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Research Article

New Pyrethroids for Use Against *Tuta Absoluta* (Lepidoptera: Gelechiidae): Their Toxicity and Control Speed

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Abstract

Insect pests are responsible for major losses in crop productivity, and insecticides are the main tools used to control these organisms. There is increasing demand for new products for pest management. Therefore, the aim of this study was to assess the toxicity of pyrethroids with acid moiety modifications to measure the insecticidal activity of these compounds on *Tuta absoluta* (Meyrick) (Lepidoptera: Gelechiidae). First, we synthesized *E/Z* mixtures of five pyrethroids: [9], [10], [11], [12], and [13]. Then, we separated the *cis* and *trans* pyrethroid isomers of [9], [10], [11], and [12]. We assessed the toxicity of these compounds against *T. absoluta.* The *E/Z* mixtures of the five pyrethroids (30 µg of substance per mg^{-1} of insect) caused high (100%) and rapid (<12 h) tomato borer mortality. The *cis* isomer of pyrethroid [10] was the most toxic to *T. absoluta,* causing mortality similar to permethrin. The other isomers were less powerful than permethrin.

Key words: pesticides synthesis, new insecticide, natural product inspired, tomato borer, isomers

Insects are the major cause of crop losses (Van Naters and Carlson 2006, Guedes and Picanço et al. 2012), and insecticides are the primary method for controlling them (Aktar et al. 2009, Picanço 2012).[AU: Please include the following citations in the reference list with full publication detail: Picanço (2012),] Thus, it is important to discover new molecules with insecticidal effects. One approach to synthesizing new agrochemicals is to use model molecules that are found in natural insecticides (Moreno et al. 2012). For example, pyrethroids were introduced to the market in the 1970s, and they are synthetic insecticides produced from a natural prototype. Pyrethroids are synthetic analogues of pyrethrins, six closely related insecticidal esters found in pyrethrum, an oleoresin extracted from the dried flowers of *Tanacetum cinerariifolium* (Asteraceae) (Casida and Quistad 1995, Katsuda 1999).

The synthetic chemistry of pyrethroids is one of the major success stories in using natural products to obtain synthetic analogues. Their synthesis has led to a series of derivatives that have been considered as efficient insecticides because of their selectivity to natural enemies, photostability, low volatility, rapid knockdown effect against insects at minimal doses, and low mammalian toxicity (Soderlund et al. 2002, Davies et al. 2007).

The insecticidal activity of pyrethroids depends on the overall shape and asymmetry of the molecule (Jeanmart 2003). According to Soderlund et al. (2002), the presence of aromatic groups on the alcoholic moiety increases the stability of pyrethroids in the presence of air and light in comparison to the natural pyrethrins. This increased stability made the use of pyrethroids possible in crop protection, which subsequently led to considerable structural modifications on this part of the molecule (Vatandoost 2004). However, there are few papers in the literature that describe pyrethroids with an aromatic ring on the acid moiety. Thus, in a search for compounds with a biological activity analogous to natural pyrethrins, we decided to synthesize novel pyrethroids by modifying the acid part. Caterpillars (Lepidoptera) are a major group of agricultural pests that includes the tomato borer, *Tuta absoluta* (Meyrick) (Lepidoptera: Gelechiidae).

T. absoluta is a neotropical oligophagous insect that attacks solanaceous crops, especially tomatoes (Suinaga et al. 1999). Since the 1960s, *T. absoluta* has become one of the key tomato pests in most South American countries (Desneux et al. 2011, Gontijo et al. 2013). More recently, *T. absoluta* has also become a serious threat to tomato production in Europe, Africa, and the Middle East, causing great concern among the plant protection agencies in the countries

where it has been found (Seplyarsky et al. 2010, Desneux et al. 2011, Baniameri and Cheraghian 2012). *T. absoluta* larvae attack tomato plants during all their growth stages. The production of large galleries in leaves, apical buds, burrowing stalk, and green and ripe fruits are the most common damages caused by this pest (Guedes and Picanço 2012).

Considering the potential of pyrethroids for pest control and the importance of *T. absoluta*, the goals of this study were to synthesize new pyrethroids with modifications to the acid part and to determine the toxicity of these substances to *T. absoluta*. To achieve these goals, we determined: 1) the efficiency and speed with which *E/Z* mixtures of new pyrethroids control *T. absoluta* and 2) the differences in toxicity of *cis* and *trans* isomers of the new pyrethroids to *T. absoluta*.

