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Stability and computational analyses of selected pesticides in use in the Republic of Serbia

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Abstract: Pesticides commonly used in the Republic of Serbia (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone) have high stability, so their potential toxicity to humans needs to be investigated. These pesticides are in use in the Republic of Serbia in various formulations. Their toxicity and interactions with acetylcholinesterase were thoroughly investigated in this study using computational tools. The ADMET (adsorption, distribution, metabolism, excretion, toxicity) study showed that all of them are efficient oral compounds, and that pendimethalin was a mutagenic compound. Glide scores ranged from –18.41 (pendimethalin) to –27.61 kJ mol^{-1} (famoxadone) in *Mus musculus*, and from –19.58 (pendimethalin) to –24.31 kJ mol^{-1} (propiconazole) in *Homo sapiens*. In addition, the experimental stability of the pesticides solutions in methanol was studied using the fast gas chromatography–mass spectrometry (GC–MS, retention times of the studied pesticides ranged from 14.47 (pendimethalin) to 22 min (famoxadone)). They showed good stability over time, apart from pyraclostrobin which decomposed mainly into its desmethoxy derivative after 20 months. Based on the promising modelling results, pyraclostrobin and famoxadone emerge as potential candidates for further investigation in the treatment of Alzheimer's disease, taking care to increase their stability.

Keywords: GC–MS; Alzheimer's disease; ADMET.

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INTRODUCTION

Five pesticides (propiconazole, famoxadone, pendimethalin, pyraclostrobin and tebuconazole) that are widely used in the Republic of Serbia were selected for this study.[1] There are numerous studies on the toxicological effects of pesticides but there is no such proposed aspect as described here, especially on humans.

The intensive use of pesticides negatively affects the health of the population and also insect pollinators worldwide, as shown in numerous studies. French researchers studied the level of uptake of selected *β*-blockers, anxiolytics, antibiotics, antiepileptics, antidepressants and fungicides (including propiconazole and tebuconazole) by the European eel (*Anguilla anguilla*). Interestingly, the eel consumed the least amount of all substances studied.[2] Dereumeaux *et al.* (2022)[3] determined the levels of five pesticides, including tebuconazole, in urine and hair samples from adults and children living near and around vineyards. The results showed that the levels of the above pesticides and their metabolites are higher in those living near vineyards and also have a stronger effect on children, so their monitoring (degradation time) is crucial. Cang *et al.* (2022)[4] studied the individual and combined effects of tetrachloranatraniliprole and tebuconazole on honey bees (*Apis mellifera* L.). According to their results, tetrachlorantraniliprole shows a higher toxic effect (96-h LC_{50} value of 298.2 mg a.i. dm^{-3}) compared to tebuconazole (96-h LC_{50} value of 1,841 mg a.i. dm^{-3}), while the combined exposure of honeybees to both pesticides leads to an enhanced toxic effect (synergism). Janoš *et al.* (2023)[5] concluded, based on their experimental results, that tebuconazole inhibits DNA glycosylase and thus reduces the DNA methylation process. Kolesárová *et al.* (2013)[6] studied the influence of fungicide formulations (with tebuconazole as one of the active components) on the activity of acetylcholinesterase and butyrylcholinesterase in domestic animals, and their results show the inhibitory properties of these formulations on both enzymes. Rico *et al.* (2016)[7] studied the lethal and sublethal capabilitiles of the common earthworm in soils used for rice cultivation treated with various pesticides, including tebuconazole, and the decrease in enzymatic activity of the following enzymes in the common earthworm: cholinesterase, lactate dehydrogenase, and alkaline phosphatase.

Pendimethalin, an herbicide used for weed control, inhibits plant cell division and mitosis. Results showed that pendimethalin interferes with mitochondrial complexes I and V, which inhibit embryo energy metabolism, leading to developmental defects in the organisms studied.[8,9]

Pyraclostrobin has been found to affect the mitochondrial function in aquatic organisms.[10] The design and synthesis of new pyraclostrobin derivatives with antifungal activities have been reported.[11]

From the available literature, there is no evidence that famoxadone inhibits acetylcholinesterase. Famoxadone and its derivatives have been shown to be

cytochrome bc_1 complex inhibitors.[12,13] How famoxadone interacts with acetylcholinesterase is described in detail here.

Recently, several pesticides different from our studied here were investigated experimentally and *in silico*.[14,15] Average quasi-valence number (*AQVN*)/ electron–ion interaction potential (*EIIP*) proved to be a good predictive tool for the behaviour of selected pesticides against acetylcholinesterase. These selected pesticides against acetylcholinesterase show *in silico* the same region for binding in both *Mus musculus* and *Homo sapiens* with some differences. Global minima or free energy of formation values may also give an indication of the degree of acute toxicity.

Therefore, the aim of this study was to investigate the stability of methanolic solutions of different pesticides (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone) using gas chromatography–mass spectrometry (GC–MS) over 9 and 20 months to obtain the necessary information for the efficient laboratory work. In addition, the previous computational studies on pesticides were extended to the above selected pesticides to gain insight into the interactions with acetylcholinesterase (AChE) and predict toxicity using two different tools based on different principles.

