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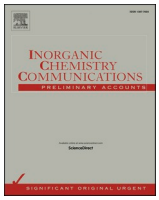

Short communication

1,2-Diboranes with strong donor substitutes: Synthesis, ovicidal and larvicidal effect on important vector species

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ABSTRACT

Novel control products are needed in the control of important insects like mosquitoes which are developing resistance to insecticides and larvicides currently in the market. Boron compounds have been demonstrated to exhibit antibacterial and anticancer effects. 1,2-diboranes with a long history and importance in boron chemistry have been described. These compounds are synthesized from reactions of 1,2-dichlordiborane derivatives with lidium amides (ArNHLi/Et_2NLi, etc.). In addition to the three previously synthesized diborane compounds, five novel 1,2-diborane compounds were synthesized in good yield using the same method for the first time. The structures of the novel derivatives were characterized by nuclear magnetic resonance spectroscopy, and the molecular structure of one of them **(2a)** was also demonstrated using single crystal X-ray diffraction. In this preliminary study, the ovicidal and larvicidal effects of new 1,2-diamino-1,2-diborane derivatives against *Aedes aegypti* and *Aedes albopictus* eggs and larvae were investigated for the first time. Of these, **2a** and **2e** showed the highest ovicidal activity against both species, while **7**, **4** and **2d** showed particularly high larvicidal activity. Some 1,2-diborane derivatives were found to be significantly toxic, with LC_{50} values ranging from 14,930 to 27,975 μg/mL. Some derivatives **(6, 2a, 2c)** were less effective against mosquito larvae. 1,2-Diborane derivatives have high ovicidal and larvicidal effects on mosquitoes and are therefore potential candidates for the development of new larvicides. Further studies are needed to evaluate its mode of action and safety. Understanding their mode of action against mosquito development is crucial to optimizing their use and reducing the potential development of resistance. Their potential effects on other mosquito species and non-target organisms need to be investigated.

1. Introduction

Mosquitoes are important hematophagous dipterous insects in the Culicidae family. They are primary vectors of several vector-borne diseases (VBDs), which still account for more than 17 % of all infectious diseases worldwide [1,2]. *Aedes aegypti* and *Ae. albopictus* are important species as they are serious biting nuisances during the day affecting people both indoors and outdoors and they are vector species that transmit arboviral and filarial infections like Dengue, Yellow fever, Zika, Chikungunya, West Nile virus, California encephalitis virus, Eastern equine encephalitis, La Crosse encephalitis, Dirofilariasis and many others [3–5]. Some of these diseases are emerging health threats around the world, disproportionately affecting poorer populations [6,7]. Dengue fever, for instance, has grown during the past few decades on a global scale [8,9]. This endemic disease affects roughly 400 million individuals, which is a 4-fold spike in incidence since the 1990 s, in tropical areas of Africa and Central and South America and spreading to new areas [10,11]. About 100 million people show symptoms, and 1 % of those cases are severe (hemorrhagic dengue fever) and can lead to death [12]. Yellow fever is another acute viral hemorrhagic disease with 200,000 cases and 30,000 deaths reported annually [9].

Ae. aegypti and *Ae. albopictus* larvae breed in artificial water containers such as water reservoirs and flowerpots, used tires etc. located in urban and *peri*-urban environments or in natural places like tree holes [13–15]. They are currently one of the most invasive species spreading around the world [16]. This spread to higher latitudes represents a

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major risk to public health and has been facilitated by their aggressive feeding behavior and ecological adaptability as well as factors such as climate change, urbanization, and international travel. Both species can produce diapausing eggs that are transported accidentally on ships during global trading [17,18].

Currently, besides vaccines for yellow fever and dengue, there are no specific treatment options for most *Aedes*-transmitted infections. Environmental management and vector control measures like the use of insecticide-treated nets, indoor residual spraying, space sprays, and larvicides are considered to be important mechanisms for effective disease management. Current control method of mosquitoes is still heavily dependent upon the use of chemical insecticides, mainly pyrethroids, even though these chemicals pose serious risks to human health and environment and they are costly and not sustainable [19–21]. Besides this, extensive spraying has also resulted in the development of insecticide resistance in *Ae. albopictus* and *Ae. aegypti* populations as well as other insect species around the world. The emergence of insecticide resistance in mosquito populations might lead to ineffective control strategies and resurgence of mosquito-borne diseases [19–21]. Treatment of breeding habitats with larvicide (e.g., Spinosad, *Bacillus thuringensis israelensis* and *Lysinibacillus sphaericus*) can effectively target immature stages and reduce adult abundance. These bioagents are safer options in terms of their impact on non-target organisms and the environment [22]. There are few reports of resistance to the larvicides [20] and such resistance development is a major constraint of their efficacy leading to undesired results in reducing mosquito population density. Therefore, discovery and development of new and alternative substances is still important.

It has been determined that some boron compounds and complexes have different biological activities [23–29]. No study has been found so far regarding the activities of diborane compounds, which are not similar to boric acid, on mosquitoes. However, in a preliminary study, it was determined that some of the 1,2-N-substituted-1,2-diborane compounds showed high ovicidal and larvicidal activities. There are no reports in the literature so far regarding the ovicidal and larvicidal activities of 1,2-diborane derivatives. Here, chemical interactions must occur through donor atoms (B-N, B-O, etc.) attached to boron atoms. We detected a similar interaction with five-ring boron compounds C_3B_2 (1,2-diborolane) in our antibacterial studies [29,54]. This finding suggests that the activity of amino-aryl and amino-alkyl 1,2-diboranes is related to the reactivity of the boron center. It reveals that these groups increase the electron density in the donor atoms and trigger an increase in the activity of the compounds.

