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Structure–activity relationships of 6-(aminomethylphenoxy)-benzoxaborole derivatives as anti-inflammatory agent

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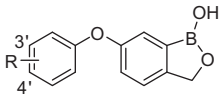
ABSTRACT

A series of novel 6-(aminomethylphenoxy)benzoxaborole analogs was synthesized for the investigation of the structure–activity relationship of the inhibition of TNF-alpha, IL-1beta, and IL-6, from lipopolysaccharide stimulated peripheral blood mononuclear cells. Compounds **9d** and **9e** showed potent activity against all three cytokines with IC_{50} values between 33 and 83 nM. Chloro substituted analog **9e** (**AN3485**) is considered to be a promising lead for novel anti-inflammatory agent with a favorable pharmacokinetic profile.

The clinical success of various biologic therapeutics has demonstrated that several cytokines are important therapeutic targets for chronic inflammatory diseases. Therapeutics targeting tumor necrosis factor-α (TNF-α) are used for rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD), and more.[1] The biologics targeting interleukin-1β (IL-1β) are approved for either RA or cryopyrin-associated periodic syndrome and the interleukin-6 (IL-6) receptor monoclonal antibody is approved for RA, Crohn's disease, and Castman's disease.[1] Although biologics have been highly effective and represent an important therapeutic advance, there remain a number of limitations for this class of agents, such as administration by injection, high cost, and poor or partial efficacy in considerable numbers of individuals. This leaves an unmet medical need for alternative therapies.[1–3] An orally or topically administered small molecule which blocks multiple inflammatory cytokines would meet the needs for ease of administration, lower cost and potentially increased efficacy.

Anacor Pharmaceuticals is focused on discovering new therapeutic agents by inclusion of boron atom into small molecule scaffolds. Using the benzoxaborole and related scaffolds as a novel drug pharmacophore, we have discovered a number of novel anti-infective and anti-inflammatory agents.[4] As part of this research, we have created a library of boron-containing compounds which has proven to be a useful source for both biochemical and phenotypic screening. In the current project, we screened our library for the inhibitory activity against the release of three cytokines, TNF-α, IL-1β, and IL-6, from lipopolysaccharide (LPS) stimulated peripheral blood mononuclear cells (PBMCs) in order to identify compounds that inhibit secretion of all three cytokines. Compounds **1a** and **1b** (Fig. 1) were found to show IC_{50} values ranging from 0.28 to 1.6 μM against all three cytokines. Preliminary structure–activity



	R		R
1a	3'-CH_2NH_2 HCl	**1e**	3'-NH_2
1b	4'-CH_2NH_2 HCl	**1f**	4'-NH_2
1c	3'-CH_2NMe_2 HCl	**1g**	3'-CO_2H
1d	4'-CH_2NMe_2 HCl	**1h**	4'-CO_2H

Figure 1. Chemical structures of compounds **1a**–**h**.

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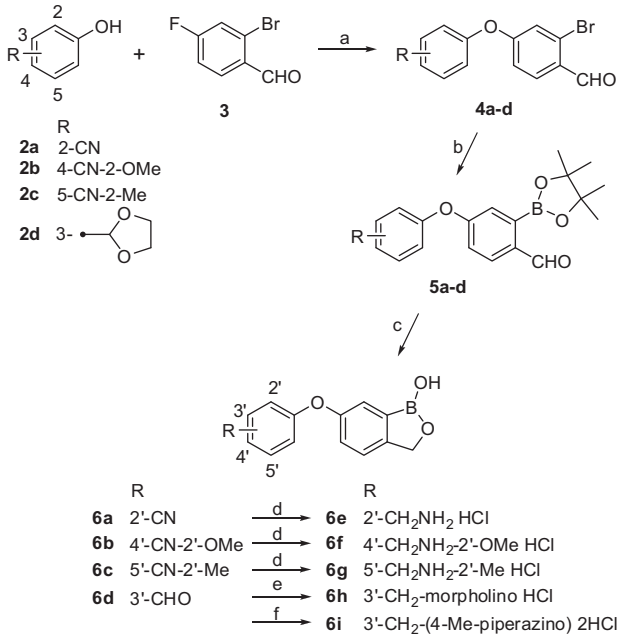


Scheme 1. Synthesis of compounds **6a**–**g**. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C, overnight (70–91%); (b) bis(pinacolato)diboron, $PdCl_2$(dppf) CH_2Cl_2, KOAc, 1,4-dioxane, 90 °C, 2–16 h (46–88%); (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h, then HCl (42–80%); (d) LAH, THF, 0 °C to rt, 1 h, then 4 M HCl in 1,4-dioxane (11–43%); (e) morpholine, $CH(OEt)_3$, $NaBH(OAc)_3$, EtOH, CH_2Cl_2, rt, 1 h (34%); (f) 1-methylpiperazine, $CH(OEt)_3$, $NaBH(OAc)_3$, EtOH, CH_2Cl_2, rt, 1 h (27%).

relationships (SAR) observed from the screening indicated that the primary aminomethyl group would be important for the activity. Based on this finding, further chemical modification was initiated.

