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New functionally substitutes cyclopropanecarboxylic acids as ethylene biosynthesis innovative regulators

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ABSTRACT

Background: Derivatives of small carbocycles (cyclobutanes and cyclopropanes) are known as bioactive molecules. Both their natural and synthetic representatives have multiple applications. Particularly, 1-aminocyclopropane-1-carboxylic acid (ACC) serves as the well-studied ethylene biosynthesis precursor. The development of new functionally substituted cyclopropane carboxylic acids, which show promise as effective inhibitors of ethylene biosynthesis, is crucial for regulating the plant cycle and preserving the quality of fruits and vegetables.

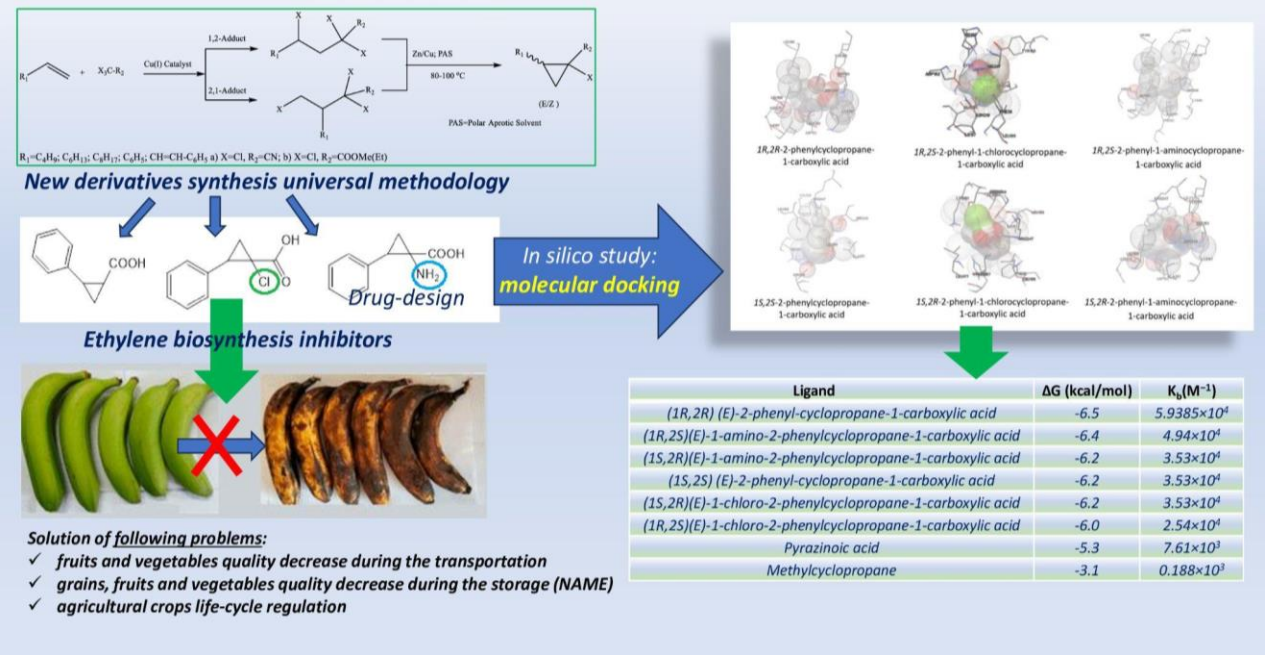
Objectives: This research focused on the in-silico studies aimed at developing a universal and affordable methodology for synthesizing new analogs of ACC and assessing their modulating activity on ethylene biosynthesis in plants. The findings from this in silico research provide a foundation for the upcoming in vitro studies.

Results: The elaborated efficient catalytic system [Cu(I) salt/amine/DMSO] enabled the synthesis of model compounds under mild conditions, resulting in increasing yields up to quantitative levels. For bioactivity preliminary assessment we performed *in silico* research of newly synthesized (*E*)-2-phenyl-1-chlorocyclopropane-1-carboxylic acid and drug-design an appropriate 1-amino-derivative as the inhibitor of 1-aminocyclopropane-1-carboxylate

oxidase 2 (ACO2) of *Arabidopsis thaliana*. Docking results showed certain advantages of the newly synthesized compound in comparison to well-known inhibitors of ethylene biosynthesis.

