1.1. DRUG DESIGN, DISCOVERY, AND DEVELOPMENT

Drug design is an innovative approach to modify an already established drug or discovering new drugs concerning their biological targets. Never ending medical needs owing to the existence of highly vulnerable to several life-threatening diseases creates excessive demand for novel drugs. The discovery and development of an ideal drug for the treatment, mitigation, and cure of diseases represent a herculean challenge for medicinal chemists. It is a highly complex, challenging, costly and time-consuming assignment [Šunjić and Parnham, 2011]. As per the statistics, it takes approximately 12-14 years of extensive research and heavy financial investment of about 1 billion US $ to discover and bring a new drug into the market [Martis and Somani, 2012].

The pressing need to discover novel drugs for the management of neurological disorders like epilepsy represents an on-going neuropharmacological urgency. Presently available antiepileptic drugs symptomatically suppress the occurrence of seizures in epilepsy patients, but they are less effective in the disease-modifying therapy [Löscher and Schmidt, 2011]. Applying the sequential methodology of lead identification and optimization for designing anticonvulsant drugs is of utmost significance for the future discovery and development of novel antiepileptic drugs [Weaver, 2008]. Fortunately, over the last few decades, computational methods are being extensively utilized by the leading pharmaceutical companies and other research groups in the design and discovery of therapeutic agents in a more cost-effective manner. Computer-aided drug design (CADD) affords a knowledge-driven methodology that generates protein-ligand interaction patterns along with the binding affinity [Macalino *et al.*, 2015]. CADD tools have paved the way for the identification and manipulation of lead drug molecules to enhance its efficacy with lesser side

effects. The method of CADD has been revolutionized with the advent of molecular modelling, dynamics simulations, homology modelling, quantitative structure-activity relationship (QSAR), atom–based 3D QSAR, pharmacophore model generations molecular similarity approaches such as comparative molecular similarity indices analysis (CoMSIA) and comparative molecular field analysis (CoMFA). CADD strategies have been successfully employed to develop *in silico* models of some proteins involved in hyper-excitation and etiopathogenesis of epilepsy. Several proteins like $GABA_A$ receptor, voltage-gated Na^+ channel, voltage-gated K^+ channel, NMDA (N-Methyl-D-aspartate) receptor and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor were explored successfully using CADD [Weaver, 2008].

Broadly, the computational approaches are categorized into structure-based drug design (SBDD) and ligand-based drug design (LBDD). SBDD approach is based upon the utilization of known 3D structure of the target protein (receptor/enzyme) for the screening or generation of potential ligands. The fitting of the ligand into the complimentary binding sites of the target protein forms the basis of SBDD [Huang *et al.,* 2010]. SBDD includes one or more of the several tools like molecular docking, dynamics simulations, homology modelling, nuclear magnetic resonance (NMR) and X-ray diffraction (X-RD). On the other hand, LBDD involves the collection of ligands with varied structures and well-known potency followed by molecular modelling to create predictive theoretical models. These models are then subjected to structural optimization to improve the potency and to identify new chemical entities by virtual screening of a large chemical database. 3D-QSAR and pharmacophore modelling is one of the widely explored tools of LBDD [Acharya *et al.,* 2011]. Some anticonvulsant drugs like levetiracetam and its analog brivaracetam

were discovered by exploiting various modern drug designing approaches [Rogawski, 2008].

However, the present work envisaged synthetic strategies including molecular hybridization and bioisosterism to design and develop novel antiepileptic drugs. Molecular hybridization is a rational approach in drug design and development, which involves the amalgamation of pharmacophoric moieties of different bioactive scaffolds to generate a new hybrid architecture with enhanced affinity and efficacy, in comparison to the parent drugs [Viegas-Junior *et al.,* 2007]. Molecular docking tools or crystallographic methods may be employed to explore the binding mode of two known ligands for the same target protein to investigate the specific involvement of pharmacophoric moieties of both ligands for the binding in diverse regions of the active site [Fraga, 2009].

Bioisosterism is another strategy of Medicinal Chemistry for the rational design of new drugs. Friedman introduced the term bioisosterism to describe the phenomenon observed between substances structurally related which presented similar or antagonistic biological properties [Friedman, 1951]. Later, Thornber broadened the definition of bio-isosteres, describing them as subunits or groups or molecules which possess physicochemical properties of similar biological effects [Thornber, 1979]. Bioisosteric replacements are carried out in designing new drugs to improve pharmacological activity together with increasing the selectivity for a receptor or isoform of an enzyme. It also optimizes the pharmacokinetic parameters [Lima and Barreiro, 2005; Patani and LaVoie, 1996]. Several $GABA_A$ receptor agonists such as muscimol, thiomuscimol, and isomuscimol have been derived bioisosterically from γ–aminobutyric acid (GABA). The bioisosteric bicyclic analogs

like isoguvacine and isonipecotic acid were successfully developed as ligands of $GABA_A$ receptor [Patani and LaVoie, 1996].

