

Chemical design, preparation, agricultural bioefficacy valuation, and molecular docking of some pyridine containing compounds

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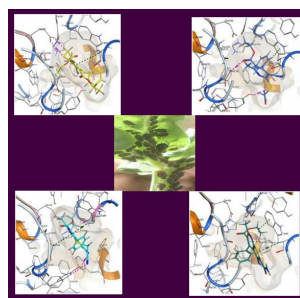
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ABSTRACT

The development of effective insecticides is crucial for sustainable agriculture. This research focuses on a series of pyridine derivatives (**3–9**) that were prepared and evaluated for their agricultural bioefficacy as potential insecticides against cowpea aphid, *Aphis craccivora* Koch (Homoptera: Aphididae). The results demonstrate significant variations in bioefficacy among the tested compounds. Toxicity index analysis revealed the following order of insecticidal activity: **8**>**4**>**6**>**3**>**5**>**7**>**9**, highlighting compound **8** as the most potent. Furthermore, potential binding interactions were elucidated through molecular docking studies between these compounds and relevant insect target proteins. So, the observed bioactivity trends were rationalized with the use of the docking data, which offered useful information on the binding affinities and molecular interactions. AChE, or acetylcholine esterase (PDB ID: 2ACE), has been docked against the seven synthetic molecules (**3–9**). Interestingly, compounds (2-(pyridin-2-ylthio)acetonitrile; **8**), (2-(pyridin-2-ylthio)acetic acid; **6**), and (ethyl 2-(pyridin-2-ylthio)acetate; **4**) had the highest binding affinity, with respective docking scores (S) of -7.51, -7.45, and -7.12 kcal/mol, while compounds (thieno[2,3-*b*]pyridine derivatives; **7** and **9**) had the lowest binding affinity (S=-6.52 and -6.73 kcal/mol, respectively). According to protein-ligand docking configurations, these compounds exhibited a range of binding interactions inside the 2ACE active site. Hence, this study contributes to the development of new pyridine-based insecticides for sustainable pest management in agricultural applications.

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Graphical Abstract

1. Introduction

Heterocyclic compounds represent a significant category within organic molecules, distinguished by the inclusion of at least one heteroatom (an atom other than carbon) in their ring systems.¹⁻⁷ These compounds can include various

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heteroatoms such as nitrogen, oxygen, and sulfur within their ring structures. Heterocycles play a crucial role in many biological processes and are fundamental building blocks in pharmaceuticals, agrochemicals, and other sciences.⁸⁻¹⁵ Among these, pyridine compounds hold a prominent position due to their unique properties and widespread applications.¹⁶⁻¹⁸

In medicinal chemistry, pyridine derivatives are often found in the structure of many bioactive molecules, including anticancer, anti-inflammatory, and antioxidant agents.¹⁹ Furthermore, the study of pyridine compounds extends beyond medicinal applications; they are also utilized in agriculture as promising insecticidal agents.²⁰⁻²²

Crop damage caused by harmful pests has become one of the most problems facing humanity. The continued use of conventional pesticides often contributes to the emergence of more resistant pest species, leading to significant crop yield losses.²³ Studies indicated that pyridine compounds possess high activity against agricultural pests.²⁴ The structure of pyridine is characterized by its ability to influence the biological systems of pests, that enable them to inhibit the growth of a wide range of insect pests such as aphids and scale insects, which contributes to reducing crop losses.²⁵ Owing to its effectiveness, it is a promising option for developing effective insecticides.²⁶⁻²⁷

Furthermore, research has shown that the effects of pyridine extend to enhancing plant growth by improving nutrient absorption, as some pyridine compounds act as growth promoters, which may increase agricultural yields.²⁸⁻²⁹ With increasing concerns about the use of traditional chemical pesticides and their negative environmental impacts and owing to their low toxic properties, pyridine compounds offer a safer and more sustainable alternative. Recent research continues to explore the potential of these compounds in developing effective and environmentally friendly insecticides.³⁰⁻³⁴

Considering the above evidences and our continued efforts in studying pyridine derivatives and the other bioactive compounds,³⁵⁻⁴⁴ this study aims to synthesize various pyridine derivatives and evaluate their insecticidal effectiveness against both nymphs and adults of cowpea aphid, *Aphis craccivora*, with the aim of identifying effective insecticides that not only demonstrate strong activity against major agricultural pests but also prioritize environmental safety.

