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Boron-containing phenoxyacetanilide derivatives as hypoxia-inducible factor (HIF)-1α inhibitors

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ABSTRACT

A series of boron-containing phenoxyacetanilide derivatives **8a–f**, **9a–f**, **15**, and **16** were synthesized as hypoxia-inducible factor (HIF)-1α inhibitors. Among the compounds synthesized, carboranylphenoxyacetanilide **16** (GN26361) was found to be a potent inhibitor against HIF-1α accumulation under hypoxic conditions and inhibited the hypoxia-induced HIF-1 transcriptional activity in HeLa cells (IC_{50} = 0.74 μM). Compound **16** suppressed hypoxia-induced HIF-1α accumulation and vascular endothelial growth factor mRNA expression in a concentration-dependent manner without affecting the expression of HIF-1α mRNA.

The formation of new blood vessels sprouting from existing host capillaries (angiogenesis), is a necessary process for tumors to grow beyond a certain critical size.[1,2] Specific inhibition of this tumor-induced angiogenesis prevents growth of many types of solid tumors and provides a novel approach for cancer treatment. Angiogenesis factors such as vascular endothelial growth factor (VEGF) and erythropoietin (EPO) are key growth factors in tumor angiogenesis.[3] Various approaches have been studied for inhibition of their signal transduction to prevent angiogenesis and suppress tumor growth.[4,5]

Hypoxia-inducible factors (HIF) are heterodimeric (α/β) transcriptional factors and major physiological stimuli for expression of angiogenesis factors.[6–8] The levels of HIF-1α are low under normal oxygen conditions (normoxia) but increase in response to hypoxia. HIF-1β, also known as the arylhydrocarbon nuclear translocator,[9] is a constitutively expressed nuclear protein. Under normoxia, HIF-1α protein undergoes hydroxylation at specific prolyl residues by prolyl hydroxylase (PHD). This modification is recognized by the von Hippel–Lindau tumor suppressor protein for rapid degradation by the ubiquitin–proteasome system.[10] Under hypoxia, the hydroxylation by PHD is compromised and HIF-1α is sufficiently stabilized to form a heterodimeric complex with HIF-1β. This complex binds to the hypoxia response element (HRE) DNA sequence with co-activators to activate various genes, including VEGF and EPO.[6] HIF-1α has been found in a wide variety of human primary tumors compared with corresponding normal tissue.[11–16] HIF-1 is considered to be a potential target for antineoplastic therapy.[17,18] Various HIF-1 inhibitors that block HIF-1 activation under hypoxic conditions have been reported (Fig. 1). Topotecan[19] and PX-478[20,21] are undergoing phase I/II clinical trials on patients expressing high levels of HIF-1α in their tumors.[22] YC-1, originally developed as a potential therapeutic agent for circulation disorders, is in the lead-optimization stage.[23] Recently, AC1-001 was developed by Lee and co-workers,[24] and its benzimidazole analog (AC-004) has been reported to exhibit antitumor activity in vivo.[25]

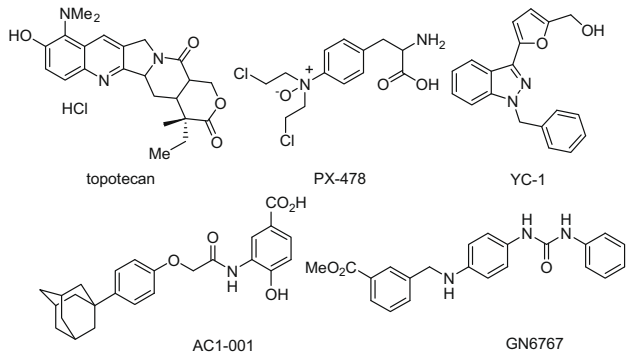

Figure 1. Structure of HIF-1 inhibitors.

