Bioorganic Chemistry 106 (2021) 104494

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

1,2-Diborolanes with strong donor substituents: Synthesis and high antimicrobial activity

Yüksel Şahin [a,*], Esin Poyrazoğlu Çoban [a], Resul Sevinçek [b], Hacı Halil Bıyık [a], Hüseyin Özgener [c], Muhittin Aygün [b]

[a] Department of Chemistry, Faculty of Arts and Sciences, Adnan Menderes University, 09010 Aydın, Turkey
[b] Department of Physics, Faculty of Science, Dokuz Eylül University, 35160 İzmir, Turkey
[c] Department of Chemistry, Faculty of Science, İzmir Institute of Technology, Urla 35430, İzmir, Turkey

ARTICLE INFO

Keywords:
Diborolane
Diboracyclopentane
Heterocycles
Antimicrobial

ABSTRACT

1,2-diborolanes with strong and without strong donor substituents have been described, and are also referred to as 1,2-diboracyclopentane. The 1,2-diaryl/alkyl-amino-1,2-diboracyclopentanes **2**, **3**, and **4** were obtained in good yield after the reaction of 1,2-dichloro-1,2-diboracyclopentane **1** with ArNHLi and Me_3Si-NR_2. The structures of these new derivatives were characterized by nuclear magnetic resonance spectroscopy. The molecular structures of **2b**, **2c**, **2e**, **4**, and **5f** were also determined by single-crystal X-ray diffraction. The newly synthesized 1,2-borolanes are stable in air and showed particularly high activity against some Gram-positive bacteria.

1. Introduction

1,2-Dichloro-1,2-diborolanes appear to be versatile materials for the synthesis of 1,2-diborolanes, which can have strong and non-strong donor substituents at the boron centres [1–4]. The highly reactive 1,2-dichloro-1,2-diborolane **1** is used in the synthesis of cyclic and bicyclic compounds and as versatile starting compounds [5]. The binding of alkyl or aromatic amines to the boron atoms in the ring leads to the stabilization of 1,2-diborolanes in the air, since they probably reach the boron atoms via the electrons of the donor atoms and have a homogeneous electron distribution with a B-B bond in the ring. Also, the binding of aromatic amines to the boron atoms in the ring, instead of alkyl amines, makes the diborolanes stable for longer in weak Lewis acid (such as $CHCl_3$). Over the years, other small molecule boron compounds have also shown promise for their potential use in pharmaceutical chemistry. Diazaborines, which are among the heterocyclic compounds, have been extensively investigated by dos Santos et al., which have strong antimicrobial properties as bioactive boron compounds [6]. Here we report easy access to **1** by the reaction of 1,2-diclordiborolane with LiNHAr and Me_3Si-NR_2 followed by the preparation of 1,2-diaril/alkyl-amino-1,2-diborolane **2** and **3**. The instability of most boron compounds in the air has limited research on their biological activity and pharmacology. As part of our efforts to produce bioactive boron compounds, we developed some of the novel 1,2-diborolane derivatives and presented them with our latest findings. Thus, for the first time, we have demonstrated the biological activities of 1,2-*N*-substituted-1,2-diborolane derivatives with strong donor groups. In addition, it was determined how the antimicrobial activity changes depending on the structure of the groups attached to boron atoms.

2. Results and discussion

2.1. Spectroscopic data

The 1,2-diborolanderivatives of **2**, **3**, and **4** were prepared from the reaction of 1,2-dichloro-1,2-diborolane **1** [4] with ArNHLi in THF/*n*-Pentane mixture and Me_3Si-NR_2 in *n*-Pentane at 0 °C in good yield (Scheme 1).

The constitutions of diborolane derivative were derived from its one- and two-dimensional ^1H, ^{11}B, and ^{13}C NMR spectra. The NMR spectroscopic data of diborolane are similar to one another, but some of the chemical shifts differ significantly. To confirm the solid-state structures of these compounds, we carried out a single-crystal X-ray diffraction study of **2b**, **2c**, **2e**, **4**, and **5f**. **5** was also previously synthesized by Berndt et al. in 2004 [4], and in this study, X-ray crystallographic study and antimicrobial properties of **5f** were also performed. The NMR spectra and some x-ray structures of diborolane derivatives show that substituents attached to the boron atoms are not symmetrical. The voluminous substituents (steric effects) twist five-membered rings, and this shows the structure of **4** very clearly. Although the substituents attached

* Corresponding author.

https://doi.org/10.1016/j.bioorg.2020.104494
Received 6 May 2020; Accepted 17 October 2020
Available online 21 November 2020

to the ring boron atom had a position that was asymmetrical relative to one another, a single broad peak was observed in the ^{11}B NMR spectra for both boron atoms. Their ^{11}B NMR spectra values range from 52 to 57 ppm; these values agree with the chemical shifts of 1,2-bis-dimethyl/ethyl-amino-1,2-dibrolane (δ = 54) given in the literature [4]. Of those, only in **4**, the ^{11}B-shift of the boron atoms was observed as wide and schwach band at 57. Surprisingly, only six signals for the 24 carbon atoms of the phenothiazinyl groups were observed in the ^{13}C NMR spectrum of **4** in the aromatic region, each signal corresponding to four carbon atoms. On the five-membered ring, the signals of the boron bound carbon atoms at around 28–30 ppm were generated as broad signals and other individual carbon atoms at around 24–25 ppm. Some aromatic amine carbon atoms of **2** were formed one above the other, like in **4**, and some are single signals. The ^{1}H NMR spectra of the diborolane derivatives, except **3**, exhibit three signals for the silyl groups (1:1:1), two signals the ring protons (2:1, t and d), and two signals the amino protons (1:1, respectively). For **3**, the framework protons appear at 0.64 ppm a doublet, at 1.45 ppm a triplet. For the pyrrolidinyl rings, protons appear at approximately 1.69 between 1.79 ppm multiplet (dq) and for the proton next to the nitrogen atom at approximately 3.22 between 3.44 ppm multiplet (dt) (see supporting information).

