific cytotoxicity.[5] Compound **1** was identified as meeting our criteria for further study. Herein we present the structure–activity relationships developed around **1**.

Compound **1** was prepared as shown in Scheme 1. The cesium salt of 4-hydroxybenzaldehyde was condensed with (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate to give the corresponding epoxyaldehyde **21**. Compound **21** was then condensed with the cesium salt of phenol **22** to give the secondary alcohol **23**. A Knoevenagel condensation with 2,4-thiazolidinedione then furnished the final compound **1**. The majority of the compounds described herein were prepared in a similar manner. Analogues racemic at the secondary alcohol were prepared using epichlorohydrin instead of (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate. Compound **2** was prepared in a similar manner using (2*S*)-(−)-glycidyl 3-nitrobenzenesulfonate. Using 1,3-dichloropropane in place of (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate gave the des-hydroxy analogue **3**. Ketone **4** was prepared by oxidation of **1** using Dess–Martin periodinane.[6] Reductive amination with ammonia furnished the primary amine **5**.

Table 1. Effect of varying the secondary hydroxyl group on antibacterial activity



Compd	X	MIC[a] (μg/mL)		
		SAUR[b]	EFAE[c]	SPNE[d]
1	(*S*) CH(OH)	2	4	2
2	(*R*) CH(OH)	1	64	1
3	CH_2	>64	>64	>64
4	C(O)	>64	>64	>64
5	(*rac*) $CH(NH_2)$	16	32	2

[a]Minimal inhibitory concentration.
[b]*S. aureus* Oxford.
[c]*E. faecalis* 7.
[d]*S. pneumoniae* ERY2.

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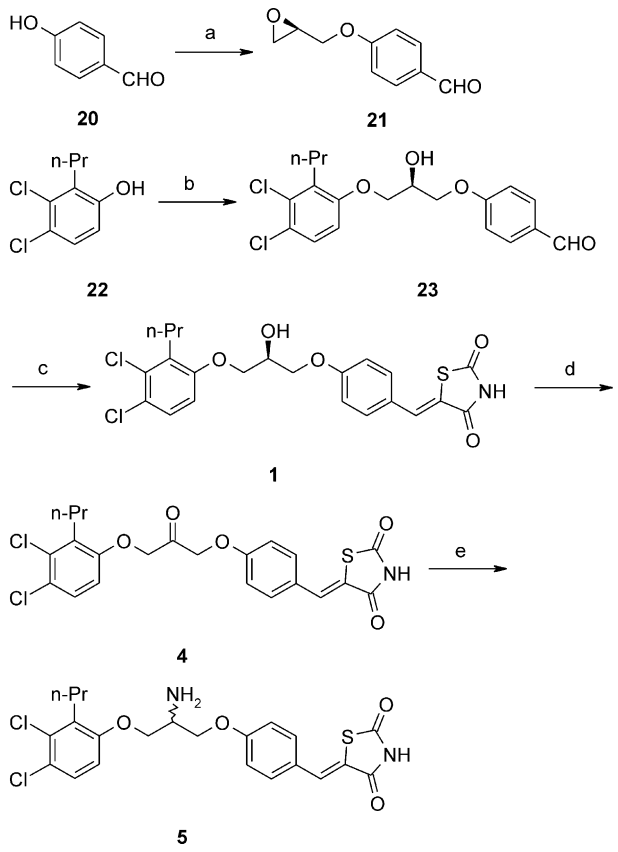
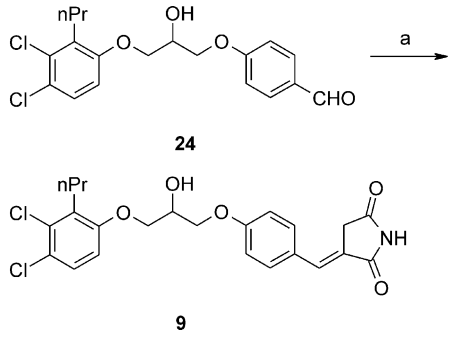


Scheme 1. Preparation of **1**, **4** and **5**: (a) (i) CsF (3 equiv), DMF, rt, 1.5 h; (ii) (2*R*)-(−)-glycidyl 3-nitrobenzenesulfonate (1.02 equiv), rt, 18 h, 86%; (b) (i) CsF (3.1 equiv), DMA, rt, 1.5 h; (ii) 21 (0.7 equiv), DMA, 150 °C, 5 h, 52%; (c) 2,4-thiazolidinedione (1.75 equiv), piperidine (0.3 equiv), benzoic acid (0.2 equiv), toluene, reflux, 5 h, 39%; (d) Dess–Martin reagent, 73%; (e) NH_3, MeOH, $NaCNBH_3$, 49%.



Scheme 2. Preparation of **9**: (a) 3-(triphenyl-l^5-phosphanyl)-pyrrolidine-2,5-dione (1 equiv), MeOH, rt, 16 h, 38%.

