3.1. Rationale and Objective

Epilepsy is a chronic neurological disorder characterized by recurrent seizures in which clusters of nerve cells signal abnormally in the brain. The underlying etiology may range from symptomatic seizures due to tumor, infection and trauma to cryptogenic forms. Cerebrovascular disease is one of the most commonly identified causes among adults, while prenatal complications seem to be the most common cause among children. An imbalance between glutamate and γ–aminobutyric acid (GABA) neurotransmitter systems can also lead to hyperexcitability. Enhancement of excitatory transmission and simultaneous failure of inhibitory mechanisms also results in repetitive neuronal discharges.

Another most common cause of seizures in developing world is due to the formation of the cyst by worm infestations in the brain known as neurocysticercosis. According to the WHO, it affects about 1% population of the world, and more than 85% of cases occur in developing countries. In India also, the prevalence is about 1% of our population and higher in rural (1.9%) as compared with the urban population (0.6%). The incidence of epilepsy in developed countries is between 40–70/100,000/year, and the ratio is much higher (120/100,000/year) in resource poor countries. The WHO has reported that 3 out of 4 people in the world with epilepsy do not receive treatment at all, due to misconceptions, lack of awareness, economic and social stigma.

In general, anticonvulsant drug discovery is based on either to target voltage–gated ion channels or influence (γ–aminobutyric acid) GABA–mediated inhibition. The newer generation of anticonvulsant drugs are pregabalin, stiripentol, lamotrigine, levetiracetam, topiramate and tiagabine. These drugs are effective in reducing seizures, but long-term therapy is marred by the incidence of side effects such as hepatotoxicity, headache, ataxia, gastrointestinal disturbances and drowsiness. These observations substantiate the opportunity and requirements for development of newer anticonvulsant drugs.

Various derivatives of quinazolin–4(3*H*)–ones have been discussed for their anticonvulsant activities in the previous chapter. Quinazolinone derivative such as methaqualone was initially explored for its sedative and hypnotic properties. Methaqualone at high dose was found to have sedative and muscle relaxant properties and at low dose it exhibit anticonvulsant activity. Mecloqualone, the chlorophenyl derivatives of methaqualone was found to be 1.5 times more potent than phenytoin

against MES induces seizures. Quinazolin–4(3*H*)–ones with a small C–6 substituent, orthogonal *N*3 phenyl ring and an aryl ring attached to C2 position elicit profound anticonvulsant activity. Further investigations revealed that the presence of small C6 substituent is not significant for exhibiting anticonvulsant activity.

On the basis of the above findings, we aimed to obtain some new quinazolinone derivatives with varying *N*3 aryl/heteroaryl ring substitution. In the present work, two series of quinazolin–4(3*H*)–ones with varying *N*3 aryl/heteroaryl ring substitution featuring the basic pharmacophoric requirements were designed, synthesized and screened for their anticonvulsant activity.

The first series of compounds possess different *N*3 substituted aryl/heteroaryl ring within a 6,7–dimethoxy–quinazolin–4(3*H*)–one nucleus while a common 2–chlorostyryl ring (two atom spacer) is attached at the C2 position of the designed molecules. The second series comprise of compounds having a benzyloxy methyl side chain at the C2 position corresponding to three atom spacer. In addition, divalent isosteric replacement of C2 side (two atom spacer) chain with a phenylthio methyl side chain was carried out for two compounds (Figure 3.1.). The above mentioned changes were carried out to observe and investigate the level of anticonvulsant activity with respect to the variation of substitution at C2, C6 and C7 along with *N*3 position of quinazolin–4(3*H*)–one nucleus.
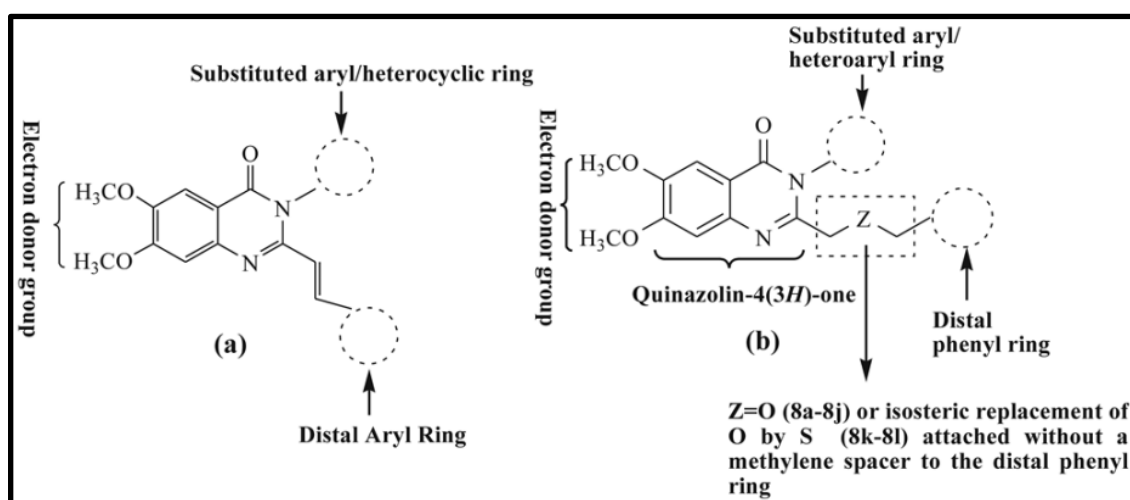
Figure 3.1. Template of compounds (**a**) series–I and (**b**) series–II.

3.2. Plan of Work

A brief outline of the research work carried out is summarized as follows:

3.2.1. Synthesis

- Synthesis of *N*3 aryl/heteroaryl substituted 2–(2–chlorostyryl)–6,7–dimethoxy–quinazolin–4(3*H*)–ones.
- Synthesis of *N*3 aryl/heteroaryl substituted 2–((benzyloxy and phenylthio) methyl) 6,7–dimethoxyquinazolin–4(3*H*)–ones.

3.2.2. Characterization of the synthesized compounds

- Physicochemical characterization including solubility, melting point, TLC analysis (R_f value) and partition coefficient.
- Structural confirmation by FTIR, ^{1}H NMR, ^{13}C NMR and Elemental (CHN) analysis. Mass spectroscopy was recorded for representative compounds.

3.2.3. Pharmacological evaluation

- Anticonvulsant Screening:
    - Maximal Electroshock (MES) induced Seizure
    - Subcutaneous Pentylenetetrazol (*sc*PTZ)
    - AMPA induced seizure
- Neurotoxicity Screening:
    - Rotarod test
- Hepatoxicity study

3.2.4. *In silico* pharmacokinetic studies, active site prediction at AMPA receptor site and docking studies