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Studies on insecticidal activities of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole against *Helicoverpa armigera*

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Abstract

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Insecticidal activity of the 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) against the global crop pest – *Helicoverpa armigera* was studied in laboratory and field, and the toxicity (LD_{50}) of the substance was evaluated against larva *H. armigera*, as well as evaluate the effectiveness against *H. armigera.*

This study aimed to determine the insecticidal activity of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) against larvae *H. armigera in vivo* and *in vitro*. Evaluate biological effectiveness in the control of *H. armigera* in fields of the Tashkent region.

For the first time, it was found that the derived 1,3,4-oxadiazoles at 0.1 mg/mL caused 65.5% mortality of cotton bollworm (*H. armigera*) after 24 h of incubation. The mortality of larvae after 48-hour incubation reached 79.9%. The toxicity of 2-BAO against larvae after 24 h was LC_{50} 0.36 mg/mL.

The insecticidal activity of the 1,3,4-oxadiazole derivative was studied for the first time *in vitro* against *Helicopvera zea, Spodoptera frugiperda*, and *Trichoplusiya ni* insect cells. The results obtained confirm that 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole at a dose of 10 µM/mL exhibits toxicity against cells of various cutworm species, which is confirmed in the experiment *in vivo*.

The results of field trials showed that on the 7th day, the effectiveness of the substance at a rate of 0.2 kg/ha against larvae *H. armigera* was 56.0% compared to the control, 11.0% more compared to the insecticide BI-58 (a.i. dimethoate). The effectiveness of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) on the 21st day reached 68.5% compared to the control.

These findings suggest that it can be assumed that 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) can control the number of larvae of pests with the best control efficiency of more than 68.5% when the increasing pest population from reaching the economic injury level.

Keywords: insecticidal activity; 1,3,4-oxadiazole; *Helicoverpa armigera; in vitro; in vivo*; effectiveness

Introduction

It is known that the natural and climatic conditions of Uzbekistan are characterized by a large amount of heat and a significant duration of vegetation in the summer, which ensures the cultivation of many heat-loving plants like cotton (Khamidov & Turgunov, 2019). Uzbekistan, having rich experience in growing cotton, occupies a leading position (in terms of area of cotton fields, production volumes, and yields) in the top ten cotton-growing countries (Abdurakhmanov et al., 2023).

One of the urgent problems in the country is the spread of the dominant pest of cotton and other crops – cotton bollworm. Cotton bollworm (*Helicoverpa armigera* Hb.), a widespread dangerous pest is a polyphage that damages many forage and industrial plants and fruit trees (Khodjaev et al., 2015).

Butterflies appear in late April or early May at an average daily temperature of +18-20°C. The larval period of cotton bollworm is completed through six instars. Young larvae skeletonize leaf blades, buds, and cotton bolls. Larvae of older ages eat buds, leaves, ovaries, gnaw boxes, and pupate in the soil, sometimes in cotton bolls (Khujamshukurov, 2016). The pupa is reddish-brown, 15–22 mm long. Females lay 300 to 3000 eggs on leaves, flowers, and cotton bracts. Under the conditions of Uzbekistan, the *H. armigera* gives 3-4 generations (Anarbaev, 2016). The duration of embryonic development in summer and spring continues – 2-5 days, and in autumn – 8-12 days.

The main period of its harmfulness occurs during the development in the larva phase, which develops inside the buds, flowers, ovaries, and fruit elements of cotton. *H. armigera* is distributed in almost all zones of Uzbekistan (Khodjaev, 2015). According to Khodjaev, when an average of 10 caterpillars of the second generation of the pest infest 100 plants, 0.1 t/ha of cotton yield is lost (Khodjaev, 2012). It is established on medium-fiber varieties of cotton if there are 10-12 larvae or 20 eggs per 100 plants, or if 3–5% of cotton bolls are damaged, and on fine fiber varieties, 5–6 larvae or 10 eggs, and larvae per 100 plants (Sulaimonov et al., 2019). In the same areas, an increase in the number of *H. armigera* was noted from June to September, which causes concern for the quality of the cotton fiber and the amount of the crop. To reduce the growing rate of pest development and obtain the desired result, it is necessary to develop and implement a scientifically based system of measures based on agricultural technology, crop rotation, timely defoliation, and selective protective treatments with effective insecticides.