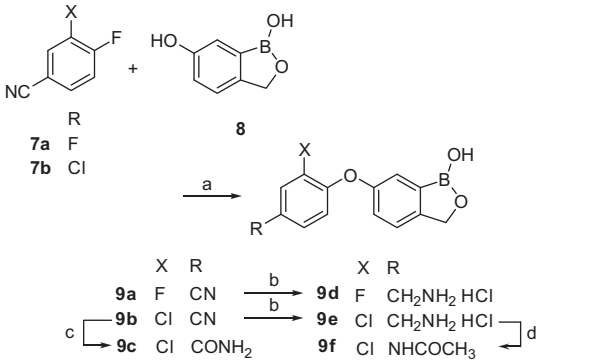
Herein we describe the in vitro SAR of novel 6-(aminomethylphenoxy)benzoxaborole derivatives as anti-inflammatory agents with inhibitory activity against TNF-α, IL-1β, and IL-6 production in PBMCs and the mouse pharmacokinetics of the most potent compounds **9d** and **9e**.

There are a number of ways to prepare substituted benzoxaborole derivatives.[4] Syntheses of compounds **1a**–**h** were reported previously.[5] Synthesis of 6-(aminomethylphenoxy)benzoxaborole analogs (**6e**–**i**) are shown in Scheme 1. SNAr reactions between substituted phenols (**2a**–**d**) and 2-bromo-4-fluorophenol (**3**) gave diphenylethers (**4a**–**d**). Miyaura-borylation[6] converted the bromide into pinacol borates (**5a**–**d**). The formyl group of compounds **5a**–**d** was reduced by $NaBH_4$ followed by acidic aqueous work-up to afforded benzoxaboroles **6a**–**d**. The cyano group of **6a**–**c** was reduced to aminomethyl group by LAH to give aminomethyl derivatives **6e**–**g**. Compound **6d** was converted into morpholinomethyl (**6h**) and 4-methylpiperazinomethyl (**6i**) derivatives by reductive amination.

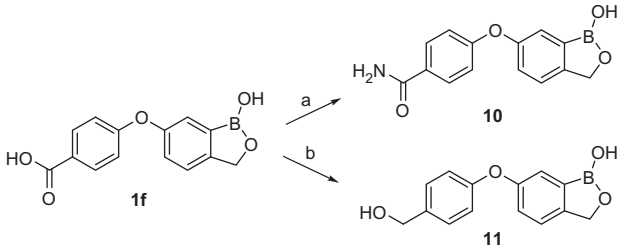
The synthesis of fluoro- and chloro-substituted analogs (**9d** and **9e**[7]) and some related analogs are shown in Scheme 2. SNAr reactions between **7a**,**b** and **8**[5] successfully gave the desired products **9a**,**b**. The cyano group of **9a**,**b** was reduced to aminomethyl group by LAH. Compound **9b** was partially hydrolyzed with sodium hydroxide in methanol to give the carboxamide (**9c**). Compound **9e** was treated with acetic anhydride to give the acetamide (**9f**).

Compounds **10** and **11** were prepared from compound **1f**[5] by the amide coupling using EDC and borane reduction, respectively, as shown in Scheme 3.

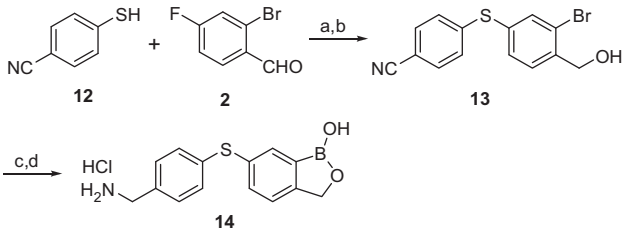
The thioether analog **14** was synthesized as shown in Scheme 4. Compounds **12** and **2** were coupled under basic condition followed by $NaBH_4$ reduction to give **13**. Compound **13** was mixed with triisopropyl borate followed by the slow addition of *n*-BuLi at −78 °C



Scheme 2. Synthesis of compounds **9a**–**e**. Reagents and conditions: (a) K_2CO_3, DMSO, 80–90 °C, overnight (33–61%); (b) LAH, THF, 0 °C to rt, 1 h, then 4 M HCl in 1,4-dioxane (43–68%); (c) aq NaOH, MeOH, 50 °C, 2 h (61%), (d) Ac_2O, pyridine, rt (79%).