In continuation of research endeavor towards the development of novel antiepileptic drugs, the present work utilizes the concept of molecular hybridization and bioisosterism to obtain a new molecular framework, to exploit their plausible anticonvulsant activity.

1.2. EPILEPSY: AN OVERVIEW

Epilepsy is a neurological disorder with a focal origin in the brain and is characterized by paroxysmal cerebral dysrhythmia, recurrent seizures, and disturbance of consciousness [Siddiqui and Ahsan, 2010; Bromfield *et al.*, 2006; Jacoby *et al.*, 2005]. Epilepsy is one of the most common disorders of the CNS affecting about 50 million of the global population [Goldenberg, 2010]. The estimated prevalence of epilepsy in low and middle-income countries is 80% of the total epilepsy burden worldwide. About 6–10 million of the Indian population has been suffering from active epilepsy, out of which less than half are treated [Megiddo *et al.*, 2016]. It is also well established that besides being a neurological disease; epilepsy is rather a stigmatised condition with an extremely high social impact [Aydemir *et al.*, 2016]. Discrimination, prejudice and social exclusion of epilepsy patients due to the unpredictability of seizures make their life miserable along with colossal emotional burden on their families [Baybaş *et al.*, 2017; Viteva and Semerdjieva, 2015]. In India, each case of epilepsy costs around INR 13,755 per annum with an overall load of about 5 million epilepsy patients. In India epilepsy exerts an overall economic burden of about INR 68.75 billion that corresponds to 0.5% of the gross national product [Sinha and Bhaumik, 2014].

The main cause of epilepsy includes disturbance in a normal neuronal activity that may generate seizure episodes. Excessive excitatory neurotransmission, diminished inhibitory neurotransmission or fluctuations in voltage-sensitive ion channels can lead to hyperexcitability and seizures [Bromfield *et al.,* 2006]. Abrupt signaling by neurons or nerve cells may be either localized in a particular area of one side of the brain (Focal seizures) or may spread in both hemispheres of the brain (generalized epilepsy) [Das *et al.,* 2012]. The disease is characterized as primary or idiopathic when no cause of the seizure is known, and secondary or symptomatic when the etiology has been identified. 40 % of the epilepsy cases worldwide are idiopathic in nature [Shorvon *et al.,* 2011]. Many idiopathic epilepsy cases exhibit a multifaceted pattern of inheritance with several genes functioning variably in each subject to create a particular phenotype [Sirven, 2015]. Symptomatic epilepsies are however attributed to several pathologic conditions, including acquired conditions and genetic anomalies. Acquired causes of epilepsy include cerebrovascular diseases, ischaemic stroke, haemorrhagic stroke, changes in glial cells, abnormal development of the brain, or any other type of brain injury that influences the normal brain functioning. Parasitic infections and bacterial/viral meningitis are also amongst the most common acquired causes of epilepsy throughout the world [Vezzani *et al.*, 2016]. Another acquired cause of secondary generalised seizures is the brain cyst formation by *Taenia solium* (pork tapeworm), a parasitic infection known as neurocysticercosis [Reddy and Volkmer, 2017]. Some investigations also suggest the involvement of several cytokines like Interleukin (IL)-1β, IL-8, IL-6, and TNF-alpha in the etiopathogenesis of seizures [Vezzani *et al.*, 2008; Youn *et al.,* 2013].

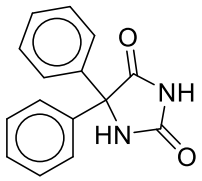
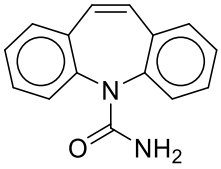
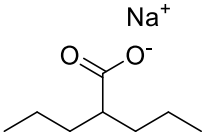
Several antiepileptic drugs are available in the market for the mainstay treatment of epilepsy. However, resistance to the presently accessible

