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Synthesis Of Ibuprofen Derivatives And Evaluation Of The Effect On The Mortality Of The Gorgulho (Callosobruchus Maculatus) Of The Common Bean (Phaseolus Vulgaris)

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Abstract:*The insect Callosobruchus maculatus, is responsible for serious damages in the storage of grains of diverse cultures, among them, the one of the beans. Therefore the development of substances capable of being an alternative to minimize agricultural losses and thus contribute to food security of the population is a current necessity. Thus, the objective of this work was to perform the synthesis of ibuprofen derivatives and to evaluate their effect on mortality of common bean weevil. toxicity tests of the derivatives were carried out with the Callosobruchus maculatus weevil through direct contact for 48h.The synthesis of the derivatives presented good yields (65 to 95%) and it was possible to perceive that they have a bioactive effect against C. maculatus, with a mortality rate of up to 100% after 24 hours of applicationusing a concentration of 1 mg/mlof each derivative in separate experiments.With this it is possible to emphasize that the derivatives produced and evaluated can be promising as pest control agents.*

Keywords: *Ibuprofen, derivatives, Phaseolus vulgaris, Callosobruchus maculatus, Mortality.*

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I. INTRODUCTION

Common bean (*Phaseolus vulgaris*) is considered a food of great importance for human consumption because of its great nutritional value (Nichols et al., 2011). The cultivation of this species is characterized by the fact that it is carried out mainly by small farmers, for whom it represents an important source of income and subsistence. Brazil is the largest producer and consumer of beans in the world, followed by India. This basic food of the rural and urban populations of Northeast Brazil is considered the most important legume of grains and serves to supply part of the protein needs of the most deprived populations in Brazil (Azevedo et al., 2017; Cabral et al., 2011).

Therefore beans are a food considered popular in Brazil, being present in the menu of a large part of the population. Its consumption offers great advantages, since the grain presents high contents of minerals, carbohydrates, fibers, vitamins, besides the high concentration of proteins (Costa et al., 2006; Marino and João, 2009). However, between the stage of planting, commercialization and consumption, this grain is frequently attacked by pests that compromise its nutritional value, affecting also the price of this product, because with losses, the product supply in the market is reduced and, consequently , its price becomes higher, reflecting directly on food security, since grain is a staple food of the population, especially the poorest.(Toledo et al., 2017).

The presence of pests is noticed during planting and storage of the grain. Being that the reduction of the quality of the seeds of the bean during the storage depends on the conditions in which they are in the beginning of the storage and the control of the environmental factors(Green et al., 2017; Medeiros et al., 2007). Among the most frequently occurring pests, the caruncho or bean beetle (*Callosobruchus maculatus*) has great prominence.

The weevil, as it is popularly known, is not an exclusive pest of beans, attacking various crops like maize, wheat and rice during storage (Tomaz et al., 2007).

The weevil *Callosobruchus maculatus* (F.) (Coleoptera: Bruchidae) is a pest that infects pods all over the world in the fields, as well as stored seeds. Grain loss due to insect pests is a serious problem around the world. The eggs are placed in pods or directly in legume seeds, the insects usually spend the larval life inside the seed, digging cavities in which they feed. Usually pupation takes place inside the seeds, however, some insects of this family can fix their larvae outside the seed (Subramanyam and Hagstrum, 1995), thus reducing the commercial value of the grain with losses that can reach 90% depending on the storage time (Dongre et al., 1996; Tanzubil and Juss, 2016).

In order to control pest infestations, agricultural pesticides with various chemical compositions and toxicities are used, which leads Brazil to be one of the largest consumers of pesticides in the world, with a national market that has moved more than US $ 7 billion and represented 19% of the world market for pesticides. Therefore, it is of fundamental importance that research applied in the search for new substances, efficient in the fight against pests, should be developed and encouraged with the objective of eliminating or mitigating the damages caused by the intensive use of pesticides, replacing them with more biologically selective substances.(Castro et al., 2010; Tavares and Vendramim, 2005)

In order to optimize the physico-chemical properties of a drug, certain functional groups can be derived by means of a biorreversible process with small organic molecules, masking some undesirable characteristics without permanently changing the bioactive properties of the molecule. Such a strategy has been successfully applied to functional groups such as alcohols which, converted to esters, can be regenerated in vivo either chemically or enzymatically. This process is termed drug latency (Chin et al., 1999; Djurendić et al., 2014; Pang et al., 2017; Sun et al., 2016).

