

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

By

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Thesis submitted to the faculty of Virginia Polytechnic Institute and State University in
partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE
IN
CHEMISTRY

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October 30, 2000

Blacksburg, Virginia

Keywords: Neuroprotection, SAR, tetrahydropyridinyl-based prodrugs, indazole, organic
reaction mechanisms

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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.

ACKNOWLEDGEMENTS

I wish to express my sincere gratitude and appreciation to my advisor Professor Neal Castagnoli, Jr. for his guidance, understanding, infinite patience and specially for helping me to appreciate the beauty of science. His dedication not only to science but also to life always will be a great source of inspiration for me.

I also would like to thank my committee members Dr. James Tanko, Dr. David Kingston, Dr. Harry Dorn and former committee member Dr. Calter for their valuable advice.

I wish to express my appreciation to the members of Castagnoli research group, Mrs. and Dr. Steyn for their guidance and assistance in the biological part of this work, Dr. Ashraf Khalil, Dr. Stephan Mabic and Dr. Phillipe Bissel for their suggestions for the chemistry part of this work, Mrs. Xueqin Shang for helping me with HPLC, Dr. Neels Van der Schyf, Mrs. Izel Fourie, and Mr. Jacques Petzer for our valuable discussions and last but not the least to Mrs. Castagnoli for her constant support.

Grateful acknowledgements are also made to two individuals Mrs. Ayşen Tulpar and Mr. Aziz Dursun for their friendship and their patience during the writing of the thesis.

I wish to express special thanks to Dr. Tom Glass and other members of the analytical services unit of the Chemistry Department for their assistance in some of the NMR experiments.

Finally I would like to thank my family and especially my mother Inci Işın and to my aunts Gülsen Koçer and Sevin Engin for their love and support.

I also wish to thank Harvey W. Peters Research Center for Parkinson's Disease and Disorders of the Central Nervous System for supporting this work and the Chemistry Department of VPI&SU for funding in the form of teaching assistantship.

dedicated to the memory of my father Dũndar A.F. Işın (1922-1996)
and all sufferers of Parkinson's disease

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