



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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



Quaternary ammonium *N,N*-dichloroamines as topical, antimicrobial agents

Charles Francavilla, Eddy Low, Satheesh Nair, Bum Kim, Timothy P. Shiao, Dmitri Debabov, Chris Celeri, Nichole Alvarez, Ashley Houchin, Ping Xu, Ron Najafi, Rakesh Jain *

NovaBay Pharmaceuticals Inc., 5980 Horton St. Suite 550, Emeryville, CA 94608, United States

ARTICLE INFO

Article history:

Received 23 February 2009

Revised 20 March 2009

Accepted 25 March 2009

Available online 28 March 2009

Keywords:

N-Chloroamines

Antimicrobial agents

Taurine

Minimum bactericidal concentration

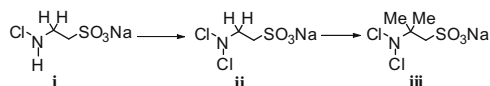
Quaternary ammonium

ABSTRACT

A series of backbone modified and sulfonic acid replacement analogs of our topical, clinical candidate (**iii**) were synthesized. Their antimicrobial activities and aqueous stabilities at pH 4 and pH 7 were determined, and has led us to identify quaternary ammonium *N,N*-dichloroamines as a new class of topical antimicrobial agents.

© 2009 Elsevier Ltd. All rights reserved.

The problem of the growing resistance to current antibiotics has led pharmaceutical programs to identify new classes of therapeutic agents, instead of improving the potency or spectrum of existing classes. This change in direction was driven by the increasing problem of multi-drug resistant pathogens. Therefore, there is an urgent need for antimicrobial agents that function with unique mechanism-of-actions, which do not show cross resistance with existing antibacterials.



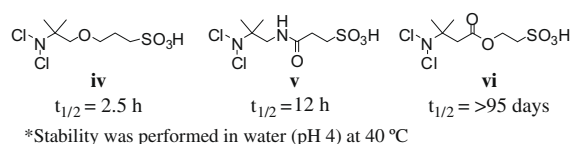
Nagl and co-workers¹ had extensively studied the bactericidal, fungicidal, and virucidal activity as well as the clinical safety of *N*-chlorotaurine (**i**). Since this class of compounds has a non-specific mechanism of action, there is a low potential for the development of resistance. 2-Dichloroamino-2-methyl-propane-1-sulfonic acid sodium salt (**iii**),² a stable derivative of endogenous 2-chloroamino-ethane-1-sulfonic acid sodium salt (**i**) and 2-dichloroamino-ethane-1-sulfonic acid sodium salt (**ii**), has been identified and is currently under development as a topical, broad-spectrum antimicrobial agent.

In our earlier studies in this class, a limited number of analogs with β -substitutions³ and backbone modifications⁴ were prepared. The structure stability/activity relationships (SSR/SAR) were evaluated to identify therapeutic agents with altered physiochemical

properties. This first study suggested that a dimethyl substitution on the carbon linked to the dichloroamino group was critical for aqueous stability of this class of compounds, but surprisingly, larger alkyl, heteroalkyl, cycloalkyl and heterocycloalkyl groups resulted in poor stability. This second study suggested that an ethyl spacer between the *N,N*-dichloroamino and sulfonic acid groups was optimal in the taurine series. Therefore, we have turned our focus towards modifications to the backbone and replacement of the sulfonic acid to identify drug-like molecules in this series to address the key issue—aqueous stability—for these compounds.

We expected that our initial lead could be further optimized for aqueous stability, topical antimicrobial potency and in vivo efficacy by suitable structural modifications. Our earlier study⁴ suggested that the ester modification in the backbone looked promising and maintained antimicrobial activity (Fig. 1).

In this Letter, we report the design, synthesis, stability and biological activity of a series of backbone modified and sulfonic acid replacement analogs (Fig. 2) of compound **iii**. Various syntheses for the preparation of these compounds are outlined in Schemes 1–7. This paper describes the structure–activity relationship and

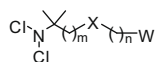


*Stability was performed in water (pH 4) at 40 °C

Figure 1. Previous SSR in backbone modification.

* Corresponding author. Tel.: +1 510 899 8871; fax: +1 510 740 3469.

E-mail address: rjain@novabaypharma.com (R. Jain).