2. Materials and methods

2.1. Instrumentation and Chemicals

The chemicals used in the study were obtained from Merck, Aldrich, and Fluka, and were utilized without undergoing any additional purification processes. Compounds (**3-9**) were obtained according to the literature procedure.⁴⁵ The melting points were determined and recorded using a Kofler melting point apparatus, without any subsequent correction. Collections of *Aphis craccivora* were obtained from Shadawel, Sohag branch of the Agricultural Research Center. The collected aphids were subjected to toxicity screening to evaluate the effects of the seven target compounds.

2.2. Laboratory bioassay

Another strong argument for investigating novel insecticidal active ingredients is the sharp increase in resistance to conventional chemical pesticides. Examining novel types of insecticidal substances with unique modes of action is essential to meeting this issue. In the process of developing insecticides, heterocyclic compounds particularly nitrogen heterocyclic are crucial. We have found new derivatives of phenyl pyridine derivatives.⁴⁶⁻⁴⁸ Using leaf dip bioassay techniques, the insecticidal efficacy of each pyridine derivative was assessed.⁴⁹⁻⁵¹ The *Aphis craccivora* strains were gathered from Shadawel, Sohag branch of the Agricultural Research Center. Finding the necessary concentrations to kill 50% (LC₅₀) of the nymphs and adults of *A. craccivora* insects was the aim of the testing. Five doses of each target synthetic phenyl pyridine derivatives were utilized in this search, along with 0.1% tween-20 as a surfactant.⁵² 50 nymphs and 50 adults of *A. craccivora* insects of almost equal size were dipped three times for 10 seconds in each concentration of the synthetic target compounds.⁵³ The test insects were allowed to stand at room temperature for approximately 30 minutes, during which time the control insects which were submerged in distilled water and tween-20 exclusively were also used. Applications are performed at a temperature of 25 °C and 5% relative humidity.⁵⁴ The used insects were moved to glass jars filled with dechlorinated water once they had dried.⁵⁵ A new binocular microscope was used to measure the aphid mortality 24 hours after the test. Aphids that were immobile were regarded as dead.⁵⁶

In order to determine the LC₅₀ values with 95% educible limits of lower and upper confidence limit, slope, standard error, chi-square, and correlation coefficient, the data on aphid mortality were subjected to probit analysis using a statistics program (LDP-line). Every synthetic compound's insecticide bioactivity test was conducted three times, and Abbott's formula was used to rectify the results.⁵⁷ Probit analysis was used to measure the mortality relapse line measurements.⁵⁸ Sun equations were used to determine the harmfulness index.⁵⁹