The stability of the non-aqueous solutions has not been reported before, which is of great importance for laboratory work and therefore represents a novelty. For the first time, molecular docking analysis was performed for five selected pesticides and a detailed study of toxicity. Based on all computational studies performed, the potential candidates for the treatment of Alzheimer's disease were proposed.

EXPERIMENTAL

Preparation of samples

Certified standards of pesticides (propiconazole, famoxadone, pendimethalin, pyraclostrobin and tebuconazole) were purchased from Dr. Ehrenstorfer (Augsburg, Germany). HPLC-grade methanol was purchased from J. T. Baker (Landsmeer, The Netherlands).

Stock solutions of the pesticides: propiconazole (0.25318 mg cm^{-3}), famoxadone (0.24058 mg cm^{-3}), pendimethalin (0.30215 mg cm^{-3}), pyraclostrobin (1.0673 mg cm^{-3}) and tebuconazole (0.23668 mg cm^{-3}) were prepared in methanol and stored at 4 °C. The methanol solutions of tebuconazole, pendimethalin, propiconazole and famoxadone were stored tightly sealed in the refrigerator for 9 months, and the methanol solution of pyraclostrobin was stored for 20 months.

GC–MS analysis

Gas chromatographic analysis of pesticides was performed on a 7890/7000B GC/MS/MS triple quadrupole system (Agilent Technologies, USA, equipped with a Combi PAL auto sampler). The fused silica capillary column HP-5MS (5 % phenylmethylsiloxane, 30 m×0.25 mm, film thickness 0.25 μm) was used with helium as carrier gas (1 cm^3 min^{-1}). The operating conditions were consistent with the previously published work.[16]

Compounds were identified by comparison of their MS with those from Wiley 6, NIST02, Mass Finder 2.3, by the application of the AMDIS software (the Automated Mass Spectral Deconvolution and Identification System, Ver. 2.1, DTRA/NIST, 2011).

*Electron–ion interaction potential (*EIIP*)/average quasi-valence number (*AQVN*)*

The specific recognition and targeting between interacting biological molecules at a distance of > 5 Å are determined by the *AQVN* and the *EIIP* derived from the general model pseudopotential:[17]

$$EIIP = 0.25(Z^*/(2\pi))\sin(1.04\pi Z^*) \quad (1)$$

where Z^* is the *AQVN* determined by:

$$Z^* = \frac{1}{N}\sum_{i=1}^{m} n_i Z_i \quad (2)$$

where Z_i is the valence number of the *i*-th atomic component, n_i is the number of atoms of the *i*-th component, *m* is the number of atomic components in the molecule, and *N* is the total number of atoms. The Z^* and *EIIP* values are expressed in Rydberg units (Ry). *AQVN* and *EIIP* are unique physical properties that characterize, among molecular descriptors, the long-range interactions between biological molecules.[15] *EIIP* and *AQVN* of organic molecules have been shown to correlate strongly with their biological activity (mutagenicity, carcinogenicity, antibiotic activity, *etc.*).[18,19]

Unconstrained conformational search

The conformational analysis of selected pesticides (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone, Fig. 1) was performed using MacroModel under Schrodinger Suite 2022-3 and Maestro, v. 13.3, as interface. Chloroform was used as the solvent. The conditions for the simulations were taken from the previously published work.[15]

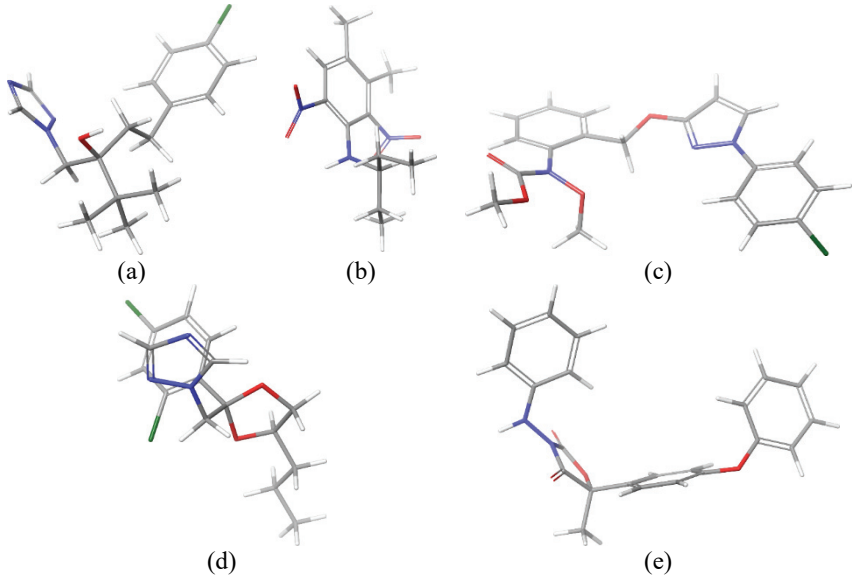


Fig. 1. 3D Structures of conformers with the lowest energies of investigated pesticides: a) tebuconazole, b) pendimethalin, c) pyraclostrobin, d) propiconazole and e) famoxadone.

