Synthesis and antifungal and antibacterial bioactivity of cyclic diamines containing boronate esters

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Novel N_2B heterocycles (**1–5**) are formed from the reaction of ethylenediamine derivatives with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (2-HC(O)C_6H_4Bpin; pin = 1,2-$O_2C_2Me_4$). X-ray diffraction studies have been carried out on four examples and show that reactions are selective in giving the isomer where the least substituted amine coordinates to the Lewis-acidic boron atom. Reaction of 2-HC(O)C_6H_4Bpin with diethylenetriamine gave a heterocycle (**6**) with a pendant primary amine group, which reacts further with 2-pyridinecarboxaldehyde to give a potential ligand (**7**) for transition metals. All new compounds show considerable antifungal activity against *Aspergillus niger* and *Aspergillus flavus* and moderate antibacterial activity against *Bacillus cereus*.

Introduction

Compounds containing boronic acids ($RB(OH)_2$) or boronate esters ($RB(OR')_2$) have received considerable attention in catalysed carbon–carbon bond formation reactions,[1–5] solid-phase synthesis,[6] macrocyclic chemistry,[7] organometallic and organic synthesis,[8–12] and as glucose sensors for diabetes therapy.[13–16] Interest in these compounds also arises from their potent biological activities.[17–32] For instance, α-aminoboronic acids ($R_2NCR'R''B(OH)_2$, Fig. 1a) are effective and reversible inhibitors of serine proteases, a diverse group of proteolytic enzymes whose numerous physiological functions include digestion, growth, differentiation, and apoptosis. Proteases are also vital in the generation of most disease processes and, as a result, much effort has focused on the synthesis of α-aminoboronic acids for possible applications as enzyme inhibitors. Analogous amino acids containing boronic acids have also been investigated for their use in boron neutron capture therapy (BNCT) for the treatment of cancer.[33–42] BNCT is a bimodal form of therapy which depends on selectively depositing boron-10 atoms into the cancerous tumour prior to irradiation by slow (thermal) neutrons. 4-Dihydroxyborylphenylalanine (BPA, 4-$H_2NCH(CO_2H)CH_2C_6H_4B(OH)_2$, Fig. 1b) is a simple second generation BNCT compound which has shown promise in the treatment of brain tumours.[42]

Recent work has shown that certain boron compounds also show considerable antifungal[43] and antibacterial[44] activity. Indeed, 2-formylphenylboronic acid (2-HC(O)$C_6H_4B(OH)_2$, Fig. 1c) is a strongly fungicidal agent against both *Aspergillus niger* and *Aspergillus flavus*. As part of our ongoing investigation into generating biologically active boron compounds, and considering the wealth of bioactivities found in aminoboronic acid derivatives, we decided to examine the reactivity of the pinacol derivative of 2-HC(O)$C_6H_4B(OH)_2$ with diamines. Initial results are presented herein.

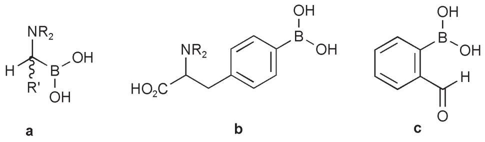

Fig. 1 Biologically active boron compounds: (a) α-aminoboronic acids, (b) BPA, and (c) 2-HC(O)$C_6H_4B(OH)_2$.

Results and discussion

Synthesis of cyclic diamines

The synthesis of simple aldimines containing boronate esters from the addition of primary amines to benzaldehydes is well established.[43,45] In an attempt to generate similar diimines we decided to examine the reactivity of diamines with organic soluble 2-HC(O)C_6H_4Bpin (pin = 1,2-$O_2C_2Me_4$). Interestingly, we found that addition of ethylenediamine ($H_2NCH_2CH_2NH_2$) to 2-HC(O)C_6H_4Bpin did not give the expected diimine product, but rather the novel heterocyclic diamine **1**.

The ^1H NMR spectra for **1** show a broad singlet at δ 5.20 ppm for the CH peak bound to both amines and two separate resonances for the CH_2 groups of the ethylene backbone. A peak at 10.8 ppm in the ^{11}B NMR spectra signifies that the boron atom lies in a tetrahedral environment,[46] arising from coordination of the amine nitrogen atom. This result is somewhat unusual as the reduced Lewis-acidic nature of the Bpin group usually precludes adduct formation.[43] An X-ray diffraction study on **1** was conducted to confirm the formation of this novel heterocycle (Fig. 2). Crystallographic data are given in Table 1 and selected bond distances and angles shown in Table 2. The B-O bond distances of 1.446(3) and 1.469(3) Å are typical for those observed in chelate complexes with diphenylborinic acid (*ca.* 1.5 Å), where the boron atom is four coordinate.[47] Likewise, the B-N(20) distance of 1.684(3) Å is similar to those reported for Schiff base complexes derived from arylboronic acids.[48] The nitrogen carbon bonds C(16)–N(20) and C(19)–N(20) are 1.535(3) and 1.500(3) Å, respectively, and are consistent with single bond lengths.