2.3. Molecular docking methodology

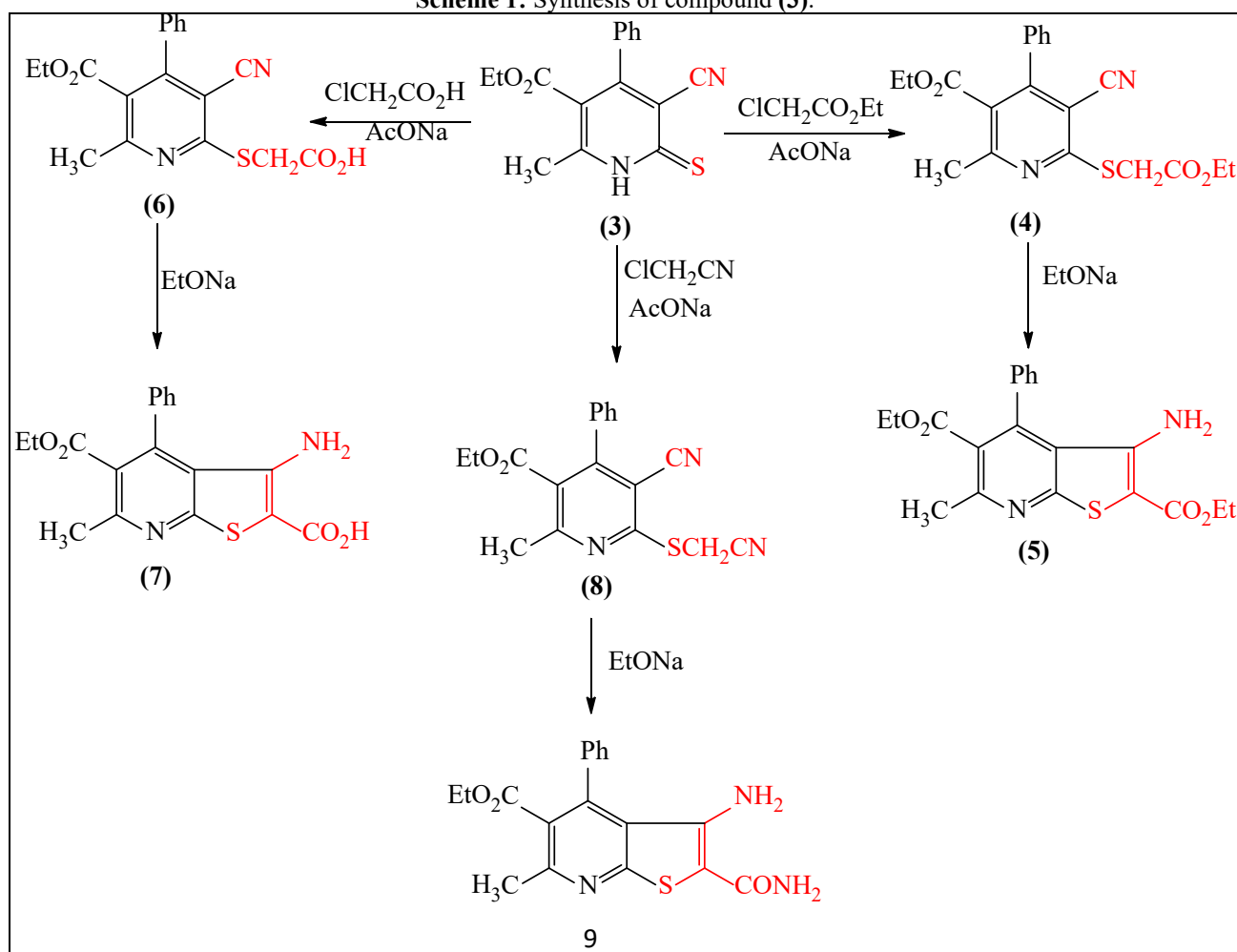
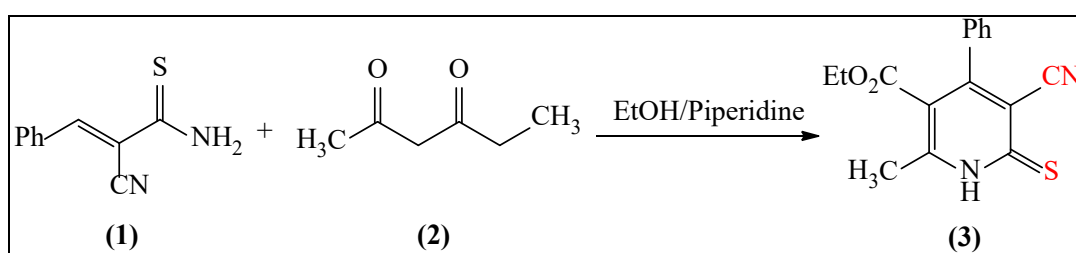
The crystal structures of acetylcholinesterase (PDB ID: 2ACE) were obtained from the Protein Data Bank (<https://www.rcsb.org>). The Quickprep protocol was employed for target preparation. Using the Molecular Operating

Environment (MOE) software (version 2019.0102), the target compounds were sketched, and subsequently subjected to energy minimization and 3D protonation. The selection of the pose relied on the S-value, RMSD and pose visualization. Validation of the docking protocol was performed by applying the same docking protocol (**Supplementary data: Fig. S1**).