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We also found that 1-[4-(*N*-benzylamino)phenyl]-3-phenylurea derivatives (e.g., GN6767) inhibit the hypoxia-induced HIF-1 transcriptional activity and suppress the secretion of VEGF without affecting the level of HIF-1α mRNA.[26]

We studied a boron-based medicinal drug design.[27–30] A boron atom has a vacant orbital and readily interconverts between the neutral sp^2 and anionic sp^3 hybridization states. This generates a new stable interaction between a boron atom and a donor molecule through a covalent bond. The X-ray crystal structure of 20S proteasome in a complex with bortezomib revealed that the boronic acid of bortezomib covalently interacts with the Thr-1 hydroxyl group in the active site of the 20S proteasome, forming a hybridized borate.[31] A B–H–B three-center two-electron bond results in stable formation of various boron clusters. In particular, carboranes (dicarba-*closo*-dodecaboranes: $C_2B_{10}H_{12}$) exhibit remarkable thermal stability, and their icosahedral geometry and exceptional hydrophobicity may allow their use as hydrophobic pharmacophores in biologically active molecules that interact with target proteins.[32–36] In this study, we focused on the structure of AC1-001 and synthesized boron-containing phenoxyacetanilide derivatives as HIF-1α inhibitors.

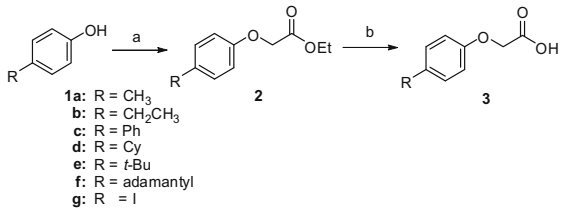
Chemistry: We first examined introduction of boronic acid into the benzene ring instead of carboxylic acid. As shown in Scheme 1, phenols **1a**–**g** having various substituents at the *para* position were treated with ethyl chloroacetate. The resulting esters **2a**–**g** were hydrolyzed with lithium hydroxide to give the corresponding aryloxyacetic acids **3a**–**g** in high yields.

Benzyl protection of 4-bromo-2-nitrophenol and 4-iodo-2-nitrophenol was carried out using benzyl bromide to give the benzyl ethers **4a** and **4b** (Scheme 2). The Suzuki–Miyaura-type diboron coupling reaction of **4a** proceeded in the presence of dichloro(diphenylphosphino-ferrocene)palladium(II) ($PdCl_2$dppf) catalyst to afford **5** in 93% yield. Hydrogenation of **5** gave anilinoboronic acid pinacol ester **6** in 87% yield. Anilines **7** was also derived from **4b** by treatment with iron under acidic conditions.

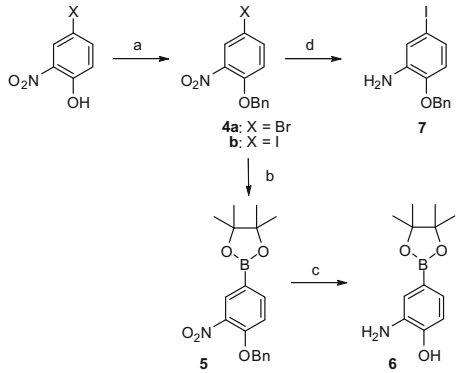
Carboxylic acids **3a**–**e** were reacted with **6** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hyroxybenzotriazole (HOBT) to give the corresponding aryloxyacetoanilides **8a**–**e** in 62–78% yields. Diisopropylethylamine (DIPEA) was an effective base for these amide formations. Finally, boronic acids **9a**–**e** were obtained in 22–63% yields from the corresponding pinacol esters **8a**–**e** by treatment with BBr_3 in dichloromethane at 0 °C (Scheme 3).

In the case of 4-adamantylphenoxyacetic acid **3f**, we first introduced the aniline moiety **7b** into **3f** using ethyl chloroformate (ECF) and *N*-methylmorphorine (NMM). The resulting anilide **10** underwent a Suzuki–Miyaura-type diboron coupling reaction followed by hydrogenation to give the boron ester **8f** in 63% yield in two steps. Deprotection of pinacol ester was carried out using BBr_3 to give the corresponding boronic acid **9f** in 72% yield (Scheme 4).

