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Antifungal activity and tautomeric cyclization equilibria of formylphenylboronic acids

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ABSTRACT

2-Formylphenylboronic acid and four isomeric fluoro-2-formylphenylboronic acids have been found active against a series of fungal strains: *Aspergillus*, *Fusarium*, *Penicillium* and *Candida*. The level of antifungal activity was evaluated by agar diffusion tests as well as the determination of minimum inhibitory concentrations (MICs) by serial dilution method. Among the tested compounds, 4-fluoro-2-formylphenylboronic acid – an analogue of the known antifungal drug Tavaborole (AN2690) – proved to be the most potent antifungal agent. The tautomeric equilibrium leading to the formation of 3-hydroxybenzoxaboroles as well as the position of the fluorine substituent were revealed to play a crucial role in the observed activity.

1. Introduction

An immense development and applicability of transition metal-catalyzed cross-coupling reactions made phenylboronic acids indispensable reagents for organic synthesis [1]. Concurrently, the boronic acids capacity to reversibly bind diols has brought about a wide range of implementations in analytical and materials chemistry [2–4]. Boronic acids are applied for the construction of polymers and nanoparticles characteristic of diol affinity and/or responsiveness [5,6]. They are used in sensors for medically relevant bioanalytes, e.g. in those designed for monitoring glucose levels [7]. These solutions attract particularly lively interest, owing to a tremendous potential to improve treatment of diabetes.

Boronic compounds also emerged as attractive pharmacophores for medicinal chemistry, resulting in the development of boronic-based anticancer [8–10], antibacterial [9,11,12], and antifungal agents [11,12]. The recent major breakthroughs in this regard were the US FDA drug approvals of two benzoxaboroles – cyclic, internal hemiesters of 2-(hydroxymethyl)phenylboronic acid [13]. First, Tavaborole (AN2690, Kerydin) was approved in 2014 for the treatment of onychomycosis, a fungal infection of the nail [14]. Next, Crisaborole (AN2728, Eucrisa) was approved in 2016 for the treatment of atopic dermatitis, a type of inflammation of the skin [15].

In current work we focus on 2-formylphenylboronic acids. Until recently, formylphenylboronic acids served mainly as cross-coupling reagents for the introduction of a formylphenyl scaffold [16]. A few reports pointed to other uses, such as reagents for chiral discrimination by NMR [17] or substrates for the synthesis of other boronic species, including benzoxaboroles [18]. Recently, 2-formyl- and 2-acetylphenylboronic acid are increasingly employed in chemical biology for bioconjugation [19]. Among these species, the fluorine-substituted compounds appear to be particularly interesting owing to higher Lewis acidity compared with the non-fluorinated analogues [20,21] and the boosting effect of fluorine substituent on the bioactivity [22].

Generally, phenylboronic acids do not display antifungal activity, whereas their benzoxaborole analogues do [23–25]. Quite surprisingly, a series of 2-formylphenylboronic acids investigated herein turned out to have antifungal properties. 2-Formylphenylboronic acids are however known to equilibrate in solution with the formation of cyclic isomers analogous to benzoxaboroles [20,26]. The equilibrium (Scheme 1, framed) has been previously studied in acetone-d_6 solution by ^{1}H NMR technique [20]. Since DMSO solutions are used in the studies of biological activity, we decided to investigate the phenomenon in this solvent. Due to numerous advantages of the ^{19}F NMR technique [27] it was used to determine the cyclization constants.