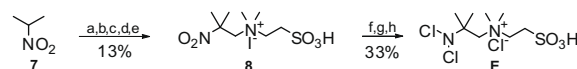
Figure 2. SSR/SAR in *N,N*-dichloroamine series.

structure–stability relationship of backbone modification (X) and sulfonic acid replacement (W) in *N,N*-dichloroamine series.

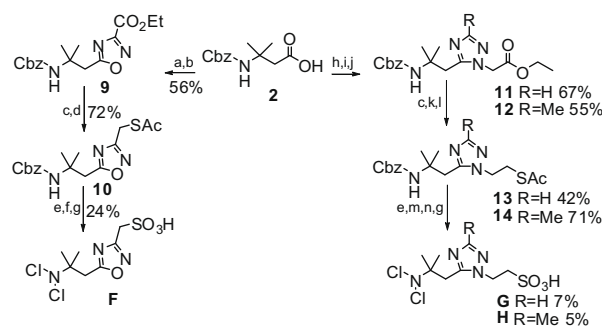
The syntheses of the amide and ester analogs of the *N,N*-dichloroamines began with the commercially available 3,3-dimethylacrylic acid **1** (Scheme 1). This acrylate was used in a conjugate addition to give a previously synthesized azide.⁵ Hydrogenation of the azide yielded the amine,⁶ followed by Cbz-protection to give the common intermediate (2). The Cbz-protected 3-amino-3-methylbutanoic acid was reacted with carbonyldiimidazole to give an imidazolide intermediate, which was treated with either an amine or alcohol.⁷ Treatment with 2-aminoethanol and 2-(methylamino)ethanol, followed by a Mitsunobu esterification reaction⁸ with thioacetic acid gave amides **3** and **4**. Treatment of the imidazolide intermediate with *N,N,N'*-trimethylethylenediamine, followed by methylation gave the ammonium salt **5**; while treatment with 1-(2-hydroxyethyl)piperidine and methyl iodide gave the ester **6**. The oxidation of thioacetates **3** and **4** to the sulfonic acids⁹ followed by N-deprotection and *N,N*-dichlorination with *t*-butyl hypochlorite¹⁰ provided **A** and **B**, respectively. The removal of *N*-Cbz group from amines **5** and **6** with HBr, halogen exchange with silver(I) oxide and aqueous HCl, followed by *N,N*-dichlorination with *t*-butyl hypochlorite yielded **C** and **D**.

Synthesis of the ammonium sulfonic acid **E** (Scheme 2) was accomplished under Mannich conditions¹¹ with commercially available 2-nitropropane, formaldehyde and 2-(methylamino)ethanol in the presence of base. The nitro aminoalcohol was converted to the thioacetate, via the mesylate. *N*-Methylation of nitro amino thioacetate with methyl iodide, followed by oxidation with performic acid, provided nitro methylammonium sulfonic acid **8**. Hydrogenation of the nitro group in the presence of Raney nickel at 500 psi,¹¹ followed by chloride exchange and *N,N*-dichlorination, gave compound **E**.

The synthesis of heterocyclic modifications **F**, **G**, and **H** in backbone began with a common intermediate, *N*-Cbz-3-amino-3-methylbutanoic acid (**2**), as shown in Scheme 3. The imidazolide, formed from **2** and CDI, was reacted with ethyl 2-amino-2-(hydroxyimino)acetate, to give a 1,2,4-oxadiazole **9**. *N*-Cbz amide prepared from **2** and ammonium chloride under CDI coupling conditions was heated with either *N,N*-dimethylformamide dimethyl acetal or *N,N*-dimethylacetamide dimethyl acetal to generate intermediate acylamidines. The cyclization of the acylamidines with ethyl