This work describes the isolation, characterization, and biological activity of a series of boron-containing compounds that may provide relatively new chemistries that may be useful against insecticide-resistant mosquitoes. The goal of developing new chemistry is valuable because currently very limited chemical classes are available for vector control. In this study, eight 1,2-diborane derivatives were synthesized for the first time and evaluated as potential ovicidal and larvicidal agents against *Ae. aegypti* and *Ae. albopictus* eggs and larvae.

2. Materials and methods

2.1. Spectroscopic Data

The 1,2-diborane derivatives of **2a**, **2b**, **2c**, **4** and **6** were prepared from the reaction of 1,2-dichloro-1,2-borane **1**, **3** and **5** with ArNHLi or EtNHLi in THF/n-Pentane mixture at 0 °C in good yield (Fig. 1). Diborane **2a**, **7** and **2e** were first synthesized by Nöth, Wrackmeyer, and Patton et al. [30,31].

The constitutions of the 1,2-diborane derivative were derived from their one- and two-dimensional nuclear magnetic resonance (^{1}H, ^{11}B, and ^{13}C NMR) spectra. The NMR spectroscopic data of 1,2-diborane were found to resemble each other, but some of the chemical shifts differed significantly. Due to partial back bonds between N and B atoms ($sp^2 + \pi$), protons of the o-alkyl group in phenyls appear in ^{1}H NMR at multiples between 1.94 and 3.88 ppm. Protons attached to the N atom show different chemical shifts between 4.28 and 6.80 ppm depending on whether the groups attached to the boron and nitrogen atoms are aliphatic or aromatic. Their ^{11}B NMR spectra ranged from 32 to 48 ppm, and these values agree with chemical shifts of similar 1,2-diboranes ($\delta = 32 \sim 45$) reported in the literature [29]. When aromatic rings are attached to boron atoms in the diborane structure, the ^{11}B shift is in the low range, and when donor groups such as dimethylamine group are added, the chemical shift is in the high range (see supporting information).

2.2. Crystal structure

Molecular and crystal structure of **2a** was determined by single crystal X-ray diffraction studies. Due to the symmetry, the asymmetric unit consists of half of the whole molecule as shown in Fig. 2, the counterpart is constructed by the symmetry code of (1-x, y, ½-z). While ortho methyl can be clearly positioned in the NMR peaks, during crystal structure solution it was found more appropriate to model it as occupational disorder instead of modelling bromine and methyl separately when the crystal structure refinement parameters were examined. Methyl carbon and bromine atoms have similar environments [32,33], but the electron density map shows that the electron densities of neither

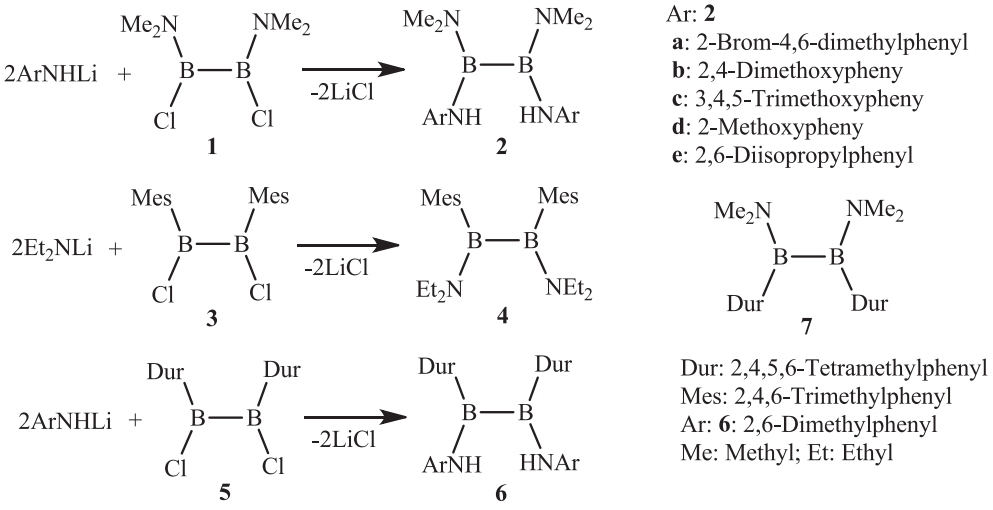

Fig. 1. The synthesis of 1,2-diboralene **4**, **6** and **2.**

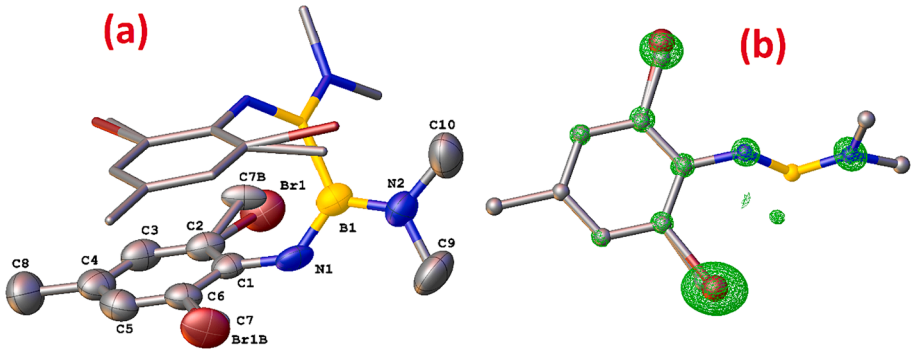

Fig. 2. **(a)** Molecular structure of the compound **2a**. Atoms at the asymmetric unit (which is half of the molecule) are shown 50 % probability. For clarity, H atoms are omitted. Selected geometric parameters are as follows. B1-B1^{i}1.710 Å, B1-N1 1.443 Å, C6-C7 1.502 Å, C2-C7B 1.578 Å, C2-Br1 1.876 Å, C6-Br1B 1.883 Å, N1-B1-B1^{i}-N1^{i} 55.9°.^{i} denotes the counterpart of the asymmetric unit with the symmetry code of (1-x, y, ½-z). **(b)** observed electron density map to enlighten the disordered structure.