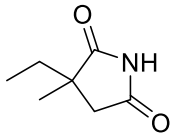
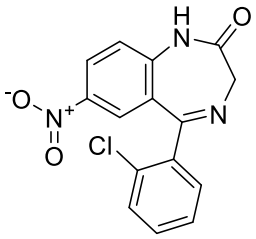
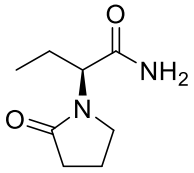
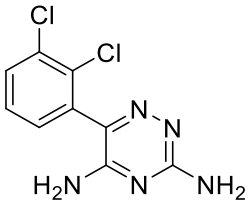
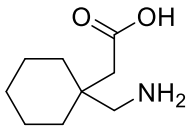
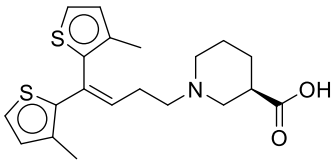
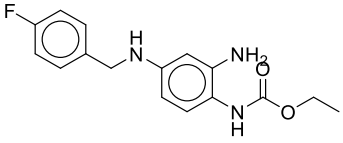
pharmacotherapy has been reported, that accounts for insufficient seizure control in about 20–30% of the 70 million epilepsy patients worldwide [Ghareb *et al.*, 2017]. Most of the antiepileptic drugs are believed to either suppress excitatory or enhance inhibitory neurotransmission. Also, the available therapeutic agents are not target specific and act on numerous molecular targets [White *et al.*, 2007]. Furthermore, currently available drugs can provide symptomatic relief by suppressing seizures. However, they are least effective to provide the complete cure or to modify the underlying disease process [Mittal *et al.*, 2013]. Various efforts have been put in the several years for the development of novel therapeutics which resulted in the design and synthesis of several new drugs as potential anticonvulsants.

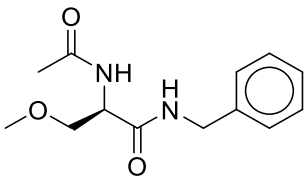
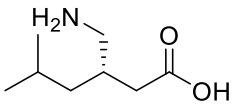
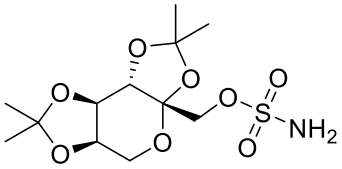
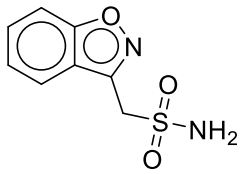
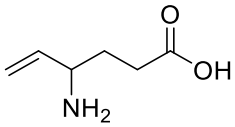
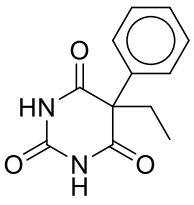
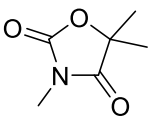
The mainstay treatment of epilepsy includes anticonvulsant drugs which are listed in Table 1.1 along with their structures and mechanism of action. Despite the continuous expansion in the field anticonvulsant drugs, they are associated with numerous side effects [Kubova, 2016]. Several first–generation anticonvulsant drugs, mainly phenytoin, carbamazepine, benzodiazepines, and primidone are associated with the considerable threat of coordination problems. These adverse effects (unsteadiness, imbalance, or ataxia) were also encountered in a meta-analysis of randomised and placebo-controlled trials of adjunctive treatment with drugs like lamotrigine, gabapentin, levetiracetam, pregabalin, tiagabine, oxcarbazepine, zonisamide and topiramate in caparison to placebo [Perucca and Gilliam, 2012]. Barbiturates possess severe sedative side effects [Bourin and Briley, 2004], and benzodiazepines lead to tolerance upon prolonged usage [Ashton, 1986; Michelini *et al.*, 1996]. The use of antiepileptic drug valproic acid is restricted because of its uncommon but life-threatening side effects, i.e. hepatotoxicity and teratogenicity [Bialer and Yagen, 2007; Shekh-Ahmad *et al.*, 2012; Shrivastava *et al.*, 1996].

Phenobarbital and topiramate are associated with impaired cognition [Park and Kwon, 2008; Perucca and Gilliam, 2012]. Hyperactivity or aggressive behavior in children is reported with gabapentin [Lee *et al.*, 1996]. Behavioral and psychiatric disturbances are observed with vigabatrin [Levinson and Devinsky, 1999]. Adverse metabolic effects of antiepileptic drug treatment were also reported [Nakken, 2011]. Thus, to address these enormous challenges, development of novel scaffolds with improved antiepileptic activity, considerable tolerability, and lower toxicity is a paramount necessity. Moreover, there is strong need to develop and discover a new generation of drugs which could be effective in disease-modifying therapy along with symptomatic relief. Owing to the range of reported adverse effects with existing conventional approaches, alternative strategies must be explored to strengthen GABA-mediated inhibition.

