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Synthesis, Structure, and Antifungal Activity of Dihydropyridones Containing Boronate Esters

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ABSTRACT: *We have prepared a series of novel 2,3-dihydro-4-pyridones containing boronate esters using the aza Diels–Alder reaction with Danishefsky's diene and imines derived from formylphenylboronic acids. This reaction can be carried out in moderate to high yields using $Yb(OTf)_3$ as a Lewis acid catalyst. Two new boron compounds exhibited moderate antifungal activity (at 100 μg disk^{-1}) using Amphotericin B as a control.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:56–63, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20512

INTRODUCTION

Compounds containing boronic acids [$RB(OH)_2$] or boronate esters [$RB(OR')_2$] are remarkably useful precursors for the Suzuki–Miyaura cross-coupling reactions [1] and as molecular recognition sensors [2]. Interest in these compounds also arises from their potent biological activities [3–10]. For instance, boron amino acid derivatives (Fig. 1a) are strong inhibitors of human arginase II, whose primary function appears to be in L-arginase homeostasis. Related α-aminoboronic acid derivatives are also well known for their ability to act as serine protease inhibitors [3]. Bortezomib (PS-341, Velcade; Fig. 1b) is a novel boronic acid dipeptide that potently, selectively, and reversibly inhibits 26S proteasome and was developed specifically for the therapy of human tumors [4]. Preclinical studies have shown that Bortezomib inhibited proliferation at a mean IC_{50} of 7 nM in 60 cell lines included in the National Cancer Institute's panel. Amino acid derivatives containing boron have also been investigated for their use in boron neutron capture therapy (BNCT) for the treatment of cancer [5]. BNCT is a bimodal form of therapy that depends on selectively depositing boron-10 atoms into the cancerous tumor before irradiation by slow neutrons. 4-Dihydroxyborylphenylalanine (Fig. 1c) has shown promise in the treatment of brain tumors. Also of importance is the recent observation that benzoxarole compounds (5-fluoro-3*H*-benzo[c] [1,2]oxaborol-1-ol, Fig. 1d) display considerable antifungal activity [6]. A remarkable property of boron, and in particular boronic acids, is their ability to selectively transport carbohydrates and other molecules across lipophilic membranes for potential applications in drug delivery [11]. A considerable amount of research has therefore focused on the synthesis of these potentially valuable compounds.

As part of our ongoing investigation into making novel boron compounds [12], and considering the wealth of bioactivities found in aminoboronic acid derivatives, we decided to examine the synthesis of boron-containing 2,3-dihydro-4-pyridones using the aza Diels–Alder reaction with Danishefsky's diene.

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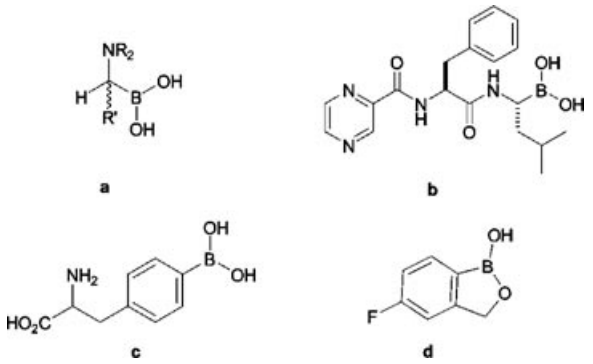


FIGURE 1 Bioactive boron compounds.

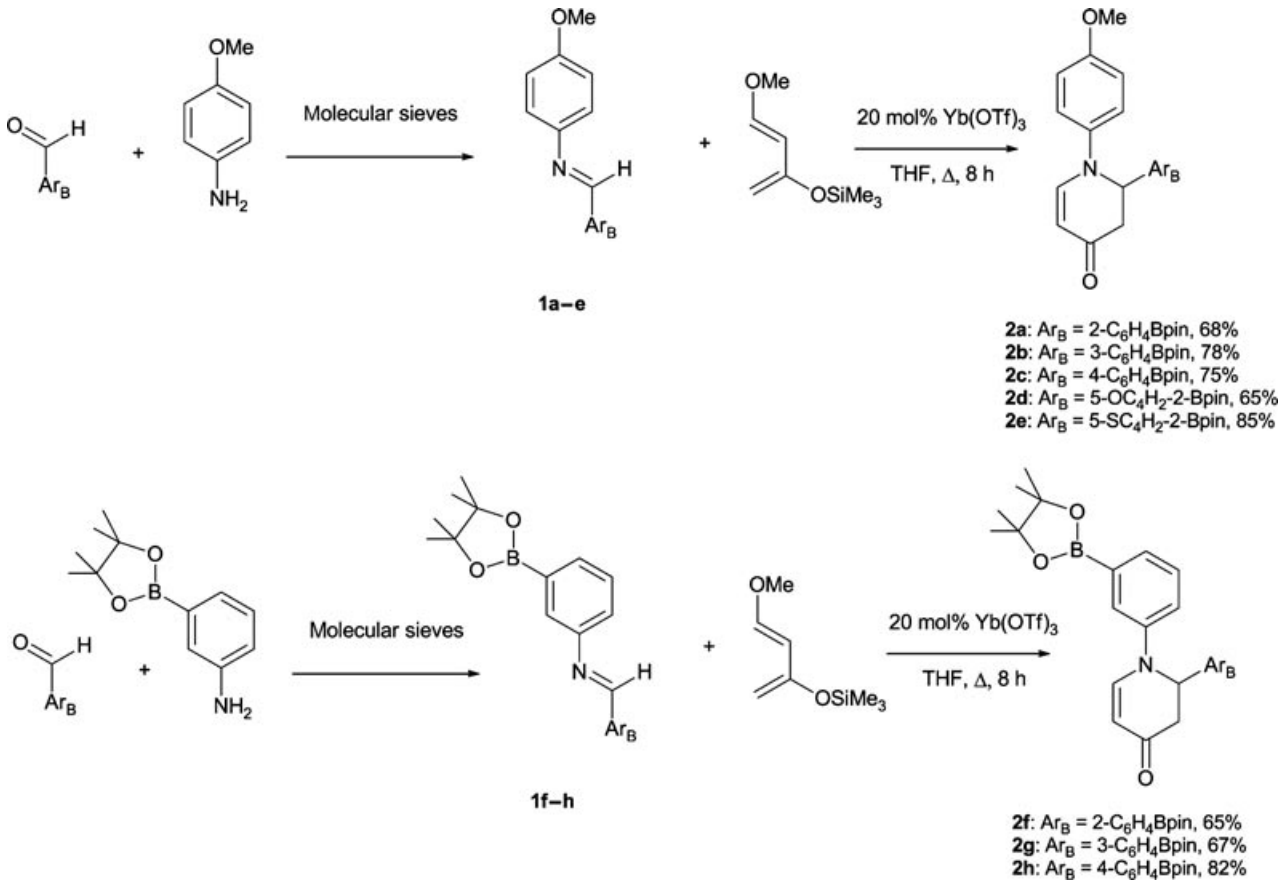
Previous studies have shown that compounds containing boronic acids can be extremely difficult to characterize in terms of elemental composition, owing to the ease with which they partially dehydrate to the corresponding trimeric and oligomeric anhydrides [13]. As such, we have decided to initially prepare the corresponding boronate ester derivatives; the results of which are presented herein.