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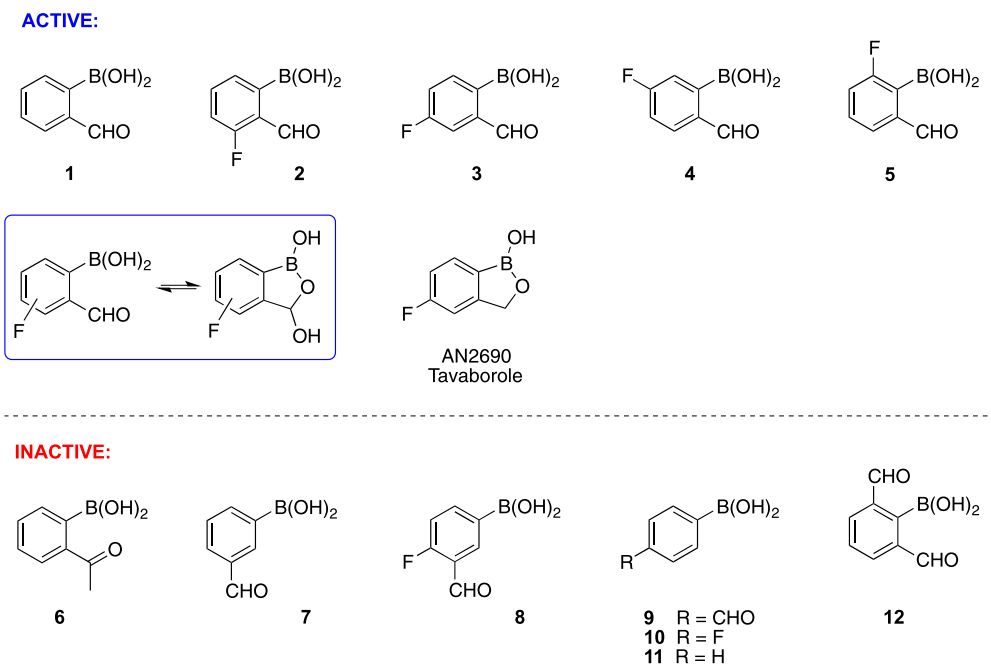


Scheme 1. Boronic compounds featured in this work.

2. Results and discussion

2.1. Microbiological studies

The key boronic compounds under investigation were: 2-formylphenylboronic acid (**1**) and four isomeric fluoro-2-formylphenylboronic acids **2–5**. It is worth mentioning that due to the tautomeric equilibrium in solution (Scheme 1, framed) compound **3** can be regarded an a 3–hydroxylanalogue of Tavaborole. To get the most out of the comparative structure-activity studies, antimicrobial activity of compounds **2–5** has been compared with that of seven reference compounds **6–12** differing in the presence, kind or position of functional groups (Scheme 1).

Tests of antimicrobial activity were run against a series of fungal pathogens: *Aspergillus niger*, *Aspergillus terreus*, *Fusarium oxysporum*, *Fusarium solani*, *Fusarium dimerum*, *Penicillium ochrochloron*, *Candida albicans*, and *Candida tenuis*. The first stage of microbiological evaluation was based on the agar diffusion method. DMSO was used as a negative control. The positive control of Amphotericin B at 50 μg is given for comparison. Table 1 presents only the compounds that revealed antifungal activity (**1–5**), whereas Table S1 (see Appendix A) covers the inactive species (**6–12**).

All of the active compounds contain a formyl group at position 2. The most potent antifungal agent proved to be 4-fluoro-2-formylphenylboronic acid (**3**), an analogue of Tavaborole (Scheme 1). It showed considerable antifungal action towards most of the studied strains at all the amounts studied, even as low as 10 μg. The second most potent agent was found to be 2-formylphenylboronic acid (**1**), with a reduced activity against *A. niger* and *A. terreus* yet comparable against *Fusarium* strains and *P. ochrochloron* at 100 μg. The next compound in terms of antifungal potency was 3-fluoro-2-formylphenylboronic acid (**2**). It remained relatively active at 100 μg and 50 μg but exerted lower effect towards certain strains at 25 μg and 10 μg quantities compared to 2-formylphenylboronic acid. 5-Fluoro-2-formylphenylboronic acid (**4**) was found to be the first compound in this sequence that showed no activity towards all but one fungus at 10 μg. Notably though, it remained appreciably active against *P. ochrochloron* and *A. terreus* at 100 μg. The least active compound in the studied set was 6-fluoro-2-formylphenylboronic acid (**5**). Among the filamentous fungi, it moderately inhibited the growth of *Aspergillus* strains at higher quantities of 100 μg and 50 μg. However, it is worth noting that it remained active against *C. tenuis*, which was also the case for the other fluoro-2-formylphenylboronic acids studied. Reduced activity of compounds **4** and **5** can result from considerably lower cyclization constant values (Table 3).

Due to analogous protocol as well as the same fungal strains used, the values presented herein (Table 1) can be compared with that of the previously reported fluorobenzoxaboroles [28]. Importantly, the most potent compounds in both classes were the ones containing fluorine atom in *para* position with respect to the boronic group – Tavaborole and compound **3**, which can be considered as its 3-hydroxyderivative. Overall, the activity of the examined fluoro-2-formylphenylboronic acids **2–5** against filamentous fungi was lower compared with analogous benzoxaboroles. Comparing results obtained for 50 μg with activity of amphotericin B at the same concentration, only compound **3** was more active than the positive control in case of *Aspergillus* fungi as well as *Fusarium dimerum* and *Penicillin ochrochloron*.