Molecular docking studies

The molecular docking studies with selected pesticides (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone) were performed using acetylcholinesterase as a target from *Mus musculus* and *Homo sapiens*. In addition, molecular docking of selected pesticides was performed at the binding site of donepezil in acetylcholinesterase from *H. sapiens*.[20] In all cases, crystal structures were obtained from the Protein Data Bank (entry ID for *M. musculus* 5DTI[21] and *H. sapiens* 4EY7[20]). Acetylcholinesterase alone was prepared for docking using the Protein Preparation and Refinement tool of Schrodinger Suite 2022-3. The previously optimized structures of selected pesticides in MacroModel were ligands in the molecular docking studies. Molecular docking was performed with Glide under Schrodinger Suite 2022-3.

ADMET in silico *studies*

ADMET parameters of selected pesticides (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone) were calculated in normal mode using QikProp v7.0 software (Schrödinger, Inc., New York, NY, USA).

ACD/Percepta 14.53.0 (Build 3577) (Advanced Chemistry Development, Inc., Toronto, Canada) was also used to generate ADMET profiles of selected pesticides based on SMILES strings of the compounds.

RESULTS AND DISCUSSION

Stability analysis of selected pesticides using GC–MS

GC–MS analysis can be used to efficiently determine the stability of methanolic solutions of the selected pesticides (tebuconazole, pendimethalin, pyraclostrobin, propiconazole and famoxadone). The stability in aqueous solutions has been well studied.[22] After nine months, the methanolic solutions of tebuconazole, pendimethalin, propiconazole and famoxadone were not degraded. Their retention times were 16.75 (tebuconazole), 14.47 (pendimethalin), 16.31–16.63 (propiconazole) and 22 min (famoxadone) (Fig. S-1–S-4 of the Supplementary material to this paper). Pyraclostrobin does not show stability in methanol solution like the others (Fig. 2). Besides pyraclostrobin (20.45 min), the solution mainly contains the des-methoxy derivative of pyraclostrobin (18.32–18.51 min, Fig. 2).

*Computational studies (*EIIP *calculation, conformational search, molecular docking and ADMET) of selected pesticides and acetylcholine esterase from* M. musculus *and* H. sapiens

The selected pesticides had AQVN values that were in the intervals of 2.5116–3.0434 (Table I). The absolute values of EIIP ranged from 0.0233 for pendimethalin to 0.0938 for tebuconazole. The previous studies have shown that tebuconazole[23] and propiconazole[24] exhibit AChE inhibitory activity. The specificity of inhibitors between insect and mammalian AChE contributes to selective toxicity.[25] In general, it is safer for insecticides to have a higher affinity for insect AChE than for human AChE.

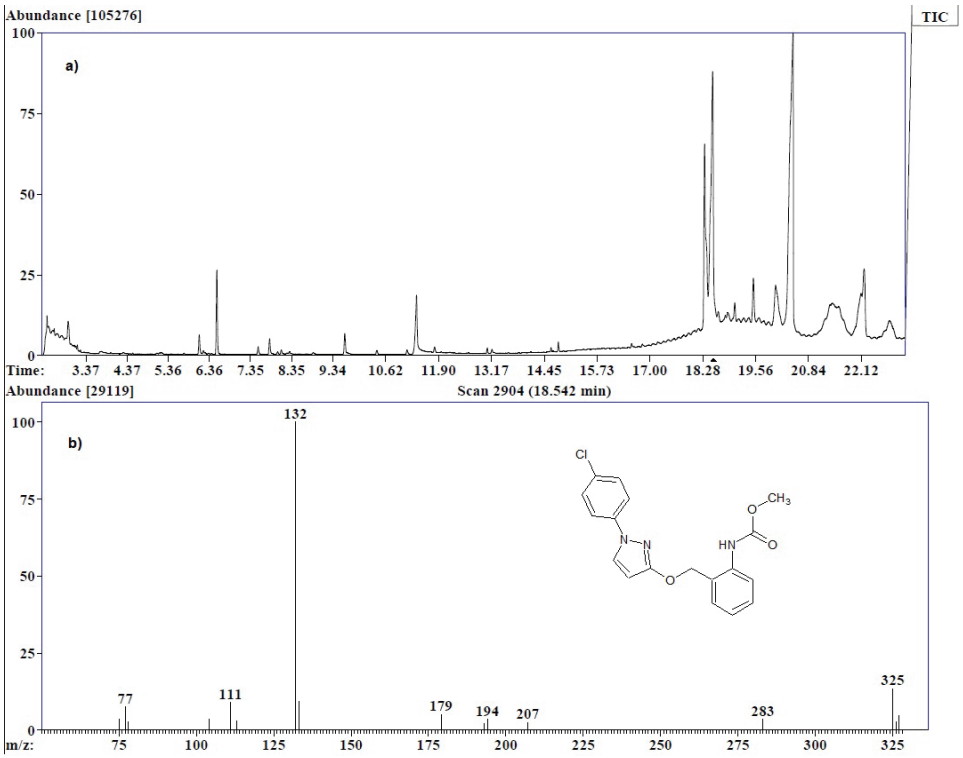


Fig. 2. a) Total-ion chromatogram (TIC) of pyraclostrobin solution, b) mass spectrum of the main degradation product (des-methoxy pyraclostrobin).