RESULTS AND DISCUSSION

Synthesis

The aza Diels–Alder reaction of Danishefsky's diene with imines is a powerful synthetic method for preparing 2-substituted 2,3-dihydro-4-pyridones that has received a considerable amount of attention. Dihydropyridone derivatives are highly versatile synthetic intermediates for the preparation of biologically important molecules [14]. As such, we have decided to prepare a series of boron-containing 2,3-dihydro-4-pyridones using Danishefsky's diene and preformed imines containing boronate esters. Imines incorporating boron groups have also received significant attention. For instance, Whiting and coworkers used imines containing boronate esters to make enantio-enriched γ-phenyl-γ-amino alcohols [15]. Incorporation of the boronate ester functionality in these cases was accomplished by deprotonation of acetophenone-derived imines followed by alkylation with ICH_2Bpin (pin = 1,2-$O_2C_2Me_4$) at low temperatures. Reduction of the imine was achieved using BH_3 reagents. In this study, we found that pinacol protected derivatives of formylphenylboronic acid [(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde] add to anisidine or 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3-APBpin) in organic solvents to give compounds having spectroscopic data consistent with the aldimines **1a–h** (Scheme 1). All imines have been characterized by multinuclear NMR spectroscopy and show a signal for the N=CH methine proton between δ 8.43 and 9.18 ppm in the ^{1}H NMR spectra. A resonance at ca. 155 ppm in the ^{13}C NMR spectra corresponds to the sp^2 carbon of the N=CH group. A broad peak at around 30 ppm in the ^{11}B NMR spectra suggests that the boron atom lies in a three-coordinate environment in solution [16]. The molecular structure of **1e** has also been confirmed by a single crystal X-ray diffraction study (Fig. 2). The imine C(10)—N(9) bond distance of 1.277(3) Å is comparable to azomethine compounds derived from salicylaldehyde and phenylboronic acid [17]. The B—O bond distances (avg. = 1.361(3) Å) are also typical for three-coordinate boron [16,18–20] and significantly shorter than those observed in chelate complexes with diphenylborinic acid [21] or phenylboronic acid derivatives (ca. 1.5 Å) [22], where the boron atom is four-coordinate.

Although a number of Lewis acids can be used to facilitate the aza Diels–Alder reaction, we have found that $Yb(OTf)_3$ effectively catalyzes the addition of these boron-containing imines to Danishefsky's diene in moderate to high yields (Scheme 1) [23–27]. Attempts to improve yields using other Lewis acids or methodologies [27] proved unsuccessful. All new 2,3-dihydro-4-pyridones **2a–h** have been characterized by a number of physical methods including multinuclear NMR spectroscopy. The ^{1}H NMR for compounds **2a–h** shows a diagnostic pair of doublets for the alkene fragment of the pyridone ring in the aromatic region and a sharp singlet at ca. δ 1.35 ppm for the pinacol hydrogens. A broad peak at around 30 ppm is once again observed in the ^{11}B NMR spectra, where the boron atom remains three coordinate. This result is somewhat surprising in light of boron's propensity to form coordinate bonds with Lewis basic atoms [28]. The corresponding ^{13}C NMR data are also consistent with the formation of these novel pyridone, and the broad peak at ca. δ 140 ppm signifies the C—B bond for the Ar-Bpin groups. Compounds **2e** and **2f** have also been characterized by single crystal X-ray diffraction studies (Figs. 3 and 4), and the average B—O bond distances of 1.357(4) (**2e**) and 1.365(4) (**2f**) Å are consistent with three-coordinate boron compounds. Bond distances and angles within the pyridone ring are well within the range observed in related compounds [29]. No appreciable intra- or intermolecular interactions between the Lewis acidic boron atom and the nitrogen groups are observed in the solid state.



SCHEME 1

Antifungal Studies

Compounds **2f–h** are of special interest as they contain two boronate ester groups and are prepared from the [4+2] addition of Danishefsky's diene with aldimines derived from 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenamine. Benzylamine compounds generated from this boron-containing aniline have shown moderate antifungal activities [30].