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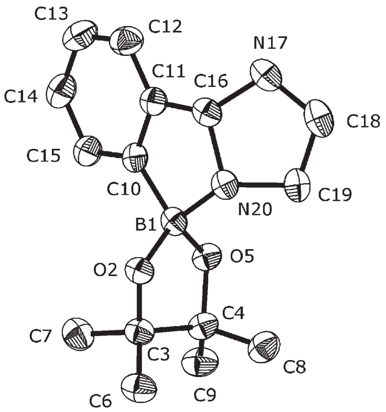


Fig. 2 View of one of the two molecules of **1** with ellipsoids drawn at 30% probability level.

Compound **1** is presumably generated in this reaction *via* initial aldimine formation at one of the amine groups followed by an intramolecular hydroamination of the activated double bond with the other amine.[49] To test this hypothesis, we prepared the aldimine derived from addition of propylamine to 2-HC(O)C_6H_4Bpin. Although ^{11}B NMR data suggested that the imine nitrogen was coordinated to the boron atom, attempts to carry out an *inter*molecular hydroamination on this imine with various primary amines proved unsuccessful. This result is not unexpected as the *intra*molecular variant of this reaction affords a thermodynamically stable five-membered ring (Scheme 1).

Several other diamines, including 1,3-diaminopropane ($H_2NCH_2CH_2CH_2NH_2$), 1,4-diaminobutane ($H_2NCH_2CH_2CH_2CH_2NH_2$), and 1,2-diamino-2-methylpropane ($H_2NCH_2C(Me)_2NH_2$) were allowed to react with 2-HC(O)C_6H_4Bpin to examine the scope of this reaction. Although reaction of 1,3-diaminopropane gave the analogous heterocycle **2** as the only new aminoboron product (Fig. 3), several products were observed with the larger 1,4-diaminobutane, including some of the diimine. Reactions with the substituted $H_2NCH_2C(Me)_2NH_2$ gave selective formation of one isomer (**3**) as indicated by NMR spectroscopy. Only one resonance was observed in the ^{1}H NMR spectra at 4.47 ppm for the CH bound to the two nitrogen atoms. A single peak was also observed for the methylene backbone resonances at 2.88 ppm.

An X-ray study on **3** (Fig. 4) shows that the nitrogen (N(20)) on the unsubstituted methylene group is coordinated to boron at a distance of 1.7023(16) Å. It is possible that steric crowding between the methyl groups on the backbone and the bulky pinacol groups precludes the formation of the other isomer, where the nitrogen on the disubstituted methylene carbon would be bound to the boron. Crystals of **3** are comprised of a racemic mixture of chiral molecules. Hydrogen bonding (O(2)···H(20)′ = 2.089 Å) leads to the formation of dimers which in turn form octamers through additional hydrogen bonding (O(5)···H(14)′ = 2.527 Å). Hydrogen bonding has been used extensively to control molecules or ions in the solid state for applications in crystal engineering and supramolecular synthesis.[50–57]

Similar reactivities were observed with *N*-phenylethylenediamine ($H_2NCH_2CH_2NHPh$), which gave **4** in high yields. Two distinct Bpin methyl resonances are observed, however, in both the ^{1}H and ^{13}C NMR spectra for **4**. The molecular structure of **4** (Fig. 5) confirms that in the solid state coordination of the least substituted amine to the boron atom is once again occurring. Bond distances are similar to **1** and **3**, except that the C(16)–N(20) distance of 1.4831(15) Å is somewhat shorter in **4** (*cf.* 1.535(3) for **1** and 1.5297(17) for **3**).

To examine the effect of introducing an aromatic group into the backbone, we attempted to prepare analogous diamines by reactions with 1,2-phenylenediamine (1,2-$(H_2N)_2C_6H_4$). Unfortunately, all attempts to affect this reaction proved unsuccessful and gave only the diimine product. Interestingly, reaction of 2-aminobenzylamine (2-$H_2NC_6H_4CH_2NH_2$) gave the novel heterocycle (**5**) in high yields (84%). Inequivalent protons arising from the benzyl methylene group are observed in the ^{1}H NMR spectra at δ 4.11 and 3.52 ppm with coupling constants of $J = 16$ Hz. The ^{11}B NMR spectra show one peak at 12.9 ppm attributed once again to a four-coordinate boron atom.

