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Novel *N*-chloroheterocyclic antimicrobials

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ABSTRACT

Antimicrobial compounds with broad-spectrum activity and minimal potential for antibiotic resistance are urgently needed. Toward this end, we prepared and investigated a novel series of *N*-chloroheterocycles. Of the compounds examined, the *N*-chloroamine series were found superior over *N*-chloroamide series in regards to exhibiting high antimicrobial activity, low cytotoxicity, and long-term aqueous stability.

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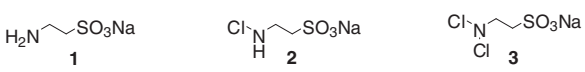
Many antimicrobial compounds used for the prevention or treatment of infections have been rendered less effective through evolved bacterial drug resistance.[1] This has engendered an urgent need for new antimicrobial compounds which display both broad-spectrum activity and reduced potential for development of antibiotic resistance. Here, we present results on a new series of *N*-chloroheterocycles being developed for various topical applications.

N-Chlorotaurine **2** and *N,N*-dichlorotaurine **3** (Scheme 1), which are part of the innate mammalian response to infection, provide an advantageous starting point for novel antibiotic drug development. During the oxidative burst in human granulocytes and monocytes, myeloperoxidase enzyme (MPO; EC 1.11.1.7) produces hypochlorite, which rapidly oxidizes amino acids.[2] Because of the abundance of taurine **1** in white blood cells, the mono-chlorinated **2** and di-chlorinated **3** compounds are produced and utilized by human neutrophils to destroy invading microorganisms to protect the body.[3] Although these compounds have been utilized as effective antimicrobials throughout the evolutionary process, there is no known bacterial resistance to this class of compounds.

Nagl et al. had focused on elucidating the bacterial, fungicidal, and virucidal activity as well as the clinical safety of *N*-chlorotaurine **2**.[4] A major challenge to our efforts has been to extend the aqueous solution half-life of *N*-chlorotaurine **2** under acidic conditions[5] to obtain a product which can be manufactured and stored for extended periods of time. We previously reported that β,β-disubstituted chlorotaurines exhibit improved aqueous stability and maintain desired biological activity.[6] This observation had ultimately led to 2,2-dimethyl-*N,N*-dichlorotaurine, NVC-422, now in phase 2 clinical trials for impetigo. We have evidence that the mechanism of action (MOA) for *N,N*-dichloroamines involves a very rapid inactivation of sulfur-containing proteins.[7] This results in dysfunction or dysregulation, leading to the death of the pathogen; we expect this to be also the case for *N*-chloroheterocycles. In consideration of the probable MOA and the influence of structure on the physiochemical properties of *N*-chloramines, we examined a new generation of related compounds which may provide new clinical candidates for various topical applications including uncomplicated skin and soft tissue infections, onychomycosis, and impetigo.



Scheme 1. Taurine, *N*-chlorotaurine, and *N,N*-dichlorotaurine.

Here, we report the synthesis and structure activity/stability relationships of novel five- and six-membered *N*-chloroheterocycles, expanding on what we learned in the *N,N*-dichloroamine series.[8] Although limited studies on *N*-chloroheterocyclics have been reported[9,10] our work encompasses a systematic effort to incorporate important pharmaceutical properties such as aqueous solubility, long-term solution stability, potent and rapid antimicrobial activity, and improved safety.

We initially looked at *N*-chlorohydantoins, since they have found applications in biocidal coatings;[11] however, their suitability for human therapeutics required chemical modifications to obtain better 'drug-like' properties. In this series (**6**–**11** and **15**), the amide nitrogen is chlorinated and the water solubilizing group, R, is linked to the imide nitrogen or the ring's 5-position. Scheme 2 outlines the synthesis of a variety of water soluble *N*-chlorohydantoins, synthesized from dimethylhydantoin **4**. The hydantoin was

