Abstract

The proportion of people with neurodegenerative diseases is rapidly increasing. The hallmarks Alzheimer's disease (AD) are extra- and intracellular protein deposits of amyloid beta and hyperphosphorylated tau, the deposition of the latter is believed to correspond better with the disease progression. By developing and optimizing modern *in vivo* techniques of detecting intracerebral protein aggregates, such as positron emission tomography (PET) imaging, it is possible to detect a neurodegenerative disease in the early stages. This is crucial for the development of treatment options. A number of molecular probes for *in vivo* detection of intracerebral protein aggregates have already been reported, however, to date there is no molecular probe that would specifically and sensitively detect hyperphosphorylated tau-protein aggregates *in vivo*. We have chosen a molecular probe 2-(1-{6-[(2-[^{18}F]fluoroethyl)-(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([^{18}F]FDDNP) as our lead compound.

By formally inserting molecular spacers between electron donating (ED) and electron accepting (EA) group found in FDDNP, we aimed to prepare new groups of molecular probes that would possess improved binding characteristics, favorable optical properties for *in vitro* detection with fluorescence and confocal microscope, and would allow for the introduction of [^{18}F] fluorine-18. This would allow for the use in autoradiography, radioactive competitive binding assay, and PET imaging *in vivo*.

The chosen synthetic path included modern coupling reactions, such as Sonogashira, Suzuki, and Heck coupling, as well as traditional Bucherer-type reaction, Knoevelagel-type condensation, and radiosynthesis. New biphenyl, diphenylacetylene, stilbene, and naphthalene-based analogues containing similar ED and EA groups as FDDNP, were synthesized, characterized, and biologically evaluated *in vitro*. Dockings of the newly obtained compounds to the VQIVYK pseudo fibril model have also been performed to obtain a rough idea of the possibility of binding inside the channel in the tau-protein aggregates. The most promising analogues have been radiolabeled with [^{18}F] and used in autoradiography and competitive binding assays.

As the result, one compound, possessed improved binding properties, compared to the lead compound FDDNP, and is ready for use in further *in vivo* experiments.

Keywords: Neurodegeneration, Alzheimer's disease, coupling reactions, radiosynthesis, optical properties, docking, fluorescence microscopy, autoradiography, competitive binding assay.