Synthesis and Antifungal Activity of a Novel Series of Alkyldimethylamine Cyanoboranes and Their Derivatives

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A series of new amine cyanoborane derivatives were synthesized and exhibited antifungal activity. A long alkyl chain attached to the nitrogen of the amine cyanoboranes and carboxyboranes enhances antifungal activity. An enhanced activity was also obtained upon the halogenation of the amine cyanoboranes as well as in the presence of C═C double bond at the end of the *N*-alkyl group. The lead compounds were dimethylundecylamine cyanoborane ($C_{11}H_{23}N(CH_3)_2BH_2CN$), **9**, and its dibromo derivative dimethylundecylamine dibromocyanoborane ($C_{11}H_{23}N(CH_3)_2BBr_2CN$), **11**. The MIC values for the lead compounds against the most important human pathogenic fungi ranged from 16.25 to 32.5 μmol/L and from 10.05 to 79 μmol/L, respectively. Both compounds were found to be relatively safe in intravenous injections to mice, (MTD = 121.9 and 73.1 μmol/kg, respectively) and active against strains that are resistant to fluconazole (a conventional antifungal medicine). These data indicate their potential to become antifungal agents.

Introduction

Promising pharmacological activities of amine cyanoboranes were reported in the early 1980s.[1,2] It was shown in model studies that these compounds have potent anticancer,[3−8] anti-inflammatory,[9] and other biological activities.[10−17] Thus, amine cyanoboranes and carboxyboranes are unique among boron-containing compounds in that they possess high biological activity in various fields with therapeutic applications. However, their use in the treatment of fungal infectious diseases has not been described. Such infections have recently emerged worldwide as a major threat to public health[18] in which fungal infections including both yeast and mould causative agents play an important role.[19,20] Cancerous and fungal cells share many traits of primitive eukaryotic cells, such as having similar metabolism that is different from that of the host cells (e.g., high growth rate, higher multiplication, and rapid metabolism). The part of the host immune system that suppresses cancer cells is also responsible for the suppression of fungal cells, and under specific circumstances, both cancer and fungal cells are not responsive to the innate neural/hormonal control mechanism of the host, resulting in unregulated growth.[21,22] Therefore, there is a rationale to look for antifungal activity among amine cyanoboranes that possess high anticancer activity. The incidence of fungal infections has increased significantly in the past two decades mainly due to the growing number of immunocompromised patients, such as cancer patients, patients who have undergone organ transplantation, and patients with AIDS, and the frequent use of cytotoxic and/or antibacterial drugs.[23−28] Until recently, amphotericin B was the standard therapy for many fungal infections, but a high frequency of renal toxicity has limited its use.[29,30] Recently, new antifungal agents, such as azoles (fluconazole), triazoles (voriconazole), and echinocandins (caspofungin), have increased our ability to treat fungal infections [29,31] However, all of them have a narrow spectrum of activity, and the development of high resistance has been documented, especially, for fluconazole, and the mortality due to fungal infections even with the novel antifungal agents is still unacceptably high.[13,29,32−34] Currently, a small number of agents are available, and all have some drawbacks regarding their spectrum, toxicity, tissue distribution, central nervous system (CNS) penetration, and high cost.[32−36] There is, therefore, a great need for new antifungal agents, particularly for the treatment of systemic mycoses.

Scheme 1. Synthesis of Alkylamine Cyanoboranes[a]

$$MeNR_1R_2BH_2CN \xrightarrow{s\text{-BuLi}} Li^+[:CH_2NR_1R_2BH_2CN]^-$$

$$\xrightarrow{R_3X} R_3CH_2NR_1R_2BH_2CN$$

[a] R_1, R_2, and R_3 = alkyl; and X = Cl, Br, or I.

In this article, a series of new amine cyanoboranes and carboxyboranes and their halo and hydroxyl derivatives were synthesized. These compounds exhibited antifungal activity against both mold and yeast-like fungi and activity against strains that are resistant to fluconazole (a conventional antifungal medicine), indicating their potential as antifungal agents. The new amine cyanoboranes are easily prepared from inexpensive starting materials and, therefore, may provide new inexpensive antifungal formulations.

Results and Discussion

Synthesis and Characterization. Preparation of Alkyldimethylamine Cyanoboranes. Synthesis of amine cyanoboranes ($R_1R_2R_3CH_2NBH_2CN$) (where R_3 is a chain alkyl) was carried out according to our previously published C-lithiation/alkylation of trimethylamine cyanoborane method.[37] One of the *N*-methyl groups is lithiated using *s*-BuLi to produce the C-lithiated intermediate, which in turn reacts with an alkyl halide to afford C−C bond formation (Scheme 1). This leads to the elongation of the alkyl group attached to the nitrogen and is controlled by the length of the alkyl group in the reacted alkyl halide.