C7 nor Br1 atoms are in agreement with the experimentally obtained electron density. Fig. 2b shows that observed electron densities of methyl and bromine sites are not equal, but electron density of methyl site is larger than classical carbon atoms. In this situation, methyl and bromine atoms are refined as occupational disordered. Refinement details are given in the Supplementary File. Crystal structure of **2a** is stabilized by π…π type intramolecular and CH…Br type intermolecular interactions. Crystallographic parameters are given in SF.

2.3. Mosquito rearing

Aedes aegypti Bora Bora and *Aedes albopictus* Mugla strains were used in the experiments. Both mosquito species were reared under controlled conditions (25 ± 2 °C, 70 ± 10 % RH, 12:12 L:D photoperiod) within an insectary at Aydin Adnan Menderes University [34]. These species are susceptible strains that have not come into contact with any insecticide. Adults were kept in cages and fed on soaked cotton balls containing 10 % (w/v) sucrose; females blood fed regularly from mice and were provided with plastic containers filled with water and sides lined with filter papers after about five days post blood feeding. Hatching (~500 egg/500 mL) occurred in separate plastic containers containing dechlorinated water, and larvae were fed ground fish food (Tetramin®) (approximately 0.2 – 0.5 g/day) until pupation [55].

2.4. Ovicidal bioassays

Four different final concentrations of concentrations (100, 75, 50, 25 ppm (mg/L) were tested against *Ae. aegypti* and *Ae. albopictus* mosquito eggs. The eggs used for this bioassay were stored at 26.5 ± 2 °C for 5–7 days after female mosquitoes had laid their eggs on a Whatman No.1® filter paper. The freshly laid eggs on paper strips were observed under stereomicroscope to evaluate viability, abnormal eggs were discarded, and normal eggs were collected for the bioassay. Eggs were transferred from dried oviposition papers into wells of 24-well plates (Sigma, Corning Costar Multiple Well Plates, CLS3524) using fine brush and exposed to the eight different 1,2-diborane compounds (**7**, **2e**, **4**, **2b**, **2c**, **6**, **2a**, **2d**).

Required concentrations of the compounds were dissolved and diluted in a solvent made up of a mix of n-hexane and ethanol (9 mL of 0.1 % ethanol was mixed with 1 mL of 0.01 % n-hexane). Experiments were done under laboratory conditions. In total four replicates per dose were prepared and 10 eggs added in each well. Negative control with the n-hexane and ethanol mix (0.1 % ethanol and 0.01 % n-hexane), while a commercial insecticide (0.05 % Permetrin) was used as the positive control. Experiments were done under laboratory conditions in an incubator maintained at a constant temperature of 28 °C and 80 % RH under light and dark conditions for 12 h each. Three independent replicate tests were carried out [35].

The number of larvae that emerged from eggs and unhatched eggs were counted after 120 h and percentage egg hatching was calculated. Data on the ratio of live and dead 1st stage larva was also determined. Larvae that failed to move after probing with a brush were recorded as dead.

2.5. Larvicidal bioassays

Four different final concentrations of concentrations (100, 75, 50, 25 ppm (mg/L) were tested against late 3rd-4th stage larvae (about 7 mm long) of *Ae. aegypti* and *Ae. albopictus* mosquitoes. The larvicidal activity of diboranes and its derivatives against the mosquito larvae were evaluated in 24-well plates (Sigma, Corning Costar Multiple Well Plates, CLS3524) [36–38]. Four replication wells were allotted for each derivative, and each well had ten larvae. Ten larvae were transferred into wells of plates with 30–40 μL droplets of water. This water was removed with a pipette and then, 985 μL of distilled water, 5 μL of feed solution (25 mg/mL), and 10 μL of derivative solution of eight different 1,2-diborane compounds (**7**, **2e**, **4**, **2b**, **2c**, **6**, **2a**, **2d**) was added. The final volume in each well was 1 mL. Required concentrations of the compounds were dissolved and diluted in a solvent made up of a mix of n-hexane and 10 % ethanol as described in the ovicidal section. Experiments were done under laboratory conditions in an incubator maintained at a constant temperature of 28 °C and 80 % RH under light and dark conditions for 12 h each. Three independent replicate tests were carried out. Negative control a mix of n-hexane and ethanol and the commercial *Bti* (0.05 g/L), (*Bacillus thuringiensis* var. *israelensis*), (VectoBac 12AS, Valent Biosciences, USA) replaced the derivative as negative and positive control groups, respectively. Larval mortality was recorded after 48 h. Larvae that failed to move after probing with a brush were recorded as dead.

2.6. Data analysis

The ovicidal and larvicidal data was subjected to probit analysis to obtain LC_{50} (The lethal concentration median) with 95 % confidence limit values. All analyses were done using SPSS version 14.0 software [39]. Data from tests with mortality < 5 % in the control group was used. The difference in the effects of the compounds, concentration and their interaction were assessed using analysis of variance with Tukey's test ($p < 0.05$) after arcsine transformation [40]. The statistical value of $p < 0.05$ was considered as significantly different.