There are many strategies to increase the yield and quality of crops, among which pest control to decrease crop loss is one of the most essential (Khidyrova et al., 2022). It should be emphasized that the chemical method remains dominant. Registered insecticides in the Republic of Uzbekistan, such as Decis, Ripcord, Ambush, Sumicidin, Karbofos, Aktellik, Arrivo, Sumi-alfa, Fufanon, and BI-58, are currently used on cotton in Uzbekistan against *H. armigera* (Sulaimonov & Ochilov, 2016).

The disadvantages of many insecticidal preparations are the development of pest resistance to them with constant use, toxicity to non-target organisms, and the content of residual amounts in products and in the soil (Mamarozikov et al., 2019).

In recent years, a large number of studies have been devoted to the study of organic compounds of the oxadiazole class, such as 5-substituted-1,3,4-oxadiazole-2-thiones, which have potential insecticidal activity against crop pests (Turaeva et al., 2021).

Various five-membered heterocyclic systems of pyrrole, oxadiazole, triazole, thiadiazole, and their derivatives are of interest since they contain the structural features of many biologically active compounds (Piccionello, 2022). Many studies have reported reactions of substituted oxadiazolthiones with various haloacetamides, as well as synthesized S-products with various biological activities: antimicrobial (Lelyukh et al., 2020; Ahsan et al., 2017), anticancer (Wróblowska et al., 2017; Damaceanu et al., 2011) and fungicidal (Salamaa, 2020).

A few examples of the studied classes of organic compounds with potential insect-acaricidal activity of 5-hydroxy-4,5-dihydro-1,2,4-oxadiazoles and trifluoroethane-substituted derivatives of 1,2,4-oxadiazoles against the tick (*Ixodes hexagons*) are known and compared. The efficiency with known analogs (Marin et al., 2020). The results indicated that compounds1,3,4-oxadiazol-2-thion are considered insecticide candidates for *Spodoptera littoralis* fourth-instar larvae. It is concluded that these compounds may represent promising insecticide candidates (Elbarbary et al., 2021).

The high migratory capacity, polyphagia, and veracity of *H. armigera*, as well as the ability to quickly develop resistance to insecticides, make the studied object a serious and constant threat to many crops.

Natural predators of this pest usually keep the population of *H. armigera* under control, but when insecticides kill these predators, infestation can become problematic. Therefore, the search for low-hazard and effective insecticides acquires meaning in plant protection.

In this article, we studied the insecticidal activity of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) in laboratory and field to assess the prospects for its application in agriculture.

Materials and Methods

Reagents and compounds

Potassium ethyl xanthate CAS No.254770 (purity 90%) was purchased from Zhongtian Chemical JV LLC. Benzocaine CAS-94-09-7 (purity 99%), benzyl chloride CAS No.100-44-7 (purity 99%), and Tween-80 were purchased from Sigma-Aldrich Chemical Co., Ltd. All other biochemical reagents, including hydrazinium hydroxide CAS No.10217-52-4 Uzbekistan, had the highest degree of purity 99%.

Upon receipt of a new benzyl derivative of oxadiazole, the reaction was carried out by boiling in dry acetone 5-(4-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione (1) and benzyl chloride in the presence of a catalytic amount of potash (Figure 1). Previously, the structures, physicochemical data, and fungicidal activity of the synthesized 2-BAO (2) was studied (Ismailova et al., 2016; Ismailova et al., 2017).

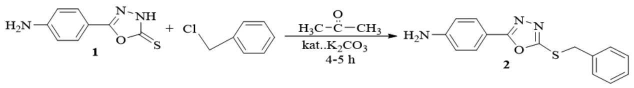

Fig. 1. Synthesis of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole (2-BAO) (2)

Insecticide Bagira was used as a reference 20.0% (a.i. imidacloprid, Agrochem, Uzbekistan), Entospilan 20.0%, (a.i. acetamiprid, Ifoda, Uzbekistan) and BI-58 400 g/l, (a.i. dimethoate, BASF, Germany).