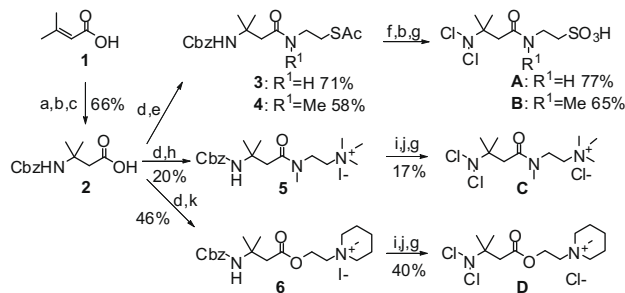
Scheme 2. Reagents and conditions: (a) 37% aq formaldehyde, 2-(methylamino)ethanol, 5 N NaOH, 10–50 °C, 2 h; (b) MeSO₂Cl, CH₂Cl₂, Et₃N, 0–20 °C, 2 h; (c) KSAc, DMF, 50 °C, 4 h; (d) MeI, EtOH, 45 °C, 72 h; (e) HCO₂H, 30% H₂O₂, 50 °C, 2 h; (f) Raney Ni, H₂ (500 psi), EtOH; (g) Ag₂O, water, 0.5 h; then aq HCl; (h) MeOH, *t*-BuOCl, 0–20 °C, 1 h.



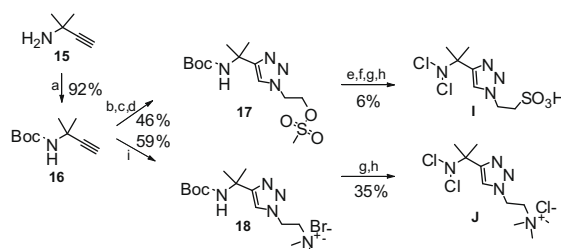
Scheme 3. Reagents and conditions: (a) Ethyl 2-amino-2-(hydroxyimino)acetate, DMF, CDI, 20 °C, 16 h; (b) xylene, 140 °C, 5 h; (c) EtOH, NaBH₄, 0–5 °C, 1 h; (d) AcSH, PPh₃, DIAD, THF, –5 to 20 °C, 16 h; (e) HCO₂H, 30% H₂O₂, 20 °C, 16 h; (f) 10% Pd-BaSO₄, H₂, MeOH, 20 °C, 4 h; (g) MeOH, *t*-BuOCl, 0–20 °C, 0.5 h; (h) NH₄Cl, CDI, DIEA, THF, 20 °C, 16 h; (i) *N,N*-dimethylformamide dimethyl acetal (for **11**) or *N,N*-dimethylacetamide dimethyl acetal (for **12**), 120 °C, 2 h; (j) ethyl hydrazinoacetate hydrochloride, 90 °C, 2 h; (k) MsCl, Et₃N, THF, 20 °C, 1 h; (l) KSAc, DMF, 90 °C, 0.5 h; (m) HBr, AcOH, 20 °C, 2 h; (n) Ag₂O, water, 0.5 h; then aq HCl.

hydrazinoacetate hydrochloride provided the desired triazoles **11** and **12**. Reduction of the ester to the alcohol, followed by Mitsunobu esterification reaction with thioacetic acid,⁷ gave thioacetates **10**, **13** and **14**. Compounds **F**, **G**, and **H** were prepared from the respective thioacetates via a similar set of reaction sequences as described for the synthesis of **A** from **3** in Scheme 1.

Syntheses of two 1,2,3-triazoles **I** and **J** from *N*-Boc protected alkyne **16** required a copper-mediated cycloaddition reaction utilizing Click chemistry (Scheme 4).¹² This was accomplished by the reaction of **16** with ethyl azidoacetate to provide an intermediate triazole compound. Reduction of the ethyl ester, followed by reaction with methanesulfonyl chloride, gave mesylate **17**. Nucleophilic displacement of the mesylate with potassium thioacetate,



Scheme 1. Reagents and conditions: (a) NaN₃, AcOH, H₂O, 95 °C, 48 h; (b) 10% Pd-C, MeOH, H₂, 20 °C, 16 h; (c) THF, Cbz-OSu, 20 °C, 16 h; (d) CDI, DMF, 20 °C, 1 h; then, 2-aminoethanol (for **3**) or 2-(methylamino)ethanol (for **4**) or *N,N,N'*-trimethylethylenediamine (for **5**) or 1-(2-hydroxyethyl)piperidine (for **6**), 20–60 °C, 16 h; (e) AcSH, PPh₃, DIAD, THF, –5 to 20 °C, 16 h; (f) 30% H₂O₂, HCO₂H, 16 h, 20 °C; (g) MeOH, *t*-BuOCl, 0–20 °C, 1 h; (h) MeI, EtOH, 20 °C, 16 h; (i) 33% HBr-AcOH, 20 °C, 1 h; (j) Ag₂O, water, 0.5 h; then aq HCl; (k) MeI, CH₂Cl₂, 20 °C, 16 h.