In this sense, ibuprofen is a drug that has aroused significant interest in the scientific community, since in addition to its recognized anti-inflammatory effect linked to its low cost and sale without prescription, it consecrates it as one of the most commercialized anti-inflammatory in Brazil and worldwide. This compound is therefore biologically active, and has been the precursor of derivatives with promising pharmacological properties, such as antimicrobials, gastroprotectors, enzyme inhibitors, among others(Abdulla, 2014; Gandomkar et al., 2015; Gundogdu-hizliates et al., 2014; Habibi et al., 2013; Kansara et al., 2009; Kong et al., 2014; Lolli et al., 2001; Pérez et al., 2017; Rashidi et al., 2008; Shu, 1998; Wang et al., 2014).

In view of the promising and recognized biological effects of ibuprofen and derivatives, the present work aimed to synthesize esters derived from ibuprofen by different synthesis routes and to evaluate the effect of these substances on mortality in bean weevil mortality, aiming to obtain new substances that are able to contribute to increase the storage time of the grains and to minimize the losses of the agricultural production.

II. EXPERIMENTAL PROCEDURE

1.1 Obtaining ibuprofen and the origin of the reagents.

The ibuprofen used were from the brand Neoquímica® 600mg with 30 tablets. The tablets were triturated and the powder placed in ethanol P.A under orbital shaking (150rpm) for two hours at room temperature. Then, vacuum filtration was performed for separation of the insoluble solids in ethanol. The liquid phase containing the ibuprofen was then concentrated in rotoevaporator under reduced pressure and the resulting solid characterized by gas chromatography coupled to mass spectrometry (90% yield).

1.2 Synthesis of ibuprofen derivatives

Substances 1 to 4: The amount of 1g ibuprofen was added in a 50 mL flask together with 20 mL alcohol (methanol, ethanol, propanol, isopropanol) and 1 mL HCl (35% m/v) in separate experiments. The reaction was refluxed for 2 hours at a temperature of 100°C (± 5 °C). The reaction was then concentrated on a rotary evaporator followed by the addition of 20 mL of hexane to the medium. The organic phase was then washed with 5x20 ml of water and then dried with anhydrous sodium sulfate (Na_2SO_4) and concentrated on a rotary evaporator.**Substance 5**: 2mmol (412mg) of ibuprofen were diluted in 10mL of dichloromethane together with 2mmol (412mg) of dicyclohexylcarboximide (DCC) and 50mg of dimethylaminopyridine (DMAP) and 1mmol (150mg) of carvacrol. The reaction was kept under stirring at room temperature for 24h and then vacuum filtered. The resulting liquid phase was treated (3x5mL) with 5% aqueous sodium bicarbonate solution followed by treatment (3x5mL) with 5% aqueous HCl solution and then with water (3x5mL). The organic phase was then dried over anhydrous sodium sulfate(Na_2SO_4) and concentrated on a rotary evaporator(Silva et al., 2018).

1.3 Purification of Derivatives

The products obtained with the reactions were purified on a chromatographic column using as adsorbent silica gel 60 (Φ = 0.025-0.020 mm), brand VETEC. The length and diameter of the columns varied according to the amount of sample to be purified and of silica used. As eluent, hexane and ethyl acetate of the Synth analytical standard (P.A.), pure or in binary mixtures in the ratio 8:2 v/v respectively and /or varying as required.The column reactions and eluates were analyzed by thin layer chromatography (TLC). For this purpose, glass plates coated with a layer of approximately 0.5 mm thickness of silica gel 60 (Φ = 0.004-0.005 mm) of the VETEC brand doped with 0.01% flurescein. After elution of the substances in (TLC) with hexane: ethyl acetate (8: 2 v / v) binary solvent mixture, the substances were visualized by use of UV light.