We then decided to examine the reactivity of 2-HC(O)C_6H_4Bpin with diethylenetriamine ($HN(CH_2CH_2NH_2)_2$) to see if we could generate a novel heterocycle with a pendant primary amine group. The availability of a primary amine would allow us to further functionalize these compounds and design ligands for transition metals. Reaction of diethylenetriamine with 2-HC(O)C_6H_4Bpin did indeed give the novel heterocycle **6**. The ^{1}H NMR spectra show the CH bound to the two nitrogen atoms at δ 4.82 ppm and the pendant amine hydrogens as a broad peak at 1.41 ppm. Addition of 2-pyridinecarboxaldehyde to **6** gave a novel iminopyridine

Table 1 Summary of data collection and refinement for crystals **1**,**3**,**4**, and **7**

	1·0.5THF	**3**	**4**·acetone	**7**·0.25Et_2O
Formula	$C_{34}H_{54}B_2N_4O_5$	$C_{17}H_{27}BN_2O_2$	$C_{24}H_{33}BN_2O_3$	$C_{96}H_{134}B_4N_{16}O_9$
M	620.54	302.22	408.40	1699.70
T/K	173(1)	173(1)	173(1)	173(1)
Cryst. syst.	Triclinic	Tetragonal	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P\bar{4}2(1)c$	$P\bar{1}$	$P2(1)/n$
a/Å	10.0250(16)	12.5263(6)	9.5447(12)	19.5646(9)
b/Å	10.9140(17)	12.5263(6)	10.5484(13)	16.3302(8)
c/Å	17.365(3)	21.7284(16)	10.9073(13)	31.1144(16)
α/deg	106.609(2)		95.987(2)	
β/deg	105.779(2)		92.320(2)	107.5480(10)
γ/deg	93.244(2)		91.666(2)	
V/Å^3	1733.4(5)	3409.4(3)	1090.7(2)	9478.3(8)
Z	2	8	2	4
μ/mm^{-1}	0.078	0.076	0.079	0.077
d/g cm^{-3}	1.189	1.178	1.207	1.194
λ/Å	0.71073	0.71073	0.71073	0.71073
R_1[a]	0.0557	0.0463	0.0391	0.0568
wR_2[b]	0.1399	0.1266	0.1126	0.1817

[a] $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] All data, $wR_2\ (F^2) = (\sum[w(F_o^2 - F_c^2)^2]/\sum[F_o^4])^{1/2}$.

Table 2 Selected bond lengths (C) and angles (°) for **1**,**3**,**4**, and **7**

	1[a]	3	4	7[b]
B(1)–O(5)	1.446(3)	1.4341(16)	1.4176(16)	1.439(3)
B(1)–O(2)	1.469(3)	1.4731(15)	1.4490(16)	1.467(3)
B(1)–C(10)	1.607(3)	1.6082(19)	1.5960(18)	1.606(3)
B(1)–N(20)	1.684(3)	1.7023(16)	1.6808(16)	1.696(3)
C(16)–N(17)	1.448(3)	1.4582(16)	1.4515(16)	1.453(2)
C(16)–N(20)	1.535(3)	1.5297(17)	1.4831(15)	1.538(2)
C(19)–N(20)	1.500(3)	1.4968(16)	1.4767(16)	1.501(3)
C(24)–N(23)				1.461(4)
O(5)–B(1)–O(2)	105.31(18)	106.48(10)	106.80(10)	106.49(16)
O(5)–B(1)–C(10)	115.56(17)	117.14(10)	116.06(10)	116.36(17)
O(2)–B(1)–C(10)	118.37(17)	116.56(10)	118.56(10)	117.44(19)
O(5)–B(1)–N(20)	113.39(17)	111.85(10)	112.40(10)	112.77(17)
O(2)–B(1)–N(20)	105.58(16)	106.23(9)	105.64(9)	105.55(16)
C(10)–B(1)–N(20)	98.22(17)	97.92(9)	96.60(9)	97.62(15)
C(19)–N(20)–C(16)	104.62(17)	105.44(9)	103.88(9)	104.79(15)
C(19)–N(20)–B(1)	119.91(16)	115.81(9)	114.21(9)	115.92(17)
C(16)–N(20)–B(1)	108.88(16)	108.76(9)	107.95(9)	108.73(15)
C(18)–N(17)–C(16)	104.60(19)	106.35(10)	110.54(10)	102.61(16)