Insects

To assess the insecticidal activity, were used larvae of *H. armigera* collected from untreated fields with pesticides, at the "Aydarova Ainur Agro" farm, Urta Chirchik district of Tashkent region. Fourth and fifth instar larvae were used in bioassay experiments. Larvae of *H. armigera* were maintained during the day at a temperature of 25-27±1°C, relative humidity of 60 ~ 70%, and in natural light, in viable conditions in the Department of Organic Synthesis and Plant Protection of the Institute of the Chemistry of Plant Substances, Academy of Sciences Republic of Uzbekistan.

Cell line

In vitro screening for insecticidal activity, three types of insect cell lines were used: *Helicopvera zea, Trichoplusiya ni,* and *Spodoptera frugiperda* stored in the collection of the Laboratory of Molecular Genetics of the Institute of Chemistry of the plant substances. Cell cultures were grown in Grace's Insect Medium (Gibco USA) containing 1.0% antimycotic antibiotic (Lonza, Belgium), 2 mM glutamine (Himedia, India), and 10% fetal bovine serum (FBS) (Gibco, USA).

Bioassay against Helicoverpa armigera in laboratory

The insecticidal activity of 2-BAO against larvae of *H. armigera* was assessed in laboratory. The insecticidal activity of the *test substance* against fourth and fifth-instar larvae of *H. armigera* was analyzed and compared with insecticides Bagira (a.i. imidacloprid) and BI-58 (a.i. dimethoate).

To evaluate the insecticidal activity, the larva *H.armigera* were exposed to different concentrations of *test substance* diluted in water with 0.1ml Tween-80 and impregnated in filter paper in a concentration of 100 μg.cm^{-2}. Then the test pests were incubated in Petri dishes. Larvae mortality assessment was performed after 24 h and 48 h. Four repetitions were performed for each concentration (10 larvae per repetition). Control larvae received only water. Mortality was corrected according to Schneider-Orelli's formula (Puntener, 1981) and then subjected to probit analysis. Larvae of *H. armigera* that failed to respond to touch or always remained ventral side up when turned over were considered dead.

The LC_{50} (lethal concentration) was statistically analyzed according to the method described by Finney (Finney, 1971). Mathematical processing of the obtained data and calculation of statistical parameters were carried out using the Microsoft Excel 2016 software package.

Bioassay against Helicopvera zea, Spodoptera frugiperda, and Trichoplusiya ni in vitro

To determine the insecticidal activity *in vitro*, three types of insect cells were used: *Helicopvera zea* (Light et al., 1993), *Trichoplusiya ni* (Lingren & Green, 1984), *Spodoptera frugiperda* (Capinera, 2002), stored in the collection of the Laboratory of Molecular Genetics of the Academy of Sciences of the Republic of Uzbekistan. The colorimetric analysis of the MTT test was used to determine the insecticidal activity (Stockert et al., 2018). Insecticide Bagira was used as a positive control and Grace's Insect Medium (Gibco USA) as a negative control.

For the MTT assay, cells suspension into a 96-well plate (Costar, USA), and each well was treated with the test substance at a density of 2×103 and with the widely used insecticide Bagira (a.i. imidacloprid) at concentrations of 10-100 μM/mL. Cells were incubated for 24 h. After 24 h, the medium in each well was replaced with fresh Grace's medium containing 0.05 mg/mL MTT. After 4 h of incubation, the MTTs in the wells were removed and 100 μl of DMSO (dimethyl sulfoxide) was added to each well. After 10 min, the results were measured on an EnSpire 2600 spectrophotometer (Perkin Elmer, USA) at a wavelength of 620 nm. Mean inhibition values were calculated after 3 repetitions. The *in vitro* screening used was based on the procedure described by Stockert (Stockert et al., 2018).

Statistical processing of the obtained results was carried out using the OriginPro 8.6 program (Origin Lab Corp, USA) The results were considered significant at r≤0.05.

Phytotoxicity screening

Before carrying out field tests on open ground, an assessment was made for the phytotoxicity of the active substance. The method of chipped leaf discs was used to evaluate the phytotoxic effect of the 2-BAO (Berestetsky et al., 2018). In studies by Turaeva et al. (2022) on the phytotoxicity of pesticides, wheat, cucumber, and tomato leaves were used as test plants.

