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Investigation of the participation of hydroxamic acid derivatives in the protection of *Malus domestica* Borkh. from pathogens

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Abstract
The aim of the article is to show the response to biotic stress (in particular, fungal attack) using hydroxamic acid derivatives in the example of fruit plants. Two new compounds were synthesized at the Institute of Organic Chemistry of the NAS of Ukraine: compound No. 2 ($C_{14}H_{20}N_2O_4S$) and No. 3 ($C_{14}H_{20}N_2O_4$), compound No. 1 $C_{12}H_{16}N_2O_4S$ was used as a control. Synthesized compounds No. 2 and No. 3 were tested *in vivo* on prototypes, representatives of the genus *Malus* Mill. are damaged by pathogenic fungi. An accumulation in the content of secondary metabolites after treatment with the compound $C_{12}H_{16}N_2O_4S$ and a decrease after treatment with the compounds $C_{14}H_{20}N_2O_4S$ and $C_{14}H_{20}N_2O_4$ were noted in the sites of hydroxamic acid application. Since substances of the flavonoid series are phytoalexins, the lesion of the plant by cytosporosis and powdery mildew leads to an increase in the content of flavonoids. Compounds No. 2 and No. 3 inhibit the development of pathogenic fungi, so there is no need for additional synthesis of flavonoids, compound No.1 does not have pronounced fungicidal properties. Considering cut the primary results, we can judge further prospects for the study and use of synthesized hydroxamic acids ($C_{14}H_{20}N_2O_4S$) and ($C_{14}H_{20}N_2O_4$).

Keywords: hydroxamic acid, protection, *Malus,* flavonols, anthocyanins, pathogens

Introduction

Malus domestica Borkh is the most common plant species and is very important from an economic, cultural and nutritional point of view [15], [16], [33]. It is for healthy and high-quality apple fruits to enter the market that it is necessary to include new approaches to the preservation of healthy plants.

This study demonstrates an attempt to deactivate bark fungal disease on twenty-year-old apple trees using new hydroxamic compounds.

For the first time, ferruginous hydroxamates during the fermentation of *Ustilago sphaerogena* were isolated by Emery and Neilands in 1959. Further research in this industry was carried out by Abe (1960), followed by Coutts (1967), who discovered that hydroxamic acids are strong chelating agents, forming insoluble complexes with many metals. In turn, Neilands (1967) also showed that these compounds are complex ligands that play an important role in metabolism in microorganisms.

Researchers Alklewlcz et al., (1957) showed that *in vitro* salicylhydroxamic acid, benzohydroxamic acid, 2-hydroxy-3-naphtohydroxainlc acid and chloro-derivatives of phenoxyacetohydroxamic acid have strong fungicidal activity.

In turn, Eckesteln and Urbanskl (1956) found that some aryloacetohydroxamic acids have fungicidal activity. Shortly thereafter, Ecsteln and Czerwinskafejgin (1959) noted that aryloxyacetohydroxamic acid may or may not have fungicidal activity depending on radical substitution. After these conclusions, many more researchers sent their tests to this industry, for example Arct et al., (1964) tested aryloxyalkangydroxamic acids, Eckesteln and Domanoka (1965) reported on the fungicidal activity of hydroxylic acid derivatives, Mostafa et al. (1966) observed the fungicidal activity of some thiohydroxamic acids. Also, Abe (1960) showed bactericidal activity, which has a relationship between antibacterial activity and chelating activity of cyclic hydroxamic acids. For the first time in a review on acyclic hydroxamic acids, Coutts (1967) concluded that their antimicrobial activity is associated with their ability to chelate metals and make them inaccessible to the growth of microorganisms.

The study of hydrolysis of hydroxamic acids was first started by Bemhelm in 1964. He studied the enzymatic hydrolysis of hydroxamic acids and concluded that there were at least two enzymes: lipase, hydrolyzing straight-chain acids, and an enzyme acting on succinyl and glutaryl monohydroxamates, but not on the corresponding malonyl and adipyl derivatives. Lipase acting on hydroxamates of monocarboxylic acids hydrolyzes those whose chain length is from five to ten carbons.