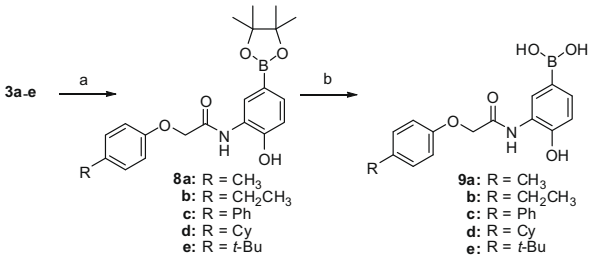
We next synthesized a carborane-containing phenoxyacetanilide derivative. The Sonogashira coupling reaction of **2g** with ethynyltrimethylsilane proceeded in the presence of $PdCl_2(PPh_3)_2$ and



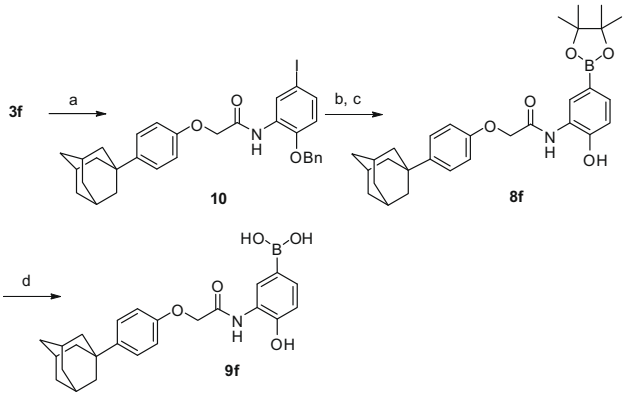
Scheme 1. Reagents and conditions: (a) $ClCH_2CO_2Et$, K_2CO_3, DMF, rt, 90–99%; (b) LiOH, THF/H_2O, 95–97%.



Scheme 2. Reagents and conditions: (a) BnBr, K_2CO_3, acetone, reflux, **4a**: 85%, **4b**: 99%; (b) pinacolatodiboron, $PdCl_2$dppf, AcOK, dioxane, 80 °C, 93% from **4a**; (c) Pd/C, H_2, EtOH, 87%; (d) Fe, HCl, $EtOH–H_2O$, reflux, 74% from **4b**.

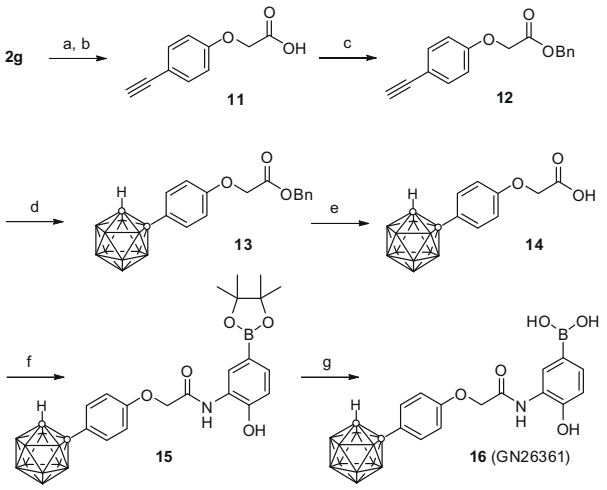


Scheme 3. Reagents and conditions: (a) **6**, EDCI, HOBT, DIPEA, 62–78%; (b) BBr_3, CH_2Cl_2, 0 °C, 22–63%.



Scheme 4. Reagents and condition: (a) **7**, ECF, NMM, TEA, THF, −20 °C, 72%; (b) pinacolatodiboron, $PdCl_2$(dppf), AcOK, DMF, 80 °C, 63%; (c) Pd/C, H_2,EtOH, 99%; (d) BBr_3, CH_2Cl_2, 0 °C, 72%.

CuI catalysts at 120 °C in a sealed vial under microwave irradiation conditions to give the corresponding coupling product in 93% yield. Removal of the tetramethylsilyl group and ester hydrolysis proceeded by treatment of LiOH in aqueous THF solution. The resulting carboxylic acid **11** was converted to benzyl ester **12**. The decaborane coupling reaction of **12** proceeded in the presence of CH_3CN as a Lewis base under toluene refluxed condition to afford the corresponding carborane **13** in 31% yield. Hydrogenation of **13** gave 4-*ortho*-carboranylphenoxyacetic acid **14** in 96% yield. Amide bond formation of **14** with **6** proceeded using isobutyl chloroformate (IBCF) and the resulting borate **15** was treated with KHF_2 in methanol to give the boronic acid **16** (GN25361) in 83% yield (Scheme 5).