Conclusions: The recommended synthetic technology has increased efficiency in yield quantification. In silico studies, a high affinity for ACO2 has been demonstrated. The synthesized compounds exhibit superior characteristics compared to widely used market preparations for regulating ethylene biosynthesis. More detailed comparative in vitro studies are planned.

Key words: plant growth regulation, cyclopropane carboxylic acids, ethylene biosynthesis inhibitors, molecular docking, atom transfer radical addition (ATRA), Cu(I) Complex catalyst.



Ligand	ΔG (kcal/mol)	$K_b(M^{-1})$
(1R,2R) (E)-2-phenyl-cyclopropane-1-carboxylic acid	-6.5	5.9385×10^4
(1R,2S)(E)-1-amino-2-phenylcyclopropane-1-carboxylic acid	-6.4	4.94×10^4
(1S,2R)(E)-1-amino-2-phenylcyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1S,2S) (E)-2-phenyl-cyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1S,2R)(E)-1-chloro-2-phenylcyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1R,2S)(E)-1-chloro-2-phenylcyclopropane-1-carboxylic acid	-6.0	2.54×10^4
Pyrazinoic acid	-5.3	7.61×10^3
Methylcyclopropane	-3.1	0.188×10^3

Graphical Abstract: New functionally substitutes cyclopropanecarboxylic acids as ethylene biosynthesis innovative regulators

INTRODUCTION:

Ethylene is one of the most important plant hormones [1]. This gaseous compound is important for the development and regulation of plants. Ethylene biosynthesis is significant not only as the agent of the growth processes regulation but also, as the stress-response processes in plants. Ethylene directly regulates various physiological processes in plants, including growth acceleration, seed dormancy breaking, fruit maturation, germination, cell elongation, fruit ripening, nodulation, plant senescence, and the abscission of flowers and leaves. Ethylene is produced in cells from methionine (Met) through a series of enzymatic reactions that begin with the formation of S-adenosylmethionine (SAM). This is followed by its catalytic transformation into 1-aminocyclopropane-1-carboxylic acid (ACC) via the activity of the enzyme ACC synthase (ACS). Finally, this compound (ACC) is converted to ethylene, carbon

dioxide, and cyanide by ACC oxidase (ACO) [4-5]. According to multiple research data, ACC is considered the direct precursor for ethylene biosynthesis. The application of exogenous ACC is being used in studies of ethylene metabolism in different tissues of plants. In accordance with the results of recent years' discoveries, ACC is being considered as a component of some signaling pathways [6-7].

Many chemical inhibitors of ethylene biosynthesis are applicable for studies of plant development, hormonal regulation, signal transduction, and other various physiological processes mechanisms [8].

There are different ethylene biosynthesis inhibitors commonly used for commercial purposes or to study the ethylene action in plants, including pyrazinamide, 2-aminoethoxyvinyl glycine (AVG), Ag^+ ions, as well as 1-methylcyclopropene (1-MCP) gas [9 - 11].

Pyrazinamide (PZA) is a drug, clinically used against tuberculosis that exerts antibacterial activity by acting as a target degrader [12]. In plant cells, this compound is converted to pyrazinoic acid, which decreases the activity of 1-aminocyclopropane-1-carboxylic acid oxidase (ACO). This enzyme ensures the catalysis of the final step of the biosynthesis of ethylene [13].

Moreover, silver nitrate and PZA is effective for *in vitro* plants salt tolerance increase by interfering with the effect of ethylene or ethylene generation. It is also associated with the reduction of H_2O_2 and malondialdehyde (MDA), as well as the modulation of catalase, ascorbate peroxidase, and superoxide dismutase (SOD) activity, which are essential components of the antioxidant system [14].