Table 1.1. Structure and mechanism of action of Anticonvulsant drugs

S. No.	Name	Structure	Mechanism	Reference
1.	Phenytoin		Blockade of voltage-gated sodium channels	[Yaari *et al.*, 1986]
2.	Carbamazepine		Blockade of sodium channel activity	[Ambrósio *et al.*, 2002]
3.	Sodium Valproate		Blockade of membrane sodium channels, Inhibition of GABA transaminase & inhibition of succinic semialdehyde dehydrogenase	[Kerwin and Taberner, 1981]

4.	Ethosuximide		Suppresses T- currents via T–type calcium channels	[Gören and Onat, 2007]
5.	Clonazepam		Binds to benzodiazepine binding site of $GABA_A$ receptors and facilitates GABA-ergic inhibitory transmission	[Riss *et al.*, 2008]
6.	Levetiracetam		Binds to synaptic vesicle protein SV2A in the brain and modulates the synaptic release of neurotransmitter	[Abou-Khalil, 2008]
7.	Lamotrigine		Blocks voltage-sensitive sodium channels and inhibit neuronal α4β2 nicotinic acetylcholine receptors.	[Coulter, 1997; Zheng *et al.*, 2010]
8.	Gabapentin		Exerts inhibitory effect on voltage-sensitive calcium channels and enhances the synthesis of GABA via modulation of glutamic acid decarboxylase	[Sills, 2006]
9.	Tiagabine		Selective inhibitor of GABA reuptake in presynaptic neurons and glial cells thereby increases the concentration of GABA at the synapse	[Ängehagen *et al.*, 2003]
10.	Retigabine		Modulates $GABA_A$ receptors as well as KCNQ2/KCNQ3 subunits of the potassium channels. Blocks sodium and calcium channels as a secondary mechanism.	[Gunthorpe *et al.*, 2012]

11.	Lacosamide		Augments slow inactivation of voltage-sensitive sodium channels and mediates neuronal plasticity by interacting with collapsin response mediator protein 2	[Kellinghaus, 2009]
12.	Pregabalin		Interact with alpha2–delta protein, a subunit of voltage-dependent calcium channels.	[Taylor *et al.*, 2007]
13.	Topiramate		Modulation of voltage-gated calcium and sodium channels, inhibition of excitatory neurotransmitter (glutamate) and also acts as carbonic anhydrase inhibitor	[Naegel and Obermann, 2010]
14.	Zonisamide		Blocks voltage-sensitive sodium and T-type calcium channels	[Leppik, 2004]
15.	Vigabatrin		Causes irreversible inhibition of GABA transaminase thereby reducing GABA breakdown	[Ben-Menachem, 2011]
16.	Phenobarbital		Potentiates GABA mediated inhibition, acts on chloride ion channels and increase influx of chloride ions into neurons, also reported to block sodium channels	[Czapinski *et al.*, 2005]
17.	Trimethadione		Suppresses T- currents via T–type calcium channels	[Macdonald and Kelly, 1995]

1.3. GABA HYPOTHESIS & EPILEPSY

The balance between excitatory and inhibitory neurotransmitters is one of the essential prerequisites for the normal functioning of the brain. Any imbalance caused due to deficit or excess of these neurotransmitters results in pathological features in the individuals that may include neurological or psychiatric diseases [Van Spronsen and Hoogenraad, 2010]. In epilepsy, an imbalance between L–glutamic acid (excitatory neurotransmitter) and GABA (inhibitory neurotransmitter) has been reported [Bonansco and Fuenzalida, 2016]. Imbalance of GABA-mediated synaptic transmission in the CNS has been associated with several nervous system disorders. Diminished activity of the GABA system has been associated with epilepsy, stress, sleep disorders, spasticity, anxiety, addiction, depression, and pain. Whereas, schizophrenic conditions are associated with the hyperactivity of the GABA-ergic neurotransmission [Bettler *et al.*, 2004].

Epilepsy is a manifestation of aberration in the inhibitory role of Gama Amino Butyric Acid (GABA), the major inhibitory neurotransmitter of the mammalian brain [Treiman, 2001]. Like other neurotransmitters of the brain, GABA also has its metabolic pathway, receptor system and transporters that constitute the target points to be modulated and corrected in case of abnormal functioning that precipitates epilepsy or other CNS disorder [Rowley *et al.*, 2012]. To understand the relationship between GABA and epilepsy, it is pertinent to look into the GABA system that comprises of synthesis, neurotransmission, metabolic pathway, receptors and transporters of GABA.

1.3.1. GABA Synthesis and Metabolism

GABA is synthesized within GABA-ergic neuron terminals through tricarboxylic acid pathway. The synthesis of GABA starts with transamination of α-

ketoglutarate to glutamic acid, followed by decarboxylation of glutamic acid to GABA [Siegel, 1999] (**Fig. 1.1**).