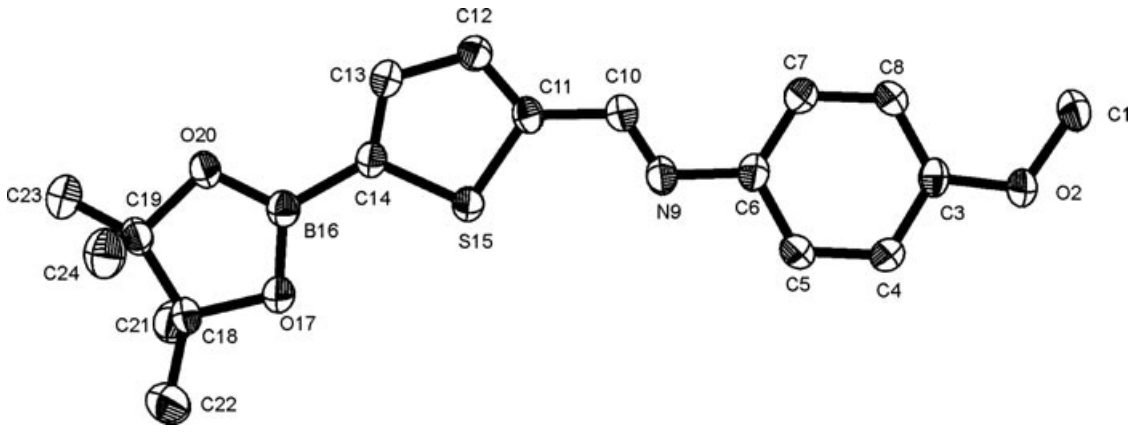


FIGURE 2 Perspective view of one of the independent molecules of **1e** with atom labeling scheme. Thermal ellipsoids are drawn at the 50% probability level, and hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): N(9)–C(10) 1.277(3), C(14)–B(16) 1.559(3), C(14)–S(15) 1.727(2), B(16)–O(20) 1.358(3), B(16)–O(17) 1.364(3), C(11)–S(15) 1.731(2); C(10)–N(9)–C(6) 120.4(2), O(20)–B(16)–O(17) 114.6(2), O(20)–B(16)–C(14) 122.5(2), O(17)–B(16)–C(14) 122.9(2).

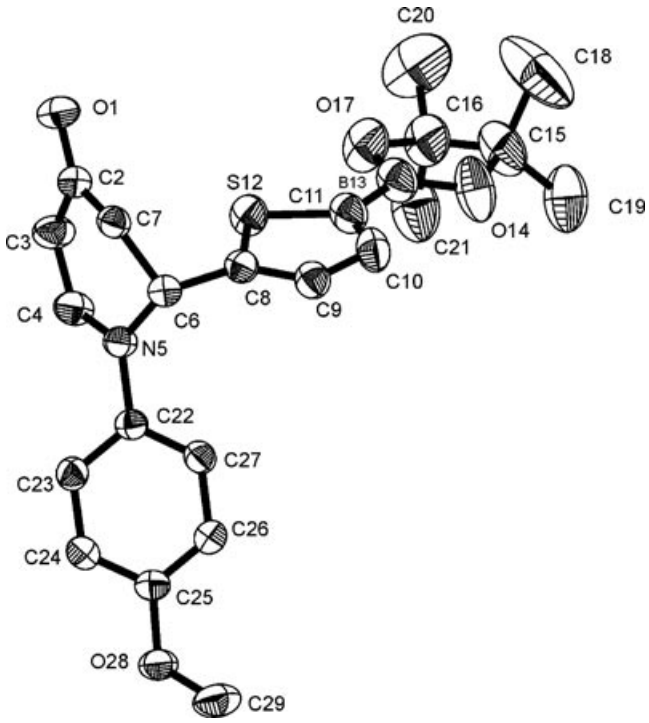


FIGURE 3 Perspective view of **2e** with atom labeling scheme. Thermal ellipsoids are drawn at the 50% probability level, and hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): O(1)–C(2) 1.234(3), C(3)–C(4) 1.364(3), C(11)–B(13) 1.559(4), B(13)–O(14) 1.355(4), B(13)–O(17) 1.358(4); O(1)–C(2)–C(3) 123.9(2), O(1)–C(2)–C(7) 121.4(2), O(14)–B(13)–O(17) 114.6(3), O(14)–B(13)–C(11) 121.6(3), O(17)–B(13)–C(11) 123.7 (3).

With this in mind, we have examined all new compounds for their ability to act as antifungal agents.

Given the wealth of bioactivities exhibited by 2,3-dihydro-4-pyridones [31] and 4-pyridone derivatives [32], we have studied the potential antifungal activity of our new boron-containing compounds. Initial studies were carried out using four fungi, *Aspergillus niger*, *A. flavus*, *Candida albicans*, and *Saccharomyces cerevisiae*, employing Amphotericin B (AmB) as a control [12,33–35]. Although compounds **2a** and **2b** both showed appreciable activity (Table 1), the para derivative **2c** was inactive (not shown). Likewise, no activity was observed for **2f**, where the para methoxy substituent of the initial aniline derivative has been replaced with a meta-substituted boronate ester functionality. The non-boron control, prepared by the methodology developed by Feng et al. [25–27], showed no appreciable antifungal activity in this study. It is unclear at this time what role the boron groups have on the observed activities, and further work is therefore needed to fully understand the structure activity relationships in these compounds in an effort to design a more powerful antifungal agent.