2.2. Crystal structures

The molecular structures of the compounds **2b**, **2c**, **2e**, **4** and **5f** were determined by single-crystal X-ray diffraction. Molecular structures are shown in Fig. 1. In all the crystals, C1 and C3 are chiral centres with the configurations of R and S, respectively. As expected due to the sp^3 hybridization of the C atoms, all five membered rings strayed from the planar geometry. The torsion angle of B1-B2-C3-C2 and B2-B1-C1-C2 of the structures **2b**, **2c**, **2e**, **4** and **5f** are as follows: −27.0°/−5.3°, 11.2°/−12.0°, −24.7°/−14.2°, −29.7°/−13.0°, –32.0°/−6.4°. Considering the geometry of five-membered ring, **2b** and **5f** are twisted on B2-C3 bonds, **2c** is envelope on C2 atom, **2e** and **4** are envelope on B2 atoms.

Comparing the B-B bond lengths with our previous study [7], in the five-member rings, the B-B, B-B bond lengths are in the range of 1.700–1.747 Å, similar to the range observed in this study. The B-B bond length of **5f** is a little shorter than that of the other compounds; this bond shortening is due to the lack of aromatic rings bonded to the N atoms. In **2b**, **2c** and **2e**, one aromatic ring is attached to the N atoms, whereas in **5f**, just two methyls are attached. In **4**, however, the N atoms are members of the aromatic phenothiazine group. This substituent difference in **4** leads to a little shortening of the B-N bond lengths, compared to those of the other compounds. The B-N bond lengths are in the range of 1.392 Å to 1.407 Å except for those of **4**. Due to substituent differences, the B-N distances are a little larger in **4** with values of d(B1-N1) = 1.426 Å and d(B2-N2) = 1.469 Å. Details regarding the data collection, refinement details, and detailed crystallographic results are given in the supplementary file.

3. Antimicrobial screening (methods)

3.1. Micro-organisms and condition for cultivation

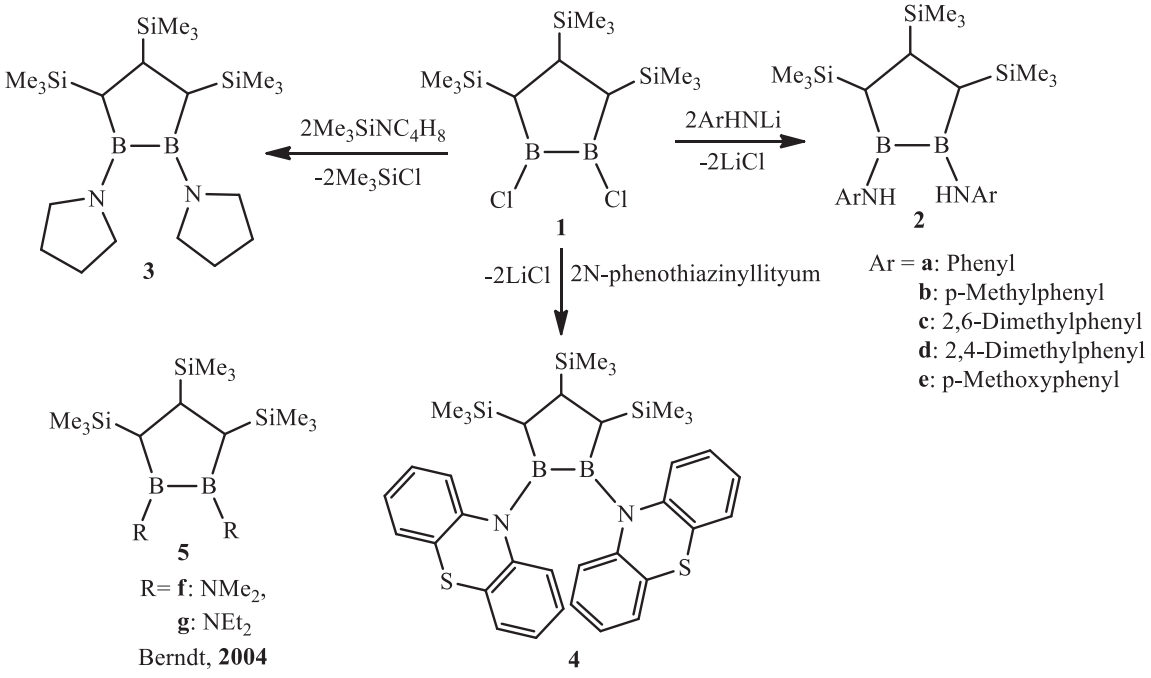
Eighteen bacteria and eleven yeast cultures were used in the study. Seventeen bacterial strains and three yeast strains were obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA) and one yeast strain was provided from the Agricultural Research Service Culture Collection (ARS, NRRL, Peoria, USA). Other strains were obtained from Department of Microbiology, Faculty of Sciences, Adnan Menderes University and Ege University. The list of Gram (+) and Gram (−) bacteria to which the compounds are applied, details of the culture conditions and methods applied are given in supplementary data S2.1 and are shown in Table 1.

3.2. Antimicrobial assay

The antimicrobial activities of all the synthesized compounds were determined by the agar well diffusion method [10–13] and the minimum inhibitory concentrations (MIC) were obtained by broth dilution method [14–16].

3.2.1. Disc diffusion method

The standard method of Antimicrobial Disc Susceptibility Tests reported by the National Committee for Clinical Laboratory Standards was used in this study [17,11,13]. Fresh stock solutions (1000 μg·mL^{-1}) of all the synthesized compounds were prepared in *n*-Hexane. The inoculums suspensions of the tested bacteria yeasts were prepared from the broth



Scheme 1. Synthesis of **2**,**3** and **4** derivatives.