The rest of the microbiologically tested compounds **6–12** (Scheme 1) was found inactive towards all the examined moulds at studied concentrations (see Appendix A, Table S1). As evidenced by the lack of activity of compounds **7** and **9**, the *ortho* position of the formyl group is crucial to the tested bioactivity. Same thing might be concluded about the high vs null activity of 4-fluoro-2-formylphenylboronic acid (**3**) and its position isomer, 4-fluoro-3-formylphenylboronic acid (**8**). The removal of the formyl group from the compound structure led to zeroing the activity as well, as observed for 4-fluorophenylboronic acid (**10**) and phenylboronic acid (**11**). Interestingly, 2-acetylphenylboronic acid (**6**) and 2,6-diformylphenylboronic acid (**12**) also showed no activity, despite the presence of a carbonyl group at the *ortho* position. In case of 2-acetylphenylboronic acid (**6**), the formation of a cyclic isomer is less probable in comparison with its formyl analogue (**1**). The cyclization of 2,6-diformylphenylboronic acid (**12**) is possible [29], however steric hindrance of two formyl groups adjacent to the boronic group may be detrimental to the antifungal activity. Steric hindrance may also be the reason of a rather low if any activity of compound **5**.

The compounds proved active in the agar diffusion tests (**1–5**) were subjected to the determination of the MIC (Minimal Inhibitory Concentration) values using the serial dilution method (Table 2) [23].

Table 1
The average diameter of the zone of inhibited growth of the examined fungi [mm] for the active compounds[§].

Fungus	Amount					
	10 μg	25 μg	50 μg	100 μg	Amphotericin B 50 μg [24]	DMSO
2-Formylphenylboronic acid (1)						
A. niger	n/d	18	20	26 (5)	(13)	0
A. terreus	10	18	20	26 (6)	12 (10)	0
F. dimerum	4	7	11 (7)	21 (14)	4	0
F. oxysporum	0	8	19 (13)	24 (16)	n/d	0
F. solani	3	5	16 (8)	23 (13)	11 (5)	0
P. ochrochloron	0	18 (5)	28 (7)	34 (11)	(11)	0
3-Fluoro-2-formylphenylboronic acid (2)						
A. niger	12	19	23	33	(13)	0
A. terreus	0	17	20	27	12 (10)	0
F. dimerum	0	8	17 (8)	25 (14)	4	0
F. oxysporum	0	9	16 (8)	24 (12)	n/d	0
F. solani	0	5	16 (9)	24 (16)	11 (5)	0
P. ochrochloron	0	0	14	19	(11)	0
C. albicans	0	0	0	12	(9)[†]	0
C. tenuis	(16)	(20)	(24)	(29)	n/d	0
4-Fluoro-2-formylphenylboronic acid (3)						
A. niger	(24)	(32)	(36)	(40)	(13)	0
A. terreus	(30)	(36)	(42)	(47)	12 (10)	0
F. dimerum	5	7	20 (15)	30 (22)	4	0
F. oxysporum	10	14	19	24	n/d	0
F. solani	0	7	9	19 (12)	11 (5)	0
P. ochrochloron	21	25	(30)	(37)	(11)	0
C. albicans	n/d	n/d	26	32	(9)[†]	0
C. tenuis	(19)	(22)	(26)	(28)	n/d	0
5-Fluoro-2-formylphenylboronic acid (4)						
A. niger	0	0	8	13 (8)	(13)	0
A. terreus	0	12	24 (6)	30 (10)	12 (10)	0
F. dimerum	0	0	7	9	4	0
F. oxysporum	0	0	(9)	(13)	n/d	0
F. solani	0	(6)	(8)	22 (12)	11 (5)	0
P. ochrochloron	0	8	23 (10)	32 (16)	(11)	0
C. albicans	0	0	0	0	(9)[†]	0
C. tenuis	(5)	(9)	(15)	(24)	n/d	0
6-Fluoro-2-formylphenylboronic acid (5)						
A. niger	0	10	19	26	(13)	0
A. terreus	0	0	10	17	12 (10)	0
F. dimerum	0	0	0	0	4	0
F. oxysporum	0	0	0	0	n/d	0
F. solani	0	0	0	0	11 (5)	0
P. ochrochloron	0	0	0	0	(11)	0
C. albicans	0	0	0	0	(9)[†]	0
C. tenuis	(15)	(20)	(24)	(28)	n/d	0

[§] Diameter of the zone of the totally inhibited growth of the fungus (no mycelium within the growth medium) is shown in parentheses. The values beyond parentheses relate to the diameter of the zone of both limited and totally inhibited growth of the fungus; nd - not determined.