TABLE I. Investigated pesticides, their classes, molecular formulae, Z^*, and absolute *EIIP*

Pesticide	Class	Molecular formula	Z^* / Ry	*EIIP* / Ry
Tebuconazole	Triazole fungicide; conazole fungicide	$C_{16}H_{22}ClN_3O$	2.5116	0.0938
Pendimethalin	Dinitroaniline herbicide	$C_{13}H_{19}N_3O_4$	2.8205	0.0233
Pyraclostrobin	Strobilurin fungicide; carbanilate fungicide; phenylpyrazole fungicide	$C_{19}H_{18}ClN_3O_4$	2.9777	0.0355
Propiconazole	Triazole fungicide; conazole fungicide	$C_{15}H_{17}Cl_2N_3O_2$	2.7180	0.0560
Famoxadone	Oxazole fungicide; dicarboximide fungicide	$C_{22}H_{18}N_2O_4$	3.0434	0.0600

Prior to molecular docking, all selected pesticides were prepared in Macro-Model. The global minimum of each pesticide was used for molecular docking. The global minimum energies and replicates of the studied structures are listed in Table II.

After optimization, the selected pesticides were subjected to molecular docking against acetylcholinesterase from *M. musculus* and *H. sapiens*, whose sequences are 89.80 % identical using BLASTP (protein BLAST: search protein databases using a protein query (nih.gov)), and the values of Glide scores[26,27] from molecular docking are listed in Table II. Acetylcholinesterase (AChE) was selected due to its involvement in numerous cholinergic signalling pathways in the central and peripheral nervous system.[28] According to the molecular docking studies performed, famoxadone is the best binder for acetylcholinesterase from the studied pesticides on *M. musculus* AChE, and the weakest is pendimethalin. In the case of *H. sapiens*, the best AChE inhibitor is propiconazole and the worst is pendimethalin.

TABLE II. Global minima energies and repeats of the investigated pesticides, and Glide scores of selected pesticides against AChE from *M. musculus* and *H. sapiens*

Pesticide	Global minimum energy, kJ mol^{-1}	Number of replicates	Glide score, kJ mol^{-1}	
			Mus musculus	*Homo sapiens*
Tebuconazole	215.6	20	–23.81	–22.51
Pendimethalin	479.3	18	–18.41	–19.58
Pyraclostrobin	201.1	17	–26.32	–20.17
Propiconazole	102.6	3	–21.59	–24.31
Famoxadone	409.8	27	–27.61	–23.93

Two interactions are common to all investigated pesticides against AChE in *M. musculus*: His 381 and Phe 531. A different situation was observed in *H. sapiens*. They have no common contact with AChE, and generally fewer interactions with AChE were observed compared to *M. musculus* (Fig. 3).

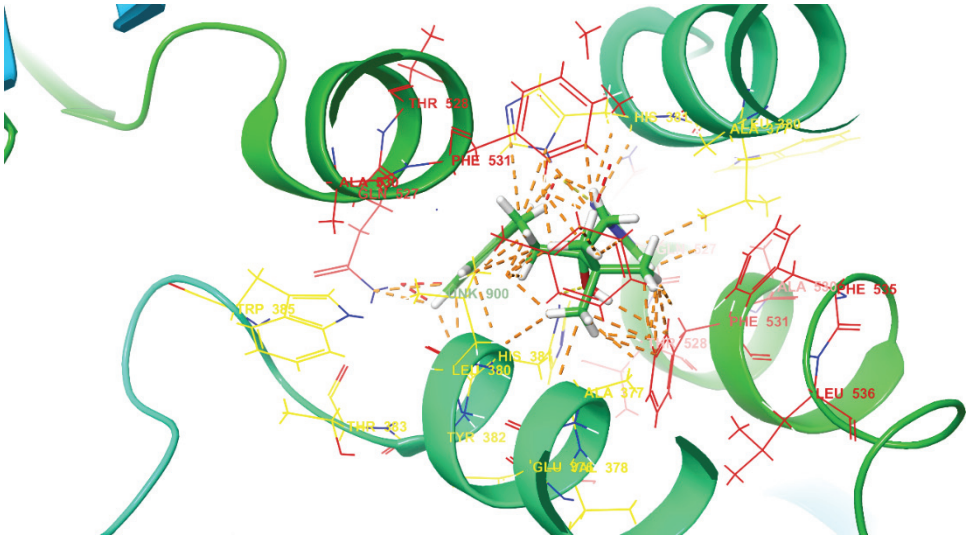
In general, pesticides are more toxic to lower organisms.[29] More interactions here are observed in *M. musculus* than in *H. sapiens*. Some pesticides have been already studied as potential candidates for drugs against Alzheimer's disease,[15] so it was reasonable to investigate *in silico* selected pesticides here with the same aim.