3. Results

3.1. Ovicidal effects of compounds on Aedes aegypti and Aedes albopictus eggs

LC_{50} values of the ovicidal activities of the eight 1,2-diborane compounds on *Ae. aegypti* and *Ae. albopictus* were determined and are described in Table 1.

Overall the tested compounds displayed a dose–response in ovicidal and larvicidal efficacy. Mortality was not recorded for concentrations ≤ 12.5 ppm for the period of 120 h and 48 h respectively.

Against *Ae. aegypti* compound **2e** was the most effective, significantly inhibiting mosquito egg hatching (91.11 %) at 100 ppm concentrations after 120 h. It was followed by **2b**, **2c**, **6**, **2a**. Compounds **7**, **4** and **2d** were the least effective. Two-way ANOVA showed significant differences between the compounds ($F = 14.182$; df = 7,576; $p < 0.001$), concentration ($F = 5.970$; df = 3,576; $p < 0.001$), and their interaction ($F = 7.197$; df = 21,576; $p < 0.001$).

For *Ae. albopictus*, compounds **2e**, **6** and **2a** were the most effective in preventing egg hatching after 120 h, followed by **2c** and **7**, **4**, **2b** and **2d** that had the least effects. Compound **2a** at 100 ppm concentrations presented the highest ovicidal effect on *Ae. albopictus* (87.22 %) eggs after 120 h. Two-way ANOVA showed significant difference between the compounds ($F = 26.466$; df = 7,576$p < 0.001$), concentrations ($F = 20.056$; df = 3,576; $p < 0.001$), and their interaction ($F = 8.959$ df = 21,576; $p < 0.001$) (Fig. 3).

After hatching **6** of the compounds (**2e**, **4**, **2b**, **6**, **2a** and **2d**) were observed to effectively kill the 1st stage mosquito larvae that emerged from *Ae. aegypti* eggs. Mortality ranged between 23.43 and 100 %. **2a** caused 100 % mortality at 100 ppm concentrations. Two-way ANOVA analysis showed that there were significant differences between the compounds ($F = 28.432$; df = 7,576$p < 0.001$), concentration ($F = 46.993$; df = 3,576; $p < 0.001$), and their interaction ($F = 3.083$; df = 21, 576; $p < 0.001$) (Fig. 4). **2b**, **2a** and **2d** killed 1st stage mosquito larvae that emerged from *Ae. albopictus* eggs. **2b** was the most effective, it killed 85.83 % of larvae, whereas **7**, **2c** and **6** were the least effective. Mortality ranged between 36.11 % − 85.83 % with significant differences between the compounds ($F = 36.013$; df = 7,576$p < 0.001$), concentration ($F = 96.313$; df = 3,576; $p < 0.001$), and their interaction ($F = 4.005$; df = 21, 576; $p < 0.001$) (Fig. 4) (Table 2).

The LC_{50} values of 1,2-diborane on *Ae. aegypti* and *Ae. albopictus* mosquito larvae were calculated and given in Table 2, except for **2c**, **6** and **2a** which exhibited mortality was < 10 %.

3.2. Larvicidal effects (3rd-4th stage larvae) of compounds on Aedes aegypti and Aedes albopictus

Additionally, the present study evaluated the impact of the compounds on mosquito larvae during their late developmental stages. The LC_{50} values of 1,2-diborane on *Ae. aegypti* and *Ae. albopictus* mosquito larvae were calculated and given in Table 2. The larvicidal effect of the commercial *Bti* was determined as 95.27 % for *Ae. aegypti* and 94.6 % for *Ae. albopictus*. Except for **2c**, **6** and **2a**, the tested compounds had significant larvicidal effects against *Ae. aegypti* larvae after 48 h with a downward trend observed after exposure to different concentrations of compounds. The highest mortality rate occurred in treatments with 100 ppm (mg/L) concentration. Two-way ANOVA analysis showed that there were significant differences between the compounds ($F = 7264.131$; df = 7,96; $p < 0.001$), concentration ($F = 191.497$; df = 3,96; $p < 0.001$), and their interaction ($F = 19.303$; df = 21,96; $p < 0.001$). Against *Ae. albopictus* larvae, **7**, **2e**, **2b** and **2d** were more effective whereas **2c**, **6** and **2a** had no effects. Mortality ranged between 29.66 and 88.66 % and there were significant differences between the compounds ($F = 6515.183$; df = 7,96; $p < 0.001$), concentration ($F = 208.555$; df = 3,96; $p < 0.001$), and their interaction ($F = 18.923$; df = 21,96; $p < 0.001$) (Fig. 5).

4. Discussion

In this study, the insecticidal potential of some 1,2-diborane derivatives against eggs and larvae of important *Aedes* mosquito species was investigated. In particular, the research revealed promising ovicidal activity of compounds 1,2-diborane **7**, **2e**, **6**, and **2a** against mosquito eggs, with significant effects observed after 120 h of exposure. Moreover, derivatives **7**, **2e**, **4**, **2b**, and **2d** showed potent larvicidal activity against both *Ae. aegypti* and *Ae. albopictus* third stage larvae within 48 h.

Table 1
LC_{50}, Chi-square X^2 values of eight 1,2-diborane compounds on the eggs of *Ae. aegypti* and *Ae. Albopictus*.