Scheme 3. Synthesis of compounds **10** and **11**. Reagents and conditions: (a) NH_4OH, EDC, HOBT, DMF, rt, 24 h (44%); (b) BH_3, THF, 0 °C to rt (quant).



Scheme 4. Synthesis of compound **14**. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C (44%); (b) $NaBH_4$, MeOH, 0 °C to rt (100%); (c) (*i*-PrO)$_3$B, *n*-BuLi, THF, −78 °C to rt (62%); (d) LAH, THF, 0 °C to rt, then 4 M HCl in 1,4-dioxane, THF, Et_2O (26%).

to form the benzoxaborole scaffold. Then the cyano group was reduced to the aminomethyl group with LAH to give **14**.

The compounds were tested for the inhibitory activity against the release of the three cytokines, TNF-α, IL-1β, and IL-6 from PBMCs stimulated by LPS.[8] The results are summarized in Table 1.

Two aminomethylphenoxy analogs (**1a**,**b**) showed IC_{50} values ranging from 0.28 to 1.6 μM against the release of the three cytokines. *N*,*N*-Dimethylaminomethyl (**1c**,**d**) and 3-amino (**1e**) analogs lost the activity. The 4-amino analog (**1f**) showed moderate activity against TNF-α (9.1 μM) and IL-1β (4.8 μM), but not against IL-6. The 3-carboxy analog (**1g**) was slightly less potent than the 3-aminomethyl analog (**1a**) against all three cytokines. The 4-carboxy analog (**1h**) showed twofold to sixfold less potent IC_{50} values than the 4-aminomethyl analog (**1b**). Relocation of the aminomethyl group to 2′-position (**6e**) resulted in loss of activity. Installation of methyl (**6f**) or methoxy (**6g**) to the same phenyl ring resulted in decrease in activity. Both morpholinomethyl (**6h**) and *N*-methylpiperazinomethyl (**6i**) derivatives also showed decreased activity. When a fluoro (**9d**) or a chloro (**9e**) atom was introduced to the 2′-position of the 4-aminomethyl derivative (**1b**), activity was

Table 1
In vitro IC_{50} results of compounds against three cytokines released from PBMCs[a,b]

Compound	IC_{50} (μM) TNF-α	IC_{50} (μM) IL1-β	IC_{50} (μM) IL-6
1a	0.42	0.32	0.34
1b	1.6	0.28	1.4
1c	>10	>10	>10
1d	>10	>10	>10
1e	>10	>10	>10
1f	9.1	4.8	>10
1g	0.75	0.40	0.57
1h	4.4	1.9	4.0
6a	>10	>10	>10
6b	>10	>10	>10
6c	>10	>10	>10
6e	>10	>10	>10
6f	>10	1.5	>10
6g	>10	>10	>10
6h	5.9	4.4	>10
6i	>10	7.1	>10
9a	>10	>10	>10
9b	>10	>10	>10
9c	>10	>10	>10
9d	0.041	0.043	0.033
9e	0.083	0.052	0.067
9f	>10	>10	>10
10	>10	>10	>10
11	>10	>10	>10
14	10	>10	>10
Clobetasol	0.0070	4.4	4.2
Dexamethasone	0.017	0.0095	43%[c]
SB-203580	1.0	0.34	>10

[a] IC_{50} values are means of ⩾2 experiments for all; except **1c** and Clobetasol for TNF-α; and **1e**, **1f**, **6i**, and **14** for IL-1β which are $n = 1$. IC_{50} for compounds with <40% inhibition at 100 μM are reported as >10 μM. Compounds with reported IC_{50}s all resulted in between 80% and 100% inhibition at 100 μM; except that 40–79% inhibition was observed for **1h**, **6f**, **6h**, and **6i** for IL1-β; and **1b** for IL-6.

[b] All curves had Hill slopes between 0.5 and 1.8; except, **1g** and **14** for TNF-α; **1h**, **1g**, and **6f** for IL1-β which displayed Hill slopes >2. Compounds **1f** for TNF-α; and **1b** for IL1-β and IL-6 had a Hill slope of <0.5.