Synthesis of Diamine Bis-cyanoboranes. Synthesis of amine bis-cyanoboranes ($NCBH_2R_1R_2N(CH_2)_{n+2}NR_1R_2BH_2CN$), where

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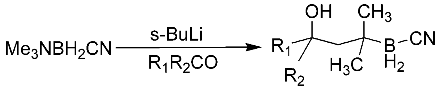
Scheme 2. Synthesis of Diamine Bis-cyanoboranes[a]

$$2\ R_1R_2MeNBH_2CN \xrightarrow[X(CH_2)_nX]{s\text{-BuLi}} NCBH_2R_1R_2N(CH_2)_{n+2}NR_1R_2BH_2CN$$

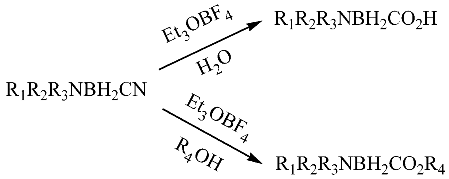
[a] R_1 and R_2 = alkyl; X = Cl, Br, or I; and $n = 1-20$.

Scheme 3. Synthesis of β-Hydroxylamine Cyanoboranes[a]



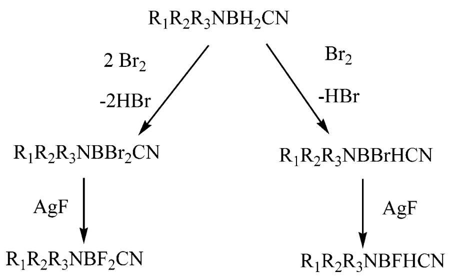
[a] R_1= alkyl and R_2= H, alkyl; and X = Cl, Br, or I.

Scheme 4. Synthesis of Amine Carboxyboranes and Amine Carboxyborane Esters[a]



[a] R_1, R_2, and R_3 = alkyl; and R_4 = e.g., alkyl, alkenyl, and aryl.

Scheme 5. Synthesis of Amine Halocyanoboranes[a]



[a] R_1, R_2, and R_3 = alkyl.

n ranges from 1 to 20, was carried out as illustrated in Scheme 2 according to the procedure described by Takrouri et al.,[37] using 0.5 equivalents of dihaloalkanes (XRX) as the electrophile and one equivalent of the C-lithiated intermediate of the trimethylamine cyanoborane.

Preparation of β-hydroxyamine Cyanoboranes. The synthesis of β-hydroxyamine cyanoboranes, with the intention of increasing the aqueous solubility of the amine cyanoborane derivatives, was carried out using either long chain aldehydes or ketones using the C-lithiation/alkylation method[37] (Scheme 3).

Preparation of Amine Carboxyboranes and Esters. The synthesis of amine carboxyboranes and amine carboxyboranes esters ($R_1R_2R_3NBH_2CO_2H$ and $R_1R_2R_3NBH_2CO_2R_4$), where R_1, R_2, and R_3 are alkyls and R_4 is an alkyl, alkenyl, aryl, etc., was carried out according to the published procedures,[17] for example, as illustrated in Scheme 4, by hydrolysis of the corresponding $R_1R_2R_3NMe_2BH_2CN$.

Preparation of Amine Halocyanoboranes. The corresponding amine monobromocyanoboranes and amine dibromocyanoboranes were prepared from the starting amine cyanoboranes as described previously in the literature (Scheme 5).[38,39] The synthesis of amine fluorocyanoboranes was carried out by reacting the corresponding amine bromocyanoboranes with silver fluoride (AgF) according to a method that was previously described by Shalom et al.[40] (Scheme 5).

Spectroscopic Analysis. All of the new compounds were fully characterized by ^{1}H, ^{11}B, and ^{13}C NMR, FT-IR, and elemental analysis. Detailed spectroscopic analysis of the prepared compounds and analytical data can be found in the Supporting Information.

Antifungal Activity. Antifungal Activity of the Various Amine Cyanoborone Compounds against Pathogenic Fungi. The antifungal activities of the various amine cyanoboranes against yeast *(Candida albicans*, *Candida glabrata*, and *Candida krusei)* and mold *(Aspergillus fumigatus)* were determined. The MIC[a] was measured according to CLSI recommendations.[41,42] The results of the antifungal activity, presented in Table 1, show that amine cyanoboranes with diverse structures exhibit considerable antifungal activity against both *C. albicans* and *A. fumigatus*, the most important causative agents of fungal infections in humans. *C. albicans* is the fourth leading organism of all bloodstream infections and a major nosocomial infection. *A. fumigatus* is an important mold pathogen responsible for infections, the incidences of which have increased significantly in recent years.[24]

The lead compound was dimethylundecylamine cyanoborane (**9**) ($C_{11}H_{23}N(CH_3)_2BH_2CN$), exhibiting MIC values of 32.5 μmol/L (Table 1). The MIC values of *C. albicans* are comparable with those documented for commonly used antifungal drugs such as azoles.[43,44] Compounds **9**−**12** and **14** exhibit the lowest MIC values of all compounds tested (Table 1), ranging from 32.5 to 65 μmol/L for *C. albicans* and 32.5−131 μmol/L for *A. fumigatus*.