1-Methylcyclopropene (1-MCP) can inhibit ethylene effect. Thus, it can have a positive impact on the quality of various horticultural and agricultural products [15]. 1-MCP is primarily used to maintain visual characteristics (such as color and flavor), internal texture, and acid/sugar taste qualities, particularly after removal from cold storage. Unlike apples, other climacteric fruits require a delay in ripening, rather than inhibition, to ensure high quality and the desired product characteristics. The other factor of 1-MCP application limits is the cost/benefit relation, which is not appropriate to the market needs [16]. This compound also has some drawbacks when applied to fruits. 1-MCP can irreversibly inhibit ripening, particularly the softening of the flesh, which is necessary for optimal food product quality. In addition, 1-MCP treatment can lead to increased shriveling in fruit. Furthermore, 1-MCP treatment delays the changes in color variables in core tissues but not in peel and cortex tissues, and it can also delay cortex and core browning. Another drawback of 1-MCP is that it can delay the second glucose peak during fruit ripening. Lastly, treatment with 1-MCP inhibits aroma emission during the early storage of peach fruit [17].

Cyclopropane carboxylic acid derivatives have been studied for their role as inhibitors of ethylene biosynthesis in plants [18]. For example, cyclopropane-1,1-dicarboxylic acid (CDA) and *trans*-2-phenylcyclopropane-1-carboxylic acid (PCCA), as the structural analogs of 1-aminocyclopropane-1-carboxylic acid (ACC) are demonstrating the inhibitory influence on the wound ethylene produced by fruit discs of *Lycopersicum esculentum* [19-20].

Known synthetic methods for the creation of scaffolds of cyclopropane carboxylic acid derivatives mainly have only laboratory-scale applications and are not useful for industrial goals. Their synthesis requires expensive reagents, and long conversion times for average yields [21-22].

In the current research we discuss the questions of elaboration of general universal methodology of cyclopropane carboxylic acid derivatives synthesis and *in silico* assessment of their biological activity as the regulators of ethylene biosynthesis with the potential application in green agriculture and food industry.

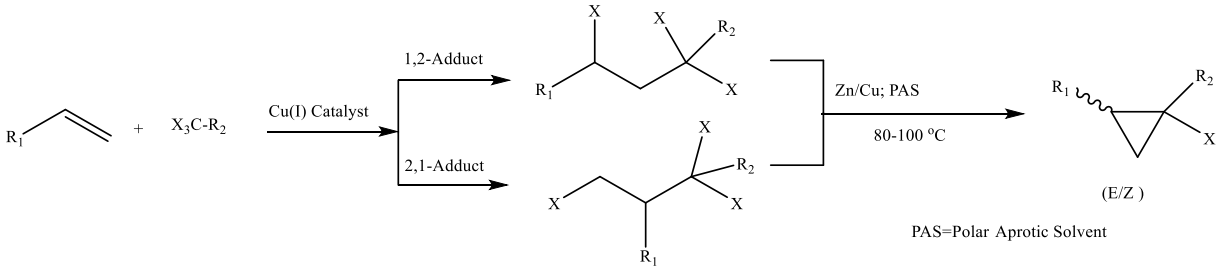
MATERIALS AND METHODS:

The easily feasible technological method of synthesis of functionally substituted carboxylic acids was advised. The first step includes ATRA (atom transfer radical addition) trihaloacetic acid derivatives to unsaturated substrates (terminal olefins). The second step is the consistent dehalogenation-cyclopropanation of the forming 1,3-dihalides with Zn/Cu pair or other metals (Fig. 1). The general synthetic techniques for ATRA were elaborated for the creation of cyclobutene carboxylic acids derivatives [23].

The chromatographic analysis and control of the consumption of starting and formation of synthesized compounds were conducted using the gas chromatograph (GC). (There were used: Agilent Technologies GC-7809B, capillary column - DB-WAX-30 m-320 µm x 0.25 mcm, FID (Flame Ionization Detector), temperature of detector is 300 °C, temperature of injector is 250 °C, flow rate gas (N_2) is 6 mL /min, column temperature is 40 °C; hold during 2 min, 7 °C/min 235 °C hold for 5 min). The mixture of reactants was separated by column and preparative chromatographic methods. Column chromatography was performed in a glass column, 200-700 mm high, 25 mm in diameter, filled with silica gel L 40/100, eluent was diethyl ether/hexane in a ratio of 1:20. The components of the mixture were detected by a selective method of light absorption of ultraviolet rays (UV-254). TLC (Thin-layer chromatography) analyses were carried out using Silufol UV-254 plates. Visualization was carried out in the presence of iodine vapor and a solution of potassium permanganate. Fisher-John's device was applied for the melting point measurements.