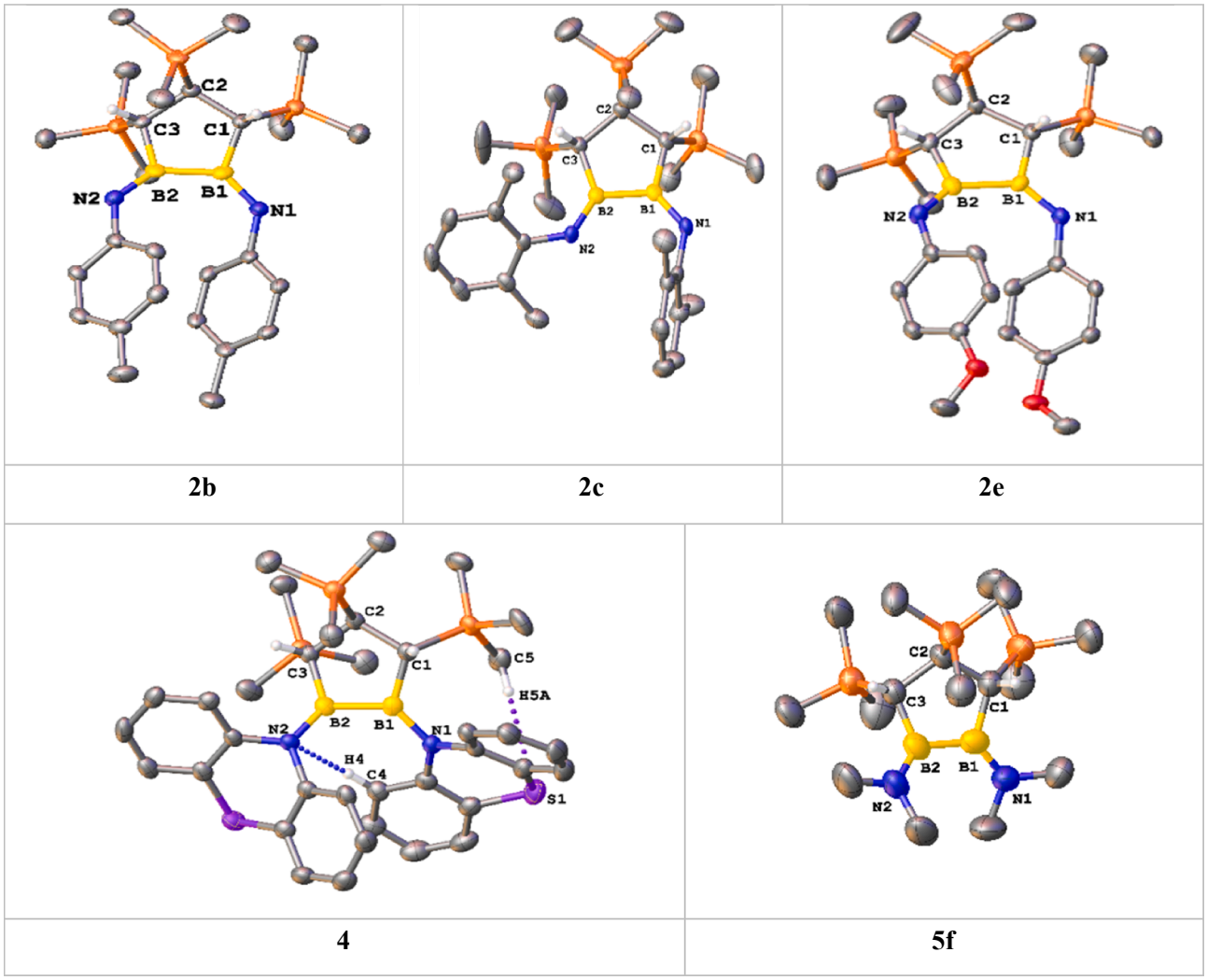


Fig. 1. Molecular structure of the compounds **2b**, **2c**, **2e**, **4** and **5f**. H atoms are omitted for clarity. The intramolecular interaction at **4** is shown by dotted lines. Selected geometric parameters are as follows. **2b**: B1-B2 1.711 Å, B1-N1 1.405 Å, B2-N2 1.407 Å, B1-C1 1.593 Å; C1-B1-B2 105.4°. **2c***: B1-B2 1.718 Å, 1.711 Å; B1-N1 1.397 Å 1.392 Å, B2-N2 1.404 Å 1.401 Å, B1-C1 1.575 Å 1.584 Å, C1-B1-B2 106.7° 106.6°. **2e**: B1-B2 1.704 Å, B1-N1 1.405 Å, B2-N2 1.398 Å, B1-C1 1.573 Å; C1-B1-B2 104.5°. **4**: B1-B2 1.712 Å, B1-N1 1.426 Å, B2-N2 1.469 Å, B1-C1 1.585 Å; C1-B1-B2 103.9°. **5f**: B1-B2 1.683 Å, B1-N1 1.403 Å, B2-N2 1.397 Å, B1-C1 1.604 Å; C1-B1-B2 104.9°. *: In asymmetric unit, **2c** has two independent molecules.

cultures (18–24 h) and the turbidity equivalent adjusted to 0.5 McFarland standard tube to give a concentration of 1×10^8 bacterial cells/mL, 1×10^6 yeast cells/mL [8,9]. Details and implementation of the method are specified in supplementary data S2.1.1.

3.2.2. Dilution method

The antibacterial and antifungal activities of synthesized compounds were examined by preparing a microdilution broth [18,14,15]. Details and implementation of the method are specified in supplementary data S2.1.2.

3.2.3. Antimicrobial analysis

The antibacterial and antifungal activities of 1,2-Diboracyclopentanes were experienced and the results were given in Tables 1 and 2. Besides the results of used references antibiotics were remarked in Table 3.

