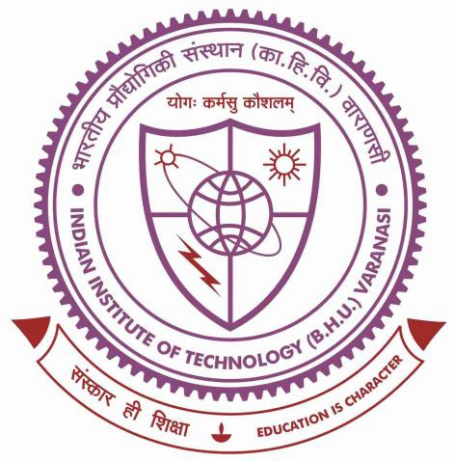
DESIGN, SYNTHESIS, PHARMACOLOGICAL EVALUATION AND MOLECULAR MODELLING STUDY OF QUINAZOLIN–4(3*H*)–ONES AS POTENTIAL ANTICONVULSANT AGENTS



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Summary and Conclusion

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. The disorder is now regarded as a major burden particularly in the developing countries because of associated cost and social stigma. The therapeutic intervention of epilepsy is primarily based on optimum use of anticonvulsant drugs. Understanding the causes of epilepsy is essential both for the management and discovery of target–specific anticonvulsant drugs. The rational drug development of new anticonvulsant drugs depends on delving insight in the pathophysiology of epilepsy and its underlying neurochemical changes. Many novel classes of therapeutics have been developed and observed for their activity by either targeting the voltage–gated ion channels or influence the GABA (γ–aminobutyric acid)–mediated inhibition. The ion channels deals with the suppression of action potential generated by sodium channels whereas decrease in the level of GABAergic inhibition caused epilepsy and augmentation of GABAergic transmission results in anticonvulsant effect. Alternatively, a decade long understanding of the structure and function of excitatory glutamatergic neurotransmission open up a new avenue for the recent developments of various anticonvulsant drugs. A growing body of evidence suggest that the glutamatergic system also contributes to the pathophysiology of epilepsy among other aspects. The receptors involved in glutamatergic neurotransmission are responsible for fast excitatory neurotransmission in the brain. Among the glutamatergic receptors, the ionotropic AMPA receptor has been explored like a viable target to combat epilepsy. Drugs acting as an AMPA receptor antagonist elicit their anticonvulsant activity by mitigating the hyperexcitability mediated by the receptor. GYKI 52466 was the prototype AMPA receptor antagonist and subsequent development led to the identification of talampanel and perampanel. Among the other bioactive molecules exhibiting anticonvulsant activity mediated by AMPA receptor, quinazoline and their derivatives have established themselves as potential anticonvulsant.

On the basis of the literature review and profound anticonvulsant activity achieved by the quinazolin–4(3*H*)–one derivative, two new series of quinazolin–4(3*H*)–ones have been synthesized. The compounds were purified and characterized by physicochemical and spectroscopic analysis. The spectroscopic analysis data were in accordance with the proposed structure of the synthesized compounds. The compounds were then evaluated against MES, *sc*PTZ and *icv* AMPA–induced seizure models. The dose that is

pharmacologically effective for 50% of the animal exposed to the drug (ED_{50}) of all the derivatives was determined by the Probit method. Probit analysis is a type of regression analysis of binomial variables for quantification of effective dose necessary for showing activity. It transforms the sigmoid dose–response curve to a straight line from where the effective dose at 50% concentration can be calculated. The results showed that some of the compounds displayed their capability to prevent seizure spread in the seizure models utilized for the present *in vivo* screening. Among the compounds evaluated in series, the least active compounds with increasing order of potency were in the order of **8e** followed by **5a<5e<8j<8b<8l<8i<8d<5b<8g<5d** compared to the other quinazolin–4(3*H*)–ones derivatives against MES induced seizures. The moderately active compounds include **5d, 5h, 5j, 5l, 8c, 5f, 8h, 5k, 8a, 5c, 5i** and **8k** and among the *N*3 heteroaryl substituted quinazolin–4(3*H*)–ones, the *N*3 pyridin–4–yl derivative **5k and 8h** showed good activity against MES–induced seizure.

The selected compounds evaluated against *sc*PTZ induced seizure displayed a dose–dependent activity pattern when compared with the level of activity obtained against MES induced seizures. In AMPA induced seizure, the ED_{50} value of **5g** and **8f** were 50.3 µmol/kg and 53.0 µmol/kg respectively and under the present experimental condition, the potency of the compounds was comparable with the standard GYKI52466 and talampanel. The compounds also showed low impairment of rotarod performance in mice. Among the selected compounds tested for hepatotoxic liability, they showed no significant changes in the activities of the enzymes AST and ALT. Further, histopathological examination of control and the representative compounds (**5g, 5i, 8f** and **8h)** revealed no observable damages to the hepatocytes.

The experimentally determined log P values of the synthesized compounds (**5a–5l, 8a–8l)** were found in the range of 2.14–2.83. The values conform to the suggested value of logP≤5 and this indicates that the synthesized compounds are suitable as CNS drugs. The molecular modelling study suggests that the preferential orientation of the representative compound **5g** and **8f** is within the pocket formed due to a cavity–shaping loop, characterised by the amino acid residues viz. Gln 16, Gln 17, Glu 20, His 21, Tyr 71, Ile 91, Arg 108, Ser 188, Phe 217, Met 218, Ile 220, Lys 269, Asp 304, Cys 305, Leu 306 (Hydrogen bond acceptor region). The C2 side chain is skewed towards the hydrophobic region of the receptor site. The side chain probably assists in orienting the quinazolin–4(3*H*)–one moiety towards the cavity forming loop of the receptor. The docked compounds showed hydrogen bonding with Arg 108 and Lys 269). The

hydrogen bond interaction of the quinazolinone –CO group was found to be with the guanidino group of Arg108.

In conclusion, few derivatives of quinazolin–4(3*H*)–ones were identified as potent anticonvulsant agent. Among the compounds evaluated, compounds **5g, 5i, 5k 8b, 8f, 8h and 8k** have shown considerable activity when compared with the standard GYKI 52466 and talampanel. The presence of the substituted aryl/heteroaryl ring at the *N*3 position of a 6,7–dimethoxy–quinazolin–4(3*H*)–one nucleus have modulatory effects on anticonvulsant activity with respect to the presence of different C2 side chain as exemplified by various representative compounds. In particular, compound **5g** and **8f** with *N*3 *para* nitrophenyl substitution showed promising activity profile and represent a new structural lead as anticonvulsant.