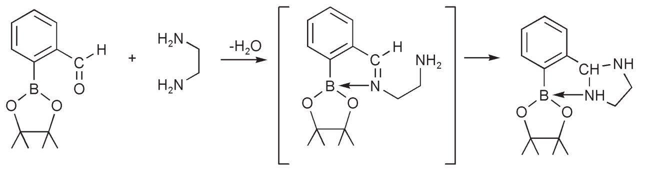
[a] Average for two independent molecules per asymmetric unit. [b] Average for four independent molecules per asymmetric unit.

system **7**. The molecular structure of **7**, shown in Fig. 6, confirms the presence of the imine functionality. The average aldimine C–N distance is 1.461(4) Å and is consistent with a carbon–nitrogen double bond found in similar structures.[43] Future work with this system will examine its potential to act as a didentate ligand for biologically-active metals, the results of which will be reported in due course.

Biological results

Recent studies have shown that related heterocyclic boron compounds show appreciable antifungal activity.[58–61] We therefore decided to examine these new heterocyclic derivatives for their antifungal and antibacterial activities. Selected results for these compounds are shown in Table 3. Benzaldehyde (Entry 8) was tested as a control and, as expected, showed no antimicrobial activity against two fungi (*Aspergillus niger* or *Aspergillus flavus*) and two bacteria (*Escherichia coli* and *Bacillus cereus*). Remarkably, all compounds strongly inhibited both *A. niger* and *A. flavus* and were moderately effective against *B. cereus*. Interesting, however, is the observation that the unprotected boronic acid **1b** (Entry 2), prepared by the addition of ethylenediamine to 2-HC(O)$C_6H_4B(OH)_2$, showed a reduced fungitoxicity compared to its pinacol derivative **1** (Entry 1). Although the pinacol group in these compounds seems to enhance toxicities, further work is needed to elucidate the role boron plays in these systems.

In summary, we have prepared a number of novel heterocyclic aminoboron compounds from the addition of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde to ethylenediamine derivatives. The least substituted amine coordinates to the boron atom to form a heterocyclic ring system. These compounds display significant antifungal and moderate antibacterial activity.



Scheme 1

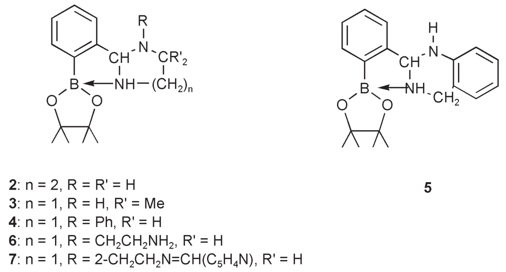
Experimental

Chemistry: materials and methods

Reagents and solvents were purchased from Aldrich Chemicals and used as received. The melting points were determined using a Mel-Temp apparatus and they are uncorrected. The infrared spectra were obtained using a Mattson Genesis II FT-IR spectrometer in Nujol and are reported in cm^{-1}. NMR spectra were recorded on a JEOL JNM-GSX270 FT NMR (^1H 270 MHz; ^{13}C 68 MHz; and ^{11}B 87 MHz) spectrometer. Chemical shifts (δ) are reported in ppm [relative to internal TMS (^1H and ^{13}C) or external $BF_3 \cdot OEt_2$ (^{11}B)] and coupling constants (*J*) in Hz. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br), and overlapping (ov). Elemental analyses were performed by Desert Analytics (Tucson, AZ) and Canadian Microanalytical Services (Delta, BC). 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde was prepared as described previously.[43]

Syntheses

Synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazolidine. The addition of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (1.04 g, 4.48 mmol) in 3 mL of diethyl ether to a 2 mL diethyl ether solution of ethylenediamine (0.27 g, 4.48 mmol) resulted in the precipitation of **1**. After 4 h, the solid was collected by suction filtration and washed with cold methylene chloride (1 mL) and diethyl ether (2 × 5 mL) to afford a white powder. Yield 0.94 g, 77%. Mp = 192 °C. IR (Nujol): 3251, 3120, 2970, 2883, 1454, 1379, 1261, 1157, 1043, 910, 733 cm^{-1}. ^1H NMR ($CDCl_3$): δ



2: n = 2, R = R' = H
3: n = 1, R = H, R' = Me
4: n = 1, R = Ph, R' = H
6: n = 1, R = $CH_2CH_2NH_2$, R' = H
7: n = 1, R = 2-$CH_2CH_2N{=}CH(C_5H_4N)$, R' = H

Fig. 3 Novel heterocycles **2–7**.