The molecular characteristic of the target compound (1-chloro-2-phenyl- derivative) was elucidated by NMR (Nuclear Magnetic Resonance) experiments and the structure of the studied compound was approved by the X-ray analyses [24-25].

The spectrometer Varian Mercury-300 at operating frequencies 300.077 MHz (^{1}H), and 75.46 MHz (^{13}C) was applied for the NMR spectral studies. The chemical shifts were reported with respect to TMS (Tetramethylsilane). The signal assignment in the ^{1}H and ^{13}C NMR spectra was performed by the application of methods standard steady-state Nuclear Overhauser Effect difference technique (NOEDIF), Heteronuclear Multiple Quantum Coherence (HMQC), and by registering ^{13}C NMR spectra without decoupling from protons [23-24].



R_1=C_4H_9; C_6H_{13}; C_8H_{17}; C_6H_5; CH=CH-C_6H_5 a) X=Cl, R_2=CN; b) X=Cl, R_2=COOMe(Et)

Figure 1. The general scheme of synthetic transformations.

The advised improvement of synthetic methodology (the application of highly active catalytical system, which is based on DMSO as catalytic co-ligand-solvent) is universal offer an opportunity to obtain not only cyclopropane carboxylic acid derivatives without Cl-substituent (in cyclopropane structure X=H, in case of dichloroacetic acid derivatives as the agents). The mentioned above methodology also is appliable for the synthesis of (*E*)-(1R, 2R)-2-phenylcyclopropane-1-carboxylic acid and (*E*)-(1S, 2S)-2-phenylcyclopropane-1-carboxylic acid. These compounds are well-known as the ethylene biosynthesis inhibitors. Their activity was tested *in vivo*.

***(E)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid**: m_p = 93-95 °C (CCl_4). ^1H NMR spectrum, δ, ppm (J, Hz): 1.92 (1H, dd, J=8.7; 6.2, *cis*-H_aH_bC–CHPh); 2.22 (1H, dd, J=10.2; 6.2, *cis*-H_aH_bC–CHPh); 3,14 (1H, dd, J=10.2; 8.7, –CHPh); 7.25-7.55 (5H, m, Ph); 10.67 (1H, br.s, COOH). ^{13}C (75.5 MHz, $CDCl_3$) δ, ppm: 176.8 (–COOH); 133.6 (–Ph); 129.7 (*o*-Ph); 128.3 (*m*-Ph); 127.9 (*p*-Ph); 44.3 (–CClCOOH); 34.5 (–CHPh); 24.3 (–CH_2–). The structure of synthesized new derivatives of cyclopropane series was summarized based on the obtained data of NMR analyses and by the comparison of appropriate spectral characteristic of analogue cyclopropane scaffoldings [26-28]. The relative configuration of phenyl- and carboxylic groups were determined by the absolute value of the vicinal $^3J_{trans}$ (^{13}C, ^1H) coupling constant. This is also evidenced by the multiplicity of signals (t_d) and spin-spin interaction constants $^3J(^1H, ^{13}C)$ values $^3J_t(^1H, ^{13}C)$=4 Hz and $^3J_t(^1H, ^{13}C)$ = 2 Hz of carboxylic group and phenyl-substituent bonded at cyclopropane ring in the *cis*-location [29-30].

Molecular Docking analyses: The molecular docking methods and the other computational analyses were applied for the carried *in silico* research. The mentioned methodology was used for the comparative study of known ethylene biosynthesis inhibitors, newly synthesized *(E)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid and for proposed drug-design of 1-amino-2-phenylcyclopropane-1-carboxylic acid, synthetic ACC derivatives [31]. Three dimensional models of studied compounds were constructed by the cheminformatics protocols [32], three-dimensional molecular models of studied structural analogues of ACC: *(E)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid [*(1S,2R)* and *(1R,2S)* isoforms], *(E)*-1-amino-2-phenylcyclopropane-1-carboxylic acid [(*1R,2S)* and (*1S,2R)* isoforms], such as like the well-known inhibitor *(E)*-2-phenylcyclopropane-1-carboxylic acid [*(1R,2R)* and *(1S,2S)* isoforms] were constructed. Same procedure was applied for the commercially widely used methylcyclopropane as well as pyrazinoic acid (fig. 2).