Molecular docking studies of approved Alzheimer's medicines and selected pesticides against acetylcholine esterase from H. sapiens

Drugs for the treatment of Alzheimer's disease (donepezil, rivastigmine and galantamine) that target AChE[30] fall within the AQVN range of 2.5 and 2.667. The pesticides and drugs for Alzheimer's disease studied have a common target – acetylcholinesterase. The crystal structure of donepezil with acetylcholinesterase from *H. sapiens* was used for our docking studies, taking into account the binding site from chain B including interactions with Ser 293, Trp 286 and Trp 86.[20] The redocking of donepezil resulted in a Glide score of –16.32 kJ mol^{-1}. Two other approved drugs for the treatment of Alzheimer's disease (rivastigmine and gal-

A)

a)



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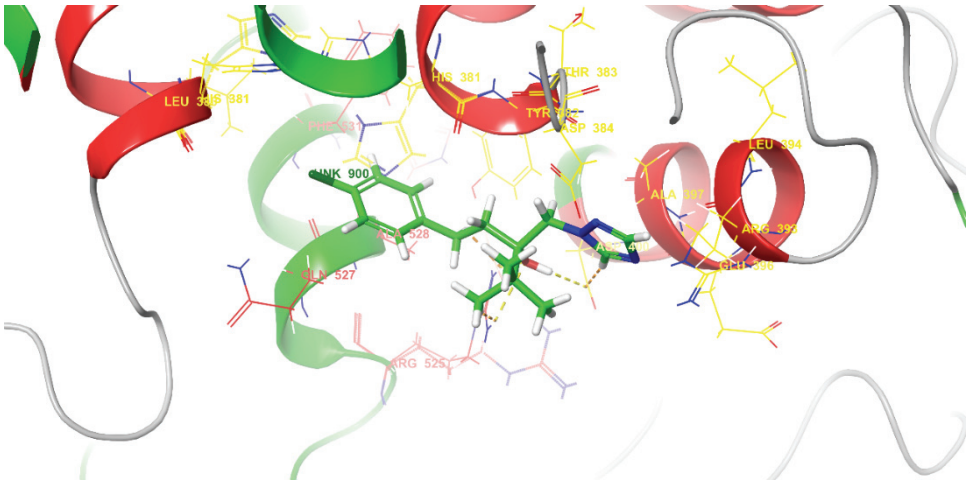
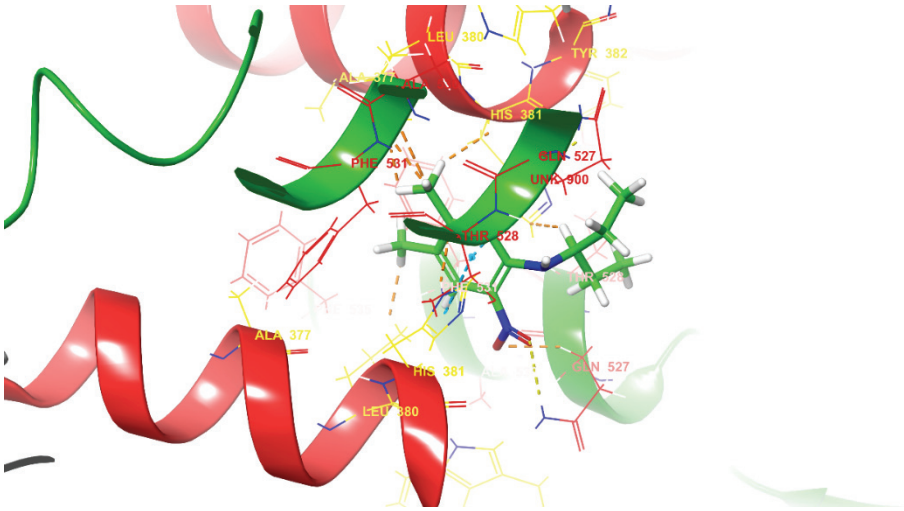


Fig 3. **A)** Graphic representation of molecular docking of tebuconazole into the acetylcholine esterase from a) *Mus musculus*, b) *Homo sapiens*.

antamine) provided better results for galantamine (–22.51 kJ mol^{-1}) and weaker results for rivastigmine (–12.30 kJ mol^{-1}). The acute oral toxicity of pendimethalin, pyraclostrobin and famoxadone in mice/rats is > 4500 mg kg^{-1},[31] therefore their *in silico* inhibitory effects on AChE in *H. sapiens* were compared with those of approved Alzheimer's drugs (donepezil, rivastigmine and galantamine). Values

B)

a)



