Bioorganic & Medicinal Chemistry Letters 21 (2011) 3029–3033

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel *N*-chloroheterocyclic antimicrobials

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ARTICLE INFO

Article history:
Received 13 January 2011
Accepted 10 March 2011
Available online 16 March 2011

Keywords:
N-Chloroheterocyclic
Antimicrobials
Broad-spectrum

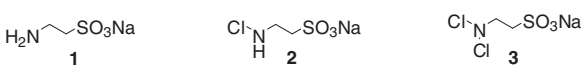
ABSTRACT

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.

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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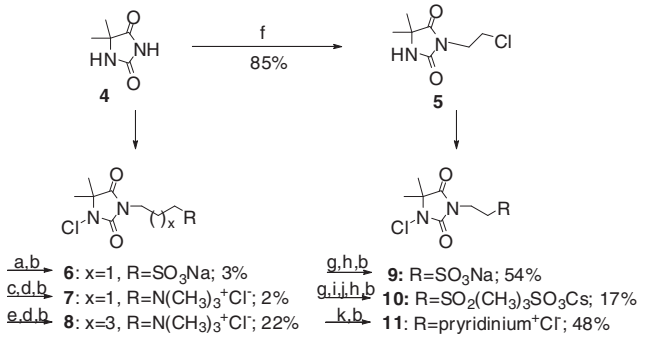
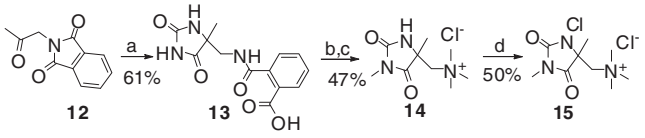
doi:10.1016/j.bmcl.2011.03.035



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.

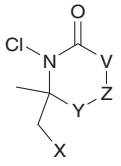
Other hydantoin analogs (**9–11**) were synthesized from the chloride intermediate **5**, obtained by alkylation of hydantoin **4** with 1,2-bromochloroethane. Substitution of the chloride with potassium thioacetate, oxidation to the sulfonate, and N-chlorination gave the ethylsulfonate analog **9**. 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**.

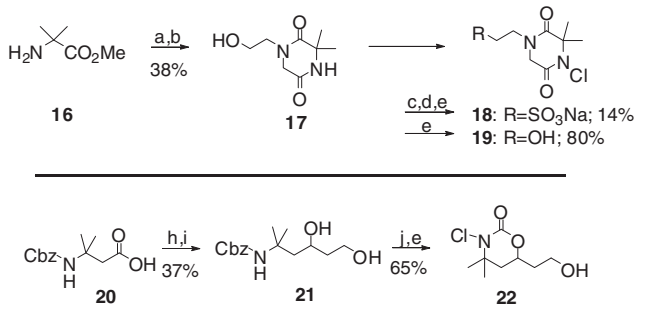
To examine the effect of expanding the size of the ring, two piperazinediones and an oxazinan-2-one were synthesized (Scheme 4). For the piperazinediones, 2-aminoisobutyric acid methyl ester **16** was acylated with 2-chloroacetyl chloride and the adduct was reacted with ethanol amine at elevated temperatures 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

