DEOXYRIBONUCLEASE I INHIBITORS AS POTENTIAL NEUROPROTECTIVE AGENTS

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Deoxyribonuclease I (DNase I), one of the best characterized mammalian endonucleases, breaks down both single-stranded and double-stranded DNA to produce 3'-OH/5'-P ends, with primarily dinucleotides, but also other oligonucleotides being the final products. DNase I is one of the major nucleases involved in DNA degradation during apoptosis, and therefore might have a crucial role in the development of many disease conditions caused by excessive cell death. Elevated DNase I levels and excessive apoptosis are associated with the development of numerous neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy, cerebellar degeneration... Thus, DNase I inhibitors represent an attractive potential target for the design of alternative strategies for the prevention and/or treatment of such neurodegenerative disorders. Inhibition of bovine pancreatic DNase I has been evaluated *in vitro* by a number of both monocyclic and polycyclic organic compounds, including furan, thiazole, benzocyclobutane, benzimidazole, thienopyrimidine and benzopyran derivatives. Among each group tested, there was at least one compound with better inhibitory properties against DNase I compared to crystal violet, used as a reference compound. The most potent DNase I inhibitors within the investigated compounds could be set as a good starting point for the development of new and more effective DNase I inhibitors with potential application in the prevention and/or treatment of neurodegenerative disorders. Moreover, due to the fact that there is no DNase I inhibitor defined as a "gold standard", these structures may represent new lead compounds in future trials.

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INHIBITORI DEZOKSIRIBONUKLEAZE I KAO POTENCIJALNI NEUROPROTEKTIVNI AGENSI

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Dezoksiribonukleaza I (DNaza I), jedna od najbolje okarakterisanih endonukleaza sisara, razlaže i jednolančanu i dvolančanu DNK proizvodeći 3'-OH/5'-P krajeve, pri čemu kao finalni proizvodi nastaju prvenstveno dinukleotidi, ali i drugi oligonukleotidi. DNaza I je jedna od glavnih nukleaza uključenih u degradaciju DNK tokom apoptoze, i stoga može imati ključnu ulogu u razvoju mnogih bolesti uzrokovanih prekomernom smrću ćelija. Povišeni nivoi DNaze I i prekomerna apoptoza dovode se u vezu sa razvojem brojnih neurodegenerativnih poremećaja, kao što su Alchajmerova bolest, Parkinsonova bolest, Hantingtonova bolest, amiotrofična lateralna skleroza, pigmentna retinopatija, spinalna mišićna atrofija, cerebelarna degeneracija... Stoga, inhibitori DNaze I predstavljaju atraktivnu potencijalnu metu za dizajn alternativnih strategija za prevenciju i/ili lečenje navedenih neurodegenerativnih poremećaja. Inhibicija goveđe pankreasne DNaze I ispitivana je u *in vitro* uslovima velikim brojem monocikličnih i policikličnih organskih jedinjenja, uključujući derivate furana, tiazola, benzociklobutana, benzimidazola, tienopirimidina i benzopirana. U svakoj od ispitivanih grupa, najmanje jedno jedinjenje je pokazalo bolja inhibitorna svojstva prema DNazi I u odnosu na kristal violet koji je korišćen kao pozitivna kontrola. Najefikasniji inhibitori DNaze I u okviru ispitivanih jedinjenja predstavljaju dobru polaznu osnovu za razvoj novih i efikasnijih inhibitora DNaze I sa potencijalnom primenom u prevenciji i/ili terapiji neurodegenerativnih poremećaja. Pored toga, usled činjenice da ne postoji inhibitor DNaze I definisan kao „zlatni standard“, ove strukture mogu predstavljati nove vodeće molekule u budućim ispitivanjima.

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