Materials and Methods

Pyrethroids Synthesis

To synthesize the novel pyrethroids, first, d-mannitol (a commercially available product) [1] was acetalated, resulting in compound [2]. Compound [2] was submitted to oxidative cleavage, resulting in the aldehyde [3]. Later, the esters [4] and [5] were prepared by the Wittig reaction. The ester [4] was submitted to three-membered ring formation (cyclopropane), characteristic of pyrethroids. This type of reaction is highly stereospecific using sulfur ylide and completely stereoselective in the presence of phosphorus ylide, i.e., both *cis* and *trans* alkenes will give *trans*-cyclopropane using the phosphorus ylide. The attack of the phosphorus ylide on α,β-unsaturated carboxylic compounds of this type occurs by the *Re* face when the molecule presents *cis* geometry as shown in Scheme 1, whereas in *trans* geometry molecules the attack happens by *Si* face.

In the ^{1}H NMR spectrum, the signals of five methyl groups and the absence of the olefinic hydrogen signals are important evidences for the formation of the compound [6] from the ester [4]. A more detailed study of this molecule was carried out using the double irradiation technique on the ^{1}H NMR. On radiating the signal at δ = 3.70 ppm, it was found that the multiplet at δ = 3.90–4.20 ppm became doublet and the doublet of doublets at δ = 1.55 became a doublet (J = 5.4 Hz). The coupling constant of 5.4 Hz confirms the *trans* geometry for the cyclopropane ring. On the basis of the proposed mechanism and NMR results, it can be concluded that the absolute configuration of carbon 1 is *S*.

The diol [7] was obtained by hydrolysis. Then, after a new oxidative cleavage, the aldehyde [8] was created. Finally, the aldehyde [8] was used in the synthesis of the pyrethroids [9]–[13] by the Wittig reaction (Scheme 2). The new pyrethroids with acid moiety modifications were patented in 2016 (Alvarenga et al. 2016).

The compounds were obtained as isomer mixtures. These were not completely separated due to the similarity of the retention factors. Therefore, the mixture of isomers was known, but the yield of each individual isomer was not certain. The compounds were purified and characterized by infrared spectroscopy, nuclear magnetic resonance (^{1}H and ^{13}C NMR), and mass spectrometry (Alvarenga et al. 2016). All reactions exhibited good yield, making this route an alternative for synthesizing pyrethroids (Scheme 2).

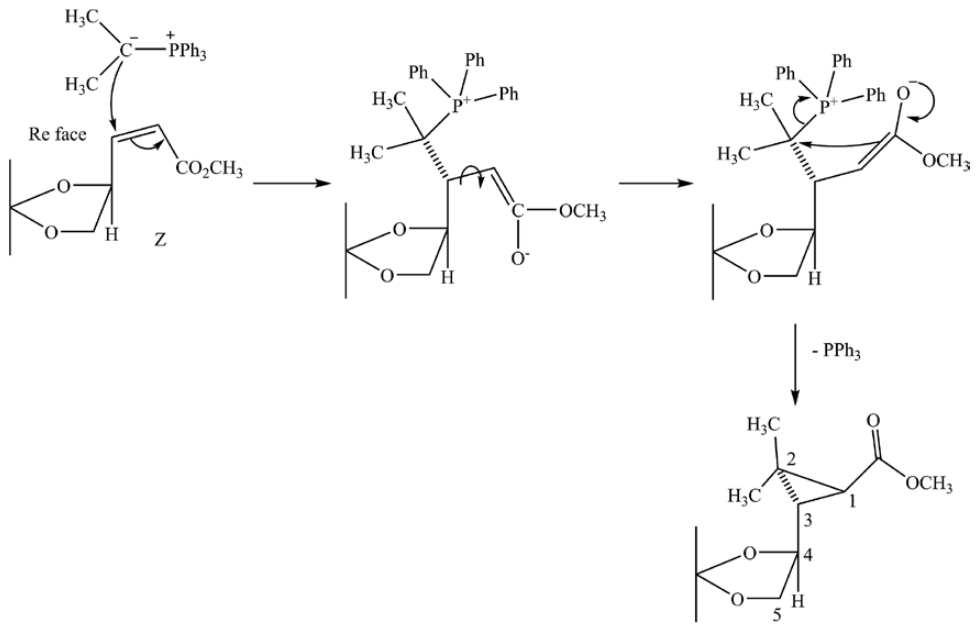
The new pyrethroids, thus, synthesized were used in most biological assays as mixtures of isomers because the synthesis of pure compounds in quantities sufficient to perform all the bioassays was impossible. Pure isomers were used only for the comparative bioassays of insecticidal activity to *T. absoluta* that depended on the stereochemistry of the compounds. It was not possible to isolate the *cis* and *trans* isomers of the new pyrethroid [13] due to their extremely proximate retention times.