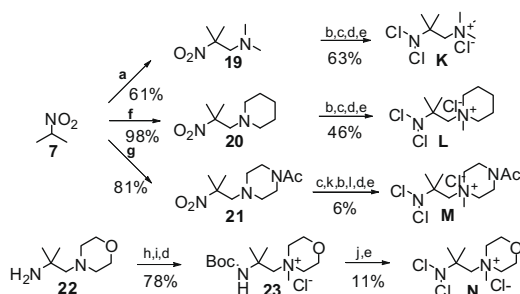
Scheme 4. Reagents and conditions: (a) di-*t*-butyl dicarbonate, THF, 20 °C, 16 h; (b) ethyl azidoacetate, DIEA, CuI, THF, 20 °C, 2 h; (c) EtOH, NaBH₄, 20 °C, 1 h; (d) MeSO₂Cl, CH₂Cl₂, Et₃N, 20 °C, 2 h; (e) KSAc, DMF, 90 °C, 0.5 h; (f) HCO₂H, 30% H₂O₂, 20 °C, 2 h; (g) 4 M HCl/dioxane, 20 °C, 2 h; (h) MeOH, *t*-BuOCl, 0–20 °C, 2 h; (i) (2-azidoethyl)trimethylammonium bromide (prepared from (2-bromoethyl)trimethylammonium bromide, NaN₃, DMF, 20 °C, 16 h), DIEA, MeOH, CuI, 20 °C, 16 h.

followed by oxidation, deprotection and N,N-dichlorination, gave the sulfonic acid **1**. Similarly, a cycloaddition of **16** and (2-azidoethyl)trimethylammonium bromide furnished triazole **18**. The removal of *N*-Boc with HCl, followed by N,N-dichlorination gave trimethylammonium compound **J**.

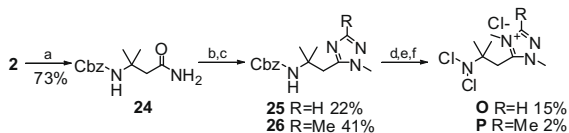
Substitution of the sulfonic acid with other water solubilizing groups, without the backbone modification, were also explored (Scheme 5 and 6). The syntheses of analogs **K**, **L**, and **M** started with reactions with the appropriate amines, formaldehyde and 2-nitropropane under Mannich conditions¹³ to give tertiary amines **19**, **20** and **21**. A common reaction sequence (methylation, nitro reduction, anion exchange and N,N-dichlorination) was used for the preparation of **K** (from **19**) and **L** (from **20**) as described earlier for the synthesis of **E**. The methylation of **21**, unlike previous analogs, failed to give the desired ammonium product. The dichloroamine **M** was obtained through an alternate sequence (nitro reduction, Cbz protection, methylation, anion exchange and N,N-dichlorination) in low yield. Compound **N** was synthesized from commercially available 2-methyl-1-morpholinopropan-2-amine **22** with di-*t*-butyl dicarbonate in THF, followed by methylation with methyl iodide and halide exchange as described earlier, to provide the quaternary ammonium **23**. The removal of *N*-Boc group with HCl, followed by N,N-dichlorination, resulted in the formation of the desired N,N-dichloroamine compound **N**.

Compounds **O** and **P** (Scheme 6) were synthesized from the Cbz-protected 3-amino-3-methylbutanoic acid **2**. Coupling of **2** with ammonium chloride under CDI conditions gave the corresponding amide **24**. Reaction of **24** with N,N-dimethylformamide dimethyl acetal or N,N-dimethylacetamide dimethyl acetal,¹⁴ followed by treatment with methyl hydrazine, gave compounds **25** and **26**. Methylation of **25** and **26** with methyl iodide, N-deprotection under acidic conditions and N,N-dichlorination provided N,N-dichloro triazole compounds **O** and **P**, respectively.