Among the compounds tested, compounds **2c**, **2e**, **5f** and **3** indicated very strong effect (30–55 mm) against some bacteria. The compounds **2b**, **2c**, **2d**, **2e**, **5g**, **3** and **4** showed high effect (18–29 mm) against some bacteria. The compounds **2a**, **2c**, **2e**, **3** demonstrated moderate effect (12–17 mm) against some bacteria and Candida species. However the compound showed very low effect (8–11 mm) against some bacteria. On the other hand, used compounds had no effect on many yeasts (Table 1).

According to Table 1, the compound **2c** indicated powerful activity (30–45 mm) against *M. luteus* ATCC 9341, *S. mutans*, *L. monocytogenes* ATCC 19112. The compound **2e** expressed very strong activity (32–40 mm) against *M. luteus* ATCC 9341, *S. pneumonia* ATCC 27336, *M. smegmatis* ATCC 607, *L. monocytogenes* ATCC 19112, *B. cereus* ATCC 11778. The compound **5f** remarked high power activity (30–50 mm) against *M. luteus* ATCC 9341, *S. aureus* ATCC 25923 and *S. epidermidis* ATCC 12228, *S. mutans*, *C. xerosis* ATCC 373, *M. smegmatis* ATCC 607, *L. monocytogenes* ATCC 19112, *P. vulgaris* ATCC 33420, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633. The compound **3** displayed vey substantial activity (32–55 mm) against *M. luteus* ATCC 9341, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633. Otherwise, the compounds **2a**, **2b**, **2d**, **5g**, **4** showed remarkable activity (12–18 mm) against *M. luteus* ATCC 9341, *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633. On the other hand, the compounds **4** indicated low activity (8–11 mm) against *S. aureus* ATCC 25923, *S. epidermidis* ATCC 12228, *M. smegmatis* ATCC 607, *B. cereus* ATCC 11778, *B. subtilis* ATCC 6633. Besides, the compounds **2e** and **3** demostrated moderate activity against *C. utilis* ATCC 9950 and *C. albicans* ATCC 10231, *C. tropicalis*, respectively.

Table 1
Antimicrobial activities of compounds (1000 μgmL^{-1}) (Inhibition zone mm).

Test microorganisms	Inhibition zones (mm) Compounds								
	2a	**2b**	**2c**	**2d**	**2e**	**5f**	**5g**	**3**	**4**
Escherichia coli ATCC 35218	–	–	–	–	–	–	–	–	–
Enterobacter aerogenes ATCC 13048	–	–	–	–	–	–	–	–	–
Salmonella typhimirium ATCC 14028	–	–	–	–	–	–	–	–	–
Micrococcus luteus, ATCC 9341	–	–	45	–	36	50	–	55	20
Stapylococcus aureus ATCC 25923	15	19	21	18	26	35	27	35	8
Stapylococcus epidermidis ATCC 12228	12	20	21	19	25	40	28	40	10
Klebsiella pneumoniae ATCC 13882	–	–	–	–	–	–	–	–	–
Streptococcus pneumoniae ATCC 27336	–	–	23	–	39	–	–	18	–
****Streptococcus mutans*	–	–	30	–	–	35	–	–	–
Pseudomonas aeruginosa ATCC 35032	–	–	–	–	–	–	–	–	–
Corynebacterium xerosis ATCC 373	–	–	–	–	–	30	–	–	–
Mycobacterium smegmatis ATCC 607	–	–	13	–	35	40	–	19	18
Listeria monocytogenes ATCC 19112	–	–	45	–	40	30	–	–	–
Serratia marcescens ATCC 13880	–	–	–	–	–	–	–	–	–
Proteus vulgaris ATCC 33420	–	–	–	–	–	45	–	–	–
Entereococcus faecalis ATCC29212	–	–	–	–	–	–	–	–	–
Bacilllus cereus ATCC 11778	17	20	18	24	32	43	23	32	8
Bacillus subtilis ATCC 6633	–	–	34	–	25	50	–	55	11
Candida albicans ATCC 10231	–	–	–	–	–	–	–	14	–
Candida utilis ATCC 9950	–	–	–	–	12	–	–	–	–
**Candida tropicalis*	–	–	–	–	–	–	–	12	–
**Candida glabrata*	–	–	–	–	–	–	–	–	–
Saccharomyces cerevisiae ATCC 9763	–	–	–	–	–	–	–	–	–
Debaryomyces hansenii NRRL Y-1458	–	–	–	–	–	–	–	–	–
**Torulaspora delbrueckii	–	–	–	–	–	–	–	–	–
***Hansenula philodendron*	–	–	–	–	–	–	–	–	–
**Pichia pastoris	–	–	–	–	–	–	–	–	–
**Kluyveromyces fragilis	–	–	–	–	–	–	–	–	–
**Dekkera *bruxellensis*	–	–	–	–	–	–	–	–	–

(-):Zone did not occur.
(*):Special gift from Adnan Menderes University Faculty of Medicine.
(**):Special gift from Ege University Faculty of Microbiology Department.

According to MIC values in Table 2 compounds **2c**, **2d**, **2e**, **5f**, **3** had very strong effect against some bacteria such as *M. luteus* ATCC 9341 (compound **2c** = 2 μg mL^{-1}, **2e** = 4 μg mL^{-1}, **5f** = 1 μgmL^{-1}, **3** = 0.5 μgmL^{-1}), *S. aureus* ATCC 25923 (compound **5f** = 4 μgmL^{-1}), *S. epidermidis* ATCC 12228 (compound **5f** and **3** = 2 μgmL^{-1}), *S. pneumoniae* ATCC 27336 (compound **2e** = 2 μgmL^{-1}), *S. mutans* (compounds **2c**, **2d** and **5f** = 4 μgmL^{-1}), *P. aeruginosa* ATCC 35032 (compound **2d** = 2 μgmL^{-1}), *C. xerosis* ATCC 373 (compound **5f** = 4 μgmL^{-1}), *M. smegmatis* ATCC 607(compound **2e** = 4 μgmL^{-1}, **5f** = 2 μg mL^{-1}, *L. monocytogenes* ATCC 19112 (compound **2c** = 2 μgmL^{-1}, **2e** = 2 μgmL^{-1}, **5f** = 4 μgmL^{-1}), *P. vulgaris* ATCC 33420 (compound **5f** = 2 μg mL^{-1}), *B. cereus* ATCC 11778 (compound **2e** = 4 μg mL^{-1}, **5f** = 2 μg mL^{-1}, **3** = 4 μgmL^{-1}), *Bacillus subtilis* ATCC 6633(compound **5f** = 1 μg mL^{-1}, 3 = 0.5 μg mL^{-1}).