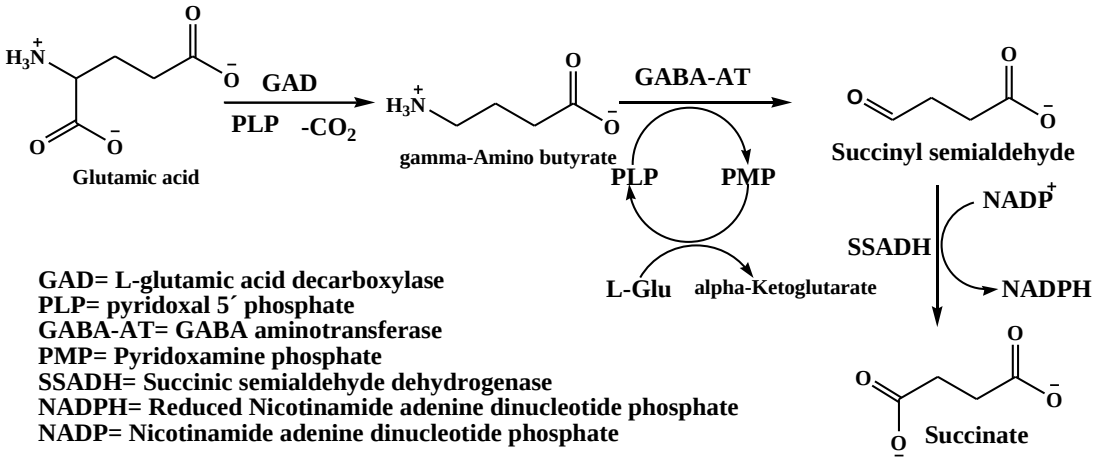


Fig. 1.1. Synthesis & metabolism of GABA

The first step of the GABA synthesis pathway involves the transamination of α-ketoglutarate, which is product of Tricarboxylic acid (TCA) cycle by α-oxoglutarate transaminase (GABA-T) into L-glutamic acid. In the next step, decarboxylation of L-glutamic acid mediated by glutamic acid decarboxylase (GAD) results in the formation of GABA. After synthesis, GABA is stored within synaptic vesicles. During neurotransmission, GABA is released in to synaptic cleft from where it is either transported to glial cells or taken back to presynaptic neuron through reuptake mechanism **(Fig 1.2)**. GABA is metabolized by GABA-transaminase (GABA-T) to form succinic acid semialdehyde (SSA). Dehydrogenation of SSA by SSA dehydrogenase (SSADH) results into succinate formation that enters in to the TCA Cycle [Roth and Draguhn, 2012].