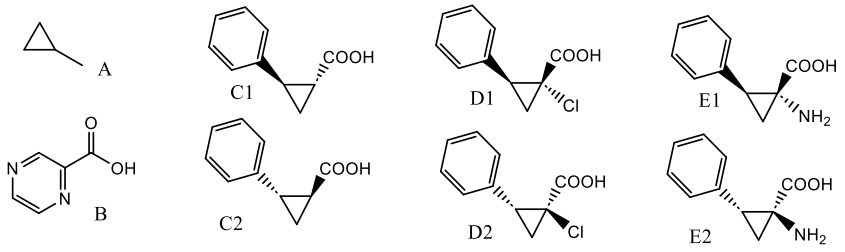


Figure 2. Structures of studied molecules: A) Methylcyclopropane; B) Pyrazinoic acid; C1) *(E)-(1R,2R)*-2-phenylcyclopropane-1-carboxylic acid; C2) *(E)-(1S,2S)*-2-phenylcyclopropane-1-carboxylic acid; D1) *(E)-(1R,2S)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid; D2) *(E)-(1S,2R)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid; E1) *(E)-(1R,2S)*-1-amino-2-phenylcyclopropane-1-carboxylic acid; E1) *(E)-(1S,2R)*-1-amino-2-phenylcyclopropane-1-carboxylic acid.

Three-dimensional model of the studied target was taken from the RCSB database [https://www.rcsb.org/] with PDB ID: 5GJ9 (ACO2, Arabidopsis thaliana); Molecular docking analysis was conducted by the software package of AutoDock Vina and AutoDock Tools. The analysis was performed independently 5 times using 20 starting conformations for each of studied compound, with the virtual box size not exceeding 27,000 Å. To determine the binding constant of the studied compounds with targets the following equation (1) was used:

$$\Delta G_{\exp} = -RT \ln\left(\frac{1}{K}\right) \quad (1),$$

where ΔG - is the Gibbs energy, R - is the gas constant, T - is the absolute temperature, K - is the binding constant [33].

RESULTS:

As a result of the conducted research the highly efficient Cu(I) catalytic system was elaborated: [Cu(I) complex Catalyst: 1) CuBr - 10 mol% to substrate, 2) secondary ammine, 3) catalytic co-ligand/solvent – DMSO. Molar

ratio 1):2):3) = 1:1:7-10], reaction time: 1.5-2 h, adducts yield: up to 95%. Previously conducted docking study of ethylene biosynthesis inhibitory activity of newly synthesized *(E)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid [*(1S,2R)* and *(1R,2S)* isoforms] showed good results in comparison to commercially applicable methylcyclopropane and known inhibitor pyrazinecarboxylic acid on ACO2 (*Arabidopsis thaliana*) enzyme.Taking into consideration these successful results of *in silico* studies of 1-chlorine- derivatives and such as the known fact that the native inhibitors are amino acids, the drug design of appropriate amino-derivatives was carried out. Docking results are presented in Tables 1-2. The graphical expression of molecular docking analyses of the interactions between different derivatives of cyclopropane carboxylic acids with ACO2 enzyme macromolecule is presented in Fig. 3.