On the other hand, other compounds (**2a**, **2b**, **5g**, **4**) indicated considerable or slight activity against used microorganisms and the MIC values ranged between 8 and 256 μgmL^{-1}). However, none of the compounds used had any effect on *E. coli* ATCC 35218, *E. aerogenes* ATCC 13048, *S. typhimirium* ATCC 14028, *K. pneumoniae* ATCC 13882, *P. aeruginosa* ATCC 35032, *S. marcescens* ATCC 13880, *E. faecalis* ATCC 29212, *C. glabrata*, *S. cerevisiae* ATCC 9763, *D. hansenii* NRRL Y-1458, *T. delbrueckii*, *H. philodendron*, *P. pastoris*, *K. fragilis* and *D. bruxellensis*.

It is concluded from the antimicrobial activity studies with Diborolan (5-membered ring) that the structures show activity through interaction with microorganisms via N atoms attached to B atoms. A similar situation applies to the reference compound streptomycin.

Considering the molecular structures obtained from the crystallographic results, if the steric hindrances of N atoms are negligible, the interaction with microorganisms is considerable. It can be concluded that N atoms interact directly with the walls of microorganisms (except

Table 2
Antimicrobial activities of compounds (MIC, μg.mL^{-1}).

Test microorganisms	2a	2b	2c	2d	2e	5f	5g	3	4	Str	Flk
Micrococcus luteus, ATCC 9341	_	_	2	_	4	1	_	0.5	16	32	NT
Stapylococcus aureus ATCC 25923	32	16	16	16	8	4	8	4	256	32	NT
Stapylococcus epidermidis ATCC 12228	64	16	16	16	8	2	8	2	128	32	NT
*Streptococcus pneumoniae*ATCC 27336	_	_	8	_	2	_	_	16	_	128	NT
***Streptococcus mutans*	_	_	4	4	_	4	_	_	_	64	NT
Corynebacterium xerosis ATCC 373	_	_	_	_	_	4	_	_	_	64	NT
Mycobacterium smegmatis ATCC 607	_	_	64	_	4	2	_	16	16	128	NT
Listeria monocytogenes ATCC 19112	_	_	2		2	4	_	_	_	64	NT
Proteus vulgaris ATCC 33420	_	_	_		_	2	_	_	_	64	NT
Bacilllus cereus ATCC 11778	32	16	16	8	4	2	8	4	256	64	NT
Bacillus subtilis ATCC 6633	_	_	8	_	8	1	_	0.5	128	64	NT
Candida albicans ATCC 10231	_	_	_	_	_	_	_	64	_	NT	64
Candida utilis ATCC 9950	_	_	64	64	_	_	_	_	_	NT	64
**Candida tropicalis*	_	_	_	_	_	_	_	64	_	NT	64

Str = Streptomycin, Flk = Flukanozol.
(-) = No effect, NT: Not tested.
(*): Special l gift from Adnan Menderes University Faculty of Medicine.
(**):Special gift from Ege University Facultyof Microbiology Department.

compound 4). In compound **4**, the steric hindrance of N atoms is large. If there is a large steric hindrance around the N atoms, the structures show low or no anti microorganisms activity. It is apparent that the activity of **5f** is considerably higher than that of **5g**. The molecular structures are similar, but the main difference is that in **5f**, the steric hindrances to N atoms are negligible.

The activities of some of the symmetrical 1,2-diamino-1,2-diboranes (4) have also been studied in this context, but have been found to show little activity. It is concluded that the examined diborans (4) cannot interact with microorganisms, such as diborolan. By examining the crystal structures of diboranes (4), the groups bound to the N atom seem to form a steric barrier on the N atoms [19].

4. Conclusion

In this study, a practical synthesis of new 1,2-amino-1,2-diborolane derivatives at high yields was presented. Amine groups bound to the B atoms of diborolane have been found to be air-stable. The produced compounds were characterized by means of one- and two-dimensional NMR spectroscopy. The structures of **2b**, **2c**, **2e**, **4** and **5f** were also confirmed by X-ray crystallography. The antibacterial activities of the synthesized compounds were assessed against Gram-positive and Gram-negative bacteria. Some of the compounds were very effective antimicrobial agents. In addition, the compounds' antioxidant properties were evaluated. Given the enormous challenges facing drug discovery in this area, the compounds described here can be a starting point to help pharmaceutical chemists find new drug candidates. However, our studies on biocidal and toxic effects are ongoing. Precise analysis of biocidal and toxic effects will be the first step in the development of new drugs.

5. Experimental

5.1. Synthesis

General considerations: All reactions were carried out under argon, using standard schlenk techniques. Solvents were dried, distilled, and saturated with argon. Glassware was dried using a heat gun under high vacuum. NMR spectra were recorded on a Varian 400 spectrom eter. The chemical shifts are given in ppm, and are referenced against residual solvent signals. Elemental analyses were done on a Leco-932. 1,2-Dichloro-3,4,5-tris(trimethylsilyl)-1,2-diborolane [4] were synthesized according to literatures. All amides and 1,2-dichloro-1,2-diboralene were synthesized according to literatures [4].