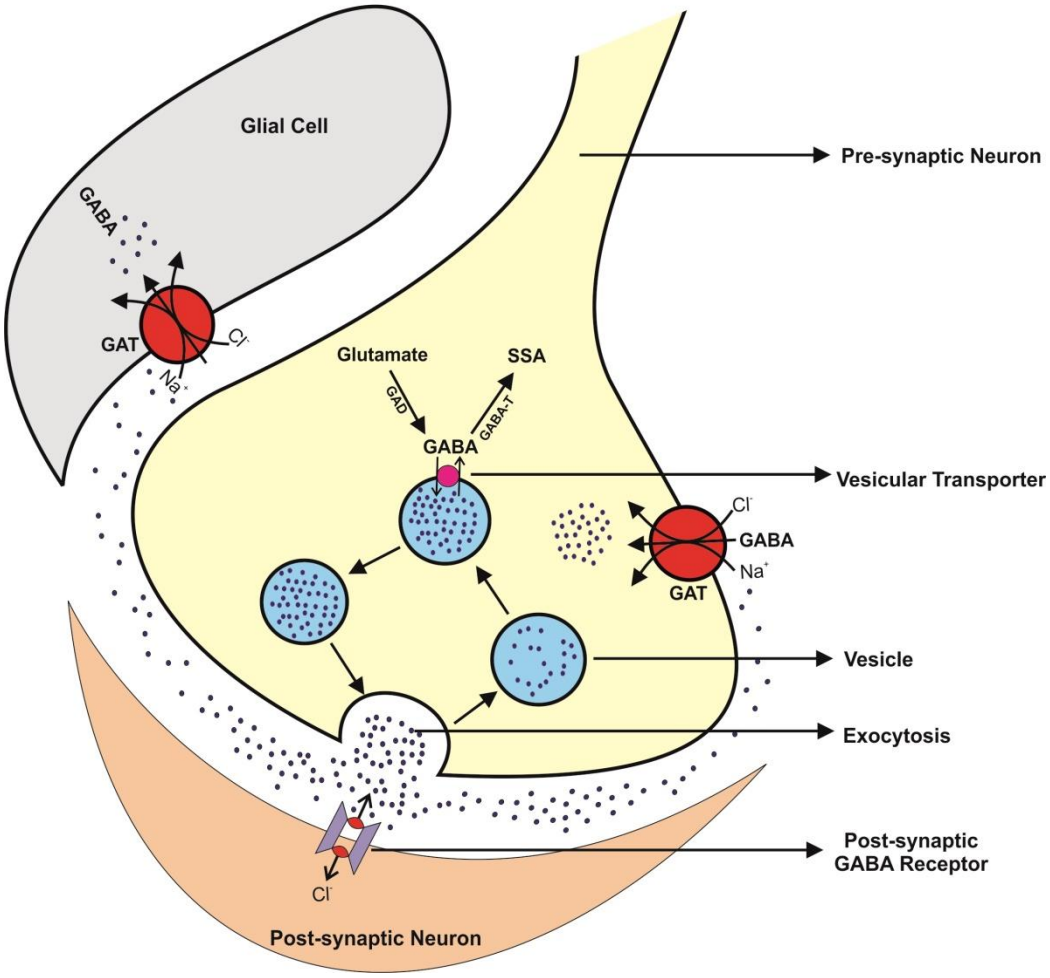


Fig. 1.2. Schematic representation of synthesis, storage, release, transport and metabolism of GABA.

1.3.2. GABA Receptors

There are three types of GABA receptors - $GABA_A$, $GABA_B$ and $GABA_C$. $GABA_A$ receptors are major receptors in mammalian brain through which GABA exert its neuroinhibitory functions. $GABA_A$ receptor belongs to Cys loop ligand-gated ion channel superfamily. The receptor comprises of five identical subunits that surrounds a central chloride ion-selective channel gated by GABA [Sigel and Steinmann, 2012]. Activation of these receptors leads to opening of Chloride ion channel, with some permeability of bicarbonate ions; causing influx of negatively

charged ions in postsynaptic membrane and hyperpolarization of depolarized membrane [Farrant and Nusser, 2005].

$GABA_B$ receptor is a G-protein-coupled receptor [Schwenk *et al.*, 2010] and is different in structure, function, and sequence from $GABA_A$ receptor. It is predominantly a presynaptic membrane receptor that inhibits the release of GABA (autoreceptors) and other neurotransmitters (heteroreceptors). $GABA_B$ receptor can couple with G protein, Ca^{2+} Channels, K^+ Channels and adenyl cyclase to yield different responses [Benke *et al.*, 2012, Olianas and Onali, 1999].

$GABA_C$ receptor has been identified recently. It is an oligomeric protein complex consisting of five subunits that are arranged into a pentameric protein complex having a centrally located chloride ion channel [Enz, 2001]. GABA binding sites and miscellaneous sites for modulatory ions such as Zn^{2+} are positioned in the extracellular portion of the protein.

1.3.3. GABA Transporters

GABA transporters (GATs) are unquestionably of utmost significance as regulators of neurotransmitter levels and control synaptic activity. GATs are the member of sodium symporters, which belongs to solute carrier 6 (SLC6) transporter gene family in humans that mediates neurotransmitter transport [Chen *et al.*, 2004]. GATs are widely expressed on the plasma membranes of neuronal and glial cells. These are responsible for the transport of GABA to glial cells as well as presynaptic neurons, and thus terminate GABA-ergic neurotransmission. Expression of four distinct subtypes of the GATs has been found in mammals, including humans. These transporters have been termed differently in human and mouse. In mouse, they are termed as GAT-1, GAT-2, GAT-3, and GAT-4 while in human being they are referred as GAT-1, BGT-1, GAT-2 and GAT-3 respectively. Transport of GABA is

an active process that requires an inward electrochemical gradient for Na^+, typically created by the membrane Na^+/K^+ ATPase rather than hydrolysis of ATP [Scimemi, 2014]. Out of the four transporters in humans, only hGAT-1 and hGAT-3 are selectively expressed in GABA-ergic neurons. hGAT-1 is mainly expressed at the presynaptic neuronal membrane and axon, while hGAT-3 is predominantly found in the glial cells as well as GABA-ergic nerve terminals [Jiang *et al.*, 2005]. It has been reported in the kinetic and thermodynamic studies that Cl^- along with Na^+ is required for the transport of GABA. Therefore, for mammalian GABA transporters, the best-documented stoichiometry is $1GABA:2Na^+:1Cl^-$ [Scimemi, 2014].