Hydroxamic acids were found in plants [36] during the study of fungal diseases of rye, after some time, they were also found in corn and are associated with resistance to the European corn petrel *Ostrinia nubilalis* (Hübner). That is why numerous breeding programs were aimed at creating maize varieties with high levels of hydroxamic acids that were resistant to leaf feeding by the first brood of the corn beetle [17], [18]. Hoffman and Hofmanovä (1969), showed that hydroxamic acids are present in intact plants in the form of glucosides, which are cleaved to active aglucones by glycosidases when tissue is damaged. During adaptation to biotic factors, plants have developed many defense mechanisms against pathogenic microorganisms, which include the production of secondary metabolites [34], [35], [26]. One of these mechanisms is the synthesis of phytoalexins.

Phytoalexins are low molecular weight antimicrobial compounds that are biosynthesized by plants in response to various forms of stress, including microbial attack [6]. For the first time, studies of phytoalexins focused mainly on the identification of antifungal compounds and correlations with disease resistance. Phytoalexins were first described by Mueller and Boerger (1940) during studies of the interaction of *Phytophthora infestans* and *Solanum tuberosum* (potato). Since then, the wide variety of phytoalexins isolated from very diverse plants indicates that their chemical structures are usually related within the same plant family [9]. For example, many phytoalexins from legumes have an isoflavonoid skeleton, cruciferous plants produce indole alkaloids, cereals produce mainly cyclic hydroxamic acids and diterpenoids, while plants of the *Solanaceae* family produce sesquiterpenoids and polyacetylenes. The importance of phytoalexins as mechanisms of protective compounds has also been investigated in tobacco (*Nicotiana tabacum*), tomato (*Lycopersicon esculentum* Mill.), and alfalfa (*Medicago sativa*) also (*Vitis vinifera*). Thus, many studies support the idea that phytoalexins play an important role in protecting plants from pathogens such as bacteria and fungi. Recently, world researchers have provided evidence that phytoalexins in plants can accumulate at the right time, at the right concentration, and in the right place to be effective in fighting diseases [19].

The purpose of the article is to study the new excretion of hydroxamic acids in the natural environment, in particular on mature apple trees, the bark of which is affected by fungus of different stages. To study the reaction after application of a chemical drug, and specifically to determine the accumulation of secondary metabolites before and after. Taken together, the results demonstrate a potential strategy for using hydroxamic acids to treat various aspects of fungal diseases in plants.

Material and Method

Fruit plants from the collection of the Department of acclimatization of fruit plants of the M.M. Gryshko National Botanical Garden of the NAS of Ukraine, located on the southeastern outskirts of Kyiv on the Pechersk slopes of the low Kyiv hills in the in the tract Zverinets. The main type of soil on the territory of the NBG is a dark gray podzol, lying on forest rocks and brown clays (the amount of humus is 0.5-2.0%).

The plant material was used on 20-year-old apple trees of the *Malus domestica* cv. *Slava Pobeditelyam* of the collection of Department of Fruit Plants Acclimatization in M.M. Gryshko National Botanical Garden (NBG) of the National academy of sciences (NAS) of Ukraine.

The studies were carried out twice. The first attempt to apply the solution was carried out on 27.05.2021, after 60 days (27.07.2021) samples were taken from the application sites for laboratory analysis (Figure 4-6). The dosage used during the study was 2g per 5 liters of water, and 2g per 1.5 liters of water.

A second attempt was carried out on 3.09.2021, after which, 30 days (4.10.2021) later, samples of the objects of study were taken and transferred to the laboratory. We present the structures of the compounds used in the studies (Figure.1-3).

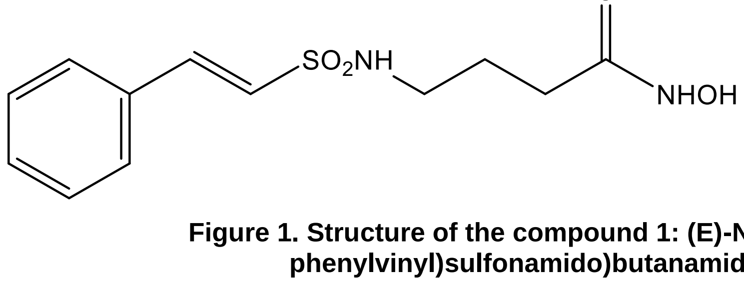

Figure 1. Structure of the compound 1: (E)-N-hydroxy-4-((2-phenylvinyl)sulfonamido)butanamide