5.2. General procedure for synthesis of 1,2-diarylamino-1,2-diborolane derivatives

An equivalent amount of *n*-BuLi (2.2 mL, 3.3 mmol, 1.6 M solution in hexane) was added dropwise to a THF/hexane mixture (approx. 1:3) (approx. 50 mL) from arylamine/amine derivative (approx. 3.2 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight. The resulting suspension of ArNHLi/LDA was cooled to −10 °C and 1,2-dichloro-1,2-bolonane **1** (2.24 g, 6.4 mmol) was added dropwise. All volatile components were removed in vacuum after the mixture was slowly warmed to room temperature. The residue was extracted 1:1 (ca. 60 mL) in hexane CH_2Cl_2 mixture. The solution was concentrated to a volume of about ca. 30 mL. The concentrated solution was kept at −25 °C and the crystals were obtained.

5.2.1. 1,2-Dianilido-3,4,5-tris(trimethylsilyl)-1,2-diborolane 2a

Yielding 70%, viscous liquid

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.02, 0.05, 0.23(je s, Me_3Si), 1.70 (d, H, $^2J_{H\text{-}H}$ = 4 Hz, HCB), 2.03 (t, H, $^3J_{H\text{-}H}$ = 4 Hz, HCSi), 6.43, 6.57 (je s, je H, NH), 7.04–7.042 (d, t, 10*H*, $^2J_{H\text{-}H}$ = 8 Hz, $^3J_{H\text{-}H}$ = 8 Hz, H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −3.0, 1.1 (9C, Me_3Si), 24.8 (C, CSi), 29.5 (br., 2C, CB), 119.8, 122.1, 122.9, 123.6, 127.8, 128.9, 129.3 (p-, o-, m-C, 10C, Ph), 144.8, 145.2 (je C, i-C, Ph); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): δ = 56 (2B).

5.2.2. 1,2-Bis(p-tolidino)-3,4,5-tris(trimethylsilyl)-1,2-diborolane 2b

Yielding 74%, m.p.: 109 °C

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.10, 0.03, 0.15(je s, Me_3Si), 1.61 (d, 2H, $^2J_{H\text{-}H}$ = 4 Hz, HCB), 1.89 (t, 1H, $^3J_{H\text{-}H}$ = 4 Hz, HCSi), 6.30, 6.44 (je s, je H, NH), 6.47–7.16 (d, t, 10*H*, $^2J_{H\text{-}H}$ = 8 Hz, $^3J_{H\text{-}H}$ = 8 Hz, H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −3.1, 1.0 (9C, Me_3Si), 20.8 (2C, p-Me, Ph), 24.7 (C, CSi), 28.0 (br., 2C, CB), 119.9 (C, p-C, PhMe), 122.0, 122.2 (4C, m-C, PhMe), 128.2 (C, p-C, PhMe),129.3, 129.7 (4C, o-

Table 3
Inhibition zone diameter of the reference antibiotics to test micro-organisms (mm).

Test microorganisms	Inhibitionzones (mm) Reference antibiotics										
	C30	CN10	TE30	E15	AMP10	P10	K30	OFX5	VA30	CTX30	NS100
Escherichia coli ATCC 35218	24	21	15	11	–	16	20	28	23	10	NT
Enterobacter aerogenes ATCC 13048	19	20	14	–	–	–	–	19	–	20	NT
Salmonella typhimirium ATCC 14028	17	16	15	8	8	15	18	25	21	13	NT
Micrococcus luteus, ATCC 9341	25	15	26	30	28	13	12	24	14	17	NT
Stapylococcus aureus ATCC 25923	23	20	22	23	20	12	13	23	13	12	NT
Stapylococcus epidermidis ATCC 12228	22	17	19	11	17	11	13	22	12	13	NT
Klebsiella pneumoniae ATCC 13882	21	19	20	14	–	18	19	27	23	14	NT
Pseudomonas aeruginosa ATCC 35032	22	20	20	21	–	14	20	29	18	14	NT
Corynebacterium xerosis ATCC 373	20	17	25	26	27	14	12	22	21	20	NT
Mycobacterium smegmatis ATCC 607	23	18	26	25	19	16	13	30	20	12	NT
Listeria monocytogenes ATCC 19112	19	14	12	–	12	10	12	29	25	16	NT
Serratia marcescens ATCC 13880	23	19	13	–	19	18	19	27	27	13	NT
Proteus vulgaris ATCC 33420	17	24	16	20	–	15	25	26	24	18	NT
Entereococcus faecalis ATCC29212	16	11	19	–	14	12	13	28	20	16	NT
Streptococcus pneumoniae ATCC 27336	24	20	25	15	14	19	21	28	29	15	NT
****Streptococcus mutans*	28	22	19	–	–	–	22	30	–	22	NT
Bacilllus cereus ATCC 11778	23	24	25	26	–	10	11	28	21	17	NT
Bacillus subtilis ATCC 6633	22	20	12	25	–	11	11	27	20	16	NT
Candida albicans ATCC 10231	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	22
Candida utilis ATCC 9950	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	21
**Candida tropicalis*	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	20
**Candida glabrata*	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	20
Saccharomyces cerevisiae ATCC 9763	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	15
Debaryomyces hansenii NRRL Y-1458	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	19
**Torulaspora delbrueckii	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	20
***Hansenula philodendron*	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	22
**Pichia pastoris	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	22
**Kluyveromyces fragilis	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	20
**Dekkera *bruxellensis*	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	19

C30: Chloramphenicol (30 mg Oxoid), CN10: Gentamycin (10 mg Oxoid), TE30: Tetracycline (30 mg Oxoid), E15: Erytromycin (15 mg Oxoid), AMP10: Ampicillin (10 mg Oxoid), Penicilin (10 mg Oxoid), Kanamisin (30 mg Oxoid), Ofloxacin (5 mg Oxoid), Vancomycin (30 mg Oxoid),Cefotaxime (30 mg Oxoid), NS: Nystatin (100 mg Oxoid).
(-):Zone did not occur. NT: Not tested.
(*):Special gift from Adnan Menderes University Faculty of Medicine.
(**):Special gift from Ege University Faculty of Microbiology Department.