CONCLUSION

In summary, we have prepared the first examples of boron-containing 2,3-dihydro-4-pyridones from the addition of imines, synthesized from commercially available aldehydes containing boronic acids, and Danishefsky's diene. Products have been characterized by a number of physical methods, including X-ray diffraction studies for **1e, 2e**, and **2f**. Although most of these compounds showed no appreciable antifungal activity, the 2- and 3-boronated derivatives **2a** and **2b**, respectively, showed good activity against four fungi. We are in the process of preparing other

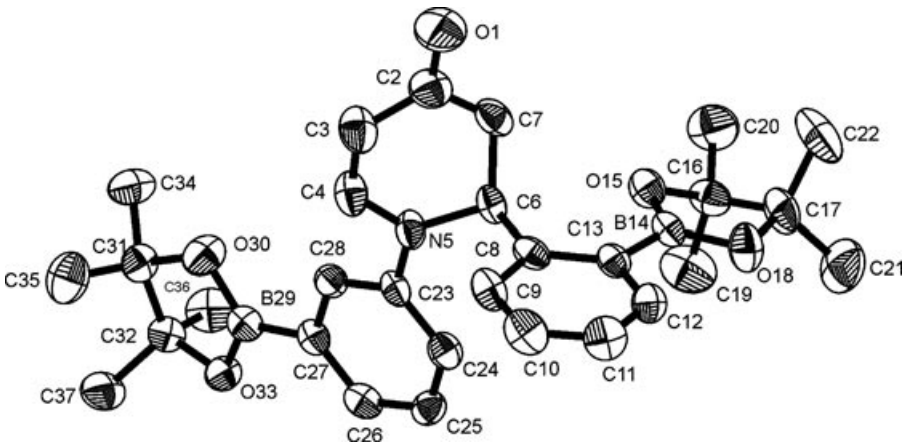


FIGURE 4 Perspective view of one of the independent molecules of **2f** with atom labeling scheme. Thermal ellipsoids are drawn at the 50% probability level, and hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): O(1)–C(2) 1.233(4), C(3)–C(4) 1.349(4), C(13)–B(14) 1.575(5), B(14)–O(15) 1.360(4), B(14)–O(18) 1.370(4), B(29)–O(33) 1.360(4), B(29)–O(30) 1.369(4); O(1)–C(2)-C(3) 123.7(4), O(1)–C(2)–C(7) 120.5(3), O(15)–B(14)–O(18) 112.9(3), O(15)–B(14)–C(13) 127.3(3), O(18)–B(14)–C(13) 119.7(3), O(33)–B(29)–O(30) 113.2(3), O(33)–B(29)–C(27) 124.7(3), O(30)–B(29)–C(27)121.9(3).

TABLE 1 Antifungal Testing at a Dosage of 100 μg Disk^{-1}

	Clear Zone (mm)			
Compound	*A. niger*	*A. flavus*	*C. albicans*	*S. cerevisiae*
2a	7	0	7 halo	7 halo
2b	10	7	7 halo	9
2c	0	0	0	0
2d	0	0	0	0
2e	0	0	0	0
2f	0	0	0	0
2g	0	0	0	0
2h	0	0	0	0
AmB	11	11	9	9

2,3-dihydro-4-pyridones derived from formylphenylboronic acids and aniline derivatives and will report our findings in due course.

EXPERIMENTAL

General

Reagents and solvents used were purchased from Aldrich Chemicals. The synthesis of imines [36] and the transesterification of boronic acids with pinacol [37] were performed by established methods. NMR spectra were recorded on a JEOL JNM-GSX270 FT spectrometer. ^{1}H NMR chemical shifts are reported in ppm and referenced to residual solvent protons in deuterated solvent at 270 MHz. ^{11}B NMR chemical shifts are reported in ppm and are referenced to $BF_3^{\cdot}$ OEt_2 as an external standard at 87 MHz. ^{13}C NMR chemical shifts are referenced to solvent carbon resonances as internal standards at 68 MHz and are reported in ppm. Multiplicities are reported as singlet (s), doublet (d), broad (br), multiplet (m), and overlapping (ov). The infrared spectra were obtained using a Mattson Genesis II FTIR spectrometer and are reported in cm^{-1}. The melting points were determined using a Mel-Temp apparatus and are uncorrected. Microanalyses for C, H, and N were carried out at Guelph Chemical Laboratories (Guelph, ON, Canada). GCMS analyses were performed by DalChem MS Lab (Halifax, NS, Canada).

General Synthesis

To a stirring solution of the appropriate boronate ester in THF (20 mL), Danishefsky's diene (2 equivalents) and a catalytic amount of $Yb(OTf)_3$ (20 mol%) at RT were added. The reaction mixture was heated at reflux for 8–24 h, at which point the solvent was removed under vacuum. The resulting solid was dissolved in $CHCl_3$ (5 mL) and flashed through a plug of silica gel. The $CHCl_3$ eluent was further purified by column chromatography, using $CHCl_3$/ethylacetate/hexanes (6:3:2) to afford the desired product.

*2,3-Dihydro-1-(4-methoxyphenyl)-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (**2a**).* Yield: 68%; mp = 72–74°C. ^{1}H NMR ($CDCl_3$) δ: 7.86 (d, $J = 6.7$ Hz, 1H), 7.70 (d, $J = 6.4$ Hz, 1H), 7.36–7.22 (ov m, 2H), 6.95 (d, $J = 8.3$ Hz, 2H), 6.77 (d, $J = 8.3$ Hz, 2H), 6.08 (dd, $J = 7.8$, 3.2 Hz, 1H), 5.27 (m, 2H), 3.72 (s, 3H), 3.30 (dd, $J = 16.4$, 7.8 Hz, 1H), 2.63 (dd, $J = 16.4$, 3.2 Hz, 1H), 1.35 (s, 12H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ: 191.7, 156.6, 150.1, 145.4, 141 (br, *C*-B), 138.6, 137.7, 131.5, 127.0, 125.5, 120.5, 114.6, 101.2, 84.0, 60.4, 55.5, 44.6, 25.0;^{11}B ($CDCl_3$) δ: 30 (br). FTIR (Nujol): 2955 (s), 2935 (s), 2919 (s), 2853 (s), 1612 (w), 1601 (w), 1537 (w), 1508 (m), 1462 (m), 1345 (w), 1236 (m), 1166 (w), 1030 (m), 762 (w), 638 (w). Anal. Calcd for $C_{24}H_{28}BNO_4$ (405.29): C 71.11, H 6.98, N 3.46; Found: C 71.22, H 6.96, N 3.07. GCMS (CI+): required $m/z = 405.2$, found $[M + H]^+ = 406.2$, $[M + Na]^+ = 428.3$.