1.4 **Characterization of products**

Gas chromatography coupled to mass spectrometry (GC/MS) was performed on Shimadzu GC/MS apparatus, model QP2010SE Plus,using a 30 m Rtx®-5MS (95% dimethylpolysiloxane and 5% diphenyl) capillary column, 0.25 mm internal diameter and 0.1 μm film thickness of the fixed phase.The injector and detector temperatures were 240 and 280°C respectively.Column conditions: 60°C to 80°C at 5° C min^{-1}, remaining for 3 minutes, then 80°C min^{-1} to 280°C at 300°C min^{-1} remaining at this temperature for 10 minutes, using He as the drag gas with flow rate of 1.60 mL min^{-1}. The analysis with the mass detector was in scan mode with analysis time in 23.67min.The mass spectra recorded in the range of 35 to 500 daltons per electron impact (EMIE) with ionization energy of 70eV (voltage of 1.5 KV), quadrupole type analyzer and source of ions at 240ºC.

2.5 **Evaluation of the toxicity of the derivatives against the bean weevil**

The adult insects of *C.maculatus* were taken from stock keeping with bean grains, at 30 ° C in the laboratory of the Federal Institute of Education, Science and Technology of Rio Grande do Norte, Apodi Campus. The breeding was maintained in 2,5 L pots, with a perforated screen, containing 1 kg of beans, and every 90 days the material was changed, removing adult insects to initiate the infestation in new pots. The substances evaluated (ibuprofen and derivatives 1 to 5) were diluted in acetone at a concentration of 1 mg / mL and then 1.0 mL of these solutions were added in circular 9cm diameter filter paper, which were then placed in plates Petri of 9,0cm in diameter. The negative control was performed with the same amount of pure acetone.After evaporation of the acetone at room temperature (approximately 30 minutes), 10 adult insects were placed per plate in 3 replicates, and the mortality of the insects was evaluated during the period of 24 and 48 hours.The same procedure was carried out with the negative control and the control (only insects, without solvent). In the evaluation of insect mortality, all insects that moved any part of the body, even those that only moved slowly when stimulated, were considered alive (modified from(Nagawa et al., 2015)). The percentage of mortality of the treatments was obtained through equation 1.

Equation 1: Mathematical representation used to obtain the percentage of mortality of *C. maculatus.*

$$\mathrm{M}(\%) = \frac{(\mathrm{N°Sample} - \mathrm{N°control})}{\mathrm{Total\ number\ of\ insects}} x100$$

Where M (%) is the percentage of mortality presented by the substance, N°sample is the average number of dead insects in the presence of the derivatives (1 to 5), N°control is the mean number of dead insects in the control (without the presence of the derivatives) and Total number of insects corresponds to the number of insects added in each test.

III. RESULTS AND DISCUSSIONS

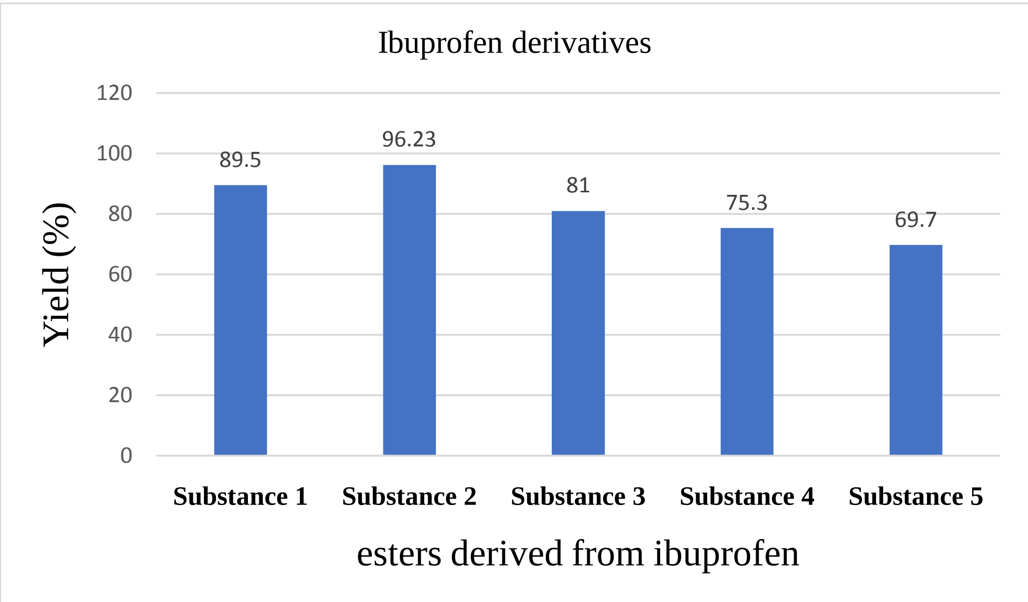
3.1. Production of Ibuprofen derivatives