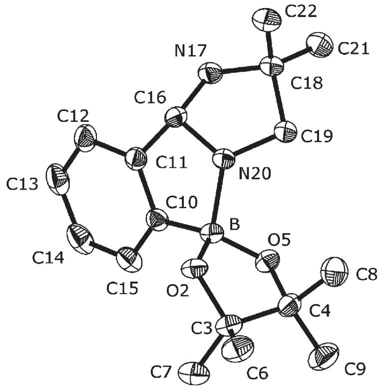


Fig. 4 The molecular structure of **3** with ellipsoids drawn at 30% probability level.

7.45 (d, 1H, Ar, $J = 7$ Hz), 7.24 (ov td, 1H, Ar, $J = 7, 1$ Hz), 7.13 (ov td, 1H, Ar, $J = 7, 1$ Hz), 6.93 (d, 1H, Ar, $J = 7$ Hz), 5.20 (s, 1H, CHN), 3.73 (br s, 1H, NH), 3.26–3.15 (2nd order m, 2H, NCH_2), 3.09–2.99 (2nd order m, 2H, NCH_2), 1.67 (br s, 1H, NH), 1.27 (s, 12H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 10.8. ^{13}C NMR ($CDCl_3$): δ 145 (br, C–B), 142.0, 130.6, 128.9, 128.1, 122.9, 82.1, 80.0, 46.8, 25.9. Anal. found: C, 58.92; H, 7.59; N, 8.92. Calcd. for $C_{15}H_{23}N_2O_2B{\cdot}0.5\ CH_2Cl_2$ (316.73): C, 58.77; H, 7.65; N, 8.85%.

Synthesis of 2-(2-phenylboronic acid)imidazolidine. The addition of $2\text{-}HC(O)C_6H_4B(OH)_2$ (0.25 g, 1.67 mmol) in 5 mL of dichloromethane to a 2 mL dichloromethane solution of ethylenediamine (0.10 g, 1.67 mmol) resulted in the precipitation of **1b**. The reaction was allowed to proceed for 3 days, at which point the solid was collected by suction filtration and washed with dichloromethane (5 × 5 mL) and diethyl ether (2 × 5 mL) to afford a white powder. Yield 0.18 g, 56%. Mp = 176 °C. IR (Nujol): 3288, 3186, 2943, 2912, 2860, 1460, 1376, 1360, 1336, 1304, 1253, 1200, 1120, 1034, 958, 841, 766, 615 cm^{-1}. ^1H NMR (D_2O): δ 7.41–7.38 (m, 1H, Ar), 7.33–7.25 (ov m, 3H, Ar), 5.61 (s, 1H, CHN), 3.06–2.92 (ov m, 4H, NCH_2CH_2N). ^{11}B NMR (D_2O): δ 7.0. ^{13}C NMR (D_2O): δ 146.4 (br, C–B), 141.8, 129.4, 128.9, 128.4, 123.4, 81.1, 46.0 (br s, NCH_2CH_2N).

Synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]hexahydropyrimidine. The addition of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (1.15 g, 4.96 mmol) in 3 mL of diethyl ether to a 2 mL diethyl ether solution of 1,3-diaminopropane (0.37 g, 4.96 mmol) resulted in the precipitation of **2**. After 2 days, the solvent was removed under vacuum and the resultant solid triturated with diethyl ether (5 × 10 mL) to afford an off-white powder. Yield 0.99 g, 69%. Mp = 156–158 °C. IR (Nujol): 3050, 2964, 2893, 1462, 1377, 1344, 1176, 1147, 1097, 1014, 975, 883, 748, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.51 (m, 1H, Ar), 7.25–7.22 (ov m, 3H, Ar), 5.33 (s, 1H, CHN), 3.00–2.82 (ov m, 4H, NCH_2-CH_2CH_2N), 2.75 (br s, 1H, NH), 1.59 (app quint, 2H, NCH_2-CH_2CH_2N, $J = 5$ Hz), 1.20 (s, 12H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 9.4. ^{13}C NMR ($CDCl_3$): δ 146.1 (br, C–B), 142.3, 130.3, 128.0, 127.4, 122.3, 79.6, 73.7, 41.3, 25.8, 24.7. Anal. found: C, 66.54; H, 8.31; N, 9.60. Calcd. for $C_{16}H_{25}N_2O_2B$ (288.24): C, 66.67; H, 8.76; N, 9.72%.

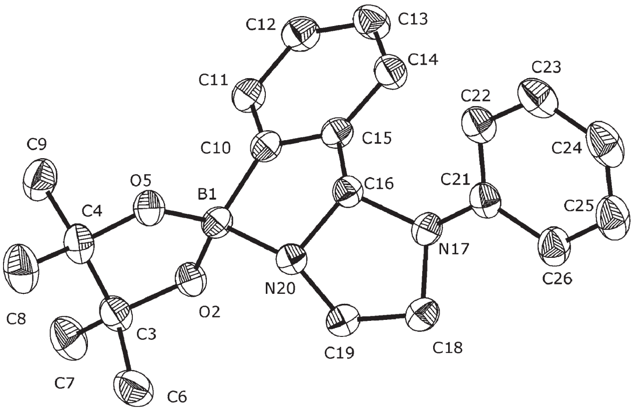


Fig. 5 The molecular structure of **4** with ellipsoids drawn at 30% probability level.