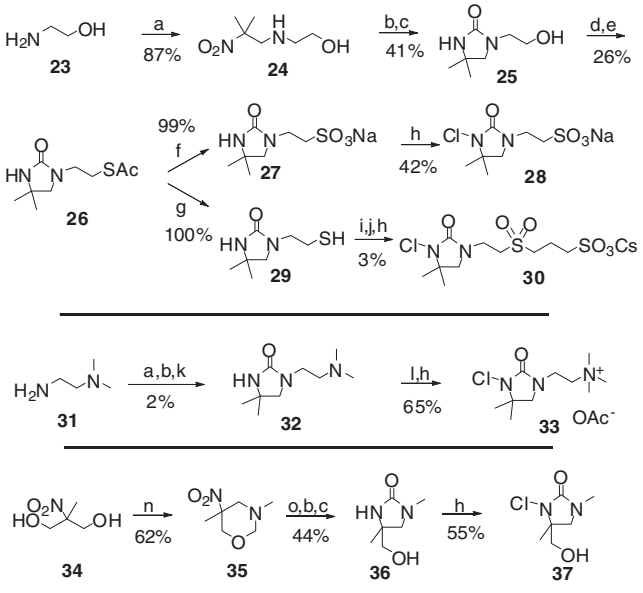
Compound					MBC or MFC (μg/mL) [a]			$t_{½}$ (days at 40 °C)	CT_{50} (mM)
	V	X	Y	Z	*Escherichia coli* [b]	*Staphylococcus aureus* [b]	*Candida albicans* [b]		
9	––	H	C=O	N–$CH_2CH_2SO_3Na$	128	128	128	65	0.7
6	––	H	C=O	N–$CH_2CH_2CH_2SO_3Na$	16	32	>256	>14	0.4
7	––	H	C=O	N-$CH_2CH_2N(CH_3)_3{}^+Cl^-$	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.



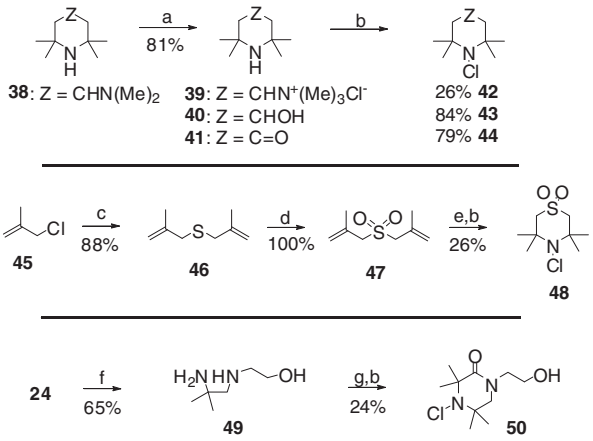
Scheme 4. Reagents and conditions: (a) $ClCH_2COCl$, EtOAc, H_2O, rt 2 h; (b) ethanolamine, THF; EtOH 140 °C, 18 h; (c) DIAD, $P(Ph)_3$, AcSH, 0 °C to rt, 26 h; (d) HCO_2H, H_2O_2, rt, 6 h; (e) *t*-BuOCl, MeOH, 0 °C to rt, 30 min to 2 h; (h) CDI, THF, rt 1 h; followed by $LiCH_2CO_2Et$, −78 °C, 2 h; (i) $NaBH_4$, EtOH, rt, 3 h; (j) NaH, THF, rt, 4 h.



Scheme 5. Reagents and conditions: (a) *i*-PrOH, CH_2O, water, $NO_2CH(CH_3)_2$, NaOH, rt, 24 h; (b) Raney Nickel®, MeOH, H_2, rt, 18 h; (c) urea, 200 °C, 1 h; (d) MsCl, pyridine, DCM, rt, 24 h; (e) KSAc, DMF, rt, 18 h; (f) H_2O_2, HCO_2H, 0 °C to rt, 16 h; (g) NaOH, MeOH, water, 0 °C to rt, 18 h; (h) *t*-BuOCl, MeOH, 0 °C, 1 h; (i) propane sultone, Cs_2CO_3, DMF, rt, 18 h; (j) *m*-CPBA, DCM, rt, 21 h; (k) CDI, DCM, rt, 20 h; (l) MeI, MeOH, rt, 18 h; (m) Ag_2O, water, AcOH, rt, 2 h; (n) CH_2O, water, CH_3NH_2; (o) HCl, EtOH, reflux, 5 h.

favored oxazinan-2-one, which was N-chlorinated to give **22**. Examination of **9** versus **18** in Table 1 reveals that ring expansion has little effect on either antifungal or antibacterial activity. It is noteworthy that the sulfonate derivative **18** possesses a profoundly greater solution stability than its alcohol counterpart **19**.

