POTENTIAL PRODRUGS OF THE NEURONAL NITRIC OXIDE SYNTHASE AND MONOAMINE OXIDASE INHIBITOR 7-NITROINDAZOLE AND STRUCTURALLY RELATED COMPOUNDS

By

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder of unknown cause that afflicts about 1.5 million Americans. The characteristic feature of PD is a deficiency of dopamine in the terminals of nigrostriatal neurons. Two enzyme systems, the neuronal form of nitric oxide synthase (nNOS) and monoamine oxidase B (MAO-B), have been linked to neurodegenerative pathways leading to PD. Several MAO-B and nNOS inhibitors have been evaluated for their neuroprotective properties in the mouse model of neurodegeneration which employs the parkinsonian inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). One such compound is 7-nitroindazole (7-NI), a compound which is reported to inhibit both enzymes.

This thesis focuses on the synthesis and biological evaluation of a potential prodrug form of 7-NI and related indazolyl containing compounds which are designed to release the active drugs following a metabolic bioactivation process. These studies have led to a detailed description of the nucleophilic aromatic substitution reactions between 4-chloro-1-methylpyridinium iodide and the indazolyl reactants that were employed as the initial step in the synthesis of the target compounds. The MAO-B substrate and inhibition properties of these "prodrugs" as well as the parent indazolyl compounds were examined. The results are discussed in relation to a previously developed active site model of MAO-B.

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dedicated to the memory of my father Dűndar A.F. Işın (1922-1996)

and all sufferers of Parkinson's disease

Table of Contents

List of Schemes

List of Figures