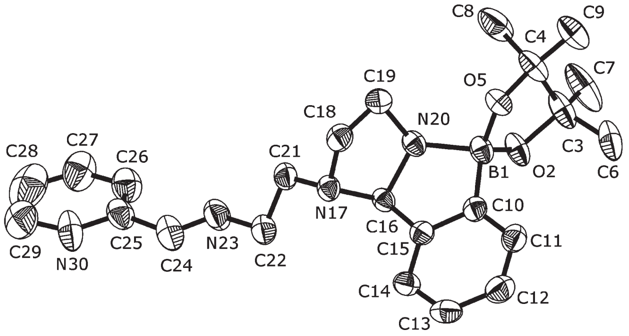


Fig. 6 View of one of the four molecules of **7** with ellipsoids drawn at 30% probability level.

Synthesis of 4,4-dimethyl-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazolidine. The addition of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.45 g, 1.94 mmol) in 3 mL of dichloromethane to a 2 mL dichloromethane solution of 1,2-diamino-2-methylpropane (0.17 g, 1.94 mmol) resulted in the precipitation of **3**. After 1 day, the solvent was removed under vacuum and the resultant solid dissolved in diethyl ether (5 mL) and stored at 5 °C for 5 days. The precipitate was then collected by suction filtration to give a white solid. Yield 0.54 g, 92%. Mp = 160–162 °C. IR (Nujol): 3288, 3118, 2941, 2872, 1464, 1377, 1362, 1261, 1228, 1192, 1153, 1109, 1086, 1043, 982, 941, 860, 781, 762, 725, 619, 584, 525 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.44 (d, 1H, Ar, $J = 7$ Hz), 7.24 (t, 1H, Ar, $J = 7$ Hz), 7.10 (t, 1H, Ar, $J = 7$ Hz), 6.65 (d, 1H, Ar, $J = 7$ Hz), 4.47 (t, 1H, CHN, $J = 7$ Hz), 2.88 (t, 2H, NCH_2, $J = 7$ Hz), 2.01 (br s, 1H, NH), 1.26 (s, 12H, $BO_2C_2(CH_3)_4$), 1.19 (s, 3H, $NCCH_3$), 1.18 (s, 3H, $NCCH_3$). ^{11}B NMR ($CDCl_3$): δ 11.5. ^{13}C NMR ($CDCl_3$): δ 143.5 (br, C–B), 142.5, 130.5, 128.9, 127.9, 123.4, 81.0, 80.0, 62.4, 56.9, 26.2, 25.9, 25.8. Anal. found: C, 67.62; H, 8.91; N, 9.35. Calcd. for $C_{17}H_{27}N_2O_2B$ (302.27): C, 67.55; H, 9.02; N, 9.27%.

Synthesis of 1-phenyl-2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]imidazolidine. A 2 mL dichloromethane solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.50 g, 2.16 mmol) was added dropwise to a 3 mL dichloromethane solution of *N*-phenylethylenediamine (0.29 g, 2.16 mmol). After 1 day, the solvent was removed under vacuum to afford a yellow solid, which was triturated with hexane (2 × 5 mL) and diethyl ether (2 × 5 mL). The resulting solid was dissolved in a minimum (3 mL) amount of ethanol and stored at 5 °C until a precipitate formed. The precipitate was filtered by suction filtration to afford a white solid. Yield 0.63 g, 83%. Mp = 163–164 °C. IR (Nujol): 3140, 2954, 2929, 2858, 1599, 1502, 1460, 1381, 1325, 1234, 1186, 1151, 1101, 1047, 995, 945, 858, 781, 742, 688, 584, 509 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.45 (d, 1H, Ar, $J = 7$ Hz), 7.34 (t, 1H, Ar, $J = 7$ Hz), 7.21 (t, 1H, Ar, $J = 7$ Hz), 7.11 (t, 2H, Ar, $J = 7$ Hz), 6.98 (d, 1H, Ar, $J = 7$ Hz), 6.77 (t, 1H, Ar, $J = 7$ Hz), 6.44 (br s, 1H, NH), 6.26 (d, 2H, Ar, $J = 7$ Hz),