*2,3-Dihydro-1-(4-methoxyphenyl)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (**2b**).* Yield: 78%; mp = 60–62°C. ^{1}H NMR ($CDCl_3$) δ: 7.84 (d, $J = 6.4$ Hz, 1H), 7.61 (d, $J = 7.3$ Hz, 1H), 7.34–7.17 (ov m, 2H), 6.90 (d, $J = 7.5$ Hz, 2H), 6.71 (d, $J = 7.5$ Hz, 2H), 6.04 (dd, $J = 7.3$, 3.2 Hz, 1H), 5.19 (m, 2H), 3.73 (s, 3H), 3.25 (dd, $J = 15.4$, 7.3 Hz, 1H), 2.60 (dd, $J = 15.4$, 3.2 Hz, 1H), 1.28 (s, 12H); ^{13}C{^{1}H} ($CDCl_3$) δ: 190.8, 156.7, 153 (br, *C*-B), 150.0, 145.5, 138.6, 137.7, 131.5, 127.0, 125.5, 120.5, 114.6, 101.3, 84.0, 60.7, 55.6, 44.6, 25.0; ^{11}B ($CDCl_3$) δ: 31 (br). FTIR (Nujol): 2933 (s), 2912 (s), 2858 (s), 1645 (w), 1590 (w), 1510 (w), 1462 (m), 1377 (m), 1348 (w), 1227 (w), 1142 (w), 1033 (w), 964 (w), 723 (w). Anal. Calcd for $C_{24}H_{28}BNO_4$ (405.29): C 71.11, H 6.98, N 3.46; Found: C 71.09, H 7.06, N 3.14. GCMS (CI+): required $m/z = 405.2$, found $[M + H]^+ = 406.4$, $[M + Na]^+ = 428.3$.

*2,3-Dihydro-1-(4-methoxyphenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (**2c**).* Yield: 75%; mp = 82–84°C. ^{1}H NMR ($CDCl_3$) δ: 7.72 (d, $J = 7.3$ Hz, 2H), 7.50 (d, $J = 7.9$ Hz, 1H), 7.24 (d, $J = 7.3$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.75 (d, $J = 8.8$ Hz, 2H), 5.20 (d, $J = 7.9$ Hz, 1H), 5.15 (m, 1H), 3.74 (s, 3H), 3.23 (dd, $J = 15.7$, 7.4 Hz, 1H), 2.75 (dd, $J = 15.7$, 4.1 Hz, 1H), 1.36 (s, 12H); ^{13}C{^{1}H} ($CDCl_3$) δ: 189.9, 156.9, 149.9, 141.5, 138.2, 135.4, 129 (br, *C*-B),

125.8, 121.2, 114.7, 101.5, 83.9, 62.4, 55.5, 43.4, 24.9; ^{11}B ($CDCl_3$) δ: 30 (br). FTIR (Nujol): 2978 (s), 2927 (s), 2918 (s), 2854 (s), 1613 (w), 1547 (w), 1508 (w), 1462 (m), 1376 (m), 1326 (w), 1251 (w), 1222 (w), 1141 (w), 1088 (w), 1029 (w), 638 (w). Anal. Calcd for $C_{24}H_{28}BNO_4$ (405.29): C 71.11, H 6.98, N 3.46; Found: C 70.89, H 6.93, N 3.08. GCMS (CI+): required $m/z = 405.2$, found $[M + Na]^+ = 428.3$.

*2,3-Dihydro-1-(4-methoxyphenyl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl)pyridin-4(1H)-one (***2d***).* Yield: 65%; mp = 145–147°C. ^{1}H NMR ($CDCl_3$) δ: 7.30 (d, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 8.8$ Hz, 2H), 6.94 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 3.2$ Hz, 1H), 5.16–5.06 (ov m, 2H), 3.67 (s, 3H), 2.99–2.69 (ov m, 2H), 1.22 (s, 6H), 1.11 (s, 6H); ^{13}C{^{1}H} ($CDCl_3$) δ: 190.3, 157.2, 155.8, 148.8, 138.1, 130 (br, *C*-B), 124.3, 121.9, 114.7, 108.9, 101.5, 84.3, 57.2, 55.5, 40.2, 24.8; ^{11}B ($CDCl_3$) δ: 26 (br). FTIR (Nujol): 2952 (s), 2918 (s), 2856 (s), 1699 (w), 1577 (w), 1510 (w), 1462 (m), 1377 (m), 1350 (w), 1105 (w), 951 (w), 762 (w), 723 (w). Anal. Calcd for $C_{22}H_{26}BNO_5$ (395.26): C 66.84, H 6.64, N 3.54, Found: C 66.27, H 6.81, N 3.23. GCMS (CI+): required $m/z = 395.3$, found $[M + Na]^+ = 418.3$.