GABA has been the main subject for the researchers to develop new drugs for the treatment of epilepsy owing to its proven role in controlling neurotransmission processes as an inhibitory neurotransmitter. GABA metabolic pathway and GABA receptors have been studied extensively to get insight in etiology of epilepsy, and many drugs have been developed by targeting these pathways to treat epilepsy patients. The main hypothesis behind treating epilepsy is to elevate the level of GABA at synapse either by inhibiting its metabolism, activating GABA receptors using agonists or blocking its reuptake. Several anticonvulsant drugs (**Table 1.1**) have been successfully developed for variable targets including inhibitors GABA metabolizing enzyme (GABA transaminase), modulators of GABA receptors and drugs acting on various voltage-gated ion channels to provide symptomatic relief in epilepsy. However, GABA transporters have been relatively less explored domains for the development of antiepileptic drugs. Currently, Tiagabine is only marketed drug that selectively inhibits GAT-1 in the cortex and hippocampus to elevate the level of GABA at the synapse [Meldrum and Chapman, 1999]. Thus there is enormous scope in exploring GABA transporters to develop suitable leads as GABA

reuptake inhibitors with an aim to fortify GABA mediated inhibitory postsynaptic potential.

1.4. PIPERIDINE 3-CARBOXYLIC ACID (NIPECOTIC ACID)

The discovery of nipecotic acid as a high-affinity substrate for GABA transporter remarkably added new prospects of targeting GABA uptake systems. It has been reported to exhibit significant *in vitro* activity as an inhibitor of uptake of GABA into neuronal and glial cells [Krogsgaard-Larsen, 1980, Krogsgaard-Larsen and Johnston, 1975]. However, it is unable to cross BBB owing to its zwitterionic and polar nature.

Initially, Morris Freifelder in 1961 has reported the synthesis of nipecotic acid by catalytic hydrogenation of the corresponding pyridines with ruthenium dioxide. [Freifelder and Stone, 1961]. Later, hydrogenation was also attempted with Rhodium on carbon, platinum oxide to successfully synthesize nipecotic acid [Freifelder *et al.*, 1962; Freifelder, 1962]. Synthesis of nipecotic acid was also reported by catalytic reduction of nicotinic acid again with rhodium on alumina as a catalyst in the presence of concentrated ammonia. [Freifelder, 1963].

The potential *in vitro* GABA reuptake inhibitory activity of nipecotic acid coupled with its synthetic versatility has led to the synthesis of structurally diverse lipophilic derivatives with marked antiepileptic activity (**Fig. 1.3**).

