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Design and synthesis of boron-containing PDE4 inhibitors using soft-drug strategy for potential dermatologic anti-inflammatory application

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ABSTRACT

PDE4 inhibitors are a validated approach as anti-inflammatory agents but are limited by systemic side effects including emesis. We report a soft-drug strategy incorporating a carboxylic ester group into boron-containing PDE4 inhibitors leading to the discovery of a series of benzoxaborole compounds with good potency (for example IC_{50} = 47 nM of compound **2**) and low emetic activity. These compounds are intended for dermatological use further limiting possible systemic side effects.

Cyclic nucleotide phosphodiesterase (PDE) enzymes have been drug targets in many diseases and several non-specific PDE inhibitors, such as theophylline and doxofylline (see Fig. 1), have been approved to treat patients.[1]

The phosphodiesterase 4 (PDE4) is one of the eleven families of PDEs and, during the last 30 years, PDE4 inhibitors have been a significant focus of research and development by numerous organizations in the quest to discover therapeutic agents for the treatment of inflammation-associated diseases such as asthma and chronic obstructive pulmonary disease (COPD).[2] More than 30 new chemical entities (NCEs) of PDE4 inhibitors have progressed to various clinical stages, but only a small portion of these NCEs are currently in active development at advanced clinical phases.[2a–c] The challenges for developing PDE4 inhibitors are multi-factorial including lack of efficacy in many cases and, more often, safety-related issues. Vomiting, nausea, arteritis and immunosuppression are among the serious adverse events of PDE4 inhibitors.[2d–f] The reported side effects take place in the brain, gastrointestinal tract, arteries or whole body due to systemic exposure of PDE4 inhibitors.

Topical therapeutic application of boron-containing NCEs has been one of our focuses[3] and recently two boron-containing PDE4 inhibitors (AN2728 & AN2898; see Fig. 2)[3d–f] have been identified as anti-inflammatory agents undergoing clinical development for potential topical treatment of psoriasis and atopic dermatitis. For a topically used drug, the possible systemic side effects are expected to be relatively low as compared to for the systemic usage. In an ideal case, a topically applied drug exerts its therapeutic action in the target area of the skin and then converts into inactive and non-toxic metabolites if any drug penetrates the skin and reaches systemic circulation. This so-called soft-drug strategy[4] may further improve the therapeutic index of boron-con-

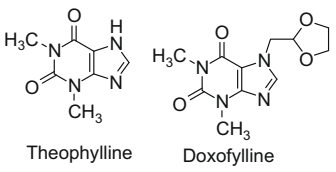

Figure 1. Theophylline has been launched as oral sustained release formulation for treating asthma and respiratory disease (once daily or twice daily). Doxofylline has been launched in Italy for treating asthma in expectation of having fewer side effects than its close analog, theophylline.

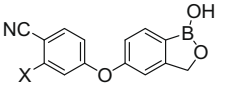

Figure 2. Chemical structures of AN2728 and AN2898 that are in clinical development.

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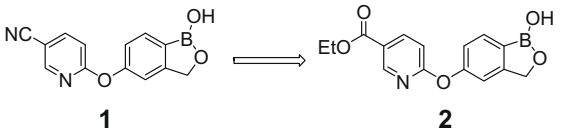
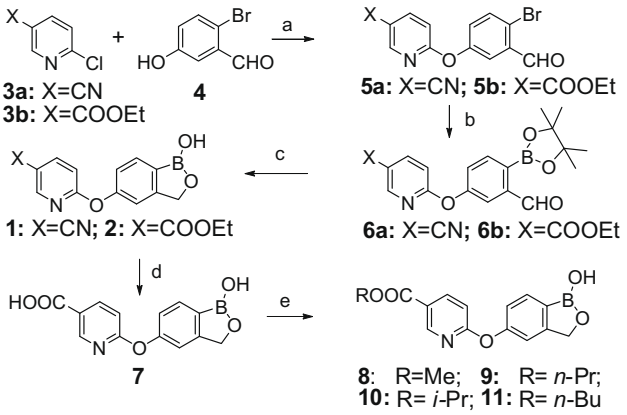


Figure 3. A boron-containing PDE4 inhibitor **1** was used as a starting point of a soft-drug approach for the discovery of more potent carboxylic ester compound **2** with fewer side effects.

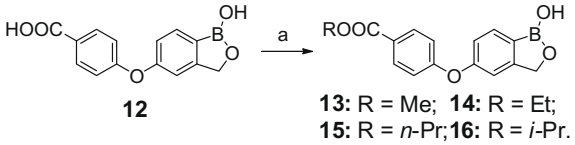


Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, 65–80 °C overnight; (b) bis(pinacolato)diboron, $PdCl_2(dppf)_2$, 1,4-dioxane, N_2, 80 °C 14 h; (c) $NaBH_4$, EtOH, and then 6 N HCl, H_2O, EtOH (overall yield 60% for **2** from 1st step; (d) NaOH, H_2O, MeOH, rt overnight, and then HCl, H_2O, yield 95%; (e) for **8** (R = Me), H_2SO_4, MeOH, reflux overnight, N_2, yield 15%; for **9–11** (R = *n*-Pr, *i*-Pr and *n*-Bu), CDI, DCM/THF/DMF (1:1:1, v/v/v), N_2, rt overnight, and then ROH and catalytic amount NaH, reflux, 2–4 h, yield 61%, 72% and 69%, respectively.

taining PDE4 inhibitors. This article describes our soft-drug approach starting from compound **1** (see Fig. 3) to the discovery of a series of benzoxaborole carboxylic ester compounds, such as compound **2**, with good potency against PDE4.