Compound		Mosquito species					
		Ae. aegypti			*Ae. albopictus*		
		LC_{50} (μg/mL) (ovicidal) (95 % CL)	LC_{90} (μg/mL) (ovicidal) (95 % CL)	Chi-square X^2	LC_{50} (μg/mL) (ovicidal) (95 % CL)	LC_{90} (μg/mL) (ovicidal) (95 % CL)	Chi-square X^2
7		22.312 (11.056–30.783)	38.349 (25.23–64.87)	4.235	26.698 (14.816–35.440)	53. 696 (45.50–85.63)	1.964
2e		11.155 (4.368–17.408)	28.627 (20.60–61.40)	4.657	11.861 (5.438–15.866)	29.65 (16.38–72.03)	7.136
4		36.148 (17.752–41.128)	80.279 (34.32—119.52)	10.599	48.779 (19.575-0.41.163)	101. 884 (66.53–213.77)	1.018
2b		33.528 (21.734–42.488)	63.988 (5.65–12.420)	0.007	41.189 (26.394–53.278)	93.88 (71.85–144.86)	1.734
2c		33.183 (11.175–28.093)	73.349 (27.09–162.63)	3.826	30.298 (12.259–37.634)	69.955 (41.73–244.98)	9.855
6		20.185 (7.402–29.731)	64.491 (39.83–126.60)	1.473	23.442 (15.086–30.081)	72.771 (64.49–127.36)	1.705
2a		16.444 (4.677–25.876)	35.236 (28.40–94.24)	0.183	19.741 (0.917–18.999)	47.559 (30.77–181.26)	4.471
2d		37.412 (12.175–37.063)	81.362 (64.49–127.36)	5.579	32.808 (13.359–45.621)	72.082 (61.30–115.31)	0.486
Mortality (%) ± SD	Negative control	0.0 ± 0.0	0.0 ± 0.0	–	0.0 ± 0.0	0.0 ± 0.0	–
	Positive control	100 ± 0.0	100 ± 0.0	–	100 ± 0.0	100 ± 0.0	–

LC values are expressed in ppm (mg/L) and they are considered significantly different when 95 % CL fail to overlap. Values are means ± S.D. Negative control: a mix of 9 mL 0.1 % ethanol and 1 mL of 0.01 % n-hexane) (v/v). Positive control: 0.05 % Permethrin for ovicidal bioassays.

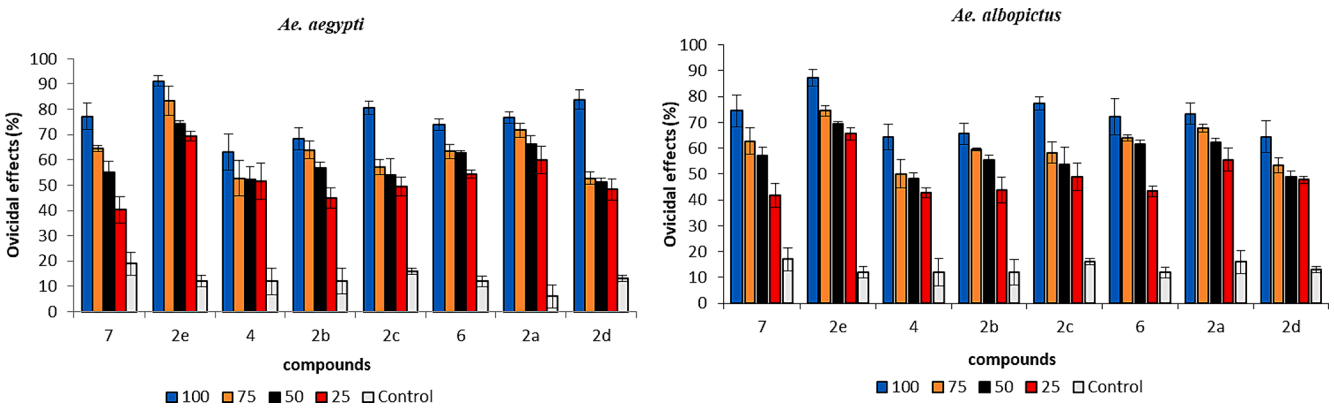

Fig. 3. Ovicidal effects of eight different compounds on *Ae. aegypti* and *Ae. Albopictus* eggs after 120 h. Data presented as mean ± SEM and analyzed using ANOVA with Tukey's test ($p < 0.05$).

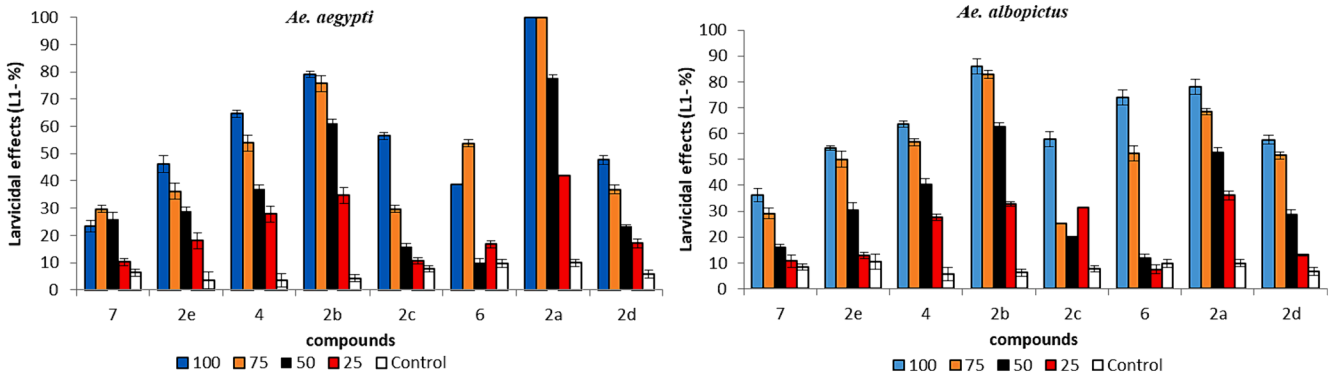

Fig. 4. Larvicidal effects of eight different compounds on *Ae.aegypti* and *Ae.albopictus* larvae (1st stage) after 120 h. Data presented as mean ± SEM and analyzed using ANOVA with Tukey's test ($p < 0.05$).