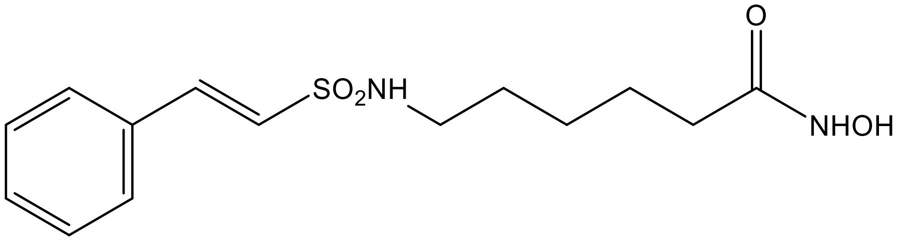

Figure 2. Structure of the compound 2: (E)-N-hydroxy-6-((2-phenylvinyl)sulfonamido)hexanamide

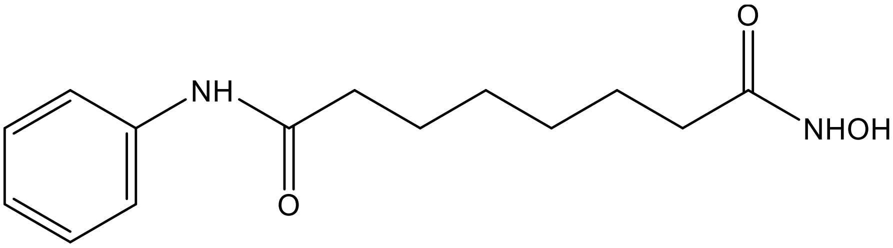

Figure 3. Structure of the compound 3: N¹-hydroxy-N⁸-phenyloctanediamide (suberoylanilidhydroxamic acid, SAHA)

The quantity of anthocyanins was determined using a spectrophotometric method at a wavelength of 530 nm, using alcohol extraction from a homogenate of plant raw materials acidified with 3.5% hydrochloric acid [23].

Quantitative determination of flavonols was carried out according to a technique based on their ability to form a colored complex with an alcoholic solution of aluminum chloride, which causes a bathochromic shift in the long-wave absorption band and, at the same time, gives the main maximum absorption at a wavelength of 390 nm. The mixture of solutions of aluminum chloride and acetic acid served as a control [3].

The number of parallel measurements was 3. The accuracy of the method was in the range of 2,3–4,8%. The obtained data were presented in mg/100 g of dry matter (DM). The optical density of all the studied solutions was measured using a Zalimp KF 77 spectrophotometer (Poland).

Statistically processed data we displayed in graphs as arithmetic means and their standard errors. The statistical analysis was performed with IBM SPSS Statistics, released 26.0.0.1.

Results and Discussion

According to the world's leading scientists [37], the hydroxamine group arises because of the oxidation of a free or bound amino group. Compounds containing one, two or three hydroxamic acid groups per molecule act as growth factors, antibiotics, cell division agents or tumor inhibitors [27], [28]. They also contribute to resistance to diseases and insects, tolerance to herbicides, and regulation of plant growth and mineral metabolism [1], [24]. Some synthetic hydroxamic acids promote plant growth, improve soil quality, etc. [30]. Hydroxamic acid derivatives also exhibit a variety of pesticide activities such as herbicides, fungicides, insecticides, etc. [4], [22].

In our work on the example of *Malus domestica* cv. *Slava Pobeditelyam*, the alleged fungicidal activity of hydroxamic acids was investigated.

Three compounds were involved: (E)-N-hydroxy-4-((2-phenylvinyl)sulfonamido)butanamide, (E)-N-hydroxy-6-((2-phenylvinyl)sulfonamido)hexanamide and the model compound N¹-hydroxy-N⁸-phenyloctanediamide (subaroylanilidohydroxamic acid, SAHA). This compound has fungicidal activity, acting as an inhibitor of histondiacetylase [14], [13], [29]. This promotes the synthesis of repressor proteins that bind DNA promoters in pathogenic fungal cells and thus inhibit mRNA synthesis at the transcription initiation stage [12], [10]. The experiment was conducted in the second half of July – early August 2021. Experimental plants with an aqueous solution of hydroxamic acids in a ratio of 1:100. Three model trees with pronounced fungal diseases were selected, and bark samples were taken before application of hydroxamic compounds, and the second sampling took place 30 days after the application of the solution (Figure 4-6). In addition to the laboratory study, field observations were also conducted. During the field observations, it was noted that the condition of the research objects improved markedly after 30 days, and fungal diseases became less

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noticeable, indicating the active action of compounds in the fight against fungal diseases specifically on the bark of representatives of the genus *Malus* Mill.

