MOLECULAR ORBITALS STUDY ON DERIVATIVES OF ARYLAMIDE IMIDAZOLES AS INHIBITORS OF BUTYRYLCHOLINESTERASE

21 Ružičkini dani
DANAS ZNANOST – SUTRA INDUSTRIJA
9. – 11. rujna 2026. • Vukovar • Hrvatska

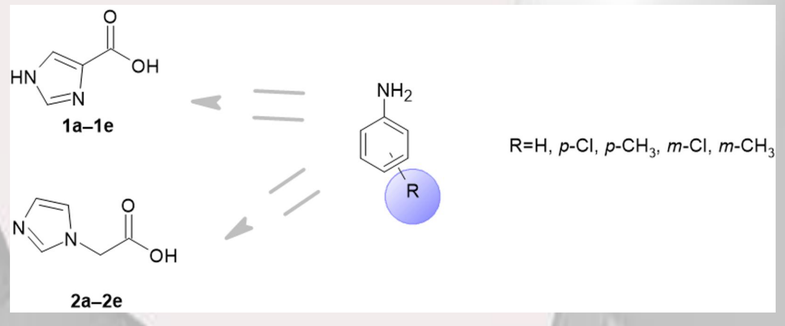
Vesna Rastija[a], Andrea Dandić[b], Martina Šrajer Gajdošik[b], Marija Paurević[b], Maja Karaš Babić[a], Domagoj Šubarić[a]

[a] *Fakultet agrobiotehničkih znanosti Osijek, Sveučilište Josipa Jurja Strossmayera u Osijeku, Vladimira Preloga 1, 31 000 Osijek*
[b] *Sveučilište Josipa Jurja Strossmayera u Osijeku-Odjel za kemiju, Ulica cara Hadrijana 8/A, 31 000 Osijek*

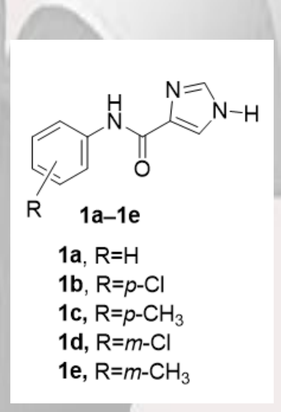
Fakultet agrobiotehničkih znanosti Osijek
Faculty of Agrobiotechnical Sciences Osijek
FAZOS

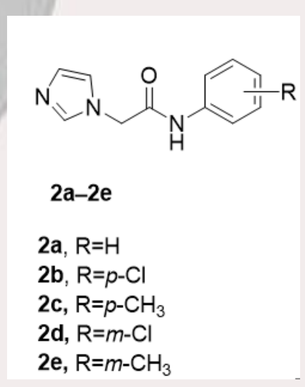
Introduction

- imidazole derivatives have a wide range of biological and pharmacological effects
- novel arylamide derivatives of imidazole were evaluated for their inhibitory activity against acetylcholinesterase (AChE), and butyrylcholinesterase (BuChE)
- frontier orbital energies highest occupied molecular orbital (HOMO), the lowest unoccupied molecular orbital (LUMO), were calculated for studied molecules in order to correlate with their inhibitory activity



The design approach of novel prepared arylamide imidazole derivatives **1a**–**1e** and **2a**–**2e**





Arylamide imidazole derivatives **1a**–**1e** and **2a**–**2e**

Methods

In vitro AChE and BuChE inhibition assay

- The inhibitory activities of cholinesterases were evaluated using the Ellman colorimetric method
- Percent inhibition was calculated using blank-corrected reaction rates according:

$$\text{inhibition (\%)} = 100 \times \left(\frac{v_i}{v_0}\right)$$

where v_i and v_0 represent inhibitor-treated and control reaction rates.

- 3D structures of 10 molecules were optimized applying HyperChem 8.0 using the molecular mechanics force field (MM+) and semiempirical PM3 method
- HOMO and LUMO energies were calculatedby HyperChem 8.0:

$GAP = E_{LUMO} - E_{HOMO}$

- Hardness (η/eV) was calculated according the equation: $\eta = (E_{LUMO} - E_{HOMO})/2$