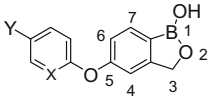
The synthetic methodologies for the preparation of cyanopyridyloxybenzoxaborole (**1**), the ester compounds (**2**, **8**–**11**) and their corresponding carboxylic acid (**7**) are shown in Scheme 1.[5] Nucleophilic substitution of the chloro atom in **3a** and **3b** by the phenolic group in 2-bromo-5-hydroxybenzaldehyde **4** in the presence of a base provided the coupling products **5a** and **5b** which were catalytically boronylated to replace the bromo with bis(pinacolato)diboron generating intermediates **6a** and **6b**. Reduction of compounds **6a** and **6b** with sodium borohydride converted the aldehyde moiety into hydroxymethyl group that was simultaneously cyclized to the adjacent borate and subsequently hydrolyzed to benzoxaborole **1** and **2** upon addition of aqueous hydrochloride. Hydrolysis of compound **2** afforded acid compound **7** that was used for the preparation of other ester analogues **8–11** under normal esterification conditions.[5]

For the SAR study, non-pyridyl phenoxybenzoxaborole acid (**12**) and esters (**13–16**) were also synthesized as shown in Scheme 2.



Scheme 2. Reagents and conditions: (a) for **13** and **14** (R = Me and Et), H_2SO_4, MeOH or EtOH, reflux overnight, N_2; for **15** and **16** (R = *n*-Pr and *i*-Pr), H_2SO_4, *n*-PrOH or *i*-PrOH, 100 °C two days, N_2.

Table 1
PDE4 IC_{50} results for benzoxaborole compounds **1**, **2**, **7–16** and **AN2728**



Compds	X	Y	PDE4 IC_{50} (μM)
1	N	CN	0.18
2	N	COOEt	0.047
7	N	COOH	5% inhib@10uM
8	N	COOMe	0.084
9	N	COOPr-*n*	0.13
10	N	COOPr-*i*	0.113
11	N	COOBu-*n*	0.0945
AN2728	CH	CN	0.49
12	CH	COOH	6.42
13	CH	COOMe	0.287
14	CH	COOEt	0.219
15	CH	COOPr-*n*	0.763
16	CH	COOPr-*i*	0.13

The acid compound **12** was conveniently converted to the corresponding esters under normal esterification condition.[5]

Since the goal of the soft-drug approach is to identify a potent boron-containing PDE4 inhibitor with an ester group that may convert to the corresponding carboxylic acid with much less activity against PDE4, screening against PDE4 of compounds **1**, **2**, **7–16** and **AN2728** have been performed using the previously described procedure[3f] and the results are summarized in Table 1.

As a starting point, 5-(5-cyano-2-pyridyloxy) benzoxaborole (**1**) has a reasonable potency of IC_{50} = 0.18 μM against PDE4. After the cyano group is replaced with carboxylic esters, improvement of potencies was observed with IC_{50} in the range of 47–130 nM. The ester alkyl group has an impact on the potency and the sequence of the potency is Et (**2**) > Me (**8**) ≈ *n*-Bu (**11**) > *i*-Pr (**10**) ≈ *n*-Pr (**9**), which is not correlated to the lipophilicity. Further modification of the functional group to COOH (**7**) resulted in the loss of activity (5% inhibition at 10 μM) against PDE4. For the 5-phenoxybenzoxaborole series, very similar activity pattern was observed, and the ester compounds (**13–16**) are generally more potent than the cyano (**AN2728**) and the acid (**12**). Again, the acid (**12**) is the least potent among this series. For cross comparison between these two pyridyloxy and phenoxy series, the pyridyloxybenzoxaboroles are more potent except the carboxylic compound (**7**). Since the most potent ester (**2**) and least potent acid (**7**) fit the soft-drug strategy well, more anti-inflammatory screenings for selected cytokine release inhibitions from THP-1 cells[3f] were conducted and the data are shown in Table 2.

IC_{50}s of the acid **7** against release of TNF-α, IL-2, IFN-γ, IL-5 and IL-10 are greater than 10 μM indicating this acid compound is inactive of inhibiting cytokine release whereas the ester **2** has good potencies of IC_{50}s in the range between 0.10 and 0.46 μM. These activity differences, in addition to the two compound's PDE4 potency difference, further support the soft-drug approach of using active ester compound that may hydrolyze in the systemic circulation into the acid. Therefore, plasma stabilities of ester compounds (**2**, **8–11** and **13–16**) and their conversion into the corresponding

Table 2
Cytokine inhibition results for compounds **2** (ester) and **7** (acid)

Compds	TNF-αIC_{50}[a] (μM)	IL-2 IC_{50}[a] (μM)	IFN-γ IC_{50}[a] (μM)	IL-5 IC_{50}[a] (μM)	IL-10 IC_{50}[a] (μM)
Ester **2**	0.20	0.10	0.10	0.20	0.46
Acid **7**	>10	>10	>10	>10	>10

[a] Values are means of triplicate.[3f]