Scheme 5. Reagents and conditions: (a) ethynyltrimethylsilane, $PdCl_2(PPh_3)_2$, CuI, DEA, DMF, microwave, 120 °C, 93%; (b) LiOH, THF–H_2O, rt, 82%; (c) BnBr, Na_2CO_3, DMF, rt, 93%; (d) $B_{10}H_{14}$, CH_3CN, toluene, reflux, 31%; (e) Pd/C, H_2, EtOH, 96%; (f) **6**, IBCF, 30%; (g) KHF_2, MeOH, 83%.

Biological activity: The synthesized boron-containing phenoxyacetanilide derivatives **8a–f**, **9a–f**, **15**, and **16** were tested for the hypoxia-induced transcriptional activity of HIF-1 using a cell-based reporter assay in HRE (×5)-Luc transfected HeLa cells and cell growth inhibition (GI_{50}) using the MTT assay. AC1-001 was used as a positive compound for comparison. The results are summarized in Table 1. The pinacol esters **8a–c** and the boronic acids **9a–c** did not show significant inhibition of the hypoxia-induced transcriptional activation by HIF-1 (IC_{50} ⩾90 μM). Enhancement of inhibition was observed along with bulky substituents at the *para* position of the benzene ring: cyclohexyl group (**8d** and **9d**, 70.4 and 84.8 μM, respectively), *tert*-butyl group (**8e** and **9e**, 35.3 and 40.3 μM, respectively), and adamantly group (**8f** and **9f**, 3.1 and 4.6 μM, respectively). The potency of compounds **8f** and **9f** were similar to that of AC1-001 (3.1 μM). It is considered that an adamantly group resembles the carborane cage in molecular size and shape.[32] Therefore, we synthesized compounds **15** and **16**, which have an *ortho*-carboranyl group substituted at the *para* position of the benzene ring, and tested for the hypoxia-induced transcriptional activity of HIF-1. The carborane substituent enhanced the inhibition of the hypoxia-induced transcriptional activity of HIF-1 (Table 1). The pinacol ester **15** displayed significant inhibition (1.7 μM), but the best result was obtained in carboranyl boronic acid **16**; the IC_{50} value was 0.74 μM, which was one-fold lower than that of AC1-001. In all cases, the pinacol ester derivatives exhibited higher inhibition in comparison with their boronic acid derivatives due to the transmembrane property of the more lipophilic pinacol ester functional group (except the carboranyl boronic acid **16**). HIF-1 inhibitors do not affect on the cell growth but affect on suppression of angiogenic factors in cancer cells. Therefore, cell growth inhibition of synthesized compounds was also investigated, and the compound concentrations required for 50% growth inhibition of HeLa cells are shown in Table 1. Although compounds **8a** and **8c** displayed relatively higher inhibition of cell growth (GI_{50} = 8.6 and 5.8 μM, respectively), GI_{50} values of other compounds were in the range of 12.1–85.9 μM.

Table 1
Inhibition of HIF-1 transcriptional activity in cell-based HRE reporter assay and cell growth inhibition

Compd	IC_{50}[a] (μM)	GI_{50}[b] (μM)
8a	90.6 ± 2.67	17.7 ± 0.66
8b	91.8 ± 8.24	8.6 ± 0.46
8c	>100	5.8 ± 0.82
8d	70.4 ± 1.88	13.4 ± 0.53
8e	35.3 ± 1.64	12.1 ± 0.67
8f	3.1 ± 0.15	16.0 ± 0.47
9a	>100	25.7 ± 0.21
9b	>100	14.9 ± 0.23
9c	>100	85.9 ± 0.73
9d	84.8 ± 5.53	29.2 ± 6.73
9e	40.3 ± 6.77	21.3 ± 0.40
9f	4.6 ± 0.86	15.2 ± 1.13
15	1.7 ± 0.58	52.4 ± 2.49
16(***GN26361***)	0.74 ± 0.24	16.2 ± 0.70
AC1-001	3.1 ± 0.07	51.6 ± 0.89