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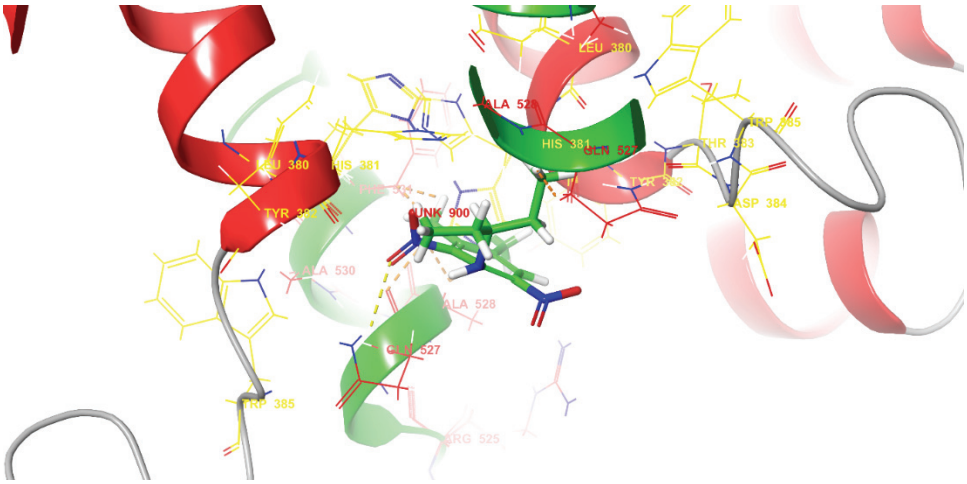
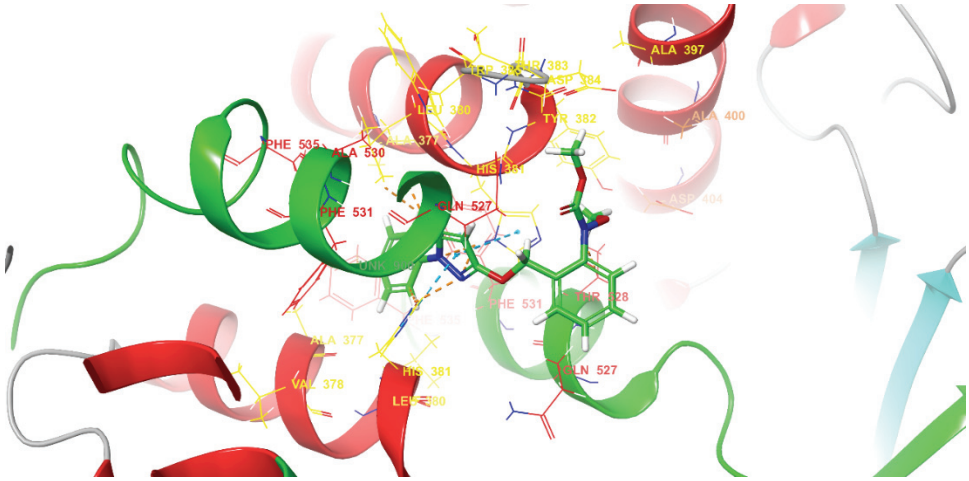


Fig 3 (continued). **B)** Graphic representation of molecular docking of pendimethalin into the acetylcholine esterase from a) *M. musculus*, b) *H. sapiens*.

(in kJ mol^{-1}) of –19.75 (pendimethalin), –18.32 (pyraclostrobin) and –20.08 (famoxadone) were obtained for the selected pesticides. The glide scores for these pesticides were better than those for donepezil and rivastigmine, so they can be further investigated as the replacements for these drugs.

C)

a)



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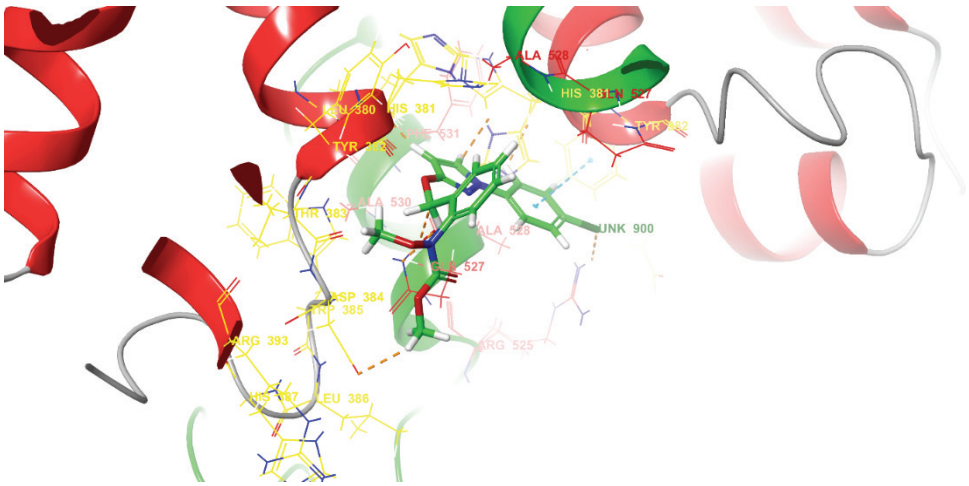


Fig 3 (continued). **C)** Graphic representation of molecular docking of pyraclostrobin into the acetylcholine esterase from a) *M. musculus*, b) *H. sapiens*.

