Heterocyclic derivatives, pharmaceutical compositions and methods of use thereof

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The present invention relates to the field of quinazoline, phthalazine and quinoxaline derivatives, as well as multimeric compounds, methods for their preparation, pharmaceutical compositions including such compounds, and methods of using these compounds, especially for treating and preventing brain damage due to traumatic brain injury (TBI) and in treating and preventing neurodegenerative diseases.

TBI is characterized by sudden physical damage to the brain. It is caused by many factors including warfare, terrorist attacks, automobile accidents, sports injuries, violent crimes, household accidents, child abuse, or by an object passing through the skull, for example gun shot wounds, or by shock waves, for example due to explosions. In the course of the research done, it was discovered that the peripheral-type benzodiazepine receptor (PBR) located on the mitochondrial membrane plays an essential role in the induction of apoptosis, which is one of the cellular processes leading to neuronal cell death in the process of secondary brain injury. PBR ligands can prevent neurodegeneration and reducing PBR expression can prevent apoptosis.

The compounds developed in the present invention bind with high affinity to PBR and block its apoptotic function. In particular, they can reduce the amount of apoptosis induced by glutamate, an important agent causing secondary brain damage after TBI and which also takes part in neurodegenerative diseases. Secondary brain injury due to TBI may therefore be prevented by providing paramedics as well as soldiers with the developed drug, thus reducing the incidence of disabilities occurring in the aftermath of TBI suffered due violence and accidents. Moreover, the new drugs may also find application in the treatment of neurodegenerative diseases, such as Alzheimer, Parkinson’s, etc., as well as non-neuronal degenerative diseases. Alternatively, other novel PBR ligands, as part of our invention, that activate PBR to induce apoptosis could find use as anticancer drugs.

Traumatic brain injury is the leading cause of disability in people under 40, severely disabling 150-200 people per million annually. Currently there is no approved treatment aimed at prevention or rescue of neurological tissue damage following TBI. The annual market potential for the first FDA-approved drug treating TBI in the U.S. alone is estimated above $500 million and the worldwide market potential above $1 billion.

Key words: peripheral-type benzodiazepine receptor (PBR), PBR ligands, traumatic brain injury (TBI), neurodegeneration, apoptosis, drug development.