Insects

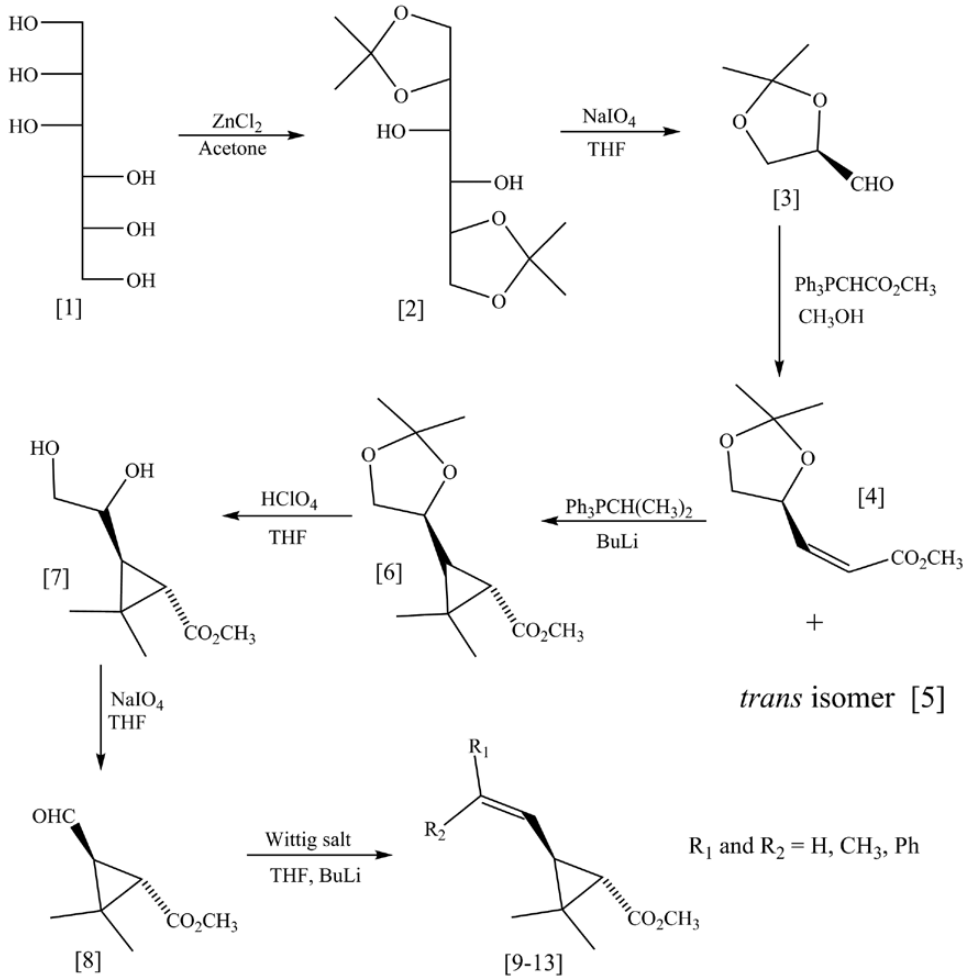
The bioassays were performed with second-instar *T. absoluta* and they were obtained from a laboratory where they were raised on tomato leaves according to Galdino et al. (2011). The colony belonged to the Integrated Pest Management Laboratory from the Universidade Federal de Viçosa campus (20° 48′45″S, 42° 56′15″ W, 600 m a.s.l., tropical climate).

Bioassays

The bioassays were performed in three steps. First, we assessed the mortality caused by a dose of the *E/Z* mixtures of the new pyrethroids to the pest *T. absoluta*. Second, we estimated the dose–mortality curves of the *E/Z* mixtures of pyrethroids to *T. absoluta*.



Scheme 1. Mechanism for the formation of the cycloprone ring with the *trans* geometry.