3. Results and Discussion

3.1. Chemistry

A selected series of thieno[2,3-*b*]pyridines were synthesized via the key intermediate 3-Cyano-5-ethoxycarbonyl-6-methyl-4-phenylpyridine-2-(1*H*)-thione (**3**), which was prepared by cyclocondensing 3-phenyl-2-cyanothioacrylamide with ethyl acetoacetate in ethanol containing piperidine as catalyst. The synthetic route to the key intermediate and the target compounds was reported before and is shown in **Schemes (1 and 2)**.⁴⁵ First, the compounds 3-Cyano-5-ethoxycarbonyl-2-ethoxycarbonylmethylsulfanyl-6-methyl-4-phenylpyridine (**4**), 2-Carboxymethylsulfanyl-3-cyano-5-ethoxycarbonyl-6-methyl-4-phenylpyridine (**6**) and 3-Cyano-2-cyanomethylsulfanyl-5-ethoxycarbonyl-6-methyl-4-phenyl pyridine (**8**) were obtained by reacting key intermediate **3** with the appropriate alkylated reagents in ethanol containing AcONa. While, other target compounds 3-Amino-2,5-diethoxycarbonyl-6-methyl-4-phenylthieno[2,3-*b*] pyridine (**5**), 3-Amino-2-carboxy-5-ethoxy carbonyl-6-methyl-4-phenylthieno[2,3-*b*]pyridine (**7**), and 3-Amino-2-carbamoyl-5-ethoxycarbonyl-6-methyl-4-phenylthieno[2,3-*b*]pyridine (**9**) were synthesized from (**4**, **6**, and **8**) using sodium ethoxide solution through a *Thorpe-Ziegler* cyclization. Confirmation of the synthesized compounds' chemical structures was achieved using spectral data (IR, ¹H-NMR and ¹³C NMR) and elemental analysis.



3.2. Insecticidal bio-efficacy screening

It was showed that (i) the prepared compounds and acetamiprid demonstrated excellent mortality against nymphs and adults of laboratory strains of *A. craccivora*. The results of insecticidal activity test of compounds (3-9) against *A. craccivora* as seen in **Table 1** and **Fig. 1**. The bioefficacy results of seven prepared compounds ranged from high to low toxicological activity against the nymphs of *A. craccivora* because a number of them was closed in activity with acetamiprid after 24 hrs of treatment. In which LC₅₀ values vary from 0.181 to 0.372 for example LC₅₀ value of compounds (3-9) were 0.266, 0.181, 0.345, 0.187, 0.275, 0.133 and 0.372 mg/L, respectively, in which acetamipride value was 0.045 mg/L.⁵¹ For this result, the toxicity of compound **8** against nymphs of *A. craccivora* was nearly in toxicity than acetamiprid after 24 h of the test. In addition, the toxicity index of compounds (3-9) were 0.169, 0.248, 0.130, 0.240, 0.163, 0.398 and 0.120, respectively. (ii) Results of the toxicity index as seen in **Table 1** of compounds (3-9) that were tested against *A. craccivora* were distributed from low to high. The insecticidal activity of compound **8** was closed to that of the reference insecticide acetamiprid after 24 h of the test because LC₅₀ value of compound **8** was 0.399 mg/L and that of acetamiprid was 0.267 mg/L.⁵¹ The other LC₅₀ values of compounds (3-9) were 0.716, 0.412, 0.918, 0.503, 0.799, 0.399 and 1.412 mg/L, respectively. Furthermore, the toxicity index of compounds (3-9) was 0.169, 0.248, 0.130, 0.240, 0.163, 0.398 and 0.120, respectively.

Table 1. Insecticidal activity of compounds (3-9) and acetamiprid as references insecticide against the *A. craccivora* insects after 24 h of treatment.

Comp.	Nymphs			Adults		
	LC ₅₀ (mg/L)	Slope	Toxic ratio	LC ₅₀ (mg/L)	slope	Toxic ratio
3	0.266	0.473 ± 0.287	0.169	0.716	0.481 ± 0.276	0.372
4	0.181	0.384 ± 0.284	0.248	0.412	0.417 ± 0.304	0.648
5	50.34	0.468 ± 0.295	0.130	0.918	0.468 ± 0.268	0.290
6	0.187	0.391 ± 0.287	0.240	0.503	0.494 ± 0.269	0.530
7	0.275	0.356 ± 0.277	0.163	0.799	0.432 ± 0.267	0.334
8	0.113	0.313 ± 0.274	0.398	0.399	0.446 ± 0.291	0.787
9	0.372	0.417 ± 0.276	0.120	1.412	0.570 ± 0.282	0.189
Acetamiprid	0.045	0.381 ± 0.283	1	0.267	0.387 ± 0.283	1

Notes: Toxic ratio is computed as the LC₅₀ value for baseline toxicity / the compounds' LC₅₀ value.