Table 3 Antifungal and antibacterial testing

		A. niger		*A. flavus*		*E. coli*		*B. cereus*	
Entry	Compound	Dose/ μg disk^{-1}	Clear zone/mm	Dose/ μg disk^{-1}	Clear zone/mm	Dose/ μg disk^{-1}	Clear zone/mm	Dose/ μg disk^{-1}	Clear zone/mm
1	**1**	25	26	25	22	100	0	50	31
2	**1b**	100	0	100	3	100	0	50	31
3	**2**	25	25	25	23	100	0	50	30
4	**3**	25	24	25	23	100	0	50	29
5	**4**	25	17	25	23	100	0	50	30
6	**5**	100	14	100	18	100	0	50	29
7	**6**	25	23	25	24	100	0	50	29
8	PhC(O)H	100	0	100	0	100	0	50	0

5.94 (s, 1H, CHN), 3.44–3.37 (ov m, 2H, NCH_2), 3.33–3.25 (ov m, 2H, NCH_2), 1.25 (s, 6H, $BO_2C_2(CH_3)_4$), 1.14 (s, 6H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 11.5. ^{13}C NMR ($CDCl_3$): δ 146.5, 143.8, 142.9 (br, C–B), 131.3, 129.3, 128.5, 128.3, 123.0, 118.3, 113.0, 79.7, 79.2, 47.1, 44.5, 25.6, 24.9. Anal. found: C, 70.39; H, 8.24; N, 7.28. Calcd. for $C_{21}H_{27}N_2O_2B\cdot 0.5\ CH_3CH_2OH$ (373.35): C, 70.77; H, 8.12; N, 7.51%.

Synthesis of 2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,2,3,4-tetrahydroquinazoline. A 2 mL diethyl ether solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (0.25 g, 1.08 mmol) was added dropwise to a 3 mL diethyl ether solution of 2-aminobenzylamine (0.13 g, 1.08 mmol). After 2 h, the reaction was filtered to afford a white solid. Yield 0.30 g, 84%. Mp = 172–176 °C. IR (Nujol): 3458, 3207, 2937, 2868, 1612, 1460, 1375, 1265, 1198, 1153, 1097, 1034, 1018, 999, 872, 845, 744, 642 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.34 (d, 1H, Ar, J = 7 Hz), 7.22–7.15 (ov m, 2H, Ar), 7.06 (d, 1H, Ar, J = 7 Hz), 6.98 (d, 1H, Ar, J = 7 Hz,), 6.91–6.80 (ov m, 3H, Ar), 5.51 (d, 1H, C(H)N or NH, J = 6 Hz), 5.13 (d, 1H, C(H)N or NH, J = 6 Hz,), 4.11 (d, 1H, CH_2N, J = 16 Hz), 3.52 (d, 1H, CH_2N, J = 16 Hz), 2.08 (br s, 1H, NH), 1.28 (s, 6H, $BO_2C_2(CH_3)_4$), 1.23 (s, 6H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 12.9. ^{13}C NMR ($CDCl_3$): δ 143.4 (br, C–B), 141.9, 131.1 (two peaks), 128.3, 128.0, 127.7, 127.6, 123.4, 121.2, 120.5, 118.9, 80.5, 71.9, 44.9, 26.3, 25.7. Anal. found: C, 71.42; H, 7.63; N, 8.38. Calcd. for $C_{20}H_{25}N_2O_2B$ (336.28): C, 71.43; H, 7.51; N, 8.33%.

Synthesis of 2-{2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazolidin-1-yl}ethylamine. The addition of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde(0.75 g, 3.23 mmol) in 5 mL of diethyl ether to a 5 mL diethyl ether solution of diethylenetriamine (0.33 g, 3.23 mmol) resulted in the precipitation of **6**. After 1 day, the precipitate was collected by suction filtration to afford an off-white solid. Yield 0.70 g, 68%. Mp 142–145 °C. IR (Nujol): 3165, 3111, 2970, 2881, 1462, 1377, 1303, 1155, 1032, 978, 845, 723 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.45 (d, 1H, Ar, J = 7 Hz), 7.27–7.17 (m, 2H, Ar), 6.87 (d, 1H, Ar, J = 7 Hz), 6.45 (br s, 1H, NH), 4.82 (s, 1H, CHN), 3.51 (m, 1H, NCH_2), 2.93 (ov m, 1H, NCH_2), 2.77–2.50 (ov m, 4H, NCH_2), 2.44–2.35 (m, 2H, NCH_2), 1.41 (br s, 2H, NH_2), 1.28 (s, 12H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 10.3. ^{13}C NMR ($CDCl_3$): δ 145.0 (br, C–B), 143.9, 130.0, 128.3, 128.1, 123.1, 86.3, 79.9, 57.9, 51.7, 42.8, 41.2, 26.3, 25.4. Anal. found: C, 64.18; H, 8.96; N, 13.08. Calcd. for $C_{17}H_{28}N_3O_2B$ (317.29): C, 64.35; H, 8.91; N, 13.25%.