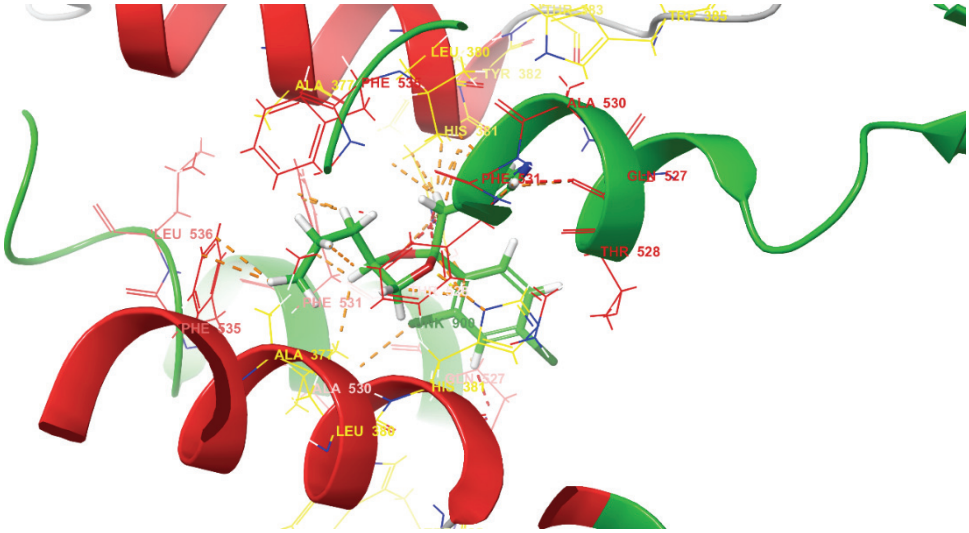
In silico *ADMET studies of selected pesticides*

The toxicity of the compounds was assessed using Lipinski's Rule of Five,[32] which includes molecular weight (<500 Da), number of hydrogen-bond acceptors (≤10) and donors (≤5), octanol/water partition coefficient (≤5), and Jorgensen's rule of three,[33] which includes log *S* (>–5.7), *PCaco* (>22 nm s^{-1}), and primary

metabolites (*PM*) (<7). The violations of these rules are essential for the optimization of biologically active compounds and should not exceed 1.

D)

a)



b)

Fig 3 (continued). **D)** Graphic representation of molecular docking of propiconazole into the acetylcholine esterase from a) *M. musculus*, b) *H. sapiens*.

Table S-I of the Supplementary material shows the ADMET properties of the selected compounds (tebuconazole, pendimethalin, pyraclostrobin, propicon-

E)

a)

b)

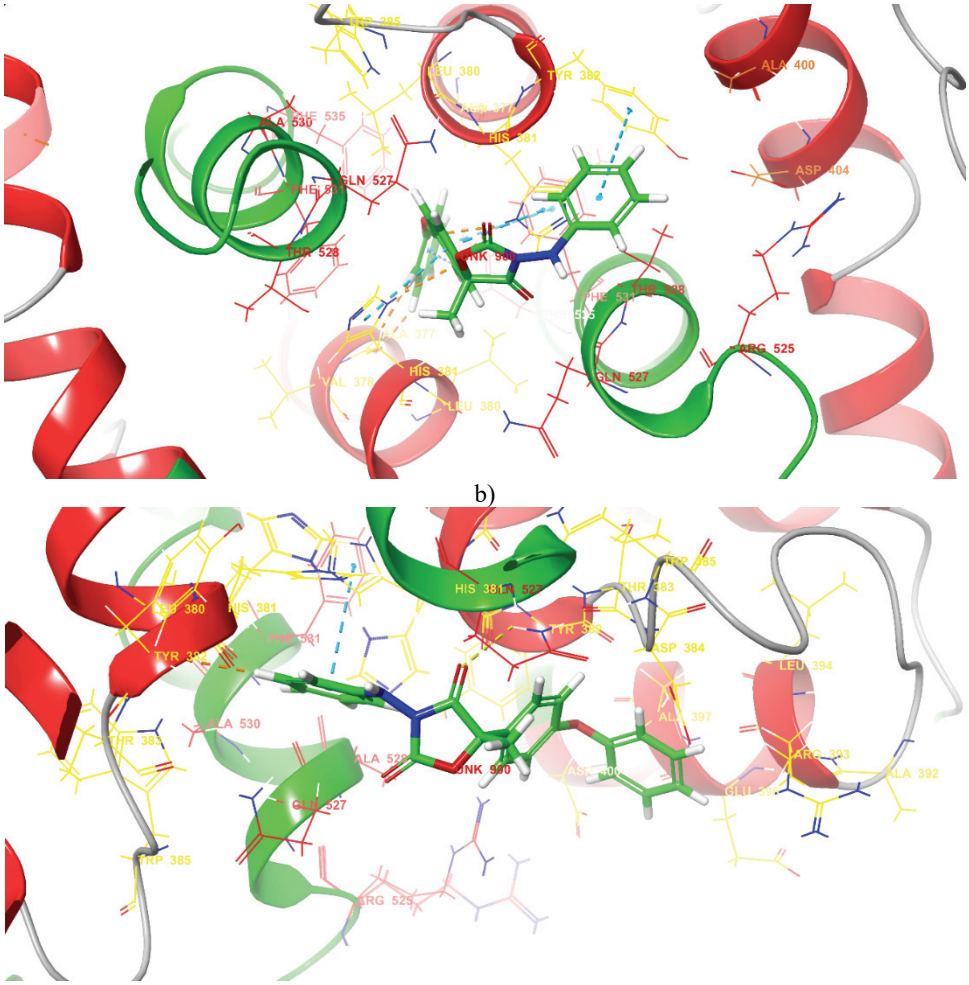


Fig 3 (continued). **E)** Graphic representation of molecular docking of famoxadone into the acetylcholine esterase from a) *M. musculus*, b) *H. sapiens*.