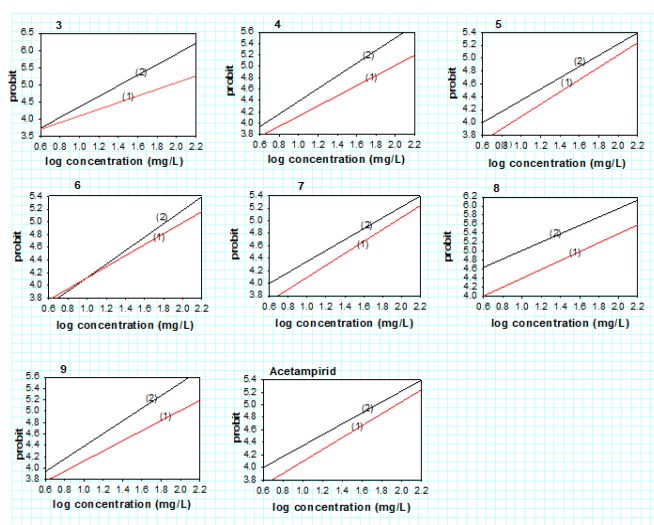


Fig. 1. Insecticidal activity of compounds (3-9) and acetamiprid against nymphs and adults of *A. craccivora* insects, which (1) was nymph aphids after 24 hrs of treatment and (2) was adult aphids after 24 hrs of treatment.

3.3. Molecular docking

In molecular docking, the optimal arrangement and binding strength of a ligand (specifically the seven tested compounds (3-9)) to a receptor (the 2ACE molecule) are predicted, leading to the formation of a stable complex. AChE plays a significant role in several physiological functions such as muscle contraction, cognition, memory,⁶⁰ and learning. It is also a target for various drugs, including anticholinesterases, which are used to treat conditions like Alzheimer's disease, myasthenia gravis, and poisoning from nerve agents.⁶¹ AChE inhibitors can increase the concentration of acetylcholine in the synapse, enhancing the communication between neurons.⁶² Conducting molecular docking against 2ACE can aid in the development of new ligands that can effectively modulate AChE activity. In summary, molecular docking is viewed as an effective method for exploring, discovering, and designing new pharmaceuticals that specifically target a particular enzyme. To start, the docking process was validated through redocking and superimposition. The redocking procedure followed the same methods that were utilized previously. The redocked native ligand of 2ACE was completely aligned with the co-crystallized native ligand (**Supplementary data: Fig. S1**).