Synthesis of pyridin-2-ylmethylene-(2-{2-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]imidazolidin-1-yl}ethylamine. Compound **6** (0.25 g, 0.79 mmol) in 5 mL of dichloromethane was added to a 5 mL dichloromethane solution of 2-pyridinecarbaldehyde (0.08 g, 0.79 mmol) and the reaction was heated for 8 hours in the presence of molecular sieves. The solvent was removed under vacuum, redissolved in 10 mL of diethyl ether and stored at 5 °C for 24 hours at which point a precipitate formed and was collected by suction filtration to afford a white solid. Yield 0.14 g, 44%. Mp = 120–121 °C. IR (Nujol): 3122, 2937, 2870, 1649, 1464, 1375, 1228, 1157, 1035, 982, 943, 851, 752, 721, 631 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.65 (d, 1H, Ar, J = 7 Hz), 8.40 (s, 1H, C(H) = N), 8.02 (d, 1H, Ar, J = 7 Hz), 7.76 (t, 1H, Ar, J = 7 Hz), 7.47 (d, 1H, Ar, J = 7 Hz), 7.32 (t, 1H, Ar, J = 7 Hz), 7.22–7.09 (ov m, 3H, Ar), 5.64 (br s, 1H, NH), 5.48 (s, 1H, CHN), 3.82 (m, 1H, NCH_2), 3.70 (m, 1H, NCH_2), 3.50–3.42 (ov m, 2H, NCH_2), 3.19–2.95 (ov m, 3H, NCH_2), 2.80 (m, 1H, NCH_2), 1.28 (s, 6H, $BO_2C_2(CH_3)_4$), 1.27 (s, 6H, $BO_2C_2(CH_3)_4$). ^{11}B NMR ($CDCl_3$): δ 10.6. ^{13}C NMR ($CDCl_3$): δ 163.9, 154.1, 149.5, 143.1, 140 (br, C–B), 136.9, 130.4, 128.5, 128.1, 125.1, 122.8, 121.6, 87.3, 80.0, 61.4, 55.7, 51.0, 43.6, 25.8, 25.3.

X-Ray data

Crystals of **1** (THF), **3** (THF), **4** (acetone), and **7** (Et_2O) were grown from saturated solutions at 5 °C. Single crystals were coated with Paratone-N oil, mounted using a glass fibre and frozen in the cold stream of the goniometer. A hemisphere of data were collected on a Bruker AXS P4/SMART 1000 diffractometer using ω and ϕ scans with a scan width of 0.3° and 10 s (**3**) or 30 s (**1**, **4**, **7**) exposure times. The detector distance was 4 cm (**3**), 5 cm (**7**), or 6 cm (**1**, **4**). The data were reduced[62] and corrected for absorption.[63] The structure was solved by direct methods and refined by full-matrix least squares on F^2.[64] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located in Fourier difference maps and refined isotropically, with the exception of the solvent molecule in **7**, where hydrogen atoms were included in calculated positions and refined using a riding molecule.

CCDC reference numbers 212668–212671. See http://www.rsc.org/suppdata/nj/b3/b304500e/ for crystallographic files in .cif or other electronic format.

Biological testing

New compounds were tested for antifungal activity against pure cultures of *Aspergillus niger* and *Aspergillus flavus*, and for antibacterial activity against pure cultures of *Escherichia coli* and *Bacillus cereus*, all of which were provided by Ward's Natural Science Ltd. (St. Catharines, Ontario, Canada). Cultures were maintained on malt agar. Six plugs (10 mm diameter) were cut from a 5–8 day-old colony and homogenized in distilled, sterilized water (4 mL). From this suspension, 0.5 mL was transferred aseptically to a Petri plate with 15 mL malt extract agar (1% malt extract, 1.5% agar) and spread evenly over the entire surface. Each plate was provided with four evenly spaced paper disks (7 mm Whatman Number 1 filter paper) containing the compound (0, 25, 50, and 100 μg respectively). Each compound was applied to the disks as a solution (5 μg of compound per 1 mL of acetone) where control disks were treated with neat acetone (20 μL). Test plates with fungal and bacterial homogenates were incubated at room temperature for 48 h. Three replicate plates were used for each test. Antifungal and antibacterial activity was taken by the diameter of the clear zone surrounding the disk.

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