PREFACE

Neurodegenerative diseases (NDDs) represent, nowadays, one of the main causes of death in industrialized countries. In the modern world, the drugs affecting central nervous system (CNS) plays a significant role and are of special interest to mankind. A new paradigm is emerging in the targeting of multiple disease etiologies that collectively lead to NDDs such as Alzheimer's disease (AD), Parkinson's disease (PD), depression, anxiety and others. This paradigm challenges the widely held assumption that 'silver bullet' agents are superior to 'dirty drugs' when it comes to drug therapy. Accumulating evidence suggests that many NDDs have multiple mechanisms in their etiologies, thus suggesting that a drug with at least two mechanisms of action targeted at multiple etiologies of same disease may offer more therapeutic benefit compared with a drug that only targets one disease etiology.

More than 70% of FDA approved drugs are known to derive their therapeutic benefit by virtue of interacting with multiple targets. Based on these evidences, presently it is widely accepted that a more effective therapy would result from the development of the "one drug, multiple target" strategy, also called the multi-target-directed ligand (MTDL) approach. MTDL approach suggests the use of compounds with multiple activities at different biological targets.

In this context, MAO isozymes (MAO-A and MAO-B) and their inhibitors have been a steady source of surprises with the highest prospect for therapeutic use in the treatment of NDDs. In addition, acetylcholinesterase (AChE) and its inhibitors have also been regarded as attractive and potential target for the treatment of widespread NDDs. The crystal structures of human MAO isoforms and human AChE have been elucidated recently, necessitating a radical revision of some long-held ideas about how the enzyme interacts with substrates and inhibitors. Some inhibitors of both the enzymes developed by MTDL approach (*e.g.* Ladostigil, M30 and HLA20) have been shown to have potential use in the treatment of neurodegenerative conditions.

In spite of considerable progress in understanding the interactions of the two enzyme forms with their corresponding substrates, no general rules are yet available for the

rational design of potent dual inhibitors. There are many diverse chemical structures of MAO and AChE inhibitors partly because the active sites of these enzymes are ambiguous, which limits the design of new, potent and selective inhibitors. The known potent MAO and AChE inhibitors belong to various structural classes including hydrazines, hydrazide, amide, thiazole, imidazole, oxazolidinone, oxadiazolone, diacylurea derivatives, etc. A common structural feature of substrates and inhibitors is an amino or imino group that is assumed to play an essential role in orientation and complex formation at the active site of these enzymes.

Recently, the hydrazide-hydrazone and semicarbazone derivatives are gaining importance because of their broad-spectrum of biological activities. Day by day, the chemistry of carbon-nitrogen double bond of hydrazone and semicarbazone is fast becoming the backbone of condensation reaction in benzo-fused N-heterocycles. Besides, isatin (indole-2,3-dione) is also an important heterocyclic scaffold possessing various CNS activities including MAO and AChE inhibition. A literature survey identified several isatin derivatives in the developmental phase as potential new drugs. Thus, from the intensive literature survey, compounds bearing hydrazone, semicarbazone and isatin scaffolds have been identified as strong candidates for treating various NDDs.

The whole thesis is divided into six chapters as follows:

Chapter-1: The first chapter describes a brief introduction on NDDs, numerous factors leading to NDDs, diverse cerebral mechanisms implicated in their treatment, strategies employed for anti-neurodegenerative drug discovery and MTDL approach. This also presents the brief review of monoamine oxidases (MAO-A and MAO-B) and their inhibitors and AChE and its inhibitors as potential targets for the treatment of widespread NDDs along with their possible mode of action.

Chapter-2: This chapter includes a detailed literature survey of hydrazones, semicarbazones and isatin and its derivatives along with their diverse CNS and other biological activities. It also comprises of chemical and biological review on thiazole, benzothiazole and 1,3-benzodioxole moieties and a brief review on MTDL approach towards the development of anti-neurodegenerative agents.

Chapter-3: This chapter summarizes the overall design and rationale for conducting this research work, the research objectives and plan of work as embodied in this thesis.

Chapter-4: This chapter deals with the experimental procedures followed for the synthesis, characterization, *in-vitro* evaluation of MAO-A, MAO-B and AChE inhibition activities, behavioral studies (antidepressant activity, anxiolytic activity, sedative-hypnotic activity), neurotoxicity screening studies, antioxidant activity, assessment of liver function, molecular modeling studies and *in-silico* molecular analysis and ADMET prediction studies of 4 different series of compounds namely, 2-amino-6-nitrobenzothiazole derived extended hydrazones (**BTA-1** to **BTA-30**), 2-amino-5-nitrothiazole derived semicarbazones (**NTA-1** to **NTA-18**), 3,4-(methylenedioxy)aniline derived semicarbazones (**MDA-1** to **MDA-14**) and 3-hydroxy-3-substituted oxindole analogues of isatin (**HPO-1** to **HPO-14**).

Chapter-5: This chapter includes the detailed results and discussion of wet and dry lab experiments conducted for each of the four series of compounds.

Chapter-6: This chapter outlines the major findings of this research work with conclusions drawn from them and suggestions for the future work.

Bibliography: This includes the references used as a source of information to carry out the entire research work.