Scheme 2. Synthetic route, yield, and structure of the new pyrethroids [9], [10], [11], [12], and [13] produced from methyl 3-formyl-2,2-dimethylcyclopropane-1-carboxylate [8].

Finally, we assessed the mortality caused by the *cis* and *trans* isomers of the new pyrethroids to *T. absoluta*.

Before performing the bioassays, we evaluated the body weights of the *T. absoluta* second instars that were to be used in the bioassays using an analytical balance (200 Gehaka AG, precision 0.1 mg). This procedure was performed because the doses were calculated in µg of substance per mg of insect body weight. The substances were diluted in acetone (Vetec P.A. 99.5%). We topically applied 0.5 µl solution to each insect using a 10 µl microsyringe (Hamilton model 701N, 0.1 µl accuracy). Control insects were treated topically with an equal volume of acetone alone.

The bioassays were conducted using a completely randomized design with four replications. Each repetition consisted of a Petri dish (9 × 2 cm [diameter by height]) containing 10 insects and a food source. We inserted two tomato leaflets in each Petri dish for the *T. absoluta* larvae to feed on. The Petri dishes were covered with organza fabric for ventilation to avoid any fumigation effect from the treatments. The Petri dishes were placed in an incubator at 25 ± 0.5°C, relative humidity of 70 ± 5% and a photoperiod of 12 h. The insects were considered dead when they did not move when touched with a brush (Galdino et al. 2011, Silva et al. 2011, Gontijo et al. 2013). The mortality data were corrected in relation to the mortality occurring in the control treatment according to Abbott's formula (Abbott 1925).

Mortality of *T. absoluta* by a Single Dose of *E/Z* Mixtures of New Pyrethroids

The treatments were the *E/Z* mixtures of the new pyrethroids [9], [10], [11], [12], and [13], permethrin (used as an efficiency standard), and acetone as a control. The dose used was 30 µg of substance per mg of insect body mass. After treatment applications, 10 larvae were placed in each Petri dish, and the Petri dishes were placed in an incubator.

We evaluated insect mortality 48 h after the treatment applications. Mortality data were submitted to analysis of variance (SAS 2013). We selected the substances that caused more than 80% mortality to *T. absoluta* for the next bioassays. This criterion was used because, in Brazil, an insecticide is considered effective when it causes >80% pest mortality (Galdino et al. 2011; Gontijo et al. 2013).

Dose–Mortality Curves of *E/Z* Mixtures of New Pyrethroids to *T. absoluta*

For this experiment, the treatments consisted of the doses of substances and the controls consisted of equivalent doses of acetone. In a preliminary bioassay, we established the doses to be used for each substance. These doses were determined so that they cause 10–90% mortality of *T. absoluta* larvae (Galdino et al. 2011). In the final bioassay, we used the following doses (µg mg^{-1}): 0.5, 1.0, 1.5, 2.0, 2.5, 3.5, 4.5, 5.0, 7.0, and 9.0 of [9]; 0.5, 1.0, 3.0, 4.0, 5.5, 7.0, and 9.0 of

Table 1. Dose–mortality curves 48 h after permethrin application and *E/Z* mixtures of the new pyrethroids [9], [10], [11], [12], and [13] for the pest *Tuta absoluta*

Insecticide		*N*	Equation	χ^2	df	*P*
Permethrin		280	$Y = 4.77 + 3.16X$	1.73	5	0.885
E/Z mixtures of the new pyrethroids	[9]	400	$Y = 4.29 + 1.61X$	2.36	8	0.968
	[10]	280	$Y = 4.12 + 1.94X$	7.63	5	0.178
	[11]	360	$Y = 3.33 + 3.55X$	5.36	7	0.617
	[12]	320	$Y = 3.61 + 2.33X$	3.09	6	0.797
	[13]	360	$Y = 2.95 + 2.52X$	2.12	7	0.953

N = (number of insects used in the bioassay), *Y* (probit mortality), *X* (logarithm of the dose [µg of the substance per mg^{-1} of insect]).