To our knowledge, this is the first study investigating the larvicidal and ovicidal efficacy of these compounds against these *Aedes* mosquitoes, highlighting their potential as novel insecticidal agents.

Mosquito-borne diseases can be managed through the use of insecticides and the elimination of potential breeding sites of vector species. However, some populations are now resistant to the pesticides used on a large scale all over the world, e.g. *Ae. albopictus* mosquito species used from the Aegean region of Türkiye are resistant to chemical insecticides like DDT [41]. It is critical to find alternatives to conventional insecticides and alternatives include insect growth regulators (IGRs), B. *thuringiensis israelensis* (Bti*), L. sphaericus* (Ls) and Spinosad, which target mosquito immatures. These products have attracted lots of interest as they are safe to humans and the environmental [22]. So far no reports of insect field resistance to *Bti* have been made but there are reports of resistance to *Bti* and *Ls* in laboratory colonies of certain mosquito species, like *Culex quinquefasciatus* [42–44], and *Cx. pipiens* [45–48]. In Brazil, a two-fold shift in resistance was determined in *Ae. aegypti* colonies treated with *Bti* for 15. Generations [49]. The results of all these studies have revealed that resistance has developed against both insecticides and biological control agents, and therefore new control agents should be developed.

In this context, Şahin et al. [29] investigated the antimicrobial activities of some 1,2-diboranes, but they determined that these compounds showed low activity. From this, it was concluded that 1,2-diboranes could not interact sufficiently with microorganisms such as 1,2-diborolanes (five-membered C_3B_2 rings) [27]. When the crystal structures of 1,2-diboranes were examined, it was suggested that they were repelled from the walls of microorganisms, probably due to the steric effects of groups attached to N atoms [29,54]. In another study [28] they performed MTT assay to determine the effects of some selected 1,2-diborolanes (C_3B_2) on cancer cell lines (MCF-7, HepG2 and Hep3B cells) and lymphocytes. They found that few of the diborolane showed high cytotoxic effects on MCF-7, HepG2, Hep3B cells [28]. Such 1,2-diborolane compounds were also used in our study. They did not show a significant larvicidal effect after 48 h, while some 1,2-diborolanes showed low activity.

Despite structural similarities in amine groups, 1,2-diborane derivatives exhibited significantly higher larvicidal and ovicidal activity against mosquito larvae and eggs compared to five-ring boron compounds C_3B_2 (1,2-diborolane This enhanced activity can be attributed to the presence of alkylamino and ortho alkyl substituted arylamino groups (e.g., methyl, isopropyl) attached to boron atoms, as exemplified by compounds **2e** and **2a**. These findings suggest the promising potential of these 1,2-diborane derivatives as novel larvicidal agents, warranting further investigation and development.

5. Conclusions

This work describes the synthesis of a novel 1,2-di(aryl/alkyl)amino-1,2-diborane derivatives. The produced compound was characterized using one- and two-dimensional NMR spectroscopy. The molecular structure of **2a** was determined using single crystal x-ray diffraction. Lethal effects of newly synthesized and previous 1,2-diborane derivatives against *Ae. aegypti* and *Ae. albopictus* larvae were determined. Current research on mosquito control is now focused on understanding mosquito resistance to synthetic insecticides and developing new strategies to overcome resistance problems. Additionally, insecticide resistance makes necessary the development of new compounds despite the difficulties in this area. Especially 1,2-diborane derivatives have the potential to be a new alternative drug against *Ae. aegypti* and *Ae.*

Table 2
LC_{50}, Chi-square X^2 values of eight 1,2-diborane compounds on the 1st and 3rd-4th stage of *Ae. aegypti* and *Ae. Albopictus* larvae.

Compound		Mosquito species									
		Ae. aegypti					*Ae. albopictus*				
		LC_{50} (μg/mL) (larvicidal) (1st stage) (95 % CL)	Chi-square X^2	LC_{50} (μg/mL) (larvicidal) (3rd-4th stage) (95 % CL)	LC_{90} (μg/mL) (larvicidal) (3rd-4th stage) (95 % CL)	Chi-square X^2	LC_{50} (μg/mL) (larvicidal) (1st stage) (95 % CL)	Chi-square X^2	LC_{50} (μg/mL) (larvicidal) (3rd-4th stage) (95 % CL)	LC_{90} (μg/mL) (larvicidal) (3rd-4th stage) (95 % CL)	Chi-square X^2
7		142. 527 (107.205–247.941)	1.951	14.930 (11.052–29.991)	34.12 (21.26–116.53)	2.219	84.819 (73.831–102.545	0.525	23.106 (17.190–28.060)	47.84 (25.92–61.93)	2.047
2e		111.368 (86.957–177.643)	2.034	23.601 (18.077–28.267)	56.52 (29.47–159.02)	2.150	62.557 (55.439–71.404)	4.113	22.394 (16.070–26.163)	43.44 (30.47–86.24)	8.885
4		33.193 (22.309–41.589)	2.719	18.044 (12.540–26.063)	41.01 (28.56-82.20)	3.898	34.974 (29.045–40.134)	5.348	24.959 (18.752–30.128)	52.99 (38.06–98.01)	0.674
2b		24.800 (14.706–32.513)	3.143	27.935 (11.171–26.033)	58. 237 (22.49–32.43)	9.957	22.692 (13.29–104.01)	2.851	27.975 (19.012—28.367)	57.85 (43.01–97.25)	7.575
2c		45.197 (34.382–55.341)	2.443	ND	ND	ND	42.310 (36.171–48.011)	4.577	ND	ND	ND
6		61.815 (50.327–78.751)	2.256	ND	ND	ND	29.342 (0.040–47.616)	6.876	ND	ND	ND
2a		16.101 (12.052–28.991)	9.383	ND	ND	ND	25.260 (13.76–78.00)	2.221	ND	ND	ND
2d		83.862 (67.946–118.877)	2.127	20.570 (16.182–26.080)	45.58 (29.88-42.31)	7.583	51.498 (45.098–58.246)	4.204	20.726 (16.285–26.080)	39.41 (27.22–81.32)	9.879
Mortality (%) ± SD	Negative control	0.0 ± 0.0	–	0.0 ± 0.0	0.0 ± 0.0	–	0.0 ± 0.0	–	0.0 ± 0.0	0.0 ± 0.0	–
	Positive control	97.27 ± 0.043	–	95.27 ± 0.031	95.27 ± 0.031	–	96.4 ± 0.018	–	94.6 ± 0.028	94.6 ± 0.028	–