The state of the bark before the research

The condition of the bark 30 days after application. Compound No 1 ($C_{12}H_{16}N_2O_4S$)

Figure 4. The difference before and after applying compound No 1 ($C_{12}H_{16}N_2O_4S$)

The state of the bark before the research

The condition of the bark 30 days after application. Compound No 2 ($C_{14}H_{20}N_2O_4S$)

Figure 5. The difference before and after applying compound No 2 ($C_{14}H_{20}N_2O_4S$)

The state of the bark before the research

The condition of the bark 30 days after application. Compound No 3 ($C_{14}H_{20}N_2O_4$)

Figure 6. The difference before and after applying compound № 3 ($C_{14}H_{20}N_2O_4$)

Bark samples were taken before the start of the experiment and, after loading with the studied compounds, were taken to the laboratory and tested for the presence of flavonols and anthocyanins, since these are secondary metabolites produced by plants as a defense against biotic and abiotic factors. In this case, the gyroxamic acids were investigated for their use in fungicidal purposes.

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Analyzing Figure 7, namely the study with compound No. 1, it is well seen that the plants themselves tried to develop defense mechanisms against pathogenic diseases by trying to produce more flavonols, that is, compound No. 1 has no clear effect on inhibiting the growth of fungal pathogens of the bark of the model object of study. Compound No. 2 had a clear correlation of flavonol content before and after the application of the aqueous solution with the addition of compound No. 2 d=32.1 mg/100 g of dry matter. Compound No. 3 had no effect before and after application to the model object of study.

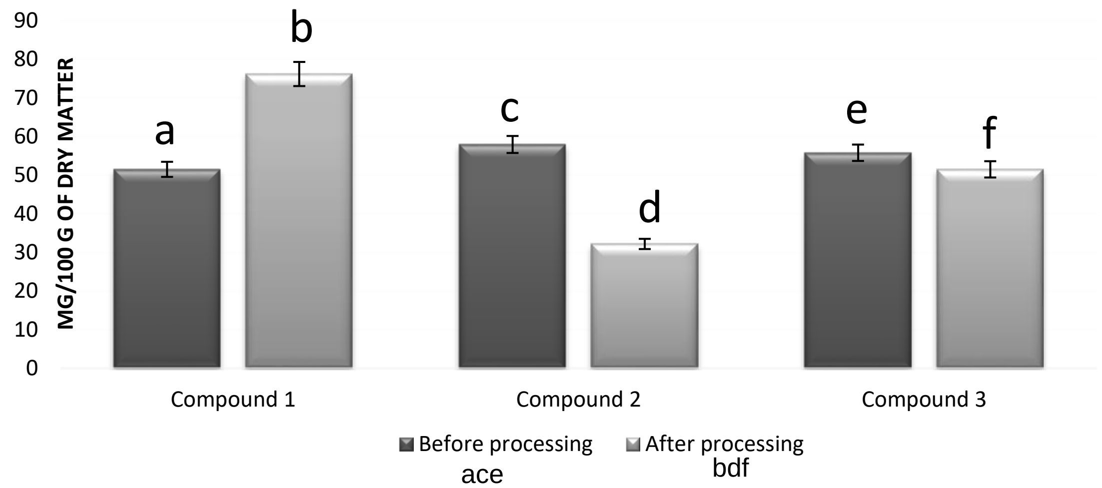

Figure 7. The content of flavonols in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

Consequently, according to the decrease in flavonols content in the bark of *Malus domestica* cv. *Slava Pobeditelyam* after the application of three compounds, it was found that the greatest effect had compound No. 2 ($C_{14}H_{20}N_2O_4S$). Therefore, it is promising for further study.

Laboratory studies are supported by the theory because if we analyze the structures of compound No. 1-3, we can note that for the manifestation of fungicidal activity it is necessary to have a carbon chain of 6-8 atoms in the structure. Compound No. 1 has only 3 carbon atoms, which is not enough to exhibit fungicidal activity.