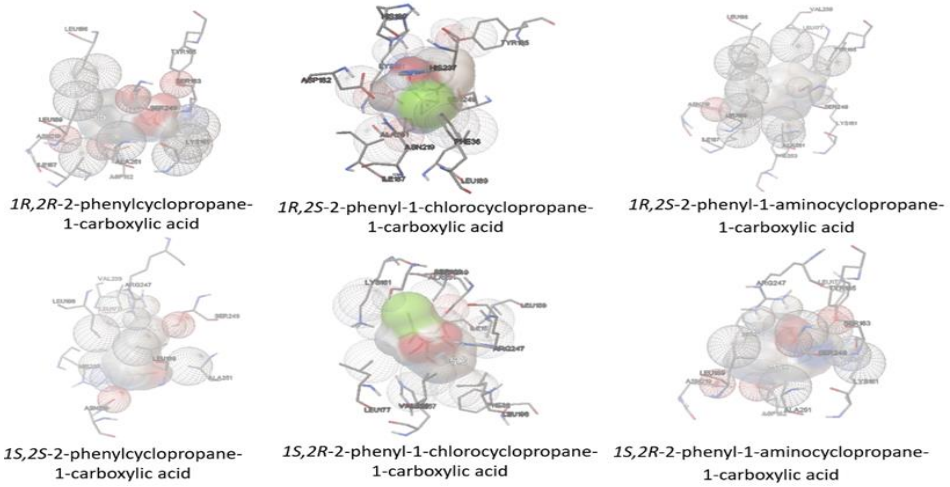


Figure 3. Molecular the interaction of various cyclopropanecarboxylic acids derivatives with 1-aminocyclopropane-1-carboxylate oxidase 2 (ACO2) enzyme.

Table 1. Binding sites of studied molecules. * - H-bond

Binding sites	Methylcyclo-propane	Pyrazinoic acid	*(E)*-1-amino-2-phenylcyclopropane-1-carboxylic acid		*(E)*-2-phenyl-cyclopropane-1-carboxylic acid		*(E)*-1-chloro-2-phenylcyclopropane-1-carboxylic acid	
			1R,2S	*1S,2R*	*1R,2R*	*1S,2S*	*1R,2S*	*1S,2R*
Leu177	-	+	+	+	-	+	-	+
Leu189	+	+	+	+	+	+	+	+
Leu198	+	+	+	-	+	+	+	+
Val239	-	-	+	-	-	+	+	+
Ser249	+	+	+	+	+	+	-	+
Tyr165	-	-	+	+	+	-	-	-
Lys161	-	+	+	+	+	-	+	+*
Ala251	-	-	+	+	+	+	+	+*
Ile187	-	-	+	-	+	-	+	+
Phe36	-	-	-	-	-	-	-	+
His237	-	+	+	+	-	+	+*	+
Phe253	-	-	+	-	-	-	+	-
Asn219	-	-	+	+	+	+	+*	-
Arg247	+	+	-	+	-	+	-	-
His180	-	+	-	-	-	-	-	-
Asp182	-	-	-	+	+	-	-	-
Ser163	-	-	-	+	+	-	+	+*

Table 2. The results of molecular docking.

Ligand	ΔG(kcal/mol)	$K_b(M^{-1})$
(1R,2R)(E)-2-phenyl-cyclopropane-1-carboxylic acid	-6.5	5.9385×10^4
(1R,2S)(E)-1-amino-2-phenylcyclopropane-1-carboxylic acid	-6.4	4.94×10^4
(1S,2R)(E)-1-amino-2-phenylcyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1S,2S)(E)-2-phenyl-cyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1S,2R)(E)-1-chloro-2-phenylcyclopropane-1-carboxylic acid	-6.2	3.53×10^4
(1R,2S)(E)-1-chloro-2-phenylcyclopropane-1-carboxylic acid	-6.0	2.54×10^4
Pyrazinoic acid	-5.3	7.61×10^3
Methylcyclopropane	-3.1	0.188×10^3

K_b – binding constant; ΔG – Gibbs free energy.

DISCUSSION:

The previously applied catalytic systems of ATRA reactions carry several drawbacks. Particularly, the high-temperature conditions are necessary for the appropriate activity level of the catalyst, which completes the conversion. Those conditions initiate the range of undesired side reactions (polymerizations, dehydrochlorinations, etc.) and as a result, it lowers the total yield of desired products. Due to the comparison of data collected from the conducted research with the literature references, the crucial role of polar solvents [dimethylformamide (DMF), dimethyl sulfoxide (DMSO)], as the control factor for the activity of Cu(I) complex catalyst and reaction intermediates stabilization was defined. DMSO significantly increases the catalytic complex activity, which reduces the reaction time to 2 hours. Also, it allows to control the temperature in the range from 40 °C up to 60 °C. The mentioned mild conditions significantly increase the reaction yields and the selectivity of target product formation [34-35].