azole and famoxadone) predicted by QikProp and includes the following parameters: molecular weight (*MW*), number of rotatable bonds (*RB*), dipole moment (*DM*), molecular volume (*MV*), number of hydrogen donors (*DHB*), number of hydrogen acceptors (*AHB*), polar surface area (*PSA*), octanol/water partition coefficient (log *P*), water solubility (log *S*), apparent Caco-2 cell permeability (*PCaco*), number of probable primary metabolic reactions (*PM*), percentage of oral absorption by humans (*%HOA*), and violations of the rule of three (*VRT*) and

rule of five (*VRF*). The theoretical calculations of ADME parameters are presented in Table S-I along with Lipinski and Jorgensen rule violations. Thus, it can be assumed that according to the predictions of the ADMET properties, all compounds are orally active.

The ADME and drug safety profiles of selected pesticides were predicted using Percepta. The results are presented in Table S-II of the Supplementary material. Based on the Caco-2 values, it can be said that all compounds have high permeability to Caco-2 cells (79×10^{-6}–196×10^{-6} cm s^{-1}). They are all also highly bound to plasma proteins (PPB) based on the values obtained (91–98 %). Based on the calculated scores (ranging from –2.80 to –2.20), they are all permeable to the CNS, implying that those with low toxicity are candidates for Alzheimer's disease because they share the same target – AChE. Percepta predicted only propiconazole not to be an inhibitor of gp-substrates, and only tebuconazole and propiconazole were found to be inhibitors of CYP3A4. Famoxadone was found to be a non-inhibitor for CYP1A2. Based on the Ames test, tebuconazole and propiconazole were found to be non-mutagenic, whereas pendimethalin was a mutagenic compound. The mutagenic effect of pendimethalin was consistent with the experimental data – high concentrations (500 and 1000 μM) which caused mutagenic effects on human umbilical vein endothelial cells.[34] This fact allows us to exclude pendimethalin as a mutagenic compound, and further studies can be proposed for famoxadone and pyraclostrobin.

CONCLUSION

Based on the obtained results from the analyses of five commonly used pesticides in the Republic of Serbia, it is obvious that computer-assisted tools such as ADMET (especially Lipinski's and Jorgensen's rules and mutagenic properties) profiling and molecular docking (Glide scores between –17 and –29 kJ mol^{-1}), with molecular descriptors, such as AQVN (2.5116–3.0434 Ry) showed that compounds, currently used as pesticides, such as pyraclostrobin and famoxadone, may be candidates for the development of effective treatments against Alzheimer's disease. Special attention should be paid to pyraclostrobin which decomposed mainly into its des-methoxy derivative after 20 months in methanol solution, and its newly developed derivative should have higher stability. GC–MS method can be easily used for studying the content and stability of various pesticides in formulations and for their determination in real samples, such as agricultural products.

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12490, or from the corresponding author on request.

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ИЗВОД

КОМПЈУТЕРСКА АНАЛИЗА И АНАЛИЗА СТАБИЛНОСТИ ОДАБРАНИХ ПЕСТИЦИДА КОЈИ СЕ КОРИСТЕ У РЕПУБЛИЦИ СРБИЈИ

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Пестициди који се често користе у Републици Србији (тебуконазол, пендиметалин, пираклостробин, пропиконазол и фамоксадон) имају високу стабилност, тако да њихова потенцијална токсичност се мора проучити. Ови пестициди се користе у Републици Србији у различитим формулацијама. Њихова токсичност и интеракције са ацетихолинестеразом су детаљно изучене у овом истраживању коришћењем компјутерских алата. ADMET (адсорпција, дистрибуција, метаболизам, екскреција, токсичност) изучавање је показало да су сви они ефикасна орална једињења, и да је пендиметалин мутагено једињење. Glide скорови су били у опсегу од –18,41 (пендиметалин) до –27,61 kJ mol^{-1} (фамоксадон) код миша, и од –19,58 (пендиметалин) до –24,31 kJ mol^{-1} (пропиконазол) код човека. Осим тога, експериментална стабилност раствора пестицида у метанолу је проучавана коришћењем GC–MS (ретенциона времена проучаваних пестицида се кретала од 14,47 (пендиметалин) до 22 min (фамоксадон)). Они показују добру стабилност током времена, осим пираклостробина који се углавном распада на свој дез-метокси дериват после 20 месеци. На основу обећавајућих резултата моделовања, пираклостробин и фамоксадон се појављују као потенцијални кандидати који се могу даље изучавати као третман за Алцхајмерову болест, водећи рачина да се повећа њихова стабилност.

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