FHAL-P6 *IN SILICO* PROCENA I ANALIZA BIORASPOLOŽIVOSTI, FARMAKOKINETIKE I TOKSIKOLOŠKIH OSOBINA ODABRANIH DERIVATA PIPERAZINA

P. Džodić
Univerzitet u Nišu, Medicinski fakultet, Katedra Farmacija, Niš, Srbija

Piperazin je fleksibilan heterociklični skelet, široko primenjivan u dizajnu lekova zbog svoje sposobnosti interakcije sa različitim biološkim ciljevima. Ovo *in silico* istraživanje evaluira bioraspoloživost, farmakokinetička i toksikološka svojstva njegovih derivata (1–27), gde su jedinjenja 1–4 komercijalno dostupni lekovi.

Parametri sličnosti sa lekovima izračunati su korišćenjem *SwissADME* veb-alata i *MoloVol* softvera (v1.2.0). *SwissADME* je predvideo gastrointestinalnu apsorpciju, permeabilnost kroz krvno-moždanu barijeru, specifično vezivanje za P-glikoprotein i inhibiciju *CYP450* izoenzima. Toksikološki profili procenjeni su pomoću *DataWarrior* softvera (v06.05.04), klasifikujući jedinjenja u kategorije mutagenih, kancerogenih, reproduktivno toksičnih i iritantnih agenasa.

Prema pravilu Lipinskog, predviđeno je da sva jedinjenja osim 17 i 19 imaju povoljnu apsorpciju i permeabilnost. Sva jedinjenja (osim 9) pokazala su *TPSA* < 140 Å², što ukazuje na dobru intestinalnu apsorpciju, dok su jedinjenja 2, 4–6, 11–13, 16–18, 23–25 i 27 imala *TPSA* < 60 Å², što sugeriše penetraciju kroz krvno-moždanu barijeru. Za većinu jedinjenja (1–4, 7–9, 14, 16, 17, 19–25) predviđeno je da su supstrati P-glikoproteina. Metaboličko profilisanje ukazuje na inhibiciju *CYP450* izoenzima, uključujući 1A2, 2C19, 2C9, 2D6 i 3A4. Nijedno jedinjenje nije pokazalo mutageni rizik. Kancerogenost je uočena kod jedinjenja 5 i 13. Reproduktivnu toksičnost ispoljavaju jedinjenja 6, 12 i 14. Iritantni efekti su prisutni kod jedinjenja 11–15.

Nakon pažljive analize svih činjenica, preporučuje se sprovođenje daljih *in vitro* i *in vivo* studija radi evaluacije jedinjenja kao potencijalnih novih antiparazitskih (7, 8, 10), antimikrobnih (11), neuroaktivnih (16), antiinflamatornih (18, 20–24), antituberkuloznih (25, 26) i antitumorskih (27) agenasa.

Zahvalnica

Autor izražava zahvalnost Ministarstvu nauke, tehnološkog razvoja i inovacija Republike Srbije na finansijskoj podršci (ugovor broj 451-03-34/2026-03/200113).

FHAL-P6 *IN SILICO* ESTIMATION AND ANALYSIS OF BIOAVAILABILITY, PHARMACOKINETICS AND TOXICOLOGICAL PROPERTIES OF SELECTED PIPERAZINE DERIVATIVES

P. Džodić
University of Niš, Faculty of Medicine, Department of Pharmacy, Niš, Serbia

Piperazine is a flexible heterocyclic scaffold widely employed in drug design due to its ability to interact with diverse biological targets. This study computationally assesses the bioavailability, pharmacokinetic, and toxicological properties of its derivatives (1-27), with compounds 1-4 being commercially available drugs.

Drug-likeness parameters were calculated using the *SwissADME* web tool and *MoloVol* software (v1.2.0). The *SwissADME* web tool predicted gastrointestinal absorption, blood–brain barrier permeability, P-glycoprotein recognition, and *CYP450* inhibition. Toxicological profiles were assessed with *DataWarrior* software (v06.05.04), classifying compounds as mutagenic, carcinogenic, reproductive toxins and irritants.

Based on *Lipinski's rule*, all compounds except 17 and 19 are predicted to have favourable absorption and permeability. All compounds (except 9) exhibited *TPSA* < 140 Å², indicating good intestinal absorption, while compounds 2, 4–6, 11–13, 16–18, 23–25, and 27 displayed *TPSA* < 60 Å², suggesting blood–brain barrier penetration. Most compounds (1–4, 7–9, 14, 16, 17, 19–25) were predicted to be P-glycoprotein substrates. Metabolic profiling indicated inhibition of multiple *CYP450* isoenzymes, including 1A2, 2C19, 2C9, 2D6, and 3A4. None of the compounds exhibited mutagenic risk. Carcinogenicity was observed for compounds 5 and 13. Reproductive toxicity was detected for compounds 6, 12, and 14. Irritant effects were present for compounds 11–15.

After careful consideration of all findings, further *in vitro* and *in vivo* studies are recommended to evaluate the compounds as potential new antiparasitic (7, 8, 10), antimicrobial (11), neuroactive (16), anti inflammatory (18, 20–24), antitubercular (25, 26), and antitumor (27) agents.

Acknowledgement

The author acknowledges the financial support of the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (grant number 451-03-34/2026-03/200113).