The advised optimization of catalytic systems and co-solvents [Cu(I) salt/amine/DMSO] increases the yields. Also, it lowers the temperatures and reduces the reaction time. For a preliminary assessment of the bioactivity of target compounds, *in silico* analyses of interaction between newly synthesized (*E*)-1-chloro-2-phenylcyclopropane-1-carboxylic acid, such as like the drug-designed target prospective molecule 1-amino-2-phenylcyclopropane-1-carboxylic acid with 1-aminocyclopropane-1-carboxylate oxidase 2 (ACO2) enzyme of *Arabidopsis thaliana* was carried out. For the comparison of ethylene biosynthesis inhibitory effects, the commercially used analogs were considered for the same procedure of *in silico* analysis.

The results of molecular docking have demonstrated that both *1S,2R,* and *1R,2S* isoforms of (*E*)-1-chloro-2-phenyl-cyclopropane-1-carboxylic acid have higher values of binding constant 3.53×10^{-4} and 2.54×10^{-4} in difference to widely used methylcyclopropane and pyrazinoic acid (also known as pyrazine carboxylic acid) with lower value of binding constant: 7.61×10^{-3} for pyrazinoic acid and 0.188×10^{-3} for methylcyclopropane. Probably, it also can be potentially effective against some spoilage agents, which have enzymatic activities able to deaminase ACC [36-38].

The elaboration of innovative inhibitors of ethylene biosynthesis is very important for the potential control of the lifecycle of plants, which has agricultural significance for both the food products industry and animal feed production (crops, fruits, vegetables). Also, ecologically safe polyfunctional inhibitors of ethylene biosynthesis are very prospective for the application of these compounds as the regulators of spoilage during the

storing and transportation of plant-derived agricultural production. It is especially important in the case of plant-derived functional foods preservation during their import and export through the borders of countries [39]. Fruits and vegetables are one of the most important food products, as the main source of the majority of vitamins, antioxidants, microelements, etc. for all people. Anyhow their consumption by children, and sportsmen (especially the Olympic athletes), sigh as like consumption by the patients on various types of rehabilitation therapy has invaluable importance [40-41]. Thus, the persistence of the quality and nutritional amount of these products is a very actual problem, including the safe preservation of products without the loss of beneficial properties of their bioactive compounds [42]. That is extremely important in terms of the overwhelming globalization of countries and the popularization of various ethnic meals of different countries, which are based on fresh fruits and vegetables [43].

Besides, the problem of fresh fruits and vegetables transportation in regions with famine problems, natural disasters of military conflicts in frames of humanitarian support also require the prevention of early premature ripening during transportation, which can cause spoilage [44-46].

CONCLUSION:

An understanding of the structural and functional aspects of ACC oxidase and its interaction with inhibitors is crucial for the development of effective ethylene biosynthesis inhibitors. It's important because that would be potentially applicable in agriculture, horticulture, and food production. Thus, taking into consideration all the above-mentioned results of preliminary *in silico* experiments, and summarizing the collected data, it might be concluded that the study of novel inhibitors of ethylene biosynthesis can expand the volume of fundamental knowledge about the physiological features of the plants. In these regards, that can allow the effective control of the lifecycle of various important agricultural crops. Besides, it might improve the green agricultural practices particularly the postharvest management of grains, fruits, and vegetables. All the mentioned makes the studied potentially bioactive molecules the prospective for furthermore detailed studies. The furthermore detailed *in vitro* laboratory experiments with the various types of plant cultures, such as *in vivo* experiments and the field trials, as the final stage of research is planned.

Abbreviations: ACC, 1-aminocyclopropane-1-carboxylic acid; SAM, S-adenosylmethionine; ACS, ACC synthase; ACO, ACC oxidase; ATRA, Atom transfer radical addition; AVG, 2-aminoethoxyvinyl glycine; DMF, dimethylformamide; DMSO, Dimethylsulfoxide; FID, Flame Ionization Detector; GC, Gase Chromatography; Heteronuclear Multiple Quantum Coherence, HMQC; MDA, Malondialdehyde; 1-MCP, 1-methylcyclopropene; Met, Methionine; NMR, nuclear magnetic resonance; SOD, superoxide dismutase; TLC, Thin-layer chromatography; PCCA, *trans*-2-phenylcyclopropane-1-carboxylic acid.

Author's Contributions: All authors contributed to this study.

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