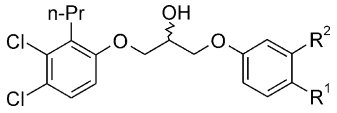
The maleimide moiety of **9** was installed following the method of Paternotte[7] as shown in Scheme 2.

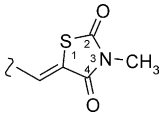
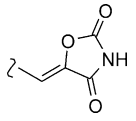
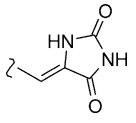
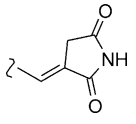
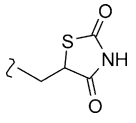
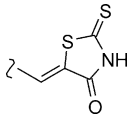
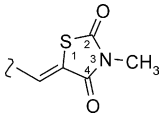
Whole-cell antimicrobial activity was determined by a broth microdilution procedure.[8] Compounds were tested in serial 2-fold dilutions ranging from 0.06 to 64 μg/mL. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth.

Further characterization of the antibacterial activity of **1** revealed this compound to be a Gram-positive agent only. No activity was seen against *Hemophilus influenzae*, *Moraxella catarrhalis* or *Escherichia coli*. The lack of Gram-negative activity does not appear to be due to enhanced efflux of the compound as no antimicrobial activity was observed when 1 was tested in the presence of a potent efflux inhibitor, MC-207,110[9,10] as well as being inactive against *E. coli* AcrAB-. This by no means precludes the possibility that the target of **1** exists in Gram-negative bacteria and that inactivity may simply be due to lack of penetration into these organisms.

While the antibacterial activity against *S. aureus* and *Staphylococcus pneumoniae* was not appreciably affected by changing the absolute steroechemistry of the secondary hydroxyl group (**1** and **2**, Table 1), a 16-fold drop in activity against *Enterococcus faecalis* was seen. This cannot be readily explained at this time. It appears that a proton or hydrogen bond donor is required at this position as the des-hydroxy compound (**3**) and the

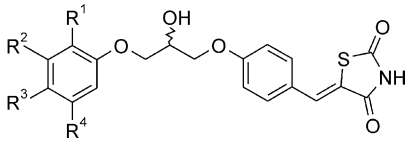
Table 2. Effect on variations around the thiazolidinedione moiety on antibacterial activity



Compd	R^1	R^2	MIC[a]		
			SAUR[b]	EFAE[c]	SPNE[d]
6		H	>64	>64	>64
7		H	16	16	32
8		H	4	4	4
9		H	>64	64	64
10[e]		H	8	16	8
11	H		8	8	4
12		H	8	4	1

[a]Minimal inhibitory concentration.
[b]*S. aureus* Oxford.
[c]*E. faecalis* 7.
[d]*S. pneumoniae* ERY2.
[e]Prepared by catalytic reduction (H_2, 1 atm, 10% Pd/C) of compound **1**.

Table 3. Terminal aryl ring variation and antibacterial activity



Compd	R^1	R^2	R^3	R^4	MIC[a] (μg/mL)		
					SAUR[b]	EFAE[c]	SPNE[d]
13	H	H	H	H	>64	>64	64
14	Me	H	H	H	64	>64	32
15	Et	H	H	H	16	32	16
16	*n*Pr	H	H	H	16	>64	2
17	*n*Pr	H	Cl	Cl	8	8	4
18	H	Cl	Cl	H	>64	>64	>64
19	Cl	Cl	Cl	H	>64	>64	64

[a]Minimal inhibitory concentration.
[b]*S. aureus* Oxford.
[c]*E. faecalis* 7.
[d]*S. pneumoniae* ERY2.

corresponding ketone (**4**) are inactive whereas the amine (**5**) retains Gram-positive antibacterial activity.

Next, we investigated the role of the thiazolidinedione moiety (Table 2). Having an N–H at the 3-position of the five-membered ring is a minimum requirement for activity. Although the thiazolidinedione moiety can be considered as a carboxylic acid isostere,[11–13] no correlation was seen between the calculated pK_a values of this group and antibacterial activity. A heteroatom at the 1-position of the five-membered ring is also needed for antibacterial activity (**9** vs **1**, **7** or **8**). A sulfur or nitrogen atom appears to confer slightly better antibacterial activity than oxygen at this position. There also appears to be improved activity for the benzylidene thiazolidinedione over the benzyl thiazolidinedione and for this group to be located *para* with respect to the ether substituent (**10** and **11**). A carbonyl or thiocarbonyl group at the 2-position is equivalent with respect to antibacterial activity (**1** and **12**).

Finally, the effect of variations on the terminal aromatic ring were examined (Table 3). An alkyl group at R^2 appears to be a minimum requirement for activity with a slight preference for a propyl group (**14**, **15**, and **16**). In addition to the propyl group, chlorination of the ring improves antibacterial activity (**17**), however, chlorination alone is not sufficient for antibiotic activity (**18** and **19**). The antimicrobial activity of this series of compounds appears to be optimized with the combination of functional groups found in **1**.

We have discovered a new series of Gram-positive antibacterial agents. The promising level of antibacterial activity seen with this series of compounds has prompted further investigation into the mode of action of this class of compounds. These studies will be reported in due course.

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