Because the MIC values obtained for the tested fungal strains in Table 1 were higher than those obtain with the conventional drug (amphotericin B and fluconazole), we tested the susceptibility of fungal strains that are resistant to fluconazole and the lead compounds. Table 2 shows that isolates of *C. glabrata*, which generate considerably high fluconazole MICs, and isolates of *C. krusei*, which are known as intrinsically resistant to fluconazole,[45] were highly susceptible to the lead compound **9** and its dibromo derivative **11**, exhibiting much lower MIC values than those obtained with fluconazole. These results suggest that these compounds may become potent antifungal agents.

Structure Activity Relationship (SAR). A number of relationships were observed according to the structure of the amine cyanoboranes and carboxyboranes and their derivatives.

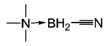
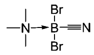
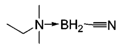
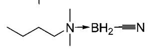
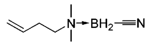
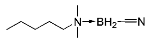
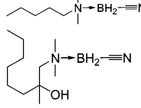
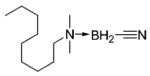
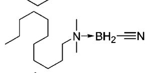
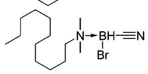
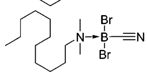
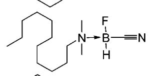
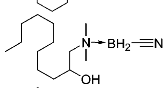
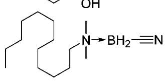
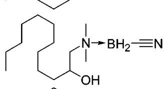
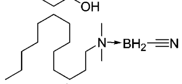
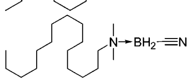
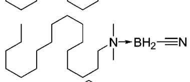
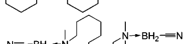
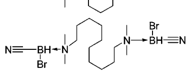
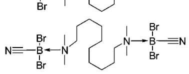
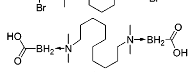
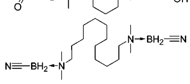
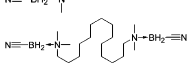
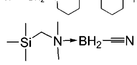
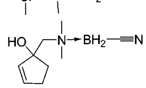
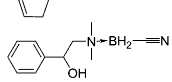
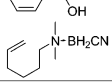
(1) According to the length of the *N*-alkyl chain in the alkyldimethylamine cyanoboranes for compounds **1**, **3**, **4**, **6**, **8**, **14**, **16**, and **17**, they have the general structure of $RNMe_2BH_2C{\equiv}N$ but vary in the length of the *N*-alkyl chain in the R group (*n*). In general, compounds with a longer *N*-alkyl chain have better activity. The optimized chain length was for compound **17** (C_{15} in the *N*-alkyl group). The chain length was restricted to this length because attempts to use longer chain lengths resulted in solubility problems, as in compound **18**, which has a C_{17} in the *N*-alkyl group.

(2) According to the length of the *N*-alkyl chain in the diamine bis-cyanoboranes for the diamine cyanoboranes **19**, **23**, and **24**, they have the general structure $N{\equiv}CBH_2Me_2N-(CH_2)_n$-$NMe_2BH_2C{\equiv}N$ but vary in the *N*-alkyl-*N* chain length (*n*). It is also obvious from Table 1 that the longer the chain length the greater the activity, until a limit of insolubility is reached. The optimized chain length was for compound **24** (C_{14} in the *N*-alkyl group) because attempts to use longer chain lengths (C_{16} and above, data not shown) resulted in solubility problems.

(3) Halogenation: As seen from Table 1, the bromination of alkyldimethylamine cyanoboranes and the diamine bis-cyanobo-

[a] Abbreviations: MIC, minimum inhibitory concentration; MTD, maximal tolerated dose; CLSI, Clinical Laboratory Standards Institute; CBS, Centraalbureau voor Schimmelcultures; ATCC, American Type Culture Collection; SDA, Sabouraud dextrose agar; NCCLS, National Committee for Clinical Laboratory Standards.

Table 1. The MICs of Various Compounds against Fungi

No	*Structure*	*Chain length*	MIC (μmol/L)			
			C. albicans			*A. fumigatus*
			CBS 562	*607*	*615*	*ATCC 64026*
1		1	5100	>5100	>5100	>5100
2		1	1970	>1970	>1970	
3		2	4460	4460	4460	
4		4	3570	>3570	>3570	>3570
5		4	470	3620	>3620	>3620
6		5	810	3240	3240	3240
7		8	2210	1100	1100	
8		9	150	150	300	300
9		11	32.5	32.5	32.5	32.5
10		11	49	49	49	131
11		11	39	39	39	79
12		11	64	64	64	129
13		11	492	492	983	492
14		12	61	61	61	
15[a]		12	--	--	--	--
16		13	58	58	117	58
17		15	53	53	106	53
18[a]		17	--	--	--	--
19		10	408	408	817	817
20		10	140	140	140	
21		10	104	104	104	
22		10	188	188	907	
23		12	96	194	46	
24		14	43	43	43	86
25		3	2940	2940	2940	2940
26		6	1388	2776	2776	
27		8	245	>245	>2450	
28		6	94	94	94	94
	Conventional antifungal agents					
	Amphotericin B		0.54	0.27	0.27	0.5
	Fluconazole		1.6	1.6	1.6	>208

[a] The tests could not be conducted because of solubility problems.