[a] HeLa cells stably transfected with HRE-Luc were incubated for 12 h with or without drugs under normoxic or hypoxic conditions. After removal of supernatant, a luciferase assay was performed using a Luciferase Assay System (Promega, Madison, WI, USA) according to manufacturer's instructions. The drug concentration required to inhibit the relative light unit by 50% (IC_{50}) was determined from semi-logarithmic dose–response plots, and results represent the mean ± SD of triplicate samples.

[b] HeLa cells were incubated for 48 h with various concentrations (100 nM to 100 μM) of compounds under normoxic condition, and viable cells were determined by MTT assay. The drug concentration required to inhibit cell growth by 50% (GI_{50}) was determined from semi-logarithmic dose–response plots, and results represent the mean ± SD of triplicate samples.

We next examined the effects of compound **16** against hypoxia-induced HIF-1α accumulation by western blot analysis and the mRNA expression level of HIF-1α and VEGF by RT-PCR analysis in HeLa cells.[20] Compound **16** suppressed HIF-1α accumulation in a concentration-dependent manner without affecting the expression level of HIF-1β protein (Fig. 2a). RT-PCR analysis revealed that compound **16** inhibited the hypoxia-induced expression of VEGF mRNA in a concentration-dependent manner (Fig. 2b); however, the levels of HIF-1α mRNA were not affected by compound **16**. These results indicated that compound **16** inhibits the hypoxia-induced expression of VEGF via suppression of HIF-1α accumulation. We also examined the effect of compound **16** on cell growth inhibition in various cell lines, such as HeLa, colon 26 (mouse colon cancer), B16 (mouse melanoma), and C6 (rat glioma). Cells were incubated for 72 h with compound **16** and viable cells were determined by MTT assay. Selective inhibition of cell growth by compound **16** was observed in colon 26 cells (GI_{50} = 5.0 μM) whereas significant inhibition was not observed at 10 μM in other cell lines. The efficacy of the boronic acid group is presumably due to the Lewis acidity. A boronic acid has a vacant p-orbital and can interact with target protein(s) not only through hydrogen bonding but also covalent bonding, which may cause enhanced biological activity, although we do not have any evidence for the role of the boronic acid group in the current study.[31,37,38]

In conclusion, carboranyl boronic acid **16** was found to be the most potent inhibitor of hypoxia-induced HIF-1α protein accumulation among the compounds synthesized. We confirmed that compound **16** showed significant suppression of the hypoxia-induced transcriptional activity (IC_{50} = 0.74 μM) and expression of

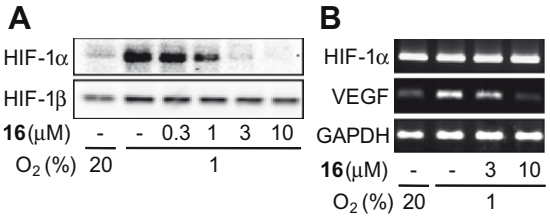


Figure 2. Effect of compound **16** on hypoxia-induced accumulation of HIF-1α protein and expression of VEGF mRNA. HeLa cells were incubated for 4 h with or without the indicated concentrations of compound **16** under hypoxic condition. (A) The levels of each protein were detected by immunoblot analysis with HIF-1α- or HIF-1β-specific antibodies. HIF-1β was used as the loading control, and '–' was DMSO used as the control. (B) HIF-1α, VEGF, and GAPDH *m*RNA expression was detected by RT-PCR.

VEGF mRNA without affecting the level of HIF-1α mRNA. These results suggest that carboranyl boronic acid **16** has the potential to be a new class of HIF-1α inhibitor. Further detailed mechanistic studies of HIF-1α inhibition by compound **16** is currently under investigation in our research group.