*2,3-Dihydro-1-(4-methoxyphenyl)-2-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl)-pyridin-4(1H)-one (***2e***).* Yield: 85%; mp = 173–175°C. ^{1}H NMR ($CDCl_3$) δ: 7.40 (d, $J = 7.3$ Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.03 (m, 1H), 6.82 (d, $J = 8.5$ Hz, 2H), 5.41 (dd, $J = 7.5$, 2.6 Hz, 1H), 5.21 (ov m, 2H), 3.78 (s, 3H), 3.28 (dd, $J = 15.3$, 7.5 Hz, 1H), 2.80 (dd, $J = 15.3$, 2.6 Hz, 1H), 1.31 (s, 12H); ^{13}C{^{1}H} ($CDCl_3$) δ: 189.8, 157.2, 149.0, 148.7, 137.8, 137.0, 129 (br, *C*-B), 127.2, 126.2, 114.5, 101.8, 84.2, 58.9, 55.5, 43.4, 24.8; ^{11}B ($CDCl_3$) δ: 28 (br). FTIR (Nujol): 2962 (s), 2945 (s), 2900 (s), 2870 (s), 1639 (w), 1576 (w), 1509 (w), 1462 (m), 1377 (m), 1346 (w), 1284 (w), 1242 (w), 1207 (w), 1142 (w), 1091 (w), 1025 (w), 955 (w), 829 (w), 665 (w). Anal. Calcd for $C_{22}H_{26}BNO_4S$ (411.32): C 64.23, H 6.38, N 3.41; Found: C 64.55, H 6.21, N 3.08. GCMS (CI+): required $m/z = 411.3$, found $[M + Na]^+ = 434.3$.

*2,3-Dihydro-2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(3-(4,4,5,5-tetramethyl-1,3,-2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (***2f***).* Yield: 65%; mp = 76–78°C. ^{1}H NMR ($CDCl_3$) δ: 7.91–7.82 (ov m, 2H), 7.58–7.47 (ov m, 2H), 7.35–7.22 (ov m, 3H), 6.98 (m, 1H), 6.17 (dd, $J = 7.5$, 2.5 Hz, 1H), 5.29–5.26 (ov m, 2H), 3.27 (dd, $J = 15.6$, 7.5 Hz, 1H), 2.64 (dd, $J = 15.6$, 2.5 Hz, 1H), 1.32 (s, 24H); ^{13}C{^{1}H} ($CDCl_3$) δ: 191.1, 149.4, 145.4, 144.3, 137.7, 131.5, 130.5, 129 (br, 2C, *C*-B), 128.9, 127.0, 125.3, 124.8, 121.2, 102.1, 84.2, 84.0, 59.8, 44.5, 24.9; ^{11}B ($CDCl_3$) δ: 31 (br). FTIR (Nujol): 2966 (s), 2935 (s), 2873 (s), 2846 (s), 1684 (w), 1645 (w), 1581 (w), 1570 (w), 1462 (m), 1377 (m), 1317 (w), 1267 (w), 1213 (w), 1144 (w), 1115 (w), 962 (w), 760 (w), 723 (w), 660 (w). Anal. Calcd. for $C_{29}H_{37}B_2NO_5$ (501.23): C 69.48, H 7.45, N, 2.79; Found: C 69.38, H 7.30, N 2.43. GCMS (CI+): required $m/z = 501.2$, found $[M + H]^+ = 502.4$, $[M + Na]^+ = 524.4$.

*2,3-Dihydro-1,2-bis(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (***2g***).* Yield: 67%; mp = 82–84°C. ^{1}H NMR ($CDCl_3$) δ: 7.76–7.67 (ov m, 3H), 7.56–7.46 (ov m, 2H), 7.32–7.21 (ov m, 3H), 6.95 (m, 1H), 5.30–5.24 (ov m, 2H), 3.25 (dd, $J = 15.4$, 6.4 Hz, 1H), 2.78 (dd, $J = 15.4$, 3.3 Hz, 1H), 1.36 (s, 24H); ^{13}C{^{1}H} ($CDCl_3$) δ: 190.4, 148.9, 144.2, 137.2, 134.3, 132.7, 131 (br, 2C, *C*-B), 130.9, 129.0, 128.8, 128.2, 125.1, 121.4, 102.8, 84.2, 84.0, 61.7, 43.6, 25.0, 24.9; ^{11}B ($CDCl_3$) δ: 30 (br). FTIR (Nujol): 2943 (s), 2902 (s), 2860 (s), 1649 (w), 1581 (w), 1570 (w), 1462 (m), 1377 (m), 1265 (w), 1213 (w), 1144 (w), 962 (w), 708 (w). Anal. Calcd for $C_{29}H_{37}B_2NO_5$ (501.23): C 69.48, H 7.45, N 2.79; Found: C 69.75, H 7.21, N 2.48. GCMS (CI+): required $m/z = 501.3$, found $[M + H]^+ = 502.5$, $[M + Na]^+ = 524.4$.