Table 2. Antifungal Activity of the Lead Compounds against Additional *Candida* species

fungal strain	MIC (μmol/L)			
	compd **9**	compd **11**	amphotericin B	fluconazole
C. glabrata 566	32.5	20.2	0.13	26.1
C. glabrata 572	32.5	40.4	1.07	>836
C. glabrata 578	32.5	40.4	2.14	>836
C. glabrata 646	32.5	20.2	0.41	52.2
C. glabrata 648	32.5	20.2	0.82	26.1
C. krusei 603	16.25	10.05	4.32	104.5[a]
C. krusei 638	16.25	10.05	4.32	104.5[a]

[a] *Candida krusei* is intrinsically resistant to fluconazole.[47]

ranes in most cases greatly enhances the activity, whereas fluorination has no such effect. The bromination of **1** to give the dibromo derivative **2** enhanced the activity against *C. albicans* CBS 562 from 5100 to 1970 μmol/L. Also, the bromination of **19** to the monobromo derivative **20** and the dibromo derivative **21** enhanced the activity against *C. albicans* CBS 562 from 408 μmol/L for compound **19** to 140 and 104 μmol/L for **20** and **21**, respectively, whereas the bromination or the fluorination of compound **9** to give **10**, **11**, and **12** had no such effect.

(4) Unsaturation: Furthermore, the presence of unsaturation in the alkyl group dramatically enhanced the activity as seen in compounds **4** and **5**, where the MIC value against *C. albicans* CBS 562 was reduced from 3570 to 470 μmol/L in the presence of a C═C double bond at the end of the alkyl group. For compounds **6** and **28**, the effect on activity with increased *N*-alkyl chain length was even greater, taking into account the difference of one CH_2 unit.

(5) Miscellaneous: Other additional structure types of amine cyanoboranes containing an hydroxyl group **7**, **13**, **15**, **26** and **17**, an aromatic group **27**, an unsaturated cyclic group **26**, and a silyl group **25** were synthesized. However, as can be seen from Table 1, none of these modifications produced a significant enhancement in activity. However, the conversion of the amine cyanoborane to the amine carboxyborane derivative as shown for compound **19** enhanced the activity. For example the activity against *C. albicans* CBS 562 was enhanced from 408 μmol/L for compound **19** to 188 μmol/L for its carboxyborane derivative **22**.

Toxicity Study in Vivo. To study the safety of lead compound **9** and its dibromo derivative **11**, we determined the MTD that did not kill ICR mice within the 8 days of the experimental period. Amphotericin B in its deoxycholate formulation (Fungizone) was used as a control. The MTD was calculated from the acute toxicity experiment that was performed according to the method described by Falk et al.[45] The average calculated MTD for both compounds were 121.9 and 73.1 μmol/kg, respectively. The MTD for amphotericin B was 2.6 μmol/kg. No changes in clinical signs, body weights, and the gross necropsy (on day 8) of mice that received these dosages were observed. These MTD values were well above that of the in vitro MIC values obtained with compound **9** (Table 1), and the ratio between the MTD and MIC values are comparable to those obtained with amphotericin B, indicating reduced toxicity and therapeutic potential.

Conclusions

Although the biological activity of amine cyanoboranes and amine carboxyboranes and their derivatives have been widely reported in the literature for the last 30 years, their use in the treatment of diseases and infections associated with pathogenic microorganisms has not been described. In this artcile, a series of new amine cyanoborane derivatives were synthesized and characterized. These derivatives are of different structural types and include alkyldimethylamine cyanoboranes, β-hydroxylalkyldimethylamine cyanoboranes, amine bromocyanoboranes, amine dibromocyanoboranes, amine carboxyboranes, amine bromocarboxyboranes, amine dibromocarboxyboranes, amine fluorocyanoboranes, diamine bis-cyanoboranes, and diamine bis-carboxyboranes. The compounds were screened for antifungal activity. A number of relationships were observed according to structural types. The following modifications in the structure significantly enhanced the activity: (1) The *N*-alkyl chain length in alkyldimethylamine cyanoboranes and diamine bis-cyanoboranes, (2) halogenation, (3) the incorporation of the C=C double bond at the end of the *N*-alkyl chain, and (4) the conversion of the amine cyanoborane to the amine carboxyborane. However, no enhancement of activity was observed with other modifications in the structure, such as addition of a hydroxyl group, an aromatic group, an unsaturated cyclic group, and a silyl group. The lead compounds were dimethylundecylamine cyanoborane ($C_{11}H_{23}N(CH_3)_2BH_2CN$) **9**, with MIC values for the most important human pathogenic fungi ranging from 16.25 to 32.5 μmol/L, and its dibromo derivative, dimethylundecylamine dibromocyanoborane ($C_{11}H_{23}N(CH_3)_2BBr_2CN$) **11**, in which the MIC values ranged from 10.05 to 79 μmol/L. These compounds possess considerable activity against fungal strains resistant to fluconazole. Reduced toxicity was also observed with these compounds. The effect of unsaturation (together with chain length) will be emphasized in future developments in this series.

