

Discovery and SAR of Diphenylborinic Acid Picolinate Esters as A Potent Antibacterial and Anti-inflammatory Agent for the Treatment of Skin Diseases

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Abstract

A series of borinic acid picolinate esters was synthesized and screened for their minimum inhibitory concentration (MIC) against Gram positive and Gram negative bacteria. Diphenylborinic acid picolinate esters were active against Gram positive bacteria in the low to sub-microgram/mL range but less active against the Gram negative strains tested. The lead compound, **AN0128**, was also found to inhibit the release of pro-inflammatory cytokines TNF- α and IL-1 β from peripheral blood mononuclear cells (PBMCs) stimulated with lipopolysaccharide (LPS). This compound is now in clinical development for dermatological conditions, such as atopic dermatitis.

Introduction

Atopic dermatitis (AD) or eczema, is an inflammatory disease affecting around 10-20 % of children and 1-3 % of adults. In 90% of cases there is a bacterial component involving the Gram positive bacterium *Staphylococcus aureus*. The primary treatment of AD focuses on the management of environmental factors along with the administration of topical or systemic corticosteroids to reduce inflammation. However, steroids are known to have a number of side effects and their chronic use is not without risk. Alternatively, the calcineurin inhibitors tacrolimus and pimecrolimus are used, which are broad spectrum immunosuppressants. Recently, the US-FDA issued a public-health advisory for these treatments. Since a bacterial component exists in most cases of AD, parallel treatment with antibacterial and anti-inflammatory agents produced an improved clinical response. Therefore, it would be desirable to develop a single drug that possesses both these activities and has a superior safety profile.

We previously reported a new class of antibacterial agents, borinic acid quinoline esters (A).¹ Here we describe a related class, borinic acid picolinate esters (B), and the identification of a new antibacterial and anti-inflammatory agent, 3-hydroxypyridine-2-carboxyloxy-bis(3-chloro-4-methyl-phenyl) borane (**5c**; **AN0128**).²

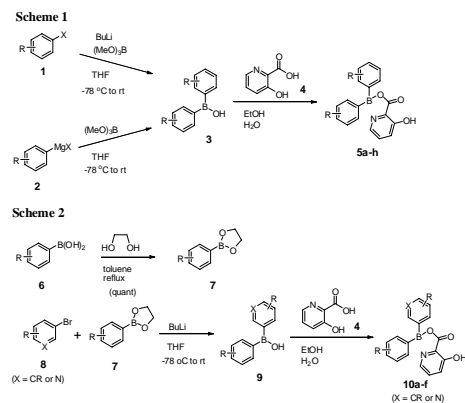
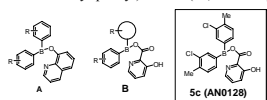


Table 1. Minimum Inhibitory Concentration (MIC; $\mu\text{g/mL}$) results for 3-hydroxypyridone esters.

| Entry | R ¹ | A | <i>S. aureus</i> | <i>S. epidermidis</i> | <i>P. acnes</i> | <i>B. subtilis</i> | <i>H. influenzae</i> |
|------------|-------------------------|-----------------------------|------------------|-----------------------|-----------------|--------------------|----------------------|
| | | Erythromycin | 0.5 | 0.15 | 0.1 | 0.1 | 4 |
| 5a | 3-Cl | 3-Cl-Ph | ≤ 0.125 | 8 | 10 | 16 | 16 |
| 5b | 4-Cl | 4-Cl-Ph | 4 | 1 | 1 | 1 | 16 |
| 10a | 3-Cl | Pyridin-3-yl | 16 | 32 | nt ^a | nt ^a | 32 |
| 10b | 4-Cl | Pyridin-3-yl | 64 | 32 | nt ^a | nt ^a | 16 |
| 10c | 4-Cl | 2-Cl-pyridin-5-yl | 32 | 32 | nt ^a | nt ^a | 32 |
| 14 | 3-Cl | Thiophen-3-yl | 32 | 32 | 10 | 16 | 32 |
| 5c | 3-Cl-4-Me | 3-Cl-4-Me-Ph | 1 | 0.5 | 0.3 | 1 | >64 |
| 17 | 3-Cl-4-Me | Me | 32 | 32 | 10 | 16 | 32 |
| 22 | 3-Cl-4-Me | Phenethyl | 0.5 | 1 | 1 | 1 | >64 |
| 5d | 3-F | 3-F-Ph | >64 | >64 | >100 | >64 | >64 |
| 10d | 3-Cl | 3-SMe-Ph | 8 | 8 | 3 | 4 | >64 |
| 10e | 3-Cl | 2-Me-Ph | 8 | 8 | 3 | 4 | >64 |
| 5e | 3-Cl-4-F | 3-Cl-4-F-Ph | 1 | 8 | 3 | 8 | 4 |
| 5f | 3-Cl-4-OEt | 3-Cl-4-OEt-Ph | 2 | 2 | 1 | 2 | >64 |
| 5g | 3-Cl-4-NMe ₂ | 3-Cl-4-NMe ₂ -Ph | 32 | 32 | nt ^a | 64 | >64 |
| 10f | 3-Cl-4-Me | 4-Me-Ph | 4 | 2 | 3 | 2 | >64 |
| 5h | 4-Cl-2-Me | 4-Cl-2-Me-Ph | 4 | 2 | 0.3 | 0.5 | 16 |