To obtain a broader therapeutic index (assessed by the in vitro CT_{50} vs antimicrobial activity) of the *N*-chloro hydantoin derivatives, we replaced one of the hydantoin carbonyls with a methylene group to afford imidazolidin-2-ones. In this series (**28**, **30**, **33**, and **37**), chlorine was bonded to the 3-position nitrogen (adjacent to the dimethylmethylene group), and the water solubilizing group was linked to either the 1-position nitrogen or the dimethylmethylene group. These heterocyclic compounds were synthesized by the series of reactions as shown in Scheme 5. Amino ethanol **23** was reacted with 2-nitropropane in a nitro-Mannich reaction to give nitro compound **24**. Synthesis of **25** was accomplished by hydrogenation of the nitro group, followed by cyclization with urea. The reaction of **25** with methanesulfonyl chloride, and displacement of the resulting mesylate with potassium thioacetate, gave thioacetate **26**. The desired *N*-chloroamine **28** was obtained by oxidation of thioacetate **36** with hydrogen peroxide in acetic acid to the sulfonate **27**, followed by N-chlorination. Similarly, compound **30** was prepared from **26** by a reaction sequence consisting of saponification, S-alkylation, oxidation to the sulfone, and N-chlorination. Imidazolidinone **32** was synthesized from **31** by a similar route used to obtain **25** from **23**. Methylation and N-chlorination of **32** provided **33**. Reaction of the diol **34** with formaldehyde under Mannich reaction conditions gave the 1,3-oxazinane intermediate **35**.[12] Acid-promoted ring opening of **35**, followed by hydrogenation, and cyclization yielded the desired 2-imidazolidinone intermediate **36**. Compound **37** was obtained after treatment of imidazolidinone **36** with *t*-butyl hypochlorite.



Scheme 6. Reagents and conditions: (a) (i) MeI, DCM, 0 °C, 30 min, (ii) Ag_2O, water, rt, 30 min, (iii) HCl, water, rt, 5 min; (b) *t*-BuOCl, MeOH, 0 °C, 1 h; (c) Na_2S, H_2O, MeOH, rt to reflux, 8 h; (d) *m*-CPBA, DCM, 0 °C, 45 min; (e) NH_4OH, 60–100 °C, 22 h; (f) Raney Nickel®, methanol, H_2, rt, 18 h; (g) acetone, $CHCl_3$, NaOH, rt to reflux, 19 h.

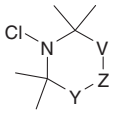
The *N*-chloroimidazolidin-2-ones (**28**, **30**, **33**, and **37**) showed improved antibacterial activity over analogously functionalized hydantoin compounds (cf. **28** vs **9**, **30** vs **10**) with significantly reduced cytotoxicity (Table 1). In addition, this series showed increased aqueous stability at 40 °C. However, the antibacterial and antifungal activities were below our expectations and further studies are planned to improve the efficacy of these compounds.

At this point, all of the *N*-chloroheterocycles have been cyclic *N*-chloroamides. From our previous work, we felt that heterocyclic derivatives which contain the *N*-chloroamine functionality may exhibit improved stability and antimicrobial activity. Thus, we prepared the six-membered, *N*-chloroheterocycles derived from piperidine (**42**–**44**), thiomorpholine (**48**) and piperazine (**50** and **54**) scaffolds. These were constructed through acyclic version of our successful route to *N*-chlorotaurine.

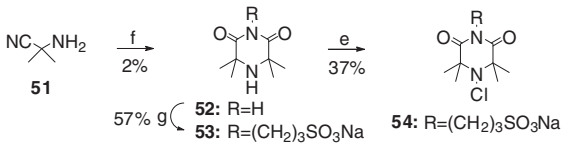
Initially, 2,2,6,6-tetramethylpiperidine was examined (Scheme 6). Dimethylamine **38** was alkylated with methyl iodide, and the iodide was exchanged with chloride ion to give ammonium salt **39**. The N-chlorination of **39** and two other commercially available compounds (**40** and **41**) gave **42**, **43**, and **44**, respectively. Reaction of sodium sulfide with 3-chloro-2-methylprop-1-ene **45**, followed by oxidation gave intermediate **47**. Cyclization and N-chlorination of the intermediate gave **48**. Compound **50** was obtained by hydrogenation, a Bargellini-type reaction,[13] and N-chlorination of intermediate **24**. Although the 2,2,6,6-tetramethylpiperidine analogs did display acceptable biological activity, the solution stability and the CT_{50} values were disappointing (Table 2).