Experimental Section

Chemistry. General Comments. All reactions were carried out under nitrogen. The solvents were dried by the usual methods and distilled before use. All other chemicals were obtained from Sigma-Aldrich and were used as received without any further purification. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded in $CDCl_3$ and D_2O solution on a Varian Unity Spectrometer (300, 75, 96 MHz) using Me_4Si as an internal standard. Infrared spectra were run for samples in NaCl cells on a Bruker Vector 22 FT-IR spectrophotometer. Melting points were measured on a Fisher Scientific melting point apparatus. Me_3NBH_2CN was prepared from $Me_3N\cdot HCl$ and $NaBH_3CN$ using the literature method.[46] Compounds **1-6**, **25**, and **27** were re-synthesized as described in our previously published articles.[37,38]

Synthesis of Compounds 8−9,14,16−18, and 28. Me_3NBH_2CN (0.098 g, 1 mmol) was dissolved in 20 mL of dry THF and cooled to −78 °C, and 1.15 mL, 1.5 mmol of 1.3 M *s*-BuLi/hexane solution was added dropwise. The reaction mixture was allowed to warm gradually to room temperature during a period of 1h and then recooled to −78 °C, and 1.5 mmol of the appropriate alkyl halide (RX) was added in one portion. After 5 min, the cooling bath was removed, and the reaction mixture was stirred for 1 h. Then, 20 mL of saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was then dissolved in 5 mL of benzene and washed with distilled water (5 ×10 mL). The organic layer was then dried over sodium sulfate, filtrated, and concentrated under vacuum.

Synthesis of Compounds 19 and 23−24. Me_3NBH_2CN (0.098 g, 1 mmol) was dissolved in 20 mL of dry THF and cooled to −78 °C, and 1.15 mL, 1.5 mmol of 1.3 M *s*-BuLi/hexane solution was added dropwise. The reaction mixture was allowed to warm gradually to room temperature during a period of 1h and then recooled to −78 °C, and 0.75 mmol of the appropriate alkyl dihalide (XRX) was added in one portion. After 5 min, the cooling bath was removed, and the reaction mixture was stirred for 2 h. Then, 20 mL of saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was then dissolved in 5 mL of benzene and washed with distilled water (5 × 10 mL). The organic layer was then dried over sodium sulfate, filtrated, and concentrated under vacuum.

Synthesis of Compounds 7, 13, 15, and 26. Me_3NBH_2CN (0.098 g, 1 mmol) was dissolved in 20 mL of dry THF and cooled to −78 °C, and 1.15 mL, 1.5 mmol of 1.3 M *s*-BuLi/hexane solution was added dropwise. The reaction mixture was allowed to warm gradually to room temperature during a period of 1 h and then recooled to −78 °C, and 0.75 mmol of the appropriate alcohol was added in one portion. After 5 min, the cooling bath was removed, and the reaction mixture was stirred for 1 h. Then 20 mL of saturated aqueous $NaHCO_3$ solution was added to the reaction mixture. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was dissolved in 5 mL of ether, stirred for 3 h with 10 mL of saturated aqueous sodium bisulfite solution. The precipitate was filtered out and discarded. The ether layer was dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was then dissolved in 5 mL of CH_2Cl_2 and washed with distilled water (5 × 10 mL). The organic layer was extracted, dried over sodium sulfate, filtered, and concentrated under vacuum.

Synthesis of Compounds 10−11. The desired amine cyanoborane was dissolved in 10 mL MeOH, cooled to 0 °C in an ice bath, and 1.2 mmol of Br_2 for compound **10** or 2.2 mmol of Br_2 for compound **11** were dissolved in 20 mL of double distilled water and added dropwise to amine cyanoborane. The reaction mixture was allowed to stir and warm gradually to room temperature and stirred for 4 h for compound **10** or for 8 h for compound **11**. MeOH was evaporated using a rotatory evaporator, and the aqueous layer was extracted with 3 × 20 mL of ether. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, decolorized by adding charcoal, filtrated, and concentrated under vacuum.