[c] % inhibition at 10 μM.

Table 2
In vivo mouse PK parameters of **9d** and **9e**

Compound		**9d**	**9e**
IV (5 mg/kg)	CL (mL/h/kg)	2280	2210
($n = 3$)	V_{ss} (mL/kg)	2140	2870
	AUC (h μg/mL)	1.74	2.26
	Terminal $t_{1/2}$ (h)	0.65	1.39
PO (10 mg/kg)	C_{max} (μg/mL)	0.142	1.45
($n = 3$)	T_{max} (h)	0.25	0.25
	AUC (h μg/mL)	0.533	2.66
	Terminal $t_{1/2}$ (h)	2.43	2.82
	Bioavailability (%)	15	67

increased 18- to 39-fold against TNF-α, fivefold to sixfold against IL-1β, and 20- to 42-fold against IL-6 compared to **1b**, respectively. IC_{50} values of these two compounds against three cytokines were ranging from 33 to 83 nM. Although the fluoro analog (**9d**) seemed to be slightly more potent than the chloro analog (**9e**), the difference might be within experimental error. The carboxamide analogs (**9c** and **10**), the acetamide (**9f**), and the hydroxymethyl analog (**11**) were all inactive. Replacement of the ether linker of **1b** with sulfur linker (**14**) resulted in losing activity. The cyano derivatives (**6a–c**, and **9a**,**b**) did not suppress cytokine secretion. Interestingly, both aminomethyl (**1a**,**b**) and carboxy analogs (**1g**,**h**) showed similar activity, while aniline analogs (**1e**,**f**) did not. These results indicate that a chargeable functional group is required at either 3′- or 4′-position and the charged atoms have to be at least one atom distance from the phenyl ring. *N*,*N*-Dialkylation of the aminomethyl group was not tolerated even with the smallest methyl groups, suggesting that the polarity would be important for the activity. The most potent compounds (**9d**,**e**) showed broader spectrum of activity than several standard anti-inflammatory agents. A corticosteroid, Clobetasol, showed very potent activity against TNF-α (7.0 nM), but moderate activity against IL-1β (4.4 μM) and IL-6 (4.2 μM). Another steroid, dexamethasone, showed IC_{50} values of 17 and 9.5 nM against TNF-α and IL-1β, respectively, while it showed only 43% inhibition against IL-6 at 10 μM. A p38 MAP kinase inhibitor, SB-203580, was active against TNF-α and IL-1β with IC_{50} values of 1.0 μM and 0.34 μM, respectively, but not active against IL-6 (>10 μM).

Mouse pharmacokinetics was examined for the most potent compounds **9d** and **9e**.[9] The results are summarized in Table 2. Both compounds showed similar clearance, volume of distribution, and AUC after intravenous administration. Compound **9e**; however, showed higher C_{max} (10-fold), AUC (fivefold), and bioavailability (4.5-fold) after oral dosing. Although **9d** showed slightly more potent IC_{50} values against cytokine production assay, **9e** showed fivefold higher oral exposure in vivo PK study, suggesting that **9e** would show better oral efficacy in vivo.

Oral administration of **9e** actually showed dose-dependent suppression of LPS-induced TNF-α and IL-6 production in mice with an ED_{90} of 30 mg/kg, and suppressed collagen-induced arthritis in mice over a 20-day period (35 mg/kg, BID).[10] Topically applied compound **9e** also showed significant inhibition of mouse ear swelling induced by either phorbol ester or oxazolone.[10]

Compounds **9d** and **9e** showed almost equal activity against the release of all three cytokines tested, which was distinct from the reference compounds, clobetasol, dexamethasone, and SB203580. Compound **9e** does not inhibit typical drug targets of anti-inflammatory agents, such as cyclooxygenases, phosphodiesterase-4, p38 MAP kinase, or JAK kinases.[10] Although the mechanism of action of the benzoxaborole analogs described in this Letter is unknown, the inhibition of cytokine release from PBMCs by compound **9e** is not due to cell general cytotoxicity, and appears to be down stream of TLRs and up stream of the transcriptional machinery.[10] Multiple benzoxaborole analogs, such as AN2690 (Tevaborole) for onychomycosis,[11] AN2728 for atopic dermatitis and psoriasis,[4b] and SCYX-7158 for human African trypanosomiasis,[12] are being clinically developed and showing good tolerability in human. Metabolism studies of several of these compounds show a general pattern of oxidative deboronation[13] or typical transformations of groups, such as primary alcohol moieties in parts of the molecule distant from the boron atom.[14] The compounds in development are free of gentotoxicy and long term carcinogenicity signals.[15] Compound **9e** (**AN3485**) is considered to be a promising lead for novel anti-inflammatory agent with potent inhibitory activity against the release of three cytokines and favorable PK profile in mice. Further structural optimization, in vivo efficacy studies in both oral and topical inflammatory disease models, and the studies on its mechanism of action are in progress.