C, PhMe), 142.3, 142.7 (je C, i-C, Ph); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 56$ (2B). Anal. Calcd. For $C_{26}H_{46}B_2N_2Si_3$ (492.54): C, 63.40; H, 9.41; N, 5.69. Found: C, 63.74; H, 10.66; N, 6.27.

5.2.3. 2,6-Dimethylphenylamino-3,4,5-tris(trimethylsilyl)-1,2-diborolane 2c

Yielding 77%, m.p.: 162 °C

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.40, −0.04, 0.15 06 (je s, Me_3Si), 1.61 (t, H, $^3J_{H\text{-}H}$ = 4 Hz, HCSi), 1.96 (br. 2H, HCB), 2.02 (br., 6H, o-Me, Ph), 2.25, 2.29 (je s, je 3H, o-Me, Ph), 4.81, 5.62 (je s, je H, NH), 6.86–7.13 (m, 6H, p-, and m-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −2,58, 0.79, 1.03 (je 3C, Me_3Si), 19.2, 20.0 (je 2C, o-Me, Ph), 25.3 (C, CSi), 28.4 (br. 2C, CB), 124.2,125.6 (je C, p-C, Ph), 128.2,128.4 (je 2C, m-C, Ph), 135.2, 135.6 (je 2C, o-C, Ph), 142.3, 142.7 (je C, i-C, Ph); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 61$ (2B).

5.2.4. 2,4-Dimethylphenylamino-3,4,5-tris(trimethylsilyl)-1,2-diborolane 2d

Yielding 73%, viscous liquid

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.07, 0.14, 0.30(je s, Me_3Si), 1.42 (d, 2H,$^2J_{H\text{-}H}$ = 4 Hz, HCB),1.74 (t, H, $^3J_{H\text{-}H}$ = 4 Hz, HCSi), 2.06, 2.36 (s, je 3H, p-Me, Ph), 2.38, 2.42 (s, je 3H, o-Me, Ph), 5.81, 6.23 (je s, je H, NH), 7.00–7.27 (m, 6H, o-, and m-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −3,00, 0.89, 1.0 (je 3C, Me_3Si), 18.1, 18.3, 20.7 (insg.,4C, o-, p-Me, Ph), 24.5 (C, CSi), 28.1 (br. 2C, CB), 123.0, 124.3,126.9, 127.4, 129.8, 130.8, 131.3, 132.6, 133.7 (10C, Ph), 141.0,

141.4 (je C, i-C, Ph); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 57$ (2B). Anal. Calcd. For $C_{28}H_{50}B_2N_2Si_3$ (520.59): C, 64.60; H, 9.68; N, 5.38. Found: C, 64.77; H, 10.40; N, 5.24

5.2.5. 1,2-Di(p-methoxyphenyl)amino-3,4,5-tris(trimethylsilyl)-1,2-diborolane 2e

Yielding 79%, m.p.: 102 °C (decomposed).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.15, −0.04, 0.13 (je s, Me_3Si), 1.58 (t, H, $^3J_{H\text{-}H} = 4$ Hz, HCSi), 1,79 (d, 2H, $^2J_{H\text{-}H} = 4$ Hz, HCB), 3.76, 3.81 (je s, je 3H, MeO), 6.07, 6.35 (je s, je H, NH), 6.26, 6.48, 6.76, 6.88, 6.89, 7.06 (je d,$^2J_{H\text{-}H} = 4$ Hz, total. 8H, Ph-OMe); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −3,07, 0.67, 0.98 (je 3C, Me_3Si), 24.6 (C, CSi), 29.8 (br. 2C, CB), 55.1, 55.4 (je C, OMe), 114.0, 114.2 (je 2C, o-C, Ph), 121.2, 123.7 (je 2C, m-C, Ph), 138.4, 138.6 (je C, i-C, Ph), 155.5, 156.2 (je C, p-C, Ph); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 56$ (2B). Anal. Calcd. For $C_{25}H_{43}B_2N_2OSi_3$ (493.50): C, 60.84; H, 8.78; N, 5.68. Found: C, 60.40; H, 8.53; N, 4.40

5.2.6. 1,2-Bis(N-phenothiaziny-3,4,5-tris(trimethylsilyl)-1,2-diborolane 4

Yielding 86%, m.p.: 167 °C (decomposed).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.27, −0.06, 0.24(je s, je 9H, Me_3Si), 1.81(t, H, $^3J_{H\text{-}H} = 4$ Hz, HCSi), 2.22, 2.35(dd, br. 2H, $^2J_{H\text{-}H} = 4$ Hz, HCB),6.53, 6.65, 6.72, 6.83, 6.99, 7.09 (d, t, br., ing.16H,phz.); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −2.1, 1.0 (9C, Me_3SiC), 24.8 (C, Me_3SiC), 29.5 (br., 2C, CB), 114.4 (4C, $C_{4,6}$, pth.), 118.2 (4C, C—S), 122.6 (4C, $C_{3,7}$ pth.), 126.8 (4C, $C_{2,8}$, pth.), 127.3 (4C, $C_{1,9}$, pth.), 141.6 (4C, C—N); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 57, 77$

5.2.7. 1,2-Dipyrrolidiniyl-3,4,5-tris(trimethylsilyl)-1,2-diborolane 3

1.05 g (7.33 mmol) pyrrolidinotrimethylsilane in approx. 30 mL in hexane at 0° C was added dropwise to a solution with 0.86 g (2.45 mmol) **1** in 30 mL hexane and the mixture was brought to room temperature warmed and stirred for 15 h. After removing all volatile constituents in vacuo, the residue was obtained as a highly viscous liquid.