Piperazinedione **52** (Scheme 7) was obtained by treatment of 2-amino-2-methylpropanenitrile **51** with ammonium hydroxide and ammonium chloride at reflux temperature.[14] The N-alkylation

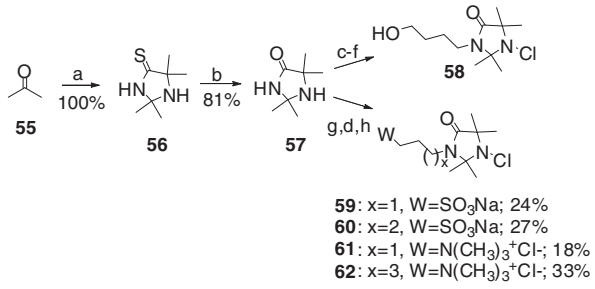
Table 2
Heterocyclic *N*-chloramines

Compound				MBC or MFC (μg/mL) [a]			$t_{½}$ (days at 40 °C)	CT_{50} (mM)
	V	Y	Z	*E. coli* [b]	*S. aureus* [b]	*C. albicans* [b]		
42	CH_2	CH_2	$CHN(CH_3)_3{}^+Cl^-$	16	8	256	28	1.8
43	CH_2	CH_2	CHOH	1	4	32	32	0.2
44	CH_2	CH_2	C=O	1	2	32	<1	0.04
48	CH_2	CH_2	SO_2	2	1	128	>113	0.1
50	CH_2	C=O	N-CH_2CH_2OH	1	2	8	––	0.1
54	C=O	C=O	N-$CH_2CH_2SO_3Na$	128	128	>256	90	1.3
58	––	C=O	N-$CH_2CH_2CH_2CH_2OH$	2	2	256	>92	2.2
59	––	C=O	N-$CH_2CH_2CH_2SO_3Na$	4	16	16	>249	14.5
60	––	C=O	N-$CH_2CH_2CH_2CH_2SO_3Na$	16	8	32	>84	23.5
61	––	C=O	N-$CH_2CH_2CH_2N(CH_3)_3{}^+Cl^-$	4	2	32	111	8.3
62	––	C=O	N-$CH_2CH_2CH_2CH_2CH_2N(CH_3)_3{}^+Cl^-$	2	2	16	>160	9.1

[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.



Scheme 7. Reagents and conditions: (e) *t*-BuOCl, MeOH, 0 °C to rt, 30 min to 2 h; (f) NH_4OH, NH_4Cl, reflux, 7 h; (g) NaH, DMF, $Br(CH_2)_3SO_3Na$, rt, 20 h.



Scheme 8. Reagents and conditions: (a) NaCN, $S(NH_4)_2$, NH_4Cl, water, 60 °C, 8 h; (b) NaOH, H_2O_2, water, 4 °C, 4 h; (c) NaH, DMF, rt, 1 h followed by $BnOCH_2(CH_2)_2CH_2Br$, DMF, rt, 18 h, 90%; (d) Ag_2O, water, rt, 1 h followed by HCl, water, 93–98%; (e) 10% Pd/C, EtOH, H_2, rt, 48 h, 26%; (f) *t*-BuOCl, MeOH, 0 °C, 1 h, 30%; (g) NaH, DMF, rt, 1 h followed by $WCH_2(CH_2)_xCH_2Br$, DMF, rt, 18 h; (f) *t*-BuOCl, MeOH, 0 °C, 1 h.

of intermediate **52** with 3-bromopropane-1-sulfonic acid sodium salt followed by N-chlorination gave the desired *N*-chloropiperazine-2,6-dione **54** (Scheme 7).