Evaluation of biological effectiveness against Helicoverpa armigera in the field

The next stage of research was field trials, which were carried out between June and September during the cropping seasons in the "Aydarova Ainur Agro" farm in the Urta-Chirchik district of Tashkent region. The economic injury level of the *H. armigera* was 5-6 larvae per 100 plants during the flowering phase.

Due to poor crop sequencing and less efficient crop rotation, these fields experienced very severe damage to *H. armigera* during testing. The effectiveness of the test substances was studied in a field experiment with an area of 0.5 ha. During the flowering period, cotton was treated with a working solution of test substances using a backpack sprayer "CP-15" with a volume of 20 l. Entospilan 20.0% (a.i. acetamiprid, Ifoda, Uzbekistan) at a rate of 0.3 kg/ha and BI-58 400 g/l (a.i. dimethoate, BASF, Germany) at a rate of 0.2 kg/ha was used as a reference. The experiment was carried out in four repetitions. The number of insects was counted before spraying and 3, 7, 14 days after the treatment of crops with insecticides. Biological efficiency was calculated using the formula Henderson-Tilton (Henderson-Tilton, 1955).

Results

Effects of insecticides against Helicoverpa armigera in laboratory

Studies have shown that 2-BAO fixes 73.3% mortality of larvae during 24 h incubation. Studies have shown that the biological effectiveness of the test substance at a dose of 0.5-0.1 mg/mL was 65.5-69.0% with a 24 h incubation and with a 48 h – 79.9-85.5% against larvae *H. armigera*. According to the insecticide Bagira 0.1 mg/mL, the efficiency reached up to 68.0% and 72.0%, respectively (Figure 2).

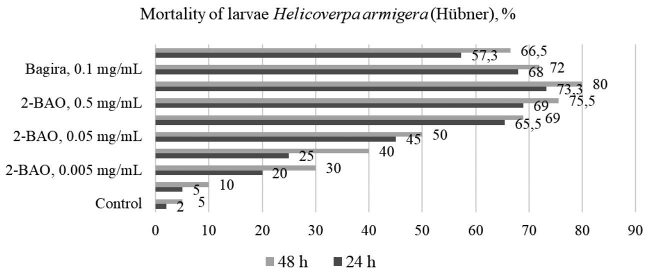

Fig. 2. Insecticidal Activities of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole against larvae *Helicoverpa armigera*

The least effective was shown in doses of 0.01 and 0.05 mg/mL of the substance causing 40.0%-50.0% mortality of larvae. A lower dose of 0.005 mg/mL test substance caused relatively low mortality in the 20 to 30% range. Only 0.001 mg/mL of the derivative of 1,3,4-oxadiazole can be judged to be non-toxic to larvae *H. armigera* as it caused less than 10.0% mortality.

The most effective doses were chosen to determine lethal concentration. The number of dead larvae and the LC_{50} values and their upper and lower fiducially limits at different 2-BAO doses was examined in related to duration (24 h and 48 h) of exposure. The number of dead larvae significantly increased in response to substances concentrations of 0.001 and 0.5 mg/mL ($P < 0.001$ for each case, Figure 2). The 24 h and 48 h LC50 values (with 95% confidence limits) of 2-BAO for the larva of *H. armigera* were estimated as 0.36 mg/mL (0.128-1.054) and 0.10 mg/mL (0.030-0.333) respectively (Table 1).

In the toxicity test probit regression slopes were significant (χ^2 = 0.994-0.990, df =5) (Figure 3).

The effect of insecticides on cell cultures of Helicopvera zea, Spodoptera frugiperda, and Trichoplusiya ni

The results of *in vitro* screening confirm that the studied derivative of 1,3,4-oxadiazole exhibits insecticidal activity against cells of various cutworm species, such as *H. zea*, *S.*

Table 1. LC_{50} of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole on larvae *H. armigera* (n = 10 each)

Test	Time Exposed, h	LC_{50} value, mg/mL	95% Confidence limits		R^2	Slope±SE	χ^2 value
			Lower limit	Upper limit			
2-BAO	24	0.36	0.128	1.054	0.882	0.663±0.23	0.994
	48	0.10	0.030	0.333	0.862	0.576±0.26	0.990