LC values are expressed in ppm (mg/L) and they are considered significantly different when 95 % CL fail to overlap. Values are means ± S.D. Negative control: a mix of 9 mL 0.1 % ethanol and 1 mL of 0.01 % n-hexane) (v/v). Positive control: *Bti* (0.05 g/L) for larvicidal bioassays. ND: Not determined.

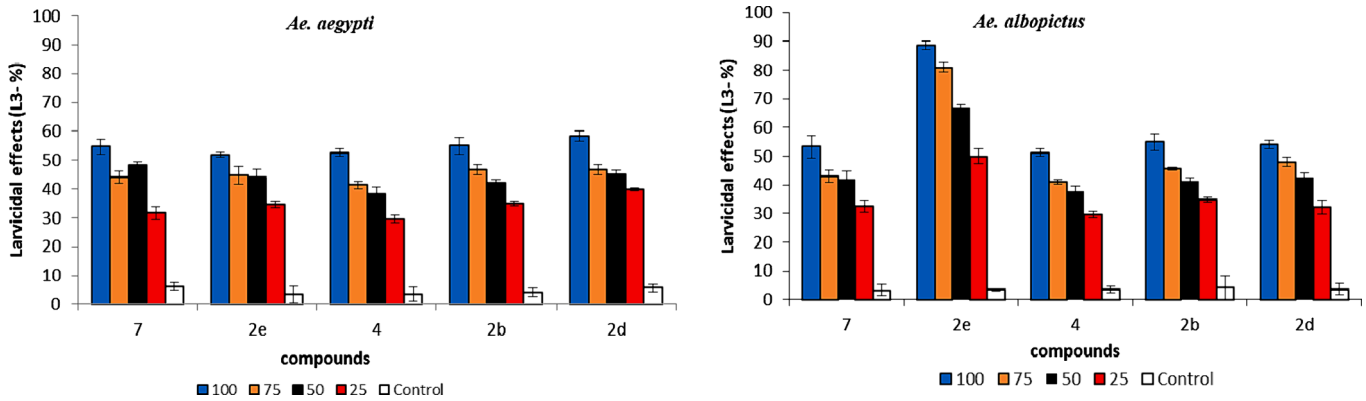

Fig. 5. Larvicidal effects of eight different compounds on *Ae. aegypti* and *Ae. albopictus* larvae (3rd-4th stage) after 120 h. Data presented as mean ± SEM and analyzed using ANOVA with Tukey's test ($p < 0.05$). Diborane compounds **2c**, **6** and **2a** were ineffective, showing no mortality.

albopictus in the future. Our findings highlight the potential of novel 1,2-diborane derivatives as novel larvicides, but more laboratory and field studies are needed. These are the first studies on the larvicidal and ovicidal activities of 1,2-Diborane derivatives.

Efforts should be directed towards the development of 1,2-diborane derivatives for use as larvicides in integrated mosquito control programs and it is thought that this study can provide a starting point. Future investigations are necessary to elucidate the mechanisms underlying the larvicidal and ovicidal effects of these novel derivatives. This knowledge is essential for optimizing their application and mitigating the potential emergence of resistance. Additionally, comprehensive evaluations of their impact on non-target organisms and diverse mosquito species are warranted.

Declarations.

Ethical approval.

Not applicable.

Author Contributions.

YŞ and FB designed the original project. Diborane compounds were synthesized by YŞ and BG. The synthesized compounds were NMR spectroscopically characterized by YŞ and HO. X-Ray analyzes of compounds were performed by MA and RS. Experimental studies were carried out by YŞ, FB, BG and HHB. All authors contributed to the final version of the text.

CRediT authorship contribution statement

Fatma Bursalı: Data curation, Methodology, Writing – original draft, Writing – review & editing. **Yüksel Şahin:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Muhittin Aygün:** Methodology, Software, Visualization. **Resul Sevincek:** Formal analysis, Software, Validation, Visualization. **H. Halil Bıyık:** Methodology, Writing – review & editing. **Hüseyin Özgener:** Formal analysis, Funding acquisition, Software, Visualization. **Burçin Gürbüz:** Conceptualization, Funding acquisition, Validation, Visualization, Writing – original draft, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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Appendix A. . Supplementary data

Crystallographic data and refinement parameter of **2a** has been deposited at the Cambridge Crystallographic Data Centre with CCDC numbers 2279004. This data can be obtained free of charge via https://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Experimental

Synthesis.