These six-membered *N*-chloroamine heterocycles typically had good antibacterial activity. This was a significant improvement over both 5- and six-membered *N*-chloroamide heterocycles. However, they lacked the level of solution stability which we were seeking for topical antimicrobial applications. Since we were quite impressed by the antibacterial and antifungal activity of **50**, we decided to synthesize the 5-membered derivative, imidazolidin-4-one.

In this series, (**58**–**62**), we investigated 5-membered, *N*-chloroamine heterocycles, where the water solublizing group was linked to the amide nitrogen. The synthesis of *N*-chloroimidazolidin-4-ones derivatives was initiated with the common intermediate **57**, readily prepared from acetone using a two step procedure (Scheme 8).[15] Alkylation was accomplished through the removal of the amide proton with sodium hydride followed by treatment with an alkyl bromide. Compound **58** was prepared by alkylation of **57** with benzyl 4-bromobutyl ether, halogen exchange, hydrogenation, and N-chlorination. Compounds (**59–62**) were obtained by alkylation of **57** with the appropriate alkyl halide, halogen exchange, and N-chlorination. All of the imidazolidin-4-ones exhibited significant improvements over both the hydantoins (**6**–**11**, and **15**) and the 2-imidazolidinones (**28**, **30**, **33**, and **37**). Both antibacterial and antifungal activities were improved as shown by the MBC and MFC values. These molecules displayed excellent aqueous solution stability at elevated temperatures. Additionally, the 4-imidazolidinones also had a greatly improved CT_{50} profile over the other heterocycles.

To hopefully improve potency, safety, and physicochemical properties over our previous *N*,*N*-dichloroamine based antimicrobials,[8] 5- and 6-membered heterocyclic *N*-chloroamide and *N*-chloroamine were prepared and evaluated in vitro. In the *N*-chloroamide series, the hydantoins (**6**–**11**, and **15**) antimicrobial activity were general poor against all the pathogens. For the 2-imidazolidinones (**28**, **30**, **33** and **37**), compound **37** had good antibacterial and antifungal activity; however, showed no improvement in its toxicity profile over our previous *N*,*N*-dichloroamines. In the *N*-chloroamine series, the 6-membered piperidine analogs (**42–44**, **48**, and **50**) had good antibacterial activity and moderate antifungal activity. Cytotoxicity profiles for these compounds were not encouraging; thus, they had a less than optimal therapeutic index. However, we had interesting results with the 5-membered analogs (**58–62**). All the 4-imidazolidinones had good antibacterial activity, antifungal activity, and solution stability. These compounds had a dramatically improved therapeutic index over all compounds tested in this paper. Additional, they are an improvement over all compounds that we have presented to date.

In summary, we have described the synthesis, antimicrobial activity, cytotoxicity, and aqueous stability of various 5- and 6-membered ring *N*-chloroheterocycles. Of these, the *N*-chloroamines analogs (Scheme 2), were found to be a significant improvement over the *N*-chloroamides analogs (Scheme 1) in antimicrobial activity. Within the *N*-chloroamines, the 5-membered 4-imidazolidinones (**58–62**) were superior to the six-membered heterocycles in terms of therapeutic index. Additionally, the 4-imidazolidinone analogs met our goal of improving antimicrobial therapeutic index and solution stability over our previous *N*,*N*-dichloroamine benchmark.[8] Thus, the imidazolidin-4-ones were found to have all the desirable physicochemical properties for developing new broad-

spectrum, fast-acting, topical antimicrobial agents with low potential to generate antibacterial resistance.

Acknowledgments

The authors wish to acknowledge Drs. John Bartell, Masood Chowhan, Howard Ketelson, and David Stroman for helpful discussions. This work was supported by Alcon Laboratories, Inc.

References and notes

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