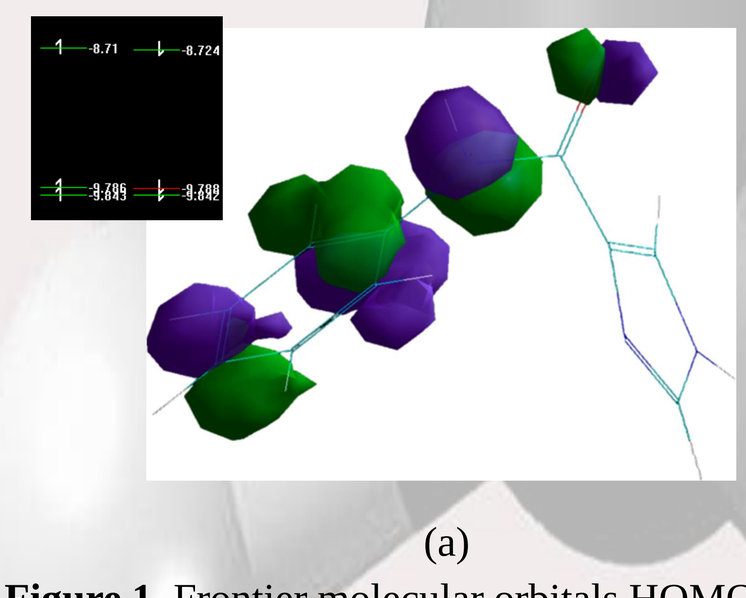
Results

AChE and BuChE inhibition

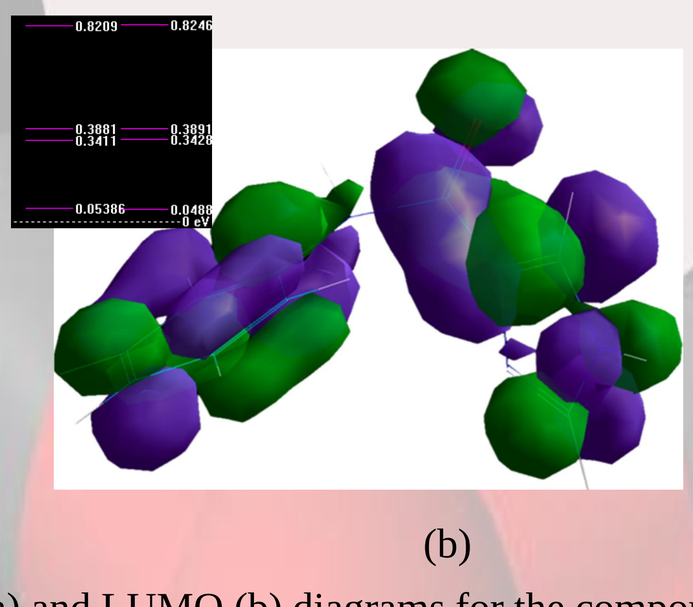
Table 1. Results of AChE and BuChE inhibition assay

Compound	Inhibitory activity against AChE	Inhibitory activity against BuChE
1a	23.52 ± 7.44	87.13 ± 0.93
1b	30.06 ± 6.34	34.02 ± 4.94
1c	29.15 ± 5.89	48.66 ± 4.32
1d	28.12 ± 7.71	35.42 ± 0.36
1e	22.80 ± 9.64	53.59 ± 2.60
2a	25.34 ± 5.80	3.92 ± 8.12
2b	26.59 ± 9.46	1.15 ± 5.84
2c	31.12 ± 10.65	1.65 ± 8.17
2d	22.46 ± 6.9	16.35 ± 1.03
2e	30.75 ± 6.44	21.49 ± 4.29

- compound **2c** shown the highest activity against AChE
- compound **1a** exhibited stronginhibitory activity against BuChE



(a)



(b)

Figure 1. Frontier molecular orbitals HOMO (a) and LUMO (b) diagrams for the compound **1a**.

- HOMO orbitals represent regions of high valence-electron density
- indicating structural moiety with a tendency to donate electrons
- localised on the phenyl ring, nitrogen and oxygen atoms from the amide group

- LUMO orbitals represent regions of electron deficiency
- indicating a molecule's capacity to accept electrons.
- extend throughout the whole molecule
- localisation of positive charge of LUMO orbital of most active inhibitors provides important information for the design of active molecules

The frontier molecular orbitals study

Table 2. Results of the frontier molecular orbitals study (HOMO, LUMO, GAP, and hardness (υ/eV); dipole moment (μ/Debye).

	HOMO	LUMO	GAP	η	μ	% Inh. Buche
1a	-8.717	0.051	8.768	4.410	4.845	87.13
1b	-8.702	-0.127	8.575	4.224	4.517	34.02
1c	-8.598	0.053	8.651	4.352	4.892	48.66
1d	-8.860	-0.082	8.778	4.348	3.943	35.42
1e	-8.720	0.078	8.798	4.438	5.081	53.59
2a	-9.490	-0.385	9.105	4.360	3.389	3.92
2b	-9.501	-0.705	8.796	4.046	4.540	1.15
2c	-9.465	-0.379	9.086	4.354	3.421	1.65
2d	-9.480	-0.651	8.829	4.089	5.372	16.35
2e	-9.469	-0.373	9.096	4.362	4.973	21.49
Galantamine	-8.842	0.107	8.949	4.528	3.644	93.64

Table 3. Correlation coefficients between the quantum properties and the BuChE inhibitory effect.

	HOMO	LUMO	GAP	η	DIPM
HOMO	1.00				
LUMO	**0.90**	1.00			
GAP	**-0.71**	-0.33	1.00		
Hardness	0.48	0.81	0.28	1.00	
DIPM	0.19	-0.05	-0.49	0.35	1.00
% Inh. Buche	**0.77**	**0.84**	-0.33	**0.65**	0.14

- HOMO and LUMO have shown significant correlation with the BuChE inhibitory effect
- Enhanced positive values of these energies imply better inhibition of the molecule. The HOMO and LUMO orbitals present an electron-rich area and electron deficiency area

Conclusion

- synthesized arylamide imidazole derivatives exhibited considerably stronger inhibitory activity toward BuChE than AChE, indicating their selectivity for BuChE inhibition.
- derivative **1a** clearly emerged as the lead compound, exhibiting the highest BuChE inhibitory activity
- binding to the enzyme is achieved primarily with LUMO orbitals of inhibitor

Funding

This work was funded by the Croatian Science Foundation under the project number
HRZZ-IP-2024-05-6164 “Innovative Approaches in the Development of Imidazoles for Plant Protection”.

DIPP INN
HRZZ Croatian Science Foundation
SCAN ME