Synthesis of Compound 12. Compound **10** (1 mmol) was dissolved in 2 mL of dry benzene, and silver (I) fluoride 99% (5 equiv) was suspended in 5 mL of dry benzene. The reaction mixture was sonicated for 5 h. Then, the solvent was filtered and removed under high vacuum.

Synthesis of Compounds 20−21. The desired amine cyanoborane (1 mmol) was dissolved in 10 mL of MeOH and cooled to 0 °C in an ice bath, and 4.2 mmol of Br_2 dissolved in 20 mL of double distilled water was added dropwise. The reaction mixture was allowed to stir at 0 °C and stirred for 16 h. MeOH was evaporated, and the aqueous layer was extracted with 3 × 20 mL of ether. The organic layer was separated, washed with brine, dried over sodium sulfate, filtered, decolorized by adding charcoal, filtrated, and concentrated under vacuum.

1-(Dimethylamino)-2-methyloctan-2-ol Cyanoborane (7). White solid, 85% (0.192 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.81 (m, 7H), 1.12 (pent, 2H, J = 6.0 Hz), 1.51 (m, 4H), 2.09 (s, 1H), 2.10 (s, 1H), 2.38 (td, 3H, J_t=12 Hz, J_d= 6.0 Hz), 2.68 (s, 3H), 2.69 (s, 3H), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.24, 22.67, 22.82, 31.78, 32.03, 43.61, 45.73, 48.58, 53.01, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −12.46 (t, J_{B-H} = 104.4 Hz). IR (neat, cm^{-1}): 3447 (O−H), 2930 (B−H), 2958 (C−H), 2361 (C≡N), 1461 (C−N), 433 (B−N). Anal. Calcd for $C_{12}H_{27}BN_2O$: C, 63.73; H, 12.03; N, 12.39. Found: C, 63.71; H, 12.01; N, 12.35.

Dimethylundecylamine Cyanoborane (9). White solid, 87% (0.207 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 7.2 Hz), 1.25 (broad s, 14H), 1.66 (hept, 2H, J = 3.6), 1.83 (pent, 2H, J = 7.2), 2.63 (s, 6H), 2.84 (t, 2H, J = 5.0), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.34, 22.89, 23.49, 27.13, 29.44, 29.52, 29.65, 32.09, 45.18, 46.97, 50.03, 63.84, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −16.67 (t, J_{B-H} = 97.1 Hz). IR (KBr, cm^{-1}):

2919 (B−H), 2852 (C−H), 2358 (C≡N), 1469 (C−N), 440 (B−N). Anal. Calcd for $C_{14}H_{31}BN_2$: C, 70.59; H, 13.12; N, 11.76. Found: C, 70.52; H, 13.11; N, 11.75.

Dimethylundecylamine Bromocyanoborane (10). Brown oil, 80% (0.254 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H, J = 7.2 Hz), 1.22 (broad s, 14H), 1.65 (hept, 2H, J = 3.6), 1.81 (pent, 2H, J = 7.2), 2.77 (s, 6H), 2.94 (t, 2H, J = 6.9), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.35, 22.89, 22.90, 27.00, 29.38, 29.51, 29.61, 32.09, 43.61, 45.24, 47.60, 47.70, 61.98, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −10.95 (d, J = 177.7 Hz). IR (KBr, cm^{-1}): 2919 (B−H), 2854 (C−H), 2358 (C≡N), 1469 (C−N), 442 (B−N). Anal. Calcd for $C_{14}H_{30}BBrN_2$: C, 53.02; H, 9.54; Br, 25.20; N, 8.83. Found: C, 53.05; H, 9.51; Br, 25.22; N, 8.80.

Dimethylundecylamine Dibromocyanoborane (11). Brown oil, 82% (0.324 g) yield. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, J = 7.2 Hz), 1.30 (broad s, 14H), 1.68 (hept, 2H, J = 3.6), 1.82 (pent, 2H, J = 7.2), 2.94 (s, 6H), 3.38 (t, 2H, J = 6.9), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.35, 22.89, 26.98, 29.37, 29.42, 29.50, 29.66, 29.73, 32.08, 46.01, 47.71, 61.98, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −9.36 (s). IR (KBr, cm^{-1}): 2854 (C−H), 2362 (C≡N), 1409 (C−N), 435 (B−N). Anal. Calcd for $C_{14}H_{29}BBr_2N_2$: C, 42.46; H, 7.38; Br, 40.35; N, 7.07. Found: C, 42.42; H, 3.35; Br, 40.37; N, 7.10.