^a nt = not tested

Table 2. Minimum Inhibitory Concentration (MIC; $\mu\text{g/mL}$) results for bis(3-chloro-4-methylphenyl)borinic acid esters.

| Entry | R ² | <i>S. aureus</i> | <i>S. epidermidis</i> | <i>P. acnes</i> | <i>B. subtilis</i> | <i>H. influenzae</i> |
|------------|---------------------|------------------|-----------------------|-----------------|--------------------|----------------------|
| 23a | H | 0.5 | >64 | nt ^a | nt ^a | nt ^a |
| 5c | 3-OH | 1 | 0.5 | 0.3 | 1 | >64 |
| 23b | 3-OAc | 2 | 1 | 1 | 0.5 | >64 |
| 23c | 3-COPh | 0.5 | 32 | 30 | 64 | >64 |
| 23d | 3-NH ₂ | >64 | >64 | 1 | 2 | >64 |
| 23e | 3-CO ₂ H | 0.125 | 4 | 3 | 8 | 8 |
| 23f | 4-CO ₂ H | 2 | 4 | 3 | nt ^a | nt ^a |
| 23g | 5-CO ₂ H | 0.5 | 8 | 3 | 8 | 8 |

^a nt = not tested.

Table 3. Percent inhibition of cytokine release from PBMCs by selected borinic acid picolinate esters at 10 μM .

| Entry | R ¹ | R ² | TNF- α ^a | IL-1 β ^b | IFN- γ ^b | IL-4 ^c | |
|------------|----------------|---------------------|----------------------------|---------------------------|----------------------------|-------------------|-----------------|
| | | | Erythromycin | 22% | -32% | nt ^a | nt ^a |
| 5c | 3-Cl-4-Me- | 3-OH | 100% | 99% | -20% | -21% | |
| 23b | 3-Cl-4-Me- | 3-OAc | 101% | -49% | nt ^a | nt ^a | |
| 5h | 4-Cl-2-Me- | 3-OH | 101% | 103% | 15% | 57% | |
| 23g | 3-Cl-4-Me- | 5-CO ₂ H | 100% | 80% | 24% | 9% | |

^a Stimulated by LPS (1 $\mu\text{g/mL}$); ^b stimulated by phyto-hemmagglutinin (2 $\mu\text{g/mL}$); ^c stimulated by concanavalin A (20 $\mu\text{g/mL}$).

Conclusions

- Both 3-chloro and 4-methyl groups on the diphenylborinic acid moiety are important for the potent activity against G(+) bacteria.
- 3-Hydroxy group on the picolinic acid moiety resulted in the most potent and broad spectrum of activity against G(+) bacteria.
- Several compounds showed good inhibition of cytokine release, and **5c** (**AN0128**) had the best selectivity against pro-inflammatory cytokines, TNF- α and IL-1 β .
- Overall, **AN0128** showed the best balance of antibacterial and anti-inflammatory activity and is under phase II clinical trial for the topical treatment of atopic dermatitis.

References (1) Baker, S. J., et al *J. Med. Chem.* **2005**, *48*, 7468-7476
(2) Baker, S. J., et al *Bioorganic Med. Chem. Lett.* In press.