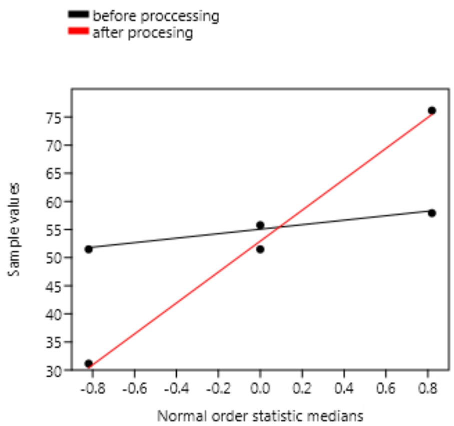

Figure 8. Normal probability plot content of flavonols in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

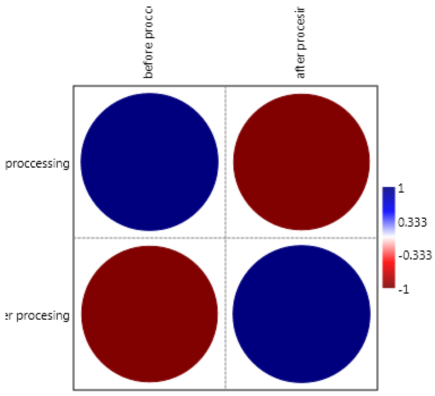

Figure 9. Pearson correlation coefficient content of flavonols in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

Analyzing the normal probability diagram of the content of flavonols before and after the experiment, the following results were obtained: before the application of substances r=0.9819, after r=0.9985 (Figure 8). According to the results of the Pearson correlation analysis, r=0.086, p>0.05 (Figure 9).

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For a similar purpose, the three hydroxamic acids described above were examined for their anthocyanin content in model test objects (Figure 10). Compound No. 1 showed no evidence of an effect on suppression of fungal growth of measles. Compound No. 3 showed little effect, as evidenced by a decrease in anthocyanin content f=26.0mg/100 g of dry matter

Compound No. 2 showed the highest correlation in reducing the number of anthocyanins in apple tree bark 30 days after the solution was applied d=20.5 mg/100 g of dry matter, thus confirming the fact that compound $C_{14}H_{20}N_2O_4S$ counteracted the development of bark fungal lesions, and the plant no longer needed to produce large amounts of anthocyanins. For a similar purpose, the three hydroxamic acids described above were examined for their anthocyanin content in model test objects (Figure 10). Compound No. 1 showed no evidence of an effect on suppression of fungal growth of measles. Compound No. 3 showed little effect, as evidenced by a decrease in anthocyanin content. Compound No. 2 showed the highest correlation in reducing the number of anthocyanins in apple tree bark 30 days after the solution was applied, thus confirming the fact that compound $C_{14}H_{20}N_2O_4S$ counteracted the development of bark fungal lesions, and the plant no longer needed to produce large amounts of anthocyanins.

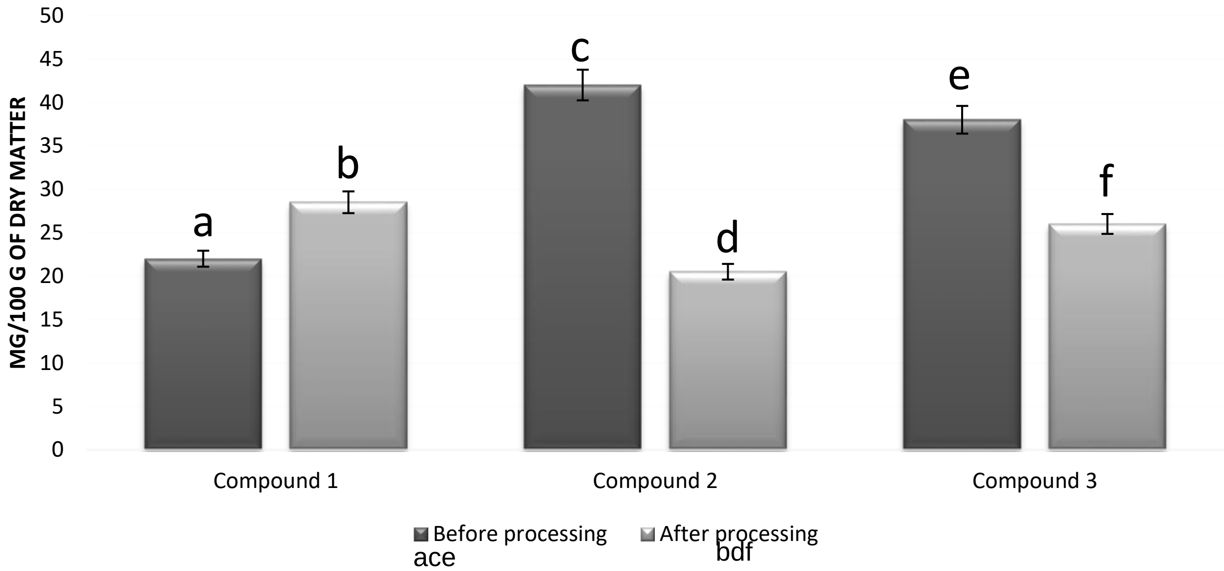

Figure 10. The content of anthocyanins in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