Dimethylundecylamine Monofluorocyanoborane (12). Brown oil, 66% yield. ^{1}H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 6.9 Hz), 1.25 (broad s, 16H), 1.4 (broad s, 2H) 2.78 (s, 6H), 3.39 (t, 2H, J = 6.9 Hz). ^{11}B NMR ($CDCl_3$): δ −2.08 (dd, J_{B-H} =75.2, J_{B-F} = 64.0 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 14.07, 22.63, 26.72, 29.33, 29.4, 31.82, 47.4, 61.71, (BC cannot be detected). ^{19}F NMR ($CDCl_3$): δ −25.09 (qd, J_{F-B} = 40 Hz, J_{F-H} = 16 Hz). IR (neat, cm^{-1}): 2924 (C−H), 2209 (C≡N), 1455 (C−N), 1074 (B−F), 2491 (B−H) stretching vibrations. Anal. Calcd for $C_{13}H_{28}BFN_2$: C, 64.47; H, 11.65; N, 4.46, F, 7.84. Found: C, 64.21; H, 11.68; N, 4.49, F, 7.86.

***N,N,N′,N′*-Tetramethyldecane-1,10-diamine Bis-cyanoborane (19).** White solid, 90% (0.276 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.29 (broad s, 8H), 1.66 (m, 4H), 1.84 (m, 4H), 2.63 (s, 12H), 2.84 (t, 4H, J = 3.9 Hz), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 23.47, 27.04, 29.27, 29.40, 50.15, 63.78, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −16.67 (t, J_{B-H} = 101.1 Hz). IR (KBr, cm^{-1}): 2923 (B−H), 2854 (C−H), 2332 (C≡N), 1542 (C−N), 433 (B−N). Anal. Calcd for $C_{16}H_{36}B_2N_4$: C, 62.78; H, 11.85; N, 18.30. Found: C, 62.73; H, 11.88; N, 18.33.

***N,N,N′,N′*-Tetramethyldecane-1,10-diamine Bis-bromocyanoborane (20).** Brown oil, 82% (0.380 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.30 (broad s, 8H), 1.68 (m, 4H), 1.86 (m, 4H), 2.78 (s, 12H), 3.05 (m, 4H), (HB cannot be detected).^{13}C, NMR ($CDCl_3$): δ 22.91, 26.89, 29.17, 29.32, 50.84 61.98, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −11.38 (d, J_{B-H} = 113.7 Hz). IR (neat, cm^{-1}): 2927 (B−H), 2856 (C−H), 2341 (C≡N), 1542 (C−N), 440 (B−N). Anal. Calcd for $C_{16}H_{34}B_2Br_2N_4$: C, 41.43; H, 7.39; Br, 34.45; N, 12.08. Found: C, 41.45; H, 7.41; Br, 34.43; N, 12.12.

***N,N,N′,N′*-Tetramethyldecane-1,10-diamine Bis-dibromocyanoborane (21).** Brown oil, 83% (0.516 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.31 (broad s, 8H), 1.70 (m, 4H), 1.88 (m, 4H), 2.95 (s, 12H), 3.38 (m, 4H), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 22.90, 26.88, 29.17, 29.31, 50.82, 61.97, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −9.38 (s). IR (neat, cm^{-1}): 2856 (C−H), 2362 (C≡N), 1542 (C−N), 440 (B−N). Anal. Calcd for $C_{16}H_{32}B_2Br_4N_4$: C, 30.91; H, 5.19; Br, 51.41; N, 9.01. Found: C, 30.88; H, 5.22; Br, 51.39; N, 9.05.

***N,N,N′,N′*-Tetramethyldecane-1,10-diamine Bis-carboxyborane (22).** White oil, 78% (0.268 g) yield. ^{1}H NMR ($CDCl_3$): δ 1.26 (broad s, 8H), 1.61 (m, 4H), 1.83 (pent, 4H, J = 6.9 Hz), 2.66 (s, 12H), 2.91 (t, 4H, J = 4.2 Hz), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 23.27, 29.31, 32.91, 34.35, 52.36, 62.78, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −8.96 (broad s). IR (KBr, cm^{-1}): 3450 (B−O), 2960 (B−H), 2716 (C−H), 2371 (C≡N), 1459 (C−N), 433 (B−N). Anal. Calcd for $C_{16}H_{38}B_2N_2O_4$: C, 55.85; H, 11.13; N, 8.14. Found: C, 55.79; H, 11.17; N, 8.21.

1-Dimethylaminomethylcyclopent-2-enol Cyanoborane (26). Yellowish solid, 80% (0.144 g) yield. ^{1}H NMR ($CDCl_3$): δ 2.00 (m, 2H), 2.15 (m, 2H), 2.87 (s, 3H), 2.89 (s, 3H), 3.14 (s, 1H), 3.16 (s, 1H), 5.78 (m, 1H), 6.01 (m, 1H), (HB cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 26.29, 33.03, 54.57, 67.82, 77.60, 129.51, 140.04, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −14.861 (t, J_{B-H} = 106.3 Hz). IR (KBr, cm^{-1}): 3450 (B−O), 2920 (B−H), 2853 (C−H), 2334 (C≡N), 1542 (C−N), 440 (B−N). Anal. Calcd for $C_9H_{17}BN_2O$: C, 60.04; H, 9.52; N, 15.56. Found: C, 59.99; H, 9.31; N, 15.51.