*2,3-Dihydro-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,-2-dioxaborolan-2-yl)phenyl)pyridin-4(1H)-one (***2h***).* Yield: 82%; mp = 86–88°C. ^{1}H NMR ($CDCl_3$) δ: 7.75–7.69 (ov m, 3H), 7.55–7.50 (ov m, 2H), 7.26–7.18 (ov m, 3H), 6.95 (dd, $J = 6.4$, 3.3 Hz, 1H), 5.30–5.24 (ov m, 2H), 3.23 (dd, $J = 15.4$, 6.4 Hz, 1H), 2.78 (dd, $J = 15.4$, 3.3 Hz, 1H), 1.32 (s, 24H); ^{13}C{^{1}H} ($CDCl_3$) δ: 190.3, 149.0, 144.2, 141.2, 135.5, 130.9, 130 (br, 2C, *C*-B), 129.1, 125.7, 125.2, 121.6, 102.7, 84.2, 83.9, 61.8, 43.4, 25.9, 24.9; ^{11}B ($CDCl_3$) δ: 30 (br). FTIR (Nujol): 2943 (s), 2904 (s), 2858 (s), 1649 (w), 1581 (w), 1570 (w), 1462 (m), 1363 (w), 1327 (m), 1265 (w), 1219 (w), 1142 (w), 1088 (w), 1030 (w), 962 (w), 858 (w), 756 (w), 705 (w). Anal. Calcd for $C_{29}H_{37}B_2NO_5 \cdot 2EtCO_2CH_3$ (677.53): C 65.59, H 7.90, N 2.07; Found: C 65.19, H 7.34, N 2.28. GCMS (CI+): required for $C_{29}H_{37}B_2NO_5$ $m/z = 501.3$, found $[M+ Na]^+ = 524.4$.

Biological Testing

Compounds were tested for antifungal activity against pure cultures of *A. niger*, *A. flavus*, *C. albicans,* and *S. cerevisiae* supplied by Ward's Natural Science Ltd. (St. Catharines, Ontario, Canada). All cultures were maintained on Sabouraud dextrose

agar. Four agar plugs (10-mm diameter) of *A. niger* or *A. flavus* were cut from a 5–8 day-old colony and homogenized in distilled, sterilized water (2 mL). From this suspension, 0.5 mL was transferred aseptically to a Petri plate with Sabouraud dextrose agar (25 mL) and spread evenly over the entire surface. A 0.5-mL aliquot of a 1-month old liquid culture medium of *C. albicans* or *S. cerevisiae* was transferred and spread aseptically and allowed to dry. Each plate was provided with four evenly spaced paper disks (6-mm Fisherbrand P8 filter paper), containing the compound (0, 25, 50, and 100 μg, respectively). Each compound was applied to the disks as a solution (15 mg compound per 3 mL of acetone) where control disks were treated with neat acetone (20 μL). Amphotericin B in acetone acted as a standard (100 μg). Test plates with fungal homogenates were incubated at 20°C for 48 h. Four replicate plates were used for each test. Antifungal activity was taken by the diameter of the clear zone surrounding the disk; a halo indicates partial inhibition of growth.

X-Ray Diffraction Studies

Crystals of **1e, 2e**, and **2f** were grown from saturated THF solutions at 20°C. Single crystals were coated with Paratone-N oil, mounted using a polyimide MicroMount and frozen in the cold nitrogen stream of the goniometer. A hemisphere of data was collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and θ scans with a scan width of 0.3° and exposure time of 10 s (**1e** and **2e**) and 40 s (**2f**). The detector distance was 5 cm. The data were reduced and corrected for absorption [38–40]. The structures were solved by direct methods and refined by full-matrix least squares on F^2. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in Fourier difference maps and refined isotropically (**1e**) or included in calculated positions and refined using a riding model (**2e** and **2f**). Crystallographic data for **1e**: $C_{18}H_{22}BNO_3S$, $M_w = 343.24$, orthorhombic, $P2(1)2(1)2(1)$, $a = 10.034(4)$ Å, $b = 12.880(5)$ Å, $c = 28.060(11)$ Å, $V = 3626(2)$ Å^3, $Z = 8$, $D_{calcd} = 1.257$ g cm^{-3}, $F(000) = 1456$, $\mu = 0.193$ mm^{-1}, $R1 = 0.0362$ $(I > 2\sigma(I))$, $wR2 = 0.0882$ (all data), GoF = 1.118. Crystallographic data for **2e**: $C_{22}H_{26}BNO_4S$, $M_w = 411.31$, monoclinic, $P2(1)/c$, $a = 16.475(4)$ Å, $b = 11.295(3)$ Å, $c = 12.109(3)$ Å, $\beta = 107.021(3)°$, $V = 2154.6(8)$ Å^3, $Z = 4$, $D_{calcd} = 1.268$ g cm^{-3}, $F(000) = 872$, $\mu = 0.178$ mm^{-1}, $R1 = 0.0487$ $(I > 2\sigma(I))$, $wR2 = 0.1489$ (all data), GoF = 1.038. Crystallographic data for **2f**: $C_{29}H_{37}B_2NO_5$, $M_w = 501.22$, monoclinic, $P2(1)$, $a = 10.0450(19)$ Å, $b = 28.599(6)$ Å, $c = 10.900(2)$ Å, $\beta = 115.904(3)°$, $V = 2816.8(9)$ Å^3, $Z = 4$, $D_{calcd} = 1.182$ g cm^{-3}, $F(000) = 1072$, $\mu = 0.078$ mm^{-1}, $R1 = 0.0518$ $(I > 2\sigma(I))$, $wR2 = 0.1203$ (all data), GoF = 1.007. Crystallographic information has also been deposited with the Cambridge Crystallographic Data Centre (CCDC 675383-675385).