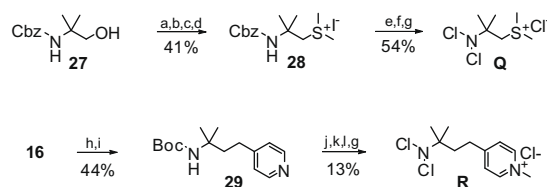
The dimethylsulfonium compound **Q** was synthesized from N-Cbz-protected amino alcohol **27** (Scheme 7). N-Cbz-protected



Scheme 5. Reagents and conditions: (a) aq dimethylamine, 37% aq formaldehyde, 50 °C, 1 h; (b) MeI, MeOH, 20 °C, 48 h; (c) Raney Ni, H₂ (500 psi), MeOH–H₂O, 20 °C, 72 h; (d) Ag₂O, water, 0.5 h; then aq HCl; (e) MeOH, *t*-BuOCl, 0–10 °C, 1 h; (f) piperidine, 37% aq formaldehyde, 10–50 °C, 1 h; (g) 1-(piperazin-1-yl)ethanone, 37% aq formaldehyde, 10–50 °C, 1 h; (h) di-*t*-butyl dicarbonate, THF, 20 °C, 16 h; (i) MeI, 20 °C, 18 h; (j) 4 M HCl/dioxane, 20 °C, 2 h; (k) THF, Cbz-OSu, 20 °C, 16 h; (l) 33% HBr–AcOH, 20 °C, 1 h.



Scheme 6. Reagents and conditions: (a) CDI, DIEA, NH₄Cl, DMF, 20 °C, 16 h; (b) N,N-dimethylformamide dimethyl acetal (for **25**) or N,N-dimethylacetamide dimethyl acetal (for **26**), 120 °C, 2 h; (c) Methyl hydrazine, acetic acid, 90 °C, 2 h; (d) MeI, MeOH, 70 °C, 16 h; (e) 33% HBr–AcOH, 20 °C, 2 h; (f) Ag₂O, water, 0.5 h; then aq HCl; (g) MeOH–H₂O (9:1), *t*-BuOCl, 20 °C, 1 h.



Scheme 7. Reagents and conditions: (a) AcSH, PPh₃, DIAD, THF, –5 to 20 °C, 16 h; (b) MeOH, 5 N NaOH, 20 °C, 0.5 h; (c) MeOH, MeI, TEA, 20 °C, 16 h; (d) EtOH, MeI, 20 °C, 72 h; (e) AcOH, Ag₂O, 0.5 h; 6 N HCl; (f) 10% Pd–C, H₂, 0.2% aq HCl, 20 °C, 20 h; (g) MeOH, *t*-BuOCl, 20 °C, 1 h; (h) 4-bromopyridine, THF, DIEA, Pd(dppf)Cl₂, 20 °C, 16 h; (i) 10% Pd–C, EtOH, 20 °C, 16 h; (j) MeI, 80 °C, 2 h; (k) Ag₂O, water, 0.5 h; (l) 4 M HCl/dioxane, 20 °C, 16 h.

dimethylsulfonium salt **28** was obtained by Mitsunobu esterification of **27** with thioacetic acid, followed by de-S-acetylation, S-methylation to the methyl sulfide, and a second S-methylation to the dimethylsulfonium iodide.¹⁵ The iodide was exchanged for chloride, with acetic acid added to prevent demethylation. Removal of the Cbz group by hydrogenation under acidic conditions (to prevent methyl transfer from sulfur to nitrogen), followed by N,N-dichlorination, gave sulfonium compound **Q**. The methyl pyridinium salt **R** was synthesized from Boc-protected 2-methyl-3-butyn-2-amine **16**. The cross-coupling of **16** with 4-bromopyridine under Sonogashira conditions¹⁶ followed by hydrogenation¹⁷ furnished compound **29**. Conversion of **29** to N-methylpyridinium compound **R** was accomplished by N-methylation of the pyridine ring, halide exchange, Boc-deprotection, and N,N-dichlorination.

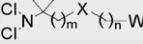
All compounds were purified by silica gel flash chromatography or preparative HPLC and their structures were confirmed by ¹H NMR spectroscopy and LC/MS analysis.

Table 1 summarizes antimicrobial assay results and aqueous solution stabilities for compounds **A–R**. Both parameters are critical in assessing the potential of this class of compounds as topical antimicrobial agents. The minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFC) for each compound was evaluated as described previously.⁴ The biological evaluation was carried out for all analogs with sufficient aqueous solution stability (>24 h at 40 °C). All analogs except **M** were active against all organisms tested; there were no significant differences between the *in vitro* activities for Gram-positive versus Gram-negative organisms. Some compounds with either a triazole functionality (**I**, **J**, **O**, and **P**) or an oxadiazole moiety (**F**) had the same or better activity against *Candida albicans* than **iii**.