Hex-5-enyldimethylamine Cyanoborane 28. Yellow oil, (0.144 g) 87% yield. ^{1}H NMR ($CDCl_3$): δ 1.39 (pent, 2H, J = 7.5 Hz), 1.68 (m, 2H), 2.10 (q, 2H, J = 7.0 Hz), 2.85 (t, 3H, J = 4.5 Hz), 5.00 (td, 2H, J_d = 0.6 Hz, J_t = 9.0 Hz), 5.74 (m, 1H), (BH cannot be detected).^{13}C {^{1}H} NMR ($CDCl_3$): δ 22.79, 26.22, 33.34, 50.07, 63.54, 115.72, 137.82, (CB cannot be detected). ^{11}B NMR ($CDCl_3$): δ −15.87 (t, J_{B-H} = 104.5 Hz). IR (neat, cm^{-1}): 2909 (B−H), 2360 (C≡N), 1645 (C═C), 1470 (C−N), 443 (B−N). Anal. Calcd for $C_9H_{19}BN_2$: C, 65.09; H, 11.53; N, 16.87. Found: C, 65.13; H, 11.47; N, 16.90.

Mycology. Susceptibility Testing by the Broth Dilution Method. Several yeast strains were used for susceptibility testing: *Candida albicans* CBS 562 (a reference type strain; Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands) and two clinical isolates, 607, and 615; *Candida glabrata* 566, 572, 578, 646, and 648 and *Candida krusei* 603 and 638 as well as the mold *Aspergillus fumigatus* ATCC 64026 (a reference strain; The American Type Culture Collection, Manassas, VA). In addition, all isolates are from disseminated candidemia patients from Hadassah-Hebrew University Medical Center (Isolate numbers refer to an internal index). The in vitro susceptibility of each compound was determined by the broth micro dilution method according to CLSI recommendations for yeasts (M27-A2[41]) and for filamentous fungi (M-38A[42]). Briefly, 2-fold serial dilutions of drugs from stock solutions were prepared in an RPMI-1640 broth medium (Sigma, St. Louis, MO.) buffered to a final pH of 7.0 with 0.165 M morpholinepropanesulfonic acid (MOPS; Sigma) and 1M NaOH, and sterilized by filtration. A stock solution of 10 mg/mL was prepared in dimethyl sulfoxide (DMSO, Sigma) for the various amine cyanoborane compounds and for amphotericin B and fluconazole, which were used as controls. The final drug concentrations in the test ranged from 1024 to 4 mg/L in a final volume of 0.1 mL.

Fungal inocula were prepared from 24-h *(Candida* sp.) or 72-h *(A. fumigatus*) cultures on SDA plates (Difco, Detroit, MI). The inocula were harvested by harvesting a single colony of yeast into a sterile saline tube. Mold cultures were suspended in plates with sterile saline containing a 0.05% (v/v) Tween-20 (Difco) suspension and pipeted into sterile tubes and allowed to rest for 30 min for the debris to sink down. The supernatant was then transferred to a new tube. Both yeast and mold were diluted into RPMI-1640 broth medium to yield a final inoculum concentration of 2×10^3 yeast per mL for *Candida* and 2×10^4 spores per mL for *Aspergillus*, as measured by counting the initial suspension with a hemacytometer. The micro dilution wells, which contained 0.1 mL of the serially diluted drug, were inoculated with 0.1 mL of the resulting suspension. The final inoculum concentration after dilution with the drug suspension was $10^3/10^4$ cells per mL. Two wells containing the drug-free medium and inoculum were used as controls. The inoculated plates were incubated at 35 °C for 24 h *(Candida* sp.) or 72 h *(A. fumigatus*). The growth in each well was then visually estimated. The MICs were determined visually, and were defined as the lowest drug concentration at which there was complete absence of growth (MIC-0).

Toxicity Testing. The acute toxicity was determined according to the method described by Falk et al.[45] Briefly, male ICR mice weighing ∼30 g were injected through the tail vein with various doses of compounds **9** and **11** and Fungizone (amphotericin B deoxycholate micellar formulation, Bristol-Myers-Squibb, Dublin, Ireland). Each dosage form (Fungizone 0.1 mg/mL; and compounds **9** and **11** 1−2 mg/mL in saline) was administered intravenously as single bolus injections (0.12 mL) of the same dose every 10 min to a group of three mice until death was observed. The survival of mice that received the maximal tolerated dose (MTD) was monitored for 8 days.

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Supporting Information Available: Habits, yields, ^{1}H, ^{11}B, ^{19}F, and ^{13}C NMR data, and FT-IR and elemental analysis data for compounds **8**, **13**−**18**, and **23**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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