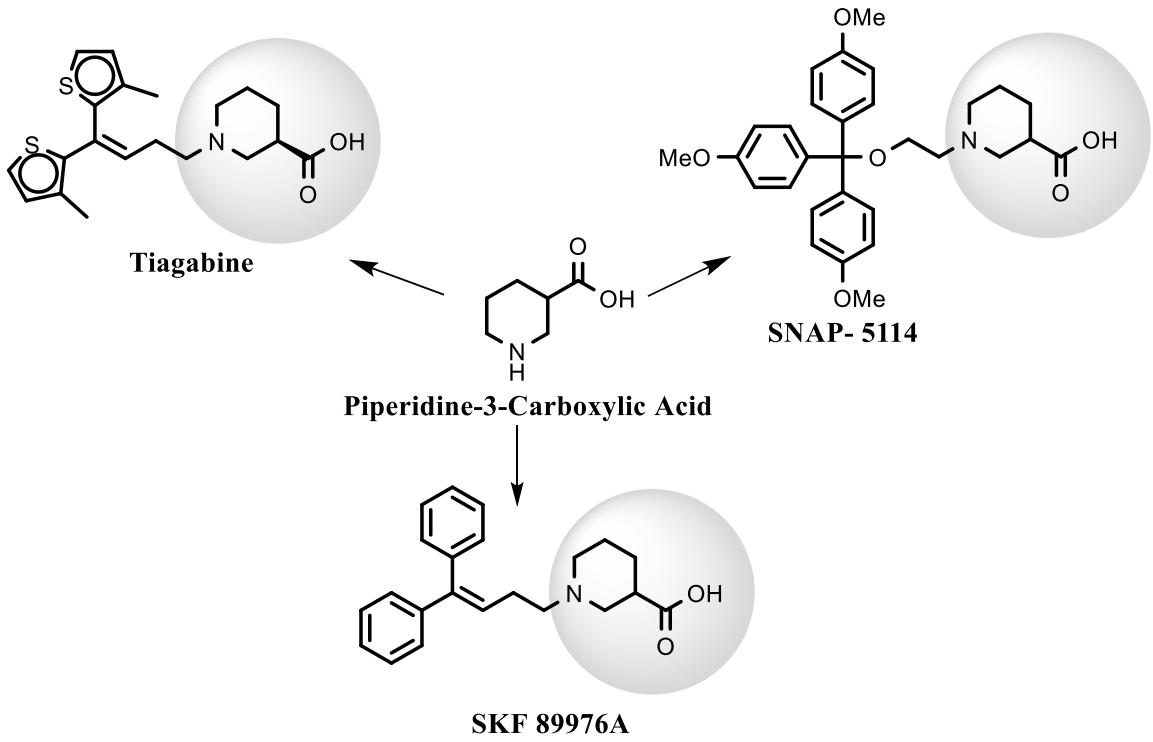


Fig. 1.3. Derivatives of nipecotic acid with reported GABA transport inhibition and anti-epileptic activity

For the first time in the early 1980s, some lipophilic derivatives of nipecotic acid such as SK&F 89976A (N-(4,4-diphenyl-3-butenyl)-nipecotic acid) have been successfully synthesized and demonstrated considerable *in vitro* GABA uptake inhibition in rat brain synaptosomes as well as promising anticonvulsant activity in some animal models [Yunger *et al.*, 1984]. Later, in another investigation N-(mono)- or N-(diarylmethoxy)alkyl substituted derivatives of nipecotic acid and guvacine has been synthesized and reported as synaptosomal GABA uptake inhibitors *in vitro* [Falch and Krogsgaard-Larsen, 1989].

In the sequence, NO- 328 (now marketed as tiagabine) has been characterized as a potent GABA reuptake inhibitor and was demonstrated to have anticonvulsant as well as antidepressant potential in several animal models [Braestrup *et al.*, 1990]. The findings have attracted scientist community to explore piperidine-3-carboxylic acid, resulting in the discovery of a highly lipophilic derivative, Cl-966, with GABA

reuptake inhibitory potential and anticonvulsant activity [Bjorge *et al.*, 1990, Taylor *et al.*, 1990]. Furthermore, in search of more lipophilic analogs of GABA uptake inhibitors, N-(benzhydryl ethyl ether) derivatives of nipecotic acid have been synthesized which exhibits *in vitro* inhibition of GABA uptake. The selected lead in this study was found to be effective in rodent models of epilepsy after oral administration, and the study was progressed to Phase 1 clinical trials. Unfortunately, due to serious neurological and psychological side effects after the administration of single dose to humans, further clinical evaluation was stopped [Pavia *et al.*, 1992].

Despite the synthesis of these diverse derivatives, BBB permeation remains the key bottleneck for brain drug delivery. The single marketed derivative of the piperidine-3-carboxylic acid, i.e., tiagabine is a GAT-1 selective GABA uptake inhibitor with considerable antiepileptic potential. Reported GABA uptake inhibition triggered by tiagabine has been attributed to the presence of GABA mimetic moiety in the form of piperidine-3-carboxylic acid and a lipophilic diaryl region connected by a linker [Jurik *et al.*, 2013]. Tiagabine is effectively used as adjunctive therapy for the management of complex partial seizures in epilepsy patients [Prescott, 1997]. However, its long-term use is associated with adverse effects like asthenia, tremor, concentration difficulties, lethargy, nervousness, and depression. Thus, there remains an enormous scope to address the existing challenges pertaining to the discovery of antiepileptic drugs which can effectively block the GABA uptake with improved BBB permeation.

On the basis of the SAR of the reported N-substituted derivatives of nipecotic acid endowed with antiepileptic potential and taking cognizance of known GABA uptake inhibitors especially tiagabine as a benchmark, an attempt was made to synthesize a series of novel derivatives of nipecotic acid. The outcome of the design

approach has been supported by *in vivo* anticonvulsant activity and *in vitro* blood–brain barrier (BBB) permeability of novel designed and synthesized molecules. Owing to the reported neurological side effects of antiepileptic drugs, the effects of leads on motor coordination and cell viability in neuroblastoma cell line have been investigated. Further, the relative safety profile of the promising compounds and the standard drug (tiagabine) will be evaluated concerning various hematological, hepatic, and renal parameters. The leads were then subjected to molecular docking on a homology modelled protein to identify and compare the complementary interactions of the compounds with the amino acid residues of the active pocket. The binding modes of the most active compound were further probed using molecular dynamics simulation at the GAT-1 active site.