Figure 1 shows the reaction scheme of the syntheses of the derivatives of ibuprofen through the esterification reaction, which resulted in the production of 5 derivatives.

Figure1. Reaction scheme of synthesis of ibuprofen derivatives through esterification reaction.

The yields of the reactions (Figure 02) show that, in general, a better conversion rate is achieved when the carbon chain of the hydroxyl group attached to the alcohol has less steric hindrance, so the esterification reaction conducted with the alcohols methanol and ethanol, which are the smaller and simpler molecules resulted in a better yield. On the other hand, isopropanol and carvacrol, with more hindered hydroxy groups, showed lower yield.

Figure2. Graph showing the yield of esterification reactions performed with ibuprofen for the synthesis of derivatives 1 to 5.



Through the analysis of the products by gas chromatography coupled to mass spectrometry (GC-MS) it was possible to show the characterization of the esters produced. Derivative **1** showed a fragmentation profile showing the molecular ion peak in m /z 220, compatible with the molar mass of the compound being expected (220g/mol). The base peak was found in m /z 161 (M-59), consistent with the formation of the benzyl cation in the molecule after loss of the carboxylate group.The retention time of the substance was 11.70 min.This fragmentation profile with base peak in m/z 161 was diagnosed in the analysis of all derivatives from **1** to **5**, and the latter (**5**), in addition to the molecular ion peak in m/z 338 also showed a peak in m/z 188 with the same base peak intensity (m/z 161). The fragmentation profile of each molecule can be visualized in the table 01 with the respective retention times.

Table1Characterization data through the fragmentation profile in mass spectrometer and retention time of the derivatives of ibuprofen.

Substance	Retention time (min)	Fragmentation Profile
Ibuprofen	12.00	206 (M), 161(100), 128, 119, 107, 91, 77, 65, 41.
(**1**)	11,70	220 (M), 177, 161(100), 145, 117, 91, 77, 59.
(**2**)	12,60	234 (M), 191, 161(100), 117, 105, 91, 77, 43.
(**3**)	13,58	248 (M), 205, 161(100),145, 119, 91, 57, 43.
(**4**)	12,53	248 (M), 205, 161(100), 145, 131, 119, 105, 91, 77, 57, 43, 41.
(**5**)	14,48	338 (M), 188(100), 161(100), 145, 117,91, 57, 43.