Analogues with backbone modifications **A–D**, **F–J** were prepared as ester replacement analogs of **vi**, which was more stable than most of the compounds reported in Ref. 4. It became apparent that a backbone modification containing an ester (**D**) had good stability at pH 4; however, it was less stable at pH 7, possibly due to saponification of the ester functionality.

Dimethylammonium salt **E** and quaternary ammonium salts (**K** and **L**) showed exceptional and surprising stability. They were the first series of analogs whose stabilities were comparable to compound **iii**. Most important, the stability of compound **K** at pH 7 has been spectacular, and has shown little degradation at elevated temperatures for over a year. Compounds **L–N** demonstrated, however, that there are still many factors which can influence compound stability distal to the dichloroamine. Substitution of the terminal sulfonic acid group in the backbone-extended analogs (comparison of **B** with **C**, **vi** with **D**, and **I** with **J**) with the trialkylammonium group looked promising in this series of molecules. Triazolium salts (**O** and **P**), dimethylsulfonium salt **Q**, and pyridinium salt **R** were prepared as variations on the theme of the trimethylammonium derivative **K**. While many of these were promising for acidic solutions, they lacked the exceptional pH 7 stability of derivative **K**.

Table 1

Compounds					MBC or MFC ^a (μg/mL)			$t_{1/2}$ pH 4 (saline) (days)	$t_{1/2}$ pH 7 (phosphate) (days)
	m	X	n	W	<i>S. aureus</i> ATCC 29213	<i>E. coli</i> ATCC 25922	<i>C. albicans</i> ATCC 10231		
iii	1	n/a	0	SO ₃ H	2	2	32	>730	>300
A	1	CONH	2	SO ₃ H	8	2	64	33	36 ^b
B	1	CONMe	2	SO ₃ H	2	1	32	1	1
C	1	CONMe	2	NMe ₃	16	2	32	4	6
D	1	CO ₂	2	Me-piperdinium	4	2	n/a	>72	7
E	1	NMe ₂	2	SO ₃ H	64	16	128	>180	19
F	1	1,2,4-Oxadiazole	1	SO ₃ H	2	4	16	106	17
G	1	1,2,4-Triazole	2	SO ₃ H	4	2	64	21	23
H	1	3-Me-1,2,4-Triazole	2	SO ₃ H	4	4	64	46	50
I	0	1,2,3-Triazole	2	SO ₃ H	8	4	32	10	5
J	0	1,2,3-Triazole	2	NMe ₃	8	4	32	52	23
K	1	n/a	0	NMe ₃	16	8	128	>325	>396
L	1	n/a	0	Me-piperdinium	16	8	64	>122	100
M	1	n/a	0	Me-piperazinium-Ac	64	16	>1024	37	6 ^b
N	1	n/a	0	Morpholinium	n/a	n/a	n/a	<1	<1
O	1	n/a	0	1,2,4-triazolium	4	2	16	67	5
P	1	n/a	0	3-Me-1,2,4-triazolium	8	4	32	61	4
Q	1	n/a	0	Dimethylsulfonium	8	4	128	>67	1
R	1	n/a	1	Me-pyridinium	8	2	1024	>60	20 ^b

^a Minimum bactericidal concentration (MBC) was determined using a modified standard method described in CLSI M26-A whereby isotonic 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 16–20 h at 35 °C to 1 h at room temperature.

^b In 0.6% borate buffer pH 7.

In summary, we have prepared a series of *N,N*-dichloroamines with backbone modifications and sulfonic acid replacements. Our SSR/SAR suggested that the trimethylammonium group is a privileged structure in this series of compounds, and serves as a near-unique replacement for a sulfonic acid in terms of stability and activity. In this report, we have identified quaternary ammonium *N,N*-dichloroamines as a new class of antimicrobial agents.

Acknowledgments

The authors wish to acknowledge Drs. Behzad Khosrovi, David Stroman, Masoud Chowan, John Bartell, Dennis Dean and Lu Wang, for helpful discussions. This work was supported by Alcon Laboratories, Inc.