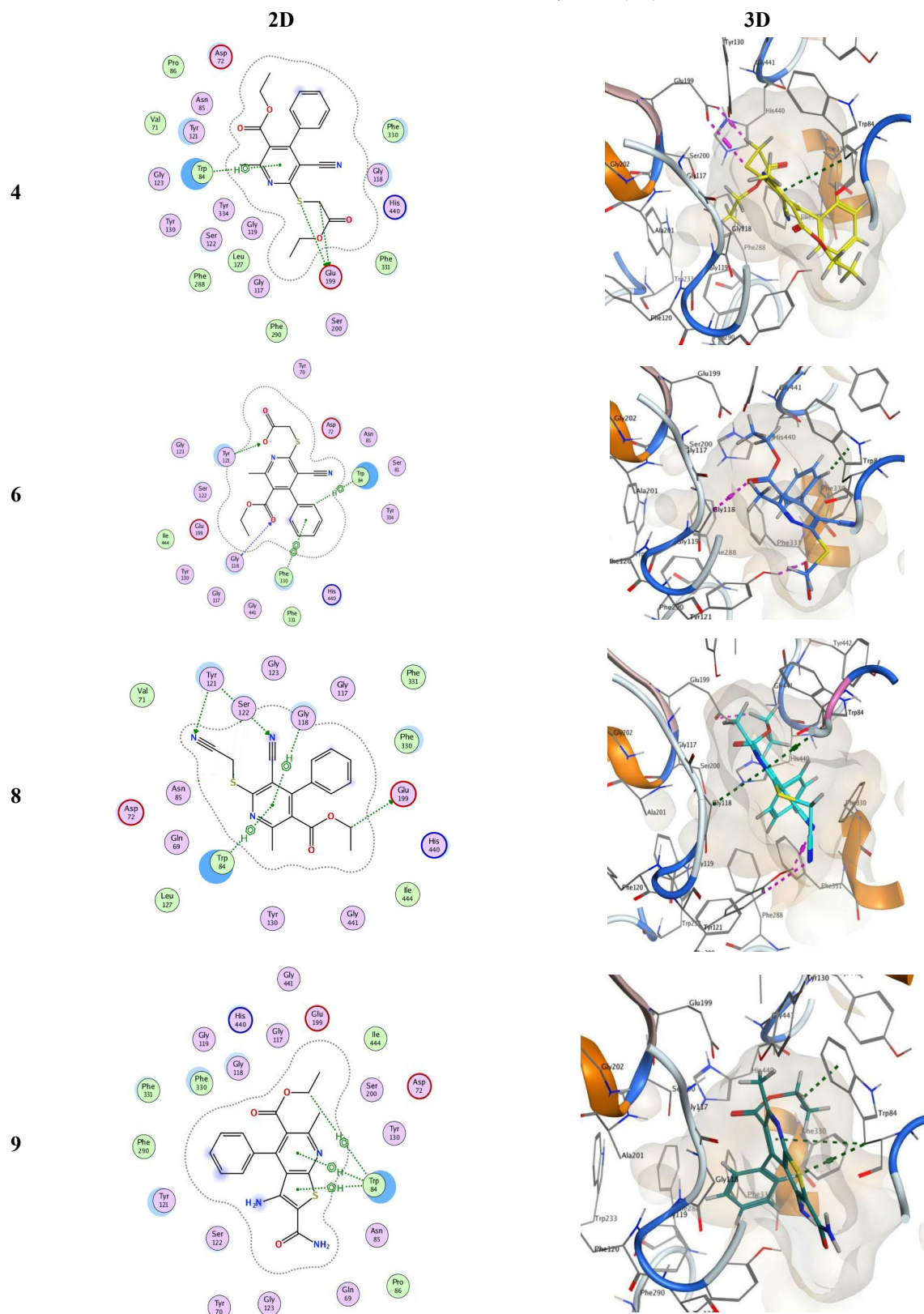


Fig. 2. 2D and 3D binding poses for compounds **4**, **6**, **8** and **9** at 2ACE binding sites.

The results from the redocking and superimposition protocol provided strong evidence supporting the validation of the docking protocol. Seven synthesized pyridine derivatives (**3-9**) were docked at 2ACE binding site. Interestingly, all compounds revealed high binding scores with S-value range of -6.52 to -7.51 kcal/mol (**Table 2** and **Table S1**) compared to co-crystallized acetylcholine ligand (S-value= -5.29 kcal/mol). Noticeably, 3-Cyano-2-cyanomethylsulfanyl-5-ethoxycarbonyl-6-methyl-4-phenyl pyridine (**8**) docking results showed the highest binding score (S= -7.51 kcal/mol), in which three hydrogen bonds (HB) were formed; one HB with Glu199 (1HB, 2.34 Å) and the other two with Tyr121 (2HB, 2.42 Å and 3.58 Å), besides formation of π -H interactions with Trp84 and Gly118, **Fig. 2**.⁶³ Moreover, 3-Cyano-5-

ethoxycarbonyl-2-ethoxycarbonylmethylsulfanyl-6-methyl-4-phenyl-pyridine (**4**; $S = -7.45$ kcal/mol) binds with Glu199 (2HB; 2.50, 3.40 Å) and with Trp84 (π -H interactions), **Fig. 2**.⁶³ Also, compound **6** revealed two HBs with Gly118 and Tyr121 in addition to π -H interactions with Trp84; **Fig. 2**. Interestingly, compound **9** showed only three π -H interactions with Trp84 which may provide an explanation for its low biological results, **Fig. 2**. Other derivatives (**3** and **5-7**) also showed interactions with Trp84, Tyr121 and Tyr130 at the 2ACE binding site (**Supplementary data: Fig. S2**). Compounds (**3-9**) revealed many interactions which were summarized in **Table S1**.