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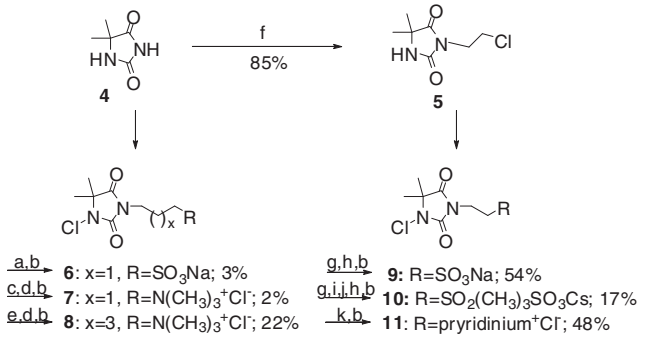
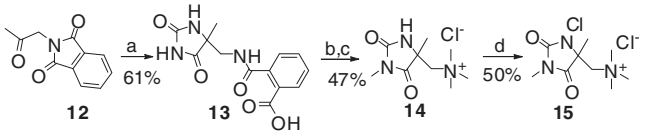


Scheme 2. Reagents and conditions: (a) NaH, DMF, rt, 1 h followed by; propane sultone, rt, 18 h; (b) *t*-BuOCl, MeOH, 0 °C, 1 h; (c) NaH, DMF, rt, 1 h; $BrCH_2CH_2CH_2N(CH_3)_3{}^+Br^-$, rt, 18 h; (d) (i) Ag_2O, water, rt 30 min, (ii) HCl, water, rt, 30 min; (e) NaH, DMF, rt, 1 h followed by $BrCH_2(CH_2)_3CH_2N(CH_3)_3{}^+Br^-$, rt, 18 h; (f) $BrCH_2CH_2Cl$, NaOH, EtOH, reflux, 18 h; (g) KSAc, DMF, 70 °C, 18 h; (h) H_2O_2, HCO_2H, 4 °C, 4 h; (i) NaOH, MeOH, 0 °C to rt, 18 h; (j) propane sultone, Cs_2CO_3 DMF, rt, 18 h; (k) pyridine, 18 h, 90 °C.



Scheme 3. Reagents and conditions: (a) $(NH_4)_2CO_3$, KCN, ethanol, 75 °C, 18 h; (b) HCl, water, 100 °C, 18 h; (c) (1) MeI, Cs_2CO_3, methanol, rt, 72 h; then HCl, water; (d) *t*-BuOCl, MeOH, 5 °C, 2 h.

deprotonated with NaH and reacted with propane sultone, followed by N-chlorination with *t*-butyl hypochlorite, to give sulfonic acid **6**. Compounds **7** and **8** were synthesized by alkylation of the hydantoin with the appropriate bromoalkylammonium salt, followed by halogen exchange with silver oxide and hydrogen chloride, and N-chlorination with *t*-butyl hypochlorite.

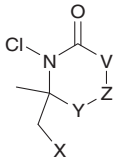
Other hydantoin analogs (**9–11**) were synthesized from the chloride intermediate **5**, obtained by alkylation of hydantoin **4** with 1,2-bromochloroethane. Substitution of the chloride with potassium thioacetate, oxidation to the sulfonate, and N-chlorination gave the ethylsulfonate analog **9**. Displacement of the chloride in **5** with potassium thioacetate, de-S-acetylation with sodium hydroxide, S-alkylation with propane sultone, oxidation to the sulfonate, and N-chlorination gave **10**. Compound **11** was obtained by reaction of **5** with pyridine, followed by N-chlorination.

Synthesis of the trimethylammonium salt **15** (Scheme 3) required a different synthetic approach. *N*-Acetonylphthalimide **12** was treated with ammonium carbonate and potassium cyanide to give intermediate **13**. The amide of the intermediate was hydrolyzed, and the product was N-methylated to give the trimethylammonium chloride **14**. Treatment of **14** with *t*-butyl hypochlorite gave the desired *N*-chlorinated hydantoin **15**. Hydantoins (**6–11** and **15**) in Table 1 exhibited moderate antibacterial activity, but generally lacked antifungal activity.