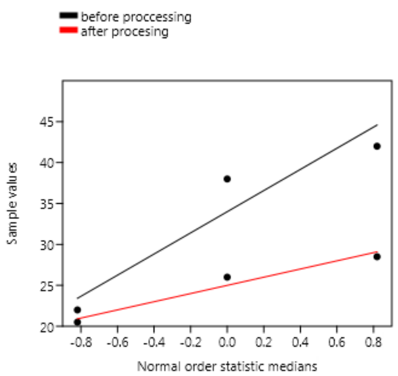

Figure 11. Normal probability plot content of anthocyanins in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

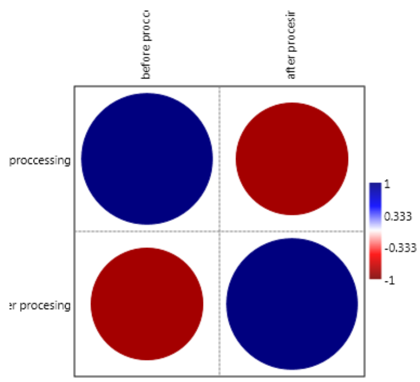

Figure 12. Pearson correlation coefficient content of anthocyanins in the bark of *Malus domestica* cv. *Slava Pobeditelyam* when treated with hydroxamic acids with suspected fungicidal activity

Analyzing the normal probability diagram of the content of anthocyanins before and after the experiment, the following results were obtained: before the application of substances r=0.9449, after r=0.9774 (Figure 11). According to the results of the Pearson correlation analysis, r=0.348, p>0.05 (Figure 12).

Investigation of the content of flavonols and anthocyanins in the bark of the studied plants *Malus domestica* cv. *Slava Pobeditelyam*, showed an increase in the content of these metabolites after treatment with compound No. 1 and a decrease in their amount after treatment with compounds No. 2 and No. 3 Since the substances of the flavonoid series are phytoalexins, the defeat of the plant by cytosporosis and powdery mildew leads to an increase in the content of flavonoids. That is, compound No. 1 does not have clearly expressed fungicidal properties. Compounds No. 2 and No. 3 lead to a decrease in the content of flavonoids, which may mean the fungicidal activity of these compounds. In this case, compounds No. 2 and No 3 inhibit the development of pathogenic fungi, so there is no need for additional synthesis of flavonoids.

Many plant defense mechanisms against pathogens involve the production of secondary metabolites, which may be constitutive, phytoanticipins [35], [36], [26], or inducible phytoalexins [32], [9], [5], [24].

In the literature, we found examples that show the mechanisms of tolerance and their role in phytopathogenic fungi. These studies were first described by VanEtten et al., (2001). It is as a defense that plants accumulate phenolic compounds that have a huge spectrum of action, including antimicrobial properties against fungi, bacteria and viruses [24].

Secondary metabolites or phenolic compounds slow down the growth of fungi by reacting with proteins and causing loss enzymatic function. Moreover, they limit viability of pathogens and can be deposited inside cell walls as an important first line of defense against penetration and infection by fungi [31]. As shown in our studies, compound No. 2 ($C_{14}H_{20}N_2O_4S$) could suppress the development of fungal diseases in plants and also had a good effect on slowing down the growth of mosses on the bark of the study objects.

Using apple trees as an example, this study attempted to study the development of self-defense mechanisms against various fungi, which will lead to a better understanding of the interactions between plants and their pathogens.

Which, in turn, will make it possible to develop antifungal drugs (for example, using compound No. 2 ($C_{14}H_{20}N_2O_4S$)) that are selective against a specific plant pathogen.

Conclusions

Based on the biological importance of hydroxamates, there is a need to develop synthetic methods and reagents for hydroxamic acids to obtain products with good yields under mild and environmentally friendly conditions. It was for this purpose that two new compounds were developed at the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine for further testing on plant material. Primary testing of newly introduced hydroxamic acids was carried out on plants of the genus *Malus* Mill. and by determining the secondary metabolites, the protective reaction of the plant organism to biotic stress was shown. Thanks to this study it was found that compound No. 2 ($C_{14}H_{20}N_2O_4S$), could suppress the development of fungal diseases in plants, so it has quite promising potential for further research and introduction into the production of a new preparation based on hydroxamic acids with fungicidal effect.

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