Acknowledgments

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38. *Spectral data for lead compounds*: 3-(4-Adamantyl-phenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester (**8f**): ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.56 (s, 1H), 8.57 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.35 (d, J = 8.0, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 4.66 (s, 2H), 2.10 (s, 3H), 1.90 (s, 6H), 1.73–1.82 (m, 6H), 1.34 (s, 12H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 168.4, 154.5, 151.9, 146.0, 134.6, 129.0, 126.3, 124.1, 119.8, 114.5, 83.8, 67.2, 43.3, 36.7, 35.7, 28.9, 24.8; IR(KBr) 3379.1, 2900.7, 2846.7, 2684.7, 2619.2, 2484.1, 1662.5, 1562.2, 1512.1, 1076.2, 1033.8, 1010.6, 856.3, 829.3 cm^{-1}; MS (ESI, positive) m/z 504 ([M+H]$^+$); Anal. Calcd for $C_{30}H_{38}BNO_5$: C, 71.57; H, 7.61; N, 2.78. Found: C, 71.25; H, 7.77; N, 2.75. 3-(4-Adamantylphenoxyacetylamino)-4-hydroxybenzene boronic acid (**9f**): ^{1}H NMR (400 MHz; CD_3OD) δ 8.23 (d, J = 11.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.71-6.76 (m, 1H), 4.50 (s, 2H), 1.93 (br s, 3H), 1.77 (s, 6H), 1.63-1.71 (m, 6H); ^{13}C NMR (75 MHz; CD_3OD) δ 169.2, 156.8, 151.0, 146.5, 132.7, 128.3, 127.9, 127.1, 125.8, 115.6, 68.9, 44.5, 37.9, 36.8, 30.5; IR(KBr) 2900.7, 2677.0, 2515.0, 2079.1, 1870.8, 1666.4, 1604.7, 1554.5, 1512.1, 1188.1, 1068.5, 806.2 cm^{-1}; MS (ESI, positive) m/z 436 ([M(OMe)+H]$^+$); Anal. Calcd for $C_{24}H_{28}BNO_5$: C, 68.42; H, 6.70; N, 3.32. Found: C, 68.14; H, 6.59; N, 3.19. 3-(4-*o*-Carboranylphenoxyacetylamino)-4-hydroxybenzene boronic acid pinacol ester (**15**): ^{1}H NMR (400 MHz; $CDCl_3$) δ 9.28 (s, 1H), 8.43 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 9.2, 2H), 7.42 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 4.66 (s, 2H), 3.91 (br s, 1H), 1.34 (s, 12H); ^{13}C NMR (75 MHz; $CDCl_3$) δ 167.3, 157.7, 151.8, 134.8, 128.9, 127.9, 123.9, 119.9, 114.9, 83.9, 67.1, 60.7, 24.9; IR(KBr) 3375.2, 2738.7, 2572.9, 2360.7, 1651.0, 1512.1, 1072.3, 1026.1, 1002.9, 964.3, 925.8, 879.5, 833.2 cm^{-1}; Anal. Calcd for $C_{22}H_{34}B_{11}NO_5$: C, 51.67; H, 6.70; N, 2.74. Found: C, 51.51; H, 6.56; N, 2.95. 3-(4-*o*-Carboranylphenoxyacetylamino)-4-hydroxybenzene boronic acid (**16**): ^{1}H NMR (400 MHz; CD_3OD) δ 8.17 (d, J = 12.4 Hz, 1H), 7.44 (d, J = 9.2 Hz, 2H), 7.20–7.33 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.71–6.77 (m, 1H), 4.92 (br s, 1H), 4.62 (s, 2H); ^{13}C NMR (75 MHz; CD_3OD) δ 168.4, 160.0, 150.6, 132.9, 130.3, 128.6, 125.8, 116.1, 115.5, 78.1, 68.6, 62.4; IR(KBr) 3066.6, 2927.7, 2866.0, 2603.7, 2341.4, 1882.4, 1670.2, 1512.1, 1188.1, 1122.5, 1072.3, 1022.2, 972.1, 918.1, 879.5, 837.0 cm^{-1}; MS (ESI, negative) m/z 428 ([M−H]$^-$); Anal. Calcd for $C_{16}H_{24}B_{11}NO_5$: C, 44.77; H, 5.64; N, 3.26. Found: C, 44.57; H, 5.47; N3.23.