CONCLUSION:

Epilepsy is one of such diseases, where selectively acting drugs are still lacking. Epilepsy is characterised by recurrent seizures which affect about 25-30 million people worldwide with high prevalence of about 0.8% in children below the age of seven years. All forms of epilepsy have their origin in the brain and are characterised by general muscle spasm. Skeletal muscle spasm is usually characterised by trauma such as over extension or bruising blow, which results in acute episode of involuntary contraction of muscle.

In comparison with other centrally acting skeletal muscle relaxants, chlorzoxazone (5-chloro-2-hydroxybenzoxazolinone) showed protection against convulsions in mice at lowest (ED$_{50}$=215 mg/kg) concentration. It acts by depressing spinal polysynaptic reflexes, preferentially over monosynaptic reflexes. It was found to be more effective in treating acute spasm (e.g. epilepsy) than in spastic conditions (e.g. hemiplegia). It displays a high anti-pentylentetrazole activity.

Since all forms of epilepsy are characterised by generalised muscle spasm, in the PART-I we tried to synthesise a new class of anti-epileptic agents that shares the features of both GABA and benzoxazoles. Total eleven compounds were synthesized in the initial series having generalised structure as follows,

![Chemical Structure]

The purity and homogeneity of these compounds were judged by their sharp melting points and Rf values. The characterisation of these compounds was done by elemental analysis, IR and NMR spectra studies. The evaluation of anti-epileptic activity of the compounds was carried out by electro-convulsiometer and chemically induced seizure respectively.

The QSAR analysis and pharmacological screening of the initial set of compounds revealed that substituents having +ve $\pi$ and +ve $\sigma$ values, if placed at 4-position in the phenyl ring should increase anti-epileptic activity. However, lipophilicity is the
main controlling factor (pharmacodynamic parameter) in governing intensity of anti-epileptic activity. Its effect is potentiated by electronic features of the substituents by providing favourable pharmacokinetic parameter. Steric properties of the substituents were found to play negligible role in influencing the anti-epileptic activity. Considering these observations, 4-bromo, 4-trifluromethyl and 4-carboxyphenyl substituted compounds were synthesized in next series. After characterisation of these compounds, they were evaluated for their anti-epileptic potential. In comparison to initial set of compounds, the second set of compounds showed increased anti-epileptic activity.

LD_{50} values were determined and reported. LD_{50} values of all these compounds were found to be greater than 550 mg/kg, which supports their therapeutic safety. Hence, actual therapeutic usefulness of these compounds in relation to toxicity interference was determined.

In comparison with therapy prevailing during 1970s, today we are much more comfortable and fortunate to have wide range of anti-epileptic agents acting on variety of sites in the CNS. Still the search for newer anti-epileptic agents is being continued because of certain pharmacokinetic drawbacks of existing anti-epileptic drugs. These drawbacks include enzyme induction (phenytoin, phenobarbital, carbamazepine), enzyme inhibition (valproate), extensive serum protein binding (phenytoin, valproate), short half-life (carbamazepine and valproate), non-linear kinetic (phenytoin) and active metabolites (primidone, valproate, carbamazepine). Thus, there is a great need to develop new anti-epileptic agents with improved pharmacokinetic properties.

Considering the fact, in the PART-II we attempted to synthesize a series of prodrugs of baclofen that would raise the potency of baclofen and improve percentage absorption of baclofen. Total eight compounds were synthesized having generalised structure,
The purity and homogeneity of these compounds were judged by their sharp melting points and Rf values. The characterisation of these compounds was done by elemental analysis, IR and NMR spectra studies. The evaluation of anti-epileptic activity of the compounds was carried out by electro-convulsimeter and chemically induced seizure respectively.

$LD_{50}$ values were determined and reported. $LD_{50}$ values of all these compounds were found to be greater than 570mg/kg, which support their therapeutic safety.

From the research work undertaken and the results obtained in the given project i.e. “Synthesis and QSAR studies of novel anti-epileptic agents” it can be summarised that potent anti-epileptic agents can be synthesized by using QSAR techniques and prodrug approach.