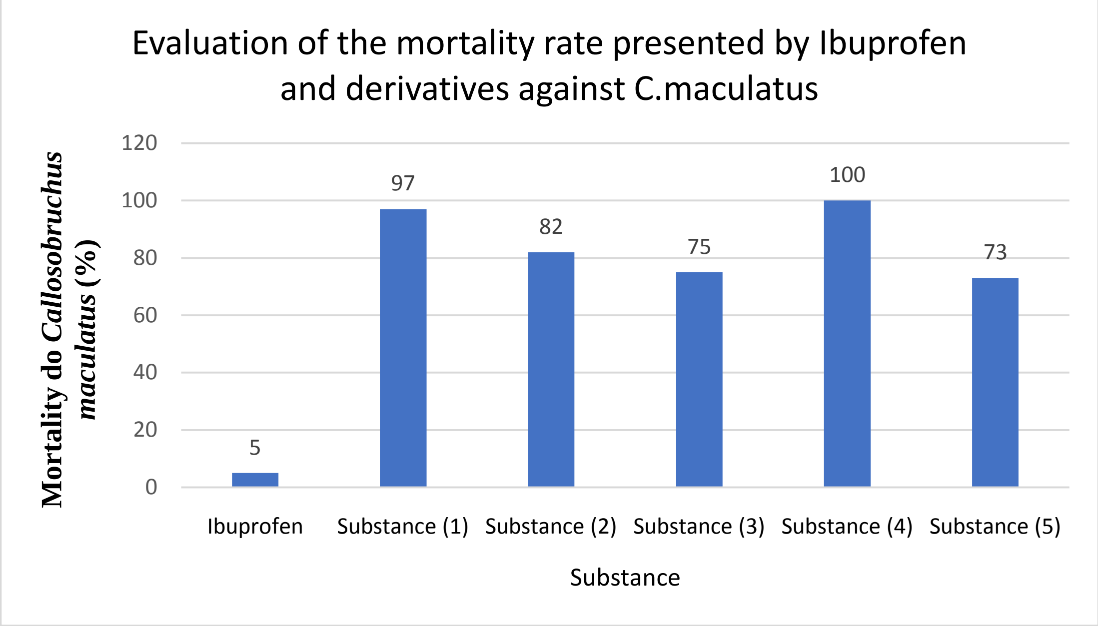
3.2 Evaluation of mortality of weevils (*Callosobruchus maculatus*) against ibuprofen and derivatives.

The evaluation of the efficiency of ibuprofen and derived esters against weevil control was carried out from the characterization of the insect involved in the study, where the adults of this species have dark coloration, presenting elliptic striated (Figure 3).

Figure3. Enlarged image of the insect (*Callosobruchus maculatus*) used in the evaluation of mortality against ibuprofen and derivatives.

The evaluation of the potential of ibuprofen and derivatives against the control of the boll weevil demonstrated a promising potential with percentages of mortality reaching 100% (Figure 04).Noting the significant change in the ability to cause insect mortality of all derivatives produced when compared to ibuprofen, which showed a low toxicity, only 5% mortality, in insects. Among the derivatives, the isopropyl ester was the most efficient in the insect combat, with mortality of 100%.

Figure4. Graph showing percentages of mortality of the weevil against ibuprofen and derivatives.



The derivative with the lowest percentage of mortality was the ester formed by the condensation of ibuprofen with carvacrol (**5**), even though it presented 73% of mortality, that is, it was also very active. The same was followed by n-propyl ibuprofenate (**3**), which presented a mortality of 75%. The esters (**1** and **2**) formed by ibuprofen and the alcohols methanol and ethanol presented 97 and 82% mortality in relation to the insect.These mortality rates are higher than those reported in the literature, which describe the use of various commercial substances in pest control, reporting a maximum mortality rate of 85.5% with rotenone use among several other commercial products evaluated against the insect, *C. maculatus*(Azevedo et al., 2007)**.**Ibuprofen derivatives also show higher toxicity to *C. maculatus* than the use of vegetable oils (Law-Ogbomo and Egharevba, 2006; Loni and Panahi, 2015; Tofel et al., 2017), secondary metabolites(Nenaah, 2013)and microorganisms(*Beauveria bassiana* e *Metarhizium anisopliae)*in control *C. maculatus*, reaching mortality of 80%(Mahdneshin et al., 2011). However, it is important to note that, from the experimental point of view, the synthesis, commercialization and storage of ibuprofen and derivatives has the advantage of being a simpler process than the isolation and cultivation of microorganisms.

IV. CONCLUSION

All Ibuprofen derivatives were effective in controlling the *Callosobruchus maculatus* pest, with mortality rates varying from 73% to 100%. It is possible to conclude that the derivatives produced have characteristics that are toxic to this species more pronounced than the drug that was the starting compound, ibuprofen, and therefore the study promotes results that may contribute to expand the stock of substances available for the control of pests, from the synthesis of the derivatives of ibuprofen.Important that studies that contribute to identify bioactive compounds produced from substances of permitted and consolidated use contribute to diversify the number of products used in pest control in order to obtain less toxic substances to man and environment and more selective in the specific combat of certain pests. As a result, the chemical synthesis reinforces its contribution to several sectors, including the pharmaceutical, agricultural and food industry, being decisive for the well-being of society and the environment.

Conflict of interest

There is no conflict to disclose.

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