



AN2898, a novel oxaborole compound with anti-inflammatory activity: mechanism of action and *in vitro* cytokine inhibition

Sanders, V., Rock, F., Kimura, R., Antunes, J., Freund, Y., Alley, M., Zhou, Y., Akama, T., Maples, K. and Plattner, J.

Anacor Pharmaceuticals, Inc., 1020 East Meadow Circle, Palo Alto, CA 94043, USA

Introduction

AN2898 is a novel phosphodiesterase 4 (PDE4) inhibitor in development to treat inflammatory dermatological diseases topically. AN2898 is a competitive, reversible inhibitor of PDE4 with a K_i of 65 ± 10 nM. The AN2898-PDE4B2 catalytic domain co-crystal structure shows that AN2898 binds directly to the metal ions and activated water molecule in the active site. This binding configuration is unique amongst classical PDE4 inhibitors. The IC_{50} values for inhibition of PDE4 activity is 0.06 μ M. AN2898 has equal activity against the four PDE4 subtypes. AN2898 does not significantly inhibit PDE 1,2,3,5, or 6; however, it does have activity against PDE7. Like other PDE4 inhibitors, AN2898 inhibits the release of $TNF\alpha$, IL-2, $IFN\gamma$, IL-5 and IL-10 and does not inhibit IL-1 β , IL-6, and IL-8. Unlike classical PDE4 inhibitors, AN2898 also inhibits IL-12 and IL-23. Because of its unique mechanism of action and anti-inflammatory activity, AN2898 has the potential to be useful in the treatment of psoriasis and other immune mediated diseases.

Figure 1. AN2898 (5-(3,4-dicyanophenoxy)-1-hydroxy-1,3-dihydro-2,1-benzoxaborole)

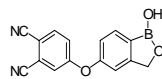


Figure 2. AN2898 Binds to Zinc and Magnesium in the Active Site of the Phosphodiesterase 4B Catalytic Domain (A) at a site different from classical PDE4 inhibitors (B).

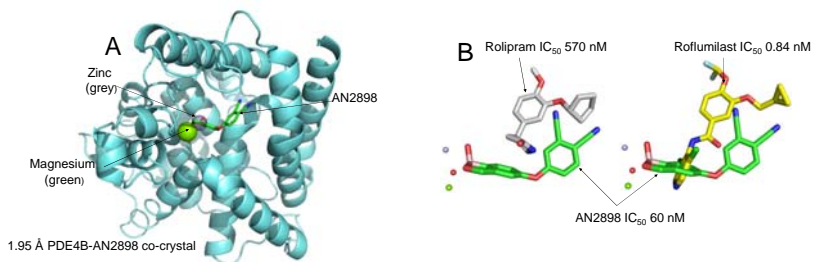


Table 1. Percent Inhibition of PDE Enzymes (A) and PDE4 isoforms (B) by AN2898 at 10 μ M

PDE1	PDE2	PDE3	PDE4 (IC_{50})	PDE5	PDE6	PDE7	PDE8	PDE9	PDE10	PDE11
85	68	66	99.8 (0.06 μ M)	25	25	88	72	0	57	67

PDE4A4	PDE4B2	PDE4C2	PDE4D3
97	96	93	93

Table 2. Selectivity of AN2898 relative to other PDE Enzymes (IC_{50})

PDE1	PDE3	PDE4	PDE7
1.7 μ M	4.1 μ M	0.03 μ M	0.2 μ M

Table 3. Broad Spectrum Anti-inflammatory Activity of AN2898 including IL-23

Cytokine Inhibition IC_{50} (μ M)										
Pro-Inflammatory				Th1		Th2				
PBMC, 24 h, 1 μ g/ml LPS				PBMC, 24 h, 20 μ g/ml PHA		PBMC, 48 h, 20 μ g/ml PHA			THP-1, 48 h, 1 μ g/ml LPS+ 100 ng/ml $IFN\gamma$	
$TNF\alpha$	IL-1 β	IL-6	IL-8	IL-2	$IFN\gamma$	IL-4	IL-5	IL-10	IL-12	IL-23
0.12	>30	>30	>30	0.14	0.05	>10	0.22	0.31	0.02	2.1

Conclusions

- AN2898 is a novel compound that has broad spectrum *in vitro* anti-inflammatory activity.
- AN2898 is a potent PDE4 inhibitor with activity against PDE7 as well.
- Because of its unique mechanism of action and anti-inflammatory profile, AN2898 has the potential to be useful in the topical treatment of psoriasis and atopic dermatitis.