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REFERENCES

[1] Alonso, F.; Beletskaya, I. P.; Yus, M. Tetrahedron 2008, 64, 3047.
[2] Gamsey, S.; Miller, A.; Olmstead, M. M.; Beavers, C. M.; Hirayama, L. C.; Pradhan, S.; Wessling, R. A.; Singaram, B. J Am Chem Soc 2007, 129, 1278.
[3] Yang, W.; Gao, X.; Wang, B. Med Res Rev 2003, 23, 346.
[4] Adams, J. Cancer Treat Rev 2003, 29, 3.
[5] Valliant, J. F.; Guenther, K. J.; King, A. S.; Morel, P.; Schaffer, P.; Sogbein, O. O.; Stephenson, K. A. Coord Chem Rev 2002, 232, 173.
[6] Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. J Med Chem 2006, 49, 4447.
[7] Amin, S. A.; Küpper, F. C.; Green, D. H.; Harris, W. R.; Carrano, C. J. J Am Chem Soc 2007, 129, 478.
[8] Tran, T.; Quan, C.; Edosada, C. Y.; Mayeda, M.; Wiesmann, C.; Sutherlin, D.; Wolf, B. B. Bioorg Med Chem Lett 2007, 17, 1438.
[9] Reddy, V. J.; Chandra, J. S.; Reddy, M. V. R. Org Biomol Chem 2007, 5, 889.
[10] Kumar, S. K.; Hager, E.; Pettit, C.; Gurulingappa, H.; Davidson, N. E.; Khan, S. R. J Med Chem 2003, 46, 2813.
[11] Altamore, T. M.; Duggan, P. J.; Krippner, G. Y. Bioorg Med Chem 2006, 14, 1126.
[12] Irving, A. M.; Vogels, C. M.; Nikolcheva, L. G.; Edwards, J. P.; He, X.-F.; Hamilton, M. G.; Baerlocher, M. O.; Baerlocher, F. J.; Decken, A.; Westcott, S. A. New J Chem 2003, 27, 1419.
[13] Blatch, A. J.; Chetina, O. V.; Howard, J. A. K.; Patrick, L. G. F.; Smethurst, C. A.; Whiting, A. Org Biomol Chem 2006, 4, 3297.
[14] Jørgensen, K. A. Angew Chem, Int Ed Engl 2000, 39, 3558.
[15] Sailes, H. E.; Watts, J. P.; Whiting, A. Tetrahedron Lett 2000, 41, 2457.
[16] Nöth, H.; Wrackmeyer, B. Nuclear Magnetic Resonance Spectroscopy of Boron Compounds; Springer-Verlag: Berlin, 1978.
[17] Coapes, R. B.; Souza, F. E. S.; Fox, M. A.; Batsanov, A. S.; Goeta, A. E.; Yufit, D. S.; Leech, M. A.; Howard,

J. A. K.; Scott, A. J.; Clegg, W.; Marder, T. B. J Chem Soc, Dalton Trans 2001, 1201.
[18] Clegg, W.; Elsegood, M. R. J.; Lawlor, F. J.; Norman, N. C.; Pickett, N. L.; Robbins, E. G.; Scott, A. J.; Nguyen, P.; Taylor, N. J.; Marder, T. B. Inorg Chem 1998, 37, 5289.
[19] Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. J Organomet Chem 2002, 652, 77.
[20] Niu, W.; Smith, M. D.; Lavigne, J. J. Cryst Growth Design 2006, 6, 1274.
[21] Grünefeld, J.; Kliegel, W.; Rettig, S. J.; Trotter, J. Can J Chem 1999, 77, 439.
[22] Rodríguez, M.; Ochoa, M. E.; Santillan, R.; Farfán, N.; Barba, V. J Organomet Chem 2005, 690, 2975.
[23] Bromidge, S.; Wilson, P. C.; Whiting, A. Tetrahedron Lett 1998, 39, 8905.
[24] Qian, C.-T.; Wang, L.-C.; Chen, R.-F. Chin J Chem 2001, 19, 419.
[25] Cheng, K.; Lin, L.; Chen, S.; Feng, X. Tetrahedron 2005, 61, 9594.
[26] Cheng, K.; Zeng, B.; Yu, Z.; Gao, B.; Feng, X.; Synlett 2005, 1018.
[27] Shang, D.; Xin, J.; Liu, Y.; Zhou, X.; Liu, X.; Feng, X. J Org Chem 2008, 73, 630.
[28] Sánchez, M.; Sánchez, O.; Höpfl, H.; Ochoa, M.-E.; Castillo, D.; Farfán, N.; Rojas-Lima, S. J Organomet Chem 2004, 689, 811.
[29] Mancheno, O. G.; Arraya, R. G.; Carretero, J. C. J Am Chem Soc 2004, 126, 456.
[30] Vogels, C. M.; Nikolcheva, L. G.; Norman, D. W.; Spinney, H. A.; Decken, A.; Baerlocher, M. O.; Baerlocher, F. J.; Westcott, S. A. Can J Chem 2001, 79, 1115.
[31] McCarthy, A. R.; Hartmann, R. W.; Abell, A. D. Bioorg Med Chem Lett 2007, 17, 3603.
[32] Kitigawa, H.; Kumura, K.; Takahata, S.; Iida, M.; Atsumi, K. Bioorg Med Chem 2007, 15, 1106.
[33] Baerlocher, F. J.; Baerlocher, M. O.; Chaulk, C. L.; Langler, R. F.; MacQuarrie, S. L. Aust J Chem 2000, 53, 399.
[34] Anderson, J.; Langler, R. F.; Bärlocher, F. Sydowia 2002, 54, 121.
[35] Babu, B. H.; Prasad, G. S.; Reddy, C. S.; Raju, C. N. Heteroatom Chem 2008, 19, 256.
[36] Nikolcheva, L. G.; Vogels, C. M.; Stefan, R. A.; Darwish, H. A.; Duffy, S. J.; Ireland, R. J.; Decken, A.; Hudson, R. H. E.; Westcott, S. A. Can J Chem 2003, 81, 269.
[37] Martichonok, V.; Jones, J. B. J Am Chem Soc 1996, 118, 950.
[38] SAINT 6.02; Bruker AXS, Inc.: Madison, WI, 1997–1999.
[39] Sheldrick, G. M. SADABS; Bruker AXS, Inc.: Madison, WI, 1999.
[40] Sheldrick, G. M. SHELXTL 5.1; Bruker AXS, Inc.: Madison, WI, 1997.