Table 2. Docking Scores of the (**4**, **6**, **8** and **9**) investigated compounds against AChE (PDB ID: 2ACE).

	Ligand	Receptor	Interactions	Score kcal/mol	Rmsd value
4	SCH ₂	Glu199	H- donor	-7.45	0.88
	SCH ₂	Glu199	H- donor		
	Pyridine ring	Trp84	π -H		
6	C=O	Gly118	H- acceptor	-7.12	1.55
	CH ₂ COO	Tyr121	H- acceptor		
	Phenyl ring	Trp84	π -H		
8	Phenyl ring	Phe330	π - π	-7.51	0.94
	CH ₂ CN	Tyr121	H- acceptor		
	CN	Tyr121	H- acceptor		
	CH ₂	Glu199	H- donor		
	Pyridine ring	Trp84	π -H		
9	Pyridine ring	Gly118	π -H	-6.73	1.16
	Pyridine ring	Trp84	π -H		
	Thiophene ring	Trp84	π -H		
	CH ₂ CO	Trp84	H- π		

3.4. Structure-Activity Relationship

The preparation of new bioactive polyfunctional substituted pyridine derivatives was deemed advantageous in this context. Furthermore, the creation of these pyridine compounds, belonging to the broad class of organic molecules, holds significant prospective due to the diverse applications of organic compounds as previously documented in published research.⁶⁴⁻⁷⁹ A computerized regression analysis tool was used to determine the targeted products' median lethal concentration (LC₅₀) and slope values, which were then reported in milligrams/liter (ppm). It is evident from the data acquired after 24 hours of treatment (**Table 1, Fig. 1**) that: (i) The investigated drugs' insecticidal activity was arranged in the following order based on the toxicity index: **8**>**4**>**6**>**3**>**5**>**7**>**9**. (ii) All tested compounds exhibited higher insecticidal activity toward *A. craccivora* nymphs than that toward adults; this finding makes sense because often adult insects are more resistant to foreign substances than nymphs. (iii) Phenyl pyridine derivative **8** possesses higher activity than the other target synthesized compounds. (iv) Owing to the appearance of the two cyano groups which also often increase the activity. (v) Followed with compounds **4** and **6**, from their chemical structures we can conclude that their toxicological activity may be due to the presence of pyridine ring, phenyl and -CN group attached to each compound.

4. Conclusion

The findings of this work underscore the potential of pyridine derivatives as effective insecticides for agricultural use. This study focused on the synthesis of seven pyridine derivatives and their subsequent evaluation for agricultural bioefficacy as insecticides. Also, the study aimed to investigate the structure-activity relationships among the compounds and conduct molecular docking analyses to better understand their interactions. The results obtained from the bioactivity evaluation revealed significant insecticidal potential among the pyridine compounds tested. Notably, compound **8** emerged as the most promising candidate, exhibiting the highest level of insecticidal activity compared to the other compounds. The exploration of structure-activity relationships provided crucial insights into the molecular determinants influencing the insecticidal properties of the pyridine derivatives. The molecular docking studies shed light on the potential mode of action and binding interactions of the selected compounds with target receptors or enzymes involved in insecticidal activity. The molecular docking results were consistent with the biological results. By integrating synthesis, bioactivity assessment, structure-activity relationship analysis, and molecular docking studies, this research contributes to a comprehensive understanding of the insecticidal properties of pyridine compounds and paves the way for the development of new and improved insecticidal agents for agricultural applications.

Author Contributions

Abdullah A. Abdalkarim Alshera'a, Eman Ali Thabet, and Fathia Mohammad Qasem Qaid: designed the study and prepared the chemical compounds. Abdel Haleem M. Hussein, Adel M. Kamal El-Dean, and Mokhtar A. Abdul-Malik: preparation of the paper, writing original draft, and revising the paper. Mohamed A. Gad: conducted and wrote the agricultural bioactivity section. Shaban A. A. Abdel-Raheem: revised the paper, performed linguistic and spelling adjustments, and adjusted the paper according to the style of the journal. Ahmed S. Abdelkhalek: performed and wrote the molecular docking part.

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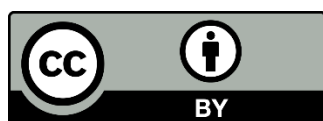
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