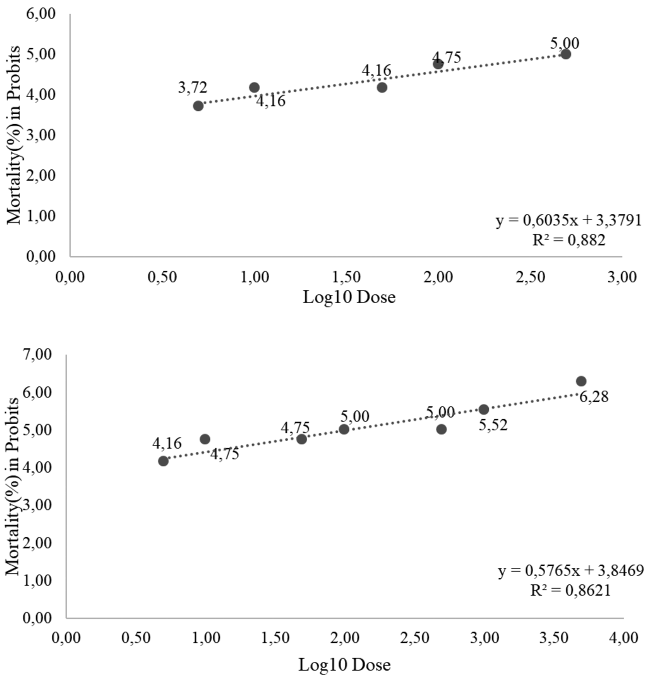

Fig. 3. Mortality curve of larvae *H. armigera* exposed to 2-BAO (24 h – a; 48 h – b)

frugiperda, and *T.ni*. The test result shows that in the presence of 100 μM/mL of the 2-BAO (per well), the number of viable cells reduced to 16.8% of the original number after 24 h of incubation and that the toxicity increased in a dose-dependent manner (Table 2). The number of live cells of three insect species was reduced to 28.4% in the incubation of 10 μM/mL of substance per well.

Thus, the results indicate that this 2-BAO can serve as the basis for new insecticides of low mammalian toxicity.

Phytotoxic activity

The phytotoxic activity of the substance at the three concentrations: 10 mg/mL, 5 mg/mL, and 1 mg/mL was studied on leaves of wheat, tomato, and cucumber.

According to the results of registration, substances with a concentration of 10 mg/ml showed moderate phytotoxicity

Table 3. Results of phytotoxic activity of the 2-BAO

Treatment	Phytotoxic activity*		
	wheat	tomato	cucumber
Control	i	i	1.1±0.4
2-BAO, 10.0 mg/mL	i	i	i
2-BAO, 5.0 mg/mL	i	i	i
2-BAO, 1.0 mg/mL	i	i	i

**Note: i – inactive; the length of the necrotic spot on the segments of plant leaves, mm*

on the leaves of cucumbers, and necrosis on the leaves did not exceed 1.1 mm (Table 3). The necrotic symptoms were not found in the remaining versions.

Biological effectiveness of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole against Helicoverpa armigera in field

The results of field experiments showed that the effectiveness of the synthesized substance on the 7th day was 56.0% compared to the control and 11.0% compared to the

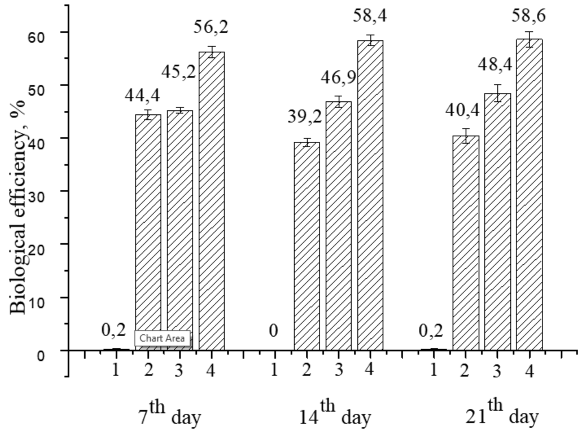

Fig. 4. Biological effectiveness of 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole against the larvae *Helicoverpa armigera*