[†] This work.

Table 2
Minimum inhibitory (fungistatic) concentrations – MICs [μg/mL].

Fungus	Compound				
	1	2	3	4	5
A. niger	16	31.3	2	62.5	< 125
A. terreus	16	31.3	< 1	31.3	< 125
F. solani	16	15.6	15.6	31.3	< 125
F. dimerum	31.2	n/d	n/d	n/d	n/d
P. ochrochloron	31.2	31.3	7.8	31.3	125
C. albicans	n/d	62.5	62.5	62.5	125
C. tenuis	n/d	62.5	125	62.5	62.5

n/d - not determined.

Table 3
The average K_{cycl} values determined based on ^{19}F NMR spectra.

Compound	Solvent	Cyclization constant (K_{cykl})
2	DMSO-d_6	1.46 ± 0.04
	DMSO-d_6 + drop of D_2O	1.35[a]
3	DMSO-d_6	0.47 ± 0.04
	DMSO-d_6 + drop of D_2O	0.49 ± 0.05
4	DMSO-d_6	0.07 ± 0.00
5	DMSO-d_6	0.04 ± 0.05

[a] As only one sample was run, no error value was determined.

The determined MICs values arranged the compounds with respect to their antifungal activity in the same order as the agar diffusion tests did. Compound **3** was confirmed to be the most potent agent against the examined filamentous fungi among the compounds studied. That effect was most pronounced in *Aspergillus* strains for which the MICs of **3** were found to be less than or equal to 2 μg/mL. The least potent compound was found to be 6-fluoro-2-formylphenylboronic acid (**5**), again pointing to the role of steric hindrance around the boronic group as well as low cyclization constant value (Table 3).

The case was yet different for the yeasts *C. albicans* and *C. tenuis*, for which three out of four fluoro-2-formylphenylboronic acids studied had the same MIC values. Interestingly, in case of *C. tenuis* compound **3** despite similar zones of the inhibited growth of the examined fungi (Table 1) had even twice as high MIC as its position isomers **2**, **4** and **5** (Table 2).

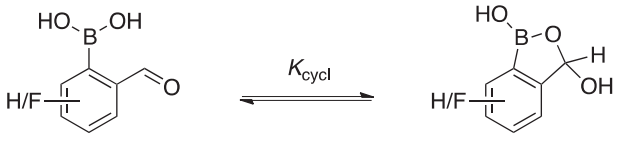
2.2. Cyclization equilibria in fluorinated 2-formylphenylboronic acids

In solutions, 2-formylphenylboronic acids tautomerize with the formation of a heterocyclic ring characteristic for benzoxaboroles (Scheme 2) [26]. Such equilibrium can be characterized with a cyclization constant:

$$K_{cycl} = [3 - \text{hydroxybenzoxaborole}]/[2 - \text{formylphenylboronicacid}],$$

which quantitatively characterizes a dynamic interconversion of an "open" form into the "closed" form. The equilibrium was found to be temperature- and solvent-dependent [26].

In their seminal work on 2-formylphenylboronic acids tautomerization in solution [26], Luliński et al. studied only one fluorine-containing compound, namely 3-fluoro-2-formylphenylboronic acid (**2**). In acetone-d_6 and DMSO-d_6 (both containing 5 wt% D_2O), the cyclic tautomer prevailed, whereas in D_2O the "open" form was found to predominate profoundly. The synthesis, solid- and solution-state characterization as well as Lewis acidity of four isomeric fluoro-2-formylphenylboronic acids were then reported in our recent work [20]. The tautomerization was previously probed in acetone-d_6 by ^1H NMR and found to be dependent on the position of fluorine substituent. For all four isomers **2–5**, the open form predominated in acetone-d_6 solutions. The highest contribution of the cyclic benzoxaboroles form was observed for 3-fluoro-2-formylphenylboronic acid (**2**). For the other isomers, the cyclization constants determined in acetone were low and comparable with the K_{cycl} value for 2-formylphenylboronic acid (**1**). Since in antifungal activity studies DMSO is used to dissolve samples, herein, we investigated the tautomeric cyclization equilibrium in DMSO-d_6 (Table 3). Most of the active compounds (**2–5**) contain fluorine atom, therefore ^{19}F NMR spectroscopy was applied to



Scheme 2. Tautomeric equilibrium of 2-formylphenylboronic acids in solution.