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7. *Synthesis of 6-(4-(aminomethyl)-2-chlorophenoxy)benzo[c][1,2]oxaborol-1(3H)-ol* (**9e**): To a solution of 3*H*-benzo[*c*][1,2]oxaborole-1,6-diol (**8**) (300 mg, 2.00 mmol) in DMSO (30 mL) were added K_2CO_3 (828 mg, 6.00 mmol) and 3-chloro-4-fluoro-benzonitrile (**7b**) (933 mg, 6.00 mmol). The reaction was heated at 90 °C for 7 h. After cooling the reaction mixture to room temperature, EtOAc (50 mL) was added. The organic layer was washed with water (5 × 50 mL). The organic layer was evaporated under vacuum. The residue was purified by reverse phase chromatography to afford 3-chloro-4-(1-hydroxy-1,3-dihydro-benzo[*c*][1,2]oxaborol-6-yloxy)-benzonitrile (**9b**) (190 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.24 (s, 1H), 8.22 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.34 (s, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 4.99 (s, 2H); ESIMS (m/z): 284 $(M-H)^-$; HPLC: 96.4% (220 nm), 96.0% (maxplot). To a solution of compound **9b** (136 mg, 0.480 mmol) in anhydrous THF (60 mL) was added lithium aluminum hydride (1 M/ether, 1.19 mL, 1.19 mmol) at 0 °C. The reaction was stirred for 2 h. Then the reaction was quenched with 1 M HCl (30 mL). MeOH (50 mL) was added and the solution was filtered. The filtrate was evaporated under vacuum. The residue was purified by reverse phase chromatography (biotage, gradient MeOH/H_2O from 10% to 100%). To a suspension of **9e** free base in MeOH (5 mL) was added 4 M HCl in 1,4-dioxane (0.2 mL). The mixture became a clear solution then precipitates formed, which were collected by filtration to afford **9e** (106 mg, 68%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.19 (s, 1H), 8.18 (br s, 3H), 7.75 (s, 1H), 7.44–7.39 (m, 2H), 7.19–7.10 (m, 3H), 4.98 (s, 2H), 4.03 (q, J = 5.5 Hz, 2H); ESIMS (m/z): 290 $(M+H)^+$; HPLC: 95.9% (220 nm), 96.9% (maxplot).
8. Cell isolation, culture and stimulation: human buffy coats from healthy donors were obtained from Stanford Blood Center (Palo Alto, CA). PBMCs were isolated from pools of human buffy coats from healthy donors. Pools of buffy coats from eight donors by using Histopaque-1077, aliquoted and frozen in liquid nitrogen. Human PBMCs, monocytes and T cells were cultured in RPMI 1640 supplemented with 10% FBS, 2 mM glutamine and 10 mM HEPES, in a 95% air/5% CO_2 incubator. 5×10^5 PBMCs in 100 μL were seeded in each well of a 96-well culture plate for 3 h, then pre-incubated with test articles for 15 min, before stimulation with 1 μg/mL of LPS in a final volume of 200 μL. After 24 h, the cell culture supernatants were collected for cytokine determinations using Cisbio HTRF cytokine determination kits. Compounds were prepared using an eight point 1:10 dilution series starting at 100 μM; the resulting dose–response curves were fit to the four parameter sigmoid equation.
9. CD-1 mice were divided into 16 groups with three mice/group, and receive **9d** or **9e** by either intravenous (IV) injection with 5 mg/kg in a solution comprising 50% saline, 40% PGE400 and 10% DMSO (50/40/10 Saline/PGE400/DMSO) (pH 5.7), or by a gavage (PO) with 10 mg/kg in 70/25/5 PGE400/PG/DMSO solution. Blood samples were collected at eight time points during a 24 h period with three mice/time point. Drug concentrations in plasma were quantitated by LC/MS/MS[16] with the sensitivity of ⩾16 ng/mL for **9d** and ⩾8 ng/mL for **9e**. The mean plasma concentration-time profiles were analyzed using WinNonlin Pro version 5.2 with a two compartmental model for the IV data and a non-compartmental model for PO data.
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