FHAL-P5 *IN SILICO* EVALUACIJA BIORASPOLOŽIVOSTI, FARMAKOKINETIKE I TOKSIKOLOŠKIH OSOBINA ODABRANIH DUALNIH INHIBITORA ACETILHOLINESTERAZE I MONOAMINO OKSIDAZE-B ZA LEČENJE ALCHAJMEROVE BOLESTI

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Alchajmerova bolest (AB) je neurodegenerativni poremećaj kompleksne patologije. Acetilholinesteraza (AChE) i monoamino oksidaza-B (MAO-B) predstavljaju ključna mesta delovanja za regulisanje nivoa neurotransmitera, a dizajnirani su dualni inhibitori (supstance 1–46) kao eksperimentalni kandidati za terapiju AB.

Parametri sličnosti sa lekovima procenjeni su korišćenjem *pkCSM*, *SwissADME veb alata* i *MoloVol softvera (v1.2.0)*. *SwissADME* je predvideo gastrointestinalnu apsorpciju i penetraciju kroz krvno-moždanu barijeru, dok je *pkCSM* evaluirao specifično vezivanje za P-glikoprotein i inhibiciju CYP450 enzima. Toksikološki profili jedinjenja (1–46) procenjeni su pomoću *DataWarrior softvera (v06.05.04)*, klasifikujući jedinjenja u kategorije mutagenih, kancerogenih, reproduktivno toksičnih i agensi koji izazivaju iritaciju.

Većina jedinjenja pokazuje usklađenost sa pravilom Lipinskog (izuzev 12 i 35), što ukazuje na povoljnu apsorpciju i permeabilnost. Sva jedinjenja pokazala su TPSA<140 Å², što ukazuje na dobru intestinalnu apsorpciju, dok su jedinjenja 1, 3–6, 8, 11–16, 18, 19, 27, 30, 31, 34, 36–38 i 44–46 imala TPSA<60 Å², što sugeriše penetraciju kroz krvno-moždanu barijeru. Za većinu jedinjenja predviđeno je da su supstrati P-glikoproteina. Metaboličko profilisanje ukazalo je na inhibiciju CYP1A2, 2C19, 2C9, 2D6 i 3A4. Toksiološka analiza je identifikovala mutagenost (jedinjenja 4, 5, 19, 20 i 27), kancerogenost (jedinjenja 4, 5, 8, 18 i 19), reproduktivnu toksičnost (jedinjenja 15, 16 i 19–23) i iritantne efekte (jedinjenja 7, 11, 17 i 20).

Dobijeni rezultati ukazuju na dalju *in vitro* i *in vivo* evaluaciju jedinjenja 1, 3, 6, 13, 14, 30, 31, 34, 36–38 i 44–46 kao dualnih AChE/MAO-B inhibitora i potencijalno novih lekova za terapiju AB.

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FHAL-P5 *IN SILICO* EVALUATION OF BIOAVAILABILITY, PHARMACOKINETICS AND TOXICOLOGICAL PROPERTIES OF SELECTED DUAL INHIBITORS OF ACETYLCHOLINESTERASE AND MONOAMINO OXIDASE-B FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is a neurodegenerative disorder with a complex pathology. Acetylcholinesterase (AChE) and monoamine oxidase-B (MAO-B) are key targets regulating neurotransmitter levels, and dual inhibitors (compounds 1–46) were designed as experimental candidates for AD therapy.

Drug-likeness parameters were estimated using *pkCSM*, *SwissADME web tools*, and *MoloVol software (v1.2.0)*. *SwissADME* predicted gastrointestinal absorption and blood–brain barrier penetration, whereas *pkCSM* evaluated P-glycoprotein recognition and CYP450 inhibition. Toxicological profiles of compounds (1–46) were assessed with *DataWarrior software (v06.05.04)*, which predicted structural alerts as mutagenic, carcinogenic, reproductive, or irritant.

Most compounds complied with *Lipinski's rule* (excluding 12 and 35) indicating favorable absorption and permeability. All compounds showed TPSA<140 Å², indicating good intestinal absorption, while compounds 1, 3–6, 8, 11-16, 18, 19, 27, 30, 31, 34, 36-38, and 44–46 displayed TPSA<60 Å², suggesting blood–brain barrier penetration. The majority of compounds were predicted P-glycoprotein substrates. Metabolic profiling predicted inhibition of CYP1A2, 2C19, 2C9, 2D6, and 3A4. Toxicological analysis predicted mutagenicity (compounds 4, 5, 19, 20 and 27), carcinogenicity (compounds 4, 5, 8, 18 and 19), reproductive toxicity (compounds 15, 16 and 19–23), and irritant effects (compounds 7, 11, 17 and 20).

Computational findings support further *in vitro* and *in vivo* evaluation of compounds 1, 3, 6, 13, 14, 30, 31, 34, 36–38, and 44–46 as dual AChE/MAO B inhibitors and potential new drug candidates for AD treatment.

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