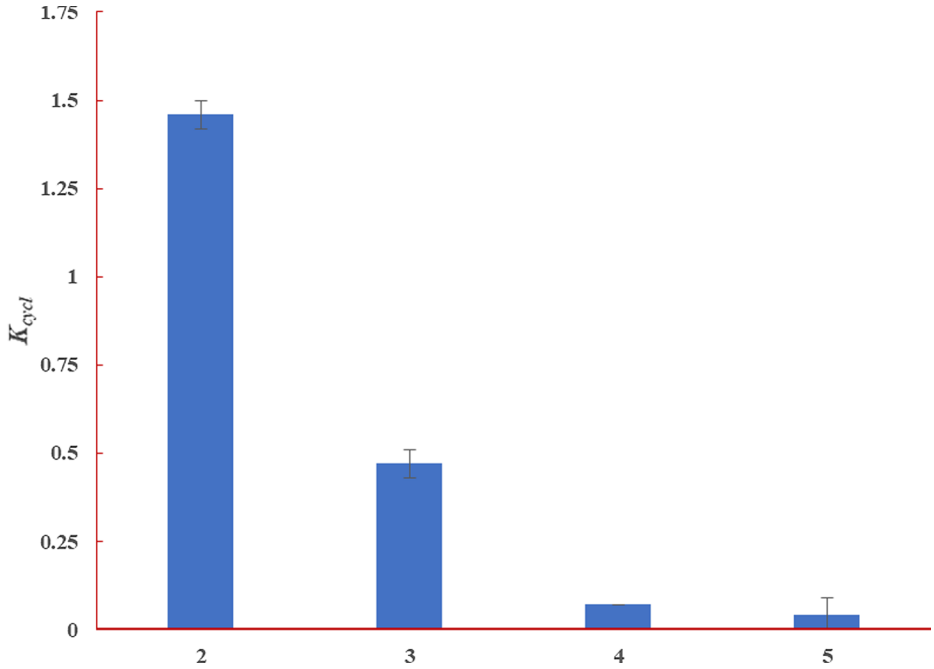


Fig. 1. Comparison of the average cyclization constants of compounds **2–5** determined by ^{19}F NMR.

determine the ratio of tautomeric forms in solution. We anticipated to observe two signals corresponding to the tautomeric forms, and this proved to be the case for all four compounds. Cyclization constants were determined based on the integration ratios of ^{19}F NMR signals. The signals were assigned comparing their intensities with the intensities of the respective characteristic signals in ^{1}H NMR spectra.

Each K_{cycl} presented in Table 3 is given as an average value based on at least two samples with different concentration of boronic acid (for details see Appendix A, Table S2 and Figs. S1–S6). Standard deviations serve as the estimates of the measurement errors.

In DMSO-d_6, 3-fluoro-2-formylphenylboronic acid (**2**) largely exists in its cyclic form. This is in sharp contrast with the predominance of the "open" form in acetone-d_6. For the other three isomers (**3–5**), however, the open form prevails in DMSO-d_6. The K_{cycl} value for 4-fluoro-2-formylphenylboronic acid (**3**) was nearly three times lower than for 3-fluoro-2-formylphenylboronic acid (**2**). For 5-fluoro- and 6-fluoro-2-formylphenylboronic acids (**4** and **5**), only a very small contribution of the cyclic forms was observed (Fig. 1).

For two compounds, samples with an additive of D_2O were investigated in order to study how D_2O affects the tautomeric equilibrium. Also, it allowed for the identification of the signals of the exchangeable protons of B-OH groups in ^{1}H NMR spectra. Comparing the K_{cycl} values determined for compounds **2** and **3** in DMSO-d_6 vs DMSO-d_6 with a drop of D_2O, it can be concluded that the presence of D_2O affects the tautomerization equilibrium to a minor extent. The difference in the cyclization constants determined by ^{19}F NMR is comparable with the estimated measurement errors.