1. Control, without insecticide; 2. Entospilan, 0.3 kg/ha; 3. BI-58, 0.2 kg/ha;
4. 2-Benzylthio-5-(4-Aminophenyl)-1,3,4-oxadiazole, 0.2 kg/ha

Table 2. Results of *in vitro* screening for insecticidal activity against *Helicopvera zea, Spodoptera frugiperda*, and *Trichoplusiya ni*

Treatment	Concentration, μM/mL	Inhibition of test objects, %		
		Helicopvera zea	*Trichoplusiya ni*	*Spodoptera frugiperda*
Control: Bagira(a.i. imidacloprid)	10	83.5±0.3	80.6±0.5	81.5±0.1
	100	98.7±0.2	98.3±0.2	96.4±0.3
2-BAO	10	68.2±0.6	67.8±0.5	63.6±0.2
	100	79.0±0.3	77.0±0.2	78.6±0.5

BI-58 insecticide. The optimal application rate for the test substance is 0.2 kg/ha.

The efficiency when spraying cotton plants with 2-BAO reached 58.0% on the 14th day and on the 21st day it remained up to 68.5% compared with the control (Figure 4). Entospilan showed less efficiency in all accounting periods – 44.0%, 39.0%, and 40.0%, respectively.

Therefore, the effectiveness of the synthesized substance is 11.0% higher than that of the insecticide BI-58 and 11.8% higher than that of Entospilan. In control before treatment, the number of larvae was 1.25 pcs for the plant, and the average number of larvae reached 9.5 on the 21st day. The effectiveness of the synthesized substance is 11.0% higher than that of the insecticide BI-58 and 11.8% higher than that of Entospilan.

Discussion

The development of new insecticidal formulations is important to overcome the burgeoning hurdle of insecticide resistance in field populations of insects and other pest arthropods.

We propose the utilization of some derivedes of 1,3,4-oxadiazoles, that will aid in development of insecticidal active compounds.

Elbarbary et al. (2021) mentioned that some 1,3,4-oxadiazole derivatives are considered candidate insecticides for fourth-instar larvae of cotton leafworm *Spodoptera littoralis*. Wang et al. (2018) mentioned that 1,3,4-oxadiazole derivatives showed the best larvicidal activity against *P. xylostella* with an LC_{50} value of 0.27 mg/mL.

Using commercially available 5-(4-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione as a starting material, 40 g of 2-BAO was successfully prepared through a four-step reaction and the total yield reached 98%. The purity of the compounds was determined by the m.p. (129-1300C) and TLC (Rf = 0.41). The assigned structure was further generated by IR, UV, spectral ^{1}H-NMR, ^{13}C NMR studies (Turaeva et al., 2023).

The results of *in vitro* and *in vivo* screening on insecticidal activity showed that the use of derived 1,3,4 – oxadiazoles can be efficient against larva cotton bollworms.

Our studies prove that toxicity of 2-BAO LC_{50} 0.36-0.10 mg/mL was for larvae of *H. armigera*. Both laboratory studies and field trials have shown that 2-BAO is an effective larva of the *H. armigera* control agent. It is expedient to use the substances on objects with medium insect populations, and its use can significantly reduce the number of insects.

Conclusions

Thus, the 1,3,4-oxadiazole derivative synthesized by us was subjected to insecticidal analyzes *in vivo* and *in vitro* for the first time. Substance 2-BAO exhibited potent insecticidal activity (69.0-79.9%) against larva of *H. armigera* with LC_{50} values of 0.36 mg/mL. 2-BAO at 0.2 kg a.i. ha^{-1} can control the number of larvae with the best control efficiency of about 68.5% in the field of the Tashkent region, suggesting that the test substance is a promising active ingredient as an insecticide. At present, further studies are underway in our laboratory to evaluate the effectiveness of 1,3,4-oxadiazole derivatives in the fight against many other types of pests of crops in Uzbekistan, as well as a study of the resistance of harmful organisms to this substance.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contributions

S.M.T.: Conceptualization, writing-original draft, investigation; D.S.I.: Investigation; Sh.Sh.Kh.: Investigation; B.Zh.E.: Reviewing and editing; Sh.S.A.: Reviewing and editing; P.A.N.: Data curation; D.T.Dj.: Data curation.

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