References and notes

- (a) Arnitz, R.; Sarg, B.; Helmut, W. O.; Neher, A.; Lindner, H.; Nagl, M. *Proteomics* **2006**, *6*, 865; (b) Teuchner, B.; Nagl, M.; Schidlauer, A.; Ishiko, H.; Dragosits, E.; Ulmer, H.; Aoki, K.; Ohno, S.; Mizuki, N.; Gottardi, W.; Larcher, C. *J. Ocul. Pharmacol. Ther.* **2005**, *21*, 157; (c) Nagl, M.; Nguyen, V. A.; Gottardi, W.; Ulmer, U.; Ho, R. *Br. J. Dermatol.* **2003**, *149*, 590; (d) Nagl, M.; Gruber, A.; Fuchs, A.; Lell, C. P.; Lemberger, E.; Zepelin, M. B.; Würzner, R. *Antimicrob. Agents Chemother.* **2002**, *46*, 1996; (e) Nagl, M.; Lass-Flörl, C.; Neher, A.; Gunkel, A.; Gottardi, W. *J. Antimicrob. Chemother.* **2001**, *47*, 871; (f) Nagl, M.; Hess, M. W.; Pfaller, K.; Hengster, P.; Gottardi, W. *Antimicrob. Agents Chemother.* **2000**, *44*, 2507; (g) Nagl, M.; Teuchner, B.; Pöttinger, E.; Ulmer, H.; Gottardi, W. *Ophthalmologia* **2000**, *214*, 111; (h) Nagl, M.; Hengster, P.; Sementiz, E.; Gottardi, W. *J. Antimicrob. Chemother.* **1999**, *43*, 805; (i) Nagl, M.; Miller, B.; Daxecker, F.; Gottardi, W. *J. Ocul. Pharmacol. Ther.* **1998**, *14*, 283; (j) Nagl, M.; Larcher, C.; Gottardi, W. *Antiviral Res.* **1998**, *38*, 25; (k) Nagl, M.; Gottardi, W. *Hyg. Med.* **1992**, *17*, 431; (l) Yazdanbakhsh, M.; Eckmann, C. M.; Roos, D. *Am. J. Trop. Med. Hyg.* **1987**, *37*, 106.
- Wang, L.; Khosrovi, B.; Najafi, M. *Tetrahedron Lett.* **2008**, *49*, 2193.
- Shiau, T. P.; Houchin, A.; Nair, S.; Xu, P.; Low, E.; Najafi, R.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1110.
- Low, E.; Nair, S.; Shiau, T.; Belisle, B.; Debabov, D.; Celeri, C.; Zuck, M.; Najafi, R.; Georgopapadakou, N.; Jain, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 196.
- (a) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1986**, *51*, 4856; (b) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248.
- Jadhav, V. D.; Schmidtchen, F. P. *J. Org. Chem.* **2008**, *73*, 1077.
- (a) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3833; (b) Becker, D. P.; Flynn, D. L.; Moormann, A. E.; Nosal, R.; Villamil, C. I.; Loeffler, R.; Gullikson, G. W.; Moumami, C.; Yang, D. *J. Med. Chem.* **2006**, *49*, 1125.
- Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487.
- Higashiura, K.; Ienaga, K. *J. Org. Chem.* **1992**, *57*, 764.
- Pogany, S. A.; Higuchi, T. U.S. Patent 4,386,103, 1983.
- Senkus, M. *J. Am. Chem. Soc.* **1946**, *68*, 10.
- Angell, Y.; Chen, D.; Brahimi, F.; Saragovi, H. U.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 556.
- Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791.
- Costanzo, A.; Guerrini, G.; Ciciani, G.; Bruni, F.; Sella, S.; Costa, B.; Martini, C.; Lucacchini, A.; Aiello, P. M.; Ipponi, A. *J. Med. Chem.* **1999**, *42*, 2218.
- Yamauchi, K.; Hisanaga, Y.; Kinoshita, M. *J. Am. Chem. Soc.* **1983**, *105*, 538.
- Glase, S. A.; Akunne, H. C.; Heffner, T. G.; Jaen, J. C.; MacKenzie, R. G.; Meltzer, L. T.; Pugsley, T. A.; Smith, S. J.; Wise, L. D. *J. Med. Chem.* **1996**, *39*, 3179.
- Perchonock, C. D.; Uzinskis, I.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Kirchner, T.; Weichman, B. M.; Mong, S.; Scott, M. O.; Chi-Rosso, G.; Wu, H.-L.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1986**, *29*, 1442.