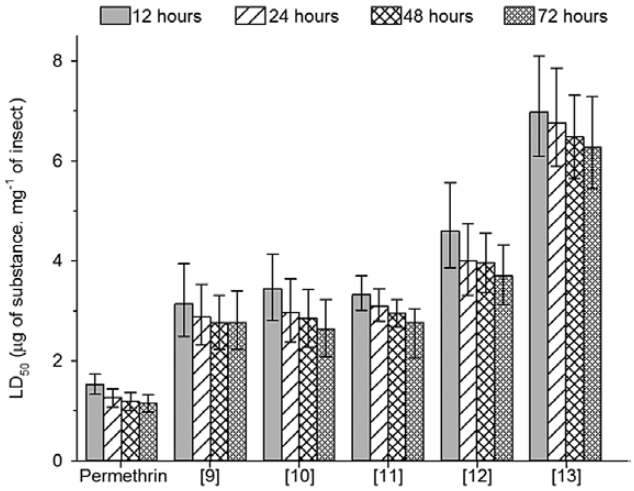


Fig. 1. LD_{50} of permethrin and *E/Z* mixtures of the new pyrethroids [9], [10], [11], [12], and [13] for the pest *Tuta absoluta* at 12, 24, 48, and 72 h after application. The vertical line segments represent the CIs of LD_{50} to the 95% probability level.

[10]; 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, and 5.0 of [11]; 1.0, 1.5, 2.5, 3.5, 4.5, 5.0, 7.0, and 10.0 of [12]; 1.0, 2.0, 3.0, 4.0, 5.0, 7.0, 9.0, 10.0, and 12.0 of [13]; and 0.5, 0.8, 1.5, 2.0, 2.5, 3.0, nd 4.0 of permethrin. After the treatment applications, 10 *T. absoluta* larvae were placed in each Petri dish, and the Petri dishes were placed in an incubator.

We evaluated the *T. absoluta* mortality at 12, 24, 48, and 72 h after the treatments. The corrected mortalities were submitted to Probit analysis (Finney 1971) using the PROC PROBIT feature in SAS (SAS 2013). The slopes that showed probabilities higher than 0.05 by χ^2 tests were accepted (Leite et al. 1998; Pereira et al. 2014). From these curves, the LD_{50} values of the substances were estimated for *T. absoluta* and the CIs for these characteristics at a 95% probability level for the 12, 24, 48, and 72-h intervals after the treatments. We compared the LD_{50} values of each substance as a function of time after the application to determine their speed of action. We also compared the LD_{50} values by substance to evaluate the relative effectiveness of each substance (Galdino et al. 2011; Moreno et al. 2012). The comparison was performed using the 95% CI from LD_{50} ratios (Wheeler et al. 2006).

Mortality of *T. absoluta* by the *cis* and *trans* Isomers of the New Pyrethroids

In this section of the study, four bioassays were made. In each bioassay, the treatments were the *cis* and *trans* isomers of one of the four new pyrethroids, permethrin, and acetone as a control. The *cis* and *trans* isomers tested in the first, second, third, and fourth bioassays were the new pyrethroids [9], [10], [11], and [12], respectively. In the first bioassay, we assessed the *T. absoluta* larvae mortality caused by the *cis* and *trans* isomers of the new pyrethroid [9], permethrin, and control (acetone) using a dose of 2.77 µg of substance per mg of insect body mass. This dose was used because it is the LD_{50} of the new pyrethroid *E/Z* mixture [9] 48 h after application. In the second, third, and fourth bioassays, the doses used were 2.85, 2.95, and 3.96 µg mg^{-1}, respectively. These doses were used because they are the LD_{50} values of the *E/Z* mixtures of the new pyrethroids [10], [11], and [12], respectively. We did not test the *cis* and *trans* isomers of the new pyrethroid [13] because, as discussed above, we were unable to separate them.

After the treatment applications, 10 *T. absoluta* larvae were placed in each Petri dish, and the Petri dishes were placed in an incubator. We evaluated insect mortality 48 h after the treatment applications. The mortality data from each bioassay were subjected to analysis of variance, and the treatment means were compared by Tukey's test at the $P < 0.05$ significance level (SAS 2013).

Results

The speed of action of the LD_{50} of permethrin and the *E/Z* mixtures of the new pyrethroids [9], [10], [11], [12], and [13] for *T. absoluta* did not vary along the timeline of 12, 24, 48, and 72 h after the topical application. However, these compounds showed a specific order of toxicity: permethrin was the most toxic, followed by the pyrethroids [9], [10], and [11], next, the *E/Z* mixture [12] and finally, but still important, the new pyrethroid [13] (Table 1; Fig. 1). This sequence is similar to the order of the atomic size/volume of the groups positioned in the *para*-position of the aromatic ring. The $–NO_2$ group is the highest volume, followed by –Br, –Cl, –F, and –H. These results indicate that the higher group in the *para*-position, the greater the toxicity of the pyrethroid.