General considerations: All reactions were carried out under argon, using standardschlenk 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 spectrometer. The chemical shifts are given in ppm, and are referenced against external Me_4Si, $BF_3.OEt_2$. 1,2-Bis(dimethylamino)diborane(4) dichloride [50,51], 1,2-dismesityldiborane(4) dichloride [30] and 1,2-bisdiduryldiborane(4) dichloride [52] and were synthesized according to literatures [53].

General procedure for synthesis of arylamino substituted diborane (4) derivatives.

Aryl/alkyl-amine derivative (1, 6 mmol) was dissolved in THF/hexane mixture (1:4, 50 mL) and n-BuLi (7.5 mL, 12 mmol, 1.6 M solution in hexane) was added dropwise at 0 °C. The solution was warmed to room temperature and stirred overnight. A hexane solution of ArClB-BClAr (0.75 g, 6 mmol) was added dropwise, resulting in a suspension of **2** at −10 °C. The mixture was slowly warmed to room temperature and removed of volatile components in vacuum (Scheme 1). The residue was extracted into hexane/CH_2Cl_2mixture (1:2, 50 mL). The concentrated solution was kept to −30 °C and the crystals were obtained.

1,2-Bis(dimethylamino)-1,2-bis(2-bromo-4,6-dimethylphenylamino)diborane 2a.

Yielding 78 %, a colorlesscrystal, m.p.: > 210 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 2.03$, 2.18 (each s, each 6H, Me_2N), 2.60, 2.87 (each s, each 6H, o- and p-Me-Ph), 4.28 (br. s, 2H, NH), 6.74, 6.90 (each s, 4H, m-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): $\delta = 19.2$, 20.2 (4C, o-, p-Me), 36.1, 41.2 (4C, Me_2N), 119.9, 119.8 (2C, o-C, Br-Ph), 129.7–132.3 (tot. 8C, Ph), 140.0 (tot. 2C, i-C, PhNH); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): $\delta = 33$ (2B).

1,2-Bis(dimethylamino)-1,2-bis(2,4-dimethoxyphenylamino)diborane 2b.

Yielding 72 %, m.p.: 139–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 2.74$, 2.78 (each s, each 6H, Me_2N), 3.73, 3.85 (each s, each 6H, MeO-Ph), 5.54 (br., s, 2H, NH), 6.31, 6.33 (dd, $^{2}J_{H\text{-}H} = 4$ Hz, H, o-H, Ph), 6.47 (d, 2H, $^{2}J_{H\text{-}H} = 4$ Hz, m-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): $\delta = 35.6$, 41.5 (2C, MeN), 55.0, 55.3 (2C, MeO-C, Ph), 98.5 (2C, m-C, Ph), 103.8 (2C, o-C, Ph), 114.9 (2C, m'-C, Ph), 129.9 (2C, i-C, Ph-N), 148.6 (2C, p-C, Ph-OMe), 152.7 (2C, o'-C, Ph-OMe); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): δ 33 (2B).

1,2-Bis(dimethylamino)-1,2-bis(3,4,5-trimethoxyphenylamino) diborane 2c.

Yielding 74 %, m.p.: 136–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 2.64$, 2.68 (each s, each 6H, Me_2N), 3.64, 3.68 (each s, 18H, MeO-Ph), 5.95 (br., s, 2H, NH), 6.14 (s, 4H, o-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = 35.6, 41.7 (2C, MeN), 55.4, 60.7 (6C, MeO-C, Ph), 94.5 (4C, m-C, Ph), 130.8.

(2C, i-C, Ph-N), 142.7 (4C, m-C, Ph-OMe), 153.1 (2C, p-C, Ph-OMe), ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): δ 31 (2B).

1,2-Bis(2,6-methylphenyl)amino-1,2-diduryldiborane 6.

Yielding 81 %, a colorlesscrystal, m.p.: > 210 °C.

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 1.94$ (s, 12H, o-Me, Ph), 2.12, 2.16 (each s, je 12H, o-, and m-Me, Dur), 6.38, 6.80 (br., je s, je H, NH), 6.84–6.88 (m, 8H, p-H, Dur and m-, o-H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): $\delta = 18.8$ (4C, o-C, Me-Ph), 19,58, 19.68 (each 4C, o-, and m-C, Me-Dur), 124.0, 128.3, 130.4, 133.0, 134.0 (20C, Ph and Dur), 131.7 (br., je C, i-C, Dur), 141.9 (je C, i-C, PhN); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): δ = 48 (2B).

1,2-Bis(diethylamino)-1,2-dimesityldiborane 4.

Yielding 72 %, m.p.: 134–136 °C (decomposed).

^{1}H NMR (400 MHz, $CDCl_3$, 300 K): $\delta = 1.14$, 1.42 (each t, 6H, $^{3}J_{H\text{-}H} = 8$ Hz, Me-N), 1.95 (br., 12H, o-Me, Mes), 2.36 (s, 6H, p-Me, Mes), 3.16, 3.77 (each q, 4H, $^{4}J_{H\text{-}H} = 8$ Hz, Me-CH_2-N), 6.74 (each s, 4H, m-H, Mes); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): $\delta = 13.8$, 14.2 (2C, Me-N), 20.9, 21.1 (each 4C, o-, m-C, Me-Mes), 40.8, 45.8 (each C, Me-CH_2-N), 126.5, 127.1, 128.2, 134.5, 135.8, 137.4, 138.3, 138.9, 139.2 (tot. 10C, o-, m- and p-C,Mes), 143.0 (2C, i-C, Mes); ^{11}B NMR (128.32 MHz, $CDCl_3$, 300 K): δ = 49 (2B).

Appendix B. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2024.112268.

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