Epilepsy is a neurological disorder that affects people of all ages worldwide. It is characterized by unpredictable and recurrent disturbances of normal brain function that leads to convulsive seizure episodes and/or loss of consciousness. Epidemiological studies estimate that more than 50 million of the global population is affected with epilepsy. Despite the availability of several antiepileptic drugs 20–30% of the epilepsy patients worldwide have insufficient control over seizures and are resistant to the currently available pharmacotherapy. Poor tolerability and reported side effects of the antiepileptic drugs like hepatotoxicity, teratogenicity, impaired cognition, behavioural and psychiatric disturbances, etc. have affected the quality of life of the epilepsy patients. Drug therapy for this dreadful disease is still in its infancy and development of novel therapeutics with improved effectiveness, and lesser side effects still represent a herculean challenge for the scientific community.

γ–aminobutyric acid (GABA), which is an inhibitory neurotransmitter, maintains the inhibitory tone that counterbalances neuronal excitation and plays a significant role in the etiology and management of epilepsy. In epilepsy, a diminution in GABA-ergic neurotransmission is observed resulting in a decreased duration of inhibitory postsynaptic potentials. One of the rational approaches for enhancing GABA neurotransmission would be the blockade of GABA uptake system leading to the elevation of GABA concentration within the synaptic cleft. GABA uptake system comprises of specific subtypes of GABA transporters that mediate neuronal and glial uptake of GABA from the synaptic cleft. The discovery of piperidine-3-carboxylic acid (nipecotic acid) as a potent *in vitro* inhibitor of GABA transport creates new possibilities of targeting GABA uptake systems. However, it is highly polar in nature and unable to cross blood brain barrier to exert *in vivo* anticonvulsant activity.

On the basis of the literature review and profound *in vitro* GABA reuptake inhibitory activity reported for nipecotic acid, two new series of lipophilic compounds have been synthesized with an aim to increase blood brain barrier permeability by invoking the concept of hybrid pharmacophore approach and bioisosterism. Compounds were synthesized and characterized by physicochemical and state of art spectroscopic analysis.

The designed molecules were evaluated for *in viv*o anticonvulsant activity against validated rodent models of epilepsy and *in vitro* evaluation of blood brain barrier permeability. The active compounds were also evaluated for their effects on muscle coordination and neurotoxicity to account for their safety. The relevant hepatic, renal and haematological safety parameters of promising compounds were also evaluated along with standard drug. The outcome of *in vivo* results were further corroborated using *in silico* studies, which included the docking analysis of promising compounds, followed by molecular dynamics study to ascertain the stability of their binding mode following active site hydration. To this date, the research work has led to the publication of two research papers and two international presentations. Suggestions and comments on the part of the readers are always welcome.

The entire thesis has been divided into eight chapters as follows:

Chapter-1: The first chapter offers an introductory section which deals with a brief account of modern drug discovery and includes basic information about epilepsy and its management followed by a background of Nipecotic acid and a short description of the related issues.

Chapter-2: This chapter focused on detailed literature survey on piperidine-3-carboxylic acid and its derivatives as potential anticonvulsants and GABA uptake

inhibitors. It also includes the literature survey on anticonvulsant potential of naphthalene derivatives.

Chapter-3: This chapter summarises the research objectives, the overall rationale for carrying out this investigation and plan of work as embodied in this thesis.

Chapter-4: This chapter describes the experimental procedure used in the synthesis, characterisation, biological evaluation and computational studies.

Chapter-5: This chapter covers the results and discussion part of the research work.

Chapter-6: This chapter outlines the summary and conclusion.

Chapter-7: This section includes the references as a source of information to carry out the research work.