The *cis* isomer of pyrethroid [10] and permethrin showed similar toxicity to *T. absoluta*. Moreover, this isomer showed a higher toxicity than its *trans* isomer (Fig. 2B). In contrast, the *cis* isomers of pyrethroids [9], [11], and [12] and the *trans* isomers of pyrethroids [9], [10], [11], and [12] were all less toxic than permethrin (Fig. 2). The *trans* isomers of pyrethroids [9] and [12] were more toxic to the tomato borer than were their *cis* isomers (Fig. 2A and D). Finally, both the *cis* and *trans* isomers of pyrethroid [11] showed similar toxicity to the pest *T. absoluta* (Fig. 2C).

Discussion

All five *E/Z* mixtures caused mortality levels similar to the commercial insecticide permethrin (the standard of efficiency in this study), which indicates the insecticidal potential of these molecules to be used as pesticides in agricultural crops.

According to Galdino et al. (2011) and Silva et al. (2011), insecticides that control *T. absoluta* in <48 h are considered compounds

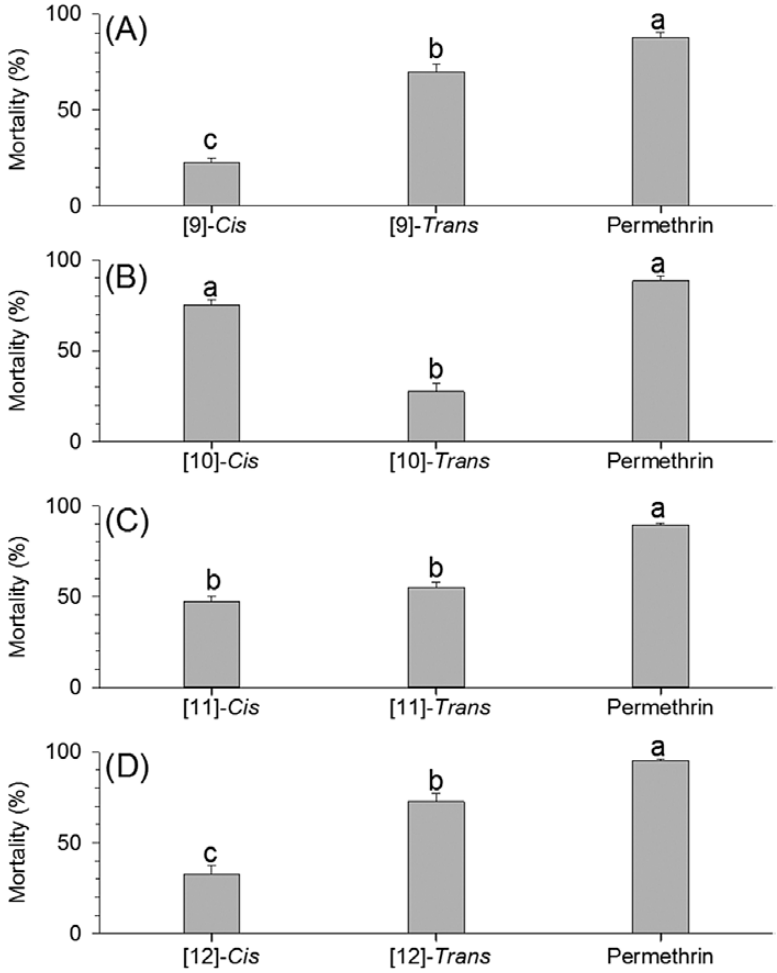


Fig. 2. Mortalities (Mean ± SE) of the pest *Tuta absoluta* by permethrin and the *cis* and *trans* isomers of the new pyrethroids in four bioassays. (A) Isomers of the new pyrethroid [9]. (B) Isomers of the new pyrethroid [10]. (C) Isomers of the new pyrethroid [11]. (D) Isomers of the new pyrethroid [12]. The dose of the substances in each bioassay was different and corresponded to the LD_{50} of the *E/Z* mixture of the new pyrethroid tested in the bioassay. Histograms followed by the same letter have averages that do not differ among themselves by Tukey's test at $P < 0.05$.