Yielding 86%, viscous liquid

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = −0.19, 0.02, 0.06 (je s, je 9H, Me_3Si), 0.64 (d, 2H, $^2J_{H\text{-}H} = 4$ Hz, HCB), 1.45 (t, H, $^3J_{H\text{-}H} = 4$ Hz, HCSi), 1.64–1.80 (m, 8H, CH_2C, Pyr.), 3.20–3.45 (m, 8H, CH_2N, Pyrl.); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = −3.2, 1.0, 1.6 (je 3C, Me_3SiC), 24.1 (C, Me_3SiC), 25.3 (br., 2C, CB), 25.7, 26.2 (je 2C, Pryl.), 50.2, 54.0 (je 2C, CN, Pryl.); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 52$ (2B).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by Adnan Menderes University BAP (project No: FEF-20011 and FEF-17004). The authors also acknowledge Dokuz Eylül University for the use of the Agilent Xcalibur Eos diffractometer (purchased under University Research Grant no.2010.KB. FEN.13).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104494.

References

[1] G.E. Herberich, C. Ganter, L. Wesemann, Neue bororganische Ringe mit benachbarten Bor-Atomen Katalysierte 1,2-Diborierung von Alkinen, Chem. Ber. 123 (1990) 49–51.
[2] G. Knörzer, H. Seyffer, W. Siebert, Z. Naturforsch, Synthese von Diboraheterocyclen mit einer BC_3B-Gruppierung, Teil B 45 (1990) 1136–1138.
[3] G.E. Herberich, C. Ganter, L. Wesemann, R. Boese, Unsaturated C3B2 Rings with Neighboring Boron Atoms: Derivatives of 4-Methylene-1,2-dibora-cyclopentane, Dilithium 2,3-diboratafulvene, and 1,2-Dibora-3-yclopentene, Angew. Chem. 102, 1990, 914-915; Angew. Chem. Int. Ed. Engl. 29, 1990, 912-913.
[4] C. Präsang, Y. Sahin, M. Hofmann, G. Geiseler, W. Massa, A. Berndt, Synthesis and reactions of a stable 1,2-dichloro-1,2-diborolane and of aromatic tetraboranes, Eur. J, Inorg. Chem. (2004) 3063–3073.
[5] C. Präsang, Y. Sahin, M. Hofmann, G. Geiseler, W. Massa, A. Berndt, 1,2-Diboracyclopentanes without strong donor substituents: synthesis, reactions and computational analysis, Eur. J. Inorg. Chem. 5046–5055 (2008).
[6] G.F.S. Fernandes, W.A. Denny, J.L. dos Santos, Boron in drug design: Recent advances in the development of new therapeutic agents, Eur. J. Med. Chem. 179 (2019) 791.
[7] E. Firinci, R. Sevincek, B. Bursali, H. Ozgener, O. Burgaz, C. Sen, M. Aygün, Y. Sahin, Synthesis and structures of 1,3,2,4,5-diazatriborolidines, Inorg. Chim. Acta 496 (2019), 119038.
[8] E.P. Çoban, R. Fırıncı, H.H. Bıyık, M.E. Günay, Unsymmetrically substituted imidazolium salts: synthesis, characterization and antimicrobial activity. Braz. J. Pharm. Sci., 53 (1):e, 2017, 15075.
[9] E.E. Oyeka, J.N. Asegbeloyin, I. Babahan, B. Eboma, O. Okpareke, J. Lane, A. Ibezim, H.H. Bıyık, B. Törün, D.C. Izuogu, Synthesis, crystal structure, computational analysis and biological properties of 1-(4-chlorobenzoyl)-3-[2-(2-{2-[3-(4-chlorobenzoyl)-thioureido]-ethoxy}ethoxy)ethyl]-thiourea and its Ni(II) and Cu(II) complexes, J. Mol. Structure 1168 (2018) 153–164.
[10] Method for antifungal disk diffusion susceptibility testing of yeasts, approved guideline, CLSI document M44-A. Wayne:CLSI, USA, Clinical and Laboratory Standards Institute 2004.
[11] M02-A12: performance standards for antimicrobial disk susceptibility tests: approved standard. 12. Ed. Wayne: CLSI, Clinical and Laboratory Standards Institute, 2015, 1-73.
[12] M. Balouiri, M. Sadiki, S.K. Ibnsouda, Methods for in vitro evaluating antimicrobial activity: A review, J. Pharm. Anal. 6 (2) (2016) 71–79.
[13] EUCAST, Disk Diffusion method for antimicrobial susceptibility testing, 2019, version 7.0.
[14] J.H. Jorgensen, M.J. Ferraro, Antimicrobial susceptibility testing: a review of general principles and contemporary practices, J. Med. Microbio. 49 (2009) 1749–1755.
[15] Methods for dilution antimicrobial susceptibility testing for bacteria that grow aerobically: approved standard. 8. Ed. Wayne: CLSI, Clinical and Laboratory Standards Institute, M07–A8, 2009, 1-65.
[16] Performance standards for antimicrobial disk and dilution susceptibility tests for bacteria isolated from animals; approved standard. CLSI document VET01–A4. 4th Ed. CLSI, Wayne, PA, Clinical and Laboratory Standards Institute 2013.
[17] C.H. Collins, P.M. Lyne, J.M. Grange, J.O. Falkinham, Collins and Lyne's microbiological methods, 8. Ed., Butterworths, London, 2004, p. 456.
[18] R.N. Jones, A.L. Barry, T.L. Gavan, Susceptibility tests: microdilution and macrodilution broth procedures. Manual of Clinical Microbiology. 4. Ed. Washington: Am. Soc. Microbio., Washington, J.A., 1985, 972-977.
[19] D.B. Celepci, E. Sepin, Y. Gökçen, M. Aygün, Y. Şahin*, New air stable diarylamino substituted diborane(4) derivatives: Synthesis and structures, Mol. Cryst. Liq. Cryst. 668 (1) (2018) 91–104.