From the hydantoin results in Table 1, it can be seen that the sulfonate substitution affords compounds with improved solution stability compared to the quaternary ammonium substituted analogs, cf. 9 and **6** versus **7** and **8**. Additionally, longer chain lengths between the hydantoin and the charged water-solubilizing group improved antibacterial activity but lowered antifungal activity, cf. **9** versus **6**.

To examine the effect of expanding the size of the ring, two piperazinediones and an oxazinan-2-one were synthesized (Scheme 4). For the piperazinediones, 2-aminoisobutyric acid methyl ester **16** was acylated with 2-chloroacetyl chloride and the adduct was reacted with ethanol amine at elevated temperatures to give the cyclized 2,5-diketopiperazine intermediate **17**. The alcohol **17** was converted to a sulfonic acid by reaction with thioacetic acid under Mitsunobu reaction conditions, followed by oxidation with hydrogen peroxide in formic acid. N-chlorination gives the desired product **18**. Alternatively, intermediate **17** was directly N-chlorinated to give **19**. For the oxazinan-2-one, carboxylic acid **20**[8] was reacted with CDI followed by (2-ethoxy-2-oxoethyl)lithium, to give a keto-ester. Reduction with sodium borohydride gave diol **21**. Treatment of the diol with sodium hydride effected cyclization to provide the thermodynamically

Table 1
Heterocyclic *N*-chloramides

Compound					MBC or MFC (μg/mL) [a]			$t_{½}$ (days at 40 °C)	CT_{50} (mM)
	V	X	Y	Z	*Escherichia coli* [b]	*Staphylococcus aureus* [b]	*Candida albicans* [b]		
9	––	H	C=O	N–$CH_2CH_2SO_3Na$	128	128	128	65	0.7
6	––	H	C=O	N–$CH_2CH_2CH_2SO_3Na$	16	32	>256	>14	0.4
7	––	H	C=O	N-$CH_2CH_2N(CH_3)_3{}^+Cl^-$	128	>128	>1024	4	––
8	––	H	C=O	N-$CH_2CH_2CH_2CH_2CH_2N(CH_3)_3{}^+Cl^-$	128	128	>1024	22	0.6
11	––	H	C=O	N–CH_2CH_2(*N*-pyridinium)$^+$	––	––	––	4	––
10	––	H	C=O	N-$CH_2CH_2SO_2CH_2CH_2CH_2SO_3{}^-Cs$	256	>256	>256	>7	0.4
15	––	$N^+(CH_3)_3$	C=O	N–CH_3	16	64	>256	5	––
18	CH_2	H	C=O	N–$CH_2CH_2SO_3Na$	128	128	>256	90	1.3
19	CH_2	H	C=O	N–CH_2CH_2OH	––	––	––	< 1	––
22	O	H	CH_2	CH–CH_2CH_2OH	––	––	––	> 14	––
28	––	H	CH_2	N–$CH_2CH_2SO_3Na$	32	64	>256	>92	4.3
30	––	H	CH_2	N-$CH_2CH_2SO_2CH_2CH_2CH_2(SO)_3{}^-Cs$	64	32	––	>112	3.2
33	––	H	CH_2	N-$CH_2CH_2N(CH_3)_3{}^+Cl^-$	512	128	––	126	0.5
37	––	OH	CH_2	N–CH_3	16	16	8	>58	0.3

[a] Minimum Bactericidal Concentration (MBC) was determined using a modified standard method described in CLSI M26-A whereby isotonic buffered saline at pH 4 is substituted for Mueller–Hinton broth (MHB) to compensate for the reactivity of chlorine to certain components of MHB. Due to the rapid cidal nature of chlorinated derivatives, the assay was shortened from 24 h at 35 °C to 1 h at room temperature.

[b] *E. coli* ATCC 25922, *S. aureus* ATCC 29213, *C. albicans* ATCC 10231.

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