3. Conclusions

The study showed that 2-formylphenylboronic acids are promising agents against a series of *Aspergillus*, *Fusarium*, *Penicillium* and *Candida* fungi. The *ortho* position of the formyl group was found to be crucial to the observed antifungal effect. The antifungal activity of 2-formylphenylboronic acids might have been assumed to result mainly from the presence of equilibrium-derived, cyclic 3-hydroxybenzoxaborole tautomers in solution. The level of antifungal activity is related to the cyclization behavior of the tested compounds in DMSO-d_6 solutions. Compounds **2** and **3**, which contain significant amounts of the cyclic tautomers in DMSO solutions, showed higher antifungal activity. Compounds **4** and **5**, existing in the cyclic forms only to a minor extent, were conversely found to have low antifungal activity. Among the compounds tested, the Tavaborole's analogue (compound **3**) was found to be the most potent one, which showed that the presence of a fluorine atom at position *para* to the boron atom boosts the antifungal action considerably.

4. Materials and methods

2-Formylphenylboronic acid (**1**) and four isomeric fluoro-2-formylphenylboronic acids **2–5** were prepared from the corresponding 2-bromobenzaldehydes [20]. All other compounds (of minimum 95% purity) and solvents were obtained from Sigma-Aldrich, Alfa-Aesar or POCh. Deuterated solvents were purchased from Armar Chemicals.

For microbiological experiments, the highest available purity DMSO, Czapek medium and YPD medium components were obtained from POCh. Medium potato dextrose agar and Tween 80 were purchased from Sigma-Aldrich.

Eight fungal strains were used for the experiments. *A. niger* (LOCK 0440), *A. terreus* (LOCK 64), *F. oxysporum* (E95) and *C. albicans* (LOCK 0001) were purchased from the Institute of Fermentation Technology and Microbiology, Technical University of Łódź, while *F. solani* (F-454), and *P. ochrochloron* (F-337) were obtained from the Czech Collection of Microorganism (CCM). *F. dimerum* (DAE-1001), originally isolated from the surface of carrot seeds, was taken from the collection of microorganisms of the Department of Analytical and Ecological Chemistry, Faculty of Chemistry, Opole University. *C. tenuis* (DSM-26797) was purchased from Leibniz-Institute DSMZ-German Collection of Microorganisms and Cell Cultures. *Aspergillus* and *Penicillium* strains were routinely maintained in potato dextrose agar while *Fusarium* strains grew in Czapek agar medium. Yeast *C. tenuis* and *C. albicans* were maintained in standard YPD agar medium. In case of filamentous fungi, the spore suspensions used as inocula were prepared by washing the surface of 10- to 14-day-old cultures with sterile 0.05% Tween solution in distilled (Milipore Q) water. These inocula were then quantified using a Thom's chamber. In case of yeast, two-day-old cultures were used directly for inoculation.

4.1. Antifungal activity – microbiological studies

4.1.1. Agar diffusion method

An inoculum (0.5 mL) containing 10^6–10^7 spores was spread on the surface of the solidified Czapek, potato dextrose or YPD medium and allowed to dry. The amounts of 100, 50, 25 and 10 μg of the tested compounds dissolved in DMSO were placed in 2 mm diameter holes, which were cut in the solidified media. The holes in control runs were filled with DMSO. The duration of fungi incubation was dependent on the vigour of their growth and was established as 48 h for *Candida* and *Aspergillus* strains and 72 h for other strains. The optimal temperature for the incubation was 27 °C for *Candida* and *Fusarium* strains and 30 °C for other strains. Each experiment, including control experiment, was carried out in at least three repetitions. The antifungal activity was evaluated by the diameter of the clear zone surrounding the holes, whereas a halo indicated partial inhibition of growth.

4.1.2. MIC determination by the serial dilution method

The investigated compounds were dissolved in DMSO and placed in the liquid Czapek medium (2 mL), ensuring the necessary concentration (final concentration ranged from 1 to 500 μg/mL). Media were inoculated with 2×10^6 fungal spores and incubated at 25 °C on a rotary shaker (60 rpm). The MIC endpoints were read visually following 48 h (for yeast) or 72 h (for filamentous fungi) of incubation and were defined as the lowest concentration at which no visible growth of fungi was observed. Each experiment (control or compound-containing medium) was repeated three times.

4.2. Cyclization equilibria – NMR studies in solution

All ^{1}H and ^{19}F NMR spectra were recorded at 298 K on a Bruker AVANCE 300 MHz spectrometer, operating at frequencies 300 and 282 MHz respectively. Chemical shifts are reported in parts per million (ppm), relative to the residual undeuterated solvent signal (^{1}H NMR) or $CFCl_3$ (^{19}F NMR). The samples have been prepared by dissolving solid boronic acids in DMSO-d_6. An additive of D_2O was introduced by adding one drop of D_2O to the sample. Details on samples concentrations as well as the NMR spectra can be found in Appendix A.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.103081.

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