with a high speed of action. Therefore, the *E/Z* mixtures of the five new pyrethroids all exhibit a high speed of action, enabling fast control of *T. absoluta*, because their LD_{50} values did not change even 12 h after application. Insecticides that exhibit a high speed of action are important tools at times when an attack by *T. absoluta* is critical (Galdino et al. 2011, Silva et al. 2011), particularly when the pest is attacking fruit or when infestations break out (Galdino et al. 2011). Fruit attacks occur when the *T. absoluta* larvae migrate from the leaves, causing damage to fruit and, consequently, losses in productivity (Galdino et al. 2011). Thus, in these situations, the use of an insecticide with a high speed of action is essential to avoid losses from *T. absoluta* attacks ([Galdino et al. 2011, Silva et al. 2011).

The power of an insecticide is inversely proportional to the dose required to control its pest targets (Villeneuve et al. 2000). On one hand, based on this definition, all five *E/Z* mixtures of pyrethroids were less powerful than permethrin, which has a lower LD_{50} for *T. absoluta*. On the other hand, the *cis* isomer of pyrethroid [10] showed similar mortality to permethrin because it caused equal mortality to the pest. Therefore, there may be two possible uses for these new pyrethroids: 1) use of the *E/Z* mixtures or 2) use of the isomers that exhibit higher activity.

The commercial feasibility of an insecticide depends on many variables including the cost of synthesis, selectivity to nontarget organisms, toxicity to mammals, molecular stability, and compound power (Paula et al. 2000, Gradish et al. 2011). In this context, the power differences among the *E/Z* mixtures and the isomers do not rule out the use of these compounds as commercial insecticides; there are commercial insecticides up to 19 times less powerful than permethrin that are recommended for *T. absoluta* control in Brazil (MAPA 2016).

Variation in the power of the *E/Z* mixtures of the five new pyrethroids and their isomers is a function of characteristics such as molecular weight and polarity (Briggs et al. 1976, Stock and Holloway 1993). These characteristics affect the ability of the compounds to penetrate the insect cuticle, the insects' ability to metabolize the compounds, and the way in which the compounds interact with the action site (Georghiou and Saito 1983, Stock and Holloway 1993).

The penetration rates of compounds through insect cuticles are related to the cuticle thickness, the compounds' molecular weights and the similarity in polarity between the compound and the insect cuticle (Leite et al. 1998, Pereira et al. 2014). Heavy compounds tend to have lower penetration rates (Stock and Holloway 1993). However, this characteristic probably did not affect the power of the studied compounds because permethrin showed higher power, but its molecular weight is greater than any of the five new pyrethroids.

A similarity in polarity with insect cuticle components can affect the power of pyrethroids. In general, lipophilic compounds have the highest penetration rates into insect bodies (Leite et al. 1998, Pereira

et al. 2014). Thus, the high power of permethrin against *T. absoluta* might be associated with its more lipophilic characteristics.

The decomposition and excretion of compounds by insects can also contribute to a compound's power. Synthetic pyrethroids are esters, which are capable of hydrolyzing the ester group, producing acids and alcohol metabolites that are eliminated from the insect body. The hydrolysis of pyrethroids is related to the ease with which esterase enzymes act on these molecules (Soderlund et al. 2002).

The insecticidal activity of pyrethroids also depends on their steric configuration (Elliott and Janes 1978, Soderlund et al. 2002). In this research, the toxicity differences among the isomers confirm the importance of stereochemistry in the insecticidal activity of pyrethroids. This has also been found for such pyrethroids as phenothrin, permethrin, resmethrin and, especially, allethrin, in which the insecticidal activity of isomers can vary up to 100-fold (Soderlund et al. 2002). In addition, in this study, it was observed that the higher chemical group bound in the *para*-position of the aromatic ring increases the toxicity, probably this group interacts better with the active site or affect the ability of the compound to penetrate the insect cuticle.

In this research, we synthesized five new promising products for *T. absoluta* control and found that they are similar to permethrin in terms of mortality, efficiency, and fast action. Thus, these new insecticides constitute a potential alternative to currently available insecticides to manage this pest. It is important to point out that this is an initial study, but essential in which we assessed the biological activity of these five new compounds. Therefore, to assess their synthesis costs, soil half-life and the effects on humans and the environment more research should be performed. These features will highlight the promising nature of these new compounds.

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